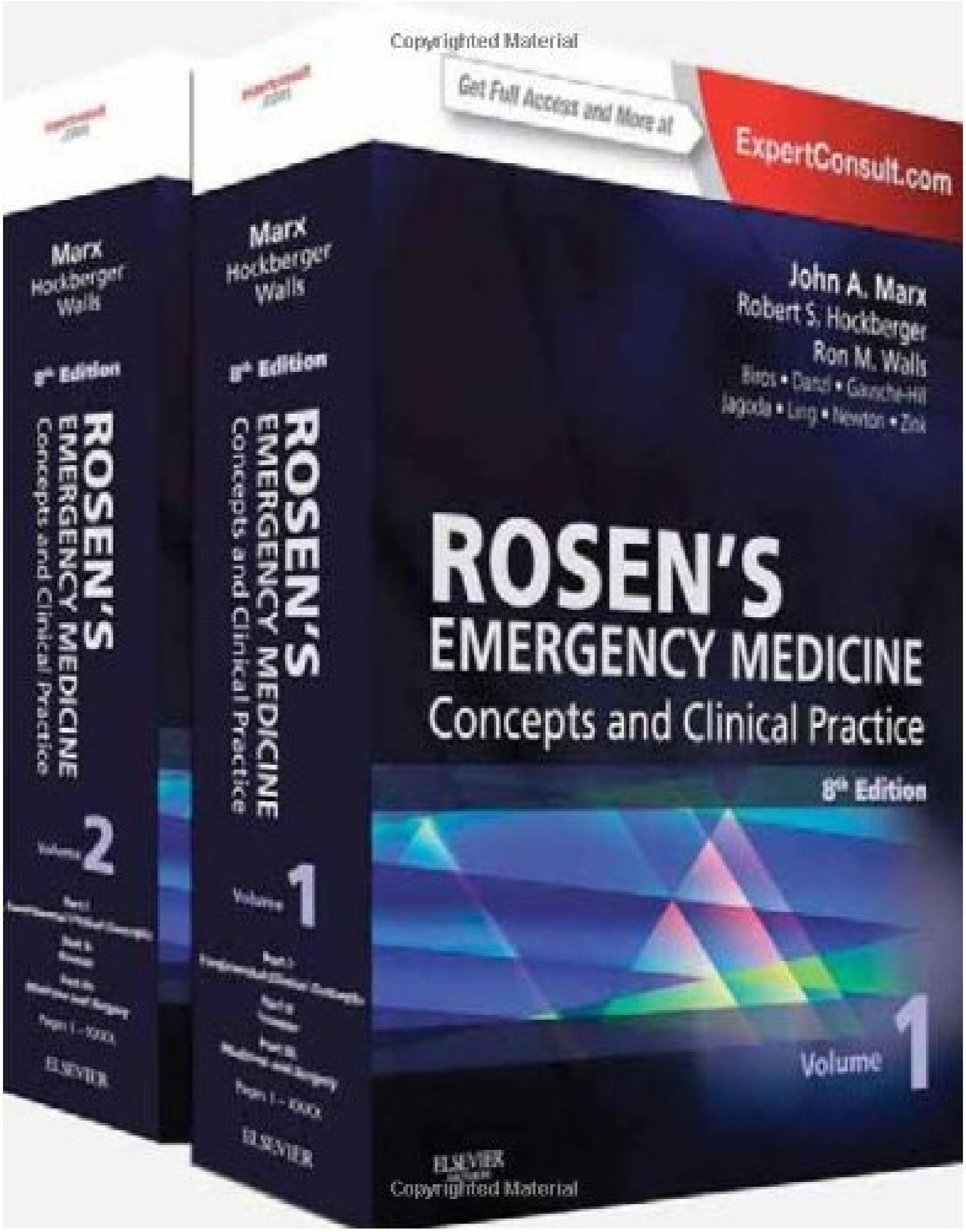
Find us on: facebook
TCS KNOWLEDGE BANK
Telegram



ROSEN'S EMERGENCY MEDICINE

Concepts and Clinical Practice

Volume 1

8th Edition

Editor-in-Chief

John A. Marx, MD
Formerly Adjunct Professor of Emergency Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; Chair Emeritus, Department of Emergency Medicine, Carolinas Medical Center, Charlotte, North Carolina

Senior Editors

Robert S. Hockberger, MD
Professor of Clinical Medicine, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California; Chair Emeritus, Harbor–UCLA Medical Center, Torrance, California

Ron M. Walls, MD
Professor and Chair, Department of Emergency Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Editors

Michelle H. Biros, MD, MS
Professor, Emergency Medicine, University of Minnesota Medical School and Hennepin County Medical Center; Vice-Chair of Research, Emergency Medicine, University of Minnesota Medical School; Associate Research Director, Hennepin County Medical Center, Minneapolis, Minnesota

Daniel F. Danzl, MD
Professor and Chair, Department of Emergency Medicine, University of Louisville School of Medicine, Louisville, Kentucky

Marianne Gausche-Hill, MD
Professor of Clinical Medicine, David Geffen School of Medicine at University of California at Los Angeles; Vice Chair and Chief of the Division of Pediatric Emergency Medicine, Director of Pediatric Emergency Medicine and Emergency Medical Services Fellowships, Department of Emergency Medicine, Harbor–University of California at Los Angeles Medical Center, Torrance, California

Andy Jagoda, MD, FACEP
Professor and Chair, Mt. Sinai School of Medicine and Medical Director, Mt. Sinai Medical Center, New York, New York

Louis J. Ling, MD
Professor of Emergency Medicine and Pharmacy, University of Minnesota Medical School; Medical Toxicology Consultant, Hennepin Regional Poison Center, Minneapolis, Minnesota; Senior Vice-President, Hospital-Based Accreditation, Accreditation Council for Graduate Medical Education, Chicago, Illinois

Edward J. Newton, MD
Professor of Emergency Medicine, Keck School of Medicine; Chair, Department of Emergency Medicine, Los Angeles County and University of Southern California Medical Center, Los Angeles, California

Brian J. Zink, MD
Professor and Chair, Department of Emergency Medicine, Warren Alpert Medical School of Brown University; Physician-in-Chief, Emergency Medicine, Rhode Island Hospital, The Miriam Hospital, and Hasbro Children's Hospital, Providence, Rhode Island

ELSEVIER
SAUNDERS

ELSEVIER
SAUNDERS

1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

ROSEN'S EMERGENCY MEDICINE:CONCEPTS AND CLINICAL PRACTICE ISBN: 978-1-4557-0605-1

Volume 1 Part Number: 996087921
Volume 2 Part Number: 996087980

Copyright © 2014 by Saunders, an imprint of Elsevier Inc.
Copyright © 2010, 2006, 2002, 1998, 1992, 1988, 1983 by Mosby, Inc., an affiliate of Elsevier Inc.

All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

With respect to any drug or pharmaceutical products identified, readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of practitioners, relying on their own experience and knowledge of their patients, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

Library of Congress Cataloging-in-Publication Data

Rosen's emergency medicine : concepts and clinical practice / editor-in-chief, John A. Marx; senior editors, Robert S. Hockberger, Ron M. Walls ; editors, Michelle H. Biros … [et al.].—8th ed.
p. ; cm.
Emergency medicine
Includes bibliographical references.
ISBN 978-1-4557-0605-1 (hardcover : alk. paper)
I. Marx, John A. II. Rosen, Peter, 1935- Emergency medicine. III. Title: Emergency medicine.
[DNLM: 1. Emergencies. 2. Emergency Medicine. WB 105]
RC86.7
616.02′5—dc23
2013015607

Senior Content Strategist: Stefanie Jewell-Thomas
Senior Content Development Specialist: Deidre Simpson
Publishing Services Manager: Patricia Tannian
Senior Project Manager: Claire Kramer
Designer: Steven Stave

Printed in China

Last digit is the print number: 9 8 7 6 5 4 3 2 1

Working together to grow libraries in developing countries
ELSEVIER Book Aid International
www.elsevier.com • www.bookaid.org

www.ketabpezeshki.com 66485457-66963820

We, the authors and editors, dedicate this edition of *Rosen's Emergency Medicine: Concepts and Clinical Practice* to our late, beloved colleague, John Andrew Marx, who died suddenly and unexpectedly in his sleep on July 1, 2012. The loss of John, as mentor, friend, colleague, and leader, has left an enormous void in our lives and in the lives of countless others in our field who were inspired or counseled by his incisive intellect and sedulous devotion to scientific rigor. This book was born in 1983, when Peter Rosen's dream of a compendium of the biology of emergency medicine, written by those who study, teach, and practice it, was realized with the publication of the first edition. For three subsequent editions, Peter guided, cajoled, and willed the book to completion, all the while grooming John as his obvious and worthy successor. John became editor in chief for the fifth edition and remained so through this eighth edition, on which, in characteristic fashion, he had discharged his duties fully and flawlessly, prior to his untimely death. As editors, we are proud to have shared this vision, Peter's vision, which became John's vision, with one of the most influential and inspiring physicians of our time. Although he did not live to hold a bound copy in his hands, John guided every aspect of this book from beginning to end, and we know that he was particularly proud that, with this edition, he had served as editor in chief for as many iterations of the book as had Peter and that he felt a sense of completeness and of the inevitability of a timeless legacy on reaching that milestone. Although John achieved professional success beyond description and received virtually every conceivable honor and recognition, including the highest awards from each of our three major societies, he remained a humble, devoted emergency physician, deeply rooted in his love for his patients and for his colleagues and trainees. He was endlessly proud of his children, Shelby and Connor, whom he loved without bound, and who were his favorite topic of conversation. He was inspired, supported, and nurtured by his wife, Karin, with whom he was deeply in love, and from whom he received the gifts of extraordinary happiness and peace. We both are humbled and honored to be able to set these final few words to paper and to gently convey this great work to posterity on behalf of our dear friend and beloved editor, John Andrew Marx.

Ron M. Walls
Robert S. Hockberger
2012

www.ketabpezeshki.com 66485457-66963820

Acknowledgments

To John, for his friendship, leadership, and unwavering commitment to our specialty; to Ron, for his friendship, vision, and ability to make hard work fun; to our editors, for their dedication, insights, and ability to get it all done "on time and under budget"; to Stefanie and Dee, for their vigilance and support; to Peter, for the leadership, mentorship, and opportunities he provided us all; and to Patty, the love of my life.

RSH

With affection, admiration, and gratitude to Barb, and to our children, Andrew, Blake, and Alexa, whom together we recognize as the most meaningful and priceless gifts we have been privileged to receive. With humble thanks to Peter Rosen, whose selfless commitment to our specialty and to us, as individuals, helped define an entirely new direction in modern medicine. To my hero, John Marx, whose incandescent brilliance changed the trajectory of my career, and to Bob Hockberger, for his consummate professionalism and skill. To our authors and editors, who are the real artists of this creation, and, finally, to my extraordinary faculty and residents at Brigham and Women's Hospital, whose intellectual curiosity and boundless intelligence inspire me to be better.

RMW

To my family, friends, students, and teachers, who have constantly provided encouragement and support. To the leadership of our specialty, especially John Marx, for the hard work and devotion that have advanced the care of emergency patients everywhere.

MHB

When Peter invited me on board in 1995 for edition four, it felt exhilarating, kind of like being called by Osler (in baritone). I reread his preface to the first edition, which was dedicated to all of our founding colleagues in emergency medicine "who have accepted its responsibilities, challenges, and excitements." Joanna observes that our daughters, now just married, were 12 and 10—girls do grow quicker than books. Emergency medicine has sure come a long way. Thanks Peter; we all owe you one.

DFD

I dedicate this book to Dr. John Marx, one of our nation's brightest leaders in emergency medicine, a respected colleague and friend, and to my family for their love and support.

MGH

To Silvana, my wife and closest colleague, who gives me inspiration and keeps me focused on the important things in life. To John, a great mentor and friend who will be missed beyond words.

ASJ

To the emergency medicine faculty and residents at Hennepin County Medical Center and all that we have learned together. To John Marx, a specially gifted teacher and leader, who had a mischievous streak but who could get it done. I am grateful to all the authors who have generously shared their time, energy, and wisdom and to my fellow editors for their commitment to this terrific book. Special thanks to Eric, who should read this book, and to Ali, Amanda, and Beth, for their patience, understanding, and love.

LJL

Thank you to my colleagues, mentors, and friends and particularly thanks to John Marx, who has been all of these for the past 20 years. His gentle guidance and quick wit will be sorely missed.

EJN

To my mother, Audrey Zink, for instilling in me a love of academics and for working so hard to advance her children, against many odds. To John Marx, whose legacy includes this tome and a generation of grateful emergency physicians.

BJZ

www.ketabpezeshki.com 66485457-66963820

FOUNDING EDITOR
Peter Rosen

PAST EDITORS
Frank J. Baker II (Editions 1 and 2)
G. Richard Braen (Editions 1, 2, and 3)
Robert H. Dailey (Editions 1, 2, and 3)
Jerris R. Hedges (Edition 3)
Richard C. Levy (Editions 1, 2, and 3)
Vincent Markovchick (Edition 4)
Mark Smith (Edition 3)
Glenn C. Hamilton (Editions 5 and 6)
James G. Adams (Editions 5, 6, and 7)
William G. Barsan (Editions 5, 6, and 7)

EMERITUS EDITORS
Peter Rosen
Roger M. Barkin

www.ketabpezeshki.com 66485457-66963820

Preface to the Eighth Edition

With heavy hearts, we commend to you the eighth edition of this comprehensive resource for the biology and practice of the specialty of emergency medicine. We are fortunate to have had the benefit of working with not one, but two iconic editors in chief. This edition marks the final stage in the evolution of John Marx's vision of a highly authoritative and pithy, timely and timeless, clinical reference for all students, devotees, and practitioners of this most honorable of the medical specialties. This edition builds on the great success of the seventh edition, with further refinement of our chapter formatting, prose, and citations. We worked diligently to balance appropriate citation support for the material presented against the prospect of a bewildering sea of references, seeking always to reduce redundancy, while providing timely and authoritative background.

Recommendations are based on the best evidence available and, in the absence of clear scientific support for a single course of action, on the collective experience and judgment of our authors and editors. This edition is more richly illustrated than any before it, both to enhance readability and to improve our effectiveness in conveying key information in the best possible format. Emergency medicine is increasingly a procedure-based specialty, but we continue to leave the detailed description of procedures to other works, focusing instead on the substantial basis of knowledge, experience, and reasoning that is necessary to achieve the highest possible levels of clinical performance. We have updated and enriched the Continuing Medical Education questions that relate to each chapter, to assist the reader both in learning and in meeting regulatory requirements. We have provided, and will continue to provide online updates, between editions, recognizing that new information flows without regard to publishing schedules, continuously complementing the comprehensive base we have provided.

A book, in the beginning, middle, and end, is about the people who make it happen. We are deeply indebted to our authors and to our editors, whose names you see on the cover and title page. We bid a fond farewell, with endless gratitude, to Jim Adams and Bill Barsan, editors of extraordinary talent who departed after the seventh edition, finally succumbing to the overwhelming demands for their time and talents. We were fortunate to recruit Brian Zink and Andy Jagoda to our cause, and it was clear within weeks that we had made the right choice, with each taking the reins as if seasoned by multiple prior editions. Our other editors, veterans all, embraced their new colleagues, and we had an extraordinary unity of purpose as we moved relentlessly toward our shared vision. We are grateful also to our skilled, patient, and brilliant publishing team at Elsevier: Judy Fletcher, our global content development director; Stefanie Jewell-Thomas, our senior content strategist; and Deidre (Dee) Simpson, our senior content development specialist. Their expertise, creativity, and dedication contribute much to the book, allowing us to develop and share its rich content. We are grateful, also, to Dr. Barry Brenner and Dr. Michael Richardson, each of whom meticulously read the entire seventh edition, providing literally dozens of suggestions for improvement, which we have incorporated into edition eight. On behalf of John, we thank Tricia Wyatt, his dedicated, long-serving assistant, whose heart we know aches as do our own. We also thank Diane Pugh and Janice Bingham (RMW) and Maria Figueroa (RSH), for without their extraordinary organizational talent and attention to detail, we would most certainly be lost. Finally, we have to thank, one final time, our beloved John, with the sadness that this is our final project together, but with the joy of having shared so much, for so long.

Ron M. Walls, MD
Robert S. Hockberger, MD
2012

www.ketabpezeshki.com 66485457-66963820

How This Medical Textbook Should Be Viewed by the Practicing Clinician and the Judicial System

The editors and authors of this textbook strongly believe that the complex practice of medicine, the vagaries of human diseases, the unpredictability of pathologic conditions, and the functions, dysfunctions, and responses of the human body cannot be defined, explained, or rigidly categorized by any written document. *Therefore, it is neither the purpose nor intent of our textbook to serve as an authoritative source on any medical condition, treatment plan, or clinical intervention, nor should our textbook be used to rigorously define a standard of care that should be practiced by all clinicians.*

Our written word provides the physician with a literature-referenced database, and a reasonable clinical guide that is combined with practical suggestions from individual experienced practitioners. We offer a general reference source and clinical roadmap on a variety of conditions and procedures that may confront clinicians who are experienced in emergency medicine practice. This text cannot replace physician judgment; cannot describe every possible aberration, nuance, clinical scenario, or presentation; and cannot define rigid standards for clinical actions or procedures. *Every medical encounter must be individualized, and every patient must be approached on a case-by-case basis.* No complex medical interaction can possibly be reduced to the written word. The treatments, procedures, and medical conditions described in this textbook do not constitute the total expertise or knowledge base expected to be possessed by all clinicians. Finally, many of the described complications and adverse outcomes associated with implementing or withholding complex medical and surgical interventions may occur, even when every aspect of the intervention has been standard or performed correctly.

The editors and authors of *Rosen's Emergency Medicine: Concepts and Clinical Practice, 8th Edition*

From Roberts JR, Marx JA: Position Statement: Use of Medical Textbooks in Malpractice Claims, Emerg Med News, Vol. XXXI, 2:3, February 2009.

www.ketabpezeshki.com 66485457-66963820

Contributors

Jean Abbott, MD, MH
Professor Emerita, Emergency Medicine, University of Colorado School of Medicine; Faculty, Center for Bioethics and Humanities, University of Colorado Health Sciences Center; Attending Physician, Emergency Department, Anschutz Medical Center, Aurora, Colorado
End of Life

Riyad B. Abu-Laban, MD, MHSc, FRCPC
Associate Professor and Research Director, Department of Emergency Medicine, University of British Columbia; Scientist, Centre for Clinical Epidemiology and Evaluation, Vancouver Coastal Health Research Institute; Attending Physician Department of Emergency Medicine, Vancouver General Hospital, Vancouver, British Columbia, Canada
Ankle and Foot

COL (Ret.) Bruce D. Adams, MD, FACEP
Professor and Chair, Department of Emergency Medicine, University of Texas School of Medicine, San Antonio, Texas
Arthritis

Stephen L. Adams, MD, FACP, FACEP
Professor of Medicine and Professor of Emergency Medicine, Chief, Division of Sports Medicine, Department of Medicine Chief Emeritus, Division of Emergency Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine; Medical Director and Attending Physician, Emergency Preparedness/Disaster Services, Northwestern Memorial Hospital; Head Team Physician and Medical Director, Chicago Cubs National League Baseball Club; Consultant, Division of Emergency Medicine, Department of Pediatrics, Anne and Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois
Tendinopathy and Bursitis

Terry A. Adirim, MD, MPH
Director, Office of Special Health Affairs, Health Resources and Services Administration, U.S. Department of Health and Human Services, Rockville, Maryland
Evaluation of the Developmentally or Physically Disabled Patient

James T. Amsterdam, DMD, MD, MMM, FACEP, FACPE
Chair, Department of Emergency Medicine, York Hospital, York, Pennsylvania; Professor of Clinical Emergency Medicine, Department of Emergency Medicine, Penn State University College of Medicine, Hershey, Pennsylvania; Adjunct Professor of Emergency Medicine, Department of Emergency Medicine, Drexel University College of Medicine, Philadelphia, Philadelphia
Oral Medicine

Deirdre Anglin, MD, MPH
Vice Chair of Academic Affairs, Professor of Emergency Medicine, Keck School of Medicine of the University of Southern California, Los Angeles, California
Intimate Partner Violence
Elder Abuse and Neglect

Felix K. Ankel, MD
Residency Director, Emergency Department, Regions Hospital, St. Paul, Minnesota; Associate Professor, Emergency Medicine, University of Minnesota, Minneapolis, Minnesota
Aortic Dissection

Robert T. Arntfield, MD, FRCPC, FCCP, RDMS
Assistant Professor, Division of Emergency Medicine and Division of Critical Care Medicine, Western University; Attending Physician, Emergency Medicine, Critical Care Medicine and Trauma, London Health Sciences Centre, London, Ontario, Canada
Systemic Lupus Erythematosus and the Vasculitides

Sanjay Arora, MD
Associate Professor, Emergency Medicine, Keck School of Medicine of the University of Southern California, Los Angeles, California
Peripheral Vascular Injury

Tom P. Aufderheide, MD
Professor of Emergency Medicine, Department of Emergency Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin
Peripheral Arteriovascular Disease

Kevin M. Ban, MD
Attending Physician, Emergency Medicine, Beth Israel Deaconess Medical Center; Assistant Clinical Professor, Medicine, Harvard Medical School, Boston, Massachusetts
Selected Urologic Problems

www.ketabpezeshki.com 66485457-66963820

Christina Hantsch Bardsley, MD
Professor, Department of Emergency Medicine, Stritch School of Medicine, Loyola University Chicago, Chicago, Illinois; Attending Physician, Emergency Medicine and Medical Toxicology, Loyola University Medical Center, Maywood, Illinois
Opioids

Adam Z. Barkin, MD, MPH
Attending Physician, Emergency Medicine, Rose Medical Center; Clinical Instructor, Emergency Medicine, University of Colorado School of Medicine, Denver, Colorado
Sepsis Syndromes

Andrew R. Barnosky, DO, MPH
Associate Professor, Department of Emergency Medicine, University of Michigan, Ann Arbor, Michigan
Wellness, Stress, and the Impaired Physician

Benjamin S. Bassin, MD
Clinical Instructor, Department of Emergency Medicine, University of Michigan, Ann Arbor, Michigan
Depressed Consciousness and Coma

Bruce M. Becker, MD, MPH
Professor, Emergency Medicine and Community Health, Warren Alpert Medical School of Brown University, Providence, Rhode Island
Parasitic Infections

Rimon N. Bengiamin, MD, RDMS
Assistant Clinical Professor of Emergency Medicine, Director of Emergency Ultrasound, Department of Emergency Medicine, University of California at San Francisco–Fresno, Fresno, California
Abdominal Pain

Rachel R. Bengtzen, MD
Assistant Professor, Department of Emergency Medicine, Department of Family Medicine (Sports Medicine), Oregon Health and Science University, Portland, Oregon
Shoulder

Robert A. Berg, MD, FAAP, FAHA, FCCM
Professor, Anesthesiology and Critical Care Medicine and Pediatrics, University of Pennsylvania Perelman School of Medicine; Division Chief, Critical Care Medicine, Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Pediatric Resuscitation

Laurel R. Berge, MD
Clinical Instructor, Department of Emergency Medicine, Oregon Health and Science University, Portland, Oregon
Upper Respiratory Tract Infections

Carol Berkowitz, MD
Executive Vice Chair, Pediatrics, Harbor–University of California at Los Angeles Medical Center, Torrance, California; Professor of Clinical Pediatrics, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California
Child Maltreatment

Edward Bernstein, MD
Professor and Vice Chair for Academic Affairs, Emergency Medicine, Boston University School of Medicine; Attending Physician, Emergency Department, Boston Medical Center; Professor, Community Health Sciences and Co-Director BNI-ART Institute, Boston University School of Public Health, Boston, Massachusetts
Multiculturalism and Care Delivery

Judith Bernstein, RNC, PhD
Professor, Community Health Sciences, School of Public Health and Emergency Medicine, Co-Director BNI-ART Institute, School of Medicine, Boston University, Boston, Massachusetts
Multiculturalism and Care Delivery

Howard A. Bessen, MD
Professor of Medicine, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California; Clinical Faculty, Department of Emergency Medicine, Harbor–University of California at Los Angeles Medical Center, Torrance, California
Abdominal Aortic Aneurysm

Kriti Bhatia, MD
Associate Residency Director, Harvard Affiliated Emergency Medicine Residency, Brigham and Women's/Massachusetts General Hospitals; Attending Physician, Department of Emergency Medicine, Brigham and Women's Hospital, Boston, Massachusetts
Trauma in Pregnancy

Diane M. Birnbaumer, MD
Professor of Clinical Medicine, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California; Senior Faculty, Department of Emergency Medicine, Harbor–University of California at Los Angeles Medical Center, Torrance, California
Sexually Transmitted Diseases

Michelle H. Biros, MD, MS
Professor, Emergency Medicine, University of Minnesota Medical School and Hennepin County Medical Center; Vice-Chair of Research, Emergency Medicine, University of Minnesota Medical School; Associate Research Director, Hennepin County Medical Center, Minneapolis, Minnesota
Fever in the Adult Patient
Head Injury

Robert A. Bitterman, MD, JD
President, Bitterman Health Law Consulting Group, Inc., Harbor Springs, Michigan
Emergency Medical Treatment and Active Labor Act and Medicolegal Issues

Thomas H. Blackwell, MD
Clinical Professor of Emergency Medicine and Academic Administrator for Clinical Education, University of South Carolina School of Medicine Greenville, Greenville, South Carolina
Emergency Medical Services: Overview and Ground Transport

Frederick C. Blum, MD, FACEP, FAAP, FIFEM
Associate Professor, Departments of Pediatrics and Emergency Medicine, West Virginia University School of Medicine, Morgantown, West Virginia
Fever in the Adult Patient

www.ketabpezeshki.com 66485457-66963820

Ira J. Blumen, MD, FACEP
Professor, Department of Medicine, Section of Emergency Medicine, University of Chicago; Professor, Department of Medicine, Section of Emergency Medicine, University of Chicago; Medical and Program Director, University of Chicago Aeromedical Network (UCAN), University of Chicago Medicine, Chicago, Illinois
Air Medical Transport

Edward B. Bolgiano, MD
Assistant Professor, Department of Emergency Medicine, University of Maryland School of Medicine, Baltimore, Maryland
Tick-Borne Illnesses

William J. Brady, MD
Professor of Emergency Medicine, Department of Emergency Medicine; Professor of Medicine, Department of Medicine, University of Virginia, Charlottesville, Virginia
Acute Coronary Syndrome

Sabina A. Braithwaite, MD, MPH
Medical Director, Wichita-Sedgwick County Emergency Medical Service System, Wichita, Kansas; Clinical Associate Professor, Emergency Medicine, University of Kansas Medical Center, Kansas City, Kansas; Clinical Associate Professor, Preventive Medicine and Public Health, University of Kansas Medical Center, Wichita, Kansas
Dyspnea

Calvin A. Brown III, MD
Associate Chief, Department of Emergency Medicine, Faulkner Hospital; Attending Emergency Medicine Physician, Brigham and Women's and Faulkner Hospitals; Assistant Professor of Medicine, Harvard Medical School, Boston, Massachusetts
Airway
Hemoptysis

James E. Brown, MD, MMM
Chair and Program Director, Department of Emergency Medicine, Boonshoft School of Medicine, Wright State University, Dayton, Ohio
Chest Pain

Douglas D. Brunette, MD
Associate Professor, Emergency Medicine, University of Minnesota Medical School; Assistant Chief, Clinical Affairs, Emergency Medicine Hennepin County Medical Center, Minneapolis, Minnesota
Ophthalmology

Gavin Budhram, MD
Assistant Professor of Emergency Medicine, Tufts University School of Medicine; Chief, Division of Emergency Ultrasound, Department of Emergency Medicine, Baystate Medical Center, Springfield, Massachusetts
Abdominal Pain

E. Bradshaw Bunney, MD, FACEP
Associate Professor, Residency Director, Department of Emergency Medicine, University of Illinois at Chicago, Chicago, Illinois
Peripheral Nerve Disorders

David B. Burbulys, MD
Associate Residency Program Director, Emergency Medicine, Harbor–University of California at Los Angeles Medical Center, Torrance, California; Associate Professor of Medicine, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California
Procedural Sedation and Analgesia

Michael J. Burns, MD
Clinical Professor, Department of Emergency Medicine and Department of Medicine, Division of Infectious Diseases, University of California Irvine School of Medicine, Irvine, California; Attending Physician, Department of Emergency Medicine, University of California Irvine Medical Center, Orange, California
The Immunocompromised Patient

John Burton, MD
Chair, Professor of Emergency Medicine, Department of Emergency Medicine, Carilion Clinic, Roanoke, Virginia
Pain Management

Richard Byyny, MD, MSc
Associate Professor, Emergency Medicine, Denver Health Medical Center, Denver, Colorado; Associate Professor, Emergency Medicine, University of Colorado, Aurora, Colorado
Scuba Diving and Dysbarism

John D. Cahill, MD
Senior Attending in Emergency Medicine and Infectious Disease; Global Health Fellowship Director, Emergency Medicine, St. Luke's Roosevelt Hospital Center, New York, New York; Senior Lecturer, International Health and Tropical Medicine, The Royal College of Surgeons, Dublin, Ireland
Parasitic Infections

Kirsten K. Calder, MD, FACEP
Department of Emergency Medicine, Los Alamitos Medical Center, Los Alamitos, California
Chronic Medical Illness during Pregnancy

Stuart M. Caplen, MD, MSM
Attending Physician, Montefiore Medical Center, Wakefield Campus, Bronx, New York
Neurologic Disorders

Andrea Carlson, MD
Assistant Residency Director, Director of Toxicology, Emergency Medicine, Advocate Christ Hospital, Oak Lawn, Illinois
Sedative Hypnotics

Andrew K. Chang, MD, MS
Associate Professor, Emergency Medicine, Albert Einstein College of Medicine; Attending Physician, Emergency Medicine, Montefiore Medical Center, Bronx, New York
Dizziness and Vertigo

Stephen Choi, MD, FRCPC
Department of Emergency Medicine, University of Ottawa, Ottawa, Ontario, Canada
Pelvic Trauma

www.ketabpezeshki.com 66485457-66963820

Richard F. Clark, MD
Professor, Emergency Medicine, University of California at San Diego School of Medicine; Director, Division of Medical Toxicology, University of California at San Diego Medical Center; Medical Director, San Diego Division, California Poison Control System, San Diego, California
Substance Abuse

Ilene Claudius, MD
Assistant Professor, Emergency Medicine, Los Angeles County and University of Southern California Medical Center, Los Angeles, California
Neck

Wendy C. Coates, MD
Professor of Clinical Medicine; Chair, Acute Care College, Educational Development and Research, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California; Director, Medical Education, Emergency Medicine; Director, Fellowship in Medical Education, Emergency Medicine, Harbor–University of California at Los Angeles Medical Center, Torrance, California
Disorders of the Anorectum

Jon B. Cole, MD
Medical Director, Hennepin Regional Poison Center; Faculty Emergency Physician, Department of Emergency Medicine, Hennepin County Medical Center; Assistant Professor of Emergency Medicine, Department of Emergency Medicine, University of Minnesota Medical School, Minneapolis, Minnesota
Cardiovascular Drugs

Robert Collier, MD
Assistant Professor of Emergency Medicine, Hennepin County Medical Center, Department of Emergency Medicine, University of Minnesota, Minneapolis, Minnesota
Diarrhea

Stephen A. Colucciello, MD
Vice Chief, Emergency Medicine, Carolinas Medical Center, Charlotte, North Carolina; Professor, Emergency Medicine, University of North Carolina, Charlotte, North Carolina
Suicide

Christopher B. Colwell, MD
Director of Service, Department of Emergency Medicine; Denver Health Professor and Vice Chair, Department of Emergency Medicine, University of Colorado School of Medicine, Denver, Colorado
Radiation Injuries

Edward E. Conway, Jr., MD, MS
Chairman and Pediatrician-in-Chief, Milton and Bernice Stern Department of Pediatrics, Beth Israel Medical Center, New York, New York; Professor of Clinical Pediatrics, Albert Einstein College of Medicine, Bronx, New York
Neurologic Disorders

Jeremy L. Cooke, MD
Staff Physician, Emergency Medicine, South Sacramento Kaiser Hospital, Sacramento, California
Depressed Consciousness and Coma

Mary Ann Cooper, MD
Professor Emerita, University of Illinois at Chicago, Chicago, Illinois
Electrical and Lightning Injuries

Randolph J. Cordle, MD
Medical Director, Division of Pediatric Emergency Medicine, Emergency Medicine, Carolinas Medical Center, Levine Children's Hospital, Charlotte, North Carolina
Pediatric Trauma

Sandy A. Craig, MD
Residency Program Director, Emergency Medicine, Carolinas Medical Center, Charlotte, North Carolina; Associate Professor, Emergency Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina
Gastroenteritis

Hilarie Cranmer, MD, MPH
Assistant Professor, Medicine, Harvard Medical School; Assistant Professor, Global Health and Population, Harvard School of Public Health; Attending Physician, Department of Emergency Medicine and Director of Disaster Response, Center for Global Health, Massachusetts General Hospital, Boston, Massachusetts
Vaginal Bleeding
Trauma in Pregnancy

Todd Crocco, MD
Professor and Chair, Department of Emergency Medicine, West Virginia University, Morgantown, West Virginia
Stroke

Pat Croskerry, MD, PhD
Professor in Emergency Medicine, Department of Emergency Medicine; Director of Critical Thinking Program, Division of Medical Education, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada
Process Improvement and Patient Safety

Jeffrey Cukor, MD
Associate Professor of Emergency Medicine, Department of Emergency Medicine, University of Massachusetts Medical School, Worcester, Massachusetts
Pediatric Respiratory Emergencies: Upper Airway Obstruction and Infections

A. Adam Cwinn, MD, FRCPC, CCPE
Professor, Emergency Medicine, University of Ottawa, Ottawa; Head of the Department of Emergency Medicine, The Ottawa Hospital, Ottawa, Ontario, Canada
Pelvic Trauma

Rita K. Cydulka, MD, MS
Professor and Vice Chair, Department of Emergency Medicine, MetroHealth Medical Center/Case Western Reserve University, Cleveland, Ohio
Dermatologic Presentations
Diabetes Mellitus and Disorders of Glucose Homeostasis

Daniel F. Danzl, MD
Professor and Chair, Department of Emergency Medicine, University of Louisville School of Medicine, Louisville, Kentucky
Frostbite
Accidental Hypothermia

Christopher Davis, MD
Assistant Professor of Emergency Medicine, Department of Emergency Medicine, University of Colorado School of Medicine, Denver, Colorado
High-Altitude Medicine

www.ketabpezeshki.com 66485457-66963820

Ana M. Davitt, MD
Attending Physician, Emergency Medicine, Pennsylvania Hospital, University of Pennsylvania Health System, Philadelphia, Pennsylvania
Seizures

Mohamud R. Daya, MD, MS
Associate Professor, Department of Emergency Medicine, Oregon Health and Science University, Portland, Oregon
Shoulder

Robert A. De Lorenzo, MD, MSM
Senior Scientist, Combat Casualty Care Research Program, United States Army Institute of Surgical Research, Fort Sam Houston, Texas; Professor, Department of Military and Emergency Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland
Syncope

Robert W. Derlet, MD
Department of Emergency Medicine, University of California Davis Health System, Sacramento, California
Tuberculosis

Shoma Desai, MD
Assistant Professor, Emergency Medicine, Los Angeles County and University of South California Medical Center, Los Angeles, California
Labor and Delivery and Their Complications

Aaron J. Donoghue, MD, MSCE
Assistant Professor, Pediatrics and Anesthesia, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania
Pediatric Resuscitation

Evelyn H. Duvivier, MD, MPH
Attending Physician, Emergency Medicine, Pennsylvania Hospital, Philadelphia, Pennsylvania
Seizure Disorder

Joshua Easter, MD
Assistant Professor, Emergency Medicine, Denver Health and Hospital Authority, Denver, Colorado
Selected Urologic Problems

Marc Eckstein, MD, MPH
Professor of Emergency Medicine, Keck School of Medicine of the University of Southern California; Medical Director, Los Angeles Fire Department; Director of Prehospital Care, Los Angeles County and University of Southern California Medical Center, Los Angeles, California
Thoracic Trauma

Matthew Emery, MD, FACEP
Assistant Professor, Associate Director for Academic Affairs, Department of Emergency Medicine, Lead Clerkship Director, Fourth Year Elective in Emergency Medicine, Department of Emergency Medicine, Michigan State University College of Human Medicine; Educational Assistant for Simulation, Emergency Medicine, Grand Rapids Medical Education Partners, Grand Rapids, Michigan
Blood and Blood Components

Michael L. Epter, DO, FAAEM
Associate Professor, Vice Chair of Education and Program Director, Department of Emergency Medicine, University of Nevada, Las Vegas, Nevada
Wellness, Stress, and the Impaired Physician

Sing-Yi Feng, MD
Assistant Professor of Pediatrics, Department of Pediatrics/Division of Emergency Medicine, University of Texas Southwestern Medical Center at Dallas; Medical Toxicologist, North Texas Poison Center, Parkland Memorial Hospital, Dallas, Texas
Anticholinergics

Madonna Fernández-Frackelton, MD
Program Director, Emergency Medicine, Harbor–University of California at Los Angeles Medical Center, Torrance, California; Associate Professor of Medicine, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California
Cyanosis
Bacteria

John T. Finnell, MD, MSc
Associate Professor of Clinical Emergency Medicine, Indiana University, Indianapolis, Indiana
Alcohol-Related Disease

Benjamin W. Friedman, MD, MS
Associate Professor, Emergency Medicine, Albert Einstein College of Medicine; Attending Physician, Emergency Medicine, Montefiore Medical Center, Bronx, New York
Headache Disorders

E. John Gallagher, MD
University Chair and Professor of Emergency Medicine, Medicine, Epidemiology and Population Health, Emergency Medicine, Albert Einstein College of Medicine; Chair, Department of Emergency Medicine, Montefiore Medical Center, Bronx, New York
Peripheral Nerve Disorders

Boris Garber, DO
Assistant Professor, School of Medicine, Case Western Reserve University; Metro Health Medical Center, Cleveland, Ohio
Dermatologic Presentations

Marianne Gausche-Hill, MD
Professor of Clinical Medicine, David Geffen School of Medicine at University of California at Los Angeles; Vice Chair and Chief of the Division of Pediatric Emergency Medicine, Director of Pediatric Emergency Medicine and Emergency Medical Services Fellowships, Department of Emergency Medicine, Harbor–University of California at Los Angeles Medical Center, Torrrance, California

Joel M. Geiderman, MD, FACEP
Professor of Medicine, Department of Medicine, Division of Emergency Medicine, David Geffen School of Medicine at University of California at Los Angeles; Co-Chairman and Professor of Emergency Medicine, Department of Emergency Medicine, Cedars-Sinai Medical Center, Los Angeles, California
General Principles of Orthopedic Injuries

Nicholas Genes, MD, PhD, FACEP
Assistant Professor, Department of Emergency Medicine, Icahn School of Medicine at Mount Sinai, New York, New York
Arthritis

www.ketabpezeshki.com 66485457-66963820

Joshua Goldstein, MD, PhD
Associate Professor, Harvard Medical School, Emergency Medicine, Massachusetts General Hospital, Boston, Massachusetts
Stroke

Jeffrey M. Goodloe, MD
Professor and Emergency Medical Service Section Chief, Department of Emergency Medicine, The University of Oklahoma School of Community Medicine, Tulsa, Oklahoma
Foreign Bodies

Eric Goralnick, MD
Instructor of Medicine, Emergency Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts
Gastrointestinal Bleeding

Prasanthi Govindarajan, MBBS, MAS
Associate Professor, Emergency Medicine, University of California at San Francisco, San Francisco, California
Rabies

Louis Graff IV, MD, FACEP, FACP
Professor of Traumatology and Emergency Medicine, University of Connecticut School of Medicine, Farmington, Connecticut; Medical Director of Quality Performance Improvement; Associate Director of Emergency Medicine, Hospital of Central Connecticut, New Britain, Connecticut
Observation Medicine and Clinical Decision Units

Sara H. Gray, MD, MPH, FRCPC
Assistant Professor, Division of Emergency Medicine, Faculty of Medicine, University of Toronto; Emergency Medicine and Critical Care, St Michael's Hospital, Toronto, Ontario, Canada
General Approach to the Pregnant Patient

Eric A. Gross, MD
Vice Chairman, Department of Emergency Medicine; Associate Professor of Clinical Emergency Medicine, University of Missouri School of Medicine, Columbia, Missouri
Multiple Trauma

Phillip F. Gruber, MD
Assistant Professor, Department of Emergency Medicine, Keck School of Medicine of the University of Southern California, Los Angeles, California
Chronic Obstructive Pulmonary Disease

Kama Guluma, MD
Associate Professor, Department of Emergency Medicine, University of California at San Diego, San Diego, California
Diplopia

Leon Gussow, MD
Lecturer, Emergency Medicine, University of Illinois, Chicago, Illinois
Sedative Hypnotics

Rania Habal, MD
Emergency Medicine, New York Medical College/Metropolitan Hospital Center, New York, New York
Drug Therapy in Pregnancy

Tenagne Haile-Mariam, MD
Assistant Professor, Emergency Medicine, The George Washington University Medical School, Washington, District of Columbia
Viral Illnesses

Glenn C. Hamilton, MD, MSM
Professor of Emergency Medicine, Department of Emergency Medicine, Wright State University, Dayton, Ohio
Anemia, Polycythemia, and White Blood Cell Disorders
Disorders of Hemostasis

Stephen W. Hargarten, MD, MPH
Chair and Professor, Department of Emergency Medicine; Director, Injury Research Center; Associate Dean for Global Health, Institute for Health and Society; Medical College of Wisconsin, Milwaukee, Wisconsin
Injury Prevention and Control

Danielle Hart, MD
Associate Program Director and Director of Simulation, Emergency Medicine, Hennepin County Medical Center, Minneapolis, Minnesota
Acute Pelvic Pain in Women

William Heegaard, MD, MPH
Assistant Chief, Department of Emergency Medicine, Hennepin County Medical Center; Associate Professor, Department of Emergency Medicine, University of Minnesota Medical School, Minneapolis, Minnesota
Acute Pelvic Pain in Women

Jag S. Heer, MD
Associate Professor of Clinical Medicine, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California; Attending Faculty Physician, Department of Emergency Medicine, Kern Medical Center, Bakersfield, California
Factitious Disorders and Malingering

Katherine Heilpern, MD
Ada Lee and Pete Correll Professor and Chair, Department of Emergency Medicine, Emory University, Atlanta, Georgia
Jaundice

Carlton E. Heine, MD, PhD
Attending Physician, Emergency Medicine, Bartlett Regional Hospital; Adjunct Faculty, Biology Department, University of Alaska Southeast, Juneau, Alaska; Clinical Instructor, Division of Emergency Medicine, University of Washington, Seattle, Washington
Bioethics

Jason D. Heiner, MD
Staff Physician, Emergency Medicine, University of Washington, Seattle, Washington
The Combative Patient

Robin R. Hemphill, MD, MPH
Deputy Chief Safety Officer for the Veterans Health Administration and Director of the National Center for Patient Safety, Washington, DC.
Disorders of the Pancreas

Sean O. Henderson, MD, MS
Professor and Chair, Department of Emergency Medicine; Chief of Emergency Services, Los Angeles County and University of Southern California Medical Center, Los Angeles, California
Thoracic Trauma
Labor and Delivery and Their Complications

www.ketabpezeshki.com 66485457-66963820

Robert Hendrickson, MD
Associate Professor, Department of Emergency Medicine; Program Director, Fellowship in Medical Toxicology, Oregon Health and Science University; Associate Medical Director and Medical Toxicologist, Oregon Poison Center, Portland, Oregon Portland, Oregon
Acetaminophen

Phillip L. Henneman, MD
Professor and Past Chair, Emergency Medicine, Tufts University School of Medicine, Boston, Massachusetts; Department of Emergency Medicine, Baystate Medical Center, Springfield, Massachusetts
Acute Appendicitis

H. Gene Hern, Jr., MD, MS
Residency Director, Emergency Medicine, Alameda County Medical Center, Oakland, California; Associate Clinical Professor, Emergency Medicine, University of California at San Francisco, San Francisco, California
Wound Management Principles

Jamie M. Hess, MD
Assistant Professor, Emergency Medicine, University of Wisconsin School of Medicine, Madison, Wisconsin
Esophagus, Stomach, and Duodenum

Christopher M. Hicks, MD, MEd, FRCPC
Staff Emergency Physician, Trauma Team Leader, Department of Emergency Medicine, St. Michael's Hospital; Assistant Professor, Department of Medicine, University of Toronto, Toronto, Ontario, Canada
Systemic Lupus Erythematosus and the Vasculitides

Robert S. Hockberger, MD
Professor of Clinical Medicine, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California; Chair Emeritus, Harbor–University of California at Los Angeles Medical Center, Torrance, California
Spinal Injuries
Thought Disorders

Robert S. Hoffman, MD, FAACT, FACMT, FRCP Edin
Professor, Emergency Medicine and Medicine, New York University School of Medicine; Attending Physician, Department of Emergency Medicine, Bellevue Hospital Center; Director, New York City Poison Control Center, New York City Department of Health and Mental Hygiene, New York, New York
Cocaine and Other Sympathomimetics
Inhaled Toxins

Diane C. Homeier, MD
Associate Professor of Clinical Family Medicine and Internal Medicine, Division of Geriatric, Hospital, Palliative, and General Internal Medicine, Keck School of Medicine of the University of Southern California; Medical Director, Adult Protection Team, Los Angeles County and University of Southern California Medical Center, Los Angeles, California
Elder Abuse and Neglect

Timothy Horeczko, MD, MSCR, FACEP, FAAP
Assistant Professor of Clinical Medicine, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California; Department of Emergency Medicine, Harbor–University of California at Los Angeles Medical Center, Torrance, California
Cardiac Disorders

Mark A. Hostetler, MD, MPH
Clinical Professor, Pediatrics and Emergency Medicine, University of Arizona College of Medicine; Associate Division Chief, Pediatric Emergency Medicine, Phoenix Children's Hospital, Phoenix, Arizona
Gastrointestinal Disorders

Debra E. Houry, MD, MPH
Vice Chair for Research, Department of Emergency Medicine, Emory University School of Medicine; Director, Center for Injury Control, Emory University, Atlanta, Georgia
Acute Complications of Pregnancy

J. Stephen Huff, MD
Associate Professor of Emergency Medicine and Neurology, Department of Emergency Medicine, University of Virginia, Charlottesville, Virginia
Confusion
Spinal Cord Disorders

Oliver Hung, MD
Assistant Clinical Professor of Emergency Medicine, Department of Emergency Medicine, Mount Sinai School of Medicine, New York, New York
Lithium

Christopher L. Hunter, MD, PhD
Clinical Assistant Professor, Emergency Medicine, University of Central Florida College of Medicine; Attending Physician, Emergency Medicine, Orlando Regional Medical Center; Associate Emergency Medical Service Medical Director, Health Services Orange County, Orlando, Florida
Heart Failure

H. Range Hutson, MD
Assistant Professor, Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts
Youth, Violence, and Street Gangs

Alson S. Inaba, MD, FAAP
Division Chief of Pediatric Emergency Medicine, Department of Pediatrics, Kapiolani Medical Center for Women and Children; Associate Professor of Pediatrics, Department of Pediatrics, University of Hawaii John A. Burns School of Medicine; Course Director, Pediatric Advanced Life Support, The Queen's Medical Center, Honolulu, Hawaii
Cardiac Disorders

Kenneth V. Iserson, MD, MBA
Professor Emeritus, Emergency Medicine, The University of Arizona, Tucson, Arizona
Bioethics

Gabrielle A. Jacquet, MD
Assistant Professor, Department of Emergency Medicine, Boston University School of Medicine, Boston, Massachusetts
Drowning

Andy Jagoda, MD
Professor and Chair, Mt. Sinai School of Medicine and Medical Director, Mt. Sinai Medical Center, New York, New York
Neuromuscular Disorders

www.ketabpezeshki.com 66485457-66963820

Thea James, MD
Associate Professor of Emergency Medicine, Emergency Medicine; Assistant Dean for Office of Diversity and Multicultural Affairs, Boston University School of Medicine; Director, Violence Intervention Advocacy Program, Boston Medical Center, Boston, Massachusetts
Multiculturalism and Care Delivery

Timothy G. Janz, MD
Professor, Department of Emergency Medicine; Professor, Pulmonary/Critical Care Division, Department of Internal Medicine, Wright State University Boonshoft School of Medicine, Dayton, Ohio
Anemia, Polycythemia, and White Blood Cell Disorders
Disorders of Hemostasis

Alan Jones, MD
Professor and Research Director, Department of Emergency Medicine, University of Mississippi School of Medicine, Jackson, Mississippi
Shock

Nicholas Jouriles, MD
Professor and Chair, Emergency Medicine, Northeast Ohio Medical University, Rootstown, Ohio; Chair, Emergency Medicine, Akron General Medical Center, Akron, Ohio
Pericardial and Myocardial Disease

Amy Kaji, MD, PhD
Associate Clinical Professor, Emergency Medicine, Harbor–University of California at Los Angeles Medical Center, Torrance, California; Attending Physician, Emergency Medicine, Long Beach Memorial Medical Center, Long Beach, California
Spinal Injuries

Dan Katz, MD
Attending Physician and Medical Director of Academic Affairs, Emergency Medicine Cedars-Sinai Medical Center; Assistant Professor of Clinical Medicine, Department of Medicine, Division of Emergency Medicine, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California
General Principles of Orthopedic Injuries

Bory Kea, MD
Adjunct Instructor and Research Fellow, Emergency Medicine, Oregon Health and Sciences University, Portland, Oregon
Musculoskeletal Back Pain

Matthew T. Keadey, MD
Chief of Service, Emergency Medicine, Emory University Hospital; Assistant Professor, Emergency Medicine, Emory University School of Medicine, Atlanta, Georgia
The Solid Organ Transplant Patient

Hyung T. Kim, MD
Assistant Professor of Clinical Emergency Medicine, Emergency Medicine, Keck School of Medicine of the University of Southern California, Los Angeles County and University of Southern California Medical Center, Los Angeles, California
Wrist and Forearm

Heidi H. Kimberly, MD, RDMS
Director of Ultrasound Education, Emergency Medicine, Brigham and Women's Hospital; Instructor, Emergency Medicine, Harvard Medical School, Boston, Massachusetts
Pleural Disease

Jeffrey A. Kline, MD
Professor and Research Director, Department of Emergency Medicine, Indiana University School of Medicine, Indianapolis, Indiana
Pulmonary Embolism and Deep Venous Thrombosis

Kristi L. Koenig, MD, FACEP, FIFEM
Director of Public Health Preparedness, Director, Center for Disaster Medical Sciences, Director, International EMS and Disaster Medical Sciences Fellowship, Emergency Department, University of California at Irvine School of Medicine, Orange, California
Disaster Preparedness
Weapons of Mass Destruction

Dina Kornblau, MD
Director, Division of Pediatric Neurology, Pediatrics, St. Barnabas Hospital; Assistant Professor of Clinical Pediatrics, Albert Einstein College of Medicine, Bronx, New York
Neurologic Disorders

Joshua M. Kosowsky, MD
Clinical Director, Emergency Medicine, Brigham and Women's Hospital; Assistant Professor, Emergency Medicine, Harvard Medical School, Boston, Massachusetts

Baruch Krauss, MD, EdM
Senior Associate Physician in Medicine, Division of Emergency Medicine, Children's Hospital Boston; Associate Professor of Pediatrics, Department of Pediatrics, Harvard Medical School, Boston, Massachusetts
Monitoring the Emergency Patient

Ken Kulig, MD
Toxicology Associates, Prof LLC, Denver, Colorado
General Approach to the Poisoned Patient

Michael C. Kurz, MD, MS
Director of Emergency Cardiac Care, Department of Emergency Medicine, Virginia Commonwealth University, Richmond, Virginia; Operational Medical Director, Division of Fire, Henrico County, Henrico, Virginia
Adult Resuscitation
Acute Coronary Syndrome

Thomas Kwiatkowski, MD
Assistant Dean of Medical Education and Professor, Emergency Medicine, Hofstra North Shore–LIJ School of Medicine, Hempstead, New York; Attending Physician, Emergency Medicine, Long Island Jewish Medical Center, New Hyde Park, New York
Headache Disorders

Eric J. Lavonas, MD
Associate Professor, Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, Colorado; Associate Director, Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority, Denver, Colorado
Antipsychotics

Christopher C. Lee, MD
Assistant Professor and Director of International Emergency Medicine, Stony Brook University, Stony Brook, New York
Thermal Burns

www.ketabpezeshki.com 66485457-66963820

David C. Lee, MD
Director of Research, Department of Emergency Medicine, North Shore University Hospital, Manhasset, New York; Associate Professor, Emergency Medicine, Hofstra School of Medicine, Hempstead, New York
Hydrocarbons

E. Brooke Lerner, PhD
Associate Professor, Department of Emergency Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin
Injury Prevention and Control

Michael Levine, MD
Department of Emergency Medicine, University of Southern California, Los Angeles, California; Department of Medical Toxicology, Banner Good Samaritan Medical Center; Center for Toxicology and Pharmacology Education and Research, University of Arizona College of Medicine at Phoenix, Phoenix, Arizona
Chemical Injuries
Antidepressants

Philip D. Levy, MD, MPH
Associate Professor, Department of Emergency Medicine and Cardiovascular Research Institute, Wayne State University, Detroit, Michigan
Hypertension

David L. Levy, DO, FACEP, FACOEP
Associate Clinical Professor, Department of Emergency Medicine, New York College of Osteopathic Medicine, Old Westbury, New York; Emergency Medicine Residency, Program Director and Attending Emergency Medicine Physician, Department of Emergency Medicine, Good Samaritan Hospital Medical Center, West Islip, New York
Thyroid and Adrenal Disorders

Roger J. Lewis, MD, PhD
Professor, Department of Medicine, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California; Vice Chair, Academic Affairs, Department of Emergency Medicine, Harbor–University of California at Los Angeles Medical Center; Senior Investigator, Emergency Medicine, Los Angeles Biomedical Research Institute, Torrance, California
Medical Literature and Evidence-Based Medicine

Michelle Lin, MD
Associate Professor, Emergency Medicine, University of California San Francisco/San Francisco General Hospital, San Francisco, California
Musculoskeletal Back Pain

Louis J. Ling, MD
Professor of Emergency Medicine and Pharmacy, University of Minnesota Medical School; Medical Toxicology Consultant, Hennepin Regional Poison Center, Minneapolis, Minnesota; Senior Vice-President, Hospital-Based Accreditation, Accreditation Council for Graduate Medical Education, Chicago, Illinois

Ari M. Lipsky, MD, PhD
Attending Physician, Emergency Department, Woman's Hospital of Texas, Houston, Texas; Vice Head of Research, Trauma and Combat Medicine Branch, Medical Corps–Israel Defense Forces, Israel
Acute Pelvic Pain in Women

Mark D. Lo, MD, MS
Clinical Assistant Professor, Department of Pediatrics, Division of Emergency Medicine, University of Washington School of Medicine and Seattle Children's Hospital, Seattle, Washington
Neonatal Resuscitation

Mark J. Lowell, MD
Associate Professor of Emergency Medicine, University of Michigan Medical School; Medical Director, Survival Flight, University of Michigan Health System, Ann Arbor, Michigan
Esophagus, Stomach, and Duodenum

Binh T. Ly, MD, FACMT, FACEP
Professor of Emergency Medicine, University of California San Diego; Director, Emergency Medicine Residency, Department of Emergency Medicine; Director, Medical Toxicology Fellowship, Division of Medical Toxicology; University of California San Diego Health System, San Diego, California
Hallucinogens

Everett T. Lyn, MD, MSc, FAAEM
Assistant Professor, Harvard Medical School; Chairman, Department of Emergency Medicine, North Shore Medical Center, Salem, Massachusetts
Hand

Malcolm Mahadevan, MD, MBBS (Singapore), MRCP(UK), FRCSEd (A&E), FAMS
Associate Professor, Yong Lo Lin School of Medicine, National University of Singapore; Senior Consultant and Head, Emergency Medicine Department, National University Hospital, Singapore
Observation Medicine and Clinical Decision Units

Brian D. Mahoney, MD
Associate Professor, Department of Emergency Medicine, University of Minnesota; Medical Director, Emergency Medical Services, Hennepin County Medical Center, Minneapolis, Minnesota
Back Pain

Thomas Mailhot, MD
Clinical Assistant, Professor of Emergency Medicine, Keck School of Medicine of the University of Southern California; Ultrasound Fellowship Director, Department of Emergency Medicine, Los Angeles County and University of Southern California Medical Center, Los Angeles, California
Hand

Gerald Maloney, Jr., DO
Attending Physician, Emergency Medicine, MetroHealth Medical Center, Cleveland, Ohio; Assistant Professor, Emergency Medicine, Case Western Reserve University, Cleveland, Ohio
Diabetes Mellitus and Disorders of Glucose Homeostasis

Mariann Manno, MD
Associate Professor Clinical Pediatrics and Emergency Medicine, Pediatrics; Interim Associate Dean for Admissions, Medical School Admissions, University of Massachusetts School of Medicine; Division Director, Pediatric Emergency Medicine Pediatrics, University of Massachusetts Memorial Children's Medical Center; Associate Chief Quality Officer, Hospital Administration, University of Massachusetts Memorial Health Care, Worcester, Massachusetts
Pediatric Respiratory Emergencies: Upper Airway Obstruction and Infections

www.ketabpezeshki.com 66485457-66963820

Marc L. Martel, MD
Faculty, Department of Emergency Medicine, Hennepin County Medical Center; Associate Professor, Department of Emergency Medicine, University of Minnesota, Minneapolis, Minnesota
Multiple Trauma

†*John A. Marx, MD*
Formerly Adjunct Professor of Emergency Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; Chair Emeritus, Department of Emergency Medicine, Carolinas Medical Center, Charlotte, North Carolina
Abdominal Trauma

Amal Mattu, MD
Professor and Vice Chair, Department of Emergency Medicine, University of Maryland School of Medicine, Baltimore, Maryland
Acute Coronary Syndrome

Larissa May, MD, MSPH
Associate Director of Clinical Research, Department of Emergency Medicine, The George Washington University, Washington, District of Columbia
Viral Illnesses

Thom Mayer, MD
Clinical Professor of Emergency Medicine, Department of Emergency Medicine, George Washington University School of Medicine, Washington, District of Columbia; Senior Lecturing Fellow, Department of Surgery, Division of Emergency Medicine, Duke University School of Medicine, Durham, North Carolina
Humerus and Elbow

Ryanne J. Mayersak, MS, MD
Assistant Professor, Department of Emergency Medicine, The George Washington University, Washington, District of Columbia
Facial Trauma

Suzan S. Mazor, MD
Associate Professor, Department of Pediatrics, Division of Emergency Medicine, University of Washington School of Medicine and Seattle Children's Hospital, Seattle, Washington
Neonatal Resuscitation

Maureen McCollough, MD, MPH
Associate Professor of Pediatrics and Emergency Medicine, Keck School of Medicine of the University of Southern California; Department of Emergency Medicine, Los Angeles County and University of Southern California Medical Center, Los Angeles, California
Genitorurinary and Renal Tract Disorders

Nathanael J. McKeown, DO
Assistant Professor, Department of Emergency Medicine, Oregon Health and Science University; Attending Physician, Department of Emergency Medicine, Portland Veterans Affairs Medical Center, Portland, Oregon
Acetaminophen

COL (Ret.) John G. McManus, MD, MBA MCR, FACEP, FAAEM
Uniformed Services University of Health Sciences, Bethesda, Maryland
Tactical Emergency Medical Support and Urban Search and Rescue

Jason T. McMullan, MD
Assistant Professor, Emergency Medicine, University of Cincinnati, Cincinnati, Ohio
Seizures

Rick McPheeters, DO, FAAEM
Associate Professor of Medicine, University of California at Los Angeles, Los Angeles, California; Chair and Residency Director, Department of Emergency Medicine, Kern Medical Center, Bakersfield, California
Anxiety Disorders

Kemedy K. McQuillen, MD
Attending Physician, Emergency Medicine, Central Maine Medical Center, Lewiston, Maine
Musculoskeletal Disorders

David A. Meguerdichian, MD
Instructor of Medicine, Emergency Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts
Gastrointestinal Bleeding

Frantz R. Melio, MD
President, Physician Practices, CHRISTUS St. Vincent Regional Medical Center, Santa Fe, New Mexico; Clinical Assistant Professor, Department of Emergency Medicine, University of New Mexico, Albuquerque, New Mexico
Upper Respiratory Tract Infections

William J. Meurer, MD, MS
Assistant Professor, Emergency Medicine; Assistant Professor, Neurology, University of Michigan, Ann Arbor, Michigan
Brain Resuscitation
Central Nervous System Infections

Nathan W. Mick, MD
Associate Chief, Department of Emergency Medicine; Director, Pediatric Emergency Medicine, Department of Emergency Medicine, Maine Medical Center, Portland, Maine
Pediatric Fever

James R. Miner, MD
Associate Professor of Emergency Medicine, University of Minnesota Medical School; Research Director, Department of Emergency Medicine, Hennepin County Medical Center, Minneapolis, Minnesota
Pain Management

Alicia B. Minns, MD
Assistant Clinical Professor of Emergency Medicine, University of California at San Diego, San Diego, California
Substance Abuse

Connie Mitchell, MD, MPH
Chief, Policy Unit, Office of Health Equity, California Department of Public Health, Sacramento, California
Intimate Partner Violence

†Deceased.

www.ketabpezeshki.com 66485457-66963820

Gregory P. Moore, MD, JD
Faculty, Emergency Medicine Residency, Madigan Army Medical Center, Tacoma, Washington
Otolaryngology
The Combative Patient

Gregory J. Moran, MD
Professor of Medicine, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California; Department of Emergency Medicine and Division of Infectious Diseases, Olive View–University of California at Los Angeles Medical Center, Sylmar, California
Pneumonia

Ravi S. Morchi, MD
Assistant Professor in Emergency Medicine, Department of Emergency Medicine, Harbor–University of California at Los Angeles Medical Center, Torrance, California
Weakness

Laurie J. Morrison, MD, MSc, FRCPC
Robert and Dorothy Pitts Chair in Acute Care and Emergency Medicine Research; Director, of Rescue, Keenan Research Centre of the Li Ka Shing Knowledge Institute, St. Michael's Hospital; Professor of Emergency Medicine, Department of Medicine, University of Toronto, Toronto, Ontario, Canada
General Approach to the Pregnant Patient

Robert L. Muelleman, MD, FACEP
Professor and Chair, Department of Emergency Medicine, University of Nebraska Medical Center, Omaha, Nebraska
Allergy, Hypersensitivity, Angioedema, and Anaphylaxis

Brittany L. Murray, MD
Clinical Fellow, Harvard Medical School; Clinical Fellow, Pediatric Emergency Medicine, Boston Children's Hospital, Boston, Massachusetts; Attending Physician, Emergency Medicine, Mount Auburn Hospital, Cambridge, Massachusetts
Pediatric Trauma
Femur and Hip

Lindsay Murray, MD, MBBS, FACEM
Senior Lecturer in Emergency Medicine, Consultant Emergency Physician, Consultant Clinical Toxicologist, New South Wales Poisons Information Centre, Children's Hospital Westmead, Sydney, New South Wales, Australia
Aspirin and Nonsteroidal Agents

Vinay Nadkarni, MD, MS
Endowed Chair, Anesthesia, Critical Care and Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania
Pediatric Resuscitation

Anthony M. Napoli, MD
Assistant Professor of Emergency Medicine, Department of Emergency Medicine, Warren Alpert Medical School of Brown University, Providence, Rhode Island
Monitoring the Emergency Patient

Denise Nassisi, MD
Emergency Medicine, Mount Sinai School of Medicine, New York, New York
Skin and Soft Tissue Infections

Lewis S. Nelson, MD
Professor of Emergency Medicine, New York University School of Medicine; Director, Fellowship in Medical Toxicology, New York University/New York City Poison Control Center, Department of Health and Mental Hygiene, New York, New York
Inhaled Toxins

Robert W. Neumar, MD, PhD
Professor and Chair, Department of Emergency Medicine, University of Michigan Health System, Ann Arbor, Michigan
Adult Resuscitation

David H. Newman, MD
Director of Clinical Research, Associate Professor of Emergency Medicine, Department of Emergency Medicine, Mt. Sinai School of Medicine, New York, New York
Sore Throat

Edward J. Newton, MD
Professor of Emergency Medicine, Keck School of Medicine; Chair, Department of Emergency Medicine, Los Angeles County and University of Southern California Medical Center, Los Angeles, California
Spinal Injuries
Peripheral Vascular Injury

Kim Newton, MD
Assistant Professor of Clinical Emergency Medicine, Keck School of Medicine of the University of Southern California, Los Angeles, California
Neck

James T. Niemann, MD
Professor of Medicine, David Geffen School of Medicine at University of California at Los Angeles, Department of Emergency Medicine, Harbor–University of California at Los Angeles Medical Center, Torrance, California
Implantable Cardiac Devices

Richard M. Nowak, MD, MBA
Emergency Medicine, Henry Ford Health System; Professor, Emergency Medicine, Wayne State Medical School, Detroit, Michigan; Clinical Associate Professor, Emergency Medicine, University of Michigan Medical School, Ann Arbor, Michigan
Asthma

John F. O'Brien, MD
Associate Residency Director, Department of Emergency Medicine, Orlando Regional Medical Center, Orlando, Florida; Associate Clinical Professor, Department of Surgery, University of Florida, Gainesville, Florida; Associate Clinical Professor, Department of Emergency Medicine, University of Central Florida, Orlando, Florida
Heart Failure

Ellen O'Connell, MD
Professor, Emergency Medicine, University of Texas Southwestern Medical Center; Staff Toxicologist, North Texas Poison Center, Dallas, Texas
Heavy Metals

Kelli N. O'Laughlin, MD, MPH
Instructor of Medicine, Harvard Medical School; Physician, Department of Emergency Medicine, Brigham and Women's Hospital; Faculty, Harvard Humanitarian Initiative, Harvard University, Boston, Massachusetts
HIV Infection and AIDS

www.ketabpezeshki.com 66485457-66963820

Jonathan S. Olshaker, MD
Chairman, Department of Emergency Medicine, Boston University School of Medicine; Chief, Department of Emergency Medicine, Boston Medical Center, Boston, Massachusetts
Dizziness and Vertigo

Edward J. Otten, MD
Professor of Emergency Medicine and Pediatrics, Director, Division of Toxicology, Emergency Medicine, University of Cincinnati, Cincinnati, Ohio
Venomous Animal Injuries

Leslie C. Oyama, MD
Associate Clinical Professor, Department of Medicine, University of California at San Diego, San Diego, California
Disorders of the Liver and Biliary Tract

Patricia Padlipsky, MD, MS
Assistant Clinical Professor of Pediatrics, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California; Department of Emergency Medicine, Harbor–University of California at Los Angeles Medical Center, Torrance, California
Infectious Diarrheal Disease and Dehydration

Daniel J. Pallin, MD, MPH
Research Director for Emergency Medicine, Chairman, Clinical Investigation Committee, Brigham and Women's Hospital; Attending Physician, Cambridge Health Alliance; Research Associate, Children's Hospital Boston; Assistant Professor of Medicine and Pediatrics, Harvard Medical School, Boston, Massachusetts
Knee and Lower Leg
Skin and Soft Tissue Infections

Ram Parekh, MD
Assistant Professor, Emergency Department, Mount Sinai School of Medicine, New York, New York; Attending Physician, Emergency Department, Elmhurst Hospital Center, Elmhurst, New York
Rhabdomyolysis

Ryan D. Paterson, MD
Kaiser Permanente Emergency Physician, Assistant Professor of Emergency Medicine, Emergency Medicine, University of Colorado and Denver Health Medical Center, Denver, Colorado
High-Altitude Medicine

Debra Perina, MD
Professor, Division Director, Prehospital Care, Regional Quality Director, Emergency Medicine, University of Virginia, Charlottesville, Virginia
Dyspnea

Andrew D. Perron, MD
Professor and Residency Program Director, Department of Emergency Medicine, Maine Medical Center, Portland, Maine
Spinal cord Disorders

Shawna J. Perry, MD
Associate Professor, Associate Chair, Emergency Medicine, Virginia Commonwealth University School of Medicine; Director, Patient Safety Systems Engineering, Virginia Commonwealth University Health System, Richmond, Virginia
Process Improvement and Patient Safety

Michael A. Peterson, MD
Professor, Department of Medicine, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California; Vice Chair, Operations, Department of Emergency Medicine, Harbor–University of California at Los Angeles Medical Center, Torrance, California
Disorders of the Large Intestine

Timothy A. Peterson, MD, MBA, FACEP
Assistant Professor, Emergency Medicine, University of Michigan, Ann Arbor, Michigan
Wellness, Stress, and the Impaired Physician

James A. Pfaff, MD
Assistant Professor, Department of Military and Emergency Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland; Department of Emergency Medicine, San Antonio Military Medical Center, Fort Sam Houston, Texas; Staff Physician, San Antonio Uniformed Services Health Education Consortium, San Antonio Military Medical Center, Fort Sam Houston, Texas
Otolaryngology

Camiron L. Pfennig, MD
Assistant Professor and Director of Undergraduate Medical Education, Emergency Medicine, Vanderbilt University, Nashville, Tennessee
Electrolyte Disorders

Melissa Platt, MD
Associate Professor, Department of Emergency Medicine, School of Medicine, University of Louisville, Louisville, Kentucky
Heat Illness

Cori McClure Poffenberger, MD
Health Sciences Assistant Clinical Professor, Department of Medicine, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California; Director, Adult Emergency Department, Department of Emergency Medicine, Harbor–University of California at Los Angeles Medical Center, Torrance, California
Abdominal Aortic Aneurysm

Charles V. Pollack, Jr., MD, MA
Professor, Emergency Medicine, Perelman School of Medicine at the University of Pennsylvania; Chairman, Emergency Medicine, Pennsylvania Hospital, Philadelphia, Pennsylvania
Seizures
Seizure Disorders

Timothy G. Price, MD
Associate Professor, Department of Emergency Medicine, University of Louisville, School of Medicine, Louisville, Kentucky
Electrical and Lightning Injuries

Michael A. Puskarich, MD
Assistant Professor, Department of Emergency Medicine, University of Mississippi Medical Center, Jackson, Mississippi
Abdominal Trauma

www.ketabpezeshki.com 66485457-66963820

Ali S. Raja, MD, MBA, MPH
Associate Director for Trauma, Department of Emergency Medicine, Brigham and Women's Hospital; Medical Director, Brewster Ambulance Service; Tactical Physician/Medical Director, New England Regional SWAT Team, Federal Bureau of Investigation, Boston, Massachusetts; Captain, United States Air Force Reserve 445th Aeromedical Staging Squadron, Wright-Patterson Air Force Base, Dayton, Ohio
Hemoptysis

Rama B. Rao, MD
Assistant Professor, Director, Medical Toxicology, Emergency Medicine, New York Presbyterian/Weill Cornell Medical Center, New York, New York
Electrical and Lightning Injuries

Neha P. Raukar, MD, MS
Assistant Professor, Emergency Medicine, Warren Alpert Medical School of Brown University; Assistant Professor, Emergency Medicine, Rhode Island/Miriam Hospital; Director, Emergency Medicine, Center for Sports Medicine, Providence, Rhode Island
Bone and Joint Infections

Robert F. Reardon, MD
Associate Professor, Department of Emergency Medicine, University of Minnesota; Faculty Physician, Department of Emergency Medicine, Hennepin County Medical Center, Minneapolis, Minnesota
Disorders of the Small Intestine

James W. Rhee, MD
Assistant Professor, Department of Emergency Medicine, Loma Linda University School of Medicine, Loma Linda, California
Pesticides

David B. Richards, MD, FACEP
Assistant Professor, Department of Emergency Medicine, University of Colorado School of Medicine; Director, Medical Student and Intern Clerkship, Department of Emergency Medicine, Denver Health Medical Center, Denver, Colorado
Drowning

John R. Richards, MD
Professor, Department of Emergency Medicine, University of California Davis Medical Center, Sacramento, California
Thought Disorders

David J. Roberts, MD
Adjunct Professor, University of Minnesota Medical School, Minneapolis, Minnesota; Staff Emergency Physician, Emergency Department, North Memorial Medical Center, Robbinsdale, Minnesota; Senior Associate Medical Director, Hennepin Regional Poison Center, Minneapolis, Minnesota
Cardiovascular Drugs

Howard Rodenberg, MD, MPH
Emergency Department, Stormont-Vail Health Care, Topeka, Kansas
Air Medical Transport

Chad E. Roline, MD
Faculty Physician, Department of Emergency Medicine, North Memorial Medical Center, Robbinsdale, Minnesota
Disorders of the Small Intestine

Nicholas G.W. Rose, MD, PhD, FRCPC, Dip Sports Med (CASEM)
Clinical Assistant Professor, Department of Emergency Medicine, University of British Columbia, Vancouver General Hospital; Sports Medicine Physician, Allan McGavin Sports Medicine Clinic, University of British Columbia, Vancouver, British Columbia, Canada
Ankle and Foot

Elizabeth D. Rosenman, MD
Clinical Instructor, Emergency Medicine, University of Washington, Seattle, Washington
Evaluation of the Developmentally or Physically Disabled Patient

David H. Rubin, MD
Chairman, Department of Pediatrics, St. Barnabas Hospital; Professor of Clinical Pediatrics, Albert Einstein College of Medicine, Bronx, New York
Neurologic Disorders

Anne-Michelle Ruha, MD
Department of Medical Toxicology, Banner Good Samaritan Medical Center; Center for Toxicology and Pharmacology Education and Research, University of Arizona College of Medicine at Phoenix, Phoenix, Arizona
Antidepressants

Douglas A. Rund, MD
Professor and Chair Emeritus, Department of Emergency Medicine, The Ohio State University, Columbus, Ohio
Mood Disorders

Michael S. Runyon, MD
Director of Research and Global Emergency Medicine, Emergency Medicine, Carolinas Medical Center, Charlotte, North Carolina
Genitourinary System

Christopher S. Russi, DO, FACEP
Assistant Professor of Emergency Medicine, Regional Director for Community Emergency Medicine (Mayo Clinic Health System), Department of Emergency Medicine, Mayo Clinic, Rochester, Minnesota
Headache

Bisan Salhi, MD
Assistant Professor, Emergency Medicine, Emory University, Atlanta, Georgia
Acute Complications of Pregnancy

Sally A. Santen, MD, PhD
Associate Chair for Education, Department of Emergency Medicine, Assistant Dean for Education Research and Quality Improvement, University of Michigan School of Medicine, Ann Arbor, Michigan
Disorders of the Pancreas

Genevieve Santillanes, MD
Assistant Professor, Clinical Emergency Medicine, Keck School of the University of Southern California; Attending Physician, Emergency Medicine, Los Angeles County and University of Southern California Medical Center, Los Angeles, California
General Approach to the Pediatric Patient

www.ketabpezeshki.com 66485457-66963820

Richard J. Scarfone, MD
Associate Professor, Pediatrics, Perelman School of Medicine at the University of Pennsylvania; Attending Physician, Division of Emergency Medicine, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Pediatric Respiratory Emergencies: Lower Airway Obstruction

Michael J. Schmidt, MD
Assistant Professor, Emergency Medicine, Northwestern University Feinberg School of Medicine; Medical Director, Northwestern Memorial Hospital, Chicago, Illinois
Tendinopathy and Bursitis

Carl H. Schultz, MD, FACEP
Professor of Clinical Emergency Medicine; Director of Research, Center for Disaster Medical Sciences; Director, Emergency Medical Services and Disaster Medical Sciences Fellowship, University of California Irvine, School of Medicine, Irvine, California; Director, Disaster Medical Services, Department of Emergency Medicine, University of California, Irvine, Medical Center, Orange, California
Disaster Preparedness
Weapons of Mass Destruction

Jeremiah D. Schuur, MD, MHS
Director of Quality, Safety, and Performance Improvement, Emergency Medicine, Brigham and Women's Hospital; Instructor of Medicine (Emergency Medicine), Harvard Medical School, Boston, Massachusetts
Geriatric Trauma

Richard B. Schwartz, MD
Professor and Chair, Department of Emergency Medicine, Georgia Regents University, Augusta, Georgia
Tactical Emergency Medical Support and Urban Search and Rescue

Donna L. Seger, MD
Professor of Clinical Medicine and Emergency Medicine; Medical Director and Executive Director, Tennessee Poison Center, Vanderbilt University Medical Center, Nashville, Tennessee
Aspirin and Nonsteroidal Agents

Jeffrey A. Seiden, MD
Assistant Professor of Clinical Pediatrics, Perelman School of Medicine at the University of Pennsylvania; Attending Physician, Division of Emergency Medicine, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Pediatric Respiratory Emergencies: Lower Airway Obstruction

Todd A. Seigel, MD
Assistant Professor of Emergency Medicine, Rhode Island and The Miriam Hospitals, Warren Alpert Medical School of Brown University, Providence, Rhode Island
Mechanical Ventilation and Noninvasive Ventilatory Support

Jennifer Seirafi, MD
Assistant Voluntary Clinical Professor of Medicine, Department of Medicine, University of Miami; Attending Physician, Emergency Care Center, Jackson Memorial Hospital, Miami, Florida; Attending Physician, Emergency Medicine, Memorial Regional Hospital, Hollywood, Florida
Delirium and Dementia

Joseph Sexton, MD, FACEP
Attending Physician, Emergency Medicine, Lehigh Valley Health Network, Allentown, Pennsylvania; Clinical Assistant Professor, Emergency Medicine, Penn State College of Medicine, Hershey, Pennsylvania
Tick-Borne Illnesses

Marc J. Shapiro, MD
Associate Professor, Emergency Department, Yale University; Attending Physician, Director of Patient Safety and Quality, Emergency Department; Medical Director, Emergency Department, Yale New Haven Hospital, New Haven, Connecticut
Process Improvement and Patient Safety

Nathan I. Shapiro, MD, MPH
Vice Chairman of Emergency Medicine Research, Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts
Sepsis Syndromes

Ghazala Q. Sharieff, MD
Medical Director, Quality and Medical Management, Scripps Health, San Diego,California; Director of Pediatric Emergency Medicine, Palomar Health, Escondido California
Genitourinary and Renal Tract Disorders

Adhi Sharma, MD
Consultant Toxicologist, New York City Poison Control Center, New York University Langone Medical Center and Bellevue Hospital, New York, New York
Thyroid and Adrenal Disorders

Rahul Sharma, MD, MBA, FACEP
Medical Director and Associate Chief of Service, Emergency Medicine, New York University Langone Medical Center, New York, New York
Ophthalmology

Peter Shearer, MD
Residency Program Director, Emergency Medicine, Mount Sinai School of Medicine, New York, New York
Neuromuscular Disorders

Richard Shih, MD
Residency Director, Emergency Medicine, Morristown Memorial Hospital, Morristown, New Jersey
Plants, Mushrooms, and Herbal Medications

Lee W. Shockley, MD, MBA
Medical Director, Emergency Department, Denver Health Medical Center; Professor and Vice Chair, Department of Emergency Medicine, The University of Colorado, Denver, Colorado
Scuba Diving and Dysbarism

Jan M. Shoenberger, MD
Program Director, Department of Emergency Medicine, Los Angeles County and University of Southern California Medical Center; Associate Professor of Clinical Emergency Medicine, Keck School of Medicine of the University of Southern California, Los Angeles, California
Constipation

Ashley E. Shreves, MD
Assistant Professor of Emergency Medicine and Geriatrics and Palliative Medicine, Departments of Emergency Medicine and Geriatric and Palliative Medicine, Mount Sinai School of Medicine, New York, New York
Sore Throat

www.ketabpezeshki.com 66485457-66963820

Robert Silbergleit, MD
Associate Professor, Emergency Medicine, University of Michigan, Ann Arbor, Michigan
Brain Resuscitation

Barry C. Simon, MD
Clinical Professor, Emergency Medicine, Alameda County Medical Center, Oakland, California; Professor, Emergency Medicine, University of California, San Francisco, California
Wound Management Principles

Adam J. Singer, MD
Professor and Vice Chairman, Emergency Medicine, Stony Brook University, Stony Brook, New York
Thermal Burns

Laura Slaughter, MD, FACP
San Luis Obispo County Suspected Abuse Response Team, San Luis Obispo, California
Sexual Assault

Corey M. Slovis, MD
Chairman, Emergency Medicine, Vanderbilt University Medical Center; Medical Director, Nashville Fire Department; Medical Director, Nashville International Airport, Nashville, Tennessee
Electrolyte Disorders

Jeffrey P. Smith, MD, MPH
Co-Director of the Ronald Reagan Institute of Emergency Medicine, Department of Emergency Medicine, The George Washington University, Washington, District of Columbia
Delirium and Dementia

William Smock, MD, MS
Police Surgeon, Louisville Metro Police Department; Clinical Professor, Department of Emergency Medicine, University of Louisville, Louisville, Kentucky
Forensic Emergency Medicine

Peter E. Sokolove, MD
Professor, Vice Chair for Academic Affairs, Department of Emergency Medicine, University of California Davis Health System, Sacramento, California
Tuberculosis

Benjamin Squire, MD, MPH
Clinical Instructor of Medicine, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California; Department of Emergency Medicine Harbor–University of California at Los Angeles Medical Center, Torrance, California
Implantable Cardiac Devices

Brian A. Stettler, MD
Assistant Professor, Emergency Medicine, University of Cincinnati, Cincinnati, Ohio
Brain and Cranial Nerve Disorders

Sara Stewart, MD, MPH
Associate Professor of Pediatrics, David Geffen School of Medicine at University of California at Los Angeles, Harbor-University of California at Los Angeles Medical Center, Torrance, California

David M. Stocker, MD, MBA
Director, Emergency Department, Sunrise Children's Hospital, Las Vegas, Nevada
Pediatric Respiratory Emergencies: Disease of the Lungs

Susan Stone, MD, MPH
Palliative Medicine, HealthCare Partners, Los Angeles, California
End of Life

Reben J. Strayer, MD
Department of Emergency Medicine, Mount Sinai School of Medicine, New York, New York
Acid-Base Disorders

Jared Strote, MD, MS
Associate Professor, Emergency Medicine, University of Washington Medical Center, Seattle, Washington
Youth, Violence, and Street Gangs

Stuart P. Swadron, MD, FRCPC
Associate Professor, Department of Emergency Medicine, Assistant Dean, Pre-Health Undergraduate Studies, Keck School of Medicine of the University of Southern California, Los Angeles, California
Chronic Obstructive Pulmonary Disease

Breena R. Taira, MD, MPH
Clinical Assistant Professor, Emergency Medicine, Olive View–University of California at Los Angeles Medical Center, Burbank, California
Thermal Burns

Sukhjit S. Takhar, MD
Instructor of Medicine (Emergency Medicine), Harvard Medical School; Attending Physician, Emergency Medicine, Brigham and Women's Hospital, Boston, Massachusetts
Infective Endocarditis and Valvular Heart Disease
HIV Infection and AIDS

David A. Talan, MD
Professor of Medicine, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California; Chairman, Department of Emergency Medicine and Division of Infectious Diseases, Olive View–University of California at Los Angeles Medical Center, Sylmar, California
Pneumonia

Vivek S. Tayal, MD
Director, Division of Emergency Ultrasound, Professor of Emergency Medicine, Carolinas Medical Center, Charlotte, North Carolina
Emergency Ultrasound

Stephen H. Thomas, MD, MPH
George Kaiser Foundation Professor and Chair, Department of Emergency Medicine, University of Oklahoma School of Community Medicine, Tulsa, Oklahoma
Foreign Bodies
Air Medical Transport

Carrie D. Tibbles, MD
Director of Graduate Medical Education/Designated Institutional Official, Beth Israel Medical Center; Associate Program Director, Harvard Affiliated Emergency Medicine Residency; Assistant Professor of Medicine, Harvard Medical School, Boston, Massachusetts
Selected Gynecologic Disorders

Joshua L. Tobias, MD
Attending Physician, Department of Emergency Medicine, San Joaquin Community Hospital, Bakersfield, California
Anxiety Disorders

www.ketabpezeshki.com 66485457-66963820

Glenn F. Tokarski, MD
Emergency Medicine, Henry Ford Hospital, Detroit, Michigan
Asthma

Alina Toma, MD, FRCPC
Lecturer, Division of Emergency Medicine, Department of Medicine, Faculty of Medicine, University of Toronto, Emergency Medicine, St. Michael's Hospital, Toronto, Ontario, Canada
General Approach to the Pregnant Patient

†*T. Paul Tran, MD, MS, FACEP*
Associate Professor, Emergency Medicine, University of Nebraska College of Medicine, Omaha, Nebraska
Allergy, Hypersensitivity, Angioedema, and Anaphylaxis

Sandra S. Ugras-Rey, DO
Associate Medical Director, Emergency Medicine Department, Newark Beth Israel Medical Center, Newark, New Jersey
Selected Oncologic Emergencies

Larissa I. Velez, MD
Professor, Division of Emergency Medicine; Program Director, Emergency Medicine Residency, University of Texas Southwestern Medical Center; Staff Toxicologist, North Texas Poison Center, Dallas, Texas
Anticholinergics
Heavy Metals

Salvator Vicario, MD
Associate Professor, Department of Emergency Medicine, School of Medicine, University of Louisville, Louisville, Kentucky
Heat Illness

Robert J. Vissers, MD
Chief, Emergency Medicine, Legacy Emanuel Health Center; Adjunct Associate Professor, Emergency Medicine, Oregon Health Sciences University, Portland, Oregon
The Difficult Patient

Ron M. Walls, MD
Professor and Chair, Department of Emergency Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts
Airway

Kevin R. Ward, MD
Professor, Emergency Medicine, University of Michigan; Michigan Critical Illness and Injury Research Center, University of Michigan, Ann Arbor, Michigan
Adult Resuscitation

Paul M. Wax, MD
Assistant Professor, Surgery (Emergency Medicine), University of Texas Southwestern School of Medicine, Dallas, Texas
Caustics

Robert L. Wears, MD, MS, PhD
Professor, Emergency Medicine, University of Florida, Jacksonville, Florida; Visiting Professor, Clinical Safety Research Unit, Imperial College London, London, United Kingdom
Process Improvement and Patient Safety

Ellen J. Weber, MD
Professor, Emergency Medicine, University of California, San Francisco, San Francisco, California
Mammalian Bites
Rabies

Hugh H. West, MD
Associate Professor, Department of Emergency Medicine, University of California, San Francisco School of Medicine, San Francisco, California
Mammalian Bites

Matthew A. Wheatley, MD
Assistant Professor, Emergency Medicine, Emory University School of Medicine; Medical Director, Clinical Decision Unit, Grady Memorial Hospital, Atlanta, Georgia
Jaundice

Suzanne R. White, MD, MBA
Professor, Emergency Medicine and Pediatrics, Wayne State University; Chief Medical Officer, Detroit Medical Center, Detroit, Michigan
Toxic Alcohols

John M. Wightman, MD, MA
Professor and Education Director, Integrated Residency in Emergency Medicine, Wright State University, Dayton, Ohio
Red and Painful Eye

David T. Williams, MD
Assistant Professor of Clinical Emergency Medicine, Emergency Medicine, Keck School of Medicine of the University of Southern California, Los Angeles County and University of Southern California Medical Center, Los Angeles, California
Wrist and Forearm

Saralyn R. Williams, MD
Associate Professor, Medicine and Emergency Medicine, Vanderbilt University, Nashville, Tennessee
Hallucinogens

Adria O. Winter, MD
Associate Clinical Professor, Department of Emergency Medicine, Kern Medical Center/University of California at Los Angeles, Bakersfield, California
Somatoform Disorders

Mary A. Wittler, MD
Assistant Professor, Emergency Medicine, Wake Forest University Baptist Medical Center, Winston-Salem, North Carolina
Antipsychotics

Jeannette Wolfe, MD
Associate Professor, Emergency Medicine, Tufts School of Medicine, Baystate Medical Center, Springfield, Massachusetts
Acute Appendicitis

Allan B. Wolfson, MD, FACEP, FACP
Professor of Emergency Medicine, Vice Chair for Education, Department of Emergency Medicine, University of Pittsburgh; Program Director, University of Pittsburgh Emergency Medicine Residency, Pittsburgh, Pennsylvania
Renal Failure

†Deceased.

www.ketabpezeshki.com 66485457-66963820

Joshua L. Wright, MD
Associate Professor, Department of Emergency Medicine, Wright State University, Dayton, Ohio
Red and Painful Eye

Michael Yaron, MD
Professor of Emergency Medicine, Department of Emergency Medicine, University of Colorado Denver School of Medicine, Aurora, Colorado
High-Altitude Medicine

Donald M. Yealy, MD
Professor and Chair of Emergency Medicine, Professor of Medicine and Clinical and Translational Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania
Dysrhythmias

Amy Young, MD
Assistant Professor, Department of Surgery, Division of Emergency Medicine, University of Texas Southwestern, Dallas, Texas
Caustics

Kelly D. Young, MD, MS
Health Sciences Clinical Professor, Department of Pediatrics, David Geffen School of Medicine at University of California at Los Angeles, Los Angeles, California; Director of Pediatric and Pain Management Education, Department of Emergency Medicine, Harbor–University of California at Los Angles Medical Center; Investigator, Emergency Medicine, Los Angeles Biomedical Research Institute, Torrance, California
Medical Literature and Evidence-Based Medicine

James Young, MD
Associate Chair for Clinical Services, Psychiatry, The Ohio State University Medical Center, Columbus, Ohio
Mood Disorders

Ken Zafren, MD, FAAEM, FACEP, FAWM
Clinical Associate Professor, Division of Emergency Medicine, Stanford University Medical Center, Stanford, California; Staff Emergency Physician, Alaska Native Medical Center, Anchorage, Alaska; Emergency Programs Medical Director, State of Alaska
Frostbite
Accidental Hypothermia

Richard Zane, MD
Chairman, Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, Colorado
Chemical Injuries

Gary D. Zimmer, MD, FACEP
Chairman, Emergency Medicine, St. Mary Medical Center, Langhorne, Pennsylvania
Sepsis Syndromes

Brian J. Zink, MD
Professor and Chair, Department of Emergency Medicine, Warren Alpert Medical School of Brown University; Physician-in-Chief, Emergency Medicine, Rhode Island Hospital, The Miriam Hospital, and Hasbro Children's Hospital, Providence, Rhode Island
Bone and Joint Infections

Leslie S. Zun, MD, MBA
Professor and Chair, Department of Emergency Medicine, Rosalind Franklin University of Medicine and Science/Chicago Medical School, North Chicago, Illinois; Chair, Department of Emergency Medicine, Mount Sinai Hospital, Chicago, Illinois
Bone and Joint Infections

www.ketabpezeshki.com 66485457-66963820

Section One

CRITICAL MANAGEMENT PRINCIPLES

Chapter 1

Airway

Calvin A. Brown III and Ron M. Walls

PERSPECTIVE

Airway management is the cornerstone of resuscitation and is a defining skill for the specialty of emergency medicine. The emergency physician has primary responsibility for management of the airway, and all airway management techniques lie within the domain of emergency medicine. Rapid sequence intubation (RSI) is the most commonly used method for emergency tracheal intubation, but emergency airway management includes various intubation techniques and devices, approaches to the difficult airway, and rescue techniques when intubation fails.

PATHOPHYSIOLOGY

Decision to Intubate

A decision to intubate should be based on careful assessment of the patient with respect to three essential criteria: (1) failure to maintain or protect the airway, (2) failure of ventilation or oxygenation, and (3) the patient's anticipated clinical course and likelihood of deterioration.

Failure to Maintain or Protect the Airway

A patent airway is essential for adequate ventilation and oxygenation. If the patient is unable to maintain an open airway, patency should be established by artificial means, such as repositioning, chin lift, jaw thrust, or insertion of an oral or nasal airway. Likewise, the patient must be able to protect against aspiration of gastric contents, which carries significant morbidity and mortality. Historically, the presence or absence of a gag reflex has been advocated as a reliable indicator of the patient's ability to protect the airway, but the gag reflex is absent in 12 to 25% of normal adults, and there is no evidence that its presence or absence corresponds to airway protective reflexes or the need for intubation.[1] The patient's ability to swallow or handle secretions is a more reliable indicator of airway protection. The recommended approach is to evaluate the patient's level of consciousness, the ability to phonate in response to voice command or query (which provides information about both the integrity of the upper airway and the level of consciousness), and the ability to manage his or her own secretions (e.g., pooling of secretions in the oropharynx, absence of swallowing spontaneously or on command.) In general, a patient who requires a maneuver to establish a patent airway or who easily tolerates an oral airway probably requires intubation for protection of that airway, unless a temporary or readily reversible condition, such as opioid overdose, is present.

Failure of Ventilation or Oxygenation

Ventilatory failure that is not reversible by clinical means or persistent hypoxemia despite maximal oxygen supplementation is a primary indication for intubation. This assessment is clinical and includes evaluation of the patient's general status, oxygen saturation by pulse oximetry, and ventilatory pattern. Continuous capnography also can be helpful but is not essential if oximetry readings are reliable. Arterial blood gases (ABGs) generally are not required to determine the patient's need for intubation. In most circumstances, clinical assessment, including pulse oximetry with or without capnography, and observation of improvement or deterioration in the patient's clinical condition lead to a correct decision. ABG results are rarely helpful, are time-consuming to obtain, and may be misleading, causing delay in intubating a deteriorating patient. If obtained, they should be interpreted carefully in the context of the patient's clinical status. Patients who are clinically improving despite severe or apparently worsening ABG alterations may not require intubation, whereas a rapidly tiring asthmatic may require intubation even though ABG values are only modestly disturbed.

Regardless of the underlying cause, the need for mechanical ventilation generally mandates intubation. External mask devices increasingly have been used to provide assisted mechanical ventilation without intubation (see Chapter 2), but despite these advances, most patients who need assisted ventilation or positive pressure to improve oxygenation require intubation.[2]

Anticipated Clinical Course

Certain conditions indicate the need for intubation even in the absence of frank airway, ventilatory, or oxygenation failure. These conditions are characterized by a moderate to high likelihood of inevitable intubation to facilitate the patient's workup and treatment or predictable airway deterioration that would require intervention. Intubation may be indicated relatively early in the course of certain overdoses. Although the patient initially may be protecting the airway and exchanging gas adequately, intubation often is advisable to guard against the strong likelihood of clinical deterioration, which can occur after the initial phase of care when the patient no longer is closely observed. Significant multiple trauma, with or without head injury, may be an indication for intubation even if the patient is ventilating normally through a patent airway and has adequate oxygen levels.[3,4] Multiple trauma with hypotension, an open femur fracture, and diffuse abdominal tenderness warrant early intubation even if the patient is initially awake and alert without airway injury or hypoxemia. Aggressive resuscitation, pain control, the need for invasive procedures and imaging

www.ketabpezeshki.com 66485457-66963820

outside of the emergency department (ED), and inevitable operative management argues strongly for early airway control. In addition, a patient with penetrating neck trauma may have a patent airway and adequate gas exchange. Nevertheless, early intubation is advisable with any evidence of vascular or direct airway injury because these patients tend to deteriorate and increasing hemorrhage or swelling in the neck tend to both compromise the airway and confound later attempts at intubation.[5,6]

The common thread among these indications for intubation is the anticipated clinical course over time. In each circumstance, it can be anticipated that future events may compromise either the patient's ability to maintain and protect the airway or the patient's ability to oxygenate and ventilate.

CLINICAL FEATURES

Identification of the Difficult Airway

In most patients, intubation is technically easy and straightforward. In large ED studies, overall intubation failure rates resulting in rescue cricothyrotomy are 0.9% for all intubations and 1.7% for trauma patients.[7-9] Intubation failure occurs in approximately 1 in 200 to 1 in 2000 elective general anesthesia cases.[10] Bag-mask ventilation (BMV) is difficult in approximately 1 in 50 general anesthesia patients and impossible in approximately 1 in 600.[11,12] BMV is difficult, however, in up to one third of patients in whom intubation failure occurs, and difficult BMV makes the likelihood of difficult intubation four times higher and the likelihood of impossible intubation 12 times higher.[11,12] The combination of failure of intubation and failure of BMV in elective anesthesia practice is estimated to be exceedingly rare: 1 in 5000 to 1 in 20,000 elective anesthesia patients.[12,13] These numbers cannot be extrapolated to populations of ED patients who are acutely ill or injured and for whom intubation is both urgent and unavoidable. Although patient selection cannot occur (as with a preanesthetic visit), a preintubation analysis of factors predicting difficult intubation can provide the operator with the information necessary to formulate a safe and effective plan for intubation.

Preintubation assessment should evaluate the patient for difficult intubation, difficult BMV, difficult ventilation with an extraglottic device (EGD; see later discussion), and difficult cricothyrotomy. Knowledge of all four domains is crucial to successful planning.[10]

Neuromuscular paralysis generally should be avoided in patients for whom a high degree of intubation difficulty is predicted, unless the administration of the neuromuscular blocking agent (NMBA) is part of a planned approach to the difficult airway. This approach may include use of a *double setup*, in which an alternative approach, such as cricothyrotomy, is simultaneously prepared.

Difficult Direct Laryngoscopy: LEMON

Most of the difficult airway markers discussed in the anesthesia and emergency medicine literature have not been scientifically validated.[14] Nevertheless, a methodical approach can be used to evaluate the patient, based on the accepted hallmarks of difficult intubation by direct laryngoscopy. Videolaryngoscopy, on the other hand, so rarely fails to provide excellent laryngeal visualization that characterization of difficult videolaryngoscopy predictors may not be possible. When direct laryngoscopy is planned, a standard screening process for difficulty should be undertaken with every patient. It is probably useful to perform this screen when videolaryngoscopy is planned, as well, because it may help to identify challenges, such as a very large tongue or poor mouth access. One such approach uses the mnemonic *LEMON* (Box 1-1).[10,15]

Box 1-1 LEMON Approach for Evaluation of Difficult Direct Laryngoscopy

*L*ook externally for signs of difficult intubation (by gestalt)
*E*valuate the "3-3-2 rule"
*M*allampati
*O*bstruction or *o*besity
*N*eck mobility

Adapted with permission from The Difficult Airway Course: Emergency and Walls RM, Murphy MF (eds). Manual of Emergency Airway Management, 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2012.

L—Look externally. The patient first should be examined for external markers of difficult intubation, which are determined based simply on the intubator's clinical impression. For example, the severely bruised and bloodied face of a combative trauma patient, immobilized in a cervical collar on a spine board, should (correctly) invoke an immediate appreciation of anticipated difficult intubation. Subjective clinical judgment can be highly specific (90%) but insensitive and so should be augmented by other evaluations.[12]

E—Evaluate 3-3-2. The second step in the evaluation of the difficult airway is to assess the patient's airway geometry to determine his or her suitability for direct laryngoscopy. Glottic visualization with a direct laryngoscope requires that the mouth open adequately, that the submandibular space be adequate to accommodate the tongue, and that the larynx be positioned low enough in the neck to be accessible. These relationships have been explored in various studies by external measurement of mouth opening, oropharyngeal size, neck movement, and thyromental distance.[16] The "3-3-2 rule" is an effective summary of these assessments.[10,15] The 3-3-2 rule requires that the patient be able to place 3 of his or her own fingers between the open incisors, 3 of his or her own fingers along the floor of the mandible beginning at the mentum, and 2 fingers from the laryngeal prominence to the floor of the mandible (Fig. 1-1). A patient with a receding mandible and high-riding larynx can be impossible to intubate using direct laryngoscopy because the operator cannot adequately displace the tongue and the angle that must be overcome for a direct view of the glottic aperture is too acute. In practice, the operator compares the size of his or her fingers with the size of the patient's fingers and then performs the three tests.

M—Mallampati scale. Oral access is assessed with the Mallampati scale (Fig. 1-2). Visibility of the oral pharynx ranges from complete visualization, including the tonsillar pillars (class I), to no visualization at all, with the tongue pressed against the hard palate (class IV). Class I and class II predict adequate oral access, class III predicts moderate difficulty, and class IV predicts a high degree of difficulty.[16,17] A meta-analysis confirmed that the four-class Mallampati score performs well as a predictor of difficult laryngoscopy (and, less so, of difficult intubation) but that the Mallampati score alone is not a sufficient assessment tool.[18] A Mallampati score may have to be improvised with the direct laryngoscope blade as a tongue depressor in obtunded or uncooperative patients.[19]

O—Obstruction or obesity. Upper airway (supraglottic) obstruction may make visualization of the glottis, or intubation itself, mechanically impossible. Conditions such as epiglottitis, head and neck cancer, Ludwig's angina, neck hematoma, or glottic polyps can compromise laryngoscopy, passage of the endotracheal tube (ETT), BMV, or all three.

www.ketabpezeshki.com 66485457-66963820

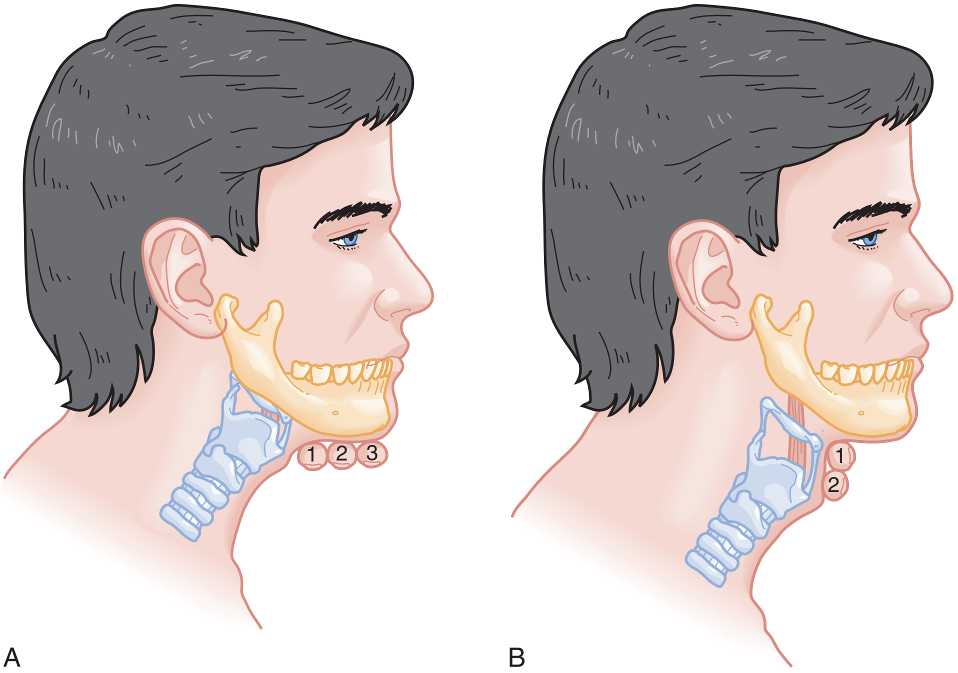


Figure 1-1. Final two steps of the 3-3-2 rule. **A,** Three fingers are placed along the floor of the mouth beginning at the mentum. **B,** Two fingers are placed in the laryngeal prominence (Adam's apple). (Adapted from Murphy MF, Walls RM: Identification of difficult and failed airways. In: Walls RM, Murphy MF, eds. Manual of Emergency Airway Management, 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2012. The 3-3-2 Rule is copyrighted © 2012 by The Airway Course and Lippincott Williams & Wilkins, publishers of The Manual of Emergency Airway Management.)

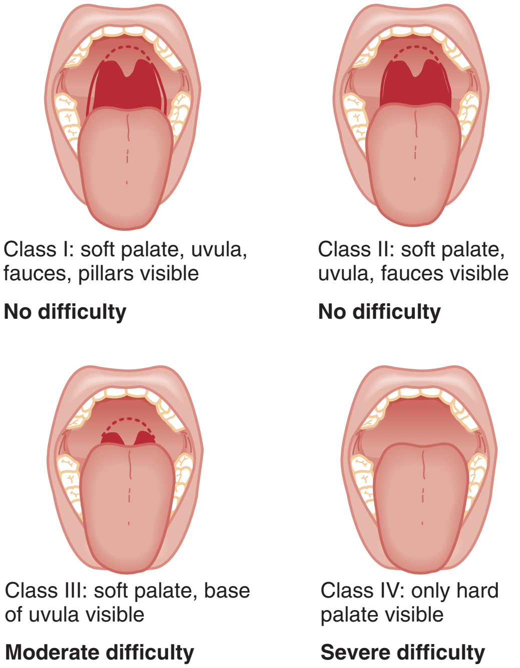


Figure 1-2. The Mallampati scale assesses oral access for intubation. (From Whitten CE: Anyone Can Intubate, 4th ed. San Diego: KW Publications; 2004; with permission.)

Examine the patient for airway obstruction and assess the patient's voice to satisfy this evaluation step. There is conflicting evidence regarding whether obesity is itself an independent marker of difficult intubation or whether patients with obesity simply are more likely to have other markers of difficult intubation.[20,21] Regardless, obese patients generally are more difficult to intubate than their nonobese counterparts, and preparations should account both for this and for the more rapid oxyhemoglobin desaturation and increased difficulty with ventilation using bag and mask or an EGD (see later) that will occur.

N—Neck mobility. Neck mobility is desirable for any intubation technique and is essential for positioning the patient for optimal direct laryngoscopy. Neck mobility is assessed with the patient's flexion and extension of the head and neck through a full range of motion. Neck extension is the most important motion, and simple extension may be as effective as the "sniffing" position in achieving an optimal laryngeal view.[22] One study found that the "extension-extension" position, in which the neck is extended on the body (opposite of the flexion used for the sniffing position) with the head extended on the neck, provides superior laryngeal views to the sniffing position.[23] Modest limitations of motion do not seriously impair direct laryngoscopy, but severe loss of motion, as can occur in ankylosing spondylitis or rheumatoid arthritis, for example, may render direct laryngoscopy impossible. Cervical spine immobilization in trauma artificially reduces cervical spine mobility, but direct laryngoscopy is still highly successful in this group of patients.[7]

Identification of a difficult intubation does not preclude use of an RSI technique. The crucial determination is whether the clinician judges that the patient has a reasonable likelihood of intubation success, despite the difficulties identified, and that ventilation with a bag and mask or an EGD will be successful in the event that intubation fails (hence the value of the BMV and EGD assessments; see Boxes 1-2 and 1-3).

Difficult Bag-mask Ventilation: MOANS

Attributes of difficult BMV have largely been validated and can be summarized with the mnemonic *MOANS* (see Box 1-2).[10-12]

*M*ask seal compromise or difficulty; *O*bstruction (particularly supraglottic obstruction, but it can be present anywhere in the airway) or *O*besity (because of redundant upper airway tissues,

www.ketabpezeshki.com 66485457-66963820

Box 1-2 MOANS Mnemonic for Evaluation of Difficult Bag-Mask Ventilation

*M*ask seal
*O*bstruction or obesity
*A*ged
*N*o teeth
*S*tiffness (resistance to ventilation)

Adapted with permission from The Difficult Airway Course: Emergency and Walls RM, Murphy MF, eds. Manual of Emergency Airway Management, 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2012.

Box 1-3 RODS Mnemonic for Evaluation of Difficult Extraglottic Device Placement

*R*estricted mouth opening
*O*bstruction or obesity
*D*istorted anatomy
*S*tiffness (resistance to ventilation)

Adapted with permission from The Difficult Airway Course: Emergency and Walls RM, Murphy MF, eds. Manual of Emergency Airway Management, 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2012.

Figure 1-3. Mask ventilation in edentulous patients can be performed by placing the lower rim if the mask on the inside of the patient's lower lip to improve mask seal. (Image courtesy Tobias Barker, MD.)

chest wall weight, and resistance of abdominal mass); advanced *Age* (best judged by the physiologic appearance of the patient, but age older than 55 years increases risk); edentulousness ("*No* teeth"), which independently interferes with mask seal; and "*Stiff*ness" or resistance to ventilation (e.g., asthma, chronic obstructive pulmonary disease, pulmonary edema, restrictive lung disease, term pregnancy) may each contribute to increased difficulty with BMV. The difficulty with BMV of the edentulous patient is the basis of the advice "Teeth out to intubate, teeth in to ventilate." Multiple studies have validated this advice.[24] A new approach involves placing the mask inside the patient's lower lip. This may limit air leak in patients without teeth and eliminates the risk of aspiration associated with dental prosthetics or rolled gauze (Fig. 1-3).[25] Difficult BMV is not uncommon, but with proper technique it usually is successful. A recent review of more than 50,000 patients undergoing elective anesthesia found that impossible BMV was exceptionally rare (0.2%) and was associated with neck changes secondary to radiation therapy, presence of a beard, male sex, history of sleep apnea, and a Mallampati class III or IV airway. Impossible BMV was five times more likely if one of these attributes was present and 25 times more likely with four or more.[26]

Box 1-4 SMART Mnemonic for Evaluation of Difficult Cricothyrotomy

*S*urgery
*M*ass (abscess, hematoma)
*A*ccess/anatomy problems (obesity, edema)
*R*adiation
*T*umor

Adapted with permission from The Difficult Airway Course: Emergency and Walls RM, Murphy MF, eds. Manual of Emergency Airway Management, 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2012.

Difficult Extraglottic Device Placement: RODS

Placement of an EGD, such as a laryngeal mask airway (LMA), a Combitube, or a similar upper airway device, often can convert a "can't intubate, can't oxygenate" situation to a "can't intubate, can oxygenate" situation, which allows time for rescue of a failed airway (see following section.) Difficulty achieving placement or ventilation with an EGD is predicted by the mnemonic *RODS.* Fortunately, if the clinician has already performed the LEMON and MOANS assessments, only the *D* for distorted anatomy remains to be evaluated (see Box 1-3). EGDs are placed blindly and have either a mask or a balloon structure that, when inflated, obstructs the oropharynx proximally and the esophageal inlet distally, permitting indirect ventilation. Distorted upper airway anatomy can result in a poor seal and ineffective ventilation.

Difficult Cricothyrotomy: SMART

Difficult cricothyrotomy can be anticipated whenever there is disturbance of the ability to locate and access the landmarks of the anterior airway via the neck and is remembered by the SMART mnemonic (Box 1-4). Prior surgery; hematoma, tumor, or abscess; scarring (as from radiation therapy or prior injury); local trauma; obesity; edema; or subcutaneous air each has the potential to make cricothyrotomy more difficult. Perform an examination for the landmarks needed to perform cricothyrotomy as part of the pre-intubation difficult airway assessment of the patient.

Measurement and Incidence of Intubation Difficulty

The actual degree to which an intubation is "difficult" is highly subjective, and quantification is challenging. The most widely used system for grading laryngoscopic view of the glottis is that of Cormack and Lehane (CL),[26a] which grades laryngoscopy according to the extent to which laryngeal and glottic structures can be seen. In grade 1 laryngoscopy, all or nearly all of the glottic aperture is seen. Grade 2 laryngoscopy visualizes only a portion of the glottis (arytenoid cartilages alone or arytenoid cartilages plus part of the vocal cords). Grade 3 laryngoscopy visualizes only the epiglottis. In grade 4 laryngoscopy, not even the epiglottis is visible.

Research conducted on elective anesthesia patients undergoing direct laryngoscopy suggests that true grade 4 laryngoscopy, which is associated with impossible intubation, occurs in less than 1% of patients. Grade 3 laryngoscopy, which represents extreme intubation difficulty, is found in less than 5% of patients. Grade 2 laryngoscopy, which occurs in 10 to 30% of patients, can be subdivided further into grade 2a, in which arytenoids and a portion of the vocal cords are seen, and grade 2b, in which only the arytenoids are seen. Intubation failure occurs in 67% of grade 2b cases but in only 4% of grade 2a cases.[27] Outside of the operating room, the rate of difficulty may be higher. In a recent review of emergency adult inpatient intubations, as many as 10% were considered difficult (either a grade 3 or 4 CL direct view or more than three

www.ketabpezeshki.com 66485457-66963820

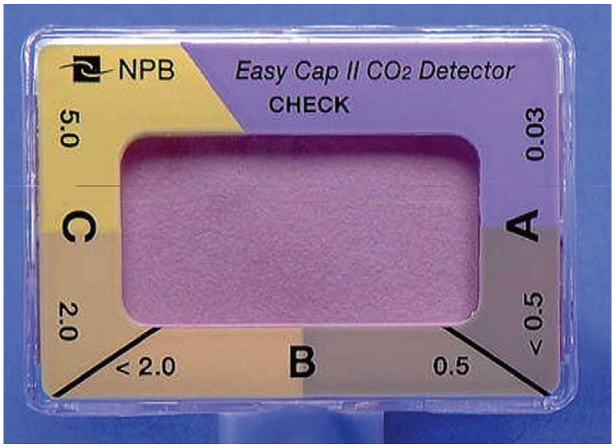


Figure 1-4. End-tidal CO_2 detector before application. The indicator is purple, which indicates failure to detect CO_2. This also is the appearance when the esophagus is intubated.

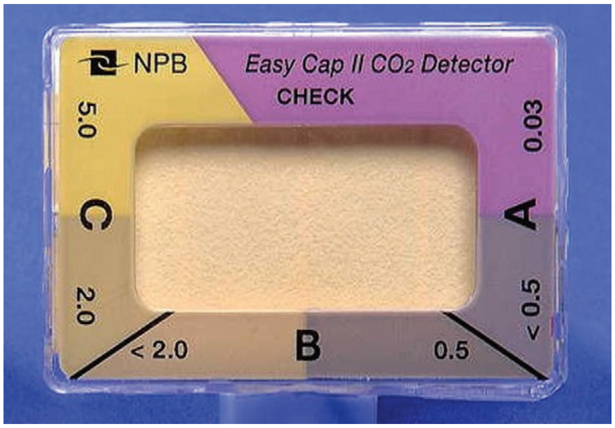


Figure 1-5. Positive detection of CO_2 turns the indicator yellow, indicating tracheal placement of the endotracheal tube.

attempts required).[28] The incidence of difficult ED intubations is unknown but is likely much higher, with some estimates between 4 and 26%.[9,29] Approximately 80% of all grade 2 laryngoscopies are grade 2a; the rest are grade 2b. A grade 1 view is associated with virtually 100% intubation success. An alternative system, POGO (percentage of glottic opening), also has been proposed and validated but is not widely used or studied.[30]

Confirmation of Endotracheal Tube Placement

The most serious complication of endotracheal intubation is unrecognized esophageal intubation with resultant hypoxic brain injury. Although direct visualization of the ETT passing through the vocal cords generally is a reliable indicator of tracheal intubation, such clinical anatomic observations are fallible, and additional means are required to ensure correct placement of the tube within the trachea. Traditional methods, such as chest auscultation, gastric auscultation, bag resistance, exhaled volume, visualization of condensation within the ETT, and chest radiography, all are prone to failure as means of confirming tracheal intubation.[31] Other clinical techniques are readily available for detecting tracheal or esophageal intubation.

Immediately after intubation, the intubator should apply an end-tidal carbon dioxide ($ETco_2$) detection device to the ETT and assess it through six manual ventilations. Disposable, colorimetric $ETco_2$ detectors are highly reliable, convenient, and easy to interpret, indicating adequate CO_2 detection by color change (Figs. 1-4 and 1-5). $ETco_2$ detection is highly reliable in determining tracheal and esophageal intubation in patients with spontaneous circulation.[32] These devices indicate the carbon dioxide (CO_2) content in exhaled air either qualitatively or quantitatively. The persistence of detected CO_2 after six manual breaths indicates that the tube is within the airway, although not necessarily within the trachea. CO_2 is detected with the tube in the mainstem bronchus, the trachea, or the supraglottic space. Correlation of $ETco_2$ detection with the depth markings on the ETT (particularly important in pediatric patients) confirms tracheal placement. Rarely, BMV before intubation or ingestion of carbonated beverages may lead to release of CO_2 from the stomach after esophageal intubation, causing a transient false indication of tracheal intubation. Washout of this phenomenon occurs within six breaths, however, so persistence of CO_2 detection after six breaths indicates tracheal intubation.

Although colorimetric $ETco_2$ measurement is highly sensitive and specific for detecting esophageal intubation, caution is required for patients with cardiopulmonary arrest. Insufficient gas exchange may hamper CO_2 detection in the exhaled air, even when the tube is correctly placed within the trachea.[32] In patients with cardiopulmonary arrest, a CO_2 level greater than 2%, which is the threshold for color change on colorimetric capnometers, should be considered definitive evidence of correct ETT placement, but the absence of such CO_2 cannot be used reliably as an indicator of esophageal intubation. This circumstance arises in approximately 25 to 40% of intubated cardiac arrest patients.[32,33] In all other patients, absence of CO_2 detection indicates failure to intubate the trachea, and rapid reintubation is indicated. When possible, continuous quantitative capnography is more accurate and yields more information than capnometry (including colorimetric devices).

When $ETco_2$ detection is not possible, tracheal tube position can be confirmed with other techniques. One novel approach involves bedside ultrasound. In both live patient and cadaver studies, ultrasonography performed over the cricothyroid membrane or upper trachea accurately confirmed ETT position in the trachea, especially during the act of intubation.[34,35]

Another method of tube placement confirmation is the aspiration technique, which is based on the anatomic differences between the trachea and the esophagus. The esophagus is a muscular structure with no support within its walls. The trachea is held patent by cartilaginous rings. Vigorous aspiration of air through the ETT with the ETT cuff deflated results in occlusion of the ETT orifices by the soft walls of the esophagus, whereas aspiration after tracheal placement of the tube is easy and rapid.

Bulb or syringe aspiration devices may be used in patients with cardiac arrest who have no detectable CO_2, but although such devices are highly reliable at detecting esophageal intubation (sensitivity > 95%), false positives, in which a correctly placed tracheal tube is incorrectly identified as esophageal, can occur in up to 25% of cardiac arrest patients.[32] Aspiration devices may be useful in the out-of-hospital setting when poor lighting hampers colorimetric $ETco_2$ determination. They also are good backup devices when cardiac arrest confounds attempts to assess placement with $ETco_2$. Detection of expired CO_2 is more reliable and should be considered the standard for confirmation of tracheal placement of an ETT and for early detection of accidental esophageal intubation. Aspiration devices have a valuable but secondary role.

Repeat laryngoscopy generally is insufficient to "confirm" that the tube is through the glottis because error and misinterpretation can occur, especially if the clinician confirming the intubation is the same person who intubated in the first place. The objective

www.ketabpezeshki.com 66485457-66963820

instrument ($ETco_2$) should be considered correct. Complete obstruction of the trachea or both mainstem bronchi, which prevents ventilation of the patient with even small tidal volumes, can lead to failure to detect CO_2 even when the tube is in the trachea. In the absence of known or suggested complete large airway obstruction, however, failure to detect CO_2 should not be ascribed to other causes, such as severe asthma, in which the physician might postulate that adequate CO_2 exchange is not occurring for physiologic reasons. In the absence of equipment failure, this generally does not occur, and detection failure should be equated with intubation failure.

Accordingly, $ETco_2$ detection, with either aspiration or ultrasound techniques as backup, should be considered the primary means of ETT placement confirmation. Secondary means include physical examination findings, oximetry, and radiography. The examiner should auscultate both lung fields and the epigastric area. Pulse oximetry is indicated as a monitoring technique in all critically ill patients, not just those who require intubation. Oximetry is useful in detecting esophageal intubation but may not show a decreasing oxygen saturation for several minutes after a failed intubation because of the oxygen reservoir (preoxygenation) created in the patient before intubation.[36] Although chest radiography is universally recommended after ETT placement, its primary purpose is to ensure that the tube is well positioned below the cords and above the carina. A single anteroposterior chest radiograph is not sufficient to detect esophageal intubation, although esophageal intubation may be detected if the ETT is clearly outside the air shadow of the trachea. In cases in which doubt persists, a fiberoptic scope can be passed through the ETT to identify tracheal rings, another "gold standard" for confirmation of tracheal placement.

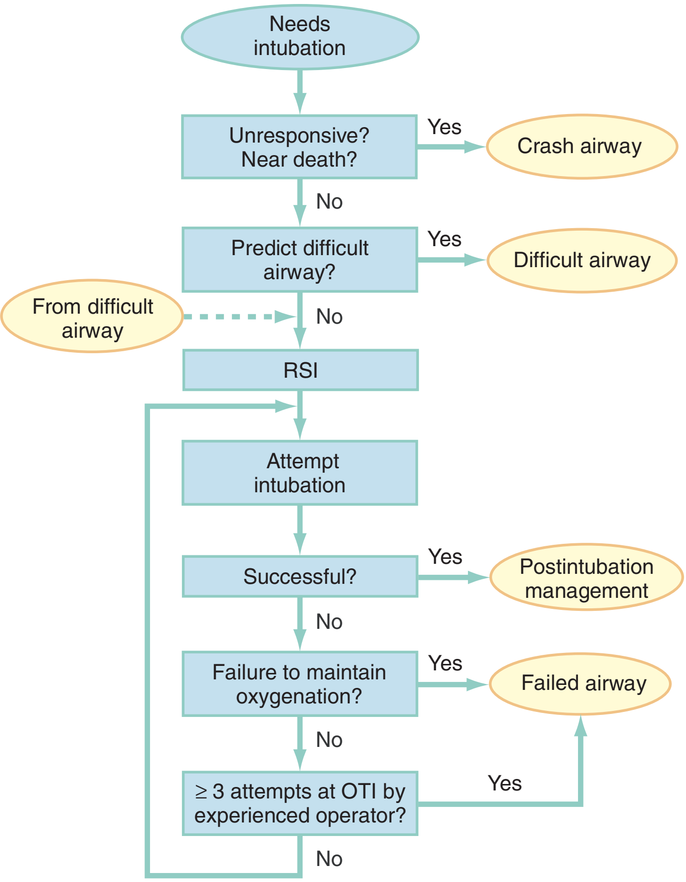


Figure 1-6. Main emergency airway management algorithm. *OTI,* orotracheal intubation; *RSI,* rapid sequence intubation. (Adapted from Walls RM: The emergency airway algorithms. In Walls RM, Murphy MF, eds: Manual of Emergency Airway Management, 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2012. Copyright © 2012 The Difficult Airway Course: Emergency and Lippincott, Williams & Wilkins.)

MANAGEMENT

Approach to Intubation

Algorithms for emergency airway management have been developed and provide a useful guide, both for planning intubation and for rescue in the event of intubation failure. The algorithm assumes that a decision to intubate has been made and outlines such an approach. The approach is predicated on two key determinations that must be made before active airway management is begun (Fig. 1-6). The first determination is whether the patient is in cardiopulmonary arrest or a state of near arrest and is predicted to be unresponsive to direct laryngoscopy. Such a patient (agonal, near death, in circulatory collapse) is called a "crash airway" patient for the purposes of emergency airway management and is treated with the crash airway algorithm by an immediate intubation attempt without use of drugs, supplemented by a single, large dose of succinylcholine if the attempt to intubate fails and the patient is thought not to be sufficiently relaxed (Fig. 1-7). Next, it must be determined whether the patient represents a difficult intubation as determined by the LEMON, MOANS, RODS, and SMART evaluations, and if so, the difficult airway algorithm is used (Fig. 1-8).

For patients who require emergency intubation but who have neither a crash airway nor a difficult airway, we recommend RSI. RSI provides the safest and quickest method of achieving intubation in such patients.[7,14,37,38] After administration of the RSI drugs, intubation attempts are repeated until the patient is intubated or a failed intubation is identified. If more than one intubation attempt is required, oxygen saturation is monitored continuously, and if saturation falls to 90% or less, BMV is performed until saturation is recovered for another attempt. If the clinician cannot maintain oxygen saturation despite optimal use of BMV or an EGD, a failed airway exists. This is referred to as a "can't intubate, can't oxygenate" situation. In addition, if three attempts at laryngoscopy have been unsuccessful, a failed airway exists because subsequent attempts at laryngoscopy by the same clinician are unlikely to succeed. The three failed laryngoscopy attempts are defined as attempts by an experienced clinician using the best possible patient positioning and technique. If available, videolaryngoscopes should be used for one or all of these attempts. Also, if the clinician ascertains after even a single attempt that intubation will be impossible (e.g., grade 4 laryngoscopic view with a direct laryngoscope despite optimal patient positioning and use of external laryngeal manipulation), and no alternative laryngoscope (e.g., videolaryngoscope) is available, a failed airway is present. The failed airway is managed according to the failed airway algorithm (Fig. 1-9).

Difficult Airway

The perception of a difficult airway is relative, and many emergency intubations could be considered "difficult." The judgment regarding whether to treat the airway as a typical emergency airway or whether to use the difficult airway algorithm is based on the degree of perceived difficulty, operator experience, the airway management devices available, and the individual circumstances of the case.[39] The LEMON, MOANS, RODS, and SMART assessments provide a systematic framework to assist in identifying the potentially difficult airway.

When preintubation evaluation identifies a potentially difficult airway (see Fig. 1-8), the approach is based on the premise that

www.ketabpezeshki.com 66485457-66963820

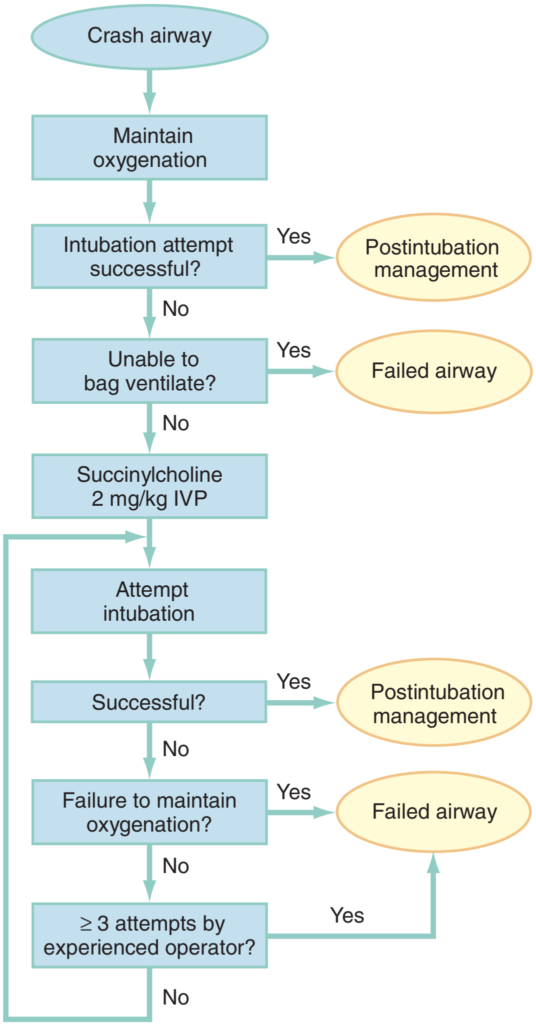


Figure 1-7. Crash airway algorithm. *IVP,* intravenous push. (Adapted from Walls RM: The emergency airway algorithms. In Walls RM, Murphy MF, eds: Manual of Emergency Airway Management, 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2012. Copyright © 2012 The Difficult Airway Course: Emergency and Lippincott, Williams & Wilkins.)

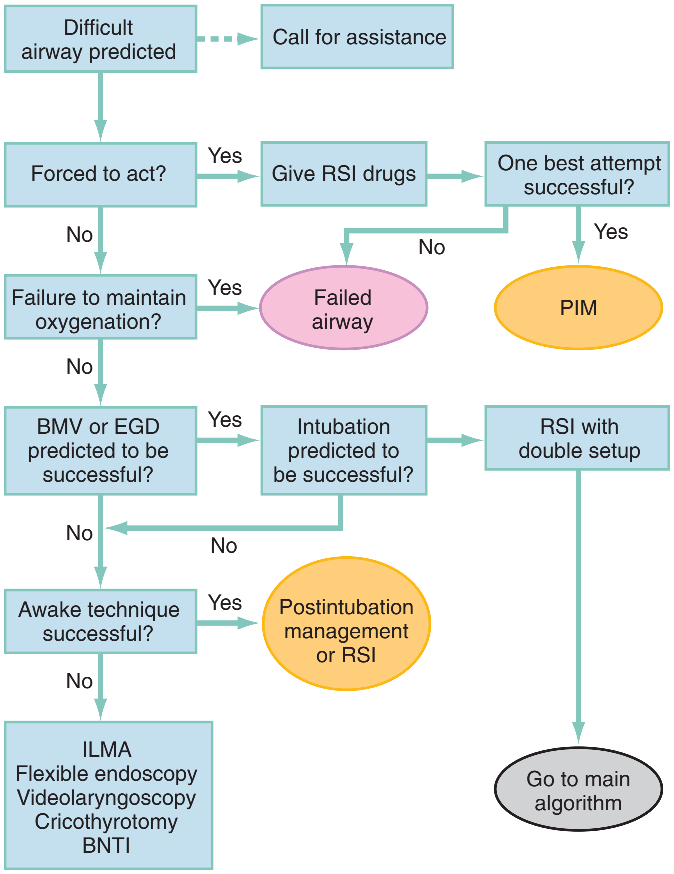


Figure 1-8. Difficult airway algorithm. *BMV,* bag-mask ventilation; *BNTI,* blind nasotracheal intubation; *DL,* direct laryngoscopy; *EGD,* extraglottic device; *ILMA,* intubating laryngeal mask airway; *PIM,* postintubation management; *RSI,* rapid sequence intubation. (Adapted from Walls RM: The emergency airway algorithms. In Walls RM, Murphy MF, eds: Manual of Emergency Airway Management, 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2012. Copyright © 2012 The Difficult Airway Course: Emergency and Lippincott, Williams & Wilkins.)

NMBAs generally should not be used unless the clinician believes that (1) intubation is likely to be successful and (2) oxygenation via BMV or EGD is likely to be successful if a first intubation attempt does not succeed and oxygenation is required.[10] The one exception to this recommendation occurs in the "forced to act" scenario.

On these rare occasions, RSI may be necessary even in a highly difficult airway situation, in which the operator is not confident of the success of laryngoscopy or of sustaining oxygenation. This occurs most often in the setting of a rapidly deteriorating patient with an obviously difficult airway and a presumed airway trajectory of precipitous deterioration. Although this is not yet a crash airway situation, the operator is "forced to act"—that is, there is a need to act immediately to intubate before orotracheal intubation quickly becomes impossible. The patient retains sufficient muscle tone and voluntary effort (including combative behavior induced by hypoxia) to require administration of drugs before intubation can be attempted. Consider an agitated patient with rapidly advancing anaphylaxis or angioedema, a morbidly obese patient in severe, end-stage status asthmaticus, or an intensive care unit (ICU) patient with inadvertent or premature extubation, respiratory failure, and a difficult airway. Within seconds to minutes, perhaps before a full difficult airway assessment can be done or preparations can be completed for an alternative airway approach (e.g., flexible endoscopy), the patient's rapid deterioration signals impending respiratory arrest. This is a unique situation in which the operator may be compelled to take the "one best chance" to secure the airway by rapidly administering RSI drugs (despite the obvious difficult airway) and attempting intubation before the airway crisis has advanced to the point that intubation is impossible or delay has caused injurious hypoxemia. If laryngoscopy fails, the RSI drugs have optimized patient conditions for cricothyrotomy or insertion of an alternative airway device, depending on the operator's judgment.

Therefore, in the difficult airway algorithm, the first determination is whether the operator is "forced to act." If so, RSI drugs are given, a best attempt at laryngoscopy is undertaken, and, if intubation is not successful, the airway is considered failed and the operator moves immediately to the failed airway algorithm. In the vast majority of difficult airway situations, however, the operator is not forced to act, and the first step is to ensure that oxygenation is sufficient to permit a planned, orderly approach (see Fig. 1-8). If oxygenation is inadequate and cannot be made adequate by supplementation with bag and mask, the airway should be considered a failed airway. Whereas inadequate oxygenation should be defined on a case-by-case basis, oxygenation saturation at or below 90% is the accepted threshold because this represents the point at which hemoglobin undergoes a conformational change,

www.ketabpezeshki.com 66485457-66963820

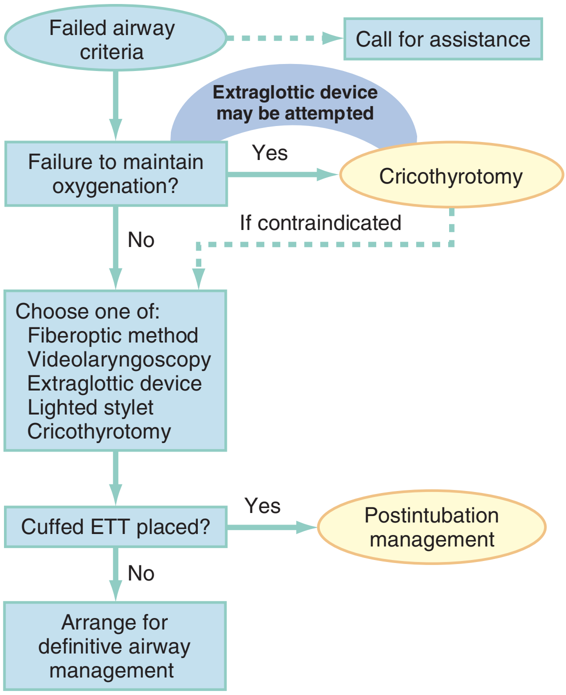


Figure 1-9. Failed airway algorithm. *ETT,* endotracheal tube. (Adapted from Walls RM: The emergency airway algorithms. In Walls RM, Murphy MF, eds: Manual of Emergency Airway Management, 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2012. Copyright © 2012 The Difficult Airway Course: Emergency and Lippincott, Williams & Wilkins.)

more readily releasing oxygen and increasing the pace of desaturation. Oxyhemoglobin saturations in the 80s, if holding steady, might be considered adequate in some circumstances, particularly if the patient is chronically hypoxemic. When oxygenation is inadequate, the failed airway algorithm should be used because the predicted high degree of intubation difficulty, combined with failure to maintain oxygen saturation, is analogous to the "can't intubate, can't oxygenate" situation. When oxygenation is adequate, however, the next consideration is whether RSI is appropriate, on the basis of the operator's assessment of the likelihood of (1) successful ventilation with a bag and mask or an EGD in the event intubation is unsuccessful, and (2) the likelihood of successful intubation by laryngoscopy. If the operator judges laryngoscopy likely to succeed and is confident of the ability to oxygenate even if intubation fails, then RSI is performed. In such cases a double setup can be used in which RSI is performed and preparations simultaneously are undertaken for rescue cricothyrotomy or another rescue technique. If RSI is not advisable and time allows, an awake technique can be used. In this context, *awake* means that the patient continues to breathe and is able to cooperate with caregivers. Usually the technique involves sedation and topical anesthesia, ideally preceded by a drying agent such as glycopyrrolate. The awake technique often is direct or flexible or rigid videolaryngoscopy, assisted by topical anesthesia and sedation (comparable to that for a painful procedure). If the glottis is adequately visualized, the patient can be intubated at that time, or, in a stable difficult airway situation, the clinician may proceed with planned RSI, now assured of intubation success. If the awake laryngoscopy is unsuccessful, the patient is intubated with any of numerous techniques shown in the last box in Figure 1-8. For each of these methods, the patient is kept breathing but variably sedated and anesthetized, and each of the methods results in placement of a cuffed ETT in the trachea. The choice among these methods depends on clinician experience and preference, device availability, and patient attributes.

Failed Airway

Management of the failed airway is dictated by whether the patient can be oxygenated.[10] If adequate oxygenation cannot be maintained, the rescue technique of first resort is cricothyrotomy (see Fig. 1-9). Multiple attempts at other methods in the context of failed oxygenation delay cricothyrotomy and place the patient at increased risk for hypoxic brain injury. If an alternative device (i.e., an EGD such as an LMA or Combitube) is immediately available, however, and the operator judges it to be an appropriate device for the patient's anatomy, an attempt can be made to use it simultaneously with preparations for immediate cricothyrotomy, as long as initiation of cricothyrotomy is not delayed. Only a single attempt with the EGD is recommended in this circumstance.

If adequate oxygenation is possible, several options are available for the failed airway. In almost all cases, cricothyrotomy is the definitive rescue technique for the failed airway if time (i.e., preservation of oxygenation) does not allow for other approaches or if they fail. The fundamental difference in philosophy between the difficult airway and the failed airway is that the difficult airway is planned for, and the standard is to place a cuffed ETT in the trachea. The failed airway is *not* planned for, and the standard is to achieve an airway that provides adequate oxygenation to avert the immediate problem of hypoxic brain injury. Some of the devices used in the failed airway (e.g., EGDs) are temporary and do not provide airway protection.

THERAPEUTIC MODALITIES

Methods of Intubation

Although many techniques are available for intubation of the emergency patient, four methods are most common, with RSI being the most frequently used in nonarrested patients.[7-9,40]

Rapid Sequence Intubation

RSI is the cornerstone of modern emergency airway management and is defined as the virtually simultaneous administration of a potent sedative (induction) agent and an NMBA, traditionally succinylcholine, for the purpose of endotracheal intubation. This approach provides optimal intubating conditions and has long been believed to minimize the risk of aspiration of gastric contents. A systematic review of the literature in 2007 failed to prove that RSI results in a lower incidence of aspiration than other techniques, but the authors correctly noted that virtually no studies have ever been designed to measure this precise endpoint.[41] RSI is nevertheless the most widely used technique for emergency intubation of patients without identifiable difficult airway attributes.[7-9]

The central concept of RSI is to take the patient from the starting point (e.g., conscious, breathing spontaneously) to a state of unconsciousness with complete neuromuscular paralysis, then to achieve intubation *without* interposed assisted ventilation. The risk of aspiration of gastric contents is felt to be significantly higher for patients who have not fasted before induction. Application of positive-pressure ventilation can cause air to pass into the stomach, resulting in gastric distention and likely increasing the risk of regurgitation and aspiration.[42] The purpose of RSI is to avoid positive-pressure ventilation until the ETT is placed correctly in the trachea with the cuff inflated. This requires a preoxygenation phase, during which the nitrogen reservoir in the functional residual capacity in the lungs is replaced with oxygen, permitting at least several minutes of apnea (see later discussion) in the normal adult before oxygen desaturation to 90% ensues (Fig. 1-10).[36]

Use of RSI also facilitates successful endotracheal intubation by causing complete relaxation of the patient's musculature, allowing

www.ketabpezeshki.com 66485457-66963820

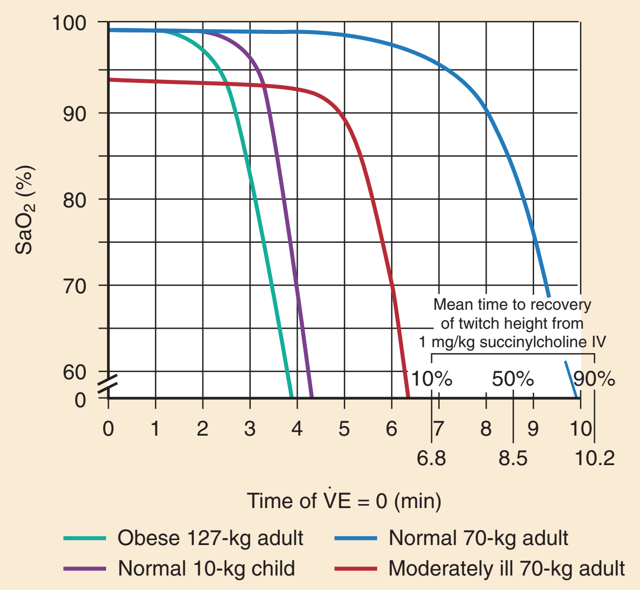


Figure 1-10. Desaturation time for apneic, fully preoxygenated patients. Children, patients with comorbidity, and obese patients desaturate much more rapidly than healthy, normal adults. The box on the lower right side of the graph depicts time to recovery from succinylcholine, which in almost all cases exceeds safe apnea time. Note also the precipitous decline of oxygen saturation from 90% to 0% for all groups. (Adapted from Benumof JL, Dagg R, Benumof R: Critical hemoglobin desaturation will occur before return to unparalyzed state following 1 mg/kg intravenous succinylcholine. Anesthesiology 87:979, 1997.)

Box 1-5 Pretreatment Agents for Rapid Sequence Intubation*

Reactive airways disease: Lidocaine 1.5 mg/kg IV, to mitigate bronchospasm. Albuterol 2.5 mg by nebulizer (if time permits and not already given).

Cardiovascular disease: Fentanyl 3 µg/kg to mitigate sympathetic discharge.

Elevated ICP: Lidocaine 1.5 mg/kg IV to mitigate ICP increase in response to airway manipulation. Fentanyl 3 µg/kg to mitigate sympathetic discharge and attendant rise in ICP.

ICP, intracranial pressure; *IV,* intravenously.
*Given 3 minutes before induction and paralysis.

Box 1-6 The Seven Ps of Rapid Sequence Intubation

1. *Preparation*
2. *Preoxygenation*
3. *Pretreatment*
4. *Paralysis with induction*
5. *Positioning*
6. *Placement of tube*
7. *Postintubation management*

better access to the airway.[37,38,43] Finally, RSI permits pharmacologic control of the physiologic responses to laryngoscopy and intubation, mitigating potential adverse effects. These effects include further intracranial pressure (ICP) increase in response to the procedure and to the sympathetic discharge resulting from laryngoscopy (Box 1-5).[44] RSI is a series of discrete steps, and every step should be planned (Box 1-6).[45]

Preparation. In the initial phase the patient is assessed for intubation difficulty (unless this has already been done), and the intubation is planned, including determining dosages and sequence of drugs, tube size, and laryngoscope type, blade, and size. Drugs are drawn up and labeled. All necessary equipment is assembled. All such patients require continuous cardiac monitoring and pulse oximetry. At least one and preferably two good-quality intravenous lines should be established. Redundancy is always desirable in case of equipment or intravenous access failure.

Preoxygenation. Administration of 100% oxygen for 3 minutes of normal, tidal volume breathing in a normal, healthy adult establishes an adequate oxygen reservoir to permit 8 minutes of apnea before oxygen desaturation to less than 90% occurs (see Fig. 1-10).[36] Additional preoxygenation does not improve arterial oxygen tension. The time to desaturation to less than 90% in children, obese adults, late-term pregnant women, and patients with significant comorbidity is considerably less.[46] Desaturation time also is reduced if the patient does not inspire 100% oxygen.[47] Nevertheless, adequate preoxygenation usually can be obtained, even in ED patients, to permit several minutes of apnea before oxygen desaturation to less than 90% occurs. In children and adults, preoxygenation is essential to the "no bagging" approach of RSI. If time is insufficient for a full 3-minute preoxygenation phase, eight vital capacity breaths with high-flow oxygen can achieve oxygen saturations and apnea times that match or exceed those obtained with traditional preoxygenation.[48] Desaturation time in obese patients can be prolonged by preoxygenating in the head up position and by continuing supplemental oxygen (by nasal cannula) after motor paralysis.[49,50] Oxygen saturation monitors permit earlier detection of desaturation during laryngoscopy, but preoxygenation remains an essential step in RSI.

Pretreatment. During this phase, drugs are administered 3 minutes before administration of the succinylcholine and induction agent to mitigate the effects of laryngoscopy and intubation on the patient's presenting or comorbid conditions. Intubation is intensely stimulating and results in sympathetic discharge (the reflex sympathetic response to laryngoscopy [RSRL]), elevation of ICP in patients with ICP disturbance, and reactive bronchospasm. Bradycardia can occur in children, particularly children younger than 1 year, but appears multifactorial, likely involving underlying parasympathetic tone, parasympathetic discharge in response to airway instrumentation, and perhaps some contributory effect of succinylcholine.

Pretreatment focuses on three main objectives in certain at-risk patients. The three groups of patients at risk are those with reactive airway disease, elevated ICP, or a cardiovascular or neurovascular condition for which an acute elevation in blood pressure and heart rate might be hazardous. Patients with reactive airway disease often experience a worsening of their bronchospasm when intubated. Controversy exists regarding whether albuterol alone, lidocaine alone, or both drugs together are effective in reducing this intubation-related bronchospasm.[51,52] Asthmatic patients being intubated in the ED for status asthmaticus will have received albuterol before intubation, and there is conflicting evidence regarding whether lidocaine has any additive protective effect in these situations. Pending larger studies, it is reasonable to administer lidocaine (1.5 mg/kg) as a pretreatment drug. When an asthmatic patient is being intubated for a condition other than acute asthma (e.g., trauma), nebulized albuterol, intravenous lidocaine, or both should be given before intubation, if possible. Patients with significant cardiovascular disease (e.g., ischemic coronary disease) who are being intubated in the ED may benefit from the administration of the synthetic opioid fentanyl in a dose of 3 µg/kg to blunt the release of catecholamines in response to airway manipulation. Similarly, patients with intracranial hemorrhage, elevated ICP, or marked hypertension may benefit from fentanyl (3 µg/kg) to mitigate the sympathetic induced rises in blood pressure. Finally, lidocaine may have a role in intracranial hypertension; however, the extent to which it can attenuate rises

www.ketabpezeshki.com 66485457-66963820

in ICP is controversial. Although there is some evidence that patients with elevated ICP may experience less exacerbation of the ICP during intubation if they are pretreated with lidocaine (1.5 mg/kg), results are not conclusive.[53,54] Nevertheless, there is evidence supporting the physiologic effects of these agents even though outcome data are lacking. Individualization is necessary, and critical time should not be lost administering pretreatment drugs if the patient requires immediate intubation. Despite the lack of outcome studies, considerable inferential evidence supports this approach, and these agents, particularly fentanyl, probably provide protection for vulnerable patients against the adverse hemodynamic and intracranial effects of laryngoscopy and intubation. Although many variations are possible for pretreatment regimens in various conditions, pretreatment can be simplified to these three basic indications (see Box 1-5).

When possible, 3 minutes should elapse between the administration of the pretreatment drug and the administration of the induction drug and NMBA. If it is not possible to wait 3 minutes, even a reduced time may provide some benefit.

Paralysis with Induction. In this phase, a potent sedative agent is administered by rapid intravenous push in a dose capable of rapidly producing unconsciousness. This is immediately followed by rapid administration of an intubating dose of an NMBA, usually succinylcholine at a dose of 1.5 mg/kg intravenously (IV). Rocuronium is an acceptable alternative agent and is the drug of choice if succinylcholine is contraindicated (see later discussion on RSI pharmacology). Rocuronium may become the NMBA of choice for all patients if sugammadex (a nondepolarizing reversal agent) is available. The intubating dose of rocuronium is 1.0 mg/kg IV. It is usual to wait 45 seconds from the time the succinylcholine is given and 60 seconds from the time rocuronium is given to allow sufficient paralysis to occur.

Positioning. The patient should be positioned for intubation as consciousness is lost. Usually, positioning involves head extension, often with flexion of the neck on the body, but there is evidence that simple extension of the head alone or extension of both the head and neck (the extension-extension position) are equivalent or superior.[22,23] (See earlier discussion.) The Sellick maneuver (application of firm backward-directed pressure over the cricoid cartilage with the goal of obstructing the cervical esophagus) has long been recommended to minimize the risk of passive regurgitation and hence aspiration but is no longer recommended.[55-57] There is evidence that the Sellick maneuver is incorrectly applied by a variety of operators, that it may make laryngoscopy or intubation more difficult in some patients, and that aspiration often occurs despite the Sellick maneuver's having been used.[56,58-61] Imaging studies suggest the cervical esophagus is positioned lateral to the cricoid ring in most patients, a relationship that is exaggerated by posterior pressure, rarely resulting in esophageal obstruction. Accordingly, the Sellick maneuver should be considered optional, applied selectively, and released or modified if laryngeal view is poor or tube passage is difficult.[62] During this phase after administration of the induction agent and NMBA, although the patient becomes unconscious and apneic, BMV should not be initiated unless the oxygen saturation falls to 90%.

Placement of Tube. Approximately 45 to 60 seconds after the administration of the NMBA, the patient is relaxed sufficiently to permit laryngoscopy; this is assessed most easily by moving the mandible to test for absence of muscle tone. Place the ETT during glottic visualization with the laryngoscope. Confirm placement as described earlier. If the first attempt is unsuccessful but oxygen saturation remains high, it is not necessary to ventilate the patient with a bag and mask between intubation attempts. If the oxygen saturation is approaching 90%, the patient may be ventilated briefly with a bag and mask between attempts to reestablish the oxygen reservoir. When BMV is performed, the Sellick maneuver is advisable to minimize passage of air into the stomach.[42]

Table 1-1 Sample Rapid Sequence Intubation Using Etomidate and Succinylcholine

TIME	STEP
Zero minus 10 min	*Preparation*
Zero minus 5 min	*Preoxygenation* 100% oxygen for 3 min *or* eight vital capacity breaths
Zero minus 3 min	*Pretreatment* As indicated
Zero	*Paralysis with induction* Etomidate 0.3 mg/kg Succinylcholine 1.5 mg/kg
Zero plus 30 sec	*Positioning* Sellick maneuver optional
Zero plus 45 sec	*Placement* Laryngoscopy and intubation End-tidal carbon dioxide confirmation
Zero plus 2 min	*Postintubation management* Sedation and analgesia as indicated Initiate mechanical ventilation NMBA only if needed after adequate sedation, analgesia

NMBA, neuromuscular blocking agent.

Postintubation Management. Obtain a chest radiograph to confirm that mainstem intubation has not occurred and to assess the lungs. In general, long-acting NMBAs (e.g., pancuronium, vecuronium) are avoided and the focus is on optimal management using opioid analgesics and sedative agents to facilitate mechanical ventilation. An adequate dose of a benzodiazepine (e.g., midazolam 0.1-0.2 mg/kg IV) and an opioid analgesic (e.g., fentanyl 3-5 µg/kg IV, or morphine 0.2-0.3 mg/kg IV) is given to improve patient comfort and decrease sympathetic response to the ETT. Propofol infusion (5-50 µg/kg/min IV) with supplemental analgesia is an effective method for managing intubated patients without hypotension or ongoing bleeding and is especially helpful for management of neurologic emergencies, as its clinical duration of action is very short (<5 minutes), allowing frequent neurologic examinations. An NMBA is added only if appropriate use of sedation and analgesia fail to adequately control the patient. Table 1-1 presents a sample RSI protocol using etomidate and succinylcholine. "Zero" refers to the time at which the induction agent and succinylcholine are pushed.

Blind Nasotracheal Intubation

Historically, blind nasotracheal intubation (BNTI) was used extensively in the ED and out-of-hospital setting, but it has fallen out of favor largely because of the superiority of RSI.[5,63] Prehospital intubation success between RSI and BNTI favors RSI, and ED studies have shown that RSI is clearly superior.[5,40]

BNTI remains a valid method of intubation in the out-of-hospital setting, where it occasionally is used. In the ED, BNTI rarely, if ever, should be used and is reserved for patients in whom the presence of a narrowly defined type of difficult airway makes RSI undesirable or contraindicated and alternatives (e.g., flexible endoscope) are not available. A recent review of nearly 9000 ED intubations showed that nasal intubation was used in only 5% of intubations performed from 1997 to 2002.[7] The incidence likely is significantly lower today.

Awake Oral Intubation

Awake oral intubation is a technique in which sedative and topical anesthetic agents are administered to permit management of a

www.ketabpezeshki.com 66485457-66963820

difficult airway without neuromuscular blockade. Sedation and analgesia are achieved in a manner analogous to that for painful procedures in the ED. Topical anesthesia may be achieved by spray, nebulization, or local anesthetic nerve block. After the patient is sedated and topical anesthesia has been achieved, gentle direct, video, or flexible endoscopic laryngoscopy is performed to determine whether the glottis is visible and intubation possible. If the glottis is visible, the patient may be intubated during initial laryngoscopy, or the operator, confident that the glottis can be visualized, may opt to perform RSI to gain benefit from pretreatment, induction, and paralysis, as might be the case in a head-injured patient.

Awake oral intubation is distinct from the practice of oral intubation with a sedative or opioid agent to obtund the patient for intubation without neuromuscular blockade. This latter technique can be referred to as "intubation with sedation alone" or, paradoxically, "nonparalytic RSI." Intubating conditions achieved even with deep anesthesia are significantly inferior to the conditions achieved when neuromuscular blockade is used.[37,38,64] The same superiority of neuromuscular blockade–assisted intubation over intubation with sedation alone has been observed in pediatric emergency medicine and in emergency medical services (EMS) care.[65] In general, the technique of administering a potent sedative agent to obtund the patient's responses and permit intubation in the absence of neuromuscular blockade is ill-advised and inappropriate for endotracheal intubation in the ED, unless it is performed as part of an "awake" intubation as described earlier.

Oral Intubation without Pharmacologic Agents

The arrested or near death patient may not require pharmacologic agents for intubation. Even an arrested patient may retain sufficient muscle tone to render intubation difficult, however. If the glottis is not adequately visualized, administration of a single dose of succinylcholine alone may facilitate laryngoscopy (see discussion of crash airway). Success rates for intubating unconscious, unresponsive patients are comparable to those achieved with RSI, presumably because the patient is in a similar physiologic state (i.e., muscle relaxation, no ability to react to laryngoscopy or tube insertion).[7] This does not apply to patients who are unconscious from neurologic catastrophe or trauma and those who overdosed or had other medical causes of coma, who warrant an induction agent and are intubated with standard RSI procedures as described earlier.

Pharmacologic Agents

Neuromuscular Blocking Agents

NMBAs are highly water-soluble, quaternary ammonium compounds that mimic the quaternary ammonium group on the acetylcholine (ACh) molecule. Their water solubility explains why these agents do not readily cross the blood-brain barrier or placenta. The NMBAs are divided into two main classes. The *depolarizing* agent, succinylcholine, exerts its effects by binding noncompetitively with ACh receptors on the motor endplate and causing sustained depolarization of the myocyte while preventing transmembrane potentials from reforming and resisting further stimulation from ACh. The other major class of NMBA comprises the *competitive,* or *nondepolarizing,* agents, which bind competitively to ACh receptors, preventing access by ACh and preventing muscular activity. The competitive agents are of two pharmacologically distinct types: steroid-based agents (aminosteroid compounds) and benzylisoquinolines. Each of these basic chemical types has distinct properties, but in general, only the aminosteroid compounds are used in the ED.

Succinylcholine. Succinylcholine is a combination of two molecules of ACh. Succinylcholine is rapidly hydrolyzed by plasma pseudocholinesterase to succinylmonocholine, which is a weak NMBA, then to succinic acid and choline, which have no NMBA activity. Pseudocholinesterase is not present at the motor endplate and exerts its effects systemically before the succinylcholine reaches the ACh receptor.[66] Only a small amount of the succinylcholine that is administered survives to reach the motor endplate. Succinylcholine is active at the motor endplate until it diffuses away. Decreased plasma pseudocholinesterase activity can increase the amount of succinylcholine reaching the motor endplate, prolonging succinylcholine block, but this is of little significance in the emergency setting because the prolongation of action rarely is significant, reaching only 23 minutes at the extreme.[66]

Uses and Dosing. Succinylcholine is rapidly active, typically producing intubating conditions within 45 seconds of administration by rapid intravenous bolus injection.[38,67] The clinical duration of action before spontaneous respiration is 6 to 10 minutes (see Fig. 1-10).[36] Full recovery of normal neuromuscular function occurs within 15 minutes. The combination of rapid onset, complete reliability, short duration of action, and absence of common serious side effects maintains succinylcholine as the drug of choice for most ED intubations.[7,8,65] The use of a competitive, or nondepolarizing, NMBA for RSI may be desirable when succinylcholine is contraindicated and in certain other settings. The appropriate dose of succinylcholine for emergency airway management is 1.5 mg/kg IV. Although the ED_{95} (dose at which paralysis is achieved in 95% of patients) for succinylcholine paralysis is much lower (0.3 mg/kg), onset of muscle paralysis is excessively long at these lower doses and not compatible with emergency intubation. Review of studies of succinylcholine pharmacokinetics supports the recommended dose of 1.5 mg/kg.[38] Multiple studies confirm that the dose of succinylcholine is based on the patient's total body weight (TBW) and is not adjusted (downward) regardless of the degree of obesity.[68,69]

Cardiovascular Effects. As an ACh analogue, succinylcholine binds to ACh receptors throughout the body, not just at the motor endplate. It is difficult to separate the effects of succinylcholine on the heart that are caused by direct cardiac muscarinic stimulation from those caused by stimulation of autonomic ganglia by succinylcholine and from the effects induced by the autonomic responses to laryngoscopy and intubation. Succinylcholine can be a negative chronotrope, especially in children, and sinus bradycardia may ensue after succinylcholine administration. Sinus bradycardia is treated with atropine, if necessary, but is often self-limiting. Some pediatric practitioners recommend pretreatment with atropine for children younger than 1 year, but there is no evidence for benefit. Other cardiac dysrhythmias, including ventricular fibrillation and asystole, have been reported with succinylcholine, but it is impossible to distinguish the effects of the drug itself from those caused by the intense vagal stimulation and catecholamine release that accompany laryngoscopy and intubation. In addition, many of these catastrophic complications occur in critically ill patients, further confounding attempts to identify whether the illness or any particular drug or procedure is the cause.

Fasciculations. The depolarizing action of succinylcholine results in fine, chaotic contractions of the muscles throughout the body for several seconds at the onset of paralysis in over 90% of patients. Muscle pain occurs in approximately 50% of patients who receive succinylcholine. Although it is widely believed that muscle pains are reduced or abolished by prior administration of a defasciculating dose of a competitive NMBA, the evidence is not conclusive.[70] Use of 1.5 mg/kg of succinylcholine results in both less fasciculation and less myalgia than occur with 1 mg/kg.[70]

Hyperkalemia. Succinylcholine has been associated with severe, fatal hyperkalemia when administered to patients with

www.ketabpezeshki.com 66485457-66963820

Table 1-2 Conditions Associated with Hyperkalemia after Succinylcholine Administration

CONDITION	PERIOD OF CONCERN
Burns >10% BSA	>5 days until healed
Crush injury	>5 days until healed
Denervation (stroke, spinal cord injury)	>5 days until 6 months postinjury
Neuromuscular disease (ALS, MS, MD)	Indefinitely
Intra-abdominal sepsis	>5 days until resolution

ALS, amyotrophic lateral sclerosis; *BSA,* body surface area; *MD,* muscular dystrophy; *MS,* multiple sclerosis.

specific predisposing clinical conditions (Table 1-2).[71] The mechanism by which severe hyperkalemia occurs is related to receptor upregulation on the postsynaptic muscle membrane. When a muscle is deprived of ACh stimulation for several days, receptor upregulation occurs, causing an increase in receptor density and a change of receptor subtypes on the muscle surface.[72,73] ACh receptors are primarily K^+ ion channels, and at-risk patients can have immediate, massive efflux of potassium as these newly recruited receptors are depolarized by succinylcholine. This occurs predominantly at the site of injury but may occur also in tissue remote from original insult.[74] Although the hyperkalemia occurs within minutes after administration of succinylcholine and may be severe or fatal, the patient's vulnerability to succinylcholine-induced hyperkalemia does not become significant until 5 days after the inciting injury or burn as receptor upregulation production of protein subunits. Succinylcholine remains the agent of choice for RSI in acute burn, trauma, stroke, and spinal cord injury if intubation occurs less than 5 days after onset of the condition. If doubt exists regarding the onset time, succinylcholine should be replaced with a competitive NMBA, usually rocuronium. Denervation syndromes or primary myopathies (e.g., multiple sclerosis, amyotrophic lateral sclerosis, Duchenne muscular dystrophy) can be particularly troubling, however, because the risk begins with the onset of the disease and continues indefinitely, regardless of the apparent stability of the symptoms. In patients with denervation caused by stroke or spinal cord injury, the up-regulated receptors eventually regress, and the patient can safely receive succinylcholine beginning six months after the original insult. Potassium release does not occur to any significant extent in the general population. Succinylcholine is not contraindicated in renal failure but probably should not be used in patients with known or presumed hyperkalemia sufficient to manifest on the electrocardiogram. Treatment for succinylcholine-induced hyperkalemia is the same as for any other hyperkalemic emergency. The only published series examining succinylcholine use in patients with preexisting hyperkalemia, many of whom had renal failure, failed to show a single adverse event related to succinylcholine administration.[75]

Increased Intraocular Pressure. Succinylcholine may cause a modest increase in intraocular pressure and historically has been considered contraindicated in penetrating globe injury. There is no published evidence to support this view, however, and several large series show safety when succinylcholine is used in patients with open globes. The admonition to avoid succinylcholine in open globe injuries is unjustified and should be abandoned.[76]

Masseter Spasm. Succinylcholine has been reported rarely to cause masseter spasm, primarily in children.[66] The clinical significance of this phenomenon is unclear, but administration of a competitive NMBA terminates the spasm. Severe, persistent spasm should raise suspicion of malignant hyperthermia.

Malignant Hyperthermia. Succinylcholine has been associated with malignant hyperthermia, a perplexing syndrome of rapid temperature rise and aggressive rhabdomyolysis. Malignant hyperthermia occurs in genetically predisposed individuals who receive certain volatile anesthetic agents or succinylcholine. The condition is extremely rare and has not been reported in the context of ED intubation. Treatment consists of cessation of any potential offending agents, administration of dantrolene (1-2.5 mg/kg IV every 5 min to a maximum dose of 10 mg/kg IV), and attempts to reduce body temperature by external means.[77] A national malignant hyperthermia hotline is available for emergency consultation at 1-800-644-9737 (then dial zero).

Refrigeration. The standard recommendation to keep succinylcholine refrigerated creates problems related to its storage, timely retrieval, and ready availability on intubation carts or kits in the ED. Succinylcholine undergoes degradation beginning at the time of manufacture, and the rate of this degradation is much lower when the drug is refrigerated. Succinylcholine retains more than 90% of its original activity when stored at room temperature for 3 months. Succinylcholine may be kept at room temperature in the ED or EMS setting, provided that a proper inventory control system ensures that all supplies are replaced not more than 3 months after introduction.

Competitive Agents. Competitive NMBAs are classified according to their chemical structure. The aminosteroid agents include pancuronium, vecuronium, and rocuronium. Vecuronium neither releases histamine nor exhibits cardiac muscarinic blockade and is an excellent agent for maintenance of neuromuscular blockade when this is desirable. Rocuronium is the best agent for use in RSI when succinylcholine is contraindicated. In a recent study of ED intubations performed with either rocuronium or succinylcholine, first-pass intubation success was independent of the NMBA used.[78]

Rocuronium. When a patient has a contraindication to succinylcholine, rocuronium bromide is the paralytic of choice. At a dose of 1.0 mg/kg IV, rocuronium achieves intubating conditions closely approaching those of succinylcholine, lasts approximately 50 minutes, and has been used in the ED with success.[64,78,79] Intubating level paralysis may take 15 to 20 seconds longer than with succinylcholine, and it is reasonable to allow 60 seconds to elapse before attempting intubation when rocuronium is used, versus 45 seconds for succinylcholine. There are no absolute contraindications to rocuronium. In the subset of critically ill patients who require frequent, serial neurologic examinations, the more prolonged duration of paralysis with rocuronium may make it less desirable than succinylcholine for routine use.

Vecuronium. Vecuronium was the first competitive NMBA to establish a role in RSI and is the only other NMBA that should be considered for emergency airway management. Pancuronium is vagolytic and has an unacceptably long clinical duration. For intubation, vecuronium is given as a split dose. First, 0.01 mg/kg is administered as a "priming" dose. Three minutes later, 0.15 mg/kg is given for paralysis, which is achieved in about 75 to 90 seconds.

Paralysis after Intubation. After intubation, prolonged paralysis may be desired to optimize mechanical ventilation; however, current management trends are away from the use of prolonged paralysis in favor of deep sedation with analgesia. If neuromuscular blockade is desired, vecuronium (0.1 mg/kg IV) can be given, but longer-term neuromuscular blockade must not be undertaken without ensuring appropriate sedation and analgesia of the patient and a means to be certain that ongoing sedation and analgesia are adequate. A sedating dose of a benzodiazepine, such as midazolam (0.1 mg/kg IV), combined with an opioid analgesic, such as fentanyl (3-5 µg/kg IV) or morphine (0.2-0.3 mg/kg IV), is required to improve patient comfort and decrease sympathetic response to the ETT. With appropriate attention to achieving optimal sedation and analgesia, ongoing NMBA usually is not necessary.

www.ketabpezeshki.com 66485457-66963820

Induction Agents

A patient with any degree of clinical responsiveness, including reactivity to noxious stimuli, requires a sedative or induction agent at the time of administration of any NMBA. Patients who are deeply unconscious and unresponsive may require only a reduced dose of an induction agent if the unconscious state is caused by drugs or alcohol (themselves general anesthetic agents.) Patients who are unconscious because of a central nervous system insult should receive a full induction dose of an appropriate agent to attenuate adverse responses to airway manipulation. Induction agents also enhance the effect of the NMBA and improve intubation conditions because the intubation is done at the earliest phase of neuromuscular blockade, and the relaxation effects of the induction agent are additive to those of the NMBA.[80]

Etomidate. Etomidate is an imidazole derivative that has been in use since 1972. Its activity profile is similar to that of thiopental, with rapid onset, rapid peak activity, and brief duration, but it is remarkable in its lack of adverse hemodynamic effects.[81] Etomidate has emerged as the agent of choice for ED RSI, and numerous reports attest to its effectiveness and safety.[7,9] The induction dose is 0.3 mg/kg IV. Because etomidate is able to decrease ICP, cerebral blood flow, and cerebral metabolic rate without adversely affecting systemic mean arterial blood pressure and cerebral perfusion pressure (CPP), it is an excellent induction agent for patients with elevated ICP, even in cases of hemodynamic instability.[82] Etomidate may cause brief myoclonus, but this is of no clinical significance. Etomidate by continuous infusion has been reported to cause suppression of endogenous cortisol production. Recently, controversy has emerged regarding the role of etomidate for intubation of patients with septic shock.[83-85] Several retrospective studies have claimed to demonstrate that etomidate, used in a single dose for intubation, causes suppression of the adrenal response to exogenously administered adrenocorticotropic hormone and have attempted to link this to increased mortality.[86-88] Other retrospective studies have shown the opposite.[89-91] Recent prospective randomized trials looking at both undifferentiated ICU admissions and those specifically involving individuals with septic shock showed that single-dose etomidate has no effect on outcome.[92,93] Ironically, much of the original criticism of etomidate arose from the belief that adrenocortical response to exogenous corticotropin predicts outcome in patients with septic shock, a belief that has since been abandoned.[94] Also, the most comprehensive study of the role of exogenous corticosteroids in septic shock failed to show any benefit, casting further doubt about any possible mortality effect of a single dose of etomidate.[95] Pending a properly constructed, prospective, randomized clinical trial, there is not sufficient evidence to support a recommendation that etomidate be avoided in patients with septic shock.[85,96] In fact, etomidate's superior hemodynamic profile makes it an excellent choice, as is ketamine, in these generally unstable patients.

Ketamine. Ketamine, a phencyclidine derivative, has been widely used as a general anesthetic agent since 1970. After an intravenous dose of 1 to 2 mg/kg, ketamine produces loss of awareness within 30 seconds, peaks in approximately 1 minute, and has a clinical duration of 10 to 15 minutes. As a dissociative anesthetic agent, ketamine induces a cataleptic state rather than a true unconscious state. The patient has profound analgesia but may have open eyes. Many protective reflexes, including airway reflexes, are preserved.

The principal uses of ketamine in emergency airway management are for the induction of patients with acute, severe asthma and for hemodynamically unstable patients. Because of its superior hemodynamic profile, ketamine is an excellent alternative to etomidate for a hemodynamically unstable patient, such as a patient with sepsis or multiple trauma. Although comparative evidence is lacking, ketamine probably has hemodynamic effects superior to those of etomidate in the severely decompensated patient. In patients with status asthmaticus, etomidate or other induction agents can be used, with the notable exception of sodium thiopental, which releases histamine. Ketamine is a direct bronchodilator and causes catecholamine release, so it may be useful both for intubation and for intermittent administration as part of sedation for mechanical ventilation in patients with severe asthma, although no outcome studies clearly demonstrate its superiority.

Controversy exists regarding the use of ketamine in patients with elevated ICP because ketamine may increase cerebral metabolic rate, ICP, and cerebral blood flow.[97] The evidence that ketamine can produce harm in this way is conflicting, however, and may be outweighed in trauma patients because of its overall favorable hemodynamic profile.[98] Ketamine does not appear to be harmful in children when given in procedural doses to patients with known elevated ICP, and may actually lower ICP.[99] Because it may cause release of catecholamines and increase blood pressure, ketamine should probably be avoided in traumatic brain injury (TBI) patients with normal or elevated blood pressure. However, we recommend use of ketamine or etomidate for induction of patients with TBI and hypotension. Ketamine may produce unpleasant emergence phenomena, especially disturbing or frightening dreams in the first 3 hours after awakening. These reactions, which are more prominent in adults than in children, in women than in men, in patients receiving larger doses, and in certain personality types, may be mitigated by benzodiazepine administration.[100] Patients who undergo RSI with ketamine should receive a benzodiazepine (e.g., lorazepam 0.05 mg/kg or midazolam 0.1 mg/kg) as part of postintubation management.

Propofol. Propofol is a highly lipophilic alkylphenol with GABAergic activity. Its primary use in the emergency setting has been for postintubation sedation in head-injured patients; however, it can be used for induction during RSI. It reduces intracranial pressure and cerebral oxygen usage and is indicated for patients with elevated ICP caused by medical or traumatic emergencies. Because of the propensity of propofol to cause hypotension, through both vasodilation and direct myocardial depression, the dosage is reduced or the drug is avoided altogether in hemodynamically compromised patients. The usual induction dose of propofol is 1.5 to 2.0 mg/kg IV, but reduced doses should be used in elderly patients or those with hemodynamic compromise or poor cardiovascular reserve. Propofol is delivered in a soybean oil and lecithin vehicle and should not be used in patients with allergies to these substances. Although propofol has traditionally been avoided in patients with egg allergy, it is likely safe unless a history of anaphylaxis to egg protein exists.[101] Propofol causes pain at the site of administration in as many as 60% of patients. Using a proximal (antecubital) vein in lieu of distal venous injection is the most important preventative measure. Pretreatment with intravenous lidocaine, coadministration of lidocaine mixed with propofol, and pretreatment with opioids or ketamine have all been shown to limit this common adverse reaction.[102]

Other Induction Agents. Given the widespread acceptance and familiarity with etomidate, propofol, and ketamine, other drug classes such as barbiturates and benzodiazepines are infrequently used as induction agents for RSI. Rapidly acting barbiturates, such as thiopental, are highly lipid soluble and readily cross the blood-brain barrier, acting on the γ-aminobutyric acid (GABA) receptor neuroinhibitory complex to rapidly depress central nervous system activity. A single dose of 3 mg/kg of thiopental produces loss of consciousness in less than 30 seconds, has a peak effect at 1 minute, and has a clinical duration of 5 to 8 minutes. Thiopental is a negative inotrope and a potent venodilator and should be used with caution in patients whose cardiovascular reserve is

www.ketabpezeshki.com 66485457-66963820

diminished. Thiopental releases histamine and should not be used in asthmatic patients. Of the benzodiazepines, only midazolam is used as an induction agent, a role for which it is inferior to other, more commonly used agents, such as etomidate and propofol. The usual induction dose is 0.2 to 0.3 mg/kg IV. At a dose of 0.3 mg/kg IV, midazolam produces loss of consciousness in about 30 seconds and has a clinical duration of 15 to 20 minutes. Midazolam is a negative inotrope and should be used with caution in hemodynamically compromised and elderly patients, for whom the dose can be reduced to 0.1 mg/kg or 0.05 mg/kg. Onset is slower at these reduced doses.

Special Clinical Circumstances

Status Asthmaticus

Status asthmaticus with supervening respiratory failure is a preterminal event. Respiratory failure in the asthmatic patient is not caused primarily by progressive worsening of the bronchospasm, but rather by eventual exhaustion and fatigue secondary to the effort of breathing against severe airway resistance. RSI is the recommended technique for intubation of a patient in status asthmaticus. Difficult airway considerations are complex in an asthmatic patient because of impending respiratory arrest and the patient's inability to tolerate attempts at awake intubation. When a difficult airway is identified, intubation preparation should begin early, so that awake methods, such as flexible endoscopic intubation, are retained as options. Even when a difficult airway is identified in an asthmatic patient, however, RSI usually is the intubation method of choice. Ventilation with a BVM or an EGD may be difficult because of high airway resistance, and technique should be optimized with the use of a low tidal volume and respiratory rate with a high inspiratory flow rate. If rescue ventilation fails despite optimal technique, prompt cricothyrotomy is indicated.

The asthmatic patient has highly reactive airways, and steps should be taken to minimize any additional bronchospasm that may occur during intubation. The bronchoconstriction that occurs with ETT placement is thought to be neurally mediated, and local anesthetics, particularly lidocaine, have been studied as a way to blunt this airway reflex. Lidocaine has been shown to suppress the coughing that occurs in response to airway manipulation and may improve ETT tolerance and reduce reactive bronchospasm in asthmatic patients.[52] Although there is not clear proof of outcome benefit, we recommend lidocaine (1.5 mg/kg) as a pretreatment drug before intubation in status asthmaticus and in asthmatic patients being intubated for reasons other than their asthma, particularly if beta-agonists have not been administered. High-dose, inhaled beta-agonists may provide maximal protection against reactive bronchospasm during intubation in asthmatics without active bronchospasm, and lidocaine may provide little additional benefit in this setting.[51] This approach has not been tested in patients in status asthmaticus, however. Ketamine has been shown to produce bronchodilation in humans and animal models and has been reported to mitigate bronchospasm in patients who are not intubated and in patients who are already intubated and who are not improving with mechanical ventilation. Although studies to date have been limited, there is a growing body of experience with ketamine that suggests that it may be the preferred induction agent for the emergency intubation of patients with status asthmaticus (Table 1-3).[103]

Table 1-3 Rapid Sequence Intubation for Status Asthmaticus

TIME	STEP
Zero minus 10 min	*Preparation*
Zero minus 5 min	*Preoxygenation (as possible)* Continuous albuterol nebulizer 100% oxygen for 3 min *or* 8 vital capacity breaths
Zero minus 3 min	*Pretreatment* Lidocaine 1.5 mg/kg
Zero	*Paralysis with induction* Ketamine 1.5 mg/kg Succinylcholine 1.5 mg/kg
Zero plus 30 sec	*Positioning*
Zero plus 45 sec	*Placement* Laryngoscopy with intubation End-tidal carbon dioxide confirmation
Zero plus 2 min	*Postintubation management* Sedation and analgesia NMBA only if required after adequate sedation, analgesia In-line albuterol nebulization Additional ketamine as indicated

NMBA, neuromuscular blocking agent.

Hemodynamic Consequences of Intubation

Laryngoscopy and intubation are potent stimuli for the reflex release of catecholamines.[104] This reflex sympatheitc response to laryngoscopy (RSRL) produces only modest increases in blood pressure and heart rate and is of little consequence in otherwise healthy patients. The RSRL is of potential clinical significance in two settings: acute elevation of ICP, and certain cardiovascular diseases (e.g., intracerebral hemorrhage, subarachnoid hemorrhage, aortic dissection or aneurysm, and ischemic heart disease). In these settings the reflexive release of catecholamines, increased myocardial oxygen demand, and attendant rise in mean arterial blood pressure and heart rate may produce deleterious effects. The synthetic opioids (e.g., fentanyl) and beta-adrenergic blocking agents (e.g., esmolol) are capable of blunting the RSRL and stabilizing heart rate and blood pressure during intubation.[104] Lidocaine also has been studied, but the results are contradictory and inconclusive.[105] In patients at risk from acute blood pressure elevation, administration of fentanyl (3 μg/kg) during the pretreatment phase of RSI attenuates the heart rate and blood pressure increase. The full sympatholytic dose of fentanyl is 5 to 9 μg/kg, but if this dose is administered as a single pretreatment bolus, hypoventilation or apnea can occur. The administration of 3 μg/kg is safer and can be supplemented with an additional 3 μg/kg immediately after intubation if greater sympathetic blockade is desired or if hypertension and tachycardia persist. Fentanyl should be given as the last pretreatment drug and is administered over 60 seconds to prevent hypoventilation or apnea.

Elevated Intracranial Pressure

When ICP is elevated as a result of head injury or acute intracranial catastrophe, maintenance of CPP and avoidance of further increases in ICP are desirable.[44] Significant reductions in mean arterial blood pressure decrease CPP with the reduction of the driving gradient between arterial pressure and ICP. If CPP falls below 50 to 60 mm Hg, cerebral ischemia may occur and cerebral autoregulation of blood flow may fail. Maintenance of the systemic mean arterial blood pressure at 100 mm Hg or greater supports CPP and reduces the likelihood of secondary injury. Therefore RSI induction agents that could lower MAP should be avoided in patients with brain injury. In patients with suspected or documented elevation of ICP, control of RSRL is desirable to avoid further elevation of ICP. Fentanyl (3 μg/kg) given as a

www.ketabpezeshki.com 66485457-66963820

Table 1-4 Rapid Sequence Intubation for Elevated Intracranial Pressure

TIME	STEP
Zero minus 10 min	*Preparation*
Zero minus 5 min	*Preoxygenation (as possible)* 100% oxygen for 3 min *or* 8 vital capacity breaths
Zero minus 3 min	*Pretreatment* Lidocaine 1.5 mg/kg Fentanyl 3 µg/kg (slowly)
Zero	*Paralysis with induction* Etomidate 0.3 mg/kg Succinylcholine 1.5 mg/kg*
Zero plus 30 sec	*Positioning*
Zero plus 45 sec	*Placement* Laryngoscopy with intubation End-tidal carbon dioxide confirmation
Zero plus 2 min	*Postintubation management* Sedation and analgesia, consider propofol to permit frequent reexamination NMBA only if required after adequate sedation, analgesia

NMBA, neuromuscular blocking agent.
*May substitute rocuronium 1 mg/kg for succinylcholine.

pretreatment drug is the best choice for this purpose in the emergency setting.[44,106]

Evidence suggests a separate reflex that increases ICP in response to laryngoscopy and intubation, although the precise mechanism is not understood. Intravenous lidocaine has been shown to reduce ICP or blunt the ICP response to laryngoscopy and intubation, although study results are mixed.[53,54] However, if time allows and in the absence of an obvious contraindication (e.g., known allergy to amide anesthetics), lidocaine (1.5 mg/kg IV), administered during the pretreatment phase of RSI, is desirable to blunt the ICP response to laryngoscopy and intubation. Similarly, RSRL and the ICP response to intubation make BNTI inadvisable in brain injury patients.

In emergency patients who may have elevated ICP, the physician should choose an induction agent that balances a favorable effect on cerebral dynamics and ICP with a stable systemic hemodynamic profile. At present, etomidate (0.3 mg/kg) appears to be the best choice in this situation, although propofol is also a good option when hemodynamic compromise is not present (Table 1-4).

Potential Cervical Spine Injury

Historically, most patients with suspected blunt cervical spine injury were intubated orally by direct laryngoscopy with in-line cervical spine immobilization, whether done as an awake procedure or with neuromuscular blockade. However, with this approach glottic views can be inadequate and excessive lifting force often is required.[107-111] Videolaryngoscopes provide superior laryngeal views without excessive lifting force or cervical spine movement and have higher intubation success rates when compared with conventional direct laryngoscopy.[112,113]

The intubating laryngeal mask airway (ILMA) also may result in less cervical spine movement during intubation than direct laryngoscopy.[114] Alternative devices to direct laryngoscopes also have shown promise for safe intubation of patients with cervical spine injury. A fluoroscopic study in which intubation with the Shikani optical stylet (SOS) was compared with direct laryngoscopy showed significantly less cervical spine movement with the SOS but a slightly longer intubation time (28 seconds vs. 17 seconds).[115] The Airtraq and Pentax Airway Scope are curved intubation devices that integrate an ETT channel and either a viewing lens or a video screen to facilitate intubation. Both devices have shown high levels of intubation success and minimal cervical spine motion compared with direct laryngoscopy.[116-118] The CTrach, a fiberoptically enhanced ILMA, also has demonstrated success both with and without in-line cervical spine stabilization.[119]

In the absence of a coexistent blunt traumatic mechanism or a neurologic examination indicating spinal cord injury, cervical spine immobilization for intubation of patients with penetrating head and neck trauma rarely is indicated.[120] It is not proven whether patients with gunshot or shotgun injuries to the head or neck are at risk of exacerbation of cervical cord injury during intubation, and there is no report of such a patient, with or without clinical evidence of spinal cord injury, who was injured by intubation. In addition, cervical spine immobilization in patients with penetrating neck injuries may be harmful. A recent large retrospective review of more than 45,000 trauma patients with penetrating injuries found that those in whom prehospital cervical collars were applied were two to three times more likely to die. Delays in transport and patient assessment and added difficulty for airway procedures were postulated as potential contributors.[121]

Pediatric Intubation

Although many considerations in pediatric intubation are the same as for adults, a few differences exist with regard to airway management. The larynx is higher in the child's neck, causing a more acute angle between the oral pharynx and the larynx. This is not a significant issue when a videolaryngoscope is used, but for direct laryngoscopy, visualization is aided by gentle posterior pressure on the anterior aspect of the thyroid cartilage. The epiglottis is high and soft and may obscure the view of the cords. If the child is very small, the prominent occiput brings the mouth to a position far anterior to the larynx; an assistant can lift the chest gently by grasping both shoulders, immobilizing the head at the same time. Again, these techniques apply to direct laryngoscopy, and anatomic issues may be minimized by use of a videolaryngoscope. The airway in the small child is short, and care must be taken not to intubate either bronchus.

For direct laryngoscopy, a straight laryngoscope blade is desirable to displace the floppy epiglottis, especially in young children, and positioning for intubation may be different. Although the product insert for succinylcholine now advises against its routine use in pediatric anesthesia because of the risk of hyperkalemia in children with undiagnosed congenital neuromuscular disorders (e.g., muscular dystrophy), it remains the drug of choice for emergency RSI of infants and children.[65] Rocuronium has been used in children, but experience is too limited to recommend that it replace succinylcholine for pediatric RSI in the ED. RSI may be used in children in a manner similar to that in adults, with two important differences. Excessive bradycardia may be seen with succinylcholine in children younger than 1 year, but it is not known whether administration of atropine (0.02 mg/kg) during the pretreatment phase prevents any possible adverse outcome. The dose of succinylcholine in infants is 2 mg/kg. Induction agents may be selected using similar criteria as for adults. Particular attention should be paid to providing appropriate postintubation sedation and pain control, just as in adults. One recent study showed that less than 25% of pediatric patients received ongoing sedation within 15 minutes after intubation.[122] The major difficulty in intubating children and infants is choosing the correct size of equipment and the correct drug doses for age or size. These obstacles can be overcome by use of a length-based system such as the Broselow-Luten color coding system, which provides dosing and equipment sizes based on the length of the child.

www.ketabpezeshki.com 66485457-66963820

Cricothyrotomy is impossible in small children, and alternative rescue airway devices (e.g., percutaneous oxygenation via the cricothyroid membrane) are required.

Evolution of Airway Devices

Direct Laryngoscopy

Historically, orotracheal intubation by direct laryngoscopy has been the standard mode of emergency airway management, principally because few alternatives for tracheal intubation existed. Despite the overall success of direct laryngoscopy, there are inherent limitations, and a significant proportion of patients are difficult, if not impossible, to intubate under direct vision despite optimal technique, proper patient positioning, and neuromuscular blockade. In response to these difficulties, dozens of modified and "novel" direct laryngoscope blades have been invented, but the limitations remain. Since 2001, there has been an explosion of new intubation devices, capitalizing principally on video technology but also on fiberoptic and other optical innovations. These devices offer, in common, the ability to visualize the glottis without creating a direct line of sight, thus obviating many of the issues that compromise direct laryngoscopy. Although direct laryngoscopy remains an acceptable technique for tracheal intubation, there is mounting evidence of the clear superiority of modern video devices, and direct laryngoscopy increasingly is relegated to the role of standby device.

Videolaryngoscopes

Modern laryngoscopes incorporate video imaging into specially designed laryngoscope blades to provide glottic visualization superior to that of a direct laryngoscope without the need to create a straight-line visual axis through the mouth. The GlideScope videolaryngoscope system (GVL) uses a modified Macintosh blade with a straightened, angulated, and elongated tip enclosing a proximally placed camera to provide a wide-angle view of the glottis and the surrounding anatomy, even in patients with difficult airways (Fig. 1-11). Video images are transmitted to a high-resolution display that can record both still pictures and video clips. Handle and blade sizes range from neonate to obese adult. The GlideScope Ranger is an ultraportable version of the device, designed for use in the out-of-hospital environment. One large series of out-of-hospital intubations showed that the Ranger significantly reduced the number of attempts needed to intubate compared with direct laryngoscopy.[123] The GlideScope Cobalt is a system designed for a single use, without the need for cleaning. It consists of a flexible video wand insert that fits inside a disposable, single-piece transparent blade or handle sheath, and comes in sizes comparable to those for the standard GlideScope. The placement of the camera distally along the blade to create a viewing field essentially negates the obstructive potential of the tongue, so GlideScope laryngoscopy, and most other videolaryngoscopy, is performed with the blade introduced in the midline of the mouth and rotated around the tongue with very little lifting. A proprietary rigid preformed stylet is available for use with the GlideScope, or a malleable stylet can be shaped to match the exaggerated curve of the GlideScope blade. Either stylet may be used, and there appears to be no advantage of one over the other, either for novice or experienced operators.[124,125] When compared with direct laryngoscopy, the GlideScope provides an equivalent or superior glottic view and has a very high intubation success rate.[126,127] Traditional predictors of difficult direct laryngoscopy likely will not apply to videolaryngoscopy, as most are based on limitations of creating a direct line of sight, which is not a part of videolaryngoscopy.[128] The GlideScope causes less cervical spine movement than conventional direct laryngoscopy and provides better glottic exposure in patients with strict cervical spine precautions.[112,129] The C-MAC videolaryngoscope (Fig. 1-12) incorporates a complementary metal oxide semiconductor (CMOS) video chip into a range of laryngoscope blades to enhance glottic view. Images are displayed on a high-resolution monitor, with image and video saving capabilities. The Macintosh blade version of the C-MAC can be used as a direct laryngoscope by a trainee while a supervisor observes the video output, providing an excellent tool for teaching direct laryngoscopy. Although head-to-head comparisons with other videolaryngoscopes are lacking, early clinical experience with the C-MAC is positive, and one study showed superior views

Figure 1-11. GlideScope AVL (Verathon Inc.) uses a high-resolution digital display; includes single-use Stats (blade sheaths) that cover the video baton; and has the ability to record still images and video clips through internal and removable storage devices. (Courtesy Verathon Inc.)

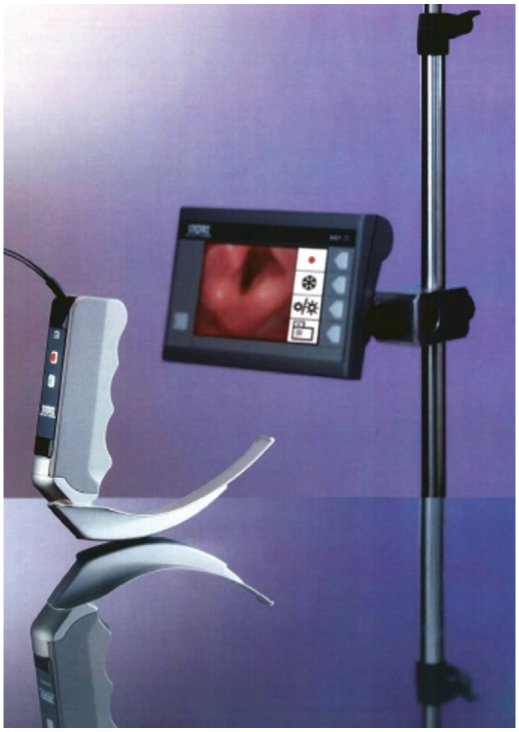


Figure 1-12. The C-MAC video laryngoscope (Karl Storz Endoscopy) uses an integrated complementary metal oxide semiconductor (CMOS) video chip to capture a video image from near the distal tip of an otherwise conventional laryngoscope blade. The image is conveyed to a video screen, where it is viewed by the intubator. (From Walls RM, Murphy MF, eds: Manual of Emergency Airway Management, 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2012; with permission.)

www.ketabpezeshki.com 66485457-66963820

obtained by videolaryngoscopy, with a forerunner of the C-MAC compared with direct laryngoscopy.[130,131] There are several other models of videolaryngoscopes in various sizes and with varying features, such as disposable sheaths or blades, and at various price points.[131-134] Individual evaluation of these devices is important in selecting the best videolaryngoscope for an individual practitioner or practice group. Overall, videolaryngoscopy offers the promise of transforming laryngoscopy and has the potential to render conventional, direct laryngoscopy obsolete.

Fiberoptic and Video Intubating Stylets

Several semirigid fiberoptic and video intubating stylets also are available. The SOS (Clarus Medical, Minneapolis, Minn.) is the most studied of these, although a newer video device (Clarus Video System; Fig. 1-13) based on the same principles likely will perform as well as or better than its fiberoptic forerunner. The ETT is placed over a semirigid stylet, consisting of a metal sheath with a distally placed fiberoptic or video image acquisition system, then advanced through the mouth and over the tongue in the midline and into the trachea under fiberoptic or video visualization (Fig. 1-14). The SOS appears to cause less movement of the cervical spine than conventional laryngoscopy during intubation with in-line stabilization.[115] A smaller version, the Levitan scope, uses a light-emitting diode (LED)–illuminated fiberoptic stylet to facilitate intubation by direct laryngoscopy. The device is recommended by the manufacturer to facilitate first-pass success when a limited glottic view is obtained by direct laryngoscopy. In the only study comparing the Levitan scope with the gum elastic bougie, however, the two devices achieved similar success.[135]

Flexible Intubating Scopes

Intubation using a flexible endoscope is an important option for certain difficult airways, particularly in those with distorted upper airway anatomy, such as angioedema or blunt anterior neck trauma. These scopes long relied on fiberoptic technology, but this largely has been supplanted by miniaturized high-quality video systems. After appropriate patient preparation, the endoscope is passed through the vocal cords under continuous visualization, serving as an introducer for an ETT, which is then placed through the glottis. Flexible endoscopic examination also is used for airway assessment to determine whether intubation is needed, such as in patients with smoke inhalation or supraglottitis. Intubation of morbidly obese patients, those with distorted airway anatomy (e.g., penetrating or blunt anterior neck injury), or those with fixed cervical spine deformity can be achieved with the flexible endoscope with topical anesthesia and judicious sedation, thus preserving the patient's ability to breathe until intubation has been achieved. Scopes also have been used successfully to intubate through an ILMA, and video systems likely would work well in this application also.[136]

There is a significant but manageable learning curve for flexible endoscopic intubation. Using the endoscope for examination of the upper airway in patients with pharyngitis or odynophagia, for example, is helpful, as it requires the same "navigation skills" as are required for intubation. Use of a video display for instruction, so that the instructor and learner can simultaneously see the same image, appears to enhance learning. The role of flexible endoscopic intubation in the ED is greatly expanding as obesity increases in the population, and, increasingly, difficult airways are handled in the ED without backup. The transition from fiberoptic to CMOS video technology will make these flexible scopes more durable, less prone to fogging, and less expensive—all desirable attributes for emergency intubation. Emergency physicians should have immediate access to flexible endoscopes and should acquire training and practice in their use.

Extraglottic Devices

Laryngeal Mask Airways. *Laryngeal mask airways* (LMAs) collectively include a number of commercially available ovoid, silicone mask devices designed to seal above the glottis and permit ventilation through a central channel with a standard bag. The most widely used is the original LMA, shown in Figure 1-15. It is

Figure 1-13. The Clarus Video System (Clarus Medical) incorporates a curved fiberoptic stylet surrounded by a malleable but rigid protective metal sheath. Images are displayed on a video screen attached to the handle. The screen can swivel for optimal viewing as the stylet is inserted into the mouth. (Image courtesy Clarus Medical, with permission.)

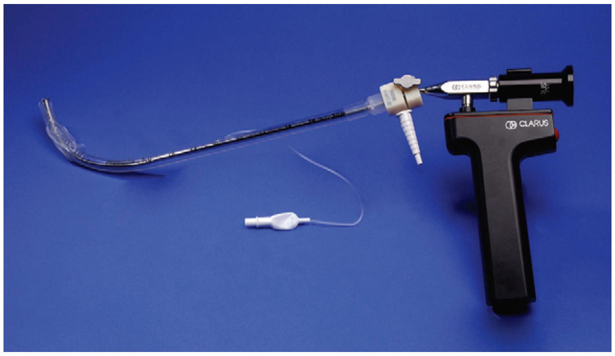


Figure 1-14. The Shikani optical stylet (SOS; Clarus Optical) with endotracheal tube mounted. The eyepiece and battery pack are at the right.

Figure 1-15. The standard laryngeal mask airway (LMA Classic) is available in sizes from infant to large adult. (Courtesy LMA North America, San Diego.)

www.ketabpezeshki.com 66485457-66963820

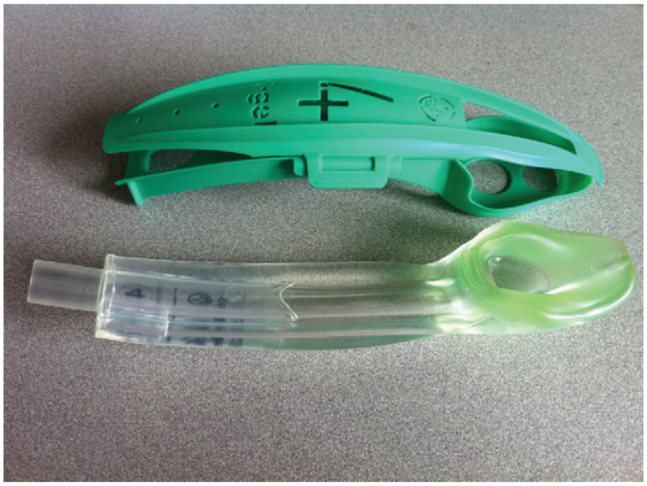


Figure 1-16. The i-gel mask airway does not have an inflatable cuff and is available in sizes from infant to adult. (Image courtesy Calvin A. Brown III, MD.)

Figure 1-17. The intubating laryngeal mask airway is modified to facilitate insertion of an endotracheal tube after placement and ventilation have been achieved. The epiglottic elevator *(arrowhead)* lifts the epiglottis to allow passage of the special endotracheal tube *(arrow)*.

available in both reusable and single-use configurations; single-use models in both conventional and intubating formats are offered by several manufacturers and are probably equivalent.[137] The mask is inserted blindly into the pharynx, then inflated, providing a seal that permits ventilation of the trachea with minimal gastric insufflation. In elective anesthesia the LMA has an extremely high insertion success rate and low complication rate, including a low incidence of tracheal aspiration.[138,139] Evaluations of LMA insertion by experienced and inexperienced personnel consistently have shown ease of insertion, high insertion success rates, and successful ventilation.[140] Novice users appear to be able to both ventilate and intubate more easily and successfully with the ILMA than with BMV and direct laryngoscopy.[140] The LMA may be a viable alternative to endotracheal intubation for in-hospital or out-of-hospital treatment of cardiac arrest, particularly when responders are inexperienced airway managers. At a minimum, the device may serve a temporizing role equal or superior to BMV until definitive airway management can be achieved. The LMA Supreme (LMAS) is a new robust LMA with a rigid angled tube, similar to an ILMA, and offers an orogastric tube channel and higher seal pressures than the standard LMA.[141] A new form of noninflatable LMA, the i-gel, has a viscous gel cuff and does not require inflation (Fig. 1-16). It is available in a variety of sizes for adults and pediatric patients. The device is placed blindly, and insertion depths are marked on the side of the device. It has an integrated bite block and a channel for passage of an orogastric tube. Initial experience with the device, even with minimally trained novice users, is promising, with high insertion success rates and shorter insertion times when compared with the LMA or laryngeal tube airway.[142,143]

The ILMA is designed to facilitate intubation through the mask after correct placement (Fig. 1-17). It differs from the LMA in two main ways: The mask is attached to a rigid, stainless steel ventilation tube that is bent almost to a right angle, and the mask incorporates an epiglottic elevator at its distal end. Placement of the ILMA results in successful ventilation in almost 100% of cases and successful subsequent intubation in 95%.[114,144-146] The ILMA can also be used for both ventilation and intubation in obese patients with similarly high success rates.[147] The ILMA has a special ETT and a stabilizer rod to remove the mask over the ETT after intubation has been accomplished, but intubation can be comparably successful with a conventional polyvinylchloride (PVC) ETT.[148]

The ILMA is a better device than the standard LMA for use in the ED because it facilitates both rescue ventilation and intubation. Intubation through the ILMA has compared favorably in terms of success with direct laryngoscopy and is superior in the hands of novice intubators.[140,144] When the ILMA is placed, intubation can be performed blindly or guided by a lighted stylet or a fiberoptic scope. The ILMA comes only in sizes 3, 4, and 5 and so is not suitable for use in patients weighing less than about 30 kg. For smaller patients, the standard LMA, which has sizes down to size 1 (infant), should be used. Intubation can be achieved through the standard LMA, but the success rate is significantly less than with the ILMA. As experience with both the LMA and ILMA grows, it is likely that there will be increasing adoption of the LMA as a primary airway management technique by nonhospital first responders, and the ILMA is gaining attention as a primary rescue device in the ED.

The CTrach ILMA incorporates fiberoptic bundles and a detachable viewing screen to provide a view of the glottis during intubation. The device performs better than the standard ILMA for first-attempt intubation, where it achieved almost 93% success versus approximately 80% for the ILMA in one well-conducted study.[149] It can be placed equally as rapidly in patients with and without cervical spine immobilization.[119] Ultimately, though, the ILMA's intubation success rate is so high (on three or fewer attempts) that it is not clear that the CTrach provides additional benefit overall. The view can be obscured by secretions, but this is easily solved by removing and reinserting the device or cleaning it with a swab through the airway lumen.[150] The greatest issue is cost, with the CTrach priced almost five times higher than the corresponding set of standard ILMAs. Whether the additional cost provides additional benefit for application in the ED is not clear.

In the ED the primary use of the LMA or ILMA is as a rescue technique to provide a temporary airway when intubation has failed, bag ventilation is satisfactory, and the patient has been paralyzed and may either require prolonged ventilation or be in need of immediate airway management. In such cases the LMA is one of numerous acceptable devices. In the "can't intubate, can't ventilate" situation, cricothyrotomy is indicated, but an ILMA may be placed rapidly in an attempt to achieve ventilation (converting the situation to "can't intubate, can ventilate") as long as this is done in parallel with preparations for cricothyrotomy and

www.ketabpezeshki.com 66485457-66963820

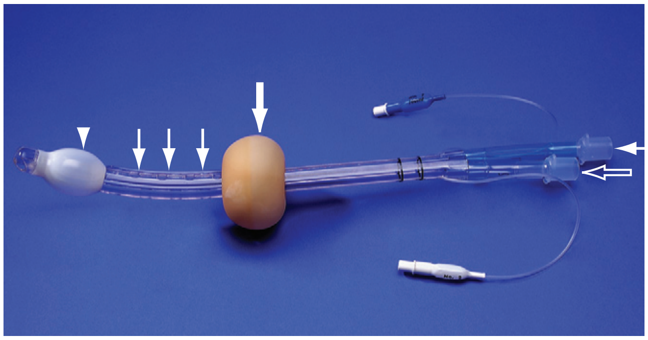


Figure 1-18. The Combitube is inserted through the mouth blindly, although a laryngoscope can be used if desired. It seats itself in the esophagus more than 95% of the time, and ventilation is performed through the proximal lumen and side ports *(white arrows)* after inflation of the two balloons. The lower balloon *(arrowhead)* occludes the esophagus. The upper (large) balloon *(thick arrow)* occludes the oropharynx. If the tube is in the trachea, the alternate lumen *(clear arrow)* is used for ventilation.

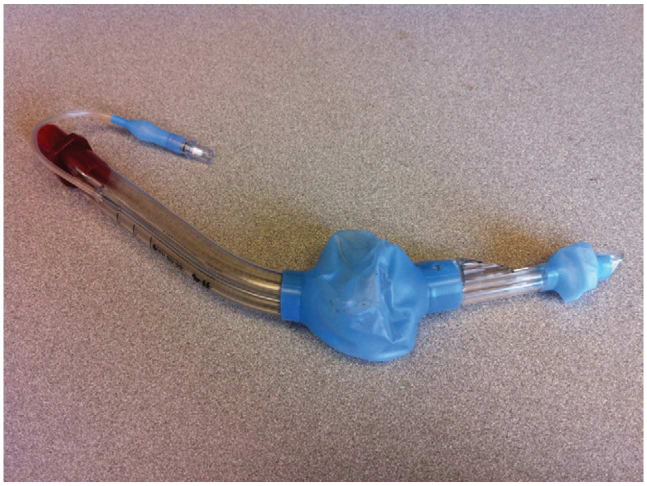


Figure 1-19. King laryngeal tube incorporates two cuffs but inflates with a single bolus of air. There is a channel in the back for passage of an orogastric tube. It is available in a variety of adult sizes.

does not delay the initiation of a surgical airway.[151] Availability of the LMA and adequate prior training of the clinician offer a legitimate option for the management of the failed airway, and the ILMA compares well with fiberoptic intubation in terms of successful intubation of difficult airways.[146] The standard LMA may also offer advantages for providing ventilation in unconventional positions, such as when the patient is lying on his or her side.[152] In the out-of-hospital setting, where concerns about esophageal placement of ETTs have focused interest on methods used for airway management, the LMA and Combitube offer excellent placement and ventilation characteristics and may be preferable to endotracheal intubation in this setting, especially when intubation is relatively infrequently performed.[153] If the patient is in a difficult position in terms of intubation access, the LMA may facilitate more rapid ventilation.[154]

Other Extraglottic Devices. In addition to LMAs, which sit above the glottis, there are several other types of EGDs, which are placed blindly posterior to the laryngeal inlet to provide oxygenation and ventilation through side ports, while inflatable cuffs occlude the pharynx above and the esophageal inlet below. Because of their positioning behind the larynx, these often are called *retroglottic devices.* The prototype for these devices is the esophagotracheal Combitube. The Combitube is a plastic double-lumen tube with one lumen functioning as an airway after esophageal insertion and the other lumen functioning as a tracheal airway (Fig. 1-18). The tube is placed blindly into the esophagus, and then proximal and distal balloons are inflated sequentially through different ports. The balloons prevent escape of ventilatory gases upward through the pharynx or downward through the esophagus. The tube is placed into the esophagus, as designed, almost 100% of the time, but both lumens are patent, so ventilation is still possible if the tube has been placed inadvertently into the trachea. It comes in two sizes and is used only in patients taller than 48 inches.

Newer types of retroglottic devices are smaller, are simpler, and can be easier to use. The King laryngeal tube airway (King LT) has a single port through which both distal and proximal low-pressure balloons are inflated as a single step (Fig. 1-19). The distal balloon, when seated correctly, obstructs the upper esophageal sphincter, and the larger proximal balloon obstructs the hypopharynx, preventing regurgitation of air. A new version of the King LT has a posterior channel that accepts a nasogastric tube, which can be passed through the device into the stomach for aspiration of gastric contents. The King LT is disposable, is rapidly placed, is easy to use by operators of various skill levels, and has seal pressures similar to those of standard LMAs. It can be safely left in place for 4 hours without mucosal pressure damage. Another device, the Rusch EasyTube, is similar in concept and appearance to the Combitube but is available in 41F and a smaller 28F size for smaller patients. All retroglottic devices are primarily a substitute for endotracheal intubation for non–ETT-trained personnel but are also used by advanced airway managers as a way to oxygenate and ventilate patients during crash and failed airway scenarios.[155-159] These devices should be considered temporary measures, do not protect against aspiration, and should be exchanged for a definitive airway as soon as possible.

Surgical Airway Management

Needle Cricothyrotomy with Transtracheal Jet Ventilation

With the advent of new airway devices, especially videolaryngoscopes, surgical airway management, which always has been distinctly uncommon, likely will be required even less. Nevertheless, certain patients will confound every other route of securing an airway, and surgical airway management remains an important option for emergency airway management. Needle cricothyrotomy involves the insertion of a large needle (ideally a large catheter designed for this purpose) through the cricothyroid membrane into the airway. When inserted, the needle is used to ventilate the patient with a standard wall oxygen source. Because of the high-velocity ventilation that ensues through the narrow catheter, this procedure is called *transtracheal jet ventilation,* and it carries significant risk of barotrauma to the airway and lung tissues. Transtracheal jet ventilation has been used successfully in humans and has been subjected to various animal experiments to determine its uses and limitations. It rarely has been used in adult or pediatric patients in EDs, however, where its role as a rescue device in the "can't intubate, can't ventilate" situation is vastly inferior to cricothyrotomy.

The jet ventilator virtually never is indicated as a primary or rescue airway device. For almost any application, other methods are superior and safer. In particular, when upper airway obstruction is present in adults, percutaneous or surgical cricothyrotomy is recommended. The primary indication for transtracheal ventilation in the ED is the initiation of emergency oxygenation for a pediatric patient who is apneic (either because of the presenting

www.ketabpezeshki.com 66485457-66963820

condition or because of administration of an NMBA) and in whom intubation and BMV are impossible because of supraglottic obstruction or disruption. Cricothyrotomy is extremely difficult or impossible in children younger than 10 years, and transtracheal ventilation should be considered the surgical rescue modality of choice in this age group. For children younger than 5 years, bag ventilation is used with the percutaneous catheter, and pressurized devices are avoided.

Cricothyrotomy

Cricothyrotomy is the creation of an opening in the cricothyroid membrane through which a cannula, usually a cuffed tracheostomy tube, is inserted to permit ventilation. The techniques and variations thereof are well described elsewhere.[160] When surgical airway management is required, cricothyrotomy is the procedure of choice in the emergency setting, where it is faster, more straightforward, and more likely to be successful than tracheotomy.

Cricothyrotomy is indicated when oral or nasal intubation is impossible or fails and when BMV cannot maintain adequate oxygen saturation (the "can't intubate, can't ventilate" situation). Several large series have established that the incidence of cricothyrotomy is approximately 1% of all ED intubations, with the highest rates seen in trauma patients.[7,40] Cricothyrotomy is relatively contraindicated by distorted neck anatomy, preexisting infection in the neck, and coagulopathy; these contraindications are relative, however, and the establishment of the airway takes precedence over all other considerations. The procedure should be avoided in children younger than 10 years, in whom anatomic limitations make it exceedingly difficult. Studies suggest that approximately five "practice" cricothyrotomies on a simulator or animal model are sufficient to achieve at least baseline capability with the procedure, although training intervals for skills maintenance have not been well defined.[161]

A number of commercial kits and devices are used to perform percutaneous cricothyrotomy. Percutaneous cricothyrotomy with the Seldinger technique appears comparable to formal open cricothyrotomy in terms of ease of learning and success rates.[162] Patients with clear landmarks are the best candidates for this procedure because patient obesity or altered anatomy may lead to paratracheal tube placement. In patients with indistinct landmarks or for novice operators, standard open cricothyrotomy may be more successful.[163] Bougie-assisted cricothyrotomy, during which a bougie is placed through the cricoid incision and used as a guidewire for ETT placement, may also improve surgical airway success for inexperienced practitioners.[164] The safety and effectiveness of the many cricothyrotomy kits and devices are not clearly established. Only two percutaneous cricothyrotomy sets on the market currently have the ability to place a cuffed tracheostomy tube. One is a dedicated Seldinger cricothyrotomy set; the other is a combination set that has all necessary equipment for either a Seldinger percutaneous cricothyrotomy or a standard surgical cricothyrotomy (Melker universal cricothyrotomy kit; Cook Critical Care, Bloomington, Ind.) (Fig. 1-20).

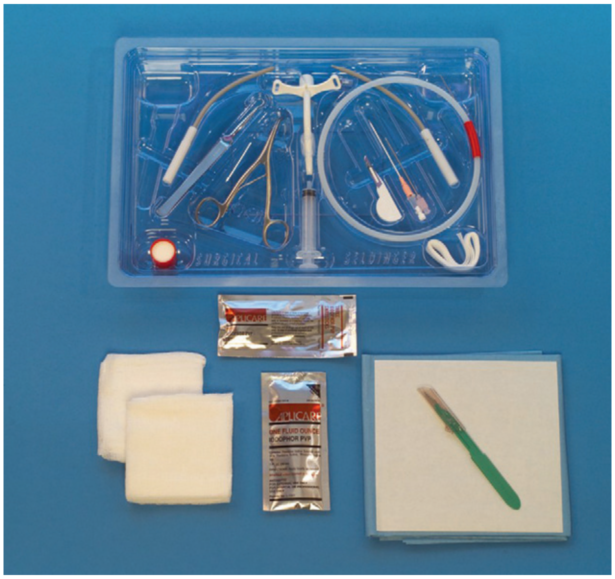


Figure 1-20. Melker universal cricothyrotomy kit. (Courtesy Cook Critical Care. Disclosure: The author assisted in the design of this kit and receives a 10-35% royalty on its sales.)

OUTCOMES

Few studies of emergency airway management have characterized complications and outcomes. The largest single-institution series reported a success rate for ED RSI of 99% and a complication rate of 9.3%; most complications were minor.[9] Phase II of the large National Emergency Airway Registry study (NEAR II) of almost 9000 ED intubations reported that most patients were intubated by emergency physicians using RSI with overall success rates of 96%. The NEAR classification system characterizes potentially adverse occurrences during intubation as "adverse events."[7,40,165] In the NEAR study the overall rate of adverse events was 12%, with recognized esophageal or mainstem intubation and hypotension being most common.[7] No studies have evaluated the long-term outcome of intubated ED patients.

KEY CONCEPTS

- Knowledge of the clinical course of the patient's condition and anticipation of possible deterioration are crucial to the decision to intubate, especially if the patient is to leave the ED for a time (e.g., interfacility transfer, diagnostic testing).
- Assessment of the patient for potential difficulty with intubation, bag-mask ventilation (BMV), ventilation using an extraglottic device (EGD), and cricothyrotomy is an essential step before neuromuscular blockers are administered. The mnemonics *LEMON, MOANS,* and *RODS* can serve as useful aids.
- In the absence of a "crash" patient (agonal, unresponsive to laryngoscopy) or a difficult airway, RSI is the airway management method of choice for ED patients.
- Tube placement confirmation using end-tidal CO_2 ($ETCO_2$) is essential after intubation, and failure to detect adequate quantities of exhaled CO_2 is evidence of esophageal intubation until proved otherwise.
- Videolaryngoscopy is transforming intubation by eliminating the traditional anatomic barriers to direct laryngoscopy. Practitioners responsible for emergency airway management should transition their routine airway management from direct laryngoscopy to videolaryngoscopy
- Cricothyrotomy is indicated in the "can't intubate, can't oxygenate" failed airway and should be performed without hesitation once this situation has been identified. Delays may increase the likelihood or severity of hypoxic injury to the patient.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Davies AE, Kidd D, Stone SP, MacMahon J: Pharyngeal sensation and gag reflex in healthy subjects. *Lancet* 1995; 345:487-488.
2. Cross AM, Cameron P, Kierce M, Ragg M, Kelly AM: Non-invasive ventilation in acute respiratory failure: A randomised comparison of continuous positive airway pressure and bi-level positive airway pressure. *Emerg Med J* 2003; 20:531-534.
3. Christensen EF, Hoyer CC: Prehospital tracheal intubation in severely injured patients: A Danish observational study. *BMJ* 2003; 327:533-534.
4. Ciesla DJ, et al: Intubation alone does not mandate trauma surgeon presence on patient arrival to the emergency department. *J Trauma* 2004; 56:937-941.
5. Weitzel N, Kendall J, Pons P: Blind nasotracheal intubation for patients with penetrating neck trauma. *J Trauma* 2004; 56:1097-1101.
6. Mandavia DP, Qualls S, Rokos I: Emergency airway management in penetrating neck injury. *Ann Emerg Med* 2000; 35:221-225.
7. Walls RM, Brown CA 3rd, Bair AE, Pallin DJ; NEAR II Investigators: Emergency Airway Management: A Multi-center Report of 8937 Emergency Department Intubations. *J Emerg Med* 2011; 41:347-354.
8. Sagarin MJ, et al: Airway management by US and Canadian emergency medicine residents: A multicenter analysis of more than 6,000 endotracheal intubation attempts. *Ann Emerg Med* 2005; 46:328-336.
9. Sakles JC, Laurin EG, Rantapaa AA, Panacek EA: Airway management in the emergency department: A one-year study of 610 tracheal intubations. *Ann Emerg Med* 1998; 31:325-332.
10. Murphy MF, Walls RM: *Identification of the difficult and failed airway*. In: Walls RM, Murphy MF, Luten RC, eds. *Manual of Emergency Airway Management*, 3rd ed. Philadelphia: Lippincott, Williams & Wilkins/Wolters Kluwer Health; 2008:81-93.
11. Langeron O, et al: Prediction of difficult mask ventilation. *Anesthesiology* 2000; 92:1229-1236.
12. Kheterpal S, et al: Incidence and predictors of difficult and impossible mask ventilation. *Anesthesiology* 2006; 105:885-891.
13. Klock A Jr, Benumof JL: *Definition and incidence of the difficult airway*. In: Hagberg CA, ed. *Benumof's Airway Management*, 2nd ed. Philadelphia: Mosby/Elsevier; 2007:215-220.
14. American Society of Anesthesiologists Task Force on Management of the Difficult Airway: Practice guidelines for management of the difficult airway: An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology* 2003; 98:1269-1277.
15. Reed MJ, Dunn MJ, McKeown DW: Can an airway assessment score predict difficulty at intubation in the emergency department? *Emerg Med J* 2005; 22:99-102.
16. Krobbuaban B, Diregpoke S, Kumkeaw S, Tanomsat M: The predictive value of the height ratio and thyromental distance: Four predictive tests for difficult laryngoscopy. *Anesth Analg* 2005; 101:1542-1545.
17. Mallampati SR, et al: A clinical sign to predict difficult tracheal intubation: A prospective study. *Can Anaesth Soc J* 1985; 32:429-434.
18. Lee A, et al: A systematic review (meta-analysis) of the accuracy of the Mallampati tests to predict the difficult airway. *Anesth Analg* 2006: 102:1867-1878.
19. Bair AE, Caravelli R, Tyler K, Laurin EG: Feasibility of the preoperative Mallampati airway assessment in emergency department patients. *J Emerg Med* 2010; 38:677-680.
20. Juvin P, et al: Difficult tracheal intubation is more common in obese than in lean patients. *Anesth Analg* 2003; 97:595-600.
21. Brodsky JB, Lemmens HJ, Brock-Utne JG, Vierra M, Saidman LJ: Morbid obesity and tracheal intubation, *Anesth Analg* 2002; 94:732-736.
22. Adnet F, et al: Randomized study comparing the "sniffing position" with simple head extension for laryngoscopic view in elective surgery patients. *Anesthesiology* 2001; 95:836-841.
23. Lee L, Weightman WM: Laryngoscopy force in the sniffing position compared to the extension-extension position. *Anaesthesia* 2008; 63:375-378.
24. Conlon NP, Sullivan RP, Herbison PG, Zacharias M, Buggy DJ: The effect of leaving dentures in place on bag-mask ventilation at induction of general anesthesia. *Anesth Analg* 2007; 105:370-373.
25. Racine SX, et al: Face mask ventilation in edentulous patients: A comparison of mandibular groove and lower lip placement. *Anesthesiology* 2010; 112:1190-1193.
26. Kheterpal S, Martin L, Shanks AM, Tremper KK: Prediction and outcomes of impossible mask ventilation: A review of 50,000 anesthetics. *Anesthesiology* 2009; 110:891-897.

26a. Cormack RS, Lehane J: Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; 39:1105-1111.

27. Yentis SM, Lee DJ: Evaluation of an improved scoring system for the grading of direct laryngoscopy. *Anaesthesia* 1998; 53:1041-1044.
28. Martin LD, Mhyre JM, Shanks AM, Tremper KK, Kheterpal S: 3,423 emergency tracheal intubations at a university hospital: Airway outcomes and complications. *Anesthesiology* 2011; 114:42-48.
29. Wong E, Ng YY: The difficult airway in the emergency department. *Int J Emerg Med* 2008; 1:107-111.
30. Levitan RM, Kinkle WC, Levin WJ, Everett WW: Laryngeal view during laryngoscopy: A randomized trial comparing cricoid pressure, backward-upward-rightward pressure, and bimanual laryngoscopy. *Ann Emerg Med* 2006; 47:548-555.
31. Knapp S, et al: The assessment of four different methods to verify tracheal tube placement in the critical care setting. *Anesth Analg* 1999; 88:766-770.
32. Takeda T, et al: The assessment of three methods to verify tracheal tube placement in the emergency setting. *Resuscitation* 2003; 56:153-157.
33. Tanigawa K, Takeda T, Goto E, Tanaka K: The efficacy of esophageal detector devices in verifying tracheal tube placement: A randomized cross-over study of out-of-hospital cardiac arrest patients. *Anesth Analg* 2001; 92:375-378.
34. Ma G, et al: The sensitivity and specificity of transcricothyroid ultrasonography to confirm endotracheal tube placement in a cadaver model. *J Emerg Med* 2007; 32:405-407.
35. Werner SL, Smith CE, Goldstein JR, Jones RA, Cydulka RK: Pilot study to evaluate the accuracy of ultrasonography in confirming endotracheal tube placement. *Ann Emerg Med* 2007; 49:75-80.
36. Benumof JL, Dagg R, Benumof R: Critical hemoglobin desaturation will occur before return to an unparalyzed state following 1 mg/kg intravenous succinylcholine. *Anesthesiology* 1997; 87:979-982.
37. Bozeman WP, Kleiner DM, Huggett V: A comparison of rapid-sequence intubation and etomidate-only intubation in the prehospital air medical setting. *Prehosp Emerg Care* 2006; 10:8-13.
38. Naguib M, et al: The dose of succinylcholine required for excellent endotracheal intubating conditions. *Anesth Analg* 2006; 102:151-155.
39. Orebaugh SL: Difficult airway management in the emergency department. *J Emerg Med* 2002; 22:31-48.
40. Bair AE, Filbin MR, Kulkarni RG, Walls RM: The failed intubation attempt in the emergency department: Analysis of prevalence, rescue techniques, and personnel. *J Emerg Med* 2002; 23:131-140.
41. Neilipovitz DT, Crosby ET: No evidence for decreased incidence of aspiration after rapid sequence induction. *Can J Anaesth* 2007; 54:748-764.
42. Lawes EG, Campbell I, Mercer D: Inflation pressure, gastric insufflation and rapid sequence induction. *Br J Anaesth* 1987; 59:315-318.
43. Pace SA, Fuller FP: Out-of-hospital succinylcholine-assisted endotracheal intubation by paramedics. *Ann Emerg Med* 2000; 35:568-572.
44. Levitt MA, Dresden GM: The efficacy of esmolol versus lidocaine to attenuate the hemodynamic response to intubation in isolated head trauma patients. *Acad Emerg Med* 2001; 8:19-24.
45. Walls RM: *The decision to intubate*. In: Walls RM, Murphy MF, Luten RC, eds. *Manual of Emergency Airway Management*, 3rd ed. Philadelphia: Lippincott, Williams & Wilkins/Wolters Kluwer Health; 2008:1-8.
46. Mort TC, Waberski BH, Clive J: Extending the preoxygenation period from 4 to 8 mins in critically ill patients undergoing emergency intubation. *Crit Care Med* 2009; 37:68-71.
47. Nimmagadda U, et al: Efficacy of preoxygenation with tidal volume breathing. Comparison of breathing systems. *Anesthesiology* 2000; 93:693-698.
48. Baraka AS, Taha SK, Aouad MT, El-Khatib MF, Kawkabani NI: Preoxygenation: Comparison of maximal breathing and tidal volume breathing techniques. *Anesthesiology* 1999; 91:612-616.
49. Dixon BJ, et al: Preoxygenation is more effective in the 25 degrees head-up position than in the supine position in severely obese patients: A randomized controlled study. *Anesthesiology* 2005; 102:1110-1115.
50. Ramachandran SK, Cosnowski A, Shanks A, Turner CR: Apneic oxygenation during prolonged laryngoscopy in obese patients: A randomized, controlled trial of nasal oxygen administration. *J Clin Anesth* 2010; 22:164-168.
51. Maslow AD, et al: Inhaled albuterol, but not intravenous lidocaine, protects against intubation-induced bronchoconstriction in asthma. *Anesthesiology* 2000; 93:1198-1204.
52. Groeben H, Silvanus MT, Beste M, Peters J: Both intravenous and inhaled lidocaine attenuate reflex bronchoconstriction but at different plasma concentrations. *Am J Respir Crit Care Med* 1999; 159:530-535.
53. Samaha T, Ravussin P, Claquin C, Ecoffey C: [Prevention of increase of blood pressure and intracranial pressure during endotracheal

www.ketabpezeshki.com 66485457-66963820

intubation in neurosurgery: Esmolol versus lidocaine]. *Ann Fr Anesth Reanim* 1996; 15:36-40.
54. Grover VK, Reddy GM, Kak VK, Singh S: Intracranial pressure changes with different doses of lignocaine under general anaesthesia. *Neurol India* 1999; 47:118-121.
55. Walls RM: *Rapid sequence intubation*. In: Walls RM, Murphy MF, Luten RC, eds. *Manual of Emergency Airway Management*, 3rd ed. Philadelphia: Lippincott, Williams & Wilkins/Wolters Kluwer Health; 2008:23-35.
56. Ellis DY, Harris T, Zideman D: Cricoid pressure in emergency department rapid sequence tracheal intubations: A risk-benefit analysis. *Ann Emerg Med* 2007; 50:653-665.
57. Sellick BA: Cricoid pressure to control regurgitation of stomach contents during induction of anaesthesia. *Lancet* 1961; 2:404-406.
58. Olsen JC, Gurr DE, Hughes M: Video analysis of emergency medicine residents performing rapid-sequence intubations. *J Emerg Med* 2000; 18:469-472.
59. Allman KG: The effect of cricoid pressure application on airway patency. *J Clin Anesth* 1995; 7:197-199.
60. Aoyama K, Takenaka I, Sata T, Shigematsu A: Cricoid pressure impedes positioning and ventilation through the laryngeal mask airway. *Can J Anaesth* 1996; 43:1035-1040.
61. Kopka A, Crawford J: Cricoid pressure: A simple, yet effective biofeedback trainer. *Eur J Anaesthesiol* 2004; 21:443-447.
62. Smith KJ, Dobranowski J, Yip G, Dauphin A, Choi PT: Cricoid pressure displaces the esophagus: An observational study using magnetic resonance imaging. *Anesthesiology* 2003; 99:60-64.
63. Roppolo LP, et al: Nasotracheal intubation in the emergency department, revisited. *J Emerg Med* 1999; 17:791-799.
64. Kirkegaard-Nielsen H, Caldwell JE, Berry PD: Rapid tracheal intubation with rocuronium: A probability approach to determining dose. *Anesthesiology* 1999; 91:131-136.
65. Sagarin MJ, et al: Rapid sequence intubation for pediatric emergency airway management. *Pediatr Emerg Care* 2002; 18:417-423.
66. Naguib M, Lien C: *Pharmacology of muscle relaxants and their antagonists*. In: Miller RD, ed. Miller's Anesthesia, 6th ed, vol 2. Philadelphia: Elsevier/Churchill Livingstone; 2005:481-572.
67. Naguib M, Samarkandi A, Riad W, Alharby SW: Optimal dose of succinylcholine revisited. *Anesthesiology* 2003; 99:1045-1049.
68. Rose JB, Theroux MC, Katz MS: The potency of succinylcholine in obese adolescents. *Anesth Analg* 2000; 90:576-578.
69. Lemmens HJ, Brodsky JB: The dose of succinylcholine in morbid obesity. *Anesth Analg* 2006; 102:438-442.
70. Schreiber JU, Lysakowski C, Fuchs-Buder T, Tramèr MR: Prevention of succinylcholine-induced fasciculation and myalgia: A meta-analysis of randomized trials. *Anesthesiology* 2005; 103:877-884.
71. Gronert GA: Cardiac arrest after succinylcholine: mortality greater with rhabdomyolysis than receptor upregulation. *Anesthesiology* 2001; 94:523-529.
72. Martyn JA, Richtsfeld M: Succinylcholine-induced hyperkalemia in acquired pathologic states: Etiologic factors and molecular mechanisms. *Anesthesiology* 2006; 104:158-169.
73. Pang YL, Tseng FL, Tsai YC, Liu YC: Suxamethonium-induced hyperkalaemia in a patient with a normal potassium level before rapid-sequence intubation. *Crit Care Resusc* 2006; 8:213-214.
74. Osta WA, et al: Nicotinic acetylcholine receptor gene expression is altered in burn patients. *Anesth Analg* 2010; 110:1355-1359.
75. Schow AJ, Lubarsky DA, Olson RP, Gan TJ: Can succinylcholine be used safely in hyperkalemic patients? *Anesth Analg* 2002; 95:119-122.
76. Vachon CA, Warner DO, Bacon DR: Succinylcholine and the open globe. Tracing the teaching. *Anesthesiology* 2003; 99:220-223.
77. Zhou J, Allen PD, Pessah IN, Naguib M: *Neuromuscular disorders and malignant hyperthermia*. In: Miller RD, ed. *Miller's Anesthesia*, 7th ed. Philadelphia: Elsevier/Churchill Livingstone; 2010:1171-1196.
78. Patanwala AE, Stahle SA, Sakles JC, Erstad BL: Comparison of succinylcholine and rocuronium for first-attempt intubation success in the emergency department. *Acad Emerg Med* 2011; 18:10-14.
79. Perry JJ, Lee J, Wells G: Are intubation conditions using rocuronium equivalent to those using succinylcholine? *Acad Emerg Med* 2002; 9:813-823.
80. Sivilotti ML, et al: Does the sedative agent facilitate emergency rapid sequence intubation? *Acad Emerg Med* 2003; 10:612-620.
81. Weiss-Bloom LJ, Reich DL: Haemodynamic responses to tracheal intubation following etomidate and fentanyl for anaesthetic induction. *Can J Anaesth* 1992; 39:780-785.
82. Caro DA, Tyler KR: *Sedative induction agents*. In: Walls RM, Murphy MF, Luten RC, eds. *Manual of Emergency Airway Management*, 3rd ed. Philadelphia: Lippincott, Williams & Wilkins/Wolters Kluwer Health; 2008:234-247.
83. Annane D: ICU physicians should abandon the use of etomidate! *Intensive Care Med* 2005; 31:325-326.
84. Jackson WL Jr: Should we use etomidate as an induction agent for endotracheal intubation in patients with septic shock? A critical appraisal. *Chest* 2005; 127:1031-1038.
85. Walls RM, Osborn TM: Special report: Should etomidate be used as an induction agent for patients with sepsis? *J Watch Emerg Med [online]*, 2008; 12(2).
86. Albert SG, Ariyan S, Rather A: The effect of etomidate on adrenal function in critical illness: A systematic review. *Intensive Care Med* 2011; 37:901-910.
87. Annane D, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862-871.
88. Lipiner-Friedman D, et al: Adrenal function in sepsis: The retrospective Corticus cohort study. *Crit Care Med* 2007; 35:1012-1018.
89. Dmello D, Taylor S, O'Brien J, Matuschak GM: Outcomes of etomidate in severe sepsis and septic shock. *Chest* 2010; 138:1327-1332.
90. Riché FC, et al: Adrenal response in patients with septic shock of abdominal origin: Relationship to survival. *Intensive Care Med* 2007; 33:1761-1766.
91. Ray DC, McKeown DW: Effect of induction agent on vasopressor and steroid use, and outcome in patients with septic shock. *Crit Care* 2007; 11:R56.
92. Tekwani KL, et al: A comparison of the effects of etomidate and midazolam on hospital length of stay in patients with suspected sepsis: A prospective, randomized study. *Ann Emerg Med* 2010; 56:481-489.
93. Jabre P, et al: Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: A multicentre randomised controlled trial. *Lancet* 2009; 374:293-300.
94. Dellinger RP, et al: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med* 2008; 34:17-60.
95. Sprung CL, et al: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358:111-124.
96. Walls RM, Murphy MF: Clinical controversies: etomidate as an induction agent for endotracheal intubation in patients with sepsis: Continue to use etomidate for intubation of patients with septic shock. *Ann Emerg Med* 2008; 52:13-14.
97. Albanèse J, et al: Ketamine decreases intracranial pressure and electroencephalographic activity in traumatic brain injury patients during propofol sedation. *Anesthesiology* 1997; 87:1328-1334.
98. Walls RM: Management of the difficult airway in the trauma patient. *Emerg Med Clin North Am* 1998; 16:45-61.
99. Bar-Joseph G, Guilburd Y, Tamir A, Guilburd JN: Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension. *J Neurosurg Pediatr* 2009; 4:40-46.
100. Sener S, Eken C, Schultz CH, Serinken M, Ozsarac M: Ketamine with and without midazolam for emergency department sedation in adults: A randomized controlled trial. *Ann Emerg Med* 2011; 57:109-114.
101. Murphy A, Campbell DE, Baines D, Mehr S: Allergic reactions to propofol in egg-allergic children. *Anesth Analg* 2011; 113:140-144.
102. Jalota L, et al: Prevention of pain on injection of propofol: Systematic review and meta-analysis. *BMJ* 2011; 342:d1110.
103. Shlamovitz GZ, Hawthorne T: Intravenous ketamine in a dissociating dose as a temporizing measure to avoid mechanical ventilation in adult patient with severe asthma exacerbation. *J Emerg Med* 2008; 41:492-494.
104. Adachi YU, Satomoto M, Higuchi H, Watanabe K: Fentanyl attenuates the hemodynamic response to endotracheal intubation more than the response to laryngoscopy. *Anesth Analg* 2002; 95:233-237.
105. Helfman SM, Gold MI, DeLisser EA, Herrington CA: Which drug prevents tachycardia and hypertension associated with tracheal intubation: Lidocaine, fentanyl, or esmolol? *Anesth Analg* 1991; 72:482-486.
106. Jagoda AS, Bruns JJ Jr: *Elevated intracranial pressure*. In: Walls RM, Murphy MF, Luten RC, eds. *Manual of Emergency Airway Management*, 4th ed. Philadelphia: Lippincott, Williams & Wilkins/Wolters Kluwer Health; 2012:395-366.
107. Crosby E: Airway management after upper cervical spine injury: What have we learned? *Can J Anaesth* 2002; 49:733-744.
108. Criswell JC, Parr MJ, Nolan JP: Emergency airway management in patients with cervical spine injuries. *Anaesthesia* 1994; 49:900-903.

www.ketabpezeshki.com 66485457-66963820

109. Santoni BG, et al: Manual in-line stabilization increases pressures applied by the laryngoscope blade during direct laryngoscopy and orotracheal intubation. *Anesthesiology* 2009; 110:24-31.
110. Manoach S, Paladino L: Laryngoscopy force, visualization, and intubation failure in acute trauma: Should we modify the practice of manual in-line stabilization? *Anesthesiology* 2009; 110:6-7.
111. Thiboutot F, Nicole PC, Trépanier CA, Turgeon AF, Lessard MR: Effect of manual in-line stabilization of the cervical spine in adults on the rate of difficult orotracheal intubation by direct laryngoscopy: A randomized controlled trial. *Can J Anaesth* 2009; 56:412-418.
112. Robitaille A, et al: Cervical spine motion during tracheal intubation with manual in-line stabilization: Direct laryngoscopy versus GlideScope videolaryngoscopy. *Anesth Analg* 2008; 106:935-941.
113. Turkstra TP, Craen RA, Pelz DM, Gelb AW: Cervical spine motion: A fluoroscopic comparison during intubation with lighted stylet, GlideScope, and Macintosh laryngoscope. *Anesth Analg* 2005; 101:910-915.
114. Walt B, et al: Tracheal intubation and cervical spine excursion: Direct laryngoscopy vs. intubating laryngeal mask. *Anaesthesia* 2001; 56:221-226.
115. Turkstra TP, Pelz DM, Shaikh AA, Craen RA: Cervical spine motion: A fluoroscopic comparison of Shikani Optical Stylet vs Macintosh laryngoscope. *Can J Anaesth* 2007; 54:441-447.
116. Turkstra TP, Pelz DM, Jones PM: Cervical spine motion: A fluoroscopic comparison of the Airtraq Laryngoscope versus the Macintosh laryngoscope. *Anesthesiology* 2009; 111:97-101.
117. Liu EH, Goy RW, Tan BH, Asai T: Tracheal intubation with videolaryngoscopes in patients with cervical spine immobilization: A randomized trial of the Airway Scope and the GlideScope. *Br J Anaesth* 2009; 103:446-451.
118. Maharaj CH, Buckley E, Harte BH, Laffey JG: Endotracheal intubation in patients with cervical spine immobilization: A comparison of Macintosh and Airtraq laryngoscopes. *Anesthesiology* 2007; 107:53-59.
119. Ng BS, Goy RW, Bain JA, Chen FG, Liu EH: The impact of manual in-line stabilisation on ventilation and visualisation of the glottis with the LMA CTrach: A randomised crossover trial. *Anaesthesia* 2009; 64:894-898.
120. Chong CL, Ware DN, Harris JH Jr: Is cervical spine imaging indicated in gunshot wounds to the cranium? *J Trauma* 1998; 44:501-502.
121. Haut ER, et al: Spine immobilization in penetrating trauma: More harm than good? *J Trauma* 2010; 68:115-120; discussion 120-121.
122. Kendrick DB, Monroe KW, Bernard DW, Tofil NM: Sedation after intubation using etomidate and a long-acting neuromuscular blocker. *Pediatr Emerg Care* 2009; 25:393-396.
123. Wane, MA, McDonnell M: Comparison of traditional versus video laryngoscopy in out-of-hospital tracheal intubation. *Prehosp Emerg Care* 2010; 14:278-282.
124. Jones PM, Loh FL, Youssef HN, Turkstra TP: A randomized comparison of the GlideRite(®) Rigid Stylet to a malleable stylet for orotracheal intubation by novices using the GlideScope(®). *Can J Anaesth* 2011; 58:256-261.
125. Turkstra TP, et al: The GlideScope-specific rigid stylet and standard malleable stylet are equally effective for GlideScope use. *Can J Anaesth* 2007; 54:891-896.
126. Cooper RM, Pacey JA, Bishop MJ, McCluskey SA: Early clinical experience with a new videolaryngoscope (GlideScope) in 728 patients. *Can J Anaesth* 2005; 52:191-198.
127. Tremblay MH, Williams S, Robitaille A, Drolet P: Poor visualization during direct laryngoscopy and high upper lip bite test score are predictors of difficult intubation with the GlideScope videolaryngoscope. *Anesth Analg* 2008; 106:1495-1500.
128. Aziz MF, et al: Routine clinical practice effectiveness of the GlideScope in difficult airway management: An analysis of 2,004 GlideScope intubations, complications, and failures from two institutions. *Anesthesiology* 2011; 114:34-41.
129. Bathory I, Frascarolo P, Kern C, Schoettker P: Evaluation of the GlideScope for tracheal intubation in patients with cervical spine immobilisation by a semi-rigid collar. *Anaesthesia* 2009; 64:1337-1341.
130. Cavus E, et al: The C-MAC videolaryngoscope: First experiences with a new device for videolaryngoscopy-guided intubation. *Anesth Analg* 2010; 110:473-477.
131. Brown CA 3rd, et al: Improved glottic exposure with the Video Macintosh Laryngoscope in adult emergency department tracheal intubations. *Ann Emerg Med* 2010; 56:83-88.
132. Komatsu R, Kamata K, Sessler DI, Ozaki M: Airway scope and Macintosh laryngoscope for tracheal intubation in patients lying on the ground. *Anesth Analg* 2010; 111:427-431.
133. Noppens RR, et al: Evaluation of the McGrath Series 5 videolaryngoscope after failed direct laryngoscopy. *Anaesthesia* 2010; 65:716-720.
134. Liu L, et al: Tracheal intubation of a difficult airway using Airway Scope, Airtraq, and Macintosh laryngoscope: A comparative manikin study of inexperienced personnel. *Anesth Analg* 2010; 110:1049-1055.
135. Greenland KB, Liu G, Tan H, Edwards M, Irwin MG: Comparison of the Levitan FPS scope and the single-use bougie for simulated difficult intubation in anaesthetised patients. *Anaesthesia* 2007; 62:509-515.
136. Asai T, Murao K, Tsutsumi T, Shingu K: Ease of tracheal intubation through the intubating laryngeal mask during manual in-line head and neck stabilisation. *Anaesthesia* 2000; 55:82-85.
137. Hagberg CA, et al: A multicenter study of the Ambu laryngeal mask in nonparalyzed, anesthetized patients. *Anesth Analg* 2005; 101:1862-1866.
138. Brimacombe JR, Berry A: The incidence of aspiration associated with the laryngeal mask airway: A meta-analysis of published literature. *J Clin Anesth* 1995; 7:297-305.
139. Choyce A, et al: A comparison of the intubating and standard laryngeal mask airways for airway management by inexperienced personnel. *Anaesthesia* 2001; 56:357-360.
140. Timmermann A, et al: Novices ventilate and intubate quicker and safer via intubating laryngeal mask than by conventional bag-mask ventilation and laryngoscopy. *Anesthesiology* 2007; 107:570-576.
141. Timmermann A, et al: Prospective clinical and fiberoptic evaluation of the Supreme laryngeal mask airway. *Anesthesiology* 2009; 110:262-265.
142. Castle N, Owen R, Hann M, Naidoo R, Reeves D: Assessment of the speed and ease of insertion of three supraglottic airway devices by paramedics: A manikin study. *Emerg Med J* 2010; 27:860-863.
143. Wharton NM, et al: I-gel insertion by novices in manikins and patients. *Anaesthesia* 2008; 63:991-995.
144. Joo HS, Rose DK: The intubating laryngeal mask airway with and without fiberoptic guidance. *Anesth Analg* 1999; 88:662-666.
145. Baskett PJ, Parr MJ, Nolan JP: The intubating laryngeal mask. Results of a multicentre trial with experience of 500 cases. *Anaesthesia* 1998; 53:1174-1179.
146. Langeron O, Semjen F, Bourgain JL, Marsac A, Cros AM: Comparison of the intubating laryngeal mask airway with the fiberoptic intubation in anticipated difficult airway management. *Anesthesiology* 2001; 94:968-972.
147. Combes X, et al: Intubating laryngeal mask airway in morbidly obese and lean patients: A comparative study. *Anesthesiology* 2005; 102:1106-1109.
148. Kundra P, Sujata N, Ravishankar M: Conventional tracheal tubes for intubation through the intubating laryngeal mask airway. *Anesth Analg* 2005; 100:284-288.
149. Liu EH, Goy RW, Lim Y, Chen FG: Success of tracheal intubation with intubating laryngeal mask airways: A randomized trial of the LMA Fastrach and LMA CTrach. *Anesthesiology* 2008; 108:621-626.
150. Maurtua MA, Maurtua DB, Zura A, Doyle DJ: Improving intubation success using the CTrach Laryngeal Mask Airway. *Anesthesiology* 2007; 106:640-641.
151. Parmet JL, et al: The laryngeal mask airway reliably provides rescue ventilation in cases of unanticipated difficult tracheal intubation along with difficult mask ventilation. *Anesth Analg* 1998; 87:661-665.
152. McCaul CL, et al: Airway management in the lateral position: A randomized controlled trial. *Anesth Analg* 2005; 101:1221-1225.
153. Katz SH, Falk JL: Misplaced endotracheal tubes by paramedics in an urban emergency medical services system. *Ann Emerg Med* 2001; 37:32-37.
154. Hoyle JD Jr, Jones JS, Deibel M, Lock DT, Reischman D: Comparative study of airway management techniques with restricted access to patient airway. *Prehosp Emerg Care* 2007; 11:330-336.
155. Lefrancois DP, Dufour DG: Use of the esophageal tracheal Combitube by basic emergency medical technicians. *Resuscitation* 2002; 52:77-83.
156. Mort TC: Laryngeal mask airway and bougie intubation failures: The Combitube as a secondary rescue device for in-hospital emergency airway management. *Anesth Analg* 2006; 103:1264-1266.
157. Russi CS, Miller L, Hartley MJ: A comparison of the King-LT to endotracheal intubation and Combitube in a simulated difficult airway. *Prehosp Emerg Care* 2008; 12:35-41.
158. Russi CS, Wilcox CL, House HR: The laryngeal tube device: A simple and timely adjunct to airway management. *Am J Emerg Med* 2007; 25:263-267.
159. Burns JB Jr, Branson R, Barnes SL, Tsuei BJ: Emergency airway placement by EMS providers: Comparison between the King LT

www.ketabpezeshki.com 66485457-66963820

supralaryngeal airway and endotracheal intubation. *Prehosp Disaster Med* 2010; 25:92-95.
160. Vissers RJ, Bair AE: *Surgical airway techniques*. In: Walls RM, Murphy MF, Luten RC, eds. *Manual of Emergency Airway Management*, 4th ed. Philadelphia: Lippincott, Williams & Wilkins/Wolters Kluwer Health; 2012:193-219.
161. Wong DT, Prabhu AJ, Coloma M, Imasogie N, Chung FF: What is the minimum training required for successful cricothyroidotomy? A study in mannequins. *Anesthesiology* 2003; 98:349-353.
162. Schaumann N, et al: Evaluation of Seldinger technique emergency cricothyroidotomy versus standard surgical cricothyroidotomy in 200 cadavers. *Anesthesiology* 2005; 102:7-11.
163. Schober P, Hegemann MC, Schwarte LA, Loer SA, Noetges P: Emergency cricothyrotomy—a comparative study of different techniques in human cadavers. *Resuscitation* 2009; 80:204-209.
164. Hill C, Reardon R, Joing S, Falvey D, Miner J: Cricothyrotomy technique using gum elastic bougie is faster than standard technique: A study of emergency medicine residents and medical students in an animal lab. *Acad Emerg Med* 2010; 17:666-669.
165. Barton ED, et al: What is a complication? Classifying events during emergency intubations. *Acad Emerg Med* 1999; 6:506-507.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 2

MECHANICAL VENTILATION AND NONINVASIVE VENTILATORY SUPPORT

Todd A. Seigel

PERSPECTIVE

Invasive and noninvasive ventilation are essential components in the management of critically ill patients. Some patients require support for respiratory failure or as part of comprehensive management of critical illness, whereas other patients require assistance primarily for airway protection. The reasons for initiating ventilatory support are varied and will influence ventilation strategy, hemodynamics, sedation strategy, and subsequent clinical course.

The decision to intubate is discussed in Chapter 1 and in various other places throughout this textbook in the context of individual conditions. This chapter describes the modalities and techniques of noninvasive and invasive mechanical ventilation.

PRINCIPLES OF MECHANICAL VENTILATION

Physiology of Positive Pressure Breathing

Spontaneous breathing in normal patients is based on the initiation of negative intrathoracic pressure and is mediated by contraction and relaxation of the diaphragm. Contraction of the diaphragm decreases pressure in the chest cavity and results in inhalation, whereas relaxation of the diaphragm and recoil of the chest wall increase pressure in the chest cavity and result in passive exhalation. The amount of force required to generate adequate inspiration is influenced by the work of breathing; when work of breathing increases, patients may be unable to generate enough negative force to sustain successful respiration and will require ventilatory support. Unlike spontaneous breathing, both invasive and noninvasive mechanical ventilation are based on the delivery of humidified air with positive pressure. The amount of positive pressure required for adequate ventilation is dependent on the patient's respiratory effort, ranging from mild assistance to full support. "Inhalation" occurs by driving air into the lungs under positive pressure; air is passively exhaled owing to chest wall recoil.

Transition from negative pressure breathing to positive pressure breathing affects cardiovascular and pulmonary physiology and can have significant clinical consequences. Pressure changes in the thoracic cavity directly affect pressures in the chambers of the heart. During spontaneous inspiration, venous return and preload are augmented, cardiac output is increased, and there is an increased pressure gradient between the left ventricle and the aorta. With the initiation of positive-pressure ventilation (PPV), venous return is diminished, cardiac output falls, and there is a decreased pressure gradient between the left ventricle and the aorta.[1] Relative hypotension can occur after ventilatory support has been initiated, and this may be exaggerated in patients with clinical hypovolemia or vasodilatory states.[2]

Invasive Mechanical Ventilation

The primary considerations regarding initiation of mechanical ventilation relate to how each breath should be delivered. This includes how a "breath" is defined, how large it should be, how fast it should be delivered, how often it should be delivered, and how to manage the interaction of the patient with the ventilator.

How the ventilator defines a breath is referred to as the *control variable.* The ventilator can give breaths based on delivery of a set pressure or a set volume, referred to as *pressure-controlled ventilation* (PCV) and *volume-controlled ventilation* (VCV), respectively. The amount of time over which the breath is delivered is defined as the inspiratory time, and the rate at which air travels through the circuit is defined as inspiratory flow.

In PCV, a set amount of pressure is applied to the airway to expand the lungs. When the target pressure is reached, gas delivery ends and passive exhalation is permitted. During PCV, target pressure and inspiratory time are set, whereas the delivered tidal volume and inspiratory flow vary as functions of dynamic lung compliance and airway resistance. Ability to control the pressure delivered to the lungs is particularly useful to prevent barotrauma (see later). In addition, because inspiratory flow is not fixed, PCV may improve ventilator synchrony in intubated patients with a high respiratory drive. A significant disadvantage of PCV is that tidal volume cannot be guaranteed or limited and can change with acute changes in lung compliance. PCV offers advantages over VCV in clinical conditions in which control of airway pressure is strictly mandated. This includes patients with the potential to develop dynamic hyperinflation and intrinsic positive end-expiratory pressure (PEEP), such as patients with severe asthma or those with respiratory failure from chronic obstructive pulmonary disease (COPD).

In VCV a breath is defined by delivery of a set tidal volume to the lungs. Inspiratory flow is fixed, and inhalation ends when a preset tidal volume has been delivered; peak inspiratory pressures (PIPs) and end-inspiratory alveolar pressures vary based on lung compliance and set tidal volume. The main benefit to VCV is the ability to control tidal volume and minute ventilation, but it may be problematic by causing high peak pressures when the compliance of the respiratory system is poor. Clinically, poor respiratory system compliance occurs in conditions that increase lung or chest wall stiffness. Such conditions include pulmonary edema, acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), pneumothorax, and obesity.[3]

www.ketabpezeshki.com 66485457-66963820

Table 2-1 Features of Pressure Control versus Volume Control

	SET PARAMETERS	VARIABLE PARAMETERS	CLINICAL IMPLICATIONS	CLINICAL CONDITIONS
Pressure-controlled ventilation (PCV)	Peak pressure target, inspiratory time, RR, PEEP	Tidal volume, inspiratory flow	Controls airway pressure, but tidal volume becomes a function of lung compliance (no guaranteed tidal volume or minute ventilation) Allows estimation of end-inspiratory alveolar pressure based on ventilator settings Variable inspiratory flow helpful for patients with high respiratory drive	Severe asthma COPD Salicylate toxicity
Volume-controlled ventilation (VCV)	Tidal volume, RR, inspiratory flow pattern, inspiratory time	PIP, end-inspiratory alveolar pressure	Guaranteed delivery of tidal volume, but may result in high or injurious lung pressures End-inspiratory alveolar pressure cannot be reliably estimated and must be measured (plateau pressure)	Acute lung injury ARDS Obesity Severe burns

ARDS, acute respiratory distress syndrome; *COPD,* chronic obstructive pulmonary disease; *PIP,* peak inspiratory pressure; *PEEP,* positive-end expiratory pressure; *RR,* respiratory rate.

When a physician is choosing between pressure-cycled ventilation versus volume-cycled ventilation, it is important to consider the underlying reason for mechanical ventilation. Volume-cycled ventilation should be used when strict control of tidal volume is mandated. Specifically, this includes patients with known ALI or ARDS, in whom low–tidal volume strategies have been proven to reduce mortality.[4] In addition, patients with decreased chest wall compliance should be placed on VCV to ensure that adequate tidal volume is delivered. This includes patients with morbid obesity or severe chest wall burns. Conversely, in conditions in which strict control of airway pressure is desired, pressure-cycled ventilation should be used. As detailed earlier, this includes patients with asthma or COPD. In addition, because inspiratory flow is not limited in pressure-cycled ventilation, this strategy may be preferred to volume-cycled ventilation in patients with a high respiratory drive, such as patients with salicylate overdose. For patients who do not require strict control of either pressure or volume, similar ventilation mechanics can generally be achieved with either pressure-cycled or volume-cycled ventilation (Table 2-1).

Newer ventilators are able to deliver breaths that combine volume and pressure strategies, referred to as *dual-control ventilation.* A common dual-control method of ventilation is pressure-release volume control (PRVC). A variation of volume control, PRVC is set to deliver a specific tidal volume while simultaneously minimizing airway pressure. Unlike with strict volume control, pressure is measured and modulated by the ventilator with each breath to ensure the delivery of the preset tidal volume. In addition, a pressure limit is set, and the ventilator sounds an alarm when that pressure has been exceeded. Theoretically, this combines the advantages of pressure and volume control to ensure the delivery of a specific tidal volume while the airway pressure is monitored. That said, because the ventilator is set to deliver a specific tidal volume, the disadvantages of volume-cycled ventilation persist. In addition, elevations in airway pressure are still possible and must be addressed if acute changes in respiratory system compliance occur. This mode of ventilation has not been specifically studied but likely does not offer significant advantage over traditional volume- or pressure-cycled ventilation, particularly if strict parameters for airway pressure are desired.

Ventilator mode refers specifically to the amount of respiratory support provided by the ventilator but more commonly represents a combination of the type of breath to be given and the way the breath is to be initiated. The most common ventilator modes can be categorized on the basis of how often the ventilator will initiate a breath for the patient and can be divided broadly into continuous mechanical ventilation (CMV), intermittent mechanical ventilation (IMV), and continuous spontaneous ventilation (CSV).[5] CMV and IMV can be delivered via pressure-control or volume-control methods. In CSV, no mandatory breaths are delivered to a patient; the size of the breath is determined by the effort of the patient and can be augmented with applied pressure to the airway. These methods are compared in Table 2-2. Other, more complex modes of ventilation include proportional-assist ventilation (PAV) and airway pressure release ventilation (APRV), though these generally are not used in the emergency department (ED).

CMV is intended to provide full ventilatory support for patients with little or no spontaneous respiratory activity. CMV, also referred to as *assist-control* (A/C) ventilation, provides a preset number of breaths per minute. In addition to preset breaths, A/C will also deliver a breath in response to patient effort. In this mode, patients can trigger a breath at any rate but will always receive at least the preset number of breaths. Notably, when a patient initiates a breath, he or she receives the full breath as set on the ventilator. For the promotion of ventilator synchrony, a spontaneous patient-initiated breath will take priority over a preset breath, meaning that if the ventilator is set to deliver 12 breaths/min, a breath is provided every 5 seconds in the absence of spontaneous inspiratory effort. When the patient makes a spontaneous effort, the ventilator provides an additional breath and the timer resets for another 5 seconds. A/C ventilation is the most useful initial mode of mechanical ventilation in ED patients, as many patients are initially paralyzed and sedated and do not interact with the ventilator. One of the biggest challenges with A/C ventilation, however, is that patient-initiated breaths are not proportional to patient effort; when inspiratory effort is detected, a full-sized breath is delivered. Clinically, this requires adequate sedation of patients when ventilated in A/C mode to prevent spontaneous respiratory efforts that will result in hyperventilation, air trapping, hypotension, and poor ventilator synchrony.[6]

Synchronized intermittent mandatory ventilation (SIMV) provides intermittent ventilatory support to patients by delivering both mandatory and spontaneous breaths. In SIMV, a mandatory breath is given at a preset rate, but the breath is synchronized as much as possible with spontaneous patient effort. Much as with A/C, the patient will receive at least the minimum number of preset mandatory breaths; if the patient provides no effort, the preset number of breaths will be given. If a patient has a rate of spontaneous respirations *lower* than the set rate, the ventilator will provide the preset number of full breaths but will deliver as many as possible in synchrony with patient effort. In these scenarios there is little difference between A/C and SIMV. If a patient has a

www.ketabpezeshki.com 66485457-66963820

Table 2-2 Selecting Ventilator Strategy: Features of Potential Options

MODE	PARAMETERS SET BY PROVIDER	CLINICAL SCENARIO
Continuous Mechanical Ventilation (CMV)		
Assist-control (A/C)	Pressure or volume control, RR	Paralyzed or deeply sedated patient, sedated patients with intermittent spontaneous respiratory effort; can lead to hyperventilation
Intermittent Mandatory Ventilation (IMV)		
Synchronized intermittent mandatory ventilation (SIMV)	Pressure or volume control, RR (backup rate)	Patients with regular but poor spontaneous respiratory effort; if used in deeply sedated patients, set RR will need to be higher
Continuous Spontaneous Ventilation (CSV)		
Pressure-support ventilation (PSV)	Level of pressure support, PEEP	Spontaneously breathing patients with good respiratory effort requiring minimal ventilatory support
Continuous positive airway pressure (CPAP)	Level of CPAP	Alert, spontaneously breathing patients with immediately reversible causes of respiratory distress; COPD and ACPE are classic indications for noninvasive ventilation
Bi-level positive airway pressure (BL-PAP)	IPAP and EPAP	Similar to CPAP

ACPE, acute cardiogenic pulmonary edema; *COPD,* chronic obstructive pulmonary disease; *EPAP,* expiratory positive airway pressure; *IPAP,* inspiratory positive airway pressure; *PEEP,* positive end-expiratory pressure; *RR,* respiratory rate.

rate of spontaneous respirations *higher* than preset rate, the patient receives all preset full breaths at the set rate, but additional breaths generated by the patient will be commensurate with his or her respiratory effort. Additional breaths can be given via pressure support (see later). SIMV is useful in patients who are sedated but who have weak respiratory efforts and combats some of the challenges of using A/C in awake patients. Delivery of extra breaths consistent with patient respiratory effort attenuates the effects of air trapping and hyperventilation and may promote patient comfort.

CSV, in contrast to A/C or SIMV, delivers a breath only on patient-initiated trigger. Pressure-support ventilation (PSV) is designed to support patients' spontaneous respiratory effort by delivering an applied pressure to the airway on the trigger of a breath. The amount of pressure required to support a full breath is variable and depends on the patient's ability to overcome the work of breathing. When inspiratory flow stops, signaling the end of inhalation, pressure support ceases and exhalation is allowed to proceed spontaneously. The level of pressure support is the only parameter determined by ventilator settings: inspiratory flow, inspiratory time, and tidal volume are determined by the patient effort. This mode of ventilation most closely resembles normal spontaneous breathing and for this reason promotes patient control and comfort. In the ED, PSV is rarely used for intubated patients because most patients who require intubation are unable to effectively breathe spontaneously and may have failed noninvasive support before intubation. PSV may prove most useful in awake and interactive patients who have been intubated for temporary airway protection rather than for respiratory failure. If PSV is used, careful monitoring and ventilatory alarms are needed to ensure against undetected hypoventilation or apnea.

Positive End-Expiratory Pressure

Regardless of the ventilatory mode chosen, PEEP is often used during invasive mechanical ventilation. *PEEP* refers to the maintenance of positive airway pressure after the completion of passive exhalation. During acute respiratory failure, lung volumes are typically decreased; application of PEEP increases functional residual capacity (FRC), improves oxygenation, and decreases intrapulmonary shunt. Use of PEEP also reduces portions of nonaerated lung that may contribute to the development of ventilator-induced lung injury[7] Notably, PEEP increases both intrapulmonary and intrathoracic pressure and may affect pulmonary and cardiovascular physiology. Potential adverse effects of PEEP include decreased cardiac output, lung overdistention, and pneumothorax.

Applied PEEP must be differentiated from *intrinsic* PEEP (iPEEP, or auto-PEEP), which may result from improper assisted ventilation when adequate time is not allowed between breaths for complete exhalation. This circumstance is discussed later.

Noninvasive Techniques

Noninvasive positive-pressure ventilation (NPPV) is the delivery of CSV via sealed mask rather than endotracheal tube. As with PSV, the ventilator is set to provide a defined level of pressure when a patient takes a breath; inspiratory flow and inspiratory time are completely patient mediated. The most common types of noninvasive ventilation in the ED are continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BL-PAP). BiPAP, a term commonly used for BL-PAP, is the proprietary name of a portable device that uses this method of noninvasive ventilation rather than a term for the ventilation itself (Philips Respironics, Murrysville, Pa.). CPAP provides constant positive pressure throughout the respiratory cycle, whereas BL-PAP alternates between higher pressure during inspiration (IPAP) and lower pressure during expiration (EPAP). Although, strictly speaking, CPAP applies positive pressure to the airway during inspiration, the amount of inspiratory assistance is minimal. Conversely, just as with invasive mechanical ventilation, IPAP augments patient respiratory effort by decreasing the work of breathing during inspiration, whereas EPAP acts as PEEP to maintain FRC and alveolar recruitment. Notably, although PEEP, CPAP, and EPAP all represent positive airway pressure at the end of expiration, PEEP by convention refers to pressure applied during invasive mechanical ventilation, whereas CPAP is the application of positive pressure (invasively or noninvasively) during spontaneous breathing. The terms are occasionally used interchangeably.

MANAGEMENT

General Approach: Noninvasive versus Invasive Ventilation

The decision to intubate carries significant implications for patients, including potentially life-threatening complications related to airway management and subsequent complications related to intensive care unit (ICU) care.[8] NPPV is an appealing option for patients requiring ventilatory assistance with potentially reversible conditions when tracheal intubation is not immediately necessary, or as a therapeutic adjunct for patients with "do-not-intubate" directives.[9,10] In appropriately selected patients,

www.ketabpezeshki.com 66485457-66963820

NPPV obviates intubation in greater than 50% of cases and improves survival.[8,11] Need for emergency intubation is a contraindication to NPPV, except as a means to improve preoxygenation in preparation for intubation. Other relative contraindications include decreased level of consciousness, lack of respiratory drive, increased secretions, hemodynamic instability, and conditions, such as facial trauma, that would prevent an adequate mask seal.[12,13] If NPPV is initiated, patients should be reassessed frequently for progress of therapy, tolerance of the mode of support, and any signs of clinical deterioration that indicate a need for intubation.

Patients most likely to respond to NPPV in the ED are those with more readily reversible causes of their distress, such as COPD exacerbation or cardiogenic pulmonary edema in which fatigue is a significant factor. Robust evidence suggests benefit of NPPV for both conditions. In patients with acute COPD exacerbations, NPPV decreases the need for subsequent intubation, hospital length of stay, and mortality when compared with standard therapy. Notably, though helpful in most patients with COPD exacerbation, NPPV has been shown to have the largest benefit for patients with hypercapnic acidosis and pH below 7.3.[14-17] Treatment failure, defined as subsequent need for intubation, is predicted by a Glasgow Coma Scale score of less than 11, a sustained arterial pH less than 7.25, and tachypnea greater than 30 breaths/min.[18]

In patients with acute cardiogenic pulmonary edema (ACPE), NPPV reduces the work of breathing while simultaneously improving cardiac output; application of NPPV causes elevations in intrathoracic pressure that decrease both left ventricular (LV) ejection pressure and LV transmural pressure. This results in afterload reduction. In addition, decreases in RV preload may improve LV compliance via ventricular interdependence.[1-3,19,20] Compared with standard therapy, multiple studies and several meta-analyses have confirmed decreased need for intubation as well as decreased mortality for patients with ACPE treated with NPPV. Benefits were independent of whether patients received CPAP or BL-PAP, and despite suggestions from early clinical data, no increased rate of acute myocardial infarction occurred in patients receiving any form of NPPV.[21-24] Though either modality can be used, a recent ED-based study suggested faster clinical improvement with BL-PAP.[25] Specific predictors of failure of NPPV in congestive heart failure (CHF) have not been systematically examined.

Use of NPPV in other patients with respiratory compromise, including asthma and pneumonia, is not well studied, though limited preliminary data suggest that NPPV may be beneficial for patients with acute asthma exacerbations.[26-28] Studies have failed to establish a role for NPPV in pneumonia. Although no data suggest harm from NPPV, the presence of pneumonia has been shown to be an independent risk factor for failure of noninvasive ventilation.[29-32]

Approach to Initial Ventilator Settings

Initial settings for noninvasive ventilation should be determined by the amount of ventilatory assistance required by the patient, as well as patient comfort and cooperation with the therapy. The first consideration in the use of NPPV is whether to provide support in the form of CPAP or BL-PAP. This was discussed earlier, and there is no clear benefit of one over the other. Support will be given by a full-face (oronasal) mask or nasal mask; this choice is determined by patient comfort, feelings of claustrophobia, and the need for the patient to effectively cough or speak. Inspiratory support (IPAP) can be initiated at 10 cm H_2O, and expiratory support (EPAP) can be initiated at 5 cm H_2O. Subsequent titration of these parameters is based on the patient's clinical response, particularly pressure tolerance, respiratory rate, and oxyhemoglobin saturation. Though blood gas analysis is confirmatory, improvement in clinical condition can be observed by decrease in work of breathing, good patient-ventilator synchrony, and patient report. If required, EPAP and IPAP can be adjusted by 1 to 2 cm H_2O at a time based on clinical response.[12] If work of breathing is unchanged, increases in IPAP and EPAP reduce hypercarbia by increasing tidal volume and minute ventilation while increasing oxygenation by combating atelectasis and promoting alveolar recruitment. IPAP greater than 20 cm H_2O can be uncomfortable and can cause gastric insufflation and should be avoided.[12,33]

For the intubated patient, initial ventilator settings should facilitate ventilation that improves gas exchange, promotes ventilatory synchrony, and minimizes the potential for complications. For an apneic or paralyzed patient, full ventilatory support is required; for this reason, A/C is the recommended mode of initial ventilation. Specific required settings depend on whether the patient is receiving PCV or VCV, but the principles underlying selection of settings are similar. Reasonable initial ventilator settings should deliver a tidal volume of 6 to 8 mL/kg of estimated ideal body weight (IBW) at rate of 12 to 14 breaths/min. If VCV is used, tidal volume can be set directly, and if PCV is used, tidal volume is determined by adjusting the targeted pressure to be delivered; initial pressure targets should not exceed 30 cm H_2O. Initial FiO_2 should be set at 1.0 but generally can be adjusted down quickly to maintain an oxygen saturation of 90% or greater. PEEP is routinely given and is set initially at 5 cm H_2O.[6] Settings for specific clinical conditions, such as status asthmaticus, are discussed later.

Ongoing Management

Mechanical ventilation requires monitoring and regular adjustment to ensure appropriate gas exchange, safe delivery of desired tidal volume, and prevention of metabolic derangement. Changes to ventilator settings are guided dynamically by multiple factors, including pulse oximetry, end-tidal carbon dioxide ($ETCO_2$) monitoring, ventilation pressures, and blood gases. For the adequacy of ventilation to be monitored, capnography may be used; arterial blood gases should be measured 15 to 20 minutes after initiation of ventilatory support to correlate $ETCO_2$ with PCO_2. Notably, venous blood gases generally correlate well with pH and PCO_2 of arterial samples,[34,35] though this correlation may be unreliable in critically ill patients.[36,37] Although there is variation in agreement between capnography and blood gas values, capnography generally correlates well with PCO_2 of arterial samples and may be useful for ventilator adjustment after initial correlation has been established.[38-41] In the event of uncertainty, arterial blood gases remain the definitive test for evaluating PaO_2 and PCO_2. Minute ventilation can subsequently be altered by adjusting tidal volume or respiratory rate. To avoid oxygen toxicity, FiO_2 should be reduced to the lowest level that provides acceptable (>90%) oxygen saturation. In many instances, increases in PEEP will allow better oxygenation for a given FiO_2 but may worsen hypotension or increase intrathoracic pressure.

Maintenance of adequate gas exchange is the primary goal of invasive ventilation, but other clinically relevant data are derived from the ventilator once a course of ventilation has been set. Pressures in the ventilator circuit and the lungs reflect potentially detrimental complications of ventilation. PIP and plateau pressure (Pplat) are the main measurements of pressure during ventilation. PIP, sometimes referred to as *peak airway pressure,* measures the maximum amount of pressure in the ventilator circuit during a breath cycle. It reflects lung compliance and airway resistance, including resistance in the circuit itself. In PCV, because pressure limits are preset, PIP can be estimated as the sum of the set pressure target and PEEP. PIP also generally reflects the amount of pressure in the alveoli at the end of inspiration, an important determinant in the development of ventilator-induced lung injury

www.ketabpezeshki.com 66485457-66963820

(VILI). In VCV, PIP is influenced greatly by airway resistance and therefore is not reflective of end-inspiratory alveolar pressure. Alveolar pressure at end inspiration in VCV is approximated by the Pplat. The respiratory therapist can measure the Pplat with the ventilator at the end of inspiration by means of an "inspiratory hold."

Acute increases in PIP indicate increased airway resistance or changes in compliance of the respiratory system (such as those associated with pneumothorax) and can indicate potentially dangerous clinical deterioration. Decreases in PIP, conversely, indicate decreased resistance or decreased air flow in the ventilatory circuit and should prompt investigation of the ventilator circuit for leaks. Large or sudden decreases in PIP suggest disconnection of the ventilator circuit or unintended extubation. For patients with underlying respiratory failure secondary to increased airway resistance, such as in asthma or COPD, more gradual decreases in PIP are associated with clinical improvement.

Other Management Considerations

Aside from specific ventilator management, considerations in the care of the intubated patient include analgesia and sedation, potential neuromuscular paralysis, and secretion management. After intubation, the primary goals of care in the ED are sustained effective ventilation and patient comfort. Intubation causes pain and anxiety for patients, and both analgesia and sedation are required to promote patient comfort and patient-ventilator synchrony.[42] In initiating sedation (see later), sedation should be titrated to comfort and therapeutic goals while avoiding both oversedation and undersedation. Desired level of sedation will differ based on patient tolerance and the clinical scenario: assuming comfort is maintained, lighter sedation may be useful in patients requiring serial neurologic examinations, whereas deep sedation maybe more beneficial for patients with severe hypoxemia or ventilator dyssynchrony. Several clinical scales have been established for this purpose; the reliability of the Richmond Agitation-Sedation Scale (RASS) has been validated in multiple studies.[43,44] Sedation should be maintained at the highest RASS score at which the patient is comfortable (between 0 and −5) and should be serially readdressed. Any paralyzed patient should remain deeply sedated (Table 2-3).

Table 2-3 The Richmond Agitation-Sedation Scale (RASS)

SCORE	TERM	DESCRIPTION
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s), aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious, but movements not aggressive or vigorous
0	Calm	Alert and calm
−1	Drowsy	Not fully alert, but has sustained awakening (>10 sec)
−2	Light sedation	Briefly awakens with eye contact to voice (<10 sec)
−3	Moderate sedation	Movement or eye opening to voice but no eye contact
−4	Deep sedation	No response to voice but movement or eye opening with physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Adapted from Ely EW, et al: Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA* 2003; 289:2983-2991.

After rapid sequence intubation, additional neuromuscular blocking agents (NBMAs) should generally be used only when poor ventilator synchrony interferes with ventilation sedation and analgesia. This may be particularly true in patients with ARDS, in whom the use of NMBAs has been associated with shorter duration of ventilation and improved mortality.[45] With proper sedation and analgesia, however, neuromuscular blockade usually is not required. If needed, longer-acting agents such as rocuronium and vecuronium should be used; note that impaired hepatic or renal function may increase duration of paralysis.

Analgesia is achieved by generous doses of opioid medications; fentanyl and morphine remain the most commonly used agents for analgesia in critically ill patients.[46] Opioids are associated with dose-dependent respiratory depression, a side effect that may be particularly beneficial for patients experiencing ventilator dyssynchrony. Both morphine and fentanyl can be used for analgesia, though dosage requirements will vary based on tolerance and drug metabolism. Sedation and analgesia should therefore be titrated with a standard sedation scale, as discussed earlier. Notably, the active metabolite of morphine (morphine-6-glucuronide) is renally cleared and has potent sedative effects. For this reason, fentanyl may be preferred in patients with renal insufficiency. Remifentanil is an ultra-short-acting opiate that is metabolized by nonspecific plasma esterases. The predictable metabolism and short half-life of remifentanil make it an emerging choice for sedation, and ICU data demonstrate decreased duration of ventilation with remifentanil compared with morphine when used for analgesia in the ICU.[47]

Sedation after intubation can be accomplished via multiple pharmacologic modalities, and though there are limited data about ED sedation practices, lorazepam and midazolam are the most commonly used agents in the ICU.[46] Benzodiazepines exert dose-dependent clinical effects by binding γ-aminobutyric acid (GABA) receptors, first producing anxiolysis, then sedation and hypnosis.[48] Benzodiazepines also cause respiratory depression, which is potentiated by concomitant opioid administration. For this reason, a sedation regimen of both opioids and benzodiazepines may improve ventilator dyssynchrony while providing an anxiolytic and amnestic effect. Benzodiazepines can be administered either as repeated boluses or by continuous infusion, though in critically ill patients, benzodiazepines have altered pharmacokinetics that result in tissue accumulation and prolonged sedation. This is particularly true in obese patients and in patients with renal or hepatic insufficiency.[49-53] For this reason, sedation with benzodiazepines should be attempted with intermittent bolus administration before a continuous infusion is used.

Similar to benzodiazepines, propofol binds to the GABA receptor to induce sedation. Propofol is lipophilic, and the ability of the drug to rapidly penetrate the blood-brain barrier and distribute into peripheral tissues is responsible for both the rapidity and the short duration of clinical effect.[54] Unlike benzodiazepines, the clearance of propofol is minimally affected in critically ill patients. In addition, propofol can precipitate hypotension by increasing venous capacitance, a side effect that is exaggerated in hypovolemic patients. For these reasons, propofol should be given as an infusion rather than as a bolus, initiated at low doses (0.1 mg/kg/min) and titrated to desired level of sedation. In comparison to benzodiazepines, continuous infusions of propofol have been demonstrated to decrease duration of mechanical ventilation,[55,56] suggesting that propofol may confer benefit when compared with benzodiazepines in the sedation regimen for mechanically ventilated patients.

www.ketabpezeshki.com 66485457-66963820

Other medications for the sedation of ventilated patients in the ED include dexmedetomidine and haloperidol. Dexmedetomidine is a centrally acting $alpha_2$-agonist with sedative and analgesic properties, largely distinguished from other sedative agents by a negligible impact on respiratory drive, even with simultaneous opioid administration. It is administered as a loading dose followed by a continuous infusion and can precipitate bradycardia and relative hypertension.[57] Studies have demonstrated dexmedetomidine to be beneficial in facilitating use of noninvasive ventilation, as well as awake fiberoptic intubations.[58-60] When dexmedetomidine was compared with continuous infusion of midazolam, a large, multicenter evaluation demonstrated that dexmedetomidine was associated with shorter duration of mechanical ventilation, as well as decreased sedation-associated delirium.[61] Although not systematically studied in the ventilated ED patients, dexmedetomidine is an emerging alternative for sedation strategy for critically ill patients and may be considered as an alternative to traditional modalities in clinical settings in which agitation or anxiety limit therapeutic goals.

Haloperidol, commonly used as a sedative for agitated patients, can also be used as an adjunct to traditional sedation regimens in mechanically ventilated patients. The use of haloperidol may be particularly useful in patients who remain acutely agitated after large doses of other sedative medications, especially because it does not affect hemodynamics. Recent limited data have suggested a mortality benefit for mechanically ventilated patients who receive haloperidol, though this requires further study.[62] Notably, however, haloperidol does not have any analgesic or amnestic properties and cannot be used as a single therapy for sedation in critically ill patients.

Other ED considerations in the care of the ventilated patient include secretion management and steps to reduce potential ventilator-associated pneumonia (VAP). Management of secretions is achieved via regular endotracheal suctioning, recognizing a balance between secretion clearance and the disruption of ventilation. In addition, a nasogastric or orogastric tube should be placed for gastrointestinal decompression. Finally, evidence demonstrates benefit in the prevention of VAP from placing the patient in the semirecumbent position by elevating the head of the bed.[63] Limited data suggest that use of VAP care "bundles," including elevation of the head of the bed, have decreased incidence of VAP in the ICU; this may warrant further study to determine benefit in the ED.[64] A recent meta-analysis also demonstrated a decrease in the incidence of VAP with continuous aspiration of subglottic secretions. This is done via a specialized endotracheal tube for this purpose, and, though not routinely used in the ED, this technique may be a direction for future investigation.[65]

Complications of Positive-Pressure Ventilation

Although initiated as a lifesaving intervention, PPV carries the risk of significant complications. As highlighted earlier, initiation of PPV and elevated intrathoracic pressure can be associated with relative hypotension, and any subsequent changes in end-inspiratory alveolar pressures or PEEP during the management of ventilation may have hemodynamic consequences.

PPV also has a direct impact on the lungs. Whether delivered as a set volume or set pressure, invasive PPV forcibly distends the lung and can be injurious. Injuries from elevated lung volume or lung pressure are known as volutrauma and barotrauma, respectively, and contribute to the development of VILI. VILI is mitigated by limiting pathologic stretch on the alveoli; current data support that maximum "safe" end-inspiratory alveolar pressures are 30 to 32 cm H_2O,[4,66-69] though this continues to be actively researched. Barotrauma can also manifest overtly with pneumothorax or pneumomediastinum, but this is relatively uncommon.[69]

Another potential complication of PPV is the development of intrinsic PEEP (iPEEP or auto-PEEP). Particularly problematic in patients with obstructive lung disease, iPEEP is accumulation of end-expiratory volume and end-expiratory pressure that occurs when exhalation cannot be fully completed. In patients with obstructive lung disease, expiratory flow is limited secondary to small airway obstruction and diminished elastic recoil. Time required for full exhalation may be significantly longer than normal, and in patients receiving mechanical ventilation, exhalation may not be complete before the next delivered breath. This phenomenon, known as "breath stacking," results in dynamic hyperinflation. Intrinsic PEEP results in unexpectedly high PIPs, difficulty in ventilation, hypotension, and potential circulatory collapse. Ventilation difficulty caused by iPEEP can be improved by decreasing the respiratory rate or decreasing the inspiratory time, both of which facilitate increased time for exhalation.

Troubleshooting the Ventilator

When a patient's condition suddenly deteriorates during mechanical ventilation, a systematic approach should be applied to immediately assess for life-threatening conditions (Fig. 2-1). The first step in evaluating the ventilated patient who has a change in clinical status is to assess vital signs. Patients with acute hemodynamic compromise or acute hypoxia should be removed from the ventilator and bagged manually on 100% oxygen. Tension pneumothorax, increased iPEEP, and accidental extubation are the most life-threatening concerns in this situation and must be immediately addressed. While the patient is bagged, the chest should be examined to ensure bilateral breath sounds. Changes in breath sounds may indicate a pneumothorax or a migration of the endotracheal tube. Clinical examination, oxygen saturation, and $ETCO_2$ monitoring can be used as surrogates for tube placement, but suspicion of inadvertent extubation should prompt direct visualization. Acute hypotension can be precipitated by extreme elevations in intrathoracic pressure; compromise from iPEEP will improve once the patient has been disconnected from the ventilator, whereas hypotension from a tension pneumothorax will not. If the patient's condition remains unstable after he or she has been disconnected from the ventilator circuit, a tension pneumothorax should be treated presumptively with needle decompression and eventual chest tube placement. Although unlikely, it is possible that a patient could sustain bilateral pneumothoraces, and this should be considered. If the patient remains unstable after chest decompression, sources for decompensation unrelated to the ventilator must be pursued.

Acute distress without hemodynamic changes can be precipitated by multiple factors, both mechanical and physiologic (Table 2-4). Again, the initial evaluation should begin by confirming position and patency of the endotracheal tube before other diagnoses are investigated, including evaluation of the tracheal balloon. Once tube placement has been confirmed, the next step in evaluation of ventilator-related causes of distress should focus on airway pressures. Acute decreases in PIP indicate discontinuity in the ventilator circuit, which could include inadvertent extubation. Patients with increased PIP can be considered in two categories: those with concomitant increases in Pplat, and those with unchanged Pplat. If both PIP and Pplat acutely increase, this suggests decreased compliance of the respiratory system. Elevated PIP with unchanged Pplat indicates problems with increased airway resistance, either in the lungs or the ventilator circuit. Specific conditions that cause decreased respiratory system compliance or increased airway resistance are detailed in Figure 2-1.

www.ketabpezeshki.com 66485457-66963820

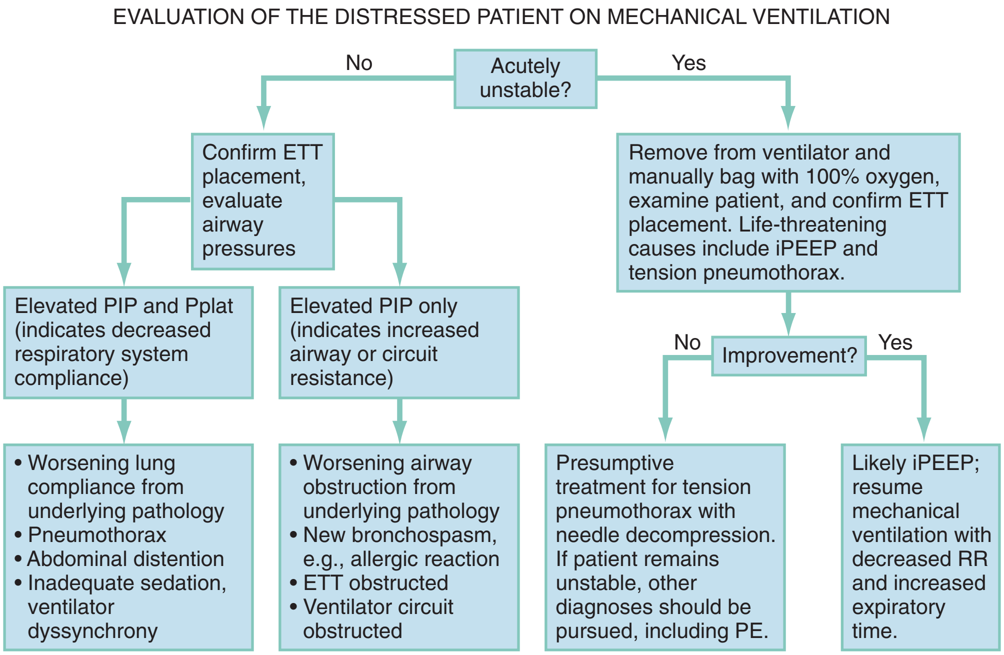


Figure 2-1. Algorithm for evaluation of the distressed patient on mechanical ventilation.

Table 2-4 Troubleshooting the Ventilator: Potential Causes of Acute Respiratory Distress

With Hemodynamic Compromise: Immediately Discontinue Mechanical Ventilation	
Increased intrinsic positive end-expiratory pressure (iPEEP)	
Tension pneumothorax	
Massive pulmonary embolus	
Without Hemodynamic Compromise: Search for Underlying Cause	
MECHANICAL	**PHYSIOLOGIC**
Endotracheal tube migration into bronchus	Worsening lung compliance
Endotracheal tube obstruction	Worsening airway obstruction
Endotracheal tube cuff leak	Abdominal distention
Inadvertent extubation	Pulmonary embolus
Discontinuity in ventilator circuit	Pain or inadequate sedation

Special Clinical Circumstances

Although generalizations can be made regarding ventilatory management in the ED, certain clinical circumstances merit specific discussion.

Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Strategies for managing intubated patients with COPD focus on improving gas exchange while minimizing iPEEP. Reduction of iPEEP is achieved by decreasing airway resistance with bronchodilators and corticosteroids and ensuring adequate expiratory time during mechanical ventilation. Adequate expiratory time is achieved by decreasing respiratory rate, tidal volume, and inspiratory time. Adequate oxygenation (saturation of 90%) is achieved while minimizing barotrauma by deliberately reducing minute ventilation, so-called "permissive hypercapnia." No data suggest the advantage of PCV versus VCV, and either method can be used. The ideal ratio of inspiratory-to-expiratory time (I/E ratio) is variable, but the ratio should initially be set at 1:4. Data in asthmatics suggest that expiratory times longer than 4 seconds have minimal impact on airflow.[70] iPEEP can also result in poor patient-ventilator synchrony, causing inadequate gas exchange. Initially, deep sedation and analgesia (or sometimes paralysis) are required to prevent ventilator asynchrony and permit effective ventilation. Corticosteroids often are indicated (see Chapter 74). NBMAs are avoided if possible, as patients receiving both NMBA and corticosteroids are at higher risk for "polymyopathy of critical illness" and subsequent increased mortality.[71]

Status Asthmaticus

Concerns in ventilating the acute asthmatic generally parallel those for patients with COPD, with small notable differences. In acute asthma, respiratory failure is both a result of airway obstruction and airway inflammation. Furthermore, unlike COPD, airway obstruction is much less dynamic and occurs predominantly in large airways. In addition, acute inflammatory changes throughout the lung contribute to decreased lung compliance, which has a direct impact on lung pressures during ventilation.[72] Strategies should focus on low respiratory rates with emphasis on maximizing expiratory time. The use of PEEP is debated and is largely thought to contribute to increased lung pressure. Though no data definitively exist supporting VCV over PCV, decreased lung compliance and potential iPEEP may make the delivery of adequate tidal volumes with PCV difficult. This is especially problematic for patients with severe, acute respiratory acidosis for whom adequate ventilation is essential. Recommendations for ventilator settings include VCV with tidal volumes of 6 to 8 mL/kg IBW, respiratory rate of 10 to 15 breaths per minute, and no PEEP.[72] Decreased inspiratory time allows greater expiratory time and is achieved by increasing the inspiratory flow rate.

Acute Lung Injury and Acute Respiratory Distress Syndrome

ALI and ARDS are on a spectrum of inflammatory lung disease characterized by heterogeneous noncardiogenic pulmonary

www.ketabpezeshki.com 66485457-66963820

edema, hypoxia, and diffuse lung consolidation. Strictly, the difference between these conditions is defined by the ratio of arterial oxygen concentration to the fraction of inspired oxygen (PaO_2/FIO_2), with ALI being less severe than ARDS. ALI and ARDS can be caused by pulmonary or extrapulmonary inflammation, including VILI. Though epidemiologic data suggest that ALI is not common on initial presentation to the ED, incidence of ALI in ventilated patients is not uncommon.[73] The impact of ventilation in the ED on development of lung injury or ARDS is unclear.[74,75] Nonetheless, development of VILI has been associated with lung overdistention and alveolar injury,[69,76-78] and attention to ventilation strategy in the ED is warranted. Studies confirm that decreased tidal volumes are of clear benefit in the management of patients with ALI and ARDS.[4,66,67,79] The majority of studies examining low–tidal volume ventilation strategies, including the landmark ARDSnet trial in 2000, used 6 to 7 mL/kg tidal volumes based on IBW,[4,66,69,80] though studies with 7 mL/kg did not demonstrate a difference in mortality. A meta-analysis of these data concluded that tidal volumes below 7 mL/kg and Pplat above 31 cm H_2O conferred mortality benefit in patients with ALI or ARDS, though more recent work suggests that low–tidal volume ventilation may improve outcome for patients without lung injury as well.[74,81] Level of PEEP in patients with ALI and ARDS continues to be actively researched. Therefore in patients with ALI or ARDS (PaO_2/$FIO_2 < 300$), low–tidal ventilation strategy should be used. Initial ventilator settings should be volume cycled, with tidal volumes based on 6 mL/kg of IBW. IBW can also be estimated by height.

OUTCOMES

Because of the heterogeneity of ventilation strategies and clinical reasons for respiratory failure, no data exist regarding the superiority of one ventilation method over another; considerations in initiating mechanical ventilation must be individualized and serially reevaluated. Nonetheless, as detailed previously, certain conclusions regarding outcome can be drawn. Data clearly indicate the effectiveness of NPPV in preventing intubation for patients with COPD and ACPE, and these benefits have resulted in decreased admission to the ICU and decreased mortality. In addition, increased alveolar volumes and pressures have been shown to contribute to VILI and to increase mortality in patients with ALI and ARDS. The implication of decreased tidal-volume ventilation on the prevention of lung injury in patients with normal lungs is not definitive, and the role of ventilation strategy in the ED on subsequent clinical course of critically ill patients remains uncertain.

Lastly, although the treatment of mechanically ventilated patients usually extends beyond the ED, delays in ICU admission can have significant implications on ED management of the critically ill ventilated patient as the role of emergency physicians extends beyond acute stabilization toward ongoing clinical management.[82,83] In addition, when boarding times are long, patients intubated solely for airway protection may be candidates for extubation in the ED if the initial insult has been reversed.

KEY CONCEPTS

- Primary goals of mechanical ventilation are improved gas exchange and decreased work of breathing while maximizing patient comfort and minimizing the potential for complications. Strategies for approaching mechanical ventilation are individualized, dependent both on the patient and the underlying cause of respiratory failure.
- Noninvasive ventilatory support is often adequate for reversal impending respiratory failure and should considered as the first-line therapy for patients with exacerbations of chronic obstructive pulmonary disease and acute cardiogenic pulmonary edema in whom immediate intubation is not required.
- Invasive mechanical ventilation is not without consequence and requires dynamic, ongoing management. After intubation, blood gas analysis should be performed to confirm appropriate ventilation and provide correlation with noninvasive monitoring modalities. In addition, hemodynamic consequences as a result of positive pressure should be anticipated. Elevated lung pressures can be deleterious and should be actively avoided.
- Sudden difficulty in the treatment of patients receiving mechanical ventilation should prompt a quick and systematic evaluation for life-threatening conditions, followed by assessment of the ventilator settings, the ventilator circuit, airway pressures, and physiologic problems. In hemodynamically unstable patients, this starts with disconnecting the patient from the ventilator and temporary use of a bag-mask with 100% oxygen.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Pinsky MR: Cardiovascular issues in respiratory care. *Chest* 2005; 128(5 Suppl 2):592S-597S.
2. Steingrub JS, Tidswell M, Higgins TL: Hemodynamic consequences of heart-lung interactions. *J Intensive Care Med* 2003; 18:92-99.
3. Grinnan DC, Truwit JD: Clinical review: Respiratory mechanics in spontaneous and assisted ventilation. *Crit Care* 2005; 9:472-484.
4. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342:1301-1308.
5. Chatburn RL: Classification of ventilator modes: Update and proposal for implementation. *Respir Care* 2007; 52:301-323.
6. Bigatello LM, Massachusetts General Hospital: *Critical Care Handbook of the Massachusetts General Hospital*, 5th ed. Philadelphia: Lippincott, Williams & Wilkins/Wolters Kluwer Health; 2009.
7. Brower RG, et al: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; 351:327-336.
8. Demoule A, Girou E, Richard JC, Taille S, Brochard L: Benefits and risks of success or failure of noninvasive ventilation. *Intensive Care Med* 2006; 32:1756-1765.
9. Levy M, et al: Outcomes of patients with do-not-intubate orders treated with noninvasive ventilation. *Crit Care Med* 2004; 32: 2002-2007.
10. Fernandez R, Baigorri F, Artigas A: Noninvasive ventilation in patients with "do-not-intubate" orders: Medium-term efficacy depends critically on patient selection. *Intensive Care Med* 2007; 33:350-354.
11. Hess DR: The evidence for noninvasive positive-pressure ventilation in the care of patients in acute respiratory failure: A systematic review of the literature. *Respir Care*, 2004; 49:810-829.
12. Hostetler MA: Use of noninvasive positive-pressure ventilation in the emergency department. *Emerg Med Clin North Am* 2008; 26:929-939, viii.
13. American Thoracic Society, European Respiratory Society, European Society of Intensive Care Medicine, Société de Réanimation de Langue Française: International Consensus Conferences in Intensive Care Medicine: Noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med* 2001; 163:283-291.
14. Keenan SP, Powers CE, McCormack DG: Noninvasive positive-pressure ventilation in patients with milder chronic obstructive pulmonary disease exacerbations: A randomized controlled trial. *Respir Care* 2005; 50:610-616.
15. Keenan SP, Sinuff T, Cook DJ, Hill NS: Which patients with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation? A systematic review of the literature. *Ann Intern Med* 2003; 138:861-870.
16. Brochard L, et al: Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995; 333:817-822.
17. Ram FS, Picot J, Lightowler J, Wedzicha JA: Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2004; 1:CD004104.
18. Confalonieri M, et al: A chart of failure risk for noninvasive ventilation in patients with COPD exacerbation. *Eur Respir J* 2005; 25:348-355.
19. Brinker JA, et al: Leftward septal displacement during right ventricular loading in man. *Circulation* 1980; 61:626-633.
20. Lenique F, et al: Ventilatory and hemodynamic effects of continuous positive airway pressure in left heart failure. *Am J Respir Crit Care Med* 1997; 155:500-505.
21. Ho KM, Wong K: A comparison of continuous and bi-level positive airway pressure non-invasive ventilation in patients with acute cardiogenic pulmonary oedema: A meta-analysis. *Crit Care* 2006; 10:R49.
22. Seupaul RA: Evidence-based emergency medicine/systematic review abstract. Should I consider treating patients with acute cardiogenic pulmonary edema with noninvasive positive-pressure ventilation? *Ann Emerg Med* 2010; 55:299-300.
23. Winck JC, Azevedo LF, Costa-Pereira A, Antonelli M, Wyatt JC: Efficacy and safety of non-invasive ventilation in the treatment of acute cardiogenic pulmonary edema—a systematic review and meta-analysis. *Crit Care* 2006; 10:R69.
24. Weng CL, et al: Meta-analysis: Noninvasive ventilation in acute cardiogenic pulmonary edema. *Ann Intern Med* 2010; 152: 590-600.
25. Nouira S, et al: Non-invasive pressure support ventilation and CPAP in cardiogenic pulmonary edema: A multicenter randomized study in the emergency department. *Intensive Care Med* 2011; 37:249-256.
26. Soroksky A, Stav D, Shpirer I: A pilot prospective, randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. *Chest* 2003; 123:1018-1025.
27. Fernández MM, Villagrá A, Blanch L, Fernández R: Non-invasive mechanical ventilation in status asthmaticus. *Intensive Care Med* 2001; 27:486-492.
28. Vital FM, et al: Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary edema. *Cochrane Database Syst Rev* 2008; 3:CD005351.
29. Keenan SP, Sinuff T, Cook DJ, Hill NS: Does noninvasive positive pressure ventilation improve outcome in acute hypoxemic respiratory failure? A systematic review. *Crit Care Med* 2004; 32:2516-2523.
30. Carron M, Freo U, Zorzi M, Ori C: Predictors of failure of noninvasive ventilation in patients with severe community-acquired pneumonia. *J Crit Care* 2010; 25:540. e9-e14.
31. Antonelli M, et al: Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: A multi-center study. *Intensive Care Med* 2001; 27:1718-1728.
32. Confalonieri M, et al: Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. *Am J Respir Crit Care Med* 1999; 160(5 Pt 1):1585-1591.
33. Liesching T, Kwok H, Hill NS: Acute applications of noninvasive positive pressure ventilation. *Chest* 2003; 124:699-713.
34. Chu YC, et al: Prediction of arterial blood gas values from venous blood gas values in patients with acute respiratory failure receiving mechanical ventilation. *J Formos Med Assoc* 2003; 102:539-543.
35. Malatesha G, Singh NK, Bharija A, Rehani B, Goel A: Comparison of arterial and venous pH, bicarbonate, Pco_2 and Po_2 in initial emergency department assessment. *Emerg Med J* 2007; 24:569-571.
36. Zhang H, Vincent JL: Arteriovenous differences in PCO2 and pH are good indicators of critical hypoperfusion. *Am Rev Respir Dis* 1993; 148(4 Pt 1):867-871.
37. Bakker J, et al: Veno-arterial carbon dioxide gradient in human septic shock. *Chest* 1992; 101:509-515.
38. Corbo J, Bijur P, Lahn M, Gallagher EJ: Concordance between capnography and arterial blood gas measurements of carbon dioxide in acute asthma. *Ann Emerg Med* 2005; 46:323-327.
39. Plewa MC, et al: Evaluation of capnography in nonintubated emergency department patients with respiratory distress. *Acad Emerg Med* 1995; 2:901-908.
40. Prause G, et al: A comparison of the end-tidal-CO2 documented by capnometry and the arterial pCO2 in emergency patients. *Resuscitation* 1997; 35:145-148.
41. Hess D, Agarwal NN: Variability of blood gases, pulse oximeter saturation, and end-tidal carbon dioxide pressure in stable, mechanically ventilated trauma patients. *J Clin Monit* 1992; 8:111-1115.
42. Kress JP, Hall JB: Sedation in the mechanically ventilated patient. *Crit Care Med* 2006; 34:2541-2546.
43. Sessler CN, et al: The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002; 166:1338-1344.
44. Ely EW, et al: Monitoring sedation status over time in ICU patients: Reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA* 2003; 289:2983-2991.
45. Papazian L, et al: Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med* 2010; 363:1107-1116.
46. Soliman HM, Melot C, Vincent JL: Sedative and analgesic practice in the intensive care unit: The results of a European survey. *Br J Anaesth* 2001; 87:186-292.
47. Dahaba AA, Grabner T, Rehak PH, List WF, Metzler H: Remifentanil versus morphine analgesia and sedation for mechanically ventilated critically ill patients: A randomized double blind study. *Anesthesiology* 2004; 101:640-646.
48. Amrein R, Hetzel W, Hartmann D, Lorscheid T: Clinical pharmacology of flumazenil. *Eur J Anaesthesiol Suppl* 1988; 2:65-80.
49. Byatt CM, Lewis LD, Dawling S, Cochrane GM: Accumulation of midazolam after repeated dosage in patients receiving mechanical ventilation in an intensive care unit. *Br Med J (Clin Res Ed)* 1984; 289:799-800.
50. Oldenhof H, de Jong M, Steenhoek A, Janknegt R: Clinical pharmacokinetics of midazolam in intensive care patients, a wide interpatient variability? *Clin Pharmacol Ther* 1988; 43:263-269.
51. Bauer TM, et al: Prolonged sedation due to accumulation of conjugated metabolites of midazolam. *Lancet* 1995; 346:145-147.

www.ketabpezeshki.com 66485457-66963820

52. Spina SP, Ensom MH: Clinical pharmacokinetic monitoring of midazolam in critically ill patients. *Pharmacotherapy* 2007; 27:389-398.
53. Kollef MH, et al: The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. *Chest* 1998; 114:541-548.
54. Shafer SL: Advances in propofol pharmacokinetics and pharmacodynamics. *J Clin Anesth* 1993; 5(6 Suppl 1):14S-21S.
55. Carson SS, et al: A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. *Crit Care Med* 2006; 34:1326-1332.
56. Ostermann ME, Keenan SP, Seiferling RA, Sibbald WJ: Sedation in the intensive care unit: A systematic review. *JAMA* 2000; 283:1451-1459.
57. Panzer O, Moitra V, Sladen RN: Pharmacology of sedative-analgesic agents: Dexmedetomidine, remifentanil, ketamine, volatile anesthetics, and the role of peripheral mu antagonists. *Crit Care Clin* 2009; 25:451-469, vii.
58. Bergese SD, et al: A Phase IIIb, randomized, double-blind, placebo-controlled, multicenter study evaluating the safety and efficacy of dexmedetomidine for sedation during awake fiberoptic intubation. *Am J Ther* 2010; 17:586-595.
59. Bergese SD, et al: A comparative study of dexmedetomidine with midazolam and midazolam alone for sedation during elective awake fiberoptic intubation. *J Clin Anesth* 2010; 22:35-40.
60. Takasaki Y, Kido T, Semba K: Dexmedetomidine facilitates induction of noninvasive positive pressure ventilation for acute respiratory failure in patients with severe asthma. *J Anesth* 2009; 23:147-150.
61. Riker RR, et al: Dexmedetomidine vs midazolam for sedation of critically ill patients: A randomized trial. *JAMA* 2009; 301:489-499.
62. Milbrandt EB, et al: Haloperidol use is associated with lower hospital mortality in mechanically ventilated patients. *Crit Care Med* 2005; 33:226-229; discussion 263-265.
63. Collard HR, Saint S, Matthay MA: Prevention of ventilator-associated pneumonia: an evidence-based systematic review. *Ann Intern Med* 2003; 138:494-501.
64. Morris AC, et al: Reducing ventilator-associated pneumonia in intensive care: Impact of implementing a care bundle. *Crit Care Med* 2011; 39:2218-2224.
65. Muscedere J, et al: Subglottic secretion drainage for the prevention of ventilator-associated pneumonia: A systematic review and meta-analysis. *Crit Care Med* 2011; 39:1985-1991.
66. Amato MB, et al: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338:347-354.
67. Petrucci N, Iacovelli W: Ventilation with smaller tidal volumes: A quantitative systematic review of randomized controlled trials. *Anesth Analg* 2004; 99:193-200.
68. Hager DL: Carpal tunnel syndrome in patients more than 65 years old. *J Hand Surg Am* 2005; 30:866-867; author reply 867.
69. Ramnath VR, Hess DR, Thompson BT: Conventional mechanical ventilation in acute lung injury and acute respiratory distress syndrome. *Clin Chest Med* 2006; 27:601-613; abstract viii.
70. Leatherman JW, McArthur C, Shapiro RS: Effect of prolongation of expiratory time on dynamic hyperinflation in mechanically ventilated patients with severe asthma. *Crit Care Med* 2004; 32:1542-1545.
71. Hermans G, De Jonghe B, Bruyninckx F, Van den Berghe G: Clinical review: Critical illness polyneuropathy and myopathy. *Crit Care* 2008; 12:238.
72. Medoff BD: Invasive and noninvasive ventilation in patients with asthma. *Respir Care* 2008; 53:740-748; discussion 749-750.
73. Roupie E, et al: Prevalence, etiologies and outcome of the acute respiratory distress syndrome among hypoxemic ventilated patients. SRLF Collaborative Group on Mechanical Ventilation. Société de Réanimation de Langue Française. *Intensive Care Med* 1999; 25:920-929.
74. Gajic O, et al: Early identification of patients at risk of acute lung injury: Evaluation of lung injury prediction score in a multicenter cohort study. *Am J Respir Crit Care Med* 2011; 183:462-470.
75. Gajic O, et al: Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med* 2004; 32:1817-1824.
76. Hoegl S, et al: Short-term exposure to high-pressure ventilation leads to pulmonary biotrauma and systemic inflammation in the rat. *Int J Mol Med* 2008; 21:513-519.
77. Dreyfuss D, Saumon G: Ventilator-induced lung injury: Lessons from experimental studies. *Am J Respir Crit Care Med* 1998; 157:294-323.
78. Slutsky AS: Ventilator-induced lung injury: From barotrauma to biotrauma. *Respir Care* 2005; 50:646-659.
79. Brochard L, et al: Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. *Am J Respir Crit Care Med* 1998; 158:1831-1838.
80. Villar J, Kacmarek RM, Pérez-Méndez L, Aguirre-Jaime A: A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: A randomized, controlled trial. *Crit Care Med* 2006; 34:1311-1318.
81. Sundar S, et al: Influence of low tidal volume ventilation on time to extubation in cardiac surgical patients. *Anesthesiology* 2011; 114:1102-1110.
82. Wood S, Winters ME: Care of the intubated emergency department patient. *J Emerg Med* 2010; 40:419-427.
83. McCarthy ML, et al: Crowding delays treatment and lengthens emergency department length of stay, even among high-acuity patients. *Ann Emerg Med* 2009; 54:492-503. e4.

www.ketabpezeshki.com 66485457-66963820

Chapter 3

Pain Management

James R. Miner and John Burton

PERSPECTIVE

Pain-related complaints represent as many as 70% of presenting concerns for patients in the emergency department (ED) setting.[1-5] Uncontrolled pain should be considered a medical emergency. The estimated degree of pain experienced by a patient should play a role in the determination of a patient's overall acuity and urgency for therapy. Pain estimations, from both provider- and patient-derived scales, should be obtained and recorded for patients as frequently as any vital sign or patient indicator. Although pain can be present in a wide variety of physical and psychosocial situations, it is almost always present in the context of tissue injury. Pain can therefore be assumed to be present in patients with physically apparent disease or injury, even in those who cannot effectively communicate their condition. Important terms relating to analgesic practices are listed in Box 3-1.

A wide variety of options are available for the treatment of pain. Despite having effective treatments available for both acute and chronic pain therapy, the treatment of pain can be difficult and is often one of the most challenging and frustrating aspects of the practice of emergency medicine.[6-10]

Patients' perceptions of their ED care are highly influenced by pain treatment. Satisfaction with emergency care often depends on the techniques and timeliness of analgesia as well as the discharge plans for pain relief.[11,12] In every interaction with a patient in pain, a balance should be achieved between relief of patient suffering and the diagnosis and treatment of the underlying medical condition.

A growing body of evidence supports the importance of pain management as a central aspect of disease treatment. Unrelieved pain is associated with a variety of potentially negative physiologic outcomes, including increases in sympathetic outflow, peripheral vascular resistance, myocardial oxygen consumption, and the production of carbon dioxide (CO_2). Other adverse effects of unrelieved pain appear to include hypercoagulability, decreases in gastric motility, and immune function impairment.

Poorly treated acute pain can promote the development of chronic pain syndromes and vegetative symptoms, as well as increase the need for pain management during any recovery period.[13-20] Pain during serial medical procedures may increase if successful analgesia was not provided during initial procedures.[21] It is also likely that a patient's experience of pain increases the ability to perceive pain from similar stimuli in the future.[22]

As an affirmation of the recognized importance of pain management in health care, The Joint Commission (TJC) requires hospitals to develop quality improvement efforts related to acute pain management in addition to comprehensive programs for the measurement, documentation, and treatment of pain. Improvements in pain management are occurring as a result of an enhanced interest in pain research, education, and regulatory efforts.[23-28]

PATHOPHYSIOLOGY

Pain can be generally described as *nociceptive or neuropathic.* Nociceptive pain results from the activation of sensory neurons that signal pain (nociceptors) in response to noxious stimuli. Neuropathic pain results from signal processing changes in the central nervous system (CNS). Neuropathic pain is usually described as burning, tingling, or shooting sensations and includes neuropathies and deafferentation. Both nociceptive and neuropathic types of pain involve peripheral and central sensitization with a complex array of mediators to sensitize peripheral nociceptors and perpetuate thalamic signals, shown in Figure 3-1. At each level in the physiologic process of pain production or transmission, interventions and therapeutic opportunities should be considered to alter the process and ultimately improve the patient's pain experience.

Pain Conduction Pathways

Pain perception can be divided into four separate processes (see Fig. 3-1): pain detection (transduction), pain transmission, pain modulation, and pain expression (perception). The transduction of painful sensory input is initiated by the activation of nociceptors, with subsequent depolarization of their axons. The axons then relay information (afferent input) to their cell bodies located in the dorsal root ganglion, lateral to the spinal cord.[29] Central dendrites of these first-order neurons synapse in the dorsal horn, where sensory input is modulated. These sensory signals travel through the CNS spinothalamic tracts and posterior columns to synapse in the reticular system and the thalamus. Thalamic and reticular signals are then projected to the cerebral cortex (Fig. 3-2).

Pain Detection

The somatosensory system is responsible for the detection of pain as well as tactile, proprioceptive, and thermal sensations. Receptors responsible for the detection of pain are termed *nociceptors.* Nociceptors include sensory nerves that are capable of detecting mechanical, thermal, or chemical stimulation. Several different subtypes of nociceptors are present in cutaneous tissues, including mechanoreceptors, polymodal nociceptors (PMNs), and a variety of thermoreceptors.[29] Most nociceptive input is derived from inflammatory mediators through PMNs, in response to intense chemical, thermal, and mechanical stimuli.

The threshold of activation of a nociceptor can be modulated, increased or decreased, by a variety of chemical mediators including prostaglandin, cyclic adenosine monophosphate, leukotrienes,

www.ketabpezeshki.com 66485457-66963820

Box 3-1 Definitions for Terms Related to Analgesia

Allodynia—pain from a stimulus that does not normally provoke pain
Amnestic—an agent the suppresses the formation of memories
Local anesthesia—an area of insensibility to pain created by the injection of a local anesthetic agent
Analgesia—relief from pain
Hypnotic—an agent that promotes the onset of sleep
Narcotic—a term with legal implications describing opioid agents together with various central nervous system depressant drugs of abuse
Nociceptor—a receptor that is sensitive to and responsible for transmitting pain stimuli
Noxious stimulus—a stimulus that is damaging or potentially damaging and results in sensation of pain
Opiate—a naturally occurring derivative of opium alkaloid that binds opiate receptors and produces effects similar to those of the endogenous endorphins
Opioid—a naturally occurring or semisynthetic derivative of opium alkaloid (includes all opiates) that binds opiate receptors and produces effects similar to those of the endogenous endorphins
Pain—an unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage
Procedural sedation—pharmacologic induction of a state of sedation or dissociation with amnesia for pain control during a painful procedure
Sedative—an agent that decreases a patient's level of awareness

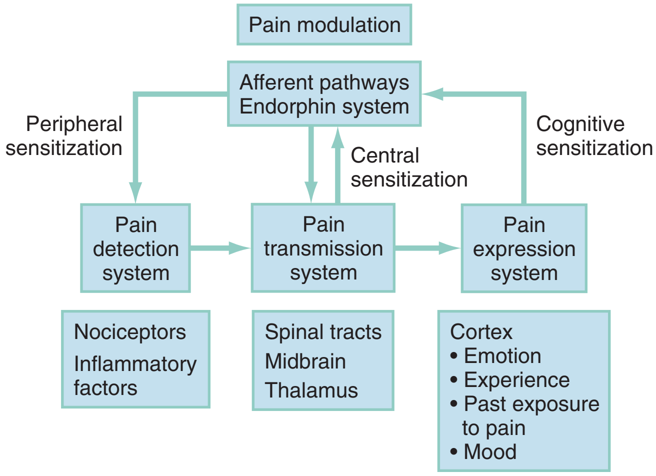


Figure 3-1. The pain system algorithm.

bradykinins, serotonin, substance P, thromboxanes, platelet-activating factor, and endorphins. This change in nociceptor activation thresholds is termed *peripheral sensitization*. Trigger points, for example, are areas of frequent or constant low-level sensory stimulation (e.g., scar tissue or a degenerative joint) that have developed peripheral sensitized nociceptors that perceive pain from otherwise innocuous stimuli.

Information Transmission

Peripheral Nerve Fibers

All sensory neurons are composed of a cell body located in the dorsal root ganglion. The dorsal root ganglia are connected by nerve axon fibers with sensory receptors located in a number of body sites, including dermatomes (cutaneous input), sclerotomes

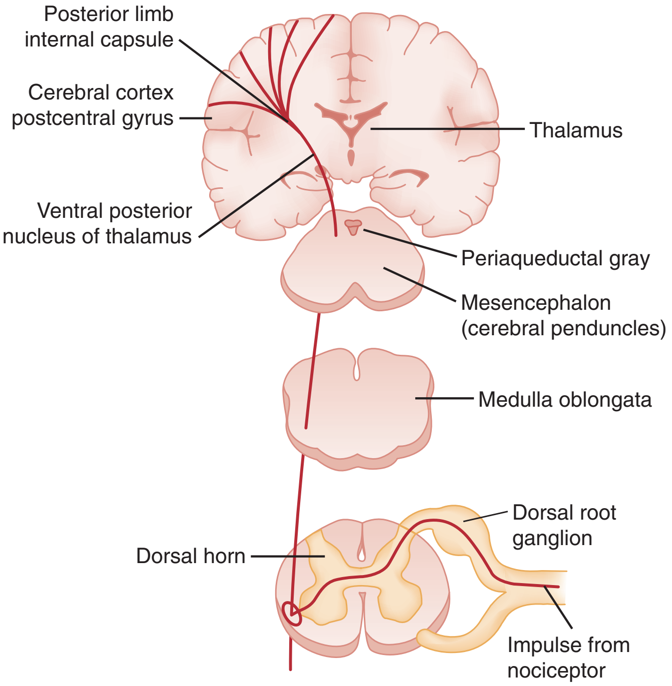


Figure 3-2. Spinal tracts.

(input from bones), and myotomes (input from muscle). The discrete areas covered by each nerve provide a sensory map of the body surface.

Peripheral nerve fibers can be classified by the roles of each fiber group (Table 3-1). A-δ and C fibers are responsible for the transmission of pain. A-δ fibers transmit sharp, initial pain. C fibers, in contrast, transmit dull, aching, or burning pain. The pain transmitted by A-δ fibers persists only as long as the initial stimulus is in effect, whereas C fiber pain persists longer than the initial stimuli, rendering a prolonged pain sensory experience.

The relative concentration of nerve fiber types, both C and A-δ, varies by body tissue. Muscles, for example, are high in C fiber concentration and create pain sensations that are aching and poorly localized in response to violent contractions, stretch, ischemia, or inflammation. Bones and joints, in contrast to muscle, possess afferents with thresholds sensitized by chemicals present during inflammation (accounting for the pain associated with arthritis). Bone periosteum has the lowest pain threshold of all deep tissues and is supplied by both A-δ and C fibers, whereas bone cortex and marrow have very few nociceptors.

Pain Transmission

Dorsal Horn

The dorsal horn is the gray matter of the posterior aspect of the spinal cord (Fig. 3-3). The dorsal horn acts as an integration system where sensory input is filtered, attenuated, or amplified before being relayed to other spinal segments or the cortex (Fig. 3-4).

The dorsal horn is a processing center for incoming information and is extensively involved in the modulation of nociceptive input. Afferents from visceral, muscle, bone, and cutaneous areas converge in the dorsal horn and likely account for the cutaneous allodynia associated with painful visceral, muscular, or bony stimuli.

Differentiation between innocuous stimuli and nociceptor input occurs in the dorsal horn by stimuli received in cells referred to as wide dynamic range neurons (WDRNs). WDRNs receive

www.ketabpezeshki.com 66485457-66963820

Table 3-1 Peripheral Nerve Fibers

FIBER	FUNCTION	MYELIN	MEAN DIAMETER (μm)	ASCENDING TRACT	CONDUCTION VELOCITY (m/s)
A-α	Skeletal muscle motor	Deep	12-20	Ipsilateral dorsal column	70-120
A-β	Light touch and pressure	Superficial	5-15	Contralateral spinothalamic tract	30-70
A-γ	Motor	Superficial	6-8	Ipsilateral dorsal column	15-30
A-δ	Sharp pain (mechanoreceptors, thermoreceptors, PMNs)	Superficial	1-4	Contralateral spinothalamic tract	12-30
B	Sympathetic		1-3	Preganglionic	3-15
C	Long-lasting burning pain	Superficial	0.5-1.5	Contralateral spinothalamic tract	0.5-2

Adapted from Paris PM, Uram M, Ginsburg MJ: Physiological mechanisms of pain. In: Paris PM, Stewart RD, eds. Pain Management in Emergency Medicine. Norwalk, Conn: Appleton & Lange; 1988.
PMNs, polymodal nociceptors.

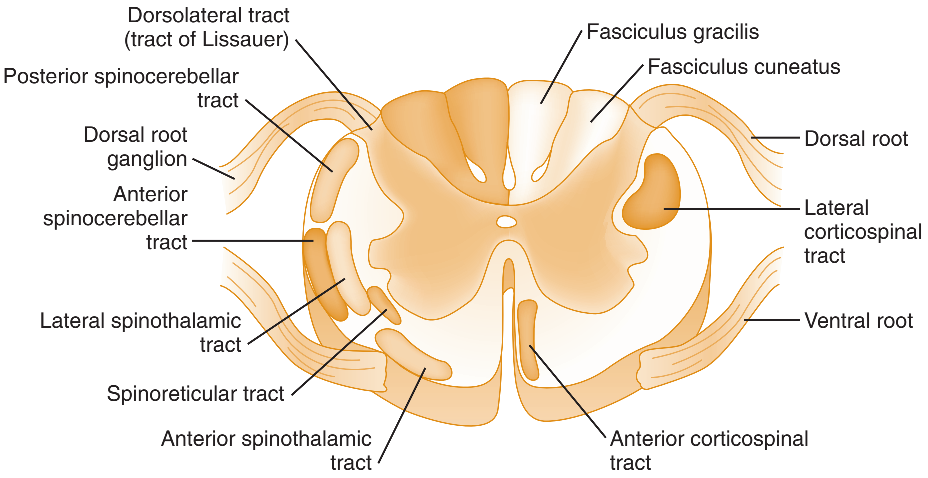


Figure 3-3. Spinal cord.

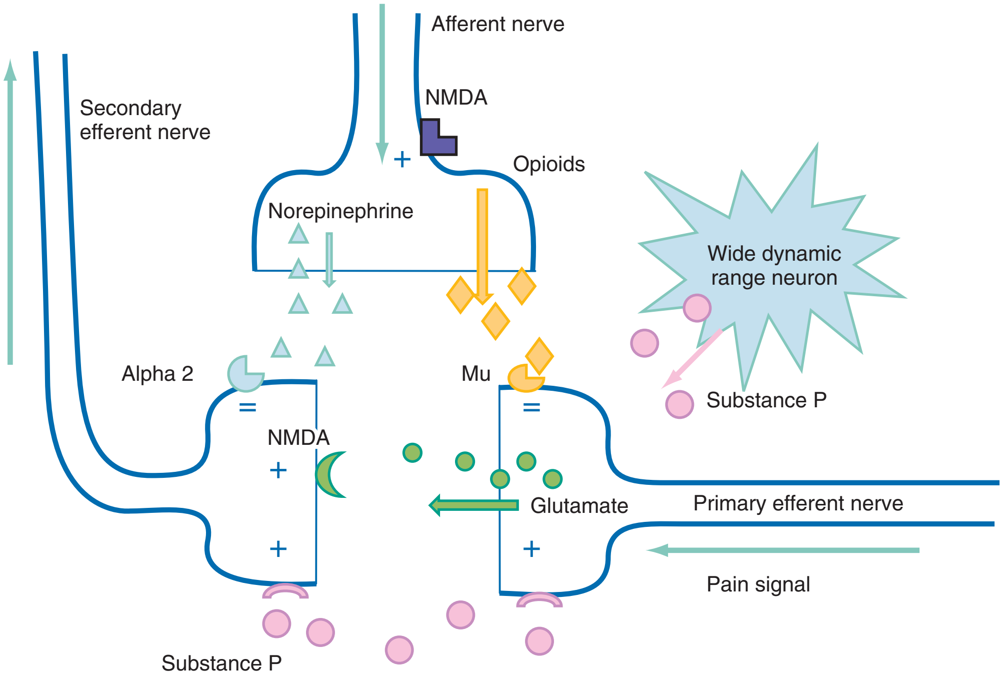


Figure 3-4. Neurotransmitters and receptors at the dorsal root ganglion. *Mu,* opioid receptor; *NMDA, N*-methyl-D-aspartate.

www.ketabpezeshki.com 66485457-66963820

modulating input from a variety of chemical pathways, such as opioids, substance P, or inflammatory factors. These cells also receive modulating input from efferent and afferent neuronal pathways.

Visceral Pain

The quantity and type of stimuli that produce pain vary among visceral structures. The myocardium, for example, is sensitive to ischemia but not mechanical stimulation. Tissues in the intestine may be severed, crushed, or burned without pain; however, traction or distention produces pain sensations.

The quality of visceral pain is unique from that of somatic pain. Somatic pain is initially sharp and later becomes burning or throbbing in nature as the response is modulated. Visceral pain in contrast tends to start as poorly localized, dull, and aching, with pronounced autonomic activation relative to somatic pain. These sensations may then develop into sharp, localized, referred pain. This progression is likely a result of the varying ratios of A to C fibers, which are 1 : 10 in visceral nerves and 1 : 2 in cutaneous nerves.

Visceral pain often produces referred pain. For example, periumbilical pain is often associated with appendicitis. This referred pain sensation occurs because of visceral afferents supplying the small bowel and traveling through the celiac ganglia and splanchnic nerves to enter the spinal cord at T10. This input sensitizes the dorsal horn at T10, leading to sensitization of all the dorsal horn nociceptive neurons, and ultimately leading to the perception of pain in the T10 dermatome. As appendicitis progresses, the pain localizes to the right lower quadrant as the inflammation extends to the parietal peritoneum with the same nerve supply as the overlying dermatome.

Ascending Tracts Associated with Pain

Fibers carrying pain impulses exit the dorsal horn and ascend the spinal cord to the brain. The predominant pathways for pain conduction through the spinal cord are the spinothalamic tract, the spinomesencephalic tract, and the spinoreticular tract, located in the anterolateral aspect of the spinal cord (see Fig. 3-3).

The spinothalamic tract is the most important pathway for pain transmission. Lesions in this tract (the anterolateral portion of the spinal cord) cause a loss of pain sensation in the contralateral side below the lesion. Axons cross the midline within two spinal segments of their origin and then ascend the tract. The axons synapse in the ventroposterolateral nucleus of the thalamus and the posteromedial thalamus, where they then project to the cortex.[29] As these tracts ascend, fibers are added to the anteromedial border, producing an organization with sacral segments located dorsolaterally and cervical segments located anteromedially.

The spinoreticular tract ends in synapses in the reticular formations of the medulla, pons, midbrain, and intralaminar thalamic nuclei. These locations ultimately project to the limbic forebrain. The spinoreticular tract is an important part of the suprasegmental reflex responses to pain and serves as a direct link between the reticular arousal centers and the dorsal horn. Spinomesencephalic tract fibers synapse in the periaqueductal gray matter and other midbrain nuclei. These fibers likely activate a system of descending pain inhibitory signals that project from the periaqueductal gray matter.

The dorsal columns of the spinal cord primarily transmit innocuous sensory information. These columns, however, may also play a role in pain through modulation of the spinothalamic tract. In addition to providing discriminatory information to localize pain, sensory input may activate cortical descending pathways that modulate the dorsal horn response to nociceptive input. The spinothalamic tract then provides precise localization of the nociceptive data, whereas the spinoreticular and spinomesencephalic tract input serves to arouse the body to ongoing tissue damage. This sequence activates the neuroendocrine, emotional, and autonomic reflexes associated with pain.[30]

Pain Modulation

Impulses from nociceptors are modulated by descending tracts in the spinal cord. The two primary descending pathways appear to be primarily serotonergic and noradrenergic. These pathways originate in the midbrain (periaqueductal gray matter and locus ceruleus) and medulla (nucleus raphe magnus and nucleus reticularis gigantocellularis) and are transmitted to the spinal cord via the dorsolateral funiculus.

Electrical stimulation of descending pathways produces analgesia comparable to that produced with opioids. Stimulation of the thalamus can also produce analgesia.[31] Inputs to this system come from the frontal cortex, the limbic system, the hypothalamus, the reticular system, the locus ceruleus, and the spinal cord. Multiple neurotransmitters are involved in these pathways, including serotonin, norepinephrine, and substance P. It is believed that the activation of this system is responsible for effects achieved by placebo, acupuncture, and transcutaneous electrical nerve stimulation (TENS) units.

Central Sensitization

Central sensitization involves the amplification of nociceptive signals. Central sensitization is mediated by multiple substances such as nitric oxide, glutamate, substance P, aspartate, prostaglandins, leukotrienes, norepinephrine, and serotonin. It can occur in the presence of chronic pain or as a result of damage at any point along the pain transmission system. Central sensitization is described in the setting of traumatic and degenerative conditions of the spinal cord and brainstem and can be associated with thalamic strokes, multiple sclerosis, Parkinson's disease, Arnold-Chiari formation, and cervical stenosis.

Pain Expression

The transduction, transmission, and modulation of pain stimuli develop the perception of the subjective emotional experience of pain. Many factors other than the stimulation of nociceptors influence the final perception of pain. The discrete cognitive processes and pathways involved in the interpretation and experience of painful stimuli remain a mystery and are affected by factors such as cultural expectations, personality, experiences, and the underlying emotional state. Many of these factors, and therefore the subsequent perception of pain, can be greatly influenced by both pharmacologic and nonpharmacologic interventions.

For drugs such as nitrous oxide and low-dose opioids, much of their analgesic effect is on the cognitive interpretation and emotional reaction to pain rather than on the transmission of the pain stimulus. Noninvasive techniques (e.g., distraction and hypnosis) can limit pain perceptions and increase tolerance. Changes in the manner in which a person experiences pain, based on previous experiences and learned behaviors, are referred to as *cognitive sensitization.*

Reflex Responses to Pain

There are two types of reflex responses to nociceptor input: spinal segmental (or suprasegmental) and cortical. Spinal reflexes are generated by the transmission of nociceptive impulses from the dorsal horn to motor and autonomic neurons in the spinal cord, provoking a range of responses, including tachycardia, vasoconstriction, paralytic ileus, and muscle spasm (Box 3-2).[32]

www.ketabpezeshki.com 66485457-66963820

Box 3-2 Reflex Responses to Pain

Increased Sympathetic Tone
Vasoconstriction producing increased peripheral resistance
Increased cardiac output from increased stroke volume and heart rate
Increased blood pressure
Increased metabolic rate and oxygen consumption
Decreased gastric tone and gastric emptying (may progress to ileus)
Decreased urinary tract tone (may lead to urinary retention)

Endocrine Responses
Decreased insulin production
Increased cortisol
Increased antidiuretic hormone
Increased growth hormone
Increased renin, angiotensin II, aldosterone
Increased glucagon
Increased catecholamines

Respiratory Responses
Hyperventilation

Cortical Responses
Anxiety and fear

Table 3-2 Opioid Receptors

OPIOID RECEPTOR CLASS	EFFECTS	ASSOCIATED ENDOGENOUS ENDORPHIN
Mu 1	Euphoria, supraspinal analgesia, confusion, dizziness, nausea, low addiction potential	Beta-endorphin
Mu 2	Respiratory depression, CV and GI effects, miosis, urinary retention	Beta-endorphin
Delta	Spinal analgesia, CV depression, decreased brain and myocardial oxygen demand	Enkephalin
Kappa	Spinal analgesia, dysphoria, psychomimetic effects, feedback inhibition of endorphin system	Dynorphin, beta-endorphin
Epsilon	Hormone	Beta-endorphin
Gamma	Dysphoria, psychomimetic effects	Beta-endorphin

CV, cardiovascular; *GI,* gastrointestinal.

Suprasegmental reflexes are transmitted through ascending tracts to the brainstem, hypothalamus, and cortex, where withdrawal reflexes and autonomic responses occur in conjunction with conscious responses. The autonomic reflex responses to pain are variable and cannot be used to quantify pain in an individual.[33,34]

Endorphin System

The endorphin system is a neuroendocrine system that serves to modulate responses to pain and stress. The endorphin system consists of widely scattered neurons that produce three types of opioids: beta-endorphin, met- and leu-enkephalins, and dynorphins. These opioids act as neurotransmitters and neuromodulators at three major classes of receptors—mu, delta, and kappa—and produce analgesia and counter the stress response (Table 3-2).

Under normal circumstances the endorphin system serves to decrease pain and stress after a person has adequately dealt with the inciting noxious stimuli. The endorphin system normally is a responsive system that can have an increased or decreased effect to produce the appropriate response to a painful event. As with other neuroendocrine systems, increasing stimulation by endorphins produces feedback inhibition on their own circulating levels. During prolonged periods of pain with high levels of stimulation, the system can become less responsive and less effective at modulating the pain response.

Like their endogenous counterparts, opiates act at chemical receptors to produce both analgesia and undesirable side effects.[35] As these drugs are given over a prolonged period, they inhibit the endogenous endorphin system, blunting the response to pain and stress and decreasing the overall endorphin effect. As these drugs are withdrawn, the normal effects of the endorphin system resume.

Table 3-3 Acute versus Chronic Pain

	ACUTE PAIN	CHRONIC PAIN
Inciting factor	Associated pathology present and recovery is expected.	Associated pathology either not identifiable or not expected to improve; recovery either unpredictable or not expected.
Relation to healing	Pain improves as the injury heals; limitation of activity because of pain assists healing.	Neither pain nor injury expected to improve; pain may limit activities that could improve condition.
Psychosocial effects	Limited to acute stress reaction.	Negative effects a prominent feature of disease.
Treatment	Analgesics, immobilization.	Psychosocial aspects must be addressed; analgesics play a smaller role.

Acute versus Chronic Pain

Acute pain is usually associated with an identifiable pathologic condition and serves an adaptive function by warning the individual that an illness or injury exists. This sequence will motivate the person to cease the activity that is causing the pain, look for a cause, seek help, and avoid the stimulus in the future.

Acute pain becomes chronic pain when the pain pattern persists, in changed or unchanged form, after the original physiologic insult has apparently resolved. All chronic pain starts as acute pain, but only small subsets of patients with acute pain develop chronic pain (Table 3-3). The physiologic transition from acute to chronic pain is a complex process with both physiologic and psychosocial components. In many circumstances the development of chronic pain is likely related to the treatment of acute pain.

Acute pain serves an important purpose in that it stimulates a person to protect the injured area and seek help. In addition, the neurochemical factors that contribute to acute pain acknowledgement will generally initiate and support recruitment of tissue repair mechanisms.[36] As an injury heals, these adaptive responses may become maladaptive if the pain persists, as this cycle can lead to a decreased range of motion and decreased function of the area and ultimately an increased susceptibility to injury and pain. Pain also causes a stress response that is initially adaptive in the face of injury. A prolonged stress response, however, causes immune system impairment, a hypercoagulable state, sleep disturbances, anxiety, and depression.[15,16,37]

Chronic pain is very common, and a large number of patients with chronic pain are seen in the ED.[5,38] It can be difficult to determine the point at which an adaptive pain response becomes maladaptive and the progression from acute pain to chronic pain occurs. Chronic pain can have a wide range of inciting events

www.ketabpezeshki.com 66485457-66963820

Numeric Rating Scale

No pain 1 2 3 4 5 6 7 8 9 10 Worst pain possible

Visual Analog Scale

No pain |————————————————| Worst pain possible

Verbal Descriptor Scale

None	Mild	Moderate	Severe
0	1	2	3

Figure 3-5. Pain scales.

including persistent tissue injury or even factors unrelated to tissue injury.

MANAGEMENT PRINCIPLES

Pain Assessment

The early, accurate recognition and assessment of a patent's pain are the most important aspects of effective acute pain management.[39] When pain is inadequately treated, inaccurate assessment is very likely the root cause of the problem.[7]

The degree to which a person experiences pain is a complex and subjective interaction between the physical stimulus and the patient's cognitive and emotional state. It is clear, however, that the degree of pain a patient perceives is not directly determined by the degree of physiologic injury. Patients in the ED with relatively identical injuries may report completely different amounts of pain.[39] Therefore pain treatments, analgesic requirements, and the manner in which a patient describes pain cannot be uniformly described based on the nature of a patient's injury.

The assessment of pain depends on the patient's ability to communicate the nature of the painful experience to the physician and the physician's ability to obtain this information. Unfortunately, there is no objective test or physiologic index to measure pain reliably.[40-47] Objective observations, such as hypertension, diaphoresis, or tachycardia, do not correlate well with the degree of pain present.[9,44,48]

Pain assessment is made through an indirect estimation by the patient's caregivers. Because pain cannot be objectively measured, a physician's assessment depends on communication with the patient, both verbal and nonverbal. Barriers to communication between patients and physicians, including linguistic, socioeconomic, and cultural differences, limit the ability to effectively assess pain. Because effective treatment is based on the assessment of pain, patients who have difficulty communicating are at particular risk of undertreatment of their pain (oligoanalgesia). Groups at particular risk for oligoanalgesia include infants and children, patients whose cultural background differs significantly from the treating physician's, and patients who are developmentally delayed, cognitively impaired, under severe emotional stress, or mentally ill.[5,9,39,49-52]

Oligoanalgesia

Oligoanalgesia, the inadequate treatment of pain, is described in most studies of pain in ED patients.[5,53-66] The National Hospital Ambulatory Medical Care Survey evaluated all isolated closed fractures of extremities and clavicles and demonstrated that only 64% of patients received an analgesic, with only 42% receiving an opioid.[53] Children, the elderly, and patients from social and ethnic minorities exhibit oligoanalgesia the most frequently.[5,52,67,68]

Even when analgesia is administered in the ED, there frequently is a long delay before therapeutic actions. When opioids are used, they are often given in subtherapeutic doses. One study of trauma centers demonstrated that of the 38% of patients who received an analgesic, the average time to administration of the first dose of analgesic was 109 minutes after arrival.[65]

There are a variety of reasons why patients do not receive adequate analgesia from health care providers. These include the ineffective assessment of pain. Other issues are prohibitive, including misconceptions about the safety and efficacy of various treatments as well as the effect of analgesic interventions on a patient's evaluation.

Pain Measurement

The use of numeric rating scales employing a verbal 0 to 10 score ("none to worst imaginable") is ubiquitous in the ED and other settings where acute pain is managed or inflicted.[68] Visual analog scales, usually consisting of a 10-cm straight line with anchors at both extremes, are frequently used in research to provide continuous data for analysis. These scales offer little practical advantage over verbal reports in the clinical setting.[40,45,67,69,70] Including a pain scale as a part of vital sign assessment is now mandated by TJC (Fig. 3-5).[70] Routine verbal or visual pain scale assessment encourages clinicians to communicate with patients to assess their pain and to evaluate responses to analgesic intervention attempts.[55,71]

Patient-derived pain scales are useful only if the patient understands the scale as communicated by the health care provider. Pain scale use also requires the patient to be able to assign a concrete value to the abstract concept of pain. In general, children younger than 7 years are unable to successfully relate to pain scale

www.ketabpezeshki.com 66485457-66963820

processes. As a consequence, children require alternate communication venues to both acknowledge and relate pain. The FACES pain scale is designed for children younger than 7 and is an example of a pain assessment tool to be used by children to describe their pain.[72] This scale has a series of cartoon faces expressing a range of emotions from happiness to severe distress. The child is asked point to the face that corresponds to how he or she feels. The FACES pain scale and others like it require less of an abstract reference than numeric and verbal scales and are useful in pain assessment for toddlers and cognitively impaired adults.[73]

In preverbal children, observer-derived scales may be used. These include scales such as the Modified Pre-Verbal, Early Verbal Pediatric Pain Scale (M-PEPPS),[74] the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS),[75] and the CRIES scale for neonates.[76] These scales use a scoring system for observed criteria that is reproducible between trained observers, making them useful for research. These scales appear to have little clinical utility over the physician's or parents' overall impression of the child's pain.[77]

Numeric rating scales can be used as communication tools between the patient and the physician to describe pain. Care must be taken, however, in using the scores derived from the scale as an absolute indicator of pain. The score a patient uses to describe pain may have as much to do with how the patient desires the health care provider(s) to respond to the pain complaint as it does a description of the pain relative to previous experiences. As a patient undergoes treatment, changes in the pain scores may represent a number of factors, including satisfaction from analgesic interventions and a desire for further treatment, as well as actual changes in experienced pain.

Pain scores have gained acceptance as the most accurate and reliable measure of assessing a patient's pain as well as response to pain treatment. Pain treatment should be targeted to a goal of reducing the pain score (e.g., by 50%, to below 3/10, or to "mild" from "moderate or severe") rather than a specific (maximum) analgesic dose.

Treatment

The approach to patients in pain should use a division of pain patients into four specific treatment groups:

1. acute pain
2. chronic pain
3. recurrent pain
4. chronic pain of malignancy

Therapy for groups other than those with acute pain should focus on a long-term, multidisciplinary approach to treat the multiple manifestations of these diseases. In addition, the approach should address the role of the emergency physician and ED as part of a patient's ongoing comprehensive strategy. Acute and chronic pain have different physiologic causes and thus require different treatment approaches (Fig. 3-6).

Chronic Pain

The assessment of pain in the absence of acute or obvious physical injury requires a great deal of communication skill on the part of the physician and the patient. Many patients with chronic pain develop a great deal of experience, some of it adaptive and some maladaptive, in describing their pain and interacting with physicians to receive pain treatment.[78] Many behaviors such as exaggerating symptoms or attempting to manipulate providers are developed around the patient's expectations for receipt of pain therapy and/or pain relief. These behaviors, combined with the negative psychosocial effects and sense of futility associated with chronic pain, can complicate the evaluation process and the care of chronic pain patients.

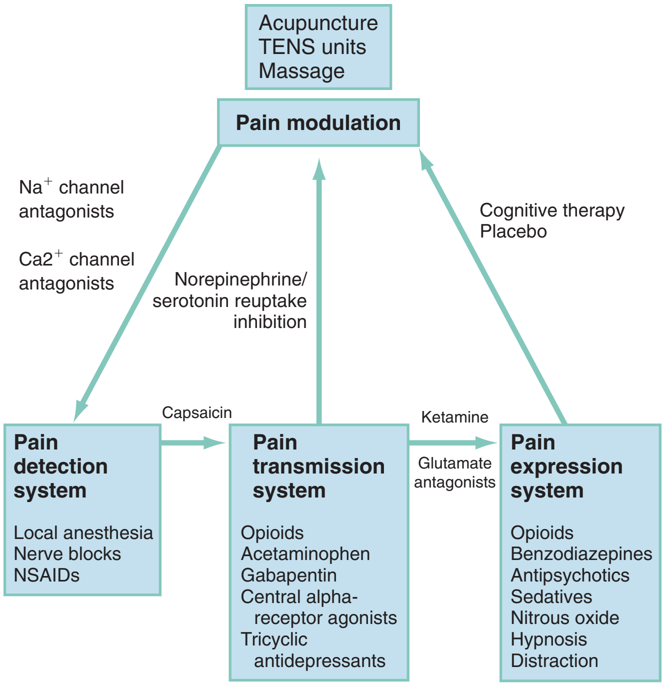


Figure 3-6. Sites for pain treatment algorithm.

The assessment of chronic pain can be one of the most challenging situations in which to obtain an accurate clinical history. Patients who are having a difficult time describing their pain should be encouraged with detailed questions about the pain, combined with multiple examples, comparisons, and summarizing statements, to facilitate accurate communication. Assuring the patient that the questions are intended to aid understanding and to enable treatment of symptoms as effectively as possible can facilitate the development of a common goal and help establish the trust necessary to develop an effective treatment strategy.

Presentation of patients with chronic pain can be either an exacerbation of their chronic pain in the setting of ongoing therapy or untreated chronic pain resulting from a gap in, or a lack of, appropriate treatment. These scenarios require different treatment approaches. For chronic pain patients with an exacerbation in their pain exceeding the pain control of their usual treatment strategy, treatment can be approached in a fashion similar to that for acute pain. The goal in these patients should be to control the exacerbation and return the patient to baseline function.

Many patients with chronic pain are in comprehensive treatment programs, most of which involve a "contract" with respect to the location for their pain management (e.g., not in an ED) and specific medications. For such patients, a review of the pain management plan in the medical records, or contact with the physician who typically manages the patient's pain, is desirable before embarking on a short-term treatment strategy in the ED.

Patients with chronic pain who have a gap in their baseline treatment, or who have never established appropriate treatment for chronic pain, require an approach that addresses the need for establishment of a chronic, consistent treatment plan. Patients with no ongoing treatment plan who are identified as having chronic pain should have a basic chronic pain treatment plan implemented during their ED visit. This should consist of acetaminophen, if not contraindicated, and a nonsteroidal anti-inflammatory drug (NSAID) if tolerated. Tramadol may be helpful in certain cases. Adjuvants appropriate for neuropathic or central pain may be added if appropriate. Opioids should not be

www.ketabpezeshki.com 66485457-66963820

prescribed until these other treatments have been maximized and should be added in addition to these other therapies rather than as an alternative.[79] In general, opioids for chronic pain management are best managed through ambulatory pain centers or through a primary care physician who can follow the patient's therapy and response.

Recurrent Pain

Recurrent pain is a subset of chronic pain and is a condition in which patients have repeated episodes of similar pain. Recurrent pain can include such disorders as back pain, myofascial pain syndrome, migraine syndrome, sickle cell disease, and inflammatory bowel disease. The approach to the treatment of recurrent pain in the ED is similar to that of acute pain, except that prevention of recurrent pain events are considered as part of the treatment strategy. These therapies may integrate nonpharmacologic approaches, such as physical therapy for back pain, in addition to preventive medication agents.

Chronic Pain of Malignancy

Chronic pain from malignancy is approached differently than other causes of chronic pain. Chronic malignant pain is similar to acute pain in its relation to ongoing nociceptive stimulation and similar to chronic pain in its duration and psychobehavioral effects. The medications used, for the most part, are similar to those used for acute pain. Similarly to chronic pain, the psychosocial effects of the pain of malignancy must also be addressed as part of an effective treatment strategy.

Patients with a significant change in the pattern of their chronic pain caused by cancer or a terminal illness, as with other chronic pain patients, should be evaluated for a new process to account for the pain. Opioids, especially in long-acting or transdermal preparations, should be used liberally to bring pain relief in patients with terminal illnesses.[80]

Neuropathic Pain

Activation of the sympathetic system does not typically result in pain. Acute nerve injury appears to modulate the development of hyperalgesia and allodynia, however, and is associated with a wide variety of neuropathies. *Complex regional pain syndrome* (CRPS) is a term that includes most sympathetically maintained pain.[81] CRPS type 1 (often referred to as *reflex sympathetic dystrophy*) develops after an injury and typically follows the distribution of a peripheral nerve.[80] It is associated with hyperalgesia, allodynia, changes in skin blood flow, and sympathetic dysfunction. CRPS type 2 (commonly referred to as *causalgia*) is associated with burning pain and allodynia in the distribution of an injured nerve with no association with sympathetic symptoms.[80-82] Opioids are ineffective in preventing CRPS after the injury has ocurred.[83] Clonidine, *N*-methyl-D-aspartate receptor antagonists, and γ-aminobutyric acid (GABA) receptor agonists are more effective in the treatment of CRPS than opioids.[81]

Antidepressants have effects on neuropathic pain that appear to be distinct from mood effects.[84] A meta-analysis of 39 placebo-controlled trials involving first-generation tricyclic antidepressants demonstrated benefits in a variety of chronic pain syndromes.[85,86] For patients with chronic pain that is thought to be unrelated to central or neuropathic origins, other antidepressants such as serotonin reuptake inhibitors may be safer and more effective.

Several anticonvulsants, including gabapentin, phenytoin, carbamazepine, and valproic acid, have been used for neuropathic pain with lancinating or burning properties. Carbamazepine is used most frequently for trigeminal neuralgia, postherpetic neuralgia, and diabetic neuropathy. Gabapentin is described for both types of CRPS, postherpetic neuralgia, and diabetic neuropathy.[87-89]

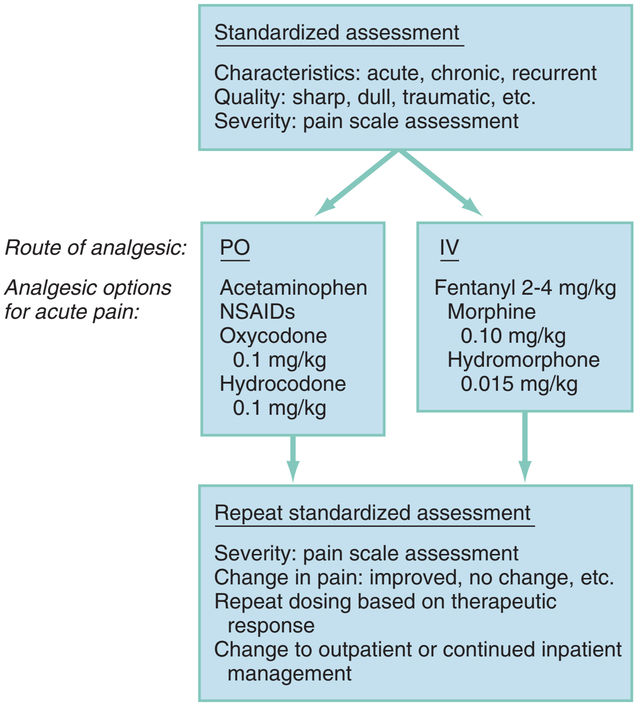


Figure 3-7. Emergency department pain therapy algorithm.

Acute Pain

Symptomatic treatment of pain should be initiated promptly, titrated to an acceptable level of relief, and continued while the investigation for a cause is proceeding (Fig. 3-7). When the cause of acute pain is uncertain, immediate relief of pain occurs in parallel with initial efforts to establish the diagnosis. It is inappropriate to delay analgesic use until a diagnosis has been made. There is no evidence that the administration of adequate doses of opioid analgesia to establish patient comfort impairs the physician's ability to diagnose the cause of an acutely painful condition. To the contrary, administration of analgesia may enhance the accuracy of physical examination and patient assessment.[90,91]

Analgesic Agents

Opioid Analgesic Agents

In 1680 Sydenham wrote, "Among the remedies it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium."[92] Centuries later, this statement is still accurate, and titrated opioids are the mainstay of therapy for acute pain.

The beneficial effects of opioids have been well documented for centuries, as have their toxicity and potential for abuse.[93] Unfortunately, opioids are often poorly used in clinical practice.[56] Concerns regarding opioid toxicity or dependence and a poor understanding of the pharmacokinetics of the drugs lead to inadequate dosage and excessively infrequent dosage intervals. The safety of the short-term use of opioids for acute pain, in terms of both toxicity and likelihood of causing future dependence, is demonstrated.[90,91] Opioids should be the first-line agents in the management of acute severe pain (Table 3-4).

Mechanism of Action and Toxic Effects. Opioids bind to specific endorphin system receptors located throughout the nervous

www.ketabpezeshki.com 66485457-66963820

Table 3-4 Opioid Analgesics

NAME	INITIAL PARENTERAL DOSE	INITIAL ORAL DOSE	DURATION OF ACTION	EQUIPOTENT INTRAVENOUS DOSE	EQUIPOTENT ORAL DOSE	COMMENTS
Morphine	0.1 mg/kg	0.5 mg/kg	3-4 hr	10 mg	50 mg	Standard opioid for comparison
Hydromorphone	0.015 mg/kg	0.075 mg/kg	2-4 hr	1.5 mg	7.5 mg	Inactive metabolites are an advantage to patients with renal or hepatic disease.
Methadone	0.1 mg/kg	0.2 mg/kg	4-8 hr	10 mg	20 mg	Used for opioid addiction therapy and chronic pain; half-life longer than duration of action.
Fentanyl	1.5 µg/kg	3 µg/kg	0.5-1.5 hr	100 µg	NA	Oral dose actually transmucosal absorption; metabolites inactive; transcutaneous patches used for chronic pain.
Oxycodone	0.1 mg/kg	0.15 mg/kg	3-4 hr	10 mg	15 mg	Excellent bioavailability renders an effective oral agent for acute pain.
Codeine	1.3 mg/kg	2.5 mg/kg	2-4 hr	130 mg	200 mg	Side effect to analgesia ratio is undesirable. Pronounced peripheral effects: constipation, nausea and vomiting, cough suppression.
Hydrocodone	NA	5-15 mg	3-4 hr	NA	30 mg	Commonly used in preparations with acetaminophen; more potent than codeine.
Meperidine	0.75 mg/kg	3 mg/kg	2-3 hr	75 mg	300 mg	Toxic metabolite normeperidine accumulates at normal doses; generally should not be used for acute analgesia.
Oxymorphone	0.01 mg/kg	0.1 mg/kg (rectal)	3-4 hr	1 mg	10 mg	Rectal administration more predictable than with other agents.
Alfentanil	10-20 µg/kg	NA	8-12 min	1 mg	NA	Short duration because of redistribution; duration of action increases with the size of the dose.
Sufentanil	0.1 µg/kg	NA	1-1.5 hr	10 µg	NA	Minimal cardiovascular side effect.
Remifentanil	0.5-1 µg/kg	NA	4-6 min	50 µg	NA	Used as a continuous infusion.
Nalbuphine	0.4 mg/kg	0.1 mg/kg	3-4 hr	40 mg	NA	Mixed agonist/antagonist; decreased respiratory depression relative to other opioids; limited analgesic effect; used in perinatal period.

NA, not applicable.

system. These receptors suppress pain detection peripherally, modify pain transmission in the spinal cord and thalamus, and alter the perception of pain at the level of the cortex. A variety of endorphin receptors are defined (see Table 3-2). The unique actions of opioids are determined by the specific binding properties of the agent to the various receptors.

Side effects sometimes can limit the success of opioid therapy, particularly in the acute treatment setting. The occurrence of these side effects varies among individual patients and opioid agents. Tolerance of many side effects develops shortly after the initiation of therapy.

The most common side effect of opioids is constipation. Constipation is attributed to opiate binding of receptors located in the antrum of the stomach and proximal small bowel.[94] Parenteral and transdermal administration routes may be superior to oral methods owing to decreased exposure of the gut to the opioids.[95,96] Constipation can be anticipated with long-term (more than a few days) opioid use. An active laxative, such as senna, lactulose, or bisacodyl, should be prescribed as needed.

Nausea and vomiting can occur with the administration of opioids, especially in opioid naïve patients.[97] It is often difficult to distinguish whether nausea and vomiting are caused by the opioid or the acute pain for which it is administered. Routine coadministration of an antiemetic with the opioid, once an almost universal practice, has largely been discontinued in clinical practice. Nausea and vomiting in the context of persistent, acute pain after opioid administration may require additional opioid and an antiemetic, such as promethazine, droperidol,[98] prochlorperazine, or one of the 5-HT_3 receptor antagonists (e.g., ondansetron).

True immunoglobulin-mediated allergies are rare for morphine and other opioids. Many patients will experience mild pruritus of the trunk and face after parenteral administration. This side effect is related to histamine release from opioid receptors on mast cells and does not constitute an allergy. To a varying degree, opioids destabilize mast cells in a dose-dependent fashion, causing histamine release and resultant urticaria, pruritus, and orthostatic hypotension This reaction may appear as localized urticaria tracking up a vein after intravenous administration of an opioid, especially morphine. Rarely, bronchospasm may be seen in patients with reactive airway disease or atopy. This effect usually subsides rapidly, with no treatment required, although the symptoms can be controlled with administration of an antihistamine.

Sedation and respiratory depression can occur with opioid administration for acute pain. Opioids decrease medullary sensitivity to CO_2 via central stimulation of the mu receptor, resulting in respiratory depression. The combination of opioids with other sedating agents, such as benzodiazepines, will increase the likelihood of respiratory depression. Patients with underlying hepatic or renal dysfunction are also at increased risk because of inability to clear opiates normally, resulting in the accumulation of active metabolites.

www.ketabpezeshki.com 66485457-66963820

Pain is a very effective stimulant of respiratory drive, rendering respiratory depression rare in the context of acute, severe pain. Fear of respiratory depression should not deter the clinician from adequately treating pain. It should be noted that patients who previously tolerated a dose of an opioid may develop respiratory depression if the source of acute pain is removed, such as by local anesthesia or the reduction and stabilization of a fracture.[99] Transient respiratory depression from opioids usually responds to simple verbal or tactile stimulation and uncommonly requires more aggressive interventions.

Tolerance and physical dependence are common effects of the prolonged use of opioids. Physical dependence is defined as the occurrence of an opioid withdrawal syndrome after abrupt cessation, rapid dose reduction, or administration of an antagonist. Tolerance is a phenomenon that occurs after prolonged exposure to opioids and is characterized by the diminution of an opioid's effect over time. Normal expected results of the prolonged use of opioids should be accounted for in planning their use for extended periods, and do not represent addiction.

Addiction is a potential risk associated with prolonged opioid use and often limits their use.[100] The term *addiction* refers to a neurobiologic disease, with many factors influencing its development and manifestations. Addiction is characterized by compulsive drug use, continued use despite harm, and craving. The iatrogenic creation of opioid addiction, a new addiction where one did not previously exist, is a relatively rare phenomenon.[101] In one trial, the Boston Drug Collaborative Study, only 4 in 11,892 hospital inpatients treated with opioid analgesic agents developed new opioid abuse behaviors.[102]

Pseudoaddiction describes patient behaviors that may occur when pain is undertreated.[103] Patients with unrelieved pain may become focused on obtaining medications and otherwise seem inappropriately "drug-seeking." Behaviors such as illicit drug use and deception can occur in the patient's efforts to obtain relief. Pseudoaddiction can be distinguished from true addiction in that it resolves when pain is effectively treated.

Suggestion of Drug-Seeking Behavior. Some patients feign or exaggerate pain to receive opioids.[104] A physician's impression that a patient is drug-seeking is associated with a reduction in the treatment of the patient's pain. These perceptions are often complicated by differences between the health care provider and patient in characteristics such as socioeconomic class, ethnic background, age, and race. These elements are frequent sources of bias in the treatment of pain.[39] Care should be taken to recognize such factors and consider their impact on treatment behaviors. Unless or until a thorough evaluation of the patient, usually including medical records related to prior visits and sometimes including telephone contact with other providers (other hospitals, primary care physician), establishes a working diagnosis of drug-seeking behavior, a patient should be given the benefit of the doubt and should be treated as though the pain is legitimate. Primary providers, chronic pain specialists, and others should note patient contracts, prescription details, and patterns of possible nontherapeutic drug-seeking in the medical record, using objective terms and descriptions.[105] Patients with repetitive episodes of drug-seeking events may benefit from a multidisciplinary review to establish specific recommendations for their care when they are seen by anyone other than their primary pain management provider.

Administration. The goal of the administration of opioids is to attain and maintain effective analgesia with minimal adverse effects. The effects of opioids vary widely among individuals. There is no "ceiling effect" to their potency. There is also no standard, fixed, or weight-related dose that can consistently produce a given clinical effect. The correct dose a particular patient requires at a particular time can be determined only by repeated assessment of the degree of pain relief and adverse effects. The use of opioids therefore requires titration based on frequent and accurate assessments.[90] The most effective and safest way to achieve pain relief is to use a deliberate intravenous titration.

Box 3-3 Disadvantages of Intramuscular Opioid Administration

- Pain on injection
- Delayed onset of action
- Inability to predict therapeutic effect
- Inability to titrate dosage
- Diurnal variation in level achieved
- Disease state may affect level achieved
- Level dependent on intramuscular injection site

The intramuscular route of administration of opioids has several disadvantages and is not advised for treatment of acute pain (Box 3-3). The principal limitation of the intramuscular route is that it does not allow effective titration. The time to achieve significant pain relief from an intramuscular injection varies substantially for each patient—from 20 to 60 minutes—and the intramuscular route offers no therapeutic advantage over the oral route. If an intramuscular injection dose is inadequate, the patient will require another painful injection to achieve effective analgesia. If too large a dose is given, the patient is at risk of side effects without the added safety of an intravenous line for reversal agents or drugs to counter side effects.

Most patients with mild to moderate pain are best treated with oral opioids. If pain is severe or if the patient is expected to require multiple doses of an agent for management, then an intravenous route of administration is desirable. If an intravenous line cannot be established and the patient cannot tolerate oral medications, the subcutaneous route is preferable to the intramuscular route. Subcutaneous injection is less painful than intramuscular injection, with a similar onset of pain relief.

Opioids can be delivered via an oral transmucosal or intranasal mucosal route.[106-108] Buprenorphine can be given by the sublingual route, and fentanyl is available in an impregnated, sweetened matrix called a Fentanyl Oralet (oral transmucosal fentanyl citrate). Nasal fentanyl, butorphanol, and sufentanil also produce rapid clinical effects via nasal mucosal absorption.[33,77,109]

The optimal use of intravenous opioids requires the administration of an initial loading dose, followed by assessment of the analgesic effect. Frequent (every 5-15 minutes) repeated doses should be administered until analgesia is achieved, followed by doses at regular intervals to prevent the return of significant discomfort. The best method to assess the need to administer repeat doses of an analgesic agent is to use the patient's subjective impression. Patient-controlled analgesia uses a computerized delivery system that allows patients to self-administer a prescribed dose of opioid based on self-assessment. Patient-controlled analgesia is safe and effective in a number of therapeutic settings, including sickle cell pain crisis in a pediatric ED.[110]

Specific Agents

Morphine. Intravenous morphine is often the first choice for treatment of acute, severe pain in ED patients. Morphine is the opioid analgesic agent with which all other opioids are compared. When administered intravenously (IV), morphine reaches a peak of action in 15 to 20 minutes; it has a half-life of 1.5 to 2 hours in healthy, young adults and slightly longer in the elderly. Its duration of action is 3 to 4 hours. An appropriate loading dose of morphine for acute severe pain is 0.1 mg/kg IV, augmented by repeated doses of approximately half the initial dose every 5 to 15 minutes, depending on the severity of the pain and patient response. Administration is continued until pain is relieved

www.ketabpezeshki.com 66485457-66963820

according to a predetermined goal, such as achievement of 3 or less (of 10) on the pain scale.

Morphine also is effective by oral administration; however, only 20% of the ingested dose reaches the tissues after first-pass metabolism, requiring a dose adjustment of 5× from an equipotent intravenous dose. There is no validity to the perception that morphine causes more smooth muscle spasm than other opioids, rendering it compatible for treatment of patients with biliary or renal colic.

Morphine is primarily metabolized by conjugation into a 3-conjugate and 6-conjugate form in the liver. The 3-conjugate form (normorphine) has no opioid analgesic activity and rarely has been associated with CNS side effects (e.g., tremors, myoclonus, delirium, or seizures). This risk is greatest in elder patients and those with renal insufficiency, although it is rarely an issue in the ED. The 6-conjugate form morphine metabolite is a strong mu- and delta-receptor agonist. This form plays an important role in the efficacy and duration of clinical effects.

Meperidine. Meperidine (Demerol), although once widely used, has several disadvantages compared with morphine and other parenteral opioids. Given these limitations, meperidine should not be used in the ED management of acute pain. The duration of action of meperidine, less than that of morphine, is only 2 to 3 hours. The greatest disadvantage of meperidine, however, is that it is metabolized by the cytochrome P_{450} system to the active metabolite normeperidine. Normeperidine is produced in much larger quantities than the toxic metabolite of morphine at a therapeutically equivalent dose. In addition, normeperidine can cause CNS toxicity at therapeutic meperidine doses.

Normeperidine has a half-life of 12 to 16 hours and blocks muscarinic receptors, resulting in significant anticholinergic effects including agitation and delirium. These effects may lead to seizures, hallucinations, and psychosis as the metabolite accumulates. Normeperidine is excreted through a renal mechanism with a subsequently longer half-life in patients with decreased renal function. Repeated administration of meperidine should be avoided.

Of particular concern with meperidine use is the potentially lethal interaction of meperidine with monoamine oxidase inhibitors as a result of serotonin accumulation. Meperidine is also associated with serotonin syndrome in patients taking a selective serotonin reuptake inhibitor or other serotonin agonist. Meperidine is no longer a formulary drug at many hospitals.

Hydromorphone. Hydromorphone is a semisynthetic derivative of morphine that is a potent analgesic agent, increasingly used in the management of acute pain in the ED. Hydromorphone is the P_{450} metabolite of hydrocodone and is seven times more potent than morphine with parental administration. Hydromorphone has a duration of action similar to that of morphine. Although 7 mg of morphine is equivalent to 1 mg of hydromorphone, nursing staff are more likely to administer "low" milligram doses of hydromorphone to patients with acute pain than "higher" equipotent doses of morphine.[111,112]

Pruritus, nausea, and vomiting may occur less frequently with hydromorphone administration than with morphine at equianalgesic doses. Hydromorphone is primarily conjugated into hydromorphone-3-glucuronide (H3G) in the liver and is excreted renally. H3G is primarily an inactive metabolite. As a result, hydromorphone is better tolerated than morphine, particularly in elderly patients and those with hepatic impairment. Patients with renal insufficiency may be at some risk of neurotoxicity after prolonged exposure owing to H3G accumulation.

Patients allergic to morphine do not consistently have cross-reactivity with hydromorphone. Hydromorphone can be given via intravenous, subcutaneous, or oral routes. A rectal preparation is available in the form of 3-mg rectal suppositories.[92]

Fentanyl. Fentanyl is a synthetic opioid that is highly lipophilic and produces analgesia within 1 to 2 minutes after intravenous infusion. Fentanyl redistributes rapidly, and its duration of therapeutic action is approximately 30 to 60 minutes.

Fentanyl is metabolized by the P_{450} system into inactive metabolites. Drug accumulation and toxicity may occur after tissue saturation following a prolonged infusion, but this is unlikely to happen during acute therapy. The short duration of action of fentanyl makes it highly titratable and ideal for use in patients who require serial examinations, such as trauma patients with possible occult head injury.

Fentanyl causes less histamine release than morphine and is associated with fewer peripheral effects at an equianalgesic dose. Fentanyl is therefore an excellent choice for treating pain in patients with bronchospastic lung disease. Fentanyl is more frequently associated with respiratory depression, however, than morphine, and patients receiving fentanyl infusions should be monitored with direct observation, supplemented by pulse oximetry or capnography.

The ED use of fentanyl is associated with a very low (1.1%) incidence of serious complications.[77,113-115] High or repeated fentanyl doses may produce muscle rigidity. This side effect, "rigid chest syndrome," usually occurs with anesthetic doses greater than 15 μg/kg and may be so severe that it interferes with respiration. Rigid chest attributed to fentanyl is exceedingly rare at doses typically used for acute analgesia. This rigidity, when observed to occur, does not uniformly respond to naloxone but is abolished by neuromuscular blockade.

Fentanyl can be administered IV, transmucosally, or transdermally.[115] Nebulized or intranasal fentanyl is described for the treatment of acute pain in patients without intravenous access at doses of 3 μg/kg.[33,77,82,116]

Oxycodone. Oxycodone is a strong opioid agonist that is highly bioavailable in an oral form. Oxycodone is widely available in combination with acetaminophen or aspirin as well as by itself, and is also available in long-acting oral formulations. Oxycodone bioavailability is 0.60 to 0.85, which is much higher than that of other opioids. It is quickly and efficiently absorbed, which may lead to its associated abuse potential.[117]

Oxycodone is not available in a parenteral form in the United States, although studies have demonstrated its intravenous form to be equianalgesic to morphine. As with other opioids, the analgesic effects of oxycodone are dose dependent. A 15-mg oxycodone dose has an efficacy similar to 10 mg of intravenous morphine. The onset of action of oral oxycodone is approximately 20 to 30 minutes.[106]

Oxycodone undergoes hepatic metabolism into oxymorphone, a strong opioid agonist that principally accounts for its analgesic effects. The inactive metabolite, noroxycodone, is also a product of oxycodone hepatic metabolism. As with codeine, approximately 10% of patients do not metabolize oxycodone well and are unable to generate the functional metabolite oxymorphone. This defect in metabolism renders these patients unable to achieve clinically meaningful pain relief with typical administration strategies and may require very large doses to achieve analgesia. This effect can also be caused by agents that compete with oxycodone for CYP2D6 metabolism, such as neuroleptics, tricyclic antidepressants, and selective serotonin reuptake inhibitors. Cases of serotonin syndrome are reported when serotonin reuptake inhibitors and oxycodone are given together, likely because of this metabolic interaction.[118,119]

Hydrocodone. Hydrocodone is metabolized in the liver to hydromorphone and is typically given orally (PO). Hydrocodone provides greater pain relief when combined with acetaminophen or NSAIDs than either component does alone. In two small studies, hydrocodone-acetaminophen (5 mg/500 mg) provided analgesia similar to that achieved with codeine-acetaminophen (30 mg/500 mg) in patients with acute musculoskeletal pain or undergoing dental surgery.[120,121] Hydrocodone may cause more

www.ketabpezeshki.com 66485457-66963820

drowsiness and dizziness but relatively less nausea than codeine. Hydrocodone combinations are less effective than oxycodone-acetaminophen combinations.[122] Hydrocodone clinical analgesia effects typically last 4 hours with typical administration of 5 mg to 20 mg.

Codeine. Codeine is a commonly prescribed opioid, usually in combination with acetaminophen, but is a weak opioid-receptor agonist and has little role in the modern ambulatory treatment of pain. Codeine is thought to exert its effects through metabolism into morphine and other active hepatic metabolites.

Approximately 10% of the population metabolizes codeine poorly. The effect of this genetic trait is a reduction in active analgesic metabolites and an enhancement in deleterious side effects including nausea, constipation, and pruritus. Although often prescribed for mild to moderate pain, codeine is a poor choice for analgesia owing to its tendency to cause side effects, especially nausea, cramping, and constipation, at doses that provide minimal analgesia.

Propoxyphene. Propoxyphene has limited indications for the treatment of acute pain. Many studies demonstrate its analgesic efficacy to be no better or only marginally better than placebo.[123] The propoxyphine metabolite, norpropoxyphene, can accumulate with repeated or large doses and cause refractory seizures, respiratory arrest, and significant risk of death as a result of torsades de pointes.[124] There is little evidence to support propoxyphene use alone or combined with acetaminophen for acute pain. As a consequence, propoxyphene generally should not be used in the ED or prescribed for the outpatient management of pain.[125]

Methadone. Methadone has several unique features that distinguish it from other opioids. It has no known neurotoxic or active metabolites and has high bioavailability. In addition to being a strong opioid agonist, methadone also has *N*-methyl-D-aspartate antagonist and serotonin reuptake–blocking properties. Methadone has a slow elimination half-life of 27 hours owing to its lipophilicity and tissue distribution. This slow clearance of methadone is the basis for its use in maintenance therapy, given that it can delay the onset of opioid withdrawal symptoms for up to 24 hours. The duration of its analgesic effects, however, is closer to 6 to 8 hours. The discrepancy between the duration of action of analgesia and the duration of the prevention of withdrawal symptoms is a result of the biphasic elimination of the drug and its redistribution.[126]

Naloxone. Naloxone is an opioid antagonist that can be given IV, intramuscularly (IM), subcutaneously (SC), or via endotracheal tube. Naloxone reverses the effects of opioids and is usually used in the setting of severe adverse events or opioid overdose. Naloxone can precipitate physiologic withdrawal in patients who are opioid dependent.

The duration of action of naloxone is approximately 45 minutes, which is shorter than that of most opioids. Therefore care should be taken to monitor for the recurrence of the opioid adverse events after this time period. Naloxone is typically given in repeat, titrated doses of 0.2 mg IV until reversed of any adverse opioid effect. In the setting of adverse events from opioid treatment, most commonly respiratory depression, careful titration allows for the smallest dose possible to be administered in order that the analgesic effect of the opioid can be maintained.

Tramadol. Tramadol is a synthetic oral compound that is a weak mu agonist with some serotonin and norepinephrine reuptake qualities. Its analgesic properties are thought to be primarily a result of mu-receptor agonism. Tramadol-induced analgesia, however, is only partially reversed by naloxone, suggesting other properties play a role in its therapeutic effects.

Tramadol, as a selective mu agonist without kappa agonist effects, should not cause physiologic dependence. Although tramadol use is associated with abuse and withdrawal similar to those of other opioids, their occurrence is sufficiently infrequent that the drug remains unscheduled.

Tramadol is metabolized in the liver by the cytochrome P_{450} system. One of its metabolites, M1, has an even greater mu-receptor affinity than tramadol and has an elimination half-life of 9 hours. Tramadol appears to have effects on GABA, norepinephrine, and serotonin receptors and the reuptake of the neurotransmitters, which may serve to activate descending pain modulation pathways.

Compared with traditional opioids, low-dose tramadol has a more favorable side effect profile and may present a lower risk of addiction with chronic use. The most common tramadol side effects are nausea, vomiting, dizziness, orthostatic hypotension, and sedation. These side effects are seen in as many as 17% of patients using the drug for chronic pain, with slightly lower rates occurring in patients receiving controlled-release versions.[127]

The occurrence of tramadol therapy side effects increases dramatically with increasing doses. Owing to reports of overdose and fatalities, a past or present history of addiction to opioids is a contraindication for the drug. The use of tramadol with other serotonergic medications (selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and serotonin norepinephrine reuptake inhibitors) is associated with serotonin syndrome.[128]

Tramadol is effective at low doses. At increasing doses it is associated with nausea and vomiting, which limits its use to low doses and effectively creates a therapeutic ceiling to its clinical use. Tramadol 37.5 mg combined with acetaminophen 325 mg appears to have similar efficacy to hydrocodone 5 mg combined with acetaminophen 325 mg.[129]

Tapentadol. Tapentadol is a mu opioid agonist and a norepinephrine reuptake inhibitor and is thought to control acute pain via both of these pathways. Tapentadol has similar efficacy to oxycodone for the treatment of acute pain with less frequent nausea and vomiting.[130-133] Its dual mechanism of action makes it a potentially effective drug for use in chronic pain, although it has not been studied for this use.

Opioid Agonist-Antagonist Analgesic Agents. The agonist-antagonist group of opioids was synthesized in an attempt to provide analgesia with little or no respiratory depression or abuse potential. It is believed that the analgesia provided by these agents is caused by agonist action at the kappa receptors, whereas the ceiling on respiratory depression is created by mu-receptor antagonism. Agonist-antagonist agents have rates of abuse similar to those for standard opioids and a ceiling effect to their analgesia that limits their use. Clinical application of these drugs is typically in situations in which brief, limited analgesia is needed and respiratory depression is the principal adverse concern, such as in the perinatal period.

Nalbuphine is a commonly used agonist-antagonist. The half-life of nalbuphine is 3.5 hours, and the effects of renal or hepatic disease on metabolism are not completely known. The usual therapeutic parenteral dose is 10 mg. As with all other opioids, the dose is individualized for the specific patient and clinical needs.

Opioid Use in Acute Abdominal Pain. Historically, pain treatment was withheld from patients with abdominal pain, to avoid confounding the diagnosis. This recommendation dates from the turn of the 20th century, predating modern diagnostic techniques, and has no place in modern emergency care. Multiple studies have confirmed the safety of providing effective opioid analgesia to patients with undiagnosed abdominal pain.[134-142]

Nonopioid Analgesic Agents

Acetaminophen. Acetaminophen is the first-line agent for the treatment of both acute and chronic pain and is the safest pharmacologic option for pain in children and adults. It has a high

www.ketabpezeshki.com 66485457-66963820

toxic-to-therapeutic ratio and lacks significant drug interactions compared with other pain medications.

Although acetaminophen has been in use since the 1880s, its pharmacologic mechanism of action is unknown. Acetaminophen has known analgesic and antipyretic activity, with no known peripheral anti-inflammatory effects. Its activity may be a result of the inhibition of prostaglandin endoperoxide H_2 synthase and a cyclooxygenase (COX) isoenzyme centrally.[143] It may also effect the activation of beta-endorphin centrally.[144] The analgesic actions of acetaminophen are comparable in magnitude to those of NSAIDs,[145] and the analgesic effects of the combination of acetaminophen with an NSAID are additive.

Acetaminophen is metabolized in the liver primarily through conjugation to sulfate or glucuronides. A minor pathway for the oxidative metabolism of acetaminophen produces the toxic metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI). NAPQI requires glutathione for detoxification and elimination. Hepatic toxicity can occur when glutathione pathways are overwhelmed by an increase in NAPQI or a decrease in glutathione. Hepatic toxicity is rare with ingestions less than 10 g in a 24-hour period unless underlying liver disease exists or there is concomitant ethanol abuse. In such cases, therapeutic doses can cause clinical hepatotoxicity.[146]

Acetaminophen is generally well tolerated when used at therapeutic doses. Mild rashes are reported, as is bone marrow suppression, manifested by neutropenia, thrombocytopenia, and agranulocytosis. Its use is associated with several important drug interactions. Many anticonvulsants, including phenytoin, barbiturates, and carbamazepine, induce hepatic microsomal enzymes. Increased conversion of acetaminophen to its toxic metabolite may occur in patients who are taking anticonvulsants, but this is rarely of clinical significance in the context of the usual doses for pain management.

Although uncommon, drug interaction resulting in an increased international normalized ratio (INR) is reported for patients taking both acetaminophen and warfarin, particularly among patients taking high doses of acetaminophen (>9100 mg/week).[147,148] Chronic use of acetaminophen should be avoided in patients with hepatic or renal disease. Renal failure can worsen with acetaminophen use, but the mechanism is unknown.[149] Patients with a history of salicylate hypersensitivity characterized by urticaria have an 11% cross-reactivity to acetaminophen, and the agent should be used with caution in this group.[150]

For mild analgesia and fever reduction, acetaminophen is the first-line agent, and it is a first choice for use in combination with other agents, usually opioids, in the treatment of patients with more severe pain. The recommended dose of acetaminophen for an adult is 650 to 1000 mg every 4 to 6 hours, not to exceed 4000 mg/day.

Nonsteroidal Anti-inflammatory Agents

NSAIDs inhibit COX and, as a result, the synthesis of prostaglandin, a key mediator of inflammation. The analgesic effect of NSAIDs is peripherally mediated by decreasing prostaglandin and effectively raising the threshold of activation of nociceptors. NSAIDs have synergistic effects with opioids and can reduce the amount of opioids needed to achieve pain relief.

Two COX isoenzymes mediate prostaglandin synthesis. COX-1 is present in all cells and plays an important role in homeostatic functions. COX-2 is induced by injury or inflammation and generates prostaglandins as part of the inflammatory process. Nonselective NSAIDs inhibit both COX-1 and COX-2, which results in multiple beneficial effects (reduction of inflammation, pain, and fever) but also some important undesirable effects.

As a group, and because of their common use, NSAIDs are responsible for more serious drug-related side effects than any other class of analgesic drugs.[151] The major side effects of NSAID analgesic agents are gastrointestinal (GI) bleeding, renal failure, anaphylaxis, and platelet dysfunction. The majority of these side effects occur in patients who are taking NSAIDs for chronic conditions. It is estimated that more than 100,000 hospital admissions and approximately 16,500 deaths each year from GI bleeding are related to NSAID use for osteoarthritis and rheumatoid arthritis.[152] One survey estimated that for every 100,000 people taking NSAIDs each year, there are 300 GI-related deaths, 5 hepatic-related deaths, 4 renal-related deaths, and some congestive heart failure–related deaths.[153]

Bone healing and repair during NSAID use is a concern in patients with acute fractures. There is limited evidence to suggest that prostaglandins promote bone formation and that NSAIDs might inhibit the process. This question has not been thoroughly pursued, nor its answer established, through properly conducted studies.[154] There is no evidence that short-term use of NSAIDs for analgesia after fracture is deleterious to healing.

In addition to prostaglandin, COX helps generate prostacyclin, a vasodilator that increases GI mucosal perfusion. In the stomach, COX-1 increases bicarbonate and mucus production, important for protecting the mucosal lining. Inhibition of COX-1 compromises these protections, predisposing patients to ulcerations and bleeding, which are then exacerbated by concomitant NSAID-induced platelet dysfunction.[155]

COX-1 and COX-2 affect the cardiovascular system through the production of endothelial prostacyclin (vasodilatory) and thromboxane (platelet aggregation). Inhibition of COX-1 produces antiplatelet activity that may be cardioprotective by inhibiting thromboxane production more than prostacyclin production. Inhibition of COX-2 inhibits prostacyclin production more than thromboxane production and may produce prothrombotic effects, increasing the risk of cardiovascular events. In the case of nonselective COX inhibitors, these two effects appear to balance each other out, resulting in few changes in cardiovascular risk in studies of these drugs. In the case of selective COX-2 inhibitors, this may result in an increase in cardiovascular risk.[156-158]

Prostaglandin produced by COX-1 causes renal vasodilation that maintains renal blood flow and the glomerular filtration rate (GFR). Inhibition of COX-1, especially in volume-depleted patients, can result in decreased GFR and even acute renal insufficiency. Sodium and water retention, hypertension, hyperkalemia, and acute renal failure may also ensue, particularly in patients with congestive heart failure.

The most common adverse effect of NSAIDs is GI mucosal injury. In patients taking NSAIDs continuously for 1 year, 10 to 60% will develop abdominal pain, dyspepsia, or nausea and 2 to 4% will develop symptomatic ulcers.[159] Risk factors include age, concomitant use of warfarin or corticosteroids, congestive heart failure, diabetes, and coronary artery disease. There is evidence that cytoprotective agents such as misoprostol and proton pump inhibitors reduce this risk.[159,160] The relative risk of GI side effects varies with the various NSAID agents and treatment strategies (Table 3-5).

Drug Interactions

Aspirin. NSAIDs may impair the cardioprotective effect of aspirin, although the available evidence is unclear and the use of daily aspirin for cardiac prophylaxis should not deter the prescribing of an NSAID for acute pain or inflammation.[161,162]

Oral Anticoagulants. The antiplatelet effects of NSAIDs add to the anticoagulant properties of warfarin, compounding the risk of significant bleeding complications, especially from GI ulcers. Furthermore, NSAIDs displace protein-bound warfarin and cause subsequent increases in prothrombin times at a constant warfarin dose.[160] NSAID use is generally avoided in patients who are taking warfarin.

www.ketabpezeshki.com 66485457-66963820

Table 3-5 Risk of Serious Gastrointestinal Effects of Nonselective Nonsteroidal Anti-inflammatory Drugs (NSAIDs)[152,153]

NSAID	RELATIVE RISK OF SERIOUS GI TOXICITY
COX-2 inhibitor	0.6
Ibuprofen	1.0
Diclofenac	1.8
Sulindac	2.1
Naproxen	2.2
Indomethacin	2.4
Tolmetin	3.0
Piroxicam	3.8
Ketoprofen	4.2
Ketorolac	24.7
Risk Reduction When Added to Ibuprofen[166]	
Proton pump inhibitor	0.09
Misoprostol	0.57

COX, cyclooxygenase; *GI,* gastrointestinal.

Angiotensin-Converting Enzyme Inhibitors. Concurrent use of NSAIDs with angiotensin-converting enzyme (ACE) inhibitors may impair renal function and impair the antihypertensive effects of ACE inhibitors.

Diuretics. Patients who are taking diuretics have a greater risk of developing renal failure caused by NSAID-mediated decreased renal blood flow. Also, the natriuretic response to diuretics depends in part on prostaglandin-mediated vasodilatation.

Glucocorticoids. Patients on corticosteroids have an increased risk of peptic ulcer disease. NSAIDs should generally be avoided in patients concurrently taking glucocorticoids unless closely supervised by an ambulatory care physician.

Lithium. NSAIDs enhance lithium reabsorption and may directly reduce lithium excretion, leading to increased lithium levels. CNS symptoms (drowsiness, confusion, vertigo, convulsions, or tremors), cardiac dysrhythmias, and QRS widening are warning signs of lithium toxicity. The lithium dosage should be reduced when an NSAID is prescribed.

Methotrexate. Chronic coadministration of NSAIDs and methotrexate has resulted in prolonged, elevated blood levels of methotrexate, resulting in severe toxicity. A possible mechanism for this effect may be decreased renal perfusion caused by NSAIDS, decreasing the elimination of methotrexate.

Nonselective Cyclooxygenase Inhibitors. NSAIDs combine analgesia and anti-inflammatory effects with low abuse potential and many different side effects compared with opioid agents. Oral NSAIDs can be as effective as oral opioids for mild to moderate pain. Parenteral NSAIDs offer little advantage over their oral forms.[160,163] Different patients respond differently to both the beneficial effects and the side effects of different NSAIDs. Therefore some experimentation may be necessary for determination of the best NSAID choice for a particular patient. No particular NSAID has been proven to be superior for any indication. Drug selection should depend on availability, side effect profile, convenience, and cost. Patients at risk for adverse events with use of NSAIDs are listed in Box 3-4.

Ketorolac Tromethamine. Ketorolac is the first nonopioid analgesic agent available for parenteral use in the United States. For acute pain management, ketorolac is rarely indicated, given that 60 mg of ketorolac administered IM is not clinically superior to 800 mg of oral ibuprofen. In addition, NSAID agents can be administered at a fraction of the cost of drugs administered via parenteral routes.[163-165] The main indication for ketorolac use is in the early treatment of renal colic (accompanied by a loading dose of intravenous morphine), a pain mechanism for which NSAIDs are particularly effective.

Box 3-4 Patients at Risk for Adverse Events during Nonsteroidal Anti-inflammatory (NSAID) Therapy

1. Patients with dehydration, hypovolemia, or impaired renal function are at increased risk for decreasing renal function or renal failure.
2. In patients with liver disease or congestive heart failure—in particular, those already taking ACE-inhibitors, ARBs, or diuretics—liver or heart conditions may worsen.
3. Elder patients are at enhanced risk for GI and renal events.
4. Patients with asthma and known aspirin hypersensitivity have an increased risk of bronchospasm.
5. In women in the third trimester of pregnancy, NSAIDs may prolong gestation or prematurely close the ductus arteriosus.
6. Patients who use tobacco or ethanol and have a history of gastritis or peptic ulcer disease are at increased risk for peptic ulcer or GI bleed.

ACE, angiotensin-converting enzyme; *ARBs,* angiotensin receptor blockers; *GI,* gastrointestinal.

Ibuprofen. Ibuprofen is the most widely used agent in the NSAID class. It is available over the counter in a variety of preparations, including tablets, liquid suspension, and suppository. Ibuprofen is rapidly absorbed from the upper GI tract and has minimal interaction with other medications. The adult analgesic dose is 400 mg, with an anti-inflammatory dose of 600 to 800 mg. No NSAID is more effective as an analgesic than ibuprofen 400 mg, including ibuprofen 800 mg.[165-167]

Cyclooxygenase-2–Specific Inhibitors. The discovery of two distinct COX isoenzymes (COX-1 and COX-2) raised expectations that an effective new class of analgesics could be developed. COX-2–specific agents were expected to control pain and inflammation with fewer adverse effects (particularly GI mucosal injury) than traditional NSAIDs.

Despite great initial promise, a dramatic pricing differential, and intensive marketing, the two classes of NSAIDs (nonselective COX inhibitors and selective COX-2 inhibitors) appear to perform similarly in clinical use, with similar side effect profiles. Agents that selectively inhibit COX-2 are expected to cause less ulceration and are associated with a lower risk of bleeding. COX-2 has been identified in normal gastric mucosa, however, and selective inhibitors may not confer any GI-protective advantage.

COX-2 inhibitors may have prothrombotic effects from greater inhibition of prostacyclin than thromboxane, thus increasing the risk of cardiovascular events. COX-2 inhibitors also decrease renal perfusion, thereby decreasing renin activity and reducing sodium excretion by the same amount (approximately 20%) as NSAIDs.

Given the higher relative price, a potential for adverse cardiovascular events related to long-term use, and the lack of superior safety or efficacy when compared with nonselective NSAIDs, there appears to be little or no role for COX-2 inhibitors in the ED or for acute pain management after discharge.

Skeletal Muscle Relaxants. Skeletal muscle relaxants are advocated as an adjunct to analgesics in the management of musculoskeletal pain with a spasm component, principally back pain. Despite the common use of skeletal muscle relaxants, relatively few data exist regarding their role in the treatment of pain. Studies demonstrate that muscle relaxants, such as cyclobenzaprine, are indistinguishable from ibuprofen in analgesic effect but have an increased side effect profile. Although a Cochrane systematic review claims that skeletal muscle relaxants are more effective than

www.ketabpezeshki.com 66485457-66963820

placebo with respect to relieving acute low back pain, it is not possible to discern any differential or additive effect to that of NSAIDs when the primary trials are reviewed.[168]

Skeletal muscle relaxants are not of benefit in the treatment of chronic low back pain, which is their most common use.[169] Skeletal muscle relaxants should not be used in the management of acute musculoskeletal pain as a substitute for proper doses of effective analgesics unless there is a high degree of anxiety accompanying the pain and it is believed that an anxiolytic might be helpful. In that case a benzodiazepine, such as diazepam 5 mg three times daily or lorazepam 1 mg twice daily, may be an effective adjunct for pain control.

Benzodiazepines have hypnotic, anxiolytic, antiepileptic, and antispasmodic properties. Muscle relaxation with these agents is probably caused by GABA-mediated presynaptic inhibition at the spinal cord level.[169]

Nitrous Oxide and Oxygen Mixtures. Nitrous oxide–oxygen mixtures can be used in the ED or the out-of-hospital care setting to reduce anxiety in patients and to manage mild to moderate pain states. The analgesic and anesthetic properties of nitrous oxide were discovered more than 200 years ago. A mixture of nitrous oxide and oxygen in a 50 : 50 ratio is safe when self-administered by the patient. This technique is one of the original forms of patient-controlled analgesia.

Nitrous oxide and oxygen administered by nasal mask have long been used by dentists for the treatment of pain and anxiety. Experience in emergency medicine with nitrous oxide–oxygen mixtures is greatest in the ratio of 50 : 50 mixtures with self-administered hand-held masks.[170,171]

The mechanisms of analgesia and anxiolysis with nitrous oxide are not fully delineated. The agent's analgesic effect appears to be similar in nature to that of low-dose opioids and is probably mediated by a variety of neuromodulators.

Some of the anxiolytic effects of nitrous oxide appear to have more in common with benzodiazepines than opioids. It has been postulated that nitrous exerts an effect on GABA receptors.[172]

Nitrous preparations are often administered in a two-tank system, with a fixed-ratio nitrous oxide–oxygen mixture delivered to the patient through a demand-valve activated with inhalation through a face mask or mouthpiece. A negative pressure of 3 to 5 cm H_2O should be produced within the mask or mouthpiece to activate the flow of gas, limiting the use of these devices in very small children. This patient administration element provides safety for the patient-controlled aspects of the system, given that patients are required to initiate a breath while holding a mask to the face to receive the medication. This delivery mechanism also may serve to minimize the amount of nitrous oxide released into ambient air.

In 10 to 15% of patients, nitrous oxide is ineffective.[170] It is much more potent as an anxiolytic than as an analgesic agent. As with all analgesic agents, nitrous oxide administration success should be determined by the patient's subjective feedback. When necessary, nitrous oxide can be supplemented with other analgesics.

Nitrous oxide is a folate antagonist and is strictly contraindicated in pregnant patients. Nitrous oxide–oxygen mixtures are relatively or absolutely contraindicated in patients with a decreased level of consciousness who are unable to follow instructions, patients with a head injury, and those with decompression sickness. Patients with severe chronic obstructive pulmonary disease who retain CO_2 should be given nitrous oxide–oxygen mixtures carefully, given that the mixture contains 50% oxygen, which may predispose to hypercapnia. Because nitrous oxide diffuses into body cavities, it can worsen a pneumothorax or bowel obstruction.[65]

Minor side effects of nitrous analgesic gas mixtures are reported in 5 to 50% of patients. The most common adverse effect is light-headedness, with paresthesias and nausea reported less frequently. No adverse hemodynamic effects have been documented with the self-administered forms of this agent. Because of their safety, these mixtures are useful in the out-of-hospital care setting.[173,174]

Side effects attributed to nitrous oxide usually resolve within minutes of discontinuation. Chronic use or abuse of nitrous oxide is associated with vitamin B_{12} antagonism and secondary hematologic effects as well as development of myelopathy.[175,176]

Nitrous oxide requires an effective scavenging and ventilation system for prevention of accumulation and toxicity in health care workers, especially pregnant health care workers. Advanced scavenger systems are necessary for the safe use of nitrous oxide in the ED.

Local Anesthesia

Mechanism of Action

Peripheral nerves are responsible for transmitting pain information from pain receptors to the spinal cord. Each fiber consists of an axon surrounded by a covering called the *Schwann cell.* A *myelinated* axon is one that is covered by the projection of a Schwann cell that wraps itself many times around the axon, hence the term *myelin sheath.*

Local anesthetics are much more effective at penetrating unmyelinated or lightly myelinated fibers than heavily myelinated ones. This difference explains the finding that local anesthetic agents provide sensory block without motor neuron effects (see Table 3-1).

Local anesthetic agents reversibly block sodium channels of the lipid membrane and prevent the influx of sodium ions into the axon, blocking depolarization and the nerve action potential. After injection of a local anesthetic, tissue buffers increase the pH of the solution surrounding the agent, driving much of the water-soluble acidic form of the agent to its lipid-soluble nonionic form. The lipid-soluble phase of the drug is able to penetrate the lipid membrane of the axon, where it then ionizes and enters the sodium channel, blocking the channel's ability to allow sodium to enter the cell.

Classes of Local Anesthetic Agents

Local anesthetic agents are chemical compounds that consist of an aromatic and an amine group separated by an intermediate chain. Agents in the class that has an ester link between the intermediate chain and aromatic portion are called *amino esters* and include procaine, chloroprocaine, and tetracaine. Esters are unstable in solution and are metabolized in the body by the plasma enzyme cholinesterase. Amides have an amide link and include lidocaine, mepivacaine, prilocaine, bupivacaine, and etidocaine. The amides, after absorption into the body, are destroyed by enzymes in the liver.[177]

Specific Agents

Each local anesthetic has a predictable effect when used in appropriate doses and by the appropriate route. The main considerations in the clinical use of these agents are potency, duration of anesthesia, and the speed of onset (Table 3-6).

Potency. The ability of a local anesthetic drug to penetrate the lipid membrane of the axon determines its potency. Agents that have high lipid solubility (e.g., tetracaine, etidocaine) are more potent than those with low lipid solubility (e.g., procaine, mepivacaine). Less potent local anesthetics should be given in more concentrated forms and in larger doses to achieve an equivalent effect.

www.ketabpezeshki.com 66485457-66963820

Table 3-6 Characteristics of Common Local Anesthetic Agents

AGENT	POTENCY (LIPID SOLUBILITY)	DURATION (min)	ONSET	COMMENTS
Procaine	1	60-90	Slow	Solutions of 0.5-2% used in infiltration and blocks
Tetracaine	8	180-600	Slow	Topical for ophthalmic use
Lidocaine	3	90-200	Rapid	Most commonly used agent; 1.5 times as toxic as procaine
Mepivacaine	2.4	120-240	Very rapid	Less potent and less toxic than lidocaine
Bupivacaine	8	180-600	Intermediate	Long-acting agent used in infiltration and blocks
Etidocaine	6	180-600	Rapid	Twice as toxic as lidocaine; used mostly in epidurals

Adapted from Paris PM, Weiss LD: Narcotic analgesics: The pure agonists. In: Paris PM, Stewart RD, eds. Pain Management in Emergency Medicine. Norwalk, Conn: Appleton & Lange; 1988.

Duration of Anesthesia. Agents that bind well to protein in the sodium channel are longer acting. Tetracaine and bupivacaine have a high affinity for protein and provide long-lasting anesthesia, whereas procaine, a poorly bound agent, does not.

Onset of Action. In most cases it is helpful to have an anesthetic agent that acts quickly. The speed of onset of any local anesthetic agent is directly related to how quickly that agent, after injection, can diffuse through tissues to the nerve and through the nerve membrane.

After injection the anesthetic agent is in two forms, ionized and nonionized. The amount of drug in the nonionized form is determined by its pK_a (the pH at which 50% of the solution is nonionized and 50% is ionized). Because only the nonionized form of the drug diffuses into the nerve, solutions with a low pK_a have a more rapid onset of anesthesia. Local anesthetic agents with higher pK_as take effect more slowly. At a tissue pH of 7.4, 5% of tetracaine (pK_a 8.5) is in the nonionized form compared with 35% of lidocaine (pK_a 7.9) solution.

Low tissue pH (5 or 6) in surrounding infected tissue delays the onset of local anesthesia in situations such as abscess incision and drainage. In this case the anesthetic primarily remains in an ionized state. The onset of action of a local anesthetic can be hastened by the alkalinization of the solution carrying the drug, which also decreases its irritant effect (pain) on injection. This can be done by adding sodium bicarbonate solution to the anesthetic at a ratio determined by the pK_a of the agent (see later).[178,179]

Several other factors influence the clinical effects of local anesthetic agents. These agents (except cocaine) are vasodilators, which tend to shorten the duration of anesthesia. Injection of the solutions into vascular tissues not only shortens the duration of anesthesia but also increases systemic absorption and the chance of systemic toxicity when larger doses are used. For these reasons, epinephrine is often added to local anesthetic solutions.

Allergy. When an allergy to local anesthetics is reported, the offending substance is often one of the preservatives used. True allergies to local anesthetics are exceedingly rare. Because the amide agents and amino ester agents do not cross-react and because different preservatives are used with them, a patient may be given a medication from another class if the allergy history is consistent with a specific anesthetic group. In one study, 236 patients with reported adverse reactions to local anesthetics underwent testing with commercial preparations of unrelated local anesthetics. No patient in the study exhibited systemic reactions.[180]

In patients reportedly allergic to all "-caine" anesthetic agents and in whom the allergy is believed to be legitimate, diphenhydramine can be used as an alternate agent. Diphenhydramine may be used with 1 mL of a 50-mg/mL ampule diluted to 5 or 10 mL (1-0.5% solution) to be used for local infiltration or nerve block. Diphenhydramine may cause direct tissue toxicity and should be avoided in areas with poor collateral circulation.[181,182]

Local and Systemic Toxicity

Local Toxicity. Local anesthetic agents, depending on the concentration, can be directly toxic to tissue. In addition, it is possible that the use of a vasoconstrictor in an anesthetic solution may produce a reduction in blood flow that could increase wound healing time and the vulnerability of the wound to infection. This concept has never been formally demonstrated. Many argue that this reasoning suggests that nerve blocks are preferable to local infiltration for wounds that are extensive, contaminated, or in areas without collateral circulation.

Epinephrine-containing solutions have traditionally been avoided on digits, the penis, the ears, or the nose. It is suggested, however, that dilute epinephrine can be used safely on digits and possibly these other areas as well.[183] A comprehensive review of the use of epinephrine in digits concludes that it is safe when diluted to 1:200,000 or less but should not be used in patients with vascular disease.

Systemic Toxicity. Systemic toxicity of local anesthetics occurs when a sufficient quantity of the drug accumulates in the body so that sodium channel blockade occurs in the heart or the brain. There is a dose-related clinical progression of local anesthetic toxicity from subtle neurologic symptoms to seizures to cardiovascular collapse.

All local anesthetics produce systemic toxicity at sufficiently high blood or CNS concentrations. Each local anesthetic has a range of therapeutic safety, beyond which systemic toxicity is more likely to occur (Table 3-7). Overdosage of local anesthetics may occur more commonly in patients with large wounds and in very small patients.

The more lipophilic anesthetic agents (e.g., etidocaine, bupivacaine) are more cardiotoxic. Cardiac toxicity may also be increased for epinephrine-containing anesthetics when inadvertent intravenous injection occurs. Special care should be exercised in children and when performing certain blocks known to produce high blood levels of the anesthetic agent (e.g., intercostal). In pediatric patients, total dose guidelines are important, and the maximum dose should be calculated before administration.

A wide variety of symptoms may be experienced from local anesthetic toxicity. These include light-headedness, headache, paresthesias, tinnitus, decreases in level of awareness, and muscle spasm.[184] The degree to which CNS symptoms are experienced is directly related to the blood level of the local anesthetic.

At the extreme, CNS toxicity may result in seizures. A typical clinical progression usually begins with circumoral paresthesias, dysarthria, and a report of tinnitus or a similar auditory phenomenon. These events may be followed by a decreased level of consciousness progressing to confusion, seizures, and coma. Longer-acting, more potent agents (e.g., bupivacaine and etidocaine) are more likely than lidocaine to cause CNS symptoms at lower blood levels.[184]

www.ketabpezeshki.com 66485457-66963820

Table 3-7 Guidelines for Maximum Doses of Commonly Used Local Anesthesia Agents*

AGENT	WITHOUT EPINEPHRINE	WITH EPINEPHRINE
Lidocaine HCl†	3-5 mg/kg	7 mg/kg
Mepivacaine HCl	8 mg/kg	7 mg/kg‡
Bupivacaine HCl§	1.5 mg/kg	3 mg/kg

Adapted from Stewart RD: Local anesthesia. In: Paris PM, Stewart RD, eds. Pain Management in Emergency Medicine. Norwalk, Conn: Appleton & Lange; 1988.
*All maximum doses should be reduced 20-25% in very young, old, and very sick patients.
†A lidocaine level of 0.5-2.0 g/mL may be reached for every 100 mg of lidocaine infiltrated for blocks.
‡Epinephrine adds to the potential cardiac toxicity of this drug.
§Not to be used for pudendal blocks or intravenous regional anesthesia. Not recommended for children younger than 12 years.
HCl, hydrochloride.

Box 3-5 Techniques That Can Be Used to Reduce the Pain of Injection

- Buffering of local anesthetic agents
- Counter-irritation
- Slower rate of injection
- Use of topical anesthetics
- Warming of solution
- Distraction techniques

Local anesthetic–induced seizures should be treated with intravenous benzodiazepines. Local anesthetic agents also have direct effects on cardiac automaticity, conductivity, contractility, and vascular tone. Management of cardiovascular collapse caused by toxic levels of local anesthetic agents should follow standard advanced cardiac life-support guidelines. Unless the overdose is massive, the toxicity should be relatively short-lived because of the redistribution of the lipophilic agents.

Reducing the Pain of Local Anesthetic Injection

Distraction by manual methods such as scratching, jiggling, or repetitively pinching the skin during needle puncture or injection reduces the discomfort experienced during local anesthetic injection (Box 3-5).[185] The addition of sodium bicarbonate to lidocaine immediately before injection significantly reduces patient discomfort.[179] A standard solution of sodium bicarbonate (8.4% in 50 mL) can be added to a syringe containing lidocaine in a ratio of 1:10 (e.g., 1 mL bicarbonate to 10 mL lidocaine, or 0.5 mL to 5 mL). Buffered lidocaine can be stocked in the ED and is effective for up to 1 week.[186] Bupivacaine also can be buffered, but the ratio should be 1:50 (i.e., 0.1 mL bicarbonate to 5 mL bupivacaine).

Slow injection of local anesthetics also attenuates the pain of infiltration, and to a greater degree than buffering of the solution.[187] Injection of local anesthetic into the edges of the laceration is less painful than injection through intact skin surrounding the wound.[188] When time permits, warming the anesthetic or applying a topical anesthetic agent can also greatly decrease the initial sensation associated with needle injection.[178]

Topical Anesthesia

Topical anesthetics are generally of two types: those that can be applied to intact skin and those used on open skin. The agents are absorbed and exert their anesthetic effect on adjacent superficial nerves. The topical application of local anesthetics should be done with just as much caution as injection of anesthetics to avoid systemic toxicity. The dose of topical anesthetic should be monitored to avoid applying doses associated with toxicity. As with injectable local anesthetic agents, topical solutions are often described in terms of percent of agent; 1% equals 10 mg/mL of anesthetic, and a 5% solution has 50 mg/mL.

Topical agents are particularly useful in children and in patients who are intimidated by needles. Topical agents do not provide anesthesia as effectively as subcutaneous infiltration or nerve blocks. These agents may provide a substantial decrease in the intensity of superficial stimuli. The long application time necessary for effective analgesia can be a principal drawback of these agents. In some patients the ritual of applying the topical anesthetic and delaying the procedure until there will be less pain can be an effective tool in controlling pain and the response to subsequent interventions.

Topical Anesthetics Applied to Intact Skin

Eutectic Mixture of Local Anesthetics. Eutectic mixture of local anesthetics (EMLA) is a mixture of lidocaine and prilocaine in an alkaline oil mixture in which the anesthetics are present primarily in their nonionized form, allowing them to diffuse through the skin. The term *eutectic* refers to mixtures that result in a melting point higher than that of either agent alone.

An EMLA mixture should be applied to the desired area with an occlusive dressing 30 to 60 minutes before the desired procedure is performed. Heating EMLA for 20 minutes improves analgesia, but the heated mixture is less effective than a routine 60-minute application with or without heat.[189] The duration of action after a 60-minute application is 1 to 5 hours.

Indications for the use of EMLA include venipuncture, arterial puncture, lumbar puncture, or arthrocentesis when a 30- to 60-minute delay in performing the procedure is not an impediment. EMLA can be applied in triage, particularly for pediatric patients, whose intravenous injection can then be started later in the ED with little or no pain.

Ethyl Chloride and Fluori-Methane sprays. Ethyl chloride and fluori-methane sprays are occasionally used for superficial analgesia. The agents evaporate quickly and cool the skin, providing brief (<1 minute) local anesthesia owing to the cold. The induced analgesia is brief, and any injection or incision should be made immediately after the application of the agent, which will typically be observed to create a brief "frosting" effect in which the skin blanches white.

Agents Applied to Mucosal Surfaces

Cocaine. Cocaine is unique among local anesthetic agents given that it is a potent vasoconstrictor in addition to being an anesthetic that can be applied to mucosal surfaces. Cocaine is frequently used in the nose, where a 4% (40 mg/mL) solution provides rapid anesthesia for the treatment of epistaxis and other nasal procedures. Although the maximum safe dose is unknown, a total of no more than 200 mg is typically applied in adults. Cocaine should not be used in patients with known coronary artery disease owing to the potential for coronary artery vasoconstriction.

Lidocaine. Both 2% and 4% lidocaine solutions are available in a viscous matrix for use on mucosal surfaces. Gel lidocaine can be used in nasal procedures, including the passing of nasogastric tubes and gastric lavage tubes. It can be used for urethral anesthesia during Foley catheter placement as well, but to be effective it is injected into the urethra with a catheter-tip syringe and be in contact with the area for 5 to 20 minutes. Lidocaine spray (4 or 10%) is useful for upper airway anesthesia, including intranasal use for nasogastric tube insertion.

Tetracaine. Tetracaine is a potent ester used for surface anesthesia of the cornea. Tetracaine stings when placed in the eye, but

www.ketabpezeshki.com 66485457-66963820

only for 10 to 15 seconds, after which there is excellent corneal anesthesia.

Benzocaine. Almost insoluble in water, benzocaine remains on mucous membranes in the mouth and is used commonly to provide superficial analgesia for oral procedures and pain.

Agents Applied to Open Skin

Tetracaine, Adrenaline, and Cocaine. The combination of tetracaine, adrenaline (epinephrine), and cocaine (TAC) has been largely replaced with lidocaine, epinephrine, and tetracaine (LET). From 5 to 10 mL of this combination of agents may be applied to an open wound with sterile cotton, which is then covered and held in place for 10 to 20 minutes. Anesthesia has been described in approximately 85% of cases of wounds of the scalp and face and a lower percentage of extremity wounds.[190] Application of the solution to mucous membranes (eye, intranasal) can result in toxic blood levels of tetracaine and should be avoided.[191]

Lidocaine, Epinephrine, and Tetracaine. LET is as effective as and less expensive than TAC.[192,193] To account for the 20-minute onset, the application can be administered at the time of triage in children with a simple laceration.[194]

Intravenous Regional Anesthesia (Bier Block)

The intravenous regional anesthesia procedure known as the *Bier block* is an effective and rapid technique to anesthetize extremities for fracture reduction or repair of extensive wounds. This method involves the intravenous injection of a local anesthetic agent (lidocaine, prilocaine) into a previously exsanguinated limb. This procedure is adapted for use in the ED in the form of a mini-dose of 100 mg of lidocaine and is described in procedure manuals. A safe alternative is to use the relatively nontoxic local anesthetic agent prilocaine.

Nonpharmacologic Interventions

Transcutaneous Electrical Nerve Stimulation

TENS systems use electrical stimulation to induce analgesia, likely through the activation of descending sensory pathways and modulation of nociceptive signals at the level of the spinal cord. TENS units include a pulse generator, an amplifier, and electrodes. Studies show varying degrees of effectiveness, and the devices are rarely indicated for use in the ED.[195,196]

Hypnosis

The induction of hypnosis allows patients to refocus attention away from pain and anxiety-producing stimuli to other images and feelings. Hypnosis can be used as an adjunct to pharmacologic interventions or as a substitute. Hypnosis can be induced with only brief interventions on the part of the clinician.[197,198] Hypnosis is usually not practical in the ED owing to time constraints and distracting ambient noise.

Pain Management in Children

Pain in children is both more difficult to assess and more challenging to treat. When used properly, most of the interventions can be used in children. The major difference in providing analgesia to children is the difficulty of accurately assessing the perception of pain, particularly in the very young.[199]

The general approach to a child can be important in developing a trusting relationship with both child and parent. Both verbal and nonverbal cues from the child and parents should be observed and appreciated, given the unique developmental aspects of each age group. Threatening equipment should be de-emphasized (e.g., syringes, scissors, and suture holders should be kept out of sight of the child). Play therapy and a slow, friendly, nonthreatening manner can be helpful. The decision to separate children from their parents should be individualized, but separation should be avoided when possible.[200]

Most principles relating to pharmacokinetics of drugs, including absorption, distribution, and elimination, are similar for children and adults. In neonates and infants younger than 3 months, opioid clearance is delayed, plasma drug levels are higher because of decreased protein binding, and the blood-brain barrier is immature and more permeable to opioids. Opioids should be given carefully to patients in this age group and at smaller weight-based doses than are used in older children. Neonates also require smaller doses of local anesthetics owing to decreased protein binding and slower metabolism. For mild pain, acetaminophen can be very effective in doses of 15 mg/kg PO or 20 mg/kg rectally (PR) every 4 hours. Sucrose solutions are effective agents in this age group when applied to a pacifier and given PO.

Pain Management in Elder Patients

Approximately 80% of elder patients have at least one chronic ailment commonly associated with pain.[201] Elders are more sensitive to analgesics, especially opioids, and reduced dosages achieve adequate analgesia while avoiding side effects.

Opioids, even in low doses, may produce sedation, confusion, or constipation in the elder patient. The patient and caregivers should be alerted to these possibilities. NSAIDs are used in reduced doses or avoided altogether in the elder patient, given the potential for adverse effects on renal function.

The assessment of pain in elder patients can be complicated by depression, dementia, and atypical patterns of pain presentation.[202] As with children, careful attention should be paid to the assessment of pain in the elderly owing to communication barriers.

Out-of-Hospital Analgesia

Out-of-hospital providers frequently encounter patients with painful conditions. Patients obtain pain relief more quickly when pain medications are initiated by out-of-hospital personnel, although pain control in the out-of-hospital setting is challenging to perform adequately.[203-206]

Protocols for the administration of fentanyl and morphine exist in most emergency medical services (EMS) systems and are usually limited to single-dose therapy before orders are obtained from the medical control physician.[207] There is no difference in the relative value of fentanyl or morphine as the initial agent for prehospital pain treatment.[208]

The out-of-hospital environment is less controlled than the ED, and the information regarding a patient's underlying condition is more limited, making the safe administration of pain medications more difficult. As in the ED, establishing rapport with the patient, providing calm reassurance, and using careful movement and handling, including proper splinting, are the first steps to which pharmacologic support can be added. Pain can be assessed in the out-of-hospital setting through use of numerical and verbal rating scales, as would occur in the ED.[209]

Unfortunately, moderate to severe pain is treated infrequently in the out-of-hospital environment.[210,211] One study of lower extremity and hip fractures demonstrated that only 18% of patients received an analgesic.[210-212] Self-administered 50% nitrous oxide offers many advantages for use in the field.[213] In addition, morphine 0.1 mg/kg is safe for out-of-hospital use and should be considered the first-line agent for severe pain as it is in the ED.

www.ketabpezeshki.com 66485457-66963820

Box 3-6 Common Outpatient Pain Agents by Type

Analgesic Options for Acute Pain
1. Acetaminophen

Opioids to Be Used in Combination with NSAIDs and Acetaminophen
2. NSAIDs
3. Oxycodone
4. Hydrocodone

Analgesic Options for Chronic Pain
1. NSAIDs
2. Tramadol

***Opioids to Be Used in Combination with NSAIDs and Acetaminophen**†*
3. Oxycodone long-acting preparation or for breakthrough pain
4. Tricyclic antidepressants

Analgesic Options for Neuropathic Pain
1. Gabapentin
2. Tricyclic antidepressants
3. Carbamazepine

NSAIDs, nonsteroidal anti-inflammatory drugs.
*A variety of opioid and acetaminophen combination agents are available.
†Chronic opioid management should be managed by the primary outpatient physician.

The National Association of EMS Physicians encourages the increased use of analgesics in the out-of-hospital environment.

TREATMENT ENDPOINTS

Pain is a subjective experience, and use of pain relief as the endpoint of treatment results in a subjective marker of treatment success or failure. In the ED, management of acute pain should specify the initial dose, the repeat dose and interval, and a specific desired endpoint, such as the patient expressing that pain is at 3 or less on a 10-point pain scale. Pain orders that are wide-ranging or vague should be avoided in the acute setting, given that they frequently lead to underdosing and inadequate pain relief.

KEY CONCEPTS

- Pain should be rapidly assessed, treated, and frequently reassessed in tandem with diagnostic evaluations (see Fig. 3-7).
- Therapy for acute pain is different from therapy for chronic pain (Box 3-6).
- Titrated intravenous opioid analgesics are the principal therapeutic approach to the treatment of moderate and severe acute pain. The intramuscular route has several disadvantages and is not recommended.
- Oral oxycodone, with an onset of action similar to that of intramuscular or subcutaneous opioids, can be used for mild to moderate pain when an intravenous injection is not otherwise needed.
- Acetaminophen and NSAIDs should be added to pain therapy when not contraindicated.
- Morphine, fentanyl, and hydromorphone are the preferred parenteral opioid agents in the ED.
- There is no validity to the belief that morphine causes more smooth muscle spasm than other opioids. Morphine is safe and appropriate for patients with acute biliary or renal colic.
- Topical and local anesthetics can be used to treat pain associated with the majority of ED procedures and should be considered for use in isolated painful conditions.
- Low tissue pH (5 or 6) in infected tissue delays the onset of local anesthesia.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Berben SA, et al: Pain prevalence and pain relief in trauma patients in the Accident & Emergency department. *Injury* 2008; 39:578-585.
2. Cordell WH, et al: The high prevalence of pain in emergency medical care. *Am J Emerg Med* 2002; 20:165-169.
3. Ducharme J: Acute pain and pain control: State of the art. *Ann Emerg Med* 2000; 35:592-603.
4. Tanabe P, Buschmann M: A prospective study of ED pain management practices and the patient's perspective. *J Emerg Nurs* 1999; 25:171-177.
5. Todd KH, et al: Pain in the emergency department: Results of the pain and emergency medicine initiative (PEMI) multicenter study. *J Pain* 2007; 8:460-466.
6. Arendts G, Fry M: Factors associated with delay to opiate analgesia in emergency departments. *J Pain* 2006; 7:682-686.
7. Bijur PE, et al: Lack of influence of patient self-report of pain intensity on administration of opioids for suspected long-bone fractures. *J Pain* 2006; 7:438-444.
8. Fosnocht DE, Swanson ER, Barton ED: Changing attitudes about pain and pain control in emergency medicine. *Emerg Med Clin North Am* 2005; 23:297-306.
9. Neighbor ML, Honner S, Kohn MA: Factors affecting emergency department opioid administration to severely injured patients. *Acad Emerg* 2004; 11:1290-1296.
10. Todd KH, Sloan EP, Chen C, Eder S, Wamstad K: Survey of pain etiology, management practices and patient satisfaction in two urban emergency departments. *CJEM* 2002; 4:252-256.
11. Fosnocht DE, Hollifield MB, Swanson ER: Patient preference for route of pain medication delivery. *J Emerg Med* 2004; 26:7-11.
12. Fosnocht DE, Swanson ER, Bossart P: Patient expectations for pain medication delivery. *Am J Emerg Med* 2001; 19:399-402.
13. Bayer BM, Brehio RM, Ding XZ, Hernandez MC: Enhanced susceptibility of the immune system to stress in morphine-tolerant rats. *Brain Behav Immun* 1994; 8:173-184.
14. Beilin B, et al: The effects of postoperative pain management on immune response to surgery. *Anesth Analg* 2003; 97:822-827.
15. Charmandari E, Kino T, Souvatzoglou E, Chrousos GP: Pediatric stress: Hormonal mediators and human development. *Horm Res* 2003; 59:161-179.
16. Koga C, et al: Anxiety and pain suppress the natural killer cell activity in oral surgery outpatients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; 91:654-658.
17. Lyte M, Bailey MT: Neuroendocrine-bacterial interactions in a neurotoxin-induced model of trauma. *J Surg Res* 1997; 70:195-201.
18. Lyte M, et al: Stimulation of *Staphylococcus epidermidis* growth and biofilm formation by catecholamine inotropes. *Lancet* 2003; 361:130-135.
19. Morrison RS, et al: The impact of post-operative pain on outcomes following hip fracture. *Pain* 2003; 103:303-311.
20. Taddio A, Goldbach M, Ipp M, Stevens B, Koren G: Effect of neonatal circumcision on pain responses during vaccination in boys. *Lancet* 1995; 345:291-292.
21. Weisman SJ, Bernstein B, Schechter NL: Consequences of inadequate analgesia during painful procedures in children. *Arch Pediatr Adolesc Med* 1998; 152:147-149.
22. Nichols ML, et al: Transmission of chronic nociception by spinal neurons expressing the substance P receptor. *Science* 1999; 286:1558-1561.
23. Ducharme J: Clinical guidelines and policies: Can they improve emergency department pain management? *J Law Med Ethics* 2005; 33:783-790.
24. Frasco PE, Sprung J, Trentman TL: The impact of the Joint Commission for Accreditation of Healthcare Organization's pain initiative on perioperative opiate consumption and recovery room length of stay. *Anesth Analg* 2005; 100:162-168.
25. Leddy KM, Wolosin RJ: Patient satisfaction with pain control during hospitalization. *Jt Comm J Qual Patient Saf* 2005; 31:507-513.
26. Pletcher MJ, Kertesz SG, Kohn MA, Gonzales R: Trends in opioid prescribing by race/ethnicity for patients seeking care in US emergency departments. *JAMA* 2008; 299:70-78.
27. Ritsema TS, Kelen GD, Pronovost PJ, Pham JC: The national trend in quality of emergency department pain management for long bone fractures. *Acad Emerg Med* 2007; 14:163-169.
28. Todd KH: Emergency medicine and pain: a topography of influence. *Ann Emerg Med* 2004; 43:504-506.
29. Gilman S: *Pain and temperature*. In: Gilman S, Newman SW, eds. *Manter & Gatz's Essentials of Clinical Neuroanatomy and Neurophysiology*, 10th ed. Philadelphia: FA Davis, 2002:48-55.
30. Honore P, et al: Murine models of inflammatory, neuropathic and cancer pain each generates a unique set of neurochemical changes in the spinal cord and sensory neurons. *Neuroscience* 2000; 98:585-598.
31. Duncan GH, et al: Stimulation of human thalamus for pain relief: Possible modulatory circuits revealed by positron emission tomography. *J Neurophysiol* 1998; 80:3326-3330.
32. Melzack R, Wall PD, Ty TC: Acute pain in an emergency clinic: Latency of onset and descriptor patterns related to different injuries. *Pain* 1982; 14:33-43.
33. Bartfield JM, Flint RD, McErlean M, Broderick J: Nebulized fentanyl for relief of abdominal pain. *Acad Emerg Med* 2003; 10:215-218.
34. Tanabe P, et al: Increased blood pressure in the emergency department: Pain, anxiety, or undiagnosed hypertension? *Ann Emerg Med* 2008; 51:221-229.
35. Holden JE, Jeong Y, Forrest JM: The endogenous opioid system and clinical pain management. *AACN Clin Issues* 2005; 16:291-301.
36. Sun YG, Yu LC: Interactions of galanin and opioids in nociceptive modulation in the arcuate nucleus of hypothalamus in rats. *Regul Pept* 2005; 124:37-43.
37. Lyte M: The role of catecholamines in gram-negative sepsis. *Med Hypotheses* 1992; 37:255-258.
38. Blyth FM, March LM, Brnabic AJ, Cousins MJ: Chronic pain and frequent use of health care. *Pain* 2004; 111:51-58.
39. Miner J, Biros MH, Trainor A, Hubbard D, Beltram M: Patient and physician perceptions as risk factors for oligoanalgesia: A prospective observational study of the relief of pain in the emergency department. *Acad Emerg Med* 2006; 13:140-146.
40. Bellamy N, Campbell J, Syrotuik J: Comparative study of self-rating pain scales in rheumatoid arthritis patients. *Curr Med Res Opin* 1999; 15:121-127.
41. Bossart P, Fosnocht D, Swanson E: Changes in heart rate do not correlate with changes in pain intensity in emergency department patients. *J Emerg Med* 2007; 32:19-22.
42. Davies GM, Watson DJ, Bellamy N: Comparison of the responsiveness and relative effect size of the western Ontario and McMaster Universities Osteoarthritis Index and the short-form Medical Outcomes Study Survey in a randomized, clinical trial of osteoarthritis patients. *Arthritis Care Res* 1999; 12:172-179.
43. Huiku M, Uutela K, van Gils M, et al: Assessment of surgical stress during general anaesthesia. *Br J Anaesth* 2007; 98:447-455.
44. Marco CA, Plewa MC, Buderer N, Hymel G, Cooper J: Self-reported pain scores in the emergency department: Lack of association with vital signs. *Acad Emerg Med* 2006; 13:974-979.
45. Miner JR, Kapella KC: Variations in perceived pain measurements within and between subjects using a standard painful stimulus. *Acad Emerg Med* 2007; 14:s283.
46. Todd KH, Funk KG, Funk JP, Bonacci R: Clinical significance of reported changes in pain severity. *Ann Emerg Med* 1996; 27: 485-489.
47. Gj H: *Assessment, measurement, history, and examination*. In: Rowbotham DJ, Macintyre PE, eds. *Clinical Pain Management: Acute Pain*. New York: Oxford University Press; 2003:93-112.
48. Bartfield JM, Janikas JS, Lee RS: Heart rate response to intravenous catheter placement. *Acad Emerg Med* 2003; 10:1005-1008.
49. Lasch KE: Culture, pain, and culturally sensitive pain care. *Pain Manag Nurs* 2000; 1(3 Suppl 1):16-22.
50. Tamayo-Sarver JH, Hinze SW, Cydulka RK, Baker DW: Racial and ethnic disparities in emergency department analgesic prescription. *Am J Public Health* 2003; 93:2067-2073.
51. Todd KH, Deaton C, D'Adamo AP, Goe L: Ethnicity and analgesic practice. *Ann Emerg Med* 2000; 35:11-16.
52. Todd KH, Samaroo N, Hoffman JR: Ethnicity as a risk factor for inadequate emergency department analgesia. *JAMA* 1993; 269:1537-1539.
53. Brown JC, Klein EJ, Lewis CW, Johnston BD, Cummings P: Emergency department analgesia for fracture pain. *Ann Emerg Med* 2003; 42:197-205.
54. Crandall M, Miaskowski C, Kools S, Savedra M: The pain experience of adolescents after acute blunt traumatic injury. *Pain Manag Nurs* 2002; 3:104-114.
55. Decosterd I, et al: Oligoanalgesia in the emergency department: Short-term beneficial effects of an education program on acute pain. *Ann Emerg Med* 2007; 50:462-471.
56. Ducharme J, Gutman J: Pain management in the emergency department. *Acad Emerg Med* 1995; 2:850-852.
57. Jantos TJ, Paris PM, Menegazzi JJ, Yealy DM: Analgesic practice for acute orthopedic trauma pain in Costa Rican emergency departments. *Ann Emerg Med* 1996; 28:145-150.

www.ketabpezeshki.com 66485457-66963820

58. Jones JS, Johnson K, McNinch M: Age as a risk factor for inadequate emergency department analgesia. *Am J Emerg Med* 1996; 14:157-160.
59. Marquie L, et al: Pain rating by patients and physicians: Evidence of systematic pain miscalibration. *Pain* 2003; 102:289-296.
60. Nguyen NL, Gun RT, Sparnon AL, Ryan P: The importance of initial management: A case series of childhood burns in Vietnam. *Burns* 2002; 28:167-172.
61. Perry S, Heidrich G: Management of pain during debridement: A survey of U.S. burn units. *Pain* 1982; 13:267-280.
62. Perry SW: Undermedication for pain on a burn unit. *Gen Hosp Psychiatry* 1984; 6:308-316.
63. Pines JM, Perron AD: Oligoanalgesia in ED patients with isolated extremity injury without documented fracture. *Am J Emerg Med* 2005; 23:580.
64. Rupp T, Delaney KA: Inadequate analgesia in emergency medicine. *Ann Emerg Med* 2004; 43:494-503.
65. Silka PA, Roth MM, Geiderman JM: Patterns of analgesic use in trauma patients in the ED. *Am J Emerg Med* 2002; 20:298-302.
66. Wilson JE, Pendleton JM: Oligoanalgesia in the emergency department. *Am J Emerg Med* 1989; 7:620-623.
67. Bijur PE, Silver W, Gallagher EJ: Reliability of the visual analog scale for measurement of acute pain. *Acad Emerg Med* 2001; 8:1153-1157.
68. Daoust R, Beaulieu P, Manzini C, Chauny JM, Lavigne G: Estimation of pain intensity in emergency medicine: A validation study. *Pain* 2008; 138:565-570.
69. Berthier F, Potel G, Leconte P, Touze MD, Baron D: Comparative study of methods of measuring acute pain intensity in an ED. *Am J Emerg Med* 1998; 16:132-136.
70. Bijur PE, Latimer CT, Gallagher EJ: Validation of a verbally administered numerical rating scale of acute pain for use in the emergency department. *Acad Emerg Med* 2003; 10:390-392.
71. Silka PA, Roth MM, Moreno G, Merrill L, Geiderman JM: Pain scores improve analgesic administration patterns for trauma patients in the emergency department. *Acad Emerg Med* 2004; 11:264-270.
72. Tyler DC, Tu A, Douthit J, Chapman CR: Toward validation of pain measurement tools for children: A pilot study. *Pain* 1993; 52: 301-309.
73. Strout T: *Patient assessment: pain scales and observation in clinical practice*. In: Burton JH, Miner J, eds. *Emergency Sedation and Pain Management*. New York: Cambridge University Press; 2008:60.
74. Schultz AA, et al: Preverbal, Early Verbal Pediatric Pain Scale (PEPPS): Development and early psychometric testing. *J Pediatr Nurs* 1999; 14:19-27.
75. Beyer JE, McGrath PJ, Berde CB: Discordance between self-report and behavioral pain measures in children aged 3-7 years after surgery. *J Pain Symptom Manage* 1990; 5:350-356.
76. Krechel SW, Bildner J: CRIES: A new neonatal postoperative pain measurement score. Initial testing of validity and reliability. *Paediatr Anaesth* 1995; 5:53-61.
77. Miner JR, Kletti C, Herold M, Hubbard D, Biros MH: Randomized clinical trial of nebulized fentanyl citrate versus i.v. fentanyl citrate in children presenting to the emergency department with acute pain. *Acad Emerg Med* 2007; 14:895-898.
78. Loeser JD, Melzack R: Pain: An overview. *Lancet* 1999; 353: 1607-1609.
79. Højsted J, Sjøgren P: An update on the role of opioids in the management of chronic pain of nonmalignant origin. *Curr Opin Anaesthesiol* 2007; 20:451-455.
80. Kim DS, et al: Changes in voltage-gated calcium channel alpha(1) gene expression in rat dorsal root ganglia following peripheral nerve injury. *Brain Res Mol Brain Res* 2001; 96:151-156.
81. Puke MJ, Wiesenfeld-Hallin Z: The differential effects of morphine and the alpha 2-adrenoceptor agonists clonidine and dexmedetomidine on the prevention and treatment of experimental neuropathic pain. *Anesth Analg* 1993; 77:104-109.
82. Rickard C, et al: A randomized controlled trial of intranasal fentanyl vs intravenous morphine for analgesia in the prehospital setting. *Am J Emerg Med* 2007; 25:911-917.
83. Rowbotham MC: Pharmacologic management of complex regional pain syndrome. *Clin J Pain* 2006; 22:425-429.
84. Watson CP: Antidepressant drugs as adjuvant analgesics. *J Pain Symptom Manage* 1994; 9:392-405.
85. McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A: Anticonvulsant drugs for management of pain: A systematic review. *BMJ* 1995; 311:1047-1052.
86. Onghena P, Van Houdenhove B: Antidepressant-induced analgesia in chronic non-malignant pain: A meta-analysis of 39 placebo-controlled studies. *Pain* 1992; 49:205-219.
87. Backonja M, et al: Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: A randomized controlled trial. *JAMA* 1998; 280:1831-1836.
88. MacFarlane BV, Wright A, O'Callaghan J, Benson HA: Chronic neuropathic pain and its control by drugs. *Pharmacol Ther* 1997; 75:1-19.
89. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L: Gabapentin for the treatment of postherpetic neuralgia: A randomized controlled trial. *JAMA* 1998; 280:1837-1842.
90. Bijur PE, Kenny MK, Gallagher EJ: Intravenous morphine at 0.1 mg/kg is not effective for controlling severe acute pain in the majority of patients. *Ann Emerg Med* 2005; 46:362-367.
91. Birnbaum A, Esses D, Bijur PE, Holden L, Gallagher EJ: Randomized double-blind placebo-controlled trial of two intravenous morphine dosages (0.10 mg/kg and 0.15 mg/kg) in emergency department patients with moderate to severe acute pain. *Ann Emerg Med* 2007; 49:445-453, e441-e442.
92. Gutstein HB, Akil H: Opioid analgesics. In: Hardman JG, Limbird LE, Gilman AG, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, ed 10. New York: McGraw-Hill; 2001:569-619.
93. Hansen RN, Oster G, Edelsberg J, Woody GE, Sullivan SD: Economic costs of nonmedical use of prescription opioids. *Clin J Pain* 2011; 27:194-202.
94. De Luca A, Coupar IM: Insights into opioid action in the intestinal tract. *Pharmacol Ther* 1996; 69:103-115.
95. Ahmedzai S, Brooks D: Transdermal fentanyl versus sustained-release oral morphine in cancer pain: Preference, efficacy, and quality of life. The TTS-Fentanyl Comparative Trial Group. *J Pain Symptom Manage* 1997; 13:254-261.
96. Radbruch L, et al: Constipation and the use of laxatives: A comparison between transdermal fentanyl and oral morphine. *Palliat Med* 2000; 14:111-119.
97. Campora E, et al: The incidence of narcotic-induced emesis. *J Pain Symptom Manage* 1991; 6:428-430.
98. Nuttall GA, et al: Does low-dose droperidol administration increase the risk of drug-induced QT prolongation and torsade de pointes in the general surgical population? *Anesthesiology* 2007; 107: 531-536.
99. Morrison RS, et al: Relationship between pain and opioid analgesics on the development of delirium following hip fracture. *J Gerontol A Biol Sci Med Sci* 2003; 58:76-81.
100. Passik SD, Byers K, Kirsh KL: Empathy and the failure to treat pain. *Palliat Support Care* 2007; 5:167-172.
101. Perry SW: Irrational attitudes toward addicts and narcotics. *Bull N Y Acad Med* 1985; 61:706-727.
102. Porter J, Jick H: Addiction rare in patients treated with narcotics. *N Engl J Med* 1980; 302:123.
103. Weissman DE, Haddox JD: Opioid pseudoaddiction—an iatrogenic syndrome. *Pain* 1989; 36:363-366.
104. Flugsrud-Breckenridge MR, Gevirtz C, Paul D, Gould HJ 3rd: Medications of abuse in pain management. *Curr Opin Anaesthesiol* 2007; 20:319-324.
105. Geiderman JM: Keeping lists and naming names: Habitual patient files for suspected nontherapeutic drug-seeking patients. *Ann Emerg Med* 2003; 41:873-881.
106. Miner JR, Moore J, Gray RO, Skinner L, Biros MH: Oral versus intravenous opioid dosing for the initial treatment of acute musculoskeletal pain in the emergency department. *Acad Emerg Med* 2008; 15:1234-1240.
107. Portenoy RK, et al: Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: A controlled dose titration study. *Pain* 1999; 79:303-312.
108. Schutzman SA, Liebelt E, Wisk M, Burg J: Comparison of oral transmucosal fentanyl citrate and intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation of children undergoing laceration repair. *Ann Emerg Med* 1996; 28:385-390.
109. Zeppetella G: Nebulized and intranasal fentanyl in the management of cancer-related breakthrough pain. *Palliat Med* 2000; 14:57-58.
110. Melzer-Lange MD, Walsh-Kelly CM, Lea G, Hillery CA, Scott JP: Patient-controlled analgesia for sickle cell pain crisis in a pediatric emergency department. *Pediatr Emerg Care* 2004; 20:2-4.
111. Chang AK, et al: Safety and efficacy of hydromorphone as an analgesic alternative to morphine in acute pain: A randomized clinical trial. *Ann Emerg Med* 2006; 48:164-172.
112. O'Connor AB, Lang VJ, Quill TE: Underdosing of morphine in comparison with other parenteral opioids in an acute hospital: A quality of care challenge. *Pain Med* 2006; 7:299-307.

www.ketabpezeshki.com 66485457-66963820

113. Chudnofsky CR, Wright SW, Dronen SC, Borron SW, Wright MB: The safety of fentanyl use in the emergency department. *Ann Emerg Med* 1989; 18:635-639.
114. Kanowitz A, Dunn TM, Kanowitz EM, Dunn WW, Vanbuskirk K: Safety and effectiveness of fentanyl administration for prehospital pain management. *Prehosp Emerg Care* 2006; 10:1-7.
115. Mahar PJ, Rana JA, Kennedy CS, Christopher NC: A randomized clinical trial of oral transmucosal fentanyl citrate versus intravenous morphine sulfate for initial control of pain in children with extremity injuries. *Pediatr Emerg Care* 2007; 23:544-548.
116. Borland M, Jacobs I, King B, O'Brien D: A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department. *Ann Emerg Med* 2007; 49:335-340.
117. Meyer MR, Maurer HH: Absorption, distribution, metabolism and excretion pharmacogenomics of drugs of abuse. *Pharmacogenomics* 2011; 12:215-233.
118. Kalso E: Oxycodone. *J Pain Symptom Manage* 2005; 29(5 Suppl):S47-S56.
119. Karunatilake H, Buckley NA: Serotonin syndrome induced by fluvoxamine and oxycodone. *Ann Pharmacother* 2006; 40:155-157.
120. Forbes JA, et al: Evaluation of two opioid-acetaminophen combinations and placebo in postoperative oral surgery pain. *Pharmacotherapy* 1994; 14:139-146.
121. Turturro MA, Paris PM, Yealy DM, Menegazzi JJ: Hydrocodone versus codeine in acute musculoskeletal pain. *Ann Emerg Med* 1991; 20:1100-1103.
122. Marco CA, Plewa MC, Buderer N, Black C, Roberts A: Comparison of oxycodone and hydrocodone for the treatment of acute pain associated with fractures: A double-blind, randomized, controlled trial. *Acad Emerg Med* 2005; 12:282-288.
123. Collins SL, Edwards JE, Moore RA, McQuay HJ: Single dose dextropropoxyphene, alone and with paracetamol (acetaminophen), for postoperative pain. *Cochrane Database Syst Rev* 2000; 2:CD001440.
124. Ulens C, Daenens P, Tytgat J: Norpropoxyphene-induced cardiotoxicity is associated with changes in ion-selectivity and gating of HERG currents. *Cardiovasc Res* 1999; 44:568-578.
125. Li Wan Po A, Zhang WY: Systematic overview of co-proxamol to assess analgesic effects of addition of dextropropoxyphene to paracetamol. *BMJ* 1997; 315:1565-1571.
126. Wolff K, et al: The pharmacokinetics of methadone in healthy subjects and opiate users. *Br J Clin Pharmacol* 1997; 44:325-334.
127. Nossol S, Schwarzbold M, Stadler T: Treatment of pain with sustained-release tramadol 100, 150, 200 mg: Results of a post-marketing surveillance study. *Int J Clin Pract* 1998; 52:115-121.
128. Gillman PK: Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. *Br J Anaesth* 2005; 95:434-441.
129. Hewitt DJ, Todd KH, Xiang J, Jordan DM, Rosenthal NR: Tramadol/acetaminophen or hydrocodone/acetaminophen for the treatment of ankle sprain: A randomized, placebo-controlled trial. *Ann Emerg Med* 2007; 49:468-480, e461-e462.
130. Daniels S, et al: A randomized, double-blind, placebo-controlled phase 3 study of the relative efficacy and tolerability of tapentadol IR and oxycodone IR for acute pain. *Curr Med Res Opin* 2009; 25:1551-1561.
131. Hartrick CT: Tapentadol immediate release for the relief of moderate-to-severe acute pain. *Expert Opin Pharmacother* 2009; 10:2687-2696.
132. Kleinert R, et al: Single dose analgesic efficacy of tapentadol in postsurgical dental pain: The results of a randomized, double-blind, placebo-controlled study. *Anesth Analg* 2008; 107:2048-2055.
133. Tzschentke TM, et al: Tapentadol hydrochloride: A next-generation, centrally acting analgesic with two mechanisms of action in a single molecule. *Drugs Today (Barc)* 2009; 45:483-496.
134. Brewster GS, Herbert ME, Hoffman JR: Medical myth: analgesia should not be given to patients with an acute abdomen because it obscures the diagnosis. *West J Med* 2000; 172:209-210.
135. Gallagher EJ, Esses D, Lee C, Lahn M, Bijur PE: Randomized clinical trial of morphine in acute abdominal pain. *Ann Emerg Med* 2006; 48:150-160, e151-e154.
136. Kim MK, Strait RT, Sato TT, Hennes HM: A randomized clinical trial of analgesia in children with acute abdominal pain. *Acad Emerg Med* 2002; 9:281-287.
137. LoVecchio F, et al: The use of analgesics in patients with acute abdominal pain. *J Emerg Med* 1997; 15:775-779.
138. McHale PM, LoVecchio F: Narcotic analgesia in the acute abdomen—a review of prospective trials. *Eur J Emerg Med* 2001; 8:131-136.
139. Neighbor ML, Baird CH, Kohn MA: Changing opioid use for right lower quadrant abdominal pain in the emergency department. *Acad Emerg Med* 2005; 12:1216-1220.
140. Pace S, Burke TF: Intravenous morphine for early pain relief in patients with acute abdominal pain. *Acad Emerg Med* 1996; 3:1086-1092.
141. Thomas SH, et al: Effects of morphine analgesia on diagnostic accuracy in Emergency Department patients with abdominal pain: A prospective, randomized trial. *J Am Coll Surg* 2003; 196:18-31.
142. Zoltie N, Cust MP: Analgesia in the acute abdomen. *Ann R Coll Surg Engl* 1986; 68:209-210.
143. Schwab JM, Schluesener HJ, Laufer S: COX-3: Just another COX or the solitary elusive target of paracetamol? *Lancet* 2003; 361:981-982.
144. Shen H, et al: Analgesic action of acetaminophen in symptomatic osteoarthritis of the knee. *Rheumatology (Oxford)* 2006; 45:765-770.
145. Towheed TE, Judd MJ, Hochberg MC, Wells G: Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* 2003; 1:CD004257.
146. Makin A, Williams R: Paracetamol hepatotoxicity and alcohol consumption in deliberate and accidental overdose. *QJM* 2000; 93:341-349.
147. Hylek EM: Paracetamol (acetaminophen) and warfarin interaction: Unraveling the pivotal role of the vitamin K cycle. *Thromb Haemost* 2004; 92:672-673.
148. Hylek EM, Heiman H, Skates SJ, Sheehan MA, Singer DE: Acetaminophen and other risk factors for excessive warfarin anticoagulation. *JAMA* 1998; 279:657-662.
149. Fored CM, et al: Acetaminophen, aspirin, and chronic renal failure. *N Engl J Med* 2001; 345:1801-1808.
150. Asero R: Risk factors for acetaminophen and nimesulide intolerance in patients with NSAID-induced skin disorders. *Ann Allergy Asthma Immunol* 1999; 82:554-558.
151. Hersh EV, Pinto A, Moore PA: Adverse drug interactions involving common prescription and over-the-counter analgesic agents. *Clin Ther* 2007; 29(Suppl):2477-2497.
152. Singh G: Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. *Am J Med* 1998; 105(1B):31S-38S.
153. Hernandez-Diaz S, Garcia-Rodriguez LA: Epidemiologic assessment of the safety of conventional nonsteroidal anti-inflammatory drugs. *Am J Med* 2001; 110(Suppl 3A):20S-27S.
154. Reuben SS, Ablett D, Kaye R: High dose nonsteroidal anti-inflammatory drugs compromise spinal fusion. *Can J Anaesth* 2005; 52:506-512.
155. Smith WL, DeWitt DL, Garavito RM: Cyclooxygenases: Structural, cellular, and molecular biology. *Annu Rev Biochem* 2000; 69:145-182.
156. Mason RP, Walter MF, Day CA, Jacob RF: A biological rationale for the cardiotoxic effects of rofecoxib: Comparative analysis with other COX-2 selective agents and NSAids. *Subcell Biochem* 2007; 42: 175-190.
157. Bhattacharyya T, Smith RM: Cardiovascular risks of coxibs: The orthopaedic perspective. *J Bone Joint Surg Am* 2005; 87:245-246.
158. Fischer LM, Schlienger RG, Matter CM, Jick H, Meier CR: Current use of nonsteroidal antiinflammatory drugs and the risk of acute myocardial infarction. *Pharmacotherapy* 2005; 25:503-510.
159. Battistella M, Mamdami MM, Juurlink DN, Rabeneck L, Laupacis A: Risk of upper gastrointestinal hemorrhage in warfarin users treated with nonselective NSAIDs or COX-2 inhibitors. *Arch Intern Med* 2005; 165:189-192.
160. Raskin JB, et al: Misoprostol and ranitidine in the prevention of NSAID-induced ulcers: A prospective, double-blind, multicenter study. *Am J Gastroenterol* 1996; 91:223-227.
161. Corman SL, Fedutes BA, Ansani NT: Impact of nonsteroidal antiinflammatory drugs on the cardioprotective effects of aspirin. *Ann Pharmacother* 2005; 39:1073-1079.
162. MacDonald TM, Wei L: Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet* 2003; 361:573-574.
163. Turturro MA, Paris PM, Seaberg DC: Intramuscular ketorolac versus oral ibuprofen in acute musculoskeletal pain. *Ann Emerg Med* 1995; 26:117-120.
164. Neighbor ML, Puntillo KA: Intramuscular ketorolac vs oral ibuprofen in emergency department patients with acute pain. *Acad Emerg Med* 1998; 5:118-122.
165. Wright JM, Price SD, Watson WA: NSAID use and efficacy in the emergency department: Single doses of oral ibuprofen versus intramuscular ketorolac. *Ann Pharmacother* 1994; 28:309-312.
166. Brown TJ, et al: A comparison of the cost-effectiveness of five strategies for the prevention of non-steroidal anti-inflammatory drug-induced gastrointestinal toxicity: A systematic review with economic modelling. *Health Technol Assess* 2006; 10:iii-iv, xi-xiii, 1-183.
167. Clark E, Plint AC, Correll R, Gaboury I, Passi B: A randomized, controlled trial of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma. *Pediatrics* 2007; 119:460-467.

www.ketabpezeshki.com 66485457-66963820

168. van Tulder MW, Touray T, Furlan AD, Solway S, Bouter LM: Muscle relaxants for non-specific low back pain. *Cochrane Database Syst Rev* 2003; 2:CD004252.
169. Dillon C, Paulose-Ram R, Hirsch R, Gu Q: Skeletal muscle relaxant use in the United States: Data from the Third National Health and Nutrition Examination Survey (NHANES III). *Spine* 2004; 29:892-896.
170. Annequin D, et al: Fixed 50% nitrous oxide oxygen mixture for painful procedures: A French survey. *Pediatrics* 2000; 105:E47.
171. Gall O, et al: Adverse events of premixed nitrous oxide and oxygen for procedural sedation in children. *Lancet* 2001; 358:1514-1515.
172. Emmanouil DE, Quock RM: Advances in understanding the actions of nitrous oxide. *Anesth Prog* 2007; 54:9-18.
173. Jaslow D, Lemecha D: Prehospital pharmacology: Nitrous oxide. *Emerg Med Serv* 2007; 36:71-73.
174. O'Sullivan I, Benger J: Nitrous oxide in emergency medicine. *Emerg Med J* 2003; 20:214-217.
175. Marie RM, et al: Nitrous oxide anesthesia–associated myelopathy. *Arch Neurol* 2000; 57:380-382.
176. Rowland AS, et al: Reduced fertility among women employed as dental assistants exposed to high levels of nitrous oxide. *N Engl J Med* 1992; 327:993-997.
177. Covino BG: Pharmacology of local anaesthetic agents. *Br J Anaesth* 1986; 58:701-716.
178. Bartfield JM, Crisafulli KM, Raccio-Robak N, Salluzzo RF: The effects of warming and buffering on pain of infiltration of lidocaine. *Acad Emerg Med* 1995; 2:254-258.
179. Bartfield JM, Ford DT, Homer PJ: Buffered versus plain lidocaine for digital nerve blocks. *Ann Emerg Med* 1993; 22:216-219.
180. Berkun Y, Ben-Zvi A, Levy Y, Galili D, Shalit M: Evaluation of adverse reactions to local anesthetics: Experience with 236 patients. *Ann Allergy Asthma Immunol* 2003; 91:342-345.
181. Bartfield JM, Jandreau SW, Raccio-Robak N: Randomized trial of diphenhydramine versus benzyl alcohol with epinephrine as an alternative to lidocaine local anesthesia. *Ann Emerg Med* 1998; 32:650-654.
182. Green SM, Rothrock SG, Gorchynski J: Validation of diphenhydramine as a dermal local anesthetic. *Ann Emerg Med* 1994; 23:1284-1289.
183. Wilhelmi BJ, Blackwell SJ, Miller J, Mancoll JS, Phillips LG: Epinephrine in digital blocks: Revisited. *Ann Plast Surg* 1998; 41:410-414.
184. de Jong RH: *Local Anesthetics*. St Louis: Mosby; 1994.
185. Ward L, Wright E, McMahon SB: A comparison of the effects of noxious and innocuous counterstimuli on experimentally induced itch and pain. *Pain* 1996; 64:129-138.
186. Fatovich DM, Jacobs IG: A randomized controlled trial of buffered lidocaine for local anesthetic infiltration in children and adults with simple lacerations. *J Emerg Med* 1999; 17:223-228.
187. Scarfone RJ, Jasani M, Gracely EJ: Pain of local anesthetics: Rate of administration and buffering. *Ann Emerg Med* 1998; 31:36-40.
188. Bartfield JM, Sokaris SJ, Raccio-Robak N: Local anesthesia for lacerations: Pain of infiltration inside vs outside the wound. *Acad Emerg Med* 1998; 5:100-104.
189. Liu DR, Kirchner HL, Petrack EM: Does using heat with eutectic mixture of local anesthetic cream shorten analgesic onset time? A randomized, placebo-controlled trial. *Ann Emerg Med* 2003; 42:27-33.
190. Hegenbarth MA, et al: Comparison of topical tetracaine, adrenaline, and cocaine anesthesia with lidocaine infiltration for repair of lacerations in children. *Ann Emerg Med* 1990; 19:63-67.
191. Dailey RH: Fatality secondary to misuse of TAC solution. *Ann Emerg Med* 1988; 17:159-160.
192. Ernst AA, Marvez-Valls E, Nick TG, Weiss SJ: LAT (lidocaine-adrenaline-tetracaine) versus TAC (tetracaine-adrenaline-cocaine) for topical anesthesia in face and scalp lacerations. *Am J Emerg Med* 1995; 13:151-154.
193. Schilling CG, Bank DE, Borchert BA, Klatzko MD, Uden DL: Tetracaine, epinephrine (adrenalin), and cocaine (TAC) versus lidocaine, epinephrine, and tetracaine (LET) for anesthesia of lacerations in children. *Ann Emerg Med* 1995; 25:203-208.
194. Priestley S, Kelly AM, Chow L, Powell C, Williams A: Application of topical local anesthetic at triage reduces treatment time for children with lacerations: A randomized controlled trial. *Ann Emerg Med* 2003; 42:34-40.
195. Bertalanffy A, et al: Transcutaneous electrical nerve stimulation reduces acute low back pain during emergency transport. *Acad Emerg Med* 2005; 12:607-611.
196. Lang T, et al: TENS relieves acute posttraumatic hip pain during emergency transport. *J Trauma* 2007; 62:184-188; discussion 188.
197. Peebles-Kleiger MJ: The use of hypnosis in emergency medicine. *Emerg Med Clin North Am* 2000; 18:327-338, x.
198. Sharav Y, Tal M: Focused hypnotic analgesia: Local and remote effects. *Pain* 2006; 124:280-286.
199. Tanabe P, Ferket K, Thomas R, Paice J, Marcantonio R: The effect of standard care, ibuprofen, and distraction on pain relief and patient satisfaction in children with musculoskeletal trauma. *J Emerg Nurs* 2002; 28:118-125.
200. Cohen LL, et al: Randomized clinical trial of distraction for infant immunization pain. *Pain* 2006; 125:165-171.
201. Nation EM, Warfield CA: Pain in the elderly. *Hosp Pract (Off Ed)* 1989; 24:113, 117-118.
202. Gloth FM 3rd: Pain management in older adults: Prevention and treatment. *J Am Geriatr Soc* 2001; 49:188-199.
203. Abbuhl FB, Reed DB: Time to analgesia for patients with painful extremity injuries transported to the emergency department by ambulance. *Prehosp Emerg Care* 2003; 7:445-447.
204. Jacob E, Mueller BU: Pain experience of children with sickle cell disease who had prolonged hospitalizations for acute painful episodes. *Pain Med* 2008; 9:13-21.
205. McManus JG Jr, Sallee DR Jr: Pain management in the prehospital environment. *Emerg Med Clin North Am* 2005; 23:415-431.
206. Swor R, McEachin CM, Seguin D, Grall KH: Prehospital pain management in children suffering traumatic injury. *Prehosp Emerg Care* 2005; 9:40-43.
207. Thomas SH, Shewakramani S: Prehospital trauma analgesia. *J Emerg Med* 2008; 35:47-57.
208. Galinski M, et al: A randomized, double-blind study comparing morphine with fentanyl in prehospital analgesia. *Am J Emerg Med* 2005; 23:114-119.
209. McLean SA, et al: The feasibility of pain assessment in the prehospital setting. *Prehosp Emerg Care* 2004; 8:155-161.
210. Lee C, Porter KM: Prehospital management of lower limb fractures. *Emerg Med J* 2005; 22:660-663.
211. Turturro MA: Pain, priorities, and prehospital care. *Prehosp Emerg Care* 2002; 6:486-488.
212. McEachin CC, McDermott JT, Swor R: Few emergency medical services patients with lower-extremity fractures receive prehospital analgesia. *Prehosp Emerg Care* 2002; 6:406-410.
213. Faddy SC, Garlick SR: A systematic review of the safety of analgesia with 50% nitrous oxide: Can lay responders use analgesic gases in the prehospital setting? *Emerg Med J* 2005; 22:901-908.

www.ketabpezeshki.com 66485457-66963820

Chapter 4

Procedural Sedation and Analgesia

David B. Burbulys

PERSPECTIVE

The performance of painful diagnostic and therapeutic procedures is common in emergency care. Many of these are associated with significant anxiety, especially in children.[1-5] Procedural sedation and analgesia (PSA) has therefore become a fundamental and required skill for emergency physicians and an integral part of the core training of emergency medicine residents.[4-8]

PSA improves the quality of patient care and satisfaction through relief of pain and anxiety and by facilitating the timeliness and success of therapeutic or diagnostic procedures.[7,9-14] These include fracture or joint reduction, incision and drainage of abscesses, cardioversion, tube thoracostomy, lumbar puncture, complex wound repair, and imaging studies in young or uncooperative patients.

Many of the agents used for PSA have the potential to cause significant respiratory, cardiovascular, or central nervous system (CNS) depression.[15-25] The Joint Commission (TJC), the Centers for Medicare and Medicaid Services (CMS), the American College of Emergency Physicians (ACEP), and the American Society of Anesthesiologists (ASA) have produced expert consensus or evidence-based documents concerning its use[26-28] (Box 4-1). Although significant controversy continues with respect to credentialing and oversight of PSA outside the operating room, the advent of these guidelines has led to PSA becoming a safe, common, and practical emergency department (ED) procedure.[9,29] It has been further improved by the development of shorter-acting, more effective drugs and the use of noninvasive monitoring devices.

With the wide variety of procedures and patient populations, the ability to individualize PSA and maximize the risk-benefit ratio for each unique situation is a necessary skill. This can be best achieved through a detailed understanding of: the preprocedural patient assessment, the protocols delineating the required personnel and their roles, the supplies and equipment required, the specific drugs used (including their routes of administration, dosages, effects, interactions, and complications), consideration for special populations and patient monitoring, recovery, and discharge criteria.

Terminology

Anxiolysis is a state of decreased apprehension concerning a particular situation in which the patient's level of awareness does not change.

Analgesia refers to the relief of pain without the intentional alteration of mental status, such as occurs in sedation. An altered mental state may be a secondary effect of the medications administered for this purpose.

Dissociation is a trancelike cataleptic state induced by an agent such as ketamine and characterized by a profound analgesia and amnesia. Protective reflexes, spontaneous respirations, and cardiopulmonary stability are retained.

Sedation is a controlled reduction of environmental awareness.

Procedural sedation and analgesia is a technique of administering a sedative or dissociative agent, usually along with an analgesic, to induce a state that allows the patient to tolerate unpleasant procedures while maintaining adequate spontaneous cardiorespiratory function. It is intended to result in a depressed level of consciousness that allows the patient to maintain oxygenation and airway control independently and continuously. The drugs, doses, and techniques used are not likely to produce a loss of the protective airway reflexes.[28]

Prior terminology defined three levels of sedation: conscious sedation, deep sedation, and general anesthesia. The term *conscious sedation* was often misinterpreted, confusing, and imprecise. It was coined in 1985 to describe lightly sedated dental patients. It was then further incorporated into pediatric sedation guidelines to distinguish a level of sedation from which the patient is easily arousable from the more advanced techniques of deep sedation, in which patients are difficult to arouse, and general anesthesia, in which patients are not arousable.[30-32] Despite the focused intent of these definitions, practitioners quickly labeled all levels of procedural sedation taking place outside the operating room as "conscious sedation."

In 2001 TJC adopted the ASA definition of sedation and analgesia that was created to better describe the continuum of sedation and analgesia[33] (Fig. 4-1). Although this truly is a continuum, the ASA divided PSA into four distinct subgroups: minimal sedation, moderate sedation, deep sedation, and general anesthesia. A fifth category, dissociative sedation, has since been added[34] (Table 4-1). This new nomenclature is more intuitive, clear, and logical.

Minimal sedation (anxiolysis) is a drug-induced state during which patients respond normally to verbal commands. Although cognitive functions and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.

Moderate sedation/analgesia (formerly called "conscious sedation") refers to a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. Reflex withdrawal from the painful stimulus is not considered a purposeful response. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is always maintained.

www.ketabpezeshki.com 66485457-66963820

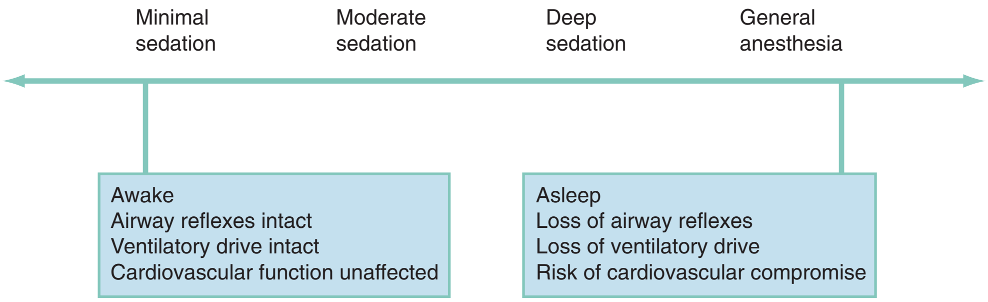


Figure 4-1. Schematic representation of the sedation continuum. As increasing doses of nondissociative agents are given, patients move along the sedation continuum, experiencing a progressive decline in their level of consciousness and an increased risk of adverse respiratory and cardiovascular events. If medication administration continues, the patient will ultimately reach a state of general anesthesia with loss of protective airway reflexes and ventilatory drive. The transition from one level of sedation to the next is often difficult to predict and varies from patient to patient.

Box 4-1 American College of Emergency Physicians Policy Statement on Sedation in the Emergency Department (January 2011)

The American College of Emergency Physicians recommends the following:

- Emergency physicians who have received the appropriate training and skills necessary to safely provide procedural sedation should be eligible for credentialing in all levels of procedural sedation.
- The decision to provide sedation and the selection of the specific pharmacologic agents should be individualized for each patient by the emergency physician and should not be otherwise restricted.
- Emergency physicians and staff are expected to be familiar with the pharmaceutical agents they use and be prepared to manage their potential complications.
- To minimize complications, the appropriate drugs and dosages must be chosen and administered in an appropriately monitored setting, and a patient evaluation should be performed before, during, and after their use.
- Institutional and departmental guidelines related to the sedation of patients should include credentialing and verification of competency of providers, selection and preparation of patients, informed consent, equipment and monitoring requirements, staff training and competency verification, criteria for discharge, and continuous quality improvement.

Dissociative sedation is a trancelike cataleptic state induced by the dissociative agent ketamine and characterized by profound analgesia and amnesia, while protective airway reflexes, spontaneous respirations, and cardiopulmonary stability are maintained.

Deep sedation/analgesia describes a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully after repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

General anesthesia is a drug-induced loss of consciousness during which patients are not arousable even with painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive-pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.

The progression from minimal sedation to general anesthesia truly is a dynamic continuum that lacks distinct separation between stages. The transition from one level of sedation to the next is often difficult to predict and varies from patient to patient. The sedation continuum is not drug-specific, and levels from mild sedation to general anesthesia can be achieved with virtually all of the PSA agents. Because of this, it is recommended that clinicians administering PSA be competent in the skills required to treat patients in at least one level greater than the intended level of sedation.

Approach to Procedural Sedation and Analgesia for Procedures

Patient Assessment

To date, no outcome-based studies have demonstrated clear benefit from extensive evaluation beyond vital signs, mental status, and airway and cardiopulmonary assessment before PSA.[35,36] Despite this, consensus guidelines suggest that an increased risk of adverse events may exist in select subsets of patients. These include patients at the extremes of age, patients with difficult facial or neck anatomy or any other reason for potential intubation or bag-valve-mask ventilation difficulty, and patients with underlying significant disease states.[15,16,25,36] A patient's general physical status is conventionally categorized according to the ASA's classification system[37] (Table 4-2). Most practice guidelines require that a history and focused physical examination be performed and documented before PSA. There is no literature to support the need for routine diagnostic testing other than diagnostic testing driven by the patient's current status, including comorbidities.

The patient's age; current illness or injury for which the PSA is intended; underlying medical problems (comorbidities); previous experiences or problems with PSA or general anesthesia; drug allergies and current medications; and tobacco, drug, and alcohol use are reviewed and recorded. A directed physical examination focuses on the vital signs, the heart and lungs, and evaluation of the airway for potential difficulty providing bag-valve-mask ventilation or intubation.

A discussion including the risks, benefits, and potential side effects of PSA should take place with patients or their families before the procedure. Written consent is obtained, unless this is not possible. Patient selection is important to the safety of the sedation. Not every patient is an appropriate candidate for PSA in the ED. Depending on the clinical circumstances, a patient with an anticipated difficult airway or an ASA classification of III or IV may require consultation with an anesthesiologist. It may be advisable in some cases to have the anesthesiologist perform the

www.ketabpezeshki.com 66485457-66963820

Table 4-1 Definition of Levels of Sedation and Analgesia

	MINIMAL SEDATION (ANXIOLYSIS)	MODERATE SEDATION/ ANALGESIA (CONSCIOUS SEDATION)	DEEP SEDATION/ ANALGESIA	DISSOCIATIVE SEDATION	GENERAL ANESTHESIA
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response to repeated or painful stimulation	Unarousable even with painful stimulus	Unarousable even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Adequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	Elevated	May be impaired

Table 4-2 American Society of Anesthesiologists Physical Status Classification

CLASS	DESCRIPTION	EXAMPLES	SEDATION RISK
I	Normal and healthy patient	No past medical history	Minimal
II	Mild systemic disease without functional limitations	Mild asthma, controlled diabetes	Low
III	Severe systemic disease with functional limitations	Pneumonia, poorly controlled seizure disorder	Intermediate
IV	Severe systemic disease that is a constant threat to life	Advanced cardiac disease, renal failure, sepsis	High
V	Moribund patient who may not survive without procedure	Septic shock, severe trauma	Extremely high

sedation or to undertake the procedure in the operating room under more controlled circumstances.

Preprocedural Fasting

The need for preprocedural fasting in PSA remains controversial.[38-49] Currently the ASA recommends a period of 2 hours after ingestion of clear liquids, a period of 4 hours after ingestion of breast milk, and a period of 6 hours after ingestion of other liquids (infant formula, nonhuman milk) or solids before PSA, but there are no outcome studies to support these recommendations.[50] These guidelines are based on expert consensus and extrapolated from data describing circumstances in which patients received sedation to the level of general anesthesia followed by the manipulation of the airway during intubation and extubation.[20] PSA in the ED attempts to avoid both of these specific situations.

Many studies fail to support the notion that gastric emptying has any effect on the incidence of complications or outcome with PSA. There have been no published studies demonstrating an increased risk of aspiration after a liquid or solid meal and no studies showing a benefit of fasting before PSA. In one large study of nearly 5000 children and 18,000 adults, no clinically significant differences with airway complications, emesis, or other adverse effects were observed between various groups of patients classified by their preprocedural fasting status.[4,40] During PSA, the combination of vomiting and the loss of the airway protective reflexes is an extremely rare occurrence. Furthermore, most episodes of vomiting and aspiration occur during airway manipulation, which is also very unlikely to occur during PSA.

Although recent food intake is not a contraindication for administering PSA, risks of pulmonary aspiration and the benefits of providing PSA are weighed in accordance with the needs of each individual patient. Some procedures, such as reduction of a dislocated joint, should not be delayed for consideration of fasting status, whereas others, such as abscess drainage, are not as time-sensitive, and the sedation plan can be adapted accordingly.

Personnel

TJC and most institutional policies suggest that PSA providers should have adequate training to administer the agents effectively and safely, the skills to monitor the patient's response to the medications given, and the expertise needed to manage all potential complications.[51-56] This generally implies that PSA in the ED should be supervised by an emergency physician or other appropriately trained and credentialed physician. It is also recommended that a qualified support person (nurse, respiratory therapist) be present for the continuous monitoring of the patient. Such support persons should focus on the patient's status and not take part in the procedure. They should also be able to recognize and respond to the complications of PSA. They may assist with minor, interruptible tasks; however, they should have no other responsibilities that would interfere with the level of monitoring and documentation appropriate for the planned level of sedation. They should be free to monitor the patient from the start of the procedure through the completion of the recovery phase.[28]

Supplies and Equipment

PSA may result in an allergic reaction, oversedation, respiratory depression, or, rarely, cardiopulmonary arrest. The incidence of these complications depends on patient selection, the drugs used, the rate and dosage of administration, and specific patient sensitivities. Consequently, appropriate equipment to monitor the patient's condition at all times; to manage airway complications, allergic reactions, and drug overdoses; and to treat respiratory or cardiopulmonary arrest should be readily available. Supportive equipment includes oxygen, suction, patient-monitoring devices, basic and advanced airway management equipment, a monitor/defibrillator, advanced life-support medications, reversal or rescue agents, and vascular access equipment (Box 4-2).

In most situations, the agents used for PSA in adult patients should be administered intravenously (IV). Nearly all adults undergoing PSA in the ED should therefore have an intravenous line placed before the procedure. This need in children is less clear and depends on the presence of comorbid conditions and the choice and route of drug to be administered. If the procedure is likely to be lengthy, or if multiple doses of drugs will be needed, an intravenous line should be considered.

www.ketabpezeshki.com 66485457-66963820

Box 4-2 Equipment for Procedural Sedation and Analgesia

High-flow oxygen source
Suction
Airway management equipment
Monitoring equipment
Pulse oximeter
- ECG monitor/defibrillator, transcutaneous pacemaker
- Blood pressure monitor
- Capnography*

Vascular access equipment
Reversal agents
Resuscitation drugs
Adequate staff

*Capnography is recommended by the American Society of Anesthesiologists for monitoring the presence of exhaled carbon dioxide during moderate or deep sedation in addition to the continual observation of qualitative clinical signs of adequate ventilation.
ECG, electrocardiogram.

The requirement for supplemental oxygen, and its benefits during PSA, have not been well studied and remain somewhat controversial.[56-62] Supplemental oxygen may prevent hypoxemia in many patients; however, significant respiratory depression in these patients may not be detected because of their normal oxygen saturation. This may delay the recognition of respiratory compromise and hypercarbia when capnography is not used. On the other hand, transient hypercarbia is not harmful, and maintenance of adequate oxygen saturation is much more important. The use of capnography eliminates this issue, because ventilatory status is displayed continuously. We recommend the use of supplemental oxygen in administering PSA to a patient in the ED.

Monitoring

The most important aspect of monitoring during PSA is the visual observation and assessment of the patient. The patient's ability to follow commands in response to varied levels of stimulation is useful in quantifying the level of consciousness. Furthermore, the patient's ventilatory rate may be readily assessed by direct observation, although depth of respiration (tidal volume) is much harder to estimate clinically. Other components of monitoring, which should be documented, include respiratory rate, heart rate, blood pressure, oxygen saturation, and perhaps cardiac rhythm and capnometry.[63-67] Pulse oximetry is a reliable and important monitoring modality, used in conjunction with close and continuous observation of the patient and the response to medications and procedures.

There is no evidence that cardiac monitoring during PSA is of any benefit, but it certainly is not harmful, is readily available, and is inexpensive to use.[68-70] We recommend continuous electrocardiographic monitoring in older patients and in patients with a history of cardiovascular disease, hypertension, or dysrhythmia. In young healthy patients without underlying significant disease, this may be safely replaced by continuous pulse oximetry, which also displays the heart rate, but, in most circumstances, monitors capable of showing heart rate, blood pressure, and pulse oximetry will also easily facilitate cardiac rhythm monitoring.

Capnometry or capnography measures end-tidal carbon dioxide (CO_2) partial pressure and has been shown to detect cases of inadequate ventilation earlier than clinical assessment or detection of hypoxemia by oximetry.[60,62,71-80] Several studies have demonstrated this, but none have shown an effect on clinical outcome to date. In July 2011, the ASA updated its procedural sedation standards to include capnography during moderate or deep sedation to evaluate the adequacy of ventilation in addition to continual observation of qualitative clinical signs.[81,82] Capnography should be used when deep sedation is planned, as respiratory depression is common in patients undergoing deep sedation. It is optional when only light sedation is planned, but even in such cases, it will help the observer recognize unintended oversedation with respiratory depression.

The Bispectral Index (BIS) is monitored via a noninvasive device attached to the patient's forehead and derives a depth of sedation level via frontal lobe electroencephalographic measurements. It has been used in the operating room as an objective measure of sedation depth.[83-85] Studies have shown that it may be beneficial in preventing oversedation in PSA and reducing the time to discharge.[86] These investigations have also suggested that its use may better guide the depth of sedation endpoint than traditional sedation scales have, and it may have further benefit for PSA in children, as they frequently require deeper levels of sedation for prevention of movement.[87-90] Early ED studies for its use in PSA to discriminate between mild-to-moderate and moderate-to-deep levels of sedation have not been reliable, nor has it been shown to be predictive of patients sedated to the point of general anesthesia from those with lesser degrees of sedation. BIS monitoring may have a beneficial role for emergency medicine use and PSA in the future but requires more investigation before its possible uses and benefits can be completely defined.

If it is necessary to perform sedation outside the ED for a diagnostic procedure, every attempt should be made to provide the same level of monitoring during the transport and the procedure as would be used within the department.

The highest risk of serious adverse events generally occurs within 5 to 20 minutes of receiving the last dose of intravenous medication and at the completion of procedures, when the patient remains sedated but is no longer receiving the painful stimulus. Similarly, patients undergoing prolonged procedures in which deeper sedation is desired to reduce motion (e.g., magnetic resonance imaging [MRI]) are also at an increased risk.[16-19,23,36,91] Patients should continue to be monitored closely at these times, and this should continue until clinical recovery has occurred.

Recovery

Monitoring as part of the PSA routine should continue until patients are spontaneously awake and able to function independently, even though they may not be completely back to baseline function or ready for discharge. Drowsy patients should not be left unattended.

Discharge Criteria and Instructions

Before discharge, baseline cognitive and motor function should be achieved. The patient should be able to follow commands, speak clearly, and ambulate or sit unassisted (infants). Vital signs and respiratory status should be back to baseline and within normal limits. Residual pain should be addressed. Nausea should be minimal, and vomiting should be resolved. It is preferable that all patients, including adults, be sent home with a responsible adult, but if this is not possible, the patient remains in the ED until normal baseline has been achieved.[4,92-96]

Patients should be advised not to drive or participate in other dangerous activities for 12 to 24 hours. Despite the short clinical duration of most of the agents used, many people may exhibit subtle signs of cognitive deficits and mild drowsiness.[94,97] It is therefore preferable that they remain in the company of a responsible adult at home for 4 to 8 hours. For children, light play at home should be the extent of activities, with no bicycle riding, swimming, or other complex motor activity until the next day. An antinauseant and progressive diet is helpful if nausea or vomiting is experienced. Standard discharge instructions should also be provided for the presenting complaint, and all patients should be

www.ketabpezeshki.com 66485457-66963820

Table 4-3 Procedural Sedation and Analgesia Agents—Recommended Adult Starting Doses

AGENT	CLASS	MAIN EFFECT	ROUTE	USUAL STARTING DOSE
Fentanyl	Opioid	Analgesia	Intravenous	1 μg/kg
Morphine	Opioid	Analgesia	Intravenous	0.1 mg/kg
Midazolam	Benzodiazepine	Sedation Amnesia	Intravenous	0.05 mg/kg
Methohexital	Barbiturate	Sedation Amnesia	Intravenous	1 mg/kg
Pentobarbital	Barbiturate	Sedation Amnesia	Intravenous Intramuscular	2 mg/kg 4 mg/kg
Ketamine	Phencyclidine derivative	Dissociation Analgesia Sedation Amnesia	Intravenous Intramuscular	1-2 mg/kg 4-5 mg/kg
Etomidate	Imidazole derivative	Sedation Amnesia	Intravenous	0.1 mg/kg
Propofol	Alkylphenol derivative	Sedation Amnesia Antiemetic	Intravenous	0.5 mg/kg
Nitrous oxide	Anesthetic gas	Analgesia	Inhaled	30-70%

instructed to immediately return if any confusion or respiratory symptoms arise.

Pharmacology

In selecting agents, consideration is given to the effects desired, the risks and benefits, and the logistics of administration for each situation. The ideal agent would provide analgesia, anxiolysis, amnesia, and somnolence. It would have a rapid onset and offset with predictable results and would have no adverse effects. This agent, of course, does not exist.

When the procedure is unpleasant but not painful (e.g., endoscopy), pure sedation may be the desired endpoint, and agents such as benzodiazepines, barbiturates, etomidate, or propofol sometimes are used alone. These agents do not provide pain relief and should not be used as the sole agent when pain management is also desired. Analgesic agents such as opioids or nitrous oxide are often added to a sedative agent to provide analgesia for painful procedures. Ketamine, on the other hand, may be an excellent single drug choice for painful or stimulating procedures in children and for some adult applications (e.g., fracture reduction). Usually a combination of analgesic and sedative agents is required. Caution is indicated, as their side effects are frequently potentiated.

The specific agents for PSA and dosage recommendations for adult patients are provided in Table 4-3 and for pediatric patients in Table 4-4. Benefits and adverse effects are provided in Table 4-5. Individual agents are discussed in greater detail in the following sections.

Route of Administration

Route of administration should also be determined by the procedure and the specific patient. In most situations, intravenous titration to the desired level of sedation and analgesia provides the safest, most rapid, and most predictable results. Drugs given by the intramuscular, oral, transmucosal, intranasal, or rectal route generally have a slower onset of action, are difficult to titrate, have unpredictable results, and may lead to prolonged sedation. These routes are virtually never used for PSA in adults. In children, however, ketamine has been shown to provide consistent and predictable results when given intramuscularly (IM).[98-100] Nitrous oxide has predictable behavior when used as a sole inhalational PSA agent in children but is also frequently used as an analgesic adjunct to a sedating agent.[101-104] In pediatric patients, the benefits of intravenous drug administration may be outweighed by the difficulty and distress to the patient in obtaining intravenous access. In this situation, drugs given by the alternative routes may be preferred.

Drugs should be administered by titrated slow intravenous bolus to minimize hypotension or respiratory depression in many situations. It is important to allow adequate time between doses to achieve and assess peak effect before an additional dose is given. Lower initial doses should be chosen in sensitive patients or when drugs from multiple classes are being administered. One exception is ketamine. Unlike the other agents described, it possesses a threshold response rather than an additive dose-response continuum. Smaller doses of ketamine cause analgesia and disorientation. Dissociation occurs when a dosage threshold of 1 to 1.5 mg/kg IV in adult patients or 2 to 2.5 mg/kg in younger pediatric patients is reached. Higher doses do not enhance or deepen the sedation.[105]

Opioids

Parenteral opioids are commonly used as analgesics before painful procedures are performed. For PSA, an opioid is rarely optimal as a single agent, and most clinicians combine an opioid with a sedative-amnestic agent to balance sedation-amnesia and analgesia with the least likelihood of respiratory depression. The most commonly used opioids in the ED for PSA are fentanyl and morphine. These are often combined with benzodiazepines such as midazolam for moderate sedation and used in smaller doses to provide analgesia during deep sedation with etomidate or propofol. Meperidine historically was used for PSA but is no longer recommended because seizures are commonly associated with the accumulation of its long-lasting metabolite normeperidine.

Fentanyl

Fentanyl has many advantages as an analgesic agent for PSA, given its rapid onset of action, short duration of activity, lack of

www.ketabpezeshki.com 66485457-66963820

Table 4-4 Procedural Sedation and Analgesia Agents—Recommended Pediatric Starting Doses

AGENT	CLASS	EFFECT	ROUTE	USUAL STARTING DOSE
Fentanyl	Opioid	Analgesia	Intravenous Transmucosal	1 μg/kg 10 μg/kg
Morphine	Opioid	Analgesia	Intravenous	0.1 mg/kg
Midazolam	Benzodiazepine	Sedation Amnesia	Intravenous Intramuscular Oral Rectal Intranasal	0.1 mg/kg 0.1 mg/kg 0.5 mg/kg 0.5 mg/kg 0.2 mg/kg
Methohexital	Barbiturate	Sedation Amnesia	Intravenous Rectal	1 mg/kg 25 mg/kg
Pentobarbital	Barbiturate	Sedation Amnesia	Intravenous Intramuscular	2 mg/kg 4 mg/kg
Ketamine	Phencyclidine derivative	Dissociation Analgesia Sedation Amnesia	Intravenous Intramuscular Oral Rectal Intranasal	1-2 mg/kg 4-5 mg/kg 10 mg/kg 10 mg/kg 6 mg/kg
Etomidate	Imidazole derivative	Sedation Amnesia	Intravenous	0.1 mg/kg
Propofol	Alkylphenol derivative	Sedation Amnesia Antiemetic	Intravenous	0.5 mg/kg
Nitrous oxide	Anesthetic gas	Analgesia	Inhaled	30-70%

Table 4-5 Procedural Sedation and Analgesia Agents—Benefits and Adverse Effects

AGENT	ROUTE	ONSET (min)	DURATION (min)	ADVANTAGES	ADVERSE EFFECTS
Fentanyl	Intravenous Transmucosal	1-2 10-30	30-40 60-120	Rapid onset Short duration ↓Histamine release Minimal CV effects	Respiratory depression Rigid chest syndrome
Morphine	Intravenous	10	240-360	Longer lasting	Hypotension Respiratory depression
Midazolam	Intravenous Intramuscular Oral Rectal Intranasal	1-2 10-15 15-30 10-30 10-15	30-60 60-120 60-90 60-90 45-60	Rapid onset Short duration Easy to titrate Multiple routes	Respiratory depression
Methohexital	Intravenous Rectal	<1 5-10	4-7 20-60	Rapid onset Short duration Airway reflexes maintained	Respiratory depression Apnea Hypotension
Pentobarbital	Intravenous	1-2	30-60	Rapid onset Airway reflexes maintained	Respiratory depression Apnea Hypotension Prolonged recovery
Ketamine	Intravenous Intramuscular Oral Rectal Intranasal	1 5 30-45 5-10 5-10	15 15-30 120-240 15-30 30-120	Airway reflexes maintained No respiratory depression Predictable	Emergence phenomena Emesis Laryngospasm ↑ICP and ↑IOP
Etomidate	Intravenous	<1	5-10	Rapid onset Short duration Minimal CV effects Cerebral protective	Respiratory depression Myoclonus Adrenal suppression
Propofol	Intravenous	<1	8-10	Rapid onset Short duration Antiemetic Cerebral protective	Respiratory depression Hypotension Injection pain
Nitrous oxide	Inhaled	1-2	3-5	Rapid onset Short duration Minimal CV effects	Expansion of gas-filled structures Emesis

CV, cardiovascular; *ICP*, intracranial pressure; *IOP*, intraocular pressure.

www.ketabpezeshki.com 66485457-66963820

histamine release, and favorable cardiovascular profile.[62,106-110] Fentanyl rapidly crosses the blood-brain barrier and produces analgesia in as little as 90 seconds. Serum levels rapidly decline from peak concentrations because of extensive tissue uptake followed by hepatic metabolism. It has a duration of action of 30 to 40 minutes and a serum half-life of approximately 90 minutes. These properties permit the administration of multiple small doses that can be easily titrated to the desired clinical effect. Because fentanyl readily creates a reservoir in the adipose tissue, accumulated large doses may result in a progressively increasing duration of effect. This does not generally occur in doses less than 10 μg/kg.[111-113]

For deep sedation, a single dose of 1 to 2 μg/kg of fentanyl is often given before the sedating agent. After adequate pain relief has been achieved, a smaller dose of a sedative agent may then be added and titrated to effect. Respiratory depression is minimized in this fashion. For moderate sedation, fentanyl can be titrated, along with a sedative agent, often midazolam, depending on whether the clinician feels that more sedative effect (midazolam) or analgesic effect (fentanyl) is required. Dosage should begin at 1 μg/kg and be slowly titrated upward every 1 to 2 minutes until the desired level of analgesia has been achieved. Sufficient analgesia for painful procedures under moderate sedation usually is accomplished with doses of 2 to 3 μg/kg and under deep sedation with 1 to 2 μg/kg. Lower doses should be used in elderly patients or when other CNS depressants have been previously administered (e.g., ethanol).

Respiratory depression is more likely at higher doses, when the drug is given rapidly, or when it is combined with other CNS depressants such as benzodiazepines or alcohol. Other side effects may include vomiting and pruritus, although these are less common than with other opioids. Hypotension and bradycardia are rare but may occur with high doses. Chest wall rigidity and glottic spasm, which may make ventilation difficult, are unique complications seen with high doses (anesthetic) of fentanyl given rapidly (generally more than 7 μg/kg).[114] Many of these adverse effects may be readily reversed by naloxone. The exception to this is chest wall rigidity, which may not reliably be antagonized and may necessitate neuromuscular blockade and intubation to enable adequate ventilation. This complication is extremely rarely reported with the doses of fentanyl used for PSA.[114]

In children, oral or transmucosal fentanyl has been used widely as a premedication for anesthesia and intravenous placement. It has also been used for PSA when intravenous access is not feasible. This is generally in the form of a fentanyl-impregnated, sweetened matrix in lozenge form on a holder—the "fentanyl lollipop." Transmucosal delivery allows rapid onset of action by avoiding first-pass metabolism in the liver. It has been shown to decrease activity and relieve pain in 10 to 30 minutes, resulting in scores similar to those after comparable intravenous doses of fentanyl.[110,115,116] Despite this fairly rapid onset, transmucosal delivery does not allow for easy titration. The general dose is 10 to 15 μg/kg. Larger doses have been shown to cause more nausea and vomiting without improving analgesia or activity scores. The combination of transmucosal fentanyl and transmucosal midazolam has not been shown to have additional benefit over either agent used singularly for laceration repair in the ED and has been shown to increase adverse events.[117] Its use before other agents such as propofol has not been studied well. The use of transmucosal fentanyl for PSA has largely been limited by unacceptable levels of nausea and vomiting, which approach 20 to 40% of patients.[118]

Morphine

Morphine is poorly lipid soluble and penetrates the blood-brain barrier more slowly after small bolus injections. A period of 10 to 30 minutes is required before its peak effects are seen, although when used for PSA, morphine performs in similar fashion to fentanyl, with comparable recovery times. A general starting dosage of 0.1 mg/kg is commonly used and then titrated to desired effect as with fentanyl. Morphine has much more histamine release and therefore is more likely to produce hypotension, especially in preload dependent patients. It has similar potential to other opioids for producing respiratory depression, especially when used with other CNS depressants such as benzodiazepines. Morphine undergoes hepatic metabolism to an active metabolite, followed by renal excretion. Insufficiency of either organ system may lead to increased serum half-life.

Benzodiazepines

Benzodiazepines are potent amnestic, hypnotic, and anxiolytic medications. They also have anticonvulsant and purported muscle relaxant properties but do not have analgesic effects. Because of this, they are commonly coadministered with an analgesic agent such as fentanyl or morphine. They may be given IV, IM, orally (PO), intranasally (IN), or per rectum (PR) but are virtually always used IV for PSA in adults.[119-121] Midazolam is the most commonly used agent because of its favorable pharmacokinetics.

Midazolam

Midazolam has many advantages for PSA, given its rapid onset of action and short duration of activity compared with other benzodiazepines. Its amnestic properties also appear to be superior to many of the others.[122] The starting intravenous dose is 0.05 mg/kg. Children may need slightly higher doses. Onset of sedation is generally within 1 to 2 minutes, and the duration of action is 30 to 60 minutes. Alternatives to the intravenous route are often used in children, particularly when sedation alone, without analgesia, is desired as for performance of a radiologic study. With intramuscular administration the same doses may be used, but the onset of action is delayed and the duration of effect is increased. Oral doses are often used in children, with a recommended starting dose of 0.5 mg/kg. Sedation is generally achieved within 30 minutes. Rectal administration may also be useful with doses of 0.5 mg/kg. The response when the drug is given by this route may be less predictable, and the rectal route is generally not accepted by older children. Intranasal administration may be useful but is irritating and often difficult in older children as well. The starting dose for this route is 0.2 mg/kg and results in sedation in 10 to 15 minutes. Of note, 1% of children younger than 5 years may experience a paradoxical reaction and become excited and agitated when given midazolam. If necessary, the agitated state is reversible by flumazenil. Midazolam has been shown to be an extremely safe and effective agent for PSA, both alone and when used in combination with fentanyl.[123-125]

Side effects include dose-dependent hypoventilation and hypoxemia. Apnea and hypotension are uncommon but occur more often at high doses or when other CNS depressants such as opioids are used. Headache, nausea, emesis, coughing, and hiccups have been shown to occur, although rarely. Lower doses should be used when other agents such as analgesics are given concomitantly and in the elderly. Prolonged effects may be seen in elderly patients or those with liver dysfunction owing to decreased hepatic or first-pass metabolism. Midazolam is highly lipophilic, and its effects may be greatly amplified in obese patients, resulting in an increased plasma half-life of up to 8 hours with high or repetitive doses. Chronic alcohol users who do not have liver dysfunction may require relatively high doses of midazolam to achieve the same clinical effects as a result of cross-tolerance.

www.ketabpezeshki.com 66485457-66963820

Barbiturates

Barbiturates are also potent hypnotics, with amnestic and anticonvulsant effects. They do not have analgesic properties. Before the widespread use of midazolam and the advent of propofol for deep sedation, barbiturates were commonly used for brief painless procedures, but they are rarely used now. They are not commonly combined with other agents owing to their narrower therapeutic window. We do not recommend the use of barbiturates for procedural sedation in adults, but these agents are still used in children, particularly for radiology procedures.

Methohexital

Methohexital is a highly lipophilic ultra-short-acting barbiturate with a rapid onset of amnesia and deep sedation in 30 to 60 seconds. It does not provide analgesia, and an opioid, such as fentanyl, is required for painful procedures. The concomitant use of fentanyl or another opioid increases the risk of apnea. Intravenous doses of 1 mg/kg produce unconsciousness for approximately 5 minutes. Methohexital may also be administered PR in children at a dose of 25 mg/kg but has a more variable effect and longer onset and duration of action.

Depressed respiratory drive and apnea are more common than with other agents but are generally transient and mild. Most patients respond to supplemental oxygen and repositioning of the airway. Its use in the ED appears to be safe and effective, particularly for brief orthopedic joint reductions, cardioversions, and radiologic imaging procedures. Only a small percentage of patients require brief periods of assisted ventilation. In several studies, no ED patients required intubation or change in disposition after having received methohexital for PSA.[126-129] Methohexital does have the potential to cause significant hypotension as well and should be used with caution in patients with hemodynamic instability or occult blood loss. It also may cause activation of the respiratory reflexes, inducing coughing, hiccups, and, rarely, laryngospasm. In contrast to the other barbiturates, methohexital may worsen or precipitate seizures, and it is prudent to avoid it in patients with a known seizure disorder.[128,130,131] Propofol has largely supplanted methohexital for PSA because it has more reliable, consistent effects, is easily titrated, and can be administered as an infusion for longer procedures.

Pentobarbital

Pentobarbital is also a barbiturate sedative agent, best used IV for nonpainful diagnostic studies in children. Its onset of action is generally within 1 to 2 minutes, with a duration of 30 minutes. It is usual to start with an initial dose of 2 mg/kg and titrate to effect, with subsequent doses of 1 to 2 mg/kg every 30 seconds as needed. The predominant complications with pentobarbital are respiratory depression, hypotension, and prolonged recovery.

Ketamine

Ketamine is a well-studied, safe, and predictable agent for use in the pediatric population for PSA.[124,128,132,133] It continues to gain popularity for use in adults as well.[124,129-131] It is a derivative of the street drug phencyclidine and is classified as a dissociative agent. It causes disruption between the thalamoneocortical and limbic systems, preventing the higher centers from perceiving visual, auditory, or painful stimuli. Because of this, its use leads to profound analgesia, amnesia, and catalepsis. It does not produce unconsciousness, but rather a trancelike state. Patients often experience nystagmus, roving eye movements, and random movements of the extremities unrelated to painful stimuli. Parents observing procedures in which ketamine is used may be disturbed at seeing this and should be forewarned.

Ketamine has several advantages over other PSA agents.[124,128,132-135] The most notable are its profound analgesic effect and the lack of significant respiratory depression. The protective airway reflexes, such as coughing, swallowing, and muscular tone of the tongue and pharynx, are well maintained or slightly enhanced. This is particularly useful in the ED setting where preprocedural fasting might not be assured. Its use further leads to blockade of catecholamine reuptake, and blood pressure is generally well supported. It also induces bronchial smooth muscle relaxation and is well tolerated in patients with reactive airway disease. It has a fast onset and offset and is predictable when given by the intravenous or intramuscular route. After administration, it is rapidly distributed and taken up by the cerebral tissues. The effects are maintained until the drug redistributes into the peripheral tissues and is metabolized by the liver. Because of this mechanism, repeat doses are well tolerated in longer procedures with predictable results but may lead to longer recovery times and increased incidence of emesis.

Ketamine may be given by multiple routes but is administered almost exclusively by the intravenous route in adults. After an intravenous dose of 1 to 2 mg/kg, a dissociative state results in approximately 1 minute, with duration of action of approximately 15 minutes. Complete recovery generally requires 1 to 2 hours. Similar cataleptic results may be seen with an intramuscular administration of 4 to 5 mg/kg in approximately 5 minutes, with effects lasting 15 to 30 minutes. For pediatric sedation, ketamine is generally administered by the intravenous or intramuscular route but may also be given PO (10 mg/kg), PR (10 mg/kg), or IN (6 mg/kg). These other routes are infrequently used because of variable onset of action, slow offset, and less predictable results.

The most common side effect seen with ketamine is the emergence phenomenon.[99,136-140] This occurs in approximately 15% of patients and is mild in almost all. They may wake up with unpleasant, vivid dreams or hallucinations or report nighttime awakenings as a result of unpleasant dreams for several days after the administration of ketamine. Less than 1 to 2% of patients have significant emergence agitation. This is more commonly seen in female patients, adolescents or adults, and in those with underlying psychiatric disorders. Its rare occurrence, especially in children, should not limit ketamine's use when indicated. Some studies have suggested that preprocedural or concurrent administration of midazolam may mitigate this reaction, but others have disputed the utility of this strategy. The most recent clinical practice guideline update does not recommend this practice in children.[53,106,141-144] We do not recommend the routine concomitant use of a benzodiazepine when administering ketamine sedation, unless it is judged to be of benefit for preprocedural anxiety. Benzodiazepines are useful for treating emergence phenomena, however, if such phenomena occur during recovery. Other side effects seen with ketamine use are transient apnea, laryngospasm, and emesis.[145-151] These are also rare but more common with rapid intravenous administration or with larger doses. Doses given slowly, at a rate of 0.5 mg/kg/min, may limit much of this. Ketamine also stimulates tracheobronchial and salivary secretions. In young children and in any patient undergoing airway examination (e.g., fiberoptic laryngoscopy), pretreatment with glycopyrrolate, 0.01 mg/kg given 10 minutes before the ketamine, may be beneficial. Because airway reflexes are maintained, this generally is not a concern in other patients. Prophylactic pretreatment with anticholinergics is unnecessary, and we no longer recommend this practice.[53,152-156] Postrecovery nausea and vomiting are also frequently seen but generally short lived and respond well to typical antiemetics such as ondansetron.[149]

Significant laryngospasm has been seen in infants younger than 3 months and in children with upper respiratory tract infections.

www.ketabpezeshki.com 66485457-66963820

It is recommended that ketamine be avoided in these patients. Because of catecholamine-mediated hypertension and tachycardia, ketamine should also be avoided in those with significant cardiovascular or coronary artery disease. Ketamine also increases intraocular pressure and should be avoided in those with open globe injuries. Ketamine is contraindicated in patients with psychosis (even when well controlled).

Etomidate

Etomidate is a short-acting sedative-hypnotic agent that is structurally unrelated to the other PSA agents and has no analgesic properties. Its use leads to the very rapid onset of profound sedation and hypnosis by enhancing neurotransmission at γ-aminobutyric acid (GABA) receptors. Etomidate has been used for deep sedation because of its rapid onset, short duration of action, and, most important, minimal effects on respiratory and cardiovascular function.[157-165]

After intravenous administration, sedation occurs in approximately 1 minute, and patients recover in 5 to 10 minutes. Etomidate induces deep sedation that borders on general anesthesia with higher doses and may be more difficult to titrate than the other sedative hypnotic agents. It is generally administered IV, with an initial dose of 0.1 mg/kg given slowly over 1 to 2 minutes. Additional doses of 0.05 to 0.1 mg/kg may be administered every 2 to 3 minutes until the desired level of sedation has been achieved. Smaller initial doses should be considered when etomidate is combined with analgesic agents or in the elderly. Because it has little effect on the cardiovascular system and is cerebral protective, it is an excellent choice for patients who have the potential for hemodynamic instability or increased intracranial pressure.

Adverse effects that may limit its usefulness include apnea, respiratory depression, myoclonus, nausea, vomiting, and adrenal suppression.[163,164,166-170] These side effects are more common with rapid intravenous administration, when higher doses are used, and in older patients. Although respiratory depression is rare and generally transient, few patients may require brief periods of assisted ventilation. Myoclonus is also typically described as mild and brief but at times may interfere with the procedure. Vomiting is unlikely with doses administered in the ED. Etomidate suppresses adrenal function by inhibiting 11-β-hydroxylase activity. This is generally not clinically relevant when a single sedating dose is used (see Chapter 1).[171-178]

Propofol

Propofol is another ultra-short-acting sedative-hypnotic agent that is structurally unrelated to the other PSA drugs and has no analgesic properties. It has an extremely rapid onset, a short duration of action, and predictable efficacy for inducing deep sedation.[10,125,164,179-192] Sedation quickly clears completely, permitting superior titration and earlier recovery and discharge. Propofol also possesses potent antiemetic properties and decreases intracranial pressure. Because of its properties, propofol is a highly desirable and widely used agent for deep sedation in the ED. It does not provide analgesia, however, and should be preceded by an opioid for painful procedures. As with all sedative agents, the addition of an opioid may increase the risk of deeper than anticipated sedation, respiratory depression, apnea, and hypotension, and smaller starting doses are recommended.

Propofol is administered with an initial intravenous bolus dose of 0.5 to 1 mg/kg that is then titrated every 1 to 3 minutes by 0.25- to 0.5-mg/kg aliquots to the desired sedation level. Children may require slightly higher doses than adults. The onset of sedation occurs in less than 1 minute, and patient recovery is in 10 minutes. For procedures lasting longer than this, additional boluses of 0.5 mg/kg may be administered, or a continuous infusion of 3 to 6 mg/kg/hr may be titrated to the desired level of sedation. Smaller doses should be used when sedating elderly patients or when administering propofol in patients pretreated with analgesics.

Adverse effects include dose-dependent respiratory depression, apnea, hypotension, and pain on injection. Other agents, such as opioids, may intensify these effects. In most cases apnea is transient, and patients will not experience significant falls in oxyhemoglobin levels before recovering their respiratory function. This underscores the values of supplemental oxygen administration during sedation. If the oxygen saturation falls into the low 90s, the patient may require a brief period of assisted ventilation. Propofol commonly results in a transient drop in systolic and diastolic blood pressure, which rarely necessitates fluid administration and is well tolerated by healthy patients. The hypotensive effect is exaggerated in the elderly and in patients with hypovolemia, and the initial dose of propofol should be reduced to 0.25 to 0.5 mg/kg in such patients. Pain associated with propofol injection occurs in the majority of patients and can be reduced with small infusions of intravenous lidocaine under tourniquet before its administration. Despite these concerns, propofol has been shown to be reliable and safe when used with proper monitoring in the ED setting. In a series of more than 25,000 pediatric patients in whom propofol was administered by emergency physicians, serious adverse effects were rare and there were no adverse outcomes.[180]

Ketamine Plus Propofol ("Ketofol")

Ketamine is commonly combined with propofol for PSA, especially in children. The two completely different agents are felt to have synergistic effects that balance each other's deficits while decreasing the overall dose of propofol. Ketamine provides the analgesic effects that propofol lacks, and the respiratory depression and hypotension caused by propofol are balanced by the cardiorespiratory stimulating effects of ketamine. Furthermore, vomiting and recovery hallucinations from ketamine are mitigated by the antiemetic and hypnotic effects of propofol.[106,141,142,144,193-197]

In several recent studies, ketofol was not shown to be clinically superior to either agent used alone with regard to respiratory depression or airway complications.[106,141,142,144] There was statistically significant benefit in provider satisfaction, sedation quality, and decreased emesis and clinically insignificant improvement in recovery time. Although the use of this combination is extremely popular, it cannot be currently recommended as superior to propofol, propofol plus fentanyl, or ketamine with or without ondansetron.

Nitrous Oxide

Nitrous oxide is a gas that, when used in combination with oxygen, provides excellent analgesia to supplement procedural sedation. It defuses rapidly across the alveoli in the lungs, providing a predictable and rapid onset in 1 to 2 minutes and rapid elimination in 3 to 5 minutes.

Nitrous oxide is administered as a 30 to 70% mixture with oxygen by a demand-valve mask or mouthpiece held by the patient. It is administered with at least 30% oxygen to avoid hypoxemia. A 30% concentration may be less than effective for PSA, especially in children, whereas a 70% mix may result in the loss of protective airway reflexes.

The need for a scavenger device and proper ventilation exhaust has limited the use of nitrous oxide in the ED. Because nitrous oxide rapidly defuses into gas-filled pockets, it can potentially worsen conditions such as pneumothoraces, small-bowel obstructions, decompression sickness, chronic obstructive pulmonary disease, and middle ear effusions. High concentrations may lead

www.ketabpezeshki.com 66485457-66963820

to nausea and vomiting, respiratory depression, and general anesthesia.

Reversal and Rescue Agents

Careful titration of PSA drugs to the desired level of sedation is the goal. At times, unanticipated deeper levels of sedation may be reached, and respiratory depression or apnea may be experienced. Airway repositioning, supplemental oxygen, and bag-valve-mask ventilation may be required. If these periods are prolonged, partial or complete reversal of agents such as opioids or benzodiazepines may be necessary. Elective reversal of PSA after the completion of the procedure is not recommended.[198,199]

Naloxone

Naloxone is a competitive antagonist of opioids and has been effectively used for the reversal of opioid-induced respiratory depression during PSA. It has a rapid onset of action and a mean plasma half-life of approximately 45 minutes, although its clinical effects last only 15 to 30 minutes. Resedation is generally not a problem for patients who have been given fentanyl or morphine in doses recommended for PSA. Nevertheless, these patients should be observed for a minimum of 1 hour after the administration of naloxone. It is especially important for patients who have received large doses of fentanyl to ensure that redistribution of fentanyl within the body does not result in the recurrence of sedation.

Naloxone may be administered IV, IM, subcutaneously, or via endotracheal routes, but it is almost universally given IV. The smallest dose necessary to restore respiratory effort should be used, because reversal of the opioid's respiratory depressant effect is matched by reversal of the analgesia. Initial dosage depends on the patient and the specific goals desired. For partial reversal, titrated doses of 0.1 to 0.2 mg may be used every 1 to 2 minutes to desired effect. Complete reversal is almost never desirable and requires doses of 1 to 2 mg. Similar doses may be used in children. In patients who are opioid dependent, these doses may precipitate an acute withdrawal state. Smaller initial doses should be considered. Large doses of naloxone may also make it more difficult to control postprocedure pain. Naloxone use has little risk, but pulmonary edema, seizure, and dysrhythmia rarely have been reported.

Flumazenil

Flumazenil is a competitive antagonist of benzodiazepines. Although it reverses the sedation effect of benzodiazepines, it is not as effective for reversing respiratory depression. In general, when oversedation occurs, brief support of ventilation permits the patient to recover sufficient spontaneous respiration without the need for reversal. Flumazenil has a rapid onset of action in 1 to 2 minutes, a peak effect in 5 to 10 minutes, and an individually variable clinical duration of 30 to 90 minutes. Continuous patient monitoring must be ensured when flumazenil is used to reverse respiratory depression associated with longer-lasting benzodiazepines because resedation is likely. Flumazenil has also been shown to be effective in reversing paradoxical excitement in children.

It is generally titrated in doses of 0.1 to 0.2 mg IV every 1 to 2 minutes to the desired effect. A maximum dose of 1 mg is generally sufficient. Common pediatric doses of 0.02 mg/kg are generally used, with a maximum of 0.2 mg. It should be used with extreme caution in patients with benzodiazepine dependence or a history of seizures, as it may precipitate life-threatening status epilepticus refractory to common treatment. Routine reversal is not recommended.

Drug Selection and Administration

When choosing a strategy for PSA, it is important to consider the type of procedure being performed (painful or not), the length of the procedure, specific procedural requirements (anxiolysis vs. immobility), and whether sedation may need to be prolonged. The need for intravenous access generally is an issue only in small children. Planned adjuncts, such as topical, local, or regional anesthesia, are also considered. Patient factors, including age, medications, alcohol and drug use, and comorbid conditions, are considered when selecting both the agent and the initial dose. Procedures necessitating sedation may be broadly divided into three categories: nonpainful procedures requiring immobilization (e.g., computed tomography [CT], MRI); low-pain, high-anxiety procedures (e.g., laceration repair, lumbar puncture); and highly painful, high-anxiety procedures (e.g., fracture or joint reduction, tube thoracostomy, abscess drainage, cardioversion). These are summarized in Table 4-6 for adult patients and Table 4-7 for pediatric patients.

For brief nonpainful procedures requiring complete immobilization, intravenous midazolam and propofol are excellent choices, and etomidate is a reasonable alternative. For longer procedures, oral or rectal midazolam or propofol infusion is reasonable.

For briefly painful procedures requiring minimal to moderate sedation and when topical or local anesthetics may be used (e.g., for reduction of a glenohumeral dislocation for which intra-articular lidocaine will be used), midazolam is a reliable and safe choice. Intravenous propofol (preceded by a modest dose of fentanyl) is an excellent choice for brief painful procedures requiring deep sedation (e.g., cardioversion, joint reduction, and other highly painful procedures). Ketamine by both the intravenous and intramuscular routes has been extensively studied in children and is highly effective with a large margin of safety. The same may be said for intravenous midazolam plus fentanyl in both the adult and pediatric populations.

Table 4-6 Adult Drug Selection Strategies

PROCEDURE TYPE	EXAMPLES	RECOMMENDATION	ALTERNATIVES	COMMENTS
Nonpainful	Radiologic imaging	Midazolam (intravenous)	Propofol (intravenous)	Midazolam has considerable support and safety.
Low pain, high anxiety	Central line placement Lumbar puncture	Midazolam (intravenous)	Propofol (intravenous) Ketamine (intravenous)	Analgesia may be accomplished with local or topical agents frequently.
High pain, high anxiety	Fracture or joint reduction Abscess drainage Burn débridement Cardioversion Chest tube placement	Midazolam + fentanyl (intravenous) Propofol + fentanyl (intravenous) Ketamine (intravenous, intramuscular)	Etomidate + fentanyl (intravenous) Propofol + ketamine (intravenous)	There are far more data supporting the safety of fentanyl and midazolam, although the other choices have significant support.

www.ketabpezeshki.com 66485457-66963820

Table 4-7 Pediatric Drug Selection Strategies

PROCEDURE TYPE	EXAMPLES	RECOMMENDATION	ALTERNATIVES	COMMENTS
Nonpainful	Radiologic imaging	Midazolam (oral, intravenous) Propofol (intravenous) Methohexital (rectal)	Methohexital (intravenous) Ketamine (intravenous, intramuscular) Pentobarbital (intravenous)	Intravenous access is often not required for brief procedures.
Low pain, high anxiety	Laceration repair Lumbar puncture Foreign body removal Sexual assault examination	Midazolam (oral, intravenous) Propofol (intravenous)	Ketamine (intravenous, intramuscular)	Analgesia may be accomplished with local or topical agents frequently.
High pain, high anxiety	Fracture or joint reduction Abscess drainage Burn débridement	Ketamine (intravenous, intramuscular) Fentanyl + midazolam (intravenous) Propofol + fentanyl (intravenous)	Propofol + ketamine (intravenous)	There are far more data supporting the safety of ketamine or fentanyl and midazolam, although propofol and fentanyl have significant support.

Special Considerations for Pediatric Populations

Performing painful procedures on children in the ED is often distressing for the parent and the provider as well as the child. This often includes obtaining intravenous access as well as performing more traditional procedures. In many cases, a calm and reassuring bedside manner, combined with distraction techniques, may be highly successful. Child life practitioners, coloring books, toys, video games, and television may be helpful.

The advent of ultrafast spiral CT scanners has nearly eliminated the need for sedation for this procedure. For prolonged CT studies or MRI, deep sedation is generally required in young children to ensure immobility. The need and desire for intravenous access in children should also be considered when planning PSA. Agents such as midazolam may be very effective in infants, but they do not reliably ensure immobility in young children except at high doses.[200-203] Methohexital and pentobarbital have demonstrated efficacy for sedating children for these longer imaging procedures.[202,204-211] Ketamine has been the most extensively studied and has been shown to be highly effective with a large margin of safety.[212-214] Many of these drugs have been largely supplanted by propofol as studies continue to show its efficacy and safety in pediatric PSA.[205,206,212,215-219]

For mildly painful procedures such as laceration repair or lumbar puncture, topical agents such as cream eutectic mixture of local anesthetics (EMLA) or lidocaine, epinephrine, tetracaine (LET) gels in combination with transmucosal or oral midazolam may preclude the need for placement of an intravenous line.

Brief painful procedures or those requiring deeper sedation may be accomplished with a single intramuscular injection of ketamine. Longer procedures or those requiring intravenous PSA agents require venous access. This should be considered a mildly painful procedure in itself, and distraction techniques, oral midazolam, and topical agents such as EMLA should be considered if time and the situation permit. Guidelines for patient preparation, personnel requirements, monitoring, drug administration, recovery care, and discharge criteria for children receiving intravenous PSA are similar to those outlined for adults.

With PSA in children, it is essential that drug dosages be calculated precisely using the child's current weight and not a parent's estimate. Equipment to manage the airway and resuscitation supplies must be size appropriate, and the physician must be skilled in pediatric airway management and resuscitation.

Chloral hydrate, a pure sedative-hypnotic agent, has been historically popular for sedating children for a wide variety of procedures. It offers no advantage over currently available agents.[209,210,220,221] It has a poor safety record, delayed onset of 45 minutes, prolonged recovery time of hours, and residual sedation of nearly a day. Its use should be discontinued. Likewise, the combination of meperidine (Demerol), promethazine (Phenergan), and chlorpromazine (Thorazine), also known as DPT, is not recommended. It has an unacceptable rate of sedation failure, prolonged sedation times, high risk of respiratory depression, and frequent dystonic reactions.[222]

KEY CONCEPTS

- Safe, effective PSA requires high-level skills and knowledge and sound protocols, including patient monitoring.
- Propofol is the agent of choice for deep sedation in the ED but requires supplementation with an opioid analgesic when a painful procedure is planned.
- Preprocedural fasting guidelines are not evidence based but represent a best consensus for minimizing risk. Absence of a preprocedure fasting period is not, however, a contraindication to procedural sedation for an emergent, time-sensitive condition.
- Pulse oximetry is mandatory during sedation, and end-tidal CO_2 should be monitored if moderate or deep sedation is the goal. Oxygen should be administered to patients undergoing procedural sedation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Atkinson P, Chesters A, Heinz P: Pain management and sedation for children in the emergency department. *BMJ* 2009; 339:b4234.
2. Cordell WH, et al: The high prevalence of pain in emergency medical care. *Am J Emerg Med* 2002; 20:165-169.
3. Ratnapalan S, Mason KP, Mace SE: Pediatric pain management and sedation. *Int J Pediatr* 2010; 2010:454731.
4. Mace SE, et al: Clinical policy: Critical issues in the sedation of pediatric patients in the emergency department. *Ann Emerg Med* 2008; 51:378-399, 399.e1-e57.
5. Mace SE, et al: Clinical policy: Evidence-based approach to pharmacologic agents used in pediatric sedation and analgesia in the emergency department. *Ann Emerg Med* 2004; 44:342-377.
6. Breakey VR, Pirie J, Goldman RD: Pediatric and emergency medicine residents' attitudes and practices for analgesia and sedation during lumbar puncture in pediatric patients. *Pediatrics* 2007; 119: e631-e636.
7. Godwin SA, et al: Clinical policy: procedural sedation and analgesia in the emergency department. *Ann Emerg Med* 2005; 45:177-196.
8. Perina DG, et al: The 2007 Model of the Clinical Practice of Emergency Medicine: The 2009 update 2009 EM Model Review Task Force. *Ann Emerg Med* 2011; 57:e1-e15.
9. O'Connor RE, et al: Procedural sedation and analgesia in the emergency department: recommendations for physician credentialing, privileging, and practice. *Ann Emerg Med* 2011; 58:365-370.
10. Zed PJ, Abu-Laban RB, Chan WW, Harrison DW: Efficacy, safety and patient satisfaction of propofol for procedural sedation and analgesia in the emergency department: A prospective study. *CJEM* 2007; 9:421-427.
11. Miner JR, Krauss B: Procedural sedation and analgesia research: State of the art. *Acad Emerg Med* 2007; 14:170-178.
12. Shavit I, Keidan I, Augarten A: The practice of pediatric procedural sedation and analgesia in the emergency department. *Eur J Emerg Med* 2006; 13:270-275.
13. Krauss B, Green SM: Procedural sedation and analgesia in children. *Lancet* 2006; 367:766-780.
14. Bahn EL, Holt KR: Procedural sedation and analgesia: A review and new concepts. *Emerg Med Clin North Am* 2005; 23:503-517.
15. Caperell K, Pitetti R: Is higher ASA class associated with an increased incidence of adverse events during procedural sedation in a pediatric emergency department? *Pediatr Emerg Care* 2009; 25:661-664.
16. Melendez E, Bachur R: Serious adverse events during procedural sedation with ketamine. *Pediatr Emerg Care* 2009; 25:325-328.
17. Cravero JP, et al: The incidence and nature of adverse events during pediatric sedation/anesthesia with propofol for procedures outside the operating room: A report from the Pediatric Sedation Research Consortium. *Anesth Analg* 2009; 108:795-804.
18. Green SM, et al: Predictors of airway and respiratory adverse events with ketamine sedation in the emergency department: An individual-patient data meta-analysis of 8,282 children. *Ann Emerg Med* 2009; 54:158-168.e1-e4.
19. Strayer RJ, Nelson LS: Adverse events associated with ketamine for procedural sedation in adults. *Am J Emerg Med* 2008; 26:985-1028.
20. Hollman GA, Schultz MM, Eickhoff JC, Christenson DK: Propofol-fentanyl versus propofol alone for lumbar puncture sedation in children with acute hematologic malignancies: Propofol dosing and adverse events. *Pediatr Crit Care Med* 2008; 9:616-622.
21. Babl FE, Oakley E, Seaman C, Barnett P, Sharwood LN: High-concentration nitrous oxide for procedural sedation in children: Adverse events and depth of sedation. *Pediatrics* 2008; 121: e528-e532.
22. Bell A, Treston G, McNabb C, Monypenny K, Cardwell R: Profiling adverse respiratory events and vomiting when using propofol for emergency department procedural sedation. *Emerg Med Australas* 2007; 19:405-410.
23. Cravero JP, et al: Incidence and nature of adverse events during pediatric sedation/anesthesia for procedures outside the operating room: Report from the Pediatric Sedation Research Consortium. *Pediatrics* 2006; 118:1087-1096.
24. Heistein LC, et al: Chloral hydrate sedation for pediatric echocardiography: Physiologic responses, adverse events, and risk factors. *Pediatrics* 2006; 117:e434-e441.
25. Roback MG, Wathen JE, Bajaj L, Bothner JP: Adverse events associated with procedural sedation and analgesia in a pediatric emergency department: A comparison of common parenteral drugs. *Acad Emerg Med* 2005; 12:508-513.
26. Administration of propofol. *Clin Privil White Pap* 2010; 1-20.
27. Moderate sedation. *Clin Privil White Pap* 2010; 1-20.
28. Pitetti R, et al: Effect on hospital-wide sedation practices after implementation of the 2001 JCAHO procedural sedation and analgesia guidelines. *Arch Pediatr Adolesc Med* 2006; 160:211-216.
29. Sedation in the emergency department. *Ann Emerg Med* 2011; 57:469.
30. Ratnapalan S, Schneeweiss S: Guidelines to practice: The process of planning and implementing a pediatric sedation program. *Pediatr Emerg Care* 2007; 23:262-266.
31. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology* 2002; 96:1004-1017.
32. Poe SS, et al: Ensuring safety of patients receiving sedation for procedures: Evaluation of clinical practice guidelines. *Jt Comm J Qual Improv* 2001; 27:28-41.
33. Epstein BS: The American Society of Anesthesiologist's efforts in developing guidelines for sedation and analgesia for nonanesthesiologists: The 40th Rovenstine Lecture. *Anesthesiology* 2003; 98:1261-1268.
34. Green SM, Mason KP: Reformulation of the sedation continuum. *JAMA* 2010; 303:876-877.
35. Misra S, Mahajan PV, Chen X, Kannikeswaran N: Safety of procedural sedation and analgesia in children less than 2 years of age in a pediatric emergency department. *Int J Emerg Med* 2008; 1:173-177.
36. Bhatt M, et al: Consensus-based recommendations for standardizing terminology and reporting adverse events for emergency department procedural sedation and analgesia in children. *Ann Emerg Med* 2009; 53:426-435.e4.
37. Fitz-Henry J: The ASA classification and peri-operative risk. *Ann R Coll Surg Engl* 2011; 93:185-187.
38. Schmitz A, et al: Fasting times and gastric contents volume in children undergoing deep propofol sedation—an assessment using magnetic resonance imaging. *Paediatr Anaesth* 2011; 21:685-690.
39. Bhatt M, Currie GR, Auld MC, Johnson DW: Current practice and tolerance for risk in performing procedural sedation and analgesia on children who have not met fasting guidelines: A Canadian survey using a stated preference discrete choice experiment. *Acad Emerg Med* 2010; 17:1207-1215.
40. Molina JA, Lobo CA, Goh HK, Seow E, Heng BH: Review of studies and guidelines on fasting and procedural sedation at the emergency department. *Int J Evid Based Healthc* 2010; 8:75-78.
41. Thorpe RJ, Benger J: Pre-procedural fasting in emergency sedation. *Emerg Med J* 2010; 27:254-261.
42. Taylor D: Pre-procedural fasting for sedation: Do we need to do it? *Emerg Med J* 2010; 27:253.
43. McGlone R, Carley S: Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. BET 3: Does the time of fasting affect complication rates during ketamine sedation? *Emerg Med J* 2008; 25:367-369.
44. Paris PM, Yealy DM: A procedural sedation and analgesia fasting consensus advisory: One small step for emergency medicine, one giant challenge remaining. *Ann Emerg Med* 2007; 49:465-467.
45. Green SM, Roback MG, Miner JR, Burton JH, Krauss B: Fasting and emergency department procedural sedation and analgesia: A consensus-based clinical practice advisory. *Ann Emerg Med* 2007; 49:454-461.
46. Roback MG, Bajaj L, Wathen JE, Bothner J: Preprocedural fasting and adverse events in procedural sedation and analgesia in a pediatric emergency department: Are they related? *Ann Emerg Med* 2004; 44:454-459.
47. Treston G: Prolonged pre-procedure fasting time is unnecessary when using titrated intravenous ketamine for paediatric procedural sedation. *Emerg Med Australas* 2004; 16:145-150.
48. Green SM: Fasting is a consideration—not a necessity—for emergency department procedural sedation and analgesia. *Ann Emerg Med* 2003; 42:647-650.
49. Agrawal D, Manzi SF, Gupta R, Krauss B: Preprocedural fasting state and adverse events in children undergoing procedural sedation and analgesia in a pediatric emergency department. *Ann Emerg Med* 2003; 42:636-646.
50. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: Application to healthy patients undergoing elective procedures: An updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. *Anesthesiology* 2011; 114:495-511.
51. Smally AJ, Nowicki TA, Simelton BH: Procedural sedation and analgesia in the emergency department. *Curr Opin Crit Care* 2011; 17:317-322.

www.ketabpezeshki.com 66485457-66963820

52. Couloures KG, Beach M, Cravero JP, Monroe KK, Hertzog JH: Impact of provider specialty on pediatric procedural sedation complication rates. *Pediatrics* 2011; 127:e1154-e1160.
53. Green SM, Roback MG, Kennedy RM, Krauss B: Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. *Ann Emerg Med* 2011; 57:449-461.
54. Metzner J, Domino KB: Risks of anesthesia or sedation outside the operating room: The role of the anesthesia care provider. *Curr Opin Anaesthesiol* 2010; 23:523-531.
55. Chambers WA, Patey RE: Sedation—is delegation appropriate? *Anaesthesia* 2010; 65:439-442.
56. Hemelaar AE, Lemson J: Patients under sedation should always be monitored by well-trained personnel and should be given supplemental oxygen. *Pediatrics* 2008; 122:1415-1416; author reply 1416.
57. Deitch K, Chudnofsky CR, Dominici P, Latta D, Salamanca Y: The utility of high-flow oxygen during emergency department procedural sedation and analgesia with propofol: A randomized, controlled trial. *Ann Emerg Med* 2011; 58:360-364.
58. Rozario L, Sloper D, Sheridan MJ: Supplemental oxygen during moderate sedation and the occurrence of clinically significant desaturation during endoscopic procedures. *Gastroenterol Nurs* 2008; 31:281-285.
59. Keidan I, et al: Supplemental oxygen compromises the use of pulse oximetry for detection of apnea and hypoventilation during sedation in simulated pediatric patients. *Pediatrics* 2008; 122:293-298.
60. Deitch K, Chudnofsky CR, Dominici P: The utility of supplemental oxygen during emergency department procedural sedation with propofol: A randomized, controlled trial. *Ann Emerg Med* 2008; 52:1-8.
61. Green SM, Krauss B: Supplemental oxygen during propofol sedation: Yes or no? *Ann Emerg Med* 2008; 52:9-10.
62. Deitch K, Chudnofsky CR, Dominici P: The utility of supplemental oxygen during emergency department procedural sedation and analgesia with midazolam and fentanyl: A randomized, controlled trial. *Ann Emerg Med* 2007; 49:1-8.
63. Eichhorn V, Henzler D, Murphy MF: Standardizing care and monitoring for anesthesia or procedural sedation delivered outside the operating room. *Curr Opin Anaesthesiol* 2010; 23:494-499.
64. Lamas A, Lopez-Herce J: Monitoring sedation in the critically ill child. *Anaesthesia* 2010; 65:516-524.
65. Wildsmith JA: Monitoring during sedation—the setting is all. *Anaesthesia* 2008; 63:1144-1145; author reply 1145.
66. Fanning RM: Monitoring during sedation given by non-anaesthetic doctors. *Anaesthesia* 2008; 63:370-374.
67. Cote CJ, Wilson S: Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: An update. *Paediatr Anaesth* 2008; 18:9-10.
68. Win NN, et al: Haemodynamic changes and heart rate variability during midazolam-propofol co-induction. *Anaesthesia* 2007; 62:561-568.
69. Win NN, Fukayama H, Kohase H, Umino M: The different effects of intravenous propofol and midazolam sedation on hemodynamic and heart rate variability. *Anesth Analg* 2005; 101:97-102, table of contents.
70. Grime ID, Robb N: Conscious sedation. The role of monitoring. *SAAD Dig* 1996; 13:7-16.
71. Sivilotti ML, Murray HE, Messenger DW: Does end-tidal CO_2 monitoring during emergency department procedural sedation and analgesia with propofol decrease the incidence of hypoxic events? *Ann Emerg Med* 2010; 56:702-703; author reply 703-704.
72. Sivilotti ML, Messenger DW, van Vlymen J, Dungey PE, Murray HE: A comparative evaluation of capnometry versus pulse oximetry during procedural sedation and analgesia on room air. *CJEM* 2010; 12:397-404.
73. Green SM, Pershad J: Should capnographic monitoring be standard practice during emergency department procedural sedation and analgesia? Pro and con. *Ann Emerg Med* 2010; 55:265-267.
74. Deitch K, Miner J, Chudnofsky CR, Dominici P, Latta D: Does end tidal CO2 monitoring during emergency department procedural sedation and analgesia with propofol decrease the incidence of hypoxic events? A randomized, controlled trial. *Ann Emerg Med* 2010; 55:258-264.
75. Krauss B, Hess DR: Capnography for procedural sedation and analgesia in the emergency department. *Ann Emerg Med* 2007; 50:172-181.
76. Green SM: Research advances in procedural sedation and analgesia. *Ann Emerg Med* 2007; 49:31-36.
77. Anderson JL, Junkins E, Pribble C, Guenther E: Capnography and depth of sedation during propofol sedation in children. *Ann Emerg Med* 2007; 49:9-13.
78. Lightdale JR, et al: Microstream capnography improves patient monitoring during moderate sedation: A randomized, controlled trial. *Pediatrics* 2006; 117:e1170-e1178.
79. Burton JH, Harrah JD, Germann CA, Dillon DC: Does end-tidal carbon dioxide monitoring detect respiratory events prior to current sedation monitoring practices? *Acad Emerg Med* 2006; 13:500-504.
80. Hatlestad D: Capnography in sedation and pain management. *Emerg Med Serv* 2005; 34:65-69.
81. Waugh JB, Epps CA, Khodneva YA: Capnography enhances surveillance of respiratory events during procedural sedation: A meta-analysis. *J Clin Anesth* 2011; 23:189-196.
82. Verschuren F, Kabayadondo MG, Thys F: Expired CO measurement in intubated or spontaneously breathing patients from the emergency department. *J Vis Exp* 2011; 47:2508.
83. Adesanya AO, Rosero E, Wyrick C, Wall MH, Joshi GP: Assessing the predictive value of the bispectral index vs patient state index on clinical assessment of sedation in postoperative cardiac surgery patients. *J Crit Care* 2009; 24:322-328.
84. Apan A, Doganci N, Ergan A, Büyükkoçak U: Bispectral index-guided intraoperative sedation with dexmedetomidine and midazolam infusion in outpatient cataract surgery. *Minerva Anestesiol* 2009; 75:239-244.
85. Mayer J, Boldt J, Schellhaass A, Hiller B, Suttner SW: Bispectral index-guided general anesthesia in combination with thoracic epidural analgesia reduces recovery time in fast-track colon surgery. *Anesth Analg* 2007; 104:1145-1149, table of contents.
86. Camci E, Koltka K, Celenk Y, Tugrul M, Pembeci K: Bispectral index-guided desflurane and propofol anesthesia in ambulatory arthroscopy: Comparison of recovery and discharge profiles. *J Anesth* 2006; 20:149-152.
87. Weaver CS, Hauter WH, Duncan CE, Brizendine EJ, Cordell WH: An assessment of the association of bispectral index with 2 clinical sedation scales for monitoring depth of procedural sedation. *Am J Emerg Med* 2007; 25:918-924.
88. Malviya S, et al: Effect of age and sedative agent on the accuracy of bispectral index in detecting depth of sedation in children. *Pediatrics* 2007; 120:e461-e470.
89. Sadhasivam S, Ganesh A, Robison A, Kaye R, Watcha MF: Validation of the bispectral index monitor for measuring the depth of sedation in children. *Anesth Analg* 2006; 102:383-388.
90. Agrawal D, Feldman HA, Krauss B, Waltzman ML: Bispectral index monitoring quantifies depth of sedation during emergency department procedural sedation and analgesia in children. *Ann Emerg Med* 2004; 43:247-255.
91. Shavit I, et al: Comparison of adverse events during procedural sedation between specially trained pediatric residents and pediatric emergency physicians in Israel. *Acad Emerg Med* 2008; 15:617-622.
92. Scherrer PD: Safe and sound: Pediatric procedural sedation and analgesia. *Minn Med* 2011; 94:43-47.
93. Sury M, Bullock I, Rabar S, Demott K; Guideline Development Group: Sedation for diagnostic and therapeutic procedures in children and young people: Summary of NICE guidance. *BMJ* 2010; 341:c6819.
94. Steurer LM, Luhmann J: Adverse effects of pediatric emergency sedation after discharge. *Pediatr Nurs* 2007; 33:403-407, 426; quiz 409.
95. Cote CJ: Discharge criteria for children sedated by nonanesthesiologists: Is "safe" really safe enough? *Anesthesiology* 2004; 100:207-209.
96. Newman DH, Azer MM, Pitetti RD, Singh S: When is a patient safe for discharge after procedural sedation? The timing of adverse effect events in 1367 pediatric procedural sedations. *Ann Emerg Med* 2003; 42:627-635.
97. Lepere AJ, Slack-Smith LM: Average recovery time from a standardized intravenous sedation protocol and standardized discharge criteria in the general dental practice setting. *Anesth Prog* 2002; 49:77-81.
98. Deasy C, Babl FE: Intravenous vs intramuscular ketamine for pediatric procedural sedation by emergency medicine specialists: A review. *Paediatr Anaesth* 2010; 20:787-796.
99. Treston G, et al: What is the nature of the emergence phenomenon when using intravenous or intramuscular ketamine for paediatric procedural sedation? *Emerg Med Australas* 2009; 21:315-322.
100. Ramaswamy P, Babl FE, Deasy C, Sharwood LN: Pediatric procedural sedation with ketamine: Time to discharge after intramuscular versus intravenous administration. *Acad Emerg Med* 2009; 16:101-107.
101. Zier JL, Tarrago R, Liu M: Level of sedation with nitrous oxide for pediatric medical procedures. *Anesth Analg* 2010; 110:1399-1405.
102. Denman WT, et al: The PediSedate device, a novel approach to pediatric sedation that provides distraction and inhaled nitrous oxide:

www.ketabpezeshki.com 66485457-66963820

Clinical evaluation in a large case series. *Paediatr Anaesth* 2007; 17:162-166.
103. Burnweit C, et al: Nitrous oxide analgesia for minor pediatric surgical procedures: An effective alternative to conscious sedation? *J Pediatr Surg* 2004; 39:495-499; discussion 495-499.
104. Luhmann JD, Kennedy RM, Jaffe DM, McAllister JD: Continuous-flow delivery of nitrous oxide and oxygen: A safe and cost-effective technique for inhalation analgesia and sedation of pediatric patients. *Pediatr Emerg Care* 1999; 15:388-392.
105. Dallimore D, Herd DW, Short T, Anderson BJ: Dosing ketamine for pediatric procedural sedation in the emergency department. *Pediatr Emerg Care* 2008; 24:529-533.
106. Nejati A, Moharari RS, Ashraf H, Labaf A, Golshani K: Ketamine/propofol versus midazolam/fentanyl for procedural sedation and analgesia in the emergency department: A randomized, prospective, double-blind trial. *Acad Emerg Med* 2011; 18:800-806.
107. McQueen A, Wright RO, Kido MM, Kaye E, Krauss B: Procedural sedation and analgesia outcomes in children after discharge from the emergency department: Ketamine versus fentanyl/midazolam. *Ann Emerg Med* 2009; 54:191-197.e1-e4.
108. Gorchynski J, Wang S, Anderson C, Montano J: Conscious sedation and emergency department length of stay: A comparison of propofol, ketamine, and fentanyl/versed. *Cal J Emerg Med* 2006; 7:4-7.
109. Godambe SA, Elliot V, Matheny D, Pershad J: Comparison of propofol/fentanyl versus ketamine/midazolam for brief orthopedic procedural sedation in a pediatric emergency department. *Pediatrics* 2003; 112(1 Pt 1):116-123.
110. Lind GH, et al: Oral transmucosal fentanyl citrate for analgesia and sedation in the emergency department. *Ann Emerg Med* 1991; 20:1117-1120.
111. Shibutani K, Inchiosa MA Jr, Sawada K, Bairamian M: Pharmacokinetic mass of fentanyl for postoperative analgesia in lean and obese patients. *Br J Anaesth* 2005; 95:377-383.
112. [Should the dosage of fentanyl be based on the body weight when the patient is obese? A proposal of the appropriate "pharmacokinetic body mass"]. *Masui* 2004; 53 Suppl:S145-S152.
113. Shibutani K, Inchiosa MA Jr, Sawada K, Bairamian M: Accuracy of pharmacokinetic models for predicting plasma fentanyl concentrations in lean and obese surgical patients: Derivation of dosing weight ("pharmacokinetic mass"). *Anesthesiology* 2004; 101:603-613.
114. Fahnenstich H, Steffan J, Kau N, Bartmann P: Fentanyl-induced chest wall rigidity and laryngospasm in preterm and term infants. *Crit Care Med* 2000; 28:836-839.
115. Epstein RH, et al: The safety and efficacy of oral transmucosal fentanyl citrate for preoperative sedation in young children. *Anesth Analg* 1996; 83:1200-1205.
116. Schutzman SA, Liebelt E, Wisk M, Burg J: Comparison of oral transmucosal fentanyl citrate and intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation of children undergoing laceration repair. *Ann Emerg Med* 1996; 28:385-390.
117. Klein EJ, et al: A randomized, clinical trial of oral midazolam plus placebo versus oral midazolam plus oral transmucosal fentanyl for sedation during laceration repair. *Pediatrics* 2002; 109:894-897.
118. Stanley TH, et al: Oral transmucosal fentanyl citrate (lollipop) premedication in human volunteers. *Anesth Analg* 1989; 69:21-27.
119. Fitch RW, Kuhn JE: Intraarticular lidocaine versus intravenous procedural sedation with narcotics and benzodiazepines for reduction of the dislocated shoulder: A systematic review. *Acad Emerg Med* 2008; 15:703-708.
120. Everitt IJ, Barnett P: Comparison of two benzodiazepines used for sedation of children undergoing suturing of a laceration in an emergency department. *Pediatr Emerg Care* 2002; 18:72-74.
121. Gempeler F, Park GR: Sedation with benzodiazepines. *Middle East J Anesthesiol* 1995; 13:117-145.
122. Bulach R, Myles PS, Russnak M: Double-blind randomized controlled trial to determine extent of amnesia with midazolam given immediately before general anaesthesia. *Br J Anaesth* 2005; 94:300-305.
123. Lamont T, Matthew L, Cousins D, Green J: Avoiding midazolam overdose: Summary of a safety report from the National Patient Safety Agency. *BMJ* 2009; 339:b4459.
124. Sim TB, Seet CM: To study the effectiveness and safety of ketamine and midazolam procedural sedation in the incision and drainage of abscesses in the adult emergency department. *Eur J Emerg Med* 2008; 15:169-172.
125. Hohl CM, Sadatsafavi M, Nosyk B, Anis AH: Safety and clinical effectiveness of midazolam versus propofol for procedural sedation in the emergency department: A systematic review. *Acad Emerg Med* 2008; 15:1-8.
126. Austin T, Vilke GM, Nyheim E, Kelly D, Chan TC: Safety and effectiveness of methohexital for procedural sedation in the emergency department. *J Emerg Med* 2003; 24:315-318.
127. Lerman B, Yoshida D, Levitt MA: A prospective evaluation of the safety and efficacy of methohexital in the emergency department. *Am J Emerg Med* 1996; 14:351-354.
128. Vardy JM, et al: Audit of the safety and effectiveness of ketamine for procedural sedation in the emergency department. *Emerg Med J* 2008; 25:579-582.
129. Newton A, Fitton L: Intravenous ketamine for adult procedural sedation in the emergency department: A prospective cohort study. *Emerg Med J* 2008; 25:498-501.
130. Chudnofsky CR, et al: A combination of midazolam and ketamine for procedural sedation and analgesia in adult emergency department patients. *Acad Emerg Med* 2000; 7:228-235.
131. Slonim AD, Ognibene FP: Sedation for pediatric procedures, using ketamine and midazolam, in a primarily adult intensive care unit: A retrospective evaluation. *Crit Care Med* 1998; 26:1900-1904.
132. Green SM, et al: Intramuscular ketamine for pediatric sedation in the emergency department: Safety profile in 1,022 cases. *Ann Emerg Med* 1998; 31:688-697.
133. Dolansky G, Shah A, Mosdossy G, Rieder M: What is the evidence for the safety and efficacy of using ketamine in children? *Paediatr Child Health* 2008; 13:307-308.
134. Bourgoin A, et al: Safety of sedation with ketamine in severe head injury patients: Comparison with sufentanil. *Crit Care Med* 2003; 31:711-717.
135. Green SM, et al: Intravenous ketamine for pediatric sedation in the emergency department: Safety profile with 156 cases. *Acad Emerg Med* 1998; 5:971-976.
136. Grace RF: The effect of variable-dose diazepam on dreaming and emergence phenomena in 400 cases of ketamine-fentanyl anaesthesia. *Anaesthesia* 2003; 58:904-910.
137. Kudoh A, Katagai H, Takazawa T: Anesthesia with ketamine, propofol, and fentanyl decreases the frequency of postoperative psychosis emergence and confusion in schizophrenic patients. *J Clin Anesth* 2002; 14:107-110.
138. Carley S, Martin B: Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. Midazolam and emergence phenomena in children undergoing ketamine sedation. *Emerg Med J* 2001; 18:273-274.
139. Green SM, Li J: Ketamine in adults: What emergency physicians need to know about patient selection and emergence reactions. *Acad Emerg Med* 2000; 7:278-281.
140. Kumar A, Bajaj A, Sarkar P, Grover VK: The effect of music on ketamine induced emergence phenomena. *Anaesthesia* 1992; 47:438-439.
141. Andolfatto G, Willman E: A prospective case series of single-syringe ketamine-propofol (ketofol) for emergency department procedural sedation and analgesia in adults. *Acad Emerg Med* 2011; 18:237-245.
142. David H, Shipp J: A randomized controlled trial of ketamine/propofol versus propofol alone for emergency department procedural sedation. *Ann Emerg Med* 2011; 57:435-441.
143. Sener S, Eken C, Schultz CH, Serinken M, Ozsarac M: Ketamine with and without midazolam for emergency department sedation in adults: A randomized controlled trial. *Ann Emerg Med* 2011; 57:109-114.e2.
144. Shah A, et al: A blinded, randomized controlled trial to evaluate ketamine/propofol versus ketamine alone for procedural sedation in children. *Ann Emerg Med* 2011; 57:425-433.e2.
145. Green SM, Rothrock SG: Transient apnea with intramuscular ketamine. *Am J Emerg Med* 1997; 15:440-441.
146. Green SM, Roback MG, Krauss B: Laryngospasm during emergency department ketamine sedation: A case-control study. *Pediatr Emerg Care* 2010; 26:798-802.
147. Cohen VG, Krauss B: Recurrent episodes of intractable laryngospasm during dissociative sedation with intramuscular ketamine. *Pediatr Emerg Care* 2006; 22:247-249.
148. Thorp AW, Brown L, Green SM: Ketamine-associated vomiting: Is it dose-related? *Pediatr Emerg Care* 2009; 25:15-18.
149. Langston WT, Wathen JE, Roback MG, Bajaj L: Effect of ondansetron on the incidence of vomiting associated with ketamine sedation in children: A double-blind, randomized, placebo-controlled trial. *Ann Emerg Med* 2008; 52:30-34.
150. Green SM, et al: Predictors of emesis and recovery agitation with emergency department ketamine sedation: An individual-patient data meta-analysis of 8,282 children. *Ann Emerg Med* 2009; 54:171-180.e1-e4.

www.ketabpezeshki.com 66485457-66963820

151. McKee MR, Sharieff GQ, Kanegaye JT, Stebel M: Oral analgesia before pediatric ketamine sedation is not associated with an increased risk of emesis and other adverse events. *J Emerg Med* 2008; 35:23-28.
152. Green SM, Roback MG, Krauss B: Anticholinergics and ketamine sedation in children: A secondary analysis of atropine versus glycopyrrolate. *Acad Emerg Med* 2010; 17:157-162.
153. Adjunctive atropine is unnecessary during ketamine sedation in children. *Emerg Med J* 2009; 26:230.
154. Carley S, Body R: Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. BET 2: Is atropine needed as an adjunct in paediatric ketamine administration? *Emerg Med J* 2008; 25:366-367.
155. Brown L, et al: Adjunctive atropine is unnecessary during ketamine sedation in children. *Acad Emerg Med* 2008; 15:314-318.
156. Heinz P, Geelhoed GC, Wee C, Pascoe EM: Is atropine needed with ketamine sedation? A prospective, randomised, double blind study. *Emerg Med J* 2006; 23:206-209.
157. Levins T: Etomidate in procedural sedation. *Air Med J* 2011; 30:45-48.
158. Cicero M, Graneto J: Etomidate for procedural sedation in the elderly: A retrospective comparison between age groups. *Am J Emerg Med* 2011; 29:1111-1116.
159. Lee-Jayaram JJ, et al: Ketamine/midazolam versus etomidate/fentanyl: Procedural sedation for pediatric orthopedic reductions. *Pediatr Emerg Care* 2010; 26:408-412.
160. Kaufman D: Etomidate versus ketamine for sedation in acutely ill patients. *Lancet* 2009; 374:1240-1241; author reply 1241.
161. Mongardon N, Singer M: Etomidate versus ketamine for sedation in acutely ill patients. *Lancet* 2009; 374:1240; author reply 1241.
162. Bordo D, Chan SB, Shin P: Patient satisfaction and return to daily activities using etomidate procedural sedation for orthopedic injuries. *West J Emerg Med* 2008; 9:86-90.
163. Di Liddo L, et al: Etomidate versus midazolam for procedural sedation in pediatric outpatients: A randomized controlled trial. *Ann Emerg Med* 2006; 48:433-440, 440.e1.
164. Miner JR, Danahy M, Moch A, Biros M: Randomized clinical trial of etomidate versus propofol for procedural sedation in the emergency department. *Ann Emerg Med* 2007; 49:15-22.
165. Hunt GS, Spencer MT, Hays DP: Etomidate and midazolam for procedural sedation: Prospective, randomized trial. *Am J Emerg Med* 2005; 23:299-303.
166. Kosarek L, et al: Increase in venous complications associated with etomidate use during a propofol shortage: An example of clinically important adverse effects related to drug substitution. *Ochsner J* 2011; 11:143-146.
167. Perrone J, Band RA, Mathew R: Agitation complicating procedural sedation with etomidate. *Am J Emerg Med* 2006; 24:511-512.
168. Van Keulen SG, Burton JH: Myoclonus associated with etomidate for ED procedural sedation and analgesia. *Am J Emerg Med* 2003; 21:556-558.
169. Vinson DR, Bradbury DR: Etomidate for procedural sedation in emergency medicine. *Ann Emerg Med* 2002; 39:592-598.
170. Yealy DM: Safe and effective … maybe: Etomidate in procedural sedation/analgesia. *Acad Emerg Med* 2001; 8:68-69.
171. Albert SG, Ariyan S, Rather A: The effect of etomidate on adrenal function in critical illness: A systematic review. *Intensive Care Med* 2011; 37:901-910.
172. Majesko A, Darby JM: Etomidate and adrenal insufficiency: The controversy continues. *Crit Care* 2010; 14:338.
173. Hildreth AN, et al: Adrenal suppression following a single dose of etomidate for rapid sequence induction: A prospective randomized study. *J Trauma* 2008; 65:573-579.
174. Mullins ME, Theodoro DL: Lack of evidence for adrenal insufficiency after single-dose etomidate. *Arch Surg* 2008; 143:808-809; author reply 809.
175. Vinclair M, et al: Duration of adrenal inhibition following a single dose of etomidate in critically ill patients. *Intensive Care Med* 2008; 34:714-719.
176. Kamp R, Kress JP: Etomidate, sepsis, and adrenal function: Not as bad as we thought? *Crit Care* 2007; 11:145.
177. Lundy JB, Slane ML, Frizzi JD: Acute adrenal insufficiency after a single dose of etomidate. *J Intensive Care Med* 2007; 22:111-117.
178. Zed PJ, Mabasa VH, Slavik RS, Abu-Laban RB: Etomidate for rapid sequence intubation in the emergency department: Is adrenal suppression a concern? *CJEM* 2006; 8:347-350.
179. McGrane O, Hopkins G, Nielson A, Kang C: Procedural sedation with propofol: a retrospective review of the experiences of an emergency medicine residency program 2005 to 2010. *Am J Emerg Med* 2011; Jun 2. [Epub ahead of print]
180. Mallory MD, et al: Emergency physician-administered propofol sedation: A report on 25,433 sedations from the pediatric sedation research consortium. *Ann Emerg Med* 2011; 57:462-468. e1.
181. Rahman NH, Hashim A: The use of propofol for procedural sedation and analgesia in the emergency department: A comparison with midazolam. *Emerg Med J* 2011; 28:861-865.
182. Lamond DW: Review article: Safety profile of propofol for paediatric procedural sedation in the emergency department. *Emerg Med Australas* 2010; 22:265-286.
183. Miner JR, Gray RO, Bahr J, Patel R, McGill JW: Randomized clinical trial of propofol versus ketamine for procedural sedation in the emergency department. *Acad Emerg Med* 2010; 17:604-611.
184. Miner JR, Gray RO, Stephens D, Biros MH: Randomized clinical trial of propofol with and without alfentanil for deep procedural sedation in the emergency department. *Acad Emerg Med* 2009; 16:825-834.
185. Hohl CM, Nosyk B, Sadatsafavi M, Anis AH: A cost-effectiveness analysis of propofol versus midazolam for procedural sedation in the emergency department. *Acad Emerg Med* 2008; 15:32-39.
186. Weaver CS, et al: Emergency department procedural sedation with propofol: Is it safe? *J Emerg Med* 2007; 33:355-361.
187. Dunn T, Mossop D, Newton A, Gammon A: Propofol for procedural sedation in the emergency department. *Emerg Med J* 2007; 24: 459-461.
188. Miner JR, Burton JH: Clinical practice advisory: Emergency department procedural sedation with propofol. *Ann Emerg Med* 2007; 50:182-187, 187.e1.
189. Symington L, Thakore S: A review of the use of propofol for procedural sedation in the emergency department. *Emerg Med J* 2006; 23:89-93.
190. Pershad J, Godambe SA: Propofol for procedural sedation in the pediatric emergency department. *J Emerg Med* 2004; 27:11-14.
191. Bassett KE, et al: Propofol for procedural sedation in children in the emergency department. *Ann Emerg Med* 2003; 42:773-782.
192. Jackson R, Carley S: Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. Use of propofol for sedation in the emergency department. *Emerg Med J* 2001; 18: 378-379.
193. Green SM, Andolfatto G, Krauss B: Ketofol for procedural sedation? Pro and con. *Ann Emerg Med* 2011; 57:444-448.
194. Andolfatto G, Willman E: A prospective case series of pediatric procedural sedation and analgesia in the emergency department using single-syringe ketamine-propofol combination (ketofol). *Acad Emerg Med* 2010; 17:194-201.
195. Arora S: Combining ketamine and propofol ("ketofol") for emergency department procedural sedation and analgesia: A review. *West J Emerg Med* 2008; 9:20-23.
196. Willman EV, Andolfatto G: A prospective evaluation of "ketofol" (ketamine/propofol combination) for procedural sedation and analgesia in the emergency department. *Ann Emerg Med* 2007; 49:23-30.
197. Babl FE, Belousoff J, Deasy C, Hopper S, Theophilos T: Paediatric procedural sedation based on nitrous oxide and ketamine: Sedation registry data from Australia. *Emerg Med J* 2010; 27:607-612.
198. George MS, Sury MR: Reversal of paradoxical excitement to diazepam sedation. *Paediatr Anaesth* 2008; 18:546-547.
199. Shannon, M, et al: Safety and efficacy of flumazenil in the reversal of benzodiazepine-induced conscious sedation. The Flumazenil Pediatric Study Group. *J Pediatr* 1997; 131:582-586.
200. Singh R, Kumar N, Vajifdar H: Midazolam as a sole sedative for computed tomography imaging in pediatric patients. *Paediatr Anaesth* 2009; 19:899-904.
201. Tschirch FT, et al: Multicenter trial: comparison of two different formulations and application systems of low-dose nasal midazolam for routine magnetic resonance imaging of claustrophobic patients. *J Magn Reson Imaging* 2008; 28:866-872.
202. Moro-Sutherland DM, Algren JT, Louis PT, Kozinetz CA, Shook JE: Comparison of intravenous midazolam with pentobarbital for sedation for head computed tomography imaging. *Acad Emerg Med* 2000; 7:1370-1375.
203. Harcke HT, Grissom LE, Meister MA: Sedation in pediatric imaging using intranasal midazolam. *Pediatr Radiol* 1995; 25:341-343.
204. Cote CJ, Ferrari LR, Liu LM: Rectal methohexital for sedation of children during imaging procedures. *AJR Am J Roentgenol* 1994; 162:465-466.
205. Mallory MD, Baxter AL, Kost SI: Propofol vs pentobarbital for sedation of children undergoing magnetic resonance imaging: Results from the Pediatric Sedation Research Consortium. *Paediatr Anaesth* 2009; 19:601-611.

www.ketabpezeshki.com 66485457-66963820

206. Pershad J, Wan J, Anghelescu DL: Comparison of propofol with pentobarbital/midazolam/fentanyl sedation for magnetic resonance imaging of the brain in children. *Pediatrics* 2007; 120:e629-e636.
207. Mason KP, et al: Infant sedation for MR imaging and CT: Oral versus intravenous pentobarbital. *Radiology* 2004; 233:723-728.
208. Kienstra AJ, et al: Etomidate versus pentobarbital for sedation of children for head and neck CT imaging. *Pediatr Emerg Care* 2004; 20:499-506.
209. Mason KP, et al: Superiority of pentobarbital versus chloral hydrate for sedation in infants during imaging. *Radiology* 2004; 230:537-542.
210. Rooks VJ, et al: Comparison of oral pentobarbital sodium (Nembutal) and oral chloral hydrate for sedation of infants during radiologic imaging: preliminary results. *AJR Am J Roentgenol* 2003; 180:1125-1128.
211. Mason KP, et al: Sedatives used in pediatric imaging: Comparison of IV pentobarbital with IV pentobarbital with midazolam added. *AJR Am J Roentgenol* 2001; 177:427-430.
212. Eich C, et al: Low-dose S-ketamine added to propofol anesthesia for magnetic resonance imaging in children is safe and ensures faster recovery—a prospective evaluation. *Paediatr Anaesth* 2011; 21: 176-178.
213. Luscri N, Tobias JD: Monitored anesthesia care with a combination of ketamine and dexmedetomidine during magnetic resonance imaging in three children with trisomy 21 and obstructive sleep apnea. *Paediatr Anaesth* 2006; 16:782-786.
214. Tomatir E, Atalay H, Gurses E, Erbay H, Bozkurt P: Effects of low dose ketamine before induction on propofol anesthesia for pediatric magnetic resonance imaging. *Paediatr Anaesth* 2004; 14:845-850.
215. Machata AM, Kabon B, Willschke H, Prayer D, Marhofer P: Upper airway size and configuration during propofol-based sedation for magnetic resonance imaging: An analysis of 138 infants and children. *Paediatr Anaesth* 2010; 20:994-1000.
216. Heard C, et al: A comparison of dexmedetomidine-midazolam with propofol for maintenance of anesthesia in children undergoing magnetic resonance imaging. *Anesth Analg* 2008; 107:1832-1839.
217. Machata AM, Willschke H, Kabon B, Kettner SC, Marhofer P: Propofol-based sedation regimen for infants and children undergoing ambulatory magnetic resonance imaging. *Br J Anaesth* 2008; 101:239-243.
218. Koroglu A, et al: A comparison of the sedative, hemodynamic, and respiratory effects of dexmedetomidine and propofol in children undergoing magnetic resonance imaging. *Anesth Analg* 2006; 103:63-67, table of contents.
219. Hasan RA, Shayevitz JR, Patel V: Deep sedation with propofol for children undergoing ambulatory magnetic resonance imaging of the brain: Experience from a pediatric intensive care unit. *Pediatr Crit Care Med* 2003; 4:454-458.
220. Allegaert K, Naulaers G: Procedural sedation of neonates with chloral hydrate: A sedation procedure does not end at the end of the acquisition of the images. *Paediatr Anaesth* 2008; 18:1270-1271.
221. D'Agostino J, Terndrup TE: Chloral hydrate versus midazolam for sedation of children for neuroimaging: A randomized clinical trial. *Pediatr Emerg Care* 2000; 16:1-4.
222. Parks BR, Snodgrass SR: Reappraisal of lytic cocktail/Demerol, Phenergan, and Thorazine (DPT) for the sedation of children. *Pediatrics* 1996; 97:779-780.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 5

Monitoring the Emergency Patient

Anthony M. Napoli and Baruch Krauss

PERSPECTIVE

Monitoring is a routine part of emergency department (ED) care. From vital sign measurement to the provision of critical care, monitoring physiologic function provides clinicians with potentially relevant clinical information as a "snapshot" in time or in continuous fashion. In the former case, it allows for screening and triage, and in the latter, it allows for ongoing evaluation of response to treatment or changes in clinical condition.

This chapter focuses on the following monitoring modalities: noninvasive blood pressure measurement, pulse oximetry, and ventilation monitoring and the use of end-tidal carbon dioxide ($ETco_2$) measurement. Fetal monitoring after trauma and cerebral function monitoring are also briefly discussed.

NONINVASIVE BLOOD PRESSURE MEASUREMENT

Blood pressure measurement by sphygmomanometer is the most common method of noninvasively measuring arterial pressure by indirectly measuring systolic, diastolic, mean arterial pressure, and pulse pressure. The pulse pressure closely resembles stroke volume when arterial compliance and resistance are accounted for. Therefore blood pressure closely represents the interplay of cardiac output and overall systemic vascular resistance, making it an important screening and monitoring tool in ED patients.

Traditional blood pressure measurement by sphygmomanometer can be obtained by Doppler, palpation, auscultation, and oscillometric methods. Palpation allows for only systolic pressure determination, is time and resource intensive, and generally is used only in noisy environments (such as emergency medical services [EMS] transport) where measurement by oscillometric means may be difficult. Doppler is particularly helpful in identifying the presence of a systolic pulse in hypotensive individuals or in internally (i.e., atherosclerosis) or externally (i.e., compartment syndrome) flow-limited extremities. Auscultation, otherwise known as "manual" blood pressure measurement, remains a common, reliable, and reproducible method of blood pressure measurement 100 years after the Korotkoff technique was discovered. This method relies on placing the stethoscope at the antecubital fossa, inflating the blood pressure cuff, and recording the pressure at which auscultation of the pulse returns (the systolic blood pressure) and when it disappears (the diastolic blood pressure). Auscultation is generally considered to underestimate the systolic blood pressure and overestimate the diastolic pressure.[1] Although accuracy has improved with standardization of the technology, this technique is occasionally prone to significant inaccuracy.[2] The oscillometric technique measures oscillations in the pressure during deflation of the cuff; the maximal point of oscillation represents the mean arterial pressure. This is the most common noninvasive method of measuring blood pressure in the ED, commonly called the "automatic" blood pressure. This method has several advantages over auscultation, including less susceptibility to noise, the lack of necessity for specific placement of a transducer over the artery, less resource usage, regular measurement intervals, and the ability to embed readings into other clinical monitors. Comparisons of auscultation and oscillometric measurement with intra-arterial measurement have found good agreement (mean percent error ≤3%).[3] Cuff-based blood pressure measurement is limited by technique and clinical circumstances. The quality of the device, cuff size, body positioning, and arm positioning are all components of the measuring technique that can affect the accuracy. Clinical circumstances such as obesity, dysrhythmias, and extremes of age (young children and elderly) may also affect the accuracy.[4] The ease of use of oscillometric blood pressure measurement makes this modality ideal for ED noninvasive monitoring.

Other methods of providing continuous, noninvasive blood pressure monitoring often rely on partial radial artery compression or arterial loading counterpressure and offer results comparable to those of an arterial catheter with the benefit of added mobility.[5,6] Newer continuous, noninvasive blood pressure monitors have the advantage of providing additional advanced hemodynamic measures, such as stroke volume and cardiac output,[7] which may be beneficial in critically ill patients.

The gold standard, and the most accurate method of measuring blood pressure, remains the intra-arterial catheter. The combination of the invasiveness of this method and the low but real risk of arterial injury or thrombosis makes its use infrequent. However, such monitoring is becoming more frequent in EDs when there are no available intensive care unit beds and prolonged resuscitation is carried out in the ED. Arterial monitoring is also increasingly a part of aggressive resuscitation management protocols in the ED. Common situations in which invasive arterial monitoring may be of benefit include (1) anticipated hemodynamic instability, (2) monitoring of conditions or treatments that result in large fluid or blood pressure shifts, (3) frequent arterial blood sampling, and (4) expected inaccuracies in noninvasive blood pressure management (e.g., because of obesity or dysrhythmias).

PULSE OXIMETRY

Pulse oximetry is widely used for ED and out-of-hospital patient monitoring. It provides a real-time assessment of the effectiveness

www.ketabpezeshki.com 66485457-66963820

of interventions and disease progression as related to oxygenation. Its use has become so widespread as both a screening and monitoring tool that it is frequently regarded as the "fifth vital sign."

Pulse oximetry is based on the essential premise of the Beer-Lambert law that the concentration of an absorbing substance can be determined if the characteristic wavelength of that substance, the intensity of the light transmitted through the substance, and the distance of transmission are known. Device design accounts for the intensity of light and the transmission distance. Two light-emitting diodes (LEDs) give off light at wavelengths characteristic of oxyhemoglobin and deoxyhemoglobin (660 nm and 940 nm). Absorption characteristics of tissue, arterial blood, and venous blood are generally static over a cardiac cycle. Therefore through measurement of transmitted light several hundred times per second, the beat-to-beat alterations that occur in pulsatile blood can be isolated and the static components filtered out. The fractional difference between the two wavelengths is measured and reflected in the pulse oximetry.

Pulse oximetry measures the percentage of arterial hemoglobin that is in the oxyhemoglobin state. It reflects the amount of oxygen that hemoglobin is carrying as a percent of the maximum it can carry; this is commonly referred to as the *percent arterial oxygen saturation* (Sao_2). Pulse oximetry does not measure the partial pressure of oxygen in the blood (Pao_2); however, Sao_2 represents by far the larger reservoir of blood. Nonetheless, an awareness of the relationship between the two measures is important, as one main advantage of pulse oximetry is to obviate the need for multiple samples for arterial blood gas measurement. The relationship between Sao_2 and Pao_2 is described by the oxyhemoglobin dissociation curve. Although the two measures correlate well, their relationship is nonlinear. Users should be aware that large changes in the Sao_2 occur with small changes in the Pao_2 in hypoxic patients, but this is generally not of concern because pulse oximeters are generally accurate between 80% and 100%. Below this range, the role is reversed, and large changes in Pao_2 may occur with small changes in Sao_2. Pulse oximetry retains its usefulness because clinically important hypoxia exists regardless of whether the pulse oximeter is reading 85% or 65%. Measurements can be made on the ears or fingers, although the fingers are generally better in patients with poor perfusion.

Early ED use of pulse oximetry came through extrapolation from anesthesiology literature, which demonstrated less frequent and shorter episodes of desaturation and earlier recognition of hypoxia during or after anesthesia.[8,9] In the ED, pulse oximetry is largely used in initial triage of patients, particularly those with cardiopulmonary complaints, or in the monitoring and management of patients who are sedated or critically ill, particularly with respiratory distress or during endotracheal intubation. In the latter case, pulse oximetry has been shown to reduce the frequency of hypoxic episodes. Sao_2 values at or below 96% have been shown to be 100% sensitive for detection of hypoxia ($Pao_2 < 70$ torr), but such a cutoff can be different in patients with obstructive lung disease.[10,11]

Pulse oximetry has several important clinical limitations. By design, pulse oximetry measures only two wavelengths. At these wavelengths, traditional pulse oximeters are unable to distinguish oxyhemoglobin and deoxyhemoglobin from two other important dyshemoglobinemias: methemoglobin (MetHb) and carboxyhemoglobin (COHb). Multiwavelength CO-oximeters are now available that can distinguish the four wavelengths.[12] Oxygen saturation by pulse oximetry will be equivalent to actual saturation, presuming insignificant amounts of MetHb and COHb exist in the blood. In the setting of MetHb or COHb exposure, the pulse oximeter will read falsely elevated levels of Sao_2 even at relatively high exposures. In heavy smokers, COHb levels of 3 to 15% can commonly be found, but this has little impact on the accuracy of the Sao_2. Although signal artifact is probably the most common technical limitation to adequate measurement, other limitations include low perfusion and therefore low pulsatile component, ambient light, deep skin pigmentation, methylene blue, and nail polish. Averaging saturation measurements over several seconds limits the impact of motion artifact and improves the accuracy.

Spo_2 (oxygen saturation as measured by pulse oximetry) may obviate the need for repeated, invasive arterial sampling to determine oxygen saturation (and to some degree Pao_2), but it does not adequately provide insight into pH or partial pressure of carbon dioxide ($Paco_2$). More important, Sao_2 does not aid in determining the adequacy of ventilation when significant hypercapnia may precede hypoxia and supplemental oxygen may mask hypoventilation. For this situation, one needs ventilation monitoring through $ETco_2$ measurement.

END-TIDAL CARBON DIOXIDE MONITORING

The concentration of carbon dioxide (CO_2) in an exhaled breath is intrinsically linked to tissue metabolism, systemic circulation, and ventilation.[13] Capnography is the graphic record, represented as a waveform, or capnogram, of the instantaneous CO_2 concentrations in respired gases during a respiratory cycle.[14,15] Capnography provides continuous, real-time, breath-to-breath feedback on the clinical status of the patient, allowing the clinician to determine the baseline ventilatory status and to track changes over time.[16] Capnography is also a diagnostic monitoring modality because certain disease conditions are associated with characteristic waveforms.[14-17] Although the concentrations of CO_2 can be displayed continuously throughout the respiratory cycle, by convention only the maximum CO_2 concentration at the end of each tidal breath, the $ETco_2$, is ordinarily displayed. Capnometry is the quantitative measurement of $ETco_2$ displayed as a number without a waveform. Colorimetric detectors use color scales to estimate ranges of $ETco_2$ but are not sufficiently accurate to give quantitative measurements. Their use is therefore limited to confirmation of correct endotracheal tube (ETT) placement and its continuous location in the trachea. Although originally used during general anesthesia in the operating room, $ETco_2$ monitoring has now become a standard monitoring modality in the ED and nonhospital medical setting.

CO_2 monitors are configured as either sidestream or mainstream, depending on the location of the photoelectric detector or sensor. Mainstream devices measure CO_2 directly from the airway, with the sensor attached directly to the ETT. Sidestream devices, more commonly used by EMS personnel and in the ED, aspirate a sample of gas through tubing into a sensor located inside the monitor and are used for both intubated and nonintubated patients. They are lightweight and may be integrated into nasal-oral cannulae that simultaneously sample CO_2 and deliver low-flow oxygen, allowing for continuous oxygen delivery during procedural sedation and analgesia.

Colorimetric CO_2 detectors use pH-sensitive filter paper impregnated with metacresol purple, which changes color from purple (<4 mm Hg CO_2) to tan (4-15 mm Hg CO_2) to yellow (>20 mm Hg CO_2) depending on the concentration of CO_2.[13,15] (See Chapter 1.) The indicator, housed in a plastic casing, is inserted between the ETT and the ventilator bag and detects changes on a breath-by-breath basis.[13] These detectors are also inexpensive and easy to use and should be available in every ED and on every EMS unit that performs intubation for confirmation of ETT placement if capnography or capnometry is not available.

In patients with normal cardiopulmonary function, there is a close correlation between alveolar CO_2 (P_{ACO_2}) and arterial CO_2

www.ketabpezeshki.com 66485457-66963820

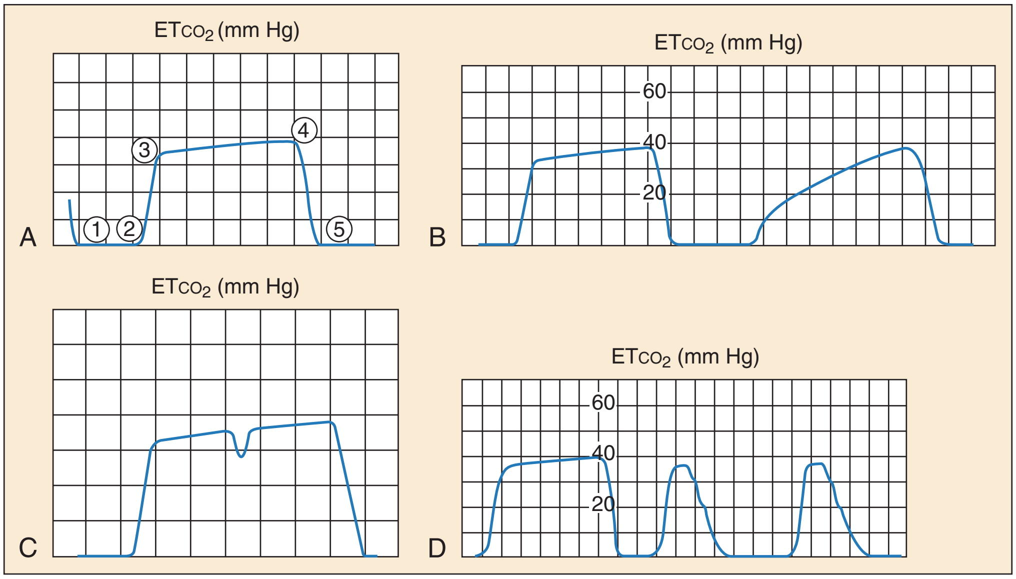


Figure 5-1. A, Four phases of a normal capnogram. *1-2,* The carbon dioxide–free portion of the respiratory cycle. *2-3,* The rapid upstroke of the curve, representing the transition from inspiration to expiration and the mixing of dead space and alveolar gas. *3-4,* The alveolar plateau, representing the alveolar gas rich in carbon dioxide and tending to slope gently upward with the uneven emptying of the alveoli. *4-5,* The respiratory downstroke, which is a nearly vertical drop to baseline. **B, C,** and **D,** See text for explanation. *ETCO₂*, end-tidal carbon dioxide (concentration).

($Paco_2$). The $ETco_2$ is usually 2 to 5 mm Hg less than the $Paco_2$ because of the dilution of the end-tidal gases by physiologic dead space gas.[18,19] Conditions that affect ventilation-perfusion ratios (including pulmonary embolism), cardiac arrest, hypovolemia, obstructive lung disease, and the lateral decubitus position can widen the Pa-$ETco_2$ gradient.[18-22] Several recent studies, however, have shown high concordance between $ETco_2$ and $Paco_2$ in adult asthmatics and in children with moderate and severe respiratory distress from bronchiolitis, asthma, and pneumonia.[20] Although $ETco_2$ may not accurately reflect the absolute $Paco_2$ in critically ill patients, it is still valuable in detecting ventilatory trends and identifying sudden airway events.

Analysis of the shape of the capnogram can yield valuable diagnostic information.[14-16] A normal capnogram has four phases (Fig. 5-1A). Phase 1-2 represents a CO_2-free portion of the respiratory cycle. Most often this is the inspiratory phase, although it may represent apnea or a disconnection of the device from the patient. An elevation of this baseline above zero implies rebreathing of CO_2, as in increased dead space in the circuit or contamination of the sensor.[14-16]

Phase 2-3, the rapid upstroke of the curve, represents the transition from inspiration to expiration and the mixing of dead space and alveolar gas. Prolongation of phase 2-3 (Fig. 5-1B) occurs with obstruction to expiratory gas flow (e.g., obstructive lung disease, bronchospasm, kinked ETT) or leaks in the breathing system.

Phase 3-4, the *alveolar plateau,* represents the predominance of CO_2-rich alveolar gas in the breath stream and tends to slope gently upward with the uneven emptying of alveoli. Point 4 (the $ETco_2$) represents the maximum CO_2 concentration in each breath and is the number that appears on the monitor. The slope of this phase can be increased by the same obstructive factors that increase the slope of phase 2-3 and is also a normal physiologic variation in pregnancy.[13] A dip in the plateau indicates a spontaneous respiratory effort during mechanical ventilation, as in hypoxia, hypercarbia, or inadequate anesthesia (Fig. 5-1C).[16,17]

Phase 4-5, the inspiratory downstroke, is a nearly vertical drop to baseline. This slope can be prolonged and blend in with the expiratory phase in endotracheal cuff leaks (Fig. 5-1D). Abnormal respiratory patterns that are fast or chaotic limit the usefulness of $ETco_2$ monitoring because characteristic waveform patterns are difficult to discern.

Capnography is used in the ED in many intubated and nonintubated clinical scenarios. It is an extremely valuable monitoring modality for intubated patients, providing information regarding respiratory function and immediate notification of accidental extubation. It can be used to confirm ETT placement in the trachea, continuously monitor tube position in the trachea during transport, provide qualitative and quantitative methods of assessing cardiac output, gauge effectiveness of cardiopulmonary resuscitation (CPR) during cardiac arrest, determine prognosis in CPR and in trauma, maintain appropriate $ETco_2$ levels in patients with elevated intracranial pressure, estimate $Paco_2$ in patients with normal lung function, assess response to treatment in patients with acute respiratory distress, determine adequacy of ventilation in patients with altered mental status (including drug-induced alterations in consciousness during procedural sedation and analgesia), assess ventilatory status of actively seizing patients, and help detect metabolic acidosis.

Along with visualizing tracheal rings on bronchoscopy, capnography is the other gold standard used to confirm intubation of the trachea (see Chapter 1). Misleading $ETco_2$ readings can occur with esophageal intubation after bag or mask ventilation and ingestion of carbonated beverages or antacids. However, detection of $ETco_2$ usually ceases after six breaths, and if capnography is used, the waveform, which initially appears normal, progressively becomes smaller, losing height until it disappears (flatline) by the sixth breath.[23] $ETco_2$ is also falsely elevated for 5 to 10 minutes after injection of sodium bicarbonate.[24] Capnography can confirm intubation of the trachea but may give false-negative results in cardiac arrest if delivery of CO_2 from the periphery to the lungs is sufficiently diminished. In these situations, it is difficult to determine whether the absence of the

www.ketabpezeshki.com 66485457-66963820

waveform is a result of esophageal intubation or poor pulmonary blood flow. In nonarrest settings the $ETco_2$ has 100% sensitivity and specificity in confirming correct tube placement and is also useful for monitoring for accidental tube dislodgement.

Airway, breathing, and circulatory assessment of critically ill or injured patients can be rapidly determined through use of $ETco_2$ values and the capnogram.[25] The presence of a normal capnogram denotes a patent airway and spontaneous breathing, and normal $ETco_2$ levels indicate adequate ventilation and perfusion. Capnography can therefore be used to assess critically ill patients (including victims of chemical terrorism with nerve gas exposure) and patients who are actively seizing.[25,26] Unlike pulse oximetry and electrocardiography, capnographic measurement is airway based and therefore is not subject to motion artifact. It also provides reliable readings in low-perfusion states.

Animal and human studies have shown that $ETco_2$ is a useful noninvasive measurement that is highly correlated with cardiac output and is the earliest indicator of return of spontaneous circulation (ROSC) in CPR.[27,28] ROSC is heralded by an almost immediate increase in $ETco_2$ from baseline. Multiple studies have shown that $ETco_2$ has prognostic value in terms of mortality during CPR.[27-32] No patient with a mean $ETco_2$ less than 10 mm Hg after 20 minutes of CPR has survived, giving $ETco_2$ measurement a high negative predictive value for failure of resuscitation. Despite these promising findings, capnography requires further prospective validation to confirm its usefulness as a prognostic tool in cardiac arrest.

Capnography is the only ventilation monitoring modality that is accurate and reliable in patients with active, generalized seizures.[25,26] Capnographic data (capnogram, $ETco_2$, respiratory rate) can be used to distinguish among actively seizing patients with apnea (flatline waveform, no $ETco_2$ readings, and no chest wall movement), ineffective ventilation with low–tidal volume breathing (small capnograms, low $ETco_2$), and effective ventilation (normal capnogram, normal $ETco_2$).

Capnography can also rapidly detect the common airway, respiratory, and central nervous system complications associated with the nerve agents in chemical terrorism, including apnea, upper airway obstruction, laryngospasm, bronchospasm, and respiratory failure.[15,25]

Capnography provides dynamic monitoring of ventilatory status in patients with acute respiratory distress, such as from asthma, bronchiolitis, chronic obstructive pulmonary disease (COPD), congestive heart failure, and cystic fibrosis. By measuring $ETco_2$ and respiratory rate with each breath, capnography provides instantaneous feedback on the clinical status of the patient. Respiratory rate is measured directly from the airway via nasal-oral cannulae, providing a more reliable reading than impedance respiratory monitoring. In upper airway obstruction and laryngospasm, for example, impedance monitoring detects chest wall movement, interprets this as a valid breath, and displays a respiratory rate, even though the patient is not ventilating. In contrast, capnography detects no ventilation and shows a flatline capnogram.

Bronchospasm in obstructive lung disease leads to upward slanting of the expiratory plateau of the capnogram (Fig. 5-2, *middle panel*). Changes in $ETco_2$ over time and the slope of this phase of the capnogram have been shown to correlate well with spirometric measurements (forced expiratory volume in 1 second [FEV_1] and peak expiratory flow rate [PEFR]).[33-35] Capnography has the advantage of being independent of effort, gender, age, and height and is a useful objective measure in asthmatic patients who are unwilling or unable to cooperate with spirometry (e.g., young children, ventilated patients, and patients in acute respiratory distress). Capnography can also be used to distinguish obstructive from restrictive lung disease.[33] Characteristic

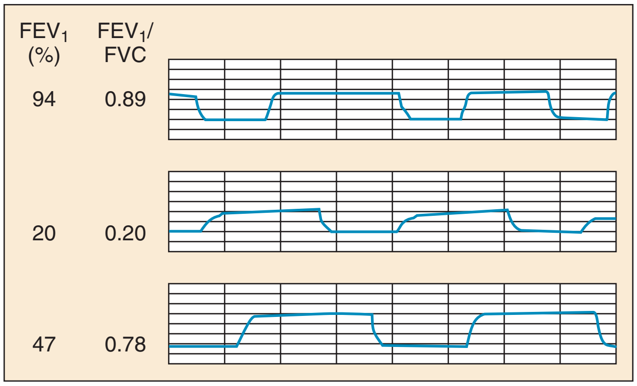


Figure 5-2. Capnogram shape in normal subjects *(top panel),* patients with bronchospasm *(middle panel),* and those with obstructive and restrictive *(bottom panel)* lung disease. *FEV_1*, forced expiratory volume in 1 second; *FVC,* forced vital capacity.

capnographic patterns associated with restrictive and obstructive lung disease are shown in Figure 5-2 *(bottom panel).*

Capnography can also detect the common adverse airway and respiratory events associated with procedural sedation and analgesia (see Chapter 4).[15] Both central and obstructive apnea can be almost instantaneously detected by capnography.[15] Capnography is the earliest indicator of airway or respiratory compromise and displays an abnormally high or low $ETco_2$ 5 to 240 seconds before pulse oximetry detects a falling oxyhemoglobin saturation, especially in patients receiving supplemental oxygen.[36,37] Low $ETco_2$—that is, hypopneic hypoventilation—is commonly seen with sedative-hypnotic agents (especially propofol) and during deep sedation, represents low–tidal volume breathing (airway dead space remains constant but tidal volume decreases), and should not be misinterpreted as hyperventilation.[15,38]

Capnography appears to be more sensitive than clinical assessment of ventilation in the detection of apnea. Soto and colleagues found that during procedural sedation 10 of 39 patients (26%) experienced 20-second periods of apnea that were detected by capnography but not by the clinicians.[39]

Two recent randomized controlled trials on the use of capnography during procedural sedation demonstrated that use of capnography decreases hypoxia and allows for delivery of supplemental oxygen during sedation without affecting the accuracy of ventilatory monitoring.[37,40] Both studies had the same design (two groups; standard monitoring blinded to capnography vs. standard monitoring and capnography) and the same outcome measure (hypoxia rate during sedation). The first study found a hypoxia rate of 42% in the no-capnography group and a rate of 25% in the capnography group. All patients with hypoxia exhibited capnographic changes before the hypoxic event. The second study found similar results: a hypoxia rate of 69% in the no-capnography group and 46% in the capnography group. The apnea rate was also significant: 62% in the no-capnography group and 41% in the capnography group.

Obtunded or unconscious patients, including those with alcohol intoxication, intentional or unintentional drug overdose, and postictal patients (especially those treated with benzodiazepines), may have impaired ventilation. Capnography can differentiate between postictal patients with effective ventilation and those with ineffective ventilation, as well as providing continuous monitoring of ventilatory trends over time to identify those patients at risk for respiratory depression and respiratory failure.

www.ketabpezeshki.com 66485457-66963820

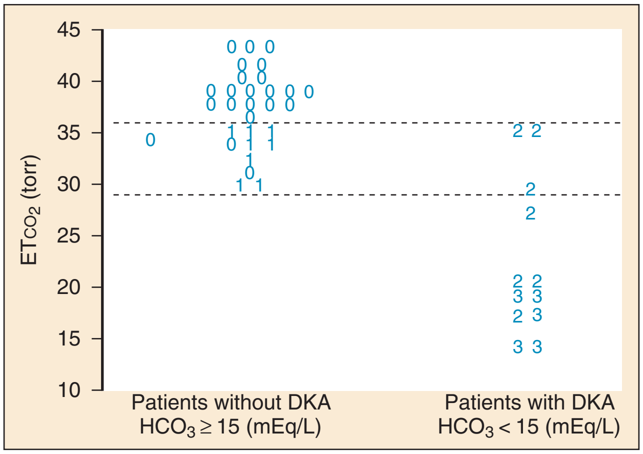


Figure 5-3. Predictive value of end-tidal carbon dioxide ($ETCO_2$) in detecting metabolic acidosis in diabetics. *DKA,* diabetic ketoacidosis; *HCO_3,* bicarbonate ion.

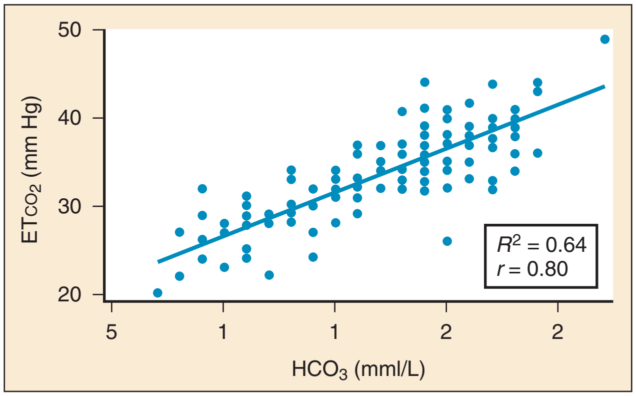


Figure 5-4. End-tidal carbon dioxide ($ETCO_2$)/serum bicarbonate (HCO_3) correlation in gastroenteritis. *r,* correlation coefficient; R^2, coefficient of determination for multivariate analysis.

In addition to its established uses for assessment of ventilation and perfusion, capnography is a valuable tool for assessing metabolic status. Studies have shown a positive linear correlation between $ETCO_2$ and serum bicarbonate (HCO_3) in diabetes and in gastroenteritis and that $ETCO_2$ can be used as an indicator of metabolic acidosis in these patients (Figs. 5-3 and 5-4, respectively).[26,41,42] As a patient becomes acidotic, HCO_3 decreases and a compensatory respiratory alkalosis develops with an increase in minute ventilation and a resultant decrease in $ETCO_2$. The more acidotic the patient, the lower the HCO_3; the higher the respiratory rate, the lower the $ETCO_2$. Furthermore, $ETCO_2$ can be used to distinguish diabetics with ketoacidosis (metabolic acidosis, compensatory tachypnea, low $ETCO_2$) from those without (nonacidotic, normal respiratory rate, normal $ETCO_2$). A similar association between $ETCO_2$ and HCO_3 was demonstrated in children with gastroenteritis.[42]

CEREBRAL FUNCTION MONITORING

The Bispectral Index (BIS) is used to monitor, analyze, and process a patient's electroencephalogram during sedation to produce a single number—the BIS score. This unitless number, ranging from 0 to 100, is used as an indicator of the depth of sedation, with 0 representing electroencephalographic silence and 100 a fully awake adult.[43]

BIS monitoring has been studied in the ED in an attempt to objectify sedation endpoints by titrating to a target BIS score.[44-46] However, the evidence of its ability to reliably reflect depth of sedation is conflicting. More important, the threshold beyond which ventilatory compromise occurs has not been determined, further limiting the usefulness of routine BIS monitoring for sedation in the ED.[44-48] A recent study found that BIS monitoring reliably distinguished patients undergoing procedural sedation and analgesia who were sedated to the point of general anesthesia from those with lesser degrees of sedation but did not discriminate mild-to-moderate sedation from moderate-to-deep sedation.[46] The findings of Miner and coauthors supported this contention in that the assignment of a preprocedural BIS target sedation level of moderate or deep procedural sedation did not influence the level of sedation achieved, the rate of respiratory depression, the occurrence of complications, the time to return of baseline mental status, or the success of the procedure. They concluded that the assignment of a preprocedural target sedation level was not an effective means of changing the outcome of procedural sedation in the ED.[47]

Two small pediatric ED studies found that BIS monitoring correlated with clinical sedation scores for nondissociative agents[44,48] but not ketamine. Determination of usefulness and effectiveness on outcome for children undergoing procedural sedation and analgesia awaits larger trials.

Another technology that monitors cerebral function is cerebral oximetry. Cerebral tissue oxygenation (i.e., regional oxygen saturation, rSO_2) is measured by near-infrared spectroscopy monitoring of the nonpulsatile signal component, reflecting tissue circulation of cerebral vasculature. This technology has been primarily studied in the operating room, with one ED study during procedural sedation showing poor correlation among changes in cerebral oximetry, pulse oximetry, and capnography.[49]

FETAL MONITORING

A small but significant percentage of all pregnancies (6-7%) are complicated by traumatic and/or accidental injury.[50] Trauma represents the leading nonobstetric cause of death and carries a mortality rate of 6 to 7%.[51] Whereas the majority of injuries are related to motor vehicle accidents, other common causes include assaults, domestic abuse, and falls. Uterine contractions occur in almost 50% of patients, although preterm labor and preterm delivery are much less common—5 to 15% and 1 to 2% of the time, respectively.[50] However, these peripartum complications and early preterm birth are difficult to predict after trauma. As a result, the Eastern Association for the Surgery of Trauma recommendations include cardiotocographic monitoring for a minimum of 6 hours after trauma in women at more than 20 weeks' gestation. In addition to serial examination, such fetal monitoring allows for the identification of uterine contractions and nonreassuring heart rate changes. Clinically concerning heart rate patterns can include persistent fetal tachycardia, bradycardia, loss of baseline variability, or late decelerations.

Although the optimal period of monitoring has not been determined, further monitoring is recommended when such abnormalities are identified or serial examination findings warrant it. Emergency physicians are generally trained and capable of recognizing such cardiotocographic findings, but availability of such monitors in the ED is variable. ED bedside ultrasonography is more commonly available and can demonstrate fetal heart rate and movement. However, ultrasonography requires intermittent examinations, has limited ability to track fetal heart tones, and is unable to measure uterine contractions.

www.ketabpezeshki.com 66485457-66963820

Monitor Alarms and Limits

Continuous vital sign monitoring, with alarm thresholds that notify staff regarding changes in physiologic conditions, has become a routine part of ED care. Although these alarms are designed to be highly sensitive, their lack of specificity has the potential to desensitize staff and reduce alarm effectiveness in identifying important changes in the clinical condition (i.e., "nuisance alarms"). Continuous monitoring in select patient populations, such as those with low-risk chest pain, has limited usefulness, with less than 1% of alarms resulting in a change in clinical management.[52,53] A multidisciplinary team-based approach that focuses on identifying optimal application of monitoring, standardizing alarm limits and the staff response, and using improved alarm technology has the potential to improve patient safety and enhance workplace efficiency and satisfaction.[54]

KEY CONCEPTS

- Monitoring modalities, when used appropriately, help to identify the effectiveness of interventions, predict deterioration, track the patient's clinical course, and inform clinical decision-making.
- Capnography supplements oximetry by providing useful information regarding pathologic conditions and response to therapy.
- Continuous monitoring can advance patient safety in select patients. Alarm limits should be adjusted to ensure reasonable warnings are delivered, optimally reducing the number of false alarms.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Breit SN, O'Rourke MF: Comparison of direct and indirect arterial pressure measurements in hospitalized patients. *Aust N Z J Med* 1974; 4:485-491.
2. Perloff D, et al: Human blood pressure determination by sphygmomanometry. *Circulation* 1993; 88(5 Pt 1):2460-2470.
3. Borow KM, Newburger JW: Noninvasive estimation of central aortic pressure using the oscillometric method for analyzing systemic artery pulsatile blood flow: Comparative study of indirect systolic, diastolic, and mean brachial artery pressure with simultaneous direct ascending aortic pressure measurements. *Am Heart J* 1982; 103:879-886.
4. Pickering TG, et al: Recommendations for blood pressure measurement in humans and experimental animals. Part 1: Blood pressure measurement in humans. A statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* 2005; 45:142-161.
5. Thomas SH, Winsor GR, Pang PS, Driscoll KA, Parry BA: Use of a radial artery compression device for noninvasive, near-continuous blood pressure monitoring in the ED. *Am J Emerg Med* 2004; 22:474-478.
6. Fortin J, et al: Continuous non-invasive blood pressure monitoring using concentrically interlocking control loops. *Comput Biol Med* 2006; 36:941-957.
7. Jansen JR, et al: A comparison of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. *Br J Anaesth* 2001; 87:212-222.
8. McKay WP, Noble WH: Critical incidents detected by pulse oximetry during anaesthesia. *Can J Anaesth* 1988; 35(3 Pt 1): 265-269.
9. Morris RW, Buschman A, Warren DL, Philip JH, Raemer DB: The prevalence of hypoxemia detected by pulse oximetry during recovery from anesthesia. *J Clin Monit* 1988; 4:16-20.
10. Witting MD, Lueck CH: The ability of pulse oximetry to screen for hypoxemia and hypercapnia in patients breathing room air. *J Emerg Med* 2001; 20:341-348.
11. Kelly AM, McAlpine R, Kyle E: How accurate are pulse oximeters in patients with acute exacerbations of chronic obstructive airways disease? *Respir Med* 2001; 95:336-340.
12. Roth D, et al: Accuracy of noninvasive multiwave pulse oximetry compared with carboxyhemoglobin from blood gas analysis in unselected emergency department patients. *Ann Emerg Med* 2011; 58:74-79.
13. Buhre W, Rossaint R: Perioperative management and monitoring in anaesthesia. *Lancet* 2003; 362:1839-1846.
14. Swedlow DB: Capnometry and capnography: The anesthesia disaster early warning system. *Semin Anesth* 1986; 5:194-205.
15. Krauss B, Hess DR: Capnography for procedural sedation and analgesia in the emergency department. *Ann Emerg Med* 2007; 50:172-181.
16. Smalhout B, Kalenda Z: *An Atlas of Capnography*. Zeist, Utrecht, The Netherlands: Kerckebusch; 1975.
17. Kalenda Z: *Mastering Infrared Capnography*. Zeist, Utrecht, The Netherlands: Kerckebusch; 1989.
18. Hoffbrand BI: The expiratory capnogram: A measure of ventilation-perfusion inequalities. *Thorax* 1966; 21:518-523.
19. Yamanaka MK, Sue DY: Comparison of arterial-end-tidal P_{CO_2} difference and dead space/tidal volume ratio in respiratory failure. *Chest* 1987; 92:832-835.
20. Corbo J, Bijur P, Lahn M, Gallagher EJ: Concordance between capnography and arterial blood gas measurements of carbon dioxide in acute asthma. *Ann Emerg Med* 2005; 46:323-327.
21. Hardman JG, Aitkenhead AR: Estimating alveolar dead space from the arterial to end-tidal CO(2) gradient: A modeling analysis. *Anesth Analg* 2003; 97:1846-1851.
22. Kline JA, Kubin AK, Patel MM, Easton EJ, Seupal RA: Alveolar dead space as a predictor of severity of pulmonary embolism. *Acad Emerg Med* 2000; 7:611-617.
23. Garnett AR, Gervin CA, Gervin AS: Capnographic waveforms in esophageal intubation: Effect of carbonated beverages. *Ann Emerg Med* 1989; 18:387-390.
24. Okamoto H, Hoka S, Kawasaki T, Okuyama T, Takahashi S: Changes in end-tidal carbon dioxide tension following sodium bicarbonate administration: Correlation with cardiac output and haemoglobin concentration. *Acta Anaesthesiol Scand* 1995; 39:79-84.
25. Krauss B: Capnography as a rapid assessment and triage tool for chemical terrorism. *Pediatr Emerg Care* 2005; 21:493-497.
26. Abramo TJ, Wiebe RA, Scott S, Goto CS, McIntire DD: Noninvasive capnometry monitoring for respiratory status during pediatric seizures. *Crit Care Med* 1997; 25:1242-1246.
27. Falk JL, Rackow EC, Weil MH: End-tidal carbon dioxide concentration during cardiopulmonary resuscitation. *N Engl J Med* 10 1988; 318:607-611.
28. Garnett AR, Ornato JP, Gonzalez ER, Johnson EB: End-tidal carbon dioxide monitoring during cardiopulmonary resuscitation. *JAMA* 1987; 257:512-515.
29. Ahrens T, et al: End-tidal carbon dioxide measurements as a prognostic indicator of outcome in cardiac arrest. *Am J Crit Care* 2001; 10:391-398.
30. Cantineau JP, et al: End-tidal carbon dioxide during cardiopulmonary resuscitation in humans presenting mostly with asystole: A predictor of outcome. *Crit Care Med* 1996; 24:791-796.
31. Deakin CD, Sado DM, Coats TJ, Davies G: Prehospital end-tidal carbon dioxide concentration and outcome in major trauma. *J Trauma* 2004; 57:65-68.
32. Levine RL, Wayne MA, Miller CC: End-tidal carbon dioxide and outcome of out-of-hospital cardiac arrest. *N Engl J Med* 1997; 337:301-306.
33. Krauss B, et al: Capnogram shape in obstructive lung disease. *Anesth Analg* 2005; 100:884-888, table of contents.
34. Yaron M, Padyk P, Hutsinpiller M, Cairns CB: Utility of the expiratory capnogram in the assessment of bronchospasm. *Ann Emerg Med* 1996; 28:403-407.
35. You B, Peslin R, Duvivier C, Vu VD, Grilliat JP: Expiratory capnography in asthma: Evaluation of various shape indices. *Eur Respir J* 1994; 7:318-323.
36. Burton JH, Harrah JD, Germann CA, Dillon DC: Does end-tidal carbon dioxide monitoring detect respiratory events prior to current sedation monitoring practices? *Acad Emerg Med* 2006; 13:500-504.
37. Deitch K, Miner J, Chudnofsky CR, Dominici P, Latta D: Does end tidal CO_2 monitoring during emergency department procedural sedation and analgesia with propofol decrease the incidence of hypoxic events? A randomized, controlled trial. *Ann Emerg Med* 2010; 55:258-264.
38. Langhan ML, Chen L, Marshall C, Santucci KA: Detection of hypoventilation by capnography and its association with hypoxia in children undergoing sedation with ketamine. *Pediatr Emerg Care* 2011; 27:394-397.
39. Soto RG, Fu ES, Vila H Jr, Miguel RV: Capnography accurately detects apnea during monitored anesthesia care. *Anesth Analg* 2004; 99: 379-382, table of contents.
40. Qadeer MA, et al: Capnographic monitoring of respiratory activity improves safety of sedation for endoscopic cholangiopancreatography and ultrasonography. *Gastroenterology* 2009; 136:1568-1576; quiz 1819-1520.
41. Fearon DM, Steele DW: End-tidal carbon dioxide predicts the presence and severity of acidosis in children with diabetes. *Acad Emerg Med* 2002; 9:1373-1378.
42. Nagler J, Wright RO, Krauss B: End-tidal carbon dioxide as a measure of acidosis among children with gastroenteritis. *Pediatrics* 2006; 118:260-267.
43. Rosow C, Manberg PJ: Bispectral index monitoring. *Anesthesiol Clin North America* 2001; 19:947-966, xi.
44. Agrawal D, Feldman HA, Krauss B, Waltzman ML: Bispectral index monitoring quantifies depth of sedation during emergency department procedural sedation and analgesia in children. *Ann Emerg Med* 2004; 43:247-255.
45. Fatovich DM, Gope M, Paech MJ: A pilot trial of BIS monitoring for procedural sedation in the emergency department. *Emerg Med Australas* 2004; 16:103-107.
46. Gill M, Green SM, Krauss B: A study of the Bispectral Index Monitor during procedural sedation and analgesia in the emergency department. *Ann Emerg Med* 2003; 41:234-241.
47. Miner JR, Huber D, Nichols S, Biros M: The effect of the assignment of a pre-sedation target level on procedural sedation using propofol. *J Emerg Med* 2007; 32:249-255.
48. Overly FL, et al: Bispectral analysis during pediatric procedural sedation. *Pediatr Emerg Care* 2005; 21:6-11.
49. Padmanabhan P, Berkenbosch JW, Lorenz D, Pierce MC: Evaluation of cerebral oxygenation during procedural sedation in children using near infrared spectroscopy. *Ann Emerg Med* 2009; 54: 205-213.
50. Connolly AM, Katz VL, Bash KL, McMahon MJ, Hansen WF: Trauma and pregnancy. *Am J Perinatol* 1997; 14:331-336.

www.ketabpezeshki.com 66485457-66963820

51. Barraco RD, et al: Practice management guidelines for the diagnosis and management of injury in the pregnant patient: The EAST Practice Management Guidelines Work Group. *J Trauma* 2010; 69:211-214.
52. Hollander JE, Sites FD, Pollack CV Jr, Shofer FS: Lack of utility of telemetry monitoring for identification of cardiac death and life-threatening ventricular dysrhythmias in low-risk patients with chest pain. *Ann Emerg Med* 2004; 43:71-76.
53. Atzema C, Schull MJ, Borgundvaag B, Slaughter GR, Lee CK: ALARMED: Adverse events in low-risk patients with chest pain receiving continuous electrocardiographic monitoring in the emergency department. A pilot study. *Am J Emerg Med* 2006; 24:62-67.
54. Graham KC, Cvach M: Monitor alarm fatigue: Standardizing use of physiological monitors and decreasing nuisance alarms. *Am J Crit Care* 2010; 19:28-34; quiz 35.

www.ketabpezeshki.com 66485457-66963820

Chapter 6

Shock

Alan E. Jones and Jeffrey A. Kline

PERSPECTIVE

In philosophic terms, shock can be viewed as a transition between life and death. Whether shock results from hemorrhage, sepsis, or cardiac failure, mortality rates exceed 20%.[1,2] In scientific lexicon, shock results from the widespread failure of the circulatory system to oxygenate and nourish the body adequately. In the laboratory the scientist defines the metabolic effect of shock quantitatively, by examining the mechanisms by which shock alters mitochondrial energy transfer, evokes the production of toxic chemicals, and reduces their removal. At the bedside, however, the clinician identifies shock by linking the clinical impression, synthesized from the patient's history of present illness, age, underlying health status, and general appearance, to quantitative data, including vital signs, blood chemistry, urine output, and direct measurements of oxygenation. When the clinical impression and the quantitative data suggest widespread organ hypoperfusion, emergent resuscitation is used to restore normal tissue oxygenation and substrate delivery to prevent deterioration into systemic inflammation, organ dysfunction, and death.

At the subcellular level, shock first affects the mitochondria. Mitochondria function at the lowest oxygen tension in the body, but paradoxically, they consume almost all the oxygen used by the body. More than 95% of aerobic chemical energy comes from mitochondrial combustion of fuel substrates (fats, carbohydrates, ketones) plus oxygen into carbon dioxide (CO_2) and water. Mitochondria therefore have been referred to as the "canaries in the coal mine" because they are affected first in conditions of inadequate tissue perfusion.[3,4] When mitochondria have inadequate oxygen, the cell catabolizes fuels to lactate, which inexorably accumulates and diffuses into the blood.

Classification

For years, shock has been classified into four broad categories based on Blalock's 1934 description: hematologic, neurologic, vasogenic, and cardiogenic. This basic organization scheme remains useful today. Box 6-1 outlines five categories of shock that generally have specific mechanisms and treatments.

Epidemiology

The epidemiology of shock in the emergency department context remains speculative because shock is rarely listed as a primary coding diagnosis and depends on defining criteria. Arterial hypotension, defined as a systolic blood pressure (BP) below 100 mm Hg, is measured at least one time in 19% of ED patients[5]; however, diagnosed traumatic, cardiogenic, or septic shock is less common, constituting about 1 to 3% of all ED visits.

This chapter reviews the metabolic, systemic, and inflammatory responses that occur in all types of circulatory shock and discusses specific pathophysiology of the major causes of shock.

Specific Causes

Hemorrhagic Shock

Hemorrhagic shock results from a rapid reduction in blood volume, which causes baroreceptor activation and leads to vasoconstriction, increased strength of cardiac contraction, and increased heart rate (HR). Cardiovascular response to hemorrhage can vary with underlying cardiopulmonary status, age, and presence of ingested drugs. Responses of HR and BP are notoriously variable in hemorrhage, so no firm conclusion can be made at the bedside about the presence or absence of hemorrhagic shock simply by evaluating HR and BP. In general, hemorrhage first increases pulse and cardiac contraction, then increases vasoconstriction. Blood loss causes an elevated pulse rate with a slight increase in the diastolic BP, causing the pulse pressure (difference between systolic and diastolic BP) to narrow. As blood loss continues, ventricular filling decreases and cardiac output drops, followed by a reduction in systolic BP. Before the total cardiac output begins to decrease, blood flow to noncritical organs and tissues begins to decrease, and their cells produce and release lactic acid.

Consequently, acidemia will often precede any significant decrease in cardiac output with hemorrhage. However, the blood contains bicarbonate ions that buffer the blood pH, keeping it near neutral, even as lactic acid accumulates in blood. The base deficit—the amount of strong base that would have to be added to a liter of blood to normalize the pH—represents an index of how far the bloodstream has dipped into its reserve of bicarbonate buffer. A normal base deficit is more positive than −2 mEq/L. Accordingly, the arterial and venous blood base deficit can become more negative early in hemorrhage even while blood pH and BP remain in the normal range. The base deficit, therefore, crudely represents the physiologic endpoint that distinguishes trivial blood loss from clinically significant hemorrhage. In addition to chemical buffering, the body responds to small reductions in arterial pH by activating brainstem chemoreceptors, which increase minute ventilation, leading to reduced partial pressure of carbon dioxide in the arterial blood ($Paco_2$).

After approximately one third of the total blood volume has been acutely lost, cardiovascular reflexes can no longer sustain adequate filling of the arterial circuit and frank hypotension supervenes. Arterial hypotension is generally and arbitrarily defined as an arterial BP below 90 mm Hg. Usually coincident with the development of hypotension, bicarbonate buffers

www.ketabpezeshki.com 66485457-66963820

Box 6-1 Categories of Shock According to Primary Treatment

Causes That Require Primarily the Infusion of Volume
- Hemorrhagic shock
  - Traumatic
  - Gastrointestinal
  - Body cavity
- Hypovolemia
  - Gastrointestinal losses
  - Dehydration from insensible losses
  - Third-space sequestration from inflammation

Causes That Require Improvement in Pump Function by Either Infusion of Inotropic Support or Reversal of the Cause of Pump Dysfunction
- Myocardial ischemia
  - Coronary artery thrombosis
  - Arterial hypotension with hypoxemia
- Cardiomyopathy
  - Acute myocarditis
  - Chronic diseases of heart muscle (ischemic, diabetic, infiltrative, endocrinologic, congenital)
- Cardiac rhythm disturbances
  - Atrial fibrillation with rapid ventricular response
  - Ventricular tachycardia
  - Supraventricular tachycardia
- Septic shock with myocardial failure ("hypodynamic shock")
- Overdose of negative inotropic drug
  - Beta-blocker
  - Calcium channel antagonist
- Structural cardiac damage
  - Traumatic (e.g., flail mitral valve)
  - Ventriculoseptal rupture
  - Papillary muscle rupture

Causes That Require Volume Support and Vasopressor Support
- Septic shock
- Anaphylactic shock
- Central neurogenic shock
- Drug overdose

Problems That Require Immediate Relief from Obstruction to Cardiac Output
- Pulmonary embolism
- Cardiac tamponade
- Pneumothorax
- Valvular dysfunction
  - Acute thrombosis of prosthetic valve
  - Critical aortic stenosis
- Congenital heart defects in newborn (e.g., closure of patent ductus arteriosus with critical aortic coarctation)
- Critical idiopathic subaortic stenosis (hypertrophic obstructive cardiomyopathy)

Cellular Poisons That Require Specific Antidotes
- Carbon monoxide
- Methemoglobinemia
- Hydrogen sulfide
- Cyanide

become overwhelmed, and increased alveolar ventilation becomes ineffective, culminating in reduced arterial pH. Hemorrhagic shock causes an activation of the hypothalamic-pituitary-adrenomedullary axis, with release of stress hormones that cause glycogenolysis, lipolysis, and mild hypokalemia. Therefore in the ED, patients who have sustained traumatic hemorrhage generally have an arterial lactate concentration greater than 4.0 mmol/L, a $Paco_2$ less than 35 mm Hg, and mild hyperglycemia (150-170 mg/dL) and hypokalemia (3.5-3.7 mEq/L). Although hemorrhagic hypotension reduces lung perfusion, arterial hypoxemia should not be attributed simply to blood loss, but instead should prompt investigation for aspiration, airway obstruction, alveolar consolidation, or lung injury.

The second phase of organ injury from hemorrhagic shock occurs during resuscitation. It has been said that the acute phase of hemorrhage "cocks the gun" by initiating the inflammatory cascade, and resuscitation "pulls the trigger" by accentuating the inflammation-induced organ injury from hemorrhagic shock. During resuscitation, neutrophils become most aggressive, binding to the lung endothelium and causing capillary leaks that characterize acute respiratory distress syndrome (ARDS). Inflammatory cytokines are liberated during resuscitation, and membrane injury occurs in many cells. In the liver, damage from inflammation and reactive oxygen species from neutrophils is compounded by persistent microischemia. During resuscitation from hemorrhagic shock, the normal balance of vasodilation by nitric oxide (NO) versus vasoconstriction by endothelins becomes distorted, producing patchy centrilobular ischemic damage in the liver, which may produce an immediate rise in blood transaminase levels. A growing body of evidence suggests that resuscitation from hemorrhage exerts greater injury on the heart than the actual hypotensive insult.[6] Depending on the degree of hypotensive insult, the kidney may manifest acute spasm of the preglomerular arterioles, causing acute tubular necrosis. Systemic metabolic changes can impair fuel delivery to the heart and brain, secondary to depressed hepatic glucose output, impaired hepatic ketone production, and inhibited peripheral lipolysis.

Septic Shock

Septic shock can be produced by infection with any microbe, although in one half or more of cases of septic shock, no organism is identified. One of the most well-studied mediators of sepsis is lipopolysaccharide, contained in the outer cell membrane of gram-negative bacteria. Infusion of lipopolysaccharide into humans or animals will produce cardiovascular, immunologic, and inflammatory changes identical to those observed with microbial infection. In recent years, multicenter trials of sepsis have suggested the emergence of gram-positive organisms as the chief cause of sepsis in hospitalized patients. Two lines of reasoning suggest that gram-positive sepsis will continue to increase in prevalence:

1. More patients are being treated at home for chronic immunocompromising diseases with indwelling catheters, which can serve as portals of entry into the vascular space for *Staphylococcus aureus* and coagulase-negative staphylococci.
2. The frequency of community-acquired infections caused by antibiotic-resistant gram-positive organisms has greatly increased in recent years, including infections caused by *S. aureus, Streptococcus pneumoniae,* and *Streptococcus pyogenes.*

Septic shock often causes three major effects that must be addressed during resuscitation: relative hypovolemia, cardiovascular depression, and induction of systemic inflammation. Septic shock produces relative hypovolemia from increased venous capacitance, which reduces right ventricular filling. Septic shock often causes absolute hypovolemia from gastrointestinal volume losses, tachypnea, sweating, and decreased ability to drink during development of the illness. Sepsis also induces capillary leak, which leads to relative loss of intravascular volume into third spaces. Recent evidence has shown that septic shock causes myocardial depression simultaneously with vasodepression and capillary leak. Direct measurements of cardiac contractility have shown that cardiac mechanical function becomes impaired early in the course of septic shock, even in the hyperdynamic stages. Multiple mechanisms may explain depressed heart function in sepsis,

www.ketabpezeshki.com 66485457-66963820

including actions of specific cytokines (most notably tumor necrosis factor alpha [TNF-α] and interleukin 1 beta [IL-1β]), overproduction of NO by nitric oxide synthase (iNOS),[7] and possibly impairment in mitochondrial oxidative phosphorylation coincident with reduced mechanical efficiency.[8,9] Evidence indicates that circulating mediators, myocardial cellular injury from inflammation, and deranged metabolism interact synergistically to injure the heart during septic shock. Systemic inflammation causes capillary leak in the lung, which may cause alveolar infiltration characteristic of ARDS early in the treatment of septic shock in up to 40% of patients. With the potential for early development of ARDS, more profound ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatching, and pneumonia or pulmonary aspiration, hypoxemia is more severe with septic shock than hemorrhagic shock.

Cardiogenic Shock

Cardiogenic shock results when more than 40% of the myocardium undergoes necrosis from ischemia, inflammation, toxins, or immune destruction. Otherwise, cardiogenic shock essentially produces the same circulatory and metabolic alterations as are observed with hemorrhagic shock. Undoubtedly, impaired baseline cardiac function can contribute to the development of circulatory shock secondary to infection, hemorrhage, or vasodilatory drug overdose. However, when shock results from a pure cardiac cause, severe left ventricular dysfunction will be evident on echocardiography early in the course. Patients with severe dysfunction are far more likely to have a cardiogenic cause of shock than patients with normal or moderate left ventricular dysfunction.[10]

CLINICAL FEATURES

Patients in the ED frequently are in shock with no obvious cause. Rapid recognition of shock requires the integration of information from immediate history and physical examination, and shock can be strongly supported by the presence of a worsening base deficit or lactic acidosis. In general, patients with shock exhibit a stress response: they are ill appearing, asthenic, pale, often sweating, and usually tachypneic or grunting, and often have a weak and rapid pulse (Box 6-2). HR can be normal or low in shock, especially in cases complicated by prescribed drugs that depress HR or by profound hypoxemia. BP initially can be normal because of adrenergic reflexes. Although arterial BP as a sole measurement remains an unreliable marker of circulatory status, the finding of a single systolic BP less than 100 mm Hg in the ED is associated with a threefold increase in in-hospital mortality and a tenfold increase in sudden and unexpected death.[5] The HR/systolic BP ratio may provide a better marker of shock than either measurement alone; a normal ratio is less than 0.8. Urine output provides an excellent indicator of organ perfusion and is readily available with insertion of a Foley catheter into the bladder. Measurement of urine output, however, requires 30 minutes to 1 hour for accurate determination of whether output is normal (>1.0 mL/kg/hr), reduced (0.5-1.0 mL/kg/hr), or severely reduced (<0.5 mL/kg/hr). Point measurements of the arterial or venous lactate concentration and the base deficit can be rapidly performed and provide accurate assessment of global perfusion status. A lactate concentration greater than 4.0 mM or a base deficit more negative than −4 mEq/L predicts the presence of circulatory insufficiency severe enough to cause subsequent multiple organ failure.[11,12] Once the empirical criteria for circulatory shock have been discovered, the next step is to consider the cause of the shock. Figure 6-1 shows a potential sequence of decisions to help arrive at a diagnosis in a patient with undifferentiated shock.

The history, vital signs, and physical examination documented by prehospital providers afford valuable insight into a patient's physiologic status before any medical intervention and can be useful in ED management. Studies suggest that both medical and trauma patients with prehospital hypotension have a threefold to

Box 6-2 Empirical Criteria for Diagnosis of Circulatory Shock*

- Ill appearance or altered mental status
- Heart rate >100 beats/min
- Respiratory rate >20 breaths/min or Pa_{CO_2} <32 mm Hg
- Arterial base deficit <−4 mEq/L or lactate >4 mM/L
- Urine output <0.5 mL/kg/hr
- Arterial hypotension >30 continuous minutes duration

*Regardless of cause. Four criteria should be met.

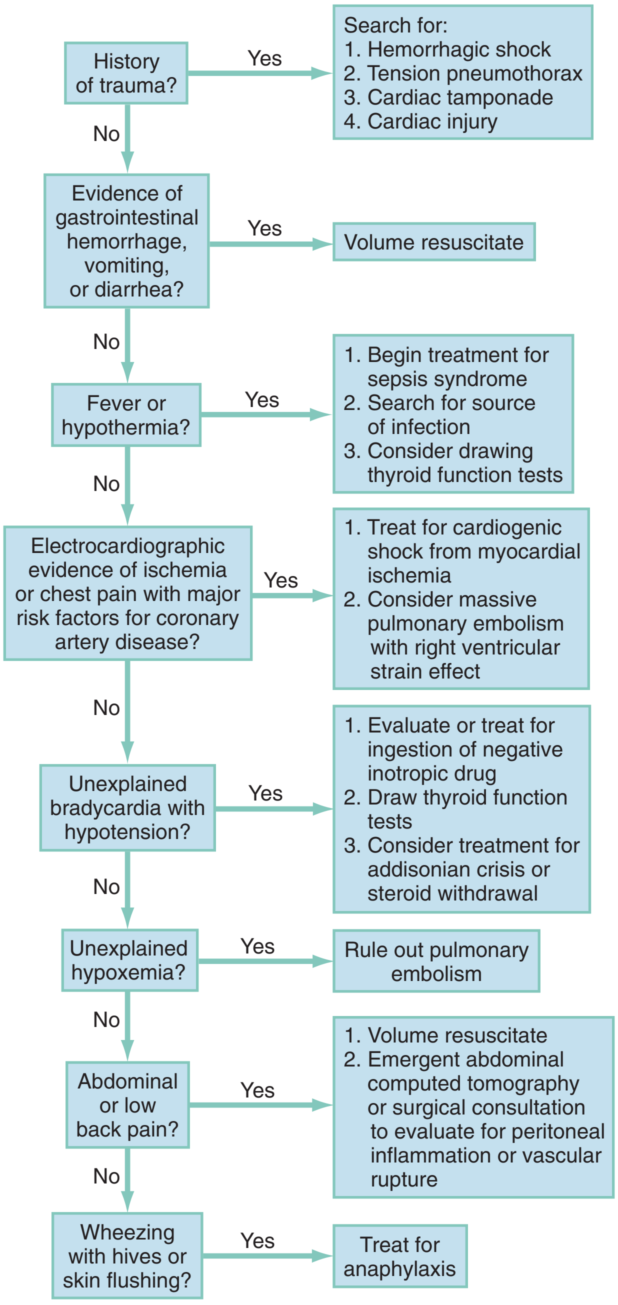


Figure 6-1. Flow diagram to classify undifferentiated shock.

www.ketabpezeshki.com 66485457-66963820

fourfold higher in-hospital mortality rate than patients without hypotension.[13,14]

On physical examination, dry mucous membranes suggest dehydration, whereas distended jugular veins suggest cardiac failure or obstruction from pulmonary embolism (PE) or cardiac tamponade. Muffled heart sounds suggest cardiac tamponade, whereas a loud machine-like systolic murmur indicates acute rupture of a papillary muscle or rupture of the interventricular septum. Bilateral pulmonary rales in a patient with a normal rectal temperature help to define presence of primary left ventricular failure. Wheezing suggests bronchospasm from anaphylaxis or, less likely, cardiac failure or PE. Abdominal tenderness may indicate peritoneal inflammation or occult trauma. Rectal examination may disclose occult gastrointestinal hemorrhage. Rectal temperature is the preferred method for measuring temperature and in general should be performed as early as is reasonable on every patient with suspected shock.

Neurologic examination documents responsiveness, cognition, and the presence of any focal deficits. In children, documentation should include level of alertness, response to parents, appropriateness of crying, pupillary function, symmetry of grimace, symmetry of extremity movements, and motor tone in infants.

Laboratory, radiographic, and other ancillary data should be ordered to assess tissue and vital organ perfusion and to diagnose injury from trauma, find the source of infection with sepsis, or identify the cause of cardiac failure. A chest radiograph, electrocardiogram, finger-stick glucose measurement, complete blood count (CBC), urinalysis, serum electrolytes, and kidney and liver function tests are all indicated in the ED assessment. Arterial blood gases are ordered for a base deficit calculation and to correlate arterial gas tensions (oxygen [Pao_2] and $Paco_2$) with those measured by pulse oximetry and capnography. Serum lactate measurement should be performed as early as possible in patients with suspected shock. Either venous or arterial lactate concentrations can be used.[15,16] If peripheral venous lactate is used, the effect of time, storage temperature, and tourniquet use have no significant effect on in vitro lactate production by erythrocytes if the measurement is done within 15 minutes after the sample has been obtained.[17] Cardiac and abdominal bedside ultrasound scanning can screen for inadequate central venous volume, occult hemoperitoneum, abdominal aortic aneurysm, left ventricular failure, and cardiac tamponade.[18] A systematic ultrasound protocol can significantly improve the physician's ability to accurately diagnose the cause of undifferentiated shock in ED patients, and the finding of hyperdynamic left ventricular function in patients with undifferentiated shock strongly suggests sepsis as the cause.[19,20]

Consensus definitions of shock show the spectrum of hypoperfusion for the following three common causes of shock (Box 6-3):

1. *Septic shock.* The American College of Chest Physicians, European Society of Intensive Care Medicine, Society for Critical Care Medicine, American Thoracic Society, and Surgical Infection Society developed international consensus definitions to distinguish septic shock from its precursor conditions—systemic inflammatory response syndrome (SIRS), sepsis, and severe sepsis.[21] Although this particular consensus definition requires persistent hypotension after fluid resuscitation to strictly define septic shock, initiation of treatment for empirically diagnosed severe sepsis or septic shock should not await the onset of hypotension. The incorporation of an indicator of tissue hypoperfusion into the clinical assessment may improve identification of hypoperfusion, particularly in subtle cases. Box 6-4 provides a list of variables that can assist with detecting tissue hypoperfusion.[22]
2. *Hemorrhagic shock.* The American College of Surgeons has divided hemorrhagic shock into four stages, depending on the severity of blood loss and the physiologic response to this loss, but such arbitrary divisions are of little value. A more useful approach defines hemorrhagic shock as being present when systemic hypoperfusion manifests as lactic acidosis with organ dysfunction.
3. *Cardiogenic shock.* Cardiogenic shock should be thought to be present whenever cardiac failure (ischemic, toxic, or obstructive) causes systemic hypoperfusion that manifests as lactic acidosis with organ dysfunction.

Box 6-3 Definitions and Criteria for Septic, Hemorrhagic, and Cardiogenic Shock

Septic Shock

Systemic Inflammatory Response Syndrome (SIRS)

Two or more of the following:

1. Temperature >38° C or <36° C
2. Heart rate >90 beats/min
3. Respiratory rate >20 breaths/min or $Paco_2$ <32 mm Hg
4. White blood cell count >12,000/mm^3, <4000/mm^3, or >10% band neutrophilia

Severe Sepsis

SIRS with suspected or confirmed infection and associated with organ dysfunction or hypotension; organ dysfunction may include presence of lactic acidosis, oliguria, or altered mental status

Septic Shock

SIRS with suspected or confirmed infection with hypotension despite adequate fluid resuscitation; septic shock should still be diagnosed if vasopressor therapy has normalized blood pressure

Hemorrhagic Shock

Simple Hemorrhage

Suspected bleeding with pulse <100 beats/min, normal respiratory rate, normal blood pressure, and normal base deficit

Hemorrhage with Hypoperfusion

Suspected bleeding with base deficit <–4 mEq/L *or* persistent pulse >100 beats/min

Hemorrhagic Shock

Suspected bleeding with at least four criteria listed in Box 6-2

Cardiogenic Shock

Cardiac Failure

Clinical evidence of impaired forward flow of the heart, including presence of dyspnea, tachycardia, pulmonary edema, peripheral edema, or cyanosis

Cardiogenic Shock

Cardiac failure plus four criteria listed in Box 6-2

Box 6-4 Variables Indicating Tissue Hypoperfusion

Hypotension
Tachycardia
Low cardiac output
Mottled skin
Delayed capillary refill
Altered mental state
Hyperlactemia
Low mixed venous oxygen saturation
Low central venous oxygen saturation

www.ketabpezeshki.com 66485457-66963820

MANAGEMENT

Monitoring Perfusion Status

In all patients with shock, HR, BP, and oxyhemoglobin saturation are continuously monitored. Cuff sphygmomanometer measurement of BP may be inaccurate in severe hypotensive states, and insertion of an arterial pressure monitoring line should considered, especially if vasoactive medications are being administered. BP and HR correlate poorly to cardiac index (CI) in shock and often underestimate the severity of systemic hypoperfusion. Moreover, children with hypovolemic shock frequently demonstrate a normal BP until they rapidly deteriorate. Urine output should be measured as an index of vital organ perfusion (0.5-1 mL/kg/hr in persons without preexisting renal disease). Downward trend of the serum lactate concentration or upward trend of the base deficit, when observed with improving vital signs and urine output, can reliably gauge the adequacy of resuscitation and prognosis in shock from any cause. A rising lactate concentration (or refractory hypotension with worsening base deficit) despite ongoing resuscitation portends high mortality and calls for more aggressive resuscitation or specific procedural intervention.

Most patients with shock can be fully resuscitated with peripheral venous access established with two catheters of at least a size 18 gauge. Patients with cardiac failure or renal failure may benefit from closer measurement of dynamic variables of fluid responsiveness that can be measured from an arterial line (such as stroke volume variation or stroke volume index) or a central venous line (central venous pressure [CVP]).[23] An 8.5-French catheter (Cordis sheath) allows for accurate measurement of the CVP and insertion of a pulmonary artery catheter or other monitoring device if needed. In children, a 3- or 5-French bilumen catheter can be placed in the femoral vein with few complications. To reduce the potential for limb damage from extravasation from a peripheral intravenous injection, vasoactive medications are optimally administered through a central venous catheter. If vasoactive medications are administered, additional peripheral intravenous catheters will be required for infusion of crystalloid and other treatments. Many patients with renal disease or cancer have indwelling catheters in place. In patients with empirical criteria for shock, this catheter should be used for intravenous access, unless satisfactory access has already been established at other anatomic sites. In EDs where the standard practice is not to use these ports at the request of other physicians, a specific hospital policy and training session should be developed to make an exception in the case of circulatory shock. In general, failure to administer fluids rapidly and in sufficient quantity outweighs considerations about preservation of the line for future therapy.

Quantitative Resuscitation

Quantitative resuscitation (also called *goal-directed therapy, goal-oriented resuscitation,* or *hemodynamic optimization*) was first described in 1988 and refers to the practice of resuscitating patients to predefined physiologic endpoints indicating that systemic perfusion and vital organ function have been restored. Since that time, many studies have evaluated the efficacy of such a therapeutic approach to shock, and a meta-analysis of these studies confirms its benefit for reducing mortality.[24,25] For many years in the intensive care unit (ICU), physicians have relied on the use of the pulmonary artery catheter to help optimize left ventricular filling indices, but this practice is controversial. Several randomized controlled trials investigating the management of critically ill patients failed to demonstrate survival or length of stay benefit in patients managed with pulmonary artery catheters.[26-30] Insufficient data have been published to support the use or avoidance of pulmonary artery catheters in ED populations, but their significant complication rate, coupled with uncertain or no benefit, argues strongly against their routine use.

The *lactate clearance* refers to serial measurements of venous or arterial lactate and is calculated according to the following formula[31-33]:

$$[(\text{Lactate}_{\text{initial}} - \text{Lactate}_{\text{delayed}}) / \text{Lactate}_{\text{initial}}] \times 100$$

Lactate clearance has been shown to be equivalent to central venous oxygen saturation as an endpoint of early septic shock resuscitation.[34] Given the increasing use of point-of-care testing platforms in the ED and the fact that lactate clearance measurements can be done from peripheral venous blood, in many patients this may be a preferred endpoint of resuscitation. If the lactate concentration has not decreased by 10 to 20% 2 hours after resuscitation has begun, additional steps are undertaken to improve systemic perfusion. Resuscitation should continue until the lactate concentration drops below 2 mM/L.

Mixed venous oxygen saturation ($S\bar{v}O_2$) measurements reflect the balance between oxygen delivery and oxygen consumption. Previous studies have suggested that the $S\bar{v}O_2$ can be used as a surrogate for CI in targeting normalization of endpoints ($S\bar{v}O_2$ 65%, or CI 2.5-3.5 L/min/m^2) for therapeutic intervention in critically ill patients. Although $S\bar{v}O_2$ requires the use of a pulmonary artery catheter, the central venous oxygen saturation ($Scvo_2$) drawn from the central circulation has been shown to parallel the $S\bar{v}O_2$ when changes or trends in the values are tracked over time.

Quantitative resuscitation, which incorporates multiple indices of circulatory and oxygenation status, has been shown in meta-analyses to significantly reduce mortality and morbidity in ED patients with severe sepsis or septic shock when instituted as early in the disease course as is practical.[25] In such an approach, patients are resuscitated within the first 6 hours of care to achieve normalization of markers of preload (CVP) and perfusion (mean BP) and adequate oxygen delivery ($Scvo_2$ 70% or lactate clearance 10%) (Fig. 6-2). The most well-known quantitative resuscitation strategy, termed *early goal-directed therapy,* has also been found effective in smaller prospective before-and-after studies of patients with sepsis.[35-37] Three large multicenter validation studies of this resuscitation strategy in sepsis are underway.

Ventilation

Rapid sequence intubation is the preferred method of airway control in most patients with refractory shock (see Chapter 1). Intubation prevents aspiration, increases oxygenation, treats acute respiratory failure, provides initial treatment for metabolic or hypercarbic acidemia, and protects the patient who will be sent to an uncontrolled environment (e.g., for tests). Intubation also reduces the work of breathing, which, in the patient with hypoperfusion, further exacerbates lactic acidemia. Strenuous use of accessory respiratory muscles can increase oxygen consumption by 50 to 100% and decrease cerebral blood flow by 50%. More important, if the patient has increased airway resistance (e.g., bronchospasm with anaphylaxis) or a decrease in lung compliance (e.g., pulmonary edema, ARDS), a more negative intrathoracic pressure must be generated to fill the lungs with each inspiration. The greater suction effect is also exerted on the left ventricle, impeding its ability to eject and increasing functional afterload. Positive-pressure ventilation removes this impedance and can improve ventricular function and cardiac output up to 30%.

Volume Replacement

The goal in volume replacement is slightly elevated left ventricular end-diastolic volume, which is a difficult measurement to make in

www.ketabpezeshki.com 66485457-66963820

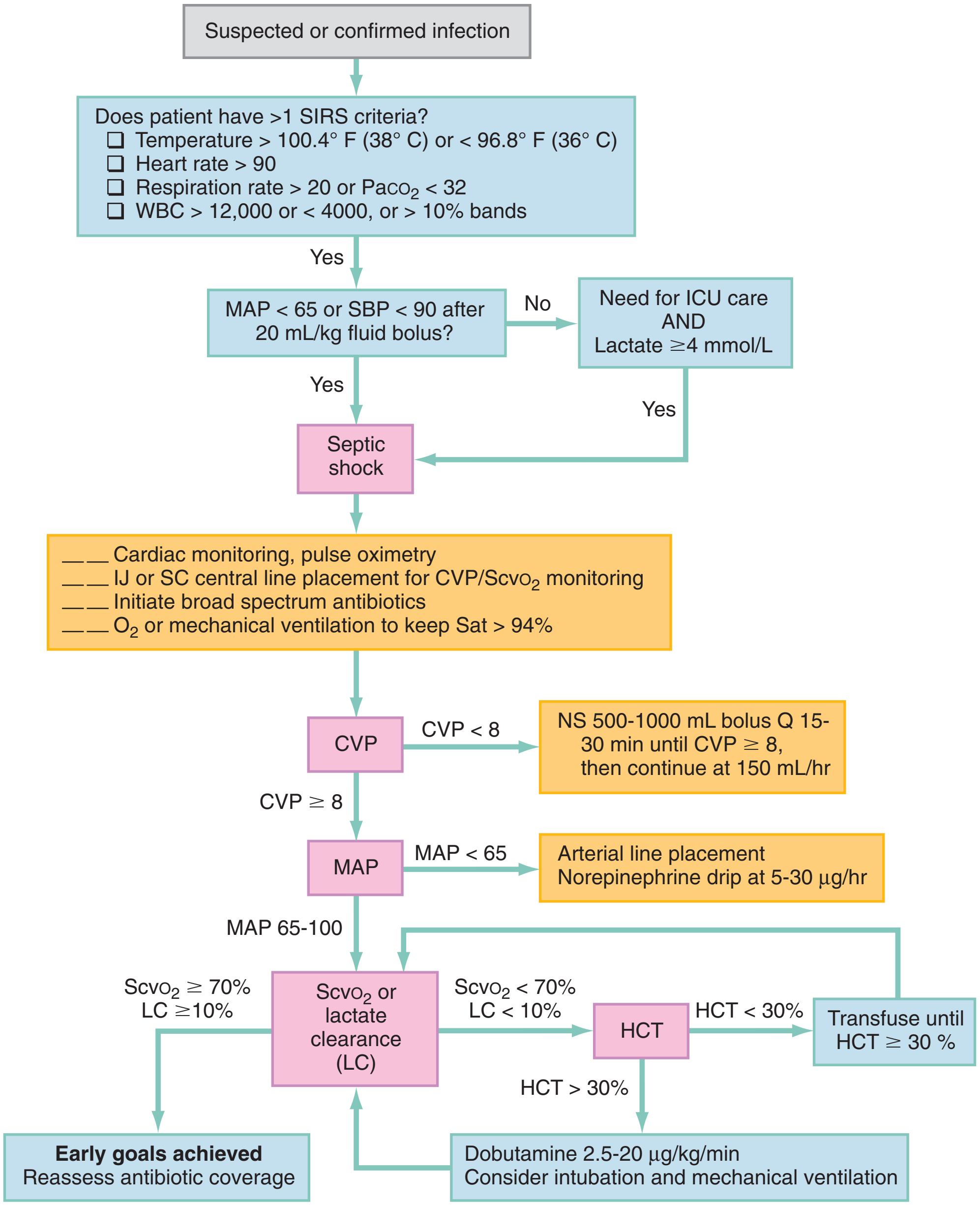


Figure 6-2. Flow diagram outlining the protocol for quantitative resuscitation in treatment of patients with severe sepsis or septic shock. This protocol outlines specific hemodynamic and physiologic parameters the clinician should seek to achieve within the first 6 hours of care. This protocol is focused on resuscitation and should be used in conjunction with standard clinical care for patients with suspected infection, such as appropriate diagnostic studies to determine the focus of infection and appropriate antimicrobial agents to treat the infection. *CVP,* central venous pressure; *HCT,* hematocrit; *ICU,* intensive care unit; *IJ,* internal jugular; *MAP,* mean arterial pressure; *NS,* normal saline; *$Paco_2$*, partial pressure of carbon dioxide, arterial; *Sat,* peripheral oxygen saturation; *SBP,* systolic blood pressure; *SC,* subclavian; *$Scvo_2$*, central venous oxygen saturation; *SIRS,* systemic inflammatory response syndrome; *WBC,* white blood cell count.

the ED. The CVP is most often used to estimate right ventricular filling pressure and is used in some quantitative resuscitation algorithms. Because both ventricles tend to stiffen during shock, a high CVP (10-15 cm H_2O) is often needed to produce adequate filling volume. CVP measurement does not accurately reflect left ventricular end-diastolic volume, and a recent systematic review demonstrated the inability of CVP to predict the hemodynamic response to a fluid challenge.[38] Thus, a presumed adequate CVP should be substantiated by increases in urine output and BP and decreasing lactate concentrations. Emerging literature suggests that the use of dynamic variables of fluid responsiveness that can be measured from an arterial line (such as stroke volume variation or stroke volume index) are superior to static variables (e.g., CVP), but their use in the ED has not been studied.[23]

Treating Specific Causes

Box 6-5 presents the general treatment approach for the three common causes of shock.

Hemorrhagic Shock

Standard treatment for hemorrhagic shock historically consisted of rapidly infusing several liters of isotonic crystalloid in adults or three successive 20-mL/kg boluses in children. Recent studies have endorsed the concept of either delayed resuscitation or hypotensive resuscitation for hemorrhagic shock. This is discussed in Chapters 36, 45, and 46. Controlling hemorrhage remains the cornerstone of treating hemorrhagic shock, and evidence

www.ketabpezeshki.com 66485457-66963820

Box 6-5 Clinical Management Guidelines for Three Common Causes of Shock

Hemorrhagic Shock
- Ensure adequate ventilation and oxygenation.
- Provide immediate control of hemorrhage, when possible (e.g., traction for long bone fractures, direct pressure).
- Initiate judicious infusion of isotonic crystalloid solution (10-20 mL/kg).
- With evidence of poor organ perfusion and 30-minute anticipated delay to hemorrhage control, begin packed red blood cell (PRBC) infusion (5-10 mL/kg).
- With suspected central nervous system trauma or Glasgow Coma Scale score <9, immediate PRBC transfusion may be preferable as initial resuscitation fluid.
- Treat coincident dysrhythmias (e.g., atrial fibrillation with synchronized cardioversion).

Cardiogenic Shock
- Ameliorate increased work of breathing; provide oxygen and positive end-expiratory pressure (PEEP) for pulmonary edema.
- Begin vasopressor or inotropic support; norepinephrine (0.5 µg/min) and dobutamine (5 µg/kg/min) are common empirical agents.
- Seek to reverse the insult (e.g., initiate thrombolysis, arrange percutaneous transluminal angioplasty).
- Consider intra-aortic balloon pump counterpulsation for refractory shock.

Septic Shock
- Ensure adequate oxygenation; remove work of breathing.
- Administer 20 mL of crystalloid per kilogram or 5 mL of colloid per kilogram, and titrate infusion to adequate central venous pressure and urine output.
- Begin antimicrobial therapy; attempt surgical drainage or débridement.
- Begin PRBC infusion for hemoglobin <8 g/dL.
- If volume restoration fails to improve organ perfusion, begin vasopressor support; initial choice includes dopamine, infused at 5-15 µg/kg/min, or norepinephrine, infused at 0.5 µg/min.

continues to support immediate surgery when direct vascular control cannot otherwise be obtained (see Chapters 36 and 46).

Colloids, including albumin and hydroxyethyl hetastarch (Hespan), can be used as well, but at considerable increase in cost and without effect on morbidity or mortality.[39] Colloids offer the theoretic advantage of a high osmotic pressure, which should help to maintain a normal intravascular volume after retransfusion from hemorrhage. A recent large multicenter trial conducted in the prehospital setting found that initial resuscitation fluid treatment with hypertonic saline or hypertonic saline and dextran, compared with normal saline, did not result in superior 28-day survival.[40] If criteria for shock persist despite crystalloid infusion (see Box 6-2), packed red blood cells (PRBCs) should be infused (1-2 units in adults or 5-10 mL/kg in children). Type-specific blood should be used when the clinical scenario permits, but uncrossmatched blood should be immediately used for patients with arterial hypotension and uncontrolled hemorrhage. O-negative blood is used in women of childbearing age and O-positive blood in all others (see Chapter 7). Substantial evidence supports the use of leukodepleted blood, which has been filtered to remove donor neutrophils. Leukodepleted blood is used in countries outside the United States because it produces less retransfusion-related organ damage.

The infusion of hemoglobin-based blood substitutes (HBBSs) as alternatives to PRBCs for resuscitation of hemorrhagic shock has been extensively studied. A recent meta-analysis that included 16 trials involving five different HBBSs in various populations showed that the use of HBBS is associated with significant increased risk of death and myocardial infarction.[41] Other artificial hemoglobin substitutes may be available in the future but at present show no benefit, and possibly harm, compared with PRBCs.

Septic Shock

Septic shock begins as an infectious nidus, which triggers a domino effect of cellular, microvascular, hematologic, and cardiovascular dysfunction. Treatment begins by establishing adequate ventilation to correct hypoxia and acidosis and to reduce systemic oxygen consumption and left ventricular work. This often requires endotracheal intubation and sedation for mechanical ventilation. The controversy regarding the use of etomidate in patients with septic shock is discussed in Chapter 1.

The second goal is to achieve adequate ventricular filling. The choice of fluids in treating septic shock is probably less important than scrupulous monitoring for adequate tissue perfusion. However, choices for fluid resuscitation should involve consideration of availability and the cost-benefit ratio. Initial volume replacement should include rapid infusion of 20 to 25 mL of crystalloid per kilogram. If hypoperfusion is persistent, 5- to 10-mL/kg boluses of a natural colloid (such as albumin) should be considered. Pending the results of current shock studies, blood should be transfused in the ED to restore hematocrit to 30%.

The third directive is to eradicate the infection with antimicrobial therapy and, where necessary, surgical drainage. The choice of antimicrobial agent can be directed by clinician experience and institutional minimal inhibitory concentration (MIC) data. Antimicrobials should be administered as soon as is practicable in a patient with septic shock. Evidence is scant, but it is intuitively appealing to administer antimicrobial medication at the earliest reasonable time.[42-44] One recent large observational study found that about 60% of patients with septic shock received antibiotics within 3 hours of ED triage, which might be a reasonable target, depending on the patient's presentation.[45] When no focus can be found in septic shock, a semisynthetic penicillin with a β-lactamase inhibitor, in combination with an aminoglycoside plus vancomycin, is a rational empirical choice. When neutropenia is suspected in a patient with sepsis syndrome, the progression to refractory, fatal septic shock can be cataclysmic. Neutropenia should be suspected in patients who have recently undergone chemotherapy. Chemotherapy patients with sepsis represent a special challenge because the pathophysiology may be complicated by anemia, thrombocytopenia, dehydration from vomiting, and the effect of adjunctive steroid therapy. Chemotherapy patients often have indwelling catheters, which predispose them to more unusual causes of sepsis, including gram-positive bacteria and fungi (see Chapter 138).[46]

Septic shock refractory to volume restoration (urine output or BP remains low; lactate increases) requires vasopressor support. The primary goal of vasopressor support is to increase cardiac output and oxygen delivery to vital organs. Several recent randomized trials and a meta-analysis have suggested that norepinephrine (0.5-30 µg/min) is associated with improved efficacy and lower rates of adverse effects, making norepinephrine the vasopressor of choice for correction of hypotension in septic shock.[47-49] Dobutamine may also be used with norepinephrine to increase cardiac output and maintain adequate oxygen delivery. A recent multicenter randomized controlled trial of 330 subjects reported that in cases in which simultaneous BP and inotropic support were necessary, there was not a difference in safety or efficacy between epinephrine (0.2 µg/kg/min starting dose) alone and norepinephrine plus dobutamine.[50]

The use of corticosteroids in the treatment of sepsis and septic shock has been investigated with mixed results. The results of two large randomized controlled trials confirm that there is no role for

www.ketabpezeshki.com 66485457-66963820

high-dose, short-course corticosteroid therapy in septic shock. Recently, two large multicenter randomized trials of low-dose hydrocortisone treatment failed to show survival benefit among all patients with septic shock.[51,52] Use of low-dose hydrocortisone among patients who did not adequately respond to a corticotropin stimulation test was supported by one small study but refuted by a larger one.[51,52] A recent meta-analysis suggested a modest 28-day mortality benefit of low-dose, short-course hydrocortisone treatment in septic shock.[53] Most current guidelines recommend that low-dose hydrocortisone be administered only to patients receiving chronic steroid replacement and in patients with refractory shock despite adequate fluid and vasopressor support. Even this use is only marginally supported, if at all, by scientific evidence. Corticotropin stimulation testing is no longer considered of value.[54]

Cardiogenic Shock

The immediate treatment of cardiogenic shock focuses on improving myocardial contractility and pump function. Cardiogenic shock is traditionally defined as the combination of systemic signs of hypoperfusion with arterial systolic BP less than 90 mm Hg. If work of breathing is tiring the patient, if severe pulmonary edema is causing significant hypoxemia, or if respiratory failure is imminent, intubation and mechanical ventilation should be initiated, followed by emergent treatment of bradydysrhythmias or tachydysrhythmias and inotropic support. Etomidate and ketamine have the least risk for hemodynamic compromise and should be used (but in reduced doses) for intubation, accompanied by a full dose of succinylcholine. Before administration of vasoactive medications, if hypovolemia is present, it should be corrected by infusion of crystalloid or blood products. Vasopressor or inotropic agents improve myocardial contractility and arteriolar tone. The choice of which agent to use depends on signs and symptoms and the systolic blood pressure (SBP). If the SBP is below 100 mm Hg and signs and symptoms of shock are present, norepinephrine is the agent of choice. However, if the SBP is 70 to 100 mm Hg and there are no signs or symptoms of shock, dobutamine is the agent of choice.[2,49] All of these agents should be started at the same doses as used for septic shock.

When pharmacologic support fails to improve indices of perfusion, the next step is to initiate intra-aortic balloon pump counterpulsation (IABPC). This requires the facilities and personnel of a high-level ICU or critical care unit (CCU). Controlled trials have shown IABPC to improve short-term survival, improve post-thrombolytic patency rates, and reduce stroke morbidity. IABPC increases cardiac output by a mean of 30% in refractory cardiogenic shock and can prolong survival until interventional procedures can be performed. IABPC may be contraindicated in patients with aortic insufficiency or severe peripheral vascular disease.

The dismal outcome of cardiogenic shock complicating acute myocardial infarction (MI) has been improved in recent years. Evidence suggests that emergent revascularization is not superior to medical management in reducing short-term mortality; however, significant improvements in mortality are seen at both 6 months and 1 year (see Chapter 81).[55] At present the management of acute MI with cardiogenic shock proceeds as follows, and this constitutes optimal therapy: (1) ensure adequate ventilation and oxygenation, (2) treat emergent dysrhythmias, (3) initiate vasopressor or inotropic support, (4) administer aspirin if the patient is not allergic, and (5) initiate heparin anticoagulation and arrangement for emergent percutaneous coronary intervention (PCI).

KEY CONCEPTS

- Circulatory shock can occur with normal arterial blood pressure, and not all patients with arterial hypotension have circulatory shock.
- A base deficit more negative than –4 mEq/L or a serum lactate level greater than 4.0 mmol/L indicates the presence of widespread circulatory insufficiency in suspected shock.
- Urine output is a reliable index of vital organ perfusion in patients with suspected shock.
- Ill patients with tachycardia, a worsening base deficit, and low urine output should be diagnosed with circulatory shock.
- Use of defined physiologic endpoints to measure systemic perfusion during resuscitation (quantitative resuscitation) is a valuable approach to optimal resuscitation in ED patients with shock.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Angus D, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303-1310.
2. Topalian S, Ginsberg F, Parrillo JE: Cardiogenic shock. *Crit Care Med* 2008; 36:S66-S74.
3. Williams RS: Canaries in the coal mine: Mitochondrial DNA and vascular injury from reactive oxygen species. *Circ Res* 2000; 86:915-916.
4. Watts J, Kline J: Bench to bedside: The role of mitochondrial medicine in the pathogenesis and treatment of cellular injury. *Acad Emerg Med* 2003; 10:985-997.
5. Jones AE, Yiannibas V, Johnson CL, Kline JA: Emergency department hypotension predicts sudden unexpected in-hospital mortality: A prospective cohort study. *Chest* 2006; 130:941-946.
6. McDonough KH, Giaimo ME, Quinn M, Miller HI: Effects of blood resuscitation versus dextran resuscitation after hemorrhage on intrinsic myocardial function. *J Trauma* 2000; 48:1122-1127.
7. Liaudet L, Soriano FG, Szabo C: Biology of nitric oxide signaling. *Crit Care Med* 2000; 28:N37-N52.
8. Tatsumi T, et al: Cytokine-induced nitric oxide production inhibits mitochondrial energy production and impairs contractile function in rat cardiac myocytes. *J Am Coll Cardiol* 2000; 35:1338-1346.
9. Watts JA, Kline JA, Thornton LR, Grattam RM, Brar SS: Metabolic dysfunction and depletion of mitochondria in hearts of septic rats. *J Mol Cell Cardiol* 2004; 36:141-150.
10. Moore C, et al: Determination of left ventricular function by emergency physician echocardiography of hypotensive patients. *Acad Emerg Med* 2002; 9:186-193.
11. Porter JM, Ivatury RR: In search of the optimal end points of resuscitation in trauma patients: A review. *J Trauma* 1998; 44:908-914.
12. Shapiro NI, et al: Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med* 2005; 45:524-528.
13. Jones A, et al: Nontraumatic out-of-hospital hypotension predicts in-hospital mortality. *Ann Emerg Med* 2004; 43:106-113.
14. Shapiro N, et al: Isolated prehospital hypotension after traumatic injuries: A predictor of mortality? *J Emerg Med* 2002; 25:175-179.
15. Middleton P, Kelly AM, Brown J, Robertson M: Agreement between arterial and central venous values for pH, bicarbonate, base excess, and lactate. *Emerg Med J* 2006; 23:622-624.
16. Lavery RF, et al: The utility of venous lactate to triage injured patients in the trauma center. *J Am Coll Surg* 2000; 190:656-664.
17. Jones AE, Leonard MM, Hernandez-Nino J, Kline JA: Determination of the effect of in vitro time, temperature, and tourniquet use on whole blood venous point-of-care lactate concentrations. *Acad Emerg Med* 2007; 14:587-591.
18. Bahner D: Trinity: A hypotensive ultrasound protocol. *J Diagn Med Sonogr* 2002; 18:193-198.
19. Jones A, Tayal V, Sullivan D, Kline J: Randomized controlled trial of immediate versus delayed goal-directed ultrasound to identify the cause of nontraumatic hypotension in emergency department patients. *Crit Care Med* 2004; 32:1703-1708.
20. Jones AE, Craddock PA, Tayal VS, Kline JA: Diagnostic accuracy of left ventricular function for identifying sepsis among emergency department patients with nontraumatic symptomatic undifferentiated hypotension. *Shock* 2005; 24:513-517.
21. Levy MM, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31:1250-1256.
22. Jones AE, Puskarich MA: Sepsis-induced tissue hypoperfusion. *Crit Care Nurs Clin North Am* 2011; 23:115-125.
23. Benington S, Ferris P, Nirmalan M: Emerging trends in minimally invasive haemodynamic monitoring and optimization of fluid therapy. *Eur J Anaesthesiol* 2009; 26:893-905.
24. Kern JW, Shoemaker WC: Meta-analysis of hemodynamic optimization in high-risk patients. *Crit Care Med* 2002; 30:1686-1692.
25. Jones AE, et al: The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: A meta-analysis. *Crit Care Med* 2008; 36:2734-2739.
26. Rhodes A, Cusack RJ, Newman PJ, Grounds RM, Bennett ED: A randomized, controlled trial of the pulmonary artery catheter in critically ill patients. *Intensive Care Med* 2002; 28:256-264.
27. Richard C, et al: Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2003; 290:2713-2720.
28. Harvey S, et al: Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): A randomized controlled trial. *Lancet* 2005; 366:472-477.
29. Binanay C, et al: Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: The ESCAPE trial. *JAMA* 2005; 294:1625-1633.
30. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, et al: Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med* 2006; 354:2213-2224.
31. Abramson D, et al: Lactate clearance and survival following injury. *J Trauma* 1993; 35:584-588.
32. Nguyen H, et al: Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med* 2004; 32:1637-1642.
33. Arnold RC, et al: Multi-center study of early lactate clearance as a determinant of survival in patients with presumed sepsis. *Shock* 2009; 32:36-39.
34. Jones AE, et al: Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: A randomized clinical trial. *JAMA* 2010; 303:739-746.
35. Rivers E, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New Engl J Med* 2001; 345:1368-1377.
36. Jones AE, Focht A, Horton JM, Kline JA: Prospective external validation of the clinical effectiveness of an emergency department-based early goal directed therapy protocol for severe sepsis and septic shock. *Chest* 2007; 132:425-432.
37. Micek ST, et al: Before-after study of a standardized hospital order set for the management of septic shock. *Crit Care Med* 2006; 34:2707-2713.
38. Marik PE, Baram M, Vahid B: Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest* 2008; 134:172-178.
39. Finfer S, et al: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350:2247-2256.
40. Bulger EM, et al: Out-of-hospital hypertonic resuscitation after traumatic hypovolemic shock: A randomized, placebo controlled trial. *Ann Surg* 2011; 253:431-441.
41. Natanson C, Kern SJ, Lurie P, Banks SM, Wolfe SM: Cell-free hemoglobin-based blood substitutes and risk of myocardial infarction and death: A meta-analysis. *JAMA* 2008; 299:2304-2312.
42. Puskarich MA, et al: Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol. *Crit Care Med* 2011; 39:2066-2071.
43. Kumar A, et al: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34:1589-1596.
44. Gaieski DF, et al: Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med* 2010; 38:1045-1053.
45. Levy MM, et al: The Surviving Sepsis Campaign: Results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med* 2010; 38:367-374.
46. Sarkodee-Adoo CB, Merz WG, Karp JE: Management of infections in patients with acute leukemia. *Oncology (Williston Park)* 2000; 14:659-666.
47. Vasu TS, et al: Norephinephrine or dopamine for septic shock: Systematic review of randomized clinical trials. *J Intensive Care Med* 2012; 27:172-178.
48. Patel GP, et al: Efficacy and safety of dopamine versus norepinephrine in the management of septic shock. *Shock* 2010; 33:375-380.
49. De Backer D, et al: Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010; 362:779-789.
50. Annane D, et al: Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: A randomized trial. *Lancet* 2007; 370:676-684.
51. Sprung CL, et al: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358:111-124.
52. Annane D, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862-871.
53. Annane D, et al: Corticosteroids in the treatment of severe sepsis and septic shock in adults: A systematic review. *JAMA* 2009; 301:2362-2375.
54. Dellinger RP, et al: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36:296-327.
55. Hochman JS, Sleeper LA, White HD, Dzavik V: One-year survival following early revascularization for cardiogenic shock. *JAMA* 2001; 285:190-192.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 7

BLOOD AND BLOOD COMPONENTS

Matthew Emery

PERSPECTIVE

The modern blood transfusion era began with discovery of the ABO red cell antigen system in the early 1900s. It was soon found that adding citrate enabled the storage of anticoagulated blood. Blood banking in the United States began during the 1930s. Energetic pioneers, such as John Lundy of the Mayo Clinic, gained a wealth of clinical experience, prompting dissemination of expert-based advice, such as Lundy's recommendation that blood transfusion was appropriate when a patient's hemoglobin (Hgb) was less than 10 g/dL or when a patient lost more than 15% of circulating blood volume. These recommendations were not, however, based on rigorous controlled trials. Rapid expansion of blood banking occurred after World War II, and in subsequent decades, research focused on such critical issues as prolonging the storage life of blood products, component therapy, and reducing the risk of transfusion reactions and transfusion-related infections.[1,2]

More recently, at a time when more than 14 million units of packed red blood cells (PRBCs) are transfused yearly in the United States, research has increasingly focused on developing a more evidence-based approach to identification of appropriate transfusion triggers for all blood components, developing massive transfusion protocols, and reassessing the overall risks and benefits of transfusion.[3-10]

PATHOPHYSIOLOGIC PRINCIPLES

Blood Banking[11]

Although traditional allogenic donation methods still predominate, increasing use is being made of red cell apheresis technology (about 10% of all units donated), by which red cells are separated from the blood at the time of collection, with everything else returned to circulation. This allows collection of about two transfusable units during a single donation. Autologous blood collection, in which the donor is also the intended recipient, peaked in the early 1990s and continues to decline.[11]

Red blood cell (RBC) storage methods aim to ensure viability of at least 75% of the cells 24 hours after infusion.[12] Blood collection bags contain an anticoagulant preservative of citrate, phosphate, dextrose, and adenine (CPDA-1), ensuring a shelf life of 35 days and hematocrit of 70 to 80% for PRBCs. Additive solutions (Adsol, Nutricel, Optisol) provide additional nutrients, extending maximum storage to 42 days and lowering viscosity, which makes infusion easier.[13]

Storage, however, impairs red cell function.[14] Stored blood initially delivers oxygen to the tissues less efficiently. Although PRBCs are maintained at 1 to 6° C, cell metabolism continues, and changes occur. These changes are collectively referred to as the "storage lesion."[14] Documented alterations are numerous and include a decrease in both pH and the level of 2,3-diphosphoglycerate (2,3-DPG). In addition, the deformability of stored RBCs changes over time, making them more spherical and rigid, increasing resistance to capillary flow. After infusion, however, many of these changes are readily reversed. The decrease in 2,3-DPG, for example, results in a left shift in the Hgb-oxygen dissociation curve, but 2,3-DPG levels begin to recover within minutes and are fully restored within 24 hours.[15] Further complicating the issue, the relationship between overall oxygen transport and oxygen delivery to tissues is complex. Depletion of *S*-nitrosohemoglobin during storage, for example, alters oxygen-dependent regulation of microcirculatory blood flow ("hypoxic vasodilation").[16] Research and debate are ongoing with regard to whether and when these and other changes are clinically significant, and how they might be addressed.[17-20]

Additional well-established changes in stored blood include cell leakage of potassium, although the amount (approximately 6 mEq/U) is readily tolerated by most otherwise healthy patients. PRBCs contain essentially no functional platelets or granulocytes.[21]

Blood Typing

The appropriate ordering of blood bank products and services is facilitated by a basic understanding of compatibility testing, which identifies clinically significant blood antigens and antibodies.

When a clinician anticipates that transfusion might be indicated, a type and screen is often ordered. A blood specimen from the patient is then sent for the following tests: ABO grouping, Rh typing, and an antibody screen for unexpected antibodies (non-ABO/Rh antibodies). Completion of these steps speeds the delivery of crossmatched blood if it is subsequently required.

Identified RBC antigens include the ABO and related carbohydrate antigens (H, P, I, and Lewis), the 48 Rh system antigens, and more than 200 non-ABO/Rh antigens. ABO incompatibility results in acute hemolysis, the most serious transfusion reaction.

ABO grouping requires that the recipient's red cells be tested with anti-A and anti-B serum and that his or her serum be tested with A and B red cells. At about 6 months of age, patients form antibodies against the A and B antigens they lack. Those with type AB blood form no ABO group antibodies. Patients with type O have antibodies against both. The major clinically significant Rh antigen is the D antigen. Rh typing is usually done by adding a commercial reagent (anti-D) to recipient RBCs.[12]

The antibody screen identifies unexpected antibodies in the patient's serum. These result from prior exposure to foreign RBC antigens during allogenic transfusion or pregnancy. The antibody screen entails mixing commercial RBC reagents (mixtures of red

www.ketabpezeshki.com 66485457-66963820

cells expressing clinically significant antigens) with the patient's serum. The incidence of these unexpected antibodies in the general population is low (<1-2%), but a positive screen prompts further compatibility testing, which can take hours to days. When transfusion is delayed by a positive antibody screen in a critically ill patient, clinicians should communicate directly with the blood bank to determine the best course of action. Although ABO compatibility is mandatory in all patients, non-ABO antigens are very unlikely to cause immediate intravascular hemolysis.[15,21,22] Administering blood that is not completely crossmatched is therefore an option if the need is emergent.

The type and screen allows for quicker selection of appropriate banked blood for complete crossmatch if a transfusion is later ordered.

When a unit of blood is ordered for transfusion, a crossmatch is done. In an ideal situation, blood identical to the patient's own ABO and Rh group is used. Local blood supplies, however, might dictate that a nonidentical but compatible unit be used. Patients with blood group AB (who lack anti-A and anti-B antigens), for example, are "universal recipients"—they can receive blood from any of the ABO groups. Type O blood (lacking the A and B antigens), also known as "universal donor" blood, conversely, can be given to anyone. Rh compatibility is also important. Rh sensitization can occur in Rh-negative patients exposed to Rh-positive blood, and this sensitization in turn can result in hemolytic disease of the newborn with subsequent pregnancies.

The traditional crossmatch requires mixing recipient serum with donor RBCs and observing for agglutination as a final compatibility test before transfusion. If the antibody screen is negative, an "immediate spin crossmatch" at room temperature serves as a final check for ABO incompatibility. A "complete crossmatch" is generally done before transfusion if the antibody screen is positive. This requires incubation to 37° C and the addition of antihuman globulin (Coombs' reagent) to promote agglutination.[13] Many blood banks also substitute a "computer crossmatch" for patients whose blood has been tested at least twice within their system. Decisions about which method is used, however, are generally made by the blood bank, not the clinician.

Special Clinical Circumstances

To select the most appropriate blood products in the emergency setting, clinicians should consider the patient's hemodynamic stability, the likelihood of ongoing hemorrhage, and the amount of time available to intervene. When time is short, waiting for fully crossmatched blood may result in a dangerous delay, and alternatives should be considered. When the clinician anticipates large and ongoing blood losses, complications resulting from massive transfusion are a concern as well.

Administering Blood before Completion of Compatibility Testing

Full compatibility testing takes time. An antibody screen and immediate spin crossmatch at a minimum take approximately 45 to 60 minutes. This assumes a negative antibody screen followed by an immediate spin crossmatch performed at room temperature. If the antibody screen is positive, the antibody is identified via more elaborate procedures, and a complete crossmatch (using a Coombs test with incubated serum) is required. This process can take up to several hours (or even days),[21] an unacceptable delay in some emergent situations.

Universal (group O) blood is used when RBCs are needed in hemorrhaging, unstable patients before any testing can be done.[23,24] Female patients receive O-negative blood to prevent hemolytic disease of the newborn unless there is no chance of subsequent pregnancy. All others receive O-positive blood, because even if sensitization occurs, Rh antibodies generally do not fix complement and therefore would be unlikely to cause an acute intravascular hemolytic reaction in the unlikely event that an Rh-negative recipient twice received emergent transfusion of Rh-positive blood. Conversely, the "universal" type for fresh frozen plasma (FFP) is type AB, which contains no antibodies to either A or B antigens.

Type-specific blood (with ABO and Rh testing) can generally be made available within 15 minutes of receiving a sample of the patient's blood.

Massive Transfusion

Massive transfusion has no formal definition. Administration of at least 10 units of RBCs in 24 hours is a commonly used cutoff.[25] Although patients receiving any amount of blood are susceptible to a variety of infectious, physiologic, and immunologic insults, this section will discuss those uniquely associated with massive transfusion.

Some of these complications are well understood and easily managed. Hypothermia is common in these patients, and can reduce clotting factor activity.[26] Warmed intravenous fluids, blood warmers, and warming lights and blankets are often needed. Frequent laboratory testing will identify electrolyte disturbances (low magnesium and calcium, and both high and low potassium), which are in general treated in a standard fashion by replenishing deficits, or administering calcium for hyperkalemia. Acidosis is a common finding with massive hemorrhage but can also be caused by hypoperfusion, and the contribution of transfused blood to acidosis is felt to be variable. Citrate from banked blood, for example, is metabolized in the liver to bicarbonate, which can sometimes result in metabolic alkalosis. With rapid infusion or reduced hepatic function, however, this pathway can be overwhelmed, and the net effect of infusing large amounts of citrate can be worsening metabolic acidosis. A rational response to metabolic acidosis is to optimize oxygen delivery and ventilation. Administering sodium bicarbonate may be considered in severe cases, but the benefits are less certain.[27]

Patients receiving massive transfusion are also prone to coagulopathy and thrombocytopenia. Consumption and dilution of clotting factors and platelets occur in these patients owing to ongoing hemorrhage, fluid boluses, and transfusion of PRBCs. This undoubtedly plays a role in the coagulopathy of trauma, but recent research asserts that coagulopathy often occurs in massive trauma even before these mechanisms have taken effect.[28-30] A number of reports (none of them from randomized prospective trials) have stated that a more proactive approach to administering plasma and platelets in massive transfusion is associated with better outcomes.[31-43] In response, many institutions have adopted massive transfusion protocols that call for plasma (and often platelets) to be given in a 1:1 ratio with RBCs.[44] When set ratios are not used, clinical assessment and judgment often augment laboratory values such as international normalized ratio (INR), partial thromboplastin time (PTT), and fibrinogen and platelet counts because there is no direct evidence supporting any particular threshold for platelet or coagulation factor replacement in patients with severe hemorrhage.[7] Commonly recommended goals in this setting would be to consider maintaining an INR below 1.5, a fibrinogen level greater than 1 to 2 g/L, and platelet count above 50,000 to 100,000/µL.[7,45]

Administration

Legal Aspects[12]

Before a blood product can be infused, two qualified personnel check it at the bedside to prevent a potentially fatal clerical error.

www.ketabpezeshki.com 66485457-66963820

This check includes recipient and unit identification, as well as confirmation of compatibility, and the expiration date.

If typed and crossmatched blood arrives with the patient from a transferring facility, it is important that the temperature be maintained between 1 and 10° C during transport. If the blood is not used right away and the blood bank is asked to hold the blood for the patient, it is processed and crossmatched as for other issued blood and quarantined for 24 hours. It can be sent back to the blood bank to have this done only if (1) it has been constantly maintained at a temperature between 1 and 10° C, (2) all container seals are intact, and (3) tubing segments have remained attached to the blood container.

Infusion Adjuncts

Urgent transfusion situations require flow rates faster than gravity can provide. An administration set with an in-line pump that is squeezed by hand is the simplest method to speed infusion. Pressure bags are also available that completely encase the blood bag and apply pressure evenly. With high-pressure infusion, large-bore needles are recommended so that hemolysis is prevented.

If only a small-gauge needle is available, the transfusion may be diluted with normal saline, but this may cause unwanted volume expansion. In elective transfusions, no significant hemolysis occurs when small-gauge needles are used if the maximum rate of infusion is less than 100 mL/hr.

MANAGEMENT

Decision-Making

In considering the use of blood component therapy, the patient's age, severity of symptoms, cause of the deficit, underlying medical condition, ability to compensate for decreased oxygen-carrying capacity, and tissue oxygen requirements are all important. Clinical evaluation, including appearance (pallor, diaphoresis), mentation (alert, confused), heart rate, blood pressure, and the nature of the bleeding (active, controlled, uncontrolled), can be supplemented by laboratory evaluation.

A review of relevant literature supports the recent trend toward more conservative red cell transfusion triggers but also highlights the need for further investigation.[46] The same can be said for FFP and other blood components.[47,48] Benefits of transfusion have been difficult to prove,[9] and the list of known and suspected associated risks is long and growing.[49]

Whole Blood

Intriguing reports on the use of fresh whole blood in military field hospitals have been published,[50,51] but in civilian practice in the United States, it is generally unavailable and rarely used.

Packed Red Blood Cells

PRBCs are indicated only to improve oxygen delivery to tissues at the microvascular level and thus improve intracellular oxygen consumption. It bears repeating that demonstration of the efficacy of red cells for this purpose (or improved clinical outcomes) has proven elusive.[52-54] A definitive randomized prospective study in which RBCs are withheld completely from one treatment group is unlikely to be done at this point. For decades, transfusion of RBCs was guided by the so-called "10/30 rule": transfusion was indicated for an Hgb of less than 10 g/dL or a hematocrit of less than 30%. This practice is outdated. The largest published randomized trial in adult patients to date, the TRICC (Transfusion Requirements in Critical Care) trial, demonstrated that in the critical care setting, a transfusion threshold of 7 g/dL was as safe as a threshold of 10 g/dL.[55] In this trial there was some concern that a higher trigger was more appropriate in patients with coronary artery disease (CAD).[56] The FOCUS trial (Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair) addresses this specific population, and results support a restrictive 8 g/dL trigger for red cell transfusion in these patients as well.[57,58]

Absent further research, the recommendations of the American Society of Anesthesiologists seem reasonable: transfusion is rarely needed with an Hgb concentration greater than 10 g/dL and is usually needed when the Hgb is less than 6 g/dL. Patients with an Hgb of 6 to 10 mg/dL require careful clinical judgment. Guidelines published in 2009 by the Eastern Association for the Surgery of Trauma and the American College of Critical Care Medicine and based on a thorough review of the available evidence likewise support this conservative strategy, advocating a cutoff of Hgb below 7 g/dL for most stable patients.[3] Lastly, most emergency physicians would still transfuse any patient with ongoing severe hemorrhage and unstable vital signs despite adequate fluid resuscitation and would occasionally consider withholding transfusion for Hgb levels even lower than 6 g/dL in a young, healthy, asymptomatic patient at low risk for further bleeding. Another interesting area of investigation is the use physiologic transfusion triggers (such as lactate or mixed venous oxygen saturation), but further research is needed.[10]

Artificial Oxygen Carriers

Research into both Hgb-based oxygen carriers and perfluorocarbon emulsions is ongoing,[59,60] but as yet none are approved for general clinical use in the United States. Several problems remain unsolved. Hgb-based carriers, for example, have been found to cause vasoconstriction through nitric oxide (NO) scavenging, endothelin release, and peripheral alpha-adrenergic receptor sensitization. Perfluorocarbon emulsions require relatively high partial pressure of oxygen (Po_2) levels. When these emulsions are used clinically, pure oxygen is usually administered as well. It appears unlikely that artificial oxygen carriers will come into widespread emergency department (ED) use anytime soon.

Fresh Frozen Plasma

As noted previously, evidence from retrospective trials supports increased use of FFP in patients undergoing massive transfusion. This should not be generalized to all patients receiving transfusion, however. A retrospective case-control trial of 1716 transfused trauma patients receiving fewer than 10 units of blood found that administration of FFP was associated with no survival benefit, yet with a higher risk of complications, including acute respiratory distress syndrome (ARDS), pneumonia, sepsis, and multiple organ dysfunction.[43] As with RBCs, indications for FFP are based primarily on observational trials and expert opinion.[48,61] The following indications seem reasonable based on current evidence: coagulopathy of trauma, hemorrhaging patients with coagulopathy resulting from hepatic dysfunction or disseminated intravascular coagulation (DIC), plasma exchange for thrombotic thrombocytopenic purpura (TTP), and emergency reversal of a vitamin K antagonist in the presence of clinically significant hemorrhage.[61] Because of the volume of FFP needed to reverse coagulopathy caused by vitamin K antagonism (at least 10 mL/kg, and perhaps as much as 30 mL/kg),[62] however, some guidelines call for the use of prothrombin complex concentrate or recombinant factor VIIa instead, although neither is currently approved by the U.S. Food and Drug Administration (FDA) for this indication in the United States.[63] FFP is not indicated for volume expansion, nonurgent reversal of a vitamin K antagonist, or treatment for abnormal INR from any cause in the absence of bleeding.

www.ketabpezeshki.com 66485457-66963820

Likewise, limited available evidence fails to support the use of FFP in patients with an elevated INR before invasive procedures such as central line placement and lumbar puncture, although it is common practice to administer FFP for an INR greater than 1.5 to 2.0.[12,64] One problem has been that the INR often proves poorly predictive of clinical bleeding. Thromboelastography, an old technology attracting renewed interest, may prove useful in guiding coagulation therapy but is not now widely used in the ED setting.[65] A full description is beyond the scope of this chapter, but this test provides information on function of both platelets and coagulation factors (including fibrinogen).

If a specific factor deficiency is identified (e.g., hemophilia), targeted replacement of that factor, if available, is usually more practical.

Platelets

Platelet transfusion is indicated prophylactically when the count is less than 10,000/µL, and this includes a margin of safety, as it appears that hemostasis is well maintained even at counts of 5000/µL (a threshold sometimes used for stable, afebrile inpatients). Platelets are often given to adults in a dose of 6 units of platelet concentrate (a "six-pack" of platelets), which typically raises the platelet count about 40,000 to 60,000/µL. Once again, however, this practice is not evidence based.[66] Because hemostasis is maintained with platelet counts as low as 5000/µL, it seems likely that smaller, more frequent platelet transfusions should be equally efficacious, but more cost-effective, particularly in hospitalized patients. This practice is supported by a randomized trial that enrolled nearly 1300 patients undergoing prophylactic platelet transfusion, which demonstrated no increase in bleeding complications with use of a low, medium, or high dose of platelets (amounts corresponding to roughly 2, 4, or 6 units of platelet concentrate).[67] This may be impractical in outpatients, in whom increasing the frequency of transfusion can be more of a burden, and discussion with the patient's hematologist is often helpful. There are no large randomized trials on which to base recommendations for the use of prophylactic platelet transfusion before invasive bedside procedures such as lumbar puncture or central line placement. Retrospective data support the safety of performing lumbar puncture with platelet counts as low as 10,000/µL.[68,69] For central line placement, a platelet count of 20,000 to 30,000/µL is generally considered adequate, and for major surgery, a count of 50,000/µL is generally acceptable, although higher cutoffs (70,000-100,000/µL) are often used for neurosurgical and retinal procedures.[12,70] Another interesting consideration is whether a patient is anemic. Red cells tend to push platelets to the periphery of the vessel, where they are needed to patch endothelial disruptions. Patients with anemia appear more prone to bleeding.[71] Lastly, when thrombocytopenia results from immune-mediated platelet destruction caused by idiopathic thrombocytopenic purpura (ITP) or TTP, transfusion is generally ineffective. If, however, immune-mediated destruction is a result of human leukocyte antigen (HLA) sensitization from prior transfusions, then HLA-matched single-donor platelets collected with apheresis methods may be helpful.[13] Consultation with a hematologist is advisable in such cases.

Autotransfusion

Autotransfusion may be used in the emergency setting in the event of severe chest trauma. This strategy has numerous advantages: immediate availability, blood compatibility, elimination of donor-to-patient disease transmission, avoidance of the storage lesion, lower risk of circulatory overload, and fewer direct complications (e.g., hyperkalemia, hypothermia, hypocalcemia, and metabolic acidosis). It is also more acceptable to patients whose religious convictions prohibit transfusions.[72] It is impractical in some settings, however, because of the limited number of appropriate trauma patients, the training required to operate the equipment, and the time required for equipment setup.[73]

Therapeutic Modalities

Packed Red Blood Cells

In acute hemorrhage, PRBCs are used to supplement initial crystalloid replacement. In an average adult, 1 unit (450 mL) of PRBCs increases the Hgb by about 1 g/dL or the hematocrit by about 3%.[74] A similar increase in pediatric patients is obtained by administering 10 mL/kg. PRBCs are run through a filter with a large-bore intravenous line with normal saline. Lactated Ringer's solution can lead to clotting secondary to the added calcium, and hemolysis may result with a hypotonic solution. Medications should not be added to the unit or pushed through the transfusion line unless it has been thoroughly flushed. Most transfusions are given over 60 to 90 minutes (never longer than 4 hours). Unused blood should be returned promptly to the blood bank. Any units unrefrigerated for more than 30 minutes are discarded.[12]

Fresh Frozen Plasma

A unit of FFP contains all clotting factors and typically has a volume of 200 to 250 mL. It must be ABO compatible and is given through blood tubing. FFP can be used to replace the most labile components (factors V and VIII), but it is given within 24 hours of thawing. An alternative product, referred to as "thawed plasma," contains the vitamin K–dependent factors, which are stable for up to 5 days after thawing.[12] One unit of activity for any coagulation factor is equal to the clotting activity found in 1 mL of FFP. As noted previously, appropriate dosage is not well grounded in evidence from clinical trials. In massive transfusion, many centers now use FFP in a 1 : 1 ratio with red cells. For other indications it seems reasonable to start with infusions of 10 to 30 mL/kg, realizing that results will be somewhat unpredictable and follow-up laboratory and clinical assessment will be necessary.[12]

Platelets

Crossmatching is generally unnecessary, but Rh-negative patients are treated with Rh-negative platelets because there may be enough red cells in the platelet concentrate to cause Rh sensitization. In adults the traditional dose has been 4 to 6 units (a "six-pack" of platelets), and in children it is 1 U/10 kg body weight. As noted earlier, however, use of smaller, more frequent transfusions is considered in patients who are being admitted. In frequently transfused patients, it is often desirable to reduce HLA sensitization with leukoreduced platelets.[13] Once sensitization has occurred and patients have developed immune-mediated platelet refractoriness, a trial of single donor (apheresis) HLA-matched or crossmatched platelets may be considered in consultation with a hematologist.[13]

OUTCOMES

Adverse effects of RBC transfusion can be divided into immune-mediated and non–immune-mediated categories, as well as acute, delayed, and chronic effects.

Immune-Mediated Adverse Effects

Acute

Intravascular Hemolytic Transfusion Reaction. Intravascular hemolytic transfusion reaction is the most serious transfusion reaction.

www.ketabpezeshki.com 66485457-66963820

It is usually the result of ABO incompatibility, most often caused by clerical error. The resulting antigen-antibody reaction leads to the intravascular destruction of transfused red cells, producing hemoglobinemia and hemoglobinuria. The onset of symptoms is immediate and may include any of the following symptoms: fever, chills, headache, nausea, vomiting, a sensation of chest restriction, severe joint or low back pain, and a burning sensation at the site of the infusion. A feeling of impending doom is often mentioned.[21] Clinical effects can include hypotension, DIC, and acute tubular necrosis. Treatment includes stopping the transfusion immediately, replacing all old tubing with new, and initiating vigorous crystalloid fluid therapy. Diuretic therapy can also be used to maintain urine output at 1 to 2 mL/kg/hr. Some patients may require pressors. Blood and urine specimens are sent to the laboratory, as well as the remainder of the transfusion and the blood tubing. Detection of free Hgb (blood and urine) and a positive result of Coombs' test on post-transfusion, but not pretransfusion, specimens confirms the diagnosis.[21]

Febrile Transfusion Reaction. Febrile transfusion reaction is the most common and least serious transfusion reaction. It is defined as a 1° C or greater temperature elevation that occurs with transfusion and for which no other medical explanation is found. Reactions are believed to result from antileukocyte antibodies, most commonly as a result of prior transfusion. Treatment is symptomatic with analgesics, antipyretics, and antihistamines. The use of leukoreduced RBCs can help decrease, but not eliminate, the risk of this reaction.[15,21] If a febrile reaction occurs in a first-time transfusion, it should be treated in the same way as an extravascular hemolytic reaction until proven otherwise.

Allergic Reactions (Urticaria to Anaphylaxis). Urticaria, or hives, may occur during a transfusion without other signs or symptoms and with no serious sequelae. It is generally attributed to an allergic, antibody-mediated response to a donor's plasma proteins. The transfusion does not need to be stopped, and treatment with an antihistamine is usually sufficient. Consider prophylactic antihistamines in patients with a history of this reaction. Occasionally, full anaphylaxis may be caused by an anti–immunoglobulin A (IgA) reaction to IgA in the donor's blood components. The patient is likely to have a genetic IgA deficiency. Presentation is similar to anaphylactic reactions from other causes. Treatment is with epinephrine and corticosteroids. Use of washed RBCs, and plasma products from IgA-deficient individuals can be used to avoid recurrence with subsequent transfusions.[15]

Transfusion-Related Acute Lung Injury. Transfusion-related acute lung injury (TRALI) is now considered the leading cause of transfusion-related mortality.[12] It has been defined as new acute lung injury (ALI) resulting in bilateral pulmonary edema and hypoxemia (ratio of arterial oxygen concentration to fraction of inspired oxygen [PaO_2/FIO_2] ≤300, or oxygen saturation as measured by pulse oximetry <90% on room air) and occurring during or within 6 hours after a transfusion without temporal relationship to an alternative explanation for ALI. If an alternative explanation is also present, the diagnosis of possible TRALI is appropriate.[75] Implicated blood components include PRBCs, FFP, platelets, and cryoprecipitate. The initial clinical presentation is that of a noncardiogenic pulmonary edema, with dyspnea, hypoxemia, and bilateral infiltrates on chest radiograph. Fever, hypotension, and transient leukopenia may also be seen. The underlying pathophysiologic mechanism is a subject of continuing debate and could involve multiple insults.[76] Proposed theories include a reaction between transfused antibodies and leukocytes in the recipient, as well as the effects of biologically active factors that accumulate in stored blood, such as cytokines and lipids.[77] One strategy suggested for reducing TRALI has been to use only male donors for plasma in order to avoid allotypic leukocyte antibodies, which can occur in women as a result of prior pregnancies, or to screen for these antibodies and exclude donors when the antibodies are found.[78-80] Appropriate treatment consists of stopping the transfusion, notifying the blood bank, and providing respiratory support, which may include intubation and mechanical ventilation. It is safe to continue transfusion of blood products from a different donor, if necessary. Complete resolution is usually seen within 48 to 96 hours. Overall prognosis is better than would be expected with many other causes of ALI, with a reported mortality rate of 6% in one series.[81] Survivors rarely show long-term adverse effects.[81]

Delayed

Extravascular Hemolytic Transfusion Reaction. Extravascular hemolytic transfusion reactions result from a non–ABO-mediated immune reaction, most often caused by an anamnestic response in a patient previously sensitized to red cell antigens by transfusion, pregnancy, or transplant. This prior exposure may result in antibody levels that are too low to detect with the antibody screen. After repeat exposure from transfusion, however, antibody levels rise, and extravascular hemolysis occurs days to weeks later. Less commonly, primary alloimmunization can occur after transfusion. The patient may have fever, anemia, and jaundice. Symptoms are not usually severe, but rare cases of oliguria or DIC do occur. Because the hemolysis is extravascular, hemoglobinemia and hemoglobinuria are generally absent.[15]

Transfusion-Associated Graft-versus-Host Disease. A rare but life-threatening complication, transfusion-associated graft-versus-host disease results when transfused lymphocytes proliferate and attack the recipient. Mortality is greater than 90%. Cell-mediated immunodeficiency puts patients at risk, as does having an HLA type that is identical between donor and recipient (most often among first-degree relatives). Symptoms, which begin 3 to 30 days after transfusion, include fever, erythematous skin rash, diarrhea, elevated liver enzymes, and pancytopenia. The only effective treatment is bone marrow transplant, and most deaths result from coagulopathy or infection. Efforts are therefore directed at prevention by using gamma irradiation of all cellular components, which renders the donor lymphocytes incapable of proliferating. The use of leukocyte-poor components is also advocated. This condition should be kept in mind when transfusion is being considered for anemic leukemia or lymphoma patients, especially those who have recently received chemotherapy.[15]

Non–Immune-Mediated Adverse Effects

Acute

Circulatory Overload. Chronically anemic, normovolemic elderly patients are at greatest risk for developing congestive heart failure with the rapid infusion of blood. Transfusing more slowly (over a period of 4 hours) and administering diuretics are useful in preventing this complication.[15]

Bacterial Contamination. Bacterial contamination, most commonly with *Yersinia enterocolitica* (which grows well in cool, iron-rich environments), occurs in fewer than 1 per million units of stored RBCs but typically results in symptoms during the transfusion and carries a 60% mortality rate.[49] The risk of bacterial contamination is greater, however, with platelets, which are stored at a higher temperature; contamination occurs as frequently as 1 per 1000 to 2000 units.[49] During or after the transfusion, the patient may develop rigors, vomiting, abdominal cramps, fever, shock, renal failure, and DIC. If contamination is suspected, the transfusion should be stopped, blood cultures obtained from both the bag and the patient, and broad-spectrum antibiotics and hemodynamic support initiated.

www.ketabpezeshki.com 66485457-66963820

Chronic

Risk of Transfusion-Transmitted Viruses. Improved techniques for selecting and testing blood donors have dramatically reduced the risk of viral transmission of disease by transfusion. It is believed that the blood supply in the United States has never been safer.[49] Current estimates for the risk of acquiring hepatitis C and human immunodeficiency virus (HIV) infection from transfusion are 1 in 1,000,000 to 2,000,000.[82] The risk of hepatitis B infection, however, remains closer to 1 in 200,000 to 500,000.[83] Cytomegalovirus (CMV) can be transmitted by blood transfusion as well, but this risk can be decreased by leukoreduction. Those at risk include recipients of allogeneic stem cell or solid-organ transplantation and neonates. CMV-negative blood products should be considered in these patients.[83,84] West Nile virus briefly emerged as a risk, although one that varied considerably by geography and season.[49] Transfusion-related infection with West Nile virus, however, has been virtually eliminated by the use of system-wide nucleic acid amplification testing.[83]

The references for this chapter can be found online by accessing th accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Spiess BD: Red cell transfusions and guidelines: A work in progress. *Hematol Oncol Clin North Am* 2007; 21:185.
2. Rabbitts JA, Bacon DR, Nuttall GA: Mayo Clinic and the origins of bloodbanking. *Mayo Clin Proc* 2007; 82:111.
3. Napolitano LM, et al: Clinical practice guideline: Red blood cell transfusion in adult trauma and critical care. *Crit Care Med* 2009; 37:3124.
4. Roback JD, et al: Evidence-based practice guidelines for plasma transfusion. *Transfusion* 2010; 50:1227.
5. Slichter SJ: Evidence-based platelet transfusion guidelines. *Hematology Am Soc Hematol Educ Program* 2007:172-178.
6. Zielinski MD, Park MS, Jenkins D: Appropriate evidence-based practice guidelines for plasma transfusion would include a high ratio of plasma to red blood cells based on the available data. *Transfusion* 2010; 50:2762; author reply 2763.
7. Rossaint R, et al: Management of bleeding following major trauma: An updated European guideline. *Crit Care* 2010; 14:R52.
8. Cotton BA, et al: Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. *J Trauma* 2009; 66:41.
9. Marik PE, Corwin HL: Efficacy of red blood cell transfusion in the critically ill: A systematic review of the literature. *Crit Care Med* 2008; 36:2667.
10. Vallet B, Robin E, Lebuffe G: Venous oxygen saturation as a physiologic transfusion trigger. *Crit Care* 2010; 14:213.
11. Whitaker BI, et al: *The 2007 National Blood Collection and Utilization Survey Report*. Available at http://www.hhs.gov/ash/bloodsafety/2007nbcus_survey.pdf.
12. Roback JD, Combs MR, Grossman BJH, Hillyer CD, eds. *Technical Manual*, 16th ed. Bethesda, Md: AABB; 2008.
13. Cushing MM, Ness PM: *Principles of red blood cell transfusion*. In: Hoffman R, et al, eds. *Hematology: Basic Principles and Practice*, 5th ed. Philadelphia: Churchill Livingstone; 2008.
14. Rao SV, Califf RM: Is old blood bad blood? *Am Heart J* 2010; 159:710-712.
15. Harmening D: *Modern Blood Banking and Transfusion Practices*, 5th ed. Philadelphia: FA Davis; 2005.
16. Reynolds JD, et al: S-nitrosohemoglobin deficiency: A mechanism for loss of physiological activity in banked blood. *Proc Natl Acad Sci U S A* 2007; 104:17058.
17. Lelubre C, Piagnerelli M, Vincent JL: Association between duration of storage of transfused red blood cells and morbidity and mortality in adult patients: Myth or reality? *Transfusion* 2009; 49:1384.
18. Shander A, Javidroozi M: A reductionistic approach to aged blood. *Anesthesiology* 2010; 113:1.
19. Lall RN, et al: Phosphodiesterase inhibition attenuates stored blood-induced neutrophil activation: A novel adjunct to blood transfusion. *J Am Coll Surg* 2006; 202:10.
20. Ho J, Sibbald WJ, Chin-Yee IH: Effects of storage on efficacy of red cell transfusion: When is it not safe? *Crit Care Med* 2003; 31:S687.
21. Despotis GJ, Zhang L, Lublin DM: Transfusion risks and transfusion-related pro-inflammatory responses. *Hematol Oncol Clin North Am* 2007; 21:147.
22. Petz LD: "Least incompatible" units for transfusion in autoimmune hemolytic anemia: Should we eliminate this meaningless term? A commentary for clinicians and transfusion medicine professionals. *Transfusion* 2003; 43:1503.
23. Dutton RP, Shih D, Edelman BB, Hess J, Scalea TM: Safety of uncrossmatched type-O red cells for resuscitation from hemorrhagic shock. *J Trauma* 2005; 59:1445-1449.
24. Ball CG: Uncrossmatched blood transfusions for trauma patients in the emergency department: Incidence, outcomes and recommendations. *Can J Surg* 2011; 54:111-115.
25. Sihler KC, Napolitano LM: Massive transfusion: New insights. *Chest* 2009; 136:1654.
26. DeLoughery TG: Coagulation defects in trauma patients: Etiology, recognition, and therapy. *Crit Care Clin* 2004; 20:13-24.
27. Forsythe SM, Schmidt GA: Sodium bicarbonate for the treatment of lactic acidosis. *Chest* 2000; 117:260.
28. Brohi K: Trauma induced coagulopathy. *J R Army Med Corps* 2009; 155:320.
29. Frith D, Brohi K: The acute coagulopathy of trauma shock: Clinical relevance. *Surgeon* 2010; 8:159.
30. Frith D, et al: Definition and drivers of acute traumatic coagulopathy: Clinical and experimental investigations. *J Thromb Haemost* 2010; 8:1919.
31. Phan HH, Wisner DH: Should we increase the ratio of plasma/platelets to red blood cells in massive transfusion: What is the evidence? *Vox Sang* 2010; 98:395.
32. Borgman MA, et al: The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma* 2007; 63:805.
33. Dente CJ, et al: Improvements in early mortality and coagulopathy are sustained better in patients with blunt trauma after institution of a massive transfusion protocol in a civilian level I trauma center. *J Trauma* 2009; 66:1616.
34. Duchesne JC, et al: Review of current blood transfusions strategies in a mature level I trauma center: Were we wrong for the last 60 years? *J Trauma* 2008; 65:272.
35. Gunter OL Jr, et al: Optimizing outcomes in damage control resuscitation: Identifying blood product ratios associated with improved survival. *J Trauma* 2008; 65:527.
36. Holcomb JB, et al: Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. *Ann Surg* 2008; 248:447.
37. Kashuk JL, et al: Postinjury life threatening coagulopathy: Is 1:1 fresh frozen plasma:packed red blood cells the answer? *J Trauma* 2008; 65:261.
38. Maegele M, et al: Red-blood-cell to plasma ratios transfused during massive transfusion are associated with mortality in severe multiple injury: A retrospective analysis from the Trauma Registry of the Deutsche Gesellschaft fur Unfallchirurgie. *Vox Sang* 2008; 95:112.
39. Perkins JG, et al: An evaluation of the impact of apheresis platelets used in the setting of massively transfused trauma patients. *J Trauma* 2009; 66:S77.
40. Riskin DJ, et al: Massive transfusion protocols: The role of aggressive resuscitation versus product ratio in mortality reduction. *J Am Coll Surg* 2009; 209:198.
41. Sperry JL, et al: An FFP:PRBC transfusion ratio >/=1:1.5 is associated with a lower risk of mortality after massive transfusion. *J Trauma* 2008; 65:986.
42. Teixeira PG, et al: Impact of plasma transfusion in massively transfused trauma patients. *J Trauma* 2009; 66:693.
43. Inaba K, et al: Impact of plasma transfusion in trauma patients who do not require massive transfusion. *J Am Coll Surg* 2010; 210:957.
44. Schuster KM, et al: The status of massive transfusion protocols in United States trauma centers: Massive transfusion or massive confusion? *Transfusion* 2010; 50:1545.
45. Thomas D, et al: Blood transfusion and the anaesthetist: Management of massive haemorrhage. *Anaesthesia* 2010; 65:1153.
46. Carless PA, et al: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev* 2010; 10:CD002042.
47. Oeyen S: Fresh frozen plasma transfusion in the critically ill: Yes, no, or maybe? *Crit Care Med* 2007; 35:1777.
48. Stanworth SJ, et al: Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. *Br J Haematol* 2004; 126:139.
49. Goodnough LT: Risks of blood transfusion. *Anesthesiol Clin North America* 2005; 23:241.
50. Spinella PC, et al: Risks associated with fresh whole blood and red blood cell transfusions in a combat support hospital. *Crit Care Med* 2007; 35:2576.
51. Spinella PC, et al: Fresh whole blood transfusions in coalition military, foreign national, and enemy combatant patients during Operation Iraqi Freedom at a U.S. combat support hospital. *World J Surg* 2008; 32:2.
52. Hébert PC, Van der Linden P, Biro G, Hu LQ: Physiologic aspects of anemia. *Crit Care Clin* 2004; 20:187-212.
53. Sakr Y, et al: Microvascular response to red blood cell transfusion in patients with severe sepsis. *Crit Care Med* 2007; 35:1639.
54. Vamvakas EC, Blajchman MA: Blood still kills: Six strategies to further reduce allogeneic blood transfusion–related mortality. *Transfus Med Rev* 2010; 24:77.
55. Hébert PC, et al: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; 340:409.
56. Wu WC, et al: Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001; 345:1230.
57. Carson JL, et al: Transfusion triggers: A systematic review of the literature. *Transfus Med Rev* 2002; 16:187.
58. Carson JL, et al: Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med* 2011; 365:2453-2462.

www.ketabpezeshki.com 66485457-66963820

59. Mackenzie CF, et al: When blood is not an option: Factors affecting survival after the use of a hemoglobin-based oxygen carrier in 54 patients with life-threatening anemia. *Anesth Analg* 2010; 110:685.
60. Cabrales P, Carlos Briceno J: Delaying blood transfusion in experimental acute anemia with a perfluorocarbon emulsion. *Anesthesiology* 2011; 114:901.
61. Pinkerton PH, Callum JL: Rationalizing the clinical use of frozen plasma. *CMAJ* 2010; 182:1019.
62. Chowdhury P, et al: Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients. *Br J Haematol* 2004; 125:69.
63. Ansell J, et al: Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133:160S.
64. Stanworth SJ, Walsh TS: Fresh frozen plasma: Friend or faux pas in critical illness? *Crit Care Med* 2005; 33:2714.
65. Chen A, Teruya J: Global hemostasis testing thromboelastography: Old technology, new applications. *Clin Lab Med* 2009; 29:391.
66. Slichter SJ: Platelet transfusion therapy. *Hematol Oncol Clin North Am* 2007; 21:697.
67. Slichter SJ, et al: Dose of prophylactic platelet transfusions and prevention of hemorrhage. *N Engl J Med* 2010; 362:600.
68. Howard SC, et al: Safety of lumbar puncture for children with acute lymphoblastic leukemia and thrombocytopenia. *JAMA* 2000; 284: 2222.
69. Vavricka SR, et al: Safety of lumbar puncture for adults with acute leukemia and restrictive prophylactic platelet transfusion. *Ann Hematol* 2003; 82:570.
70. Babic A: *Principles of platelet transfusion therapy*. In: Hoffman R, et al, eds. *Hematology: Basic Principles and Practice*, 5th ed. Philadelphia: Churchill Livingstone; 2008.
71. Valeri CR, et al: Anemia-induced increase in the bleeding time: Implications for treatment of nonsurgical blood loss. *Transfusion* 2001; 41:977.
72. Kulvatuny N, Heard SO: Care of the injured Jehovah's Witness patient: Case report and review of the literature. *J Clin Anesth* 2004; 16:548-553.
73. Pena ME, Irvin CB: *Autotransfusion*. In: Roberts JR, Hedges JR, eds: *Clinical Procedures in Emergency Medicine*, 5th ed. Philadelphia: Saunders; 2010.
74. Armas-Loughran B, Kalra R, Carson JL: Evaluation and management of anemia and bleeding disorders in surgical patients. *Med Clin North Am* 2003; 87:229.
75. Kleinman S, et al: Toward an understanding of transfusion-related acute lung injury: Statement of a consensus panel. *Transfusion* 2004; 44:1774.
76. Marik PE, Corwin HL: Acute lung injury following blood transfusion: Expanding the definition. *Crit Care Med* 2008; 36:3080.
77. Sheppard CA, et al: Transfusion-related acute lung injury. *Hematol Oncol Clin North Am* 2007; 21:163.
78. Eder AF, et al: Effective reduction of transfusion-related acute lung injury risk with male-predominant plasma strategy in the American Red Cross (2006-2008). *Transfusion* 2010; 50:1732.
79. Wright SE, et al: Acute lung injury after ruptured abdominal aortic aneurysm repair: The effect of excluding donations from females from the production of fresh frozen plasma. *Crit Care Med* 2008; 36:1796.
80. Vlaar AP, et al: The incidence, risk factors, and outcome of transfusion-related acute lung injury in a cohort of cardiac surgery patients: A prospective nested case-control study. *Blood* 2011; 117:4218.
81. Looney MR: Transfusion-related acute lung injury: A review. *Chest* 2004; 126:249-258.
82. Zou S, et al: Prevalence, incidence, and residual risk of human immunodeficiency virus and hepatitis C virus infections among United States blood donors since the introduction of nucleic acid testing. *Transfusion* 2010; 50:1495.
83. Stramer SL: Current risks of transfusion-transmitted agents: A review. *Arch Pathol Lab Med* 2007; 131:702.
84. Mintz PD: Transfusion Therapy: Clinical Principles and Practice, 2nd ed. Bethesda, Md: American Association of Blood Banks; 2005.

www.ketabpezeshki.com 66485457-66963820

Chapter 8

Brain Resuscitation

William J. Meurer and Robert Silbergleit

PERSPECTIVE

Recognition of the dominant role of the brain in determining the quality of human life dates back to the dawn of recorded medical history. Until recently, however, medical efforts after cardiac arrest have focused exclusively on cardiac resuscitation. Recent advances in the understanding of the pathophysiologic mechanisms of brain ischemia have encouraged attention to cerebral resuscitation as a critical component of what is now recognized as a complex multisystem pathophysiologic state called post–cardiac arrest syndrome.[1] This chapter reviews the pathophysiology of postischemic encephalopathy and discusses therapies for improving neurologic recovery after cardiac arrest.

PATHOPHYSIOLOGY

The human brain consists of 10 billion neurons, each with multiple connections to other cells, totaling an estimated 500 trillion synapses. Although the brain constitutes only 2% of body weight, it receives 15% of the body's cardiac output and accounts for 20% of the body's overall oxygen use because of its high metabolic activity. Although no mechanical or secretory work is performed by the brain, energy expenditures include the synthesis of cellular constituents (e.g., an estimated 2000 mitochondria are reproduced each day by each cell) and neurotransmitter substances, the axoplasmic transport of these substances, and the transmembrane pumping of ions.

When the brain is deprived of adequate blood flow, the resulting ischemia is characterized by a bewildering array of inter-related physiologic and cellular responses that ultimately result in neuronal cell death (Fig. 8-1).[2,3] Although this complex cascade of events can be triggered by periods of ischemia lasting only a few minutes, the resulting neuronal death is usually delayed by hours or days. Furthermore, the biology of cerebral cell death after global cerebral ischemia follows (with slight variations) the pattern of delayed cerebral cell death that follows stroke, traumatic brain injury, and other forms of hypoxic or toxic brain injury. Increased understanding of the brain's response to injury during the period between insult and neuronal cell death will eventually allow more specific brain resuscitation therapies.

MANAGEMENT

Standard management of cardiac arrest and subsequent ischemic brain damage involves restoring cerebral blood flow (CBF) and preventing secondary insult. These treatments have generally not been studied in prospective, randomized controlled trials, but they are supported by clinical experience and limited experimental data. Although proposed and experimental therapies are generally aimed at specific molecular interventions in the pathophysiology of ischemic brain injuries, none of these as yet have proven effective in clinical trials. The most comprehensive review and consensus guideline statement on care of patients with post–cardiac arrest syndrome was produced by the International Liaison Committee on Resuscitation and its constituent bodies, with the endorsement of the American College of Emergency Physicians, Society for Academic Emergency Medicine, Society of Critical Care Medicine, and Neurocritical Care Society.[1] Improvements in post–cardiac arrest care, through an inclusive multisystem approach, can increase the likelihood of meaningful recovery in these patients. Implementation of standardized protocols for postresuscitation care that include many or all of the following components have demonstrated increases in survival with a favorable neurologic outcome of up to 27 to 30% in repeated (although poorly controlled) before-and-after studies.[4,5]

Standard Strategies

Return of Spontaneous Circulation

Cardiac resuscitation is the first priority in cerebral resuscitation. The degree of brain injury after cardiac arrest depends on both the duration of complete cerebral ischemia (the "downtime," or time before the initiation of cardiopulmonary resuscitation [CPR]) and the duration of relative ischemia that occurs during CPR and that may occur from cardiogenic shock preceding or subsequent to the period of cardiac arrest. Extensive clinical evidence on hospital discharge rates and neurologic recovery rates supports the concept first proposed nearly 100 years ago that success in resuscitation is inversely proportional to the duration of cardiac arrest. Although duration of arrest generally predicts outcome in the population of patients with sudden cardiac death, it cannot be used reliably to predict the outcome of individual patients. The epidemiology of neurologic outcome of survivors is described in detail in the following section and is influenced by patient comorbidity and other individual characteristics. Depending on their timing and severity, low-flow states, hypotension, or hypoxia preceding cardiac arrest may provide protective preconditioning or may increase the risk of poor neurologic outcome.

The efficacy of closed-chest CPR in generating adequate cerebral perfusion is somewhat controversial. Cardiac output during optimal standard closed-chest CPR has previously been estimated to be only 20 to 30% of normal, but more recent data suggest that higher cardiac outputs are possible in clinical practice, and, unquestionably, effective CPR is essential to neurologic

www.ketabpezeshki.com 66485457-66963820

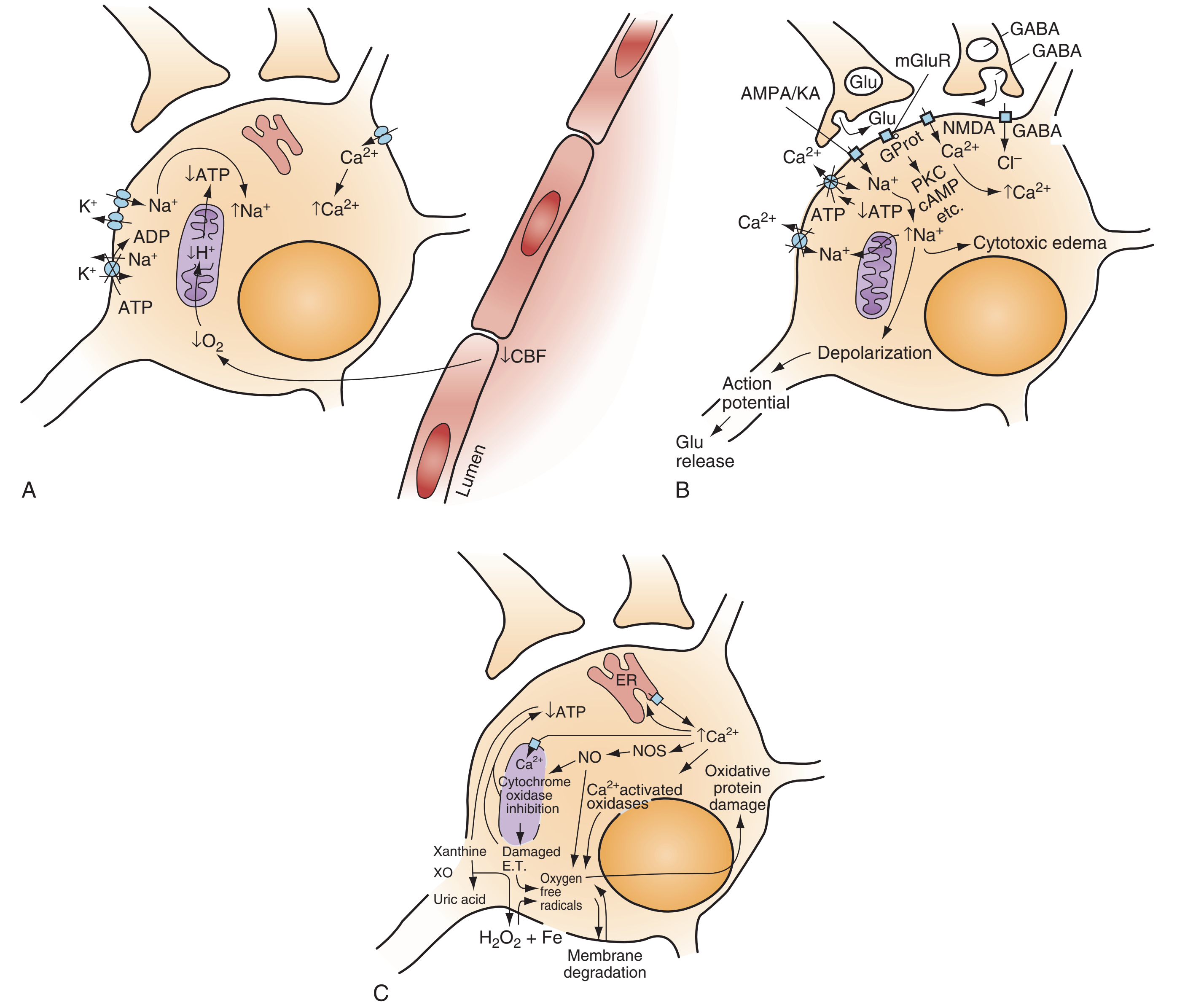


Figure 8-1. Synopsis of events contributing to neuron cell death cascade after ischemia. **A,** Decreased cerebral flow *(CBF)* and arterial oxygen content during ischemia cause decreased adenosine triphosphate *(ATP)* production, failure of ATP-driven ion pump efflux of potassium ions *(K^+)*, and influx of sodium ions *(Na^+)* and calcium ions *(Ca^{2+})* through voltage-gated channels. *ADP,* adenosine diphosphate. **B,** Na^+ influx causes depolarization and glutamate *(Glu)* release, opening Glu receptor α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate *(AMPA)* and kainate *(KA)* channels and exacerbating intracellular Na^+ overload. Increased Na^+ concentration ($[Na^+]i$) leads to cytotoxic edema. Glu-mediated *N*-methyl-D-aspartate *(NMDA)* channels allow intracellular Ca^{2+} overload. Insufficient ATP causes failure of energy-dependent Ca^{2+} pumps, and high $[Na^+]i$ prevents removal of Ca^{2+} by Na^+/Ca^{2+} exchange pumps. γ-Aminobutyric acid *(GABA)* release can attenuate excitatory changes by opening a receptor-gated Cl^-. $[Ca^{2+}]i$, Ca^{2+} concentration; *cAMP,* cyclic adenosine monophosphate; *PKC,* protein kinase C. **C,** Increased $[Ca^{2+}]i$ is amplified by calcium-induced release of Ca^{2+} from the endoplasmic reticulum *(ER)*. Mitochondria may be injured attempting to buffer increasing $[Ca^{2+}]i$, resulting in further metabolic failure and diminished ATP. Ca^{2+} activates nitric oxide synthase *(NOS),* transforming it to nitric oxide *(NO),* which is amplified by NO activation of NOS. NO contributes to the formation of damaging oxygen free radicals and inhibits mitochondrial cytochrome oxidase function. ATP degradation to xanthine and then uric acid by xanthine oxidase *(XO)* yields hydrogen peroxide *(H_2O_2)*, which reacts with iron to form dangerous oxygen radicals. Oxygen free radicals react with lipids in the cell membrane, which produces membrane degradation and more free radicals. Oxygen free radicals also can damage proteins.

recovery after cardiac arrest. Considerable effort has been directed toward the investigation of improved CPR techniques that will prove to be even more effective and for longer periods (see Chapter 9).

Treatment of Hypotension, Hypoperfusion, and Hypoxia

Maintaining cerebral oxygen delivery after cardiac resuscitation is a mainstay of therapy. Oxygen delivery requires a sufficiently high cerebral perfusion pressure, a sufficiently low cerebrovascular resistance (CVR), and adequate blood oxygen saturation.

Hypotension in the postarrest period can dangerously lower cerebral perfusion pressure. Although CBF is normally independent of perfusion pressure over a wide range of arterial blood pressure, such autoregulation is often lost in the injured brain. As a result, perfusion of ischemic tissue becomes passively dependent on arterial pressure, and hypotension can compromise CBF and result in significant additional brain damage.[6] Therefore, after return of spontaneous circulation (ROSC), low arterial pressures

www.ketabpezeshki.com 66485457-66963820

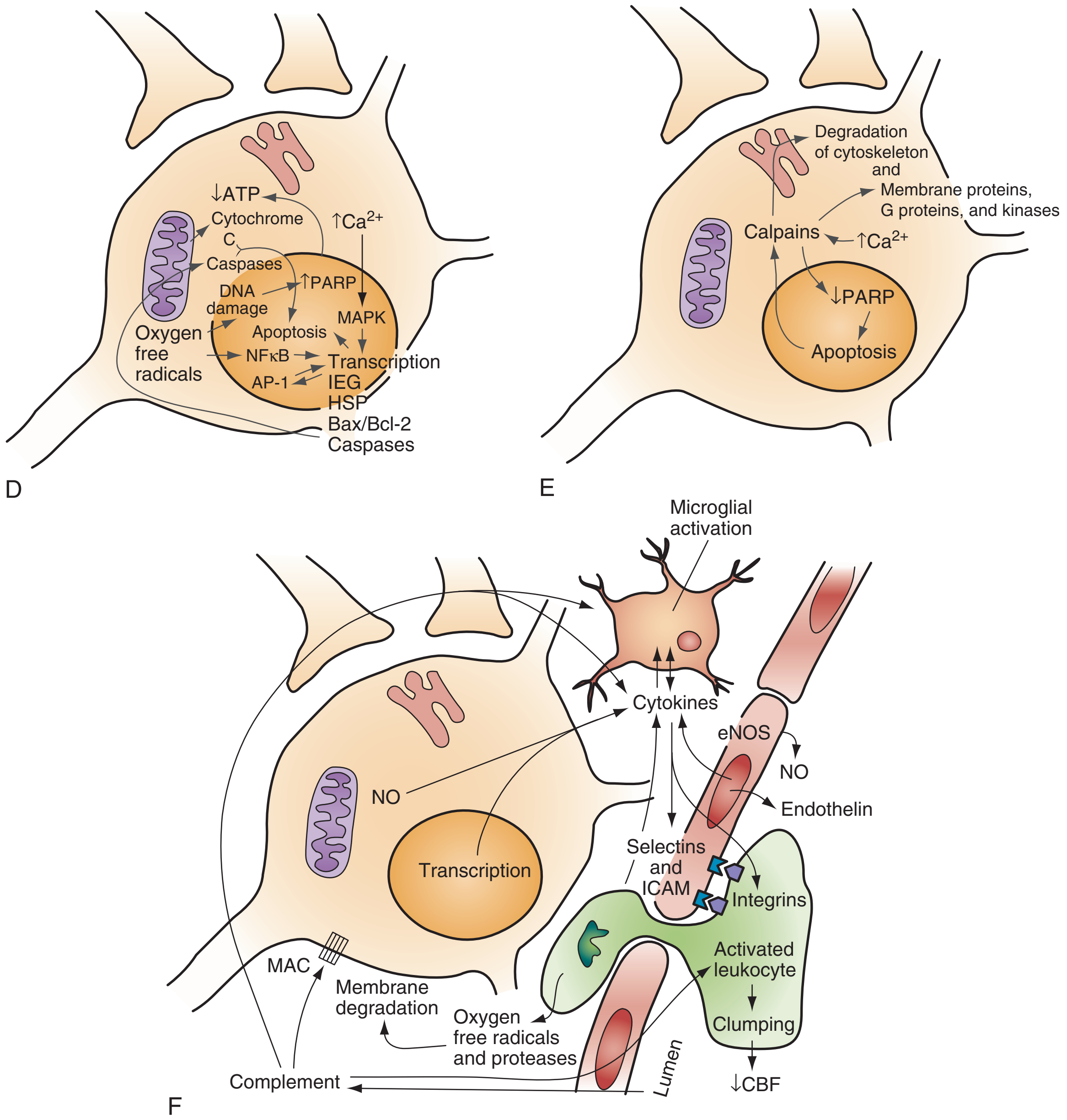


Figure 8-1, cont'd. **D,** Ca^{2+} also activates kinase transcription factors, such as mitogen-activated protein kinase *(MAPK).* Oxygen radicals trigger nuclear factor κB *(NFκB)*, another transcription factor. Many genes, including immediate early genes *(IEG)*, heat-shock protein *(HSP)* genes, genes for caspases, and the *Bax/Bcl-2* systems, are activated. IEG products include AP-1, another transcription factor. Mitochondrial release of cytochrome c, existing and newly formed caspases, and other factors trigger apoptosis. DNA is damaged by oxygen free radicals and by endonucleases formed in apoptosis. DNA damage activates poly(ADP-ribose) polymerase *(PARP),* which further depletes ATP stores. **E,** Ca^{2+} and apoptosis activate calpains, proteases that degrade a variety of structural elements (e.g., cytoskeletal and membrane proteins), signaling elements (e.g., G proteins, kinases), and PARP. **F,** Transcription and NO contribute to neuronal expression of cytokines, chemokines, and growth factors. These intercellular signals activate complement, epithelial cells, leukocytes, and microglia. Complement can amplify chemotactic signals, activate microglia directly, or cause cellular damage by creation of the membrane attack complex *(MAC).* Leukocyte integrins, epithelial cell selectins, and intercellular adhesion molecules *(ICAM)* allow demargination. Activated leukocytes cause neuronal injury by releasing potent oxidants and protease. Cerebrovascular resistance may be affected by epithelial release of NO and endothelin and by leukocyte clumping. *eNOS,* endothelial nitric oxide synthase.

should be rapidly normalized, with intravascular volume administration and vasopressors used as needed. Because elevated arterial pressures may be needed to provide sufficient CBF, hypertension usually should not be treated in the postresuscitation period. Very high blood pressures may require treatment, but specific cutoffs are controversial. In general, diastolic pressures may be allowed to run as high as 120 mm Hg without requiring treatment. In fact, hypertension is sometimes induced clinically or experimentally with vasopressors in an attempt to raise cerebral perfusion pressure and improve neurologic recovery.[6] Because it is unproved, and because risks of this therapy include blood-brain barrier disruption and worsening of vasogenic edema, induced hypertension is not currently a standard therapy.

CVR after resuscitation from cardiac arrest is another determinant of CBF and may be affected by hyperventilation and microvascular patency. Although the cerebral circulation may lose its ability to adjust to blood pressure changes after ischemia, attenuated responsiveness to carbon dioxide and oxygen levels in arterial blood can still be present.[7] Carbon dioxide is a potent vasoactive agent, and lowering of the arterial carbon dioxide partial pressure

www.ketabpezeshki.com 66485457-66963820

(Pa_{CO_2}) by hyperventilation results in rapid reduction of CBF. Because reductions in CBF reduce total cerebral blood volume, hyperventilation may transiently abort brainstem herniation in the presence of critically elevated intracranial pressure (ICP) until osmotherapy or ventriculostomy can be initiated. When ICP is not elevated, however, the vasoconstriction and increased CVR caused by hyperventilation can cause potentially dangerous reductions in CBF.[7] Although controversy surrounds whether increases in ICP are clinically significant after global ischemia, the measurement of ICP is generally not recommended in the management of adult cardiac arrest survivors.[8] In general, ventilation to maintain a Pa_{CO_2} of 35 to 40 mm Hg is safe and appropriate, and inadvertent hyperventilation should be avoided. CVR may also be elevated after cardiac arrest by endothelin-induced vasospasm or microvascular occlusion by leukocyte clumping or coagulation. Hemodilution, anticoagulation, and antiplatelet agents have been studied in animals for effectiveness in mitigating microvascular occlusion with mostly negative results.[9] Acute use of these agents to improve microcirculatory flow has not been studied in human cerebral ischemia.

Normal arterial oxygen saturation should be maintained after resuscitation from cardiac arrest. Because the injured brain may not be able to compensate for hypoxia by augmenting CBF, cerebral oxygen delivery may diminish rapidly as the oxygen content of blood decreases. Hyperoxia secondary to the use of 100% oxygen in the immediate postarrest period, however, has also been shown to increase oxidative brain injury in animal models of cardiac arrest and resuscitation.[10] Normoxia or mild hyperoxia (arterial partial pressure of oxygen [Pa_{O_2}] of 80-120 mm Hg with oxyhemoglobin saturation percentage maintained in the high nineties) should be maintained through use of the lowest fraction of inspired oxygen (F_{IO_2}) possible. The use of 100% oxygen is appropriate during cardiac arrest, but F_{IO_2} should be titrated downward shortly after the ROSC. A large multicenter cohort study found hyperoxia (defined as Pa_{O_2} 300 mm Hg or above on first intensive care unit [ICU]–obtained arterial blood gas [ABG] measurement) to be associated with an 18% (95% confidence interval [CI] 14-22%) higher absolute mortality.[11] An important clinical trial to compare earlier use of normoxia after ROSC with the more typical prolonged period of postresuscitative hyperoxia has been proposed. Because hypoxia, hypocapnia, and hypercapnia must be avoided, controlled ventilation is appropriate in the period after resuscitation, with muscle relaxation and sedation if needed.

Maintenance of Body Temperature

Hyperthermia (or fever) exacerbates brain injury and worsens neurologic outcome.[12,13] Elevated body temperature increases cerebral metabolic demand by 8 to 13% per degree Celsius, escalates glutamate release, increases oxygen free radical production, and increases cytoskeletal and blood-brain barrier breakdown with increased vasogenic edema.[14] Core body temperature (usually rectal, bladder, or esophageal) should be accurately measured in patients resuscitated from cerebral ischemia.[15] Hyperthermia may be treated with antipyretics, circulating air or water cooling systems, or evaporative cooling via water mist and fans.[15] Aggressive treatment should, at a minimum, be used to prevent temperature increases in the postischemic period in all patients, and the practice of inducing therapeutic hypothermia has emerged as a therapy for comatose survivors of cardiac arrest.

Resuscitative Mild Hypothermia

Hypothermia was first reported more than 50 years ago to have a protective effect in global and focal brain ischemia and ranges from mild (32-34° C) to profound (5° C).[16] The mechanism by which hypothermia conveys protection is uncertain, but several possibilities have been suggested. Hypothermia reduces glutamate release, metabolic demand, free radical formation, and production of inflammatory cytokines.[14] Cell-signaling and genetic responses to cellular injury are also affected by hypothermia, and hypothermia may protect the brain from programmed neuronal cell death.[17,18]

Mild hypothermia is easier to achieve and has fewer adverse effects than lower temperatures and has consistently been found to be neuroprotective in experimental cerebral ischemia.[17] Two multicenter prospective, randomized, controlled trials of mild hypothermia have now shown marked improvements in neurologic outcome in comatose survivors of out-of-hospital cardiac arrest.[19,20] The improvements in neurologic outcome (recovery with minimal or no neurologic deficits at hospital discharge) and in mortality in patients treated with hypothermia in these trials are shown in Table 8-1. In these trials, the number needed to treat to have one additional patient with a good neurologic outcome was only about seven. The 2005 and 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care and those of the International Liaison Committee on Resuscitation recommend cooling unconscious adult patients after cardiac arrest to 33° C for 12 to 24 hours.[21,22] Implementation of these guidelines has been slow and represents a failure of clinical translation. Barriers to adoption and the public health impact of widespread use have been reported.[23]

Table 8-1 Clinical Outcomes in Randomized Controlled Trials of Hypothermia in Comatose Survivors of Cardiac Arrest

CLINICAL TRIAL	HYPOTHERMIA, *N* (%)	NORMOTHERMIA, *N* (%)	*P* VALUE
Hypothermia after cardiac arrest (HACA)[19]	137	138	
Good neurologic outcome*	75 (55)	54 (39)	<.01
Death	56 (41)	76 (55)	.02
Bernard and colleagues[20]	43	34	
Good neurologic outcome†	21 (49)	9 (26)	.05
Death	22 (51)	23 (68)	.14

*Good neurologic outcome defined as recovery with no neurologic deficits or with moderate disability but living independently and working at least part time at 6 months.

†Good neurologic outcome defined as recovery with moderate, minimal, or no neurologic deficits at hospital discharge and discharge to home or acute rehabilitation facility.

Techniques used to induce hypothermia in comatose survivors of cardiac arrest, including traditional and advanced surface cooling, administration of ice-cold saline, and endovascular cooling, are discussed in Chapter 9. The optimal method of cooling patients resuscitated from cardiac arrest has not been established.

The rate of cooling needed for effective neuroprotection, the optimal duration of cooling, and the best process for rewarming after hypothermia are all unknown.[24,25] Animal experimentation and the consensus recommendations suggest that cooling should be initiated as early and as rapidly as possible.[26] Cooling may begin during the out-of-hospital phase of resuscitation and may even be initiated before ROSC. In the positive clinical trials, hypothermia

www.ketabpezeshki.com 66485457-66963820

at 33 ± 1° C was achieved by 2 hours or 8 hours after ROSC and was maintained for either 12 hours or 24 hours.[19,20] Patients were then allowed to rewarm passively or with a combination of passive and active rewarming.[19,20] Rebound hyperthermia is common with passive rewarming and should be avoided.[27] Although the clinical trials enrolled only patients resuscitated from cardiac arrest caused by ventricular fibrillation, there is clinical experience with resuscitative hypothermia in patients with cardiac arrest from other causes,[28] and consensus recommendations support its use in such cases.[26]

The clinical importance of initiating hypothermia in the prehospital setting remains unclear. Implementation of prehospital cooling in patients with cardiac arrest appeared effective as part of a comprehensive postarrest program in an observational before-and-after study at Wake Forest,[5] but a randomized Australian trial of prehospital cooling versus rapid cooling shortly after emergency department (ED) arrival in Australia did not demonstrate any added benefit in those cooled in the field.[29]

Cooling of comatose survivors of out-of-hospital cardiac arrest requires a multidisciplinary hospital policy and should be initiated as early as possible (Box 8-1). In hospitals capable of hypothermic resuscitation, cooling is optimally started in the field or the ED and maintained in the ICU.[8,25] Regardless of cooling technique, patients cooled after cardiac arrest require pharmacologic therapy to prevent shivering because shivering effectively warms the patient. In the two clinical trials, shivering was prevented with a nondepolarizing paralytic, and sedation was maintained with midazolam with or without fentanyl.[19,20] When paralysis is not clinically desirable, it may be possible to sufficiently lower the shivering threshold in awake patients with meperidine, buspirone, dexmedetomidine, or a combination of these.[30,31] Shivering can sometimes also be reduced in a patient cooled by an endovascular catheter even when the core temperature is 33° C by applying a warming blanket, because surface temperature receptors control thermoregulation to a much greater extent than core temperature receptors. Other pharmacologic treatments that may be used during induced hypothermia include antipyretics, which lower the core body temperature set point, even in normothermic patients, although to such a small degree that the effect is unlikely to be clinically relevant.[32] More effective pharmacologic lowering of core body temperature is, however, being investigated. Neurotensin is an endogenous neuropeptide involved in thermoregulation that can induce hypothermia and neuroprotection in experimental models of cerebral ischemia.[33]

Therapeutic hypothermia has also been proven effective in neonatal hypoxic ischemic encephalopathy, a condition similar in many ways to the global cerebral ischemic injury resulting from cardiac arrest. Cooling after resuscitation from cardiac arrest is also currently being studied in other infants and children. Clinical trials of mild hypothermia in adults and children with traumatic brain injury have repeatedly shown no benefit, but another trial focusing on even earlier and more rapid cooling after injury is underway in Australia and New Zealand. Cooling during the resuscitation of patients with acute ischemic stroke is also being investigated.[34] Ongoing efforts to develop feasible methods of selective cooling of the brain after cardiac arrest[35,36] and studies of profound systemic hypothermia are still experimental.

Box 8-1 Abbreviated Protocol for Induced Hypothermia after Cardiac Arrest

For access to a wide variety of detailed post–cardiac arrest care and hypothermia protocols collected by the University of Pennsylvania, see www.med.upenn.edu/resuscitation/hypothermia/protocols.shtml.

Hypothermia is most effective as part of an institutional comprehensive post–cardiac arrest critical care program that begins in the emergency department (ED) and continues into the intensive care unit (ICU) and into recovery and rehabilitation.

Early resuscitation, excellent cardiopulmonary resuscitation (CPR), rapid return of spontaneous circulation (ROSC), and quick transport to definitive care are fundamental. The value of prehospital cooling is unproven, but if cooling is initiated by emergency medical services (EMS), transport should be to an institution capable of maintaining hypothermia on arrival and avoiding any early (even transient) rewarming.

Skeleton Protocol (Abstracted from University of Michigan Protocol)

Evaluate adult survivors of cardiac arrest by following institutional criteria for appropriateness of induced hypothermia.

Begin cooling by rapidly infusing 2 L of cold (4° C) intravenous saline immediately after arrival or ROSC.

Expose patient; avoid external warming—no blankets and no heated ventilator circuit.

Place temperature-sensing urinary catheter and esophageal temperature probe. (Redundant monitoring allows esophageal temperature probe connection to cooling device, and bladder temperature probe to patient monitoring system.)

Initiate definitive cooling by endovascular temperature-control device at maximal rate to target temperature of 33° C.

Prevent shivering with sedation and nondepolarizing paralytic. Bolus in ED. Bolus or drip in ICU.

Avoid hypotension and hypoxia.

Most ED diagnostic workup, if needed, should follow initiation of cooling. (In patients with acute myocardial infarction [MI] who are going to primary coronary intervention, cooling should not delay door-to-balloon time. Cooling is initiated in the ED if there is time before the catheterization laboratory is ready; otherwise, cooling is initiated in the laboratory.)

Admit to ICU.

Continuous electroencephalogram (EEG) monitoring for occult status epilepticus recommended. Treat seizures if present.

Manage arterial blood gases in a consistent manner (may choose pH-stat or alpha-stat).

At 24 hours after initiation of cooling, initiate rewarming to a target temperature of 36.5° C at a rate of 0.15°/hr.

Discontinue paralytics at the onset of warming. Control shivering with sedation, narcotics, and surface counter warming.

Lighten sedation as tolerated as rewarming progresses.

Discontinue endovascular temperature control device after 48 hours. (May use the device to maintain normothermia after rewarming is complete until it is removed.)

Remove or minimize sedation to allow neurologic evaluation before 72 hours to allow the best possible clinical prognostication at that time point. Neurology consultation recommended.

Treatment of Hyperglycemia

Postischemic hyperglycemia has detrimental effects on CBF, metabolism, edema formation, and neurologic outcome. In experimental focal cerebral ischemia, profound hyperglycemia (>500 mg/dL) causes a more pronounced decrease in intracellular pH, increases brain lactate levels, and increases neuronal loss. Increased neuronal damage from hyperglycemia in global cerebral ischemia may also be glutamate mediated. Observational studies in patients with stroke and survivors of cardiac arrest have shown that hyperglycemia after brain ischemia is strongly associated with worse outcomes in both diabetics and nondiabetics.[37,38] In experimental studies, normoglycemia and mild insulin-induced

www.ketabpezeshki.com 66485457-66963820

hypoglycemia have been shown to improve neurologic function after focal and global ischemia. It is interesting to note that insulin itself may have a neuronal growth factor–like effect that may theoretically also be neuroprotective. Thus the best available evidence supports active treatment of hyperglycemia after global brain ischemia, and the administration of glucose should be avoided except in verified hypoglycemia.[22]

Seizure Management

Seizures may result from global cerebral ischemia and may exacerbate the underlying brain injury. Seizure activity can increase brain metabolism by 300 to 400%, worsening the mismatch between oxygen delivery and demand in the postarrest period, with greater metabolic failure and neuronal loss and worsened neurologic outcome. Although prevention of seizures has not been demonstrated to improve neurologic recovery, seizures are clearly not desirable in the postischemic period.[8] The prophylactic use of anticonvulsant drugs in patients resuscitated from cardiac arrest is controversial and is not standard care, but it is generally agreed that seizures should be quickly and effectively treated. Common therapeutic agents include benzodiazepines, phenytoin, and barbiturates. Each of these anticonvulsant drugs has also been considered as specific therapy for cerebral ischemia because of the antagonism of excitatory amino acids, sodium channel blockade, or effects on cerebral metabolism. Although these drugs are of proven value as anticonvulsants, other uses in cerebral ischemia are experimental and unproved.

Immobilization, Sedation, and Head Position

The comatose brain responds to external stimuli (e.g., physical examination, airway suctioning) with increases in cerebral metabolism. This elevation of regional brain metabolism requires increased regional CBF at a time when the oxygen demand/perfusion ratios may be precariously balanced. Protection from afferent sensory stimuli with administration of titrated doses of sedative-anesthetic drugs and muscle relaxants may prevent oxygen supply/demand imbalance and improve the chances for neuronal recovery.

All activity that increases ICP (e.g., straining, coughing) should be restricted, and tracheal suction should be performed only when necessary and with care. There is no evidence to support the commonly recommended practice of elevating the head of the bed to reduce intracranial venous pressure, and this practice may even be harmful. Torsion or compression of neck veins should be avoided by eliminating compressive dressings and not rotating or flexing the head.

CLINICAL OUTCOMES

Global cerebral ischemia resulting from a period of cardiac arrest is a frequently fatal and highly morbid condition, but the prognosis for its victims is not universally poor. An increasing body of data is providing more complete and precise estimates of the functional outcomes and quality of life of survivors of cardiac arrest, and the results are better than many physicians assume.

The published experience in Olmsted County, Minnesota, between 1990 and 2000 may represent the best possible outcomes with currently available therapy.[39] First responders (including police and firefighters) with automated external defibrillators in that county responded to 330 patients with cardiac arrest, 200 (61%) of whom had ventricular fibrillation at presentation. The majority of patients with ventricular fibrillation (145 patients, 44% of all arrests) survived to hospital admission, and 84 patients (25%) were discharged alive. Remarkably, among these 84 survivors, 79 (24% of all arrests) left the hospital neurologically intact.[39]

More typical outcomes were identified by a recent very large cohort study of outcomes in 8091 patients with cardiac arrest in Ontario, Canada.[40] Survival was 5.2% at hospital discharge, and was 4.0% at 1 year. The vast majority of 1-year survivors (3% of all those with cardiac arrest), however, had no or minimal neurologic deficits, and the average quality of life indices of all survivors were as good as those for patients without a history of cardiac arrest.[40] The Ontario experience echoes that of a Portuguese study,[41] but other recent data on 6240 patients from studies in the Netherlands,[42] Norway,[43] and Switzerland all confirm a rate of survival to discharge home with minimal or no deficit of 8% in all out-of-hospital cardiac arrests.[44] Quality of life among long-term survivors of cardiac arrest is consistently high in all of these studies, with low rates of patients in persistent vegetative states or requiring skilled nursing care. Overall, among those surviving to hospital admission, 14 to 55% of patients will have good long-term neurologic outcomes.[39,41] A large, prospective observational study from the Resuscitation Outcomes Consortium found significant regional variation in survival to hospital discharge among out-of-hospital cardiac arrest patients.[45] Across the 10 regions from North America, survival ranged from 3 to 16.3%, with a median of 8.4%.

Despite these data, nihilism is common among physicians treating patients with cardiac arrest and ischemic brain injury. This may arise in part from the fact that most survivors of cardiac arrest are comatose at the time of admission and are without early prognostic findings suggesting which patients will have a favorable outcome. Guidelines for neurologists regarding prognostication are largely driven by data from the pre–therapeutic hypothermia era, but absent cortical somatosensory evoked potentials and an unreactive electroencephalographic background pattern at 72 hours appear to be incompatible with long-term recovery; on the other hand, hypothermia-treated patients with absent motor responses to pain and incomplete recovery of brainstem reflexes were found to survive, in contrast to findings of prior meta-analyses.[46-48] The prognostic usefulness of the examination in the immediate postresuscitation period is likely quite limited, with little consensus on the minimum observation period required to establish brain death.[49] Despite continued work to identify an imaging biomarker for outcome after cardiac arrest, there is no established role for either early magnetic resonance imaging or computed tomography in prognostication in survivors of cardiac arrest.[50,51] Nihilism is of particular concern, however, and should be avoided because of the potential for poor prognoses to be self-fulfilling. In the near future, serum biomarkers of brain injury may identify the potential for neurologic recovery early in a patient's course and help guide therapy. Until early predictions of outcome can be accurately made, the emergency physician should consider every survivor of cardiac arrest as having a significant chance of full recovery (14-55%) and should know that bad neurologic outcomes are usually fatal rather than chronically debilitating.

SUMMARY

Rapidly expanding knowledge about the pathophysiology of postischemic brain injury has stimulated the search for effective cerebral resuscitation therapies. Newly proven therapies such as resuscitative hypothermia will continue to be developed and will improve the outcomes of patients with ischemic brain injury in future years. Although experimental work suggests many potentially promising brain resuscitation therapies, attention should also be paid to determining the benefits of existing "standard" therapies.

www.ketabpezeshki.com 66485457-66963820

Because of the complexity and interconnectedness of the pathophysiologic cascades that occur after global cerebral ischemia, it is likely that a multifaceted therapeutic approach or a "cocktail," rather than a single pharmacologic agent, is needed to reduce neurologic damage after cardiac arrest.

It is crucial that the emergency physician recognize that the patient resuscitated from cardiac arrest is, contrary to outward appearance, in a dynamic stage of brain injury. At present, patients should be protected from further brain injury caused by hypotension, hypoperfusion, hypoxia, hyperthermia, hyperglycemia, or seizures. Comatose survivors of out-of-hospital cardiac arrest should now also undergo resuscitative hypothermia. In the future, cerebral resuscitation may also involve other specific pharmacologic interventions to derail the process by which brain cells slowly die after ischemic brain injury.

KEY CONCEPTS

- Neuronal injury is a dynamic process that continues for hours or days after an ischemic insult to the brain.
- Hypotension, hypoperfusion, and hypoxia must be avoided during brain resuscitation.
- Hyperthermia, hyperglycemia, and seizures should be treated promptly during brain resuscitation.
- Comatose survivors of out-of-hospital cardiac arrest should be rapidly cooled in the ED and maintained at 33° C in an ICU setting for 12 to 24 hours after resuscitation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Neumar RW, et al: Post-cardiac arrest syndrome. *Circulation* 2008; 118:2452-2483.
2. Lipton P: Ischemic cell death in brain neurons. *Physiol Rev* 1999; 79:1431-1568.
3. Harukuni I, Bhardwaj A: Mechanisms of brain injury after global cerebral ischemia. *Neurol Clin* 2006; 24:1-21.
4. Sunde K, et al: Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation* 2007; 73:29-39.
5. Hinchey PR, et al: Improved out-of-hospital cardiac arrest survival after the sequential implementation of 2005 AHA guidelines for compressions, ventilations, and induced hypothermia: The Wake County experience. *Ann Emerg Med* 2010; 56:348-357.
6. Marzan AS, Hungerbühler HJ, Studer A, Baumgartner RW, Georgiadis D: Feasibility and safety of norepinephrine-induced arterial hypertension in acute ischemic stroke. *Neurology* 2004; 62:1193-1195.
7. O'Neill JF, Deakin CD: Do we hyperventilate cardiac arrest patients? *Resuscitation* 2007; 73:82-85.
8. Geocadin RG, Koenig MA, Jia X, Stevens RD, Peberdy MA: Management of brain injury after resuscitation from cardiac arrest. *Neurol Clin* 2008; 26:487-506.
9. Chaves C, Caplan L: Heparin and oral anticoagulants in the treatment of brain ischemia. *J Neurol Sci* 2000; 173:3-9.
10. Shi H, Liu KJ: Cerebral tissue oxygenation and oxidative brain injury during ischemia and reperfusion. *Front Biosci* 2007; 12:1318-1328.
11. Kilgannon JH, et al: Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA* 2010; 303:2165-2171.
12. Hajat C, Hajat S, Sharma P: Effects of poststroke pyrexia on stroke outcome: A meta-analysis of studies in patients. *Stroke* 2000; 31:410-414.
13. Hickey RW, et al: Induced hyperthermia exacerbates neurologic neuronal histologic damage after asphyxial cardiac arrest in rats. *Crit Care Med* 2003; 31:531-535.
14. Corbett D, Thornhill J: Temperature modulation (hypothermic and hyperthermic conditions) and its influence on histologic and behavioral outcomes following cerebral ischemia. *Brain Pathol* 2000; 10:145-152.
15. Marion DW: Controlled normothermia in neurologic intensive care. *Crit Care Med* 2004; 32(2 Suppl):S43-S45.
16. Marshall SB, Owens JC, Swan H: Temporary circulatory occlusion to the brain of the hypothermic dog. *AMA Arch Surg* 1956; 72:98.
17. Hicks S, DeFranco D, Callaway C: Hypothermia during reperfusion after asphyxial cardiac arrest improves functional recovery and selectively alters stress protein expression. *J Cereb Blood Flow Metab* 2000; 20:520-530.
18. Yenari M, et al: Gene therapy and hypothermia for stroke treatment. *Ann N Y Acad Sci* 2003; 993:54-68.
19. The Hypothermia after Cardiac Arrest Study Group: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002; 346:549-556.
20. Bernard SA, et al: Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; 346:557-563.
21. Peberdy MA, et al: Part 9: Post-cardiac arrest care. *Circulation* 2010; 122(18 Suppl 3):S768-S786.
22. Morrison LJ, et al: Part 8: Advanced life support. *Circulation* 2010; 122(16 Suppl 2):S345-S421.
23. Majersik JJ, et al: Public health impact of full implementation of therapeutic hypothermia after cardiac arrest. *Resuscitation* 2008; 77:189-194.
24. Bernard S: Hypothermia after cardiac arrest: How to cool and for how long? *Crit Care Med* 2004; 32:897-899.
25. Dine CJ, Abella BS: Therapeutic hypothermia for neuroprotection. *Emerg Med Clin North Am* 2009; 27:137-149.
26. Nolan JP, et al: Therapeutic hypothermia after cardiac arrest: An advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation. *Circulation* 2003; 108:118-121.
27. Felberg RA, et al: Hypothermia after cardiac arrest: Feasibility and safety of an external cooling protocol. *Circulation* 2001; 104:1799-1804.
28. Silfvast T, Tiainen M, Poutiainen E, Roine RO: Therapeutic hypothermia after prolonged cardiac arrest due to non-coronary causes. *Resuscitation* 2003; 57:109-112.
29. Bernard SA, et al: Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest. *Circulation* 2010; 122:737-742.
30. Mokhtarani M, et al: Buspirone and meperidine synergistically reduce the shivering threshold. *Anesth Analg* 2001; 93:1233-1239.
31. Doufas AG, et al: Dexmedetomidine and meperidine additively reduce the shivering threshold in humans. *Stroke* 2003; 34:1218-1223.
32. Kasner SE, et al: Acetaminophen for altering body temperature in acute stroke: A randomized clinical trial. *Stroke* 2002; 33:130-135.
33. Katz LM, Young A, Frank JE, Wang Y, Park K: Neurotensin-induced hypothermia improves neurologic outcome after hypoxic-ischemia. *Crit Care Med* 2004; 32:806-810.
34. Guluma KZ, et al: Effect of endovascular hypothermia on acute ischemic edema: Morphometric analysis of the ICTuS trial. *Neurocrit Care* 2008; 8:42-47.
35. Wagner KR, Zuccarello M: Local brain hypothermia for neuroprotection in stroke treatment and aneurysm repair. *Neurol Res* 2005; 27:238-245.
36. Wang H, et al: Rapid and selective cerebral hypothermia achieved using a cooling helmet. *J Neurosurg* 2004; 100:272-277.
37. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC: Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: A systematic overview. *Stroke* 2001; 32:2426-2432.
38. Skrifvars MB, Pettila V, Rosenberg PH, Castren M: A multiple logistic regression analysis of in-hospital factors related to survival at six months in patients resuscitated from out-of-hospital ventricular fibrillation. *Resuscitation* 2003; 59:319-328.
39. Bunch TJ, et al: Long-term outcomes of out-of-hospital cardiac arrest after successful early defibrillation. *N Engl J Med* 2003; 348:2626-2633.
40. Stiell I, et al: Health-related quality of life is better for cardiac arrest survivors who received citizen cardiopulmonary resuscitation. *Circulation* 2003; 108:1939-1944.
41. Granja C, Cabral G, Pinto AT, Costa-Pereira A: Quality of life 6-months after cardiac arrest. *Resuscitation* 2002; 55:37-44.
42. van Alem AP, Waalewijn RA, Koster RW, de Vos R: Assessment of quality of life and cognitive function after out-of-hospital cardiac arrest with successful resuscitation. *Am J Cardiol* 2004; 93:131-135.
43. Naess AC, Steen PA: Long term survival and costs per life year gained after out-of-hospital cardiac arrest. *Resuscitation* 2004; 60:57-64.
44. Saner H, Borner Rodriguez E, Kummer-Bangerter A, Schuppel R, von Planta M: Quality of life in long-term survivors of out-of-hospital cardiac arrest. *Resuscitation* 2002; 53:7-13.
45. Nichol G, et al: Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA* 2008; 300:1423-1431.
46. Rossetti AO, Oddo M, Logroscino G, Kaplan PW: Prognostication after cardiac arrest and hypothermia: A prospective study. *Ann Neurol* 2010; 67:301-307.
47. Booth CM, Boone RH, Tomlinson G, Detsky AS: Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. *JAMA* 2004; 291:870-879.
48. Wijdicks EFM, Hijdra A, Young GB, Bassetti CL, Wiebe S: Practice parameter: Prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review). *Neurology* 2006; 67:203-210.
49. Wijdicks EFM, Varelas PN, Gronseth GS, Greer DM: Evidence-based guideline update: Determining brain death in adults. *Neurology* 2010; 74:1911-1918.
50. Weiss N, Galanaud D, Carpentier A, Naccache L, Puybasset L: Clinical review: Prognostic value of magnetic resonance imaging in acute brain injury and coma. *Crit Care* 2007; 11:230.
51. Metter RB, Rittenberger JC, Guyette FX, Callaway CW: Association between a quantitative CT scan measure of brain edema and outcome after cardiac arrest. *Resuscitation* 2011; 82:1180-1185.

www.ketabpezeshki.com 66485457-66963820

Chapter 9

Adult Resuscitation

Kevin R. Ward, Michael C. Kurz, and Robert W. Neumar

PERSPECTIVE

Epidemiology

It is estimated that 236,000 to 325,000 patients are treated for out-of-hospital cardiac arrest each year in the United States. The proportion of emergency medical services (EMS)–treated cardiac arrest patients with an initial rhythm of ventricular fibrillation (VF) has declined over time to one third or less in recent U.S. studies.[1-4] Furthermore, the number of patients receiving bystander cardiopulmonary resuscitation (CPR) remains low, averaging only 26% in the home and 45% in public locations.[5] Bystander automated external defibrillators (AEDs) are applied in 1% of home arrests and 8% of arrests in public settings.[5]

There is tremendous variability in survival to hospital discharge after EMS-treated cardiac arrest, ranging from 3 to 16.7% with a median of 7.9%.[1] For the subset of patients who achieve return of spontaneous circulation (ROSC) long enough to be admitted to the hospital, there is significant interinstitutional variability in survival ranging from 19 to 59%.[6] Of patients surviving to hospital discharge, one third have persistent neurologic deficits, and less than half return to prearrest function. In patients meeting the inclusion criteria for clinical therapeutic hypothermia trials, favorable outcome has been reported in approximately 50% of comatose cardiac arrest survivors treated with hypothermia.[7,8] Subsequent studies implementing therapeutic hypothermia as part of a goal-directed post–cardiac arrest treatment protocol have reported rates of survival with good neurologic outcome ranging from 44 to 56%.[9,10] It is important to recognize that the entire system of care affects patient outcomes, and the variability in outcomes across the country likely reflects variability in how well these systems function.

PRINCIPLES OF DISEASE

Etiology

Understanding the causes of cardiac arrest helps direct therapy and diagnostic testing during resuscitation and in the immediate post–cardiac arrest period (Table 9-1). Cardiac arrest from a primary cardiac origin typically manifests as VF or much less often as pulseless ventricular tachycardia (VT). Coronary artery disease is the most common pathologic condition found in patients who die suddenly from VF; autopsy studies show a 75% incidence of previous myocardial infarction (MI) and a 20 to 30% incidence of acute MI.[11] Other anatomic abnormalities associated with sudden cardiac death caused by VF or VT include myocardial hypertrophy, cardiomyopathy, and specific structural abnormalities. Pulseless electrical activity (PEA) and asystole are less common presenting rhythms in patients with a cardiac cause of arrest. These rhythms most often occur as a deterioration of VF or VT or develop in response to resuscitation treatments, such as defibrillation.

Primary respiratory failure generally causes initial hypertension and tachycardia, followed by hypotension and bradycardia and progressing to PEA, VF, or asystole. Circulatory obstruction (e.g., tension pneumothorax, pericardial tamponade) and hypovolemia generally manifest with initial tachycardia and hypotension, progressing through bradycardia to PEA, but also may deteriorate to VF or asystole.

The most common metabolic cause of cardiac arrest is hyperkalemia, which is seen most frequently in patients with renal failure. Hyperkalemia results in progressive widening of the QRS complex, which can deteriorate to VT, VF, asystole, or PEA. Other electrolyte abnormalities (e.g., hypomagnesemia, hypermagnesemia, hypokalemia) may lead to significant dysrhythmias, but the frequency with which they cause cardiac arrest is not documented.

Cardiac arrest from drug toxicity has specific characteristics depending on the drug involved. Specific therapy directed at drug toxicity is essential but may not be immediately effective. Prolonged resuscitation efforts involving a method that provides adequate perfusion may be needed.

Electrocution causes cardiac arrest through primary dysrhythmias or apnea. Alternating current in the range of 100 mA to 1 A generally causes VF, whereas currents greater than 10 A can cause ventricular asystole. Lightning produces a massive direct current electrocution that can result in asystole and prolonged apnea.

Hypothermia-induced cardiac arrest can manifest with any electrocardiogram (ECG) rhythm, and successful resuscitation depends on rapid rewarming, which often requires aggressive and invasive measures (e.g., intravascular rewarming, peritoneal lavage, cardiopulmonary bypass [CPB], open-chest cardiac massage [OCCM]). Drowning is a form of asphyxia usually resulting in bradyasystolic arrest. Because drowning often is accompanied by hypothermia, the victim may benefit from prolonged resuscitation efforts similar to resuscitation efforts for hypothermia.

CLINICAL FEATURES AND MANAGEMENT

Most cardiac arrest cases managed in the emergency department (ED) initially occur outside the hospital. An increasing number of first responders, nontraditional providers, and public venues are being equipped with AEDs. Dramatic resuscitation rates have been achieved when these programs enable providers and the lay public to deliver defibrillation within the first few minutes of arrest.[12-15] Programs that fail to enable a significant number of patients to be

www.ketabpezeshki.com 66485457-66963820

Table 9-1 Common Causes of Nontraumatic Cardiac Arrest

GENERAL	SPECIFIC	DISEASE OR AGENT
Cardiac		Coronary artery disease Cardiomyopathies Structural abnormalities Valve dysfunction
Respiratory	Hypoventilation	CNS dysfunction Neuromuscular disease Toxic and metabolic encephalopathies
	Upper airway obstruction	CNS dysfunction Foreign body Infection Trauma Neoplasm
	Pulmonary dysfunction	Asthma, COPD Pulmonary edema Pulmonary embolus Pneumonia
Circulatory	Mechanical obstruction	Tension pneumothorax Pericardial tamponade Pulmonary embolus
	Hypovolemia	Hemorrhage
	Vascular tone	Sepsis Neurogenic
Metabolic	Electrolyte abnormalities	Hypokalemia or hyperkalemia Hypermagnesemia Hypomagnesemia Hypocalcemia
Toxic	Prescription medications	Antidysrhythmics Digitalis beta-blockers Calcium channel blockers Tricyclic antidepressants
	Drugs of abuse	Cocaine Heroin
	Toxins	Carbon monoxide Cyanide
Environmental		Lightning Electrocution Hypothermia or hyperthermia Drowning or near drowning

CNS, central nervous system; *COPD,* chronic obstructive pulmonary disease.

defibrillated within this critical time window have limited or no effect on survival.[16,17]

Advanced life support (ALS) units staffed by paramedics often have standing orders to follow advanced protocols. Because quality of CPR and time to defibrillation are the two most important determinants of outcome, there is no evidence to support interrupting properly performed advanced measures to transport a patient who is still in cardiac arrest. In cases of cardiac arrest refractory to properly performed advanced measures, the patient may be pronounced dead at the scene if appropriate protocols have been outlined within the system.[18]

Simultaneous assessment and management of cardiac arrest occurs in an orchestrated effort by a health care team led by an emergency physician who can make an ongoing assessment and monitor the efficacy and response to therapeutic interventions. It is often difficult or impossible to determine the cause of cardiac arrest at presentation. Although a differential diagnosis can be formulated based on history, physical examination, and ECG rhythm on arrival, key information often is not available or is unreliable.[19] The differential diagnosis potentially can be narrowed by the patient's age, underlying diseases, and medications when known.

History and Physical Examination

Historical information from the family, bystanders, and EMS personnel provides key information regarding cause and prognosis. Information surrounding the event includes whether the arrest was witnessed, the time of arrest, what the patient was doing (e.g., eating, exercising, trauma), the possibility of drug ingestion, time of initial CPR, initial ECG rhythm, and interventions by EMS providers. Important past medical history includes baseline health and mental status; previous heart, lung, renal, or malignant disease; hemorrhage; infection; and risk factors for coronary artery disease and pulmonary embolism. The patient's current medications and allergies also should be obtained, if possible.

Physical examination of a cardiac arrest patient is necessarily focused on a few key goals: (1) ensure adequacy of airway maintenance and ventilation, (2) confirm the diagnosis of cardiac arrest, (3) find evidence of cause, and (4) monitor for complications of therapeutic interventions. This examination occurs in descending order of importance, simultaneously with therapeutic interventions, and is repeated frequently to assess for response to therapy and occurrence of complications (Table 9-2).

Cardiopulmonary arrest is defined by the triad of unconsciousness, apnea, and pulselessness. The pulse is palpated for in a large artery (carotid or femoral). If any question exists as to the diagnosis of pulselessness, CPR should be initiated. With sudden onset of cardiac arrest, as in VF, loss of consciousness occurs within 15 seconds, although agonal gasping respirations may persist for several minutes. A brief seizure may result from cessation of cerebral blood flow. Primary respiratory arrest results in transient tachycardia and hypertension that progress to loss of consciousness, bradycardia, and pulselessness.

After the initial minutes of cardiac arrest, physical examination may provide little evidence of the duration of arrest. Pupils dilate within 1 minute but constrict if CPR is initiated immediately and performed effectively. Dependent lividity and rigor mortis develop after hours of cardiac arrest. Temperature is an unreliable predictor of duration of cardiac arrest because it does not decrease significantly during the first hours of arrest. Moderate to severe hypothermia may cause cardiac arrest or may be caused by prolonged arrest, with opposite prognostic implications.

Monitoring

Traditional monitoring during CPR has relied on evaluation of the ECG in one or more leads and palpation of carotid or femoral artery pulses. Although the lack of a palpable pulse during CPR may indicate inadequate forward flow, the degree of forward flow cannot be estimated accurately in the presence of a palpable pulse because pressures generated during CPR may be transmitted equally to the venous and the arterial vasculatures. In addition, myocardial blood flow does not depend on the palpated arterial pressure during chest compression (CPR systole), but rather on the difference between aortic and right atrial pressure during relaxation (CPR diastole), which is defined as the coronary perfusion pressure (CPP). ECG monitoring during cardiac arrest indicates the presence or absence of electrical but not mechanical activity. Although these two monitoring modalities may be the best attainable in certain circumstances, they do not provide reliable information regarding the effectiveness of CPR and interventions or prognosis.

Unfortunately, no ideal monitoring technique provides all the information that might be desired during resuscitation, and even the modalities discussed next are often difficult or impossible to establish or interpret during CPR. A brief overview is provided of CPP, end-tidal carbon dioxide ($ETCO_2$), and central venous oxygen saturation ($ScvO_2$) monitoring, which if available can be used to detect inadequate CPR with high specificity (Table 9-3). In

www.ketabpezeshki.com 66485457-66963820

addition, several of these techniques are useful in the immediate post–cardiac arrest period.

Arterial Blood Pressure and Coronary Perfusion Pressure

Successful resuscitation of the arrested heart depends on generating adequate CPP during CPR, which has been directly correlated with myocardial blood flow.[20] Animal and human studies indicate that a minimum CPP of 15 mm Hg is necessary to achieve ROSC if initial defibrillation attempts have failed.[20,21] Unfortunately, CPP monitoring is rarely feasible in ED resuscitations of cardiac arrest patients, because it requires both an indwelling arterial pressure catheter and a central venous catheter, both transduced properly to provide simultaneous readings.

Invasive arterial blood pressure monitoring alone can be helpful in guiding resuscitation and should be used when an indwelling arterial pressure catheter is already in place. When adequate personnel are available, it is often feasible to cannulate the femoral artery during CPR, especially with ultrasound guidance. Human studies have shown that radial or femoral arterial relaxation pressures reliably reflect aortic relaxation pressures during CPR.[22,23] Researchers have also reported that a CPP of 15 mm Hg or more was required to achieve ROSC and that no patient with an aortic relaxation pressure of less than 17 mm Hg achieved ROSC.[21,24] Titrating resuscitation efforts to arterial relaxation (diastolic) pressure is less reliable than CPP because improper CPR (e.g., leaning on chest during CPR diastole and hyperventilation) can cause undetected elevations in right atrial pressure, reducing coronary perfusion. Despite this limitation, it is reasonable to titrate resuscitation efforts to achieve an arterial relaxation (diastolic) pressure of 40 mm Hg or more when invasive arterial pressure monitoring is available. Invasive arterial pressure monitoring during CPR may also be useful to facilitate distinguishing PEA that does or does not result in mechanical heart contraction, to detect ROSC, and to assist in serial arterial blood gas monitoring. Although arterial and central venous catheters are most often placed in the post–cardiac arrest phase of care, a significant number of patients initially achieving ROSC will rearrest in the ED, making these modalities helpful during the patient's subsequent resuscitation.

End-tidal Carbon Dioxide

The partial pressure of CO_2 in exhaled air at the end of expiration ($PETco_2$) can be a reliable indicator of cardiac output during CPR. This is most reliably measured through waveform capnography after endotracheal intubation. $PETco_2$ depends on CO_2 production, alveolar ventilation, and pulmonary blood flow (i.e., cardiac output) and correlates well with CPP and cerebral perfusion pressure during CPR.[24,25] Therefore when minute ventilation is held constant (a desirable but often unmet goal) and no exogenous CO_2 is introduced (e.g., sodium bicarbonate [$NaHCO_3$] administration), only increased cardiac output during CPR and ROSC significantly increases $PETco_2$. Resuscitation after cardiac arrest is likely to fail if $PETco_2$ values are less than 10 mm Hg,[26,27] and such values should prompt the clinician to enhance the quality of CPR (either rate or force of compression) or consider more invasive maneuvers such as extracorporeal membrane oxygenation (ECMO) if the situation warrants and a good neurologic outcome is believed to be possible.[28]

$PETco_2$ monitoring also can aid in the diagnosis and treatment of PEA. Patients in a state of PEA with mechanical heart activity may have pulsatile flow that simply cannot be detected by palpation of a pulse. In such circumstances, $PETco_2$ levels may be elevated even without compressions. Use of cardiac ultrasound in such cases can prove to be helpful in identifying corresponding

Table 9-2 Physical Examination Findings Indicating Potential Cause of Cardiac Arrest and Complications of Therapy

PHYSICAL EXAMINATION	ABNORMALITIES	POTENTIAL CAUSES
General	Pallor Cold	Hemorrhage Hypothermia
Airway	Secretions, vomitus, or blood	Aspiration Airway obstruction
	Resistance to positive-pressure ventilation	Tension pneumothorax Airway obstruction Bronchospasm
Neck	Jugular venous distention	Tension pneumothorax Cardiac tamponade Pulmonary embolus
	Tracheal deviation	Tension pneumothorax
Chest	Median sternotomy scar	Underlying cardiac disease
Lungs	Unilateral breath sounds	Tension pneumothorax Right mainstem intubation Aspiration
	Distant or no breath sounds or no chest expansion	Esophageal intubation Airway obstruction Severe bronchospasm
	Wheezing	Aspiration Bronchospasm Pulmonary edema
	Rales	Aspiration Pulmonary edema Pneumonia
Heart	Audible heart tones	Hypovolemia Cardiac tamponade Tension pneumothorax Pulmonary embolus
Abdomen	Distended and dull	Ruptured abdominal aortic aneurysm or ruptured ectopic pregnancy
	Distended, tympanitic	Esophageal intubation Gastric insufflation
Rectal	Blood, melena	Gastrointestinal hemorrhage
Extremities	Asymmetrical pulses Arteriovenous shunt or fistula	Aortic dissection Hyperkalemia
Skin	Needle tracks or abscesses	Intravenous drug abuse
	Burns	Smoke inhalation Electrocution

Table 9-3 Indicators of Inadequate Blood Flow During Cardiopulmonary Resuscitation

MONITORING TECHNIQUE	INDICATOR
Carotid or femoral pulse	Not palpable
CPP	<15 mm Hg
Arterial relaxation (diastolic) pressure	<40 mm Hg
$PETco_2$	<10 mm Hg (before vasopressor)
$Scvo_2$	<40%

CPP, coronary perfusion pressure; *$PETco_2$*, partial pressure of CO_2 in exhaled air at the end of expiration; *$Scvo_2$*, central venous oxygen saturation.

www.ketabpezeshki.com 66485457-66963820

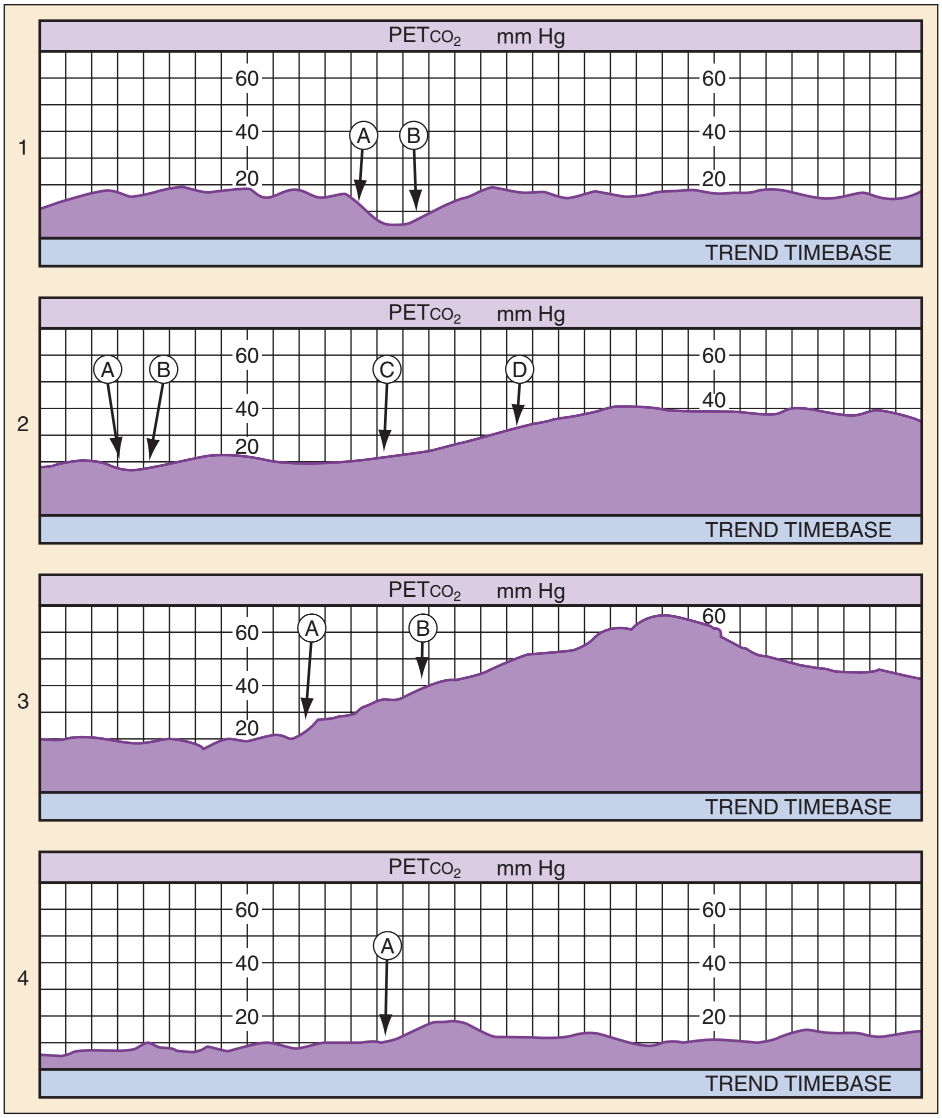


Figure 9-1. Capnogram tracings of end-tidal carbon dioxide partial pressure (PETCO_2) during human cardiopulmonary resuscitation (CPR). **1,** Effect of rescuer fatigue is shown at point A. Point B shows the effect of changing to a fresh rescuer. **2,** Patient with pseudoelectromechanical dissociation. At point A, the patient is pulseless but has a persistent PETCO_2 value of 20 mm Hg without CPR; at point B, CPR is restarted; at point C, dopamine infusion is started; and at point D, CPR is stopped and a pulse is palpated. **3,** Sudden increase in PETCO_2 (point A) heralds the return of spontaneous circulation; pulses are palpated at point B. **4,** Point A shows a transient increase in PETCO_2 such as occurs during bolus administration of sodium bicarbonate.

cardiac activity. In such cases, volume expansion or the use of vasopressors and inotropes should be considered. PETCO_2 monitoring also is useful in rapidly detecting success of tension pneumothorax decompression, pericardiocentesis for pericardial tamponade, and fluid resuscitation for hypovolemia. ROSC causes immediate and significant increases in PETCO_2. Therefore PETCO_2 monitoring can detect ROSC at any time during the chest compression cycle, providing valuable guidance for pharmacologic therapies and minimizing the need for a pulse check when organized rhythms are detected (Fig. 9-1).

Finally, PETCO_2 monitoring is valuable in patients after ROSC to monitor endotracheal tube placement (waveform capnography recommended), titrate minute ventilation to avoid hyperventilation, and detect sudden hemodynamic deterioration.

Central Venous Oxygen Saturation

ScvO_2, when available, provides an additional method to monitor adequacy of resuscitative measures. The mixed venous blood oxygen saturation in the pulmonary artery ($S\bar{v}O_2$) represents the oxygen remaining in the blood after systemic extraction. Studies have shown a close correlation between ScvO_2 and $S\bar{v}O_2$ during CPR.[29] Because oxygen consumption remains relatively constant during CPR, as do arterial oxygen saturation (SaO_2) and hemoglobin, changes in ScvO_2 reflect changes in oxygen delivery by means of changes in cardiac output.

Although used primarily in the intensive care unit (ICU) setting, multilumen oximetric ScvO_2 catheters are placed in the same manner as regular central venous catheters and can be used to monitor ScvO_2 continuously in real time. ScvO_2 values normally range from 60 to 80%. During cardiac arrest and CPR, these values range from 25 to 35%, indicating greatly enhanced oxygen extraction of tissues owing to the inadequacy of oxygen delivery during CPR. Failure to achieve an ScvO_2 of 40% or greater has a negative predictive value for ROSC of almost 100%.[29] ScvO_2 also helps to rapidly detect ROSC without interruption of chest compressions, as ROSC will result in a rapid increase in ScvO_2 as a result of a dramatic increase in oxygen delivery to tissues. ScvO_2 monitoring

www.ketabpezeshki.com 66485457-66963820

is also useful in the post–cardiac arrest period for hemodynamic optimization and for recognition of any sudden deterioration in the patient's clinical condition.

Echocardiography

The main usefulness of echocardiography is diagnostic, especially in patients with PEA. Echocardiography distinguishes organized pulseless cardiac activity that does or does not result in mechanical heart contraction. It also may be helpful in diagnosing mechanical causes of PEA, such as tension pneumothorax, pericardial tamponade, and pulmonary embolism.[30] Echocardiography also is useful in guiding pericardiocentesis. In the postarrest period, echocardiography could prove to be valuable in determining the need for postarrest cardiac intervention or mechanical assistance of the failing heart.[31]

Laboratory Testing

Intermittent arterial and venous blood sampling for gas or chemistry analysis is of limited usefulness during CPR. Typical blood gas findings during CPR demonstrate venous respiratory acidosis and arterial respiratory alkalosis. Sao_2 is usually greater than 94% during CPR and of little value in titrating resuscitation therapy except in the case of massive pulmonary embolism or unrecognized esophageal intubation. Although $Scvo_2$ indicates adequacy of CPR, a single measurement may not be as useful as continuous oximetric $Scvo_2$ monitoring.

Other laboratory studies during CPR serve more to confirm a diagnosis than to guide therapy because results are usually available too late to make a difference. Serum electrolytes may be ordered to rule out hyperkalemia, hypokalemia, hypomagnesemia, hypercalcemia, and hypocalcemia; however, empirical therapy should be initiated immediately if a high clinical suspicion exists. Hemoglobin levels may indicate hemorrhage, but initial hemoglobin may be normal even in acute exsanguinating hemorrhage owing to a lack of rapid vascular and interstitial compartment equilibration.

Resuscitation

Restoration of adequate cardiac function is the defining factor of ROSC, but restoration of normal brain function is the defining factor of successful resuscitation. The likelihood of achieving both of these goals decreases with every minute the patient remains in cardiac arrest. Although many interventions are specific to the presenting ECG rhythm, most therapeutic modalities and monitoring techniques are used in all rhythms, making separate algorithms redundant. In addition, a patient rarely remains in one ECG rhythm during the course of prolonged resuscitation.

Interventions are performed rapidly and efficiently to maximize the chances of a good neurologic outcome. The quality of CPR is perhaps the most underappreciated component of the resuscitation effort.[32] Important quality performance measures include compression rate (at least 100 per minute), compression depth (>5 cm), duty cycle (CPR being performed at >50% of pulseless interval) full relaxation, and minimum pauses, especially before and after defibrillation.[33] Furthermore, hyperventilation has been shown to be common and reduces cardiac output during CPR.[34,35] A 30:2 compression-to-ventilation ratio is currently recommended for health care professionals in all adult resuscitation scenarios until an advanced airway has been established.[36] Once the airway is secured, CPR should be performed continuously without pausing, while providing six to eight ventilations every minute.[36] As indicated earlier, if $PETco_2$ is to be helpful as an indicator of cardiac output during CPR, minute ventilation should be relatively constant. Although recent evidence suggests that chest-compression–only CPR is as effective as traditional CPR when performed by bystanders in the out-of-hospital setting, there is inadequate evidence to recommend this as an alternative strategy for heath care professionals. Whereas oxygen uptake from the lungs is low during CPR, oxygen remaining in the functional residual capacity of the lung will reach a critically low value as CPR progresses if not replenished. The exception to this is when inadequate personnel are present to provide compressions, ventilation, and other resuscitative activites.[37] Intubation should be performed only when capable personnel are available and without interruption of chest compressions. Use of supraglottic airway adjuncts such as the esophageal tracheal Combitube or laryngeal mask airway may be good alternatives for airway management in the out-of-hospital phase of resuscitation, with the main disadvantage being the inability to use the trachea as a route of drug administration and lack of evidence regarding the reliability of use of $PETco_2$ to monitor cardiac output during CPR. In addition to monitoring specific CPR performance parameters, physiologic monitoring, if available, can help optimize CPR quality for the individual patient (see Table 9-3). If the inadequacy of CPR is recognized early in the resuscitation despite optimized therapy, the physician in charge may consider more invasive measures such as ECMO if ROSC and a good neurologic outcome are possible. After prolonged arrest, however, clear indications that CPR is inadequate (based on appropriate monitoring techniques) should prompt cessation of resuscitation efforts. Figure 9-2 is an algorithm for management of cardiac arrest. Interventions specific to each rhythm are discussed in the following sections.

Ventricular Fibrillation and Pulseless Ventricular Tachycardia

VF and pulseless VT are treated identically because they are generally caused by the same mechanisms and respond to the same interventions. Traditional monophasic defibrillators that use either a monophasic truncated exponential (MTE) or a monophasic dampened sinusoidal (MDS) waveform have almost completely been replaced by defibrillators that use biphasic waveforms. With biphasic defibrillation, the energy required for successful defibrillation, or the "defibrillation threshold," is less than with monophasic defibrillation. When used, the biphasic waveform increases the likelihood of initial defibrillation success and decreases the likelihood of postcountershock myocardial dysfunction. Despite documented advantages of lower defibrillation threshold and reduced myocardial injury with use of biphasic defibrillation, data are currently inadequate to conclude that any specific waveform (biphasic or monophasic) is superior to any other in achieving ROSC or survival to hospital discharge. New defibrillation technologies have stimulated reevaluation of optimal defibrillation strategies. Current consensus suggests that the most effective strategy is delivery of single countershocks at optimal energy levels with minimal pauses in CPR both before and immediately afterward.[38] This is facilitated by placement of defibrillation pads early in the resuscitation sequence, thus not requiring a pause while defibrillation paddles and conducting gel are placed for each shock. Manufacturer-recommended countershock energies range from 120 to 360 J for biphasic defibrillators.[38] Health professionals should use the manufacturer-recommended countershock energies for biphasic defibrillator(s). The recommended energy for single monophasic defibrillation is 360 J.[36]

A patient who develops VF or pulseless VT while on a cardiac monitor may remain conscious for 15 to 30 seconds. The patient should be encouraged to cough vigorously until a defibrillator is available. This "cough CPR" has been demonstrated to keep patients conscious for up to a minute or more. If the patient is unresponsive, chest compressions should be initiated immediately and continued until a defibrillator is available. Defibrillation

www.ketabpezeshki.com 66485457-66963820

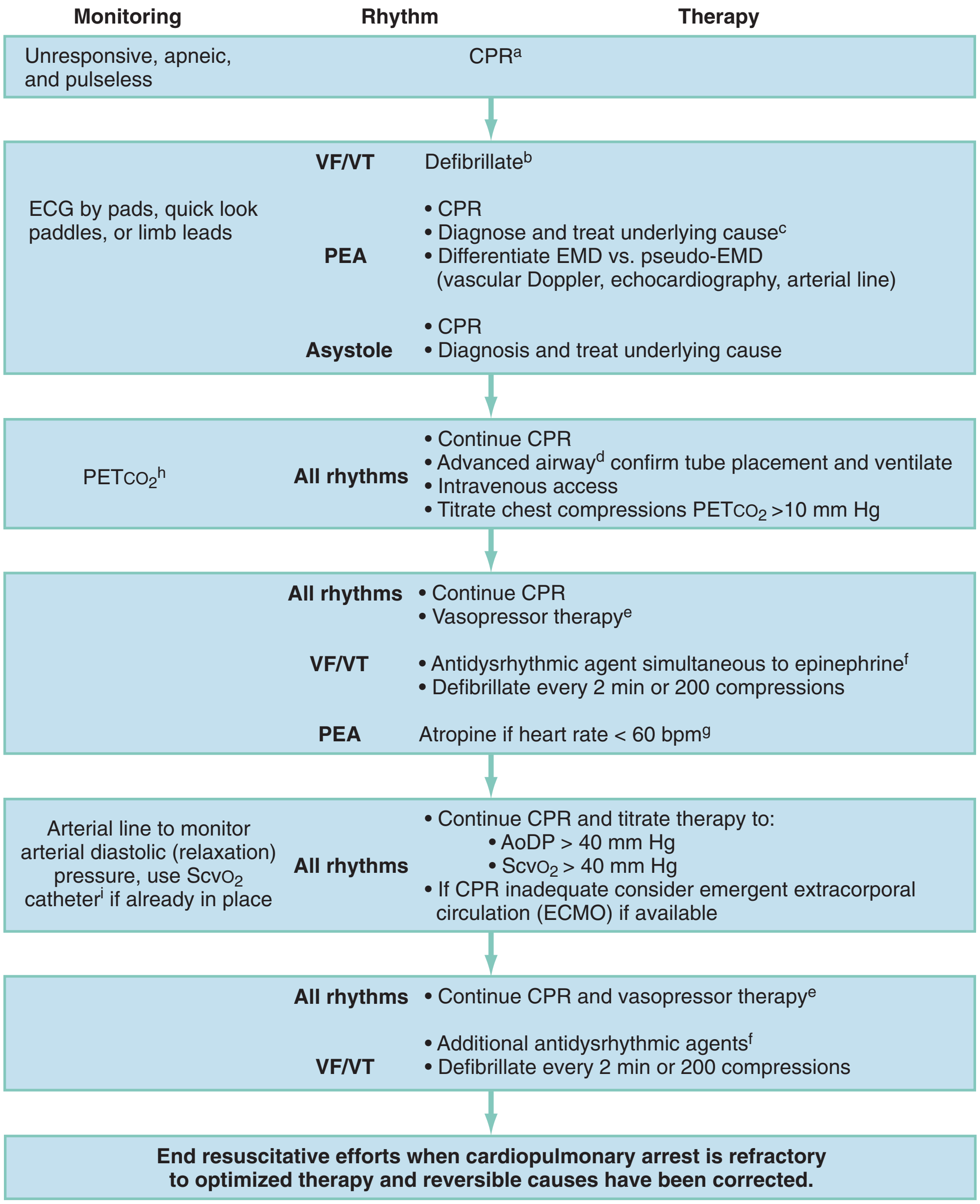


Figure 9-2. Emergency treatment algorithm for treatment of cardiac arrest. [a]If arrest is witnessed and known to be of short duration, immediate rhythm assessment and defibrillation or ventricular fibrillation/ventricular tachycardia *(VF/VT)* precede cardiopulmonary resuscitation *(CPR).* In cases of prolonged untreated VF/VT, 1 to 2 minutes of CPR before defibrillation may enhance the ability to achieve return of spontaneous circulation. *EMD,* electromechanical dissociation; *PEA,* pulseless electrical activity. [b]Biphasic defibrillation should use manufacturer-recommended energy versus monophasic defibrillation (360 J). [c]See Table 9-4. [d]Endotracheal intubation or supraglottic airway when feasible with minimal interruption in chest compressions. [e]Epinephrine, initial dose of 1 mg intravenously (IV) or intraosseously (IO) or 2.5 mg by endotracheal tube (ETT). Repeat every 3 to 5 minutes. Subsequent doses may be increased up to 0.1 mg/kg. An alternative to epinephrine is vasopressin, 40 U via intravenous push. Vasopressin is potentially more effective if the presenting rhythm is asystole. The dose (40 U) can be repeated once in 3 minutes, followed by administration of epinephrine every 3 to 5 minutes. [f]Amiodarone, 300 mg via intravenous push followed by 150 mg every 30 minutes. Lidocaine is an alternative antidysrhythmic if amiodarone is not available. Magnesium sulfate, 1 to 2 g via intravenous push in torsades de pointes or known hypomagnesemia. [g]Atropine, 1 mg via intravenous push or 2.5 mg by ETT. Repeat dose every 3 to 5 minutes to a total dose of 0.04 mg/kg. *AoDP,* aortic diastolic pressure; *ECG,* electrocardiogram; *ScvO₂*, central venous oxygen saturation. [h]Changes in the partial pressure of end-tidal carbon dioxide (PETCO_2) may not be predictive of myocardial blood flow in the setting of high-dose vasopressor therapy. [i]Invasive monitoring should be performed only if adequate personnel are available and if it would not delay therapeutic interventions.

without antecedent CPR is most likely to result in ROSC when administered in the early minutes of arrest. If the duration of untreated arrest is prolonged (>4-5 minutes), a brief period of chest compressions and ventilations (90-180 seconds) before defibrillation may improve the likelihood of ROSC and survival.[34,39,40] The current consensus favors delivering a single countershock with minimal pause in chest compressions before defibrillation.[38] Defibrillation is followed immediately by resumption of chest compressions for 2 minutes before a rhythm check and additional defibrillation as appropriate.[36]

VF and pulseless VT refractory to initial defibrillation should be treated with assisted ventilation and chest compression.

www.ketabpezeshki.com 66485457-66963820

Intravenous access and vasopressor therapy (epinephrine or vasopressin) should be administered and repeated every 3 to 5 minutes. Simultaneous administration of epinephrine and vasopressin does not improve outcome relative to epinephrine alone regardless of presenting rhythm.[41]

Defibrillation attempts should be preceded and followed by minimal interruptions of chest compression.[36] Subsequent therapy for refractory VF and pulseless VT includes continued administration of vasopressors and antidysrhythmic agents, followed by repeated countershocks. Antidysrhythmics should be administered up to their maximum loading dose. The use of magnesium sulfate during VF and pulseless VT is of no proven efficacy except in torsades de pointes and possible hypomagnesemia. Beyond the specific indications for $NaHCO_3$ therapy of hyperkalemia and tricyclic antidepressant overdose, there is no evidence to support use of $NaHCO_3$ or other buffers as empirical treatment for metabolic acidosis during cardiac arrest. If a patient is defibrillated into a different pulseless rhythm, such as PEA or asystole, subsequent treatment should be modified to address those specific rhythms.

Pulseless Electrical Activity

PEA is defined as coordinated electrical activity of the heart (other than VT/VF) without a palpable pulse. This group of dysrhythmias includes electromechanical dissociation (EMD), in which no myocardial contractions occur, and pseudo-EMD, in which myocardial contractions occur but no pulse can be palpated. Although distinguishing EMD from pseudo-EMD may be useful in determining cause and guiding treatment, in most cases of primary PEA there is a natural progression from hypotension to pseudo-EMD to EMD.

True EMD is the result of a primary disorder of electromechanical coupling in myocardial cells. It often is associated with abnormal automaticity and conduction resulting in bradycardia and a wide QRS complex. Although the mechanism of uncoupling is unclear, it most often is associated with global myocardial energy depletion and acidosis resulting from ischemia or hypoxia. True EMD typically occurs after defibrillation following prolonged VF and is associated with hyperkalemia, hypothermia, and drug overdose.

Pseudo-EMD caused by global myocardial dysfunction is a transient state in the progression to EMD and has the same cause. An additional cardiac cause of pseudo-EMD is papillary muscle and myocardial wall rupture, in which the ventricle continues to contract, but forward flow is greatly diminished. Pseudo-EMD also may be caused by primary supraventricular tachycardia. Additional extracardiac causes of pseudo-EMD include hypovolemia, tension pneumothorax, pericardial tamponade, and massive pulmonary embolism. Pseudo-EMD of extracardiac origin most often has narrow-complex tachycardia initially, which can progress to bradycardia with conduction abnormalities and QRS widening.

Treatment of PEA requires all general resuscitation measures, including CPR, intubation with assisted ventilation, intravenous access, and repeated administration of vasopressors. Initial assessment also should include vascular Doppler ultrasound, echocardiography, or $PETCO_2$ monitoring to distinguish EMD from pseudo-EMD. This is important because volume loading or continuous vasopressor infusion, which is not typically used in routine cardiac arrest resuscitation, may be helpful in cases of pseudo-EMD. In contrast, routine use of atropine during PEA, previously a mainstay of drug therapy, is unlikely to have a therapeutic benefit.[38] PEA thought to result from supraventricular tachycardia should be immediately cardioverted. These interventions alone are generally inadequate, unless the underlying cause of PEA is primary respiratory arrest or supraventricular tachycardia. Successful resuscitation of patients with PEA hinges on rapid diagnosis and treatment of the underlying cause. Physical examination may provide valuable clues to the underlying cause (Table 9-4). In hypoxia and hypovolemia, the diagnosis is based on response to empirical therapy, whereas other causes, such as pericardial tamponade, tension pneumothorax, and hypothermia, can be definitively diagnosed during resuscitation. Physical examination and monitoring are used to guide ongoing resuscitation efforts.

Asystole

Asystole represents complete cessation of myocardial electrical activity. Although asystole may occur early in cardiac arrest as a consequence of progressive bradycardia, asystole generally represents the end-stage rhythm after prolonged cardiac arrest caused by VF or PEA. Because the potential exists for an organized rhythm or VF to appear as asystole in a single lead (if the rhythm vector is completely perpendicular to the lead vector), asystole should be confirmed in at least two limb leads. Although asystole may be difficult to distinguish from extremely fine VF, routine countershock of asystole has not been shown to improve survival.

Table 9-4 Diagnosis and Treatment of Common Causes of Pulseless Electrical Activity

CAUSE	DIAGNOSIS	PALLIATIVE THERAPY	DEFINITIVE THERAPY
Hypovolemia	Response to volume infusion	Volume infusion, consider OCCM	Hemostasis if hemorrhage
Hypoxia	Response to oxygenation	Oxygenation, assisted ventilation	Treat underlying cause
Cardiac tamponade	Echocardiogram, pericardiocentesis	Pericardiocentesis	Thoracotomy and pericardiotomy
Tension pneumothorax	Asymmetrical breath sounds, tracheal deviation	Needle thoracostomy	Tube thoracostomy
Hypothermia	Rectal temperature		Warm peritoneal or thoracic lavage, OCCM or CPB
Pulmonary embolus	Risk factors or evidence of deep venous thrombosis	OCCM or CPB	Lytic therapy, pulmonary embolectomy
Drug overdose	History of drug ingestion	Drug specific	Drug-specific
Hyperkalemia	History of renal failure or elevated serum potassium	Calcium chloride, insulin and glucose, sodium bicarbonate	Hemodialysis
Acidosis	Arterial blood gas	Hyperventilation, sodium bicarbonate	Treat underlying cause

CPB, cardiopulmonary bypass; *OCCM,* open-chest cardiac massage.

www.ketabpezeshki.com 66485457-66963820

Treatment of asystole requires all general resuscitation measures, including CPR, intubation with assisted ventilation, intravenous access, and repeated administration of vasopressors. In one randomized prospective out-of-hospital trial, improved survival to hospital admission and discharge was observed in patients in asystole when two doses of vasopressin (40 IU) were given initially during resuscitation compared with standard-dose epinephrine (1 mg), followed by additional epinephrine if needed.[42] In a more recent study, simultaneous administration of epinephrine and vasopressin did not improve outcome relative to epinephrine alone, regardless of presenting rhythm.[41] Available evidence indicates that routine administration of atropine is not beneficial.[36] Extensive research has shown that asystole in the out-of-hospital setting seldom responds to pacing. To be effective, pacing must be initiated within several minutes of arrest.

Post–Cardiac Arrest

Resuscitation of a cardiac arrest victim does not end with ROSC. Management includes rapid diagnosis and treatment of the disorders that caused the arrest and the complications of prolonged global ischemia. Simultaneous management of these two entities makes caring for a post–cardiac arrest patient particularly challenging. A comprehensive goal-driven program of post–cardiac arrest care is most successful in affecting survival and neurologic status.[9,10]

Induction of prolonged therapeutic hypothermia in comatose survivors of cardiac arrest has been shown to improve survival and functional outcome in two prospective randomized clinical trials.[7,8] Both studies enrolled only out-of-hospital patients with witnessed arrest and an initial rhythm of VF. The time to achieve target temperature (<34° C) ranged from less than 2 hours to a median of 8 hours (interquartile range 4-16 hours),[7,8] suggesting a broad therapeutic window. Hypothermia was maintained for 12 to 24 hours, followed by gradual rewarming over 12 to 24 hours. Although these parameters provide guidelines within which post–cardiac arrest hypothermia is effective, additional preclinical and clinical data are needed to determine the optimal temperature, time to achieve target temperature, and duration of therapy. In both studies, the rates of complications were not statistically different between groups. Although there are no absolute contraindications, relative contraindications include severe cardiogenic shock, life- threatening dysrhythmias, uncontrolled bleeding, preexisting coagulopathy, pregnancy, another obvious reason for coma (e.g., drug overdose or status epilepticus), known end-stage terminal illness, and a preexisting do-not-resuscitate status. Thrombolytic therapy does not preclude the use of hypothermia.[8] Finally, whereas initial studies were limited to patients with witnessed VF out-of-hospital cardiac arrest, evidence is accumulating that induced post–cardiac arrest therapeutic hypothermia is effective in patients with other presenting rhythms including PEA and asystole.[43,44]

When the decision is made to treat the patient with therapeutic hypothermia, cooling efforts should be initiated as soon as possible. Practical methods of rapidly inducing hypothermia include ice packs (applied to the neck, inguinal areas, and axilla), fan cooling of dampened exposed skin, cooling blankets underneath and on top of the patient, and disabling of ventilator warming circuits. Rapid intravenous infusion of limited volumes (1-2 L) of 4° C saline facilitates rapid cooling, but additional measures are needed to maintain hypothermia as this initial cold fluid bolus will lose its heat transfer properties during circulation.[45] A number of automated surface cooling devices are now available that use chest and thigh pads and continuous temperature feedback from bladder or esophageal temperature probes. Although these devices were developed to make cooling less labor intensive and faster, some difficulties inherent with surface cooling remain, including overshooting and maintaining target temperature (SD usually > 1° C),[46] uncontrolled rewarming with frequent rebound hyperthermia, and inability to assess skin for cutaneous reactions and injury.[47] Automated endovascular cooling systems are also available that require placement of a central venous catheter. Although more invasive, cooling with a heat exchange catheter inserted in the inferior vena cava is the most rapid practical method of cooling and offers the tightest control of temperature at target (SD usually < 0.3° C) and during controlled rewarming.[48] Endovascular systems are far less nursing labor-intensive than surface cooling because they monitor core temperature and are automatically controlled through a feedback loop.[49] No one cooling strategy or device has been demonstrated to result in superior clinical outcomes.

Shivering, which inhibits cooling, can be prevented with sedation and neuromuscular blockade. If neuromuscular blockade is continued during the maintenance phase of therapeutic hypothermia, continuous electroencephalographic monitoring is strongly encouraged because seizures are common in post–cardiac arrest patients (5-20%).[9] Target core body temperature is 32 to 34° C and is best monitored by an indwelling temperature-sensitive bladder catheter or esophageal temperature probe.[50] When the patient is stabilized and cooling efforts are initiated, transfer to a critical care unit should occur as soon as possible. Although the optimal duration of post–cardiac arrest hypothermia is unknown and may be related to the total ischemic time,[51] target temperatures are typically actively maintained for at least 12 to 24 hours, followed by gradual rewarming over 8 to 12 hours.[52] Effective application of therapeutic hypothermia in comatose cardiac arrest survivors requires a coordinated interdisciplinary effort and is best carried out through use of a predetermined goal-directed algorithm developed with input from emergency medicine, cardiology, and critical care physicians and nurses.

A simultaneous immediate concern in a comatose cardiac arrest survivor is whether the patient has an acute coronary syndrome. Diagnosing acute coronary syndrome in an unconscious patient after cardiac arrest presents a unique challenge. A standard 12-lead ECG should be obtained as soon as feasible after ROSC, with additional right-sided and/or posterior leads as indicated. In one study, 50% of patients achieving ROSC after out-of-hospital cardiac arrest were found to have acute coronary occlusion on cardiac catheterization; 10% of them did not have ST segment elevation.[19] Subsequent studies have reported that successful immediate percutaneous coronary intervention (PCI) is associated with improved hospital survival in post–cardiac arrest patients with or without ST segment elevation.[53]

Immediate PCI is indicated in post-ROSC patients with ST segment elevation MI or new left bundle branch block (LBBB), or high clinical suspicion of acute MI, and can be performed during therapeutic hypothermia.[54-58] When PCI is indicated but not available, either early transfer of post–cardiac arrest patients to a center capable of PCI or fibrinolytic therapy should be considered.[59] Relative exclusion criteria for fibrinolytic therapy unique to the post–cardiac arrest patient include evidence of significant CPR trauma (e.g., pneumothorax, flail chest, pulmonary contusion with hemorrhage), but the effects of therapeutic hypothermia on the efficacy and complications of fibrinolytic therapy in postarrest patients have not been formally studied.

Antiplatelet and anticoagulant therapy should be administered to all patients after ROSC, whether or not therapeutic hypothermia is induced, if no evidence of hemorrhage exists and profound hypertension is absent. The choice of antiplatelet and anticoagulant therapy depends in part on the presence of active ischemia, renal function, and plans for acute angioplasty.[60] There is no proven benefit of prophylactic antiarrhythmic therapy or continuous infusion of an antiarrhythmic drug that has been associated with restoration of a stable rhythm during CPR. Concomitant

www.ketabpezeshki.com 66485457-66963820

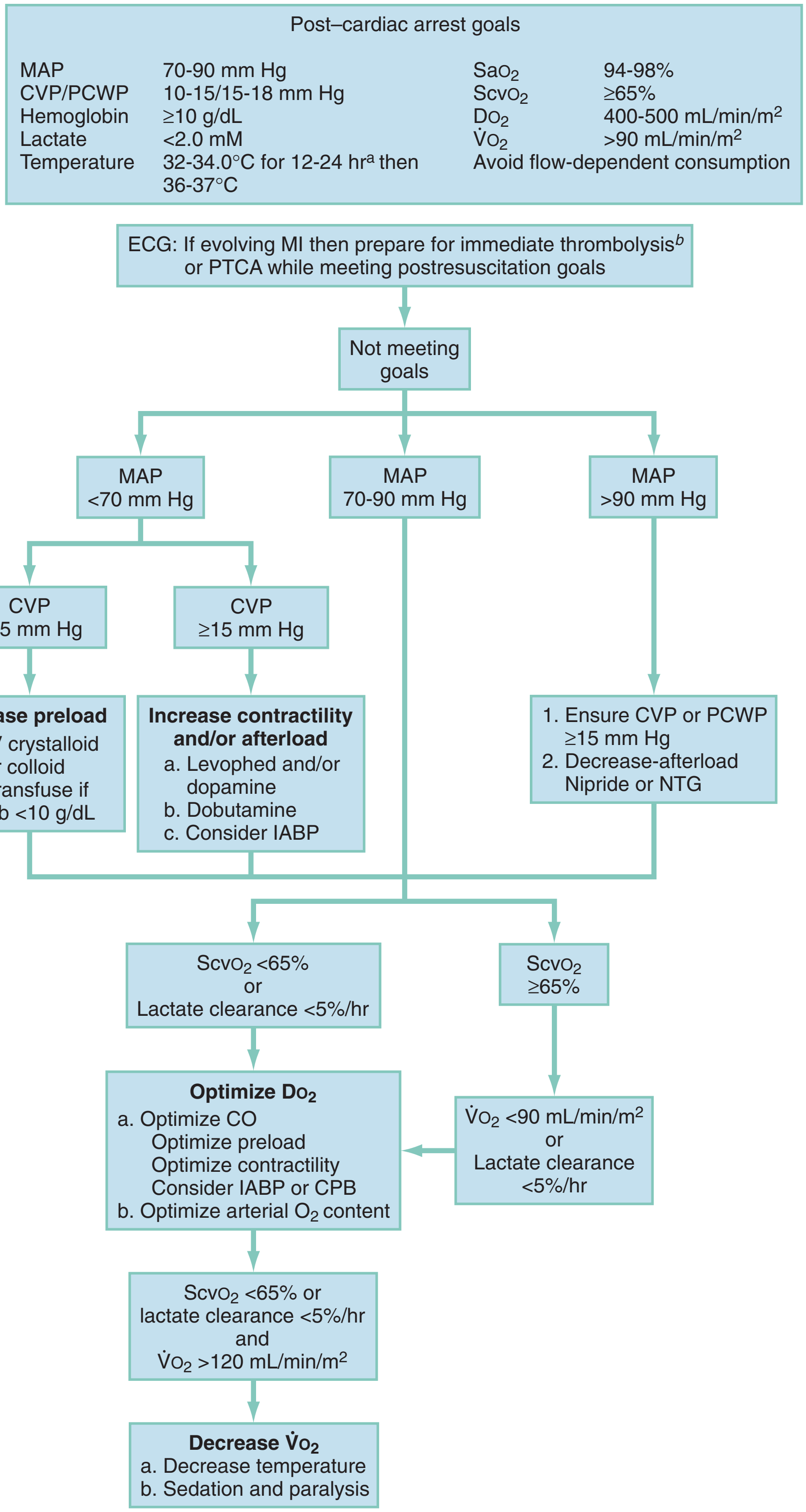


Figure 9-3. Goal-directed postarrest treatment algorithm. [a]Therapeutic hypothermia is indicated in comatose survivors of witnessed cardiac arrest who had a presenting rhythm of ventricular fibrillation. It may also be effective in patients resuscitated from other cardiac arrest presentations. Relative contraindications include an unwitnessed cardiac arrest, severe cardiogenic shock, life-threatening dysrhythmias, uncontrolled bleeding, preexisting coagulopathy, pregnancy, another obvious reason for coma (e.g., drug overdose or status epilepticus), known end-stage terminal illness, and a preexisting do-not-resuscitate status. [b]Initiation of therapeutic hypothermia is not a contraindication to thrombolytic therapy. *CPB,* cardiopulmonary bypass; *CVP,* central venous pressure; *DO_2,* oxygen delivery; *ECG,* electrocardiogram; *Hb,* hemoglobin; *IABP,* intra-aortic balloon pulsation; *MAP,* mean arterial pressure; *MI,* myocardial infarction; *NTG,* nitroglycerin; *PCWP,* pulmonary capillary wedge pressure; *PTCA,* percutaneous transluminal angioplasty; *SaO_2,* arterial oxygen saturation; *$ScvO_2$,* central venous oxygen saturation; *$\dot{V}O_2$,* oxygen consumption.

www.ketabpezeshki.com 66485457-66963820

therapies (e.g., nitrates, beta-blockers) are best performed in conjunction with careful hemodynamic monitoring. If indicated, intravenous preparations of nitrates and short-acting beta-blockers (e.g., esmolol) should be used because they have a brief duration of action and are easily titrated. In patients with new LBBB, right bundle branch block with left anterior or posterior hemiblock, second-degree type II block, or third-degree block, transthoracic pacing pads are immediately applied in case they are needed to treat bradycardic rhythms. Placement of transvenous pacing catheters also can be considered but is less often done with the increasing use and demonstrated efficacy of transthoracic cardiac pacing.[61]

Inadequate oxygen delivery (Do_2) causes cells to convert to anaerobic metabolism, resulting in increased lactate production (dysoxia). Continued resuscitation efforts to optimize Do_2 may help to stabilize the patient and potentially prevent subsequent multiorgan dysfunction and recurrent arrest. However, supranormal arterial oxygen partial pressure can exacerbate oxidative brain injury during the first minutes to hours after cardiac arrest. Therefore the fraction of inspired oxygen (Fio_2) can be titrated to the minimum concentration required to maintain an arterial oxyhemoglobin saturation around 94%. This level of oxygenation avoids detrimental hyperoxia while ensuring appropriate oxygen delivery.[62]

During cardiac arrest and CPR, Do_2 is well below necessary levels. On ROSC, resuscitation efforts should continue to establish adequate systemic Do_2. Serum lactate levels provide an indirect measure of whether Do_2 is adequate to prevent anaerobic metabolism. A single lactate level is almost universally elevated after resuscitation from cardiac arrest. Detection of ongoing lactate production requires monitoring of serial lactate levels. Insufficient Do_2 also causes increased oxygen extraction, resulting in decreased $S\bar{v}O_2$. Low $S\bar{v}O_2$ coupled with persistently elevated lactate levels indicates inadequate Do_2. Patients with prolonged duration of CPR and those who have received high-dose vasopressor therapy during CPR may develop impaired tissue oxygen extraction· In such patients, $S\bar{v}O_2$ is abnormally high (venous hyperoxia) in the face of inadequate Do_2 and likely represents a state of severe systemic shunting resulting in an increase in non-nutritive blood flow. Lactate levels in these circumstances continue to be elevated. Thus the combination of sustained elevated lactate levels along with normal or elevated $Scvo_2$ levels indicate severe systemic shunting. Treatments for this include carefully reducing any continuous infusion of vasopressors and more aggressive volume loading. The use of guided vasodilator therapy to open up underperfused tissue beds as well as consideration of mechanical adjuncts such as intra-aortic balloon pumping may also be necessary in this situation.

The use of combined hemodynamic and metabolic endpoints to guide resuscitation in the ED has been shown to improve the outcome of patients with septic shock states.[63] Because the post–cardiac arrest condition represents a complex state of cardiovascular shock, the use of such goal-directed therapy is inherently valuable to reduce mismatches of oxygen delivery and consumption that cannot be determined by simple physical examination and vital signs. Use of goal-directed hemodynamic therapy is relatively straightforward and requires only the insertion of a supradiaphragmatic central venous catheter. $Scvo_2$ can be used as a reliable surrogate for $S\bar{v}O_2$, which eliminates the need for a pulmonary artery catheter.[29] If $Scvo_2$ is abnormally low (<65%) but hemoglobin and Sao_2 values are normal, cardiac output is insufficient. Central venous pressure (CVP) is used to deduce whether inadequate cardiac output is secondary to hypovolemia or impaired myocardial function. Augmenting CVP to levels between 10 and 15 mm Hg ensures adequate preload in most patients. If CVP is adequate and the patient has a mean arterial pressure of at least 70 mm Hg, therapy with an inotropic agent, such as dobutamine, should be initiated while reperfusion strategies are considered. CVP measurements may decrease rapidly on initiation of dobutamine therapy. Additional volume expansion while the hemoglobin value is kept at least at 10 g/dL should be provided as needed to maintain an adequate CVP.

The response to Do_2-optimizing interventions can be monitored by continuous or serial $Scvo_2$ measurements and serial lactate levels. An increase in $Scvo_2$ coupled with a decrease in lactate levels indicates improved Do_2. An unchanging $Scvo_2$ level indicates the need to continue to increase delivery. Persistently elevated lactate levels and low $Scvo_2$ despite maximum pharmacologic support and volume management signal the need for additional interventions to optimize Do_2. If this is not done, further accumulation of oxygen debt will occur, which will lead to either death or the development of multisystem organ failure. Options to consider include revascularization or mechanical assistance in the form of intra-aortic balloon pulsation or extracorporeal support. The induction of therapeutic hypothermia may assist in lowering the metabolic demands of tissues in the postarrest state. Figure 9-3 provides a goal-directed guide to care of the postarrest patient. Similar options should be considered in a patient with venous hyperoxia and elevated levels of lactate because the combination of these findings indicates severe microvascular dysfunction, which also leads to the accumulation of oxygen debt incompatible with survival. The incidence of this condition may increase with the increased use of potent vasopressors, such as vasopressin.

Hospital protocols and systems can be designed to ensure prompt transfer of post–cardiac arrest patients from the ED to the cardiac catheterization laboratory or an ICU, where intensive monitoring can guide subsequent therapy to achieve the optimal patient outcome. At this point, family members are fully informed of the circumstances and the patient's transfer out of the ED. Unless prompt transfer to the ICU is anticipated and achieved, comprehensive post–cardiac arrest care is initiated in the ED.

KEY CONCEPTS

- CPR quality, including minimization of chest compression pauses, is critical to successful resuscitation from cardiac arrest.
- Restoration of adequate cardiac function is the defining factor of ROSC. Restoration of normal brain function is the defining factor of successful resuscitation.
- Resuscitation of a cardiac arrest victim does not end with ROSC. Rapid diagnosis and proper management of the pathologic conditions that precipitated and resulted from the arrest as well as goal-directed hemodynamic management can improve outcome.
- Induced prolonged hypothermia (32-34° C for 12-24 hours) is the first and only post-ROSC intervention shown to improve survival and functional outcome of comatose cardiac arrest survivors.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Nichol G, et al: Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA* 2008; 300:1423-1431.
2. Bobrow B, et al: Chest compression–only CPR by lay rescuers and survival from out-of-hospital cardiac arrest. *JAMA* 2010; 304:1447-1454.
3. Rea T, et al: CPR with chest compression alone or with rescue breathing. *N Engl J Med* 2010; 363:423-433.
4. Aufderheide T, et al: Standard cardiopulmonary resuscitation versus active compression-decompression cardiopulmonary resuscitation with augmentation of negative intrathoracic pressure for out-of-hospital cardiac arrest: A randomised trial. *Lancet* 2011; 377:301-311.
5. Weisfeldt ML, et al: Ventricular tachyarrhythmias after cardiac arrest in public versus at home. *N Engl J Med* 2011; 364:313-321.
6. Carr BG, Kahn JM, Merchant RM, Kramer AA, Neumar RW: Inter-hospital variability in post–cardiac arrest mortality. *Resuscitation* 2009; 80:30-34.
7. Bernard SA, et al: Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; 346:557.
8. Hypothermia after Cardiac Arrest Study Group: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002; 346:549-556. Erratum in *N Engl J Med* 2002; 346:1756.
9. Sunde K, et al: Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation* 2007; 73:29-39.
10. Gaieski DF, et al: Early goal-directed hemodynamic optimization combined with therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Resuscitation* 2009; 80:418-424.
11. Myerburg RJ, Kessler KM, Castellanos A: Sudden cardiac death: Structure, function, and time-dependence of risk. *Circulation* 1992; 85:I2.
12. Caffrey SL, et al: Public use of automated external defibrillators. *N Engl J Med* 2002; 347:1242.
13. Hallstrom AP, et al: Public-access defibrillation and survival after out-of-hospital cardiac arrest. *N Engl J Med* 2004; 351:637.
14. Page RL, et al: Use of automated external defibrillators by a U.S. airline. *N Engl J Med* 2000; 343:1210.
15. Valenzuela TD, et al: Outcomes of rapid defibrillation by security officers after cardiac arrest in casinos. *N Engl J Med* 2000; 343:1206.
16. Myerburg RJ, et al: Impact of community-wide police car deployment of automated external defibrillators on survival from out-of-hospital cardiac arrest. *Circulation* 2002; 106:1058.
17. van Alem AP, et al: Use of automated external defibrillator by first responders in out of hospital cardiac arrest: Prospective controlled trial. *BMJ* 2003; 327:1312.
18. Bonnin MJ, et al: Distinct criteria for termination of resuscitation in the out-of-hospital setting. *JAMA* 1993; 270:1457.
19. Spaulding CM, et al: Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. *N Engl J Med* 1997; 336:1629.
20. Niemann JT, et al: Predictive indices of successful cardiac resuscitation after prolonged arrest and experimental cardiopulmonary resuscitation. *Ann Emerg Med* 1985; 14:521.
21. Paradis NA, et al: Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. *JAMA* 1990; 263:1106.
22. Ornato JP, et al: The effect of applied chest compression force on systemic arterial pressure and end-tidal carbon dioxide concentration during CPR in human beings. *Ann Emerg Med* 1989; 18:732-737.
23. Rivers EP, et al: Simultaneous radial, femoral, and aortic arterial pressures during human cardiopulmonary resuscitation. *Crit Care Med* 1993; 21:878-883.
24. Lewis LM, et al: Correlation of end-tidal CO_2 to cerebral perfusion during CPR. *Ann Emerg Med* 1992; 21:1131.
25. Sanders AB, et al: Expired P_{CO_2} as an index of coronary perfusion pressure. *Am J Emerg Med* 1985; 3:147.
26. Callaham M, Barton C: Prediction of outcome of cardiopulmonary resuscitation from end-tidal carbon dioxide concentration. *Crit Care Med* 1990; 18:358.
27. Sanders AB, et al: End-tidal carbon dioxide monitoring during cardiopulmonary resuscitation: A prognostic indicator for survival. *JAMA* 1989; 262:1347.
28. Kagawa E, et al: Outcomes of extracorporeal membrane oxygenation in adult patients with refractory shock and cardiac arrest. *Circulation* 2010; 122:A271.
29. Emerman CL, et al: A comparison of venous blood gases during cardiac arrest. *Am J Emerg Med* 1988; 6:580.
30. Hernandez C, et al: C.A.U.S.E.: Cardiac arrest ultrasound exam—A better approach to managing patients in primary non-arrhythmogenic cardiac arrest. *Resuscitation* 2008; 76:198-206.
31. Gruenewald M, et al: Visual evaluation of left ventricular performance predicts volume responsiveness early after resuscitation from cardiac arrest. *Resuscitation* 2011; 82:1553-1557.
32. Wik L, et al: Quality of cardiopulmonary resuscitation during out-of-hospital cardiac arrest. *JAMA* 2005; 293:299.
33. Berg RA, et al: Part 5: Adult basic life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122(Suppl 3): S685-S705.
34. Aufderheide TP, Lurie KG: Death by hyperventilation: A common and life-threatening problem during cardiopulmonary resuscitation. *Crit Care Med* 2004; 32:S345.
35. Aufderheide TP, et al: Hyperventilation-induced hypotension during cardiopulmonary resuscitation. *Circulation* 2004; 109:1960.
36. Neumar RW, et al: Part 8: Adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122(18 Suppl 3):S729-S767.
37. Sayre MR, et al: Hands-only (compression-only) cardiopulmonary resuscitation: A call to action for bystander response to adults who experience out-of-hospital sudden cardiac arrest—a science advisory for the public from the American Heart Association Emergency Cardiovascular Care Committee. *Circulation* 2008; 117:2162.
38. Link MS, et al: Part 6: Electrical therapies: Automated external defibrillators, defibrillation, cardioversion, and pacing—2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122(18 Suppl 3): S706-S719.
39. Stiell IG, et al: Early versus later rhythm analysis in patients with out-of-hospital cardiac arrest. *N Engl J Med* 2011; 365:787-797.
40. Wik L, et al: Delaying defibrillation to give basic cardiopulmonary resuscitation to patients with out-of-hospital ventricular fibrillation: A randomized trial. *JAMA* 2003; 289:1389.
41. Wenzel V, et al: A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med* 2004; 350:105.
42. Gueugniaud PY, et al: Vasopressin and epinephrine vs epinephrine alone in cardiopulmonary resuscitation. *N Engl J Med* 2008; 359:21.
43. Arrich J, European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group: Clinical application of mild therapeutic hypothermia after cardiac arrest. *Crit Care Med* 2007; 35:1041-1047.
44. Derwall M, Stoppe C, Brücken D, Rossaint R, Fries M: Changes in S-100 protein serum levels in survivors of out-of-hospital cardiac arrest treated with mild therapeutic hypothermia: A prospective, observational study. *Crit Care* 2009; 13:R58.
45. Kliegel A, et al: Cold infusions alone are more effective for induction of therapeutic hypothermia but do not keep patients cool after cardiac arrest. *Resuscitation* 2007; 73:46-53.
46. Heard KJ, et al: A randomized controlled trial comparing the Arctic Sun to standard cooling induction of hypothermia after cardiac arrest. *Resuscitation* 2010; 81:9-14.
47. Merchant MR, et al: Therapeutic hypothermia after cardiac arrest: Unintentional overcooling is common using ice packs and conventional cooling blankets. *Crit Care Med* 2006; 34:S490-S494.
48. Gillies MA, et al: Therapeutic hypothermia after cardiac arrest: A retrospective comparison of surface and endovascular cooling techniques. *Resuscitation* 2010; 81:1117-1122.
49. Finley Caulfield A, et al: A comparison of cooling techniques to treat cardiac arrest patients with hypothermia. *Stroke Res Treat* 2011; 2011:690506.
50. Nolan JP, et al: Therapeutic hypothermia after cardiac arrest: An advisory statement by the Advancement Life Support Task Force of the International Liaison Committee on Resuscitation. *Resuscitation* 2003; 57:231.
51. Sawyer KN, et al: Derivation of a novel hypothermic to ischemic ratio as an indicator for predicting and improving survival from out of hospital cardiac arrest. *Circulation* 2011; 124:A1.
52. Peberdy MA, et al: Part 9: Post–cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122(18 Suppl 3): S768-S786.
53. Dumas F, et al: Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: Insights from the PROCAT (Parisian Region Out of hospital Cardiac ArresT) registry. *Circ Cardiovasc Interv* 2010; 3:200-207.

www.ketabpezeshki.com 66485457-66963820

54. Garot P, et al: Six-month outcome of emergency percutaneous coronary intervention in resuscitated patients after cardiac arrest complicating ST-elevation myocardial infarction. *Circulation* 2007; 115:1354.
55. Keelan PC, et al: Early direct coronary angioplasty in survivors of out-of-hospital cardiac arrest. *Am J Cardiol* 2003; 91:1461.
56. Bendz B, et al: Long-term prognosis after out-of-hospital cardiac arrest and primary percutaneous coronary intervention. *Resuscitation* 2004; 63:49.
57. Knafelj R, et al: Primary percutaneous coronary intervention and mild induced hypothermia in comatose survivors of ventricular fibrillation with ST-elevation acute myocardial infarction. *Resuscitation* 2007; 74:227.
58. O'Connor RE, et al: Part 10: Acute coronary syndromes: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122(18 Suppl 3): S787-S817.
59. Peels HO, et al: Outcome in transferred and nontransferred patients after primary percutaneous coronary intervention for ischaemic out-of-hospital cardiac arrest. *Catheter Cardiovasc Interv* 2008; 71:147.
60. Anderson JL, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients with Unstable Angina/Non ST-Elevation Myocardial Infarction): Developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Circulation* 2007; 116:e148.
61. Zimetbaum PJ, Josephson ME: Use of the electrocardiogram in acute myocardial infarction. *N Engl J Med* 2003; 348:933.
62. Neumar RW: Optimal oxygenation during and after cardiopulmonary resuscitation. *Curr Opin Crit Care* 2011; 17:236.
63. Rivers E, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368.

www.ketabpezeshki.com 66485457-66963820

Chapter 10

Pediatric Resuscitation

Aaron J. Donoghue, Robert A. Berg, and Vinay Nadkarni

CARDIAC ARREST AND CARDIOPULMONARY RESUSCITATION

Perspective

In absolute terms, cardiac arrest is not rare in pediatric patients; it occurs in 2 to 6% of children admitted to a pediatric intensive care unit (PICU) and about 16,000 children per year out of hospital in the United States (i.e., 8-20 per 100,000 children per year).[1-4] From the perspective of the individual care provider in the prehospital or inpatient medical setting outside the intensive care unit (ICU), however, pediatric resuscitations constitute an infrequent occurrence.[5-10] Significant disparity in favorable outcomes continues to exist between out-of-hospital and in-hospital pediatric cardiac arrest.

Epidemiology

Data from the National Heart, Lung, and Blood Institute (NHLBI)–funded Resuscitation Outcomes Consortium demonstrated an overall population-based incidence of nontraumatic pediatric out-of-hospital cardiac arrests (OOHCAs) of 8 per 100,000 pediatric person-years compared with 125 per 100,000 adult person-years; however, the rate among infants (73 per 100,000) was on the same order of magnitude as in adults. More important, pediatric patients were more likely to survive to discharge than adults (6.4% vs. 4.5%). Specifically, children and adolescents were twice as likely to survive to hospital discharge as infants and adults. The number needed to treat (NNT) of 13 to save a pediatric life compares favorably with NNT for other aggressive interventions considered quite effective, such as implantation of a cardioverter-defibrillator in patients with ventricular arrhythmias (NNT of 8) and immediate revascularization in patients with cardiogenic shock (NNT of 13). Furthermore, the potential years of life gained for pediatric survivors are much greater than for adult survivors.[11]

Among published studies of out-of-hospital pediatric cardiac arrest, the most common causes are sudden infant death syndrome (SIDS; 20-23%), trauma (15-20%), and submersion injury (8-12%).[4,12] Prognosis after cardiac arrest varies considerably based on the underlying cause, with outcomes after SIDS and trauma being particularly dismal[13-15] and outcomes after submersion including a higher prevalence of survival.[3,16,17] Table 10-1 shows the prevalence of survival to discharge after out-of-hospital and in-hospital pediatric cardiac arrest as reported by multiple studies over the past three decades.[4,11,18-22] It is noteworthy that survival after in-hospital cardiac arrest has improved substantially from less than 10% in the 1980s to greater than 25% in the first decade of the 21st century. By contrast, survival after OOHCA has changed very little in 30 years, with survival less than 10% in virtually all studies over that time period.[4,11,12,23,24] The American Heart Association (AHA) National Registry of Cardiopulmonary Resuscitation (Get With The Guidelines—Resuscitation [GWTG-R], formerly known as NRCPR) database has yielded analyses demonstrating specific epidemiologic features of in-hospital pediatric arrest associated with improved survival, including young age and events occurring in hospitals with higher levels of pediatric staffing.[25,26]

Cardiac arrest occurring in the emergency department (ED) (as distinct from out-of-hospital arrest with continued resuscitation in the ED) accounts for a minority (approximately 11-13%) of in-hospital events for children and adults.[19,25,27] Historical outcomes for children who arrest while in the ED suggest that survival outcomes are less prevalent than in cases of in-hospital arrest but better than in out-of-hospital arrest.[28] More recent controlled analyses from the GWTG-R demonstrate a significant discrepancy between outcomes among children who arrest in the ED, with an adjusted odds ratio of 0.39 for survival compared with other in-hospital locations, highlighting differences in pathophysiology of ED versus in-hospital cardiac arrest in children.[25] These data stand in stark contrast to data in adults, in whom arrests in the ED were associated with significantly improved survival of 22% compared with 10-15% for events in the ICU or wards.[29]

Pathophysiologic Principles

Physiology of Cardiac Arrest

Three common pathways to arrest have been identified: asphyxial, ischemic, and arrhythmogenic. Asphyxial cardiac arrests are precipitated by acute hypoxia or hypercarbia and are the most common in children.[4,19,30] Ischemic arrests are precipitated by inadequate myocardial blood flow, in children most commonly as a result of shock from hypovolemia, sepsis, or myocardial dysfunction. Arrhythmogenic arrests are most often sudden, precipitated by ventricular fibrillation (VF) or ventricular tachycardia (VT). The immediate causes of arrest in two recent in-hospital studies were arrhythmogenic in 10%, asphyxial in 67%, and ischemic in 61% (many patients had both asphyxia and ischemia).[19,30] The vast majority of out-of-hospital arrests are also either asphyxial or ischemic, and 5 to 20% are arrhythmogenic.[3]

Pediatric Anatomy Relevant to Cardiopulmonary Resuscitation

Appropriate pediatric cardiopulmonary resuscitation (CPR) differs from that for adults owing to children's differences in

www.ketabpezeshki.com 66485457-66963820

Table 10-1 Outcomes after Pediatric Cardiac Arrest

In-Hospital Cardiac Arrest				*Out-of-Hospital Cardiac Arrest*			
AUTHOR	DATE	ROSC	SURVIVAL TO DISCHARGE	AUTHOR	DATE	ROSC	SURVIVAL TO DISCHARGE
Zaritsky	1987	51%	9%	Eisenberg	1983	18%	7%
Reis	2002	64%	15%	Schindler	1996	54%	8%
Nadkarni	2006	52%	27%	Young	2004	29%	9%
				Atkins	2009	NR	6.4%

NR, data not reported; *ROSC,* return of spontaneous circulation.

anatomy and physiology, as well as the differences in the pathogenesis of cardiac arrest and the common rhythm disturbances in children. Prolonged hypoxia and acidosis impair cardiac function and ultimately lead to cardiac arrest.

The use of closed-chest cardiac massage to provide adequate circulation during cardiac arrest was initially demonstrated in small dogs with compliant chest walls.[31] Therefore children were among the first patients successfully treated with this technique. The presumed mechanism of blood flow was direct compression of the heart between the sternum and the spine in children with compliant chest walls. Later investigations indicated that blood could also be circulated during CPR by the thoracic pump mechanism. That is, chest compression–induced increases in intrathoracic pressure can generate a gradient for blood to flow from the pulmonary vasculature, through the heart, and into the peripheral circulation.[32,33]

Clinical Features

The triad of pulselessness, apnea, and unresponsiveness defines the clinical state of cardiac arrest. For decades, published guidelines by the International Liaison Committee on Resuscitation (ILCOR) on the assessment of patients suspected to be in cardiac arrest used the mnemonic *ABC* (airway, breathing, circulation) for the stepwise assessment and intervention sequence. This sequence included opening the airway, assessing respirations with the "look-listen-feel" technique for up to 10 seconds, providing two rescue breaths, and checking for a central pulse (brachial or femoral in children, carotid in adults). For the first time, in 2005, treatment recommendations published by ILCOR removed the pulse check as a necessary step for lay rescuers, based on data demonstrating poor specificity and sensitivity of a 10-second carotid pulse check by health care providers in anesthetized adults undergoing aortic cross-clamping.[34,35] The implication for rescuers is that any patient who is unresponsive and apneic and appears hypoperfused by gross appearance (i.e., "appears dead") should have chest compressions initiated immediately without a check for a pulse. This recommendation may have particular pertinence for children, given the high prevalence of bradycardia and hypoperfusion in the prearrest phase and the potential improvement in outcomes when CPR is provided for bradycardia (see later).

In 2010 the AHA made the recommendation to change the algorithmic sequence of rescue interventions for the arrested patient from ABC to CAB (compressions, airway, breathing) because blood flow during cardiac arrest depends on chest compressions, and efforts to address A and B first delay the time to reestablishment of blood flow. The value of this approach is most dramatically demonstrated by the success of compression-only CPR (i.e., without rescue breathing) in adults. Therefore CAB is the adult recommendation, and it is reasonable to use the same approach in children to simplify training for the lay rescuer. In addition, starting resuscitation for an arrested child with compressions instead of ventilations will result in only a brief delay before the first rescue breath (estimated 18 seconds for the lone rescuer, 9 seconds for multiple rescuers). Finally, in a health care setting where a team of providers responds to an arrest, multiple tasks are undertaken simultaneously by task-specific personnel; given that chest compressions can be applied instantaneously and positive-pressure ventilation requires several seconds of equipment preparation and application to the patient's face, CAB is unlikely to produce different results in in-hospital events.

Studies on the pulse check in pediatrics have predominantly focused on healthy children, where the data on the accuracy of brachial and femoral pulse checks are varied.[36,37] A recent pediatric ICU study examined the accuracy of the pulse check by health care providers on children receiving extracorporeal circulatory support (i.e., either extracorporeal membrane oxygenation [ECMO] or a ventricular assist device [VAD]) in whom native pulsatile cardiac activity was variably diminished or absent; it was found that a 10-second femoral or brachial pulse check had a sensitivity of 86% and a specificity of 64%.[38] In other words, making a decision to provide CPR based on the pulse check alone in this patient set would have resulted in chest compressions being given to 36% of patients in whom they were not indicated and compressions being withheld from 14% of children who were either pulseless or critically hypoperfused enough to require them. Based largely on this study, the 2010 ILCOR guidelines for pediatric resuscitation have removed the pulse check for lay rescuers. Health care providers may spend up to 10 seconds assessing a central pulse, but the empirical provision of chest compressions without a pulse check for the child who appears dead is appropriate.

Four Phases of Cardiac Arrest

Cardiac arrest may be categorized into four phases, each with unique physiology and treatment strategies: (1) prearrest, (2) no flow (untreated cardiac arrest), (3) low flow (CPR), and (4) postresuscitation.

Prearrest Phase. Because most out-of-hospital pediatric cardiac arrests are caused by progressive asphyxia or ischemia, they can often be prevented by avoiding the precipitating insult. For example, infant and child car seats and seat belts for older children can prevent cardiac arrests resulting from motor vehicle collisions. Similarly, fences around swimming pools with self-closing gates can prevent drowning.

Both the BRESUS study in the United Kingdom and the AHA's GWTG-R national registry data clearly demonstrate that most in-hospital cardiac arrests are asphyxial or ischemic rather than sudden arrhythmia-induced events.[19,27,39] Most important, many of these arrests could be prevented by early recognition and treatment of respiratory failure and shock. These issues were appreciated by the founders of the Pediatric Advanced Life Support (PALS) course, which was therefore designed to prevent cardiac arrests by early recognition and treatment of respiratory failure and shock in children.[40]

No-Flow Phase (Untreated Cardiac Arrest). Interventions during the no-flow phase of untreated pulseless cardiac arrest focus on early recognition of cardiac arrest and initiation of basic and

www.ketabpezeshki.com 66485457-66963820

advanced life support. Yet only a third of children with OOHCA are provided with bystander CPR.

Low-Flow Phase (Resuscitation). During untreated cardiac arrest, circulation has stopped (i.e., the no-flow phase). The low-flow phase begins once resuscitation measures (chest compressions) are implemented to generate blood flow. Specific considerations related to chest compressions and advanced life support medications are discussed later.

Postresuscitation Phase. The postarrest syndrome is a unique and complex combination of pathophysiologic processes that occurs after successful resuscitation. This postarrest syndrome includes (1) postarrest brain injury, (2) postarrest myocardial dysfunction, (3) systemic ischemia-reperfusion response, and (4) the unresolved pathologic process that caused the cardiac arrest.

Clinical manifestations of postarrest brain injury include coma, seizures, myoclonus, varying degrees of neurocognitive dysfunction (ranging from memory deficits to persistent vegetative state), and brain death. Mild induced hypothermia is the best-established postresuscitation therapy for adult postarrest brain injury. Two seminal articles established that induced hypothermia (32-34° C) could improve outcome for comatose adults after resuscitation from VF cardiac arrest.[41,42] In both randomized controlled trials, the inclusion criteria included patients older than 18 years who were persistently comatose after successful resuscitation from nontraumatic VF. Interpretation and extrapolation of these studies to children are difficult. Hyperthermia after resuscitation from cardiac arrest is common in children because of inflammatory mediators.[43] It is reasonable to believe that mild induced systemic hypothermia may benefit children resuscitated from nontraumatic cardiac arrest. However, benefit from this treatment has not been rigorously studied and reported in children or in any patients with non-VF arrests. Multicenter trials of induced hypothermia in children after both in-hospital cardiac arrest and traumatic arrest are ongoing. Emerging neonatal trials of selective brain cooling and whole-body cooling show improved outcomes for this therapy in neonatal hypoxic-ischemic encephalopathy.[44,44A]

Postarrest myocardial dysfunction and hypotensive shock are very common among pediatric survivors of cardiac arrest. It is interesting to note that postarrest myocardial dysfunction appears to be pathophysiologically similar to sepsis-related myocardial dysfunction, including increases in inflammatory mediator and nitric oxide production.[45-47] Although the optimal management of postarrest hypotension and myocardial dysfunction have not been defined, data suggest that aggressive hemodynamic support may improve outcomes. Controlled trials in animal models have shown that dobutamine, milrinone, or levosimendan can effectively ameliorate postarrest myocardial dysfunction.[48-51] In clinical observational studies, fluid resuscitation has been provided for pediatric patients with hypotension and concomitant low central venous pressure, and various vasoactive infusions, including epinephrine, dobutamine, and dopamine, have been provided for the myocardial dysfunction.*

Management

Chest Compressions

Blood flow during CPR is generated by chest compressions. For children the main mechanism of blood flow is from cardiac compression. The cardiac output (CO) depends on the product of the stroke volume and heart rate. The force of compressions is a major determinant of stroke volume, and the rate of compressions is the sole determinant of heart rate. Stroke volume also depends on preload. Therefore patients with cardiac arrests precipitated by circulatory shock (e.g., hypovolemic or septic shock) may need additional intravascular volume to generate an adequate stroke volume with chest compressions. Notably, excellent CPR can result in a CO 10 to 25% of that in normal sinus rhythm.

Adequate myocardial blood flow is necessary for return of spontaneous circulation. During CPR, myocardial blood flow depends on coronary perfusion pressure or the "driving pressure" of blood into the coronary arteries from the aorta (i.e., the difference between the aortic and right atrial pressures during the relaxation phase). If the coronary perfusion pressure falls below 15 mm Hg during CPR in adults, the likelihood for a return of spontaneous circulation is substantially decreased.[54] Animal data suggest that outcomes improve as coronary perfusion pressure increases above 25 mm Hg.[55] Moreover, even relatively brief interruptions to chest compressions (e.g., 4-second pauses for two rescue breaths) lead to substantial decreases in the aortic relaxation pressure and coronary perfusion pressure, thereby resulting in inadequate myocardial perfusion[56,57] (Fig. 10-1).

Circumferential versus Focal Sternal Compressions

In animal models of cardiac arrest, circumferential CPR (e.g., vest or load-distributing band CPR, encircling hands and compression with two thumbs) provides better CPR hemodynamics than focal compressions (e.g., hands on chest, two-finger technique). In smaller infants, the recommended CPR technique for two rescuers is to encircle the chest with both hands and depress the sternum with the thumbs while compressing the thorax circumferentially (when the resuscitator's hands are relatively large enough to do so[58] (Fig. 10-2). This "two-thumb" circumferential compression technique results in higher systolic and diastolic blood pressures and a higher pulse pressure than traditional two-finger compression of the sternum.[59]

Chest Compression Rate

Although the optimal chest compression rate is unknown, data from large studies of animals have shown that coronary perfusion pressure, CO, and survival are substantially superior with chest compression rates of 100 per minute compared with rates of less than 80 per minute.[28,29] In addition, clinical studies in adults have shown that end-tidal carbon dioxide levels, a marker of cardiac output during CPR, were significantly higher with chest compressions at 120 versus 80 per minute.[60]

Although restoration of coronary perfusion during CPR is critical for successful return of spontaneous circulation, adequate cerebral perfusion is important for mitigating the injurious effects of cerebral anoxia during cardiac arrest. Unlike myocardial blood flow, cerebral blood flow is generated during the compression phase of CPR. Forceful, uninterrupted chest compressions at a rate of 120 per minute compared with 60 per minute improves both cerebral and coronary perfusion pressures compared with less forceful compressions or compressions at a lower rate.[61,62] In addition, vasoconstrictors, such as epinephrine or vasopressin, preferentially direct the CO during CPR to the coronary and cerebral circulations.

During this phase, the only source of coronary and cerebral perfusion comes from the blood pressure generated by good chest compressions. Any interruption in chest compressions, whether to perform procedures, analyze rhythms, check for pulses, or change compressors, is potentially harmful. For VF and pulseless VT, rapid determination of electrocardiographic rhythm and prompt defibrillation when appropriate are important. For cardiac arrests resulting from asphyxia or ischemia, adequate myocardial perfusion and myocardial oxygen delivery with ventilation to match blood flow is important.

Despite evidence-based guidelines, extensive provider training, and provider credentialing in resuscitation medicine, the quality of

*References 41, 42, 45, 46, 52, 53.

www.ketabpezeshki.com 66485457-66963820

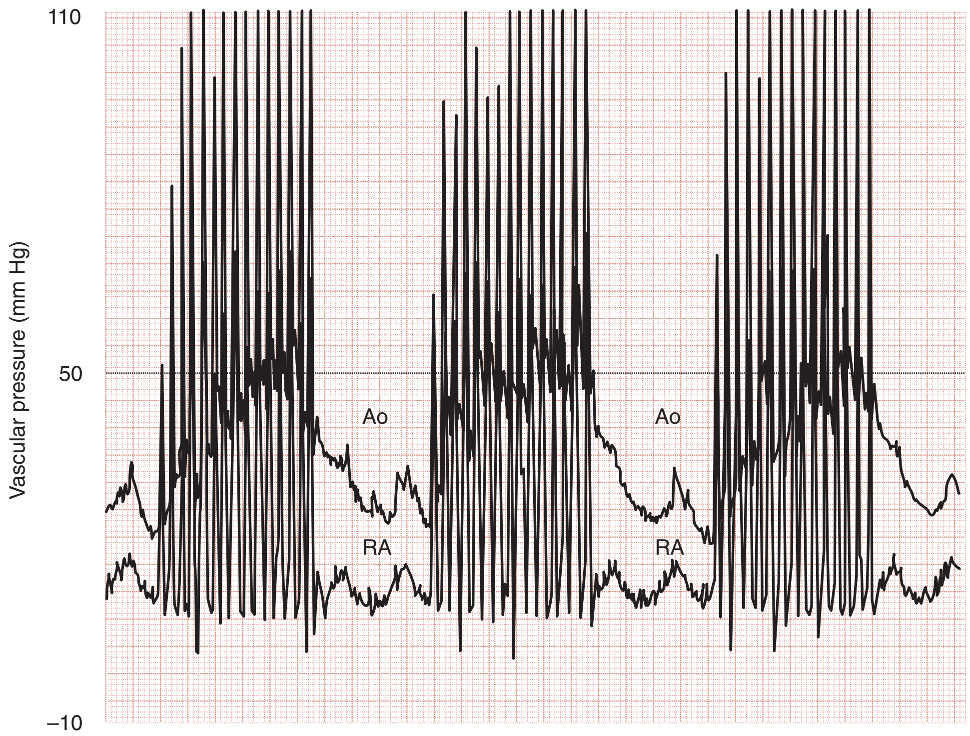


Figure 10-1. Cerebral perfusion pressure with cardiopulmonary resuscitation. *Ao,* aorta; *RA,* right atrium. (Courtesy University of Arizona, Department of Pediatrics, Division of Pediatric Critical Care.)

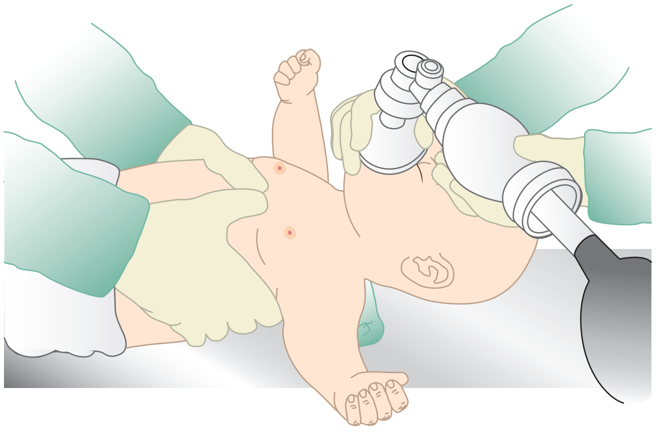


Figure 10-2. Hand-thumbs encircling technique for chest compression in infants with cardiopulmonary failure.

CPR is typically poor. Slow compression rates, inadequate depth of compression, and substantial pauses are the norm.[63-65] Moreover, observed ventilation rates during professional rescuer CPR are often too high, potentially leading to deleterious effects on venous return and outcome.[66] The resuscitation mantra is *Push hard, push fast, minimize interruptions, allow full chest recoil, and do not over-ventilate.* This approach can markedly improve myocardial, cerebral, and systemic perfusion and will likely improve outcomes.[67]

Chest Compression–Ventilation Ratios (Table 10-2)

Ideal compression-to-ventilation ratios for pediatric patients are unknown. Physiologic estimates suggest that the amount of ventilation needed during CPR is much less than the amount needed during a normal perfusing rhythm because the CO (and therefore pulmonary blood flow) during CPR is only 10 to 25% of that during normal sinus rhythm.[68] The best ratio of compressions to

Table 10-2 American Heart Association–Recommended Compression-Ventilation (C:V) Ratios by Age

NEONATE	INFANT OR CHILD—SINGLE RESCUER	INFANT OR CHILD—TWO RESCUERS	ADULT
3:1	30:2	15:2	30:2

ventilations depends on many factors, including the compression rate, the tidal volume, the blood flow generated by compressions, and the time that compressions are interrupted to perform ventilations. In a manikin model of pediatric CPR, a chest compression-to-ventilation (CC:V) ratio of 15:2 delivered the same minute ventilation as CPR with a CC:V ratio of 5:1, but the number of chest compressions delivered was 48% higher with the 15:2 ratio.[69,70] The benefits of positive pressure ventilation (increased arterial oxygen content and carbon dioxide elimination) are balanced against the adverse consequence of impeding circulation because of increases in intrathoracic pressure and venous return to the heart.

For adults, mathematical models of oxygen delivery during CPR suggest that the optimal CC:V ratio is approximately 30:2 for two-rescuer health care provider CPR and is closer to 50:2 for single-lay rescuers.[71] Similar mathematical models adjusted to the known physiologic variables in children indicate that CC:V ratios from 10:2 to 30:2 would be reasonable to optimize tissue oxygen delivery during CPR.[72]

The present recommendations for CC:V ratios during CPR are based on rational conjecture from animal, manikin, and mathematical models, as well as educational theory on the retention of skills in adult learners. In the 2010 AHA guidelines, a universal CC:V ratio of 30:2 is recommended for single-person bystander CPR. For two-rescuer CPR, a 15:2 ratio is recommended for neonates, infants, and children beyond the newly born (infant at the time of birth) period. For the newly born, a ratio of 3:1 is recommended, resulting in a greater number of ventilations

www.ketabpezeshki.com 66485457-66963820

per minute, but nearly the same number of compressions (100 vs. 90 per minute).[58] This recommended ratio was arrived at by consensus to balance educational issues (i.e., the benefit to single-rescuer bystanders of remembering only one compression-to-ventilation ratio of 30:2) with what is known about the physiology of the cardiac and pulmonary circulations of children during cardiac arrest.

Leaning

In a large observational study of OOHCAs, incomplete release or "leaning" occurred in more than 10% of compressions and was observed in 16 of 173 (9%) CPR episodes.[73,74] Observations during in-hospital pediatric CPR indicate that leaning is a common phenomenon, occurring in 23% of chest compressions.[75] Leaning pressures of approximately 15% of body weight may affect intrathoracic pressure and impede the hemodynamics of CPR.[75,76]

Real-Time Cardiopulmonary Resuscitation Feedback

In an effort to optimize CPR quality, new technology has been developed that monitors CPR through a force sensor and accelerometer on the chest. This information is transmitted to a defibrillator monitor to provide quantitative verbal feedback to the rescuer on the rate and force of compressions as well as the frequency and volume of ventilations. Recent studies document that poor-quality CPR, as analyzed by a feedback device, reduces the likelihood of defibrillation success,[74] and rescuers can use this type of automated feedback to improve CPR quality and compliance with current guidelines.[77] The optimal goals for aortic pressures during pediatric CPR are unknown. Animal data and adult data suggest that a reasonable goal for the aortic diastolic (or relaxation) pressure is greater than 20 to 30 mm Hg.[54,55] Similarly, a reasonable goal for the aortic systolic (or compression) pressure is greater than 50 mm Hg for a newborn, 60 mm Hg for an infant, 70 to 80 mm Hg for a child, and 80 to 90 mm Hg for an adolescent.

Compression-Ventilation (Standard) versus Compression-Only ("Hands-Only") Cardiopulmonary Resuscitation

Foregoing ventilation in the pediatric patient during CPR provided by trained providers is not prudent because respiratory arrest and asphyxia generally precede pediatric cardiac arrest.

Multiple studies in adults with OOHCA have demonstrated that chest compressions alone ("hands-only" CPR) yielded survival outcomes that were as good if not better than standard CPR with ventilations included.[78-80] Not surprising, animal studies of bystander CPR for asphyxia-precipitated cardiac arrests demonstrate that the addition of rescue breathing to compressions results in much better outcomes than chest compressions alone.[81,82] Chest compressions alone, however, were superior to no CPR at all, even with hypoxia-induced cardiac arrest. These studies support the need for rescue breathing as a critical component of CPR for pediatric asphyxia-precipitated cardiac arrests. A large population-based study in Japan found that children with OOHCA of noncardiac origin (i.e., asphyxial or ischemic) had significantly improved survival when standard bystander CPR (with ventilation included) was provided when compared with compression-only CPR. This survival benefit, however, was not found to be present among children whose OOHCA was of primary cardiac origin.[83] Thus, compression-only CPR is not recommended for the majority of pediatric cardiac arrests. For an older child with a sudden collapse from cardiac arrest (i.e., presumed VF or VT), compression-only CPR is a reasonable choice for bystander CPR.

Advanced Life Support Medications during the Low-Flow Phase of Cardiopulmonary Resuscitation

Figure 10-3 demonstrates a simplified algorithm for pediatric pulseless cardiac arrest. Table 10-3 lists medications commonly used during pediatric resuscitation including dosages and indications.

Although animal studies indicate that epinephrine can improve initial resuscitation success after both asphyxial and VF cardiac arrests, no single medication has been shown to improve survival to hospital discharge outcome after pediatric cardiac arrests. Medications commonly used for CPR in children are vasopressors (epinephrine or vasopressin), calcium salts, sodium bicarbonate, and antiarrhythmics (amiodarone or lidocaine). During CPR, epinephrine's alpha-adrenergic effect increases systemic vascular resistance (SVR), increasing diastolic blood pressure, which in turn increases coronary perfusion pressure and blood flow and increases the likelihood of the return of spontaneous circulation (ROSC). Epinephrine also increases cerebral blood flow during CPR because peripheral vasoconstriction directs a greater proportion of flow to the cerebral circulation. The beta-adrenergic effect increases myocardial contractility and heart rate and relaxes smooth muscle in the skeletal muscle vascular bed and bronchi, although this effect is of less importance. Epinephrine also changes the character of VF (i.e., higher amplitude, more "coarse"), increasing the likelihood of successful defibrillation.

Prospective and retrospective studies indicate that use of high-dose epinephrine in adults or children (0.05-0.2 mg/kg) does not improve survival and may be associated with a worse neurologic outcome.[66-69] A randomized, blinded, controlled trial of rescue high-dose epinephrine versus standard-dose epinephrine after failed initial standard-dose epinephrine for pediatric in-hospital cardiac arrest demonstrated a worse 24-hour survival rate in the high-dose epinephrine group.[84] *High-dose epinephrine cannot be recommended for routine use during CPR.*

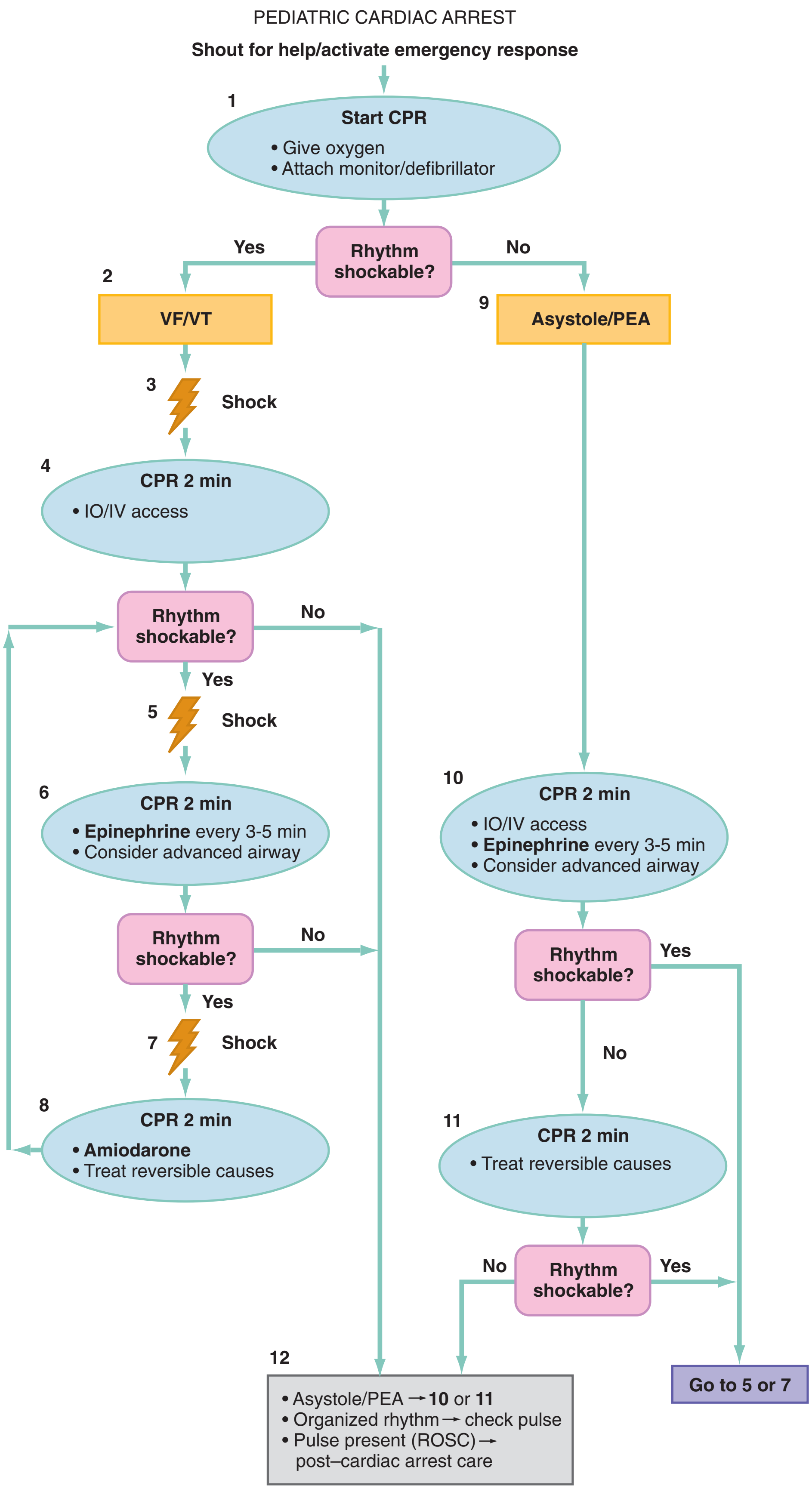
Calcium salts (calcium gluconate, calcium chloride) are commonly used in pediatric resuscitation for sepsis, transfusion-associated ionized hypocalcemia, specific toxidromes, and in newborns after cardiac surgery. Data on calcium salts in cardiac arrest, however, do not support its routine use. A controlled analysis of the GWTG-R database demonstrated significantly decreased survival to hospital discharge among children receiving calcium salts during CPR.[85] Current recommendations for calcium salts during CPR are limited to cases of documented hypocalcemia, hyperkalemia, hypermagnesemia, or known or suspected intoxication with calcium channel blockers.[86]

Pediatric Ventricular Fibrillation and Ventricular Tachycardia

Although asystole and pulseless electrical activity (PEA) are the most common rhythms seen with in-hospital pediatric cardiac arrest, VF and pulseless VT are not rare.[19] VF/VT may occur as the primary inciting arrest rhythm (i.e., arrhythmogenic arrest), arising from a variety of underlying myocardial pathologies (e.g., acute infectious cardiomyopathies, congenital heart disease, Wolff-Parkinson-White syndrome, channelopathies, or electrolyte derangements. Of 1005 pediatric in-hospital cardiac arrests in the GWTG-R database, 25% of the patients had VF/VT at some point during the resuscitation, 10% as an initial rhythm and an additional 15% as subsequent VF/VT (i.e., some time later during the resuscitation effort).[30] Asphyxia-associated VF (presumably subsequent VF) is also well documented in pediatric drowning patients.[87]

Traditionally, VF and VT have been considered "good" cardiac arrest rhythms, resulting in much better outcomes than after

www.ketabpezeshki.com 66485457-66963820



Doses/Details

CPR quality
- Push hard (≥1/3 of anterior-posterior diameter of chest) and fast (at least 100/min) and allow complete chest recoil
- Minimize interruptions in compressions
- Avoid excessive ventilation
- Rotate compressor every 2 minutes
- If no advanced airway, 15:2 compression-ventilation ratio. If advanced airway, 8-10 breaths per minute with continuous chest compressions

Shock energy for defibrillation
- First shock 2 J/kg, second shock 4 J/kg, subsequent shocks ≥4 J/kg, maximum 10 J/kg or adult dose.

Drug therapy
- **Epinephrine IO/IV dose:** 0.01 mg/kg (0.1 mL/kg of 1:10,000 concentration). Repeat every 3-5 minutes. If no IO/IV access, may give endotracheal dose: 0.1 mg/kg (0.1 mL/kg of 1:1000 concentration).
- **Amiodarone IO/IV dose:** 5 mg/kg bolus during cardiac arrest. May repeat up to 2 times for refractory VF/pulseless VT.

Advanced airway
- Endotracheal intubation or supraglottic advanced airway
- Waveform capnography or capnometry to confirm and monitor ET tube placement
- Once advanced airway in place, give 1 breath every 6-8 seconds (8-10 breaths per minute)

Return of spontaneous circulation (ROSC)
- Pulse and blood pressure
- Spontaneous arterial pressure waves with intra-arterial monitoring

Reversible causes
- **H**ypovolemia
- **H**ypoxia
- **H**ydrogen ion (acidosis)
- **H**ypoglycemia
- **H**ypo-/hyperkalemia
- **H**ypothermia
- **T**ension pneumothorax
- **T**amponade, cardiac
- **T**oxins
- **T**hrombosis, pulmonary
- **T**hrombosis, coronary

Figure 10-3. Management algorithm for infants and children with cardiopulmonary arrest. *AED,* automated external defibrillator; *CPR,* cardiopulmonary resuscitation; *IO,* intraosseous; *IV,* intravenous; *PEA,* pulseless electrical activity; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia. (Adapted from Pediatric Advanced Life Support Course Guide. Copyright © 2010, American Heart Association.)

www.ketabpezeshki.com 66485457-66963820

Table 10-3 Medications Used in Pediatric Resuscitation

DRUG	INDICATIONS AND DOSAGE
Adenosine	SVT 0.1 mg/kg IV/IO rapid push (max 6 mg), second dose 0.2 mg/kg IV/IO rapid push (max 12 mg)
Alprostadil (PGE_1)	Ductal-dependent congenital heart disease (all forms) 0.05-0.1 µg/kg/min IV/IO infusion initially, then 0.01-0.05 µg/kg/min IV/IO
Amiodarone	SVT, VT (with pulses) 5 mg/kg IV/IO load over 20-60 min (max 300 mg), repeat to daily max 15 mg/kg (or 2.2 g) Pulseless arrest (i.e., VF/pulseless VT) 5 mg/kg IV/IO bolus (max 300 mg), repeat to daily max 15 mg/kg (or 2.2 g)
Atropine sulfate	Bradycardia (symptomatic) 0.02 mg/kg IV/IO (min dose 0.1 mg, max single dose child 0.5 mg, max single dose adolescent 1 mg), may repeat dose once, max total dose child 1 mg, max total dose adolescent 2 mg 0.04-0.06 mg/kg ETT
Calcium chloride 10%	Hypocalcemia, hyperkalemia, hypermagnesemia, calcium channel blocker overdose 20 mg/kg (0.2 mL/kg) IV/IO slow push during arrest or if severe hypotension, repeat PRN
Dextrose (glucose)	Hypoglycemia 0.5-1 g/kg IV/IO ($D_{25}W$ 2-4 mL/kg; $D_{10}W$ 5-10 mL/kg)
Dobutamine	Congestive heart failure, cardiogenic shock 2-20 µg/kg/min IV/IO infusion; titrate to desired effect
Dopamine	Cardiogenic shock, distributive shock 2-20 µg/kg/min IV/IO infusion; titrate to desired effect
Epinephrine	Pulseless arrest, bradycardia (symptomatic) 0.01 mg/kg (0.1 mL/kg) 1 : 10,000 IV/IO q3-5 min (max 1 mg; 1 mL) 0.1 mg/kg (0.1 mL/kg) 1 : 1000 ETT q3-5 min Hypotensive shock 0.1-1 µg/kg/min IV/IO infusion (consider higher doses if needed)
Hydrocortisone	Adrenal insufficiency 2 mg/kg IV bolus (max 100 mg)
Lidocaine	VF/pulseless VT, wide-complex tachycardia (with pulses) 1 mg/kg IV/IO bolus Maintenance: 20-50 µg/kg/min IV/IO infusion (repeat bolus dose if infusion initiated >15 min after initial bolus) 2-3 mg/kg ETT
Milrinone	Myocardial dysfunction and increased SVR, PVR Loading dose: 50-75 µg/kg IV/IO over 10-60 min followed by 0.5-0.75 µg/kg/min IV/IO infusion
Norepinephrine	Hypotensive (usually distributive) shock (i.e., low SVR and fluid refractory) 0.1-2 µg/kg/min IV/IO infusion; titrate to desired effect
Oxygen	Hypoxia, hypoxemia, shock, trauma, cardiopulmonary failure, cardiac arrest Administer 100% O_2 via high-flow O_2 delivery system (if spontaneous ventilations) or ETT (if intubated); titrate to desired effect
Procainamide	SVT, atrial flutter, VT (with pulses) 15 mg/kg IV/IO load over 30-60 min (do not use routinely with amiodarone)
Sodium bicarbonate ($NaHCO_3$)	Metabolic acidosis (severe), hyperkalemia 1 mEq/kg IV/IO slow bolus Sodium channel blocker overdose (e.g., tricyclic antidepressant) 1-2 mEq/kg IV/IO bolus until serum pH > 7.45 (7.50-7.55 for severe overdose) followed by IV/IO infusion of 150 mEq $NaHCO_3$/L solution to maintain alkalosis

$D_{10}W$, dextrose 10% in water; *$D_{25}W$,* dextrose 25% in water; *ETT,* endotracheal tube; *IV,* intravenously; *IO,* intraosseously; *O_2,* molecular oxygen; *PRN,* as needed; *PVR,* pulmonary vascular resistance; *SVR,* systemic vascular resistance; *SVT,* supraventricular tachycardia; *VT,* ventricular tachycardia.

asystole and PEA. However, GWTG-R data establish that survival to discharge was more common among children with *initial* VF/VT than among children with *subsequent* VF/VT (35% vs. 11%; odds ratio 2.6, 95% confidence interval [CI] 1.2-5.8).[30] Surprisingly, the subsequent VF/VT group had worse outcomes than children with asystole/PEA (11% vs. 27% survival). These data suggest that outcomes after *initial* VF/VT in children (an arrhythmogenic arrest) are "good," but outcomes after *subsequent* VF/VT (i.e., VF/VT in the setting of an asphyxial or ischemic arrest) are worse, even compared with initial asystole/PEA without subsequent VF/VT.

Defibrillation

Defibrillation is necessary for successful resuscitation from VF cardiac arrest. When prompt defibrillation is provided soon after the induction of VF in a cardiac catheterization laboratory, the rates of successful defibrillation and survival approach 100%. In general, the mortality rate increases by 5 to 10% per minute of delay to defibrillation.[88] Because pediatric cardiac arrests are commonly a result of progressive asphyxia or shock (or both), the initial treatment of choice is prompt CPR, not defibrillation. This emphasis is balanced against the increasing evidence that VF in children is not rare, that outcomes after arrhythmogenic VF arrests

www.ketabpezeshki.com 66485457-66963820

are superior to those after other types of cardiac arrests, and that early rhythm recognition is necessary for optimal care.

Because of the increasing awareness that "shockable" rhythms are not uncommon in children, greater attention has been focused on the dose for pediatric defibrillation. The recommended shock dose is 2 to 4 joules (J)/kg, which is based on animal studies of short-duration VF and a single retrospective study of in-hospital (short-duration) VF with 91% (52 of 57) defibrillation success.[89] More recent animal and pediatric data indicate that 2 J/kg is often ineffective at terminating fibrillation, and higher doses up to 10 J/kg may be needed to terminate VF.[89,91] Thus recent recommendations suggest an initial dose of 2 to 4 J/kg followed by 4 J/kg if VF is not terminated; if VF continues, consider increasing the defibrillation dose up to 10 J/kg, not to exceed adult maximum doses.

Cardiopulmonary Resuscitation in Pediatric Bradycardia

Neonates, infants, and children are primarily dependent on heart rate for maintenance of CO. Their ability to augment stroke volume to increase CO is limited, and physiologic or pathophysiologic states leading to an increase in CO are hallmarked by tachycardia. Conversely, illnesses or injuries resulting in negative chronotropy (e.g., heart block, toxicity from beta-blockers or calcium channel blockers) tend to result in more profound shock and hypoperfusion in children than in adults with similar processes.

Bradycardia with hypoperfusion (without pulselessness) is a very common hemodynamic state for critically ill children during the prearrest phase. Early clinical studies of terminally ill children demonstrated almost ubiquitous prevalence of bradycardia before the onset of cardiac arrest.[93] Animal models of asphyxia have demonstrated a predictable hemodynamic progression from tachycardia to bradycardia with hypotension, followed by PEA and asystole,[94] and that CPR earlier in this continuum is associated with more favorable outcomes.[82,95] Given that the majority of children with cardiac arrest experience respiratory insufficiency or circulatory insufficiency or both before the onset of pulselessness, *a bradycardic child in shock should be considered to be in a prearrest state.* Multiple reversible causes need to be considered, but immediate support of cardiovascular status is essential.

Neonatal resuscitation algorithms have recommended escalation of respiratory and cardiac support for the neonate whose heart rate is less than 60 beats/min, including the provision of chest compressions if bradycardia does not resolve with effective ventilation and oxygenation. Multiple studies of pediatric patients from the GWTG-R database have shown that 18 to 54% of patients younger than age 18 who receive chest compressions in the hospital are in a state of bradycardia and hypoperfusion, as opposed to pulselessness, when CPR is initiated.[19,25,96] A multivariate analysis from the NRCPR demonstrated an association between CPR for bradycardia (as opposed to pulseless arrest) and survival to discharge, even when controlling for age, diagnosis, and event characteristics.[96] Current AHA guidelines recommend the consideration of immediate chest compressions for a child with a heart rate of less than 60 with obvious hypoperfusion.[86]

Extracorporeal Circulatory Support during Cardiac Arrest

The use of extracorporeal cardiovascular support for cardiac arrest depends on the rapid availability of the resources, equipment, and personnel to establish mechanical circulatory support, most typically ECMO or, less commonly, VADs. Multiple case series have reported favorable outcomes in children placed on ECMO during cardiac arrest, with some demonstrating a relationship between shorter duration of CPR before ECMO support and survival.[97-99] One retrospective series of 66 children placed on ECMO for cardiac arrest demonstrated an overall survival to hospital discharge of 45%; the median time of CPR before established ECMO circulation was 46 minutes.[100] Another single-center study demonstrated 7 of 31 patients (22.5%) surviving to discharge after extracorporeal cardiopulmonary resuscitation (ECPR).[101] Current consensus statements from the AHA state that there is insufficient evidence for a time-based threshold within which ECPR may be beneficial.[86] Centers with resources for ECPR may consider its use for patients with other epidemiologic features known to be favorable (e.g., witnessed arrests, short CPR times).

SEPTIC SHOCK IN THE PEDIATRIC PATIENT

Perspective

Worldwide, sepsis is the leading cause of death in children. In the United States the annual incidence of severe sepsis (defined as sepsis with organ system dysfunction) is 0.56 cases per 1000; mortality for severe sepsis in the pediatric population is 10% overall, with a higher mortality (14%) among children with chronic medical conditions.[102] With historical cohorts exhibiting mortality above 90%, these figures represent a substantial decline in mortality from pediatric sepsis in the past 30 years.[103] In the past decade, both the American College of Critical Care Medicine (ACCM) and the International Consensus Conference on Pediatric Sepsis have put forth recommendations for rigorous definitions and treatment recommendations[104-105]; these efforts have effectively summarized the existing data on pediatric sepsis but are also illustrative of the need for rigorous clinical trials to improve outcomes further.

Pathophysiologic Principles

By definition, shock represents the physiologic state in which cellular oxygen demand for adenosine triphosphate (ATP) production is in excess of oxygen supply. Disruptions in oxygen supply (hypoxia), oxygenation of pulmonary capillary beds (respiratory illness), oxygen content (e.g., anemia or altered oxyhemoglobin binding such as methemoglobinemia), oxygen delivery (hypoperfusion), or oxygen usage at the tissue or cellular level (mitochondrial dysfunction, as in cyanide poisoning) can result in shock. The International Consensus Conference on Pediatric Sepsis defines *septic shock* as the simultaneous presence of (1) systemic inflammatory response, as evidenced by elevation or depression of temperature, heart rate, respiratory rate, and white blood cell count, (2) a documented or suspected infection, and (3) cardiovascular dysfunction, defined as hypotension or need for vasoactive medications despite more than 40 mL/kg crystalloid resuscitation.[105]

The developmental progression of cardiovascular physiology from neonate to adult has important bearings on shock physiology. Adults with sepsis most commonly exhibit a hemodynamic profile consistent with vasomotor paralysis, marked by vasodilatation and increased CO ("warm" shock). By contrast, infants and children with sepsis exhibit greater variability in their hemodynamic profile in sepsis and are most frequently in "cold" shock, marked by relative hypovolemia, vasoconstriction, and myocardial failure. One ICU-based study of children with sepsis with thermodilution catheters found that 58% of patients had low CO and increased SVR as opposed to 20% having low SVR and increased or normal CO.[106] A more recent study of 30 children in an ICU with fluid-resistant shock showed that the majority (94%) of children with catheter-associated bloodstream infections demonstrated low SVR–high CO (warm) shock, whereas children with community-acquired infections were predominantly (86%) in high SVR–low CO (cold) shock.[107] Neonates have a particular sensitivity to acidosis with respect to increased pulmonary vascular resistance and decreased

www.ketabpezeshki.com 66485457-66963820

Table 10-4 Signs of Shock in Children

COMPENSATED	ADVANCED COMPENSATED	DECOMPENSATED
Tachycardia Cool extremities Prolonged capillary refill Weak peripheral pulses (compared with central pulses)	Depressed mental status Tachypnea Decreased urine output Weak central pulses Acidosis Narrowed or widened pulse pressure (with normal systolic blood pressure)	Any of the signs of compensated shock plus: Hypotension Nondetectable distal pulses

myocardial function. The syndrome of persistent pulmonary hypertension of the newborn (PPHN) is among the prevalent manifestations of sepsis in the newly born; therapy in these children frequently includes a hemodynamic therapeutic regimen targeted toward right ventricular failure.

Clinical Features

Table 10-4 demonstrates the physical signs of compensated, advanced compensated, and decompensated shock as summarized in PALS.[40] Given the dependence of the pediatric patient on heart rate for CO, it can be intuited that tachycardia is the most sensitive sign of shock in children. It is important to note that hypotension is a very late sign in children with shock, and its absence should not be construed as a reassuring sign; patients may have decompensated shock with existing end-organ hypoperfusion and still have a measured blood pressure within normal limits.

Current guidelines from the ACCM recommend that the combined clinical signs of tachycardia, fever, and altered perfusion and altered mental status be used to diagnose sepsis in children.[104] Unfortunately, this clinical triad is lacking in specificity and positive predictive value. Fever is among the most common chief complaints for children presented to an ED, occurring in more than 25% of all patients[108]; discerning what degree of alteration in behavior in a febrile child constitutes altered mentation can be very challenging. A study from a pediatric ED examining children with fever, tachycardia, and tachypnea found that altered mental status (as judged by attending physicians) was present in 19% of children, and its presence had a specificity of 84% and positive predictive value of 24% in predicting sepsis with clinically significant organ system dysfunction.[109] Conversely, data on prehospital care of children in shock have demonstrated that shock may be just as easily underappreciated clinically. A study of children referred to a tertiary PICU found that among 1803 children transported to a tertiary care center with shock, only 335 (19%) were referred specifically for shock, suggesting that signs of hypoperfusion were underappreciated in a substantial subset of patients.[110] Despite these shortcomings of relying on the physical signs alone, the consensus of the ACCM is to recommend "early recognition of pediatric septic shock by clinical examination, not biochemical tests."[104]

Given the difficulty with lack of precision of the physical examination as discussed previously, laboratory and radiologic studies with greater precision for identifying sepsis are desirable. In adult patients, data supporting the use of serum lactate in initial diagnosis as well as in ongoing sepsis management have been repeatedly demonstrated in both ED and ICU studies.[111-114] Additional markers used in adults include procalcitonin,[115] B-natriuretic peptide,[116,117] and markers of coagulopathy or disseminated intravascular coagulation[118,119]; reports examining these laboratory markers in pediatric patients have demonstrated some promise, but robust clinical trials have not yet been performed.[120-123]

Multiple noninvasive techniques for directly assessing hemodynamic states have been examined in pediatric patients; the use of focused bedside ultrasound examining cardiac function,[124] inferior vena cava diameter,[125] aortic pulse wave contour analysis,[107] and electrical velocimetry to measure preload status as well as cardiac index have been documented in small studies.[126] These techniques may hold promise for a more objective hemodynamic assessment in the febrile child to enable an emergency physician to distinguish a child with a harmless febrile illness from one with early septic shock.

Management

Figure 10-4 is an algorithm of the recommended sequence of care in the pediatric patient with sepsis.[104] The pathway is designed to encompass the continuum of care from initial presentation in the ED through definitive management in the ICU setting. The remainder of this chapter focuses on the management elements pertinent to the ED.

Substrate Correction: Hypoglycemia and Hypocalcemia

Hypoglycemia is common among children with sepsis, especially the very young child with poor glycogen stores and underdeveloped capacity for gluconeogenesis. Documented hypoglycemia should be immediately corrected with an IV bolus of dextrose from 0.5 to 1 g/kg. The "rule of 50s" (5 mL/kg of 10% dextrose, 2 mL/kg of 25% dextrose, or 1 mL/kg of 50% dextrose) can be used to rapidly calculate the weight-based dose of dextrose. Given the association of hyperglycemia and poor outcomes among critically ill children and adults, empirical use of glucose (in the absence of documented hypoglycemia) should be avoided.

Developmental cellular physiology is pertinent to calcium metabolism in children; neonates and young infants have poorer capacity for calcium storage in the sarcoplasmic reticulum and underdeveloped T-tubule systems for propagation of calcium channel–associated cardiac myocyte depolarization and maintenance of tetanic contraction.[128] Ionized hypocalcemia has been shown to be prevalent in critically ill children, particularly those having cardiac arrest in the context of septic shock.[22,128]

Fluid Resuscitation

Studies documenting the relationship between amount of initial crystalloid resuscitation and survival in children with sepsis have existed for decades.[129] Current AHA recommendations state that isotonic crystalloid fluids (normal saline, lactated Ringer's) are the initial resuscitation fluid of choice for pediatric patients in shock, irrespective of cause or physiology.[86] Septic shock in children is most frequently marked by relative or absolute hypovolemia; outcomes from shock in children have been shown to be substantially improved when the shock state is reversed as early as possible.[110,130] Volumes of up to and above 60 mL/kg of crystalloid given intravenously (IV) or intraosseously (IO) are frequently necessary for children in shock.

The administration of fluids to the child in shock should be regarded differently than fluid administration in the child who is hypovolemic but not in shock. Current guidelines from the ACCM recommend the administration of fluid in a rapid fashion, ideally with 20 mL/kg being given in a 5-minute period.[104] This rate of fluid administration would permit 60 mL/kg of saline to be given to a septic patient in 15 minutes. A recent study in children in an ED examined multiple methods of fluid administration, showing that 58% of patients received 20 mL/kg in 5 minutes when a pressure bag was used, 68% of patients when a manual push-pull system was used, and none when fluid was administered by gravity

www.ketabpezeshki.com 66485457-66963820

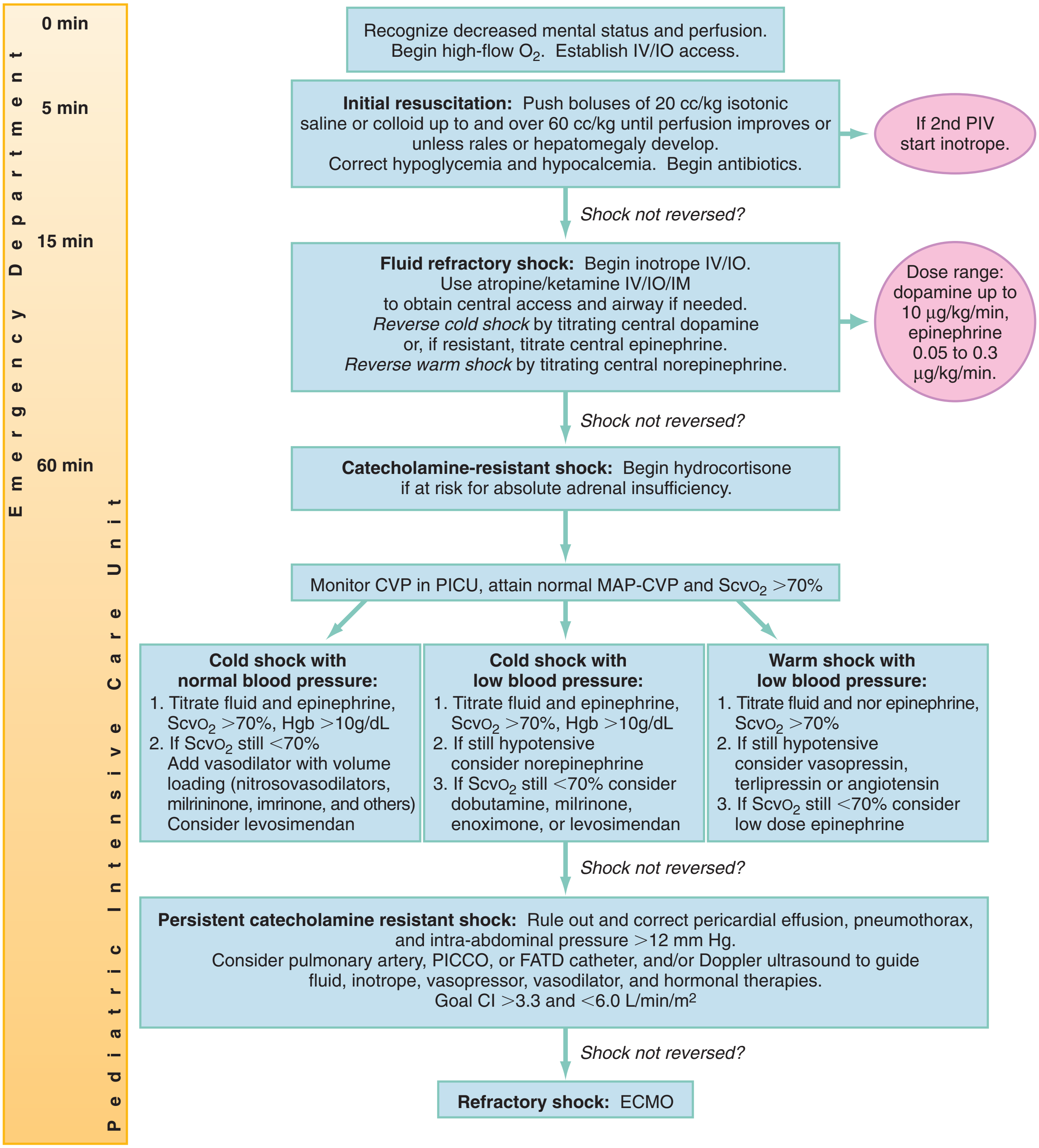


Figure 10-4. Algorithm for time-sensitive, goal-directed stepwise management for hemodynamic support for infants and children with septic shock. *CI,* cardiac index; *CVP,* central venous pressure; *ECMO,* extracorporeal membrane oxygenation; *FATD,* femoral arterial thermodilution; *Hgb,* hemoglobin; *IM,* intramuscular; *IO,* intraosseous; *IV,* intravenous; *MAP,* mean arterial pressure; O_2, oxygen; *PICCO,* pulse-induced contour cardiac output; *PICU,* pediatric intensive care unit; $Scvo_2$, central venous oxygen saturation. (Adapted from Brierly J, et al: Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med 37:666-688, 2009.)

alone.[131] Whatever method is used, it is essential that fluid administration to a child in shock be conceived of as an active process; "hanging fluids" for administration by gravity as would typically be done for a child with mild or moderate dehydration is insufficient.

Vasoactive Medications

The choice to use vasoactive infusions in children with fluid-refractory septic shock takes multiple considerations into account. First, the hemodynamic profile of a child in septic shock is variable and often changes over time. Second, obtaining central venous access in an ill child is an uncommon procedure in most EDs and can be challenging in a hypovolemic patient.[132] Among available agents, dopamine may have the greatest usefulness as a first-line agent given its safety in peripheral venous or intraosseous administration and the ability to titrate the dose to target dopaminergic, beta, and alpha receptors. Dopamine has been associated with leukopenia and a possible risk of infectious complications based on its downregulation of pituitary prolactin and

www.ketabpezeshki.com 66485457-66963820

thyrotropin-releasing hormone secretion; adult ICU data on dopamine use for shock have shown an association between dopamine use and adverse outcomes.[133] Epinephrine and dobutamine may both be prepared in concentrations that are safe for temporary peripheral administration and, depending on the patient's hemodynamic profile, may be appropriate first choices as well.

Corticosteroids

Adrenal insufficiency in sepsis has been reported as a moderately prevalent phenomenon in children and adults.[134-136] Studies on the use of hydrocortisone replacement for sepsis showed early promise in adults,[137] but the most robust randomized trial to date (the CORTICUS trial) showed no significant survival benefit conferred by hydrocortisone compared with placebo.[138] Studies in pediatric patients have yielded inconclusive results.[139,140] Current treatment recommendations by the AHA state that there is insufficient evidence to support or refute the use of exogenous corticosteroids in children with sepsis, nor is there a clear diagnostic modality for adrenal insufficiency that is of optimal reliability.[86] In cases where corticosteroid supplementation is deemed to be warranted, an initial dose of 100 mg/m^2 of hydrocortisone is recommended.

RESPIRATORY FAILURE

Perspective and Epidemiology

Some of the earliest studies in pediatric resuscitation clearly demonstrated improved outcomes among children experiencing respiratory arrest alone compared with patients with cardiac arrest.[21,141] The recognition and management of respiratory failure in children is a focal point of the AHA PALS curriculum; this is based on the fact that effective management of respiratory failure is, in effect, preventative of cardiac arrest in many children.

Pathophysiologic Principles

Anatomic Features Pertinent to Laryngoscopy and Intubation in Children

- *Size*—airway structures are smaller, and the field of vision is more narrow.
- *Adenoidal hypertrophy*—common in young children.
- *Developing teeth*—young infants are edentulous, but the underlying alveolar ridge contains developing tooth buds that are susceptible to disruption.
- *Primary teeth*—in young children, primary teeth can be easily avulsed or aspirated.
- *Tongue*—large relative to size of oropharynx.
- *Superior larynx*—often referred to as *anterior,* the laryngeal opening in infants and young children is actually located in a *superior* position (in infants, the larynx is opposite C_3-C_4 as opposed to C_4-C_5 in adults). This makes the angle of the laryngeal opening with respect to the base of the tongue more acute and visualization more difficult.
- *Hyoepiglottic ligament* (connects base of tongue to epiglottis)—has less strength in young children; thus a laryngoscope blade in the vallecula will not elevate the epiglottis as efficiently as in an adult.
- *Epiglottis*—in children, the epiglottis is narrow and angled acutely with respect to the tracheal axis; thus the epiglottis covers the tracheal opening to a greater extent and can be more difficult to mobilize.
- *Narrowest point* of the young child's airway—occurs at the level of the *cricoid cartilage* instead of at the level of the glottic opening itself.

Clinical Features

Pediatric Respiratory Physiology

Lung. Infants have fewer and smaller alveoli than young children, and their overall gas exchange surface area is disproportionately small. Surface area reaches proportions similar to that in adulthood by 8 years of age. Channels for collateral ventilation (pores of Kuhn and Lambert's channels) are absent in infancy. The overall effect of these phenomena is a greater tendency for alveolar hypoventilation and for the development of atelectasis during a respiratory illness.

Respiratory Mechanics. The pediatric thoracic skeleton is largely cartilaginous and much more compliant than the adult skeleton. Elastic recoil of the chest wall in the young child is essentially absent. A given change in thoracic pressure will result in a larger change in lung volume, similar to the physiology seen in an adult with emphysema. A given change in volume is associated with little or no change in pressure, so a greater amount of work is required to generate a tidal breath.

The high compliance of the pediatric chest wall results in a closing volume (CV; volume at which terminal bronchioles collapse because they are no longer supported by elastic recoil) that can be elevated with respect to functional residual capacity (FRC). If the already diminished elastic recoil is impaired—for example, by supine positioning—CV can exceed FRC to an even greater extent, resulting in the absence of ventilation of some lung segments during normal tidal breathing. Young patients therefore have a greater tendency for intrapulmonary shunting and hypoxemia with the positioning required for airway management.

Accessory respiratory muscles in young children are composed of a lower percentage of slow-twitch muscle fibers and are more susceptible to fatigue compared with the diaphragm. Also, the architecture of the pediatric thorax (horizontal rib orientation with extensive cartilage composition) is such that intercostal and suprasternal muscles are poorly recruited to assist in respiratory effort.

Airway. Airway diameter and length increase with age. The distal airway (bronchioles) lags in growth behind the proximal airway during the first few years of life. Poiseuille's law states that airway resistance is inversely proportional to the fourth power of the radius of the airway. Thus young children have higher resistance to airflow at baseline in their lower airways, and a change in airway diameter of a given dimension will have a much more profound effect on airway resistance in a small child than in an older child or adult. Illnesses that affect the caliber of small airways (such as asthma and viral bronchiolitis) produce a disproportionate increase in work of breathing in infants and children.

Cellular Oxygenation. Resting oxygen consumption in the newborn is twice that of an adult (6 mL/kg/min vs. 3 mL/kg/min). Oxygen consumption in infants is extremely sensitive to physiologic derangement such as fever and hypothermia. The oxyhemoglobin dissociation curve for young infants is shifted to the left (greater affinity for oxygen and poorer tissue oxygen delivery) by the presence of elevated amounts of fetal hemoglobin (HbF). HbF is the main oxygen transport protein in the fetus during the last seven months of development in the uterus and in the newborn until roughly 6 months of age. Functionally, HbF differs most from adult hemoglobin in that it is able to bind oxygen with greater affinity than the adult form, giving the developing fetus better access to oxygen from the mother's bloodstream. In newborns, HbF is nearly completely replaced by adult hemoglobin by approximately the 12th week of postnatal life.

In a clinical study of elective surgery patients, the mean time to desaturation to 90% was 118 seconds in infants, 168 seconds in toddlers, and 248 seconds in children older than 3 years. The time

www.ketabpezeshki.com 66485457-66963820

required for the saturation to fall from 95% to 90% was significantly shorter in infants than in older children as well (8 seconds compared with 16 seconds).[141] These findings occurred after a 2-minute period of ventilation with 100% oxygen before neuromuscular blockade, a preoxygenation time determined by some of the same authors in a separate clinical study to be optimal for minimizing risk of early desaturation.[143] It is logical to conclude that these times to critical desaturation occur even more rapidly in ill children.

Management Considerations Specific to Pediatrics

Effectiveness of Tracheal Intubation versus Bag-Valve Mask Ventilation in Prehospital Care

Pediatric patients constitute a small minority of patients cared for by prehospital personnel[144-146]; reported frequency of tracheal intubation for individual prehospital care communities is generally very low, with incidence for an individual provider being as infrequent as once every 3 years.[10,145] Optimal methods of maintaining competency for prehospital care providers have not been established.

Previous studies of prehospital airway management in children with cardiac arrest found some associations between successful intubations and improved short-term outcomes, although no strong association with survival.[24,147] The most robust trial to date examining prehospital management of pediatric respiratory failure involved a controlled trial of bag-valve-mask ventilation versus tracheal intubation (performed on alternate days) by prehospital care providers in California.[148] In this trial, 820 patients were enrolled; no significant difference in survival or neurologically intact survival was demonstrated between the two groups. Limitations ascribed to this landmark study include relatively short prehospital care times (median 20-23 minutes) and the fact that intubation was at that time a new skill for the provider community in question.

Equipment Considerations for Pediatric Intubation

Endotracheal Tubes. The two most commonly applied rules of thumb for sizing of endotracheal tubes (ETTs) are the age-based rule and selection based on body length (the Broselow-Luten tape). The age-based rule is as follows:

$$[\text{Age in years}/4] + 4 = \text{ETT size}$$

King and colleagues found this rule to correctly predict ETT size within a range of 1 mm in 97.5% of patients.[149] The Broselow-Luten tape selects size of ETT based on the length of the patient. The initial study of the validity of the Broselow-Luten tape found it to be more accurate than age-based selection criteria.[150] A more recent study by Hofer and colleagues also found that the Broselow-Luten tape was more accurate (correct in 55% of patients) than the age-based rule (correct in 41%), but also found that the Broselow-Luten tape was prone to underestimating ETT size (in 39% of patients) whereas the age-based rule tended to overestimate (in 57% of patients).[151] Another recent study found that there was no difference between the accuracy rates of the two methods, and that Broselow-Luten tape measurement and the age-based rule predicted the same size of ETT in 66% of patients.[152] Either method may be used to determine ETT size in children, but the advantage of the Broselow-Luten tape is that mathematical calculations do not need to be used and therefore this method is preferred in most settings.

Cuffed ETTs exist in sizes as small as 2.5 mm inner diameter (ID). Multiple studies in the pediatric operating room (OR) and ICU have demonstrated no significant difference in the incidence of postextubation stridor or extubation failure when comparing children intubated with cuffed versus uncuffed ETTs.[153-155] Current AHA recommendations state that either cuffed or uncuffed tubes may be considered for emergency intubation for children but that cuffed tubes may be more appropriate when high inflating pressures are anticipated. If a cuffed tube is to be used, select a tube that is one half size smaller than the size determined by standard calculations for an uncuffed ETT tube.

Medications

Atropine. Premedication with atropine is recommended by the American College of Emergency Physicians for children younger than 1 year and those undergoing intubation with succinylcholine (SCh). Atropine premedication is believed to minimize bradycardia during laryngoscopy and ETT placement, given the increased vagal tone in the pediatric patient. Clinical data supporting the efficacy of this recommendation are lacking; a study of pediatric ED intubations showed a very low incidence of bradycardia during intubation and no significant difference in its occurrence between patients premedicated with atropine and those who were not.[156]

Succinylcholine. The U.S. Food and Drug Administration (FDA) Advisory Committee for Anesthetic and Life Support Drugs recommended a labeling revision for SCh at its meeting in 1992. The new label states that routine use of SCh in children should be avoided and alternative agents (nondepolarizing neuromuscular blockers [NMBs]) used except in specific circumstances, including laryngospasm, full stomach, or intramuscular use when intravenous access is difficult or absent.[157] Succinylcholine, however, remains in widespread use in children for rapid sequence intubation (RSI) despite the labeling change. In one large multihospital database, SCh was the NMB used in 91% of patients who underwent RSI.[158] Succinylcholine may still be considered a first-line NMB for RSI in children; initial administration of SCh in children should be at a higher dose of 2 mg/kg.

Rescue Devices

The laryngeal mask airway (LMA) is the airway rescue device of choice in children. Studies have documented ease of placement and use by multiple classes of care providers with a minimal incidence of complications.[159] No consistent rule of sizing exists for LMAs in children; all LMAs are labeled with parameters of the appropriate weight of patients in whom the device can be used, and the Broselow-Luten resuscitation tape has LMA sizes based on length. As with ETTs, a range of sizes should be available for use in the event of an initial device performing suboptimally. One OR-based study found that an LMA can be accurately sized in the majority of children by comparing the width of the cuff with the width of the patient's second, third, and fourth digits; however, this method is not routinely used by emergency providers.[160]

ACUTE LIFE-THREATENING EVENTS

Acute life-threatening event (ALTE) is a description of a characteristic clinical presentation; therefore the pathophysiology of an ALTE has not been clearly defined. Children with ALTE pose a diagnostic and therapeutic challenge to emergency physicians because the cause of such events is diverse and ranges from minor to life-threatening. In addition, studies of children with ALTE reveal that in 50% of the cases, a definitive diagnosis will not be made.[161,162]

The etiology of ALTE is extensive and includes infection (sepsis; respiratory syncytial virus or other respiratory viruses; pertussis; or central nervous system infection), gastroesophageal reflux disease (GERD) with or without obstructive apnea, congenital

www.ketabpezeshki.com 66485457-66963820

malformations (tracheomalacia, vascular rings, pulmonary slings), seizure disorder, cardiac dysrhythmias, congenital cardiac malformations, metabolic derangements (hypoglycemia), and child abuse.[162] A number of authors suggest clues to the various categories of diagnoses; however, many of the signs and symptoms of these conditions overlap. In a retrospective study of 196 infants presented with an ALTE, the discharge diagnoses included seizure (25%), GERD (18%), febrile convulsion (12%), bronchiolitis (9%), apnea (9%), pertussis (6%), choking (5%), upper respiratory tract infections (4%), cyanotic episode (2%), gastroenteritis (2%), asthma (1%), head injury (1%), feeding difficulties (1%), urinary tract infection (1%), and breath-holding (1%).[163]

The infant with a history of an ALTE may look well and act normally at the time of the evaluation by the nonhospital medical provider or the emergency physician. However, infants who are judged by nonhospital personnel to have choked, who have turned blue, or who are showing other signs suggestive of a possible ALTE should be considered seriously ill and transported to the ED for evaluation.[162] Fifty percent of children brought to the ED after an ALTE have an entirely normal clinical examination, and the final diagnosis often correlates poorly with the presenting signs and symptoms, which often include cyanosis, breathing difficulties, abnormal movements, loss of consciousness, vomiting, pallor, and choking.[162]

The ED evaluation of children with ALTE is tailored to the child's history and physical examination findings but often includes laboratory and radiographic studies. Laboratory evaluation may include complete blood count, serum glucose, electrolytes, blood and urine cultures if the child is younger than 1 month or febrile, a toxicology screen, and an electrocardiogram.[164] The infant may also undergo a screen for inborn errors of metabolism, chest radiograph, computed tomographic scan of the head, and lumbar puncture depending on signs and symptoms at presentation, although few diagnostic test results are positive.[165] Several studies have evaluated the risk of bacteremia in infants with an ALTE. Essentially, the risk of serious bacterial infections in this population is similar to age-matched cohorts without ALTE.[166,167] However, in a study by Zuckerbraun of 182 well-appearing infants less than 60 days of age with ALTE, prematurity increased the risk of bacterial infection significantly (6.7% vs. 0.8%, $P = .04$), and thus in these patients microbiologic testing for a source of infection is warranted.[169]

Inpatient evaluation often includes electroencephalogram, an evaluation for GERD (24-hour pH probe and barium esophagram), polysomnography for sleep disorders, and possibly flexible and rigid laryngoscopy.

The outcome of an ALTE depends on the underlying cause. In a retrospective patient review of 196 ALTE patients, there were no deaths.[163] The follow-up revealed a high percentage of asthma and seizures, as well as GERD necessitating Nissen fundoplication. Infants who survive an ALTE generally do well in follow-up. However, some rare complications do occur, including pulmonary edema, aspiration pneumonia, and neurologic sequelae secondary to hypoxia.[166]

Multiple studies show that 84% of patients with ALTE are admitted by emergency physicians for evaluation and monitoring. Based on the results of a study of 59 infants with ALTE, Claudius and Keens developed a clinical decision rule suggesting that infants younger than 1 month of age and those with recurrent ALTE should be admitted for evaluation, but other well-appearing children with ALTE may be discharged with close follow-up.[167] Mittal and colleagues showed in a cohort of 300 infants with ALTE that premature birth (relative risk [RR] 2.8, 95% CI 1.5-5.1); absence of choking (RR 2.6, 95% CI 1.4-4.7), color change to blue (RR 2.1, 95% CI 1.2-3.8), and abnormal examination findings in ED (RR 2.8, 95% CI 1.6-4.9) were significantly associated with the need for admission.[168] Fu and Moon suggest other conditions under which it may be safe to discharge a patient with an ALTE, and these include the following: (1) the episode is brief, nonsevere, and self-resolving; (2) the cause is probably a nonprogressive condition such as GERD; and (3) the infant has no comorbidities and appears well.[170] Kaji and others[170a] developed and validated a clinical decision rule for ALTE in 832 infants. In addition to patients in whom it is obvious that admission is necessary at the end of the ED stay, other predictors of those warranting hospitalization include a significant medical history (OR = 2.1, 95% CI 1.1-4.3) and greater than one ALTE in 24 hours (OR = 2.1, 95% CI 1.2-4.6). Any infant not appearing well at the time of ED evaluation should be admitted for monitoring and further evaluation, but this rule allows for the option to discharge with close follow-up.

SUDDEN INFANT DEATH SYNDROME

The National Center for Health Statistics reports that SIDS is the third leading cause of death in infants, accounting for 8% of deaths in children younger than 1 year.[171] SIDS may occur at any time during the first 2 years of life, but it is rare (1%) in children younger than 1 month and in those older than 1 year (2%). Ninety-five percent of SIDS infants die before 6 to 8 months, with a peak occurring at 2 to 4 months of age.[171,172] Some epidemiologic variation occurs among different racial and ethnic groups, with black, Native American, and Alaskan Native infants having rates two to three times higher than the national average.[173] Other epidemiologic risk factors include male sex and multiple births.[174,175]

The most important modifiable risk factor for SIDS is prone sleeping. In 1992 the American Academy of Pediatrics (AAP) recommended that infants be placed to sleep in a nonprone position to reduce the risk of SIDS.[176] The "Back to Sleep" (BTS) campaign was initiated in 1994 under the leadership of the National Institute of Child Health and Human Development (NICHD), as a collaborative effort of the U.S. Public Health Service, the AAP, the SIDS Alliance, and the Association of SIDS and Infant Mortality Programs. Since then, the frequency of prone sleeping has decreased 50 to 90% worldwide, as has the rate of SIDS.[174,177,178]

Because CPR is unsuccessful in the majority of cases, the emergency physician should provide supportive care for the family. When the cause of death is unknown, appropriate samples (blood, urine) should be obtained. Recent data have shown that 10 to 20% of SIDS cases are caused by genetic variants in either ion channel or ion channel–associated proteins.[179,180] Therefore an autopsy and postmortem genetic testing should be performed by a competent and experienced pathologist on all infants who have died from SIDS so that families can be appropriately counseled on risk of sudden death in other family members.[180]

Psychosocial Considerations for Sudden Infant Death Syndrome

The emergency physician and pediatrician address psychosocial considerations in any SIDS case. The physician should be direct when informing parents that their child has died. The word *dead* or *died* should be used instead of confusing euphemisms such as *passed on.*[182,183] Parents universally experience intense guilt, and siblings may also have guilt over the loss of their brother or sister. In addition, parents may further intensify the guilt by accusing each other of not taking adequate care of the infant. The police investigation may arouse suspicion in neighbors and friends and leave the parents and caretakers socially alienated. The overall toll of guilt and social alienation is enormous, and the effects are manifested in increased rates of miscarriage, divorce, and infertility after a SIDS death. The outcome of SIDS for the family depends on the support they receive. Thus, the team approach, which includes the nurse, social worker, chaplain, emergency physician, and pediatrician, may provide comfort and information to the grieving family. The emergency physician and the pediatrician

www.ketabpezeshki.com 66485457-66963820

should recognize that they can play a pivotal role in helping the family to adjust to their loss, initiate the process of grieving, and educate the family about SIDS prevention.[152,153] The AAP and the American College of Emergency Physicians have outlined recommendations for emergency physicians in a joint policy statement entitled "Death of a Child in the Emergency Department."

KEY CONCEPTS

- Excellent CPR is the foundation for successful resuscitation from cardiac arrest. The mantra for excellent CPR is "Push hard, push fast, allow full chest recoil, and minimize interruptions."
- Despite evidence supporting the efficacy of chest compression–only CPR in adults, children in cardiac arrest should receive ventilation plus chest compressions.
- Bradycardia with hypoperfusion should be considered a prearrest state in children, and chest compressions for bradycardia may improve survival.
- Septic shock in children is most commonly associated with hypovolemia and myocardial failure as opposed to vasomotor paralysis. Rapid administration of isotonic fluids is the initial step in resuscitation for all forms of pediatric shock.
- The diagnosis of septic shock in children is primarily clinical, and distinguishing the child with an innocent febrile illness from one with early sepsis is difficult. The role of ancillary biochemical and radiologic testing remains unclear.
- Respiratory failure in children is more common than cardiac arrest and is the most important pathophysiologic cause of cardiac arrest. Pediatric anatomy, physiology, and pathophysiology are important considerations in managing respiratory failure and performing tracheal intubation.
- The availability of a range of equipment for airway management is essential. Cuffed endotracheal tubes can be safely and effectively used throughout the pediatric age range. Laryngeal mask airways (LMAs) are the airway rescue device of choice in pediatric patients.
- Acute life-threatening events constitute a range of clinical phenomena with an incidence of serious bacterial infection that is no different from that in the overall pediatric population; however, in young infants with a history of prematurity, microbiologic testing may be warranted to search for a potential infectious source. There is no association between ALTE and SIDS; workup in the ED should be driven by the clinical presentation.
- Sudden infant death syndrome remains the most common cause of death among patients younger than 1 year. The supine sleeping position for infants is believed to be the major contributor to the decreasing incidence over time. Channelopathies may be an important cause and warrant postmortem genetic testing. Psychological considerations for both families and care team members should be borne in mind when dealing with infants who die in the ED as a result of SIDS.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Slonim AD, Patel KM, Ruttimann UE, Pollack MM: Cardiopulmonary resuscitation in pediatric intensive care units. *Crit Care Med* 1997; 25:1951-1955.
2. Suominen P, et al: Utstein style reporting of in-hospital paediatric cardiopulmonary resuscitation. *Resuscitation* 2000; 45:17-25.
3. Donoghue AJ, et al: Out-of-hospital pediatric cardiac arrest: An epidemiologic review and assessment of current knowledge. *Ann Emerg Med* 2005; 46:512-522.
4. Young KD, Gausche-Hill M, McClung CD, Lewis RJ: A prospective, population-based study of the epidemiology and outcome of out-of-hospital pediatric cardiopulmonary arrest. *Pediatrics* 2004; 114:157-164.
5. Capizzani AR, Drongowski R, Ehrlich PF: Assessment of termination of trauma resuscitation guidelines: Are children small adults? *J Pediatr Surg* 2010; 45:903-907.
6. Donoghue AJ, et al: Effect of high-fidelity simulation on Pediatric Advanced Life Support training in pediatric house staff: A randomized trial. *Pediatr Emerg Care* 2009; 25:139-144.
7. Hunt EA, Patel S, Vera K, Shaffner DH, Pronovost PJ: Survey of pediatric resident experiences with resuscitation training and attendance at actual cardiopulmonary arrests. *Pediatr Crit Care Med* 2009; 10:96-105.
8. Hunt EA, et al: Delays and errors in cardiopulmonary resuscitation and defibrillation by pediatric residents during simulated cardiopulmonary arrests. *Resuscitation* 2009; 80:819-825.
9. Pitetti R, Glustein JZ, Bhende MS: Prehospital care and outcome of pediatric out-of-hospital cardiac arrest. *Prehosp Emerg Care* 2002; 6:283-290.
10. Richard J, Osmond MH, Nesbitt L, Stiell IG: Management and outcomes of pediatric patients transported by emergency medical services in a Canadian prehospital system. *CJEM* 2006; 8:6-12.
11. Atkins DL, et al: Epidemiology and outcomes from out-of-hospital cardiac arrest in children: The Resuscitation Outcomes Consortium Epistry—Cardiac Arrest. *Circulation* 2009; 119:1484-1491.
12. Gerein RB, Osmond MH, Stiell IG, Nesbitt LP, Burns S: What are the etiology and epidemiology of out-of-hospital pediatric cardiopulmonary arrest in Ontario, Canada? *Acad Emerg Med* 2006; 13:653-658.
13. Calkins CM, Bensard DD, Partrick DA, Karrer FM: A critical analysis of outcome for children sustaining cardiac arrest after blunt trauma. *J Pediatr Surg* 2002; 37:180-184.
14. Fisher B, Worthen M: Cardiac arrest induced by blunt trauma in children. *Pediatr Emerg Care* 1999; 15:274-276.
15. Brindis S, Gausche-Hill M, Young KD, Putnum B: Universally poor outcomes of pediatric traumatic arrest: A prospective case series and review of the literature. *Pediatr Emerg Care* 2011; 27:616-621.
16. Quan L, Kinder D: Pediatric submersions: Prehospital predictors of outcome. *Pediatrics* 1992; 90:909-913.
17. Quan L, Wentz KR, Gore EJ, Copass MK: Outcome and predictors of outcome in pediatric submersion victims receiving prehospital care in King County, Washington. *Pediatrics* 1990; 86:586-593.
18. Eisenberg M, Bergner L, Hallstrom A: Epidemiology of cardiac arrest and resuscitation in children. *Ann Emerg Med* 1983; 12: 672-674.
19. Nadkarni VM, et al: First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. *JAMA* 2006; 295:50-57.
20. Reis AG, Nadkarni V, Perondi MB, Grisi S, Berg RA: A prospective investigation into the epidemiology of in-hospital pediatric cardiopulmonary resuscitation using the international Utstein reporting style. *Pediatrics* 2002; 109:200-209.
21. Schindler MB, et al: Outcome of out-of-hospital cardiac or respiratory arrest in children. *N Engl J Med* 1996; 335:1473-1479.
22. Zaritsky A, Nadkarni V, Getson P, Kuehl K: CPR in children. *Ann Emerg Med* 1987; 16:1107-1111.
23. O'Rourke PP: Outcome of children who are apneic and pulseless in the emergency room. *Crit Care Med* 1986; 14:466-468.
24. Sirbaugh PE, et al: A prospective, population-based study of the demographics, epidemiology, management, and outcome of out-of-hospital pediatric cardiopulmonary arrest. *Ann Emerg Med* 1999; 33:174-184.
25. Donoghue AJ, Nadkarni VM, Elliott M, Durbin D: Effect of hospital characteristics on outcomes from pediatric cardiopulmonary resuscitation: A report from the national registry of cardiopulmonary resuscitation. *Pediatrics* 2006; 118:995-1001.
26. Meaney PA, et al: Higher survival rates among younger patients after pediatric intensive care unit cardiac arrests. *Pediatrics* 2006; 118: 2424-2433.
27. Peberdy MA, et al: Cardiopulmonary resuscitation of adults in the hospital: A report of 14720 cardiac arrests from the National Registry of Cardiopulmonary Resuscitation. *Resuscitation* 2003; 58:297-308.
28. Teach SJ, Moore PE, Fleisher GR: Death and resuscitation in the pediatric emergency department. *Ann Emerg Med* 1995; 25:799-803.
29. Kayser RG, Ornato JP, Peberdy MA: Cardiac arrest in the emergency department: A report from the National Registry of Cardiopulmonary Resuscitation. *Resuscitation* 2008; 78:151-160.
30. Samson RA, et al: Outcomes of in-hospital ventricular fibrillation in children. *N Engl J Med* 2006; 354:2328-2339.
31. Kouwenhoven WB, Jude JR, Knickerbocker GG: Closed-chest cardiac massage. *JAMA* 1960; 173:1064-1067.
32. Dean JM, et al: Age-related changes in chest geometry during cardiopulmonary resuscitation. *J Appl Physiol* 1987; 62:2212-2219.
33. Zuercher M, et al: Leaning during chest compressions impairs cardiac output and left ventricular myocardial blood flow in piglet cardiac arrest. *Crit Care Med* 2010; 38:1141-1146.
34. Dick WF, Eberle B, Wisser G, Schneider T: The carotid pulse check revisited: What if there is no pulse? *Crit Care Med* 2000; 28(11 Suppl): N183-N185.
35. Eberle B, et al: Checking the carotid pulse check: Diagnostic accuracy of first responders in patients with and without a pulse. *Resuscitation* 1996; 33:107-116.
36. Inagawa G, et al: A comparison of five techniques for detecting cardiac activity in infants. *Paediatr Anaesth* 2003; 13:141-146.
37. Sarti A, Savron F, Ronfani L, Pelizzo G, Barbi E: Comparison of three sites to check the pulse and count heart rate in hypotensive infants. *Paediatr Anaesth* 2006; 16:394-398.
38. Tibballs J, Russell P: Reliability of pulse palpation by healthcare personnel to diagnose paediatric cardiac arrest. *Resuscitation* 2009; 80:61-64.
39. Tunstall-Pedoe H, et al: Survey of 3765 cardiopulmonary resuscitations in British hospitals (the BRESUS Study): Methods and overall results. *BMJ* 1992; 304:1347-1351.
40. Ralston M, Hazinkski M, Zaritsky A, Schexnayder S, Kleinman ME, eds: *Pediatric Advanced Life Support Provider Manual*. Dallas: American Heart Association; 2006.
41. Hypothermia after Cardiac Arrest Study Group: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002; 346:549-556.
42. Bernard SA, et al: Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; 346: 557-563.
43. Hickey RW, Kochanek PM, Ferimer H, Graham SH, Safar P: Hypothermia and hyperthermia in children after resuscitation from cardiac arrest. *Pediatrics* 2000; 106(1 Pt 1):118-122.
44. Gluckman PD, et al: Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: Multicentre randomised trial. *Lancet* 2005; 365:663-670.

44a. Jacobs SE, et al: Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: A randomized controlled trial. *Arch Pediatr Adolesc Med* 2011; 165:692-700.

45. Adrie C, et al: Successful cardiopulmonary resuscitation after cardiac arrest as a "sepsis-like" syndrome. *Circulation* 2002; 106:562-568.
46. Laurent I, et al: Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. *J Am Coll Cardiol* 2002; 40:2110-2116.
47. Niemann JT, Garner D, Lewis RJ: Tumor necrosis factor–alpha is associated with early postresuscitation myocardial dysfunction. *Crit Care Med* 2004; 32:1753-1758.
48. Huang L, Weil MH, Tang W, Sun S, Wang J: Comparison between dobutamine and levosimendan for management of postresuscitation myocardial dysfunction. *Crit Care Med* 2005; 33:487-491.
49. Kern KB, et al: Postresuscitation left ventricular systolic and diastolic dysfunction. Treatment with dobutamine. *Circulation* 1997; 95:2610-2613.
50. Meyer RJ, Kern KB, Berg RA, Hilwig RW, Ewy GA: Post-resuscitation right ventricular dysfunction: Delineation and treatment with dobutamine. *Resuscitation* 2002; 55:187-191.
51. Vasquez A, et al: Optimal dosing of dobutamine for treating post-resuscitation left ventricular dysfunction. *Resuscitation* 2004; 61:199-207.
52. Mullner M, et al: Measurement of myocardial contractility following successful resuscitation: Quantitated left ventricular systolic function utilising non-invasive wall stress analysis. *Resuscitation* 1998; 39: 51-59.

www.ketabpezeshki.com 66485457-66963820

53. Sunde K, et al: Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation* 2007; 73:29-39.
54. Paradis NA, et al: Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. *JAMA* 1990; 263:1106-1113.
55. Kern KB, Ewy GA, Voorhees WD, Babbs CF, Tacker WA: Myocardial perfusion pressure: A predictor of 24-hour survival during prolonged cardiac arrest in dogs. *Resuscitation* 1988; 16:241-250.
56. Berg RA, et al: Adverse hemodynamic effects of interrupting chest compressions for rescue breathing during cardiopulmonary resuscitation for ventricular fibrillation cardiac arrest. *Circulation* 2001; 104:2465-2470.
57. Kern KB, Hilwig RW, Berg RA, Sanders AB, Ewy GA: Importance of continuous chest compressions during cardiopulmonary resuscitation: Improved outcome during a simulated single lay-rescuer scenario. *Circulation* 2002; 105:645-649.
58. Kleinman ME, et al: Part 10: Pediatric basic and advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Circulation* 2010; 122(16 Suppl 2):S466-S515.
59. Menegazzi JJ, et al: Two-thumb versus two-finger chest compression during CRP in a swine infant model of cardiac arrest. *Ann Emerg Med* 1993; 22:240-243.
60. Kern KB, et al: A study of chest compression rates during cardiopulmonary resuscitation in humans. The importance of rate-directed chest compressions. *Arch Intern Med* 1992; 152:145-149.
61. Maier GW, et al: The physiology of external cardiac massage: High-impulse cardiopulmonary resuscitation. *Circulation* 1984; 70:86-101.
62. Feneley MP, et al: Influence of compression rate on initial success of resuscitation and 24 hour survival after prolonged manual cardiopulmonary resuscitation in dogs. *Circulation* 1988; 77:240-250.
63. Milander MM, et al: Chest compression and ventilation rates during cardiopulmonary resuscitation: The effects of audible tone guidance. *Acad Emerg Med* 1995; 2:708-713.
64. Berg RA, et al: Efficacy of audio-prompted rate guidance in improving resuscitator performance of cardiopulmonary resuscitation on children. *Acad Emerg Med* 1994; 1:35-40.
65. Abella BS, et al: Quality of cardiopulmonary resuscitation during in-hospital cardiac arrest. *JAMA* 2005; 293:305-310.
66. Aufderheide TP, et al: Hyperventilation-induced hypotension during cardiopulmonary resuscitation. *Circulation* 2004; 109:1960-1965.
67. Edelson DP, et al: Effects of compression depth and pre-shock pauses predict defibrillation failure during cardiac arrest. *Resuscitation* 2006; 71:137-145.
68. Idris AH, et al: Effect of ventilation on acid-base balance and oxygenation in low blood-flow states. *Crit Care Med* 1994; 22: 1827-1834.
69. Kinney SB, Tibballs J: An analysis of the efficacy of bag-valve-mask ventilation and chest compression during different compression-ventilation ratios in manikin-simulated paediatric resuscitation. *Resuscitation* 2000; 43:115-120.
70. Srikantan SK, Berg RA, Cox T, Tice L, Nadkarni VM: Effect of one-rescuer compression/ventilation ratios on cardiopulmonary resuscitation in infant, pediatric, and adult manikins. *Pediatr Crit Care Med* 2005; 6:293-297.
71. Babbs CF: Circulatory adjuncts. Newer methods of cardiopulmonary resuscitation. *Cardiol Clin* 2002; 20:37-59.
72. Babbs CF, Nadkarni V: Optimizing chest compression to rescue ventilation ratios during one-rescuer CPR by professionals and lay persons: Children are not just little adults. *Resuscitation* 2004; 61: 173-181.
73. Aufderheide TP, et al: Incomplete chest wall decompression: A clinical evaluation of CPR performance by trained laypersons and an assessment of alternative manual chest compression-decompression techniques. *Resuscitation* 2006; 71:341-351.
74. Wik L, et al: Quality of cardiopulmonary resuscitation during out-of-hospital cardiac arrest. *JAMA* 2005; 293:299-304.
75. Niles D, et al: Leaning is common during in-hospital pediatric CPR, and decreased with automated corrective feedback. *Resuscitation* 2009; 80:553-557.
76. Roberts K, et al: Does change in thoracic impedance measured via defibrillator electrode pads accurately detect ventilation breaths in children? *Resuscitation* 2010; 81:1544-1549.
77. Abella BS, et al: CPR quality improvement during in-hospital cardiac arrest using a real-time audiovisual feedback system. *Resuscitation* 2007; 73:54-61.
78. Bobrow BJ, et al: Chest compression–only CPR by lay rescuers and survival from out-of-hospital cardiac arrest. *JAMA* 2010; 304: 1447-1454.
79. Hallstrom A, Cobb L, Johnson E, Copass M: Cardiopulmonary resuscitation by chest compression alone or with mouth-to-mouth ventilation. *N Engl J Med* 2000; 342:1546-1553.
80. Ong ME, et al: Comparison of chest compression only and standard cardiopulmonary resuscitation for out-of-hospital cardiac arrest in Singapore. *Resuscitation* 2008; 78:119-126.
81. Berg RA, Hilwig RW, Kern KB, Babar I, Ewy GA: Simulated mouth-to-mouth ventilation and chest compressions (bystander cardiopulmonary resuscitation) improves outcome in a swine model of prehospital pediatric asphyxial cardiac arrest. *Crit Care Med* 1999; 27: 1893-1899.
82. Berg RA, Hilwig RW, Kern KB, Ewy GA: "Bystander" chest compressions and assisted ventilation independently improve outcome from piglet asphyxial pulseless "cardiac arrest." *Circulation* 2000; 101: 1743-1748.
83. Kitamura T, et al: Conventional and chest-compression–only cardiopulmonary resuscitation by bystanders for children who have out-of-hospital cardiac arrests: A prospective, nationwide, population-based cohort study. *Lancet* 2010; 375:1347-1354.
84. Perondi MB, Reis AG, Paiva EF, Nadkarni VM, Berg RA: A comparison of high-dose and standard-dose epinephrine in children with cardiac arrest. *N Engl J Med* 2004; 350:1722-1730.
85. Srinivasan V, Morris MC, Helfaer MA, Berg RA, Nadkarni VM: Calcium use during in-hospital pediatric cardiopulmonary resuscitation: A report from the National Registry of Cardiopulmonary Resuscitation. *Pediatrics* 2008; 121:e1144-e1151.
86. Kleinman ME, et al: Part 14: Pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122(18 Suppl 3):S876-S908.
87. Graf WD, Cummings P, Quan L, Brutocao D: Predicting outcome in pediatric submersion victims. *Ann Emerg Med* 1995; 26:312-319.
88. Larsen MP, Eisenberg MS, Cummins RO, Hallstrom AP: Predicting survival from out-of-hospital cardiac arrest: A graphic model. *Ann Emerg Med* 1993; 22:1652-1658.
89. Berg MD, et al: Pediatric defibrillation doses often fail to terminate prolonged out-of-hospital ventricular fibrillation in children. *Resuscitation* 2005; 67:63-67.
90. Reference deleted in proofs.
91. Berg RA, et al: Better outcome after pediatric defibrillation dosage than adult dosage in a swine model of pediatric ventricular fibrillation. *J Am Coll Cardiol* 2005; 45:786-789.
92. Meaney PA, et al: Effect of defibrillation energy dose during in-hospital pediatric cardiac arrest. *Pediatrics* 2011; 127:e16-e23.
93. Walsh CK, Krongrad E: Terminal cardiac electrical activity in pediatric patients. *Am J Cardiol* 1983; 51(3):557-561.
94. DeBehnke DJ, Hilander SJ, Dobler DW, Wickman LL, Swart GL: The hemodynamic and arterial blood gas response to asphyxiation: A canine model of pulseless electrical activity. *Resuscitation* 1995; 30:169-175.
95. Berg RA, et al: Ventricular fibrillation in a swine model of acute pediatric asphyxial cardiac arrest. *Resuscitation* 1996; 33:147-153.
96. Donoghue A, et al: Cardiopulmonary resuscitation for bradycardia with poor perfusion versus pulseless cardiac arrest. *Pediatrics* 2009; 124:1541-1548.
97. Allan CK, Thiagarajan RR, Armsby LR, del Nido PJ, Laussen PC: Emergent use of extracorporeal membrane oxygenation during pediatric cardiac catheterization. *Pediatr Crit Care Med* 2006; 7:212-219.
98. Alsoufi B, et al: Survival outcomes after rescue extracorporeal cardiopulmonary resuscitation in pediatric patients with refractory cardiac arrest. *J Thorac Cardiovasc Surg* 2007; 134: 952-959.
99. Huang SC, et al: Extracorporeal membrane oxygenation rescue for cardiopulmonary resuscitation in pediatric patients. *Crit Care Med* 2008; 36:1607-1613.
100. Morris MC, Wernovsky G, Nadkarni VM: Survival outcomes after extracorporeal cardiopulmonary resuscitation instituted during active chest compressions following refractory in-hospital pediatric cardiac arrest. *Pediatr Crit Care Med* 2004; 5:440-446.
101. Kelly MP, Lee FT, Smyth FE, Brechbiel MW, Scott AM: Enhanced efficacy of 90Y-radiolabeled anti-Lewis Y humanized monoclonal antibody hu3S193 and paclitaxel combined-modality radioimmunotherapy in a breast cancer model. *J Nucl Med* 2006; 47:716-725.

www.ketabpezeshki.com 66485457-66963820

102. Watson RS, Carcillo JA: Scope and epidemiology of pediatric sepsis. *Pediatr Crit Care Med* 2005; 6(3 Suppl):S3-S5.
103. Stoll BJ, Holman RC, Schuchat A: Decline in sepsis-associated neonatal and infant deaths in the United States, 1979 through 1994. *Pediatrics* 1998; 102:e18.
104. Brierley J, et al: Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. *Crit Care Med* 2009; 37:666-688.
105. Goldstein B, Giroir B, Randolph A: International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005; 6:2-8.
106. Ceneviva G, Paschall JA, Maffei F, Carcillo JA: Hemodynamic support in fluid-refractory pediatric septic shock. *Pediatrics* 1998; 102:e19.
107. Brierley J, Peters MJ: Distinct hemodynamic patterns of septic shock at presentation to pediatric intensive care. *Pediatrics* 2008; 122: 752-759.
108. Mistry RD, Stevens MW, Gorelick MH: Short-term outcomes of pediatric emergency department febrile illnesses. *Pediatr Emerg Care* 2007; 23:617-623.
109. Scott H, Marchese R, Gaieski D, Donoghue A, Mistry R: Early physical exam findings are not sufficient to predict illness severity in children with sepsis in the pediatric emergency department. American Academy of Pediatrics National Conference and Exhibition, San Francisco, Calif, 2010.
110. Carcillo JA, et al: Mortality and functional morbidity after use of PALS/APLS by community physicians. *Pediatrics* 2009; 124:500-508.
111. del Portal DA, et al: Emergency department lactate is associated with mortality in older adults admitted with and without infections. *Acad Emerg Med* 2010; 17:260-268.
112. Mikkelsen ME, et al: Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med* 2009; 37:1670-1677.
113. Goyal M, Pines JM, Drumheller BC, Gaieski DF: Point-of-care testing at triage decreases time to lactate level in septic patients. *J Emerg Med* 2010; 38:578-581.
114. Gaieski DF, Goyal M: Serum lactate as a predictor of mortality in emergency department patients with infection: Does the lactate level tell the whole story? *Ann Emerg Med* 2005; 46:561-562; author reply 562.
115. Reinhart K, Meisner M: Biomarkers in the critically ill patient: Procalcitonin. *Crit Care Clin* 2011; 27:253-263.
116. Perman SM, et al: Relationship between B-type natriuretic peptide and adverse outcome in patients with clinical evidence of sepsis presenting to the emergency department. *Acad Emerg Med* 2011; 18:219-222.
117. Pirracchio R, Salem R, Mebazaa A: Use of B-type natriuretic peptide in critically ill patients. *Biomark Med* 2009; 3:541-547.
118. Goebel PJ, Williams JB, Gerhardt RT: A pilot study of the performance characteristics of the D-dimer in presumed sepsis. *West J Emerg Med* 2010; 11:173-179.
119. Oh D, et al: Evaluation of modified non-overt DIC criteria on the prediction of poor outcome in patients with sepsis. *Thromb Res* 2010; 126:18-23.
120. Samransamruajkit R, et al: Levels of protein C activity and clinical factors in early phase of pediatric septic shock may be associated with the risk of death. *Shock* 2007; 28:518-523.
121. Fioretto JR, et al: Comparison between procalcitonin and C-reactive protein for early diagnosis of children with sepsis or septic shock. *Inflamm Res* 2010; 59:581-586.
122. Standage SW, Wong HR: Biomarkers for pediatric sepsis and septic shock. *Expert Rev Anti Infect Ther* 2011; 9:71-79.
123. Dugas MA, Proulx F, de Jaeger A, Lacroix J, Lambert M: Markers of tissue hypoperfusion in pediatric septic shock. *Intensive Care Med* 2000; 26:75-83.
124. Pershad J, et al: Bedside limited echocardiography by the emergency physician is accurate during evaluation of the critically ill patient. *Pediatrics* 2004; 114:e667-e671.
125. Chen L, Hsiao A, Langhan M, Riera A, Santucci KA: Use of bedside ultrasound to assess degree of dehydration in children with gastroenteritis. *Acad Emerg Med* 2010; 17:1042-1047.
126. Norozi K, et al: Electrical velocimetry for measuring cardiac output in children with congenital heart disease. *Br J Anaesth* 2008; 100: 88-94.
127. Reference deleted in proofs.
128. Cardenas-Rivero N, Chernow B, Stoiko MA, Nussbaum SR, Todres ID: Hypocalcemia in critically ill children. *J Pediatr* 1989; 114:946-951.
129. Carcillo JA, Davis AL, Zaritsky A: Role of early fluid resuscitation in pediatric septic shock. *JAMA* 1991; 266:1242-1245.
130. Han YY, et al: Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. *Pediatrics* 2003; 112:793-799.
131. Stoner MJ, Goodman DG, Cohen DM, Fernandez SA, Hall MW: Rapid fluid resuscitation in pediatrics: Testing the American College of Critical Care Medicine guideline. *Ann Emerg Med* 2007; 50:601-607.
132. Guilfoyle FJ, Milner R, Kissoon N: Resuscitation interventions in a tertiary level pediatric emergency department: Implications for maintenance of skills. *CJEM* 2011; 13:90-95.
133. Sakr Y, et al: Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study. *Crit Care Med* 2006; 34:589-597.
134. Pizarro CF, Troster EJ, Damiani D, Carcillo JA: Absolute and relative adrenal insufficiency in children with septic shock. *Crit Care Med* 2005; 33:855-859.
135. Hebbar K, Rigby MR, Felner EI, Easley KA, Fortenberry JD: Neuroendocrine dysfunction in pediatric critical illness. *Pediatr Crit Care Med* 2009; 10:35-40.
136. Annane D: Adrenal insufficiency in sepsis. *Curr Pharm Des* 2008; 14:1882-1886.
137. Annane D: Replacement therapy with hydrocortisone in catecholamine-dependent septic shock. *J Endotoxin Res* 2001; 7:305-309.
138. Sprung CL, et al: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 10 2008; 358:111-124.
139. Slusher T, et al: Randomized, placebo-controlled, double blinded trial of dexamethasone in African children with sepsis. *Pediatr Infect Dis J* 1996; 15:579-583.
140. Valoor HT, Singhi S, Jayashree M: Low-dose hydrocortisone in pediatric septic shock: An exploratory study in a third world setting. *Pediatr Crit Care Med* 2009; 10:121-125.
141. Xue FS, et al: Study of the safe threshold of apneic period in children during anesthesia induction. *J Clin Anesth* 1996; 8:568-574.
142. Reference deleted in proofs.
143. Xue FS, Tong SY, Wang XL, Deng XM, An G: Study of the optimal duration of preoxygenation in children. *J Clin Anesth* 1995; 7:93-96.
144. Kumar VR, Bachman DT, Kiskaddon RT: Children and adults in cardiopulmonary arrest: Are advanced life support guidelines followed in the prehospital setting? *Ann Emerg Med* 1997; 29:743-747.
145. Babl FE, Vinci RJ, Bauchner H, Mottley L: Pediatric pre-hospital advanced life support care in an urban setting. *Pediatr Emerg Care* 2001; 17:5-9.
146. Shah MN, et al: The epidemiology of emergency medical services use by children: An analysis of the National Hospital Ambulatory Medical Care Survey. *Prehosp Emerg Care* 2008; 12:269-276.
147. Losek JD, Hennes H, Glaeser P, Hendley G, Nelson DB: Prehospital care of the pulseless, nonbreathing pediatric patient. *Am J Emerg Med* Sep 1987; 5:370-374.
148. Gausche M, et al: Effect of out-of-hospital pediatric endotracheal intubation on survival and neurological outcome: A controlled clinical trial. *JAMA* 2000; 283:783-790.
149. King BR, Baker MD, Braitman LE, Seidl-Friedman J, Schreiner MS: Endotracheal tube selection in children: A comparison of four methods. *Ann Emerg Med* 1993; 22:530-534.
150. Luten RC, et al: Length-based endotracheal tube and emergency equipment in pediatrics. *Ann Emerg Med* 1992; 21:900-904 [erratum *Ann Emerg Med* 1993; 22:155].
151. Hofer CK, Ganter M, Tucci M, Klaghofer R, Zollinger A: How reliable is length-based determination of body weight and tracheal tube size in the paediatric age group? The Broselow tape reconsidered. *Br J Anaesth* 2002; 88:283-285.
152. Davis D, Barbee L, Ririe D: Pediatric endotracheal tube selection: A comparison of age-based and height-based criteria. *AANA J* 1998; 66:299-303.
153. Deakers TW, Reynolds G, Stretton M, Newth CJ: Cuffed endotracheal tubes in pediatric intensive care. *J Pediatr* 1994; 125:57-62.
154. Khine HH, et al: Comparison of cuffed and uncuffed endotracheal tubes in young children during general anesthesia. *Anesthesiology* 1997; 86:627-631; discussion 627A.
155. Newth CJ, Rachman B, Patel N, Hammer J: The use of cuffed versus uncuffed endotracheal tubes in pediatric intensive care. *J Pediatr* 2004; 144:333-337.
156. Fastle RK, Roback MG: Pediatric rapid sequence intubation: Incidence of reflex bradycardia and effects of pretreatment with atropine. *Pediatr Emerg Care* 2004; 20:651-655.
157. Badgwell JM, Hall SC, Lockhart C: Revised label regarding use of succinylcholine in children and adolescents. *Anesthesiology* 1994; 80:243-245.

www.ketabpezeshki.com 66485457-66963820

158. Sagarin MJ, et al: Rapid sequence intubation for pediatric emergency airway management. *Pediatr Emerg Care* 2002; 18:417-423.
159. Lopez-Gil M, Brimacombe J, Cebrian J, Arranz J: Laryngeal mask airway in pediatric practice: A prospective study of skill acquisition by anesthesia residents. *Anesthesiology* 1996; 84:807-811.
160. Gallart L, et al: Simple method to determine the size of the laryngeal mask airway in children. *Eur J Anaesthesiol* 2003; 20:570-574.
161. McGovern MC, Smith MB: Causes of apparent life threatening events in infants: A systematic review. *Arch Dis Child* 2004; 89:1043-1048.
162. Stratton SJ, et al: Apparent life-threatening events in infants: High risk in the out-of-hospital environment. *Ann Emerg Med* 2004; 43:711-717.
163. Gray C, Davies F, Molyneux E: Apparent life-threatening events presenting to a pediatric emergency department. *Pediatr Emerg Care* 1999; 15:195-199.
164. De Piero AD, Teach SJ, Chamberlain JM: ED evaluation of infants after an apparent life-threatening event. *Am J Emerg Med* 2004; 22:83-86.
165. Kahn A: Recommended clinical evaluation of infants with an apparent life-threatening event. Consensus document of the European Society for the Study and Prevention of Infant Death, 2003. *Eur J Pediatr* 2004; 163:108-115.
166. Esani N, Hodgman JE, Ehsani N, Hoppenbrouwers T: Apparent life-threatening events and sudden infant death syndrome: Comparison of risk factors. *J Pediatr* 2008; 152:365-370.
167. Claudius I, Keens T: Do all infants with apparent life-threatening events need to be admitted? *Pediatrics* 2007; 119:679-683.
168. Mittal MK, Shofer FS, Baren JM: Serious bacterial infections in infants who have experienced an apparent life-threatening event. *Ann Emerg Med* 2009; 54:523-527.
169. Zuckerbraun NS, Zomorrodi A, Pitetti RD: Occurrence of serious bacterial infection in infants aged 60 days or younger with an apparent life-threatening event. *Pediatr Emerg Care* 2009; 25:19-25.
170. Fu LY, Moon RY: Apparent life-threatening events (ALTEs) and the role of home monitors. *Pediatr Rev* 2007; 28:203-208.
170a. Kaji AH, et al: Apparent life-threatening event: multicenter prospective cohort study to develop a clinical decision rule for admission to the hospital. *Ann Emerg Med* 2013; 61:379-387.
171. Mathews TJ, MacDorman MF: Infant mortality statistics from the 2004 period linked birth/infant death data set. *Natl Vital Stat Rep* 2007; 55:1-32.
172. Peterson DR, Sabotta EE, Strickland D: Sudden infant death syndrome in epidemiologic perspective: Etiologic implications of variation with season of the year. *Ann N Y Acad Sci* 1988; 533:6-12.
173. Adams EJ, et al: Changes in the epidemiologic profile of sudden infant death syndrome as rates decline among California infants: 1990-1995. *Pediatrics* 1998; 102:1445-1451.
174. Moon RY, Horne RS, Hauck FR: Sudden infant death syndrome. *Lancet* 2007; 370:1578-1587.
175. Hunt CE, Hauck FR: Sudden infant death syndrome. *CMAJ* 2006; 174:1861-1869.
176. Hoffman HJ, Damus K, Hillman L, Krongrad E: Risk factors for SIDS. Results of the National Institute of Child Health and Human Development SIDS Cooperative Epidemiological Study. *Ann N Y Acad Sci* 1988; 533:13-30.
177. Kattwinkel J, Brooks J, Keenan ME, Malloy M: Infant sleep position and sudden infant death syndrome (SIDS) in the United States: Joint commentary from the American Academy of Pediatrics and selected agencies of the federal government. *Pediatrics* 1994; 93:820.
178. Willinger M, et al: Factors associated with the transition to nonprone sleep positions of infants in the United States: The National Infant Sleep Position Study. *JAMA* 1998; 280:329-335.
179. Tfelt-Hansen J, Winkel BG, Grunnet M, Jespersen T: Cardiac channelopathies and sudden infant death syndrome. *Cardiology* 2011; 119:21-33.
180. Ackerman MJ: State of postmortem genetic testing known as the cardiac channel molecular autopsy in the forensic evaluation of unexplained sudden cardiac death in the young. *Pacing Clin Electrophysiol* 2009; 32(Suppl 2):S86-S89.
181. Willinger M, Hoffman HJ, Hartford RB: Infant sleep position and risk for sudden infant death syndrome: Report of meeting held January 13 and 14, 1994, National Institutes of Health, Bethesda, Md. *Pediatrics* 1994; 93:814-819.
182. Death of a child in the emergency department, a joint statement by the American Academy of Pediatrics and the American College of Emergency Physicians. *Ann Emerg Med* 2002; 40:409-410.
183. Smialek Z: Observations on immediate reactions of families to sudden infant death. *Pediatrics* 1978; 62:160-165.

www.ketabpezeshki.com 66485457-66963820

Chapter 11

Neonatal Resuscitation

Mark D. Lo and Suzan S. Mazor

PERSPECTIVE

Approximately 10% of newborns require some resuscitative assistance at birth, and approximately 1% require extensive resuscitative measures.[1] Appropriate equipment and preparation, knowledge of neonatal physiology and response to stress, and skill in performing the necessary procedures are essential to successful resuscitation. Preparation for neonatal resuscitation requires an understanding of how it differs from pediatric and adult resuscitation, as follows:

1. Newborns have rapidly changing cardiopulmonary physiology, their own range of normal vital signs (Table 11-1), and unique responses to stress.[2,3]
2. The approach to newborn resuscitation focuses almost *entirely* on respiratory, not cardiac, management.[2]
3. Because of their small size, infants require special equipment.

PATHOPHYSIOLOGY

Transition from Fetal to Extrauterine Life

The successful transition from the fetal to the extrauterine environment requires two major cardiorespiratory changes: (1) removal of fluid from unexpanded alveoli to allow ventilation and (2) redistribution of cardiac output to provide lung perfusion. Failure of the development of either adequate ventilation or adequate perfusion leads to shunting, hypoxia, and ultimately reversion to fetal physiology.[2]

In utero, the pulmonary alveoli are filled with pulmonary fluid and amniotic fluid. Removal of this fluid is partially accomplished by vaginal delivery, which compresses the fluid out of the alveoli into the bronchi, trachea, and pulmonary capillary bed. Most fluid is removed by the first few breaths. Expansion of alveoli requires the generation of high intrathoracic pressures and the presence of surfactant to maintain alveolar patency. The quality of the first few breaths is crucial to the establishment of adequate ventilation.

The fetal lung is poorly perfused. Because the pulmonary arterial bed is intensely vasoconstricted, the fetal lung receives only 40% of the right ventricular cardiac output; most of the right ventricular output is shunted from the pulmonary artery through the ductus arteriosus to the descending aorta.[4] After the first few breaths, with exposure to alveolar oxygen, pulmonary vascular resistance decreases. The fetal shunt through the ductus arteriosus reverses as systemic vascular resistance increases; then the shunt usually ceases by 15 hours of age as the ductus also constricts. This reversal of flow allows all right ventricular output to perfuse the lungs. If hypoxia or severe acidosis occurs, however, the muscular pulmonary vascular bed constricts again, and the ductus may reopen. The reinstitution of fetal circulation, with its attendant shunting, leads to ongoing hypoxia and is termed *persistent fetal circulation*.[2,4] Resuscitation facilitates the first few breaths, prevents and reverses ongoing hypoxia and acidosis, and assists the newborn in the transition to extrauterine life.

Neonatal Responses

Hypoxia

The newborn's clinical response to severe hypoxia is unique. In utero or intrapartum asphyxia (pathologic lack of oxygen to the fetus before or during delivery) precipitates a sequence of events termed *primary apnea* and *secondary apnea.* After initial hypoxia, the infant gasps rapidly, followed by cessation of respirations (primary apnea) and a decreasing heart rate (HR). At this point, only simple stimulation is needed to reverse bradycardia and assist the development of ventilation. With ongoing asphyxia, however, the infant takes several final deep, gasping respirations, followed by cessation of respirations (secondary apnea), worsening bradycardia, and decreasing blood pressure. In secondary apnea, more vigorous and prolonged resuscitation is needed to restore ventilation and an adequate circulation.[2]

The presence of respirations may not ensure adequate ventilation. In addition, signs of hypoxia (e.g., cyanosis, lethargy, unresponsiveness) may have other causes. Bradycardia in the newborn (HR <100 beats/min) almost always reflects inadequate ventilation and oxygenation. *Bradycardia is a major indicator of hypoxia.*[1,2] Pulse oximetry may assist in determining hypoxemia, but it may take several minutes for a reliable waveform to be achieved.[5,6]

Hypothermia

The newborn's inability to maintain body temperature (>36.5° C) has severe physiologic consequences. The newborn cannot generate heat by shivering, cannot retain heat due to low fat stores, and has a relatively large surface-to-volume area. In addition, the newborn is at risk for heat loss because of a high metabolic rate, wet amniotic fluid covering, and exposure to a relatively cool environment, especially in contrast to intrauterine temperature. The body temperature easily and rapidly decreases, and low body temperatures can lead to metabolic acidosis, increased oxygen consumption, hypoglycemia, and apnea.[1-3] Drying and warming the newborn are vital to initial resuscitation.

www.ketabpezeshki.com 66485457-66963820

Table 11-1 Normal Vital Signs in the Newborn

Mean arterial pressure = Diastolic pressure + (Pulse pressure/3)

Pulse pressure = (Systolic pressure – Diastolic pressure)

HEART RATE (beats/min)	RESPIRATORY RATE (breaths/min)	MEAN ARTERIAL PRESSURE (mm Hg)	TARGETED OXYGEN SATURATION BY PULSE OXIMETRY (RIGHT UPPER EXTREMITY)
100-180	40-60	Should be equivalent to gestational age	85-95% by 10 minutes

Hypoglycemia

The newborn is at risk for developing hypoglycemia when stressed because of poor glycogen stores and immature liver enzymes. Hypoglycemia is common in premature or small-for-gestational-age infants and in infants born to diabetic mothers. It also develops in response to respiratory illness, hypothermia, polycythemia, asphyxia, and sepsis. Hypoglycemia may be asymptomatic or may cause an array of symptoms, including apnea, color changes, respiratory distress, lethargy, jitteriness, seizures, acidosis, and poor myocardial contractility.[7,8] Low blood glucose has been associated with adverse neurologic outcomes in both animal and clinical studies.[7] Neonatal hypoglycemia is generally defined as less than 40 mg/dL, although this number is not scientifically proven. Newborns showing symptoms of hypoglycemia together with glucose level less than 40 mg/dL should be treated with intravenous glucose. Of note, bedside glucometers generally result in lower glucose readings than plasma glucose levels by approximately 10 mg/dL.[8]

INDICATIONS FOR RESUSCITATION

Any infant born outside of the controlled environment of the delivery room should be considered in need of resuscitation.[1-3] Minimal intervention may be required, but a standardized approach as described in this chapter should be followed. Adequate ventilation and warming are essential to a successful resuscitation. Some specific conditions such as the ones presented here increase the likelihood that resuscitation will be required.

Premature infants, especially those born before 34 weeks of gestational age, pose a special problem because of their immature lungs and susceptibility to hypothermia. Rapid intubation should be initiated if the premature infant appears to be in respiratory distress with signs of retractions, desaturation, or tachypnea. Surfactant (approximately 100 mg/kg divided in four doses) may be delivered via the endotracheal tube (ETT) shortly after birth. Premature infants are also more susceptible to infection, so blood cultures and a complete blood count should be drawn, followed by intravenous antibiotics. The gastrointestinal system of the premature infant may not be capable of digesting maternal breast milk, so total parenteral nutrition is often required until the infant matures.

The presence of meconium in the amniotic fluid at delivery indicates that the infant has been stressed before delivery and warrants special consideration in resuscitation. When delivered, a nonvigorous infant with meconium in the amniotic fluid has the trachea suctioned before other steps in resuscitation are taken, to prevent aspiration of meconium.

Medications given to the mother or illicit drugs taken before delivery can lead to respiratory depression in the newborn. Maternal opioid administration or opioid use should be considered in any newborn with isolated respiratory depression that persists after successful initial resuscitation. As in adults, 0.1 mg/kg of naloxone administered to newborns may reverse respiratory depression caused by opioids. Naloxone may have a shorter half-life than the original maternal opioid; therefore the neonate should be monitored closely for recurrent apnea or hypoventilation, and subsequent doses of naloxone may be required.[9,10] However, use of naloxone may precipitate acute withdrawal, seizures, or both in infants who have had prolonged intrauterine opioid exposure, and the overall effect and side effects of naloxone in the newborn are not fully known.[9,10] Therefore naloxone is not recommended as a first-line treatment in the initial resuscitation efforts. Support of ventilation may be preferable to reversal with naloxone.

Hemorrhage caused by abruptio placentae, placenta previa, trauma, or other complications can lead to respiratory depression and shock in the newborn. In the newborn, hemorrhage is one of the few situations in which fluid resuscitation is initially required.

No reliable set of parameters has been identified for newborns who should *not* receive resuscitative efforts.[11] Currently, resuscitation is not recommended for neonates with confirmed gestational age less than 23 weeks; those with birth weight less than 400 g; and those with confirmed anencephaly, trisomy 13, or trisomy 18.[11,12] If unsure of gestational age or birth weight limitations, the recommendation is to initiate resuscitation. In the out-of-hospital setting or in the emergency department, every attempt should be made to stabilize the neonate until it is clear that attempted or continued resuscitation would not improve the patient's chance of survival. Infants with no signs of life (no heart beat and no respiratory effort) after 10 minutes of resuscitation show either a high mortality rate or severe later developmental delay. After 10 minutes of continuous and adequate resuscitative efforts, discontinuation may be justified if there are no signs of life.[12,13] It is important to communicate openly with the parent(s) and to acknowledge their opinions regarding risk of morbidity, including participation in the decision of whether or not to continue resuscitation.

Few specific disorders require deviations from the approach described here. The presence of meconium may necessitate intervention after delivery. Other anatomic anomalies require special care and include diaphragmatic hernia, meningomyelocele, abdominal anomalies (e.g., gastroschisis, omphalocele), and upper airway obstructive lesions (e.g., bilateral choanal atresia, Pierre Robin sequence).

SPECIFIC DISORDERS

Meconium Aspiration

Meconium in the amniotic fluid is a sign of in utero distress, and the presence of thick or particulate meconium before or at delivery should raise concern about the potential for aspiration. Aspiration of meconium and its consequences can be avoided by rapid intervention. Previous recommendations included suctioning meconium from the infant's airway after delivery of the head but before delivery of the shoulders (intrapartum suctioning). However, evidence from a large multicenter trial did not show benefit from intrapartum suctioning.[14-16] Therefore current recommendations no longer advise routine intrapartum suctioning for infants born to mothers with meconium-stained fluid. The decision to perform endotracheal intubation with tracheal suctioning after delivery of the infant should be made based on the *vigor* of the infant, rather than on the presence or consistency of the meconium (e.g., thick or particulate vs. thin). Infants with meconium-stained fluid and with any of the following are candidates for tracheal suctioning: (1) absent or depressed respirations, (2) poor muscle tone, or

www.ketabpezeshki.com 66485457-66963820

(3) HR less than 100 beats/min.[2] In such newborns, a meconium aspirator should be attached to the ETT and connected to wall suction at 100 mm Hg or less. The ETT is withdrawn as suction is being applied. After intubation, the ETT with meconium aspirator serves as the ideal suction catheter. Because of its narrower width, a suction catheter placed in the ETT does *not* suction meconium effectively. Reintubation and suction should be repeated until the meconium clears. Two passes of intubation and suctioning are usually sufficient. When these steps have been completed, the resuscitation should continue, beginning with the steps at the top of the neonatal flow algorithm (Fig. 11-1). If bradycardia or apnea continues beyond two passes, resuscitation should include bag-mask ventilation and consideration of intubation with ETT to secure the airway.

Anatomic Anomalies

Diaphragmatic Hernia

The neonate should be intubated as soon as possible if a prenatal diagnosis of diaphragmatic hernia has been made or if a diaphragmatic hernia is diagnosed on chest radiograph. Bag-mask

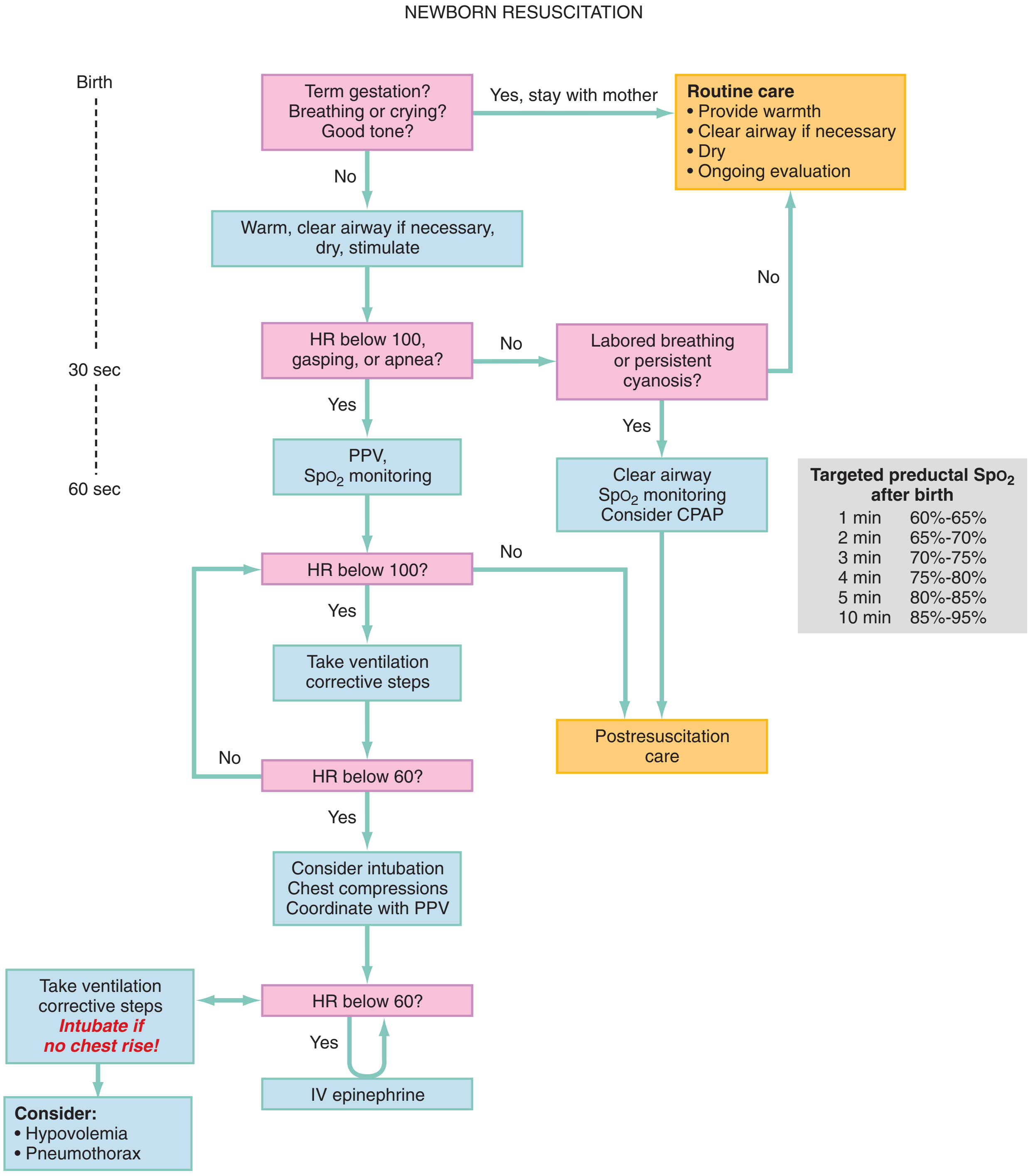


Figure 11-1. Neonatal resuscitation flow algorithm. Endotracheal intubation may be considered at several steps. *CPAP,* continuous positive airway pressure; *HR,* heart rate; *IV,* intravenous; *PPV,* positive pressure ventilation; *SpO_2,* oxygen saturation. (Modified from Kattwinkel J, et al: Part 15: Neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation; 122:S909-S919, 2010. Copyright © 2010 American Heart Association.)

www.ketabpezeshki.com 66485457-66963820

Box 11-1 Equipment Needed for Neonatal Resuscitation

1. Gown, gloves, and eye protection (universal precautions)
2. Blankets (to warm and dry infant)
3. Radiant warmer
4. Bulb syringe
5. Suction and suction catheters (French #5, #8, and #10)
6. Self-inflating bags (450 and 750 mL)
7. Masks (premature, newborn, and infant sizes)
8. Laryngoscope with straight blades (No. 00, 0, and 1)
9. Endotracheal tubes with stylets (2.5, 3.0, 3.5, and 4 mm)
10. Scissors and tape to stabilize endotracheal tube
11. CO_2 detector
12. Meconium aspirator
13. Umbilical catheters (French #3.5 and #5)
14. Hemostats, sterile drapes and gloves, povidone-iodine solution, scalpel, umbilical tape, suture, and three-way stopcock for umbilical vessel catheterization

ventilation distends the stomach and worsens respiratory distress because of the presence of the stomach in the chest cavity.

Meningomyelocele and Omphalocele

To avoid pressure on the defect, infants with meningomyelocele should not be placed on their backs but on their stomachs or sides. The resuscitation should be conducted in this position if possible. The spinal defect should be covered with sterile gauze pads soaked in warm sterile saline and covered with a plastic covering. Infants with gastroschisis or omphalocele should be resuscitated as needed, and the defect should be covered with an occlusive plastic covering to decrease water and heat loss.

Choanal Atresia

Because newborns are obligate nose breathers, bilateral choanal atresia causes upper airway obstruction and respiratory distress. It is diagnosed by the inability to pass a catheter through either naris into the oropharynx. An oral airway bypasses the obstruction.

Pierre Robin Sequence

Patients with Pierre Robin sequence have small jaws, and the relatively large tongue can lead to upper airway obstruction. A nasal or oral airway should be able to bypass the obstruction; if not, intubation may be necessary. It is technically difficult to intubate a patient with Pierre Robin sequence, so a laryngeal mask airway (LMA) may be placed instead.[17] Consultation with anesthesiology may be needed.

PREPARATION

To maximize the effectiveness of resuscitation, the emergency department should have a prestocked drug pack, standardized equipment (Box 11-1), and staff familiar with newborn resuscitation.[1,3] The pediatric length-based resuscitation tape (Broselow-Luten tape) has a section that can be used to determine equipment size and drug dosages for newborn resuscitation for infants weighing 3 kg or more.[18,19]

It is crucial to use universal precautions and to wear gown, gloves, and eye protection during neonatal resuscitation. For adequate preparation, the heat source is turned on early, and the resuscitation table should be warm when the newborn is placed on it. Equipment of proper size is essential (especially respiratory equipment because it is most likely to be used), and ventilation is the key to most resuscitative efforts. Appropriately sized self-inflating devices and ventilation masks decrease complications

Table 11-2 Resuscitation Equipment Sized by Birth Weight/Gestational Age[2]

BIRTH WEIGHT	GESTATIONAL AGE	ETT TUBE SIZE	DEPTH OF INSERTION
<1 kg	<28 wk	2.5 mm uncuffed	7 cm
1-2 kg	28-34 wk	3 mm uncuffed	8 cm
2-3 kg	34-38 wk	3.5 mm uncuffed	9 cm
3+ kg	38+ wk	3.5-4 mm uncuffed	10 cm

ETT, endotracheal tube.

Box 11-2 Maternal History Questions

1. What is the estimated gestational age?
2. Is this a multiple gestation?
3. Is meconium present?
4. Is there a history of vaginal bleeding?
5. Were medications given or drugs taken?

from overventilation and prevent injury or inability to ventilate due to improper mask fit. See Table 11-2 for recommended ETT sizes by birth weight and gestational age of the newborn.

If available, additional information may be helpful in preparing for resuscitation (Box 11-2). The estimated gestational age provides information about possible prematurity and associated complications. Multiple births require more equipment and personnel, and the newborns are at greater risk for prematurity and its complications. A history of maternal vaginal bleeding increases the likelihood of hypovolemic shock and respiratory distress in the newborn. A history of medication administration or drug use may provide clues to the cause of respiratory depression in the neonate.

MANAGEMENT

An organized approach is key to successful resuscitation both outside and inside the delivery room. The American Heart Association and the American Academy of Pediatrics have published a neonatal flow algorithm (see Fig. 11-1)—a stepwise approach to neonatal resuscitation. These steps are discussed in this section.[1-3]

Dry, Warm, Position, Suction, Stimulate, Assess Need for Further Intervention

To prevent complications caused by hypothermia, all newborns should be dried off as soon as possible after delivery and placed under a radiant heat source. Wet blankets should be replaced with dry and preferably warm blankets. Next, the neonate should be positioned to maximize air entry and avoid obstruction of airflow. Because of the infant's relatively large occiput and anterior airway, an open airway is best achieved with the neck in slight extension. The slightly extended position is best accomplished by placing a rolled diaper or small towel *under the infant's shoulders.* Placement under the neck is not useful, and a towel that is too large and under the shoulders leads to hyperextension at the neck and possible airway occlusion. The head of the neonate should be positioned closest to the resuscitation provider, usually at the head of the bed.

If meconium is present and the newborn has poor tone, poor respirations, or bradycardia (HR <100 beats/min), the trachea should be suctioned with an ETT with meconium aspirator attachment before any other intervention is performed. If no meconium is present but the newborn has poor respirations and obvious obstruction from secretions, the newborn may be suctioned with bulb or mechanical suction (approximately

www.ketabpezeshki.com 66485457-66963820

Table 11-3 Apgar Score

SIGN	0	1	2
Heart rate (beats/min)	Absent	Slow (<100)	≥100
Respirations	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexion	Active, good flexion
Reflex irritability	No response	Grimace	Cough, sneeze
Color	Blue, pale	Pink body, blue hands and feet	Pink

100 mm Hg wall suction). The mouth should be suctioned first, followed by the nose. The mouth is suctioned first to avoid aspiration of material if the infant takes in a breath after suctioning of the nose. Vigorous or deep suctioning can lead to a vagal response with subsequent bradycardia or apnea and should be avoided.[2,20] There is no benefit to suctioning of the oropharynx in newborns without respiratory distress, bradycardia, or poor tone.

Usually these measures adequately stimulate the infant to breathe effectively and may be the only measures needed to resuscitate a newborn. If adequate respirations are not present at this point, stimulation of the infant is needed; this is best done by flicking the soles of the feet and rubbing the back. If stimulation is not effective in initiating respirations, bag-mask ventilation is required followed by intubation if necessary.

Time is of the essence in resuscitating a newborn. Within the first 30 seconds of life, the newborn should be assessed and warmed, dried, and stimulated; the airway is cleared if necessary; and HR is counted (see Fig. 11-1). If the HR is below 100 beats/min or if the newborn has apnea or respiratory distress, positive pressure ventilation (PPV) and pulse oximetry should be initiated within the next 30 seconds. If bradycardia (HR <60 beats/min) persists despite adequate ventilation after 60 seconds total, then chest compressions are initiated. The reason for the persistent bradycardia is likely inadequate ventilation. If chest compressions are initiated, intubation is recommended at that point.

Apgar scores can also be counted at 1 and 5 minutes of life. The Apgar score is composed of scores for HR, respiratory effort, muscle tone, reflex irritability, and color. The score has been used as a prognostic indicator in newborns (Table 11-3) but is not useful in initial resuscitation management.[21] Muscle tone and reflex irritability do not aid in the assessment of the newborn during resuscitation.[21,22] HR and respiratory effort are the important indicators of hypoxia and should be monitored continuously. Further resuscitative efforts are required if respiratory effort is insufficient or if the HR is less than 100 beats/min. Evidence suggests that skin color may be a poor indicator for oxyhemoglobin status during the first several minutes of life as the transition from fetal to infant circulation is established. Pulse oximetry may be a useful tool to assess the oxygenation status of the newborn in the first few minutes of life.[5,6,23-25]

Ventilation, Oxygen, Intubation

Any infant who is cyanotic or appears to be in respiratory distress (grunting, nasal flaring, tachypnea) should be given respiratory assistance with either continuous positive airway pressure (CPAP) or PPV. If the infant is apneic, appears to be in severe respiratory distress, or has an HR of less than 100 beats/min, bag-mask ventilation (with a manometer, if available) should be initiated. The initial breaths require higher pressure (30-40 mm Hg) to remove lung fluid, and adequacy of ventilation is assessed by chest rise. Subsequent breaths generally require 20 mm Hg.[1,2] Excessive pressures (defined as more pressure than is needed to achieve chest rise) should be avoided because barotrauma may result. The primary measure of adequate initial ventilation is a prompt improvement in HR. An appropriately sized mask with a good seal (covering the mouth and nose but not the eyes), proper positioning of the infant, and use of appropriate pressure to attain chest wall movement are essential for effective ventilation. The newborn should be ventilated at 40 to 60 breaths/min unless blood gases dictate otherwise. If bag-mask ventilation is required for more than 2 minutes, an orogastric tube should be placed to prevent respiratory compromise from stomach distention.[2]

Resuscitation with 100% oxygen was previously recommended, but more recent studies support the effectiveness of room air for resuscitation and bag-mask ventilation.[26-29] Guidelines now recommend initiating resuscitation with room air, then blending in increasing oxygen concentration as needed. Use of 100% oxygen for resuscitation occurs only if the newborn has a persistent HR below 60 after 90 seconds. Attempts to restore adequate ventilation are more useful than increasing oxygen concentration. Increasing evidence points to lower initial preductal oxygen saturations in healthy uncomplicated newborns, which may contribute to the appearance of cyanosis. Figure 11-1 shows that targeted oxygen saturation after birth may not reach 90% or more until 10 minutes of life. Studies suggest that neurologic survival rates are improved when resuscitation of neonates is initiated with room air versus 100% oxygen because of the reduction in creation of free radicals in the brain.[1,3,26-29]

Endotracheal intubation may be indicated at several points during neonatal resuscitation: when tracheal suctioning for meconium is needed, if bag-mask ventilation is ineffective or prolonged, when chest compressions are performed, and for extremely low-birth-weight infants or infants with anatomic anomalies (e.g., diaphragmatic hernia). Box 11-1 lists the equipment needed for endotracheal intubation. Confirmation of proper ETT placement should include detection of expired carbon dioxide.[30-32]

Acute deterioration (bradycardia, decreased oxygen saturation) after intubation should suggest one of the following problems (*DOPE*)[33]:

1. *D*islodgment: The ETT is no longer in the trachea (right mainstem bronchus or esophagus).
2. *O*bstruction: Secretions are obstructing airflow through the ETT.
3. *P*neumothorax.
4. *E*quipment: Oxygen is not being delivered to the patient, or an air leak is present (check equipment).

If the patient acutely deteriorates after intubation, the equipment should be checked quickly; if no explanation is obvious, the patient should be extubated and ventilated with a self-inflating resuscitator (bag-mask ventilation device). Time should not be wasted adjusting or suctioning the ETT if the patient is bradycardic. If unequal breath sounds are present after extubation, or if the patient's condition is not improving with effective ventilation, needle aspiration of the chest should be considered for treatment of a possible pneumothorax.

The LMA has been shown to be effective for ventilating full-term newborns[34-36]; however, there are limited data on LMA use in preterm infants (<2000 g or <34 weeks' gestation). The usefulness of the LMA has not been evaluated in meconium aspiration syndrome or during cardiopulmonary resuscitation (CPR).

Chest Compressions

Bradycardia (HR <100 beats/min) is the major indicator of hypoxia. Most infants respond promptly to effective ventilation. If a neonate has an HR of less than 60 beats/min despite oxygen and adequate ventilation (good air movement and chest rise) for at least 30 seconds, chest compressions should also be provided.[1,2,37]

www.ketabpezeshki.com 66485457-66963820

Table 11-4 Resuscitation Medications

MEDICATION	CONCENTRATION	DOSE	ROUTE	CONSIDER
Oxygen	100%		Blow-by, ETT	
Epinephrine	1:10,000	0.01-0.03 mg/kg (0.1-0.3 mL/kg)	Intravenous (preferred), ETT	
Naloxone	0.4 mg/mL	0.1 mg/kg (0.25 mL/kg)	Intravenous, intramuscular, intraosseous, subcutaneous	
Glucose	$D_{10}W$	2-4 mL/kg	Intravenous	Avoid higher concentrations
Volume expanders	O-negative packed RBCs	10 mL/kg	Intravenous	Give over 5-10 min for acute bleeding; repeat as needed
	Normal saline	10 mL/kg	Intravenous	Give over 5-10 min; repeat as needed
	Ringer's lactate	10 mL/kg	Intravenous	Give over 5-10 min; repeat as needed
Dopamine	Concentration varies among institutions	Continuous intravenous infusion at 5 µg/kg/min Increase to 20 µg/kg/min as needed	Intravenous	

$D_{10}W$, 10% dextrose in water; *ETT,* endotracheal tube; *RBCs,* red blood cells.

Chest compressions should be performed at a rate of 90 per minute with 30 breaths/min for a total of 120 events per minute. The preferred neonatal resuscitation ratio is 3:1 (three compressions to one ventilation). If the resuscitation provider is sure that the bradycardia/cardiac arrest has a cardiac and not a respiratory cause, a compression:ventilation ratio of 15:2 may be considered.[1,3] The preferred method for performing chest compressions is as follows: the fingers of both hands encircle the chest and support the back. The thumbs of both hands are placed side by side or one over the other on the sternum just below the nipple line. The depth of compression is one third the anteroposterior diameter of the chest.[2,38,39]

Respirations and HR should be reassessed about every 30 seconds, and coordinated chest compressions and ventilation should continue until the spontaneous HR is greater than or equal to 60 beats/min.[1,2]

Medications

Few neonates require the use of medications during resuscitation.[40] Medications are indicated for bradycardia or asystole that does not respond to effective ventilation and chest compressions, and for hemorrhage (maternal, fetal, or placental) that necessitates fluid resuscitation.[1-3]

The only medications that should be used during the early phase of neonatal resuscitation are oxygen, epinephrine, and volume expanders (Table 11-4). Albumin has been removed as an initial resuscitation drug. Dopamine should be reserved for prolonged hypotension and extended resuscitation. Naloxone should be used only after the neonate is adequately ventilated. Sodium bicarbonate should not be used in most resuscitations; it may be beneficial in the neonatal intensive care setting when ventilation is known to be adequate.[1,41] Atropine or calcium are not routinely recommended in neonatal resuscitation, but calcium may be given if hypocalcemia is documented.

Vascular access is a challenge in neonatal resuscitation. The preferred route of immediate vascular access is the umbilical vein because it is easily identified and cannulated. Because of potentially serious complications (infection, portal vein thrombosis), the umbilical vein cannula should be removed immediately after stabilization and other access has been attained. Other vascular access routes include peripheral veins, peripherally inserted central catheter (PICC), and femoral vein. Intraosseous access can be problematic in neonates (especially premature infants) because of bone fragility and the small size of the intraosseous space. If vascular access cannot be achieved, some drugs such as epinephrine can be given through the ETT. The medication should be injected directly into the ETT, followed by a 1-mL saline flush and several positive pressure ventilations.[2]

Oxygen

Indications for oxygen use include persistent bradycardia (<60 beats/min) and respiratory distress (nasal flaring, grunting, tachypnea, apnea) beyond 90 seconds. Oxygen should be blended with room air if possible and titrated to achieve desirable targeted oxygen saturation (see Fig. 11-1) or to raise the HR to greater than 60 beats/min. Establishing effective ventilation is important because increased concentration of oxygen will not be delivered if ventilation is not adequate.

Epinephrine

Epinephrine is indicated for asystole, and for an HR less than 60 beats/min despite effective ventilation with 100% oxygen and chest compressions. Although epinephrine may be given by ETT, the preferred administration route is intravenous. The intravenous dose is 0.01 to 0.03 mg/kg or 0.1 to 0.3 mL/kg of 1:10,000 solution. Repeat doses may be given every 3 to 5 minutes.[1,2,42] If the endotracheal route is used, higher doses are needed. While access is being obtained, administration of 0.05 to 0.1 mg/kg of 1:10,000 solution through the ETT may be considered, but the safety and efficacy of this practice have not been evaluated.[1,2,42,43]

Naloxone

Respiratory depression induced by opioids given to or taken by the mother within 3 to 4 hours of delivery can be reversed with naloxone. Naloxone is infrequently needed in a newborn with respiratory depression. It may precipitate withdrawal seizures in an infant born to a drug-addicted mother.[9,10] The priority of care is support of ventilation with bag-mask device and intubation, if necessary. Naloxone should be considered only after ventilatory support is achieved. If respiratory depression is persistently present, and if it is unclear whether the mother took opioids before delivery, reversal with naloxone may be attempted. The dose is 0.1 mg/kg intravenously (IV), intraosseously (IO), subcutaneously (SQ), or intramuscularly (IM). Administration of naloxone by ETT is not recommended in newborn resuscitation.[1,44]

www.ketabpezeshki.com 66485457-66963820

The duration of action of naloxone is 1 to 4 hours, depending on route of administration. Repeat dosing may be necessary, and the patient should be monitored carefully.

Glucose

Hypoglycemia should be considered in a neonate undergoing resuscitation. Hypoglycemia is diagnosed with a rapid bedside glucose or serum glucose measurement. Neonates with glucose level less than 40 mg/dL and with symptoms of hypoglycemia (irritability, tremors, jitteriness, apnea, tachypnea, seizures, cyanosis, lethargy, poor feeding) should be treated with intravenous glucose. Hypoglycemia is treated with 2 mL of 10% dextrose in water ($D_{10}W$) per kilogram as well as by starting a continuous infusion of $D_{10}W$ at 80 to 100 mL/kg/day.[8] Higher concentrations of glucose (e.g., 25% dextrose in water, $D_{25}W$) are hyperosmolar and should be avoided. If the newborn is able to tolerate feeds, then oral glucose solution, maternal breast milk, or formula may be given by mouth on demand. Repeat glucose measurement should be obtained 10 to 20 minutes after glucose administration. Asymptomatic neonates with hypoglycemia should be encouraged to feed more often and are treated with intravenous glucose only when the glucose level is severely low (<25 mg/dL at birth to 4 hours of age or <35 mg/dL at 4-24 hours of age).[8]

Volume Expanders

Volume expanders are indicated when acute bleeding is evident with signs of hypovolemia (pallor despite oxygenation, weak pulses with a rapid HR, poor response to resuscitation), when a history of maternal hemorrhage during delivery is present, when the newborn appears to be in shock, or when CPR is required.[1,2,3,40] Volume expanders include packed red blood cells (Rh-negative type O blood), normal saline, or Ringer's lactate solution. Normal saline and Ringer's lactate (e.g., isotonic crystalloid solutions) should be readily available and may be considered the fluid of choice overall for volume expansion. Expanders are given in small intravenous boluses of 10 mL/kg over 5 to 10 minutes. When premature infants are being resuscitated, rapid administration of volume expanders should be avoided, as this has been associated with intraventricular hemorrhage.[2] Higher-volume (e.g., 20 mL/kg) fluid boluses are recommended for older infants. Boluses may be repeated several times, guided by patient assessment. The use of albumin 5% with saline is currently not recommended for the initial resuscitation.

Dopamine

Dopamine is indicated only when signs of shock (e.g., poor peripheral perfusion, thready pulses) are still present despite adequate volume replacement. Given as a continuous infusion beginning at 5 µg/kg/min, dopamine may be increased to 20 µg/kg/min as necessary.

Therapeutic Hypothermia

When moderate to severe hypoxic-ischemic encephalopathy is suspected, studies now suggest that selective cerebral hypothermia in asphyxiated infants may protect against brain injury.[1,45-53] Several randomized controlled trials have shown that therapeutic hypothermia of 33.5 to 34.5° C in this population leads to lower mortality and less neurologic disability at 18 months of age, compared with infants who did not have therapeutic hypothermia. Current guidelines recommend therapeutic hypothermia for patients with suspected early neonatal asphyxia. Symptoms may include abnormal levels of consciousness, seizures, hypotonia, or hyporeflexia.[53] It is unknown whether cooling the head alone versus the entire body is more neuroprotective. The current studies suggest that the recommended cooling is to be initiated within 6 hours of birth and to be continued for 72 hours with only slow rewarming over at least 4 hours afterward. Therapeutic hypothermia is not without risk; it may also lead to complications such as thrombocytopenia or hypotension.[45-52]

DISPOSITION

Early consultation with a neonatologist can assist in the resuscitation and postresuscitation phases of care. When the neonate's condition has been stabilized, the monitoring of oxygenation, ventilation, perfusion, temperature, and glucose continues. Preparations should be made for transport of the newborn to a neonatal intensive care unit. A transport team with personnel skilled in neonatal resuscitation should be used. Ideally, parents should see and touch (and hold if medically appropriate) their newborn before transport.

KEY CONCEPTS

- The necessary equipment must be readily available for neonatal resuscitation in the emergency department.
- Preparation is most effective with an adequate maternal and prenatal history.
- The neonatal flow algorithm provides a guide for management.
- Drying, warming, positioning, and stimulating the infant are usually sufficient resuscitative measures in most deliveries.
- Endotracheal suctioning for neonates at risk for meconium aspiration is reserved for nonvigorous infants.
- Adequate ventilation will reverse most bradycardia.
- In general, 100% oxygen is not indicated for initial resuscitation.
- Transport of the neonate to a neonatal intensive care unit allows continued treatment.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Kattwinkel J, et al: Part 15: Neonatal resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122:S909-S919.
2. American Academy of Pediatrics and American Heart Association: *Neonatal Resuscitation Textbook*, 6th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2011.
3. Perlman JM, et al: Part 11. Neonatal resuscitation. International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Circulation* 2010; 122(Suppl 2):S516-S538.
4. Hamrick SE, Hansmann G: Patent ductus arteriosus of the preterm infant. *Pediatrics* 2010; 125:1020-1030.
5. Kamlin CO, et al: Accuracy of pulse oximetry measurement of heart rate of newborn infants in the delivery room. *J Pediatr* 2008; 152:756-760.
6. O'Donnell CP, Kamlin CO, Davis PG, Morley CJ: Feasibility of and delay in obtaining pulse oximetry during neonatal resuscitation. *J Pediatr* 2005; 147:698-699.
7. Salhab WA, Wyckoff MH, Laptook AR, Perlman JM: Initial hypoglycemia and neonatal brain injury in term infants with severe fetal acidemia. *Pediatrics* 2004; 114:361.
8. Adamkin D, Committee on Fetus and Newborn: Clinical report—postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics* 2011; 127:575-579.
9. Herschel M, Khoshnood B, Lass NA: Role of naloxone in newborn resuscitation. *Pediatrics* 2000; 106:831-834.
10. McGuire W, Fowlie PW: Naloxone for opiate-exposed newborn infants. *Cochrane Database Syst Rev* 2002; 4:CD003483.
11. Landwirth J: Ethical issues in pediatric and neonatal resuscitation. *Ann Emerg Med* 1993; 22:502.
12. Paris JJ: What standards apply to resuscitation at the borderline of gestational age? *J Perinatol* 2005; 25:683-684.
13. Niermeyer S, et al: Resuscitation in newborns. *Ann Emerg Med* 2001; 37:S110.
14. Haddad B, Mercer BM, Livingston JC, Talati A, Sibai BM: Outcome after successful resuscitation of babies born with Apgar scored of 0 at both 1 and 5 minutes. *Am J Obstet Gynecol* 2000; 182:1210.
15. Vain NE, et al: Oropharyngeal and nasopharyngeal suctioning of meconium-stained neonates before delivery of their shoulders: Multicentre, randomised controlled trial. *Lancet* 2004; 364:597.
16. Wiswell TE, et al: Delivery room management of the apparently vigorous meconium-stained neonate: Results of the multicenter, international collaborative trial. *Pediatrics* 2000; 105(1 Pt 1):1-7.
17. Cain JM, Mason LJ, Martin RB: Airway management in two of newborns with Pierre Robin sequence: The use of disposable vs multiuse LMA for fiberoptic intubation. *Pediatr Anesth* 2006; 16:1274.
18. Kempley ST, Moreiras JW, Petrone FL: Endotracheal tube length for neonatal intubation. *Resuscitation* 2008; 77:369.
19. Luten R, Kahn N, Wears R, Kissoon N: Predicting endotracheal tube size by length in newborns. *J Emerg Med* 2007; 32:343.
20. Cordero L, Hon EH: Neonatal bradycardia following nasopharyngeal stimulation. *J Pediatr* 1971; 78:441.
21. Papile L: The Apgar score in the 21st century. *N Engl J Med* 2001; 344:519-520.
22. Laptook AR, et al: Outcome of term infants using Apgar scores at 10 minutes following hypoxic-ischemic encephalopathy. *Pediatrics* 2009; 124:1619-1626.
23. Altuncu E, Ozek E, Bilgen H, Topuzoglu A, Kavuncuoglu S: Percentiles of oxygen saturations in healthy term newborns in the first minutes of life. *Eur J Pediatr* 2008; 167:687-688.
24. Kamlin CO, O'Donnell CP, Davis PG, Morley CJ: Oxygen saturation in healthy infants immediately after birth. *J Pediatr* 2006; 148:585-589.
25. Rabi Y, Yee W, Chen SY, Singhal N: Oxygen saturation trends immediately after birth. *J Pediatr* 2006; 148:590-594.
26. Davis PG, Tan A, O'Donnell CP, Schulze A: Resuscitation of newborn infants with 100% oxygen or air: Systematic review and meta-analysis. *Lancet* 2004; 364:1329.
27. Saugstad OD, Rootwelt T, Aalen O: Resuscitation of asphyxiated newborn infants with room air or oxygen—an international controlled trial: The Resair 2 study. *Pediatrics* 1998; 102:e1.
28. Tan A, Schulze A, O'Donnell CP, Davis PG: Air versus oxygen for resuscitation of infants at birth. *Cochrane Database Syst Rev* 2005; 18:CD002273.
29. Rabi Y, Rabi D, Yee W: Room air resuscitation of the depressed newborn: A systematic review and meta-analysis. *Resuscitation* 2007; 72:353-363.
30. Aziz HF, Martin JB, Moore JJ: The pediatric disposable end-tidal carbon dioxide detector role in endotracheal intubation in newborns. *J Perinatol* 1999; 19:110.
31. Hosano S, et al: A role of end-tidal CO monitoring for assessment of tracheal intubations in very low birth weight infants during neonatal resuscitation at birth. *J Perinat Med* 2009; 37:79-84.
32. Repetto JE, Donohue PA-C PK, Baker SF, Kelly L, Nogee LM: Use of capnography in the delivery room for assessment of endotracheal tube placement. *J Perinatol* 2001; 21:284.
33. Ralston M, Hazinski MF, eds: *Textbook of Pediatric Advanced Life Support*. Dallas: American Heart Association; 2005.
34. Esmail N, et al: Laryngeal mask airway versus endotracheal intubation for Apgar score improvement in neonatal resuscitation. *Egypt J Anesthesiol* 2002; 18:115.
35. Gandini D, Brimacombe JR: Neonatal resuscitation with the laryngeal mask airway in normal and low birth weight infants. *Anesth Analg* 1999; 9:178.
36. Grein AJ, Weiner GM: Laryngeal mask airway versus bag/mask ventilation or endotracheal intubation for neonatal resuscitation. *Cochrane Database Syst Rev* 2004; 18:CD003314.
37. Perlman JM, Risser R: Cardiopulmonary resuscitation in the delivery room: Associated clinical events. *Arch Pediatr Adolesc Med* 1995; 149:20.
38. Orlowski JP: Optimum position for external cardiac compression in infants and young children. *Ann Emerg Med* 1986; 15:667-673.
39. Kitamura T, et al: Conventional and chest-compression-only cardiopulmonary resuscitation by bystanders for children who have out-of-hospital cardiac arrests: A prospective, nationwide, population-based cohort study. *Lancet* 2010; 375:1347-1354.
40. Wyckoff MH, Perlman JM, Laptook AR: Use of volume expansion during delivery room resuscitation in near-term and term infants. *Pediatrics* 2005; 115:950-955.
41. Aschner JL, Poland RL: Sodium bicarbonate: Basically useless therapy. *Pediatrics* 2008; 122:831-835.
42. Perondi MB, Reis AG, Paiva EF, Nadkarni VM, Berg RA: A comparison of high-dose and standard-dose epinephrine in children with cardiac arrest. *N Engl J Med* 2004; 350:1722-1730.
43. Quinton DN, O'Byrne G, Aitkenhead AR: Comparison of endotracheal and peripheral intravenous adrenaline in cardiac arrest: Is the endotracheal route reliable? *Lancet* 1987; 1:828.
44. Guinsburg R, Wyckoff MH: Naloxone during neonatal resuscitation: Acknowledging the unknown. *Clin Perinatol* 2006; 33:121-132.
45. Gunn AJ: Cerebral hypothermia for prevention of brain injury following perinatal asphyxia. *Curr Opin Pediatr* 2000; 12:111.
46. Gluckman PD, et al: Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: Multicentre randomised trial. *Lancet* 2005; 365:63.
47. Lin ZL, et al: Mild hypothermia via selective head cooling as neuroprotective therapy in term neonates with perinatal asphyxia: An experience from a single neonatal intensive care unit. *J Perinatol* 2006; 26:180-184.
48. Shankaran S, et al: Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med* 2005; 353:1574-1584.
49. Eicher DJ, et al: Moderate hypothermia in neonatal encephalopathy: Safety outcomes. *Pediatr Neurol* 2005; 32:18.
50. Eicher DJ, et al: Moderate hypothermia in neonatal encephalopathy: Efficacy outcomes. *Pediatr Neurol* 2005; 32:11.
51. Shankaran S, et al: Childhood outcomes after hypothermia for neonatal encephalopathy. *N Engl J Med* 2012; 366:2085-2092.
52. Azzopardi DV, et al: Moderate hypothermia to treat perinatal asphyxia encephalopathy. *N Engl J Med* 2009; 361:1349-1358.
53. Pfister RH, Soll RF: Hypothermia for treatment of infants with hypoxic-ischemic encephalopathy. *J Perinatology* 2010; 30:S82-S87.

www.ketabpezeshki.com 66485457-66963820

Section Two

CARDINAL PRESENTATIONS

Chapter 12

Fever in the Adult Patient

Frederick C. Blum and Michelle H. Biros

PERSPECTIVE

Epidemiology

Fever is a common presenting complaint in both pediatric and adult (aged 18-65 years) emergency department (ED) patients. Patients often confuse fever with a disease process itself, rather than a sign of an illness. Morbidity and mortality rates from febrile illnesses vary dramatically with age. Younger adults with fever usually have benign self-limited disease, with less than 1% mortality. The challenge in this group is to identify the rare meningitis or septic conditions when confronted with a predominance of self-limited viral and focal bacterial diseases. Patients older than 65 years, or those with chronic disease who have fever, represent a group at high risk for serious disease. Morbidity and mortality rates in this group are significant. From 70 to 90% are hospitalized, and 7 to 9% die within 1 month of admission.[1] Infection is the most common cause of fever in these patients, and most of these infections are bacterial in nature. Three body systems—the respiratory tract, the urinary tract, and the skin and soft tissue—are the target for more than 80% of these infections.[1,2] The relative mortality and morbidity for any given infection are much higher in the geriatric population. For example, elders are at 5 to 10 times greater risk for urinary tract infections and 15 to 20 times for appendicitis.[1,3] Even viral illnesses that are generally not fatal, such as influenza, can be highly lethal in elder persons.

Pathophysiology

Body temperature is normally controlled within a narrow range by the preoptic area of the hypothalamus. This range is usually 36.0 to 37.8° C (96.8-100.0° F). There is a circadian rhythm within this range, with lower temperatures in the morning and higher temperatures in the late afternoon. Fever occurs when this normal range is reset to a higher value. Fever is defined by the Centers for Disease Control and Prevention as a core temperature greater than 37.8° C in the absence of fever-reducing medication. Fever should not be confused with hyperthermia. Hyperthermia is an elevation of the temperature related to the inability of the body to dissipate heat. Most cases of temperatures higher than 41.0° C (105.8° F) are a result of hyperthermia, but febrile illness also is considered.

In the anterior hypothalamus, neurons directly sense the blood temperature. Temperature is subsequently controlled by a combination of vasomotor changes, shivering, changes in metabolic heat production, and behavioral changes.

Fever may be produced by a number of endogenous and exogenous substances referred to as *pyrogens.* Endogenous pyrogens include a variety of cytokines released by leukocytes in response to infectious and inflammatory and neoplastic processes. Exogenous pyrogens include a large number of bacterial and viral products and toxins. Toxins induce fever by stimulating cells of the immune system to release endogenous pyrogens. These cytokines, such as interleukin-1 (IL-1), IL-6, tumor necrosis factor, and interferon, travel to the hypothalamus and induce the production of prostaglandin E_2 (PGE_2).

PGE_2 raises the set point of the temperature range by a combination of effects, including peripheral vasoconstriction, increased metabolic heat production, shivering, and behavioral changes that conserve heat. Fever is maintained as long as the levels of endogenous pyrogens and PGE_2 are high. Cyclooxygenase inhibitors, such as aspirin, decrease fever by blocking the production of PGE_2. Age, malnutrition, and chronic disease may also blunt the febrile response.

Moderate elevations of the body temperature may serve to aid the host defense by increasing chemotaxis, decreasing microbial replication, and improving lymphocyte function. Elevated temperatures directly inhibit the growth of certain bacteria and viruses.[4]

Fever also results in certain increased physiologic costs to the host, including increased oxygen consumption, metabolic demands, protein breakdown, and gluconeogenesis. These costs are particularly problematic in elders, who typically have a smaller margin of reserve for any given body system. It is well established that the ability to develop fever in elders is somewhat impaired. Older individuals also are known to have lower baseline temperatures than younger adults.[5] It has not been shown that treatment of fever with antipyretics has a beneficial effect on outcome or prevents complications; however, treatment to reduce the fever makes febrile patients more comfortable.[4]

The initial step in the process of fever is the resetting of the thermostatic set point in the hypothalamus to a higher temperature while actual body temperature remains normal. This mismatch of the thermostat with the "sensed" body temperature causes the patient to feel chilled (chills). If the chills are reported to a caregiver and the temperature is taken, it is usually found to be normal or minimally elevated. To the examiner's touch, the patient's skin temperature will feel normal. The patient remains chilled until the body temperature rises to near the (elevated) hypothalamic set point. At this point, the patient feels euthermic (but may feel fatigued or ill), but to the caregiver the skin temperature or thermometer reading is now elevated. The sequence of chills followed by febrile illness is the basis of the (incorrect) popular belief that getting chilled leads to infection (classically pneumonia). When the thermostatic set point is reduced to normal, the patient suddenly feels hot and sweats until the body temperature falls to match the (now normal) set point.

www.ketabpezeshki.com 66485457-66963820

Table 12-1 Differential Diagnoses—Infectious Causes

ORGAN SYSTEM	CRITICAL DIAGNOSES	EMERGENT DIAGNOSES	NONEMERGENT DIAGNOSES
Respiratory	Bacterial pneumonia with respiratory failure	Bacterial pneumonia, peritonsillar abscess, retropharyngeal abscess, epiglottitis	Otitis media, sinusitis, pharyngitis, bronchitis, influenza, tuberculosis
Cardiovascular		Endocarditis, pericarditis	
Gastrointestinal	Peritonitis	Appendicitis, cholecystitis, diverticulitis, intra-abdominal abscess	Colitis or enteritis
Genitourinary		Pyelonephritis, tubo-ovarian abscess, pelvic inflammatory disease	Cystitis, epididymitis, prostatitis
Neurologic	Meningitis, cavernous sinus, thrombosis	Encephalitis, brain abscess	
Skin and soft tissue		Cellulitis, infected decubitus ulcer, soft tissue abscess	
Systemic	Sepsis or septic shock, meningococcemia		

Box 12-1 Differential Diagnosis—Noninfectious Causes of Fever

Critical Diagnoses
Acute myocardial infarction
Pulmonary embolism or infarction
Intracranial hemorrhage
Cerebrovascular accident
Neuroleptic-malignant syndrome
Thyroid storm
Acute adrenal insufficiency
Transfusion reaction
Pulmonary edema

Emergent Diagnoses
Congestive heart failure
Dehydration
Recent seizure
Sickle cell disease
Transplant rejection
Pancreatitis
Deep vein thrombosis

Nonemergent Diagnoses
Drug fever
Malignancy
Gout
Sarcoidosis
Crohn's disease
Postmyocardiotomy syndrome

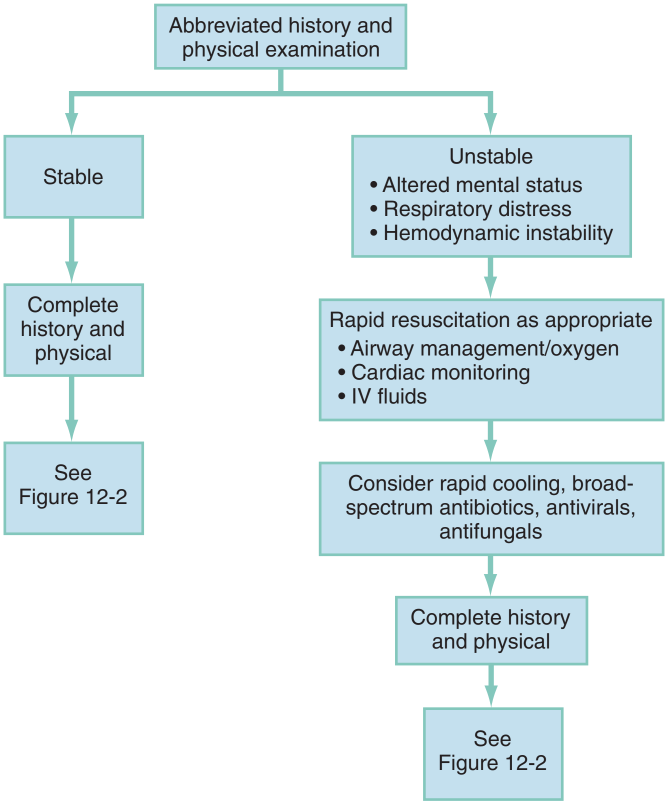


Figure 12-1. Approach to the critically ill febrile adult patient. *IV,* intravenous.

DIAGNOSTIC APPROACH

Differential Considerations

The complete differential diagnosis for the patient in the ED with fever is extensive. The major infectious and noninfectious causes are summarized in Table 12-1 and Box 12-1, respectively. The vast majority of serious causes are infectious in origin. Immediate threats to life are from decompensated shock (usually septic), respiratory failure (related to shock or pneumonia), or central nervous system infection (meningitis). Some critical noninfectious causes of fever also exist (see Box 12-1), but these are relatively rare and frequently do not occur with fever as the primary symptom.

A primary medical decision in acute febrile illness is based on assessment of patient stability (Fig. 12-1). Patients with life-threatening signs and symptoms, including significant alterations in mental status, respiratory distress, and cardiovascular instability, may require rapid, vigorous treatment. Prompt airway management and initiation of monitoring, intravenous access, fluid resuscitation, supplemental oxygen, and respiratory support are often necessary despite incomplete information concerning the cause of the fever. Sustained temperatures above 41.0° C are rare but can be damaging to neural tissue and require rapid cooling (e.g., misting, fans, cooling blankets).

In the younger, otherwise healthy patient with fever, immediate threats to life such as toxic or septic shock, meningitis, meningococcemia, and peritonitis should be considered and treated empirically. In older, chronically ill patients with fever, most of the serious illnesses originate from infections in the respiratory tract, the genitourinary tract, and the skin and soft tissues.[2] Meningitis, although less common, can also be a significant cause of morbidity and mortality in this group.

www.ketabpezeshki.com 66485457-66963820

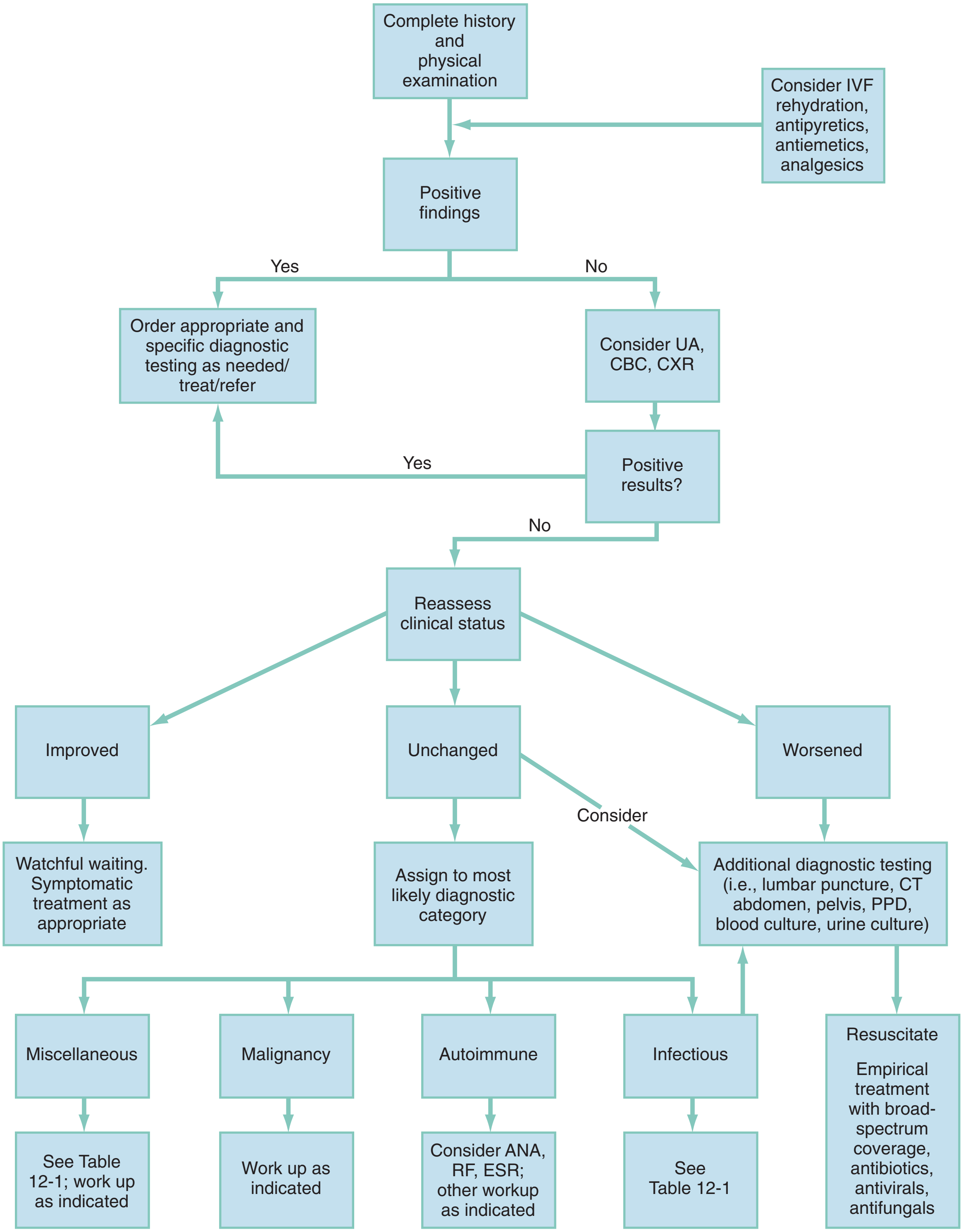


Figure 12-2. Approach to the stable adult with an acute febrile illness. *ANA,* antinuclear antibody; *CBC,* complete blood count; *CT,* computed tomography; *CXR,* chest x-ray; *ESR,* erythrocyte sedimentation rate; *IVF,* intravenous fluids; *PPD,* purified protein derivative; *RF,* rheumatoid factor; *UA,* urinalysis. (Adapted from Holder BM, Ledbetter C: Fever of unknown origin: An evidence-based approach. Nurse Pract 36:46-52, 2011.)

Pivotal Findings

Although the differential diagnosis of fever is broad, most of the treatable causes are of infectious origin. Most of these causes of fever may be diagnosed by careful history and physical examination alone.[6] Age and the presence of underlying medical conditions can substantially influence the evaluation and subsequent decision-making regarding management.

An approach to diagnosis and management of the healthy, otherwise well, stable adult patient with acute febrile illness is shown in Figure 12-2. In younger and otherwise healthy adults, self-limited, localized bacterial infections or benign systemic viral infections are usually the cause of fever. The challenge with this group is to identify the rare life-threatening illness, such as meningococcemia, meningitis, or systemic methicillin-resistant *Staphylococcus aureus* (MRSA) infection.

In the older or chronically ill population, fever is frequently a sign of severe illness. Usually the cause is infectious. In addition to the most common infectious causes of illness (respiratory,

www.ketabpezeshki.com 66485457-66963820

urinary, or skin sources), infections such as meningitis, cholecystitis, appendicitis, and diverticulitis are considered and may cause atypical signs and symptoms in elders or immunosuppressed patients. In these populations, subtle changes in behavior may be the only sign of severe infection. Abnormal vital signs, especially significant tachypnea and hypotension, may portend a complicated and severe course. Seventy-five percent of the cases of functional decline in nursing home patients are a result of infection.[1,2]

Symptoms

The *onset* of the fever, its *duration* and *magnitude,* and any *associated symptoms* help identify possible causes and severity of illness. Localizing symptoms such as dysuria or productive cough are especially helpful. The *timing* of the fever and its *patterns* may implicate certain diseases (e.g., malaria). *Recent or remote travel, chronic illnesses,* past surgeries, hospitalizations, and treatment modalities may raise the suspicion of exotic or nosocomial infections. The presence of prosthetic heart valves or any indwelling device may be critical to the diagnosis. With the emergence of community-acquired MRSA, it is important to seek a history of skin infections in close family members or other close contacts. MRSA should also be considered in military personnel, prisoners, and persons involved in competitive sports that involve close contact.[7,8]

Also important in the medical history is a list of all the patient's medications, including any antipyretic medications. Family members are frequently an important source of information in elder and very young patients.

Atypical symptoms of illness are common in elder patients. Pneumonia or urinary tract infection in the older patient may be heralded by only a change in mental status, difficulty ambulating, or some other functional decline. Dysuria, frequency, and flank pain often are absent entirely in elders with urinary tract infection. Patients with pneumonia may inconsistently demonstrate productive cough or shortness of breath. Other frequent but nonspecific symptoms include anorexia, weight loss, weakness, lethargy, nausea, and recurrent falls.[1,2] A history of cancer with recent chemotherapy or radiation therapy may be a clue to leukopenia or other immunodepressed states. Assessment of the patient's baseline mental and physical function often relies on the reports of others who know the patient well.

Signs

The presence and magnitude of fever are important elements of the examination, but the elder, very young, or chronically ill patient may not mount a febrile response to significant infection. Temperatures may fluctuate, and rechecks may be necessary.

Although the most accurate measure of core body temperature is thought to be via the thermistor of a pulmonary artery catheter, in the ED, rectal temperature measurements or, when a Foley catheter is indicated, bladder thermistors are the most practical and accurate.[9] Axillary and tympanic temperatures often are unreliable. Oral temperatures may be transiently distorted by recent ingestion of hot or cold liquids, smoking, or hyperventilation. For example, rectal temperatures are typically 0.7 to 1.0° C higher than oral temperatures.[9]

Fever is inconsistently associated with tachycardia and tachypnea. The heart rate may increase by 10 beats/min for each 0.55° C (1° F) degree rise in temperature. Relative bradycardia may be caused by medication such as beta-blockers, but it also can suggest factitious or drug-related fevers, typhoid fever, brucellosis, or leptospirosis. Frank bradycardia may occur with rheumatic fever, Lyme disease, viral myocarditis, and endocarditis. The respiratory rate may increase 2 to 4 breaths/min per degree Celsius. More significant tachypnea may be caused by respiratory infection or the acidosis related to shock.

In many patients the examination is directed by the patient's localization of symptoms. The head and neck examination focuses on treatable foci of infection, such as otitis media, sinusitis, pharyngitis, peritonsillar abscess, retropharyngeal abscess, and dental infections. A muffled, "hot potato" voice with severe sore throat may be a clue to adult epiglottitis or upper airway abscess. Fundoscopy rarely may reveal evidence of disseminated candidiasis, miliary tuberculosis, endocarditis, toxoplasmosis, or leukemia.

The neck is examined for lymphadenopathy, masses, or thyroid pathology (thyromegaly or mass). Nuchal rigidity or pain on flexion of the neck is a useful sign for meningismus if present but may not be prominent in many patients, particularly the very young or debilitated patient, even if meningitis is present. Conversely, cervical arthritis or Parkinson's disease may cause preexisting nuchal rigidity.

The lungs are examined for rales, pleural rubs, or dullness to percussion. Localized rales or rhonchi may be subtle clues to the presence of pneumonia. The presence of concomitant chronic obstructive pulmonary disease or congestive heart failure, as well as poor respiratory effort, may hamper the diagnosis of pneumonia in elders. The heart is examined for pericardial rubs or new murmurs.

The abdominal examination may be deceptively benign in older patients, patients with diabetes, or patients taking immunosuppressive drugs or steroids. When indicated by history or other findings, a rectal examination should be performed to check for evidence of enteritis, perirectal abscess, or prostatitis. The external genitalia examination may reveal evidence of Bartholin's abscess, urethral or vaginal discharge, or evidence of epididymitis or orchitis. In women, symptoms of lower abdominal pain, vaginal discharge, and dyspareunia suggest the need for a pelvic examination to evaluate for pelvic inflammatory disease or tubo-ovarian abscess.

The skin and extremities should be evaluated for rash, petechiae, joint inflammation, or evidence of soft tissue infection. In the absence of trauma, tenderness over the long bones or the spine may be evidence of osteomyelitis or neoplastic processes. Elders and bedridden patients should be checked for the presence of pressure sores or decubitus ulcers.[2]

Ancillary Testing

Ancillary testing is directed by the history and physical examination. The two most useful ancillary tests, especially in elder patients, are urinalysis and chest radiography. Chest radiographs are often helpful in the diagnosis of pulmonary infection but may be difficult to interpret in the patient with concurrent chronic obstructive pulmonary disease, congestive heart failure, dehydration, or other chronic lung disease. The urinalysis, although not foolproof, is highly accurate for urinary tract infection, especially in men. Although the white blood cell count is almost universally used in the evaluation of febrile patients, it lacks the sensitivity and specificity to be of discriminatory value. The white blood cell count may incorrectly indicate serious infection when none is present or may be normal in the presence of life-threatening infection.[10] Other indirect tests of infection and inflammation, such as the erythrocyte sedimentation rate, are also plagued with irregular sensitivity and poor specificity. Gram's stain of appropriate specimens may be helpful, and cultures may be ordered, although the results do not often influence emergency evaluation and treatment. With the emergence of MRSA, it has become increasingly important to obtain cultures from soft tissue skin abscesses in patients considered at risk for MRSA infection. In elder or chronically ill patients with acute fever of unknown source, blood and urine cultures are frequently appropriate. Outpatient blood

www.ketabpezeshki.com 66485457-66963820

cultures should rarely, if ever, be done. A patient ill enough to require blood cultures from the ED generally requires hospitalization and empirical antibiotic coverage. Cerebrospinal fluid evaluation should be considered when mental status changes are evident, or if headache, meningismus, or other unexplained neurologic symptoms are present and cannot be clearly accounted for by infection outside the central nervous system. Thyroid function studies may be helpful when thyroid storm is suspected. Arterial or venous blood gas studies may help identify patients with critical disease who require prompt treatment.

Plain films of the abdomen are rarely indicated or helpful unless perforation or obstruction is suspected. Abdominal computed tomography (CT) is helpful if appendicitis, diverticulitis, cholecystitis, or intra-abdominal abscess is suspected. Ultrasonography may be helpful in the patient with potential cholecystitis.

Cranial CT scanning may be indicated before lumbar puncture in patients with focal neurologic findings or an embolic source, such as suspected endocarditis, to exclude mass lesions such as tumor or brain abscess. This test should not delay antibiotics in patients with suspected meningitis.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses of infectious causes of fever are summarized in Table 12-1. The differential diagnoses of noninfectious causes of fever are listed in Box 12-1. However, differences in patient characteristics can cause different manifestations of the same illness. For example, pneumonia or a urinary tract infection manifests in and is tolerated by an 80-year-old very differently compared with a young adult. A careful history and physical examination, along with strategic ancillary testing, will allow the practitioner to identify when a critical condition is present and will determine the operational tempo of subsequent evaluation and treatment.

EMPIRICAL MANAGEMENT

Patients with temperatures greater than 41.0° C require prompt and vigorous treatment with antipyretics and possibly external cooling measures. Temperatures above this range can result in damage to neuronal tissue. There is no evidence for improved outcome by routine use of antipyretic therapy, such as acetaminophen, in patients without extreme temperature elevation, but it is not harmful, and patients often feel better when their temperature declines.[4] Recent studies have shown that intravenous acetaminophen is as effective as oral acetaminophen and may be used in patients who are unable to take oral medication.[11]

Patients with signs and symptoms of septic shock require prompt and vigorous treatment. Patients with evidence of respiratory failure from either shock or pneumonia require ventilatory support. Soft tissue infections of the head and neck may compromise the airway because of mechanical obstruction. These may require acute intervention to provide a secure airway.

In many cases, early empirical antibiotic therapy is appropriate. The choice of antibiotics is based on the likely cause of the fever as well as concomitant conditions such as absolute neutropenia and end-stage renal disease. If a specific infection is subsequently identified, antibiotic therapy should be specific to that infection. In the absence of a clear source of infection, broad-spectrum coverage of gram-positive and gram-negative aerobic and anaerobic bacteria is indicated. In acutely ill febrile patients, especially those who are immunocompromised, antiviral and antifungal treatment should also be considered.

DISPOSITION

Localized bacterial infections can most frequently be treated with outpatient oral antibiotics. Relatively young, healthy patients with systemic viral illness can be treated as outpatients. These illnesses are often accompanied by vomiting and poor oral intake, and treatment in the ED with antipyretics, antinausea medications, and intravenous hydration may help prepare the patient for a successful outpatient course.

When no clear infection is identified in older patients or those with chronic illness, such as diabetes or chronic renal failure, admission to the hospital often is necessary to further elucidate the possible causes of the presentation. In this subset of patients, a diligent search for evidence of bacterial infection is required. Also, admission to an inpatient unit or ED observation unit may be advisable when fever or other systemic symptoms accompany a suspected MRSA infection. In patients with unexplained severe febrile illness, blood and urine cultures and broad-spectrum antibiotics are indicated to treat possible life-threatening infection, until a specific disease process or pathogen is identified. Indwelling devices, such as percutaneous intravenous access ports, frequently require culture and may need to be removed. Neutropenic patients with fever require prompt treatment with broad-spectrum parenteral antibiotics, pending results of cultures. Patients with unstable vital signs or life-threatening infections may require admission to a special care unit if they cannot be adequately stabilized in the ED before admission.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Angus DA, et al: Epidemiology of severe sepsis in the United States: Analysis of the incidence, outcome and associated costs of care. *Crit Care Med* 2011; 29:1303-1310.
2. High KP, et al: Clinical practice guideline for the evaluation of fever and infection in older adults residents of long term care facilities: 2008 update by the Infectious Disease Society of America. *Clin Infect Dis* 2009; 48:149-171.
3. Tal S, Guller V, Gurevich A, Levi S: Fever of unknown origin in the elderly. *J Intern Med* 2002; 252:295-304.
4. Greisman LA, Mackowiak PA: Fever: Beneficial and detrimental effects of antipyretics. *Curr Opin Infect Dis* 2002; 15;241-245.
5. Roghhmann MC, Warner J, Mackowiak PA: The relationship between age and fever magnitude. *Am J Med Sci* 2001; 322:68-70.
6. Tolan RW Jr: Fever of unknown origin: A diagnostic approach to this vexing problem. *Clin Pediatr (Phila)* 2010; 49:207-210.
7. Aiello AE, Lowy FD, Wright LN, Larson EL: Meticillin-resistant *Staphylococcus aureus* among U.S. prisoners and military personnel: Review and recommendations for future studies. *Lancet Infect Dis* 2006; 6:335-341.
8. Turbeville SD, Cowan LD, Greenfield RA: Infectious disease outbreaks in competitive sports: A review of the literature. *Am J Sports Med* 2006; 34:1860-1865.
9. O'Grady N, et al: Guidelines for the evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. *Crit Care Med* 2008; 36:1330-1353.
10. Furer V, Raveh D, Picard E, Goldberg S, Izbicki G: Absence of leukocytosis in bacteraemic pneumococcal pneumonia. *Prim Care Respir J* 2011; 20:276-281.
11. Peacock WF, Breitmeyer JB, Pan C, Smith WB, Royal MA: A randomized study of the efficacy and safety of intravenous acetaminophen compared to oral acetaminophen for the treatment of fever. *Acad Emerg Med* 2011; 18:360-366.

www.ketabpezeshki.com 66485457-66963820

Chapter 13

Weakness

Ravi S. Morchi

PERSPECTIVE

The complaint of weakness is common in emergency department (ED) patients and may be vague, subjective, and difficult to characterize. True loss of strength from a neurologic or muscle fiber lesion must be distinguished from other systemic conditions that result in fatigue, dyspnea, or imbalance because of inadequate substrate delivery to the nervous system or muscle unit. Such conditions may be described as weakness by the patient but are likely caused by cardiovascular, pulmonary, infectious, or metabolic processes. This chapter focuses on the evaluation of acute neuromuscular weakness; it may be focal or generalized and may originate in central or peripheral nerves, the neuromuscular junction (NMJ), or myofibers themselves. Other chapters provide more detail on peripheral nerve (Chapter 107) and neuromuscular disorders (Chapter 108).

Epidemiology

The epidemiology of weakness is closely linked to the epidemiology of other diseases and medical conditions. Although weakness can be a presenting problem at all ages, patients who are elderly or chronically ill are more likely to develop weakness. Advanced diabetes, cardiovascular and pulmonary diseases, chronic infectious diseases, and cancer may produce neuromuscular weakness through secondary effects on the brain and neuromuscular system. Brain, spinal cord, peripheral nerve, and neuromuscular causes of weakness are much less common than weakness that is secondary to other medical conditions.[1]

Pathophysiology

There are a number of physiologic considerations for the patient with diffuse weakness (Box 13-1).

Focal weakness confined to one area in the face or body (left, right, distal, or proximal) indicates a localized problem arising in the brain, spinal cord, peripheral nerve, or muscle.

Conditions that affect the upper motor neuron (UMN) produce signs that include spasticity to extension in the upper extremities, spasticity to flexion in the lower extremities, hyper-reflexia, pronator drift, Hoffmann's sign, and Babinski's sign (upgoing toes). UMN signs signify a lesion within the cerebral cortex or corticospinal tracts (CSTs) of the brainstem or spinal cord. Although these findings are not always detectable in the acute period, the presence of even one of them indicates pathology within the central nervous system.

Weakness caused by lower motor neuron (LMN) dysfunction is often accompanied by flaccidity, decreased reflexes, fasciculations, or muscle cramps. Lesions in the anterior horn of the spinal cord and its axonal extensions at the nerve root and peripheral nerve produce these findings.

Conditions that have only peripheral effects at the NMJ and muscle have preserved reflexes.

Differential Considerations

In the diffusely weak patient, first consideration is given to a systemic deficiency in substrate delivery to the nervous system or skeletal muscle unit. In patients with cardiac disease, myocardial ischemia can also be a source of generalized weakness.

History regarding circumstances at onset, progression, exacerbating or alleviating factors, and any fluctuations in severity may help the emergency physician discern if weakness is a result of cardiovascular disease, pulmonary insufficiency, the metabolic demands of a recent infection, or cancer. Review of systems can reveal orthopnea and symptoms of congestive heart failure in the fatigued patient with significant cardiac disease, chronic blood loss in the anemic patient, or incontinence in an elderly person with urosepsis.

Vital sign abnormalities, including tachycardia, tachypnea, fever, hypothermia, or hypotension, prompt immediate intervention and a search for a systemic cause of weakness. Cardiac, pulmonary, skin, and mucous membrane examinations may give the emergency physician a sense of the adequacy of the cardiovascular system in delivering substrate to brain and muscle. In such patients the neurologic examination should not demonstrate focal changes of the central or peripheral nervous system.

If by history, physical examination, and bedside ancillary testing the patient does not appear to have derangements in intravascular volume or cardiopulmonary function, metabolic abnormalities, or a source of infection, the investigation turns to a neural or primary muscular cause for weakness. Often these patients will have some asymmetrical finding on their neurologic examination. The critical and emergent diagnoses for neuromuscular weakness are listed in Table 13-1.

Diagnostic Algorithm

Deciphering loss of muscle power means following the pattern of a patient's weakness from the myofiber back to a particular site within the central or peripheral nervous system (Fig. 13-1).

www.ketabpezeshki.com 66485457-66963820

Box 13-1 Non-neurologic Weakness

Alterations in plasma volume (dehydration)
Alterations in plasma composition (glucose, electrolytes).
Derangement in circulating red blood cells (anemia or polycythemia)
Decrement in cardiac pump function (myocardial ischemia)
Drop in systemic vascular resistance (vasodilatory shock from any cause)
Increased metabolic demand (local or systemic infection, endocrinopathy, toxin)
Mitochondrial dysfunction (severe sepsis or toxin-mediated)
Global depression of the central nervous system (sedatives, stimulant withdrawal)

Table 13-1 Critical and Emergent Causes of Neuromuscular Weakness

Critical Diagnoses	
Cerebral cortex or subcortical	Ischemic or hemorrhagic cerebrovascular accident (CVA)
Brainstem	Ischemic or hemorrhagic CVA
Spinal cord	Ischemia, compression (disk, abscess, or hematoma)
Peripheral nerve	Acute demyelination (Guillain-Barré syndrome)
Neuromuscular junction	Myasthenic or cholinergic crisis Botulism Tick paralysis Organophosphate poisoning
Muscle	Rhabdomyolysis
Emergent Diagnoses	
Cerebral cortex or subcortical	Tumor, abscess, demyelination
Brainstem	Demyelination
Spinal cord	Demyelination (transverse myelitis) Compression (disk, spondylosis)
Peripheral nerve	Compressive plexopathy (hematoma, aneurysm) Paraneoplastic vasculitis uremia
Muscle	Inflammatory myositis

Common clinical patterns of weakness can be classified and assessed as discussed in the following sections.

Unilateral Weakness with a Combination of Arm, Hand, or Leg with Ipsilateral Facial Involvement

This presentation is generally caused by a lesion in the contralateral cerebral cortex or the CSTs coursing down the corona radiata and forming the internal capsule. Mild forms can be limited to a loss of dexterity and coordination with hand movements. Moderate loss of power is termed *paresis,* and complete loss of motion is termed *plegia*. UMN signs are useful corroborative findings but may not always be present. Sensory disturbances commonly occur over the areas of weakness. Look for associated neglect, a visual field cut, or an expressive or receptive aphasia to localize the problem to the cortex.[2] Patients with equal loss of strength to the face, hand, and leg are more likely to have a subcortical lesion disrupting all of these fibers as they funnel close together in the internal capsule. Concomitant headache is suggestive of a brain hemorrhage or mass lesion.[3] Sudden onset of this weakness pattern implies hemorrhage or ischemia, whereas a gradual onset may be seen in demyelination or neoplasm.

Unilateral Weakness: A Combination of Arm, Hand, or Leg but with Contralateral Facial Involvement

This pattern indicates a brainstem lesion. A careful cranial nerve (CN) examination can provide more clues. If the patient has contralateral facial findings, there will likely be ptosis (CN III or sympathetic fibers) or a facial droop with forehead involvement (CN VII nucleus). Signs of CN V, VI, VIII, IX, or XII dysfunction will help to localize to a particular level within the brainstem.[4] Cerebellar findings or nystagmus may also be present on examination. Sensory disturbances can parallel the weakness, and some patients will report double vision, trouble swallowing, slurred speech, vertigo, or nausea and vomiting. The CST courses ventrally through the brainstem, and extremity weakness with UMN signs in the involved limbs may accompany brainstem lesions. Depressed consciousness can also occur if the brainstem reticular activating system is involved. The two main underlying processes that cause unilateral extremity weakness with contralateral facial involvement are vertebrobasilar insufficiency and demyelinating diseases.

Unilateral Weakness: A Combination of Arm, Hand, or Leg without Facial Involvement

Before a patient is placed in this category, a careful examination of facial symmetry is required to determine that subtle facial droop or effacement of the nasolabial fold is *not* present. If there is truly no facial involvement, the source of extremity weakness without facial involvement is most likely to be a result of one of the following processes:

- A lesion in the medial, contralateral, cerebral homonculus (over the area where the lower extremity is represented)
- A discrete internal capsule or brainstem lesion involving only the corticospinal rather than the corticobulbar tracts
- Brown-Séquard hemicord syndrome if the patient also has contralateral hemibody pain and temperature sensory disturbances below the level of motor weakness

Unilateral Weakness: One Limb Only (Monomelic Weakness, Monoparesis, or Monoplegia)

Isolated weakness of one extremity is most commonly caused by a spinal cord or peripheral nerve lesion. Examination for UMN signs in the affected limb will help to uncover rare monomelic presentations of central nervous system lesions. If UMN signs such as hyper-reflexia or spasticity are present, a careful evaluation is performed for facial weakness or involvement of the contralateral or involvement of the contralateral or other ipsilateral limb as indicative of a central process. If weakness is in the entirety of one lower limb, one should ensure that the patient does not have a contralateral pinprick level indicative of Brown-Séquard hemicord syndrome. Monomelic weakness is often the result of a radiculopathy, plexopathy, peripheral neuropathy, or NMJ disorder. See Table 13-1 for emergent and critical peripheral nervous system diagnoses.

The examination for monomelic weakness presentations includes detailed strength testing and determination if weakness localizes to one ventral nerve root myotome or one particular peripheral nerve within the limb. Reflexes with a peripheral nerve disorder will be diminished, not hyperactive. Although radiculopathies can occasionally be purely motor, most peripheral lesions have some sensory component to their presentation; therefore a careful sensory examination in the distribution of dorsal nerve root dermatomes and peripheral nerves is essential. See Box 13-2 for a list of nonemergent causes of peripheral neuropathy.

If suspicion is low for a UMN source of isolated extremity weakness, reflexes are intact, and there are no sensory deficits to suggest

www.ketabpezeshki.com 66485457-66963820

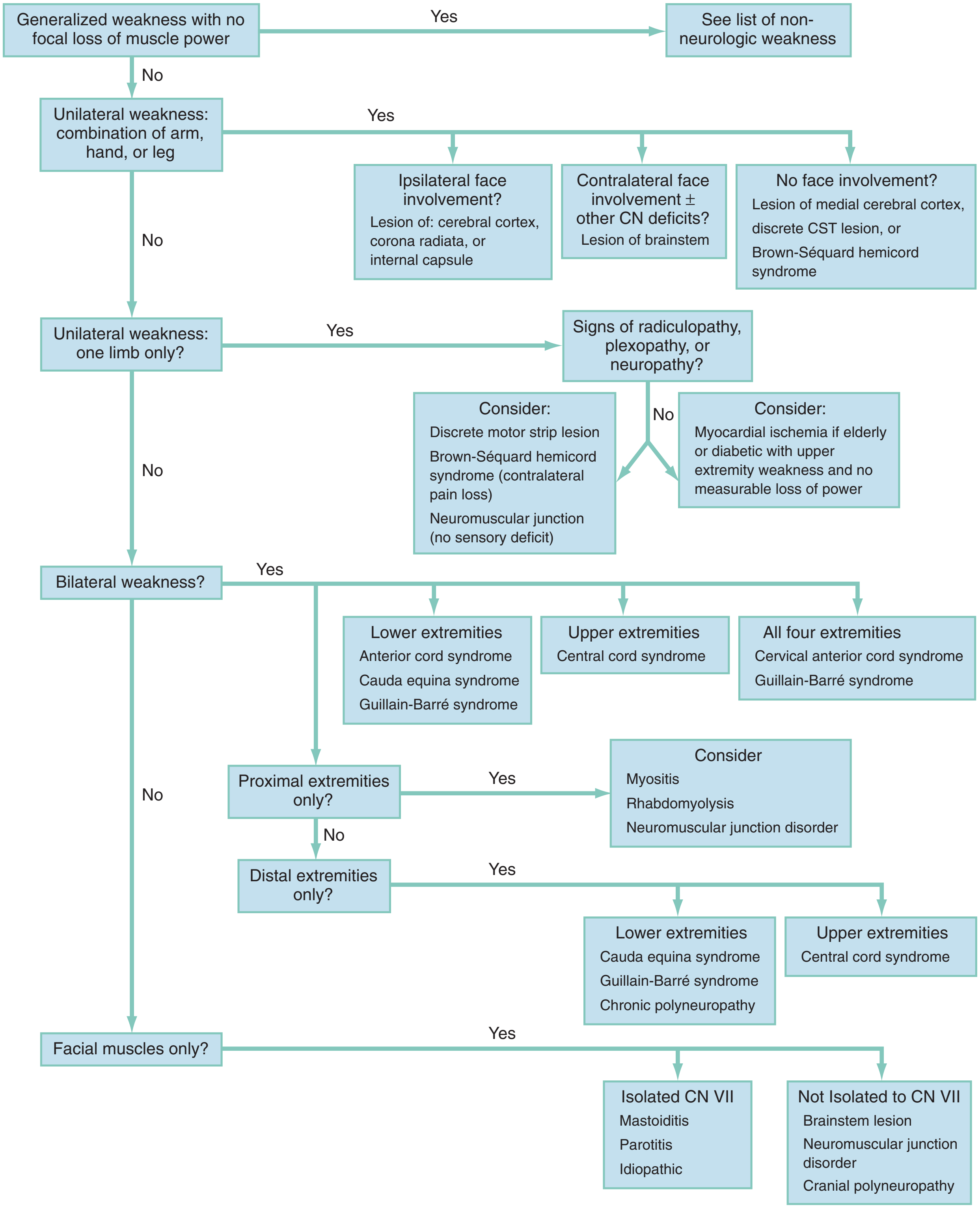


Figure 13-1. Common clinical patterns of weakness, classified and assessed.

a nerve or root problem, then NMJ disorders are considered. In such cases the weakness is often mild, fluctuating, and worse later in the day. It usually involves the proximal arm or leg muscles, wrist extensors, finger extensors, or ankle dorsiflexors. NMJ disorder–induced weakness with only monomelic symptoms will be an uncommon diagnosis in the ED (see Chapter 108). In elderly patients and others with significant cardiac risk factors, myocardial ischemia is considered if arm sensory symptoms or arm weakness that does not demonstrate measurable loss of motor power is reported.

Bilateral Weakness: Lower Extremities Only (Paraparesis or Paraplegia)

The first consideration with this presentation pattern is a spinal cord lesion. If this is the case, UMN signs *may* be absent in the

www.ketabpezeshki.com 66485457-66963820

Box 13-2 Nonemergent Causes of Peripheral Neuropathy

Connective tissue disorder
External compression (entrapment syndrome, compressive plexopathy)
Endocrinopathy (diabetes)
Paraneoplastic syndromes
Toxins (alcohol)
Trauma
Vitamin deficiency

acute period. Because the lateral spinothalamic tracts (LSTs) run in proximity to the CST, patients with bilateral lower extremity weakness frequently have alteration to their perception of pain or temperature. Examination may reveal a loss of pinprick sensation to a particular spinal level within the thoracic cord or terminal first lumbar segment. The lesion may be as high as T2 without producing upper extremity findings. The main causes of anterior cord syndrome are external compression, ischemia, or demyelination. In the absence of UMN signs or a clear thoracic pinprick level, evaluation of perianal sensation, rectal tone, and urinary retention can identify deficits that point to cauda equina syndrome—compression of peripheral nerve roots running below the termination of the spinal cord. If the physical examination does not support a cord syndrome or cauda equina compression, the patient may have a peripheral neuropathy affecting the longest nerve tracts first. The acute presentation that is most concerning is Guillain-Barré syndrome (GBS). Rapid demyelination of peripheral nerves can result in symmetrical weakness ascending from the feet. Sensory findings parallel the weakness, and reflexes should be decreased at some point in the patient's clinical course.[5]

Bilateral Weakness: Upper Extremities Only

This "central cord" pattern localizes to the central portion of the cervical spinal cord where corticospinal fibers designated for hand and arm strength are located. The patient may have pinprick sensory loss over the upper extremities from involvement of crossing sensory axons destined for the contralateral LST. However, light touch sensation, mediated by the posterior columns, should remain intact. Causes of central cord syndrome include cervical spine hyperextension injuries and syringomyelia.

Bilateral Weakness: All Four Extremities without Facial Involvement (Quadriparesis or Quadriplegia)

The obvious concern with this pattern is for a cervical spinal cord injury or process, but the patient is first assessed for medical conditions that produce global weakness.

The more dense the extremity weakness, the more likely the patient has a cervical spinal cord problem. Although all four extremities will test poorly for muscle strength, there is frequently some discrepancy between the lower and upper limbs in quadriparesis.

Determination of sensory dermatomes by pinprick testing in the arms and hands along with strength testing of specific myotomes will allow localization of the level within the cervical spinal cord. One physical examination confounder with disorders that cause cord compression or ischemia is that upper extremity myotomes corresponding to the site of spine involvement will actually have LMN signs of flaccid weakness and decreased reflexes because anterior horn cells are involved at this particular level.[6] However, UMN signs may be elicited below that level. A C5 lesion, for example, can cause diminished biceps reflexes but exaggerated triceps and patellar reflexes.

Bilateral extremity weakness may occur in patients with GBS that has ascended from the lower extremity peripheral nerve myelin sheaths to the upper extremities. In this case the lower limbs are usually weaker than the upper limbs.

Bilateral Weakness: Proximal Portions of Extremities Only

Provided that there are no UMN signs and no sensory deficits, this pattern points to a myofiber disorder.[7] Patients may report general fatigue or trouble raising the arms above the head, climbing stairs, or rising from a chair. The common acute and progressive causes of proximal muscular weakness are inflammatory diseases such as polymyositis or dermatomyositis, or necrosis as in rhabdomyolysis from HMG-CoA reductase inhibitors. Muscles are commonly but not always tender to palpation. Myositis patients can also have dysarthria and dysphagia from weakness of the pharyngeal muscles. Airway protective mechanisms may eventually be compromised.

Chronic or recurrent myofiber pathology includes abnormalities to anchoring proteins supporting fibrils to the cytoskeleton and cell membrane (muscular dystrophies), dysfunctional ion channels responsible for depolarization of the muscle fiber cell (channelopathies such as hyperkalemic and hypokalemic periodic paralysis), or an impaired ability to use carbohydrate and lipid energy sources (metabolic myopathies and mitochondrial myopathies). The presentation of these varied conditions ranges from insidious and progressive to sudden onset and episodic. Occasionally, a patient with an NMJ disorder will demonstrate proximal extremity or neck muscle weakness mimicking myofiber disease.

Bilateral Weakness: Distal Portions of Extremities Only

This pattern is almost always caused by a peripheral neuropathy (see Box 13-2). Patients will have weakness and poor coordination with fine movements of their feet or hands. If this type of distal weakness is present in both lower extremities only, the patient will most likely have a chronic peripheral neuropathy or an acute demyelinating neuropathy (GBS). The patient will have some sensory disturbance over the feet as well. Examination for perianal sensory deficits or issues with fecal or urine continence will help to exclude the compressive polyradiculopathy of cauda equina syndrome as a cause of bilateral distal lower extremity weakness. If only the fingers and hands are involved, evaluation for central cord syndrome is performed. Bilateral lower cervical radiculopathies or symmetrical polyneuropathies are possible but much less likely.

Facial Weakness without Extremity Involvement

This will appear in one of two forms, as follows:

1. *Unilateral facial droop.* If the weakness is a result of a CN VII problem, unilateral weakness in the upper and lower half of the face should be present on examination. Causes for an isolated CN VII neuropathy are Bell's palsy, mastoiditis, and parotitis. The examination must confirm that there is no extremity involvement and that other CNs, cerebellar testing results, and visual fields are normal. This will ensure that a brainstem lesion is not causing the weakness.
2. Facial weakness not limited to CN VII and the muscle of expression, but including some combination of ptosis, binocular diplopia, dysarthria, or dysphagia. This can be caused by a brainstem lesion, multiple cranial neuropathies, or an NMJ problem. If there are no cerebellar findings, visual field deficits, sensory

www.ketabpezeshki.com 66485457-66963820

disturbances, or extremity UMN signs, posterior cerebral circulation and brainstem disorders are less likely, and an NMJ disorder is more likely. Dysfunction of one or more ocular, facial, or pharyngeal muscles will be the most common presentation for NMJ pathology.[8] The history may indicate that the facial weakness is acute and progressive (botulism) or chronic and fluctuating (myasthenia gravis). Signs of these diseases can be determined by examining extraocular motion, facial expression, and soft palate rise. Generalized fatigue is often reported, and neck, extremity, and respiratory muscle weakness caused by involvement of these neuromuscular units may be present on examination.[9]

Patients with an abnormality of the presynaptic release of acetylcholine (botulism, Eaton-Lambert syndrome, organophosphate poisoning) can have autonomic ganglia involvement and hence abnormal pupillary response to light, dry mouth, fluctuations in heart rate and blood pressure, anhidrosis, or gastrointestinal and bladder dysmotility.

Facial weakness from cranial polyneuropathy manifests with more than one CN deficit not localizing to a brainstem level and without any other long tract signs. Such patients may have a variant of GBS or irritation of multiple CNs after they have exited the brainstem and pierced through inflamed meninges or malignant skull base metastases.

PIVOTAL FINDINGS

1. Patients with tachypnea or shallow respirations should be considered at higher risk for respiratory failure from diaphragmatic, intercostal, and accessory muscle fatigue. Consideration should be given to quantify respiratory effort with pulmonary function tests and/or intervene with positive pressure ventilation.
2. In any patient with sudden onset of focal weakness, a vascular cause (either occlusion or hemorrhage) is strongly considered until proven otherwise by an adequate imaging study.
3. The presence of a severe headache with unilateral weakness, or midline back pain with lower extremity weakness, alerts the emergency physician to a compressive space-occupying lesion.
4. Patients with UMN signs have weakness that localizes to the spinal cord CST or above and are considered to have an emergent problem. They may be at risk for progression to sympathetic autonomic failure or obtundation from enlarging space-occupying spinal or cerebral lesions, respectively.
5. The presence of anorectal or bladder insufficiency without another explanation suggests a UMN or cauda equina lesion.
6. Laboratory tests are most useful in excluding non-neuromuscular causes of weakness (electrocardiogram [ECG], hemoglobin, glucose, electrolytes, troponin, lactate, urinalysis). Two exceptions are creatinine kinase level in inflammatory myositis and potassium level in channelopathies.

EMPIRICAL MANAGEMENT

The ED management of neuromuscular weakness is based on the underlying cause; however, basic emergency tenets are followed for all patients.

1. Neck and pharyngeal muscle weakness may herald a risk for aspiration or insufficiency of the diaphragm with paradoxical abdominal wall motion. Signs of inadequate hypopharyngeal muscle control or respiratory muscle fatigue should prompt protection of the airway and/or positive pressure ventilation.
2. During rapid sequence intubation (RSI), succinylcholine is avoided in suspected cases of progressive denervation of muscle. Nondepolarizing neuromuscular blocking agents such as rocuronium or vecuronium are used in this situation.
3. New quadriparesis or quadriplegia and hypotension without another cause is assumed to be caused by failure of autonomic sympathetic fibers in the cervical spinal cord. Consider a volume load and pressor support in addition to emergent imaging of this area.
4. Although new weakness localizing to the spinal cord or above calls for immediate imaging, weakness from the spinal roots down does not always necessitate imaging in the ED.
5. Patients with suspected GBS need pulmonary function testing in addition to admission to a critical care setting for further management.
6. An infectious or metabolic trigger is sought in patients with myasthenic crisis. If the patient is currently on acetylcholinesterase inhibitors, consideration should be given to a cholinergic crisis.
7. Be aware of medications that may worsen weakness in patients with NMJ disease (e.g., aminoglycosides, quinolones, beta-blockers).
8. Rhabdomyolysis is treated with aggressive fluid resuscitation and intervention directed at the primary cause, if known.

DISPOSITION

Patients with mild LMN or myofiber weakness of benign origin may be discharged with close follow-up, provided the condition is not believed to be rapidly progressing.

Those with more severe or progressive LMN or myofiber weakness and any patient with new UMN weakness should be admitted for further testing. Patients requiring positive pressure ventilation for respiratory muscle fatigue or blood pressure support for sympathetic failure should receive an intensive care unit level of care.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Pinto A, Tuttolomondo A, Di Raimondo D, Fernandez P, Licata G: Cerebrovascular risk factors and clinical classification of strokes. *Semin Vasc Med* 2004; 4:287-303.
2. Yew KS, Chang E: Acute stroke diagnosis. *Am Fam Physician* 2009; 80:33-40.
3. Jamieson DG: Diagnosis of ischemic stroke. *Am J Med* 2009; 122(4 Suppl 2):S14-S20.
4. Querol-Pascual MR: Clinical approach to brainstem lesions. *Semin Ultrasound CT MR* 2010; 31:220-229.
5. McGillicuddy DC, Walker O, Shapiro NI, Edlow JA: Guillain-Barré syndrome in the emergency department. *Ann Emerg Med* 2006; 47:390-393.
6. Harrop JS, Hanna A, Silva MT, Sharan A: Neurological manifestations of cervical spondylosis. *Neurosurgery* 2007; 60:S14-S20.
7. Amato AA, Barohn RJ: Evaluation and treatment of inflammatory myopathies. *J Neurol Neurosurg Psychiatry* 2009; 80:1060-1068.
8. Newsom-Davis J: The emerging diversity of neuromuscular junction disorders. *Acta Myol* 2007; 26:5-10.
9. Engstrom JW: Myasthenia gravis: Diagnostic mimics. *Semin Neurol* 2004; 24:141-147.

www.ketabpezeshki.com 66485457-66963820

Chapter 14

Cyanosis

Madonna Fernández-Frackelton

PERSPECTIVE

Epidemiology

Cyanosis is a blue or purple appearance of the skin or mucous membranes. This clinical finding is caused by inadequately oxygenated blood perfusing peripheral tissues or the presence of abnormal hemoglobin forms unable to bind oxygen or to supply adequate oxygen to end organs and tissues. Cyanosis is a relatively rare presenting chief complaint in the emergency department (ED) and is most commonly noted in patients with a hypoperfused state or known cardiopulmonary disease, including congenital heart disease. Although carbon monoxide poisoning and cyanide toxicity result in inadequate hemoglobin oxygenation and tissue hypoxia, these entities typically do not manifest with the clinical finding of cyanosis and are discussed in other chapters.

Pathophysiology

Cyanosis is evident on physical examination when the absolute amount of desaturated (unoxygenated) hemoglobin in the circulating capillary blood is elevated to approximately 5 g/dL.[1,2] It is not a percent of desaturated total hemoglobin mass or a decreased amount of oxyhemoglobin. For this reason, patients with a relatively low hemoglobin level exhibit cyanosis at a much lower partial pressure of oxygen (Pao_2) and arterial oxygen saturation (Sao_2) than those with normal hemoglobin levels. Cyanosis is an insensitive indicator of tissue oxygenation.[3] Its presence suggests hypoxia, buts its absence does not exclude it.

Abnormal hemoglobin forms contribute significantly to cyanotic disease. Under normal conditions, red blood cells (RBCs) contain hemoglobin with iron in the reduced ferrous state (Fe^{2+}). The iron molecule may be oxidized to the ferric state (Fe^{3+}) to produce methemoglobin. This reaction impairs the ability of hemoglobin to transport oxygen to and carbon dioxide from the tissues. The oxygen dissociation curve is shifted to the left, resulting in tissue hypoxia and lactic acid production (Fig. 14-1). Methemoglobin normally accounts for less than 1% of total hemoglobin.[4] Cyanosis results when greater than 10 to 25% of the total hemoglobin is methemoglobin (approximately 1.5 g/dL), which has a dark purple-brown or chocolate brown color even when exposed to room air. Methemoglobin is reduced to ferrous hemoglobin primarily by nicotinamide adenine dinucleotide (NADH) cytochrome-b_5 reductase, an enzyme system present within RBCs. A secondary system dependent on nicotinamide adenine dinucleotide phosphate (NADPH)-reductase uses glutathione production and glucose-6-phosphate dehydrogenase (G6PD) to reduce methemoglobin to hemoglobin. This secondary pathway normally plays a minor role but is accelerated by methylene blue.[4]

Primary methemoglobinemia is the result of a congenital error in enzyme metabolism, with either diminished levels of NADH reductase or an abnormally functioning enzyme. Patients may have cyanosis in a stable compensated state. Acquired methemoglobinemia occurs when methemoglobin production (hemoglobin oxidation) is accelerated beyond the capacity of NADH reductase activity. This usually occurs as a drug reaction. (See Box 14-1 for common causes.) Newborns are at risk for methemoglobinemia because their NADH reductase activity is relatively low.[5]

DIAGNOSTIC APPROACH

Differential considerations for patients with cyanosis are listed in Box 14-2.

Pivotal Findings

Symptoms

The onset, duration, and time of day of symptoms and any previous episodes should be noted. Precipitating factors may include exposure to cold air or water, high altitude, or exercise in patients with a history of cardiopulmonary disease. Additional history should include known congenital heart disease or cardiopulmonary disease, hypercoagulable states, and any family history of cyanotic disease or hematologic illness. A history of home or occupational exposures to fumes or chemicals should be obtained, including aniline, azo dyes (phenazopyridine [Pyridium]), phenacetin, and nitrates.[6] A drug history should be reviewed, including use of prescription and over-the-counter medications, health food supplements, and herbal or alternative preparations.[7] The potential of pseudocyanosis resulting from exposure to dyes, heavy metals, or topically absorbed pigments should be explored.[8]

In infants, congenital heart disease is suggested by difficulty feeding, sweating, lethargy, poor weight gain, or respiratory distress. Episodic cyanotic events, or "tet spells," may be seen in children with tetralogy of Fallot (ventricular septal defect, overriding aorta, pulmonic stenosis or atresia, and right ventricular hypertrophy with outlet obstruction). These patients have cyanosis, tachypnea, and anxiety owing to decreased pulmonary blood flow with shunting of unoxygenated blood into the peripheral circulation.[9,10]

Signs

There is significant interobserver variability in detecting cyanosis on physical examination. Room lighting and temperature may affect examination of the skin and mucous membranes. A patient's

www.ketabpezeshki.com 66485457-66963820

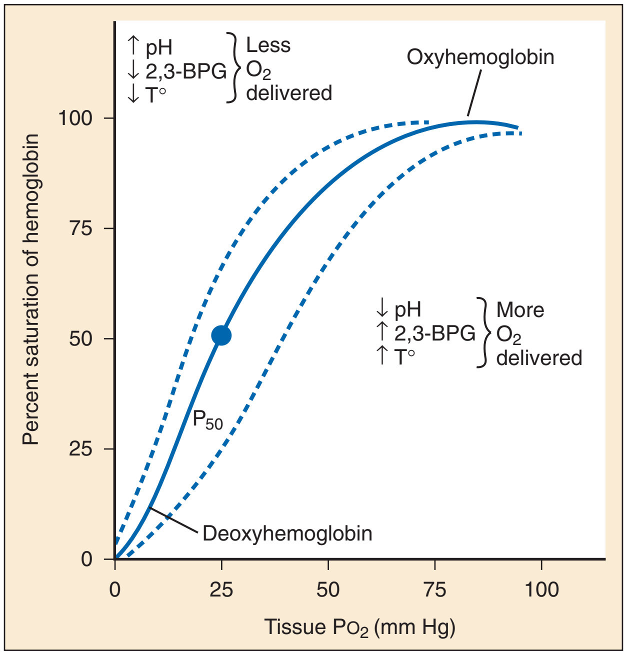


Figure 14-1. Hemoglobin-oxygen dissociation curve. Deoxyhemoglobin does not bind oxygen efficiently. Methemoglobin has a high affinity for oxygen molecules and does not readily release oxygen to the peripheral tissues. This shifts the normal oxygen dissociation curve to the left, resulting in hypoxia and lactic acid production. Typically, when acid is produced in the tissues, the dissociation curve shifts back to the right, facilitating oxygen release; however, the high affinity of methemoglobin prevents this normal process. *2,3-BPG,* 2,3-bisphosphoglycerate; *P_{O_2},* partial pressure of oxygen; *P-50,* oxygen half saturation pressure of hemoglobin; *T°*, temperature. (Redrawn from Benz EJ Jr: Hemoglobinopathies. In Harrison's online.)

Box 14-1 Common Causes of Methemoglobinemia

Hereditary
Hemoglobin M
NADH methemoglobin reductase deficiency (homozygote and heterozygote)
G6PD deficiency

Acquired
Medications
Amyl nitrite
Antineoplastics (cyclophosphamide, ifosfamide, flutamide)
Dapsone
Local anesthetics (benzocaine, lidocaine, prilocaine)
Nitroglycerin
Nitroprusside
Phenacetin
Phenazopyridine (Pyridium)
Quinones (chloroquine, primaquine)
Sulfonamides (sulfanilamide, sulfathiazide, sulfapyridine, sulfamethoxazole)

Chemical Agents
Aniline dye derivatives (shoe dyes, marking inks)
Butyl nitrite
Chlorobenzene
Fires (heat-induced denaturation)
Food adulterated with nitrites
Food high in nitrates
Isobutyl nitrite
Naphthalene (mothballs)
Nitrophenol
Nitrous gases (seen in arc welders)
Paraquat
Silver nitrate
Trinitrotoluene
Well water (nitrates)

Pediatric
Reduced NADH methemoglobin reductase activity in infants (<4 mo)
Seen in association with low birth weight, prematurity, dehydration, acidosis, diarrhea, and hyperchloremia

Adapted from Goldfrank LR: Toxicologic Emergencies, 9th ed. New York: McGraw-Hill; 2010.
G6PD, glucose-6-phosphate dehydrogenase; *NADH,* reduced nicotinamide adenine dinucleotide.

natural skin tone, thickness, and pigmentation also may alter findings.[3]

Central cyanosis is often secondary to the shunting of venous unsaturated hemoglobin into the arterial circulation or the presence of abnormal hemoglobin. A bluish discoloration of the skin and mucous membranes is best seen on perioral skin, oral mucosa, or conjunctivae.

Peripheral cyanosis is secondary to vasoconstriction and slow flow of normally oxygenated hemoglobin in arterial blood, allowing for greater oxygen extraction by the tissues. Peripheral cyanosis affects capillary beds and typically is seen in the extremities and nail beds. Differential cyanosis may occur in either the upper or lower (or the right or the left) half of the body, with the remainder appearing well oxygenated. This form of cyanosis is usually seen in patients with cyanotic heart disease with multiple anomalies.

Vital signs should be obtained from all patients. Temperature is typically normal. Blood pressure and heart rate vary unpredictably. Upper airway obstruction and other signs of respiratory insufficiency should be sought. Intermittent apnea in infants suggests central nervous system immaturity or a central lesion. Infants with cyanosis, increased respiratory depth, periodic apnea episodes, or diaphoresis with feeding may have congenital heart disease.[9,10] Tachypnea (>60 breaths/min) in a newborn may indicate a pulmonary disorder, congenital heart disease, infection, metabolic disorder, or gastrointestinal or central nervous system pathology.[11]

General appearance and mental status should be evaluated. The head, eyes, ears, nose, and throat examination may reveal central cyanosis. Funduscopic examination may detect dilated tortuous veins and papilledema in patients with cyanotic congenital heart disease.[12] Jugular venous distention may be seen on the neck examination in patients with pulmonary edema.

The chest examination may reveal crackles, wheezing, or inadequate ventilation. Heart sounds should be assessed for tachycardia, abnormal rhythm, or gallops, and the presence and quality of murmurs, especially in newborns. Central pulse strength should be noted. The abdomen should be examined for the presence of hepatosplenomegaly, a pulsatile mass, or abdominal bruit.

Extremity examination includes evaluation of nail beds for peripheral cyanosis, strength and symmetry of distal pulses, and capillary refill. Evidence of chronic vascular disease, such as hair loss and temperature difference, should be noted. Clubbing of the nails may occur because of increased soft tissue and expansion of the capillary beds (Fig. 14-2). Clubbing may be idiopathic or hereditary but is usually the result of chronic hypoxemic states, such as cyanotic heart disease, infective endocarditis, pulmonary disease (chronic obstructive pulmonary disease, cystic fibrosis), and some gastrointestinal disorders (cirrhosis, Crohn's disease, and regional enteritis). Thrombotic events should also be considered with findings of skin and nail bed hemorrhages or end-organ damage (eye, kidney).

www.ketabpezeshki.com 66485457-66963820

Box 14-2 Differential Diagnosis of Cyanosis

I. Peripheral cyanosis
  A. Low cardiac output states
    1. Shock
    2. Left ventricular failure
    3. Hypovolemia
  B. Environmental exposure (cold)
    1. Air or water
  C. Arterial occlusion
    1. Thrombosis
    2. Embolism
    3. Vasospasm (Raynaud's phenomenon)
    4. Peripheral vascular disease
  D. Venous obstruction
  E. Redistribution of blood flow from extremities
II. Central cyanosis
  A. Decreased arterial oxygen saturation
    1. High altitude (>8000 ft)
    2. Impaired pulmonary function
      a. Hypoventilation
      b. Impaired oxygen diffusion
      c. Ventilation-perfusion mismatching
        (1) Pulmonary embolism
        (2) Acute respiratory distress syndrome
        (3) Pulmonary hypertension
      d. Respiratory compromise
        (1) Upper airway obstruction
        (2) Pneumonia
        (3) Diaphragmatic hernia
        (4) Tension pneumothorax
        (5) Polycythemia
  B. Anatomic shunts
    1. Pulmonary arteriovenous fistulae and intrapulmonary shunts
    2. Cerebral, hepatic, peripheral arteriovenous fistulae
    3. Cyanotic congenital heart disease
      a. Endocardial cushion defects
      b. Ventricular septal defects
      c. Coarctation of aorta
      d. Tetralogy of Fallot
      e. Total anomalous pulmonary venous drainage
      f. Hypoplastic left ventricle
      g. Pulmonary vein stenosis
      h. Tricuspid atresia and anomalies
      i. Premature closure of foramen ovale
      j. Dextrocardia
      k. Pulmonary stenosis of atrial septal defect
      l. Patent ductus arteriosus with reversed shunt
  C. Abnormal hemoglobin
    1. Methemoglobinemia
      a. Hereditary
      b. Acquired
    2. Sulfhemoglobinemia
    3. Mutant hemoglobin with low oxygen affinity (e.g., hemoglobin Kansas)

A neurologic examination should be performed focusing on mental status, symmetry of motor and sensory function, and any gross deficit.

Laboratory and Ancillary Testing

The complete blood count should be checked to assess for erythrocytosis, polycythemia, or anemia.[13] Peripheral smear assesses RBC morphology and fragments, as well as white blood cell differential count. A D-dimer level may be obtained if pulmonary embolism (PE) is suspected. A normal D-dimer is useful in ruling out PE in patients with a low pretest probability for the disease.[14]

Figure 14-2. Symmetrical clubbing. Equal cyanosis and clubbing of hands and feet resulting from transposition of great vessels and a ventricular septal defect without patent ductus arteriosus.

The peripheral blood classically appears chocolate brown in color. Normally a small drop of blood placed on a white sheet or filter paper will turn bright red in color when exposed to 100% oxygen. No change in color is highly suggestive of methemoglobinemia.[4]

Interpretation of pulse oximetry is problematic in the setting of cyanosis (see Chapter 5). Assessment of distal perfusion usually determines if poor circulation is a cause of low pulse oximetry. Pulse oximetry measures light absorbance of tissue at 660 nm (red, reduced hemoglobin) and 940 nm (infrared, oxyhemoglobin). The ratio of these two readings is the basis of the pulse oximetry calculation. Methemoglobin absorbs well at both wavelengths, resulting in a saturation approximation of 85%, regardless of the actual Pao_2 and Sao_2.[15,16]

Arterial blood gas testing assesses Sao_2, often sampled when the patient is breathing room air (see Fig. 14-1). CO-oximetry measurements should be specifically ordered if carbon monoxide exposure or methemoglobinemia is suspected. Sulfhemoglobin is reported as methemoglobin on CO-oximetry, so if sulfhemoglobinemia is possible, measured oxygen saturation should be specifically requested. Newer devices designed to measure methemoglobin levels noninvasively (pulse CO-oximetry) may be useful but have decreasing accuracy at lower Sao_2 levels (<95%) and higher methemoglobin levels (>14%).[17,18]

Imaging

A chest radiograph should be ordered to evaluate lung fields for consolidation, infiltrates, and increased vasculature or pulmonary edema. The cardiac silhouette and mediastinum may suggest congenital heart disease. In patients thought to have PE, an elevated D-dimer level may indicate the need for lower extremity venous Doppler ultrasound, computerized tomography pulmonary angiogram, or rarely ventilation-perfusion scanning.

Electrocardiogram and Echocardiogram

An electrocardiogram should be performed on all patients with cyanosis to assess for arrhythmias and acute ischemic changes. Right-axis deviation or right ventricular hypertrophy may be seen

www.ketabpezeshki.com 66485457-66963820

with significant cardiopulmonary disease (e.g., cor pulmonale, acute pulmonary hypertension). An echocardiogram may be helpful in detecting septal defects in infants or valvular disease in infants and adults.

DIFFERENTIAL ALGORITHMS

Figures 14-3 and 14-4 outline an approach to the differential diagnosis and treatment for peripheral and central cyanosis, respectively. During the initial assessment, as the distribution of cyanosis is noted, the clinician should initiate oxygen therapy and follow steps to determine the cause of cyanosis. Clinical improvement with oxygen suggests diffusion impairment. Patients who do not respond to high-concentration oxygen are more likely to have ventilation-perfusion ratio abnormalities, such as shunting from a consolidated pulmonary lobule or congenital heart disease with right-to-left shunting. Cardiac size and silhouette on a chest radiograph may provide a clue to the presence of congenital cardiac disease. If heart size is normal, impaired pulmonary function, pulmonary embolus, or other noncardiac causes should be considered. If no improvement occurs with 100% oxygen therapy, the patient's respiratory status should be reassessed, and tension pneumothorax or upper airway obstruction considered. Pulmonary embolus should be considered and a computed tomography pulmonary angiogram performed. If a patient exhibits no respiratory distress and remains resistant to oxygen therapy, cardiac shunting or abnormal hemoglobin forms should be considered and treated accordingly. Superior vena cava (SVC) syndrome should be suspected in patients with central cyanosis with facial, neck, and upper extremity swelling with venous distention and plethora.[19]

Critical Diagnoses

Acute cardiovascular and respiratory compromise is considered in a patient with cyanosis and symptoms or signs of shock. The differential diagnosis for these critical presentations includes acute heart failure, acute coronary syndrome, and hypovolemic or cardiogenic shock. In addition, consider acute respiratory insufficiency or failure, massive PE, an exacerbation or decompensation in a patient with known congenital heart disease, or the first presentation of pediatric congenital heart disease.

Emergent Diagnoses

Methemoglobinemia is an infrequent cause of cyanosis but should be considered in patients without a history or physical findings suggestive of cardiovascular or pulmonary disease.

Sulfhemoglobinemia is a rare cause of cyanosis most commonly occurring after exposure to hydrogen sulfide from organic sources,

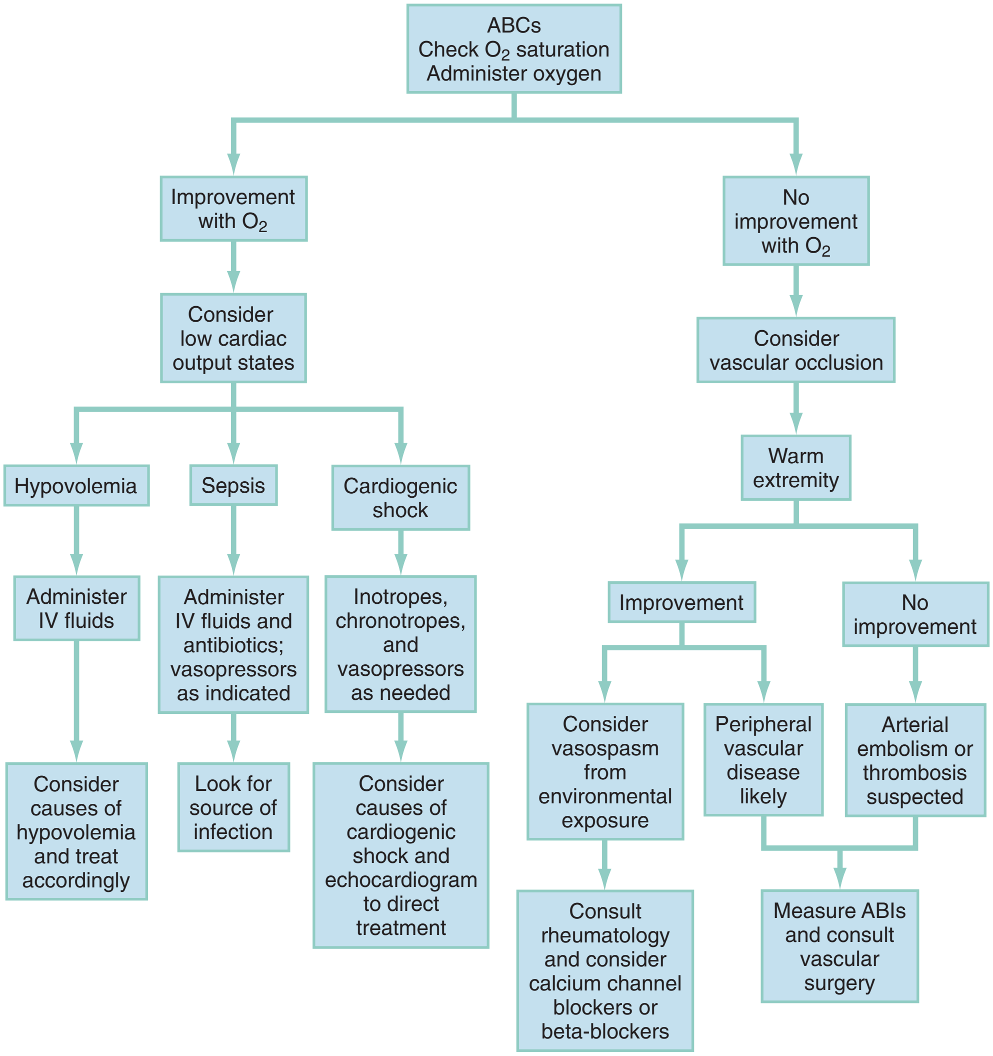


Figure 14-3. An algorithmic approach to peripheral cyanosis. *ABCs,* airway, breathing, circulation; *ABI,* ankle brachial index; *IV,* intravenous.

www.ketabpezeshki.com 66485457-66963820

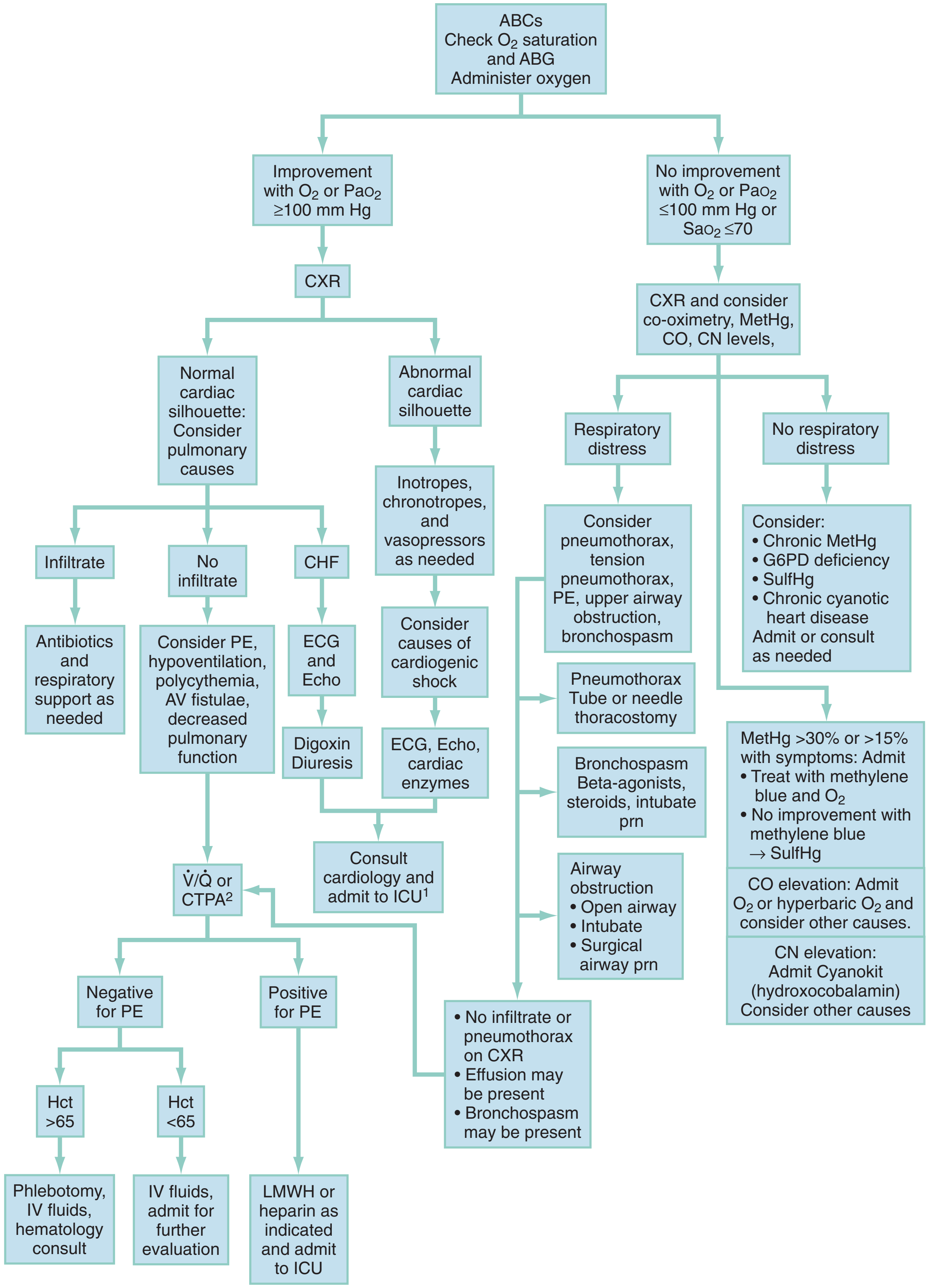


Figure 14-4. An algorithmic approach to central cyanosis. *ABCs,* airway, breathing, circulation; *ABG,* arterial blood gas; *AV,* arteriovenous; *CHF,* congestive heart failure; *CN,* cyanide; *CO,* carbon monoxide; *CTPA,* computed tomography pulmonary angiography; *CXR,* chest radiograph; *ECG,* electrocardiogram; *Echo,* echocardiogram; *G6PD,* glucose-6-phosphate dehydrogenase; *Hct,* hematocrit; *ICU,* intensive care unit; *IV,* intravenous; *LMWH,* low-molecular-weight heparin; *MetHgb,* methemoglobin; *O_2,* molecular oxygen; *Pa_{O_2}*, partial pressure of arterial oxygen; *PE,* pulmonary embolus; *prn,* as needed; *RA,* room air; *Sa_{O_2}*, arterial oxygen saturation; *SulfHg,* sulfhemoglobin; V̇/Q̇, ventilation-perfusion scan.
[1]Patients with chronic cyanotic heart disease may not require ICU care or even hospital admission. Disposition should be discussed with patient's cardiologist.
[2]V̇/Q̇ may be performed when CTPA is unavailable or contraindicated.

www.ketabpezeshki.com 66485457-66963820

medications that are sulfonamide derivatives, or gastrointestinal sources (bacterial overgrowth).[20] Strong consideration should be given to sulfhemoglobin toxicity in patients with cyanotic findings and methemoglobin on CO-oximetry but who do not improve with methylene blue treatment.

Polycythemia is defined as an elevated RBC mass from one of three causes. Polycythemia vera is a disorder of bone marrow stem cells with increased RBC mass, cyanosis, and splenomegaly. Patients may demonstrate hyperviscosity syndrome. Secondary polycythemia occurs with either an appropriate or inappropriate increase of erythropoietin, a physiologic response to chronic hypoxemia (<92% oxygen saturation), cyanotic congenital heart disease, cigarette smoking, or high altitude exposures. Relative polycythemia is an increased RBC mass, often resulting from dehydration or reduced plasma volume.

Finally, vascular disease, such as Raynaud's phenomenon, may cause a cyanotic appearance. Raynaud's phenomenon occurs in 15% of the population and has a female predominance. Patients have an abnormal response to excessive cold or emotional stress and report vasoconstriction, profound cold sensitivity, and recurrent events of sharply demarcated pallor or cyanosis of the digits. Most commonly the cutaneous arterial capillary beds of the fingers and toes are affected,[21] but tongue, ear, and other distal areas may also be affected.

EMPIRICAL MANAGEMENT

Administration of high-flow oxygen is the first therapy for patients with cyanosis. Any clinical improvement, or lack thereof, should be noted. Thereafter, consideration of abnormal hemoglobin and toxin-induced cyanosis is crucial because the administration of appropriate antidotes and systemic therapies may decrease morbidity.

Intravenous fluid resuscitation should be initiated in patients with hypovolemia. Treatment of congestive heart failure, arrhythmias, or poor cardiac output should occur as clinical conditions indicate. Cardiology consultation is recommended in patients thought to have congenital or ischemic heart disease. Although several specific treatments are discussed here, the cause of the cyanosis may be elusive, and hospitalization is required in all but chronic stable cases.

Specific Strategies

Methemoglobinemia and Sulfhemoglobinemia

If cutaneous exposure to an inciting agent (i.e., aniline dyes) occurred, complete decontamination with soap and water is recommended. The staff should use appropriate protective equipment. Urgent treatment with oxygen and methylene blue (1-2 mg/kg intravenously [IV] over 5 minutes) is indicated for patients with symptomatic hypoxia (dysrhythmias, angina, respiratory distress, seizures, or coma) or methemoglobin levels greater than 30%. Sulfhemoglobinemia is suggested when the laboratory reports an elevated methemoglobin level and the patient does not respond to methylene blue. Treatment of sulfhemoglobinemia is supportive in addition to removing the causative agent.

Other Causes of Cyanosis

Acute therapy for patients with symptomatic hyperviscosity syndrome and secondary polycythemia includes phlebotomy and volume expansion with isotonic crystalloid. The goal of therapy is a normal hematocrit (45%).[22] Long-term therapy is focused on the underlying cause, and patients require referral to a hematologist.

Patients with SVC syndrome require further evaluation for mediastinal mass or vascular abnormality. Conservative management with oxygen and elevation of the head of the bed often provide significant symptomatic relief. Vascular stenting may be necessary, and radiation or chemotherapy may be indicated in cases caused by malignancy.[19]

Raynaud's phenomenon is treated by warming the affected digits and extremities. Systemic vasodilating agents (e.g., calcium channel blockers [nifedipine] or nitrates, endothelin antagonists, statins, phosphodiesterase inhibitors, and botulinum toxin) may be useful in the acute setting.[21] If there is no improvement of peripheral cyanosis with warming and administration of 100% oxygen, arterial insufficiency or occlusion may be present. In cases of critical limb ischemia, intravenous heparin should be considered in consultation with a vascular surgeon. Embolic sources, such as endocarditis and abdominal aortic aneurysms, should be considered. Vascular bypass, intra-arterial thrombolysis, or stenting may be indicated.

Carbon monoxide and cyanide poisoning do not typically cause cyanosis and are covered elsewhere.

PATIENT DISPOSITION

Admission

All patients with a first episode of cyanosis or an uncertain cause require hospital admission. Cardiology consultation and referral are recommended for children with a first episode of congestive heart failure and newly diagnosed or suggested congenital heart disease. Surgical consultation and intervention are indicated for acute arterial occlusion from embolic or thrombotic sources. Multiple consultations may be appropriate in patients with SVC syndrome, including a vascular surgeon, interventional radiologist, oncologist, and radiation oncologist.

Discharge

Patients with peripheral cyanosis from vasospasm, those with asymptomatic methemoglobinemia less than 15%, and stable patients with primary pulmonary disease may be treated as outpatients after several hours of monitoring in the ED. Follow-up should occur within 24 hours unless the patient has a previous diagnosis of chronic cyanosis. Instructions should clearly state that if the cyanosis worsens, or if dyspnea, altered mentation, or chest pain occurs after discharge, the patient should return immediately to the ED.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Da Silva SS, Sajan IS, Underwood JP 3rd: Congenital methemoglobinemia: A rare cause of cyanosis in the newborn—a case report. *Pediatrics* 2003; 112:e158.
2. Martin L, Khalil H: How much reduced hemoglobin is necessary to generate central cyanosis? *Chest* 1990; 97:182-185.
3. Comroe JH, Botelho S: The unreliability of cyanosis in the recognition of arterial anoxemia. *Am J Med Sci* 1947; 214:1-6.
4. El-Husseini A, Azarov N: Is threshold for treatment of methemoglobinemia the same for all? A case report and literature review. *Am J Emerg Med* 2010; 28:748e5-748e10.
5. Lin CY, et al: Anesthetic management of a patient with congenital methemoglobinemia. *Acta Anaesthesiol Taiwan* 2009; 47: 143-146.
6. Bradberry SM: Occupational methemoglobinemia: Mechanisms of production, features, diagnosis and management including the use of methylene blue. *Toxicol Rev* 2003; 22:13.
7. Chan B, et al: Methemoglobinemia after ingestion of Chinese herbal medicine in a 9-day-old infant. *Clin Toxicol* 2007; 45:281.
8. Zillich AJ, Kuhn RJ, Petersen TJ: Skin discoloration with blue food coloring. *Ann Pharmacother* 2000; 34:868-870.
9. Rao PS: Diagnosis and management of cyanotic congenital heart disease: Part I. *Indian J Pediatr* 2009; 76:57-70.
10. Rao PS: Diagnosis and management of cyanotic congenital heart disease: Part II. *Indian J Pediatr* 2009; 76:297-308.
11. Brousseau T, Sharieff GQ: Newborn emergencies: The first 30 days of life. *Pediatric Clin North Am* 2006; 53:69-84.
12. Goel N, Kumar V, Seth A, Ghosh B: Proliferative retinopathy in a child with congenital cyanotic heart disease. *J AAPOS* 2010; 14:455-456.
13. Shelonitda SR, Shah AA, Hoover DR, Saidi P: Cyanotic congenital heart disease (CCHD) with symptomatic erythrocytosis. *J Gen Intern Med* 2007; 22:1775-1777.
14. Fesmire FM, et al: Critical issues in the evaluation and management of adult patients presenting to the emergency department with suspected pulmonary embolism. *Ann Emerg Med* 2011; 57:628-652.
15. Zijlstra WG, Buursma A, Meeuwsen-van der Roest WP: Absorption spectra of human fetal and adult oxyhemoglobin, de-oxyhemoglobin, carboxyhemoglobin, and methemoglobin. *Clin Chem* 1991; 37:1633-1638.
16. Haymond S, Cariappa R, Eby CS, Scott MG: Laboratory assessment of oxygenation in methemoglobinemia. *Clin Chem* 2005; 51:434-444.
17. Feiner JR, Bickler PE: Improved accuracy of methemoglobin detection by pulse co-oximetry during hypoxia. *Anesth Analg* 2010; 111:1160-1167.
18. Feiner JR, Bickler PE, Mannheimer PD: Accuracy of methemoglobin detection by pulse co-oximetry during hypoxia. *Anesth Analg* 2010; 111:143-148.
19. Kogon BE, et al: Cyanosis produced by superior vena caval stenosis. *Ann Thorac Surg* 2008; 85:1083-1085.
20. Harangi M, et al: Identification of sulfhemoglobinemia after surgical polypectomy. *Clin Toxicol (Phila)* 2007; 45:189-192.
21. Levien TL: Advances in the treatment of Raynaud's phenomenon. *Vasc Health Risk Manag* 6:167-177, 2010.
22. Ruggeri M, Finotto S, Fortuna S, Rodeghiero F: Treatment outcome in a cohort of young patients with polycythemia vera. *Intern Emerg Med* 2010; 5:411-413.

www.ketabpezeshki.com 66485457-66963820

Chapter 15

Syncope

Robert A. De Lorenzo

PERSPECTIVE

Syncope is the sudden transient loss of consciousness with a loss of postural tone. It is a common presenting complaint in the emergency department (ED). Despite improved understanding of risk and outcomes, consensus on the diagnostic approach and disposition remains elusive. This is in part because of the varied causes of syncope and lack of definitive diagnostic studies, and in part because of confusion and lack of standard terminology to describe the disorder.[1] Diagnostic accuracy relies largely on the synthesis of patient risk factors and reported symptoms, with limited reliance on the physical examination and ancillary testing.

Epidemiology

The prevalence of syncope in the general population is approximately 19%.[2] Patients come to the ED at a rate of 2.8 visits per 1000 population, which accounts for 0.8% of ED visits.[2,3] Approximately 32% of these patients are admitted, and syncope accounts for 1 to 6% of all hospitalized patients.[2,4] Persons aged 65 years and older account for 80% of such admissions. In the pediatric population, 15% experience at least one episode of syncope.

Risk factors for syncope include cerebrovascular disease, cardiac medications, and hypertension.[5] Most causes of syncope are benign and have favorable outcomes. Patients with preexisting cardiovascular disease and syncope from any cause are at the greatest short- and long-term risk of mortality.[4,6] Age, congestive heart failure, and coronary artery disease are key predictors of mortality in patients with syncope, but syncope alone does not appear to alter risk.[7] In contrast, there is no increased risk of cardiovascular morbidity or mortality associated with neurocardiogenic (vasovagal), orthostatic, and medication-related syncope.[6] Recurrence of syncope may be as high as 50% and is not correlated with age or sex.[2]

Benign causes of syncope predominate in adolescents and young adults. Approximately 30% of athletes who have died during exercise, however, had a prior episode of syncope as a sentinel event.[8] Prospective outcome studies in children are lacking, but most reports suggest that mortality rates are extremely low. Significant trauma may result from syncope and can contribute to increased risk of morbidity and mortality, particularly in the elderly.[9] The overall U.S. medical cost of syncope is estimated at $2.4 billion annually.[10]

Pathophysiology

The final common pathway resulting in syncope is dysfunction of either both cerebral hemispheres or the brainstem (reticular activating system), usually from acute hypoperfusion. Reduced blood flow may be regional (cerebral vasoconstriction) or systemic (hypotension).[11] Loss of consciousness results in loss of postural tone, with the resulting syncopal episode. Less severe derangements may result in sensations of presyncope or light-headedness. In this fashion, presyncope and syncope may be considered on a continuum with shared etiologies and mechanisms. By definition, syncope is transient; therefore the cause of central nervous system (CNS) dysfunction should likewise be transient.[6,12] Persistent causes of significant CNS dysfunction result in coma or depressed consciousness (see Chapter 16).

Hypoperfusion resulting in approximately 35% or more reduction in cerebral blood flow usually produces unconsciousness, and any mechanism that adversely affects the components of perfusion (cardiac output, systemic vascular resistance, blood volume, regional vascular resistance) can cause or contribute to syncope. Other mechanisms of CNS dysfunction resulting in syncope include hypoglycemia, toxins, metabolic abnormalities, failure of autoregulation, and primary neurologic derangements.

DIAGNOSTIC APPROACH

Differential Considerations

The potential causes of syncope are numerous and can be categorized according to their primary mechanism (Box 15-1). The first differential diagnostic consideration is to distinguish syncope from other causes of an apparent sudden loss of consciousness, especially seizure and uncommon disorders such as cataplexy. When syncope is established as the working diagnosis, the life-threatening causes, primarily cardiovascular in origin, are considered first. The principal serious causes of syncope are dysrhythmias and myocardial ischemia.[12] Cerebrovascular disease, principally subarachnoid hemorrhage, is less frequently encountered, but equally serious. Toxic-metabolic abnormalities may induce syncope through alterations in blood pressure or cardiac rhythm. Structural cardiac lesions, such as critical aortic stenosis, and sudden interruption of right ventricular outflow by pulmonary embolism can also cause sudden loss of consciousness.[12]

Disclaimer: The opinions or assertions are those of the author and do not necessarily reflect the position of the Army Medical Department or the Department of Defense.

www.ketabpezeshki.com 66485457-66963820

Box 15-1 Causes of Syncope

Focal Hypoperfusion of CNS Structures
- Cerebrovascular disease
- Hyperventilation
- Subclavian steal
- Subarachnoid hemorrhage
- Basilar artery migraine
- Cerebral syncope

Systemic Hypoperfusion Resulting in CNS Dysfunction
- Outflow obstruction
  - Mitral, aortic, or pulmonic stenosis
  - Hypertrophic cardiomyopathy
  - Atrial myxoma
  - Pulmonary embolism
  - Pulmonary hypertension
  - Cardiac tamponade
  - Congenital heart disease
- Reduced cardiac output
  - Tachycardia
    - Supraventricular tachycardia
    - Ventricular tachycardia
    - Ventricular fibrillation
    - Wolff-Parkinson-White syndrome
    - Torsades de pointes
  - Bradycardia
    - Sinus node disease
    - Second-degree and third-degree AV block
    - Prolonged QT syndrome
    - Brugada's syndrome
    - Pacemaker malfunction
    - Implanted cardioverter-defibrillator malfunction
  - Other cardiovascular disease
    - Aortic dissection
    - Myocardial infarction
    - Cardiomyopathy
- Vasomotor—neurally mediated (reflex vasodepressor)
  - Neurocardiogenic (vasovagal)
  - Emotion
  - Pain
  - Situational
- Carotid sinus sensitivity
  - Necktie syncope
  - Shaving syncope
- Miscellaneous reflex
  - Tussive, sneeze
  - Exercise, postexercise
  - Gastrointestinal—swallowing, vomiting, defecation
  - Postmicturition
  - Elevated intrathoracic pressure (weightlifting)
- Other causes of hypoperfusion
  - Orthostatic hypotension—volume depletion
  - Anemia
  - Drug-induced

CNS Dysfunction with Normal Cerebral Perfusion
- Hypoglycemia
- Hypoxemia—asphyxiation
- Seizure
- Narcolepsy
- Psychogenic
  - Anxiety disorder
  - Conversion disorder
  - Somatization disorder
  - Panic disorder
  - Breath-holding spells
- Toxic
  - Drugs
  - Carbon monoxide
  - Other agents
  - Undetermined causes

AV, atrioventricular; *CNS,* central nervous system.

Dissection of the thoracic aorta rarely manifests primarily as syncope but is potentially catastrophic.

Pivotal Findings

The majority of cases of syncope arise from benign causes, so the evaluation is largely focused on excluding serious pathology. The patient's history, particularly the setting of the syncope (e.g., postmicturition, venipuncture), patient position (e.g., sitting, standing), prior episodes, and the presence or absence of prodromal symptoms, is central to separating benign from serious causes of the syncopal episode. Young, healthy patients with clearly benign syncope disclosed by a thorough history require little more than a physical examination for anemia or other benign precipitating factors.[13-15] The yield of an electrocardiogram (ECG) is generally low; however, it is broadly recommended and has the additional advantages of being noninvasive and relatively inexpensive.[13-16] The clinical examination (history and physical examination) alone can suggest the diagnosis in 45% of cases.[17] For a large portion of the remainder, however, a clear diagnosis for the syncope may not be established in the ED.[17]

Symptoms

Symptoms can often suggest the diagnosis, although the relative weight of the history diminishes in older patients and in those not able to remember clearly the events leading up to the loss of consciousness.[18] The patient is asked to describe the *character* of the syncopal event.[12] Witnesses may be able to supplement and corroborate the patient's incomplete recall, and that history should be solicited. Key characteristics include the rate of onset (gradual or abrupt), position on symptom onset (e.g., standing, sitting, or supine), and duration and rate of recovery. Abrupt onset, occurrence while sitting or supine, and duration of more than a few seconds are usually ascribed to serious, often cardiac, causes of syncope, but firm data are lacking. Similarly, incomplete or near-syncope may be less serious, but at least one study suggests that onset associated with a prodrome or presyncope may herald cardiac origin, and thus the prognostic value of this aspect of the history is unsettled.[18] The diagnostic approach to presyncope, however, is the same as for syncope.

Additional history regarding the events *preceding* the syncope is helpful.[12] Occurrence during significant exertion suggests outflow obstruction, whereas occurrence after exercise or a prolonged exposure to heat stress suggests orthostasis. The myriad mechanisms that may mediate a neurocardiogenic response, including significant emotional events, micturition, eating, bowel movements, emesis, and movement or manipulation of the neck causing stimulation of the carotid sinus, should be addressed. Occurrence in supine position or the presence of acute palpitations is relatively specific for syncope of cardiac origin.[18] Seizures may be preceded by an aura and followed by a typical postictal state.

Events *during* the syncopal episode do not usually clarify the cause.[12] Tonic-clonic movements, related to inadequate cerebral perfusion, can occur in any form of syncope, including benign neurocardiogenic syncope, and should be differentiated from the

www.ketabpezeshki.com 66485457-66963820

Box 15-2 Medications That May Induce Syncope

Cardiovascular agents
Beta-blockers
Vasodilators (beta-blockers, calcium channel blockers, nitrates, hydralazine, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, phenothiazines, phosphodiesterase inhibitors)
Diuretics
Central antihypertensives (clonidine, methyldopa)
Other antihypertensives (guanethidine)
QT-prolonging agents (amiodarone, disopyramide, flecainide, procainamide, quinidine, sotalol)
Other antidysrhythmics
Psychoactive agents
Anticonvulsants (carbamazepine, phenytoin)
Antiparkinsonian agents
Central nervous system depressants (barbiturates, benzodiazepines)
Monoamine oxidase inhibitors
Antidepressants
Narcotic analgesics
Sedating and nonsedating antihistamines
Cholinesterase inhibitors (donepezil, tacrine, galantamine)
Drugs with other mechanisms
Drugs of abuse (cannabis, cocaine, alcohol, heroin)
Digitalis
Insulin and oral hypoglycemics
Neuropathic agents (vincristine)
Nonsteroidal anti-inflammatory drugs
Bromocriptine

prolonged activity with subsequent postictal depression of consciousness seen in seizure disorders (see Chapter 102). Trauma from a fall or other mechanism may distract the examiner from evaluating for the underlying syncope that caused the injury.[9]

The postsyncopal events should be queried. Symptoms consistent with a postictal state are characteristic of seizures. Initial vital signs and cardiac monitoring by out-of-hospital medical providers may provide clues to primary cardiac dysrhythmias.

Associated symptoms can offer potentially important clues. Chest pain or dyspnea can suggest myocardial ischemia, aortic dissection, or pulmonary embolism. Diaphoresis and lightheadedness are nonspecific, but if prominent and accompanied by a graying of vision may suggest orthostasis or vasovagal causes. Tongue biting and incontinence of urine or stool suggest seizures.

The *past medical history* is critical in stratifying risk.[4,7,18] Congestive heart failure is a key determinant of increased short- and long-term mortality in the setting of syncope.[4,7,10,14-16] Prior coronary artery or cerebrovascular disease, diabetes, hypertension, and other significant chronic disease also appear to increase the risk of mortality after syncope.[5,10]

Certain *medications* are well established to be associated with syncope (Box 15-2). QT interval–prolonging agents, beta-blockers, insulin, and oral hypoglycemics, in particular, deserve attention because of the likelihood of repeated syncope without careful medication monitoring.[5]

Signs

The physical examination focuses primarily on the elements affecting the cardiovascular and neurologic systems.[18] Specific findings are detailed in Table 15-1. Signs of orthostasis should be sought in all cases in which this mechanism is suggested.[19] Carotid massage is both safe and occasionally revealing; it is indicated in cases in which the history is suggestive of carotid sinus hypersensitivity.[10,14,15] Rectal examination for gross blood or melena is recommended if anemia or gastrointestinal hemorrhage is suspected.

Table 15-1 Directed Physical Examination in Syncope

SYSTEM	PIVOTAL FINDING	SIGNIFICANCE
Vital signs	Pulse rate and rhythm	Tachycardia, bradycardia, other dysrhythmias
	Respiratory rate and depth	Tachypnea suggests hypoxia, hyperventilation, or pulmonary embolus
	Blood pressure	Shock may cause decreased cerebral perfusion; hypovolemia or medication use may lead to orthostasis
	Temperature	Fever from sepsis may cause volume depletion and orthostasis
Skin	Color, diaphoresis	Signs of decreased organ perfusion
HEENT	Tenderness and deformity	Signs of trauma
	Papilledema	Increased intracranial pressure, head injury
	Breath	Ketones from ketoacidosis
Neck	Bruits	Identify presence of cerebrovascular disease
	Jugular venous distention	Right-sided heart failure from myocardial ischemia, tamponade, pulmonary embolism
Lungs	Breath sounds, crackles, wheezes	Infection, left-sided heart failure from myocardial ischemia, rarely pulmonary embolism
Heart	Systolic murmur	Aortic stenosis, hypertrophic cardiomyopathy
	Rub	Pericarditis, tamponade
Abdomen	Pulsatile mass	Abdominal aortic aneurysm
Rectum	Stool for gross blood or melena	Anemia, gastrointestinal bleed
Pelvis	Uterine bleeding, adnexal tenderness	Anemia, ectopic pregnancy, hypovolemia
Extremities	Pulse equality in upper extremities	Subclavian steal, thoracic aortic dissection
Neurologic	Mental status, focal neurologic findings	Seizure, stroke, or other primary neurologic disease

HEENT, head, eyes, ears, nose, and throat.

Ancillary Studies

The chief diagnostic adjunct in evaluating syncope is the 12-lead ECG (Table 15-2). It is warranted in all cases of syncope except in young, otherwise healthy patients with a clear history and setting for benign neurocardiogenic (vasovagal) syncope.[10,14,15] Dysrhythmias and shortened PR or prolonged QT intervals may be identified on the 12-lead ECG. A right bundle branch block in association with ST elevation in leads V_1 through V_3 suggests Brugada's syndrome.[20] Unanticipated cardiac hypertrophy may be revealed. Continuous limb-lead ECG monitoring in the ED may also identify transient dysrhythmias. An ECG showing right ventricular strain pattern may suggest pulmonary embolism, whereas diffuse ST elevation or electrical alternans helps diagnose pericarditis associated with pericardial tamponade.

www.ketabpezeshki.com 66485457-66963820

Table 15-2 Ancillary Studies in Syncope

STUDY	INDICATION
12-Lead ECG/limb-lead ECG monitoring	Cardiac dysrhythmia, ischemia, cardiomyopathy
Orthostatic vital signs	Orthostatic hypotension or bradycardia
Hemogram	Anemia
Electrolytes, serum	Metabolic abnormality, especially hyponatremia, hyperkalemia, or hypokalemia
Glucose, serum or blood	Hypoglycemia
D-dimer, serum	Pulmonary embolism
Cardiac enzymes, serum	Myocardial infarction
β-hCG	Pregnancy
Toxicologic screen	Drug-related syncope
Arterial blood gas	Acid-base disturbance
Chest x-ray examination	Thoracic aortic dissection
Cranial CT or MRI	New-onset or focal seizure, trauma, intracranial hemorrhage
Echocardiogram	Cardiac outflow obstruction, tamponade, thoracic dissection
Ventilation-perfusion scan	Pulmonary embolism
CT pulmonary angiogram	Pulmonary embolism, thoracic aortic dissection
Abdominal ultrasound or CT	Abdominal aortic aneurysm
Pelvic ultrasound	Ectopic pregnancy
Tests Usually Performed as Part of an Inpatient or Outpatient Evaluation	
Holter or loop ECG	Dysrhythmia
Echocardiogram	Cardiomyopathy, valvular disease
Exercise and ^{99m}Tc sestamibi ECG	Myocardial ischemia
Electrophysiologic study	Dysrhythmia
Carotid ultrasound	Stroke, TIA
Head-up tilt-table test	Orthostatic hypotension
Electroencephalogram	Seizures

CT, computed tomography; *ECG,* electrocardiogram; *hCG,* human chorionic gonadotropin; *MRI,* magnetic resonance imaging; *^{99m}Tc,* technetium 99m; *TIA,* transient ischemic attack.

Routine hematologic and urine studies have limited usefulness in the evaluation of syncope and are generally not indicated.[21] When suggested by the history and physical examination findings, however, selective use of the hemogram, serum electrolytes and glucose, urine drug screen, and pregnancy test may identify or exclude some uncommon causes of syncope (see Table 15-2). Chest radiography and serum B-type natriuretic peptide (BNP) testing are warranted if heart failure is suspected or known by history. Other than seizure or intracranial hemorrhage, primary neurologic events rarely are the cause of syncope. Cranial computed tomography is indicated only when intracerebral hemorrhage is suspected on the basis of sudden syncope with accompanying headache, particularly of sudden onset, or in the presence of abnormalities on neurologic examination.[22]

In otherwise healthy patients in whom a benign dysrhythmia, such as episodic supraventricular tachycardia or atrial fibrillation, is suspected, Holter or event ECG monitoring may be helpful. In patients with significant underlying cardiac disease or when a significant dysrhythmia is a possible cause of the syncope, echocardiography, continuous monitoring, or cardiovascular stress testing may be helpful in the inpatient or ED observation unit setting. Depending on the results of initial evaluation, electrophysiologic studies or magnetic resonance imaging may be indicated. Electroencephalography is useful only when a seizure episode is suspected. Tilt table testing, although infrequently used in the United States, may have diagnostic value in elderly patients and children in whom chronic orthostatic hypotension is possible.[15] Orthostatic vital signs, although unreliable in evaluation of volume status, may be helpful when positional changes are accompanied by typical presyncopal symptoms and a significant rise in heart rate or fall in blood pressure.[19,21] A schematic of selected diagnostic testing strategies for syncope is depicted in Figure 15-1.

Table 15-3 Critical Diagnoses to Consider in Syncope

Myocardial infarction
Life-threatening dysrhythmias
Thoracic aortic dissection
Critical aortic stenosis
Hypertrophic cardiomyopathy
Pericardial tamponade
Abdominal aortic aneurysm
Pulmonary embolism
Subarachnoid hemorrhage
Stroke
Toxic-metabolic derangements
Severe hypovolemia or hemorrhage

DIAGNOSTIC ALGORITHM

The critical diagnoses to consider are listed in Table 15-3.

The emergent causes of syncope are protean and are included in Box 15-1. Many other causes such as neurocardiogenic and reflex-mediated syncope have benign mechanisms.

After stabilization and assessment, the clinical features coupled with onset and recovery can suggest the cause (Table 15-4). A logical approach to the history, physical examination, and diagnostic testing is depicted in Figure 15-2. The emphasis is on risk stratification because short-term mortality risk in syncope is related to structural cardiac disease, heart failure, and dysrhythmias.[23]

EMPIRICAL MANAGEMENT

Syncope is by definition a transient event, so most patients are asymptomatic on presentation. Patients with significantly abnormal vital signs, recurrent syncope, or associated symptoms of a concerning nature such as chest pain, hypotension, abdominal or back pain, or shortness of breath should undergo rapid evaluation.

Patients with critical diagnoses are stabilized in the ED and admitted to the intensive care unit (ICU) or other appropriate inpatient unit. Those with emergent diagnoses are typically admitted to telemetry units. Patients with nonemergent diagnoses can be treated as outpatients.

Several scoring systems have been proposed as aids in the admission decision-making process, most notably the San Francisco Syncope Rule.[24] In essence, this guideline suggests that in the absence of abnormal ECG findings, shortness of breath, hypotension (systolic blood pressure <90 mm Hg), anemia (hematocrit <30%), or a history of heart failure, the patient is at sufficiently low risk for outpatient disposition to be considered. The safety and efficacy of the San Francisco Syncope Rule as well as other

www.ketabpezeshki.com 66485457-66963820

Table 15-4 Clinical Features of Common and Serious Causes of Syncope

CAUSE	ONSET AND RECOVERY	FEATURES
Dysrhythmia	Classically abrupt onset and rapid recovery	Classic presentation uncommon; past cardiac history, risk factors for CAD more common in elderly; implanted pacemaker or cardioverter-defibrillator
Cardiac outflow obstruction	Exertion causes abrupt symptoms; rapid recovery with rest	Murmurs not always audible; mechanical valves warrant close monitoring
Myocardial infarction	Exertion or at rest; recovery often incomplete with chest pain persisting	Past cardiac history, risk factors for CAD; chest pain and shortness of breath common but frequently absent in diabetics and the elderly
Pulmonary embolism	Abrupt onset; recovery often incomplete with dyspnea persisting	Chest pain, dyspnea, hypercoagulable state, DVT, pregnancy
Thoracic aortic dissection	Spontaneous; recovery often incomplete with chest or upper back pain persisting	Tearing chest pain; associated with hypertension, Marfan syndrome, cystic medial necrosis
Abdominal aortic aneurysm	Spontaneous onset; recovery often incomplete with abdominal pain persisting	Abdominal or low back pain; associated with peripheral vascular disease
Pericardial tamponade	Penetrating chest trauma or thoracic cancers	Beck's triad of hypotension, JVD, muffled heart sounds
Anomalous left coronary artery	Onset with exercise, Valsalva maneuver	Left coronary artery arises from pulmonary artery; usually detected in childhood
Subarachnoid hemorrhage	Rapid onset; sentinel event may resolve	Focal neurologic findings; "thunderclap" worst headache; nuchal rigidity
Vertebrobasilar insufficiency	Posture change or neck movement	Vertigo, nausea, dysphagia, dysarthria, blurry vision common associated symptoms
Hypovolemia	Bleeding, emesis, heat stress, dehydration; gradual onset	Orthostatic hypotension
Anemia	Bleeding, often occult or gradual from menses or gastrointestinal sources; iron deficiency or decreased red blood cell production	Orthostatic hypotension commonly associated
Hypoglycemia	Gradual onset; incomplete spontaneous recovery common	Diabetes, ingestion or injection of hypoglycemics or insulin; diaphoresis, anxiety, jitteriness
Hypoxemia	Usually gradual onset; spontaneous recovery if asphyxiating circumstance is reversed	Carbon monoxide, natural gas, sewer gas, bleach-ammonia mix
Subdural hematoma	Onset with or after trauma (which may be trivial in high-risk patients)	Elderly, alcoholics, patients on anticoagulants at greater risk
Air embolus	Diving	Hyperbaric oxygen a key treatment
Pulmonary hypertension	Associated with myocardial infarction or pulmonary embolus	Risk factors for myocardial infarction or pulmonary embolism
Drug syncope	Medication associated with syncope	Consider illicit and alternative drug use; elderly at risk for polypharmacy and drug interactions
Ruptured ectopic pregnancy	Patient often unaware of pregnancy	Abdominal pain, abnormal tenderness; positive β-hCG test
Seizure	Abrupt or with aura; postictal state common	Past history common
Carotid sinus sensitivity	Carotid sinus sensitivity; rapid onset and recovery	Shaving, necktie, sudden neck movement; carotid massage may provoke symptoms
Reflex syncope	Gastrointestinal, genitourinary, or thoracic stimulation	Urination, defecation, cough, eating, swallowing, weightlifting
Neurocardiogenic (vasovagal)	Emotion, pain are common triggers; upright posture; gradual onset; rapid recovery once supine	Prodrome of light-headedness, graying or blurring of vision, nausea, sweats common
Hyperventilation	Emotion, pain; gradual onset; patient often unaware of rapid respirations	Perioral tingling, carpopedal spasms, extremity numbness
Narcolepsy	Often spontaneous	Known history
Basilar artery migraine	Specific triggers often known to patient	Visual prodrome often absent; more common in young women; vertigo and nausea common
Trigeminal or glossopharyngeal neuralgia	Sudden onset; specific triggers often known to patient	Lancinating pain in characteristic location
Subclavian steal	Moving affected arm	Thoracic outlet syndrome
Psychogenic	Variable	Anxiety or psychiatric history; diagnosis by examining symptom pattern and excluding organic cause
Breath-holding	Deliberate breath-holding	Usually toddlers or young children
Drop attack	Unpredictable	Not true syncope—no loss of consciousness; usually elderly; loss of tone, ataxia, vertigo

CAD, coronary artery disease; *DVT,* deep vein thrombosis; *hCG,* human chorionic gonadotropin; *JVD,* jugular venous distention; *TIA,* transient ischemic attack.

www.ketabpezeshki.com 66485457-66963820

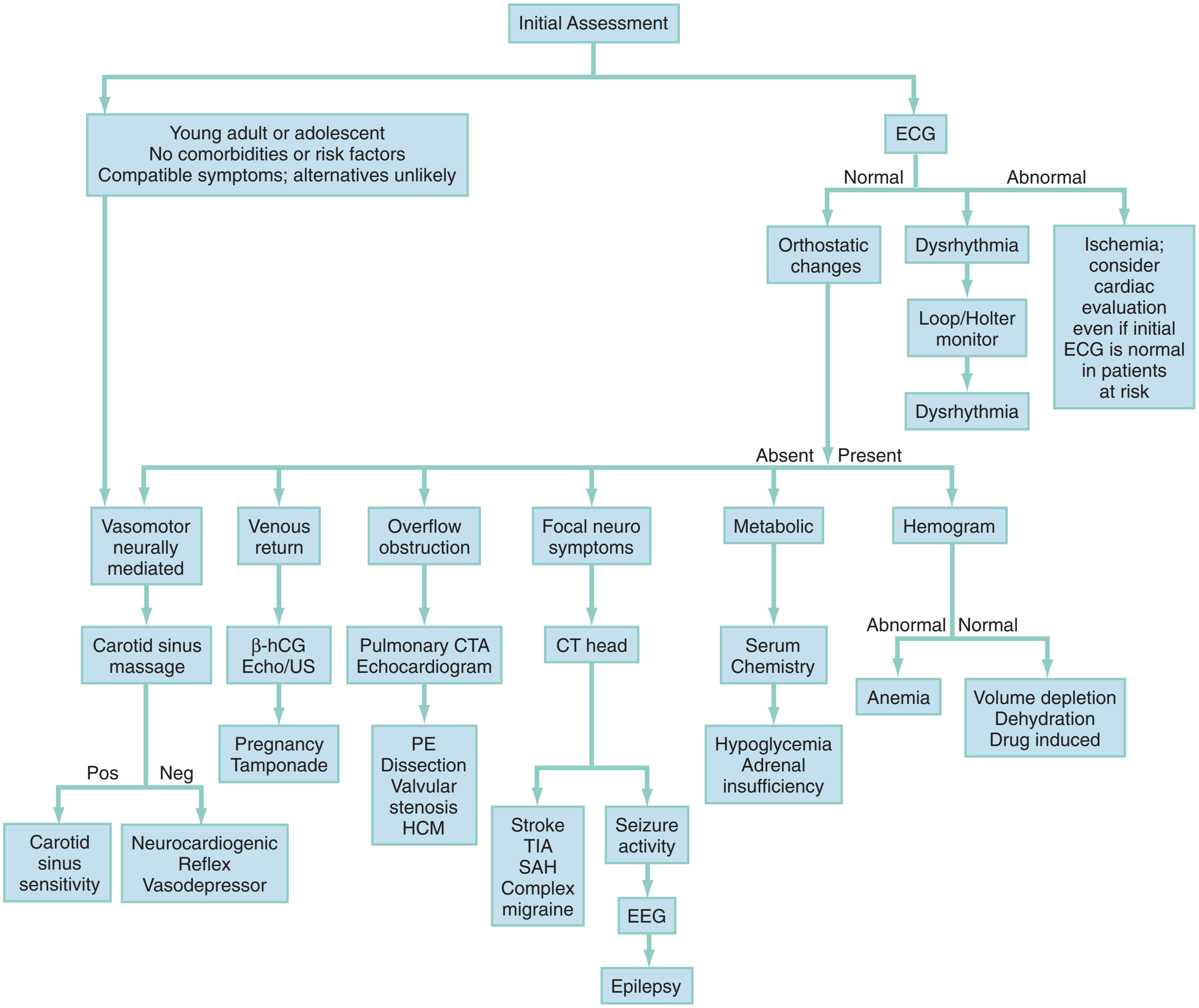


Figure 15-1. Management algorithm for patients with syncope.

www.ketabpezeshki.com 66485457-66963820

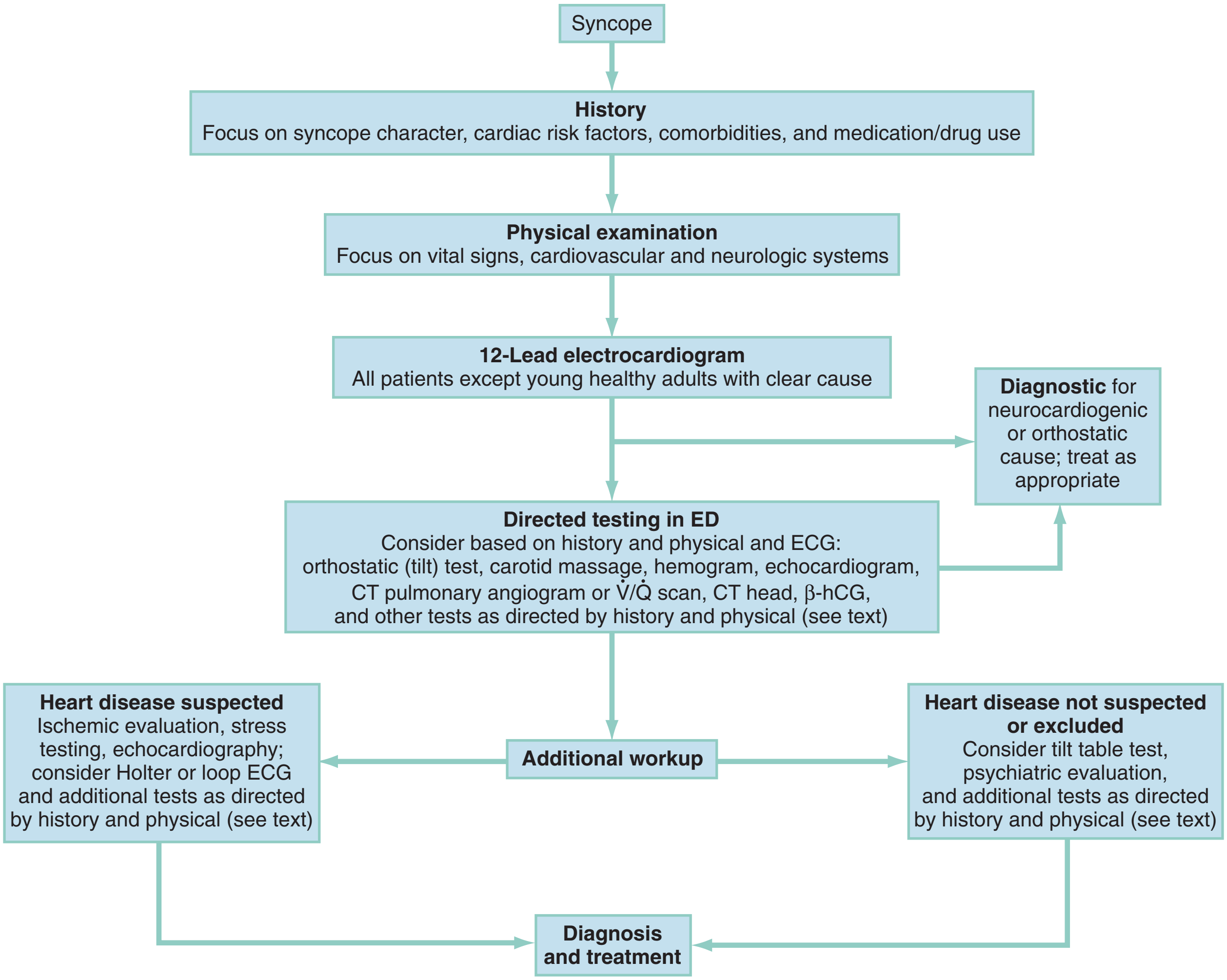


Figure 15-2. Diagnosis algorithm for syncope.

proposed rules, however, have not been established, and routine application cannot yet be recommeded.[4,7,25-29]

Hospitalization is required for patients with chest pain, unexplained shortness of breath, a history of significant congestive heart failure, or valvular disease.[12,16,29] Patients with ECG evidence of ventricular dysrhythmias, ischemia, significantly prolonged QT interval, or new bundle branch block are also admitted.[12,15,16,30] The clinician should consider monitoring patients with any of the following indications: age older than 45 years, preexisting cardiovascular or congenital heart disease, family history of sudden death, serious comorbidities such as diabetes, or exertional syncope.[15,16,21,31]

The ED evaluation of syncope is often inconclusive. After a history, physical examination, and 12-lead ECG, up to 50% of patients do not have a firm diagnosis.[17,31] Patients younger than 45 years and without worrisome symptoms, signs, or ECG findings are generally at very low risk for adverse outcome and may often be treated as outpatients. Discharged patients should be warned of the hazards of recurrent syncope occurring during activities such as driving or working at heights.[15]

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Thijs RD, et al: Unconscious confusion—a literature search for definitions of syncope and related disorders. *Clin Auton Res* 2005; 15:35.
2. Chen LY, Shen WK, Mahoney DW, Jacobsen SJ, Rodeheffer RJ: Prevalence of syncope in population aged more than 45 years. *Am J Med* 2006; 119:1088.
3. Sun BC, Emond JA, Camargo CA Jr: Characteristics and admission patterns of patients presenting with syncope to U.S. emergency departments. *Acad Emerg Med* 2004; 11:1029.
4. Colivicchi F, et al: Development and prospective validation of a risk stratification system for patients with syncope in the emergency department: The OESIL risk score. *Eur Heart J* 2004; 24:811.
5. Chen L, et al: Risk factors for syncope in a community-based sample (the Framingham Heart Study). *Am J Cardiol* 1999; 85:1189.
6. Soteriades ES, et al: Incidence and prognosis of syncope. *N Engl J Med* 2002; 347:878.
7. Kessler C, Tristano J, De Lorenzo RA: The emergency department approach to syncope: Evidence-based guidelines and prediction rules. *Emerg Med Clin North Am* 2010; 28:487.
8. Maron BJ, Epstein SE, Roberts WC: Causes of sudden death in competitive athletes. *J Am Coll Cardiol* 1986; 7:204.
9. Rubenstein LZ, Josephson KR: The epidemiology of falls and syncope. *Clin Geriatr Med* 2002; 18:141.
10. Smars PA, Decker WW, Shen WK: Syncope evaluation in the emergency department. *Curr Opinion Cardiol* 2007; 22:44.
11. Folino FA: Cerebral autoregulation and syncope. *Prog Cardiovasc Dis* 2007; 50:49.
12. Kapoor WN: Syncope. *N Engl J Med* 2000; 343:1856.
13. Sun BC, et al: Low diagnostic yield of electrocardiogram testing in younger patients with syncope. *Ann Emerg Med* 2008; 51:240.
14. Strickberger SA, et al: American Heart Association, Quality of Care and Outcomes Research Interdisciplinary Working Group, American College of Cardiology Foundation, Heart Rhythm Society: AHA/ACCF scientific statement on the evaluation of syncope. *Circulation* 2006; 13:316.
15. Brignole M, et al: Guidelines on management (diagnosis and treatment) of syncope—update 2004. *Europace* 2005; 6:467.
16. Huff JS, et al: Clinical policy: Critical issues in the evaluation and management of adult patients presenting to the emergency department with syncope. *Ann Emerg Med* 2007; 49:431.
17. Linzer M, et al: Diagnosing syncope. Part 1: Value of history, physical examination, and electrocardiography. Clinical Efficacy Assessment Project of the American College of Physicians. *Ann Intern Med* 1997; 126:989.
18. Alboni P, et al: Diagnostic value of history in patients with syncope with or without heart disease. *J Am Coll Cardiol* 2001; 37:1921.
19. Sarasin FP, et al: Prevalence of orthostatic hypotension among patients presenting with syncope in the ED. *Am J Emerg Med* 2002; 20:497.
20. Dovgalyuk J, Holstege C, Mattu A, Brady WJ: The electrocardiogram in the patient with syncope. *Am J Emerg Med* 2007; 25:688.
21. Meyer MD, Handler J: Evaluation of the patient with syncope: An evidence based approach. *Emerg Med Clin North Am* 1999; 17:189.
22. Goyal N, et al: The utility of head computed tomography in the emergency department evaluation of syncope. *Intern Emerg Med* 2006; 2:148.
23. Reed MJ, Gray A: Collapse query cause: The management of adult syncope in the emergency department. *Emerg Med J* 2006; 23:589.
24. Quinn JV, et al: Derivation of the San Francisco Syncope Rule to predict patients with short-term serious outcomes. *Ann Emerg Med* 2004; 43:224.
25. Quinn J, McDermott D, Stiell I, Kohn M, Wells G: Prospective validation of the San Francisco Syncope Rule to predict patients. *Ann Emerg Med* 2006; 47:448.
26. Sun BC, et al: External validation of the San Francisco Syncope Rule. *Ann Emerg Med* 2007; 49:420.
27. Serrano LA, et al: Accuracy and quality of clinical decision rules for syncope in the emergency department: A systematic review and meta-analysis. *Ann Emerg Med* 2010; 56:362.
28. Birnbaum A, Esses D, Bijur P, Wollowitz A, Gallagher EJ: Failure to validate the San Francisco Syncope Rule in an independent emergency department population. *Ann Emerg Med* 2008; 52:151.
29. Reed, MJ, et al: The Risk stratification Of Syncope in the Emergency department (ROSE) pilot study: A comparison of existing syncope guidelines. *Emerg Med J* 2007; 24:270.
30. Sarasin FP, et al: A risk score to predict arrhythmias in patients with unexplained syncope. *Acad Emerg Med* 2003; 10:1312.
31. Costantino G, et al: Short- and long-term prognosis of syncope, risk factors, and role of hospital admission: Results from the STePS (Short-Term Prognosis of Syncope) study. *J Am Coll Cardiol* 2008; 51:276.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 16

Depressed Consciousness and Coma

Benjamin S. Bassin and Jeremy L. Cooke

PERSPECTIVE

Epidemiology

Depressed mental status represents an alteration in arousal and is a common presenting complaint in the emergency department (ED). This presentation can be the manifestation of a wide spectrum of diseases, with the degree of impairment ranging along a continuum from sleepiness to decreased alertness to frank coma. The differential diagnosis of stupor and coma is broad and diverse (Table 16-1) but can usually be categorized into metabolic and systemic, structural, or psychogenic causes. The majority of cases are caused by metabolic or systemic derangements, whereas the remainder are usually caused by structural lesions. Psychogenic presentations are much less common. The differential diagnosis for depressed level of consciousness often overlaps with that for confusion (see Chapter 17). Frequently, diagnosis and management occur simultaneously, and a structured systematic approach is used. A thorough grasp of the underlying pathophysiology leading to the acute depressed mental state will lead to timely diagnosis and treatment.

Pathophysiology

Consciousness is defined as the awareness of one's self or surroundings; it includes the properties of *arousal* and *cognition.* Alterations in arousal frequently are described as *levels* of consciousness, although they actually refer to dynamic points on a continuum ranging from fully alert to stuporous to comatose or complete unconsciousness. Conversely, *cognition* frequently refers to *states* of consciousness or awareness and is defined as the combination of *orientation,* the accurate perception of what is experienced; *judgment,* the ability to process input data to generate more meaningful information; and *memory,* the ability to store and retrieve information. There are many examples of medical states that alter cognition, including confusion, inattention, delusions, and dementia. However, these states do not depress the level of arousal and therefore are discussed in other chapters in this book.

The *ascending reticular activating system* (ARAS) is the neuroanatomic structure primarily responsible for arousal and cortical activation. It is located in the paramedian tegmental zone in the dorsal part of the brainstem (Fig. 16-1). The input of somatic and sensory stimuli to the cerebral cortex is controlled by the ARAS and functions to initiate arousal from sleep. The brain's cognition centers are located primarily in the cerebral cortex and serve to determine the content of consciousness.

Insults to the cerebral cortex or brainstem can each independently cause depressed consciousness or coma. These structures are vulnerable to metabolic derangements, toxins, or mechanical injury. Typically, both cerebral hemispheres need to be affected to induce coma, and this also depends on the size and speed of progression of the insult. Localized, unilateral lesions in the cerebral cortex usually do not induce depressed consciousness or coma even if other cognitive functions are impaired. In contrast, a completely intact brainstem is necessary for arousal. Small focal lesions in the brainstem can affect the ARAS. If the ARAS is impaired, the cerebral cortex cannot be aroused, and depressed consciousness or coma occurs.

DIAGNOSTIC APPROACH

Differential Considerations

Potential causes of depressed consciousness can be divided into a few general categories. Metabolic or systemic causes of coma can include hypoxia, hypoperfusion, infection, toxic drug effects, or electrolyte disturbances. Hypoxia can be the result of congestive heart failure (CHF), pulmonary embolism, carbon monoxide poisoning, or severe pulmonary compromise such as occurs in chronic obstructive pulmonary disease (COPD), cystic fibrosis, and asthma. The various causes of shock can result in global hypoperfusion states leading to depression of consciousness. These include anaphylactic, septic, hypovolemic, cardiogenic, and neurogenic origins of shock. Each type of shock has its own unique characteristics, which are detailed in other chapters. Infection, both systemic (sepsis) and focal, can be another general cause of depressed consciousness. This is particularly true if central nervous system (CNS) structures are involved, as in meningitis, encephalitis, or CNS abscess. Toxic drug effects ranging from recreational drug use and intentional overdoses to therapeutic doses with adverse side effects are common general causes of depressed consciousness seen in the ED. In the elderly, adverse side effects from prescription medications are common. In addition, electrolyte and glucose abnormalities can be caused by multiple conditions, including diabetes, renal dysfunction, malignancy, and medication interactions or dosage errors.

Head trauma, stroke, tumor, and infection are the most common structural causes of coma and depressed consciousness. Traumatic causes can include subdural and epidural hematomas, intraparenchymal or subarachnoid hemorrhage, or simply contusion or concussion. Strokes occur with embolic, thrombotic, or hemorrhagic mechanisms, but it is extremely unusual for ischemic (i.e., nonhemorrhagic) stroke to depress consciousness unless a massive insult to both hemispheres has occurred (e.g., diffuse severe cerebral edema after a massive infarct) or a high-grade basilar artery stenosis or occlusion is present.[1] Depression of consciousness with CNS infections may be caused by mass effect and is common with

www.ketabpezeshki.com 66485457-66963820

Table 16-1 Differential Diagnosis

ORGAN SYSTEM	CRITICAL DIAGNOSES	EMERGENT DIAGNOSES	NONEMERGENT DIAGNOSES
Neurologic or CNS	Hemorrhage • Subarachnoid • Pontine • Cerebellar • Intracerebral Ischemic stroke Status epilepticus Acute hydrocephalus	Subdural hematoma Epidural hematoma Acute hydrocephalus Primary brain tumor Metastatic disease Venous sinus thrombosis CNS vasculitis Pseudotumor cerebri Seizures (limited)	Concussion or contusion
Infectious	Bacterial meningitis Encephalitis Septic shock	Brain abscess Viral meningitis Sepsis from other sources	
Metabolic	Hypoglycemia	Hyperglycemia (DKA, HONK) Thiamine deficiency (Wernicke-Korsakoff syndrome) Hyponatremia or hypernatremia Hypocalcemia or hypercalcemia Hyperammonemia Myxedema coma Thyrotoxicosis Uremia Porphyria	Hypophosphatemia Hypomagnesemia or hypermagnesemia Hypoparathyroidism or hyperparathyroidism
Toxic	Carbon monoxide Cyanide Heroin or opiates Beta-blockers Calcium channel blockers Cardiac glycosides (digoxin) Tricyclic antidepressant	Alcohol Benzodiazepines Cocaine, amphetamines γ-Hydroxybutyrate (GHB) Isoniazid Organophosphates Acetaminophen Anticonvulsants Aspirin Lithium PCP SSRIs	Marijuana LSD Mushrooms NSAIDs
Environmental	High-altitude cerebral edema Heat stroke Hypothermia Malignant hyperthermia Neuroleptic malignant syndrome	Dysbarism	
Pulmonary, hypoxia	Anaphylaxis Pulmonary embolus	Asthma, COPD	
Cardiovascular	Acute MI Aortic dissection Cardiogenic shock Cardiac tamponade Hypovolemic shock Hypertensive crisis Malignant arrhythmia	Congestive heart failure Anemia	

CNS, central nervous system; *COPD,* chronic obstructive pulmonary disease; *DKA,* diabetic ketoacidosis; *HONK,* hyperosmolar nonketotic coma; *LSD,* lysergic acid diethylamide; *MI,* myocardial infarction; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *PCP,* phencyclidine; *SSRIs,* selective serotonin reuptake inhibitors.

severe bacterial meningitis, cerebral abscess or empyema, or parasitic mass. Malignancies, whether primary or metastatic, can cause depressed consciousness if the tumor mass elevates intracranial pressure (ICP) or reduces cerebral blood flow, or if surrounding edema develops rapidly.

Special consideration should be given to specific populations of patients. The elderly, in particular, are susceptible to alterations in therapeutic medication dosage and drug-drug interactions. Even seemingly minor infections, such as urinary tract infections, upper respiratory infections, or viral gastroenteritis, may cause altered mental status (see Chapter 13), depressed consciousness, or coma. In addition, immunocompromised patients with acquired immunodeficiency syndrome (AIDS) or those undergoing chemotherapy treatments for transplants, and patients with malignancy or immunologic disease are vulnerable to a multitude of opportunistic infections not commonly seen in the general patient population.

The clinical evaluation and stabilization of patients with depressed consciousness occur simultaneously with the diagnosis in the ED. The differential diagnosis of depression of consciousness is extensive but can be greatly simplified by focusing attention on the distinguishing characteristics of the available patient history and physical examination (Box 16-1).[2] Approaching the patient's presentation systematically, beginning with a broad differential diagnosis, usually allows development of a short list of likely diagnoses early in the encounter.

www.ketabpezeshki.com 66485457-66963820

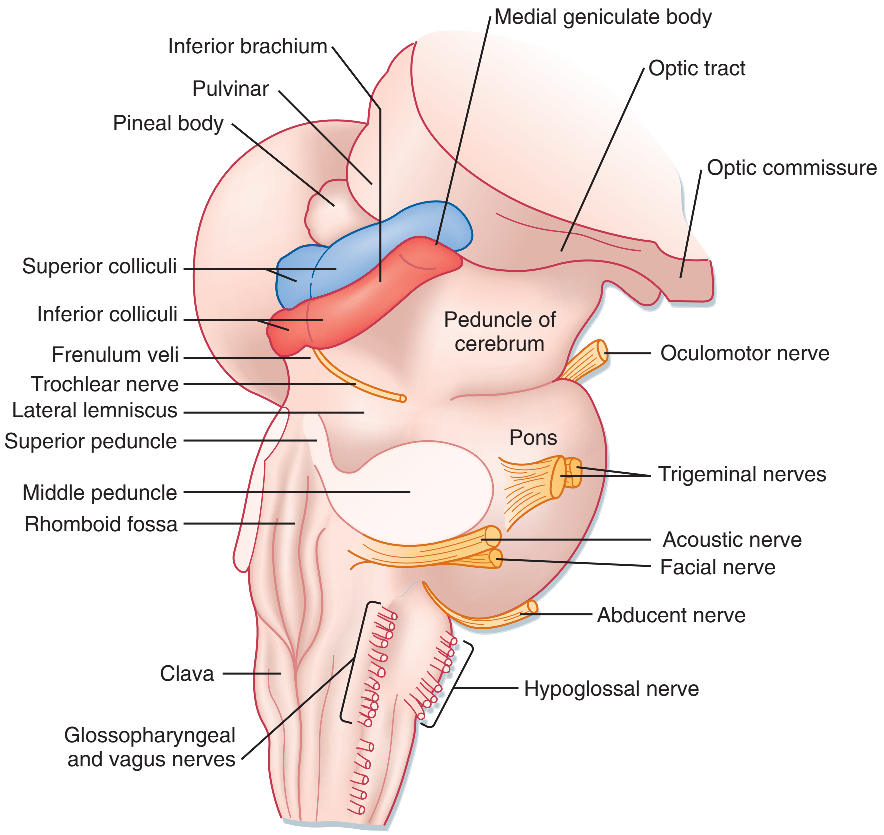


Figure 16-1. Brainstem anatomy. (Adapted from Adams J: Emergency Medicine. Philadelphia: Elsevier; 2008.)

Box 16-1 Structural Etiology of Altered Mental Status and Coma

Trauma
Subdural hematoma
Epidural hematoma
Cerebral concussion or contusion

Stroke Syndromes
Embolism
- Cardiac (atrial fibrillation, endocarditis)
- Paradoxical (fat embolus)

Thrombosis
- Cerebral venous sinus thrombosis

Hemorrhage
- Subarachnoid hemorrhage (SAH)
- Pontine hemorrhage
- Cerebellar hemorrhage
- Intracerebral hemorrhage

Tumor
Brainstem tumors
Metastatic disease
Angiomas
Pituitary apoplexy
Acute hydrocephalus

Infection
Subdural empyema or abscess

Pivotal Findings

History

Chief complaints relating to depressed consciousness vary widely. Family members may report the patient as being more difficult to arouse from sleep or less interactive. Often, family members or friends have alerted emergency medical services after the patient is "found down" or unarousable even with vigorous stimulation.

Often, information from alternate sources guides the diagnostic workup. Common sources of information include family members, neighbors, prehospital personnel, law enforcement, and nursing home staff.[3] They may know of preceding symptoms such as headache, nausea, vomiting, or fever. Key historical information includes the rate of symptom onset, a history of trauma, exposure to drugs or toxins, or new medications or change in dosage. Rate of symptom onset is important, as an abrupt onset of decreased alertness may suggest structural phenomena or vascular insult, whereas a gradual onset would be more indicative of the slow, indolent course frequently seen with toxic, metabolic, or infectious causes. Family members usually have some knowledge regarding the patient's past medical history, which may include diabetes, liver or renal disease, vascular disease such as hypertension, coronary disease, stroke or transient ischemic attacks, malignancy, seizures, immunocompromised states such as human immunodeficiency virus (HIV) infection, sickle cell disease, organ transplantation, or psychiatric illness. Family members may also be able to relay additional diagnostic clues such as rate of onset or waxing-waning characteristics of the patient's symptoms.

In addition, previous medical records should be reviewed whenever possible to augment or confirm the information provided. Items with the patient such as a card in the wallet containing lists of medical conditions and/or medications or a medical alert bracelet or necklace can provide valuable information. If the patient's historical baseline mental status cannot be established, the current presentation is assumed to be an acute change.[4]

Causes of depression of consciousness vary with patient age (Box 16-2). The elderly are particularly vulnerable to infectious causes, medication changes, and alterations in their living environments. Young adults and adolescents are more likely to be affected after recreational drug use or trauma. Accidental toxic ingestions are often seen in younger children. In infants, infectious

www.ketabpezeshki.com 66485457-66963820

Box 16-2 Common Age-Related Etiology of Altered Mental Status

Infant
Infection
Trauma, abuse
Metabolic

Child
Toxic ingestion

Adolescent or Young Adult
Toxic ingestion
Recreational drug use
Trauma

Elderly
Medication changes
Over-the-counter medications
Infection
Alterations in living environment
Stroke

Box 16-3 Glasgow Coma Scale

		Score
Eye opening	Spontaneous	4
	To voice	3
	To pain	2
	None	1
Verbal response		
Adult	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible words	2
	None	1
Pediatric	Appropriate	5
	Cries, consolable	4
	Persistently irritable	3
	Restless, agitated	2
	None	1
Motor response	Obeys commands	6
	Localizes pain	5
	Withdraws to pain	4
	Flexion to pain	3
	Extension to pain	2
	None	1

causes of depressed consciousness are most common; however, trauma secondary to physical abuse and metabolic derangements from inborn errors of metabolism can be seen.[5]

Physical Examination

The severity of presenting symptoms dictates the speed needed for stabilization and diagnosis. After necessary stabilization measures have been instituted (e.g., intubation of the frankly comatose patient), a systematic physical examination is conducted. Level of consciousness is determined by the patient's ability to speak in full, coherent sentences and to respond appropriately to the examiner. A rapid, directed neurologic screening examination can determine whether the patient has a significant focal motor deficit. The presence of a distinctive odor on the breath, although uncommon, can cue the examiner to the presence of alcohol, ketones (diabetic or alcoholic ketoacidosis), or bitter almonds (cyanide toxicity). Undressing the patient completely permits evaluation for signs of trauma or skin lesions suggesting overwhelming infection or needle track marks.

Significant hypotension with depressed consciousness suggests shock with resultant cerebral hypoperfusion, and both causes and therapy should be addressed immediately. Hypertension can be seen as a result of subarachnoid hemorrhage or cerebral or brainstem infarction or may be secondary to any condition resulting in increased ICP. Late-stage, severe elevation in ICP can cause bradycardia and hypertension, also known as the Cushing reflex. This is an ominous sign and is seen most commonly in lesions affecting the posterior fossa and in children. Bradycardia is also seen in medication overdoses such as with beta-blockers, calcium channel blockers, cardiac glycosides, and clonidine. Myocardial conduction blocks may also cause severe bradycardia, hypotension, and subsequent stupor or coma. Tachycardia has a broad differential in the altered patient and can be the result of hypovolemia, fever, severe anemia, thyrotoxicosis, and drugs such as anticholinergics and stimulants. Both hypothermia and hyperthermia can result in altered mental status whether from infectious, structural, toxic or metabolic, or environmental causes. Hyperventilation, Kussmaul's or Cheyne-Stokes breathing, agonal breathing, apnea, or other alterations in respiratory patterns can suggest primary CNS abnormalities or toxic or metabolic derangements. Changes in respiratory patterns can be challenging for the clinician in an unresponsive patient, as they can represent the sequelae of a primary CNS insult or compensation for an underlying toxic or metabolic process.

Immediately after an assessment of the patient's vital signs, a head-to-toe physical examination is performed.[6] A methodical and complete head and neck examination is conducted, with particular emphasis on examination of the pupillary reflexes and eye movements (see later discussion) and any indications of head trauma, including hemotympanum, periorbital ecchymosis, Battle's sign, scalp hematoma, or CSF otorrhea or rhinorrhea. The hydration of the mucous membranes may give clues to specific toxidromes. Laceration or bruising of the tongue may indicate a recent seizure.

Examination of the neck should focus on evidence of meningismus, which can be seen in meningitis, subarachnoid hemorrhage, and some cases of herniation. The cervical spine should be immobilized if there are signs of neck trauma, such as cervical spine tenderness or evidence of blunt external trauma, or if the history indicates a potential mechanism for neck injury. Stridor indicates respiratory distress typically from infection, allergic reaction, or foreign body aspiration. Presence of a goiter may indicate underlying thyroid pathology.

Cardiopulmonary examination should focus on respiratory effort, ventilatory patterns, presence of arrhythmia or murmurs, cardiac output, and the presence of injury. Potentially helpful abdominal findings include hepatosplenomegaly, pulsatile masses, ecchymosis, or sequelae of liver failure such as ascites, caput medusa, or spider angiomata. Gross blood, purulent drainage, or retained foreign bodies should be sought on genitourinary and rectal examination. In the absence or presence of signs of trauma, lesions on the skin such as rashes, signs of drug use (needle tracks or medication patches), or embolic phenomena can be differential clues.

A systematic neurologic examination, with particular attention paid to the eyes, is the most useful tool in differentiating a structural from a systemic or metabolic cause of depressed consciousness or coma. A head-to-toe approach is a proven strategy. This should include evaluation of the patient's Glasgow Coma Scale (GCS) score (Box 16-3), level of alertness, cranial nerves, strength, reflexes, and cerebellar functions with emphasis on gait, pronator drift, finger-to-nose, heel-to-shin, rapid alternating movements, and Romberg testing. The GCS measures the best motor and verbal responses and the degree of stimulus required to elicit eye

www.ketabpezeshki.com 66485457-66963820

opening and is measured serially, as level of consciousness frequently is dynamic after the initial insult and subsequent response to therapy. The GCS does not differentiate among causes of altered mental status or coma or assess cognition but is useful in monitoring changes in mental status when serial examinations are performed and serves as an objective reference for communicating with consultants.[7] A change of two or more points in serial GCS testing represents a significant change.

Discovery of a focal neurologic deficit is suggestive of a structural cause. Particular attention should be paid to a focused eye examination, during which a helpful amount of information can be obtained. Unilateral dilatation of a pupil ("blown pupil") and loss of reactivity in a comatose patient are ominous signs of uncal herniation and necessitate immediate neurosurgical consultation and intervention. Papilledema, which may indicate increased ICP or retinal hemorrhages associated with trauma, can be identified on funduscopic examination. The eye examination should also include testing of eye movements, which are coordinated by the medial longitudinal fasciculus located in the brainstem and ocular centers located in the cerebral cortex. Cranial nerves III, IV, and VI are responsible for control of the extraocular muscles. Cranial nerve III paralysis results in a persistently abducted eye, whereas a persistently adducted eye is caused by paralysis of cranial nerve VI. In the setting of trauma, a unilateral third cranial nerve palsy suggests an ipsilateral compressive lesion such as seen with epidural hematoma. Cranial nerve VI palsies are often nonlocalizing, as the nerve has a long intracranial course and compressive forces from intracranial mass effects (e.g., tumor, traumatic hematoma, increased ICP) may compromise cranial nerve function anywhere in its course. Horizontal disconjugate gaze is an important finding and is commonly seen in patients who are sedated, drowsy, or intoxicated. Disconjugate gaze found in the vertical plane is usually more serious and suggests cerebellar or pontine dysfunction. Normal ocular motility suggests that a significant portion of the brainstem remains intact.

Oculocephalic (doll's eyes) and oculovestibular reflex testing are useful in looking at the functional integrity of the brainstem. These tests, if results are negative, make structural lesions in the brainstem very unlikely as the source of the patient's altered mental status.

If there are no contraindications, such as suspected cervical spine injury, oculocephalic testing is accomplished by observing the patient's eye movements while the head is turned from side to side. Patients who exhibit a maintained forward gaze despite head turning (doll's eye reflex) are unlikely to have a brainstem-mediated cause of coma. If the eyes remain in a fixed position within the orbits, turning in unison with the head, brainstem dysfunction is suggested. Oculovestibular or "cold water caloric" testing is a more sensitive test for brainstem involvement and cannot voluntarily be resisted (Fig. 16-2). After elevation of the patient's head to 30 degrees (this can be done in patients whose cervical spine is not cleared by placing the bed in the reverse Trendelenburg position), 10 to 30 mL of ice water is used to irrigate the external auditory canal. Tympanic membrane perforation and cerumen impaction should be ruled out before this test is performed. In patients who have an intact brainstem, the response is a slow conjugate deviation of gaze toward the side of the cold water stimulus for 30 to 120 seconds. The reflex is short-lived and followed by corrective fast beats of nystagmus toward the midline. This corrective nystagmus is described by the mnemonic COWS, which stands for "cold-opposite, warm-same." If there is no response to the irrigation, brainstem dysfunction is possible.

Recently, literature on the phenomenon of basilar artery stenosis or occlusion manifesting as depressed consciousness or coma has increasingly been published. A review of the Lausanne Stroke Registry showed that 100% of patients with poor outcome from high-grade basilar stenosis or occlusion had either stupor or

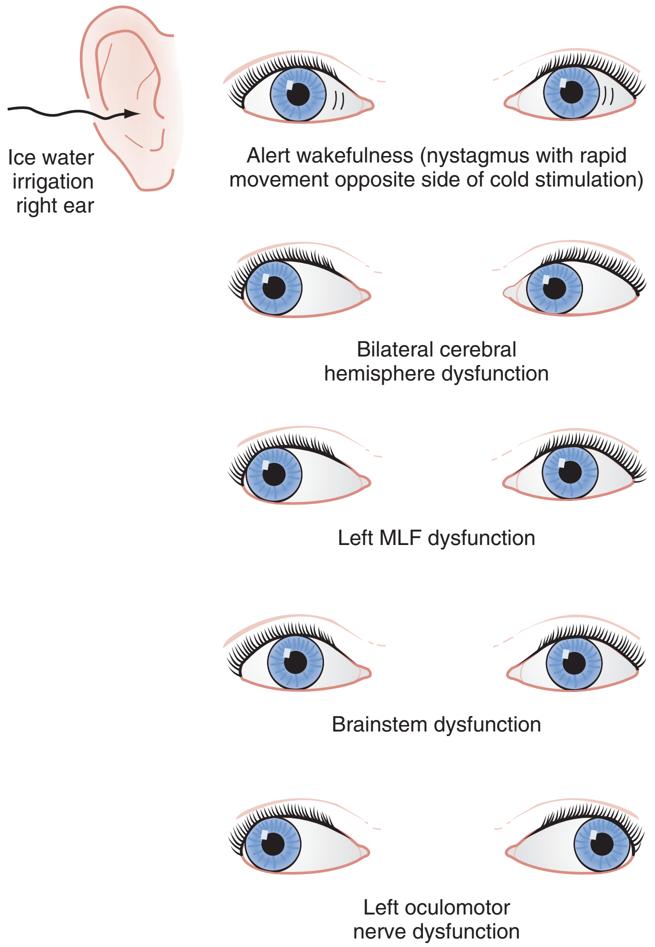


Figure 16-2. Oculocephalogyric (caloric) responses to various central nervous system pathologic conditions. *MLF,* medial longitudinal fasciculus.

coma or the triad of pupillary abnormalities, dysarthria, and bulbar findings on presentation.[1]

Ancillary Testing (Refer to Table 16-2)

Laboratory Studies

Bedside glucose testing definitively confirms or excludes hypoglycemia and can frequently limit further extensive metabolic testing in diabetic or intoxicated patients. Serum electrolytes and renal function measurement identify the presence of a metabolic acidosis, anion gap, uremia, or derangements in sodium or potassium. Changes in serum calcium can be a marker for metastatic disease, and severe hypercalcemia can cause altered mental status. Arterial blood gas analysis rapidly assesses acid-base status and the presence of hypercarbia or hypoxia and allows calculation of arterial-alveolar gradient in conditions in which shunting is suspected. Carbon monoxide (CO)–oximetry can be added to confirm methemoglobinemia or carbon monoxide exposure.

A urine dip test is a quick way to screen for the presence of ketones, the spilling of glucose as seen in hyperosmolar states, or infection, which can frequently precipitate changes in mentation, especially in the elderly. Urinalysis itself provides valuable information regarding hydration status (specific gravity) and the possible presence of calcium oxalate crystals in the setting of ethylene glycol ingestion. Urine drug testing may confirm a suspected ingestion or be helpful if another cause is not readily apparent.

www.ketabpezeshki.com 66485457-66963820

Table 16-2 Ancillary Testing in the Altered Patient

TEST	FINDING	POTENTIAL DIAGNOSIS
Laboratory		
ABGs	Hypoxemia	Pulmonary embolus, intracranial event, central hypoventilation, CHF
	Hypercarbia	
	Metabolic vs. respiratory acidosis	Obstructive or restrictive pulmonary condition, high altitude cerebral edema, intracerebral process
		Multiple—DKA, toxic ingestion, sepsis, respiratory failure
	A-a Gradient	Pulmonary embolus
Electrolytes	Carboxyhemoglobin—elevated	Carbon monoxide exposure (consider cyanide in inhalational exposure)
	Sodium—increased	Dehydration, diuretic overuse, diabetes insipidus, osmotic diuresis
	Sodium—decreased	Adrenal insufficiency, CHF, cirrhosis, DKA, infant formula dilution, myxedema coma, renal failure, SIADH
BUN, creatinine, glucose	Bicarbonate—decreased	Metabolic acidosis—multiple causes (anion vs. non–anion gap)
Complete blood count	Calcium—elevated	Malignancy, hyperparathyroidism, thyrotoxicosis
	BUN, creatinine-elevated	Acute renal failure, uremia
	Glucose-elevated	DKA, hyperosmolar hyperglycemic state (HHS)
	Decreased	Alcohol abuse, cirrhosis, insulin overdose, sepsis
	WBCs—elevated	Nonspecific—infection, inflammation, steroids, stress
	WBCs—decreased	Immunocompromised—malignancy, drug, alcohol, or viral marrow suppression
	Hgb and Hct—elevated	Polycythemia
	Hgb and Hct—decreased	Severe anemia
	Platelets—elevated	Hereditary thrombocytosis, acute phase reactant
	Platelets—decreased	Sepsis, DIC, intracranial hemorrhage
Coagulation	PT and INR—elevated	Bleeding dyscrasias, liver disease, warfarin use
ammonia	Elevated	Hepatic encephalopathy, valproic acid toxicity, inborn errors of metabolism
Thyroid studies	Elevated	Thyrotoxicosis
	Decreased	Myxedema coma
	WBCs—elevated	Meningitis
Cerebrospinal fluid	RBCs—elevated	Subarachnoid hemorrhage
	Specific gravity—elevated	Dehydration
Urinalysis	WBCs, leukocyte esterase, nitrites	Urinary tract Infection
	RBCs—elevated	Retroperitoneal hemorrhage
	Glucosuria	DKA, HHS
	Calcium oxalate crystals	Ethylene glycol ingestion
		Ingestion
Urine drug screen	Multiple possibilities	
Imaging		
Head CT—non-contrast	Blood	Intracerebral hemorrhage, epidural hematoma, subdural hematoma, subarachnoid hemorrhage, hemorrhagic stroke
Head CT—contrast	Enlarged ventricles	Obstructive hydrocephalus, shunt malfunction
CT angiography or venography	Mass or edema	Ischemic stroke, tumor, or metastatic disease
MRI	Mass or edema	Tumor, metastatic disease
Chest radiograph	Ring-enhancing lesion	Abscess
Ultrasound	Vascular clot	Basilar or vertebral artery occlusion or stenosis, venous sinus thrombosis
Other Studies	Vascular dilation	Aneurysm, arteriovenous malformation,
ECG	Hypoperfusion	Ischemic stroke, basilar or vertebral artery occlusion or stenosis, venous sinus thrombosis
EEG	Mass	Tumor, metastatic disease, abscess (superior to CT for posterior fossa lesions)
	Meningeal enhancement	Meningitis, encephalitis, neurosarcoidosis, carcinomatosis, post–lumbar puncture
	Consolidation or mass	Pneumonia, tumor, foreign body
	Pulmonary edema	CHF, cardiogenic shock
	Radiolucency, mediastinal shift	Pneumothorax
	Widened mediastinum	Aortic dissection
	Hampton's hump, Westermark's sign	Pulmonary embolus
	Intra-abdominal blood	Ruptured abdominal aortic aneurysm; spleen, kidney, or liver laceration (trauma)
	ST segment changes, Q waves	Ischemia or infarction
	T wave inversions	Ischemia, intracerebral hemorrhage
	Abnormal intervals	Conduction blocks, drug ingestion, electrolyte abnormality
	Osborne wave (J wave)	Hypothermia
	Right-sided heart strain	Pulmonary embolus
	Multiple findings	Status epilepticus (convulsive or nonconvulsive)

ABGs, arterial blood gases; *BUN,* blood urea nitrogen; *CHF,* congestive heart failure; *CT,* computed tomography; *DIC,* disseminated intravascular coagulation; *DKA,* diabetic ketoacidosis; *ECG,* electrocardiogram; *EEG,* electroencephalogram; *Hct,* hematocrit; *Hgb,* hemoglobin; *INR,* international normalized ratio; *MRI,* magnetic resonance imaging; *PT,* prothrombin time; *RBCs,* red blood cells; *SIADH,* syndrome of inappropriate antidiuretic hormone secretion; *WBCs,* white blood cells.

www.ketabpezeshki.com 66485457-66963820

A complete blood count can be useful. Although an elevated white blood cell count can be a marker for infection, it is nonspecific and rarely helpful in discerning a toxic or metabolic cause. An abnormally low white blood cell count, however, suggests an immunocompromised state and should urgently direct clinical investigation toward an infectious cause. Profound anemia may be seen from witnessed or occult blood loss. Thrombocytopenia can be a marker for sepsis, intracranial hemorrhage, or disseminated intravascular coagulation.

Elevated results from serum coagulation studies can be a marker for bleeding dyscrasias, liver disease, or supratherapeutic levels of anticoagulation drugs. Both platelets and coagulation studies should be checked before invasive procedures are performed at noncompressible sites such as lumbar punctures and central venous access, if the patient's condition allows.

Serum ammonia levels are controversial and have not been shown to be a reliable marker for the cause of depressed consciousness. Although usually associated with severe liver disease, ammonia levels can be elevated in other conditions such as valproic acid toxicity and inborn errors of metabolism and can be normal in patients with hepatic encephalopathy.[8] Thyroid function studies can help confirm myxedema coma or thyrotoxicosis. When CNS pathology such as infection or hemorrhage is suggested but not seen on neuroimaging studies, cerebrospinal fluid analysis is undertaken.

Imaging Studies

Noncontrast computed tomography (CT) of the brain is the initial imaging modality of choice in the setting of depressed consciousness and coma. In the majority of ED settings, it is available and quickly obtained, and this makes CT more suitable than other imaging tests for the patient with borderline hemodynamic instability. Brain CT is sufficiently sensitive to detect most intracranial hemorrhages that are large enough to cause coma. In addition, the presence of hydrocephalus can quickly be assessed. Despite its utility, linear artifacts created by the thick skull base can limit the view of the posterior fossa on CT. In this case, magnetic resonance imaging (MRI) of the brain is generally much better for identifying structural lesions in this region. However, this modality is less practical in most ED settings because of its cost, limited availability, and duration of acquiring each study, which consequently limits the ability to monitor or access the unstable patient.[4]

Contrast-enhanced CT may be used if a tumor, metastatic disease, or intracerebral infection is suspected. CT or magnetic resonance angiography or venography may be available in larger tertiary care centers for use in the diagnosis and/or treatment of intracerebral aneurysms, arteriovenous malformations, cerebral venous sinus thrombosis, or basilar or vertebral artery stenosis or occlusion.

Plain radiography may identify severe pneumonia or acute respiratory distress syndrome. In ingestions, it may rarely reveal specific types of heavy metals such as mercury, iron, or lead in the pediatric population or packages of ingested illicit substances in body packers or stuffers.

Additional Testing

Electrocardiograms (ECGs) can reveal cardiac ischemia, conduction blocks, or arrhythmia or can help corroborate certain ingestions (tricyclic antidepressants), electrolyte abnormalities (e.g., potassium, calcium), or hypothermia. If nonconvulsive status epilepticus is suggested, or if a patient with status epilepticus has required neuromuscular blockade, continuous electroencephalographic monitoring, if available, can provide key information about the patient's status and guide therapy.

DIAGNOSTIC ALGORITHM

Critical diagnoses to consider are listed in Table 16-1.

Information gathered from the history and physical examination of the patient with depressed consciousness is used to direct the approach to diagnostic testing. Most often, this information points toward a systemic or metabolic cause rather than a structural cause. Neuroimaging studies are performed early in patients with suspected structural causes but should not precede treatment of quickly reversible conditions such as opioid overdose or hypoglycemia. Systemic or metabolic causes of depressed consciousness and coma are most often found on analysis of laboratory studies. Consequently, in the undifferentiated patient, diagnostic tests should be performed in parallel whenever possible to avoid unnecessary delays in initiation of treatment.

Similarly, owing to the severe morbidity and mortality associated with many causes of depressed consciousness and the ability for rapid reversal of several conditions, initial stabilization, treatment, and assessment are performed simultaneously. A logical approach to the history, physical examination, and diagnostic testing is presented in Figure 16-3.

EMPIRICAL MANAGEMENT

Initial establishment of airway, breathing, and circulation (ABCs) is of primary importance in stabilizing the patient with altered mental status. Initiation of intravenous access combined with the administration of oxygen and continuous telemetry monitoring should happen concomitantly within the first few minutes of the patient's arrival.[2] In patients with a GCS score lower than 8, intubation is indicated unless the coma is readily reversible, such as that caused by hypoglycemia or opioid overdose (see Chapter 1). All patients should receive a thorough neurologic examination before sedation and chemical paralysis for intubation. Trauma patients require spinal immobilization in addition to indicated fluid resuscitation.

Reversible causes of the patient's condition should be sought concomitantly with initial stabilization. Administration of the components of the "coma cocktail," which include dextrose, naloxone, and thiamine, can quickly reverse the alterations in mental status caused by hypoglycemia, narcotic overdose, and thiamine deficiency, respectively, and can substantially narrow the differential diagnosis. Bedside capillary blood glucose, blood, and urine studies should be sent while ECG and emergent noncontrast head CT are ordered. Further therapy and workup will be dictated by the patient's history and physical examination. Specific attention should be given to identifying the focal neurologic abnormalities, including pupillary reflexes and pathologic eye movements that suggest mass effect or depressed brainstem function, prompting neuroimaging and evaluation by a neurosurgeon. Empirical administration of mannitol and elevation of the head of the bed are indicated when there is clear evidence of transtentorial herniation (see Chapters 41 and 101). In patients with compromised brainstem function who lack evidence of herniation, investigation of possible exposure to toxins or metabolic imbalances should proceed with consideration of basilar artery or bilateral vertebral artery occlusion requiring CT or magnetic resonance angiography. Basilar stenosis or occlusion is one of the few stroke syndromes that can manifest as stupor or coma, and administration of antiplatelet, anticoagulation and thrombolytic agents should be considered in consultation with a neurologist or stroke team.

In patients who demonstrate normal brainstem function, the workup proceeds as supportive care is provided. When an infectious cause is suggested, empirical administration of a broad-spectrum antibiotic should not be delayed for lumbar puncture or other diagnostic tools.[9] Lesions or masses found on brain

www.ketabpezeshki.com 66485457-66963820

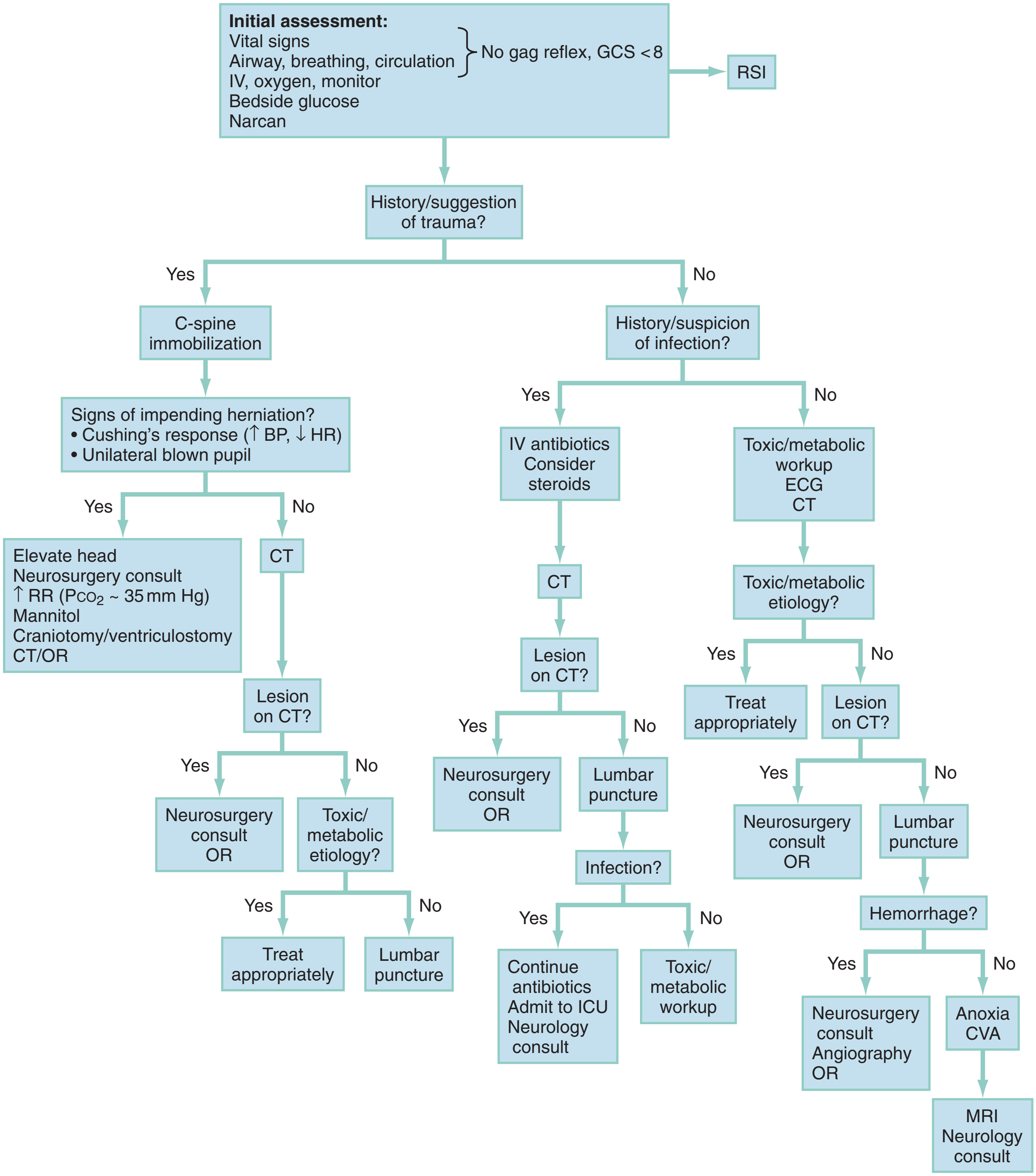


Figure 16-3. Algorithm for diagnostic approach to altered mental status and coma. *BP,* blood pressure; *C-spine,* cervical spine; *CT,* computed tomography of brain; *CVA,* cerebrovascular accident; *HR,* heart rate; *ICU,* intensive care unit; *IV,* intravenous; *OR,* operating room; *RR,* respiration rate; *RSI,* rapid sequence intubation. (Adapted from Adams J: Emergency Medicine. Philadelphia: Elsevier; 2008.)

www.ketabpezeshki.com 66485457-66963820

imaging should prompt evaluation by a neurosurgeon and, if indicated, early operative intervention. In patients in whom a toxic ingestion is possible, activated charcoal is of little benefit in most cases. Specific toxin antidotes, if indicated, can be given, with consultation with a local or regional poison center when required. Early hemodialysis after consultation with a nephrologist should also be considered in patients who have toxic or metabolic abnormalities amenable to this therapy.

DISPOSITION

Patients with structural lesions on imaging require immediate neurosurgical consultation and frequently will require operative intervention. Patients are urgently transferred to a center with neurosurgical capabilities once hemodynamically stabilized if these services are not available at the site of initial patient presentation.

The vast majority of patients with depressed consciousness or coma require admission to the hospital for further treatment and workup. Some patients who have returned to their baseline mental status after reversal of hypoglycemia or opioid overdose may be suitable for discharge directly from the ED or ED observation unit after a period of observation. Patients with alcohol or recreational drug intoxication and no other discernible cause of altered mental status can be discharged when they are clinically sober.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Devuyst G, et al: Stroke or transient ischemic attacks with basilar artery stenosis or occlusion: Clinical patterns and outcome. *Arch Neurol* 2002; 59:567-573.
2. Hoffman RS, Goldfrank LR: The poisoned patient with altered consciousness. Controversies in the use of a "coma cocktail." *JAMA* 1995; 274:562-569.
3. Kanich W, et al: Altered mental status: Evaluation and etiology in the ED. *Am J Emerg Med* 2002; 20:613-617.
4. American College of Emergency Physicians: Clinical policy for the initial approach to patients presenting with altered mental status. *Ann Emerg Med* 1999; 33:251-281.
5. Kirkham FJ: Non-traumatic coma in children. *Arch Dis Child* 2001; 85:303-312.
6. Bateman DE: Neurological assessment of coma. *J Neurol Neurosurg Psychiatry* 2001; 71(Suppl 1):i13-i17.
7. Koita J, Riggio S, Jagoda A: The mental status examination in emergency practice. *Emerg Med Clin North Am* 2010; 28:439-451.
8. Elgouhari HM, O'Shea R: What is the utility of measuring the serum ammonia level in patients with altered mental status? *Cleve Clin J Med* 2009; 76:252-254.
9. Brouwer MC, et al: Nationwide implementation of adjunctive dexamethasone therapy for pneumococcal meningitis. *Neurology* 2010; 75:1533-1539.

www.ketabpezeshki.com 66485457-66963820

Chapter 17

Confusion

J. Stephen Huff

PERSPECTIVE

The term *confusion* connotes an alteration in higher cerebral functions, such as memory, attention, or awareness. In addition, the ability to sustain and focus attention is impaired. Confusion is a symptom, not a diagnosis. The degree of confusion may fluctuate, as may the patient's level of consciousness. Clinical jargon includes the phrases "altered mental status," "delta MS" (change in mental status), "altered mentation," and "change from baseline." Implicit in the definition is a recent change in behavior. Chronic mental status changes such as dementia typically have a different clinical chronology. Other forms of altered mentation include states of diminished alertness on the coma spectrum; these presentations may result from some of the same pathophysiologic processes causing confusion and are discussed in Chapter 16. Confusion may range in severity from a mild disturbance of short-term memory to a global inability to relate to the environment and process sensory input. This extreme state is termed *delirium*. Delirium has two subtypes: hyperactive and hypoactive.[1] Hyperactive delirium is characterized as an acute confusional state associated with increased alertness, increased psychomotor activity, and disorientation and is often accompanied by hallucinations. In hypoactive delirium (sometimes referred to as *quiet delirium*), the confusional state is present but the patient has a reduction in alertness and behavior. Hypoactive delirium may be the more common type in emergency department (ED) patients.[2] Confusion has many causes, and an orderly approach is necessary to discover the causative diagnosis. The assessment of mental status and cognitive impairment in elderly ED patients has been proposed as a key quality indicator in the care of elderly patients by the Society for Academic Emergency Medicine Geriatric Emergency Medicine Task Force.[3]

Epidemiology

Physicians underestimate the incidence of confusion in patients.[4,5] Often, confusion is accepted as an incidental or secondary component of another condition. A patient with injuries from a motor vehicle crash or with dyspnea may be confused, but the primary condition overshadows the underlying abnormal mental status. When confusion exists as an isolated or unexplained finding, it is more likely to receive full and immediate consideration by the clinician. Confusion is estimated to occur in 2% of ED patients, 10% of all hospitalized patients, and 50% of elderly hospitalized patients.[4,6] Delirium in older ED patients was found to be an independent predictor of increased mortality within 6 months in one study.[7]

Pathophysiology

Conceptually, consciousness may be divided into elements of alertness or arousal and elements constituting content of consciousness. Confusion is largely a problem of the content portion of consciousness. Many different clinical processes may disrupt optimal cortical functioning and result in confusion. The pathophysiology is not straightforward. Widespread cortical dysfunction is thought to result from substrate deficiencies (hypoglycemia or hypoxemia), neurotransmitter dysfunction, or circulatory dysfunction. Compounding this problem is the concept that the reserve of central nervous system (CNS) function varies from individual to individual; individuals with a preexisting impairment may become confused after even minor changes in their normal physiologic state.

DIAGNOSTIC APPROACH

Differential Considerations

The observation of acute confusion prompts a search for an underlying cause. Four groups of disorders encompass most causes of diffuse cortical dysfunction: (1) systemic diseases secondarily affecting the CNS, (2) primary intracranial disease, (3) exogenous toxins, and (4) drug withdrawal states (Box 17-1).[1] Focal cortical dysfunction, such as from tumor or stroke, typically does not cause confusion, although occasionally, receptive or expressive dysphasia may be mistaken for confusion. Likewise, subcortical or brainstem dysfunction most frequently results in a diminished level of alertness and consciousness, not confusion.

Rapid Assessment and Stabilization

Most patients with acute confusion do not require immediate interventions. Three crucial exceptions are hypoglycemia, hypoxemia, and shock. A complete set of vital signs, including temperature and oxyhemoglobin saturation, and a bedside blood glucose level should be determined promptly for all confused patients. Oral or intravenous glucose therapy is indicated if low blood glucose is discovered. Supplemental oxygen and intravenous fluid are administered as necessary. In a patient with abnormal or unstable vital signs, initial diagnostic and management efforts are directed toward treatment of the systemic condition. A confused patient with acute pulmonary edema, hypoxia, and confusion obviously requires evaluation and treatment of the pulmonary edema, not a screening test for cognitive functioning.

www.ketabpezeshki.com 66485457-66963820

Box 17-1 Major Categories: Differential Considerations

Primary intracranial disease
Systemic diseases secondarily affecting the central nervous system
Exogenous toxins
Drug withdrawal

Box 17-2 Findings That May Help Differentiate between Organic and Functional Causes of Confusion

Organic	Functional (Psychiatric)
History	History
Acute onset	Onset over weeks to months
Any age	Onset ages 12 to 40 years
Mental status examination	Mental status examination
Fluctuating level of consciousness	Alert
Disoriented	Oriented
Attention disturbances	Agitated, anxious
Poor recent memory	Poor immediate memory
Hallucinations: visual, tactile, auditory	Hallucinations: most commonly auditory
Cognitive changes	Delusions, illusions
Physical examination	Physical examination
Abnormal vital signs	Normal vital signs
Nystagmus	No nystagmus
Focal neurologic signs	Purposeful movement
Signs of trauma	No signs of trauma

Confused patients should be protected from harming themselves or others. Close observation may need to be supplemented by medications or physical restraint. Family members may offer valuable assistance in observing and comforting the patient.

In general, in patients with schizophrenia and other psychiatric disorders, results of tests of cognition, orientation, and attention are normal unless the condition is severe. The term *psychosis* implies a disorder of reality testing and thought organization severe enough to interfere with normal daily functioning. Psychosis is a nonspecific syndrome, and careful evaluation is required to differentiate between psychiatric and organic origins (e.g., drug intoxication or other systemic process) (Box 17-2).

Pivotal Findings

A patient with an altered state of consciousness including confusion is evaluated through a focused history and a pertinent examination, performance of rapid bedside screening investigations, and observation of the response to certain therapies (e.g., dextrose or naloxone). Additional evaluation may include laboratory testing and diagnostic imaging with various modalities. Information that suggests the cause of confusion is found roughly in descending order from the patient's history, the examination findings including results of rapid bedside testing, and the response to ED therapies; the results of laboratory testing and diagnostic imaging are less often useful.[8]

History

Confusion is often reported by family members or caregivers; frequently the patient is not aware of the confusion and seemingly glosses over problems. Families may articulate the complaint as confusion but also may describe rambling, disorientation, speaking to persons not there, the patient's inability to find his or her way around familiar surroundings, or simply "not being right." An essential goal of the history is to determine when the patient last exhibited "normal" thinking and behavior.

ORIENTATION TO TIME
"What is the date?"

REGISTRATION
"Listen carefully. I am going to say three words.
You say them back after I stop.
Ready? Here they are . . .
HOUSE (pause), CAR (pause), LAKE (pause).
Now repeat those words back to me."
[Repeat up to 5 times, but score only the first trial.]

NAMING
"What is this?" [Point to a pencil or pen.]

READING
"Please read this and do what it says."
[Show examinee the words on the stimulus form.]
CLOSE YOUR EYES

Figure 17-1. Mini-Mental State Examination sample items. (Reproduced by special permission of the Publisher, Psychological Assessment Resources, Inc., 16204 North Florida Avenue, Lutz, Florida 33549, from the Mini-Mental State Examination, by Marshal Folstein and Susan Folstein. Copyright © 1975, 1998, 2001 by Mini Mental LLC, Inc. Published 2001 by Psychological Assessment Resources, Inc. Further reproduction is prohibited without permission of PAR, Inc. The MMSE can be purchased from PAR, Inc., by calling [800] 331-8378 or [813] 968-3003.)

Attention deficit is the common denominator in confusional states. The initial task in evaluating the patient is to define the symptoms and severity of confusion. The specific behaviors that are of concern to the patient or caregivers should be defined. Often the family is the most valuable source for information; a physician or other caregiver with an established relationship with the patient also may be helpful. The duration of the confusion, any recent changes in medications, and recent illnesses are important points in the clinical history. Hallucinations are not unique to psychiatric illness and can commonly occur in confusion states, especially delirium. Hallucinations in delirium tend to be visual (with or without auditory components), powerful, fleeting, and poorly organized. A history of medication or substance abuse and any recent changes, especially cessation of benzodiazepines or ethanol, should be sought.

Physical Examination

The patient's confusion may be obvious at the bedside. In other cases, confusion may be subtle, and informal assessment of mental status and cognitive abilities may fail to detect it. The Mini-Mental State Examination (MMSE) (Fig. 17-1) commonly is recommended as a screening instrument but is used infrequently in the ED because of the time required for administration.[8,9] A more rapidly performed screening tool, the Quick Confusion Scale (QCS; Fig. 17-2), has been developed and tested in ED patients.[9,10] This tool objectively measures elements of the patient's mental status in 2 to 3 minutes and correlates well with the MMSE.[10,11] Another rapid scale, the Six-Item Screener, has similar performance against the MMSE.[12,13] The tasks measured by either the MMSE or the QCS require adequate attention on the part of the patient. If the patient's attention span is greatly impaired, detailed testing may be impossible. Digit repetition forward (five or six digits) and backward (four digits) is a brief screen for attention function. Alternatively, spelling a commonly used word backward ("world" is frequently used) measures a patient's ability to concentrate. Screening tests may detect confusion not obvious in casual conversation, identifying the need for further

www.ketabpezeshki.com 66485457-66963820

ITEM	SCORE (highest number in category indicates correct response; decreased scoring indicates increased number of errors)	WEIGHT	SCORE
What year is it now?	0 or 1 (score 1 if correct; 0 if incorrect)	x2	
What month is it?	0 or 1 (score 1 if correct; 0 if incorrect)	x2	
Repeat phrase and remember it: "John Brown, 42 Market Street, New York"			
About what time is it? (answer correct if within the hour)	0 or 1 (score 1 if correct; 0 if incorrect)	x2	
Count backward from 20 to 1	0, 1, or 2 (score 2 if correct; 1 if 1 error; score 0 if more than 2 errors)	x1	
Say the months in reverse	0, 1, or 2 (score 2 if correct; 1 if 1 error; score 0 if more than 2 errors)	x1	
Repeat the memory phrase (each underlined portion is worth 1 point)	0, 1, 2, 3, 4, 5 (score 5 if correctly performed; each error drops score by one)	x1	
		TOTAL	______

Final score is sum of the totals; score less than 15 suggests the presence of altered cognition and need for further assessment.

Figure 17-2. Quick Confusion Scale.

investigations.[12,14] A recently described cognitive assessment tool, the Sweet 16, has been studied in patients in the posthospitalization period.[15] A variety of other bedside instruments are available as screening tests for delirium.[16]

The physical examination may suggest a cause of confusion such as congestive heart failure, pneumonia, or stigmata of illicit drug use. Fever suggests an infection as the cause of altered mental status and should prompt a search for the source, particularly urinary tract infection in the elderly patient. Any new focal neurologic findings suggest a possible mass lesion or stroke, but these would manifest with confusion only if global cortical dysfunction was caused by surrounding cerebral edema or elevated intracranial pressure by severe mass effect. In this regard, testing of gait and tandem gait, if possible, may be invaluable. Aphasia, fluent or nonfluent, is a focal sign suggesting a lesion in the dominant cerebral hemisphere. In confusional states, speech may be abnormal and is often incoherent, and the rate of speech may be either rapid or slowed. Involuntary movements, such as asterixis or tremor, may be present. The various toxidromes may assist in the identification of an intoxication or drug effect as the cause of confusion.

Laboratory Tests

The results of the history and physical examination frequently guide the clinician in the choice of laboratory tests most likely to yield valuable diagnostic information. Pulse oximetry may reveal hypoxia, or bedside glucose testing may reveal hypoglycemia or hyperglycemia. In the presence of a fever, chest radiography and urinalysis often reveal the source of the infection causing the altered mentation. In elder patients, urinalysis should be performed whether or not fever is present. A careful inspection of the skin, especially in dependent areas, such as the buttocks, may reveal a culprit skin infection. Serum electrolyte testing (especially sodium) is indicated in all cases. Broader chemistry panels, including liver enzymes, help identify hepatic encephalopathy. If there are clinical findings suggestive of hypothyroidism, thyroid testing is indicated. (See Chapter 128.) Electrocardiography is indicated in elderly patients because myocardial infarction may manifest atypically as confusion. The complete blood count, although commonly performed, is unlikely to provide useful diagnostic clues, unless profound anemia is suspected. Arterial blood gas testing is rarely indicated or useful unless pulse oximetry is not reliable.

If common and simple tests do not suggest a solution, more complex tests are initiated in the ED, observation unit, or inpatient service. The clinical situation and overall condition of the patient determine the speed and direction of evaluation. Additional laboratory work is often of decreasing yield but may reveal the cause of confusion. Serum ammonia, calcium, and selected drug and toxicologic testing may be ordered in this second tier of evaluation. Blood and urine cultures are obtained in the febrile patient when hospital admission is anticipated and a clear infectious source is not evident. Paracentesis or thoracentesis may be appropriate if ascites or pleural effusion is present. Cranial computed tomography (CT) scanning is usually done to screen for CNS lesions in the absence of another identified source of the confusion. Focal findings on examination increase the yield of this test, but unanticipated abnormalities are often found on neuroimaging. Lumbar puncture may allow discovery or exclusion of CNS infection if no other source has been identified. Cerebrospinal fluid examination may clarify a diagnosis of bacterial meningitis, encephalitis, aseptic meningitis, or subarachnoid hemorrhage. If the cause of confusion remains unclear or if the patient is unable to function safely in his or her current environment, admission may be necessary for additional ongoing assessment, including diagnostic testing not usually available in the ED, such as magnetic resonance imaging or electroencephalography.[8]

www.ketabpezeshki.com 66485457-66963820

Box 17-3 Critical and Emergent Diagnoses

Critical

Hypoxia, diffuse cerebral ischemia
- Respiratory failure
- Congestive heart failure
- Myocardial infarction
- Shock

Systemic processes
- Hypoglycemia

CNS infections

Hypertensive encephalopathy

Elevated intracranial pressure—medical and surgical origin

Emergent

Hypoxia, diffuse cerebral ischemia
- Severe anemia

Systemic diseases
- Electrolyte and fluid disturbance
- Endocrine disease
  - Thyroid
  - Adrenal
- Hepatic failure
- Nutrition, Wernicke's encephalopathy
- Sepsis, infection

Intoxications and withdrawal
- CNS sedatives
- Ethanol
- Other medication side effects, particularly anticholinergics

CNS disease
- Trauma
- Infections
- Stroke
- Subarachnoid hemorrhage
- Epilepsy, seizures
  - Postictal state
  - Nonconvulsive status epilepticus
  - Complex partial status epilepticus

Neoplasm

Note: These represent a partial diagnosis; causes are myriad. "Critical" in this case means conditions that need immediate assessment and correction within moments, such as oxygenation and ventilation problems or hypoglycemia. Because confusion represents CNS failure, other problems may be considered critical as well and may necessitate intensive care unit admission, depending on severity.

CNS, central nervous system.

DIFFERENTIAL DIAGNOSIS

Certain critical and emergent diagnoses require prompt recognition for morbidity or mortality to be prevented (Box 17-3). The diagnosis of confusion implies the exclusion of other states of altered mental status, such as coma and decompensated psychiatric syndromes. A new focal neurologic deficit points to a focal defect of the CNS, which is less likely to cause the global cortical dysfunction necessary for confusion. Stroke rarely causes confusion, but resulting disturbances in speech or understanding may mimic a confusional state. The diagnosis of stroke is relatively straightforward if a new motor deficit is present. Occasionally, other focal neurologic abnormalities may mimic a confusional state. A person with a new visual field deficit and visual neglect may have difficulty ambulating in familiar surroundings and be labeled as confused, but this reflects focal neurologic injury and not a confusional state from global CNS dysfunction. Careful assessment of mental status assists in resolving the diagnostic dilemma. Frontal lobe dysfunction from stroke, subdural hematoma, or tumor may result in personality changes and the report of "confusion" by family or friends.

Altered mental status may be divided into three different categories depending on the finding of diminished level of consciousness, acute focal neurologic deficit, or abnormal attention span.

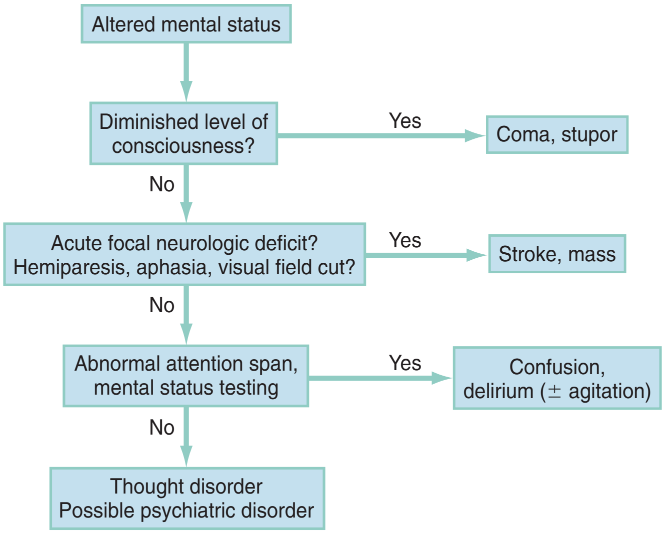


Figure 17-3. Diagnostic algorithm for confusion.

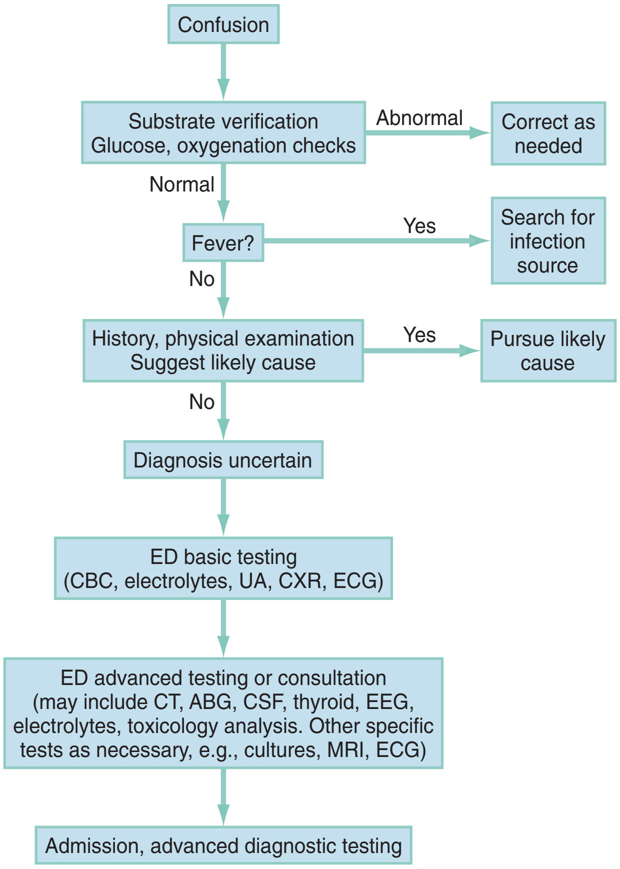


Figure 17-4. Management algorithm for confusion. *ABG,* arterial blood gas; *CBC,* complete blood count; *CT,* computed tomography; *CSF,* cerebrospinal fluid; *CXR,* chest x-ray examination; *ECG,* electrocardiogram; *ED,* emergency department; *MRI,* magnetic resonance imaging; *UA,* urinalysis.

Placement into one of these categories may guide the differential assessment and therapy (Fig. 17-3).

EMPIRICAL MANAGEMENT

Ideally, treatment is directed at the underlying cause of the confusion. Investigations continue until a likely diagnosis is discovered or consultation and admission are deemed necessary (Fig. 17-4).

www.ketabpezeshki.com 66485457-66963820

Many febrile patients are found to have a systemic infectious cause of the confusion. Urinary tract infections and pneumonia are the more common sources, but soft tissue infections also warrant consideration. CNS infections are encountered less frequently but have potentially devastating consequences if not recognized promptly. Antibiotic treatment for coverage of common causes of meningitis may be considered in ill febrile patients while definitive evaluation is in progress.

Postictal confusion is common in patients with seizures but should improve within 20 to 30 minutes. If the patient remains unconscious or confused after a seizure, the possibility of ongoing or intermittent seizure activity (i.e., nonconvulsive seizures) should be considered. Nonconvulsive status epilepticus, an epileptic twilight state, is unusual but does occur and may be particularly difficult to recognize in the elderly (see also Chapters 18 and 102).[17]

Sometimes it may be necessary to treat confusion or agitation for patient safety. Environmental manipulations such as dim lighting or provision of psychosocial support may be helpful. Confinement or physical restraint may be necessary at times for patient safety with careful adherence to institutional guidelines. Benzodiazepines, butyrophenones, or newer antipsychotic medications may be used if necessary to decrease agitation, but any of these might confound evaluation of the confusional state.

DISPOSITION

Most patients with a presenting sign of confusion are admitted to the hospital or ED observation unit for additional diagnostic procedures, extended observation, and treatment. Exceptions include patients with rapidly resolved confusional states after treatment for insulin-induced hypoglycemia, or after recovery from intoxications or withdrawal states, such as those related to ethanol or recreational drugs. These patients may be observed and then discharged after successful identification and resolution of the acute confusional state. Unresolved confusion or unexplained findings on repeat mental status screening should prompt admission or careful reevaluation before consideration of discharge.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Lipowski ZJ: Delirium (acute confusional states). *JAMA* 1987; 258:1789.
2. Han JH, et al: Delirium in older emergency department patients: Recognition, risk factors, and psychomotor subtypes. *Acad Emerg Med* 2009; 16:193.
3. Terrell KM, et al: Quality indicators for geriatric emergency care. *Acad Emerg Med* 2009; 16:441.
4. Hustey FM, Meldon SW: The prevalence and documentation of impaired mental status in elderly emergency department patients. *Ann Emerg Med* 2002; 39:248.
5. Sanders AB: Missed delirium in older emergency department patients: A quality-of-care problem. *Ann Emerg Med* 2002; 39:338.
6. Wofford JL, Loehr LR, Schwartz E: Acute cognitive impairment in elderly ED patients: Etiologies and outcomes. *Am J Emerg Med* 1996; 14:649.
7. Han JH, et al: Delirium in the emergency department: An independent predictor of death within 6 months. *Ann Emerg Med* 2010; 56:244.
8. American College of Emergency Physicians: Clinical policy for the initial approach to patients presenting with altered mental status. *Ann Emerg Med* 1999; 33:251.
9. Folstein MF, Folstein SE, McHugh PR: “Mini-mental state”: A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12:189.
10. Huff JS, Farace E, Brady WJ, Kheir J, Shawver G: The Quick Confusion Scale in the ED: Comparison with the Mini-Mental State Examination. *Am J Emerg Med* 2001; 19:461.
11. Irons MJ, Farace E, Brady WJ, Huff JS: Mental status screening of emergency department patients: Normative study of the Quick Confusion Scale. *Acad Emerg Med* 2002; 9:989.
12. Wilber ST, Lofgren SD, Mager TG, Blanda M, Gerson LW: An evaluation of two screening tools for cognitive impairment in older emergency department patients. *Acad Emerg Med* 2005; 12:612.
13. Stair TO, Morrissey J, Jaradeh I, Zhou TX, Goldstein JN: Validation of the Quick Confusion Scale for mental status screening in the emergency department. *Intern Emerg Med* 2007; 2:130.
14. Hustey FM, Meldon SW, Smith MD, Lex CK: The effect of mental status screening on the care of elderly emergency department patients. *Ann Emerg Med* 2003; 41:678.
15. Fong TG, et al: Development and validation of a brief cognitive assessment tool: The sweet 16. *Arch Intern Med* 2011; 171:432.
16. Wong CL, Holroyd-Leduc J, Simel DL, Straus SE: Does this patient have delirium? Value of bedside instruments. *JAMA* 2010; 304:779.
17. Beyenburg S, Elger CE, Reuber M: Acute confusion or altered mental state: Consider nonconvulsive status epilepticus. *Gerontology* 2007; 53:150.

www.ketabpezeshki.com 66485457-66963820

Chapter 18

Seizures

Jason T. McMullan, Ana M. Davitt, and Charles V. Pollack, Jr.

PERSPECTIVE

Seizures are episodes of abnormal neurologic functioning caused by pathologically excessive activation of neurons, either in the cerebral cortex or in the deep limbic system. *Epilepsy* is defined as recurrent unprovoked seizures caused by a genetically determined or acquired brain disorder[1]; it is not an appropriate term for seizures that occur intermittently or predictably after a known insult, such as alcohol intoxication and withdrawal.

Presentation to the emergency department (ED) with a generalized convulsive seizure prompts immediate concern for airway protection and treatment to stop the ictal activity, followed by a focused search for the cause. Nonconvulsive seizures, which are much less common, may be relatively obscure in their presentation, are more diverse in their etiology, and are sometimes more difficult to recognize and acutely control.

Epidemiology and Classification

More than 10% of the United States population will experience at least one seizure during their lifetime; however, only 3% will be diagnosed with epilepsy. Seizures account for 3% of transports by emergency medical services, 2% of pediatric ED visits, and 1% of all ED visits. Alcohol and central nervous system pathologies (tumor, stroke, trauma, infection) are common causes in adults. Metabolic derangements and infection more frequently cause seizures in infants than adults, but febrile seizures are the most common type of seizure in infants and young children. Approximately 7% of patients who come to the ED with seizures are in status epilepticus.[2]

Seizures can be classified based on cause (primary or secondary), effect on mentation (generalized or focal), and motor activity (convulsive or nonconvulsive). Primary seizures are unprovoked and not linked to an inciting event. Secondary seizures may be caused by trauma, illness, intoxications and poisonings, organ failure, other metabolic disturbances, cerebral tumors, pregnancy, and, paradoxically, supratherapeutic levels of some anticonvulsants.[3,4]

A newer terminology scheme has been developed and may affect communications between emergency physicians and epileptologists or patients. The "partial" classification is now solely "focal," and the distinctions between "complex partial" and "simple partial" have been eliminated. The terms *genetic, structural-metabolic,* and *unknown* have replaced *idiopathic, symptomatic,* and *cryptogenic.*[3]

A generalized seizure is defined as abnormal neuronal activity in both cerebral hemispheres causing an alteration in the level of consciousness. Generalized seizures may be further divided into tonic-clonic, absence, atonic, and myoclonic; some patients may experience only the tonic or clonic phase. Focal seizures usually involve one cerebral hemisphere, thereby preserving consciousness, though these seizures may progress and cause an altered sensorium. Some seizures are impossible to classify because of inadequate or inaccurate description of the ictal activity.[3,4]

Convulsive seizures are characterized by uncontrolled, rhythmic motor movements and can affect part or all of the body. Nonconvulsive seizures do not result in abnormal motor activity; patients may display confusion, altered mental status, abnormal behavior, or coma.

Status epilepticus has been classically defined as at least 30 minutes of persistent seizures or a series of recurrent seizures without intervening return to full consciousness.[5] The time criterion has been shortened to 5 minutes with recognition that the duration of seizure activity is related to outcome and that the likelihood of achieving seizure cessation with typical treatments decreases with ictal duration.[4,6] Common causes of status epilepticus in adults are shown in Table 18-1.[7]

Seizures in children follow a different distribution, primarily because of the relatively high incidence of febrile seizures and the inherent limitations of the observational history of possible ictal activity. Febrile seizure is the most common pediatric seizure, occurring in 2 to 5% of children 6 months to 5 years of age; 20 to 30% of those children have at least one recurrence. It is important to differentiate between the febrile seizure, which is typically of short duration, has a limited postictal phase, and is related to the slope of the body temperature rise, and the seizure with fever, which is often more serious and prolonged and indicates more significant underlying infection.[8] First-time seizures in infants younger than 6 months may indicate important underlying pathology and necessitate a full assessment.[9]

Pathophysiology

Seizures occur when the abnormal increased electrical activity of initiating neurons activates adjacent neurons and propagates until the thalamus and other subcortical structures are similarly stimulated. At a cellular level, the pathophysiology is not well understood, although research in specific epilepsy syndromes is elucidating possible mechanisms. Investigation of rare inherited epilepsy syndromes has identified mutations in neuronal ion channel proteins, limiting intracellular passage of potassium. Given that the potassium current is the primary force behind repolarization of membranes, depolarization is prolonged in these patients, leading to an increase in neuronal hyperexcitability.[1] Other studies have found that malformations of cortical development and glial cells may play a role in epileptogenesis.[1]

Clinical seizure activity typically, but not always, reflects the initiating focus. When the ictal discharge extends below the cortex

www.ketabpezeshki.com 66485457-66963820

Table 18-1 Etiology of Status Epilepticus in Adults

ETIOLOGY	PERCENTAGE OF CASES
AED noncompliance or withdrawal of AED	25-26
Alcohol related	15-24
Drug toxicity	2-10
Infection	8
Cerebral tumor	5-6
Trauma	3-5
Cerebrovascular disease or stroke	4-23
Metabolic abnormality	4-13
Hypoxia or cardiac arrest	4-12
Idiopathic	4-5

Adapted from Bassin S, Smith TL, Bleck TP: Clinical review: Status epilepticus. Crit Care 6:137-142, 2010.
AED, antiepileptic drug.

to deeper structures, the reticular activating system in the brainstem may be affected, altering consciousness. In generalized seizures, the focus is often deep and midline, which explains the prompt loss of consciousness and bilateral involvement. Seizures are typically self-limited; at some point the hyperpolarization subsides and the bursts of electrical discharges from the focus terminate. This cessation may be related to reflex inhibition, neuronal exhaustion, or alteration of the local balance of neurotransmitters.

Focal seizures may represent a similar pathophysiologic process in which less recruitment occurs and the ictal activity does not cross the midline. Because of the more limited focus of abnormal activity, convulsive motor activity may not be the predominant clinical manifestation.[10]

DIAGNOSTIC APPROACH

Differential Considerations

Because a diagnosis of seizure has major consequences for the patient in the ED—including loss of driving privileges and exposure to potentially toxic medicines—the first diagnostic task is to determine whether the patient actually experienced a seizure.[11,12] Ictal activity can be irrefutably verified only by electroencephalography. Other abnormal movements and states of consciousness, including nonepileptic convulsions (pseudoseizures), can be confused with ictal activity. The differential diagnoses to consider when evaluating for seizure are listed in Table 18-2.[12]

Syncope, whether vasodepressive (vagal syncope), orthostatic, or dysrhythmia related, can be confused with seizures by observers. A sudden loss of consciousness followed by abnormal movements can be ictal or syncopal in origin, hence the consideration "fit versus faint." One video analysis of 56 brief syncopal episodes showed myoclonic activity in 90% of patients, together with frequent head turns, upward gaze, oral automatisms, and righting movements. These are likely a transient response by the brain to sudden deprivation of blood flow. In general, ictal tonic-clonic movements are more forceful and prolonged than the brief convulsive activity sometimes associated with fainting. In addition, most generalized seizures are characterized by a postictal state that syncope patients do not manifest.[13] An important exception to this is an atonic seizure, or "drop attack," in which the patient experiences a sudden and complete loss of muscle tone associated with altered mentation; in this type of generalized seizure, motor activity is not displayed and a postictal state may not occur.[4]

The cause of an unwitnessed, unprovoked loss of consciousness with a fall, after which the patient visits the ED, may be difficult to determine. Suggestions of seizure as the cause include retrograde amnesia, loss of continence (which also can occur with vasogenic and other forms of syncope), and evidence of oral trauma such as maceration of the buccal mucosa or bite lacerations of the tongue. Blood drawn soon after a true seizure may demonstrate a lactic acidosis that may resolve by the time a repeat analysis is performed in the ED.[14]

Rapid Assessment and Stabilization

The patient who arrives with a history of possible seizure activity should be placed in a monitored area of the ED and prepared for prompt physician examination.[5] An intravenous line or saline lock catheter should be placed in case anticonvulsants are emergently indicated. Blood glucose is checked at the bedside, and a thorough list of all medications currently being used by the patient is obtained. Hypoglycemia is the most common metabolic cause of seizure activity. The only treatment required for the patient may be administration of intravenous glucose. *Prolonged* seizure activity may also *cause* hypoglycemia, so the cause-and-effect relationship may sometimes be reversed; but in either case, glucose therapy is required. If the patient stopped seizing before arrival in the ED, the history, physical examination, and diagnostic course should focus on possible precipitants of the seizure. The patient should be protected from self-injury during this time.

If the patient is seizing in the ED, the first step is to confirm that a pulse is present and that the convulsions are not the result of cerebral hypoxia from lack of blood flow. After this, attention is paid to protecting and maintaining the airway, although airway obstruction during ictus usually is transient. Nasopharyngeal airways and positioning the patient on the side generally are all that is required for airway management. Oropharyngeal airways are less useful because the mouth often is clenched, and damage to teeth or tongue may ensue during attempts to insert an oral airway. Oxygen may be administered by nasal cannula if the saturation is below 90% or the patient appears cyanotic (when saturation cannot be measured.) Suction should be available but not used during seizure activity because of risk of injury to teeth, tongue, or lips. Vascular access should be established, but benzodiazepine treatment can be initiated before placement of an intravenous line.

If the patient is immobilized on a spine board after trauma, the entire board can be tipped to one side to place the patient in the semiprone position for protection against aspiration. If the seizure persists after administration of anticonvulsant medication, preparation is made for endotracheal intubation.

Most seizures will terminate without intervention. If a patient begins to seize while under ED observation, it is prudent to administer low-dose benzodiazepines (approximately half of the doses for status epilepticus, Table 18-3). Patients who arrive at the ED with continued seizure activity, experience recurrent seizure without recovering from the postictal period, or experience witnessed convulsions lasting longer than 5 minutes are considered in status epilepticus and treated as indicated in Table 18-3.

Benzodiazepines are the optimal first-line agents for stopping seizure activity in patients of all ages. Available agents include lorazepam, diazepam, and midazolam; all three are effective in terminating seizure activity. If intravenous access is established, lorazepam is the preferred first agent for the management of status epilepticus, particularly because of a long half-life, which decreases risk of seizure recurrence.[15] For the patient without vascular access, immediate intramuscular midazolam is preferred over delayed intravenous lorazepam.[16] Diazepam and midazolam can both be administered via alternate routes, and buccal midazolam is more effective than rectal diazepam in achieving seizure cessation.[17]

www.ketabpezeshki.com 66485457-66963820

Table 18-2 Differential Considerations for the Diagnosis of Seizure

EPILEPTIC		NONEPILEPTIC	
Drugs of abuse Intoxication or withdrawal	Alcohol Stimulants LSD, PCP, NMDA Herbal products	Cardiac	Vasovagal (neurocardiogenic) syncope Orthostatic syncope Cardiogenic syncope
Medications	Antibiotics Antiarrhythmic agents Pain medications Antidepressants Antipsychotics	Neurologic	Vertebrobasilar TIA, CVA Global transitory amnesia Migraine Movement disorders
Metabolic	Hypoglycemia or hyperglycemia Hyponatremia or hypernatremia Hypoxia Hypocalcemia Hypomagnesemia	Sleep disorders	Cataplexy Periodic leg movements of sleep Arousal disorders Parasomnia associated with REM sleep
Infectious	Meningitis Cerebritis Encephalitis Cerebral abscess Non-CNS infections	Metabolic	Hypoglycemia or hyperglycemia Hyponatremia or hypernatremia Hyperthyroidism Pheochromocytoma
Structural lesions	Tumor Intracranial hemorrhage Subarachnoid hemorrhage Ischemic CVA	Psychogenic	Panic attacks Nonepileptic convulsion (pseudoseizure)
Systemic	Eclampsia Extreme fever Thyrotoxicosis	Toxic	Extrapyramidal symptoms of antipsychotics Delirium tremens Tetanus
Other	Trauma Posterior reversible encephalopathy syndrome		

Adapted from Carreno M: Recognition of nonepileptic events. Semin Neurol 28:297-304, 2008; and Slattery DE, Pollack CV Jr: Seizures as a cause of altered mental status. Emerg Med Clin North Am 28:517-534, 2010.

CNS, central nervous system; *CVA*, cerebrovascular accident; *LSD*, lysergic acid diethylamide; *NMDA*, *N*-methyl-D-aspartate; *PCP*, phencyclidine; *REM*, rapid eye movement; *TIA*, transient ischemic attack.

Table 18-3 Medications and Dosages for Emergency Treatment of Prolonged Seizures and Status Epilepticus

MEDICATION	ADULT DOSE	PEDIATRIC DOSE	COMMENTS
Initial Therapy			
Diazepam	10 mg IV or 10-20 mg PR	0.15 mg/kg IV; 0.2-0.5 mg/kg PR (max 20 mg)	May repeat in 5-10 minutes; monitor respiratory status
Lorazepam	4 mg IV	<13 kg: 0.1 mg/kg IV (max 2 mg); 13-39 kg: 2 mg IV; >39 kg: 4 mg IV	Preferred IV benzodiazepine; may repeat in 10 minutes; monitor respiratory status
Midazolam	10 mg IV, IM, IN, buccal	0.2 mg/kg IV, IN (max 5 mg); 0.5 mg/kg buccal (max 5 mg); <13 kg: 0.2 mg/kg IM (max 5 mg); 13-39 kg: 5 mg IM; >39 kg: 10 mg IM	Preferred IM benzodiazepine; may repeat in 10 minutes; monitor respiratory status
Second-Tier Treatments			
Phenytoin	20 mg/kg IV infusion	20 mg/kg IV infusion	May cause hypotension and dysrhythmia
Fosphenytoin	20 mg PE/kg IV infusion or 20 mg PE/kg IM	20 mg PE/kg IV infusion	
Valproate sodium	20-40 mg/kg IV infusion		Max dose 60 mg/kg/day
Pentobarbital	5-15 mg/kg IV bolus then 0.5-5.0 mg/kg/hr		Titrate to EEG; intubation and hemodynamic support required
Phenobarbital	20-30 mg/kg IV infusion		Intubation likely required
Midazolam infusion	0.05-2 mg/kg/hr	0.5-2 mg/kg/hr	Monitor respiratory status
Propofol infusion	1-2 mg/kg IV bolus then 20-200 µg/kg/min infusion		Intubation required
Isoflurane inhalation			Titrate to EEG; intubation and hemodynamic support required

Adapted from Brophy GM, et al: Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 17:3-23, 2012.

EEG, electroencephalogram; *ET*, endotracheally; *IM*, intramuscular; *IN*, intranasally; *IV*, intravenous; *PR*, per rectum.

Intraosseous administration is an acceptable alternative for intravenous medications.

www.ketabpezeshki.com 66485457-66963820

Table 18-3 Medications and Dosages for Emergency Treatment of Prolonged Seizures and Status Epilepticus—cont'd

MEDICATION	ADULT DOSE	PEDIATRIC DOSE	COMMENTS
Special Situations			
Glucose	25 g IV (50 mL $D_{50}W$)	0-1 mo: 2 mL/kg IV $D_{10}W$ 1 mo-2 yr: 2 mL/kg IV $D_{25}W$ >2 years: 2 mL/kg $D_{50}W$ (max 50 mL)	Titrate for blood glucose >100 mg/dL
Magnesium sulfate	6 g IV over 15 min, then 2 g/hr		First-line treatment for eclampsia; consider in women between 20 weeks' gestation and 6 weeks postpartum
Pyridoxine	Equal dosage of isoniazid ingestion (max 5 g) given 0.5 g/min IV until seizure stops, with remainder given over 4-6 hr	Max dose 70 mg/kg (up to 5 g)	
3% Hypertonic saline	100-200 mL over 1-2 hr	4-6 mL/kg over 1 hr (up to 100 mL)	Reserved for actively seizing and comatose hyponatremic patients; goal is to avoid raising serum sodium by > 12 mEq in 24 hr

EEG, electroencephalogram; *ET,* endotracheally; *IM,* intramuscular; *IN,* intranasally; *IV,* intravenous; *PR,* per rectum.
Intraosseous administration is an acceptable alternative for intravenous medications.

If repeated doses of benzodiazepines do not abort seizure activity, or if the patient's oxygen saturation remains persistently below 90%, emergent intubation is indicated. (See Chapter 1.) If possible, the patient should not receive long-acting neuromuscular blockade, so that recurrence or persistence of seizure activity can be monitored.

Medications for the treatment of status epilepticus are shown in Table 18-3. There is little evidence on which to base the choice and timing of second-line medications in the treatment of benzodiazepine-refractory status epilepticus; most recommendations are supported by expert consensus.[6,15,18] However, moving quickly to a second-line agent is supported, and phenytoin is the most recommended second-line therapy for adults with persistent seizure activity.[6,18] The prodrug, fosphenytoin, can be administered more quickly, can be given intramuscularly, and has less tendency to cause hypotension, but it is significantly more expensive.[19] Second-line therapy for children is intravenous phenobarbital. Third-line therapy is phenytoin for children and phenobarbital for adults.[20-22] Intravenous valproate sodium is safe and is an alternative for patients who are on chronic valproic therapy and whose levels are subtherapeutic.[23,24] The role of newer antiepileptic drugs such as levetiracetam and lacosamide in the management of status epilepticus has not yet been established.

Seizures refractory to these initial treatments prompt an evaluation for nonepileptic causes of the convulsions. Isoniazid overdose can cause prolonged seizures refractory to benzodiazepines. Pyridoxine is the only fully effective pharmacologic treatment for toxic isoniazid seizures, although benzodiazepines have been shown to suppress seizure activity in some cases.[25] In seizing female patients of childbearing age, eclampsia may be the cause, and intravenous magnesium is the initial treatment (see Chapter 177). Eclamptic seizures refractory to magnesium may respond to benzodiazepines or barbiturates with or without phenytoin. Children and psychiatric patients at risk for water intoxication may be potential candidates for hypertonic saline therapy, after laboratory confirmation of hyponatremia.

Patients who remain unresponsive to the third-level choice of pharmacologic intervention are by definition in *refractory* status epilepticus. Further choices for therapy are general anesthetic doses of midazolam or propofol, barbiturate coma, and isoflurane anesthesia; all of these treatments necessitate endotracheal intubation.[21,23] A nondepolarizing neuromuscular blocking agent such as rocuronium or vecuronium is administered concomitantly to reduce the metabolic burden and potential hyperthermia that can ensue from prolonged status seizures; continuous electroencephalographic monitoring should be used, if possible, in these cases.

Pivotal Findings

When the patient is stabilized with a secure airway and ictal activity has been controlled, attention is turned to gathering more complete data.

History

History taking in the patient with seizure is directed by two main questions. First, "Was the incident truly a seizure?" This is important because of the broad differential diagnosis for seizures (see Table 18-2) and the frequency of inaccurate descriptions of seizure-like activity from laypersons. In general, ictal events have six properties:

1. *Abrupt onset:* Generalized seizures typically occur without an aura.
2. *Brief duration:* Seizures rarely last longer than 90 to 120 seconds, although bystanders may overestimate the duration.
3. *Loss of consciousness:* Present by definition, except for focal seizures.
4. *Purposeless activity:* For example, automatisms and undirected tonic-clonic movements.
5. *Unprovoked:* Especially with regard to emotional stimuli; fever in children and substance withdrawal in adults are notable exceptions.
6. *Postictal state:* An acute confusion state that typically occurs with all seizure types except focal and absence.

Information regarding focality of onset, loss of bowel or bladder control, or tongue biting should also be elicited. Presence or absence of these findings, however, does not confirm or exclude the possibility that a seizure occurred.

The second question to direct the history is, "Does this patient have a history of seizures?" If there is a documented history of seizures, ED evaluation may be limited to a thorough history and consideration of measurement of anticonvulsant drug levels. History should focus on recent illness or trauma, drug or alcohol use, potential adverse drug-drug interactions with anticonvulsants, medication compliance, a recent change in anticonvulsant dosing regimens, or a change in ictal pattern or characteristics.

www.ketabpezeshki.com 66485457-66963820

Evaluation of injuries sustained during the seizure is also warranted.

Supratherapeutic and toxic levels of some anticonvulsants such as phenytoin and carbamazepine, whether attained chronically or after acute overdose, may *cause* seizures. If empirical anticonvulsant therapy is indicated before the serum level is available, only 50% of a full loading dose is given unless the patient is known reliably not to be taking anticonvulsant medication.

If the patient does not have a history of seizures and the description of the event is truly consistent with a seizure, the history should focus on potential underlying medical, toxicologic, or neurologic causes.

A personal history from the patient, close friend, relative, or medical record may reveal potential ictogenic factors such as recent or remote head trauma, developmental abnormalities, metabolic diseases, drug or alcohol abuse, sleep deprivation, pregnancy, recent travel, previous seizures, or use of herbal supplements. When no witness or family member is available, extensive questioning awaits clearance of the postictal state.

Physical Examination

The physical manifestations of convulsive ictal activity include hypertension, tachycardia, and tachypnea from sympathetic stimulation. These signs typically resolve quickly after the seizure activity ceases. With more prolonged convulsions, skeletal muscle damage, lactic acidosis, and, rarely, frank rhabdomyolysis may ensue. Autonomic discharges and bulbar muscle involvement may result in urinary or fecal incontinence, vomiting (with significant aspiration risk), tongue biting, and airway impairment. All of these signs are helpful discriminators in the differential evaluation of seizure-like spells, although presence or absence of these findings neither confirms nor excludes seizure occurrence.

After the seizure activity has ceased, resting vital signs are evaluated. Fever and underlying infection can cause seizures, although there may be a low-grade temperature elevation immediately after a convulsive generalized seizure. Tachypnea, tachycardia, or an abnormal blood pressure that persists beyond the immediate postictal period may indicate toxic exposure, hypoxia, or a central nervous system lesion. Pertinent physical findings may include nuchal rigidity, stigmata of substance abuse, lymphadenopathy suggestive of human immunodeficiency virus (HIV) disease or malignancy, dysmorphic features, or skin lesions. The examination should also focus on potential adverse sequelae of convulsive seizures, such as head trauma, oral and tongue injury, posterior shoulder dislocation, or back pain.

Finally, a complete neurologic examination is performed. A persistent focal deficit after a seizure (e.g., Todd's paralysis) often indicates the focal origin of the event but also can be evidence of an underlying stroke. The patient should be carefully examined for papilledema; elevated intracranial pressure can both cause and result from ictal activity. Failure to note steady improvement of postictal depression of consciousness suggests the possibility of an underlying encephalopathy or nonconvulsive status epilepticus.

Ancillary Testing

Laboratory. Routine screening studies such as a complete blood count and chemistry profile have little use in the neurologically normal, otherwise healthy, postictal patient with a known seizure disorder for whom a reliable history can be obtained. In patients with new onset of seizure or those with a known seizure disorder but with a significant change in seizure pattern (e.g., a substantial increase in seizure frequency despite medication compliance), limited blood testing is indicated.[5]

Bedside blood glucose levels should be measured in every patient, whether he or she is known to have a seizure disorder or not. Serum sodium is the most important electrolyte to assess, particularly if mental status remains altered after apparent recovery from the postictal state. Anticonvulsant levels are appropriate in patients known or thought to be taking anticonvulsant medication. Febrile patients are evaluated for the source of the fever, including consideration of lumbar puncture. Leukocytosis, with or without bandemia, however, is a common finding after a seizure and is not a reliable indicator of infection. For medically ill adults (e.g., those with diabetes, cancer, or liver disease or those taking medications that can affect serum electrolyte levels) and in patients with a first-time seizure or substantial change in seizure pattern, serum electrolytes, including calcium and magnesium, are indicated. Liver function tests may be helpful if physical examination reveals liver disease or if there is history of liver infection or alcoholism.[11] Directed toxicology screens are performed if substance abuse is suspected, particularly cocaine, amphetamines, and other sympathomimetic agents. Eclampsia occurs late in pregnancy or in the early postpartum period, so pregnancy usually is clinically evident in such cases. Headache may be a feature of the patient's postictal state, but otherwise, presence of fever and headache or sudden onset of headache is an indication for computed tomography (CT) scan, lumbar puncture, or both.[26]

Imaging. When feasible, cranial CT is recommended for patients in the ED with new-onset seizures and is mandatory if neurologic examination identifies focal abnormalities postseizure.[5] Cranial CT is indicated in any age group when there is a possibility of head trauma, elevated intracranial pressure, intracranial mass, persistently abnormal mental status or focal neurologic abnormality, or HIV disease.

In the fully recovered patient without headache and with fully normal mental status and neurologic examination findings who has had a single, brief seizure, a cranial CT scan can be performed in the ED or at a follow-up visit at the discretion of the treating physician.[5] Box 18-1 lists the circumstances under which a head CT is recommended in the ED because of a higher likelihood of discovering an acute abnormality.[5]

The literature on head CT imaging for first-time, nonfebrile seizures in children is inconclusive.[27]

Electroencephalography. Electroencephalography is not consistently available in the ED. It may be particularly useful in specific cases, such as the diagnosis of nonconvulsive status epilepticus, to monitor seizure activity after intubation and neuromuscular blockade, and to help differentiate seizures from other similar presentations. In general, electroencephalograms (EEGs)

Box 18-1 Indications for Cranial Computed Tomography in Patients with Seizure in the Emergency Department

- First seizure
- Acute intracranial process suspected
- History of acute head trauma
- History of malignancy
- Immunocompromised status
- Fever
- Persistent headache
- History of anticoagulation
- New focal neurologic examination
- Age older than 40 years without epilepsy history
- Focal onset before generalization
- Persistently altered mental status

Adapted from ACEP Clinical Policies Committee; Clinical Policies Subcommittee on Seizures: Clinical policy: Critical issues in the evaluation and management of adult patients presenting to the emergency department with seizures. Ann Emerg Med 2004; 43:605-625.

www.ketabpezeshki.com 66485457-66963820

are most appropriate for the follow-up evaluation of patients with first-time seizures without clear cause after a complete ED evaluation.[28]

MANAGEMENT

Usually an acute seizure self-terminates or can be pharmacologically terminated before a need arises for active airway management. Rapidly reversible disorders (e.g., hypoglycemia, hypoxemia, isoniazid ingestion) should be considered and, if found, treated. Primary abortive therapy in the ED is accomplished as described earlier. Although a number of newer antiepileptic medications have become available, their therapeutic purpose is directed toward chronic rather than acute seizures.[29]

Identifying a new-onset seizure in the ED generates consideration for further management. The choice to initiate anticonvulsant therapy depends on the risk of seizure recurrence, any underlying predisposing disease, and the risk of initiating anticonvulsant therapy. Chronic anticonvulsant medication may be advisable, even in the short term, pending further outpatient evaluation, and the decision to initiate this is made in consultation with the neurologist who will be following the patient after discharge from the ED.[30,31] Prompt treatment of any apparent causative disorder discovered in the ED, however, is appropriate.

DISPOSITION

Disposition plans are individualized according to the findings of the ED evaluation and the presence or absence of underlying disease. One quarter of adult patients with seizure-related complaints have new-onset seizures.[10,16] Almost half of them require admission, often because of abnormal CT scans or persistent focal abnormalities; 95% of those who retrospectively required admission are correctly identified through use of an ED evaluation consistent with that recommended previously. Patients may be discharged home with early referral to a neurologist if they have normal neurologic examination findings, no significant medical comorbidities, and no known structural brain disease; do not require the use of an antiepileptic drug or multiple doses of benzodiazepines in the ED; and are felt to have sufficient resources to reliably comply with follow-up instructions.[5] Patients discharged home from the ED should receive appropriate state-specific guidance regarding driver's license privileges, warning about potentially dangerous activities (e.g., swimming, climbing ladders and heights, operating machinery), and information for prompt follow-up with a neurologist.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Chang BS, Lowenstein DH: Epilepsy. *N Engl J Med* 2003; 349:1257-1266.
2. Martindale JL, Goldstein JN, Pallin DJ: Emergency department seizure epidemiology. *Emerg Med Clin North Am* 2011; 29:15-27.
3. Berg AT, et al: Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia* 2010; 51:676-685.
4. Huff JS, Fountain NB: Pathophysiology and definitions of seizures and status epilepticus. *Emerg Med Clin North Am* 2011; 29:1-13.
5. ACEP Clinical Policies Committee; Clinical Policies Subcommittee on Seizures: Clinical policy: Critical issues in the evaluation and management of adult patients presenting to the emergency department with seizures. *Ann Emerg Med* 2004; 43:605-625.
6. Millikan D, Rice B, Silbergleit R: Emergency treatment of status epilepticus: Current thinking. *Emerg Med Clin North Am* 2009; 27:101-113, ix.
7. Bassin S, Smith TL, Bleck TP: Clinical review: Status epilepticus. *Crit Care* 2002; 6:137-142.
8. Hirtz D, et al: Practice parameter: Treatment of the child with a first unprovoked seizure: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2003; 60:166-175.
9. Bui TT, Delgado CA, Simon HK: Infant seizures not so infantile: First-time seizures in children under six months of age presenting to the ED. *Am J Emerg Med* 2002; 20:518-520.
10. Huff JS, Morris DL, Kothari RU, Gibbs MA: Emergency department management of patients with seizures: A multicenter study. *Acad Emerg Med* 2001; 8:622-628.
11. Browne TR, Holmes GL: Epilepsy. *N Engl J Med* 2001; 344:1145-1151.
12. Carreno M: Recognition of nonepileptic events. *Semin Neurol* 2008; 28:297-304.
13. Schmidt D: Syncopes and seizures. *Curr Opin Neurol* 1996; 9:78-81.
14. Bakes KM, Faragher J, Markovchick VJ, Donahoe K, Haukoos JS: The Denver Seizure Score: Anion gap metabolic acidosis predicts generalized seizure. *Am J Emerg Med* 2011; 29:1097-1102.
15. Treiman DM: Treatment of convulsive status epilepticus. *Int Rev Neurobiol* 2007; 81:273-285.
16. Silbergleit R, et al: Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med* 2012; 366:591-600.
17. McMullan J, Sasson C, Pancioli A, Silbergleit R: Midazolam versus diazepam for the treatment of status epilepticus in children and young adults: A meta-analysis. *Acad Emerg Med* 2010; 17:575-582.
18. Manno EM: New management strategies in the treatment of status epilepticus. *Mayo Clin Proc* 2003; 78:508-518.
19. Pryor FM, Gidal B, Ramsay RE, DeToledo J, Morgan RO: Fosphenytoin: Pharmacokinetics and tolerance of intramuscular loading doses. *Epilepsia* 2001; 42:245-250.
20. Hanhan UA, Fiallos MR, Orlowski JP: Status epilepticus. *Pediatr Clin North Am* 2001; 48:683-694.
21. Smith BJ: Treatment of status epilepticus. *Neurol Clin* 2001; 19:347-369.
22. Prasad AN, Seshia SS: Status epilepticus in pediatric practice: Neonate to adolescent. *Adv Neurol* 2006; 97:229-243.
23. Lowenstein DH: The management of refractory status epilepticus: An update. *Epilepsia* 2006; 47(Suppl 1):35-40.
24. Sinha S, Naritoku DK: Intravenous valproate is well tolerated in unstable patients with status epilepticus. *Neurology* 2000; 55:722-724.
25. Minns AB, Ghafouri N, Clark RF: Isoniazid-induced status epilepticus in a pediatric patient after inadequate pyridoxine therapy. *Pediatr Emerg Care* 2010; 26:380-381.
26. Hasbun R, Abrahams J, Jekel J, Quagliarello VJ: Computed tomography of the head before lumbar puncture in adults with suspected meningitis. *N Engl J Med* 2001; 345:1727-1733.
27. Sharma S, Riviello JJ, Harper MB, Baskin MN: The role of emergent neuroimaging in children with new-onset afebrile seizures. *Pediatrics* 2003; 111:1-5.
28. Quigg M, Shneker B, Domer P: Current practice in administration and clinical criteria of emergent EEG. *J Clin Neurophysiol* 2001; 18:162-165.
29. French JA, et al. Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy: Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 2004; 62:1252-1260.
30. Jacoby A, Gamble C, Doughty J, Marson A, Chadwick D: Quality of life outcomes of immediate or delayed treatment of early epilepsy and single seizures. *Neurology* 2007; 68:1188-1196.
31. Marson A, et al: Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: A randomised controlled trial. *Lancet* 2005; 365:2007-2013.

www.ketabpezeshki.com 66485457-66963820

Chapter 19

Dizziness and Vertigo

Andrew K. Chang and Jonathan S. Olshaker

PERSPECTIVE

Dizziness is an extremely common yet complex neurologic symptom that reflects a disturbance of normal balance perception and spatial orientation. An estimated 7.5 million patients with dizziness are seen each year in ambulatory care settings.[1] Dizziness is also one of the most common principal complaints in the emergency department (ED) and is responsible for 2.5% of all ED visits.[2] Among patients older than 60 years, 20% have experienced dizziness severe enough to affect their daily activity.[3]

"Dizziness" is an imprecise descriptor. Patients use the term to describe a variety of experiences, including sensations of motion, weakness, lightheadedness, unsteadiness, and depression. Even clinical experts do not uniformly agree to precise definitions, with some defining it broadly and others more narrowly. Dizziness is historically categorized into one of four categories based on symptom quality: vertigo (illusion of motion, often spinning), near syncope (feeling of impending faint), disequilibrium (loss of equilibrium when walking), and nonspecific dizziness.[4]

Dizziness can be caused by a myriad diseases. In older persons it is associated with a variety of cardiovascular, neurosensory, and psychiatric conditions and with the use of multiple medications.[5] The challenge for the emergency physician is to sift out the rare patient with a dangerous underlying disorder from the many others who have benign causes.

Pathophysiology

The maintenance of equilibrium and awareness of the body in relationship to its surroundings depend on the interaction of the visual, proprioceptive, and vestibular systems. The eyes, muscles, joints, and otic labyrinths continuously supply information to the brain about the position of the body. Visual impulses, mediated through the higher brain centers, provide information about body position in space. Impulses from proprioceptors of the joints and muscles supply data about the relative positions of the parts of the body. Impulses from the neck are of special importance in relating the position of the head to the rest of the body. The sense organs of the visual, vestibular, and proprioceptive systems are connected to the cerebellum by way of the vestibular nuclei in the brainstem. Any disease that interrupts the integration of these three systems may give rise to symptoms of vertigo.

The vestibular apparatus helps maintain head position and stabilize head movement. It is housed in the inner ear, or labyrinth, which lies embedded in the petrous portion of the temporal bone. Here it is vulnerable to trauma, blood-borne toxins, and infections in nearby structures, including the middle ear and meninges. The vestibular apparatus consists of three semicircular canals and two otolithic structures (the utricle and the saccule). The semicircular canals and the utricle are connected to each other and contain endolymph. The semicircular canals provide information about movement and angular momentum, whereas the utricle (via otoliths, which are calcium carbonate particles) provides information about the orientation of the body with respect to gravity.

The semicircular canals are paired (left and right ears) structures that normally respond to motion in a symmetrical manner. With inner ear disease, the resting discharge or the discharge stimulated by motion can be altered in one ear. This alteration produces asymmetrical responses and results in the perception of vertigo. For example, freely moving otoliths that are inappropriately located within the semicircular canals, as in benign paroxysmal positional vertigo (BPPV), can produce positional vertigo as the otoliths move under the influence of gravity.

Impulses leave the vestibular apparatus by the vestibular part of the acoustic nerve (cranial nerve VIII), enter the brainstem just below the pons and anterior to the cerebellum, and proceed to the four vestibular nuclei of the brainstem and to the cerebellum. From there, impulses travel along two pathways that contribute to the clinical manifestations of vertigo: the medial longitudinal fasciculus (MLF) and the vestibulospinal tract. In individuals with healthy vestibular systems, these connections allow the eyes to compensate for body movement in different directions and to maintain a visual axis that is stable with respect to the environment.

Nystagmus occurs when the synchronized vestibular information becomes unbalanced. Typically, it results from unilateral vestibular disease, which causes asymmetrical stimulation of the medial and lateral rectus muscles of the eye. This unopposed activity causes a slow movement of the eyes toward the side of the stimulus, regardless of the direction of deviation of the eyes. The cerebral cortex then corrects for these eye movements and rapidly brings the eyes back to the midline, only to have the process repeated.

By convention, the direction of nystagmus is denoted by the direction of the fast "cortical" component. Nystagmus caused by vestibular disease tends to be unidirectional and horizontorotatory. If the nystagmus is vertical, a central lesion (either brainstem or cerebral) is usually the cause.

The vestibular nuclei send information to the lateral vestibulospinal tract, where they connect with motor neurons that supply the muscles of the extremities. This explains the phenomenon of false steps or other body movements made by people with a defective vestibular apparatus who are attempting to correct for an imagined change in position. Connections between the vestibular nuclei and the autonomic system account for the perspiration, nausea, and vomiting that commonly accompany an attack of

www.ketabpezeshki.com 66485457-66963820

vertigo. Connections between the vestibular nuclei and the cerebellum account for the modulating influence of this organ on motor activity.

DIAGNOSTIC APPROACH

Differential Considerations

It is often helpful to have dizzy patients describe the sensation they are experiencing without using the word *dizzy*. When this is done, one can generally categorize the dizziness into one of four categories: vertigo, near syncope, disequilibrium, and nonspecific dizziness. Vertigo is an illusion of motion, classically described as the room spinning. Some further subdivide this into objective vertigo (external environment is spinning) and subjective vertigo (spinning of self). Near syncope is usually described as feeling faint or lightheaded. Disequilibrium is usually described as an unsteady gait. Nonspecific dizziness is generally thought to be related to anxiety. The validity of this symptom-oriented method of categorizing dizziness has been recently challenged.[6] For some patients, dizziness is simply a metaphor for malaise, representing a variety of causes, such as anemia, viral illness, or depression. The primary focus of this chapter is to provide a framework to differentiate vertigo from other types of dizziness and to identify potentially life-threatening causes of these symptoms.

If the patient has true vertigo, the clinician should determine whether the cause is a peripheral lesion, such as from the vestibular system, or a central process, such as cerebrovascular disease or a neoplasm. In most cases, peripheral disorders are benign, whereas central disorders have more serious consequences. Occasionally, as in the case of a cerebellar hemorrhage, immediate therapeutic intervention is indicated. Acute suppurative labyrinthitis is the only cause of peripheral vertigo that requires urgent intervention. Box 19-1 lists causes of vertigo and identifies the peripheral, central, and systemic diagnoses. Table 19-1 summarizes the different characteristics of peripheral and central vertigo.

Box 19-1 Causes of Vertigo

Peripheral Causes
Benign paroxysmal positional vertigo (BPPV)
Vestibular neuritis (or neuronitis)
Labyrinthitis (suppurative, serous, toxic, chronic)
Ménière's disease
Foreign body in ear canal
Acute otitis media
Perilymphatic fistula
Trauma (labyrinth concussion)
Motion sickness
Acoustic neuroma*

Central Causes
Infection (encephalitis, meningitis, brain abscess)
Vertebral basilar artery insufficiency
Subclavian steal syndrome
Cerebellar hemorrhage or infarction
Vertebral basilar migraine
Post-traumatic injury (temporal bone fracture)
Postconcussive syndrome
Temporal lobe epilepsy
Tumor
Multiple sclerosis

Systemic Causes
Diabetes mellitus
Hypothyroidism

*Cause of peripheral vertigo that proceeds centrally.

Pivotal Findings

History

The medical history is used to determine if true vertigo exists. Although usually described as the environment spinning, any sensation of disorientation in space or sensation of motion can qualify as vertigo. Some nausea, vomiting, pallor, and perspiration accompany almost all but the mildest forms of vertigo. A sensation of imbalance often accompanies vertigo, and this can be extremely difficult to distinguish from true instability until after the patient's symptoms have been reduced by treatment. True instability, disequilibrium, or ataxia indicates a higher likelihood of a central process.[7] Because the labyrinth has no effect on the level of consciousness, the patient should not have an associated change in mentation or syncope.

The *time of onset* and the *duration of vertigo* are important clues to the cause. Episodic vertigo that is severe, lasts up to several hours, and has symptom-free intervals between episodes suggests a peripheral labyrinth disorder. Vertigo produced primarily by a change in position also suggests a peripheral disorder, usually BPPV.

The presence of *auditory symptoms* suggests a peripheral cause of the vertigo, as in middle and inner ear problems. The ear with abnormal hearing is usually on the side of end-organ disturbance. Although vertigo can occur with acoustic neuroma, it is usually a progressive unilateral hearing loss, typically of several months' duration, that prompts the patient with acoustic neuroma to seek medical attention. Hearing loss, vertigo, and tinnitus form the characteristic triad of Ménière's disease.

Head injury can cause vertigo occasionally from intracerebral injury and more commonly from labyrinth concussion. Neck injury can cause vertigo from vertebral artery dissection, resulting in posterior circulation ischemia.[8]

Vestibular neuritis and labyrinthitis are very similar, though in labyrinthitis hearing is affected. Patients often develop continuous vertigo that can be worsened by movement and may take several months to fully resolve.

Are there associated neurologic symptoms? The patient or family members should be questioned about the time of onset of ataxia or gait disturbances. Ataxia of recent and relatively sudden onset suggests cerebellar hemorrhage or infarction in the distribution of the posterior inferior cerebellar artery or the superior cerebellar artery. Ataxia that is slowly progressive suggests chronic cerebellar

Table 19-1 Characteristics of Peripheral and Central Vertigo

CHARACTERISTIC	PERIPHERAL	CENTRAL
Onset	Sudden	Gradual or sudden
Intensity	Severe	Mild
Duration	Usually seconds or minutes; occasionally hours, days (intermittent)	Usually weeks, months (continuous) but can be seconds or minutes with vascular causes
Direction of nystagmus	One direction (usually horizontorotary)	Vertical, downbeating
Effect of head position	Worsened by position, often single critical position	Little change, associated with more than one position
Associated neurologic findings	None	Usually present
Associated auditory findings	May be present, including tinnitus	None

www.ketabpezeshki.com 66485457-66963820

disorders. True ataxia may be difficult to discern from the unsteadiness that occurs when a patient with significant vertigo attempts to walk, though other findings such as nystagmus and dysmetria can often help narrow the differential diagnosis. The symptom of imbalance raises the likelihood of TIA and stroke. Isolated vertigo can be the only initial symptom of cerebellar and other posterior circulation bleeds, transient ischemic attacks (TIAs), and infarction.[9,10] One study showed that emergency physicians often did not make the correct diagnosis in patients with validated strokes or TIAs whose presenting symptom was only vertigo.[7] Identifying these individuals is a significant and important challenge for clinicians taking care of vertiginous patients. The vast majority of patients with isolated dizziness do not have TIA or stroke, but the risk of not identifying the few who do is significant for ultimate patient outcomes. Stroke has been seen in 3.2% of patients with dizziness syndrome, but only 0.7% of those with isolated dizziness had a stroke.[7] A recent study also showed that fewer than 1 in 500 patients discharged with a diagnosis of dizziness or vertigo experienced a major vascular event in the month after discharge.[11]

Past Medical History. Older age, male sex, hypertension, coronary heart disease, diabetes, and atrial fibrillation are examples of diseases that put patients at higher risk for TIA and stroke. It is important to identify what medications patients are taking, because many have direct vestibulotoxicity. The most commonly encountered are the aminoglycosides, anticonvulsants, alcohols, quinine, quinidine, and minocycline. Daily consumed substances such as caffeine and nicotine, which are not often thought of as medications, can have wide-ranging autonomic effects that may exacerbate vestibular symptoms.

Physical Examination

Vital Signs. Presence of hypotension suggests near syncope as the cause of dizziness. When subclavian steal syndrome, which also can cause vertebrobasilar insufficiency (VBI), is suspected, the pulse and blood pressure should be checked on both sides.

Head and Neck. Carotid or vertebral artery bruits suggest atherosclerosis and risk for TIA or stroke. The vertebral artery can be auscultated in the supraclavicular region.

Accumulation of fluid in the middle ear as a result of a middle ear infection may cause mild vertigo, as can occlusion of the eustachian tubes associated with an upper respiratory tract infection or descent barotrauma. A perforated or scarred eardrum may indicate a perilymphatic fistula, especially if the history includes previous trauma.

Examination of the eyes is key in assessing a patient with vertigo. Pupillary abnormalities may indicate third cranial nerve or descending sympathetic tract involvement. Papilledema suggests increased intracranial pressure. Extraocular movements should be assessed carefully because relatively subtle ocular movement abnormalities can be the only clue to a cerebellar hemorrhage. A sixth cranial nerve palsy ipsilateral to the hemorrhage may result from early brainstem compression by the expanding hematoma. Internuclear ophthalmoplegia, which indicates brainstem pathology, is recognized when the eyes are in a normal position on straight-ahead gaze, but on eye movement the adducting eye (cranial nerve III) is weak or shows no movement while the abducting eye (cranial nerve VI) moves normally, although often displaying a coarse nystagmus. This finding indicates an interruption of the MLF on the side of the third cranial nerve weakness and is virtually pathognomonic of multiple sclerosis.

Abnormal nystagmus is the cardinal sign of inner ear disease and the principal objective evidence of abnormal vestibular function. In nystagmus, the patient has difficulty maintaining the conjugate deviation of the eyes or has a postural control imbalance of eye movements.

The abnormal jerk nystagmus of inner ear disease consists of slow and quick components. The eyes slowly "drift" in the direction of the diseased, hypoactive ear, then quickly jerk back to the intended direction of gaze. Positional nystagmus, induced by changing the position of the head, strongly suggests an organic vestibular disorder, typically BPPV. Central nervous system causes of nystagmus are considered when the pattern of nystagmus is purely vertical, downbeating (fast phase beating toward the nose, or nonfatigable) or when the nystagmus is neither provoked nor relieved by repositioning maneuvers. The characteristics of nystagmus are one of the most valuable tools for distinguishing peripheral from central causes of vertigo (Table 19-2).

Table 19-2 Distinguishing Characteristics of Nystagmus with Central and Peripheral Vertigo

CHARACTERISTIC	CENTRAL	PERIPHERAL
Direction	Can be any direction, downbeating (fast phase beats toward nose)	Horizontal or horizontorotary, upbeating (fast phase beats toward forehead)
Position testing effects		
Latency	Short	Long
Duration	Sustained	Transient
Intensity	Mild	Mild to severe
Fatigability	Nonfatigable	Fatigable
Effect of visual fixation	Not suppressed, may be enhanced	Suppressed

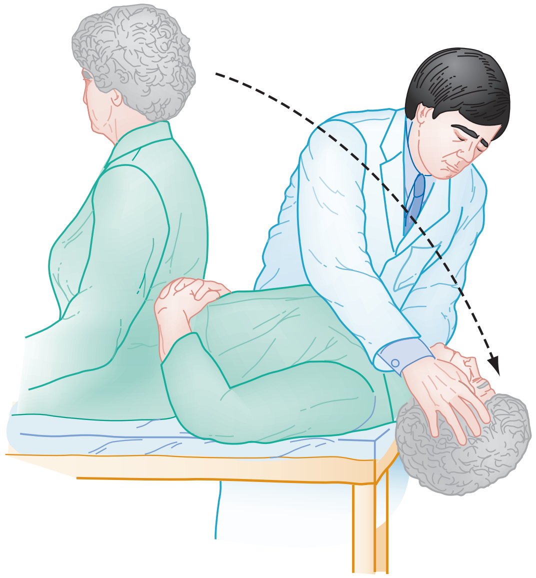


Figure 19-1. Testing for positional vertigo and nystagmus.

Positional Testing. Positional testing can confirm the diagnosis of some causes of peripheral vertigo. The Hallpike test,[12] also known as the Dix-Hallpike test or the Nylen-Barany test, confirms the diagnosis of posterior canal BPPV. The head is turned 45 degrees to one side and then the patient is moved from an upright seated position to a supine position with the head overhanging the edge of the gurney (Fig. 19-1). The eyes are observed for nystagmus, and the patient is queried for the occurrence of vertigo. The patient is then brought back up to the seated position and the test is repeated with the head turned 45 degrees to the other side. In general, if the patient has posterior canal BPPV, only one side should be positive, and this indicates the involved side. Once the diagnosis has been confirmed, the patient can be treated with the Epley maneuver (see later). If the Hallpike test result is negative or seems to be positive bilaterally, one can use the roll test to test for the horizontal canal variant of BPPV. Unlike in the Hallpike

www.ketabpezeshki.com 66485457-66963820

test, the head does not need to overhang the edge of the gurney, and the patient will have reproduction of symptoms and horizontal nystagmus with the head turned in either direction. In the roll test the patient lies flat on the gurney (unlike the Hallpike test, the head does not need to overhang the edge of the gurney) and the examiner turns the patient's head up to 90 degrees to one side. If the otoliths are located in the horizontal canal, the patient will develop vertigo and horizontal nystagmus. The examiner then turns the head to the other side. Again, if otoliths are located in the horizontal canal, the patient will develop vertigo and horizontal nystagmus (note that the direction of the nystagmus will change). Thus, unlike the patient with posterior canal BPPV, the patient with horizontal canal BPPV will have reproduction of symptoms and horizontal nystagmus with the head turned in either direction. The side that is involved is the one with the more violent symptoms and more dramatic nystagmus. The horizontal canal variant of BPPV can be treated with the "barbecue roll" (see later).

The head thrust, or head impulse test, is used to diagnose vestibular neuritis and labyrinthitis.[13] The physician stands face to face with the patient and places both hands on the sides of the patient's head. The patient stares at the examiner's nose while the examiner rapidly turns the patient's head approximately 10 degrees to one side. Normally the patient's eyes should keep focusing on the examiner's nose. If there is a problem with the vestibular nerve, the eyes will temporarily move along with the head. A corrective saccade will then occur, in which the eyes jerk back toward the midline. If a saccade is seen, this denotes a positive head-thrust test result and indicates vestibular nerve dysfunction and confirms the diagnosis of vestibular neuritis.

Neurologic Examination. The presence of cranial nerve deficits suggests a space-occupying lesion in the brainstem or cerebellopontine angle. The corneal reflex is a sensory cranial nerve V and motor cranial nerve VII circuit. Its diminution or absence can be one of the early signs of an acoustic neuroma, which is a slow-growing tumor of the vestibular-cochlear nerve (the eighth cranial nerve). Acoustic neuromas rarely manifest with vertigo and instead typically manifest with sensorineural hearing loss. The Rinne and Weber tests are used in patients with hearing loss. In the Rinne test, which tests for conductive hearing loss, a vibrating tuning fork is held against the mastoid bone. Once the patient can no longer hear the sound from the tuning fork, the tuning fork is moved toward the ear. If there is no conductive hearing loss, the patient will be able to hear the tuning fork. With acoustic neuroma, the result of the Rinne test is normal (the patient can still hear the tuning fork), though both air and bone conduction are reduced as compared with someone who does not have an acoustic neuroma. In the Weber test, which tests for sensorineural hearing loss, a vibrating tuning fork is held against the middle of the forehead. If there is no sensorineural hearing loss, the sound is heard equally in both ears. In patients with acoustic neuroma, the sound will localize to the normal ear. Seventh cranial nerve involvement (e.g., Bell's palsy) causes facial palsy that affects the entire side of the face. In supranuclear facial paralysis, the forehead is spared because these muscles receive bilateral cortical innervation.

The patient is evaluated specifically for evidence of cerebellar dysfunction. This examination is performed when the patient is both sitting and standing because truncal ataxia may become obvious only when the patient has to sit, stand, or walk unaided. Dysmetria is the inability to arrest a muscular movement at the desired point and should be assessed with finger-to-finger or finger-to-nose pointing. Dysdiadochokinesia (an inability to perform coordinated muscular movement smoothly) is assessed with rapid alternating movements. Gait is evaluated when the patient gives a history suggesting ataxia, although examination may be impossible during an attack of vertigo. Any marked abnormality (e.g., consistent falling or a grossly abnormal gait) should suggest a central lesion, especially in a patient whose vertiginous symptoms have subsided. The main features of a cerebellar gait are a wide base (separation of legs), unsteadiness, irregularity of steps, tremor of the trunk, and lurching from side to side. The unsteadiness is most prominent on arising quickly from a sitting position, turning quickly, or stopping suddenly while walking. Patients with gait ataxia cannot perform heel-to-toe walking.

Ancillary Testing

Most routine laboratory testing is not helpful in the evaluation of a vertiginous patient except for a finger-stick blood glucose test.[14] Blood counts and blood chemistries are sometimes helpful when it is difficult to distinguish whether "dizziness" is vertigo or near syncope. An electrocardiogram should be obtained if there is a possibility of myocardial ischemia or dysrhythmia.

Radiologic Imaging. A cross-sectional study of the National Hospital Ambulatory Medical Care Survey (NHAMCS) suggests significant overuse of computed tomography (CT) in low-risk patients.[15] Risk factor assessment and symptom patterns can be extremely helpful in deciding which patients warrant imaging and admission. Older age, male sex, hypertension, coronary artery disease, diabetes, and atrial fibrillation put patients at higher risk for more serious causes of dizziness and vertigo.

If cerebellar hemorrhage, cerebellar infarction, or other central lesions are suggested, emergent CT or magnetic resonance imaging (MRI) of the brain is indicated. MRI, when available, has become the diagnostic modality of choice when cerebellar processes other than acute hemorrhage are possible. MRI is particularly useful for the diagnosis of acoustic neuromas and for sclerotic and demyelinating lesions of the white matter, as seen in multiple sclerosis. Acute vertigo by itself does not warrant urgent CT or MRI in all patients, particularly patients in whom a clear picture of peripheral vertigo emerges. But as mentioned earlier, many studies strongly support the use of imaging in patients of advanced age or at risk for cerebrovascular disease.[7,9,16] CT, although often useful for identifying hemorrhage, is insensitive for acute stroke presentations, especially for infarction within the posterior fossa. MRI with magnetic resonance angiography (MRA) is considered a much more sensitive modality and should be performed quickly in patients with changing neurologic signs and symptoms, suggesting impending posterior circulation occlusion.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for other peripheral, central, and systemic causes of vertigo is large (see Box 19-1). More detailed information is given on selected causes in Table 19-3, including the most common peripheral causes of true vertigo: BPPV, vestibular neuritis, labyrinthitis, and Ménière's disease.

Diagnostic Algorithm

Most cases of vertigo are of peripheral origin and are not usually life-threatening. The diagnostic approach focuses on identifying entities that either immediately or in the near future can lead to death or significant morbidity (Fig. 19-2).

MANAGEMENT

Management is based on an accurate diagnosis that distinguishes the serious central causes of vertigo from the less serious, albeit more debilitating, peripheral causes (Fig. 19-3). Any suggestion of cerebellar hemorrhage warrants immediate imaging with CT or MRI and neurosurgery consultations. VBI should be considered in any patient of advanced age or at high risk of cerebrovascular disease with isolated, new-onset vertigo without an obvious cause.[17,18] Because of the possibility of progression of new-onset VBI in the first 24 to 72 hours, hospital or observation unit

www.ketabpezeshki.com 66485457-66963820

Table 19-3 Differential Diagnosis of Patients with True Vertigo

CAUSE	HISTORY	ASSOCIATED SYMPTOMS	PHYSICAL
Peripheral			
1. Benign paroxysmal positional vertigo	Short-lived, positional, fatigable episodes.	Nausea, vomiting.	Single position can precipitate vertigo. Positive result on Hallpike test (posterior semicircular canal) or Roll test (horizontal canal).
2. Labyrinthitis			
A. Serous	Mild to severe positional symptoms. Usually coexisting or antecedent infection of ear, nose, throat, or meninges.	Mild to severe hearing loss can occur.	Usually nontoxic patient with minimal fever elevation.
B. Acute suppurative	Coexisting acute exudative infection of the inner ear. Severe symptoms.	Usually severe hearing loss, nausea, vomiting.	Febrile patient showing signs of toxicity. Acute otitis media.
C. Toxic	Gradually progressive symptoms: Patients on medication causing toxicity.	Hearing loss that may become rapid and severe, nausea and vomiting.	Hearing loss. Ataxia common feature in chronic phase.
3. Ménière's disease	Recurrent episodes of severe rotational vertigo usually lasting hours. Onset usually abrupt. Attacks may occur in clusters. Long symptom-free remissions.	Nausea, vomiting, tinnitus, hearing loss.	Positional nystagmus not present.
4. Vestibular neuritis	Sudden onset of severe vertigo, increasing in intensity for hours, then gradually subsiding over several days but can last weeks to months. Can be worsened with positional change. Sometimes history of infection or toxic exposure that precedes initial attack. Highest incidence is found in third and fifth decades.	Nausea, vomiting. Auditory symptoms do not occur.	Spontaneous nystagmus toward the involved ear may be present.
5. Acoustic neuroma	Gradual onset and increase in symptoms. Neurologic signs in later stages. Most occur in women aged 30 to 60.	Hearing loss, tinnitus. True ataxia and neurologic signs as tumor enlarges.	Unilateral decreased hearing. True truncal ataxia and other neurologic signs when tumor enlarges. May have diminution or absence of corneal reflex. Eighth cranial nerve deficit may be present.
Central			
1. Vascular disorders			
A. Vertebrobasilar insufficiency	Should be considered in any patient of advanced age with isolated new-onset vertigo without an obvious cause. More likely with history of atherosclerosis. Can occur with neck trauma. Initial episode usually lasts seconds to minutes.	Often headache. Usually neurologic symptoms including dysarthria, ataxia, weakness, numbness, double vision. Tinnitus and deafness uncommon.	Neurologic deficits usually present, but initially neurologic examination can be normal.
B. Cerebellar hemorrhage	Sudden onset of severe symptoms.	Headache, vomiting, ataxia.	Signs of toxicity. Dysmetria, true ataxia. Ipsilateral sixth cranial nerve palsy may be present.
C. Occlusion of posterior inferior cerebellar artery (Wallenberg's syndrome)	Vertigo associated with significant neurologic complaints.	Nausea, vomiting, loss of pain and temperature sensation, ataxia, hoarseness.	Loss of pain and temperature sensation on the side of the face ipsilateral to the lesion and on the opposite side of the body, paralysis of the palate, pharynx, and larynx. Horner's syndrome (ipsilateral ptosis, miosis, and decreased facial sweating).
2. Head trauma	Symptoms begin with or shortly after head trauma. Positional symptoms most common type after trauma. Self-limited symptoms that can persist weeks to months.	Usually mild nausea.	Occasionally, basilar skull fracture.

www.ketabpezeshki.com 66485457-66963820

Table 19-3 Differential Diagnosis of Patients with True Vertigo—cont'd

CAUSE	HISTORY	ASSOCIATED SYMPTOMS	PHYSICAL
3. Vertebrobasilar migraine	Vertigo almost always followed by headache. Patient has usually had similar episodes in past. Most patients have a family history of migraine. Syndrome usually begins in adolescence.	Dysarthria, ataxia, visual disturbances, or paresthesias usually precede headache.	No residual neurologic or otologic signs are present after attack.
4. Multiple sclerosis	Vertigo presenting symptom in 7-10% and appears in the course of the disease in a third. Onset may be severe and suggest labyrinth disease. Disease onset usually between ages 20 and 40. Often history of other attacks with varying neurologic signs or symptoms.	Nausea and vomiting, which may be severe.	May have horizontal, rotary, or vertical nystagmus. Nystagmus may persist after the vertiginous symptoms have subsided. Bilateral internuclear ophthalmoplegia and ataxic eye movements suggest multiple sclerosis.
5. Temporal lobe epilepsy	Can be initial or prominent symptom in some patients with the disorder.	Memory impairment, hallucinations, trancelike states, seizures.	May have aphasia or convulsions.
6. Hypoglycemia	Should be considered in diabetics and any other patient with unexplained symptoms.	Sweating, anxiety.	Tachycardia, mental status change may be present.

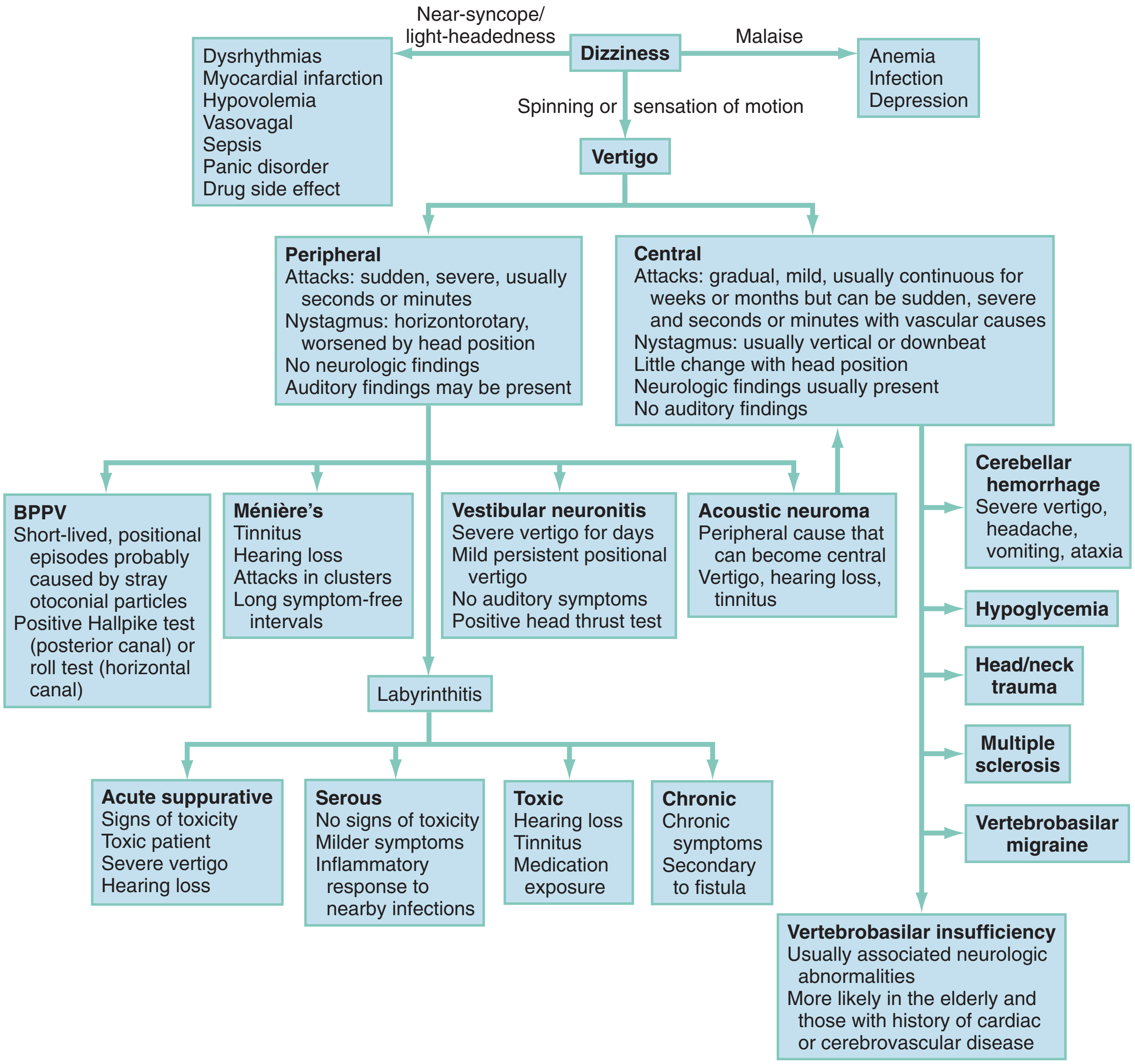


Figure 19-2. Diagnostic algorithm for dizziness and vertigo. *BPPV,* benign paroxysmal positional vertigo.

www.ketabpezeshki.com 66485457-66963820

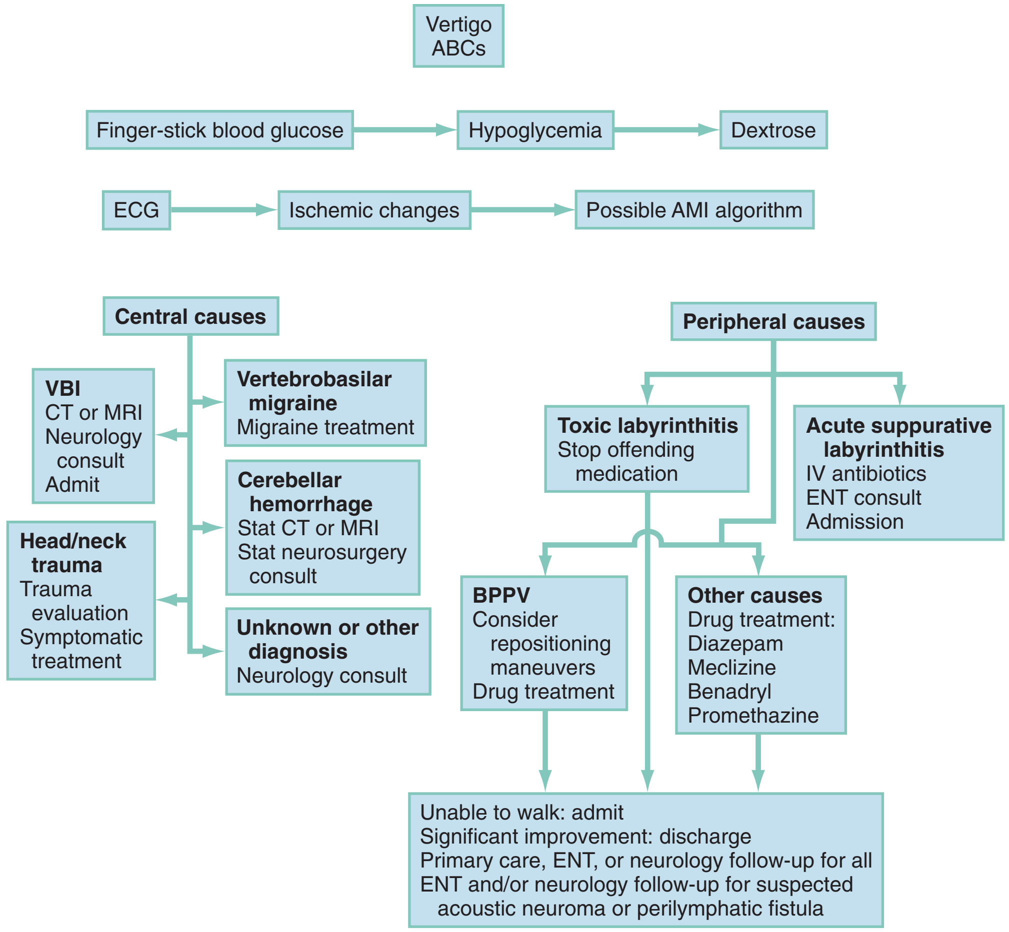


Figure 19-3. Management algorithm for vertigo. *AMI,* acute myocardial infarction; *BPPV,* benign paroxysmal positional vertigo; *CT,* computed tomography; *ECG,* electrocardiogram; *ENT,* ear, nose, and throat; *MRI,* magnetic resonance imaging; *VBI,* vertebrobasilar insufficiency.

admission and consideration of early MRA are reasonable, even in a stable patient. Changing or rapidly progressive symptoms suggest impending posterior circulation occlusion. If CT or MRI excludes hemorrhage as the source of the patient's symptoms, an immediate neurologic consultation, emergency angiography, and possible anticoagulation are indicated.

Acute bacterial labyrinthitis (see Table 19-3) requires hospital admission, intravenous antibiotics, and, occasionally, surgical drainage and débridement. In cases of toxic labyrinthitis, the offending medication is discontinued immediately.

Some cases of Ménière's disease have been treated successfully with vasodilation and diuretic therapy. Diets low in sodium and caffeine and cessation of smoking also have been helpful. Chemical ablation of vestibular function with gentamicin and streptomycin is an option in severe Ménière's disease.

Vestibular neuritis is often thought of as similar to Bell's palsy. A large multicenter randomized clinical trial[19] showed that corticosteroids were helpful in the treatment of vestibular neuritis but antivirals, such as acyclovir, were not. In this study a 22-day taper of methylprednisolone was used beginning with a dose of 100 mg each morning.

Canalith repositioning procedures, such as the Epley maneuver, are extremely effective in treating BPPV.[20,21] The Epley maneuver involves sequential rotations of the head, holding each position for approximately 30 seconds, as demonstrated in Figure 19-4. The "barbecue roll"[22] is a simple maneuver that can be used to treat the horizontal canal variant of BPPV (diagnosed by the roll test). The patient lies flat on the gurney with the head turned 90 degrees to the involved side. The head is then rotated in 45-degree intervals away from the involved side (each turn is held approximately 30 seconds or until nystagmus and vertigo resolve). Eventually the patient needs to turn over into the prone position. The maneuver is completed once the head has returned to the original starting position.

Two relatively recent practice guidelines were published that included information on the use of medications to treat BPPV. One found no evidence to support a recommendation of any medication in the routine treatment of BPPV.[23] The other concluded that clinicians should not routinely treat BPPV with vestibular suppressant medications. However, both guidelines were from specialty societies whose patients often have chronic and likely milder forms of BPPV than patients who develop acute BPPV and come to the ED. For ED patients who either fail canalith repositioning maneuvers or are actively vomiting and/or too symptomatic to undergo repositioning maneuvers, it is reasonable to administer vestibular suppressants. The most commonly used are the antiemetic medications, which not only suppress nausea and vomiting but also decrease the sensation of vertigo. Although promethazine (Phenergan) is likely the most effective parenteral vestibular suppressant, the U.S. Food and Drug Administration (FDA) recently gave intravenous use of promethazine a black box warning, and it is now recommended to be administered only in intramuscular or oral forms. Intravenous ondansetron is an effective alternative parenteral vestibular suppressant.[24] Intravenous metoclopramide is not thought to be helpful with acute vertigo, and there is controversy as to whether intravenous prochlorperazine is effective. Patients with intractable vertigo and vomiting that are unresponsive to antiemetics can be given an

www.ketabpezeshki.com 66485457-66963820

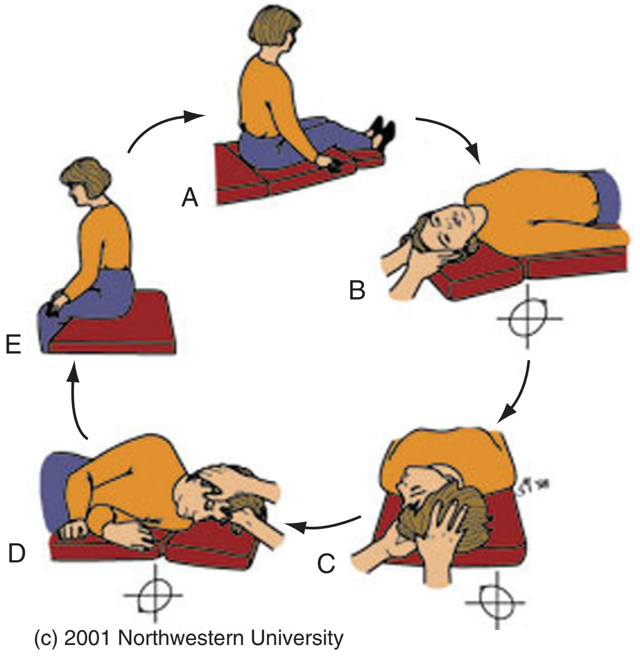


Figure 19-4. The Epley maneuver for benign paroxysmal peripheral vertigo, also known as the *particle repositioning* or *canalith repositioning procedure.* (Image used with permission of Timothy C. Hain, Professor of Neurology, Feinberg School of Medicine, Northwestern University, www.dizziness-and-balance.com/disorders/bppv/bppv.html.)

intravenous benzodiazepine, such as intravenous diazepam. However, it is generally recommended not to discharge patients with oral benzodiazepines because their use can interfere with the process of vestibular habituation, in which the vestibular system learns to adapt to the mismatch of information it is receiving.

Meclizine (Antivert) is the primary oral medication for ambulatory treatment of acute BPPV. It is usually prescribed as 25 mg every 6 to 8 hours as needed. This medication can exacerbate symptoms in patients with nonvertiginous types of dizziness, such as near syncope or disequilibrium, so the physician should be reasonably confident of the diagnosis of BPPV before prescribing meclizine. Transdermal scopolamine has shown disappointing results for treatment of peripheral vertigo but may be considered a third-line option.

Most patients with vertigo have self-limited disease processes that have a specific organic cause. With patient education combined with reassurance and judicious use of medications, the treatment of a dizzy patient can be rewarding for the patient and the physician.

DISPOSITION

Documented or suspected cerebellar hemorrhage or infarction, VBI, and acute bacterial labyrinthitis require diagnostic evaluation, treatment, and, usually, hospitalization. In patients older than age 55, particularly patients with vascular disease, admission for observation and imaging of cerebral vasculature should be considered if the diagnosis of BPPV is uncertain. Most younger patients with peripheral causes of vertigo can be discharged from the ED after symptoms have been controlled. Some patients may have such severe symptoms (e.g., intractable vomiting, inability to walk) despite medications that they require hospital admission for observation status for intravenous hydration, vestibular suppressants, and antiemetics. Reassessment of neurologic examination findings and response to therapy are important to ensure that the vertigo is not of central origin. Discharged patients should receive primary care, neurology, or otolaryngology follow-up, particularly if symptoms are not significantly improved within 72 hours or are worsening despite symptomatic treatment.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Burt CW, Schappert SM: Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 1999-2000. *Vital Health Stat* 2004; 157:1-70.
2. Kerber KA, Meurer WJ, West BT, Fendrick AM: Dizziness presentations in U.S. emergency departments, 1995-2004. *Acad Emerg Med* 2008; 15:744-750.
3. Lawson J, Fitzgerald J, Birchall J, Aldren CP, Kenny RA: Diagnosis of geriatric patients with severe dizziness. *J Am Geriatr Soc* 1999; 47:12-17.
4. Drachman DA, Hart CW: An approach to the dizzy patient. *Neurology* 1972; 22:323-334.
5. Sloane PD, Coeytaux RR, Beck RS, Dallara J: Dizziness: State of the science. *Ann Intern Med* 2001; 134:823-832.
6. Newman-Toker DE, et al: Imprecision in patient reports of dizziness symptom quality: A cross-sectional study conducted in an acute care setting. *Mayo Clin Proc* 2007; 82:1329-1340.
7. Kerber KA, Brown DL, Lisabeth LD, Smith MA, Morgenstern LB: Stroke among patients with dizziness, vertigo, and imbalance in the emergency department: A population-based study. *Stroke* 2006; 37:2484-2487.
8. Young YH, Chen CH: Acute vertigo following cervical manipulation. *Laryngoscope* 2003; 113:659-662.
9. Lee H, et al: Cerebellar infarction presenting isolated vertigo: Frequency and vascular topographical patterns. *Neurology* 2006; 67:1178-1183.
10. Son EJ, Bang JH, Kang JG: Anterior inferior cerebellar artery infarction presenting with sudden hearing loss and vertigo. *Laryngoscope* 2007; 117:556-558.
11. Kim AS, Fullerton HJ, Johnston SC: Risk of vascular events in emergency department patients discharged home with diagnosis of dizziness or vertigo. *Ann Emerg Med* 2011; 57:34-41.
12. Halker RB, Barrs DM, Wellik KE, Wingerchuk DM, Demaerschalk BM: Establishing a diagnosis of benign paroxysmal positional vertigo through the Dix-Hallpike and side-lying maneuvers: A critically appraised topic. *Neurologist* 2008; 14:201-204.
13. Weber KP, et al: Head impulse test in unilateral vestibular loss: Vestibulo-ocular reflex and catch-up saccades. *Neurology* 2008; 70:454-463.
14. Herr RD, Zun L, Mathews JJ: A directed approach to the dizzy patient. *Ann Emerg Med* 1989; 18:664-672.
15. Newman-Toker DE, et al: Spectrum of dizziness visits to U.S. emergency departments: Cross-sectional analysis from a nationally representative sample. *Mayo Clin Proc* 2008; 83:765-775.
16. Gizzi M, Riley E, Molinari S: The diagnostic value of imaging the patient with dizziness. A Bayesian approach. *Arch Neurol* 1996; 53:1299-1304.
17. Norrving B, Magnusson M, Holtas S: Isolated acute vertigo in the elderly; vestibular or vascular disease? *Acta Neurol Scand* 1995; 91:43-48.
18. Rathore SS, Hinn AR, Cooper LS, Tyroler HA, Rosamond WD: Characterization of incident stroke signs and symptoms: Findings from the atherosclerosis risk in communities study. *Stroke* 2002; 33:2718-2721.
19. Strupp M, et al: Methylprednisolone, valacyclovir, or the combination for vestibular neuritis. *N Engl J Med* 2004; 351:354-361.
20. Chang AK, Schoeman G, Hill M: A randomized clinical trial to assess the efficacy of the Epley maneuver in the treatment of acute benign positional vertigo. *Acad Emerg Med* 2004; 11:918-924.
21. Hilton M, Pinder D: The Epley (canalith repositioning) manoeuvre for benign paroxysmal positional vertigo. *Cochrane Database Syst Rev* 2004; 2:CD003162.
22. Escher A, Ruffieux C, Maire R: Efficacy of the barbecue manoeuvre in benign paroxysmal vertigo of the horizontal canal. *Eur Arch Otorhinolaryngol* 2007; 264:1239-1241.
23. Fife TD, et al: Practice parameter: Therapies for benign paroxysmal positional vertigo (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2008; 70:2067-2074.
24. Bhattacharyya N, et al: Clinical practice guideline: Benign paroxysmal positional vertigo. *Otolaryngol Head Neck Surg* 2008; 139:S47-S81.

www.ketabpezeshki.com 66485457-66963820

Chapter 20

Headache

Christopher S. Russi

PERSPECTIVE

Epidemiology

Up to 85% of the U.S. adult population reports significant headaches at least occasionally, and 15% does so on a regular basis. Headache as a primary complaint represents 3 to 5% of all emergency department (ED) visits. The vast majority of patients who have a primary complaint of headache do not have a serious medical cause for the problem. Tension headache accounts for approximately 50% of patients visiting the ED, another 30% have headache of unidentified origin, 10% have migraine-type pain, and 8% have headache from other potentially serious causes (e.g., tumor, glaucoma). It is estimated that less than 1% of patients who come to the ED with headache have a life-threatening organic disease.[1] These percentages can create a false sense of security, and headache is disproportionately represented in emergency medicine malpractice claims. Although still rare, the most commonly encountered life-threatening cause of severe sudden head pain is subarachnoid hemorrhage (SAH); approximately 20,000 potentially salvageable cases of SAH are seen in EDs each year. It is estimated that 25 to 50% of these are missed on the first presentation to a physician.[2] The other significant, potentially life-threatening causes of headache occur even less frequently. Meningitis, carbon monoxide poisoning, temporal arteritis, acute angle-closure glaucoma, intracranial hemorrhage (ICH), cerebral venous sinus thrombosis, and increased intracranial pressure can often be linked with specific historical elements and physical findings that facilitate their diagnosis.

Pathophysiology

The brain parenchyma is insensitive to pain. The pain-sensitive areas of the head include the coverings of the brain (the meninges), the blood vessels (both arteries and veins supplying the brain) and the various tissues lining the cavities within the skull. The ability of the patient to specifically localize head pain is often poor. Much of the pain associated with headache, particularly with vascular headache and migraines, is mediated through the fifth cranial nerve. Such pain may proceed back to the nucleus and then be radiated through various branches of the fifth cranial nerve to areas not directly involved. A specific inflammation in a specific structure (e.g., periapical abscess, sinusitis, or tic douloureux) is much easier to localize than the relatively diffuse pain that may be generated by tension or traction headaches. Pains in the head and neck may easily overlap. They should be thought of as a unit when complaints of headache are considered.

DIAGNOSTIC APPROACH

Differential Considerations

The differential diagnosis of headache is complex because of the large number of potential disease entities and the diffuse nature of many types of pain in the head and neck region (Table 20-1). However, in evaluating the patient with a headache complaint, the top priority is to exclude the life-threatening causes: SAH and ICH, meningitis, encephalitis, and mass lesions. Carbon monoxide is an exogenous toxin, the effects of which may be reversible by removing the patient from the source and administering oxygen. Carbon monoxide poisoning is a rare example of a headache in which relatively simple interventions may quickly improve a critical situation. On the contrary, returning the patient to the poisoned environment without a diagnosis could be lethal.

Rapid Assessment and Stabilization

If the patient is in a critical or comatose state, initial stabilization, including airway management, is prioritized and, if at all possible, preceded by a neurologic examination. For purposes of the initial assessment, headache can be divided into two categories: accompanied by altered mental status and without altered mental status. Whenever a patient's mental status is impaired, brain tissue is initially assumed to be compromised. The principles of care centered on cerebral resuscitation address the seven major causes of evolving brain injury: lack of substrate (glucose, oxygen), cerebral edema, intracranial mass lesion, endogenous or exogenous toxins, metabolic alterations (fever, seizure), ischemia, or elevated intracranial pressure.

Pivotal Findings

History

The history is the pivotal part of the workup for the patient with headache (Table 20-2).

1. The patient should be asked to describe the *pattern and onset of the pain.* Patients often relate having had frequent and recurrent headaches similar to the one they have on the current ED visit. A marked variation in headache pattern can signal a new or serious problem. The rate of onset of pain may have significance. Pain with rapid onset of a few seconds to minutes is more likely to be vascular in origin than pain that developed over several hours or days. However, a slow onset should not be solely

www.ketabpezeshki.com 66485457-66963820

Table 20-1 Differential Diagnosis

ORGAN SYSTEM	CRITICAL DIAGNOSES	EMERGENT DIAGNOSES	NONEMERGENT DIAGNOSES
Neurologic, CNS, vessels	Subarachnoid hemorrhage	Shunt failure Traction headaches Tumor or other masses Subdural hematomas	Migraine, various types Vascular, various types Trigeminal neuralgia Post-trauma Postlumbar puncture Headaches
Toxic or metabolic	Carbon monoxide poisoning	Mountain sickness	
Environmental			
Collagen vascular disease	Temporal arteritis		
Eye or ENT		Glaucoma or sinusitis	Dental problems, temporomandibular joint disease
Musculoskeletal			Tension headaches Cervical strain
Allergy			Cluster or histamine headaches
Infectious disease	Bacterial meningitis, encephalitis	Brain abscess	Febrile headaches, non-neurologic source of infection
Pulmonary or O_2		Anoxic headache Anemia	
Cardiovascular		Hypertensive crisis	Hypertension (rare)
Unspecified			Effort-dependent or coital headaches

CNS, central nervous system; *ENT,* ear, nose, and throat.

Table 20-2 Significant Symptoms

SYMPTOM	FINDING	POSSIBLE DIAGNOSES
Sudden onset of pain	Lightning strike or thunder clap with any decreased mentation, any positive focal finding, or intractable pain	Subarachnoid hemorrhage
"Worst headache of my life"	Associated with sudden onset	Subarachnoid hemorrhage
Near syncope or syncope	Associated with sudden onset	Subarachnoid hemorrhage
Increase with jaw movement	Clicking or snapping; pain with jaw movement	Temporomandibular joint disease
Facial pain	Fulminant pain of the forehead and area of maxillary sinus; nasal congestion	Sinus pressure or dental infection
Forehead or temporal area pain (or both)	Tender temporal arteries	Temporal arteritis
Periorbital or retro-orbital pain	Sudden onset with tearing	Temporal arteritis or acute angle-closure glaucoma

relied on to rule out potential life-threatening causes for headache.

Almost all studies dealing with subarachnoid bleeding report that patients moved from the pain-free state to severe pain within seconds to minutes. The "thunder clap" or "lightning strike" headache is common in acute presentations of SAH but is not highly specific. If the patient with moderate or severe headache can indicate the precise activity in which he or she was engaging at the time of the onset of the headache (e.g., "I was just getting up out of the chair to answer the doorbell"), the suddenness of onset should warrant consideration of SAH.

Careful questioning about the onset of headache may lead to the correct diagnosis of SAH, even if the pain is improving at the time of evaluation.[3]

2. The patient's *activity at the onset of the pain* may be helpful. Headaches that come on during severe exertion have a relationship to vascular bleeding, but there is enough variation to make assignment to any specific cause highly variable. The syndrome of postcoital headache is well known, but coitus is also a common time of onset for SAH. These headaches require the same evaluation on initial presentation as any other exertion-related head pain.
3. If there is a history of head trauma, the differential diagnosis and emergent causes are narrowed significantly. The considerations now focus on epidural and subdural hematoma, traumatic SAH, skull fracture, and closed-head injury (i.e., concussion and diffuse axonal injury).
4. The *intensity of head pain* is difficult to quantify objectively. Almost all patients who come to the ED consider their headaches to be severe. Use of a pain scale may help differentiate patients initially but has more value in monitoring their response to therapy. Rapid resolution of pain in the ED, either from time or therapy, also should not be relied on to rule out serious causes of headache.
5. The *character of the pain* (e.g., throbbing, steady), although sometimes helpful, may not be adequate to differentiate one type of headache from another.
6. The *location of head pain* is helpful when the patient can identify a specific area. It is useful to have the patient point or try to indicate the area of pain; the emergency physician can then properly examine that area. Unilateral pain is more suggestive of migraine or a localized inflammatory process in the skull (e.g., sinus) or soft tissue.[4] Occipital headaches are classically associated with hypertension. Temporal arteritis, temporomandibular joint (TMJ) disease, dental infections, and sinus infections frequently have a highly localized area of discomfort.

www.ketabpezeshki.com 66485457-66963820

Meningitis, encephalitis, SAH, and even severe migraine, although intense in nature, are usually more diffuse in their localization.

7. *Exacerbating* or *alleviating factors* may be important. Patients whose headaches rapidly improve when they are removed from their environment or recur each time they are exposed to a particular environment (e.g., basement workshop) may have carbon monoxide poisoning. Most other severe causes of head pain are not rapidly relieved or improved when patients get to the ED. Headaches on awakening are typically described with brain tumors. Intracranial infections, dental infections, and other regional causes of head pain tend not to be improved or alleviated before therapy is given.
8. *Associated symptoms and risk factors* may relate to the severity of headache but rarely point to the specific causes (Box 20-1). Nausea and vomiting are completely nonspecific. Migraine headaches, increased intracranial pressure, temporal arteritis, and glaucoma can all manifest with severe nausea and vomiting, as can some systemic viral infections with headache. Such factors may point toward the intensity of the discomfort but are not specific in establishing the diagnosis. Immunocompromised patients are at risk for unusual infectious causes of headache. Toxoplasmosis, cryptococcal meningitis, and abscess are very rare but may be seen in patients with a *history of HIV or another immunocompromised state.* This subset of patients may have serious central nervous system infection without typical signs or symptoms of systemic illness (e.g., fever and meningismus).
9. A *prior history of headache,* although helpful, does not rule out current serious problems. It is extremely helpful, however, to know that the patient has had a workup for severe disease. Previous ED and outpatient visits and computed tomography (CT), magnetic resonance imaging, and other forms of testing can provide support for or help rule out a specific diagnosis. Patients with migraine, cluster, and tension headaches tend to have a stereotypical recurrent pattern. Adherence to these patterns is also helpful in deciding the degree to which a patient's symptoms are pursued.

Physical Examination

Physical findings associated with various forms of headache are listed in Table 20-3.

Ancillary Testing

The vast majority of headache patients do not require additional testing (Table 20-4). The most common and consequential mistake made by emergency physicians in the workup of the headache patient is believing that a single CT scan clears the patient of the possibility of SAH or other serious intracranial disease. Brain CT can miss 6 to 8% of patients with SAH, especially patients with minor (grade I) SAH, who are most treatable.[5,6] The sensitivity of CT for identifying SAH is reduced by nearly 10% for symptom onset greater than 12 hours and by almost 20% at 3 to 5 days. The basic approach to integrating CT and lumbar puncture in the assessment of headache is outlined in Figure 20-1.[7-10]

Obtaining cerebrospinal fluid should not delay antimicrobial treatment if intracranial infection is suggested. Intravenous antibiotics are given before lumbar puncture. Abnormal mental status, signs of increased intracranial pressure, papilledema, focal findings on neurologic examination, or any other indication suggestive of a focal intracranial mass lesion requires CT before lumbar puncture.

Box 20-1 Risk Factors Associated with Potentially Catastrophic Illness

1. Carbon monoxide poisoning
   a. Breathing in enclosed or confined spaces with engine exhaust or ventilation of heating equipment
   b. Multiple family members with the same symptoms
   c. Pattern of recurrence in one setting (where the exposure is occurring), relief when not in that setting
   d. Wintertime and working around machinery or equipment producing carbon monoxide (e.g., furnaces)
2. Meningitis, encephalitis, abscess
   a. History of sinus or ear infection or recent surgical procedure
   b. Immunocompromised state
   c. General debilitation with decreased immunologic system function
   d. Acute febrile illness—any type
   e. Extremes of age
   f. Impacted living conditions (e.g., military barracks, college dormitories)
   g. Lack of primary immunizations
3. Temporal arteritis
   a. Age >50
   b. Females more often than males (4 : 1)
   c. History of other collagen vascular diseases (e.g., systemic lupus)
   d. Previous chronic meningitis
   e. Previous chronic illness such as tuberculosis, parasitic or fungal infection
4. Glaucoma—sudden angle-closure
   a. Not associated with any usual or customary headache pattern
   b. History of previous glaucoma
   c. Age >30
   d. History of pain increasing in a dark environment
5. Increased intracranial pressure
   a. History of previous benign intracranial hypertension
   b. Presence of a cerebrospinal fluid shunt
   c. History of congenital brain or skull abnormalities
6. Cerebral venous sinus thrombosis
7. Intracranial hemorrhage (ICH)
   a. Subarachnoid hemorrhage (SAH)
      i. Sudden severe pain; "worst headache of life"
      ii. Acute severe pain after sexual intercourse or straining (i.e., heavy lifting)
      iii. History of SAH or cerebral aneurysm
      iv. History of polycystic kidney disease
      v. Family history of subarachnoid hemorrhage
      vi. Hypertension—severe
      vii. Previous vascular lesions in other areas of the body
      viii. Young and middle-aged
   b. Subdural hematoma (SDH)
      i. History of alcohol dependency with or without trauma
      ii. Current use of anticoagulants
   c. Epidural hematoma (EDH)
      i. Traumatic injury
      ii. Lucid mentation followed by acute altered mentation or somnolence
      iii. Anisocoria on physical examination

DIFFERENTIAL CONSIDERATIONS

Certain historical and physical findings can help determine whether the patient's condition warrants further investigation. Indications of patients at higher risk for serious causes of headache who are candidates for more comprehensive evaluation include (1) sudden onset of headache, (2) patient description of the headache as "the worst ever," (3) altered mental status, (4) meningismus, (5) unexplained fever, (6) focal neurologic

www.ketabpezeshki.com 66485457-66963820

Table 20-3 Pivotal Findings on Physical Examination

SIGN	FINDING	POSSIBLE DIAGNOSES
General appearance	Alteration of mental status—nonfocal	Meningitis, encephalitis Subarachnoid hemorrhage Anoxia Increased CSF pressure
	Alterations of mental status with focal findings	Intraparenchymal bleed Tentorial herniation Stroke
	Severe nausea, vomiting	Increased CSF pressure Acute angle-closure glaucoma Subarachnoid hemorrhage
Vital signs	Hypertension with normal heart rate or bradycardia	Increased CSF pressure Subarachnoid hemorrhage Tentorial herniation Intraparenchymal bleed
	Tachycardia	Anoxia, anemia Febrile headache Exertional or coital headaches
	Fever	Febrile headaches Meningitis, encephalitis
HEENT	Tender temporal arteries	Temporal arteritis
Fundi—loss of spontaneous venous pulsations or presence of papilledema	Increased CSF pressure	Mass lesions
	Subhyaloid hemorrhage	Subarachnoid hemorrhage
	Acute red eye (severe ciliary flushing) and poorly reactive pupils	Acute angle-closure glaucoma
	Enlarged pupil with third nerve palsy	Tentorial pressure cone Mass effect (i.e., subdural or epidural hematoma, tumor, intraparenchymal hemorrhage)
Neurologic	Lateralized motor or sensory deficit	Stroke (rare) Subdural hematoma, epidural hematoma, hemiplegic or anesthetic migraine (rare)
	Acute cerebellar ataxia	Acute cerebellar hemorrhage Acute cerebellitis (mostly children) Chemical intoxication—various types

CSF, cerebrospinal fluid; *HEENT,* head, eyes, ears, nose, and throat.

Table 20-4 Diagnostic Adjuncts in Headache Assessment

TEST	FINDING	DIAGNOSIS
Erythrocyte sedimentation rate (ESR)	Significant elevation	Temporal arteritis
ECG	Nonspecific ST-T wave changes	Subarachnoid hemorrhage Increased CSF pressure
CBC	Severe anemia	Anoxia
CT—head	Increased ventricular size	Increased CSF pressure
	Blood in subarachnoid space	Subarachnoid hemorrhage
	Blood in epidural or subdural space	Epidural or subdural hematoma
	Bleeding into parenchyma of brain	Intraparenchymal hemorrhage
	Areas of poor vascular flow	Pale infarct
	Structural, mass lesion	Traction headache secondary to mass effect
Lumbar puncture and CSF analysis	Increased pressure	Pseudotumor cerebri Mass lesions Shunt failure
	Increased protein	Tumor or other structural lesions
	Increased RBCs	Subarachnoid hemorrhage
	Increased WBCs	Infection
	Positive Gram's stain	Infection
	Decreased glucose	Infection

CBC, complete blood count; *CSF,* cerebrospinal fluid; *CT,* computed tomography; *ECG,* electrocardiogram; *RBC,* red blood cell; *WBC,* white blood cell.

www.ketabpezeshki.com 66485457-66963820

Table 20-5 Causes and Differentiation of Potentially Catastrophic Illness Manifesting with Nontraumatic Headache

DISEASE ENTITIES	PAIN HISTORY	ASSOCIATED SYMPTOMS	SUPPORT HISTORY	PREVALENCE	PHYSICAL EXAMINATION	USEFUL TESTS	ATYPICAL OR IMPORTANT ASPECTS
Carbon monoxide poisoning	Usually gradual, subtle, dull, nonfocal throbbing pain	May wax and wane as individual leaves and enters the involved area of carbon monoxide; throbbing may vary considerably	Exposure to engine exhaust, old or defective heating systems, most common in winter months	Rare	No focal neurologic findings May need cognitive testing	Carbon monoxide level, cognitive testing	May improve on the way to the hospital Occurs in groups, may involve entire families or groups of people exposed to the carbon monoxide
Subarachnoid hemorrhage	Sudden onset, "thunder clap" or "lightning strike," severe throbbing	Whenever altered mental status is present, the outcome is decidedly worse	History of polycystic kidney disease. History of chronic hypertension	Uncommon	Frequently decreased mentation—meningismus, increased blood pressure, decreased pulse, decreased spontaneous venous pulsations, rarely subhyaloid hemorrhage	CT, lumbar puncture	If CT positive, immediate involvement of neurosurgery; if CT negative, lumbar puncture
Meningitis, encephalitis, abscess	Gradual—as general symptoms increase, headache increases—nonfocal	Decreased mentation prominent, irritability prominent With abscess, focal neurologic findings may be present	Recent infection Recent facial or dental surgery or other ENT surgery	Uncommon	Fever—late in course, decreased spontaneous venous pulsations	CT, lumbar puncture	When such infection suspected, treat Do not delay antibiotics and steroids while awaiting laboratory results
Temporal arteritis	Often pain developing over a few hours from mild to severe Virtually always focal in nature	Decreased vision, nausea, vomiting intense—may confuse diagnosis	Age over 50 Other collagen vascular diseases or inflammatory diseases	Uncommon	Tender temporal arteries	Sedimentation rate	Usually unrelated and rapidly progressive
Acute angle-closure glaucoma	Sudden in onset	Nausea, vomiting, decreased vision	History of glaucoma History of pain going into dark area	Rare	"Steamy" cornea Midposition pupil poorly reactive Acute red eye	Measurement of intraocular pressure	Rapid intervention with medications required—if no relief, immediate surgery may be required
Increased intracranial pressure syndromes	Gradual, dull, nonfocal	Vomiting, decreased mentation	History of CSF shunt or other congenital brain or skull abnormality	Uncommon	Papilledema; loss of spontaneous venous pulsations	CT, shunt function study; if normal, lumbar puncture	Shunt failure or other cause of significant increased CSF pressure requires involvement of neurosurgery

CSF, cerebrospinal fluid; *CT,* computed tomography; *ENT,* ear, nose, and throat.

www.ketabpezeshki.com 66485457-66963820

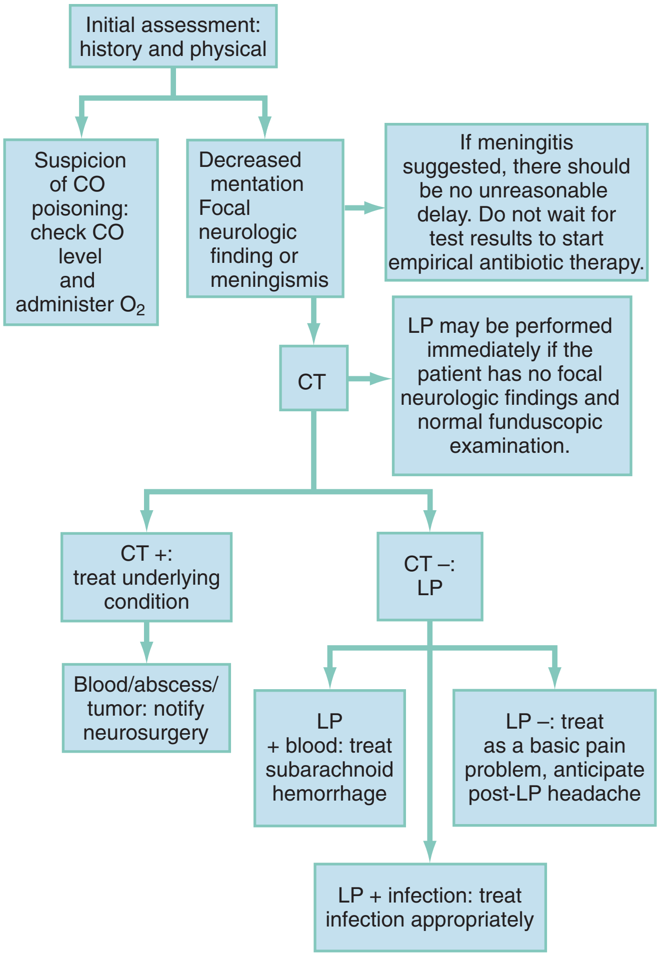


Figure 20-1. Initial assessment and treatment of headache. *CO,* carbon monoxide; O_2, oxygen; *CT,* computed tomography; *LP,* lumbar puncture.

deficit on examination, (7) symptoms refractory to appropriate treatment or worsening despite treatment, (8) onset of headache during exertion, or (9) history of human immunodeficiency virus (HIV) infection or immunosuppression.

Patients with a headache that is similar in location and intensity to an established history of recurrent headache (e.g., migraine) or of minor severity and gradual onset (e.g., typical tension headache); with normal neurologic examination findings including mental status; with absence of fever or meningismus; and showing improvement with appropriate treatment generally require no laboratory testing or imaging.

Sequential evaluation of the patient's condition and response to therapy and assessment of ancillary data will confirm a working diagnosis or trigger a reconsideration of alternatives, including more serious conditions (Table 20-5).[7]

MANAGEMENT

Empirical

Headache, although a frequent chief complaint, is a nonspecific symptom, and the speed and intensity of the initial evaluation and treatment are guided by the initial presentation (described earlier) and, particularly, the patient's mental status. Pain should be mitigated as soon as possible. The pain medication of choice depends on the working diagnosis of the patient's headache. If migraine is suspected, parenteral therapy is directed accordingly (see Chapter 103). For nonspecific mild to moderate headache, oral nonsteroidal anti-inflammatory medication is appropriate, in analgesic doses. Opioids generally are not first-line management for any type of headache pain, except when ICH (including SAH) is thought to be present, conditions for which opioid analgesia is effective and beneficial.

Specific

Specific management for headache is described in Chapter 103. The challenge in emergency medicine, however, is to eliminate life-threatening causes of headache and to treat the patient's pain.

DISPOSITION

Most patients with headache are discharged from the ED with appropriate analgesia and follow-up, unless evaluation has determined a serious underlying condition.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Barton CW: Evaluation and treatment of headache patients in the emergency department: A survey. *Headache* 1994; 34:91.
2. Mayer PL, et al: Misdiagnosis of symptomatic cerebral aneurysm: Prevalence and correlation with outcome at four institutions. *Stroke* 1996; 27:1558.
3. Day JW, Raskin NH: Thunderclap headache: Symptom of unruptured cerebral aneurysm. *Lancet* 1986; 2:1247.
4. Olesen J, Lipton RB: Migraine classification and diagnosis: International Headache Society criteria. *Neurology* 1994; 44(Suppl 4):S6.
5. Edlow J, Caplan L: Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. *N Engl J Med* 2000; 342:29.
6. McCormack RF, Hutson A: Can computed tomography angiography of the brain replace lumbar puncture in the evaluation of acute-onset headache after a negative noncontrast cranial computed tomography scan? *Acad Emerg Med* 2010; 17:444-451.
7. Edmeads J: Emergency management of headache. *Headache* 1988; 28:675.
8. Silberstein SD: Evaluation and emergency treatment of headache. *Headache* 1992; 32:396.
9. Byyny RL, et al: Sensitivity of noncontrast cranial computed tomography for the emergency department diagnosis of subarachnoid hemorrhage. *Ann Emerg Med* 2008; 51:697-703.
10. Perry JJ, et al: Is the combination of negative computed tomography result and negative lumbar puncture result sufficient to rule out subarachnoid hemorrhage? *Ann Emerg Med* 2008; 51:707-713.

www.ketabpezeshki.com 66485457-66963820

Chapter 21

Diplopia

Kama Guluma

PERSPECTIVE

Epidemiology

Diplopia, or double vision, comes in two varieties—monocular and binocular—and constitutes approximately 1.4% of ophthalmologic emergencies. For patients who visit the emergency department (ED) with diplopia, the majority of cases are binocular, with cranial nerve (CN; especially sixth nerve) palsies being among the most common causes.[1] The remainder (approximately 15%) are monocular.

Pathophysiology

Monocular diplopia, or double vision that persists in one affected eye even with the other eye closed, is an ophthalmologic problem related to distortions in the light path.

Binocular diplopia, or double vision that resolves when either eye is closed, is the result of a misalignment in the visual axes and has a wide range of causes, which can be organized in a progression from the eye, distally, to the brainstem, proximally. The culprit process might involve oculomotor muscle dysfunction, CN dysfunction, or intranuclear or supranuclear lesions in the brainstem or above.

DIAGNOSTIC APPROACH

The refinement of the differential diagnosis for the ED patient with diplopia involves parsing out the exact nature of the diplopia, determining the functional location of the defect, and screening for associated symptoms and findings that may suggest the underlying cause. The majority of this diagnostic resolution is done at the bedside, followed by targeted neuro-ophthalmologic imaging as indicated. The causes of diplopia are myriad, with pathologies relatively benign to relatively fulminant, and the tactical approach to diplopia in the ED entails sorting out those that may result in rapid and profound morbidity from those that are less acute. Table 21-1 outlines some key causes of diplopia prioritized by immediate acuity, with mechanism and distinguishing features.

Important Historical Elements

There are four aspects of questioning that guide the formulation of the differential diagnosis: (1) the cadence of onset and symptoms, (2) the directionality and orientation of the diplopia, (3) the presence of pain, and (4) the presence of other associated symptoms.[2,3] In terms of the cadence of onset, a truly sudden onset suggests an ischemic cause, either cerebrovascular or microvascular, especially if the intensity or degree of diplopia was maximal at onset. A fluctuation of symptoms over time may suggest transient ischemic attacks or an impending stroke but also generally implies a neuromuscular disease.[2,3] Regarding the directionality of the diplopia, the directions of gaze that elicit or worsen the diplopia, and the general orientation of that diplopia—that is, horizontal, vertical, or torsional—should be carefully determined in order to localize the problem. Finally, symptoms associated with the diplopia (such as pain or neurologic or neuromuscular symptoms) are critical to forming a differential diagnosis, if not to making the diagnosis. The presence of pain suggests an inflammatory or infectious process and narrows the differential significantly.

The Examination

The patient complaining of diplopia should undergo a thorough neurologic examination with attention to the CNs and an evaluation of the six cardinal movements of gaze. Each extraocular muscle (and the nerve that supplies it) has a maximal action in a specific direction, and the evaluation of gaze should therefore specifically follow the configuration of a six-limbed asterisk, or an H[2] (Fig. 21-1). The patient should also undergo a careful pupillary and facial examination for signs of pupillary asymmetry, ptosis, lid lag, conjunctival injection or chemosis, periorbital swelling, or proptosis[2] and assessment of overall head positioning.

The Diagnostic Approach

The acuity of onset and presence or absence of pain can be used to prestratify diagnostic possibilities as shown in Figure 21-2, especially with regard to vascular, potentially ischemic events. Through use of the lines of questioning and examination elements outlined previously, the differential diagnosis can then be rapidly winnowed down by means of a phased, systematic approach that incorporates the following queries (reflected in the algorithm in Figure 21-3):

1. Is the diplopia monocular?
2. Is the binocular diplopia a result of a restrictive, mechanical orbitopathy?
3. Is the binocular diplopia a result of a palsy of the oculomotor CNs (III, IV, or VI) in a single eye?
4. Is the binocular diplopia a result of a neuroaxial process involving the brainstem and related CNs?
5. Is the binocular diplopia a result of a neuromuscular disorder?

1. Is the Diplopia Monocular?

The first key assessment is to determine if the diplopia is purely monocular. Monocular diplopia is an ophthalmologic problem

www.ketabpezeshki.com 66485457-66963820

Table 21-1 Important Causes of Diplopia

DIPLOPIA-CAUSING ENTITY	MECHANISM AND MORTALITY	DISTINGUISHING FEATURES
Tier 1—Critical		
Basilar artery thrombosis	Acute thrombosis of the basilar artery with brainstem ischemia; untreated, mortality 70-90%	Vertigo, dysarthria, other cranial nerve involvement; risk factors for stroke
Botulism	Toxin inhibits of release of acetylcholine (ACh) at cholinergic synapses and presynaptic myoneural junctions; untreated, mortality 60%	Dysarthria, dysphagia, autonomic dysreflexia, pupillary dysfunction
Basilar meningitis	Infection; untreated, mortality close to 100% if bacterial (25-40% if treated)	Headache, meningismus, fever
Aneurysm	Enlarging aneurysm directly compresses cranial nerve; untreated, rupture risk is 1% per year; mortality 26-50% per rupture	CN III palsy with pupillary involvement
Tier 2—Emergent		
Vertebral dissection	Dissection causes vertebrobasilar ischemia; acute untreated, mortality 28% (2-5% if neurologically asymptomatic)	Neck pain, vertigo; risk factors for vertebral dissection
Myasthenia gravis	Autoantibodies develop against ACh nicotinic postsynaptic receptors; untreated, crisis mortality 42% (5% if treated)	Fluctuating muscle weakness, ptosis, and diplopia worsen with activity and improve with rest
Wernicke's encephalopathy	Thiamine-dependent metabolic failure and tissue injury; untreated, mortality 20%	Nystagmus, ataxia, altered mental status, and ophthalmoplegia; risk factors and nutritional deficiency
Orbital apex syndrome, cavernous sinus process	Inflammation or infection in the orbital apex or cavernous sinus directly affects oculomotor cranial nerves; acute mortality low unless infectious and complicated by meningitis	A combination of palsies of CN III, IV, or VI, with retro-orbital pain, conjunctival injection, and possible periorbital or facial numbness
Tier 3—Urgent		
Brainstem tumor	Tumor involvement at the supranuclear level; acute mortality low (long-term mortality variable)	Skew deviation vertical diplopia, internuclear ophthalmoplegia
Miller-Fisher syndrome	Autoantibodies develop to a cranial nerve ganglioside, GQ1b; acute mortality low if fully differentiated from GBS; mortality 2-12% if GBS	Ophthalmoplegia, ataxia, areflexia
Multiple sclerosis	Demyelinating lesions; acute mortality low	Internuclear ophthalmoplegia
Thyroid myopathy (Graves' disease)	Autoimmune myopathy; acute mortality low with regard to ocular complaints	Proptosis, restriction of elevation and abduction of the eye, signs of Graves' disease
Ophthalmoplegic migraine	Inflammatory cranial neuropathy; low mortality—self-limited disease	Ipsilateral headache, CN (usually III) palsy
Ischemic neuropathy	Microvascular ischemia; mortality low—self-limited disease	Isolated CN palsy (pupil-sparing if CN III)
Orbital myositis, pseudotumor	Autoimmune or idiopathic myositis; acute mortality low with regard to ocular complaints	Eye pain, restriction of movement, periorbital edema; exophthalmos and chemosis when more severe
Orbital apex mass	A tumor, infiltration, or mass effect in the orbital apex or cavernous sinus directly compresses oculomotor cranial nerves; acute mortality low	A combination of palsies of CN III, IV, or VI, and possible periorbital or facial numbness, with retro-orbital pain, proptosis, signs of venous congestion

CN, cranial nerve; *GBS,* Guillain-Barre syndrome.

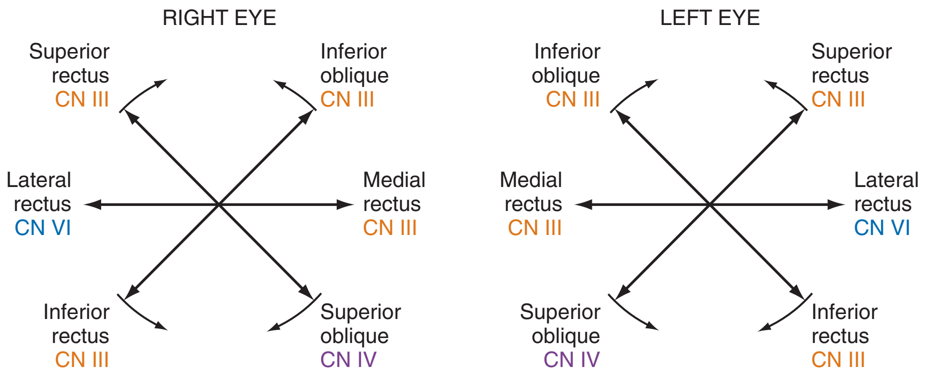


Figure 21-1. Cardinal movements of the eyes, with the oculomotor muscles that create them, and the nerves that supply those muscles. Small curved arrows denote intorsion or extorsion of the eye by the muscle indicated. *CN,* cranial nerve.

www.ketabpezeshki.com 66485457-66963820

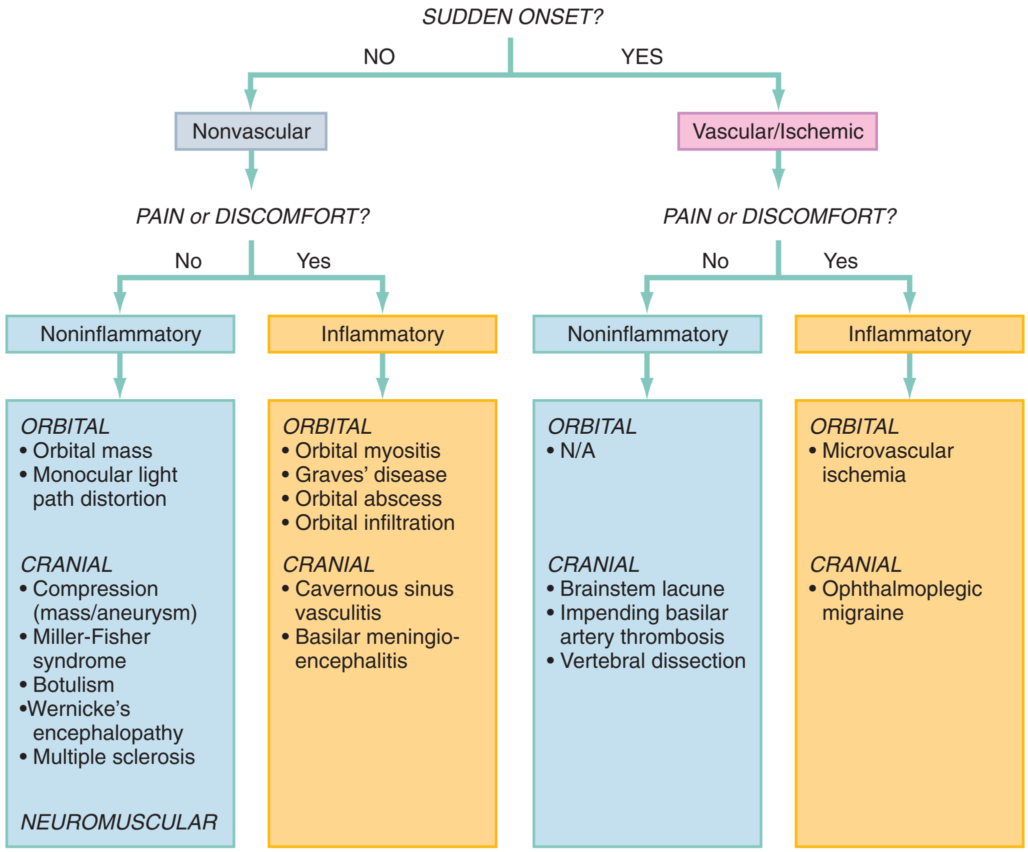


Figure 21-2. Prestratification of the differential diagnosis in a patient with diplopia.

related to distortions in the light path from dry eyes, a corneal irregularity, cataract, or lens dislocation,[3,4] or rarely to retinal wrinkles involving the macula.[5] The patient with monocular diplopia may require a slit-lamp, funduscopic examination and evaluation by an ophthalmologist and will not typically require an extensive neuro-ophthalmologic workup.

Symptoms. If the patient reports that the diplopia persists in the affected eye with the normal eye closed, this immediately suggests a monocular cause.

Signs. With monocular diplopia—which is typically a problem with abnormal refraction—the diplopia from the affected eye will typically resolve when a pinhole is used,[6] unless it is caused by a retinal abnormality.

2. Is the Binocular Diplopia a Result of a Restrictive, Mechanical Orbitopathy?

If the diplopia is determined to be monocular, the evaluation essentially ends with the previous question. If the diplopia is determined to be binocular, on the other hand, the next question is whether or not there is a simple mechanical orbitopathy in one of the orbits causing the diplopia. This type of orbitopathy can be caused by orbital myositis, trauma, or infection (abscess) or by craniofacial masses, any of which can cause direct restriction of the movement of a single eye. Orbital myositis may involve as little as a single extraocular muscle and may be a manifestation of a variety of steroid-responsive conditions, such as Wegener's granulomatosis, giant cell arteritis, systemic lupus erythematosus, dermatomyositis, sarcoidosis, rheumatoid arthritis, or idiopathic orbital inflammatory syndrome (orbital pseudotumor).[7]

If both eyes are involved, then thyroid disease (Graves' orbitopathy) is a consideration. It is the most common cause of ocular myopathy in older adults and is bilateral in at least 85% of cases.[9] The patient with thyroid-related diplopia will likely have a preexisting diagnosis of Graves' disease but may have isolated diplopia before the onset of systemic symptoms (and diagnosis).[9]

A restrictive orbitopathy is identified by characteristic symptoms and signs combined with the absence of any other focal neurologic deficits. If it is clearly apparent, it implies a largely ophthalmologic, infectious, or rheumatologic process, and the initial evaluation can proceed along these lines.

Symptoms. A structural restriction of motion of a single eye, typically gradual in onset, may cause diplopia in a single or multiple directions of gaze, depending on the type and extent of muscular involvement. A sensation of mass effect, discomfort, or pain in the culprit eye is a characteristic symptom. If the cause is infectious, the patient may describe subjective fever. Diplopia that is worse in the morning suggests Graves' myopathy, which is presumably worsened owing to the venous congestion of the ocular muscle associated with being supine.[2]

Signs. Signs of a structural orbitopathy or myositis include proptosis, periorbital swelling, edema, conjunctival or scleral hyperemia, or palpebral swelling involving a single eye.[2] Although findings may mimic a neurogenic palsy to some extent, the signs induced on testing extraocular eye movements will not reflect the deficits typical of palsies of the oculomotor CNs (discussed subsequently). Ocular myositis can be distinguished from a neurogenic palsy in that it *abruptly* restricts eye movement *away* from the muscle, whereas a CN palsy *smoothly and progressively* impairs movement *toward* the weakened muscle.[10]

The signs of Graves' disease include lid lag,[2] diffuse conjunctival edema and vascular injection,[9] and—because it classically affects the inferior and medial recti muscles first—restriction of elevation and abduction of the eye.[2] Patients with thyroid-related diplopia may tilt the head back to accommodate for the restriction of the inferior rectus muscle.[2,3]

www.ketabpezeshki.com 66485457-66963820

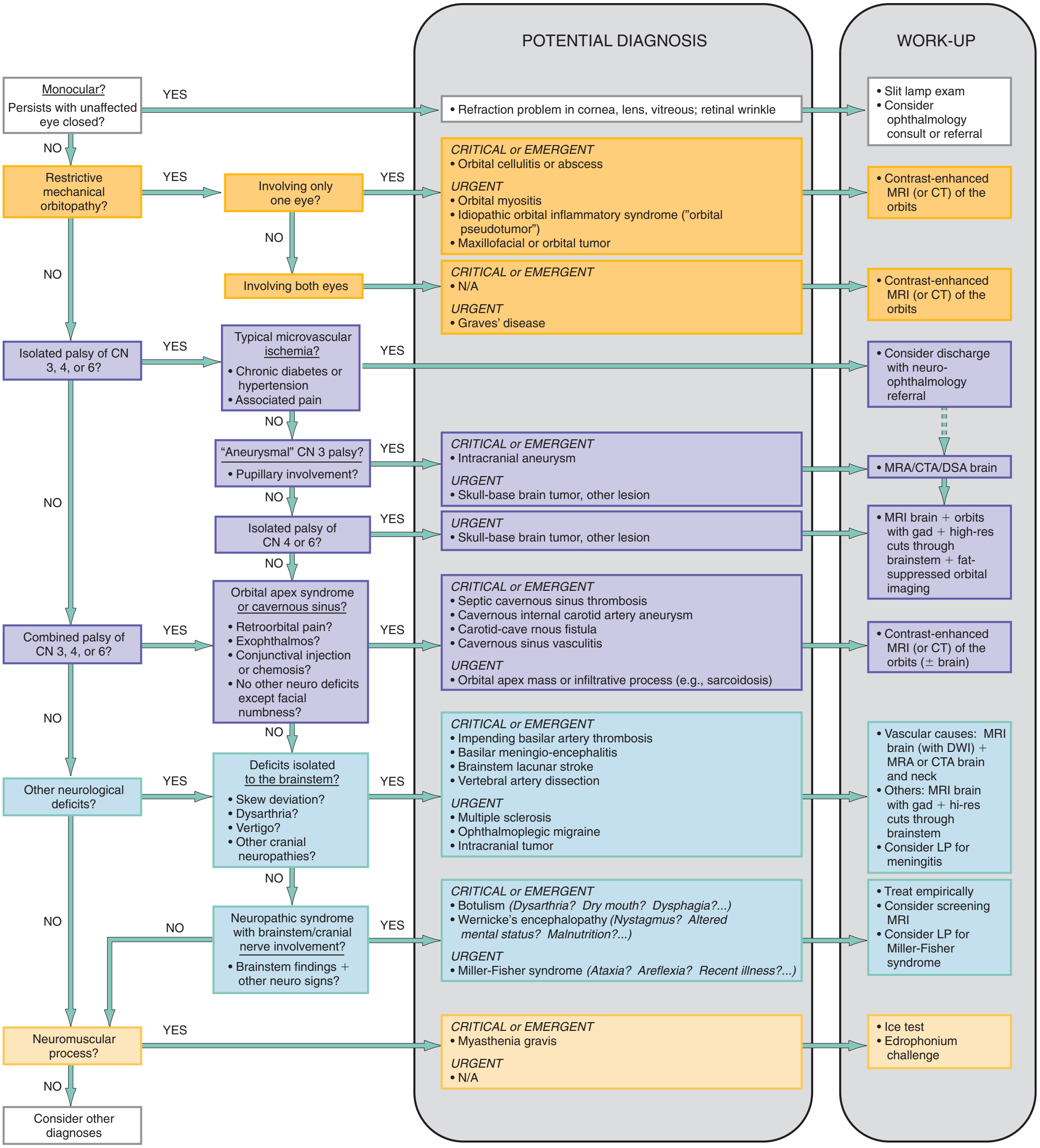


Figure 21-3. Algorithm for the diagnostic approach to diplopia in the emergency department—a guideline. *CN,* cranial nerve; *CT,* computed tomography; *CTA,* CT angiogram; *DSA,* digital subtraction angiography (conventional angiography); *DWI,* diffusion-weighted imaging; *gad,* gadolinium; *hi-res,* high-resolution; *LP,* lumbar puncture; *MRA,* magnetic resonance angiography; *MRI,* magnetic resonance imaging.

3. Is the Binocular Diplopia a Result of a Palsy of the Oculomotor Cranial Nerves (III, IV, or VI) in a Single Eye?

If there is no obvious mechanical restriction evident, the next question is whether or not there is a neuropathic cause of the diplopia. The first consideration in this regard is whether there is a unilateral palsy in one or more of the oculomotor nerves. The oculomotor (CN III), trochlear (CN IV), and abducens (CN VI) CNs innervate the muscles that move the eye. CN VI is the most commonly affected, followed by CN III and then CN IV.[3,11] The clinical distinction to be made at this point is whether the oculomotor palsy is caused by an isolated mononeuropathy of single nerve or by a unilateral simultaneous palsy involving multiple oculomotor nerves.

www.ketabpezeshki.com 66485457-66963820

An isolated, simple mononeuropathy in CN III, IV, or VI may be from a demyelinating process (such as multiple sclerosis[12]), hypertensive or diabetic vasculopathy, or compression. Although in a significant proportion of cases the cause of the palsy is not determinable,[11] each nerve has characteristic predilections to which it is vulnerable. In adults, CN III is most commonly affected by diabetic or hypertensive vasculopathy.[11] Aneurysms in the posterior communicating, basilar, superior cerebellar, posterior cerebral, and cavernous internal carotid arteries are a close second. CN IV is most commonly affected by trauma from abutment against the tentorium (typically not an isolated symptom or finding, however), followed by vascular causes.[11] CN VI is the most common nerve to be affected by tumor and elevated intracranial pressure.

A unilateral simultaneous palsy of more than one oculomotor nerve (but with no other CN involvement or other neurologic signs beyond possible involvement of the upper branches of the trigeminal nerve) suggests a process in the posterior orbit (orbital apex) or cavernous sinus. A cavernous sinus infection, mass, or vasculitis may affect CNs III, IV, and VI simultaneously but typically affects CN VI first because it traverses through the cavernous sinus as opposed to within its wall as do CNs III and VI.[6] Causes include carotid-cavernous fistula, inflammatory vasculitides such as giant cell arteritis, Tolosa-Hunt syndrome (a rare idiopathic vasculitis), or tumor or infiltration (e.g., sarcoidosis) in the orbital apex.[13] A complex palsy in the cavernous sinus may also be iatrogenic, from an intraoral dental anesthetic nerve block, presumably because of intravascular injection or diffusion of anesthetic along tissue planes into the pterygoid venous plexus.[14]

If the diplopia clearly appears to be related to either an isolated oculomotor palsy or to a unilateral combination of distinct palsies of CN III, IV, or VI, then the evaluation can be initially focused on the considerations outlined previously.

Symptoms. An isolated oculomotor nerve palsy has characteristic symptoms. The patient with a CN III palsy typically reports diplopia in all directions of gaze except on lateral gaze to the affected side.[6] A rotational diplopia that worsens on looking down and toward the nose implies a superior oblique (CN IV) palsy. A CN IV palsy makes descending stairs, reading, and watching television in bed difficult.[2] Diplopia that worsens on lateral gaze to one direction implies an issue with CN VI on that side.[3] A patient with diplopia from an isolated palsy of CN III, IV, or VI will typically not have associated symptoms beyond the diplopia. Pain and speed of onset are differentiators; a sudden isolated CN III, IV, or VI palsy associated with orbital discomfort in a patient with chronic diabetes or hypertension strongly suggests that microvascular ischemia is the cause.[2,13]

The diplopia from a cavernous sinus problem, unlike an isolated mononeuropathy, may manifest as a combination of any of the gaze abnormalities noted previously, given that more than one oculomotor nerve may be involved. It may be gradual in onset and associated with retro-orbital pain or blurred vision as a result of venous congestion.[13] Because branches of the trigeminal nerve travel though the orbital apex, the patient may have associated ipsilateral periorbital facial numbness or dysesthesia.[13]

Signs. Palsies from an isolated mononeuropathy in each oculomotor nerve manifest with typical findings as outlined in Figure 21-4. CN III also innervates the levator palpebrae superioris muscle, which lifts the upper eyelid and provides parasympathetic innervation to two intrinsic ocular muscles, the ciliary and constrictor pupillae muscles, which constrict the pupil.[2,6] A CN III palsy, when complete, therefore results in an eye that is deviated "down and out" with a dilated pupil and ptosis.[2] Diplopia caused by microvascular ischemia, typically seen in older patients with vascular risk factors such as diabetes and hypertension, may manifest with an isolated palsy associated with pain in CN III, CN IV,

NERVE PALSY	MUSCLE(S) "OFF"	SYMPTOMS	EXAM FINDINGS
Normal	N/A	N/A	
Oculomotor (CN III)	Medial, inferior, and superior rectii muscles • Inferior oblique muscle • Levator palpebrae (eye lid) • Ciliary and constrictor pupillae muscles (pupil)	Multidirectional horizontal and vertical diplopia, except on lateral gaze to the affected side • eyelid "droop"	Ptosis; Pupillary dilation; "Down and out"
Trochlear (CN IV)	Superior oblique muscle	Rotational diplopia that worsens on looking down and toward the nose	Extorsion on downward gaze
Abducens (CN VI)	Lateral rectus muscle	Horizontal diplopia on gaze toward the affected side	Lateral gaze palsy

Figure 21-4. Corresponding muscle dysfunction, symptoms, and examination findings for each oculomotor cranial nerve palsy. *CN,* cranial nerve.

www.ketabpezeshki.com 66485457-66963820

or CN VI. A CN III palsy from this process classically spares the pupil, whereas a CN III palsy that develops from compression (i.e., from an aneurysm) does not and typically results in pupillary mydriasis owing to compression of pupillomotor parasympathetic fibers that run in the peripheral and superomedial surface of the nerve.[15] The "rule of the pupil" (more of a guideline than a rule) is that an otherwise complete CN III palsy (complete ptosis, completely "down and out") with normal pupillary size and reactivity essentially rules out compression as the source.[15,16]

In contrast to a mononeuropathy, the combination of ipsilateral palsies of CN III, IV, and VI from an orbital apex syndrome or cavernous sinus process will typically manifest with additional findings of exophthalmos, chemosis, and injection.[6,13] Sensory deficits corresponding to the ophthalmic (V1) and maxillary (V2) divisions of the trigeminal nerve may be present, given their course through the orbital apex.[13]

4. Is the Binocular Diplopia a Result of a Neuroaxial Process Involving the Brainstem and Related Cranial Nerves?

If a unilateral process limited exclusively to the oculomotor CNs is not clearly identifiable, the next consideration is a lesion or process involving the brainstem and associated CNs. This level of involvement is signified by a deficit that either does not exactly correspond to an oculomotor palsy or is associated with other nonoculomotor neurologic signs. The diagnostic goal at this point is to determine whether the problem is a focal lesion in the brainstem or part of a more diffuse neurologic syndrome, keeping in mind that the neuropathic signs suggesting the former may actually be a mild presentation of the latter.

A focal brainstem lesion may be from multiple sclerosis (as a so-called "clinically isolated syndrome," of which 68% manifest as diplopia).[12] A more diffuse but localized brainstem process may be caused by brainstem tumor, a brainstem lacunar stroke,[3] an impending basilar artery thrombosis or a vertebral artery dissection,[17,18] or an ophthalmoplegic migraine.[6,19] A vertebral artery dissection may manifest with diplopia alone,[17] as can an impending basilar artery thrombosis, which can then go on to acute cause coma.[18]

A more diffuse process involving the brainstem and/or CNs III, IV, and VI may be infectious, autoimmune, neurotoxic, or metabolic and may involve other neurologic structures, resulting in additional symptoms and signs. Possibilities include basilar meningio-encephalitis, botulism,[20] an autoimmune syndrome such as Miller-Fisher or Guillain-Barré syndrome,[21,22] and Wernicke's encephalopathy syndrome, in which the ophthalmologic manifestations are a result of metabolically induced lesions in the pontine tegmentum, abducens nucleus, and oculomotor nucleus.[24]

The exact cause underlying a neuroaxial presentation of diplopia may not be immediately determinable at the bedside, but it can be anatomically localized and generally characterized through screening for associated symptoms and physical signs.

Symptoms. Double vision may be the most prominent symptom (and therefore the presenting complaint) in a neurologic syndrome in which it is one of many components, making it important to actively screen for those other symptoms and signs. A focal brainstem lesion (as in multiple sclerosis) may result in an isolated diplopia, but localized brainstem lesions such as those from mass effect or ischemia typically result in so-called "neighborhood" symptoms and signs (from anatomically contiguous involvement). A brainstem lacunar stroke may cause sudden diplopia and symptoms of other CN involvement, such as facial weakness. Nausea, vertigo, or slurred speech raises concern for an impending basilar artery occlusion, especially if symptoms are sudden in onset, are painless, and fluctuate or may represent a brainstem mass if gradual in onset and progressive. A young person with a history of migraine headaches who has an ophthalmoplegic migraine may have a presentation similar to that of someone with a brainstem stroke but will typically develop an associated ipsilateral headache.

Diplopia from a more diffuse neurologic syndrome that happens to involve the brainstem and CNs is usually gradual in onset and manifests with a variety of more discordant symptoms. A gradually evolving combination of double vision, slurred speech, and problems swallowing suggests food-borne botulism[20,23] especially if additional symptoms of dry mouth, nausea, and diffuse muscle weakness are present. Double vision, clumsiness, and altered mentation in a patient with chronic alcoholism, malnutrition, or a history of bariatric surgery should raise the possibility of Wernicke's encephalopathy.[24] Diplopia and other CN symptoms, together with headache, photophobia, stiff neck, or fever, should raise suspicion regarding basilar meningio-encephalitis.

Signs. Vertical diplopia without the torsional component seen with CN IV palsy, called a *vertical skew deviation,* suggests a brainstem lesion. An internuclear ophthalmoplegia, suggested by an ability to adduct the eye on one side in the contralateral direction during lateral gaze that resolves during convergence, implicates a lesion in the medial longitudinal fasciculus (MLF), such as that classically found in patients with multiple sclerosis.[3] In multiple sclerosis, diplopia may appear alone as a clinically isolated syndrome[12] or may be associated with a host of additional heterogeneous neurologic findings that typify this disorder, such as nystagmus, optic neuritis (with blurred vision and eye pain), or focal motor or sensory abnormalities. A brainstem lacunar stroke may manifest as any of a number of identifiable syndromes (Box 21-1). An impending basilar occlusion may cause additional symptoms of nystagmus, dysmetria, gait ataxia, and dysarthria.

A brainstem or cranial neuropathy that is part of a more diffuse neurologic syndrome may cause a stereotypical assortment of additional associated deficits. With food-borne botulism, patients have a descending flaccid paralysis that begins with multiple CN palsies. There may also be autonomic signs, such as dry mouth, ileus, postural hypotension, respiratory muscle weakness, and pupillary abnormalities.[20,24] Patients with Miller-Fisher syndrome may have an isolated ophthalmoplegia,[25] considered a *forme fruste* of the disease, but more typically have the classic triad of ophthalmoplegia, ataxia, and areflexia.[22] Muscle weakness should not be present[21]; if it is, the case may be better classified as Guillain-Barré

Box 21-1 Lacunar Stroke Syndromes Manifesting with Diplopia[3,33]

Weber's syndrome (midbrain lacune)	Ipsilateral CN III palsy and contralateral hemiparesis
Benedikt's syndrome (midbrain lacune)	Ipsilateral CN III palsy and contralateral tremor or dysmetria
Claude's syndrome (midbrain lacune)	Ipsilateral CN III palsy and contralateral weakness, tremor, and ataxia
Millard-Gubler syndrome (pontine lacune)	Ipsilateral CN VI palsy, ipsilateral facial weakness (CN VII), and contralateral arm and leg weakness
Foville's syndrome (pontine tegmentum)	Ipsilateral CN VI palsy, ipsilateral facial weakness (CN VII), contralateral ataxia and hemiparesis
One-and-a-half syndrome (CN VI nuclei, parapontine reticular formation)	Bilateral CN VI (abduction) palsies with a unilateral adduction palsy

www.ketabpezeshki.com 66485457-66963820

syndrome with ophthalmoplegia.[21,22] Almost a third of patients with Wernicke's encephalopathy have ocular abnormalities including nystagmus and ophthalmoplegia, typically associated with the classic triad of nystagmus, altered mental status, and truncal and gait ataxia. Other findings might include sluggish pupillary reaction to light, anisocoria, papilledema, limb ataxia and dysarthria, as well as hypothermia resulting from involvement of the posterior hypothalamic regions.[24] On the other hand, a temperature elevation or fever suggests the possibility of an infectious process such as basilar meningio-encephalitis.

5. Is the Binocular Diplopia a Result of a Neuromuscular Disorder?

If none of the previous considerations seem applicable, and specifically if there are no anatomically distinct neurologic deficits evident, then a neuromuscular disorder should be considered. Although clinical entities such as snake envenomation and tick paralysis can on rare occasion cause isolated diplopia, the prototypical neuromuscular cause of diplopia is myasthenia gravis.[26] Unlike other causes of diplopia, myasthenia will typically manifest with diplopia in a setting of a preestablished diagnosis, which facilitates a determination, if not immediate recognition, of the cause.

Symptoms. Diplopia that is variably triggered in multiple directions (without a distinct structural or neuropathic cause evident) implies a neuromuscular cause such as myasthenia gravis. Milder versions of each of these may result in a diplopia isolated to one direction, however. Diplopia from neuromuscular disease generally fluctuates over time.[2,3] The diplopia of myasthenia gravis typically gets worse as the patient fatigues and improves with rest.[26] Associated symptoms of proximal muscle weakness (e.g., difficulty holding arms above the head or climbing stairs), shortness of breath, or difficulty swallowing imply a systemic neuromuscular disease.[2]

Signs. The signs of neuromuscular disease, such as muscle atrophy or weakness, may be readily apparent on inspection of the patient.[2] Patients with myasthenia gravis may have unilateral or bilateral ptosis, weakness on forced eyelid closure, and generalized muscle weakness, but with normal reflexes and no sensory abnormalities[11]; about half have isolated ocular abnormalities.[26,27] The diplopia may represent a myasthenic crisis, possibly associated with occult respiratory muscle weakness and ventilatory insufficiency.[28]

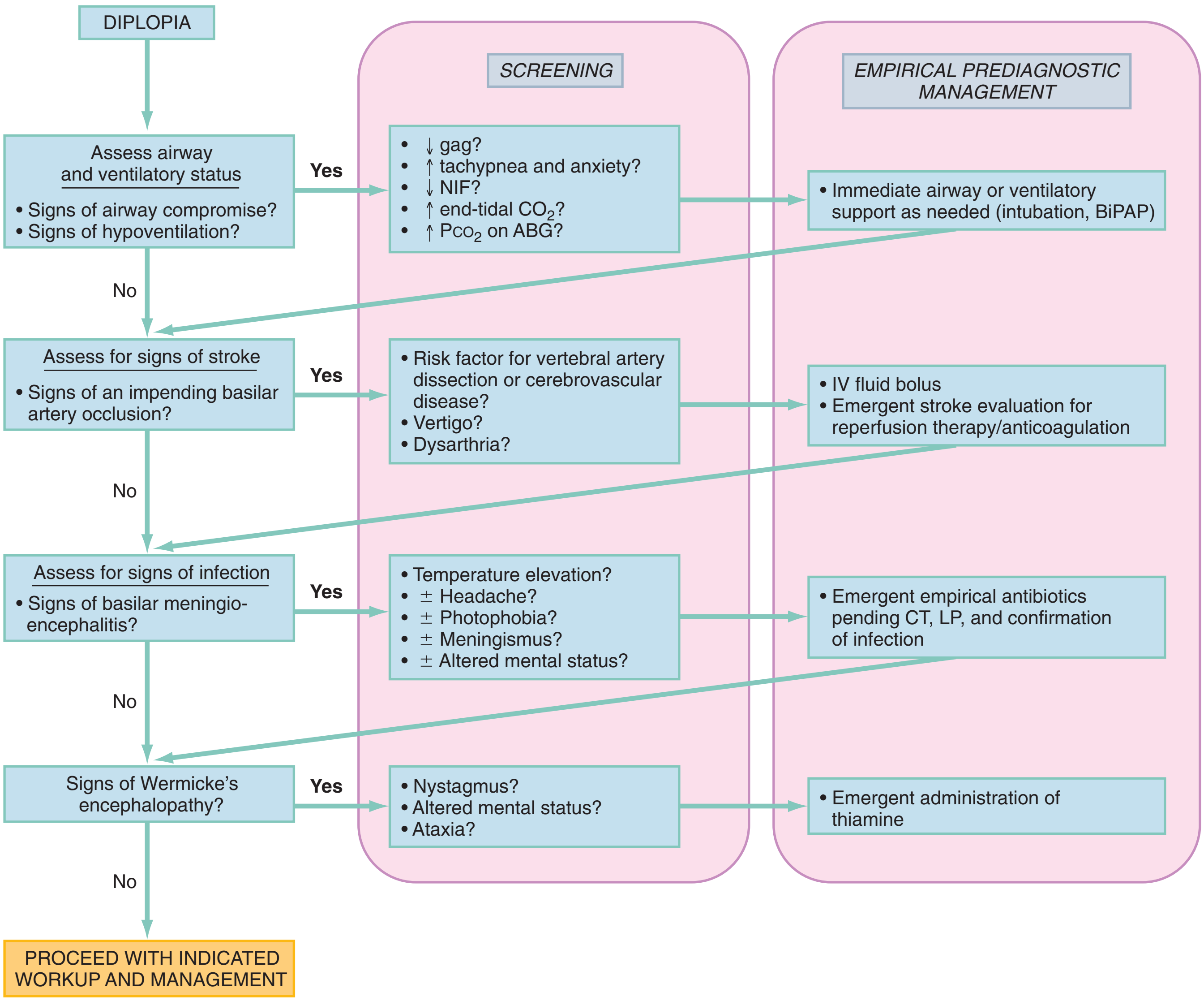


Figure 21-5. Algorithm for the initial stabilization of the patient with diplopia in the emergency department—a guideline. *ABG,* arterial blood gas; *BiPAP,* biphasic positive airway pressure; CO_2, carbon dioxide; *CT,* computed tomography (of the cranium); *IV,* intravenous; *LP,* lumbar puncture; *NIF,* negative inspiratory force; P_{CO_2}, partial pressure of carbon dioxide.

www.ketabpezeshki.com 66485457-66963820

If myasthenia gravis is suspected, a bedside test that can be performed is the "ice test." An ice-filled glove or bag is applied to the patient's closed eye or eyes, held there for about 5 minutes, and withdrawn; any improvement in ptosis (typically about 5 mm[29]) or diplopia is noted. Cold is believed to mitigate the effect of myasthenia-related acetylcholine-receptor blockade by decreasing cholinesterase activity and by promoting efficiency of acetylcholine at the end plate.[30] An edrophonium (Tensilon) challenge can also be performed if the drug is available (see Chapter 108).

Diagnostics

The diagnostics applicable to each of the differential considerations in the previous sections are outlined in Figure 21-3. Most patients with undifferentiated binocular diplopia will need imaging, the mainstay of the workup. Imaging may be deferred in the older diabetic or hypertensive patient with a clear-cut, isolated microvascular ischemic CN III palsy, although it may be helpful to confirm the diagnosis. Routine laboratory studies, except for specialized tests such as a thyroid panel to screen for thyroid disease or a lumbar puncture when meningitis or Miller-Fisher syndrome is considered, are of little diagnostic utility. Furthermore, routine noncontrast computed tomography (CT) of the brain may yield little information when compared with CT angiography (CTA) or magnetic resonance angiography (MRA) of the cerebral circulation, and contrast-enhanced magnetic resonance imaging (MRI) of the orbits, brain, and brainstem.

In the patient with a suspected or evident mechanical orbitopathy, an MRI of the orbits with gadolinium can allow an assessment for enlargement or enhancement in extraocular muscles and orbital structures,[2] although a contrast-enhanced cranial CT scan with fine cuts through the orbit can be used as a second-line option in this case.[8] The same imaging paradigm applies to a localization of the process within the cavernous sinus or orbital apex, because it will highlight infiltrative, inflammatory, or compressive pathology.[8]

For an isolated neuropathy of CN III, IV, or VI without evidence of an aneurysm, the most optimal study is MRI of the brain and orbits with gadolinium, high-resolution cuts through the brainstem, and fat-suppressed orbital imaging to assess for inflammation, neoplasm, or demyelination along the course of the nerves.[31a] If an aneurysm is suspected, the imaging chosen should be standard for that required to assess for an aneurysm and is detailed in other chapters specifically devoted to the topic. MRA and CTA are now considered first-line alternatives to the traditional cerebral angiogram, but because the sensitivity of MRA decreases with aneurysm sizes less than 5 mm, MRA should be used cautiously as the definitive screening test in cases in which the likelihood of aneurysm is high.[31]

For a presentation suggestive of a subarachnoid space (e.g., cerebellopontine angle) or brainstem process, an MRI with and without gadolinium is highly recommended.[31a] If acute brainstem ischemia is a consideration, then adding an MRI diffusion-weighted imaging protocol may be helpful.

EMPIRICAL MANAGEMENT

Because the treatment of diplopia depends entirely on the cause, there is little in the way of a primary treatment for diplopia in the ED beyond addressing whatever secondary disorder is causing it (approaches to which are outlined in individual chapters in this text). Certain emergent therapeutic measures may be indicated in the context of potentially serious underlying causes, as outlined in the algorithm in Figure 21-5. The priority is to consider imminent threats to CNS tissue viability, such as an impending basilar artery thrombosis, and then consider rapidly evolving threats to CNS tissue viability, such as meningio-encephalitis or Wernicke's encephalopathy, and empirically institute indicated treatments as the workup gets underway.

The patient with diplopia will typically require an admission for further workup and treatment of the underlying disorder, unless diagnosed with a low-acuity condition such as microvascular ischemia. A CN III or CN VI palsy from microvascular ischemia is generally self-limited; the pain usually resolves after a few days, and complete spontaneous resolution is the norm, occurring in up to 95% of patients.[32] These patients can typically be discharged home with close outpatient follow-up.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Comer RM, Dawson E, Plant G, Acheson JF, Lee JP: Causes and outcomes for patients presenting with diplopia to an eye casualty department. *Eye* 2007; 21:413-418.
2. Rucker JC, Tomsak RL: Binocular diplopia. A practical approach. *Neurologist* 2005; 11:98-110.
3. Friedman DI: Pearls: Diplopia. *Semin Neurol* 2010; 30:54-65.
4. Coffeen P, Guyton DL: Monocular diplopia accompanying ordinary refractive errors. *Am J Ophthalmol* 1988; 105:451.
5. Barton JJ: "Retinal diplopia" associated with macular wrinkling. *Neurology* 2004; 63:925-927.
6. Duong DK, Leo MM, Mitchell EL: Neuro-ophthalmology. *Emerg Med Clin North Am* 2008; 26:137-180, vii.
7. Lutt JR, Lim LL, Phal PM, Rosenbaum JT: Orbital inflammatory disease. *Semin Arthritis Rheum* 2008; 37:207-222.
8. Reference deleted in proofs.
9. Lee HB, Rodgers IR, Woog JJ: Evaluation and management of Graves' orbitopathy. *Otolaryngol Clin North Am* 2006; 39:923-942, vi.
10. Danchaivijitr C, Kennard C: Diplopia and eye movement disorders. *J Neurol Neurosurg Psychiatry* 2004; 75(Suppl 4):iv, 24-31.
11. Richards BW, Jones FR Jr, Younge BR: Causes and prognosis in 4278 cases of paralysis of the oculomotor, trochlear, and abducens cranial nerves. *Am J Ophthalmol* 1992; 113:489-496.
12. Jacobs DA, Galetta SL: Multiple sclerosis and the visual system. *Ophthalmol Clin North Am* 2004; 17:265-273, v.
13. La Mantia L, Erbetta A, Bussone G: Painful ophthalmoplegia: An unresolved clinical problem. *Neurol Sci* 2005; 26(Suppl 2):s79-s82.
14. Choi EH, Seo JY, Jung BY, Park W: Diplopia after inferior alveolar nerve block anesthesia: Report of 2 cases and literature review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009; 107:e21-e24.
15. Purvin VA: Neuro-ophthalmic aspects of aneurysms. *Int Ophthalmol Clin* 2009; 49:119-132.
16. Trobe JD: Third nerve palsy and the pupil. Footnotes to the rule. *Arch Ophthalmol* 1988; 106:601-602.
17. Jickling G, et al: Left vertebral artery dissection causing bilateral internuclear ophthalmoplegia. *CJEM* 2008; 10:485-487.
18. Mennel S, Hergan K, Peter S: Skew deviation: A precursor to basilar artery thrombosis. *Clin Experiment Ophthalmol* 2005; 33:536-538.
19. Lal V, Sahota P, Singh P, Gupta A, Prabhakar S: Ophthalmoplegia with migraine in adults: Is it ophthalmoplegic migraine? *Headache* 2009; 49:838-850.
20. Kongsaengdao S, et al: An outbreak of botulism in Thailand: Clinical manifestations and management of severe respiratory failure. *Clin Infect Dis* 2006; 43:1247-1256.
21. Bushra JS: Miller Fisher syndrome: An uncommon acute neuropathy. *J Emerg Med* 2000; 18:427-430.
22. Overell JR, Willison HJ: Recent developments in Miller Fisher syndrome and related disorders. *Curr Opin Neurol* 2005; 18:562-566.
23. Ruthman JC, Hendricksen DK, Bonefeld R: ED presentation of type A botulism. *Am J Emerg Med* 1985; 3:203-205.
24. Sechi G, Serra A. Wernicke's encephalopathy: New clinical settings and recent advances in diagnosis and management. *Lancet Neurol* 2007; 6:442-455.
25. Yuki N, Odaka M, Hirata K: Acute ophthalmoparesis (without ataxia) associated with anti-GQ1b IgG antibody: Clinical features. *Ophthalmology* 2001; 108:196-200.
26. Kusner LL, Puwanant A, Kaminski HJ: Ocular myasthenia: Diagnosis, treatment, and pathogenesis. *Neurologist* 2006; 12:231-239.
27. Barton JJ, Fouladvand M: Ocular aspects of myasthenia gravis. *Semin Neurol* 2000; 20:7-20.
28. Lacomis D: Myasthenic crisis. *Neurocrit Care* 2005; 3:189-194.
29. Kubis KC, Danesh-Meyer HV, Savino PJ, Sergott RC: The ice test versus the rest test in myasthenia gravis. *Ophthalmology* 2000; 107:1995-1998.
30. Hubbard JI, Jones SF, Landau EM: The effect of temperature change upon transmitter release, facilitation and post-tetanic potentiation. *J Physiol* 1971; 216:591-609.
31. Vaphiades MS, Cure J, Kline L: Management of intracranial aneurysm causing a third cranial nerve palsy: MRA, CTA or DSA? *Semin Ophthalmol* 2008; 23:143-150.

31a. Wippold FJ II, et al: *ACR Appropriateness Criteria orbits, vision and visual loss*. Reston, Va: American College of Radiology (ACR); 2009. Accessed via the National Guideline Clearing House, www.guideline.gov, 2011.

32. Sanders SK, Kawasaki A, Purvin VA: Long-term prognosis in patients with vasculopathic sixth nerve palsy. *Am J Ophthalmol* 2002; 134:81-84.
33. Lewandowski CA, Rao CP, Silver B: Transient ischemic attack: Definitions and clinical presentations. *Ann Emerg Med* 2008; 52:S7-S16.

www.ketabpezeshki.com 66485457-66963820

Chapter 22

Red and Painful Eye

Joshua L. Wright and John M. Wightman

PERSPECTIVE

Epidemiology and Pathophysiology

Most eye complaints are not immediately sight-threatening and can be managed by an emergency physician. Nontraumatic diseases, such as glaucoma and peripheral vascular disease leading to retinal ischemia, are more common with advancing age. Ocular injuries are the leading cause of visual impairment and blindness in the United States.[1] More patients with postoperative complications can be expected to visit the emergency department (ED) as more vision correction surgeries are performed.

The external and internal anatomy of the eye is depicted in Figure 22-1A and B. The globe has a complex layer of blood vessels in the conjunctiva, sclera, and retina. Redness reflects vascular dilation and may occur with processes that produce inflammation of the eye or surrounding tissues. Eye pain may originate from the cornea, conjunctiva, iris, or vasculature. Each is sensitive to processes causing irritation or inflammation.

DIAGNOSTIC APPROACH

Rapid and accurate triage is the most critical consideration in the approach to the red and painful eye. The first question should be, "Did anything get in your eye?" If so, the second question should be, "What do you think it was?" This helps separate trauma from nontrauma, but, more important, seeks to identify quickly eyes that may have been exposed to a caustic substance. Patients exposed to caustic substances require rapid decontamination to prevent permanent loss of visual acuity.

Differential Considerations

Diagnoses are classically divided into traumatic and nontraumatic. Traumatic pain and redness can be caused by caustic fluids and solid materials, low-velocity contact with a host of materials that can fall or be rubbed into the eye, higher-velocity blunt-force impacts to the orbit or globe, or potentially penetrating injuries. Causes of nontraumatic pain and redness require a more detailed history, including contact lens use and questions directed toward determining the likelihood of systemic illnesses.

Pivotal Findings

Measurement of the patient's best corrected visual acuity (i.e., with glasses on, if available) with each eye individually and with both eyes together provides vital information in evaluation of eye complaints. Only a few situations preclude early and accurate visual acuity testing. Eyes exposed to caustic materials should be irrigated as soon as possible. Patients with sudden and complete visual loss in one eye require prompt funduscopic examination to determine the possibility of acute central retinal artery occlusion. This condition is readily apparent as a diffusely pale retina with indistinct or unseen retinal arteries (Fig. 22-2).

Other pivotal findings, which are more likely to be associated with a serious diagnosis, in patients with a red or painful eye are listed in Box 22-1.

History

Chief complaints of pain can be manifestations of a variety of sensations. When carefully questioned, some patients may differentiate among itching, burning, dull pain, sharp pain, and perception of a foreign body. Itching tends to be more often caused by blepharitis, conjunctivitis, or dry eye syndrome. Burning is associated with these conditions and with other mostly superficial problems, such as irritation of a pterygium or pinguecula, episcleritis, or limbic keratoconjunctivitis. A foreign body sensation is more typical of corneal irritation (abrasion, ulcer) or inflammation (keratitis). Sharp pain generally results from abnormalities of the anterior eye, such as keratitis, uveitis, and acute angle–closure glaucoma. Dull pain may be a manifestation of increased intraocular pressure (IOP) or referred from an extraorbital process, such as sinusitis, migraine headache, or temporal arteritis.

A chief complaint of redness commonly results from palpebral or limbal injection of the conjunctiva. However, free blood can be noted behind the bulbar conjunctiva (i.e., subconjunctival hemorrhage) or in the anterior chamber (i.e., hyphema). Both of these can be spontaneous or post-traumatic. Spontaneous subconjunctival hemorrhages may follow coughing or straining. Spontaneous subconjunctival hemorrhage is painless, and the presence of pain raises concern for a more serious cause of the hemorrhage, such as direct globe injury. Often, it occurs without any identifiable precipitating incident and is simply noticed by the patient when looking in a mirror. Hyphema of sufficient size to be noted by the patient or bystander usually arises with pain and blurred vision.

Other subjective findings may be transient and detected only by history. The patient may relate lid swelling, tearing, discharge, crusting, or sensitivity to light. Lid swelling can be caused by inflammatory and noninflammatory processes. Concurrent erythema of the lid favors the former. In the absence of trauma or other external irritant (e.g., contact dermatitis), inflammatory processes include primary lid problems, such as hordeolum (i.e., stye) or blepharitis as well as extension from concomitant conjunctivitis or cellulitis in orbital or periorbital structures. When pain is present, tearing is usually secondary. Discharge and crusting are most commonly associated with conjunctivitis, whether allergic, viral, or bacterial. Blepharitis, dacryocystitis, and

www.ketabpezeshki.com 66485457-66963820

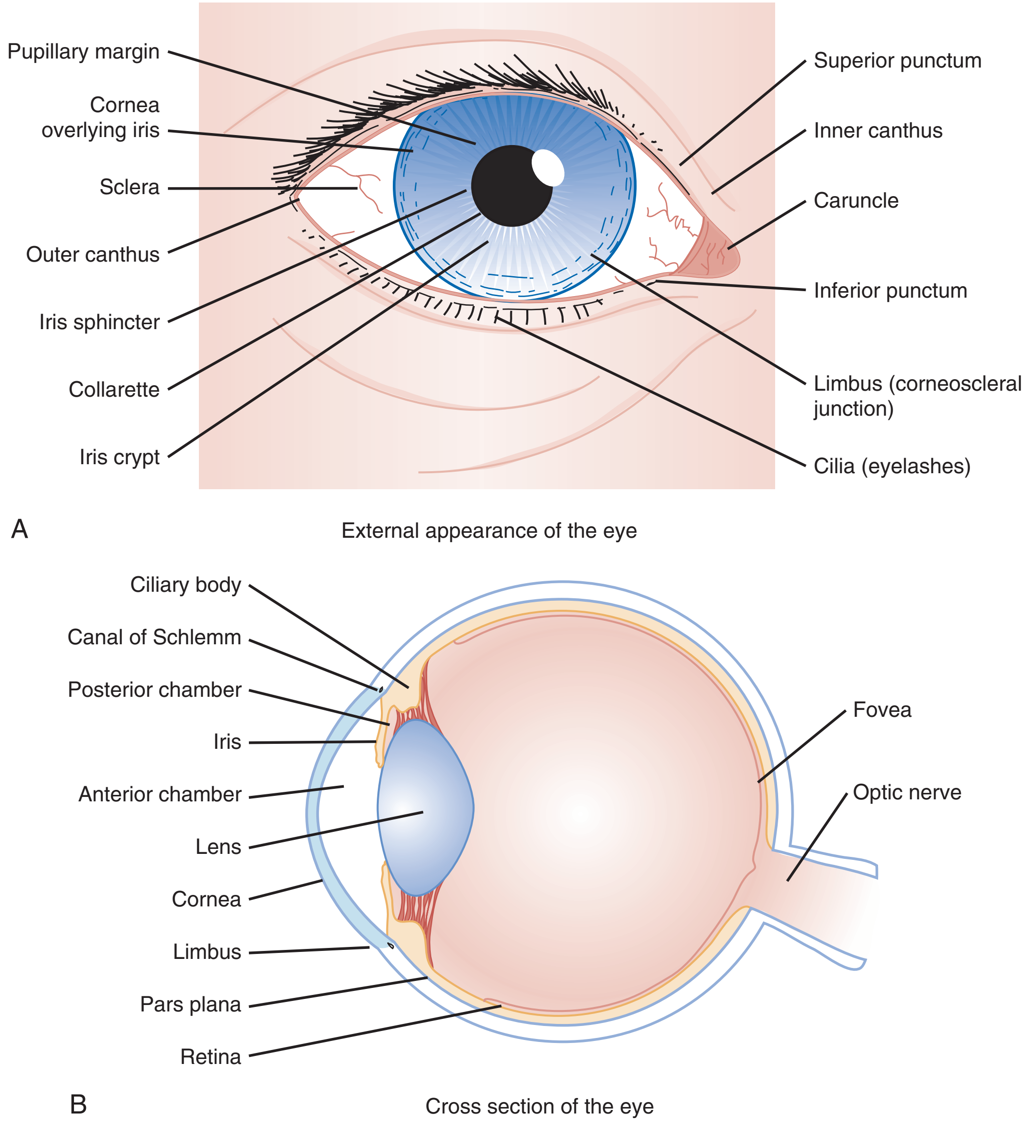


Figure 22-1. External **(A)** and internal **(B)** anatomy. (From Ragge NK, Easty DL: Immediate Eye Care. St Louis: Mosby-Year Book; 1990.)

canaliculitis are other inflammatory processes that may create a discharge and subsequent crusting.

Other eye status review questions include the following:

- Are contact lenses used? If so, what type, how are they cleaned, and how old are the lenses? Has there been a change in the pattern of use (especially increased use)? Were the lenses worn for a particularly long period recently? Are there problems with the lenses drying out? Does insertion of the lenses worsen or relieve the symptoms? Contact lenses alter the physiology of the cornea, making it relatively hypoxic, drier, and more susceptible to bacterial infection with subsequent ulceration.
- Are glasses worn? If so, when was the last assessment for adequate refraction? When the patient is examined for objective abnormalities in visual acuity, the patient's subjective interpretation of changes from his or her baseline may be all that is available when corrective lenses are not available or their prescription is out of date.
- Has previous injury or eye surgery occurred? Abnormal examination findings, such as an eccentric or irregularly shaped pupil, may be the patient's baseline. Pain and redness are expected shortly after eye surgery, but many surgical complications also manifest with a red and painful eye.
- What is the patient's usual state of health? Several systemic diseases may cause symptoms and signs in and around the eye. Giant-cell arteritis is a vasculitis with subacute systemic manifestations but often acute eye complaints.
- What medications are being taken? Medications that affect the sympathetic or parasympathetic nervous systems may affect ocular physiology, such as aqueous production, or pupil size and reactivity. Bleeding may be potentiated by anticoagulant or antiplatelet medications.
- Are there any known or suspected allergies? Environmental allergens are a common cause of conjunctivitis. Other superficial manifestations can be from chemicals (e.g., contact lens-cleaning solution) or other materials (e.g., makeup).

Physical Examination

A complete eye examination usually includes eight components, although many patients require only a limited or directed eye examination, depending on the presentation. The mnemonic *VVEEPP* (pronounced "veep") plus slit-lamp and funduscopic examinations represent these components (Box 22-2). Slit-lamp examination is recommended for any complaint involving trauma

www.ketabpezeshki.com 66485457-66963820

and for any medical presentation involving foreign body sensation or alteration of vision. Funduscopic examination is usually pursued if there is visual loss, visual alteration, or suggestion of serious pathology in the history and initial physical examination. A thorough physical examination can be conducted in the following order.

Visual Acuity

The initial determination of a patient's visual acuity provides a baseline from which deterioration or improvement may be followed. It is also predictive of functional outcome after ocular trauma. Visual acuity is quantitatively assessed by use of a Snellen chart test at a distance of 20 feet (6 m) or a Rosenbaum chart at a distance of 14 inches. Young patients who cannot yet read letters and numbers should be tested with an Allen chart that depicts easily recognizable shapes. Each eye is tested separately, with the opposite eye carefully covered. Patients who do not have their prescribed corrective lenses may be evaluated by having them view the chart through a pinhole eye cover, which negates most refractive errors in vision.

If the patient cannot distinguish letters or shapes on a chart, visual acuity is determined qualitatively. Any printed material suffices. The result may be recorded as, for example, "patient able to read newsprint at 3 feet." If this is not possible, visual acuity is recorded as:

- Unable or able to count fingers (CF)
- Unable or able to perceive hand motion (HM)
- Unable or able to perceive light (LP)

Visual Field Testing

Confrontation is the most common method of testing visual fields in the ED but is unreliable for detection of anything short of an extensive field deficit. Fortunately, visual field examination rarely adds useful information in the evaluation of the acutely red and painful eye. Detection of a scotoma usually represents a retinal problem. However, glaucoma may cause scotomata that can be crescent shaped, involve just the binasal visual fields, or affect all peripheral vision. Hemianopia or quadrantanopia is more commonly a problem of the neural pathways to the brain.

External Examination

Gross abnormalities are assessed by a visual inspection of both eyes simultaneously. Findings may be more apparent if compared with the opposite side. Fractures of facial bones are associated with ocular injuries, some of which require immediate intervention by an ophthalmologist.[2]

Globe position is part of the external examination. Subtle exophthalmos and enophthalmos are rare and are best detected by looking inferiorly, tangentially across the forehead, from over the patient's scalp. Exophthalmos (proptosis) may have traumatic or nontraumatic causes but is a result of increased pressure or a space-occupying lesion within the orbit, which may manifest as pain. Medical causes include cellulitis or intraorbital or lacrimal tumors. Hyperthyroidism may cause enlargement of extraocular muscles. The most important cause of exophthalmos in the ED is retrobulbar hematoma, a condition characterized by hemorrhage within the bony orbit, behind the globe. Orbital compartment syndrome pushes the globe forward, stretching the optic nerve and retinal artery and increasing IOP. The resulting microvascular ischemia is sight-threatening if sufficiently severe and persistent. Orbital emphysema and inflammation caused by a retained foreign body behind the eye are other causes of exophthalmos. The discovery of exophthalmos should prompt ocular tonometry measurements to determine the urgency of intervention. Trauma,

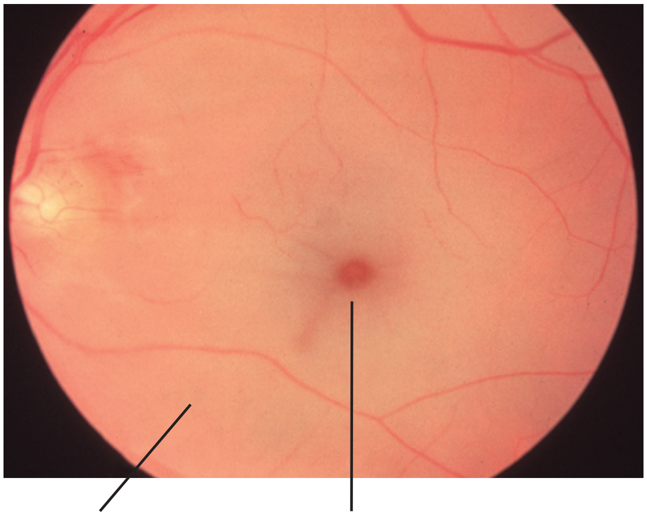


Figure 22-2. Key funduscopic findings in acute central retinal artery occlusion include general pallor of the retina (except for a characteristic cherry-red spot where the perfused choroid shows through the thinner fovea) and attenuation of retinal arteries (possibly with retinal veins preserved as in the photograph). (From Kaiser PK, Friedman NJ, Pineda R II: The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd ed. Philadelphia: WB Saunders; 2004.)

Box 22-1 Pivotal Findings More Likely Associated with a Serious Diagnosis in Patients with a Red or Painful Eye

Severe ocular pain
Persistently blurred vision
Proptosis
Reduced ocular light reflection
Corneal epithelial defect or opacity
Limbal injection (i.e., ciliary flush)
Pupil unreactive to a direct light stimulus
Wearer of soft contact lenses
Neonate
Immunocompromised host
Worsening signs after 3 days of pharmacologic treatment

Adapted and reprinted, with permission, from Trobe JD: The Physician's Guide to Eye Care. San Francisco: Foundation of the American Academy of Ophthalmology; 2001.

Box 22-2 Complete Eye Examination

Visual acuity (best possible with use of correction)
Visual fields (tested by confrontation)
External examination
- Globe position in orbit
- Conjugate gaze
- Periorbital soft tissues, bones, and sensation

Extraocular muscle movement
Pupillary evaluation (absolute and relative)
Pressure determination (tonometry)
Slit-lamp examination
- Lids and lashes
- Conjunctiva and sclera
- Cornea (with fluorescein in some cases)
- Anterior chamber
- Iris
- Lens

Funduscopic examination

Adapted from Wightman JM, Hurley LD: Emergency department management of eye injuries. Crit Decis Emerg Med 1998; 12:1-11.

www.ketabpezeshki.com 66485457-66963820

particularly penetrating globe injury with extrusion of vitreous, can cause the globe to recede into the orbit, but the most common cause of enophthalmos is actually pseudoenophthalmos when the contralateral globe is proptotic.

Inspection also involves examination of the upper and lower palpebral sulci for foreign bodies or other abnormalities. The lower sulcus is easily viewed after manual retraction of the lower lid toward the cheek and having the patient gaze upward. The upper sulcus is inspected by pulling its lashes directly forward and looking under the lid with white light. The lid can then be everted by pressing a cotton-tipped applicator in the external lid crease and folding the lid margin over the applicator.

Conjunctivitis is a common diagnosis after evaluation of patients with red and painful eyes, but determination of cause is much more difficult on clinical grounds. Patients may be unaware of exposures that could cause a chemical conjunctivitis. Without a known history of environmental allergies or other symptoms and signs to suggest an allergic reaction, allergic conjunctivitis may be mistaken for an infection. However, these are usually managed with removal of any known offending agent and symptomatic relief only. On the other hand, acute infectious conjunctivitis can be bacterial or viral, and management should ideally be directed toward the specific microbiologic cause. The acute management of infectious conjunctivitis accounts for over one-half billion dollars in indirect lost productivity and direct costs of antibiotic prescriptions,[3] when many patients do not need them.[4]

The presence of punctate "follicles" (i.e., hypertrophy of lymphoid tissue in Bruch's glands) along the conjunctival surfaces of one or both lower lids has been touted to be relatively specific for a nonbacterial (i.e., viral or toxic) cause—though one notable exception is trachoma, a chronic keratoconjunctivitis caused by *Chlamydia trachomatis.* Indeed, the "typical" viral "pinkeye" has been called *acute follicular conjunctivitis.*[5] Some authorities also believe that the mucoid discharge associated with viral conjunctivitis can be clinically differentiated from the purulent discharge associated with bacterial infection.[6] However, most research studying the association of symptoms and signs with positive bacterial cultures have grouped "mucoid or purulent" discharges into one finding, not requiring primary care physician participants to discriminate between the two during data collection.[7,8] Thus no experimental evidence supports or refutes these expert opinions.[9]

Eyelids sticking together, particularly in the morning, is commonly cited as clinical evidence of bacterial, as opposed to viral, conjunctivitis, but this is unreliable. One multicenter primary care study in the Netherlands used logistic regression analysis to conclude that its presence plus the absence of itch and a prior history of conjunctivitis was associated with bacterial conjunctivitis; however, the 95% confidence intervals for the area under the receiver operating characteristic curve ranged from 0.63 to 0.80, thus making it a poor to only fair clinical prediction rule.[7] In a single U.S. pediatric ED spanning ages from 1 month to 18 years, a similar analysis found sticky eyelids and either mucoid or purulent discharge to have a positive likelihood ratio of 3.1, and a post-test probability of 96% for positive bacterial cultures in their population; however, this likelihood ratio also indicates only a poor-to-fair test.[8] Viral cultures were not performed in either of these studies, so the possibilities of copathogens or bacterial culture of nonpathogenic flora was not assessed. Therefore no good evidence exists for differentiating bacterial from viral causes on clinical grounds.

Extraocular Muscle Function

Limitation of ocular movement in one eye may be detected by having the patient follow the examiner's finger or a bright light through the cardinal movements of gaze. The eyes may move in a disconjugate fashion, or the patient may admit to diplopia if asked. Diplopia on extreme gaze in one direction may indicate entrapment of one of the extraocular muscles within a fracture site but more often is caused simply by edema or hemorrhage related to the injury and is functional rather than actual entrapment. In the absence of trauma, diplopia is rarely associated with redness or pain.

Pupillary Evaluation

The pupils are inspected for abnormalities of shape, size, and reactivity. These examinations are conducted with light specifically directed into the pupil and by means of the swinging flashlight test.

Blunt or penetrating trauma, previous surgery (e.g., iridotomy for cataract extraction), and synechiae from prior iritis or another inflammatory condition are the most common causes of irregularly shaped pupils.

Asymmetrically sized pupils may represent normal or pathologic conditions. Physiologic anisocoria is a slight difference in pupil size that occurs in up to 10% of the population. Topical or systemic medications, drugs, and toxins may cause abnormal pupillary constriction or dilation.

Pathologic reasons for failure of one pupil to constrict with a direct light stimulus include globe injury, abnormalities of afferent or efferent nerves, and paralysis of the ciliaris or sphincter pupillae muscles in the iris. Potentially serious problems that also cause pain and redness include uveitis and acute angle–closure glaucoma.

The swinging flashlight test is used to determine whether a relative afferent pupillary defect (RAPD) exists. The patient fixes the gaze on a distant object, and the examination room is darkened. The size of the pupils in lowered light is noted, and unless there is physiologic anisocoria, the pupils should be equal in size. The direct and consensual light responses of the eyes are compared as a light source, angled into the pupil from in front of the cheeks, is swung back and forth between the two. When the light source shines into an eye with an RAPD, the pupil dilates because the consensual response from withdrawal of light from the opposite eye with normal afferent activity is stronger than the direct constrictive response to light in the affected eye with inhibited afferent activity. It is termed "relative" because the response is compared with that of the opposite side as the light source is alternated between eyes. An RAPD may be partial or complete and may result from inhibition of light transmission to the retina because of vitreous hemorrhage, loss of some or all of the retinal surface for light contact because of ischemia or detachment, or the presence of lesions affecting the prechiasmal optic nerve (e.g., optic neuritis).

Pressure Determination

Ocular tonometry is usually the last examination performed in the ED. Common methods of determining the IOP in the ED include use of electronic, manual (e.g., Schiøtz), or applanation tonometers. IOPs in the 10- to 20-mm Hg range are considered normal. Causes of intraocular hypertension include glaucoma in its many forms, suprachoroidal hemorrhage, and space-occupying retrobulbar pathology.[10] Patients with IOPs exceeding 20 mm Hg should undergo ophthalmologic consultation. Rapid treatment is usually not necessary until the pressure exceeds 30 mm Hg.

Slit-Lamp Examination

The slit lamp permits a magnified, binocular view of the conjunctivae and anterior globe for diagnostic purposes and to facilitate delicate procedures. It allows depth perception in otherwise clear

www.ketabpezeshki.com 66485457-66963820

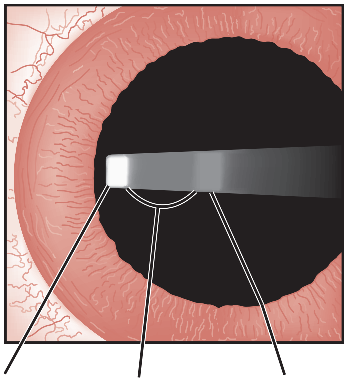


Figure 22-3. Technique of slit-lamp examination with a short, narrow light beam projected from an extreme temporal angle across the contrasting black pupil to better find cells or "flare" indicative of acute anterior uveitis. (From Ragge NK, Easty DL: Immediate Eye Care. St Louis: Mosby-Year Book; 1990.)

structures, such as the cornea, aqueous humor, and lens. The slit-lamp examination can include the following:

- Lids and lashes may be inspected for blepharitis and pointing of a lid abscess (i.e., hordeolum). The inner canthus and lacrimal punctum may be better viewed for evidence of dacryocystitis.
- Punctures, lacerations, and inflammatory patterns of the conjunctiva or sclera may be discovered with magnification.
- Corneal abrasions, ulcers, foreign bodies, and other abnormalities may be seen. The depth of these lesions may be accurately assessed with an angled beam. Edema, which appears as a white haze or cloudiness within clear structures, can be differentiated within the epithelium or deeper stroma.
- The anterior chamber may be examined for cells (e.g., red and white blood cells) and "flare." Cells are seen as small floating objects caught in the beam of a highly angulated slit-lamp light, as dust floating in the movie theater glows from the reflected light of the projector beam. Flare is a diffuse haziness, is related to cells and proteins suspended in the aqueous humor, is often visible only when illuminated directly (Fig. 22-3). It usually represents deep inflammation of the eye and is often seen in iritis. Collections of layered blood or pus in the dependent portions of the anterior chamber are called *hyphema* or *hypopyon,* respectively, and are graded by the percentage of the vertical diameter of the visible iris when the head is upright. Foreign bodies that have penetrated the cornea may be found floating in the anterior chamber.
- The trabeculated pattern of the iris can be seen in detail. Spiraling muscle fibers may be seen in acute angle–closure glaucoma. If the beam is shown almost coaxially with the examiner's line of sight such that the red reflex is elicited, tears in the iris may be seen by light returning through the iris itself instead of just through the pupil.
- The lens should be examined for position, general clarity, and the presence of opacities or foreign bodies. The type and position of any lens implants can also be better assessed during a slit-lamp examination.

Direct Funduscopic Examination

Emergency physicians most commonly perform a nondilated funduscopic examination because there are several eye conditions in which dilation may be harmful (e.g., glaucoma). Iridodialysis, lens dislocation, and conditions requiring early intervention are usually identifiable along the visual axis.

Inability to obtain a red reflex or visualize the fundus of the eye can be caused by the following:

- Opacification of the cornea, most commonly from edema secondary to injury or infection
- Hyphema or hypopyon within the anterior chamber
- Extremely miotic pupil
- Cataract of the lens
- Blood in the vitreous or posterior eye wall
- Retinal detachment

In the absence of trauma, few posterior findings are associated with chief complaints of external redness. Findings associated with visual loss include pallor of the retina indicating ischemia, "cupping" of the optic disk indicating glaucoma, indistinctness of disk margins indicating papilledema or optic neuritis or neuropathy, air or plaque emboli in retinal arteries, and a host of other signs indicating more chronic ocular or systemic pathology not normally amenable to management in the ED.

Bedside Testing

Fluorescein solution and slit-lamp examination with use of the cobalt blue light source are the best means for identifying damage to the corneal epithelium, including damage that cannot be seen with conventional slit-lamp examination. Fluorescein is not taken up by intact corneal epithelium but is absorbed into corneal defects, making them easy to identify. When doubt exists as to whether the fluorescein in an area of interest is on or in the corneal epithelium, absence of movement on blinking confirms corneal absorption and hence a corneal lesion. Use of fluorescein may reveal corneal abrasions and ulcers as well as damage from keratitides related to chemicals, ultraviolet light, or infections (e.g., herpes).

Relief of discomfort after instillation of a topical anesthetic can be used as a diagnostic test for an external source of pain. In general, abolition of pain by local anesthetic drops indicates pain of corneal origin. Modest but incomplete relief suggests a conjunctival process. Intraocular pain is not diminished by local anesthetic solution. When ocular penetration is suggested, Seidel's test can be used. This test involves placing a fluorescein strip directly over an area of possible corneal disruption. The highly localized concentration of fluorescein may facilitate identification of the corneal defect with a slit lamp by allowing visualization of leaking aqueous fluid diluting the fluorescein. This test does not work on the conjunctiva overlying the sclera, and a negative test result does not rule out a full-thickness corneal injury.

Ancillary Testing

Temporal arteritis may manifest with eye pain and decreased visual acuity. Use of an erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) can be helpful tools in the acute phase if they are elevated; however, temporal arteritis can occur with normal levels of ESR and CRP if the clinical history and examination findings are typical.[11]

Infections are usually evident on examination, and laboratory tests such as a complete blood count are not necessary. Microbiologic cultures are rarely ordered in the ED.

Plain radiography may be used to identify facial fractures associated with facial or ocular trauma or indirectly by detecting an air-fluid level in the orbit or fluid in the paranasal sinuses, but use of this simple ancillary study is waning rapidly, likely because of consultants' desires for computed tomography (CT). CT, through use of 1.5-mm axial and coronal cuts, does provide superior imaging that affects definitive care decisions.[12-14]

www.ketabpezeshki.com 66485457-66963820

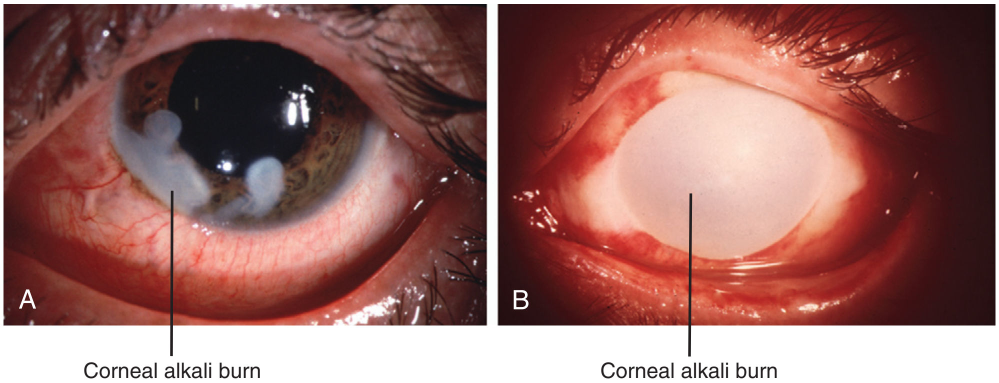


Figure 22-4. A, Alkali burn demonstrating corneal burns and conjunctival injection on the day of the accident. B, Complete corneal tissue destruction 7 days after alkali burn. (From Kaiser PK, Friedman NJ, Pineda R II: The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd ed. Philadelphia: WB Saunders; 2004.)

CT also reliably localizes metal and many nonradiopaque foreign bodies in the globe and orbit. It can also detect small amounts of intraocular air after penetrating trauma. Ultrasonography is more sensitive for detecting intraocular foreign bodies, but CT is better at delineating the damage caused by them, so they are complementary tests. Magnetic resonance imaging (MRI) clearly delineates the orbital and retro-orbital structures but cannot be used unless ferromagnetic foreign bodies can first be definitively excluded by CT.[12-16]

DIFFERENTIAL DIAGNOSIS

Clinical findings most indicative of serious eye disorders are listed in Box 22-1.

Critical Diagnoses

Caustic injury to the eye can rapidly lead to a destructive keratoconjunctivitis (Fig. 22-4A and B) if the agent is not removed immediately. The diagnosis is made on history alone, before any other examination is performed. Early and copious irrigation is indicated. Many patients will have already undergone extensive irrigation at the job site, but when the exposure has occurred in the home, irrigation before arrival in the ED is uncommon. Alkaline caustic agents cause a liquefactive necrosis of the cornea by progressively reacting with the corneal layers, and destruction is severe and relentless. Continuous irrigation is the only effective method to terminate the reaction and should be continued for at least 30 minutes. Acid injury is much less severe and requires less irrigation than alkaline exposures. Both types require irrigation until the pH of the tears is neutral and the patient is essentially asymptomatic.

Acute angle–closure glaucoma is a relatively rare but important critical diagnosis to make in the ED. Patients report pain, the onset of which is often sudden in low-light conditions requiring pupillary dilation through contraction and thickening of the iris peripherally. The iris becomes immobile and often irregular, and the pupil is commonly fixed at 5 to 6 mm in diameter. Inability of the pupil to constrict may result in photophobia, and accommodation may be affected. These reactions and the increased IOP can lead to frontal headache, nausea, and vomiting. As inflammation progresses, limbal injection of the conjunctiva is almost universally seen. Figure 22-5 demonstrates many of these findings. Immediate medical intervention in the ED and urgent ophthalmologic consultation are warranted.

Retrobulbar hematoma (blood) is usually caused by orbital trauma, but it can also occur spontaneously in patients with coagulopathy. Retrobulbar abscess (pus) or emphysema (air) can also

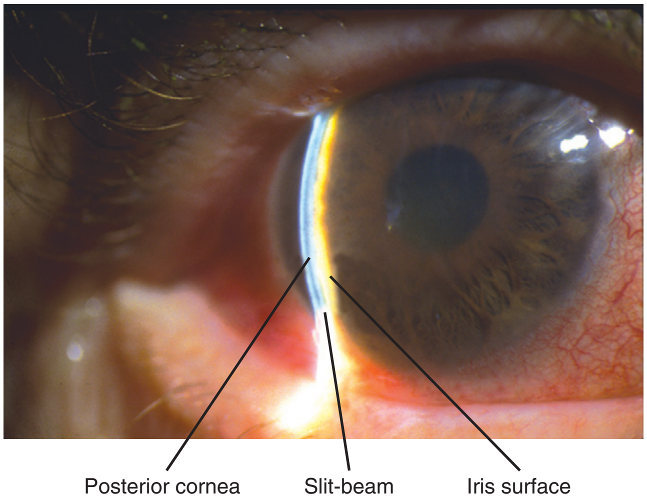


Figure 22-5. Primary angle–closure glaucoma with very shallow anterior chamber and iridocorneal touch (no space between slit-beam view of cornea and iris). (From Kaiser PK, Friedman NJ, Pineda R II: The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd ed. Philadelphia: WB Saunders; 2004.)

occur. Elevated IOP in any of these conditions constitutes orbital compartment syndrome and a surgical emergency.[17,18] Emergency intervention requires decompressing the orbit by performing lateral canthotomy and inferior cantholysis.[17,18]

Emergent Diagnoses

Most emergent diagnoses involve some kind of inflammation secondary to trauma, infection, or systemic disease. These include keratitis, anterior uveitis, scleritis, and endophthalmitis. Any of these may be complications of surgical procedures, and an appropriate ophthalmologic history should be obtained.

Keratitis, or inflammation of the cornea, is most commonly viral in origin but can also be caused by exposure to intense ultraviolet light (e.g., snow blindness, arc welder's blindness), various chemicals, or ischemia related to contact lens use. Patients report an intense foreign-body sensation, ciliary spasm causes photophobia that is often severe, and the affected eyes are often clenched shut. Topical anesthesia provides immediate (but temporary) relief of pain, thus reinforcing the corneal origin of the process and facilitating examination and definitive diagnosis. Corneal abrasions are very common and may be identified by white light or fluorescein-facilitated blue light with use of a slit lamp or any

www.ketabpezeshki.com 66485457-66963820

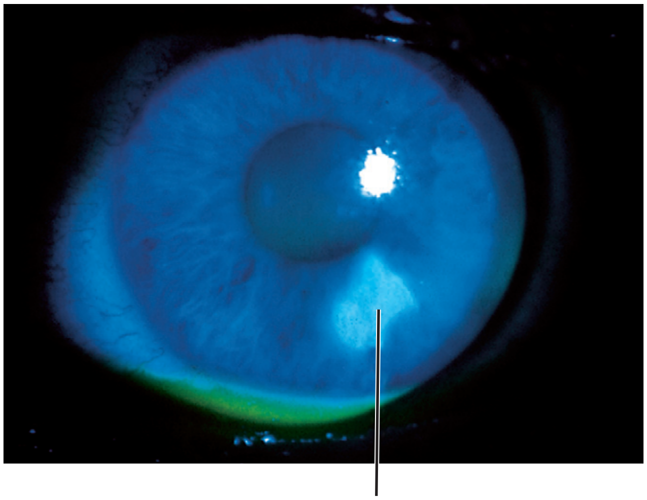


Figure 22-6. Corneal abrasion demonstrating fluorescein pooling of a small inferior epithelial defect. (From Kaiser PK, Friedman NJ, Pineda R II: The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd ed. Philadelphia: WB Saunders; 2004.)

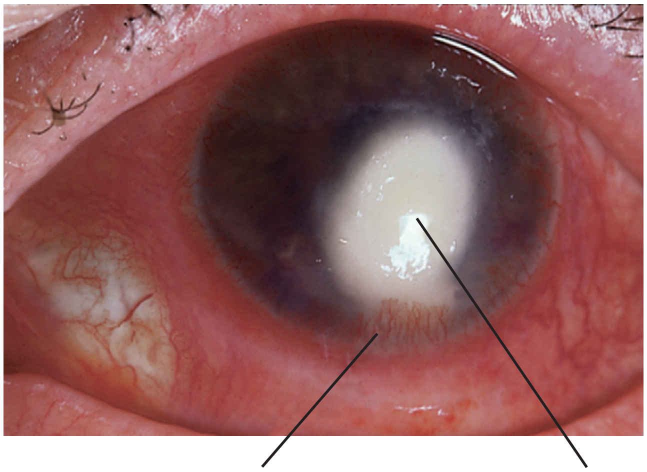


Figure 22-7. Bacterial keratitis demonstrating large, central *Streptococcus pneumoniae* corneal ulcer. Note the dense, white corneal infiltrate and the extreme conjunctival injection. (From Kaiser PK, Friedman NJ, Pineda R II: The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd ed. Philadelphia: WB Saunders; 2004.)

other magnification (Fig. 22-6). After thorough irrigation, thermal and chemical burns receive a careful slit-lamp examination for potential full-thickness injury. If this is not found, superficial corneal burns may be treated similarly to abrasions.

In immunocompetent hosts, corneal ulcerations are most commonly caused by overuse of contact lenses.[19] Ulcers can be large and easy to visualize (Fig. 22-7) or small and difficult to detect. They are best identified under slit-lamp examination by noting a denuding of epithelium with surrounding edema, the increased interstitial water of which is seen as whitish clouding of the normally clear tissue. Almost all ulcerations require evaluation by an ophthalmologist within 24 hours. Infections of the cornea with herpes simplex virus can rapidly lead to opacification and significant visual loss. It is most commonly recognized by a characteristic dendritic pattern of fluorescein pooling under blue light (Fig. 22-8). Anterior uveitis, which includes iritis and iridocyclitis, often

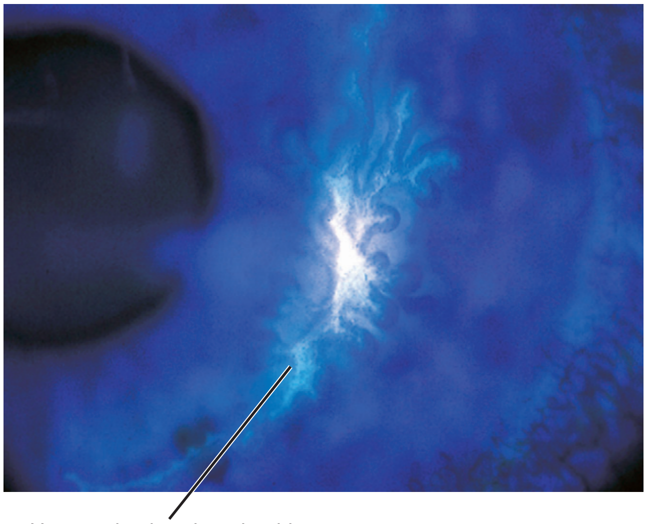


Figure 22-8. Patient demonstrating fluorescein pooling of herpes simplex virus dendrite. (From Kaiser PK, Friedman NJ, Pineda R II: The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd ed. Philadelphia: WB Saunders; 2004.)

occurs secondary to a traumatic injury or infectious process or can be associated with serious systemic immune diseases, such as adult and juvenile rheumatoid arthritis, sarcoidosis, and ankylosing spondylitis.

Scleritis is rare and may be difficult to differentiate from episcleritis, which is a somewhat more common and more benign inflammation. The former is commonly idiopathic but may be associated with a systemic inflammatory process, such as a connective tissue disease, gout, or infection (e.g., Lyme disease, syphilis, tuberculosis). Eye redness in episcleritis results from dilation of the episcleral blood vessels just underneath the conjunctiva, usually in a small sector of the visible portion of the globe. If the location of the involved layer is in doubt, administration of topical phenylephrine 2.5 to 10% can help to differentiate episcleritis from scleritis by causing blanching of the superficial episcleral vessels while not affecting the deeper scleral vessels.[20,21] The pain of scleritis is typically slower in onset but is often described as a severe "boring" pain that radiates to the ipsilateral forehead, cheek, or jaw. Engorgement of scleral vessels is usually more prominent and more diffuse than that of the episcleral vessels in episcleritis. A bluish hue may be seen as the underlying pigmented epithelium shows through the edematous, and hence more translucent, sclera (Fig. 22-9). Scleritis may be associated with anterior uveitis, cataract, and secondary glaucoma.

Endophthalmitis usually results from an infection of structures inside the globe. It is most common after penetrating trauma but may begin after hematogenous seeding from a remote or systemic infection, particularly in immunocompromised hosts. Unless it is detected early and is responsive to aggressive antimicrobial therapy, endophthalmitis is a devastating process that frequently necessitates enucleation.

Urgent Diagnoses

Penetrating ocular trauma is evaluated by history (e.g., working with high-speed grinding equipment), examination (extrusion of aqueous humor or other globe content; direct visualization of a foreign body in the anterior chamber, vitreous, or retina), or identification of the offending object by biplanar plain radiography, thin-cut CT, or ultrasonography. MRI should not be used if there is any possibility that the foreign object may be metallic. Indirect indicators of globe penetration are hyphema, an irregularly shaped

www.ketabpezeshki.com 66485457-66963820

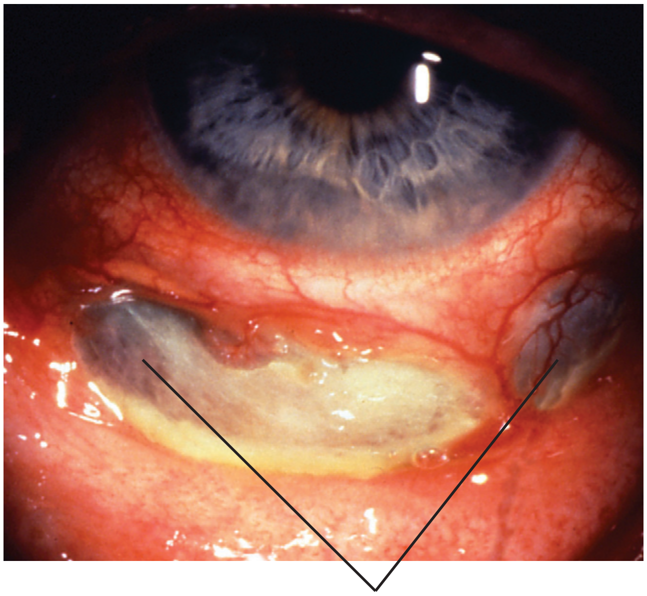


Figure 22-9. Diffuse scleritis with slight bluish region in addition to injection of scleral, episcleral, and conjunctival vessels. (From Kaiser PK, Friedman NJ, Pineda R II: The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd ed. Philadelphia: WB Saunders; 2004.)

pupil from traction on or injury to the iris's attachments, or lack of a red reflex. If penetrating ocular injury is confirmed or if the possibility persists after evaluation, an ophthalmologic consultation is indicated.

Spontaneous or traumatic hyphema is often managed conservatively. Blood in the anterior chamber is usually the result of direct ocular trauma and may be associated with traumatic mydriasis or an obvious tear of the iris. If penetration and rupture can be reasonably excluded, the hyphema should be graded and IOP determined. Intraocular hypertension (or hypotension in the case of occult globe rupture) after trauma is also evaluated by an ophthalmologist urgently. Inability to view posterior structures through the anterior blood may necessitate radiologic or ultrasonographic imaging.

Diagnostic Algorithm

A recommended algorithmic approach to the patient with an acute red eye is provided in Figure 22-10.

EMPIRICAL MANAGEMENT

Irrigation

Any clean water is appropriate for irrigation, and prompt initiation takes precedence over procurement of a particular irrigating solution. The most important principles are *rapid and copious* dilution and removal of the offending material. An eyewash station or faucet with tap water may be employed. Normal saline may be instilled through the cut end of a liter bag of normal saline or through the end of macrodrip intravenous administration tubing. If there is no gross eye injury, a Morgan lens may be attached to this tubing so the ED staff does not have to help the patient hold the eye open. Quickly administering two drops of topical anesthetic and allowing 30 seconds or so for the anesthetic to become effective greatly facilitates patients' tolerance of the prolonged irrigation required. It is recommended that the first 500 to 1000 mL of irrigation fluid be administered while the eye is being examined; then the Morgan lens may be placed.

Table 22-1 Duration of Action for Common Mydriatic and Cycloplegic Medications

NAME	CONCENTRATION (%)	COMMON DURATION	MAXIMUM DURATION
Ephedrine*	5.0	0.5-1 hr	3 hr
Phenylephrine*	2.5	0.5-1 hr	3 hr
Tropicamide	0.5	3-4 hr	6 hr
Cyclopentolate	0.5	12-18 hr	24 hr
Homatropine	1.0	1-2 days	3 days
Scopolamine	0.5	2-5 days	7 days
Atropine	0.5	5-10 days	14 days

*Mydriatic action only; no cycloplegic effect. Combination products such as Cyclomydril, which is cyclopentolate 0.2% and phenylephrine 10%, are also available.

Pain Relief

Pain often interferes with obtaining an adequate assessment. A topical anesthetic, such as proparacaine 0.5%, may facilitate cooperation in patients with possible injury or inflammation of the anterior eye by reducing pain and blepharospasm long enough for a targeted history to be obtained and a focused examination to be performed. Topical anesthetic agents should not be given to patients to use at home. Parenteral or oral analgesics can be used for severe deep pain not amenable to topical relief in the ED, or for outpatient management of discomfort after discharge.

Mydriatic and Cycloplegic Agents

Dilation of the pupil is not usually necessary in the ED for funduscopic examination but may relieve pain associated with ciliary spasm in anterior uveitis. Mydriatic agents (e.g., phenylephrine, tropicamide) merely prevent constriction of the pupil by paralyzing the sphincter pupillae muscle of the iris. Cycloplegic agents (e.g., cyclopentolate, homatropine) paralyze the ciliaris muscle, with an accompanying mydriatic effect. The agent chosen should be guided by the desired duration of mydriasis for the particular condition being treated (Table 22-1). Mydriatic agents are contraindicated in patients with narrow-angle glaucoma.

Antimicrobial Agents

Most conjunctivitis of viral origin does not require antiviral treatment. Important exceptions are viruses in the Herpesviridae family. Trachoma has been the most common infectious cause of blindness and can be treated with azithromycin.[22] The most common causes of bacterial conjunctivitis are nontypable *Haemophilus influenzae, Streptococcus pneumoniae,* and *Staphylococcus aureus.*[8,23]

The use of broad-spectrum topical antibiotics in cases of proven bacterial conjunctivitis has been associated with benefit, showing significantly higher clinical remission rates. When used for empirical treating for presumed bacterial conjunctivitis, inexpensive combination products such as polymyxin B plus trimethoprim solution or polymyxin B plus bacitracin ointment are good initial choices. Many other antibiotics have been tested. Chloramphenicol is the most frequently prescribed ophthalmic antibiotic in Europe.

Empirical treatment of all common acute infectious conjunctivitis with topical antibiotics is quite controversial from both

www.ketabpezeshki.com 66485457-66963820

clinical and societal perspectives. As discussed in the physical examination section of this chapter, distinguishing bacterial from viral causes is clinically difficult, and no good clinical prediction rules exist to assist decision-making. Nonetheless, acute infectious conjunctivitis from all causes is usually mild, resolves on its own, and very rarely leads to serious complications.[23] Therefore treating all patients is expensive, potentially risky, and generally unnecessary.[24] However, one meta-analysis of five relatively heterogeneous clinical trials not including ED populations found that almost two thirds of cases resolved with placebo, but it also found an increase in bacterial eradication and clinical cure with antibiotics (number needed to treat was 6 if treated in the first 5 days after symptom onset, and was 13 if treated in the second 5 days).[23]

One study interviewed a small sample of patients seen in a primary care setting in the United Kingdom. The researchers found that most patients knew that conjunctivitis was a minor illness yet believed that it would not resolve without treatment, though they were open to alternative management approaches after a brief education.[25] Consistent with several authors, we recommend a delayed treatment strategy wherein patients are educated on the normally self-limiting nature of the process but are not prescribed antibiotics and are given advice to seek follow-up evaluation by their primary care physician if symptoms are not improving after 72 hours. Alternatively, an antibiotic prescription can be provided at the initial visit, but the patient is told not to fill the prescription or use the medication unless symptoms are not improving after 72 hours.[4,26,27] In one randomized controlled trial, time to resolution of symptoms was about the same between groups starting antibiotics immediately and those given antibiotics to use only if not improved—3.3 and 3.9 days, respectively—suggesting that many of the latter group would have resolved spontaneously. Furthermore, patients given delayed antibiotics returned within 2 weeks for reevaluation at a lower rate than either the immediate-antibiotic or no-antibiotic groups.[26]

Topical antibiotics used to treat bacterial conjunctivitis have been used for prophylaxis of bacterial keratitis after corneal abrasions, though there is no convincing evidence that it prevents infection or facilitates uncomplicated healing.[28,29]

Bacterial keratitis is usually seen in contact lens wearers, particularly those who wear them overnight.[30] In descending order of frequency of cultured organisms, these microbial keratitides are caused by *Pseudomonas aeruginosa*, streptococcal or staphylococcal species, filamentous fungi, nonpseudomonal gram-negative rods, *Acanthamoeba*, other bacteria, and yeast.[31] Topical fluoroquinolones are typically recommended for empirical treatment.[19]

The most common organisms cultured from deeper eye structures, particularly after open-globe injuries, are *Bacillus cereus*, *Propionibacterium acnes*, and various species of *Bacillus*, *Streptococcus*, and *Staphylococcus*.[32] While awaiting emergent ophthalmologic consultation, prophylactic or empirical parenteral antibiotic combinations that may be used include cefazolin plus gentamicin or vancomycin plus cefotaxime, ceftazidime, or ceftriaxone. Possible cases of mycotic endophthalmitis have historically been treated with amphotericin B, though voriconazole has been shown to have good intraocular penetration, broad-spectrum activity, and relatively low systemic toxicity.[33]

Open wounds also necessitate tetanus prophylaxis if the patient's immunization status is not up to date. There is no current evidence supporting the practice of administering tetanus immunization to patients with superficial corneal abrasions.[34]

Other Protective Interventions

Significantly increased IOP should be reversed as rapidly as possible, often before the specific cause is known. After placement of the patient in at least a 30-degree head-up position, two drops of

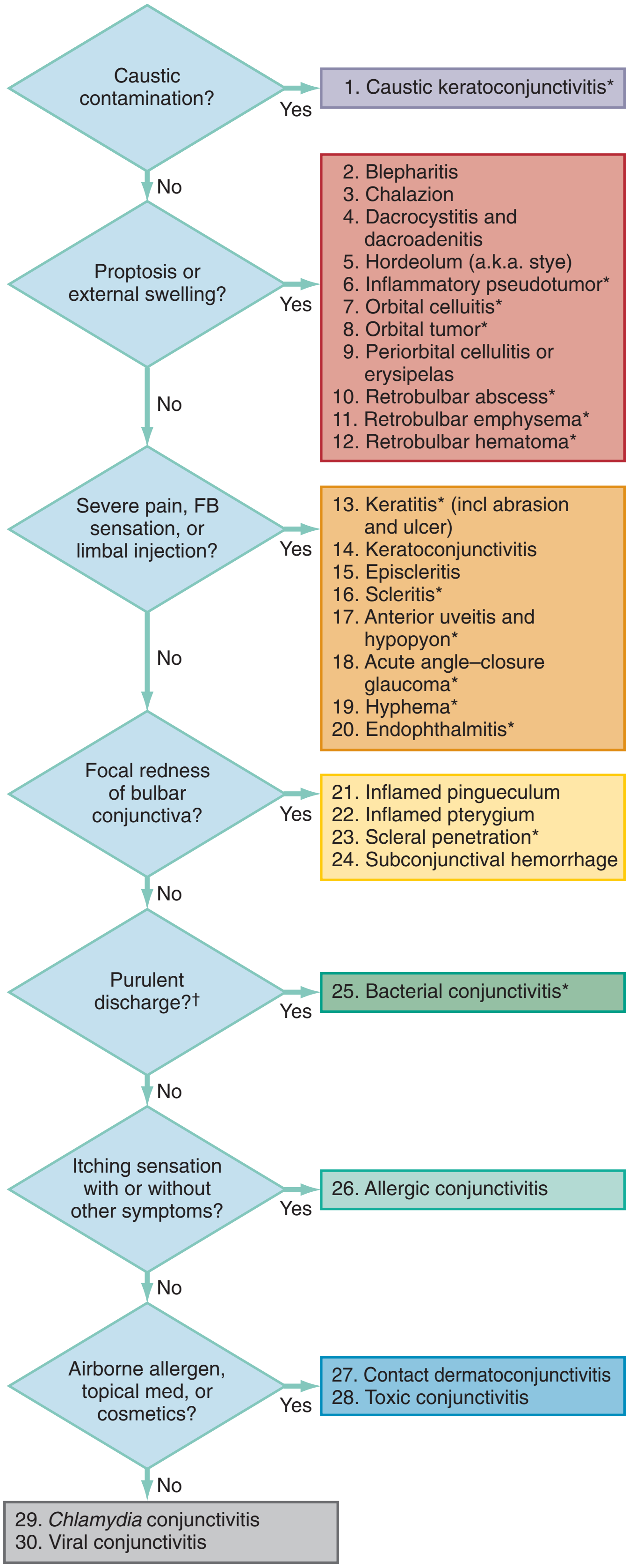


Figure 22-10. Diagnostic algorithm for red eyes. *a.k.a.,* also known as; *FB,* foreign body; *incl,* including; *med,* medicine.
*Indicates potentially serious diagnoses if not identified on initial emergency department evaluation.
†Purulent implies true pus, as opposed to the mucoid discharge more commonly associated with nonbacterial causes of conjunctivitis. (Modified from Trobe JB: The Physician's Guide to Eye Care. San Francisco: Foundation of the American Academy of Ophthalmology; 2001.)

www.ketabpezeshki.com 66485457-66963820

timolol 0.5%, a topical beta-adrenergic receptor antagonist, are administered to decrease the production of aqueous humor. This may be followed by two drops of dorzolamide 2%, a topical carbonic anhydrase inhibitor, to reduce aqueous humor production further. If not available, 500 mg of acetazolamide may be given orally or intravenously. If the patient has sickle cell disease or trait, oral methazolamide 50 mg is used instead. Patients with suspected intraocular hypertension who also have nausea or vomiting should receive a parenteral antiemetic so that they do not gag or vomit, which may further increase IOP.

Specific Management

Management of the specific entities listed in the diagnostic algorithm presented in Figure 22-10 is presented in Table 22-2. Specific management of ophthalmologic conditions is also discussed in Chapter 71.

SPECIAL CONSIDERATIONS

Pediatrics

A red eye in a neonate or infant is abnormal. It is usually caused by corneal abrasion or infection. Corneal abrasions can also be a cause of inconsolable crying in an infant. Fluorescein examination helps to identify abrasions, and herpes keratitis acquired from the birth canal. *Chlamydia* infections may also be acquired during vaginal deliveries but may not arise for weeks. These infections should be treated with oral azithromycin as well as parenteral ceftriaxone to cover *Neisseria gonorrhoeae*. Open wounds also necessitate tetanus prophylaxis if the patient's immunizations are not up to date. Conjunctivitis associated with respiratory symptoms or infiltrates on a chest radiograph in an infant younger than 3 months should be treated with an oral macrolide. Oral antibiotics are also indicated for conjunctivitis associated with otitis media. *Mycoplasma* has been a common infectious agent in these cases, but *H. influenzae* accounted for 82% of isolates in a more recent study, and 29% of those were resistant to β-lactam antibiotics.[35]

There is no good medical evidence to support the requirements of most daycare and school facilities for antibiotic treatment for acute conjunctivitis before the child may return to activities with other children. First, some causes of pinkeye are not infectious. Second, in patients enrolled in clinical trials for acute infectious conjunctivitis, bacteria continue to be cultured many days after treatment is started, and viruses continue to be shed for 2 weeks or more with or without antibiotics. Therefore return after 1 to 3 days of treatment (depending on policy) might actually

Table 22-2 Management Algorithm for Red Eyes Extended from Diagnostic Algorithm in Figure 22-10

DIAGNOSIS FROM FIGURE 22-10	MANAGEMENT	CONSULTATION	DISPOSITION
1. Caustic keratoconjunctivitis	Immediate and copious irrigation with tap water or sterile normal saline until tear-film pH = 7. *Solids*: lift particles out with dry swab before irrigation. *Acids*: minimum of 2 L *and* 20 min. *Alkalis*: minimum of 4 L *and* 40 min.	Ophthalmologist comes to ED if there is any abnormal visual acuity or objective finding on examination after sufficient irrigation, with exception of expected injection of conjunctiva secondary to treatment.	May discharge only if tear film pH = 7 *and* no findings on examination except conjunctival injection; then ophthalmologist can reevaluate next day.
2. Blepharitis Inflammation of eyelid margins often a/w crusts on awakening, FB sensation, and tearing.	None except artificial tears for dry eye.	Outpatient referral only for treatment failure after 2 wk.	Discharge with instructions to apply warm compresses to eyelids for 15 min qid and scrub lid margins and lashes with mild shampoo on washcloth bid.
3. Chalazion Inflammation of meibomian gland causing subcutaneous nodule within the eyelid.	None.	Outpatient referral only for treatment failure after 2 wk.	Discharge with instructions to apply warm compresses to eyelids for 15 min and gently massage nodule qid.
4. Dacryocystitis and dacryoadenitis Eye tearing and inflammation of lower eyelid inferior to lacrimal punctum with redness and tenderness over nasal aspect of lower lid and adjacent periorbital skin.	First r/o periorbital cellulitis (#9) and orbital cellulitis (#7). Inspect for obstruction of punctum by SLE, may express pus by pressing on sac, oral Rx for nasal and skin flora if not admitting.	Ophthalmologist may admit if systemically ill, case is moderate or severe, or no social support for patient. Ask about culturing before Rx if admitting, then Rx as for periorbital cellulitis (#9).	May discharge mild cases with oral analgesics and antibiotics (e.g., amoxicillin/clavulanate), and instructions to apply warm compresses to eyelids for 15 min and gently massage inner canthal area qid.
5. Hordeolum (i.e., stye) Abscess in eyelash follicle or modified sebaceous gland at lid margin: *external* or *internal* based on side of lid margin to which abscess is pointing.	*External*: warm compresses often all that is needed, may Rx anti-*Staph* ointment bid. *Internal*: oral Rx for β-lactamase *Staph.*	Outpatient referral only for treatment failure after 2 wk.	Discharge with instructions to apply warm compresses to eyelids for 15 min and gently massage abscess qid.
6. Inflammatory pseudotumor* Nonspecific idiopathic retrobulbar inflammation with eyelid swelling, palpebral injection of conjunctiva, chemosis, proptosis, blurred vision, painful or limited ocular mobility, binocular diplopia, edema of optic disk, or venous engorgement of retina.	Measure IOP. Evaluate for infection, diabetes mellitus, and vasculitis with CBC, BMP, UA, and ESR. Obtain axial CT scan of brain and axial and coronal CT scan of orbits and sinuses.	IOP > 20 mm Hg may be surgical emergency, Rx to decrease IOP in ED.	May discharge if no systemic problems, no findings of particular concern on CT, and IOP < 20 mm Hg. Start high-dose oral steroids after discussion with ophthalmologist and ensure reevaluation in 2-3 days.

Continued

www.ketabpezeshki.com 66485457-66963820

Table 22-2 Management Algorithm for Red Eyes Extended from Diagnostic Algorithm in Figure 22-10—cont'd

DIAGNOSIS FROM FIGURE 22-10	MANAGEMENT	CONSULTATION	DISPOSITION
7. Orbital cellulitis* Eyelid swelling, redness, and warmth of skin overlying orbit, tenderness of skin overlying bone, palpebral injection of conjunctiva, and chemosis. Differentiated from periorbital cellulitis by presence of any finding of fever, ill appearance, blurred vision, proptosis, painful or limited ocular mobility, binocular diplopia, edema of optic disk, or venous engorgement of retina.	Measure IOP. Start intravenous therapy with second-generation cephalosporin (e.g., cefuroxime, cefoxitin, or cefotetan) or with ampicillin/sulbactam to cover sinus and skin flora. Alternative Rx is ticarcillin/clavulanate, piperacillin/tazobactam, vancomycin, or clindamycin + third-generation cephalosporin (e.g., cefotaxime or ceftriaxone).	IOP > 20 mm Hg may be surgical emergency, Rx to decrease IOP in ED. Obtain blood cultures and start antibiotics. Axial and coronal CT of orbits and sinuses to r/o FB, retrobulbar abscess, orbital gas, subperiosteal abscess, osteomyelitis, and changes in cavernous sinus. Consider LP.	Admit all patients with orbital cellulitis.
8. Orbital tumor* Blurred vision, proptosis or other displacement of globe, painful or limited ocular mobility, or binocular diplopia (but can be asymptomatic).	Measure IOP. Evaluate for extraocular signs of malignancy. Obtain axial CT of brain and axial and coronal CT of orbits and sinuses.	IOP > 20 mm Hg may be surgical emergency, Rx to decrease IOP in ED. Ophthalmologist may want MRI, MRA, or orbital US.	Based on findings and discussion with consultant.
9. Periorbital cellulitis or erysipelas Eyelid swelling, redness and warmth of skin overlying orbit, tenderness of skin overlying bone, palpebral injection of conjunctiva, and chemosis. Differentiated from orbital cellulitis by absence of any other finding listed in #7.	First r/o orbital cellulitis (#7). Oral Rx for sinus and skin flora if not admitting.	Ophthalmologist may admit if systemically ill, case is moderate or severe, or no social support for patient.	May discharge mild cases with oral antibiotics. Ophthalmologist reevaluates next day to ensure no orbital extension.
10. Retrobulbar abscess* Findings of orbital cellulitis (#7) but a/w increased IOP. **11. Retrobulbar emphysema*** Findings of pseudotumor (#6) but a/w increased IOP. **12. Retrobulbar hematoma*** Findings of pseudotumor (#6) but occurs because of trauma, coagulopathy, or thrombocytopenia and a/w diffuse subconjunctival hemorrhage anteriorly and extending posteriorly as well as increased IOP.	Measure IOP unless possibility of ruptured globe. IOP > 30 mm Hg may require emergent needle aspiration or lateral canthotomy and inferior cantholysis in ED. *Abscess*: antibiotics as in orbital cellulitis (#7). *Emphysema*: prophylaxis with antibiotics to cover sinus flora. *Hematoma*: correct any coagulopathy or thrombocytopenia.	IOP > 20 mm Hg may be surgical emergency, Rx to decrease IOP in ED. Obtain axial CT scan of brain and axial and coronal CT scan of orbits and sinuses.	Admit all cases of retrobulbar pathology causing increased IOP. Others might be candidates for discharge depending on cause of problem.
13. Keratitis (abrasion or UV injury) Pain, FB sensation, blepharospasm, tearing, photophobia, epithelial disruption on inspection under white light or fluorescein pooling under blue light. SPK appears as stippling of corneal surface [often lower two thirds of cornea if caused by light exposure].	First r/o corneal penetration either grossly or through Seidel's test. Relieve pain and blepharospasm with topical anesthetic. Inspect all conjunctival recesses and superficial cornea for any foreign material that can be removed by irrigation or manually lifted from surface.	Ophthalmologist comes to ED if there is any concern for globe penetration. Otherwise consult for follow-up examination in 1-2 days.	May discharge cases not infected or ulcerated. May provide topical antibiotic prophylaxis with polymyxin B combinations with bacitracin (ointment) or trimethoprim (solution). Erythromycin, gentamicin, and sulfacetamide are less desirable single-agent alternatives. Oral NSAIDs or narcotics for analgesia. No patch.
Keratitis (ulceration)* Symptoms and signs as above. Ulceration from complications of contact wear or neglected corneal abrasion has "scooped out" epithelium with surrounding edema appearing as white "cloudiness" in clear tissue.	Relieve pain and blepharospasm with topical anesthetic. *Staph* and *Strep* species still most common organisms, but *Pseudomonas* greater percentage in existing infections (especially contact lens wearer), so Rx with topical fluoroquinolone is preferred.	Discuss any potential need to débride or culture before starting antibiotic.	Based on findings and discussion with consultant. Typical ciprofloxacin or moxifloxacin dosage is 2 gtt q15min × 6 hr, then 2 gtt q30 for the next 18 hours until seen by consultant the same or next day. PO NSAIDs or narcotics for analgesia. No patch.

www.ketabpezeshki.com 66485457-66963820

Table 22-2 Management Algorithm for Red Eyes Extended from Diagnostic Algorithm in Figure 22-10—cont'd

DIAGNOSIS FROM FIGURE 22-10	MANAGEMENT	CONSULTATION	DISPOSITION
Keratitis (herpetic infection)* Symptoms and signs as above. Look for other signs of herpes, varicella, zoster (or CMV infection in immunocompromised patient). Look for "dendritic" defects of cornea with fluorescein under blue light.	Relieve pain and blepharospasm with topical anesthetic. Rx with trifluridine 1% solution, vidarabine ointment, or acyclovir ointment. Patients with varicella-zoster and CMV not normally given antivirals if immunocompetent.	Discuss with ophthalmologist any potential need to débride or culture before starting antiviral.	Based on findings and discussion with consultant. Typical trifluridine dosage is 1 gtt q2h while awake for 7 days, then taper over 2 more wk. Typical vidarabine or acyclovir dosage is five times a day for 7 days, then taper over 2 more wk. Oral NSAIDs or narcotics for analgesia. No patch.
14. Keratoconjunctivitis Conjunctivitis with subepithelial infiltrates in cornea causing pain and decreased vision, possibly with halos reported.	Treat for conjunctivitis by likely causative category (#25-30).	Discuss findings and use of prednisolone acetate 1% (frequency determined by ophthalmologist).	May discharge patient with medications recommended by ophthalmologist and ensure reevaluation in 2-3 days.
15. Episcleritis Rapid onset of localized pain, injection of episcleral vessels, and localized tenderness.	Relieve irritation with artificial tears and decrease inflammation with ketorolac gtt.	Outpatient referral only for treatment failure after 2 wk.	May discharge patient with oral NSAIDs alone or in combination with topical ketorolac gtt.
16. Scleritis* Progressively increasing eye pain with radiation to ipsilateral face and decreasing vision, photophobia, tearing, and possible pain with eye motion.	Decrease inflammation with oral NSAIDs.	Discuss findings and use of topical or PO steroids.	May discharge patient with medications recommended by ophthalmologist and ensure reevaluation in 2-3 days.
17. Anterior uveitis and hypopyon* Eye pain, photophobia, tearing, limbal injection of conjunctiva, and cells or flare in anterior chamber. Hypopyon is layering of white cells (pus) in anterior chamber.	First r/o glaucoma with IOP measurement. Rx in ED if IOP > 20 mm Hg. Otherwise dilate pupil with 2 gtt of cyclopentolate 1%.	Discuss findings and use of prednisolone acetate 1% (frequency determined by ophthalmologist but range is q1-6h).	May discharge patient with medications recommended by ophthalmologist and ensure reevaluation in 2-3 days. Patients with hypopyon are generally admitted.
18. Acute angle–closure glaucoma Sudden-onset eye pain and blurred vision that may be a/w frontal headache, nausea, and vomiting. Anterior eye may manifest shallow or closed angle between iris and cornea, pupil fixed in mid-dilation, or limbal injection of conjunctiva.	Decrease production of aqueous humor. Timolol 0.5% 1 gt, then repeat in 30 min. Apraclonidine 1% 1 gt once. Dorzolamide 2% 2 gtt *or if sickle cell disease or trait* then methazolamide 50 mg PO. Decrease inflammation. Prednisolone 1% 1 gt every 15 min four times.	Discuss any IOP > 20 mm Hg with ophthalmologist.	Based on findings and discussion with consultant, which primarily depends on speed of onset and response to treatment.
Rx in ED if IOP > 30 mm Hg.	Constrict pupil. Pilocarpine 4% 1 gt, then repeat in 15 min. Consider establishing osmotic gradient. Mannitol 2 g/kg IV.		
19. Hyphema* Pain, decreased visual acuity, gross or microscopic blood in anterior chamber, may be a/w dilated and fixed pupil following blunt trauma. Graded by amount of blood. Percentage of vertical diameter of anterior chamber when blood layers with patient in upright position. Microhyphema shows no layering and only suspended red blood cells.	First r/o globe rupture. May require ultrasound if cannot visualize posterior structures. Measure IOP unless possibility of ruptured globe. IOP > 30 mm Hg may require acute treatment as in glaucoma (#18). If IOP > 20 mm Hg and no iridodialysis, may use cycloplegic to prevent iris motion.	Discuss findings and use of ε-aminocaproic acid and steroids, other medical therapy, best disposition, and follow-up examination by ophthalmologist within 2 days. Some patients may be admitted for observation, bed-rest, head elevation, and frequent medication administration.	Most patients can be discharged with careful instructions to return for any increased pain or change in vision. Patients should decrease physical activity and sleep with an eye shield in place. Eyes should be left open while awake, so any change in vision can be immediately recognized. Oral NSAIDs or narcotics for analgesia.
20. Endophthalmitis* Progressively increasing eye pain and decreasing vision, diminished red reflex, cells and flare (and possibly hypopyon) in anterior chamber, chemosis, and eyelid swelling.	Empirical parenteral antibiotic administration with cefazolin + gentamicin *or* vancomycin + cefotaxime, ceftazidime, *or* ceftriaxone to cover *Bacillus, Enterococcus*, and *Staphylococcus* species.	Ophthalmologist admits for parenteral and possibly intraocular antibiotics.	Admit all patients with endophthalmitis.

Continued

www.ketabpezeshki.com 66485457-66963820

Table 22-2 Management Algorithm for Red Eyes Extended from Diagnostic Algorithm in Figure 22-10—cont'd

DIAGNOSIS FROM FIGURE 22-10	MANAGEMENT	CONSULTATION	DISPOSITION
21. Inflamed pinguecula Inflammation of soft yellow patches in temporal and nasal edges of limbal margin. **22. Inflamed pterygium** Inflammation of firmer white nodules extending from limbal conjunctiva onto cornea.	Decrease inflammation with naphazoline or ketorolac gtt.	Outpatient referral only for treatment failure after 2 wk.	Discharge to follow-up with ophthalmologist for possible steroid therapy or surgical removal.
23. Scleral penetration* Localized redness at site of entry, teardrop pupil, blood in anterior chamber or loss of red reflex.	Protect eye from further pressure, provide pain relief, and prevent vomiting. Tetanus prophylaxis.	Ophthalmologist comes to ED if there is any concern for globe penetration.	Admit for intravenous antibiotics and possible procedural intervention.
24. Subconjunctival hemorrhage Red blood beneath clear conjunctival membrane.	Exclude coagulopathy or thrombocytopenia, if indicated by history.	None required if no concerns for underlying ocular pathology and no acute complications.	Reassure patient that discoloration should resolve over 2-3 wk.
25. Bacterial conjunctivitis* Hyperpurulent discharge not typical of common "pinkeye" and more commonly unilateral in adults. Inflammation of eyelid margins a/w lid edema, chemosis, and possibly subconjunctival hemorrhage, but usually little or no follicular "cobblestoning."	Topical polymyxin B trimethoprim in infants and children because more *Staph* species. Topical sulfacetamide or gentamicin clinically effective in 90% of uncomplicated adult cases. Use topical fluoroquinolone if *Pseudomonas* possible.	Culture drainage and ophthalmology consultation in all neonates and those at risk for vision loss or systemic sepsis. *Neisseria gonorrhoeae* can be rapidly sight-threatening.	Discharge patients with uncomplicated cases with 10 days of topical antibiotics in both eyes, regardless of laterality of apparent infection. Use ointments in infants and gtt in others.
26. Allergic conjunctivitis Often bilateral palpebral injection of conjunctiva and chemosis that may be seasonal and a/w other allergic symptoms such as rhinitis.	Decrease irritation with naphazoline gtt.	Outpatient referral only for treatment failure after 2 wk.	Identify antigen if possible. Consider treating other allergic symptoms with oral antihistamines.
27. Contact dermatoconjunctivitis Localized lid and conjunctival redness and swelling. **28. Toxic conjunctivitis** Diffuse conjunctival injection, chemosis, and lid edema.	Irrigation with tap water or sterile normal saline. Decrease irritation with naphazoline gtt.	Outpatient referral only for severe cases or treatment failure after 2 wk.	Identify offending agent and avoid subsequent exposure. Discharge uncomplicated cases on continued naphazoline.
29. *Chlamydia* conjunctivitis Often bilateral palpebral injection of conjunctiva in neonate or other individual at risk for sexually transmitted disease.	Empirical oral azithromycin for *Chlamydia.* Consider empirical parenteral ceftriaxone for concurrent *Neisseria gonorrhoeae.*	Culture drainage and consult ophthalmology in all neonates and those at risk for vision loss or systemic sepsis.	Discharge uncomplicated cases on 5 days of oral azithromycin.
30. Viral conjunctivitis Often bilateral palpebral injection of conjunctiva and follicular cobblestoning of inner surface of lower lid. Inflammation of eyelid margins often a/w crusts on awakening, FB sensation, and tearing.	Decrease irritation with artificial tears, naphazoline, or ketorolac gtt.	Culture drainage and consult ophthalmology in all neonates and those at risk for vision loss or systemic sepsis.	Ask about pregnant mothers, infants, and immunocompromised individuals in close contact. Discharge uncomplicated cases with instructions on respiratory and direct-contact contagion for 2 wk.

a/w, associated with; *bid,* twice daily; *BMP,* basic metabolic profile (includes electrolytes, glucose, and renal function tests); *CBC,* complete blood count; *CMV,* cytomegalovirus; *CT,* computed tomography; *ED,* emergency department; *ESR,* erythrocyte sedimentation rate; *FB,* foreign body; *gt,* drop; *gtt* drops; *IOP,* intraocular pressure; *IV,* intravenously; *LP,* lumbar puncture; *MRA,* magnetic resonance angiography; *MRI,* magnetic resonance imaging; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *PO,* orally; *q,* every; *qid,* four times a day; *r/o,* rule out; *Rx,* prescribe; *SLE,* slit-lamp examination; *SPK,* superficial punctuate keratitis; *Staph., Staphylococcus; Strep., Streptococcus; UA;* urinalysis; *US,* ultrasonography; *UV,* ultraviolet.

*Potentially serious diagnoses if not identified on initial emergency department evaluation. Antibiotic choices should be based on current practice.

expose more children owing to the false sense of security antibiotics provide.

Trauma

Blunt trauma is a common cause of a red and painful eye. Patients with large hyphemas and hyphemas with clots are likely to require hospitalization for bed rest with 30 degrees of head elevation. Systemic analgesia and, if required, antiemetics are indicated. Medications affecting platelet function should be avoided. Treatment may be indicated when the IOP exceeds 30 mm Hg, as it is in acute angle–closure glaucoma. If the iris is not injured, a long-acting cycloplegic agent (e.g., topical homatropine) may be recommended to prevent repetitive motion of the iris. Some reliable adult patients may be discharged with daily follow-up by a specialist. Strong analgesia and patching are not indicated, so that the patient may immediately identify increases in pain or decreases in visual acuity, though a rigid shield to protect the eye during sleep is prudent.

Corneal abrasions are common problems in the ED. When the emergency physician is convinced that the cornea has not received a full-thickness laceration or penetration by a foreign

www.ketabpezeshki.com 66485457-66963820

body, management is relatively simple. Foreign bodies (on or in the epithelium only) should be removed when possible. These frequently adhere to a saline-moistened cotton-tipped applicator. Ones that do not may sometimes be lifted off with a blunt-tipped tool ("spud") under the binocular magnification of a slit lamp. The common use of hypodermic needle removal may damage surrounding cornea and is not recommended. Whether or not the object can be successfully removed, management is the same as for corneal abrasions. Rust staining of the corneal epithelium does not require removal in the ED, but patients are referred to a specialist for examination within 3 days. Antimicrobial prophylaxis with topical antibiotics for all superficial epithelial defects of the cornea is common practice but not supported by evidence.[28,29] Larger lesions may necessitate use of a cycloplegic agent for the pain associated with secondary iritis, but administration prophylactically is also not supported in the literature.[29,36] Systemic analgesia appropriate to the patient's level of pain should be provided. Topical anesthetics should not be given to the patient for home use. Patching is not necessary and may be harmful.

DISPOSITION

Most ED patients with eye complaints are candidates for discharge and, if indicated, follow-up in the ED or with an ophthalmologist in 1 to 2 days. Others may require referral only if there is lack of resolution or treatment fails. A few patients require admission for procedural intervention, parenteral antibiotic regimens, management of intractable pain, or further diagnostic evaluation. General consultation and disposition considerations for the most important entities are outlined in Table 22-2.

KEY CONCEPTS

- Prompt and prolonged irrigation is advised for patients who experience caustic injury to the eye.
- Headache and nausea may be prominent symptoms in patients with acute angle–closure glaucoma.
- Complete abolition of a foreign body sensation after instillation of local anesthesia solution indicates a corneal lesion.
- Keratitis, inflammation of the cornea, is most commonly caused by a viral infection but may also be caused by recent ultraviolet light exposure, chemical injury, or hypoxic injury from contact lens use.
- A localized corneal defect with edematous, inflammatory changes may signal corneal ulceration.
- A corneal dendritic pattern may signal a herpetic infection, which can progress to corneal opacification and visual loss.
- Pain, consensual photophobia, perilimbic conjunctival infection, and a miotic pupil that is caused by ciliary spasm could signal iritis, which is inflammation of the iris and ciliary body, or uveitis, inflammation of the iris, ciliary body, and also choroids. The cause may be trauma or underlying autoimmune disease. The presence of cells and flare in the anterior chamber can help identify these conditions.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Kuhn F, et al: Epidemiology and socioeconomics. *Ophthalmol Clin North Am* 2002; 15:145-151.
2. Cook T: Ocular and periocular injuries from orbital fractures. *J Am Coll Surg* 2002; 195:831-834.
3. Smith AF, Waycaster C: Estimate of the direct and indirect cost of bacterial conjunctivitis in the United States. *BMC Ophthalmol* 2009; 9:13.
4. Visscher KL, Hutnik CML, Thomas M: Evidence-based treatment of acute infective conjunctivitis: Breaking the cycle of antibiotic prescribing. *Can Fam Physician* 2009; 55:1071-1075.
5. Edward S: *Harkness Eye Institute: Cornea and external diseases*. In: *Digital Reference of Ophthalmology*, Columbia University, 2003. Available at http://dro.hs.columbia.edu/follicularcs.htm.
6. Greenberg MF, Pollard ZF: The red eye in childhood. *Pediatr Clin North Am* 2003; 50:105-124.
7. Rietveld RP, ter Riet G, Bindels PJ, Sloos JH, van Weert HC: Predicting bacterial cause of infectious conjunctivitis: Cohort study on informativeness of combinations of signs and symptoms. *BMJ* 2004; 329:206-210.
8. Patel PB, Diaz MCG, Bennett JE, Attia MW: Clinical features of bacterial conjunctivitis in children. *Acad Emerg Med* 2007; 14:1-5.
9. Rietveld RP, van Weert HC, ter Riet G, Bindels PJ: Diagnostic impact of signs and symptoms in acute infectious conjunctivitis: Systematic literature search. *BMJ* 2003; 327:789.
10. Nassr MA, Morris CL, Netland PA, Karicioglu ZA: Intraocular pressure change in orbital disease. *Surv Ophthalmol* 2009; 54:519-544.
11. Dasgupta B, et al: BSR and BHPR guidelines for the management of giant cell arteritis. *Rheumatology (Oxford)* 2010; 49:1594-1597.
12. Go JL, Vu VN, Lee KJ, Becker TS: Orbital trauma. *Neuroimaging Clin North Am* 2002; 12:311-324.
13. Kubal WS: Imaging of orbital trauma. *Radiographics* 2008; 28:1729-1739.
14. Mehta N, Butala P, Bernstein MP: The imaging of maxillofacial trauma and its pertinence to surgical intervention. *Radiol Clin North Am* 2012; 50:43-57.
15. Mester V, Kuhn F: Intraocular foreign bodies. *Ophthalmol Clin North Am* 2002; 15:235-242.
16. Dunkin JM, Crum AV, Swanger RS, Bokhari SAJ: Globe trauma. *Semin Ultrasound CT MRI* 2011; 32:51-56.
17. Carrim ZI, Anderson IW, Kyle PM: Traumatic orbital compartment syndrome: Importance of prompt recognition and management. *Eur J Emerg Med* 2007; 14:174-176.
18. Lima V, et al: Orbital compartment syndrome: The ophthalmic surgical emergency. *Surv Ophthalmol* 2009; 54:441-449.
19. Suchecki JK, Donshik P, Ehlers WH: Contact lens complications. *Ophthalmol Clin North Am* 2003; 471-484.
20. Okhravi N, Odufuwa B, McCluskey P, Lightman S: Scleritis. *Surv Ophthalmol* 2005; 50:351-363.
21. Mahmood AR, Narang AT: Diagnosis and management of the acute red eye. *Emerg Med Clin North Am* 2008; 26:35-55.
22. Solomon AW, et al: Mass treatment with single-dose azithromycin for trachoma. *N Engl J Med* 2004; 351:1962-1971.
23. Sheikh A, Hurwitz B: Antibiotics versus placebo for acute bacterial conjunctivitis. *Cochrane Database Syst Rev* 2006; 4:CD001211.
24. Rose P: Management strategies for acute infective conjunctivitis in primary care: A systematic review. *Curr Opin Pharmacother* 2007; 8:1903-1921.
25. Everitt H, Kumar S, Little P: A qualitative study of patients' perceptions of acute infective conjunctivitis. *Br J Gen Pract* 2003; 53:36-41.
26. Everitt HA, Little PS, Smith PWF: A randomised controlled trial of management strategies for acute infective conjunctivitis in general practice. *BMJ* 2006; 333:321.
27. Oliver GF, Wilson GA, Everts RJ: Acute infective conjunctivitis: Evidence review and management advice for New Zealand practitioners. *N Z Med J* 2009; 122:69-75.
28. Wilson SA, Last A: Management of corneal abrasions. *Am Fam Physician* 2004; 70:123-128.
29. Dargin JM, Lowenstein RA: The painful eye. *Emerg Med Clin North Am* 2008; 26:199-216.
30. Willcox MD: *Pseudomonas aeruginosa* infection and inflammation during contact lens wear: A review. *Optom Vis Sci* 2007; 84:273-278.
31. Dahlgren MA, Lingappan A, Wilhelmus KR: The clinical diagnosis of microbial keratitis. *Am J Ophthalmol* 2007; 143:940-944.
32. Essex RW, Yi Q, Charles PGP, Allen PJ: Post-traumatic endophthalmitis. *Ophthalmology* 2004; 111:2015-2022.
33. Hariprasad SM, et al: Determination of vitreous, aqueous, and plasma concentration of orally administered voriconazole in humans. *Arch Ophthalmol* 2004; 122:42-47.
34. Mukherjee P, Sivakumar A, Mackway-Jones K: Tetanus prophylaxis in superficial corneal abrasions. *Emerg Med J* 2003; 20:62-64.
35. Buznach N, Dagan R, Greenberg D: Clinical and bacterial characteristics of acute bacterial conjunctivitis in children in the antibiotic resistance era. *Pediatr Infect Dis J* 2005; 24:823-828.
36. Carley F, Carley S: Mydriatics in corneal abrasion. *Emerg Med J* 2001; 18:273.

www.ketabpezeshki.com 66485457-66963820

Chapter 23

Sore Throat

David H. Newman and Ashley E. Shreves

PERSPECTIVE

Epidemiology

In 2007 the National Hospital Ambulatory Medical Care Survey reported more than 2 million emergency department visits for sore throat and "throat-related" complaints.[1] Thus sore throat remains among the most common presenting complaints in both emergency departments and outpatient care settings in the United States.[1,2] Although some subtypes of pharyngitis and peripharyngeal disorders are more common in children and adolescents, individuals of all ages commonly develop sore throat.

Pathophysiology

Sore throat, or pharyngitis, is generally caused by inflammation in the soft tissue of the pharynx. There are three anatomically distinct regions of the pharynx: the nasopharynx, oropharynx, and hypopharynx (Fig. 23-1). Pathology involving one site usually involves the others, but inflammation at any of these levels can manifest as a sore throat. The nasopharynx encompasses the area superior to the oral cavity, between the base of the skull and the soft palate. The eustachian tubes, connecting the middle ear and pharynx, open into this space. The oropharynx is the region directly visible on examination, lying behind the oral cavity, between the uvula and hyoid, including the vallecula and epiglottis. Laterally, it is defined by the tonsillar pillars. The hypopharynx is the most caudal aspect of the pharynx. It lies inferior to the epiglottis and terminates where the aerodigestive paths become distinct, at the esophagus and larynx; the vocal cords define the inferior pole. If one looks directly at a patient, this region is posterior and slightly superior to the thyroid cartilage. There are several important potential spaces surrounding the pharynx; disease in the retropharyngeal and submandibular spaces can manifest as not only pain but airway compromise.

The terms *pharyngitis* and *tonsillitis* are often used interchangeably; however, the tonsils are distinct lymph tissue located throughout the pharynx. Waldeyer's tonsillar ring, or the pharyngeal lymphoid ring, consists of the pharyngeal (adenoids), tubal, palatine, and lingual tonsils. The palatine tonsils are located on the sides of the oropharynx, between the palatoglossal and palatopharyngeal arches. These immunologic masses are commonly implicated in sore throat and are referred to colloquially as "the tonsils." Regional infections, both viral and bacterial, commonly trigger inflammatory changes in this collection of lymphatic tissue. Whereas inflammation and swelling of the soft tissues in the oropharynx are the most likely cause in patients with a sore throat, any of the anatomic structures or surfaces within the nasopharynx or hypopharynx can be affected by disease leading to a sore throat. Cranial nerves 9 and 10 supply sensory innervation to this region.

DIAGNOSTIC APPROACH

Airway Assessment and General Appearance

The evaluation of sore throat begins with a simultaneous assessment of the airway and the patient's general appearance. A history of rapidly progressive symptoms, difficulty breathing, or a sensation of tightness in the throat suggests potential threats to the airway. Examination begins with direct observation. Patients with airway compromise often sit upright or lean forward, with the neck extended and jaw thrust forward, and appear restless and distressed. Drooling may indicate an inability to swallow oral secretions and thus inflammation or pathology in the oropharynx or hypopharynx. Drooling is a sign of an advanced airway process, requiring prompt preparation for detailed evaluation and intervention. Presence of a muffled voice prompts consideration of a supraglottic threat to airway patency. The floor of the mouth should be visualized, and the submental region palpated as "brawny" induration or tenderness in this area is classically associated with Ludwig's angina (Table 23-1). Stridor, a high-pitched noise heard on inspiration, indicates a process involving the glottic or infraglottic structures. Stridor indicates a true airway emergency, except when occurring in young children (<10 years old) with croup (see Chapter 168). Stridor is associated with ominous conditions such as epiglottitis, retropharyngeal abscess, and angioedema, and the severity and rate of onset and progression of symptoms indicates the urgency of the required intervention.

General appearance is assessed with attention to hydration status and markers of systemic toxicity. Patients, particularly children, with significant pain from uncomplicated pharyngitis often have difficulty with oral intake and may become dehydrated. Fever and mild tachycardia are common vital sign derangements in those with viral or bacterial pharyngitis and do not typically indicate dangerous pathology. A prolonged fever (greater than 5-7 days) in children may be associated with Kawasaki disease.[3]

Source of Pain Visualized on Examination

Direct visualization of the pharynx is typically the most helpful portion of the encounter in establishing a diagnosis; thus complete and unencumbered visualization of the pharyngeal structures is mandatory. Lingual resistance may require coaching or stimulation of a gag reflex, and trismus and pain often need to be managed with appropriate analgesia. If tonsillar erythema or exudates are observed in a symmetrical distribution and the patient has no

www.ketabpezeshki.com 66485457-66963820

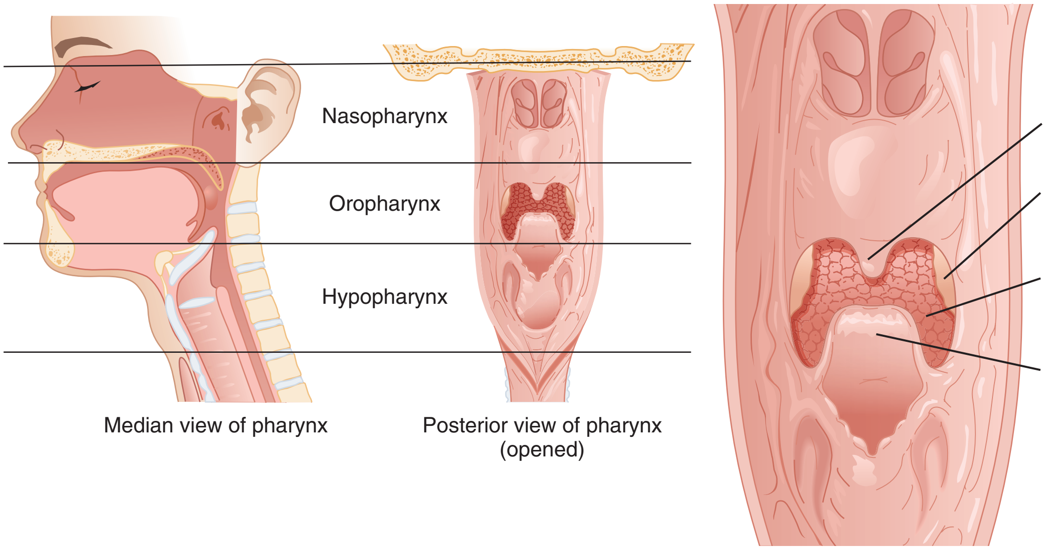


Figure 23-1. Anatomy of the nasopharynx, oropharynx, and hypopharynx.

Table 23-1 Differential Diagnosis for Sore Throat

Infectious Causes				
	AEROBES			
VIRAL	COMMON	UNCOMMON	ANAEROBES	OTHER
Rhinovirus	*Streptococcus pyogenes* (GABHS)	*Haemophilus influenzae*	*Bacteroides* species	*Candida* species
Adenovirus	GABHS *Peptostreptococcus* species	*Haemophilus parainfluenzae* *Coccidioides* species		
Coronavirus	Non–group A streptococcus	*Corynebacterium diphtheriae*	*Peptococcus* species	
Herpes simplex virus 1, 2	*Neisseria gonorrhoeae*	*Streptococcus pneumoniae*	*Clostridium* species	
Influenza A, B	*Neisseria meningitides*	*Yersinia enterocolitica*	*Fusobacterium* species	
Parainfluenza	*Mycoplasma pneumoniae*	*Treponema pallidum*	*Prevotella* species	
Cytomegalovirus	*Arcanobacterium haemolyticum*	*Francisella tularensis*		
Epstein-Barr virus	*Chlamydia trachomatis*	*Legionella pneumophila*		
Varicella-zoster virus	*Staphylococcus aureus*	*Mycobacterium* species		
Hepatitis virus				

Noninfectious Causes		
SYSTEMIC	TRAUMA, MISCELLANEOUS	TUMOR
Kawasaki disease	Penetrating injury Angioneurotic edema	Tongue
Stevens-Johnson syndrome	Retained foreign body Anomalous aortic arch	Larynx
Cyclic neutropenia	Laryngeal fracture Calcific retropharyngeal tendinitis	Thyroid
Thyroiditis	Retropharyngeal hematoma	Leukemia
Connective tissue disease	Caustic exposure	

GABHS, group A beta-hemolytic streptococcus.

signs of airway involvement, acute tonsillitis is present and further investigation is rarely warranted. Unilateral swelling and contralateral uvular deviation suggest peritonsillar abscess. Involvement of the entire oropharyngeal area indicates pharyngitis. If, however, the patient has significant symptoms and no clear oropharyngeal pathology on examination, evaluation for disease in the hypopharynx, especially epiglottitis, by direct or indirect visualization of this region is indicated.

Viral versus Bacterial Pharyngitis

In the context of acute uncomplicated pharyngitis, considerable attention has been focused on differentiating between bacterial and viral infection through either bedside testing or clinical scoring. Various scoring systems, the most famous of which is the Centor criteria system, incorporate components of the history and physical examination to generate an estimate of group A

www.ketabpezeshki.com 66485457-66963820

streptococcus (GAS) infection.[4] The four Centor criteria are history of fever, tonsillar exudates, tender anterior cervical adenopathy, and absence of cough. In a large prospective study including both children and adults that evaluated a modified Centor score (if age was greater than 45 years, 1 point subtracted), the prevalence of GAS increased with the number of criteria present. The prevalence of GAS was 1% with a score of −1 to 0, 10% with a score of 1, 17% with a score of 2, 35% with a score of 3, and 51% when the score was 4 or more. The distinction between viral and bacterial disease is, however, largely academic. With increasing emphasis on symptomatic relief and decreasing emphasis on eradication of the infecting agent, treatment, prognosis, and follow-up are virtually identical regardless of microbiologic cause[5] (see Chapter 72).

Special Considerations on History

Although most patients with a sore throat have an uncomplicated infectious pharyngitis, certain components of the history are suggestive of more unusual pathology. Patients with human immunodeficiency virus (HIV) are at risk for oral candidiasis or thrush. In addition, primary HIV infection can manifest with upper respiratory infection (URI)–like symptoms, including acute pharyngitis in up to 75% of cases.[6] Angiotensin-converting enzyme inhibitors predispose patients to angioedema, and although the lips and face are often visibly edematous, the process can be limited to the tongue, oropharynx, or hypopharynx. Nonimmunized children are at risk for epiglottitis and severe, life-threatening infections caused by *Corynebacterium diphtheriae,* and adults may have epiglottitis regardless of immunization status. Dental procedures, particularly involving the lower third molars, can be complicated by postoperative infections, the most potentially serious of which is Ludwig's angina. Recent orogenital contact should broaden the differential diagnosis, as gonococcus and herpes simplex virus (HSV) can be pathogens in the pharynx. Pharyngitis in teenagers or young adults with significant cervical lymphadenopathy and fatigue suggests infectious mononucleosis caused by the Epstein-Barr virus. In one large case series of patients with head and neck cancers, hoarseness and sore throat were the two most common presenting complaints. In older patients, particularly men with a history of smoking, neoplastic causes should be considered.[7]

Finally, as with any painful anatomic structure, it is critical to consider sources of pain referral, both common and uncommon. Thyroid disease, lymphadenitis, gastroesophageal reflux, and (perhaps most commonly) postnasal drip are all conditions arising from physically contiguous structures that may lead to sore throat. Unfortunately, there are no reliable estimates of prevalence for these conditions among populations of sore throat presentation, and the clinician is left to exercise to judgment in determining if and when further investigation or wider consideration is necessary. In many cases, clinical context will be the most important arbiter of this decision. For instance, among patients with nasal discharge symptoms of URI or allergy, postnasal drip will be a likely explanation for sore throat. Among patients with clinically apparent goiter or symptoms of systemic thyroid disease, thyroiditis will be an intuitively apparent consideration. Thus in many cases, a more thorough history, exploring in detail the onset, pattern, persistence, and recurrence of symptoms, accompanied by a supporting physical examination may ultimately be the most helpful steps in proper diagnosis and management decisions.

Ancillary Testing

Laboratory testing is of very limited use in the context of acute pharyngitis. Most professional societies in the United States, including the American College of Physicians, the American Academy of Family Physicians, the Centers for Disease Control and Prevention, the Infectious Diseases Society of America, the American Heart Association, and the American Academy of Pediatrics recommend various diagnostic strategies to distinguish between GAS and non-GAS pharyngitis. These include the combination of a clinical scoring system that allows a reliable estimation of pretest probability with a rapid antigen-detection test or throat culture. Treatment of proven GAS pharyngitis with antibiotics confers only a modest reduction in the duration of symptoms, and most western nations have abandoned this approach because the inaccuracy and risks of testing and treatment for GAS seem to outweigh the benefits in industrialized settings where rheumatic fever tends to be exceedingly rare. In the United States, however, guidelines still recommend a combination of clinical assessment and bacteriologic testing, with the goal of treating with antibiotics when GAS is identified or strongly suspected (e.g., by scoring criteria). This is described in detail in Chapter 72. Heterophile antibody testing for mononucleosis may be considered in patients with an extended clinical course or treatment failure; however, confirmation of this disease is important only to exclude "treatable" causes of pharyngitis and to ensure appropriate advice regarding contagion, limitations of activity, and so on (see Chapters 72 and 130).[8]

Imaging

Although radiographic imaging has long been recommended for evaluation of the epiglottis and structures in the hypopharynx, direct visualization of the structures of interest by examination is preferable, providing definitive diagnosis, assessment of the extent of the threat to the airway, and the ability to either plan for or perform intubation. In adults with possible epiglottitis, particularly those with severe symptoms such as drooling, distress, or muffled voice, examination via nasopharyngoscopy at the bedside or via laryngoscopy in the operating room setting is the best approach. Examination of this sort, however, should occur under a "double setup," with availability of and preparation for an emergent rescue airway, usually cricothyrotomy, because manipulation of the irritated upper airway tissues may precipitate laryngospasm and obstruction. Endoscopic examination also allows identification of other life-threatening causes beyond infection, such as foreign bodies, polyps, and angioedema. If there is concern for epiglottis but upper airway examination by endoscopy is not possible (e.g., equipment is not available) and the patient has a stable airway, plain film radiography can be used for screening purposes. Findings on plain film suggestive of epiglottitis include the "thumb sign" (widening of the epiglottis silhouette) and the "vallecula sign" (opacification of this space).[9] The approach to pediatric airway infection, including epiglottis, is described in Chapter 168.

Ultrasound is an emerging technology with applications for the detection of hypopharyngeal conditions including epiglottitis. In a convenience sample of adults, the epiglottis was easily visualized and measured in both males and females.[11] A recent case report documenting the use of ultrasound in a patient with epiglottitis suggests this noninvasive bedside tool could prove useful in the diagnostic approach to the disease.[12]

In a child or adult with signs and symptoms of a deep neck infection, such as retropharyngeal abscess, and whose airway security has been ensured, the most useful imaging modality is computed tomography of the neck. The lateral neck x-ray examination is a relatively sensitive test for this disease, so in lower-risk patients a normal film (no widening of the prevertebral space, normal lordotic curve of the spine, and absence of soft tissue air) can be a useful risk stratification tool.[13] Ultimately, however, CT is the definitive evaluation for deep neck infection. It is highly accurate at detecting infection in the deep tissues, but its ability to differentiate between cellulitis and abscess is variable.[14] In children with

www.ketabpezeshki.com 66485457-66963820

a sore throat and a visible inflammatory neck mass, ultrasound diagnosis can be definitive.[15]

EMPIRICAL MANAGEMENT

Figure 23-2 shows a clinical algorithm for the initial approach to, and management of, the sore throat presentation. Airway compromise and impending airway compromise, when present, must be addressed first. Infectious syndromes suggesting severe systemic illness or sepsis should be treated accordingly. Patients who clinically appear to have no potential for airway compromise and no signs of invasive or systemic disease can be managed according to presumptive causes.

Most commonly, sore throat will be caused by acute pharyngitis, in which case pain management with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) is the mainstay of care and the most important initial step in empirical management. Regimented administration of these agents, rather than use of as-needed approaches that fail to prevent or interrupt spiraling pain, is often helpful in maximizing their impact. In comparative studies of pharyngitis in patients with confirmed streptococcal infection, antibiotics have not been shown to be superior to NSAIDs for symptom reduction and therefore should not be used for this purpose.[16] For moderate to severe pharyngitis, corticosteroid therapy reduces pain and duration of pain, with most studies using 0.6 mg/kg (maximum dose 10 mg) of

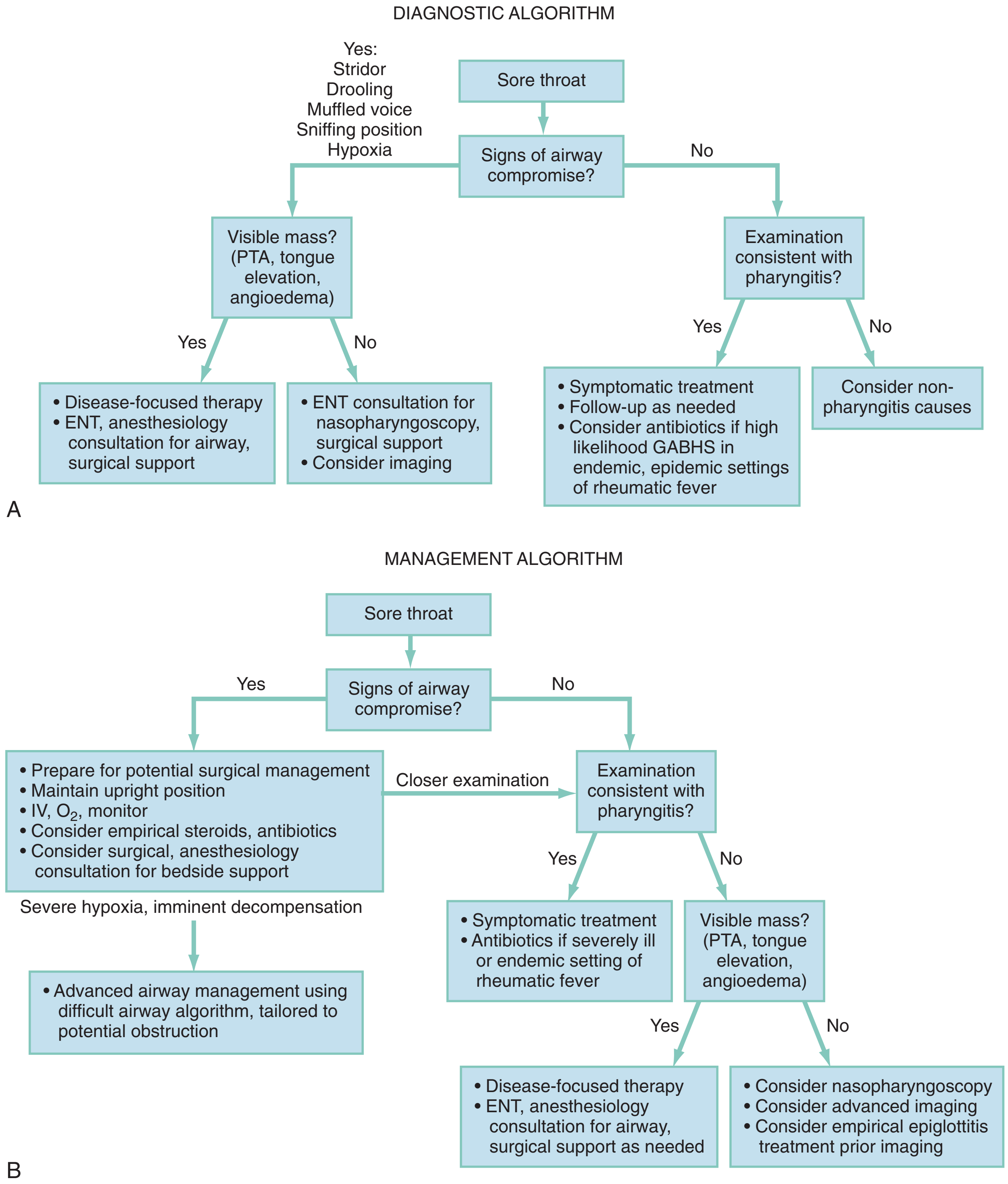


Figure 23-2. Clinical approach to the patient with sore throat—diagnosis and management. *ENT,* ear-nose-throat; *GABHS,* group A beta-hemolytic streptococcus; *IV,* intravenous; *PTA,* peritonsillar abscess.

www.ketabpezeshki.com 66485457-66963820

dexamethasone, orally or parenterally, in a single dose.[17] Opioid pain medication is appropriate in select cases of more severe pain, but the consideration of opioid analgesia may also indicate a more severe syndrome requiring additional evaluation. Proper pain management should be targeted to allow patients to reestablish nutritional balance, achieve and maintain a hydrated state, and ingest medications as necessary.

In the setting of clinical pharyngitis a fluctuant unilateral peritonsillar mass should be drained whenever possible. Drainage in such cases constitutes definitive care.[18] Antibiotics often are used in cases of unilateral swelling and redness that appears not to be fluctuant (i.e., "peritonsillar cellulitis"); however, there are no data to support or refute this approach. For patients with manifestations of severe, systemic illness (i.e., those requiring hospitalization or those with impending airway compromise), antibiotic coverage for streptococcal and anaerobic bacteria may theoretically be helpful, and therefore we recommend antibiotic administration in this setting (see Chapter 72). However, no explicit evidence is available to support or refute this practice.

With the possible exception of gonococcal disease, two systematic reviews of the literature have concluded that acute pharyngitis should not typically be treated with antibiotics.[5,19] The great majority of cases are viral in origin, and suppurative complications following streptococcal infection are both easily treated and too rare to justify routine use of antibiotics. In particular, antibiotics were beneficial in reducing rheumatic fever only during a single military epidemic in the mid-twentieth century, and the decline of rheumatic fever is unrelated to trends in antibiotic use, but rather is a result of factors associated with industrialization including improved living conditions, access to care, hygiene, and nutrition.[20] This helps to explain the present day epidemiology of rheumatic fever, a disease that is extremely rare in developed nations but continues to be an important public health threat in developing regions throughout the world.[21] Antibiotics should therefore be used to prevent rheumatic fever and other nonsuppurative complications only in endemic and epidemic settings.

It is important to note that adverse events caused by antibiotics are common and frequently result in emergency department visits,[22] and the overuse of antibiotics for self-limiting conditions such as pharyngitis remains rampant.[23] Thus for both public health reasons and the prevention of unnecessary harm to individual patients, antibiotics should be avoided in the management of this common, mostly self-limited condition.

Education of patients, who will often expect or desire antibiotics, is a key part of management. Education should provide a careful explanation of (1) the self-limited nature of infectious pharyngitis, (2) the lack of symptomatic benefit with antibiotics, and (3) the potential harm of antibiotics (individual and population resistance, fungal infections in women, rashes, gastrointestinal effects, recurrence of pharyngitis, and occasionally dangerous allergic reactions). It is often most important to emphasize symptom reduction with patients and the various interventions that target pain control, for example, NSAIDs and, for severe cases, corticosteroids.

Other specific empirical therapies or consultation may be necessary for severe or unusual presentations of disease.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Niska R, Bhuiya F, Xu J: National Hospital Ambulatory Medical Care Survey: 2007 emergency department summary. *Natl Health Stat Report* 2010; 26:1-32.
2. Hsiao CJ, Cherry DK, Beatty PC, Rechtsteiner EA: National Ambulatory Medical Care Survey: 2007 summary. *Natl Health Stat Report* 2010; 27:1-32.
3. Harnden A, Takahashi M, Burgner D: Kawasaki disease. *BMJ* 2009; 338:b1514.
4. Centor RM, Witherspoon JM, Dalton HP, Brody CE, Link K: The diagnosis of strep throat in adults in the emergency room. *Med Decis Making* 1981; 1:239-246.
5. Kenealy T. Sore throat. *Clin Evid (Online)* Jan 13, 2011. Available at www.ncbi.nlm.nih.gov/pubmed/21477389. Accessed May 3, 2011.
6. Apoola A, Ahmad S, Radcliffe K: Primary HIV infection. *Int J STD AIDS* 2002; 13:71-78.
7. Alho OP, Teppo H, Mäntyselkä P, Kantola S: Head and neck cancer in primary care: Presenting symptoms and the effect of delayed diagnosis of cancer cases. *CMAJ* 2006; 174:779-784.
8. Luzuriaga K, Sullivan JL: Infectious mononucleosis. *N Engl J Med* 2010; 362:1993-2000.
9. Grover C: Images in clinical medicine: "Thumb sign" of epiglottitis. *N Engl J Med* 2011; 365:447.
10. Reference deleted in proofs.
11. Werner SL, Jones RA, Emerman CL: Sonographic assessment of the epiglottis. *Acad Emerg Med* 2004; 11:1358-1360.
12. Hung TY, et al: Bedside ultrasonography as a safe and effective tool to diagnose acute epiglottitis. *Am J Emerg Med* 2011; 29:359.e1-3.
13. Nagy M, Backstrom J: Comparison of the sensitivity of lateral neck radiographs and computed tomography scanning in pediatric deep-neck infections. *Laryngoscope* 1999; 109:775-779.
14. Vural C, Gungor A, Comerci S: Accuracy of computerized tomography in deep neck infections in the pediatric population. *Am J Otolaryngol* 2003; 24:143-148.
15. Rozovsky K, Hiller N, Koplewitz BZ, Simanovsky N: Does CT have an additional diagnostic value over ultrasound in the evaluation of acute inflammatory neck masses in children? *Eur Radiol* 2010; 20:484-490.
16. Thomas M, Del Mar C, Glasziou P: How effective are treatments other than antibiotics for acute sore throat? *Br J Gen Pract* 2000; 50:817-820.
17. Wing A, et al: Effectiveness of corticosteroid treatment in acute pharyngitis: A systematic review of the literature. *Acad Emerg Med* 2010; 17:476-483.
18. Johnson RF, Stewart MG: The contemporary approach to diagnosis and management of peritonsillar abscess. *Curr Opin Otolaryngol Head Neck Surg* 2005; 13:157-160.
19. Del Mar CB, Glasziou PP, Spinks AB: Antibiotics for sore throat. *Cochrane Database Syst Rev* 2006; 4:CD000023.
20. Olivier C: Rheumatic fever—is it still a problem? *J Antimicrob Chemother* 2000; 45:13-21.
21. Tibazarwa KB, Volmink JA, Mayosi BM: Incidence of acute rheumatic fever in the world: A systematic review of population-based studies. *Heart* 2008; 94:1534-1540.
22. Budnitz DS, et al: National surveillance of emergency department visits for outpatient adverse drug events. *JAMA* 2006; 296:1858-1866.
23. Grijalva CG, Nuorti JP, Griffin MR: Antibiotic prescription rates for acute respiratory tract infections in U.S. ambulatory settings. *JAMA* 2009; 302:758-766.

www.ketabpezeshki.com 66485457-66963820

Chapter 24

Hemoptysis

Calvin A. Brown III and Ali S. Raja

PERSPECTIVE

Epidemiology

Hemoptysis is defined as the expectoration of blood from the respiratory tract below the vocal cords. Most cases seen in the emergency department (ED) are mild episodes of small-volume hemoptysis, typically consisting of either blood-tinged sputum or minute amounts of frank blood and are most commonly caused by bronchitis. Although hemoptysis is commonly seen in the ED, only 1 to 5% of hemoptysis patients have massive or life-threatening hemorrhage (generally accepted as 100 to 600 mL of blood loss in any 24-hour period), which can result in hemodynamic instability, shock, or impaired alveolar gas exchange and has a mortality rate approaching 80%.

Large, contemporary series of patients with massive hemoptysis are lacking, and most causative data originate from small, often rural, studies in which tuberculosis (TB) and bronchiectasis are responsible for the majority of cases.[1] In developed nations, cancer, cystic fibrosis, arteriovenous malformations, and postprocedural complications play more prominent roles. Pediatric hemoptysis is rare but can be caused by infection, congenital heart disease, cystic fibrosis, or bleeding from a preexisting tracheostomy.[2]

Pathophysiology

Trace hemoptysis typically originates from tracheobronchial capillaries that are disrupted by vigorous coughing or minor bronchial infections. Conversely, massive hemoptysis nearly always involves disruption of bronchial or pulmonary arteries, the two sets of vessels that constitute the lung's dual blood supply. Bronchial arteries, which are direct branches from the thoracic aorta, are responsible for supplying oxygenated blood to lung parenchyma, and disruption of these vessels from arteritis, trauma, bronchiectasis or malignant erosion can result in sudden and profound hemorrhage. Although small in caliber, the bronchial circulation is a high-pressure system and the culprit in nearly 90% of the cases of massive hemoptysis requiring embolization. Pulmonary arteries, although transmitting large volumes of blood, do so at much lower pressures and, unless affected centrally, are less likely to cause massive hemoptysis.

Nearly all causes of hemoptysis have a common mechanism—vascular disruption within the trachea, bronchi, small-caliber airways, or lung parenchyma. Modes of vessel injury include acute and chronic inflammation (from bronchitis and arteritis), local infection (especially lung abscesses, TB, and aspergillosis), trauma, malignant invasion, infarction following a pulmonary embolus, and fistula formation (specifically aortobronchial fistulae).

Bronchiectasis, a chronic necrotizing infection resulting in bronchial wall inflammation and dilation, is one of the most common causes of massive hemoptysis. As tissue destruction and remodeling occur, rupture of nearby bronchial vessels can result in bleeding. Bronchiectasis can complicate chronic airway obstruction, necrotizing pneumonia, TB, or cystic fibrosis. Broncholithiasis, the formation of calcified endobronchial lesions following a wide array of granulomatous infections, is an uncommon problem with a similar propensity to erode nearby vessels. Hemorrhage control often requires surgical intervention.[3-5]

Iatrogenic hemoptysis complicates 2 to 10% of all endobronchial procedures, especially percutaneous lung biopsies.[6,7] Diffuse alveolar hemorrhage can be seen with autoimmune vasculitides such as Wegener's granulomatosis, systemic lupus erythematosus, and Goodpasture's syndrome. An uncommon cause of hemoptysis occurs when ectopic endometrial tissue within the lung results in monthly catamenial episodes of bleeding.[8] Less common causes include pulmonary hereditary telangiectasias and hydatidiform infections. Any episode of hemoptysis can be exacerbated by coagulopathy and thrombocytopenia.

DIAGNOSTIC APPROACH

Differential Considerations

For a patient with apparent hemoptysis, two other potential sources of bleeding should be investigated. Nasal, oral, or hypopharyngeal bleeding sometimes contaminates the tracheobronchial tree, mimicking true hemoptysis. The clinician should closely inspect the nasopharynx and oral cavity to exclude this possibility. Gastric or proximal duodenal bleeding can similarly mimic hemoptysis, and differentiating a gastrointestinal (GI) source of bleeding is especially important because further evaluation and management of these two pathologies follow divergent pathways. Usually differentiation can be done by the patient and physician working together to differentiate coughing from vomiting. In unclear cases, inspection and pH testing may help to distinguish GI from tracheobronchial hemorrhage. Unless an active, brisk upper GI hemorrhage is present, the acidification of blood in the stomach results in fragmentation and darkening, producing specks of brown or black material often referred to as coffee-ground emesis. Pulmonary blood appears bright red or as only slightly darker clots and is alkaline.

Rapid Assessment and Stabilization

Although hemodynamic instability can occur as a result of hemorrhage, the most lethal sequela of massive hemoptysis is hypoxia,

www.ketabpezeshki.com 66485457-66963820

which results from the ventilation-perfusion mismatch that follows submersion of the small airways and alveoli with blood.

As a mitigating maneuver in patients with a known lateralizing source of bleeding, the "lung-down" position can be employed. For this position the patient is turned such that the bleeding lung is more dependent, promoting continued protection and ventilation of the unaffected lung and improved oxygenation. If intubation is required, a large diameter (8.0) endotracheal tube should be used to facilitate emergent fiberoptic bronchoscopy. In selected cases of confirmed left-sided bleeding, a single-lumen right-mainstem intubation often can be successfully performed through advancement of the tube in the neutral position or use of a 90-degree rotational technique, during which the tube is rotated 90 degrees in the direction of desired placement and advanced until resistance is met.[9] Left-mainstem intubations are more difficult but may be attempted when the bleeding site is the right lung and simple lung-down positioning is not sufficient to stabilize the patient's airway and oxygenation.

When these measures fail or the hemoptysis is life-threatening, anesthesia consultation is sought for consideration of placement of a double-lumen endotracheal tubes for lung isolation. The correct positioning of blindly placed double-lumen tubes is difficult and requires confirmation by auscultation and fiberoptic bronchoscopy, both of which have are severely impaired by massive hemoptysis. Complications of double-lumen tubes include unilateral and bilateral pneumothoraces, pneumomediastinum, carinal rupture, lobar collapse, and tube malposition.[10]

Pivotal Findings

History

Although patient reports of bleeding severity can be inaccurate, an estimate of the rate, volume, and appearance of expectorated blood should be obtained. Additional pertinent history includes prior episodes of hemoptysis or parenchymal pulmonary disorders, including bronchiectasis, recurrent pneumonia, chronic obstructive pulmonary disease, bronchitis, TB, and fungal infection. Inflammatory disorders that secondarily involve the lungs or pulmonary vasculature include Wegener's granulomatosis, Goodpasture's syndrome, and systemic lupus erythematosus, and a history of these should be elicited. Any risk factors for platelet dysfunction, thrombocytopenia, and coagulopathy should be noted, as should, conversely, any hypercoagulable states that might contribute to venous thromboembolic disease.

Primary or metastatic cancer can cause hemoptysis by erosion into pulmonary and bronchial vessels. Recent percutaneous or transbronchial procedures can cause immediate or delayed post-procedural bleeding, and any recent history of trauma should also be noted. A pertinent travel history to areas in which TB or pulmonary paragonimiasis is endemic is crucial.

Physical Examination

After a primary survey and stabilization, a targeted examination may suggest the location and cause of bleeding but does so in less than 50% of cases.[11] Focal adventitious breath sounds may indicate pneumonia or pulmonary abscess. A new heart murmur, especially in a febrile patient, may reflect endocarditis causing septic pulmonary emboli. Symptoms and signs of deep venous thrombosis should suggest pulmonary embolism. Ecchymoses and petechiae can indicate coagulopathy and thrombocytopenia, respectively.

Ancillary Testing

Initial laboratory studies include a complete blood count, coagulation tests, and a type and screen or crossmatch. Renal function tests should be performed if vasculitis is suggested or contrast computed tomography (CT) is planned. Plain chest radiography screens for causes of hemoptysis (including infection and malignancy), although its sensitivity is poor. A prospective study of 184 consecutive patients with varying degrees of hemoptysis revealed that more than 40% of patients with a normal chest radiograph had positive findings on chest CT.[12]

In patients with massive hemoptysis, plain films may localize the site of hemorrhage in as many as 80% of patients; however, high-resolution multidetector CT of the chest is the principle diagnostic test for investigating both bronchial and nonbronchial causes of massive hemoptysis.[13] A chest CT scan should be obtained in the high-risk patient (smokers, oncology patients) or in any patient with moderate to severe bleeding even if the initial chest radiograph is normal. CT localization of hemorrhage can expedite bronchoscopic evaluation and guide subsequent interventional procedures.

CT is diagnostically comparable to conventional angiography but less invasive and more rapidly available. Angiography is the first-line study when the cause of the hemoptysis is known (e.g., malignancy) and angiography-assisted embolization therapy is contemplated.[14-16]

DIAGNOSTIC ALGORITHM

Differential Diagnosis

Potential causes of hemoptysis vary and include systemic illnesses as well as pulmonary parenchymal diseases. Box 24-1 includes the most common causes.

Management

Since the advent of high-resolution CT, radiologic evaluation has had an integral role in the evaluation and treatment of patients with hemoptysis. The challenge to the emergency physician is to rapidly assess the need for airway control before radiographic evaluation and hemodynamic stabilization. Unless the initial chest radiograph is diagnostic or the patient is hemodynamically unstable, a chest CT should be obtained. Further management decisions should be guided by the CT results and made in conjunction with pulmonary and thoracic surgery consultants (Fig. 24-1).

Bronchoscopy

Early bronchoscopy facilitates both localization of bleeding and therapeutic intervention. Balloon and topical hemostatic tamponade, thermocoagulation, and injection of vasoactive agents can all effectively control arterial bleeding. Optimal timing for bronchoscopy remains conjectural; although stable patients with mild to moderate bleeding may benefit from early bronchoscopy, in unstable patients or those with brisk hemorrhage, bronchoscopy may facilitate airway management but is less likely to control bleeding.

Chest CT is as diagnostically accurate as bronchoscopy in locating bleeding peripheral vessels not accessible by a flexible bronchoscope.[17] Chest CT can be used to identify the site of bleeding to determine whether angiography is indicated. There may be little added benefit to bronchoscopy before interventional angiography if the bleeding source has already been accurately identified on CT.[18]

Interventional Angiography

Bronchial arterial embolization is an effective first-line therapy for massive hemoptysis and is the procedure of choice for patients either unable to tolerate surgery or in whom bronchoscopy has

www.ketabpezeshki.com 66485457-66963820

Box 24-1 Differential Diagnosis: Hemoptysis

Airway Disease
Bronchitis (acute or chronic)
Bronchiectasis
Neoplasm (primary and metastatic)
Trauma
Foreign body

Parenchymal Disease
Tuberculosis
Pneumonia, lung abscess
Fungal infection
Neoplasm

Vascular Disease
Pulmonary embolism
Arteriovenous malformation
Aortic aneurysm
Pulmonary hypertension
Vasculitis (Wegener's granulomatosis, systemic lupus erythematosus [SLE], Goodpasture's syndrome)

Hematologic Disease
Coagulopathy (cirrhosis or warfarin therapy)
Disseminated intravascular coagulation
Platelet dysfunction
Thrombocytopenia

Cardiac Disease
Congenital heart disease (especially in children)
Valvular heart disease
Endocarditis

Miscellaneous
Cocaine
Postprocedural injury
Tracheal-arterial fistula
SLE

been unsuccessful. Hemostatic rates range from 91 to 98%, but as many as 20 to 50% of patients have early episodes of repeat bleeding. The risk of delayed bleeding may exist for up to 36 months.[19-21] To guide therapy, initial localization of bleeding by bronchoscopy or CT is preferred. Rare complications include arterial perforation and dissection.

Surgery

Emergency thoracotomy, in the operating room, is reserved for life-threatening hemoptysis or for persistent, rapid bleeding that is uncontrolled by bronchoscopy and percutaneous embolization. Pulmonary arterial hemorrhage from tumor necrosis represents a surgical emergency.

DISPOSITION

Healthy patients with blood-streaked sputum or intermittent small-volume hemoptysis that has resolved and who have normal vital signs do not require imaging beyond plain chest radiography and can be discharged. Follow-up should be arranged for a few days to a week later if symptoms persist, or sooner (including return to the ED) if symptoms are worsening. High-risk patients with minor hemoptysis and all patients with moderate or large amounts of hemoptysis should undergo emergent chest CT scan. There is little value in obtaining a plain chest radiograph before CT, and a plain x-ray film should not be obtained if chest CT is planned regardless of the findings on the plain film. Brief hospitalization or admission to an observation unit for bronchoscopy should be considered. All patients with massive hemoptysis require admission to an intensive care unit and expedited multidisciplinary treatment involving the emergency physician, pulmonologist, and thoracic surgeon.

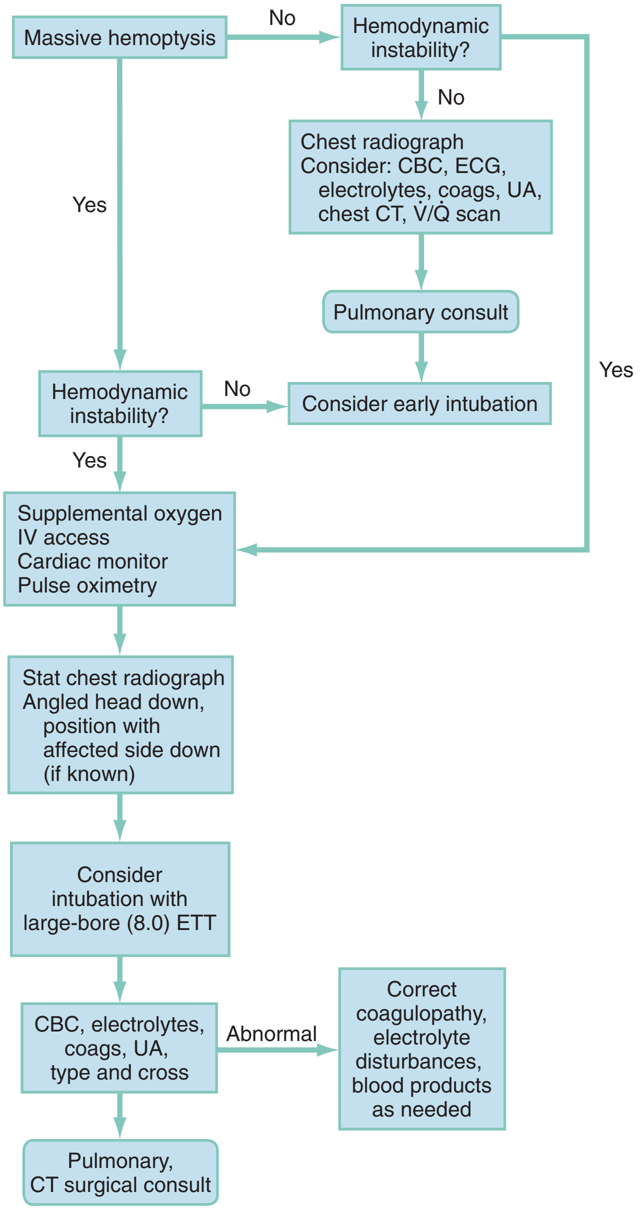


Figure 24-1. Emergency department management of hemoptysis. *CBC,* complete blood count; *coags,* coagulation studies; *CT,* computed tomography; *ECG,* electrocardiogram; *ETT,* endotracheal tube; *IV,* intravenous; *UA,* urinalysis; *V̇/Q̇,* ventilation-perfusion.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Reechaipichitkul W, Latong S: Etiology and treatment outcomes of massive hemoptysis. *Southeast Asian J Trop Med Public Health* 2005; 36:2.
2. Batra PS, Holinger LD: Etiology and management of pediatric hemoptysis. *Arch Otolaryngol Head Neck Surg* 2001; 127:377.
3. Minami H, Sano I, Matsuo S: Broncholithiasis managed by surgical resection. *Gen Thorac Cardiovasc Surg* 2007; 55:138.
4. Reza B, Ziaollah H: Surgical management of TB broncholithiasis with hemoptysis: Experience with five operated cases. *Ann Thorac Cardiovasc Surg* 2007; 13:185.
5. Potaris K, Miller DL, Trastek VF: Role of surgical resection in broncholithiasis. *Ann Thorac Surg* 2000; 70:248.
6. Wescott JL: Percutaneous transthoracic needle biopsy. *Radiology* 1988; 169:593.
7. Cordasco EM Jr, Mehta AC, Ahmad M: Bronchoscopically induced bleeding: A summary of nine years' Cleveland Clinic experience and review of the literature. *Chest* 1991; 100:1141.
8. Augoulea A, Lambrinoudaki I, Christodoulakos G: Thoracic endometriosis syndrome. *Respiration* 2008; 75:113.
9. Bair AE, Doherty MJ, Harper R, Albertson TE: An evaluation of a blind rotational technique for selective mainstem intubation. *Acad Emerg Med* 2004; 11:1105.
10. Sucato DJ, Girgis M: Bilateral pneumothoraces, pneumomediastinum, pneumoperitoneum, pneumoretroperitoneum, and subcutaneous emphysema following intubation with a double-lumen endotracheal tube for thoracoscopic anterior spinal release and fusion in a patient with idiopathic scoliosis. *J Spinal Disord Tech* 2002; 15:133.
11. Haro Estarriol M, et al: Utility of history, physical examination and radiography in the localization of bleeding in patients with hemoptysis. *An Med Interna* 2002; 19:289.
12. Tsoumakidai M, et al: A prospective analysis of 184 cases of hemoptysis: Diagnostic impact of chest x-ray, computed tomography, bronchoscopy. *Respiration* 2006; 73:808.
13. Khalil A, et al: Severe hemoptysis of pulmonary arterial origin: Signs and role of multidetector row CT angiography. *Chest* 2008; 133:212.
14. Remy-Jardin M, et al: Bronchial and nonbronchial systemic arteries at multi-detector row CT angiography: Comparison with conventional angiography. *Radiology* 2004; 233:741.
15. Yoon YC, et al: Hemoptysis: Bronchial and nonbronchial systemic arteries at 16-detector row CT. *Radiology* 2005; 234:292.
16. Yoon W, et al: Massive hemoptysis: Prediction of nonbronchial systemic arterial supply with chest CT. *Radiology* 2003; 227:232.
17. Revel MP, et al: Can CT replace bronchoscopy in the detection of the site and cause of bleeding in patients with large or massive hemoptysis? *AJR Am J Roentgenol* 2002; 179:1217.
18. Hsiao EI, Kirsch CM, Kagawa FT: Utility of fiberoptic bronchoscopy before bronchial artery embolization for massive hemoptysis. *AJR Am J Roentgenol* 2001; 177:861.
19. Swanson KL, et al: Bronchial artery embolization: Experience with 54 patients. *Chest* 2001; 121:789.
20. Osaki S, et al: Prognosis of bronchial artery embolization in the management of hemoptysis. *Respiration* 2000; 67:412.
21. Poyanli A, et al: Endovascular therapy in the management of moderate and massive haemoptysis. *Br J Radiol* 2007; 80:331.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 25

Dyspnea

Sabina A. Braithwaite and Debra Perina

PERSPECTIVE

Dyspnea is the term applied to the sensation of breathlessness and the patient's reaction to that sensation. It is an uncomfortable awareness of breathing difficulties that in the extreme manifests as "air hunger." Dyspnea is often ill defined by patients, who may describe the feeling as shortness of breath, chest tightness, or difficulty breathing. Dyspnea results from a variety of conditions, ranging from nonurgent to life-threatening. Neither the clinical severity nor the patient's perception correlates well with the seriousness of underlying pathology and may be affected by emotions, behavioral and cultural influences, and external stimuli.[1,2]

The following terms may be used in the assessment of the dyspneic patient:

Tachypnea: A respiratory rate greater than normal. Normal rates range from 44 cycles/min in a newborn to 14 to 18 cycles/min in adults.

Hyperpnea: Greater than normal minute ventilation to meet metabolic requirements.

Hyperventilation: A minute ventilation (determined by respiratory rate and tidal volume) that exceeds metabolic demand. Arterial blood gases (ABGs) characteristically show a normal partial pressure of oxygen (Po_2) with an uncompensated respiratory alkalosis (low partial pressure of carbon dioxide [Pco_2] and elevated pH).

Dyspnea on exertion: Dyspnea provoked by physical effort or exertion. It often is quantified in simple terms, such as the number of stairs or number of blocks a patient can manage before the onset of dyspnea.

Orthopnea: Dyspnea in a recumbent position. It usually is measured in number of pillows the patient uses to lie in bed (e.g., two-pillow orthopnea).

Paroxysmal nocturnal dyspnea: Sudden onset of dyspnea occurring while reclining at night, usually related to the presence of congestive heart failure.

Epidemiology

Dyspnea is a common presenting complaint among emergency department (ED) patients of all ages. Causes vary widely and may include benign, self-limited conditions or significant pathology that can produce long-term morbidity and premature mortality.

Pathophysiology

The actual mechanisms responsible for dyspnea are unknown. Normal breathing is controlled both centrally by the respiratory control center in the medulla oblongata and peripherally by chemoreceptors located near the carotid bodies, and mechanoreceptors in the diaphragm and skeletal muscles.[3] Any imbalance among these sites is perceived as dyspnea. This imbalance generally results from ventilatory demand being greater than capacity.[4]

The perception and sensation of dyspnea are believed to occur by one or more of the following mechanisms: increased work of breathing, such as the increased lung resistance or decreased compliance that occurs with asthma or chronic obstructive pulmonary disease (COPD), or increased respiratory drive, such as results from severe hypoxemia, acidosis, or centrally acting stimuli (toxins, central nervous system events). Pulmonary stretch receptors also play a role.

DIAGNOSTIC APPROACH

Differential Considerations

Dyspnea is subjective and has many different potential causes. The differential diagnosis can be divided into acute and chronic causes, of which many are pulmonary. Other causes include cardiac, metabolic, infectious, neuromuscular, traumatic, and hematologic conditions (Table 25-1).

Pivotal Findings

History

Duration of Dyspnea. Chronic or progressive dyspnea usually denotes primary cardiac or pulmonary disease.[5] Acute dyspneic spells may result from asthma exacerbation; infection; pulmonary embolus; intermittent cardiac dysfunction; psychogenic causes; or inhalation of irritants, allergens, or foreign bodies.

Onset of Dyspnea. Sudden onset of dyspnea should lead to consideration of pulmonary embolism (PE) or spontaneous pneumothorax. Dyspnea that builds slowly over hours or days may represent a flare of asthma or COPD; pneumonia; recurrent, small pulmonary emboli; congestive heart failure; or malignancy.

Positional Changes. Orthopnea can result from left-sided heart failure, COPD, or neuromuscular disorders. One of the earliest symptoms seen in patients with diaphragmatic weakness from neuromuscular disease is orthopnea.[6] Paroxysmal nocturnal dyspnea is most common in patients with left-sided heart failure[5] but also occurs in COPD. Exertional dyspnea commonly is associated with COPD but also can be seen with poor cardiac reserve and abdominal loading. Abdominal loading, caused by ascites, obesity, or pregnancy, leads to elevation of the diaphragm, resulting in less effective ventilation and dyspnea.

www.ketabpezeshki.com 66485457-66963820

Table 25-1 Differential Diagnoses for Acute Dyspnea

ORGAN SYSTEM	CRITICAL DIAGNOSES	EMERGENT DIAGNOSES	NONEMERGENT DIAGNOSES
Pulmonary	Airway obstruction Pulmonary embolus Noncardiogenic edema Anaphylaxis Ventilatory failure	Spontaneous pneumothorax Asthma Cor pulmonale Aspiration Pneumonia (CAP score >70)	Pleural effusion Neoplasm Pneumonia (CAP score ≤ 70) COPD
Cardiac	Pulmonary edema Myocardial infarction Cardiac tamponade	Pericarditis	Congenital heart disease Valvular heart disease Cardiomyopathy
Primarily Associated with Normal or Increased Respiratory Effort			
Abdominal		Mechanical interference Hypotension, sepsis from ruptured viscus, bowel obstruction, inflammatory or infectious process	Pregnancy Ascites Obesity
Psychogenic			Hyperventilation syndrome Somatization disorder Panic attack
Metabolic or endocrine	Toxic ingestion DKA	Renal failure Electrolyte abnormalities Metabolic acidosis	Fever Thyroid disease
Infectious	Epiglottitis	Pneumonia (CAP score >70)	Pneumonia (CAP score ≤ 70)
Traumatic	Tension pneumothorax Cardiac tamponade Flail chest	Simple pneumothorax, hemothorax Diaphragmatic rupture	Rib fractures
Hematologic	Carbon monoxide poisoning Acute chest syndrome	Anemia	
Primarily Associated with Decreased Respiratory Effort			
Neuromuscular	CVA, intracranial insult Organophosphate poisoning	Multiple sclerosis Guillain-Barré syndrome Tick paralysis	ALS Polymyositis Porphyria

ALS, amyotrophic lateral sclerosis; *CAP,* community-acquired pneumonia; *COPD,* chronic obstructive pulmonary disease; *CVA,* cerebrovascular accident; *DKA,* diabetic ketoacidosis.

Trauma. Dyspnea can result from trauma, causing fractured ribs, flail chest, hemothorax, pneumothorax, diaphragmatic rupture, pericardial effusion, cardiac tamponade, or neurologic injury.

Symptoms

Patient descriptions of dyspnea vary significantly and generally correlate poorly with severity. Fever suggests an infectious cause. Anxiety or overwhelming fear, particularly if it precedes the onset of dyspnea, may point to panic attack or psychogenic dyspnea, if no organic cause can be isolated. PE or myocardial infarction may cause isolated dyspnea with or without associated chest pain, particularly if the pain is constant, dull, or visceral.[7] If the pain is sharp and worsened by deep breathing but not by movement, pleural effusion, pleurisy, or pleural irritation from pneumonia or PE are possible. Spontaneous pneumothorax also may produce sharp pain with deep breathing that is not worsened by movement.

Signs

Physical signs in dyspneic patients may be consistent with specific illnesses (Table 25-2). Physical findings found in specific diseases also can be grouped as presenting patterns (Table 25-3).

Ancillary Studies

Specific findings obtained from the history and physical examination should be used to determine which ancillary studies are needed (Table 25-4). Bedside oxygen saturation determinations, or selective use of ABGs when oximetry is not reliable, are useful in determining the degree of hypoxia and the need for supplemental oxygen or assisted ventilation. An additional resource for quickly assessing ventilatory status is noninvasive waveform capnography. End-tidal carbon dioxide ($ETco_2$) values correlate well with arterial carbon dioxide (CO_2), and together with the shape of the capnogram can be helpful in assessing the adequacy of ventilations as well as underlying causes of the dyspnea (see Chapter 5).[8] An electrocardiogram may be useful if history or physical examination findings suggest heart failure, ischemic cardiac disease, dysrhythmia, or pulmonary hypertension. Bedside ultrasound is useful to rapidly diagnose pulmonary edema, pneumothorax, and COPD, as well as deep venous thrombosis.[9,10]

Serum electrolytes may confirm metabolic acidosis or a less common cause, such as hypokalemia, hypophosphatemia, or hypocalcemia. A complete blood count may identify severe anemia or thrombocytopenia associated with sepsis. The white blood cell count is not sufficiently sensitive or specific to be of discriminatory value.

Expanded availability of specific blood biomarkers relevant to emergent evaluation of dyspnea provides improved immediate decision support and allows for short- and long-term prognostication.[11-14] These include cardiac markers and D-dimer assay, which are useful in pursuing causes such as cardiac ischemia or venous thromboembolic disease. Amino-terminal pro-B–type natriuretic peptide (NT-proBNP) analysis adds both diagnostic and prognostic value for several causes of dyspnea, including heart failure, PE, and ischemic cardiac disease.[13-16]

www.ketabpezeshki.com 66485457-66963820

Table 25-2 Pivotal Findings in Physical Examination

SIGN	PHYSICAL FINDING	DIAGNOSES TO CONSIDER
Vital signs	Tachypnea	Pneumonia, pneumothorax
	Hypopnea	Intracranial insult, drug or toxin ingestion
	Tachycardia	PE, traumatic chest injury
	Hypotension	Tension pneumothorax
	Fever	Pneumonia, PE
General appearance	Cachexia, weight loss	Malignancy, acquired immune disorder, mycobacterial infection
	Obesity	Hypoventilation, sleep apnea, PE
	Pregnancy	PE
	Barrel chest	COPD
	"Sniffing" position	Epiglottitis
	"Tripoding" position	COPD or asthma with severe distress
	Traumatic injury	Pneumothorax (simple, tension), rib fractures, flail chest, hemothorax, pulmonary contusion
Skin and nails	Tobacco stains or odor	COPD, malignancy, infection
	Clubbing	Chronic hypoxia, intracardiac shunts, or pulmonary vascular anomalies
	Pallid skin or conjunctivae	Anemia
	Muscle wasting	Neuromuscular disease
	Bruising	Chest wall: rib fractures, pneumothorax Diffuse: thrombocytopenia, chronic steroid use, anticoagulation
	Subcutaneous emphysema	Rib fractures, pneumothorax, tracheobronchial disruption
	Hives, rash	Allergic reaction, infection, tick-borne illness
Neck	Stridor	Upper airway edema or infection, foreign body, traumatic injury, anaphylaxis
	JVD	Tension pneumothorax, COPD or asthma exacerbation, fluid overload or CHF, PE
Lung examination	Wheezes	CHF, anaphylaxis Bronchospasm
	Rales	CHF, pneumonia, PE
	Unilateral decrease	Pneumothorax, pleural effusion, consolidation, rib fractures or contusion, pulmonary contusion
	Hemoptysis	Malignancy, infection, bleeding disorder, CHF
	Sputum production	Infection (viral, bacterial)
	Friction rub	Pleurisy
	Abnormal respiratory pattern (e.g., Cheyne-Stokes)	Intracranial insult
Chest examination	Crepitance or pain on palpation	Rib or sternal fractures
	Subcutaneous emphysema	Pneumothorax, tracheobronchial rupture
	Thoracoabdominal desynchrony	Diaphragmatic injury with herniation; cervical spinal cord trauma
	Flail segment	Flail chest, pulmonary contusion
Cardiac examination	Murmur	PE
	S_3 or S_4 gallop	PE
	S_2 accentuation	PE
	Muffled heart sounds	Cardiac tamponade
Extremities	Calf tenderness, Homans' sign	PE
	Edema	CHF
Neurologic examination	Focal deficits (motor, sensory, cognitive)	Stroke, intracranial hemorrhage causing central abnormal respiratory drive; if long-standing, risk of aspiration pneumonia
	Symmetrical deficits	Neuromuscular disease
	Diffuse weakness	Metabolic or electrolyte abnormality (hypocalcemia, hypomagnesemia, hypophosphatemia), anemia
	Hyporeflexia	Hypermagnesemia
	Ascending weakness	Guillain-Barré syndrome

CHF, congestive heart failure; *COPD*, chronic obstructive pulmonary disease; *JVD*, jugular venous distention; *PE*, pulmonary embolism.

If venous thromboembolism is suspected, D-dimer testing, with or without chest computed tomographic angiography, duplex venous ultrasonography, or, rarely, ventilation-perfusion scanning, is performed.[17] If dyspnea is believed to be upper airway in origin, direct or fiberoptic laryngoscopy or a soft tissue lateral radiograph of the neck may be useful.

DIFFERENTIAL DIAGNOSIS

The range and diversity of pathophysiologic conditions that produce dyspnea render a simple algorithmic approach difficult. The primary branch point is the determination of whether the dyspnea primarily is cardiopulmonary or toxic-metabolic in origin. After initial stabilization and assessment, findings from the history, physical examination, and ancillary testing are collated to match patterns of disease that produce dyspnea. This process is updated periodically as new information becomes available. Table 25-3 presents recognizable patterns of disease for common dyspnea-producing conditions, along with specific associated symptoms.

Critical Diagnoses

Several critical diagnoses should be promptly considered to determine the best treatment options to stabilize the patient. Tension pneumothorax is such a critical diagnosis and is diagnosed by

www.ketabpezeshki.com 66485457-66963820

Table 25-3 Diagnostic Table: Patterns of Diseases Often Resulting in Dyspnea

DISEASE	HISTORY (DYSPNEA)	ASSOCIATED SYMPTOMS	SIGNS AND PHYSICAL FINDINGS	TESTS
Pulmonary embolism	HPI: abrupt onset, pleuritic pain, immobility (travel, recent surgery) PMH: malignancy, DVT, PE, hypercoagulability, oral contraception, obesity	Diaphoresis, exertional dyspnea	Tachycardia, tachypnea, low-grade fever	Pulse oximetry, ABG (A-a gradient), D-dimer ECG (dysrhythmia, right-sided heart strain) CXR (Westermark sign, Hampton's hump), spiral CT, MRV Pulmonary angiogram Ultrasound positive for DVT
Pneumonia	Fever, productive cough, chest pain	Anorexia, chills, nausea, vomiting, exertional dyspnea, cough	Fever, tachycardia, tachypnea, rales or decreased breath sounds	CXR, CBC, sputum and blood cultures
Bacterial	SH: tobacco use			Pulse oximetry Waveform capnography if altered mental status, ABG if capnography unavailable and acid-base derangement or hypercarbia suspected
Viral	Exposure (e.g., influenza, varicella)			
Opportunistic	Immune disorder, chemotherapy			
Fungal or parasitic	Exposure (e.g., birds), indolent onset	Episodic fever, nonproductive cough		
Pneumothorax	Abrupt onset: trauma, chest pain, thin males more likely to have spontaneous pneumothorax	Localized chest pain	Decreased breath sounds, subcutaneous emphysema, chest wall wounds or instability	CXR: pneumothorax, rib fractures, hemothorax Ultrasound: pneumothorax, pleural effusion
Simple				Ultrasound positive for pneumothorax
Tension	Decompensation of simple pneumothorax	Diaphoresis	JVD, tracheal deviation, muffled heart sounds, cardiovascular collapse	Clinical diagnosis: requires immediate decompression. May verify via bedside ultrasound
COPD or asthma	Tobacco use, medication noncompliance, URI symptoms, sudden weather change PMH: environmental allergies FH: asthma	Air hunger, diaphoresis	Retractions, accessory muscle use, tripoding, cyanosis "Shark fin" capnograph	CXR: rule out infiltrate, pneumothorax, atelectasis (mucus plug) Ultrasound: distinguish from heart failure Waveform capnography
Malignancy	Weight loss, tobacco, or other occupational exposure	Dysphagia	Hemoptysis	CXR, chest CT: mass, hilar adenopathy, focal atelectasis
Fluid overload	Gradual onset, dietary indiscretion or medication noncompliance, chest pain PMH: recent MI, diabetes, CHF	Worsening orthopnea, PND	JVD, peripheral edema, S_3 or S_4 gallop, new cardiac dysrhythmia, hepatojugular reflux	CXR and/or ultrasound: pleural effusion, interstitial edema, Kerley B lines, cardiomegaly ECG: ischemia, dysrhythmia NT-proBNP
Anaphylaxis	Abrupt onset, exposure to allergen	Dysphagia	Oral swelling, stridor, wheezing, hives	

A-a, alveolar-arterial; *ABG,* arterial blood gas; *CBC,* complete blood count; *CHF,* congestive heart failure; *CT,* computed tomography; *CXR,* chest x-ray examination; *DVT,* deep vein thrombosis; *ECG,* electrocardiogram; *FH,* family history; *HPI,* history of present illness; *JVD,* jugular venous distention; *MI,* myocardial infarction; *MRV,* magnetic resonance venography; *NT-proBNP,* amino-terminal pro-B–type natriuretic peptide; *PE,* pulmonary embolism; *PMH,* past medical history; *PND,* paroxysmal nocturnal dyspnea; *SH,* social history; *URI,* upper respiratory infection.

history and physical examination. If a dyspneic patient has diminished breath sounds on one side, ipsilateral hyper-resonance, severe respiratory distress, hypotension, and oxygen desaturation, prompt decompression of presumptive tension pneumothorax is indicated. Bedside ultrasonography can confirm pneumothorax in less obvious cases. If dyspnea and stridor indicate upper airway obstruction, early, definitive assessment and intervention occur in the ED or operating room. Complete obstruction by a foreign body warrants the Heimlich maneuver until the obstruction is relieved or the patient is unconscious, followed rapidly by direct laryngoscopy for foreign body removal. Heart failure and pulmonary edema can produce dyspnea and respiratory failure and require prompt intervention if severe.[18] Significant dyspnea and wheezing in anaphylaxis require immediate use of parenteral epinephrine in addition to supportive measures. Severe bronchospastic exacerbations of asthma at any age may lead rapidly to respiratory failure and arrest and should receive vigorous attention, including continuous or frequent administration of a beta-agonist aerosol and steroid therapy.[19] Ultrasound may also be of benefit in rapidly distinguishing between COPD and heart

www.ketabpezeshki.com 66485457-66963820

Table 25-4 Ancillary Testing in the Dyspneic Patient

CATEGORY	TEST	FINDINGS AND POTENTIAL DIAGNOSES
Laboratory	Pulse oximetry, selective ABG use	Hypoxia, hyperventilation (muscular weakness, intracranial event)
	Waveform capnography	CO_2 retention (COPD, sleep apnea), obstructive or restrictive pulmonary pattern
		Metabolic versus respiratory acidosis (DKA, ingestions)
		A-a gradient (PE)
		Elevated carboxyhemoglobin (inhalation injury or CO poisoning)
	Complete blood count	WBC
		Increase: infection, stress demargination, hematologic malignancy
		Decrease: neutropenia, sepsis
		Hgb, Hct: anemia, polycythemia
		Smear: abnormal Hgb (i.e., sickling), inclusions
		Platelets: thrombocytopenia (marrow toxicity)
	Chemistry	BUN, Cr: acute or chronic renal failure
		K, Mg, Phos: low levels resulting in muscular weakness
		Glucose: DKA
		D-dimer: abnormal clotting activity
		NT-proBNP: heart failure, PE
		Troponin: cardiac ischemia or infarct
Cardiac	ECG	Ischemia, dysrhythmia, $S_1Q_3T_3$ (PE), right-sided heart strain
	Echocardiogram	Pulmonary hypertension, valvular disorders
		Wall motion abnormalities related to ischemia, intracardiac shunts
Radiologic	Chest radiograph	Bony structures: fractures, lytic lesions, pectus, kyphoscoliosis
		Mass: malignancy, cavitary lesion, infiltrate, foreign body
		Diaphragm: eventration, elevation of hemidiaphragm, bowel herniation
		Mediastinum: adenopathy (infection, sarcoid), air
		Cardiac silhouette: enlarged (cardiomyopathy, fluid overload)
		Soft tissue: subcutaneous air
		Lung parenchyma: blebs, pneumothorax, effusions (blood, infectious), interstitial edema, local consolidation, air bronchograms, Hampton's hump, Westermark's sign
	$\dot{V}/\dot{Q}$ scan	PE
	Pulmonary angiogram	PE, intervention (thrombolysis)
	CT	Mass lesion, adenopathy, trauma, PE
	MRI	PE, bony and soft tissue lesions, vascular abnormality
	Soft tissue neck radiograph	Epiglottitis, foreign body
	Ultrasound	Pneumothorax, pleural effusion, impaired cardiac function or pericardial effusion
Fiberoptic	Bronchoscopy	Mass lesion, foreign body
		Intervention (stenting, biopsy)
	Laryngoscopy	Mass lesion, edema, epiglottitis, foreign body

A-a, alveolar-arterial; *ABG,* arterial blood gas; *BUN,* blood urea nitrogen; *CO,* carbon monoxide; *CO_2,* carbon dioxide; *COPD,* chronic obstructive pulmonary disease; *Cr,* creatinine; *CT,* computed tomography; *DKA,* diabetic ketoacidosis; *ECG,* electrocardiogram; *Hct,* hematocrit; *Hgb,* hemoglobin; *K,* potassium; *Mg,* magnesium; *MRI,* magnetic resonance imaging; *NT-proBNP,* amino-terminal pro-B–type natriuretic peptide; *PE,* pulmonary embolism; *Phos,* phosphate; $\dot{V}/\dot{Q}$, ventilation-perfusion; *WBC,* white blood cell.

failure.[10,20] As mentioned earlier, waveform capnography is a valuable adjunct for assessing the severity and determining the cause of respiratory distress.

Emergent Diagnoses

Asthma and COPD exacerbations can result in marked dyspnea with bronchospasm and decreased ventilatory volumes.[21] Sudden onset of dyspnea with a decreased oxygen saturation on room air accompanied by sharp chest pain may represent PE. Dyspnea accompanied by decreased breath sounds and tympany on percussion on one side is seen with spontaneous pneumothorax. Dyspnea associated with decreased respiratory effort may represent a neuromuscular process, such as multiple sclerosis, Guillain-Barré syndrome, or myasthenia gravis. Unilateral rales, cough, fever, and dyspnea usually indicate pneumonia.

Figure 25-1 provides an algorithm for assessment and stabilization of a dyspneic patient. The initial division is based on the degree of breathing effort associated with the symptoms. The most critical diagnoses are considered first, and appropriate intervention undertaken.

All patients experiencing dyspnea, regardless of possible cause, should be promptly evaluated in the treatment area. Bedside pulse oximetry readings should be obtained, and the patient should be placed on a cardiac monitor. If the pulse oximetry result is less than 95% on room air, the patient should be placed on supplemental oxygen either by nasal cannula or mask, depending on the degree of desaturation detected. If necessary, breathing should be assisted with manual or mechanical ventilation, either noninvasively for the short term, or with the patient tracheally intubated for airway protection or prolonged ventilation.[22]

When the airway has been secured, rapid assessment of the patient's appearance and vital signs can help determine the need for further stabilization. Decreased mental alertness, inability to speak in more than one-syllable words, or certain types of body positioning signal the presence of significant respiratory distress and the need for rapid intervention. After airway stabilization, the cause of the dyspnea can be further investigated.

Empirical Management and Disposition

The management algorithm for dyspnea (Fig. 25-2) outlines the approach to treatment for most identifiable diseases. Unstable patients or patients with critical diagnoses must be stabilized and may require admission to an intensive care unit. Emergent patients

www.ketabpezeshki.com 66485457-66963820

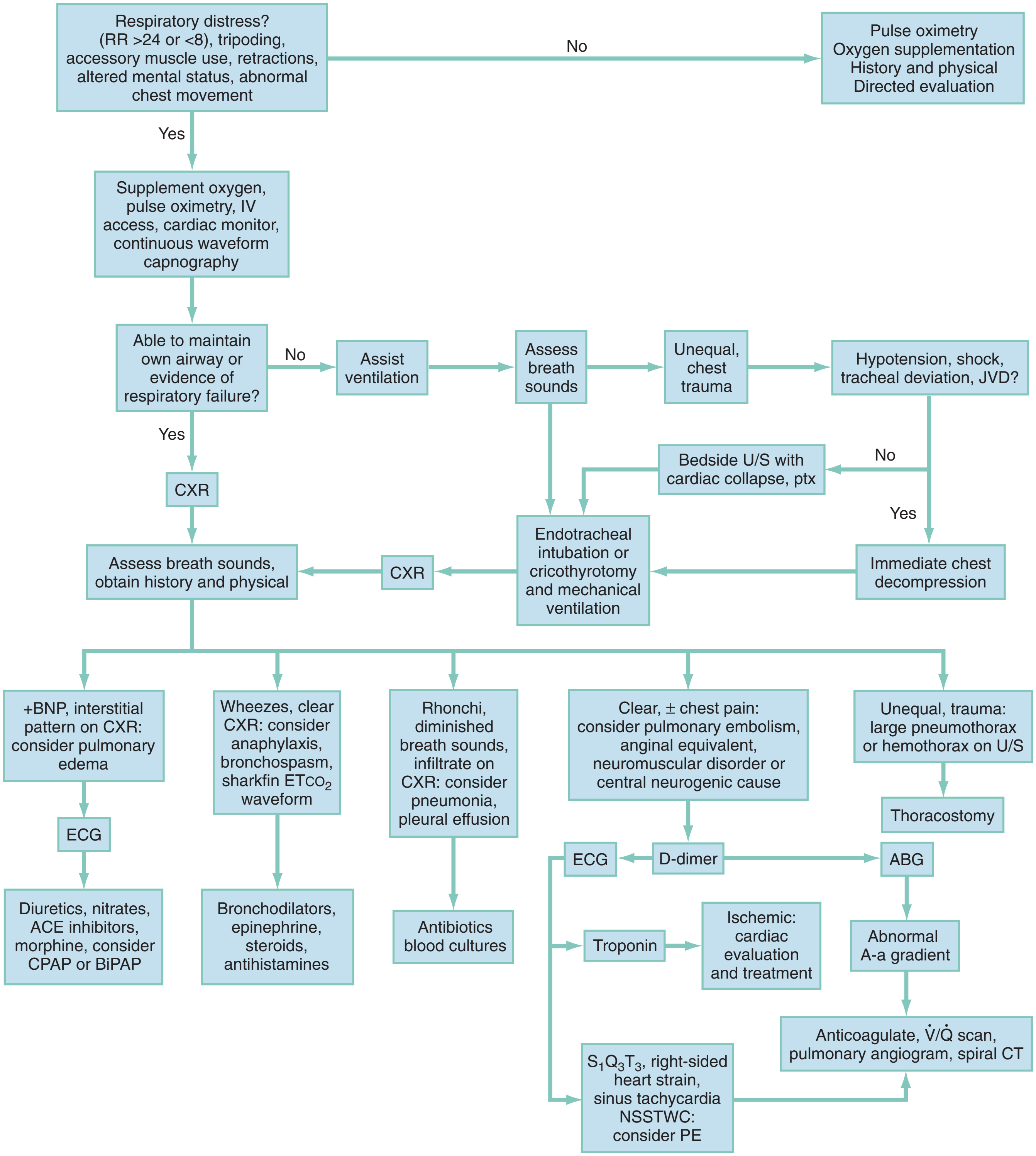


Figure 25-1. Rapid assessment and stabilization of a dyspneic patient. *A-a,* arterial-alveolar; *ABG,* arterial blood gas; *ACE,* angiotensin-converting enzyme; *BiPAP,* biphasic positive airway pressure; *BNP,* B-type natriuretic peptide; *CPAP,* continuous positive airway pressure; *CT,* computed tomography; *CXR,* chest x-ray; *ECG,* electrocardiogram; $ETco_2$, end-tidal carbon dioxide; *IV,* intravenous; *JVD,* jugular venous distention; *NSSTWC,* nonspecific ST wave changes (on ECG); *PE,* pulmonary embolism; *ptx,* pneumothorax; *RR,* respiratory rate; $\dot{V}/\dot{Q}$ ventilation-perfusion ratio; *U/S,* ultrasound.

www.ketabpezeshki.com 66485457-66963820

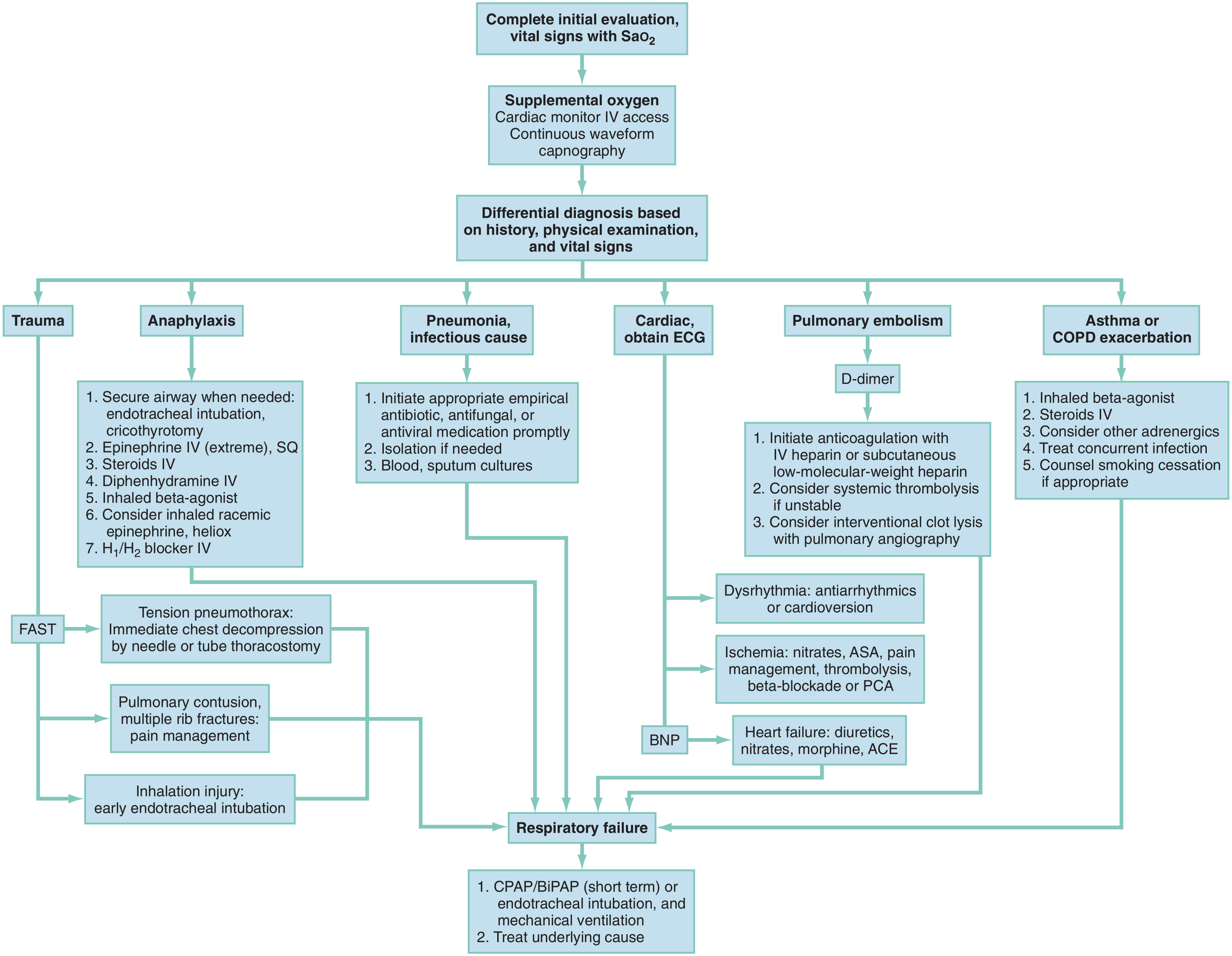


Figure 25-2. Clinical guidelines for emergency department management of dyspnea. *ACE,* angiotensin-converting enzyme; *ASA,* acetylsalicylic acid; *BNP,* B-type natriuretic peptide; *COPD,* chronic obstructive pulmonary disease; *CPAP/BiPAP,* continuous positive airway pressure/biphasic positive airway pressure; *ECG,* electrocardiogram; *IV,* intravenous; *PCA,* patient-controlled analgesia; SaO_2, arterial oxygen saturation; *SQ,* subcutaneously.

www.ketabpezeshki.com 66485457-66963820

who have improved with ED management may be admitted to an intermediate care unit. Patients diagnosed with urgent conditions in danger of deterioration without proper treatment or patients with severe comorbidities, such as diabetes, immunosuppression, or cancer, may also require admission for observation and treatment.

Most patients in the nonurgent category can be treated as outpatients if medical follow-up can be arranged. If dyspnea persists despite therapy and no definitive cause has been delineated, the best course of action is hospitalization for observation and ongoing evaluation. If no definitive diagnosis can be obtained and the symptoms have abated, the patient may be discharged with medical follow-up and instructions to return if symptoms recur.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Hravnak M, et al: Symptom expression in coronary heart disease and revascularization recommendations for black and white patients. *Am J Public Health* 2007; 97:1701.
2. Coli C, et al: Is there a link between the qualitative descriptors and the quantitative perception of dyspnea in asthma? *Chest* 2006; 130:436.
3. Dyspnea. Mechanisms, assessment, and management: A consensus statement. American Thoracic Society. *Am J Respir Crit Care Med* 1999; 159:321.
4. Ofir D, Laveneziana P, Webb KA, Lam YM, O'Donnell DE: Mechanisms of dyspnea during cycle exercise in symptomatic patients with GOLD stage I chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008; 177:622.
5. Ailani RK, et al: Dyspnea differentiation index: A new method for rapid separation of cardiac versus pulmonary dyspnea. *Chest* 1999; 119:1100.
6. Katz SL, et al: Nocturnal hypoventilation: Predictors and outcomes in childhood progressive neuromuscular disease. *Arch Dis Child* 2010; 95:998.
7. Lobo JL, et al: Clinical syndromes and clinical outcome in patients with pulmonary embolism: Findings from the RIETE registry. *Chest* 2006; 130:1817.
8. Cinar O, et al: Can mainstream end-tidal carbon dioxide measurement accurately predict the arterial carbon dioxide level of patients with acute dyspnea in ED. *Am J Emerg Med* 2012; 30:358-361.
9. Zanobetti M, Poggioni C, Pini R: Can chest ultrasonography replace standard chest radiography for evaluation of acute dyspnea in the ED? *Chest* 2010; 139:1140.
10. Zechner PM, Aichinger G, Rigaud M, Wildner G, Prause G: Prehospital lung ultrasound in the distinction between pulmonary edema and exacerbation of chronic obstructive pulmonary disease. *Am J Emerg Med* 2010; 28:389.
11. Januzzi JL Jr, Rehman S, Mueller T, van Kimmenade RR, Lloyd-Jones DM: Importance of biomarkers for long-term mortality prediction in acutely dyspneic patients. *Clin Chem* 2010; 56:1814.
12. Gori CS, Magrini L, Travaglino F, Di Somma S: Role of biomarkers in patients with dyspnea. *Eur Rev Med Pharmacol Sci* 2011; 15:229.
13. Baggish AL, et al: A validated clinical and biochemical score for the diagnosis of acute heart failure: The ProBNP investigation of dyspnea in the emergency department (PRIDE) acute heart failure score. *Am Heart J* 2006; 151:48.
14. Lam LL, et al: Meta-analysis: Effect of B-type natriuretic peptide testing on clinical outcomes in patients with acute dyspnea in the emergency setting. *Ann Intern Med* 2010; 153:728.
15. de Lemos JA, Morrow DA: Combining natriuretic peptides and necrosis markers in the assessment of acute coronary syndromes. *Rev Cardiovasc Med* 2003; 4:S37.
16. Melanson SE, et al: Combination of D-dimer and amino-terminal pro-B–type natriuretic peptide testing for the evaluation of dyspneic patients with and without acute pulmonary embolism. *Arch Pathol Lab Med* 2006; 130:1326.
17. Kline JA, Wells PS: Methodology for a rapid protocol to rule out pulmonary embolism in the emergency department. *Ann Emerg Med* 2003; 42:266.
18. Murray S: Bi-level positive airway pressure (BiPAP) and acute cardiogenic pulmonary oedema (ACPO) in the emergency department. *Aust Crit Care* 2002; 15:51.
19. National Heart, Lung, and Blood Institute National Asthma Education and Prevention Program: *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. U.S. Department of Health and Human Services, 2007. Available at www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed November 20, 2011.
20. Cibinel GA, et al: Diagnostic accuracy and reproducibility of pleural and lung ultrasound in discriminating cardiogenic causes of acute dyspnea in the emergency department. *Intern Emerg Med* 2012; 7:65-70.
21. O'Donnell DE, Guenette JA, Maltais F, Webb KA: Decline of resting inspiratory capacity in COPD: Impact on breathing pattern, dyspnea and inspiratory capacity during exercise. *Chest* 2012; 141:753-762.
22. Schmidbauer W, et al: Early prehospital use of non-invasive ventilation improves acute respiratory failure in acute exacerbation of chronic obstructive pulmonary disease. *Emerg Med J* 2011; 28:626-627.

www.ketabpezeshki.com 66485457-66963820

Chapter 26

Chest Pain

James E. Brown

PERSPECTIVE

Approximately 6 million patients visit the emergency department (ED) each year with complaints of chest pain, constituting 9% of all patients seen in EDs in the United States.[1] Over the last 10 years, the total number of ED patients with noninjury complaints increased by 22%, whereas the percentage of patients with chest pain decreased slightly.[2] Chest pain is a symptom caused by several life-threatening diseases and has a broad differential diagnosis. It is complicated by a frequent disassociation between intensity of symptoms and signs and seriousness of underlying pathology.

Epidemiology

The epidemiology of the critical diagnoses causing chest pain varies widely. Acute coronary syndrome (ACS), aortic dissection, pulmonary embolism (PE), pneumothorax, pericarditis with tamponade, and esophageal rupture are potentially catastrophic causes of chest pain. These are discussed in the relevant chapters. Chest pain that is atypical or of unclear cause is a daily presentation in virtually every ED—big or small, academic or community, urban, suburban, or rural.

Pathophysiology

Afferent fibers from the heart, lungs, great vessels, and esophagus enter the same thoracic dorsal ganglia. Through these visceral fibers, each organ produces the same indistinct quality and location of pain. The quality of visceral chest pain varies widely and is described as "burning," "aching," "stabbing," or "pressure." Because dorsal segments overlap three segments above and below a level, disease of a thoracic origin can produce pain anywhere from the jaw to the epigastrium. Radiation of pain is caused by somatic afferent fibers synapsing in the same dorsal root ganglia as the thoracic viscera. This stimulation can "confuse" the patient's central nervous system into misperceiving that the pain originates in the arms or shoulders.

DIAGNOSTIC APPROACH

Differential Considerations

Because of the indistinct nature of visceral pain, the differential diagnosis of chest pain is broad and includes many of the most critical diagnoses in medicine and many nonemergent conditions (Table 26-1).

Rapid Stabilization and Assessment

All patients, except those with obvious benign causes of chest pain, undergo electrocardiography as soon as possible after reporting their pain. The electrocardiogram (ECG) should be read for acute myocardial infarction (MI) by the emergency physician as soon as it is completed. Patients with positive ECG findings and those considered at high risk are triaged directly to the treatment area and monitored.

In clinical evaluation of the patient, the initial questions are "Should I intervene immediately?" and "What are the life-threatening possibilities in this patient?" The answers are usually apparent within the first few minutes after assessment of the patient's appearance, ECG, and vital signs. If a patient has unilateral chest pain, respiratory distress, shock, and unilateral reduction or absence of breath sounds, immediate intervention with needle or tube thoracostomy is required. In addition, patients with severe derangements in vital signs require stabilizing treatment during a search for the precipitating cause. Patients with respiratory distress require immediate intervention and lead the emergency physician to consider a more serious cause of the pain (Fig. 26-1; also see Chapter 25).

Symptomatic derangements in vital signs are addressed. If vital signs are stable, a focused history and physical examination are performed. Most patients also require a chest radiograph to evaluate the chest pain. If myocardial ischemia is suspected, aspirin and nitroglycerin may be appropriate. Patients with pain and findings suggestive of aortic dissection and with significant hypertension are candidates for immediate reduction of blood pressure (see Chapter 85). Patients with low voltage on the ECG, diffuse ST segment elevation, elevated jugular venous pressure on examination,[3] and signs of shock should undergo prompt bedside cardiac ultrasound.

Pivotal Findings

The broad and complex nature of chest pain defies application of a simple algorithm. An organized approach to a patient with chest pain is essential, however, to ensure that all causes are evaluated appropriately. The history and physical examination are key to diagnosis. Information pertinent to the differential diagnosis is obtained through the history, physical examination, and ECG in 80 to 90% of patients.

History

1. The patient is asked to describe the character of the pain or discomfort. Descriptions such as "squeezing," "crushing," or

www.ketabpezeshki.com 66485457-66963820

Table 26-1 Differential Diagnosis of Chest Pain

ORGAN SYSTEM	CRITICAL DIAGNOSES	EMERGENT DIAGNOSES	NONEMERGENT DIAGNOSES
Cardiovascular	Acute myocardial infarction Acute coronary ischemia Aortic dissection Cardiac tamponade	Unstable angina Coronary spasm Prinzmetal's angina Cocaine-induced pericarditis or myocarditis	Valvular heart disease Aortic stenosis Mitral valve prolapse Hypertrophic cardiomyopathy
Pulmonary	Pulmonary embolus Tension pneumothorax	Pneumothorax Mediastinitis	Pneumonia Pleuritis Tumor Pneumomediastinum
Gastrointestinal	Esophageal rupture (Boerhaave's syndrome)	Esophageal tear (Mallory-Weiss) Cholecystitis Pancreatitis	Esophageal spasm Esophageal reflux Peptic ulcer Biliary colic
Musculoskeletal			Muscle strain Rib fracture Arthritis Tumor Costochondritis Nonspecific chest wall pain
Neurologic			Spinal root compression Thoracic outlet Herpes zoster Postherpetic neuralgia
Other			Psychological Hyperventilation

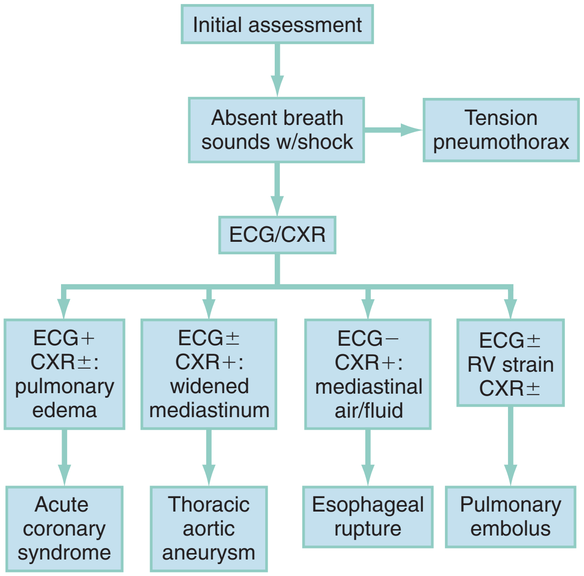


Figure 26-1. Initial assessment of critical diagnoses. *CXR,* chest x-ray study; *ECG,* electrocardiogram; *RV,* right ventricular.

"pressure" lead the emergency physician to suspect a cardiac ischemic syndrome, although cardiac ischemia can also be characterized by nonspecific discomfort, such as "bloating" or "indigestion." "Tearing" pain that may migrate from the front to back or back to front is the classic description in aortic dissection. "Sharp" or "stabbing" pain is seen more in pulmonary and musculoskeletal diagnoses. Patients reporting a "burning" or "indigestion" type of pain may initially be thought to have a gastrointestinal condition, but owing to the visceral nature of chest pain, patients with all causes of pain may use any of the preceding descriptions. Of note, descriptors may vary among ethnic groups, and, for example, "sharp" may mean "severe."

2. Additional history about the patient's activity at the onset of pain may be helpful. Pain occurring during exertion suggests an ischemic coronary syndrome, whereas progressive onset of pain at rest suggests acute MI. Pain of sudden onset is more typical with aortic dissection, PE, or pneumothorax. Pain after meals is more indicative of a gastrointestinal cause.
3. The severity of pain is commonly quantified with a 1-to-10 pain scale. Alterations in pain severity are documented at times of onset, peak, present, and after intervention.
4. The location of the discomfort is described. Pain that is localized to a small area is more likely to be somatic versus visceral in origin. Pain localized at the periphery of the chest is more likely to have a pulmonary rather than a cardiac cause. Lower chest or upper abdominal pain may be of cardiac or gastrointestinal origin.
5. Any description of radiation of pain should be noted. Transthoracic pain through to the back should suggest aortic dissection or gastrointestinal causes, especially pancreatitis or posterior ulcer. Inferoposterior myocardial ischemia may also manifest primarily as thoracic back pain. Radiation to the arms, neck, or jaw increases the likelihood of cardiac ischemia.[4,5] Pain located primarily in the back, especially interscapular back pain that migrates to the base of the neck, suggests aortic dissection.[6]
6. Duration of pain is another important historical factor. Pain that lasts a few seconds or minutes is rarely of cardiac origin.[7] Pain that is exertional but abates with a few minutes of rest may be a manifestation of cardiac ischemia.[4] Pain that is maximal at onset may be caused by aortic dissection.[6] Pain that is not severe and persists over the course of days is less likely to be of serious origin than pain that is severe or has a stuttering or fluctuating course.
7. The clinician should consider aggravating or alleviating factors. Pain that worsens with exertion and improves with rest is more likely related to coronary ischemia.[4] Pain related to meals is more suggestive of a gastrointestinal cause. Pain that worsens with respiration is seen more often with pulmonary, pericardial, and musculoskeletal causes.

www.ketabpezeshki.com 66485457-66963820

Table 26-2 Significant Symptoms of Chest Pain

SYMPTOM	FINDING	DIAGNOSIS
Pain	Severe, crushing, pressure, substernal, exertional, radiation to jaw, neck, shoulder, arm	Acute MI Coronary ischemia Unstable angina Coronary spasm
	Tearing, severe, radiating to or located in back, maximum at onset, may migrate to upper back or neck	Aortic dissection
	Pleuritic	Esophageal rupture Pneumothorax Cholecystitis Pericarditis Myocarditis
	Indigestion or burning	Acute MI Coronary ischemia Esophageal rupture Unstable angina Coronary spasm Esophageal tear Cholecystitis
Associated syncope or near-syncope		Aortic dissection PE Acute MI Pericarditis Myocarditis
Associated dyspnea (SOB, DOE, PND, orthopnea)		Acute MI Coronary ischemia PE Tension pneumothorax Pneumothorax Unstable angina Pericarditis
Associated hemoptysis		PE
Associated nausea, vomiting		Esophageal rupture Acute MI Coronary ischemia Unstable angina Coronary spasm Esophageal tear Cholecystitis

DOE, dyspnea on exertion; *MI,* myocardial infarction; *PE,* Pulmonary embolism; *PND,* paroxysmal nocturnal dyspnea; *SOB,* shortness of breath.

Box 26-1 Risk Factors Associated with Potentially Catastrophic Causes of Chest Pain

Acute coronary syndromes
- Past or family history of coronary artery disease
- Age
  - Men older than 33 years
  - Women older than 40 years
- Diabetes mellitus
- Hypertension
- Cigarette use or possible passive exposure
- Elevated cholesterol (low-density lipoprotein [LDL]) or triglycerides
- Sedentary lifestyle
- Obesity
- Postmenopausal
- Left ventricular hypertrophy
- Cocaine abuse

Pulmonary embolism
- Prolonged immobilization
- Surgery longer than 30 minutes in last 3 months
- Prior deep vein thrombosis or pulmonary embolus
- Pregnancy or recent pregnancy
- Pelvic or lower extremity trauma
- Oral contraceptives with cigarette smoking
- Congestive heart failure
- Chronic obstructive pulmonary disease
- Obesity
- Past medical or family history of hypercoagulability

Aortic dissection
- Hypertension
- Congenital disease of the aorta or aortic valve
- Inflammatory aortic disease
- Connective tissue disease
- Pregnancy
- Arteriosclerosis
- Cigarette use

Pericarditis or myocarditis
- Infection
- Autoimmune disease (e.g., systemic lupus erythematosus)
- Acute rheumatic fever
- Recent myocardial infarction or cardiac surgery
- Malignancy
- Radiation therapy to mediastinum
- Uremia
- Drugs
- Prior pericarditis

Pneumothorax
- Prior pneumothorax
- Valsalva's maneuver
- Chronic lung disease
- Cigarette use

8. Other associated symptoms may suggest the visceral nature of the pain (Table 26-2). Diaphoresis should lead to an increased clinical suspicion for a serious or visceral cause. Hemoptysis, a classic PE sign, is rarely seen.[8] Near-syncope and syncope lead to higher likelihood of a cardiovascular cause or PE. Dyspnea is seen in cardiovascular and pulmonary disease. Nausea and vomiting may be seen in cardiovascular and gastrointestinal complaints.
9. A history of prior pain and the diagnosis of that episode can facilitate the diagnostic process, but the physician should be wary of prior presumptive diagnoses that may be misleading. A prior history of cardiac testing, such as stress testing, echocardiography, or angiography, may be useful in determining if the current episode is suggestive of cardiac disease. Similarly, patients with previous spontaneous pneumothorax or PE[9] are at increased risk of recurrence.
10. The presence of risk factors for a particular disease is primarily of value as an epidemiologic marker for large population studies (Box 26-1). In the ED, presence of risk factors in an individual patient without established disease has minimal or no effect on the clinical likelihood (pretest probability) of a specific disease process.

Physical Examination

Specific findings may be found in a variety of causes (Table 26-3).

Ancillary Studies

The two most commonly performed studies in patients with chest pain are the chest radiograph and 12-lead ECG (Table 26-4). An ECG should be performed within 10 minutes of arrival in all patients with chest pain in whom myocardial ischemia is a

www.ketabpezeshki.com 66485457-66963820

Table 26-3 Pivotal Findings in Physical Examination

SIGN	FINDING	DIAGNOSES
Appearance	Acute respiratory distress	PE Tension pneumothorax Acute MI Pneumothorax
	Diaphoresis	Acute MI Aortic dissection Coronary ischemia PE Esophageal rupture Unstable angina Cholecystitis Perforated peptic ulcer
Vital signs	Hypotension	Tension pneumothorax PE Acute MI Aortic dissection (late) Coronary ischemia Esophageal rupture Pericarditis Myocarditis
	Tachycardia	Acute MI PE Aortic dissection Coronary ischemia Tension pneumothorax Esophageal rupture Coronary spasm Pericarditis Myocarditis Mediastinitis Cholecystitis Esophageal tear (Mallory-Weiss)
	Bradycardia	Acute MI Coronary ischemia Unstable angina
	Hypertension	Acute MI Coronary ischemia Aortic dissection (early)
	Fever	PE Esophageal rupture Pericarditis Myocarditis Mediastinitis Cholecystitis
	Hypoxemia	PE Tension pneumothorax Pneumothorax
Cardiovascular examination	Significant difference in upper extremity blood pressures	Aortic dissection
	Narrow pulse pressure	Pericarditis (with effusion)
	New murmur	Acute MI Aortic dissection Coronary ischemia
	S_3/S_4 gallop	Acute MI Coronary ischemia
	Pericardial rub	Pericarditis
	Audible systolic "crunch" on cardiac auscultation (Hamman's sign)	Esophageal rupture Mediastinitis
	JVD	Acute MI Coronary ischemia Tension pneumothorax PE Pericarditis

Continued

possibility.[10,11] This generally includes all male patients 33 years old and older and female patients older than 39 who report pain from the umbilicus to the mandible unless a noncardiac cause is readily apparent. Rapid acquisition of the ECG facilitates the diagnosis of acute MI and expedites the National Heart, Lung, and Blood Institute's recommended "door to treatment" times from arrival to percutaneous coronary intervention (PCI) or thrombolytic therapy in acute MI. Patients with a new injury pattern on ECG (Table 26-5) or new ischemic ECG changes should have appropriate therapy instituted at this point (Fig. 26-2; see also Chapter 78). An ECG showing right ventricular strain pattern, in the appropriate setting, should raise the clinical suspicion for

www.ketabpezeshki.com 66485457-66963820

Table 26-3 Pivotal Findings in Physical Examination—cont'd

SIGN	FINDING	DIAGNOSES
Pulmonary examination	Unilateral diminished or absent breath sounds	Tension pneumothorax Pneumothorax
	Pleural rub	PE
	Subcutaneous emphysema	Tension pneumothorax Esophageal rupture Pneumothorax Mediastinitis
	Rales	Acute MI Coronary ischemia Unstable angina
Abdominal examination	Epigastric tenderness	Esophageal rupture Esophageal tear Cholecystitis Pancreatitis
	Left upper quadrant tenderness	Pancreatitis
	Right upper quadrant tenderness	Cholecystitis
Extremity examination	Unilateral leg swelling, warmth, pain, tenderness, or erythema	PE
Neurologic examination	Focal findings Stroke	Aortic dissection Acute MI Coronary ischemia Aortic dissection Coronary spasm

JVD, jugular venous distention; *MI,* myocardial infarction; *PE,* pulmonary embolism.

Table 26-4 Ancillary Testing of Patients with Chest Pain

TEST	FINDING	DIAGNOSIS
ECG	New injury	Acute MI Aortic dissection
	New ischemia	Coronary ischemia Coronary spasm
	RV strain	PE
	Diffuse ST segment elevation	Pericarditis
CXR	Pneumothorax with mediastinal shift	Tension pneumothorax
	Wide mediastinum	Aortic dissection
	Pneumothorax	Esophageal rupture Pneumothorax
	Effusion	Esophageal rupture
	Increased cardiac silhouette	Pericarditis
	Pneumomediastinum	Esophageal rupture Mediastinitis
ABG	Hypoxemia, A-a gradient	PE
Spiral CT or $\dot{V}/\dot{Q}$ scan	High probability or any positive in patient with high clinical suspicion	PE

A-a, alveolar-arterial; *ABG,* arterial blood gas; *CT,* computed tomography; *CXR,* chest x-ray examination; *ECG,* electrocardiogram; *MI,* myocardial infarction; *PE,* pulmonary embolism; *RV,* right ventricular; $\dot{V}/\dot{Q}$, ventilation-perfusion.

Table 26-5 Electrocardiogram Findings in Ischemic Chest Pain

Classic myocardial infarction	ST segment elevation (>1 mm) in contiguous leads; new LBBB Q waves >0.04 sec duration
Subendocardial infarction	T wave inversion or ST segment depression in concordant leads
Unstable angina	Most often normal or nonspecific changes; may see T wave inversion
Pericarditis	Diffuse ST segment elevation; PR segment depression

LBBB, left bundle-branch block.

PE. Diffuse ST segment elevation helps make the diagnosis of pericarditis.

Chest radiography is performed for patients with a possibly serious cause of chest pain. Pneumothorax, pneumonia, empyema, and pleural effusion are definitively diagnosed at this point. A wide mediastinum or ill-defined aortic knob increases the clinical suspicion for acute aortic dissection. Pleural effusion, subcutaneous air, or mediastinal air-fluid level may be seen in esophageal rupture. Increased cardiac silhouette may indicate pericarditis or cardiomyopathy.

Pneumomediastinum is seen with esophageal rupture and mediastinitis. A serum D-dimer assay may help discriminate patients with PE from those with a possible gastrointestinal cause. A low serum D-dimer in a patient without a high pretest probability of PE effectively excludes the diagnosis.[8,12,13] Patients with low pretest probability who meet certain defined criteria do not require further testing (see Chapter 88).[14]

Patients at high pretest probability for PE should undergo diagnostic imaging (multidetector computed tomography [CT] or, far less commonly, pulmonary angiography or a ventilation-perfusion lung scan).[15] High pretest probability warrants initiation of anticoagulation (heparin or low-molecular-weight heparin) therapy in the ED before the imaging study, in the absence of a contraindication.

Patients with suspected thoracic aortic dissection may be evaluated by CT angiography, transesophageal echocardiography, or magnetic resonance imaging. Selection of imaging modality depends on patient status and availability of the testing.[16]

CT with a 64 or higher detector scanner has the potential to rule out all of the life-threatening causes of chest pain. Although ACS, PE, and thoracic dissection (the "triple rule out") are the causes most commonly discussed, pneumothorax, mediastinitis, and pericardial effusions are also diagnosed with CT.[17,18]

Laboratory testing is useful in the evaluation of ACS. Creatine kinase (CK) is associated with multiple false-positive results and

www.ketabpezeshki.com 66485457-66963820

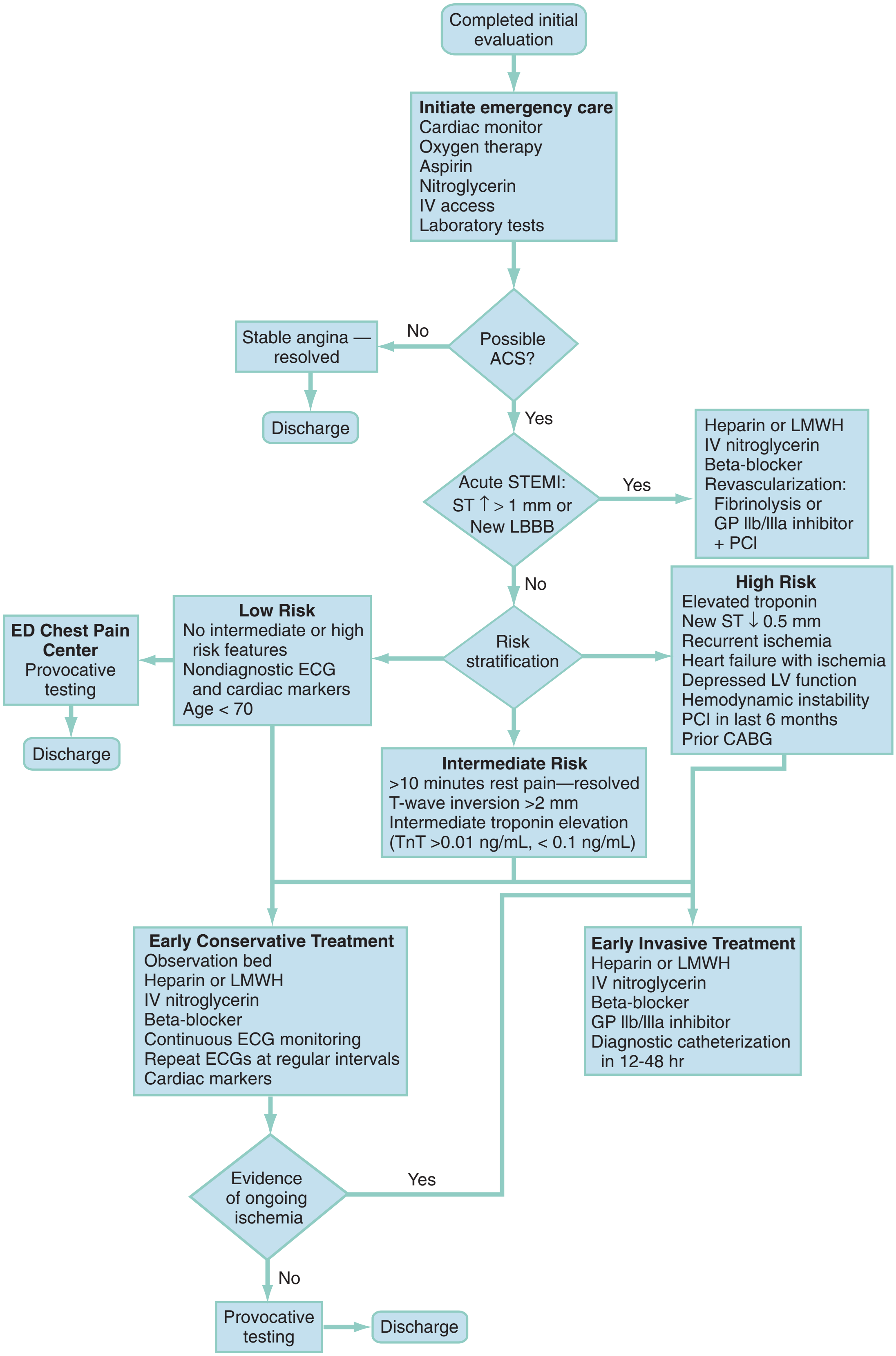


Figure 26-2. Clinical guidelines for emergency department management of chest pain of myocardial ischemic origin. *ACS,* acute coronary syndrome; *CABG,* coronary artery bypass graft; *ECG,* electrocardiogram; *ED,* emergency department; *GP,* glycoprotein; *IV,* intravenous; *LBBB,* left bundle-branch block; *LMWH,* low-molecular-weight heparin; *LV,* left ventricular; *PCI,* percutaneous coronary intervention; *ST,* echocardiographic peak; *STEMI,* ST segment elevation myocardial infarction; *TnT,* troponin T. (Adapted from Gibler WB, et al: Practical implementation of the guidelines for unstable angina/non-ST-segment elevation myocardial infarction in the emergency department: A scientific statement from the American Heart Association Council on Clinical Cardiology [Subcommittee on Acute Cardiac Care], Council on Cardiovascular Nursing, and Quality of Care and Outcomes Research Interdisciplinary Working Group, in Collaboration with the Society of Chest Pain Centers. Circulation 111:2699, 2005.)

www.ketabpezeshki.com 66485457-66963820

Table 26-6 Causes and Differentiation of Potentially Catastrophic Illness Manifesting with Central Chest Pain or Discomfort

	PAIN HISTORY	ASSOCIATED SYMPTOMS	SUPPORTING HISTORY	PREVALENCE IN EMERGENCY DEPARTMENT	PHYSICAL EXAMINATION	USEFUL TESTS	ATYPICAL OR ADDITIONAL ASPECTS
Myocardial infarction	Discomfort is usually moderately severe to severe and rapid in onset. May be more "pressure" than pain. Usually retrosternal, may radiate to neck, jaw, both arms, upper back, epigastrium, and sides of chest (left more than right). Lasts more than 15-30 min and is unrelieved by NTG.	Diaphoresis, nausea, vomiting, dyspnea.	May be precipitated by emotional stress or exertion. Often comes on at rest. May come on in early awakening period. Prodromal pain pattern often elicited. Previous history of MI or angina. Age >40 years, positive risk factors, and male sex increase possibility.	Common.	Patients are anxious and uncomfortable. Blood pressure usually is elevated, but normotension and hypotension are seen. The heart rate is usually mildly increased, but bradycardia can be seen. Patients may be diaphoretic and show peripheral poor perfusion. There are no diagnostic examination findings for MI, although S_3 and S_4 heart sounds and new murmur are supportive.	ECG changes (new Q waves or ST segment–T wave changes) occur in 80% of patients. CK-MB and troponins are helpful if elevated, but may be normal.	Pain may be reported as "indigestion" or "unable to describe." Other atypical presentations include altered mental status, stroke, angina pattern without extended pain, severe fatigue, syncope. Elderly may have weakness, congestive heart failure, or chest tightness. 25% of nonfatal MIs are unrecognized by patient. The pain may have resolved by the time of evaluation.
Unstable angina	Changes in pattern of preexisting angina with more severe, prolonged, or frequent pain (crescendo angina). Pain usually lasts >10 min. Angina at rest lasting 15-20 min or new-onset angina (duration <2 mo) with minimal exertion. Pattern of pain change important in gauging risk for AMI. Unpredictable responses to NTG and rest.	Often minimal. May have mild diaphoresis, nausea, dyspnea with pain. Increasing pattern of dyspnea on exertion.	Not clearly related to precipitating factors. May be a decrease in amount of physical activity that initiates pain. Previous history of MI or angina. Older than 40 years, presence of risk factors, and male sex increase probability.	Common.	Nonspecific findings of a transient nature, may have similar cardiac findings as in MI, especially intermittent diaphoresis.	Often no ECG or enzyme changes. Variant angina (Prinzmetal's) has episodic pain, at rest, often severe, with prominent ST segment elevation.	May be pain-free at presentation. Full history is essential. Fewer than 15% of patients hospitalized for unstable angina go on to acute MI. May respond to NTG. May manifest similarly to non–Q wave infarction.
Aortic dissection	90% of patients have rapid-onset severe chest pain that is maximal at beginning. Radiates anteriorly in chest to the back interscapular area or into abdomen. Pain often has a "tearing" sensation and may migrate.	Neurologic complications of stroke, peripheral neuropathy, paresis or paraplegia, abdominal and extremity ischemia possible.	Median age 59 years. History of hypertension in 70-90% of patients. 3:1 ratio males to females. Marfan syndrome and congenital bicuspid aortic valves have increased incidence.	Rare.	Often poorly perfused peripherally but with elevated BP. In 50-60% of cases, there is asymmetrical decrease or absence of peripheral pulses. 50% of proximal dissections cause aortic insufficiency. Other vascular occlusions: coronary (1-2%), mesentery, renal, spinal cord. New-onset pericardial friction rub or aortic insufficiency murmur supportive of diagnosis.	ECG usually shows left ventricular hypertrophy, nonspecific changes. Chest film shows abnormal aortic silhouette (90%). Aortic angiography has diagnostic accuracy of 95-99%. Transesophageal echocardiogram, CT, MRI most useful in screening.	Rare for patient to be pain-free. May have neurologic complications. Physical examination findings may be minimal. Dissection into coronary arteries can mimic MI. Ascending aortic aneurysms are more often approached surgically. Descending are generally managed medically.

www.ketabpezeshki.com 66485457-66963820

Table 26-6 Causes and Differentiation of Potentially Catastrophic Illness Manifesting with Central Chest Pain or Discomfort—cont'd

	PAIN HISTORY	ASSOCIATED SYMPTOMS	SUPPORTING HISTORY	PREVALENCE IN EMERGENCY DEPARTMENT	PHYSICAL EXAMINATION	USEFUL TESTS	ATYPICAL OR ADDITIONAL ASPECTS
Pulmonary embolism	Pain is more often lateral-pleuritic. Central pain is more consistent with massive embolus. Abrupt in onset and maximal at beginning. May be episodic or intermittent.	Dyspnea and apprehension play a prominent role, often more than pain. Cough accompanies about half the cases. Hemoptysis occurs in <20%. Angina-like pain may occur in 5%.	Often some period of immobilization has occurred, e.g., postoperative. Pregnancy, oral contraceptives, heart disease, and cancer are all risk factors. Previous DVT or PE is the greatest risk factor.	Uncommon in ambulatory patients but common in departments with high volumes of elderly or medically complex patients.	Patients are anxious and often have a respiratory rate >16 breaths/min. Tachycardia, inspiratory rales, and an increased pulmonic second sound are common. Fever, phlebitis, and diaphoresis are seen in 30-40% of patients. Wheezes and peripheral cyanosis are less common.	Arterial blood gases show Po_2 <80 mm Hg in 90%. Widened A-a gradient is helpful. Chest film is usually normal, although 40% show some volume loss, oligemia, or signs of consolidation caused by pulmonary infarction. Lung perfusion scan rules out, if truly negative.	Patients may have dyspnea with or without bronchospasm. Acute mortality rate is 10%. Emboli usually from lower extremities above knee, prostate or pelvis venous plexus, right side of heart. May be subtle cause of COPD exacerbation.
Pneumothorax	Pain is usually acute and maximal at onset. Most often lateral-pleuritic, but central pain can occur in large pneumothorax.	Dyspnea has a prominent role. Hypotension and altered mental states occur in tension pneumothorax.	Chest trauma, previous episode, or asthenic body type.	Infrequent.	Decreased breath sounds, increased resonance on percussion. Elevated pressure in neck veins occurs in tension pneumothorax.	Chest film definitive. Inspiratory and expiratory films may enhance contrast between air and lung parenchyma. Tension pneumothorax should be diagnosed on physical examination.	May be subtle in COPD, asthma, cystic fibrosis. Can be complicated by pneumomediastinum.
Esophageal rupture	Pain usually is preceded by vomiting and is abrupt in onset. Pain is persistent and unrelieved, localized along the esophagus, and increased by swallowing and neck flexion.	Diaphoresis, dyspnea (late), shock.	Older individual with known gastrointestinal problems. History of violent emesis, foreign body, caustic ingestion, blunt trauma, alcoholism, esophageal disease.	Rare.	Signs of lung consolidation, subcutaneous emphysema may be present.	Chest film usually has mediastinal air, a left-sided pleural effusion, pneumothorax, or a widened mediastinum. pH of pleural effusion is <6.0. Diagnosis supported by water-soluble contrast esophagram or esophagoscopy.	Patient may be in shock state. This entity often considered late in differential diagnostic process.
Pericarditis	Dull, aching recurrent pain unrelated to exercises or meals, or it may be a sharp, stabbing, pleuritic-type pain that does not change with chest wall motion. May be severe. Not relieved by NTG.	Dyspnea, diaphoresis.	Pain is often worse when supine but improves sitting up. Often preceded by viral illness or underlying disease (SLE or uremia).	Rare. Tamponade even more rare complication.	Friction rub may be heard, often fleeting, position dependent (50% of patients).	ECG pattern typical for ST segment elevation across the precordial leads. Erythrocyte sedimentation rate may be elevated.	More common in 20- to 50-year-olds. May have associated tachycardias, ventricular dysrhythmias. Idiopathic most common (80%). Treated with aspirin, NSAID.

A-a, alveolar-arterial; *AMI,* acute myocardial infarction; *BP,* blood pressure; *CK-MB,* an isoform of creatine kinase; *COPD,* chronic obstructive pulmonary disease; *CT,* computed tomography; *DVT,* deep vein thrombosis; *ECG,* electrocardiogram; *MI,* myocardial infarction; *MRI,* magnetic resonance imaging; *NSAID,* nonsteroidal anti-inflammatory drug; *NTG,* nitroglycerin; *PE,* pulmonary embolus; Po_2, partial pressure of oxygen; *SLE,* systemic lupus erythematosus.

www.ketabpezeshki.com 66485457-66963820

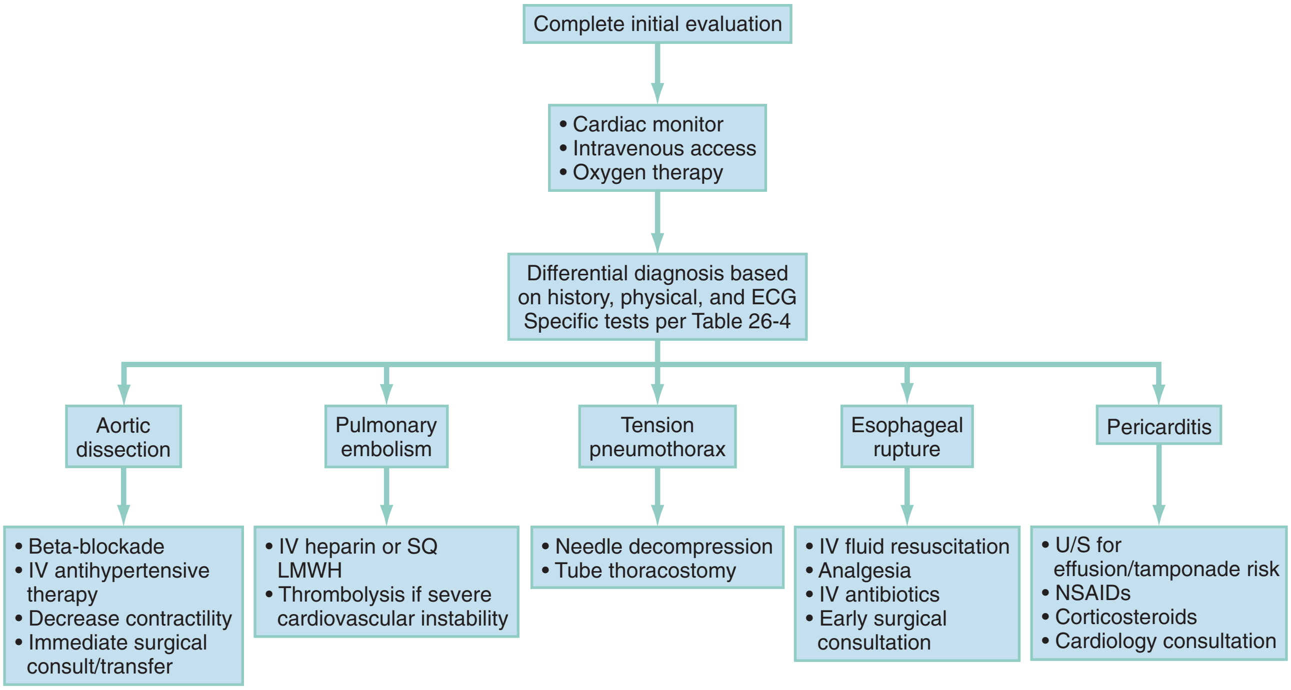


Figure 26-3. Clinical guidelines for emergency department management of chest pain from potentially catastrophic nonmyocardial origins. *ECG,* electrocardiogram; *IV,* intravenous; *LMWH,* low-molecular-weight heparin; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *SQ,* subcutaneous; *U/S,* ultrasound.

has no use in the evaluation of unstable angina. CK-MB, an isoform of CK, is more specific for cardiac ischemia but largely has been supplanted by troponin testing. CK-MB produces fewer false-positive results than CK, and peak sensitivity approaches 98%. Sensitivity at 4 hours is, however, only about 60%. CK-MB isoforms improve sensitivity at 4 hours to 80%, approaching 93% at 6 hours. The current universal definition of MI places CK and CK-MB in a secondary role to troponins.[19]

Troponins (I and T), when elevated, identify patients with ACS who have the highest risk for an adverse outcome.[19,20] Sensitivity for acute MI at 4 hours is 60%, rising to nearly 100% by 12 hours.[21,22] Elevated troponin in the correct clinical setting is synonymous with acute MI and is embedded in the universal definition of MI.[19]

DIAGNOSTIC TABLE

After the patient is stabilized and assessment is completed, the findings are matched to the classic and atypical patterns of the seven potentially critical diseases causing chest pain. This matching process is continual while the patient is evaluated and the response to therapy is monitored. Any inconsistency in findings with the primary working diagnoses requires a rapid review of the pivotal findings and the potential diagnoses (Table 26-6).

MANAGEMENT AND DISPOSITION

The management of ACS is discussed in Chapter 78. Figure 26-3 outlines the approach to treatment of critical noncardiac diagnoses. Patients with critical diagnoses generally are admitted to the intensive care unit. Patients with emergent diagnoses typically are admitted to the hospital, most often on telemetry units. Patients with nonemergent diagnoses are most frequently treated as outpatients. Hospitalization is required in certain circumstances, particularly when patients have other comorbid conditions.

Frequently, no definitive diagnosis is established. Any patient with almost any type of chest pain may be having coronary ischemia, PE, or aortic dissection. When a clear pattern does not emerge to allow the emergency physician to make an alternative diagnosis confidently, or if the pattern of symptoms clearly is not compatible with a serious disorder, such as coronary ischemia, continued evaluation, hospitalization, or observation admission may be the best course.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Niska R, Bhuiya F, Xu J: National Hospital Ambulatory Medical Care Survey: 2007 emergency department summary. *Natl Health Stat Report* 2010; 26:1.
2. Bhuiya F, Pitts S, McCaig L: Emergency department visits for chest pain and abdominal pain: United States, 1999-2008. *NCHS Data Brief* 2010; 43:1.
3. McGee SR: *Evidence-Based Physical Diagnosis*. Philadelphia: WB Saunders; 2001.
4. Goodacre S, Locker T, Morris F, Campbell S: How useful are clinical features in the diagnosis of acute, undifferentiated chest pain? *Acad Emerg Med* 2002; 9:203.
5. Panju AA, Hemmelgarn BR, Guyatt GH, Simel DL: The rational clinical examination. Is this patient having a myocardial infarction? *JAMA* 1998; 280:1256.
6. Klompas M: Does this patient have an acute thoracic aortic dissection? *JAMA* 2002; 287:2262.
7. Lee TH, et al: Acute chest pain in the emergency room. Identification and examination of low-risk patients. *Arch Intern Med* 1985; 145:65.
8. Kline JA, Wells PS: Methodology for a rapid protocol to rule out pulmonary embolism in the emergency department. *Ann Emerg Med* 2003; 42:266.
9. Eichinger S, et al: Symptomatic pulmonary embolism and the risk of recurrent venous thromboembolism. *Arch Intern Med* 2004; 164:92.
10. Antman EM, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 2004; 110:588.
11. Diercks DB, et al: Door-to-ECG time in patients with chest pain presenting to the ED. *Am J Emerg Med* 2006; 24:1.
12. American College of Emergency Physicians Clinical Policies Committee; Clinical Policies Committee Subcommittee on Suspected Pulmonary Embolism: Clinical policy: Critical issues in the evaluation and management of adult patients presenting with suspected pulmonary embolism. *Ann Emerg Med* 2003; 41:257.
13. Wells PS, et al: Excluding pulmonary embolism at the bedside without diagnostic imaging: Management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. *Ann Intern Med* 2001; 135:98.
14. Kline JA, et al: Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J Thromb Haemost* 2008; 6:772.
15. Stein PD, et al: Multidetector computed tomography for acute pulmonary embolism. *N Engl J Med* 2006; 354:2317.
16. Shiga T, Wajima Z, Apfel CC, Inoue T, Ohe Y: Diagnostic accuracy of transesophageal echocardiography, helical computed tomography, and magnetic resonance imaging for suspected thoracic aortic dissection: Systematic review and meta-analysis. *Arch Intern Med* 2006; 166:1350.
17. Limkakeng AT, Halpern E, Takakuwa KM: Sixty-four slice multidetector computed tomography: The future of ED cardiac care. *Am J Emerg Med* 2007; 25:450.
18. Rubinshtein R, et al: Usefulness of 64-slice cardiac computed tomographic angiography for diagnosing acute coronary syndromes and predicting clinical outcome in emergency department patients with chest pain of uncertain origin. *Circulation* 2007; 115:1762.
19. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction: Universal definition of the myocardial infarction. *Circulation* 2007; 116:2634.
20. Ohman EM, et al: Cardiac troponin T levels for risk stratification in acute myocardial ischemia. GUSTO IIA Investigators. *N Engl J Med* 1996; 335:1333.
21. Fesmire FM, et al: Clinical policy: Critical issues in the evaluation and management of adult patients with non–ST-segment elevation acute coronary syndromes. *Ann Emerg Med* 2006; 48:270.
22. Morrow DA, et al: National Academy of Clinical Biochemistry Laboratory Medicine practice guidelines: Clinical characteristics and utilization of biochemical markers in acute coronary syndromes. *Circulation* 2007; 115:e356, 2007.

www.ketabpezeshki.com 66485457-66963820

Chapter 27

Abdominal Pain

Gavin R. Budhram and Rimon N. Bengiamin

PERSPECTIVE

Abdominal pain is a common emergency department (ED) complaint but for many reasons is often diagnostically challenging. The nature and quality of abdominal pain may be difficult for the patient to convey. Physical examination findings are variable and can be misleading. The location and severity of the pain may change over time. Initially benign symptoms and presentations may evolve into life-threatening conditions. Conversely, patients with severe symptoms may carry a relatively benign diagnosis. All of these factors make evaluation of patients with acute abdominal pain challenging in the ED setting.

Epidemiology

Abdominal pain accounts for up to 10% of all ED visits. Some of the most common causes of acute abdominal pain are listed in Table 27-1. Many patients have pain and other symptoms that are not typical of any specific disease process. Even after ED workup, a diagnosis may not be found in some patients. In addition, several adult groups deserve special consideration: elders (those older than 65 years of age), the immunocompromised, and women of reproductive age.

Elders with acute abdominal pain are more likely to have a life-threatening process as the cause of their pain. Conditions such as diverticulitis, ruptured abdominal aneurysm, or mesenteric ischemia may manifest atypically and be rapidly progressive. Decreased diagnostic accuracy, coupled with increased probability of severe disease, results in increased mortality in elderly patients with abdominal pain.

Increasingly, emergency physicians are seeing patients in immunocompromised states secondary to human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS), uncontrolled diabetes, chronic liver disease, chemotherapy, and immunosuppressive drugs. For many reasons, these patients also prove challenging. Their clinical presentation can be misleading owing to atypical physical and laboratory findings, such as lack of fever. The white blood cell (WBC) count, which is unreliable in all cases of abdominal pain, may be frankly misleading in such patients, such as in those with persistent elevations. With regard to infection, the scope of the differential diagnosis also should be broader than usual.[1,2] Presentations in the immunocompromised patient may be highly variable and subtle and are discussed in Chapter 183.

The evaluation of abdominal pain in women involves a differential diagnosis of considerable extent and often requires a more in-depth physical examination and further diagnostic testing. Pelvic organs may be the source of significant pathology in both the pregnant and the nonpregnant patient. The possibility of ectopic pregnancy in women of reproductive age greatly increases the risk of serious disease with a high potential for misdiagnosis. During pregnancy the uterus becomes an abdominal rather than a pelvic organ and may displace the normal intraperitoneal contents, adding complexity to the evaluation of these patients. Nonpregnant patients require evaluation for various ovarian and uterine pathologic states.

Pathophysiology

Pathology in the gastrointestinal and genitourinary tracts remains the most common source of pain perceived in the abdomen. Also, pain can arise from a multitude of other intra-abdominal and extra-abdominal locations (Box 27-1). Abdominal pain is derived from one or more of three distinct pain pathways: visceral, somatic, and referred.

Visceral pain results from stimulation of autonomic nerves invested in the visceral peritoneum surrounding internal organs. It is often the earliest manifestation of a particular disease process. Distention of hollow organs by fluid or gas and capsular stretching of solid organs from edema, blood, cysts, or abscesses are the most common stimuli. This discomfort is poorly characterized and difficult to localize. If the involved organ is affected by peristalsis, the pain often is described as intermittent, crampy, or colicky. In general, visceral pain is perceived from the abdominal region that correlates with the embryonic somatic segment, as follows:

- *Foregut* structures (stomach, duodenum, liver, and pancreas) are associated with *upper abdominal pain.*
- *Midgut* derivatives (small bowel, proximal colon, and appendix) are associated with *periumbilical pain.*
- *Hindgut* structures (distal colon and genitourinary tract) are associated with *lower abdominal pain.*

Visceral pain can be perceived in a location remote from the actual disease process. Localization occurs with the extension of the disease process beyond the viscera. A classic example is that of the early periumbilical pain of appendicitis (midgut). When the parietal peritoneum becomes involved, the pain localizes to the right lower quadrant of the abdomen, the usual location of the appendix.

Somatic pain occurs with irritation of the parietal peritoneum. This is usually caused by infection, chemical irritation, or another inflammatory process. Sensations are conducted by the peripheral nerves and are better localized than the visceral pain component. Figure 27-1 illustrates some more typical pain locations corresponding to specific disease entities. Somatic pain is often described as intense and constant. As disease processes evolve to peritoneal irritation with inflammation, better localization of the pain to the area of pathology generally occurs.

www.ketabpezeshki.com 66485457-66963820

Table 27-1 Common Causes of Abdominal Pain

CAUSATIVE DISORDER OR CONDITION	EPIDEMIOLOGY	ETIOLOGY	PRESENTATION	PHYSICAL EXAMINATION	USEFUL TEST(S)
Gastric, esophageal, or duodenal inflammation	Occurs in all age groups.	Caused by gastric hypersecretion, breakdown of mucoprotective barriers, infection, or exogenous sources.	Epigastric radiating or localized, associated with certain foods. Pain may be burning. In some cases, exacerbation in supine position.	Epigastric tenderness without rebound or guarding. Perforation or bleeding leads to more severe clinical findings.	Uncomplicated cases are treated with antacids or histamine H_2 blockers before invasive studies are contemplated. Gastroduodenoscopy is valuable in diagnosis and biopsy. Testing for *Helicobacter pylori* with blood or biopsy specimens. If perforation is suspected, an upright chest radiograph is obtained early to rule out free air. CT may be beneficial.
Acute appendicitis	Peak age in adolescence and young adulthood; less common in children and elders. Higher perforation rate in women, children, and elders and in pregnancy. Mortality rate is 0.1% but increases to 2-6% with perforation.	Appendiceal lumen obstruction leads to swelling, ischemia, infection, and perforation.	Epigastric or periumbilical pain migrates to RLQ over 8-12 hr (50-60%). Later presentations associated with higher perforation rates. Pain, low-grade fever (15%), and anorexia (80%) common; vomiting less common (50-70%).	Mean temperature 38° C (100.5° F). Higher temperature associated with perforation. RLQ tenderness (90-95%) with rebound (40-70%) in majority of cases. Rectal tenderness in 30%.	Leukocyte count usually elevated or may show left shift. Urinalysis may show sterile pyuria. CT is sensitive and specific. US may have use in women, pregnancy, and children with RLQ pain.
Biliary tract disease	Peak age 35-60 yr; rare in patients younger than 20. Female-to-male ratio of 3:1. Risk factors include multiparity, obesity, alcohol intake, and use of birth control pills.	Passage of gallstones causes biliary colic. Impaction of a stone in cystic duct or common duct causes cholecystitis or cholangitis.	Crampy RUQ pain radiates to right subscapular area. Prior history of pain is common. May have nausea or postprandial pain. Longer duration of pain favors diagnosis of cholecystitis or cholangitis.	Temperature normal in biliary colic, elevated in cholecystitis and cholangitis. RUQ tenderness, rebound, and jaundice (less common) may be present.	WBC count elevated in cholecystitis and cholangitis. Lipase and liver function tests may help differentiate this from gastritis or ulcer disease. US shows wall thickening, pericholecystic fluid, stones, or duct dilatation. Hepatobiliary scintigraphy diagnoses gallbladder function.
Ureteral colic	Average age 30-40 yr, primarily in men. Prior history or family history of stones is common.	Family history, gout, *Proteus* infection. Renal tubular acidosis and cystinuria lead to stone formation.	Acute onset of flank pain radiating to groin. Nausea, vomiting, and pallor are common. Patient usually writhing in pain.	Vital signs usually normal. Tenderness on CVA percussion with benign abdominal examination.	Urinalysis usually shows hematuria. Noncontrast CT is sensitive and specific. US with fluid bolus useful diagnostically.
Diverticulitis	Incidence increases with advancing age, affects males more often than females. Recurrences are common. Often called "left-sided" appendicitis.	Colonic diverticula may become infected or perforated or cause local colitis. Obstruction, peritonitis, abscesses, fistulae result from infection or swelling.	Change in stool frequency or consistency commonly reported. LLQ pain is common. Associated with fever, nausea and vomiting; rectal bleeding may be seen.	Fever usually of low grade. LLQ pain without rebound is common. Stool may be heme positive.	Results on most tests usually normal. Plain radiographs may show obstruction or mass effect. CT is often diagnostic.
Acute gastroenteritis	Common diagnosis. Seasonal. Most common misdiagnosis of appendicitis. May be seen in multiple family members. History of travel or immunocompromise.	Usually viral. Consider invasive bacterial or parasitic cause in prolonged cases, in travelers, or immunocompromised patients.	Pain usually poorly localized, intermittent, crampy, and diffuse. Diarrhea is key element in diagnosis; usually large volume, watery. Nausea and vomiting usually begin before pain.	Abdominal examination usually nonspecific without peritoneal signs. Watery diarrhea or no stool noted on rectal examination. Fever is usually present.	Usually symptomatic care with antiemetics and volume repletion. Heme-positive stools may be a clue to invasive pathogens. Key is not using this as a "default" diagnosis and missing more serious disease.

www.ketabpezeshki.com 66485457-66963820

Table 27-1 Common Causes of Abdominal Pain—cont'd

CAUSATIVE DISORDER OR CONDITION	EPIDEMIOLOGY	ETIOLOGY	PRESENTATION	PHYSICAL EXAMINATION	USEFUL TEST(S)
Constipation and obstipation	More common in females, elders, the very young, and patients on narcotics.	Idiopathic or hypokinesis secondary to disease states (low motility) or exogenous sources (diet, medications).	Abdominal pain; change in bowel habits.	Variable, nonspecific without peritoneal signs. Rectal examination may reveal hard stool or impaction.	Radiographs may show large amounts of stool. This is a diagnosis of exclusion.
Nonspecific abdominal pain	More common in persons of young and middle age, women of childbearing age, or persons of low socioeconomic status and patients with psychiatric disorders. Up to 10% of patients older than 50 years of age will have intra-abdominal cancer.	Unknown. Early or undiagnosed presentation of pathologic conditions.	Variable but tends to be chronic or recurrent.	Variable but no peritoneal signs. Rectal examination should be done to evaluate for subtle signs of pathology, including heme-positive stool, fistulae, and fissures.	Variable and often can be done on an outpatient basis.

CT, computed tomography; *CVA*, costovertebral angle; *LLQ*, left lower quadrant; *RLQ*, right lower quadrant; *RUQ*, right upper quadrant; *US*, ultrasonography; *WBC*, white blood cell.

Box 27-1 Important Extra-abdominopelvic Causes of Abdominal Pain

Thoracic
Myocardial infarction or unstable angina
Pneumonia
Pulmonary embolism
Herniated thoracic disk (neuralgia)
Pericarditis or myocarditis

Genitourinary
Testicular torsion

Abdominal Wall
Muscle spasm
Muscle hematoma
Herpes zoster

Infectious
Streptococcal pharyngitis (more often in children)
Rocky Mountain spotted fever
Mononucleosis

Systemic
Diabetic ketoacidosis
Alcoholic ketoacidosis
Uremia
Sickle cell disease
Porphyria
Systemic lupus erythematosus
Vasculitis
Glaucoma
Hyperthyroidism

Toxic
Methanol poisoning
Heavy metal toxicity
Scorpion bite
Snake bite
Black widow spider bite

Adapted from Purcell TB: Nonsurgical and extraperitoneal causes of abdominal pain. Emerg Med Clin North Am 7:721, 1989.

Referred pain is defined as pain felt at a distance from its source because peripheral afferent nerve fibers from many internal organs enter the spinal cord through nerve roots that also carry nociceptive fibers from other locations, as illustrated in Figure 27-2. This makes interpretation of the location of noxious stimuli difficult for the brain. Both visceral pain and somatic pain can manifest as referred pain. Two examples of referred pain are the epigastric pain associated with an inferior myocardial infarction and the shoulder pain associated with blood in the peritoneal cavity irritating the diaphragm. It is common for a patient to interpret pain originating from the hips as pelvic pain, especially in the very young or elderly. Lower lobe pneumonias can cause referred abdominal pain secondary to diaphragmatic irritation. Finally, some metabolic disorders and toxidromes may manifest with abdominal pain.

Gynecologic and obstetric presentations are discussed in other chapters. Notably, abdominal pain in a female may represent referred pain from pelvic structures or an extension of a pelvic process, as in the case of perihepatic inflammation with pelvic inflammatory disease.

DIAGNOSTIC APPROACH

The clinical approach should focus on early stabilization, history, physical examination, and any ancillary tests collectively facilitating appropriate management and disposition plans.

Differential Considerations

Classically, potential diagnoses are divided into intra-abdominopelvic (intraperitoneal, retroperitoneal, and pelvic) causes (e.g., appendicitis, cholecystitis, pancreatitis) and extra-abdominopelvic processes (e.g., pneumonia, myocardial infarction, ketoacidosis, toxicologic).

Although significant morbidity and mortality can result from many disorders causing abdominal pain, a few processes warrant careful consideration in the ED. Table 27-2 lists important potentially life-threatening nontraumatic causes of abdominal pain. This group represents the major causative disorders likely to be

www.ketabpezeshki.com 66485457-66963820

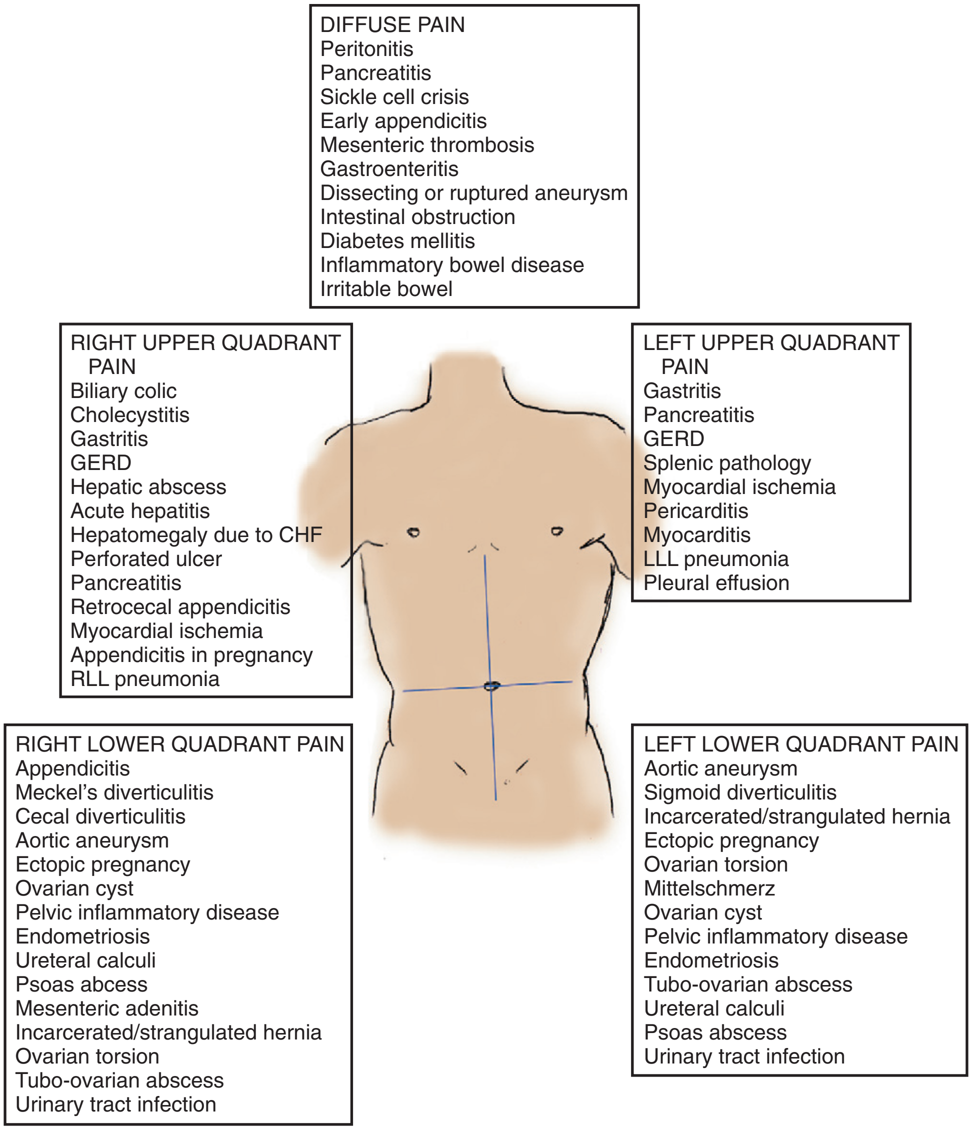


Figure 27-1. Differential diagnosis of acute abdominal pain. *CHF,* congestive heart failure; *GERD,* gastroesophageal reflux disease; *LLL,* left lower lobe; *RLL,* right lower lobe.

associated with hemodynamic compromise and for which early therapeutic intervention is critical.

Rapid Assessment and Stabilization

As with any complaint, triage is the first critical step in management. Most patients with abdominal pain do not have hemodynamic instability, although a small proportion of these stable-appearing patients may have a life-threatening process. This percentage is higher in elders and immunocompromised patients.

Physiologically compromised patients should be brought to a treatment area immediately, and resuscitation initiated. Sepsis or protracted severe volume loss (emesis, diarrhea) can lead to shock; prompt resuscitation is required.

Extreme conditions, such as ruptured abdominal aortic aneurysm, massive gastrointestinal hemorrhage, ruptured ectopic pregnancy, ruptured spleen, and hemorrhagic pancreatitis, may necessitate blood or blood product replacement. Bedside ultrasonography can be used to quickly evaluate patients for free intraperitoneal fluid, volume status, and presence of aortic pathology. Ultrasound assessment should be part of the initial physical examination and can be invaluable in guiding treatment and disposition. Because any of the immediately life-threatening entities may necessitate surgical intervention or management, early surgical consultation is indicated.

Pivotal Findings

Symptoms

A careful and focused history is central to unlocking the puzzle of abdominal pain. Box 27-2 lists some historical questions with high yields for serious pathology. Language and cultural differences may influence accurate communication and mutual understanding; therefore use of an accurate interpreter can be invaluable.

Abrupt onset often is indicative of a more serious cause; however, delayed presentations also may represent a surgical condition. Surgical causes of abdominal pain are more likely to manifest with pain first, followed by nausea and vomiting, rather than with nausea and vomiting followed by pain, although in elder patients the progression may be reversed or pain may be absent entirely. Localization and pain migration also are helpful components of the pain history. Diffuse pain generally is nonsurgical, but it may represent the early visceral component of a surgical

www.ketabpezeshki.com 66485457-66963820

process. Colicky pain is indicative of hollow viscus distention, and duration and time of colic may give clues to the identity of the culprit organ, as displayed in Figure 27-3.

The severity and descriptive nature of the pain are the most subjective aspects of the pain history, but a few classic descriptions are recognized, such as the following:

- The diffuse, severe, colicky pain of bowel obstruction
- The "pain out of proportion to examination" observed in patients with mesenteric ischemia
- The radiation of pain from the epigastrium straight through to the midback associated with pancreatitis, either related to primary organ inflammation or secondary to a penetrating ulcer
- The radiation of pain to the left shoulder or independent pain in the left shoulder associated with splenic pathology, diaphragmatic irritation, or free intraperitoneal fluid
- The onset of pain associated with syncope seen in perforation of gastric or duodenal ulcer, ruptured aortic aneurysm, or ruptured ectopic pregnancy

A thorough review of the patient's past medical history and medications is also mandatory, as this frequently provides key information about the current presentation. A history of immunocompromised state or immunosuppressive medications may point to infection. A patient undergoing anticoagulation therapy or taking nonsteroidal anti-inflammatory medications may have

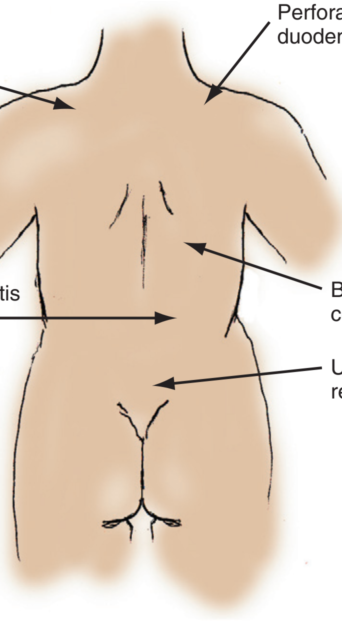


Figure 27-2. Common locations of referred pain from abdominal cause.

Table 27-2 Potentially Life-threatening Causes of Abdominal Pain

CAUSE	EPIDEMIOLOGY	ETIOLOGY	PRESENTATION	PHYSICAL EXAMINATION	USEFUL TOOL(S)
Ruptured ectopic pregnancy	Occurs in females of childbearing age. No method of contraception prevents ectopic pregnancy. Approximately 1 in every 100 pregnancies.	Risk factors include nonwhite race, older age, history of STD or PID, infertility treatment, intrauterine contraceptive device placed within the past year, tubal sterilization, and previous ectopic pregnancy.	Severe, sharp constant pain localized to the affected side. More diffuse abdominal pain with intraperitoneal hemorrhage. Signs of shock may be present. Midline pain tends not to be ectopic pregnancy.	Shock or evidence of peritonitis may be present. Lateralized abdominal tenderness. Localized adnexal tenderness or cervical motion tenderness increases the likelihood of ectopic pregnancy. Vaginal bleeding does not have to be present.	β-hCG testing necessary in all females of childbearing age (10-55 yr); combined with ultrasonography, preferably transvaginal in early pregnancy, usually is diagnostic. FAST examination is useful in evaluating for free fluid in patients with shock or peritonitis.
Ruptured or leaking abdominal aneurysm	Incidence increases with advancing age. More frequent in men. Risk factors include HTN, DM, smoking, COPD, and CAD.	Exact cause is undetermined. Contributing factors include atherosclerosis, genetic predisposition, HTN, connective tissue disease, trauma, and infection.	Patient often asymptomatic until rupture. Acute epigastric and back pain often associated with or followed by syncope or signs of shock. Pain may radiate to back, groin, or testes.	Vital signs may be normal (in 70%) to severely hypotensive. Palpation of a pulsatile mass is usually possible in aneurysms 5 cm or greater. The physical examination may be nonspecific. Bruits or inequality of femoral pulses may be evident.	Abdominal plain films abnormal in 80% of cases. Ultrasound can define diameter and length but can be limited by obesity and bowel gas. FAST examination can be helpful in evaluating for leak by looking for free fluid. Spiral CT test of choice in stable patients.
Mesenteric ischemia	Occurs most commonly in elders with CV disease, CHF, cardiac dysrhythmias, DM, sepsis, and dehydration. Responsible for 1 of 1000 hospital admissions. Mortality 70%. Mesenteric venous thrombosis associated with hypercoagulable states, hematologic inflammation, and trauma.	20-30% of lesions are nonocclusive. The causes of ischemia are multifactorial, including transient hypotension in the presence of preexisting atherosclerotic lesion. The arterial occlusive causes (65%) are secondary to emboli (75%) or acute arterial thrombosis (25%).	Severe pain, colicky, that starts in periumbilical region and then becomes diffuse. Often associated with vomiting and diarrhea. Sometimes postprandial. "Mesenteric or abdominal angina."	Early examination results can be remarkably benign in the presence of severe ischemia. Bowel sounds often still present. Rectal examination important because mild bleeding with positive guaiac stools can be present.	Often a pronounced leukocytosis is present. Elevations of amylase and creatine kinase levels are seen. Metabolic acidosis caused by lactic acidemia is often seen with infarction. Plain radiographs of limited benefit. CT, MRI, and angiography are accurate to varying degrees.

Continued

www.ketabpezeshki.com 66485457-66963820

Table 27-2 Potentially Life-threatening Causes of Abdominal Pain—cont'd

CAUSE	EPIDEMIOLOGY	ETIOLOGY	PRESENTATION	PHYSICAL EXAMINATION	USEFUL TOOL(S)
Intestinal obstruction	Peaks in infancy and elders. More common with history of previous abdominal surgery.	Adhesions, carcinoma, hernias, abscesses, volvulus, and infarction. Obstruction leads to vomiting, "third spacing" of fluid, or strangulation and necrosis of bowel.	Crampy diffuse abdominal pain associated with vomiting.	Vital signs usually normal unless dehydration or bowel strangulation has occurred. Abdominal distention, hyperactive bowel sounds, and diffuse tenderness. Local peritoneal signs indicate strangulation.	Elevated WBC count suggests strangulation. Electrolytes may be abnormal if associated with vomiting or prolonged symptoms. Abdominal radiographs and CT are useful in diagnosis.
Perforated viscus	Incidence increases with advancing age. History of peptic ulcer disease or diverticular disease common.	More often a duodenal ulcer that erodes through the serosa. Colonic diverticula, large bowel, and gallbladder perforations are rare. Spillage of bowel contents causes peritonitis.	Acute onset of epigastric pain is common. Vomiting in 50%. Fever may develop later. Pain may localize with omental walling off of peritonitis. Shock may be present with bleeding or sepsis.	Fever, usually of low grade, is common; worsens over time. Tachycardia is common. Abdominal examination reveals diffuse guarding and rebound. "Boardlike" abdomen in later stages. Bowel sounds are decreased.	WBC count usually elevated owing to peritonitis. Amylase may be elevated; LFT results are variable. Upright radiographic view reveals free air in 70-80% of cases with perforated ulcers.
Acute pancreatitis	Peak age in adulthood; rare in children and elders. Male preponderance. Alcohol abuse and biliary tract disease are risk factors.	Alcohol, gallstones, hyperlipidemia, hypercalcemia, or endoscopic retrograde pancreatography causing pancreatic damage, saponification, and necrosis. ARDS, sepsis, hemorrhage, and renal failure are secondary.	Acute onset of epigastric pain radiating to the back. Nausea and vomiting are common. Pain disproportionate to physical findings. Adequate volume repletion is important in the initial therapy.	Low-grade fever common. Patient may be hypotensive or tachypneic. Some epigastric tenderness usually present. Because pancreas is retroperitoneal organ, guarding or rebound not present unless condition is severe. Flank ecchymosis or periumbilical ecchymosis may be seen if process is hemorrhagic.	Lipase determination is test of choice. Ultrasound examination may show edema, pseudocyst, or biliary tract disease. CT scan may show abscesses, necrosis, hemorrhage, or pseudocysts. CT is ordered if severe acute pancreatitis is suspected. Rule out gallstones with ultrasound examination.

ARDS, acute respiratory distress syndrome; β-*hCG,* β-human chorionic gonadotropin; *CAD,* coronary artery disease; *CHF,* congestive heart failure; *COPD,* chronic obstructive pulmonary disease; *CT,* computed tomography; *CV,* cardiovascular; *DM,* diabetes mellitus; *FAST,* focused assessment with sonography in trauma; *HTN,* hypertension; *LFT,* liver function test; *MRI,* magnetic resonance imaging; *PID,* pelvic inflammatory disease; *STD,* sexually transmitted disease; *WBC,* white blood cell.

Box 27-2 High-Yield Historical Questions

1. *How old are you?* Advanced age means increased risk.
2. *Which came first—pain or vomiting?* Pain first is worse (i.e., more likely to be caused by surgical disease).
3. *How long have you had the pain?* Pain for less than 48 hours is worse.
4. *Have you ever had abdominal surgery?* Consider obstruction in patients who report previous abdominal surgery.
5. *Is the pain constant or intermittent?* Constant pain is worse.
6. *Have you ever had this before?* A report of no prior episodes is worse.
7. *Do you have a history of cancer, diverticulosis, pancreatitis, kidney failure, gallstones, or inflammatory bowel disease?* All are suggestive of more serious disease.
8. *Do you have human immunodeficiency virus (HIV)?* Consider occult infection or drug-related pancreatitis.
9. *How much alcohol do you drink per day?* Consider pancreatitis, hepatitis, or cirrhosis in patients with history or signs of significant intake.
10. *Are you pregnant?* Test for pregnancy—consider ectopic pregnancy.
11. *Are you taking antibiotics or steroids?* Effects of these drugs may mask infection.
12. *Did the pain start centrally and migrate to the right lower quadrant?* High specificity for appendicitis.
13. *Do you have a history of vascular or heart disease, hypertension, or atrial fibrillation?* Consider mesenteric ischemia and abdominal aneurysm.

From Colucciello SA, Lukens TW, Morgan DL: Abdominal pain: An evidence-based approach. Emerg Med Pract 1:2, 1999.

www.ketabpezeshki.com 66485457-66963820

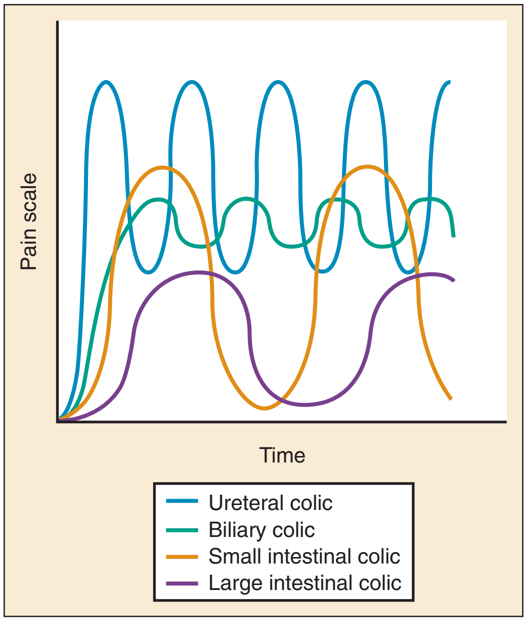


Figure 27-3. The characteristics of colicky abdominal pain.

gastrointestinal bleeding. Diabetics may be experiencing abdominal pain as a feature of ketoacidosis. A patient undergoing chronic narcotic therapy may have constipation or even a bowel obstruction.

Signs

The objective evaluation begins with measurement of the vital signs. Significant tachycardia and hypotension are indicators that hypovolemia or sepsis may be present. Tachypnea may be an indication of metabolic acidosis from gangrenous viscera or sepsis, hypoxemia from pneumonia, or simply a catecholamine-induced reaction to pain. Elevated temperature often is associated with intra-abdominal infections. Although important, vital signs may be misleading and should be interpreted in the context of the entire presentation. Tachycardia may develop late for various reasons in hypovolemia. Temperature often is normal in elderly patients with laparotomy-proven intraperitoneal infections. Elders with sepsis also may demonstrate hypothermia.

A thorough abdominal examination is an essential part of evaluation of the patient with abdominal pain. This requires properly positioning the patient supine and exposing the abdomen. The examination should begin with inspection for any signs of trauma, bruising, or skin lesions. The patient should be asked to localize the area of maximal tenderness by pointing with one finger. The abdomen can be divided into four quadrants: right upper, right lower, left upper, and left lower; each area is then examined individually. Tenderness in one quadrant often corresponds with the location of the diseased organ, which will direct the workup (see Fig. 27-1). Some disease processes may manifest with pain that is not exclusively within one specific quadrant, such as the suprapubic pain of a urinary tract infection or the midepigastic pain of a gastric ulcer. Although most patients with suspected appendicitis have right lower quadrant abdominal tenderness, a small percentage of patients with proven appendicitis do not.

Rectal examination may have limited use in the evaluation of abdominal pain, except that associated with intraluminal gastrointestinal hemorrhage, prostatitis, or perirectal disease. The main utility of the rectal examination is in the detection of heme-positive stool, anal fissures or fistulae, or stool impaction. Rectal examination has not been shown to increase diagnostic accuracy for appendicitis when added to external physical examination of the abdomen.

The abdominal evaluation should include a pelvic examination in female patients with lower abdominal pain and genital examination in male patients. The pelvic examination should be done early in the evaluation of the female patient with abdominal pain to help differentiate an abdominal from a pelvic source. This information is helpful in choosing an imaging modality. Pelvic ultrasound examination is helpful in evaluating uterine and ovarian pathology, whereas computed tomography (CT) is more beneficial in evaluation of suspected intra-abdominal pathology. Although the pelvic examination may guide the initial choice of imaging modality, overlap in examination findings is common. For example, a patient with right lower quadrant tenderness may have both right adnexal tenderness and tenderness over McBurney's point, necessitating exclusion of both appendicitis and ovarian torsion. The diagnosis highest on the differential list should be ruled out first through use of the corresponding imaging modality.

In the male patient with abdominal pain, the urogenital examination is a routine and required part of the evaluation. Diseases such as prostatitis, orchitis, and epididymitis commonly cause abdominal pain in males. Furthermore, inguinal hernias are more common in males, with the possibility of strangulation or incarceration in the inguinal canal, necessitating a thorough genitourinary examination.

In view of the evolving nature of abdominal pain, repetitive examinations may be useful. This is common practice with respect to suspected appendicitis and has improved the diagnostic accuracy in patients whose presentations were atypical.

Ancillary Testing

Urinalysis and testing for pregnancy are perhaps the most time- and cost-effective adjunctive laboratory tests available. Results often can be obtained quickly, so the former can lead to an early diagnosis and the latter may significantly affect further evaluation and management approaches. It is necessary to interpret urinalysis results within the context of the patient's clinical picture. Pyuria, with or without bacteriuria, often is present in a variety of conditions besides a simple urinary tract infection. For example, appendicitis may feature sterile pyuria. Similarly, hematuria usually is present with the relatively benign condition of nephrolithiasis but also may indicate a more severe pathology.

Complete blood counts frequently are ordered for patients with abdominal pain, but findings seldom are contributory to a diagnosis. Despite the association of elevated WBC counts with many infectious and inflammatory processes, the WBC count is neither sufficiently sensitive nor sufficiently specific to be considered a discriminatory test to help establish or rule out a serious cause for the pain. Even serial WBC counts have failed to differentiate surgical from nonsurgical conditions. The WBC count is therefore not helpful for diagnosis, except when a low WBC indicates immunosuppression. Serum electrolytes, even in the presence of protracted emesis or diarrhea, are abnormal in less than 1% of patients. Blood urea nitrogen concentrations can be elevated in gastrointestinal hemorrhage and dehydration, but such conditions are better detected and quantified by history and physical examination. Increased serum creatinine usually is indicative of renal dysfunction. Blood glucose, anion gap, and serum ketone determinations are useful in diabetic ketoacidosis, one cause of acute abdominal pain and tachypnea.

Liver enzymes and coagulation studies are helpful only in a small subset of patients with suspected liver disease. If pancreatitis is suspected, the most useful diagnostic result is serum lipase elevated to at least double the normal value, because it is more specific and more sensitive than serum amylase for this process.

www.ketabpezeshki.com 66485457-66963820

Measurement of serum amylase is of no value if a serum lipase level is available.[3] Serum lactate levels are elevated late in bowel ischemia, and such determination may be useful if this entity is suspected, but serum lactate levels cannot be considered either sufficiently sensitive or specific enough to establish or exclude the diagnosis on their own.

Plain radiography of the abdomen has limited usefulness in the evaluation of acute abdominal pain and should be performed only when bowel obstruction or radiopaque foreign body is suspected and there is no intent to obtain a CT scan. For suspected perforated hollow viscus, an upright chest radiograph is a better study than an abdominal film but is not indicated if the plan is to proceed to CT scan regardless of the findings on the plain film. CT of the abdomen has become the imaging modality of choice with nonobstetric, nonbiliary abdominal pain. It allows visualization of both intraperitoneal and extraperitoneal structures and has a high degree of accuracy. Incidental findings are common on CT scans and may lead to a diagnosis. CT scan results often lead to a change in diagnosis.[4] The proper execution and interpretation of CT studies will reduce morbidity, mortality, and medical expenses.[5,6] CT is not indicated for biliary disease, however, for which ultrasound is a much better modality.

CT has increased diagnostic utility in elderly patients for several reasons. Older people with abdominal pain are significantly more likely to require surgery and have a greatly increased mortality compared with younger adults. Furthermore, evaluation of abdominal pain in elders often is more challenging owing to unreliable findings on physical examination, including vital signs, difficulties in history taking, physiologic age-related changes, and comorbid conditions. In the elderly population, CT results change management or disposition decisions in a significant proportion of patients.[7] Table 27-3 lists the most common findings on CT scans in elders with abdominal pain.

Some controversy surrounds the use of oral contrast in abdominal CT in the critically ill ED patient. Technologic advances have improved image acquisition and resolution, and several studies have shown that intravenous contrast alone may now be adequate in the evaluation of certain suspected pathologic processes, such as solid organ or bowel wall disease.[8] CT with intravenous contrast alone also has been shown to be sensitive and specific for the confirmation or exclusion of acute appendicitis.[9] The exclusion of oral contrast in these patients significantly decreases ED time to disposition and improves patient satisfaction.

Controversy also surrounds the use of CT with regard to radiation exposure that patients receive. Several studies have attempted to quantify the radiation exposure associated with CT, but in reality there is a wide variation in dosage among different types of CT studies. One study estimated an abdominal CT with intravenous contrast to produce a dose of 10 to 50 millisieverts (mSv), enough to increase the lifetime risk of cancer to 1 in 470 in a 20-year-old woman.[10] Another study demonstrated that although patients were more confident when CT imaging was part of their ED workup, they had a very poor understanding of the radiation dose involved.[11] CT is an important adjunct in ED care, but the decision to scan is carefully weighed against the patient's history, physical examination findings, age, and gender. In particular, a patient with a history of chronic undifferentiated abdominal pain, multiple previous CT scans, and alternative diagnoses may benefit from observation as opposed to another CT scan.

Bedside transabdominal and transvaginal ultrasonography have emerged as extremely useful adjuncts, decreasing time to diagnosis of life-threatening abdominopelvic conditions. Useful indications include the following:

- Identification of an intrauterine pregnancy
- Measurement of the cross-sectional diameter of the abdominal aorta to determine the presence of an abdominal aortic aneurysm
- Detection of free intraperitoneal fluid indicating hemorrhage, pus, or extrusion of gut contents
- Use as a diagnostic aid for detection of the following non–life-threatening conditions:
  - Gallstones or a dilated common bile duct, which may be a clue to the presence of choledocholithiasis
  - Pericholecystic fluid or gallbladder wall thickening, which may be indicative of cholecystitis
  - Free intraperitoneal fluid indicating ascites
  - Hydronephrosis indicating possible obstructive uropathy
  - Inferior vena cava distention or collapse as an indicator of volume status

The results of sonographic examinations are operator dependent, and misdiagnosis can occur because of failure to detect or identify pathology, incorrect identification of normal anatomy as pathologic, or overinterpretation of correctly identified findings (e.g., the mere presence of gallstones does not indicate that cholelithiasis is the cause of the pain). Emergency physicians should receive proper training in image acquisition and interpretation, and ultrasound evaluation in the radiology department or other confirmatory imaging such as CT should be sought if there is ambiguity or uncertainty in findings.

DIFFERENTIAL DIAGNOSIS

The differential considerations with abdominal pain include a significant number of potentially life- or organ-threatening entities, particularly in the setting of a hemodynamically unstable or toxic-appearing patient. Severely ill patients require timely resuscitation and expeditious evaluation for potentially life-threatening conditions. A focused history and examination should be conducted, and the patient should be placed in a monitored acute care area well equipped for airway control, quick intravenous access, and fluid administration. Only then should appropriate diagnostics be initiated (bedside focused assessment with sonography in trauma [FAST], aorta ultrasound assessment, and radiographic, electrocardiographic, and laboratory studies). This approach is particularly important in dealing with elder or potentially pregnant patients (see Tables 27-1 and 27-2).

Women of reproductive age with abdominal pain should undergo pregnancy testing early, and a known pregnancy or a positive result on urine or serum pregnancy testing associated with abdominal pain in the ED should be considered to represent an ectopic pregnancy until proved otherwise. If evidence of blood loss is present, early obstetric consultation and diagnostic ultrasonography should be promptly sought. Bedside transabdominal

Table 27-3 Most Common Diagnostic Computed Tomography (CT) Findings in Older Patients in the Emergency Department with Acute Abdominal Pain

FINDING	PERCENT OF ABDOMINAL CT SCANS
Small bowel obstruction or ileus	18%
Diverticulitis	18%
Urolithiasis	10%
Cholelithiasis	10%
Abdominal mass or neoplasm	8%
Pyelonephritis	7%
Pancreatitis	6%

From Hustey FM, et al: The use of abdominal computed tomography in older ED patients with acute abdominal pain. Am J Emerg Med 23:259-265, 2005.

www.ketabpezeshki.com 66485457-66963820

sonography may identify free intraperitoneal fluid during the evaluation of shock, which may be sufficient evidence to justify operative intervention in the context of a positive pregnancy test and appropriate history and physical examination findings.

Despite the limitations already described, the approach to the differential diagnosis of abdominal pain generally is based on the location of maximum tenderness. Figure 27-1 shows locations of subjective pain and maximal tenderness on palpation related to various underlying causes. In women of childbearing age, a positive result on pregnancy testing may indicate ectopic pregnancy, but the entire spectrum of intra-abdominal conditions remains in the differential diagnosis, as for the nonpregnant patient. When the very broad differential list is compartmentalized by both history and physical examination, ancillary testing should proceed to either confirm or support the clinical suspicion.

Despite the significant variety of tests available, close to one half of the patients in the ED with acute abdominal pain will have no conclusive diagnosis. It is incumbent on the clinician to reconsider the extra-abdominal causes of abdominal pain (see Box 27-1), with special consideration in elders and immunocompromised patients, before arriving at the diagnosis of "nonspecific abdominal pain."

EMPIRICAL MANAGEMENT

The main therapeutic goals in managing acute abdominal pain are physiologic stabilization, mitigation of symptoms (e.g., emesis control, pain relief), and expeditious diagnosis, with consultation if required.

There is no evidence to support withholding analgesics from patients with acute abdominal pain to preserve the accuracy of subsequent abdominal examinations; in fact, the preponderance of evidence supports the opposite. Pain relief may facilitate the diagnosis in patients ultimately requiring surgery.[12] In the acute setting, analgesia usually is accomplished with intravenously titrated opioids. Meperidine (Demerol) has an unfavorable side effect profile and should be avoided. Intravenous ketorolac, the only parenteral nonsteroidal anti-inflammatory drug available in North America, is useful for both ureteral and biliary colic,[13] as well as some gynecologic conditions, but is not indicated for general treatment of undifferentiated abdominal pain. Ketorolac has been shown to cause increased bleeding times in healthy volunteers; it should be avoided in patients with gastrointestinal bleeding and potential surgical candidates.[14]

Aside from analgesics, a variety of other medications may be helpful to patients with abdominal pain. The burning pain caused by gastric acid may be relieved by antacids.[15] Intestinal cramping may be diminished with oral anticholinergics, such as the combination agent atropine-scopolamine-hyoscyamine-phenobarbital (Donnatal), although evidence for this is scant and highly variable.

Antiemetics such as promethazine, prochlorperazine, ondansetron, or droperidol can be useful for nausea and vomiting. Gastric emptying by nasogastric tube with suction is appropriate for suspected small bowel obstruction with intractable pain and vomiting.

If intra-abdominal infection is suspected, broad-spectrum antibiotic therapy should be initiated promptly. Abdominal infections are often polymicrobial, and coverage for enteric gram-negative, gram-positive, and anaerobic bacteria is included. In the choice of antibiotic or combination, the following should be considered:

- Unless local antibiotic resistance dictates otherwise, second-generation cephalosporins (e.g., cefamandole, cefotetan, cefoxitin) or quinolone (ciprofloxacin, levofloxacin) may be combined with metronidazole for the initial dose of antibiotics in the ED. Other noncephalosporin, β-lactam agents with β-lactamase antagonists (e.g., ampicillin-sulbactam, piperacillin-tazobactam, ticarcillin-clavulanate) are alternatives.
- Many enteric gram-negative bacilli mutate rapidly to produce β-lactamases that are poorly antagonized by specific drug combinations containing clavulanate, sulbactam, or tazobactam. A carbapenem (e.g., imipenem, meropenem) or cefepime is an alternative for patients who may have recently received other antibiotics.

Whether to provide coverage for *Enterococcus* species is still a subject of debate, and the decision to treat for these bacteria specifically can be made after consultation. Immunocompromised patients may require antifungal agents.

DISPOSITION

Because up to 40% of patients with acute abdominal pain receive the diagnosis of nonspecific abdominal pain, decisions regarding disposition can be as difficult as the diagnosis in these patients. Categories for disposition may include surgical versus nonsurgical consultation and management, admission for observation, and discharge to home with follow-up evaluation. The decision to admit a patient to an observation unit or a hospital bed factors in the following:

- Information gained from the history, physical examination, and test results
- The likelihood of any suspected disease
- Any potential ramifications of progression of a known disease, or of incorrect diagnosis or management
- The likelihood of appropriate and timely follow-up after hospital discharge
- The ability of the patient to return if symptoms worsen

Clinically stable patients may be discharged from the ED with appropriate follow-up care, possibly to include repeated physical examination or additional diagnostic imaging if indicated.

In the case of nonspecific abdominal pain that is considered potentially worrisome, CT scan, observation (i.e., in the ED observation unit), or follow-up reevaluation after 8 to 12 hours all are valid options. Follow-up evaluation can be done through a return visit to the ED, via an appointment with a primary care physician, or as part of an observation unit protocol.

Before discharge of a patient with an undiagnosed cause of nonspecific abdominal pain, several conditions should be met. The abdominal examination findings should not indicate serious organ pathology or peritoneal irritation, and the patient should have normal or near-normal vital signs. Pain and nausea should be controlled, and the patient should be able to take fluids by mouth. If a patient is to be discharged home without a specific diagnosis, clear instructions are given and include the following information:

- What to do for relief of symptoms or to maximize chances of resolution of the condition (e.g., avoiding exacerbating food or activities, taking medications as prescribed)
- Under what circumstances, with whom, and in what time frame to seek follow-up evaluation, if all goes as desired on the basis of what is known when the patient is in the ED
- Under what conditions to seek more urgent care because of unexpected changes in the condition (such as with natural progression of the process before improvement, incorrect diagnosis made in the ED, or untoward reactions to medications)

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Mönkemüller KE, Lazenby AJ, Lee DH, Loudon R, Wilcox CM: Occurrence of gastrointestinal opportunistic disorders in AIDS despite the use of highly active antiretroviral therapy. *Dig Dis Sci* 2005; 50:230.
2. Wernck-Silva AL, Prado IB: Dyspepsia in HIV-infected patients under highly active antiretroviral therapy. *J Gastroenterol Hepatol* 2007; 22:1712.
3. Pratt DS, Kaplan MM: Evaluation of abnormal liver-enzyme results in asymptomatic patients. *N Engl J Med* 2000; 342:1266.
4. Lewis LM, et al: Quantifying the usefulness of CT in evaluating seniors with abdominal pain. *Eur J Radiol* 2007; 61:290.
5. Federle MP: CT of the acute (emergency) abdomen. *Eur Radiol* 2005; 15(Suppl 4):D100.
6. Stromberg C, Johansson G, Adolfson A: Acute abdominal pain: Diagnostic impact of immediate CT scanning. *World J Surg* 2007; 31:2347.
7. Esses D, et al: Ability of CT to alter decision making in elderly patients with acute abdominal pain. *Am J Emerg Med* 2004; 22:270.
8. Lee SY, et al: Prospective comparison of helical CT of the abdomen and pelvis without and with oral contrast in assessing acute abdominal pain in adult emergency department patients. *Emerg Radiol* 2006; 12:150.
9. Mun S, et al: Rapid diagnosis of acute appendicitis with IV contrast material. *Emerg Radiol* 2006; 12:99.
10. Smith-Bindman R, et al: Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Radiology* 2009; 169:2078.
11. Baumann BM, et al: Patient perceptions of computed tomographic imaging and their understanding of radiation risk and exposure. *Ann Emerg Med* 2011; 58:1-7.
12. Thomas SH, et al: Effects of morphine analgesia on diagnostic accuracy in emergency department patients with abdominal pain: A prospective, randomized trial. *J Am Coll Surg* 2003; 196:18.
13. Henderson SO, Swadron S, Newton E: Comparison of intravenous ketorolac and meperidine in the treatment of biliary colic. *J Emerg Med* 2002; 23:237.
14. Singer AJ, Mynster CJ, McMahon BJ: The effect of IM ketorolac tromethamine on bleeding time: A prospective, interventional, controlled study. *Am J Emerg Med* 2003; 21:441.
15. Berman DA, Porter RS, Graber M: The GI cocktail is no more effective than plain liquid antacid: A randomized, double blind clinical trial. *J Emerg Med* 2003; 25:239.

www.ketabpezeshki.com 66485457-66963820

Chapter 28

Jaundice

Matthew A. Wheatley and Katherine L. Heilpern

PERSPECTIVE

Epidemiology

Jaundice is the manifestation of elevated serum bilirubin; thus an understanding of the metabolism of bilirubin is crucial for the evaluation and management of the emergency department (ED) patient with jaundice.

Pathophysiology

Normal Bilirubin Metabolism

Bilirubin is generated from heme products, primarily senescent red blood cells. A small portion is derived from myoglobin and maturing erythroid cells. Within the reticuloendothelial system, heme is oxidized to biliverdin, which is then converted to bilirubin. Bilirubin forms a tight but reversible bond with albumin in circulation. It is passively taken into the hepatocytes, where it undergoes glucuronidation. This conjugated fraction is secreted into the biliary system and emptied into the gut. Colonic bacteria metabolize the majority of the bilirubin to urobilinogen and stercobilin. Stercobilin is excreted in the stool, and urobilinogen is reabsorbed and excreted in the urine. The remaining conjugated bilirubin is deconjugated and reenters the portal circulation to be taken up again by the hepatocytes (enterohepatic circulation). In the laboratory, conjugated bilirubin and unconjugated bilirubin are reported as direct and indirect fractions, respectively.

Abnormalities in Bilirubin Metabolism

Clinical jaundice is usually not evident until the total serum bilirubin concentration rises above 2.5 mg/dL. It is observed in tissues with high albumin concentrations, for example, the skin and eyes. It is absent in albumin-poor fluids, such as tears or saliva. The physiology of bile metabolism may be altered in three principal areas: overproduction of heme products (hemolysis); failure of the hepatocyte to take up, conjugate, and excrete bilirubin (hepatocellular dysfunction); or obstruction of biliary excretion into the intestine. Unconjugated bilirubin that is not bound to albumin can cross the blood-brain barrier, causing adverse neurologic effects ranging from subtle developmental abnormalities to encephalopathy and death. Conditions that favor the unbound fraction of unconjugated bilirubin, including hemolysis, hypoalbuminemia, acidemia, and drugs that bind competitively to albumin, increase the risk of neurotoxicity. Conjugated bilirubins are not neurotoxic, although they may indicate serious disease.

DIAGNOSTIC APPROACH

Differential Considerations

The three major diagnostic categories to consider are liver injury or dysfunction (cholestasis), biliary obstructive disorders, and disorders of hemolysis. Figure 28-1 outlines a laboratory-based approach to differentiating among these three categories.

Pivotal Findings

The pivotal findings related to history, physical examination, and ancillary testing are listed in Figure 28-2.

Symptoms

Patients may be asymptomatic at presentation or have nonspecific symptoms such as pruritus, malaise, or nausea. There are a few symptom complexes that can help narrow the differential diagnosis. Jaundice with abdominal pain suggests biliary obstruction or significant hepatic inflammation. New-onset painless jaundice is the classic presentation for a neoplasm involving the head of the pancreas. Patients may complain of ill-fitting clothing because of weight loss or increasing abdominal girth related to ascites. The patient or caregiver may note subtle personality changes or frank confusion, suggestive of hepatic encephalopathy.

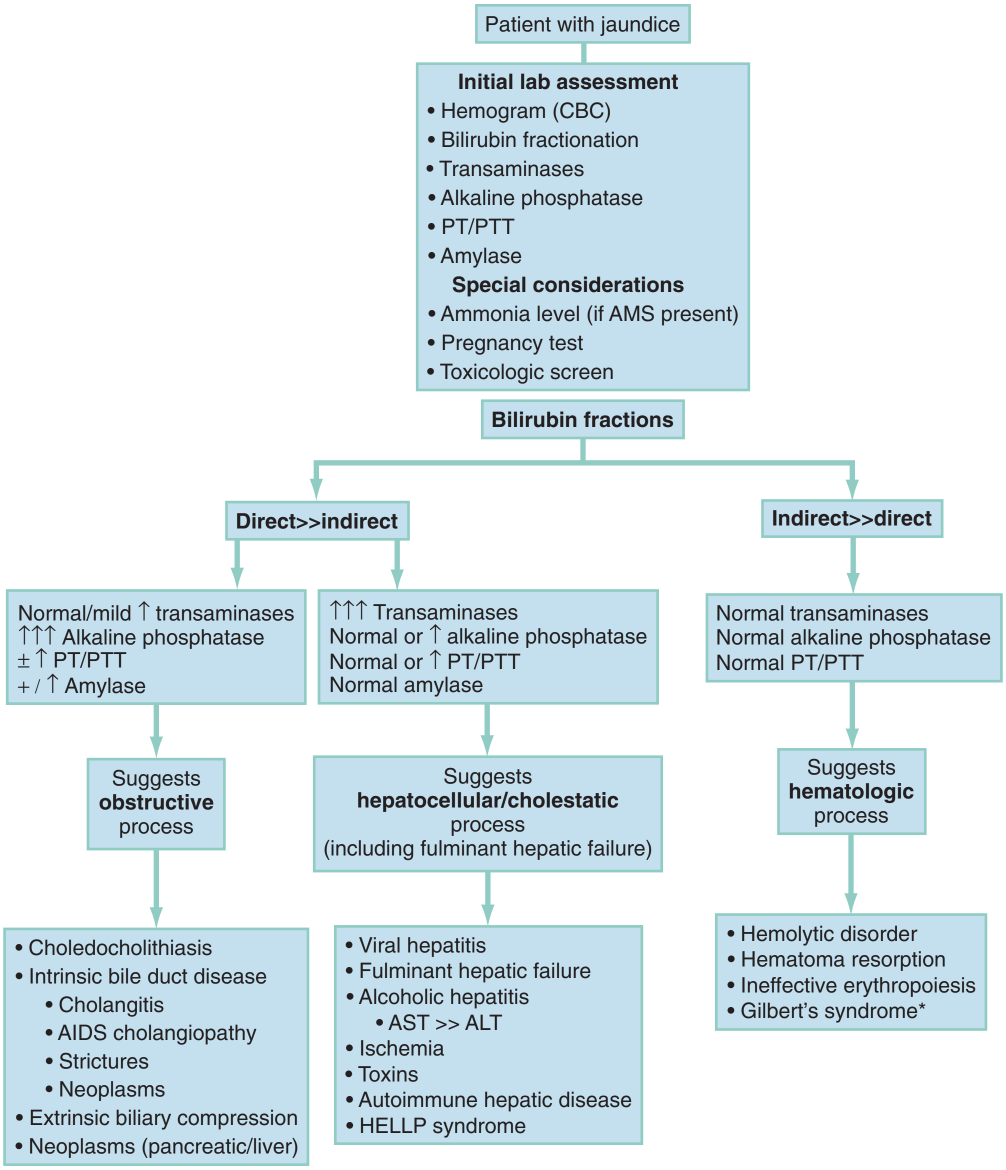
Signs

Pertinent physical examination findings are summarized in Figure 28-2. Examination of the skin and the abdomen is particularly helpful in narrowing the differential diagnosis.

Skin findings can point to acute or chronic liver disease. Jaundice is first apparent sublingually, in the conjunctiva and on the hard palate. From there, it spreads caudally; however, the extent of cephalocaudal progression does not accurately reflect the serum bilirubin concentration. Adequate lighting is necessary to detect the initial presentation of jaundice. Cutaneous findings of chronic liver disease include angiomas, excoriations from pruritus, and caput medusa.

The abdominal examination should begin with a thorough visual inspection. A distended or protuberant abdomen can indicate the presence of ascites. On palpation, an enlarged, tender liver suggests hepatic inflammation or engorgement caused by biliary obstruction. An enlarged nontender liver is concerning for malignant infiltration. A nonpalpable liver can indicate fibrosis caused by cirrhosis. A palpable gallbladder, a rare finding, suggests chronic

www.ketabpezeshki.com 66485457-66963820



*A benign hereditary condition characterized by hyperbilirubinemia and jaundice due to inadequate hepatic conjugation of bilirubin.

Figure 28-1. Laboratory approach to differential diagnosis of jaundice. *AIDS,* acquired immunodeficiency syndrome; *ALT,* alanine aminotransferase; *AMS,* altered mental status; *AST,* aspartate aminotransferase; *CBC,* complete blood count; *HELLP,* hemolysis, elevated liver enzymes, and low platelets; *PT,* prothrombin time; *PTT,* partial thromboplastin time.

cholestasis or malignancy. The presence of splenomegaly suggests hemolysis, malignancy, or portal hypertension.

Neurologic examination of the jaundiced patient may show depressed mental status, indicating hepatic encephalopathy or cerebral dysfunction caused by sepsis. Asterixis is a specific finding of hepatic encephalopathy. Table 28-1 addresses the clinical stages of hepatic encephalopathy.

Laboratory Tests

Figure 28-2 lists the laboratory tests that are helpful in the evaluation of a patient with jaundice. Serum γ-glutamyl transpeptidase (GGT) rises in parallel with alkaline phosphatase (AP) in the setting of liver disease.[1] Although AP also can be elevated in diseases affecting bone or placenta, the concomitant increase in serum GGT or 5′-nucleotidase confirms a hepatic source. A reticulocyte count and evaluation of the peripheral blood smear may identify hemolysis. In cases of unexplained hepatocellular injury, a quantitative acetaminophen level may be helpful. Bedside stool guaiac testing assesses for the presence of gastrointestinal bleeding. Both glucose and ammonia metabolism can be altered in the presence of hepatocellular injury, and patients with altered mental status should have glucose and ammonia levels determined. The degree of elevation in serum ammonia does not correlate directly with the level of hepatic encephalopathy. Ascitic fluid should be analyzed in patients with new-onset ascites and in those with established ascites but new complaints of fever, abdominal pain, gastrointestinal bleeding, hepatic encephalopathy, hypotension, or renal failure. Cell count and differential, albumin, and total protein concentration are sufficient initial screening tests. In the setting of suspected bacterial peritonitis, fluid culture is also necessary; Gram stain is rarely helpful. Two sets of blood cultures

www.ketabpezeshki.com 66485457-66963820

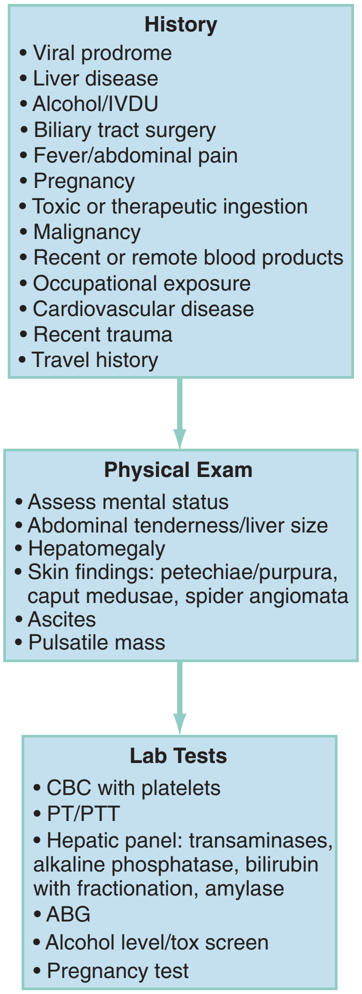


Figure 28-2. Pivotal points in the assessment of the jaundiced patient. *ABG,* arterial blood gas; *CBC,* complete blood count; *IVDU,* intravenous drug use; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *tox,* toxicology.

Table 28-1 Clinical Stages of Hepatic Encephalopathy

CLINICAL STAGE	INTELLECTUAL FUNCTION	NEUROMUSCULAR FUNCTION
Subclinical	Normal examination findings, but work or driving may be impaired	Subtle changes in psychometric testing
Stage 1	Impaired attention, irritability, depression, or personality changes	Tremor, incoordination, apraxia
Stage 2	Drowsiness, behavioral changes, poor memory, disturbed sleep	Asterixis, slowed or slurred speech, ataxia
Stage 3	Confusion, disorientation, somnolence, amnesia	Hypoactive reflexes, nystagmus, clonus, muscular rigidity
Stage 4	Stupor and coma	Dilated pupils and decerebrate posturing; oculocephalic reflex

From Fitz G: Systemic complications of liver disease. In Feldman M, Sleisenger M, eds: Gastrointestinal and Liver Disease, Philadelphia: WB Saunders; 1998.

should be performed for patients with fever and jaundice. If there is evidence of gastrointestinal bleeding with hemodynamic instability or severe anemia, a type and crossmatch should be performed by the laboratory.

Imaging

Although not always necessary, abdominal imaging can help narrow the differential diagnosis of jaundice, especially in patients for whom biliary obstruction is a concern. The primary role of imaging is in the characterization of obstructive biliary disease. The first choice of study remains somewhat controversial. Ultrasonography (US) and computed tomography (CT) are available in most EDs and are reasonably sensitive in diagnosing obstruction. The choice of imaging procedure depends on the pretest probability that there is biliary obstruction and that the obstruction is malignant. For patients with painless, progressive jaundice and without suspicion of hepatocellular injury (e.g., hepatitis, alcoholism), malignant obstruction has a high pretest probability, so CT is the preferred method owing to its improved sensitivity in locating the site of the obstruction, determining resectability, and assessing for disseminated disease. Patients with a high likelihood of biliary disease and benign obstruction are best screened with US. Ultrasonography is less expensive and less invasive than CT but has a lower sensitivity in identifying common bile duct stones.[2,3] US with Doppler flow can detect obstruction in the hepatic, portal, and splenic veins. Sonographic features of cholecystitis are discussed in Chapter 90. In patients with low or intermediate clinical likelihood of mechanical obstruction, US is the preferred modality to evaluate whether or not biliary obstruction is present. CT is preferred if the entire abdomen needs to be evaluated.

DIAGNOSTIC ALGORITHM

The differential considerations for jaundice are broad; there are critical and emergent causes that should be ruled in or out in the ED. Table 28-2 lists these conditions by organ system. Patients are considered in a critical state if they have jaundice and any of the following: altered level of consciousness, hypotension, fever with abdominal pain, or active bleeding.

Further characterization of the cause of jaundice involves analysis of the laboratory studies (Fig. 28-1). Indirect bilirubinemia points to a hematologic cause, whereas direct bilirubinemia indicates hepatobiliary pathology. Elevated direct bilirubin with transaminase elevation is indicative of hepatocellular inflammation or necrosis. Quantitative acetaminophen level, hepatitis serologies, and prothrombin time (PT) should be assessed. Prolongation of PT indicates significant hepatocellular dysfunction. Elevated AP with elevated direct bilirubin indicates extrinsic biliary obstruction. Patients with biliary obstruction require CT or US in the ED to determine the cause and site of the obstruction.

The identification of critical or emergent causes of jaundice requires the clinician to identify patterns in the patient's signs, symptoms, and ancillary testing. For instance, patients with a triad of jaundice, encephalopathy, and coagulopathy (international normalized ratio [INR] >1.5) have acute hepatic failure.[4] Fever, right upper quadrant pain, and jaundice can indicate biliary obstruction with infection (e.g., cholangitis, cholecystitis, or hepatitis). Ascites with abdominal tenderness raises suspicion for spontaneous bacterial peritonitis (SBP). Rapid onset of hepatomegaly and ascites can point to portal vein thrombosis (Budd-Chiari syndrome).

EMPIRICAL MANAGEMENT

General supportive therapies and specific therapies depend on the presumptive cause of the jaundice (Fig. 28-3). If coagulopathy is

www.ketabpezeshki.com 66485457-66963820

Table 28-2 Jaundice: Differential Diagnosis of Critical and Emergent Diagnoses

SYSTEM	CRITICAL	EMERGENT	NONEMERGENT
Hepatic	Fulminant hepatic failure Toxin Virus Alcohol Ischemic insult Reye's syndrome	Hepatitis of any cause with confusion, bleeding, or coagulopathy Wilson's disease Primary biliary cirrhosis Autoimmune hepatitis Liver transplant rejection Infiltrative liver disease Drug induced (isoniazid, phenytoin, acetaminophen, ritonavir, halothane, sulfonamides) Toxin ingestion or exposure	Hepatitis with normal mental status, normal vital signs, and no active bleeding
Biliary	Cholangitis	Bile duct obstruction (stone, inflammation, stricture, neoplasm)	
Systemic	Sepsis Heatstroke	Sarcoidosis Amyloidosis Graft-versus-host disease	Post-traumatic hematoma resorption Total parenteral nutrition
Cardiovascular	Obstructing AAA Budd-Chiari syndrome Severe congestive heart failure	Right-sided congestive heart failure Veno-occlusive disease	
Hematologic-oncologic	Transfusion reaction	Hemolytic anemia Massive malignant infiltration Inborn error of metabolism Pancreatic head tumor Metastatic disease	Gilbert's syndrome Physiologic neonatal jaundice
Reproductive	Preeclampsia or HELLP syndrome Acute fatty liver of pregnancy	Hyperemesis gravidarum	Cholestasis of pregnancy

AAA, abdominal aortic aneurysm; *HELLP,* hemolysis, elevated liver enzymes, low platelets.

known or suspected, compressible sites and ultrasound guidance should be used for central venous access. Coagulopathy in the context of acute hemorrhage should be corrected with fresh frozen plasma and blood volume repletion accomplished with packed red blood cells.

If ascites is present and SBP is suspected, paracentesis is diagnostic. The presence of more than 250 polymorphonuclear cells per cubic millimeter of ascitic fluid is diagnostic for SBP. The empirical antibiotic of choice is a third-generation cephalosporin.

Patients with jaundice and transaminases out of proportion to elevation of AP have a hepatocellular injury pattern. Treatment of hepatic encephalopathy is described in Chapter 90. Patients with fulminant hepatic failure should be admitted to the intensive care unit or transferred to a hospital with expertise in severe liver disease, depending on the severity of the illness. Acetaminophen toxicity and indications for *N*-acetylcysteine therapy are discussed in Chapter 148.

In the absence of liver failure, patients with encephalopathy or unstable vital signs should be admitted. Patients with new-onset jaundice should be hospitalized if transaminases are greater than 1000 IU/L, the bilirubin exceeds 10 mg/dL, or there is evidence of coagulopathy. Any of these laboratory abnormalities suggests significant hepatic dysfunction. Patients with hepatitis or cholestatic jaundice may be managed as outpatients if they have a normal mental status, stable vital signs, ability to take oral fluids, no evidence of acute bleeding or significant coagulopathy, and no complicating infectious process. Intravenous fluids and antiemetics may be required in the ED. Alcohol and medications with potential hepatotoxicity, particularly acetaminophen, should be avoided.

Fever, abdominal pain, and obstructive jaundice suggest ascending cholangitis. Antibiotic recommendations for ascending cholangitis are in Chapter 90. In addition to antibiotics, patients should be resuscitated with intravenous fluids as necessary and have any metabolic derangements corrected. Because biliary excretion of most antibiotics is compromised in the setting of obstruction, all patients will require biliary drainage.[5] This generally should be done urgently but may be deferred 24 to 48 hours in stable patients.[6] Drainage can be accomplished by endoscopic, percutaneous, or open surgical approaches. Prompt consultation with general surgery or gastroenterology is necessary to determine which approach and timing are appropriate.

Patients with extrahepatic obstructive jaundice without cholangitis should also be admitted for drainage. Endoscopic retrograde cholangiopancreatography (ERCP) is therapeutic for benign obstructions such as gallstones or strictures. Patients with obstructive jaundice caused by malignancy also benefit from biliary decompression, whether operative or endoscopic. Malignancy with jaundice heralds more advanced disease and increased morbidity and mortality.[7,8]

In general, patients with uncomplicated cholecystitis should receive intravenous fluids in the ED, parenteral analgesics, and antiemetics as needed and should be hospitalized. Antibiotic therapy for acute cholecystitis is discussed in Chapter 90. These patients should undergo emergent imaging and consultation with a surgeon or gastroenterologist.

Patients with confirmed or suspected choledocholithiasis, stones in the common bile duct, require admission for possible ERCP or cholecystectomy.[9-11] Neither CT nor US is 100% sensitive in identifying a common bile duct stone, but they are reasonably sensitive in identifying a dilated common bile duct, which is highly suggestive of obstruction.

In immune-mediated hemolytic anemia, the decision to transfuse should be based on the patient's ability to oxygenate and the ability to institute alternative treatments. An urgent hematology consultation is recommended (see Chapter 121) In the case of drug-induced hemolytic anemia, the mainstay of treatment involves removal of the offending agent. For patients with

www.ketabpezeshki.com 66485457-66963820

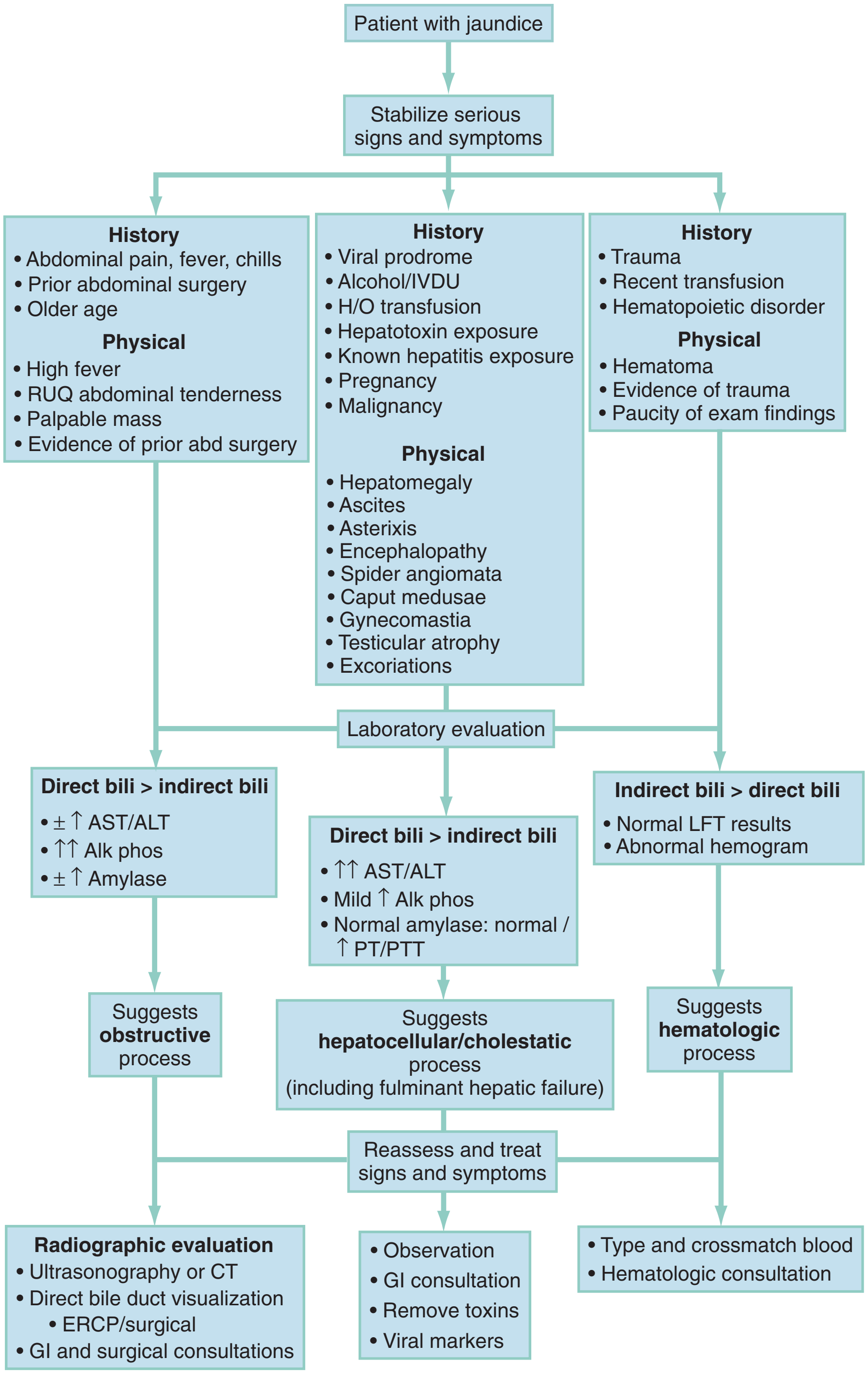


Figure 28-3. Management of the patient with jaundice. *abd,* abdominal; *Alk phos,* alkaline phosphatase; *ALT,* alanine aminotransferase; *AST,* aspartate aminotransferase; *bili,* bilirubin; *CT,* computed tomography; *ERCP,* endoscopic retrograde cholangiopancreatography; *GI,* gastrointestinal; *H/O,* history of; *IVDU,* intravenous drug use; *LFT,* liver function test; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *RUQ,* right upper quadrant.

glucose-6-phosphate deficiency, blood transfusions are rarely indicated, and the focus of management should be on maintaining urine output to prevent renal failure. Patients with hemoglobinopathies rarely require transfusion therapy unless they have severe anemia without evidence of reticulocytosis. Fluids, oxygen, and analgesics can be given for an acute crisis.

SPECIAL POPULATIONS

One specific presentation that warrants discussion is the pregnant patient with jaundice. Normal physiologic changes in pregnancy have little effect on the liver, so jaundice indicates pathology. Jaundice can occur in pregnancy as a result of any of the conditions discussed previously as well as conditions specific to pregnancy, such as hyperemesis gravidarum, acute fatty liver of pregnancy (AFLP), and intrahepatic cholestasis of pregnancy.

Hyperemesis gravidarum usually manifests in the first trimester. The exact mechanism for jaundice is unknown but is likely related to malnutrition and impaired excretion of bilirubin. The liver panel can be abnormal in up to 50% of cases. This includes transaminases elevated up to 20 times the upper limit of normal and mild jaundice.[12] ED treatment is unchanged in these cases:

www.ketabpezeshki.com 66485457-66963820

hydration and antiemetics. Liver enzymes will normalize with the resolution of vomiting; patients with hyperemesis and jaundice may require admission for intravenous hydration.

Intrahepatic cholestasis of pregnancy is an idiopathic cause of jaundice that occurs in the second or third trimester. It manifests with pruritus mainly in the trunk, extremities, and palms and soles, followed by jaundice after 1 to 4 weeks. Other features of obstructive jaundice such as acholic stools and dark urine may be present. Laboratory analysis reveals a cholestatic picture. These patients are at increased risk for preterm delivery and intrauterine fetal demise and should therefore be managed in conjunction with the obstetric team or transferred to a center capable of caring for premature neonates. Specific treatments include ursodeoxycholic acid or cholestyramine for pruritus and vitamin K.[13,14] These treatments should be initiated in conjunction with obstetric and gastroenterologic specialists.

AFLP occurs in the third trimester and is characterized by accumulation of microvesicular fat within hepatocytes. It is rare, occurring in 1 in 13,000 deliveries. There is a slight predilection toward primiparous and multiple gestation pregnancies. Clinical manifestations include nausea, vomiting, right upper quadrant or epigastric pain, malaise, anorexia, and jaundice progressing to fulminant hepatic failure and encephalopathy. Treatment consists of prompt delivery. Jaundice and liver dysfunction may progress after delivery but generally resolve. AFLP generally does not recur in subsequent pregnancies. Liver transplantation has been successful for this condition.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Lewis JR, Mohanty SR: Nonalcoholic fatty liver disease: A review and update. *Dig Dis Sci* 2010; 55:560.
2. Sugiyama M, Atomi Y: Endoscopic ultrasonography for diagnosing choledocholithiasis: A prospective comparative study with ultrasonography and computed tomography. *Gastrointest Endosc* 1997; 45:143.
3. Williams EJ, et al: Guidelines on the management of common bile duct stones (CBDS). *Gut* 2008; 57:1004.
4. Bernal W, Auzinger G, Dhawan A, Wendon J: Acute liver failure. *Lancet* 2010; 376:190.
5. Tanaka A, et al: Antimicrobial therapy for acute cholangitis: Tokyo guidelines. *J Hepatobiliary Pancreat Surg* 2007; 14:59.
6. Wada K, et al: Diagnostic criteria and severity assessment of acute cholangitis: Tokyo Guidelines. *J Hepatobiliary Pancreat Surg* 2007; 14:52.
7. Hawkins WG, et al: Jaundice predicts advanced disease and early mortality in patients with gallbladder cancer. *Ann Surg Oncol* 2004; 11:310.
8. Qin L, Tang Z: Hepatocellular carcinoma with obstructive jaundice: Diagnosis, treatment and prognosis. *World J Gastroenterol* 2003; 9:385.
9. NIH state-of-the-science statement on endoscopic retrograde cholangiopancreatography (ERCP) for diagnosis and therapy. *NIH Consens State Sci Statements* 2002; 19:1.
10. Eisen GM, et al: An annotated algorithm of the evaluation of choledocholithiasis. *Gastrointest Endosc* 2001; 53:864.
11. Adler DG, et al: ASGE guideline: The role of ERCP in diseases of the biliary tract and pancreas. *Gastrointest Endosc* 2005; 62:1.
12. Hay JE: Liver disease in pregnancy. *Hepatology* 2008; 47:1067.
13. Kondrackiene J, Beuers U, Kupcinskas L: Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. *Gastroenterology* 2005; 129:894.
14. Binder T, Salaj P, Zima T, Vitek L: Randomized prospective comparative study of ursodeoxycholic acid and 5-adenosyl-l-methioninie in the treatment of intrahepatic cholestasis of pregnancy. *J Perinat Med* 2006; 34:383.

www.ketabpezeshki.com 66485457-66963820

Chapter 29

Nausea and Vomiting

Leslie S. Zun

PERSPECTIVE

Nausea and vomiting may constitute the primary presentation of many gastrointestinal (GI) disorders (e.g., bowel obstruction, gastroenteritis) or the secondary presentation of numerous systemic conditions (1) caused by severe pain, especially visceral pain; (2) caused by or related to severe systemic illness, such as myocardial infarction, sepsis, or shock; or (3) related to definitive conditions by specific mechanisms, such as pregnancy (hormones), increased intracranial pressure (central mechanism), toxins (homeostatic response), motion sickness (neuroendocrine), and chemotherapy (chemoreceptor trigger zone [CTZ]). In addition, vomiting may cause serious sequelae, such as aspiration pneumonia, Mallory-Weiss syndrome, esophageal rupture, volume depletion, and metabolic derangement. Classification by duration and frequency of the vomiting (acute, recurrent, chronic, or cyclic) may assist in determination of the underlying cause.

Epidemiology

The most common causes of nausea and vomiting are acute gastroenteritis, febrile systemic illnesses, and drug effects. Acute viral gastroenteritis is the most common GI disease in the United States. Emesis associated with pregnancy is common, especially in the first trimester, and sometimes represents hyperemesis gravidarum. Nausea and vomiting are most commonly caused by medications in the adult population. Although the scope of the differential diagnosis in the pediatric population is broad, acute vomiting is commonly seen with infectious disorders affecting the GI tract as well as with infections in other areas of the body.

Pathophysiology

The act of vomiting can be divided into three distinct phases: nausea, retching, and actual vomiting (Fig. 29-1). Nausea may occur without retching or vomiting, and retching may occur without vomiting. *Nausea* is defined as a vague and extremely unpleasant feeling that often precedes vomiting. The exact neural pathways mediating nausea are not clear, but they are likely to be the same pathways that mediate vomiting. Mild activation of the pathways may result in nausea, whereas more intense stimulation results in vomiting. During nausea there is an increase in tone in the musculature in the duodenum and jejunum, with a concomitant decrease in gastric tone; this leads to reflux of intestinal contents into the stomach. There is often associated hypersalivation, repetitive swallowing, and tachycardia.

Retching is characterized as rhythmic, synchronous contractions of the diaphragm, abdominal muscles, and intercostal muscles that occur against a closed glottis. There is a resultant increase in abdominal pressure with a concurrent decrease in intrathoracic pressure. This pressure gradient causes gastric contents to move up into the esophagus. The mouth is usually closed.

Vomiting is the forceful expulsion of gastric contents through the mouth. There is contraction of the external oblique and abdominal rectus muscles, and the hiatal portion of the diaphragm relaxes; this increases the pressure in the abdominal and the thoracic compartments. There is contraction of the pyloric portion of the stomach. Simultaneously, there is relaxation of the gastric fundus, cardia, and upper esophageal sphincter as the vomitus is brought up and out the mouth. The glottis closes to prevent aspiration.

The complex act of vomiting is not completely understood but is thought to be coordinated by a *vomiting center* located in the lateral reticular formation of the medulla (Fig. 29-2). The efferent pathways from the vomiting center are mainly through the vagus, phrenic, and spinal nerves. These pathways are responsible for the integrated response of the diaphragm, intercostal muscles, abdominal muscles, stomach, and esophagus. The vomiting center is activated by afferent stimuli from a variety of sources. These include vagal and sympathetic impulses directly from the GI tract. Direct irritation of the stomach lining causes vomiting in this way. Other GI sources of afferent impulses include the pharynx, small bowel, colon, biliary system, and peritoneum. Receptors also are found outside the GI tract in the vestibular system, heart, and genitalia.

The other major source of impulses to the vomiting center is the CTZ. The CTZ is located in the area postrema, the floor of the fourth ventricle. Part of this area is located outside of the blood-brain barrier, enabling it to respond to endogenous and exogenous substances that activate vomiting. It is activated by hormones, peptides, medications, or toxins in the circulation, including opiates, digitalis, chemotherapy agents, salicylate, syrup of ipecac, and dopamine neurotransmitters.

The discovery of various neurotransmitters and their receptor sites within the medulla has improved the understanding and development of therapeutic agents. The CTZ area is rich in dopamine D_2 receptors, which are antagonized by drugs such as prochlorperazine, metoclopramide, and droperidol. The serotonin receptor has been found widely in the area postrema and the GI tract. It may act directly and through the release of dopamine. The serotonin receptor antagonists ondansetron and granisetron have been shown to be effective in preventing chemotherapy-induced nausea and vomiting. Concentrations of cholinergic and histamine receptors are found in the lateral vestibular nucleus and are important in motion sickness. Meclizine, diphenhydramine, and scopolamine act by antagonizing these receptors. Activation of cannabinoid receptors has been found to inhibit the emetic reflex.

www.ketabpezeshki.com 66485457-66963820

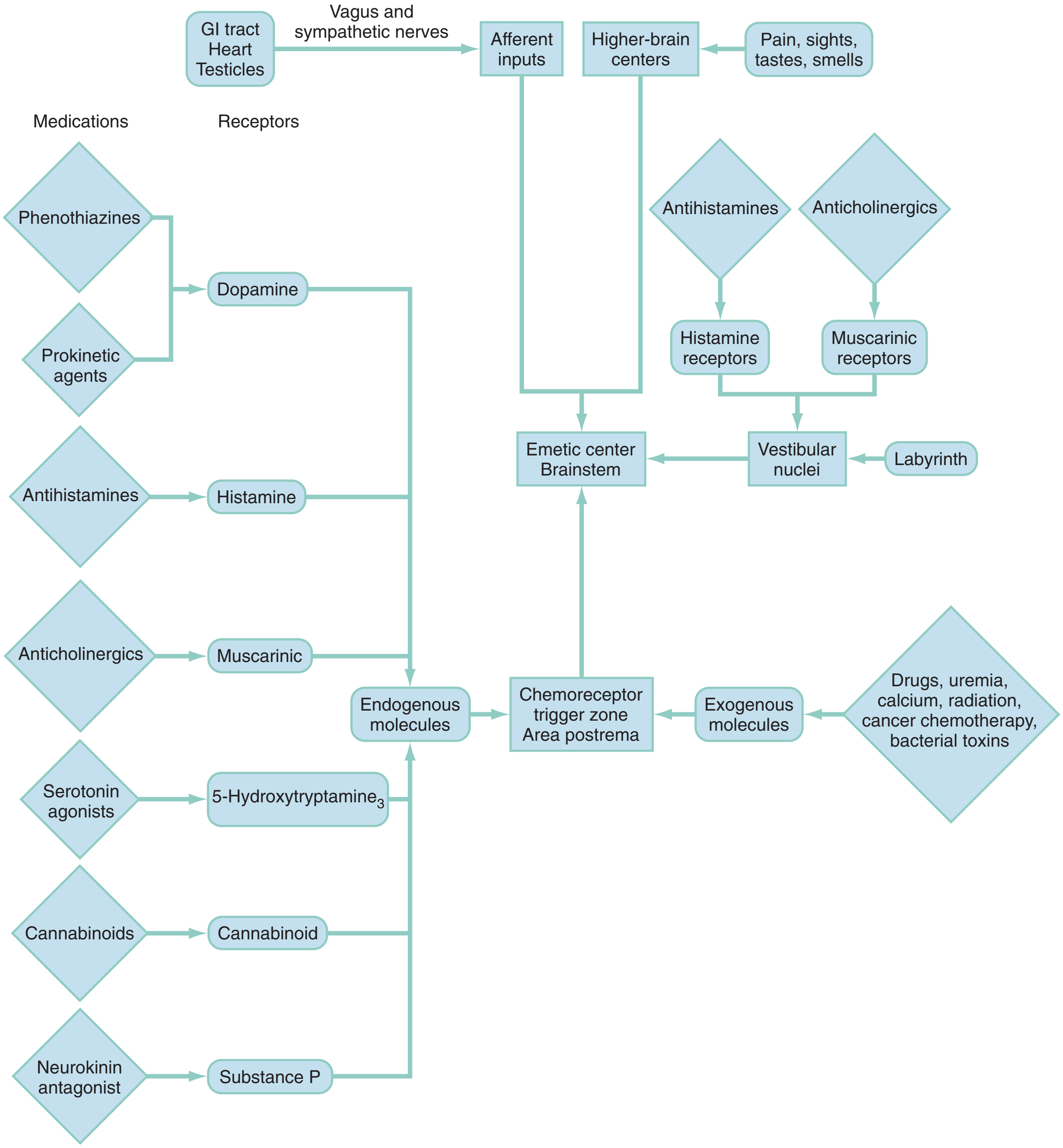


Figure 29-1. Pathophysiology of nausea and vomiting. *GI,* gastrointestinal.

DIAGNOSTIC APPROACH

Differential Considerations

The differential diagnosis for nausea and vomiting is particularly broad in scope; almost any organ system can be involved (Table 29-1). Vomiting also can result in complications, which must be considered in addition to the causes. The sequelae of vomiting may include the following:

Hypovolemia is caused by loss of water and sodium chloride in the vomitus. The contraction of the extracellular fluid space leads to activation of the renin-angiotensin-aldosterone system.

Metabolic alkalosis is produced by loss of hydrogen ions in the vomitus. Many factors serve to maintain the alkalosis, including volume contractions, hypokalemia, chloride depletion, shift of extracellular hydrogen ions into cells, and increased aldosterone.

Hypokalemia is produced primarily by loss of potassium in the urine. The metabolic alkalosis leads to large amounts of sodium bicarbonate being delivered to the distal tubule. Secondary hyperaldosteronism from volume depletion causes reabsorption of sodium and excretion of large amounts of potassium in the urine.

Mallory-Weiss tears typically result from a forceful bout of retching and vomiting. The lesion itself is a 1- to 4-cm tear through the mucosa and submucosa; 75% of cases occur in the stomach, with the remainder near the gastroesophageal junction. Bleeding usually is mild and self-limited; however,

www.ketabpezeshki.com 66485457-66963820

3% of deaths from upper GI bleeds are a result of Mallory-Weiss tears.

Boerhaave's syndrome refers to a perforation of all layers of the esophagus occurring as a result of forceful retching or vomiting. The overlying pleura is torn so that there is free passage of esophageal contents into the mediastinum and thorax; 80% of cases involve the posterolateral aspect of the distal esophagus. Boerhaave's syndrome constitutes a surgical emergency. The mortality rate has been reported as 50% if surgical repair is not performed within 24 hours.

Aspiration of gastric contents is a concern in patients who have altered mental status or pulmonary findings after an episode of vomiting. Patients with pulmonary findings after vomiting need further evaluation for aspiration.

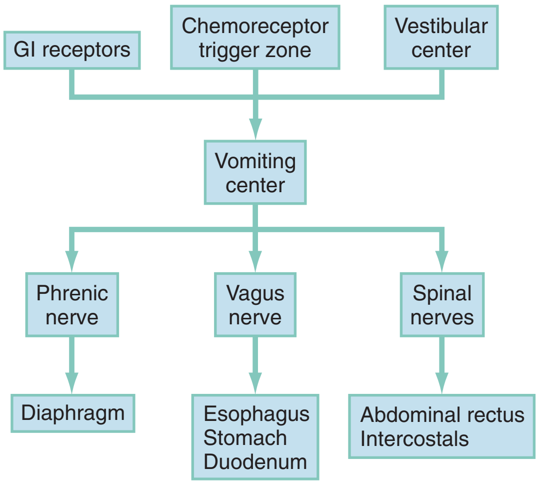


Figure 29-2. Vomiting process. *GI,* gastrointestinal.

Rapid Assessment and Stabilization

The initial assessment is directed toward the patient's hemodynamic status and identification of the critical causes or sequelae of vomiting (see Table 29-1). Data gathered include duration of vomiting, whether blood is in the vomitus, symptoms of volume depletion, and associated symptoms pointing to serious underlying disease. Physical findings include level of consciousness, abdominal examination, rapid neurologic screen, and serial vital signs. Initial stabilization may include establishing intravenous access and fluid resuscitation in patients with signs of volume depletion, cardiac monitoring, and therapeutic measures directed toward specific underlying diseases (e.g., nasogastric tube for intractable vomiting in the setting of a small bowel obstruction) (Fig. 29-3).

Pivotal Findings

History

Duration of the vomiting can lead to a diagnosis. *Acute* vomiting is episodic vomiting that occurs for less than 1 week and is associated

Table 29-1 Differential Diagnosis of Nausea and Vomiting

ETIOLOGIC CATEGORY	CRITICAL DIAGNOSES	EMERGENT DIAGNOSES	NONEMERGENT DIAGNOSES
Gastrointestinal (GI)	Boerhaave's syndrome Ischemic bowel GI bleeding	Gastric outlet obstruction Pancreatitis Cholecystitis or cholangitis Bowel obstruction or ileus Ruptured viscus Appendicitis Peritonitis Spontaneous bacterial peritonitis	Gastritis Gastroparesis Peptic ulcer disease Inflammatory bowel disease Biliary colic Hepatitis Gastroenteritis
Neurologic	Intracerebral bleed Meningitis	Migraine CNS tumor Raised ICP	
Endocrine	DKA	Adrenal insufficiency Uremia	Thyroid
Pregnancy		Hyperemesis gravidarum	Nausea and vomiting of pregnancy
Drug toxicity		Acetaminophen Digoxin Aspirin Theophylline	
Therapeutic drug use			Aspirin Antibiotics Erythromycin Ibuprofen Chemotherapy
Drugs of abuse			Narcotics Narcotic withdrawal Alcohol
Genitourinary		Gonadal torsion	Urinary tract infection Poisoning Nephrolithiasis
Miscellaneous	Myocardial infarction Sepsis	Carbon monoxide Electrolyte disorders Organophosphate poisoning	Motion sickness Labyrinthitis

CNS, central nervous system; *DKA,* diabetic ketoacidosis; *ICP,* intracranial pressure.

www.ketabpezeshki.com 66485457-66963820

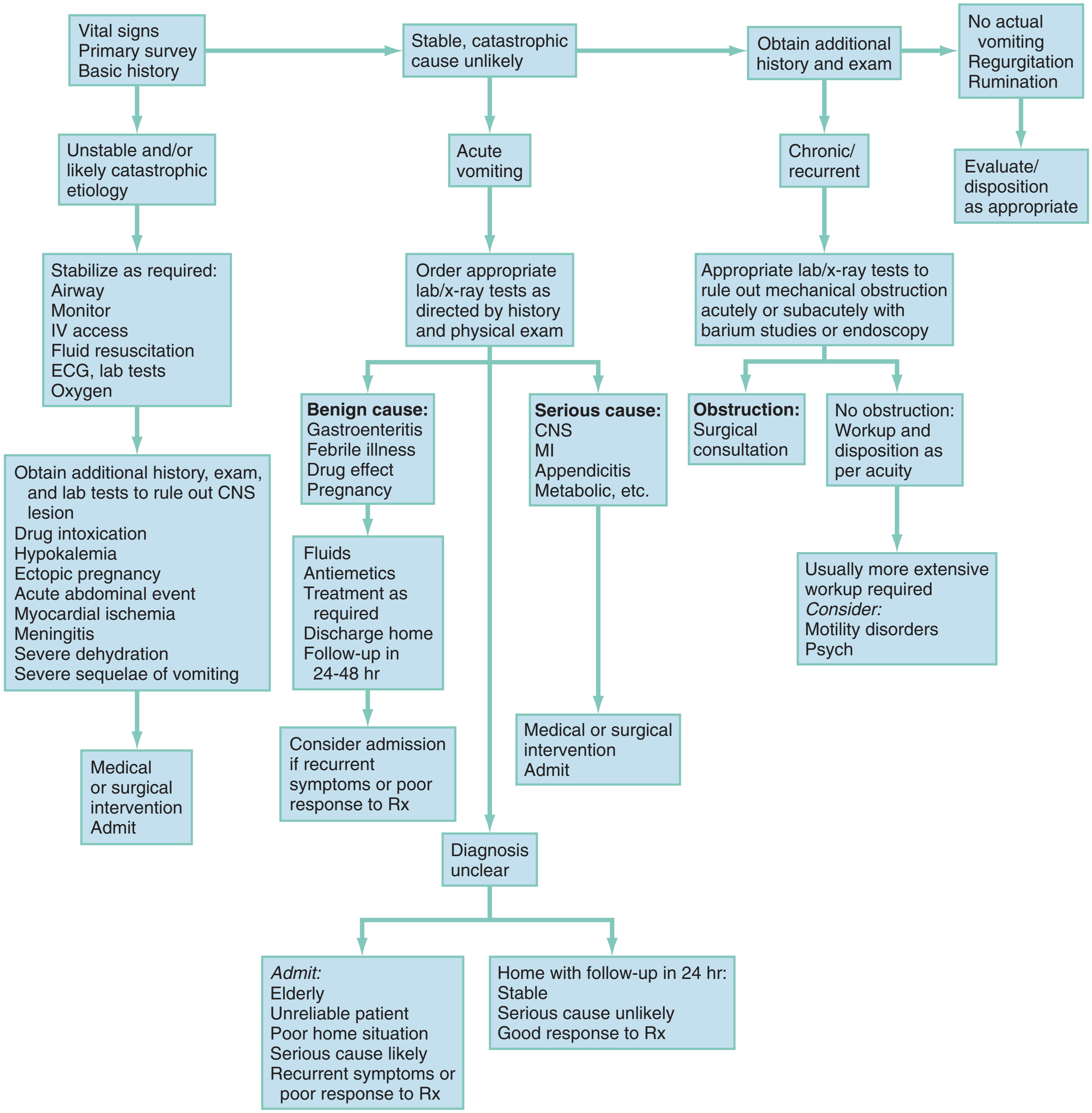


Figure 29-3. Approach to the patient with nausea and vomiting. *CNS,* central nervous system; *ECG,* electrocardiogram; *IV,* intravenous; *MI,* myocardial infarction; *Psych,* psychogenic; *Rx,* treatment.

with obstructive, ischemic, toxic, metabolic, infectious, neurologic, and postoperative causes. *Chronic* vomiting occurs with partial obstructions, motility disorders, and neurologic conditions or may be related to pregnancy or psychogenic in origin.

Timing of the vomiting may be important. An acute onset of nausea and vomiting suggests gastroenteritis, pancreatitis, cholecystitis, or a drug-related side effect. Symptoms occurring primarily in the morning suggest pregnancy, although this pattern also may be seen with uremia, alcohol ingestion, or increased intracranial pressure. Delayed vomiting more than 1 hour after eating suggests gastric outlet obstruction or gastroparesis. Vomiting of material eaten more than 12 hours previously is pathognomonic for outlet obstruction. Episodic nausea and vomiting occurring for more than 1 month are considered chronic. Discrete episodes of intractable vomiting with intervening asymptomatic periods are considered cyclic.

Content of the vomitus may provide clues to its cause. The presence of bile indicates a patent connection between the duodenum and the stomach and essentially rules out a gastric outlet obstruction. Regurgitation of undigested food can suggest achalasia, esophageal stricture, or Zenker's diverticulum. Feculent material usually suggests a distal bowel obstruction but also may be seen with gastrocolic fistula or bacterial overgrowth of stomach contents in long-standing outlet obstruction.

Associated symptoms and signs may be helpful. Chronic headaches with nausea and vomiting should raise suspicion of elevated intracranial pressure. Vomiting without preceding nausea is typical of central nervous system (CNS) pathology. The *social history* should include inquiries about alcohol or other substance use. The *past medical history* will reveal the presence of any GI disease or previous surgeries. Nutritional history is valuable in the consideration of failure to thrive in infancy. Finally, a thorough

www.ketabpezeshki.com 66485457-66963820

Table 29-2 Physical Examination of the Patient with Nausea and Vomiting

ORGAN SYSTEM	FINDING	SUGGESTED DIAGNOSES
General	Poor skin turgor Dry mucous membranes	Dehydration
Vital signs	Fever	Gastroenteritis, cholecystitis, appendicitis, hepatitis Bowel perforation
	Tachycardia, orthostatic changes	Dehydration
HEENT	Nystagmus	Labyrinthitis Vertebrobasilar insufficiency Cerebellar infarct or bleed CPA tumor
	Papilledema	Increased ICP from CNS tumor or bleeding
Neck	Goiter	Thyroid disease
Lungs	Rales	Pneumonia
Heart	Arrhythmia Murmur	Acute myocardial infarction or other cardiac pathology
Abdomen	Abdominal distention	Bowel obstruction, gastroparesis
	Peristaltic waves	Gastric outlet obstruction
	High-pitched bowel sounds	Bowel obstruction
	Decreased bowel sounds	Ileus
	Hernias or surgical scars	Possible bowel obstruction
	Peritoneal signs	Appendicitis, cholecystitis Perforated viscus
	Mass	Pyloric stenosis
Neurologic	Abnormal mental status Cerebellar findings Cranial nerve findings	CNS pathology

CNS, central nervous system; *CPA,* cerebellopontine angle; *HEENT,* head, eyes, ears, nose, throat; *ICP,* intracranial pressure.

medication list, including over-the-counter drugs and supplements, should be elicited in the history.

Physical Examination

The important physical examination findings are outlined in Table 29-2. During evaluation, findings of jaundice, lymphadenopathy, nystagmus, fever, and goiter can help determine the cause of the disease. Oral examination may reveal loss of dental enamel commonly seen with bulimia. Abdominal examination may reveal ascites, distention, hernias, abdominal tenderness and masses, organomegaly, or hyperactive or hypoactive bowel sounds, with appropriate laboratory testing for occult blood in the stool. Orthostatic vital signs often are obtained but are of limited value in determination of the extent of dehydration, and results should not alter clinical decision-making. It also is important to evaluate neurologic status (including cranial nerve evaluation, funduscopic examination, and gait observation) to rule out a central cause of a patient's symptoms. Provocative testing for vertigo such as with the Nylen-Barany test may elicit nausea and vomiting. Attentive physicians may elicit evidence of depression or anxiety that may lead to a psychiatric diagnosis.

In children the examination should search for other additional diagnostic clues. A bulging fontanelle (meningitis), projective vomiting (pyloric stenosis), unusual odors (metabolic cause), visible bowel loops (obstruction), enlarged parotid, and loss of dental enamel (bulimia) point to specific causative disorders. Most of these disorders are age dependent.

Ancillary Studies

Because of the broad differential diagnosis for nausea and vomiting, there is no standard panel of laboratory tests. Appropriate testing is determined by the specifics of the history and physical examination. The following general guidelines regarding specific tests are useful.

Complete blood count: Most patients do not require a complete blood count for the diagnosis and management of nausea and vomiting. Elevated hemoglobin may suggest dehydration, but other tests are better for this purpose. An elevated white blood count is entirely nonspecific and of no discriminatory value.

Serum electrolytes: Measurement of serum electrolytes is not indicated in most cases of vomiting. Severe, protracted vomiting can cause a hypochloremic, hypokalemic metabolic alkalosis. Patients with this history or with clinical evidence of dehydration should undergo electrolyte testing. In general, serum electrolyte testing is indicated only in patients with symptoms lasting longer than 3 days or signs of significant dehydration who require intravenous fluid to replenish vascular volume.

Blood urea nitrogen and creatinine: A blood urea nitrogen–to-creatinine ratio greater than 20:1 implies significant dehydration.

Serum lipase: Lipase determination is indicated in cases of suspected pancreatitis.

Urine tests: A urine pregnancy test should be performed in all women of childbearing age with nausea and vomiting. A urine analysis that shows nitrites, leukocyte esterase, white blood cells, and bacteria suggests a urinary tract infection. Ketones may support a diagnosis of diabetic ketoacidosis or prolonged starvation state. Hematuria indicates a possible renal calculus.

Cultures: Blood cultures may be indicated in the febrile patient with nausea and vomiting who requires admission to hospital. Urine cultures may be necessary to determine an underlying cause of fever, and stool cultures looking for enteric pathogens, parasites, or leukocytes may be valuable.

Liver function and ammonia tests: Liver function tests are indicated in cases of suspected hepatitis or biliary disease. Ammonia testing is useful if liver failure is suspected.

Serum drug levels: Serum drug levels may be important in determining the cause of nausea and vomiting in patients on theophylline, digoxin, or salicylates, especially in elders who are taking medication without supervision.

Abdominal imaging: Flat and upright plain radiographs are indicated only for patients with suspected bowel obstruction or ileus in whom computed tomography (CT) scanning is not planned. CT scan of the abdomen has supplanted plain radiography for the evaluation of many patients with suspected obstruction because of the improved ability to discern the cause of the problem in addition to the presence of obstruction. An abdominal ultrasound study is indicated in cases of suspected choledocholithiasis or cholecystitis in adults and suspected pyloric stenosis and intussusception in children. Imaging studies such as cranial CT scan or magnetic resonance imaging (MRI) may be needed for evaluation for possible CNS trauma, tumor, or infectious causes of nausea and vomiting.

Electrocardiogram: An electrocardiogram (ECG) is indicated in cases of suspected coronary artery ischemia.

Thyroid function tests: Although not usually available during the patient's stay in the ED, thyroid function tests may indicate a thyroid cause for the vomiting.

DIFFERENTIAL DIAGNOSIS

Clinical and diagnostic findings are helpful in differentiating among the common and catastrophic causes of nausea and vomiting (Table 29-3). The differential diagnosis in adults is extensive;

www.ketabpezeshki.com 66485457-66963820

Table 29-3 Disorders Commonly Associated with Vomiting

DISORDER	HISTORY	PREVALENCE	PHYSICAL EXAMINATION	USEFUL TESTS	COMMENTS
Nausea and vomiting of pregnancy (NVP)	Vomiting occurs predominantly in the morning. Associated breast tenderness. NVP typically starts in weeks 4-7, peaks in weeks 10-16, and disappears by week 20. Vomiting that begins after week 12 or continues past week 20 should prompt a search for another cause.	Very common Affects 75% of all pregnancies	Benign abdomen	Urine pregnancy test Serum electrolytes, urine ketones to exclude hyperemesis gravidarum	Consider NVP in all females of childbearing age. Prognosis for mother and infant is excellent. NVP is associated with a decreased risk of miscarriage, fetal growth retardation, and fetal mortality.
Hyperemesis gravidarum	Severe, protracted form of NVP. No universally accepted definition of the disease. Generally accepted hallmarks include 5% weight loss, ketonuria, and electrolyte disturbance. Hyperemesis is associated with multiple gestation, molar pregnancy, and nulliparity.	Uncommon Affects <1% of pregnancies	Signs of dehydration Benign abdomen	β-hCG Urinalysis for ketones Serum electrolytes Ultrasound examination to exclude molar pregnancy or multiple gestation	Most studies have found no adverse outcomes for the fetus. A few studies, however, have shown a correlation with fetal growth retardation.
Gastroenteritis	Fever, diarrhea, and crampy abdominal pain. Vomiting and pain occur early, usually followed by diarrhea within 24 hr.	Very common	Benign abdomen	Usually not necessary	Early gastroenteritis, when only vomiting and periumbilical pain are present, may be confused with early appendicitis. Diarrhea is usually in the diagnosis of gastroenteritis.
Gastritis	Epigastric pain, belching, bloating, fullness, heartburn, and food intolerance. Use of NSAIDs or ETOH common.	Very common	Mild epigastric tenderness may be present.	Lipase and pregnancy test may be necessary to exclude other diagnoses.	Removal of inciting agent along with antacid therapy will resolve symptoms in most patients.
Peptic ulcer disease (PUD)	Epigastric pain present in 90% of cases. Classically, duodenal ulcer pain is relieved by food whereas gastric ulcer pain is made worse. Presence of severe pain should raise suspicion of perforation.	Very common	Mild epigastric tenderness	Hemoglobin if bleeding is suspected Heme-positive stool Upright abdominal film if perforation is suspected	Three major causes of PUD are NSAIDs, *Helicobacter pylori* infection, and hypersecretory states.
Biliary disease	Abdominal pain may be midepigastric or right upper quadrant (RUQ). Onset frequently after a fatty meal. May have history of similar episodes in the past.	Very common	RUQ tenderness present in most cases. If instructed to breathe deeply during palpation in the RUQ, the patient experiences heightened tenderness and inspiratory arrest (Murphy's sign).	WBCs Lipase Serum bilirubin Alkaline phosphatase RUQ ultrasound examination ERCP	Normal temperature, WBCs, and spontaneous resolution of symptoms suggest biliary colic. Fever, Murphy's sign, elevated WBCs, and suggestive ultrasound indicate cholecystitis.
Myocardial infarction (MI)	Patients typically have substernal chest pain that may radiate to left arm or jaw. Often associated with dyspnea, diaphoresis, or dizziness.	Common	Patients often are anxious and in distress from pain. No diagnostic examination findings.	ECG (new Q waves, ST segment changes, or T wave inversions) troponin	Not all patients have chest pain. A subset of patients, particularly diabetics and elders, may have only nausea, vomiting, and epigastric discomfort.

Continued

etiologic categories include medication-induced causes, infectious and toxic causes, disorders of the GI tract, CNS causes, pregnancy-related nausea and vomiting, endocrine and metabolic disorders, radiation-induced nausea and vomiting, postoperative nausea and vomiting (PONV), unknown (as in cyclic vomiting), psychogenic causes, and other causes such as acute myocardial infarction and acute graft-versus-host disease.

PEDIATRIC CONSIDERATIONS

The evaluation and management of pediatric patients with nausea and vomiting depend on age and likely causative disorders (Table 29-4). Mild degrees of reflux and associated regurgitation are common in the first few months of life, but vomiting in infancy can be associated with life-threatening illness. In the first week of

www.ketabpezeshki.com 66485457-66963820

Table 29-3 Disorders Commonly Associated with Vomiting—cont'd

DISORDER	HISTORY	PREVALENCE	PHYSICAL EXAMINATION	USEFUL TESTS	COMMENTS
Diabetic ketoacidosis (DKA)	Polydipsia and polyuria occur early. Without treatment, altered mental status and coma may develop. In patients with long-standing diabetes, DKA may be triggered by infection, trauma, MI, or surgery.	Common	"Fruity" breath odor results from serum acetone. Tachypnea occurs with attempts to "blow off" carbon dioxide to compensate for metabolic acidosis. Signs of dehydration may be present. Severe cases often manifest with altered mental status or coma.	Serum glucose, urine ketones, ABGs	DKA may be the first manifestation of diabetes in some patients. These patients often do not recognize the importance of polydipsia and polyuria. They often report only nausea, vomiting, and epigastric pain.
Pancreatitis	Presenting symptom is epigastric pain, which often radiates to the back. Most cases are caused by gallstones or alcoholism. Other causes include hypercalcemia, hyperlipidemia, drugs (sulfas and thiazides), ERCP.	Common	Epigastric tenderness is present. Associated paralytic ileus may cause abdominal distention and decreased bowel sounds. Frank shock may be present in severe cases.	Lipase WBCs, serum glucose, LDH, AST Hematocrit, BUN, calcium, ABGs	Criteria correlating with higher mortality: *At admission*—age >55 yr, WBCs >16,000/mm^3, glucose >200 dL, base deficit >4, LDH >350 IU/L, AST >250 U/L *Within 48 hours*—Hct drop of 10%, BUN >2 mg/dL, Po_2 <60 mm Hg, calcium <8 mg, fluid sequestration >4 L
Appendicitis	Abdominal pain classically begins in periumbilical region and later moves to right lower quadrant. Anorexia is common.	Common	Localized tenderness over right lower quadrant. Low-grade fever may be present.	WBCs Ultrasound Abdominal CT	Early appendicitis can be a difficult diagnosis to make. It is still frequently missed on the first physician encounter.
Bowel obstruction	Classically, abdominal pain consists of intermittent cramps occurring at regular intervals. The frequency of the cramps varies with the level of the obstruction; the higher the level, the more frequent the cramps. The location of the pain also varies with the level of the obstruction; high obstruction causes epigastric pain, midlevel obstruction causes periumbilical pain, colonic obstruction causes hypogastric pain.	Common	Abdominal distention, mild diffuse tenderness, and high-pitched "tinkling" bowel sounds may be present. Thorough search for hernias should be performed.	Supine and upright plain abdominal films Abdominal CT	Adhesions, hernias, and tumors account for 90% of bowel obstructions. Other causes include intussusception, volvulus, foreign bodies, gallstone ileus, inflammatory bowel disease, stricture, cystic fibrosis, and hematoma.
Carbon monoxide (CO) poisoning	Headache is usually present. CO poisoning often occurs during winter months when furnaces are turned on. Family members may have similar symptoms if they also have been exposed.	Uncommon	No reliable signs of early CO poisoning	CO level	Because CO is a tasteless, odorless gas, patients may not realize they have been exposed. It is important to keep a high index of suspicion during the cold months.
Boerhaave's syndrome	Patients may have neck, chest, or epigastric pain. Forceful, protracted vomiting usually causes the tear. Most cases follow a bout of heavy eating and drinking. Other reported causes include childbirth, defecation, seizures, and heavy lifting.	Uncommon	Tachypnea, tachycardia, and hypotension may be present. Escaped air from the esophagus may produce subcutaneous emphysema. Air in the mediastinum produces a "crunching" sound as the heart beats (Hamman's sign).	CXR may show pleural effusion, widened mediastinum, pneumothorax, or pneumomediastinum. Esophagogram with water-soluble contrast is definitive.	The classic presentation includes forceful vomiting, severe chest pain, subcutaneous emphysema, and multiple CXR findings. There is a growing body of evidence that most cases do not have this "classic" picture. In more subtle presentations, the diagnosis can be difficult to make.

ABGs, arterial blood gases; *AST,* aspartate aminotransferase; *β-hCG,* β-human chorionic gonadotropin; *BUN,* blood urea nitrogen; *CT,* computed tomography; *CXR,* chest radiography; *ECG,* electrocardiogram; *ERCP,* endoscopic retrograde cholangiopancreatography; *ETOH,* ethyl alcohol; *Hct,* hematocrit; *LDH,* lactate dehydrogenase; *NSAID,* nonsteroidal anti-inflammatory drug; *Po_2,* partial pressure of oxygen; *WBC,* white blood cell.

www.ketabpezeshki.com 66485457-66963820

Table 29-4 Etiology of Nausea and Vomiting in Pediatric Age Groups

ETIOLOGIC CATEGORY	NEWBORN	INFANT	CHILD	ADOLESCENT
Infectious	Sepsis, meningitis, UTI, thrush	Pneumonia, otitis media, thrush	Gastroenteritis	Gastroenteritis, URI
Anatomic	Atresia and webs, malrotation, stenosis, meconium ileus, Hirschsprung's disease	Pyloric stenosis, intussusception, Hirschsprung's disease	Bezoars, chronic granulomatous disease	PUD, superior mesenteric syndrome
Gastrointestinal	Reflux, overfeeding, gastric outlet obstruction, volvulus	Reflux, gastritis, milk intolerance	Appendicitis, pancreatic, hepatitis, other food intolerance	Achalasia, hepatitis
Neurologic	Subdural hematoma, hydrocephalus	Subdural hematoma	Neoplasia, migraine, Reye's syndrome, motion sickness, hypertension	Neoplasia, migraine, motion sickness, hypertension
Metabolic	Organic or amino acidemias, urea cycle defects, galactosemia, hypercalcemia, phenylketonuria, kernicterus	Hereditary fructose intolerance, disorders of fatty acid metabolism, uremia, adrenal hyperplasia, kernicterus	Diabetes, vitamin A excess	Diabetes, pregnancy, acute intermittent porphyria
Other	Idiopathic, cardiac failure	Rumination, cardiac failure	Cyclic vomiting syndrome, toxins, food poisoning, Munchausen syndrome by proxy	Psychogenic, anorexia

Adapted from Li HK, Sunku BK: Vomiting and nausea. In Wyllie R, Hyams JS, eds: Pediatric Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management. Philadelphia: WB Saunders; 2005:127-149.
PUD, peptic ulcer disease; *URI,* upper respiratory infection; *UTI,* urinary tract infection.

life, obstructive lesions of the alimentary tract, inborn errors of metabolism, and serious infectious processes are associated with vomiting. After the first week of life, pyloric stenosis needs to be considered. The diagnosis of "feeding problems" should be considered a diagnosis of exclusion. After the first month of life, infections, metabolic diseases, cow's milk intolerance, failure to thrive, and subdural hematoma from abuse should be prime considerations. Thereafter, various disorders are associated with vomiting, including recurrent cyclic vomiting, acute surgical emergencies, food poisoning, toxic ingestion, Henoch-Schönlein purpura, pneumonia, and diabetic ketoacidosis. Anorexia nervosa and bulimia should be considered in teenagers with recurrent vomiting.

MANAGEMENT

Symptomatic relief of nausea and vomiting should not await identification of the underlying cause. Decreased oral intake is a major cause of dehydration and malnutrition. If the patient is able to take oral liquids, a solution containing sodium, carbohydrate, and water is recommended. Many sports drinks contain the proper balance of these elements.[1] Patients who are dehydrated and in whom intake of oral fluids is not possible or is contraindicated should be given intravenous fluids. Hypokalemia is rarely of clinical significance but may be found with profound vomiting secondary to contraction metabolic alkalosis. Treatment of the underlying condition with administration of intravenous fluids is indicated. Placement of a nasogastric tube is an option in some cases of refractory vomiting in patients with gastroparesis, pancreatitis, or bowel obstruction.

Pharmacologic management of patients with nausea and vomiting is outlined in Table 29-5. To allow the physician to make an appropriate choice for each patient, the pharmacologic therapies available may be classified into histamine antagonists, muscarinic antagonists, dopamine antagonists, and serotonin antagonists.

The phenothiazines are widely used as general-purpose antiemetics. These agents have multiple complex mechanisms of action. The antiemetic effect is apparently through blockade of the dopamine D_2 receptor in the CTZ. Prochlorperazine (Compazine), droperidol (Inapsine), haloperidol (Haldol), and promethazine

Table 29-5 Commonly Used Medications for the Treatment of Nausea and Vomiting

MEDICATION	DOSE	COMMENTS
Promethazine (Phenergan)	*Adult:* 12.5-25 mg IV, IM, PO, or by rectum *Pediatric:* 0.25-1 mg/kg/dose q4-6h prn IV, IM, PO, or by rectum; max 25 mg/dose	May be repeated every 4-6 hr until cessation of vomiting. May cause dry mouth, dizziness, blurred vision. Boxed warning for use under 2 yr old.
Prochlorperazine (Compazine)	*Adult:* 5-10 mg IM or PO; 2.5-10 mg IV; 25 mg by rectum *Pediatric:* 0.4 mg/kg/24 hr tid-qid PO or by rectum; 0.1-0.15 mg/kg/dose tid-qid IM; max 40 mg/24 hr	May be repeated every 4 hr IV or IM or every 12 hr by rectum until cessation of vomiting. May cause lethargy, hypotension, extrapyramidal effects.
Metoclopramide (Reglan)	*Adult:* 10 mg IM or IV, may repeat q6h *Pediatric:* 1-2 mg/kg/dose q2-6h IV q2-3h	May cause dystonic reactions, tardive dyskinesia, neuroleptic malignant syndrome.
Ondansetron (Zofran)	*Adult:* 4 mg IV single dose *Pediatric:* up to 40 kg: 0.1 mg/kg; >40 kg: 4 mg/dose IV single dose	May cause headache, dizziness, and musculoskeletal pain.

IM, intramuscularly; *IV,* intravenously; *PO,* orally; *prn,* as needed.

(Phenergan) are commonly used medications in this class. Mild to moderate side effects are fairly common and include dystonic reactions, sedation, and feelings of restlessness. These side effects may be treated with diphenhydramine (Benadryl) or benztropine (Cogentin). Although prochlorperazine was found to be more effective in reducing vomiting than promethazine, use of prochlorperazine has been reported to be associated with a 16% incidence of akathisia and a 4% incidence of dystonia, so patients should be advised about this potential and its mitigation with diphenhydramine or benztropine. Neuroleptic malignant syndrome, blood dyscrasias, and cholestatic jaundice have been documented with use of phenothiazines but are extremely rare.

www.ketabpezeshki.com 66485457-66963820

The serotonin receptor antagonists, such as ondansetron, granisetron, and tropisetron, have generated much interest because of their beneficial effect in chemotherapy-induced emesis. Their principal site of action is the area postrema, although they also affect receptors in the GI tract. The antiserotonin agents have been used with success for vomiting related to various drug ingestions.

The side effects of the serotonin receptor antagonists are mild and include headache and constipation.

The prokinetic agents are useful in patients with gastroparesis, gastroesophageal reflux disease, and other putative dysmotility syndromes. Metoclopramide (Reglan) has the most applicability in the ED. It has dopamine antagonist activity at the CTZ and exerts anticholinergic and antiserotonin effects. The primary effect is increased gastric emptying; the exact mechanism for this is not understood. Metoclopramide has multiple antiemetic actions and may be used as a general-purpose agent. Metoclopramide has been associated with tardive dyskinesia, prompting the Food and Drug Administration to issue a black box warning.[2] The most common side effects of metoclopramide are restlessness, drowsiness, and diarrhea. These effects are usually mild and transient.

Antihistamines are useful in nausea and vomiting associated with motion sickness and vertigo. Agents such as dimenhydrinate (Gravol, Dramamine) and meclizine (Antivert) directly inhibit vestibular stimulation and vestibular-cerebellar pathways. Their anticholinergic effect also may contribute to their effectiveness in vertigo and motion sickness. Antihistamines have some role as general antiemetics but are better used in the prevention of motion sickness; for nausea and vomiting, they are less effective than the phenothiazines. The most common side effects of antihistamines are drowsiness, blurred vision, dry mouth, and hypotension. The newer, less-sedating antihistamines, such as cetirizine and fexofenadine, are thought to be less effective as antiemetics.

The anticholinergic agent scopolamine in a transdermal patch (Transderm Scop) or hyoscine (Buscopan) in an oral form may be used for prophylaxis and treatment of motion sickness. These agents also have mild efficacy in preventing cytotoxic chemotherapy-related nausea and vomiting but are not useful in the emergency department (ED).

Benzodiazepine medications have been used for nausea and vomiting with variable results. Limited studies have evaluated the efficacy of benzodiazepines in the treatment of hyperemesis gravidarum, in prophylaxis for emetogenic chemotherapy, and preoperatively for minor gynecologic surgery. Although this aspect was not directly measured in these studies, the researchers inferred that part of the response may be related to the anxiolytic component.[3-5] No studies have addressed the use of benzodiazepines to treat nonspecific nausea and vomiting in an ED population.

An oral neurokinin-1 antagonist, aprepitant (Emend), has been found to be an effective adjunctive agent for use in patients undergoing cancer chemotherapy.[6] Aprepitant blocks the effects of substance P in the brain. Currently, it is not indicated for use in patients with established nausea and vomiting.

Adjuncts to pharmacologic agents have been investigated with limited results. Increased inhaled oxygen as well as ginger and ginger extract have not been found to be effective. Investigations of intravenous fluids have not been definitive in the treatment of nausea and vomiting. The use of acupressure point P6 on the wrist has been found to be effective as compared with placebo.[7]

The medication choice is directed at the underlying cause of the nausea and vomiting, if known, such as motion sickness, PONV, or nausea and vomiting related to cancer chemotherapy. For all other patients, the choice of antiemetic agent has not been well studied in emergency medicine. One study found droperidol to be more effective than prochlorperazine or metoclopramide as compared with placebo for moderate to severe nausea of any cause.[8] There also has been limited research regarding the preferred agents for the treatment of nausea and vomiting in the field. One study found that ondansetron was moderately effective in the treatment of nausea and vomiting in this setting.[9] The need for antiemetics and the response to therapy may be measured with scales similar to those used for pain assessment, such as the visual analog scale and the verbal categorical scale.[10]

As with adults, the underlying cause of nausea and vomiting in children is first addressed in determining treatment choices. Most agents used in adults are recommended for children in a weight-based dosing regimen. Ondansetron and metoclopramide have value for antiemetic treatment to reduce nausea and vomiting in pediatric patients. These agents are particularly effective in improving the ability of patients with gastroenteritis to maintain oral hydration.[11]

Special Situations

Medications such as antihistamines are frequently used in the mistaken belief that they reduce the incidence of nausea and vomiting when opioid analgesics are administered in the ED for pain control. Studies have demonstrated that the incidence of nausea and vomiting related to opioid administration in the ED is low and that these medications have little efficacy in reducing nausea and vomiting.[12,13]

Many agents have been advocated for the treatment of nausea and vomiting of pregnancy (NVP). The treatments include nonpharmacologic methods—avoiding triggers, making dietary changes, using acupuncture or acupressure, taking ginger, and undergoing behavioral therapy—and pharmacologic therapies—pyridoxine, antihistamines, metoclopramide, ondansetron, or prochlorperazine. Hyperemesis gravidarum is treated essentially the same as NVP. For mild symptoms, pyridoxine (vitamin B_6), acupressure, ginger, and administration of antiemetics including antihistamines, metoclopramide, ondansetron, prochlorperazine, and phenothiazines may be used. Pyridoxine, acupressure, and ginger are thought to be of benefit but are not commonly used in the ED. For severe symptoms, hospitalization, fluids, corticosteroids, and electrolyte replacement may be needed. No specific medication has been shown to be superior to others in the treatment of hyperemesis gravidarum.[11]

Chemotherapy-related nausea and vomiting may be seen in ED patients. The chemotherapy-induced nausea and vomiting may be acute (up to 24 hours) or delayed (after 24 hours).[13] The incidence of nausea and vomiting is correlated with the emetic potential of the chemotherapeutic agents, the patient's risk factors and other comorbid disorders, and antiemetic treatment. Patients commonly are given the serotonin antagonists dexamethasone and aprepitant for both immediate and delayed prophylaxis. Cannabinoids also have been used to control chemotherapy-induced nausea and vomiting. Choice of agents for the ED treatment of chemotherapy-induced vomiting has not been studied, but the serotonin antagonists and aprepitant are often used.

DISPOSITION

Hospital admission is appropriate when the patient has a significant underlying disease, has an unclear diagnosis and responds poorly to fluid and antiemetic therapy, continues to experience uncontrolled emesis refractory to medication, or is at the extremes of age with poor response to treatment. More difficult disposition decisions are related to patients in whom the diagnosis is unclear and prospects for timely follow-up are poor (e.g., the patient has no family physician, lacks transportation, is indigent, habitually abuses drugs or alcohol, or has a language barrier). Discharge may be considered if no serious underlying illness is present, the

www.ketabpezeshki.com 66485457-66963820

response to fluid and antiemetic therapy is good, the patient is able to take clear liquids before discharge, and the prospects for follow-up and observation at home are favorable.

Close follow-up often is advisable for discharged patients, preferably with their primary care physician, in 24 to 48 hours. At discharge, the patient is prescribed medications as needed and is advised to restart oral intake with small feedings of a liquid diet with gradual return to a normal diet. Some experts have recommended the nausea and vomiting diet, which requires the least amount of gastric neuromuscular work. It is a three-step diet: Sports drinks and bouillon are recommended in step 1; soups are recommended in step 2; and foods that require the least amount of gastric "work" are recommended in step 3, such as meals high in protein and low in lipids.[13] Evidence supporting this recommendation, though, is scant. Clear instructions are given to return to the ED if there is a recurrence, change, or deterioration in symptoms.

Causes for nausea and vomiting frequently remain undiagnosed. Some cases declare themselves or resolve over time; reevaluation and close follow-up are imperative for patients with continuing symptoms. In patients with persistent or recurring symptoms, psychogenic causes or cyclic vomiting syndrome should be considered.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Hartling L, et al: Oral versus intravenous rehydration for treating dehydration due to gastroenteritis in children. *Cochrane Database Syst Rev* 2006; (3):CD004390.
2. U.S. Food and Drug Administration: *Metoclopramide-containing drugs*. Available at www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumaNMedicalProducts/ucm106942.htm. Accessed July 1, 2011.
3. Tasci Y, Demir B, Dilbaz S, Haberal A: Use of diazepam for hyperemesis gravidarum. *J Matern Fetal Neonatal Med* 2009; 22:353-356.
4. Perwitasari DA, et al: Anti-emetic drugs in oncology: pharmacology and individualization by pharmacogenetics. *Int J Clin Pharm* 2011; 33:33-43.
5. Fujii Y, Itakura M: A prospective, randomized, double-blind, placebo controlled study to assess the antiemetic effects of midazolam on postoperative nausea and vomiting in women undergoing laparoscopic gynecologic surgery. *Clin Ther* 2010; 32;1633-1637.
6. Braude D, et al: Antiemetics in the ED: A randomized controlled trial comparing 3 common agents. *Am J Emerg Med* 2006; 24:177.
7. Meek R, Epi MC, Kelly AM, Hu XF: Use of the visual analog scale to rate and monitor severity of nausea and monitor severity of nausea in the emergency department. *Acad Emerg Med* 2009; 16:1304-1310.
8. Stork CM, Brown KM, Reilly TH, Secreti L, Brown LH: Emergency department treatment of viral gastritis using intravenous ondansetron or dexamethasone in children. *Acad Emerg Med* 2006; 13:1027.
9. Paoloni R, Talbot-Stern J: Low incidence of nausea and vomiting with intravenous opiate analgesia in the ED. *Am J Emerg Med* 2002; 20:604.
10. Bradshaw M, Sen A: Use of a prophylactic antiemetic with morphine in acute pain: Randomized controlled trial. *Emerg Med J* 2006; 23:210.
11. Jewell D, Young G: Interventions for nausea and vomiting in early pregnancy. *Cochrane Database Syst Rev* 2003; 4:CD000145.
12. Carlisle JB, Stevenson CA: Drugs for preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev* 2006; 3:CD004125.
13. Herrstedt J, Dombernowsky P: Anti-emetic therapy in cancer chemotherapy: Current status. *Basic Clin Pharmacol Toxicol* 2007; 101:143.

www.ketabpezeshki.com 66485457-66963820

Chapter 30

Gastrointestinal Bleeding

Eric Goralnick and David A. Meguerdichian

PERSPECTIVE

Epidemiology

Gastrointestinal bleeding (GIB) accounts for more than 1 million hospitalizations annually in the United States, with significant morbidity, mortality, and economic burden.[1] GIB is traditionally classified by the bleeding source—upper GIB (UGIB) is proximal and lower GIB (LGIB) is distal to the ligament of Treitz in the terminal duodenum.

UGIB accounts for more than 500,000 U.S. hospital admissions annually, with approximately 165 incidents per 100,000 patients.[1] Mortality rates have remained consistent at 13 to 14% over the past two decades despite advances in medical therapy, intensive care unit (ICU) management, endoscopy, and surgery.[2] An increasing proportion of elderly patients, who may die owing to comorbid conditions, and increases in the number of cirrhotic and variceal patients may contribute to the lack of change in mortality rates. In the United States, hospitalized patients with and without complications of nonvariceal UGIB had a mean length of stay of 4.4 and 2.7 days and hospitalization costs of $5632 and $3402 (2004 U.S. dollars), respectively.[3]

The incidence of LGIB in the United States is approximately 20.5 per 100,000 patients, with a mortality rate of 4%. Age greater than 70 years, intestinal ischemia, comorbid illness, coagulation defects, transfusion of packed red blood cells (RBCs), and male gender are the predictors of increased LGIB mortality.

DIAGNOSTIC APPROACH

Differential Considerations

The characteristics of the bleed and the age of the patient can help determine the cause of the GIB. UGIB can routinely manifest as bloody or coffee-ground–like vomit known as *hematemesis* or as dark, tarry stools known as *melena.* In adults, peptic ulcer disease, erosive gastritis, and esophageal varices account for the majority of these cases[4,5] (Table 30-1). In fact, peptic ulcers make up more than half of all acute cases of UGIB seen in the emergency department (ED). However, in inner city populations, varices and gastritis are more prevalent. In pediatric patients, gastric and duodenal ulcers, esophagitis, gastritis, esophageal varices, and Mallory-Weiss tears account for most cases of UGIB, in descending order of frequency. Contrary to this, LGIB usually produces bright red or maroon blood per rectum, known as *hematochezia.* Anorectal sources, such as hemorrhoids, are the most common causes of LGIB in all age groups.[6] In adults, the most common sources of hematochezia are colonic diverticula and angiodysplasia.[7] Other noteworthy causes include colitis caused by ischemia, infection, and inflammatory bowel disease. Major causes of LGIB in children include anorectal fissures and infectious colitis. Bleeding can also be caused by intussusception and Meckel's diverticulum in infants and toddlers. Despite diagnostic advances for all ages, the source of GIB is not identified in 8 to 14% of patients.[2]

Death from exsanguination resulting from GIB is rare. However, there are two causes of GIB that may rapidly cause death if not recognized and mitigated: esophageal varices and aortoenteric fistula. The former is the single most common source of massive UGIB and has a mortality rate of 30%. The latter is caused when an abdominal aortic aneurysm or, more commonly, an aortic graft adheres to and erodes through a bowel wall. Aortoenteric fistula is a rare but rapidly fatal cause of LGIB.[7] As is the case for any patient with acute massive hemorrhage, prompt consultation with a surgeon is warranted when aortoenteric fistula is a likely diagnosis.

Finally, in the differential considerations, one must determine if in fact the patient is having actual GIB. Epistaxis, dental bleeding, or red food coloring can mimic the appearance of hematemesis. Bismuth-containing medications and iron supplements can create melanotic-appearing (but guaiac-negative) stools. Vaginal bleeding, gross hematuria, and partially digested red foods (such as beets) can all be mistaken for hematochezia.[8] Unless an alternative diagnosis is clearly evident, the appropriate approach is to continue with the workup for GIB.

Pivotal Findings

The approach to the GIB patient requires a thorough history centering on the gastrointestinal tract and on the timing, quantity, and appearance of the bleeding. Relevant comorbid conditions should be reviewed as well. The extent of the history will be dictated by the severity of the complaint and the hemodynamic stability of the patient on ED arrival. Reviewing the patient's vital signs, appearance of the stool, and basic laboratory studies will help in triaging and initiating the workup of the bleeding source.

Medical History

A useful starting point for the clinician is to determine the time of onset, duration of symptoms, and relevant supporting historical facts.

1. *Context:* The context of the bleeding can help explain its cause. For instance, if a patient complains of bright red blood per rectum after several days of constipation and straining, that presentation suggests an anorectal source for the bleeding. Alternatively, a patient with hematemesis after several earlier episodes of retching would lead one to

www.ketabpezeshki.com 66485457-66963820

Table 30-1 Common Causes of Gastrointestinal (GI) Bleeding in Adults and Children

	ADULTS	CHILDREN
Common causes of upper GI bleeds	Peptic ulcers (gastric more than duodenal) Gastric erosion Esophagogastric varices Mallory-Weiss tears Esophagitis Gastric cancer	Duodenal ulcers Gastric ulcers Esophagitis Gastric erosion Esophageal varices Mallory-Weiss tears
Common causes of lower GI bleeds	Diverticular disease Angiodysplasia Colitis (inflammatory, infectious, ischemic) Anorectal sources Neoplasm Upper GI bleeding	Anorectal fissure Infectious colitis Inflammatory bowel disease Juvenile polyps Intussusception Meckel's diverticulum

Table 30-2 Characteristics of Patients with High-Risk Gastrointestinal (GI) Bleeds

Medication use
- Aspirin
- Nonsteroidal anti-inflammatory drugs
- Steroids
- Anticoagulants (warfarin, heparin)
- Chemotherapeutic agents

History of peptic ulcer disease
Known liver disease, cirrhosis
Advanced age (older than 60 years)
Alcoholism
Current smoker
Chronic medical comorbidities
- Congestive heart failure
- Diabetes
- Chronic renal failure
- Malignancy
- Coronary artery disease

History of abdominal aortic aneurysm graft

suspect an esophageal tear. Finally, a patient with easy bruising and recurrent gingival bleeding might suggest a long-standing, underlying coagulopathy.

2. *Quantity:* Efforts should also be made to quantify the amount of blood lost during the bleeding event. Patients may describe the passage of large clots, blood changing the toilet bowl water red, or simply streaks of blood on the toilet paper. The patient's recollection of the bleed and its amount is usually poorly quantified and inaccurate. Often, the degree of bleeding is better gauged by assessing symptoms associated with significant intravascular loss such as dyspnea, lightheadedness, or chest pain.[9] These findings demonstrate signs of decreased oxygen-carrying capacity that often accompanies significant blood loss and should prompt a thorough and expeditious workup.
3. *Appearance:* Classifying the blood as hematemesis, melena, or hematochezia provides the initial clues to the source of bleeding. Vomiting of fresh blood or blood with the appearance of coffee grounds strongly suggests an upper GI (UGI) source. The passage of melena, dark digested stools, also suggests likely UGIB. In contrast, the presence of hematochezia, bright red or maroon stools, usually signifies LGIB. There are exceptions, however. In a hemodynamically unstable patient, bright red blood per rectum can represent brisk UGIB. Hematemesis rarely can arise from a source in the lower GI (LGI) tract that is proximal to an obstruction. Although the definitive cause and location of the bleed will usually be determined by the gastroenterologist, the emergency clinician uses the history to make a rough estimate of the source and help guide the initial workup.[8]
4. *Relevant medical history:* A review of the patient's relevant medical history and risk factors for bleeding should note whether a patient has had similar bleeding before and the location of the causative lesion (Table 30-2). This is especially important with UGIB, as the majority of these presentations are caused by rebleeding of previously identified sources. Next, identification of relevant comorbid diseases helps to risk stratify these patients in the context of their bleed. Patients with GIB and a history of coronary artery disease, congestive heart failure, liver disease, or diabetes have a higher mortality and therefore may require earlier or more extensive intervention.[8] A review of the patient's medications should pay particular attention to gastrotoxic substances, anticoagulants, and antiplatelet drugs. Medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, warfarin, clopidogrel, corticosteroids, and certain chemotherapeutic agents are known to increase the risk of GIB.[5,8] In addition, reviewing the patient's social history can identify activities that increase risk for GIB. Alcohol abuse is associated with gastritis and peptic ulcer disease. It can also result in cirrhosis, portal hypertension, and ultimately esophageal variceal bleeding. Smoking cigarettes results in slower healing and greater recurrence of ulcers. These two social habits are also closely associated with gastrointestinal malignancy—another, albeit rare, risk factor for GIB.

Physical Examination

Vital Signs. Hypotension and tachycardia can suggest moderate hypovolemia and can be the early indicators of impending shock.[5,8] Orthostatic vital signs, although frequently used, are of dubious value in determining volume status in the context of acute blood loss.

General Examination. Eye examination may show conjunctival pallor, suggesting blood loss anemia. In similar fashion, dermatologic changes can lend supporting evidence to the presence and cause of a GI bleed. Generalized pallor in a hemodynamically stable patient might indicate the anemia of a subacute or chronic GIB; in the unstable patient, pallor might reinforce the impression of massive blood loss. Cold, clammy skin on the extremities might signal significant volume loss consistent with hemorrhagic shock. Ecchymoses or petechiae suggest a coagulopathy. Finally, jaundice, palmar erythema, or spider angiomata suggests the possibility of UGIB from esophageal varices.[5]

The abdomen should be carefully examined for subtle findings that can help identify the source of bleeding. Hyperactive bowel sounds are a nonspecific finding, but might indicate UGIB, as intraluminal blood is a known cathartic that can stimulate peristalsis.[5] Tenderness to palpation can be seen in many cases of peptic ulcer disease. Severe, diffuse tenderness on examination warrants the consideration of bowel ischemia, mechanical obstruction, ileus, or bowel perforation. Evidence of peritonitis merits a rapid surgical consultation for possible operative management. The abdominal examination may also show further signs of portal hypertension with the presence of hepatomegaly, ascites, or caput medusae.[5] A rectal examination, with determination of the type of bleeding, should be performed in most patients with GIB. The examination should include evaluation of the external anus, a digital rectal examination, and anoscopy looking to

www.ketabpezeshki.com 66485457-66963820

identify possible bleeding sources such as hemorrhoids, polyps, or fissures.[5,7,8]

Emergency Department Studies

Occult Blood and Guaiac Bedside Testing. In patients with suspected UGIB, guaiac testing can be performed at the bedside to evaluate for occult blood even when stool appears normal. The test makes use of the pseudoperoxidase activity found in hemoglobin. When hydrogen peroxide is dripped onto the guaiac paper containing the stool sample, an oxidative reaction rapidly turns the paper blue. The test can actually be positive for up to 2 weeks after an acute bleed and thus is more useful at diagnosing chronic occult bleeding.[8] False positives can be triggered by ingestions of red meat, turnips, horseradish, vitamin C, methylene blue, and bromide preparations. Iron- and bismuth-containing medications can cause dark stools that will be guaiac negative. Similar testing is available for gastric contents but can be unreliable if minor trauma from the passage of a nasogastric (NG) tube or vomiting has caused occult bleeding.

Clinical Laboratory Testing

Laboratory studies can assist in the risk stratification of GIB. Minimum testing should include evaluation of the patient's hemoglobin, blood urea nitrogen (BUN), coagulation studies, and platelets. Hemoglobin does not immediately decline in the setting of an acute bleed, as whole blood is initially lost. Declines are appreciated after dilution from shifting extravascular fluids and intravenous hydration with crystalloid. Nevertheless, hemoglobin levels less than 10 have been positively correlated with higher rates of rebleeding and mortality. If significantly depressed, the hemoglobin level may also guide whether transfusion is required for the patient's resuscitation. In general, a hemoglobin less than 8 to 10 g/dL in a patient with GIB should prompt strong consideration of blood transfusion, with greater attention and a much lower threshold to transfuse in elders and those with significant comorbidities such as coronary artery disease.

BUN levels can be elevated in the setting of UGIB owing to the absorption of digested blood into the circulatory system during intestinal transit. The BUN can also be elevated from prerenal azotemia in the setting of hypovolemia. A BUN-to-creatinine ratio greater than 36 in the setting of no renal failure can be highly suggestive of UGIB.[5,8]

Coagulation studies, particularly prothrombin time (PT), should be undertaken to ensure that coagulopathy is not worsening the patient's blood loss. This becomes especially important in patients with liver disease or those taking therapeutic anticoagulants such as warfarin.

Other laboratory tests may be useful in a small percentage of patients with GIB. Electrolyte abnormalities may be present in patients with repeated or prolonged episodes of vomiting or diarrhea. Leukocytosis may represent the stress of the acute bleed, but the possibility of underlying infection should also be considered. A lactate level may be elevated in the setting of bowel ischemia or secondary to shock from hypovolemia and the resultant hypoperfusion. Laboratory findings may help guide risk stratification, resuscitation, and ultimate disposition.

Blood Bank

A blood bank sample should be sent for type and screen or type and crossmatch studies, depending on the severity of the patient's presentation. In cases of refractory shock or other unstable presentations, immediate transfusion can be provided with O-positive blood in most patients and with O-negative blood for women of childbearing age with an unknown Rh status. Type-specific blood should also be available within 15 minutes of the sample arriving at the blood bank. These options may be used as adjuncts, with few resultant transfusion reactions, until appropriate crossmatched blood is available.

Electrocardiogram

Because GIB and its subsequent anemia can reduce the oxygen-carrying capacity of blood, patients should be screened for signs of myocardial ischemia. An electrocardiogram (ECG) is recommended and is especially relevant in elders and those with known coronary artery disease who are at higher risk for ischemic events.[5,8-10] ECG findings consistent with myocardial ischemia should prompt immediate treatment according to current American College of Cardiology (ACC) guidelines; transfusion with packed RBCs will optimize oxygen delivery to the ischemic tissue.

Radiographic Imaging

Emergent imaging of the chest and abdomen in the ED setting is rarely indicated in the patient with acute GIB.[11] Although an upright chest radiograph may show free air if hollow viscus perforation has occurred, it is insensitive and nonspecific, and abdominal computed tomography (CT) scan is the preferred imaging modality. Identification of subdiaphragmatic air and peritoneal findings on abdominal examination suggest the possibility of bowel perforation and the need for immediate surgical evaluation. Abdominal plain radiographs are of no value for patients with GIB, unless bowel obstruction is strongly suspected. Unless perforation or significant gut ischemia is suspected, CT imaging of the solid abdominal organs is not indicated and does not alter the acute management and disposition of the patient with a GIB. Multidetector CT may have a role in identifying angiodysplasia and other localized bleeding sites throughout the GI tract.[4] Scintigraphy and angiography can also be used to localize the source of bleeding, and angiography may allow for therapeutic options via embolization.[4,12] These imaging modalities are rarely used in the acute ED setting, and their use is often based on hospital availability and consultant preference.

DIAGNOSTIC ALGORITHM

The diagnostic approach to the GIB patient involves a number of key decision points. First, the clinician should assess the patient's general appearance, vital signs, and volume status. This initial assessment can help triage the patient into a stable or unstable category. If the patient is unstable, resuscitation begins with the immediate placement of two large-bore intravenous catheters (18 gauge or larger) and crystalloid infusion with the aim of hemodynamic stabilization. Endpoints of adequate resuscitation would include appropriate vital signs, urine output greater than 1 mL/kg/hr, and appropriate mental status. Prompt blood transfusion is also considered.

The second decision point involves use of the historical facts and physical examination findings to determine if the patient has UGIB or LGIB. These details will help further risk stratify the GIB patient and establish the differential diagnosis. Once the presumptive origin of the bleed has been determined, the clinician should consider the anticipated hospital course of the patient.

The third decision point relies on the severity of the UGIB or LGIB to determine the ED management and disposition. Unstable UGIB will require emergent gastroenterology consultation for early endoscopy, consideration of definitive airway management, and admission to an ICU for continued resuscitation. Alternatively, patients who are young, reliable, and hemodynamically stable after a minor bleed in a clear context of a Mallory-Weiss tear can be discharged after an observation period of 12 hours in

www.ketabpezeshki.com 66485457-66963820

the ED or ED observation unit. Unstable LGIB patients require emergent surgical consultation. Management initially centers on proper resuscitation with fluids, blood products, and admission to the ICU. If the patient has been properly resuscitated in the ED and remains stable, admission to the medical floors for further workup and inpatient management is indicated. LGIB patients who are hemodynamically stable, are reliable, have no significant risk factors, and have a clearly visualized source of bleeding on examination can be safely discharged to follow up with their outpatient provider.

EMPIRICAL MANAGEMENT

Rapid identification of the bleeding source (i.e., UGI versus LGI tract), risk stratification, resuscitation, consultation, and disposition are the integral elements of this process. Initial management includes an assessment of airway, breathing, and circulation. Massive bleeding, active hematemesis, hypoxia, severe tachypnea, or altered mental status may necessitate tracheal intubation for protection and to supplement tissue oxygenation. Figure 30-1 outlines both diagnostic and management guidelines.

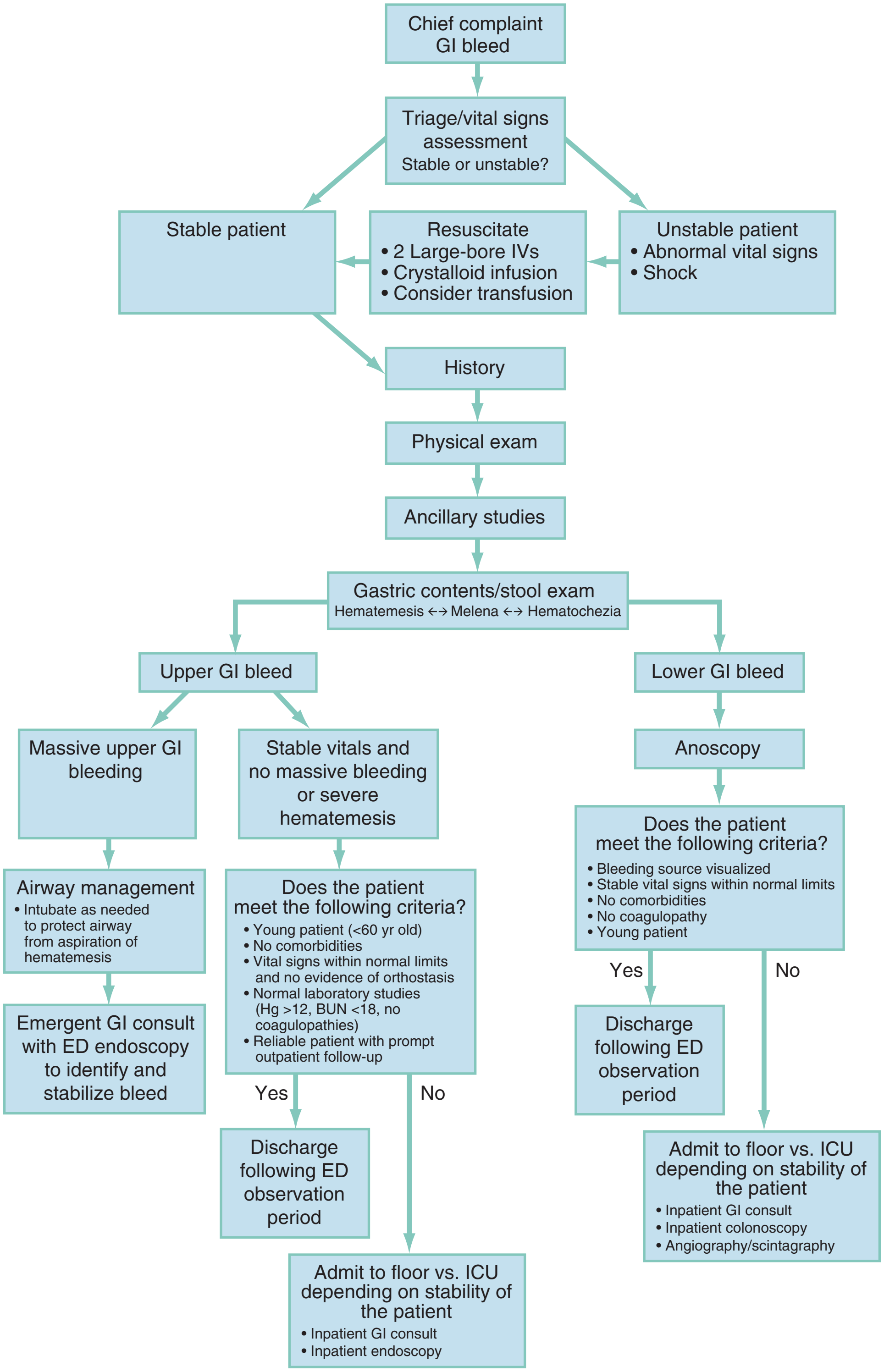


Figure 30-1. Diagnostic and management strategies for gastrointestinal bleeding. *BUN,* blood urea nitrogen; *ED,* emergency department; *GI,* gastrointestinal; *Hg,* hemoglobin; *ICU,* intensive care unit; *IV,* intravenous.

www.ketabpezeshki.com 66485457-66963820

Resuscitation

Hemodynamic instability and estimated volume loss should guide initial resuscitation. Patients should be placed on pulse oximetry, be administered supplemental oxygen, and receive early aggressive crystalloid resuscitation with two peripheral large-bore intravenous catheters. Cardiac telemetry should be initiated because demand ischemia and myocardial infarctions may occur in patients with GIB.

Blood Product Transfusion

Continued hemodynamic instability and/or ongoing hemorrhage dictates the need for blood transfusion. Factors such as age, comorbidities (ischemic heart disease, peripheral vascular disease, or heart failure), baseline hemoglobin and hematocrit levels, and evidence of cardiac, renal, or cerebral hypoperfusion should be considered in determining transfusion quantity. Blood transfusion side effects should be weighed against adverse outcomes of anemia. A recent meta-analysis of trauma, surgical, and intensive care observational studies found that massive transfusion was associated with a higher risk of death, nosocomial infection, multiorgan dysfunction, and acute respiratory distress.[13]

Coagulopathy, especially in patients with underlying liver disease or those requiring massive transfusions, should be corrected promptly. Correction of coagulopathy with fresh frozen plasma (FFP) or platelets is recommended but should not delay endoscopy.[14] Consensus guidelines call for the transfusion of one unit of FFP for every four units of packed RBCs transfused to replace coagulation factors.[14] Patients with fewer than 50,000 platelets/µL and active bleeding may need platelet transfusion.

Nasogastric Aspiration and Lavage

Once considered a standard emergent intervention, NG aspiration with gastric lavage is generally not indicated for evaluation of GIB. The sensitivity of NG aspiration and lavage for predicting UGIB is low, and the negative likelihood ratio in patients with melena or hematochezia without hematemesis is poor.[15] Fifteen percent of patients without bloody or coffee-ground material in NG aspirates are found to have high-risk lesions on endoscopy.[16] NG tube placement has been associated with severe complications including aspiration, pneumothorax, perforation, and gastric lesions and is a painful procedure. On some occasions a consulting gastroenterologist may wish to place an NG tube in hopes of improving endoscopic visibility (and accuracy) by evacuating gastric blood, but absent such an indication, placement of an NG tube in patients with suspected UGIB is not recommended.

Sengstaken-Blakemore Tube

Bedside balloon tamponade should be considered only in exsanguinating patients with likely variceal bleeding when endoscopy is not immediately available. Complications are common and significant, but intervention is indicated in the appropriate patient population owing to the high mortality associated with uncontrolled bleeding.

Medications

Several medications improve GIB outcomes. Infusion of high-dose proton pump inhibitors (PPIs) before endoscopy accelerates the resolution of signs of bleeding in ulcers and reduces the need for endoscopic therapy.[17] The recommended dosage is an 80-mg bolus of omeprazole intravenously, followed by 8 mg/hr for 3 days. High-dose oral PPIs have been shown in Asian populations to reduce the risk of rebleeding, the need for surgery, and the risk of death, but additional data are needed to determine whether those findings are generalizable to Western patient populations.[16]

Somatostatin and octreotide, synthetic analogues, are splanchnic vasoconstrictors that reduce portal hypertension and the risk of persistent bleeding, rebleeding, and transfusion requirements in patients with variceal bleeding.[18] Octreotide therapy should be empirically administered in patients with GIB and significant liver disease, a history of variceal bleeding, a history of alcoholism, or highly abnormal liver function tests. The recommended dose of octreotide is a 50-µg bolus followed by 50 µg/hr intravenously.

Vasopressin, administered by continuous intravenous infusion, also reduces splanchnic blood flow and portal hypertension. However, it has limited use owing to significant complications that include myocardial and mesenteric ischemia and infarction.

DEFINITIVE MANAGEMENT

Consultation

For patients with hemodynamic instability and severe bleeding, prompt gastroenterology consultation should be sought. Exsanguinating hemorrhage warrants emergent surgical consultation as well. Patients with severe LGIB warrant surgical consultation. Ongoing bleeding, severe anemia, or significant comorbidity (including advanced age, ischemic coronary disease, and so on) prompts consideration of admission to an ICU.

Endoscopy

Upper endoscopy is the most effective diagnostic and therapeutic intervention for UGIB, achieving hemostasis in more than 90% of cases. Endoscopic hemostasis has been shown to decrease rates of rebleeding, mortality, and urgent surgery.[19] Endoscopic treatments include injection therapy (e.g., saline, vasoconstrictors, sclerosing agents, tissue adhesives, or a combination thereof), thermal therapy (with the use of contact methods, such as multipolar electrocoagulation and heater probe, or noncontact methods, such as argon plasma coagulation), and mechanical therapy (principally endoscopic clips). Endoscopy within 13 hours of bleeding reduces mortality in high-risk patients.[20]

Colonoscopy

Urgent colonoscopy has variable diagnostic value for identification of a bleeding source in LGIB. Lesion visualization is maximized by bowel preparation with polyethylene glycol in brisk but not in severe hemorrhage.

Angiography

Angiography is used in a very small proportion of cases of GIB and requires a hemorrhage rate of greater than 0.5 mL/min to optimize detection of acute bleed. Although also potentially therapeutic, angiography has a high rate of complications, including acute renal failure, contrast reactions, and bowel infarction. CT angiography also has variable sensitivities reported for the detection of acute GIB.

Tagged Red Blood Cell Imaging

Tagged RBC imaging or nuclear scintigraphy involves erythrocyte injection to detect indolent or elusive bleeding and is primarily useful in the inpatient setting. Timing is essential—95 to 100% of scans performed within 2 hours of injection correctly localize bleeding sites, whereas substantially fewer scans performed after 2 hours localize bleeding accurately.

www.ketabpezeshki.com 66485457-66963820

Table 30-3 Blatchford Score*

ADMISSION RISK MARKER	SCORE COMPONENT VALUE
Blood urea nitrogen level (mg/dL)	
≥18.2 to <22.4	2
>22.4 to <28	3
>28 to <70	4
>70	6
Hemoglobin level for men (g/dL)	
>12 to <13	1
≥10 to <12	3
<10	6
Hemoglobin level for women (g/dL)	
≥10 to <12	1
<10	6
Systolic blood pressure (mm Hg)	
≥100 to <109	1
>90 to <99	2
<90	3
Other markers	
Pulse rate ≥100 beats/min	1
Presentation with melena	1
Presentation with syncope	2
Hepatic disease	2
Heart failure	2

*Range of scores is from 0 to 23 with high risk greater than 0.

Table 30-4 Clinical Rockall Risk Score*

	Score			
VARIABLE	0	1	2	3
Age (years)	<60	60-79	≥80	
Shock		HR >100 beats/min	SBP <100 mm Hg, IHD, CHF, any major comorbidity	Renal failure, liver failure, metastatic malignancy

CHF, congestive heart failure; *HR,* heart rate; *IHD,* ischemic heart disease; *SBP,* systolic blood pressure.
*Scores are calculated without endoscopic findings, and patients with scores greater than 0 are considered at high risk for developing adverse outcomes (recurrent bleeding, death).

DISPOSITION

Traditionally, all patients with GIB were hospitalized, but the changing health care and economic landscape has refocused efforts on outpatient management guidelines.

Several scoring systems to risk stratify UGIB patients into low- and high-risk groups have been developed and have undergone trials. These groups are based on adverse outcomes that are usually defined as a risk of recurrent bleeding of greater than 5% and greater than 1% mortality. Unfortunately, many of these scores rely on both clinical and endoscopic variables.

A consensus panel of 34 multidisciplinary experts from 34 countries identified the following clinical predictors as high risk: age older than 65 years; shock; poor overall health status; comorbid illness; low initial hemoglobin levels; melena; transfusion requirement; fresh red blood on rectal examination, in the emesis, or in the NG aspirate; sepsis; and elevated urea, creatinine, or serum aminotransferase levels.[14]

The Blatchford score (Table 30-3) and clinical (or pre-endoscopic) Rockall score (Table 30-4) use only clinical and laboratory data to risk stratify patients. In a recent retrospective review of 354 patients, the Blatchford score was 99.6% sensitive and the clinical Rockall was 90.2% sensitive at identifying patients as high risk (high-risk patients were defined as those who required a blood transfusion or endoscopic or surgical intervention during their admission).[21]

Once identified, high-risk UGIB patients require admission for inpatient monitoring, assessment, and consultation for definitive diagnosis and treatment.

Through use of these scores and others, low-risk UGI bleed patients can be identified as those with no comorbid diseases, normal vital signs, normal or trace positive result on stool guaiac testing, negative findings on gastric aspiration, normal hemoglobin and hematocrit, good support systems, proper understanding of signs and symptoms of significant bleeding, immediate access to emergent care, and follow-up within 24 hours.

Low-risk patients deemed appropriate candidates for discharge should be given clear instructions reviewing the signs and symptoms of significant GIB and when to contact the primary care physician or return to the ED. Specific education should include information regarding the likely source of bleeding, medication side effects, alcohol abstinence, and discontinuation of the use of aspirin and NSAIDs. These patients require early follow-up for a specific evaluation.

There are no clear guidelines on risk stratification for outpatient management of LGIB patients; therefore most are hospitalized for inpatient workups. Patients with LGIB not clearly caused by hemorrhoids, fissure, or proctitis should be admitted for nuclear medicine imaging or colonoscopy.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Lewis JD, Bilker WB, Brensinger C, Farrar JT, Strom BL: Hospitalization and mortality rates from peptic ulcer disease and GI bleeding in the 1990s: Relationship to sales of nonsteroidal anti-inflammatory drugs and acid suppression medications. *Am J Gastroenterol* 2002; 97:2540-2549.
2. van Leerdam ME, et al: Acute upper GI bleeding: Did anything change? Time trend analysis of incidence and outcome of acute upper GI bleeding between 1993/1994 and 2000. *Am J Gastroenterol* 2003; 98:1494-1499.
3. Viviane A, Alan BN: Estimates of costs of hospital stay for variceal and nonvariceal upper gastrointestinal bleeding in the United States. *Value Health* 2008; 11:1-3.
4. Farrell JJ, Friedman LS: Review article: The management of lower gastrointestinal bleeding. *Aliment Pharmacol Ther* 2005; 21:1281-1298.
5. Cappell MS, Friedel D: Initial management of acute upper gastrointestinal bleeding: From initial evaluation up to gastrointestinal endoscopy. *Med Clin North Am* 2008; 92:491-509, xi.
6. Manning-Dimmitt LL, Dimmitt SG, Wilson GR: Diagnosis of gastrointestinal bleeding in adults. *Am Fam Physician* 2005;71:1339-1346.
7. Barnert J, Messmann H: Management of lower gastrointestinal tract bleeding. *Best Pract Res Clin Gastroenterol* 2008; 22:295-312.
8. Westhoff J: Gastrointestinal bleeding: An evidence based ED approach to risk stratification. *Emerg Med Pract* 2004; 6:1-20.
9. Bellotto F, et al: Anemia and ischemia: Myocardial injury in patients with gastrointestinal bleeding. *Am J Med* 2005; 118:548-551.
10. Prendergast HM, Sloan EP, Cumpston K, Schlichting AB: Myocardial infarction and cardiac complications in emergency department patients admitted to the intensive care unit with gastrointestinal hemorrhage. *J Emerg Med* 2005; 28:19-25.
11. Andrews AH, Lake JM, Shorr AF: Ineffectiveness of routine abdominal radiography in patients with gastrointestinal hemorrhage admitted to an intensive care unit. *J Clin Gastroenterol* 2005; 39:228-231.
12. Mellinger JD, Bittner JG, Edwards MA, Bates W, Williams HT: Imaging of gastrointestinal bleeding. *Surg Clin North Am* 2011; 91:93-108.
13. Marik PE, Corwin HL: Efficacy of red blood cell transfusion in the critically ill: A systematic review of the literature. *Crit Care Med* 2008; 36:2667-2674.
14. Barkun AN, et al: International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med* 2010; 152:101-113.
15. Palamidessi N, Sinert R, Falzon L, Zehtabchi S: Nasogastric aspiration and lavage in emergency department patients with hematochezia or melena without hematemesis. *Acad Emerg Med* 2010; 17:126-132.
16. Gralnek IM, Barkun AN, Bardou M: Management of acute bleeding from a peptic ulcer. *N Engl J Med* 2008; 359:928-937.
17. Lau JY, et al: Omeprazole before endoscopy in patients with gastrointestinal bleeding. *N Engl J Med* 2007; 356:1631-1640.
18. Thabut D, Bernard-Chabert B: Management of acute bleeding from portal hypertension. *Best Pract Res Clin Gastroenterol* 2007; 21:19-29.
19. Barkun A, Bardou M, Marshall JK; Nonvariceal Upper GI Bleeding Consensus Conference Group: Consensus recommendations for managing patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med* 2003; 139:843-857.
20. Lim LG, et al: Urgent endoscopy is associated with lower mortality in high-risk but not low-risk nonvariceal upper gastrointestinal bleeding. *Endoscopy* 2011; 43:300-306.
21. Chen IC, Hung MS, Chiu TF, Chen JC, Hsiao CT: Risk scoring systems to predict need for clinical intervention for patients with nonvariceal upper gastrointestinal tract bleeding. *Am J Emerg Med* 2007; 25:774-779.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 31

Diarrhea

Robert E. Collier

PERSPECTIVE

Most cases of diarrhea are self-limited and require only supportive care. Conversely, patients with more serious infection and associated comorbidity may have life-threatening dehydration and shock. Associated sepsis and septic shock can be complications of severe diarrheal disease. Numerous but relatively rare, noninfectious causes of diarrhea should be considered.

Incidence

Worldwide, diarrhea remains a major health problem, accounting for approximately 4% of all deaths each year, which is estimated by the World Health Organization (WHO) to be 2.2 million victims.[1] A large proportion of these deaths occur in small children in developing countries. Diarrheal disease kills 1.5 million children every year.[1] Globally, there are about 2 billion cases of diarrheal disease every year.[1]

Rotavirus causes 25 to 65% of childhood-associated diarrheal illnesses (3.5 million cases per year in the United States), whereas adults experience 74 million episodes of diarrhea annually. In the United States, 90% of diarrheal illnesses are caused by noroviruses (caliciviruses), of which more than 100 different strains are recognized.[2-4] Patients at the extremes of age, those with significant comorbidity, those who are immunologically compromised, and those with iatrogenic illness are most vulnerable to significant morbidity and mortality. An estimated 60% of patients infected with human immunodeficiency virus (HIV) experience significant diarrhea during the course of their illness.[5]

Natural disasters, environmental changes, and wars or political uprisings can result in mass migrations of refugees to neighboring countries. This can lead to starvation and thirst in areas with limited resources, a setup for water contamination and epidemic diarrhea. As witnessed in Haiti after the 2010 earthquake, lack of clean water and poor sanitation led to an epidemic of a deadly form of *Vibrio* cholera.[6] Most adults experience diarrhea many times during their lifetime. Diarrheal illnesses are the primary cause of many hospitalizations and hours of lost work.

Definition and Categorization

The term *diarrhea* is derived from the Greek words *dia* ("through") and *rhein* ("to flow"). The two main categories of diarrhea-associated illness are infectious and noninfectious. Infectious causes represent about 85% of cases, whereas noninfectious causes account for only 15% of the total. Infectious diarrhea may be divided into viral, bacterial, and parasitic causes (Box 31-1), with estimates of their relative contributions being 70% for viral, 24% for bacterial, and 6% for parasitic infections.[7]

Definitions for diarrhea have been proposed to standardize nomenclature, help the clinician determine a probable cause, and direct empirical therapy if indicated[7]:

Acute diarrhea is defined as lasting for 14 days or less.

Persistent diarrhea lasts for longer than 14 days.

Chronic diarrhea lasts 30 days or longer.

Acute diarrhea presentations usually will be infectious. A majority of these cases are self-limited and caused by viral and bacterial pathogens. Persistent diarrhea suggests an enteric pathogen other than viral, such as bacterial or protozoan. Chronic diarrhea usually is associated with noninfectious causes and requires further testing to determine the cause.

Normally, the small and large bowels absorb 99% of gastrointestinal tract secretions produced and liquids ingested each day. Any pathologic state that reduces water absorption by 1% can cause diarrhea.[8] Diarrhea results from one or more of four different pathologic processes that are characteristic of the primary cause and that contribute to the decreased absorption of the gut.

Secretory diarrhea is caused by pathogens that produce cytotoxins that increase cellular permeability and cause the oversecretion of water and electrolytes. Most cases of diarrhea encountered in the emergency department (ED) are secretory. Noninfectious causes of secretory diarrhea include medications, toxic substances, endocrine disorders, and neoplasias (Box 31-2).

Inflammatory diarrhea, also described as *invasive* or *severe diarrhea,* or dysentery, results from cellular damage to the intestinal mucosa, leading to the hypersecretion of water, electrolytes, blood, mucus, and plasma proteins. Inflammatory diarrhea most commonly is caused by invasive bacterial and parasitic pathogens that produce dysenteric illnesses (see Box 31-1). Some noninfectious causes of inflammatory diarrhea include chemotherapy, radiation therapy, hypersensitivity reactions, autoimmune disorders, ischemic colitis, and inflammatory bowel disease. With inflammatory diarrhea, fecal leukocytes and erythrocytes typically are present, as are systemic symptoms, and the diarrhea continues despite fasting.

Osmotic diarrhea occurs with the ingestion or malabsorption of osmotically active solutes. These solutes cause the osmotic movement of water into the intestinal lumen, which then overwhelms the gut's ability to reabsorb it. Examples include the effects of osmotic laxatives and carbohydrate malabsorption. Steatorrhea results from osmotic effects of lipids not absorbed in malabsorption and maldigestion syndromes.

Abnormal motility generally is seen in patients with chronic diarrhea but is also a component of acute diarrhea. Hypermotility decreases contact time between luminal contents and the absorbing mucosa, limiting water and electrolyte absorption.

www.ketabpezeshki.com 66485457-66963820

Box 31-1 Causative Agents of Infectious Diarrhea

Viral (60% of Cases)
Astrovirus
Calicivirus
Coronavirus
Cytomegalovirus*
Enteric adenovirus
Hepatitis A through G
Herpes simplex virus
HIV enteropathy
Norwalk-like agents
Norwalk virus
Pararotavirus
Picornavirus
Rotavirus
Small round viruses

Bacterial (20% of Cases)
Invasive*
Aeromonas species
Campylobacter species
Clostridium difficile
Enteroinvasive *Escherichia coli*
Mycobacterium species
Plesiomonas shigelloides
Salmonella species
Shigella species
Vibrio fluvialis
Vibrio parahaemolyticus
Vibrio vulnificus
Yersinia enterocolitica
Yersinia pseudotuberculosis

Toxigenic
FOOD POISONING WITH PREFORMED TOXINS
Bacillus cereus
Clostridium botulinum
Staphylococcus aureus

TOXIN FORMATION AFTER COLONIZATION
Aeromonas hydrophila
Clostridium perfringens
Enterohemorrhagic *E. coli** O157:H7
Enterotoxigenic *E. coli*
Klebsiella pneumoniae
Shigella species
Vibrio cholerae

Other Bacteria

Parasitic (5% of Cases)

Protozoa
*Balantidium coli**
Blastocystis hominis
Cryptosporidium
Cyclospora
Dientamoeba fragilis
*Entamoeba histolytica**
Entamoeba polecki
Enteromonas hominis
Giardia lamblia
Isospora belli
Microsporidia
Sarcocystis hominis

Helminths
Angiostrongylus costaricensis
Anisakiasis
Ascaris lumbricoides
Diphyllobothrium latum
Enterobius vermicularis
Hookworms
Schistosoma species
Strongyloides stercoralis
Taenia species
Trichinella spiralis
Trichuris trichiura

HIV, human immunodeficiency virus.
*Associated with fever, abdominal pain, and fecal red blood cells or white blood cells. % indicates the estimated contribution to total cases.

Box 31-2 Causes of Noninfectious Diarrhea

Toxins
Drugs
ACE inhibitors
Alprazolam (Xanax)
Antacids (magnesium)
Antibiotics
Antidepressants
Antiepileptic drugs
Antihypertensives
Antiparkinson drugs
Beta-blockers
Caffeine
Cardiac antiarrhythmics
Chemotherapy agents
Cholesterol-lowering drugs
Cholinergic agents
Cholinesterase inhibitors
Colchicine
Digitalis
Diuretics
Fluorouracil
Fluoxetine (Prozac)
Histamine H_2-receptor antagonists
Hydralazine
Lactulose
Laxatives, cathartics
Levodopa
Lithium
NSAIDs
Neomycin
Podophyllin
Procainamide
Prostaglandins
Quinidine
Ricinoleic acid
Theophylline
Thyroid hormone
Valproic acid

Dietetic Foods
Mannitol
Sorbitol
Xylitol

Fish-Associated Toxins
Amnestic shellfish poisoning
Ciguatera
Echinoderms
Neurotoxic shellfish poisoning

Continued

www.ketabpezeshki.com 66485457-66963820

Box 31-2 Causes of Noninfectious Diarrhea—cont'd

Paralytic shellfish poisoning
Scombroid
Tetrodotoxin

Plant-Associated Toxins

Herbal preparations
Horse chestnut
Mushrooms—*Amanita* species
Nicotine
Other plant toxins
- Pesticides—organophosphates
- Pokeweed
- Rhubarb

Miscellaneous
- Allergic reactions
- Carbon monoxide poisoning
- Ethanol
- Heavy metals
- Monosodium glutamate (MSG)
- Opiate withdrawal

Gastrointestinal Pathology

Appendicitis
Autonomic dysfunction
Bile acid malabsorption
Blind loop
Bowel obstruction
Celiac disease
Cirrhosis
Defects in amino acid transport
Diverticular disease
Familial dysautonomia
Fecal impaction
Fecal incontinence
GI bleed
GI cancer
Hirschsprung's disease
Inflammatory bowel disease (ulcerative colitis, Crohn's disease)
Intussusception
Irritable bowel syndrome
Ischemic bowel
Lactose or fructose intolerance
Malabsorption syndromes
Malrotation
Postsurgical
Postvagotomy
Radiation therapy
Short gut syndrome
Small bowel resection
Strictures
Toxic megacolon
Tropical sprue
Volvulus
Whipple's disease

Endocrine-Related Conditions

Carcinoid syndrome (serotonin)
Hormonal hypersecretion
Hyperthyroidism (thyroid hormone)
Medullary carcinoma of the thyroid (calcitonin)
Pancreatic cholera (VIP)
Somatostatinoma (somatostatin)
Systemic mastocytosis (histamine)
Zollinger-Ellison syndrome (gastrin)

Endocrine Pathology

Adrenal insufficiency
Diabetes enteropathy
Hypoparathyroidism
Pancreatic insufficiency

Systemic Illness and Other Causes

Alcoholism
Amyloidosis
Connective tissue disease
Cystic fibrosis
Ectopic pregnancy
Hemolytic-uremic syndrome
Henoch-Schönlein purpura
Lymphoma
Otitis media—infants
Pelvic inflammatory disease
Pneumonia, sepsis
Pyelonephritis
Scleroderma, SLE
Severe malnutrition
Stevens-Johnson syndrome
Toxic shock syndrome
Wilson's disease
Miscellaneous
Factitious diarrhea
Runner's diarrhea

ACE, angiotensin-converting enzyme; *GI,* gastrointestinal; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *SLE,* systemic lupus erythematosus; *VIP,* vasoactive intestinal polypeptide.

CLINICAL APPROACH

Emergency Assessment and Stabilization

An immediate assessment should be made of the patient's stability, including maintenance of the airway, adequacy of oxygenation and ventilation, and circulation, with particular attention to volume status. Tachycardia, orthostatic hypotension, poor skin turgor and color, diaphoresis, and mental status changes all are characteristic of hypovolemia and hypoperfusion. The bedside ultrasound can be used quickly to check volume status. Patients with a poorly filled, rapidly beating heart and a collapsed inferior vena cava require immediate rehydration.[9,10] Associated septic shock may contribute to the hypotension and general organ hypoperfusion, and diarrhea may be a manifestation of toxic shock syndrome. A diarrhea-associated acid-base disorder should be suspected in patients with Kussmaul's respirations, a significant anion gap on basic metabolic panel reflecting lactic acidosis from significant volume loss, or a nonanion gap metabolic acidosis associated with massive bicarbonate loss. After stabilization, a secondary survey may elucidate the potential cause of the diarrhea and direct further evaluation and treatment.

Secondary Survey

The physical examination should assess the patient's overall health, toxicity, fever, volume status, and signs of a surgical abdomen and determine the presence of blood in the stool. Young healthy adults may maintain a normal blood pressure and heart rate even with significant dehydration. In patients who are taking antiarrhythmic or beta-blocker medications or have conduction disease or fixed-paced rhythms, heart rate may not be a reliable indicator of volume status. Signs of volume depletion and impending shock include dry mucosa, poor skin turgor, decreased urine output, and mental status changes. Children will have sunken eyes, depression of the fontanel, decrease in urine output (number of wet diapers), and decrease in alertness and activity.[11]

www.ketabpezeshki.com 66485457-66963820

Table 31-1 Factors Increasing Probability of Nonbenign Diarrhea

FACTOR	SPECIFIC PATHOGEN(S) AND OTHER CONSIDERATIONS
Presentation to a health care facility	Degree of illness overall greater in patients seeking evaluation; increased probability of "not norovirus" cause to 50%
Travel history	Especially foreign travel and to endemic areas of dysenteric disease
Recent hospitalization	*Clostridium difficile* from antibiotic exposure
Day care attendance	Rotavirus, *Shigella, Giardia*
Nursing home residence	C. *difficile,* medication side effects, tube feedings, ischemic colitis, fecal impaction, and overflow diarrhea
Wilderness exposure	*Giardia* or *Cryptosporidium*
Antibiotic therapy	C. *difficile,* antibiotic side effects
Raw shellfish, farm animals and fair livestock, pet reptiles or amphibians, petting zoos	*Salmonella* species, *Escherichia coli* O157:H7 and non-O157 Shiga toxin–producing *E. coli*, *Vibrio* species
Epidemic of multiple patients with a short time of onset	Norovirus; less commonly, *Campylobacter jejuni, Salmonella* species, *Cryptosporidium*
Acute vomiting and diarrhea after eating suspected contaminated food	*Bacillus cereus, Clostridium botulinum*, *Staphylococcus aureus*
Epidemic of severe gastroenteritis traced to eggs, poultry, meat, or dairy products	*C. jejuni*, *Salmonella* species
Homosexuality (males)	*Giardia lamblia*, *Entamoeba histolytica*
Abdominal pain Nausea, vomiting Bloody stool Fever Rectal pain Tenesmus	Severe bacterial infections: *Salmonella*, *Campylobacter*, *Shigella*, EPEC, *Yersinia* or *Vibrio* species Also consider surgical abdomen, GI bleeding Inflammatory bowel disease
Diarrhea >7-14 days' duration	Protozoa and microsporidia, *C. difficile*, *Campylobacter*, Shiga toxin–producing *E. coli*
Hemolytic uremic syndrome	*E. coli* O157:H7 or other species
Stool WBC count	Not reliable for diagnosis of bacterial cause
Colonic ulcerations	Inflammatory bowel disease
Proctitis	Bacterial cause highly probable
Pseudomembranes	Toxic megacolon, *C. difficile*
Chronic disease (e.g., cirrhosis, DM)	Complicated course expected with any form of diarrheal illness
Organ transplantation	Abnormally severe illness from rotavirus and adenovirus Increased frequency of cytomegalovirus Severe illness from dysenteric diarrhea Spore-forming protozoa and microsporidia
HIV infection, other immunodeficiency disorders	Severe illness from common bacteria, spore-forming protozoa, and microsporidia Increased frequency of cytomegalovirus and *Mycobacterium avium* complex

DM, diabetes mellitus; *EPEC,* enteropathogenic *E. coli*; *GI,* gastrointestinal; *HIV,* human immunodeficiency virus; *WBC,* white blood cell.

Particular attention should be given to the abdominal examination. Focal abdominal pain with peritoneal findings may be caused by an acute surgical abdomen with symptoms mimicking those of severe gastroenteritis. A rectal examination should be performed to detect fecal impaction, melena, or hematochezia. Gross blood may be consistent with invasive, infectious diarrhea but may be the harbinger of many other pathologic states that manifest with gastrointestinal bleeding. Histamine-induced skin changes may be indicative of an intestinal parasitic infection. The patient should be assessed for specific toxidromes, such as cholinergic or sympathomimetic states that may be clues to a noninfectious cause.

Characterization of the Diarrheal Syndrome

Acute Infectious Diarrhea. Most viral and many bacterial agents cause a self-limited, secretory diarrhea that lasts less than 14 days and causes only mild dehydration and minimal systemic symptoms. These infections do not require extensive testing and are treated symptomatically. In the United States, monitoring of pathogens causing this type of acute gastroenteritis demonstrates that 90% of the infections are caused by norovirus species.[12] All other potential causes of diarrhea are highly improbable unless certain historical and clinical findings are present. Bacterial and protozoal agents less commonly cause diarrhea syndromes indistinguishable from norovirus infection with a nontoxic, self-limited course. A Bayesian approach to diagnosing and treating acute diarrhea has been proposed.[12] The clinical evaluation should screen for all factors (Table 31-1) that may change the probability of "not norovirus" from 10% to 50% or greater.[12] With one or more of these findings present, empirical antibiotic or other specific therapy may be indicated, as well as clinical testing to determine the exact causative disorder.

www.ketabpezeshki.com 66485457-66963820

Persistent diarrhea is defined as that lasting for more than 14 days, and *chronic* diarrhea, more than 30 days.[7] Infectious agents of persistent and chronic diarrhea include bacteria, parasites, and rarely viruses.[13] Common bacterial pathogens include *Aeromonas, Plesiomonas, Campylobacter, Clostridium difficile, Salmonella,* and *Mycobacterium tuberculosis.* Parasites causing chronic diarrhea are colonic forms such as *Amoeba, Trichuris, Yersinia,* and *Schistosoma* species or small intestinal pathogens such as *Giardia, Cryptosporidium, Cyclospora, Isospora,* and *Strongyloides.*[13] In developing countries, chronic diarrhea is more likely to have a bacterial cause. In developed countries, chronic diarrhea is caused by noninfectious disorders such as irritable bowel syndrome, malabsorption syndromes, laxative abuse, and inflammatory bowel disease.[12] Categorization of the stool type as watery, inflammatory, or fatty may assist in proper classification of the chronic diarrhea syndrome as infectious or noninfectious. Testing for HIV or immunodeficiency is important because patients with these conditions commonly have chronic diarrhea. Evaluation should include testing for cryptosporidia, microsporidia, mycobacteria (i.e., *Mycobacterium avium* complex), herpes simplex virus (HSV), *Isospora, Cyclospora,* and cytomegalovirus. In addition, parasitic and helminthic infections should be ruled out.

Noninfectious Diarrhea. Noninfectious causes of diarrhea (see Box 31-2) are responsible for approximately 15% of all cases of diarrheal illness. The distinction between infectious and noninfectious causes may not be clinically apparent. A complete evaluation should consider possible surgical pathology of the abdomen, including gastrointestinal bleeding, ischemic bowel, acute appendicitis, intussusception, ectopic pregnancy, and partial bowel obstruction.[11] The differential diagnosis also includes possible toxic exposures or ingestions, such as heavy metal poisoning, or ingestion of plant-borne or fish-borne toxins. Endocrine pathology, such as adrenal insufficiency, hyperthyroidism, diabetic enteropathy, and hormone-secreting tumors, and other systemic illnesses should be considered, and special attention should be directed at underlying medical conditions, medication use, and past surgical history.

Ancillary Testing

Most cases of acute diarrhea are self-limited, and laboratory and diagnostic tests should be kept to a minimum unless required for epidemiologic studies. Testing is indicated in patients who have a high probability of a "non-norovirus" clinical picture and have worrisome historical data, signs, and symptoms associated with an increased probability of those causes. Ancillary testing should never compromise empirical treatment when indicated (as discussed later). Fever with a toxic appearance and volume depletion, blood- or mucus-containing stools, frequent voluminous stools, and other risk factors (see Table 31-1) should prompt a diligent search for a specific causative disorder in order to guide appropriate therapy.[12,14] A white blood cell count is rarely helpful and not sensitive or specific enough to aid in diagnostic decision-making, although hemoglobin determination is useful to screen for anemia from blood loss, and abnormalities in platelet and coagulation parameters may contribute to identification of a cause for gastrointestinal bleeding. A comprehensive chemistry panel, including renal function tests, can be important when significant volume loss is suspected or when significant diarrhea has been present for 48 to 72 hours. Liver function studies, thyroid tests, serum lipase assay, and a pregnancy test may be helpful in selected cases.

Hemoccult and fecal cell count: The presence of fecal leukocytes is not specific or sensitive enough to use as the sole criterion to decide which patients with presumed bacterial gastroenteritis should be treated empirically with antibiotics. With inflammatory diarrhea of various causes, red and white blood cells are seen on stool examination. Included are bacterial, parasitic, and noninfectious causes, such as chemotherapy, radiation therapy, hypersensitivity reactions, autoimmune disorders, and inflammatory bowel disease. The presence of fecal leukocytes does not delineate which patients would benefit from empirical antimicrobial therapy. The presence of blood does not always correlate with the presence of fecal leukocytes, so reliance on positive stool guaiac test result alone as a rationale for antibiotic therapy is not recommended. The presence of blood without fecal leukocytes may indicate amebiasis, malignancies, heavy metal poisoning, fissures, hemorrhoids, bowel ischemia, or primary gastrointestinal bleeding.

Assays for calprotectin and lactoferrin, produced by leukocytes, are sensitive and specific and may be more useful than microscopic examination of the stool, but these tests are rarely, if ever, of use in the ED.[8]

C. difficile toxin assay: This test is indicated if the patient reports recent antibiotic use. *C. difficile*–associated diarrhea most commonly occurs during or shortly after the antibiotic course. In 25% to 40% of cases, however, onset of the diarrhea may be delayed as long as 12 weeks after antibiotic therapy. The most commonly implicated antibiotics are cephalosporins, penicillins, and clindamycin. Although *C. difficile* accounts for only 10 to 20% of antibiotic-associated diarrhea, an assay for *C. difficile* toxin gives a positive result in nearly all cases of antibiotic-associated pseudomembranous colitis.[15] Approximately 3% of adult patients and 65% of newborns may be colonized with *C. difficile.*

Escherichia coli O157:H7 toxin assay: This test is considered in endemic areas and in patients with suspected hemolytic-uremic syndrome.[16]

Stool culture for bacteria: Stool cultures may be warranted in patients who are febrile, toxic appearing, immunocompromised, at the extremes of age, experiencing a prolonged course, or not responding to conventional treatment. Studies have shown a 2% positive rate, thus proving that routine cultures are of limited value.[16]

Stool examination for ova and parasites: The assessment of stool for ova and parasites is not routinely recommended. This study is used in patients with chronic diarrhea *(Entamoeba histolytica, Cryptosporidium);* patients with a history of travel to developing countries, particularly to Nepal or areas of Russia *(Cryptosporidium, Giardia, Cyclospora)*[17]; patients with exposure to infants in daycare centers *(Cryptosporidium, Giardia);* and patients with HIV infection *(E. histolytica, Giardia).*[18]

Giardia antigen assay and serologic testing for amebiasis may be considered in patients exposed to poor sanitation, HIV-infected patients, patients with a history of travel to developing countries, patients with a history of backpacking, and patients with daycare exposures.

Urinalysis: A urinalysis and a urine pregnancy test should be obtained only when urinary tract infection is a possibility, a gastrointestinal origin for the symptoms is not clear, or pregnancy is suspected.

Radiographic studies: Plain radiographs and contrast computed tomography (CT) may be indicated for patients thought to have a surgical abdomen and to identify pathologic abnormalities, such as tumor, obstruction, free air, fistulae, blind loops, and those associated with Crohn's disease.

Gastrointestinal referral: Referral may be indicated in the evaluation of chronic diarrhea and for workup beyond the scope of the ED (e.g., endoscopy, further stool studies, biopsy).

EMPIRICAL MANAGEMENT

Oral rehydration is the treatment of choice for mild to moderate fluid losses (Fig. 31-1). Oral rehydration can be accomplished with sports beverages, commercial rehydration solutions, or a balanced clear liquid diet in the home (e.g., consisting of water,

www.ketabpezeshki.com 66485457-66963820

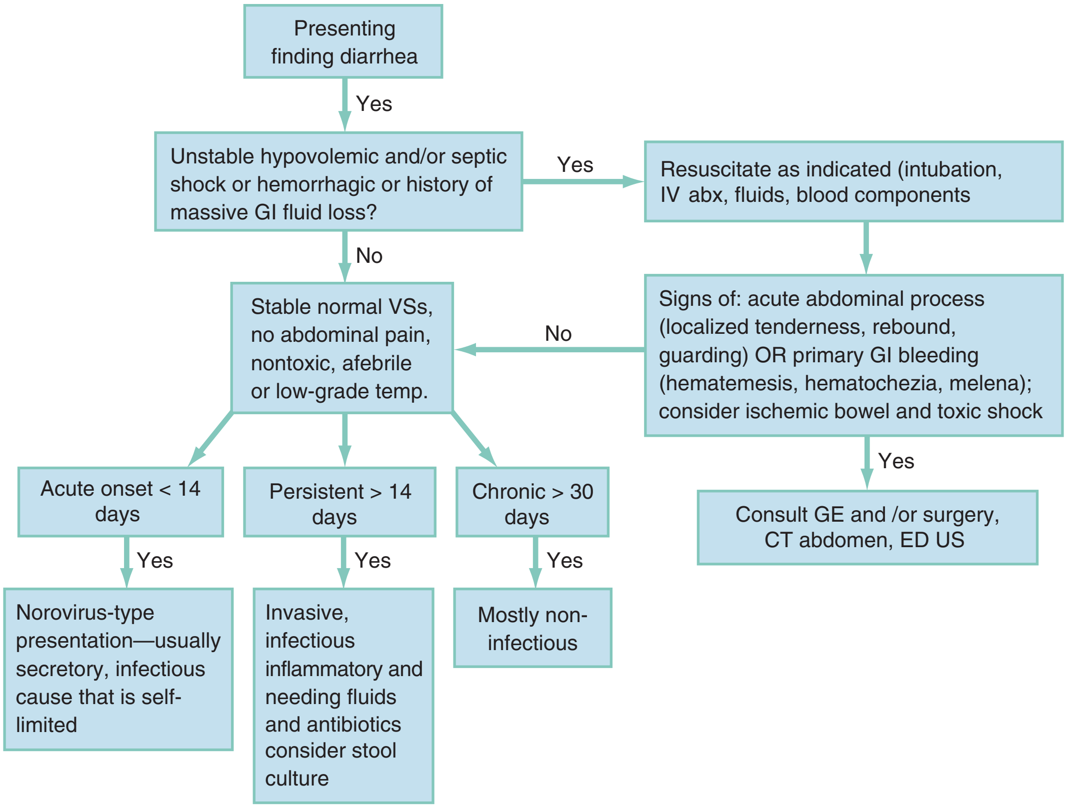


Figure 31-1. Approach to the patient with acute diarrhea. *Abx,* antibiotics; *CT,* computed tomography; *ED,* emergency department; *GE,* gastroenterologist; *GI,* gastrointestinal; *IV,* intravenous; *temp.,* temperature; *US,* ultrasonography; *VSs,* vital signs.

salt-containing liquids such as canned soups, and potassium from oranges or bananas). The WHO has defined an oral rehydration solution (WHO-ORS) that can be made by dissolving the following in 1 L of clean water:

3.5 g of sodium chloride
2.9 g of trisodium citrate or 2.5 g of sodium bicarbonate
1.5 g of potassium chloride
20 g of glucose or 40 g of sucrose

Replacement of micronutrients, particularly copper and zinc, has been recommended, especially in developing countries.[19] The concept of bowel rest has been abandoned because it may worsen diarrhea and lead to more severe dehydration. The choice of oral rehydration fluids depends on the extent of dehydration and the underlying health of the patient. In otherwise healthy patients with mild to moderate dehydration, fluids such as sports drinks, diluted fruit juices, and soft drinks supplemented with soups, broths, or crackers may be sufficient to replace the fluid and sodium losses associated with acute diarrhea. Such frequently used "clear liquids" may contain excess sugars and insufficient sodium content, however, leading to an osmotic diarrhea. Beverages containing caffeine should be avoided because caffeine increases cyclic adenosine monophosphate levels and may cause a secretory diarrhea. Milk and other products containing lactose also should be avoided because viral and bacterial pathogens, responsible for many cases of diarrhea, may cause a transient lactase deficiency, leading to malabsorption and osmotic diarrhea. Food intake is encouraged, but foods high in simple sugars should be avoided because the osmotic effect is counterproductive. Foods with a high fat content may delay gastric emptying and should be avoided. The *BRAT* (bananas, rice, apples, and toast) *diet* has long been recommended, particularly with pediatric patients. Although no controlled studies have examined the efficacy of the BRAT diet, it remains a commonly recommended strategy. The pectin in the peel of apples is constipating (pectin, found in fruit peel, is the "pectate" in Kaopectate), and bananas provide potassium. If this diet is used for extended periods, adequate provision of protein and energy needs of the patient becomes a concern.

In patients with evidence of more severe dehydration, intravenous fluid resuscitation with normal saline or lactated Ringer's solution is the preferred treatment. Pediatric patients should receive a bolus of 20 mL/kg of normal saline, which may be repeated as indicated. Specific treatment for diarrhea should be directed toward the suspected cause. In patients with suspected surgical pathology, further diagnostic testing and surgical consultation may be required. With toxic exposures, treatment consists of early decontamination, supportive care, and, if appropriate, administration of specific antidotes. Other noninfectious causes of diarrhea are treated as indicated.

Because the specific pathogen causing infectious diarrhea is rarely identified in the ED and the results of cultures are usually unavailable, any antimicrobial treatment is empirical and guided by knowledge of the common causes of infectious diarrhea (see Box 31-1). Viral and noninvasive bacterial gastroenteritis tend to be self-limiting and require only supportive therapy. Empirical antibiotic treatment is directed against invasive bacterial and parasitic organisms that cause the greatest harm. Antibiotic treatment is initiated in patients with a suspected invasive process and severe diarrhea, systemic symptoms, fever, or abdominal pain and in patients who appear toxic. The current recommendation for empirical treatment of a systemically ill–appearing adult is ciprofloxacin, 500 mg orally twice a day, or levofloxacin, 500 mg orally every 24 hours for 3 to 5 days.[20] Fluoroquinolones are efficacious against most organisms that cause dysenteric illnesses and have been shown to be more effective than trimethoprim-sulfamethoxazole.[17,21] Fluoroquinolones should not be administered to pregnant patients or children younger than 18 years. The antibiotic treatment of severe gastroenteritis in children has been associated with the development of hemolytic-uremic syndrome

www.ketabpezeshki.com 66485457-66963820

and thrombotic thrombocytopenic purpura if the bacterial cause is enterohemorrhagic *E. coli* O157:H7, although *Salmonella, Shigella,* and *Campylobacter* also have been implicated. If possible, treatment for pediatric patients should be based on culture results with supportive care initially.

If amebic dysentery is of concern in high-risk patients (see Table 31-1), treatment with metronidazole after stool analysis for ova and parasites is recommended. In patients with a history of recent antibiotic use suspected of having *C. difficile* colitis, a *C. difficile* toxin assay followed by vancomycin or metronidazole is appropriate.[22]

The use of antimotility agents in the treatment of acute enteritis has been controversial, with the literature divided over this issue. Patients with simple, acute viral gastroenteritis benefit from antimotility agents and often obtain significant relief of symptoms, with less fluid loss and without significant complications. Loperamide is the safest and most effective medication. Relief of symptoms is achieved much more rapidly than with bismuth subsalicylate (Pepto-Bismol) in patients with inflammatory diarrhea or antibiotic-associated colitis. In pediatric age groups, the use of opioids, loperamide, or diphenoxylate with atropine rarely has been associated with the precipitation of toxic megacolon and hemolytic-uremic syndrome. Because the beneficial effects of these medications are modest, they should be avoided or used with extreme caution in these high-risk patients.

Probiotics have been used as an alternative to traditional antibiotic therapy for diarrhea. *Lactobacillus* and other bacteria have proved to be effective in restoring the normal gastrointestinal flora that is disrupted during diarrhea illness. This approach has been most effective with traveler's diarrhea and nonspecific diarrhea in children.

DISPOSITION

Most patients with uncomplicated, acute diarrhea can be discharged home after assessment and symptomatic relief. Hospitalization rarely is required for diarrhea secondary to viral and many forms of bacterial gastroenteritis, which tend to be self-limiting. Often the exact causative agent of diarrhea is not identified in the ED. An understanding of common causes and their treatment and recognition of patients at risk for a more severe clinical course are essential for the appropriate disposition. In patients with severe dehydration, hemodynamic instability, or a toxic appearance and in high-risk groups, hospital admission is warranted for continuous monitoring, further treatment, and definitive management when initial evaluation and stabilization are complete.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. *World Health Report 2000*. World Health Organization; 2009. Available at http://www.who.int/vaccine_research/diseases/diarrhoeal/en/index1.html.
2. Grimwood K, Forbes DA: Acute and persistent diarrhea. *Pediatr Clin North Am* 2009; 56:1343-1361.
3. Musher DM, Musher BL: Contagious acute gastrointestinal infections. *N Engl J Med* 2004; 351:2417.
4. Goodgame RW: Viral causes of diarrhea. *Gastroenterol Clin* 2001; 30:779.
5. Clement PA, Gardiner JA: *Diarrhea and vomiting*. In: Stone CK, Humphries RL, eds. *Current Emergency Diagnosis and Treatment*, 5th ed. New York: Lange/McGraw-Hill; 2004:296-310.
6. Chin C, Sorenson J: The origin of the Haitian cholera outbreak strain. *N Engl J Med* 2011; 364:33-42.
7. Guerrant RL, et al: Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis* 2001; 32:331.
8. Schiller LR, Sellin JH: *Diarrhea*. In: Feldman M, Friedman LS, Brandt LJ, eds. *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 8th ed. Philadelphia: WB Saunders; 2006:160-162.
9. Perera P, Mailhot T, Riley D, Mandavia D: The RUSH Exam: Rapid Ultrasound in SHock in the evaluation of the critically ill. *Emerg Med Clin North Am* 2010; 28:29-56.
10. Labovitz AJ, et al: Focused cardiac ultrasound in the emergent setting: A consensus statement of the American Society of Echocardiography and American College of Emergency Physicians. *J Am Soc Echocardiogr* 2010; 23:1225-1230.
11. Armon K, Stephenson T, MacFaul R, Eccleston P, Werneke U: An evidence and consensus based guideline for acute diarrhoea management. *Arch Dis Child* 2001; 85:132.
12. Goodgame RW: A Bayesian approach to acute infectious diarrhea in adults. *Gastroenterol Clin North Am* 2006; 35:249.
13. Lee SD, Surawicz CM: Infectious causes of chronic diarrhea. *Gastroenterol Clin North Am* 2001; 30:679.
14. Aranda-Michel J, Giannella RA: Acute diarrhea: A practical review. *Am J Med* 1999; 106:670.
15. Högenauer C, Hammer HF, Krejs GJ, Reisinger EC: Mechanisms and management of antibiotic-associated diarrhea. *Clin Infect Dis* 27:702, 1998.
16. Klein EJ, et al: Shiga toxin-producing *Escherichia coli* in children with diarrhea: A prospective point-of-care study. *J Pediatr* 2002; 141:172.
17. Gomi H, et al: In vitro antimicrobial susceptibility testing of bacterial enteropathogens causing traveler's diarrhea in four geographic regions. *Antimicrob Agents Chemother* 2001; 45:212.
18. Oldfield EC: Evaluation of chronic diarrhea in patients with human immunodeficiency virus infection. *Gastroenterol Disord* 2002; 2:176.
19. Patel AB, Dhande LA, Rawat MS: Economic evaluation of zinc and copper use in treating acute diarrhea in children: A randomized controlled trial. *Cost Eff Resour Alloc* 2003; 1:7.
20. Gilbert DN, et al: *The Sanford Guide to Antimicrobial Therapy*, 41st ed. Sperryville, Va: Antimicrobial Therapy; 2011.
21. Oldfield EC 3rd, Wallace MR: The role of antibiotics in the treatment of infectious diarrhea. *Gastroenterol Clin North Am* 2001; 30:817.
22. Thielman MT, Guerrant RL: Acute infectious diarrhea. *N Engl J Med* 2004; 350:38.

www.ketabpezeshki.com 66485457-66963820

Chapter 32

Constipation

Jan M. Shoenberger

PERSPECTIVE

The term *constipation* refers to a symptom or complex of symptoms and not a specific diagnosis. Patients and health care providers often define constipation differently. Most health care providers define constipation based on stool frequency. Patients often use the term *constipation* to describe a broad set of complaints, including straining, hard or infrequent stools, pain during a bowel movement, a feeling of incomplete evacuation, or abdominal bloating. Constipation may be acute (new for the patient) or chronic. *Chronic constipation* is defined as the presence of symptoms for at least 3 months. In clinical practice, attempting to identify the cause of the symptoms will often result in the best chance of effective treatment and will help determine disposition. A definitive diagnosis often is not possible in the emergency department (ED), and appropriate follow-up evaluation should be arranged in those cases. When constipation becomes severe with constant pain, some clinicians use the term *obstipation.* Obstipation represents the progression of the symptom of constipation toward bowel obstruction.

In the ED, the complaint of constipation should be of concern when it represents a significant change from a patient's own normal pattern that is creating discomfort for the patient. This change may manifest as a decrease in frequency of defecation, sudden and persistent change in the character or amount of stools (especially decrease in stool caliber), blood in the stool, or problems expelling the stool.[1]

Epidemiology

The prevalence of constipation varies worldwide. In North America the prevalence is approximately 16%.[2] In adults, constipation is more common in women, the elderly, those with high body mass index, and those with low socioeconomic status.[2] A consistent trend of increasing prevalence of constipation is observed with age, with significant increases after the age of 70 years. The high prevalence among elderly patients is multifactorial and related to a diet low in fiber, sedentary habits, multiple medications, and various disease processes that impair neurologic and motor control.

Pathophysiology

Normally the gastrointestinal tract is presented with 9 to 10 L/day of secretions and ingested fluids. The small intestine usually absorbs all of this except for approximately 500 mL. The colon mixes the ileal effluent, ferments and salvages the unabsorbed carbohydrate residues, and desiccates the contents to form stool. The process of stool transport and evacuation is complex and is regulated by neurotransmitters, intrinsic colonic reflexes, and a multitude of learned and reflex mechanisms that are not fully understood. Constipation may result from structural, metabolic, mechanical, neurologic, or behavioral disorders that affect the colon or anorectum either directly or indirectly.[3-5]

DIAGNOSTIC APPROACH

Differential Considerations

The causes of constipation are numerous. Causes of constipation can be divided into *primary* (no apparent external cause) and *secondary* causes (summarized in Box 32-1). These two groupings have some overlap. In the ED, patients most commonly have acute constipation resulting from side effects of medications or avoidance of defecation secondary to presence of painful perianal lesions such as fissures, hemorrhoids, or perirectal abscesses.

Pivotal Findings

History

A thorough, detailed history usually identifies the most likely cause of the patient's constipation. Defining what the patient means by "constipation" is a good starting point. Essential information includes the presence or absence of signs or symptoms that the American College of Gastroenterology terms "alarm symptoms." These include fever, anorexia, nausea, vomiting, blood in the stool, anemia, weight loss of more than 10 lb, a family history of colon cancer, onset of constipation after the age of 50, and acute onset of constipation in an elderly patient.[1]

Additional elements of the history are directed toward elucidating a possible cause. Questions about the character of the stools may reveal a decrease in caliber of the stool, suggesting possible mass lesion, or diarrhea alternating with constipation, which may indicate irritable bowel syndrome. Frequency of stools and what the patient considers "normal" should be assessed.

The review of systems may need to include questions regarding associated symptoms if no obvious cause is elicited in the cursory history. Questions directed at associated neurologic symptoms, activity level, and status of comorbid diseases may provide clues to contributing factors.

A medication history is essential and should include any recent changes in dosage of any prescription medications, herbal agents, and over-the-counter (OTC) medications. Many patients experience constipation as a side effect of medication. Drugs of abuse also may cause changes in bowel patterns. Opioid medications are the most common cause of constipation among medications and drugs of abuse. Because of this, elderly patients who are prescribed

www.ketabpezeshki.com 66485457-66963820

Box 32-1 Causes of Constipation

Congenital
Hirschsprung's disease
Imperforate anus
Anorectal atresia
Aganglionosis

Primary Causes (e.g., Functional Disorders)
Idiopathic slow transit
Irritable bowel syndrome

Secondary Causes
Neurologic
Chronic diseases (multiple sclerosis, Parkinson's disease)
Spinal cord injury

Metabolic
Diabetes
Hypercalcemia
Hypokalemia
Hypothyroidism
Hypomagnesemia

Myopathies
Systemic sclerosis
Amyloidosis

Structural
Obstructing tumor or stricture
Intussusception
Rectocele
Rectal prolapse

Medication Side Effect (Most Common Listed Here)
Opiates
Iron or calcium supplements
Calcium channel blockers
Antidepressants
Diuretics
Antipsychotics
Anticholinergics
Antiepileptics
Antiparkinson drugs

Psychological
Abuse (psychological, physical, sexual)
Eating disorders (bulimia, anorexia nervosa)
Affective disorders

Others
Dehydration
Immobility
Pregnancy
Postoperative pain
Dietary factors

Adapted from Chatoor D, Emmanuel A: Constipation and evacuation disorders. Best Pract Res Clin Gastroenterol 2009; 23:517.

opiates from the ED for home use should be warned about constipation and given instructions to prevent and treat it.

Physical Examination

The physical examination should initially focus on two major aspects: the abdominal and rectal examinations. The abdominal examination usually yields normal findings but may reveal tenderness, a mass, distention, or possibly evidence of obstruction. Bowel sounds should be auscultated.

The anorectal examination and an evaluation of the stool are important parts of the physical assessment. Anorectal inspection may reveal fissures, hemorrhoids, or rectal prolapse. The digital rectal examination should include palpation for masses, and the presence or absence of pain should be noted. Other possible findings include strictures, high sphincter tone, and the presence of blood. Having the patient bear down may be helpful in assessing sphincter function and may reveal milder forms of prolapse. The quantity and the characteristics of the stool should be recorded. Testing the stool for occult blood may yield additional information, although straining with stooling can produce local anal lesions and bleeding. If results of occult blood testing are positive, diverticular disease, carcinoma, and trauma from repeated attempts at straining all are possibilities. Results of rectal examination have not been shown, however, to correlate with complaints of constipation or with evidence of colonic loading on abdominal radiographs. The rectal examination alone should not be used to confirm or exclude the presence of constipation.[4]

Ancillary Testing

The majority of patients who visit the ED with a chief complaint of constipation do not need any testing. Plain abdominal radiographs may provide information about extent of stool retention but also may suggest emergent diagnoses such as megacolon or volvulus. Although constipation can cause cramping and abdominal pain, plain radiographs documenting an increased stool load in the constipated patient should not be used to rule out more serious underlying causative disorders, especially if the patient has a significant amount of abdominal pain or tenderness on examination. Also, several studies have shown that interpretation of abdominal films in the evaluation of constipation is highly variable and subjective.[6,7]

Clinical laboratory studies are not routinely indicated in the workup for constipation. When blood is found in the stool, a hemoglobin level or complete blood count (CBC) may reveal an accompanying anemia, which may suggest an occult carcinoma. The white blood cell count is nonspecific and not helpful.

Patients with acute constipation for which the cause is not readily apparent should receive symptomatic treatment, with referral for outpatient evaluation and reassessment as needed. The patient in the ED with chronic constipation and no alarming signs or symptoms should receive empirical treatment without any ancillary testing. Outpatient tests may eventually include blood tests to investigate metabolic or endocrine causes and possibly specialized tests such as colonic transit studies and anorectal manometry. Consensus recommendations state that the routine use of colonoscopy to exclude organic disorders in patients with chronic constipation symptoms is not indicated, although it is still recommended for colon cancer screening in all patients older than 50 years.[3-5]

DIAGNOSTIC ALGORITHM

The approach to the patient with constipation starts with assessing whether or not this symptom is accompanied by the additional symptom of abdominal pain. If such pain is present, the workup should be geared toward this symptom, which may ultimately reveal the cause of the constipation. Constipation may itself cause abdominal pain; however, this should be a diagnosis of exclusion once other, more serious potential causative disorders have been ruled out.

Figure 32-1 presents a diagnostic algorithm. If the physical examination reveals a structural or mechanical cause, such as pain from hemorrhoids, fissures, or mass lesion, the appropriate treatment or referral is indicated; the constipation will resolve once the cause is addressed. If no obvious cause is found on examination, then determination of the presence or absence of stool in the rectal vault may be helpful. History will be very helpful in differentiating

www.ketabpezeshki.com 66485457-66963820

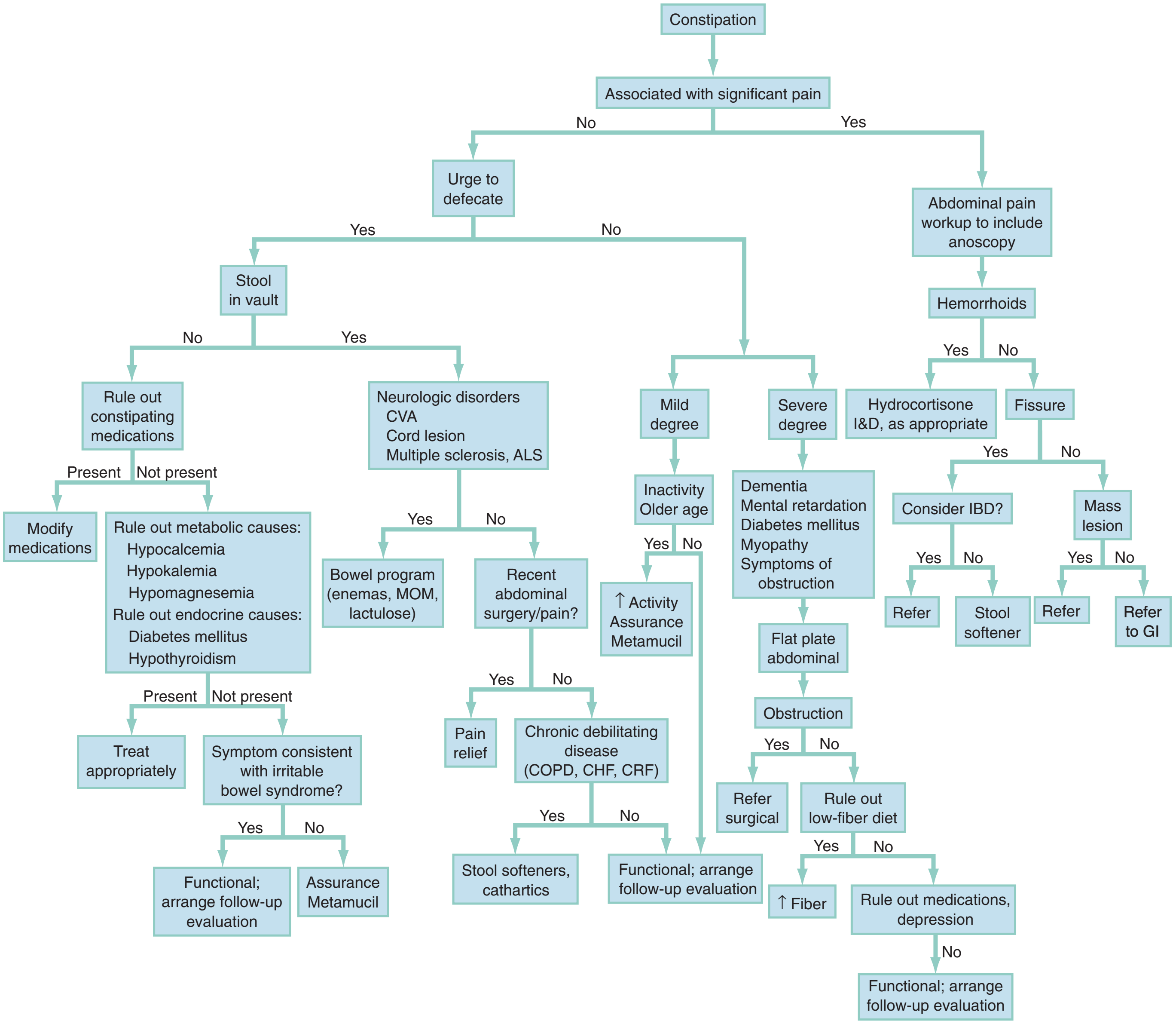


Figure 32-1. Algorithmic approach to the diagnosis of constipation. *ALS,* amyotrophic lateral sclerosis; *CHF,* congestive heart failure; *COPD,* chronic obstructive pulmonary disease; *CRF,* chronic renal failure; *CVA,* cerebrovascular accident; *GI,* gastroenterology; *IBD,* inflammatory bowel disease; *I&D,* incision and drainage; *MOM,* milk of magnesia.

among causes such as medication side effect and possible neurologic disease.

Constipation is rarely associated with morbidity or mortality. Most bad outcomes are a result of missed diagnosis of bowel obstruction or perforation. These conditions are generally diagnosed through physical examination, plain radiographs, and computed tomography (CT) scan if needed. Surgical consultation is needed for suspected perforation and obstruction.

EMPIRICAL MANAGEMENT

Treatment of acute constipation is directed toward eradicating the underlying cause and providing symptom relief. Prevention of further episodes of constipation may include recommending increased fluid intake, increased exercise, increased dietary fiber, and, if necessary, additional sources of bulk in the form of synthetic bulk agents. These interventions will not usually help the acutely constipated patient in the short term. Therapeutic choices and recommendations for patients should be customized based on patient preferences as well as history of efficacy of treatments used in the past. See Box 32-2 for further details. Specific recommendations may also include withholding a causal medication, management of an anal fissure, or draining of a perirectal abscess. Stool softeners (e.g., docusate sodium), although commonly recommended to patients, should not be used as a first-line agent for most patients with constipation. Docusate has not been shown to be any more effective than placebo in relieving acute constipation, although it may be somewhat helpful in patients with anal fissures or hemorrhoids, which can make defecation painful.

Specific agents for symptomatic treatment of constipation are listed in Table 32-1. There are five classes of commonly used laxatives. These are bulking agents, osmotic salts, poorly absorbed sugars, stool softeners, and stimulant laxatives. These agents aid defecation by decreasing stool consistency and/or by stimulating colon motility.[8] There are also several new pharmacologic classes being used or investigated for the treatment of constipation in specific groups of patients.

www.ketabpezeshki.com 66485457-66963820

Box 32-2 General Approach to Treatment of Constipation

For specific agents, dosages, and precautions, see Table 32-1.

I. Core Program for All Patients

A. Adequate intake of fluid and fiber is one key to preventing constipation. Fiber is available primarily from grains and bran cereals. Flatulence, bloating, and cramps are common side effects encountered when bran fiber is introduced.

B. Another source of bulk is from synthetic bulk agents (e.g., psyllium). Bulk agents require an adequate amount of fluid intake; otherwise, they may worsen constipation.

C. Avoid irritant laxatives as part of a core program because long-term use may decrease bowel motility. Encourage the patient to exercise and respond promptly to the urge to defecate.

II. Individualized Program-Specific Indications and General Comments

A. *Stimulant laxatives (e.g., senna, bisacodyl):* Many believe that long-term use of these agents leads to dependency and habituation, but this is not substantiated. When used appropriately, these medications are not harmful and are very effective. Senna is probably the first-line choice among this class of laxatives.

B. *Osmotic laxatives (e.g., polyethylene glycol [PEG], lactulose, milk of magnesia, magnesium citrate):* These agents are most commonly used for colonic preparation before bowel procedures. These agents are safe and well tolerated. PEG has been shown to be slightly more effective than lactulose and causes less bloating and flatus.

C. *Lubricants and stool softeners:* Oral mineral oil lubricants and stool softeners are particularly helpful in patients who have acute painful perianal lesions. The softening and coating of the stool can make passage much easier and less painful, preventing constipation. Mineral oil is contraindicated in patients with swallowing problems or in those who are particularly debilitated, to prevent aspiration leading to lipid pneumonia.

D. *Suppositories and enemas:* These agents may be helpful in patients who tend to have trouble expelling soft stool from the rectum. Glycerin suppositories may have a soothing effect and be helpful in patients with constipation caused by local, painful perianal lesions. Tap-water enemas are helpful when disimpaction is necessary.

Table 32-1 Preparations Used in the Symptomatic Treatment of Constipation

MEDICATION	MAXIMAL RECOMMENDED DOSE	ONSET OF ACTION	COMMENTS
Bulk Laxatives			Undigestible fiber attracts water, which leads to larger, softer fecal mass.
Psyllium (Metamucil)	Titrate up to 20 g	12-72 hr	Natural fiber that undergoes bacterial degradation, which may contribute to bloating and flatus. Should be taken with plenty of water to avoid intestinal obstruction.
Methylcellulose (Citrucel)	Titrate up to 20 g		Semisynthetic cellulose fiber that is relatively resistant to colonic bacterial degradation.
Polycarbophil (Fibercon)	Titrate up to 20 g		Synthetic fiber of polymer of acrylic acid, resistant to bacterial degradation.
Osmotic Laxatives			Draw water into the intestines along osmotic gradient.
Magnesium or Sodium Salts			
Magnesium hydroxide (milk of magnesia)	30-45 mL once daily	1-6 hr	A small percentage of magnesium is absorbed—use caution in patients with renal insufficiency and in children.
Magnesium citrate	150-300 mL as needed	3-6 hr	
Sodium phosphate (Fleet Phospho-soda)	20-45 mL with 12 oz of water as needed		Hyperphosphatemia may result if patient has renal insufficiency. Commonly used before colonoscopy.
Poorly Absorbed Sugars			
Lactulose	15-30 mL once or twice a day	24-48 hr	Synthetic disaccharide not absorbed by the small intestine. Gas and bloating common.
Sorbitol	15-30 mL once or twice a day		Poorly absorbed by small intestine.
Polyethylene glycol and electrolytes (GoLYTELY, MiraLax)	17 g two or three times a day	12-24 hr	Organic polymers that are poorly absorbed and not metabolized by bacteria, thus may cause less bloating and cramping. Can be mixed with noncarbonated beverages.
Stimulant Laxatives			Stimulate intestinal motility or secretion.
Senna (Senokot, Ex-Lax)	8-34 mg daily	6-12 hr	Stimulates secretion and motility of small intestine and colon.
Bisacodyl (Dulcolax, Correctol)	5-10 mg daily		

www.ketabpezeshki.com 66485457-66963820

Table 32-1 Preparations Used in the Symptomatic Treatment of Constipation—cont'd

MEDICATION	MAXIMAL RECOMMENDED DOSE	ONSET OF ACTION	COMMENTS
Stool Softeners			Increase water penetration and soften stool.
Docusate sodium (Colace)	100 mg twice a day; some use higher doses	24-48 hr	In many studies, no better than placebo. Not recommended as first-line or solo therapy.
Mineral oil (Fleet mineral oil)	5-15 mL orally at night		Provides lubrication for the passage of stool. Long-term use is not recommended. Lipid pneumonia can occur in patients predisposed to aspiration.
Newer Agents			
Lubiprostone (Amitiza)	24 µg once or twice per day	1 hr	A chloride channel activator. FDA approved for treatment of chronic idiopathic constipation in adults. Adverse effects: headache, nausea, diarrhea.
Methylnaltrexone (Relistor)	8-12 mg SQ		Used in refractory opioid-induced constipation.

FDA, U.S. Food and Drug Administration; *SQ,* subcutaneously.

A group of patients that often experiences constipation are those who are on chronic, medically necessary medications that cause constipation (e.g., opioids in patients with chronic pain or cancer). These patients should be on bowel regimens designed to prevent constipation. These regimens usually include such measures as high levels of dietary fiber (e.g., added prunes or figs) as well as daily administration of stimulant laxatives.[9] A recent advance in the treatment of refractory opioid-induced constipation is methylnaltrexone (Relistor). Methylnaltrexone is a specific peripheral mu opioid receptor antagonist and is administered subcutaneously. It selectively blocks the gastrointestinal mu opioid receptors without compromising central mediated effects of opioid analgesia or precipitating withdrawal. Its use in palliative care patients was recently supported in a Cochrane review.[10]

Enemas are sometimes necessary if laxatives have failed to provide relief or if the patient has a large volume of stool in the lower colon or rectum that cannot be expelled. Warm tap-water enemas are the safest choice. For immediate relief, manual disimpaction may be necessary in some patients, especially in elders with large amounts of stool present in the rectal vault. In rare cases, disimpaction may need to be performed with procedural sedation.

There are alternatives to the traditional laxatives and enemas for patients with chronic constipation. Patients with recalcitrant constipation may benefit from interventions such as biofeedback and bowel training.[5]

DISPOSITION

Constipation is appropriately treated at home, and only the most severe cases require disimpaction or enema treatment in the ED. With complications or presence of a serious disorder as a cause for the constipation, such as fecal impaction beyond that able to be resolved by digital disimpaction, megacolon, volvulus, or bowel obstruction, the patient should be admitted to the hospital for further evaluation and treatment.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. American College of Gastroenterology Chronic Constipation Task Force: An evidence-based approach to the management of chronic constipation in North America. *Am J Gastroenterol* 2005; 100:S1.
2. Mugie SM, Benninga MA, Di Lorenzo C: Epidemiology of constipation in children and adults: A systematic review. *Best Pract Res Clin Gastroenterol* 2011; 25:3.
3. Salles N: Basic mechanisms of the aging gastrointestinal tract. *Dig Dis* 2007; 25:1127.
4. Bouras E, Tangaloas E: Chronic constipation in the elderly. *Gastroenterol Clin North Am* 2009; 38:463.
5. Chatoor D, Emmanuel A: Constipation and evacuation disorders. *Best Pract Res Clin Gastroenterol* 2009; 23:517.
6. Moylan S, et al: Are abdominal x-rays a reliable way to assess for constipation? *J Urol* 2010; 184:1692.
7. Jackson CR, Lee RE, Wylie AB, Adams C, Jaffray B: Diagnostic accuracy of the Barr and Blethyn radiological scoring systems for childhood constipation assessed using colonic transit time as the gold standard. *Pediatr Radiol* 2009; 29:664.
8. Singh S, Rao SS: Pharmacologic management of chronic constipation. *Gastroenterol Clin North Am* 2010; 29:509.
9. Librach SL, et al: Consensus recommendations for the management of constipation in patients with advanced, progressive illness. *J Pain Symptom Manage* 2010; 40:761.
10. Candy B, Jones L, Goodman ML, Drake R, Tookman A: Laxatives or methylnaltrexone for the management of constipation in palliative care patients. *Cochrane Database Syst Rev* 2011; 19:CD003448.

www.ketabpezeshki.com 66485457-66963820

Chapter 33

Acute Pelvic Pain in Women

Danielle Hart and Ari Lipsky

PERSPECTIVE

Women of childbearing age with low abdominal pain often have pathologic conditions related to the female reproductive system or bladder, although additional causes also should be considered.

Epidemiology

Acute pain caused by pelvic pathology is common, and the presenting complaint may be diffuse or lower abdominal pain, pelvic pain, or low back pain. A patient with chronic pelvic pain may also have an acute process, either related to the chronic condition or arising de novo.

Over one third of reproductive-age women will experience nonmenstrual pelvic pain. Among diagnoses for women with pain caused by gynecologic disorders in the emergency department, pelvic inflammatory disease (PID) and lower genital tract infections (e.g., cervicitis, candidiasis, Bartholin's abscess) account for almost half. Other common diagnoses are menstrual disorders, noninflammatory ovarian and tubal pathology (including cysts and torsion), and ectopic pregnancy. In the general population, ectopic pregnancy accounts for 2% of first-trimester pregnancies; however, among women visiting the emergency department with vaginal bleeding or abdominal pain in the first trimester of pregnancy, the incidence of ectopic pregnancy is as high as 18%.[1]

Younger patients and those with multiple sexual partners are more likely to have PID, and a previous episode increases the likelihood of a subsequent episode.[2] The risk of ectopic pregnancy is higher in women who have had PID, pelvic surgery, or a prior ectopic pregnancy, as well as in women with an intrauterine device. Heterotopic pregnancy is of special concern in women undergoing fertility treatment. The incidence of heterotopic pregnancy in the general population was 1 in 30,000 patients in 1948 and is currently reported to be as high as 1 in 8000. It is much more common in women undergoing assisted reproductive techniques (in vitro fertilization and ovulation-stimulating medications), with an incidence of 1 in 100.[3] Common nongynecologic diseases, such as appendicitis, diverticulitis, urinary tract infection, and urolithiasis, remain important considerations in the woman with acute pelvic pain. Box 33-1 lists conditions accounting for pelvic pain in most women.

Some causes of pelvic pain may lead to serious sequelae. PID carries the short-term risk of tubo-ovarian abscess and the long-term risks of impaired fertility, chronic pelvic pain, and increased predisposition to ectopic pregnancy.[5] Rupture of an ectopic pregnancy or a hemorrhagic ovarian cyst may be life-threatening. Unrecognized abuse may have serious or lethal consequences as well.

Pathophysiology

The female pelvis contains the vagina, uterus, fallopian tubes and ovaries, ureters and urinary bladder, and sigmoid colon and rectum, as well as components of the vascular and musculoskeletal systems. Although pelvic pain often originates from the reproductive organs, it may arise from any structures that lie adjacent to or course through the pelvis. Visceral pain afferents supplying the pelvic organs have common innervation with the appendix, ureters, and colon. Their significant overlap makes accurate localization difficult for both patient and clinician. Pain may be initiated by inflammation, distention, or ischemia of an organ or by spillage of blood, pus, or other material into the pelvis. Parietal pain develops when the afferent nerves in the parietal peritoneum adjacent to an affected organ are stimulated.

DIAGNOSTIC APPROACH

Differential Considerations

The differential diagnosis of pelvic pain is broad (see Box 33-1). Most causes of pelvic pain fit into three categories: (1) the reproductive tract, (2) the urinary tract, and (3) the intestinal tract. Because a subset of pelvic pain is found only in pregnancy, the pregnancy test is a key branch point in the diagnostic process. Potential pregnancy-related disorders can be divided into complications of early pregnancy and complications that occur further along in pregnancy. Although the specific cause of pelvic pain cannot always be determined at the initial ED visit, an organized approach usually leads to the confirmation or exclusion of disorders most likely to result in significant morbidity and/or mortality.

Pivotal Findings

It is rare that any particular finding on history or physical examination (summarized in Table 33-1) is reliable enough to conclusively make or exclude a particular diagnosis, so ancillary testing (beyond a simple pregnancy test) is commonly required in the evaluation of patients with acute pelvic pain.

The bimanual examination may at times provide important information; however, findings on pelvic examination can be

www.ketabpezeshki.com 66485457-66963820

Box 33-1 Causes of Pelvic Pain in Women

Reproductive Tract
Ovarian torsion
Ovarian cyst
Pelvic inflammatory disease
Salpingitis, tubo-ovarian abscess
Endometritis
Endometriosis
Uterine perforation
Uterine fibroids
Dysmenorrhea
Neoplasm

Pregnancy-Related
First Trimester
Ectopic pregnancy
Threatened abortion
Nonviable pregnancy
Ovarian hyperstimulation syndrome

Second and Third Trimesters
Placenta previa
Placental abruption
Round ligament pain
Labor or Braxton-Hicks contractions
Uterine rupture

Intestinal Tract
Appendicitis
Diverticulitis
Ischemic bowel
Perforated viscus
Bowel obstruction
Incarcerated or strangulated hernia
Fecal impaction or constipation
Inflammatory bowel disease
Gastroenteritis
Irritable bowel syndrome

Urinary Tract
Pyelonephritis
Cystitis
Ureteral stone

Vascular
Septic pelvic thrombophlebitis
Ovarian vein thrombosis
Sickle cell disease
Pelvic congestion syndrome

Musculoskeletal
Muscular strain or sprain
Hernia
Abdominal wall hematoma

Neurologic or Psychiatric
Depression
Abdominal migraine
Herpes zoster

Table 33-1 Differentiation of Common or Potentially Catastrophic Causes of Pelvic Pain

CAUSATIVE DISORDER OR CONDITION	PAIN HISTORY	ASSOCIATED SYMPTOMS	SUPPORTING HISTORY	PREVALENCE IN ED	PHYSICAL EXAMINATION	USEFUL TESTS	ATYPICAL OR ADDITIONAL ASPECTS
Ectopic pregnancy (critical if ruptured)	Classically severe, sharp, lateral pelvic pain, but severity, location, and quality highly variable.	Vaginal bleeding (often mild, can be absent).	Missed period; history of previous ectopic pregnancy, infertility, pelvic surgery, PID, or IUD use.	Common	Classically unilateral adnexal tenderness, adnexal mass, and CMT.	Pelvic US, quantitative β-hCG, T&C, laparoscopy.	Cannot reliably exclude diagnosis based on history and physical examination. Severe pain, hypotension, or peritonitis suggests rupture.
Ruptured ovarian cyst (emergent—critical with significant hemorrhage; otherwise, urgent)	Abrupt moderate to severe lateral pain.	Light-headedness if bleeding is severe; rectal pain arises from fluid in cul-de-sac.		Uncommon	Hypotension and tachycardia if blood loss is significant; possible peritonitis.	Pelvic US, CBC, T&C.	Physical examination findings often do not correlate with volume of blood in pelvis at US.
Ovarian torsion (emergent)	Acute onset of moderate to severe lateral pain.	Nausea and vomiting.	History of ovarian mass or cyst.	Uncommon	Adnexal mass and tenderness, possible peritonitis.	US with Doppler flow studies, laparoscopy.	Torsion can be intermittent.
Appendicitis (emergent)	Duration often <48 hr, generalized followed by localized RLQ pain.	Low-grade fever, nausea, anorexia.	Migration of pain to RLQ from center, abdominal pain before vomiting.	Common	RLQ tenderness, possible peritonitis.	US or CT in unclear cases.	Early in course, tenderness may be minimal or poorly localized.

Continued

www.ketabpezeshki.com 66485457-66963820

Table 33-1 Differentiation of Common or Potentially Catastrophic Causes of Pelvic Pain—cont'd

CAUSATIVE DISORDER OR CONDITION	PAIN HISTORY	ASSOCIATED SYMPTOMS	SUPPORTING HISTORY	PREVALENCE IN ED	PHYSICAL EXAMINATION	USEFUL TESTS	ATYPICAL OR ADDITIONAL ASPECTS
PID, TOA (TOA: emergent; PID: urgent-emergent)	Without TOA, pain usually bilateral. May manifest acutely within 48 hr or subacutely with up to 3 wk of pain.	Fever, vaginal discharge.	Vaginal discharge, history of PID, history of unprotected intercourse or multiple partners.	PID: common TOA: uncommon	Pus from cervical os, CMT, adnexal tenderness. Peritonitis suggests severe PID or TOA.	CBC, ESR, CRP, pelvic US, laparoscopy, cervical cultures, cervical smear for WBCs.	History and physical examination may be inaccurate for diagnosis, particularly in patients with subacute presentation.
UTI (urgent)	Pain with urination. Patient may have flank pain from associated pyelonephritis.	Urinary urgency and frequency; fever and vomiting if patient has associated pyelonephritis.	Recent urologic procedure, prior history of UTI.	Common	Suprapubic tenderness, flank tenderness and fever with pyelonephritis.	Urinalysis, urine culture (if recurrent or complicated).	WBCs can be present in urine with PID and appendicitis. RBCs present in urine with hemorrhagic cystitis.
Ureteral colic (urgent)	Acute onset, manifests within hours. Pain is lateral, usually moderate to severe. Often radiates into the groin or costovertebral angle or flank.	Nausea and vomiting.	Prior history of stones.	Common	Patient often appears uncomfortable, but physical examination can be otherwise unremarkable.	Urinalysis: hematuria present in approximately 80% of cases. Renal ultrasound for hydronephrosis. Abdominal CT.	If stone is at ureterovesicular junction, patient can have localized pain that can mimic appendicitis or other acute pelvic pathology.
Unruptured ovarian cyst or tumor	Lateral ache, gradual onset.	Often minimal.	Prior history of similar pain.	Common	Lateral pelvic tenderness, with or without a mass.	Pelvic US.	
Endometriosis	Unilateral or bilateral pelvic pain, often recurrent.	Dysmenorrhea, dyspareunia.	Prior history of same type of pain in association with menstrual cycle.	Common	Unilateral or bilateral adnexal tenderness, occasionally pelvic mass present, peritoneal findings uncommon.	Pelvic US, laparoscopy.	Symptoms can mimic other types of pelvic pathology; laparoscopy often is needed for confirmation.

CBC, complete blood count; *CMT,* cervical motion tenderness; *CRP,* C-reactive protein; *CT,* computed tomography; *ED,* emergency department; *ESR,* erythrocyte sedimentation rate; *β-hCG,* β-human chorionic gonadotropin; *IUD,* intrauterine device; *PID,* pelvic inflammatory disease; *RBC,* red blood cell; *RLQ,* right lower quadrant; *T&C,* type and crossmatch; *TOA,* tubo-ovarian abscess; *US,* ultrasonography; *UTI,* urinary tract infection; *WBC,* white blood cell.

subjective and unreliable[4,5] and may be most helpful to localize the process to one side or the other or to help focus the workup of the pathologic process to the reproductive organs.

A sequential approach, as outlined next, can progressively limit the diagnostic possibilities until a sound provisional diagnosis is reached.

Symptoms

The location of pain and the radiation pattern often are helpful in focusing the differential diagnosis toward a specific cause or group of causes. Lateral pelvic pain is often related to a process in the tube or ovary. However, with right-sided pain, appendicitis is considered, and in left-sided pain (especially in patients older than 40 years), the differential diagnosis includes diverticulitis and colitis. Urolithiasis may also manifest as lateral pelvic pain, especially when the stone is at the ureterovesicular junction. Central pelvic pain usually is caused by processes involving the uterus or bladder or both adnexae. Pain radiating to the rectum may be secondary to pooling of fluid or blood in the cul-de-sac. Diffuse pain may occur with a central or bilateral process, such as PID, or with diffuse peritonitis from infection or intra-abdominal hemorrhage.

Information regarding the onset and duration of pain may be useful. Patients with uncomplicated appendicitis (without perforation or abscess) typically are seen within 48 hours of symptom onset. Sudden-onset pain suggests acute intrapelvic hemorrhage, cystic rupture, ovarian torsion, or ureterolithiasis. Gradual-onset pain is more consistent with inflammation (such as in PID) or obstruction. Chronic or recurrent pain is consistent with endometriosis, recurrent ovarian cysts, or a persistent ovarian mass. The quality of pain may often but not always differentiate the crampy,

www.ketabpezeshki.com 66485457-66963820

intermittent pattern of muscular contractions along a hollow viscus (arising from, e.g., uterine, ureteral, or bowel pathology) from the steady, progressive pain associated with inflammatory or neoplastic causes. Pain associated with PID often manifests at the end of menses. Ovarian cyst pain may fluctuate through several menstrual cycles and result in rupture, which often occurs in the middle of the menstrual cycle.

Fever and chills are more common with an infectious process. Nausea and vomiting occur more frequently when the process originates within the gastrointestinal tract but also may accompany ovarian torsion, ureteral colic, other causes of severe pain, and pregnancy. Dysuria occurs in many local vulvar and vaginal processes, such as herpesvirus infection, candidiasis, and other types of vulvovaginitis, but urinary urgency typically signals an irritated bladder or urethra and should focus attention on the urinary tract.

Information about the patient's last menstrual period, pattern of menses, and sexual activity pattern is useful but cannot rule out pregnancy. In a pregnant patient, the obstetric history may provide some helpful diagnostic clues. Recurrent spontaneous abortion or previous ectopic pregnancy increases the likelihood of these conditions, respectively. Patients who are actively undergoing infertility treatment are at increased risk for ectopic pregnancy, heterotopic pregnancy, ovarian torsion, and ovarian hyperstimulation syndrome. Round ligament pain is usually noted in the second trimester. Postpartum patients are at increased risk for endometritis.

The presence, quantity, and duration of associated vaginal bleeding should be ascertained. (See also Chapters 34 and 178.) In a nonpregnant patient, bleeding may be associated with PID, trauma, dysfunctional uterine bleeding, or cervical or uterine cancer. In a pregnant patient, bleeding may be associated with a subchorionic hemorrhage in an otherwise viable pregnancy, an ectopic pregnancy, a nonviable intrauterine pregnancy (IUP) (which may continue to cause bleeding after expulsion of the uterine contents, especially if any products of conception are retained), or later in pregnancy with placenta previa or abruption. In some cases the amount of bleeding may be substantial enough to necessitate blood transfusion and surgical intervention.

As part of the past medical history, any recent procedures should be ascertained. All women should be interviewed in private to permit disclosure of sensitive information, such as a sexual history, a known pregnancy, or a recent abortion. The onset of pelvic pain shortly after uterine instrumentation increases the possibility of uterine perforation or infection. Sexual history is important, with an emphasis on recent sexual contact and previous history of sexually transmitted disease.

Signs

The physical examination is directed toward the abdomen and pelvis. Pelvic examination is performed in virtually all patients, including pregnant patients at less than 20 weeks of gestation. Pregnant patients beyond 20 weeks of gestation with complaints of vaginal bleeding should undergo transabdominal pelvic ultrasound study for placental localization before the pelvic examination (see Chapter 178), have a fetal heart rate measured and documented, and may need a timely obstetric consultation.

Abnormal vaginal discharge may be seen in a variety of conditions, including vaginitis, cervicitis, endometritis, PID, and retained foreign body. Cervical motion tenderness most commonly indicates reproductive tract inflammation but also occurs with irritation of adjacent structures (e.g., cystitis, appendicitis). Although an open os is most consistent with an incomplete or inevitable abortion, it does not definitively exclude an ectopic pregnancy. A large uterus in a nonpregnant patient may indicate fibroids. Fundal tenderness is often difficult to distinguish from cystitis but can suggest PID, endometritis, or necrotic fibroids. Unilateral adnexal masses and tenderness are suggestive of an ovarian cyst, ectopic pregnancy, tubo-ovarian abscess, or ovarian torsion.

The constellation of adnexal tenderness, uterine tenderness, and cervical motion tenderness is classically associated with PID, although the diagnosis should be made without the presence of all three signs and may be initiated with only one sign in an at risk patient per the CDC 2010 Guidelines.

Laboratory Tests and Imaging

A pregnancy test is required in almost all patients of childbearing age with a complaint of abdominal pain, irrespective of sexual history or reported contraception use. Very few exceptions to this rule exist, such as a documented hysterosalpingectomy. A positive test result may indicate intrauterine or extrauterine pregnancy or, rarely, molar pregnancy or cancer. Urinalysis of a clean-catch specimen can identify nitrites and pyuria from a urinary tract infection, or hematuria, consistent with urolithiasis and hemorrhagic cystitis. The absence of hematuria does not rule out a ureteral stone, although it lowers the likelihood, and pyuria can be seen in extravesicular conditions, such as appendicitis. Urinalysis should be performed in all pregnant patients with pelvic pain even if their symptoms do not include urinary tract complaints, as urinary tract infection is associated with prematurity, low birth weight, and other complications of pregnancy.

Patients who may be hemorrhaging either internally or externally should have the hemoglobin and hematocrit checked, and type and crossmatch should be performed. Pregnant patients with mild vaginal bleeding also require blood typing to identify Rh-negative patients who will require RhoGAM.

Patients with a positive pregnancy test result should undergo a bedside ED ultrasound or formal ultrasound examination to evaluate for ectopic pregnancy.[7] Identification of an IUP by ultrasound imaging excludes ectopic pregnancy with a high degree of certainty, as heterotopic pregnancy is exceedingly rare in patients who are not undergoing assisted reproduction. Conversely, a patient with a positive pregnancy test in whom a definite IUP cannot be seen is presumed to have an ectopic pregnancy until proven otherwise. In addition, the presence of a gestational sac alone is not enough to confirm an IUP; experienced sonographers can use the double decidual sign, but it is recommended that less experienced sonographers visualize a yolk sac or an embryo for definitive ultrasonographic confirmation of an IUP. A complex adnexal mass, tubal ring, extrauterine yolk sac or embryo, or free fluid is indicative of a probable ectopic pregnancy.[6] The presence of free intra-abdominal fluid on ultrasound with a negative urine pregnancy test is consistent with hemorrhage or a ruptured hemorrhagic ovarian cyst. Regardless of cause, intra-abdominal free fluid is presumed to be blood and is addressed expediently.

DIAGNOSTIC ALGORITHM

The algorithm in Figure 33-1 is designed to help focus further testing and progress to a rational provisional diagnosis. It is not unusual, however, for common diseases to manifest in uncommon ways or for more than one disease to be present, and tests are interpreted carefully in the context of the individual patient's presentation. As examples, patients with a positive result on urinalysis testing may also have appendicitis, and pregnant patients may also have ovarian torsion. With certain diseases, such as endometriosis, definitive testing is not available in the ED, and the patient's history may be the most important discriminator.

After an initial history and physical examination, the pregnancy test determines the subsequent priorities. When a threatened

www.ketabpezeshki.com 66485457-66963820

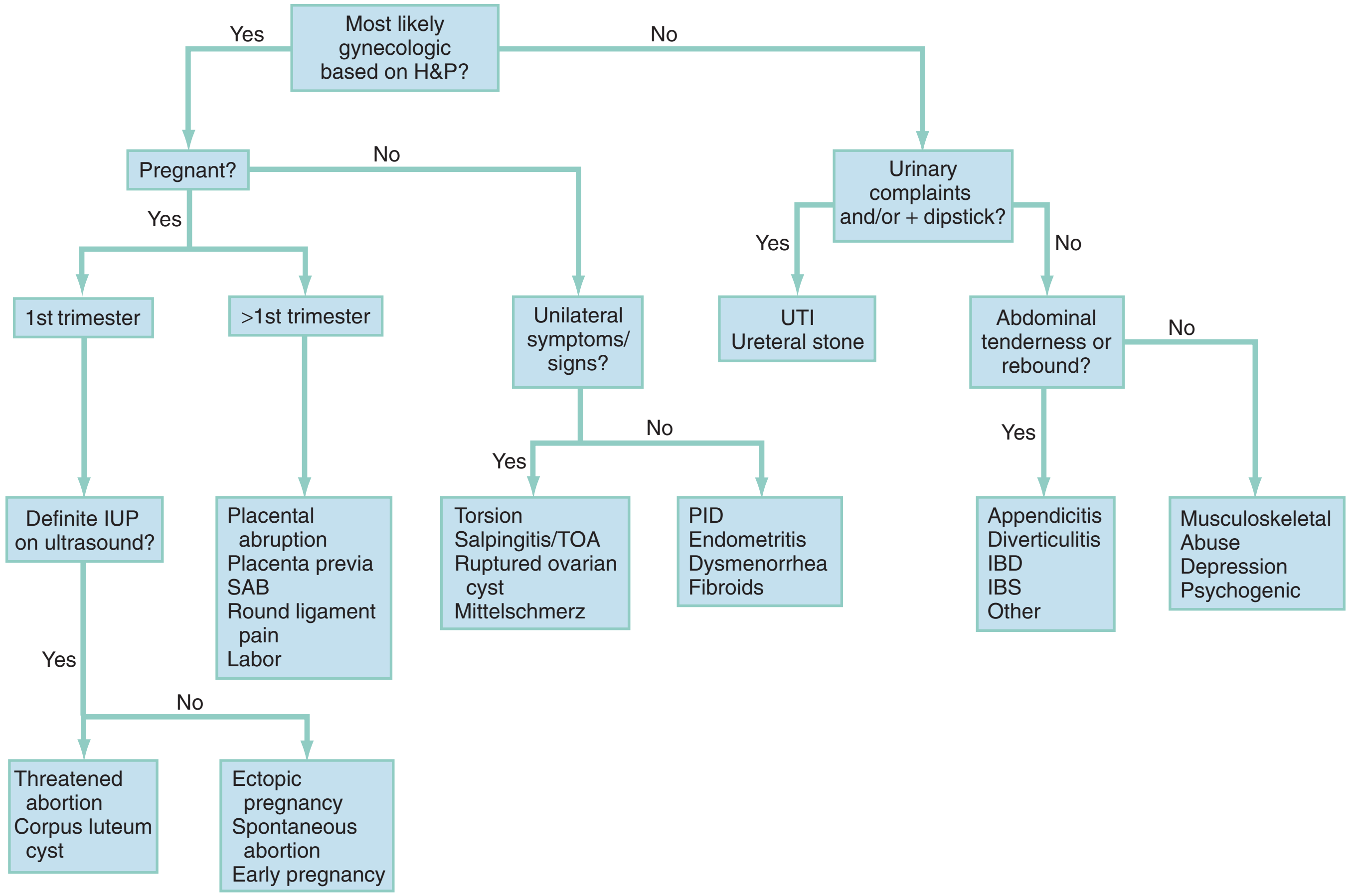


Figure 33-1. Diagnostic algorithm for acute pelvic pain. *H&P,* history and physical; *IBD,* inflammatory bowel disease; *IBS,* irritable bowel syndrome; *IUP,* intrauterine pregnancy; *PID,* pelvic inflammatory disease; *SAB,* spontaneous abortion; *TOA,* tubo-ovarian abscess; *UTI,* urinary tract infection.

abortion is most likely, unilateral pain may prompt further evaluation for torsion. An empty uterus on ultrasound imaging, or any ultrasound study that cannot confirm a definite IUP, could be consistent with an ectopic pregnancy, a spontaneous abortion, or a very early normal pregnancy. Patients past 20 weeks of gestation will require observation with fetal monitoring.

Nonpregnant patients with pain that seems to be gynecologic in nature should be assessed for hemorrhage from a ruptured ovarian cyst; for ovarian torsion (see Chapter 100); and for infection, including cervicitis, endometritis, PID, salpingitis, and tubo-ovarian abscess. Although the history and physical examination often are sufficient to diagnose infection, ultrasound assessment is helpful if torsion, tubo-ovarian abscess, or ruptured hemorrhagic cyst is suspected. Ultrasound findings also may support a diagnosis of PID if evidence of salpingitis is noted, or of a simple ruptured cyst if a characteristic ovarian appearance is combined with presence of a small amount of free fluid. Although not as reliable as CT scanning, ultrasound may be used to examine the appendix.

Because in practice it is difficult to differentiate some gynecologic origins of pain from classic intra-abdominal causes (such as right ovarian pathology from appendicitis), the workup may require an ultrasound study or a CT scan, or both. If the cause appears to be most likely gynecologic, then an ultrasound examination of the ovary and then the appendix is more reasonable, followed by a CT scan if the ultrasound findings are negative and the presentation is possibly consistent with appendicitis or other alternate diagnoses. Patients whose pain does not seem to be from the reproductive tract often have urinary infections or stones, abdominal sources of pain (see Chapter 27), musculoskeletal pathology, may be victims of abuse, or may have depression. Vascular causes of pain are possible but uncommon.

If the available data either do not make sense or conflict with the clinical gestalt, execution of the following three steps should be considered. (1) Ensure that emergent, life-threatening diagnoses have been addressed (e.g., ectopic pregnancy is ruled out). (2) Move back up the algorithm and reassess whether the presentation may be atypical (e.g., reconsider appendicitis as a consideration). (3) If emergent causes are unlikely and sufficient consideration was given to less likely disorders without uncovering a cause, consider the possibility of depression or abuse before disposition. Follow-up planning for all patients is recommended.

EMPIRICAL MANAGEMENT

An algorithm for management of patients with acute pelvic pain is presented in Figure 33-2. Patients who are in extremis are most likely to be hemorrhaging, although on occasion septic shock may be the cause. Ectopic pregnancy, placental abruption, and hemorrhagic ovarian cyst may cause life-threatening hemorrhage with no or minimal vaginal bleeding. Patients with these disorders need rapid treatment with fluid and blood products and may require surgical intervention before stabilization can be achieved. A bedside ultrasound may help the clinician reach the presumptive diagnosis expediently. Septic shock may be a consequence

www.ketabpezeshki.com 66485457-66963820

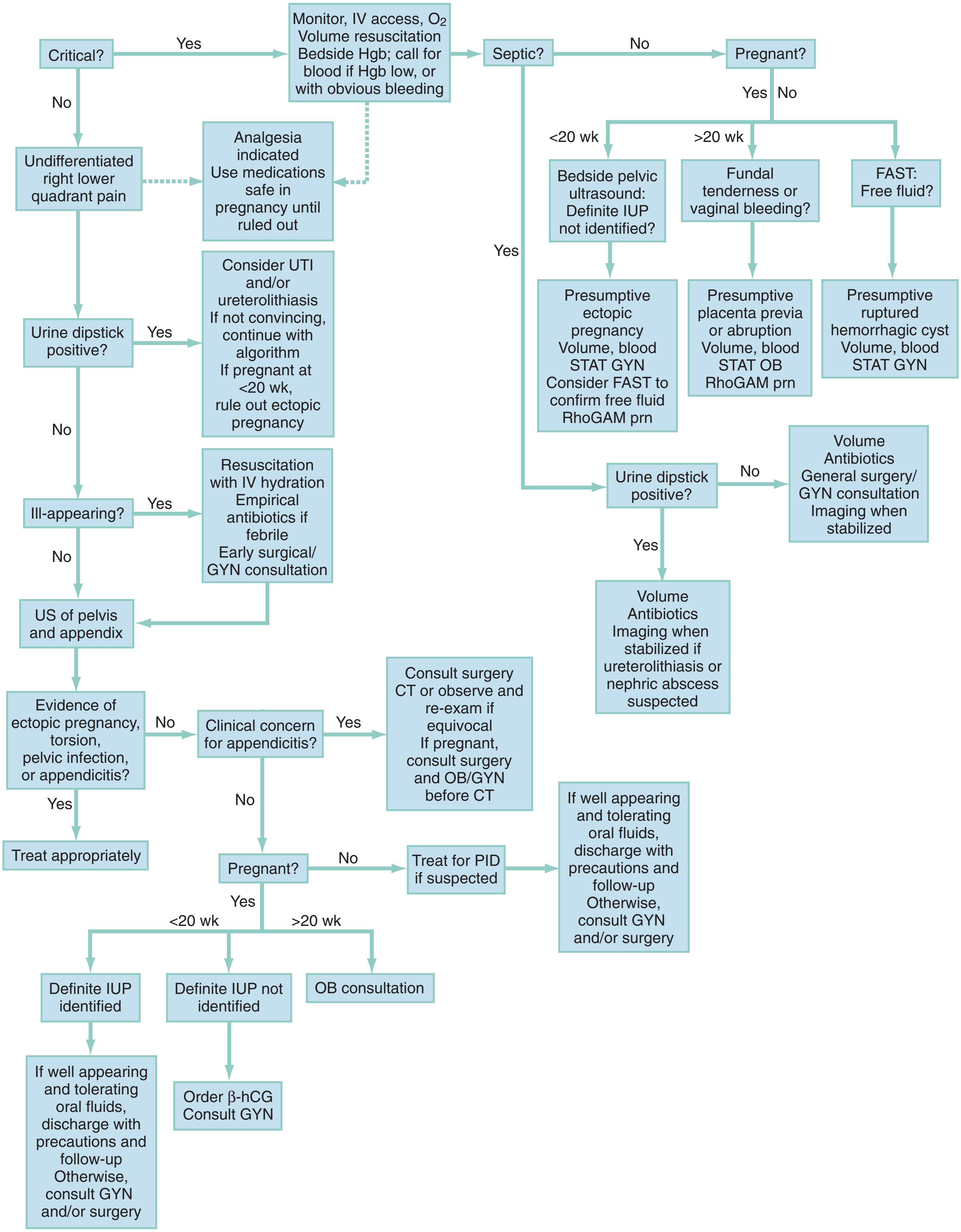


Figure 33-2. Management algorithm for acute pelvic pain: critical patients and right lower quadrant pain presentations. *CT,* computed tomography; *FAST,* focused assessment with sonography for trauma; *GYN,* gynecology; β-*hCG,* β-human chorionic gonadotropin; *Hgb,* hemoglobin; *IUP,* intrauterine pregnancy; *IV,* intravenous; *OB,* obstetrics; *PID,* pelvic inflammatory disease; *STAT,* immediately; *US,* ultrasound; *UTI,* urinary tract infection.

www.ketabpezeshki.com 66485457-66963820

of abdominal or pelvic processes and may require both general surgical and gynecologic consultations, as well as admission to an intensive care setting.

In patients with both critical and noncritical conditions, early administration of analgesia is advisable, both for patient comfort and to improve the yield of examinations. Intravenous opioids, such as morphine, are rapid and effective, titratable, and safe in pregnancy. Patients who do not appear ill and for whom a sound provisional diagnosis is reached may be discharged with close follow-up and appropriate precautions. However, pregnant patients who are at more than 20 weeks of gestation should be referred to the obstetric service for observation. Abdominal trauma in pregnancy, especially later in pregnancy, arouses additional concerns not addressed in this chapter, and patients should undergo monitoring before discharge.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. American College of Obstetricians and Gynecologists: ACOG practice bulletin. Medical management of ectopic pregnancy. *Obstet Gynecol* 2008; 111:1479.
2. Beigi RH, Wiesenfeld HC: Pelvic inflammatory disease: New diagnostic criteria and treatment. *Obstet Gynecol Clin North Am* 2003; 30:777.
3. Rabbani I, Polson DW: Heterotopic pregnancy is not rare: A case report and literature review. *J Obstet Gynaecol* 2005; 25:204.
4. Close RJ, Sachs CJ, Dyne PL: Reliability of bimanual pelvic examinations performed in emergency departments. *West J Med* 2001; 175:240.
5. Padilla LA, Radosevich DM, Milad MP: Limitations of the pelvic examination for evaluation of the female pelvic organs. *Int J Gynaecol Obstet* 2005; 88:84.
6. Reardon RF, Joing SA: *First trimester pregnancy*. In: Ma OJ, Mateer J, Blaivas M, eds: *Emergency Ultrasound*, 2nd ed. New York: McGraw-Hill; 2008.

www.ketabpezeshki.com 66485457-66963820

Chapter 34

Vaginal Bleeding

Hilarie Cranmer

PERSPECTIVE

Vaginal bleeding includes uterine and extrauterine causes. Uterine causes include the constellation of normal uterine bleeding, abnormal uterine bleeding, and dysfunctional uterine bleeding, which is abnormal uterine bleeding in the absence of organic disease. Normal menstrual bleeding occurs cyclically in women who have achieved menarche (the onset of menses), mean age 12.5 years, until menopause (the cessation of menses), mean age 51 years, in North America. The normal cycle, defined as the first day of bleeding of one cycle to the first day of bleeding of the next cycle, lasts 28 days, plus or minus 7 days, and the average volume of blood loss is 60 mL. Vaginal bleeding is defined temporally as midcycle (ovulatory, or at the release of an ova), premenstrual, menstrual, and postmenstrual. Abnormal vaginal bleeding is classified on the basis of the duration, amount, and frequency of bleeding (Table 34-1). Abnormal vaginal bleeding occurs in women of all ages, and it can result from a number of causes, including anatomic abnormalities, complications of pregnancy, hematologic disorders, infections, malignancies, medications, obesity, systemic diseases, and endocrinologic imbalances. Premenarchal or postmenopausal vaginal bleeding is rarely life-threatening, but bleeding as a complication of pregnancy has a significantly increased risk of morbidity and mortality for the mother and fetus[1,2] (see Chapter 178).

Epidemiology

Approximately 5% of women aged 30 to 45 years will see a physician for vaginal bleeding annually. Menorrhagia (regular heavy bleeding) secondary to anovulation is seen in 10 to 15% of all gynecologic patients. Excessive menstrual bleeding accounts for two thirds of all hysterectomies and most endoscopic endometrial destructive surgery. The consequences of menorrhagia include anemia and iron deficiency, reduced quality of life, and increased health care costs.[3] Because black women are more likely to have leiomyomas (fibroids), they experience disproportionately more morbidity from menorrhagia. Invasive neoplasms of the female pelvic organs account for almost 15% of all cancers in women. The most common of these malignancies is uterine cancer, specifically, endometrial cancer. Approximately 10% of postmenopausal bleeding is eventually diagnosed as endometrial cancer. Endometrial cancer is associated with obesity, diabetes mellitus, anovulatory cycles, nulliparity, and age older than 35 years. Both squamous cell carcinoma and adenocarcinoma of the cervix are causally related to infection with the human papillomavirus (HPV), especially types 16 and 18. Smoking and possible dietary factors, such as decreased circulating vitamin A, appear to be cofactors. Preinvasive cancer (cervical intraepithelial neoplasia [CIN III]) is a common diagnosis in women 25 to 40 years of age.

Pregnant Patients

Approximately 20% of all pregnant patients have vaginal bleeding before the 20th week of gestation; more than 50% of these women spontaneously abort, but often before they know they are pregnant. Vaginal bleeding is reported in 50 to 80% of ectopic pregnancies. Ectopic pregnancy is the most common cause of maternal death in the first trimester of pregnancy and accounts for 9% of pregnancy-related maternal deaths in the United States. It is the second leading cause of overall maternal death, following postpartum hemorrhage. Teenagers and women of color have the highest risk of death related to ectopic pregnancy.

Vaginal bleeding after the 20th week of gestation occurs in approximately 4% of pregnancies; approximately 30% of cases are caused by placental abruption (abruptio placentae), and 20% are caused by placenta previa. The most common cause of postpartum hemorrhage in the first 24 hours is uterine atony, but after 24 hours the presence of retained products of conception is the more frequent cause.[4]

Pathophysiology

Nonpregnant Patients

Causes of vaginal bleeding in nonpregnant women are classified as ovulatory, anovulatory, and nonuterine. Ovulation bleeding, a single episode of spotting between regular menses, is quite common. Approximately 90% of dysfunctional uterine bleeding cases result from anovulation, and the other 10% of cases occur with ovulatory cycles. When ovulation does not occur, there is overgrowth of the endometrium because of estrogen stimulation without progesterone to stabilize growth. This results in a persistent proliferative endometrium. Patients at the extremes of menarche are more likely to have endocrinologic causes of disruption of the hypothalamic-pituitary-ovarian system resulting in anovulation. In addition, disruption of this axis is seen with excessive stress, weight loss, and exercise. Bleeding outside the uterus also is considered, including lesions of the vulva, vagina, or cervix, as well as uterine tumors, adnexal masses, and urethral, rectal, and anal disorders.[5] Prepubertal female children may have foreign bodies, genital trauma, or severe vulvovaginitis causing mucosal breakdown and hemorrhage. Exogenous hormone use, most commonly in progesterone-only oral contraceptives and in intrauterine devices, is very common in reproductive-age women. Leiomyomas (fibroids) cause hemorrhage by disrupting the endometrial

www.ketabpezeshki.com 66485457-66963820

Table 34-1 Definitions and Pathophysiology of Vaginal Bleeding

TYPE OF VAGINAL BLEEDING	DURATION, OR NUMBER OF DAYS, OF BLEEDING (NORMAL LASTS 4 DAYS WITH RANGE 2-7 DAYS)	AMOUNT (MEAN BLOOD LOSS IS 40-60 mL)	FREQUENCY (NORMAL CYCLE IS 28 DAYS)
Polymenorrhea	Shorter (<7 days)	Normal	Decreased (<21 days)
Oligomenorrhea	Normal	Normal	Increased (>35 days)
Menorrhagia	Longer (>7 days)	And/or more than 80 mL of blood	Normal
Hypomenorrhea	Normal	Decreased	Normal
Ovulatory bleeding	Normal	Decreased	Normal
Metrorrhagia (intermenstrual or breakthrough bleeding that is frequent and irregular)	Varies	Increased	Irregular
Menometrorrhagia (when metrorrhagia becomes prolonged)	Varies	Increased	Irregular
Dysfunctional uterine bleeding	Longer (>7 days)	And/or more than 80 mL of blood	Irregular
Postmenopausal bleeding	Varies	Varies	Any bleeding that occurs >6 months but <1 year after the cessation of cycles

Table 34-2 Differential Diagnoses of Vaginal Bleeding by Age in Descending Order of Frequency

	PREPUBERTAL	ADOLESCENT	REPRODUCTIVE	PERIMENOPAUSAL	POSTMENOPAUSAL
Most common	Vaginitis	Anovulation	Pregnancy	Anovulation	Endometrial lesions, including cancer (30%)
↓	Anovulation	Pregnancy	Anovulation	Uterine leiomyomas	Exogenous hormone use (30%)
	Genital trauma or foreign bodies	Exogenous hormone use	Exogenous hormone use	Cervical and endometrial polyps	Atrophic vaginitis (30%)
		Coagulopathy (von Willebrand's disease, ITP)	Uterine leiomyomas	Thyroid dysfunction	Other tumor: vulvar, vaginal, cervical (10%)
			Cervical and endometrial polyps		
Least common			Thyroid dysfunction		

ITP, idiopathic thrombotic purpura.

vascular supply and the ability of the uterus to contract to stop bleeding. Cervical and endometrial polyps have vascular pedicles and are prone to bleed.

Pregnant Patients

The differential diagnosis of vaginal bleeding in early pregnancy (before the 20th week of gestation) includes ectopic pregnancy; spontaneous, threatened, complete, incomplete, inevitable, missed, or infected (septic) abortions; implantation bleeding; cervicitis; cervical conditions such as polyp or ectropion; bleeding from the urinary or gastrointestinal tract; trauma and cervical carcinoma; and gestational trophoblastic disease (hydatidiform mole, molar pregnancy). Risk factors for ectopic pregnancy include tubal abnormalities caused by past infection, surgical scarring, or assisted reproductive techniques. Disruption of the blood supply to the ectopic gestational sac can cause hemorrhage into the fallopian tube, or the size of the developing fetus can lead to rupture through the tubal wall.[6,7] Life-threatening vaginal bleeding after the first trimester is often a result of placental abruption. This can occur spontaneously or secondary to abdominal trauma with transmission of forces to the uterus. An increased incidence is seen in association with cocaine use, hypertension, preeclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, smoking, increased maternal age, and abnormal implantation of the placenta (e.g., placenta previa, accreta, increta, or percreta). Placenta previa occurs when the implanted placenta overlays the cervical os. Bleeding is caused by partial separation of the placenta from the uterine wall. Postpartum uterine atony occurs when myometrial dysfunction prevents the uterine corpus from contracting, allowing continued bleeding at the placental site. Atony is more likely to occur with conditions that overdistend the uterus, such as polyhydramnios, multiparity, prolonged labor, induced labor, high Pitocin use during labor, precipitous labor, magnesium therapy, or intrauterine infection (chorioamnionitis).[8] Complications of pregnancy, including vaginal bleeding, are discussed in Chapter 178.

DIAGNOSTIC APPROACH

Differential Considerations

The differential diagnosis can be categorized by age of presentation and frequency of cause (Table 34-2). Primary coagulation disorders account for almost 20% of acute menorrhagia in adolescents. Von Willebrand's disease is the most common; however, myeloproliferative disorders and immune thrombocytopenia are also possibilities.[9] Ectopic pregnancy should be considered in all women of childbearing age with abdominal or pelvic complaints or with unexplained signs or symptoms of hypovolemia.

www.ketabpezeshki.com 66485457-66963820

Additional uterine disorders include endometrial cancer, endometriosis, leiomyomata, adenomas, and sarcomas.

Nonuterine causes of vaginal bleeding are included in the differential diagnosis, systematically addressed during the history taking and physical examination, and pursued with relevant and timely investigations and consultations, if indicated. Potential sources of nonuterine bleeding include the cervix, vagina, adnexa, lower urinary tract, and lower gastrointestinal tract. Cervical causes include carcinoma, polyps, condylomata, eversion of squamocolumnar junction associated with oral contraceptive use or pregnancy, trauma, and some infections, including pelvic inflammatory disease. Adnexal sources include hemorrhagic cysts, ovarian tumors, and polycystic ovarian syndrome. Vaginal sources of bleeding include carcinoma, sarcoma, adenosis, lacerations, infections, and retained foreign bodies. Endometriosis can extend beyond the uterus, and arteriovenous malformations can affect any part of the genital tract. Lower urinary tract lesions, such as urethral furuncles and infected urethral diverticula, may also mimic vaginal bleeding. Rectal and anal causes include cancers, fistulae, and inflammatory disorders that extend to the genital tract.

Pivotal Findings (Symptoms, Signs, and Laboratory)

Symptoms

The volume, duration, and timing of bleeding should be ascertained. The average tampon or pad absorbs 20 to 30 mL of vaginal effluent, although the number of pads or tampons used is unreliable because personal habits vary greatly among women. Bleeding during or after intercourse may indicate a cervical lesion and is more common in pregnancy because of increased blood flow to the cervix. Abdominal pain may indicate critical, emergent, or noncritical causes, depending on the severity of pain, bleeding, and hemodynamic state. Amenorrhea may not indicate pregnancy, and bleeding during approximately the time of the last expected period does not exclude pregnancy. Associated symptoms of nausea, breast tenderness, urinary frequency, and fatigue may indicate that the patient is pregnant. A history of trauma should be considered in an adolescent with bleeding, and sexual assault should be considered in a patient of any age in whom signs of abuse are also present. In the pregnant patient there is significant increased risk of maternal and fetal morbidity and mortality after blunt trauma, such as a motor vehicle accident, interpersonal violence, or a fall. During active labor, a history of previous cesarean section, cocaine abuse, or high doses of oxytocin or prostaglandins should raise the suspicion of uterine rupture.

Signs

A thorough evaluation includes recording and interpreting vital signs, abdominal and pelvic examinations, and, in the pregnant patient of sufficient gestational age, fetal heart tones and fundal height. Vaginal bleeding associated with hemodynamic shock alerts the clinician to ruptured ectopic pregnancy. Fetal heart tones that are below 100 or absent may indicate fetal distress. Pelvic examination may reveal the source of bleeding; however, after the 20th week of gestation, ultrasound should precede pelvic examination to avoid disruption of a possible placenta previa. Bedside transabdominal ultrasound imaging may detect free intraperitoneal fluid in an unstable patient, which should lead to immediate gynecologic or surgical evaluation.

Uterine size, measured from the symphysis pubis to the fundus, is the quickest means of estimating gestational age. This distance in centimeters equals the gestational age in weeks (e.g., 24 cm = 24 weeks), which allows some early estimation of fetal viability if delivery is necessary. As a general guide, the fetus is potentially viable when the dome of the uterus extends beyond the umbilicus. Fetal heart tones can be detected by auscultation at 20 weeks of gestation or by Doppler probe at 10 to 14 weeks. If either the uterus is less than 24 cm in size or fetal heart tones are absent, the pregnancy is probably too early to be viable, and treatment is directed solely at the mother. The limit of viability is the gestational age at which a prematurely born fetus/infant has a 50% chance of long-term survival outside its mother's womb. The cutoff point of 24 weeks has not changed in 12 years, and in general, neonatologists would not resuscitate before 23 weeks. The grey area is 24 to 25 weeks' gestation, accounting for approximately 2 per 1000 births.[9]

Ancillary Testing

In hemodynamically compromised patients, hematocrit, platelet count, prothrombin time, partial thromboplastin time, ABO and Rh typing, and crossmatching of blood should be done. Bedside ultrasound is the imaging modality of choice for simultaneous assessment of the mother and the fetus. In the pregnant trauma patient, it is useful in the detection of major abdominal injury (sensitivity 80%, specificity 100%) and for establishing fetal well-being or demise, gestational age, and placental location.[10] Computed tomography and magnetic resonance imaging are rarely indicated in the evaluation of vaginal bleeding, except in the case of pregnant trauma patients to diagnose potentially life-threatening injuries in those patients not proceeding directly to surgical intervention.

Qualitative pregnancy tests in clinical use are typically reported as positive when the β-human chorionic gonadotropin (β-hCG) concentration is 20 mIU/mL or higher in urine and 10 mIU/mL or higher in serum. At this level of detection, the false-negative rate for detection of pregnancy is less than 1% for urine and 0.5% or less for serum. In clinical use the performance of urine qualitative testing has been found to be 95 to 100% sensitive and specific compared with serum testing. When a urine test result is negative and ectopic pregnancy is still being considered, a quantitative serum test should be performed. The sensitivity of quantitative serum testing for the diagnosis of pregnancy is virtually 100% when an assay capable of detecting 5 mIU/mL or more of β-hCG is used.[11] The discriminatory level of serum β-hCG for ectopic pregnancy is 1500 to 2000 mIU/mL.[12] Additional testing, such as progesterone level, may help to distinguish normal versus abnormal pregnancy. A progesterone level of 5 ng/mL or less indicates a nonviable pregnancy, such as ectopic pregnancy or miscarriage, and excludes a normal pregnancy with 100% sensitivity.[12] Management of ectopic pregnancy is discussed in Chapter 178.

Additional testing for the stable, nonpregnant emergency department patient may be considered on an outpatient basis, depending on availability of follow-up with appropriate, that is, gynecologic, hematologic, or endocrinologic, specialists. This includes thyroid function testing, prolactin levels, or other disorders of the hypothalamic-pituitary tract, including progesterone. For coagulation pathway investigation, a blood smear can determine if there are shistocytes, which would indicate thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), or hemolytic uremic syndrome (HUS) and warrants further inpatient workup and treatment.[14]

DIAGNOSTIC ALGORITHM

The most critical diagnoses to make are ectopic and heterotopic pregnancy, miscarriage, placenta previa or accreta or placental abruption, uterine rupture or trauma, and arteriovenous malformation. The most important factor is to determine the pregnancy status. This may be done by history, for example for the immediate

www.ketabpezeshki.com 66485457-66963820

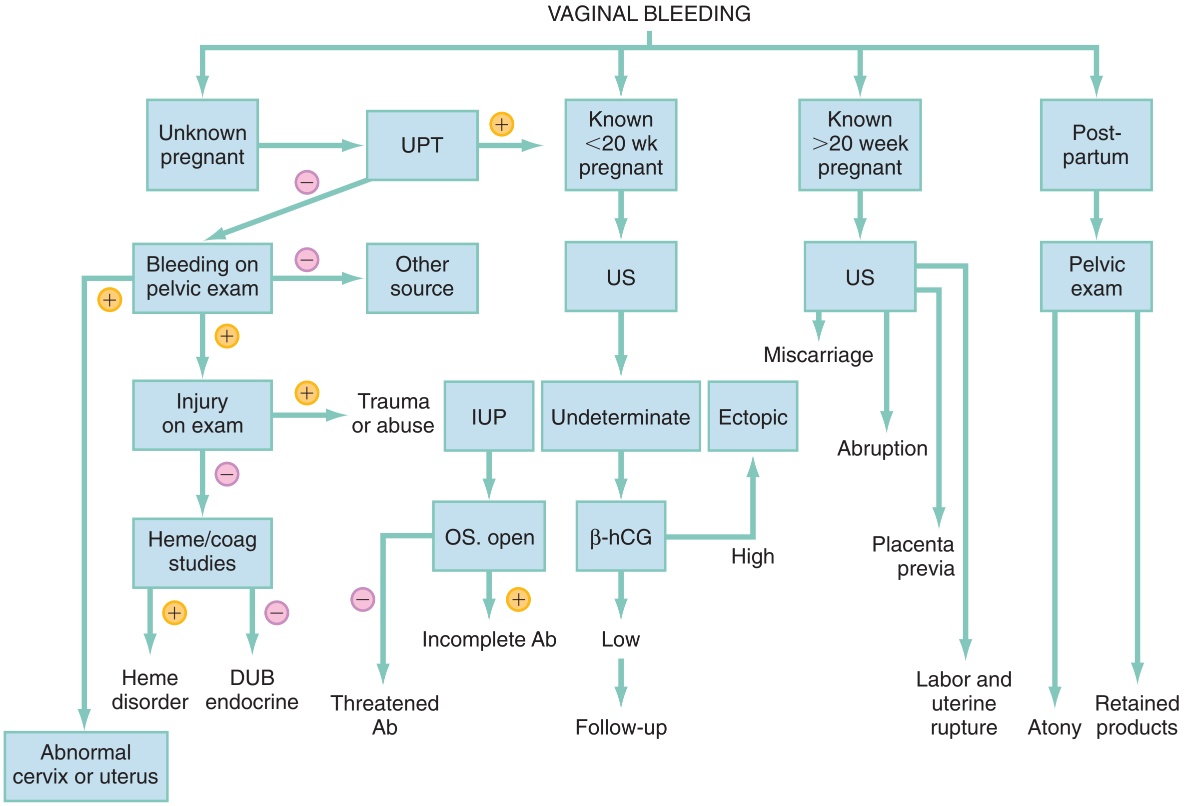


Figure 34-1. Diagnostic algorithm for patient with vaginal bleeding. *Ab,* abortion; β-*hCG,* β-human chorionic gonadotropin; *coag,* coagulation; *DUB,* dysfunctional uterine bleeding; *IUP,* intrauterine pregnancy; *OS,* cervical os; *UPT,* urine pregnancy test; *US,* ultrasonography.

postpartum patient, but when unknown or in doubt, the urine pregnancy test can be obtained. Bedside transabdominal ultrasound helps to determine whether or not there is an IUP and whether or not there is intra-abdominal fluid. Transvaginal ultrasound is optimal, especially with suspected ectopic pregnancy, but may not be immediately available. If there is an IUP of viable age (24 weeks) with no intra-abdominal free fluid, avoid manipulation of the cervix but consider placenta previa or accreta or placental abruption, miscarriage, or arteriovenous malformation. In following the diagnostic algorithm (Fig. 34-1) for early pregnancy, the most frequent diagnosis will be threatened abortion.

A small number of women will have extrauterine bleeding, and those with abnormalities of the urethra, perineum, and rectoanal areas should be referred to the appropriate surgical specialists. The pelvic examination may identify women with injury from trauma and sexual abuse. On speculum examination of the cervix, obtain cultures. If the cervix is abnormal, consider cancer, polyps, infection, or dysplasia. Outpatient gynecologic evaluation including a Pap smear, should be planned. Most nonpregnant women will have vaginal bleeding but no other abnormalities, and other possibilities should be considered. Possible medication causes include anticoagulants, selective serotonin reuptake inhibitor (SSRIs), antipsychotics, corticosteroids, hormonal medications and devices, and tamoxifen (Nolvadex). Possible herbal supplements include ginseng, ginkgo, and soy supplements. This will require medication adjustment and outpatient management. For possible systemic conditions, consider hepatic disease, hematologic disorders, and conditions of the thyroid, adrenal, pituitary, and hypothalamic systems. With vulval or vaginal sources, gynecologist consultation will help investigate cancer, infection, trauma, fistulae, and prior gynecologic surgical complications. After this algorithm has been completed, most patients will not have a known organic cause and will be diagnosed with dysfunctional uterine bleeding.

EMPIRICAL MANAGEMENT

All patients should be resuscitated with oxygen, intravenous crystalloid, and blood transfusion as needed. Use Rh-negative blood in women of child-bearing age with unknown Rh status. A patient in shock with a surgical abdomen or evidence of intra-abdominal free fluid should be resuscitated and promptly evaluated with immediate consideration of operative intervention in consultation with obstetrics and gynecology or general surgery. For a viable pregnancy to be saved, possible emergent cesarean section in the operating room may be required. For IUP of nonviable age, arteriovenous malformation (AVM), ectopic or heterotopic pregnancy, and miscarriage are considered; possible management includes dilation and evacuation or curettage. Management of the pregnant patient is discussed in detail in Chapter 178. When intra-abdominal fluid is present, regardless of pregnancy status, surgical and possible interventional radiology consultation should be undertaken. Consideration is given to ruptured uterus, ruptured ectopic or heterotopic pregnancy, or ruptured spleen or liver, and the patient should be brought the operating room for surgical and radiologic intervention. If vaginal bleeding is persistent and life-threatening, hysterectomy may be performed (Fig. 34-2).

If the os is open larger than a finger tip in pregnancy <20 weeks, the result will be a spontaneous miscarriage or necessitate a therapeutic abortion. The patient should have Rh status checked and should be treated with RhoGAM if Rh negative in the emergency department.

In nonpregnant patients, heavy vaginal bleeding may be under ovulatory control or related to anovulatory dysfunctional uterine bleeding. Nonsteroidal anti-inflammatory drugs are the mainstay of treatment for both conditions, although the exact mechanism of action is not clearly understood.[15] In nonpregnant hemodynamically unstable patients, intravenous (IV) or intramuscular

www.ketabpezeshki.com 66485457-66963820

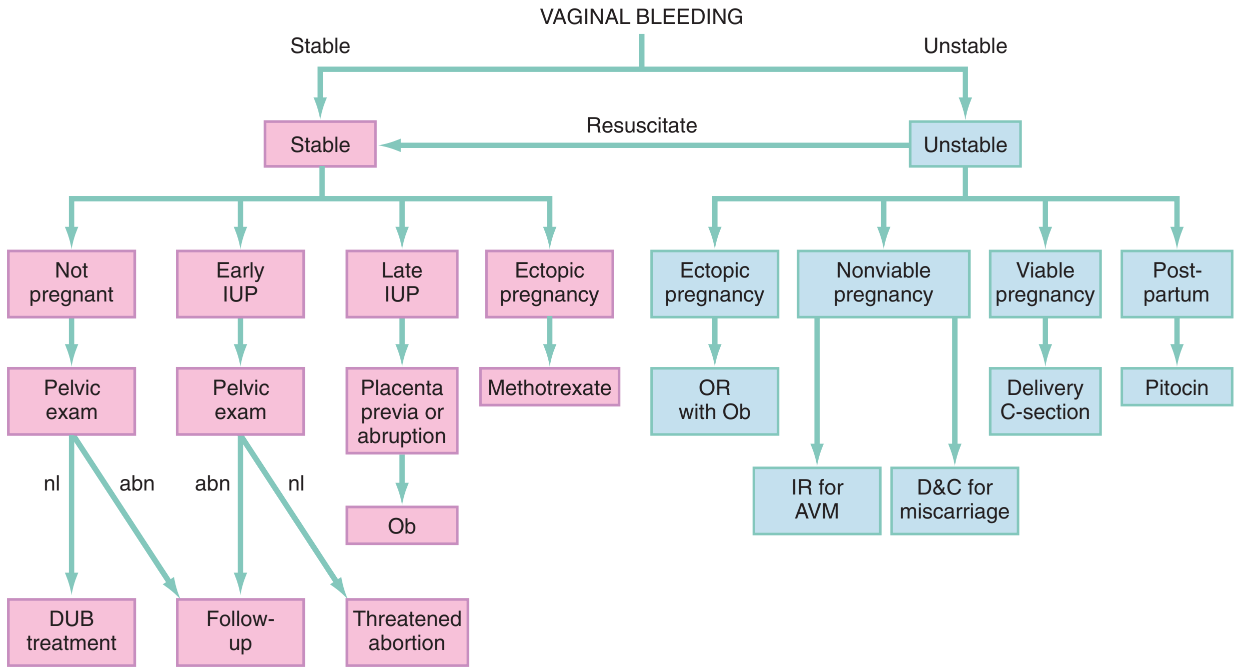


Figure 34-2. Empirical management of the patient with vaginal bleeding. *abn,* abnormal; *AVM,* arteriovenous malformation; *D&C,* dilation and curettage; *DUB,* dysfunctinoal uterine bleeding; *IR,* interventional radiology; *nl,* normal; *Ob,* obstetrician; *OR,* operating room.

(IM) conjugated estrogen (Premarin) 25 mg may be administered, with repeat doses in 4 to 6 hours. If bleeding continues after IV or IM, a pediatric Foley catheter inserted into the cervical os and inflated can tamponade the bleeding. The balloon is distended with saline until the bleeding stops. A larger balloon may be needed, and this can be left in place for 12 to 24 hours.[16]

Hemodynamically stable patients can be referred for follow-up. Outpatient treatment with oral contraceptives can arrest bleeding An oral contraceptive with 35 µg of ethinyl estradiol can be taken twice a day until the bleeding stops or up to 7 days. The dose is decreased to once a day until the pack is completed. Patients with contraindications to estrogen therapy (history of thromboembolic event or stroke, estrogen-dependent tumor, active liver disease, pregnancy, hypertriglyceridemia, smoking when older than age 35) can be treated with progesterone-only hormonal therapy—10 mg of medroxyprogesterone (Provera) once a day for 14 days—and outpatient follow-up in 2 to 4 weeks.

Patients older than 35 years or with risk factors for endometrial cancer should undergo endometrial biopsy within 1 week of starting hormonal manipulation. Baseline hemoglobin and hematocrit are recommended. Finally, other medical causes, such as hypothyroidism, hemostasis disorders, or anticoagulant therapy, are considered, and appropriate outpatient consultation should be undertaken.

DISPOSITION

Any patient with continued symptomatic bleeding, especially with persistent hypotension and low hematocrit, should be admitted to the hospital for management and possible transfusion. In a patient with stable vaginal bleeding, medical management is often sufficient. In a preadolescent patient, abuse should be ruled out before the patient is discharged to her current environment. All patients with abnormal uterine bleeding should receive close follow-up from a primary care physician or gynecologist. In a nonpregnant stable patient, malignancy should be considered, and additional inpatient or timely outpatient gynecologic follow-up is indicated. Laboratory studies, such as thyroid function and prolactin levels, may be helpful to the consultant or in the initial outpatient workup of dysfunctional uterine bleeding, but they are not required in the emergency department.[17]

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Clinical policy for the initial approach to patients presenting with a chief complaint of vaginal bleeding. American College of Emergency Physicians. *Ann Emerg Med* 1997; 29:435.
2. ACEP Clinical Policies Committee and Clinical Policies Subcommittee on Early Pregnancy. American College of Emergency Physicians: Clinical policy: Critical issues in the initial evaluation and management of patients presenting to the emergency department in early pregnancy. *Ann Emerg Med* 2003; 41:123.
3. Frick KD, et al: Financial and quality-of-life burden of dysfunctional uterine bleeding among women agreeing to obtain surgical treatment. *Womens Health Issues* 2009; 19:70-78.
4. Oyelese Y, Scorza WE, Mastrolia R, Smulian JC: Postpartum hemorrhage. *Obstet Gynecol Clin North Am* 34:421, 2007.
5. Daniels R, McCuskey C: Abnormal vaginal bleeding in the non-pregnant patient. *Emerg Med Clin North Am* 2003; 21:45.
6. Coppola P, Coppola M: Vaginal bleeding in the first 20 weeks of pregnancy. *Emerg Med Clin North Am* 2003; 21:41.
7. Della-Giustina D, Denny M: Ectopic pregnancy. *Emerg Med Clin North Am* 2003; 21:565.
8. Ananth CV, Oyelese Y, Yeo L, Pradhan A, Vintzileos AM: Placental abruption in the United States, 1979 through 2001: Temporal trends and potential determinants. *Am J Obstet Gynecol* 2005; 192:191.
9. Vavasseur C, Foran A, Murphy JF: Consensus statements on the borderlands of neonatal viability: From uncertainty to grey areas. *Ir Med J* 2007; 100:561-564.
10. Brown MA, Sirlin CB, Farahmand N, Hoyt DB, Casola G: Screening sonography in pregnant patients with blunt abdominal trauma. *J Ultrasound Med* 2005; 24:175.
11. Pitkin J: Dysfunctional uterine bleeding. *BMJ* 2007; 334:1110-1111.
12. Kaplan BC, et al: Ectopic pregnancy: Prospective study with improved diagnostic accuracy. *Ann Emerg Med* 1996; 28:10.
13. Reference deleted in proofs.
14. James AH, et al: Von Willebrand disease and other bleeding disorders in women: Consensus on diagnosis and management from an international expert panel. *Am J Obstet Gynecol* 2009; 201:12.e1-e8.
15. Lethaby A, Augood C, Duckitt K, Farquhar C: Nonsteroidal anti-inflammatory drugs for heavy menstrual bleeding. *Cochrane Database Syst Rev* 2007; 4:CD000400.
16. Estaphan A, Dyne PL: Dysfunctional uterine bleeding: treatment and management. Available at http://emedicine.medscape.com/article/795587-treatment. Accessed September 28, 2012.
17. Dickersin K, et al: Hysterectomy compared with endometrial ablation for dysfunctional uterine bleeding: A randomized controlled trial. *Obstet Gynecol* 2007; 110:1279-1289.

www.ketabpezeshki.com 66485457-66963820

Chapter 35

Back Pain

Brian D. Mahoney

PERSPECTIVE

Back pain is a common symptom causing patients to seek care in the emergency department (ED). It accounts for 2.3% of all physician visits,[1] and 84% of the adult population have experienced low back pain in their lifetime.[2] Forty-nine percent have experienced low back pain in the last 6 months,[2] and 26% in the last 3 months.[1] Total costs of low back pain in the United States exceed $100 billion per year.[3] Although mechanical or nonspecific low back is the most common cause, the differential diagnosis includes several life-threatening and disabling conditions (Box 35-1). Developing a systematic approach that screens all the potential causes of back pain is the key to accurate clinical decision-making.

Epidemiology

Ninety-seven percent of patients visiting a physician for evaluation of acute low back pain, defined as lasting less than 6 weeks, are ultimately diagnosed with mechanical or nonspecific low back pain.[4] The vast majority of these are strain and degenerative in origin, but a few percent have herniated disk, spinal stenosis, fracture, and congenital disorders. Seventy-two percent will have completely recovered at 1 year.[5] For those with chronic back pain, defined as lasting longer than 3 months, persistence or a recurrence within 12 months is very common.[6] About 1% of all patients with back pain have true sciatica.[6] Back pain is the second most common cause of lost time in the workplace and an enormous source of health care expenditures and lost productivity.[7,8] The prevalence of chronic low back pain is rising.[9]

Before these common mechanical causes are considered, several emergent diagnoses should be excluded, including aortic dissection, abdominal aortic aneurysm, cauda equina syndrome, epidural abscess, osteomyelitis, and tumor. The presence of certain symptoms (Box 35-2) should prompt a more thorough examination of these possibilities. Visceral causes constitute about 2% of the diagnoses in patients with back pain.[4] Aortic dissection is a rare but catastrophic event, with mortality rates exceeding 90% if it is not diagnosed. Cauda equina syndrome (bilateral leg pain and weakness, urinary retention with overflow incontinence, fecal incontinence or decreased rectal tone, and "saddle anesthesia") is a rare but rapidly progressive disabling complication usually caused by a large central herniated disk and less often by tumor or infection. Epidural abscess and vertebral osteomyelitis constitute 0.01% of the diagnoses in patients complaining primarily of back pain.[4] Spinal carcinoma is uncommon (0.7%) in the general population with back pain,[4] but in cancer patients, 80% who report back pain have spinal metastases. Metastasis to bone is seen commonly in breast, lung, prostate, kidney, and thyroid carcinomas. Other tumors include primary bone cancers, multiple myeloma, lymphoma, and retroperitoneal tumors. Inflammatory arthritis is the diagnosis for 0.3% of patients with back pain.[4]

Pathophysiology

Reasons for back pain include vascular, visceral, infectious, mechanical, and rheumatologic causes. Pain may originate in the spinal column, cord or root, or musculature or from thoracic, abdominal, or pelvic organs.

The gelatinous nucleus pulposus is surrounded by the tough anulus fibrosus. The anulus thins posteriorly, creating the opportunity for the nucleus pulposus to herniate. This varies from bulging to protrusion to extrusion to sequestration. Ninety-five percent of clinically significant herniations occur at the L4-5 and L5-S1 disk spaces, causing radicular pain in the L5 and S1 dermatomes.[4] Involvement of the L5 nerve root manifests with decreased sensation in the first web space, weakness with extension of the great toe, but normal reflexes. An S1 radiculopathy is characterized by diminished sensation of the lateral foot and small toe, impaired plantar flexion, and a decreased or absent ankle jerk. Anatomic disk bulging (52-81%) and annular tears with focal disk protrusion (32-67%) usually do not cause symptoms, whereas disk extrusion (0-18%) is usually symptomatic.[10-13] Serial magnetic resonance imaging (MRI) studies show that two thirds of herniated disks regress or resolve over 6 months.[4] Three fourths of patients' symptoms improve within 6 weeks. In the absence of suspected cauda equina syndrome, computed tomography (CT) or MRI is not indicated in the evaluation of patients with suspected disk herniation. Many patients with a herniated disk improve over time, and many asymptomatic patients have radiographic findings, so imaging is not helpful and may be misleading. This natural resolution of symptoms in disk disease is in contrast to spinal stenosis, which tends to remain the same or worsen over time.[4] The ligamentum flavum can thicken with age and along with degenerative changes contributes to spinal stenosis.

The spinal cord ends at L1 in the adult, where it gives rise to the cauda equina. Compressive lesions above the cauda equina cause upper motor neurologic signs. Compression of the cauda equina leads to lower motor neurologic findings.

DIAGNOSTIC APPROACH

Differential Considerations

The emergency physician first evaluates for potential life-threatening and disabling causes of back pain, including thoracic aortic dissection, ruptured abdominal aortic aneurysm, epidural abscess or compressive mass, spinal column injury with cord or root compression, and cauda equina syndrome. An accurate

www.ketabpezeshki.com 66485457-66963820

Box 35-1 Differential Considerations in Acute Low Back Pain

Emergent
Aortic dissection
Cauda equina syndrome
Epidural abscess or hematoma
Meningitis
Ruptured or expanding aortic aneurysm
Spinal fracture or subluxation with cord or root impingement

Urgent
Back pain with neurologic deficits
Disk herniation causing neurologic compromise
Malignancy
Sciatica with motor nerve root compression
Spinal fractures without cord impingement
Spinal stenosis
Transverse myelitis
Vertebral osteomyelitis

Common or Stable
Acute ligamentous injury
Acute muscle strain
Ankylosing spondylitis
Degenerative joint disease
Herpes zoster
Intervertebral disk disease without impingement
Pathologic fracture without impingement
Seropositive arthritis
Spondylolisthesis

Referred or Visceral
Cholecystitis or biliary colic
Esophageal disease
Nephrolithiasis
Ovarian torsion, mass, or tumor
Pancreatitis
Peptic ulcer disease
Pelvic inflammatory disease, endometriosis
Pleural effusion
Pneumonia
Prostatitis
Pulmonary embolism
Pyelonephritis
Retroperitoneal hemorrhage or tumor

Box 35-2 Important Elements of History and Physical Examination

Historical Information
Recent significant trauma
Recent mild trauma in patients older than 50 years
History of prolonged steroid use
History of osteoporosis
Patients older than 70 years
Children without clear mechanism
Syncope
Acute onset of back, flank, or testicular pain
Diaphoresis or nausea associated with pain
History of cancer
Low back pain worse at rest or night pain
Unexplained weight loss
Recent bacterial infection
Unexplained fever >38° C (>100° F)
Intravenous drug use
Immunocompromised status
Failure to improve after 6 weeks of conservative therapy

Physical Examination
Abnormal vital signs—hypotension, hypertension, tachycardia, fever
Unequal blood pressure readings in the upper extremities
Murmur of aortic insufficiency
Pulse deficit or circulatory compromise of the lower extremities
Pulsatile abdominal mass
Urinary retention, loss of rectal sphincter tone
Focal lower extremity weakness
Focal back pain with fever

history and physical examination guide the investigation of possible more serious underlying pathologic process (see Boxes 35-1 and 35-2).[4] Laboratory tests and imaging are needed in some cases, but it is usually possible to rule out significant pathology without recourse to extensive testing.

Rapid Assessment and Stabilization

If the initial history and physical examination identify any suggestion of serious disease, rapid stabilization measures should ensue consistent with the cause of concern (Fig. 35-1). Management of aortic dissection, ruptured abdominal aortic aneurysm, and spinal cord and column injuries are covered in other chapters. If epidural abscess, hematoma, or cauda equina syndrome is suspected, emergent MRI is obtained, with neurosurgical consultation when indicated by the results of the scan. For epidural abscess, blood cultures are obtained, followed by intravenous administration of antibiotics against *Staphylococcus aureus.* For cauda equina syndrome,[14] an urgent neurosurgical consultation is required. Once urinary retention occurs, the prognosis worsens and emergent spinal decompression is indicated. Although the evidence supporting steroid use is conflicting, dexamethasone is commonly used with the hope of decreasing compression from inflammation or to shrink tumor mass. For all patients with significant pain, including patients with "benign" causes for back pain, effective analgesia should be provided early in the evaluation.

Pivotal Findings

The history and physical examination should help sort patients into unstable and stable categories (see Fig 35-1). Certain findings will guide additional workup to discover causes for patients with neurologic deficits, and more serious spinal or visceral sources (see Box 35-2).

History

History of Present Illness. The history helps to localize pain to the most likely structure and mechanism. The following questions are useful in differentiating between mechanical and nonmechanical causes and between unstable and stable patients and help guide appropriate management.

Where is the pain? The patient is asked to point with one finger to the one spot where it hurts the most. Does the pain radiate, and if so, specifically where? Does the pain conform to a specific dermatomal area? Radicular pain, particularly extending below the knee in a dermatomal distribution, implies nerve root involvement. Sciatica radiates below the knees, causing focal motor and sensory loss. It worsens with bending, sitting, coughing, sneezing, and straining. Pain mainly in the paralumbar musculature without dermatomal radiculopathy implies nonspecific low back pain. Any associated chest or abdominal pain may indicate a visceral cause. Flank location implies a renal or retroperitoneal origin, and a higher location can be from the chest or pleura.

When did the pain start? The patient should describe in detail what he or she was doing when the pain started. Has there been a recent change in type or intensity of physical activity? Is

www.ketabpezeshki.com 66485457-66963820

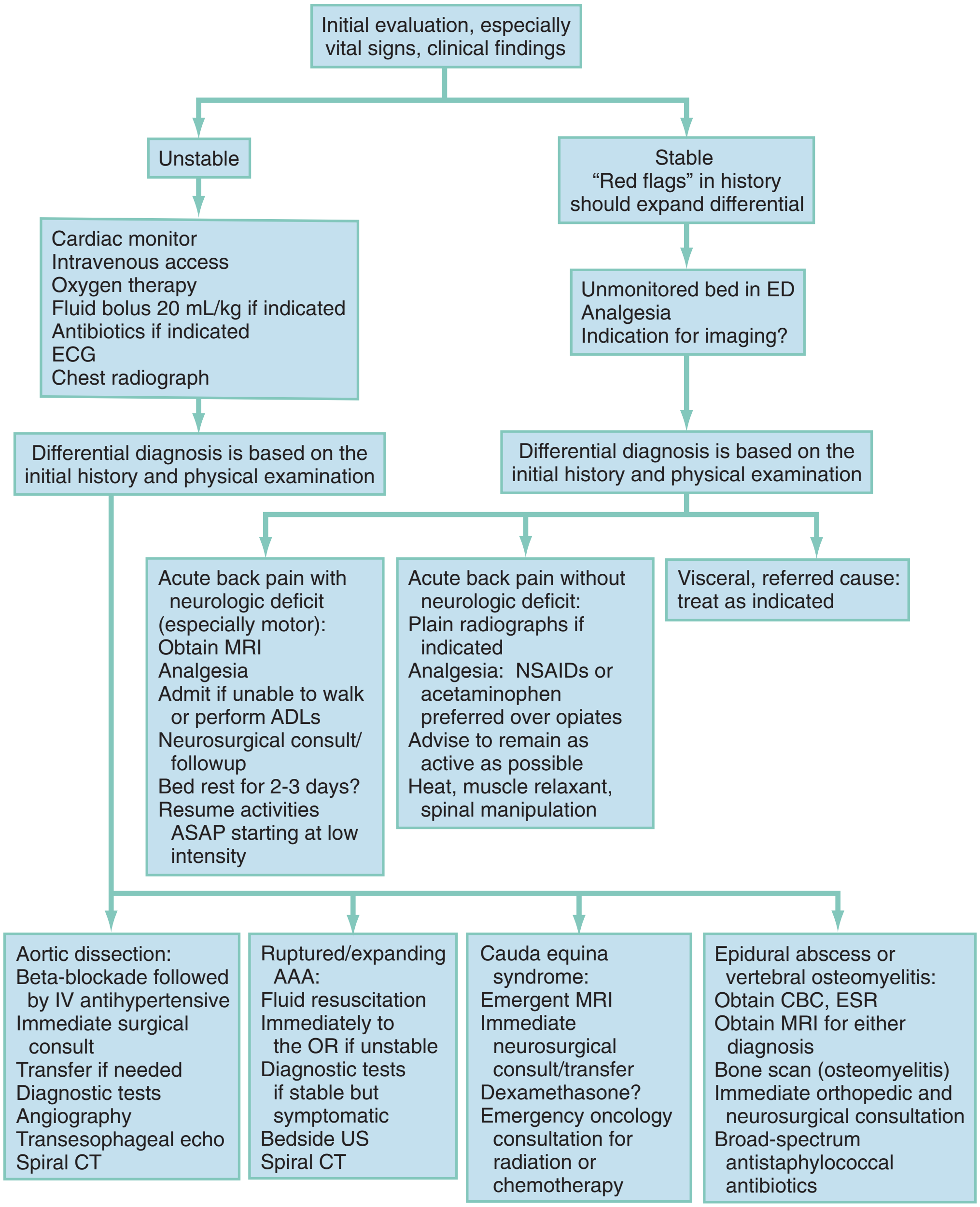


Figure 35-1. Management of acute low back pain. *AAA,* abdominal aortic aneurysm; *ADLs,* activities of daily living; *ASAP,* as soon as possible; *CBC,* complete blood count; *CT,* computed tomography; *ECG,* electrocardiogram; *echo,* echocardiogram; *ED,* emergency department; *ESR,* erythrocyte sedimentation rate; *IV,* intravenous; *MRI,* magnetic resonance imaging; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *US,* ultrasound.

there any past history of back pain, and what therapeutic modalities were used to treat it? If there is a history of back pain, is there any difference between present and past pain? Acute onset associated with a specific task suggests a mechanical cause. Sudden-onset, severe back pain suggests a vascular cause. Slow onset or onset unrelated to activity suggests a nonmechanical cause (e.g., tumor). Nonmechanical pain may improve then recur, but the trend is progressive worsening.

Are there any aggravating or alleviating factors? Cough or Valsalva maneuver that aggravates the pain in general favors a mechanical cause and may suggest a herniated disk. Back pain associated with tumors and infections often involves nighttime pain and persistent pain unrelieved by rest and analgesics. Spinal stenosis causes diffuse back pain, numbness, and tingling in one or both legs (pseudoclaudication). Symptoms are aggravated by ambulation (especially "downhill") and relieved with spinal flexion (shopping cart sign), which increases spinal canal diameter, temporarily relieving the stenosis. Direct trauma may suggest contusion, strain, or fracture, whereas sudden deceleration is a risk for aortic dissection.

Is there motor or sensory loss, bowel or bladder dysfunction? Back pain associated with progressive or severe neurologic symptoms, motor loss, urinary retention, or bowel incontinence requires MRI, which may indicate the need for emergent decompression.

Is there other pertinent history? Other pertinent history should include past and present work history (a history of repeated loading would suggest mechanical cause); fever (suggesting infectious cause); medications (anticoagulants are associated with epidural hematomas, steroids are associated with infection and compression fractures); hematuria (suggesting nephrolithiasis or pyelonephritis); colic (nephrolithiasis, cholelithiasis); and pending litigation or worker's compensation status (possible secondary gains).

www.ketabpezeshki.com 66485457-66963820

Past Medical History. In addition to any history of back disorders, a thorough inquiry about any systemic disease is important, including (1) cancer (metastatic disease), (2) inflammatory disease, (3) intravenous drug abuse (diskitis), (4) arthropathies, (5) endocrinopathies (hyperparathyroidism), (6) bleeding disorders, (7) osteoporosis, or (8) sickle cell disease. Previous atherosclerotic or vascular disease suggests aortic disease; previous kidney stones or alcohol-related disease may suggest related diseases. The medications or other modalities used to treat present and past symptoms may suggest possible treatment. Knowledge of current medications used by the patient gives clues about the presence of other systemic disease. Some diseases such as spondyloarthropathies (e.g., ankylosing spondylitis) have a familial component.

Physical Examination

Vital Signs. Abnormal vital signs may suggest a life-threatening process (e.g., hypotension and tachycardia with ruptured abdominal aortic aneurysm, hypertension with aortic dissection, fever with abscess, osteomyelitis, or diskitis).

Lower Back Inspection

1. Observe the patient's gait and movement in the examining room. Does the patient move cautiously, protecting himself or herself, or freely, appearing to be in little pain?
2. Examine the patient while he or she is standing, searching for scoliosis (may be structural or secondary to muscle spasm), increase or decrease in lumbar lordosis or thoracic kyphosis (may predispose to mechanical pain), or pelvic obliquity (may indicate muscle spasm, leg-length discrepancy, or uncompensated scoliosis).
3. Assess the range of motion for the low back. Significant mechanical pain usually worsens with flexion. Extension often eases pain caused by disk disease but may aggravate facet pain.
4. Perform the palpation in an orderly fashion with the fingertips to localize the area of greatest tenderness (e.g., specific spinous process; paravertebral musculature; sacroiliac joint suggesting inflammatory spondylitis).

Other Examinations, Including Neurologic Examination

1. The neurologic assessment evaluates the asymmetry of reflexes (clinically, reflexes diminish with age, and uncovering asymmetry is key), dermatomal sensory loss, and focal muscle weakness (suggests nerve root impingement). If possible, motor testing of the legs is best done with the patient standing. Heel-walking and toe-walking indicate normal plantar and dorsiflexion strength, and a partial knee bend while bearing weight on one leg, then the other, indicates normal hip, buttock, and thigh muscle strength. A patient with a long history of back pain should be asked about previous motor, sensory, or reflex abnormality. The presence of clonus, hyper-reflexia, or upgoing toes (Babinski's sign) indicates an upper motor neuron lesion.
2. A rectal examination can assess sphincter tone and anal wink. Testing for perianal sensation is necessary if there is any history of bowel or bladder dysfunction.
3. An examination for signs of systemic disease should include cardiac and pulmonary auscultation; abdominal examination for tenderness, aneurysm, or masses; and palpation of peripheral pulses.
4. The hips are examined for a musculoskeletal or inflammatory focus other than the back.

Straight Leg Raise. The straight leg raise is the classic test for sciatic nerve root irritation. It is 92% sensitive but only 28% specific for disk disease.[15] This test is often negative in patients with spinal stenosis. With the knee extended, the leg is elevated until pain is elicited. A positive result is pain radiating down the leg below the knee (not back, buttocks, or thigh pain) in a dermatomal distribution, reproductive of the patient's symptoms, when the leg is elevated between 30 and 70 degrees. The crossed straight leg test (pain radiates below the knee on the side of nerve root irritation when the unaffected leg is raised) is only 28% sensitive but 90% specific for nerve root irritation on the contralateral side resulting from disk herniation. In a patient who may be malingering, the straight leg raise can be done with the patient sitting with the knees flexed at the side of the bed and then passively straightening the legs. If there is true nerve root irritation, results should be similar in the sitting and the supine positions.

Ancillary Testing

Laboratory Tests. For mechanical causes of back pain, laboratory studies are of little use and are rarely ordered. For nonmechanical causes, erythrocyte sedimentation rate and white blood cell count are often obtained, but poor specificity, sensitivity, or both severely limit any meaningful interpretation of the results. Urinalysis is helpful in suspected cases of renal disease with referred back pain (nephrolithiasis, pyelonephritis, urinary tract infection).

Imaging. Although patient satisfaction is reportedly higher when imaging is performed,[16] early imaging is not useful and does not change management with uncomplicated mechanical low back pain of less than 6 weeks' duration.[17] Plain radiographs may be helpful if the patient has a history of trauma with bony tenderness. Pathologic fracture can occur with minimal or no trauma and is suspected in patients with rapid onset of back pain in the context of cancer, advanced age, osteoporosis, or prolonged glucocorticoid use,[16] but plain radiographs should not be obtained if advanced imaging (e.g., CT, MRI) is planned. The vast majority of patients do not require radiographic evaluation in the ED.[18,19]

Whether to use plain film, CT, or MRI is influenced by several factors, including cost (plain film < CT < MRI), radiation exposure of the patient (MRI < plain film < CT), the detail of the information the imaging will provide (plain film < CT < MRI), and off-hours accessibility of an imaging modality at a particular facility (MRI < CT < plain film). Plain films give reasonable detail in showing fracture, particularly in the lumbar spine. However, CT will add greatly to bone detail over plain films. CT will often show additional lesser fractures after the plain film has already demonstrated the major fracture. The neurosurgeon or orthopedic surgeon will likely want CT or MRI after plain films have shown bone pathology in the back. In general, CT gives excellent bone detail and only moderate detail of soft tissue. MRI gives excellent detail of soft tissue and only moderate detail of bone. Plain film is used for straightforward evaluation for fracture, or as a screening tool for other issues when the prior probability of serious injury or pathology is low. CT is used if a spine fracture has been identified or a more complex fracture is suspected. MRI is used if a disk condition, hematoma, infection, or a mass is suspected to be the cause of the problem. Emergency MRI, CT, or, rarely, myelogram (in order of preference) is indicated if an acute, significant neurologic deficit such as motor loss, loss of reflexes, cauda equina syndrome, or one of the serious nonmechanical back pain sources is suspected.[19,20] It can be difficult to differentiate true motor weakness from apparent weakness caused by pain during motor testing. For patients with acute back and radicular pain but no motor weakness and for those with chronic low back pain without neurologic deficit, use of MRI and CT increases costs and radiation exposure but does not improve outcome.[21-23] The majority of patients with sciatica recover without surgery.[24] Patients with chronic low back pain or radiculopathy without motor loss should undergo MRI or CT only if surgery or epidural steroid injection is indicated.[19] For patients in whom infection or tumor is suspected, MRI (or bone scan followed by MRI) is the diagnostic test of choice.[25] The degree of neurologic impairment,

www.ketabpezeshki.com 66485457-66963820

duration, and rate of worsening dictate whether these tests are performed on an emergent or urgent basis. If the motor loss in a muscle segment is rapidly progressive or 3/5 or less, MRI and neurosurgical consultation should be undertaken emergently. If motor loss is subacute, stable, and with 4/5 strength, it is possible to wait a day or two for imaging, with neurosurgical follow-up soon after. This should be arranged with the on-call neurosurgeon and medical imaging. The patient is instructed to return sooner if worsening weakness occurs.

DIFFERENTIAL DIAGNOSIS

After stabilization and assessment, the clinical findings aid in narrowing the differential diagnosis (Table 35-1). An algorithm (see Fig. 35-1) that takes into account important differential considerations, such as abnormal vital signs, the presence of fever, and an abnormal neurologic examination, is a useful tool. After collecting this information, the emergency physician should be able to answer two additional key questions: *Does the patient need emergent, urgent, or routine treatment? Does the patient need surgical or medical treatment?* Young children with no clear explanation for their back pain should have early and more extensive evaluation for infection and tumor.

EMPIRICAL MANAGEMENT

The initial empirical management of acute back pain depends on the presenting vital signs and the patient's overall appearance.

Table 35-1 Classic Findings in Selected Serious Causes of Acute Back Pain

	DIAGNOSES	HISTORY	IMPORTANT PHYSICAL EXAMINATION FINDINGS	ANCILLARY TESTING	COMMENTS
Critical					
Vascular	Aortic dissection	Often sudden-onset, "tearing" severe pain. Associated nausea, vomiting, acute anxiety are common. Syncope and chest pain can occur.	Associated diaphoresis, unstable vital signs. Hypertension is common. Unequal upper extremity blood pressure. New-onset aortic insufficiency murmur. Central and peripheral neurologic deficits secondary to ischemia.	Choice of CT, aortogram, transesophageal echo, MRI; depends on patient stability and availability of equipment.	More common as a thoracic back pain cause, but low back pain may be only complaint.
	Abdominal aortic aneurysm (ruptured, expanding)	Pain may radiate to back, flank, or testicle. Syncope may be present.	Pulsatile abdominal mass, abdominal bruits. Hypoperfusion.	Bedside US. If "stable," abdominal CT with contrast. Plain films may show a calcified enlarged aortic contour.	Can also mimic renal colic, GI bleeding, diverticulitis, and myocardial infarction. 30% of signs are misdiagnosed.
Infectious	Spinal epidural abscess	At-risk population with diabetes, chronic renal failure, intravenous drug use, alcoholism, cancer, or recent spinal surgery or trauma. Sepsis-linked history is common.	Fever, reproducible radicular pain, other signs of sepsis. Localized body tenderness along spine. Focal neurologic deficits are late findings (<50% of patients). Rare cauda equina–like syndrome.	CBC, blood cultures useful but insensitive and nonspecific. MRI modality of choice. CT or myelography can be used. Search for source of infection. *Staphylococcus aureus* common cause (70%).	Manifests as mass-occupying lesion compressing spinal cord; may be hematoma, malignancy, disk. Often begins as focal pyogenic infection in disk. Biopsy may be necessary.
Mechanical	Cauda equina syndrome	Usually a history of back pain. Symptoms may develop over hours.	Urinary retention and fecal incontinence. Saddle anesthesia, bilateral leg pain. Lower extremity weakness with hyporeflexia.	CT with or without contrast, or MRI.	Can result in severe dysfunction. An emergent condition caused by compression of lumbosacral nerve roots.
	Spinal fracture with cord impingement, or unstable fracture	Acute onset, localized pain. Usually trauma history. Older population or chronic steroids with osteoporosis also at risk.	Bone tenderness, radicular, or cord compression findings.	Plain films initially, then CT or MRI.	Symptoms and signs depend on level.
	Epidural hematoma	Usually patient with coagulation disorder, hereditary or acquired (e.g., anticoagulants). May occur after epidural anesthesia.	Radicular findings (neurologic defects). Neurologic pattern similar to abscess.	MRI, CT, or myelography.	Can also occur in AV malformations.

www.ketabpezeshki.com 66485457-66963820

Table 35-1 Classic Findings in Selected Serious Causes of Acute Back Pain—cont'd

	DIAGNOSES	HISTORY	IMPORTANT PHYSICAL EXAMINATION FINDINGS	ANCILLARY TESTING	COMMENTS
Emergent					
Infectious	Vertebral osteomyelitis	At-risk group similar to that for epidural abscess. Onset may be insidious. Back pain, tenderness, and stiffness may precede neurologic findings by significant time period.	Fever and other constitutional symptoms. Localized body tenderness of two adjacent vertebrae.	CBC, blood cultures generally low yield and nonspecific. Plain films diagnostic 80-95%, but MRI more accurate and detailed.	Biopsy may be necessary for diagnosis. *S. aureus* most common—start antibiotic.
Immune	Transverse myelitis	Back pain and neurologic deficits. Almost 50% of patients worsen maximally in 24 hr.	Partial or total loss of sensory, motor, autonomic, and sphincter function below the level of the lesion. Leg weakness more common; arm involvement is rare. Bladder (bowel control) involved in most patients.	Goal is to rule out mass lesion compressing the cord. Thought to be autoimmune origin. MRI is imaging modality of choice. Contrast CT and CT myelogram may be obtained.	May be associated with multiple sclerosis, SLE, sarcoidosis. Also associated with Lyme disease, Epstein-Barr virus, and other viral (herpes, enterovirus) or bacterial (tuberculosis, syphilis) infections.
Mechanical	Back pain with neurologic deficits Intervertebral disk herniation Spinal stenosis Spinal fractures without cord impingement Malignancy Sciatica with potential of nerve root compression	Most patients recall atraumatic mechanisms (lifting, twisting). Common complaints are stiffness, tenderness, decreased range of motion.	Positive straight leg raise test. Muscular weakness, sensory deficits. Absent or diminished deep tendon reflexes.	Plain films not indicated. CT or MRI performed for complete assessment when cauda equine syndrome, osteomyelitis or diskitis, mass, cord hematoma, or cord compression suspected.	Search for "red flags" (see Box 35-2) to rule out serious underlying disease.

AV, arteriovenous; *CBC,* complete blood count; *CT,* computed tomography; *echo,* echocardiogram; *GI,* gastrointestinal; *MRI,* magnetic resonance imaging; *SLE,* systemic lupus erythematosus; *US,* ultrasound.

Figure 35-2 details the specific management considerations for treating unstable patients.[14,26-29] For a stable patient, early effective pain management can be of significant value. The choice of analgesic is dictated by the patient's and physician's perception of the degree of pain. Physicians notoriously underestimate and undertreat acute pain. If the pain is severe, intravenous opioids such as morphine or hydromorphone are the preferred analgesic and should be given in a titrated fashion. Frequent reassessment of the patient for an adequate response is required. After adequate response to the initial intravenous opioid, an oral agent can be administered in preparation for discharge. For patients with less severe symptoms, the first choice should be acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID).[19] NSAIDs are effective for short-term relief of acute low back pain but are not superior to acetaminophen.[30] Their safety profiles are considered in patients with acid peptic disease, renal insufficiency, diabetes, and cardiac or liver pathology. A short course of an oral opioid may be necessary. Benzodiazepines are often prescribed as an adjunct to opioid and nonopioid analgesia, and their anxiolytic and sedative properties may promote sleep and synergize pain relief. There is no credible evidence supporting the use or effectiveness of "muscle relaxants" or "antispasmodic agents," such as methocarbamol (Robaxin and others) and cyclobenzaprine (Flexeril), and they have significant adverse effects.[31,32] The best approach is to provide adequate analgesia for the patient, supplemented by a benzodiazepine when the pain syndrome is particularly severe. Other interventions shown to be effective include advice to be as active as pain allows,[33] heat,[34] and spinal manipulation (in highly selected cases).[35-37]

For some patients, chronic recurrent mechanical back pain is a long-term issue, and they may visit the ED during an acute exacerbation. Such patients need support and often a multidisciplinary approach to help manage their chronic pain or recurrent flare-ups. Management requires referral and follow-up at primary care or a pain clinic. This approach is discussed in Chapter 3. Primary care or pain management clinics often use adjuncts, such as lumbar supports,[38] traction,[39] acupuncture,[40] spinal manipulative therapy,[35] physical therapy or chiropractic therapy,[36,37] back education,[19,41] massage,[42] exercise therapy,[43,44] transcutaneous electrical nerve stimulation (TENS),[45] heat therapy,[34] cognitive behavioral therapy,[46] epidural injection of methylprednisolone,[47] gabapentin for lumbar stenosis,[48] duloxetine,[49] and tricyclic or tetracyclic antidepressant therapy.[50] Evidence for most of these treatments is modest, at best.

DISPOSITION

The disposition of patients with back pain depends on their diagnosis. Patients with one of the life-threatening or disabling causes require admission and further emergent treatment. Patients with acute cord compression from a fracture, disk protrusion, abscess, or hematoma require urgent neurosurgical evaluation.

Patients who are unable to walk or require continued intravenous analgesics for adequate pain control should be considered

www.ketabpezeshki.com 66485457-66963820

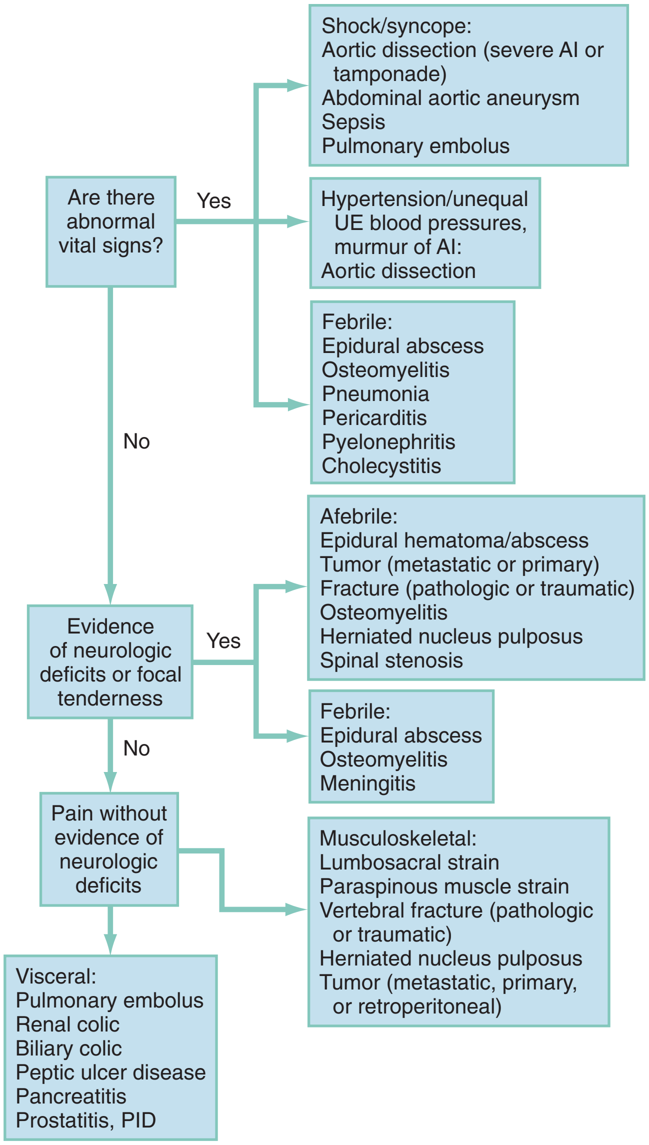


Figure 35-2. Rapid assessment of acute low back pain. *AI,* aortic insufficiency; *PID,* pelvic inflammatory disease; *UE,* upper extremity.

for admission to the hospital or the ED observation unit. If pain can be adequately controlled with oral analgesics, patients can be discharged with appropriate follow-up. Encourage patients to maintain activities as their pain allows, avoiding heavy lifting or twisting during the acute phase. Reassure the patient with acute mechanical back pain that the vast majority of patients eventually experience spontaneous relief of pain. Prescribe NSAIDs or acetaminophen, supplemented with short-course oral opioids for moderate to severe pain, and refer the patient for primary care. Oral opioids are highly effective for short-term relief and should be prescribed in adequate doses. With chronic back pain, however, opioid efficacy is less clear, and aberrant medication taking occurs in up to 24% of cases.[51,52] Repeat visits to the ED for chronic back pain should prompt counseling of the patient regarding the necessity of management by the primary care physician or a pain management center. Opioid medication should not be administered or prescribed in the ED for such patients, absent a new, acute condition. In the chronic back pain population, prescription opioid abuse is epidemic. For such patients, simple analgesics such as NSAIDs are indicated. (See Chapters 3 and 189.) Patients should be advised to avoid strict or prolonged bed rest, as it is no more effective and may be worse than maintaining reasonable activities.[33]

ACKNOWLEDGMENTS

The author would like to thank Kevin G. Rodgers, and James B. Jones who wrote this chapter in previous editions.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Deyo RA, Mirza SK, Martin BI: Back pain prevalence and visit rates: Estimates from U.S. national surveys, 2002. *Spine* 2006; 31:2724.
2. Cassidy JD, Carroll LJ, Côté P: The Saskatchewan health and back pain survey: The prevalence of low back pain and related disability in Saskatchewan adults. *Spine* 1998; 23:1860.
3. Katz JN: Lumbar disc disorders and low-back pain: Socioeconomic factors and consequences. *J Bone Joint Surg Am* 2006; 88(Suppl 2):21.
4. Deyo RA, Weinstein JN: Primary care: Low back pain. *N Engl J Med* 2001; 344:363.
5. Henschke N, et al: Prognosis in patients with recent onset low back pain in Australian primary care: Inception cohort study. *BMJ* 2008; 337:a171.
6. Borenstein DG: Epidemiology, etiology, diagnostic evaluation, and treatment of low back pain. *Curr Opin Rheumatol* 1999; 11:151.
7. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R: Lost productive time and cost due to common pain conditions in the U.S. workforce. *JAMA* 2003; 290:2443.
8. Luo X, Pietrobon R, Sun SX, Liu GG, Hey L: Estimates and patterns of direct health care expenditures among individuals with back pain in the United States. *Spine* 2004; 29:79.
9. Freburger JK, et al: The rising prevalence of chronic low back pain. *Arch Intern Med* 2009; 169:251.
10. Jarvik JJ, Hollingworth W, Heagerty P, Haynor DR, Deyo RA: The longitudinal assessment of imaging and disability of the back (LAIDBack) study: Baseline data. *Spine* 2001; 26:1158.
11. Jensen MC, et al: Magnetic resonance imaging of the lumbar spine in people without back pain. *N Engl J Med* 1994; 331:69.
12. Stadnik TW, et al: Annular tears and disk herniation: Prevalence and contrast enhancement on MR images in the absence of low back pain or sciatica. *Radiology* 1998; 206:49.
13. Weishaupt D, Zanetti M, Hodler J, Boos N: MR imaging of the lumbar spine: Prevalence of intervertebral disk extrusion and sequestration, nerve root compression, end plate abnormalities, and osteoarthritis of the facet joints in asymptomatic volunteers. *Radiology* 1998; 209:661.
14. Lavy C, James A, Wilson-MacDonald J, Fairbank J: Cauda equine syndrome. *BMJ* 2009; 338:b936.
15. van der Windt D, et al: Physical examination for lumbar radiculopathy due to disc herniation in patients with low-back pain. *Cochrane Database Syst Rev* 2010; 17:CD007431.
16. Kendrick D, et al: Radiography of the lumbar spine in primary care patients with low back pain: Randomised controlled trial. *BMJ* 2001; 322:400.
17. Chou R, Fu R, Carrino JA, Deyo RA: Imaging strategies for low back pain: Systematic review and meta-analysis. *Lancet* 2009; 373:463.
18. Atlas SJ, Deyo RA: Evaluating and managing acute low back pain in the primary care setting. *J Gen Intern Med* 2001; 16:120.
19. Chou R, et al: Diagnosis and treatment of low back pain: A joint clinical practice guideline from the American Pain Society. *Ann Intern Med* 2007; 147:478.
20. Chou R, et al: Diagnostic imaging for low back pain: Advice for high-value health care from the American College of Physicians. *Ann Intern Med* 2011; 154:181.
21. Gilbert FJ, et al: Low back pain: Influence of early MR imaging or CT on treatment and outcome-multicenter randomized trial. *Radiology* 2004; 231:342.
22. Modic MT, et al: Acute low back pain and radiculopathy: MR imaging findings and their prognostic role and effect on outcome. *Radiology* 2005; 237:597.
23. Jarvik JG, et al: Rapid magnetic resonance imaging vs radiographs for patients with low back pain: A randomized controlled trial. *JAMA* 2003; 289:2810.
24. Peul WC, et al: Surgery versus prolonged conservative treatment for sciatica. *N Engl J Med* 2007; 356:2245.
25. Joines JD, McNutt RA, Carey TS, Deyo RA, Rouhani R: Finding cancer in primary care outpatients with low back pain. *J Gen Intern Med* 2001; 16:14.
26. Hiratzka LF, et al: Guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol* 2010; 55:e27-e129.
27. Hirsch AT, et al: ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease. *J Am Coll Cardiol* 2006; 47:1239.
28. Darouiche RO: Spinal epidural abscess. *N Engl J Med* 2006; 355:2012.
29. Frohman EM, Wingerchuk DM: Clinical practice. Transverse myelitis. *N Engl J Med* 2010; 363:564.
30. Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW: Non-steroidal anti-inflammatory drugs for low back pain. *Cochrane Database Syst Rev* 2008; 1:CD000396.
31. Chou R, Peterson K, Helfand M: Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal condition: A systematic review. *J Pain Symptom Manage* 2004; 28:140.
32. van Tulder MW, Touray T, Furlan AD, Solway S, Bouter LM: Muscle relaxants for non-specific low-back pain. *Cochrane Database Syst Rev* 2003; 2:CD004252.
33. Dahm KT, Brurberg KG, Jamtvedt G, Hagen KB: Advice to rest in bed versus advice to stay active for acute low-back pain and sciatica. *Cochrane Database Syst Rev* 2010; 6:CD007612.
34. French SD, Cameron M, Walker BF, Reggars JW, Esterman AJ: Superficial heat or cold for low back pain. *Cochrane Database Syst Rev* 2006; 1:CD004750.
35. Assendelft WJ, Morton SC, Yu EI, Suttorp MJ, Shekelle PG: Spinal manipulative therapy for low back pain. *Cochrane Database Syst Rev* 2004; 1:CD000447.
36. Cherkin DC, Sherman KJ, Deyo RA, Shekelle PG: A review of the evidence for the effectiveness, safety and cost of acupuncture, massage therapy, and spinal manipulation for back pain. *Ann Intern Med* 2003; 138:898.
37. Walker BF, French SD, Grant W, Green S: Combined chiropractic interventions for low-back pain. *Cochrane Database Syst Rev* 2010; 4:CD005427.
38. van Duijvenbode IC, Jellema P, van Poppel MN, van Tulder MW: Lumbar supports for prevention and treatment of low-back pain. *Cochrane Database Syst Rev* 2008; 2:CD001823.
39. Clarke JA, et al: Traction for low-back pain with or without sciatica. *Cochrane Database Syst Rev* 2005; 4:CD003010.
40. Furlan AD, et al: Acupuncture and dry-needling for low back pain. *Cochrane Database Syst Rev* 2008; 1:CD001351.
41. Engers A, et al: Individual patient education for low back pain. *Cochrane Database Syst Rev* 2008; 1:CD004057.
42. Furlan AD, Imamura M, Dryden T, Irvin E: Massage for low-back pain. *Cochrane Database Syst Rev* 2008; 1:CD001929.
43. Hayden JA, van Tulder MW, Malmivaara A, Koes BW: Exercise therapy for treatment of non-specific low back pain. *Cochrane Database Syst Rev* 2005; 3:CD000335.
44. Choi BK, Verbeek JH, Tam WW, Jiang JY: Exercises for prevention of recurrences of low-back pain. *Cochrane Database Syst Rev* 2010; 1:CD006555.
45. Khadilkar A, Odebiyi DO, Brosseau L, Wells GA: Transcutaneous electrical nerve stimulation (TENS) for chronic low-back pain. *Cochrane Database Syst Rev* 2005; 3:CD003008.
46. Linton SJ, Andersson T: Can chronic disability be prevented? A randomized trial of a cognitive behavior intervention and two forms of information for patients with spinal pain. *Spine* 2000; 25:2825.
47. Wilson-MacDonald J, Burt G, Griffin D, Glynn C: Epidural steroid injection for nerve root compression: A randomised, controlled trial. *J Bone Joint Surg Br* 2005; 87:352.
48. Yaksi A, Ozgönenel L, Ozgönenel B: The efficiency of gabapentin therapy in patients with lumbar spinal stenosis. *Spine* 2007; 32:939.
49. Skijarevski V, et al: Efficacy and safety of duloxetine in patients with chronic low back pain. *Spine* 2010; 35:e578.
50. Staiger TO, Gaster B, Sullivan MD, Deyo RA: Systematic review of antidepressants in the treatment of chronic low back pain. *Spine* 2003; 28:2540.
51. Deshpande A, Furlan A, Mailis-Gagnon A, Atlas S, Turk D: Opioids for chronic low-back pain. *Cochrane Database Syst Rev* 2008; 1:CD004959.
52. Martell BA, et al: Systematic review: Opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med* 2007; 146:116.

www.ketabpezeshki.com 66485457-66963820

Section One

GENERAL CONCEPTS

CHAPTER 36

MULTIPLE TRAUMA

Eric A. Gross and Marc L. Martel

PERSPECTIVE

The care of the injured patient remains one of the mainstays of emergency medicine practice. Emergency physicians play a vital role in the stabilization and diagnostic phases of trauma care. Management of trauma patients involves complex, time-dependent decision-making, leadership capability, and technical skill. Proper resuscitation can enhance functional outcomes, even in severely injured patients.[1]

Epidemiology

In 2009, there were 117,176 deaths from unintentional injury, of which 31% were motor vehicle related. Accidents continue to be the leading cause of death in people aged 1 to 44 years.[2] The motor vehicle fatality rate has declined over the past decade from 15.3 deaths per 100,000 population in 1999 to 11.0 deaths per 100,000 in 2009.[3] Likewise, the number of people injured in motor vehicle collisions (MVCs) has declined as well, to 2.2 million people in 2009.[4] Firearm deaths continue to be of significant concern in the United States. In 2009, there were 31,228 deaths by firearm.[2] The economic cost of traumatic injuries is staggering. It is estimated that the total cost of injuries that occurred in 2000 is $406 billion; this includes medical costs and lost productivity. Motor vehicle and fall injuries account for 22% ($89 billion) and 20% ($81 billion) of this total, respectively.[5]

Many of these injuries are avoidable. Proper use of lap and shoulder belts can reduce the risk of fatal injury from an MVC; it is estimated that in 2009 alone, seatbelts saved 12,713 lives.[6] In 2009, 29% of occupant MVC fatalities involved individuals who were not restrained.[3] The number of MVC fatalities has been decreasing steadily since 1994, but there is room for improvement. Young adults continue to use restraints at a lower rate than the national average, but usage by this age group is increasing. Eighty-four percent of adults aged 25 to 69 years use seatbelts compared with 81% of 16- to 24-year-olds.[7] It is interesting to note that there are racial differences in seat belt use. Seventy-nine percent of blacks use seatbelts compared with 84% of whites and 89% of other races.[7] It is estimated that proper restraint use in vehicles by occupants age 5 years and older would have prevented 3688 MVC-related deaths.[6] Child safety seats reduce the risk of death in passenger cars by 71% for infants and by 54% for toddlers ages 1 to 4 years.[8] Educational and law enforcement initiatives addressing seat belts, proper child restraint, drinking and driving, gun safety, and fall prevention can assist in raising public awareness. For example, the National Highway Traffic Safety Administration (NHTSA) “Click It or Ticket” campaign increased belt use in 41 of 50 states and the District of Columbia during a 2-month time period.[9] NHTSA recently finished a small pilot study of a device to provide haptic feedback to the gas pedal when drivers attempted to drive over 25 mph. The researchers noted 100% seat belt use when this technology was implemented.[10] Further study of new technologies may improve restraint use. The effect of firearm laws on decreasing firearm violence is less concrete (even though a decrease in injuries related to firearm violence has been seen).[11] Further study is needed to determine the impact of legislation, public education, and prevention programs on firearm violence.

TRAUMA SYSTEMS

The first document to set criteria for categorizing hospitals as trauma centers was promulgated by the American College of Surgeons (ACS) Committee on Trauma in 1976.[12] As other groups recognized the importance of structured trauma care, legislation and funding to promote the development of trauma systems grew. In the early 1990s the Health Resources and Services Administration developed the Model Trauma Care System Plan, a well-designed framework for progress measurement in trauma systems. Unfortunately, this program lost funding in 2006. As of 1998, 38 states and the District of Columbia had at least one critical element in place for a formal trauma system.[10] More up-to-date data are not readily available because the program was the main source for this information.

Data on the benefit of regionalized trauma systems are convincing. The National Study on the Costs and Outcomes of Trauma showed a 25% reduction in mortality for severely injured patients who received care at a level I trauma center versus patients at a non–trauma center.[13] A meta-analysis of 14 studies demonstrated an overall 15% decline in mortality caused in the presence of a trauma system.[14] However, this apparent reduction in fatalities may be confounded by other factors. A nationwide study suggests that mortality reduction could not be solely attributed to the presence of a trauma system because its impact was small and statistically not significant. Rather, the presence of a primary seat belt law and mean per capita income were associated with a reduction in occupant mortality rates, whereas rural population and speed limits faster than 65 mph were associated with an increase in mortality rates.[15] As new trauma systems mature, more research will be needed to guide implementation of new system strategies to further reduce morbidity and mortality from traumatic injury.

One goal of the out-of-hospital trauma system is to transport the patient to the closest appropriate facility in a timely manner. Problems with over-triage and under-triage occur. Most efforts are aimed at reducing under-triage (transport of severely injured patients to lower-level trauma centers), which may result in preventable morbidity and mortality owing to a delay in definitive care. Over-triage (transport of minimally injured patients to

www.ketabpezeshki.com 66485457-66963820

higher-level trauma centers) has no deleterious effects on patient care; however, it may contribute to unnecessary resource utilization and potential overcrowding in tertiary care, level 1 trauma centers. The Centers for Disease Control and Prevention (CDC) worked with experts in 2006 to establish the Field Triage Decision Scheme. Based on initial work by the ACS Committee on Trauma, this scheme outlines triage criteria to assist in proper triage of the injured patient (Fig. 36-1).[16] The scheme is endorsed by the American College of Emergency Physicians, the ACS, and many other organizations.

Limitations to effective use of regionalized trauma systems remain. Hospital crowding, ambulance diversion, lack of specialist on-call availability, and reimbursement issues all contribute. In addition, from 1990 to 2009 the number of hospital emergency departments (EDs) in nonrural areas declined from 2446 to 1779. During this time, 1041 EDs closed and 374 hospitals opened EDs.[17] Trends such as this increase the burden of emergency care on those remaining hospitals, potentially compromising care. Future funding and legislative decisions at the state and national levels will have a significant impact on the future of high-quality trauma care in the United States.

PRINCIPLES OF DISEASE

The emergency physician faces significant clinical uncertainty when a multiple trauma patient arrives in the ED. Much of the diagnostic dilemma and subsequent evaluation can be guided by knowledge of the mechanism of injury. Although mechanisms of injury alone are not good predictors of major trauma,[18] common patterns of injuries can be anticipated and specifically assessed in ED patients. Table 36-1 outlines several blunt trauma mechanisms of injury with potential associated clinical findings.

Basic anatomic principles are useful in the assessment of patients with penetrating trauma. In contrast to penetrating trauma from knife wounds, in which injuries can be expected along the track of the weapon, gunshot wounds depend on several factors. The amount of tissue damage is related to the kinetic energy of the bullet imparted to the patient. The bullet weight (caliber) and velocity (determined by the weapon) play a role in anticipating injuries. Gunshot wounds result in trauma to the surrounding tissue by direct laceration, crush injury, shock waves, and cavitation—the displacement of tissue forward and radially. Because of these dynamic forces, the emergency physician should anticipate more widespread injuries from high-velocity weapons, such as rifles, than from low-velocity weapons, such as handguns. Similar to knives, handguns generally cause injury based on direct laceration and crush generated by the missile along its track. Shotgun wounds from close range are characterized by massive tissue injury.

Injury patterns can differ significantly between adults and children subjected to similar mechanisms of trauma. The major anatomic distinctions relate to the smaller size and surface area, larger head-to-body ratio, and less protected abdominal cavity of the child. As a result, children are more vulnerable to multisystem injury in blunt trauma, more frequently sustain significant head and intra-abdominal injuries, and are more at risk for hypothermia.[15-18]

Accidents were the fifth leading cause of death in 2009.[2] Elder patients commonly sustain extremity, craniofacial, and closed head injuries. The majority of these occur as the result of a fall or an MVC. Elder trauma patients typically have normal, age-related changes in organ system function related to decreased cardiopulmonary functional reserve, decreased renal function, decreased bone density, and cerebral atrophy. These changes can increase susceptibility to shear forces and other aspects of trauma.[19]

Comorbidities and preexisting medication use further complicate the management of elder trauma patients. Lower extremity weakness, gait disturbances, decreased visual acuity, and the use of psychotropics, antihypertensives, and sedatives have been associated with falls in elders, resulting in major injury.[20] The use of these medications, particularly antihypertensives, should not be considered causative in trauma patients with hypotension until acute hemorrhage has been assessed and managed. In addition, anticoagulants, antiplatelet drugs, and aspirin are commonly prescribed, and their effects should be suspected and reversed if possible in elder trauma patients.

MANAGEMENT

Out-of-Hospital Management

Management of the trauma patient frequently is begun before arrival in the ED by first responders. The goals of out-of-hospital care include intervention in immediately life-threatening injuries, prevention of additional injury, and rapid transport to trauma centers for definitive care. Although these goals are accepted as tenets of out-of-hospital care, controversy exists regarding each of them.

The majority of life-threatening injuries that require intervention by out-of-hospital providers are related to airway, breathing, and circulation (the ABCs). Preventing aspiration of gastric contents and providing adequate tissue oxygenation are the primary goals of endotracheal intubation. Although controversy exists regarding the use of out-of-hospital rapid sequence induction,[21-27] securing an unprotected airway is essential in this phase of trauma management. Tension pneumothorax is the fundamental threat to adequate ventilation and requires immediate needle thoracostomy. Systemic hypotension with impaired end-organ perfusion necessitates treatment in the trauma patient, despite the debate surrounding controlled hypotension versus aggressive fluid resuscitation.

Preventing additional injury requires an awareness of not only clinically evident abnormalities but also potentially more serious injuries. Coordinated extrication and transport with rigid cervical immobilization, complete spinal precautions, intensive hemodynamic monitoring, and stabilization of fractures to prevent neurovascular compromise are examples of assuming the most serious injuries exist in multiple trauma patients.

In the United States, rapid transport to the nearest appropriate facility is one of the fundamental concepts in trauma management. Much of the controversy regarding various out-of-hospital approaches to the ABCs is rooted in attempts to limit transport times and avoid further infringement on the "golden hour" of trauma care. In contrast, physician-operated emergency medical services (EMS) systems more aggressively manage airway and ventilatory issues and are more likely to commit out-of-hospital time resources to establishing hemodynamic stability before transport.[28,29] Rural EMS systems in the United States, where transport times may be prolonged because of the distance to a receiving facility, may benefit from more advanced interventions, such as rapid sequence induction and intubation and more aggressive fluid resuscitative measures.

Emergency Department

General Principles

Care of the multiple trauma patient is complex and involves the coordination of multiple providers, including EMS personnel, emergency physicians, nurses, technicians, trauma surgeons, and subspecialists. A systematic and comprehensive approach to these patients is necessary, incorporating providers from each discipline. Advanced Trauma Life Support (ATLS) guidelines delineate the use of defined trauma response teams, with providers performing

www.ketabpezeshki.com 66485457-66963820

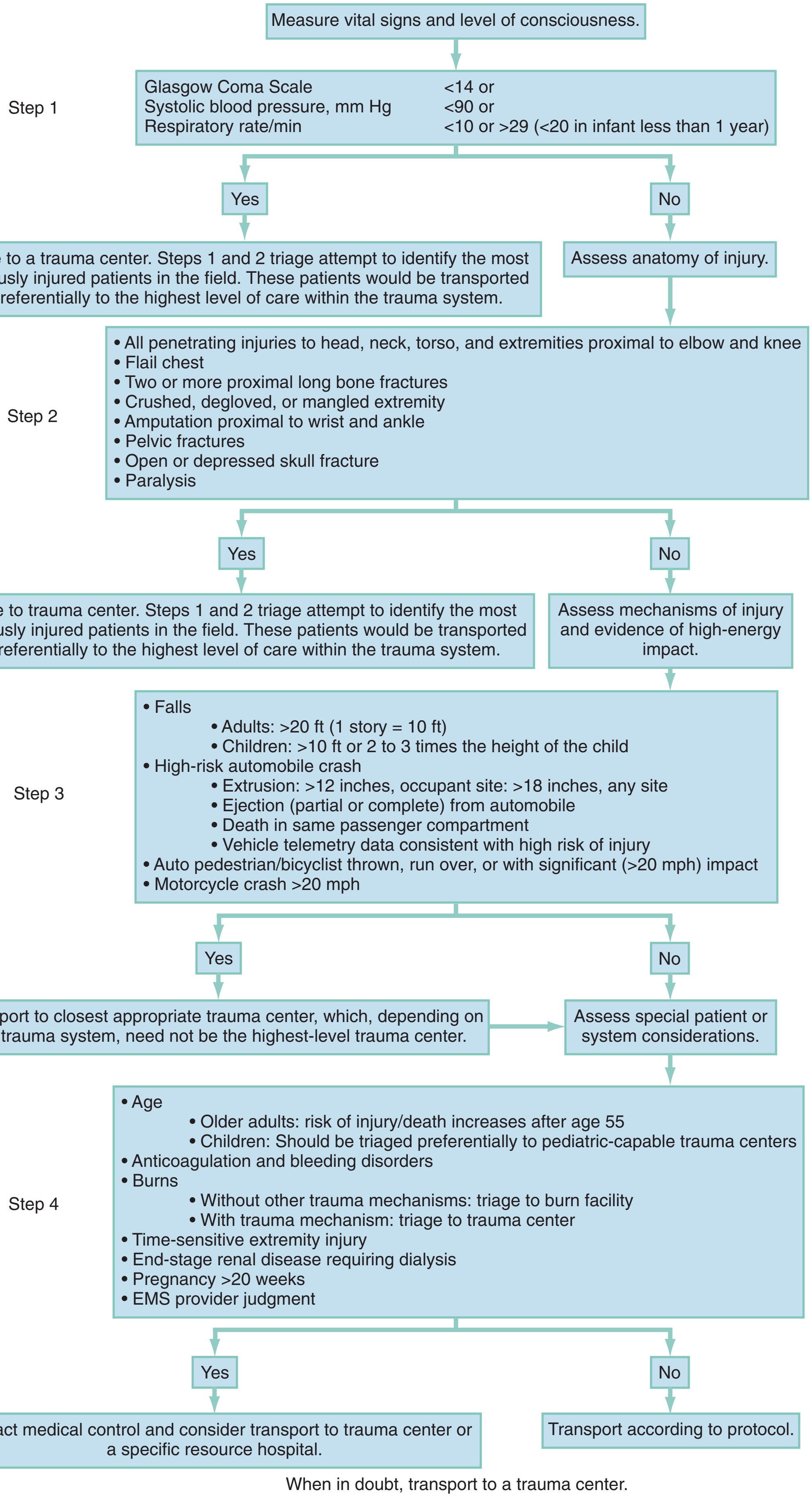


Figure 36-1. Triage decision scheme. *EMS,* emergency medical services. (Redrawn from American College of Surgeons, Committee on Trauma: Resources for the Optimal Care of the Injured Patient. Chicago: American College of Surgeons; 2006.)

www.ketabpezeshki.com 66485457-66963820

Table 36-1 Blunt Trauma Mechanisms and Associated Injuries

MECHANISM OF INJURY	ADDITIONAL CONSIDERATIONS	POTENTIAL ASSOCIATED INJURIES
Motor Vehicle Collisions		
Head-on collision		Facial injuries Lower extremity injuries Aortic injuries
Rear-end collision		Hyperextension injuries of cervical spine Cervical spine fractures Central cord syndrome
Lateral (T-bone) collision		Thoracic injuries Abdominal injuries—spleen, liver Pelvic injuries Clavicle, humerus, rib fractures
Rollover	Greater chance of ejection Significant mechanism of injury	Crush injuries Compression fractures of spine
Ejected from vehicle	Likely unrestrained Significant mortality	Spinal injuries
Windshield damage	Likely unrestrained	Closed head injuries, coup and countercoup injuries Facial fractures Skull fractures Cervical spine fractures
Steering wheel damage	Likely unrestrained	Thoracic injuries Sternal and rib fractures, flail chest Cardiac contusion Aortic injuries Hemothorax, pneumothorax
Dashboard involvement or damage		Pelvic and acetabular injuries Dislocated hip
Restraint or seat belt use		
Proper three-point restraint Lap belt only Shoulder belt only	Decreased morbidity	Sternal and rib fractures, pulmonary contusions Chance fractures, abdominal injuries, head and facial injuries and fractures Cervical spine injuries and fractures, "submarine" out of restraint devices (possible ejection)
Air bag deployment	Front-end collisions Less severe head and upper torso injuries Not effective for lateral impacts More severe injuries in children (improper front seat placement)	Upper extremity soft tissue injuries and fractures Lower extremity injuries and fractures
Pedestrian versus Automobile		
Low speed (braking automobile)		Tibia and fibula fractures, knee injuries
High speed		Waddle's triad—tibia and fibula or femur fractures, truncal injuries, craniofacial injuries "Thrown" pedestrians at risk for multisystem injuries
Bicycle		
Automobile related		Closed head injuries "Handlebar" injuries Spleen or liver lacerations Additional intra-abdominal injuries Consider penetrating injuries
Nonautomobile related		Extremity injuries "Handlebar" injuries
Falls	LD_{50} 36-60 ft	
Vertical impact		Calcaneal and lower extremity fractures Pelvic fractures Closed head injuries Cervical spine fractures Renal and renal vascular injuries
Horizontal impact		Craniofacial fractures Hand and wrist fractures Abdominal and thoracic visceral injuries Aortic injuries

LD50, the height of fall that would be fatal for 50% of those falling.

www.ketabpezeshki.com 66485457-66963820

Box 36-1 American College of Surgeons Requirements for the Presence of a Surgeon in Major Resuscitations

A surgeon should be present in the emergency department on trauma patient arrival or within 15 minutes if any of the following major criteria are found:

- Confirmed hypotension (systolic blood pressure <90 mm Hg)
- Respiratory compromise requiring intubation
- Penetrating gunshot wound to the neck, chest, abdomen, or pelvis
- Glasgow Coma Scale score of <8 attributed to trauma

or at the discretion of the emergency physician

assessments, diagnostics, and interventions simultaneously. With this approach, the physician team leader coordinates the management of the patient, considering the presence of life- or limb-threatening injuries in a sequential manner.

For level 1 trauma centers, the ACS requires the presence of a surgeon or an appropriate representative (e.g., a fourth- or fifth-year surgery resident) to be present in the hospital 24 hours a day. The attending surgeon is expected to be present in the ED no later than 15 minutes after the ED arrival of trauma patients (Box 36-1).[30] As the specialty of emergency medicine has evolved and the number of residency-trained and board-certified emergency physicians has increased, the need for a surgeon for all trauma patients has been increasingly debated; study has shown equivalent outcomes when the trauma team is led by either a surgeon or an emergency medicine physician.[31-33] Optimal patient care is best provided in a collaborative, patient-centered manner.

The priorities in the treatment of trauma patients are similar to those for any other life-threatening condition. Securing the airway, maintaining ventilation, controlling hemorrhage, and treating shock are first priorities because of their crucial importance for survival. The emergency physician should give consideration to the worst possible injury and act accordingly until the diagnosis has been confirmed or excluded. The consequences of an overzealous evaluation are more acceptable than those of a missed injury. Based on ATLS, the phases of ED care are divided into the primary survey with interventions and adjuncts, consideration of transfer, the secondary survey and adjuncts, and continued monitoring and disposition.[34]

Primary Survey

Airway and Breathing. Proper assessment and management of airway, oxygenation, and ventilation in the trauma patient are of utmost importance but can be challenging. In a review of 44,404 trauma patient admissions and 2594 deaths, airway management was responsible for 16% of preventable errors likely contributing to trauma mortality.[35] The goals of airway management are threefold: airway protection, adequate oxygenation, and adequate ventilation.

Airway protection is necessary in many trauma patients. Airway obstruction necessitates immediate intervention. Obstruction from debris, blood, or vomitus may be easily removed with suction. Neck or facial trauma may cause more complicated problems. Swelling, distorted anatomy, and hematoma formation may all contribute to impending obstruction. Early airway control is safest because these conditions may rapidly worsen. Inability to adequately protect the airway, such as in patients with depressed levels of consciousness, is another indication for intervention. Airway control is recommended in patients with significant head injury (Glasgow Coma Scale [GCS] score below 9).[36] Low GCS scores from intoxication, and not injury, may not necessitate intubation, as loss of airway reflexes cannot be predicted by GCS alone in this group.[37]

As a general rule, all trauma patients should be placed on supplemental oxygen. Adequate oxygenation has a direct effect on outcome of many trauma patients. In head-injured patients, hypoxia and extreme hyperoxia in both out-of-hospital and hospital phases of resuscitation have been associated with poorer outcomes.[38-41] Hypoxia may also worsen outcome in spinal cord injury.[42] Maintenance of arterial oxygen concentration (Pao_2) above 60 mm Hg has been recommended.[43] Inadequate ventilation, which may lead to respiratory acidosis, can be noted by the rate and quality of respirations. Signs of inadequate oxygenation may be more subtle and include agitation and restlessness. Assessment for injury that may compromise oxygenation, ventilation, or both requires careful inspection and auscultation of the chest. Signs of such compromising injury include increased work of breathing, tachypnea, penetrating wounds, flail segments, tracheal deviation, and distended neck veins. In determining the need for more aggressive airway management, these data are put into the context of the patient's overall presentation. Certain ventilatory problems, such as pneumothorax or hemothorax, may require tube thoracostomy in addition to intubation. Early intervention is preferable in the tenuous patient.

Once the decision to intubate the patient has been made, many considerations are taken into account. If the patient's condition allows, a brief neurologic examination before paralytics can be helpful in determining the extent of injury. Also, cervical spine injury precautions should be considered for patients with blunt trauma and gunshot wounds to the neck. Rapid sequence induction and orotracheal intubation with in-line cervical stabilization provide a safe method. There have been no reported cases of spinal cord injury from orotracheal intubation if proper stabilization has been applied.[44] There are many approaches to airway control, and many alternative devices, such as video-assisted laryngoscopy, the flexible fiberoptic scope, and the intubating laryngeal mask airway, are now available to assist in intubation. In particular, video-assisted laryngoscopy causes less cervical spine motion and results in improved vocal cord view when compared with direct laryngoscopy.[45,46] However, the choice will be based on clinical scenario and physician comfort. Nasotracheal intubation is generally undesirable in trauma patients owing to the lower success rate[36] and higher complication rate[47] than that for orotracheal intubation, the potential for abrupt rises in intracranial pressure, and the relative contraindications of severe midface trauma or severe basilar skull fracture.

Surgical airways are indicated in cases of failure of or contraindication to orotracheal or nasotracheal intubation. Cricothyrotomy is the preferred method, although it is performed in less than 0.5% of cases.[48] Given the rarity of use, we recommend the use of the four-step method described by Brofeldt and colleagues, either with or without a bougie.[49,50] A variety of devices for percutaneous cricothyrotomy are also available that show good success rates and are easy to use.[51-53] If there is any question about the ability to identify the cricothyroid membrane, the traditional surgical approach with a vertical incision should be used.

Circulation. Assessment of hemodynamics and circulatory status is of critical importance after the airway has been evaluated and controlled and adequate ventilation has been ensured. The assessment of circulation is multidimensional. Clinical indicators of adequate perfusion include mental status, skin color and temperature, heart rate, blood pressure, and capillary refill. A normal finding for any single sign does not rule out shock. Mental status changes associated with hypoperfusion can include anxiety, agitation, or sedation. Cool, pale skin or extremities with delayed capillary refill suggest inadequate perfusion and shock. A normal heart

www.ketabpezeshki.com 66485457-66963820

rate, blood pressure, or both can be present despite significant hemorrhage. Conversely, tachycardia may be seen without evidence of significant volume loss.

Control of external hemorrhage is crucial. Traditionally, direct pressure to external bleeding sites has been advocated, and the use of tourniquets has been discouraged. The use of direct pressure on the bleeding site remains first-line therapy; recent data have suggested the more liberal use of tourniquets for massive extremity bleeding that is not easily controlled.[54-57] Similarly, recent studies of newer hemostatic agents have shown potential application in both combat and out-of-hospital settings.[58-60]

Intravenous access is required early in the assessment of circulation. Two large-bore (14- or 16-gauge) intravenous catheters are recommended. Routine intravenous access may be difficult or unobtainable in certain cases. Intraosseous vascular access can be obtained rapidly in both pediatric[61] and adult[62] patients and allows the safe infusion of large amounts of fluid or blood products. Compact, battery-operated intraosseous drills have recently been introduced. Ultrasound-guided peripheral venous access by both nurses and physicians should be considered in patients when blind peripheral attempts are unsuccessful.[63,64] Central venous access may also be indicated in the appropriate clinical scenario or based on physician discretion. The use of ultrasound has been shown to increase successful vein cannulation and decrease complications in the placement of central venous lines.[65-68] Central venous pressure measurements may be used to direct resuscitative efforts but should not delay definitive care.

The choice of fluids for resuscitation includes crystalloid, colloid, and blood products. Fluid replacement is generally based on a 3:1 ratio of fluids to blood loss. There are few clinically significant differences between lactated Ringer's and normal saline. The debate regarding the choice of fluid for resuscitation is ongoing. No indisputable advantages of colloids have been demonstrated. Therefore the less expensive and more readily available crystalloids are the routine mainstay as first line of therapy. No clear benefit to the use of hypertonic saline has been established.[69-72] Current ATLS guidelines standardize the ratio of replacement fluids to loss and recommend 2 L of crystalloid be infused in all patients in shock, followed by blood products. O-positive blood should be used except in women of childbearing age. Type-specific blood should be used when available, but emergent transfusion should not be delayed. The use of the antifibrinolytic agent tranexamic acid has been shown to decrease mortality in trauma patients at risk of major bleeding.[73,74]

The concept of "permissive hypotension" is based on the concern that resuscitation to normal blood pressures may increase bleeding from a site that is contained and not actively hemorrhaging.[75] Clinically, restoration of normal blood pressure is delayed until active bleeding foci have been ruled out. Although data exist to support this strategy,[75,76] a Cochrane review of the six available clinical trials meeting inclusion criteria did not support (or disprove) the use of early or larger-volume intravenous fluids in uncontrolled bleeding.[77] Permissive hypotension is contraindicated in the management of traumatic brain injury because of the risk of hypoperfusion.[78,79]

The extended focused abdominal sonography in trauma (eFAST) examination should be performed on all patients as an adjunct to the assessment of circulation. The presence or absence of free intra-abdominal, intrathoracic, or intrapelvic hemorrhage or pneumothorax diagnosed by ultrasound will direct the management of trauma patients. Pericardial effusions or tamponade can be readily identified. In addition, ultrasound evaluation of the inferior vena cava may be useful in the overall assessment of fluid status in resuscitation.[80-85]

Disability. A rapid assessment of the patient's neurologic status is necessary early in the ED course. The GCS score is commonly used (see Chapter 41).

Exposure. The final phase of the primary survey is completely undressing the patient to assess for inconspicuous injuries. Special attention to the axilla, perineum, and skin folds is needed. Preventing hypothermia is essential in this phase. Blankets, warming lights, and warm fluids may be used as indicated.

Secondary Survey

The goals of the secondary survey are to obtain pertinent historical data about the patient and injury as well as evaluate and treat injuries not found on the primary survey. An AMPLE (*a*llergies, *m*edications, *p*ast medical history, *l*ast meal, *e*nvironments and events) history should be obtained. Frequent reassessment of the ABCs throughout the ED phase of management is necessary. If deterioration occurs, a complete reevaluation of the primary survey should be initiated. Features of the secondary survey and management are listed in Table 36-2.

Table 36-2 Secondary Survey of Trauma Patients

REGION OR SYSTEM	ASSESSMENT OR EXAMINATION
General	Level of consciousness Glasgow Coma Scale score Specific complaints
Head	Pupils (size, shape, reactivity, visual fields) Contusions Lacerations Evidence of skull fracture (hemotympanum, Battle's sign, raccoon eyes, palpable defects)
Face	Contusions Lacerations Midface instability Malocclusion
Neck (maintain cervical immobilization)	Penetrating injury, lacerations Tracheal deviation Jugular venous distention Subcutaneous emphysema Hematoma Midline cervical tenderness
Chest	Respiratory effort, excursion Contusions Lacerations Focal tenderness, crepitus Subcutaneous emphysema Heart tones (muffled) Breath sounds (symmetrical)
Abdomen, flank	Contusions Penetrating injury, lacerations Tenderness Peritoneal signs
Pelvis, genitourinary	Contusions Lacerations Stability, symphyseal tenderness Blood (urethral meatus, vaginal bleeding, hematuria) Rectal examination
Neurologic, spinal cord	Midline bony spinal tenderness Mental status Paresthesias Sensory level Motor function, including sphincter tone
Extremities	Contusions Lacerations Deformity Focal tenderness Pulses Capillary refill Evaluation of compartments

www.ketabpezeshki.com 66485457-66963820

Pitfalls

The goal of trauma management in the ED is to provide lifesaving interventions and evaluate for injuries. The tenets of ATLS provide a structured approach to ensure a thorough assessment is performed. Because multiple trauma patients have a variety of injuries from varying mechanisms, the initial focus is directed at defining the most serious pathology. The emergency physician should be aware of potential pitfalls. Studies from large trauma centers have shown that preventable deaths frequently result from human error and are related to the inability to intubate or secure the airway; delayed control of thoracic, abdominal, and pelvic hemorrhage; and several inpatient factors.[35,86] Head-injured, unconscious, and intubated patients frequently have injuries that are not identified early in their hospital course.[87-89] More aggressive diagnostics may be indicated in this subset of patients when history and patient-specific complaints are not obtainable. When cervical radiography is indicated, it is essential that the imaging obtained be complete and adequate. Limited radiographic series and inadequate cervical spine imaging have been shown to result in missed or delayed diagnosis of injuries.[90,91]

Radiographic Evaluation

The approach to radiographic evaluation of the trauma patient has changed in recent years. The mantra of C-spine, chest, and pelvic radiographs for all trauma patients has been challenged, and new recommendations continue to emerge. However, in the critically injured patient, imaging of the chest and pelvis and an eFAST examination should be performed early in the evaluation. These studies provide essential information on possible sources of hemorrhage in either the chest or abdomen or from a pelvic fracture.

Imaging of the cervical spine can usually be delayed; however, in a patient with neurologic findings and persistent moderate hypotension (e.g., 70 mm Hg), neurogenic shock should be considered. A positive finding on C-spine imaging (e.g., fracture, soft tissue swelling, and subluxation) may confirm this if other causes of hypotension have been ruled out. A single cross-table lateral cervical radiograph is not adequate to fully assess the cervical spine; in trauma patients, the sensitivity is too low to rule out fracture.[92,93]

Imaging of the cervical spine in trauma patients is a topic of some controversy. Radiographs are not necessary in all trauma patients.[94] The NEXUS (*N*ational *E*mergency *X*-Radiography *U*tilization *S*tudy) criteria allow clinical clearance of the cervical spine in patients without posterior midline tenderness, focal neurologic deficit, altered mental status, intoxication, or distracting injury.[95] The Canadian C-spine rule uses a different set of criteria and, although more complex, has higher specificity and therefore allows the elimination of a higher percentage of unnecessary x-ray studies.[96] In a patient with a concerning mechanism of injury or physical examination findings, computed tomography (CT) scanning is more efficient and effective than plain radiography.[92] However, routine use of CT scan in all post–blunt trauma patients is associated with higher cost and radiation dose. An algorithm to help determine which blunt trauma patients should undergo CT versus plain radiography to screen for cervical spine fracture was shown to have a 100% negative predictive value for cervical spine fracture.[97,98] This algorithm combines the NEXUS criteria,[95] the Canadian Head CT rule,[99] and Hanson's high-risk criteria.[100] If plain radiography is used, three views of the cervical spine (lateral, anteroposterior, and odontoid) should be obtained.[101]

Imaging studies of the thoracolumbar spine and extremities can also be delayed until higher-priority assessments and interventions are complete. Once the patient has been stabilized, the clinical examination can direct whether additional radiographic examinations are necessary. If CT is performed, reformatted sagittal and coronal images will be more sensitive than axial images alone.[102]

Imaging of the thorax early in the evaluation of the trauma patient can give important information about potentially life-threatening injuries. However, the dogmatic "chest x-ray (CXR) for all trauma patients" approach to radiographic evaluation of the chest has undergone some recent challenges. Plain radiography of the chest is considered an acceptable first screening modality. The sensitivity of chest x-ray examination alone, even in patients with normal physical examination findings, may be too low for its use as the primary screening tool to rule out injury to the mediastinum or a blunt aortic dissection,[103,104] and the results of those radiographs likely do not affect decision-making.[105] The combination of chest x-ray examination with abdominal and pelvic CT (already being performed in a number of these patients) may provide sufficient screening, thereby limiting thoracic CT to only those patients with significant worrisome injury mechanisms.[106] Other preliminary evidence suggests that some patients may not require chest imaging.[107,108] Ultrasound is gaining favor as the initial screening tool for pneumothorax and hemothorax because it shows better sensitivity and is more rapid than chest x-ray examination.[109,110] One possible approach for initial screening of the blunt trauma patient with a significant mechanism of injury could be carried out by thoracic ultrasound to identify life-threatening pneumothorax or hemothorax that must be immediately managed, followed by abdominopelvic CT scan, chest CT scan, or both to further elucidate other injuries. In patients with penetrating thoracic injury, primary CT scan, rather than repeat chest x-ray examinations, can speed disposition.[111] Cost and radiation considerations are, of course, taken into account.

Pelvic radiographs are useful in the severely injured trauma patient. Pelvic fractures can account for significant hemorrhage, and early recognition of fracture and closure of the pelvic space can mitigate hypotension in these patients. Although not validated in large multicenter studies, evidence suggests that pelvic radiographs may be omitted in patients without altered level of consciousness, and with no complaints of pelvic pain, pelvic tenderness on examination, distracting injury, or clinical intoxication.[112,113] Smaller similar studies have suggested the same for pediatric patients.[114] Stable patients undergoing CT scan of the abdomen and pelvis can be further evaluated by bone windows of the CT scan.

As mentioned previously, the eFAST examination should take place early in the evaluation of the trauma patient, ideally as part of the primary survey. A positive scan in hypotensive patients can identify, with good sensitivity, those in need of emergent laparotomy.[115] In addition, valuable information regarding the presence or absence of pericardial effusion can be obtained. False-negative scans can occur with hollow viscus injuries or solid organ injuries without free fluid.[116] A normal scan does not eliminate the need for further abdominal imaging in significantly injured patients.[117] Further discussion and suggested algorithms are found in Chapter 46.

Laboratory Evaluation

Laboratory evaluation of the trauma patient can provide an objective measure of the adequacy of resuscitation. It also provides much needed information for proper transfusion products and the onset of coagulopathy. Finally, it provides baseline information and values for follow-up studies (e.g., tracking hemoglobin values in a patient with a nonoperative splenic injury).

Lactate and base deficit have both been used to measure adequacy of resuscitation and predict outcome in the trauma patient.[118,119] New noninvasive methods, such as near-infrared

www.ketabpezeshki.com 66485457-66963820

spectroscopy, tissue oxygen saturation, and sublingual capnometry, have shown promise in assessing severity of shock and predicting multiorgan dysfunction and mortality.[120-122] Following changes in the central venous oxygen saturation may also be worthwhile; low values in hemodynamically stabilized trauma patients have been shown to worsen outcome.[123] Use of one of these objective markers can assist in ensuring proper resuscitation of these patients.

All patients with potentially serious injuries should undergo blood type and screening. Cross-matched blood should be immediately ordered for those with apparent serious hemorrhage. As transfusion requirements increase, attention should be paid to the development of coagulopathy. International normalized ratio and fibrinogen should be followed in these patients. Routine electrolytes, blood urea nitrogen, creatinine, complete blood count, and pregnancy testing (when appropriate) should be obtained as well.

DISPOSITION

The ED management of the multiple trauma patient is but one critical phase of the spectrum of care. The decision to admit the patient or transfer to a tertiary care facility should be coordinated based on available resources, consultation with the trauma surgeon, and consideration of institutional and regional guidelines.

Ultimate disposition is dictated by a number of factors, including the patient's condition, the nature of the injury, and the availability of surgeons, subspecialists, and anesthesiologists. Possible dispositions include transfer to the operating room, admission to the surgical service, limited observation in the ED, or transfer to another hospital. The level of care and monitoring established in the ED should be maintained throughout transfer. All equipment and medications needed for resuscitation and maintenance of vital functions should be available during the transfer, as should qualified personnel to oversee the patient's care.

In cases of inter-hospital transfers, all arrangements should be carefully coordinated by physicians at the two institutions. Stabilizing measures are begun before the patient's transfer, but decompensation in transit should be anticipated. Qualified personnel and necessary resuscitative equipment should accompany the patient. The compelling reason for transferring a patient with life-threatening trauma is the lack of resources or personnel to care for the patient's particular injuries. Transfer should not be delayed for nonessential diagnostic procedures. All documentation and results of ancillary testing should accompany the patient in transfer.

In certain circumstances the multiple trauma patient may not need admission or inter-hospital transfer. The decision to discharge these patients is evaluated carefully because many traumatic injuries may manifest in a delayed manner. When discharge is considered, thorough ED evaluation is necessary with resources in place to ensure an optimal outcome: surgical consultation where appropriate, attending radiologist support for radiographic image interpretation, and timely, scheduled follow-up on an outpatient basis.

SPECIAL CONSIDERATIONS

The role of ED thoracotomy (EDT) has become more selective to limit futile resuscitation efforts and minimize risk to providers. Patients with penetrating trauma who have cardiac arrest while in transport or the ED are most likely to benefit from EDT. In contrast, cardiac arrest patients with blunt trauma, prolonged cardiopulmonary resuscitation (CPR), or delayed transport times generally have dismal outcomes not altered by EDT.[124-126] Most

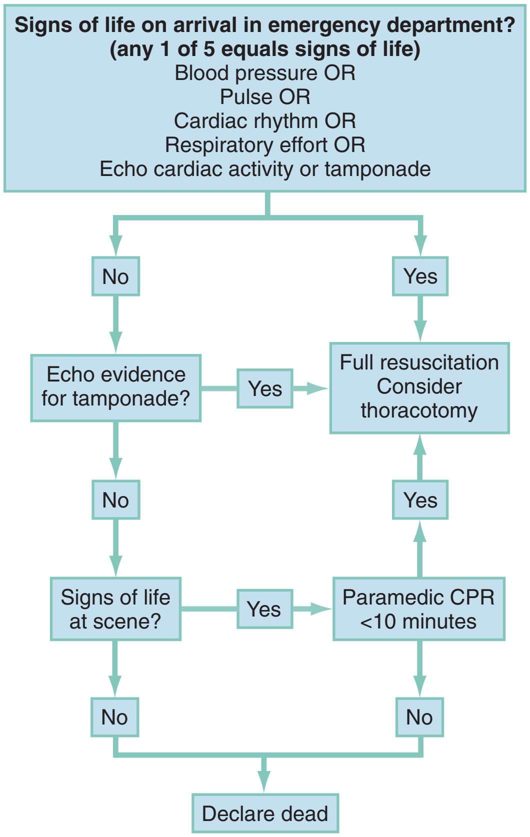


Figure 36-2. Penetrating chest trauma emergency department thoracotomy algorithm. *CPR,* cardiopulmonary resuscitation.

institutions have protocols in place outlining criteria regarding when EDT should be performed. The National Association of EMS Physicians and the ACS Committee on Trauma have published guidelines for withholding or terminating resuscitation efforts in out-of-hospital traumatic cardiac arrest patients. As a result, these guidelines often limit the transport of patients who would not likely benefit from EDT. Patients who may not be transported include any blunt trauma patient without vital signs at the scene, apneic or pulseless penetrating trauma victims without other signs of life, patients receiving more than 15 minutes of CPR, or patients with transport times of more than 15 minutes after arrest.[127] Suggested algorithms for the application of EDT are outlined in Figures 36-2 and 36-3.

When EDT is performed, the goal is to manage rapidly correctable traumatic injuries and allow for transfer to definitive operative intervention. Ultrasound should be used to assist in determining the presence or absence of pericardial effusions and tamponade. When the chest is open, a number of therapeutic measures can be undertaken, depending on the injuries present. After identification of the phrenic nerve, tamponade should be relieved by pericardotomy. Cardiac injuries are sutured or hemorrhage is controlled with digital pressure or placement of a Foley catheter balloon. Compressing or cross-clamping the pulmonary hilum can control major pulmonary bleeding, but damage to the bronchus is likely to occur and may require repair if the patient survives. The descending aorta is compressed to maximize coronary and cerebral perfusion. The aorta should remain compressed until hemorrhage has been controlled and volume replaced. Open cardiac massage can also be performed.

www.ketabpezeshki.com 66485457-66963820

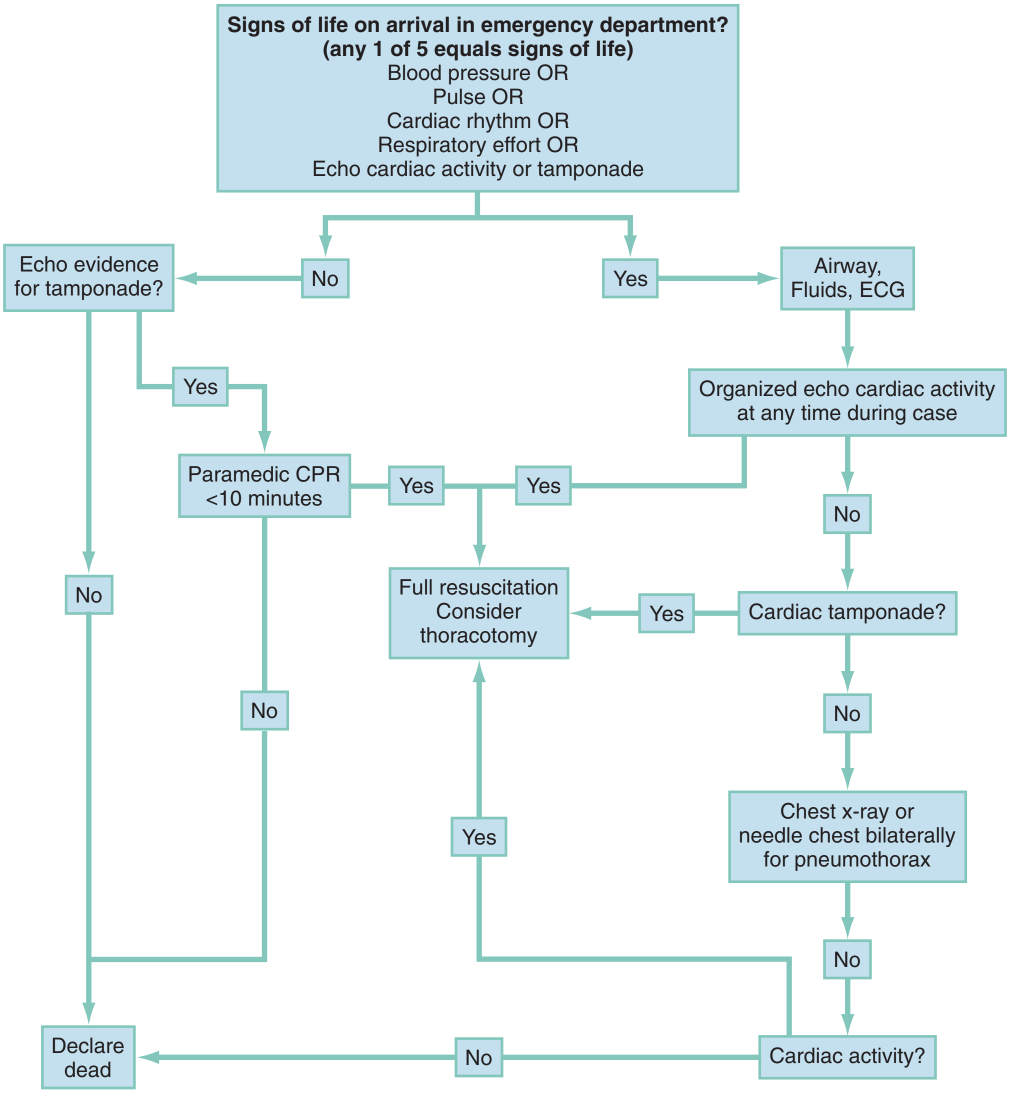


Figure 36-3. Blunt chest trauma emergency department thoracotomy algorithm. *CPR,* cardiopulmonary resuscitation; *ECG,* electrocardiogram.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Nijboer JM, van der Sluis CK, van der Naalt J, Nijsten MW, Ten Duis HJ: Two cohorts of severely injured trauma patients, nearly two decades apart: Unchanged mortality but improved quality of life despite higher age. *J Trauma* 2007; 63:670-675.
2. Kochanek KD, et al: Deaths: Preliminary data for 2009. *Natl Vital Stat Rep* 2011; 59:29-30.
3. National Highway Traffic Safety System: *Fatality Analysis Reporting System Encyclopedia*; 2011. Available at http://www-fars.nhtsa.dot.gov/. Accessed May 3, 2011.
4. National Highway Traffic Safety Administration: *Traffic Safety Facts 2009*. Report No. DOT HS 811 402. Washington, DC: National Highway Traffic Safety Administration; 2010.
5. Finkelstein EA, Corso PS, Miller TR: *Incidence and Economic Burden of Injuries in the United States*. New York: Oxford University Press; 2006.
6. National Highway Traffic Safety Administration: *Traffic Safety Facts: Lives Saved in 2009 by Restraint Use and Minimum-Drinking-Age Laws*. Report No. DOT HS 811 383. Washington, DC: National Highway Traffic Safety Administration; 2010.
7. Pickrell TM, Ye TJ: *Occupant Restraint Use in 2009—Results from the National Occupant Protection Use Survey Controlled Intersection Study*. Report No. DOT HS 811 414. Washington, DC: National Highway Traffic Safety Administration; 2010.
8. National Highway Traffic Safety Administration: *Traffic Safety Facts 2005: Children.* Report No. DOT HS 810 618. Washington, DC: National Highway Traffic Safety Administration; 2006.
9. Solomon MG, Chaffe RHB, Cosgrove LA: *May 2004 Click It or Ticket Seat Belt Mobilization Evaluation*. Report No. DOT HS 810 716. Washington, DC: National Highway Traffic Safety Administration; 2007.
10. Houten RV, Hilton B, Schulman R, Reagan I: *Using Haptic Feedback to Increase Seat Belt Use of Service Vehicle Drivers*. Report No. DOT HS 811 434. Washington, DC: National Highway Traffic Safety Administration; 2011.
11. Centers for Disease Control and Prevention: Violence-related firearm deaths among residents of metropolitan areas and cities—United States, 2006-2007. *MMWR Morb Mortal Wkly Rep* 2011; 60:573-578.
12. Committee on Trauma, American College of Surgeons: Optimal hospital resources for care of the seriously injured. *Bull Am Coll Surg* 1976; 61:15-22.
13. MacKenzie EJ, et al: A national evaluation of the effect of trauma center care on mortality. *N Engl J Med* 2006; 354:366-378.
14. Celso B, et al: A systematic review and meta-analysis comparing outcome of severely injured patients treated in trauma centers following the establishment of trauma systems. *J Trauma* 2006; 60:371-378.
15. Shafi S, Nathens AB, Elliott AC, Gentilello L: Effect of trauma systems on motor vehicle occupant mortality: A comparison between states with and without a formal system. *J Trauma* 2006; 61:1374-1379.
16. Centers for Disease Control and Prevention: Guidelines for field triage of injured patients. *MMWR Morb Mortal Wkly Rep* 2009; 58:2-12.
17. Hsai RY, Kellerman AL, Shen Y: Factors associated with closures of emergency departments in the United States. *JAMA* 2011; 305:1978-1985.
18. Boyle MJ: Is mechanism of injury alone in the prehopital setting a predictor of major trauma—a review of the literature. *J Trauma Manag Outcomes* 2007; 1:4.
19. Aschkenasy MT, Rothenhaus TC: Trauma and falls in the elderly. *Emerg Med Clin North Am* 2006; 24:413-432.
20. Koski K, Luukinen H, Laippala P, Kivela SL: Physiological factors and medications as predictors of injurious falls by elderly people: A prospective population-based study. *Age Ageing* 1996; 25:29-38.
21. Bulger EM, et al: An analysis of advanced prehospital airway management. *J Emerg Med* 2002; 23:183-189.
22. Wang HE, Balasubramani GK, Cook LJ, Lave JR, Yealy DM: Out-of-hospital endotracheal intubation experience and patient outcomes. *Ann Emerg Med* 2010; 55:527-537.
23. Wang HE, Cook LJ, Chang CC, Yealy DM, Lave JR: Outcomes after out-of-hospital endotracheal intubation errors. *Resuscitation* 2009; 80:50-55.
24. Davis DP, et al: The effect of paramedic rapid sequence intubation on outcome in patients with severe traumatic brain injury. *J Trauma* 2003; 54:444-453.
25. Poste JC, et al: Air medical transport of severely head-injured patients undergoing paramedic rapid sequence intubation. *Air Med J* 2004; 23:36-40.
26. Gausche M, et al: Effect of out-of-hospital pediatric endotracheal intubation on survival and neurological outcome: A controlled clinical trial. *JAMA* 2000; 283:783-790.
27. Bernard SA, et al: Prehospital rapid sequence intubation improves functional outcome for patients with severe traumatic brain injury: A randomized controlled trial. *Ann Surg* 2010; 252:959-965.
28. Roudsari BS, et al: Emergency medical services (EMS) systems in developed and developing countries. *Injury* 2007; 38:1001-1013.
29. Roudsari BS, et al: International comparison of prehospital trauma care systems. *Injury* 2007; 38:993-1000.
30. Committee on Trauma, American College of Surgeons: *Resources for the Optimal Care of the Injured Patient*. Chicago: American College of Surgeons; 2006.
31. Green SM: Is there evidence to support the need for routine surgeon presence on trauma patient arrival? *Ann Emerg Med* 2006; 47: 413-414.
32. Moore EE: Role of the acute care surgeon in the emergency department management of trauma. *Ann Emerg Med* 2006; 47:413-414.
33. Cummings GE, Mayes DC: A comparative study of designated trauma team leaders on trauma patient survival and emergency department length-of-stay. *CJEM* 2007; 9:105-110.
34. American College of Surgeons: *Advanced Trauma Life Support for Doctors*, 8th ed. Chicago: American College of Surgeons; 2008.
35. Gruen RL, Jurkovich GJ, McIntyre LK, Foy HM, Maier RV: Patterns of errors contributing to trauma mortality: Lessons learned from 2,594 deaths. *Ann Surg* 2006; 244:371-380.
36. Dunham CM, et al: Guidelines for emergency tracheal intubation immediately after traumatic injury. *J Trauma* 2003; 55:162-179.
37. Duncan R, Thakore S: Decreased Glasgow Coma Scale score does not mandate endotracheal intubation in the emergency department. *J Emerg Med* 2009; 37:451-455.
38. Miller JD, Sweet RC, Narayan R, Becker DP: Early insults to the injured brain. *JAMA* 1978; 240:439-442.
39. Spiotta AM, et al: Brain tissue oxygen-directed management and outcome in patients with severe traumatic brain injury. *J Neurosurg* 2010; 113:571-580.
40. Davis DP, et al: Both hypoxemia and extreme hyperoxemia may be detrimental in patients with severe traumatic brain injury. *J Neurotrauma* 2009; 26:2217-2223.
41. Davis DP, et al: The impact of hypoxia and hyperventilation on outcome after paramedic rapid sequence intubation of severely head-injured patients. *J Trauma* 2004; 57:1-8.
42. Yanagawa Y, Marcillo A, Garcia-Rojas R, Loor KE, Dietrich WD: Influence of posttraumatic hypoxia on behavioral recovery and histopathological outcome following moderate spinal cord injury in rats. *J Neurotrauma* 2001; 18:635-644.
43. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Resuscitation of blood pressure and oxygenation. *J Neurotrauma* 2000; 17:471-478.
44. McGill J: Airway management in trauma: An update. *Emerg Med Clin North Am* 2007; 25:603-622.
45. Turkstra TP, Pelz DM, Jones PM: Cervical spine motion: A fluoroscopic comparison of the AirTraq laryngoscope versus the Macintosh laryngoscope. *Anesthesiology* 2009; 111:97-101.
46. Serocki G, Bein B, Scholz J, Dörges V: Management of the predicted difficult airway: A comparison of conventional blade laryngoscopy with video-assisted blade laryngoscopy and the GlideScope. *Eur J Anaesthesiol* 2010; 27:24-30.
47. Dronen SC: A comparison of blind nasotracheal and succinylcholine-assisted intubation in the poisoned patient. *Ann Emerg Med* 1987; 16:650.
48. Stephens CT, Kahntroff S, Dutton RP: The success of emergency endotracheal intubation in trauma patients: A 10-year experience at a major adult trauma referral center. *Anesth Analg* 2009; 109:866-872.
49. Brofeldt BT, Panacek EA, Richards JR: An easy cricothyrotomy approach: The rapid four-step technique. *Acad Emerg Med* 1996; 3:1060-1063.
50. Hill C, Reardon R, Joing S, Falvey D, Miner J: Cricothyrotomy technique using gum elastic bougie is faster than standard technique: A study of emergency medicine residents and medical students in an animal lab. *Acad Emerg Med* 2010; 17:666-669.
51. Mouadeb DA, Rees CJ, Belafsky PC: Utilization of the LifeStat emergency airway device. *Ann Otol Rhinol Laryngol* 2008; 117:1-4.
52. Melker JS, Gabrielli A: Melker cricothyrotomy kit: An alternative to the surgical technique. *Ann Otol Rhinol Laryngol* 2005; 114:525-528.

www.ketabpezeshki.com 66485457-66963820

53. Fikkers BG, van Vugt S, van der Hoeven JG, van den Hoogen FJ, Marres HA: Emergency cricothyrotomy: A randomised crossover trial comparing the wire-guided and catheter-over-needle techniques. *Anaesthesia* 2004; 59:1008-1011.
54. Doyle GS, Taillac PP: Tourniquets: A review of current use with proposals for expanded prehospital use. *Prehosp Emerg Care* 2008; 12:241-256.
55. Beekley AC, et al: Prehospital tourniquet use in operation Iraqi Freedom: Effect on hemorrhage control and outcomes. *J Trauma* 2008; 63:S28-S37.
56. Kragh JF Jr, et al: Survival with emergency tourniquet use to stop bleeding in major limb trauma. *Ann Surg* 2009; 249:1-7.
57. Kragh JF Jr, et al: Practical use of emergency tourniquets to stop bleeding in major limb trauma. *J Trauma* 2008; 64:S38-S50.
58. Cox ED, Schreiber MA, McManus J, Wade CE, Holcomb JB: New hemostatic agents in the combat setting. *Transfusion* 2009; 49:248S-255S.
59. Achneck HE, et al: A comprehensive review of topical hemostatic agents: Efficacy and recommendations for use. *Ann Surg* 2010; 251:217-228.
60. Granville-Chapman J, Jacobs N, Midwinter MJ: Pre-hospital haemostatic dressings: A systematic review. *Injury* 2011; 42:447-459.
61. Guy J, Haley K, Zuspan SJ: Use of intraosseous infusion in the pediatric trauma patient. *J Pediatr Surg* 1993; 28:158-161.
62. Greaves I, Evans G, Boyle A: Intraosseous infusions in the adult. *Trauma* 1999; 1:291-299.
63. Mahler SA, Wang H, Lester C, Conrad SA: Ultrasound-guided peripheral intravenous access in the emergency department using a modified Seldinger technique. *J Emerg Med* 2010; 39:325-329.
64. White A, Lopez F, Stone P: Developing and sustaining an ultrasound-guided peripheral intravenous access program for emergency nurses. *Adv Emerg Nurs J* 2010; 32:173-188.
65. Stone MB, Nagdev A, Murphy MC, Sisson CA: Ultrasound detection of guidewire position during central venous catheterization. *Am J Emerg Med* 2010; 28:82-84.
66. Balls A, et al: Ultrasound guidance for central venous catheter placement: Results from the central line emergency access registry database. *Am J Emerg Med* 2010; 28:561-567.
67. Froehlich CD, et al: Ultrasound-guided central venous catheter placement decreases complications and decreases placement attempts compared with the landmark technique in patients in a pediatric intensive care unit. *Crit Care Med* 2009; 37:1090-1096.
68. Leung J, Duffy M, Finckh A: Real-time ultrasonographically-guided internal jugular vein catheterization in the emergency department increases success rates and reduces complications: A randomized, prospective study. *Ann Emerg Med* 2006; 48:540-547.
69. Bulger EM, et al: Hypertonic resuscitation of hypovolemic shock after blunt trauma. *Arch Surg* 2008; 143:139-148.
70. Brod VI, Krausz MM, Hirsh M, Adir Y, Bitterman H: Hemodynamic effects of combined treatment with oxygen and hypertonic saline in hemorrhagic shock. *Crit Care Med* 2006; 34:2784-2791.
71. Oda J, et al: Hypertonic lactated saline resuscitation reduces the risk of abdominal compartment syndrome in severely burned patients. *J Trauma* 2006; 60:64-71.
72. Bernard SS, Ponsford J: Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: A randomized controlled trial. *JAMA* 2004; 291:1350-1357.
73. CRASH-2 collaborators, et al: Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomised, placebo-controlled trial. *Lancet* 2010; 376:23-32.
74. CRASH-2 collaborators, et al: The importance of early treatment with tranexamic acid in bleeding trauma patients: An exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 2011; 377: 1096-1101.
75. Bickell WH, et al: Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med* 1994; 331:1105-1109.
76. Dutton RP, Mackenzie CF, Scalea TM: Hypotensive resuscitation during active hemorrhage: Impact on in-hospital mortality. *J Trauma* 2002; 52:1141-1146.
77. Kwan I, Burn F, Roberts I: Timing and volume of fluid administration for patients bleeding following trauma (Cochrane review). In: *The Cochrane Library*, Issue 3. Oxford: Update Software; 2001.
78. Henzler D, Cooper DJ, Tremayne AB, Rossaint R, Higgins A: Early modifiable factors associated with fatal outcome in patients with severe traumatic brain injury: A case control study. *Crit Care Med* 2007; 35:1027-1031.
79. Shutter LA, Narayan RK: Blood pressure management in traumatic brain injury. *Ann Emerg Med* 2008; 51:S37-S38.
80. Prekker ME, et al: Ultrasound measurement of inferior vena caval diameter is more accurate than the internal jugular vein aspect ratio to estimate central venous pressure in ICU patients. *Am J Respir Crit Care Med* 2010; 181:A4580.
81. Fields JM, et al: The interrater reliability of inferior vena cava ultrasound by bedside clinician sonographers in emergency department patients. *Acad Emerg Med* 2011; 18:98-101.
82. Avyazyan S, et al: Ultrasound of the inferior vena cava can assess volume status in pediatric patients. *J Emerg Med* 2009; 37:219.
83. Yanagawa Y, Nishi K, Sakamoto T, Okada Y: Early diagnosis of hypovolemic shock by sonographic measurement of inferior vena cava in trauma patients. *J Trauma* 2005; 58:825-829.
84. Lyon M, Blaivas M, Brannam L: Sonographic measurement of the inferior vena cava as a marker of blood loss. *Am J Emerg Med* 2005; 23:45-50.
85. Baumann UA, et al: Estimation of central venous pressure by ultrasound. *Resuscitation* 2005; 64:193-199.
86. Teixeira PGR, et al: Preventable or potentially preventable mortality at a mature trauma center. *J Trauma* 2007; 63:1338-1347.
87. Thomson CB, Greaves I: Missed injury and the tertiary trauma survey. *Injury* 2008; 39:107-114.
88. Wurmb TE, Frühwald P, Hopfner W, Roewer N, Brederlau J: Whole-body multislice computed tomography as the primary and sole diagnostic tool in patients with blunt trauma: Searching for its appropriate indication. *Am J Emerg Med* 2007; 25:1057-1062.
89. Enderson BL, et al: The tertiary trauma survey: A prospective study of missed injury. *J Trauma* 1990; 30:666-670.
90. Hashem R, Evans CC, Farrokhyar F, Kahnamoui K: Plain radiography does not add any clinically significant advantage to multidetector row computed tomography in diagnosing cervical spine injuries in blunt trauma patients. *J Trauma* 2009; 66:423-428.
91. Rana AR, Drongowski R, Breckner G, Ehrlich PF: Traumatic cervical spine injuries: Characteristics of missed injuries. *J Pediatr Surg* 2009; 44:151-155.
92. Bailitz J, et al: CT should replace three-view radiographs as the initial screening test in patients at high, moderate, and low risk for blunt cervical spine injury: A prospective comparison. *J Trauma* 2009; 66:1605-1609.
93. Mathen R, et al: Prospective evaluation of multislice computed tomography versus plain radiographic cervical spine clearance in trauma patients. *J Trauma* 2007; 62:1427-1431.
94. Gonzalez RP, Cummings GR, Phelan HA, Bosarge PL, Rodning CB: Clinical examination in complement with computed tomography scan: An effective method for identification of cervical spine injury. *J Trauma* 2009; 67:1297-1304.
95. Hoffman JR, Mower WR, Wolfson AB, Todd KH, Zucker MI: Validity of a set of clinical criteria to rule out injury to the cervical spine in patients with blunt trauma. *N Engl J Med* 2000; 343:94-99.
96. Stiell IG, et al: The Canadian C-spine rule for radiography in alert and stable trauma patients. *JAMA* 2001; 286:1841-1848.
97. Kokabi N, Raper DM, Xing M, Giuffre BM: Application of imaging guidelines in patients with suspected cervical spine trauma: Retrospective analysis and literature review. *Emerg Radiol* 2011; 18:31-38.
98. Goergen SK, Fong C, Dalziel K, Fennessy G: Can an evidence-based guideline reduce unnecessary imaging of road trauma patients with cervical spine injury in the emergency department? *Australas Radiol* 2006; 50:563-569.
99. Stiell IG, et al: The Canadian CT head rule for patients with minor head injury. *Lancet* 2001; 357:1391-1396.
100. Hanson JA, Blackmore CC, Mann FA, Wilson AJ: Cervical spine injury: A clinical decision rule to identify high-risk patients for helical CT screening. *AJR Am J Roentgenol* 2000; 174:713-717.
101. West OC, Anbari MM, Pilgram TK: Acute cervical spine trauma: Diagnostic performance of single-view versus three-view radiographic screening. *Radiology* 1997; 204:819-823.
102. Gross EA: CT screening for thoracic and lumbar fractures: Is spine reformatting necessary? *Am J Emerg Med* 2010; 28:73-75.
103. Salim A, et al: Whole body imaging in blunt multisystem trauma patients without obvious signs of injury: Results of a prospective study. *Arch Surg* 2006; 141:473-475.
104. Exadaktylos AK, Sclabas G, Schmid SW, Schaller B, Zimmermann H: Do we really need routine computed tomographic scanning in the primary evaluation of blunt chest trauma in patients with "normal" chest radiograph? *J Trauma* 2001; 51:1173-1176.

www.ketabpezeshki.com 66485457-66963820

105. Wisbach GG, et al: What is the role of chest x-ray in the initial assessment of stable trauma patients? *J Trauma* 2007; 62:74-78.
106. Barrios C Jr, et al: Ability of a chest x-ray and an abdominal computed tomography scan to identify traumatic thoracic injury. *Am J Surg* 2010; 200:741-744.
107. Rodriguez RM, Hendey GW, Marek G, Dery RA, Bjoring A: A pilot study to derive clinical variables for selective chest radiography in blunt trauma patients. *Ann Emerg Med* 2006; 47:415-418.
108. Traub M, et al: The use of chest computed tomography versus chest x-ray in patients with major blunt trauma. *Injury* 2007; 38:43-47.
109. Wilkerson RG, Stone MB: Sensitivity of bedside ultrasound and supine anteroposterior chest radiographs for the identification of pneumothorax after blunt trauma. *Acad Emerg Med* 2010; 17:11-17.
110. McEwan K, Thompson P: Ultrasound to detect haemothorax after chest injury. *Emerg Med J* 2007; 24:581-582.
111. Magnotti LJ, Weinberg JA, Schroeppel TJ, et al: Initial chest CT obviates the need for repeat chest radiograph after penetrating thoracic trauma. *Am Surg* 2007; 73:572-573.
112. Gross EA, Neidens BA: Validation of a decision instrument to limit pelvic radiography in blunt trauma. *J Emerg Med* 2005; 28:263-266.
113. Duane TM, et al: Blunt trauma and the role of routine pelvic radiographs: A prospective analysis. *J Trauma* 2002; 53:463-468.
114. Ramirez DW, Schuette JJ, Knight V: Necessity of routing pelvic radiograph in the pediatric blunt trauma patient. *Clin Pediatr* 2008; 47:935-940.
115. Lee BC, Ormsby EL, McGahan JP, Melendres GM, Richards JR: The utility of sonography for the triage of blunt abdominal trauma patients to exploratory laparotomy. *AJR Am J Roentgenol* 2007; 188:415-421.
116. Shanmuganathan K, Mirvis SE, Sherbourne CD, Chiu WC, Rodriguez A: Hemoperitoneum as the sole indicator of abdominal visceral injuries: A potential limitation of screening abdominal US for trauma. *Radiology* 1999; 212:423-430.
117. Gaarder C, et al: Ultrasound performed by radiologists—confirming the truth about FAST in trauma. *J Trauma* 2009; 67:323-329.
118. Guyette F, et al: Prehospital serum lactate as a predictor of outcomes in trauma patients: A retrospective observational study. *J Trauma* 2011; 70:782-786.
119. Mofidi M, Hasani A, Kianmehr N: Determining the accuracy of base deficit in diagnosis of intra-abdominal injury in patients with blunt abdominal trauma. *Am J Emerg Med* 2010; 28:933-936.
120. Baron BJ, et al: Sublingual capnometry for rapid determination of the severity of hemorrhagic shock. *J Trauma* 2007; 62:120-124.
121. Beekley AC, et al: Continuous noninvasive tissue oximetry in the early evaluation of the combat casualty: A prospective study. *J Trauma* 2010; 69(Suppl 1):S14-S25.
122. Cohn SM, et al: Tissue oxygen saturation predicts the development of organ dysfunction during traumatic shock resuscitation. *J Trauma* 2007; 62:44-54.
123. Hosking C, et al: Low central venous oxygen saturation in haemodynamically stabilized trauma patients is associated with poor outcome. *Acta Anaesthesiol Scand* 2011; 55:713-721.
124. Moore EE, et al: Defining the limits of resuscitative emergency department thoracotomy: A contemporary Western Trauma Association perspective. *J Trauma* 2011; 70:334-339.
125. Rhee PM, et al: Survival after emergency department thoracotomy: Review of published data from the past 25 years. *J Am Coll Surg* 2000; 190:288-298.
126. Branney SW, Moore EE, Feldhaus KM, Wolfe RE: Critical analysis of two decades of experience with postinjury emergency department thoracotomy in a regional trauma center. *J Trauma* 1998; 45:87-94.
127. Hopson LR, et al: Guidelines for withholding or termination of resuscitation in prehospital traumatic cardiopulmonary arrest: Joint position statement of the National Association of EMS Physicians and the American College of Surgeons Committee on Trauma. *J Am Coll Surg* 2003; 196:106-112.

www.ketabpezeshki.com 66485457-66963820

Chapter 37

Trauma in Pregnancy

Kriti Bhatia and Hilarie H. Cranmer

PERSPECTIVE

Trauma occurs in 6 to 7% of all pregnancies. It is the leading nonobstetric cause of maternal death, accounting for close to 50% of fatalities in pregnant women.[1] The most common causes of injury in pregnancy, in order of frequency, that result in emergency department (ED) visits are motor vehicle collisions (MVCs), interpersonal violence, and falls.[2-5] Patients with penetrating injuries are seen more frequently in EDs in inner city medical centers.[6] Of note, 8% of women aged 15 to 40 admitted to a trauma center do not yet know they are pregnant.[7] Commonly used thresholds of fetal viability are an estimated gestational age of 24 to 26 weeks or an estimated fetal weight of 500 g. Only viable fetuses are monitored, because no obstetric intervention will alter the outcome with a previable fetus.[8] Counseling on proper seatbelt and alcohol use and screening for interpersonal violence may help to reduce the morbidity and mortality rates for pregnant patients. Although the essential principles of trauma management remain unchanged in the pregnant patient, a number of special points need to be considered. Pregnancy causes alterations in physiology and anatomy that affect multiple organ systems. Although there are two lives involved, maternal life takes priority.

PRINCIPLES OF DISEASE—CHANGES OF PREGNANCY

Physiology

Cardiovascular

The normal cardiovascular changes of pregnancy can alter the presentation of shock and vascular events (Table 37-1).

Some Alterations Mimic Shock. Blood pressure declines in the first trimester, levels out in the second trimester, and then returns to nonpregnant levels during the third trimester. The decline in systole is small, 2 to 4 mm Hg, whereas diastole falls 5 to 15 mm Hg. Heart rate increases in pregnancy but does not rise by more than 10 to 15 beats per minute above baseline (mean of approximately 90 beats/min).

A major contributor to maternal hypotension is the supine hypotensive syndrome. After 20 weeks' gestation, the uterus has risen to the level of the inferior vena cava, resulting in compression when the mother is supine. Such caval obstruction diminishes cardiac preload, which can decrease cardiac output by as much as 28%, resulting in reduced systolic blood pressure by 30 mm Hg. In late pregnancy, it is common for the inferior vena cava to become completely occluded when the pregnant patient is supine. Attempts at resuscitation will be improved if compression is relieved. In determining whether observed hypotension is related to positioning, the pregnant woman's pelvis can be tilted so that the uterus is displaced from the inferior vena cava, (i.e, tilt the patient onto her left side unless otherwise prevented because of other injuries). The uterus can also be manually pushed to the left by with two hands, pushing the uterus toward the patient's head. One early study found that tilting limited to only about 15 degrees may only partially resolve vena caval obstruction[9]; thus, maintaining a position between 15 and 30 degrees is optimal. Elevating the patient's legs, where blood may pool owing to increased capacitance, will improve venous return.

Similarly, central venous pressure (CVP) measurements can be lowered in the last two trimesters by inferior vena caval compression. Normal CVP during pregnancy is approximately 12 mm Hg.

Alterations That May Mask Hypovolemic Shock. Blood volume gradually increases during pregnancy, starting at 6 to 8 weeks' gestation, to as much as 45% above normal, peaking at 32 to 34 weeks' gestation. Blood volumes become increasingly larger for multigravidas, twins, triplets, and quadruplets. With this increased circulatory reserve, clinical signs of maternal hypotension from acute traumatic bleeding may be delayed.

Some Alterations Can Exacerbate Traumatic Bleeding. By the beginning of the second trimester and throughout the remaining pregnancy, cardiac output is increased 40%, to 6 L/min. Blood flow to the uterus increases from 60 mL/min before pregnancy to 600 mL/min at term. This hyperdynamic state is needed to maintain adequate oxygen delivery to the fetus. Because the mother's total circulating blood volume flows through the uterus every 8 to 11 minutes at term, this organ can be a major source of blood loss when injured. By the third trimester, there is also marked venous congestion in the pelvis and lower extremities, increasing the potential for hemorrhage from both bony and soft tissue pelvic injuries.

Compression of the lower abdominal venous system by the gravid uterus increases peripheral venous pressure and volume in the legs, creating the potential for brisk blood loss from leg wounds. This alteration can play an important role in procedures that may be necessary for maternal resuscitation, such as central venous catheter placement.

Pulmonary

The pregnant woman at term has a significantly reduced oxygen reserve. This effect comes from a reduction in functional residual capacity caused by diaphragm elevation and an increase in oxygen consumption related to the growing fetus, uterus, and placenta. In a classic study, Archer and Marx observed that mean arterial oxygen tension dropped by 29% in pregnant women at term during 60 seconds of apnea but just 11% in nonpregnant women. Labor accelerates this decline by a further 7%.[10] In addition,

www.ketabpezeshki.com 66485457-66963820

Table 37-1 Hemodynamic Changes of Pregnancy (Mean Values)

PARAMETER	NONPREGNANT	TRIMESTER 1	TRIMESTER 2	TRIMESTER 3
Heart rate (beats/min)	70	78	82	85
Systolic blood pressure (mm Hg)	115	112	112	114
Diastolic blood pressure (mm Hg)	70	60	63	70
Cardiac output (L/min)	4.5	4.5	6	6
Central venous pressure (mm Hg)	9.0	7.5	4.0	3.8
Blood volume (mL)	4000	4200	5000	5600
Hematocrit without iron (%)	40	36	33	34
Hematocrit with iron (%)	40	36	34	36
White blood cells (cells/mm^3)	7200	9100	9700	9800

Data from de Swiet M: The cardiovascular system. In Hytten F, Chamberlain G, eds: Clinical Physiology in Obstetrics. Oxford, UK: Blackwell Scientific Publications, 1980, pp 3-42; Colditz RB, Josey WE: Central venous pressure in supine position during normal pregnancy. Comparative determinations during first, second and third trimesters. Obstet Gynecol 36:769, 1970; Letsky E: The haematological system. In Hytten RF, Chamberlin G, eds: Clinical Physiology in Obstetrics. Oxford, UK: Blackwell Scientific Publications, 1980, pp 43-78; and Cruikshank DP: Anatomic and physiologic alterations of pregnancy that modify the response to trauma. In Buchsbaum HJ, ed: Trauma in Pregnancy. Philadelphia: WB Saunders, 1979, pp 21-39.

minute ventilation increases, leading to hypocapnea. Therefore an arterial partial pressure of carbon dioxide ($Paco_2$) of 35 to 40 mm Hg may indicate inadequate ventilation and impending respiratory decompensation in the pregnant patient. At signs of respiratory compromise or hypoxia, endotracheal intubation should be considered, as maternal hypoxia rapidly leads to fetal hypoxia, distress, and possibly demise. There are no contraindications to rapid sequence intubation during pregnancy. Bag-valve-mask ventilation is more difficult in the pregnant patient.

Gastrointestinal

Gastroesophageal sphincter response is reduced in pregnancy and gastrointestinal motility is decreased, both of which increase the possibility of aspiration during reduced levels of consciousness and intubation. The stomach's increased acid production in pregnancy makes aspiration more ominous than usual. Therefore early gastric decompression should be considered in appropriate circumstances.

Anatomic Changes in Pregnancy

The uterus remains an intrapelvic organ until approximately the 12th week of gestation. It reaches the umbilicus by 20 weeks and the costal margins by 34 to 36 weeks. It grows from a 7-cm, 70-g organ to a 36-cm, 1000-g structure at term. As a result of this growing mass, the normal anatomic location and function of multiple structures are altered.

The diaphragm progressively rises in pregnancy, with compensatory flaring of the ribs. Pneumothorax may be exacerbated and tension pneumothorax can develop more quickly in pregnancy because of this diaphragm elevation, combined with pulmonary hyperventilation. For thoracostomies done in the third trimester, the chest tube should be placed one or two interspaces higher than the usual fifth interspace site to allow for diaphragm elevation.

Abdominal viscera are pushed upward by the enlarging uterus, resulting in altered pain location patterns. The gravid uterus itself tends to protect abdominal organs from trauma but substantially increases the likelihood of bowel injury with penetrating trauma to the upper abdomen. Conversely, the upward displacement of the bowel makes it less susceptible to blunt trauma. The stretching of the abdominal wall modifies the normal response to peritoneal irritation. Therefore expected muscle guarding and rebound can be progressively blunted as pregnancy approaches term, despite significant intra-abdominal bleeding and organ injury, another factor that may lead to underestimation of the extent and gravity of maternal trauma.

In the first trimester, the bony pelvis shields the uterus. After the third month, the uterus rises out of the pelvis and becomes vulnerable to direct injury. The bladder is also displaced into the abdominal cavity beyond 12 weeks' gestation, thereby becoming more vulnerable to injury. Like the uterus, the bladder becomes hyperemic, and injury may lead to a marked increase in blood loss compared with similar injury in a nonpregnant patient.

Imaging studies may show ureteral dilation that can be physiologic secondary to smooth muscle relaxation or caused by compression from the gravid uterus. Thus hydronephrosis is not necessarily pathologic. The ligaments of the symphysis pubis and sacroiliac joints are loosened during pregnancy. As a result, a baseline diastasis of the pubic symphysis may exist that can be mistaken for pelvic disruption on a radiograph.

Changes in Laboratory Values with Pregnancy

The physiologic anemia of pregnancy, resulting from a 48 to 58% increase in plasma volume and only an 18% increase in red blood cells, causes hematocrits of 32 to 34% by the 32nd to 34th week. Despite the lower hematocrit, there is actually an overall increase in oxygen-carrying capacity because of an increased total red blood cell mass.

Placental progesterone directly stimulates the medullary respiratory center, producing a $Paco_2$ of 30 mm Hg from the second trimester until term. The subsequent compensatory lowering of serum bicarbonate slightly reduces blood-buffering capacity for stress situations. A $Paco_2$ of 40 mm Hg in the latter half of pregnancy reflects inadequate ventilation and potential respiratory acidosis that could precipitate fetal distress.

Electrocardiographic changes include a left-axis shift averaging 15 degrees, caused by diaphragm elevation. Consequently, flattened T waves or Q waves in leads III and augmented voltage unipolar left limb lead may be seen.

CLINICAL FEATURES OF TRAUMA IN PREGNANCY

Blunt and Penetrating Trauma

The findings of the physical examination in the pregnant woman with blunt trauma are not reliable in predicting adverse obstetric

www.ketabpezeshki.com 66485457-66963820

outcomes. However, risk factors that are significantly predictive of contractions or preterm labor include gestational age greater than 35 weeks, assaults, and pedestrian collisions. In gravid patients, penetrating trauma of the abdomen has an increased likelihood of causing injuries of the bowel, liver, or spleen.

Fetal mortality rates range from 4 to 40% after maternal trauma, with most likely causes of fetal death occurring from placental abruption, maternal shock, and maternal death, in order of decreasing incidence.[11] Risk factors significantly predictive of fetal death include ejections, motorcycle and pedestrian collisions, maternal death, maternal tachycardia, abnormal fetal heart rate, lack of restraints, and an Injury Severity Score greater than 9.[8]

Unbelted or improperly restrained pregnant women are twice as likely to experience excessive maternal bleeding, and fetal death is three times more likely to occur.[11-13] For low- to moderate-severity crashes (constituting 95% of all MVCs), proper restraint use, with or without air bag deployment, generally leads to acceptable fetal outcomes. For high-severity crashes, even proper restraint does not improve fetal outcome.[14]

Pregnant crash-test-dummy trials show that improper placement of the lap belt over the pregnant abdomen causes a threefold to fourfold increase in force transmission through the uterus. The lowest force transmission readings through the uterus occur when a three-point seat belt is used properly. For correct position, the lap belt should be placed under the gravid abdomen, snugly over the thighs, with the shoulder harness off to the side of the uterus, between the breasts and over the midline of the clavicle.[15] Women who receive information on seat belt use during pregnancy from a health care worker are statistically more likely to use seat belts and to use them properly than uninformed controls.[15]

Interpersonal Violence

Although it has been previously documented that intimate partner violence against women affects one in four U.S. women, and numerous health consequences have been associated with being a victim of such violence, a 2006 study by Silverman and colleagues conclusively demonstrated that physical abuse from husbands or boyfriends compromises a woman's health during pregnancy, as well as her likelihood of carrying a child to term and the health of her newborn.[16] Women experiencing abuse in the year before or during a pregnancy were 40 to 60% more likely than nonabused women to report high blood pressure, vaginal bleeding, severe nausea, kidney or urinary tract infections, and hospitalization during that pregnancy. Abused pregnant women were 37% more likely to deliver preterm, and children of abused pregnant women were 17% more likely to be born underweight. These conditions pose grave health risks to newborns, and children born to abused mothers were over 30% more likely than other children to require intensive care at birth.[16-18] Physicians detect only a minority of cases, which supports the need for routine screening for interpersonal violence in pregnant patients.

Falls

Falls become more prevalent after the 20th week of pregnancy.[2] Protuberance of the abdomen, loosening of pelvic ligaments, strain on the lower back, and fatigability contribute to this problem. In a given pregnancy, about 2% of pregnant women sustain repeated direct blows to the abdomen because of falling more than once. Although repeated falls often trigger premature contractions, they seldom result in immediate labor and delivery.

Penetrating Trauma

The gravid uterus alters injury patterns to the mother. There is an increased probability of harm (approaching 100%) to the bowel, liver, or spleen if the entrance of the penetrating object is in the upper abdomen. When the entry site is anterior and below the uterine fundus, visceral injuries are less likely. Although the enlarging uterus can act as a shield against intra-abdominal injuries in the mother, it makes the fetus more susceptible to injury. A high fetal death rate from penetrating trauma to the uterus has been reported, but a lower fetal death rate for maternal injuries above the uterus.[19]

Fetal Injury

Pregnancy does not alter rates of maternal mortality caused by trauma. However, trauma is associated with a high risk of fetal loss. When the mother sustains a severe level of injury, poor fetal outcome is predicted by maternal hypotension and acidosis (hypoxia, lowered pH, lowered bicarbonate) and a fetal heart rate of less than 110 beats/min.[5,6,20] When the mother sustains life-threatening injuries, there is a 40% chance of fetal demise, compared with a less than 2% chance in cases of non–life-threatening maternal injuries. Maternal age and gestational age may also be important factors in determining fetal outcome.[21]

Maternal disseminated intravascular coagulation (DIC), which may be caused by placental products entering the maternal circulation, is a significant predictor of fetal mortality.[11] For women with less severe trauma, fetal outcome is not predicted by maternal vital signs, abdominal tenderness, blood tests, or ultrasonography (US) results. Only cardiotocographic monitoring for a minimum of 4 hours is useful in predicting fetal outcome.[3]

Fatal in utero fetal injuries from blunt trauma usually involve intracranial hemorrhage and skull fractures. Such head injury is often secondary to fractured maternal pelvic bones striking the fetal skull as a result of vertex lie. Pelvic and acetabular fractures during pregnancy are associated with a high maternal (9%) and a higher fetal (38%) mortality rate.[22] With penetrating trauma, gunshot wounds to the uterus are associated with a high incidence of fetal injury and fetal mortality. Stab wounds to the uterus produce substantial morbidity and mortality to the fetus.[11]

Placental Injury

In blunt trauma, 50 to 70% of all fetal losses result from placental abruption.[19,23] It is the leading cause of fetal death after blunt trauma.

Placental separation results when the inelastic placenta shears away from the elastic uterus during sudden deformation of the uterus. Because deceleration forces can be as damaging to the placenta as direct uterine trauma, abruption can occur with little or no external sign of injury to the abdominal wall. Because all gas exchange between the mother and fetus occurs across the placenta, abruption inhibits the flow of oxygen to the fetus and causes in utero carbon dioxide (CO_2) accumulation. Such hypoxia and acidosis can lead to fetal distress. Sustained uterine contractions induced by intrauterine hemorrhage also inhibit uterine blood flow, further contributing to fetal hypoxia.[24]

The diagnosis of abruption is a clinical one, and US and the Kleihauer-Betke test are of limited value.[24] Classic clinical findings of abruption may include vaginal bleeding, abdominal cramps, uterine tenderness, maternal hypovolemia (up to 2 L of blood can accumulate in the gravid uterus), or a change in the fetal heart rate. However, many cases of placental abruption after trauma show no evidence of vaginal bleeding.[11]

The most sensitive indicator of placental abruption is fetal distress. Therefore prompt fetal monitoring is a very important assessment technique in trauma during pregnancy. There is also a close linkage of abruption to uterine activity, with increased frequency of contractions associated with abruption. US is less

www.ketabpezeshki.com 66485457-66963820

than 50% accurate as a first-line test in detecting placental abruption.[19,25] If the abruption bleeds externally, not enough blood collects to be seen sonographically. Even with significant intrauterine blood accumulation, accurate US diagnosis may be difficult because of placental position (i.e., posterior) and confounding uterine or placental structural conditions.

Placental abruption is associated with an overall 8.9-fold increased risk of stillbirth (>20 weeks) and a 3.9-fold increased risk of preterm delivery (before 37 weeks). The extent of placental separation affects stillbirth rates. At 50% separation, there is a fourfold increased risk of stillbirth, and a more profound 31.5-fold increased risk of stillbirth is present at 75% separation. The risk of preterm delivery is substantially increased with even mild abruptions; a 25% separation carries a 5.5-fold increased risk of preterm delivery.[24,25]

When mother and fetus are stable, expectant management can be tried for partial placental abruptions of less than 25%. This usually applies to fetuses of less than 32 weeks' gestation in which the likelihood of morbidity and mortality associated with prematurity makes delivery management risky. Expectant care in stable patients may allow further fetal maturation and improved outcome. If expectant management is pursued, close maternal and fetal monitoring is needed to ensure the well-being of both patients. The ability to perform an immediate cesarean section is necessary because there may be little time between the appearance of fetal distress from further placental separation and the occurrence of fetal death. After 32 weeks' gestation the risk of further placental separation outweighs the benefits of further fetal maturation, so intervention may be indicated.[11,25]

Women with placental abruption are more likely to have coagulopathies than those without abruption. The injured placenta can release thromboplastin into the maternal circulation, resulting in DIC, whereas the damaged uterus can disperse plasminogen activator and trigger fibrinolysis. The precipitation of DIC is directly related to the degree of placental separation. Severe clotting disorders rarely occur unless separation of the placenta is significant enough to result in fetal demise.[24,25]

Uterine Injury

The most common obstetric problem caused by maternal trauma is uterine contractions.[3,4] Myometrial and decidual cells, irritated by contusion or placental separation, release prostaglandins that stimulate uterine contractions. Progression to labor depends on the extent of uterine damage, the amount of prostaglandins released, and the gestational age of the pregnancy. The routine use of tocolytics for premature labor has come under question because most contractions stop spontaneously. Contractions that are not self-limited are often induced by some pathologic condition, such as underlying placental abruption, which is a contraindication to tocolytic therapy. Older studies describe this risk as relative and have used tocolysis successfully with careful evaluation and intensive monitoring to continue the pregnancy and enhance fetal maturity.[26] The option to use tocolytics ends when cervical dilation reaches 4 cm.

Uterine rupture is a rare event. It is most often caused by severe vehicular crashes in which pelvic fractures strike directly against the uterus. Uterine rupture may occur from stab wounds and gunshot injuries, but this appears to be rare.[11,19] Maternal shock, abdominal pain, easily palpable fetal anatomy caused by extrusion into the abdomen, and fetal demise are typical findings on examination. Diagnosing uterine rupture can be difficult. A fractured liver or spleen can produce similar signs and symptoms of peritoneal irritation, hemoperitoneum, and unstable vital signs. Optimal treatment, between suturing the tear or performing a hysterectomy, depends on the extent of uterus and uterine vessel tears and the importance of future childbearing.

DIAGNOSTIC STRATEGIES

Radiography

Plain Radiographs

Adverse effects to the fetus are unlikely if radiation exposure is less than 5 to 10 radiation-absorbed doses (rad). Less than 1% of trauma patients are exposed to more than 3 rad. Sensitivity to radiation is greater during intrauterine development than at any other time of life, especially in the first trimester (i.e., when the embryo undergoes organogenesis in weeks 2-9). However, the risk to the fetus of a 1-rad (1000 mrad) exposure, approximately 0.003%, is thousands of times smaller than the spontaneous risks of malformations, abortions, or genetic disease. Intrauterine exposure to 10 rad does not appear to cause a significant increase in congenital malformations, intrauterine growth retardation, or miscarriage but is associated with a small increase in the number of childhood cancers.[27] Pathologic conditions more readily appear with intrauterine radiation doses of 15 rad or greater.

Providing information on radiation exposure from diagnostic radiographs is difficult. The individual amount of fetal dosage may vary by a factor of 50 or more, depending on the equipment used, technique, number of radiographs done in a complete study, maternal size, and fetal-uterine size. Diagnostic radiographic studies should be performed with regard for fetal protection, but necessary diagnostic studies of the traumatized pregnant patient should not be withheld out of concern for fetal radiation exposure.[11,19] When appropriate, fetal irradiation should be minimized by limiting the scope of the examination and using technical means such as shielding and collimation. Table 37-2 provides estimated radiation doses from various types of examinations.

Table 37-2 Estimated Radiation Dose to the Unshielded Ovaries and Pelvic Uterus

IMAGING STUDY	UTERINE RADIATION DOSE (MRAD)*
Plain-Film Radiography	
Cervical spine	Undetectable
Thoracic spine	<1
Chest (PA)	<1
Chest (AP)	<5
Extremities (femur)	<50
Hip	10-210
Lumbar spine	31-400
Pelvis	140-2200
KUB	200-503
Intravenous pyelogram	503-880
Urethrocystogram	1500
Computed Tomography	
Head	<50
Thorax	10-590
Abdomen	2800-4600
Pelvis	1940-5000
Angiography	
Cerebral	<100
Cardiac catheterization	<500
Aortography	<100

Data from Berlin L: Radiation exposure and the pregnant patient. AJR Am J Roentgenol 1996; 167:1377; North DL: Radiation doses in pregnant women. J Am Coll Surg 2002; 194:100; Damilakis J, Perisinakis K, Voloudaki A, Gourtsoyiannis N: Estimation of fetal radiation dose from computed tomography scanning in late pregnancy: Depth-dose data from routine examinations. Invest Radiol 35:527, 2000. [published correction appears in Invest Radiol 35:706, 2000].

AP, anteroposterior; *KUB*, kidney, ureter, and bladder; *PA*, posteroanterior.

**mrad*, millirad; dose increases as the fetus grows to occupy more of the abdomen.

www.ketabpezeshki.com 66485457-66963820

Ultrasonography

US is the best modality for simultaneous assessment of both the mother and the fetus. It has a sensitivity of 88%, a specificity of 99%, and an accuracy of 97% for detecting intra-abdominal injuries in blunt trauma in all patients. In the pregnant patient, it is most useful in detecting major abdominal injury (sensitivity 80%, specificity 100%) and establishing fetal well-being or demise, gestational age, and placental location.[28,29]

Sonography is a safe and effective screening examination that can obviate more hazardous tests such as computed tomography (CT), cystography, and diagnostic peritoneal lavage (DPL) in most pregnant patients with trauma who require an objective evaluation of the abdomen. Limitations in accuracy include operator experience, patient obesity, the presence of subcutaneous air, and a history of multiple abdominal operations. If ultrasound findings are equivocal and the patient is hemodynamically unstable, DPL performed in an open and suprauterine fashion is indicated. Diagnostic peritoneal aspiration (DPA) may be considered in conjunction with a trauma surgeon; however, this procedure also poses risks.

Computed Tomography and Magnetic Resonance Imaging Scans

CT and, increasingly, magnetic resonance imaging (MRI) studies are used in evaluating abdominal trauma in pregnancy. If US is indeterminate and the patient's condition is stable, CT and MRI have the potential to identify specific organ damage. They are particularly useful in assessing penetrating wounds of the flank and back. CT can miss diaphragm and bowel injuries. Both of these studies generally lack portability, and trauma patients may have to be taken from the closely monitored environment of the ED to a distant radiography suite.

Radiation from CT is a concern in the pregnant trauma patient. However, with shielding, fetal exposure from head and chest CT scans can be kept below an acceptable 1-rad limit. CT of the abdomen above the uterus can be done with less than 3 rad of exposure to the fetus.[30] Pelvic CT, centered over the fetus, produces a more prohibitive 3- to 9-rad dose; spiral CT can further reduce radiation dosage.[30] Radiation exposure ultimately depends on the patient, scanner, and technique used in performing the study (see Table 37-2). MRI scanners use no radiation and have not been associated with significant fetal disease or disability.

SPECIAL PROCEDURES

Diagnostic Peritoneal Lavage

In unstable trauma patients with equivocal or negative findings on US, DPL can be done in any trimester by an open technique above the uterus. The gravid uterus, in the later trimesters, makes the procedure more risky and technically challenging. In blunt trauma the gravid uterus does not compartmentalize intraperitoneal hemorrhage and does not reduce the accuracy of DPL for selecting patients who need operative intervention for intra-abdominal bleeding. DPL is limited in detecting bowel perforations and does not assess retroperitoneal and intrauterine pathology.

MANAGEMENT

As with any trauma, advance notification and preparation can be helpful. Depending on mechanism, maternal condition, and gestational age, the emergency physician should consider early notification or consultation with an obstetrician, neonatologist, or pediatrician (or all three). A fetal monitor, portable US, and neonatal resuscitation equipment should be immediately available.

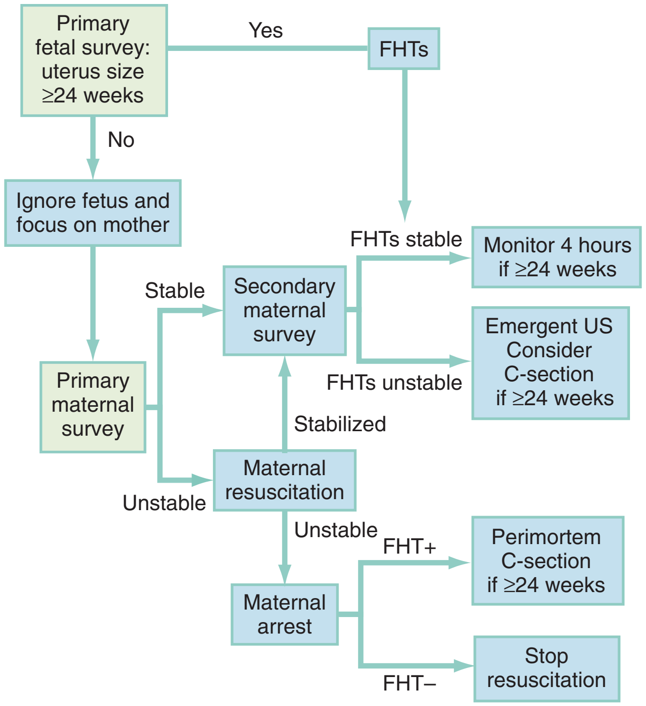


Figure 37-1. Decision-making algorithm in emergency obstetric care. *C-section,* cesarean section; *FHTs,* fetal heart tones; *US,* ultrasonography.

Maternal Resuscitation

Primary Survey

The primary survey focuses on the mother. However, because two patients are present, it is reasonable also to gather preliminary information about the fetus in the primary survey (Fig. 37-1).

Airway and Breathing. Oxygen therapy should be instituted early. Because of reduced oxygen reserve and increased oxygen consumption, the traumatized pregnant woman can quickly become hypoxic. The fetus is very vulnerable to any reduction in oxygen delivery. Supplemental oxygen should be continued throughout maternal resuscitation and evaluation.

A secure airway is critical to an optimum outcome. Not only does it enable proper oxygenation, but it negates the higher risk of aspiration in pregnancy. Rapid sequence intubation is recommended when intubation is performed. Mechanical respirators need to be adjusted for increased tidal volumes and respiratory alkalosis consistent with the physiologic $PaCO_2$ of 30 mm Hg in the last stage of pregnancy.

Circulation. Any time significant maternal injury is suggested by the mechanism of injury or clinical findings, early intravenous access for volume resuscitation is indicated. Maternal blood pressure and heart rate are not consistently reliable predictors of fetal and maternal well-being.[11,19] Because of an expanded circulating volume, the mother can be bleeding but not show early signs of hypotension. The uterus is not a critical organ, and its blood flow is markedly reduced when the maternal circulation is compromised. As a result, after an acute blood loss, uterine blood flow can be substantially decreased while maternal blood pressure remains normal. Consequently, the pregnant woman with borderline hemodynamic stability probably already has a jeopardized fetus. When traditional signs of shock appear, fetal compromise can be

www.ketabpezeshki.com 66485457-66963820

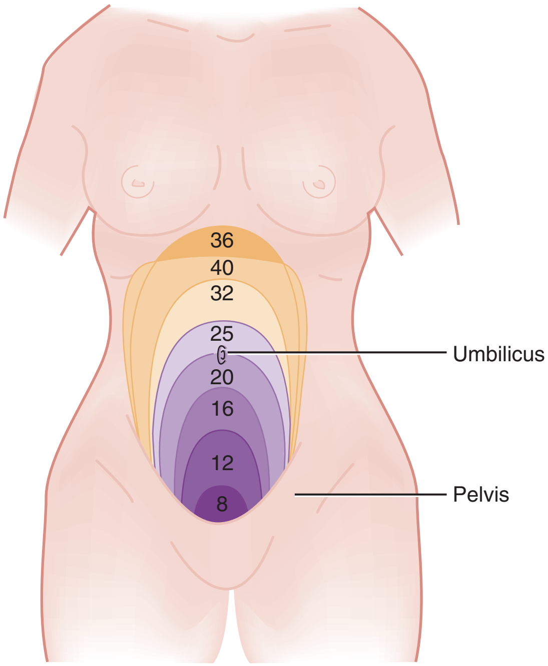


Figure 37-2. Uterine size at different weeks of gestation. (From Kravis TC, Warner CG, eds: Emergency Medicine: A Comprehensive Review. Rockville, Md, Aspen Publishers, 1979.)

Table 37-3 Fetal Viability

WEEKS OF GESTATION	6-MONTH SURVIVAL (%)	SURVIVAL WITH NO SEVERE ABNORMALITIES (%)
22	0	0
23	15	2
24	56	21
25	79	69

Data from Morris JA Jr, et al: Infant survival after cesarean section for trauma. Ann Surg 223:481, 1996.

far advanced. Vasopressors should be avoided because they produce fetal distress by further decreasing uterine blood flow.

Beyond 20 weeks' gestation, tilting the patient to approximately 30 degrees to the left on a backboard or elevating the right hip reduces the compression on the inferior vena cava caused by the gravid uterus. Tilting to the right is less effective in removing the uterus from the inferior vena cava; manually displacing the uterus upward and leftward is more effective.

For severe injuries, a CVP line is helpful in assessing cardiac preload. CVP pressures decline as pregnancy progresses because of inferior vena caval compression by the gravid uterus. Therefore correction to nonpregnant normal pressures may be unnecessary. Instead, it is more valuable to focus on trends of how the CVP responds to fluid challenges. A Foley catheter for measuring urine output provides further information on circulatory volume status.

With trauma in pregnancy, the primary survey can be modified to assess uterine size and the presence of fetal heart tones. Uterine size, measured from the symphysis pubis to the fundus, is the quickest means of estimating gestational age. This distance in centimeters equals the gestational age in weeks (e.g., 24 cm = 24 weeks), which allows some early indication of fetal viability if delivery is necessary (Fig. 37-2). Usually, 24 to 26 weeks is used as the cutoff point for fetal viability (Table 37-3). As a rough guide, the fetus is potentially viable when the dome of the uterus extends beyond the umbilicus. Fetal heart tones can be detected by auscultation at 20 weeks' gestation or by Doppler probe at 10 to 14 weeks. If either the uterus is less than 24 cm in size or fetal heart tones are absent, the pregnancy is probably too early to be viable, and treatment is directed solely at the mother.

Secondary Survey

The secondary survey involves a detailed examination of the patient but is also modified to gather additional information about the maternal abdomen and the fetus. Physical examination of the abdomen, frequently unreliable in the nonpregnant patient, is more inaccurate with changing organ position, abdominal wall stretching in advancing pregnancy, and uterine contraction pains. Still, information can be gathered about uterine tenderness, contraction frequency, and vaginal bleeding.

Pelvic examination begins with sterile speculum examination to allow direct visualization to enable detection of possible trauma in the genital tract, the degree of cervical dilation, and the source of any observed vaginal fluid. Vaginal bleeding suggests placental abruption, and a watery discharge suggests rupture of the membranes. If a vaginal fluid sample placed on a slide dries and crystallizes in a ferning pattern, it is amniotic fluid and not urine. Cervical cultures for group B streptococci, *Neisseria gonorrhoeae*, and *Chlamydia* should be performed if there is evidence of amniotic fluid leak. Bimanual examination should be limited to assessing for pelvic bone injury or progression of advanced labor. If the mechanism of injury is significant enough and the fetus is judged to be viable, early involvement of an obstetrician may enhance the fetal outcome.

Fetal Evaluation

Fetal evaluation in the secondary survey focuses on the fetal heart rate and detection of fetal movement. When the presence of fetal heart tones has been confirmed, intermittent monitoring of fetal heart rate is sufficient for the previable fetus. If the fetus is viable (i.e., 24 weeks or more), continuous external monitoring initiated quickly and maintained throughout all diagnostic and therapeutic procedures may be useful in directing management. Such monitoring can also benefit the mother because fetal hemodynamics are more sensitive to decreases in maternal blood flow and oxygenation than are most measures of the mother. Fetal distress can be a sign of occult maternal distress. However, fetal distress and even demise can occur with seemingly minor maternal trauma. Signs of fetal distress include an abnormal baseline heart rate, decreased variability of heart rate, and fetal decelerations after contractions.[11]

The normal fetal heart rate ranges from 120 to 160 beats/min; rates outside or trending toward these limits are ominous. Heart rate variability has two components. Beat-to-beat variability measures autonomic nervous function, whereas long-term variability indicates fetal activity. Heart rate variability increases with gestational age. The loss of beat-to-beat and long-term variability warns of fetal central nervous system depression and reduced fetal movement caused by fetal distress (Fig. 37-3).[11,19]

Late decelerations are an indication of fetal hypoxia. These decelerations are relatively small in amplitude and occur after the peak or conclusion of a uterine contraction. By comparison, early decelerations are larger, occur with the contraction, and recover to baseline immediately after the contraction. Early decelerations may be vagally mediated when uterine contractions squeeze the fetal head, stretch the neck, or compress the umbilical cord. Variable decelerations are large, occur at any time, and are possibly caused by umbilical cord compression (Fig. 37-4).

www.ketabpezeshki.com 66485457-66963820

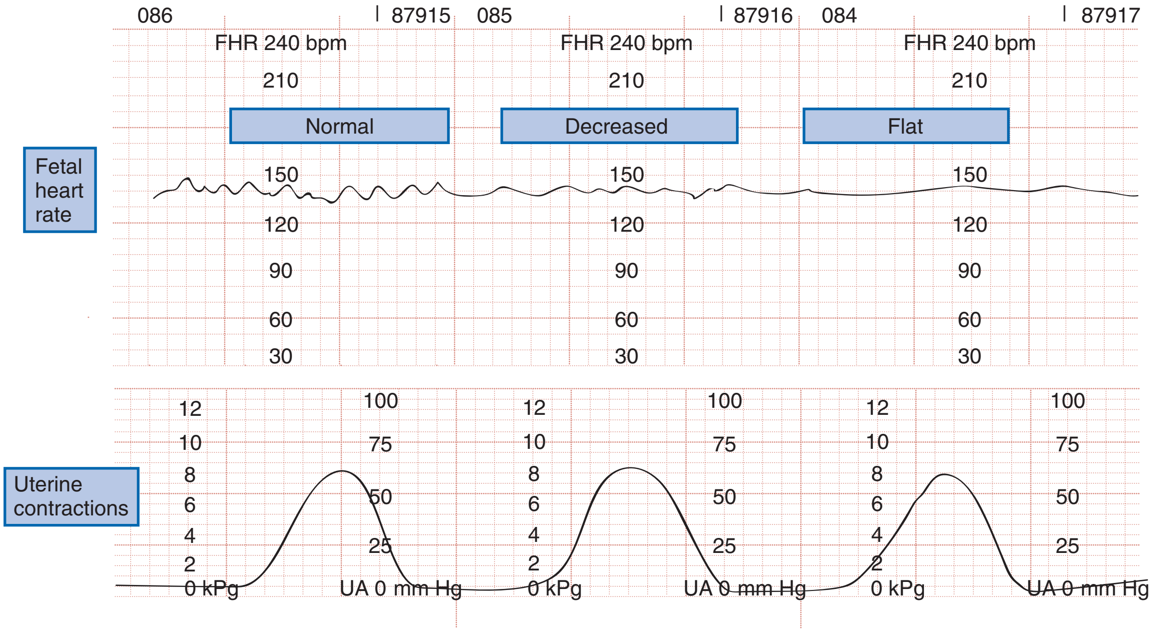


Figure 37-3. Types of fetal heart rate variability. *bpm,* beats per minute; *FHR,* fetal heart rate; *UA,* uterine activity.

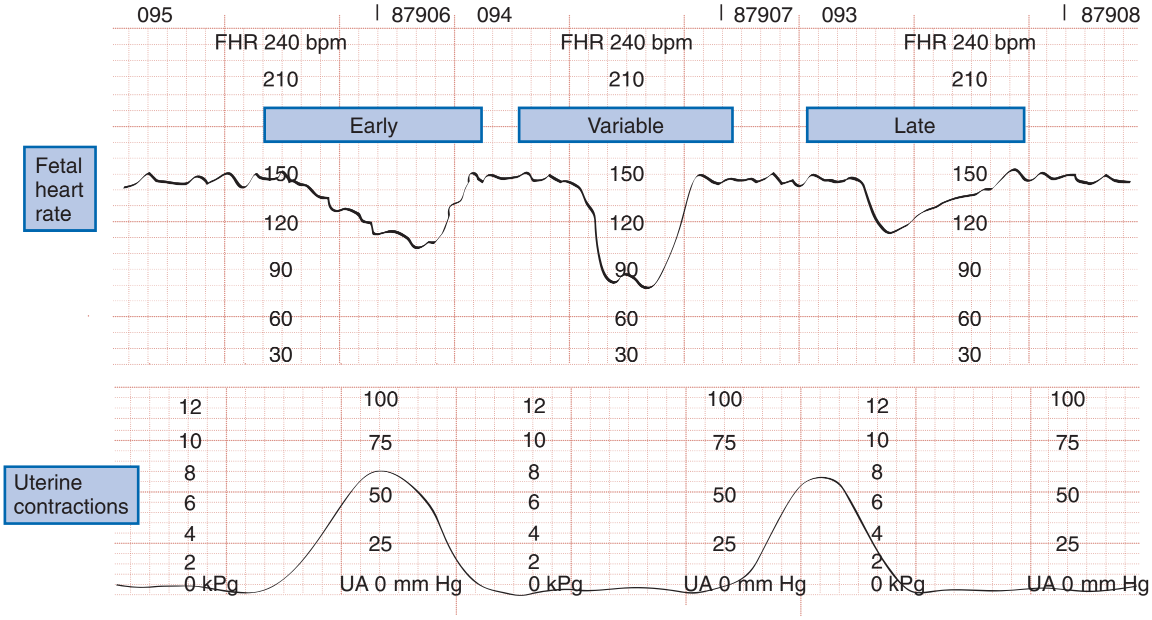


Figure 37-4. Types of fetal heart rate decelerations. *bpm,* beats per minute; *FHR,* fetal heart rate; *UA,* uterine activity.

Laboratory

Besides routine trauma blood work, emergency laboratory tests for a traumatized pregnant patient include a blood type with Rh status. In apparently stable pregnant patients, a low serum bicarbonate level may indicate occult maternal shock. Interpretation of bicarbonate results requires consideration of the physiologic changes of the bicarbonate level that occur in the later stages of pregnancy as a result of respiratory alkalosis. Arterial blood gases can allow detection of maternal hypoxia and acidosis, whereas pulse oximetry can be used to monitor oxygen saturation. Coagulation studies are important in directing management of patients with multisystem trauma or when the diagnosis of placental abruption is considered. The main difference in the laboratory workup between the nonpregnant and the pregnant trauma patient is the need to determine Rh status and quantitative β-human chorionic gonadotropin (β-hCG) in the pregnant patient; besides this, the physician should order any and all laboratory tests that would be ordered for any trauma patient.

Kleihauer-Betke Test and Fetomaternal Hemorrhage

Fetomaternal hemorrhage (FMH), the transplacental bleeding of fetal blood into the normally separate maternal circulation, is a unique complication of pregnancy. The reported incidence of FMH after trauma is 8 to 30% (with a range of 2.5-115 mL of blood) compared with 2 to 8% (range of 0.1-8 mL) for control

www.ketabpezeshki.com 66485457-66963820

studies. MVCs, anterior placental location, and uterine tenderness are associated with an increased risk of FMH, but gestational age is not.[3,4] Massive fetomaternal transplacental hemorrhage causes alloimmunization in Rh incompatibility but also endangers the fetus by severe fetal anemia and resulting fetal distress and possible exsanguination. ABO incompatibility causes less severe disease.

In theory, it is possible that trauma can result in FMH as early as the fourth week of gestation, when the fetal and placental circulations first form. In practice, FMH is usually of more concern after 12 weeks' gestation, when the uterus rises above the pelvis and becomes susceptible to direct trauma.

The Kleihauer-Betke test quantifies the amount of FMH. Most laboratories screen for FMH of 5 mL or more. Unfortunately, the amount of FMH sufficient to sensitize most Rh-negative women is well below this 5-mL sensitivity level. Therefore it is advisable that all Rh-negative mothers who have a history of abdominal trauma receive one prophylactic dose of Rhesus immune globulin (RhIG) within 72 hours of the incident. In the first trimester, one 50-μg dose is sufficient because total fetal blood volume is only 4.2 mL by 12 weeks' gestation, and a 50 μg-dose covers 5 mL of bleeding. During the second and third trimesters, a 300-μg dose of RhIG is given, which protects against 30 mL of FMH. Beyond 16 weeks' gestation, the total fetal blood volume reaches 30 mL or more. Massive FMH likely exceeds the efficacy of one 300-μg dose of RhIG, so the Kleihauer-Betke test can be used to guide effective dosing.

Trauma patients at risk for massive FMH have major injuries or abnormal obstetric findings, such as uterine tenderness, contractions, or vaginal bleeding. Less than 1% of all pregnant trauma patients and only 3.1% of major trauma cases exceed the coverage of one 300-μg RhIG dose.[4]

Because RhIG can effectively prevent Rh isoimmunization when administered as late as after 72 hours of antigenic exposure, the results of the Kleihauer-Betke test are not immediately needed in the ED.

Mother Stable, Fetus Stable

Minor trauma does not necessarily exempt the fetus from significant injury. It is estimated that 1 to 3% of all minor trauma results in fetal loss, typically from placental abruption.[11,19] Therefore, once the traumatized mother is stabilized, the focus of care is directed toward the fetus. For the viable fetus (greater than 24 weeks' gestation), monitoring is the next step. Continuous monitoring maintained throughout all diagnostic and therapeutic actions is advisable. Because direct impact is not necessary for fetoplacental pathology to occur, the traumatized pregnant woman with no obvious abdominal injury still benefits from monitoring.[11]

The recommended 4 hours of cardiotocographic observation of the viable fetus is extended to 24 hours if at any time during the first 4 hours there are more than three uterine contractions per hour, uterine tenderness persists, results on a fetal monitor strip are worrisome, vaginal bleeding occurs, the membranes rupture, or any serious maternal injury is present. Most cases of placental abruption after maternal trauma are detected within the first 4 hours of monitoring.[11,19]

On release from the hospital, the pregnant woman should be instructed to record fetal movements during the next week. If fewer than four movements per monitored hour are noted, the patient should see her obstetrician immediately and a nonstress test is warranted. The occurrence of preterm labor, membrane rupture, vaginal bleeding, or uterine pain also necessitates prompt reevaluation. Serial US and fetal heart rate tests on viable fetuses a few days after maternal trauma and periodically throughout the remaining portion of the pregnancy are helpful in monitoring fetal well-being.

Mother Stable, Fetus Unstable

Fetal death rates after maternal trauma are three to nine times higher than maternal death rates.[5] If a viable fetus remains in distress despite optimization of maternal physiology, cesarean section should be considered.

Although fetal viability is first reached at 24 weeks, the ultimate determinant of the age of fetal viability is the level of neonatal care provided by the intensive care nursery unit in each hospital or accessible regional facility. Determining gestational age for fetuses of less than 29 weeks may be difficult. Emergency decisions on fetal viability are therefore made on the basis of the best US and gestational age information available.

The presence of fetal heart tones is an important survival marker for fetuses about to undergo emergency cesarean section. No infant survives if there is no fetal heart tone before emergency cesarean section commences. If fetal heart tones are present and the gestational age is 26 weeks or more, then infant survival rate may be as high as 75%.[11,19]

Besides fetal distress, other reasons for a cesarean section include uterine rupture, placental rupture with significant vaginal bleeding, fetal malpresentation during premature labor, and situations in which the uterus mechanically limits maternal repair. Fetal demise without any of the aforementioned conditions is not an indication for cesarean section because most will pass spontaneously within 1 week.

Mother Unstable, Fetus Unstable

If the mother's condition is critical, primary repair of her wounds is the best course. This may apply even when the fetus is in distress because a critically ill mother may not be able to withstand an additional operative procedure such as cesarean section, which prolongs laparotomy time and likely substantially increases blood loss. The best initial action on behalf of the fetus is early restoration of normal maternal physiology. If it is felt that the unstable mother can tolerate an emergency cesarean section, it should be considered for the distressed, viable fetus.[11]

As with nonpregnant patients, operative intervention for blunt trauma and above-the-uterus stab wounds is dictated by clinical findings and diagnostic testing results. Above-the-uterus intraperitoneal gunshot wounds require exploration.

There is little evidence to support a definitive management strategy for penetrating trauma to the gravid uterus. In situations of a hemodynamically stable mother, expectant management has been recommended. However, no prospective study has verified this. Damage to the uterus alone can be quite devastating because of its increased circulation. Without exploration, it is impossible to know the occurrence, size, or depth of uterine penetration, and there are no guidelines indicating whether a uterine wound can be left unsutured without incurring an increased risk of infection or delayed uterine rupture. Laparotomy or laparoscopy seems to be the safest means of managing penetrating uterine wounds because missed maternal injuries can quickly compromise the fragile fetus.

Perimortem Cesarean Section

Restoration of maternal and thus fetal circulation is the optimal goal. However, extended and exclusive attention to the mother in cardiopulmonary arrest may prevent recovery of a potentially viable fetus. During maternal resuscitation, adequate oxygenation, fluid loading, and a 30-degree left tilting position may improve maternal circulation. If there is no response to advanced cardiac life support, a decision for perimortem cesarean section is made. If there are no fetal heart tones, a cesarean section is not warranted.[31]

www.ketabpezeshki.com 66485457-66963820

Perimortem cesarean section in the ED should be considered only if uterine size exceeds the umbilicus and fetal heart tones are present.[11,19,31] Time since maternal circulation ceased is the critical factor in fetal outcome. Published reports support but fall short of proving that perimortem cesarean delivery should be initiated within 4 minutes of the onset of maternal cardiac arrest.[19] Beyond 20 minutes, there is virtually never survival or favorable neurologic outcome for either mother or fetus.[19]

In the event of maternal cardiopulmonary arrest, perimortem cesarean section may be indicated. The most experienced physician available should perform the procedure as cardiopulmonary resuscitation is continuing. A midline vertical incision is made from the epigastrium to the symphysis pubis. The uterus is then entered with a midline vertical incision. If necessary, the placenta is incised to reach the fetus; once the fetus has been delivered, the cord is clamped and cut.[32] Maternal revival after delivery of the fetus has been reported in a few perimortem circumstances, presumably because vena caval compression is relieved.[33]

DISPOSITION

Any pregnant woman at 24 or more weeks of gestation who has sustained blunt body trauma should undergo at least 4 hours of fetal monitoring even if she looks well.[11,19] Other admission and operative criteria are similar for pregnant and nonpregnant trauma patients. The emergency physician should consider the stability of the mother and the viability of the growing fetus when making management and disposition decisions.

MISCELLANEOUS

Tetanus toxoid and immune globulin have no detrimental effect on the fetus. Proper immunization of pregnant women decreases the incidence of neonatal tetanus because the tetanus antibody crosses the placenta.

Electrical flow that bypasses the fetus has little effect on the pregnancy. Maternal elective and emergent cardioversion has been performed safely for cardiac dysrhythmias in all three stages of pregnancy. Energies up to 300 watt-seconds have been used without affecting the fetus or inducing premature labor. Cullhead reported no disruption of a monitored fetal heart rhythm during maternal cardioversion with 80 and 200 watt-seconds.[34] Although the amount of energy reaching the fetal heart is thought to be small, it is advisable to monitor the fetal heart during maternal cardioversion.

KEY CONCEPTS

- Management of life- and limb-threatening injury in the mother comes first.
- Even in the stable pregnant trauma patient, the fetus is at increased risk of morbidity and mortality.
- The fetus is viable at 24 weeks' gestation. This usually corresponds to when the fundus is at or above the umbilicus.
- In assessing the injured pregnant patient, it is important to consider the alterations in anatomy and physiology that occur during pregnancy.
- Stable pregnancies with a viable fetus should be monitored continuously for a minimum of 4 hours after trauma.
- Keeping the mother tilted 30 degrees to the left or in the left lateral decubitus position may alleviate hypotension and improve perfusion for the mother and fetus.
- Perimortem cesarean section should be considered only for a viable fetus with signs of life.
- The use of ionizing radiation to the pregnant patient, including CT and plain radiography, should be minimized, but imaging should not be withheld if it may provide significant diagnostic information.
- If available, nonionizing radiation, including ultrasound and MRI, is preferred for the evaluation of pregnant trauma patients.

ACKNOWLEDGMENT

The contributors would like to sincerely thank John D. G. Neufeld, MD, for his previous work on this chapter.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Tinker SC, Reefhuis J, Dellinger AM, Jamieson DJ; National Birth Defects Prevention Study: Epidemiology of maternal injuries during pregnancy in a population-based study, 1997-2005. *J Womens Health (Larchmt)* 2010; 19:2211-2218.
2. Petrone P, et al: Abdominal injuries in pregnancy: A 155-month study at two level 1 trauma centers. *Injury* 2010; 42:47-49,
3. Schiff MA: Pregnancy outcomes following hospitalisation for a fall in Washington State from 1987 to 2004. *BJOG* 2008; 115:1648.
4. El-Kady D, et al: Trauma during pregnancy: An analysis of maternal and fetal outcomes in a large population. *Am J Obstet Gynecol* 2004; 190:1661.
5. John PR, et al: An assessment of the impact of pregnancy on trauma mortality. *Surgery* 2011; 149:94.
6. El Kady D, Gilbert WM, Xing G, Smith LH: Maternal and neonatal outcomes of assaults during pregnancy. *Obstet Gynecol* 2005; 105:357.
7. Bochicchio GV, Napolitano LM, Haan J, Champion H, Scalea T: Incidental pregnancy in trauma patients. *J Am Coll Surg* 2001; 192:566.
8. Curet MJ, Schermer CR, Demarest GB, Bieneik EJ 3rd, Curet LB: Predictors of outcome in trauma during pregnancy: Identification of patients who can be monitored for less than 6 hours. *J Trauma* 2000; 49:18.
9. Kerr MD, Scott DB, Samuel E: Studies of the inferior vena cava in late pregnancy. *Br Med J* 1964; 1:532.
10. Archer GW Jr, Marx GF: Arterial oxygen tension during apnoea in parturient women. *Br J Anaesth* 1974; 46:358.
11. Brown HL: Trauma in pregnancy. *Obstet Gynecol* 2009; 114:147-160.
12. Schiff MA, Mack CD, Kaufman RP, Holt VL, Grossman DC: The effect of air bags on pregnancy outcomes in Washington State: 2002-2005. *Obstet Gynecol* 2010; 115:85.
13. Hyde LK, Cook LJ, Olson LM, Weiss HB, Dean JM: Effect of motor vehicle crashes on adverse fetal outcomes. *Obstet Gynecol* 2003; 102:279.
14. Klinich KD, Schneider LW, Moore JL, Pearlman MD: Investigations of crashes involving pregnant occupants. *Annu Proc Assoc Adv Automot Med* 2000; 44:37.
15. McGwin G Jr, et al: A focused educational intervention can promote the proper application of seat belts during pregnancy. *J Trauma* 2004; 56:1016.
16. Silverman J, Raj A: Intimate partner violence victimization prior to and during pregnancy among women residing in 26 U.S. states: Associations with maternal and neonatal health. *Am J Obstet Gynecol* 2006; 195:140.
17. Guth AA, Pachter L: Domestic violence and the trauma surgeon. *Am J Surg* 2000; 179:134.
18. Hedin LW, Janson PO: Domestic violence during pregnancy: The prevalence of physical injuries, substance abuse, abortions and miscarriages. *Acta Obstet Gyncecol Scand* 2000; 79:625.
19. Sugrue ME, O'Connor MC, D' Amours SK: Trauma during pregnancy. *ADF Health* 2004; 5:24-28.
20. Theodorou DA, et al: Fetal death after trauma in pregnancy. *Am Surg* 2000; 66:809.
21. Aboutanos MB, et al: Significance of motor vehicle crashes and pelvic injury on fetal mortality: A five-year institutional review. *J Trauma* 2008; 65:616.
22. Leggon RE, Wood GC, Indeck MC: Pelvic fractures in pregnancy: Factors influencing maternal and fetal outcomes. *J Trauma* 2002; 53:796.
23. Barraco RD, et al: Practice management guidelines for the diagnosis and management of injury in the pregnant patient: The EAST Practice Management Guidelines Work Group. *J Trauma* 2010; 69:211.
24. Oyelese Y, Ananth CV: Placental abruption. *Obstet Gynecol* 2006; 108:1005.
25. Reis PM, Sander CM, Pearlman MD: Abruptio placentae after auto accidents. *J Reprod Med* 2000; 45:6.
26. Henderson DE, Goldman B, Divon MY: Ritodrine therapy in the presence of chronic abruptio placentae. *Obstet Gynecol* 1992; 80:510.
27. North DL: Radiation doses in pregnant women. *J Am Coll Surg* 2002; 194:100-101.
28. Brown MA, Sirlin CB, Farahmand N, Hoyt DB, Casola G: Screening sonography in pregnant patients with blunt abdominal trauma. *J Ultrasound Med* 2005; 24:175.
29. Ormsby EL, Geng J, McGahan JP, Richards JR: Pelvic free fluid: Clinical importance for reproductive age women with blunt abdominal trauma. *Ultrasound Obstet Gynecol* 2005; 26:271.
30. Damilakis J, Perisinakis K, Voloudaki A, Gourtsoyiannis N: Estimation of fetal radiation dose from computed tomography scanning in late pregnancy: Depth-dose data from routine examinations. *Invest Radiol* 2000; 35:527. (Correction in *Invest Radiol* 2000; 35:706).
31. Katz V, Balderston K, DeFreest M: Perimortem cesarean delivery: Were our assumptions correct? *Am J Obstet Gynecol* 2005; 192:1916.
32. Warraich Q, Esen U: Perimortem caesarean section. *J Obstet Gynaecol* 2009; 29:690-693.
33. DePace NL, Betesh JS, Kotler MN: "Postmortem" cesarean section with recovery of both mother and offspring. *JAMA* 1982; 248:971.
34. Cullhead I: Cardioversion during pregnancy. *Acta Med Scand* 1983; 214:169.

www.ketabpezeshki.com 66485457-66963820

Chapter 38

Pediatric Trauma

Brittany L. Murray and Randolph J. Cordle

PERSPECTIVE

Injuries to children (<18 years old) account for more than 8 million visits to emergency departments in the United States each year. More than half of all deaths in this age group are the direct result of injury, with more than 10,000 traumatic deaths annually.[1] Motor vehicle collisions (MVCs) account for more than half of all pediatric traumatic deaths.[1] In the United States, estimates of mortality for children hospitalized after injury are uniformly low; however, most fatalities occur in the field before arrival at a health care facility, which contributes to an underestimation of the magnitude of overall mortality figures.

Multiple injuries are common in pediatric trauma patients, and the emergency physician should evaluate all organ systems in any injured child when the mechanism of injury is concerning. The most common single organ system injury associated with death in injured children is head trauma, but the great majority of pediatric trauma deaths involve multisystem injury.[2]

Accidental falls predominate nonfatal injuries in all pediatric age groups. Other nonfatal injuries vary by age. Young children (<4 years of age) experience higher rates of animal bites and burns. School-age children (5 to 9 years old) are more likely to experience bicycle and pedestrian injuries. Older children (>9 years) have high incidences of both fatal and nonfatal motor vehicle–related trauma, and higher incidences of suicide and self-inflicted harm. Homicide by firearm shows a fourfold and tenfold increase when the 5- to 9-year age group is compared with the 10- to 14- and 15- to 24-year age groups, respectively. Homicide by firearm is nearly 31 times more common in the 15- to 24-year age group when compared with the 10- to 14-year age group.[1,2]

Throughout the United States the number of children who are victims of violent acts has increased. Some children's hospitals report that 7% of all pediatric injuries seen in emergency departments and 25 to 35% of all pediatric trauma deaths are caused by nonaccidental trauma.[3]

PRINCIPLES OF DISEASE

Between pediatric and adult patients, there are major anatomic and physiologic differences that play a significant role in the evaluation and management of a pediatric trauma patient (Box 38-1). Any given force is more widely distributed through the body of a child than the body of an adult, making multiple injuries significantly more likely to occur in children. The proportionately large surface area of infants and children relative to weight predisposes them to greater amounts of heat loss as a result of evaporation. During resuscitation, even mild to moderate hypothermia has direct negative effects on cardiac function, inotropy, left-ventricular contractility, catecholamine responsiveness, platelet function, renal and hepatic drug clearance, and metabolic acidemia. Therefore maintenance requirements for free water, electrolytes, and minerals are proportionally greater compared with those for adults. Oxygen extraction and consumption as well as glucose utilization are much higher per kilogram in infants and small children than in adults. These factors contribute to a significantly higher energy and caloric requirement for an injured child compared with an injured adult. A child's physiologic response to injury is different from an adult's response, depending on the age and maturation of the child and the severity of the injury. Children have a great capacity to maintain blood pressure despite significant acute blood losses constituting 25 to 30% of total blood volume.[4] A child's cardiac output is primarily determined by the heart rate and systemic vascular resistance. Changes in inotropy play a relatively minor role in children after trauma, compared with adults. Compensated shock should be considered and promptly addressed when a child's heart rate is elevated, especially if the capillary refill time is delayed. Changes in heart rate, blood pressure, and extremity perfusion commonly precede cardiorespiratory failure and should not be overlooked.

CLINICAL FEATURES

Initial Assessment Priorities and Primary Survey

The highest priority in the approach to the injured child is ruling out the presence of life-threatening or limb-threatening injury. Treatment of these injuries occurs before the rest of the physical examination proceeds. This initial assessment (the primary survey) and necessary initial resuscitation efforts occur simultaneously. In general, the assessment and resuscitation should be addressed within the first 5 to 10 minutes of evaluation. Any infant or child with a potentially serious or unstable injury requires continual reassessment. Vital signs should be repeated every 5 minutes during the primary survey and until the patient is considered stable, then every 15 minutes thereafter. The elements of the primary survey for pediatric trauma patients can be remembered by *A, B, C, D, E,* and *F.*

A—Airway and Cervical Spine Stabilization

Table 38-1 describes anatomic considerations that have implications in the management of the pediatric airway. The physician assesses for possible airway obstruction or inability of the child to maintain his or her own airway. While the neck is being stabilized, the airway can be opened with a jaw-thrust maneuver. Maxillofacial trauma, loose teeth, blood, swelling, or vomitus may obstruct

www.ketabpezeshki.com 66485457-66963820

Box 38-1 Specific Anatomic Differences in Adults and Children: Implications for Pediatric Trauma Management

- The child's head-to-body ratio is greater, the brain is less myelinated, and cranial bones are thinner, resulting in more serious head injury.
- The child's internal organs are more susceptible to injury based on more anterior placement of liver and spleen, and less protective musculature and subcutaneous tissue mass.
- Small children respond to decreased cardiac output primarily through an increase in heart rate and systemic vascular resistance; therefore a fast heart rate and slow capillary refill may be the first signs of shock.
- The child's kidney is less well protected and more mobile, making it susceptible to deceleration injury.
- The elasticity of the child's chest wall allows for pulmonary injury without skeletal injury.
- Growth plates are not yet closed in pediatric patients, leading to Salter-type fractures with possible resultant limb-length abnormalities.
- Children have a more tenuous spinal cord blood supply and a greater elasticity of the vertebral column, predisposing them to spinal cord injury without radiographic abnormality (SCIWORA).

the airway, and efforts should be made toward clearing the oropharynx of debris. Gurgling or stridor may indicate upper airway obstruction. The physician must know normal pediatric oral anatomy and tooth development to recognize the possibility of missing primary or secondary teeth. Efforts to perform cricoid pressure, or ligatures such as ties on gowns, can easily occlude the infant's or child's airway with as little as 0.2 pounds of direct force.[5] Table 38-2 describes priorities in the assessment of the pediatric airway.

Indications for endotracheal intubation of a pediatric trauma patient include (1) any inability to ventilate by bag-valve-mask (BMV) methods or the need for prolonged control of the airway, (2) Glasgow Coma Scale (GCS) score of less than 9 (to secure the airway and provide controlled hyperventilation if indicated), (3) respiratory failure from hypoxemia (e.g., flail chest and pulmonary contusions) or hypoventilation (e.g., injury to airway structures or spinal cord injury [SCI]), and (4) the presence of decompensated shock resistant to initial fluid administration.

Intubation of pediatric patients involves special considerations (see Table 38-1). In general, the orotracheal approach is recommended. In children, nasotracheal intubation can be complicated by the acute angle of the posterior pharynx, the potential for bleeding, and infection (sinusitis). Furthermore, nasotracheal intubation can cause increased intracranial pressure (ICP). In children younger than age 8, the cricoid ring is the narrowest portion of the airway. The cricoid ring may form a physiologic cuff on endotracheal tubes (ETT). However, the use of a cuffed tube allows for greater airway protection and may be considered in the injured child. Appropriate ETT size can be estimated through use of a length-based resuscitation tape or by the formulas in Box 38-2.

The clinician should consider the possibility of cervical cord injuries in all seriously traumatized children. Spinal column stabilization should be maintained until injury is ruled out. (Evaluation of the cervical spine in children is discussed later in this chapter.) A gentle, developmentally appropriate approach is used if reliable information is to be gained. Any complaint of past or current neurologic deficit, neck pain, or significant trauma to the head, chest, abdomen, or other spinal level injury should raise concern for spinal injury.

Table 38-1 Anatomic Differences in the Pediatric Airway—Implications in Pediatric Trauma Management

DIFFERENCES	IMPLICATIONS
Increased vagal response to laryngoscopy	Bradycardia during intubation; in infants and small children may be abated through the use of glycopyrrolate or atropine
Relatively larger tongue	Most common cause of airway obstruction in children May necessitate better head positioning or use of airway adjunct (oropharyngeal or nasopharyngeal airway)
Larger mass of adenoidal tissues	Nasotracheal intubation may be more difficult Nasopharyngeal airways may also be more difficult to pass in infants
Epiglottis floppy and more U shaped	Necessitates use of a straight blade in young children
Larynx more cephalad and anterior	More difficult to visualize the cords; may need to get lower than the patient and look up at 45-degree angle or greater while intubating
Cricoid ring the narrowest portion of the airway	Although cuffed tubes may be used in all children, this allows for the use of uncuffed tubes in children up to approximately 8 years of age, or a size 6-mm ETT; see Table 38-2 for endotracheal tube sizing
Narrow tracheal diameter and distance between the rings	Needle cricothyrotomy for the difficult airway in children younger than 12 years of age versus a surgical cricothyrotomy in older children and adults
Shorter tracheal length (4-5 cm in newborns and 7-8 cm in 18-month-olds)	Leads to intubation of right main stem or dislodgement of the endotracheal tube Ensure tube position is checked before taping with head in neutral position or tube can be driven into the right main stem when the head is flexed or withdrawn when the head is extended to get to neutral
Large airways more narrow	Leads to greater airway resistance (R proportional to $1/\text{radius}^4$)

B—Breathing and Ventilation

The physician assesses for breath sounds and adequacy of chest rise. In a young child, this rise occurs in the lower chest and upper abdomen. Both the chest and the abdomen should move concordantly. Discordant motion with significant inward chest motion is referred to as *paradoxical breathing* and is a sign of impending respiratory failure. Respiratory rates that are too fast or too slow can also indicate impending respiratory failure. Treatment is assisted ventilation. If ventilation is necessary, a BMV device is recommended initially. Only the volume necessary to cause the chest to rise should be provided because excessive volume or rate of ventilation can increase the likelihood of gastric distention (increasing the risk of vomiting and aspiration) and impair ventilation further. Gentle cricoid pressure may help decrease the amount of air entering the esophagus during positive pressure ventilation. After intubation a nasogastric (NG) or orogastric (OG) tube should be placed within the first few minutes. Gastric distention often leads to respiratory embarrassment and potential hypotension caused by decreased venous return and impaired

www.ketabpezeshki.com 66485457-66963820

Table 38-2 Airway: Assessment and Treatment

ASSESSMENT PRIORITIES	INTERVENTIONS
Airway patency	Jaw thrust, suction, airway adjuncts Stabilize or remove loose teeth or other foreign bodies Monitor patient closely for emesis, swelling, and other changes in airway patency
Level of consciousness	Intubate for Glasgow Coma Scale score less than 9 or absent gag reflex in a patient with a clinically concerning head injury
Stridor or cyanosis	Apply 100% O_2 by mask Intubate for Po_2 <50 mm Hg or Pco_2 >50 mm Hg Needle cricothyrotomy or surgical cricothyrotomy if intubation impossible and cannot oxygenate and ventilate by bag-valve-mask

O_2, oxygen; Pco_2, partial pressure of carbon dioxide; Po_2, partial pressure of oxygen.

Box 38-2 Equipment Size Estimates for Pediatric Trauma

Endotracheal Tube (ETT) Size Estimates (Sizing in Millimeters Internal Diameter) and Depth

Neonatal endotracheal tube sizing is weight based:
- <1 kg = 2.5 mm
- 1 kg = 2.5-3 mm
- 2 kg = 3 mm
- 3 kg = 3 mm
- 3½ kg+ = 3-3.5 mm
- 4 kg = 3.5 mm

Neonatal depth of insertion is weight based:
- ≤1 kg = 6 cm
- 2 kg = 7 cm
- 3 kg = 8 cm
- 4 kg = 9 cm

For children 1 to 10 years of age, a length-based resuscitation tape may be used, or ETT size can be estimated by the following formulas. An ETT 0.5 mm larger and 0.5 mm smaller in internal diameter should also be ready at the bedside.
- Cuffed endotracheal tube size (mm) = (Age in years/4) + 3.5
- Uncuffed endotracheal tube size (mm) = (Age in years/4) +4
- Tube depth (cm) = Age in years/2 + 12

Largest Chest Tube Size

Largest chest tube diameter = 4 × the endotracheal tube size

Orogastric (OG), Nasogastric (NG), or Foley Size

OG, NG, or Foley diameter = 2 × ETT size

Femoral Line Sizing Estimates (weight based)

- ≤3 kg = 3 F
- 3-10 kg = 4 F
- 10-20 kg = 5 F
- >20 kg = 6 F

diaphragmatic function. Occasionally, BMV and air swallowing can lead to gastric distention, necessitating an NG tube. An NG tube should not be used if basilar skull fracture is possible. In conscious children, placement of an NG or OG tube should be preceded by local anesthesia with use of agents such as atomized or nebulized lidocaine plus lidocaine jelly. If a child with an NG or OG tube requires intubation, the gastric tube should be placed to suction to empty the stomach before rapid sequence intubation (RSI), because the gastric tube disrupts the gastroesophageal junction and can otherwise lead to aspiration.

Many factors may compromise ventilatory function in an injured child. These include depressed sensorium, occlusion of the airway, painful restriction of lung expansion, diaphragmatic

Table 38-3 Breathing: Assessment and Treatment

ASSESSMENT PRIORITIES	INTERVENTIONS
Respiratory rate	Fast rates may indicate impending respiratory failure and need for intubation, shock and need for fluid resuscitation, or pain and need for analgesics. Slow rates may indicate impending respiratory failure, head injury, or oversedation.
Chest wall movements	Paradoxical breathing and flail segments may represent impending respiratory failure. 100% oxygen should be provided by non-rebreather mask, and intubation may be considered.
Percussion and breath sounds	Consider pneumothorax, hemothorax, or diaphragmatic rupture. For significant pneumothorax or hemothorax: place chest tube. A small pneumothorax in a patient spontaneously breathing may require only close monitoring and oxygen. For hemothorax, transfer to operating room if initial drainage > 15 mL/kg or subsequent output > 2 mL/kg/hr. For open pneumothorax: seal with three-sided occlusive dressing followed by tube thoracostomy, then seal the remaining side of the occlusive dressing. Diaphragmatic rupture requires surgical consultation.
Tracheal deviation	Tension pneumothorax: needle decompression at second intercostal space, midclavicular line, followed by placement of chest tube; if a chest tube can be immediately placed, needle decompression is not needed.

fatigue, and direct pulmonary injury. Determination of adequate ventilation is possible only in the face of airway patency and adequate air exchange.

For assessment of "ventilation," pulse oximetry is useful; however, pulse oximetry measures adequacy of oxygenation only. The measurement of exhaled carbon dioxide (CO_2) is useful to confirm ETT position. Historically, a colorimetric semiquantitative device has been used to detect the presence of exhaled CO_2 in patients with perfusion. Continuous end-tidal CO_2 capnography provides far more information and continues to be underused.[6] In a patient with adequate perfusion, in addition to serving as an initial qualitative device to confirm successful intubation of the trachea, it may also provide an early warning of unintended extubation, tube kinking or partial occlusion, or ventilator malfunction. Continuous end-tidal CO_2 capnography also characterizes the response to therapeutic maneuvers instantaneously, provides a quantitative tool to manage the ventilatory aspects of respiration, and may provide prognostic information when used in patients with cardiac arrest. It can also be used to measure the effectiveness of cardiopulmonary resuscitation (CPR). The lack of appropriate CO_2 detection when the tube is in proper position often indicates poor perfusion. The use of end-tidal CO_2 capnography allows better ventilatory management during head injury resuscitation, and its values can be confirmed with a single venous or arterial blood gas measurement. This can assist greatly with continuing ventilatory management without the need for recurrent blood draws and the inherent delays and discomfort of acquiring blood gases (assuming stable pulmonary function). Table 38-3 describes priorities in the assessment of breathing in pediatric trauma patients.

www.ketabpezeshki.com 66485457-66963820

Box 38-3 Circulation Assessment and Treatment

Assessment

Increased heart rate, slow capillary refill, decreased peripheral pulses, and altered sensorium may indicate poor circulation.
Vital signs should be monitored every 5 min during the initial assessment.
Continuous oximeter and cardiac monitor.

Treatment and Interventions

Place two large-bore intravenous sites (above and below diaphragm when indicated).
Consider central line or intraosseous line placement if peripheral venous access is difficult.
Bolus with 20 mL of warmed normal saline per kilogram, and repeat if necessary.
Consider intubation and ventilation to decrease work of breathing.
Transfuse 10-20 mL/kg for decompensated shock secondary to blood loss.

Box 38-4 Disability: Neurologic Assessment and Treatment

Assessment

Level of consciousness—use AVPU scale and age-appropriate Glasgow Coma Scale (GCS)
Pupil size and reactivity
Extremity movement and tone
Posturing and reflexes

Treatment and Interventions

Stabilize spinal column.
If GCS score < 9: rapid sequence intubation (RSI).
If altered mental status, obtain a head computed tomography scan and neurosurgical consultation as needed.
With signs of herniation, consider mannitol 0.25 to 0.5 g/kg IV, and hyperventilate to a P_{CO_2} of 30 to 35 mm Hg.
Maintain cerebral perfusion pressure of at least 50 mm Hg in children and 70 mm Hg in adults.
Assess for signs of spinal injury, including respiratory failure and bulbocavernosus reflex or presence of anal wink.

AVPU, alert, verbal, painful, unresponsive; P_{CO_2}, partial pressure of carbon dioxide.

Box 38-5 AVPU System

A—*A*lert
V—Responds to *v*erbal stimuli
P—Responds to *p*ainful stimuli
U—*U*nresponsive

C—Circulation and Hemorrhage Control

Shock is not defined by any specific blood pressure but is, instead, a state in which the body is unable to maintain adequate tissue perfusion. Maintenance of systolic blood pressure does not ensure that the patient is not in shock. The pediatric vasculature has the ability to constrict and increase systemic vascular resistance in an attempt to maintain perfusion. Signs of poor perfusion (cool distal extremities, decreases in peripheral versus central pulse quality, and delayed capillary refill time) are signs of pediatric shock, even when blood pressure is maintained at normal levels. Palpable pulses are detectable at a systolic blood pressure greater than 80 mm Hg in children over approximately 10 years of age; however, pulses may be felt at even lower pressures in infants and younger children. Normal capillary refill time is less than 2 seconds; however, many variables affect this clinical finding. Alteration in a child's response to the environment or interaction with caregivers may indicate respiratory failure or shock. External hemorrhage should be sought and controlled with direct pressure. The assessment of circulation in pediatric trauma patients is described in Box 38-3.

D—Disability Assessment (Thorough Neurologic Examination)

For assessment of patient disability, a rapid neurologic and mental status evaluation is needed. The assessment of disability in pediatric trauma patients is described in Box 38-4. The AVPU system (Box 38-5) and the modified pediatric GCS (Table 38-4) can also be useful to the clinician.

E—Exposure and Thorough Examination

Fully undressing the patient to assess for hidden trauma is essential in injured children. Maintenance of normothermia is paramount in the undressed infant and toddler because metabolic needs are greatly increased by hypothermia. In addition to increased ambient temperature, additional warming methods such as warmed humidified oxygen, warmed fluids, warmed blood, head wraps, and convective warmers or radiant heat sources should be used as soon as possible. Preventing and treating hypothermia is not a matter of comfort for traumatized infants and children but, instead, one of survival. The exposure phase of the survey is often a good time to concurrently begin imaging and further diagnostic testing (Table 38-5).

F—FAST and Family

The focused assessment with sonography in trauma (FAST) can be a very useful examination in injured children.[7] Bedside ultrasound evaluates for traumatic free fluid in the peritoneum (hepatorenal, perisplenic, and retrovesicular views) and pericardial space. In hemodynamically unstable children, a FAST may point to hemorrhage in the abdomen or the pericardial space and the need for intervention. In hemodynamically stable children, the FAST examination may indicate the need for computed tomography (CT) imaging, closer observation, repeat abdominal examinations, or repeat ultrasound examinations.

In the management of children, the family (caregivers) could be added to the primary survey. Rapidly informing the family of what has happened and of the evaluation and progress helps to lessen their stress. Allowing family members to be present during resuscitations is acceptable and often preferred by families. Some family members choose not to be present, but that choice should be given to them. If a family member is present, it is advisable to assign a staff member to be with him or her during the trauma resuscitation to explain the process.

Child life specialists and clergy are valuable members of the resuscitation team. They not only serve the patient directly through their provision of comfort and developmentally appropriate explanations of medical activities, but also serve as a single caring person for the child to focus on throughout the evaluation. They can also be instrumental in assisting the family to better understand what they may and may not do during and soon after the resuscitation. Families often wonder, but are sometimes afraid to ask, if they may touch the child and what the next step is. These specialists can play a role as the quintessential patient advocate, ensuring that the health care providers focus on the patient and not only on the individual medical issue at hand. Child life specialists should be viewed as part of the resuscitation team.

www.ketabpezeshki.com 66485457-66963820

Table 38-4 Glasgow Coma Scale Modified for Pediatric Patients*

Eye Opening Response

SCORE	>1 YR	<1 YR
4	Spontaneous	Spontaneous
3	To verbal command	To shout
2	To pain	To pain
1	None	None

Motor Response

SCORE	>1 YR	<1 YR
6	Obeys commands	Spontaneous
5	Localizes pain	Localizes pain
4	Withdraws to pain	Withdraws to pain
3	Abnormal flexion to pain (decorticate)	Abnormal flexion to pain (decorticate)
2	Abnormal extension to pain (decerebrate)	Abnormal extension to pain (decerebrate)
1	None	None

Verbal Response

SCORE	>5 YR	2-5 YR	0-2 YR
5	Oriented and converses	Appropriate words and phrases	Babbles, coos appropriately
4	Confused conversation	Inappropriate words	Cries but is consolable
3	Inappropriate words	Persistent crying or screaming to pain	Persistent crying or screaming to pain
2	Incomprehensible sounds	Grunts or moans to pain	Grunts or moans to pain
1	None	None	None

*Total score key: severe, <9; moderate, 9-13; mild, 14-15.

Table 38-5 Exposure: Assessment and Treatment

ASSESSMENT PRIORITIES	INTERVENTIONS
Full examination	Fully undress. Look under collar and splints. Log roll and examine back. Perform rectal examination if indicated.
Imaging	Consider chest, and pelvis radiographs. Consider additional imaging of any area of pain or trauma. Perform a bedside FAST examination.
Laboratory	Complete blood cell count, type and crossmatch, urinalysis, urine pregnancy test, urine drug screen.
Supportive interventions	For pelvic fracture, consider binding to decrease pelvic volume and aid hemostasis. For extremity fractures, consider reduction and splinting. Place urinary catheter and nasogastric or orogastric tube as indicated.
Medications	Provide analgesia with intravenous medications. Tetanus vaccine and tetanus immune globulin for appropriate cases. Antibiotics when indicated.

FAST, focused assessment with sonography in trauma.

Secondary Survey

After completion of the primary survey and requisite procedures, the secondary survey is performed. The secondary survey is an organized, complete assessment to detect additional injury not found on the primary survey. A more complete and detailed history is obtained at this time. Features of the history that need to be obtained can be remembered by the mnemonic *AMPLE* (Box 38-6). Ongoing assessment of the patient occurs after the secondary survey, and key points are summarized in Box 38-7.

Box 38-6 AMPLE History

A—Allergies
M—Medications
P—Past medical history
L—Last meal
E—Environments and events

Box 38-7 Tasks to Be Completed after the Secondary Survey

- Continuous monitoring of vital signs
- Provision of analgesia, and continuous reassessment of pain
- Antibiotics and tetanus as appropriate
- Ensure urine output of 1 mL/kg/hr
- If patient is intubated, ensure adequate sedation and analgesia
- If head injury is present, frequent neurologic assessment

MANAGEMENT AND DIAGNOSTIC STRATEGIES

General Management Principles

All pediatric patients who have sustained major trauma should be placed on a cardiac monitor; receive supplemental oxygen; and

www.ketabpezeshki.com 66485457-66963820

have constant reassessment of vital signs, oximetry, and end-tidal CO_2 monitoring. Vascular access is best obtained by accessing the upper extremity for the establishment of two large-bore intravenous lines. In the absence of available upper extremity peripheral sites, lower extremity sites can be used. Many clinicians favor the femoral vein as a safe site for insertion of a central line by use of a guidewire technique. A guide to suggested sizing of femoral catheters is shown in Box 38-2.

If vascular access is unobtainable or delayed, intraosseous access is a safe, quick, and reliable procedure to access the vascular space. Essentially, samples for all laboratory tests, with the exception of the peripheral white blood cell (WBC) count and peripheral smear, can be obtained from an intraosseous needle (including blood type and crossmatch). Although most commonly started in the proximal medial tibia just below the growth plate, intraosseous access can be obtained in the proximal humerus, the flattened area of the anterior distal femur, the distal tibia, or even the sternum. In patients older than 6 years, the proximal humerus may be an advantageous site, as it has a higher flow rate than the tibia. The intraosseous route serves as an appropriate venous access site; however, the delivery rate of large amounts of crystalloid solutions may be slower than venous access. More than one intraosseous needle may need to be placed (in separate bones), and a separate peripheral or a central line may be more easily inserted once fluids have been given via the intraosseous route. Intraosseous placement in a fractured extremity is contraindicated. Venous cutdowns may occasionally be necessary, and the greater saphenous vein at the ankle is the preferred site. Umbilical vein cannulation can be achieved in infants up to approximately 2 weeks of age; 3-F and 5-F single and 5-F double-lumen catheters are available for use in the umbilical vein. If a specialized catheter is not available, a feeding tube or even a flexible intravenous catheter can be used for the infusion of crystalloid or blood. If vasopressors or highly osmotic agents are to be used, a more formal umbilical venous line placed above the liver should be considered to avoid hepatic injury.

Most hypovolemic pediatric trauma patients respond to 20-mL/kg boluses of isotonic crystalloid solutions. If 40 mL/kg has not reversed systemic signs of hypoperfusion, an additional 20-mL/kg bolus of crystalloid may be given, but the infusion of packed red blood cells at 10 mL/kg should be considered. In patients in decompensated hemorrhagic shock or cardiopulmonary failure secondary to severe anemia, crystalloid and blood products may be prudently administered simultaneously. With massive transfusion (>1 blood volume = approximately 80 mL/kg), it is important to add additional blood products to correct coagulopathy. Some experts now recommend (based predominantly on adult studies) that blood and fresh frozen plasma (FFP) be given in a near 1:1 ratio if massive transfusion is expected. Other experts believe a ratio closer to 2.5:1 may suffice and may decrease the risk of multiorgan failure. In general, FFP should be administered at 15 to 25 mL/kg. Platelet transfusion dosage can be very confusing. Practically all platelet units currently used are apheretic platelets from a single donor. Each apheretic unit roughly equates to six of the older concentrate units (a “six-pack” of platelets). The usual dose in trauma is 10 mL/kg; however, the response may be quite variable (i.e., it can vary by more than a factor of two) owing partly to the heterogeneity of the concentration of platelets between apheretic units. A general goal in trauma patients is to raise the platelet count above 50×10^9/L. The platelet count should be rechecked at 1 and 24 hours after transfusion, or more often if the patient has ongoing difficulties with hemostasis or need for recurrent transfusion of red blood cells. The primary goal of giving cryoprecipitate is to increase the fibrinogen to levels of 1 to 1.5 g/dL, especially after central nervous system trauma. Although dependent on the fibrinogen concentration in the individual cryoprecipitate bags, the dose is typically 0.1 to 0.2 bags/kg. Each bag of cryoprecipitate contains approximately 150 mg of fibrinogen and 80 units of factor VIII.[8]

In the case of trauma, shock is most likely to be hemorrhagic in nature; however, other causes of shock are possible and should be evaluated. Cardiogenic shock is a rare event in childhood injury. However, any degree of chest trauma associated with the presence of shock should alert the clinician to the possibility of concomitant myocardial injury, pericardial tamponade, or both. Neurogenic and spinal shock can occur in traumatic injury and are discussed later in this chapter.

Physical Examination

After the primary survey, a head-to-toe examination is carefully performed. Specifics of the head examination include pupillary size and reactivity and palpation of the skull. A funduscopic examination may be considered in young children with possible nonaccidental trauma. A Wood’s lamp evaluation with fluorescein should be considered if there is possibility of occult injury to the eye.

Assessment of the cervical spine is done carefully, with the patient in full cervical spine immobilization. As soon as feasible, the patient should be removed from the backboard with cervical spine immobilization maintained. Backboards are uncomfortable and can cause rapid necrosis at pressure points. There are no common indications to justify leaving children on backboards after their initial evaluation. When the patient is rolled to remove the backboard, palpation of the rest of the spine can take place with an emphasis on evaluating for ecchymosis, tenderness, and step-offs. Obtunded patients and those with signs or symptoms of thoracic or lumbar spine injuries should be carefully moved and positioned to protect them from possible further injury until imaging or return of consciousness allows more definitive assessment.

Assessment of the chest and internal structures involves inspection for wounds and flail segments; palpation for tenderness, crepitus, and point of maximal cardiac impulse; and auscultation for asymmetry or poorly transmitted breath sounds. When air bags have deployed, occult trauma such as pulmonary contusions, myocardial injury, pneumothorax, and especially aortic injury should be specifically considered and ruled out.

The abdominal examination consists of inspection, palpation, and a FAST examination. A “lap belt sign” or “seat belt sign” across the abdomen is a significant harbinger of serious traumatic injury. Palpation is best done on a cooperative patient but is an insensitive screening test for the presence of an injury.

A rectal examination is not required in all cases of pediatric trauma and should be performed only when its result has a reasonable chance of meaningfully changing the patient’s treatment.[9,10] A rectal examination may provide information on sphincter tone in possible spinal injury and the presence of blood in penetrating trauma. Unfortunately, the rectal examination lacks sensitivity. Its findings, when negative, are often misleading, and additional workup should be considered.

Although urethral injury is rare in children, all trauma patients should be assessed for a perineal, scrotal, penile, or lower abdominal hematoma and blood from the urethral meatus. If there is clinical concern for injury to the urethra, a retrograde urethrogram should be completed before the insertion of a urinary catheter.

Examination of the extremities is directed toward the evaluation of any deformities, penetrations, neurologic deficits, and interruptions of perfusion. Most fracture sites may be stabilized with splinting until surgical intervention can be carried out. Careful vascular and neurologic examinations should be performed in all cases of significant extremity injury and should be repeated frequently (especially after interventions such as splinting or reduction). Early orthopedic consultation is advisable.

www.ketabpezeshki.com 66485457-66963820

Reexamination of trauma patients throughout their time in the emergency department is of utmost importance to ensure that their condition has not changed, that their pain is controlled, and that no injuries are overlooked. Up to 70% of injuries with delayed diagnosis in pediatric trauma are orthopedic in nature.[11]

Pain Control

Pain control is an essential part of any trauma patient's management. Yet when asked if they want pain medicine, many children in pain will say "No" because they are afraid of getting a shot or they interpret "pain medicine" as medicine that will cause pain. Therefore basing pain medication on pain scales and common sense seems to be most appropriate.

The mainstay of pain control is narcotic analgesics. Fentanyl has an advantage over morphine owing to its hemodynamic profile. It does not cause the release of histamine commonly seen with morphine and has a lower incidence of causing hypotension. Initial orders should generally be for both an initial dose and an as-needed (PRN) dose so that the nurse can continue to adequately control and assess the patient's pain after the physician has left the bedside.

In head-injured patients, fentanyl has the additional advantage of a short duration of action. If the patient has a mental status change, fentanyl clears quickly, making it possible to differentiate worsening brain injury from side effects of the medication. This is generally a better option than reversing the pain medicine and pain control with a narcotic antagonist. It is not humane to withhold pain medication completely in a traumatized patient whose mental status is of concern; it is better to titrate with smaller doses of short-lived medications. If immediate concern arises, or there is respiratory depression, the narcotic can be reversed with very small doses of a narcotic antagonist.

In addition to use of narcotics for pain control, immobilization of fractures and extremities with significant soft tissue injury can help control pain. Visual imagery and distraction techniques can divert the patient's attention away from noxious stimuli and toward more pleasant experiences. Child life specialists, patient representatives, chaplains, and most parents can assist in this endeavor. Assessment of pain control practice during pediatric trauma care should be part of each emergency department's trauma protocols and quality improvement program.

Diagnostic Evaluation

Laboratory Studies

Blood sampling for a pediatric trauma patient is no different than that for an adult trauma patient; however, use of smaller blood collection tubes and microtechnique by laboratory staff may be necessary in infants and small children.

In patients with hypovolemic shock, the hemoglobin alone is unreliable because equilibration will not have occurred at the time of presentation to the emergency department.[12] Serial hemoglobin measurements may be useful to assess the possibility of ongoing bleeding.[13]

Bedside glucose testing should be performed on all patients with significant trauma. Children's glucose utilization and metabolic rate per kilogram are much greater than those of an adult, and they have far less substrate reserve in the form of glycogen stores. Any child with a change in mental status after trauma should have a glucose level checked immediately. Any child requiring dextrose owing to hypoglycemia will likely need an ongoing dextrose supply to prevent recurrence of hypoglycemia. In patients who can eat, this may be a meal with starches, fats, and protein. In others, it may require intravenous dextrose.

All older pediatric trauma patients should be assessed for the possible use of drugs or alcohol and depression as contributing factors to the traumatic event. Female adolescents should also be tested for pregnancy.

Radiology

Chest and pelvic radiographs can assess for causes of respiratory failure, sites of blood loss, and causes of shock. In stable, alert children without distracting injuries, the pelvic film may be eliminated if no suggestion of sacral or pelvic fracture is found on thorough clinical examination. The following seven criteria are required to rule out any relevant pelvic fracture: patient age older than 3 years, no impairment of consciousness, no other major distracting injury, no complaint of pelvic pain, no signs of fracture on inspection, no pain on iliac or pubic symphysis compression, and no pain on hip rotation or flexion.[14-16] In patients with remarkable sacral tenderness and negative plain radiographs, a CT scan should be strongly considered. Sacral fractures can be difficult to discern reliably on plain films.

Other imaging is obtained based on the physical examination. For patients sustaining minor trauma, no imaging may be needed. Children younger than 2 years with injuries consistent with child abuse should undergo a skeletal survey. In general, this survey should be completed on a nonemergent basis after admission to the hospital. In most cases, it can be scheduled in the inpatient radiology department with the pediatric radiologist or the most experienced radiologist available to interpret the films. Additional imaging for specific injuries is discussed later in the chapter.

SPECIFIC DISORDERS AND INJURIES

Head Injury

Perspective

Each year, more than 500,000 children (ages 0 to 14 years) visit emergency departments in the United States after head injury.[17] Falls account for 50.2% of pediatric head injuries. On an age-related basis, infants and toddlers are more prone to falls from their own height, school-age children are involved in sports injuries and MVCs, and children of all ages are subject to the sequelae of abuse. Although MVCs account for only 6.8% of pediatric head injuries, they represent more than 30% of fatal head injuries.[17]

Principles of Disease

Important anatomic variations lead to differences in pediatric and adult head trauma. The cranial vault of a child is larger and heavier in proportion to the total body mass. This predisposes children, specifically toddlers and infants, to high degrees of torque that are generated by any forces along the cervical spine axis. Sutures within the pediatric skull are both protective and detrimental to the outcome of head injury. Although the cranium may be more pliable relative to traumatic insult, forces are generated internally that predispose the pediatric patient to parenchymal injury in the absence of skull fractures. The pediatric brain is less myelinated, with a higher water content, predisposing it to shearing forces and further injury.

Clinical Features

The clinician obtains as many details regarding the traumatic event as possible. The height of the fall or injury is particularly important with regard to the development of associated injury. Most children fall from their own height. It is important to consider the quality of the surface at the point of impact, specifically the presence or absence of carpeting at the location where the

www.ketabpezeshki.com 66485457-66963820

injury occurred. Impact with an object increases the localized force, even after a short fall, and may lead to increased risk for fracture and intraparenchymal injury. Children involved in MVCs are best evaluated by the degree of restraint that was present during the time of the accident. Unrestrained and improperly restrained children involved in high-speed crashes are prone to serious injury.

It is also important to establish whether there was alteration of consciousness at the time of the injury event. With playground trauma, the history may be vague, and the interpretation of any change in consciousness of the child may be regarded as an actual loss of consciousness. The behavior of the child after the event should be assessed with questions related to the presence or absence of irritability, lethargy, personality change, abnormal gait, or other alterations in behavior. Any worsening of these symptoms after the injury should also be reported.

The prognostic significance of vomiting after pediatric head trauma is unclear. There is no adequate study defining an acceptable time frame in which vomiting after head injury is benign in nature. Vomiting appears to be more strongly correlated to personal or familial tendency to vomit than to intracranial injury; however, recurrent vomiting is commonly seen in patients with significant head injury and is often considered in the decision to obtain a CT study.[18]

The development of seizures after head trauma has been well studied.[19] A brief seizure that occurs immediately after an insult (with rapid return to normal level of consciousness) is commonly called an *impact seizure.* This type of seizure is not usually associated with intracranial parenchymal injury. A CT scan is not necessary if the only concern is the impact seizure; the decision to scan should take into account the mechanism of injury and current neurologic status of the child. An isolated impact seizure does not require anticonvulsant therapy. Seizures that occur later (more than 20 minutes after the insult) portend the greater possibility of traumatic brain injury and the development of seizures at a later date. A CT scan is indicated for these later post-traumatic seizures. These patients may benefit from treatment with anticonvulsants, benzodiazepines for sedation if intubated, or both as the seizure threshold is generally lower in children. Having one later seizure (nonimpact) raises the risk of subsequent additional seizure, and seizure activity raises ICP while often decreasing oxygenation and ventilation. Children who experience later seizures often require neurosurgical evaluation.

The physical examination of a head-injured child includes strict attention to the ABCs (airway, breathing, and circulation) of emergency care. The maintenance of oxygenation and perfusion is paramount in eliminating further insult. Because the pediatric brain is sensitive to decreases in glucose, oxygen, and perfusion, their maintenance optimizes the chances of good recovery. Strict attention is paid to the maintenance of euvolemia because cerebral perfusion pressure (CPP) is adequate only in the face of a normal mean arterial pressure (MAP). Conceptually, CPP is equal to MAP minus ICP:

$$\text{CPP} = \text{MAP} - \text{ICP}$$

As MAP is reduced, so is CPP. Localized CPP at the site of injury and in the areas surrounding it may vary greatly from the approximations of this formula. Pediatric patients with any form of head injury should also be evaluated for and protected from cervical spine injury.

Several methods are available for evaluating the mental status of head-injured patients, including the AVPU system and the GCS. A commonly used modification of the GCS for children is shown in Table 38-4. Although the pediatric GCS is widely used, none of the pediatric modifications of the GCS has the inter-rater reliability or predictive validity of the adult GCS. Even children with low initial GCS scores can have favorable outcomes and

Box 38-8 Common Symptoms and Signs of Increased Intracranial Pressure in Infants

- Full fontanel
- Split sutures
- Altered state of consciousness
- Paradoxical irritability
- Persistent emesis
- "Setting sun" sign (bilateral downward gaze of the eyes with apparent inability to elevate the eyes superiorly in a normal manner leading to an area of sclera being seen between the iris and the upper palpebra when the child attempts to look upward). This finding can be a normal finding when intermittent in infants younger than 7 months, especially with the withdrawal of a light stimulus.

Box 38-9 Common Symptoms and Signs of Increased Intracranial Pressure in Children

- Headache
- Stiff neck
- Photophobia
- Altered state of consciousness
- Persistent emesis
- Cranial nerve involvement
- Papilledema
- Hypertension, bradycardia, and hypoventilation
- Decorticate or decerebrate posturing

neurologic status. The important message is that no matter what the patient's neurologic presentation, all efforts should be initiated to ensure survival and maintain stable neurologic status in the emergency department.

Examining a brain-injured child involves mental status testing, cranial nerve testing, motor testing, sensory testing, and memory testing. The evaluation of cranial nerve function is essentially no different from that in an adult. The most important aspect of motor and cranial nerve evaluation involves ruling out the presence of increased ICP. Common symptoms and signs of increased ICP in infants and children should be sought (Boxes 38-8 and 38-9).

Specific Injuries

Concussion. Strictly speaking, a *concussion* is defined as a brain insult with transient alteration of consciousness. Patients who sustain concussive insults may have anorexia, amnesia, vomiting, unsteadiness, or pallor after the insult. Simple concussions are those in which symptoms resolve within 10 days of the injury, and complex concussions have symptoms lasting longer than 10 days. All children with concussive symptoms should rest until the symptoms are resolved then return slowly to their baseline activities. Children with complex concussions should have further medical examination by their primary care provider or formal neuropsychological testing before returning to baseline activities or sport.

Scalp Injuries. Minor injury to the scalp of infants and children involves the development of three common injury complexes.[20-23] For these injury complexes to be better understood, the layers of the SCALP (skin, connective tissue, aponeurosis, loose areolar tissue, and periosteum) should be considered (Fig. 38-1). *Caput succedaneum* refers to injury with a hematoma in the connective tissue layer. This is freely mobile and crosses suture lines. A *subgaleal hematoma* refers to a hematoma that is subgaleal within the loose areolar tissue above the periosteum. Lastly, *cephalohematoma* refers to a collection of blood under the periosteum. Because the periosteum adheres tightly to the various suture lines, the

www.ketabpezeshki.com 66485457-66963820

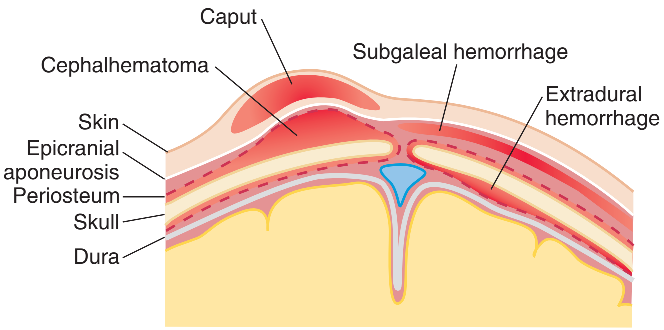


Figure 38-1. Sites of extracranial hemorrhages in the infant. (From Volpe JJ: Neurology of the Newborn, 4th ed. Philadelphia, WB Saunders, 2001.)

cephalohematoma does not cross them. Bleeding from scalp wounds is often profuse and can lead to hemodynamic embarrassment in infants and small children if not quickly controlled. Although children may develop shock from a scalp injury, it is prudent to search for other causes of shock while this bleeding is being controlled.

Skull Fractures. In children, skull fractures occur in many different configurations. Simple linear fractures, the most common type of skull fracture, rarely require therapy and often are associated with good outcomes. Factors associated with poor outcomes include the presence of a fracture overlying a vascular channel, a depressed fracture, a diastatic fracture, or a fracture that extends over the area of the middle meningeal artery. Diastatic fractures, or defects extending through suture lines, are different from simple linear fractures in that leptomeningeal cysts ("growing fractures") may develop at these sites. Fractures of the basilar portions of the occipital, temporal, sphenoid, or ethmoid bones commonly occur in children. The presence of cerebrospinal fluid rhinorrhea and otorrhea has been associated with these injuries. Signs of basilar skull fractures in children are similar to signs in adults and include the presence of periorbital subcutaneous hematoma (raccoon eyes), and posterior auricular ecchymosis (Battle's sign).

Cerebral Contusions. Cerebral contusions are often the result of coup and contrecoup forces at work. Cerebral contusions may not be associated with any loss of consciousness at the time of insult. Patients often have associated symptoms, such as altered level of consciousness, severe headache, vomiting, or focal deficits on neurologic assessment. Contusions are clearly demonstrable on CT.

Epidural Hematoma. Traditional teaching regarding the development of epidural hematomas involves the typical triad of head injury followed by a lucid interval, followed by rapid deterioration as intracranial hemorrhage worsens. In contrast to epidural hematomas in adults, pediatric epidural hematomas may be the result of venous bleeding, which predisposes them to a delay in the development of symptoms. After head trauma, guardians are informed of the delayed signs and symptoms that should prompt immediate reassessment. In any event, epidural hematomas are associated with a high incidence of overlying skull fractures (60-95% of cases). Patients with small fracture-related epidural hematomas localized only to the site of the inner table fracture should be monitored closely in the hospital but often do not require surgical intervention.

Subdural Hematoma. Special attention should be directed toward infants and toddlers to rule out the presence of subdural hematomas. This clinical scenario is most often secondary to rupture of bridging veins and is only occasionally associated with the presence of overlying fractures (<30%). Subdural hematomas most commonly occur in patients younger than 2 years of age. Chronic subdural hematomas are most often encountered in patients who have been subjected to what has been termed the "shaken baby syndrome." This clinical complex involves forcible shaking of the child with accelerating and decelerating forces affecting the cranial vault.[24] This syndrome is most often a result of nonaccidental trauma, and 22% of abused children have central nervous system injuries. These patients have nonspecific findings, such as vomiting, failure to thrive, change in level of consciousness, or seizures. Retinal hemorrhages are present in the majority of cases, and all head injury patients should undergo careful funduscopic examinations to rule out the presence of these nearly pathognomonic findings. Definitive examinations should be performed by an ophthalmologist after pupil dilation to characterize the specific type of retinal hemorrhage. Those that are diffuse, occur in multiple retinal layers, or extend to the periphery are more likely secondary to abuse.[25] Retinal hemorrhages are not observed in children with mild to moderate trauma from other causes and are not associated with a prior history of CPR; the presence of retinal hemorrhages suggests nonaccidental trauma. Similarly, subdural hematomas at multiple sites, over areas other than the convexities, in the posterior fossa, or in the posterior interhemispheric fissure should strongly suggest the possibility of nonaccidental trauma.[26,27] Left to their own development, the worst cases may manifest with signs of increased ICP. Coagulation studies, platelet count, and platelet function assays should be performed in these cases. When indicated, metabolic tests for glutaric aciduria should also be considered.

Diagnostic Strategies and Management

As a basic rule, serial examinations are the most reliable indicators of clinical deterioration.[28] The presence of focality is a reliable indicator of a localized insult, whereas the absence of focality may be misleading. The signs of increased ICP usually develop late in the course of the process in infants. As in an adult, papilledema may require days to develop. The classic Cushing's response (bradycardia and hypertension) does not always occur in children, but when it occurs, it is often an ominous sign. If ICP elevation is suspected, emergency intervention and neurosurgical consultation are initiated immediately (Table 38-6).

The contents of the skull are composed of essentially three compartments: brain, cerebrospinal fluid, and blood. The volume of the skull is fixed. Although not a perfect model, the Monroe-Kellie doctrine suggests the effects that changes in each compartment may have on the others. For example, in the presence of an intracerebral hemorrhage of significant volume, either cerebral spinal fluid or brain must leave the cranial vault. Similarly, if the brain swells, cerebral spinal fluid, blood, or both must leave the cranial vault. When this balance is disrupted and the autoregulatory system's capacity to adapt is exceeded, the ICP rapidly increases. ICP can quickly reach a level that is not conducive to localized brain survival or continued blood flow to the brain. If the condition is left untreated, herniation may occur. An ICP more than 20 to 25 mm Hg should be treated, but the absolute value less than this that should trigger treatment is unclear. From the standpoint of global cerebral perfusion, CPP is equated with MAP minus ICP. However, this model does not allow the accurate prediction of CPP at the specific site of injury or within the ischemic penumbra. Measurement of oxygen extraction (through use of modifications of the Fick principle) and outcome studies have played a role in the following recommendations. In general, it is best to keep the CPP above 50 to 65 mm Hg in children and above 70 mm Hg in adults. There appears to be an age continuum with regard to necessary CPP. Hackbarth and co-workers demonstrated that the single greatest prognostic sign of outcome from traumatic brain injury in children is the ability to maintain a CPP greater than 50 mm Hg.[28] Many have adopted this as the minimum acceptable CPP.

www.ketabpezeshki.com 66485457-66963820

Table 38-6 Emergent Management of Increased Intracranial Pressure

THERAPY	DOSE	MECHANISM OF ACTION
Head elevation (30 degrees)		Lowers intracranial venous pressure.
Head in midline		Prevents jugular vein compression.
Hyperventilation	Maintenance Pa_{CO_2} 38-42 mm Hg If acute increase in ICP then reduce Pa_{CO_2} to 30-35 mm Hg	Promptly but temporarily decreases cerebral blood volume and thus intracranial pressure. Recommended only for short-term treatment of acute ICP elevation.
Hyperosmolar agents Mannitol	0.25-0.5 g/kg IV	Both agents effect rapid osmotic diuresis. Diuresis may decrease BP and CPP. Mannitol should be given through filter. HTS may require a central line. Effect from osmotic and rheologic effects. Avoid dehydration.
Hypertonic saline (HTS)	0.1-1 mL/kg of 3% Titrate to effect	
Pentobarbital	5-10 mg/kg over 30 minutes, then 5 mg/kg/hr for 3 hours, then 1 mg/kg/hr Rarely indicated or started in emergency department	Thought to lower cerebral metabolism; also may have some effect on free radical formation. Other barbiturates (phenobarbital) have also been used. May decrease BP and CPP.
Decompressive craniotomy		Allows more space for swelling and decreases ICP.
Mild hypothermia (35° C)		Thought to decrease cerebral blood flow and metabolic rate. Can cause cardiac dysrhythmias. Is currently under investigation.
Maintain euvolemia	Clinically or invasive monitoring	Maintenance of mean arterial pressure.
Pressors if needed to maintain CBF	Depends on agent used	Maintain CBF and CPP by increasing MAP.
Neuromuscular blockade	Depends on agent used	Helps maintain lower ICP.
Sedation	Depends on agent used	Do not assume patient is completely incapable of response to noxious stimuli or situation.
Prevent fever	Acetaminophen 15 mg/kg OG	Fever raises ICP and metabolic demand.
Treat seizure aggressively	Depends on agent used	Prophylactic treatment controversial. Treatment of seizure is not controversial and is aggressive to prevent increased ICP, hypoxia, hyperpyrexia, and hypercarbia.

BP, blood pressure; *CBF,* cerebral blood flow; *CPP,* cerebral perfusion pressure; *ICP,* intracranial pressure; *IV,* intravenously; *MAP,* mean arterial pressure; *OG,* orogastrically; Pa_{CO_2}, arterial carbon dioxide partial pressure.

Most clinicians favor early and controlled intubation in pediatric patients with GCS scores that are deteriorating or are less than 9. However, in the out-of-hospital phase of care, or if the physician is not knowledgeable and experienced in pediatric rapid sequence induction, BMV ventilation should be strongly considered during short transports and until additional, more experienced support personnel are available.[29,30] An OG tube should be considered if BMV ventilation is used, to decrease the chance of emesis and to prevent respiratory embarrassment from gastric distention with air. Isolated head injury is uncommon; a careful search for other injuries should be made via meticulous and repetitive examinations as well as indicated laboratory and imaging tests.

The use of anticonvulsants after moderate to severe head injury in children is controversial. Early prophylaxis does not decrease the incidence of late seizures and is not recommended for this purpose.[31] Clearly, the effects on temperature, intracranial oxygenation, and cerebral perfusion during an early seizure after trauma are discordant with the management principles of acute brain injury. In addition, early seizures often disrupt the evaluation and management of the patient's head injury and other trauma. However, the evidence for phenytoin effectiveness in preventing early seizures after trauma is weak. It has now been demonstrated that in moderate to severe head injury the incidence of early seizure was much lower than expected. Phenytoin did not substantially lower this risk in a study by Young.[31] Others have suggested that topiramate or levetiracetam may be more effective with decreased risks of side effects, but research in this area is ongoing.[32,33] It may be prudent to treat seizures aggressively if they occur and to consider use of sedative medications with anticonvulsant properties, such as benzodiazepines, reserving the use of prophylactic anticonvulsants for the highest-risk patients in consultation with the neurosurgical service.

Herniation syndromes in children are similar to those in adults. Uncal herniation is suggested early on by the presence of a unilaterally dilated pupil (compression of ipsilateral third nerve parasympathetic fibers), contralateral hemiplegia (caused by ipsilateral cerebral peduncle compression against the tentorium), and spontaneous hyperventilation. With progression, the ipsilateral eye may be noted to be looking downward and outward secondary to the loss of third nerve motor function but continued fourth and sixth cranial nerve function. Often, bilateral third nerve compression occurs very early, leading to bilateral "blown" pupils. In Kernohan's phenomenon, the temporal lobe compresses the contralateral cerebral peduncle against the tentorium, leading to ipsilateral paresis, making localization of the lesion challenging without neuroimaging. Small pupils, sluggish pupils, decorticate posturing, and Cheyne-Stokes respirations characterize early central diencephalic herniation. If this progresses and extends to

www.ketabpezeshki.com 66485457-66963820

the pons or medulla, the patient will have fixed and dilated pupils, flaccid muscle tone, and slow or apneustic breathing or frank apnea and cardiorespiratory arrest. Management of suspected acute herniation begins with immediate controlled hyperventilation.[33] Clinical endpoints of hyperventilation are improved patient status or constriction of dilated pupils. End-tidal CO_2 capnography is used with arterial or venous blood gas correlation to assess adequacy of hyperventilation with a target partial pressure of carbon dioxide (Pco_2) of 30 to 35 mm Hg. Excessive hyperventilation can result in excessive cerebral vasoconstriction and secondary brain injury; ventilation should be started at an age-appropriate rate, and then the rate should be increased until pupillary function returns. Subsequent management of herniation includes hyperosmolar agents, followed by other specific interventions in the intensive care unit (ICU).[34,35]

Radiology

Skull Radiographs. Most clinicians agree that firm indications for skull radiographs alone include the skeletal survey involved with the evaluation of child abuse, establishment of a functioning ventricular peritoneal shunt, some penetrating wounds of the scalp, or the suspicion of foreign bodies underlying scalp lacerations. In children requiring neuroimaging because of concern for intracranial injury, a noncontrast CT scan is the recommended test because plain skull radiography lacks sufficient sensitivity to be used as a screening tool.

Computed Tomography of the Head. There has been a considerable amount of research on the indications and relative value of CT scanning in pediatric head-injured patients. Multiple decision rules have been proposed and continue to be evaluated; however, the need for further research remains. Two variables have been highly associated with the presence of intracranial hemorrhage: the presenting neurologic status and the presence of multiple systemic injuries. It has been suggested that children with isolated head injury with any loss of consciousness can be discharged without a CT scan after careful examination alone, if they are older than 2 years and are neurologically normal. Other authorities contradict those suggestions, establishing a clear association with parenchymal injury and loss of consciousness.[36]

Other than the controversial issue of loss of consciousness, recommendations for CT scanning include the presence of neurologic deficits, GCS scores of less than 15, and injury patterns that are the result of major forcible insults. Studies have shown various combinations of characteristics that make significant intracranial injury very unlikely but have provided less guidance in selection of which patients actually need a head CT scan (high negative predictive value but low positive predictive value).[37] Dunning and coauthors' meta-analysis showed a statistically significant correlation of intracranial hemorrhage with focality (relative risk [RR] = 9.4), skull fracture (RR = 6.1), altered level of consciousness (RR = 2.23), and GCS scores less than 15 (RR = 5.51).[38] Children younger than 1 year are a special challenge to the clinician because their neurologic milestones are more difficult to evaluate. Within this age group, any loss of consciousness, protracted vomiting, irritability, poor feeding, or suspicion of abuse should trigger strong consideration for CT scanning. The value of brief loss of consciousness and the determination of the need for CT in children older than 1 year are less clear, but loss of consciousness lasting longer than a minute is considered an indication for neuroimaging by many practitioners. The presence of a significant cephalohematoma has also been highly correlated with underlying parenchymal brain injury and should also be an indication for neuroimaging.

All children who sustain head injury, with or without diagnostic imaging, should be observed closely for any signs of deterioration. The parents of patients discharged to home should be given specific return precautions for any focal deficit, lethargy, increase in vomiting, or alteration of consciousness.

Spinal Injury

Perspective

In the United States, more than 1400 children sustain spinal injury annually.[39] Although cervical spinal injury is rare, representing only 1 to 2% of pediatric traumatic injuries, higher cord level injuries are more common in children than adults and can lead to devastating outcomes. Cervical injury patterns vary with the age of the patient. Fractures below the C3 level account for only 30% of spinal lesions in children younger than 8 years , which differs dramatically from the patterns seen in adults and older children. Likewise, SCI without obvious radiographic abnormality (SCIWORA) has been found in 25 to 50% of spinal cord injuries in this same age group.[40] SCIWORA may be a misnomer in the era of magnetic resonance imaging (MRI). Intraneural or extraneural findings are usually seen immediately on MRI but may be delayed, necessitating immobilization and a follow-up MRI to prevent late or recurrent injury. Length of immobilization is controversial, but it may be up to 12 weeks. Whenever a spinal injury is noted or suspected, careful attention is paid to the entire spine as multilevel injuries are common.[41]

Principles of Disease

Anatomic features of the cervical spine approach adult patterns between the ages of 8 and 10 years (Box 38-10). However, injury patterns identical to those of adults often do not fully manifest until 15 years of age. The pediatric spine has greater elasticity of

Box 38-10 Anatomic Differences in the Pediatric Cervical Spine

- Cervical spine fulcrum changes from C2-C3 in toddlers to C5-C6 by age 8 to 12 years.
- Relatively larger head size, resulting in greater flexion and extension injuries.
- Relatively large occiput in children younger than 2 years leads to flexion of cervical spine if they are laid flat on standard backboard without support under their scapula and pelvis.
- Smaller neck muscle mass with ligamentous injuries more common than fractures.
- Anterior wedge appearance of cervical vertebral bodies is common.
- Increased flexibility of interspinous ligaments.
- Flatter facet joints with a more horizontal orientation.
- Incomplete ossification, making interpretation of bony alignment difficult (synchondrosis).
- Uncinate processes do not calcify until approximately 7 years of age.
- Basilar odontoid synchondrosis fuses at 3 to 7 years of age.
- Apical odontoid epiphyses radiographically apparent at 7 years of age but may not fuse until approximately 12 years of age.
- Posterior arch of C1 fuses at 4 years of age.
- Anterior C1 arch may not be visible until 1 year of age and fuses at 7 to 10 years of age.
- Neural arches fuse to body by approximately 7 years of age.
- Posterior arches fuse by 3 to 5 years of age.
- Epiphyses of spinous process tips may mimic fractures.
- Preodontoid space 4 to 5 mm in those <8 years of age and <3 mm in those 8 years or older.
- Pseudosubluxation of C2 on C3 seen in 40% of children 8 to 12 years of age.
- Prevertebral space size varies with phase of respiration.

www.ketabpezeshki.com 66485457-66963820

the supporting ligamentous structures than the adult spine. The joint capsules of the child have greater elastic properties, and the cartilaginous structures are less calcified than in adults. In the spine, there is a relatively horizontal orientation of the facet joints and uncinate processes, and the anterior surfaces of the vertebral bodies have a more wedge-shaped appearance. Compared with the adult, the child has relatively underdeveloped neck musculature and a head that is disproportionately large and heavy compared with the body. Both of these differences lead to an "anatomic fulcrum of the spine" in children that is at the level of the C2 and C3 vertebrae versus the lower cervical vertebrae as found in adults. These combined anatomic features lead to higher cervical cord injuries and an increased incidence of SCIWORA in children.[42]

Clinical Features

Any patient with severe multiple injuries should be considered to have an SCI until proved otherwise. Likewise, significant head, neck, or back trauma, trauma associated with high-speed MVCs, and falls from any height (especially those with associated head injury) should raise suspicions for SCI and be evaluated appropriately. The evaluation of a pediatric patient should begin with a primary survey to assess airway patency, ventilatory status, and perfusion. After initial evaluation and stabilization, the cervical region can be examined. Palpation of the neck for pain and bony deformity should be performed. If the patient has pain or tenderness, closely watching his or her facial expression will generally indicate more than asking, "Do you have pain?" Any continued concern or perceived discomfort should be taken seriously because ligamentous discomfort is sometimes subtle. In academic institutions, it is common for three or four people to repeat each aspect of the examination. It is not uncommon for children who originally state that something hurts to tell new examiners that it does not hurt. Children quickly learn that when they affirm that they have pain, stimulus will continue to be applied, making the pain worse. One examiner finding tenderness should be enough to consider further evaluation.

Some factors, such as tenderness or pain with palpation, may be underappreciated in a child who is not yet old enough to talk. Similarly, patients with head injury, decreased level of consciousness, or distracting injury and those who are intoxicated may not reliably localize pain in the cervical region, and spinal precautions should be maintained to avoid potential additional injury.

The neurologic examination in a pediatric patient can be difficult, but several factors should be evaluated in a patient with suspected SCI. Pain in the cervical region should raise suspicion of cervical spine injury. Paralysis, perceived paresthesias, ptosis, and priapism are neurologic signs highly correlated with SCIs. Complaints of paralysis or paresthesias, even if completely resolved at the time of examination, should be considered an indication of SCI until proven otherwise. Finally, upper extremity position and function can help elucidate the presence and level of an SCI.

Several characteristic SCI syndromes can be diagnosed on initial emergency department evaluation. Spinal cord injuries are generally described as either complete or incomplete depending on the presence or absence of sensory or motor function. Incomplete SCI has a better prognosis for recovery of some motor function after spinal shock resolves. Incomplete lesions have some preservation, even if slight, of sensory or motor function below the area of SCI and at the area of sacral nerve distribution. The determination of complete or incomplete lesions is not a one-time assessment and cannot be reliably made until after spinal shock has resolved. The performance of a rectal examination (or anal wink testing) or bulbocavernosus reflex testing in males can assess for sensation and motor ability in the sacral distribution. Central cord syndrome (seen mostly in extension injuries to the cervical spine) typically consists of arm findings (e.g., decreased tone) greater than leg findings and distal symptoms greater than proximal symptoms (e.g., burning pain in the fingers and hands). Anterior cord syndrome (associated with flexion injuries to the cervical spine) is characterized by complete motor paralysis with loss of pain and temperature sensation; however, position and vibration sensation are preserved in this disorder. Finally, Brown-Séquard syndrome represents hemisection of the spinal cord with ipsilateral loss of motor function and proprioception at the level of the lesion and contralateral loss of pain and temperature sensation beginning one or two levels below the lesion.

Radiology

Some experts believe that children with neck pain, involvement in an MVC, or any suspicion of cervical injury should receive radiographic evaluation because these factors may be very sensitive in identifying cervical spine injuries in this patient population. Other experts support the use of the National Emergency X-Radiography Utilization Study (NEXUS) criteria to determine who needs cervical radiographs. These criteria were derived from a study of 3065 children younger than 18 years; however, only 4 of 30 cervical spine fractures were in children younger than 9 years, and none of the 88 children younger than 2 years had cervical fractures.[43,44] No pediatric cases of SCIWORA were found, and the data showed that 45.9% of cervical spine injuries in the NEXUS study cohort were between the levels of C5 and C7. This may reflect the fact that 2160 of the pediatric patients were 8 to 17 years old. The sensitivity for detection of cervical fractures was reported as 100% (95% confidence interval 87.8-100%); however, less than 1% of children in the study had an injury, making the 100% negative predictive value less meaningful and the sensitivity (at least in young infants) difficult to rely on.[43] The majority of injured patients were older than age 9 years and had characteristics more similar to adults than infants.[44] Because of the limitations of the NEXUS criteria as they pertain to children, a low threshold for imaging is maintained in children with mechanisms worrisome for cervical injury. A report of discomfort, any distracting injury, or even transient neurologic symptoms should be considered an indication for radiologic evaluation.

Cervical spine CT should be considered as a first-line imaging modality in children receiving a head CT scan for a head injury, and in children with a high clinical pretest likelihood for cervical fracture. Although the negative predictive value of plain radiographs in low-risk populations seems high, the sensitivity of plain films to detect fractures is far less impressive. When obtained, plain radiographic evaluation should routinely consist of three views: a cross-table lateral, an anteroposterior, and an open-mouth odontoid view. The sensitivity of the three-view cervical spine series is highly variable. Interpretation of plain cervical spine radiographs in children may be especially challenging because of the anatomic changes that occur with growth (see Box 38-10). In addition, pseudosubluxation of C2 on C3 is common on nonextended cervical spine radiographs in children up to adolescence, occurring in approximately 40% of patients.[42] The emergency physician distinguishes between pseudosubluxation and true subluxation on nonextended cervical spine radiographs through use of the posterior cervical line and the relationship of the spinolaminar line (also called the *line of Swischuk*) to the anterior cortical margin of the spinous process at C2. A line is drawn from the anterior cortical margin of the spinous process of C1 down through the anterior cortical margin of C3. If this line at C2 crosses the anterior cortical margin of the spinous process at C2 or is anterior to it by less than 2 mm, no anterior cervical soft tissue swelling is seen, and no fractures are visualized, the patient likely has pseudosubluxation versus true subluxation at that level (Fig. 38-2). Pseudosubluxation may be seen less commonly at C3-C4 as well. Exceptions to this guideline do occur, and the clinical scenario is taken into account before it is applied.

www.ketabpezeshki.com 66485457-66963820

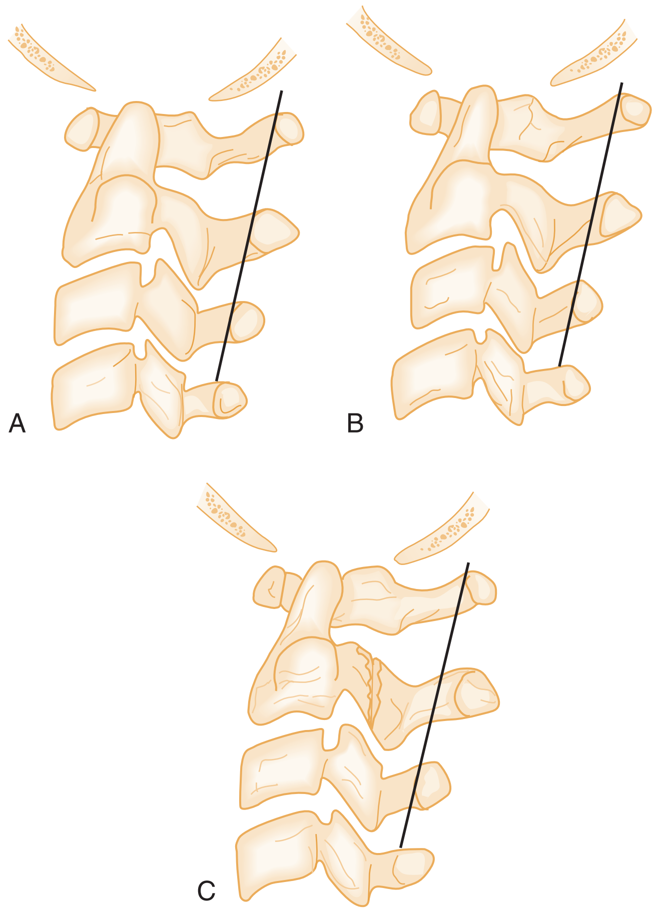


Figure 38-2. Spinolaminar line. Use only to access anterior displacement of C2 on C3. A line is drawn from the cortex of the spinous process of C1 to the cortex of the spinous process of C3, and the relationship of the spinous process of C2 is noted. **A,** Normal line passing through the cortex of C2. **B,** Normal line passing within 1.5 mm of the cortex of C2. **C,** Abnormal line passing more than 2 mm anterior to the cortex of C2, suggesting underlying fracture of posterior elements of C2. (From American Academy of Pediatrics and American College of Emergency Physicians: APLS: The Pediatric Emergency Medicine Resource, 4th ed. Sudbury, Mass, Jones and Bartlett Publishers, 2004.)

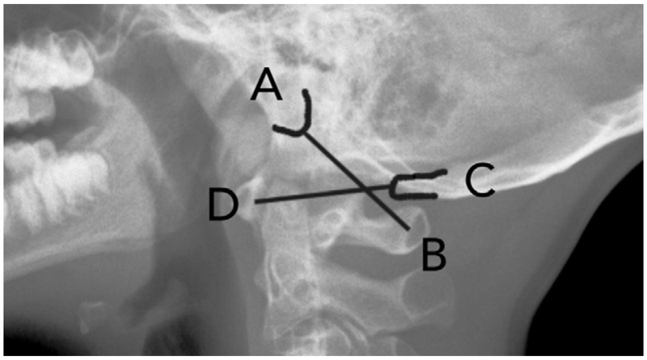


Figure 38-3. Power's ratio is calculated as the ratio of the distance from the basion *(C)* to the anterior cortex of the posterior arch of the atlas *(D)* divided by the distance from the opisthion *(B)* to the posterior cortex of the anterior arch of the atlas *(A)*. A ratio of greater than 1 indicates an atlanto-occipital dislocation. The figure shows a normal Power's ratio.

An important criterion for radiographic clearing of the cervical spine is complete visualization of all seven cervical vertebral bodies on plain film down to and including the C7-T1 interface. The predental space should be less than 6 mm in children younger than 6 years, and the prevertebral soft tissue space should not be greater than normal (variable but generally one third to one half the vertebral body width). The four cervical radiographic lines should be evaluated, and the atlanto-occipital alignment should be assessed for dislocation in this region. If there is any question of injury, thin-section CT and MRI can be used to delineate injury. If the dens cannot be adequately assessed by the open-mouth odontoid view, then a transforaminal view or CT scan should be used. Patients with high clinical suspicion for fracture but negative plain radiographs should be considered candidates for computed tomographic evaluation and radiologic, orthopedic, or neurosurgical consultation.

The pretest likelihood of fracture is considered when decisions are being made regarding the removal of cervical immobilization in children with apparently normal imaging. Patients with continued neck pain despite negative radiographs or CT may require MRI evaluation.[45] Rare cases may necessitate evaluation by neurosurgery under fluoroscopy. The use of flexion-extension views is rarely indicated or helpful.

Classically, young children have been considered at greater risk for upper cervical spine injury. Unfortunately, many occipital cervical junction injuries are immediately fatal. However, survival is possible in some cases.[46] Early detection and immobilization is crucial. Occipital cervical junction injuries should be suspected in any child pedestrian versus vehicle accident, especially if the child has a laceration under the chin from a forward fall. In many fatal cases, distraction and displacement are obvious. However, in nonfatal cases, they can be subtle. A Power's ratio greater than 1 indicates an atlanto-occipital dislocation until proven otherwise (normal, approximately 0.77). Power's ratio is shown in Figure 38-3. It is calculated as the ratio of the distance from the basion to the anterior cortex of the posterior arch of the atlas divided by the distance from the opisthion to the posterior cortex of the anterior arch of the atlas. An additional method to suggest this injury is to draw a vertical line from the posterior border of the odontoid and then measure the distance from this line to the basion. If this distance is greater than 12 mm, then atlanto-occipital separation should be suspected.

A traumatic or even sometimes nontraumatic atlantoaxial rotatory subluxation should be suspected in a child with a fixed rotatory cervical abnormality. Classically, this can be differentiated from a muscular torticollis in nontraumatic cases by the history, the time course, and the presence of palpable spasm of the sternocleidomastoid muscle on the side contralateral to the direction in which the chin is pointing in the case of torticollis. When atlantoaxial rotatory subluxation cannot be confidently ruled out clinically, plain radiographs or CT should be used.

In children with upper cervical spine tenderness, it is prudent to consider a fracture of the synchondrosis between the odontoid and C2. This can be difficult to diagnose on plain radiographs, but it is often recognized as a subtle anterior tilt to the odontoid on C2. A CT scan with sagittal reconstructions will clarify this entity and in many cases should be considered as a first-line imaging modality.[47,48]

Management

There are two phases of SCI. Direct injury (initial phase) results in largely irreversible injury to the spinal cord. Indirect injury results from preventable or reversible injury to the spinal cord secondary to ischemia, hypoxemia, and tissue toxicity.

www.ketabpezeshki.com 66485457-66963820

Resuscitation of a patient with injury to the cervical spine should focus on prevention or minimization of the indirect causes of injury to the cervical spine. Management of possible spinal cord or column injury should begin in the out-of-hospital phase of emergency care. Most injured children arrive at the emergency department with adequate immobilization. Some more recent evaluations of traditional cervical collars and rigid backboards have shown less than adequate neutral positioning of pediatric patients related to their relatively large cranium in proportion to the rest of their body. Nevertheless, in the absence of modified backboards with cutouts for the occiput of the child, the child should be immobilized with a stiff cervical collar, a rigid backboard, and external fixation by means of head blocks, cloth tape, or straps to provide adequate precautions. Appropriate padding should be placed under the shoulder blades of the patient to approximate neutral alignment of the cervical spine and help prevent pressure-related injury. Some emergency medical service agencies' protocols call for small children to be immobilized in their car seats in some circumstances.

Breathing should be assessed to determine the presence of hypoventilation. Patients with SCI may hypoventilate because of diminished diaphragmatic activity or intercostal muscle paralysis. Head or chest injury or pulmonary compromise related to contusion, aspiration, or other causes may also contribute to ventilatory embarrassment. Supplemental oxygen should be given routinely, and ventilatory assistance by BMV ventilation or definitive airway management should be considered in the presence of clinically significant hypoventilation. Finally, circulatory status is assessed early in the trauma patient and needs to be addressed promptly to prevent end-organ perfusion deficits. Hypotension can result from hypovolemia, neurogenic shock, spinal shock, or other, less common causes. Spinal shock usually results from injury above the level of T1. It manifests with lower extremity findings of SCI, with flaccid paralysis of skeletal and smooth muscle leading to the appearance of a relative hypovolemia caused by diminished systemic vascular resistance. Spinal shock generally resolves in hours to approximately 1 day once some spinal level reflexes return below the site of injury. Neurogenic shock typically occurs after injury to the spinal cord above the level of approximately T6. Patients with neurogenic shock lose their sympathetic tone and demonstrate hypotension in the face of unopposed parasympathetic action such as bradycardia. In each case, fluid administration, parasympathetic receptor blocking agents, such as atropine or glycopyrrolate, and vasopressors with chronotropic, vasoactive, and inotropic characteristics (e.g., dopamine), are used. If spinal shock with normal chronotropy and inotropy is found, then fluids and agents with more peripheral vascular vasoconstrictive properties may be preferable, such as phenylephrine or norepinephrine. Spinal shock remains a diagnosis of exclusion, once hemorrhagic shock has been definitively eliminated.

Any patient with definite SCI requires added precautions to ensure appropriate immobilization of the cervical spine. Immediate evaluation by a spinal cord specialist should be sought for all children with SCI. In the absence of such a specialist, the patient should be transported to a center with adequate facilities to care for spinal cord–injured patients.

Even when thoracic or lumbar fractures exist, patients should be expeditiously removed from the backboard to prevent discomfort and morbidity. Sliding boards (smooth movers) can be used to move patients onto scanner tables and back to their trauma beds. Mandatory inter-hospital transfer rules that require patients to remain on backboards during transport should be discouraged. The physician who initially receives the patient should be able to determine the necessity of the backboard for cervical spine immobilization during transport and, when appropriate, remove the patient from the board before transport.

Cardiothoracic Injury

Perspective

Most serious chest injuries in children (>80%) are caused by blunt trauma and result from MVCs, pedestrian accidents, and falls.[49] Isolated chest injury is a relatively infrequent occurrence considering the typical mechanisms of blunt trauma in the pediatric patient. Pediatric trauma patients with thoracic injury have a twentyfold increase in mortality over pediatric trauma patients without thoracic trauma.[49,50] Sequelae of blunt injury include rib fractures, pulmonary contusion, pneumothorax, hemothorax, myocardial injury, pericardial injury, and vascular injury.

Children subjected to penetrating trauma, in contrast to the injuries associated with blunt trauma, often die from the primary insult. Penetrating trauma accounts for 5 to 15% of thoracic insults in children.[49] Nationwide misuse of firearms has resulted in an increasing incidence of penetrating trauma, often with children as victims. The vast majority of these cases are related to the criminal use of handguns; however, improper storage and poor parental supervision lead to devastating consequences in a relatively small, but nevertheless preventable, number of cases each year. Families of children with emotional difficulties or depression should consider removing guns from their homes because of their lethality when used as instruments of suicide. All patients with self-inflicted penetrating trauma should also be assessed for ingested toxins.

Specific clinical patterns should alert the clinician to the potential for concurrent abdominal and thoracic injury. Any patient with penetrating trauma at or below the level of the nipples falls into this category.[51] Apparent isolated thoracic trauma does not exclude abdominal injury.

Principles of Disease

It is important to understand the physiology of pediatric respiration in considering the potential for early decompensation after chest injury. Infants and young children are preferential diaphragm breathers, and any impairment of diaphragmatic mobility compromises ventilation. The presence of gastric distention elevates the diaphragm and severely diminishes the vital capacity of a child. In addition, the particular types of muscle fibers involved in the diaphragm of infants and young children predispose them to the sudden development of apnea when these muscles become fatigued. Unlike adults, whose thoracic wall musculature can pull the ribs up anteriorly to give a larger circumference to the chest wall, children's chest wall circumference does not change drastically during respiration because a child's chest is barrel-like throughout the respiratory cycle. This also decreases the ability of children to increase their vital capacity. For these reasons, children will increase ventilation typically by increasing their respiratory rate. Most important, the presence of adequate oxygenation in a pediatric patient does not always ensure sufficiency of ventilation; confirmatory auscultatory and other physical findings are essential. End-tidal CO_2 capnography can be very useful in this regard in both the intubated and the nonintubated trauma patient.

Infants and children are anatomically protected against blunt thoracic cage trauma because of the compliance of the rib cage. Compressibility of the rib cage dissipates the force of impact, which lessens the likelihood of bony injury. This protective mechanism also may mask fairly complex pediatric thoracic insults. The compliance of the rib cage allows significant injury to occur with little apparent external signs of trauma. Multiple rib fractures are a marker of serious injury in children, with child abuse being the most likely cause, especially when fractures are posterior and in various stages of healing. In addition, the pediatric mediastinum

www.ketabpezeshki.com 66485457-66963820

is mobile, which favors the development of rapid ventilatory and circulatory collapse in the presence of a tension pneumothorax.

Specific Disorders

Pneumothorax. The development of a traumatic pneumothorax is commonly associated with significant pulmonary injury. In contrast to spontaneous pneumothoraces, these insults do not resolve spontaneously and often are associated with the presence of a hemothorax. Signs and symptoms include external evidence of chest trauma, such as abrasion, contusion, or ecchymoses; tachypnea; respiratory distress; hypoxemia; and chest pain. Decreased breath sounds may not be appreciated in children with pneumothoraces because of the wide transmission of breath sounds in the chest and upper abdomen. It is critical to listen to the chest from the axilla in children. This location helps with lateralization to distinguish decreased breath sounds on one side compared with the other and, after intubation, to assess for proper ETT position.

Management of a hemopneumothorax includes the placement of a large-caliber chest tube far enough posteriorly, near the mid-axillary line, to prevent encroaching on more anterior soft tissue that will later become part of the breast. Chest tube size for hemopneumothorax management can be found in Box 38-2 or can be found on a length-based resuscitation tape. A chest tube should be considered for any patient with a pneumothorax who will be undergoing mechanical ventilation. In the most conservative of scenarios, such as small (<20%) simple pneumothoraces without tension in a child who will not be mechanically ventilated, the child may be observed carefully for extended periods with 100% oxygen supplementation for nitrogen washout. Reassessment can be accomplished by repeat chest radiographs at selected intervals, or a pigtail catheter can be placed percutaneously with a modified Seldinger technique.

Open Pneumothorax. An open pneumothorax exists when the chest wall is injured sufficiently to allow bidirectional flow of air through the wound. The patient is unable to expand the lung because of equalization of pressures between the atmosphere and the chest cavity. Ventilation and oxygenation are severely impaired.

Management of an open pneumothorax is dictated by the size of the defect and the amount of respiratory compromise. A simple, small, open pneumothorax in a breathing patient may be treated by covering the chest wall defect with occlusive dressing, such as sterile petroleum gauze, and performing a separate incision for a thoracostomy tube. As in all cases, patients with defects that are too large to seal adequately or patients who are severely impaired with regard to ventilation are candidates for intubation.

In the out-of-hospital setting, a bandage applied over an open pneumothorax wound and taped on three sides as a temporizing measure may allow air to escape during expiration but not to enter during inspiration.

Tension Pneumothorax. Pulmonary air leaks that occur in a one-way valve arrangement favor the development of a tension pneumothorax. Increasing amounts of free air within the pleural cavity cause the mediastinal structures to shift toward the opposite side, compromising cardiac output. The final common pathway involves hypoxia, hypotension, and refractory shock. Most patients with tension pneumothoraces have severe respiratory distress, decreased breath sounds (often bilaterally), and a shift in the point of maximal cardiac impulse. In the worst scenario, there is mediastinal shift, contralateral tracheal deviation, and distention of the neck veins with decreased venous return to the thorax. In pediatric patients, signs of tension pneumothorax are often subtle. A short neck and increased soft tissue may make detection of tracheal deviation difficult. Pediatric patients with tension pneumothorax may have only subtle signs or only tachycardia, shock, and respiratory distress. The emergency physician should consider the diagnosis of tension pneumothorax and, if it is detected or strongly suspected, should treat the patient immediately with decompression. Respiratory embarrassment, hypotension, and circulatory collapse will occur without adequate decompression.

In the out-of-hospital setting, treatment includes needle thoracostomy placed in the second intercostal space in the midclavicular line or possibly in the fourth intercostal space just above the rib and anterior to the mid-axillary line. The needle should be placed above the rib margin to avoid injuring the intercostal vessels. In the emergency department, definitive treatment involves the use of a large-caliber thoracostomy tube that favors drainage of the tension pneumothorax and any accompanying hemothorax.

Hemothorax. Significant bleeding may occur when injury is directed toward the intercostal vessels, internal mammary vessels, or lung parenchyma. Without an upright chest radiograph, it is difficult to quantify the degree of bleeding on plain films. The only sign of hemothorax on a supine radiograph may be a slightly less radiolucent appearance on the affected side of the chest. Development of a massive hemothorax is rare in children and is associated most often with severe impact, such as that seen in high-velocity MVCs, falls from extreme heights, or the use of high-powered firearms. These injuries are evaluated and treated quickly. Clinically, patients have decreased breath sounds and dullness to percussion on the affected side. A pneumothorax may coexist with a hemothorax. The pediatric patient may demonstrate early or late signs of hypovolemic shock.

Any alteration in cardiovascular sufficiency should be treated with rapid fluid replacement with isotonic crystalloid solutions. The clinician should also prepare for transfusion with the institution of red blood cell replacement as necessary. Patients with profound shock may receive either type-specific or O-negative blood; crossmatched blood may be used for more stable patients. The amount of blood that is salvaged from the chest tube should be quantified to help determine the need for red blood cell replacement. Many centers have the capability to salvage blood from hemothoraces and to reinfuse it through use of an autotransfuser. As in all cases of trauma, initial measurement of the hemoglobin is often unreliable and typically underestimates the amount of blood loss caused by inadequate time for equilibration.

The treatment of hemothorax includes a tube thoracostomy. The tube needs to be large enough to occupy most of the intercostal space and should be placed laterally and directed posteriorly. In the supine patient with simple pneumothorax, chest tubes are directed superiorly; in hemopneumothorax, they are directed posteromedially. As in all interventions, repeat chest radiographs should be obtained to confirm tube position and document improvement in lung expansion. The emergency physician is often able to stabilize the patient with red blood cell replacement until surgical intervention is achieved.

Indications for thoracotomy in an operating room include evacuated blood volumes exceeding 15 mL of blood per kilogram immediately after the placement of the chest tube, persistent blood loss (e.g., exceeding 2-4 mL/kg/hr over 3 hours), or continued air leak. Emergency department thoracotomy is reserved for patients with thoracic trauma who deteriorate to cardiopulmonary failure despite maximal resuscitation in the out-of-hospital setting or emergency department. Guidelines for emergency pediatric thoracotomy are often institution specific. There are few published data on pediatric emergency department thoracotomy, and guidelines are often based on adult data. For both children and adults, more liberal use in penetrating injury and limited use in blunt trauma are recommended. In patients with penetrating chest trauma and CPR for less than 15 minutes, a left anterior thoracotomy may be warranted, whereas patients with blunt trauma should undergo rapid assessment by ultrasound for tamponade.

www.ketabpezeshki.com 66485457-66963820

If tamponade is present and CPR has been performed for less than 10 minutes, then a left anterior thoracotomy may be indicated.[52] Suggested contraindications to emergency department resuscitative thoracotomy after out-of-hospital CPR include (1) blunt trauma with CPR for longer than 10 minutes with asystole and no signs of life on presentation without ultrasound evidence of cardiac tamponade and (2) penetrating trauma with CPR for greater than 15 minutes and asystole with no signs of life on arrival without ultrasound evidence of cardiac tamponade.

Pulmonary Contusion. Penetrating and blunt thoracic trauma may result in the development of a pulmonary contusion. The compliance of the rib cage in children renders them susceptible to the development of pulmonary contusion even in the absence of external signs of chest trauma. Injury to capillary membranes allows blood to collect within the interstitial spaces, resulting in hypoxia and respiratory distress. If bleeding is severe enough, oxygenation and ventilation are impaired. Initial chest radiographs may not show the classic findings of pulmonary consolidation. In addition, in the early stages of injury, blood gases may be normal.

Treatment of pulmonary contusions includes a careful evaluation for the presence of additional injuries because significant force is necessary to cause the contusions. Most patients may be treated with supplemental oxygen and close monitoring. Most pulmonary contusions resolve without sequelae. Rare cases are associated with the development of acute respiratory distress syndrome.

Traumatic Diaphragmatic Hernia. Children involved in MVCs who are wearing lap belts are predisposed to the development of diaphragmatic herniation.[50,53] Mechanisms of injury involve sudden increases in intra-abdominal pressure. Patients initially are in stable condition, with the degree of respiratory distress directly proportional to the amount of abdominal contents that protrude into the pulmonary space. The presence of bruising from lap belt–only compression should alert the clinician to the possibility of diaphragmatic hernia and other intra-abdominal injuries (small bowel injury) and the possibility of associated thoracolumbar spinal insults such as Chance fractures. Most commonly, the herniation occurs on the left side because the liver prevents herniation of bowel on the right.[53]

Initial management for these patients involves placement of an NG tube to decompress the stomach. In cases of severe respiratory distress, intubation is indicated. BMV ventilation is avoided whenever possible. Surgery is required for repair of the injury.

Cardiac and Vascular Injuries. Injuries to the heart and large vessels are uncommon in children.[54] In cardiac and vascular injuries, an electrocardiogram may show tachycardia with low voltage (pericardial tamponade), findings consistent with acute myocardial injury (ST segment elevation), or a variety of other nonspecific abnormalities.

The most common traumatic cardiovascular injury sustained by children is myocardial contusion. Patients often have chest wall tenderness or may report generalized chest pain. Tachycardia is the most common finding. Echocardiogram may be diagnostic. Patients with myocardial contusions should be monitored closely for the development of dysrhythmias and impaired myocardial function; however, in most cases of myocardial contusion, there are no long-term sequelae.

The most life-threatening scenario involving the cardiac structures is the development of cardiac tamponade. Penetrating wounds with myocardial penetration and tamponade are potentially survivable if recognized immediately. Extravasated blood fills the pericardial space and impairs cardiac filling during diastole. Clinically, patients demonstrate tachycardia, distant heart sounds, narrow pulse pressure, jugular venous distention, and pulsus paradoxus. In the scenario of profound hypovolemia, venous distention is absent. The final common pathway involves the development of pulseless electrical activity. Ultrasound can characterize cardiac tamponade in seconds and guide therapy.

Bedside ultrasound or echocardiography defines the degree of pericardial effusion present and the significance of any diastolic dysfunction present. A simple single subxyphoid view provides the emergency physician with an excellent view of the pericardial sac and heart. Pericardiocentesis may be attempted, as treatment involves drainage of the fluid from the pericardial sac. However, significant hemodynamic compromise from an acute traumatic pericardial effusion is rarely adequately addressed with a needle pericardiocentesis owing to the amount of cardiac bleeding and subpericardial clot. Performance of a thoracotomy or pericardial window is often necessary to evacuate the pericardium adequately.

Commotio Cordis. Commotio cordis is a disorder described in pediatric patients that results from sudden impact to the anterior chest wall (e.g., when a child is struck in the chest with a thrown or hit baseball), which causes cessation of normal cardiac function. The patient may have an immediate dysrhythmia or ventricular fibrillation that is refractory to resuscitation efforts. Significant morbidity and mortality are associated with this disorder, and although most patients recover completely, some require extended treatment with antiarrhythmic agents, cardiac pacemaker placement, inotropic agents, or intra-aortic balloon pump. In patients with prolonged cardiac instability, cardiogenic shock and death are common despite maximal therapeutic intervention.

Abdominal Injury

Perspective

Serious abdominal injury accounts for approximately 8% of admissions to pediatric trauma centers. Abdominal trauma is the third leading cause of traumatic death in children after head and thoracic injuries. Abdominal trauma is the most common cause of unrecognized fatal injury in children. Pediatric abdominal trauma results from blunt causes in the vast majority of cases.

Blunt trauma related to MVCs causes more than 50% of abdominal injuries in children and is the most lethal. "Lap belt" injury, including small bowel injury and Chance fractures, may occur in restrained children involved in MVCs.[55-57] Another common cause of abdominal injury involves bicycle crashes. Handlebars are a serious cause of injury and subsequent hospitalization for the pediatric population. Often the effects of bicycle injuries may not be seen on initial presentation, with the mean elapsed time to onset of symptoms being nearly 24 hours after injury. All children with epigastric pain after blunt trauma, especially when concentrated force has been applied in this area, should be considered to have duodenal hematoma until proven otherwise. Pancreatic injury, including transection, should be strongly considered as well.

Sports-related injuries are another common cause of pediatric abdominal trauma. Sports-related injuries are associated most commonly with isolated organ injury as a result of a blow to the abdomen. At particular risk are the spleen, kidney, and intestinal tract in children. Finally, abdominal injury is second only to head injury as a cause of death in child abuse cases. All abuse victims should be screened carefully for abdominal trauma.

Principles of Disease

The anatomy of the child lends special protection from some abdominal injury patterns and predisposes the child to other types of injuries in blunt and penetrating abdominal trauma. Children have proportionally larger solid organs, less subcutaneous fat, and less protective abdominal musculature than adults. Therefore they

www.ketabpezeshki.com 66485457-66963820

have relatively more solid-organ injury from blunt and penetrating mechanisms. Children have relatively larger kidneys with fetal lobulations that predispose them to renal injury. Children also have a fairly flexible cartilaginous rib cage that allows for significant excursion of the lower chest wall, permitting compression of the internal organs. The combination of these factors provides the basis for the differences in abdominal injury patterns seen between children and adults.

Clinical Features

Pediatric patients with multiple injuries often have blunt abdominal injury. In children, history is often limited, traditional signs of decompensation seen in adults are often not as evident, and physical examination can be difficult. Subtle, early abdominal findings may be overlooked, leading to significant morbidity and mortality. The history and examination of young children who have sustained trauma is challenging because it may be difficult to know if the child hurts "all over" or has focal findings. The emergency physician may use distraction with toys, lights, bubbles, or keys to get the child's mind off the examiner and onto the distraction; in this way, areas of tenderness may be located.

Signs and symptoms of abdominal injury in children include tachypnea from impaired diaphragmatic excursion, abdominal tenderness, ecchymoses, and signs of shock. Restrained children involved in MVCs with abdominal bruising are much more likely to have an intra-abdominal injury than those without bruising.[57] Abdominal distention is a common nonspecific finding that is often the result of air swallowing subsequent to a painful event. Children with hepatic and splenic injuries may have trouble localizing their pain. Kehr's sign (left shoulder pain with spleen injury) may be the only indication of an intra-abdominal injury. Any abdominal tenderness on examination should prompt further evaluation of the abdomen. Vomiting can be associated with duodenal hematoma or traumatic pancreatic injury but is usually a late sign. Signs of small bowel injury may be delayed and noted clinically only with serial examinations. Pelvic bone stability should be assessed in cases of abdominal trauma, and a genital examination searching for signs of injury should be performed. Rectal examination is insensitive and nonspecific when used as a general screening test for all patients after serious trauma. Patients with suspected injury should receive further evaluation even if rectal examination findings are unremarkable.

Even minor falls can result in significant splenic injury. Repeated examination, prolonged observation, and close attention to vital signs are warranted for children who have sustained a direct blow to the abdomen. Any child with clinically suspicious abdominal examination findings or significant direct trauma should be evaluated further with additional radiologic and laboratory studies and/or admission for serial examination.

Diagnostic Strategies and Management

In patients with suspected abdominal injury or with mechanisms of possible injury, management and resuscitation must be rapid. Because of fear and pain, children can compound the difficulties in the management of serious penetrating or blunt abdominal trauma. Children tend to distend the stomach greatly with ingested air, which can decrease the diaphragmatic excursion. This can compromise respiratory efforts, and early decompression with an NG or OG tube should be considered. In children who have undergone major trauma and have a stable pelvis without risk of urethral trauma, a urinary catheter should be considered for decompression of the bladder, evaluation for the presence of urinary retention, examination for the presence of blood in the urine, and measurement of urine output. The bladder should be decompressed before any invasive evaluation of the abdomen to prevent accidental laceration during the procedure. Urinary catheter size estimates are shown in Box 38-2.

Box 38-11 Indications for Laparotomy

- Hemodynamic instability despite aggressive resuscitation and appropriate emergency department procedures (e.g., a decompression hemothorax or tension pneumothorax)
- Hemodynamic instability and evidence of intraperitoneal free fluid on bedside ultrasound examination (focused assessment with sonography in trauma [FAST])
- Transfusion of ≥50% of total blood volume because of massive intraperitoneal bleeding
- Radiographic evidence of pneumoperitoneum, intraperitoneal bladder rupture, grade V renovascular injury
- Gunshot wound to the abdomen
- Evisceration of intraperitoneal or stomach contents
- Signs of peritonitis

The diagnostic test of choice to assess intra-abdominal injury in stable trauma patients is rapid abdominal CT. The FAST examination can be a useful adjunct that is often readily available bedside. The finding of intraperitoneal hemorrhage alone is not necessarily an indication for surgery in a stable pediatric patient, but when the FAST is positive, it will clarify the need for abdominal CT, close observation, and possible repeat ultrasound examinations. In hemodynamically unstable children, FAST may point to the abdomen as the primary area in need of hemorrhage control and may expedite the decision to operate.

Indications for laparotomy are listed in Box 38-11. Whatever the surgical preference within a health care facility, it is important to establish a protocol for approaching these challenging patients. Patients who remain hypotensive after adequate crystalloid infusion, have active arterial bleeding on CT scan, or have consistent decreases in their hemoglobin level are likely candidates for early invasive intervention. Exploratory laparoscopy or laparotomy is often required, but patients with a known source of bleeding may be appropriate candidates for arterial embolization in an angiography suite.

Spleen Injury. Injuries to the spleen are the most common injuries in pediatric abdominal trauma. Children with injuries from MVCs, sudden deceleration injuries, and contact sports–related injuries may sustain splenic trauma. Typical findings include left upper quadrant abdominal pain radiating to the left shoulder. The abdominal examination may show evidence of peritoneal irritation in the left upper quadrant of the abdomen. Patients may be hemodynamically stable or, after significant splenic rupture or laceration, may be persistently hypotensive or in fulminant cardiovascular collapse. Stable patients may undergo CT for radiologic evaluation. Most often with minor splenic trauma, bleeding is controlled spontaneously without operative intervention; however, all patients with a splenic injury should be evaluated by a surgeon. In patients with a contained splenic subcapsular hematoma, extracapsular bleeding may occur days after capsular rupture. Patients with splenic injury should be admitted to the hospital for close observation and repeated examinations. Because of the desire for splenic salvage to maintain immunocompetency, an injured spleen is often left in place as long as the patient can be resuscitated adequately with crystalloid and blood products.

Liver Injury. The liver is the second most commonly injured solid organ in the pediatric patient with abdominal trauma. However, it is the most common cause of lethal hemorrhage, with a mortality of 10 to 20% in severe liver injury. Mechanisms of injury causing splenic injury also may cause liver trauma. Tenderness on palpation of the right upper quadrant of the abdomen and the complaint of abdominal pain in this region or in the right shoulder are signs of possible liver injury. Patients managed

www.ketabpezeshki.com 66485457-66963820

conservatively often do well; however, patients who are initially treated conservatively but then go on to require delayed laparotomy often have significant morbidity and mortality. Close observation in the hospital, serial abdominal examinations, and serial hemoglobin measurements are recommended.

Renal Injury. The kidney is less susceptible to trauma from forces applied to the anterior abdomen, but it is often injured in the pediatric patient with multiple injuries.[58] Because this organ is retroperitoneal, signs and symptoms of kidney injury are often less obvious and more diffuse than signs and symptoms of other abdominal organ injuries. Often, dull back pain, ecchymosis in the costovertebral region, and hematuria are the only clues to renal injury.[59] Renal ultrasound and CT may be used in a stable patient to assess the degree of renal involvement. Other organs, such as the pancreas and gastrointestinal tract, are less frequently injured in pediatric patients.

Penetrating Injury. Penetrating wounds to the abdomen usually require rapid evaluation by a surgeon and, in some cases, operative intervention. With hemodynamic instability, or peritonitis, urgent laparotomy is indicated. In the hemodynamically stable patient, further workup with a CT scan, local wound exploration, diagnostic laparoscopy, and observation may be warranted.

Diagnostic peritoneal tap (DPT) and diagnostic peritoneal lavage (DPL) have been largely supplanted by other diagnostic modalities in modern practice, such as CT and diagnostic laparoscopy.[60] However, they may be necessary in resource-poor areas and in large-scale disasters. The aspiration of 10 mL of blood or fecal or vegetable matter from the abdomen with DPT would typically indicate intraperitoneal hemorrhage, bowel injury, or both, and the likely need for laparotomy. DPL is performed by placing 15 mL of warm sodium chloride per kilogram in the peritoneal space and then removing the fluid by gravity. In blunt trauma, a positive DPL is defined as a finding of more than 100,000 red blood cells per milliliter, more than 500 white blood cells per milliliter, or gram-negative bacteria or vegetative material (stool) seen on microscopy. DPL does not evaluate for retroperitoneal bleeding. The threshold values must be lowered for penetrating trauma. In general, DPLs are not performed on stable patients because CT scanning can be done quickly and give the clinician far more information, especially about intraparenchymal injury and retroperitoneal injury.

Radiology. Pediatric patients frequently sustain injury to the spleen, liver, kidneys, and gastrointestinal tract. CT of the abdomen can provide high sensitivity and specificity for identification of these injuries while being relatively noninvasive.[61,62] Abdominal CT has a high negative predictive value.[61,62] Oral contrast does not add to the accuracy of CT for trauma; thus one can avoid oral contrast–related delays in evaluation, difficulty with administration, and risk of aspiration.

Another useful procedure in an acutely traumatized pediatric patient is the FAST examination. When used by an experienced clinician, ultrasonography can provide sensitive information about intraperitoneal hemorrhage without invasive measures.

Although radiologic evaluation can provide important diagnostic information in a pediatric patient with possible abdominal trauma, any patient with unstable vital signs from an obvious surgically correctable cause should receive immediate operative intervention and not be subjected to delay while radiographic screening studies are obtained. Children with persistent or recurrent hypotension, continued abdominal pain, or persistent abdominal distention should undergo expedient evaluation by a surgeon.

DISPOSITION

A key decision for the emergency physician is whether to admit a pediatric trauma patient or transfer the patient to a tertiary care facility. The decision for admission in questionable cases should be based on consultation with the surgeon and the patient's primary care physician. Infants and children who are moderately to severely injured have improved outcomes in a pediatric (specific) ICU versus an adult ICU or an adult ICU with a few segregated pediatric beds. The primary role of the emergency physician is to evaluate and stabilize the patient before admission to a pediatric ICU or before transfer to a tertiary care facility. Before transport, it is vital that the child be maximally stabilized. This may include the involvement of general surgeons, definitive surgery, or temporizing surgery (such as packing the abdomen). The emergency physician should communicate directly with the accepting physician at the tertiary care center. In general, the emergency physician should refrain from completing extensive radiologic testing in a facility that is potentially unable to manage the injury being screened for, unless the emergency physician is confident that it will not delay the transfer to more definitive care and has discussed the plan with the receiving physician. All radiographs, documents, and results of laboratory testing should be sent with the patient. Parents should be informed of the exact location to which the child is being taken and given directions to the receiving facility. Under no circumstances should the child's likely outcome be downplayed to the patient's parents before transfer because this leads to false expectations and the assumption of poor care if the promised outcome is not achieved.

Indications for admission are many, but the main criterion is to admit patients requiring ongoing monitoring for deterioration or complications of their injuries. The threshold for admission should be very low in cases in which the health care team does not believe the child will have the social support or oversight necessary to be appropriately observed or to recover in the home environment. The family should be asked if they have transportation, a phone, and access to emergency medical services if needed. In addition, children with suspected physical injury from child abuse are admitted for their protection and for medical treatment.

Cessation of Care

Despite advances in trauma care and system improvement, some injured children will die—some in the emergency department. Cases in which death is certain or has already clearly occurred, such as with decapitation and findings of livor mortis or rigor mortis, do not present treatment dilemmas. For patients with signs of life (respirations, blood pressure, pulse, pupil reactivity, or cardiac and electrical activity), resuscitative efforts should be initiated. Bedside cardiac echo can be helpful in some cases to confirm the lack of cardiac activity in patients without a pulse who continue to have electrical activity. Patients who lose their vital signs en route to or in the resuscitation room should receive maximum resuscitative efforts, potentially including emergency thoracotomy.

A final review after each death should be performed. Signs of maltreatment, congenital abnormality not previously recognized, possible personal identifying marks in patients with an unknown identity, and points for future education and study can be gained from one last mental and visual review, as can the potential for some insight related to the cause of death. Organ donation should be offered under local and state guidelines to all families of deceased children. Often it is viewed as one way that parents can make sense of the death of their child. Knowing that their child's death helped many others to live can help parents in their healing.

Parental presence should be considered in all pediatric resuscitation cases. Assigning someone to be with the parent to explain what is happening is essential. Often the parents' presence can be useful to the resuscitative effort. Information can be obtained immediately when needed from the parents, and they witness the

www.ketabpezeshki.com 66485457-66963820

effort that goes into trauma resuscitation. Very rarely, parental presence can present a true hindrance to medical care, in which case the parent can be asked to leave or can be escorted out of the room. Parents who witness what the team does for their child during resuscitation seem to better understand the abilities and limitations of medicine. In the final analysis, most parents want to be there, and frankly, at the time of death, their presence is more important than the presence of the medical team.

KEY CONCEPTS

- Trauma is the leading cause of death in children in the United States. It accounts for more than half of all pediatric deaths and more than 8 million visits to U.S. emergency departments each year.
- Proper management of a pediatric trauma patient involves most of the components of standard adult trauma protocols. If strict attention is paid to the anatomic and physiologic differences in children, the pediatric patient should achieve better outcomes.
- Continuous monitoring and reassessment of the trauma patient is essential to recognize early signs of deterioration and to discover all injuries.
- The leading cause of traumatic shock in children is hypovolemia; management priorities include appropriate ventilation, oxygenation, and fluid resuscitation to maintain perfusion.
- The diagnostic test of choice for the evaluation of intra-abdominal injury in a stable patient is CT of the abdomen.
- Controlled hyperventilation should be performed on children with signs of impending brain herniation, and P_{CO_2} levels should be maintained at 30 to 35 mm Hg to prevent secondary brain injury from excessive hyperventilation and subsequent cerebral vasoconstriction.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Centers for Disease Control and Prevention: *Web-Based Injury Statistics Query and Reporting System (WISQARS)*. Available at www.cdc.gov/injury/wisqars/index.html. Accessed January 2, 2012.
2. Sharma O, Oswanski M, Stringfellow K, Raj S: Pediatric blunt trauma: A retrospective analysis in a Level I trauma center. *Am Surg* 2006; 72:538-543.
3. Roaten J, et al: Nonaccidental trauma is a major cause of morbidity and mortality among patients at a regional level 1 pediatric trauma center. *J Pediatr Surg* 2006; 41: 2013-2015.
4. Partrick D, Bensard D, Janik J, Karrer F: Is hypotension a reliable indicator of blood loss from traumatic injury in children? *Am J Surg* 2002; 184:555-559.
5. Milkovich SM, Owens J, Stool D, Chen X, Beran M: Accidental childhood strangulation by human hair. *J Pediatr Otorhinolaryngol* 2005; 69:1621.
6. Langhan M, Chen L: Current utilization of continuous end-tidal carbon dioxide monitoring in pediatric emergency departments. *Pediatr Emerg Care* 2008; 24:211-213.
7. Murphy R, Ghosh A: Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. The accuracy of abdominal ultrasound in paediatric trauma. *Emerg Med J* 2001; 18:208-209.
8. Dehmer J, Adamson W: Massive transfusion and blood product use in the pediatric trauma patient. *Semin Pediatr Surg* 2010; 19:286-291.
9. Ball C, et al: Traumatic urethral injuries: Does the digital rectal examination really help us? *Injury* 2009; 40:984-986.
10. Shlamovitz G, et al: Lack of evidence to support routine digital rectal examination in pediatric trauma patients. *Pediatr Emerg Care* 2007; 23:537.
11. Willner E, Jackson H, Nager AL: Delayed diagnosis of injuries in pediatric trauma: The role of radiographic ordering practices. *Am J Emerg Med* 2012; 30:115-123.
12. Capraro A, Mooney D, Waltzman M: The use of routine laboratory studies as screening tools in pediatric abdominal trauma. *Pediatr Emerg Care* 2006; 22:480-484.
13. Zehtabchi S, Sinert R, Goldman M, Kapitanyan R, Ballas J: Diagnostic performance of serial haematocrit measurements in identifying major injury in adult trauma patients. *Injury* 2006; 37:46-52.
14. Sauerland S, et al: The reliability of clinical examination in detecting pelvic fractures in blunt trauma patients: A meta analysis. *Arch Orthop Trauma Surg* 2003; 124:123-128.
15. Junkins E, Furnival R, Bolte R: The clinical presentation of pediatric pelvic fractures. *Pediatr Emerg Care* 2001; 17:15-18.
16. Junkins E, Nelson D, Carroll K: A prospective evaluation of the clinical presentation of pediatric pelvic fractures. *J Trauma* 2001; 51:64-68.
17. Faul M, Xu L, Wald MM, Coronado VG: *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002-2006*. Atlanta, Ga: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
18. Da Dalt L, et al: Characteristics of children with vomiting after minor head trauma: A case control study. *J Pediatr* 2007; 150:274-278.
19. Holmes J, Palchak M, Conklin M, Kuppermann N: Do children require hospitalization after immediate posttraumatic seizures? *Ann Emerg Med* 2004; 43:706-710.
20. Yoshikawa H: Benign setting sun phenomenon in full term infants. *J Child Neurol* 2003; 18:424-425.
21. Sorantin E, Brader P, Thimary F: Neonatal trauma. *Eur J Radiol* 2006; 60:199-207.
22. Amar A, Aryan H, Meltzer H, Levy M: Neonatal subgaleal hematoma causing brain compression: Report of two cases and review of the literature. *Neurosurgery* 2003; 52:1470-1474.
23. Kilani R, Wetmore J: Neonatal subgaleal hematoma: Presentation and outcome—radiological findings and factors associated with mortality. *Am J Perinatol* 2006; 23:41-48.
24. Oehmihen M, Meissner C, Saternus KS: Fall or shaken: Traumatic brain injury in children caused by falls or abuse at home—a review on biomechanics and diagnosis. *Neuropediatrics* 2005; 36:240-245.
25. Togioka B, et al: Retinal hemorrhages and shaken baby syndrome: An evidence-based review. *J Emerg Med* 2009; 37:98-106.
26. Stoodley N: Controversies in non-accidental head injury in infants. *Br J Radiol* 2006; 79:550-559.
27. Gerber P: Nonaccidental head trauma in infants. *Childs Nerv Syst* 2007; 23:499-507.
28. Hackbarth R, et al: Survival and functional outcome in pediatric traumatic brain injury: A retrospective review and analysis of predictive factors. *Crit Care Med* 2002; 30:1630-1635.
29. Gausche M, et al: Effect of out-of-hospital pediatric endotracheal intubation on survival and neurologic outcome. *JAMA* 2000; 283:783-790.
30. Gerritse B, Draaisma J, Schalkwijk A, van Grunsven P, Scheffer G: Should EMS-paramedics perform paediatric tracheal intubation in the field? *Resuscitation* 2008; 79:225-229.
31. Young K, et al: A randomized double blinded placebo controlled trial of phenytoin for the prevention of early posttraumatic seizures in children with moderate to severe blunt head injury. *Ann Emerg Med* 2004; 43:435-436.
32. Giza C, Mink R, Madikians A: Pediatric traumatic brain injury: Not just little adults. *Crit Care* 2007; 13:143-182.
33. Szaflarski J, Sangha K, Lindsell C, Shutter L: Prospective, randomized, single-blinded comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis. *Neurocrit Care* 2010; 12: 165-172.
34. Adelson P, Bratton S, Carney N: Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. *Pediatr Crit Care Med* 2003; 4(3 Suppl):S1.
35. Scaife E: Traumatic brain injury: Preferred methods and targets for resuscitation. *Curr Opin Pediatr* 2010; 22:339-345.
36. Davis R: The use of cranial CT scans in the triage of pediatric patients with mild head injuries. *Pediatrics* 1995; 95:345-349.
37. Güzel A, et al: Indications for brain computed tomography and hospital admission in pediatric patients with minor head injury: How much can we rely upon clinical findings? *Pediatr Neurosurg* 2009; 45:262-270.
38. Dunning J, et al: A meta analysis of variables that predict significant intracranial injury in minor head trauma. *Arch Dis Child* 2004; 89:653-659.
39. Vitale MG, Goss JM, Matsumoto H, Roye DP Jr: Epidemiology of pediatric spinal cord injury in the United States: Years 1997 and 2000. *J Pediatr Orthop* 2006; 26:745-749.
40. Trigylidas T, Yuh S, Vassilyadi M, Matzinger M, Mikrogianakis A: Spinal cord injuries without radiographic abnormality at two pediatric trauma centers in Ontario. *Pediatr Neurosurg* 2010; 46:283-289, 2010.
41. Mortazavi M, et al: Pediatric multilevel spine injuries: An institutional experience. *Childs Nerv Syst* 2011; 27:1095-1100.
42. Gore P, Chang S, Theodore N: Cervical spine injuries in children: Attention to radiographic differences and stability compared to those in the adult patient. *Semin Pediatr Neurol* 2009; 16:42-58.
43. Viccellio P, et al: A prospective multicenter study of cervical spine injury in children. *Pediatrics* 2008; 108:E20.
44. Sun B, Hoffman J, Mower W: Evaluation of a modified prediction instrument to identify significant pediatric intracranial injury after blunt head trauma. *Ann Emerg Med* 2007; 49:325-332.
45. Eubanks J, Gilmore A, Bess S, Cooperman D: Clearing the pediatric cervical spine following injury. *J Am Acad Orthop Surg* 2006; 14: 552-564.
46. Salinsky J, Scuderi G, Crawford A: Occipito-atlanto-axial dissociation in a child with preservation of life: A case report and review of the literature. *Pediatr Neurosurg* 2007; 43:137-141.
47. Hutchings L, Willett K: Cervical spine clearance in pediatric trauma: A review of current literature. *J Trauma* 2009; 67:687-691.
48. Silva C, et al: Do additional views improve the diagnostic performance of cervical spine radiography in pediatric trauma? *AJR Am J Roentgenol* 2010; 194:500-508.
49. Sartorelli K, Vane D: The diagnosis and management of children with blunt injury of the chest. *Semin Pediatr Surg* 2004; 13:98-105.
50. Woosley C, Mayes T: The pediatric patient and thoracic trauma. *Semin Thorac Cardiovasc Surg* 2008; 20:58-63.
51. Balci A, et al: Blunt thoracic trauma in children: Review of 137 cases. *Eur J Cardiothorac Surg* 2004; 26:387-392.
52. Moore E, et al: Defining the limits of resuscitative emergency department thoracotomy: A contemporary Western Trauma Association perspective. *J Trauma* 2011; 70:334-339.
53. Turhan K, et al: Traumatic diaphragmatic rupture: Look to see. *Eur J Cardiothorac Surg* 2008; 33:1082-1085.
54. Tiao G, Griffith P, Szmuszkovicz J, Hossein Mahour G: Cardiac and great vessel injuries in children after blunt trauma: An institutional review. *J Pediatr Surg* 2000; 35:1656-1660.
55. Achildi O, Betz R, Grewal H: Lapbelt injuries and the seatbelt syndrome in pediatric spinal cord injury. *J Spinal Cord Med* 2007; 30(Suppl 1): S21-S24.
56. Santschi M, Echavé V, Laflamme S, McFadden N, Cyr C: Seat-belt injuries in children involved in motor vehicle crashes. *Can J Surg* 2005; 48:373-376.

www.ketabpezeshki.com 66485457-66963820

57. Lutz N, et al: Incidence and clinical significance of abdominal wall bruising in restrained children involved in motor vehicle crashes. *J Pediatr Surg* 2006; 39:972-975.
58. Tsui A, Lazarus J, Sebastian van As AB: Non-operative management of renal trauma in very young children: Experiences from a dedicated South African paediatric trauma unit. *Injury* 2011; Jan 24. [Epub ahead of print]
59. Abou-Jaoude WA, Sugarman JM, Fallat ME, Casale AJ: Indicators of genitourinary tract injury or anomaly in cases of pediatric blunt trauma. *J Pediatr Surg* 1996; 31:86-89.
60. Como J, et al: *Practice Management Guidelines for Nonoperative Management of Penetrating Abdominal Trauma*. Chicago: Eastern Association for the Surgery of Trauma (EAST); 2007.
61. Hom J: The risk of intra-abdominal injuries in pediatric patients with stable blunt abdominal trauma and negative abdominal computer tomography. *Acad Emerg Med* 2010; 17:469-475.
62. Awashti S, et al: Is hospital admission and observation required after a normal abdominal computed tomography scan in children with blunt abdominal trauma. *Acad Emerg Med* 2008; 15:895-899.

www.ketabpezeshki.com 66485457-66963820

Chapter 39
Geriatric Trauma

Jeremiah D. Schuur

PERSPECTIVE

Background

Traumatic injuries are important causes of morbidity and mortality in older adults, and older adults make up a growing proportion of trauma patients in emergency departments (EDs). Trauma systems and protocols that were developed in the United States over the last half-century were largely informed by advances from military medicine and primarily designed to serve younger adult patients. Although the general principles of trauma care for younger adults apply to elders, there are special considerations for the older trauma patient. This chapter highlights the epidemiology, pathophysiology, diagnosis, and management of trauma in older adults and focuses on decisions that may differ from those in younger adults.

Definition of Geriatric Trauma

There is no standard definition of "geriatric trauma"; studies include patients older than 45 to 65 years. Some studies further stratify the elderly population into those aged 65 to 80 or 85 years and the "oldest old," those older than 80 or 85 years. The literature on trauma in older adults has several limitations. Older adults are frequently excluded from clinical trials, a limitation in considering high-risk interventions such as surgery or invasive hemodynamic monitoring. Furthermore, studies conducted via trauma databases include only trauma center patients evaluated by a trauma team; the results may not be generalizable to non–trauma center ED populations.

Demographics and Epidemiology

The U.S. population is aging, and the elderly are living more active lifestyles—which explains the dramatic rise in geriatric trauma. About one in eight Americans were aged 60 or older in 1994, whereas by 2030 one in five will be.[1] In 2008, U.S. adults aged 65 and older made more than 5.8 million ED visits for injuries, accounting for 30% of all visits by older adults and almost 14% of all injury-related ED visits.[2] Older trauma patients have increased morbidity and mortality owing to the severity of injury, comorbid disease, and the independent effects of age. In similar accidents, the elderly sustain more severe injuries than younger adults, a strong predictor of mortality. In 2009, unintentional injury was the ninth leading cause of death among those older than 65 years.[3] Older adults are more likely to have significant underlying medical conditions that limit their physiologic response to injury and increase the risk of death after trauma, especially in less severe injuries.[4,5] Age is independently predictive of morbidity and mortality even when comorbidities and Injury Severity Score (ISS) are controlled for.[6,7]

Age as a Triage Criterion

Age should be considered in determining criteria for transfer to a trauma center and for activation of trauma teams.[8] Traditional triage criteria based on mechanism and vital signs miss many elders with major injuries.[9-12] Fewer older patients are transported to trauma centers despite meeting trauma center criteria,[9,13] and elders are less likely to be admitted to trauma centers than younger adults.[14] In response, the Advanced Trauma Life Support (ATLS) program recommends that emergency medical services (EMS) transfer patients older than 55 years to a trauma center regardless of injury severity.[15] Yet the effect of trauma center care on elders is not clear; although an early study showed that elderly patients with severe injuries have better outcomes when treated at a trauma center,[16] a larger, more recent study of 69 hospitals in 14 states found no survival difference.[17] At trauma centers, age is often a criterion for trauma team activation, and one study showed a trend toward decreased mortality after trauma team activation criteria were changed to include age older than 70 years.[18]

Mechanisms of Injury

Falls are the leading mechanism of injury and the leading cause of injury-related death in patients older than 65 years.[19] In 2008, there were 2.1 million ED visits for falls among those 65 and older—10 times more common than motor vehicle collisions (MVCs).[20] Up to one third of elders sustain a significant fall each year, and serious injuries occur in up to a quarter.[21] Most falls are from standing and occur at the elder's place of residence.[19] Risk factors for falling include (in decreasing relative risk) weakness, balance or gait deficit, visual deficit, mobility limitation, cognitive impairment, impaired functional status, and postural hypotension.[22] Fractures are the most common injuries sustained by elders during falls, occurring in 5 to 10% of falls.[21] Up to 10% of fallers sustain a major injury, with head injury being most frequent.[23] Although the height of the fall is associated with severity, falls from standing carry significant risk for older adults; same-level falls result in serious injury (ISS >15) 30% of the time in older patients, and peri-injury mortality from low falls is up to 10%.[23-25]

MVCs and pedestrians struck by a motor vehicle are the second and third most frequent causes of trauma in older adults.[6,19] Elders are more likely than younger adults to be involved in daytime crashes occurring close to home.[26] A detailed crash history is important, and single-vehicle crashes should raise the suspicion

www.ketabpezeshki.com 66485457-66963820

that a medical problem caused the crash (e.g., syncope). The mortality rate of older MVC victims is up to 21%.[19,27] Elders are more likely to be struck by a motor vehicle than younger pedestrians, because of poor eyesight, limited mobility, and slower reaction time. Pedestrians struck sustain significant injury patterns and have the highest fatality rate among injuries, 30 to 55%.[19]

Self-injury, elder abuse, and thermal injuries are less common but important injury patterns in the elderly population. Older adults have a lower likelihood of attempting self-injury but a higher likelihood of completing suicide attempts than any other age group, with men at higher risk. Thermal injuries such as burns and smoke inhalation occur more frequently and are more severe in older adults owing to decreased mobility and physiologic skin changes.[28] Elder abuse is a complex problem that can involve psychologic, social (e.g., financial), and physical abuse. Studies have identified that around 5% of elders self-report abuse in the previous month, although lower rates of physical abuse are reported to protective services.[29] All older adults with injuries should be asked if they feel safe at home and if there is anyone in their life who is threatening or injuring them.

DISTINGUISHING PRINCIPLES OF DISEASE

Older adults are more vulnerable to trauma owing to age-related changes in anatomy, physiology, and pathophysiology. Aging's main effects on human physiology are decreased functional reserve, seen across organ systems, due to reductions in volume of viable tissue and intrinsic function of the tissues. Older adults are more likely to have comorbidities and to be taking multiple medications that affect their likelihood to get injured and their response to injury. Aging physiology, comorbid disease, and medications lead to different signs and symptoms of trauma in older adults and should inform the assessment of the geriatric trauma patient.

Decreased Physiologic Reserve

A primary effect of aging on human physiology is decreased functional reserve, a progressive process seen in all organ systems. Older adults are less able to compensate for physiologic demands of hypovolemia and stress resulting from hemorrhage associated with trauma. Whereas older adults in a good state of health have sufficient reserves to accomplish activities of daily living, when they are stressed by acute trauma and the subsequent response to injury, the decrease in physiologic reserve can lead to tissue hypoperfusion and organ failure, a common cause of death in older trauma patients.

Comorbidities

Older adults are likely to have significant comorbidities at the time of injury. The percentage of the elderly population experiencing at least one of five chronic diseases (arthritis, cerebrovascular accident, chronic lower respiratory tract disease, coronary heart disease, and diabetes mellitus) varies from 15 to 47%, with only 33% of men and 25% of women having none of these comorbidities.[30]

Effect of Medications

Medication use is common in older adults. A representative survey of community-dwelling U.S. adults (aged 57 through 85 years) showed that 81% used at least one prescription medication, and 29% used five or more prescription medications.[31] Aspirin was the most common medication, used by 28% of older adults. Medications increase the likelihood of older adults getting into traumatic accidents (e.g., sedative hypnotics causing falls). Some, such as beta-blockers, affect the physiologic response to trauma. Medications' effect on vital signs should be considered during the primary survey, and a full medication history should be taken early in the secondary survey.

Modifications to the Trauma Assessment of Older Adults

A systematic trauma assessment, as described in previous chapters, including a primary and secondary survey and concomitant resuscitation should be conducted in older adults. Yet many signs and symptoms of injury in the younger adult, such as hypotension, tachycardia, and pain, will be mild or absent in many older adults. Normal vital signs should not be reassuring, as significantly injured older adults often display delayed hemodynamic signs of injury.

Primary Assessment and Resuscitation

Airway

Establishing and maintaining a patent airway is the primary objective. As elderly patients are likely to have multiple risk factors for a difficult airway, physicians should perform a systematic airway assessment, focusing on the ability to mask ventilate, to perform endotracheal intubation, and to perform a cricothyrotomy. Early intubation is indicated for unstable patients as defined by signs of shock, altered mental status, and significant chest trauma.[15] As direct laryngoscopy is more difficult in older adults because of limited cervical mobility and less mobility at the temporal mandibular joint, videolaryngoscopy is recommended.[32] Cricothyrotomy is more likely to be complex in older adults as they are more likely to have had neck surgery, radiation, or tumor and are more likely to be anticoagulated.

Rapid sequence intubation (RSI) medications should be tailored to the older adult. The main risk from RSI in the older trauma patient is hypotension from medications, so dosages of induction agents should be reduced (e.g., etomidate, regular strength 0.3 mg/kg, or half strength 0.15 mg/kg; midazolam, 0.1 mg/kg in average older adults, or 0.05 mg/kg in frail elders). Older adults are more likely to have risk factors for succinylcholine-related hyperkalemia, such as recent stroke or neuromuscular disease. With a good history, succinylcholine at a regular dose (1.5 mg/kg) is safe, but in the trauma patient without clear history, it is reasonable to use a nondepolarizing neuromuscular blocker such as rocuronium (1 mg/kg).

Breathing

High-flow supplemental oxygen should be applied to all patients, including those with chronic pulmonary disease. The short-term benefits of avoiding hypoxia and increasing oxygen reserves are critical as older adults have reduced pulmonary reserve, which can lead systemic pulmonary injuries to overwhelm the ability to oxygenate and ventilate. Respiratory rate should be closely followed as older adults are more likely to tire and can rapidly decompensate as a result of pulmonary injuries or aggressive fluid resuscitation.

Circulation

Elderly patients are particularly vulnerable to shock, as their blunted response to stress and limited physiologic reserve raises the risk of organ dysfunction. Assessment of circulatory status is complicated as responses to hypovolemia, such as tachycardia and hypotension, are blunted by physiologic changes and medications, such as beta-blockers and calcium channel blockers. Vital signs are

www.ketabpezeshki.com 66485457-66963820

insensitive, as normal blood pressure does not reliably exclude significant hemorrhage or shock. As systolic hypertension is more common among elders, normotension may indicate significant hypovolemia. Vitals signs should be frequently reassessed; in elderly trauma patients, trends are more important than specific cutoffs.

First, life-threatening bleeding is identified and stopped; this includes external bleeding, such as scalp hemorrhage, which can be significant in older adults. The focused assessment with sonography in trauma (FAST) is an important adjunct to the primary survey but has not been specifically studied in elderly patients. A urinary catheter can be placed to monitor urine output, although this is a less sensitive predictor of renal blood flow than in younger patients.

Fluid resuscitation should be initiated with defined boluses (e.g., 500 mL) of warmed isotonic crystalloid. Start resuscitation with blood in the patient with significant bleeding, signs of hemodynamic instability, or significant injuries (e.g., unstable pelvic fracture), as older adults do not tolerate large-volume resuscitation well. Hemodynamic status should be reassessed frequently after small fluid boluses to avoid causing respiratory failure from fluid overload.

Invasive hemodynamic monitoring is appropriate for severely injured elders, but routine use is not justified. In a single-center, pre-post study, Scalea and colleagues showed reduced mortality with early invasive monitoring, leading some to recommend this as standard for older trauma patients.[33] Yet this has not been replicated, and multiple randomized trials of invasive monitoring in other critically ill populations have not shown a survival benefit.

Prompt reversal of anticoagulation is important, as approximately 5% of the elderly population is on warfarin and others have pathologic coagulopathy.[31] Specific considerations for reversing coagulation abnormalities in elderly trauma patients are the volume of reversal agents required and the corresponding risk of fluid overload. Prothrombin complex concentrates (PCCs) require minimal volume compared with fresh frozen plasma (FFP) but are costly. To fully reverse anticoagulation, 2 to 4 L of FFP may be required, presenting a limitation to rapid reversal in older patients at risk of fluid overload.

Disability

Evaluation of the elderly for disability includes examination for traumatic brain injury (TBI), spinal cord injury (SCI), and vertebral fractures and injuries. Primary neurologic examination of older adults should focus on mental status, verbal responsiveness, pupil responsiveness, and gross motor examination. The Glasgow Coma Scale (GCS) is often used to detect mental status changes after TBI but was not designed for this purpose and lacks sensitivity for mild injuries. Any GCS score less than 15 is concerning for TBI, and a GCS below 8 is highly predictive of poor outcome.[34,35] In addition to application of the GCS, other means of assessing mental status changes are useful. Subtle changes in mental status, such as confusion or decreased alertness, or symptoms such as headache may be the only signs of TBI. The mental status examination in elders is complicated by comorbidities such as previous stroke or dementia and the increasing prevalence of cognitive impairment in older adults, including dementia and delirium. Delirium can be the cause of traumatic injury, such as falls, or the result of traumatic injuries.[36] Abnormal pupillary responsiveness or motor function should raise concerns for significant intracranial hemorrhage (ICH) with associated increased intracranial pressure (ICP). Ultimately, no combination of historical features and physical findings has been shown to reliably predict the absence of intracranial injuries in the elderly trauma population. Brain computed tomography (CT) is prudent in older adults with head trauma, significant multisystem trauma, and symptoms or signs of TBI.

Older adults are at higher risk of vertebral fractures, and cervical fractures in particular, and they are more likely to sustain SCI as a result of trauma. Vertebral examination can be confounded by preexisting osteoarthritis. Clinical decision rules are available for cervical spine imaging in trauma, but their use is not recommended in older adults. The Canadian C-Spine Rule (CCR) classifies all patients 65 years and older as inherently "high risk," requiring radiography, as the derivation study found that age older than 65 had an odds ratio of 3.7 (95% confidence interval [CI] 2.4-5.6) for clinically significant cervical spine injury.[37] The National Emergency X-Ray Utilization Study (NEXUS) included all ages but found that patients aged 65 and older had a relative risk of 2.1 (1.8-2.6) for clinically significant cervical spine injury.[38] Although a subgroup analysis of the NEXUS study in elderly patients concluded that no clinically significant injuries were missed, there was likely selection bias, as the NEXUS study was observational and clinicians are more likely to order imaging in older adults. Other studies show that only 45% of elderly patients with cervical spine fractures had cervical spine tenderness on examination.[39] Elders are also at increased risk of thoracic, lumbar, and sacral vertebral fractures, for which CT is more sensitive than the physical examination or plain radiography.[40,41] Physicians should have a low threshold for CT imaging of the spine.

Elders are at higher risk for SCI without obvious radiographic abnormality (SCIWORA) owing to spinal cord stenosis and cervical kyphosis. Preexisting spinal canal stenosis increases the risk for central and anterior cord syndromes.[42] Evaluation for ligamentous injury and SCI with magnetic resonance imaging (MRI) is appropriate in patients with focal neurologic deficits.

Exposure

Older trauma patients are more likely to develop hypothermia because of physiologic changes and mechanisms of injury. With aging, skin thins, muscle and fat mass decrease, and thermoregulatory mechanisms do not work as well. Prolonged immobilization with exposure to the elements is common when elders fall and cannot get up. A rectal temperature should be routinely taken, and hypothermia should be rapidly treated with active external rewarming and warmed fluid resuscitation. Because skin breakdown and relatively minor wounds can cause serious complications in older patients, elders should be removed from backboards as soon as possible, be examined for pressure ulcers, and receive tetanus immunization if it is not up-to-date.

Secondary Assessment

The stable geriatric trauma patient requires a thorough secondary assessment. A complete history should be obtained from the patient or a care provider with particular emphasis on corroborating the accident history, past medical history, medications and allergies, and social history including baseline functional status and living arrangements. Screening questions for alcohol and substance abuse and elder abuse should be routinely asked. A valid screening question for elder abuse is "Has anyone close to you tried to hurt you or harm you recently?"

Laboratory Testing

Reasonable routine laboratory tests include complete blood count, comprehensive metabolic profile, coagulation studies (international normalized ratio [INR]), urinalysis, cardiac enzymes, and toxicology. Lactate and base deficit, which can signal tissue hypoxia and organ dysfunction, are predictive of mortality and can help

www.ketabpezeshki.com 66485457-66963820

determine the prognosis in elders with normal vital signs.[43] An electrocardiogram and cardiac monitoring are advised.

Imaging

Unstable elders should undergo plain radiography of the chest and pelvis. CT is the imaging modality of choice for stable older trauma patients, as plain radiography is less sensitive in elders owing to osteoarthritis and other comorbidities. Elders have less additional lifetime risk from the radiation associated with CT scans than younger adults owing to their lower life expectancy, but they are at greater risk from contrast-introduced nephropathy. When possible, intravenous contrast should be avoided, and renal protective strategies should be used, including intravenous fluids, bicarbonate, or *N*-acetylcysteine.[44]

SPECIFIC DISORDERS

Traumatic Brain Injury

TBI is common in older adults, can occur with minimal head trauma, and can be asymptomatic. Increasing age is an independent predictor of disability and mortality in patients with TBI, with overall mortality rates ranging from 30 to 80%.[34,45]

Pathophysiology and Mechanisms of Injury

Physiologic changes of aging and the frequent use of anticoagulant medication increase the likelihood and severity of TBI in older adults. With aging, the size of the brain decreases by 10% on average, resulting in less tortuous bridging veins and increased intracranial free space. The atrophied brain is more mobile within the skull, and trauma is more likely to shear bridging veins, leading to ICH. Diagnosis of TBI is more difficult in elders as increased intracranial free space can allow the accumulation of blood without changes in mental status,[46] and preexisting cognitive impairment is increasingly prevalent in older adults. Approximately 5% of older adults are on warfarin, and more than 30% are on an antiplatelet agent, increasing the likelihood and severity of TBI.[31]

Assessment and Diagnosis

If there is concern for intracranial injury, cranial CT and INR are indicated. Clinical variables alone are insufficient to reliably identify all cases of significant intracranial injury following trauma in elderly patients, and both the New Orleans Criteria (exclude age >60) and the Canadian Head CT Rule (excludes age ≥65) exclude older adults.[47,48]

Treatment

Treatment of TBI includes supportive care, rapid reversal of anticoagulation, and evaluation for decompressive surgical intervention. Supportive care aims to avoid cerebral hypoxia and hypoperfusion, which are significant predictors of adverse outcomes in patients with TBI. All patients should initially receive high-flow oxygen to maintain high oxygen saturation. Patients with hypercarbic respiratory conditions (e.g., chronic obstructive pulmonary disease [COPD]) will require an individualized determination of the appropriate oxygen saturation. Preventing cerebral hypoperfusion requires close monitoring of blood pressure, urine output, and other hemodynamic parameters, and individual patients may benefit from invasive hemodynamic monitoring. Early neurosurgical consultation is indicated to assess the need for and usefulness of surgical ICP monitoring and decompression. The current guidelines for ICP management have not been studied in older adults with TBI.[34]

Prompt reversal of anticoagulation with FFP or PCC is indicated in elders with TBI. The evidence supporting PCCs is from several studies of atraumatic ICH, which showed that immediate administration of PCC was associated with more rapid reversal and less hematoma growth than vitamin K and FFP, but not better outcomes. To date, there is not clinical evidence to support the use of platelet transfusion in elders taking antiplatelet agents.

Prognosis and Disposition

TBI in older adults is associated with significant morbidity and mortality, yet ED prognosis is not precise. Negative prognostic factors include increasing age, anticoagulation,[49-53] use of antiplatelet medications,[54] greater severity of TBI, and lower GCS. Although many patients with severe injuries, significant comorbidities, or anticoagulation may have no chance of meaningful outcome, others can return to living in the community.[55] Elderly patients with TBI should undergo prompt neurosurgical consultation. This is problematic for emergency physicians at hospitals without neurosurgical coverage, as it requires transferring patients with a grave prognosis, potentially for long distances. Patients with moderate or severe TBI, or any TBI and anticoagulation, require intensive care in which frequent neurologic checks and rapid reversal of anticoagulation can be accomplished. When an elder with TBI is being transferred, reversal of anticoagulation and prevention of hypoxia and hypotension are important early management steps.

Elderly patients with isolated head trauma, a normal cranial CT, and a normal INR are safe for discharge if they have a safe environment, a responsible care provider, and reliable follow-up. Although case reports suggest that anticoagulated patients with isolated head trauma and a normal cranial CT may be at risk of a delayed bleed, one study found that routine performance of a follow-up head CT scan at 24 hours was not necessary.[56] Such patients can be discharged to the care of a responsible provider who can observe them closely.

Vertebral Fractures and Spinal Cord Injuries

Vertebral fractures and SCIs show a bimodal distribution with one peak in young adults and a second peak in the geriatric population. Age-related changes to the vertebral bones, intervertebral disks, and spinal canal place patients at greater risk of vertebral fractures, result in a greater likelihood of SCI, and make physical examination and diagnostic imaging less accurate. Based on radiologic studies, approximately one quarter of patients older than 65 years have cervical stenosis, and 90% of men older than 50 years and 90% of women older than 60 years have evidence of degenerative changes in the cervical spine.[57] These changes have the effect of creating leverage on the spinal column when an external force is applied, such as in a fall with impact to the head, concentrating force on weakened bone, and increasing the risk of fracture and SCI. Spinal canal stenosis and the resulting spinal cord compression are clinically manifested as a myelopathy, with impairment of coordination, gait, bowel or bladder function, and motor or sensory function or both. Geriatric patients with vertebral injuries and SCIs are more likely to sustain incomplete neurologic injuries of less severity than younger patients, largely because they have lower-force injuries. In cases of suspected vertebral fracture or SCI, continued immobilization, neurosurgical consultation, and admission are indicated.[38] The majority of geriatric vertebral fractures and SCIs are represented by three types of injuries: (1) central cord syndrome, (2) cervical extension-distraction injuries ("open book" fractures), and (3) odontoid fractures.[42]

www.ketabpezeshki.com 66485457-66963820

Central Cord Syndrome

Central cord syndrome is a clinical syndrome with weakness disproportionately greater in the arms than in the legs after a hyperextension injury. The majority of cases of central cord syndrome in older adults are the result of hyperextension injuries in patients with canal stenosis and no bony fracture. Injuries associated with central cord syndrome are typically stable and require immobilization with a hard collar. Surgical decompression may be indicated. Patients with symptoms concerning for central cord syndrome and without fracture should undergo MRI.

Cervical Extension-Distraction Injury

Cervical extension-distraction injury is caused by reduced cervical range of motion as a result of degenerative spondylolysis, disk space collapse, and osteophyte formation. A hyperextension injury of the cervical spine and external signs of trauma to the forehead or face in an older adult raise suspicion for an extension-distraction injury. The patient may report that he or she is able to touch the pillow on the bed with the back of the head, which he or she was unable to do before the injury. This is a result of the fracture, which opens and lengthens the anterior column of the spine, resulting in the terminology "open book" fracture. These fractures are typically unstable and require surgical fixation.

Odontoid Fractures

Fracture of the C2 vertebral body, specifically the odontoid process, is usually the result of a fall with impact to the head, resulting in anterior or posterior displacement of the odontoid process. Although the majority of odontoid process fractures are displaced, less than 10% cause neurologic deficits. Type II odontoid fractures, at the base of the dens at its attachment to the body of C2, are the most common C-spine fracture in older trauma patients.

Thoracic Trauma

Older adults are at increased risk of rib and sternal fractures, pulmonary contusions, and their complications with low-force injuries. More than half of elderly patients admitted to hospitals with rib fractures sustained them during a fall, and a significant number occurred during low- or moderate-speed MVCs.[58] The risk of pneumonia and complications increases with the number of ribs fractured.[59] Pulmonary contusions are more frequent with minimal trauma and can cause significant morbidity and mortality in older adults. Chest CT is recommended for elderly patients with significant chest trauma, multiple rib fractures by plain film, or respiratory complications from trauma.

Patients with significant chest trauma require airway monitoring with consideration of early intubation to anticipate their clinical course, pulmonary therapy, and pain control. Pain control is of particular importance, as rib fractures will lead to splinting and atelectasis and increase the risk of pneumonia. Analgesia can be administered with intravenous opioids via patient-controlled analgesia or with an epidural analgesic. Geriatric trauma patients with severe pain from rib fractures often require hospitalization to allow adequate and safe pain management, and those with flail segments or larger numbers of rib fractures may require intensive care admissions.

Abdominal Trauma

Older adults are more likely to sustain intra-abdominal injuries and have higher mortality from such injuries. The general management principles are similar to those in younger adults, although there is less clinical evidence supporting nonoperative management (NOM) and angiographic embolization (AE) of solid organ injuries. The focus of the emergency physician is on the early diagnosis of intra-abdominal injuries, vigilant hemodynamic monitoring, and early resuscitation. The physical examination is unreliable for detecting intra-abdominal injury in older adults. The FAST examination is part of the initial evaluation and can be repeated as part of ongoing hemodynamic monitoring. Elderly patients with abdominal tenderness, significant multisystem trauma, or hemodynamic instability often require CT scanning to establish or eliminate dangerous diagnoses.

Although advanced age was initially an exclusion from NOM of solid organ injuries, there is more than a decade of evidence showing that carefully selected older adults are candidates for NOM. In several case series, approximately 80% of elders with splenic injuries were successfully managed nonoperatively, with the caveat that grade III injuries were more likely to fail NOM and all geriatric patients with grade IV or V injuries required an operation.[60,61] There are limited data on NOM of liver injuries in older adults. As AE has been used successfully in older adults,[62] angiography is a reasonable option for the elderly trauma patient with solid organ injury and a blush or extravasation on CT.

Extremities

Fractures are the most common injuries in elders with trauma. Fractures that affect mobility and the ability to live independently, such as hip fractures, are associated with significant perioperative and 1-year mortality in older adults. The most common fractures in order of frequency sustained by older adults are distal radius fractures (Colles' fractures), proximal humerus fractures, and elbow fractures, which usually occur during a fall onto an outstretched arm. Older adults with proximal humoral fractures can have remarkably few symptoms.

The most common lower extremity fractures in older adults are ankle fractures, hip and pelvic fractures, and tibial plateau fractures. Pelvic fractures can occur with relatively little force in elders and are less likely to be classified as severe; fracture patterns are similar between the elderly and younger adults, with lateral compression fractures more common than anteroposterior fractures. In older adults, both fracture types are associated with significant hemorrhage.[63] Overall pelvic fracture mortality is 9 to 30%, and up to 81% in older patients with open pelvic fractures.[63,64] Emergent treatment of pelvic fractures consists of hemodynamic monitoring, resuscitation with blood, stabilization of the fracture with wrapping or external fixation, and control of bleeding with consideration of AE to address retroperitoneal hemorrhage.

Hip fractures are common in older adults, occurring in approximately 1% of men and 2% of women per year. Whereas isolated hip fractures are not associated with significant immediate hemorrhage or mortality such as seen in pelvic fractures, they are associated with an 8 to 30% 1-year mortality.[65] Hip fractures are usually seen on plain x-ray films (sensitivity approximately 90%) and CT scans, but occult fractures are a well-described phenomenon in older adults. Patients with inability to ambulate or persistent pain after trauma require further evaluation; MRI and bone scan are useful imaging studies to delineate the pathology.[66] Elders with fractures may have better outcomes with distinct orthogeriatric services.[67,68]

END-OF-LIFE DECISIONS

Emergency physicians are faced with difficult decisions regarding prognosis, the usefulness of aggressive care, and end-of-life decisions in geriatric trauma. Elderly trauma patients have a uniformly worse prognosis than younger adults. Several factors that portend a grave prognosis from the ED include a GCS of 3, a GCS below

www.ketabpezeshki.com 66485457-66963820

8 with anticoagulation, and hemodynamic instability from internal hemorrhage with anticoagulation. Yet initial injury in the ED does not perfectly predict an individual patient's long-term prognosis,[69] and emergency physicians have not traditionally withheld aggressive trauma care, which usually includes the involvement of trauma surgeons. Emergency physicians should discuss end-of-life decisions, such as intubation, cardiopulmonary resuscitation (CPR), transfer, and surgery, with patients, family members, and surgical consultants. Although age alone is not an indication to withhold aggressive treatment, in select cases with a grave prognosis and when the patient's goals of care are known, comfort measures may be more appropriate than transferring patients to a trauma center.

KEY CONCEPTS

- Older adults are prone to significant injuries with low-force trauma such as falls from standing. Vigilance for occult injuries, including TBI, cervical spine injuries, hip and pelvis fractures, and solid organ injuries, should be maintained.
- Vital signs, including tachycardia and hypotension, are unreliable to detect hemodynamic instability in older adults owing to changes in physiology, comorbidities, and medications. Clinicians should expand their assessment for shock by including alterations in mental status, urine output, and skin perfusion and should have a low threshold for considering shock in elderly trauma patients.
- Elders are at significant risk from shock, yet they are also at risk from overly aggressive resuscitation. Resuscitation should be rapid but should include frequent reassessments of vitals signs, respiratory status, and other potential indicators of shock. Invasive hemodynamic monitoring may be beneficial.
- Clinical decision rules for radiographic imaging have generally excluded elderly patients. A low threshold is advised for imaging in older adults with trauma.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Wan H, Sengupta M, Velkoff VA, DeBarros KA: *U.S. Census Bureau, Current Population Reports, 65+ in the United States: 2005*. Washington, DC: U.S. Government Printing Office; 2005:23-209.
2. National Center for Health Statistics, National Hospital Ambulatory Medical Care Survey: 2008 Emergency Department Summary Tables. Available at http://www.cdc.gov/nchs/data/ahcd/nhamcs_emergency/2008_ed_web_tables.pdf. Accessed November 17, 2012.
3. Heron M: Deaths: Leading causes for 2009. *National vital statistics reports*; vol 61 no 7. Hyattsville, Md: National Center for Health Statistics. 2012. p 17.
4. Hollis S, Lecky F, Yates DW, Woodford M: The effect of pre-existing medical conditions and age on mortality after injury. *J Trauma* 2006; 61:1255-1260.
5. Wutzler S, et al: Association of preexisting medical conditions with in-hospital mortality in multiple-trauma patients. *J Am Coll Surg* 2009; 209:75-81.
6. Labib N, et al: Severely injured geriatric population: Morbidity, mortality, and risk factors. *J Trauma* 2011; 71:1908-1914.
7. Perdue PW, Watts DD, Kaufmann CR, Trask AL: Differences in mortality between elderly and younger adult trauma patients: Geriatric status increases risk of delayed death. *J Trauma* 1998; 45:805-810.
8. Chang TT, Schecter WP: Injury in the elderly and end-of-life decisions. *Surg Clin North Am* 2007; 87:229-245, viii.
9. Zimmer-Gembeck MJ, et al: Triage in an established trauma system. *J Trauma* 1995; 39:922-928.
10. Phillips S, Rond PC 3rd, Kelly SM, Swartz PD: The failure of triage criteria to identify geriatric patients with trauma: Results from the Florida trauma triage study. *J Trauma* 1996; 40:278-283.
11. Lehmann R, Beekley A, Casey L, Salim A, Martin M: The impact of advanced age on trauma triage decisions and outcomes: A statewide analysis. *Am J Surg* 2009; 197:571-575.
12. Zarzaur BL, Croce MA, Magnotti LJ, Fabian TC: Identifying life-threatening shock in the older injured patient: An analysis of the national trauma data bank. *J Trauma* 2010; 68:1134-1138.
13. Chang DC, Bass RR, Cornwell EE, Mackenzie EJ: Undertriage of elderly trauma patients to state-designated trauma centers. *Arch Surg* 2008; 143:776-782.
14. Hsia RY, et al: Factors associated with trauma center use for elderly patients with trauma: A statewide analysis, 1999-2008. *Arch Surg* 2011; 146:585-592.
15. ATLS: *Advanced Trauma Life Support for Doctors: Student Course Manual*, 8th ed. Chicago: American College of Surgeons; 2008.
16. Meldon SW, Reilly M, Drew BL, Mancuso C, Fallon W Jr: Trauma in the very elderly: A community-based study of outcomes at trauma and nontrauma centers. *J Trauma* 2002; 52:79-84.
17. MacKenzie EJ, et al: A national evaluation of the effect of trauma-center care on mortality. *N Engl J Med* 2006; 354:366-378.
18. Demetriades D, et al: Effect on outcome of early intensive management of geriatric trauma patients. *Br J Surg* 2002; 89:1319-1322.
19. Bergen G, Chen LH, Warner M, Fingerhut LA, eds: *Injury in the United States: 2007 Chartbook*. Hyattsville, Md: National Center for Health Statistics; 2008.
20. Centers for Disease Control and Prevention (CDC): *Injury Prevention and Control: Data and Statistics (WISQARS)*. Available at www.cdc.gov/injury/wisqars/index.html. Accessed December 21, 2011.
21. Centers for Disease Control and Prevention (CDC): Fatalities and injuries from falls among older adults—United States, 1993-2003 and 2001-2005. *MMWR Morb Mortal Wkly Rep* 2006; 55:1221-1224.
22. Rubenstein LZ: Falls in older people: Epidemiology, risk factors and strategies for prevention. *Age Ageing* 2006; 35(Suppl 2):ii37-ii41.
23. Chisholm KM, Harruff RC: Elderly deaths due to ground-level falls. *Am J Forensic Med Pathol* 2010; 31:350-354.
24. Helling TS, et al: Low falls: An underappreciated mechanism of injury. *J Trauma* 1999; 46:453-456.
25. Sterling DA, O'Connor JA, Bonadies J: Geriatric falls: Injury severity is high and disproportionate to mechanism. *J Trauma* 2001; 50:116-119.
26. Mayhew DR, Simpson HM, Ferguson SA: Collisions involving senior drivers: High-risk conditions and locations. *Traffic Inj Prev* 2006; 7:117-124.
27. Cook LJ, Knight S, Olson LM, Nechodom PJ, Dean JM: Motor vehicle crash characteristics and medical outcomes among older drivers in Utah, 1992-1995. *Ann Emerg Med* 2000; 35:585-591.
28. Lionelli GT, Pickus EJ, Beckum OK, Decoursey RL, Korentager RA: A three decade analysis of factors affecting burn mortality in the elderly. *Burns* 2005; 31:958-963.
29. Cooper C, Selwood A, Livingston G: The prevalence of elder abuse and neglect: A systematic review. *Age Ageing* 2008; 37:151-160.
30. Weiss CO, Boyd CM, Yu Q, Wolff JL, Leff B: Patterns of prevalent major chronic disease among older adults in the United States. *JAMA* 2007; 298:1160-1162.
31. Qato DM, et al: Use of prescription and over-the-counter medications and dietary supplements among older adults in the united states. *JAMA* 2008; 300:2867-2878.
32. Brown CA 3rd, et al: Improved glottic exposure with the video Macintosh laryngoscope in adult emergency department tracheal intubations. *Ann Emerg Med* 2010; 56:83-88.
33. Scalea TM, et al: Geriatric blunt multiple trauma: Improved survival with early invasive monitoring. *J Trauma* 1990; 30:129-136.
34. Thompson HJ, McCormick WC, Kagan SH: Traumatic brain injury in older adults: Epidemiology, outcomes, and future implications. *J Am Geriatr Soc* 2006; 54:1590-1595.
35. Petridis AK, et al: Acute subdural hematoma in the elderly: Clinical and CT factors influencing the surgical treatment decision. *Cent Eur Neurosurg* 2009; 70:73-78.
36. Pandharipande P, et al: Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *J Trauma* 2008; 65:34-41.
37. Stiell IG, et al: The Canadian C-Spine Rule for radiography in alert and stable trauma patients. *JAMA* 2001; 286:1841-1848.
38. Lowery DW, Wald MM, Browne BJ, et al: Epidemiology of cervical spine injury victims. *Ann Emerg Med* 2001; 38:12-16.
39. Schrag SP, Toedter LJ, McQuay N Jr: Cervical spine fractures in geriatric blunt trauma patients with low-energy mechanism: Are clinical predictors adequate? *Am J Surg* 2008; 195:170-173.
40. Berry GE, et al: Are plain radiographs of the spine necessary during evaluation after blunt trauma? Accuracy of screening torso computed tomography in thoracic/lumbar spine fracture diagnosis. *J Trauma* 2005; 59:1410-1413.
41. O'Connor E, Walsham J: Review article: Indications for thoracolumbar imaging in blunt trauma patients: A review of current literature. *Emerg Med Australas* 2009; 21:94-101.
42. Jabbour P, Fehlings M, Vaccaro AR, Harrop JS: Traumatic spine injuries in the geriatric population. *Neurosurg Focus* 2008; 25:E16.
43. Callaway DW, Shapiro NI, Donnino MW, Baker C, Rosen CL: Serum lactate and base deficit as predictors of mortality in normotensive elderly blunt trauma patients. *J Trauma* 2009; 66:1040-1044.
44. Chronopoulos A, Rosner MH, Cruz DN, Ronco C: Acute kidney injury in the elderly: A review. *Contrib Nephrol* 2010; 165:315-321.
45. Susman M, et al: Traumatic brain injury in the elderly: Increased mortality and worse functional outcome at discharge despite lower injury severity. *J Trauma* 2002; 53:219-224.
46. Mack LR, Chan SB, Silva JC, Hogan TM: The use of head computed tomography in elderly patients sustaining minor head trauma. *J Emerg Med* 2003; 24:157-162.
47. Haydel MJ, et al: Indications for computed tomography in patients with minor head injury. *N Engl J Med* 2000; 343:100-105.
48. Stiell IG, et al: The Canadian CT head rule for patients with minor head injury. *Lancet* 2001; 357:1391-1396.
49. Lavoie A, et al: Preinjury warfarin use among elderly patients with closed head injuries in a trauma center. *J Trauma* 2004; 56:802-807.
50. Franko J, Kish KJ, O'Connell BG, Subramanian S, Yuschak JV: Advanced age and preinjury warfarin anticoagulation increase the risk of mortality after head trauma. *J Trauma* 2006; 61:107-110.
51. Pieracci FM, Eachempati SR, Shou J, Hydo LJ, Barie PS: Degree of anticoagulation, but not warfarin use itself, predicts adverse outcomes after traumatic brain injury in elderly trauma patients. *J Trauma* 2007; 63:525-530.
52. Grandhi R, et al: Anticoagulation and the elderly head trauma patient. *Am Surg* 2008; 74:802-805.
53. Fortuna GR, Mueller EW, James LE, Shutter LA, Butler KL: The impact of preinjury antiplatelet and anticoagulant pharmacotherapy on outcomes in elderly patients with hemorrhagic brain injury. *Surgery* 2008; 144:598-605.
54. Wong DK, Lurie F, Wong LL: The effects of clopidogrel on elderly traumatic brain injured patients. *J Trauma* 2008; 65:1303-1308.
55. Flanagan SR, Hibbard MR, Gordon WA: The impact of age on traumatic brain injury. *Phys Med Rehabil Clin N Am* 2005; 16:163-177.
56. Kaen A, et al: The value of sequential computed tomography scanning in anticoagulated patients suffering from minor head injury. *J Trauma* 2010; 68:895-898.

www.ketabpezeshki.com 66485457-66963820

57. Young WF: Cervical spondylotic myelopathy: A common cause of spinal cord dysfunction in older persons. *Am Fam Physician* 2000; 62: 1064-1070, 1073.
58. Bergeron E, et al: Elderly trauma patients with rib fractures are at greater risk of death and pneumonia. *J Trauma* 2003; 54:478-485.
59. Bulger EM, Arneson MA, Mock CN, Jurkovich GJ: Rib fractures in the elderly. *J Trauma* 2000; 48:1040-1047.
60. Harbrecht BG, et al: Contribution of age and gender to outcome of blunt splenic injury in adults: Multicenter study of the eastern association for the surgery of trauma. *J Trauma* 2001; 51:887-895.
61. Siriratsivawong K, Zenati M, Watson GA, Harbrecht BG: Nonoperative management of blunt splenic trauma in the elderly: Does age play a role? *Am Surg* 2007; 73:585-590.
62. Gaarder C, et al: Nonoperative management of splenic injuries: Improved results with angioembolization. *J Trauma* 2006; 61:192-198.
63. Rice PL Jr, Rudolph M: Pelvic fractures. *Emerg Med Clin North Am* 2007; 25:795-802, x.
64. Dechert TA, et al: Elderly patients with pelvic fracture: Interventions and outcomes. *Am Surg* 2009; 75:291-295.
65. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C: Excess mortality following hip fracture: A systematic epidemiological review. *Osteoporos Int* 2009; 20:1633-1650.
66. Cannon J, Silvestri S, Munro M: Imaging choices in occult hip fracture. *J Emerg Med* 2009; 37:144-152.
67. Friedman SM, Mendelson DA, Bingham KW, Kates SL: Impact of a comanaged geriatric fracture center on short-term hip fracture outcomes. *Arch Intern Med* 2009; 169:1712-1717.
68. Carpenter CR, Stern ME. Emergency orthogeriatrics: Concepts and therapeutic alternatives. *Emerg Med Clin North Am* 2010; 28:927-949.
69. van Aalst JA, Morris JA Jr, Yates HK, Miller RS, Bass SM: Severely injured geriatric patients return to independent living: A study of factors influencing function and independence. *J Trauma* 1991; 31:1096-1102.

www.ketabpezeshki.com 66485457-66963820

Chapter 40

Injury Prevention and Control

E. Brooke Lerner and Stephen W. Hargarten

PERSPECTIVE

The science of injury control is based on the concept that trauma is like a disease rather than just the consequence of fate or random occurrences. The principles of disease control are applied to injury as they are successfully applied to infectious diseases. Control of a disease as widespread and multifactorial as injury can occur only through broad interdisciplinary effort, including that of medicine, public health, policy makers, law enforcement, educated citizens, and others (Box 40-1).

Emergency medicine plays a pivotal role in the care of injured patients and in injury control. In the United States, approximately one third of all emergency department visits are for the care of injuries, representing 13.3 visits per 100 people per year.[1] Injury is the leading cause of death for many age groups (Table 40-1). In 2004, 29.6 million people were treated in U.S. emergency departments for injuries, of whom 93% were not admitted to the hospital.[2] The medical cost of injury-related medical care in the United States is estimated to be $117 billion annually.[2] Because the emergency care system may be the patient's only contact with the health care system, emergency physicians should provide preventive services in addition to acute medical care for injured patients.[3-5] Emergency physicians work with trauma surgeons, pediatricians, and others to decrease injuries through clinical and policy-relevant research and education.[6]

PRINCIPLES OF THE DISEASE OF INJURY

The major causes of injury include falls, motor vehicle collisions, gunshots, suffocation, and poisonings. Similar to other disease models, injury occurs from the interaction of agent and host through a vector and an environment that is conducive to exposure (Fig. 40-1). *Injury* is a harmful event caused by the acute transfer of energy to a patient that results in tissue and/or organ damage.[7] The energy may be in any form, such as kinetic (e.g., falls and motor vehicle crashes), thermal (e.g., burns and hypothermia), chemical (e.g., poisoning), or electrical (e.g., lightning strike) energy or the absence of energy (e.g., hanging or drowning).[8] Energy is the agent that is delivered to the host (patient) by a vector in an environment with variable risk. Cars and guns are examples of vectors of energy transmission that cause the injury. A car on an icy road is an example of the interaction of the environment and the vector to increase the likelihood of kinetic energy reaching the host and causing injury.

The goal of injury control is to prevent or decrease the transfer of energy to the host by (1) separating the host from the agent through modification of the environment, (2) equipping the host with protection against the agent, or (3) eliminating or modifying the vector that transmits the energy.[8-13]

The first step in the control of injuries is recognizing that injury is preventable. Public perception is that injuries result from accidents or random, unexpected events, similar to the way in which infections were regarded before the discovery of bacteria. As in other diseases, characteristics of the host affect prevention strategies, acute care, and rehabilitation outcomes. These include physical characteristics, such as age, gender, size, and motor skills, and mental or behavioral characteristics, such as intelligence, fatigue, alcohol use, emotional stability, social norms, and lifestyle. Risks for injury and death vary by age (see Table 40-1). For the likelihood of an injury to be decreased, changes in some of these predisposing factors can be made in the host (e.g., through improvement in driving skills or a commitment to wear a seat belt or not to drink and drive) and should be age specific for maximum effect.

Energy is transmitted to the host through a *vector,* such as motorized and nonmotorized vehicles (e.g., car, bicycle, and skateboard), firearms, piercing instruments (e.g., knife and arrow), explosives, and lit cigarettes. Modifying the vector (by elimination or modification of design) and separating the vector from the host are important methods to reduce injury. For example, the understanding of biomechanical forces released during an injury event is crucial to understanding vehicle modification.[14-16] Physicians should educate patients and families to modify or eliminate vectors they encounter during their daily lives—for example, recommending that families properly store household firearms and use gun locks.[17] Another example is storing drugs that look similar in different locations on an ambulance or changing the packaging to reduce the risk of injuries caused by administering the wrong medication.

When an injury occurs, host-agent interaction and energy transfer take place in an *environment.* This environment can be modified to decrease injury. If the environment does not permit energy transmission, the risk of injury, including intentional injuries to the host (patient), is eliminated.[18] Most environmental modifications require no cooperation or action by the host and are more effective than altering host risk factors. Examples are implementing safer road design and lighting to prevent motor vehicle collisions, removing throw rugs to prevent falls, placing fences around pools, and separating bicycle paths from roadways.[12,19]

William Haddon, the first physician administrator for the National Highway Traffic Safety Administration (NHTSA), first described this type of approach in a landmark article on injury control in 1970.[20] He laid out 10 methods for preventing injury (Table 40-2). Haddon later expanded these ideas to incorporate

www.ketabpezeshki.com 66485457-66963820

Box 40-1 Multidisciplinary Team Approach to Injury Control: Prevention, Acute Care, and Rehabilitation

Prevention
Epidemiology
Biomechanics
Education
Public policy
Law enforcement
Engineering
Outcomes research
Emergency preparedness

Acute Care
Trauma system
Emergency medical services
Emergency department care
Hospital care
Clinical guidelines
Clinical prevention services
Outcomes research

Rehabilitation
Physical therapy
Occupational therapy
Mental health providers

time and developed the Haddon matrix. The matrix recognizes that preventative interventions should be considered for the host, agent, vector, and environment before the event, during the event, and after the event. Any type or cluster of injuries can be prevented or reduced in severity through use of this matrix when the environment, vector, and population most at risk are identified and modified. An example of this process to reduce motor vehicle collision injuries is given in Table 40-3. The key to energy transfer reduction or prevention is understanding that (1) injuries are predictable, (2) they follow predictable patterns (e.g., by age or gender), and (3) reliance solely on human factors for prevention has significant limits. A fragile item sent through the mail arrives at its destination intact only if it has been properly packaged to reduce the energy to which it is subjected during transport. Likewise, injuries to people can be prevented by use of the cells of the Haddon matrix to mitigate the energy transfer of predictable events.

History of Injury Control

Decreasing personal injury is a goal of modern public health, but until the 1940s and 1950s, unintentional injuries were attributed primarily to human error, and prevention was based on educating people to act safely.[10] Unsafe roads were built, and motorized vehicles and other consumer products were manufactured without regard to safety design flaws.[21] This is analogous to supplying untreated tap water to homes and relying on educating people to purify their drinking water to prevent cholera.[11]

In the 1920s, attributing vehicle crashes to poor driver performance led to mandatory licensing of drivers. In the 1930s, when it was realized that vehicle crashes were caused not simply by human error but by mechanical factors as well, President Roosevelt called for automobiles to be made more crashworthy.[8] In 1942, Hugh DeHaven, a former World War I pilot turned physiologist, pondering his own survival in an airplane crash when another occupant had been killed, suggested structural provisions be made to vehicles that would distribute the forces of energy over the human body to attenuate the energy transfer and reduce injuries in crashes. He focused on defining the physical factors that influence survival rather than the human error that caused the crash.[8] As the United States embarked on its space program, Air Force researchers showed that humans could withstand splashdown with a sled that decelerates from 30 to 0 mph over a stopping distance of 2 feet.[22] This demonstration was a significant advance in understanding the biomechanics of sudden deceleration.

The recognition that injuries could be addressed similarly to diseases occurred in the 1940s, when John Gordon, an epidemiologist, suggested that injuries have epidemic patterns, seasonal variation, long-term trends, and demographic distribution and can be examined with methodologies applied to infectious diseases. Gordon also believed that, similar to infectious diseases, injury results from the interaction of the agent, host, and environment.[8] In the 1960s, Haddon developed a two-dimensional approach to injury analysis by dividing the factors of agent, host, and environment into three phases: preinjury, injury, and postinjury. This phase-factor matrix has become a mainstay of injury control development. Any injury event can be broken down into the component factors, allowing specific interventions to target specific factors (Table 40-4).[12,23]

In 1985, the publication *Injury in America: A Continuing Public Health Problem* by the National Research Council and the Institute of Medicine called on the public health and health care community to address the injury epidemic.[13] With the establishment of the National Center for Injury Prevention and Control (NCIP) in the Centers for Disease Control and Prevention (CDC), it was acknowledged that the control of injuries belongs in the disease control community and includes health care providers such as emergency physicians.

Soon after its inception, the NCIP began sponsoring injury control research centers at academic institutions throughout the country. These centers, frequently led by physicians, including emergency physicians, conduct research in all three core phases of injury control (i.e., prevention, acute care, and rehabilitation) and serve as training centers for injury control specialists and as information centers for the public.[24] To expand this work, the Society for the Advancement of Violence and Injury Research is open to any group or individual with an interest in advancing research in violence and injury (www.savirweb.org).

In 2003 the NCIP began updating the CDC Injury Research Agenda to include acute care research, focusing on research that will improve acute injury care systems.[25] After this, the NCIP Division of Injury and Disability Outcomes and Programs changed its name to the Division of Injury Response, with a mission "to increase the capacity to prevent injuries and their adverse health effects by working with partners to develop, evaluate, and promote evidence-based surveillance, prevention, and care practices."[26] This center became a home for acute injury care and acknowledges its importance for prevention. This division has also become a focal point for response to terrorist-related injuries, an important area of injury control. In 2009 the NCIP published a revised research agenda continuing the Center's commitment to acute care research.[27]

Methods of Prevention

The history of injury control began with the first injury. Pain from injury is a powerful stimulus for avoidance behaviors. Early prevention technology is seen in the instruments and garb of the earliest armies, shielding people from the harmful kinetic energy of weapons. Such technology included helmets, shields, and suits of armor. As the delivery of kinetic energy became more sophisticated, prevention technology did not keep pace.[15,16] Firearms and automobiles represent new plateaus in harnessing kinetic energy as well as creating new sources of morbidity and mortality.[21,28] The cultural belief was that individuals could avoid vehicular injury by safe driving, and if they did not drive safely, an "accident" would occur. It took more than 50 years to acknowledge that behavior modification alone was insufficient to mitigate high-energy

www.ketabpezeshki.com 66485457-66963820

Table 40-1 Ten Leading Causes of Death, United States, 2007, All Races, Both Sexes

	Age Group										
RANK	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	ALL AGES
1	Congenital anomalies 5785	Unintentional injury 1588	Unintentional injury 965	Unintentional injury 1229	Unintentional injury 15,897	Unintentional injury 14,977	Unintentional injury 16,931	Malignant neoplasms 50,167	Malignant neoplasms 103,171	Heart disease 496,095	Heart disease 616,067
2	Short gestation 4857	Congenital anomalies 546	Malignant neoplasms 480	Malignant neoplasms 479	Homicide 5551	Suicide 5278	Malignant neoplasms 13,288	Heart disease 37,434	Heart disease 65,527	Malignant neoplasms 389,730	Malignant neoplasms 562,875
3	SIDS 2453	Homicide 398	Congenital anomalies 196	Homicide 213	Suicide 4140	Homicide 4758	Heart disease 11,839	Unintentional injury 20,315	Chronic lower respiratory disease 12,777	Cerebrovascular 115,961	Cerebrovascular 135,952
4	Maternal pregnancy complications 1769	Malignant neoplasms 364	Homicide 133	Suicide 180	Malignant neoplasms 1653	Malignant neoplasms 3463	Suicide 6722	Liver disease 8212	Unintentional injury 12,193	Chronic lower respiratory disease 109,562	Chronic lower respiratory disease 127,924
5	Unintentional injury 1285	Heart disease 173	Heart disease 110	Congenital anomalies 178	Heart disease 1084	Heart disease 3223	HIV 3572	Suicide 7778	Diabetes mellitus 11,304	Alzheimer's disease 73,797	Unintentional injury 123,706
6	Placenta cord membranes 1135	Influenza and pneumonia 109	Chronic lower respiratory disease 54	Heart disease 131	Congenital anomalies 402	HIV 1091	Homicide 3052	Cerebrovascular 6385	Cerebrovascular 10,500	Diabetes mellitus 51,528	Alzheimer's disease 74,632
7	Bacterial sepsis 820	Septicemia 78	Influenza and pneumonia 48	Chronic lower respiratory disease 64	Cerebrovascular 195	Diabetes mellitus 610	Liver disease 2570	Diabetes mellitus 5753	Liver disease 8004	Influenza and pneumonia 45,941	Diabetes mellitus 71,382
8	Respiratory distress 789	Perinatal period 70	Benign neoplasms 41	Influenza and pneumonia 55	Diabetes mellitus 168	Cerebrovascular 505	Cerebrovascular 2133	HIV 4156	Suicide 5069	Nephritis 38,484	Influenza and pneumonia 52,717
9	Circulatory system disease 624	Benign neoplasms 59	Cerebrovascular disease 38	Cerebrovascular disease 45	Influenza and pneumonia 163	Congenital anomalies 417	Diabetes mellitus 1984	Chronic lower respiratory disease 4153	Nephritis 4440	Unintentional injury 38,292	Nephritis 46,448
10	Neonatal hemorrhage 597	Chronic lower respiratory disease 57	Septicemia 36	Benign neoplasms 43	Three tied* 160	Liver disease 384	Septicemia 910	Viral hepatitis 2815	Septicemia 4231	Septicemia 26,362	Septicemia 34,828

Data from the National Center for Health Statistics, National Vital Statistics System.
HIV, human immunodeficiency virus; *SIDS,* sudden infant death syndrome.
*Complicated pregnancy, HIV, and septicemia had 160 deaths each in 2007.

www.ketabpezeshki.com 66485457-66963820

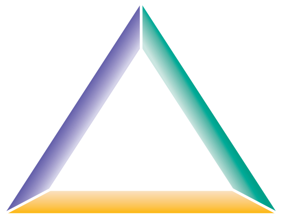


Figure 40-1. The epidemiologic triad can be used as a framework for injury prevention. An injury occurs by the interaction of the host and agent through a vector and an environment that is conducive to injury. Alteration of any of these interactions prevents the injury.[115]

transmission to humans in a hazardous environment. Cars were not uniformly equipped with seat belts until the 1960s.[21] It took another two decades before air bags became standard.[15,16,29]

Implementation of effective injury control strategies depends on collaborative efforts by a number of individuals, including physicians, nurses, out-of-hospital care providers, epidemiologists, biomechanical engineers, public policy makers, law enforcement officers, lawyers, and other stakeholders.[19,29,30] A major challenge is the wide diversity of disciplines and interests involved in safety and injury control, many of which are isolated from one another.[10] In the 1990s, important strides were made in community-based injury control programs that rely on coalitions of existing resources with the support of the NHTSA, the CDC, and the State and Territorial Injury Prevention Directors Association. These community coalitions were created to garner existing resources and implement injury countermeasures through use of "the 3 Es"

Table 40-2 Haddon's Strategies for Preventing the Transfer of Energy to the Host

TECHNIQUE	CAR CRASH	FALLS
1. Prevent the initial marshaling of energy	Manual task, breathalyzer ignition interlocks Use of alternative transportation	Remove floor obstacles Prevent unnecessary climbing
2. Reduce the amount of energy marshaled	Speed reduction Vehicle mass restrictions	Climbing height restrictions
3. Prevent the release of energy	Breakaway light poles, roadway obstacle removal	Ambulation aids for elderly Worker safety harnesses
4. Modify the rate of spatial distribution of the release of energy from its source	Auto body crumple zones Safety belts, air bags Water barrel barriers	Land with a "roll" Use of safety nets
5. Separate the energy from the host in space or time	Reduce traffic density Homogeneous traffic flow Increase following distance Sidewalks for pedestrians	Safety zones at edge of raised work areas
6. Separate the energy from the host by barrier	Guardrails, concrete median barriers	Guardrails for scaffolds, raised work areas
7. Modify the surface or structure of impact	Collapsible steering columns, padded pillars and bolsters, safety glass	Padded flooring Helmets and hard hats
8. Strengthen the host receiving the energy	Detect and treat premorbid medical conditions	Prevent and treat osteoporosis and strengthen hip flexion in elderly patients
9. Rapidly detect and evaluate damage and counter its continuation and extension	911 and EMS availability Trauma system planning and implementations, and provision of state-of-the-art emergency care	911 and EMS availability Trauma system planning and implementation, and provision of state-of-the-art emergency care
10. Reparative and rehabilitative measures	Provision of state-of-the-art trauma care, rehabilitation, and aftercare	Provision of state-of-the-art trauma care, rehabilitation, and aftercare

EMS, emergency medical services.

Table 40-3 Typical Haddon Matrix (Constructed for Motor Vehicle Injury)

	HOST (DRIVER)	AGENT OR VECTOR (CAR)	ENVIRONMENT
Pre-event (before the crash)	Alcohol use Fatigue Experience and judgment Vision	Brake condition Tire quality Center of gravity Load weight	Visibility of hazards Road curvature and gradient Surface coefficient of friction Shoulder height
Event (during the crash)	Medications Motor skills Cognitive function Age	Speed capacity Visual obstructions Speed at impact Vehicle size	Intersections, access control Weather Signalization Speed limits
Postevent (after the crash)	Age Physical condition Medications Social situation	Load containment Deformation zones Fuel system integrity	911 access EMS response Triage and transfer protocols Nearby level 1 trauma center

Adapted from Baker SP, O'Neill B, Ginsburg MJ, Li G: The Injury Fact Book, 2nd ed. New York, Oxford University Press, 1992.
EMS, emergency medical services.

www.ketabpezeshki.com 66485457-66963820

Table 40-4 Ten Leading Causes of Injury Deaths, United States, 2007, All Races, Both Sexes

	Age Group										
RANK	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	ALL AGES
1	Unintentional suffocation 959	Unintentional drowning 458	Unintentional MVC traffic 456	Unintentional MVC traffic 696	Unintentional MVC traffic 10,272	Unintentional MVC traffic 6842	Unintentional poisoning 7575	Unintentional poisoning 9006	Unintentional MVC traffic 4177	Unintentional fall 18,334	Unintentional MVC traffic 42,031
2	Homicide Unspecified 174	Unintentional MVC traffic 428	Unintentional Fire/burn 136	Homicide Firearm 154	Homicide Firearm 4669	Unintentional poisoning 5700	Unintentional MVC traffic 6135	Unintentional MVC traffic 6262	Unintentional poisoning 3120	Unintentional MVC traffic 6632	Unintentional poisoning 29,846
3	Unintentional MVC traffic 122	Unintentional Fire/burn 204	Unintentional drowning 122	Suicide Suffocation 119	Unintentional poisoning 3159	Homicide Firearm 3751	Suicide Firearm 2879	Suicide Firearm 3531	Suicide Firearm 2786	Unintentional Unspecified 4855	Unintentional fall 22,631
4	Homicide Other, spec., classifiable 86	Homicide Unspecified 174	Homicide Firearm 47	Unintentional drowning 102	Suicide Firearm 1900	Suicide Firearm 2306	Homicide Firearm 2038	Suicide Poisoning 2015	Unintentional fall 1739	Suicide Firearm 3895	Suicide Firearm 17,352
5	Unintentional drowning 57	Unintentional suffocation 149	Unintentional suffocation 42	Unintentional Other land transport 80	Suicide Suffocation 1533	Suicide Suffocation 1770	Suicide Suffocation 1839	Suicide Suffocation 1589	Suicide Poisoning 1147	Unintentional suffocation 3209	Homicide Firearm 12,632
6	Unintentional fire, burning 39	Unintentional Pedestrian, other 124	Unintentional Other land transport 40	Unintentional Fire/burn 78	Unintentional drowning 630	Suicide Poisoning 802	Suicide Poisoning 1419	Unintentional fall 1304	Suicide Suffocation 725	Adverse effects 1631	Suicide Suffocation 8161
7	Undetermined Suffocation 34	Homicide Other, spec., classifiable 61	Unintentional Pedestrian, other 32	Unintentional poisoning 69	Homicide Cut/pierce 444	Undetermined Poisoning 687	Undetermined Poisoning 1020	Homicide Firearm 1159	Unintentional Fire/burn 505	Unintentional Fire/burn 1179	Suicide Poisoning 6358
8	Homicide Suffocation 30	Homicide Firearm 48	Homicide Suffocation 21	Unintentional suffocation 60	Undetermined Poisoning 365	Homicide Cut/pierce 466	Unintentional fall 593	Undetermined poisoning 1155	Unintentional suffocation 484	Unintentional poisoning 1149	Unintentional Unspecified 6019
9	Undetermined Unspecified 28	Unintentional Struck by or against 44	Unintentional Firearm 20	Suicide Firearm 53	Suicide Poisoning 362	Unintentional drowning 381	Unintentional drowning 417	Unintentional Fire/burn 496	Homicide Fire 446	Suicide Poisoning 604	Unintentional suffocation 5997
10	Unintentional fall 24	Unintentional fall 36	Unintentional Struck by or against 20	Unintentional Firearm 26	Unintentional Other land transport 310	Unintentional fall 334	Homicide Cut/pierce 409	Unintentional drowning 481	Adverse effects 398	Suicide Suffocation 583	Undetermined Poisoning 3770

Data from the National Center for Health Statistics, National Vital Statistics System.
MVC, motor vehicle crash; *spec.,* specific.

www.ketabpezeshki.com 66485457-66963820

of public *e*ducation, *e*nforcement of laws, and *e*ngineering modification of hazardous devices and environmental conditions.[19]

INJURY CONTROL IN MEDICAL PRACTICE

Traditionally, physicians have focused on treating the patient after the disease has occurred. As the causes of many diseases have become better understood, education about risk assessment and clinically based prevention has been integrated into medical practice, particularly in infections (immunizations) and cardiovascular disease (smoking cessation). Emergency physicians are incorporating risk assessment, counseling, and referral of patients in high-risk groups for injury, such as those experiencing domestic violence.[3,5] The Joint Commission has emergency department requirements for addressing abused patients.[31]

Emergency care providers are pivotal in the recording and accumulation of data about the injury event, which is useful for surveillance and epidemiologic analysis. Injury control techniques can be incorporated easily into emergency medicine practice as well.[5,32-35] A rational approach to improve injury care in a community (Box 40-2) requires that physicians from a variety of specialties (e.g., emergency physicians, surgeons, pediatricians, and physiatrists) assume specific roles and activities in promoting injury control. This role for emergency physicians in injury control has been advocated by the American College of Emergency Physicians.[36] Documentation of injury information in the medical record, assessment of risk factors in individual patients, counseling and referral, provision of systematized acute trauma care, and public health advocacy are all important.[37-39]

Injury Epidemiology and Documentation

Gathering accurate data is essential to understanding the characteristics of a disease—its endemic populations, cyclic variations, geographic characteristics, and effectiveness of interventions. Consistent and comprehensive data should be gathered across the population of injured patients and used for hypothesis testing,[40,41] hypothesis generation, ongoing monitoring of disease patterns and characteristics,[35,42] and understanding of outcomes of prevention and policy interventions. The goal of injury data collection is to discover who is being injured (host), what is injuring them (vector), and the circumstances surrounding the injury (environment).[43,44]

Until recently, reliable data on the disease of injury were limited to mortality data collected by coroners and medical examiners.[45] The Fatal Analysis Reporting System, a comprehensive data set on all car crash deaths in the United States, was established by the NHTSA in 1975[46] for examination of the epidemiology of motor vehicle crashes.[40]

Because death is uncommon compared with the large number of injured people who receive medical care, conclusions based solely on mortality data are limited.[13,47,48] The advent of trauma registries in the 1980s increased the sample from patients who die to patients admitted to trauma centers. Because these data are skewed toward the most severe injuries, the conclusions based on these data are still limited when generalized to all injured people.[49]

Approximately 93% of injured patients seeking medical care for injury are treated and discharged from the emergency department, and many of them experience significant morbidity resulting in long-term disability and significant cost to society.[13,35,42,47] To capture reliable emergency department data, the CDC developed Data Elements for Emergency Department Systems to define the minimum data set essential for physicians and information systems developers.[50,51] The most crucial data element for the understanding of injury is the *E code,* a system for identifying the cause of injury in a patient's medical record according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).[19] The *E* stands for external cause of injury, such as car crash, fall, or bicycle crash. The cause of injury cannot be extracted from diagnosis codes in medical records. These are N codes—the nature of the injury, such as skull fracture, laceration, or contusion. Because injury control depends on identifying the vector that is causing injuries and not just the resultant injuries, the only way to accomplish this systematically is by documenting the appropriate E code for each patient visit. Several states have mandated documentation of E codes for all emergency department discharges[35,42-44]; however, the completeness of this documentation is variable. The CDC found that 37% of hospital discharges after injuries were missing valid external cause of injury codes.[48]

The greatest barrier to the collection of E codes in the emergency department is inadequate physician documentation to assign accurate E codes retrospectively from the medical record.[47,52,53] The first step in data gathering is complete and legible documentation of the cause of injury in patient medical records. Because injury problems in a community differ greatly from region to region, community-specific injury control efforts can be generated, implemented, and evaluated.[19,41]

E-coded hospital records can provide the *who, what,* and *when* of injury. The question of *where* can be either place of occurrence or place of residence, both of which are important and have implications for planned countermeasures. Hospital records are helpful in determining place of residence of injured patients, which is useful for community education in high-risk neighborhoods. Location-of-injury data are available only from other sources, such as emergency medical services (EMS), police, or other records. These data are more likely to be useful for environmental modification through engineering enhancements, police enforcement, or hazard removal. Linkage of these records to patient visits, either manually for specific research studies or electronically for surveillance, is the next step in gaining a comprehensive understanding of the epidemiology of injury.[54,55] New desktop computer–based geographic information system programs can be used to study injury locations with minimal training and resources. The maps generated by these programs can identify areas with injury clusters to focus prevention efforts on areas with the greatest need.[56,57]

Box 40-2 Injury Control in Emergency Medicine Practice

Clinical Preventive Services

- Document injury information in the medical record
- Ensure that medical records of injury cases contain E codes
- Assess behavioral and comorbid risk factors for future injury
- Provide risk screening, counseling, and referral
- Assess biomechanical risk factors in individual patients
- Use biomechanical risk factors for directed evaluation of injured patients
- Provide systematized acute trauma care

Population Health, Research, and Policy

- Participate in and advocate for inclusive trauma systems
- Direct and advocate for rapid, competent emergency medical services response
- Lead efforts in policy development, implementation, and evaluation
- Lead efforts in educating high-risk groups
- Lead efforts to address and modify the environment to reduce risk of injury
- Collaborate in multidisciplinary research to reduce injury risk and to improve care

www.ketabpezeshki.com 66485457-66963820

Statewide injury data linkages exist in some states and are available for surveillance information[58] and research for unintentional and intentional injuries.[32,41,59] For example, the Crash Outcome Data Evaluation System uses probabilistic linkage to create a database of crash, hospital, EMS, and emergency department information for motor vehicle crashes.[60]

Interest and opportunity to apply injury control principles for medical injuries, also known as *medical errors,* are growing. Medical injuries account for an estimated 50,000 to 98,000 deaths each year in the United States, with hundreds of thousands of nonfatal events occurring in emergency departments, intensive care units, and operating rooms.[45] Emergency physicians can play an important role in use of injury control principles and science to reduce medical injuries.[61-64] Application of injury control principles for the identification of injury patterns and for the development and evaluation of injury prevention strategies has great potential.[63,64]

Risk Factor Assessment

Biomechanical Risk Factors

Biomechanical factors responsible for the injury are challenging to understand, occurring in car crashes or gunshots in less than a 10th of a second. Emergency physicians are not trained in engineering principles and have limited exposure to this "pathophysiology" during training. Ascertaining the forces released on the patient during a blunt injury (car crash or fall) or penetrating injury (gunshot or stabbing) leads to a directed approach to injury management.[65-68] Extensive research has been done with crash dummies, mathematical models, and computer models to understand the mechanical forces applied in injury and human impact tolerance.[15,16] Although used extensively by the engineering community for design of products, such knowledge is also valuable to the emergency physician in guiding evaluation and treatment based on energy transfer, tissue tolerance, and risk of occult injury.[7] Furthermore, as this information becomes more readily available at the time of crash response through automatic crash notification (e.g., General Motor's On-Star system), it will become more important to understand and correctly interpret what it means in terms of potential injuries.[69]

Injury occurs when energy is delivered to the host in levels that exceed tissue and organ tolerance. This energy can be expressed in g-forces. The g-force that results from a motor vehicle crash, for instance, can be expressed with the following formula:

$$g = \Delta v^2/(\text{stopping distance} \times k)$$

where Δv is the change in velocity, *stopping distance* is the distance over which the change in velocity occurs, and k is a constant. The g-force is inversely related to stopping distance. To minimize energy transfer to the body during a motor vehicle collision, one maximizes the stopping distance during the event. The formula shows that doubling the stopping distance reduces the g-force by half, but doubling the speed quadruples the force. Less g-force is applied as velocity is reduced over increasing distance, as the vehicle slows during preimpact braking or deforms during a crash. The same principle underlies engineering features, such as interior padding, collapsible steering columns, water barrel barriers at bridge abutments, and flexible guardrails. All are designed to increase stopping distance, a major principle of automobile and highway safety engineering.[15,16,70]

In the mid-1980s, the air bag was a significant improvement in safety engineering because it resulted in increased occupant stopping distance during a crash, saving nearly 20,000 lives by 2005.[71] Initially, these benefits were confined to frontal crashes, but side curtain air bags have also greatly contributed to the number of lives saved.[72]

As with many new safety countermeasures, there are unintended consequences. First-generation air bags deployed with tremendous force at speeds of 140 to 200 mph over 50 msec.[73] Such forces can be lethal to children in the front passenger seat, especially when unrestrained by safety belts, or seated in rear-facing infant seats.[74,75] A new generation of advanced, less aggressive air bags has been in use since the late 1990s to reduce air bag–associated injuries. It is essential to understand the differences in risk posed by seating position, restraint type and use, and vehicle type when assessing crash victims and to counsel patients properly on safety belt and child restraint use.[40,76] Motor vehicle crashes are the leading cause of death for children older than 24 months in the United States (see Tables 40-4 and Table 40-1). The risk of death in a motor vehicle crash can be reduced by half with the use of age-appropriate child restraints. Every pediatric visit is an opportunity to counsel parents on the safe transport of their children.

In March 2011 the NHTSA revised its recommendations, stating that anyone younger than 13 years should ride only in the rear seats of vehicles.[77] Infant seats should never be positioned in the front seat within range of the air bag. Infants 12 months old or younger should always ride in a rear-facing car seat. Children 1 to 3 years old should ride in a rear-facing seat, and children aged 4 to 7 years should ride in a forward-facing car seat until they outgrow the manufacturer's specifications. A booster seat should be used for children from 8 to 12 years old, allowing for better seat belt positioning and discouraging the child from sitting out of position to see out the windows. If a smaller child must ride in the front passenger seat, that seat should be as far to the rear as possible and a seat belt should always be worn.[78] Federal rules allow for air bags to be disabled if there are circumstances necessitating that small children ride in the front seat and for certain medical conditions.[78] Increasingly, more vehicles are equipped with sensors that turn off the airbag when certain weight thresholds are not met. Physicians caring for short-stature individuals should counsel these patients about the risk of air bag injuries and recommend they sit with at least 10 inches between the sternum and the steering wheel equipped with an air bag. This distance should be measured objectively because people tend not to estimate this distance correctly.[79]

Other safety features have been associated with specific injuries. Automatic "passive" shoulder belts that require manual fastening of the lap portion may result in "submarining" of the torso toward the floorboard when the lap portion is not fastened, while the shoulder belt squeezes the lower rib cage. These devices were associated with liver, spleen, and lung injuries[80] and have been discontinued. However, because cars can be driven over a number of years, it takes many years to completely remove these dangers from the streets. Because automotive safety improves with each new model year, it is important to learn about these safety features and how they might change an injured patient's presentation.

Knowing the contact surface in falls affects diagnostic and therapeutic interventions because soft surfaces increase stopping distance compared with concrete or packed earth.[15,16] Understanding the biomechanical risks of other injuries, such as tissue forces from the ballistics of bullet wounds, can also guide treatment decisions (see Chapter 65).[14,81]

Behavioral and Comorbid Risk Factors

Recognition of patients at high risk of injury affords opportunity for intervention. Counseling a patient about specific ways to avoid injury in the "teachable moment" after injury is more likely to have an effect than diffuse public education.[82] Family or friends can be recruited to enforce the message to patients or to assist patients in modifying their behavior or environment. Other

www.ketabpezeshki.com 66485457-66963820

patient encounters may be used as an opportunity to counsel high-risk patients, such as children at developmental stages that put them at risk for auto versus pedestrian injuries, climbing injuries, or poisoning. It is particularly important to explore the circumstances surrounding injuries to children. A brief review of the injury incident would help physicians and parents identify risks for future injury and opportunities for intervention.[83] Children who come to the emergency department after an injury are likely to be injured again, commonly during falls and motor vehicle crashes.[84] Preschool-age children admitted to the hospital after injury were found to be twice as likely as community controls to have been treated previously in the emergency department for injury and more likely to have an emergency department visit.[85]

Risk factors for intentional injury are complex and involve behavioral, social, and environmental factors, but risk factors for all types of injury include male sex, low income, illicit drug involvement, previous arrest, and young age.[85-87] In studies using psychosocial inventories, recidivists are more likely to have a low sense of autonomy, to have low levels of spirituality, and to have been a crime victim in the past.[85] The most obvious risk factor for future violent injury is prior violent injury. A history of prior significant injury is a strong predictor of injury recidivism, with 10 times the risk of patients with no prior trauma.[87,88] Emergency departments should have protocols in place for the detection and referral of patients likely to be victims of injury in the future, including victims of domestic violence,[3] and for children younger than 18 years injured intentionally, regardless of the age of the perpetrator. In many states, there are mandatory reporting laws for gunshot wounds, stabbings, and other violent acts.[89,90] Interventions provided to injured patients in the health care setting can reduce injury recidivism.[86,91]

In the case of motor vehicle injury, the three behavioral risk factors most likely to result in future injury are speeding, seat belt nonuse, and driving after drinking alcohol. Giving patients the necessary data for them to make an accurate self-assessment about their risks is the essence of patient behavioral intervention.[92] These messages should be part of every injury patient's encounter, when feasible. Particularly important in this context is the screening and referral for alcohol use disorders (AUDs). Alcohol-related crash injury is a national epidemic in the United States, with 32% of all motor vehicle traffic fatalities involving an alcohol-impaired driver.[93] Reductions in alcohol-related deaths as a result of more stringent laws, more vigilant public education, and a societal shift toward the condemnation of driving while impaired have not had significant effects on people with AUD. Of patients seen in the emergency department after a motor vehicle crash, 17 to 20% meet criteria for AUD.[94,95] Patients with AUD have higher rates of illness and motor vehicle crash injury than the rest of the population, and patients with AUD are more likely to drive after drinking.[90]

Emergency physicians have a unique role to play in the identification of high-risk patients. In particular, patients with AUD should be detected and referred for formal evaluation and treatment. A structured approach to detect and treat the disease should be brief and effective if it is to be used in a busy emergency department. Screening techniques validated in the emergency department and methods of brief intervention have been thoroughly described.[90]

Successful treatment of AUD leads to reduction in alcohol consumption and binge drinking and consequently fewer impaired driving episodes, thus leading to a reduction in alcohol-related crash injuries. Being treated for injury in the emergency department may be an important motivational opportunity to reduce drinking and presents a "teachable moment."[90,95-97] The American College of Surgeons Committee on Trauma recommends that all trauma centers screen for alcohol and provide interventions as a "part of routine trauma care."[98]

Acute Care

The acute care component of injury control involves trauma system planning, medical direction of out-of-hospital care, and provision of systematized resuscitative care after the injury, whether it occurs close to or far from a trauma center.[99] A crucial part of injury assessment is identification of local resources for management of the injured patient. Algorithms and agreements to transfer the patient to definitive care should be established to avoid secondary injury from delays in transfer or inappropriate care.[100] Areas with ready availability of trauma physician specialists should have clear protocols in place for use of those resources.[101] For cost-effective care, in-hospital triage criteria should be developed to avoid unneeded overuse of trauma surgery teams.[39,102,103]

Trauma systems can be created that recognize and complement the exigencies of budgetary, geographic, and political constraints that are specific to states or regions, but such flexibility is often impossible when a trauma system is based only on the hospitals that seek trauma center verification or designation.[102]

An *inclusive* trauma care system uses all acute care and rehabilitation facilities that treat injured patients and deals with the issues of community access, EMS dispatch and response, triage, transport and transfer protocols, training, communications, availability of definitive care and rehabilitation, and a data collection system. In an inclusive trauma care system, every injured patient (not just patients who live near trauma centers) is cared for by a part of the system, and every hospital has a role according to the services it can offer, whether it is the expeditious transfer of patients, the treatment of patients without neurotrauma, or the definitive care provided at a trauma center. The system should be designed to monitor patient outcomes and system performance.[104] Level 1 trauma centers improve severe trauma patient outcomes by 25%, demonstrating the value of an inclusive trauma care system.[105]

Out-of-hospital emergency care is an integral part of injury control.[38] EMS response, triage, and treatment are the first critical steps in injury control, and triage protocols should be well established to avoid unnecessary delays in definitive care.[100] The Field Triage Decision Scheme, first developed by the American College of Surgeons and recently updated in collaboration with the CDC, is designed to guide EMS providers in identifying patients who need the resources of a trauma center.[106] EMS providers have a unique vantage point from which to help the trauma physician assess a patient's risk factors for immediate injuries and the risk of injury recurrence. EMS providers can observe the environment for information about mechanism of injury. Accurate reporting of vehicle damage and other environmental circumstances associated with the injury event elucidates important biomechanical risk factors.[107] EMS providers are also involved in primary injury prevention through injury risk identification, documentation of injury data, and safety education programs.[38]

Emergency Medicine Leadership: Advocacy of Public Policy

Passing and enforcing laws are much more effective than education for increasing seat belt and helmet use.[8,29] Emergency physicians and trauma physicians can provide lawmakers with factual information and the perspective of firsthand experience of the effects of injury. Effective prevention interventions and policies with documented cost savings are more likely to occur when sound, scientific studies are made available to policy makers.[108] Most public health regulations and traffic safety laws are under the jurisdiction of state legislatures and local governments. State and local policy makers are generally much more accessible to physicians and in need of local expertise than policy makers at the

www.ketabpezeshki.com 66485457-66963820

federal level. Emergency physicians need to accept an important advocacy role for reducing injuries and value injury control as a professional activity.[6,109,110]

Community education aimed at people not yet injured may be effective when provided by an emergency physician. Emergency physicians are in a leadership role to deliver the message to school systems, local housing authorities, law enforcement, community service organizations, and policy makers.[33,34] Emergency physicians can be effective spokespersons for injury prevention through the news media, especially after a newsworthy event, and can reframe the event from one of personal blame and behavioral failure to a broader biosocial issue that requires environmental and policy interventions.[111]

Public policy also determines where resources are used in a community. Environmental modifications and elimination of hazards are effective but often expensive. In contrast to education and law enforcement, environmental modifications are *passive countermeasures* that do not require any action by people. Such modifications might be lengthening a "walk" signal at a busy intersection to reduce auto-pedestrian injuries, especially in the elderly[112]; increasing lighting in areas where personal assaults occur[18]; or changing a playground surface from hard-packed earth to wood mulch.[113] The need for such modifications may be known only if the physician is alert to the circumstances by asking "How did this happen?" and documenting the location and circumstances of injuries seen in daily practice.

KEY CONCEPTS

- Injury is the second most costly disease to society and the most serious disease of young people.[114]
- Through interdisciplinary research, a better understanding of the epidemiology and biomechanics of injury will lead to new control strategies. These strategies would complement advances in acute care and trauma systems, which improve care to the patient after the injury has occurred.
- Emergency physicians can incorporate injury control techniques into daily practice through clinical prevention services.
- Increasingly, emergency physicians are leaders in addressing and preventing injuries and complex biosocial problems.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Niska RW, Bhuiya F, Xu J: National Hospital Ambulatory Medical Care Survey: 2007 emergency department summary. *Natl Health Stat Report* 2010; 6:1-31.
2. National Center for Injury Prevention and Control: *CDC Injury Fact Book*. Atlanta, Ga: Centers for Disease Control and Prevention; 2006.
3. Krasnoff M, Moscati R: Domestic violence screening and referral can be effective. *Ann Emerg Med* 2002; 40:485.
4. Maas Cortes L, Hargarten SW: Preventive care in the emergency department: A systematic literature review on emergency department-based interventions that address smoke detectors in the home. *Acad Emerg Med* 2001; 8:925.
5. Stiffler KA, Gerson LW: Health promotion and disease prevention in the emergency department. *Emerg Med Clin North Am* 2006; 24:849.
6. Gruen RL, Pearson SD, Brennan TA: Physician-citizens—public roles and professional obligations. *JAMA* 2004; 291:94.
7. Martinez R: Injury control: A primer for physicians. *Ann Emerg Med* 1990; 19:72.
8. Robertson L: *Injury Epidemiology: Research and Control Strategies*, 2nd ed. New York: Oxford University Press; 1998.
9. Rosenberg M, Fenley M: *Violence in America: A Public Health Approach*. New York: Oxford University Press; 1991.
10. National Committee for Injury Prevention and Control: *Injury Prevention: Meeting the Challenge*. Oxford: Oxford University Press; 1989.
11. Mohan D: *Injury Control and Safety Promotion: Ethics, Science and Practice*. New York: Taylor & Francis; 2000.
12. Haddon W Jr: A logical framework for categorizing highway safety phenomena and activity. *J Trauma* 1972; 12:193.
13. Committee on Trauma Research, Commission on Life Sciences, National Research Council, Institute of Medicine: *Injury in America: A Continuing Public Health Problem*. Washington, DC: National Academy Press; 1985.
14. Yoganandan N, Pintar FA, Kumaresan S, Maiman DJ, Hargarten SW: Dynamic analysis of penetrating trauma. *J Trauma* 1997; 42:266.
15. Whiting W, Zernicke R: *Biomechanics of Musculoskeletal Injury*. Champaign, Ill: Human Kinetics; 1998.
16. Nahum A, Melvin J: *Accidental Injury: Biomechanics and Prevention*, 2nd ed. New York: Springer-Verlag; 2001.
17. Carbone PS, Clemens CJ, Ball TM: Effectiveness of gun-safety counseling and a gun lock giveaway in a Hispanic community. *Arch Pediatr Adolesc Med* 2005; 159:1049.
18. Mair JS, Mair M: Violence prevention and control through environmental modifications. *Annu Rev Public Health* 2003; 24:209.
19. Christoffel T, Gallagher S: *Injury Prevention and Public Health*. Gaithersburg, Md: Aspen; 1999.
20. Haddon W Jr: On the escape of tigers: An ecologic note. *Am J Public Health Nations Health* 1970; 60:2229.
21. Nader R: *Unsafe at Any Speed: The Designed-In Dangers of the American Automobile*. New York: Grossman; 1965.
22. Stapp JP, Gell CF: Human exposure to linear declarative force in the backward and forward facing seated positions. *Mil Surg* 1951; 109:106.
23. Lambrecht C, Hargarten S: Hunting-related injuries and deaths in Montana: The scope of the problem and a framework for prevention. *J Wilderness Med* 1993; 4:175.
24. *National Center for Injury Prevention and Control: Funded Injury Control Research Centers (ICRCs)*, 2010. Available at www.cdc.gov/ncipc/profiles/icrcs. Accessed April 12, 2011.
25. National Center for Injury Prevention and Control: *CDC Acute Injury Care Research Agenda: Guiding Research for the Future*. Atlanta, Ga: Centers for Disease Control and Prevention; 2005.
26. National Center for Injury Prevention and Control: *CDC's Injury Response Activities: 2006-2007*. Atlanta, Ga: Centers for Disease Control and Prevention; 2007.
27. National Center for Injury Prevention and Control: *CDC Injury Research Agenda, 2009-2018*. Atlanta, Ga: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2009. Available at http://www.cdc.gov/injury/researchagenda. Accessed October 16, 2012.
28. Karlson T, Hargarten S: *Reducing Injury and Death: A Public Health Sourcebook on Guns*. New Brunswick, NJ: Rutgers University Press; 1997.
29. Chistoffel T, Teret S: *Protecting the Public: Legal Issues in Injury Prevention*. New York: Oxford University Press; 1993.
30. Rivara FP, Cummings P, Koepsell TD, Grossman DC: *Injury Control: A Guide to Research and Program Evaluation*. Cambridge, UK: Cambridge University Press; 2001.
31. Joint Commission on Accreditation of Healthcare Organizations: *Accreditation Manual for Hospitals,* vol. 1: *Standards*. Oakbrook Terrace, Ill: Joint Commission on Accreditation of Healthcare Organizations; 1992.
32. Anglin D, Hutson HR, Kyriacou DN: Emergency medicine residents' perspectives on injury prevention. *Ann Emerg Med* 1996; 28:31.
33. Hargarten SW, Karlson T: Injury control: A crucial aspect of emergency medicine. *Emerg Med Clin North Am* 1993; 11:255.
34. Bernstein E, Roth PB, Yeh C, Lefkowits DJ: The emergency physician's role in injury prevention. *Pediatr Emerg Care* 1988; 4:207.
35. Ribbeck BM, Runge JW, Thomason MH, Baker JW: Injury surveillance: A method for recording E codes for injured emergency department patients. *Ann Emerg Med* 1992; 21:37.
36. American College of Emergency Physicians: *Role of the Emergency Physician in Injury Prevention and Control for Adult and Pediatric Patients*, 2012. Available at www.acep.org/Content.aspx?id=29820. Accessed April 12, 2011.
37. Rivara FP, Thompson DC, Patterson MQ, Thompson RS: Prevention of bicycle-related injuries: Helmets, education, and legislation. *Annu Rev Public Health* 1998; 19:293
38. Garrison HG, et al: The role of emergency medical services in primary injury prevention. Consensus workshop, Arlington, Virginia, August 25-26, 1995. *Ann Emerg Med* 1997; 30:84.
39. Mann NC, Mullins RJ: Research recommendations and proposed action items to facilitate trauma system implementation and evaluation. *J Trauma* 1999; 47:S75.
40. Cummings P, Rivara FP: Car occupant death according to the restraint use of other occupants: A matched cohort study. *JAMA* 2004; 291:343.
41. Runge JW: Linking data for injury control research. *Ann Emerg Med* 2000; 35:613.
42. Wadman MC, Muelleman RL, Coto JA, Kellermann AL: The pyramid of injury: Using ecodes to accurately describe the burden of injury. *Ann Emerg Med* 2003; 42:468.
43. Sniezek JE, Finklea JF, Graitcer PL: Injury coding and hospital discharge data. *JAMA* 1989; 262:2270.
44. Muelleman RL, Hansen K, Sears W: Decoding the E-code. *Nebr Med J* 1993; 78:184.
45. Institute of Medicine: *To Err Is Human: Building a Safer Health System*. Washington, DC: National Academy Press; 1999.
46. National Highway Traffic Safety Administration, Office of Statistics and Analysis: *Fatal Accident Reporting System, 1975 Annual Report*. Washington, DC: U.S. Department of Transportation; 1976.
47. Rice D, et al: *Cost of Injury in the United States: A Report to Congress*. San Francisco: Institute for Health & Aging, University of California, and Injury Prevention Center, Johns Hopkins University; 1989.
48. Bergen G, Chen LH, Warner M, Fingerhut LA: *Injury in the United States: 2007 Chartbook*. Hyattsville, Md: National Center for Health Statistics; 2008.
49. Waller J: *Injury Control: A Guide to the Causes and Prevention of Trauma*. Lanham, Md: Lexington Books; 1985.
50. Centers for Disease Control and Prevention: *Data Elements for Emergency Department Systems (DEEDS)*. Washington, DC: U.S. Department of Health and Human Services; 1996.
51. Hirshon JM: The rationale for developing public health surveillance systems based on emergency department data. *Acad Emerg Med* 2000; 7:1428.
52. Schwartz RJ, Nightingale BS, Boisoneau D, Jacobs LM: Accuracy of E-codes assigned to emergency department records. *Acad Emerg Med* 1995; 2:615.
53. Sheane K, Wright A, Bierlein LA: *A Comprehensive Statewide Injury Surveillance System: What Are the Issues?* Tempe, Ariz: Morrison Institute for Public Policy; 1995.
54. Hargarten SW, Karlson TA, O'Brien M, Hancock J, Quebbeman E: Characteristics of firearms involved in fatalities. *JAMA* 1996; 275:42.
55. Johnson S, Walker J: *The Crash Outcome Evaluation System (CODES)*. DOT HS 808 338. Washington, DC: Department of Transportation, National Highway Traffic Safety Administration; 1996.
56. Weiner EJ, Tepas JJ 3rd: Application of electronic surveillance and global information system mapping to track the epidemiology of pediatric pedestrian injury. *J Trauma* 2009; 66(3 Suppl):S10-S16.
57. Lerner EB, Billittier AJ 4th, Sikora J, Moscati RM: Use of a geographic information system to determine appropriate means of trauma patient transport. *Acad Emerg Med* 1999; 6:1127.
58. National Violent Injury Statistics System Work Group: *Violent Death Reporting System Training Manual*. Milwaukee, Wis: Firearm Injury Center and National Violent Injury Statistics System; 2002.
59. Muelleman RL, Watson WA, Land GH, Davis JD, Hoskins BS: Missouri's emergency department E-code data reporting: A new level

www.ketabpezeshki.com 66485457-66963820

of data resource for injury prevention and control. *J Public Health Manag Pract* 1997; 3:8.
60. National Center for Statistics and Analysis: *Crash Outcome Data Evaluation System (CODES)*. Available at http://www-nrd.nhtsa.dot.gov/Pubs/808-338.pdf. Accessed October 16, 2012.
61. Adams JG, Bohan JS: System contributions to error. *Acad Emerg Med* 2000; 7:1189.
62. Kyriacou DN, Coben JH: Errors in emergency medicine: Research strategies. *Acad Emerg Med* 2000; 7:1201.
63. Brasel KJ, Layde PM, Hargarten S: Evaluation of error in medicine: Application of a public health model. *Acad Emerg Med* 2000; 7:1298.
64. Layde PM, et al: Patient safety efforts should focus on medical injuries. *JAMA* 2002; 287:1993.
65. Norcross ED, et al: Application of American College of Surgeons' field triage guidelines by pre-hospital personnel. *J Am Coll Surg* 1995; 181:539.
66. Ryan GA, Taylor GW, Moore VM, Dolinis J: Neck strain in car occupants: Injury status after 6 months and crash-related factors. *Injury* 1994; 25:533.
67. Velmahos GC, et al: Radiographic cervical spine evaluation in the alert asymptomatic blunt trauma victim: Much ado about nothing. *J Trauma* 1996; 40:768.
68. Ono K, Kanno M: Influences of the physical parameters on the risk to neck injuries in low impact speed rear-end collisions. *Accid Anal Prev* 1996; 28:493.
69. National Center for Injury Prevention and Control: *Recommendations from the Expert Panel: Advanced Automatic Collision Notification and Triage of the Injured Patient*. Atlanta, Ga: Centers for Disease Control and Prevention; 2008.
70. Peterson TD, Tilman Jolly B, Runge JW, Hunt RC: Motor vehicle safety: Current concepts and challenges for emergency physicians. *Ann Emerg Med* 1999; 34:384.
71. U.S. Department of Transportation/National Highway Traffic Safety Administration: *Traffic Safety Facts* 2005 Early Edition, Dec. 21, 2006. Available at http://www-nrd.nhtsa.dot.gov/Pubs/TSF05DataSummary.pdf. Accessed October 16, 2012.
72. Insurance Institute for Highway Safety: Surviving Side Crashes. *Status Report* 2006; 41:1-3, 7. Available at http://www.iihs.org/externaldata/srdata/docs/sr4108.pdf.
73. National Highway Traffic Safety Administration: Update: Fatal air bag-related injuries to children—United States, 1993-1996. *MMWR Morb Mortal Wkly Rep* 1996; 45:1073.
74. Arbogast KB, Durbin DR, Kallan MJ, Winston FK: Effect of vehicle type on the performance of second generation air bags for child occupants. *Annu Proc Assoc Adv Automot Med* 2003; 47:85.
75. Moran SG, McGwin G Jr, Metzger JS, Alonso JE, Rue LW 3rd: Relationship between age and lower extremity fractures in frontal motor vehicle collisions. *J Trauma* 2003; 54:261.
76. Durbin DR, Elliott MR, Winston FK: Belt-positioning booster seats and reduction in risk of injury among children in vehicle crashes. *JAMA* 2003; 289:2835.
77. National Highway Traffic Safety Administration: *Car Seat Recommendations for Children*, March 2011. Available at www.nhtsa.gov/DOT/NHTSA/Traffic%20Injury%20Control/Articles/Associated%20Files/4StepsFlyer.pdf. Accessed April 15, 2011.
78. Jolly BT: Commentary: Air bags—the changing landscape. *Ann Emerg Med* 31:783, 1998.
79. Segui-Gomez M, Levy J, Graham JD: Airbag safety and the distance of the driver from the steering wheel. *N Engl J Med* 1998; 339:132.
80. Augenstein J, et al: *Chest and Abdominal Injuries Suffered by Restraint Occupants*. Document No. 950657. Detroit, Mich: Society of Automotive Engineers; 1995.
81. Pryor JP, Reilly PM, Dabrowski GP, Grossman MD, Schwab CW: Nonoperative management of abdominal gunshot wounds. *Ann Emerg Med* 2004; 43:344.
82. Hazinski MF, Francescutti LH, Lapidus GD, Micik S, Rivara FP: Pediatric injury prevention. *Ann Emerg Med* 22:456, 1993.
83. Mace SE, et al: Injury prevention and control in children. *Ann Emerg Med* 2001; 38:405.
84. McCaig LF, Burt CW: Poisoning-related visits to emergency departments in the United States, 1993-1996. *J Toxicol Clin Toxicol* 1999; 37:817.
85. Redeker NS, Smeltzer SC, Kirkpatrick J, Parchment S: Risk factors of adolescent and young adult trauma victims. *Am J Crit Care* 1995; 4:370.
86. Cooper C, Eslinger D, Nash D, al-Zawahri J, Stolley P: Repeat victims of violence: Report of a large concurrent case-control study. *Arch Surg* 2000; 135:837.
87. Kaufmann CR, Branas CC, Brawley ML: A population-based study of trauma recidivism. *J Trauma* 1998; 45:325.
88. Sayfan J, Berlin Y: Previous trauma as a risk factor for recurrent trauma in rural northern Israel. *J Trauma* 1997; 43:123.
89. Hargarten SW, Waeckerle JF: Docs and cops: A collaborating or colliding partnership? *Ann Emerg Med* 2001; 38:438.
90. National Highway Traffic Safety Administration: *Identification and Referral of Impaired Drivers through Emergency Department Protocols*. DOT HS 809 412. Washington, DC: U.S. Department of Transportation; 2002.
91. Cooper C, Eslinger DM, Stolley PD: Hospital-based violence intervention programs work. *J Trauma* 2006; 61:534.
92. Miller W, Rollnick S: *Motivational Interviewing: Preparing People to Change Addictive Behavior*. New York: Guilford; 1991.
93. NHTSA's National Center for Statistics and Analysis: *Traffic Safety Facts: 2009 Data: Alcohol-Impaired Driving*. Available at www-nrd.nhtsa.dot.gov/Pubs/811385.PDF. Accessed April 14, 2011.
94. Cherpitel CJ: Alcohol consumption among emergency room patients: Comparison of county/community hospitals and an HMO. *J Stud Alcohol* 1993; 54:432.
95. Becker B, et al: Alcohol use among subcritically injured emergency department patients. *Acad Emerg Med* 1995; 2:784.
96. Hungerford D, Pollock D, eds. *Alcohol Problems among Emergency Department Patients: Proceedings of a Research Conference on Identification and Intervention*. Atlanta, Ga: National Center for Injury Prevention and Control, Centers for Disease Control and Prevention; 2002.
97. Hungerford DW, Pollock DA: Emergency department services for patients with alcohol problems: Research directions. *Acad Emerg Med* 2003; 10:79.
98. American College of Surgeons, Committee on Trauma: *Alcohol Screening and Brief Intervention (SBI) for Trauma Patients. COT Quick Guide.* Available at www.facs.org/trauma/publications/sbirtguide.pdf. Accessed April 13, 2011.
99. Mullins RJ, Mann NC: Population-based research assessing the effectiveness of trauma systems. *J Trauma* 1999; 47:S59.
100. Mullins RJ, et al: Survival of seriously injured patients first treated in rural hospitals. *J Trauma* 2002; 52:1019.
101. Shatney CH, Sensaki K: Trauma team activation for "mechanism of injury" blunt trauma victims: Time for a change? *J Trauma* 37:275, 1994.
102. MacKenzie EJ, et al: National inventory of hospital trauma centers. *JAMA* 2003; 289:1515.
103. Eastman AB: Blood in our streets: The status and evolution of trauma care systems. *Arch Surg* 1992; 127:677.
104. Trunkey DD: Trauma centers and trauma systems. *JAMA* 2003; 289:1566.
105. Mackenzie EJ, et al: A national evaluation of the effect of trauma-center care on mortality. *N Engl J Med* 2006; 354:366.
106. Sasser SM, et al. Guidelines for field triage of injured patients. Recommendations of the National Expert Panel on Field Triage. *MMWR Recomm Rep* 2009; 58(RR-1):1-35.
107. Augenstein JS, et al: Occult abdominal injuries to airbag-protected crash victims: A challenge to trauma systems. *J Trauma* 1995; 38:502.
108. Thacker SB, et al: Assessing prevention effectiveness using data to drive program decisions. *Public Health Rep* 1994; 109:187.
109. Medical professionalism in the new millennium: A physicians' charter. *Lancet* 2002; 359:520.
110. Medical professionalism in the new millennium: A physicians' charter. *Ann Intern Med* 2002; 136:243.
111. Woodruff K: Physicians as advocates: Promoting healthy public policy via the media. *Cal Physician* 1994; 11:48.
112. Retting RA, Ferguson SA, McCartt AT: A review of evidence-based traffic engineering measures designed to reduce pedestrian-motor vehicle crashes. *Am J Public Health* 2003; 93:1456.
113. Lewis LM, Naunheim R, Standeven J, Naunheim KS: Quantitation of impact attenuation of different playground surfaces under various environmental conditions using a tri-axial accelerometer. *J Trauma* 1993; 35:932.
114. Soni A: *The Five Most Costly Conditions, 1996 and 2006: Estimates for the U.S. Civilian Noninstitutionalized Population*. Statistical Brief #248. July 2009. Agency for Healthcare Research and Quality. Available at www.meps.ahrq.gov/mepsweb/data_files/publications/st248/stat248.pdf. Accessed April 13, 2011.
115. Haddon W Jr: Advances in the epidemiology of injuries as a basis for public policy. *Public Health Rep* 1980; 95:411

www.ketabpezeshki.com 66485457-66963820

Section Two

SYSTEM INJURIES

Chapter 41

Head Injury

William G. Heegaard and Michelle H. Biros

PERSPECTIVE

Epidemiology

The devastating consequences of head injury have been recorded since ancient times. Early neurosurgical records were primarily observational, with very few suggestions for treatment (Fig. 41-1). Despite centuries of investigation and the development of new and better intensive care, we still have not discovered effective therapies that can be applied after the injury to reverse most pathologic aspects of traumatic brain injury (TBI).

In 1996, Congress approved the Traumatic Brain Injury Act (Public Law 104-166), which charged the Centers for Disease Control and Prevention (CDC) with "determining the incidence and prevalence of traumatic brain injury in all age groups in the general population of the United States."[1]

Each year, an estimated 1.7 million people sustain head injury in the United States.[1]

Of these, 1.36 million (1.4% of all emergency department [ED] visits) undergo emergency evaluation, including approximately 470,000 children younger than age 14 years. TBI accounts for 15.1% of all injury-related hospitalizations in the United States. Overall, 80% sustain minor head trauma (Glasgow Coma Scale [GCS] score of 14 or 15), 10% have moderate head injuries (GCS score of 9-13), and 10% have severe head injuries (GCS score of 8). Almost 20% of all head-injured patients are hospitalized, and approximately 52,000 patients die each year from TBI (Table 41-1).

The leading causes of head injury in the civilian population are falls (43.7%) and motor vehicle collisions (MVCs) (21.5%).[1] TBI caused by blasts has been called the signature injury of the wars in Iraq and Afghanistan: TBI of any severity is estimated to affect as many as 10 to 20% of wartime service members.[2-4] Head injury is the leading cause of traumatic death in patients younger than 25 years and accounts for nearly one third of all trauma deaths.[1] Head injury from child abuse is common.[5] New data suggest that with children younger than 12 months of age, TBIs and/or fractures attributable to abuse occurred in 1 of 2000 infants.[6] The CDC estimates that there are at least 5.3 million Americans currently experiencing some degree of disability as a result of TBI. As veterans return to the United States, the number of patients experiencing the consequences of TBI has increased markedly.

These facts confirm that TBI is a major public health problem. The emergency physician sees patients with head injuries of different clinical severity caused by a variety of mechanisms. External physical signs of head trauma only confirm that injury has occurred; they are not always present in the patient who has sustained serious underlying TBI. The ultimate survival and neurologic outcome of the head trauma patient depend on the extent of TBI occurring at the time of injury, alone or in combination with secondary systemic insults, such as hypotension and hypoxia, that worsen the resulting neurochemical and neuroanatomic pathophysiology. Research aimed at reducing or preventing the neurologic consequences of head trauma is ongoing, but currently the clinical outcome after TBI depends on the circumstances of injury and early clinical management aimed at reducing the occurrence of secondary brain insults. No effective intervention has been found to reverse the pathologic events initiated by the traumatic event.

PRINCIPLES OF DISEASE

Anatomy and Physiology

Scalp and Cranium

The scalp consists of five tissue layers. The dermis is the outermost layer and is among the thickest layers of skin on the body. The underlying subcutaneous tissue contains the hair follicles and the rich blood supply of the scalp. The large blood vessels of the scalp do not fully constrict if they are lacerated and can be the source of significant blood loss. The middle scalp layer is the galea, which is made of tough fascial tissue. It contains the occipitofrontalis and temporoparietalis muscles, which move the scalp backward and forward, elevate the eyebrows, and wrinkle the forehead. Under the galea is a loose areolar tissue layer. Because the areolar attachments to the rest of the scalp are loose, scalp avulsions frequently occur through this layer. This is also the site for development of subgaleal hematomas, which can become quite large because blood easily dissects through the loose areolar tissue. The deepest layer of the scalp, the pericranium, is firmly adhered to the skull.

The skull comprises the frontal, ethmoid, sphenoid, and occipital bones and two parietal and two temporal bones. The unique layered architecture of the bones of the skull enhances its strength. Each bone consists of solid inner and outer layers separated by a layer of cancellous bone tissue (the diploë). In adults the bones of the skull average 2 to 6 mm in thickness; the bones in the temporal region are usually the thinnest of the skull.[7] The cranial bones form a smooth outer surface of the skull, but within the cranial vault are many bone protrusions and ridges. Contrecoup injuries and contusions far from the site of head impact often occur as the accelerating brain strikes against these uneven bone surfaces.

The inner aspect of the skull is lined with the periosteal dura, which is a thick connective tissue layer that adheres closely to the bone surface. The inner meningeal layer of the dura is the outermost covering of the brain. This dural membrane reflects back on itself to make folds within the cranial space. These folds serve to

www.ketabpezeshki.com 66485457-66963820

protect and compartmentalize different components of the brain. The midline falx cerebri separates the two cerebral hemispheres from each other. The tentorium cerebelli partitions the cerebellum and brainstem from the cerebral hemispheres. The U-shaped free margin of this dural fold is important in the pathology of the transtentorial herniation syndromes that can complicate severe head injury. Within the margins of the dural reflections, the two dural layers separate to form large dural venous sinuses. Injury to the dural sinuses is associated with significant morbidity and mortality because of the potential for uncontrolled hemorrhage and the difficulty in repairing these structures.

The cranial vault is rigid and nonexpandable, with an average volume in adults of approximately 1900 mL.[8] Cranial contents exit or enter the skull through many foramina. The largest, the foramen magnum, is the site of exit of the brainstem and spinal cord from the cranium.

Figure 41-1. Title page of a 16th-century neurosurgical textbook. (From Fringer S: Origins of Science. New York, Oxford University Press, 2001, p 422.)

Brain and Cerebrospinal Fluid

The brain is a semisolid structure that weighs approximately 1400 g (3 lb) and occupies approximately 80% of the cranial vault. It is covered by three distinct membranes: the meningeal dura, the arachnoid layer, and the pia. The location of traumatic hematomas relative to these membranes defines the pathologic condition and determines the consequences of the injury.

The major divisions of the brain are the cerebrum, cerebellum, and brainstem. Each lobe of the cerebrum is the source of highly specific neurobehavior, and specific injury to each lobe can disrupt normal behavior patterns. The brain is suspended in the cerebrospinal fluid (CSF), which provides some buffering for the brain during trauma. CSF is produced by the choroid plexus, located primarily in the lateral ventricles of the brain. CSF passes from the ventricular system into the subarachnoid space that surrounds the brain and spinal cord. CSF provides a fluid pathway for delivery of substances to brain cells, elimination of the products of brain metabolism, and transport of peptide hormones and hormone-stimulating proteins from their site of production within the central nervous system (CNS) to their peripheral sites of action.

The normal pressure exerted by the CSF is 65 to 195 mm H_2O or 5 to 15 mm Hg. Blood within the ventricles can obstruct the flow of CSF, causing a traumatic hydrocephalus. Brain injury and its complications can also alter the pH of CSF. Because the pH of CSF influences pulmonary drive and cerebral blood flow (CBF), any alteration can produce detrimental neurophysiologic consequences.

Cerebral Hemodynamics

Blood-Brain Barrier. The blood-brain barrier (BBB) maintains the microenvironment of the brain tissue. Extracellular ion and neurotransmitter concentrations are regulated by movement across this barrier. When the BBB is intact, the ability of neuroactive drugs to penetrate into the brain tissue usually depends on their lipid solubility. Post-traumatic cerebral edema and possibly the biomechanics of the injury itself can cause a prolonged disruption of the BBB for up to several hours after trauma.[9,10] Prolonged disruption of the BBB contributes to the development of post-traumatic vasogenic cerebral edema.

The brain has an extremely high metabolic rate, using approximately 20% of the entire oxygen volume consumed by the body. To provide for its high metabolic demands, the brain requires approximately 15% of the total cardiac output. Optimal regional CBF is maintained by the ability of cerebral vessels to alter their diameter in response to changing physiologic conditions.[10] Hypertension, alkalosis, and hypocarbia promote cerebral vasoconstriction; hypotension, acidosis, and hypercarbia cause cerebral vasodilation. In the normal brain, CBF is maintained at constant levels with a mean arterial pressure (MAP) of 60 to

Table 41-1 Traumatic Brain Injury (TBI) as a Portion of All Injuries and Emergency Department (ED) Visits

		All Injuries		*TBIs*		
	ALL VISITS	NUMBER	PERCENT OF ALL VISITS	NUMBER	PERCENT OF ALL INJURIES	PERCENT OF ALL VISITS
ED visits*	96,839,411	28,697,028	29.6	1,364,797	4.8	1.4
Hospitalizations†	36,693,646	1,826,548	5.0	275,146	15.1	0.7
Deaths	2,432,714	169,055	6.9	51,538‡	30.5	2.1
Total	135,965,771	30,692,631	22.6	1,691,481	5.5	1.2

(Adapted from Faul M XL, Wald MM, Coronado VG: Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002-2006. Atlanta, Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, 2010, pp 1-74.)
*Persons who were hospitalized, died, or were transferred to another facility were excluded.
†In-hospital deaths and patients who transferred from another hospital were excluded.
‡128 mortality records (from 2002-2006) were omitted because of missing age information.

www.ketabpezeshki.com 66485457-66963820

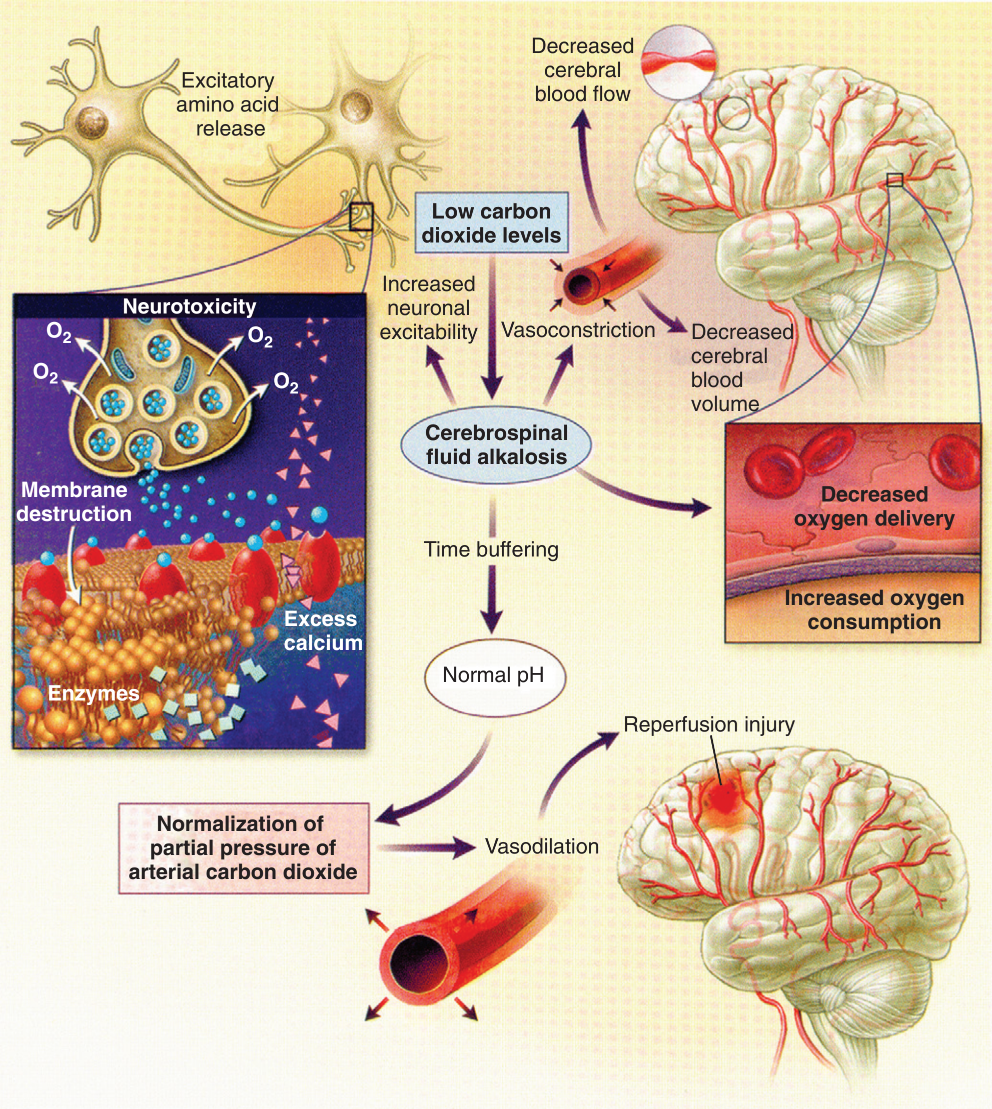


Figure 41-2. Neurologic effects of hypocapnia. Systemic hypocapnia results in cerebrospinal fluid alkalosis, which decreases cerebral blood flow, cerebral oxygen delivery, and, to a lesser extent, cerebral blood volume. The reduction in intracranial pressure may be lifesaving in patients in whom the pressure is severely elevated. However, hypocapnia-induced brain ischemia may occur because of vasoconstriction (impairing cerebral perfusion), reduced oxygen release from hemoglobin, and increased neuronal excitability, with the possible release of excitotoxins such as glutamate. Over time, cerebrospinal fluid pH and hence cerebral blood flow gradually return to normal. Subsequent normalization of the partial pressure of arterial carbon dioxide can then result in cerebral hyperemia, causing reperfusion injury to previously ischemic brain regions. (From Laffey JG, Kavanagh BP: Hypocapnia. N Engl J Med 347:43, 2002.)

150 mm Hg. This is referred to as *autoregulation*. Outside this range, the CBF varies linearly with MAP.

Cerebral vasoactivity is very sensitive to changes in systemic carbon dioxide and oxygen partial pressures (P_{CO_2} and P_{O_2}, respectively). The response to changes in P_{CO_2} is nearly linear between P_{CO_2} values of 20 and 60 mm Hg.[11] In this range, lowering P_{CO_2} by as little as 1 mm Hg decreases the diameter of cerebral vessels by 2 or 3%, which corresponds to an overall change in CBF of 1.1 mL per 100 g of tissue per minute. The physiologic response of blood vessels to P_{CO_2} is the rationale for the acute use of brief hyperventilation to control increased intracranial pressure (ICP) after head injury. As P_{CO_2} decreases with hyperventilation, cerebral vasoconstriction occurs. As a result, the volume of blood per unit area of brain tissue decreases. This decrease (even if small) may buffer the effects of increasing edema or an expanding hematoma within the rigid cranial vault. The vasoconstriction produced by extreme changes in P_{CO_2} (20 mm Hg or less) can be so pronounced that some areas of brain experience ischemia; subsequently, tissue hypoxia can occur.[10,12,13] Therefore hyperventilation is controlled and monitored, with a goal of maintaining the P_{CO_2} between 30 and 35 mm Hg during prolonged hyperventilation, and is reserved for patients who are showing signs of acute herniation.[12,13] Over 12 to 24 hours, injured vessels may lose their responsiveness to hyperventilation-induced hypocarbia and become vasodilated. Blood may then be shunted to the injured area, resulting in increased brain swelling and mass effect. Prolonged (i.e., beyond the acute resuscitation) or prophylactic hyperventilation is therefore not recommended as a treatment for increased ICP, and hyperventilation is not used for the routine management of head-injured patients with no signs of increased ICP.[12,13] The neurologic effects of hypocapnia are illustrated in Figure 41-2.

The cerebral vessels also respond to changes in P_{O_2}. As P_{O_2} declines, cerebral vessels dilate to ensure adequate oxygen delivery to brain tissue. When brain injury has occurred, increased CBF in the presence of a disrupted BBB can promote the formation of vasogenic edema. Avoiding or reversing hypoxia is therefore an essential goal in the acute management of the head-injured patient.[14] The responses of the cerebral vasculature to changing

www.ketabpezeshki.com 66485457-66963820

physiologic conditions protect the brain by increasing the delivery of oxygen to tissue, enhancing the removal of metabolic end products, and allowing nearly instantaneous adjustments of regional blood flow to meet the changing metabolic demands.

Cerebral Perfusion Pressure. CBF also depends on cerebral perfusion pressure (CPP), which is the pressure gradient across the brain. The determinants of CPP are MAP and the resistance to CBF produced by mean systemic venous pressure and ICP. Because ICP is higher than mean systemic venous pressure, ICP effects predominate. Therefore CPP is estimated as

$$CPP = MAP - ICP$$

CBF remains constant when CPP is 50 to 160 mm Hg. If CPP falls below 40 mm Hg, the autoregulation of CBF is lost, CBF declines, and the resultant tissue ischemia critically affects cerebral metabolism. It is essential to avoid or correct hypotension in the patient with multiple trauma who is also head injured so that the CPP can be maintained. Management is also directed at reducing or preventing increased ICP to ensure adequate CPP to sustain cerebral metabolic needs.

Biomechanics of Head Trauma

Direct Injury. Direct impact head injury occurs when the head is struck by an object or its motion is arrested by another object. The resulting damage depends on the consistency, mass, surface area, and velocity of the object striking the head. Direct injury can also be caused by compression of the head. External signs of trauma are frequently noted at the site of application of the impact or compression force. The skull initially bends inward at the point of contact. If the force is sufficient, a skull fracture can occur. The cranium absorbs some of the applied energy, and some energy is transmitted to the brain by shock waves that travel distant to the site of impact or compression. These shock waves distort and disrupt intracranial contents and temporarily alter regional ICP as they propagate. In general, the more rapidly a force is applied, the greater the damage it causes. The extent of direct injury depends on the vasoelastic properties of the underlying region of brain tissue, the duration of the force applied, the magnitude of the force reaching the brain tissue, and the surface area of the brain that is affected by the application of the force. In cases of penetrating trauma, the mass, shape, direction, and speed of the penetrating object also affect the extent of direct injury.

Direct injury from compression of the head requires significant force because the architecture of the skull provides substantial resistance to deformation. In the clinical setting, compression injury is less common than other types of direct impact. With sufficient and prolonged application of compression force, the ability of the skull to absorb the force is overcome, and multiple linear skull fractures occur. Resulting fractures can be depressed if a high-energy rapid compression force is applied to a small area of the skull. Isolated direct impact injury is rare; direct impact usually sets the head in motion, resulting in simultaneous direct and indirect injury.

Indirect Injury. In indirect brain injury, the cranial contents are set into motion by forces other than the direct contact of the skull with another object. A common example is acceleration-deceleration injury, such as the shaken impact syndrome.[15,16] No direct mechanical impact is sustained, but the cranial contents are set into vigorous motion. The brain moves within the skull, and bridging subdural vessels are strained. Subdural hematomas (SDHs) may result. Differential acceleration of the cranial contents occurs, depending on the physical characteristics of the brain region. As one brain region slides past another, shear and strain injuries are produced. This movement results in diffuse injuries, such as diffuse axonal injury (DAI) or concussion. Additional injury occurs as the movement of the intracranial contents is abruptly arrested and the brain strikes the skull or a dural structure. Contrecoup contusions are an example of the injury produced in this manner. In penetrating injury the traversal of the object produces pressure waves that can strike structures distal to the path of the missile.

Brain Cellular Damage and Death

Primary and Secondary Brain Injuries

The acute clinical picture of the patient with TBI is dynamic and represents the sum of primary and secondary injury. Primary brain injury is mechanical damage that occurs at the time of head trauma and includes brain lacerations, hemorrhages, contusions, and tissue avulsions. On the microscopic level, primary injury causes permanent mechanical cellular disruption and microvascular injury. Other than the evacuation of traumatic hematomas, no specific intervention exists to repair or reverse primary brain injury; the only way to reduce the incidence of primary brain injury is through public health interventions aimed at reducing the occurrence and severity of head trauma.

The circumstances and extent of the primary injury are not the only contributors to the final neurologic outcome after head injury. The traumatic event also produces injury at the functional and anatomic cellular level, which begins soon after the impact and continues for several hours and even days after injury. Secondary brain injury results from intracellular and extracellular derangements that are probably initiated at the time of trauma by a massive depolarization of brain cells and subsequent ionic shifts.[17] Animal studies have revealed a complicated series of neurochemical, neuroanatomic, and neurophysiologic reactions after head injury (Fig. 41-3). The cell has some compensatory mechanisms to protect itself from widespread damage, such as endogenous free radical scavengers and antioxidants. With significant trauma, however, these systems are quickly overwhelmed, and the functional and structural integrity of the cell is threatened. Human studies document similar changes. The relative importance and contribution of each adverse reaction to the final functional status of the damaged cell are uncertain, as are the rate and duration of each detrimental event. All currently used acute therapies for TBI

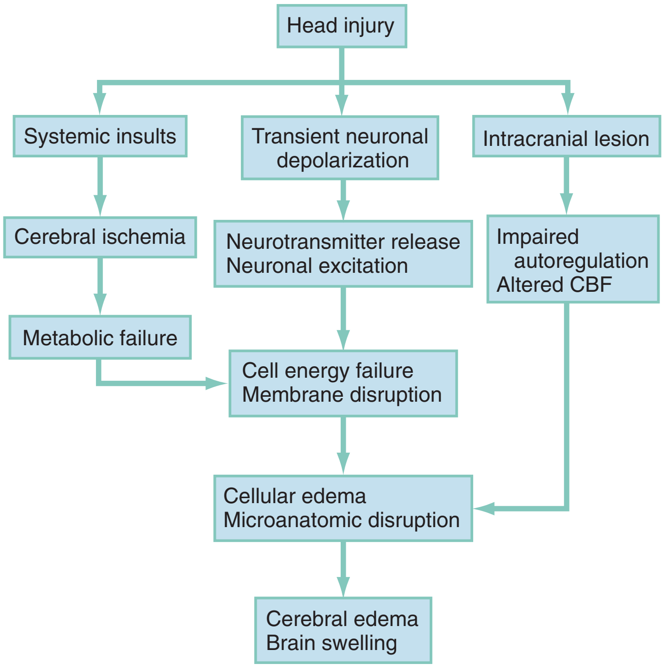


Figure 41-3. Contributing events in the pathophysiology of secondary brain injury. *CBF,* cerebral blood flow.

www.ketabpezeshki.com 66485457-66963820

are directed at reversing or preventing secondary injury. Experimental evidence for many investigational agents aimed at specific steps in the destructive processes suggests that some aspects of secondary brain injury may be reversed or modified. Multiple ongoing head injury trials have been performed with numerous investigational therapeutic interventions; to date, none have proved useful in the clinical setting.[18,19]

Secondary Systemic Insults

The final neurologic outcome after head trauma is influenced by the extent and degree of secondary brain injury. In turn, the amount of secondary brain injury depends on certain premorbid and comorbid conditions, such as the age of the patient and trauma-related systemic events.[19-21] A primary goal in the emergency care of the head-injured patient is prevention or reduction of systemic conditions that are known to worsen outcome after TBI.

Common secondary systemic insults in trauma patients include hypotension, hypoxia, and anemia and hyperpyrexia. *Hypotension,* defined as a systolic blood pressure less than 90 mm Hg, has been found to have negative impact on severe head injury outcome.[18,19,21,22] Systemic hypotension reduces cerebral perfusion, thereby potentiating ischemia and infarction. The presence of hypotension nearly doubles the mortality from head injury and worsens the outcome of the patients who survive.[17,21-23]

Hyperpyrexia (core body temperature of 38.5° C) is also correlated with worsened outcomes after TBI, and both its magnitude and its duration seem to contribute. The exact mechanism by which it causes damage is yet to be determined but likely involves stimulation of metabolism in injured areas of the brain, thus recruiting blood flow with a resultant increase in ICP.[18,21]

Hypoxia, defined as a Po_2 less than 60 mm Hg, probably occurs often in the head-injured patient. Causes include (1) transient or prolonged apnea caused by brainstem compression or injury after the traumatic event; (2) partial airway obstruction caused by blood, vomitus, or other debris in the airway of the traumatized patient; (3) injury to the chest wall that interferes with normal respiratory excursion; (4) pulmonary injury that reduces effective oxygenation; and (5) ineffective airway management, such as the inability to bag-valve-mask or intubate the patient in an effective or timely manner. The exact incidence of hypoxia in the head-injured patient is difficult to estimate because it is often unnoticed or undocumented in the out-of-hospital setting. When its occurrence is documented, the overall mortality from severe head injury may double.[18,22-24] Increased recognition of the potentially devastating consequences of hypoxia and associated hypercarbia has led to more vigilance in out-of-hospital and emergency settings.

Anemia caused by blood loss can be detrimental to the head-injured patient by reducing the oxygen-carrying capacity of the blood, thus reducing the amount of necessary substrate delivered to the injured brain tissue. When anemia (hematocrit 30%) occurs in patients with severe head injury, the mortality rate increases.[18,21] Other potential reversible causes of systemic insult in head injury include hypercarbia, coagulopathy, and seizures.

Pathophysiology

Increased Intracranial Pressure

ICP represents a balance of the pressures exerted by the contents of the cranial cavity. This relationship is explained by the Monro-Kellie doctrine.[25,26] Because the craniospinal intradural space is almost nonexpandable, the sum of the volume of brain, CSF, and blood within the cranium will remain constant. If the volume of any of these components increases, the volume of another must decrease for a constant ICP to be maintained. Increased ICP is defined as CSF pressure greater than 15 mm Hg (or 195 mm H_2O) and is a frequent consequence of severe head injury. Initially, as ICP increases as a result of a traumatic mass lesion or edema formation, the CSF is displaced from the cranial vault to the spinal canal, offsetting the increased blood or brain volume. When this compensatory mechanism is overwhelmed, the elastic properties of the brain substance allow tissue compression to provide buffering for the increasing pressure. Depending on the location and the rate of expansion of the traumatic mass lesion and the rate of cerebral edema formation, the intracranial compensatory mechanisms can accommodate an increased volume of 50 to 100 mL. Beyond that, even small additional changes in intracranial volume relationships, such as those caused by vasodilation, CSF obstruction, or small areas of focal edema, cause a dramatic increase in ICP. If ICP increases to the point at which CPP is compromised, vasoparalysis occurs and autoregulation is lost. The CBF then depends directly on the systemic MAP. With the loss of autoregulation, massive cerebral vasodilation occurs. Systemic pressure is transmitted to the capillaries, and the outpouring of fluids into the extravascular space can contribute to vasogenic edema and thus further increase ICP. If ICP rises to the level of the systemic arterial pressure, CBF ceases and brain death occurs.

Methods to reduce elevated ICP include hyperventilation, use of osmotic and diuretic agents, and CSF drainage. Uncontrollable increased ICP is defined as an ICP of 20 mm Hg or higher refractory to treatment. If ICP is not controlled, herniation syndromes can occur, resulting in brainstem compression and subsequent cardiorespiratory arrest. In the United States, the use of ICP monitoring and control has become standard in cases of moderate and severe TBI despite the lack of prospective controlled research showing clear efficacy as an individual patient treatment modality.[18]

Brain Swelling and Cerebral Edema

Two primary types of brain swelling occur after head injury: congestive brain swelling and cerebral edema. *Congestive brain swelling* results from an increased intracranial blood volume. Hyperemia occurs early after trauma and can persist for the first few days after injury.[23,27] It is especially common in children. The increased blood volume is most likely caused by vasodilation, which occurs as a compensatory mechanism to maintain optimal CBF in the presence of increased metabolic needs of the damaged brain tissue.

Cerebral edema is an increase in brain volume caused by an absolute increase in cerebral tissue water content. Diffuse cerebral edema may develop soon after head injury; however, its presence and extent do not always correlate with the severity of head injury. On computed tomography (CT) scans, diffuse edema manifests as bilateral compression of the ventricles, loss of definition of the cortical sulci, or effacement of the basal cisterns (Fig. 41-4). Focal edema adjacent to traumatic mass lesions demonstrates decreased density on CT scans compared with normal tissue. CT can also detect a *mass effect,* caused by edema surrounding a traumatic lesion.

Both vasogenic and cytotoxic cerebral edema occur in the setting of trauma; the incidence and onset of each relative to the other depend on the nature of the injury. *Vasogenic edema* arises from transvascular leakage caused by mechanical failure of the tight endothelial junctions of the BBB.[23,27] Vasogenic edema accumulates preferentially in white matter and can become widespread. It is frequently associated with focal contusions or hematomas. Vasogenic edema eventually resolves as edema fluid is reabsorbed into the vascular space or the ventricular system.

www.ketabpezeshki.com 66485457-66963820

Figure 41-4. Non–contrast-enhanced computed tomography scan showing diffuse cerebral edema. Loss of gray-white differentiation in brain parenchyma is present. Bilateral compression of the ventricles has occurred with loss of cortical sulci.

Cytotoxic edema is an intracellular process that results from membrane pump failure. It is common after head injury and is frequently associated with post-traumatic ischemia and tissue hypoxia. Normal membrane pump activity depends on adequate CBF to ensure adequate substrate and oxygen delivery to brain tissue. If the CBF is reduced to 40% or less of baseline, cytotoxic edema begins to develop. If CBF drops to 25% of baseline, membrane pumps fail and cells begin to die. Congestive brain swelling can contribute to cytotoxic edema if it becomes severe enough to increase ICP and reduce CPP so that cerebral circulation cannot be maintained. Recent work suggests that cytotoxic cerebral edema is the predominant form of edema in patients who have experienced TBI.[23,28]

Altered Levels of Consciousness

Consciousness is the state of awareness of the self and of the environment, and it requires intact functioning of the cerebral cortices and the reticular activating system (RAS) of the brainstem. An altered level of consciousness is the hallmark of brain insult from any cause and results from an interruption of the RAS or a global event that affects the cortices of both hemispheres.

A patient who has sustained TBI typically has an altered level of consciousness. Head trauma patients may be hypoxic from injury to respiratory centers or from concomitant pulmonary injury. Hypotension from other associated injuries can compromise CBF and affect consciousness. Global suppression may result from an intoxicant consumed before the injury, hypoglycemia, a post-traumatic seizure (PTS), or a postictal period after a seizure from any cause. With increasing ICP from brain swelling or an expanding mass lesion, brainstem compression and subsequent RAS compression can occur.

Patients with altered levels of consciousness require careful monitoring and observation. Reversible conditions that can alter mental status, such as hypoxia, hypotension, or hypoglycemia, should be corrected as they are identified.

Cushing's Reflex

Progressive hypertension associated with bradycardia and diminished respiratory effort is a specific response to acute, potentially lethal increases in ICP. This response is called *Cushing's reflex* or *Cushing's phenomenon,* and its occurrence indicates that the ICP has reached life-threatening levels. Cushing's reflex can occur whenever ICP is increased, regardless of the cause. The full triad of hypertension, bradycardia, and respiratory irregularity is seen in only one third of cases of life-threatening increased ICP.[23,29]

Cerebral herniation occurs when increasing cranial volume and ICP overwhelm the natural compensatory capacities of the CNS (Fig. 41-5). Increased ICP may be the result of post-traumatic brain swelling, edema formation, traumatic mass lesion expansion, or any combination of the three. When increasing ICP cannot be controlled, the intracranial contents shift and herniate through the cranial foramen. Herniation can occur within minutes or up to days after TBI. When the signs of herniation syndrome are present, however, mortality approaches 100% without rapid implementation of temporizing emergency measures and definitive neurosurgical therapy.

Uncal Herniation. The most common clinically significant traumatic herniation syndrome is uncal herniation, a form of transtentorial herniation. Uncal herniation is often associated with traumatic extra-axial hematomas in the lateral middle fossa or the temporal lobe. The classic signs and symptoms are caused by compression of the ipsilateral uncus of the temporal lobe on the U-shaped edge of the tentorium cerebelli as the brain is forced through the tentorial hiatus. As compression of the uncus begins, the third cranial nerve (CN) is compressed; anisocoria, ptosis, impaired extraocular movements, and a sluggish pupillary light reflex develop on the side ipsilateral to the expanding mass lesion. This phase may last for minutes to hours, depending on how rapidly the expanding lesion is changing. As the herniation progresses, compression of the ipsilateral oculomotor nerve eventually causes ipsilateral pupillary dilation and nonreactivity.

Initially in the uncal herniation process, motor examination findings can be normal, but contralateral Babinski's responses develop early.[23] Babinski's sign is dorsiflexion of the great toe and fanning of the other toes. Contralateral hemiparesis develops as the ipsilateral peduncle is compressed against the tentorium. With continued progression of the herniation, bilateral decerebrate posturing eventually occurs; decorticate posturing is not always seen with the uncal herniation syndrome. Pupillary dilation and nonreactivity are the most reliable physical examination findings with regard to lesion location.

In a certain percentage of TBI patients, the contralateral cerebral peduncle is forced against the opposite edge of the tentorial hiatus. Hemiparesis is then detected ipsilateral to the dilated pupil and the mass lesion. This is termed *Kernohan's notch syndrome* and causes false-localizing motor findings. As uncal herniation progresses, direct brainstem compression causes additional alterations in the level of consciousness, respiratory pattern, and cardiovascular system. Mental status changes may initially be quite subtle, such as agitation, restlessness, or confusion, but soon lethargy occurs with progression to frank coma. The patient's respiratory pattern may initially be normal, followed by sustained hyperventilation. With continued brainstem compression, an ataxic respiratory pattern develops. The patient's hemodynamic status may change, with rapid fluctuations in blood pressure and cardiac conduction. Herniation that is uncontrolled progresses rapidly to brainstem failure, cardiovascular collapse, and death.

Central Transtentorial Herniation. The central transtentorial herniation syndrome is demonstrated by rostrocaudal neurologic deterioration caused by an expanding lesion at the vertex or the frontal or occipital pole of the brain. It is less common than uncal

www.ketabpezeshki.com 66485457-66963820

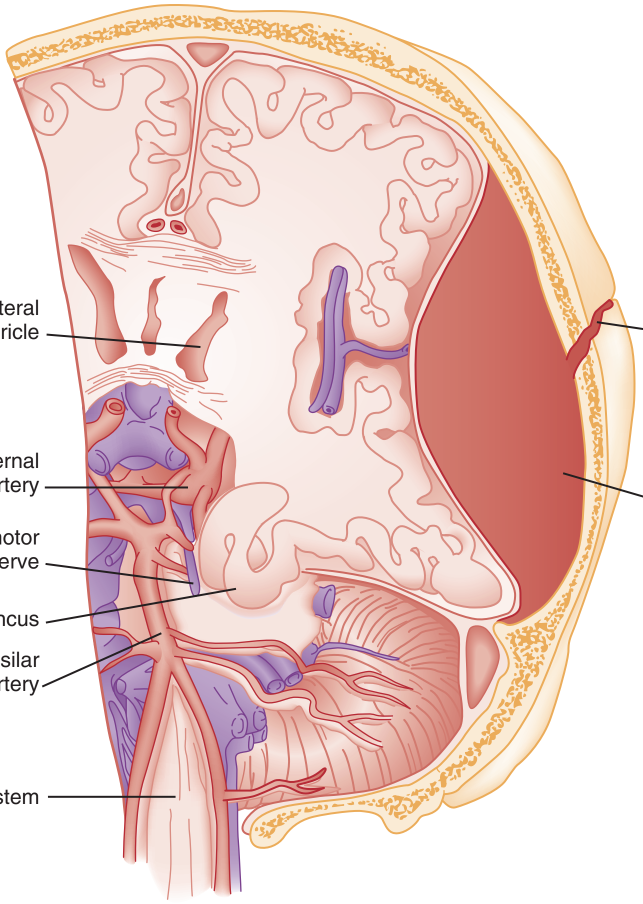


Figure 41-5. Anterior view of transtentorial herniation caused by large epidural hematoma. Skull fracture overlies hematoma. (From Rockswold GL: Head injury. In Tintinalli JE, et al [eds]: Emergency Medicine. New York, McGraw-Hill, 1992, p 915.)

transtentorial herniation. Clinical deterioration occurs as bilateral central pressure is exerted on the brain from above. The initial clinical manifestation may be a subtle change in mental status or decreased level of consciousness, bilateral motor weakness, and pinpoint pupils (2 mm). Light reflexes are still present but are often difficult to detect. Muscle tone is increased bilaterally, and bilateral Babinski's signs may be present. As central herniation progresses, both pupils become midpoint and lose light responsiveness. Respiratory patterns are affected, and sustained hyperventilation may occur. Motor tone increases. Decorticate posturing is elicited by noxious stimuli. This progresses to bilateral decorticate and then spontaneous decerebrate posturing. Respiratory patterns initially include yawns and sighs and progress to sustained tachypnea, followed by shallow slow and irregular breaths immediately before respiratory arrest.

Cerebellotonsillar Herniation. Cerebellotonsillar herniation occurs when the cerebellar tonsils herniate downward through the foramen magnum. This is usually caused by a cerebellar mass or a large central vertex mass causing the rapid displacement of the entire brainstem.[23] Clinically, patients demonstrate sudden respiratory and cardiovascular collapse as the medulla is affected. Pinpoint pupils are noted. Flaccid quadriplegia is the most common motor presentation because of bilateral compression of the corticospinal tracts. Mortality from cerebellar herniation approaches 70%.[23]

Upward Transtentorial Herniation. Upward transtentorial herniation occasionally occurs as a result of an expanding posterior fossa lesion. Level of consciousness declines rapidly. These patients may have pinpoint pupils from compression of the pons. Downward conjugate gaze is accompanied by the absence of vertical eye movements.

CLINICAL FEATURES AND DIAGNOSTIC STRATEGIES

History

Details regarding the mechanism of injury should be solicited from witnesses or the victim to determine whether the head-injured patient is at high risk for intracranial injury. The patient's condition before trauma may give clues to important, otherwise unsuspected, comorbid factors such as preexisting coagulopathy (e.g., hemophilia). Past medical history, medications (particularly anticoagulants), recent drug or alcohol use, and complaints immediately before the traumatic event should be determined.

The patient's current level of consciousness, as well as that immediately before and after the injury and at the arrival of first responders, should be determined. Witnessed PTSs or apnea should be reported. If the patient is now awake but was unconscious at some point, it should be determined if the patient has returned to baseline mental status.

Acute Neurologic Examination

General

The goals of the acute neurologic assessment of head-injured patients include detection of life-threatening injuries and identification of neurologic changes in the immediate post-trauma period. An awake, stable patient can undergo a relatively complete neurologic examination. In other patients, an efficient neurologic examination in the emergency setting includes evaluation of mental status, GCS score, pupillary size and responsiveness, and

www.ketabpezeshki.com 66485457-66963820

motor strength and symmetry. An accurate neurologic assessment in the immediate post-trauma period serves as a basis for comparison in subsequent examinations. If a formal GCS measure is not possible or is difficult because of comorbid confounders, the patient's mental status should be described in as much detail as possible. Declining mental status after head trauma suggests increasing ICP from an expanding mass lesion or worsening cerebral edema, which may rapidly become life-threatening.

Glasgow Coma Scale

The GCS is an objective method of following the patient's neurologic status (Table 41-2). The GCS assesses a patient's best eye, verbal, and motor responsiveness. It was developed for the clinical evaluation of head trauma patients at 6 hours after trauma, and all initial validation studies investigated its application at this time. It was designed for assessment of patients with isolated head trauma who were hemodynamically stable and adequately oxygenated.[26] The GCS is only one aspect of the neurologic examination (e.g., the motor score reflects best limb movement, and it cannot detect subtle changes in mental status). However, because of its inter-rater reliability, reliance on objective clinical data, and ease of application, the GCS has become a standard acute measure of neurologic function in patients with altered mental status from any cause, including head trauma.

The acute application (within 6 hours) of the GCS in head-injured patients has limitations. Hypoxia, hypotension, and intoxication can falsely lower the initial GCS score.[26] Intubation lowers the patient's GCS score by automatically assigning a score of 1 for verbal response, regardless of the actual contribution of head injury to the clinical examination. Periorbital edema from direct eye trauma may make assessment of spontaneous eye opening difficult. Extremity fractures or occult spinal cord injuries may interfere with the motor examination. Children and patients with difficulty communicating are challenging to assess with the GCS. The GCS may miss subtle mental status changes and does not assess brainstem reflexes or pupillary reflexes. Decisions regarding continued resuscitation of severely head-injured patients should not be based on the initial GCS score because of these limitations. Patients should be fully resuscitated, with evacuation of all surgical lesions, and remain hemodynamically stable, and not be intoxicated before the GCS can be used to predict their prognosis.[26]

Table 41-2 Glasgow Coma Scale

RESPONSE	SCORE	SIGNIFICANCE
Eye Opening		
Spontaneously	4	Reticular activating system is intact; patient may not be aware
To verbal command	3	Opens eyes when told to do so
To pain	2	Opens eyes in response to pain
None	1	Does not open eyes to any stimuli
Verbal Stimuli		
Oriented, converses	5	Relatively intact CNS, aware of self and environment
Disoriented, converses	4	Well articulated, organized, but disoriented
Inappropriate words	3	Random exclamatory words
Incomprehensible	2	Moaning, no recognizable words
No response	1	No response or intubated
Motor Response		
Obeys verbal commands	6	Readily moves limbs when told to
Localizes to painful stimuli	5	Moves limb in an effort to remove painful stimuli
Flexion withdrawal	4	Pulls away from pain in flexion
Abnormal flexion	3	Decorticate rigidity
Extension	2	Decerebrate rigidity
No response	1	Hypotonia, flaccid: suggests loss of medullary function or concomitant spinal cord injury

CNS, central nervous system.

Pupillary Examination

An evaluation of the patient's pupil size and responsiveness is performed early in the initial assessment of the head-injured patient. Pupillary asymmetry, the loss of the light reflex, or a dilated pupil suggests herniation syndrome. Traumatic mydriasis, resulting from direct injury to the eye and periorbital structures, may confuse the assessment of the pupillary responsiveness.

Motor Examination: Posturing

The patient's acute motor examination assesses for strength and symmetry. Paralysis obscures involuntary reflexes; attempts should be made to perform the motor examination before paralytic agents are given. Hemiparesis contralateral to a fixed and dilated pupil suggests herniation syndrome. A false-localizing motor examination can be caused by contralateral cerebral parenchymal injury occurring simultaneously with the expanding mass lesion or by Kernohan's notch syndrome (compression of the contralateral cerebral peduncle). False-localizing motor signs can also be caused by extremity trauma, spinal cord, or nerve root injury that makes the examination painful or difficult. If the patient is not cooperative or is comatose, motor movement should be elicited by application of noxious stimuli. Any movement should be recorded. Voluntary purposeful movement must be distinguished from abnormal motor posturing. *Decorticate posturing* is abnormal flexion of the upper extremity and extension of the lower extremity. The arm, wrist, and elbow slowly flex, and the arm is adducted. The leg extends and internally rotates, with plantar flexion of the foot. Decorticate posturing implies injury above the midbrain. *Decerebrate posturing* is the result of a more caudal injury and therefore is associated with a worse prognosis.[19] The arms extend abnormally and become adducted. The wrist and fingers are flexed, and the entire arm is internally rotated at the shoulder. The neck undergoes abnormal extension, and the teeth may become clenched. The leg is internally rotated and extended, and the feet and toes are plantar flexed.

Brainstem Function

In the acute setting, brainstem activity is assessed by the patient's respiratory pattern, pupillary size, and eye movements. The *oculocephalic response* (doll's eyes maneuver) tests the integrity of the pontine gaze centers. This response cannot be tested until cervical spine fractures have been ruled out. The *oculovestibular response* (cold water calorics) also permits assessment of the brainstem. Comatose patients no longer demonstrate nystagmus when cold water is placed in the ear canal; the only response is tonic deviation of the eyes toward the instilled cold water.[24] This response is dampened by cerumen or blood in the patient's ear canal, and the tympanic membrane needs to be intact for this test to be performed.

www.ketabpezeshki.com 66485457-66963820

Box 41-1 Clinical Characteristics of Basilar Skull Fractures

Blood in ear canal
Hemotympanum
Rhinorrhea
Otorrhea
Battle's sign (retroauricular hematoma)
Raccoon sign (periorbital ecchymosis)
Cranial nerve deficits
- Facial paralysis
- Decreased auditory acuity
- Dizziness
- Tinnitus
- Nystagmus

In the severely head-injured patient, the CN examination is often limited to the pupillary responses (CN III), gag reflex (CNs IX and X), and corneal reflex (CNs V and VII). Facial symmetry (CN VII) can sometimes be assessed if the patient grimaces with noxious stimuli. In patients who are awake and cooperative, a formal CN examination should be performed.

Deep Tendon Reflexes and Pathologic Reflexes

Tendon reflexes should be tested for symmetry. An extensor plantar reflex (Babinski's sign) is nonspecific and can be caused by injury anywhere along the corticospinal tract. Rectal sphincter tone and anal reflexes should be determined to assess for spinal cord integrity.

Other Examination Findings

The head and neck should be carefully examined for external signs of trauma that may have also produced underlying TBI. A scalp laceration, contusion, abrasion, or avulsion may overlie a depressed skull fracture. Basilar skull fractures are usually diagnosed by the clinical examination (Box 41-1). Although not always related to severe brain injury, their presence implies that a significant impact force was sustained during head trauma. Carotid artery dissections caused by a hyperflexion-extension neck injury can occasionally be detected by auscultation of a carotid bruit.[24] In these patients, a careful neurologic examination should assess for subtle asymmetry between the carotid arteries. The percentage of concurrent cervical spine injury in patients with severe head trauma may be as high as 10.2%.[27] Often, other spinal regions are also injured.

MANAGEMENT

Severe Traumatic Brain Injury

The neurosurgical literature defines severe head injury as TBI manifested by a postresuscitation GCS score of 8 or lower within 48 hours. In the emergency setting, however, this definition is not practical because the outcome for the patient beyond the initial resuscitation is not known. Most emergency medicine research defines severe head injury by a GCS score of 8 or lower at the acute presentation after injury. The presence of any intracranial contusion, hematoma, or laceration is also considered severe injury (see Fig. 41-5).

Approximately 10% of all head-injured patients who reach the ED alive have severe head trauma.[1,30] The clinical prognostic indicators in the acute setting are initial motor activity, pupillary responsiveness, the patient's age and premorbid condition, and the occurrence of secondary systemic insult during the acute period.[23,28,31] Up to 25% of these patients have lesions requiring neurosurgical evacuation.[18] The prognosis cannot be reliably predicted by the initial GCS score or initial CT scan.

The overall mortality in severe head trauma has improved over the years and now remains stable at approximately 35%.[32,33] Mortality for children is lower. For nonsurvivors of head injury who reach the hospital alive, the average time to death is 2 days after trauma. Adult survivors of severe head trauma are usually severely disabled; currently, only 7% have moderate disability or a good outcome. Children older than 2 years who survive a severe closed head injury have a better outcome than adults.

Out-of-Hospital Care

The goals of out-of-hospital management of the head-injured patient are the necessary airway interventions to prevent hypoxia and the establishment of intravenous access to treat trauma-related hypotension. An accurate neurologic assessment provides a means to determine the subsequent effectiveness of treatment and should focus on the GCS score, pupillary responsiveness and size, level of consciousness, and motor strength and symmetry.

Head trauma can produce profound effects on the cardiovascular system if compression of the brainstem and medulla occurs. Any cardiac dysrhythmia can occur and produce cardiac instability.[23,34] All head-injured patients should be placed on a cardiac monitor during transport from the accident scene.

The secondary survey of the head-injured patient should include a search for external signs of head trauma. Scalp lacerations may bleed a large volume into a bulky dressing. A less bulky dressing should be used with firm constant manual pressure applied to avoid excessive blood loss. Many severely head-injured patients are initially combative or agitated. Transporting an agitated patient who is fighting against physical restraints may exacerbate physical injury, cause an increase in ICP, and interfere with appropriate stabilization and management. It may be necessary to use out-of-hospital sedation or neuromuscular blockade for control. The use of sedatives or neuromuscular blockade may influence the initial ED evaluation of the neurotrauma patient. Therefore the risks and benefits of this acute intervention are carefully considered and decisions made on a case-by-case basis. Out-of-hospital protocols allowing the use of sedative agents for selected agitated head-injured patients should be established. Currently used agents include lorazepam (Ativan), diazepam (Valium), midazolam (Versed), and certain butyrophenones (e.g., haloperidol, droperidol). Some investigators are looking at the use of ketamine for prehospital sedation in combative head-injured patients. Recent research questions whether the widely held belief that ketamine increases ICP and CBF is accurate.[35] Currently, the existing prehospital data are insufficient to recommend ketamine use in combative prehospital head-injured patients.

Severe head injury is the most common reason for helicopter transfers in trauma care. Although the decision to transport by helicopter should be made on a case-by-case basis, considerations for helicopter use from an accident scene include a long extrication time, ground transport of longer than 30 minutes to an appropriate ED and trauma care facility, two or more severely injured patients at a scene, and assistance in performing expedient lifesaving procedures, especially airway management. Several recent studies have supported that the use of helicopter emergency services improves outcomes in severely head-injured patients.[24,36-38]

Controversy exists regarding the benefits of out-of-hospital intubations in patients with severe and moderate head injuries. It is unclear whether field intubations truly improve neurologic outcome or survival. Unsuccessful attempts at field intubations may add to out-of-hospital time and increase the risk of aspiration or hypoxia.[39-41]

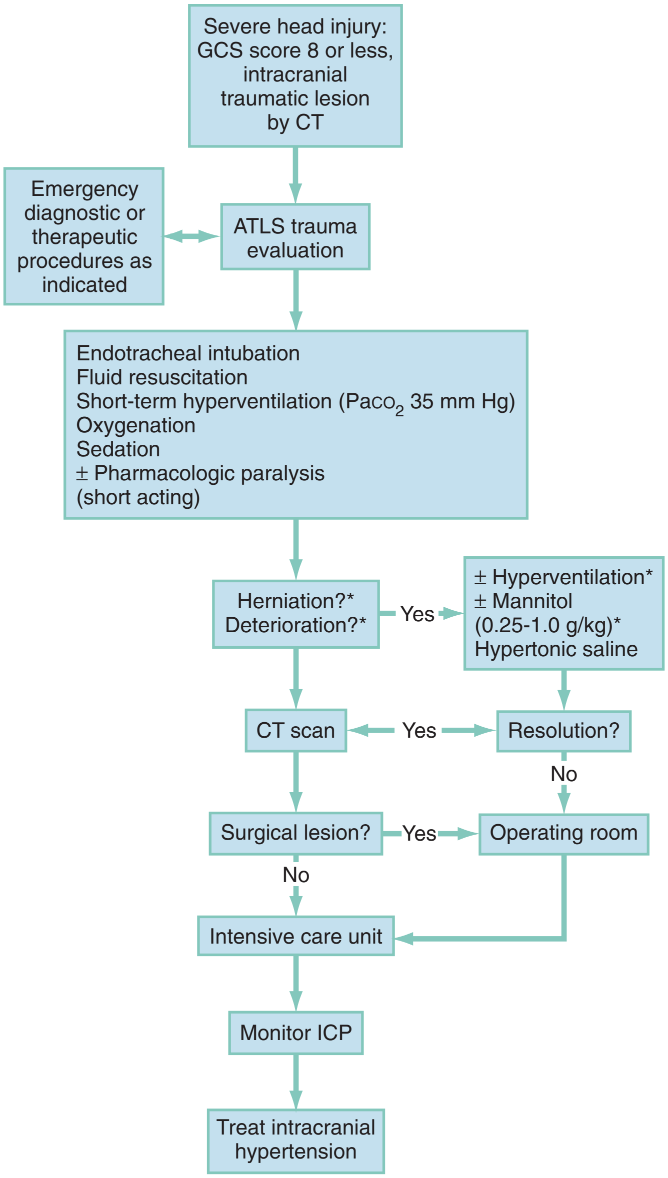
www.ketabpezeshki.com 66485457-66963820

In 1997 Winchell and Hoyt showed that patients who had sustained severe head injuries and who were intubated in the out-of-hospital setting had an improved survival compared with those who were not intubated.[29] Since that time, others have challenged this finding. In the San Diego paramedic rapid sequence intubation (RSI) trial, Davis and colleagues[42] found an increase in mortality and morbidity in patients who sustained severe head injuries and underwent out-of-hospital RSI compared with matched historical controls.[42] Potential explanations included frequent hypoxic episodes with associated bradycardia, unintentional hyperventilation, and prolonged scene times for those undergoing out-of-hospital RSI. Wang and colleagues found a fourfold increase in mortality among patients who sustained severe TBI and received ground ambulance intubation compared with ED intubation.[24] Flight clinician out-of-hospital intubation has been associated with decreased mortality and improved neurologic outcome, likely because of the higher airway management training requirements of air medical programs.[24,37-40] These studies are somewhat limited by lack of generalizability[24,42-46] (e.g., most emergency medical service systems do not have RSI capabilities) or by the use of nonvalidated outcome measures of neurologic function.[24] Out-of-hospital intubation carries the following risks: frequent hypoxic episodes during intubation attempts, with or without concurrent bradycardia; unintentional hyperventilation of intubated patients; prolonged scene times because of the time demands associated with the intubation process; and persistent hypotension, likely from other injuries that go unattended while the airway management occurs. However, hypoxia must be avoided in head-injured patients, and out-of-hospital airway protocols balance the risks of emergency intubation in an uncontrolled setting with the need to secure an airway at risk.

The key to a successful out-of-hospital RSI program involves well-trained clinicians with specific RSI protocols, involved medical control, frequent continuing education, and consistent quality assurance and improvement. Fakhry and colleagues[47] reported that their helicopter clinicians had a 96.6% RSI success rate with few complications and no esophageal intubations.

Emergency Department (Fig. 41-6)

Airway. RSI is the preferred method for securing the airway in combative or agitated patients. If possible, a brief neurologic examination should be performed before the patient is given any sedative or neuromuscular blocking agents. In general, the agents used for RSI in the head-injured patient are the same as those used for other patients, although attention is given to the increased ICP that can potentially occur with any physical stimulation of the respiratory tract. Lidocaine (1.5-2 mg/kg intravenous push) may attenuate the cough reflex, hypertensive response, and increased ICP associated with intubation, although this is vigorously debated.[47-49] If succinylcholine is used, premedication with a subparalytic dose of a nondepolarizing agent can be considered if time permits because fasciculations produced by succinylcholine may increase ICP. The degree of ICP elevation and its clinical significance are unclear, however, and are balanced against the need for rapid establishment of an airway. Etomidate (0.3 mg/kg intravenously [IV]), a short-acting sedative-hypnotic agent, has beneficial effects on ICP by reducing CBF and metabolism.[50] In addition, etomidate has minimal adverse effects on blood pressure and cardiac output and fewer respiratory depressant effects than other agents. Concern has been raised that single-dose etomidate used during RSI may adversely affect patient outcome by modulating the inflammatory response and transient adrenal suppression.[51] However, research both supporting and refuting this position exists, and no definitive answer has yet been established.[51-56]



*Only in the presence of signs of herniation or progressive neurologic deterioration not attributable to extracranial factors.

Figure 41-6. Initial resuscitation of patient with severe head injury: treatment options. *ATLS,* advanced trauma life support; *CT,* computed tomography; *GCS,* Glasgow Coma Scale; *ICP,* intracranial pressure; $Paco_2$, arterial carbon dioxide partial pressure. (From the Brain Trauma Foundation, American Association of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care: Introduction. Guidelines for the management of severe traumatic brain injury. J Neurotrauma 17:465, 2000.)

Hypotension. Hypotension is rarely caused by head injury except as a terminal event. If hypotension is detected at any time in the emergent management of a head-injured patient, a cause other than the head injury should be sought. Some important exceptions occur. Profound blood loss from scalp lacerations can cause hypovolemic hypotension. In infants, hemorrhage into an epidural or subgaleal hematoma can produce profound hypovolemic shock. In the presence of a concomitant high spinal cord injury, neurogenic hypotension may occur. This is rare, and usually the cord injury is apparent on physical examination. In less obvious cases, neurogenic hypotension can be differentiated from hypovolemic hypotension by its nonresponsiveness to fluid

www.ketabpezeshki.com 66485457-66963820

administration and by the presence of inappropriate bradycardia in the face of hypotension.

Systemic hypotension cannot be tolerated in the head-injured patient without profound worsening of neurologic outcome; fluids or blood transfusion should therefore be delivered to maintain a systolic blood pressure of at least 90 mm Hg.[22] The delivery of large amounts of fluid to severely head-injured patients who are hypotensive from other injuries does not produce clinically significant increases in ICP; fluids should never be withheld in the head trauma patient with hypovolemic hypotension for fear of increasing cerebral edema and ICP. The resuscitation goal is to keep the CPP at 50 or above. Hypotension may interfere with the accurate neurologic assessment of the brain-injured patient. Often, when blood pressure is restored, an improved neurologic status is observed.

Traditionally, normal saline or lactated Ringer's solution has been used for resuscitation of trauma patients with hypovolemic hypotension. Some research suggests that fluid resuscitation with hypertonic saline (HTS) rather than normal saline may improve neurologic outcome after TBI. However, recent data from the Resuscitation Outcomes Consortium showed no improvement in neurologic outcome when HTS was administered in the prehospital setting in severely head-injured patients not in hemorrhagic shock.[57]

As many as 50% of patients with severe head injury are victims of multiple trauma.[22] The dramatic presentation of the head injury should not distract the clinician from a thorough search for other life threats.

The ED neurologic assessment should be compared with the initial out-of-hospital examination, with a focus on evidence of neurologic deterioration or signs of increasing ICP. If the patient is deteriorating or has signs of increased ICP, active intervention is initiated in the ED.

Hyperventilation. Acute hyperventilation is a lifesaving intervention that can prevent or delay herniation in the patient with severe TBI while more definitive resources are mobilized. The goal is to reduce the Pco_2 to the range of 30 to 35 mm Hg. Hyperventilation will reduce ICP by causing cerebral vasoconstriction; the onset of effect is within 30 seconds[23] and probably peaks within 8 minutes after the Pco_2 drops to the desired range. In most patients, hyperventilation lowers the ICP by 25%; if the patient does not rapidly respond, the prognosis for survival is generally poor.

Prolonged hyperventilation is not recommended because it may cause profound vasoconstriction and ischemia. This vasoconstriction worsens CBF that is already severely compromised during the first 24 hours after TBI.[12] Hyperventilation should be viewed as a short-term lifesaving intervention and should be used only when a patient experiences an acute neurologic decline or demonstrates signs consistent with herniation.

Osmotic Agents. Additional therapy for increased ICP includes the use of osmotic diuretics, such as mannitol and HTS. With deepening coma, pupil inequality, or other deterioration of the neurologic examination, osmotic agents may be lifesaving.

Mannitol is the mainstay for control of elevated ICP in acute severe TBI. The Brain Trauma Foundation and the European Brain Injury Consortium recommend mannitol as the osmotic drug of choice.[40,41] However, few comparative data exist on mannitol and other ICP-lowering medications.[58] A Cochrane database review concluded that mannitol may have a small beneficial effect compared with pentobarbital.[59] ICP-directed therapy based on neurologic signs may also be beneficial. However, other evidence suggests that mannitol may be detrimental compared with HTS.[59,60] Further research is needed on optimal osmotic therapy in severe head trauma.

Mannitol (0.25-1 g/kg) can effectively reduce cerebral edema by producing an osmotic gradient that prevents the movement of water from the vascular space into the cells during membrane pump failure and draws tissue water into the vascular space. This reduces brain volume and provides increased space for an expanding hematoma or brain swelling. The osmotic effects of mannitol occur within minutes and peak approximately 60 minutes after bolus administration. The ICP-lowering effects of a single bolus may last for 6 to 8 hours.[61] Mannitol has many other neuroprotective properties. It is an effective volume expander in the presence of hypovolemic hypotension and therefore may maintain systemic blood pressure required for adequate cerebral perfusion. It also promotes CBF by reducing blood viscosity and microcirculatory resistance. It is an effective free radical scavenger, reducing the concentration of oxygen free radicals that may promote cell membrane lipid peroxidation. However, mannitol can produce renal failure or hypotension if given in large doses. It may also induce a paradoxical effect of increased bleeding into a traumatic lesion by decompressing the tamponade effect of a hematoma. Because of these and other potential problems, the use of mannitol should be reserved for head-injured patients with evidence of increasing ICP and neurologic deterioration.[61]

HTS has been used for severe TBI since 1919.[62] Numerous clinical studies have demonstrated that HTS can significantly reduce ICP; however, the total number of enrolled patients in these trials is small.[58,59,62,63] The interpretation of these clinical studies is complicated by variation in protocols, HTS concentration, and administration. Potential adverse events associated with HTS include renal failure, central pontine myelinolysis, and rebound ICP elevation.[64]

Encouraging clinical data are available on hospitalized pediatric TBI patients treated with a continuous infusion of 3% normal saline for control of intracranial hypertension.[65,66] The clinical studies using HTS for acute field resuscitation of severe TBI have had conflicting results. Using a post hoc analysis of adult trauma data, Vassar and colleagues[67] and Wade and colleagues[68] showed beneficial effects of HTS on patients with severe TBI. However, Cooper and colleagues[69] found no benefit for out-of-hospital use of HTS in reducing elevated ICP and improving CPP compared with lactated Ringer's in hypotensive patients who had a head injury. As noted earlier, a large, multicenter, double-blinded, randomized, placebo-controlled clinical trial showed no improvement in neurologic outcome when HTS was administered in the prehospital setting in severely head-injured patients not in hemorrhagic shock.[57]

Barbiturates. Barbiturate therapy is occasionally used in severely head-injured patients to reduce cerebral metabolic demands of the injured brain tissue. Barbiturates also affect vascular tone and inhibit free radical–mediated cell membrane lipid peroxidation. The effects of barbiturates are delayed relative to other acute interventions for reducing ICP; therefore they are rarely initiated in the ED. If other methods of reducing ICP have been unsuccessful, barbiturates may be added in the hemodynamically stable patient. Pentobarbital is the barbiturate most often used.[70]

Steroids. Despite their popularity in the past, there is no benefit to giving steroids in head-injured patients. They do not lower ICP, and high-dose methylprednisolone in moderate and severe TBI is associated with increased mortality.[71]

Hypothermia. Although hypothermia remains a significant area of research and promise for patients with severe and moderate TBI, the available scientific evidence is inconclusive with regard to improved mortality or morbidity with prophylactic hypothermia in patients with severe and moderate TBI. In a meta-analysis performed by the Brain Trauma Foundation, duration of hypothermic treatment for more than 48 hours was associated with a reduction in mortality. This finding is significantly limited owing to small sample sizes.[72] A large trial of hypothermia use in moderate and severe TBI has recently begun in Europe. The Eurotherm3235 Trial will enroll 1800 patients over 41 months.[73]

www.ketabpezeshki.com 66485457-66963820

Cranial Decompression. Patients with signs of herniation who have not responded to other means of ICP reduction and who are rapidly deteriorating in the ED should be considered for placement of emergency burr holes. Emergency trephination has been described for centuries. It is a blind invasive procedure, and the chances of localizing the expanding lesions are uncertain. In patients who do not respond to hyperventilation and osmotic agents and have a unilateral dilated pupil with a history of "talk and deteriorate" after head trauma, emergency cranial decompression may temporarily reverse or arrest the herniation syndrome.[74-77] In this setting, emergency trephination may allow enough time for a patient to undergo a formal craniotomy in the operating room.

Most patients who have been unconscious since an accident occurred—with erratic or absent respiratory effort, bilateral fixed and dilated pupils, no spontaneous eye movements, and decerebrate posturing—have sustained diffuse massive brain injury with no focal lesion amenable to emergency decompression. These patients do not benefit from emergent burr holes. Instead, these patients should undergo rapid CT scanning or formal surgical decompression.

There has been renewed interest among neurosurgeons in the role of emergent decompressive craniectomy. Numerous papers have been published promoting more liberal use of decompressive craniectomy in patients with severe brain swelling and high ICPs.[21] Outcome measurements have not been consistent, and results have been mixed. If performed, the procedure should be done early in the patient's course. Two ongoing randomized studies may provide better direction regarding when this treatment is best indicated.[21]

Seizure Prophylaxis. Up to 12% of all patients who sustain blunt head trauma and 50% of those with penetrating head injury develop early post-traumatic seizures (PTSs).[78] Although the occurrence of seizures in the immediate post-trauma period has no predictive value for future epilepsy, early seizures can cause hypoxia, hypercarbia, release of excitatory neurotransmitters, and increased ICP, which can worsen secondary brain injury. Constantly firing neurons are soon depleted of their energy sources, and in the head trauma patient with compromised cerebral metabolism, uncontrolled seizures exacerbate the neurologic deficit.[23]

Box 41-2 lists accepted indications for early anticonvulsant therapy after head trauma. If the patient is actively seizing, benzodiazepines are administered as effective, rapid-acting first-line anticonvulsants. Lorazepam (0.05-0.1 mg/kg IV over 2-5 minutes up to a total of 4 mg) has been found to be most effective at aborting status epilepticus.[23] Diazepam (0.1 mg/kg, up to 5 mg IV, every 10 minutes up to a total of 20 mg) is an alternative. For long-term anticonvulsant activity, phenytoin (18-20 mg/kg IV) or fosphenytoin (15-18 phenytoin equivalents/kg) can be given. Fosphenytoin has the advantages of rapid administration, a smaller volume of fluid for the dose delivered, and less hypotension than phenytoin. In a Cochrane review, the use of antiepileptic drugs reduced the risk of early seizures by 66%.[79] Early seizure prophylaxis does not prevent late PTSs; the goal is to prevent additional insult to the damaged brain.[78-80]

If the patient has been paralyzed to facilitate management, clinical manifestations of generalized seizures are obscured. Therefore all paralyzed severely head-injured patients should receive prophylactic anticonvulsant therapy in the acute phase. Continuous electroencephalographic monitoring is necessary for the ongoing assessment of seizure activity in paralyzed patients and if available should be initiated in the ED or the intensive care unit.

Antibiotic Prophylaxis. Infection may occur as a complication of penetrating head injury, open skull fractures, and complicated scalp lacerations. Prophylactic antibiotics may be used in these circumstances but are not recommended in patients with only otorrhea or rhinorrhea from a basilar skull fracture.[81]

Recombinant factor VIIa (rFVIIa) is a hemostatic agent that was originally developed to treat bleeding in hemophiliacs. Considerable interest has arisen regarding its potential use in intracerebral hemorrhage.[82,83] rFVIIa costs approximately $1000/mg. Experience from the Iraq war and civilian use in multitrauma patients has produced conflicting results regarding its benefits in traumatic intracranial hemorrhage.[82-85] Use of rFVIIa for traumatic head bleeds should be individualized and undertaken in concert with an institution's treatment protocol. A recent review concluded that although off-label use of rFVIIa increased 140-fold from 2000 to 2008, no evidence exists that rFVIIa improves outcomes in five off-label indications. Specifically, the data regarding the use of rFVIIa in TBI are too limited for determination of the risks and benefits.[86] Head-injured patients taking anticoagulants who require an emergent craniotomy may benefit from rFVIIa administration because it decreases the time to operating room intervention.[82,83,85,86]

Ancillary Evaluation

Laboratory Tests. The acute management of the severely head-injured patient is directed by physical examination and diagnostic imaging. Ancillary laboratory tests that may provide useful information in the subsequent management of the patient include a urine toxicology screen, blood alcohol level, complete blood count, electrolytes, glucose, and coagulation studies.

Neuroimaging. In the acute phase the most useful imaging technique is a non–contrast-enhanced head CT scan. This scan delineates acute intra-axial and extra-axial bleeding, subarachnoid blood, cerebral swelling, ischemic infarction caused by hypoxia after trauma, evidence of increased ICP, and pneumocephalus. Emergency management decisions are strongly influenced by these acute CT scan findings. The bone windows of the CT scan can detect skull fractures (including basilar fractures); plain skull radiographs are not necessary in patients who undergo CT scanning.

Magnetic resonance imaging (MRI) is better than CT in detecting post-traumatic ischemic infarctions, subacute nonhemorrhagic lesions and contusions, axonal shear injury, and lesions in the brainstem or posterior fossa. Monitoring and managing patients in the MRI suite can be very difficult, especially patients with severe TBI who have other life-threatening injuries. MRI is not recommended as the first-line imaging modality for severe or moderate head injury.

Disposition

Consultation. All patients with severe head trauma require an imaging modality to determine the extent and nature of the brain injury and the necessity of neurosurgical intervention. Neurosurgical consultation should be obtained as soon as possible to help direct the patient's subsequent management.

Transfer. Severely head-injured patients require admission to an institution capable of intensive neurosurgical care and acute neurosurgical intervention. If this is not available at the receiving

Box 41-2 Indications for Acute Seizure Prophylaxis in Severe Head Trauma

- Depressed skull fracture
- Paralyzed and intubated patient
- Seizure at the time of injury
- Seizure at emergency department presentation
- Penetrating brain injury
- Severe head injury (Glasgow Coma Scale score 8 or lower)
- Acute subdural hematoma
- Acute epidural hematoma
- Acute intracranial hemorrhage
- Prior history of seizures

www.ketabpezeshki.com 66485457-66963820

hospital, the patient should be transferred to an appropriate institution by the most expedient transport method available.

Priority Management. The hemodynamically unstable patient with multiple trauma that includes head injury presents difficult emergency management decisions. The emergency physician should decide on the sequence that best addresses the most life-threatening pathologic conditions while still preventing morbidity and mortality from other serious injury. If the patient requires immediate surgical intervention for a life-threatening chest or abdominal injury, complete evaluation of the head injury may be curtailed. Moreover, these patients are anesthetized for surgery, and any neurologic deterioration is not detected. Some patients may be too unstable for even an abbreviated head CT scan to be obtained before emergent surgical intervention for other life threats. In this circumstance, early neurosurgical and general surgical consultation should be coordinated by the emergency physician. Intraoperative ventriculostomies or bilateral trephinations may provide some temporary protection from increasing ICP while the patient undergoes surgical correction of the life-threatening injury. A CT scan is performed after the primary life threats have been corrected.

Moderate Head Trauma

Approximately 10% of all patients with head injury have sustained moderate TBI, defined as a postresuscitation GCS score of 9 to 13. Moderate TBI is often caused by MVCs. Most patients with moderate TBI do not die at the scene from their initial head injury and are brought to the ED for stabilization and evaluation.

Moderate TBI produces a number of physiologic abnormalities, including neuronal cell membrane dysfunction and a mild, brief acidosis with no concurrent depletion of adenosine triphosphate. These changes are probably reversible and therefore may be amenable to acute intervention to correct or prevent progression. The neuropathology of moderate brain injury probably represents the front end of the spectrum of pathophysiology seen with severe head trauma. Because of this, patients are vigilantly monitored to avoid hypoxia and hypotension and other secondary systemic insults that could worsen neurologic outcome.

Clinical Features and Acute Management

A wide variety of clinical presentations occur with moderate head injury. Patients often have experienced a change in consciousness at the time of injury, a progressive headache, PTSs, vomiting, and post-traumatic amnesia. On ED presentation, patients are often confused or somnolent, but most can still follow commands. Focal neurologic deficits may be present. Many patients with moderate head trauma have concurrent serious facial injuries that may interfere with attempts at securing their airway. Other systemic trauma should also be ruled out.

An important clinical scenario in the spectrum of moderate head injury is that of the talk and deteriorate patient. These patients have a GCS score of 13 or greater on presentation but deteriorate to a status of a severe head injury (GCS score 8) within 48 hours.[87] Although this description can include patients with minor head trauma, most patients who talk and deteriorate initially have GCS scores suggesting moderate head trauma. When the syndrome was first described by Reilly more than 30 years ago,[88] the mortality in head-injured patients who were talking at presentation was estimated to be as high as 38%.[87-90] However, CT scans were not readily available at that time, and the GCS was not in widespread use. With the current availability of early CT scanning, as well as rapid transport via emergency medical services, injuries are detected earlier, and the mortality of talk and deteriorate is lower—estimated to be 2.5 to 12%.[87,91] In early descriptions of talk and deteriorate, most patients were found to have sustained subdural or epidural hematomas (EDHs). More recently, an equal number have been found to have contusions with subsequent edema.[87,91] Patients who talk and deteriorate are generally elders with higher injury severity scores.[87,91,92] In addition, anticoagulation puts patients at increased risk.

Successful management of moderately head-injured patients involves close clinical observation for changing mental status or focal neurologic findings, early CT scanning, and aggressive neurosurgical intervention. When no neurosurgeon is available and the patient develops symptoms consistent with herniation syndrome not reversed by acute hyperventilation and mannitol, ED trephination and hematoma evacuation of any amenable lesion should be considered.

Because of the varied presentation of patients with moderate head trauma, the initial examination alone cannot accurately predict who will have surgically correctable intracranial lesions. Traumatic intracranial lesions are frequent in moderately head-injured patients. Even patients with a GCS score of 14 have a reported rate of 14% traumatic intracranial lesions.[21] A CT scan is essential in patients with moderate head trauma to avoid delayed diagnosis of traumatic mass lesions or diffuse injury. This is especially true for elders or patients on anticoagulation therapy.[93,94] Skull radiographs may be useful if the patient has sustained a depressed skull fracture or a penetrating injury but are otherwise rarely helpful.

Disposition

All patients with moderate head injury should be admitted for observation, even with an initial apparently normal CT scan. Most patients improve over the first few days after injury.[23] Frequent neurologic checks should be initiated, and a repeated CT scan is indicated if the patient's condition deteriorates or fails to improve over the first 48 hours after trauma.

Complications

The overall mortality of patients with isolated moderate TBI is approximately 20%, but the morbidity is substantial. Most patients with moderate TBI remain symptomatic for extended periods after head injury. At 3 months after trauma, up to 70% are unable to return to work, 90% have memory difficulties, and more than 90% complain of persistent headaches.[95-98] TBI increases long-term mortality. One research group found that with regard to life expectancy, on average, TBI shortens the life span compared with non-TBI patients.[99,100] Almost 50% are left with a long-term disability that interferes with their previous daily activities.[98] In patients with persistent symptoms of headache, confusion, or memory difficulties, delayed MRI may define lesions in the regions related to cognition that cannot be seen on CT. Although not useful in the acute setting, MRI has prognostic value during subsequent care and assists in directing the future rehabilitation of these patients.

Minor Head Trauma

Minor or minor head trauma (MHT) is an injury to the brain resulting in a temporary and brief interruption of neurologic function after head trauma, which may involve a loss of consciousness (LOC).[56,101] The neuropathology involved in producing signs and symptoms of minor TBI may remain at the neurobiochemical level without damage to the microstructure. Heightened ionic flux, surges in levels of glutamate transmitters, disruption of enzymatic pathways, and accumulation of lactate and nitric oxide have

www.ketabpezeshki.com 66485457-66963820

been reported in brain tissue after experimental minor TBI.[17] Axonal stretching or twisting may occur with some mechanisms producing minor TBI. This injury pattern may promote glutamine-induced neurotoxic cascades that lead to the axonal damage typically described as DAI.[102] Experimental models of blast injury also produce these same changes.[103]

Most authorities, clinical policies, and decision rules now classify minor TBI as that producing a GCS score of 14 or 15.[17,101,102,104-106] In fact, the GCS is not sensitive enough to be of prognostic usefulness in minor TBI; a perfect score of 15 in the ED does not take into account the level of alertness or neurologic status immediately after trauma or the presence or absence of focal neurologic injury.[31,102,107]

From a practical standpoint, minor TBI is a clinical diagnosis. The diagnosis requires a credible mechanism of injury. In civilian life, most mechanisms that do not involve direct craniofacial impact cannot produce minor TBI. For example, belted drivers in low-velocity rear end–impact MVCs are not subjected to high enough acceleration-deceleration or rotary forces to the head to reach the force threshold needed to produce cerebral injury unless there is also direct impact to the head against a stationary object.[102,108] It is therefore unlikely that a patient with a whiplash or "jolt" injury would also have minor TBI. Collision sports–related minor TBI can be caused by acceleration-deceleration. Although the extent of this mechanism is not yet known, forces generated in blast injuries in wounded service personnel are the most common cause of minor TBI without direct head impact. Mild TBIs from blast injuries have been called the signature injury of the wars in Iraq and Afghanistan.[103]

Clinical and Historical Features

By the time most patients with minor TBI reach the ED, their symptoms are resolving or have completely resolved. The most common complaint after minor TBI is headache. Other common problems are nausea and emesis. Patients may also report transient disorientation, confusion, or amnesia. There is little evidence to correlate these symptoms with the presence of intracranial lesions in patients with minor TBI.

Clinical signs and symptoms of minor TBI include balance deficits, impaired verbal memory, delayed language comprehension, slowed speech, amnesia regarding the impact, a period of disordered awareness (with or without LOC), and a finite period of post-trauma amnesia (PTA).[91,102,108] Retrograde amnesia is impaired information retrieval and begins with and includes the traumatic event. In minor TBI, it generally lasts up to several minutes and then very rapidly resolves. PTA is impairment of information encoding and therefore does not resolve. PTA is the period of time from the injury to the return of conscious recall: events during this interval are essentially lost to the patient. PTA is a better predictor of injury severity and eventual outcome than the duration of retrograde amnesia or the GCS score.[102]

Approximately 5 to 15% of patients with minor TBI in the ED with a GCS score of 15 have abnormal CT scans.[102,104,109] This estimate is probably inflated, because at least 25% of patients with minor TBI never seek medical care. The incidence of life-threatening lesions that require neurosurgical intervention after minor TBI is variably reported but likely less than 1%[104]; the goal of emergency evaluation and management of patients with minor TBI is to identify these high-risk patients. Further diagnostic workup hinges on risk stratification in patients with minor TBI (Box 41-3). The criteria are based on several large studies, but because of inconsistent methodology and reporting, they have limitations. For example, LOC in minor head trauma has historically been considered a risk factor for significant injury, but the negative predictive value of LOC has not been determined, and many patients with minor TBI may have sustained only brief or no LOC.[110,111] Animal studies and anecdotal reports on humans suggest that the longer the duration of LOC, the more likely that an intracranial lesion exists, but the actual correlation between the duration of the LOC and the incidence of intracranial lesions or injury severity has not been determined.[108-112] Other high-risk minor head trauma criteria have also been proposed. The key for the emergency physician, however, is to determine the low-risk patient, and these criteria are less controversial.

Box 41-3 Risk Stratification in Patients with Minor Head Trauma

High Risk
Focal neurologic findings
Asymmetrical pupils
Skull fracture on clinical examination
Multiple trauma
Serious, painful, distracting injuries
External signs of trauma above the clavicles
Initial Glasgow Coma Scale score of 14 or 15
Loss of consciousness
Post-traumatic confusion or amnesia
Progressively worsening headache
Vomiting
Post-traumatic seizure
History of bleeding disorder or anticoagulation
Recent ingestion of intoxicants
Unreliable or unknown history of injury
Previous neurologic diagnosis
Previous epilepsy
Suspected child abuse
Age above 60 years or below 2 years

Medium Risk
Initial Glasgow Coma Scale score of 15
Brief loss of consciousness
Post-traumatic amnesia
Vomiting
Headache
Intoxication

Low Risk
Currently asymptomatic
No other injuries
No focality on examination
Normal pupils
No change in consciousness
Intact orientation and memory
Initial Glasgow Coma Scale score of 15
Accurate history
Trivial mechanism
Injury less than 24 hours ago
No or mild headache
No vomiting
No preexisting high-risk factors

Imaging Studies

A major decision regarding the emergency management of minor TBI is whether imaging studies should be performed. Several approaches have recently been described, but the research behind these suggestions remains confusing primarily because of differences in study populations, definitions, methods, risk factors included in analysis, and selection of acceptable outcomes. Based on critical assessment of the literature designed to address this question, the American College of Emergency Physicians (ACEP) has developed a clinical policy on neuroimaging of adult ED patients with mild TBI.[104] The recommendations from the ACEP clinical policy are summarized in Box 41-4.

www.ketabpezeshki.com 66485457-66963820

Box 41-4 American College of Emergency Physicians Clinical Policy Regarding Neuroimaging in Adults with Mild Traumatic Brain Injury

A noncontrast head CT is indicated (level one recommendation) in adults with LOC or post-traumatic amnesia only if one or more of the following is present:

- Headache
- Vomiting
- Age older than 60 years
- Drug or alcohol intoxication
- Deficits in short-term memory
- Physical evidence of trauma above the clavicle
- Post-traumatic seizure
- GCS score below 15
- Focal neurologic deficit
- Coagulopathy

A noncontrast head CT should be considered (level two recommendation) in head trauma patients with no LOC or post-traumatic amnesia if there is:

- Focal neurologic deficit
- Vomiting
- Severe headache
- Age 65 years or older
- Physical signs of a basilar skull fracture
- GCS score below 15
- Coagulopathy
- A dangerous mechanism (e.g., ejection from motor vehicle, pedestrian struck, fall of more than 3 feet or 5 stairs)

CT, computed tomography; *GCS*, Glasgow Coma Scale; *LOC*, loss of consciousness.

A critical comparison of six common decision-making strategies for neuroimaging in mild TBI has been made.[113] Although there are differences in the number of scans performed if each of the rules were applied to the same population, the sensitivity in detection of surgically important hematomas was not different among the rules. The final choice of which clinical decision rule to apply, and therefore the level of acceptable risk, rests on the clinician's attitude toward uncertainty.

The most practical approach regarding imaging in the ED patient is probably selective CT scanning or observation based on risk stratification of the patient with minor TBI. If the low-risk patient is fully awake and not intoxicated, has no focal neurologic findings, has no clinical evidence of skull fracture, and can be kept under competent observation for 12 to 24 hours, neuroimaging is usually not indicated. Patients with moderate-risk minor head trauma (see Box 41-3) should probably undergo CT scanning or prolonged ED observation.

Skull radiography after head trauma in adults has been largely replaced by more sophisticated imaging when imaging is performed. Patients with clinical signs of skull fracture have a substantially increased incidence of intracranial lesions associated with their minor head trauma. When the clinical examination shows evidence of skull fractures, CT scanning should be performed and plain radiographs should be forgone.

Although CT scanning is extremely sensitive for acute blood, MRI is more sensitive than CT for detecting DAI, ischemia after TBI, and some hemorrhagic lesions, especially those located at the base of the skull or in the posterior fossa.[114,115] However, there is no current evidence favoring the use of MRI over CT for MHT in the ED setting.[104] Many studies suggest that significant long-term neuropsychiatric sequelae after minor head trauma can occur despite an initial negative head CT scan, and these may be related to lesions seen initially only through MRI or functional imaging.[116] Functional imaging is not currently within the scope of emergency assessment of patients with minor TBI but can direct rehabilitation strategies for the small subset of patients with significant morbidity after minor TBI.

Ancillary Studies

No routine laboratory tests are needed for patients with isolated minor head trauma. A urine toxicology screen and blood alcohol level may be useful in interpreting the patient's mental status. Alcohol can affect the GCS, but this effect is not observed until the blood alcohol concentration is greater than 200 mg/dL; until that level, changes in mental status cannot be explained solely by acute alcohol intoxication.[102]

When shear injury occurs, proteins are released from neuronal axons. These proteins cross the BBB and can be detected in the peripheral circulation. A number of CNS biomarkers, such as S-100B, neuron-specific enolase, myelin basic protein, cleaved tau, and creatine kinase isoenzyme BB, have been investigated in minor TBI. None have been shown to strongly correlate with long-term outcome, and only S-100B predicts abnormal CT findings in minor TBI if measured within 4 hours of injury.[18] However, S-100B appears to lack CNS specificity and is found in adipose, skin, and cartilage; it is therefore often elevated in multiple-trauma patients with no head injury.[117] To date, serum biomarkers have lacked the precision needed for meaningful application in the emergency setting.[118]

Disposition

Most patients with low-risk minor TBI can be discharged from the ED with normal examination findings and after a reasonable period of ED observation (i.e., 4 to 6 hours). If the emergency physician decides that the patient with moderate- or high-risk minor TBI can be sent home, an appropriate early follow-up should be arranged. Patients should be discharged with instructions describing the signs and symptoms of delayed complications of head injury, should have access to a telephone, and should be monitored in the acute post-trauma period by a responsible, sober adult. If any doubt exists regarding the safety of the discharged patient with minor head injury, a brief inpatient observation period (i.e., 12 to 24 hours) is advisable.

If resources allow, prolonged ED observation may be practical in some circumstances. For example, intoxicated patients with minor TBI who otherwise fulfill low-risk criteria should undergo meticulous serial evaluations in the ED until clinical sobriety is achieved. In these patients, a CT scan may be unnecessary, and ED observation is beneficial.

If a patient with minor head trauma returns to the ED because of persistent symptoms, delayed complications of minor head injury should be sought. If a CT scan was not initially performed, the intensity of symptoms may guide the decision to obtain a CT scan at the second visit. If a negative scan was initially obtained, the likelihood of the subsequent development of an intracranial lesion is small.[104] The decision to rescan is more complex in patients from certain subgroups who may be considered more likely to develop delayed complications. These include patients on anticoagulation, those with preexisting neurologic injuries that may obscure an examination, and those with previous neurosurgical procedures (such as ventriculoperitoneal [VP] shunts). The literature about repeat CT scanning in mild traumatic brain injury (MTBI) is scant; however, in one systematic review of severe and moderate TBI, progression of lesions most commonly correlated with overall injury severity and the patients' use of anticoagulants.[119]

Patients on Anticoagulation. All current minor head injury decision-making rules exclude patients who are taking Coumadin or antiplatelet medications. Most current practice guidelines promote that patients who sustain head trauma and are on anticoagulation treatment should have the international normalized ratio (INR) determined and should undergo a CT scan without contrast.

www.ketabpezeshki.com 66485457-66963820

Concussion. Almost all patients with minor TBI will have rapid and complete resolution of their symptoms. However, a subset of patients with mild TBI report symptoms that persist for long periods after trauma. A concussion (or complicated minor TBI) is a type of minor TBI usually caused by acceleration-deceleration or rotational injury to a freely mobile head and is most commonly associated with collision sports.[101,120] It is a complex pathophysiologic state resulting in short-lived distortion of axons, vasculature, and brain neuroanatomy. As with other types of minor TBI, acute CT or MRI abnormalities are not usually found[108,120] but functional imaging (i.e., positron emission tomography [PET]) reveals abnormalities with glucose uptake and blood flow.[116] Levels of neurotransmitters remain elevated, and a hypermetabolic state may persist in the brain for several days to weeks after the initial injury. This period is vulnerable to cumulative dysfunction if a second injury occurs, especially in children.[121]

The persistent symptoms after MHT are called the *postconcussive syndrome* (PCS) and generally include the domains of cognitive, psychomotor, and behavioral performance. The severity and duration of postconcussive symptoms may correlate with the abnormalities found with early functional imaging.[116,120] The incidence of PCS after MHT is reported to be 10 to 58% at 1 month after injury,[122] but these estimates are based on inpatient studies and are therefore likely to be high.

The most common delayed or persistent postconcussive complaints are headache, sensory sensitivity, memory or concentration difficulties, irritability, sleep disturbances, dizziness, depression, and amnesia regarding the traumatic event. In young children, acute symptoms of concussion differ from those in adults and may include restlessness, lethargy, confusion, or irritability.[120] The appearance of symptoms may occur long after the concussion, and they persist long after the acute symptoms of uncomplicated MHT.[120] It was once believed that persistent postconcussive symptoms were psychosomatic, litigious, or factitious; however, the presence of abnormalities on functional imaging and with sophisticated neuropsychometric testing suggests a pathophysiologic basis for PCS.[17,122] Studies of concussed athletes (for whom preinjury baseline data are available) show that the cognitive domain most frequently involved in PCS is memory.[17] Dizziness, headache, and nausea occurring early after trauma are associated with prolonged PCS; patients with all three symptoms have a 50% chance of persistent symptoms at 6 months, compared with a 28% chance for those with MHT with none of these symptoms at presentation.[122] Most adult patients with PCS recover within 3 to 12 months after injury.[100,104,115,120]

Approximately 300,000 sports-related concussions occur annually each year. Among these, about 135,000 are in child athletes aged 5 to 18 years.[123] A study of concussed football players showed acute symptoms lasting at least 5 days, cognitive impairments lasting 5 to 7 days, and balance deficits lasting 3 to 5 days after concussion; 91% were back to their preinjury baseline by 7 days, but some had deficits on verbal fluency tests as long as 90 days after injury.[124] As a result of these and other data, educational campaigns have been launched for athletes on the signs and symptoms of concussion and steps to take when a concussion has occurred during play. The CDC has developed a number of "Heads Up" tool kits aimed at players, parents, and coaches to address these goals.[123] The CDC, National Football League (NFL), NFL Players Association, Professional Football Athletic Trainers Society, and NFL Physician's Society initiated a joint effort in 2010 with similar aims.

The demonstrated period of neurodysfunction and the delayed return to cognitive and physical baseline that follows concussive impact have lead to the development of several scoring systems to grade severity of concussions with the goal of determining when it is safe for an athlete to return to play. No single set of guidelines has emerged that has been universally accepted, but all are predicated on the concern about a period of vulnerability after impact. Football players sustaining concussion appear susceptible to an additional concussion, with the majority of reinjury occurring within 10 days after the first injury. This is variably attributed to balance defects, delayed reflexes, delayed speed of information processing, or simply continued exposure to collision sports.[123] Recent consensus of sports medicine experts emphasizes physical and cognitive rest after sports-related concussion until complete symptom resolution.[123,125] Although some organizations have published guidelines for rapid return to play (RTP) after a concussion (including same-day return), most are applicable only to professional or elite athletes and only when adequate sideline resources are available to detect subtle symptoms (e.g., on-site sports doctors, formal sideline neuropsychometric testing). For high school and collegiate athletes, a stepwise strategy has been developed to clear the athlete for RTP[107] (Table 41-3). Progression from one step to the next requires that the athlete be asymptomatic; if symptoms recur, the patient drops back one step in the progression. This graduated RTP protocol cannot be achieved without referral and long-term care; in the ED management of concussed athletes, no RTP should be allowed until such follow-up and progress have occurred. The second impact syndrome (SIS) occurs when an athlete sustains a second concussion before being completely asymptomatic from the first and then experiences a rapid, usually fatal, neurologic decline. It is postulated that persistent neurochemical disruptions and altered autoregulatory mechanisms after a first injury make the brain particularly vulnerable to marked brain swelling and subsequent herniation after a seemingly minor second impact. Although the existence and frequency of the SIS are controversial and hotly debated in the sports medicine literature, its serious implications affect subsequent management decisions regarding head-injured athletes and others with concussion.[126] All current recommendations for RTP after a sports-related concussion, including the graduated RTP protocol described earlier, state that players with concussion should not return to play for at least 1 week after they have become asymptomatic.

Table 41-3 Graduated Return-to-Play Protocol

REHABILITATION STAGE	FUNCTIONAL EXERCISE AT EACH STAGE OF REHABILITATION	OBJECTIVE OF EACH STAGE
1. No activity	Complete physical and cognitive rest	Recovery
2. Light aerobic exercise	Walking, swimming, or stationary cycling, keep intensity to <70% of maximum predicted heart rate; no resistance training	Increase heart rate
3. Sport-specific exercise	Skating drills in ice hockey, running drills in soccer; no head impact activities	Add movement
4. Noncontact training drills	Progression to more complex training drills, for example, passing drills in football and ice hockey; may start progressive resistance training	Exercise, coordination, and cognitive load
5. Full-contact practice	With medical clearance, participate in normal training activities	Restore athlete's confidence; coaching staff assesses functional skills
6. Return to play	Normal game play	

Adapted from McCrory P, et al: Consensus statement on concussion in sport: The 3rd International Conference on Concussion in Sport held in Zurich, November 2008. J Athl Train 44:434-448, 2009.

www.ketabpezeshki.com 66485457-66963820

PEDIATRIC HEAD INJURIES

Epidemiology

Approximately 650,000 to 1 million children are emergently evaluated yearly in the United States for head trauma, with 80 to 90% classified as mild.[127,128] However, TBI accounts for the largest source of childhood mortality and morbidity after trauma. The etiology of TBI is age related; in infants and the very young, abusive injury is a major cause of TBI. In toddlers, abusive injury must be considered, but injury from falls appears more common. Once children enter school, injuries from physical activities (such as bicycle riding) and MVCs (especially pedestrians stuck by cars) are the most common causes of TBI.[129-131]

Pathophysiology

Until the cranial sutures close, children's skulls are more distensible than those of adults. As a result, young children often sustain less TBI after head trauma than adults with comparable nonfatal mechanisms of injury.[132] However, children appear to have an age-dependent brain vulnerability. Very young children (younger than 1 year) have higher mortality after head trauma than older children with injuries with the same severity of injury. Many factors contribute to this. Medical attention is often delayed in children with nonaccidental injuries. Because of limited language and comprehension, an accurate formal neurologic examination in young children is sometimes difficult. Medical personnel tend to underestimate the extent of the injuries in small children and are often reluctant to initiate invasive procedures that may be necessary to aid in the diagnostic workup, such as intravenous access for sedation in CT scanning.

The types of TBI sustained after head trauma in children differ from those in adults. Children have fewer traumatic mass lesions (with the exception of SDHs in the very young), fewer hemorrhagic contusions, more diffuse brain swelling, and more diffuse axonal injury. Of head-injured patients younger than 20 years who talk and deteriorate, 39% have brain swelling only (i.e., no mass lesions), whereas 87% of patients older than 40 who talk and deteriorate have mass lesions.[89]

Clinical Features

As with adults, an accurate description of the mechanism of injury, the appearance of the child immediately before and after the injury, and subsequent events can provide useful information to assist in the evaluation and management of the acutely head-injured child.

The initial physical presentation of a child with TBI may have minimal predictive value in terms of the severity of trauma sustained.[133] Therefore repeated examinations to detect changes in the neurologic status are paramount.

In principle, the acute neurologic assessment of head-injured children is the same as that of adults. Because of its reliance on developed language skills and the patient's attention and cooperation, the GCS is difficult to apply to very young children. A modified scale (see Table 38-4) has been developed[134] and has been shown to accurately predict the need for neurosurgical intervention in head-injured preverbal children.[135]

Children with severe or moderate head injury are clinically similar to adults with these degrees of injury, although children have an increased incidence of early (i.e., within the first week after trauma) PTSs after severe head injury.[23] Low GCS score and young age are associated with an increased early PTS risk. Even after adjustment for GCS score, children younger than 2 years have up to a threefold increased risk compared with older (i.e., older than 12 years) children.[66] Overall, up to 6% of all head-injured children and 20% of severely head-injured children have early PTS. Most PTSs occur within the first 24 hours and do not predict seizures later in the post-traumatic period. However, early PTS can exacerbate secondary brain injury by creating hypoxia and increasing cerebral metabolism and ICP. Although prophylactic use of anticonvulsants is not recommended to prevent late PTSs, acute anticonvulsant prophylaxis is a treatment option in severely head-injured infants and young children to prevent early PTSs.[66]

The clinical presentation of post-traumatic *intracranial lesions* in infants who have sustained moderate or severe TBI can be extremely subtle, especially in those younger than age 6 months. Often these lesions are associated with scalp injuries and skull fractures but no other symptoms. Toddlers are also difficult to assess; the only symptom of an intracranial injury may be irritability.[138,139] Recommendations are also offered regarding the ED workup in these very young children.

Inflicted head injury, also described as *abusive head injury* or *nonaccidental head injury,* is the most common cause of head injury deaths in infants. Child abuse is considered in all children with unexplained head injuries or injuries not consistent with the history provided. The *shaken baby syndrome* is most often seen in children younger than 1 year and is inflicted by violently shaking an infant while holding him or her by the torso or extremities. The uncontrolled head movement causes an acceleration-deceleration brain injury, with a rotary component, as the moving brain strikes against the interior of the skull. The resultant shearing injury causes widespread damage. Patients have a broad range of symptoms, from nonspecific complaints such as vomiting or sleepiness, to seizures and coma. Classically described findings include SDHs, and subarachnoid hemorrhage (SAH) without signs of external trauma. Diffuse retinal hemorrhages are seen in 50 to 100% of all patients with shaken baby syndrome; the extent of hemorrhage appears related to injury severity and may predict the prognosis.[130]

Children who sustain minor head trauma often have more pronounced physical signs and symptoms than adults. Despite apparently trivial trauma, children may appear pale, be lethargic, and have frequent emesis and complaints of headaches and dizziness.

Children with concussions tend to be symptomatic longer after mild TBI than adults. As in adults, postconcussive symptoms in children include neurocognitive changes. The severity and duration of postconcussive symptoms is related to the severity of initial injury, as well as personal and environmental factors. Children who have sustained LOC, post-traumatic amnesia, a GCS score less than 15 at presentation, or mental status changes are more likely to have prolonged postconcussive symptoms.[140,141] Thus children should not return to sports or play activities until completely symptom free, and then only at the discretion of their primary physician.[120] Concussive injuries in children also produce two unique clinical circumstances. Many children experience a brief *impact seizure* at the time of relatively minor head injury. By the time the child is evaluated, he or she is at baseline neurologic function. Impact seizures do not appear to predict subsequent early PTSs. However, a post-traumatic impact seizure may confuse the initial assessment of the severity of the head injury and prompt a more aggressive workup than needed. *Postconcussive blindness,* another serious complication of concussive injuries in children, is usually associated with impact to the back of the head. Children experience a temporary loss of vision that can persist from minutes to hours before normal vision returns.

Diagnosis and Management

As with adults, pediatric head-injured patients should be assessed for other major trauma and assumed to have cervical spine injury until proved otherwise. Goals of ED management are also

www.ketabpezeshki.com 66485457-66963820

generally the same: to prevent secondary injury and systemic insults, to prevent increasing ICP, and to detect traumatic mass lesions requiring emergency surgery.

Children with severe TBI who are transported directly to a pediatric trauma center or an adult trauma center with pediatric capabilities have better outcomes than those transported to non-trauma hospitals.[66] Hypoxia and hypoventilation are common in pediatric head-injured patients, and they develop more rapidly in children than in adults. In children with a GCS score below 8, airway management should be aggressive to prevent hypoxia, aspiration, and hypercarbia and to allow mild hyperventilation if the patient has signs of herniation. There is no evidence to support the advantage of out-of-hospital intubation over bag-valve-mask ventilation of pediatric patients with TBI[66,142]; scene time should not be prolonged with multiple attempts at endotracheal intubation.

Hypotension is a late finding in children in shock; poor perfusion should be clinically identified and corrected as soon as possible to ensure adequate CPP. There is no evidence to suggest that aggressive fluid resuscitation exacerbates cerebral edema in head-injured children. In children, unlike in adults, hypovolemic hypotension can occur because of head trauma. Hypotension from intracranial bleeding can occur in children younger than 1 year with a large linear skull fracture and an underlying large EDH.[132] The intracranial blood can seep through the fracture and produce a large galeal or subperiosteal hematoma. Hypotension from intracranial bleeding can also occur in a child with hydrocephalus and a functioning shunt. Blood may accumulate without much evidence of increased ICP. Scalp lacerations can also produce significant hemorrhage and subsequent hypotension.

Up to 80% of children with severe head trauma have elevated ICP.[132] In infants, a bulging fontanel suggests elevated ICP. Other signs of elevated ICP include bradycardia, papilledema, declining level of consciousness, and seizures. When increased ICP is indicated by physical examination, methods to reduce ICP should be initiated. As with adults, acute hyperventilation has immediate effects but is never indicated for prophylaxis or for prolonged management of increased ICP.[66] Hyperosmolar therapy is effective at reducing ICP. There have been no studies describing the superiority of one osmotic agent over another in the treatment of TBI, and no direct comparisons have been done. Although efficacy studies were based only on adults, mannitol at doses of 0.25 to 1.0 g/kg has become a mainstay in the treatment of elevated ICP in children with severe TBI. Bolus therapy has a theoretic benefit compared with continuous treatment; over prolonged periods, mannitol may accumulate in injured areas of the brain where the BBB is no longer intact, thus creating a reverse osmotic shift.[143,144] Several studies support the effectiveness of HTS in lieu of mannitol for elevated ICP in pediatric head-injured patients. Treatment is with a continuous infusion of 3% normal saline at 0.1 to 1.0 mL/kg body weight per hour, titrated to effect.[66]

Severely head-injured children are less likely to have a surgically amenable lesion than adults. Because diffuse brain swelling is the most common finding in severely head-injured children, emergency burr holes are generally ineffective.

When minor head injury is considered in children, age is an important consideration in interpreting clinical and historical findings. Children younger than age 2 years are often difficult to assess and may have subtle clinical findings. In general, the literature supports the conclusion that younger patients are at higher risk for intracranial injury. One clinical sign of potential brain injury in children younger than age 2 years is the presence of a scalp hematoma, especially a large parietal scalp hematoma.[143-145] In an observational cohort study involving children with low risk for brain injuries, scalp hematomas were present in 93% of children 2 years old or younger who had brain injuries.[144]

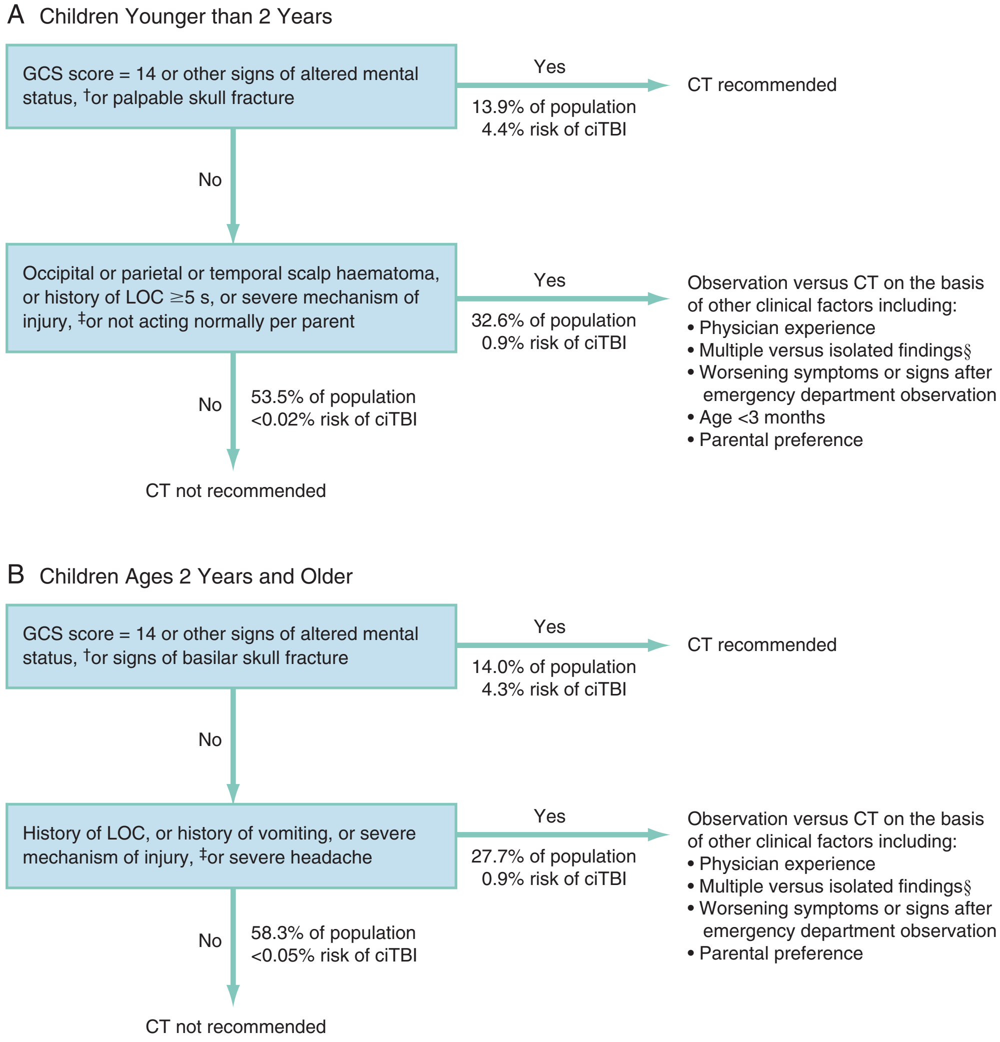
More than 50% of children with head injury of all severities in the United States undergo emergent cranial CT scanning.[127,146] Cranial CT is the diagnostic imaging modality of choice in the evaluation of moderate or severe pediatric TBI and should also be strongly considered in pediatric patients with high-risk minor TBI. However, potential risks are associated with childhood exposure to radiation. Children are more sensitive to radiation than adults because of rapidly dividing cells during normal growth. The younger the child, the more potential risk. Increased rates of solid tumor cancers[146] and decreased cognitive performance have been associated with radiation doses similar to that of a single head CT scan.[147] An additional safety concern is the frequent need to sedate young children in order to perform an adequate imaging study. In these circumstances, the risks of radiation exposure and sedation should be weighed against the likelihood of an intracranial lesion in the child with minor head trauma.

It is estimated that up to 98% of cranial CT scans done to assess head injury in children are negative.[145,148] Several clinical prediction rules have been developed to assist in decision-making for emergent neuroimaging of children with minor TBI. Comparison of these various rules is difficult because of variable methods and inclusion criteria. Most have not been validated in a separate population.[148,149] Unless both sensitivity and specificity are high, such rules may actually result in an increased number of CT scans being performed. Kupperman and colleagues,[145] with a research network including 25 EDs and 4200 patients, have derived and validated a clinical prediction rule for minor head trauma that includes subsets of children younger than 2 years and from 2 to 18 years old. The rule performs well with a very low risk of missed clinically important TBI in both age subgroups. An algorithm suggested by this study is presented in Figure 41-7. The CATCH study derived a decision rule that identified two levels of risk for children with minor head injury.[150] The large cohort of 3800 patients was identified from 10 Canadian pediatric teaching institutions. Children with a GCS score below 15 at 2 hours after trauma, a suspected open or depressed skull fracture, a worsening headache, or persistent irritability were found to be at increased risk for the need for a neurosurgical intervention and considered high risk; moderate risk (brain injury on CT with no need for neurosurgical intervention) was associated with any sign of basal skull fracture, a large boggy scalp hematoma, or a dangerous mechanism of injury (e.g., MVC or fall greater than 3 feet).

The use of skull radiographs in the diagnostic workup of head-injured children is controversial but may be appropriate in some circumstances. As with adults, when a CT scan is indicated, skull radiographs are not necessary. Up to 11% of children younger than age 2 years will sustain a skull fracture associated with head trauma, and 15 to 30% of these will have TBI. Therefore in children younger than age 2 years, a skull fracture is a predictor of TBI.[151] The presence of a skull fracture in children significantly increases the likelihood of intracranial pathology; conversely, a negative radiographic skull screen does not guarantee the absence of TBI. Parietal skull fractures are the most common. Often, fractures occur in infants who sustain relatively minor head injury. Skull films may be useful as a screening tool in determining the need for a CT scan, especially in children 2 years old or younger whose neurologic examination is difficult to obtain and interpret. In alert children younger than age 2 years with minor head injury, a low-risk history, normal findings on physical examination that includes a neurologic and mental status examination appropriate for age, and a scalp hematoma, skull radiographs may be a useful screen.[139] If the skull radiograph is negative for a fracture, a CT scan may be unnecessary. If the skull radiograph shows a fracture, CT imaging is indicated.

In older children, skull radiographs are rarely useful unless a specific lesion is suspected, such as a depressed skull fracture or a

www.ketabpezeshki.com 66485457-66963820



GCS = Glasgow Coma Scale. ciTBI = clinically important traumatic brain injury. LOC = loss of consciousness. Data are from the combined derivation and validation populations. †Other signs of altered mental status: agitation, somnolence, repetitive questioning, or slow response to verbal communication. ‡Severe mechanism of injury: motor vehicle crash with patient ejection, death of another passenger, or rollover; pedestrian or bicyclist without helmet struck by a motorized vehicle; falls of more than 0·9 m (3 feet) (or more than 1·5 m [5 feet] for panel B); or head struck by a high-impact object. §Patients with certain isolated findings (i.e., with no other findings suggestive of traumatic brain injury), such as isolated LOC,[39,40] isolated headache,[41] isolated vomiting,[41] and certain types of isolated scalp hematomas in infants older than 3 months,[31,42] have a risk of ciTBI substantially lower than 1%. Risk of ciTBI exceedingly low, generally lower than risk of CT-induced malignancies. Therefore CT scans are not indicated for most patients in this group.

Figure 41-7. Suggested computed tomography algorithm for **(A)** children younger than 2 years and **(B)** children aged 2 year and older with GCS scores of 14-15 after head trauma. (Adapted from Kuppermann N, et al: Identification of children at very low risk of clinically important brain injuries after head trauma: A prospective cohort study. Lancet 374:1160-1170, 2009.)

penetrating foreign object. Skull fractures are more clinically significant in children than in adults. Fractures, especially complex stellate or multiple injuries, are often seen in abused children, and skull films should be obtained if abuse is suspected. *Ping-Pong fractures* occur with concentrated forces that indent the skull. These fractures are unique to infants and appear as multiple indentations in the skull with no significant bone discontinuity. Skull fractures are common in children who have sustained deep scalp lacerations or who have a large scalp hematoma.

Post-traumatic leptomeningeal cysts or *growing skull fractures* are delayed complications of linear skull fractures in infancy. If a tear in the dura accompanies the linear fracture, the meninges may fill with CSF and prolapse through the fracture margins, thus preventing fracture healing.[23,139] These cysts can grow in size and have the potential to cause a mass effect. If a linear fracture is found by skull radiography, close follow-up is indicated to assess for this rare delayed complication.

Overall, children who sustain severe head injury have lower mortality and a better neurologic outcome than comparably injured adults. This is probably because of the neuroplasticity of the young brain; however, in children younger than age 2 years, the prognosis after severe head injury is poor.[152] Very young children have immature cerebrovascular autoregulation, which increases the risk of cerebral edema formation. The immature brain has increased susceptibility to permanent injury because of incomplete myelination.

The emergency evaluation of children with minor head injury is especially challenging, given their potentially dramatic presentation and the added difficulty of obtaining an accurate neurologic assessment. Evidence-based consensus guidelines have been proposed for the evaluation and management of minor head injury in children.[23,127,138,139] Parents should be educated about the warning signs and symptoms of delayed complications of minor head trauma.

www.ketabpezeshki.com 66485457-66963820

PENETRATING HEAD INJURIES

Epidemiology

Penetrating brain injury (PBI) occurs at a rate of 12 per 100,000 population and can be caused by missile injuries or impalement.[153] The United States has the highest penetrating head injury rate among developed countries in the world, with the most common cause being gunshot wounds (GSWs). These dramatic injuries are increasing in frequency, and the neuroscientific understanding of the complicated cerebral events that occur with penetrating head injury does not yet equal our understanding of the pathophysiology of blunt injuries.

Civilian GSWs to the head account for approximately 31,000 deaths per year, and up to 70% of all patients who sustain a GSW to the head are dead at the scene.[154,155] Overall, the mortality caused by a GSW to the head is estimated to be 90%.[156] If the patient is hemodynamically stable, has not sustained secondary systemic insults such as hypoxia or hypotension, has no expanding mass lesions from the missile injury, and has not ingested intoxicants that may interfere with assessment, prognosis after a GSW to the head can be predicted by the GCS score and pupillary responsiveness at presentation.[157] If the GCS score at presentation is less than 5, mortality approaches 100%. If the GCS score at presentation is greater than 8 and the pupils are reactive, survival approaches 75%. Survivors of GSWs to the head tend to do well, with up to 60% returning to their former employment.[157]

Pathophysiology

Missile injuries to the head can result in several different patterns of damage. *Tangential wounds* are caused by an impact that occurs at an oblique angle to the skull. If the missile has high velocity but low energy, it can travel around the skull under the scalp without passing through the skull. Intracranial damage, primarily cortical contusions, can occur at the initial site of impact because of pressure waves generated by the impact. In one study, 24% of patients with tangential GSWs also had intracranial hemorrhage, and 16% sustained skull fractures.[158,159] Many patients with tangential GSWs have a GCS score of 15 on presentation.

Perforating wounds are usually caused by high-velocity projectiles, which cause through-and-through injuries of the brain with an entrance and an exit wound. This type of injury is largely discussed within the context of military GSWs to the head.

Penetrating missile wounds are produced with moderate- to high-velocity projectiles discharged at close range. The majority of the civilian PBI literature deals with penetrating missile wounds.[156] The penetrating object may travel through the entire skull, bounce off the opposite inner table of the skull and ricochet within the brain, or stop somewhere within the cranial cavity. Bullets that penetrate the skull do not travel in a straight path. The wounding capacity of a firearm is related to the kinetic energy of its missile on impact and how much energy is dissipated in the tissues. Low-velocity missiles tend to be deflected by intracranial structures. The final track is therefore erratic and occasionally bears no relation to the exit or entrance site of the missile.[160,161] High-velocity missiles can project straight through the tissues and easily fracture bones. Flight stability and the angle at which the bullet strikes its target affect the path through the brain. Within tissue, destabilizing motions include deviation of the longitudinal axis of the bullet from a straight line (yaw), forward rotation of the bullet around its center of mass (tumbling), and oscillatory motion of the bullet axis around its center of mass (rotation). As the bullet passes through the brain, a tissue cavity is created. This cavity can be as much as 10 times the diameter of the missile. A percussion shock wave is also created, lasting 2 msec but causing little tissue destruction.[156,160,161]

The morbidity and mortality from missile injuries to the head depend on the intracranial path, speed of entry, and the size and type of the penetrating object. Projectiles that cross the midline or the geographic center of the brain, pass through the ventricles, or come to rest in the posterior fossa are associated with extremely high mortality.[157,160,161] High-velocity wounds are associated with greater mortality than low-velocity injuries. Large missiles or missiles that fragment within the cranial vault are usually fatal. The design of the bullet and its fragmentation potential (capacity to deform or fragment) also contribute to final tissue destruction and patients' morbidity and mortality.

Many GSWs to the head are intentionally self-inflicted injuries. The percentage of penetrating head injuries caused by self-inflicted GSWs ranges from 13 to 88%.[157] Characteristics of self-inflicted GSWs include injury on the dominant side, powder burns at the entrance site, and large stellate scalp lacerations caused by dissection of the subgaleal layer by exploding gases released close to the scalp. In suicide attempts, GSWs to the head tend to traverse the midline in the coronal plane and often involve major vascular structures. If the self-inflicted GSW has an entrance through the mouth, injury to the hard palate may occur with potential upper airway compromise. The careful aim and close range of self-inflicted GSWs to the head make these injuries particularly devastating; mortality is higher than with non–self-inflicted penetrating injuries, and odds ratios of death vary from 1.63 to 5.83.[157]

Clinical Features

Physical assessment of the patient with a missile wound to the head focuses on the presenting GCS score and pupillary responsiveness. The entire scalp is carefully inspected for occult GSWs. In addition to the physical damage to brain tissue caused by the penetrating injury, other devastating physiologic changes occur immediately after injury. ICP increases, the BBB breaks down, CBF is altered, and cerebral edema develops. Cerebral autoregulation is lost, and CPP may fall.

Management

The ED management is directed at reducing the occurrence of the secondary systemic insults of hypoxia and ischemia, with emergent intervention if signs of herniation syndrome develop and the patient is viable. Management should be aggressive until the prognosis can be established by examination and neuroimaging data. When penetration of the cranial vault is established, the patient should be intubated. If the physician waits for coma before intubating the patient, mortality approaches 100%.

Emergency treatment should include intravenous antibiotics because penetrating missiles are contaminated with skin, bone, and hair. Tissue contamination may be widespread because of the cavitation caused by the missile as it passes through the brain.[162] Approximately 90% of all CNS infections associated with penetrating TBI injuries occur within 6 weeks. Most neurosurgeons do not automatically débride bone and missile fragments owing to a growing body of literature that shows no evidence that removal of these foreign bodies decreases infection rate.[18,156]

Between 30 and 50% of patients with PBI develop seizures; 10% of these occur in the first week.[18,156] Anticonvulsants should be given in the acute setting to prevent early PTSs in the patient with PBI, especially if the patient is to be transported to another institution after acute stabilization. Anticonvulsants should not be given beyond the first week after PBI because this has not been shown to prevent the development of late seizures.

Skull radiographs may be useful in determining the number of penetrating fragments and their track. A CT scan defines the precise location of the missile, its intracranial path, the presence

www.ketabpezeshki.com 66485457-66963820

of bone or missile fragments, extra-axial or intracerebral blood collections or other traumatic lesions, and pneumocephalus. CT scanning is the radiologic test of choice for PBI.[163] Pneumocephalus is often associated with missile wounds that penetrate the sinuses but can be caused by free air sucked into the penetration cavity behind the projectile.

All tangential GSWs should be evaluated with a head CT scan secondary to the high incidence of associated intracranial injury.[159] When a penetrating head injury is caused by *impalement,* the penetrating object should be left in place to be removed at surgery. A skull radiograph shows the size of the object, the angle of impalement, and the depth of penetration. Angiography may be indicated to better discern location referable to key vascular structures.

COMPLICATIONS AFTER HEAD INJURY

Neurologic Complications

Seizures

PTSs are relatively common in the acute or subacute period. Acute PTSs are usually brief and are probably caused by transient mechanical and neurochemical changes within the brain. After the acute seizure, the patient often has no additional seizure activity. In the subacute period, 24 to 48 hours after trauma, seizures are caused by worsening cerebral edema, small hemorrhages, or penetrating injuries. PTSs are common in children and can be precipitated by relatively minor head injury.[164] Acute PTS prophylaxis in the ED is recommended for some head-injured patients even if they have not had a seizure (see Box 41-2).[78,80,164] This is especially important in patients who will have neuromuscular blockade to facilitate management or transfer because the clinical manifestations of seizures are lost in these patients. Phenytoin and fosphenytoin are used as first-line agents for prophylaxis. The decision to maintain the head-injured patient on long-term anticonvulsant therapy during the recovery period depends on the patient's subsequent course. Long-term seizure prophylaxis is not indicated for all patients who have had PTSs in the acute or subacute period. The utility of prophylactic anticonvulsants to prevent late PTSs has not been proved, and their use is not recommended.[78] However, if a seizure occurs after the acute or subacute period, anticonvulsants are indicated. TBI has been estimated to account for 20% of all epilepsy in the general population.[165,166] It is the leading cause of epilepsy in young adults. In a longitudinal cohort study following individuals with moderate and severe head injury, Yasseen and colleagues[167] found that 9% of this population was being treated for epilepsy. Estimates of late PTSs in patients with moderate and severe TBI range from 4.2 to 25.3% and manifest themselves as long as 12 years postinjury.[168]

Central Nervous System Infections

Meningitis after Basilar Fractures. Post-traumatic meningitis is caused by a variety of microbes, depending on the portal of bacterial entry. Patients have typical signs and symptoms of meningitis, including fever, altered mental status, and occasional focal neurologic signs. In patients with a CSF leak after basilar fracture, early meningitis (i.e., within 3 days of injury) is usually caused by pneumococci. Ceftriaxone or cefotaxime is a reasonable antibiotic choice with the addition of vancomycin. Gram-negative organisms often cause meningitis that develops more than 3 days after trauma.[169] A third-generation cephalosporin, with nafcillin or vancomycin added to ensure coverage of *Staphylococcus aureus,* should be started. In children, post-traumatic meningitis may be caused by *Haemophilus influenzae.* Prophylactic antibiotics are not consistently recommended in the acute setting in patients with CSF leaks caused by basilar skull fractures during the first 7 days.[169] However, Friedman and colleagues found that prophylactic antibiotics administered in the first week reduced meningitis risk by one half.[170] The risk of meningitis does increase after 7 days of CSF leakage, and prophylactic antibiotics may be warranted.[171]

Brain Abscess. Brain abscesses develop infrequently after penetrating missile injuries to the head. Abscesses can also develop after open depressed skull fractures if bone fragments are not removed or as a postoperative complication. Post-traumatic CSF fistulae and fractures that disrupt air-filled sinuses predispose to the formation of brain abscesses. Clinical manifestations include headaches, nausea, vomiting, declining mental status, signs of increased ICP, or new focal neurologic findings in patients who had been improving after trauma. Occasionally, nuchal rigidity, hemiparesis, or seizures may be present. Systemic signs are often subtle, and CSF leukocytosis may be absent.

Contrast-enhanced CT scanning makes the diagnosis of brain abscess. A ring pattern with a low-density center is characteristic. The enhanced ring represents surrounding altered vascular permeability and therefore is also seen in the cerebritis stage early in abscess formation. Lumbar puncture is often not helpful and should not be performed in the patient with signs of increased ICP (e.g., headache, vomiting, and papilledema).

The treatment of brain abscess is usually operative drainage. The patient with cerebritis may respond to intravenous antibiotics but requires close monitoring with repeated CT scans. Common organisms isolated from post-traumatic abscesses are *S. aureus* and gram-negative aerobes.[169]

Cranial Osteomyelitis. Cranial osteomyelitis can occur after penetrating injury to the skull. The clinical manifestations include pain, tenderness, swelling, and warmth at the infected site. More than 50% of cases are obvious on plain skull radiographs.[169] Technetium bone scans can help in the diagnosis when the skull radiographs are negative, but false-positive bone scans occur in patients with previous trauma or craniotomy. Adding a gallium scan helps to differentiate infection from other causes of a positive technetium scan. Patients with post-traumatic cranial osteomyelitis require surgical débridement and removal of the infected bone. Antibiotic choice is determined by culture results. If systemic symptoms are present, an underlying subdural or epidural empyema is often present.

Medical Complications

Disseminated Intravascular Coagulation

The injured brain is a source of tissue thromboplastin that activates the extrinsic clotting system. Disseminated intravascular coagulation (DIC) can develop within hours after any injury disrupting brain tissue. It has been detected in nearly all patients with severe TBI.[93,172] DIC increases morbidity and mortality after severe head trauma as well as the risk of delayed intracranial hemorrhage. If a stable patient with DIC suddenly deteriorates, a repeat CT scan should be obtained to rule out hemorrhage.

The extent of tissue destruction determines the degree of DIC that develops. The diagnosis is based on abnormalities in INR, prothrombin and partial thromboplastin time, platelets, plasma fibrinogen levels, and fibrin degradation products. Patients with coagulopathy or abnormal platelet function require interventions to correct these. Patients with moderate or severe head trauma are at extremely high risk to experience venous thromboembolic events (VTEs) after admission to the hospital. Recent evidence suggests that patients with moderate or severe head trauma can be safely treated with low-molecular-weight heparin to reduce the risk of VTE without significantly increasing the risk of intracerebral hematoma expansion.[172]

www.ketabpezeshki.com 66485457-66963820

Neurogenic Pulmonary Edema

Neurogenic pulmonary edema can develop minutes to days after head trauma. Two theories exist on its pathophysiology: catecholamine surge or blast with elevated hydrostatic forces and increased capillary permeability directly caused by brain injury versus a systematic inflammatory reaction.[173-175] Lowering the ICP appears to reverse the neurogenic stimulation that causes this edema.[176] Close ventilator management is essential to improved outcomes in patients with acute lung injury secondary to TBI.[175]

Cardiac Dysfunction

A variety of cardiac rhythm, rate, and conduction abnormalities are detected after head injury. Harvey Cushing noted a connection between cardiac dysrhythmias and intracranial bleeding in the beginning of the 20th century.[177] These abnormalities can be life-threatening and require aggressive therapy. In addition, adequate cardiac output is essential in head-injured patients to ensure cerebral perfusion. Many head-injured patients with cardiac dysfunction have concurrent myocardial injury from underlying disease or from chest injury. However, brain injury can cause primary cardiac dysfunction. Cardiac rhythm abnormalities have been reported in up to 70% of all patients with SAH and more than 50% of all patients with intracranial hemorrhage.[34,174] In SAH the cardiac dysrhythmias may result from autonomic nervous system dysfunction that subsequently affects ventricular polarization. High levels of circulating catecholamines have been measured in head-injured patients, with increased sympathetic nervous system activation.[34]

The most common cardiac dysrhythmia after head injury is *supraventricular tachycardia,* but many other rhythms have been observed. Findings on the electrocardiogram include diffuse large upright or inverted T waves, prolonged QT intervals, ST segment depression or elevation, and U waves. The primary goal in the emergency management of cardiac dysfunction after head trauma is ensuring adequate tissue perfusion and avoiding hypoxia. Dysrhythmias in head-injured patients often resolve as ICP is reduced.[34,174] Standard advanced cardiac life support protocols should then be used because concurrent cardiac injury may also be present in multiply traumatized patients.

SPECIFIC INJURIES

Scalp Wounds

Scalp lacerations are extremely common after head injury and may be a source of significant bleeding because hemostasis may be difficult to achieve. Methods to achieve hemostasis include direct digital compression of the bleeding vessel against the skull, infiltration of the wound edges with lidocaine with epinephrine, and ligation of identified bleeding vessels. If the galea is lacerated, it can be pulled up with a clamp and its edges folded over the lacerated skin edges to tamponade the bleeding vessels. Raney scalp clips applied to the edges of the wound are also effective. In stable patients, quick closure of the wound, after proper débridement and irrigation, is the most effective way to stop a bleeding scalp laceration and prevent the tissue crush injury that may occur if other compressive methods are used for too long.

When hemostasis is obtained, the wound should be irrigated to rinse away any debris. The emissary vessels of the subgaleal layer of the scalp drain directly into the diploë veins of the skull. These in turn drain into the venous sinuses. Contaminated or infected scalp wounds therefore have the potential to cause serious intracranial infections. Blood clots and other debris should be removed and the galea and underlying cranium palpated to detect any remaining debris, disruptions, or bone step-offs. Shear injuries to the scalp may deposit contaminants at sites distant from the apparent injury. The complexity of stellate lacerations often interferes with thorough inspection and débridement; stellate lacerations are particularly susceptible to infection. Digital exploration of a scalp wound should be carefully performed; if it is done too vigorously, comminuted or depressed bone pieces may be depressed further.

It is easy to confuse a disruption in the galea or a tear in the periosteum with a skull fracture. The base of the laceration should therefore be directly visualized. Clipping away a small area of hair parallel to the edges of the wound may facilitate this. Alternatively, an antibiotic ointment can be applied to the hair immediately surrounding the wound and used to plaster the hair away from the injury site. If the laceration begins on the forehead and extends upward beyond the hairline, surrounding hair should not be removed. Removal obliterates a useful landmark for cosmetic closure and may result in malalignment of the two laceration edges. If hair is accidentally embedded within the repaired laceration, it can delay healing by producing an inflammatory reaction or by serving as a nidus of infection.

Disruption of the galea results in a gaping scalp laceration. Large lacerations of the galea are closed to prevent the edges of the wound from pulling apart as the muscles within the galea contract. The skin, dermis, and galea can usually be repaired in a single layer with interrupted or vertical mattress sutures of 0-3.0 nylon or polypropylene.[178] Several recent studies have evaluated the use of staples versus sutures to close scalp lacerations that do not involve the galea. For both adult and pediatric scalp lacerations that begin beyond the hairline, staples have been shown to be cheaper, take less time, and have the same outcome than sutures if used in the appropriate manner.[179-181] Staples cannot be used to close the galea and may not be effective alone when hemostasis is a problem.[181] Recently an alternative method of scalp laceration closure has been described in which bundles of the patient's hair on each side of the wound are twisted together and then secured with tissue glue.[182,183] This may provide another method of effective repair and prevent the need to remove the closure material after the wound has healed.

Because of the rich blood supply of the scalp, even very large scalp avulsions can survive. If the avulsion remains attached to the rest of the scalp by a tissue bridge, it should be reattached to the surrounding tissue. If the avulsion is completely detached from the scalp, it should be treated as any other amputated part and reimplanted as soon as possible.[178] Scalp abrasions are often contaminated with pieces of dirt or other debris. The wound should be cleaned as thoroughly as possible and inspected for puncture wounds or other areas that penetrate beyond the superficial layers of the skin to ensure the removal of unsuspected foreign bodies. A careful inspection often reveals a small scalp laceration within the abraded area. Antibiotics are usually not needed for carefully managed scalp wounds because rapid healing is facilitated by the rich blood supply of the scalp.

Skull Fractures

Clinical Assessment and Significance

Skull fractures are local injuries caused by direct impact to the skull. The presence of a skull fracture does not always indicate underlying brain injury. However, the force required to fracture the skull is substantial, and all patients with skull fractures are carefully evaluated to ensure that no additional injury is present. With increasing severity of head injury, the likelihood of skull fracture increases, and the presence of a skull fracture after trauma increases the likelihood of a TBI.[184-186] It is often difficult to predict the presence of a skull fracture by clinical examination, and if this can be done, it is likely that substantial underlying brain injury is

www.ketabpezeshki.com 66485457-66963820

also present. The pattern, extent, and type of skull fracture depend on the force of the impact applied and the ratio of the impact force to the impact area. The fracture usually starts at the point of maximum impact.

Clinically significant skull fractures result in intracranial air and pass through an air-filled space (e.g., sinus), are associated with an overlying scalp laceration (open skull fracture), are depressed below the level of the skull's inner table, or overlie a major dural venous sinus or the middle meningeal artery.[166,187]

A noncontrast head CT scan with bone windows has become the imaging modality of choice for patients with suspected skull fractures.[186,187] Plain radiographs can be useful when CT scan is not available; if an intracranial foreign body or a linear or depressed fracture is detected, a noncontrast head CT is indicated to rule out intracranial traumatic pathology.[187]

Linear Fractures

A linear skull fracture is a single fracture that goes through the entire thickness of the skull. Linear skull fractures are clinically important if they cross the middle meningeal groove or major venous dural sinuses; they can disrupt these vascular structures and cause the formation of EDHs. Most other linear skull fractures are not clinically significant

Sutural diastasis is the traumatic disruption of a cranial suture. In adults, sutural diastasis often involves the coronal or lambdoid sutures. Sutural diastasis usually occurs when a linear fracture extends into the suture line, and it is rare after sutures have undergone bone fusion *Comminuted* skull fractures are multiple linear fractures that radiate from the impact site. Usually this injury suggests a more severe blow to the head than that producing a single linear fracture. A linear *vault* fracture substantially increases the risk of intracranial injury.

Patients with nonsignificant linear fractures can usually be discharged from the ED with competent home observation. In patients with significant linear fractures, admission for observation is warranted.[186]

Depressed Fractures

Depressed skull fractures are clinically important because they predispose to significant underlying brain injury and to complications of head trauma, such as infection and seizures. When a depressed fracture occurs, traumatic impact drives the bone piece below the plane of the skull. The edges of the depressed portion of skull may become locked underneath the adjacent intact bone and fail to rebound into their previous position. As a result, the depressed piece of bone can penetrate tissue and lacerate the dura. Depressed skull fractures are usually caused by direct impact injury with small blunt objects, such as a hammer or a baseball bat. Most depressed skull fractures occur over the parietal or temporal regions. If the free piece of bone is depressed deeper than the adjacent inner table of the skull, most neurosurgeons consider this injury significant enough to require surgical elevation.[23,186]

When a CT scan is not available, detection of depressed skull fractures can be attempted with plain radiographs. However, depressed fractures may be difficult to visualize on plain skull radiographs. The free piece of bone demonstrates increased or double density because it often overlaps the nonfractured bone, or it is viewed relatively rotated from the rest of the adjacent cranium. Tangential views of the skull may increase the ability to visualize the fracture.

Depressed skull fractures are most often open fractures with disruption of the galea. They can often be felt with palpation of the skull beneath a scalp laceration. This examination should be done cautiously to avoid driving a depressed bone fragment deeper into the cranial tissue. The clinical examination for a depressed skull fracture may be misleading. The mobility of the scalp can result in nonalignment of the fracture with an overlying scalp laceration. As a result, the skull underlying the laceration may be normal, with the depressed area several centimeters away. Scalp swelling may also interfere with physical examination findings and hide any palpable bone defects. The signs and symptoms of a depressed skull fracture depend on the depth of depression of the free bone piece. About 25% of patients sustaining a depressed skull fracture report LOC.[186] Neurologic deficits may be present, depending on the extent of underlying brain tissue injury.

A CT scan is indicated for patients with a history or physical examination findings that suggest a depressed skull fracture. The CT scan should include bone windows to determine the depth of depression and the presence of concurrent traumatic intracranial lesions. Patients with depressed skull fractures should be admitted for continued observation.

Depressed skull fractures, as well as any type of penetrating skull injury, may increase the risk for developing seizures.[188] ED patients suspected of having a depressed skull fracture warrant prophylaxis for PTSs, especially if they have an altered level of consciousness or require chemical paralysis. Depressed skull fractures may also increase the risk for intracranial and meningeal infections; patients with depressed skull fractures should receive prophylactic antibiotics.[23,166,186,188]

Basilar Fractures

Basilar fractures are linear fractures at the base of the skull. The fracture usually occurs through the temporal bone, with bleeding into the middle ear producing hemotympanum. Patients with basilar fractures are at risk for extra-axial hematomas because of the proximity of the fracture to the middle cerebral artery. Often, the fracture has caused a dural tear, which produces a communication among the subarachnoid space, the paranasal sinuses, and the middle ear. This offers a route for the introduction of infection into the cranial cavity and is suggested by a CSF leak.[23] As with linear skull fractures, a basilar fracture is not always associated with significant underlying brain injury; these fractures are the result of considerable impact force, however, and TBI must be ruled out.

Basilar fractures can compress and entrap the CNs that pass through the basal foramina, can dislocate the bones of the auricular chain, and can disrupt the otic canal or cavernous sinuses, with subsequent injury to CNs III, IV, and V. Fractures of the sphenoid bone can disrupt the intracavernous internal carotid artery, creating the potential for the formation of pseudoaneurysms or carotid venous fistulae. The diagnosis of a basilar skull fracture is based on associated clinical signs and symptoms (see Box 41-1).

Patients with clinical evidence suggesting a basilar skull fracture should have a CT scan, to define the fracture and to rule out concurrent intracranial pathology, and should be admitted for observation. Because the basilar skull fracture may afford an entrance for bacteria, antibiotics are often considered. However, most CSF leaks resolve spontaneously in about 1 week with no complications, and, in general, antibiotics are not given prophylactically during the first week of CSF rhinorrhea.[23] Counter to this approach, Friedman and colleagues found prophylactic antibiotics to reduce the risk of meningitis by half.[170] If a patient with a previously diagnosed CSF leak returns to the ED later with fever, the diagnosis of meningitis should be strongly suspected and appropriate workup (i.e., lumbar puncture) and antibiotic treatment initiated immediately.

Open Fractures

A skull fracture is open when a scalp laceration overlies a fracture. If the fracture has disrupted the dura, a communication exists between the external environment and the brain. A fracture that

www.ketabpezeshki.com 66485457-66963820

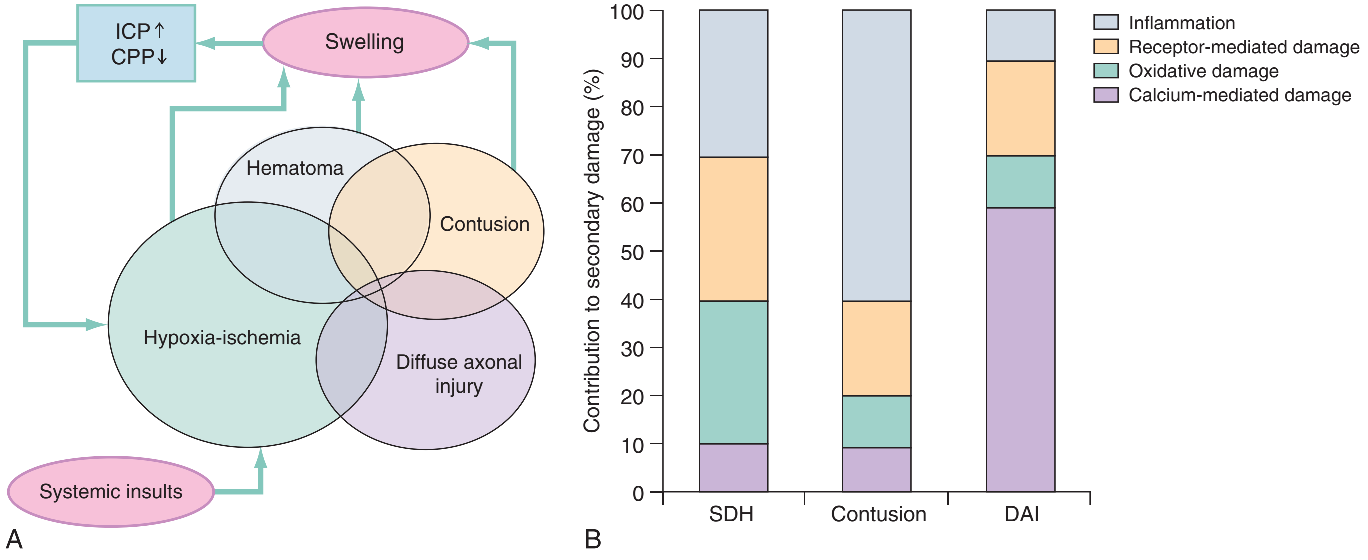


Figure 41-8. Multiple contributing factors in the pathophysiology of head trauma section. *CPP,* cerebral perfusion pressure; *DAI,* diffuse axonal injury; *ICP,* intracranial pressure; *SDH,* subdural hematoma. (Adapted from Maas AI, Stocchetti N, Bullock R: Moderate and severe traumatic brain injury in adults. Lancet Neurol 7:728-741, 2008.)

disrupts the paranasal sinuses or the middle ear structures is also considered open. An open skull fracture requires careful irrigation and débridement. Blind probing of the wound should be avoided because it can introduce contaminants into the wound and can further depress comminuted fracture pieces.

Diffuse Axonal Injury

Prolonged traumatic coma not caused by mass lesions, ischemic insult, or nontraumatic causes of coma is thought to result from DAI. DAI or diffuse traumatic axonal injury is a pathologic process in which axons sustain a primary insult in which they are torn (axotomy) and secondary insults that can result in progressive cellular pathologic changes and eventual axon death (Fig. 41-8).[155] Affected axons are dispersed between areas of undamaged cells (Fig. 41-9). Badly damaged axons become edematous and eventually begin to separate from one another, causing widespread disruption of cortical physiology and microanatomy in the white matter of the brain and brainstem. Complete separation of axons does not always cause cell death; acute uncoupling of CBF and metabolism and apoptosis are thought to be the primary factors linked to axonal cell death after DAI.[21,155] Experimental laboratory data have indicated that neurons can partially repair and regenerate damaged axons. Recovery depends on the reversal or correction of structural and physiologic abnormalities.[17]

DAI is thought to be the cause of persistent traumatic coma that begins immediately at the time of trauma; however, some patients with DAI may recover consciousness briefly before lapsing into prolonged coma. No specific acute focal traumatic lesions are noted on a head CT scan. MRI is more sensitive in detecting subtle injury in DAI, but it is often not practical to perform MRI on critically injured patients. Occasionally, small petechial hemorrhages in proximity to the third ventricle and within the white matter of the corpus callosum or within the internal capsule of the brainstem are detected. DAI is the most common CT finding after severe head trauma, estimated to occur in 50% of all comatose head-injured patients.[166]

Because diagnostic studies cannot predict the extent of the axonal damage, the severity of the injury is determined by the clinical course. Patients with *mild* DAI are in coma for 6 to 24 hours. Approximately one third of patients with mild DAI demonstrate decorticate or decerebrate posturing, but by 24 hours they are following commands.[166] The mortality in this group is 15% and is associated with infectious complications or concurrent intracranial injuries. Most patients who recover have mild or no permanent disabilities.

Moderate DAI is the most common clinical picture. Patients with moderate DAI are in coma for longer than 24 hours. Often, they are victims of falls or vehicular crashes and have associated basilar skull fractures. Patients may exhibit transient decortication or decerebration but eventually recover purposeful movements. On awakening, patients have prolonged severe post-traumatic amnesia and moderate to severe persistent cognitive deficits. Almost 25% die of complications of prolonged coma.[166]

Severe DAI is almost always caused by vehicular crashes. Patients remain in coma for prolonged periods and demonstrate persistent brainstem dysfunction (posturing) and autonomic dysfunction (e.g., hypertension and hyperpyrexia). Diffuse brain swelling subsequent to injury causes intracranial hypertension. Herniation syndrome can occur if elevated ICP does not respond to medical or surgical intervention. Some patients with severe DAI eventually awaken but are severely disabled. Some patients remain in a persistent vegetative state, but most with severe DAI die from their head injury. All patients with DAI have an identical presentation of coma. Recent research has identified several biomarkers that may have clinical relevance in the future.[155] However, currently no early clinical or biomarker predictor exists that differentiates patients with mild, moderate, or severe DAI.

Cerebral Contusions

Contusions are bruises on the surface of the brain, usually caused by impact injury. Most often, contusions occur at the poles and the inferior surfaces of the frontal and temporal lobes where the brain comes into contact with bone protuberances in the base of the skull. If the contusion occurs on the same side as the impact injury, it is a *coup injury;* if it occurs on the opposite side, the contusion is a *contrecoup injury.* Contusions also often develop in the brain tissue that underlies a depressed skull fracture. Multiple areas of contused tissue may be produced with a single impact, often in association with other intracranial injuries.

Contusions are produced when parenchymal blood vessels are damaged, resulting in scattered areas of petechial hemorrhage and subsequent edema. Contusions develop in the gray matter on the

www.ketabpezeshki.com 66485457-66963820

surface of the brain and taper into the white matter. Often, subarachnoid blood is found overlying the involved gyrus. With time, the associated hemorrhages and edema of a contusion can become widespread and serve as a nidus for hemorrhage or swelling, thus producing a local mass effect. Compression of the underlying tissue can cause local areas of ischemia, and tissue infarction is possible if the compression is significant and unrelieved. Eventually, these ischemic areas become necrotic, and cystic cavities form within them.

The clinical presentation of patients with contusions is frequently delayed. They may have sustained only a brief LOC, but the duration of post-traumatic confusion and obtundation may be prolonged. If contusions occur near the sensorimotor cortex, focal neurologic deficits may be present. Many patients with significant contusions make uneventful recoveries, but contusions may cause significant neurologic problems, including increased ICP, PTSs, and focal deficits. Agrawal and colleagues[189] showed that significant progression of cerebral contusions is not an infrequent occurrence. Patients with lower GCS scores and larger cerebral contusions are at higher risk for needing delayed surgical intervention.[189]

Non–contrast-enhanced CT is the best diagnostic test to discover contusions in the early post-traumatic period. These appear heterogeneous and irregular because of mixed regions of hemorrhage, necrosis, and infarction. Often, the surrounding edematous tissue appears hypodense. By post-trauma days 3 and 4, the blood located within the contusions has begun to degrade, and MRI becomes more useful.

Epidural Hematoma

EDHs are blood clots that form between the inner table of the skull and the dura. Most EDHs are caused by direct impact injury that causes a forceful deformity of the skull. Often, a fracture occurs across the middle meningeal artery, vein, or a dural sinus.

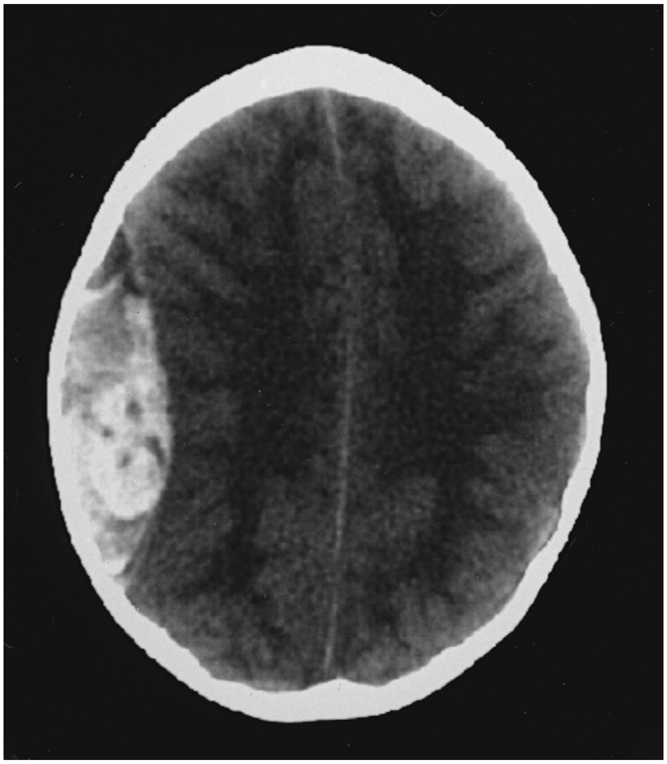


Figure 41-9. Non–contrast-enhanced computed tomography scan of acute epidural hematoma at the level of right midconvexity. There is an associated mass effect and moderate midline shift.

The temporoparietal region is the most likely site for an EDH.[159] The high arterial pressure of the bleeding vessel dissects the dura away from the skull, permitting the formation of the hematoma.

An EDH is usually unilateral, and 20% of patients have other intracranial lesions, usually SDHs or contusions.[23] The deterioration of a patient who has an EDH from arterial bleeding can be rapid and dramatic. Because of their rapid formation, EDHs from arterial bleeding are usually detected within hours after injury and often earlier in children. EDHs that develop from a dural sinus tear develop more slowly, and clinical manifestations may be delayed, with resultant delays in detection.

EDH is primarily a disease of the young and accounts for 2.7 to 4% of all patients who have experienced TBI.[23,190] EDHs are rare in elders and children younger than 2 years of age because of the close attachment of the dura to the skull in both patient populations. The classic presentation of an EDH is described as head trauma producing a decreased level of consciousness followed by a "lucid" interval. Although the patient's consciousness is less decreased during the lucid interval, a completely normal mental status may not return before a second episode of decreased consciousness occurs. The lucid interval is not pathognomonic for an EDH and occurs in patients who sustain other expanding mass lesions. Approximately 47% of patients with EDHs present classically.[190] The development of symptoms and signs of EDH is entirely dependent on how quickly the EDH is developing within the cranial vault. Patients with an EDH often complain of a severe headache, sleepiness, dizziness, nausea, and vomiting. A small EDH may remain asymptomatic, but this is rare.

If the patient is not in coma when the diagnosis of EDH is established and if the condition is rapidly treated, the mortality is 5 to 10%. If the patient is in coma, the mortality from EDH is approximately 20%. The mortality in pediatric patients undergoing surgical evacuation is 5%.[190] If the EDH is rapidly detected and evacuated, the functional outcome is excellent.

On CT scan, an EDH appears hyperdense, biconvex, ovoid, and lenticular. The EDH does not usually extend beyond the dural attachments at the suture lines. The margins are sharply defined, and the hematoma usually bulges inward toward the brain (see Fig. 41-9). EDHs of mixed density on CT may be actively bleeding.

A posterior fossa EDH is the most common traumatic mass lesion of the posterior fossa and accounts for 5% of EDHs.[23] Direct occipital trauma resulting in a skull fracture that disrupts a venous sinus is the usual cause, and most patients have external evidence of occipital injury. Most patients become symptomatic within 24 hours after injury, with complaints of headache, nausea, vomiting, and nuchal rigidity. Most patients eventually have a decreased level of consciousness. On CT scan, a posterior fossa EDH looks similar to other EDHs, but it may cross the midline and extend above the tentorium to the supratentorial compartment (Fig. 41-10). Expert consensus guidelines support rapid surgical evacuation for any patient who has mass effect on CT or progressive neurologic deterioration.[175] Mortality approaches 26%.[23]

Recent studies have investigated the indications for immediate operative intervention for EDHs. Epidurals greater than 30 cm^3 in volume should be evacuated surgically, regardless of the patient's GCS score. Furthermore, it is strongly recommended that comatose patients with an acute EDH and anisocoria on pupillary examination undergo surgical evacuation as soon as possible.[190]

Subdural Hematoma

SDHs are blood clots that form between the dura and the brain. Usually they are caused by the movement of the brain relative to the skull, as seen in acceleration-deceleration injuries. These hematomas are common in patients with brain atrophy, such as alcoholic or elder patients. In these patients, the superficial bridging vessels traverse greater distances than in patients with no

www.ketabpezeshki.com 66485457-66963820

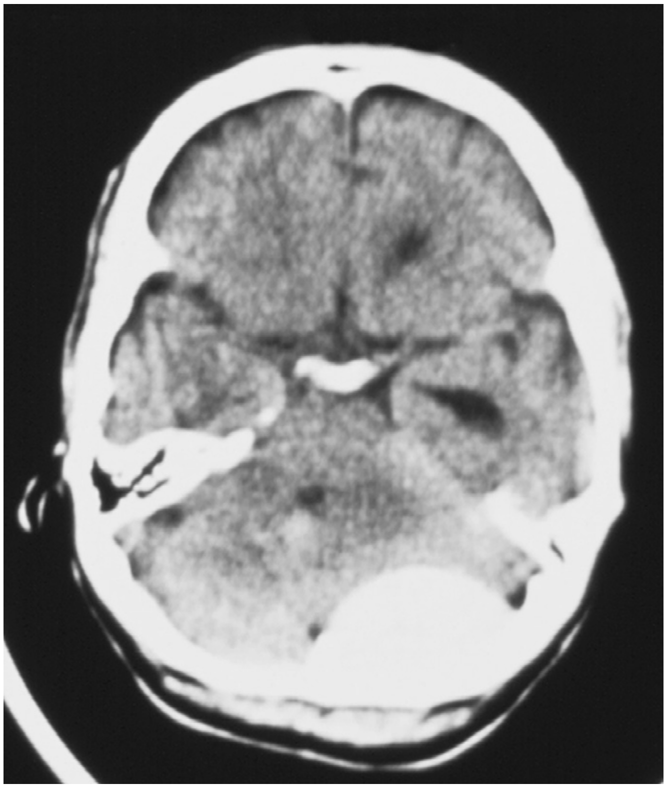


Figure 41-10. Non–contrast-enhanced computed tomography scan of large left posterior fossa, epidural hematoma. The size of the lesion at this high level suggests that it crosses into the supratentorial compartment. This lesion is often associated with occipital bone fracture that disrupts transverse sinus.

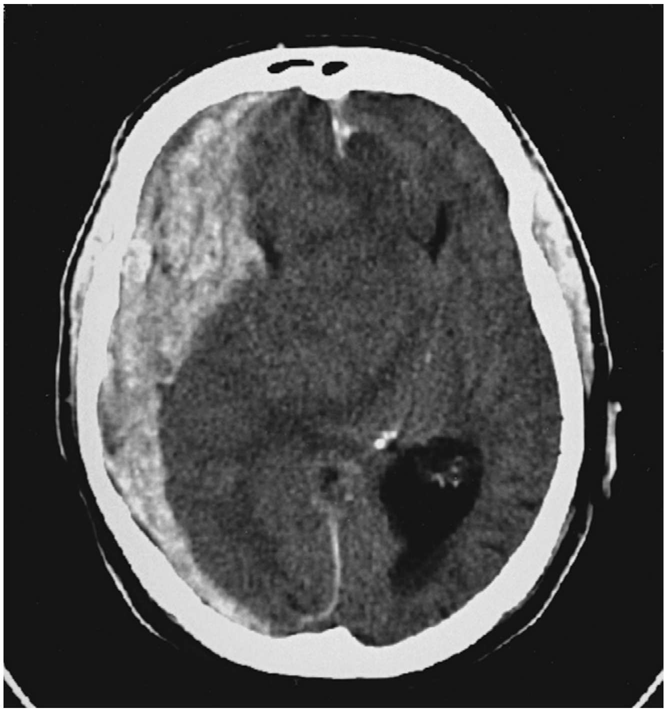


Figure 41-11. Non–contrast-enhanced computed tomography scan of acute right temporal subdural hematoma. There is acute bleeding as well as delayed bleeding, which explains the mixed density. Mass effect is large, with midline shift measuring approximately 2.7 cm right to left. The right lateral ventricle has been obliterated.

atrophy. As a result, the vessels are more likely to rupture with rapid movement of the head. Once they are ruptured, blood can fill the potential space between the dura and arachnoid.

SDHs are more common than EDHs, occurring in up to 30% of patients with severe head trauma.[159] The slow bleeding of venous structures delays the development of clinical signs and symptoms. As a result, the hematoma compresses the underlying brain tissue for prolonged periods and can cause significant tissue ischemia and damage.

The patient's clinical presentation depends on the amount of brain injury sustained at the time of trauma and the rate of SDH expansion. If the patient with an SDH was rendered unconscious at the time of trauma, the prognosis is poor; these patients often have concurrent DAI. The signs and symptoms after injury that produces an SDH are initially related to the other intracranial injuries that may have been sustained and then to the slow expansion of the SDH.

SDHs are classified by the time to clinical presentation. *Acute* SDHs are symptomatic within 24 hours after trauma. Patients with acute SDHs often have a decreased level of consciousness. Most patients with an SDH have a GCS score less than 8. Approximately 12 to 38% of patients will have a lucid period at some point in their presentation. The overall mortality of patients who have an SDH and require surgical intervention is 40 to 60%.[159]

Because of associated brain injury caused by the SDH, the delay in clinical signs and symptoms, and the more advanced mean age of the at-risk population, the mortality associated with SDH is much higher than that associated with EDH. Pupil inequality, motor deficit, and other signs consistent with increased brain swelling may be present on the initial examination. If the patient is deeply comatose at presentation with flaccidity and without signs of brainstem activity, supportive care should be considered in the ED. Subsequent management decisions should be discussed with the patient's family and the attending neurosurgeon.

If the SDH is very small (only a few millimeters thick at its widest point on CT scan), some neurosurgeons may choose careful observation for these patients. Even a small SDH may be accompanied by extensive brain tissue damage that can cause an increase in ICP sufficient to precipitate a herniation syndrome. Current consensus guidelines recommend that acute SDHs with a thickness greater than 10 mm or a midline shift of more than 5 mm on CT should be evacuated surgically, regardless of the patient's GCS score.[159] Research indicates that the longer the time between clinical worsening and operative treatment, the worse the patient's clinical outcome. In these cases, surgical evacuation should be performed as soon as possible.[159]

Unlike EDHs, SDHs often extend beyond the suture lines (Fig. 41-11). An SDH may follow the contour of the tentorium and be detected within the interhemispheric fissure (Fig. 41-12). Many patients with an acute SDH also show CT evidence of intracerebral lesions contralateral to the SDH.

A *subacute* SDH is symptomatic between 24 hours and 2 weeks after injury. It may appear hypodense or isodense on CT scans. Contrast increases detection of isodense lesions. Patients complain of a headache, altered mental status, or focal deficits. Most patients with subacute SDH require surgical evacuation of the lesion.

A *chronic* SDH becomes symptomatic 2 weeks or more after trauma. The signs and symptoms may be very subtle or nonspecific, but many patients demonstrate unilateral weakness or hemiparesis.[23] Most report an altered level of consciousness, but some patients are unable to recall their head injury or describe only a minor injury. In 20% of cases, chronic subdurals are bilateral. A chronic SDH may have initially been a small asymptomatic SDH that eventually expanded owing to a combination of recurrent

www.ketabpezeshki.com 66485457-66963820

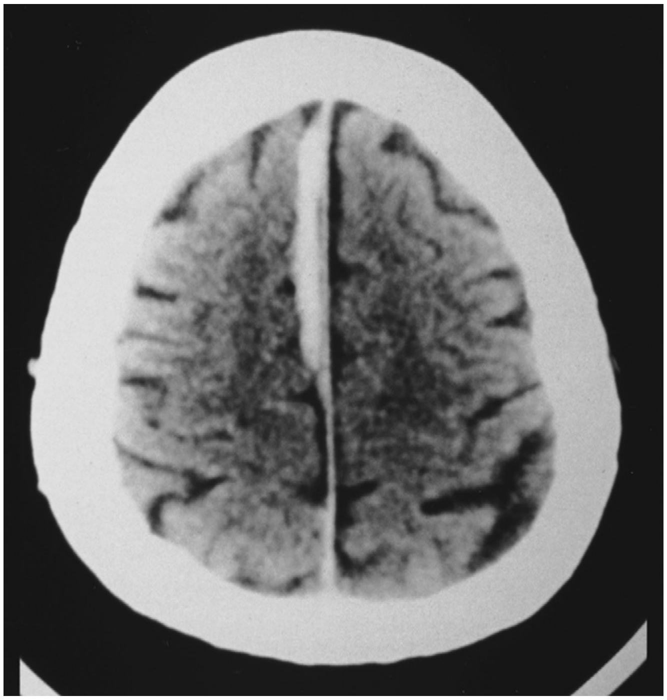


Figure 41-12. Non–contrast-enhanced computed tomography scan of intrahemispheric acute subdural hematoma.

hemorrhage and escape of plasma into the hematoma. At some point, a critical mass is reached and the chronic SDH becomes symptomatic. On CT scan, a chronic SDH may appear isodense or hypodense to brain parenchyma. In these cases, indirect evidence of the lesion includes a midline shift, effacement of the ipsilateral cortical sulci, and ventricular compression. Contrast may increase the likelihood of identifying a chronic SDH that has become isodense. On CT scan, blood of various ages is seen as a mixed-density lesion. On MRI, a chronic SDH appears hyperdense. The treatment of chronic SDHs is controversial. If they become symptomatic, chronic SDHs require surgical evacuation. Most patients have a good outcome after surgery. Overall, the mortality from surgically drained chronic SDH approaches 4%, with decreased survival in elders.[23]

The prognosis of SDH does not entirely depend on the size of the hematoma but rather on the degree of brain injury caused by the pressure of the expanding hematoma on underlying tissue or by other intracranial injury caused by the initial impact. Mortality is highest in older people, in patients who have a GCS score of 8 or less, and in those with signs of acute herniation syndrome on initial ED presentation. Posterior fossa SDHs make up less than 1% of all reported SDHs. They are caused by occipital trauma that tears bridging vessels or venous sinuses. Clinical manifestations of posterior SDH vary but usually include nausea, vomiting, headache, and decreased level of consciousness. Occasionally, CN palsies may be found, as well as nuchal rigidity, cerebellar signs and symptoms, and papilledema. On a CT scan, a posterior fossa SDH does not cross the midline or extend above the tentorium. The outcome of a posterior SDH is very poor.

In children the presence of an SDH should prompt consideration of child abuse. Many types of injury can produce SDH in children, but the infant who is repeatedly and forcibly shaken is especially susceptible.[130] Infants may have SDH because of birth trauma. In these cases the initial clinical manifestation may be a generalized seizure within the first 6 months of life. On examination the infant may have a bulging fontanel or an enlarged head circumference. A careful history may elicit long-standing constitutional symptoms, such as failure to thrive or lethargy.

Subdural Hygroma

A subdural hygroma (SDHG) is a collection of clear, xanthochromic blood-tinged fluid in the dural space. The pathogenesis of an SDHG is not certain. It may result from a tear in the arachnoid that permits CSF to escape into the dural space or effusions from injured vessels through areas of abnormal permeability in the meninges or in the underlying parenchyma. They may accumulate immediately after trauma or in a delayed manner. Clinically, an SDHG cannot be distinguished from other mass lesions. Often, patients have a decreased level of consciousness or focal motor deficits. They may complain of headaches, nausea, and vomiting. The ICP can increase because of the mass effect, and signs of increased ICP may be present on examination.

On CT scans, SDHGs appear crescent shaped in the extra-axial space. The CT density is the same as that of CSF. Bilateral SDHGs are common. If SDHGs are asymptomatic, observation is reasonable management. Otherwise, they are surgically evacuated. Mortality approaches 20% and appears to depend on the severity of other intracranial injury.[23]

Traumatic Subarachnoid Hemorrhage

Traumatic subarachnoid hemorrhage (TSAH) is blood within the CSF and meningeal intima and probably results from tears of small subarachnoid vessels. TSAH is detected on the first CT scan in up to 33% of patients with severe TBI and has an incidence of 44% in all cases of severe head trauma. It is therefore the most common CT scan abnormality seen after head injury. Data from the National Traumatic Coma Data Bank demonstrate a 60% unfavorable outcome in severely brain-injured patients in the presence of TSAH compared with a 30% unfavorable outcome if no TSAH occurs.[191] An increased incidence of skull fractures and contusions is found in patients with TSAH compared with patients with no TSAH. The amount of blood within the TSAH correlates directly with the outcome and inversely with the presenting GCS score.

Patients may complain of headache and photophobia. A noncontrast CT scan allows the diagnosis to be made, with increased density noted within the basilar cisterns. Blood can also be seen within the interhemispheric fissures and sulci.

TSAH with no other brain injury does not generally carry a poor prognosis. The most serious complication of TSAH is worsening of cerebral vasospasm, which may be severe enough to induce cerebral ischemia. Post-traumatic vasospasm is common, occurring approximately 48 hours after injury and persisting for up to 2 weeks. Calcium channel blockers (e.g., nimodipine and nicardipine) have been used in the acute intensive care unit setting to prevent or reduce vasospasm after TSAH.

Intracerebral Hematoma

Intracerebral hematomas (ICHs) are formed deep within the brain tissue and are usually caused by shearing or tensile forces that mechanically stretch and tear deep small-caliber arterioles as the brain is propelled against irregular surfaces in the cranial vault. Resulting small petechial hemorrhages subsequently coalesce to form ICHs. Approximately 85% are in the frontal and temporal lobes. They are often found in the presence of extra-axial hematomas, and in many patients multiple ICHs are present.[192,193] Isolated ICHs may be detected in as many as 12% of all patients with severe head trauma.

The clinical effects of ICH depend on size, location, and whether the bleeding is continuing. ICHs have been reported with all degrees of severity of head trauma. More than 50% of patients with ICH sustain LOC at the time of impact. The patient's subsequent level of consciousness depends on the severity of the impact

www.ketabpezeshki.com 66485457-66963820

Figure 41-13. Non–contrast-enhanced computed tomography scan of intracerebral hematoma and contusion in the left occipital region. The scan also shows layering of tentorial subdural hematoma. Mass effect and early uncal herniation are visible as well.

Figure 41-14. Non–contrast-enhanced computed tomography scan of right occipital and temporal intracerebral hematomas, surrounded by mild edema and hemorrhagic contusion. Small intrahemispheric subdural hematoma is visible in posterior interhemispheric fissure. Midline shift is obvious. Ventriculostomy has been placed and is visible as high-density image within ventricles.

and coexisting lesions. Combined with contusions, other concurrent lesions, and subsequent perilesion edema, an ICH can produce substantial mass effects and precipitate a herniation syndrome (Fig. 41-13).

An ICH may be detected on the first CT scan immediately after injury but often is not seen for several hours or days. Unlike contusions, ICHs are usually deep in the brain tissue and often become well demarcated over time. On CT scan, an ICH appears as a well-defined hyperdense homogeneous area of hemorrhage (Fig. 41-14).

Many patients with an ICH require emergent intervention or surgery to control elevated ICP. Mortality is low in patients who are conscious before surgery; in unconscious patients, mortality approaches 45%.[192,193] ICHs that bleed into the ventricles or cerebellum also carry a high mortality rate.

Traumatic Intracerebellar Hematoma

Primary traumatic intracerebellar hematomas are rare but can occur after a direct blow to the occipital area. Often, these patients also have a skull fracture or a posterior fossa EDH or SDH. Supratentorial contrecoup hematomas and contusions are also common associated findings.

The clinical presentation of an isolated traumatic cerebellar hematoma is similar to that of other posterior lesions. When other traumatic lesions are present, the picture may be quite confusing. The acute management should first address the most clinically significant lesion. The mortality from isolated traumatic intracerebellar hematoma is very high. Emergent neurosurgical consultation is indicated.

KEY CONCEPTS

Severe and Moderate Head Injuries

- These injuries require emergent noncontrast head CT.
- Patients undergo serial neurologic examinations for early detection of herniation syndrome.
- Acute herniation syndrome should initially be managed with short-term hyperventilation Surgical intervention is indicated as soon as possible.
- Long-term hyperventilation is not indicated and is detrimental.
- Mannitol or HTS should be used only in patients with increasing ICP or acute neurologic deterioration.
- Secondary systemic insults such as hypoxia and hypotension worsen neurologic outcome and should be corrected as soon as detected in the out-of-hospital or ED setting.
- Head-injured patients who have been chemically paralyzed do not have clinical manifestations of seizures; consideration should be given to prophylactic anticonvulsant administration.
- Factor VIIa has a limited role in the ED emergent management of moderate and severe head trauma. Emergency departments should have established protocols on when factor VIIa will be initiated in patients with severe and moderate head trauma.
- Most "talk and deteriorate" adult patients with moderate head injury have subdural or epidural hematomas. Early detection, CT scan, and expedient surgical intervention are the keys to a good outcome.
- Caution should given to out-of-hospital RSI in severe head injury if the intubation may be prolonged or significantly challenging. Alternative airway management should be considered.

www.ketabpezeshki.com 66485457-66963820

Minor Head Trauma

- Risk stratification of patients with minor head injury into low-risk and high-risk categories can help direct the emergency physician to an appropriate diagnostic workup.
- The decision to perform a head CT scan in patients with minor head trauma should be individualized but based on consideration of high- and moderate-risk criteria. Clinical decision-making algorithms such as the Canadian Head CT Rule are helpful to emergency medicine clinicians and their patients.
- Alcohol affects the GCS score and significantly obscures the neurologic examination. Intoxicated individuals are high-risk patients.
- Most patients with minor head trauma can be discharged from the ED after a period of observation but require a competent observer.
- Patients sustaining a concussion are at risk for prolonged and substantial morbidity. Athletes should not be allowed to return immediately to sports activities because of the potential risk of second impact syndrome. Most guidelines support a gradual stepwise strategy to have collegiate and high school athletes return to play.

Pediatric Head Injuries

- Children with severe head trauma have fewer intracranial lesions than adults but more edema. In children, increasing edema alone can cause talk and deteriorate or other significant neurologic decline.
- Clinical decision rules such as Kupperman and colleagues[145] algorithm can significantly reduce the number of head CT scans performed on children who experience head trauma.
- Skull fractures have more clinical significance in children than in adults.
- In infants, head injury often occurs from nonaccidental causes. Child abuse should be suspected in young children with head trauma, especially those younger than 2 years of age.

Penetrating Head Injuries

- Tangential gunshot wounds are associated with a high frequency of intracranial traumatic lesions; CT scanning should be performed.
- Anticonvulsant prophylaxis and antibiotics should be given to a patient with penetrating head injuries.
- The clinical outcome after gunshot wounds to the head can be predicted by the initial clinical presentation and the missile path through the brain.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Faul M, Xu L, Wald MM, Coronado VG: *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths, 2002-2006*. Atlanta: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
2. Brenner LA, et al: Traumatic brain injury, posttraumatic stress disorder, and postconcussive symptom reporting among troops returning from Iraq. *J Head Trauma Rehabil* 2010; 25:307-312.
3. Hoge CW, et al: Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *N Engl J Med* 2008; 358:4534-4563.
4. Jaffee MS, et al: Acute clinical care and care coordination for traumatic brain injury within Department of Defense. *J Rehabil Res Dev* 2009; 46:655-666.
5. Greenwald BD, Burnett DM, Miller MA: Congenital and acquired brain injury. 1. Brain injury: Epidemiology and pathophysiology. *Arch Phys Med Rehabil* 2003; 84:S3-S7.
6. Leventhal JM, Martin KD, Asnes AG: Fractures and traumatic brain injuries: Abuse versus accidents in a U.S. database of hospitalized children. *Pediatrics* 2010; 126:e104-e115.
7. Carpenter M: *Gross anatomy of the brain*. In: Carpenter MB, ed. *Core Text of Neuroanatomy*, 4th ed. Baltimore: Williams & Wilkins; 1991.
8. Rockswold G: *Head injury*. In: Tintanelli J, ed. *Emergency Medicine*. New York: McGraw-Hill; 1996.
9. Lenzlinger P: *Overview of basic mechanisms underlying neuropathological consequences of head trauma*. In: Miller LP, Hayes RL, Newcomb JK, eds. *Head Trauma: Basic, Preclinical, and Clinical Directions*. New York: Wiley-Liss; 2001:4-5.
10. Zwienenberg M, Muizellar J: *Vascular aspects of severe head injury*. In: Miller LP, Hayes RL, Newcomb JK, eds. *Head Trauma: Basic, Preclinical, and Clinical Directions*. New York: Wiley-Liss; 2001:303-326.
11. Reivich M: Arterial Pco_2 and cerebral hemodynamics. *Am J Physiol* 1964; 206:25-35.
12. Brain Trauma Foundation, et al: Guidelines for the management of severe traumatic brain injury. XIV. Hyperventilation. *J Neurotrauma* 2007; 24(Suppl 1):S87-S90.
13. Laffey JG, Kavanagh BP: Hypocapnia. *N Engl J Med* 2002; 347:43-53.
14. Biros MH, Heegaard W: Prehospital and resuscitative care of the head-injured patient. *Curr Opin Crit Care* 2001; 7:444-449.
15. Gordon KE: Pediatric minor traumatic brain injury. *Semin Pediatr Neurol* 2006; 13:243-255.
16. Gordon KE, Dooley JM, Fitzpatrick EA, Wren P, Wood EP: Concussion or mild traumatic brain injury: Parents appreciate the nuances of nosology. *Pediatr Neurol* 2010; 43:253-257.
17. Bazarian JJ, Blyth B, Cimpello L: Bench to bedside: Evidence for brain injury after concussion—looking beyond the computed tomography scan. *Acad Emerg Med* 2006; 13:199-214.
18. Chesnut RM: Care of central nervous system injuries. *Surg Clin North Am* 2007; 87:119-156, vii.
19. Greve MW, Zink BJ: Pathophysiology of traumatic brain injury. *Mt Sinai J Med* 2009; 76:97-104.
20. Brain Trauma Foundation, et al: Guidelines for the management of severe traumatic brain injury. Introduction. *J Neurotrauma* 2007; 24(Suppl 1):S1-S2.
21. Maas AI, Stocchetti N, Bullock R: Moderate and severe traumatic brain injury in adults. *Lancet Neurol* 2008; 7:728-741.
22. Brain Trauma Foundation, et al: Guidelines for the management of severe traumatic brain injury. I. Blood pressure and oxygenation. *J Neurotrauma* 2007; 24(Suppl 1):S7-S13.
23. Greenberg M: *Handbook of Neurosurgery*, 7th ed. New York: Thieme; 2010.
24. Wang HE, Peitzman AB, Cassidy LD, Adelson PD, Yealy DM: Out-of-hospital endotracheal intubation and outcome after traumatic brain injury. *Ann Emerg Med* 2004; 44:439-450.
25. Kellie G: An account of the appearances observed in the dissection of two of the three individuals presumed to have perished in the storm of the third, and his bodies were discovered in the vicinity of Leith on the morning of the 4th November 1821 with some reflections on the pathology of the brain. *Trans Med Chir Sci (Edinburgh)* 1824; 1:84-169.
26. Monroe A: *Observation on the Structure and Function of the Nervous System*. Edinburgh: Creek and Johnson; 1783.
27. Graham D, Gennarelli T: *Pathology of brain damage after head injury*. In: Cooper P, Golfinos J, eds. *Head Injury*, 4th ed. New York: McGraw-Hill; 2000:133-154.
28. Marmarou A, et al: Predominance of cellular edema in traumatic brain swelling in patients with severe head injuries. *J Neurosurg* 2006; 104:720-730.
29. Fodstad H, Kelly PJ, Buchfelder M: History of the Cushing reflex. *Neurosurgery* 2006; 59:1132-1137.
30. Langlois JA, Rutland-Brown W, Thomas KE: *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths*. Atlanta: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2006.
31. Teasdale G, Jennett B: Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974; 2:81-84.
32. Marmarou A, et al: IMPACT database of traumatic brain injury: Design and description. *J Neurotrauma* 2007; 24:239-250.
33. Stein SC, Georgoff P, Meghan S, Mizra K, Sonnad SS: 150 years of treating severe traumatic brain injury: A systematic review of progress in mortality. *J Neurotrauma* 2010; 27:1343-1353.
34. Provencio J, Bleck T: *Cardiovascular disorders related to neuroemergencies*. In: Cruz J, ed. *Neurologic and Neurosurgical Emergencies*. Philadelphia: WB Saunders; 1998:39-50.
35. Bar-Joseph G, Guilburd Y, Tamir A, Guilburd JN: Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension. *J Neurosurg Pediatr* 2009; 4:40-46.
36. Davis DP, et al: The impact of aeromedical response to patients with moderate to severe traumatic brain injury. *Ann Emerg Med* 2005; 46:115-122.
37. McVey J, Petrie DA, Tallon JM: Air versus ground transport of the major trauma patient: A natural experiment. *Prehosp Emerg Care* 2010; 14:45-50.
38. Thomas SH: Helicopter EMS transport outcomes literature: Annotated review of articles published 2004-2006. *Prehosp Emerg Care* 2007; 11:477-488.
39. Bernard SA, et al: Prehospital rapid sequence intubation improves functional outcome for patients with severe traumatic brain injury: A randomized controlled trial. *Ann Surg* 2010; 252:959-965.
40. Davis DP, et al: Prehospital airway and ventilation management: A trauma score and injury severity score–based analysis. *J Trauma* 2010; 69:294-301.
41. Dumont TM, Visioni AJ, Rughani AI, Tranmer BI, Crookes B: Inappropriate prehospital ventilation in severe traumatic brain injury increases in-hospital mortality. *J Neurotrauma* 2010; 27:1233-1241.
42. Davis DP, et al: The effect of paramedic rapid sequence intubation on outcome in patients with severe traumatic brain injury. *J Trauma* 2003; 54:444-453.
43. Davis DP, et al: Paramedic rapid sequence intubation for severe traumatic brain injury: Perspectives from an expert panel. *Prehosp Emerg Care* 2007; 11:1-8.
44. Davis DP, Kimbro TA, Vilke GM: The use of midazolam for prehospital rapid-sequence intubation may be associated with a dose-related increase in hypotension. *Prehosp Emerg Care* 2001; 5:163-168.
45. Davis DP, et al: Paramedic-administered neuromuscular blockade improves prehospital intubation success in severely head-injured patients. *J Trauma* 2003; 55:713-719.
46. Davis DP, et al: The impact of prehospital endotracheal intubation on outcome in moderate to severe traumatic brain injury. *J Trauma* 2005; 58:933-939.
47. Fakhry SM, et al: Prehospital rapid sequence intubation for head trauma: Conditions for a successful program. *J Trauma* 2006; 60:997-1001.
48. Salhi B, Stettner E: In defense of the use of lidocaine in rapid sequence intubation. *Ann Emerg Med* 2007; 49:84-86.
49. Vaillancourt C, Kapur AK: Opposition to the use of lidocaine in rapid sequence intubation. *Ann Emerg Med* 2007; 49:86-87.
50. Modica PA, Tempelhoff R: Intracranial pressure during induction of anaesthesia and tracheal intubation with etomidate-induced EEG burst suppression. *Can J Anaesth* 1992; 39:236-241.
51. Yeung JK, Zed PJ: A review of etomidate for rapid sequence intubation in the emergency department. *CJEM* 2002; 4:194-198.
52. Albert SG, Ariyan S, Rather A: The effect of etomidate on adrenal function in critical illness: A systematic review. *Intensive Care Med* 2011; 37:901-910.
53. Dmello D, Taylor S, O'Brien J, Matuschak GM: Outcomes of etomidate in severe sepsis and septic shock. *Chest* 2010; 138:1327-1332.
54. Warner KJ, Cuschieri J, Jurkovich GJ, Bulger EM: Single-dose etomidate for rapid sequence intubation may impact outcome after severe injury. *J Trauma* 2009; 67:45-50.
55. Jabre P, et al: Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: A multicentre randomised controlled trial. *Lancet* 2009; 374:293-300.
56. Hohl CM, et al: The effect of a bolus dose of etomidate on cortisol levels, mortality, and health services utilization: A systematic review. *Ann Emerg Med* 2010; 56:105-113.

www.ketabpezeshki.com 66485457-66963820

57. Bulger EM, et al: Out-of-hospital hypertonic resuscitation following severe traumatic brain injury: A randomized controlled trial. *JAMA* 2010; 304:1455-1464.
58. Oddo M, et al: Effect of mannitol and hypertonic saline on cerebral oxygenation in patients with severe traumatic brain injury and refractory intracranial hypertension. *J Neurol Neurosurg Psychiatry* 2009; 80:916-920.
59. Wakai A, Roberts I, Schierhout G: Mannitol for acute traumatic brain injury. *Cochrane Database Syst Rev* 2007; 1:CD001049.
60. Wakai A, Roberts I, Schierhout G: Mannitol for acute traumatic brain injury. *Cochrane Database Syst Rev* 2005; 4:CD001049.
61. Brain Trauma Foundation, et al: Guidelines for the management of severe traumatic brain injury. II. Hyperosmolar therapy. *J Neurotrauma* 2007; 24(Suppl 1):S14-S20.
62. Weed L, McKibben P: Experimental alteration of brain bulk. *Am J Physiol* 1919; 48:531-558.
63. Rockswold GL, et al: Hypertonic saline and its effect on intracranial pressure, cerebral perfusion pressure, and brain tissue oxygen. *Neurosurgery* 2009; 65:1035-1042.
64. White H, Cook D, Venkatesh B: The use of hypertonic saline for treating intracranial hypertension after traumatic brain injury. *Anesth Analg* 2006; 102:1836-1846.
65. Walker PA, et al: Modern approaches to pediatric brain injury therapy. *J Trauma* 2009; 67:S120-S127.
66. Adelson PD, et al: Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents. Chapter 11. Use of hyperosmolar therapy in the management of severe pediatric traumatic brain injury. *Pediatr Crit Care Med* 2003; 4:S40-S44.
67. Vassar MJ, Perry CA, Gannaway WL, Holcroft JW: 7.5% sodium chloride/dextran for resuscitation of trauma patients undergoing helicopter transport. *Arch Surg* 1991; 126:1065-1072.
68. Wade CE, et al: Individual patient cohort analysis of the efficacy of hypertonic saline/dextran in patients with traumatic brain injury and hypotension. *J Trauma* 1997; 42:S61-S65.
69. Cooper DJ, et al: Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: A randomized controlled trial. *JAMA* 2004; 291:1350-1357.
70. Brain Trauma Foundation, et al: Guidelines for the management of severe traumatic brain injury. XI. Anesthetics, analgesics, and sedatives. *J Neurotrauma* 2007; 24(Suppl 1):S71-S76.
71. Brain Trauma Foundation, et al: Guidelines for the management of severe traumatic brain injury. XV. Steroids. *J Neurotrauma* 2007; 24(Suppl 1):S91-S95.
72. Brain Trauma Foundation, et al: Guidelines for the management of severe traumatic brain injury. III. Prophylactic hypothermia. *J Neurotrauma* 2007; 24(Suppl 1):S21-S25.
73. Sinclair HL, Andrews PJ: Bench-to-bedside review: Hypothermia in traumatic brain injury. *Crit Care* 2010; 14:204.
74. Nelson JA: Local skull trephination before transfer is associated with favorable outcomes in cerebral herniation from epidural hematoma. *Acad Emerg Med* 2011; 18:78-85.
75. Smith SW, et al: Emergency department skull trephination for epidural hematoma in patients who are awake but deteriorate rapidly. *J Emerg Med* 2010; 39:377-383.
76. Nelson JA: Local skull trephination before transfer is associated with favorable outcomes in cerebral herniation from epidural hematoma. *Acad Emerg Med* 2011; 18:78-85.
77. Smith SW, et al: Emergency department skull trephination for epidural hematoma in patients who are awake but deteriorate rapidly. *J Emerg Med* 2010; 39:377-383.
78. Brain Trauma Foundation, et al: Guidelines for the management of severe traumatic brain injury. XIII. Antiseizure prophylaxis. *J Neurotrauma* 2007; 24(Suppl 1):S83-S86.
79. Schierhout G, Roberts I: Anti-epileptic drugs for preventing seizures following acute traumatic brain injury. *Cochrane Database Syst Rev* 2001; 4:CD000173.
80. Chang BS, Lowenstein DH: Practice parameter: Antiepileptic drug prophylaxis in severe traumatic brain injury: Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2003; 60:10-16.
81. Brain Trauma Foundation, et al: Guidelines for the management of severe traumatic brain injury. IV. Infection prophylaxis. *J Neurotrauma* 2007; 24(Suppl 1):S26-S31.
82. McQuay N Jr, Cipolla J, Franges EZ, Thompson GE: The use of recombinant activated factor VIIa in coagulopathic traumatic brain injuries requiring emergent craniotomy: Is it beneficial? *J Neurosurg* 2009; 111:666-671.
83. Stein DM, Dutton RP, Kramer ME, Handley C, Scalea TM: Recombinant factor VIIa: Decreasing time to intervention in coagulopathic patients with severe traumatic brain injury. *J Trauma* 2008; 64:620-628.
84. Hauser CJ, et al: Results of the CONTROL trial: Efficacy and safety of recombinant activated factor VII in the management of refractory traumatic hemorrhage. *J Trauma* 2010; 69:489-500.
85. Brown CV, et al: Recombinant factor VIIa for the correction of coagulopathy before emergent craniotomy in blunt trauma patients. *J Trauma* 2010; 68:348-352.
86. Yank V, et al: Systematic review: Benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. *Ann Intern Med* 2011; 154:529-540.
87. Tan JE, Ng I, Lim J, Wong HB, Yeo TT: Patients who talk and deteriorate: A new look at an old problem. *Ann Acad Med Singapore* 2004; 33:489-493.
88. Reilly PL, Graham DI, Adams JH, Jennett B: Patients with head injury who talk and die. *Lancet* 1975; 2:375-377.
89. Lobato RD, et al: Head-injured patients who talk and deteriorate into coma. Analysis of 211 cases studied with computerized tomography. *J Neurosurg* 1991; 75:256-261.
90. Rockswold GL, Pheley PJ: Patients who talk and deteriorate. *Ann Emerg Med* 1993; 22:1004-1007.
91. Goldschlager T, Rosenfeld JV, Winter CD: 'Talk and die' patients presenting to a major trauma centre over a 10 year period: A critical review. *J Clin Neurosci* 2007; 14:618-624.
92. Dunn LT, Fitzpatrick MO, Beard D, Henry JM: Patients with a head injury who "talk and die" in the 1990s. *J Trauma* 2003; 54:497-502.
93. Stein SC, Chen XH, Sinson GP, Smith DH: Intravascular coagulation: A major secondary insult in nonfatal traumatic brain injury. *J Neurosurg* 2002; 97:1373-1377.
94. Stein SC, Smith DH: Coagulopathy in traumatic brain injury. *Neurocrit Care* 2004;1:479-488.
95. Colohan AR, Oyesiku NM: Moderate head injury: An overview. *J Neurotrauma* 1992; 9(Suppl 1):S259-S264.
96. Ruttan L, Martin K, Liu A, Colella B, Green RE: Long-term cognitive outcome in moderate to severe traumatic brain injury: A meta-analysis examining timed and untimed tests at 1 and 4.5 or more years after injury. *Arch Phys Med Rehabil* 2008; 89:S69-S76.
97. Stein SC, Ross SE: Moderate head injury: A guide to initial management. *J Neurosurg* 1992; 77:562-564.
98. van Velzen JM, van Bennekom CA, Edelaar MJ, Sluiter JK, Frings-Dresen MH: How many people return to work after acquired brain injury? A systematic review. *Brain Inj* 2009; 23:473-488.
99. Schievink WI: Spontaneous spinal cerebrospinal fluid leaks: A review. *Neurosurg Focus* 2000; 9:e8.
100. Schlosser RJ, Woodworth BA, Wilensky EM, Grady MS, Bolger WE: Spontaneous cerebrospinal fluid leaks: A variant of benign intracranial hypertension. *Ann Otol Rhinol Laryngol* 2006; 115:495-500.
101. Kulstad EB, Kalimullah EA, Tekwani KL, Courtney DM: Etomidate as an induction agent in septic patients: Red flags or false alarms? *West J Emerg Med* 2010; 11:161-172.
102. Ching KY, Baum CR: Newer agents for rapid sequence intubation: Etomidate and rocuronium. *Pediatr Emerg Care* 2009; 25:200-210.
103. Elder GA, Cristian A: Blast-related mild traumatic brain injury: Mechanisms of injury and impact on clinical care. *Mt Sinai J Med* 2009; 76:111-118.
104. Wilbur K, Zed PJ: Is propofol an optimal agent for procedural sedation and rapid sequence intubation in the emergency department? *CJEM* 2001; 3:302-310.
105. Matis G, Birbilis T: The Glasgow Coma Scale—a brief review. Past, present, future. *Acta Neurol Belg* 2008; 108:75-89.
106. Smits M, et al: Predicting intracranial traumatic findings on computed tomography in patients with minor head injury: The CHIP prediction rule. *Ann Intern Med* 2007; 146:397-405.
107. Johnston KM, et al: Current concepts in concussion rehabilitation. *Curr Sports Med Rep* 2004; 3:316-323.
108. Sheedy J, Geffen G, Donnelly J, Faux S: Emergency department assessment of mild traumatic brain injury and prediction of post-concussion symptoms at one month post injury. *J Clin Exp Neuropsychol* 2006; 28:755-772.
109. Iverson GL: Outcome from mild traumatic brain injury. *Curr Opin Psychiatry* 2005; 18:301-317.
110. Fabbri A, et al: Clinical performance of NICE recommendations versus NCWFNS proposal in patients with mild head injury. *J Neurotrauma* 2005; 22:1419-1427.

www.ketabpezeshki.com 66485457-66963820

111. Smits M, et al: A history of loss of consciousness or post-traumatic amnesia in minor head injury: "conditio sine qua non" or one of the risk factors? *J Neurol Neurosurg Psychiatry* 2007; 78:1359-1364.
112. Haydel MJ, et al: Indications for computed tomography in patients with minor head injury. *N Engl J Med* 2000; 343:100-105.
113. Stein SC, Fabbri A, Servadei F, Glick HA: A critical comparison of clinical decision instruments for computed tomographic scanning in mild closed traumatic brain injury in adolescents and adults. *Ann Emerg Med* 2009; 53:180-188.
114. Mittl RL, et al: Prevalence of MR evidence of diffuse axonal injury in patients with mild head injury and normal head CT findings. *AJNR Am J Neuroradiol* 1994; 15:1583-1589.
115. Hijaz TA, Cento EA, Walker MT: Imaging of head trauma. *Radiol Clin North Am* 2011; 49:81-103.
116. Wilde EA, et al: Diffusion tensor imaging of acute mild traumatic brain injury in adolescents. *Neurology* 2008; 70:948-955.
117. Townend W, et al: Rapid elimination of protein S-100B from serum after minor head trauma. *J Neurotrauma* 2006; 23:149-155.
118. Siman R, et al: A panel of neuron-enriched proteins as markers for traumatic brain injury in humans. *J Neurotrauma* 2009; 26:1867-1877.
119. Wang MC, Linnau KF, Tirschwell DL, Hollingworth W: Utility of repeat head computed tomography after blunt head trauma: A systematic review. *J Trauma* 2006; 61:226-233.
120. McCrory P, et al: Consensus statement on concussion in sport: The 3rd International Conference on Concussion in Sport held in Zurich, November 2008. *J Athl Train* 2009; 44:434-448.
121. Thomas DG, et al: Identifying neurocognitive deficits in adolescents following concussion. *Acad Emerg Med* 2011; 18:246-254.
122. Bazarian JJ, Atabaki S: Predicting postconcussion syndrome after minor traumatic brain injury. *Acad Emerg Med* 2001; 8:788-795.
123. Centers for Disease Control and Prevention (CDC): Nonfatal traumatic brain injuries from sports and recreation activities—United States, 2001-2005. *MMWR Morb Mortal Wkly Rep* 2007; 56:733-737.
124. McCrory P. Does second impact syndrome exist? *Clin J Sport Med* 2001; 11:144-149.
125. McCrory P, et al: Consensus statement on concussion in sport—the Third International Conference on Concussion in Sport held in Zurich, November 2008. *Phys Sportsmed* 2009; 37:141-159.
126. McCrory P, Johnston KM, Mohtadi NG, Meeuwisse W: Evidence-based review of sport-related concussion: Basic science. *Clin J Sport Med* 2001; 11:160-165.
127. Kuppermann N: Pediatric head trauma: The evidence regarding indications for emergent neuroimaging. *Pediatr Radiol* 2008; 38(Suppl 4):S670-S674.
128. Atabaki SM, et al: A clinical decision rule for cranial computed tomography in minor pediatric head trauma. *Arch Pediatr Adolesc Med* 2008; 162:439-445.
129. Duhaime AC, Christian CW, Rorke LB, Zimmerman RA: Nonaccidental head injury in infants—the "shaken-baby syndrome." *N Engl J Med* 1998; 338:1822-1829.
130. Matschke J, et al: Shaken baby syndrome: A common variant of non-accidental head injury in infants. *Dtsch Arztebl Int* 2009; 106:211-217.
131. Huh JW, Raghupathi R: New concepts in treatment of pediatric traumatic brain injury. *Anesthesiol Clin* 2009; 27:213-240.
132. Weiner H, Weinberg J: *Head injury in the pediatric age group*. In: Cooper P, Golfinos J, eds. *Head Injury*, 4th ed. New York: McGraw-Hill; 2000.
133. Falk AC, Cederfjall C, von Wendt L, Klang Soderkvist B: Management and classification of children with head injury. *Childs Nerv Syst* 2005; 21:430-436.
134. James HE: Neurologic evaluation and support in the child with an acute brain insult. *Pediatr Ann* 1986; 15:16-22.
135. Holmes JF, Palchak MJ, MacFarlane T, Kuppermann N: Performance of the pediatric Glasgow Coma Scale in children with blunt head trauma. *Acad Emerg Med* 2005; 12:814-819.
136. Reference deleted in proofs.
137. Fink EL, Kochanek PM, Clark RS, Bell MJ: How I cool children in neurocritical care. *Neurocrit Care* 2010; 12:414-420.
138. Schutzman SA, et al: Evaluation and management of children younger than two years old with apparently minor head trauma: Proposed guidelines. *Pediatrics* 2001; 107:983-993.
139. Schutzman SA, Greenes DS: Pediatric minor head trauma. *Ann Emerg Med* 2001; 37:65-74.
140. Kirkwood MW, et al: Management of pediatric mild traumatic brain injury: A neuropsychological review from injury through recovery. *Clin Neuropsychol* 2008; 22:769-800.
141. Yeates KO, et al: Longitudinal trajectories of postconcussive symptoms in children with mild traumatic brain injuries and their relationship to acute clinical status. *Pediatrics* 2009; 123:735-743.
142. Gausche M, et al: Effect of out-of-hospital pediatric endotracheal intubation on survival and neurological outcome: A controlled clinical trial. *JAMA* 2000; 283:783-790.
143. Palchak MJ, Holmes JF, Kuppermann N: Clinician judgment versus a decision rule for identifying children at risk of traumatic brain injury on computed tomography after blunt head trauma. *Pediatr Emerg Care* 2009; 25:61-65.
144. Palchak MJ, et al: A decision rule for identifying children at low risk for brain injuries after blunt head trauma. *Ann Emerg Med* 2003; 42:492-506.
145. Kuppermann N, et al: Identification of children at very low risk of clinically important brain injuries after head trauma: A prospective cohort study. *Lancet* 2009; 374:1160-1170.
146. Klemetti S, Uhari M, Pokka T, Rantala H: Evaluation of decision rules for identifying serious consequences of traumatic head injuries in pediatric patients. *Pediatr Emerg Care* 2009; 25:811-815.
147. Hall P, et al: Effect of low doses of ionising radiation in infancy on cognitive function in adulthood: Swedish population based cohort study. *BMJ* 2004; 328:19.
148. Maguire JL, Boutis K, Uleryk EM, Laupacis A, Parkin PC: Should a head-injured child receive a head CT scan? A systematic review of clinical prediction rules. *Pediatrics* 2009; 124:e145-154.
149. Klig JE, Kaplan CP: Minor head injury in children. *Curr Opin Pediatr* 2010; 22:257-261.
150. Osmond MH, et al: CATCH: A clinical decision rule for the use of computed tomography in children with minor head injury. *CMAJ* 2010; 182:341-348.
151. Dunning J, et al: Derivation of the children's head injury algorithm for the prediction of important clinical events decision rule for head injury in children. *Arch Dis Child* 2006; 91:885-891.
152. Beaudin M, Saint-Vil D, Ouimet A, Mercier C, Crevier L: Clinical algorithm and resource use in the management of children with minor head trauma. *J Pediatr Surg* 2007; 42:849-852.
153. Kaufman HH: Civilian gunshot wounds to the head. *Neurosurgery* 1993; 32:962-964.
154. Adekoya N, Thurman DJ, White DD, Webb KW: Surveillance for traumatic brain injury deaths—United States, 1989-1998. *MMWR Surveill Summ* 2002; 51:1-14.
155. Beaman V, Annest JL, Mercy JA, Kresnow M, Pollock DA: Lethality of firearm-related injuries in the United States population. *Ann Emerg Med* 2000; 35:258-266.
156. Part 1: Guidelines for the management of penetrating brain injury. Introduction and methodology. *J Trauma* 2001; 51:S3-S6.
157. Part 2: Prognosis in penetrating brain injury. *J Trauma* 2001; 51:S44-S86.
158. Anglin D, Hutson HR, Luftman J, Qualls S, Moradzadeh D: Intracranial hemorrhage associated with tangential gunshot wounds to the head. *Acad Emerg Med* 1998; 5:672-678.
159. Farhat HI, Hood B, Bullock MR: A tangential gunshot wound to the head: Case report and review of the literature. *J Emerg Med* 2009; Dec 21. [Epub ahead of print]
160. Maiden N: Ballistics reviews: Mechanisms of bullet wound trauma. *Forensic Sci Med Pathol* 2009; 5:204-209.
161. Maiden N: Historical overview of wound ballistics research. *Forensic Sci Med Pathol* 2009; 5:85-89.
162. Antibiotic prophylaxis for penetrating brain injury. *J Trauma* 2001; 51:S34-S40.
163. Neuroimaging in the management of penetrating brain injury. *J Trauma* 2001; 51:S7-S11.
164. Mazzola CA, Adelson PD: Critical care management of head trauma in children. *Crit Care Med* 2002; 30:S393-S401.
165. Hauser WA, Annegers JF, Kurland LT: Prevalence of epilepsy in Rochester, Minnesota: 1940-1980. *Epilepsia* 1991; 32:429-445.
166. Lowenstein DH: Epilepsy after head injury: An overview. *Epilepsia* 2009; 50(Suppl 2):4-9.
167. Yasseen B, Colantonio A, Ratcliff G: Prescription medication use in persons many years following traumatic brain injury. *Brain Inj* 2008; 22:752-757.
168. Masel BE, DeWitt DS: Traumatic brain injury: A disease process, not an event. *J Neurotrauma* 2010; 27:1529-1540.
169. Lapointe M: *Basic principles of antimicrobial therapy of CNS infections*. In: Cooper P, Golfinos J, eds. *Head Injury*, 4th ed. New York: McGraw-Hill; 2000:483.
170. Friedman JA, Ebersold MJ, Quast LM: Persistent posttraumatic cerebrospinal fluid leakage. *Neurosurg Focus* 2000; 9:e1.

www.ketabpezeshki.com 66485457-66963820

171. Brodie HA, Thompson TC: Management of complications from 820 temporal bone fractures. *Am J Otol* 1997; 18:188-197.
172. Dudley RR, et al: Early venous thromboembolic event prophylaxis in traumatic brain injury with low-molecular-weight heparin: Risks and benefits. *J Neurotrauma* 2010; 27:2165-2172.
173. Rogers FB, et al: Neurogenic pulmonary edema in fatal and nonfatal head injuries. *J Trauma* 1995; 39:860-868.
174. Szerlip NJ, Bholat O, McCunn MM, Aarabi B, Scalea TM: Extracorporeal life support as a treatment for neurogenic pulmonary edema and cardiac failure secondary to intractable intracranial hypertension: A case report and review of the literature. *J Trauma* 2009; 67:E69-E71.
175. Mascia L: Acute lung injury in patients with severe brain injury: A double hit model. *Neurocrit Care* 2009;11:417-426.
176. Hanson W: *Acute respiratory failure in neuroemergencies*. In: Cruz J, ed. *Neurologic and Neurosurgical Emergencies*. Philadelphia: WB Saunders; 1998:28-29.
177. Cushing H: The blood pressure reaction of acute cerebral compression illustrated by cases of intracranial hemorrhage. *Am J Med Sci* 1903; 125:1017-1044.
178. Lammers R: *Principles of wound management*. In: Roberts J, Hedges J, eds. *Clinical Procedures in Emergency Medicine*. Philadelphia: WB Saunders; 2004:623-655.
179. Hogg K, Carley S: Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. Staples or sutures in children with scalp lacerations. *Emerg Med J* 2002; 19:328-329.
180. Hogg K, Carley S: Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. Staples or sutures for repair of scalp laceration in adults. *Emerg Med J* 2002; 19:327-328.
181. Singer A, McBride M: *Surgical staples*. In: Singer A, Hollander J, Blumm R, eds. *Skin and Soft Tissue Infection: A Practical Evidence Based Guide*. Shelton, Conn: Peoples Medical Publishing House; 2011:79-82.
182. Karaduman S, Yuruktumen A, Guryay SM, Bengi F, Fowler JR Jr: Modified hair apposition technique as the primary closure method for scalp lacerations. *Am J Emerg Med* 2009; 27:1050-1055.
183. Ong ME, et al: Hair apposition technique for scalp laceration repair: A randomized controlled trial comparing physicians and nurses (HAT 2 study). *Am J Emerg Med* 2008; 26:433-438.
184. Carson HJ: Brain trauma in head injuries presenting with and without concurrent skull fractures. *J Forensic Leg Med* 2009; 16:115-120.
185. Muñoz-Sánchez MA, et al: Skull fracture, with or without clinical signs, in mTBI is an independent risk marker for neurosurgically relevant intracranial lesion: A cohort study. *Brain Inj* 2009; 23:39-44.
186. Bullock MR, et al: Surgical management of depressed cranial fractures. *Neurosurgery* 2006; 58:S56-S60; discussion Si-iv.
187. Heegaard W, Biros M: Skull fractures in adults. *Up to Date* 2012.
188. Chen JW, Ruff RL, Eavey R, Wasterlain CG: Posttraumatic epilepsy and treatment. *J Rehabil Res Dev* 2009; 46:685-696.
189. Agrawal A, Timothy J, Pandit L, Manju M: Post-traumatic epilepsy: An overview. *Clin Neurol Neurosurg* 2006; 108:433-439.
190. Daele JJ, Goffart Y, Machiels S: Traumatic, iatrogenic, and spontaneous cerebrospinal fluid (CSF) leak: Endoscopic repair. *B-ENT* 2011; 7(Suppl 17):47-60.
191. Chan EK, Yan B, Ryan MM: Spontaneous intracranial hypotension in childhood: A case report and review of the literature. *J Child Neurol* 2011; 26:761-766.
192. Schievink WI: Spontaneous spinal cerebrospinal fluid leaks. *Cephalalgia* 2008; 28:1345-1356.
193. Cheuret E, et al: Intracranial hypotension in a girl with Marfan syndrome: Case report and review of the literature. *Childs Nerv Syst* 2008; 24:509-513.

www.ketabpezeshki.com 66485457-66963820

Chapter 42

Facial Trauma

Ryanne J. Mayersak

PERSPECTIVE

This chapter discusses the epidemiology, diagnosis, and treatment of injuries to the skin, soft tissue, and bones of the face. A complex structure vital to the function of the person, the face comprises airway openings, entry to the gastrointestinal tract, and special sensory organs, including eyes, ears, and nose. Facial functioning is essential for eating, speaking, and effective nonverbal communication. The appearance and attractiveness of the face have significant implications for social interactions,[1,2] sexual attraction,[3] and self-esteem.[4] In one study, patients who had sustained facial trauma experienced long-term sequelae including unemployment, incarceration, marital difficulties, and negative body image.[3a]

Apart from immediate threat to the patient's airway and special sense organs, injuries to the face can have serious implications for the patient's mental health[5,6] and future functioning. Post-traumatic patients with facial injuries often describe physical, financial, social, and psychological loss.[7] In one study of predominantly unemployed young African American and Hispanic men, 25% had symptoms of post-traumatic stress disorder 1 month after having been treated emergently for a midface fracture.[5,8,9] Some institutions are now including screening evaluations regarding supportive interventions as well as initiating support groups and online resources for facial trauma patients.[7]

Although the emergency physician's first goal is to address life-threatening problems successfully, the care of facial injuries is aimed at optimizing the patient's function and cosmetic appearance.

Four main specialties—ophthalmology, plastic surgery, otolaryngology, and oral and maxillofacial surgery—participate in the care of facial injuries. In teaching hospitals, the specialties of plastic surgery, otolaryngology, and oral and maxillofacial surgery participate in approximately equal proportions.[10] In level 1 trauma centers, plastic surgeons and oral and maxillofacial surgeons predominate.[11] Early consultation with the appropriate specialist can expedite the care of facial injuries.

Epidemiology

In 2008 there were more than 40 million injury-related visits to U.S. emergency departments (EDs).[12] Facial injuries accounted for a significant proportion of these visits and resulted from either intentional violence (assaults and attempted suicide) or unintentional trauma (falls, sports injuries, and motor vehicle crashes [MVCs]). The type of injury mechanism can be a good predictor of the extent of facial trauma sustained; for example, MVCs were related to multiple facial fractures, whereas assaults more often involved isolated mandibular fractures.[13] Although MVCs used to be the most common cause of facial injuries, windshield improvements, increased use of safety belts, and the prevalence of air bags in vehicles are changing the epidemiology of facial trauma. Dual front-impact air bags have been required in all new vehicles since 1999, and safety belts are required for all passengers in the front row in 49 states (all except New Hampshire).[14] Seat belts and air bags significantly reduce the incidence and severity of facial injury in adults.[15-21] Because they effectively prevent ejection, safety belts specifically avert the extensive scalp and facial degloving injuries associated with being ejected through the windshield.

Alcohol use by vehicle occupants decreases safety belt use and independently increases the risk of facial injury in MVCs.[22] It also increases the risk of interpersonal violence. In one series, alcohol played a role in 49% of all maxillofacial fractures in patients requiring subspecialty care. Of the fractures related to alcohol use, 78% were a result of interpersonal violence and 13% of MVCs.[23,24] Interpersonal violence is increasingly cited as the cause of facial injury, particularly in inner-city populations.[25-28] Falls, dog bites, some athletic activities, and flying debris are other common causes of facial injuries.

Because of the lack of external protection, facial injuries are common among riders of other motorized vehicles, particularly those who are not wearing helmets with face guards, including all-terrain vehicles (ATVs) and motorcycles. In one series in Alabama, 32% of injured ATV riders had a facial injury, and the presence of a facial injury was associated with increased overall injury severity.[29] Among the youngest riders, facial injuries predominate: 31.1% of 0- to 5-year-olds injured while riding an ATV required emergency treatment for a facial injury in 2001 through 2003, although multiple safety and medical groups recommend no ATV use by people younger than age 16 years.[30]

In motorcyclists, there is a significant association between facial injury and brain injury.[31] Helmets reduce the risk of brain injury but may not protect against facial trauma unless they include a face guard.[32]

Unfortunately, a separate group of the injured must now be considered: combat veterans. A review of injuries sustained in battle by combatants in Operation Iraqi Freedom and Operation Enduring Freedom and treated by U.S. military medical facilities for at least 72 hours revealed that 19% of patients sustained injuries to the face, ears, or eyes. Of all these injuries, 19% were caused by gunshots, 79% by explosive devices, and 2% by MVCs.[33]

In children younger than age 17 years, sports injuries account for 21% of facial and 29% of nasal fractures requiring specialist evaluation.[34,35] Baseball and football helmets with face guards are successful at preventing childhood facial injuries, and their use should be encouraged by emergency physicians.[36] Children younger than age 6 years seem to be at significant risk

www.ketabpezeshki.com 66485457-66963820

for severe facial injuries from bites from the family dog.[37] Interactions between pet dogs and young children require careful supervision.

Facial injuries are a common acute presentation for victims of domestic violence. In one series, 81% of domestic violence victims had maxillofacial injuries on presentation, 30% of them with facial fractures. The location of the injury was consistent with the predominance of fisted assaults; left-sided injuries predominated.[38,39] Women visiting the ED with facial injuries should be interviewed privately to allow an opportunity for disclosure and intervention for domestic violence.

Pediatric facial injury accounts for less than 10% of all facial trauma, and the face is the most common area of trauma in children suspected of being victims of abuse.[40] However, the epidemiology of facial trauma among children reflects their physical development and behavioral patterns: toddlers learning to walk have a "falling zone" of trauma to the perioral region, nose, and forehead. Younger children are significantly more likely to have minor soft tissue injuries and to have been the recipient of a dog bite. Severe facial injuries in all pediatric age groups are more likely to be the result of an MVC or assault.[41] Care should be taken by the emergency physician to correlate the child's age and behavioral ability with the history of the injury and the physical findings. In particular, injuries to the lips or frenulum in a nonambulatory infant suggest "bottle jamming," and bruises to the cheeks or neck are less common in falls. Although dental fractures in young children are relatively common, facial fractures before age 5 years are rare. If there is any question, the appropriate local authorities are contacted.

Even in high-energy MVCs, appropriate use of child safety restraints protects against many facial injuries. The law in all 50 states requires the use of such restraints for children younger than age 4 years, and currently 48 states require booster seats until at least age 7 years and many beyond that age.[14] Children younger than age 15 years involved in frontal crashes or exposed to a deploying frontal impact air bag had a higher incidence of minor facial and chest injuries and severe upper extremity injuries, mostly related to being struck by the bag.[43] As part of preventing facial trauma, parents should be encouraged to ensure that children younger than 12 years ride in the rear seat of the vehicle and that all are properly restrained.

PRINCIPLES OF DISEASE

Anatomy

The face is a complex hollow space encapsulated by a bony structure overlaid with muscle and skin. It includes several special sensory organs: the eyes, ears, nose, and mouth.

Bones

The posterior portions of the face form the anterior wall of the calvaria, placing the face and its features in an intimate relationship with the structures of the central nervous system. The anterior facial skeleton is composed of the frontal bone, nasal bones, zygomata, maxillary bones, and mandible (Fig. 42-1). The sphenoid, ethmoid, lacrimal, vomer, and temporal bones lie deep within the facial structure, providing support and important sites for muscular attachments, including the muscles of mastication, speech, and deglutition. This musculature is innervated by cranial nerves IX and X.

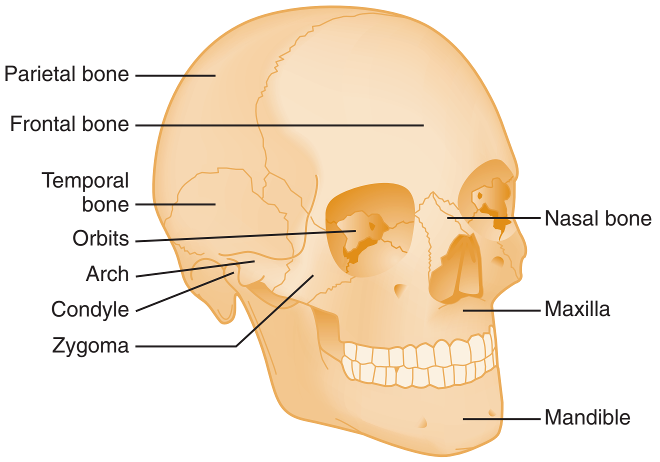


Figure 42-1. Bones of the facial skeleton.

Nerve Supply

The most anterior muscle layer includes the muscles of facial expression that are innervated by the seventh cranial nerve, which lies just inferior to the external auditory canal. The trigeminal nerve (cranial nerve V) supplies sensation to the face through three major divisions (I-III). The ophthalmic division (cranial nerve V1) supplies the upper third of the face, including the eye and the nose down to the tip. The maxillary division (cranial nerve V2) provides sensory innervation to the midface and includes the infraorbital nerve. The mandibular division (cranial nerve V3) supplies sensation to the lower third of the face.

Ears

The ears lie laterally along the sides of the face with the auditory canal exiting through the mastoid process of the temporal bone. The skeleton of the pinna is cartilage covered in closely apposed skin and rolled into a helical shape with a second ridge, the antihelix, defining the inner concha. The external auditory canal, middle ear, cochlea, semicircular canals, and superior origin of the eustachian tube all lie within the temporal bone.

Eyes

The structure of the globe and surrounding ocular musculature is discussed in detail in Chapter 71. The bony orbit is composed superiorly of the frontal bone. The zygoma forms the lateral wall and lateral floor of the orbit. The medial floor and anteromedial wall are formed by the maxilla. The lacrimal and ethmoid bones complete the medial wall, where the orbit is at its most delicate. The medial wall of the orbit forms the lateral walls of the intranasal space.

Nose

The nose serves as a major entryway for air and is composed of cartilage and bone covered by skin with mucosa lining the internal surface. Alar cartilage arches over the entrances to the symmetrical, mucosa-lined nares, separated by the anterior cartilage of the septum. Superiorly, the nasal bones create the bridge of the nose. With the head held in a neutral upright position, the floor of the nose is perpendicular to the ground and leads back into the nasopharynx, passing the turbinates laterally and the bony septum medially. The ethmoid bone lies superiorly and crosses midline, behind the nasal bridge, to form the superior portion of the bony nasal septum and the cribriform plate. The vomer makes up the inferior portion of the bony septum, and the palatine process of the maxillary bone forms the posterior floor of the nose and the hard palate.

www.ketabpezeshki.com 66485457-66963820

Air-containing sinuses are structural features unique to the facial skeleton. They warm and humidify inhaled air and form chambers that create the unique tone of human voices. These sinuses develop over the period of human growth. At birth, only the ethmoid air cells and the mastoid antrum are aerated. The sphenoid sinus and the remainder of the mastoid air cells become aerated at approximately age 3 years. Frontal sinuses form at approximately age 6 years, and maxillary sinuses are not fully developed until age 10 years.

Mouth

The mouth serves as an entryway for the respiratory and gastrointestinal tracts. In addition, the fine motor movements of the mouth and tongue give humans the ability to communicate through speech. With the mouth in the closed position, the tongue fills the oral cavity. Single rows of teeth lie within the alveolar ridges of the maxilla and the mandible. With the mouth closed, the teeth in normal individuals occlude, with the lower row lying just internal to the upper row. The "usual" occlusion for individuals varies widely; the patient's perception may be the best determinant of whether or not the teeth are meeting as usual. Anterior to the teeth is the vestibule, a fold of mucosa and flexible soft tissue that allows the lips to remain closed while various motor movements occur behind them. The mandible is a U-shaped bone that forms the chin and completes the lower facial skeleton. Containing the lower row of teeth, the body of the mandible meets in midline at the symphysis, which is completely fused by age 2 years. Posterior to the last molar, the bone turns to form the angle of the jaw and continues upward as the ramus of the mandible. At the most superior point of the ramus is the articular surface of the condyle, separated from the superior surface of the temporomandibular joint (TMJ) by an intervening meniscus of fibrocartilage. Anterior to the condyle lies a thin projection, the coronoid process, which provides the insertion point for the temporal muscle.

The skin of the face is among the thinnest of the body, draping over the underlying musculature. Facial skin falls visibly into predictable creases with age, following Langer's lines (Fig. 42-2). At the mouth, nares, and palpebral fissures, the skin is contiguous with the mucosa lining these structures. The skin of the lips is particularly thin and lined with vascular papillae, which give the lips their vermilion hue. Lips are particularly important as part of communication; understanding their movement can allow language without sound (lip reading).

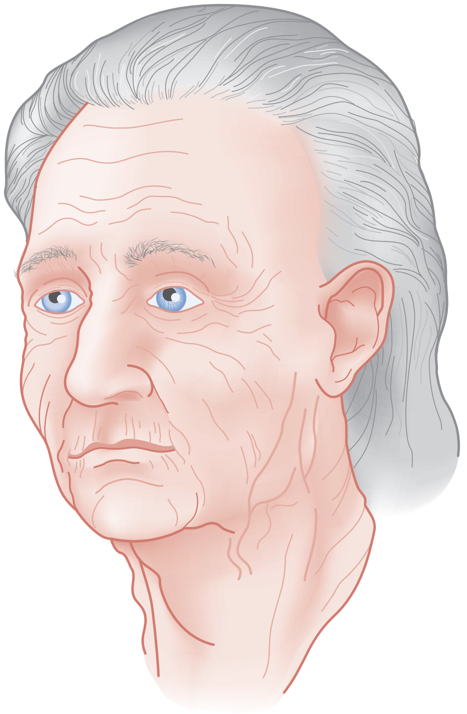


Figure 42-2. Langer's lines: lines of facial expression.

The face is a highly vascular structure; this can have grave implications for the treatment of facial injuries. With the exception of the ophthalmic artery, the superficial blood supply comes from the external carotid artery via the facial, superficial temporal, and maxillary arteries (Fig. 42-3). Soft tissue injuries and fractures that involve these vessels can lead to significant hematomas or exsanguinations. Because the face has extensive anastomotic connections across the midline and between arterial territories, however, ligation of major branches causes minimal ischemia.

Buried within the structure of the face are a series of glandular structures and ducts that are susceptible to injury. In the eye, the lacrimal glands lie within the orbits, superior and lateral to the globes, and secrete tears through ductules into the folds of the conjunctiva. The liquid flows medially into the puncta of the lacrimal canaliculi and drains into the lacrimal sac and then via the nasolacrimal duct into the nasopharynx.

The salivary system consists of the parotid, sublingual, and submandibular glands. The parotid is the largest of these glands, lying just anterior to the ear and wrapping around the mandible. The parotid is superficial to the masseter muscle and drains via Stensen's duct, a 5-cm tube that curves around the anterior edge of the masseter to enter the mouth opposite the second upper molar. In normal subjects, this duct is large enough to be palpated with the masseter clenched (Fig. 42-4). The sublingual glands lie entirely within the floor of the mouth and drain into the mouth via ductules. They surround the ducts draining the submandibular glands (Wharton's ducts). The body of the submandibular gland is folded around the mylohyoid muscle so that a portion lies within the floor of the mouth and a portion lies external to it. The submandibular (Wharton's) ducts run from the external portion of the gland to empty into the mouth on either side of the frenulum of the tongue.

Pathophysiology

The basic mechanism of all injury is the transfer of energy, most often kinetic, to the structures of the body. When the energy overcomes the tolerance of the underlying tissue, injury results. Trauma traditionally has been classified as blunt or penetrating, but in many cases the effect is a combination of the two, such as the forehead injury (contusion and complex laceration) resulting from a child's fall against the sharp corner of a coffee table. The likelihood of injury is related to the amount of energy transferred and the condition of the underlying tissue. Significant injury may result when an 80-year-old falls from standing to a carpeted floor, but it is more likely to result when the face strikes the steering wheel or dashboard in a high-speed MVC.

The mechanism can be broken down into *low-energy* events, such as a fall from standing or walking into the corner of a piece of furniture, and *high-energy* events, such as an MVC. Understanding the mechanism of injury can help predict not only the severity of the facial injury but also the risk of associated cervical or brain injuries.

Traditional teaching has been that the face protects the brain from injury and that patients with facial trauma are less likely to have a significant brain injury. This does not appear to be correct. Instead, recent work suggests a significant increase in risk for brain injury among blunt trauma patients with facial fractures.[44]

The association between cervical injury and facial injury is unclear. The traditional teaching has been that the presence of a facial injury should increase the suspicion of an injury to the

www.ketabpezeshki.com 66485457-66963820

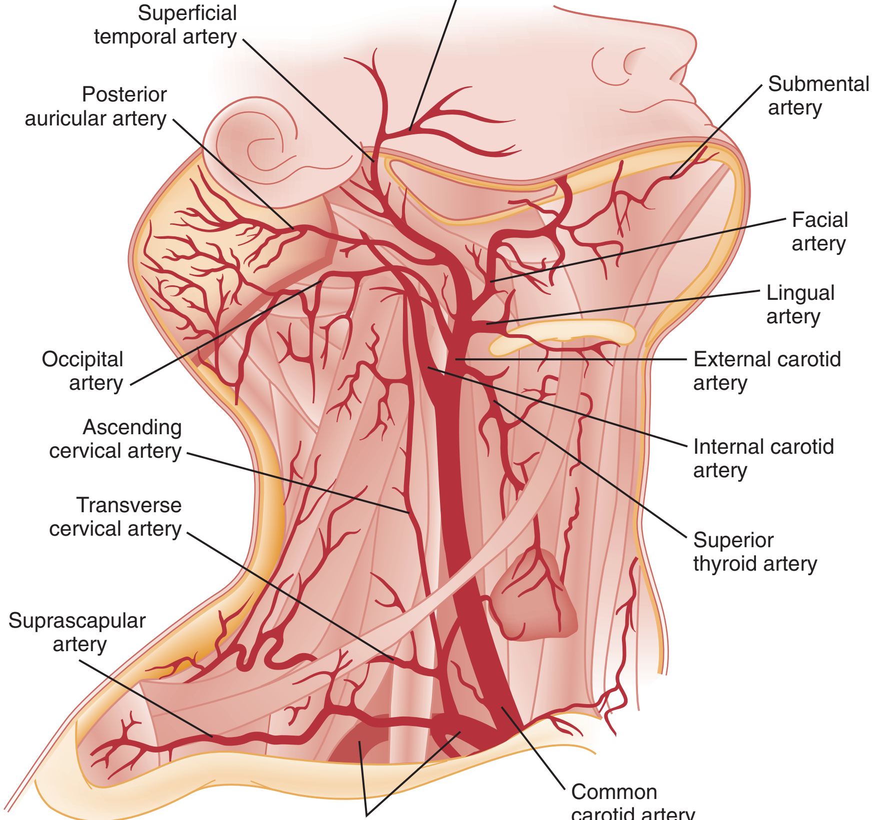


Figure 42-3. Vessels of the face. (Redrawn from Gray H: Gray's Anatomy, Philadelphia, Lea & Febiger, 1918.)

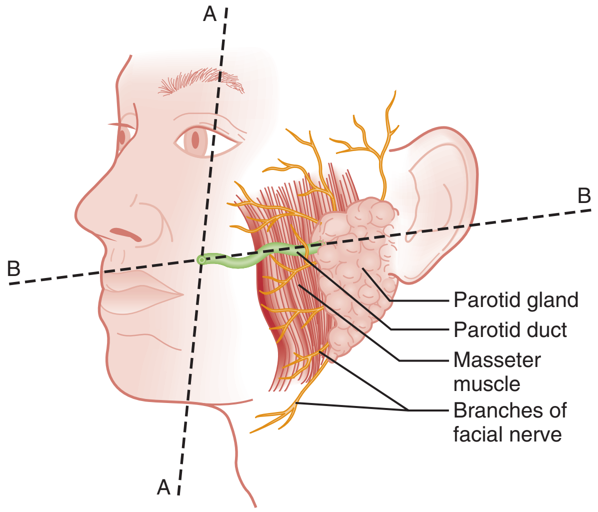


Figure 42-4. Parotid gland and duct (Stensen's) with the surrounding branches of the facial nerve. Line B approximates the course of the duct, which enters the mouth at the junction of lines A and B.

cervical spine. However, most of the studies supporting this idea are assessments of the incidence of cervical spine injury in patients with facial injury.[45] When more sophisticated methods are used to assess any association between the two while correcting for the mechanism of injury, patients with facial injury appear to be less likely to have a significant cord injury, and there is no relationship with bony spinal injury.[46] Thus in a particular patient, cervical and brain injuries should be considered based on the mechanism of injury and presentation of the patient without allowing the presence or absence of a facial injury to change the level of suspicion.

Penetrating trauma to the face from gunshots, stab wounds, blast debris, or impalement is often obvious and dramatic (Fig. 42-5). The astute emergency physician should search avidly for associated intracranial, spinal, or vascular injuries, which are common in these cases.[47] Facial penetration from pellets (BBs) or small blast debris or shrapnel may be less obvious, and the emergency physician should be alert to the possibility based on the history and should carefully search for small skin lesions.[48] Recreational hobbies such as paintball and new law enforcement weapons such as the "flash ball," which can have substantial kinetic energy, have caused significant facial and upper body trauma.[48a,48b]

CLINICAL FEATURES

History

The history can provide information about the mechanism of the patient's injury. The emergency physician, however, should be alert to limitations of the history in cases in which the patient's consciousness is altered by head injury or intoxication, there is an issue of secondary gain, the police are involved, or abuse is suspected. Patients with a clear sensorium are able to describe the events leading up to the injury and localize pain; deficits in motor or sensory function; and abnormalities of vision, hearing, taste, or

www.ketabpezeshki.com 66485457-66963820

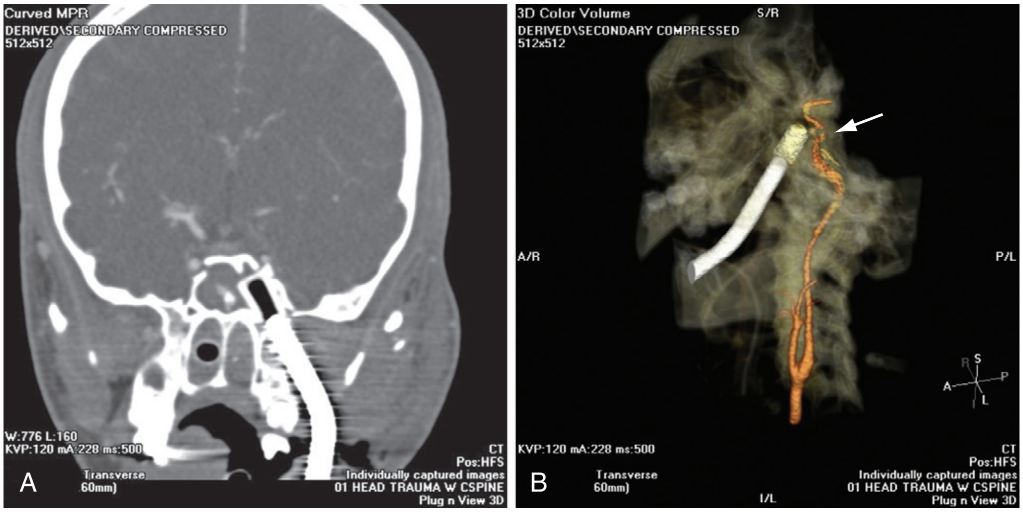


Figure 42-5. Impalement by a turn-signal lever. Computed tomography **(A)** and three-dimensional reconstruction **(B)** from a patient impaled through the face into the cranial cavity by the turn-signal lever from his steering column when his vehicle rolled over in a single-car crash. The color three-dimensional reconstruction reveals a significant injury to the facial artery *(arrow)*.

smell. Although the association between facial trauma and brain or cervical spine injury is unclear, these possibilities should be considered, and the patient should be questioned regarding headache, peripheral weakness, numbness, or paresthesias.

Physical Examination

Many facial injuries can be identified by simple inspection. During the primary assessment, attention is initially on the patient's airway, and inspection of the oropharynx is an essential first step. Airway compromise is often a result of intraoral trauma, and the examiner should note excessive bleeding, drooling, dysphonia, swelling of the tongue or posterior pharynx, and the presence of avulsed teeth. When the patient is stabilized, a secondary survey should include a systematic examination of all facial structures and functions. Bony prominences should be palpated for abnormal motion, bony crepitus, tenderness, or step-off. Tenderness and massive swelling associated with facial trauma may preclude reliable palpation of a fracture. Consequently, areas of significant swelling should be imaged radiographically. Assessment of bony integrity includes testing for possible Le Fort fracture. The upper incisors are grasped and pulled anteriorly. Movement of the upper alveolar ridge (type I), midface (type II), or entire face (type III) indicates a fracture. Wounds may need to be palpated for underlying bony injury or foreign objects; anesthesia may be required for a thorough examination within the wound. Complex lacerations involving the cartilage of the nose or ear, eyelids, lacrimal apparatus, eyebrows, or vermilion border of the lips should be identified because their repair requires special techniques.

Eyes and Orbits

In addition to examination of lacerations and contusions, the face should be evaluated for symmetry. The appearance of the zygomata may be evaluated by looking at the patient from above. This technique also draws attention to the relative position of the eyeballs. Orbital fractures may result in enophthalmos, and a large retrobulbar hematoma may cause exophthalmos. The anterior chamber of the globe should be inspected for hyphema or globe rupture. A hyphema is caused by bleeding in the anterior chamber and appears as a layer of blood in the dependent portion of the anterior chamber. A complete examination of the eye requires specific testing. If the patient is able to cooperate, visual acuity should be documented. Contact lenses should be removed. In the event of a significant potential chemical exposure, the pH of the eye may need to be measured. Fluorescein examination of the eye should be performed if there is any concern about corneal abrasion. Victims of MVCs often have particles of glass in the conjunctiva or on the cornea, and these should be sought and removed. Extraocular motions should be tested. Blow-out fractures of the orbit may result in diplopia on upward gaze secondary to entrapment of the inferior rectus muscle or anesthesia of the midface and upper lip in the distribution of the second division of the fifth cranial nerve secondary to neuropraxia resulting from a fracture through the infraorbital foramen or compression by a local hematoma.

Oropharynx

The integrity of the mouth and nasal complex may be evaluated by listening to the patient's speech. A muffled or overly nasal voice may indicate occlusion of the nose or nasopharynx, whereas dysarthria may indicate a mandibular fracture, tongue injury, or neurologic problem. Oral injury may result in progressive airway compromise, and dysphonia should alert the clinician to the possible need for active airway management. The intraoral examination includes inspection of the palate, teeth, tongue, and gums and palpation with a gloved finger (the latter only if the patient is able to cooperate). The range of motion of the mandible should be determined. If the maximal incisor opening is less than 5 cm, a mandibular fracture may be present. Trismus is likely to indicate a fracture or significant hematoma within the face. If awake, the patient's impression about the normalcy of bite occlusion is a more sensitive determinant of a fracture of the mandible than the physician's impression. Being able to perform a tongue blade test (grasping and holding a tongue blade between the teeth while the examiner pulls gently) is associated with greatly reduced probability of mandibular fracture. If the patient is able to crack the tongue blade by biting on both sides of the mouth, the negative predictive value for a mandibular fracture is 95%.[49] Injury to the parotid area should raise suspicion of disruption of Stensen's duct. The opening of the duct opposite the second upper molar should be examined for bleeding while the gland is compressed. If blood

www.ketabpezeshki.com 66485457-66963820

is expressed from the duct or the severed ends of the duct are identified within a facial wound, specialized repair over a stent is required to prevent formation of a cutaneous fistula.

Ears

Otoscopy is performed to evaluate the integrity of the external canal, look for hemotympanum, and assess for otorrhea. Clear fluid from the ear after trauma should raise the possibility of a cerebrospinal fluid (CSF) leak. At the bedside, a drop of the fluid may be placed onto filter paper. A rapidly advancing halo of clear fluid around red blood defines a positive test result. This is a quick bedside test with good sensitivity (>86%) as long as the mix is approximately 50:50 between blood and other fluid, but it does not differentiate between CSF and saline, saliva, or other clear fluids.[50]

The ear should be inspected for subcutaneous hematomas because these need to be drained.

Nose

The nose is palpated for tenderness, crepitus, or abnormal movement, and then each naris is held closed in turn to ensure the patient is able to breathe through either side. The septum should be examined visually to look for septal hematoma, which appears as a large purple mass extending from the septum. If there is any concern about CSF rhinorrhea, the aforementioned filter test may be performed.

Neurologic Examination

Light touch should be tested for all three branches of the fifth cranial nerve. Motor function (cranial nerve VII) can be examined by having the patient actively wrinkle the forehead, fully open and close the eyelids, smile widely, and bare the teeth. Asymmetry of these movements indicates a potential nerve injury. Peripheral injuries to the seventh cranial nerve should cause discernible weakness in the forehead as well as the orbital and oral musculature, whereas central injuries will result in preserved forehead function because of crossing fibers distal in the course of the nerve. The fifth cranial nerve (the ophthalmic branch of the trigeminal nerve) and the seventh cranial nerve in an altered or uncooperative patient can be assessed by testing the corneal reflex.

The final part of the physical examination is documentation. Facial injuries may be evidence of assault, domestic violence, or child abuse. Careful documentation of findings, including photographs or drawings or both, not only communicates initial findings to other practitioners but also can provide crucial legal evidence because many of these cases have forensic implications or result in litigation.

DIAGNOSTIC STRATEGIES

Imaging

The choice of imaging for facial fractures depends on the patient's stability, the patient's ability to cooperate, and the availability of various options. The two main options are plain x-ray examination and computed tomography (CT). Fractures are better visualized with CT than with magnetic resonance imaging, so magnetic resonance imaging is not an optimal imaging choice. In patients who cannot cooperate for plain x-ray examination or in whom a fracture or penetrating injury is obvious from the physical examination, CT is the imaging modality of choice.[51] For a complete evaluation, CT scans of the face should include coronal and sagittal reconstructions. Interpreting facial CT scans is an art that requires attention to bones, sinuses, orbital contents, and soft tissue and is best handled by radiologists.

With the increasing use of CT in emergency medicine and the advent of telemedicine, most 24-hour EDs have access to CT scanners for facial injuries. CT is now the first choice for all patients in whom a midface fracture is suspected. However, when no scanner is available and in patients with low to moderate pretest probability of a midface or maxillary fracture and who are stable and able to cooperate, the current recommendation is for a single screening view (Water's or occipitomental view), followed by CT if the film is positive for a fracture or air-fluid level in any sinus.[52-54]

The U shape of the mandible and the presence of nearby bony structures make isolating the mandible on flat film impossible. Simple radiographs of the mandible are less sensitive than panorex radiographs and particularly tend to miss fractures of the condyle (Fig. 42-6). If available, panorex imaging is indicated for isolated mandibular fractures, dental fractures, or fractures of the alveolar ridge. In children, if fracture of the condyle is suspected, coronal CT is more sensitive and specific than panorex studies.[55] Although the traditional teaching has been that the mandible's shape results in two fractures if it is fractured at all (Fig. 42-7), a case series using CT evaluation found that 42% of mandibular fractures were unifocal.[56]

For patients with complex fractures, new imaging techniques may help improve surgical planning and esthetic outcomes. In displaced orbital fractures, use of CT data to measure orbital

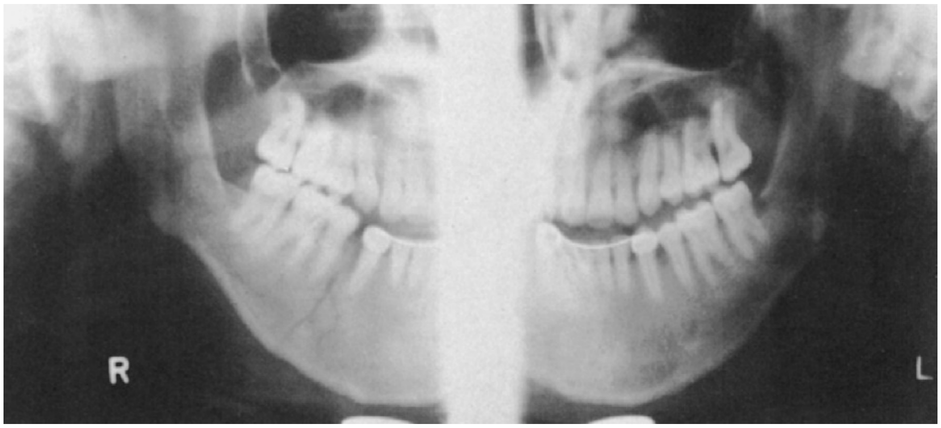


Figure 42-6. Panoramic radiograph of the mandible shows fractures through the left angle and the right body. A dental appliance is in place on the lower incisors.

www.ketabpezeshki.com 66485457-66963820

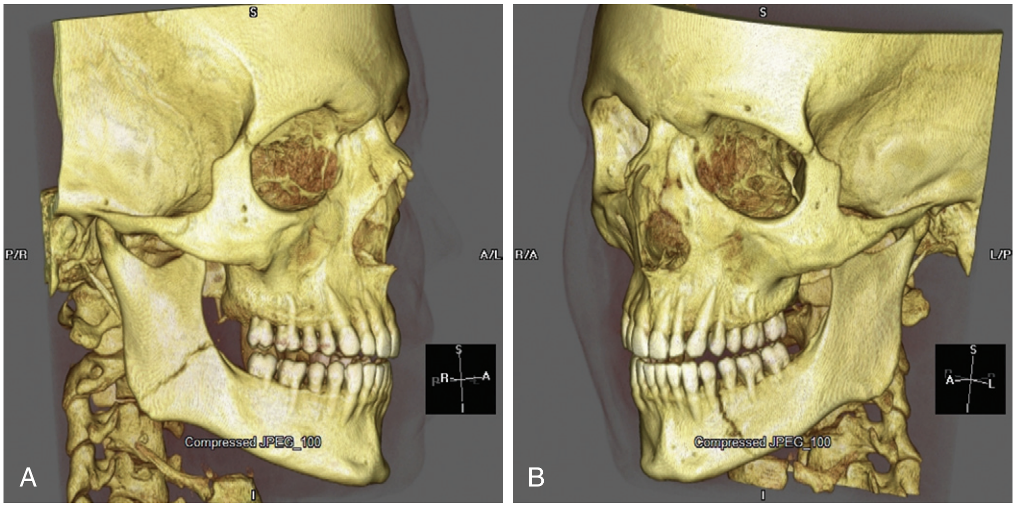


Figure 42-7. Three-dimensional computed tomography reconstructions of minimally displaced mandibular fractures in the same patient as in Figure 42-5.

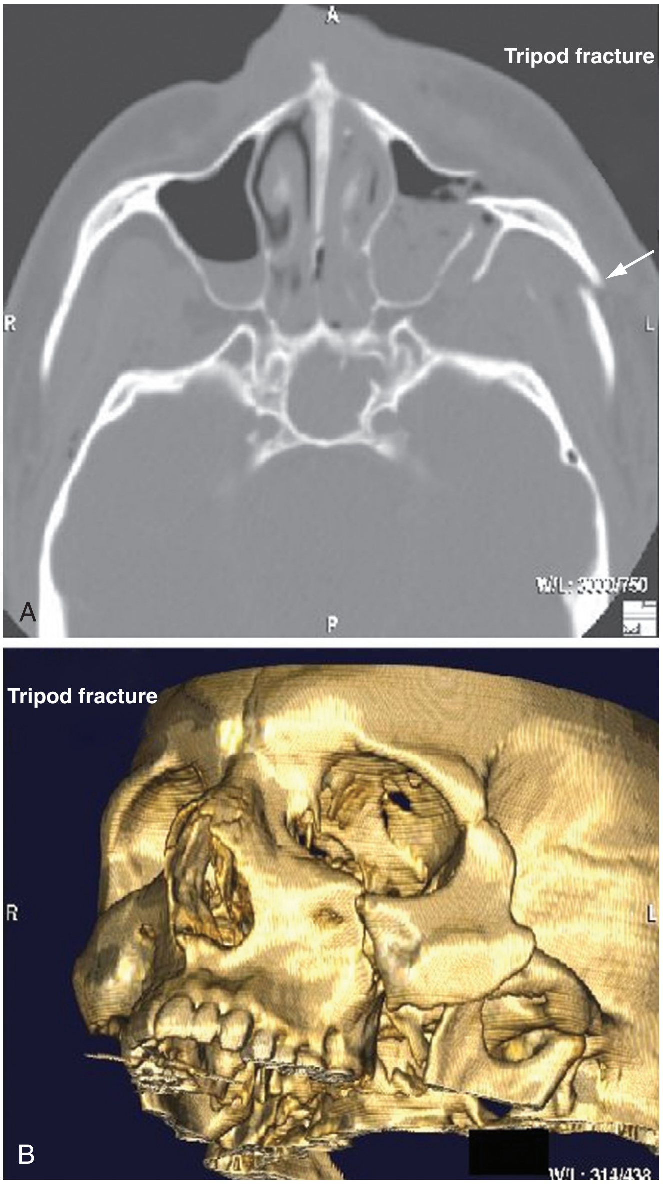


Figure 42-8. Tripod fracture. Computed tomography (**A**) and three-dimensional reconstruction (**B**).

volumes has shown that after repair an orbital volume greater than 4% larger than on the unfractured side is associated with visible postoperative enophthalmos.[57] This method seems to be useful in predicting which patients might benefit from operative repair.[58] In conjunction with more standard two-dimensional facial CT scans, three-dimensional CT scans seem to improve the diagnosis and aid preoperative planning for patients with complex fractures of the midface (Fig. 42-8B).[59-62]

Patients with tenderness and swelling isolated to the bony bridge of the nose who do not have a septal hematoma, can breathe through each naris, and have a straight nose do not require nasal bone radiographs in the ED because imaging results would not alter treatment. If these criteria are not met, early reduction or referral for surgical intervention may be indicated, and plain films (for truly isolated injuries) or CT scanning (if concern for other injuries exists) is indicated. Plain x-ray examination may also be performed in the setting of legal concerns. If there is concern for a foreign body in a superficial wound, two standard x-ray views (Water's and Caldwell's or occipitofrontal view) are indicated to triangulate the position of the observed foreign material.

Patients with suspected ocular injuries may benefit from a bedside ultrasound as a noninvasive and economical diagnostic tool, particularly if there is a need for urgent operative management of other injuries and no time for a dedicated facial CT. The different acoustic impedances of the orbit's anatomic structures make the modality operator friendly, and an ultrasound of the eye can readily detect vitreous hemorrhage, retinal detachment, and globe rupture (Figs. 42-9 and 42-10). The operator should position the transducer in a transverse orientation, scanning in a cephalad-to-caudad direction, making sure to scan the entire anatomy of the eye, and using special care to minimize the pressure exerted over the eye, especially when evaluating for specific ocular emergencies. Prior findings have suggested that high-resolution ultrasound has at least a 94% correlation with axial and coronal CT imaging in the detection of orbital fractures and emphysema.[63,64]

MANAGEMENT

Management of facial injuries occurs within the overall resuscitation of the patient. Unless the airway is threatened or exsanguination is a concern, treatment of most facial injuries can be deferred until more life-threatening injuries have been stabilized. Care of the patient with penetrating trauma to the face should center

www.ketabpezeshki.com 66485457-66963820

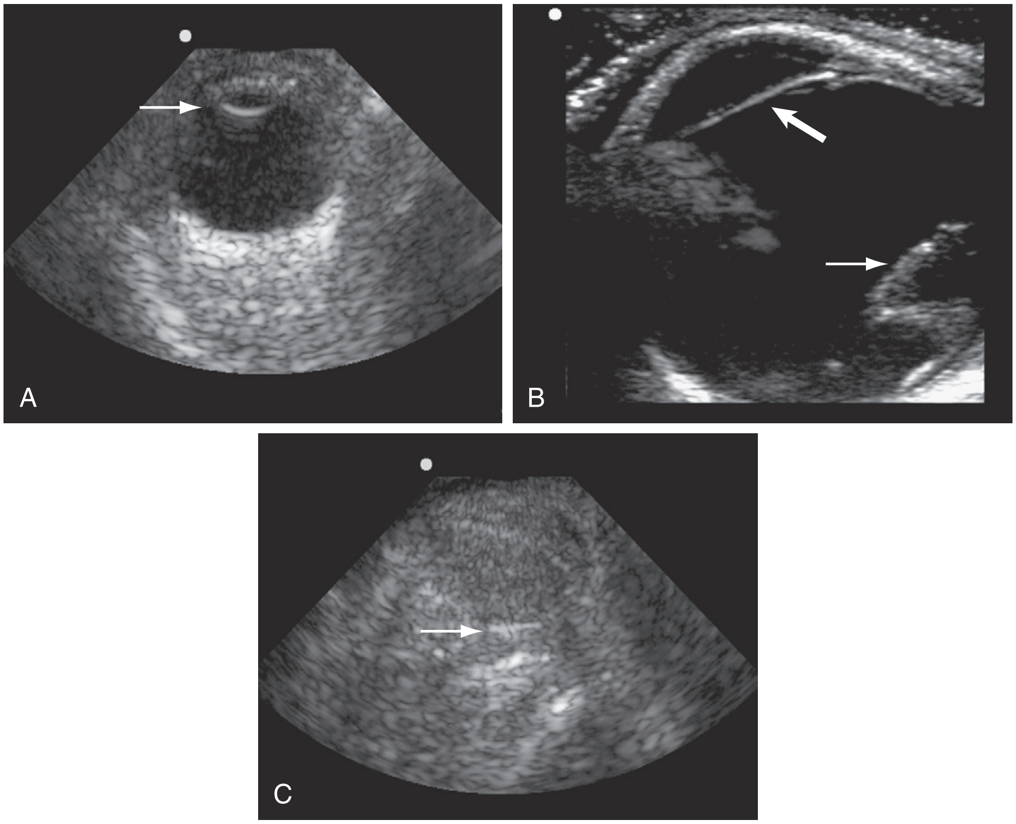


Figure 42-9. Bedside sonograms of the eye. In each image, a small white dot is placed to identify the front of the eye, and thin arrows identify the lens. Sonogram **A** demonstrates a normal eye. Sonogram **B** shows a detached retina *(large arrow),* and sonogram **C** demonstrates a ruptured globe. (Images courtesy Keith Boniface, MD.)

on standard trauma care, with initial attention focused on maintenance of a patent airway, adequate ventilation, and systemic perfusion.

Out-of-Hospital Care

The indications for airway management of a patient with a facial injury are the same as those for other patients: Does the patient have a currently patent airway and, if so, can the patient be expected to maintain it without intervention? If the answer to either question is “no,” the patient needs to be intubated. If other injuries preclude the patient from ventilating appropriately, intubation is also required.

Patients with expanding hematomas after facial injury present a special dilemma. Injuries to the facial vasculature may cause significant hematomas that can extend into the neck or down to the supraclavicular area. Such hematomas greatly distort the normal anatomy of the pharynx and neck, making intubation and cricothyroidotomy particularly difficult. If the patient has a patent airway, he or she can speak without difficulty, and the transport time is expected to be short, no intervention should be performed and the receiving institution should be notified so that planning can begin for a difficult airway. If intubation must occur in the field, awake orotracheal intubation should be considered. If certified in its use, emergency medical services personnel should be ready to perform a surgical airway as needed. Gunshot wounds to the lower third of the face are particularly likely to require intubation for airway protection, and a significant proportion of these require a surgical airway.[65]

In the setting of significant facial trauma, active bleeding can obscure the view and make intubation considerably more difficult.

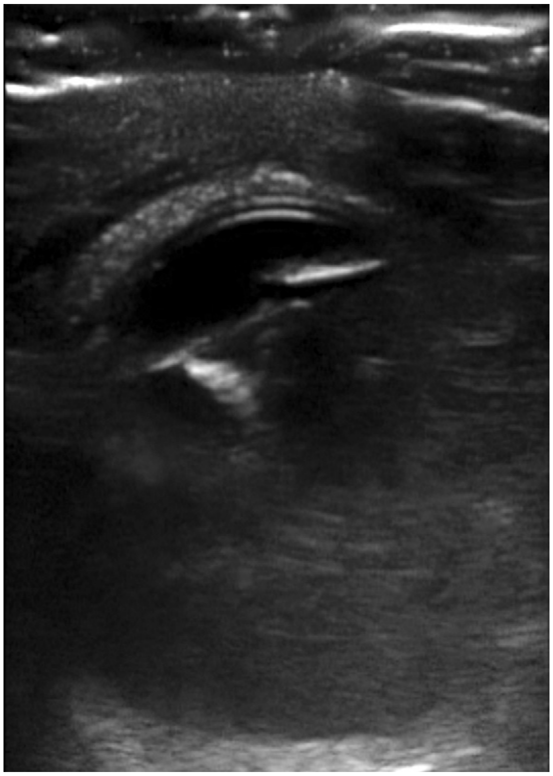


Figure 42-10. Ultrasound image of a globe rupture with lens dislocation. At the top of the image the cornea is visible, and just below that is the dislocation with hemorrhage visible posteriorly.

www.ketabpezeshki.com 66485457-66963820

Double suctioning may be required, which involves an assistant holding one suction catheter in the posterior oropharynx while the operator uses a second device more anteriorly or inferiorly as needed during the procedure. Conversely, patients with fractures of the mandible may be easier to intubate because increased mobility of the mandible may allow wider opening of the mouth.

Blind nasotracheal intubation is controversial in the literature and is rarely indicated in facial trauma because of concerns about complications.[66] Patients with multiple injuries who require intubation may not be breathing actively enough for this method to be of use, and out-of-hospital rapid sequence intubation is associated with a higher success rate and fewer complications.[67] Some alternative airway techniques may include submental or submandibular intubations or anesthesiology-assisted intubations with the use of adjuncts such as the GlideScope or lighted stylet.[67a,67b] Although reports of intracranial placement of an endotracheal tube in facial trauma are rare, this catastrophic complication is known to occur after blind nasotracheal intubation.[68,68a] Any concern about an injury to the skull base or cribriform plate is a contraindication to this method of intubation.

Control of local bleeding is the other significant out-of-hospital consideration in facial trauma. In many areas, external compression is sufficient to control bleeding during transport. Epistaxis and significant intraoral bleeding can be more difficult to treat. Even in the setting of significant nasal trauma, the soft portions of the nares can be compressed to stop anterior nasal bleeding. In an awake, alert patient with intraoral bleeding, 4 × 4-inch gauze packing may be placed into the buccal space to provide control. If these maneuvers are insufficient and the patient's injuries require spinal immobilization, intubation may be a necessary first step to control intraoral or nasopharyngeal bleeding. After intubation, large amounts of gauze can be placed via the mouth into the oropharynx and nasopharynx to obtain control via direct pressure.

If out-of-hospital personnel suspect a ruptured globe, special protection against compression of the eye (eye cup or noncontact shielding) should be provided in the field. Avulsed parts, including ears, the tip of the nose, teeth, or completely avulsed flaps, should be transported with the patient in saline-soaked gauze.

Completely avulsed teeth should be removed and carried with the patient during transport. Neurologically normal, unintoxicated patients may be able to carry avulsed teeth in their mouths, held between gum and buccal mucosa. Patients who are not neurologically normal, who are intoxicated, who require cervical spine immobilization, who are nauseated, or who cannot be transported upright should not be transported with avulsed teeth held in the mouth. In such cases, the risk of aspirating the teeth outweighs any other concerns, and the teeth should be transported in a container with sterile saline. Incompletely avulsed teeth should be left in place and not manipulated.

General Measures

The initial evaluation in the ED should readdress the question of intubation. In the setting of significant distortion of the mouth, oropharynx, or upper neck by avulsion or hematoma, the awake fiberoptic method may optimize the chances of a successful intubation. When there is significant distortion of the oropharynx or larynx, a laryngeal mask airway may not achieve a sufficiently tight fit to allow ventilation. Emergent cricothyroidotomy is the procedure of choice if endotracheal intubation is impossible.

Unless there is life-threatening hemorrhage from the face, after the airway has been secured, facial injuries can be safely left to the secondary survey. The emergency physician should avoid being distracted by a facial injury and search intensively for head, neck, chest, abdominal, pelvic, and extremity injuries. In-depth ocular examinations and other special testing should not be performed until other serious injuries have been managed emergently.

Significant bleeding can often be controlled by compression. If compression fails, hemostasis can be achieved in the ED by ligation of the relevant vessel. Great care should be taken, however, not to clamp or tie structures blindly deep within the face because serious iatrogenic injury of nerve or ductal structures could result. Massive, uncontrollable bleeding from facial fractures occurs rarely and is best treated with arterial embolization, if available.[69,70] Intra-arterial vasopressin has recently been suggested as an option for hemostasis.[71]

In the rare case of a patient acutely exsanguinating from a facial wound, the external carotid artery can be emergently ligated. This ligation is best accomplished with surgical assistance.

Bite wounds, gross contamination, or significant tattooing from foreign bodies should be addressed definitively as soon as possible, given the needs of the patient's other injuries. Definitive treatment of simple soft tissue injuries can be left for 24 hours, if needed, after irrigation and temporary approximation. Ideally, facial fractures are treated early, before significant swelling occurs, or after several days when return of more normal facial contours can aid in the repair. The need for tetanus prophylaxis should be considered for all open wounds. If the injury is an animal bite, the need for rabies prophylaxis should be considered. Because the rabies virus is transmitted to the brain along nerve axons, and symptomatic disease theoretically may occur sooner with wounds of the head, face, and neck, initiating rabies treatment within 5 days of the injury is recommended.

Finally, because lead poisoning has been reported from the ingestion of shotgun pellets in patients with primarily facial injuries, consideration should be given to looking for the presence of pellets in the gastrointestinal tracts of these victims. A plain x-ray film of the abdomen suffices. Early endoscopic removal of the pellets should limit future toxicity.[72]

Soft Tissue Injuries

Soft tissue injuries to the face present an acute cosmetic concern for the patient. Areas may be contused, lacerated, abraded, or any combination of the three. When cleaned of any debris, abrasions may be covered in a thin layer of antibiotic ointment and left exposed or covered (as possible given their location). Patients with significant tattooing will benefit from topical lidocaine for anesthesia before vigorous scrubbing is begun to remove the embedded material. Careful attention should be paid to removing all of the embedded material as soon as possible because epithelialization requires the creation of a new wound to remove debris later. For contusions, ice and sleeping with the head elevated may limit the degree of swelling anticipated on days 2 and 3. The patient should be cautioned to anticipate the development of periorbital swelling or ecchymosis or both over time as a result of gravity when the primary contusion has been to the brow, forehead, or bridge of the nose.

The most appropriate person to close an open wound may be either the emergency physician or a consultant. Decisions about which wounds to close personally and which to ask a consultant to repair are based on the personal judgment of the emergency physician. Factors that may be considered in the decision include resource availability; the size, shape, depth, and location of the wound; and the time commitment that careful, cosmetic wound closure can entail for the emergency physician in a busy ED. The patient's priority with facial lacerations is cosmesis, and therefore a patient may request specialty services for even minor wounds.[73] Children and patients with behavioral problems may require

www.ketabpezeshki.com 66485457-66963820

sedation to allow sufficient control for a cosmetic repair. Repair of facial wounds in uncooperative patients who are acutely intoxicated may be delayed until they become sober enough to cooperate for the procedure.

After anesthesia has been achieved, wounds should be explored for depth, foreign bodies, and underlying fractures. Irrigation may not be necessary in simple, clean facial wounds closed within 6 hours.[74] For nongaping wounds less than 3 cm, a single-layer closure may be sufficient.[75] For gaping wounds deeper than the dermis, subcuticular buried sutures of absorbable materials should be placed to close any potential space and relieve any tension on the skin. For skin closure, tissue adhesive is faster and less painful, results in equal cosmetic results in adults and children, and can be used to close the skin over deeper sutures.[76,76a] Compared with sutures, tissue adhesive has the additional benefit of not requiring later removal, but care must be taken not to unintentionally glue the eye, nares, or mouth closed.

Antibiotics are not required for simple facial wounds, which rarely become infected. Bite wounds, wounds with any evidence of devascularization, wounds through and through the buccal mucosa, wounds involving the cartilage of the ear or nose, and wounds with extensive contamination (particularly with barnyard or fecal matter) are exceptions to this rule.

The choice of antibiotic therapy will likely be an evolving topic in light of the emergence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA). Among spontaneous skin infections requiring an ED visit, the prevalence of CA-MRSA is now quite significant for both adults and children.[77-79] In addition, it appears that the incidence of such spontaneous infections requiring ED care is also increasing.[78] However, current literature does not suggest choosing antibiotics with MRSA coverage for wound prophylaxis. If prophylactic antibiotic therapy is needed, the antibiotic should be selected based on the normal bacterial flora associated with the affected site.[80,81]

SPECIAL CONSIDERATIONS BY SITE

Mouth

Lacerations

Lip lacerations are common and require special consideration to maintain the appearance of the lip edge or vermilion border and the natural architecture of the philtrum. Because infiltration of even a small volume of local anesthetic may distort and blanch the soft tissue, marking the vermilion border (with nonpermanent ink or a scratch of a sterile needle) before anesthesia facilitates a cosmetic repair. To minimize any divots and maximize cosmesis and function, wounds that include the muscular layer should be closed in multiple layers. Skin may be closed with nylon or other nonabsorbable suture; the lip and mucosa should be closed with absorbable suture. Lip lacerations are not amenable to closure with wound adhesives.

Through-and-through lacerations of the mouth should be closed in layers, beginning with the intraoral mucosa and working outward in layers toward the skin. After closure of the mucosal layer, copious irrigation of the external wound is indicated to remove lingering bacteria that otherwise would be incorporated into the wound. In small case series, prophylactic treatment with penicillin has been shown to decrease the risk of infection after significant through-and-through lacerations.[82] Lacerations that approach the parotid (Stensen's) or submandibular (Wharton's) ducts should be evaluated before intervention for ductal integrity. Saliva milked from the gland should be thin and clear and should readily exit the duct. If a duct is involved or there is any doubt, a facial specialist should be consulted for evaluation and repair.

Small lacerations of the tongue or oral mucosa do not require repair. Lacerations that gape (including deep tongue lacerations), collect food, and are likely to heal with a significant divot or thick scar that may hinder eating and speaking functions require repair. Deep or gaping lacerations of the tongue or oral mucosa should be closed (in layers if necessary) with absorbable sutures that do not require removal. To facilitate repair, an assistant may be needed to expose the laceration by grasping the tongue between gauze and holding a segment outside of the mouth. Some advocate placing a thick temporary suture through the distal tongue (after appropriate anesthesia) to facilitate this exposure. Discharge instructions for intraoral lacerations (whether or not repaired) should include gentle cleansing (swish and spit) with a mild antiseptic.

Perioral Burns

Young children use their mouths to explore their environment and may lick electrical outlets or bite electrical cords. The wet oral mucosa provides little electrical resistance, and the current penetrates to deeper structures, often causing a full-thickness burn at the commissure of the lip. These children need a systemic evaluation for other electrical injuries (see Chapter 142); this discussion is limited to the evaluation and treatment of facial wounds. Perioral burns resulting from electrical injury can result in severe cosmetic problems and microstomia. The initial appearance of the wound may be misleadingly trivial; edema and necrosis progress over several days, and even with healing the defect may become quite disfiguring. Traditionally, a more acute concern has been bleeding from the labial artery when the maturing burn eschar separates from underlying structures 5 to 21 days postburn, and it was previously recommended that patients be admitted so that such bleeding could be urgently addressed if it occurred. In general, current practice is discharge with close observation at home and follow-up with otolaryngology specialists, plastic surgery specialists, or both to address cosmesis. Large wounds can cause significant early difficulty with eating, however, and patients may require placement of a nasogastric tube for maintenance of nutrition. Initial ED treatment of the wound is aimed at treating discomfort and keeping the area clean.

Treatment of these injuries is controversial; options include conservative treatment with early oral splinting, immediate surgery aimed at reconstruction, or delayed excision of the burned area. Later reconstructive repair may be required to preserve mouth opening, eating, and speech clarity.[83] Early involvement of consultants is indicated, even when the burn seems to be trivial. The possibility of abuse or neglect should be considered when a child is presented with a perioral burn.

Cheeks

Contusions of the cheek should raise concern for an underlying zygomatic or maxillary fracture. Lacerations of the lateral cheek may involve the parotid gland or Stensen's duct. Failure to identify and repair ductal injury results in retention of salivary fluid and enlargement of the gland or formation of a cutaneous fistula. Lacerations in the area anterior to the tragus may include injury to the facial nerve, and careful neurologic examination should be carried out before closure. Langer's lines change from mostly horizontal in the superior cheek to diagonal at the nasolabial fold, then curve convexly around the mouth; these changes should be taken into consideration when débridement is required as part of a complex repair.

www.ketabpezeshki.com 66485457-66963820

Nose

Because of its anterior position, soft tissue injuries to the nose are common. Almost any trauma can result in epistaxis. In general, epistaxis is controllable by pinching the cartilaginous anterior nose closed between two fingers and holding compression for approximately 10 minutes. If it is not controlled, anterior packing is indicated. Intranasal inspection is required in any nasal injury to assess for a septal hematoma, which appears as a dark purple or bluish mass against the septum. Hematomas require drainage because they are associated with necrosis of the septum if left untreated. Simple incision and expression of the clot followed by anterior packing are sufficient. Traditional teaching has been that any patient with nasal packing should receive prophylactic antibiotics to cover *Staphylococcus* and *Streptococcus* species to prevent sinusitis and toxic shock syndrome. Toxic shock syndrome is a rare but measurable complication of postoperative nasal packing, occurring in approximately 16 per 100,000 cases; the incidence with primary packing is unknown.[84] There is no evidence that prophylactic antibiotics change the risk of developing toxic shock syndrome or sinusitis in postoperative or primary packing[85]; the few studies that have been done have had sample sizes far too small to show an effect.

Because of the location and structure of the nasal bridge, fractures of the thin bones of this area are common. Patients with contusion or tenderness over the bridge of the nose may be assumed to have a fracture of the nasal bones. If the nose is acceptably straight on initial evaluation, there is no septal hematoma, epistaxis is controlled, and the patient is able to breathe out of each naris, no further evaluation is required emergently for isolated nasal injuries. Although radiographs of the nasal bones are still in use, they have no clinical utility.[86-88]

Swelling over the bridge often precludes determination of the acceptability of the appearance at the time of injury. The patient may be provided with a referral for outpatient specialty follow-up in 3 to 5 days if the appearance at that time (when the swelling has improved) is unacceptable. In a series of surgically repaired simple nasal bone fractures, septal fractures were present in more than 50% of cases. CT did not provide any advantage in diagnosing septal fractures and should be reserved for evaluating patients suspected of having other, more complex fractures.[89,90]

Children with nasal fractures may have premature closure of sutures and uneven growth, particularly of the vomeroseptal line. In a child, no imaging studies are indicated, but a consultant should evaluate swelling and tenderness over the nose, preferably within 4 days of the injury.[91]

Simple lacerations of the nasal skin may be closed with sutures or tissue adhesive. If needed, anesthesia may be achieved with a nerve block of the infraorbital or supratrochlear nerves. The large pores typically present in the area of the nasal ala increase the likelihood of stitch abscesses after laceration closure in this area. Closure with an absorbable running subcuticular suture may limit the risk of this outcome. If involved, the cartilaginous portions of the ala should be closed in a separate layer with absorbable 4-0 suture. For lacerations through and through the nose, repair should be carried out from the mucosal layer outward, with copious irrigation between layers.

Ears

Blunt trauma to the ear may cause hematoma formation in the subperichondrial potential space. Such hematomas are the prelude to the development of a "cauliflower ear" and should be drained by aspiration. Reaccumulation of the hematoma is prevented with a compressive dressing of the ear, but reexamination is crucial, and reaspiration should be performed as necessary.

Ear lacerations often involve the cartilage. The ear may be anesthetized with a field block: 1% lidocaine *without* epinephrine is injected subcutaneously into the skin around the base of the ear. Simple skin wounds may be closed in a single layer. Lacerations to the underlying cartilage should be repaired with absorbable material. If there is significant degloving or loss of overlying tissue, a consultant should be involved; portions of aural cartilage may be saved temporarily in a distant dermal pocket for later reconstruction. Because cartilage is avascular, chondritis, when it occurs, requires extensive débridement and is disfiguring. No randomized trials have been performed, but when the cartilage of the pinna requires repair, antibiotic prophylaxis is recommended. Compressive ear dressings (splints) are indicated after any significant repair. Ear injuries occurring before age 1 year or injuries to both ears in children are rare and should raise the suspicion of abuse.[92]

Eyes

Simple eyelid lacerations may be repaired in a single layer. Wound adhesives should be used with great caution anywhere near the eye; care must be taken not to glue the eyelids open or shut. Lacerations that involve deeper structures, loss of tissue, or the lid margin should be referred to a consultant. The integrity of the lacrimal apparatus can be assessed by instilling fluorescein into the eye and assessing for dye in the wound. A consultant should handle any injury to the sac or lacrimal duct.

Eyebrow lacerations are common because of the overhanging supraorbital ridge. Careful wound exploration should be performed to assess the integrity of the underlying bony structure. No shaving should be performed because the brow hairs may not regrow, and the hairs are necessary for realignment. If débridement is required, it should be done parallel to the hair follicles (skived) rather than perpendicular to the skin. This approach minimizes the bald area of the scar. Closing the deeper muscular layers preserves the normal expressive function of the brow. Injuries to the globe are discussed in Chapter 71.

FRACTURES AND DISLOCATIONS

For the emergency physician, the key to facial fractures is accurate diagnosis and appropriate referral. Many nondisplaced or minimally displaced facial fractures may be handled on an outpatient basis, with definitive repair or fixation delayed several days. In adults, fractures develop firm fibrous union within approximately 10 to 14 days; however, definitive repair is performed most easily before day 7. Methods for diagnosing fractures were discussed previously. Fractures to the face of young children are relatively rare and may be incomplete or greenstick fractures. Fibrous union in these cases is rapid; early reduction (within 3 days) is recommended.

Antibiotics are indicated for open fractures and fractures that violate a sinus. Patients with fractures through the nasoethmoid complex that violate the maxillary bones or the floor of the orbit should be cautioned to avoid sneezing and blowing the nose because these activities force air out into the soft tissues of the face.

Surgical repair of simple nasal fractures may be performed closed and the nose splinted internally or packed. Repair of fractures of the floor of the orbit, when necessary, may require the placement of a silicone patch to occlude the opening into the maxillary sinus. Operative repair of most other fractures of the face is performed with use of small metal plates (microplates), screws, or wires to stabilize fragments by attaching them to unbroken segments of bone. Efforts are made to return the features to their unfractured locations and to regain facial symmetry, if possible. Complex facial fractures may have to be repaired in a staged fashion, depending on the patient's degree of illness and the amount and quality of the bone remaining. Much of this surgery

www.ketabpezeshki.com 66485457-66963820

is best accomplished when the fragments are still freely mobile but initial swelling has been reduced, on postinjury days 3 to 5.

Specific Considerations by Site

Forehead

Fractures through the superior forehead may occur above the level of the frontal sinus. These are actually skull fractures rather than facial fractures and should be addressed with special attention to risk of injury to the underlying brain. Unlike other skull fractures, frontal skull fractures often require repair for cosmesis alone. More often, fractures in this area involve the anterior portion of the frontal sinus. If even minimally displaced, these fractures require elevation for cosmesis. Fractures through the anterior wall of the frontal sinus are likely to continue through the posterior wall, and a CT scan should be performed to look carefully for this complication; if present, a CSF leak should be assumed until proved otherwise. CSF leaks into the frontal sinus may also manifest in a delayed manner, days or years after the initial injury.[93] With many frontal sinus fractures, complex repair or obliteration may be required to treat this complication.[94]

Orbit

The most common simple fracture of the orbit is blow-out fracture of the orbital floor, often caused by a fisted blow or ball striking the globe, increasing intraorbital pressure enough to force orbital contents through the floor. This injury may happen without other significant bony facial injury. When displaced, the bony fragments sag into the underlying maxillary sinus. If the inferior rectus muscle is entrapped in the defect, the patient is unable to elevate the globe on the affected side, resulting in diplopia on upward gaze. Stretch or compression of the infraorbital nerve, which passes through the floor, may cause anesthesia over the anteromedial cheek and upper lip. Because signs of entrapment may result from contusion and edema and be self-limited, immediate repair is not necessary, but careful follow-up is required. Repair typically is performed 1 or 2 weeks after the injury for persistent enophthalmos or diplopia. Because of the acute limitation in the visual field, discharge instructions for patients with acute diplopia should include patching for comfort and a request not to drive until the diplopia is resolved.

Fractures of the medial orbital wall, through the lamina papyracea, are often associated with nasal injury or more general midface fractures, particularly with telescoping of the midfacial skeleton. Herniation of orbital contents into the ethmoids may occur. In one study, patients with orbital fractures with a medial component were more likely to have ocular signs of diplopia or exophthalmos than patients with fractures that did not involve the medial wall.[95] Fractures involving the superior orbit include the base of the frontal sinus, and all of the concerns about the anterior skull mentioned previously apply. Herniation of orbital structures into the frontal sinus is rare but can occur.

Many orbital fractures involve more than one wall of the orbit and may be present in a constellation with complex midface fractures (Fig. 42-11). Several classification schemes aimed at improving communication among emergency physicians, radiologists, and maxillofacial surgeons have been proposed,[96-98] but no classification system is generally accepted.

Injury to the orbit, particularly fractures, can cause a hematoma to form within the orbit, behind the globe. If significant in size, a retro-orbital hematoma can elevate retro-orbital pressure causing acute exophthalmos and a compartment syndrome of the retro-orbital space. Stretch on the retinal artery limiting flow to the retina or neuropraxia of the retinal nerve may cause decreased visual acuity or blindness. Orbital emphysema associated with fractures of the medial wall or floor rarely results in a space-filling lesion with the same effect. This is a true emergency; drainage of the air or blood via lateral canthotomy with cantholysis is indicated to save the patient's vision. Needle aspiration of entrapped air may also be attempted, but this may be best left to a consultant, given the proximity of the globe.

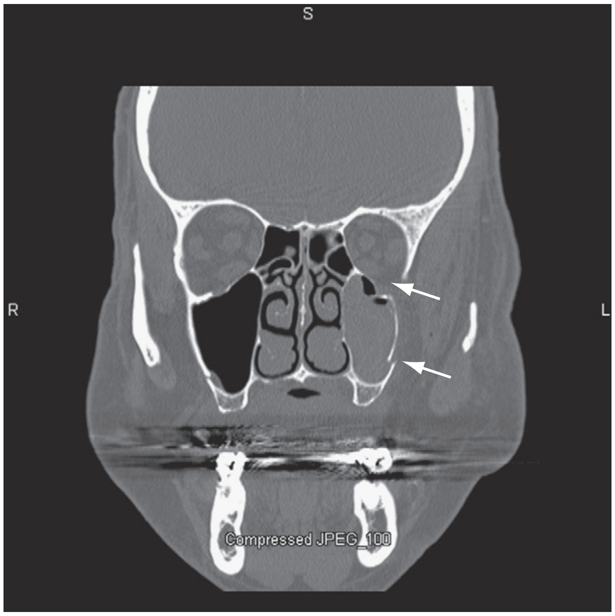


Figure 42-11. Computed tomography shows fractures of the left orbital floor (*top arrow*) and left lateral maxillary wall (*bottom arrow*). There is streak artifact from dental devices.

Midface

Tripod (or trimalar) fractures are among the simplest fractures of the midface and include fractures of three bones: the lateral orbit, the zygoma, and the maxilla (see Fig. 42-10). Typically caused by a direct blow, these fractures are often displaced and require operative stabilization. If left untreated, the area may "sink" posteriorly and inferiorly, giving an unacceptable appearance of facial asymmetry emphasized by the inferior position of the orbit and malar flattening. On the initial physical examination, there may be a large contusion over the cheekbone, enophthalmos, or malocclusion of the upper teeth. Fractures through the anterior wall of the maxillary sinus may denervate the maxillary teeth because the dentoalveolar nerves run in tunnels in this area.

More complex fractures of the midface are classified with the Le Fort system, although many complex fractures defy classification with this system. A Le Fort I fracture involves a transverse fracture through the maxilla above the roots of the teeth and may be unilateral or bilateral. Patients may report malocclusion, and the maxilla may be mobile when the upper teeth are grasped and rocked. A Le Fort II fracture is typically bilateral and pyramidal in shape. It extends superiorly in the midface to include the fracture of the nasal bridge, maxilla, lacrimal bones, orbital floor, and rim. In these cases the nasal complex moves as a unit with the maxilla when the teeth are grasped and rocked. In the current age of CT scans, in which the full extent of comminution can be appreciated, simple Le Fort III fractures are rare but essentially involve fracturing of the connections between the elements of the skull and the face (craniofacial dysjunction). These fractures start at the bridge of the nose; extend posteriorly along the medial wall of the orbit (ethmoids), along the floor of the orbit (maxilla), and through the lateral orbital wall; and finally break through the zygomatic arch.

www.ketabpezeshki.com 66485457-66963820

Intranasally, they extend through all the lesser bones to the base of the sphenoid and frequently are associated with a CSF leak.

Significant force to the bridge of the nose may fracture the deep nasoethmoid complex without creating a formal Le Fort pattern. CT is the initial test of choice in this setting. Fractures to the central portion of the ethmoid bone (cribriform plate) are likely to be associated with a CSF leak and commonly result in anosmia.

If possible, patients with a CSF leak should have the head elevated 40 to 60 degrees. Head elevation minimizes the intracranial pressure, with the idea of decreasing the flow and allowing the leak to seal. Often these patients are treated with antibiotics; however, this practice is controversial, and most of the studies supporting it involve small, local case series.[93] In one meta-analysis, antibiotics did not decrease the rate of meningitis in the setting of CSF leak.[100] Neurosurgeons should be involved in the care of patients with CSF leaks, although many leaks will spontaneously resolve.[101]

Fractures involving the deeper structures of the midface may be associated with significant bleeding into the nose or oropharynx. Anterior nasal packing may be performed safely in the adult patient with multiple trauma. Even a 10-cm anterior pack should not reach the skull base in a skeletally mature person. Significant or massive bleeding into the posterior nasopharynx presents a complex problem and occurs in less than 1% of patients with midface fractures. It may be treated with nasal packing and immediate fracture reduction.[47,69] Unless the anatomy is well understood and the skull base known to be intact, the use of a long balloon catheter (Foley) should be avoided for control of posterior bleeding. The unintended positioning of these items within the intracranial[103,104] or intraspinal space[105] during blind nasal insertion has been well documented, and when the face is grossly distorted, preinsertion measurement or other methods of preventing this outcome have not been adequately tested. There are no reports of the intracranial placement of commercial catheters designed for posterior epistaxis, but if the midface is significantly distorted or telescoped, they may be long enough to reach the intracranial space. An alternative method for containing posterior nasal bleeding is to provide compression by packing the area with gauze by hand from the oropharynx after intubation.

Zygoma

Isolated fractures of the zygoma are relatively rare, usually the result of a direct blow, and are often displaced. Because the condyle of the mandible may disturb zygomatic fragments while moving, fractures with significant displacement are likely to result in trismus or discomfort with mouth opening. Surgical repair is usually required to return the cheekbone to an acceptable position.

Mandible

Fractures of the mandible can result from any significant force applied to its U shape. Because of its shape, multiple fractures may result from a single blow, and the fracture sites may be distant from the site of impact. Depending on the location of the fractures, the patient may have trismus (fractures of the coronoid process, neck, or rami), dental malocclusion, swelling, and tenderness intraorally or externally. Anesthesia of the lower lip may occur if there is damage to the inferior dental nerve.

Fractures of the symphysis, body, angle, or rami usually require early splinting, typically by the placement of arch bars to accomplish interdental fixation, commonly known as “wiring the jaw shut.” Fixation limits fracture motion, decreases the patient’s discomfort, and, if the fracture is minimally displaced, may provide complete fracture care. Impacted and nondisplaced fractures occasionally are treated with only a soft diet, and fractures of the coronoid alone usually require no intervention, but these decisions should be made in consultation with an oral surgeon or other specialist. Arch bars may be placed in the ED or operating room and typically are placed by a specialist (see Fig. 42-6). Fracture reduction may require the extraction of teeth adjacent to the fracture line. Patients with open fractures require antibiotics and usually hospitalization. When the fractures are closed and adequate stabilization can be obtained, elective operative repair can be performed as an outpatient procedure in 3 to 5 days.

In one study, 17 to 22% of pediatric patients 4 to 11 years old developed facial growth disturbances after a fractured mandible and required later orthognathic surgery for correction. Children younger than 4 or older than 11 years were much less likely to develop this complication.[106,107] Because of the frequency of this complication, children in this age group who have sustained a blow to the chin and who have any trismus or tenderness over the TMJ should be assessed carefully with panorex imaging for condylar fracture and referred appropriately.

Dental and Alveolar Trauma

Trauma to the teeth may occur with or without other facial injury. In the setting of caries, tooth fractures may occur with eating relatively soft foods. Tooth fractures are classified by the Ellis system. Class I fractures involve only the enamel of the tooth, are not painful, and can await dental evaluation on an outpatient basis. Class II fractures expose the yellow dentin and may be painful. These also can await dental care, but they may be covered with a dressing of calcium hydroxide and aluminum foil. Class III fractures expose the dental pulp, seen as a red line or dot, and are exquisitely painful. These require early evaluation by dentists or endodontists.

Sufficient energy to the area avulses teeth from their sockets. Multitrauma patients, particularly patients who are intoxicated, required to be supine for cervical spine immobilization, or neurologically impaired, should have avulsed or mostly avulsed teeth removed from the mouth and placed externally in saline as an aspiration precaution. In a critically ill multitrauma patient, avulsed teeth should be among the lowest priorities and are reimplanted only if the care of other injuries allows it and there is no risk of aspiration if the teeth loosen.

To perform a reimplantation, the physician disturbs the socket as little as possible, gently rinses off the tooth (the root should not be wiped), and places it into the socket where it “clicks” into place. If the tooth is only partially avulsed, extruded, or laterally luxated, it should not be removed; it should be reimplanted or relocated. Intruded teeth should not be manipulated. Reimplantation can be painful and may require local anesthesia with a regional dental block. Alternatively, the area of a single socket may be anesthetized by placing approximately 0.5 mL of 1% lidocaine without epinephrine into the buccal sulcus and gum on the outer side of the alveolar ridge. After reimplantation, the tooth requires stabilization with acrylic splint or wiring to the adjacent teeth.

Reimplanted teeth may or may not “take” acutely, but it can take weeks to assess the final success of reimplantation. The length of time out of the socket and storage process seem to play a critical role in the initial success.[108] Among teeth successfully reimplanted in less than 1 hour, more than 66% have been found to be radiographically healed and functionally normal after 5 years. For teeth successfully reimplanted after 3 hours, more than 80% have been found to have signs of inflammation and bone resorption after the same period of time.[109,109a]

In children, the front maxillary incisors are most commonly avulsed. After reimplantation, these teeth may ankylose and fail to “grow out” normally, requiring later extraction or orthodontic intervention for cosmesis. This situation is most common in children age 6 to 10 years with avulsed adult teeth.[110]

www.ketabpezeshki.com 66485457-66963820

Avulsed teeth missing after significant trauma should be carefully sought, including via a chest x-ray examination. In an acute event, the patient may not recall aspirating a tooth; this is more likely if the patient is intoxicated or neurologically impaired. If the tooth is below the diaphragm on the film, it does not require retrieval. Teeth lodged in a bronchus or the esophagus require bronchoscopic or endoscopic retrieval. Aspirated teeth result in pulmonary abscess formation unless removed.

Fractures through the alveolar ridge may result in a group of teeth being dislodged and out of position, often leaning inward. These teeth require stabilization with wire or acrylic splinting after fracture reduction has returned the teeth to their correct location. The involved teeth may or may not survive after such a fracture, and careful follow-up with a dentist or oral surgeon is required.

Temporomandibular Joint

The TMJ is complex, with the condyle of the mandible undergoing rotation and translation anteriorly during normal mouth opening. The function of the joint is preserved by a meniscus, which overlies the condyle. Essentially, the joint between the meniscus and the condyle is a hinged joint, allowing rotation, and the joint between the meniscus and the temporal bone is a sliding joint, allowing translation. A formal, thick joint capsule does not exist at the anteromedial portion of the joint; loose, relatively weak synovial tissue is positioned here to allow translation to occur.

Trauma to the TMJ may tear the meniscus or injure the collateral ligaments holding it in a normal position. This injury can cause the meniscus to fail to translate normally, resulting in clicking or popping as it catches up to the condyle or inability to open the mouth fully because the meniscus completely fails to translate. Patients without fracture but with acute pain and difficulty with mouth opening should be placed on soft foods, asked not to yawn or struggle to open their mouths widely, and referred to an oral surgeon with expertise in TMJ pathology. Pediatric patients with post-traumatic internal derangements of the TMJ are prone to asymmetry of facial growth and retrognathia. In one study, 88% of children injured before their ninth birthday had significant facial abnormalities years later.[111]

Because of the anatomy and function of the joint, anterior dislocation of the TMJ can occur after widely yawning, laughing, kissing, singing, or other activities that involve spontaneous, wide opening of the mouth. When the condyle is out, spasm of the muscles of mastication prevents spontaneous reduction. Significant trauma is more likely to cause a fracture-dislocation. Simple dislocation may be unilateral or bilateral, and the patient reports being unable to close the mouth. In unilateral dislocation, the jaw is rotated laterally away from the affected joint; bilateral dislocation causes significant protrusion of the jaw. The jaws of these patients are often so widely open that they cannot swallow their secretions and are actively drooling. Speech is often garbled by the patient's inability to touch the tongue to the roof of the mouth or the maxillary teeth. There is a depression in the area of the affected TMJ on inspection of the patient's face.

If the mechanism of injury suggests a fracture, the area should be imaged with plain x-ray or panorex examination before reduction is attempted. For reduction of a simple dislocation, the patient should be seated upright. For leverage to be maximized, the best position may be for the patient to be seated in a regular chair with the operator standing in front of the patient. As in dislocations of other joints, adequate analgesia and sedation are required for success. With the thumb or index finger placed into the buccal sulcus on either side of the mouth, the angle of the jaw is pressed downward while the symphysis is rotated (chin) upward and backward. Care should be taken not to place fingers along the crowns of the teeth; when relocation occurs, spasm of the muscles of mastication snaps the mouth shut with force. If this is the only location possible for the physician's fingers, gauze wrappings should be placed to protect them.

Panorex or x-ray films are suggested after the first episode of dislocation. The patient is discharged with pain medicine, a soft diet for 2 weeks, and outpatient follow-up with an oral surgeon. Patients with an episode of dislocation are predisposed to a recurrence. In patients who experience frequent dislocation, interdental fixation may be required for 2 or 3 weeks.

DISPOSITION

The decision to discharge or admit patients with facial trauma depends on their associated injuries, general injury severity, and plans for treatment. Patients with isolated facial trauma that has been repaired or stabilized and with no airway issues are usually discharged.

KEY CONCEPTS

- The face is central to the patient's ability to breathe, eat, and communicate. Injuries to the face can have serious psychological and psychosocial consequences.
- Facial injuries may be prevented by the appropriate use of safety belts, child restraints, air bags, helmets, and mouth and face guards.
- The epidemiology of facial injury is changing, with an increasing proportion of injuries occurring as a result of interpersonal violence. A careful history is required, and the possibility of abuse should be considered for every patient.
- Shock from facial trauma is rare and results only from obvious external bleeding. Facial injuries should not distract the emergency physician from aggressively searching for other causes of shock.
- Assertive management of the airway is indicated in a patient with significant facial injuries. Surgical management (cricothyroidotomy) may be required, particularly with gunshot wounds.
- Directed facial CT scanning is the best imaging technique in patients with obvious injuries.
- Definitive treatment may be delayed if necessary to allow other serious injuries to be addressed.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Rankin M, Borah GL: Perceived functional impact of abnormal facial appearance. *Plast Reconstr Surg* 2003; 111:2140.
2. Langlois JH, et al: Maxims or myths of beauty? A meta-analytic and theoretical review. *Psychol Bull* 2000; 126:390.
3. Pashos A, Niemitz C: Results of an explorative empirical study on human mating in Germany: Handsome men, not high-status men, succeed in courtship. *Anthropol Anz* 2003; 61:331.

3a. Levine E, Degutis L, Pruzinsky T, Shin J, Persing JA: Quality of life and facial trauma: Psychological and body image effects. *Ann Plast Surg* 2005; 54:502-510.

4. Rankin M, Borah GL: Appearance is a function of the face. *Plast Reconstr Surg* 2010; 125:873-878.
5. Glynn SM, et al: Chronic posttraumatic stress disorder after facial injury: A 1-year prospective study. *J Trauma* 2007; 62:410.
6. Shetty V, Dent DM, Glynn S, Brown KE: Psychosocial sequelae and correlates of orofacial injury. *Dent Clin North Am* 2003; 47:141.
7. Gironda M, Lui A: Social support and resource needs as mediators of recovery after facial injury. *Oral Maxillofac Surg Clin North Am* 2010; 22:251-259.
8. Wong EC: Survivors of violence-related facial injury: Psychiatric needs and barriers to mental health care. *Gen Hosp Psychiatry* 2007; 29:117.
9. Glynn SM, et al: The development of acute post-traumatic stress disorder after orofacial injury: A prospective study in a large urban hospital. *J Oral Maxillofac Surg* 2003; 61:785.
10. Le BT, Holmgren EP, Holmes JD, Ueeck BA, Dierks EJ: Referral patterns for the treatment of facial trauma in teaching hospitals in the United States. *J Oral Maxillofac Surg* 2003; 61:557.
11. Bagheri SC, et al: Facial trauma coverage among level-1 trauma centers of the United States. *J Oral Maxillofac Surg* 2008; 66:963.
12. National Center for Injury Prevention and Control, Centers for Disease Control and Prevention: *Web-based Injury Statistics Query and Reporting System (WISQARS)*, 2006. Available at www.cdc.gov/ncipc/wisqars. Accessed March 2011.
13. Erdmann D: A retrospective analysis of facial fracture etiologies. *Ann Plast Surg* 2008; 60:398-403.
14. Insurance Institute for Highway Safety: *Safety Belt and Child Restraint Laws. Insurance Institute for Highway Safety*. Available at www.iihs.org/laws/SafetyBeltUse.aspx. Accessed March 2011.
15. Murphy RX Jr, Birmingham KL, Okunski WJ, Wasser T: The influence of airbag and restraining devices on the patterns of facial trauma in motor vehicle collisions. *Plast Reconstr Surg* 2006; 105:516.
16. Simoni P, Ostendorf R, Cox AJ 3rd: Effect of air bags and restraining devices on the pattern of facial fractures in motor vehicle crashes. *Arch Facial Plast Surg* 2003; 5:113.
17. Mouzakes J, et al: The impact of airbags and seat belts on the incidence and severity of maxillofacial injuries in automobile accidents in New York State. *Arch Otolaryngol Head Neck Surg* 2001; 127:1189.
18. Duma SM, Jernigan MV: The effects of airbags on orbital fracture patterns in frontal automobile crashes. *Ophthalmol Plast Reconstr Surg* 2003; 19:107.
19. Murphy RX Jr, Birmingham KL, Okunski WJ, Wasser TE: Influence of restraining devices on patterns of pediatric facial trauma in motor vehicle collisions. *Plast Reconstr Surg* 2001; 107:34.
20. Major MS, MacGregor A, Bumpous JM: Patterns of maxillofacial injuries as a function of automobile restraint use. *Laryngoscope* 2000; 110:608.
21. Stacey DH: Safety device use affects the incidence patterns of facial trauma in motor vehicle collisions: An analysis of the National Trauma Database from 2000 to 2004. *Plast Reconstr Surg* 2008; 121:2057-2064.
22. Shapiro AJ, Johnson RM, Miller SF, McCarthy MC: Facial fractures in a level I trauma centre: The importance of protective devices and alcohol abuse. *Injury* 2001; 32:353.
23. Lee HK, Snape L: Role of alcohol in maxillofacial fractures. *N Z Med J* 2008; 121:15.
24. Murphy D: Substance use and facial injury. *Oral Maxillofac Surg Clin North Am* 2010; 22:231-238.
25. Ogundare BO, Bonnick A, Bayley N: Pattern of mandibular fractures in an urban major trauma center. *J Oral Maxillofac Surg* 2003; 61:713.
26. Leathers R, Le AD, Black E, McQuirter JL: Orofacial injury in underserved minority populations. *Dent Clin North Am* 2003; 47:127.
27. Fraioli RE, Branstetter BF 4th, Deleyiannis FW: Facial fractures: beyond Le Fort. *Otolaryngol Clin North Am* 2008; 41:51-76.
28. Kim J, Huoh K: Maxillofacial (midface) fractures. *Neuroimag Clin N Am* 2010; 20:581-596.
29. Holmes PJ, Koehler J, McGwin G Jr, Rue LW 3rd: Frequency of maxillofacial injuries in all-terrain vehicle collisions. *J Oral Maxillofac Surg* 2004; 62:697.
30. Shults RA, Wiles SD, Vajani M, Helmkamp JC: All-terrain vehicle-related nonfatal injuries among young riders: United States, 2001-2003. *Pediatrics* 2005; 116:e608.
31. Kraus JF, Rice TM, Peek-Asa C, McArthur DL: Facial trauma and the risk of intracranial injury in motorcycle riders. *Ann Emerg Med* 2003; 41:18.
32. Liu BC, et al: Helmets for preventing injury in motorcycle riders. *Cochrane Database Syst Rev* 2008; 1:CD004333.
33. Owens BD, et al: Combat wounds in Operation Iraqi Freedom and Operation Enduring Freedom. *J Trauma* 2008; 64:295.
34. Reehal P: Facial injury in sport. *Curr Sports Med Rep* 2010; 9:27-34.
35. Perkins SW, Dayan SH, Sklarew EC, Hamilton M, Bussell GS: The incidence of sports-related facial trauma in children. *Ear Nose Throat J* 2000; 79:632.
36. Marshall SW, Mueller FO, Kirby DP, Yang J: Evaluation of safety balls and faceguards for prevention of injuries in youth baseball. *JAMA* 2003; 289:568.
37. Bernardo LM, Gardner MJ, Rosenfield RL, Cohen B, Pitetti R: A comparison of dog bite injuries in younger and older children treated in a pediatric emergency department. *Pediatr Emerg Care* 2002; 18:247.
38. Le BT, Dierks EJ, Ueeck BA, Homer LD, Potter BF: Maxillofacial injuries associated with domestic violence. *J Oral Maxillofac Surg* 2001; 59:1277.
39. Arosarena OA, Fritsch TA, Hsueh Y, Aynehchi B, Haug R: Maxillofacial injuries and violence against women. *Arch Facial Plast Surg* 2009; 11:48-52.
40. Fenton SF, Bouquot JE, Unkel JH: Orofacial considerations for pediatric, adult, and elderly victims of abuse. *Emerg Med Clin North Am* 2000; 18:601.
41. Shaikh ZS, Worrall SF: Epidemiology of facial trauma in a sample of patients aged 1-18 years. *Injury* 2002; 33:669.
42. Deleted in proofs.
43. Durbin DR, et al: Risk of injury to restrained children from passenger air bags. *Traffic Inj Prev* 2003; 4:58.
44. Martin RC 2nd, Spain DA, Richardson JD: Do facial fractures protect the brain or are they a marker for severe head injury? *Am Surg* 2002; 68:477.
45. Hackl W, Fink C, Hausberger K, Ulmer H, Gassner R: The incidence of combined facial and cervical spine injuries. *J Trauma* 2001; 50:41.
46. Roccia F: Cervical spine fractures associated with maxillofacial trauma: An 11-year review. *J Craniofac Surg* 2007; 18:1259.
47. McLean JN, Moore CE, Yellin SA: Gunshot wounds to the face—acute management. *Facial Plast Surg* 2005; 21:191.
48. Koren I, Shimonove M, Shvero Y, Feinmesser R: Unusual primary and secondary facial blast injuries. *Am J Otolaryngol* 2003; 24:75.

48a. Wahl P, Schreyer N, Yersin B: Injury pattern of the Flash-Ball, a less-lethal weapon used for law enforcement: report of two cases and review of the literature. *J Emerg Med* 2006; 31:325-330.

48b. Fineman MS: Ocular paintball injuries. *Curr Opin Ophthalmol* 2001; 12:186-190.

49. Alonso LL, Purcell TB: Accuracy of the tongue blade test in patients with suspected mandibular fracture. *J Emerg Med* 1995; 13:297.
50. Kerr JT, Chu FW, Bayles SW: Cerebrospinal fluid rhinorrhea: Diagnosis and management. *Otolaryngol Clin North Am* 2005; 38:597-611.
51. Sun JK, LeMay DR: Imaging of facial trauma. *Neuroimaging Clin N Am* 2002; 12:295.
52. Pogrel MA, Podlesh SW, Goldman KE: Efficacy of a single occipitomental radiograph to screen for midfacial fractures. *J Oral Maxillofac Surg* 2000; 58:24.
53. McGhee A, Guse J: Radiography for midfacial trauma: Is a single OM 15 degrees radiograph as sensitive as OM 15 degrees and OM 30 degrees combined? *Br J Radiol* 2000; 73:883.
54. Goh SH, Low BY: Radiologic screening for midfacial fractures: A single 30-degree occipitomental view is enough. *J Trauma* 2002; 52:688.
55. Chacon GE, Dawson KH, Myall RW, Beirne OR: A comparative study of 2 imaging techniques for the diagnosis of condylar fractures in children. *J Oral Maxillofac Surg* 2003; 61:668.
56. Escott EJ, Branstetter BF: Incidence and characterization of unifocal mandible fractures on CT. *Am J Neuroradiol* 2008; 29:890.
57. Dolynchuk KN, Tadjalli HE, Manson PN: Orbital volumetric analysis: Clinical application in orbitozygomatic complex injuries. *J Craniomaxillofac Trauma* 1996; 2:56.
58. Fan X, Li J, Zhu J, Li H, Zhang D: Computer-assisted orbital volume measurement in the surgical correction of late enophthalmos caused by blowout fractures. *Ophthal Plast Reconstr Surg* 2003; 19:207-211.

www.ketabpezeshki.com 66485457-66963820

59. Remmler D, Denny A, Gosain A, Subichin S: Role of three-dimensional computed tomography in the assessment of nasoorbitoethmoidal fractures. *Ann Plast Surg* 2000; 44:553.
60. Saigal K, Winokur RS, Finden S, Taub D, Pribitkin E: Use of three-dimensional computerized tomography reconstruction in complex facial trauma. *Facial Plast Surg* 2005; 21:214.
61. Avery L, Susarla S, Novelline R: Multidetector and three-dimensional CT evaluation of the patient with maxillofacial injury. *Radiol Clin North Am* 2011; 49:183-203.
62. Kelley P, Hopper R, Gruss J: Evaluation and treatment of zygomatic fractures. *Plast Reconstr Surg* 2007; 120:5S.
63. Sargent LA: Nasoethmoid orbital fractures: Diagnosis and treatment. *Plast Reconstr Surg* 2007; 120:16S.
64. McIlraith TS: Diagnosis of periorbital gas on ocular ultrasound after facial trauma. *Am J Emerg Med* 2005; 23:517.
65. Hollier L, Grantcharova EP, Kattash M: Facial gunshot wounds: A 4-year experience. *J Oral Maxillofac Surg* 2001; 59:277.
66. Rosen CL, Wolfe RE, Chew SE, Branney SW, Roe EJ: Blind nasotracheal intubation in the presence of facial trauma. *J Emerg Med* 1997; 15:141.
67. Walls RM: Blind nasotracheal intubation in the presence of facial trauma: Is it safe? *J Emerg Med* 1997; 15:243.
67a. Krausz AA, El-Naaj IA, Barak M: Maxillofacial trauma patient: Coping with the difficult airway. *World J Emerg Surg* 2009; 27:4-21.
67b. Mohan R, Iyer R, Thaller S: Airway management in patients with facial trauma. *J Craniofac Surg* 2009; 20:21-23.
68. Roppolo L, et al: Nasotracheal intubation in the emergency department revisited. *J Emerg Med* 1999; 17:791.
68a. Weitzl N, Kendall J, Pons P: Blind nasotracheal intubation for patients with penetrating neck trauma. *J Trauma* 2004; 56:1097-1101.
69. Shimoyama T, Kaneko T, Horie N: Initial management of massive oral bleeding after midfacial fracture. *J Trauma* 2003; 54:332.
70. Bynoe RP, et al: Maxillofacial injuries and life-threatening hemorrhage: Treatment with transcatheter arterial embolization. *J Trauma* 2003; 55:74.
71. Okada Y, Higa T, Hori T, Shima T, Yoshida A: Intra-arterial vasopressin injection for the treatment of massive bleeding from the external carotid artery after craniofacial trauma—technical note. *Neurol Med Chir (Tokyo)* 2004; 44:611.
72. McQuirter JL, et al: Elevated blood lead resulting from maxillofacial gunshot injuries with lead ingestion. *J Oral Maxillofac Surg* 2003; 61:593.
73. Singer AJ, et al: Patient priorities with traumatic lacerations. *Am J Emerg Med* 2000; 18:683.
74. Hollander JE, et al: Irrigation in facial and scalp lacerations: Does it alter outcome? *Ann Emerg Med* 1998; 31:73.
75. Singer AJ, et al: Single-layer versus double-layer closure of facial lacerations: A randomized controlled trial. *Plast Reconstr Surg* 2005; 116:363.
76. Farion K, et al: Tissue adhesives for traumatic lacerations in children and adults. *Cochrane Database Syst Rev* 2002; 3:CD003326.
76a. Singer AJ, Kinariwala M, Lirov R, Thode HC Jr: Patterns of use of topical skin adhesives in the emergency department. *Acad Emerg Med* 2010; 17:670-672.
77. Lauder A: Antibiotic prophylaxis in the management of complex midface and frontal sinus trauma. *Laryngoscope* 2010; 120:1940-1945.
78. Frazee BW, et al: High prevalence of methicillin-resistant *Staphylococcus aureus* in emergency department skin and soft tissue infections. *Ann Emerg Med* 2005; 45:311.
79. Hasty MB, et al: Cutaneous community-associated methicillin-resistant *Staphylococcus aureus* among all skin and soft tissue infections in two geographically distant pediatric emergency departments. *Acad Emerg Med* 2007; 14:35.
80. Pallin DJ, et al: Increased U.S. emergency department visits for skin and soft tissue infections, and changes in antibiotic choices, during the emergence of community-associated methicillin-resistant *Staphylococcus aureus*. *Ann Emerg Med* 2008; 51:291.
81. Moran J: Antimicrobial prophylaxis for wounds and procedures in the emergency department. *Infect Dis Clin North Am* 2008; 22:117.
82. Capellan O, Hollander JE: Management of lacerations in the emergency department. *Emerg Med Clin North Am* 2003; 21:205.
83. Hashem FK, Al Khayal Z: Oral burn contractures in children. *Ann Plast Surg* 2003; 51:468.
84. Weber R, et al: Packing in endonasal surgery. *Am J Otoaryngol* 2001; 22:306-320.
85. Biswas D, Mal RK: Are systemic prophylactic antibiotics indicated with anterior nasal packing for spontaneous epistaxis. *Acta Otolaryngol* 2009; 129:179-181.
86. Oluwasanmi AF, Pinto AL: Management of nasal trauma—widespread misuse of radiographs. *Clin Perform Qual Health Care* 2000; 8:83.
87. Kucik CJ, Clenney T, Phelan J: Management of acute nasal fractures. *Am Fam Phys* 2004; 70:1315.
88. Ziccardi V, Braidy H: Management of nasal fractures. *Oral Maxillofac Surg Clin North Am* 2009; 21:203-208.
89. Thiede O, et al: Comparison of ultrasonography and conventional radiography in the diagnosis of nasal fractures. *Arch Otolaryngol Head Neck Surg* 2005; 131:434.
90. Rhee SC, Kim YK, Cha JH, Kang SR, Park HS: Septal fracture in simple nasal bone fracture. *Plast Reconstr Surg* 2004; 113:45.
91. Haug RH, Foss J: Maxillofacial injuries in the pediatric patient. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; 90:126.
92. Steele BD, Brennan PO: A prospective survey of patients with presumed accidental ear injury presenting to a paediatric accident and emergency department. *Emerg Med J* 2002; 19:226
93. Friedman JA, Ebersold MJ, Quast LM: Post-traumatic cerebrospinal fluid leakage. *World J Surg* 2001; 25:1062.
94. Manolidis S, Hollier LH Jr: Management of frontal sinus fractures. *Plast Reconstr Surg* 2007; 120:32S.
95. Jank S, et al: Clinical signs of orbital wall fractures as a function of anatomic location. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003; 96:149.
96. Manolidis S, Weeks BH, Kirby M, Scarlett M, Hollier L: Classification and surgical management of orbital fractures: Experience with 111 orbital reconstructions. *J Craniofac Surg* 2002; 13:726.
97. Follmar KE, et al: A clinically applicable reporting system for the diagnosis of facial fractures. *Int J Oral Maxillofac Surg* 2007; 36:593.
98. Carinci F, Zollino I, Brunelli G, Cenzi R: Orbital fractures: A new classification and staging of 190 patients. *J Craniofac Surg* 2006; 17:1040.
99. Reference deleted in proofs.
100. Villalobos T, Arango C, Kubilis P, Rathore M: Antibiotic prophylaxis after basilar skull fractures: A meta-analysis. *Clin Infect Dis* 1998; 27:364.
101. Bell RB, Dierks EJ, Homer L, Potter BE: Management of cerebrospinal fluid leak associated with craniomaxillofacial trauma. *J Oral Maxillofac Surg* 2004; 62:676.
102. Reference deleted in proofs.
103. Pawar SJ, Sharma RR, Lad SD: Intracranial migration of Foley catheter—an unusual complication. *J Clin Neurosci* 2003; 10:248.
104. Spurrier EJ, Johnston AM. Use of nasogastric tubes in trauma patients—a review. *J R Army Med Corps* 2008; 154:10-13.
105. Porras LF, Cabezudo JM, Lorenzana L, Garcia-Yagüe LM, Rodriguez-Sanchez JA: Inadvertent intraspinal placement of a Foley catheter in severe craniofacial injury with associated atlanto-occipital dislocation: Case report. *Neurosurgery* 1993; 33:310.
106. Demianczuk AN, Verchere C, Phillips JH: The effect on facial growth of pediatric mandibular fractures. *J Craniofac Surg* 1999; 10:323.
107. Cole P, Kaufman Y, Izaddoost S, Hatef DA, Hollier L: Principles of pediatric mandibular fracture management. *Plast Reconstr Surg* 2009; 123:1022-1024.
108. Petrovic B, Marković D, Peric T, Blagojevic D: Factors related to treatment and outcomes of avulsed teeth. *Dent Traumatol* 2010; 26:52-59.
109. Schatz JP, Hausherr C, Joho JP: A retrospective clinical and radiologic study of teeth reimplanted following traumatic avulsion. *Endod Dent Traumatol* 1995; 11:235.
109a. Soares Ade J, Gomes BP, Zaia AA, Ferraz CC, de Souza-Filho FJ: Relationship between clinical-radiographic evaluation and outcome of teeth replantation. *Dent Traumatol* 2008; 2:183-188. doi: 10.1111/j.1600-9657.2007.00528.x.
110. Malmgren B, Malmgren O: Rate of infraposition of reimplanted ankylosed incisors related to age and growth in children and adolescents. *Dent Traumatol* 2002; 18:28.
111. Defabianis P: Post-traumatic TMJ internal derangement impact on facial growth (findings in a pediatric age group). *J Clin Pediatr Dent* 2003; 27:297.

www.ketabpezeshki.com 66485457-66963820

Chapter 43

Spinal Injuries

Amy H. Kaji, Edward J. Newton, and Robert S. Hockberger

PERSPECTIVE

Background

Prehistoric humans undoubtedly suffered little in the way of significant spinal injury. Their semierect posture combined with well-developed posterior cervical muscles protected the cervical spine against day-to-day trauma. Evolution, however, did much to undo this initial protective state. As humans assumed an upright posture, the shoulders dropped away from the newly elevated head, and the hypertrophied paraspinous muscles atrophied. This increased the head's range of motion but diminished the spine's protection. Although civilization heightened man's inventiveness, it unfortunately did little to curb his aggressiveness. Automobiles replaced horse-drawn carriages, and fists and clubs gave way to knives and guns, making spinal injuries more common in the modern era.

Epidemiology

Statistics from the National Spinal Cord Injury Database show that motor vehicle collisions (MVCs) account for roughly 40% of all spinal injuries.[1] Speeding, alcohol intoxication, and failure to use restraints are major risk factors. The next most common cause of spinal cord injury (SCI) is falls, followed by acts of violence (primarily gunshot wounds) and sporting activities. There are currently more than 260,000 spinal injury victims living in the United States, and 12,000 new cases occur each year. Approximately 80% of victims are male, and the average age at injury is 40 years. The lifetime cost to care for SCI victims ranges from $500,000 for people older than 50 years with incomplete motor function to over $3 million for people younger than 25 years with complete paraplegia. The total cost to society from lifelong medical expenses and lost productivity for all age groups and types of spinal injuries is estimated to be more than $5 billion.[2] The devastating emotional and psychological impact on the victims and their families is incalculable.

PRINCIPLES OF DISEASE

Anatomy and Physiology

The human spine consists of 33 bony vertebrae: 7 cervical, 12 thoracic, 5 lumbar, 5 sacral (fused into one), and 4 coccygeal (usually fused into one) (Fig. 43-1).[3] These 26 individual units are separated from one another by flexible intervertebral disks and connected to form a single functioning unit by a complex network of ligaments. In addition to providing basic structural support, the vertebral column protects the spinal cord, which extends from the midbrain to the level of the second lumbar vertebra. Nerves that receive and transmit sensory, motor, and autonomic impulses pass to and from the spinal cord through intervertebral foramina.

Spinal injuries involve fractures in 85% of cases. Ten percent are purely ligamentous injuries, and 5% are SCI without radiographic abnormality (SCIWORA) in which the spinal cord is injured directly without any radiographic evidence of bony or ligamentous injury.[4] *Stability* of a spinal injury refers to the resistance to displacement of fracture fragments or, in the case of ligamentous injury, the entire vertebral unit. Displacement may occur at the time of injury or progressively over hours to weeks and can cause or worsen damage to the spinal cord or nerve roots. There are several conceptual models for assessing the stability of subaxial spinal column injuries, but the most commonly used one is the three parallel vertical column model proposed by Denis (Fig. 43-2)[5] The anterior column is formed by alternating vertebral bodies and intervertebral disks surrounded by the annulus fibrosus capsule and the anterior longitudinal ligament. The middle column consists of the posterior part of the annulus fibrosus and posterior vertebral wall, the posterior longitudinal ligament, the spinal cord, the paired laminae and pedicles, the articulating facets, the transverse processes, and the nerve roots and vertebral arteries and veins. The posterior column consists of the spinous processes, nuchal ligament, interspinous and supraspinous ligaments, and ligamentum flavum. Disruption of only a single column usually preserves a high degree of stability but does not preclude SCI from displaced fracture fragments. Disruption of two columns results in an injury that is stable in one direction but unstable in another (e.g., stable in flexion but unstable in extension). Disruption of all three columns produces a highly unstable injury. Until the full extent of the injury is clear, all spinal injuries should be treated as potentially unstable, and spinal immobilization should be maintained.

Pathophysiology

Classification of Spinal Column Injuries

Acute spinal injuries are classified according to the mechanism of trauma: flexion, flexion-rotation, extension, and vertical compression (Table 43-1).[6,7]

Flexion. Pure flexion injuries involving the C1-C2 complex can cause unstable *atlanto-occipital* or *atlantoaxial joint dislocation,* with or without an associated fracture of the odontoid (Fig. 43-3). These injuries are considered unstable because of their location and the relative lack of muscle and ligamentous support.

In pure flexion injuries below C2, a longitudinal pull is exerted on the strong nuchal ligament complex, which usually remains intact. Most of the force is expended on the vertebral body

www.ketabpezeshki.com 66485457-66963820

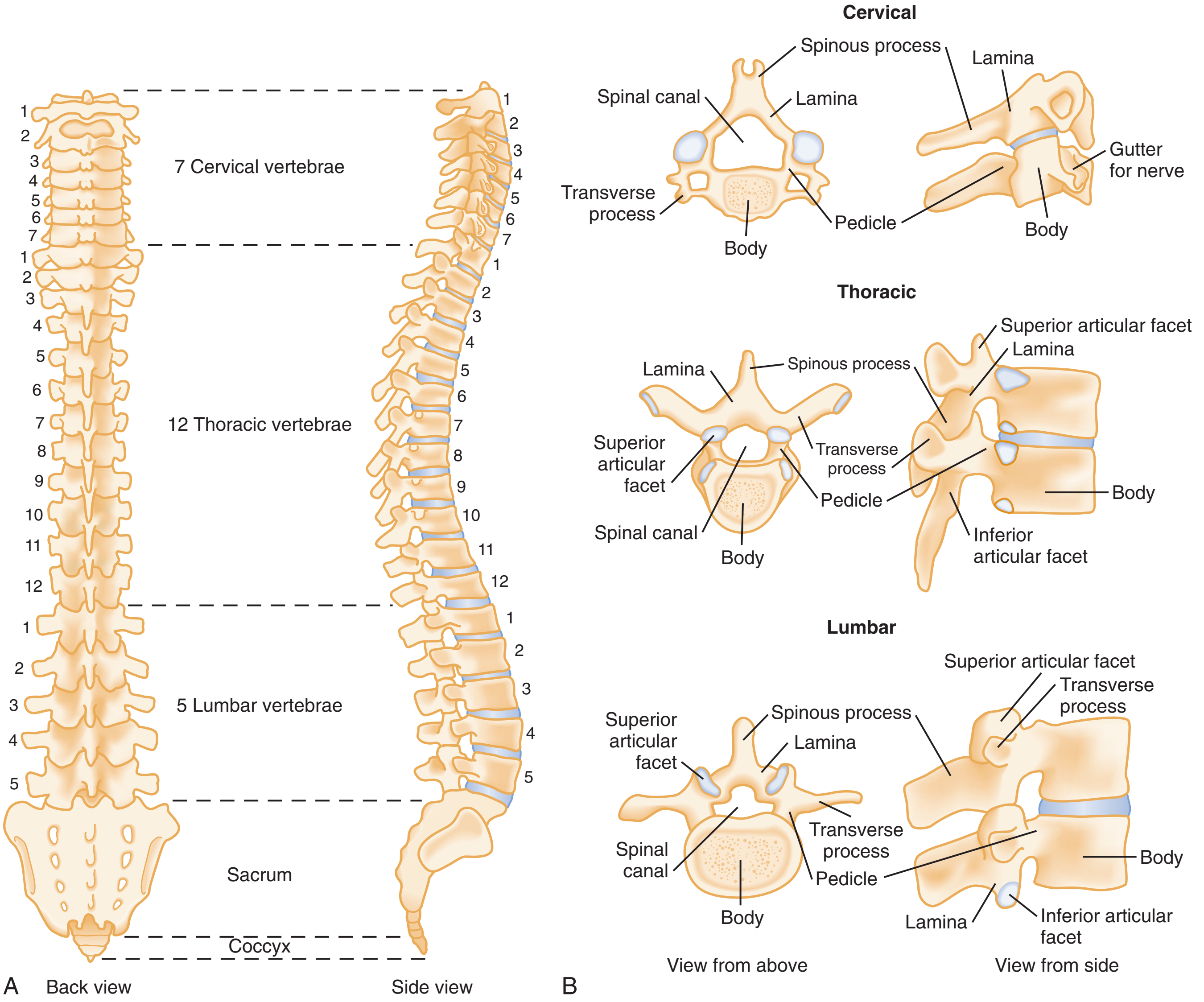


Figure 43-1. **A**, Vertebral column. **B**, Typical vertebrae.

www.ketabpezeshki.com 66485457-66963820

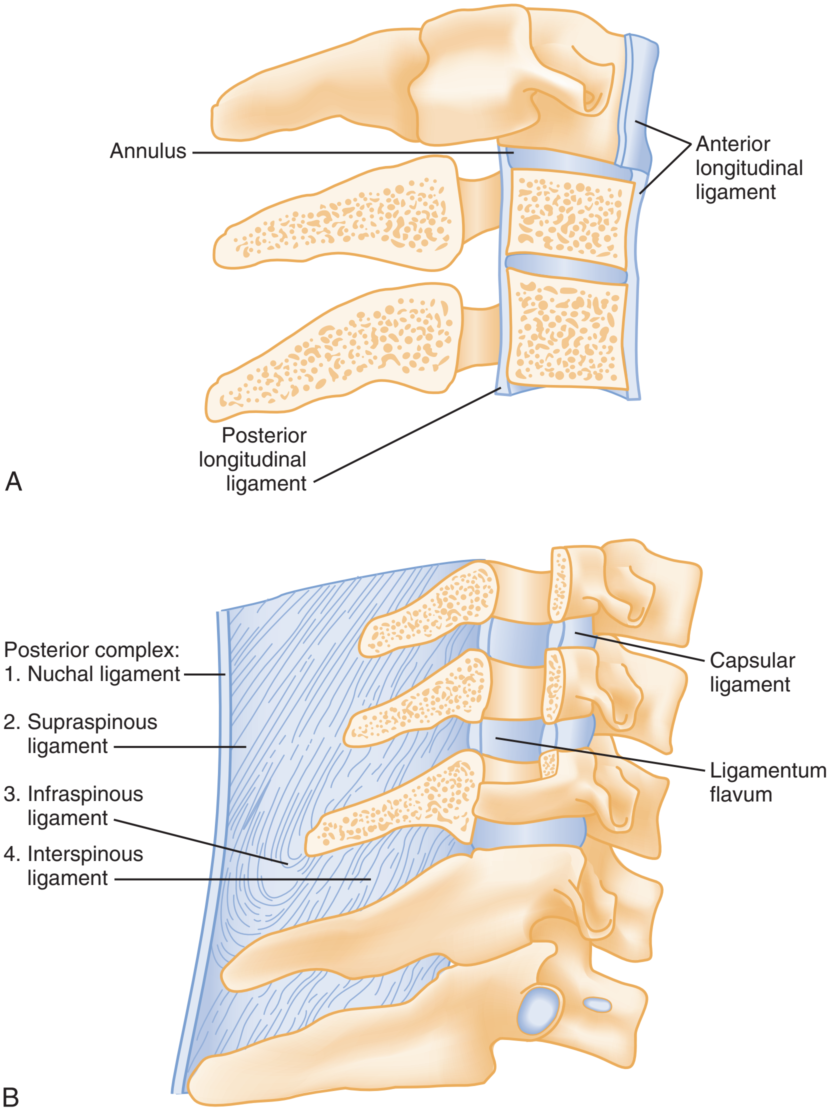


Figure 43-2. A, Ligaments of the anterior column. B, Ligaments of the posterior column.

www.ketabpezeshki.com 66485457-66963820

Table 43-1 Classification of Spinal Injuries

MECHANISM OF SPINAL INJURY	STABILITY
Flexion	
Wedge fracture	Stable
Flexion teardrop fracture	Extremely unstable
Clay shoveler's fracture	Stable
Subluxation	Potentially unstable
Bilateral facet dislocation	Always unstable
Atlanto-occipital dislocation	Unstable
Anterior atlantoaxial dislocation with or without fracture	Unstable
Odontoid fracture with lateral displacement fracture	Unstable
Fracture of transverse process	Stable
Flexion-Rotation	
Unilateral facet dislocation	Stable
Rotary atlantoaxial dislocation	Unstable
Extension	
Posterior neural arch fracture (C1)	Unstable
Hangman's fracture (C2)	Unstable
Extension teardrop fracture	Usually stable in flexion; unstable in extension
Posterior atlantoaxial dislocation with or without fracture	Unstable
Vertical Compression	
Bursting fracture of vertebral body	Stable
Jefferson fracture (C1)	Extremely unstable
Isolated fractures of articular pillar and vertebral body	Stable

anteriorly, causing a *simple wedge fracture.* Radiographically, there is a diminished height and increased concavity of the anterior border of the vertebral body, an increased density of the vertebral body resulting from bony impaction, and prevertebral soft tissue swelling (Fig. 43-4). Because the posterior column remains intact, this injury is usually stable and rarely accompanied by nervous system damage. However, spinal instability may occur with severe wedge fractures (loss of more than half the vertebral height) or multiple adjacent wedge fractures, and such injuries are best treated as being potentially unstable.

A *flexion teardrop fracture* results when severe flexion forces cause anterior displacement of a wedge-shaped fragment (resembling a teardrop) of the anteroinferior portion of the involved vertebral body (Fig. 43-5). Because this injury commonly involves anterior and posterior ligamentous disruption, it is often associated with neurologic injury and is highly unstable.

The *clay shoveler's fracture* is an oblique fracture of the base of the spinous process of one of the lower cervical segments (Fig. 43-6). The injury derives its name from its common occurrence in clay miners in Australia during the 1930s. When a miner lifted a heavy shovelful of clay, abrupt head flexion against the supraspinous ligament resulted in an avulsion fracture of the spinous process. Today, this fracture is more commonly seen after direct trauma to the spinous process and after sudden deceleration MVCs that result in forced neck flexion. Because this injury involves only the spinous process, it is stable and not associated with neurologic involvement.

Pure *spinal subluxation* occurs when the ligamentous complexes rupture without an associated bony injury. This injury begins posteriorly in the nuchal ligament and proceeds anteriorly to involve other ligaments. The lateral radiograph with the neck in the neutral position may show a widening of both interspinous and intervertebral spaces posteriorly at the level of injury, and oblique views may demonstrate a widening or abnormal alignment of the facets (Fig. 43-7). These findings are often subtle and may be missed if flexion and extension views are not obtained. Although rarely associated with neurologic damage, this injury is potentially unstable.

Bilateral facet dislocations occur when a greater force of flexion causes soft tissue disruption to continue anteriorly to the annulus fibrosis of the intervertebral disk and the anterior longitudinal ligament, resulting in an extremely unstable condition. The forward movement of the spine causes the inferior articulating facets of the upper vertebra to pass upward and over the superior facets of the lower vertebra, resulting in anterior displacement of the spine above the level of injury. Radiographically, the anterior displacement will appear to be greater than one half of the anteroposterior (AP) diameter of the lower vertebral body with the superior facets anterior to the inferior facets (Fig. 43-8).

Shear Injury. Trauma to the head directed in an AP direction may result in fracture of the odontoid process above the transverse ligaments (type I) or, more commonly, at the base of the odontoid process where it attaches to C2 (type II) (Fig. 43-9). Slight angulation of the force may result in extension of the fracture into the body of C2 (type III). Type I odontoid fractures are usually stable because they are an avulsion injury to the odontoid tip. However, if traction forces injure the apical and alar ligaments, then the fracture may become unstable. Type II odontoid fractures are unstable and often complicated by nonunion. SCI is uncommon but can occur. Type III odontoid fractures are also mechanically unstable as they can extend laterally into the superior articular facet of the atlas.

Flexion-Rotation. *Rotary atlantoaxial dislocation* is an unstable injury visualized best on open-mouth odontoid radiographs (Fig. 43-10). If the skull is shown obliquely, there may be a false-positive asymmetry between the odontoid process and the lateral masses of C1. However, when the x-ray film reveals symmetrical basilar skull structures, a unilaterally magnified lateral mass confirms a C1-C2 dislocation.

A *unilateral facet dislocation* involves both flexion and rotation. The rotational component of this injury occurs around one of the facet joints, which acts as a fulcrum. Simultaneous flexion and rotation cause the contralateral facet joint to dislocate, with the superior facet riding forward and over the tip of the inferior facet and coming to rest within the intervertebral foramen. In this position, the dislocated articular mass is mechanically locked in place, making this a stable injury, although the posterior ligament complex is disrupted. The frontal radiograph shows the spinous processes above the level of dislocation displaced from the midline in the direction of the rotation (Fig. 43-11A and B). The lateral radiograph shows a forward displacement of the dislocated segment on the vertebra below (less than one half the AP diameter of this vertebral body) and a rotation of the dislocated vertebra and those above it (Fig. 43-11C and D).

Any cervical fracture or dislocation may cause torticollis, but torticollis may also be caused by a benign process such as a muscle spasm. It may be difficult to differentiate torticollis caused by cervical fracture or dislocation from torticollis caused by severe muscle spasm, however, and oblique projections may be necessary to demonstrate the dislocated facet joint (Fig. 43-11E and F).

Owing to the varying shapes of the articular processes, particularly between the cervical and lumbar regions, different types of flexion-rotation injuries result. In the cervical region, where

Text continued on p. 393

www.ketabpezeshki.com 66485457-66963820

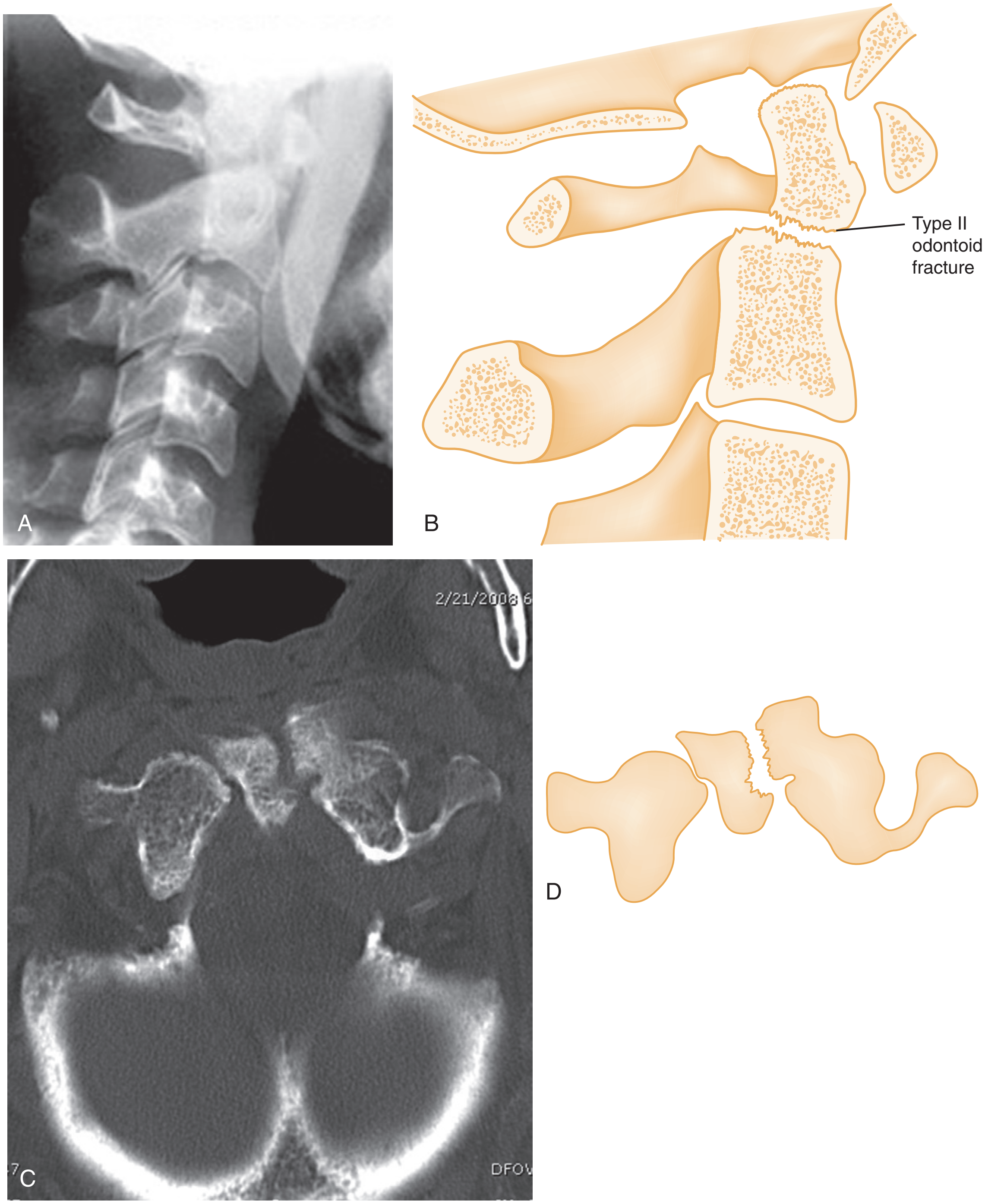


Figure 43-3. A and B, Odontoid fracture with anterior dislocation. Mechanism: flexion with shearing. Stability: unstable. C and D, A fracture through the odontoid process is demonstrated along with retropharyngeal swelling.

www.ketabpezeshki.com 66485457-66963820

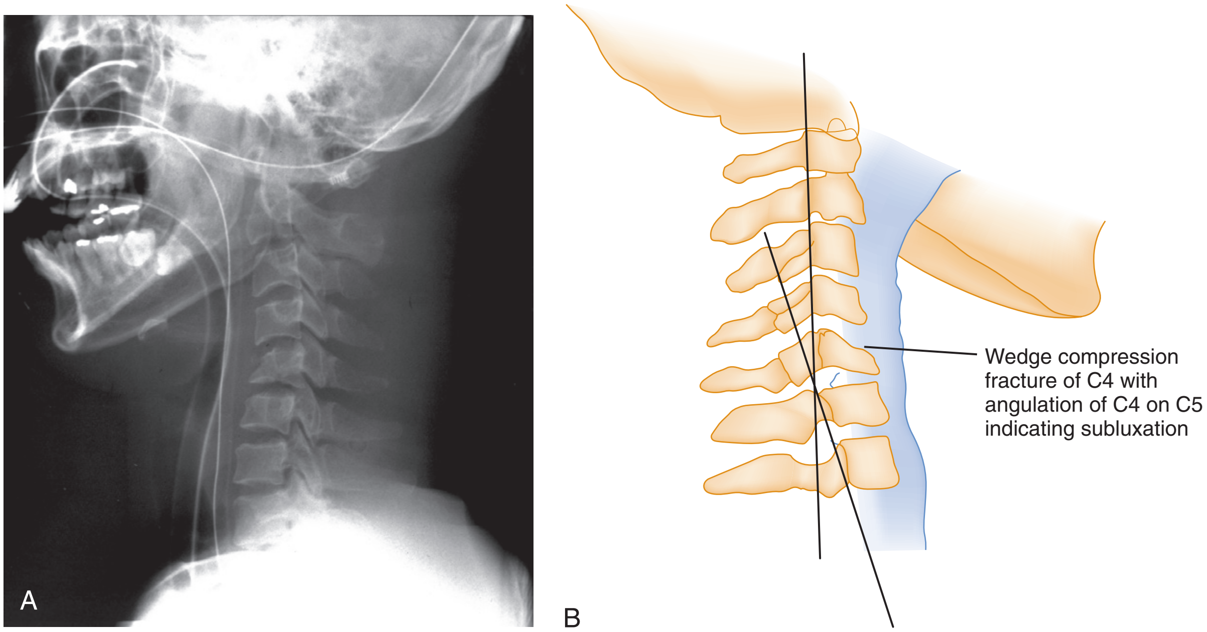


Figure 43-4. A, Lateral view of a wedge fracture of C5 with angulation. Mechanism: flexion. Stability: mechanically stable. B, Note the anterior wedging of the C4 vertebral body and angulation of C4 on C5.

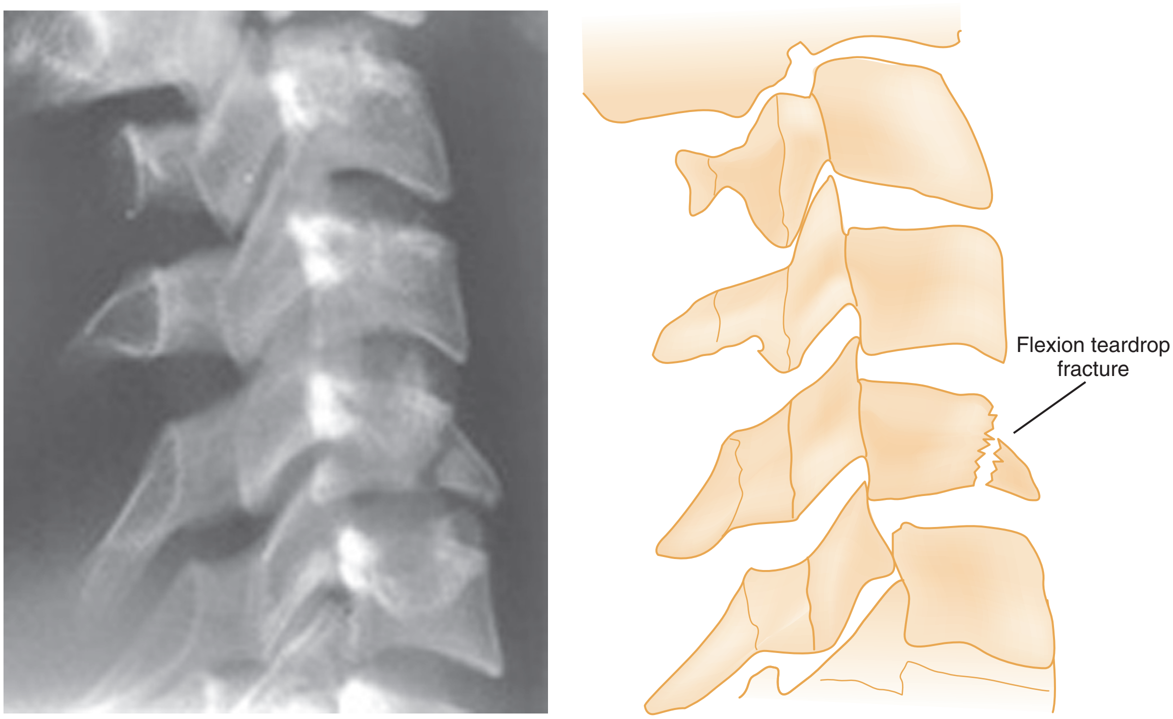


Figure 43-5. Lateral view of a teardrop fracture. Mechanism: flexion. Stability: unstable. The fractured fragment off the C5 body resembles a teardrop.

www.ketabpezeshki.com 66485457-66963820

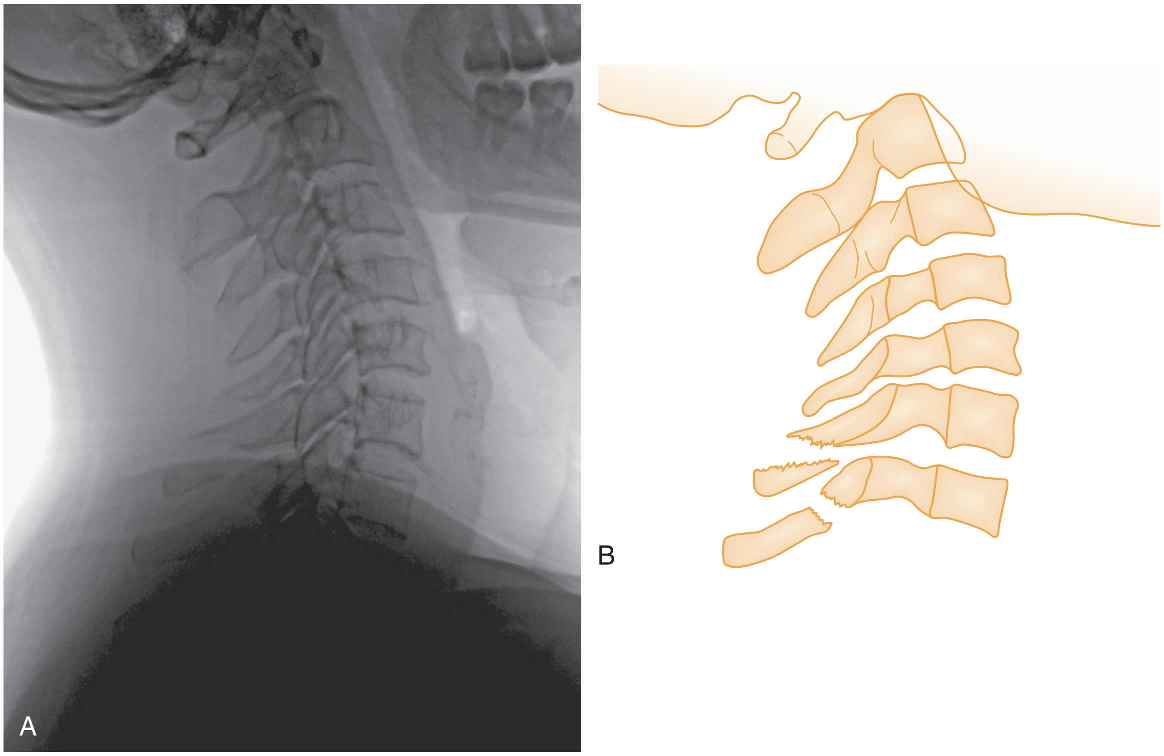


Figure 43-6. Clay shoveler's fracture. Mechanism: flexion. Stability: mechanically stable. Note the avulsed fragment off the tip of the C7 spinous process in an underpenetrated lateral view.

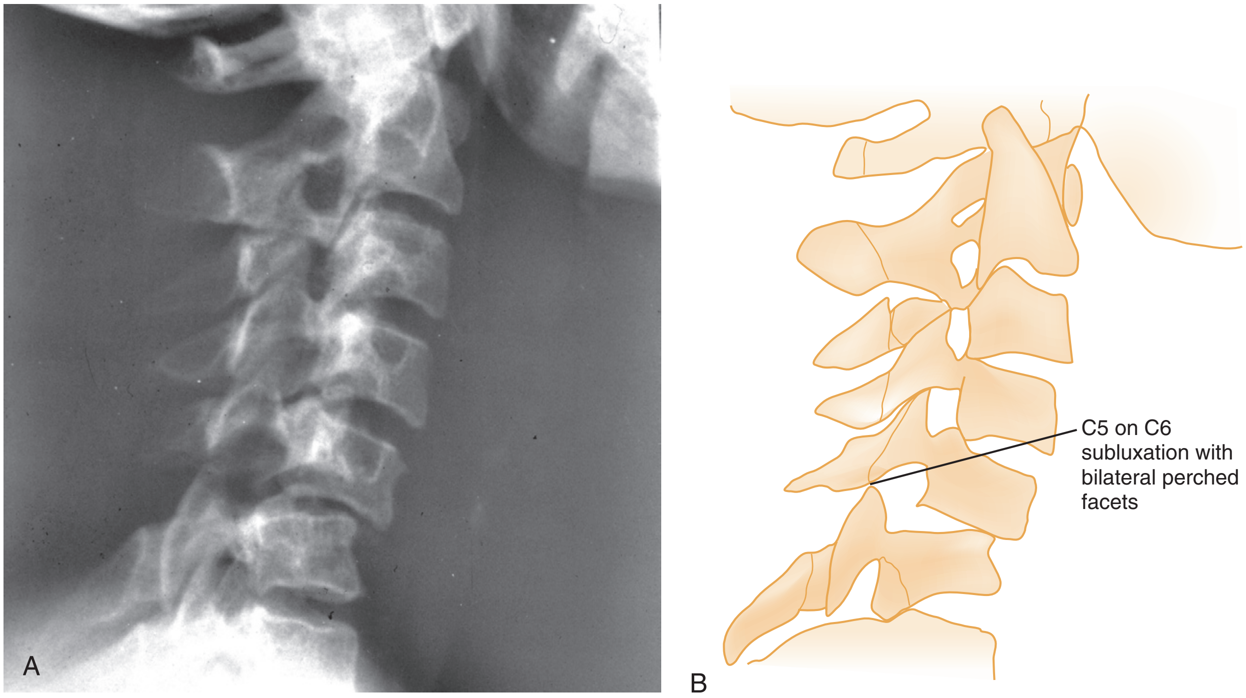


Figure 43-7. Subluxation with bilateral "perched" facets at C5 and C6. Mechanism: flexion. Stability: unstable. Lateral view shows severe subluxation of C5 on C6.

www.ketabpezeshki.com 66485457-66963820

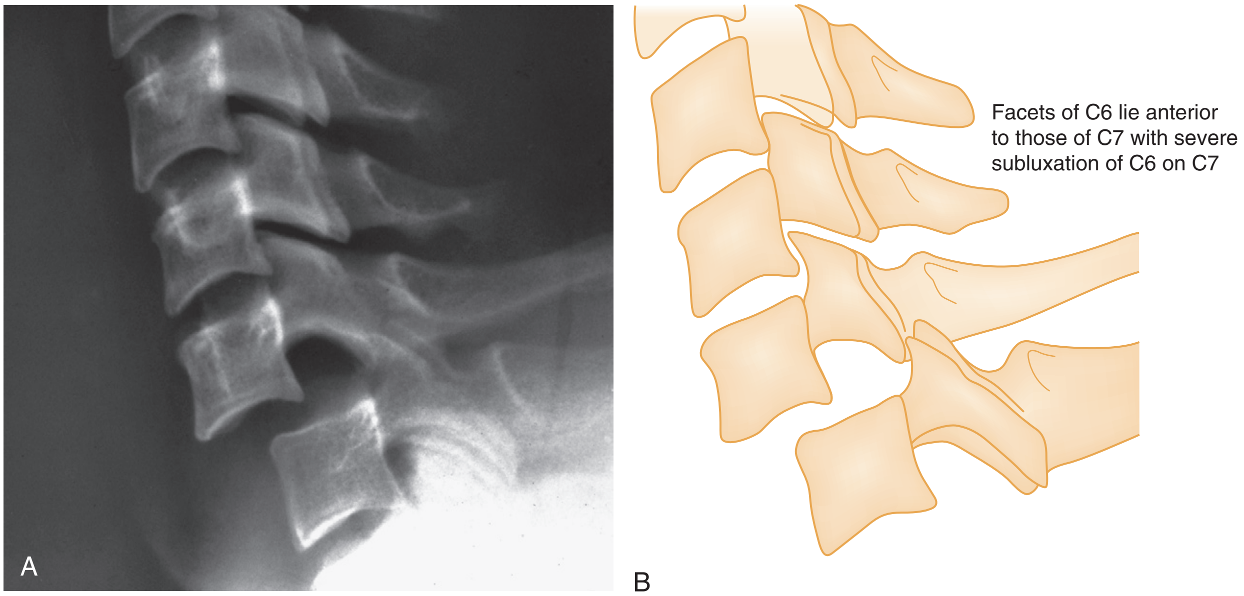


Figure 43-8. Facets of C6 lie anterior to those of C7 with severe subluxation of C6 on C7.

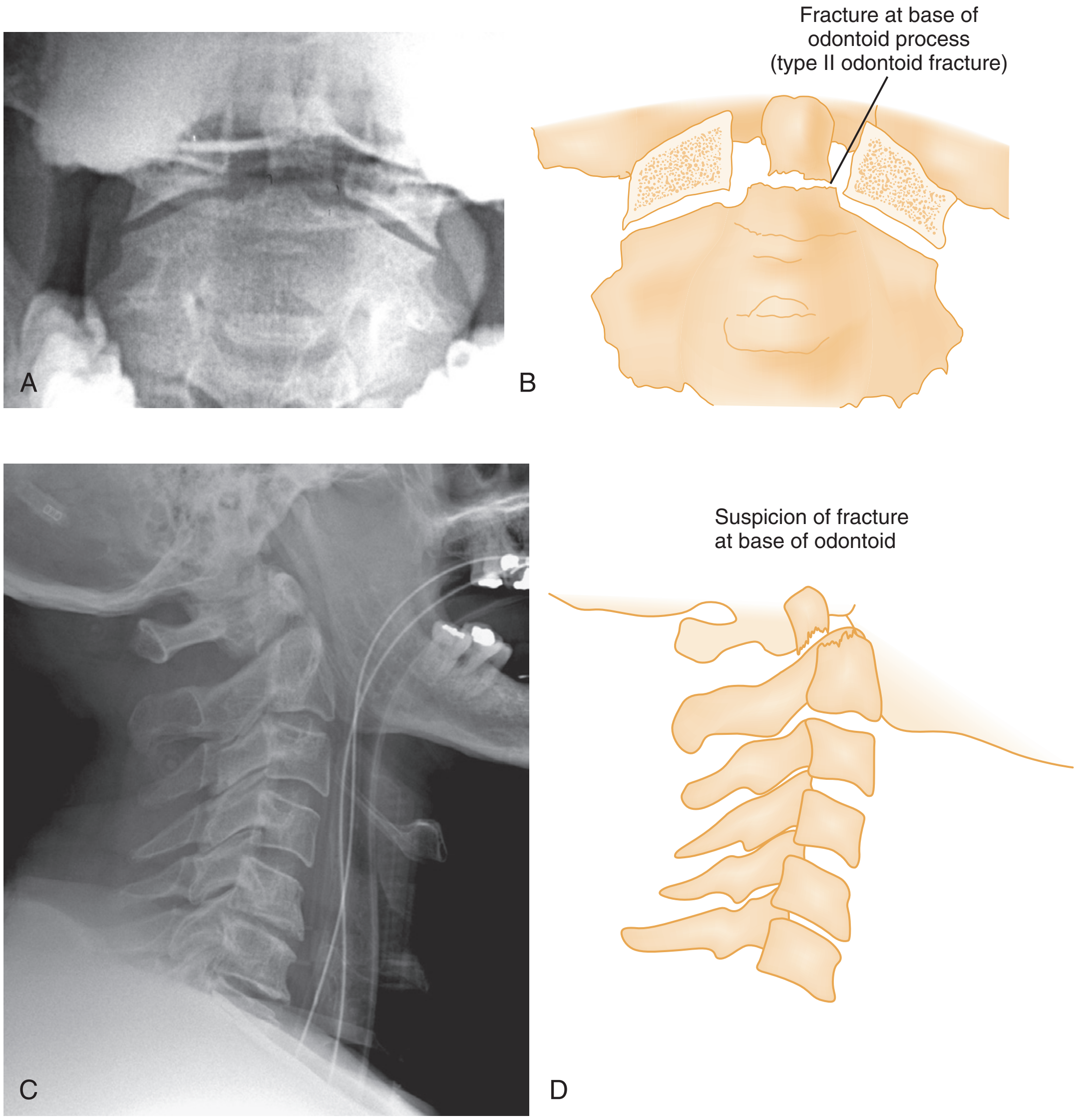


Figure 43-9. A and B, Odontoid fracture with lateral displacement. Mechanism: flexion. Stability: unstable. The tip of the odontoid process is laterally displaced in this lateral flexion injury. C and D, Lateral radiograph with suspicion of an odontoid fracture.

Continued

www.ketabpezeshki.com 66485457-66963820

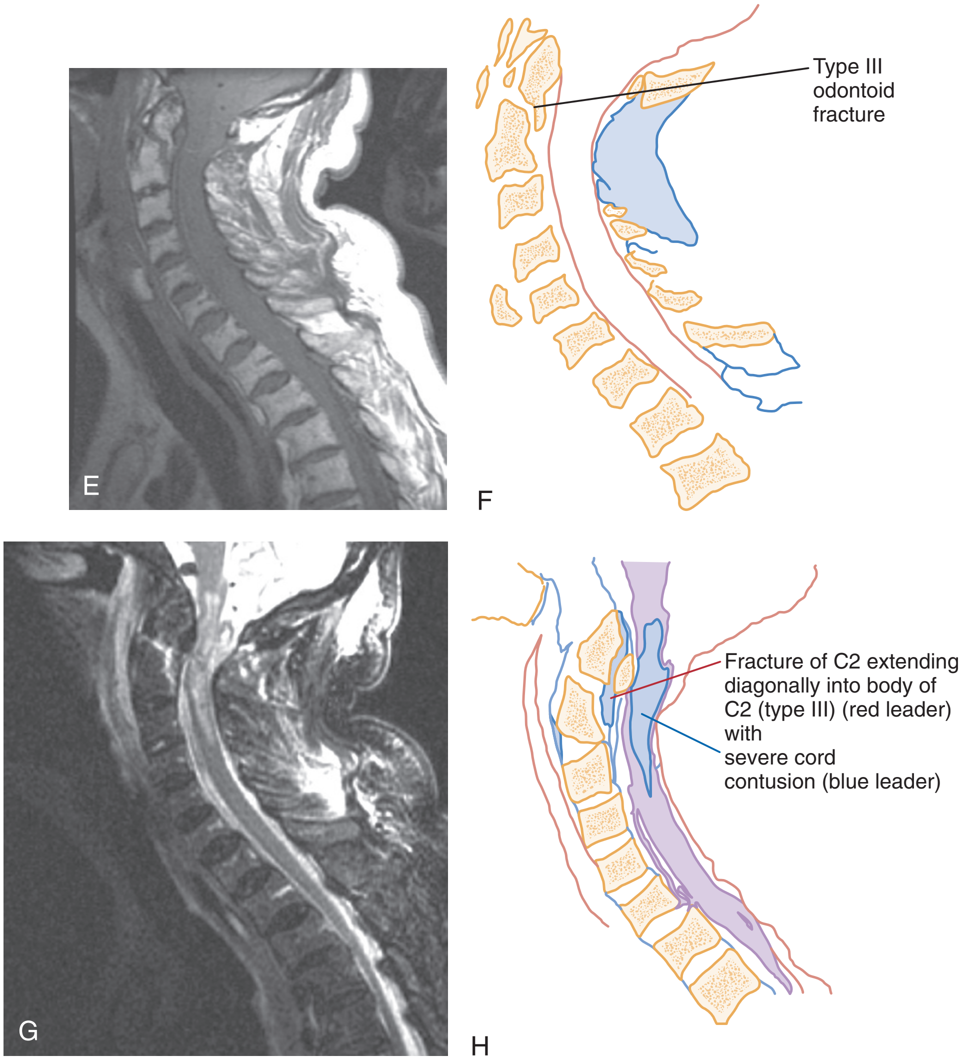


Figure 43-9, cont'd. **E** and **F**, T1-weighted magnetic resonance image clearly shows a type III odontoid fracture. **G** and **H**, T2-weighted magnetic resonance image shows severe spinal cord contusion associated with this fracture.

www.ketabpezeshki.com 66485457-66963820

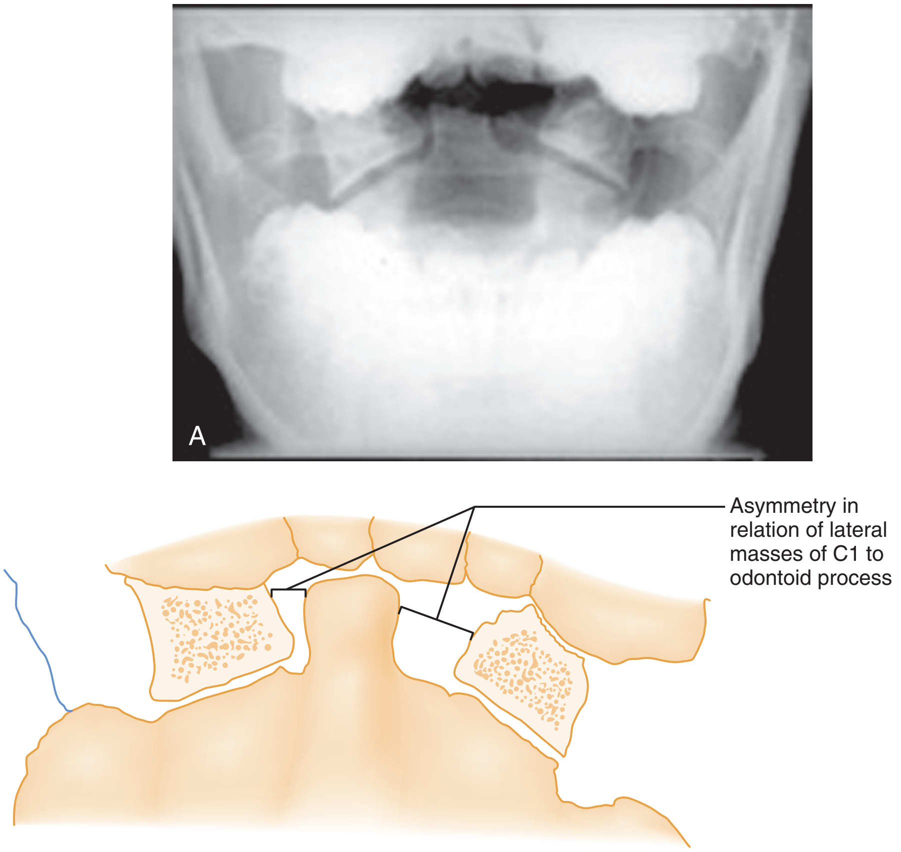


Figure 43-10. Rotatory subluxation of C1 on C2. Mechanism: rotation. Stability: unstable. There is marked asymmetry in the relationship of the lateral masses of C1 to the odontoid process. Rotation causes the right lateral mass to appear slightly larger (farther from the x-ray film) than the left (closer to the x-ray film).

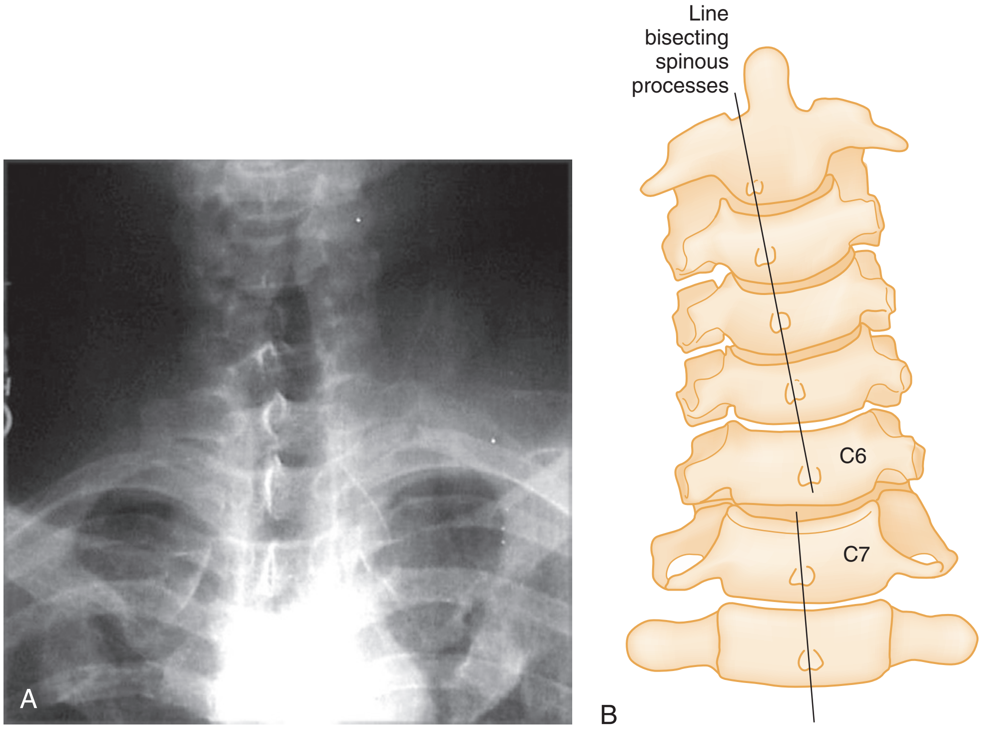


Figure 43-11. Unilateral facet dislocation. Mechanism: flexion and rotation. Stability: stable. A and B, Anterior view showing the spinous processes of the cervical vertebrae offset in relation to the thoracic vertebrae.

Continued

www.ketabpezeshki.com 66485457-66963820

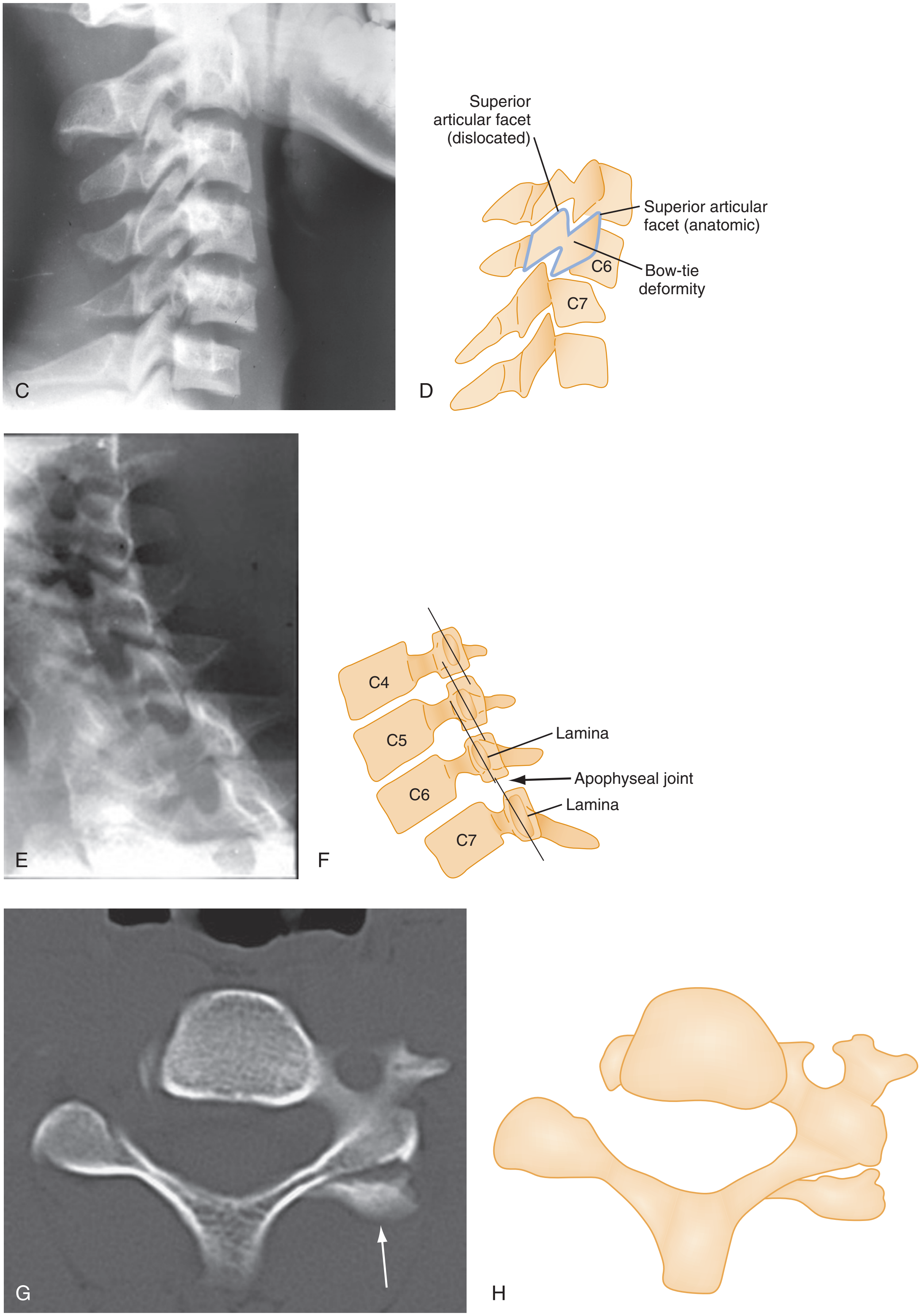


Figure 43-11, cont'd. **C** and **D,** Lateral view showing one dislocated articular facet of C5 lying anterior to the corresponding facet of C6 and creating a "bow-tie" deformity. The C5 vertebral body is subluxed anteriorly on C6. **E** and **F,** Oblique view of unilateral facet dislocation with the lamina of C6 projecting into the neural foramen. **G** and **H,** CT scan showing facet dislocation. Inferior facet *(arrow)* lies posterior to superior facet.

www.ketabpezeshki.com 66485457-66963820

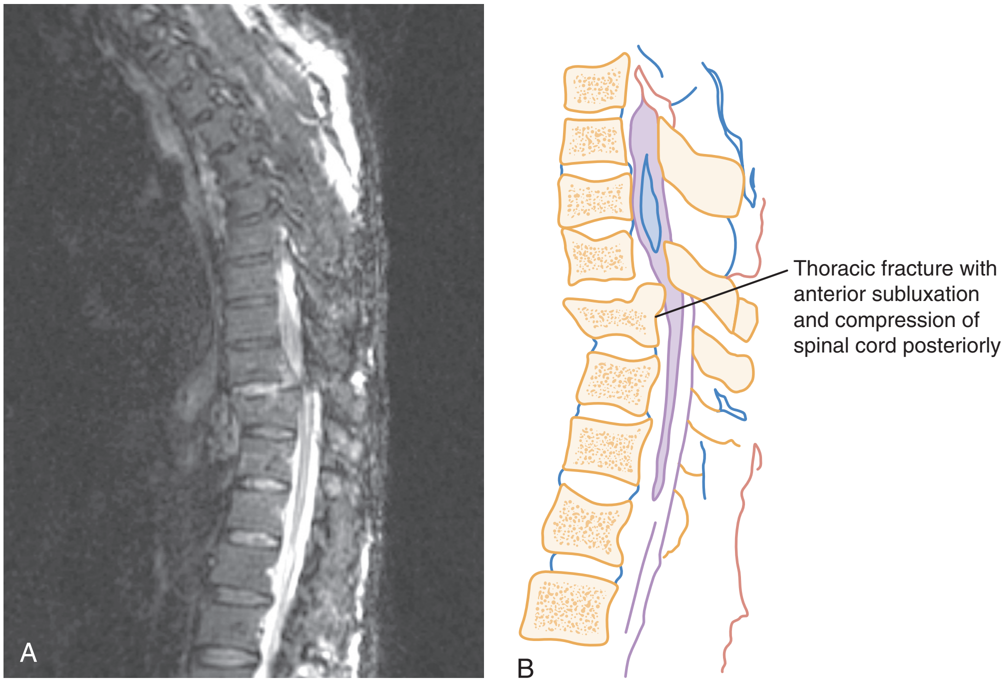


Figure 43-12. A and B, Magnetic resonance image showing fracture-dislocation of the thoracic spine.

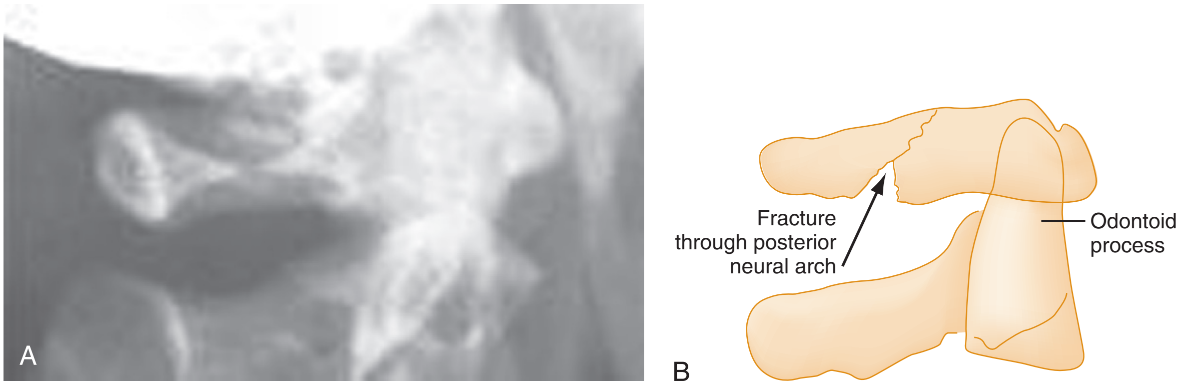


Figure 43-13. Posterior neural arch fracture of C1. Mechanism: extension. Stability: unstable. The fracture line is well visualized.

articular processes are small, flat, and almost horizontal, unilateral facet dislocations occur as described previously. In the lumbar region, however, where articular processes are large, curved, and nearly vertical, unilateral facet dislocation is rare. Instead, one or both articular processes fracture, and the upper vertebra swings forward. Commonly seen in the thoracolumbar and lumbar region, this rotation fracture-dislocation is unstable (Fig. 43-12).

Extension. The *posterior neural arch fracture* of the atlas (C1) results from the compression of the posterior elements between the occiput and the spinous process of the axis (C2) during forced neck extension (Fig. 43-13). Although the anterior arch and the transverse ligament remain intact, this fracture is potentially unstable because of its location.

The *hangman's fracture,* or traumatic spondylolysis of C2, occurs when the cervicocranium (the skull, atlas, and axis functioning as a unit) is thrown into extreme hyperextension as a result of abrupt deceleration. Bilateral fractures of the pedicles of the axis occur with or without dislocation (Fig. 43-14). Although this lesion is unstable, cord damage is often minimal because the AP diameter of the neural canal is greatest at the C2 level, and the bilateral pedicular fractures permit the spinal canal to decompress itself. Originally described in victims of hanging injury, today it is most often the result of head-on MVCs.

The *extension teardrop fracture* occurs when abrupt extension of the neck causes the anterior longitudinal ligament to pull the anteroinferior corner of a vertebral body away from the remainder of the vertebra, producing a triangular fracture that is radiographically similar to the flexion teardrop fracture. Often occurring in lower cervical vertebrae (C5-C7) from diving accidents, this injury may be associated with a central cord syndrome, which is discussed later, and is caused by the ligamentum flavum buckling into the spinal cord.[8] Because the posterior elements remain intact, this injury is stable in flexion but potentially unstable in extension.

Vertical Compression. Vertical compression injuries occur in the cervical and lumbar regions, which are capable of straightening at the time of impact. When forces are applied from either above (skull) or below (pelvis or feet), one or more vertebral body endplates may fracture. The nucleus pulposus of the intervertebral disk is forced into the vertebral body, which is shattered outward, resulting in a *burst fracture* (Fig. 43-15). The lateral radiograph shows a comminuted vertebral body, and there will typically be greater than 40% compression of the anterior vertebral body,

www.ketabpezeshki.com 66485457-66963820

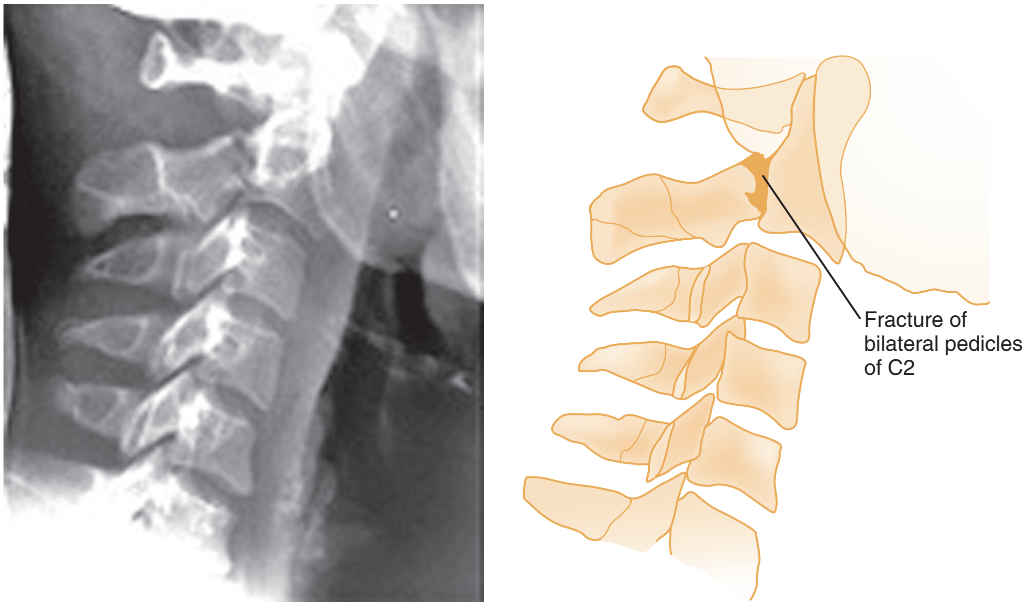


Figure 43-14. Hangman's fracture. Mechanism: extension. Stability: unstable. Fracture lines extending through the pedicles of C2 are well visualized. Retropharyngeal soft tissue swelling is apparent.

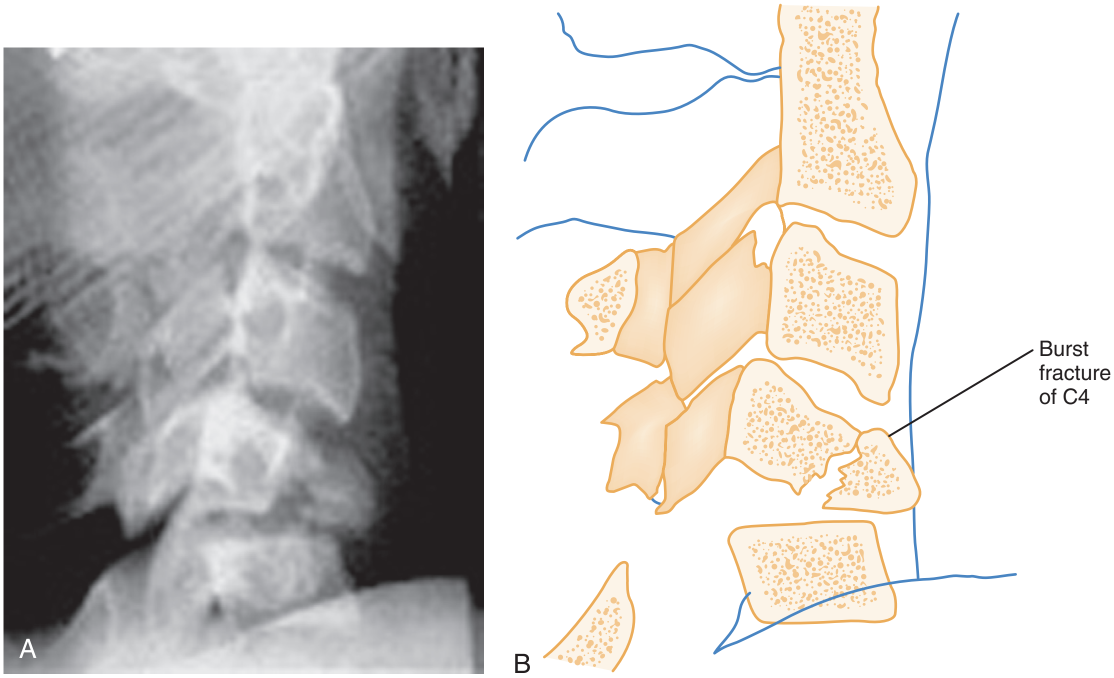


Figure 43-15. Burst fracture of a vertebral body. Mechanism: vertical compression and flexion. Stability: unstable. **A** and **B,** There is a compression fracture of the C4 vertebral body. During the bursting process, the anterior segment of the fracture protrudes anteriorly, and its posterior aspect protrudes posteriorly into the spinal canal. Such protrusion is often associated with anterior cord syndrome. The cervical spine is abnormally angulated.

www.ketabpezeshki.com 66485457-66963820

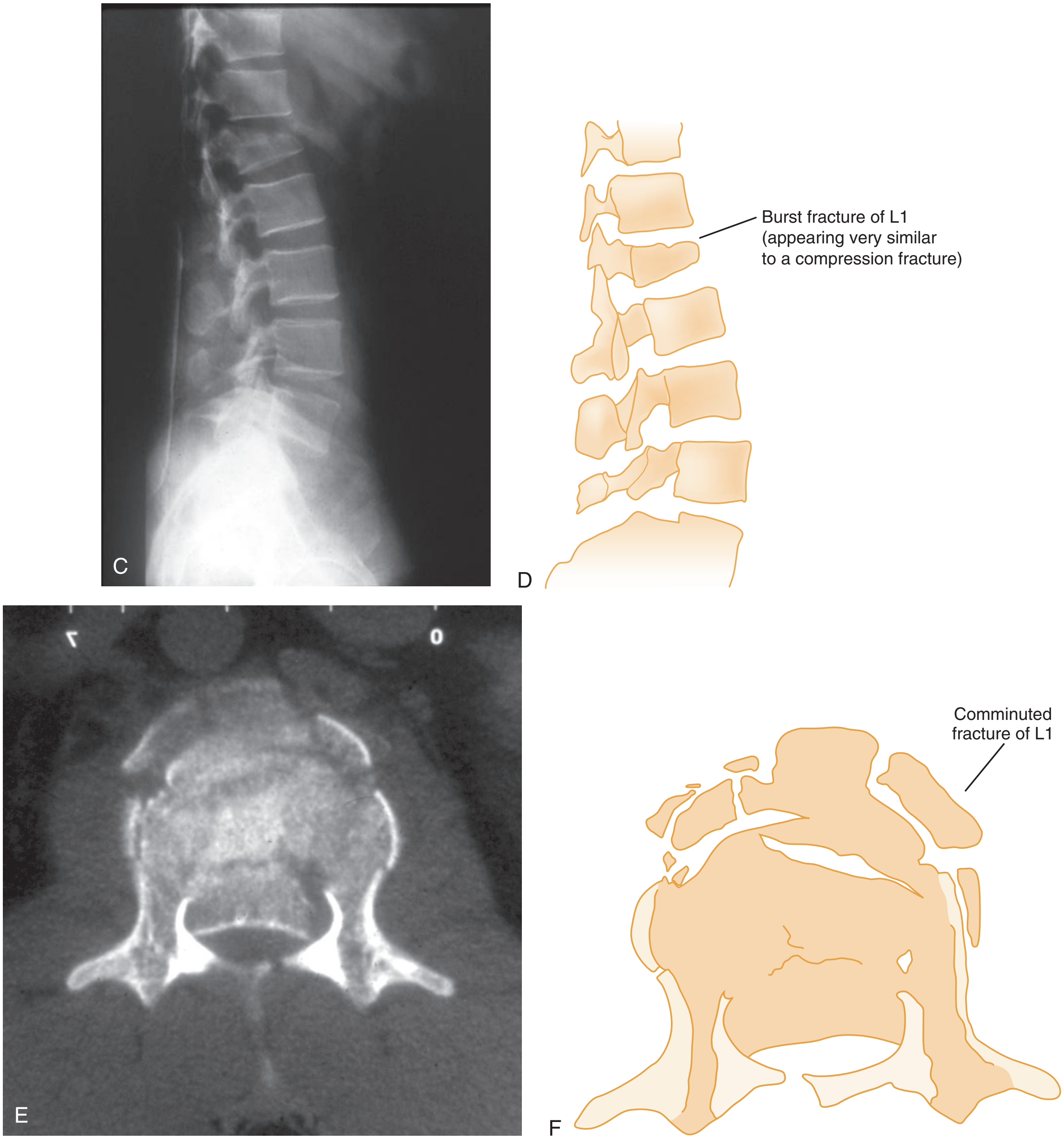


Figure 43-15, cont'd. **C** and **D,** Lateral radiograph showing a burst fracture of L1, appearing very similar to a compression fracture. Mechanism: flexion. Stability: usually stable. **E** and **F,** Computed tomographic scan of L1 in the same patient showing comminution of the fracture and retropulsion of fragments into the spinal canal.

Continued

www.ketabpezeshki.com 66485457-66963820

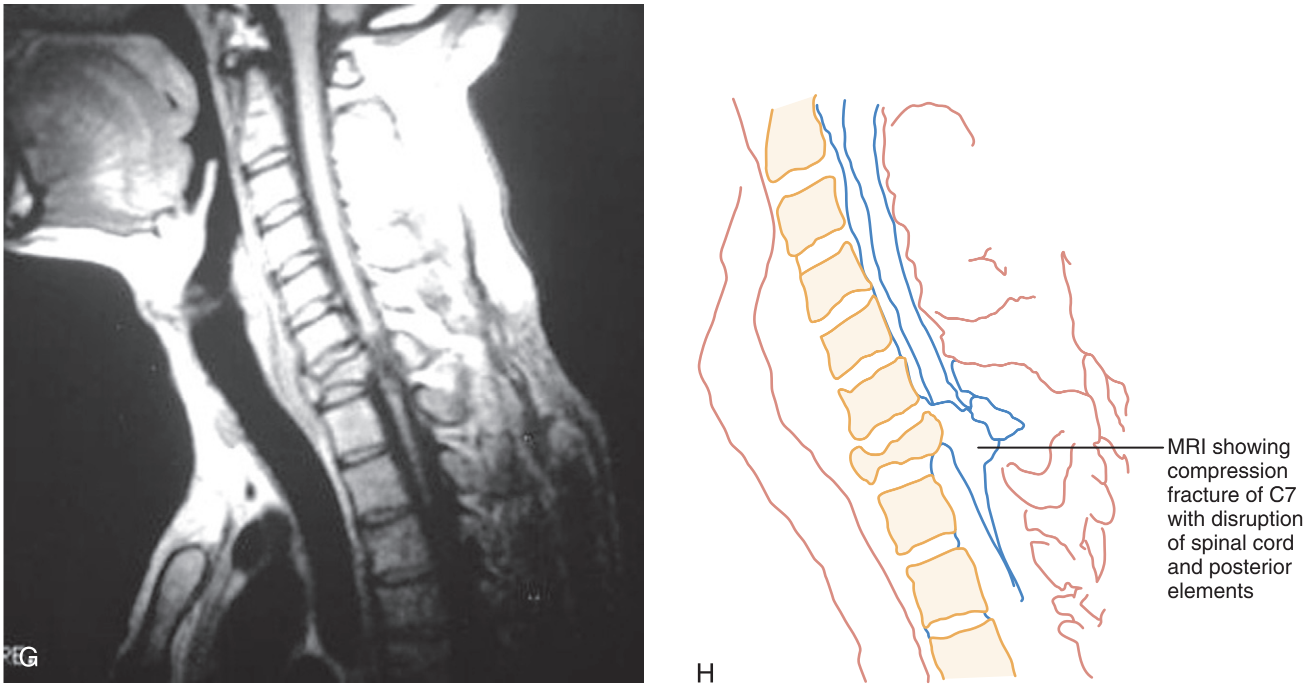


Figure 43-15, cont'd. G and H, Magnetic resonance image showing a burst fracture of C7 with complete spinal cord disruption.

which helps differentiate it from the simple wedge fracture. The frontal radiograph demonstrates a characteristic vertical fracture of the vertebral body, which will also help differentiate it from the simple wedge fracture and the flexion teardrop fracture. This is a stable fracture because all the ligaments remain intact. However, fracture fragments may impinge on or penetrate the ventral surface of the spinal cord and cause an anterior cord syndrome (see Fig. 43-15).

The *Jefferson fracture* of C1 is an extremely unstable injury that occurs when a vertical compression force is transmitted through the occipital condyles to the superior articular surfaces of the lateral masses of the atlas. This force drives the lateral masses outward, resulting in fractures of the anterior and posterior arches of the atlas and a disruption of the transverse ligament. Because this injury is often associated with prevertebral hemorrhage and retropharyngeal swelling, the lateral film may demonstrate a widening of the predental space between the anterior arch of C1 and the odontoid, or dens. The open-mouth view will demonstrate a bilateral offset of both right and left lateral masses of C1 relative to the lateral masses of C2. A fracture should be diagnosed when the sum of the offset distances from the right and left sides exceeds 7 mm (Fig. 43-16). However, when the fragments are minimally displaced, the Jefferson fracture is difficult to recognize, and computed tomography (CT) may be necessary.

Vertical compression fractures may rarely result in isolated fractures of the articular pillar or the vertebral body, exhibiting vertical and oblique lines of fracture.

Classification of Spinal Cord Injuries

Primary Spinal Cord Injury. The spinal cord may be injured in a number of ways.[8] First, penetrating trauma or massive blunt trauma with disruption of the vertebral column may cause the transection of neural elements. Because neurons within the central nervous system do not regenerate, such injuries are irreversible. Less severe blunt trauma may have similar effects resulting from a displaced bony fragment or a herniated disk.

Second, when elderly patients with cervical osteoarthritis and spondylosis are subjected to forcible cervical spine extension, the spinal cord may be compressed between an arthritically enlarged anterior vertebral ridge and a posteriorly located hypertrophic ligamentum flavum (Fig. 43-17). This injury frequently results in a central cord syndrome.

Primary vascular damage to the spinal cord, a third mechanism of injury, may occur in several ways. The spinal cord may be compressed by an extradural hematoma, particularly in patients who are on anticoagulants or have bleeding disorders. Vascular injuries should also be suspected when there is a discrepancy between the clinically apparent neurologic deficit and the known level of spinal injury. For example, a lower cervical dislocation may compress the vertebral arteries as they travel within the spinal foramina of the vertebrae. This compression may result in thrombosis and decreased blood flow through the anterior spinal artery that originates from both vertebral arteries at the level of C1 (Fig. 43-18). On physical examination, such an injury may erroneously appear to be localized to the level of C1 or C2. Also, the great radicular artery of Adamkiewicz, originating from the aorta and entering the spinal canal at the level of L1, sends branches as cephalad as T4. Therefore a lumbar fracture or dislocation can produce a neurologic deficit as high as T4.

Secondary Spinal Cord Injury. The maximum neurologic deficit after blunt spinal cord trauma is often not seen immediately and may instead progress over many hours. The histopathology of the so-called "secondary SCI" has been studied extensively in experimental animal models.[9-11] It is now thought that primary SCI initiates a complex cascade of biochemical events that result in progressive ischemia of gray and white matter during the postinjury period (Fig. 43-19). Other factors, such as hypoxia, hypotension, hyperthermia, hypoglycemia, and mishandling by medical personnel, also affect the ultimate extent of SCI.

CLINICAL FEATURES

Neurologic Evaluation

The initial neurologic evaluation of a patient with a suspected spinal injury should begin with simple observation. Careful inspection, beginning with the head and proceeding downward,

www.ketabpezeshki.com 66485457-66963820

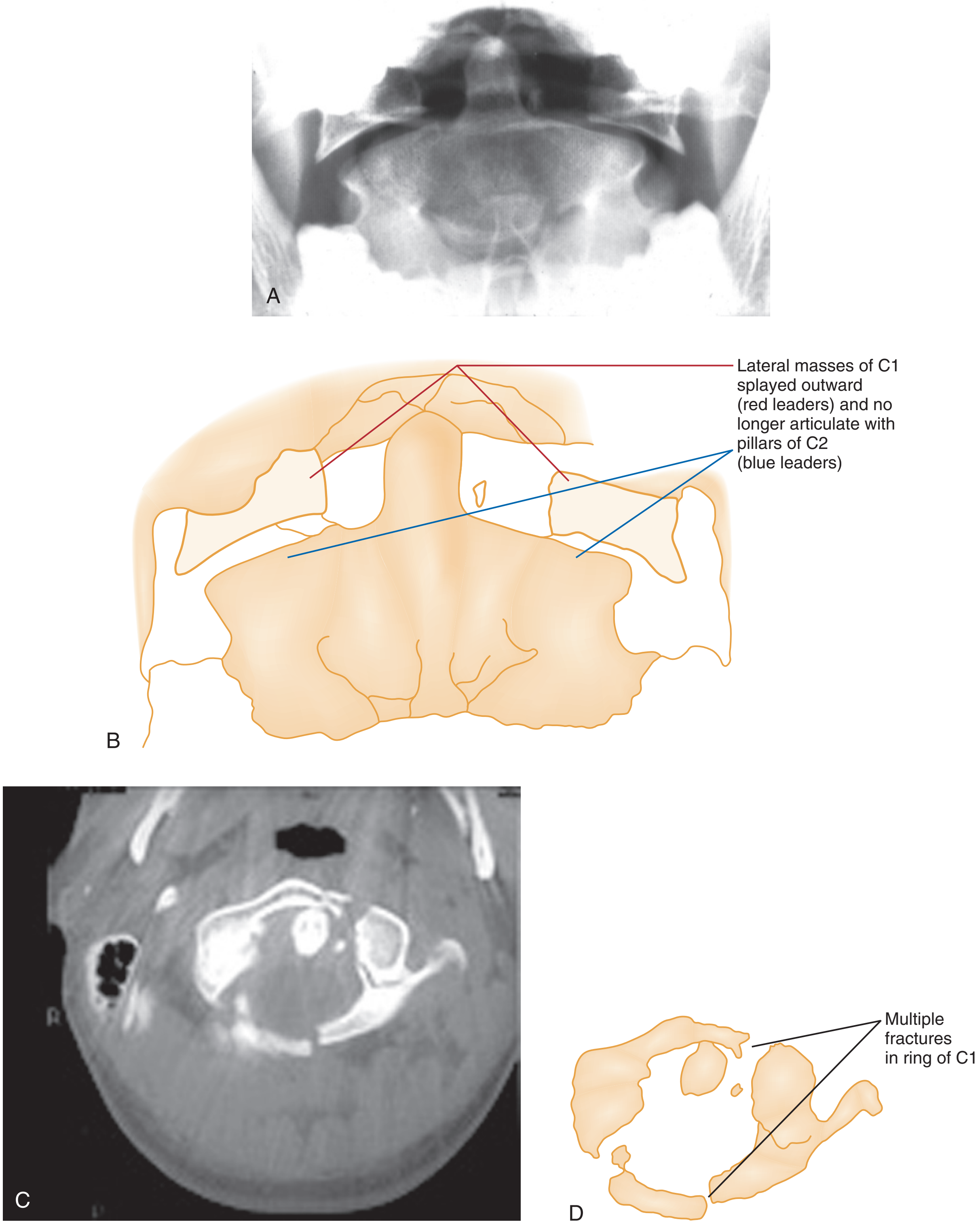


Figure 43-16. Jefferson fracture. Mechanism: vertical compression. Stability: unstable. **A** and **B,** Bilateral lateral displacement of the lateral masses of C1 with respect to the articular pillars of C2 confirms a Jefferson fracture and differentiates it from fracture of the posterior neural arch of C1 on an anteroposterior view. **C** and **D,** Computed tomographic scan of C1 showing two fracture sites in the ring of C1 with lateral displacement of the lateral mass on the right.

www.ketabpezeshki.com 66485457-66963820

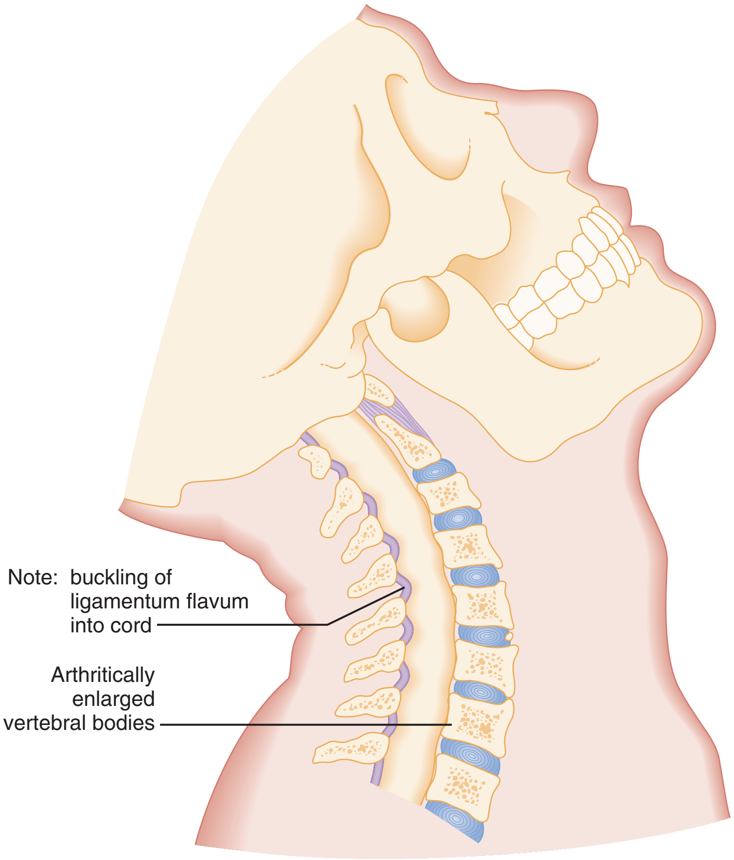


Figure 43-17. Elderly patients subjected to extension forces can sustain cervical spinal cord injury as a result of compression of the spinal cord between the posterior hypertrophic ligamentum flavum and the arthritically enlarged anterior vertebral bodies.

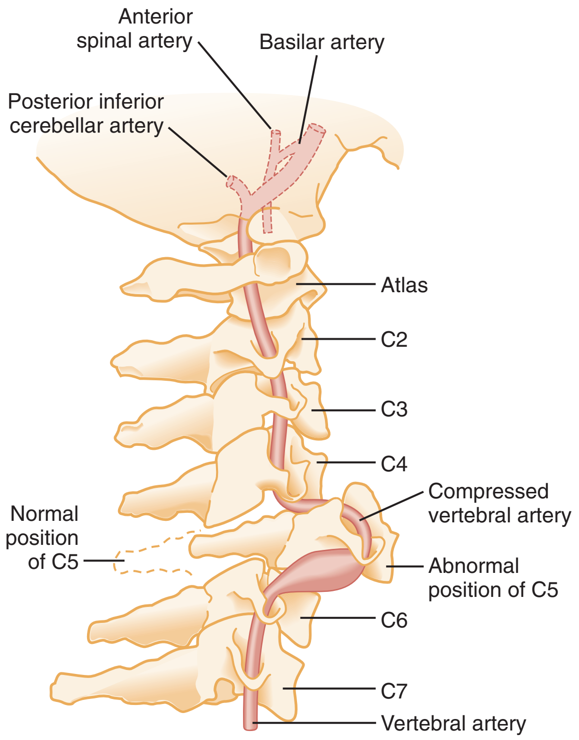


Figure 43-18. Mechanism of vascular injury of the spinal cord resulting from cervical vertebral injury.

may reveal signs of possible spinal involvement. Significant head and facial trauma have a 5 to 10% incidence of associated cervical spine injuries.[12,13] Scapular contusions suggest a rotation or flexion-rotation injury of the thoracic spine. Chest and neck abrasions from automobile shoulder belts and lower abdominal markings from lap belts indicate possible blunt carotid and vertebral injuries, as well as spinal, intrathoracic, and intra-abdominal injuries. As occurs with falls from considerable heights, injuries to the gluteal region, calcaneal fractures, and severe ankle fractures suggest a compression type of spinal injury.

The patient should be observed for the presence and symmetry of both voluntary and involuntary movements. Because the diaphragm is innervated by the phrenic nerve, which originates at C3-C4, an abnormal, abdominal breathing pattern may provide an important clue to a cervical injury. The presence of Horner's syndrome, characterized by unilateral ptosis, miosis, and anhidrosis, may result from disruption of the cervical sympathetic chain, usually between C7 and T2.[5] Priapism may occur with severe SCI, and it is often associated with spinal shock, which is a transient reflex depression of the spinal cord below the level of the injury.

The physician should speak with the patient during the inspection process. This important part of the patient's assessment should not be overlooked, because it provides the patient with reassurance and the physician with valuable information. Patients may experience pain in the sensory dermatome corresponding to the injured spinal level. For example, a C2 lesion may cause occipital pain, whereas discomfort in the trapezius muscle, particularly in the absence of signs of local trauma, suggests a C5 injury. Past medical history is important because certain conditions predispose patients to cervical injury. Patients with Down syndrome are

www.ketabpezeshki.com 66485457-66963820

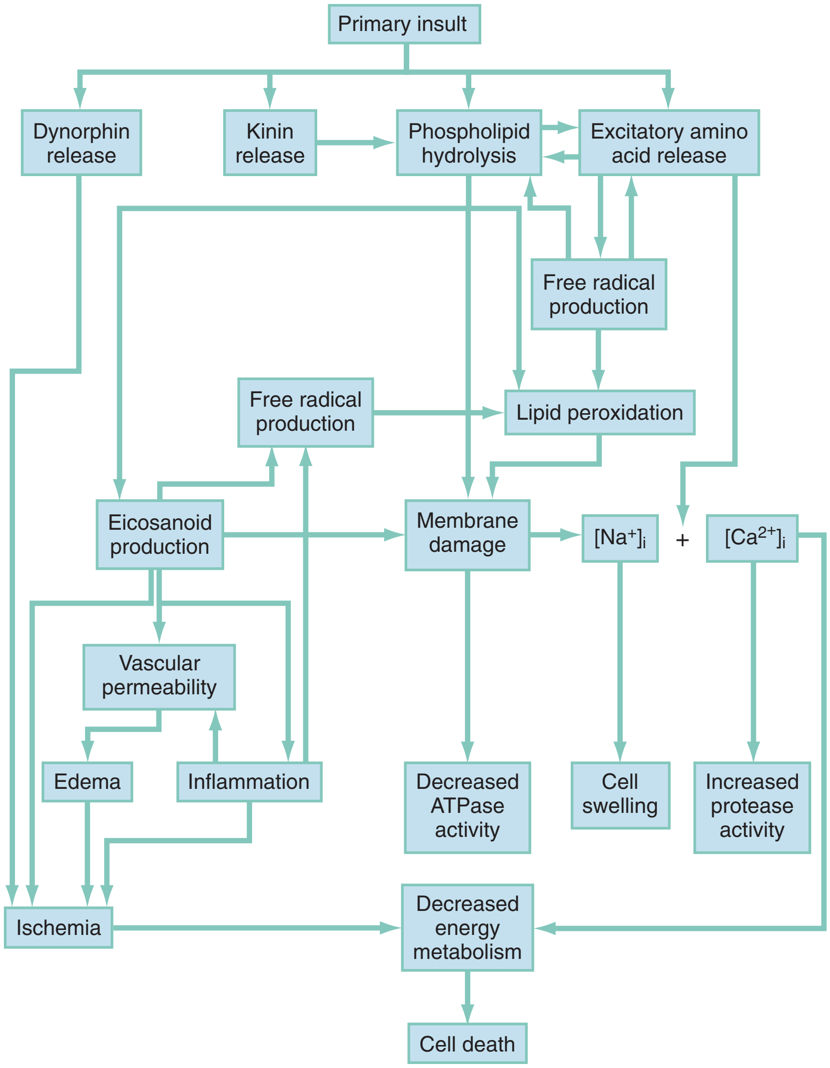


Figure 43-19. Speculative paradigm of secondary pathophysiologic events after primary traumatic injury to the spinal cord. *Ca*$^{2+}$, calcium ion; *Na*$^{+}$, sodium ion. (From Anderson D, Hall E: Pathophysiology of spinal cord trauma. Ann Emerg Med 22:989, 1993.)

predisposed to atlanto-occipital dislocation, whereas rheumatoid arthritis patients are prone to rupture of the transverse ligament of C2.

Palpation of the entire spine and paraspinal musculature may reveal areas of tenderness, deformity, or muscle spasm. A "gibbus" deformity or step-off may be appreciated with severe subluxation. Widening of an interspinous space indicates a tear in the posterior ligament complex and a potentially unstable spinal injury.

The motor activity of the body is complex. Because a single motion is often governed by muscles innervated by multiple spinal segments, localizing a spinal lesion based solely on an assessment of motor function is extremely difficult. Testing the presence and strength of those motions outlined in Table 43-2, however, provides a rapid baseline assessment. When a deficit is noted, the motor and neurologic examination should be repeated at frequent intervals because progression of dysfunction may occur. If there is apparent total loss of function, every effort should be made to elicit the most minimal of motor responses because any response markedly improves the prognosis. A slight toe flicker in an otherwise paralyzed individual indicates that the patient may again eventually walk unassisted.

The presence of cord-mediated *deep tendon reflexes* can be helpful as a localizing, diagnostic aid (Table 43-3). Classically,

Table 43-2 Spinal Motor Examination

LEVEL OF LESION	RESULTING LOSS OF FUNCTION
C4	Spontaneous breathing
C5	Shrugging of shoulders
C6	Flexion at elbow
C7	Extension at elbow
C8-T1	Flexion of fingers
T1-T12	Intercostal and abdominal muscles*
L1-L2	Flexion at hip
L3	Adduction at hip
L4	Abduction at hip
L5	Dorsiflexion of foot
S1-S2	Plantar flexion of foot
S2-S4	Rectal sphincter tone

*Localization of lesions in this area is best accomplished with the sensory examination.

www.ketabpezeshki.com 66485457-66963820

Table 43-3 Spinal Reflex Examination

LEVEL OF LESION (AT OR ABOVE)	RESULTING LOSS OF REFLEX
C6	Biceps
C7	Triceps
L4	Patellar
S1	Achilles

Table 43-4 Spinal Sensory Examination

LEVEL OF LESION	RESULTING LEVEL OF LOSS OF SENSATION
C2	Occiput
C3	Thyroid cartilage
C4	Suprasternal notch
C5	Below clavicle
C6	Thumb
C7	Index finger
C8	Small finger
T4	Nipple line
T10	Umbilicus
L1	Femoral pulse
L2-L3	Medial aspect of thigh
L4	Knee
L5	Lateral aspect of calf
S1	Lateral aspect of foot
S2-S4	Perianal region

muscle paralysis associated with intact deep tendon reflexes indicates an upper motor neuron (spinal cord) lesion, whereas paralysis associated with absent deep tendon reflexes indicates a lower motor neuron (nerve root or cauda equina) lesion. This differentiation is important because the latter condition is often caused by a surgically correctable lesion. After the initial period of areflexia, reflexes gradually return after 1 to 3 days, and after 1 to 4 weeks, patients with SCI will manifest characteristic hyper-reflexia and spasticity.[14] Because reflexes are typically absent during the initial phase of spinal shock, the examination of reflexes is less useful in the emergency department.

Sensory function can be quickly evaluated through use of a structured approach (Table 43-4) or a graphic sensory dermatome chart (Fig. 43-20). After locating an area of hypesthesia, one should move the sensory stimulus from areas of decreased sensation outward, rather than the reverse, because patients are more sensitive to the appearance of sensation than to its disappearance. This test should be performed first with a cotton wisp to assess sensitivity to light touch, a posterior column function. A pin should be used to assess pain sensation, which is an anterior spinothalamic tract function. The presence of islands of preserved sensation within an affected dermatome or below the level of apparent total dysfunction, even in the presence of complete motor paralysis, indicates potential for functional motor recovery.[15] An accurate baseline sensory examination is imperative because a cephalad progression of hypesthesia is the most sensitive indicator of deterioration. When this is observed in the cervical region, one should anticipate impending respiratory failure and stabilize the airway.

Complete Spinal Cord Lesions

A *complete spinal cord lesion* is defined as total loss of motor power and sensation distal to the site of an SCI. Functional motor recovery is rare in a patient with a complete cord syndrome that persists for longer than 24 hours after the injury.[7] Before diagnosis of a complete cord syndrome, however, two points should be considered. First, any evidence of minimal cord function, such as sacral sparing, excludes the patient from this group. Signs of sacral sparing include perianal sensation, normal rectal sphincter tone, or flexor toe movement. The presence of any of these signs indicates a partial lesion, usually a central cord syndrome, and the patient may have marked functional recovery, including bowel and bladder control and eventual ambulation.

Second, it is important to note that a complete spinal cord lesion may be mimicked by a condition known as *spinal shock,* which may persist from a few days to a few weeks. Spinal shock results from a concussive injury to the spinal cord that causes total neurologic dysfunction distal to the site of injury.[16] The end of spinal shock is heralded by the return of the bulbocavernosus reflex, which is a normal cord-mediated reflex elicited by placing a gloved finger in the patient's rectum and then squeezing the glans penis or clitoris or by tugging gently on the Foley catheter. An intact reflex results in rectal sphincter contraction. Absence of this reflex indicates the presence of spinal shock, during which time the patient's prognosis cannot be accurately assessed. A complete spinal cord lesion will remain unchanged after the cessation of spinal shock.

Incomplete Spinal Cord Lesions

Approximately 90% of incomplete spinal injuries can be classified as one of three clinical syndromes: the central cord syndrome, the Brown-Séquard syndrome, and the anterior cord syndrome (Fig. 43-21).[7] The most common is the *central cord syndrome,* often seen in patients with degenerative arthritis of the cervical vertebrae when their necks are hyperextended. The ligamentum flavum buckles into the cord, resulting in a concussion or contusion of the central gray matter in the most central portions of the pyramidal and spinothalamic tracts. Because fibers that innervate distal structures are located in the periphery of the spinal cord, the upper extremities are more severely affected than the lower extremities. With more severe injuries, patients may appear to be almost completely quadriplegic and have only sacral sparing. The prognosis is variable, but more than 50% of patients with central cord syndrome become ambulatory and regain bowel and bladder control, as well as some hand function.[15]

The *Brown-Séquard syndrome,* or hemisection of the spinal cord, usually results from penetrating trauma but may also be seen after lateral mass fractures of the cervical spine. Patients with this lesion have ipsilateral loss of position and vibration sense as well as motor paralysis but contralateral loss of pain and temperature sensation distal to the level of injury; however, either finding may predominate depending on the exact location and extent of injury. Moreover, because the fibers of the lateral spinal thalamic tract cross at a different level to the contralateral side, the pain and temperature loss may be found variably one or two segments above the lesion. Virtually all patients maintain bowel and bladder function and unilateral motor strength, and most become ambulatory.[7]

The *anterior cord syndrome* usually results from hyperflexion injuries causing cord contusion, by the protrusion of a bony fragment or herniated disk into the spinal canal, or by laceration or thrombosis of the anterior spinal artery. It can also occur

www.ketabpezeshki.com 66485457-66963820

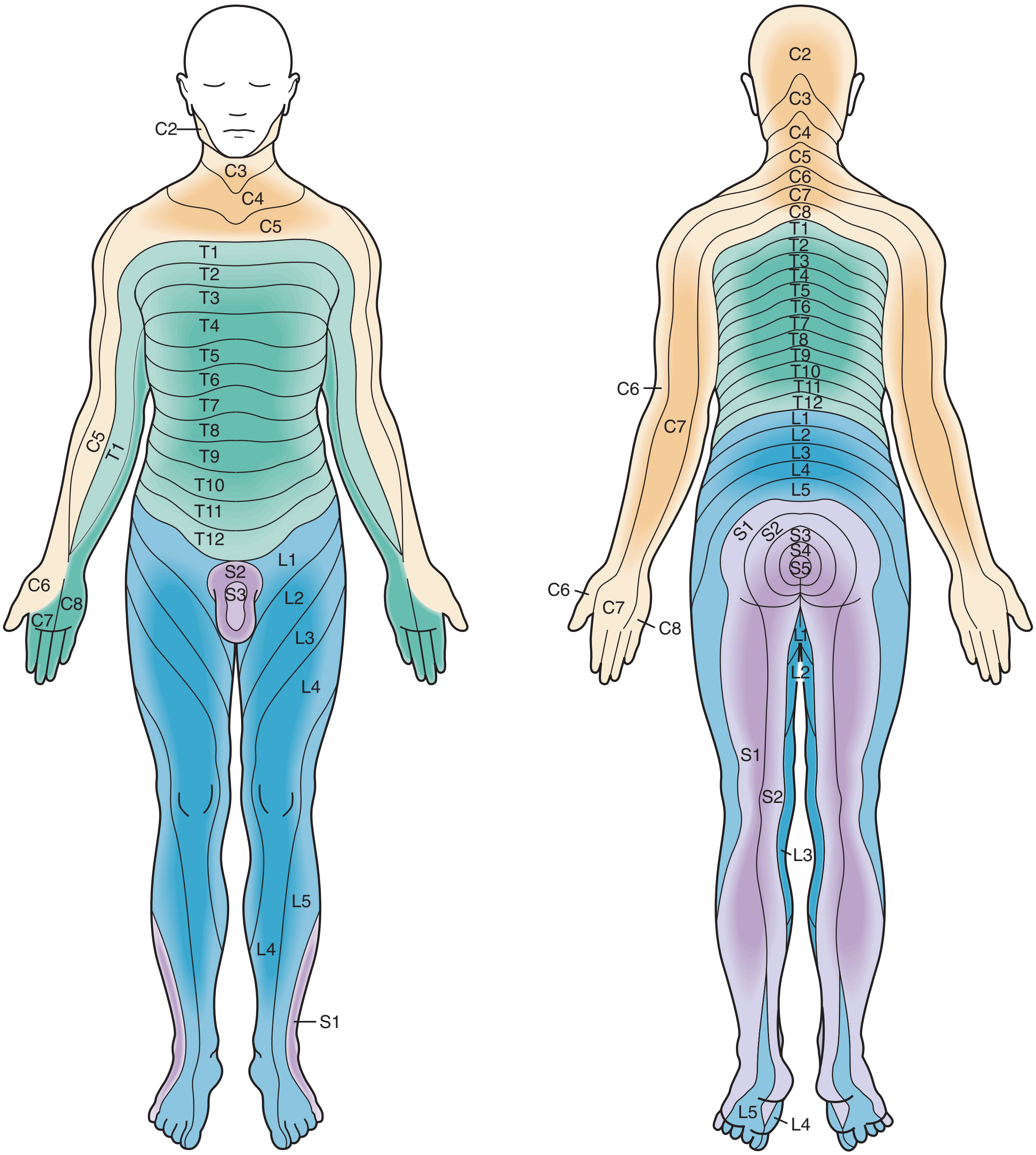


Figure 43-20. Sensory dermatomes.

after prolonged (longer than 30 minutes) cross-clamping of the aorta. This syndrome is characterized by paralysis and hypalgesia below the level of injury with preservation of posterior column functions, including position, touch, and vibratory sensations. Suspicion for an acute anterior cord syndrome warrants immediate neurosurgical consultation because it may be a result of a surgically correctable lesion. After surgical intervention, patients have variable degrees of recovery during the first 24 hours but little improvement thereafter.[7]

There are several less common spinal cord syndromes that may result from a direct injury to the cervicomedullary junction and upper cervical segments or from vertebral artery occlusion resulting from severe hyperextension (Fig. 43-22).[7] The *posteroinferior cerebellar artery syndrome* may produce dysphagia, dysphonia, hiccups, nausea, vomiting, dizziness or vertigo, and cerebellar ataxia. The *Dejeune onion skin pattern* of analgesia of the face is caused by damage to the spinal trigeminal tract. *Horner's syndrome* results from damage to the cervical sympathetic chain and is characterized by ipsilateral ptosis, miosis, and anhidrosis. Injuries below the L2 level can result in an *acute cauda equina syndrome,* characterized by perineal or bilateral leg pain, bowel or bladder dysfunction, perianal anesthesia, diminished rectal sphincter tone, and lower extremity weakness.

The syndrome of SCIWORA is seen primarily in younger children but may occur in any age group.[17-19] The mechanism is unclear but has been ascribed to the increased ligamentous

www.ketabpezeshki.com 66485457-66963820

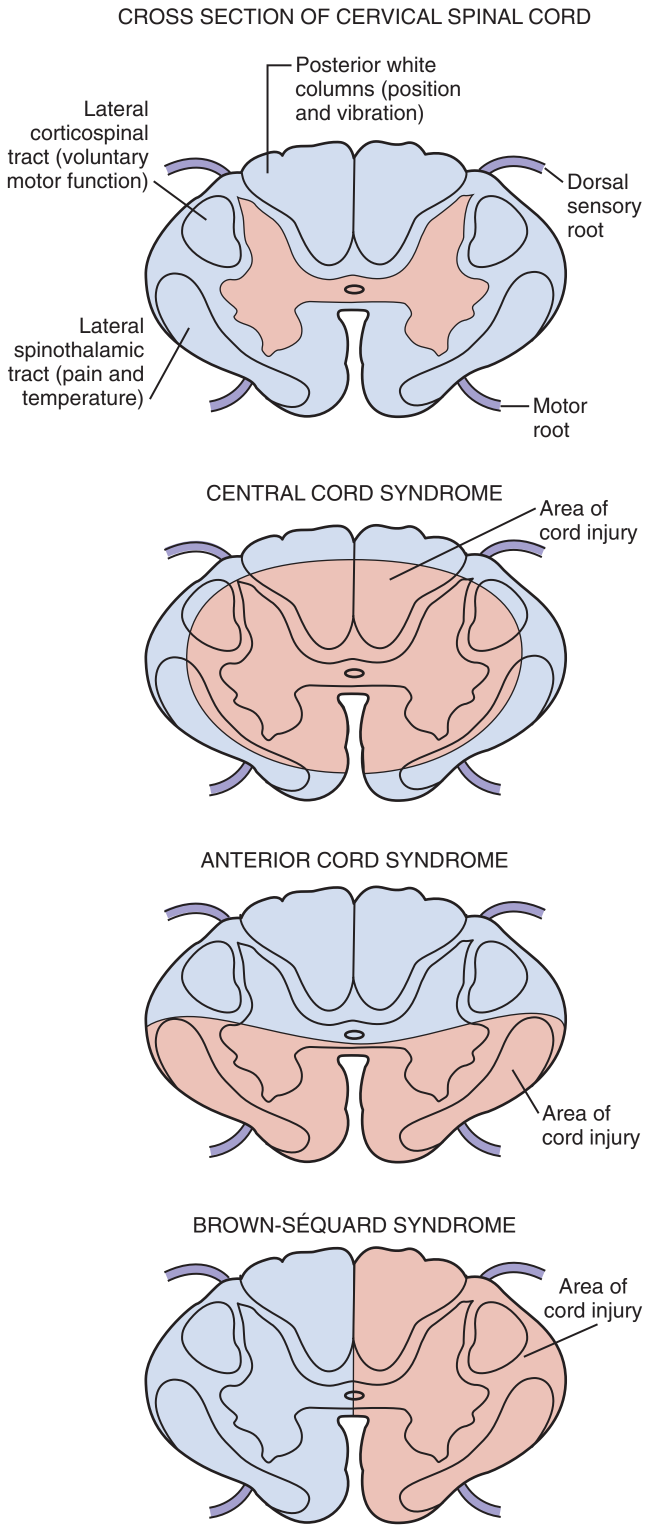


Figure 43-21. Incomplete spinal cord syndromes.

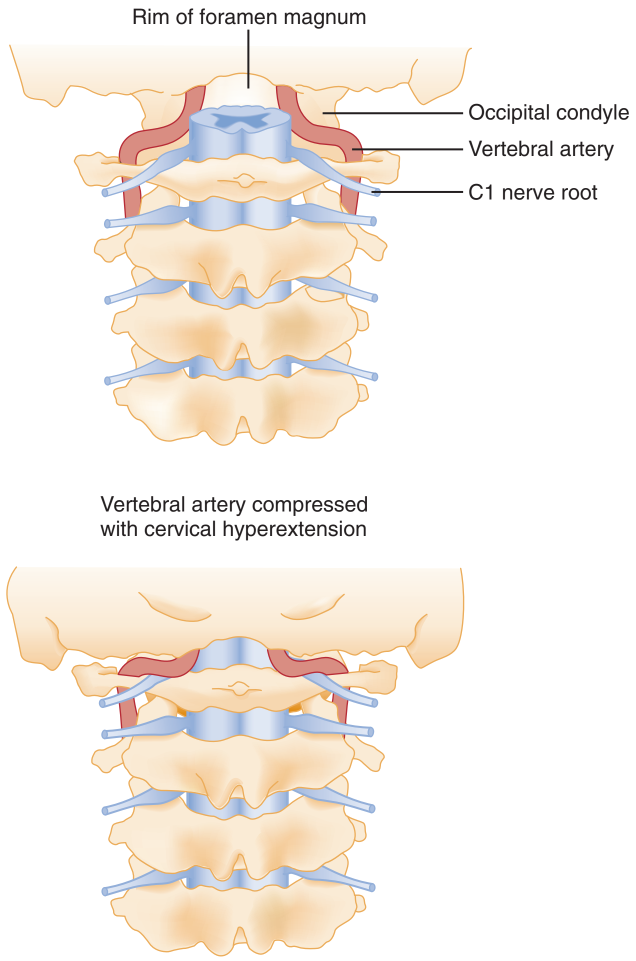


Figure 43-22. Mechanism of vertebral artery injury in extension injuries of the cervical spine.

elasticity seen in the young, leading to transient spinal column subluxation, stretching of the spinal cord, and vascular compromise. Patients often experience a brief episode of upper extremity weakness or paresthesias followed by neurologic deficits that appear hours to days later. The prognosis for patients with SCIWORA is variable, depending on the degree of neurologic impairment and the rate of resolution.

DIAGNOSTIC STRATEGIES

Radiographic Evaluation

Indications

Clinicians have historically taken a liberal approach to imaging the cervical spine in the setting of trauma because failure to recognize an SCI may result in devastating neurologic consequences. According to the National Hospital Ambulatory Medical Care Survey, only 4% of all cervical spine radiographs demonstrate a fracture.[20] However, there is controversy as to what is the most efficient and accurate method of imaging, leading to great practice variation among emergency physicians, with a sixfold range in radiography ordering rates.[21]

In an effort to standardize clinical practice and guide physicians to be more selective in their use of radiography without jeopardizing patient care, two clinical decision rules have been developed. Use of selective but safe imaging may decrease overall health care costs, reduce radiation exposure, and avoid the discomfort and complications (e.g., aspiration and decubitus ulcerations) associated with patients lying flat on backboards with rigid collars while waiting for spine imaging. The first rule to be developed, the National Emergency X-Radiography Utilization Study (NEXUS) Low-Risk Criteria (NLC), was based on a multicenter prospective observational study involving 34,069 trauma patients seen at 21 U.S. emergency departments. The decision instrument required

www.ketabpezeshki.com 66485457-66963820

patients to meet five criteria to be classified as having a low probability of injury: (1) no midline cervical tenderness; (2) no focal neurologic deficit; (3) normal alertness; (4) no intoxication; and (5) no painful, distracting injury. The decision rule identified all but eight of the 818 patients who had spinal injuries. Only two of these patients had a clinically significant injury, only one of whom required surgical stabilization, and neither sustained a permanent neurologic injury.[22] Sensitivity, specificity, and negative predictive value of the NLC were calculated and were found to be 99.6, 12.9, and 99.8%, respectively.[22]

Owing to concerns about the low specificity of the NLC, Stiell and colleagues developed the Canadian C-Spine Rule (CCR) based on 25 selected clinical predictor variables associated with spine injury. In 2003 the CCR was prospectively studied and compared with the NLC in the nine Canadian tertiary care hospitals. Of 8283 patients, 162 were found to have "clinically significant" injuries, and the sensitivity, specificity, and negative predictive values of the CCR were, respectively, 99.4, 45.1, and 100%.[23] The CCR is composed of the following three questions:

1. Are there any high-risk factors that mandate radiography?
2. Are there any low-risk factors that allow safe assessment of range of motion?
3. Is the patient able to actively rotate his or her neck 45 degrees to the left and right?

High-risk factors include age older than 65 years, a "dangerous mechanism of injury" (a fall from a height >1 m, an axial loading injury, high-speed MVC [>100 km/hr], rollover, ejection, motorized recreational vehicle or bicycle collision), or the presence of paresthesias. Low-risk factors include simple rear-end vehicle crashes, sitting position in the emergency department, ambulatory at any time, delayed onset of neck pain, and the absence of midline neck tenderness. Although the NEXUS criteria are more widely used in the United States, both studies recommend obtaining cervical spine radiographs only for patients in whom spinal injury is clinically suspected.

There is some controversy as to which of the two rules to implement. There are methodological differences in the respective study designs, such as different inclusion and exclusion criteria.[23] Note that both studies excluded patients with penetrating trauma and those who had sustained direct blows to the neck. Still, both rules have been well validated and are sensitive, and the use of either rule has been shown to significantly limit the number of unnecessary radiographs while missing only rare patients with clinically significant injuries.

Cervical Plain Radiographs

Normal cervical spine radiographs in AP, lateral, swimmer's, oblique, and odontoid views are presented in Figures 43-23 and 43-24. All vertebrae suspected of being injured must be visualized. The C7-T1 vertebra may be obscured in muscular or obese patients, as well as in patients with spinal lesions that result in paralysis of the muscles that act to depress the shoulders. The paralysis leaves the trapezius muscles, which elevate the shoulders, unopposed. Such lesions are located in the lower cervical region. The shoulders can usually be depressed by pulling the patient's hands toward the feet, using slow, steady traction, but caution is exercised to avoid causing or worsening a distraction injury. Movement should occur only at the shoulder girdle while the head and neck remain immobilized. Note that the head and neck should not be pulled in opposition to the person pulling down the shoulders because this may induce a distraction injury. If this maneuver is unsuccessful or difficult to perform because of upper extremity injuries, a transaxillary or swimmer's view of the lower cervical vertebrae may be helpful. The upper three or four thoracic vertebrae are also difficult to visualize on routine lateral views of either the cervical or thoracic spine, and a swimmer's view, an oblique radiograph, or CT is often needed for adequate evaluation of the thoracic spine.

Although the cross-table lateral view of the cervical spine is the most helpful x-ray study in diagnosing spinal injures, its inadequacy as the sole view is well documented.[24] Because the diagnostic yield is significantly increased when the AP and odontoid views are included, all three views of the cervical spine should be evaluated before discontinuation of cervical spine immobilization.[25] The NLC shows that a technically adequate three-view trauma series will fail to diagnose spinal injury in only 0.07% of patients with injuries and in only 0.008% of patients with unstable injuries.[26]

Cross-Table Lateral View. The inspection of the lateral cervical spine film should be methodical and complete. For this to be accomplished, it is helpful to remember the "ABCs" of interpreting the lateral film, where *A* stands for alignment, *B* for bony abnormalities, *C* for cartilage-space assessment, and *s* for soft tissues.

For the alignment to be checked, two imaginary lines are drawn that separately connect the anterior and posterior margins of the vertebral bodies, the anterior and posterior contour lines. A third line, the spinolaminal line, connects the bases of the spinous processes extending to the posterior aspect of the foramen magnum (Fig. 43-25). All three lines should form a smooth, continuous lordotic curve, and any disruption of these lines suggests a bony or ligamentous injury. An exception to this rule is the pseudosubluxation of C2 and C3, which is commonly seen in infants and children. This phenomenon is attributed to their immature muscular development and a hypermobile spine. Thus if a high cervical injury is suspected in a child, the posterior cervical line, which connects the points bisecting the bases of the spinous processes of C1 and C3, should be used (Fig. 43-26). If the base of C2 lies more than 2 mm anterior or posterior to the posterior cervical line, an injury at that level should be suspected.[27] On the lateral view, the predental space, which is the distance between the anterior aspect of the odontoid process and the posterior aspect of the anterior ring of C1, should not exceed 3 mm in an adult or 5 mm in a child (see Fig. 43-26). A widening of this space may indicate a Jefferson fracture of C1.

Next, bony abnormalities should be assessed. Subtle changes in bony density should be noted. Areas of decreased density, seen in patients with rheumatoid arthritis, osteoporosis, or metastatic osteolytic lesions, are more apt to succumb under stress. Acute compression fractures of the vertebral bodies and metastatic osteoblastic lesions result in areas of increased bone density.

The emergency physician may diagnose subluxations and dislocations through cartilage-space assessment. A slight anterior or posterior widening of the intervertebral space or the interspinous space may be the only clue to an unstable dislocation.

Finally, the soft tissues of the retropharyngeal space should be assessed for the presence of prevertebral swelling and hemorrhage, often the only radiographic sign of spinal injury. The retropharyngeal space, measured from the anterior border of the body of C2 to the posterior wall of the pharynx, should not exceed 6 mm in children or adults (Fig. 43-27A and C). At the level of C3 and C4, this measurement should not exceed 5 mm or should be less than one half the width of the vertebral body at that level. Below the level of C4, the prevertebral soft tissue space is widened by the esophagus and the cricopharyngeal muscle. Here, the retrotracheal space, measured from the anterior border of the body of C6 to the posterior wall of the trachea, should not exceed 22 mm in adults or 14 mm in children younger than age 15 years. In children younger than age 2 years, the retropharyngeal space may normally appear widened during expiration; therefore inspiratory films

www.ketabpezeshki.com 66485457-66963820

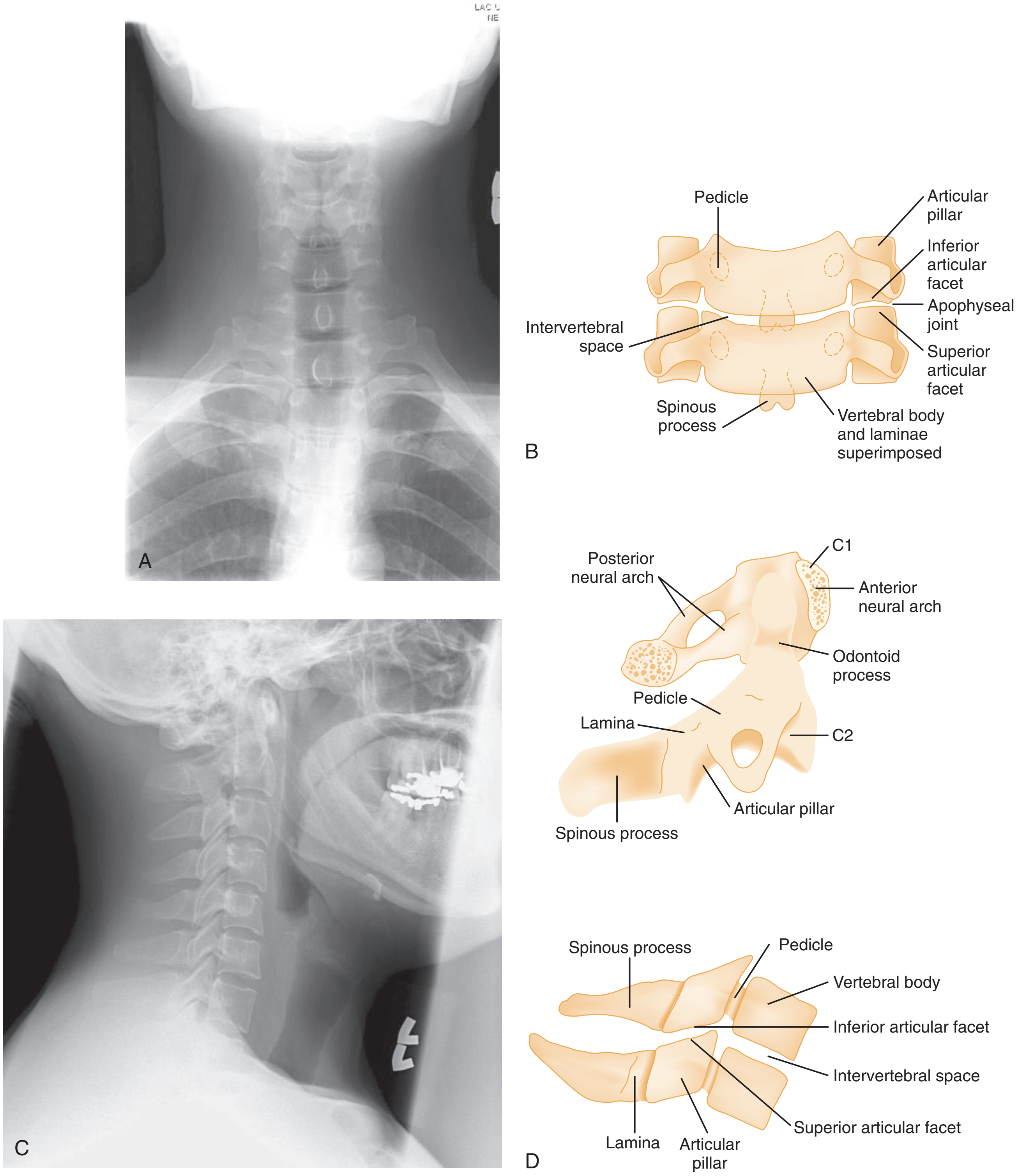


Figure 43-23. Views of the cervical spine. **A** and **B,** Anteroposterior view. **C** and **D,** Lateral view.

www.ketabpezeshki.com 66485457-66963820

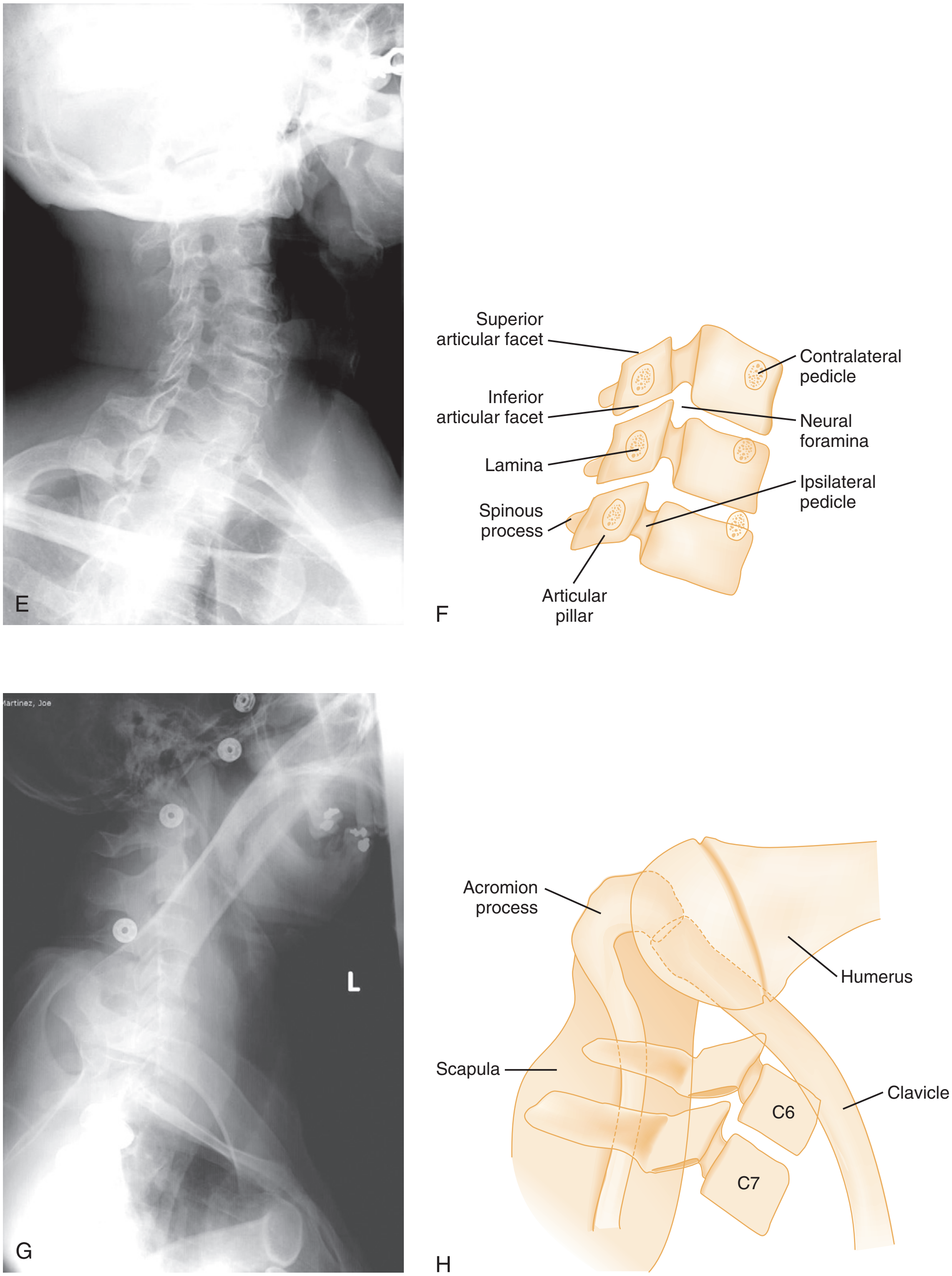


Figure 43-23, cont'd. E and F, Oblique view. G and H, Swimmer's view.

www.ketabpezeshki.com 66485457-66963820

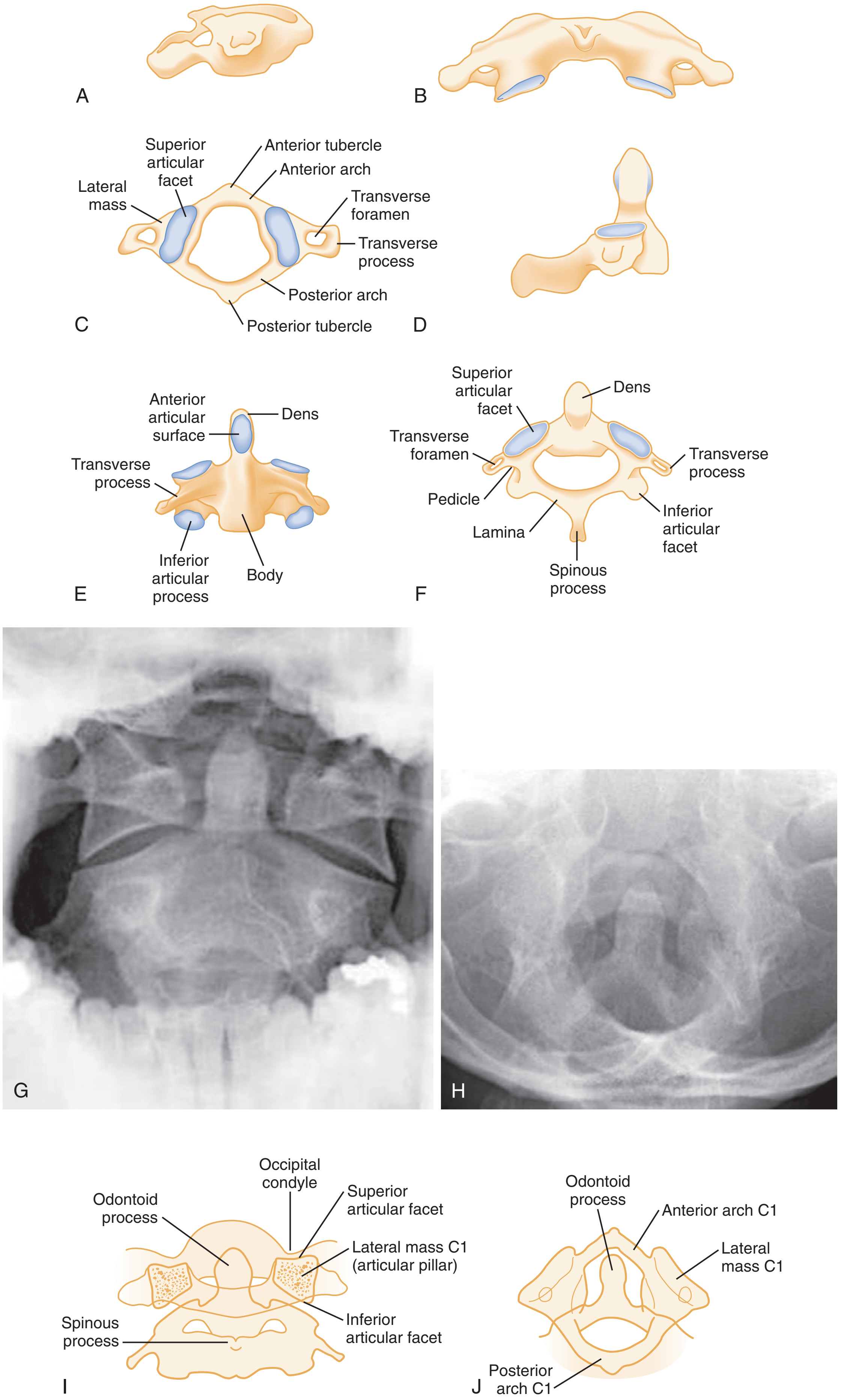


Figure 43-24. Views of C1 and C2. **A,** Atlas in a lateral view. **B,** Atlas in a frontal view. **C,** Atlas in an above view. **D,** Axis in a lateral view. **E,** Axis in a frontal view. **F,** Axis in an above view. **G** and **H,** Open-mouth view. **I** and **J,** Closed-mouth view.

www.ketabpezeshki.com 66485457-66963820

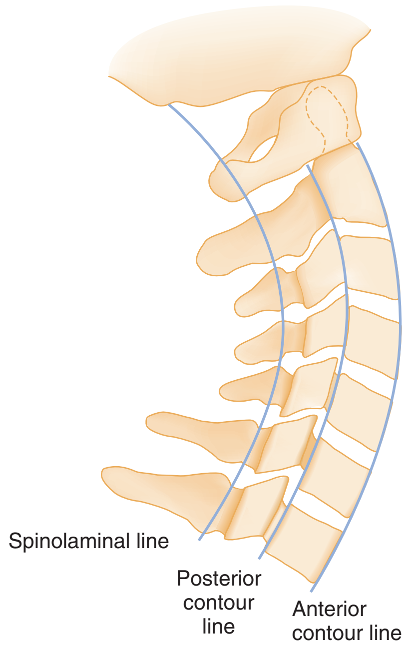


Figure 43-25. Normal structural relationships of the lateral cervical spine.

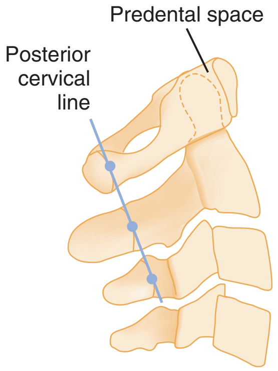


Figure 43-26. Posterior cervical line of a normal lateral spine.

should be obtained.[28] Air in the prevertebral space may indicate rupture of the esophagus or some portion of the respiratory tree, and anterior bulging of the prevertebral fat stripe is an excellent sign of an underlying bony or soft tissue injury.

Odontoid View. The second film obtained in the emergency department is the open-mouth or closed-mouth view of the atlas and axis (see Fig. 43-24G-J). Nonfusion of the odontoid in children and congenital anomalies of the odontoid in adults may mimic fractures.

Anteroposterior View. The AP spinal film completes the spinal series. The spinous processes should form a straight line, and the laryngeal and tracheal air shadows should be midline (see Figs. 43-23B and 43-27D). The regular outline of the lateral masses should be verified, and the pedicles viewed end on can be checked for fracture. Widening of the interpedicular distance compared with adjacent vertebrae suggests a burst fracture (Fig. 43-28).

In addition to searching for fractures of vertebral bodies and transverse processes, bulging of the mediastinal stripe may be the only evidence of a thoracic vertebral body fracture. Fractures of the upper thoracic vertebrae may cause a posterior mediastinal hemorrhage that produces mediastinal widening on the chest x-ray film similar to that seen with aortic rupture.

Oblique Views

Oblique views of the cervical spine may be helpful to confirm a suspected posterior laminar fracture, a unilateral facet dislocation, or a real subluxation.[29] However, with the advent of high-resolution CT, suspicion of these injuries on plain films ordinarily leads to CT rather than the obtaining of oblique views. The normal lamina appears as an intact ellipse (see Fig. 43-23E and F), and a posterior laminar fracture disrupts the appearance of this ellipse (Fig. 43-29). Normal overlapping laminae have the appearance of shingles on a roof (see Fig. 43-27A and B). Integrity of these shingles excludes the presence of a unilateral facet dislocation, whereas disruption confirms it (see Fig. 43-11E and F). The normal interlaminar distance, measured from the center points of successive laminar ellipses on an oblique view, should be equidistant. An increased interlaminar distance, caused by lack of capsular ligamentous integrity, indicates true subluxation (Fig. 43-30).

Flexion and Extension Views

There is controversy as to the role of flexion and extension (F/E) views in blunt cervical trauma, but they are often obtained when there is concern for ligamentous injury, despite negative standard radiographs when magnetic resonance imaging (MRI) is not available. F/E views should be obtained only in patients who are alert and able to articulate the presence of pain, numbness, or paresthesias, because such symptomatology may indicate instability. Other potential indicators of instability of the cervical spine include any of the following: more than 3.5 mm of horizontal displacement between the disks, displaced apophyseal joints, widened disk spaces, loss of greater than 30% of the disk height, or the presence of a prevertebral hematoma.[30] The NEXUS investigators demonstrated that 86 of the 818 (10.5%) patients ultimately found to have cervical injury underwent F/E testing.[31] Although two patients had bony injuries and four patients had subluxations demonstrated only on F/E views, all 6 patients had other injuries apparent on routine radiographs. F/E views are also deemed inadequate for interpretation in nearly one third of studies.[32] In addition, in the acute setting, F/E radiographs have been reported to have unacceptably high false-positive and false-negative rates because minor subluxations may be masked by concomitant muscle spasm.[33] Thus delayed F/E views obtained a week or two after injury may be more helpful. Moreover, other studies, such as CT and MRI, appear to be superior imaging modalities in patients with severe, localized symptoms who have normal radiographs.[34]

Computed Tomography

Conventional radiography is limited as a result of the nature of equipment, difficulties in positioning, lack of patient cooperation, and the often critical status of trauma patients. The incidence of an inadequate lateral cervical view, specifically visualization of C7 to T1, is as high as 25%.[29] The CT scan effectively deals with these limitations and in many cases is the technique of choice for the definitive evaluation of acute cervical spine trauma.[35-38] CT also permits examination without moving the patient from the supine position and is thus preferable in terms of fracture stabilization, airway control, and other life-support measures. In fact, practice guidelines from the Eastern Association for the Surgery of Trauma (EAST) recommend that CT from the occiput to T1 be used as the primary screening method in blunt cervical trauma patients.[39]

www.ketabpezeshki.com 66485457-66963820

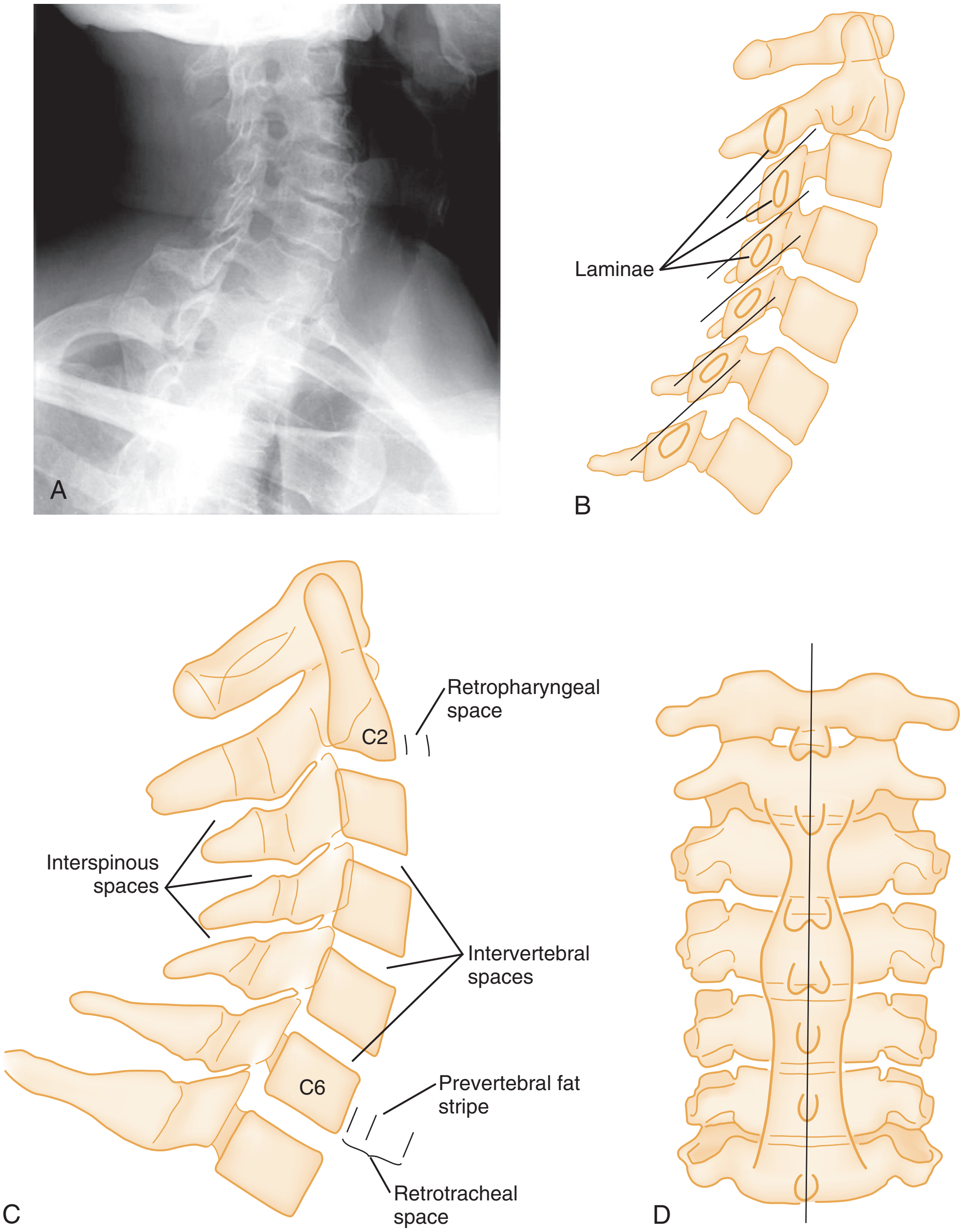


Figure 43-27. A and B, Normal structural relationships of the cervical spine laminae in an oblique view form a "shingles on a roof" appearance. C and D, Normal relationship between soft tissues and bony structures of the cervical spine in the lateral and anteroposterior (AP) views. C, In the lateral view, the intervertebral spaces and interspinous spaces should be compared with the spaces above and below for asymmetry and important clues in flexion and extension injuries. The retropharyngeal and retrotracheal soft tissues are measured at the C2 and C6 levels for swelling. D, In the AP view, the tracheal and laryngeal air shadows should be within the midline. A straight line should connect points bisecting the spinous processes. If such is not the case, rotatory injuries are suspected.

www.ketabpezeshki.com 66485457-66963820

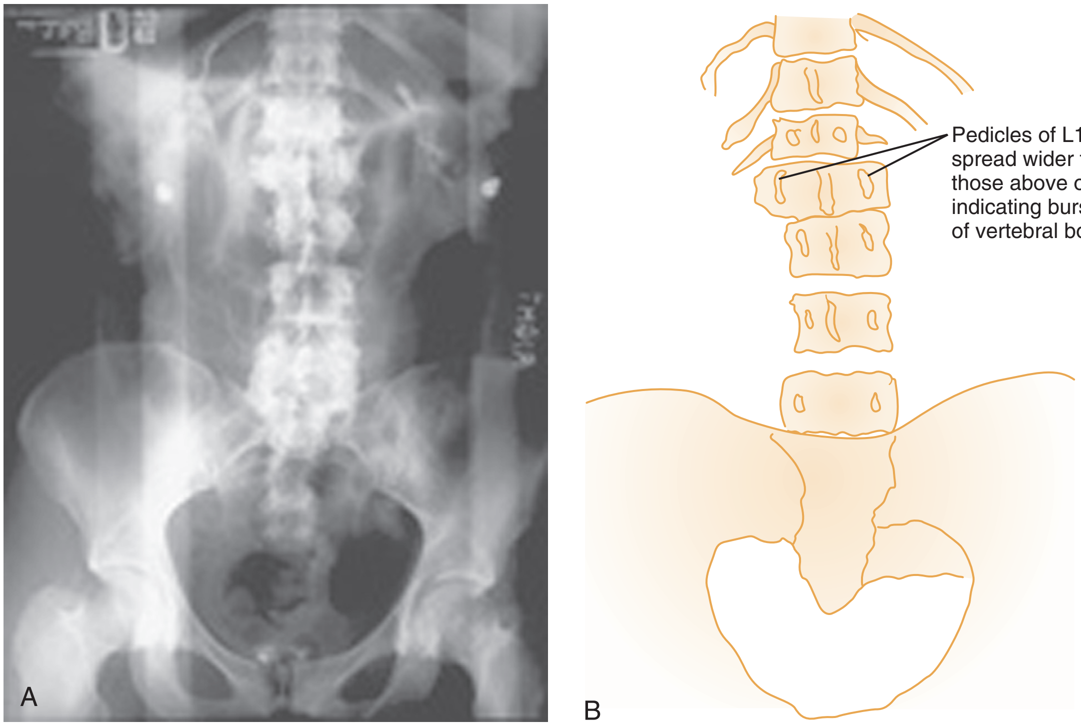


Figure 43-28. A and B, Burst fracture of L1. An anteroposterior radiograph shows increased distance between the pedicles of L1 in comparison to adjacent vertebrae. An intravenous pyelogram showed renal injury on the left.

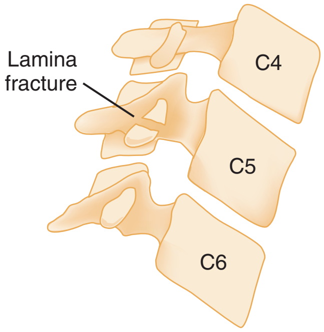


Figure 43-29. Oblique view of a laminar fracture. A fracture line extending through the lamina of C5 is well demonstrated on an oblique view.

The superiority of CT in fracture detection is a critical advantage (Figs. 43-31, 43-32, and 43-33); therefore unclear fractures or displacements on standard radiographs should be further evaluated by a CT scan. Because fractures in contiguous and noncontiguous vertebrae are fairly common, CT scan should be obtained to visualize the entire cervical spine. CT can also identify bony fragments, acute disk herniation, a foreign body, paraspinal hematoma, or an extramedullary hematoma.

A study comparing CT with plain radiography demonstrated the sensitivity in the detection of spine fractures to be 70% for plain radiography compared with 100% for CT, and there was a significant reduction in mean time in the radiology department with CT (1.0 vs. 1.9 hours, $P < .001$).[40] In another study, CT identified 99.3% of all fractures of the cervical, thoracic, and lumbar spine after high-energy trauma, and those missed by CT required minimal or no treatment.[41] Finally, a systematic review of studies comparing plain radiography and CT also demonstrated CT to be superior with a pooled sensitivity of 52% (95% confidence interval [CI] 47-56) for plain radiography versus 98% (95% CI 96-99) for CT.[42]

Owing to the advantages of CT, some authorities argue that routine plain radiographs of the spine are unnecessary when CT is readily available. Investigators have assessed whether vertebral images reconstructed from CT scans of the abdomen and pelvis obtained for the evaluation of chest and abdominal injuries provide sufficient data to screen for spinal fractures, thereby decreasing the time and cost of spine injury evaluation. CT is also thought to be adequate to clear cervical spines even in the obtunded blunt trauma patient.[43]

The spiral (helical) CT scan provides continuous acquisition of data (volume scan) via a rotating x-ray tube and simultaneous patient movement through the CT gantry (Fig. 43-34). The ability to reconstruct axial CT data in two-dimensional and three-dimensional formats is helpful to nonradiologists, who are less accustomed to performing the mental integration of multiplanar images (Fig. 43-35). The spiral CT scan can demonstrate cervical spine injuries not apparent on plain film or axial CT images (Fig. 43-36).

Potential disadvantages of CT include cost and radiation exposure. However, in one study, although CT was associated with higher mean overall spinal imaging charges than plain radiography ($4386 vs. $513, $P < .001$), there was no statistically significant difference when comparing spinal imaging cost per patient ($172 vs. $164, $P > .05$).[40] In the same study, radiation exposure for CT was higher than for plain radiography for cervical spine imaging (26 vs. 4 mSv), but CT had lower levels of radiation exposure for thoracolumbar imaging (13 vs. 26 mSv).[40]

Magnetic Resonance Imaging

CT has a higher sensitivity than MRI to detect fractures and dislocations at the craniocervical junction, as well as fractures of the posterior elements of the spine.[45] However, MRI, with its superior resolution and lack of ionizing radiation, also has the primary advantage of the ability to directly image nonosseous structures, including intramedullary and extramedullary spinal

www.ketabpezeshki.com 66485457-66963820

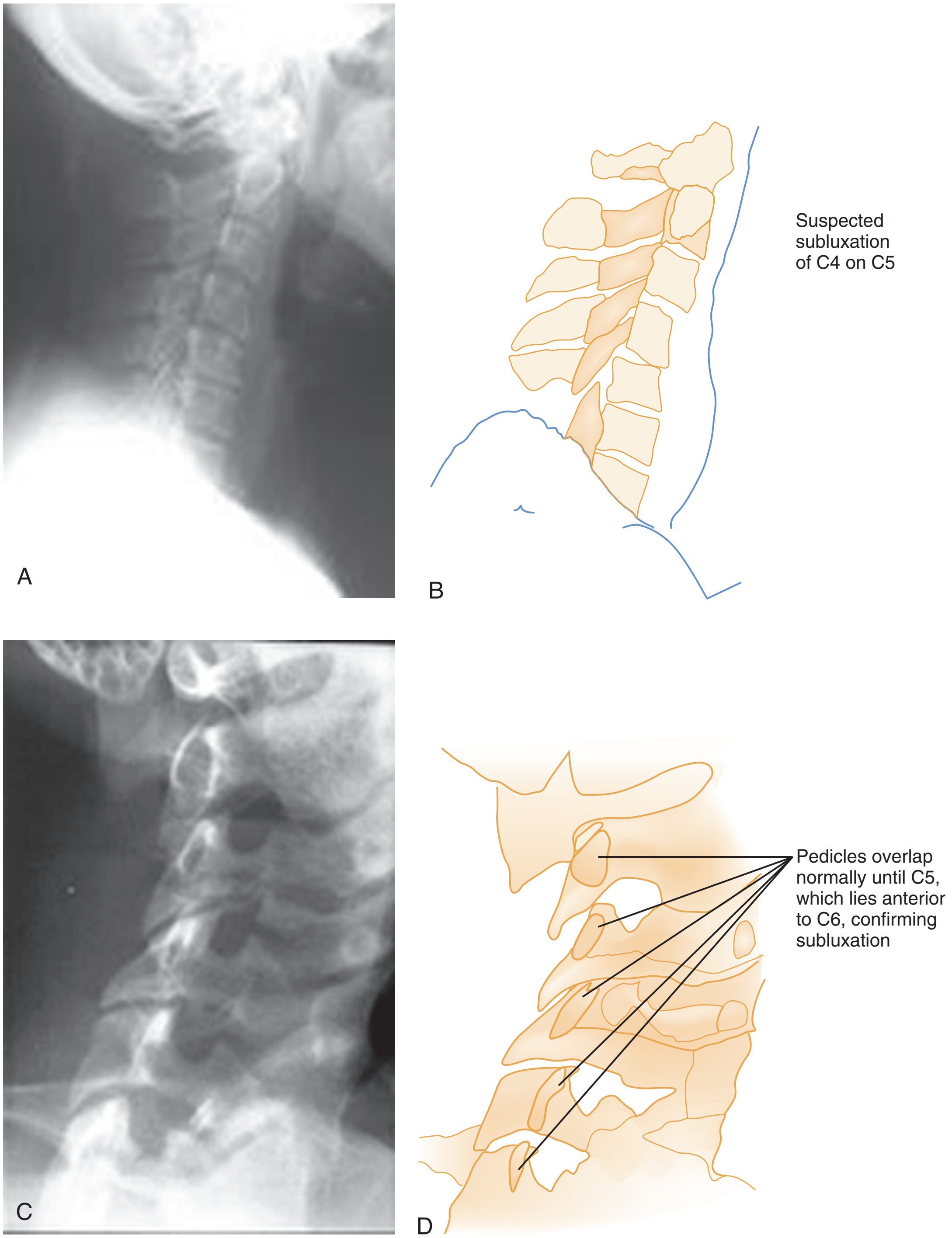


Figure 43-30. A and B, True subluxation, lateral view. Anterior subluxation of C5 on C6 is questionable. C and D, True subluxation, oblique view. The pedicle of C5 lies slightly anterior to that of C6, thus confirming subluxation.

www.ketabpezeshki.com 66485457-66963820

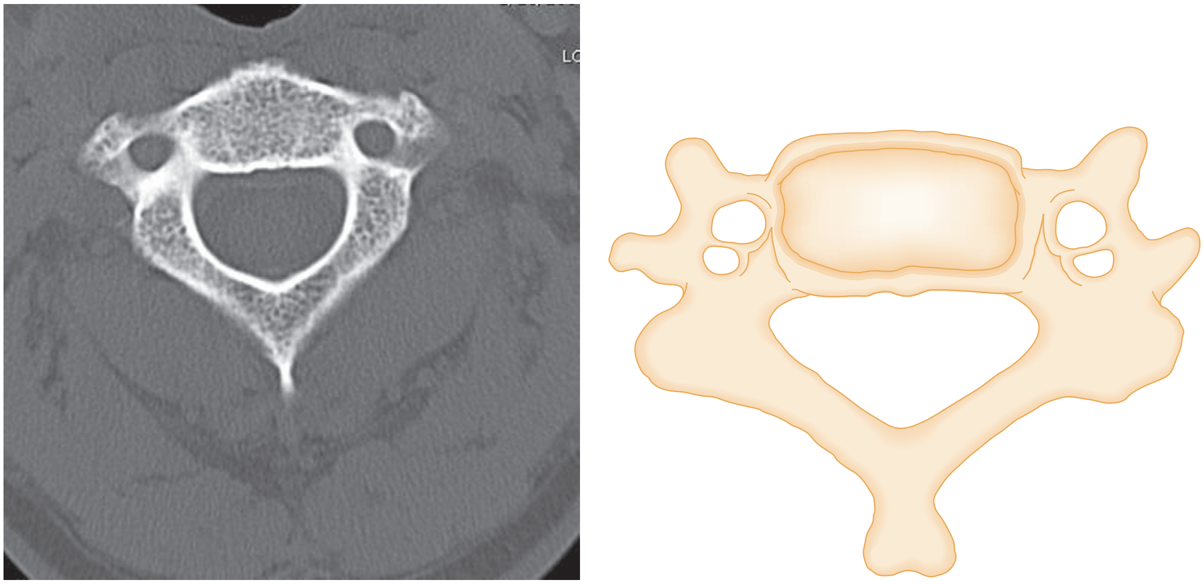


Figure 43-31. Normal axial computed tomographic section of the cervical vertebra.

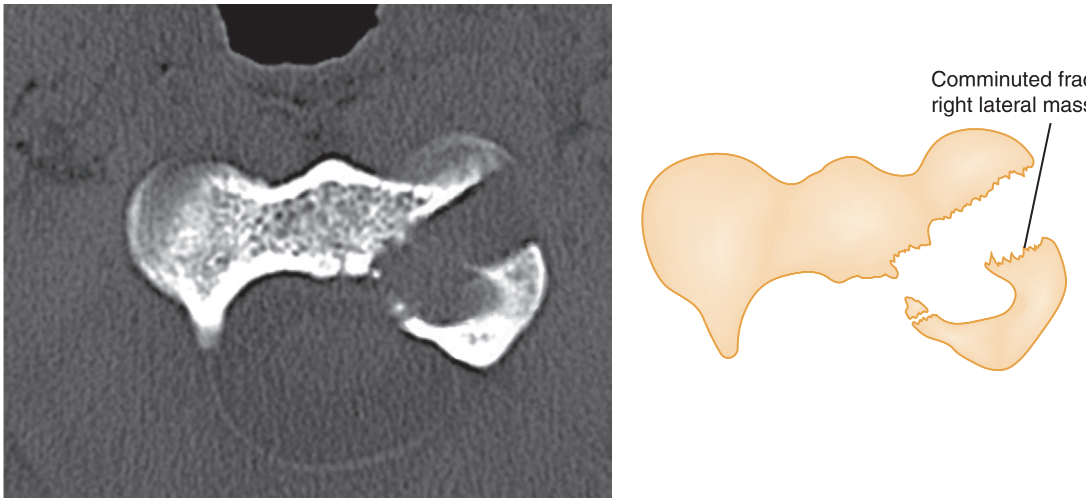


Figure 43-32. C1 fracture through the left lateral mass.

www.ketabpezeshki.com 66485457-66963820

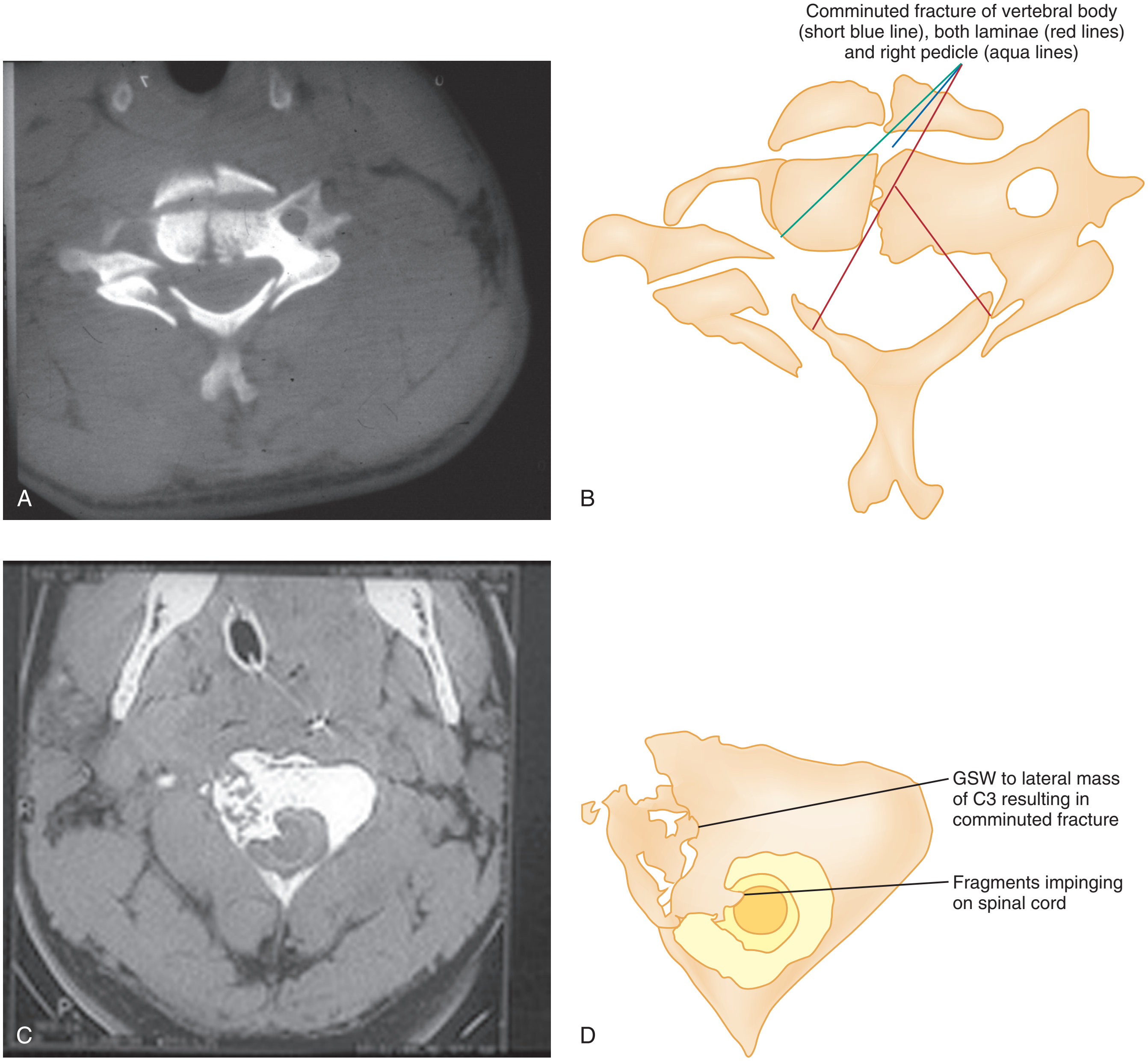


Figure 43-33. **A** and **B,** Axial computed tomography of C5 showing a comminuted vertebral body fracture and bilateral lamina fractures with narrowing of the spinal canal. **C** and **D,** Gunshot wound (GSW) of the lateral mass with fragments impinging on the spinal cord.

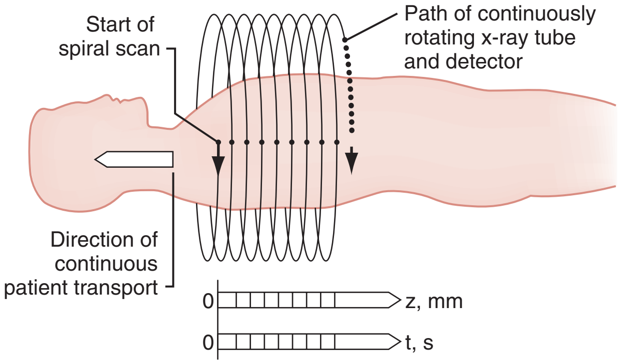


Figure 43-34. Technique for performing a spiral computed tomographic scan.

abnormalities that potentially cause neurologic deficit (Fig. 43-37). Its major impact has therefore been in demonstrating potentially surgically correctable lesions, including acute disk herniation, ligamentous injury, bony compression, epidural and subdural hemorrhage, and vertebral artery occlusion (Fig. 43-38). MRI can identify three separate patterns of SCI, including acute cord hemorrhage, cord edema or contusion, and mixed cord injury. Patients with cord edema or contusion show significant neurologic improvement, whereas those with cord hemorrhage (Fig. 43-39) fare far worse. MRI therefore has diagnostic and prognostic capabilities in the evaluation of cervical spine injury. MRI is also viewed as the best diagnostic imaging modality for SCIWORA, in which MRI may demonstrate central disk herniation, spinal stenosis, cord edema, and contusion.

Contraindications to MRI include the presence of a pacemaker, cerebral aneurysm clips (MRI-compatible clips are now available), and metallic (ferromagnetic) foreign bodies. There are risks to performing an MRI, as well, such as aspiration, secondary brain

www.ketabpezeshki.com 66485457-66963820

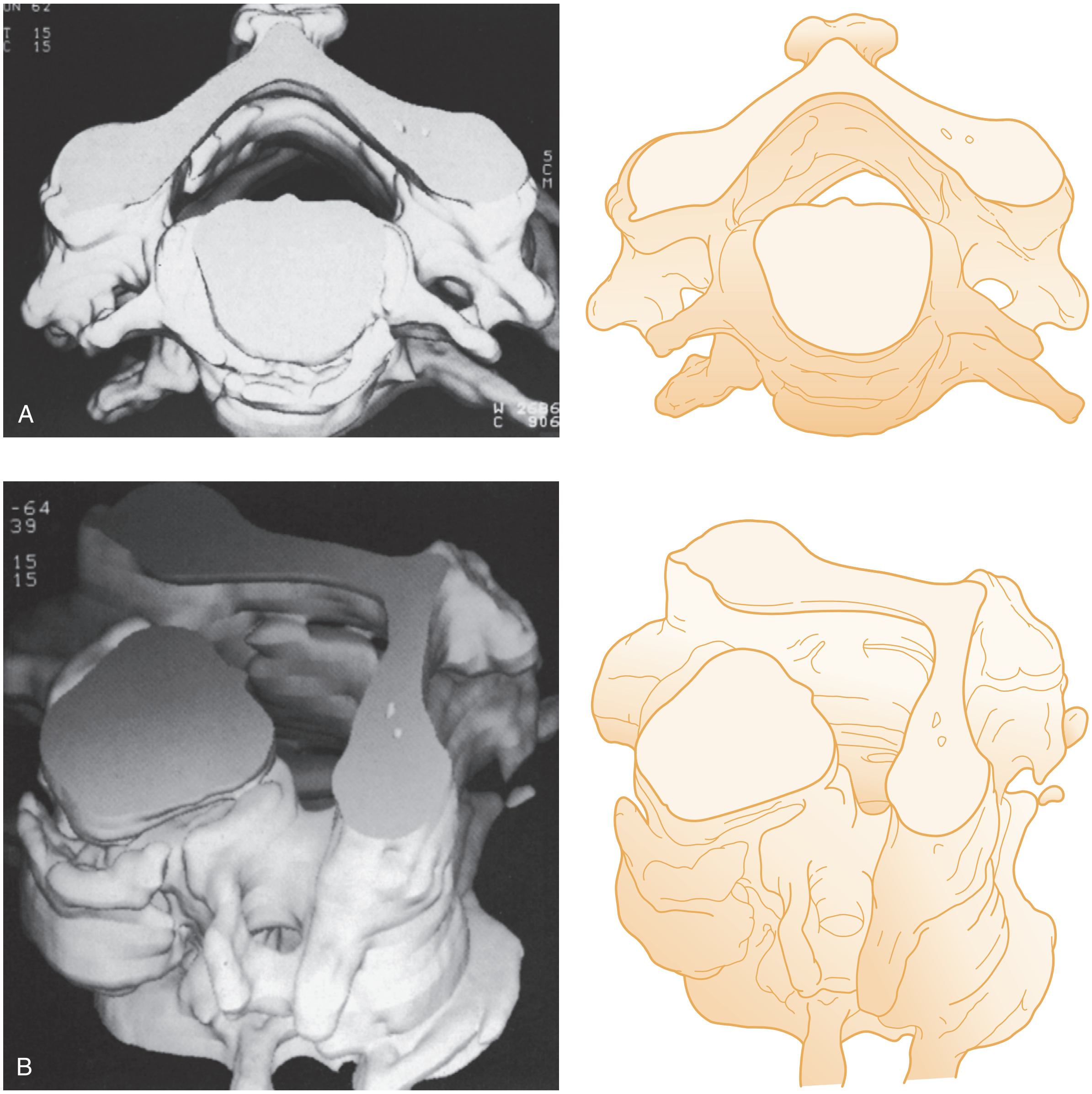


Figure 43-35. Three-dimensional computed tomography images of the cervical vertebrae. **A,** Superior view. **B,** Oblique view.

www.ketabpezeshki.com 66485457-66963820

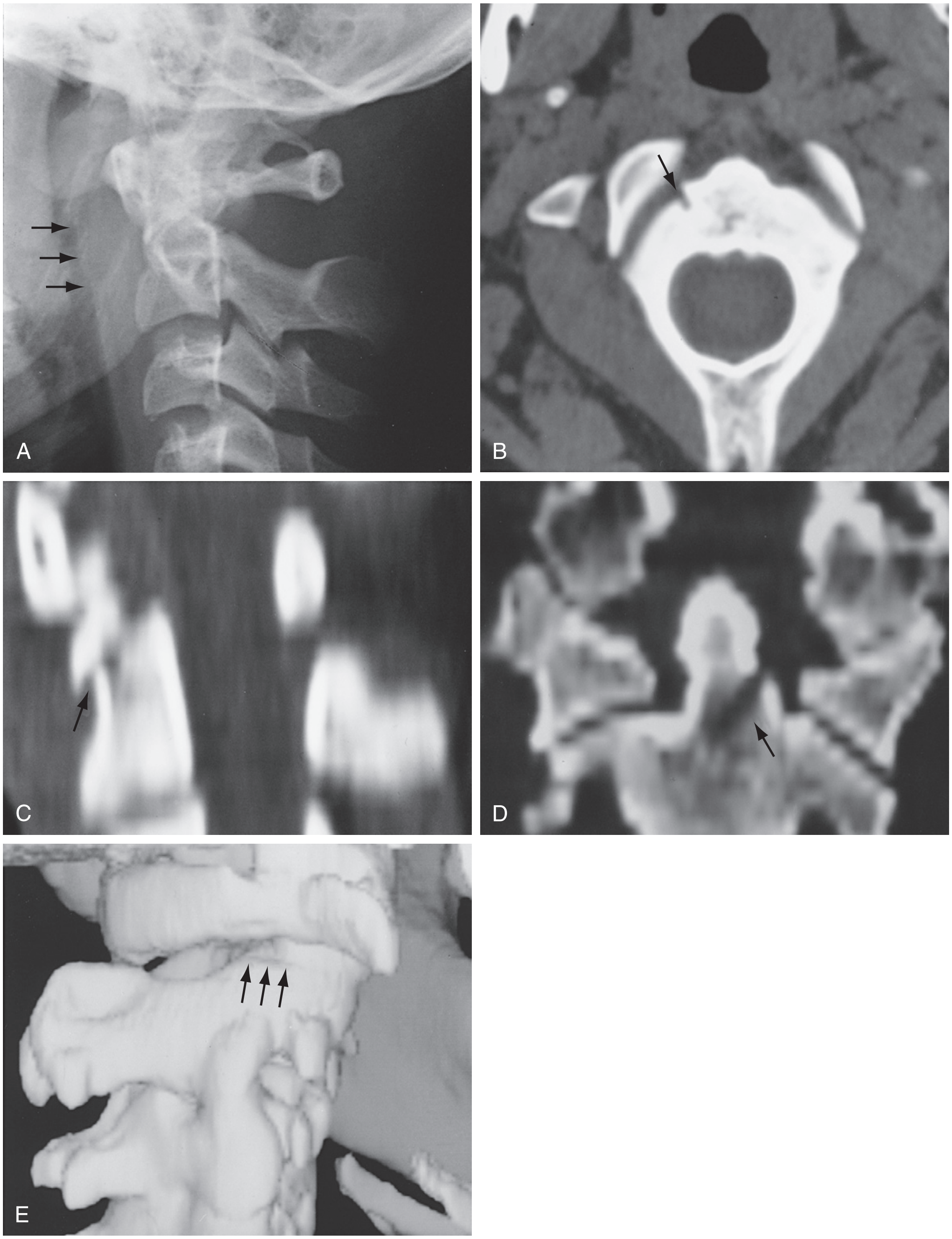


Figure 43-36. Type III odontoid fracture. **A,** Lateral cervical spine radiograph showing prevertebral soft tissue swelling at the C2 level *(arrows).* **B**, An axial computed tomography (CT) scan section through C2 demonstrates a questionable fracture near the base of the odontoid process *(arrow).* **C** and **D,** Sagittal and coronal two-dimensional CT scan reconstructions confirm a fracture *(arrows).* **E,** Three-dimensional CT scan reconstruction (lateral view) of the fracture *(arrows).*

www.ketabpezeshki.com 66485457-66963820

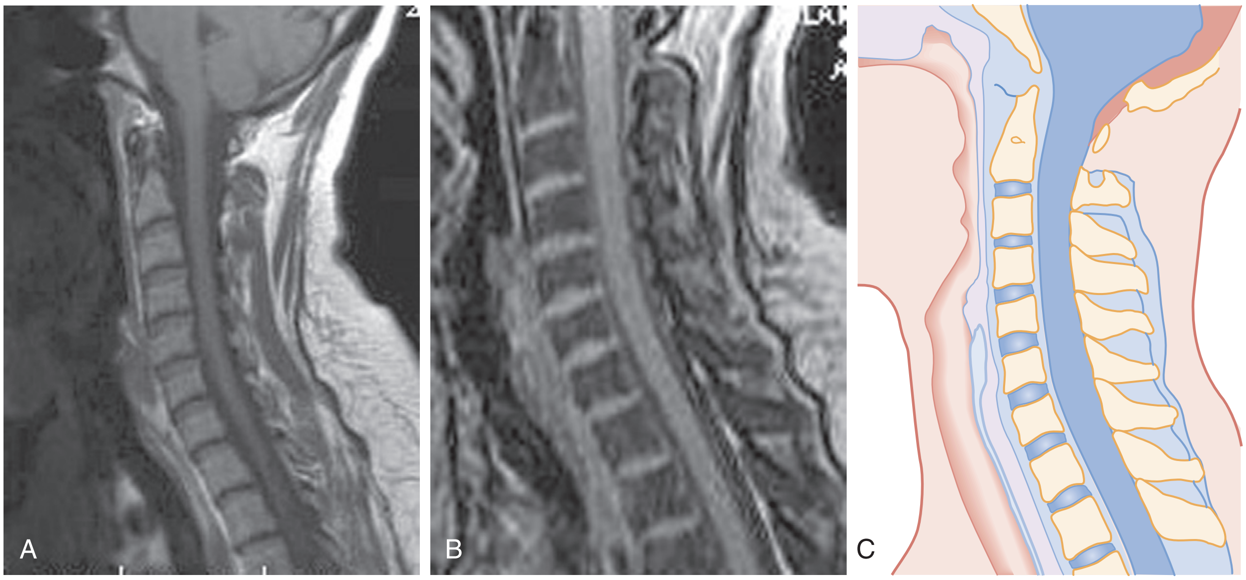


Figure 43-37. Normal sagittal magnetic resonance images of the cervical spine: T1-weighted **(A)** and flip-angle **(B)** scans. **C,** Illustration of the cervical spine.

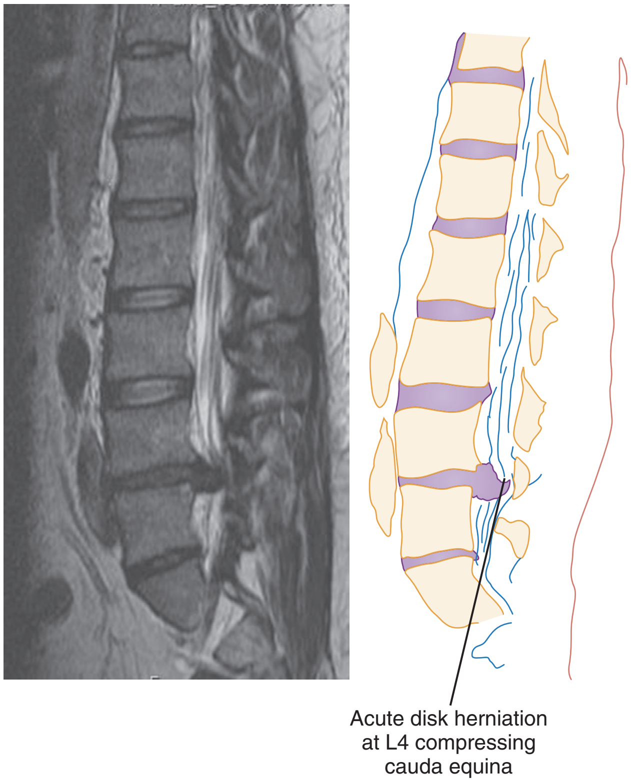


Figure 43-38. Magnetic resonance image showing acute L4 disk herniation with compression of the cauda equina.

injury, and the difficulty of monitoring and resuscitating a patient in the MRI suite.[46] In addition, MRI cannot be used when MRI-incompatible life-support, monitoring systems, and cervical traction devices are employed (although MRI-compatible support systems exist). Plain films and CT are still superior to MRI in evaluating osseous anatomy and fractures, particularly posterior-element fractures.

The role of MRI in the evaluation of acute cervical spine trauma continues to evolve, and some advocate an immediate MRI in patients with clinical signs or plain film evidence suggesting ligamentous injury, particularly when prevertebral swelling is noted (Fig. 43-40). Most recommend MRI for patients with a strong clinical suggestion of an occult spine injury who have normal plain radiographs, including those with persistent neck pain or neurologic deficit. However, when CT findings are normal, some studies have demonstrated that MRI may not be necessary to exclude unstable injuries, even in the obtunded or "unreliable" patient.[47,48] A recent prospective study of the use of cervical spine CT in 402 obtunded patients reported a sensitivity of greater than 99%.[49] MRI, however, is useful in the evaluation of the previously traumatized spinal cord.[50] Progressive neurologic dysfunction in a previously stable cord-injury patient may indicate undiagnosed disk or bone impingement on the spinal cord, myelomalacia, a developing intramedullary (post-traumatic) syrinx, or subarachnoid cystic changes (Fig. 43-41), which can all be diagnosed by MRI. For fractures involving the transverse foramina or C1-C3, which are associated with vertebral artery dissection or thrombosis in up 22% of cases, as well as basilar artery stroke, magnetic resonance angiography (MRA), CT angiography (CTA), or four-vessel angiogram should be considered.[51]

MANAGEMENT

A spinal injury should be suspected in all trauma victims with an unknown or suggestive mechanism of injury associated with complaints of neck or back pain, evidence of significant head or facial trauma, spinal tenderness, signs of focal neurologic deficit, impaired consciousness, potentially distracting injuries, or unexplained hypotension (see Fig. 43-42 for management algorithm).

Spinal Column Stabilization

Out-of-Hospital Care

Paramedical personnel should suspect a spinal injury in any victim of trauma, especially those with craniofacial injuries caused by motor vehicle crashes, assaults, falls, and sports. Trauma victims may have an altered state of consciousness resulting from drug or alcohol intoxication, head trauma, or shock that makes cooperation difficult and spinal movement likely, unless steps are taken to immobilize the potentially traumatized spine.

www.ketabpezeshki.com 66485457-66963820

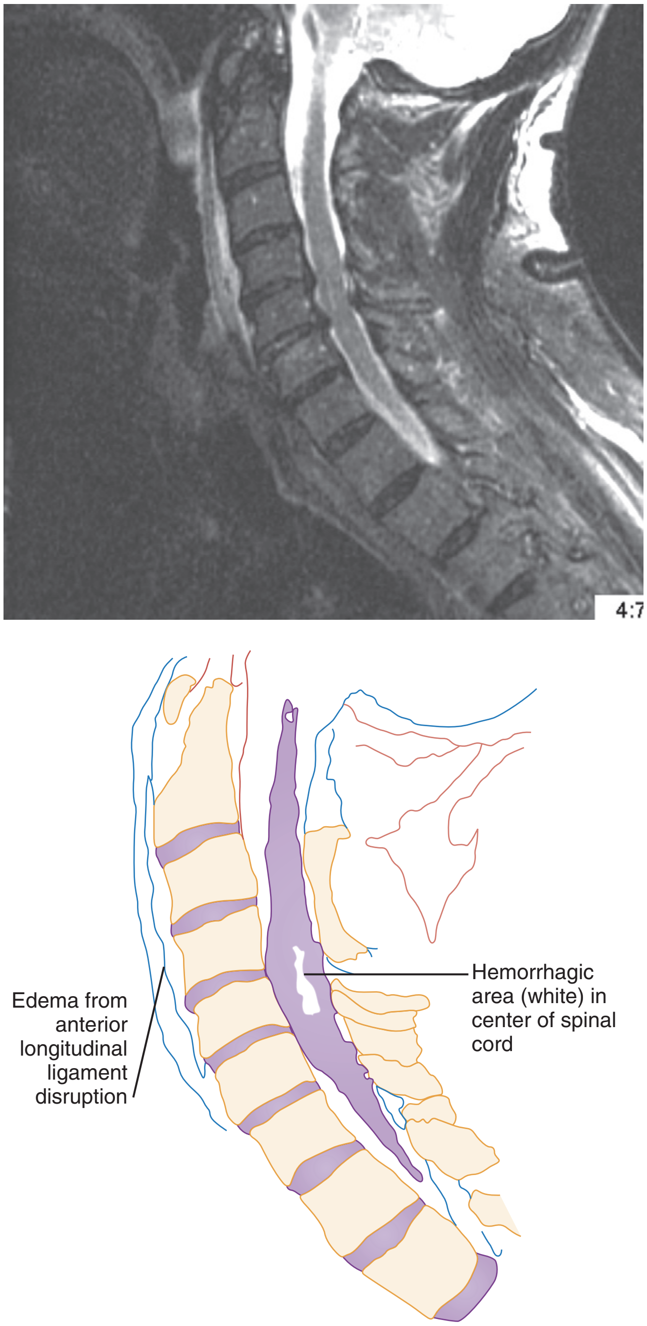


Figure 43-39. Magnetic resonance image showing a small area of central cord hemorrhage and both anterior and posterior ligamentous disruption.

Spinal immobilization should be initiated at the scene and maintained until a spinal injury is excluded in the emergency department. A variety of effective spinal immobilization orthoses are commercially available. The most widely used, and perhaps most effective, approach uses the combination of a spinal backboard, a rigid cervical collar, and supportive blocks placed on both sides of the head, which is held in place by straps or tape stretched across the forehead.[52-56] The heads of children younger than age 8 are somewhat large in proportion to their bodies, resulting in mild neck flexion when they are placed on a flat backboard. This can be avoided by use of a special backboard with an occipital recess or by placing a rolled sheet under the shoulders.[55] Further out-of-hospital care should be directed at evaluation and stabilization of associated injuries or problems requiring immediate intervention.

Emergency Department

Trauma victims who arrive at the emergency department with spinal immobilization should be quickly assessed by a physician. If the probability of spinal injury is moderate to high, it is advisable to remove the patient's clothes, evaluate any associated injuries, and perform resuscitative maneuvers without removing the immobilization apparatus. If the patient's spine can be clinically cleared by use of either the NEXUS criteria or the CCR, as described earlier, the immobilization device may be carefully removed. In addition, if the trauma victim was wearing a helmet and the helmet was not removed in the field, the face mask and/or the helmet may be carefully removed while immobilization is maintained.[56a] Ideally, at least two or three providers should be present to perform the task of helmet and face mask removal. The first provider should position himself or herself at the head of the bed and immobilize the cervical spine by placing both hands on the sides of the helmet while securing the patient's mandibles bilaterally. The chin strap should then be cut while a second provider takes over the job of in-line stabilization by placing one hand on the patient's occiput and another hand on the patient's chin. The first provider may then use a screwdriver to remove the four screws from the face mask and remove the face mask, which opens access to the airway. Note that face mask removal is all that is necessary to intubate the patient. The helmet and the shoulder pads should be removed simultaneously; one provider pulls the sides of the helmet away from the patient's ears while the second provider prevents hyperextension of the neck or overextension of the head onto the bed.[56b] Once the helmet and shoulder pads have been removed, a rigid collar should be placed if the patient's cervical spine cannot be cleared by use of the NEXUS criteria or the CCR.

Patients with probable spinal injury who are conscious and cooperative should be cautioned against attempted movement until radiographic studies have been performed. Patients who are uncooperative because of head injury, drug or alcohol intoxication, hypotension, or the presence of multiple painful injuries require a more aggressive approach, including consideration of the use of chemical sedation and mechanical restraints. Suspected thoracic and lumbar spinal injuries are best managed by keeping the patient supine and immobile. The goal of stabilization in cervical spine trauma is to immobilize both the neck and the body because any movement may extend the initial injury. If the patient is not already immobilized on a backboard, the torso should be firmly anchored to the examining table by straps or rolled sheets. A combative patient may require an assigned individual to hold the patient's head in alignment with the longitudinal axis of the body. Sedation, drug-induced paralysis, and intubation may be required for patients who pose a danger to themselves because of excessive movement. Spinal precautions should be maintained in patients with an altered sensorium until the presence of an injury can be excluded clinically or radiographically. Suctioning should be immediately available to prevent aspiration, and emergency department personnel must be aware of this ever-present possibility. When vomiting occurs, patients should immediately be placed on their side by logrolling, while spinal alignment is maintained, and suctioning performed.

Airway Management

The emergency physician should anticipate airway management problems in patients with cervical spinal injuries. Lesions above C3 may cause immediate respiratory paralysis, and the spread of edema from a lower injury may cause delayed phrenic nerve paralysis, as well as ascension of the neurologic injury above the level of C3. Cervical injuries may also be associated with airway obstruction from retropharyngeal hemorrhage or edema or maxillofacial

www.ketabpezeshki.com 66485457-66963820

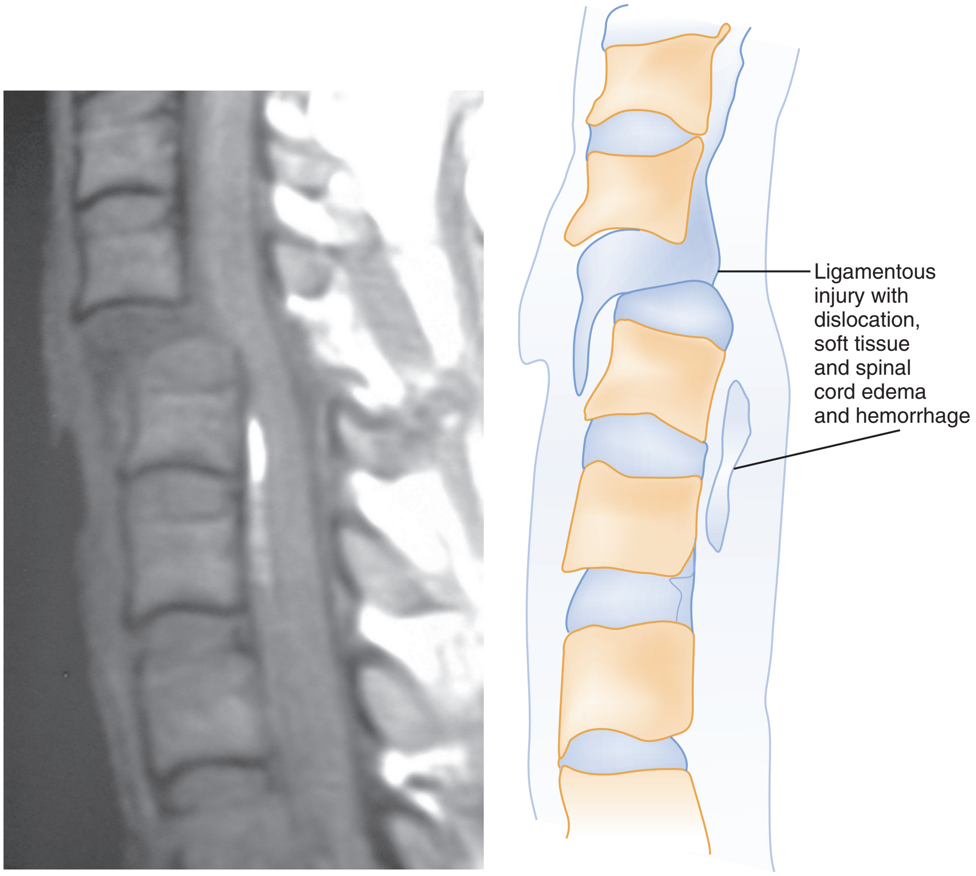


Figure 43-40. Anteroposterior longitudinal ligament disruption. A sagittal magnetic resonance image demonstrates ligamentous disruption between C4 and C5 with blood tracking in the anterior spinal canal.

trauma. In addition, acute pulmonary edema has also occurred after cervical spine injuries unassociated with significant head or chest injury.

According to the American College of Surgeons (ACS) Advanced Trauma Life Support guidelines, the preferred method of airway management for patients with traumatic cardiopulmonary arrest, even with evidence of spinal injury, is rapid sequence intubation (RSI) orotracheally with in-line spinal stabilization.[57] This is also the recommended approach for patients who are breathing but unconscious and in need of airway control or ventilatory support.[58-67] Hypoxia should be prevented, as it may contribute to apoptosis and further cord damage.[68]

The value of in-line spinal stabilization has been questioned in a review of the topic that notes that the data supporting its use come from cadaver studies, observations on uninjured volunteers, and several case series; that there is little evidence to support the contention that orotracheal intubation without in-line stabilization, which causes less spinal motion than the chin thrust maneuver, is unsafe in spinal-injured patients; that the incidence of spinal injury in trauma patients requiring intubation, who often have intracranial injuries, is quite low; and that there is evidence that in-line stabilization diminishes the laryngoscopic view, possibly leading to failed intubation and severe hypoxemia, which has been shown to predict poor outcomes in central nervous system injury.[69] The authors note that despite this information, clinicians will be hesitant to forgo in-line stabilization because it is recommended by the ACS and suggest that further studies in trauma airway management be performed with use of intubating supraglottic airways, optical stylets, and videolaryngoscopes. Cricothyrotomy or percutaneous jet ventilation should be considered for patients with severe maxillofacial injuries and when RSI is contraindicated or if attempts at orotracheal intubation fail (see Chapter 1).

Figure 43-41. Magnetic resonance image showing post-traumatic syrinx of the spinal cord.

www.ketabpezeshki.com 66485457-66963820

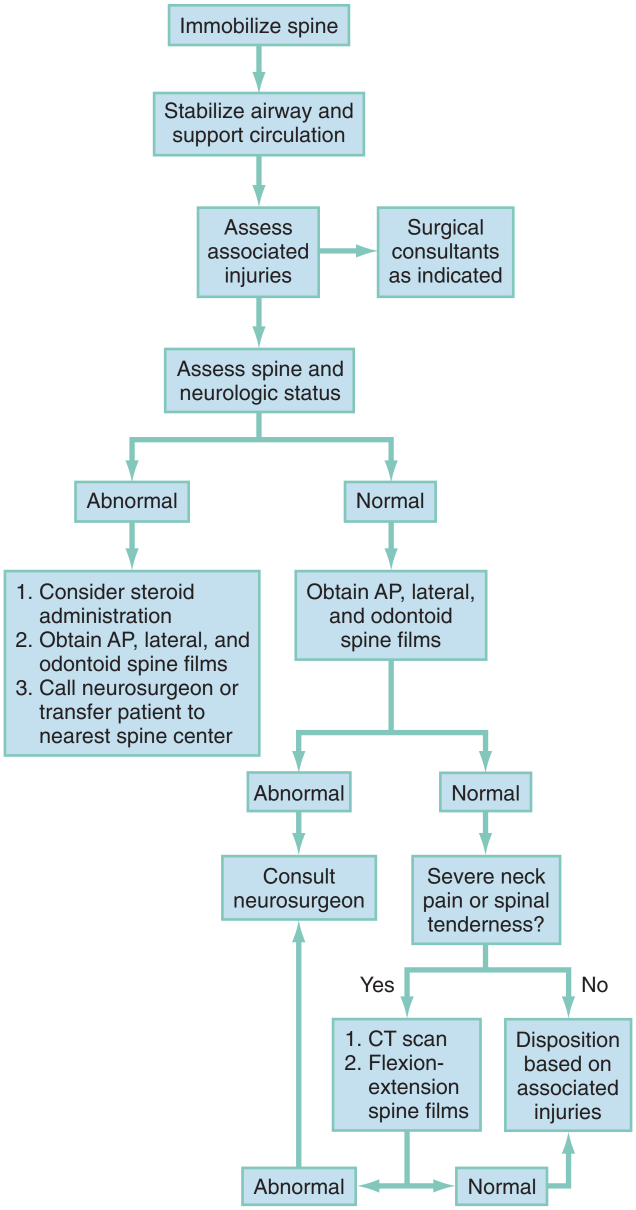


Figure 43-42. Approach to a patient with suspected cervical spine injury. *AP,* anteroposterior; *CT,* computed tomography.

Spinal Shock

Spinal shock is a clinical syndrome characterized by the temporary loss of neurologic function and autonomic tone below the level of an acute spinal cord lesion.[16] Patients usually exhibit flaccid paralysis with loss of sensation, deep tendon reflexes, and urinary retention, along with bradycardia, hypotension, hypothermia, and intestinal ileus. The cessation of spinal shock, which may last from less than 24 hours to more than 2 weeks,[70] is heralded by the return of the bulbocavernosus reflex.

Neurogenic hypotension secondary to spinal shock, caused by loss of vasomotor tone and lack of reflex tachycardia from disruption of autonomic ganglia, is a diagnosis of exclusion in the trauma victim. It should not be considered the cause of hypotension unless the patient is flaccid and areflexic; reflex tachycardia and peripheral vasoconstriction are absent; and, most important, the possibilities of coexisting hemorrhagic shock, cardiac tamponade, or tension pneumothorax have been eliminated. The absence of vasomotor activity in patients experiencing neurogenic hypotension can mask the usual presentation of these life-threatening injuries.

Although there is no consensus in the literature regarding the most appropriate treatment of neurogenic hypotension, it is prudent to begin the resuscitation of all newly arrived, hypotensive trauma victims with crystalloid fluid infusion. Most cases of pure neurogenic hypotension are mild (e.g., systolic blood pressure >90) and will initially respond to fluids. Severe (e.g., systolic blood pressure <70) neurogenic hypotension, seen in 20 to 30% of all patients with spinal injuries, usually occurs with high cervical injuries associated with total or near-total loss of neurologic function.[16] Hypotension can lead to hypoperfusion and secondary ischemic injury of the spinal cord, which can adversely affect prognosis. Therefore prolonged, severe hypotension must be prevented and treated.[71] Fluid resuscitation is often ineffective in such patients and may result in fluid overload if aggressively pursued. As a result, symptomatic neurogenic hypotension should be managed with fluids, Trendelenburg positioning (unless contraindicated because of concomitant head injury), vasopressors, or cardiac pacing—based on hemodynamic monitoring—once the diagnosis is established and other causes of traumatic shock have been excluded.

Pharmacologics for Incomplete Cord Injury

Experimental animal models of SCI support the concept that delayed biochemical damage, occurring hours to days after an initial traumatic insult, contributes to ongoing tissue loss and worsening neurologic function. As a result, numerous neuroprotective and neuroregenerative treatment strategies, including induction of hypothermia, have been investigated in both laboratory animal studies and human clinical trials (Box 43-1).[72-89]

Methylprednisolone is currently the only agent used for human victims of SCI outside of the research setting, and its use is highly controversial. The National Acute Spinal Cord Injury Study (NASCIS) investigators published several flawed studies showing that early administration of high-dose methylprednisolone improves the neurologic outcome of SCI victims.[77-80] Methylprednisolone is administered as an initial 30 mg/kg intravenous bolus followed by an infusion of 5.4 mg/kg/hr. The infusion is maintained for 24 hours in patients who are treated within 3 hours after injury, and it is maintained for 48 hours in patients who are treated within 3 to 8 hours after injury. The administration of steroids resulted in a worse outcome when started after 8 hours.

The NASCIS studies have been criticized for methodological flaws and for failing to assess whether the mild neurologic improvement seen in patients treated with methylprednisolone actually results in improved day-to-day functioning.[90,91] Moreover, other studies have reported that patients treated with methylprednisolone have a higher rate of infectious, gastrointestinal, and metabolic complications compared with placebo.[92] The most recent guidelines published by the Consortium for Spinal Cord Medicine (which includes the American Association of Neurological Surgeons, the American College of Emergency Physicians, the Congress of Neurological Surgeons, the American Association of Orthopaedic Surgeons, and the International Spinal Cord Society) in 2008 state that "no clinical evidence exists to definitively recommend the use of any neuroprotective pharmacologic agent, including steroids, in the treatment of acute SCI to improve functional recovery."[93] Despite this, the *Cochrane Database* review maintains that "high-dose methylprednisolone steroid therapy is the only pharmacologic therapy shown to have efficacy in a Phase Three randomized trial when it can be administered within 8 hours of injury…and…there may be additional benefit by extending the maintenance dose from 24 to 48 hours if treatment is not started until between 3 and 8 hours after injury."[94] Surveys performed in

www.ketabpezeshki.com 66485457-66963820

Box 43-1 Treatment Strategies for Acute Spinal Cord Injury Currently under Investigation

A. Reduce the effects of the damage
 1. Maintain circulation
 2. Maintain oxygenation
 3. Reduce neurotoxins and free radicals (methylprednisolone, glutamate receptor antagonists)
 4. Reduce inflammation (cytokine, Rho, interleukin-10, tumor necrosis factor blockers)
 5. Reduce apoptosis (nitric oxide inhibitors, calpains)
 6. Cooling with induction of hypothermia
B. Encourage correct neuron function and connections
 1. With cells
  a. Schwann cells
  b. Olfactory ensheathing glial cells
  c. Astrocytes
  d. Reengineered fibroblasts
  e. Macrophages
  f. Oligodendrocyte precursors
  g. Electrical stimulation
 2. With matrix modifiers
  a. Netrins
  b. Neural glues (polyethylene glycol [PEG], synthetic hydrogels)
 3. With nerve grafts
  a. Peripheral nerve implants
C. Enhance regeneration and axon growth
 1. Inhibitor neutralizing antibody
  a. Anti-Nogo
 2. Neurotrophin-3
 3. Acidic fibroblast growth factor
 4. Brain-derived neurotropic factor
 5. Rho antagonists
D. Replace lost nerve cells
 1. Fetal tissue
 2. Stem cells
E. Inhibit scar and gliosis formation
 1. Decorin
 2. Chondroitinases
F. Reduce neurocircuit deficits
 1. Potassium channel blockers
 2. Sodium channel blockers
 3. Glutamate receptor blockers

Adapted from Cappuccino A, et al: The use of systemic hypothermia for the treatment of an acute cervical spinal cord injury in a professional football player. Spine (Phila Pa 1976) 35:E57, 2010.

the United States, the United Kingdom, and Canada between 2006 and 2009 reveal the number of spine surgeons using steroids to treat patients with blunt SCI diminishing to a minority in recent times, with many of those still using steroids listing "fear of litigation" as the reason.[93-96] Some authors continue to support the use of steroids until more effective treatments are discovered, feeling that the effectiveness of steroids in this setting has not been definitely disproved and that the majority of complications associated with steroid use in otherwise healthy young adults are most often minor and manageable.[97-101] There is currently no substantive scientific evidence to support the use of prednisolone for acute blunt SCI, and because of the possibility of severe complications and side effects[92,102,103] its use can be considered only, at best, a treatment option rather than the treatment standard. A risk-benefit assessment should be performed on a case-by-case basis.

Associated Injuries

Cardiopulmonary

Although deterioration in a trauma victim's cardiopulmonary status is usually the result of hemorrhagic shock or direct injury to the heart or lungs, it may reflect the development of pulmonary edema that occasionally occurs in response to brain injury and SCI.[104] Spinal cord trauma may stimulate an intense sympathetic discharge with two subsequent effects. First, pulmonary capillary endothelial cells are disrupted, leading to the pulmonary capillary leak syndrome, in which pulmonary edema occurs in the presence of normal pulmonary artery pressures (<18 mm Hg). Second, marked increases in afterload may cause left ventricular dysfunction, leading to pulmonary edema associated with a high pulmonary artery pressure (>18 mm Hg). Aggressive fluid resuscitation can also contribute to pulmonary edema. As a result, the management of such patients is often complex and requires carefully balancing fluid requirements, afterload-reducing agents, and artificial ventilation with positive end-expiratory pressure.[97] In addition, because of the autonomic dysfunction that often occurs in response to SCI, patients may demonstrate extremely volatile fluctuations in blood pressure, sometimes resulting in a life-threatening hypertensive emergency.

Gastrointestinal and Genitourinary

If SCI renders the abdominal examination unreliable, an abdominal CT scan, ultrasound, diagnostic peritoneal lavage, or some combination is often necessary.[105] In the acute stages of SCI, both the gastrointestinal tract and the bladder become atonic. Thus, once a patient has been stabilized, a nasogastric tube should be placed to prevent gastric distention, and a Foley catheter inserted to prevent bladder distention and to monitor fluid output. Because gastrointestinal bleeding from stress ulcers occurs in 2 to 20% of spinal trauma patients,[106] ulcer prophylaxis with histamine H_2 receptor antagonists or proton pump inhibitors should be initiated.[93]

Skin

Denervated skin is extremely susceptible to pressure necrosis, and sores can develop in less than 1 hour on unpadded spinal carts. Therefore backboards should be removed as soon as possible after spinal stabilization has been achieved. Padding pressure areas with sheepskin or foam padding early in the course of therapy can help minimize decubitus ulcers.

Definitive Treatment and Prognosis

The role of immediate surgical intervention in the management of spinal injuries is currently limited to relieving impingement on the spinal cord caused by foreign bodies, herniated disks, bony fracture fragments, or an epidural hematoma.[101,107] Surgery may be necessary later to stabilize severe bony injuries or to reduce spinal dislocations. The timing of surgical intervention is controversial, and there are no well-designed studies that have determined whether early (<12 hours) versus late decompression is beneficial.[93]

Once almost uniformly fatal, major spinal injury caused death as a result of pulmonary complications or sepsis resulting from skin necrosis or urinary infection. The advent of antibiotic therapy made long-term survival not only possible but also expected. Today, patients with SCIs are best managed by early referral to a regional spine injury center, where a team of neurosurgeons, orthopedic surgeons, psychologists, and physical therapists can initiate rehabilitation. Specialized SCI treatment centers offer patients a chance to return to a productive life within the limits of their disability. With the exception of patients with high cervical lesions (above C5), most patients attain sufficient independence to live outside of a high-level care environment.[109]

www.ketabpezeshki.com 66485457-66963820

DISPOSITION

Cervical Sprain

Patients with musculoskeletal injuries of the spine who have only mild to moderate discomfort without neurologic impairment or abnormal radiographic findings are best managed as outpatients. Treatment should include analgesics and referral for follow-up evaluation. Up to 27% of patients experiencing neck pain in the emergency department after trauma will continue to have symptoms at 1 year.[110,111]

Minor Fractures

Most patients with spinal fractures require hospitalization. Patients with isolated cervical vertebral body compression fractures or spinous process fractures may be managed as outpatients if the mechanism of injury is not significant, there is no evidence of neurologic impairment or associated ligamentous instability, and the degree of patient distress is not severe. Appropriate follow-up should be arranged in all instances because even minor spinal injuries may be associated with prolonged disability resulting from chronic pain.[110-114]

For patients with minor wedge fractures (<10% wedge fractures) who do not have an associated ileus or neurologic deficit, outpatient management may also be possible. However, most wedge fractures of the thoracic and lumbar spine are usually best managed in the hospital for several reasons.[115,116] First, patients with these injuries usually have marked discomfort, often requiring parenteral narcotics. Second, significant force is generally required to fracture thoracic or lumbar vertebrae, and associated intrathoracic or abdominal injuries are common. Elderly patients who have vertebral fractures and only minor associated injuries may require admission to facilitate assessment of fall risks and to expedite rehabilitation. Finally, lower thoracic and lumbar fractures are associated with prolonged and occasionally delayed gastrointestinal ileus, requiring continuous nasogastric suction.

KEY CONCEPTS

- Victims of motor vehicle collisions, falls from heights, and sports-related injuries should have their entire spines examined for evidence of injury. Spinal radiographs should be obtained in the presence of suggestive symptoms or signs, or when an abnormal mental status or distracting injuries hamper clinical assessment.
- To prevent inadvertent movement of the spinal column, spinal precautions should be maintained in patients with altered mentation until the presence of a spinal injury can be excluded either clinically or radiographically.
- Evidence that high-dose methylprednisolone is a clinically efficacious intervention in the management of acute blunt partial SCI is lacking, and because of the possibility of severe side effects, its use can only be considered, at best, an option.
- Emergency department management includes prevention of secondary ischemic spinal cord injury by maintaining adequate oxygenation and avoiding hypotension; care should also be taken to prevent pressure ulcers, bladder distention, and gastric distention.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Spinal Cord Information Network: *Spinal Cord Injury: Facts and Figures at a Glance*. Available at https://www.nscisc.uab.edu. Last updated February 2010.
2. Berkowitz M: Assessing the socioeconomic impact of improved treatment of head and spinal cord injuries. *J Emerg Med* 1993; 11:63
3. Snell RS, Smith MS, eds: *Clinical Anatomy for Emergency Medicine*. St Louis: Mosby; 1993.
4. Demetriades D, Newton E: *Atlas of Emergency Trauma*, 2nd ed. Cambridge UK: Cambridge University Press; 2011.
5. Looby S, Flaanders A: Spine trauma. *Radiol Clin North Am* 2011; 49:129-163.
6. Harris JH, Harris WH, eds: *The Radiology of Emergency Medicine*, 4th ed. Philadelphia: Lippincott, Williams & Wilkins, 2000.
7. Maroon JC, Abla AA: Classification of acute spinal cord injury, neurological evaluation and neurosurgical considerations. *Crit Care Med* 1987; 3:655.
8. Guthkelch AN, Fleischer AS: Patterns of cervical spine injury and their associated lesions. *West J Med* 1987; 147:428.
9. Ankeny DP, Popovich PG: Mechanisms and implications of adaptive immune responses after traumatic spinal cord injury. *Neuroscience* 2009; 158:1112.
10. Matis GK, Birbilis TA: Erythropoietin in spinal cord injury. *Eur Spine* 2009; 18:314.
11. Darian-Smith C: Synaptic plasticity, neurogenesis, and functional recovery after spinal cord injury. *Neuroscientist* 2009; 15:149.
12. Sinclair D, Schwartz M, Gruss J, McLellan B: A retrospective review of the relationship between facial fractures, head injuries and cervical spine injuries. *J Emerg Med* 1988; 6:109.
13. Tator CH: *Management of associated spine injures in head injured patients*. In: Narayan RK, Wilberger JE, Poulishock JT, eds. *Neurotrauma*. New York: McGraw-Hill; 1996.
14. Ditunno JF, Little JW, Tessler A, Burns AS: Spinal shock revisited: A four phase model. *Spinal Cord* 2004; 42:383.
15. Merriam WF, Taylor TK, Ruff SJ, McPhail MJ: A reappraisal of acute traumatic central cord syndrome. *J Bone Joint Surg Br* 1986; 68:708.
16. Atkinson PP, Atkinson LD: Spinal shock. *Mayo Clin Proc* 1996; 71:384.
17. Pang D, Pollack IF: Spinal cord injury without radiographic abnormality in children—the SCIWORA syndrome. *Trauma* 1989; 29:658.
18. Kokoska ER, Keller MS, Rallo MC, Weber TR: Characteristics of pediatric cervical spine injures. *J Pediatr Surg* 2001; 36:10.
19. Apuzzo ML: Spinal cord injury without radiographic abnormality. *Neurosurgery* 2002; 50:S100.
20. McCaig LF, Burt CW: National Hospital Ambulatory Medical Care Survey: 2003 emergency department summary. *Adv Data* 2006; 358:1.
21. Stiell IG, et al: Variation in emergency department use of cervical spine radiography for alert, stable trauma patients. *CMAJ* 1997; 156:1537.
22. Hoffman JR, Mower WR, Wolfson AB, Todd KH, Zucker MI: Validity of a set of clinical criteria to rule out injury to the cervical spine in patients with blunt trauma. *N Engl J Med* 2000; 343:94.
23. Stiell IG, et al: The Canadian C-spine Rule for radiography in alert and stable trauma patients. *JAMA* 2011; 286:1841.
24. West OC, Anbari MM, Pilgram TK, Wilson AJ: Acute cervical spine trauma: Diagnostic performance of single-view versus three-view radiographic screening. *Radiology* 1997; 204:819.
25. Petri R, Gimbel R: Evaluation of the patient with spinal trauma and back pain: An evidence based approach. *Emerg Med Clin North Am* 1999; 17:25.
26. Mower WR, et al: Use of plain radiography to screen for cervical spine injuries. *Ann Emerg Med* 2001; 38:1.
27. Cadoux CG, White JD, Hedberg MC: High-yield roentgenographic criteria for cervical spine injuries. *Ann Emerg Med* 1987; 16:738.
28. Fesmire FM, Luten RC: The pediatric cervical spine: Developmental anatomy and clinical aspects. *J Emerg Med* 1989; 7:133.
29. Mann FA, et al: Supine oblique views of the cervical spine: A poor proxy for the lateral view. *Emerg Radiol* 1995; 2:214.
30. Bagley LJ: Imaging of spinal trauma. *Radiol Clin North Am* 2006; 44:1.
31. Pollack C, et al: Use of flexion-extension radiographs of the cervical spine in blunt trauma. *Ann Emerg Med* 2001; 38:8.
32. Khan SN, Erickson G, Sena MJ, Gupta MC: Use of flexion and extension radiographs of the cervical spine to rule out acute instability in patients with negative computed tomography scans. *J Orthop Trauma* 2011; 25:132.
33. Panacek EA, Mower WR, Holmes JF, Hoffman JR; NEXUS Group: Test performance of the individual NEXUS low-risk clinical screening criteria for cervical spine injury. *Ann Emerg Med* 2001; 38:22.
34. Pitt E, Thakore S: Role of flexion/extension radiography in neck injuries in adults. *Emerg Med J* 2004; 21:587.
35. Murphey MD, Batnitzky S, Bramble JM: Diagnostic imaging of spinal trauma. *Radiol Clin North Am* 1989; 27:855.
36. Domenicucci M, et al: Three-dimensional computed tomographic imaging in the diagnosis of vertebral column trauma: Experience based on 21 patients and review of the literature. *J Trauma* 1997; 42:254.
37. Acheson MB, Livingston RR, Richardson ML, Stimac GK: High-resolution CT scanning in the evaluation of cervical spine fractures: Comparison with plain film examinations. *Am J Radiol* 1987; 148:1179.
38. Schleehauf K, Ross SE, Civil ID, Schwab CW: Computed tomography in the initial evaluation of the cervical spine. *Ann Emerg Med* 1989; 18:815.
39. Como JJ, et al: Practice management guidelines for identification of cervical spine injuries following trauma: Update from the Eastern Association for the Surgery of Trauma practice management guidelines committee. *J Trauma* 2009; 67:651.
40. Antevil JL, et al: Spiral computed tomography for the initial evaluation of spine trauma: A new standard of care? *J Trauma* 2006; 61:382.
41. McCulloch PT, et al: Helical computed tomography alone compared with plain radiographs with adjunct computed tomography to evaluate the cervical spine after high-energy trauma. *J Bone Joint Surg Am* 2005; 87:2388.
42. Holmes JF, Akkinepalli R: Computed tomography versus plain radiography to screen for cervical spin injury: A meta-analysis. *J Trauma* 2005; 58:902.
43. Widder S, et al: Prospective evaluation of computed tomographic scanning for the spinal clearance of obtunded trauma patients: Preliminary results. *J Trauma* 2004; 56:1179.
44. Reference deleted in proofs.
45. Holmes JF, et al: Variability in computed tomography and magnetic resonance imaging in patients with cervical spine injuries. *J Trauma* 2002; 53:524.
46. Dunham CM, Brocker BP, Collier BD, Gemmel DJ: Risks associated with magnetic resonance imaging and cervical collar in comatose, blunt trauma patients with negative comprehensive cervical spine computed tomography and no apparent spinal deficit. *Crit Care* 2008; 12:R89.
47. Schuster R, et al: Magnetic resonance imaging is not needed to clear cervical spines in blunt trauma patients with normal computed tomographic results and no motor deficits. *Arch Surg* 2005; 140:762.
48. Hogan GJ, Mirvis SE, Shanmuganathan K, Scalea TM: Exclusion of unstable cervical spine injury in obtunded patients with blunt trauma: Is MR imaging needed when multi-detector row CT findings are normal? *Radiology* 2005; 237:106.
49. Hennessy D, et al: Cervical spine clearance in obtunded trauma patients: A prospective study. *J Trauma* 2010; 68:576.
50. Pimentel L, Diegelmann L: Evaluation and management of acute cervical spine trauma. *Emerg Med Clin North Am* 2010; 28:719-738.
51. Cothren C, et al: Cervical spine fracture patterns predictive of blunt vertebral artery injury. *J Trauma* 2003; 55:811-813.
52. Solot JA, Winzelberg GG: Clinical and radiographic evaluation of vertebrae extrication collars. *J Emerg Med* 1990; 8:79.
53. Chandler DR, Nemejc C, Adkins RH, Waters RL: Emergency cervical spine immobilization. *Ann Emerg Med* 1992; 21:1185.
54. Apuzzo ML: Cervical spine immobilization before admission to the hospital. *Neurosurgery* 2002; 50:S7.
55. Apuzzo ML: Management of pediatric cervical spine and spinal cord injuries. *Neurosurgery* 2002; 50:S85.
56. DeLorenzo RA: A review of spinal immobilization techniques. *J Emerg Med* 1996; 14:603.

56a. Waninger KN: Management of the helmeted athlete with suspected cervical spine injury. *Am J Sports Med* 2004; 32:1331-1350.

56b. Peris MD, Donaldson WF 3rd, Towers J, Blanc R, Mussonigro TS: Helmet and shoulder pad removal in suspected cervical spine injury: human control model. *Spine (Phila Pa 1976)* 2002; 27:995-999.

57. American College of Surgeons: *ATLS: Advanced Trauma Life Support Student Course Manual*, 8th ed. Chicago: American College of Surgeons; 2008.
58. Ghafoor AU, Martin TW, Gopalakrishnan S, Viswamitra S: Caring for the patients with cervical spine injuries: What have we learned? *J Clin Anesth* 2005; 17:640.
59. Ollerton JE, Parr MJ, Harrison K, Hanrahan B, Sugrue M: Potential cervical spine injury and difficult airway management for emergency intubation of trauma adults in the emergency department—a systematic review. *Emerg Med J* 2006; 23:3.
60. Crosby ET: Airway management in adults after cervical spine trauma. *Anesthesiology* 2006; 104:1293.

www.ketabpezeshki.com 66485457-66963820

61. Bivins HG, Ford S, Bezmalinovic Z, Price HM, Williams JL: The effect of axial traction during orotracheal intubation of the trauma victim with an unstable cervical spine. *Ann Emerg Med* 1988; 17:25.
62. Rhee KJ, O'Malley RJ: Neuromuscular blockade-assisted oral intubation versus nasotracheal intubation in the prehospital care of injured patients. *Ann Emerg Med* 1994; 23:37.
63. Talucci RC, Shaikh KA, Schwab CW: Rapid sequence induction with oral endotracheal intubation in the multiply injured patient. *Am Surg* 1988; 54:185.
64. Holley J, Jordon R: Airway management in patients with unstable cervical spine fractures. *Ann Emerg Med* 1989; 18:1237.
65. Rhee KJ, Green W, Holcroft JW, Mangili JA: Oral intubation in the multiply injured patient: The risk of exacerbating spinal cord damage. *Ann Emerg Med* 1990; 19:511.
66. Wright SW, Robinson GG 2nd, Wright MB: Cervical spine injuries in blunt trauma patients requiring emergent endotracheal intubation. *J Emerg Med* 1992; 10:104.
67. Scannell G, Waxman K, Tominaga G, Barker S, Annas C: Orotracheal intubation in trauma patients with cervical fractures. *Arch Surg* 1993; 128:903.
68. Bilello JF, et al: Cervical spinal cord injury and the need for cardiovascular intervention. *Arch Surg* 2003; 138:1127.
69. Manoach S, Paladino L: Manual in-line stabilization of suspected cervical spine injury: Historical review and current questions. *Ann Emerg Med* 2007; 50:236.
70. Srivastava R: Spinal shock in spinal cord injury—is duration level dependent? *J Bone Joint Surg* 2006; 88:144.
71. Sekhan L, Fehlings MG: Epidemiology, demographics, and pathophysiology of acute spinal cord injury. *Spine* 2001; 26:S2-S12.
72. Straley KS, Foo CW, Heilshorn SC: Biomaterial design strategies for the treatment of spinal cord injuries. *J Neurotrauma* 2009; 27:1.
73. Bracken MB: Pharmacological treatment of acute spinal cord injury: Current status and future projects. *J Emerg Med* 1993; 11:43.
74. Xu XM, Onifer SM: Transplantation-mediated strategies to promote axonal regeneration following spinal cord injury. *Respir Physiol Neurobiol* 2009; 169:171.
75. Cappuccino A, et al: The use of systemic hypothermia for the treatment of an acute cervical spinal cord injury in a professional football player. *Spine (Phila Pa 1976)* 2010; 35:E57.
76. Geisler FH, Dorsey FC, Coleman WP: Past and current clinical studies with GM-1 ganglioside in acute spinal cord injury. *Ann Emerg Med* 1993; 22:1041.
77. Bracken MB, et al: A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal cord injury. *N Engl J Med* 1990; 322:1405.
78. Bracken MB, et al: Methylprednisolone or naloxone treatment after acute spinal cord injury: 1-year follow-up data. Results of the second National Acute Spinal Cord Injury Study. *J Neurosurg* 1992; 76:23.
79. Bracken MB, et al: Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. *JAMA* 1997; 277:20.
80. Bracken MB, et al: Methylprednisolone or tirilizad mesylate administration after acute spinal cord injury: 1-year follow-up. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. *J Neurosurg* 1998; 89:699.
81. Faden AI, Stoica B: Neuroprotection: Challenges and opportunities. *Arch Neurol* 2007; 64:794.
82. Qaio F, et al: Complement plays an important role in spinal cord injury and represents a therapeutic target for improving recovery following trauma. *Am J Pathol* 2006; 169:1039.
83. Brewer KL, Hardin JS: Neuroprotective effects of nicotinamide after experimental spinal cord injury. *Acad Emerg Med* 2004; 11:125.
84. Nikulina E, Tidwell JL, Dai HN, Bregman BS, Filbin MT: The phosphodiesterase inhibitor rolipram delivered after a spinal cord lesion promotes axonal regeneration and functional recovery. *Proc Natl Acad Sci U S A* 2004; 101:8786.
85. Hata K, et al: RGMa inhibition promotes axonal growth and recovery after spinal cord injury. *J Cell Biol* 2006; 173:47.
86. Nakayama T, et al: Atrial natriuretic peptide reduces ischemia/reperfusion-induced spinal cord injury in rats by enhancing sensory neuron activation. *J Pharmacol Exp Ther* 2007; 322:582.
87. Cao Q, et al: Functional recovery in traumatic spinal cord injury after transplantation of multineurotrophin-expressing glial-restricted precursor cells. *J Neurosci* 2005; 25:6947.
88. Fuller DD, Johnson SM, Olson EB Jr, Mitchell GS: Synaptic pathways to phrenic motoneurons are enhanced by chronic intermittent hypoxia after cervical spinal cord injury. *J Neurosci* 2003; 23:2993.
89. Donovan WH: Spinal cord injury—past, present and future. *J Spinal Cord Med* 2007; 30:85.
90. Coleman WP, et al: A critical appraisal of the reporting of the National Acute Spinal Cord Injury Studies (II and III) of methylprednisolone in acute spinal cord injury. *J Spinal Disord* 2000; 13:185.
91. Nesathurai S: Steroids and spinal cord injury: Revisiting the NASCIS 2 and NASCIS 3 trials. *J Trauma* 1998; 45:1088.
92. Matusmoto T, et al: Early complications of high-dose methylprednisolone sodium succinate treatment in the follow-up of acute cervical spinal cord injury. *Spine (Phila Pa 1976)* 2001; 26:426.
93. Consortium for Spinal Cord Medicine: *Early Acute Management in Adults with Spinal Cord Injury: A Clinical Practice Guideline for Healthcare Providers*. Washington, DC: Consortium for Spinal Cord Medicine; 2008.
94. Bracken MB: Steroids for acute spinal cord injury. *Cochrane Database Syst Rev* 2002; 2:CD001046 (updated 2007).
95. Eck JC, Nachtigall D, Humphreys SC, Hodges SD: Questionnaire survey of spine surgeons on the use of methylprednisolone for acute spinal cord injury. *Spine (Phila Pa 1976)* 2006; 31:E250.
96. Frampton AE, Eynon CA: High dose methylprednisolone in the immediate management of acute, blunt spinal cord injury: What is the current practice in emergency departments, spinal units and neurosurgical units in the UK? *Emerg Med J* 2006; 23:550.
97. Hurlbert RJ, Hamilton MG: Methylprednisolone for acute spinal cord injury: 5-year practice reversal. *Can J Neurol Sci* 2008; 35:41.
98 Nicholas JS, Selassie AW, Lineberry LA, Pickelsimer EE, Haines SJ: Use and determinants of the methylprednisolone protocol for traumatic spinal cord injury in South Carolina acute care hospitals. *J Trauma* 2009; 66:1446, 2009.
99. Rozet IR: Methylprednisolone in acute spinal cord injury: Is there any other ethical choice? *J Neurosurg Anesthesiol* 2008; 20:137.
100. Walsh KA, Weant KA, Cook AM: Potential benefits of high-dose methylprednisolone in acute spinal cord injuries. *Orthopedics* 2010; 33:249.
101. Liu JC, Patel A, Vaccaro AR, Lammertse DP, Chen D: Methylprednisolone after traumatic spinal cord injury: Yes or no? *PM R* 2009; 1:669.
102. Suberviola B, González-Castro A, Llorca J, Ortiz-Melón F, Miñambres E: Early complications of high-dose methylprednisolone in acute spinal cord injury patients. *Injury* 2008; 39:748.
103. Ito Y, Sugimoto Y, Tomioka M, Kai N, Tanaka M: Does high dose methylprednisolone sodium succinate really improve neurological status in patients with acute cervical cord injury? A prospective study about neurological recovery and early complications. *Spine (Phila Pa 1976)* 2009; 34:2121.
104. Lemons VR, Wagner FC: Respiratory complications after cervical spinal cord injury. *Spine (Phila Pa 1976)* 1994; 19:2315.
105. Soderstrom CA, McArdle DQ, Ducker TB, Militello PR: The diagnosis of intra-abdominal injury in patients with cervical cord trauma. *J Trauma* 1983; 23:1061.
106. Matsumura JS, et al: Gastrointestinal tract complications after acute spine injury. *Arch Surg* 1995; 130:751.
107. Vaccaro AR, et al: Neurologic outcome of early versus late surgery for cervical spinal cord injury. *Spine (Phila Pa 1976)* 1997; 22:2609.
108. Reference deleted in proofs.
109. Mizra SK, et al: Early versus delayed surgery for acute cervical spinal cord injury. *Clin Orthop Relat Res* 1999; 359:104.
110. Dollfus P: Rehabilitation following injury to the spinal cord. *J Emerg Med* 1993; 11:57.
111. McNamara RM, O'Brien MC, Davidheiser S: Post-traumatic neck pain: A prospective and follow-up study. *Ann Emerg Med* 1988; 17:906.
112. Atherton K, et al: Predictors of persistent neck pain after whiplash injury. *Emerg Med J* 2006; 23:195.
113. Ditunno JF, Formal CS: Chronic spinal cord injury. *N Engl J Med* 1994; 330:550.
114. Ross PD: Clinical consequences of vertebral fractures. *Am J Med* 1997; 103:305.
115. Savitsky E, Votey S: Emergency department approach to acute thoracolumbar spine injury. *J Emerg Med* 1996; 15:49.
116. Vollmer DE, Gegg C: Classification and acute management of thoracolumbar fractures. *Neurosurg Clin N Am* 1997; 8:499.

www.ketabpezeshki.com 66485457-66963820

Chapter 44

Neck

Kim Newton and Ilene Claudius

PERSPECTIVE

Neck trauma can result in a spectrum of injuries and complications ranging from incidental to life-threatening, including hemorrhagic shock, acute neurologic injury, and airway obstruction. Vascular and laryngeal injuries can rapidly compromise the airway, challenging the most experienced physician. Stable-appearing patients may harbor insidious injuries associated with high morbidity and mortality if not recognized and treated in a timely manner. Emergency physicians should be familiar with neck anatomy, the spectrum of injuries and subtle presentations associated with neck trauma, as well as diagnostic evaluation, management controversies, and airway salvage techniques.

Neck trauma is divided into three major mechanisms: blunt, penetrating, and strangulation or near hanging. The injuries caused by these mechanisms can be further categorized into injuries of the airway (laryngotracheal), digestive tract (pharyngoesophageal), vascular system, and neurologic system. Each of these types of injuries has unique features and is discussed separately.

PRINCIPLES OF DISEASE

Pathophysiology

Penetrating Trauma

The incidence of neck trauma is reported to be 0.55 to 5% of all traumatic injuries. Neck trauma typically results from one of three major mechanisms: gunshot wounds (GSWs), stab wounds (SWs), and miscellaneous injuries, including impalement and shrapnel wounds.[1,2] GSWs are further divided into high-velocity and low-velocity injuries. High-velocity missiles include military-style weapons and hunting rifles that can achieve bullet velocities of 2000 to 3200 ft/s or greater. These missiles can easily penetrate soft tissue or bone. Their pathway is generally direct and predictable unless deflected, although they can also cause remote injuries through a blast effect. Bone penetration requires a minimum velocity of 350 ft/s. Low-velocity injuries (small-caliber handguns and air guns) are caused by missiles that travel at significantly slower velocities (e.g., 300 ft/s for .22-caliber pistols). Slower-moving missiles tend to produce erratic pathways, often demonstrating no direct relationship to the entrance or exit wounds.[3] Blast or cavitation effect pertains mainly to moderate- or high-velocity missiles (>1100 ft/s). *Cavitation* refers to the immediate release of kinetic energy as the bullet enters the tissue. This energy release causes temporary displacement of the surrounding tissue with cavity formation along the bullet's pathway. Cavitation can cause extensive soft tissue damage beyond that caused directly by the bullet.

The neck zone and mechanism of injury should be noted because lower-energy injuries (knife, handgun, or long-range birdshot or buckshot) cause a 50% lower incidence of clinically significant lesions (Fig. 44-1).[4] Zone I and III injuries pose a greater surgical challenge, and clinicians are more likely to order preoperative diagnostic tests to determine the best surgical approach (Table 44-1).[4]

SWs, being of very low velocity compared with missiles and most often limited to one side of the neck, are more amenable to nonsurgical management. Miscellaneous penetrating neck wounds can occur from any object capable of impalement, puncture, or laceration but most often result from glass fragments after motor vehicle collisions (MVCs) or from dog bites. The overall mortality rate for penetrating neck injuries is 2 to 6%, and the leading cause of immediate death is exsanguination.[1,5]

Blunt Trauma

Blunt neck trauma most frequently results from MVCs but can occur after assaults, "clothesline" injuries, strangulation, and sports injuries.[6] Blunt vascular injuries are rare[7] but represent some of the most underdiagnosed injuries seen by emergency physicians and trauma surgeons.[4] Blunt injuries to the aerodigestive and vascular tracts are uncommon compared with penetrating injuries but can cause acute airway compromise and serious delayed complications.

Anatomy

The neck is a complex, closed anatomic area dense with vital structures and invested with fascia creating several compartments. Because of this close anatomic relationship, vascular injury with hemorrhage may be tamponaded by fascial planes and neighboring structures but can lead to marked anatomic distortion, making evaluation and airway management extremely difficult. Two methods are used to describe the external neck: zones and triangles.[8] Anatomically, the neck has been divided into triangles (anterior and posterior). The *anterior triangle* is laden with vital structures (neurovascular and aerodigestive tracts) and is bordered anteriorly by the midline, posteriorly by the sternocleidomastoid muscle, and superiorly by the lower edge of the mandible. The *posterior triangle* is located within the boundaries of the sternocleidomastoid muscle anteriorly, the clavicle inferiorly, and the anterior border of the trapezius muscle posteriorly. Excluding spinal trauma, injury to this region often has a more favorable prognosis because of the relative paucity of vital structures.

Current practice favors division of the neck into zones I, II, and III. The widespread acceptance that many injuries span multiple

www.ketabpezeshki.com 66485457-66963820

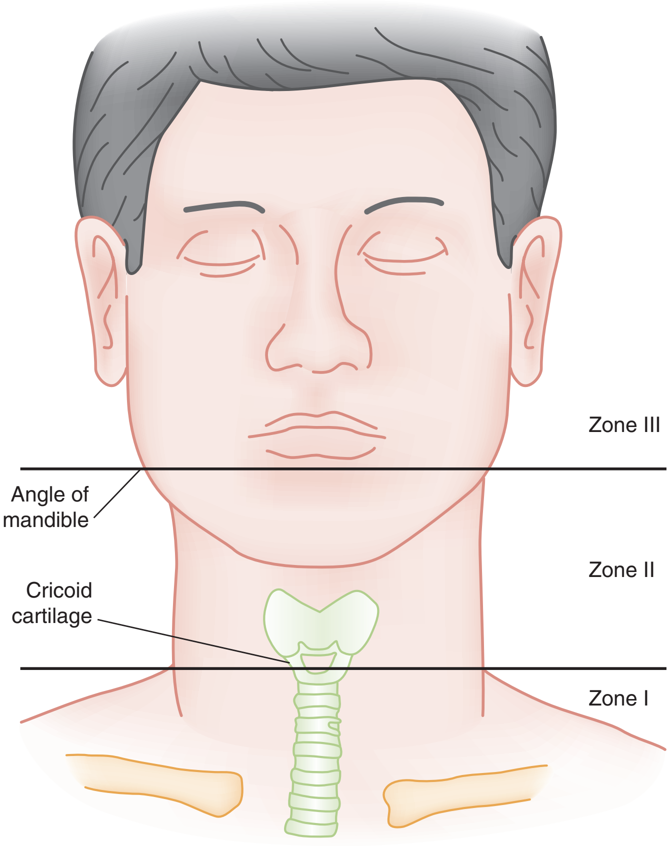


Figure 44-1. Zones of the neck.

Box 44-1 Vascular and Other Contents in Neck Zones

Zone I
Proximal common carotid artery
Vertebral artery
Subclavian artery
Major vessels of upper mediastinum
Apices of lungs
Esophagus
Trachea
Thyroid
Thoracic duct
Spinal cord

Zone II
Carotid artery
Vertebral artery
Larynx
Trachea
Esophagus
Pharynx
Jugular vein
Vagus nerve
Recurrent laryngeal nerve
Spinal cord

Zone III
Distal carotid artery
Vertebral artery
Distal jugular vein
Salivary and parotid glands
Cranial nerves IX to XII
Spinal cord

Table 44-1 Incidence of Injuries in Penetrating Neck Trauma

LOCATION	NUMBER (1275 TOTAL)	PERCENTAGE*
Arterial	320	12.8
Venous	281	11.3
Tracheolaryngeal	253	10.1
Pharyngoesophageal	240	9.6
Spinal cord	76	3
Neurologic, other	85	3.4
Thoracic duct	20	0

From McConnell DB, Trunkey D: Management of penetrating trauma to the neck. Adv Surg 27:97, 1994.
*Incidence based on other reported series.

zones means this anatomic description may be less helpful than previously thought. Zone division has both anatomic and management implications for penetrating neck trauma. *Zone I* (base of neck) extends superiorly from the sternal notch and clavicles to the cricoid cartilage. It includes the thoracic outlet below the cricoid cartilage. Injury to this region can affect both neck and mediastinal structures. *Zone II* (midneck) is the area between the cricoid cartilage and the angle of the mandible. Zone II injuries are therapeutically distinct because they lie in the most exposed region of the neck, making them accessible to direct surgical visualization with easier proximal and distal vascular control. *Zone III* (upper neck) extends from the angle of the mandible to the base of the skull. As with zone I injuries, proximal and distal vascular control in this region is difficult to achieve (Box 44-1).

Two fascial layers, the superficial fascia and the deep cervical fascia, cover neck structures. The superficial fascia covers the platysma muscle and is located just below the skin. The deep cervical fascia is divided into three parts: The *investing layer* surrounds the neck and splits to encase the sternocleidomastoid and trapezius muscles; the *pretracheal layer* adheres to the cricoid and thyroid cartilages and travels caudally behind the sternum to insert on the anterior pericardium; and the *prevertebral layer* envelops the cervical prevertebral muscles and extends to form the axillary sheath, which covers the subclavian artery. The pretracheal layer is clinically important because of its connection from the neck to the anterior mediastinum. Missed aerodigestive injuries can result in mediastinitis because of this anatomic continuity. The carotid sheath is made of portions from all three divisions of the deep cervical fascia. The *platysma muscle,* sandwiched between the superficial and deep cervical fascia, covers the anterolateral neck. It has clinical significance because of its superficial location and proximity to vital structures. If the platysma muscle is violated, injury to deep structures should be suspected, and by definition the injury is penetrating. Examination of any penetrating neck wound should document the zone or zones of injury and presence of platysma violation. Blind probing is discouraged as it may cause further injury or dislodge a clot and induce major hemorrhage.

CLINICAL FEATURES

Patients with neck injury can manifest numerous signs and symptoms, but most are nonspecific. This makes diagnostic strategies difficult, especially in the stable patient. Much debate in the current literature centers on the safest and most cost-effective approach for evaluating patients with possible neck injury. Serial examination is crucial to search for evidence of progressive airway or vascular compromise. Features that suggest decompensation in

www.ketabpezeshki.com 66485457-66963820

Box 44-2 "Soft" and "Hard" Signs of Penetrating Neck Trauma

Soft Signs
Hemoptysis, hematemesis
Oropharyngeal blood
Dyspnea
Dysphonia, dysphagia
Subcutaneous or mediastinal air
Chest tube air leak
Nonexpanding hematoma
Focal neurologic deficits

Hard Signs
Expanding hematoma
Severe active bleeding
Shock not responding to fluids
Decreased or absent radial pulse
Vascular bruit or thrill
Cerebral ischemia
Airway obstruction

a previously stable patient can include dyspnea, dysphonia, stridor, drooling, expanding hematoma, bruit, cerebral ischemia, or shock.

DIAGNOSTIC STRATEGIES

Researchers historically remained divided between those who did and those who did not believe that physical examination alone was adequate in determining which patients needed ancillary studies.[9-12] The literature is mixed on the sensitivity of physical examination for diagnosis of significant injury; however, a prospective series of 223 patients with penetrating neck wounds found that physical examination was reliable in determining which patients needed vascular or esophageal diagnostic studies.[9] Stable patients should be evaluated for the presence of "soft" and "hard" signs of aerodigestive or neurovascular injury (Box 44-2). Hard signs (expanding hematoma, severe active bleeding, fluid-nonresponsive shock, decreased or absent pulse, vascular bruit or thrill, cerebral ischemia, airway obstruction) indicate the need for emergent intervention. Soft signs (hemoptysis or hematemesis, oropharyngeal blood, dyspnea, dysphonia or dysphagia, subcutaneous or mediastinal air, chest tube air leak, nonexpanding hematoma, focal neurologic deficits) necessitate further evaluation but less commonly require surgical repair. Most patients with hard signs require surgical intervention. Controversy surfaced over the stable patient with soft or no signs of injury. Historically, management of penetrating neck trauma has undergone a similar evolution to trauma in other body regions in that management has progressed from a policy of mandatory exploration to one of selective management based on ancillary studies and serial physical examination.[13,14]

MANAGEMENT

Stable Patients

Ideally, stable patients with neck injury should be transported to a trauma center. Despite a stable initial appearance, airway compromise can ensue rapidly, and intervention is essential at the first sign of airway distress. Necessary interventions should be initiated during transport to the emergency department rather than at the scene to avoid delays in definitive care. Open wounds should be covered and sufficient compression applied to control bleeding and prevent air embolus without occluding the airway or blood flow to the brain. Consideration of cervical spine damage, especially in the face of blunt trauma or in the presence of neurologic deficits, should prompt the application of a cervical collar.

Unstable Patients

Airway

Airway management is the highest initial priority in the unstable patient. Cervical spine immobilization is typically unnecessary in penetrating neck trauma unless the patient has coexistent blunt trauma or evidence of a spinal cord injury. Oral intubation with rapid sequence intubation (RSI) is considered safe in most patients with neck trauma.[14,15] When the airway has been stabilized, breathing assessment is standard, with consideration of the associated risk of hemothorax or pneumothorax, seen primarily with penetrating zone I injuries.

Air Embolism

Caution is required when bag-valve-mask ventilation is necessary because air can be forced into injured tissue planes, resulting in massive subcutaneous emphysema and subsequent airway distortion or, rarely, air embolus.

Vascular Concerns

Wounds with active bleeding or blood clots should not be probed because massive hemorrhage can ensue. Ideally, bleeding is controlled by direct pressure. Blind clamping of active bleeding sites should be avoided because of the high concentration of neurovascular structures in the neck. If a vascular injury is suspected, mild Trendelenburg's position is recommended to reduce the risk of air embolism. Intravenous access is best placed on the uninjured side, avoiding the ipsilateral neck or upper extremity until vascular injury has been excluded.

Cervical Spine

Cervical collars might obscure neck pathology and preclude adequate examination. Partial removal of the collar while maintaining in-line stabilization may be necessary for adequate serial examinations to be performed.

Thoracotomy

The presence of profound shock or cardiopulmonary arrest unresponsive to fluids or emergency department thoracotomy should prompt the physician to consider venous air embolism (VAE). If this condition is suspected, the patient should be placed in a head-down, left lateral decubitus position to cause intracardiac air to accumulate in the apex of the right ventricle. If this maneuver alone does not improve cardiac output, aspiration of air from the apex of the right ventricle either by use of an ultrasound-guided pericardiocentesis needle or under direct vision after emergency department thoracotomy may be lifesaving. Evidence of cerebral ischemia, as manifested by profound alteration in consciousness or strokelike symptoms, suggests injury to the cervical vessels or cerebral arterial air embolism.

Nasogastric Tubes

Caution is advised in any patient with suspected vascular injury who requires a nasogastric tube (NGT). The retching typically seen with placement might dislodge a hematoma, resulting in immediate hemorrhage. If indicated, an NGT should ideally be placed after the patient has been intubated. Conversely, an NGT can be therapeutic if used to remove gastric contents to prevent

www.ketabpezeshki.com 66485457-66963820

aspiration, and it can be diagnostic because a bloody aspiration implies visceral injury.

Airway Management

Orotracheal Rapid Sequence Intubation

Although the ideal airway technique for neck trauma patients has been debated during the past decade, orotracheal intubation with RSI has been shown to be safe and effective and should be considered the first-line airway technique unless contraindications exist.[14,15] Orotracheal RSI is often successful even after neck trauma with airway distortion.[16] RSI has also been shown to be superior to intubation without neuromuscular blocking agents[17]; however, RSI medications should be used only by an experienced intubator. Concern that complete muscle relaxation would lead to airway collapse or that excessive movement might worsen unstable cervical spine fractures has not been borne out.[14,18] There are numerous alternatives for achieving intubation, but the emergency physician should be familiar with their limitations in the setting of neck trauma.[19] Less commonly used airway salvage techniques, however, may diminish the emergency physician's comfort level and prolong the airway stabilization procedure.

If the cervical spine must remain immobilized, an assistant should maintain in-line stabilization of the head and neck.[20] Relative contraindications to RSI include massive facial trauma or suspected laryngeal injury. When time allows, an initial inspection of the airway can be made with a laryngoscope in the awake patient. In cases in which orotracheal intubation is expected to be difficult, an attempt to intubate over a nasopharyngoscope may be prudent in patients who do not have massive bleeding into the oropharynx. All emergency physicians require a thorough knowledge of alternative techniques for intubation in the event that orotracheal RSI fails.[19,21,22] Nasopharyngoscopy, videolaryngoscopy, or surgical airways should be readily available if standard orotracheal intubation fails. In addition, it may be valuable to consult an anesthesiologist or otolaryngologist in the urgent situation if the patient remains stable.

Nasotracheal Intubation

Historically, nasotracheal intubation was recommended for the majority of trauma patients, especially if cervical spine injury was suspected. Early versions of the Advanced Trauma Life Support courses also taught that blind nasotracheal intubation (BNTI) was the procedure of choice in patients with neck trauma.[23] BNTI may have serious complications, including bleeding, vomiting, aspiration, increased intracranial pressure, turbinate damage, and sinusitis. In addition, if cervical spine injury has not been excluded, cervical protection can be difficult to maintain because of the retching and neck movement resulting from procedural discomfort often seen during BNTI in awake patients. Older studies have shown that success rates for BNTI range from 66 to 93%.[24] Although a more recent study demonstrated a 90% success rate with BNTI for trauma patients, it should be considered only in spontaneously breathing patients in whom other techniques described have been unsuccessful.[25] Nasotracheal intubation is contraindicated in those with suspected midface or basilar skull fractures or laryngeal injury but, barring contraindications, may be possible in an apneic patient with use of Magill forceps.

Surgical-Invasive Airways

Cricothyrotomy remains a common airway salvage technique used by many emergency physicians when endotracheal intubation is not possible.[19] Despite clear descriptions of this technique in the literature,[26] it is not always simple to perform. Anterior neck hematoma or potential laryngeal injury should make the intubator consider a different means of securing the airway because release of a tamponaded cervical hematoma may prove devastating. Although out-of-hospital cricothyrotomy performed by emergency medical services (EMS) personnel appears efficacious, controversy surrounds its safety.[27] Percutaneous transtracheal jet insufflation is an effective method of providing a temporizing airway but is not definitive and has potential complications, including inadvertent catheter dislodgment resulting in massive subcutaneous emphysema, catheter kinking, perforation of the posterior wall of the trachea and esophagus, pneumothorax, and hypercarbia. Performance of this procedure in a patient with complete upper airway obstruction can result in barotrauma from inadequate exhalation.[19,28]

Miscellaneous Techniques

Other airway techniques include fiberoptic laryngoscopy and bronchoscopy, which have been used successfully for difficult airways, although excessive bleeding can render visualization difficult. Lack of experience and time constraints are cited as reasons why these techniques are not preferred in the emergency department.[1,14] Emergency tracheostomy is not a common emergency department procedure because it is technically difficult and time-consuming to perform. It should be attempted only in select cases in which other techniques are contraindicated or not available. Although reported in the literature, esophageal obturator airway, retrograde intubation, laryngeal mask airway (LMA), and awake endotracheal intubation are generally not used as primary procedures or airway salvage techniques in trauma patients.[29,30]

Pediatric Considerations

Airway management in the pediatric trauma patient tends to be more anxiety-provoking, in part because of the different anatomic considerations. Ideally, the approach to the pediatric airway is similar to the adult airway, with use of orotracheal RSI. The incidence of unstable cervical fractures in children is lower than in adults.[31] As in adults, airway salvage techniques may be necessary, but fewer options are available in young children. The airway of the young child and infant is higher and more anterior, with the narrowest region of the airway at the cricoid cartilage.[32] The small cricothyroid membrane and the soft, poorly mineralized pediatric larynx make cricothyrotomy contraindicated in children younger than 10 years. Emergency tracheostomy, which is a difficult procedure in young children, or transtracheal jet ventilation can serve as a salvage technique.[33] Although the risks associated with transtracheal jet ventilation in adults are applicable to pediatrics, it is likely to be the quickest and safest surgical option in young children. BNTI in the infant and very young child is also not recommended, in part because the smaller endotracheal tubes are too pliable to be consistently passed.

Cervical Spine

Numerous papers have been written on the safety of orotracheal intubation in patients with known or suspected cervical spine injury.[16,20] Historically, cadaver studies generated fear of head movement during intubation, causing some to abandon the orotracheal route of intubation. However, RSI with in-line stabilization has not been shown to produce neurologic sequelae in humans and is believed to be a safe means of securing the airway in patients with both penetrating and blunt cervical trauma.[14,29] Neurologically intact patients with unstable cervical fractures secondary to penetrating trauma rarely manifest delayed neurologic sequelae.[5,34] There is greater concern for occult or overt cervical spine injury in the patient with blunt neck or multisystem trauma,

www.ketabpezeshki.com 66485457-66963820

although cervical spine injuries in this population are not as common as once thought. Armed with this knowledge and barring contraindications, emergency physicians should use the airway technique with which they are most comfortable. Delays in securing an airway because of indecision regarding which technique to use can lead to hypoxic brain injury and death.

Mandatory versus Selective Exploration

The debate is ongoing in the trauma literature concerning the best way to manage penetrating neck injuries. Before World War II, patients with penetrating neck trauma were treated expectantly rather than aggressively despite unacceptably high mortality rates (18-35%).[1] In an attempt to reduce the mortality associated with penetrating neck injuries, the concept of mandatory surgical exploration of all penetrating neck wounds was developed.[35] Mandatory surgery drastically reduced mortality rates to 6%.[4] Wartime experience justified the ongoing use of mandatory surgery in victims with penetrating neck injury, and this was widely accepted for decades.

Despite low mortality rates achieved with mandatory surgery, negative neck explorations concurrently increased 40 to 63% during the mid-to-late 1900s as many institutions adopted a mandatory surgical approach.[2] As with other traumatic injuries, an effort to reduce the negative exploration rate while maintaining low morbidity and mortality rates led to the concept of *selective surgical management,* which remains institution specific. Selective management offers a spectrum of approaches, ranging from serial physical examinations to an array of diagnostic tests in the stable patient. A selective approach is justified because (1) military injuries were often secondary to high-velocity missiles, as opposed to currently used weapons (e.g., knives and handguns) and animal bites; and (2) improved technology currently allows much greater accuracy in the detection of injuries. A review of zone II penetrating neck trauma cites similar overall mortality rates of 5.85% in the mandatory group and 3.74% in the selective group.[36] Current literature favors a selective approach, with the trend in the past decade being to minimize unnecessary invasive procedures.[37,38]

Transcervical Gunshot Wounds

Transcervical gunshot wounds (TC-GSWs) represent a subset of penetrating neck trauma and are included in the debate between mandatory and selective management schools. TC-GSWs are associated with a twofold-increased incidence of injuries compared with GSWs that do not cross the midline (79 vs. 31%). The most common injury seen is vascular (48%), followed by spinal cord (24%).[39] Although some centers still practice mandatory exploration for these injuries, prospective studies suggest that stable patients with TC-GSWs can be safely evaluated with a selective surgical approach with the appropriate diagnostic studies and frequent serial examinations.[39] GSWs in the anterior midline also involve an increased incidence of vascular and visceral injuries, and a more aggressive diagnostic approach should be considered in these patients.

DISPOSITION

Many patients in the emergency department with penetrating or blunt neck trauma have predetermined disposition, especially when their condition warrants further diagnostic studies, surgery, or intensive care. Most stable patients should be admitted for observation. All patients with platysma muscle violation should be admitted to the surgical service for ongoing observation, regardless of their stability. Careful observation should be maintained for patients with blunt neck injury because they can manifest delayed signs and symptoms of viscerovascular injury with serious consequences.

Because smaller hospitals may have neither the ancillary support nor the personnel to perform serial bedside examinations, mandatory exploration might be in the patient's best interest in these facilities. Level I trauma centers generally have sufficient ancillary support and diagnostic tools and are more suited to avoid surgery safely in stable patients. Patients deemed to be stable may be transferred to trauma centers via high-level EMS systems with particular expertise in airway management. Studies suggest that surgeons with trauma experience tend to perform fewer neck explorations.[20]

SPECIFIC INJURIES

Pharyngoesophageal Trauma

Epidemiology

Esophageal injuries are infrequently reported after penetrating neck trauma, representing only 0.11% of all trauma admissions.[40] Blunt esophageal perforation is even less common, with only 10 case reports in the literature before 1990. The low incidence of injury most likely results from the relatively protected position of the esophagus. The cervical esophagus is injured more often than the distal segment.

Pathophysiology

Early diagnosis of esophageal injury is crucial because spillage of orogastric contents with bacterial contamination can lead to florid inflammation, infection (abscess and mediastinitis), and death. Esophageal injuries represent the most frequently missed injuries in the neck,[34] and mortality from esophageal injuries has remained relatively high during the past two decades, with an overall rate of 19 to 22%.[35,40]

Clinical Features

Although there are no pathognomonic signs of esophageal injury, soft signs of injury include hematemesis, odynophagia, dysphagia, subcutaneous emphysema, and blood in the saliva or NGT. Other associated findings include dyspnea, hoarseness, stridor, cough, pain and tenderness in the neck, and resistance to passive neck movement.

Physical examination is considered unreliable in diagnosing esophageal injury, although one trial found no operative injuries without accompanying signs or symptoms.[9] Because timely diagnosis is very important, most believe that sole reliance on physical examination is not warranted in stable patients with soft signs of esophageal injury.[35,36]

Diagnostic Strategies

Unfortunately, esophageal injuries are difficult to diagnose. Timely diagnosis is believed to be associated with decreases in morbidity and mortality, with poorer outcomes found in patients treated beyond 24 hours from the time of injury.[35,37,40]

Diagnosing esophageal injury often depends on more than a high clinical suspicion. Plain films of the neck and chest radiographs are inadequate but may suggest esophageal perforation if pneumomediastinum or retropharyngeal air is present.[38,39] Contrast esophagography alone is considered relatively unreliable for diagnosing esophageal injuries, with a sensitivity of 80 to 89%.[40] This study requires adequate views for accurate interpretation and thus requires the patient's cooperation. Typically, a Gastrografin study is performed initially, followed by thin barium only if the

www.ketabpezeshki.com 66485457-66963820

Gastrografin study is negative; however, some authors recommend the use of water-soluble contrast as a safer alternative.[41] Flexible endoscopy has also been reported as insensitive, primarily missing proximal esophageal injuries because the scope is unable to efface the mucosa in this region.[4] Currently the combination of contrast swallow and flexible endoscopy appears to be accurate in diagnosing esophageal injuries, with one study demonstrating a sensitivity of 100%.[42] A prospective study suggested that only obtunded or symptomatic patients (hematemesis, painful swallowing, or subcutaneous emphysema) need studies to exclude esophageal injuries.[9] Many agree that only select populations should undergo a watch-and-wait approach and that the vast majority of patients with suspected esophageal injury need definitive diagnosis and treatment.[39]

The advent of the higher-resolution computed tomography (CT) scan may increase the sensitivity for penetrating zone II esophageal injuries and either supplement the physical examination in selectively managed patients or theoretically negate the need for other diagnostic studies.[43] However, sole reliance on this diagnostic modality in searching for esophageal injuries is currently not supported by the literature. Extravasation of contrast is rarely seen, and CT depends on visualization of indirect signs such as paraesophageal air or fluid, esophageal wall thickening, or edema.[44] CT scan can be useful to look at the wound track or trajectory of a bullet in the instance of penetrating trauma, thus helping to determine if a proximity wound is likely, but it has not been shown to be sensitive as a stand-alone diagnostic modality.[43,45]

Management

When esophageal injury is suspected, broad-spectrum antibiotics with anaerobic coverage should be administered, and the patient should receive nothing by mouth. Preoperative placement of an NGT under endoscopic guidance may reduce the spillage of gastric contents into the wound. Any uncontained perforation of the esophagus requires prompt surgical therapy, and small contained perforations may be candidates for observation and reimaging.[46] Esophageal stents are gaining popularity for certain nontraumatic perforations, and case reports exist for their use in trauma.[46] Isolated pharyngeal injury can be managed nonoperatively in the majority of cases.[38]

Laryngotracheal Trauma

Mechanisms of Disease

Laryngotracheal (LT) injuries account for less than 1% of all trauma injuries, with most confined to the cervical trachea. Most LT injuries result from direct blunt force sustained in MVCs, in which the extended neck strikes the steering wheel or dashboard and the larynx is compressed between the fixed object and the cervical spine. Other mechanisms leading to LT injuries include clothesline injuries, improperly fitting shoulder harnesses, near hanging, assaults, athletic events, attempted strangulation, and iatrogenic wounds. Penetrating LT injuries make up 10% of all penetrating neck trauma.[4] Associated cervical spine injuries should always be considered simultaneously, especially in evaluating a patient with blunt neck trauma.

The cricoid cartilage is the only complete solid ring in the larynx. Fractures of the cricoid cartilage can lead to death through acute airway obstruction and are the most serious laryngeal injuries. Calcification of the laryngeal cartilages begins during the teenage years, and fractures before this age are much less likely to appear on plain neck films. The degree of airway obstruction after blunt trauma to the larynx is inversely related to the degree of cartilage calcification, putting children at highest risk.

Clinical Features

There is no consensus on whether all surgically significant LT injuries will manifest clinically at the time of initial evaluation in the emergency department.[18,47] Bubbling or air leakage from a neck wound should signal injury to the respiratory tract and is considered a hard sign of LT injury. Massive subcutaneous air and bony crepitus over the larynx suggest LT injury, as does a clothesline mechanism.[48] Other clinical features of LT injury include dysphonia, aphonia, dyspnea, stridor, hemoptysis, subcutaneous emphysema, laryngeal crepitus, neck tenderness or pain over the larynx, a visible neck wound, or loss of anatomic landmarks secondary to hematoma. Pain with tongue movement implies injury to the epiglottis, hyoid bone, or laryngeal cartilage.[1] In one study, neck pain, hoarseness, and dyspnea were the most common signs of injury in children with LT trauma.[49] Others cite subcutaneous air found by examination or on radiographs and tenderness over the larynx or trachea as the most common findings.[50]

Diagnostic Strategies

Diagnostic evaluation options exist for the stable patient. Missed injuries can lead to long-term sequelae, including recurrent pneumonia, dyspnea, voice change, dysphagia, laryngeal stenosis, and chronic pain. Patients with penetrating trauma are managed by a mandatory or selective protocol. Plain radiographs should be evaluated for extraluminal air, edema, foreign bodies, and fracture of the cartilaginous laryngeal structures. Laryngoscopy or flexible nasopharyngoscopy allows direct evaluation of laryngeal integrity. With appropriate local anesthesia, laryngoscopy is well tolerated by most patients who remain in cervical spine immobilization, and it can detect hypopharyngeal tears. Rigid endoscopy is useful to evaluate injury distal to the larynx but requires general anesthesia.

Spiral CT scanning is a valuable adjunct, quickly providing detailed information about laryngeal integrity and the surrounding region.[45] Rather than reliance on a cervical spine CT, 1-mm cuts should be obtained and multiplanar reconstructions performed to optimize the study. Its sensitivity ranges from 85 to 100%, depending in part on whether presence of mediastinal or subcutaneous air is included as a diagnostic feature.[51,52] CT is more useful for detecting fractures of the hyoid bone, disrupted laryngeal or tracheal cartilages, significant exolaryngeal or endolaryngeal hematoma, and dislocations of the cricothyroid or cricoarytenoid joints and for assessing airway diameter and vocal cord integrity. CT is less useful for the detection of mucosal perforations, degloving injuries of the cartilage with denuded mucosa, and certain types of LT separation. Typically, injuries missed by CT scan are group 1 (minor hematoma or laceration) and 2 (edema, hematoma, minor mucosal disruption, or nondisplaced fracture) injuries, which would be unlikely to require surgical management.[53] CT may be less helpful in evaluation of poorly calcified pediatric cartilaginous structures.

Widespread access to ultrasound has led to an increase in its use for trauma patients. Some advocate ultrasound to detect blunt laryngotracheal injuries such as laryngotracheal separation; however, larger studies are needed to confirm the usefulness of this modality.[54]

Management

Airway compromise in patients with LT trauma can be immediate or delayed. Clinical judgment is exercised in patients who initially appear to have stable, patent airways if they are to be sent to other departments for further diagnostic testing. Delayed airway occlusion can be rapid and life-threatening, and these patients require

www.ketabpezeshki.com 66485457-66963820

close monitoring. Airway management controversies persist, and the question regarding the safest technique for intubation (orotracheal, cricothyrotomy, tracheostomy, fiberoptic scope, or adjuncts) is unresolved. If available, an awake, fiberoptic-guided oral intubation is likely the best route.[55,56] If this is not feasible given the status of the patient, the American College of Surgeons recommends a single attempt at orotracheal intubation before moving to a surgical airway.[23] Use of an ETT one size smaller than typical has been advocated owing to the potential for edema caused by the original trauma making intubation with a standard-sized tube difficult to impossible.[57] Nearly 70% of patients can be intubated in a standard fashion,[58] but the possibility of completing a partial LT separation or creating a false passage exists, and confirmation of tube placement is of paramount importance. No attempt at intubation with paralysis should be performed without the accessibility of a surgical airway. Tracheostomy is preferred over cricothyroidotomy because of the potential for the latter to further damage an injured larynx. In cases with a large neck wound, intubation can be performed through the wound, provided the trachea can be visualized.[59] If complete LT separation is present with distal retraction of the trachea, orotracheal intubation is likely to be unsuccessful, and tracheostomy might unknowingly be performed proximal to the tracheal segment. Tracheal hooks can be used to recover the distal end of the trachea, and tracheostomy performed at the fourth or fifth tracheal ring to avoid the larynx. BNTI or use of an LMA is discouraged in these injuries.[60] Because blunt LT injuries are often seen in association with multisystem trauma, they can be easily overlooked when other overt injuries are present, but these injuries in association with the need for emergent airway stabilization portend a higher mortality.[61]

Definitively, most small mucosal injuries, hematomas, and nondisplaced fractures can be managed conservatively with analgesia, humidified air, elevation of the head of the bed, antibiotics, steroids, antireflux medications, vocal rest, and a clear diet[60,62,63] Unstable patients or those with higher-grade injuries require surgical repair.

Vascular Trauma

The great vessels of concern in the neck include the carotid, subclavian, and vertebral arteries and the internal and external jugular veins. Injury to these vessels can produce morbidity and mortality through exsanguination, hematoma expansion with subsequent airway distortion and compromise, direct vessel injury leading to vascular occlusion, or embolization of a foreign body (e.g., shotgun pellet to brain or heart). Carotid artery dissection may follow even trivial neck trauma and can result in stroke in young, otherwise healthy patients. The presence of delayed-onset, evolving, central neurologic deficits in a patient with neck trauma should prompt assessment of the carotid arteries for dissection. Combined data from 16 studies of penetrating neck trauma during a 25-year period found that the carotid artery was the most commonly injured artery, with an incidence of 6.7%. This was followed by subclavian artery injuries (2.2% incidence) and vertebral artery injuries (1.3%).[4] Overall, the jugular vein is the most commonly injured of the neck vessels.[64]

Epidemiology

Penetrating Injury. Vascular injuries represent 25% of all penetrating neck wounds, and mortality rates range from 10 to 50%.[64] GSWs are more likely to be associated with hard signs of vascular injury than are SWs. Hard signs of vascular injury include pulsatile bleeding, rapidly expanding hematoma, bruit, shock unresponsive to fluid resuscitation, massive hematemesis or hemoptysis, or focal neurologic deficits consistent with carotid or vertebrobasilar arterial occlusion. Exsanguination from vascular injuries is the most common cause of immediate death after penetrating neck trauma.

Blunt Injury. Blunt carotid injuries affect 0.33 to 0.67% of blunt trauma victims.[65] Mortality rates for blunt cervical vascular injuries range from 31 to 59%.[66] Because the internal carotid artery is the most frequently injured artery, many studies use blunt vascular and carotid artery injuries synonymously, although the vertebral artery is injured in up to 15 to 20% of cases.[67,68] The actual incidence of blunt vascular injuries may be higher because of asymptomatic cases and difficulties in making the diagnosis. Blunt vascular injury should be suspected in patients with flexion-extension mechanisms, diffuse axonal brain injury, and midface, mandibular, or basilar skull fractures.[7] Vertebrobasilar arterial injuries may follow relatively minor trauma, such as chiropractic neck manipulation, but most commonly occur in association with fractures of the spinal column. Symptoms typically arise after a delay of hours to months with signs of posterior circulation embolus or infarction, and they portend a poor prognosis.

Pathophysiology

Penetrating Injury. Most cases of penetrating trauma in adults are caused by knife or bullet wounds.[9] Vessel damage most often results from direct injury, although the blast effect can cause intimal injury without directly striking the vessel, making the vascular insult similar to that seen with blunt trauma.

Blunt Injury. Blunt trauma to the cervical vessels can result in a spectrum of arterial injuries, including intimal tears, thrombosis, dissection, and pseudoaneurysm.[6,66] Embolization can occur from a thrombus that develops at the injury site. The most common mechanism for blunt internal carotid artery injury is sudden, forceful hyperextension and lateral rotation of the neck. This mechanism can cause stretching of the carotid artery over the transverse processes of the upper cervical vertebrae, resulting in intimal injury.[66] Other mechanisms responsible for this type of injury include direct blunt force to the side of the neck, intraoral trauma (e.g., children falling on lollipops), and basilar skull fractures involving the petrous or sphenoid portions of the canal, which have rarely been associated with injury to the intracranial portion of the carotid artery. Blunt carotid artery injuries most often result from MVCs but have also been reported after fights, athletic events, seat belt injuries, and strangulations.[65]

Clinical Features

The debate regarding whether the physical examination is sensitive enough to detect vascular injuries in stable patients with minimal signs and symptoms is unresolved. Angiographically documented arterial injuries have not been reliably detected by physical examination in some series.[67] Others argue that although discrepancies may exist, they are not clinically relevant in the asymptomatic patient and rarely change management, and thus these clinicians conclude that serial examinations are adequate.

Penetrating Injury. In a recent study of patients with penetrating neck trauma, 39 patients with hard signs of vascular neck injury (active hemorrhage, expanding or pulsatile hematoma, bruit or thrill, fluid-unresponsive shock, massive hemoptysis or hematemesis) or aerodigestive injury (air leaking through injury site) had a total of 38 vascular injuries that were identified. In 189 patients with soft signs of vascular injury (venous oozing, nonpulsatile, nonexpanding hematomas, minor hemoptysis) or nonvascular neck injury (dysphonia, dysphagia, subcutaneous emphysema), 16 patients were found to have vascular injuries. No injuries were identified in the 228 patients with neither hard nor soft signs either by CT-angiogram or observation, attesting to the potential

www.ketabpezeshki.com 66485457-66963820

for risk-stratification of penetrating neck trauma patients based on presence of hard and soft signs.[69]

Blunt Trauma. Specifically with regard to dissections from blunt trauma, approximately half of patients are asymptomatic. When symptomatic, carotid injuries cause contralateral sensory or motor deficits, and vertebral injuries cause ataxia, vertigo, emesis, and visual field deficits.[66] The Western Trauma Association suggests emergent diagnostic evaluation and management for any blunt neck trauma patient with arterial hemorrhage from the neck, mouth, or nose; any patient with a large or expanding cervical hematoma; patients older than 50 years with cervical bruit; and patients with focal or lateralizing neurological deficit, transient ischemic attack (TIA), Horner's syndrome, vertebrobasilar insufficiency, or evidence of infarct on imaging. Other patients at sufficiently high risk in whom screening is recommended include those with cervical hyperextension or hyperflexion with rotation, direct cervical trauma, intraoral trauma, basilar skull fracture involving the carotid canal, Le Fort II or III fracture, closed head injury with diffuse axonal injury and Glasgow Coma Scale score below 6, cervical vertebral body or transverse foramen fracture, any fracture at C1 to C3, cervical spine ligamentous injury, near hanging resulting in anoxia, seat belt or clothesline-type injury with significant cervical pain, or any patient with altered mental status.[70] Several other screening tools exist, including the Denver criteria and Memphis criteria, as well as a Denver grading system to predict stroke risk and mortality. Seat belt signs on the neck may suggest insidious vascular injury, but a review of 131 patients with a seat belt sign at the neck found that only 0.76% had a significant vascular injury.[71]

Delayed presentation of a vascular injury is most often neurologic in nature, with symptoms ranging from TIA to global cerebral ischemia. Horner's syndrome has been associated with vascular injury, particularly carotid artery dissection.[68] Seventeen to 35% of patients do not develop neurologic symptoms for more than 24 hours,[72] and delay in onset of neurologic sequelae of weeks to years has been reported. TIAs usually result from release of small emboli from the injured vessel, which can herald the onset of a profound deficit. Thus any focal neurologic abnormality discovered by history or examination should prompt the emergency physician to include vascular injuries in the differential diagnosis. Blunt cervical vascular injuries represent some of the most under-reported injuries because of their insidious presentation but ultimate association with a catastrophic neurologic outcome.

Diagnostic Strategies

Some centers routinely obtain contrast studies of all potentially significant neck wounds; others restrict imaging to zone I and zone III injuries. Zone I injuries in particular can harbor clinically occult arterial injuries, and routine preoperative imaging has been historically advocated to detect injury and facilitate a judicious surgical approach when positive. Likewise, zone III vascular injuries can be exceedingly difficult to approach surgically, and thus some surgeons still prefer preoperative imaging followed by exploration for any positive or equivocal findings. Many surgeons believe that pre-exploratory vascular studies are noncontributory in zone II injuries and may lead to delays in definitive care because these lesions are easily approached surgically.

With the advent of newer-generation machines, CT-A (64-slice or more CT angiography) has largely replaced conventional angiography. Part of the attraction is that it is rapid, readily available, and accurate.[73-75] CT-A allows for the detection of many types of vascular injuries, and it characterizes cervical soft tissues, cervical vertebrae, and spinal cord as well as aerodigestive structures. Increasingly more centers rely on CT-A when no clear surgical indications are apparent, although CT-A can potentially miss lethal lesions, such as pseudoaneurysms. Centers that prefer a selective approach are increasingly reporting success with this modality in the face of platysma violation.[76] CT-A for the diagnosis of vascular injury in penetrating trauma has been shown to have a sensitivity and specificity of 90 to 100% and 99 to 100%.[77-80] For victims of blunt trauma, the sensitivity of CT-A may be substantially lower, 47 to 74%, possibly because of the nature of the injuries as well as the fact that many of the data come from images obtained on single-slice scanners,[69,81-83] Three studies using newer generation technology found a sensitivity close to 100% when compared with digital subtraction angiography or long-term clinical outcome.[84-86] One systematic review found a pooled sensitivity of 76.8% and negative predictive value of 89.9% across the existing literature.[87] It seems likely that CT-A is a reasonable diagnostic choice if performed in a 16-slice or greater scanner.[88] As some of these patients have focal or hemispheric neurologic findings that prompt head CT, performance of CT-A immediately afterward streamlines the workup, especially considering that ischemic changes may be initially occult on the head CT.

Historically, conventional arteriography has been used extensively to detect vascular injury in patients with both blunt and penetrating injuries. Four-vessel arteriography is time-consuming and expensive but historically felt to be helpful in planning the best surgical approach. If ordered, this contrast study should include the intracranial portion of the carotid artery with zone III injuries or suspected blunt cervical trauma. Zone I injuries should include the aortic arch with its branches. Despite a sensitivity and specificity of nearly 100% and a complication rate of less than 2% for arteriography, other, less invasive diagnostic tests, such as CT-A, have been suggested because of their accuracy, speed, cost, and efficacy.[89]

Duplex ultrasonography has been used in combination with or instead of arteriography to exclude cervical vascular injury in patients with both penetrating and blunt trauma. Despite clinical success, limitations of ultrasonography include the risk of missing zone I and zone III injuries and the lack of 24-hour availability at many centers. For penetrating injury, carotid duplex Doppler has been shown to diagnose vascular injuries with a sensitivity of 91 to 95%, with higher accuracy in more clinically important injuries.[35,90] For all symptomatic dissection patients without obvious evidence of stroke, sensitivity of ultrasound is 70% for carotid and 75 to 86% for vertebral arteries,[91,92] though rates as low as 38.5% were found in one study.[77] Much of the lost sensitivity in the imaging of the carotid artery is a result of poor visualization of the distal third of the vessel.[65]

Magnetic resonance angiography (MRA) has also been reported to be helpful despite high cost and potential lack of 24-hour availability. MRA has additional distinct disadvantages that include remote location in many centers, the contraindication of metallic foreign bodies (bullet fragments), and the inability to directly visualize the neck during the procedure for expanding hematoma. Its sensitivity is likely equivalent to that of CT-A, and possibly inferior for vertebral dissections.[93] Although not indicated in most cases of suspected vascular injury, plain films can occasionally be useful. Anteroposterior and lateral neck films can help determine a bullet trajectory by allowing comparison of the entrance wound with the location of the foreign body, if present, though ricochet off a bone may render the estimated trajectory inaccurate. Chest radiographs allow evaluation of the mediastinum and identification of hemothorax or pneumothorax.

Management

Penetrating Injury. The ideal management strategy for injuries of the vascular system resulting from penetrating trauma has

www.ketabpezeshki.com 66485457-66963820

not been determined. Because many of these patients are young with anticipated "clean" carotid arteries, some surgeons routinely attempt surgical repair. Because of concern that reperfusion might convert an ischemic infarction to a hemorrhagic infarction in patients with profound neurologic deficit, others prefer ligation over repair in a select population of patients.

Blunt Injury. Treatment options for blunt artery injuries depend in part on the mechanism and type of injury and location of the lesion. Treatment modalities include surgery, anticoagulation, and observation. Recommendations are mixed as to whether antiplatelet therapy or anticoagulation is most appropriate to prevent clot propagation in arterial dissections.[94] Antiplatelet agents and heparin have comparable injury healing rates.[95] Because of high complication rates in trauma patients, treatment modalities should be initiated with appropriate consultation. Surgical treatment includes ligation, resection, thrombectomy, and endovascular stent placement. Delayed formation of pseudoaneurysms can be a complication of even low-grade injuries.

Venous Air Embolism. VAE is a subset of vascular injuries that can lead to life-threatening complications if not detected. VAE has been reported after blunt, penetrating, and iatrogenic mechanisms. VAE occurs when air enters the injured vessel, usually during inspiration, resulting in distal vascular occlusion and infarction. In any patient with a suspected major venous injury, direct pressure should be maintained over the wound while the patient is kept in Trendelenburg's position and left lateral decubitus position if injuries allow. Autopsy reports on such trauma victims reveal air in both the right side of the heart and the pulmonary artery. When standard treatment fails in a pulseless trauma patient, VAE should be immediately suspected and the right ventricle aspirated for air after the aorta has been cross-clamped. Rarely, air embolism has been reported with arterial injuries as well.[1]

Nervous System

When evaluating any patient with neck trauma, the examiner should remember that the brachial plexus, peripheral nerve roots, cervical sympathetic chain, and cranial nerves VII, IX, X, XI, and XII are vulnerable, as well as the spinal cord. Neurologic deficit can also result from vascular injury with subsequent cerebral ischemia. Complete cord injury can result in spinal (neurogenic) shock with paraplegia, bradycardia, and hypotension. Brown-Séquard syndrome (hemisection of the spinal cord) arises with ipsilateral hemiplegia and contralateral sensory deficit. Cervical spine fractures and cord injuries are most commonly found in GSWs (1.35% and 0.94%, respectively), followed by direct blunt trauma. Either injury is rare from SWs (0.12% and 0.11%).[96] Brachial plexus, spinal root, and peripheral nerve injuries have been reported after neck trauma and can result in both sensory and motor deficits. Phrenic nerve injury may compromise spontaneous respiration by causing ipsilateral diaphragmatic paralysis. Hoarseness can result from direct laryngeal trauma, but injury to the recurrent laryngeal nerve, which branches off the vagus nerve (cranial nerve X), should also be suspected, with vocal cord paralysis on the affected side.

Thoracic Duct, Glandular, and Retropharyngeal Injuries

Other, less common injuries have been reported in association with neck trauma with variable signs and symptoms. Thoracic duct injuries are less likely to be apparent initially and are frequently diagnosed intraoperatively or after development of a chylothorax. Glandular wounds, including those of the thyroid, parathyroid, and salivary glands, are reported rarely. Retropharyngeal hematomas are also extremely rare but can result in life-threatening airway compromise.[1,97]

Near Hanging and Strangulation

Epidemiology

Hanging and strangulation represent the second most common form of suicide in the United States after firearm use.[98] Approximately 9000 strangulation deaths occur annually in the United States.[99]

The terms *hanging* and *strangulation* are often used interchangeably, with hanging being a subset of strangulation. Hanging is categorized as judicial (complete hanging) or nonjudicial (incomplete hanging). *Complete hanging* refers to the presence of a ligature around the victim's neck and a subsequent drop resulting in the victim being freely suspended. In contrast, *incomplete hanging* refers to the partial suspension of the victim's body with some part still in contact with the ground. Judicial hanging victims classically fall at least the height of their body, whereas incomplete hanging is more likely to be seen in confined spaces (e.g., homes and jail cells), where a fall from height resulting in full body suspension is less possible. On the basis of the location of the ligature knot, hanging is further divided into atypical and typical categories. *Typical hanging* refers to the knot being midline directly under the occiput, which leads to a higher likelihood of complete arterial occlusion. *Atypical hanging* refers to all other knot placements.[100]

Manual strangulation and *ligature strangulation* refer to external compression of the neck, usually by hands or ligature, but independent of the weight of the victim.[101] *Postural strangulation,* generally seen in the younger pediatric population, refers to death sustained by the victim's body weight compressing the anterior neck against a firm object.

Pathophysiology

Judicial hanging with adequate fall distance results in forceful distraction of the head from the neck and body. This leads to high cervical fractures, such as the classic hangman's fracture (fracture through both pedicles of C2), complete cord transection, and death. Attempted-suicide hangings frequently occur at inadequate height and therefore tend to mimic nonjudicial strangulation. In essentially all types of nonjudicial strangulation, the ligature or external force initially applied causes venous congestion with stasis of cerebral blood flow leading to unconsciousness. Once the person is limp, the ligature or external force can tighten further, leading to complete arterial occlusion and ultimately to brain injury or death. Vagal reflexes resulting from pressure on the carotid body may contribute to fatal dysrhythmias, as may increased sympathetic tone from pericarotid sinus pressure. Compression of the airway does not play as significant a role in incomplete hanging as vascular occlusion.[100]

Pulmonary sequelae are frequently seen in near-hanging victims and include pulmonary edema, bronchopneumonia, and acute respiratory distress syndrome (ARDS).[100] These complications are responsible for most in-hospital deaths after near hanging. Pulmonary edema occurs from one of two mechanisms. *Neurogenic* pulmonary edema results from centrally mediated, massive sympathetic discharge. Because it is more often seen in association with serious brain injury, neurogenic pulmonary edema has poor prognostic implications. *Postobstructive* pulmonary edema is generally associated with a better neurologic outcome. It is initiated by marked negative intrapleural pressure, which is generated by forceful inspiratory effort against an extrathoracic obstruction.

www.ketabpezeshki.com 66485457-66963820

When the obstruction is removed, the onset of pulmonary edema can be rapid and can lead to ARDS.[100]

Clinical Features

External trauma may or may not be evident, depending on the mechanism of injury. If present, ligature marks appear as indentations around the neck, ranging from mild erythema to leather-like grooves following the course of the ligature. Fingernail scratches, abrasions, and contusions are variably present on the external neck as well. *Tardieu's spots* are highly correlated with asphyxial deaths; these petechial hemorrhages are seen in the conjunctiva, mucous membranes, and skin cephalad to the ligature marks. They occur when the venous pressure rises in response to ligature tightening. Laryngeal injuries are reported in near-hanging victims. Thyroid cartilage fractures are seen in approximately 50% of all nonjudicial hanging deaths, and hyoid bone fractures occur in 20%. Cricoid cartilage fractures are rarely reported and typically occur with manual strangulation.[100] Resulting laryngeal fractures are rarely clinically significant in survivors, and standard airway techniques are recommended.

Vascular injury leading to delayed neurologic sequelae after near hanging is rare, but reported, and is more frequent in fatal cases.[102] It most often results from carotid intimal dissection or thrombus formation, resulting in partial or complete vascular occlusion or embolism.[103] Carotid vascular studies should be considered in patients with unexplained focal or global neurologic deficits. Cervical spine fractures, subluxations, and cord injury are uncommon in nonjudicial near hangings but have been reported.[104,105] Although not reported, phrenic nerve injury and resultant diaphragmatic paralysis is a theoretic possibility as well.[106]

Management

Suggested radiographic workup includes head CT and neck CT-A.[105] Ventilatory support is indicated for maintenance of adequate oxygenation and ventilation in the comatose patient. The addition of positive end-expiratory pressure is often necessary, especially when pulmonary edema or ARDS develops.[73] Aggressive resuscitation is warranted in the unconscious patient; the initial Glasgow Coma Scale score is generally not predictive of outcome.[105,107] The altered or comatose patient should be assumed to have cerebral edema with elevated intracranial pressure, and cerebral resuscitation measures are actively initiated with use of standard technique.

Definitive studies providing guidelines for the management of hypoxic brain injury specifically related to near-hanging or strangulation injuries are lacking. Several small recent series indicate a potential role for induced mild hypothermia in comatose survivors of strangulation.[108-110]

KEY CONCEPTS

- Neck trauma results from one of three major mechanisms: blunt injury, penetrating injury, or near hanging or strangulation.
- The leading cause of immediate death after neck trauma is exsanguination secondary to vascular injury.
- The leading cause of delayed death after neck trauma is esophageal injury. These wounds are rare, frequently insidious, and associated with high mortality rates if missed.
- Neck wounds should never be probed through the platysma muscle because massive hemorrhage or air embolus can ensue.
- Cervical collars can obscure impending airway disasters (e.g., expanding hematomas) and other signs suggestive of injury if not removed periodically to allow serial examinations.
- Unless a contraindication exists, orotracheal rapid sequence intubation is safe and effective in the hands of an experienced intubator.
- Vascular injuries resulting from blunt trauma represent some of the most under-reported injuries because of their propensity for delayed neurologic sequelae.
- There is ongoing debate regarding whether physical examination is sensitive at detecting visceral or vascular injury, and the role of CT-A is increasing.
- Suspicion of venous air embolism should prompt direct wound pressure, occlusive dressings, Trendelenburg's position, and, if the patient is in cardiopulmonary arrest, aspiration of air from the right side of the heart.
- Transcervical gunshot wounds are a subset of injuries with a twofold-increased incidence of visceral-vascular injuries compared with injuries that do not cross the midline.
- All near-hanging or strangulation patients who are comatose or have altered consciousness may have elevated intracranial pressure, and appropriate cerebral resuscitation measures should be initiated.
- The leading cause of in-hospital death in victims of near hanging or strangulation is pulmonary complications (pneumonia, pulmonary edema, and ARDS).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Nathens AB, ed: *National Trauma Data Bank 2010 Annual Report.* Available at www.facs.org/trauma/ntdb/pdf/ntdbannualreport2010.pdf. Accessed December 27, 2011.
2. Desjardins G, Varon AJ: Airway management for penetrating airway injuries: The Miami experience. *Resuscitation* 2001; 48:71.
3. Volgas DA, Stannard JP, Alonso JE: Ballistics: A primer for the surgeon. *Injury* 2005; 36:373.
4. McConnell DB, Trunkey DD: Management of penetrating trauma to the neck. *Adv Surg* 1994; 27:97.
5. Kendall JL, Anglin D, Demetriades D: Penetrating neck trauma. *Emerg Med Clin North Am* 1998; 16:85.
6. Rathlev NK, Medzon R, Bracken ME: Evaluation and management of neck trauma. *Emerg Med Clin North Am* 2007; 25:679.
7. Mayberry JC: Blunt carotid artery injury: The futility of aggressive screening and diagnosis. *Arch Surg* 2004; 138:609.
8. Hollinshead WH: *Textbook of Anatomy*, 4th ed. Philadelphia: Harper & Row; 1985.
9. Demetriades D, et al: Evaluation of penetrating injuries of the neck: Prospective study of 223 patients. *World J Surg* 1997; 21:41.
10. Azuaje RE, et al: Reliability of physical examination as a predictor of vascular injury after penetrating neck trauma. *Am Surg* 2003; 69:806.
11. van As AB, van Deurzen DF, Verleisdonk EJ: Gunshots to the neck: Selective angiography as a part of conservative management. *Injury* 2002; 33:453.
12. Sekharan J, Dennis JW, Veldenz HC, Miranda F, Frykberg ER: Continued experience with physical examination alone for evaluation and management of penetrating zone 2 neck injuries: Results of 145 cases. *J Vasc Surg* 2000; 32:483.
13. Bell RB, Osborn T, Dierks EJ, Potter BE, Long WB: Management of penetrating neck injuries: A new paradigm for civilian trauma. *J Oral Maxillofac Surg* 2007; 65:691.
14. Mandavia DP, Qualls S, Rokos I: Emergency airway management in penetrating neck injury. *Ann Emerg Med* 2000; 35:221
15. Crosby ET: Airway management in adults after cervical spine trauma. *Anesthesiology* 2006; 104:1293.
16. Drummond GB: Comparison of sedation with midazolam and ketamine: Effects on airway muscle activity. *Br J Anaesth* 1996; 76:663.
17. Li J, Murphy-Lavoie H, Bugas C, Martinez J, Preston C: Complications of emergency intubation with and without paralysis. *Am J Emerg Med* 1999; 17:141.
18. Vassiliu P, et al: Aerodigestive injuries of the neck. *Am Surg* 2001; 67:295.
19. McGill J: Airway management in trauma: An update. *Emerg Med Clin North Am* 2007; 25:603.
20. Manoach S, Paladino L: Manual in-line stabilization for acute airway management of suspected cervical spine injury: Historical review and current questions. *Ann Emerg Med* 2007; 50:236.
21. Blanda M, Gallo UE: Emergency airway management. *Emerg Med Clin North Am* 2003; 21:1.
22. Butler KH, Clyne B: Management of the difficult airway: Alternative airway techniques and adjuncts. *Emerg Med Clin North Am* 2003; 21:259.
23. American College of Surgeons: *Advanced Trauma Life Support Instructor Manual*. Chicago: American College of Surgeons; 1984.
24. O'Brien DJ, Danzl DF, Sowers MB, Hooker EA: Airway management of aeromedically transported trauma patients. *J Emerg Med* 1988; 6:49, 1988.
25. Weitzel N, Kendall J, Pons P: Blind nasotracheal intubation for patients with penetrating neck trauma. *J Trauma* 2004; 56:1097.
26. Bair AE, Panacek EA, Wisner DH, Bales R, Sakles JC: Cricothyrotomy: A 5-year experience at one institution. *J Emerg Med* 2003; 24:151-156.
27. Robinson KJ, Katz R, Jacobson LM: A 12-year experience with prehospital cricothyrotomies. *Air Med J* 2001; 20:27.
28. Mace SE: Needle cricothyrotomy. *Emerg Med Clin North Am* 2008; 26:1085-1101.
29. Leiss BD, Schedt TD, Templer JW: The difficult airway. *Otolaryngol Clin North Am* 2005; 41:567.
30. Pierre EJ, McNeer RR, Shamir MY: Early management of the traumatized airway. *Anesthesiol Clin North America* 2007; 25:1, 2007.
31. Proctor MR: Spinal cord injury. *Crit Care Med* 2002; 30:S489.
32. Litman RS, Weissend EE, Shibata D, Westesson PL: Developmental changes of laryngeal dimensions in unparalyzed, sedated children. *Anesthesiology* 2003; 98:41.
33. Mandell DL: Traumatic emergencies involving the pediatric airway. *Clin Pediatr Emerg Med* 2005; 6:41.
34. Vanderlan WB, et al: Neurological sequelae of penetrating cervical trauma. *Spine (Phila Pa 1976)* 2009; 34:2646-2653.
35. Asensio JA, et al: Penetrating esophageal injuries: Multicenter study of the American Association for the Surgery of Trauma. *J Trauma* 2001; 50:289.
36. Wu JT, Mattox KL, Wall MJ: Esophageal perforations: New perspectives and treatment paradigms. *J Trauma* 2007; 63:1173.
37. Breigeiron R, de Souza HP, Sidou JPP: Risk factors for surgical site infection after surgery for esophageal perforation. *Dis Esophagus* 2007; 21:266.
38. Thoma M, Navsaria PH, Edu S, Nicol AJ: Analysis of 203 patients with penetrating neck injuries. *World J Surg* 2008; 32:2716-2723.
39. Bryant AS, Cerfolio RJ: Esophageal trauma. *Thorac Surg Clin* 2007; 17:63.
40. Asensio JA, et al: Penetrating esophageal injuries: Time interval of safety for preoperative evaluation—how long is safe? *J Trauma* 1997; 43:319.
41. Hardcastle TC: The spectrum, diagnosis, and current management options of cervical, thoracic, and intra-abdominal esophageal perforation. *J Trauma* 2008; 65:495.
42. Weigelt JA, et al: Diagnosis of penetrating cervical esophageal injuries. *Am J Surg* 1987; 154:619.
43. Mazolewski PJ, Curry JD, Browder T, Fildes J: Computed tomographic scan can be used for surgical decision making in zone II penetrating neck injuries. *J Trauma* 2001; 51:315.
44. de Lutio di Castelguidone E, et al: Esophageal injuries: Spectrum of multidetector row CT findings. *Eur J Radiol* 2006; 59:344.
45. Gonzalez RP, Falimirski M, Holevar MR, Turk B: Penetrating zone II neck injury: Does dynamic computed tomographic scan contribute to the diagnostic sensitivity of physical examination for surgically significant injury? A prospective blinded study. *J Trauma* 2003; 54:61.
46. Eroglu A, Turkyilmaz A, Aydin Y, Yekeler E, Karaoglanoglu N: Current management of esophageal perforation: 20 years experience. *Dis Esophagus* 2009; 22:374.
47. Back MR, Baumgartner FJ, Klein SR: Detection and evaluation of aerodigestive tract injuries caused by cervical and transmediastinal gunshot wounds. *J Trauma* 1997; 42:680.
48. Stassen NA, et al: Laryngotracheal injuries: Does injury mechanism matter? *Am Surg* 2004; 70:522-525.
49. Wootten CT, Bromwich MA, Myer CM 3rd: Trends in blunt laryngotracheal trauma in children. *Int J Pediatr Otorhinolaryngol* 2009; 73:1071-1075.
50. Kadish H, Schunk J, Woodward GA: Blunt pediatric laryngotracheal trauma: Case reports and review of the literature. *Am J Emerg Med* 1994; 12:207.
51. Faure A, et al: Multiplanar reconstruction: A new method for the diagnosis of tracheobronchial rupture? *Intensive Care Med* 2007; 33:2173.
52. Scaglione M, et al: Acute tracheobronchial injuries: Impact of imaging on diagnosis and management implications. *Eur J Radiol* 2006; 59:336.
53. Robinson S, Juutilainen M, Suomalainen A, Mäkitie AA: Multidetector row computed tomography of the injured larynx after trauma. *Semin Ultrasound CT MR* 2009; 30:188.
54. Moriwaki Y, et al: Application of ultrasonography for blunt laryngo-cervical-tracheal injury. *J Trauma* 2006; 61:1156.
55. Koletsis E, et al: Surgical decision making in tracheobronchial injuries on the basis of clinical evidences and the injuries anatomical setting: A retrospective analysis. *Injury* 2010; Sep 21. [Epub ahead of print].
56. Comer BT, Gal TK: Recognition and management of the spectrum of acute laryngeal trauma. *J Emerg Med* 2010; Jun 28. [Epub ahead of print].
57. Losek JD, Tecklenberg FW, White DR: Blunt laryngeal trauma in children: Case report and review of initial airway management. *Pediatr Emerg Care* 2008; 24:370.
58. Kummer C, Netto FS, Rizoli S, Yee D: A review of traumatic airway injuries: Potential implications for airway assessment and management. *Injury* 2007; 38:27.
59. Bhattacharya P, Mandal MC, Das S, Mukhopadhyay S, Basu SR: Airway management of two patients with penetrating neck trauma. *Indian J Anaesth* 2009; 53:348.
60. Cornielle MG, Stewart RM, Cohn SM: Upper airway injury and its management. *Semin Thorac Cardiovasc Surg* 2008; 20:8.
61. Bhojani RA, et al: Contemporary assessment of laryngotracheal trauma. *J Thorac Cardiovasc Surg* 2005; 130:426.
62. Bell RB, Verschueren DS, Dierks EJ: Management of laryngeal trauma. *Surg Clin North Am* 2008; 20:415.

www.ketabpezeshki.com 66485457-66963820

63. Tohill RM, Gupta DK: Severe laryngeal injuries masked by fractured mandible. *Dent Update* 2008; 35:535.
64. Asensio JA, Valenziano CP, Falcone RE, Grosh JD: Management of penetrating neck injuries: The controversy surrounding zone II injuries. *Surg Clin North Am* 1991; 71:267.
65. Larsen DW: Traumatic vascular injuries and their management. *Neuroimaging Clin N Am* 2002; 12:249-269.
66. Arthurs ZM, Starnes BW: Blunt carotid and vertebral artery injuries. *Injury* 2008; 30:1232-1241.
67. Mohammed GS, Pillay WR, Barker P, Robbs JV: The role of clinical examination in excluding vascular injury in haemodynamically stable patients with gunshot wounds to the neck: A prospective study of 59 patients. *Eur J Vasc Endovasc Surg* 2004; 28:425.
68. Thanvi B, Munshi SK, Dawson SL, Robinson TG: Carotid and vertebral artery dissection syndromes. *Postgrad Med J* 2005; 81:383.
69. Inaba K, et al: Evaluation of multidetector computed tomography for penetrating neck injury: a prospective multicenter study. *J Trauma Acute Care Surg* 2012; 72:576.
70. Stuhlfaut JW, Barest G, Sakai O, Lucey B, Soto JA: Impact of MDCT angiography on the use of catheter angiography for the assessment of cervical arterial injury after blunt or penetrating trauma. *AJR Am J Roentgenol* 2005; 185:1063.
71. DiPerna CA, et al: Clinical importance of the "seat belt sign" in blunt trauma to the neck. *Am Surg* 2002; 68:441.
72. Bilbao R, Amoros S, Murube J: Horner syndrome as an isolated manifestation of an intrapetrous internal carotid artery dissection. *Am J Ophthalmol* 1997; 123:562.
73. Múnera F, Cohn S, Rivas L: Penetrating injuries of the neck: Use of helical computed tomographic angiography. *J Trauma* 2005; 58:413.
74. Utter GH, Hollingworth W, Hallam DK, Jarvik JG, Jurkovich GJ: Sixteen-slice CT angiography in patients with suspected blunt carotid and vertebral artery injuries. *J Am Coll Surg* 2006; 203:838.
75. McKevitt EC, Kirkpatrick AW, Vertesi L, Granger R, Simons RK: Blunt vascular neck injuries: Diagnosis and outcomes of extracranial vessel injury. *J Trauma* 2002; 53:472.
76. Brywczynski JJ, Barrett TW, Lyon JA, Cotton BA: Management of penetrating neck injury in the emergency department: A structured literature review. *Emerg Med J* 2008; 25:711.
77. Mutze S, Rademacher G, Matthes G, Hosten N, Stengel D: Blunt cerebrovascular injury in patients with blunt multiple trauma: Diagnostic accuracy of duplex Doppler US and early CT angiography. *Radiology* 2005; 237:884.
78. Inaba K, et al: Prospective evaluation of screening multislice helical computed tomographic angiography in the initial evaluation of penetrating neck injuries. *J Trauma* 2006; 61:144.
79. de Vries C, et al: The imaging of stab injuries. *Acta Radiol* 2010; 51:92
80. Munera F, Danton G, Rivas LA, Henry RP, Ferrari MG: Multidetector row computed tomography in the management of penetrating neck injuries. *Semin Ultrasound CT MR* 2009; 30:195.
81. Malhotra AK, et al: Computed tomographic angiography for the diagnosis of blunt carotid/vertebral artery injury: A note of caution. *Ann Surg* 2007; 246:642.
82. Sliker CW, Shanmuganathan K, Mirvis SE: Diagnosis of blunt cerebrovascular injuries with 16-MDCT: Accuracy of whole-body MDCT compared with neck MDCT angiography. *AJR Am J Roentgenol* 2008; 190:790.
83. DiCocco JM, et al: Blunt cerebrovascular injury screening with 32-channel multidetector computed tomography: More slices still don't cut it. *Ann Surg* 2011; 253:444-450.
84. Eastman AL, Muraliraj V, Sperry JL, Minei J: CTA-based screening reduces time diagnosis and stroke rate in blunt cervical vascular injury. *J Trauma* 2009; 67:551.
85. Berne JD, et al: Sixteen-slice multi-detector computed tomographic angiography improves the accuracy of screening for blunt cerebrovascular injury. *J Trauma* 2006; 60:1204.
86. Biffl WL, Egglin T, Benedetto B, Gibbs F, Cioffi WG: Sixteen-slice computed tomographic angiography is a reliable noninvasive screening test for clinically significant blunt cerebrovascular injuries. *J Trauma* 2006; 60:745.
87. Anaya C, Munera F, Bloomer CW, Danton GH, Caban K: Screening multidetector computed tomography angiography in the evaluation of blunt neck injuries: An evidence-based approach. *Semin Ultrasound CT MR* 2009; 30:205.
88. Burlew CC, Biffl WL: Imaging for blunt carotid and vertebral artery injuries. *Surg Clin North Am* 2011; 91:217.
89. Múnera F, Soto JA, Palacio D, Velez SM, Medina E: Diagnosis of arterial injuries caused by penetrating trauma to the neck: Comparison of helical CT angiography and conventional angiography. *Radiology* 2000; 216:356.
90. Bynoe RP, et al: Noninvasive diagnosis of vascular trauma by duplex ultrasonography. *J Vasc Surg* 1991; 14:346.
91. Arnold M, et al: Ultrasound diagnosis of spontaneous carotid dissection with isolated Horner syndrome. *Stroke* 2007; 39:82.
92. Benniger DH, Baumgartner RW: Ultrasound diagnosis of cervical artery dissection. *Front Neurol Neurosci* 2006; 21:70.
93. Vertinsky AT, et al: Comparison of multidetector CT angiography and MR imaging of cervical artery dissection. *Am J Neuroradiol* 2008; 29:1753.
94. Edwards NM, et al: Antithrombotic therapy and endovascular stents are effective treatment for blunt carotid injuries: Results from longterm follow-up. *J Am Coll Surg* 2007; 204:1007.
95. Cothren CC, et al: Anticoagulation is the gold standard therapy for blunt carotid injuries to reduce stroke rate. *Arch Surg* 2004; 138:540.
96. Rhee P, et al: Cervical spine injury is highly dependent on the mechanism of injury following blunt and penetrating assault. *J Trauma* 2006; 61:1166.
97. Lazott LW, et al: Severe upper airway obstruction due to delayed retropharyngeal hematoma formation following blunt cervical trauma. *BMC Anesthesiol* 2007; 7:2.
98. Heninger MD, Hanzlick R: Nonnatural deaths of adolescents and teenagers: Fulton County, Georgia, 1985-2004. *Am J Forensic Med Pathol* 2008; 29:208.
99. Centers for Disease Control and Prevention: Deaths and mortality. Available at http://www.cdc.gov/nchs/fastats/deaths.htm. Accessed February 8, 2011.
100. Kaki A, Crosby ET, Lui AC: Airway and respiratory management following non-lethal hanging. *Can J Anaesth* 1997; 44:445.
101. Sauvageau A, Boghossian E: Classification of asphyxia: The need for standardization. *J Forensic Sci* 2010; 55:1259.
102. Suárez-Peñaranda JM, et al: Characterization of lesions in hanging deaths. *J Forensic Sci* 2008; 53:720.
103. Maier W, Fradis M, Malatskey S, Krebs A: Diagnostic and therapeutic management of bilateral carotid artery occlusion caused by near-suicide hanging. *Ann Otol Rhinol Laryngol* 1999; 108:189.
104. Salim A, et al: Near-hanging injuries: A 10-year experience. *Injury* 2006; 37:435.
105. Nichols SD, et al: Outcome of cervical near-hanging injuries. *J Trauma* 2009; 66:174.
106. Davies SJ: "C3, 4, 5 keeps the diaphragm alive." Is phrenic nerve palsy of the pathophysiological mechanism in strangulation and hanging? Should diaphragm paralysis be excluded in survival cases?: A review of the literature. *Am J Forensic Med Pathol* 2010; 31:100.
107. Wahlen BM, Thierbach AR: Near-hanging. *Eur J Emerg Med* 2002; 9:348.
108. Baldursdottir S, Sigvaldason K, Karason S, Valsson F, Sigurdsson GH: Induced hypothermia in comatose survivors of asphyxia: A case series of 14 consecutive cases. *Acta Anaesthesiol Scand* 2010; 54:821.
109. Jehle D, Meyer M, Gemme S: Beneficial response to mild therapeutic hypothermia for comatose survivors of near-hanging. *Am J Emerg Med* 2010; 28:390.
110. Borgquist O, Friberg H: Therapeutic hypothermia for comatose survivors after near-hanging—a retrospective analysis. *Resuscitation* 2009; 80:210.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 45

THORACIC TRAUMA

Marc Eckstein and Sean O. Henderson

EPIDEMIOLOGY

Thoracic injury directly accounts for 20 to 25% of deaths from trauma, resulting in more than 16,000 deaths annually in the United States. The most common cause of injuries leading to accidental death in the United States is motor vehicle collisions (MVCs) in which immediate deaths are often caused by rupture of the myocardial wall or the thoracic aorta. Early deaths (within the first 30 minutes to 3 hours) resulting from thoracic trauma are often preventable. Causes of these include tension pneumothorax, cardiac tamponade, airway obstruction, and uncontrolled hemorrhage. Because these problems are often reversible or may be temporized nonoperatively, it is vital that emergency physicians be thoroughly familiar with their pathophysiology, clinical presentation, diagnosis, and treatment.[1]

Approximately 75% of patients with thoracic trauma can be managed expectantly with simple tube thoracostomy and volume resuscitation. Therefore initial care and disposition of these patients is usually performed by emergency physicians. Definitive care of these patients is often multidisciplinary in nature, involving trauma surgeons, cardiothoracic surgeons, and intensivists. Improvement in the understanding of the underlying physiologic mechanisms involved, the advancement of newer imaging modalities, minimally invasive approaches, and pharmacologic therapy contribute to decreasing the morbidity and mortality of these injured patients. The role of multidetector helical computed tomography (CT) scanning in the evaluation of trauma patients continues to expand. Although CT scans provide much greater diagnostic sensitivity than plain radiography, the precise indications for CT scanning in trauma patients remain unclear. Concerns regarding cost, contrast-induced nephrotoxicity, and cumulative radiation exposure to the thorax have been mounting.[2]

Injuries to the lung parenchyma are common in severely injured patients and include contusion, laceration, and hematoma.[1] Hemothorax and pneumothorax are also common injuries in patients with thoracic trauma. Treatment of these injuries has changed during the past decade primarily because of advances in diagnostic imaging techniques and an increased understanding of the pathophysiology.

CHEST WALL INJURY

Epidemiology

Among victims sustaining thoracic trauma, approximately 50% will have chest wall injury: 10% minor, 35% major, and 5% flail chest injuries.[1] Chest wall injuries are not always obvious and can easily be overlooked during the initial evaluation.

Anatomy and Pathophysiology

An intact chest wall is necessary for normal ventilation. Outward expansion of the thorax by the respiratory muscles with descent of the diaphragm creates negative intrathoracic pressure. This causes passive air entry into the lungs during inspiration. Chest trauma, particularly blunt trauma, can severely disturb the physiology of respiration. Fortunately, most individuals have substantial respiratory reserve and can tolerate significant chest wall injury with adequate support.

Clinical Features

Elderly patients or those with preexisting pulmonary disease are sometimes unable to compensate for even minor chest wall trauma and therefore require closer attention. It is important to completely disrobe the patient and observe the respiratory rate, adequacy of tidal volume, and respiratory effort. Many chest wall injuries may be detected only by careful palpation of the chest wall, noting any areas of deformity, tenderness, or crepitus.

RIB FRACTURE

Epidemiology

Simple rib fractures are the most common form of significant chest injury, accounting for more than half the cases of blunt trauma.[1] The susceptibility to rib fracture increases with age. The importance of this injury is not the fracture itself but rather the associated potential complications, particularly pneumothorax, hemothorax, pulmonary contusions, and post-traumatic pneumonia. Rib fractures in children signify serious trauma to the thorax and have a high incidence of underlying injury.

Anatomy and Pathophysiology

Ribs usually break at the point of impact or at the posterior angle or posterolateral area, which is structurally the weakest area. The fourth through ninth ribs are most commonly involved. Ribs 1 to 3 are relatively protected, and ribs 9 to 12 are more mobile at the anterior end. This confers the relative resistance to fracture of the "high" and "low" ribs. Fractures occur more commonly in adults than in children, and this is attributed to the relative inelasticity of the older chest wall compared with the more compliant chest wall in children.

The true danger of rib fracture involves not the rib itself but the potential for penetrating injury to the pleura, lung, liver, or spleen. Fractures of ribs 9 to 11 are associated with intra-abdominal

www.ketabpezeshki.com 66485457-66963820

injury. Patients with right-sided rib fractures are almost three times more likely to have a hepatic injury, and patients with left-sided rib fractures are almost four times more likely to have a splenic injury.[3] Fractures of ribs 1 to 3 may indicate severe intrathoracic injury. The presence of two or more rib fractures at any level is associated with a higher incidence of internal injuries. Elderly patients with multiple rib fractures have a greater incidence of pneumonia and a higher mortality compared with patients younger than age 65 years.[4-6] To prevent a minor injury from developing into a serious complication, these fractures should be diagnosed rapidly and treated expectantly.

Clinical Features

The diagnosis can be suspected clinically, with tenderness, bony crepitus, ecchymosis, and muscle spasm over the rib being the most common findings. Also, bimanual compression of the thoracic cage remote from the site of injury (barrel compression test) usually produces pain at the site of fracture.

Diagnostic Strategies

Although clinical impression and physical findings are sensitive, they are not specific and are therefore unreliable for making an accurate diagnosis. Chest x-ray films often do not demonstrate the presence of rib fractures but are of greatest value in suggesting significant intrathoracic and mediastinal injuries. Although the upright posteroanterior chest radiograph has a higher yield in detecting rib fractures or their complications compared with other views, CT scans are significantly more effective than chest x-ray examination in detecting rib fractures (Fig. 45-1).[7] Rib series and expiratory, oblique, and cone-down views should not be used routinely. However, if simple rib fractures are strongly suspected or recognized on a clinical basis, there is no need to routinely obtain a CT scan unless other intrathoracic pathology needs to be studied.

Nonetheless, x-ray studies are often ordered, even though 50% of single-rib fractures are not seen on the initial x-ray film. A CT scan should be considered based on the mechanism of injury, physical examination, hemodynamic and respiratory parameters, abnormal findings on chest x-ray examination (especially widened mediastinum), or clinical evidence of multiple rib fractures, especially of the lower ribs (which may herald a splenic or hepatic injury).

Figure 45-1. Multiple rib fractures seen on chest computed tomography scan. (Also note presence of bilateral hemothoraces.)

Management

Treatment of patients with acute rib fractures is based on adequate pain relief and the maintenance of pulmonary function. Oral pain medications are usually sufficient for young and healthy patients. Continuing daily activities and deep breathing should be stressed to ensure ventilation and prevent atelectasis. It is helpful to advise patients to take their pain medications and wait 30 to 45 minutes before performing deep breathing exercises, perhaps with an incentive spirometer. Pain relief should be effective or patients will not maintain activity. Binders, belts, and other restrictive devices should not be used because although they can decrease pain, they also promote hypoventilation with subsequent atelectasis and pneumonia.

The greater the number of fractured ribs, the higher the mortality and morbidity rates. Patients with three or more fractured ribs, despite the lack of other traumatic injuries, should likely be hospitalized to receive aggressive pulmonary therapy and appropriate effective analgesia. Elderly patients with six or more fractured ribs should be treated in intensive care units owing to high morbidity and mortality. Older patients will probably require narcotic preparations, but care should be taken to avoid oversedation because of the potential for respiratory failure.[8]

Multiple rib fractures in trauma patients are associated with significant morbidity and mortality. Intercostal nerve blocks with a long-acting anesthetic such as bupivacaine with epinephrine may relieve symptoms up to 12 hours with excellent results. Such nerve blocks are achieved by administration of 1 or 2% lidocaine or 0.25% bupivacaine along the inferior rib margin several centimeters posterior to the site of the fracture. One rib above and one rib below the fractured rib should also be blocked for optimal analgesia. Other alternatives for hospitalized patients include patient-controlled analgesia, parenteral opiates, and thoracic epidural analgesia.[9]

Clinical Course

Most rib fractures heal uneventfully within 3 to 6 weeks, and patients should expect a gradual decrease in their discomfort during this period. Analgesics are usually necessary during the first 1 or 2 weeks. However, in addition to the complications of hemopneumothorax, atelectasis, pulmonary contusion, and pneumonia, rib fractures can result in post-traumatic neuroma or costochondral separation. These unusual complications are painful and heal slowly. Special attention should be paid to patients with displaced rib fractures, who may develop delayed hemorrhage resulting in death, typically from intercostal artery tears that clot off and then rebleed.[10] In these patients, admission and close observation for these delayed sequelae are typically warranted.

STERNAL FRACTURE

Epidemiology

Sternal fractures and dislocations are caused primarily by anterior blunt chest trauma, usually from MVCs when the chest strikes the steering wheel. Risk factors for sternal fracture from blunt trauma include types of vehicular passenger restraint systems and patient age. Restrained passengers are more likely than unrestrained passengers to sustain sternal fracture. In fact, the rate of occurrence of sternal fractures has increased threefold since the use of across-the-shoulder seat belts became widespread.

Anatomy and Pathophysiology

Sternal fracture usually results from the diagonal strap of a seat belt restraining the upper part of the sternum. During rapid

www.ketabpezeshki.com 66485457-66963820

deceleration from a frontal impact, the forward thrust of the body against the fixed seat belt across the sternum results in a fracture at that location. The location of the sternal fracture varies depending on the position of the belt, patient size, the magnitude of the impact, and the vector of the forces.

Similarly, depending on patient age, the likelihood of sternal fracture is variable. In general, sternal fractures are more common in older patients than in younger patients, and they are slightly more common in women than in men. It is believed that the more elastic and pliable chest wall of younger people allows more efficient transmission of kinetic energy to the underlying mediastinum. Although skeletal injury is less likely to occur in younger patients, damage to soft tissue structures underneath is greater. In older patients, the energy of impact is dissipated in the sternum, resulting in fewer intrathoracic injuries but a higher frequency of sternal fractures. Multiple rib fractures and lung contusion are concomitant injuries in more than 10% of diagnosed sternal fractures.

The natural history of a nondisplaced sternal fracture is contrary to intuition. It had been thought that the magnitude of the forces required to fracture the sternum must be associated with significant trauma to the mediastinal structures. However, isolated sternal fractures are relatively benign, with low mortality (<1%) and low intrathoracic morbidity.[11]

Cardiac complications, such as myocardial contusion, occur in 1.5 to 6% of cases. There is no association between sternal fracture and aortic rupture. Spinal fractures are seen in less than 10% of cases and rib fractures in 21%.[12] Although sternal fractures may occur in the context of major blunt chest trauma, the presence of a sternal fracture does not imply other major life-threatening conditions. However, associated mediastinal injuries should be considered.

Mediastinal hematomas, whether or not they are related to aortic injuries, can be life-threatening. The dual problem of acute blood loss and sudden alterations in cardiopulmonary physiology can result in hemodynamic deterioration. In addition to circulatory collapse from exsanguination, mediastinal hematomas can cause death from compression of adjacent structures.

Clinical Features

Sternal fractures typically cause anterior chest pain, point tenderness over the sternum, ecchymosis, soft tissue swelling, or palpable deformity. These findings together with the history can often lead to the diagnosis.

Diagnostic Strategies

Most sternal fractures are transverse, and a lateral radiographic view is often diagnostic. These fractures can be missed radiographically because a lateral plain chest x-ray film is not usually obtained during the initial trauma evaluation. Furthermore, plain films are sometimes inconclusive. Even if the sternal fracture is diagnosed by plain radiographs, the extent of the injury is often underappreciated. The advent of helical CT, especially with three-dimensional images of the skeletal system, has resulted in markedly improved diagnosis of sternal fractures. Emerging literature suggests that ultrasound (US) may be more sensitive than plain radiography.[13]

Although most nondisplaced sternal fractures are not associated with significant intrathoracic injuries, a conservative approach is to obtain a chest CT scan to rule out any other pathology. This may be clinically important in determining the best management of the sternal fracture in terms of conservative management versus surgical fixation.[14] Chest CT also helps to rule out any associated mediastinal injuries. A 12-lead electrocardiogram (ECG) should also be obtained during the initial evaluation.

Management

Treatment consists of providing adequate analgesia. In the absence of associated injuries, more than 95% of patients with isolated sternal fractures who can achieve adequate pain control with oral medications can be safely discharged home. However, a small subset of patients have sternal fractures that are displaced or produce overlying bone fragments that may cause severe pain, respiratory compromise, or physical deformity and, if untreated mechanically, result in nonunion. These patients are best referred for operative fixation.[15]

COSTOCHONDRAL SEPARATION

Costochondral separation may also be caused by blunt anterior chest trauma. The signs and symptoms are similar to those of rib fracture, but because of the poor vascularity of healing cartilage, pain may persist for many weeks. The chest x-ray film is usually normal, but there is a snapping sensation with deep respiration. Outpatient management of these patients is similar to that of patients with rib fractures. Flail chest can also occur from massive costochondral separation at one or multiple points, but this is uncommon.

FLAIL CHEST

Epidemiology

Flail chest is a fairly uncommon injury that is most often accompanied by a significant underlying pulmonary parenchymal injury and can be a life-threatening thoracic injury. Its management is often complicated by the other injuries with which it is frequently associated.

Anatomy and Pathophysiology

Flail chest results when three or more adjacent ribs are fractured at two points, allowing a freely moving segment of the chest wall to move in paradoxical motion (Fig. 45-2). It can also occur with costochondral separation or vertical sternal fracture in combination with rib fractures. Because of its common association with pulmonary contusion, it is one of the most serious chest wall injuries (Fig. 45-3).

The physiology of respiration is adversely affected by flail chest in a number of ways. The paradoxical motion of the chest wall is

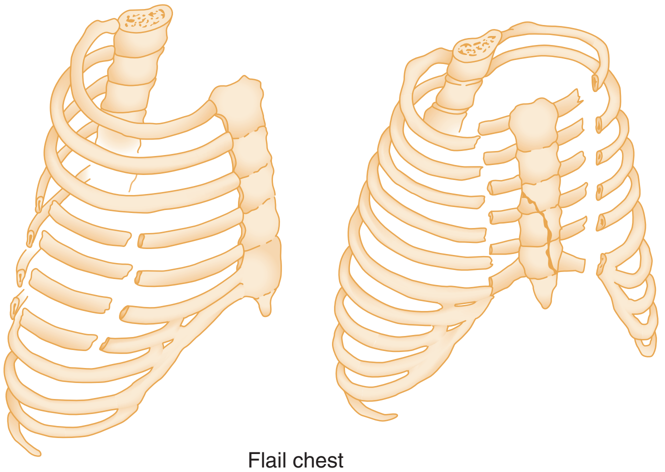


Figure 45-2. Flail chest. Fracture of several adjacent ribs in two places with lateral flail or central flail segments.

www.ketabpezeshki.com 66485457-66963820

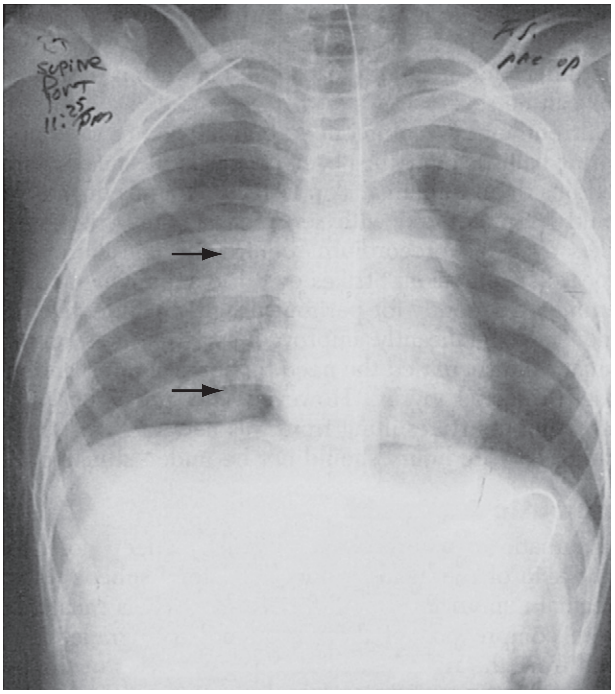


Figure 45-3. Bilateral alveolar infiltrates (*arrows*) suggesting pulmonary contusion. Pneumopericardium and pneumomediastinum are also present.

the hallmark of this condition, with the flail segment moving inward with inspiration and outward with expiration. Underlying pulmonary contusion is considered to be the major cause of respiratory insufficiency with flail chest. In addition, the pain of the injury causes muscular splinting with resultant atelectasis, hypoxemia, and decreased cardiac output.

Clinical Features

Flail chest is usually diagnosed by physical examination. This requires exposure of the patient's thorax and examination of the chest wall for paradoxical motion. Pain, tenderness, and crepitus can direct the examiner. In addition, the flail segment can sometimes be visualized to move separately and in an opposite direction from the rest of the thoracic cage during the respiratory cycle. Endotracheal intubation and positive-pressure ventilation will internally splint the chest wall, making the flail segment difficult to detect on physical examination.

Diagnostic Strategies

Multiple rib fractures can usually be identified on chest x-ray films. CT scan is much more accurate than plain films in detecting the presence and extent of underlying injury and contusion to the lung parenchyma. It is used routinely in some centers for all patients with major chest trauma.

Management

Out-of-hospital or emergency department (ED) stabilization of the flail segment by positioning the person with the injured side down or placing a sandbag on the affected segments has been abandoned. These interventions actually inhibit expansion of the chest and increase atelectasis of the injured lung. Oxygen should be administered, cardiac and oximetry monitors applied if available, and the patient observed for signs of an associated injury such as tension pneumothorax. A 12-lead ECG and cardiac enzymes should be obtained, with consideration given to obtaining an echocardiogram for significant dysrhythmias, high-grade blocks, or hemodynamic instability unexplained by other causes such as hemorrhage.

The outcome of flail chest injury is a function of associated injuries. Because many different physiologic mechanisms have been implicated in flail chest, there is no consensus about hospital treatment. The cornerstones of therapy include aggressive pulmonary physiotherapy, effective analgesia, selective use of endotracheal intubation and mechanical ventilation, and close observation for respiratory compromise.

Respiratory decompensation is the primary indication for endotracheal intubation and mechanical ventilation for patients with flail chest. Obvious problems, such as hemopneumothorax or severe pain, should be corrected before intubation and ventilation are presumed necessary. In fact, in the awake and cooperative patient, noninvasive continuous positive airway pressure (CPAP) by mask may obviate the need for intubation.[16] In general, the most conservative methods for maintaining adequate oxygenation and preventing complications should be used. Adequate analgesia is of paramount importance in patient recovery and may contribute to the return of normal respiratory mechanics.

Patients without respiratory compromise generally do well without ventilatory assistance. Several studies have found that patients treated with intercostal nerve blocks or high segmental epidural analgesia, oxygen, intensive chest physiotherapy, careful fluid management, and CPAP, with intubation reserved for patients in whom this therapy fails, have shorter hospital courses, fewer complications, and lower mortality rates.[17] Avoidance of endotracheal intubation, particularly prolonged intubation, is important in preventing pulmonary morbidity because intubation increases the risk of pneumonia.[18]

There is also evidence that early operative internal fixation of the flail segment results in a speedier recovery, decreased complications, and better cosmetic and functional results, and that it is cost-effective. Indications for open fixation for flail chest include patients who are unable to be weaned from the ventilator secondary to the mechanics of flail chest, persistent pain, severe chest wall instability, and a progressive decline in pulmonary functions.[15,19]

The patient with flail chest should be treated in the ED as if pulmonary contusion exists regardless of whether mechanical ventilation is used. The mortality rate associated with flail chest is between 8 and 35% and is directly related to the underlying and associated injuries. However, unilateral flail chest was reported to be infrequently associated with death in one large series.[20] Those who recover from flail chest may develop long-term disability with dyspnea, chronic thoracic pain, and exercise intolerance.

NONPENETRATING BALLISTIC INJURY

Epidemiology

Many law enforcement officers, emergency medical services personnel, and private security guards wear lightweight synthetic body armor for protection against gunshot injury. In addition, there have been a number of reports of armed robbers wearing such vests in anticipation of exchanging gunfire with police or security personnel.[21] These vests are "bullet resistant" rather than "bulletproof," depending on the weapon being used against them. They are composed of many different combinations of synthetic fibers such as Kevlar.

Another type of nonpenetrating ballistic injury is caused by rubber bullets and beanbag shotgun shells. Rubber bullets have been used for many years by police agencies throughout the world

www.ketabpezeshki.com 66485457-66963820

for crowd dispersal and for nonlethal use of force. Beanbag shotgun shells are nylon bags filled with pellets, which are fired from a standard shotgun. Both of these projectiles have the potential to cause serious injury despite their classification of "nonmetal" or "less-than-lethal" use of force.[22]

Anatomy and Pathophysiology

Although bullet penetration is usually prevented, the heart, liver, spleen, lung, and spinal cord are vulnerable to nonpenetrating ballistic injury that may occur despite innocent-appearing skin lesions.

Bullet-resistant vests are usually capable of stopping penetration by the low-velocity missiles of most handguns, but the kinetic energy of the missile can be transmitted through the layers of protective cloth or armor and produce significant injury without penetration.

Clinical Features

Patients who have been shot with "less-than-lethal projectiles" or with standard bullets while wearing bullet-resistant vests usually have erythema, ecchymosis, and marked tenderness to palpation over the affected area. There may be a projectile, such as a beanbag, still located in the wound. The area of tenderness and surrounding structures should be carefully palpated to identify any subcutaneous emphysema, crepitus, or bony step-offs.

Diagnostic Strategies

Plain film radiography should be used to identify any retained foreign bodies and any fractures or cortical violation. Strong consideration should be given to CT scanning, based on the type of projectile, the clinical examination, and the degree of tenderness and location of the wounds, to look for retained foreign bodies or "occult" injuries, such as pneumothorax, hemothorax, or intraperitoneal penetration.

Management

It is recommended that all victims of nonpenetrating ballistic injury be observed closely, with overnight observation considered. This is particularly true for injuries over the abdomen, where serial examinations in coordination with CT scanning will help to detect internal injuries that may manifest in a delayed manner.[23] Use of protective body armor has resulted in significantly improved survival rates and has dramatically decreased the need for surgical intervention in those protected by it. In addition, "less-than-lethal" projectiles, such as rubber bullets and beanbag shotgun shells, offer law enforcement an alternative to conventional weapons that are considered "use of deadly force." However, the possibility of an underlying injury resulting from this form of nonpenetrating ballistic injury should not be underestimated.

TRAUMATIC ASPHYXIA

Anatomy and Pathophysiology

Traumatic asphyxia is a rare syndrome caused by a severe compression of the thorax by a very heavy object causing a marked increase in thoracic and superior vena caval pressure, resulting in retrograde flow of blood from the right side of the heart into the great veins of the head and neck. The vena cava and the large veins of the head and neck do not have valves and therefore allow the transmission of pressure to the capillaries of the head and neck, which become engorged with blood.

Clinical Features

Traumatic asphyxia is characterized by a deep violet color of the skin of the head and neck, bilateral subconjunctival hemorrhages, petechiae, and facial edema. Stagnation develops from capillary atony and dilation, and as the blood desaturates, purplish discoloration of the skin occurs.[24] Although the appearance of these patients can be quite dramatic, the condition is usually benign and self-limited if the heavy object was removed before any hypoxic complications such as anoxic encephalopathy occurred.[25]

Diagnostic Strategies

The clinical significance lies with the possibility of intrathoracic injury from the violent force necessary to produce traumatic asphyxia. Chest wall and pulmonary injuries are most common. If the patient's examination and chest x-ray film show worrisome features, CT scanning of the chest should be performed.

Disturbance of vision has been attributed both to retinal hemorrhage, which is generally a permanent injury, and to retinal edema, which may cause transient changes in vision. One third of these patients lose consciousness, usually at the time of injury. Intracranial hemorrhages are rare, probably because of the shock-absorbing ability of the venous sinuses, but CT scan of the head should be done in patients with neurologic complaints. Neurologic manifestations typically clear within 24 to 48 hours, and long-term sequelae are uncommon.[25]

PULMONARY INJURIES

Subcutaneous Emphysema

Anatomy and Pathophysiology

Subcutaneous emphysema in the presence of chest wall trauma usually indicates a more serious thoracic injury. Although the presence of air in the tissues is a benign condition, in the context of chest trauma it usually represents serious injury to any air-containing structure within the thorax. Air enters the tissues either extrapleurally or intrapleurally. Extrapleural tears in the tracheobronchial tree allow air to leak into the mediastinum and soft tissues of the anterior neck, producing a pneumomediastinum, which rarely may progress to a tension pneumomediastinum. This most often occurs in patients who are undergoing positive-pressure ventilation and have a pneumopericardium visible on chest x-ray examination. They may also have Hamman's crunch, which is a crackling sound with each heartbeat, heard on cardiac auscultation. Intrapleural lesions, however, usually produce a pneumothorax by allowing air to escape the lung through the visceral pleura into the pleural space and then through the parietal pleura into the thoracic wall.

An esophageal tear resulting from Boerhaave's syndrome or penetrating injury may also produce a pneumomediastinum manifested by subcutaneous emphysema over the supraclavicular area and anterior neck. An additional cause of subcutaneous emphysema, which may or may not be indicative of intrathoracic injury, is found immediately adjacent to a penetrating wound of the thorax. A small amount of air may be introduced into the adjacent subcutaneous tissues from the outside at the time of penetration. However, it is assumed that this is secondary to a pneumothorax or pneumomediastinum, and appropriate diagnostic and therapeutic maneuvers to rule out or treat the intrathoracic injury should be carried out.

The presence of localized subcutaneous emphysema over the chest wall in the presence of blunt trauma is usually indicative of the presence of a traumatic pneumothorax, whereas the presence

www.ketabpezeshki.com 66485457-66963820

of subcutaneous emphysema over the supraclavicular area and anterior neck usually indicates a pneumomediastinum.

Management

Tension pneumothorax is considered and treated appropriately. If a tension pneumopericardium is suspected, then immediate pericardiocentesis with aspiration of air from the pericardial space may be lifesaving.

Although subcutaneous emphysema is a benign condition, massive accumulations can be uncomfortable to the patient. The underlying cause, such as pneumothorax, ruptured bronchus, or ruptured esophagus, is treated appropriately. Benign pneumomediastinum secondary to a Valsalva maneuver is treated with observation and high-flow oxygen to facilitate the reabsorption of nitrogen from tissues because the volume of nitrogen causes the discomfort.

Pulmonary Contusion

Epidemiology

Pulmonary contusion is reported to be present in 30 to 75% of patients with significant blunt chest trauma, most often from MVCs with rapid deceleration.[1] Pulmonary contusion can also be caused by high-velocity missile wounds and the high-energy shock waves of an explosion in air or water. Pulmonary contusion is the most common significant chest injury in children, and it is most commonly caused by an MVC or an automobile versus pedestrian accident.[21]

Anatomy and Pathophysiology

Pulmonary contusion is a direct bruise of the lung parenchyma followed by alveolar edema and hemorrhage but without an accompanying pulmonary laceration, as first described by Morgagni in 1761.[26]

The early diagnosis of pulmonary contusion is important if treatment is to be successful. The onset may be insidious, and therefore it should be suspected from the history of the mechanism of injury rather than the initial chest radiograph. Great force is required to produce pulmonary contusion, such as from a fall from height, an MVC, and other forms of significant trauma.

Clinical Features

The clinical manifestations include dyspnea, tachypnea, cyanosis, tachycardia, hypotension, and chest wall bruising. There are no specific signs for pulmonary contusion, but hemoptysis may be seen sometime during the patient's course, and moist rales or absent breath sounds may be heard on auscultation. Palpation of the chest wall commonly reveals fractured ribs. If flail chest is discovered, pulmonary contusion is commonly present.

Surprisingly, many of the worst contusions occur in patients without rib fractures. It has been theorized that the more elastic chest wall, as in younger individuals, transmits increased force to the thoracic contents. Although isolated pulmonary contusions can exist, they are associated with extrathoracic injuries in the majority of patients.[27]

Diagnostic Strategies

Care is taken not to focus exclusively on more dramatic injuries at the expense of failing to recognize the evolving pulmonary contusion. This is particularly true with the initial x-ray studies when overlying rib fracture, pneumothorax, aspiration pneumonitis, or poor radiograph quality may mask the contusion.

Figure 45-4. Chest computed tomography scan showing bilateral alveolar infiltrates suggesting pulmonary contusion. There are also multiple rib fractures and subcutaneous emphysema.

Typical radiographic findings begin to appear within minutes of injury and range from patchy, irregular, alveolar infiltrate to frank consolidation (Fig. 45-4). Usually, these changes are present on the initial examination, and they are almost always present within 6 hours. The rapidity of changes on chest x-ray visualization usually correlates with the severity of the contusion. Pulmonary contusion should be differentiated from acute respiratory distress syndrome (ARDS), with which it is often confused because the radiographic appearance of the two conditions may be similar. The contusion usually manifests within minutes of the initial injury, is usually localized to a segment or a lobe, is often apparent on the initial chest study, and tends to last 48 to 72 hours. ARDS is diffuse, and its development is usually delayed, with onset typically between 24 and 72 hours after injury.[28]

The increased frequency of CT scans for blunt trauma patients has resulted in a corresponding increase in the diagnosis of pulmonary contusion. CT scans have been shown to detect twice as many pulmonary contusions as plain radiographs.[7] Some authors suggest that pulmonary contusions visible only on CT scan and not on plain radiographs may not be clinically significant.[29]

Chest CT scan is particularly valuable to identify a pulmonary contusion in the acute phase after injury because plain chest x-ray films have a low sensitivity.[7] Although CT scan may not be necessary to make the diagnosis of a pulmonary contusion that is evident on plain chest radiography, it may be helpful to further define the extent of the contusion and to identify other thoracic injuries. Infectious complications, sternoclavicular joint dislocation, pneumothorax, misplaced endotracheal tube, intraperitoneal air, and vertebral fracture have all been identified by CT scan in the trauma patient. Occult pulmonary contusions are those that are visible only on CT scan, not plain radiographs, and usually involve more than 20% of the lung volume. These "occult" pulmonary contusions are not associated with a worse clinical outcome as compared with blunt trauma patients without pulmonary contusion.[29] Patients with pulmonary contusion visible on both conventional chest radiographs and the CT scan frequently have a higher contusion volume and a worse outcome than patients with occult pulmonary contusion. Thus pulmonary contusions that are visible on plain chest radiographs have a higher morbidity and mortality and should therefore receive special medical attention as compared with contusions only seen on the chest CT scan.

Arterial blood gases may be helpful in making the diagnosis of pulmonary contusion because most patients are hypoxemic at the time of admission. A low partial pressure of oxygen (Po_2) alone may be reason to suspect pulmonary contusion. A widening alveolar-arterial oxygen difference indicates a decreasing

www.ketabpezeshki.com 66485457-66963820

pulmonary diffusion capacity of the patient's contused lung, and it is one of the earliest and most accurate means of assessing the current status, progress, and prognosis.

Management

Treatment for pulmonary contusion is primarily supportive.[29] When only one lung has been severely contused and has caused significant hypoxemia, consideration should be given to intubating and ventilating each lung separately with a dual-lumen endotracheal tube and two ventilators. This allows for the difference in compliance between the injured and the normal lung and prevents hyperexpansion of one lung and gradual collapse of the other.[30] As with flail chest, however, intubation and mechanical ventilation should be avoided if possible because they are associated with an increase in morbidity, including pneumonia, sepsis, pneumothorax, hypercoagulability, and longer hospitalization.[31] The need for mechanical ventilation increases significantly when the area of pulmonary contusion exceeds 20% of total lung volume.[32]

Certain patients may benefit from a trial of noninvasive positive-pressure ventilation with BPAP or CPAP to avoid intubation and mechanical ventilation. In those patients most severely injured with extensive pulmonary contusions and the development of ARDS with severe hypoxia refractory to conventional therapy, some small studies suggest a possible role for extracorporeal membrane oxygenation.[33]

Certain procedures may ameliorate the pulmonary contusion, including the restriction of intravenous fluids to maintain intravascular volume within strict limits and aggressive supportive care consisting of vigorous tracheobronchial toilet, suctioning, and pain relief. These maneuvers may preclude the need for ventilator support and allow a more selective approach to flail chest and pulmonary contusion.

Another area of controversy in the management of pulmonary contusions is the appropriate use of crystalloid versus colloid solutions in resuscitation of the multiply injured patient with suspected contusion. Because of the potential for colloid sequestration within the pulmonary alveoli as a result of capillary leak, colloids are not recommended for use in treating these patients.

Pneumonia is the most common complication of pulmonary contusions, and it significantly worsens the prognosis. It develops insidiously, especially in patients treated with prophylactic antibiotics. Antibiotics should be reserved for use with specific organisms rather than given prophylactically.

Pulmonary Laceration

The lungs are most often lacerated from penetrating injury, but they may also be injured by the inward projection of a fractured rib or avulsion of a pleural adhesion. These injuries are usually minor and rarely life-threatening, and they can usually be treated with continuous oxygen therapy, observation, or tube thoracostomy. Severe lacerations are present in only 3% of patients with thoracic trauma, and they are usually associated with hemopneumothorax, multiple displaced rib fractures, and hemoptysis. Often, these life-threatening lacerations require thoracotomy with resection or tractotomy to control bleeding.

Pneumothorax

Epidemiology

Pneumothorax, which is the accumulation of air in the pleural space, is a common complication of chest trauma. It is reported to be present in 15 to 50% of patients who sustain significant chest trauma, and it is invariably present in those with transpleural penetrating injuries.[1]

Anatomy and Pathophysiology

Pneumothorax can be divided into three types depending on whether air has direct access to the pleural cavity: simple, communicating, and tension. A pneumothorax is considered simple (Fig. 45-5) when there is no communication with the atmosphere or any shift of the mediastinum or hemidiaphragm resulting from the accumulation of air. It can be graded according to the degree of collapse as visualized on the chest radiograph. A small pneumothorax occupies 15% or less of the pleural cavity, a moderate one 15 to 60%, and a large pneumothorax more than 60%. Traumatic pneumothorax is most often caused by a fractured rib that is driven inward, lacerating the pleura. It may also occur without a fracture when the impact is delivered at full inspiration with the glottis closed, leading to a tremendous increase in intra-alveolar pressure and the subsequent rupture of the alveoli. A penetrating injury, such as a gunshot or stab wound, may also produce a simple pneumothorax if there is no free communication with the atmosphere (Fig. 45-6).

Communicating Pneumothorax. A communicating pneumothorax (Fig. 45-7) is associated with a defect in the chest wall and most commonly occurs in combat injuries. In the civilian sector, this injury is typically secondary to shotgun wounds. Air can sometimes be heard flowing sonorously in and out of the defect, prompting the term "sucking chest wound." The loss of chest wall

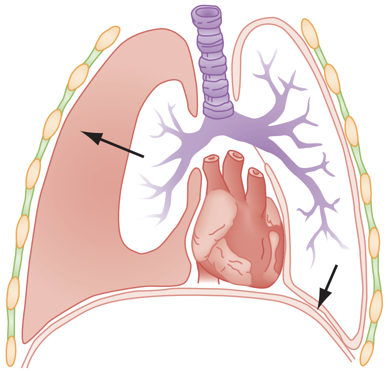


Figure 45-5. Closed pneumothorax. Simple pneumothorax is present in the right lung with air in the pleural cavity and collapse of the right lung.

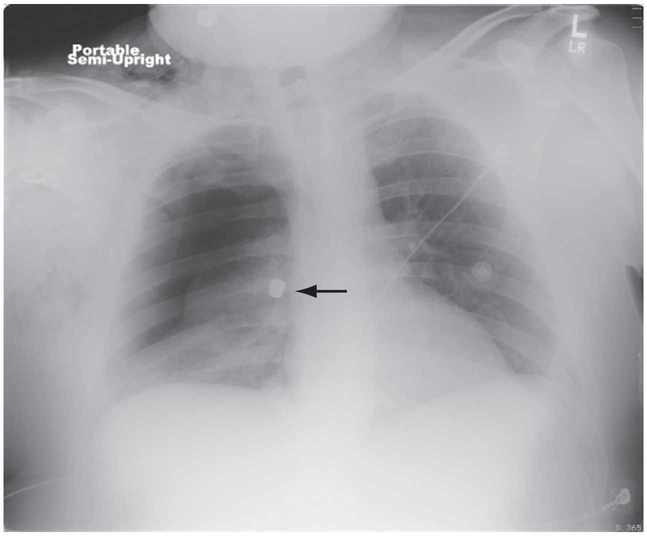


Figure 45-6. Chest radiograph showing a moderate-sized right pneumothorax. A bullet (*arrow*) can be seen near the right mediastinum.

www.ketabpezeshki.com 66485457-66963820

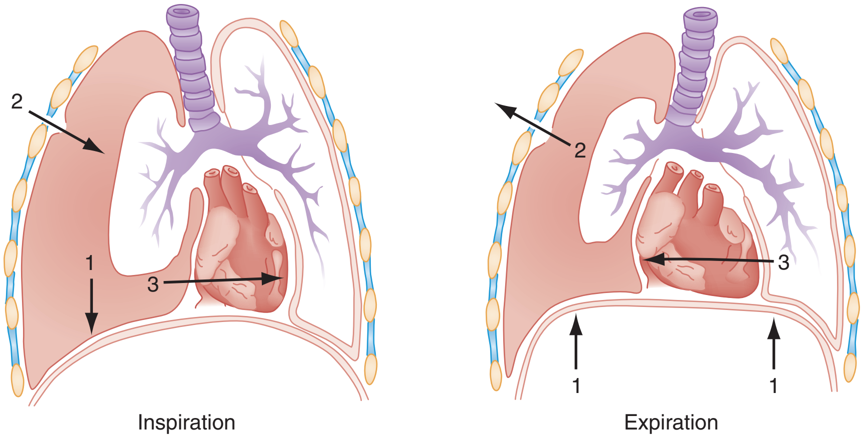


Figure 45-7. Inspiration: The diaphragm contracts causing negative intrathoracic pressure (*arrow 1*) that draws air through the sucking chest wound in the pleural cavity (*arrow 2*) and causing the mediastinal structures to shift to the patient's left (*arrow 3*). Expiration: the diaphragm recoils (*arrow 1*) causing air to exit the chest (*arrow 2*) and allowing the mediastium to shift back to normal position (*arrow 3*). The collapsed lung paradoxically shrinks on inspiration and expands on expiration.

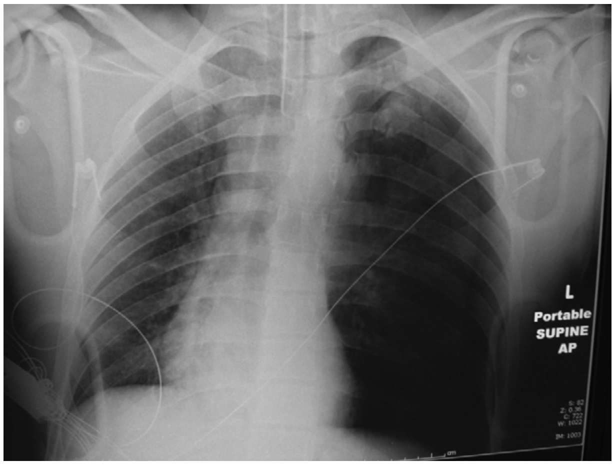


Figure 45-8. Tension pneumothorax seen in intubated patient.

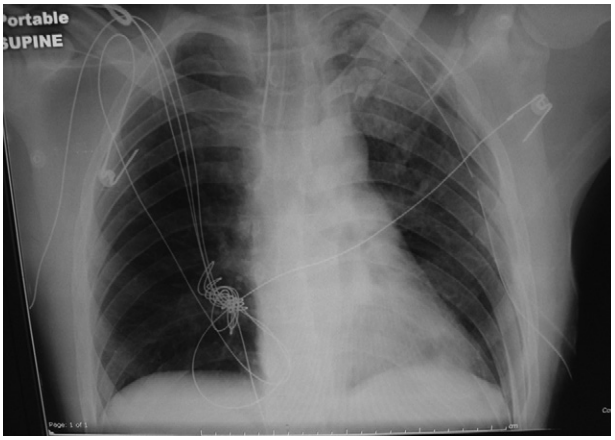


Figure 45-9. Resolution of the tension pneumothorax shown in Figure 45-7 with placement of a left-sided tube thoracostomy.

integrity causes the involved lung to paradoxically collapse on inspiration and expand slightly on expiration, forcing air in and out of the wound. This results in a large functional dead space for the normal lung and, together with the loss of ventilation of the involved lung, produces a severe ventilatory disturbance.

Tension Pneumothorax. The progressive accumulation of air under pressure within the pleural cavity, with shift of the mediastinum to the opposite hemithorax and compression of the contralateral lung and great vessels, is the constellations of findings in tension pneumothorax (Figs. 45-8 and 45-9). It occurs when the injury acts like a one-way valve, prevents free bilateral communication with the atmosphere, and leads to a progressive increase of intrapleural pressure. Air enters on inspiration but cannot exit with expiration. The resulting shift of mediastinal contents compresses the vena cava and distorts the cavoatrial junction, leading to decreased diastolic filling of the heart and subsequent decreased cardiac output. These changes result in the rapid onset of hypoxia, acidosis, and shock.

Clinical Features

Shortness of breath and chest pain are the most common presenting complaints of pneumothorax. The patient's appearance is highly variable, ranging from acutely ill with cyanosis and tachypnea to misleadingly healthy. The signs and symptoms are not always correlated with the degree of pneumothorax. The physical examination may reveal decreased or absent breath sounds and hyper-resonance over the involved side as well as subcutaneous emphysema, but small pneumothoraces may not be detectable on physical examination.

Patients with tension pneumothorax become acutely ill within minutes and develop severe cardiovascular and respiratory distress. They are dyspneic, agitated, restless, cyanotic, tachycardic, and hypotensive and display decreasing mental activity. The cardinal signs of tension pneumothorax are tachycardia, jugular venous distention (JVD), and absent breath sounds on the ipsilateral side. However, JVD may not reliably be present with massive blood loss. Hypotension will not occur as early as hypoxia and may represent a preterminal event.

Diagnostic Strategies

Because intrapleural air tends to collect at the apex of the lung, the initial chest radiograph should be an upright full inspiratory film if the patient's condition permits. An upright film will often reveal small pleural effusions that are not visible on supine films, and it also allows better visualization of the mediastinum. Although the chest radiograph has traditionally been the preferred initial study for diagnosing a simple pneumothorax, emerging literature suggests that a simple pneumothorax can be identified during the initial US examination of the trauma patient as part of the extended focused assessment with sonography in trauma (E-FAST)

www.ketabpezeshki.com 66485457-66963820

examination. Because FAST is becoming part of the routine initial evaluation of trauma patients, evaluation for the presence of a pneumothorax should be included in this rapid bedside examination, especially because this is performed before chest radiography. In fact, several studies have found that the US has greater sensitivity for pneumothorax than chest radiography.[34-36]

If a pneumothorax is suspected but not visualized on the initial inspiratory film, an expiratory film should be obtained because it makes the pneumothorax more apparent by reducing the lung volume. Notably, as many as one third of initial chest x-ray films will not detect a pneumothorax in trauma patients.[7] Although it is not recommended as a primary method of diagnosing pneumothorax, CT is very sensitive in finding small pneumothoraces even in supine patients. When CT scans are obtained to evaluate the abdomen, it may be helpful to take a few low cuts into the chest to exclude the presence of a small pneumothorax.

Occult Pneumothorax

A pneumothorax that is absent on the initial chest radiograph but is identified on subsequent chest or abdominal CT is called an *occult pneumothorax*. Occult pneumothorax is being diagnosed more frequently given the increased use of CT.[37,38] Studies have found rates as high as 75% for diagnosis on CT scan of occult pneumothorax that was absent on initial chest radiographs (Fig. 45-10).[7,37-39]

The diagnosis and treatment of tension pneumothorax should not be delayed. Although tension pneumothorax usually occurs dramatically, the clinical diagnosis is occasionally obscure, and chest x-ray examination may be required to suggest the diagnosis, particularly in patients on mechanical ventilation. This film will show complete lung collapse and shift of the mediastinum to the opposite side. Ideally, the diagnosis and treatment should be completed without a chest x-ray examination because the delay in obtaining this radiograph may adversely affect patient outcome. As previously stated, tension pneumothorax will typically cause significant hemodynamic compromise and therefore remains a clinical diagnosis.

Management

In the setting of penetrating trauma in which the patient is asymptomatic and the initial chest x-ray study is negative, the patient can be safely observed and the x-ray examination repeated. Previously, it was thought that if the patient was still asymptomatic and the radiograph negative after 6 hours, the patient could be discharged. Recent experience indicates that 3 hours is probably effective and safe for observation, with repeat x-ray film before discharge for patients with penetrating trauma.[40] Patients with blunt trauma in whom clinical suspicion for pneumothorax is high should still undergo a 6-hour delayed chest x-ray examination before discharge. However, if the stable patient undergoes initial screening chest CT that is negative for pneumothorax or hemothorax, the literature suggests that obtaining a delayed chest x-ray film is unnecessary, and these patients may be discharged from the ED.[41]

Simple Pneumothorax. Treatment of a simple pneumothorax depends on its cause and size. Most advocate treating a traumatic pneumothorax with a chest tube to correct any respiratory compromise; treatment with a chest tube is generally thought to be safer than observation in these patients. Small pneumothoraces (i.e., <15%), whether spontaneous or traumatic, have been treated with hospitalization and careful observation if the patient is otherwise healthy and symptom free, if the patient does not need anesthesia or positive-pressure ventilation, and the pneumothorax is not increasing in size.

Isolated apical pneumothoraces of less than 25% may be observed in patients with stab wounds. This conservative method seldom has application in multisystem trauma, and a chest tube should be inserted immediately on any signs of deterioration. Some suggest that because it is small and lacks symptoms, occult traumatic pneumothorax found only on CT scan can be managed with observation and does not need treatment. Studies indicate that these injuries can be handled as small but initially detectable pneumothoraces, with observation in hemodynamically stable patients without symptoms. The data regarding the frequency with which patients with occult pneumothorax on mechanical ventilation will require tube thoracostomy are conflicting.[42-44] However, an occult pneumothorax may be observed in a stable patient even if he or she is placed on positive-pressure ventilation.[44]

Any moderate to large pneumothorax should be treated with a chest tube. The indications for tube thoracostomy (chest tube) are listed in Box 45-1. The preferred site for insertion is the fourth or fifth intercostal space at the midaxillary line. If the tube is positioned posteriorly and directed toward the apex, it can effectively remove both air and fluid. This lateral placement of the tube is preferred not only because it is more efficient but also because it does not produce an easily visible cosmetic defect, as does the anterior site at the second interspace at the midclavicular line. With multisystem trauma, an adequate size chest tube (36-F to 40-F in adults and 16-F to 32-F in children) should be used,

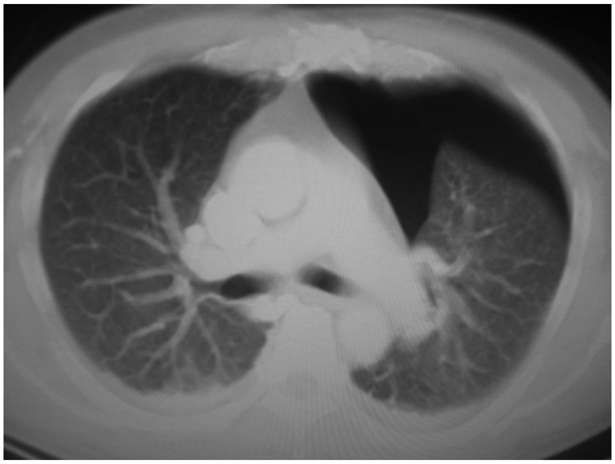


Figure 45-10. Occult pneumothorax. Large left-sided pneumothorax visible on chest computed tomography scan, which was not visible on chest x-ray film.

Box 45-1 Indications for Tube Thoracostomy

- Traumatic cause of pneumothorax (except asymptomatic, apical pneumothorax)
- Moderate to large pneumothorax
- Respiratory symptoms regardless of size of pneumothorax
- Increasing size of pneumothorax after initial conservative therapy
- Recurrence of pneumothorax after removal of the initial chest tube
- Patient requires ventilator support
- Patient requires general anesthesia
- Associated hemothorax
- Bilateral pneumothorax regardless of size
- Tension pneumothorax

From Dougall AM, et al: Chest trauma—current morbidity and mortality. J Trauma 17:547, 1977.

www.ketabpezeshki.com 66485457-66963820

particularly in cases of major trauma, when hemothorax is likely to occur.

Care is taken to be certain the vent holes along the side of the tube are all inside the chest cavity. A radiopaque line along the side of the tube with interruptions at these drainage holes helps greatly in radiographically interpreting tube position. The tube should be attached to a water seal drainage system that allows reexpansion of the pneumothorax. If there is significant air leak or a large hemothorax, the tube may be connected to a source of constant vacuum at 20 to 30 cm H_2O for more rapid reexpansion.

Tube thoracostomy does have some potentially serious complications, including the formation of a hemothorax, pulmonary edema, bronchopleural fistula, pleural leaks, empyema, subcutaneous emphysema, infection, intercostal artery laceration, contralateral pneumothorax, and parenchymal injury.[45-47] To reduce the incidence of empyema and pneumonitis, current recommendations include the administration of empirical antibiotics with all tube thoracostomy placements.[48] Pneumothoraces that have been present for more than 3 days should be reexpanded gradually without suction to avoid reexpansion pulmonary edema.

Communicating Pneumothorax. For a patient with a communicating pneumothorax in the out-of-hospital setting, the defect should be covered immediately, which helps convert the condition to a closed pneumothorax and eliminates the major physiologic abnormality. An occlusive dressing of petrolatum gauze can be applied, but care should be taken because this can convert the injury to a tension pneumothorax, especially in patients who are intubated and undergoing positive-pressure ventilation. The wound should never be packed because the negative pressure during inspiration can suck the dressing into the chest cavity. These considerations are not as important once the patient is in the ED, where endotracheal intubation and tube thoracostomy can be performed. Positive-pressure ventilation can then be started without the fear of producing a tension pneumothorax, and the patient can be prepared for definitive surgical repair.

Tension Pneumothorax. When the diagnosis of tension pneumothorax is suspected clinically, the pressure should be relieved immediately with needle thoracostomy, which is performed by inserting a large-bore (14-gauge or larger) catheter, at least 5 cm in length, through the second or third interspace anteriorly or the fourth or fifth interspace laterally on the involved side. Recent studies have suggested that some catheters may not be of sufficient length to penetrate the pleural space and that the lateral approach may be preferred. This method can be easily performed in the field or ED, allowing vital signs to improve during transport or preparation for a tube thoracostomy.[49]

The intubated patient in the ED who is receiving positive-pressure ventilation and external cardiac compressions is at particular risk for developing tension pneumothorax. Fractured ribs from cardiopulmonary resuscitation (CPR) can penetrate lung parenchyma and cause pneumothorax. Positive-pressure ventilation then increases intrapleural pressure and produces a tension pneumothorax. The earliest sign of this complication is an increase in resistance to ventilation. If the patient has vital signs, the blood pressure will fall and the central venous pressure (CVP) will rise. Misplacement of an endotracheal tube does not result in tension pneumothorax but, rather, asymmetry of breath sounds. If tension pneumothorax is suggested, the clinician should proceed with empirical emergent therapy.

Hemothorax

Epidemiology

Hemothorax, which is the accumulation of blood in the pleural space after blunt or penetrating chest trauma, is a common complication that may produce hypovolemic shock and dangerously reduce vital capacity. It is commonly associated with pneumothorax (25% of cases) as well as extrathoracic injuries (73% of cases).[50]

Box 45-2 Indications for Thoracotomy

- Initial thoracostomy tube drainage is more than 20 mL of blood per kilogram.
- Persistent bleeding at a rate greater than 7 mL/kg/hr is present.
- Increasing hemothorax seen on chest x-ray films.
- Patient remains hypotensive despite adequate blood replacement, and other sites of blood loss have been ruled out.
- Patient decompensates after initial response to resuscitation.

Anatomy and Pathophysiology

Hemorrhage from injured lung parenchyma is the most common cause of hemothorax, but this tends to be self-limited unless there is a major laceration. Specific vessels are less often the source of hemorrhage, with intercostal and internal mammary arteries causing hemothorax more often than hilar or great vessels. Bleeding from the intercostal arteries may be brisk, however, because they branch directly from the aorta.

Management

Close monitoring of the initial and ongoing rate of blood loss is performed. Immediate drainage of more than 1500 mL of blood from the pleural cavity is usually considered an indication for urgent thoracotomy. Perhaps even more predictive of the need for thoracotomy is a continued output of at least 200 mL/hr for 3 hours. General considerations for urgent thoracotomy are outlined in Box 45-2.[51]

Clinical Features

Depending on the rate and quantity of hemorrhage, varying degrees of hypovolemic shock will be manifested. Tactile fremitus is decreased, and breath sounds are diminished or absent.

Diagnostic Strategies

The upright chest radiograph remains the primary diagnostic study in the acute evaluation of hemothorax. A hemothorax is noted as meniscus of fluid blunting the costophrenic angle and tracking up the pleural margins of the chest wall when viewed on the upright chest x-ray film. Blunting of the costophrenic angles on upright chest radiograph requires at least 200 to 300 mL of fluid. The supine view chest film is less accurate, and it may be more difficult to make the diagnosis with the patient in this position. Unfortunately, this is often the only film available because of the patient's unstable condition. In the supine patient, blood layers posteriorly, creating a diffuse haziness that can be rather subtle, depending on the volume of the hemothorax (Fig. 45-11). With a massive hemothorax, the large volume of blood can create a tension hemothorax, with signs and symptoms of both obstructive and hemorrhagic shock (Fig. 45-12).

As is the case with pneumothoraces, US has much greater sensitivity than chest radiography in the detection of a small hemothorax, but CT scanning has the highest sensitivity, with some studies reporting up to a 25% incidence of hemothoraces diagnosed by CT that were not detected on chest radiography (Fig. 45-13).[7] Perhaps more important, almost half of these occult hemothoraces underwent drainage with tube thoracostomy.[52] Furthermore, one drawback of ultrasonography for the identification

www.ketabpezeshki.com 66485457-66963820

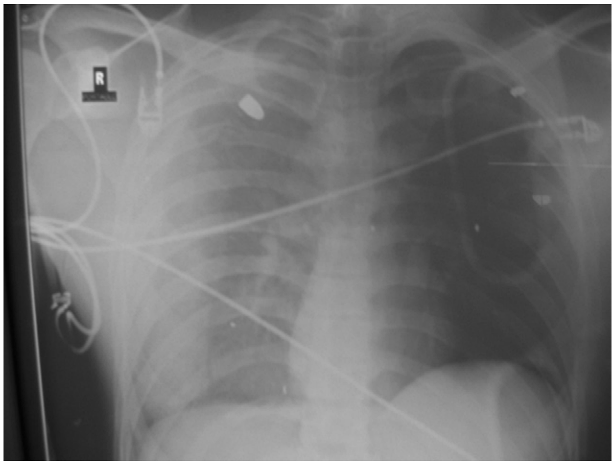


Figure 45-11. Hemothorax secondary to gunshot wound. Note haziness over right hemithorax with bullet seen in right upper lobe.

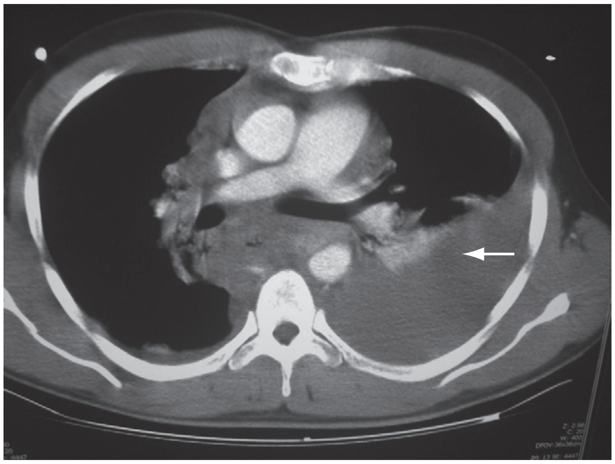


Figure 45-13. Left-sided hemothorax visible on chest computed tomography scan (*arrow*).

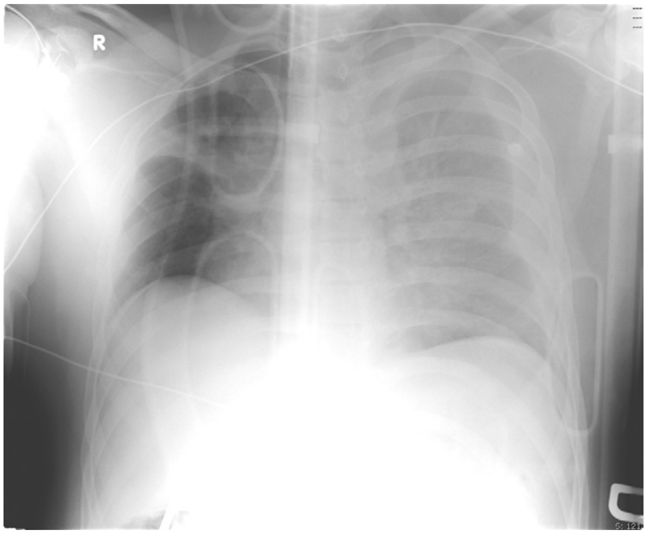


Figure 45-12. Tension hemothorax.

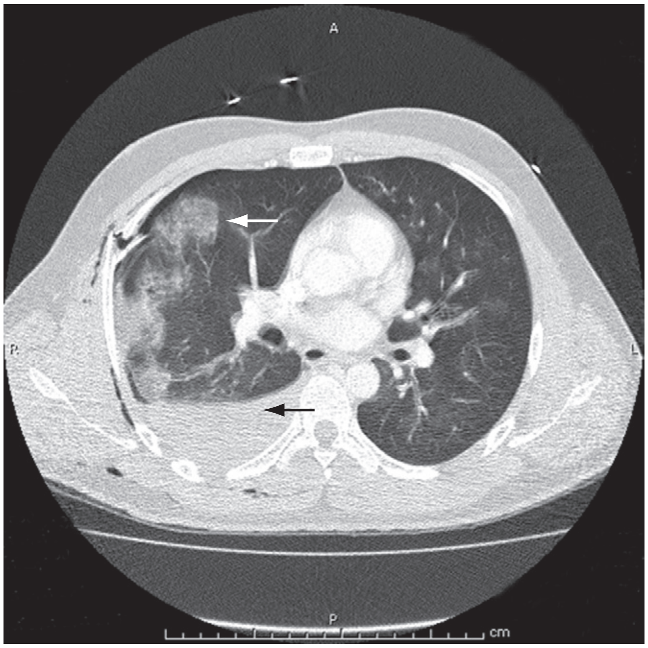


Figure 45-14. Rib fracture resulting in pneumothorax, with associated hemothorax (*bottom arrow*) and pulmonary contusion (*top arrow*) seen on chest computed tomography scan.

of traumatic hemothorax is that associated injuries readily seen on chest radiographs in the trauma patient, such as fractures or a widened mediastinum, are not readily identifiable on chest ultrasonography (Fig. 45-14). However, chest radiography and early bedside ultrasonography usually detect clinically significant hemothoraces and should routinely be performed. Delayed hemothorax may be associated with significant morbidity because the residual blood may serve as a nidus for the development of empyema or fibrothorax.

Management

Treatment of hemothorax consists of restoring the circulating blood volume, controlling the airway as necessary, and evacuating the accumulated blood. Tube thoracostomy allows constant monitoring of the blood loss, and serial chest radiographs help monitor lung reexpansion. A large-bore tube (36-F to 40-F) should be inserted in the fifth interspace at the anterior axillary line and connected to underwater seal drainage and suction (20-30 mL H_2O).

Although small hemothoraces may be observed in stable patients, a moderate hemothorax or any hemothorax in an unstable or symptomatic patient requires tube thoracostomy. Severe or persistent hemorrhage requires thoracostomy or open thoracotomy. Studies are required to better delineate the size of a hemothorax detected on CT scan that requires tube thoracostomy drainage.

Autotransfusion has been successfully used in tube thoracostomy. Recent simplification and commercial availability of the equipment have made autotransfusion feasible in most EDs. Autotransfusion also eliminates the risk of incompatibility reactions and transmission of certain diseases such as hepatitis C. Because the majority of blood loss occurs immediately after tube thoracostomy placement, autotransfusion apparatus should be immediately available in the ED.

As a result of the increasing frequency of chest CT scans, it has been found that there may be a greater frequency of misplaced thoracostomy tubes than is evident on conventional chest

www.ketabpezeshki.com 66485457-66963820

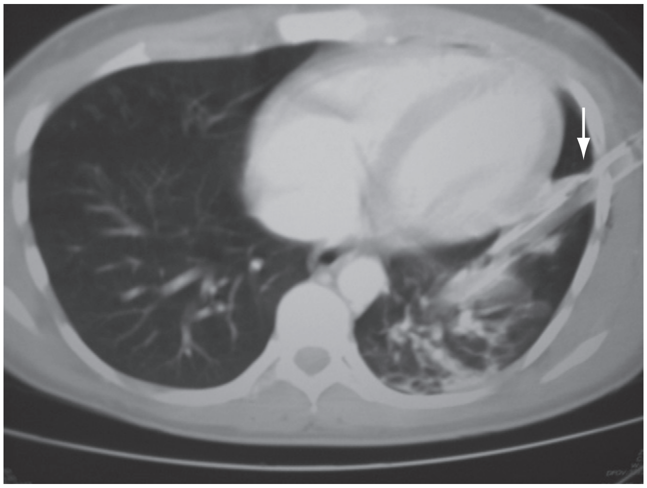


Figure 45-15. Penetration of lung parenchyma by tube thoracostomy (*arrow*), with large residual pneumothorax, visible on computed tomography scan.

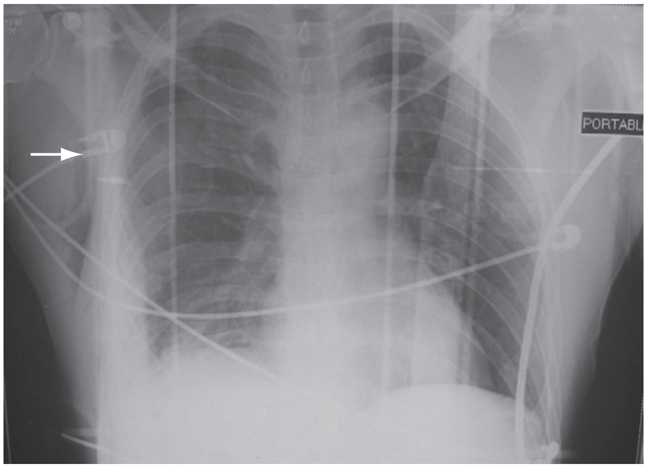


Figure 45-16. Multiple rib fractures with extensive subcutaneous emphysema (*arrow*), with no pneumothorax seen.

radiographs. Almost 25% of patients in one series subsequently required operative intervention as a result of complications from penetration of the lung parenchyma from tube thoracostomies.[53] However, the true incidence of complications that require some surgical intervention remains unknown (Fig. 45-15).

Although beyond the scope of emergency medicine, mention is made of the role of thoracoscopy. Video-assisted thoracic surgery (VATS) is particularly useful for evaluation and evacuation of retained hemothorax, control of bleeding from intercostal vessels, and diagnosis and repair of diaphragmatic injuries.[54,55] As surgeons gain more experience with the technique, VATS will likely become more widely used for other indications as well, given the decreased morbidity and length of hospital stay compared with open thoracotomy.[56]

TRACHEOBRONCHIAL INJURY

Epidemiology

Tracheobronchial injuries may occur with either blunt or penetrating injuries of the neck or chest. Penetrating injuries tend to be more obvious because of their nature, alerting both the patient and the physician, whereas blunt injuries can be occult. MVCs are the most frequent mechanism causing tracheobronchial injury, accounting for more than half of all cases.[57]

Although there has been an increase in the occurrence of tracheobronchial disruption, it is still a relatively rare injury, occurring in fewer than 3% of patients with significant chest injury. Its associated mortality rate is reported to be approximately 10%, although mortality rates are significantly affected by associated injuries and the timing of diagnosis and surgical repair.[58,59]

Anatomy and Pathophysiology

Tracheobronchial injuries caused by knife wounds develop almost exclusively from wounds in the cervical trachea, whereas gunshot wounds may damage the tracheobronchial tree at any point. Intrathoracic injury to the tracheobronchial tree occurs most commonly from blunt trauma. These injuries may result from direct blows, shearing stresses, or burst injury. A direct blow to the neck may crush the cervical trachea against the vertebral bodies and transect the tracheal rings or cricoid cartilage. Shear forces on the trachea will produce injury at the carina and the cricoid cartilage, which are its relatively fixed points.

Sudden deceleration of the thoracic cage, as occurs in a decelerating auto accident, pulls the lungs away from the mediastinum, producing traction on the trachea at the carina. When the elasticity of the tracheobronchial tree is exceeded, it ruptures. It has also been suggested that if the glottis is closed at the time of impact, the sudden increase in intrabronchial pressure will rupture the tracheobronchial tree. Regardless of the mechanism, more than 80% of these injuries occur within 2 cm of the carina.

Clinical Features

Massive air leak through a chest tube, hemoptysis, and subcutaneous emphysema should suggest the diagnosis of major airway damage. Subcutaneous emphysema is typically the most common physical finding.[57] Auscultation of the heart may reveal Hamman's crunch if air tracks into the mediastinum. Hamman's crunch is a crunching, rasping sound that is synchronous with the pulse and is best heard over the precordium. It is the result of the heart beating against air-filled tissues. Patients with tracheobronchial disruption have one of two distinct clinical pictures. In the first group of patients, the wound opens into the pleural space, producing a large pneumothorax. A chest tube fails to evacuate the space and reexpand the lung, and there is continuous bubbling of air in the underwater seal device.

In the second group of patients there is complete transection of the tracheobronchial tree but little or no communication with the pleural space. A pneumothorax is usually not present. The peribronchial tissues support the airway enough to maintain respiration, but within 3 weeks granulation tissue will obstruct the lumen and produce atelectasis. These patients are relatively free of symptoms at the time of injury but weeks later have unexplained atelectasis or pneumonia. Radiographic signs in either group of patients are pneumomediastinum, extensive subcutaneous emphysema (Fig. 45-16), pneumothorax, fracture of the upper ribs (first through fifth), air surrounding the bronchus, and obstruction in the course of an air-filled bronchus.

Diagnostic Strategies

When tracheobronchial injury is suspected, bronchoscopy should be performed. Fiberoptic bronchoscopy is the most reliable means of establishing the diagnosis and determining the site and extent of the injury. However, CT scan has been shown to have high sensitivity in detecting tracheobronchial injury.[60]

www.ketabpezeshki.com 66485457-66963820

Bronchopleural fistula (a communication between a bronchus and the lung parenchyma) can occur as a complication of tracheobronchial disruption and in some cases has been treated successfully via the fiberoptic bronchoscope. A mediastinal fluid collection, evidence of mediastinitis, or both may be noted on chest CT. However, bronchoscopy is usually preferred to make the diagnosis.

Management

If possible, endotracheal intubation over a bronchoscope should be performed because it allows visualization of the tube as it passes beyond the site of injury. In attempting blind intubation, care is taken not to place the endotracheal tube through a transected airway into the soft tissue or a false passage or to convert a partial tracheal tear into a complete one.

The standard treatment for tracheobronchial injury has been surgery. However, conservative medical treatment of such injuries has been reported for tracheobronchial injury patients who meet strict selection criteria. These include patients without any major symptoms, including esophageal-associated injuries, progressive subcutaneous or mediastinal emphysema, severe dyspnea requiring intubation, difficulty with mechanical ventilation, pneumothorax with an air leak through the chest drains, open tracheal injuries, or mediastinitis.[46] In most cases, thoracotomy with intraoperative tracheostomy and surgical repair of the disrupted airway should be performed as soon as possible.

DIAPHRAGMATIC INJURY

Epidemiology

Diaphragmatic rupture is present in 1 to 6% of major thoracic injuries. Diaphragmatic rupture occurs most commonly after blunt thoracoabdominal trauma, such as occurs in MVCs or falls from heights, but can also occur from penetrating trauma.[61]

Anatomy and Pathophysiology

Diaphragmatic hernia is a herniation of abdominal structures within the thoracic cavity through a defect on the diaphragm. Because of pressure gradients across the diaphragm, these injuries are associated with herniation and a potential risk of strangulation of abdominal viscera, especially the small bowel. Signs and symptoms may not occur during the initial admission and may be delayed for as long as months to years.[62] In one study, delayed recognition of incarcerated diaphragmatic hernia after stab wounds to the lower chest and upper abdomen was associated with a mortality rate of 36%.[63]

When diaphragmatic rupture secondary to blunt trauma occurs, the right hemidiaphragm is ruptured in 15 to 24% of cases and the left in 70 to 80%. Five percent to 8% of cases are bilateral. It is generally accepted that this is because of the protective effect of the liver on the right hemidiaphragm against herniation of small bowel. In penetrating injuries of the upper abdomen and lower thorax, such as from gunshot wounds and stab wounds, possible diaphragmatic injury should be considered.

In cases of blunt injury, the raised pressure within the abdominal cavity causes the tear of the diaphragm, and a pressure difference of generally 5 to 10 mm Hg forces the abdominal organs through the diaphragmatic defect. Because blunt trauma can cause multiple organ injuries, these coexisting injuries can mask the more silent diaphragmatic injuries, and diaphragmatic rupture may be initially overlooked. Over time, negative intrathoracic pressure generated by inspiration tends to draw abdominal contents into the thorax. This effect is lost with the use of intubation and positive-pressure ventilation. Because there is also a plugging effect of the viscera over the defect, migration of the abdominal organs within the thorax is usually delayed, so these injuries are diagnosed in only 10% of cases in the acute phase.[63] An overlooked diaphragmatic injury in the acute phase sometimes manifests as respiratory compromise or a hernia with obstruction, incarceration, or perforation of bowel months or decades later.

Diagnostic Strategies

The diagnosis and management of diaphragmatic injuries are problematic because these injuries cause variable clinical and radiologic signs. Accurate diagnosis of traumatic diaphragmatic hernia is essential because prompt surgical repair is the treatment of choice.

Chest radiography is the first imaging study to determine the presence of diaphragmatic rupture, but a plain chest radiograph immediately after the accident arouses suspicion about the diagnosis of a ruptured diaphragm in only 20 to 34% of cases. CT examination of the abdomen and chest is a very useful and reliable tool in the evaluation of blunt diaphragmatic injury, but the injury site and type affect its sensitivity.[64] CT can demonstrate findings consistent with diaphragmatic injury, such as diaphragmatic discontinuity, intrathoracic herniation of abdominal contents, and waistlike constriction of abdominal viscera (the "collar sign"). An isolated omental herniation is clearly detectable on nonenhanced CT because of its fatty nature and crescent shape, and a CT with intravenous contrast will more clearly reveal the contrast-enhancing omental vessels. If the stomach or intestine is herniated, distended intestinal segments containing air-fluid levels are visualized on the supine position images. It is reported that helical CT can be used to detect 78% of left-sided and 50% of right-sided injuries.[65] Albeit highly unusual, efflux of peritoneal lavage fluid through a thoracostomy tube is also diagnostic of a diaphragmatic hernia.

Although magnetic resonance imaging is not useful in most traumatic diaphragmatic hernia cases owing to its relatively long duration and increased sensitivity for motion artifact, it is preferred in selected patients, especially in delayed traumatic diaphragmatic herniation cases from small penetrating injuries. In hemodynamically stable patients with penetrating left thoracoabdominal trauma, the incidence of injury to the diaphragm is very high, and thoracoscopy or laparoscopy is recommended for the diagnosis and repair of a diaphragmatic injury.[61,66,67] Patients with right-sided small penetrating lesions typically do not experience herniation because of the protective effect of the dome of the liver on the right side.

Management

Diaphragmatic injuries may be a predictor of serious associated injuries in trauma and a marker of severity,[4] but they do not ordinarily require urgent repair. The treatment of choice is surgery. CT scan should identify the site and extent of herniation, herniated organs, complications, and damage to associated organs. Although they are not without complications, laparoscopy and thoracoscopy may be used for diaphragmatic hernia repair.

The incidence of diaphragmatic involvement after penetrating left-sided thoracoabdominal injury is high, making nonoperative, expectant management of these patients potentially unsafe. Mandatory evaluation of the diaphragm with laparoscopy to exclude injury in all asymptomatic, hemodynamically normal patients is recommended.[68] In the absence of significant hemoperitoneum or other factors preventing adequate visualization of the diaphragm, laparoscopy or thoracoscopy is a sensitive means of excluding occult diaphragmatic injury in these patients. When significant hemoperitoneum is encountered on laparoscopy or other factors are present that prohibit adequate evaluation of

www.ketabpezeshki.com 66485457-66963820

the diaphragm, conversion to an open exploration should be considered to fully visualize the diaphragm at risk and exclude additional injuries.

CARDIOVASCULAR TRAUMA

Blunt Cardiac Trauma

Epidemiology

Blunt cardiac injury usually results from high-speed MVCs in which the chest wall strikes the steering wheel. Other causes, such as falls from heights, crushing injuries, blast injuries, and direct blows, are less common. The significance of blunt injuries as a cause of myocardial or cardiac contusion was described more than 50 years ago by Bright and Beck.[69] Nevertheless, the diagnosis of a blunt injury to the heart remains elusive because of the usual concomitant serious injuries to other body organs and, more important, because there is no gold standard for making the diagnosis.

The importance of detecting blunt myocardial injury lies in the recognition of associated potentially fatal complications. Life-threatening dysrhythmias, conduction abnormalities, congestive heart failure, cardiogenic shock, hemopericardium with tamponade, cardiac rupture, valvular rupture, intraventricular thrombi, thromboembolic phenomena, coronary artery occlusion, ventricular aneurysms, and constrictive pericarditis have all been reported as complications.

Anatomy and Pathophysiology

Blunt cardiac trauma may be viewed as part of a continuous spectrum (i.e., myocardial concussion, contusion, infarction, and rupture).[70] Myocardial concussion occurs when a blunt injury to the interior chest produces a “stun” response in the myocardium. No permanent cellular injury occurs, but transient clinical effects may result. Myocardial contusion is the least severe form of injury that can be demonstrated pathologically. Cellular injury occurs with extravasation of red blood cells into the muscle wall, along with localized myocardial cellular necrosis. Permanent myocardial damage is rare.[71] Traumatic myocardial infarction (MI) results from either direct trauma to the coronary arteries or a severe contusion of the myocardium, leading to irreversible cellular injury and ultimately cell death. Direct injury to the coronary arteries via laceration, thrombosis, or spasm is thought to be the most common mechanism for traumatic MI. Cardiac rupture is obviously the most severe form of blunt cardiac injury.

Myocardial Concussion

The term *myocardial concussion* or *commotio cordis* is used to describe an acute form of blunt cardiac trauma that is usually produced by a sharp, direct blow to the midanterior chest that stuns the myocardium and results in brief dysrhythmia, hypotension, and loss of consciousness.[72] If the patient survives the initial dysrhythmia, there are no lasting or discernible histopathologic changes, and it is difficult to make the definitive diagnosis of myocardial concussion. This presumptively explains those cases of sudden death after a blow to the chest in which no histopathologic changes in the myocardium are demonstrated at autopsy.[72]

If prolonged cellular dysfunction occurs, it may result in a nonperfusing rhythm, such as asystole or ventricular fibrillation, and irreversible cardiac arrest. There are a number of documented cases of successful resuscitation with rapid provision of CPR and the use of an automated external defibrillator in children who were struck in the chest while playing Little League baseball.[73]

Myocardial Contusion

Epidemiology

Myocardial contusion has been a diagnosis describing a very poorly understood and nebulous condition. Decades of research and widely varied clinical practice have failed to produce a consensus regarding its diagnosis, complication rate, and proper disposition. The incidence of myocardial contusion varies from 3 to 55% in reported series of severe closed-chest trauma, depending on the criteria used for establishing the diagnosis.[74,75]

Anatomy and Pathophysiology

Several mechanisms have been postulated by which the heart may be injured in cases of blunt trauma. A direct blow to the chest transmits energy through the ribs to the spine. When a large force is applied to the chest wall over an extended period, the sternum is displaced posteriorly and the heart is compressed between the sternum and vertebrae or an elevated diaphragm. Either can result in cardiac injury. Increased intrathoracic pressure from a direct blow to the chest may contribute to the injury. In addition, compression of the abdomen and pelvis may displace abdominal viscera upward and result in cardiac injury.

A myocardial contusion is histologically characterized by intramyocardial hemorrhage, edema, and necrosis of myocardial muscle cells. These histologic findings are similar to those seen in acute MI. An accumulation of edema and cellular infiltrate in the wall of the heart may cause a decrease in ventricular compliance, resulting in cardiac dysfunction.

Most myocardial contusions heal spontaneously, with resolution of cellular infiltrate and hemorrhage leading to scar formation. Small pericardial effusions occur in more than 50% of cases of contusion, usually during the second week. These are probably caused by pericardial irritation, and they neither imply significant cardiac injury nor increase the risk of tamponade, and they require no therapy such as pericardiocentesis. A fibrinous reaction at the contusion site may also occur, resulting in pain, a friction rub, and adhesion to the pericardium. In a few cases, the reabsorption of the hematoma is accompanied by necrosis of the ventricular wall, which may result in a delayed rupture of the myocardium or a scarred and weakened area with subsequent development of a ventricular aneurysm. If necrosis occurs, it will usually be manifested in the second week after injury and is one of the causes of delayed sudden death after blunt trauma to the chest. However, this is a rare phenomenon.

Clinical Features

Myocardial contusion manifests clinically as a spectrum of injuries of varying severity. Although the majority of patients with myocardial contusion have external signs of thoracic trauma (e.g., contusions, abrasions, palpable crepitus, rib fractures, or visible flail segments), the absence of thoracic lesions decreases the suspicion but never excludes cardiac injury. Other associated injuries may include pulmonary contusion, pneumothorax, hemothorax, external fracture, and great vessel injury. The most sensitive but least specific sign of myocardial contusion is sinus tachycardia, which is present in approximately 70% of patients with documented myocardial contusions and is a very common vital sign in trauma patients. A reduction in cardiac output, which can be clinically insignificant or manifest as pronounced cardiogenic shock, may occur in patients with significant cardiac contusion.

www.ketabpezeshki.com 66485457-66963820

Diagnostic Strategies

Significant controversy exists regarding the importance and manner of establishing the diagnosis of myocardial contusion in otherwise hemodynamically stable patients.[76]

Even when the diagnosis of a myocardial contusion is considered, confirming the diagnosis without a true gold standard is problematic. Clinical evidence is often nonspecific, especially in the setting of multiple trauma. Patients may have dysrhythmias or ST wave changes caused by significant hypoxia as a result of pulmonary injuries or blood loss, which resolve once the hypoxemia or blood loss has been corrected. Likewise, severe intracranial injury, electrolyte abnormalities, and excessive vagal or sympathetic tone may give rise to dysrhythmias or an abnormal ECG. Under these conditions, ECG abnormalities may not represent true myocardial damage. On the contrary, they may cause one to overlook the potential for traumatic cardiac injury. One large series of blunt trauma patients found that blunt cardiac injury was a significant risk factor for cardiac dysrhythmia.[76]

Because myocardial contusion cannot be positively identified short of biopsy or autopsy, there is much confusion regarding the role of the various laboratory and imaging studies used to diagnose myocardial injury. Multiple studies using cardiac biomarkers have been unhelpful in establishing or excluding the diagnosis. Furthermore, the vast majority of myocardial contusions probably do not cause clinically significant complications. Based on mechanism alone, the relative risk of a life-threatening dysrhythmia is far too low to warrant routine admission to rule out myocardial contusion in all patients with blunt chest trauma. Several studies suggest that very few patients diagnosed with myocardial contusion develop cardiac complications requiring therapeutic intervention or a change in management. Therefore a routine cardiac workup is not indicated in most blunt thoracic trauma victims.[77] The usefulness of diagnostic studies is to identify patients at low risk who can be safely discharged from the ED and not to diagnose the presence of a myocardial contusion.

Diagnostic strategies that have been used to "diagnose" myocardial contusion and assess the risk of complications and the need for admission include ECG, biochemical cardiac markers (serum creatine kinase [CK-MB] isoenzyme levels or troponin levels), two-dimensional echocardiography, and CT scan.

Electrocardiogram. The ECG after blunt chest trauma may be normal or may show nonspecific abnormalities. Because of its anterior position in the thorax and proximity to the sternum, the right ventricle is far more likely to be injured than the left ventricle. The standard 12-lead ECG is relatively insensitive to right ventricular damage, as demonstrated by pathologic evidence of cellular damage in patients with normal ECGs. A cardiac contusion usually results in moderate right ventricular damage with only minor electrical changes, which can easily be missed on ECG. Right-sided ECGs (the addition of V_4R) have not been found to be of any benefit.[78]

Little is known about the relative risk of dysrhythmia as a function of the ECG abnormality, and any new ECG finding warrants consideration of further diagnostic studies or admission for further monitoring. A severely injured right ventricle may cause a right bundle branch block, usually transient. Less commonly, various degrees of atrioventricular block have been documented after blunt chest trauma. Sinus tachycardia and ventricular and atrial extrasystoles are the most frequently reported rhythm disorders. More serious arrhythmias, such as atrial fibrillation, ventricular tachycardia, and ventricular fibrillation, occur less often but may acutely compromise the hemodynamic state or even result in sudden death.[76]

A few cases of delayed life-threatening dysrhythmia have been reported up to 12 hours after injury, and patients may develop less lethal dysrhythmias up to 72 hours after injury. The onset of ECG changes may be delayed up to 48 hours after injury, and all ECG changes usually resolve in 4 to 60 days.[76] The presence of ECG abnormalities is neither specific enough to confirm the diagnosis of myocardial contusion nor reliable enough to predict subsequent complications.

Cardiac Enzymes. Because myocardial contusion is histologically characterized by intramyocardial hemorrhage and necrosis of myocardial muscle cells, similar to those seen in acute MI, cardiac enzymes were the first screening tool used to detect myocardial injury. CK is nonspecifically increased in trauma patients owing to associated skeletal muscle injury, and CK-MB levels have also been found to be falsely elevated and therefore are very nonspecific in multitrauma patients. Thus the use of CK-MB levels is of very limited utility in screening for myocardial contusion and is no longer recommended.[79-81]

Although serum cardiac troponin is highly specific for myocardial injury in the setting of acute MI, elevated troponin levels have been found to have much lower sensitivity for myocardial contusion, and they may occur in the absence of a significant direct myocardial contusion.[81] However, such studies are limited because no true gold standard exists to confirm the diagnosis. Several studies have suggested that the combination of a normal troponin level and a normal 12-lead ECG has a negative predictive value to "rule out" myocardial contusion of 100%, suggesting that these patients do not need any other workup or monitoring specific to possible myocardial contusion.[81] If there is concern because of nonspecific ECG abnormalities or an elevated troponin level on initial evaluation in the ED, a secondary measurement after 4 to 6 hours should be performed to reliably exclude myocardial injury.[80,81]

Echocardiography. Echocardiography provides a means of direct visualization of cardiac structures and chambers. Because contused myocardium resembles infarcted myocardial tissue both histologically and functionally, two-dimensional echocardiography is useful in diagnosing myocardial contusion by evaluating wall motion abnormalities. It is also useful in identifying associated lesions, such as thrombi, pericardial effusion, and valvular disruption. Furthermore, echocardiography offers the practical advantages of being portable, noninvasive, and easy to use at the bedside. If patients have painful chest wall injuries, transthoracic echocardiography may be limited. In these cases, transesophageal echocardiography (TEE) is an alternative.[74]

Management

Appropriate workup and treatment of the patient with suspected myocardial contusion begins with accurate out-of-hospital evaluation. Paramedics should observe and relay information to the ED concerning mechanism of injury, status of the motor vehicle, steering wheel and dashboard damage, use of seat belts and air bags, speed of the vehicle before the accident, and position of the patient when found. Pertinent clinical data to be recorded include vital signs, level of consciousness, cardiac rhythm, and the presence of chest wall trauma.

The value of admitting and carefully monitoring patients with suspected mild (i.e., hemodynamically asymptomatic) cardiac contusions is not supported. The latest studies do suggest that troponin levels are very helpful in risk stratification of patients suspected of having myocardial contusion.[77,80,81] One such strategy is to perform emergent echocardiography for all severely injured patients with hemodynamic instability who are suspected to have structural damage to the heart and/or great vessels. Elevated troponin levels or ECG abnormalities indicate a higher risk of developing cardiac complications. A similar recommendation exists for severely injured patients with a sternal fracture, although the presence of an isolated sternal fracture is not necessarily a sign of cardiac injury. Increased troponin levels or ECG abnormalities

www.ketabpezeshki.com 66485457-66963820

indicate a higher risk of developing cardiac complications. Further investigation, including echocardiography, serial ECGs, and serial troponin levels, is recommended.

In patients who have minor injuries and are otherwise asymptomatic, elevated troponin levels and minor ECG abnormalities do not necessarily indicate a clinically significant myocardial contusion. Very few of these patients will develop complications. However, normal troponin levels (4-6 hours after injury) along with normal (or unchanged) ECGs correlate with minimal risk of cardiac complications. Therefore in-hospital monitoring may be limited to those patients with significant, acute ECG abnormalities, elevated troponin concentrations, or both. Serial ECGs and troponin levels should be obtained until the results return to normal.

Echocardiography is rarely required in this low-risk subset of patients who have minor injuries and are otherwise asymptomatic. If the patient's clinical status deteriorates or there is inconsistency between the troponin levels and ECG changes, echocardiography can be very useful to rule out structurally significant myocardial injuries, which may include wall motion or valvular abnormalities.

On admission, treatment of a suspected myocardial contusion should be similar to that of an MI: intravenous line, cardiac monitoring, and administration of oxygen and analgesic agents. Dysrhythmias should be treated with appropriate medications as per current Advanced Cardiac Life Support guidelines.[82] No data exist to support prophylactic pharmacologic agents for dysrhythmia suppression. Measures should be taken to treat and prevent any conditions that increase myocardial irritability (e.g., metabolic acidosis). Thrombolytic agents and aspirin are contraindicated in the setting of acute trauma. In rare instances there may be an acute MI associated with trauma, which can arise from lacerations or blunt injury to the coronary arteries. These cases should be managed by percutaneous coronary intervention (PCI), with cardiothoracic surgery for definitive repair as indicated.

In the setting of depressed cardiac output caused by myocardial contusion, judicious fluid administration is required. Dobutamine may be useful after optimal preload is ensured. Intra-aortic balloon counterpulsation has been used successfully in refractory cardiogenic shock. The priority is to be certain that the decreased cardiac output is not the result of other undiagnosed injuries, particularly aortic rupture.

Prognosis

The prognosis of a patient with myocardial contusion depends on the character and magnitude of the initial trauma, the size and location of the contusion, the preexisting condition of the coronary arteries, and, most important, any other organ trauma and its complications. Major morbidity and mortality correlate most closely with the number of associated serious injuries. Recovery without complications is the usual course.

Myocardial Rupture

Myocardial rupture refers to an acute traumatic perforation of the ventricles or atria, but it may also include a pericardial rupture or laceration or rupture of the interventricular septum, interatrial septum, chordae, papillary muscles, valves, and lacerated coronary arteries. A delayed rupture of the heart may also occur weeks after nonpenetrating trauma, probably as a result of necrosis of a contused or infarcted area of myocardium.

Epidemiology

High-speed MVCs are responsible for most cases of traumatic myocardial rupture. Myocardial rupture is almost always immediately fatal and accounts for 15% of fatal thoracic injuries. It has been estimated that blunt cardiac rupture accounts for 5% of the 50,000 annual highway deaths in the United States.[1] In various series, the incidence of cardiac rupture in cases of blunt chest trauma ranges from 0.5 to 2%.[83] The most common cause of death in cases of nonpenetrating cardiac injuries is myocardial rupture. Approximately one third of these patients have multiple chamber rupture, and one fourth have an associated ascending aortic rupture. Bright and Beck reviewed 152 autopsy cases of traumatic cardiac ruptures and found that 20% of patients survived 30 minutes or more, which would have allowed them to reach the operating room had the problem been recognized.[69] The first report of successful repair of blunt cardiac rupture was published in 1955 and involved a patient with right atrial rupture.[84]

Anatomy and Pathophysiology

The chambers most commonly involved in cardiac rupture are the ventricles, with right ventricular rupture being most common. Ruptures of the atria are less common, with right atrial rupture being more common than left. Multiple chamber involvement occurs in 20% of patients.[83] Twenty percent of nonsurvivors have concomitant aortic rupture.

A rupture occurs during closure of the outflow track when there is ventricular compression of blood-filled chambers by a pressure sufficient to rupture the chamber wall, septum, or valve. This is the most likely mechanism for ventricular rupture when injury occurs in diastole or early systole concomitant with maximal ventricular distention. The atria are most susceptible to rupture by sudden compression in late systole when these chambers are maximally distended with venous blood and the atrial ventricular valves are closed. Other proposed mechanisms of rupture include (1) deceleration shearing stresses acting on the "fixed" attachment of the inferior and superior vena cava at the right atrium; (2) upward displacement of blood and abdominal viscera from blunt abdominal injury that causes a sudden increase in intracardiac pressure; (3) direct compression of the heart between the sternum and vertebral bodies; (4) laceration from a fractured rib or sternum; and (5) complications of a myocardial contusion, necrosis, and subsequent cardiac rupture.

Because of the nature of the mechanisms involved in cardiac rupture, associated multisystem injuries are common. More than 70% of reported survivors of myocardial rupture have other major associated injuries, including pulmonary contusions, liver and spleen lacerations, closed head injuries, and major fractures. Twenty percent of nonsurvivors have concomitant aortic ruptures.[83]

The immediate ability of the patient to survive cardiac rupture depends on the integrity of the pericardium. Two thirds of patients with cardiac rupture have an intact pericardium and are protected from immediate exsanguination. These patients may survive for variable periods but eventually develop significant hemopericardium and pericardial tamponade. One third of patients with cardiac rupture have associated pericardial tears and succumb promptly to exsanguination.

Occasionally, patients survive if the pericardial tear is small or the rupture is small enough to seal itself. A small pericardial laceration may allow partial and intermittent release of tamponade while still controlling bleeding. In one series of patients with confirmed myocardial rupture, 40% of patients had isolated rupture of the right atrium. The overall mortality rate was 81%, with none of the patients with two-chamber rupture, ventricular rupture, or absence of vital signs on arrival at the ED surviving.[83]

Clinical Features

The clinical presentation of a patient who has sustained a myocardial rupture is usually that of cardiac tamponade or severe

www.ketabpezeshki.com 66485457-66963820

hemorrhage. Rarely, a patient is seen with a large hemothorax, hypotension, and hypovolemia, suggesting rupture with associated pericardial tear. A patient with an intact pericardial sac and developing tamponade displays physical findings of tamponade, usually with subsequent clinical deterioration. Initial inspection of the torso may reveal little more than a bruised area over the sternum or no external physical evidence. More often, however, signs of significant chest trauma or other associated injuries will be present, indicating a mechanism of injury that could result in myocardial rupture. Auscultation may reveal a harsh murmur, known as a "bruit de moulin," which sounds like a splashing mill wheel. This is caused by pneumopericardium.

In a review of survivors of myocardial rupture, common symptoms and signs included hypotension (100%); elevated CVP (95%); tachycardia (89%); distended neck veins (80%); cyanosis of the head, neck, arms, and upper chest (76%); unresponsiveness (74%); distant heart sounds (61%); and associated chest injuries (50%).[83-86]

The following findings are suggestive of pericardial rupture:

1. Hypotension disproportionate to the suspected injury
2. Hypotension unresponsive to rapid fluid resuscitation
3. Massive hemothorax unresponsive to thoracostomy and fluid resuscitation
4. Persistent metabolic acidosis
5. The presence of pericardial effusion on echocardiography or elevation of CVP and neck veins with continuing hypotension despite fluid resuscitation

Diagnostic Strategies

Early use of ED US may facilitate the early diagnosis of cardiac rupture and pericardial tamponade.[87] The combination of shock and jugular venous distention (or an elevated CVP) in a patient with blunt chest trauma should immediately suggest pericardial tamponade. However, in patients with coexistent hemorrhage from other injuries, JVD may be absent. Other considerations include tension pneumothorax, right ventricular myocardial contusion, superior vena cava obstruction, and ruptured tricuspid valve. Sonographic visualization of pericardial fluid in this setting should be followed by emergent thoracotomy (Fig. 45-17).

A chest radiograph should be obtained immediately in all cases of acute, blunt chest injuries. Although this study usually does not help diagnose cases of myocardial rupture, it notes the presence of other intrathoracic injuries (e.g., hemothorax, pneumothorax, and signs of possible aortic dissection). An increase in the size of the cardiac silhouette more commonly reflects preexisting disease or valvular incompetence with chamber enlargement caused by increased filling pressures. ECG changes may occur with myocardial injury, but these are often nonspecific for myocardial rupture. Early use of bedside echocardiography in the ED should be performed in any case of suspected cardiac rupture, pericardial tamponade, a previously undiagnosed murmur, or shock unexplained by other causes (e.g., exsanguination).

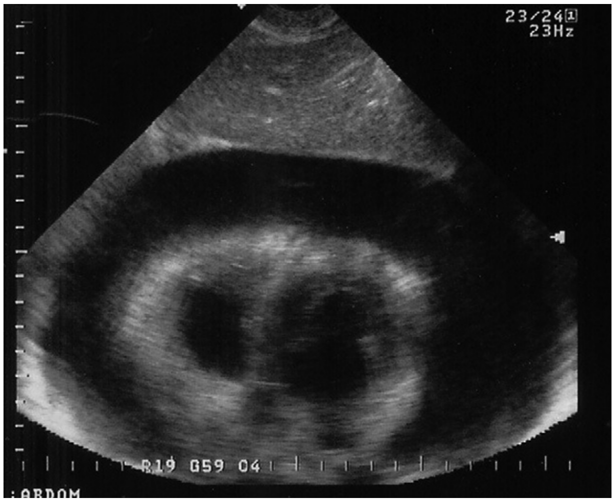


Figure 45-17. Echocardiogram demonstrating pericardial fluid with cardiac tamponade.

Management

When nonhospital medical personnel evaluate a patient who has sustained blunt chest trauma, they should concentrate on rapid transport and pay attention for any signs of pericardial tamponade. En route to the hospital, the possibility of a tension pneumothorax should be considered as well.

In the ED, treatment of patients with a myocardial rupture is directed toward immediate decompression of cardiac tamponade and control of hemorrhage. Pericardiocentesis may be effective in cases of a small rupture, but it is usually performed as a diagnostic or temporizing therapeutic procedure until surgical correction can be undertaken. Emergency thoracotomy and pericardiotomy may be required in the ED if the patient has rapidly deteriorating vital signs or a cardiac arrest. After emergency thoracotomy and pericardiotomy, the myocardial rupture should be controlled until the patient can be transported to the operating room for definitive repair. Hemorrhage from a ruptured atrium can often be controlled by finger occlusion or application of a vascular clamp. Insertion of a Foley catheter through the defect, followed by inflation of the balloon and traction on the catheter, may also control the bleeding. Ventricular rupture can usually be controlled by direct digital pressure or by suturing with nonabsorbable vascular sutures.

Cardiopulmonary bypass is commonly required in only 10% of successful repairs of myocardial rupture.[83] Therefore, for patients with suspected myocardial rupture, it is appropriate to undertake emergency thoracotomy in institutions that have qualified surgeons but no immediate access to cardiopulmonary bypass.

Prognosis

Reported survival rates for patients with myocardial rupture and an intact pericardium vary widely. Although only a small number of survivors of ventricular rupture had been previously reported,[81,82,84] a small case series reported that four out of a total of five patients with blunt cardiac rupture who arrived at the ED with vital signs ultimately survived.[85] Most survivors of cardiac rupture are patients with atrial rupture, including one patient with multiple atrial tears. Most undergo surgical repair within 3 or 4 hours of injury. Approximately 60% of successful repairs have been performed more than 60 minutes after injury.

Miscellaneous Cardiac Injuries

The occurrence of intracardiac injuries that result from blunt chest trauma (e.g., septal defects or valvular injuries) is less common. Valve rupture may involve the chordae tendineae, leaflets, or papillary muscles. Involvement of the aortic valve is more common than involvement of the mitral or tricuspid valves. Mitral and tricuspid valve injuries associated with a pericardial laceration have been reported in a survivor of blunt chest trauma. The exact incidence of cardiac valvular injuries and septal defects is unknown. Serial echocardiography and monitoring of ECG changes as well as frequent auscultation may aid in earlier diagnosis of these lesions.

www.ketabpezeshki.com 66485457-66963820

Clinical Features

The clinical presentation of these patients depends on which valve or septum is involved and whether coincident cardiac injuries are present. A complete rupture of the mitral valve usually results in immediate death. The clinical presentation of an incomplete rupture depends on the hemodynamic state of the patient. Cardiogenic shock is common. Findings of acute mitral insufficiency and rapidly developing pulmonary edema are usually predominant. A loud, harsh diastolic murmur with frank left heart failure suggests acute aortic insufficiency. If the patient is in a low output state, the associated thrills and murmurs of aortic or mitral insufficiency may not be appreciated. The signs and symptoms of tricuspid insufficiency that follow a rupture of that valve may be less dramatic or even minimal. Examination may reveal only a diastolic murmur and prominent V waves of the jugular venous pulsations.

Patients with isolated septal defects may have minimal symptoms of exertional dyspnea or severe progressive shock and pulmonary edema, depending on the size and location of the defect. Dysrhythmias and conduction defects are rare because the lower muscular septum is principally involved. The typical holosystolic murmur along the left sternal border is an important clue in diagnosing a ventricular septal defect, but it may not appear for days or months after the injury. Serial echocardiography and ultimately cardiac catheterization for both valvular and septal defects are necessary for a definitive diagnosis.

Management

The therapy selected depends primarily on how well the patient tolerates the insult. Many years may elapse before operative treatment is required. In cases of ventricular septal defects, a period of observation is valuable because there have been reports of the spontaneous closure of traumatic ventricular septal defects months after the injury when the defects and resultant shunt are small. Medical therapy commonly relieves the symptoms of congestive failure, but intractable or progressive heart failure or the development of pulmonary hypertension usually indicates the need for surgery.

Penetrating Cardiac Injury

Penetrating cardiac injuries are one of the leading causes of death in the setting of urban violence. Patients with penetrating cardiac injury who survive to arrive at the hospital have an overall mortality rate of almost 80%.[88] Improvements in emergency medical services systems during the past few years, along with an emphasis on rapid transport, are responsible for an increasing number of cardiac injury patients arriving in impending or full cardiopulmonary arrest at busy urban trauma centers. The proportion of gunshot wounds versus stab wounds varies widely in reported case series, depending on the location of the trauma center.

The right ventricle is affected more often (43%) than the left ventricle (34%) owing to its anterior anatomic location. The left or right atrium is affected in 20% of cases.[89] One third of penetrating cardiac wounds affect multiple chambers, and survival is much worse in these cases. In 5% of cases, a coronary artery is lacerated, although these injuries usually involve a distal segment of the artery and rarely produce significant acute MI when they are ligated. More proximal coronary artery lacerations require coronary bypass.[90] Rarely, the interventricular septum, a valve, papillary muscle, or chordae tendineae are lacerated, producing an acute shunt or valvular insufficiency. These lesions are poorly tolerated and can quickly produce massive pulmonary edema and cardiogenic shock.

Box 45-3 Indications for Emergency Department Thoracotomy

Penetrating Traumatic Cardiac Arrest
Cardiac arrest at any point with initial signs of life in the field
Systolic blood pressure below 50 mm Hg after fluid resuscitation
Severe shock with clinical signs of cardiac tamponade

Blunt Trauma
Cardiac arrest in the emergency department

Miscellaneous
Suspected air embolus

Two conditions may occur after penetrating heart injury: (1) exsanguinating hemorrhage if the cardiac lesion communicates freely with the pleural cavity, or (2) cardiac tamponade if the hemorrhage is contained within the pericardium. Patients with exsanguinating wounds frequently die before they reach medical attention, or they have rapidly progressive hemorrhagic shock on presentation, culminating in cardiac arrest. This presentation is most typically seen in patients sustaining gunshot wounds to the heart. Cardiac tamponade is a life-threatening condition but appears to offer some degree of protection and increased survival in patients with penetrating cardiac wounds. These patients often require immediate resuscitation by ED thoracotomy (EDT) if they meet the criteria listed in Box 45-3.

Acute Pericardial Tamponade

Epidemiology

The reported incidence of acute pericardial tamponade is approximately 2% in patients with penetrating trauma to the chest and upper abdomen; it is rarely seen after blunt chest trauma. It occurs more commonly with stab wounds than with gunshot wounds, and 60 to 80% of patients with stab wounds involving the heart develop tamponade.[89] Patients with acute pericardial tamponade can deteriorate in minutes, but many can be saved if proper steps are taken.

Anatomy and Pathophysiology

The primary feature of a pericardial tamponade is an increase in intrapericardial pressure and volume. As the volume of the pericardial fluid encroaches on the capacity of the atria and ventricles to fill adequately, ventricular filling is mechanically limited, and thus the stroke volume is reduced. This results in decreased cardiac output and ultimately diminished arterial systolic blood pressure and decreased pulse pressure. As little as 60 to 100 mL of blood and clots in the pericardium may produce the clinical picture of tamponade. Concomitantly, CVP rises because of the mechanical backup of blood into the vena cava.

Several compensatory mechanisms then occur. The heart rate and total peripheral resistance rise in an attempt to maintain adequate cardiac output and blood pressure. A less effective compensatory response, resulting in a greater rise in CVP, is an increase in venomotor tone caused by contractions of the smooth muscles within the wall of the vena cava.

The diagnosis of pericardial tamponade should be suspected in any patient who has sustained a penetrating wound or blunt trauma to the thorax or upper abdomen. One is never certain of the trajectory of the bullet or the length, force, and direction of a knife thrust on initial evaluation. Obviously, wounds directly over the precordium and epigastrium are more likely to produce a cardiac injury resulting in tamponade than those in the posterior or lateral thorax. Nevertheless, it is assumed that a penetrating

www.ketabpezeshki.com 66485457-66963820

wound, particularly a gunshot wound, anywhere in the thorax or upper abdomen may have injured the heart. Rapid bedside echocardiography, performed as part of the standard FAST examination, easily detects a pericardial effusion causing cardiac tamponade.[91,92]

Clinical Features

Patients with cardiac tamponade may initially appear deceptively stable if the rate of bleeding into the pericardial space is slow or if the pericardial wound allows intermittent decompression. Other patients may complain primarily of difficulty breathing, which suggests pulmonary rather than cardiac pathology.

The physical findings of pericardial tamponade are hypotension, distended neck veins, and, rarely, distant or muffled heart tones.[93] This so-called *Beck's triad* is sometimes difficult to demonstrate clinically, especially in the midst of a major resuscitation with concomitant hypovolemia, when the neck veins may be flat.[91] Although the most reliable signs of pericardial tamponade are an elevated CVP (>15 cm H_2O) in association with hypotension and tachycardia, bedside echocardiography performed as part of the FAST examination rapidly identifies pericardial tamponade and has largely replaced the use of CVP measurements to make the diagnosis. Echocardiography also distinguishes pericardial tamponade versus tension pneumothorax when the triad of elevated CVP, hypotension, and tachycardia is present.

Acute pericardial tamponade may be seen with three distinct clinical pictures. If the hemorrhage is confined to the pericardial space, the patient is initially normotensive but will have a tachycardia and elevated CVP. If untreated, most of these patients go on to develop hypotension. If significant hemorrhage has occurred outside the pericardial sac, either through a tear in the pericardium or from associated trauma, the clinical picture is that of hypovolemic shock with hypotension, tachycardia, and a low CVP. If the CVP rises to a level of 15 to 20 cm H_2O with volume replacement and hypotension and tachycardia persist, the presence of a pericardial tamponade is considered. Also considered are other causes, such as a tension pneumothorax, Valsalva maneuver, or pulmonary edema secondary to fluid overload.

The third clinical picture is that of an intermittently decompressing tamponade. In this case, intermittent hemorrhage from the intrapericardial space occurs, decompressing and partially relieving the tamponade. The clinical picture may wax and wane depending on the intrapericardial pressure and volume and total blood loss. In general, this condition is compatible with a longer survival than are the first two clinical presentations.

Pulsus paradoxus is defined as an excessive drop in systolic blood pressure during the inspiratory phase of the normal respiratory cycle. This sign may be an additional clue to the presence of pericardial tamponade, but it is often difficult to measure during an intensive resuscitation or in the presence of shock.

Diagnostic Strategies

Ultrasound. US, which is now widely available in EDs throughout the world, enables rapid, accurate, and noninvasive diagnosis of pericardial tamponade.[92,94] This study can be performed at the bedside in the ED during the initial resuscitation of the patient as part of the FAST examination. Although the sonographic definition of tamponade is the simultaneous presence of pericardial fluid and diastolic collapse of the right ventricle or atrium, the presence of pericardial fluid in a patient with chest trauma is highly suggestive of pericardial hemorrhage (see Fig. 45-17). An indirect sonographic sign of tamponade is the demonstration of a dilated inferior vena cava in a hypotensive patient. EDs in which cardiac ultrasonography is performed with subcostal and long parasternal views have reported a sensitivity of 98.1% and a specificity of 99.9% for the detection of pericardial effusion.[92,93] Because US is noninvasive and extremely accurate, its immediate availability in the initial phase of a major trauma resuscitation can be very helpful in detecting pericardial fluid before the patient deteriorates hemodynamically.

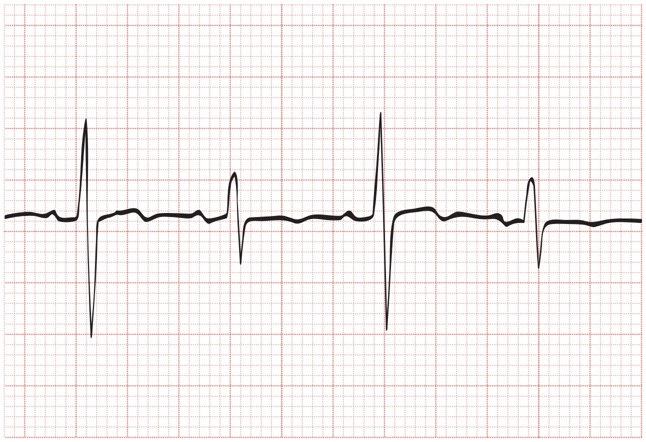


Figure 45-18. Lewis lead electrocardiogram revealing total electrical alternans of the QRS complexes. (From Sotolongo RP, Horton JD: Total electrical alternans in pericardial tamponade. Am Heart J 101:853, 1981.)

Electrocardiography. Many ECG changes of pericardial tamponade have been described in the literature, but few are diagnostic, and each is more likely to be seen with chronic rather than acute tamponade. Electrical alternans has been reported to be a highly specific marker of pericardial tamponade. Electrical alternans is an ECG change in which the morphology and amplitude of the P, QRS, and ST-T waves in any single lead alternate in every other beat (Fig. 45-18). The postulated cause is the mechanical oscillation of the heart in the pericardial fluid, which is called the *swinging heart phenomenon.* In uncomplicated pericardial effusion, the heart swings back and forth but returns to approximately the same position before the next systole. Electrical alternans does not occur in this situation.

Echocardiographic studies have revealed that when fluid accumulates to a critical extent and cardiac tamponade ensues, the frequency of cardiac oscillation may abruptly decrease to half the heart rate. The cardiac position will alternate, with the heart returning to its original position with every other beat, and electrical alternans may be seen. Electrical alternans, when present, is pathognomonic for tamponade. However, it is much more common in chronic pericardial effusions that evolve into a tamponade, and it is rarely seen in acute pericardial tamponade. However, low amplitude of the QRS complexes may be seen as a result of the presence of pericardial effusion.

Radiography. The radiographic evaluation of the cardiac silhouette in acute pericardial tamponade generally is not helpful, unless a traumatic pneumopericardium is present. Because small volumes of hemopericardium lead to tamponade in the acute setting, the heart will typically appear normal. This is in contrast to the "water-bottle" appearance of the heart with chronic pericardial effusion. Usually the latter condition is tolerated for a long period.

Management

Out-of-Hospital Care. Field treatment for cases of pericardial tamponade is essentially the same as that outlined for any victim of major trauma. The diagnosis of tamponade should be suspected by the location of penetrating wounds or by the patient's poor response to vigorous volume resuscitation. Tension pneumothorax, which is much more common, may mimic certain aspects of

www.ketabpezeshki.com 66485457-66963820

acute pericardial tamponade. If the patient is in extremis or the clinical condition rapidly deteriorates, consideration should be given to performing a needle thoracostomy, which, if not therapeutic, suggests pericardial tamponade under the appropriate clinical presentation by virtue of "diagnosis of exclusion." Expedient transport to the nearest trauma center should be of paramount concern.

Emergency Department. When the patient arrives in the ED, volume expansion with crystalloid solution via two or three large-bore (14- or 16-gauge) catheters should be established immediately. The presence of a pneumothorax or hemothorax, which is often associated with penetrating cardiac trauma, is treated expeditiously with tube thoracostomy. Bedside echocardiography should be performed as quickly as possible to establish the diagnosis of pericardial tamponade, which then should be followed by emergent surgical repair.

There is increasing controversy regarding the role of pericardiocentesis. In the past, it was recommended that pericardiocentesis be performed for both diagnostic and therapeutic reasons. Aspiration of as little as 5 to 10 mL of blood may result in dramatic clinical improvement. However, it should be emphasized that pericardiocentesis is not a benign or invariably successful procedure. Blood in the pericardial space tends to be clotted, and aspiration may not be possible. Possible complications include the production of pericardial tamponade, the laceration of coronary artery or lung, and induction of cardiac dysrhythmias. Whenever possible, pericardiocentesis should be performed under sonographic guidance because this approach will increase the success rate and decrease the incidence of complications. A pigtail catheter may be introduced into the pericardial space for repeated aspirations while preparations are underway to quickly transport the patient to the operating room for definitive therapy. If pericardiocentesis is unsuccessful or the clinical status deteriorates, and if acute pericardial tamponade remains important in the differential diagnosis, thoracotomy should be performed as quickly as possible.[81] Patients with penetrating cardiac injury invariably require surgical repair. The location (operating room vs. ED) and timing (immediate vs. urgent) depend on the patient's clinical status.

Emergency Department Thoracotomy. EDT is a drastic, dramatic, and potentially lifesaving procedure in which emergency physicians should be proficient. Although the procedure is not described in detail here, a few technical points merit discussion. A left lateral incision is preferred because it is rapidly accomplished; allows the best exposure of the heart, aorta, and left hilum; and facilitates open cardiac massage and internal defibrillation[95] (Fig. 45-19). With right-sided or multiple injuries, it may be necessary to extend the incision across the sternum and right chest wall, creating a "clamshell" incision. The internal mammary arteries need to be ligated if this maneuver restores effective perfusion. After the heart is sufficiently exposed, the pericardium is vertically incised anterior to the phrenic nerve. Release of a tamponade may rapidly restore cardiac output. The heart is then delivered through the pericardium, and penetrating wounds are identified.

There are several alternatives for repairing cardiac wounds. Small wounds can be compressed by digital pressure to control bleeding en route to the operating room. If the injury is quite large, balloon tamponade can be achieved by applying gentle traction on a Foley catheter inserted into the wound with the balloon inflated with saline. This can temporarily stop the hemorrhage to allow suture repair of the injury (cardiorrhaphy) or to gain time while the patient is transferred to the operating room for a more definitive surgical procedure. Lacerations of the atria can be temporarily controlled with a vascular clamp.[95]

Suture of cardiac wounds over pledgets is the time-honored and effective technique but is technically more difficult and more time-consuming. The use of a monofilament suture, such as 2-0 Prolene, is recommended. Some trauma surgeons recommend

Figure 45-19. Emergency department thoracotomy.

stapling cardiac wounds with standard skin staplers because this technique has been shown to be much quicker and equally effective in closing these wounds, and there is also a report on the use of a collagen mesh attached with fibrin glue mesh to rapidly repair a ventricular laceration.[96,97]

Care is taken to avoid ligating coronary arteries during the repair. Direct insertion of a large-bore catheter (e.g., a 5-F catheter) into the left atrial appendage provides a route for rapid infusion of fluids. If the heart is empty or the patient fails to respond to rapid fluid administration, the aorta is cross-clamped to divert cardiac output to the brain and heart. Prolonged ischemia and severe acidosis often result in postresuscitation myocardial depression with ineffective contraction and diminished cardiac output. Thus the cross-clamp should be temporarily released every 30 to 45 minutes to minimize ischemic complications.

Indications for Emergency Department Thoracotomy. Although it is often tempting to perform EDT on all traumatic arrest victims in the ED, there are many cases in which patients have virtually no chance of survival.[98] In addition, EDT is costly; requires the undivided attention of all personnel in the ED, diverting care from other, more salvageable patients in critical condition; and poses a risk to ED personnel for injury from needle sticks and other blood-contaminated exposures. Consequently, guidelines have been established by the National Association of EMS Physicians and the American College of Surgeons Committee on Trauma (ACSCOT) to withhold EDT or terminate resuscitative efforts on scene.[99] These guidelines, along with the most recent Advanced Trauma Life Support text, include withholding EDT for patients in cardiopulmonary arrest secondary to blunt trauma (see Box 45-3).[100]

However, several recently published case series have questioned whether these guidelines are overly restrictive. One large, multicenter study reported three neurologically intact survivors of EDT who had asystole at ED arrival (all of whom had pericardial tamponade) and five survivors after blunt traumatic arrest who had mild to no neurologic deficits, and another study also reported

www.ketabpezeshki.com 66485457-66963820

survivors of EDT who did not meet the traditional survival predictors.[101,102] Other authors have noted that some patients who survive EDT may be suitable organ donors.[103] Patients with penetrating trauma with signs of life in the field, even if only electrical activity on cardiac monitor or agonal respirations, are candidates for EDT if transport times are less than 10 minutes.[102-104]

Prognosis

After penetrating wounds to the heart, several factors adversely affect survival, including gunshot wound mechanisms and wounds that involve the left ventricle, multiple cardiac chambers, intrapericardial great vessels, or one or more coronary arteries. The factors favorable to survival include stab wound mechanisms with minor perforations, isolated right ventricular wounds, a systolic blood pressure greater than 50 mm Hg on arrival at the ED, and the presence of cardiac tamponade.

Survival rates after EDT have been correlated with the mechanism and location of injury, field and transport times, the duration of arrest, and the physiologic status of the patient in the out-of-hospital and hospital settings. Although reported survival rates after EDT vary widely, they are consistently higher in victims with isolated cardiac injuries secondary to stab wounds versus gunshot wounds.[99-102,104]

A meta-analysis of the literature found that EDT had an overall survival rate of 7.4%, with normal neurologic outcomes noted in 92.4% of surviving patients. Survival rates according to mechanism of injury were 9% for penetrating injuries and 1% for blunt injuries. When penetrating injuries were further separated, the survival rates were 17% for stab wounds and 4% for gunshot wounds. The presence of pericardial tamponade is a favorable prognostic finding.[105,106]

Blunt Aortic Injury

Epidemiology

Blunt aortic injury is a life-threatening injury, usually resulting from sudden deceleration, usually from automobile crashes. Other mechanisms of injury include pedestrians struck by automobiles, motorcycle crashes, airplane crashes, and falls from heights.[107] In an analysis of automobile crash data, the impact was most often head-on (72%), followed by side impact (24%) and rear impact (4%).[108] Despite the improvement in and increased use of restraint systems, the overall incidence of blunt aortic injury associated with fatal automobile crashes has remained unchanged over the past decade.[109]

Blunt aortic injury includes a spectrum of lesions, ranging from a small intimal tear to frank rupture, which usually cause rapid lethal hemorrhage. The most common sites of injury are the aortic isthmus and the ascending aorta just proximal to the origin of the brachiocephalic vessels.[107] Sixty percent to 90% of patients with blunt aortic injury die at the site of accident or within hours of hospital admission.[109,110] However, an increasing number of patients arrive at a treatment facility because of improvement in out-of-hospital care, more aggressive resuscitation in the field, and rapid transportation to a trauma center. The early survival rate of such patients depends on the initial resuscitation and/or the timeliness and correct choice of the diagnostic procedures. A rapid and accurate diagnosis is thus mandatory to optimize treatment and maximize patient survival.

Anatomy and Pathophysiology

Blunt aortic injury encompasses various histologic lesions. Minor blunt aortic injuries (grade 1, intramural hematoma or limited intimal flap) and major blunt aortic injuries (grade 2, subadventitial rupture or modification of the geometric shape of the aorta; and grade 3, aortic transection with active bleeding or aortic obstruction with ischemia) can be differentiated by TEE. Whereas minor blunt aortic injuries appear to have a good prognosis, major blunt aortic injuries involve the entire depth of both the intimal and the medial layers and may lead to adventitial rupture, resulting in sudden death at the scene of the accident or during the first hours of hospitalization.[111]

Several theories about the mechanism of aortic rupture have predominated in the literature. The descending thoracic aorta is relatively fixed and immobile because of its tethering by intercostal arteries and the ligamentum arteriosum. With sudden deceleration, the more mobile aortic arch swings forward, producing a shearing force or "whiplash effect" on the aorta at the isthmus. A bending stress at the isthmus, created by sudden lateral oblique chest compression, may also result in rupture by causing flexion of the aortic arch on the left mainstem bronchus and the pulmonary artery. It has been suggested that the forces created by the whiplash effect or lateral oblique compression may not be sufficient to provoke aortic tears. It is now postulated that those injuries may be caused by inferior and posterior rotation of anterior thoracic osseous structures (manubrium, first rib, and medial clavicles), pinching and shearing the interposed aorta as they strike the vertebral column.

Rupture of the ascending aorta just distal to the aortic valve likely occurs through a different mechanism. At the time of rapid deceleration and chest compression, the heart is displaced into the left posterior chest, which causes a shearing stress just above the aortic valve. A sudden increase in intra-aortic pressure, "the water-hammer effect," may also cause an explosive rupture of the aorta at this location. Involvement of the coronary ostia with coronary artery occlusion may occur in association with tears to the ascending arch. The intraluminal pressure tolerance of the aorta may be exceeded in a high-speed motor vehicle crash. It is likely that a combination of the preceding mechanisms accounts for the multiple aortic ruptures that have been found in 20% of traffic accident victims examined at autopsy.[109]

A total of 80 to 90% of aortic tears occur in the descending aorta at the isthmus, just distal to the left subclavian artery (Fig. 45-20).[107,110,111] Less common sites of involvement are the

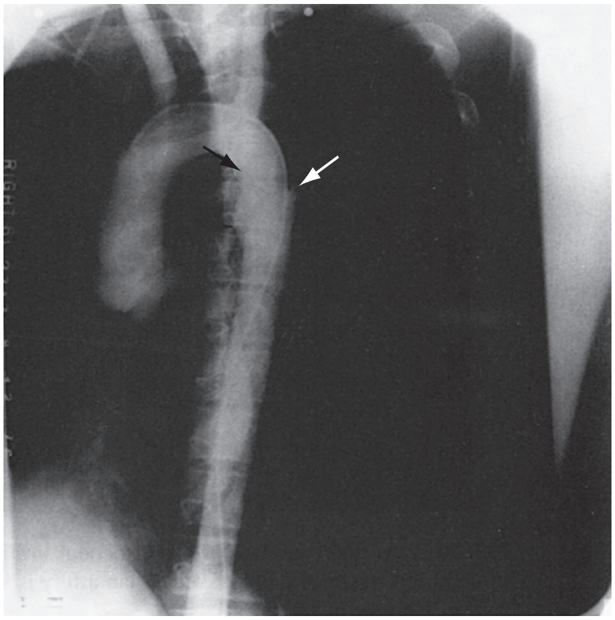


Figure 45-20. Aortogram shows tear in aorta *(arrows)* at the most common location, at or just distal to takeoff point of left subclavian artery, which is not visualized.

www.ketabpezeshki.com 66485457-66963820

ascending aorta, the distal descending aorta at the level of the diaphragm, the midthoracic descending aorta, and the origin of the left subclavian artery. Although ruptures of the ascending aorta are much less common than those of the descending aorta, they have a 70 to 80% incidence of associated lethal cardiac injuries. This is in contrast to ruptures at the isthmus, which have a 25% incidence of associated cardiac injuries. Lethal cardiac injuries commonly include pericardial tamponade, aortic valve tears, myocardial contusion, or coronary artery injuries. Passenger ejection, pedestrian impact, severe falls, and crush injuries commonly result in ascending thoracic aortic ruptures. Survival long enough to be evaluated in the ED is rare among patients who sustain an ascending aortic rupture.[111]

Aortic rupture may occur from causes other than high-speed MVC deceleration. Rupture has been documented as a complication of external cardiac massage and has been known to occur after fracture-dislocations of the thoracic spine, presumably as a result of direct shearing force. Vertical deceleration injuries resulting from falls can cause a rupture of the ascending aorta by producing an acute lengthening of the ascending aorta. This is the likely mechanism responsible for aortic rupture in the setting of airplane and elevator accidents. Direct kicks by animals, crush injuries, sudden burial by landslide, and air bag deployment have also been reported as causes of aortic rupture. Direct compression of the compliant thorax has been postulated to contribute to aortic rupture in children. Displaced fractures of the sternum, ribs, and clavicle have also been shown to directly lacerate the aorta.

Clinical Features

The possibility of aortic disruption is considered in every patient who sustains a severe deceleration injury, because approximately 30% of surviving patients with blunt aortic injury will die within the first 24 hours without treatment.[112] This is especially true if the automobile was moving in excess of 45 mph or if there is evidence of severe blunt force to the chest (e.g., from a damaged steering wheel).[109] In the case of any moderate- or high-speed motor vehicle accident, it is imperative that paramedics carefully evaluate the extent of damage to the vehicle, the complaints of the victims, and the physical manifestations of blunt chest trauma. This information should be promptly relayed to the emergency physician.

Despite the severe nature of the injury, the clinical manifestations of an aortic rupture are often deceptively meager. Associated pulmonary, neurologic, orthopedic, facial, and abdominal injuries are commonly present. Coexisting injuries can mask the signs and symptoms of an aortic injury or divert the physician's attention away from the more lethal aortic rupture. The absence of any external evidence of a chest injury does not eliminate the possibility of an aortic tear. One third to one half of patients reported in the literature have no external signs of chest trauma.[107,111]

The most common symptom is interscapular or retrosternal pain. It is often found in nontraumatic aortic dissection but is present in only 25% of patients with a traumatic aortic disruption. Other symptoms described in the literature but uncommonly present include dyspnea resulting from tracheal compression and deviation, stridor or hoarseness caused by compression of the laryngeal nerve, dysphagia caused by esophageal compression, and extremity pain caused by ischemia from decreased arterial flow.

Clinical signs are uncommon and nonspecific. Generalized hypertension, when present, may be an important clinical sign. Sympathetic afferent nerve fibers, located in the area of the aortic isthmus, are capable of causing reflex hypertension as a response to a stretching stimulus. A less common clinical finding is the acute onset of upper extremity hypertension, along with absent or diminished femoral pulses. This pseudocoarctation syndrome has been reported to occur in up to one third of these patients and is attributed to compression of the aortic lumen by a periaortic hematoma.

The presence of a harsh systolic murmur over the precordium or posterior interscapular area may be heard in up to one third of patients. The murmur is thought to result from the turbulent flow across the area of transection. A less commonly encountered physical finding is a swelling at the base of the neck caused by the extravasation of blood from the mediastinum, which results in an increased neck circumference or a pulsatile neck mass. Other clinical signs suggestive of aortic rupture include lower extremity pulse deficit and lower extremity paralysis. Initial chest tube placement output in excess of 750 mL is also suggestive of aortic rupture, especially if the hemothorax is left sided. However, the physical examination is neither sensitive nor specific for aortic injury, preventing accurate diagnosis without ancillary studies.

Diagnostic Strategies

Chest Radiography. Radiography of the chest is a valuable tool when aortic rupture is suspected. Many patients have died because the presence and significance of radiographic findings were not appreciated. An increase in the width of the superior mediastinum is the most sensitive sign and is found in 50 to 92% of aortic ruptures (Fig. 45-21).[113,114] However, specificity of this radiologic sign is as low as 10%.

Mediastinal widening may be caused by venous bleeding from a clavicle, thoracic spine, or sternal fracture; pulmonary contusions; a previous mediastinal mass; a misplaced CVP catheter; or magnification caused by the anteroposterior and supine position of a portable chest radiograph. Hence the sign is not pathognomonic for aortic rupture.

Commonly cited guidelines for abnormal mediastinal widening include a mediastinal width greater than 6 cm in the erect posteroanterior film, greater than 8 cm in the supine anteroposterior chest film, or greater than 7.5 cm at the aortic knob or a ratio of mediastinal width to chest width greater than 0.25 at the aortic knob. There is disagreement regarding the reliability of these parameters in confirming or excluding aortic rupture. A subjective interpretation of mediastinal widening is more reliable than direct measurement of mediastinal width.[114] Positioning of the patient and the degree of inspiration are important factors in assessing

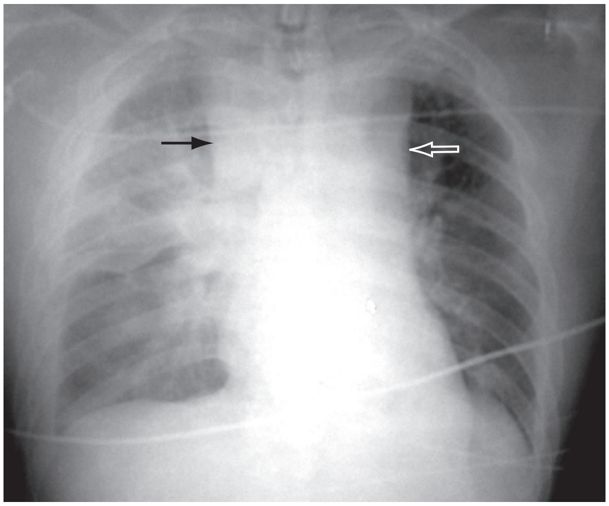


Figure 45-21. Anteroposterior radiograph of the chest showing wide mediastinum *(arrows)*.

www.ketabpezeshki.com 66485457-66963820

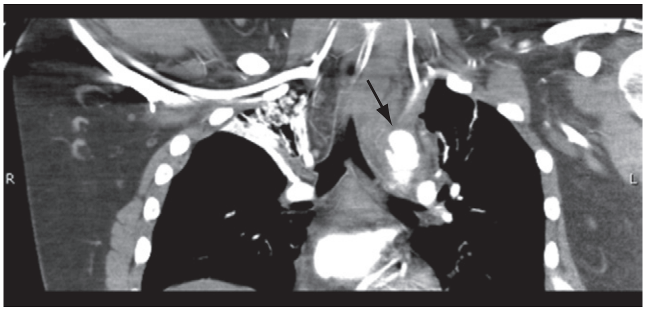


Figure 45-22. Chest computed tomography scan showing aortic intimal tear with surrounding mediastinal hematoma (*arrow*).

the mediastinum. Every effort should be made to obtain a standard upright inspiratory posteroanterior film, if clinically feasible, before a mediastinum is declared abnormal, to avoid false-positive interpretations.

Current literature is replete with various diagnostic radiologic criteria thought to be sensitive indicators of aortic rupture.[115,116] Several authors have shown that an interpretation of widened mediastinum and an obscured aortic knob are the most reliable signs of aortic rupture. The opacification of the clear space between the aorta and the pulmonary artery, displaced nasogastric tube, widened paratracheal stripe, or widened right paraspinal interface is thought to provide the most specific evidence for aortic rupture.[113,115,116] Others believe that deviation of the nasogastric tube to the right in combination with depression of the left mainstem bronchus below 40 degrees from the horizontal is the most reliable sign positively associated with the diagnosis.

Other reported radiologic signs of a ruptured aorta include left hemithorax, obliteration of the medial aspect of the left upper lobe apex (left apical pleural cap), deviation of the trachea to the right, and multiple rib fractures. Fractures of the first and second ribs, once classically described as highly suggestive of aortic injury, do not appear to be associated with increased risk compared with that of patients without these fractures.

Although previous reports suggested that a negative chest radiograph is highly predictive of a normal aortogram, several studies have challenged this widely held belief. Between 7 and 44% of patients with blunt aortic injury may have a normal mediastinum on chest radiography[117-119]; thus the sensitivity of a negative chest radiograph (i.e., normal mediastinum) is limited. These findings have led to the liberal use of helical chest CT scanning in patients with high-speed deceleration mechanisms of injury.[118]

Chest Computed Tomography Scan. Chest CT scanning has largely replaced the need for aortography to detect aortic rupture and is now the diagnostic test of choice.[120-122] The development of multidetector helical CT scanning in the early 1990s revolutionized trauma radiology with its speed and superior definition, thereby largely negating the negative results obtained with conventional scans. New helical CT scans have almost 100% sensitivity and specificity for rapidly detecting aortic injury while requiring only intravenous contrast administration (Figs. 45-22 and 45-23). A normal aortic contour on CT, even in the presence of a mediastinal hematoma, has been shown to be highly accurate in excluding thoracic aortic disruption (Figs. 45-24 and 45-25).[118,119,121]

A chest CT scan with intravascular contrast offers a number of advantages over aortography. It is noninvasive, provides significantly more information on other thoracic injuries than chest radiography, and can be performed more rapidly than angiography. At most centers, an immediate chest CT scan is readily available. In addition, in the group of patients with a widened mediastinum, CT evaluation may be useful in evaluating not only the aorta but also the spine because spinal fractures may be the

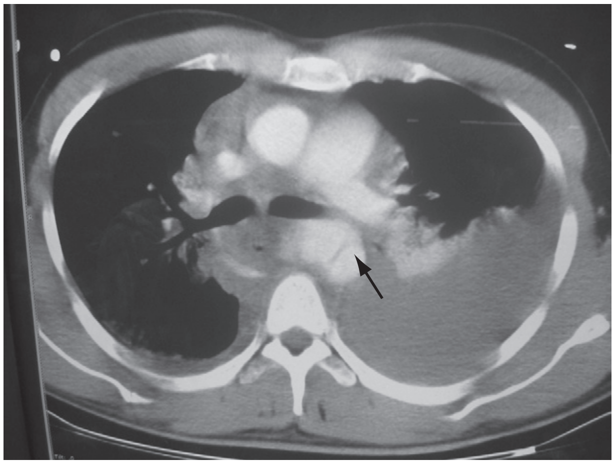


Figure 45-23. Chest computed tomography scan demonstrating periaortic hemorrhage and an intimal flap (*arrow*).

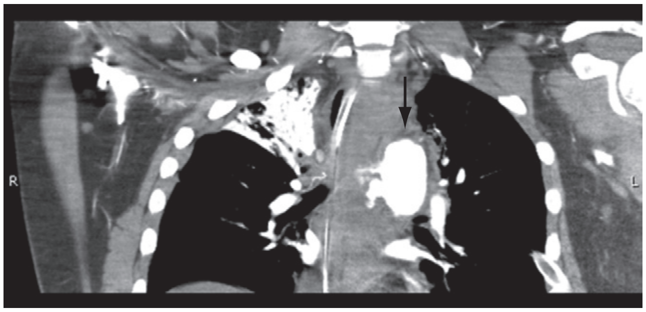


Figure 45-24. Chest computed tomography scan showing aortic injury with active extravasation (*arrow*).

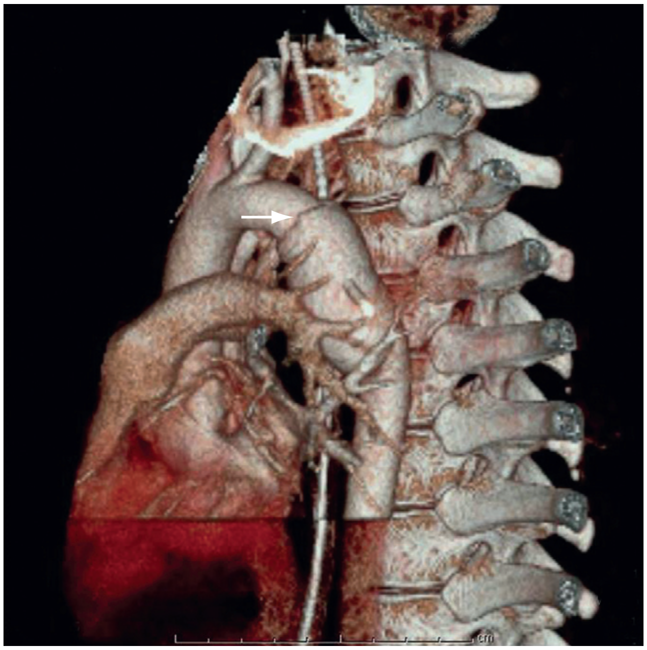


Figure 45-25. Three-dimensional reconstruction of chest computed tomography scan showing aortic injury (*arrow*).

www.ketabpezeshki.com 66485457-66963820

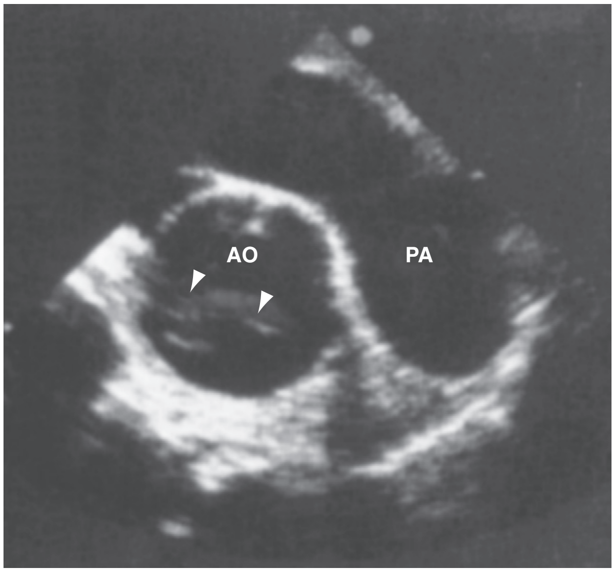


Figure 45-26. Transesophageal echocardiogram shows periaortic hemorrhage and aortic dissection *(arrows). AO,* aorta; *PA,* periaortic.

cause of a widened mediastinum. It is now recommended that all patients with a mechanism of injury suggestive of potential aortic injury undergo CT evaluation of the mediastinum, irrespective of chest radiographic findings.[118]

As a result of the improvements in CT scanning technology, more subtle aortic lesions are now being identified, which has led to the term "minimal aortic injury." A minimal aortic injury is defined as an aortic injury with an intimal flap less than 1 cm, and no or minimal periaortic mediastinal hematoma.[123] Up to 10% of patients with blunt aortic injury diagnosed on CT scan may have a minimal aortic injury. It is felt that minimal aortic injuries carry a relatively low risk of rupture. Some centers opt to follow these patients with serial CT scans. If the injury is associated with significant thrombus, periaortic hematoma, lumen encroachment, or pseudoaneurysm, many centers will then proceed to endograft coverage via interventional radiology.[123]

Transesophageal Echocardiography. TEE is an alternative method to CT scanning or aortography for establishing the diagnosis of aortic rupture.[124-126] It offers a number of advantages over other diagnostic studies: It is fast, does not require intravenous contrast or radiation exposure, provides concomitant evaluation of cardiac function, and can be performed in the ED. Sedation is necessary to avoid hypertension while the probe is inserted. TEE is contraindicated in patients with esophageal injury.

TEE allows identification of an intimal flap, as well as a periaortic hematoma (Fig. 45-26). When only a monoplane TEE is used, the upper portion of the ascending aorta represents a blind zone because of the interposition of the air-filled trachea. However, because the vast majority of injuries are located at the isthmus, TEE is highly accurate, with a reported sensitivity of 87 to 100% and a specificity of 98 to 100%.[124-126] When available, TEE offers an alternative to a chest CT scan as a diagnostic screening test for aortic injury.

In patients with severe blunt chest trauma, TEE and CT have been found to have similar diagnostic accuracy for the identification of surgical acute traumatic aortic injury. In addition, TEE also allows the diagnosis of associated cardiac injuries and is more sensitive than CT for the identification of intimal or medial lesions of the thoracic aorta.[126]

Aortic repair may be feasible based on TEE alone, but aortography is still needed when TEE results are equivocal, when TEE is not tolerated or contraindicated, or when other suspected vascular injuries require evaluation by arteriography.[111]

Intravascular Ultrasound. Intravascular US has been described in the detection of subtle injuries to the aorta. This modality involves a small US probe that is inserted through the femoral artery and guided up the aorta. Currently, availability is limited to a few trauma centers because the technique requires sophisticated equipment and is performed in the operating room or angiography suite. Preliminary data suggest that intravascular US is extremely sensitive and specific in detecting blunt aortic injury.[127,128]

Aortography. Aortography, long considered the gold standard for establishing the diagnosis of aortic disruption, has been replaced almost completely by high-resolution helical CT scanners.[129,130] The major objective for patients with a ruptured aorta is the early recognition of the lesion before adventitial disruption and exsanguination. Multiple aortic tears occur in 15 to 20% of cases, necessitating precise anatomic localization of these injuries. Before the widespread availability of helical CT scanners, aortography was recommended not only for patients with a widened mediastinum but also for those who had sustained significant blunt chest trauma and who had any of the radiologic signs previously mentioned. An aggressive approach is particularly warranted in elderly patients.

Aortography should be delayed in patients with more immediate life-threatening injuries to the abdomen, pelvis, and head. In circumstances in which aortography is be delayed, it is important to provide medical management and maintain the systolic blood pressure below 120 mm Hg with antihypertensive agents.[128]

High-quality aortography can be performed with the aid of a rapid film changer by directly injecting the contrast medium into the root of the aorta through a catheter. The procedure involves a risk of further damage to the aorta or other ruptured vessel if the catheter crosses the site of the injury; however, this risk can be reduced by use of meticulous technique, a soft-tipped C-curve guidewire, and fluoroscopy. Simultaneous coronary angiography is often indicated, particularly in patients with an aortogram that shows a tear in the ascending aorta, because involvement of the coronary ostia by the dissection or the presence of significant arteriosclerotic disease may warrant coronary artery bypass grafting together with surgical repair of the aorta.

As surgeons have gained more experience with the diagnostic capabilities of helical CT scanning, the need for preoperative angiography has declined. Aortography should now be reserved for high-risk patients with indeterminate helical chest CT scans.[118,130]

Management

Out-of-Hospital Management. In the out-of-hospital care of any patient who has sustained blunt chest trauma, evaluation for possible aortic rupture should concentrate on identifying a mechanism of injury compatible with aortic rupture and treating hypotension, tension pneumothorax, and pericardial tamponade. Immediate communication of the patient's condition and expeditious transport to a trauma center will increase the patient's chance for survival.

Emergency Department. Because of the ever-present risk of sudden free rupture and exsanguination, repair of the lesion should be performed as soon as the diagnosis is made. Management of the patient with multiple injuries who has documented rupture of the thoracic aorta depends on the nature of associated injuries. Surgical repair of the aortic rupture should be delayed in the presence of life-threatening intracranial or intra-abdominal injury or profuse retroperitoneal hemorrhage.[118] Consideration for delay of the procedure should be made for patients at high risk for infection (e.g., those who have extensive body surface burns,

www.ketabpezeshki.com 66485457-66963820

contaminated large open wounds, established sepsis, or severe respiratory insufficiency caused by thoracic trauma).

Careful regulation of blood pressure is mandatory until definitive surgical repair can be performed. If operative repair is delayed, the systolic blood pressure should be maintained between 100 and 120 mm Hg. The objective of lowering the blood pressure is to decrease the shearing jet effect of an elevated pulse pressure, thus decreasing the possibility of continued adventitial dissection and subsequent free rupture.[130]

Esmolol, a short-acting titratable beta-blocker, may be ideally suited for this purpose because, unlike nitroprusside sodium, it decreases the pulse pressure and minimizes the shearing effect on the intact adventitia of the aorta. If blood pressure is not adequately controlled, nitroprusside sodium can be added as a second agent after the pulse pressure has been decreased with a short-acting beta-blocker.

Surgical Techniques

Many surgical techniques have been described since the first successful repair by Passaro and Pace in 1959.[131] In those patients who survive operative repair, paraplegia from spinal cord ischemia has been a significant complication, traditionally affecting as many as 10 to 20% of such patients.[132,133] The major variable thought to be related to spinal cord ischemia and subsequent development of paraplegia has been aortic cross-clamp times.[134] Blunt aortic injury ranges from a simple tear (usually distal to the origin of the subclavian artery) to complex injuries involving the proximal aorta and branch vessels.

Many surgeons have reported the use of cardiopulmonary bypass techniques in surgical repair to allow for distal spinal cord perfusion with significantly reduced incidence of paraplegia.[135,136] This is especially true for patients with complex aortic injuries, for which the aortic cross-clamp times are typically prolonged.[130]

The pathologic condition found dictates the type of repair. A synthetic graft is often required because of extensive tension on the vessel walls or jagged torn ends of the vessel. Data on successful primary repair of aortic disruption are encouraging. The procedure requires less operative time and has a lower potential infection risk, blood loss through a prosthesis is avoided, the possibility of pseudoaneurysm formation is eliminated, and secondary embolism arising from mural thrombosis is avoided. Multiple tears of the descending thoracic aorta have been successfully repaired with the primary suture technique. Direct end-to-end anastomosis appears to be most feasible in the younger population.

For patients who arrive at the hospital alive but who have descending thoracic aortic injuries, the incidence of mortality during surgery ranges from 20 to 30%, and the paraplegia rate is 5 to 7%.[132,135,136] Younger patients have the highest survival rate. Mortality is related to the presence or absence of extensive dissection and to the preoperative condition of the patient.

Endovascular Repair

There is a growing body of evidence demonstrating the safety and efficacy of endovascular repair of traumatic aortic tears.[137-141] This involves the use of a stent placed through a femoral or iliac artery approach. Preliminary data indicate that success rates and complication rates are comparable if not better than those of traditional open surgical repairs and that the risk of major surgery and subsequent paraplegia from prolonged aortic clamping is significantly reduced with endovascular repair.[142] Emerging literature suggests that endovascular repair with stenting is replacing open repair as the treatment of choice for blunt aortic injury (see Fig. 45-26).[143-148]

ESOPHAGEAL PERFORATION

Epidemiology

Perforation of the esophagus has been called the most rapidly fatal perforation of the gastrointestinal tract because death is almost ensured if the diagnosis is delayed more than 24 hours.[149] The classic description of esophageal perforation resulting from forceful vomiting was published in 1724 by Boerhaave, and from 1724 to 1941 the occurrence of Boerhaave's syndrome was almost uniformly fatal.[150] In 1941 the first successful surgical treatment, a drainage procedure, was reported, and in 1947 the first successful closure of a ruptured esophagus was described. Since then, improved surgical techniques, a greater physician awareness leading to a more prompt diagnosis, the availability of more effective antibiotics, and better general supportive measures have reduced the mortality to approximately 20%.[151] Mortality data cited for perforation are affected by several variables, such as location (with perforations of the thoracic segment having the highest mortality rate), mechanism of injury, time elapsed between injury and diagnosis, the presence of preexisting esophageal disease, and general health of the patient.

Anatomy and Pathophysiology

The anatomic feature responsible for the prolonged morbidity and high mortality associated with esophageal perforation is the lack of an esophageal serosal covering that allows perforation at any level direct access to the mediastinum. Perforations in the upper or cervical esophagus enter the retropharyngeal space, where fascial planes extend from the base of the skull to the bifurcation of the trachea. Perforations in the midesophagus and lower esophagus enter directly into the mediastinum. Only the thin mediastinal pleura prevents free access to the entire pleural cavity, and this barrier is commonly overcome by continued drainage and the massive exudative inflammatory reaction induced by chemical and bacterial mediastinitis. When the mediastinal pleura is penetrated, the negative pressure generated by respiratory efforts tends to increase the soilage by promoting drainage from the gastrointestinal tract into the mediastinum and pleural space.

When esophageal rupture results from emetic pressure, as in cases of Boerhaave's syndrome, the intrinsic weakness of the left posterior distal esophagus is important. Other areas (including cervical, midthoracic, and infradiaphragmatic sites) have been reported only rarely to rupture secondary to emesis. In addition, the esophagus has three areas of anatomic narrowing: the cricopharyngeal muscle near the esophageal introitus, the level at which the esophagus crosses the left mainstem bronchus and the aortic arch, and the gastroesophageal junction. In the absence of a preexisting esophageal disease such as carcinoma, it is unusual for a perforation caused by a foreign body to occur anywhere other than at these three sites. Foreign bodies may cause perforation by direct penetration, pressure, or chemical necrosis.

Etiology

The most common causes of an esophageal perforation are shown in Box 45-4.

Iatrogenic

Most esophageal perforations are iatrogenic, most commonly as a complication of instrumentation (59% of all patients).[152] The rigid endoscope is the most common offender, particularly when general anesthesia is used. Although use of the flexible endoscope has made this complication less likely, the total number of perforations has increased as more procedures are performed. Injuries

www.ketabpezeshki.com 66485457-66963820

Box 45-4 Most Common Causes of Esophageal Perforation

1. Iatrogenic
2. Foreign bodies
3. Caustic burns
4. Blunt or penetrating trauma
5. Spontaneous rupture (Boerhaave's syndrome)
6. Postoperative breakdown of anastomosis

tend to occur near either the cricopharynx or the cervical esophagus as the endoscope is inserted.[152] Endoscopic procedures that are too vigorous in the presence of a corrosive burn or carcinoma are also a common cause of iatrogenic esophageal injury.

Esophageal dilation performed for benign or malignant strictures of the esophagus is the second most common iatrogenic cause of esophageal perforations.[153] Increasing the dilator size too rapidly during these procedures may lead to perforation. The preexisting fibrotic process that resulted in the stricture tends to scar the surrounding mediastinal tissues, however, limiting free access to the mediastinum provided by many other perforations. In the ED, nasotracheal or nasogastric intubations are the most common causes of iatrogenic perforation, with the perforation usually occurring in the pyriform sinus. In a closed claims analysis published in 1999, esophageal injuries by anesthesiologists were overwhelmingly associated with difficult intubations.[154] Risk factors for a difficult airway include obesity, cervical arthritis, haste, and improper muscle relaxation. Claims involving airways that were classified as "nondifficult" involved other esophageal instrumentation, such as a nasogastric tube, esophageal dilator, or esophageal stethoscope. In all cases, esophageal injuries were more severe than any other type of airway injury sustained during airway maneuvers.

The use of an esophageal obturator airway was also associated with occasional esophageal trauma, specifically midesophageal perforation. Use of the esophageal obturator airway's successors, the laryngotracheal Combitube and the King airway, do not seem to be associated with trauma more severe than occasional esophageal abrasions or contusions.[155]

Several cases of esophageal rupture secondary to compressed air have been reported, including two cases of pharyngoesophageal perforation secondary to gas in carbonated beverages and in tartaric acid–sodium bicarbonate mixtures administered to treat esophageal food impactions. Esophageal perforation has also been caused by placement of a cervical fixation device and secondary to the Heimlich maneuver.

Foreign Bodies

Foreign bodies can cause an esophageal injury by direct laceration, by pressure necrosis, or during endoscopic removal.[156] Small perforations tend to seal without sequelae, but pressure necrosis or lacerating injuries provide ample access to the mediastinum.[153] Foreign bodies usually lodge in the cervical esophagus, but if a distal stricture is present, this too is a common site. In children younger than 4 years, the cricopharyngeal narrowing is the usual point of foreign body impaction. After age 4 years, most objects pass this region and traverse the remaining normal esophagus. In adults, a foreign body impaction, especially in cases of repeated episodes, raises the possibility of a stricture and warrants further investigation.

In elderly patients, foreign bodies commonly enter the esophagus because of a loss of oral tactile sensation resulting from intoxication or a poorly fitting set of dentures.[152] Inadequate dentures may also lead to the swallowing of large pieces of poorly chewed food. Other esophageal foreign bodies include sharp fish or chicken bones and corn chips that may impale the esophageal wall leading to eventual leakage.

Caustic Burns

Caustic burns of the esophagus occur from intentional or accidental ingestion of acid or alkali. There are two peaks of incidence: 1 to 5 years of age, when ingestion is usually of a small amount of material and accidental, and in the teens and 20s, when larger quantities are ingested during suicide attempts. Symptoms include hematemesis, respiratory distress, vomiting, drooling, or the presence of oropharyngeal lesions on physical examination.[157] Perforation usually occurs during the latent granulation stage of the disease, approximately 4 to 14 days after ingestion.

The liquefaction necrosis classically resulting from strong alkali burns (pH >12) is more likely to cause esophageal perforation than the coagulation necrosis resulting from strong acid burns (pH <2). Individuals ingesting alkali substances with a pH less than 11.5 rarely sustain injuries more serious than superficial mucosal burns. Acid ingestions cause damage more frequently in the stomach than in the esophagus.[157]

In treating a patient who has ingested a caustic substance, decontamination should involve only the rinsing of the mouth. Dilution of the substance with milk or water has been suggested; however, further liquid ingestion should be avoided if there is suspicion of perforation. Emesis, gastric lavage, and charcoal should be avoided.[154]

Endoscopy within the first 6 to 18 hours may be used to determine the extent of the injury and to guide therapy. Antibiotics are reserved for patients with evidence of perforation, and steroids are suggested by some authors if the burns are circumferential or transmural. Other authors have shown that in the setting of large alkali ingestions, corticosteroids not only did not prevent the formation of esophageal stenosis but also increased the risk of other complications.[157]

Although admission after significant ingestion is the rule, some authors suggest that in the setting of accidental ingestion in children and in the absence of symptoms, endoscopy and admission may not be indicated.[158,159] Esophagoscopy is commonly undertaken to ascertain the presence or absence of esophageal injury. Advancing the esophagoscope beyond the first burn in the esophagus increases the risk of perforation and is a common iatrogenic cause of esophageal perforation.

Penetrating and Blunt Trauma

Because of its well-protected position posteriorly, esophageal trauma occurs in approximately 5% of patients with injuries to the neck, but only 1% of blunt trauma victims, and it is usually not an isolated injury.[152] Cervical esophageal injuries are the most common because of a lack of protection by the bony thorax, and the trachea is the most common associated site of injury.[152] In some cases, the esophageal injury may be overlooked initially because of the dramatic presentation of a patient with a tracheal injury.

Typical symptoms seen in cervical esophageal injuries include neck pain, dysphagia, cough, voice changes, and hematemesis. Physical findings may include neck tenderness, resistance to flexion, crepitus, or stridor.[152,158] In one large series, the most common life-threatening problem in the ED was compromise of the airway. Most of these cases were handled with rapid sequence intubation, but a significant number (12%) of patients required cricothyroidotomy.[152]

If the patient's condition is stable, a preoperative esophagogram with a water-soluble agent should precede any endoscopy. Although chest and neck radiograph and CT also may be used to diagnose this injury, emergent bedside flexible endoscopy seems

www.ketabpezeshki.com 66485457-66963820

to be the test of choice to confirm negative findings on esophagography (especially in the setting of penetrating trauma).[160] Operative repair is indicated in most of these injuries (>90%) and should be done as quickly as possible to avoid the development of fistulae, mediastinitis, or abscess formation.[158]

Blunt traumatic injuries to the esophagus occur much less often than penetrating injuries. The pathophysiology and prognosis of blunt injuries to the esophagus are similar to those of spontaneous rupture or emesis. In some cases, rupture of the cervical esophagus has been reported in association with cervical spine fracture.[161]

Spontaneous Rupture

Spontaneous esophageal rupture, postemetic rupture, and *Boerhaave's syndrome* are synonymous terms. This esophageal injury is associated with a poor prognosis because the forces required to rupture the esophagus result in almost instantaneous and massive mediastinal contamination. The distal esophagus is the usual site of injury, with a longitudinal tear occurring in the left posterolateral aspect. More than 80% of these injuries occur in middle-aged men who have ingested alcohol and large meals.

In vitro, a tear similar to that seen in cases of Boerhaave's syndrome requires a force of 3 to 6 psi, which may be generated in vivo by gastric pressure caused by the reverse peristalsis (seen with emesis) pushing against a closed cricopharyngeal muscle. The role of preexisting gastrointestinal disease in spontaneous rupture of the esophagus is unclear. Some authors emphasize its importance, whereas others report that 80% of esophageal ruptures occur in a previously normal esophagus.[160] Less pressure is required to perforate a diseased esophagus. Approximately 25% of patients with Boerhaave's syndrome have no history of emesis.[152] Increases in intra-abdominal pressure resulting from blunt trauma, seizures, childbirth, laughing, straining at stool, and heavy lifting have all been reported to cause this injury.

Diagnostic Findings

The diagnosis of esophageal perforation is aided by consideration of clinical circumstances. In patients with classic Boerhaave's syndrome, emesis is followed by severe chest pain, subcutaneous emphysema, and cardiopulmonary collapse. Development of these signs and symptoms after instrumentation of the esophagus or removal of an esophageal foreign body is relatively straightforward. One third of cases of perforated esophagus are atypical, however. Only a careful history and physical examination supplemented by appropriate laboratory and diagnostic studies enable the clinician to diagnose a subtle case at an early stage. In considering any of the diagnoses listed in Box 45-5, a perforated esophagus should also be considered.

Clinical Features

The most reliable symptom of an esophageal injury is pleuritic pain localized along the course of the esophagus that is exacerbated by swallowing or neck flexion (Fig. 45-27). Pain may be located in the epigastrium, substernal area, or back; usually worsens over time; and may migrate from the upper abdomen to the chest. As the infectious process worsens, dyspnea usually ensues.

The early physical signs of an esophageal perforation are sparse. As air and caustic contaminated material move through the esophageal tear into the mediastinum and pleural space, and before any subcutaneous air is palpable at the root of the neck, the mediastinal air may impart a nasal quality to the voice. Mediastinal air may surround the heart and produce a systolic crunching sound (Hamman's crunch). As air and fluid move into the pleural space, signs of a hydropneumothorax or an empyema may develop. Eventually the air travels into the subcutaneous tissues, dissecting into the neck, where subcutaneous emphysema may first become evident. This classic sign is present in only approximately 60% of patients, however, and in the absence of a tracheal injury, it may occur in only 30%.[162] As the infectious and inflammatory process advances, the patient's general appearance and vital signs begin to manifest the signs of cardiopulmonary collapse and sepsis with fever, cyanosis, hypotension, anuria, and eventually death.

Box 45-5 Clinical Conditions That May Mimic Esophageal Perforation

1. Spontaneous pneumomediastinum
2. Aortic aneurysm (thoracic)
3. Pulmonary embolus
4. Perforated peptic ulcer
5. Myocardial infarction
6. Pancreatitis
7. Mesenteric thrombosis
8. Cholecystitis
9. Pneumonia

Diagnostic Strategies

Laboratory studies provide largely nonspecific findings. If tested, the pleural effusion of esophageal perforation may show a high salivary amylase level and a low pH. The radiographic examination usually suggests the diagnosis of an esophageal perforation. The classic chest radiograph findings are as follows:

1. Mediastinal air with or without subcutaneous emphysema
2. Left-sided pleural effusion
3. Pneumothorax
4. Widened mediastinum

Lateral views of the cervical spine may reveal air or fluid in the retropharyngeal area that is characteristic of a cervical esophageal perforation but also is found when perforations in the lower parts of the esophagus release air or fluid that dissects superiorly (Fig. 45-28). Most patients exhibit one or more of these abnormalities at some point in the course of the illness, but radiographic evidence of the perforation may be absent early.

The literature is not conclusive regarding whether insoluble barium contrast medium or water-soluble diatrizoate meglumine (Gastrografin) is the preferred initial study. Gastrografin does not obscure visualization with subsequent endoscopy, and it produces less mediastinal soiling than does barium. It is generally recommended that the initial study use this water-soluble agent; then, if no leak is shown, a barium study may be undertaken to better define the mucosal detail.

Endoscopy, similar to contrast studies, is not an infallible aid in establishing the presence or absence of an esophageal perforation. The size and location of the perforation and the skill of the endoscopist are important factors in the low incidence of false-negative studies.[164] If the accuracy of the endoscopy is in doubt, an esophagogram should be performed. Helical CT with dilute oral contrast has been reported as a safer, faster, and less manpower-intensive diagnostic examination.[165] Some of the abnormalities that may be seen on CT scan include extraluminal air, periesophageal fluid, esophageal thickening, and extraluminal contrast. These CT findings may be the first clue to the correct diagnosis of esophageal perforation.

Management

Early diagnosis can best be accomplished if one is aware of the pathophysiology and clinical settings in which esophageal perforations occur. Time is crucial in minimizing the mortality and morbidity of this condition. If the diagnosis is strongly suggested or confirmed, management should include broad-spectrum

www.ketabpezeshki.com 66485457-66963820

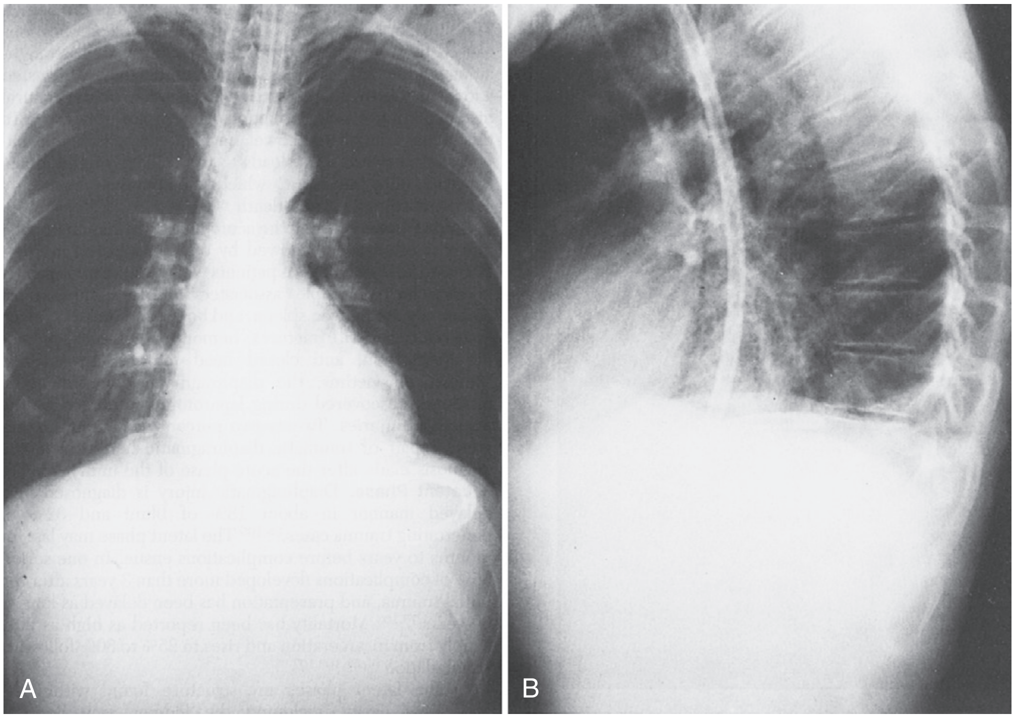


Figure 45-27. **A,** Chest radiograph of a 36-year-old man with acute onset of pleuritic chest pain after forceful vomiting. **B,** Chest radiograph shows mediastinal and subcutaneous air typical of ruptured esophagus. Mediastinum is not yet widened, and there is no soilage of the pleural cavity.

Figure 45-28. Lateral view of the cervical spine revealing air in the retropharyngeal area (*arrow*).

antibiotics (covering oral flora), volume replacement, and airway maintenance.[163-165] An emergency surgical consultation should be obtained because prognosis worsens as time passes, with mortality almost doubling in the first 12 hours.

Although operative therapy is standard, nonoperative therapy is an option for patients with well-contained perforations, with minimal mediastinal involvement, and without evidence of sepsis.[165] In such cases the patient is placed on nothing-by-mouth (NPO) status for at least 72 hours, broad-spectrum antibiotics are initiated, and usually total parenteral nutrition treatment is begun. The use of nasogastric tubes should be discouraged because they may increase gastroesophageal reflux and worsen the contamination of the mediastinum.[164,165]

KEY CONCEPTS

- Even relatively minor chest wall injuries, such as rib fractures, may result in serious complications in elderly patients and patients with preexisting pulmonary disease.
- Children are more susceptible to pulmonary contusion because of greater compliance of the chest wall.
- Unless there are abnormalities on the initial ECG, there is no need to pursue the diagnosis of myocardial contusion with more sophisticated tests.
- Many patients with myocardial rupture or traumatic aortic rupture survive to reach the hospital and can be salvaged with rapid diagnosis and intervention.
- Pericardial tamponade can be diagnosed accurately before hemodynamic decompensation occurs by standard cardiac ultrasound performed by emergency physicians.
- Chest CT should be considered for patients with mechanisms of injury that raise concern regarding blunt aortic injury even in the presence of normal chest radiographs.
- Injury of the esophagus is relatively common with penetrating trauma of the chest or neck. Because the presentation is initially subtle and the potential complications are severe, the diagnosis of esophageal perforation is actively pursued in cases in which the trajectory of the penetrating wound potentially involves the esophagus.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Khandhar SJ, Johnson SB, Calhoon JH: Overview of thoracic trauma in the United States. *Thorac Surg Clin* 2007; 17:1.
2. Brenner DJ, Hall EJ: Computed tomography—an increasing source of radiation exposure. *N Engl J Med* 2007; 357:2277.
3. Shweiki E, Klena J, Wood GC, Indeck M: Assessing the true risk of abdominal solid organ injury in hospitalized rib fracture patients. *J Trauma* 2001; 48:684.
4. Bergeron E, et al: Elderly trauma patients with rib fractures are at greater risk of death and pneumonia. *J Trauma* 2003; 54:478.
5. Holcomb JB, McMullin NR, Kozar RA, Lygas MH, Moore FA: Morbidity from rib fractures increases after age 45. *J Am Coll Surg* 2003; 196:549.
6. Brasel KJ, Guse CE, Layde P, Weigelt JA: Rib fractures: Relationship with pneumonia and mortality. *Crit Care Med* 2006; 34:1642.
7. Traub M, et al: The use of chest computed tomography versus chest x-ray in patients with major blunt trauma. *Injury* 2007; 38:43.
8. Sirmali M, et al: A comprehensive analysis of traumatic rib fractures: Morbidity, mortality and management. *Eur J Cardiothorac Surg* 2003; 24:133.
9. Todd SR, et al: A multidisciplinary clinical pathway decreases rib fracture-associated infectious morbidity and mortality in high-risk trauma patients. *Am J Surg* 2006; 192:806.
10. Simon BJ, Chu Q, Emhoff TA, Fiallo VM, Lee KF: Delayed hemothorax after blunt thoracic trauma: An uncommon entity with significant morbidity. *J Trauma* 1998; 45:673.
11. Knobloch K, et al: Sternal fractures occur most often in old cars to seat-belted drivers without any airbag often with concomitant spinal injuries: Clinical findings and technical collision variables among 42,055 crash victims. *Ann Thorac Surg* 2006; 82:444.
12. Brookes JG, Dunn RJ, Rogers LR: Sternal fractures: A retrospective analysis of 272 cases. *J Trauma* 1993; 35:46.
13. You JS, Chung YE, Kim D, Park S, Chung SP: Role of sonography in the emergency room to diagnose sternal fractures. *J Clin Ultrasound* 2010; 38:135-137.
14. Kehdy F, Richardson JD: The utility of 3-D CT scan in the diagnosis and evaluation of sternal fractures. *J Trauma* 2006; 60:635.
15. Richardson JD, Franklin GA, Heffley S, Seligson D: Operative fixation of chest wall fractures: An underused procedure? *Am Surg* 2007; 73:591.
16. Xirouchaki N, et al: Noninvasive bilevel positive pressure ventilation in patients with blunt thoracic trauma. *Respiration* 2005; 72:517.
17. Pettiford BL, Luketich JD, Landreneau RJ: The management of flail chest. *Thorac Surg Clin* 2007; 17:25.
18. Gunduz M, Unlugenc H, Ozalevli M, Inanoglu K, Akman H: A comparative study of continuous positive airway pressure (CPAP) and intermittent positive pressure ventilation (IPPV) in patients with flail chest. *Emerg Med J* 2005; 22:325-329.
19. Lafferty PM, Anavian J, Will RE, Cole PA: Operative treatment of chest wall injuries: Indications, technique, and outcomes. *J Bone Joint Surg Am* 2011; 93:97-110.
20. Borman JB, Aharonson-Daniel L, Savitsky B, Peleg K; Israeli Trauma Group: Unilateral flail chest is seldom a lethal injury. *Emerg Med J* 2006; 23:903.
21. Eckstein M, Cowen AR: Scene safety in the face of automatic weapons fire: A new dilemma for EMS? *Prehosp Emerg Care* 1998; 2:117.
22. de Brito D, Challoner KR, Sehgal A, Mallon W: The injury pattern of a new law enforcement weapon: The police bean bag. *Ann Emerg Med* 2001; 38:383.
23. Olivas T, Jones B, Canulla M: Abdominal wall penetration by a police "bean bag." *Am Surg* 2001; 67:407-409.
24. Byard RW, Wick R, Simpson E, Gilbert JD: The pathological features and circumstances of death of lethal crush/traumatic asphyxia in adults—a 25-year study. *Forensic Sci Int* 2006; 159:200.
25. Balci AE, et al: Blunt thoracic trauma in children: Review of 137 cases. *Eur J Cardiothorac Surg* 2004; 26:387.
26. Morgagni JB: *Epistola* 54:140, 1761.
27. Wanek S, Mayberry JC: Blunt thoracic trauma: Flail chest, pulmonary contusion, and blast injury. *Crit Care Clin* 2004; 20:71.
28. Kwon A, et al: Isolated computed tomography diagnosis of pulmonary contusion does not correlate with increased morbidity. *J Pediatr Surg* 2006; 41:78.
29. Cohn SM, Dubose JJ: Pulmonary contusion: An update on recent advances in clinical management. *World J Surg* 2011; 34:1959-1970.
30. Adoumie R, Shennib H, Brown R, Slinger P, Chiu RC: Differential lung ventilation. *J Thorac Cardiovasc Surg* 1993; 105:229.
31. Deunk J, et al: The clinical outcome of occult pulmonary contusion on multidetector-row computed tomography in blunt trauma patients. *J Trauma* 2010; 68:387-394.
32. Hamrick MC, Duhn RD, Ochsner MG: Critical evaluation of pulmonary contusion in the early post-traumatic period: Risk of assisted ventilation. *Am Surg* 2009; 75:1054-1058.
33. Mielck F, Quintel M: Extracorporeal membrane oxygenation. *Curr Opin Crit Care* 2005; 11:87.
34. Kirkpatrick AW, et al: Hand-held thoracic sonography for detecting post-traumatic pneumothoraces: The Extended Focused Assessment with Sonography for Trauma (EFAST). *J Trauma* 2004; 57:288.
35. Blaivas M, Lyon M, Duggal S: A prospective comparison of supine chest radiography and bedside ultrasound for the diagnosis of traumatic pneumothorax. *Acad Emerg Med* 2005; 12:844.
36. Volpicelli G: Sonographic diagnosis of pneumothorax. *Intensive Care Med* 2011; 37:224-232.
37. Hill SL, Edmisten T, Holtzman G, Wright A: The occult pneumothorax: An increasing diagnostic entity in trauma. *Am Surg* 1999; 65:254-258.
38. Ball CG: 2005 Incidence, risk factors, and outcomes for occult pneumothoraces in victims of major trauma. *J Trauma* 2005; 59:917-924.
39. Neff MA, Monk JS Jr, Peters K, Nikhilesh A: Detection of occult pneumothoraces on abdominal computed tomographic scans in trauma patients. *J Trauma* 2000; 49:281.
40. Kiev J, Kerstein MD: Role of three hour roentgenogram of the chest in penetrating and non-penetrating injuries. *Surg Gynecol Obstet* 1992; 175:249.
41. Magnotti LJ, et al: Initial chest CT obviates the need for repeat chest radiograph after penetrating thoracic trauma. *Am Surg* 2007; 73:569.
42. McGillicudy D, Rosen P: Diagnostic dilemmas and current controversies in chest trauma. *Emerg Med Clin North Am* 2007; 25:695.
43. Yadav K, Jalili M, Zehtabchi S: Management of traumatic occult pneumothorax. *Resuscitation* 2010; 81:1063-1068.
44. Mowery NT, et al: Practice management guidelines for management of hemothorax and occult pneumothorax. *J Trauma* 2011; 70:510-518.
45. Sethuraman KN, et al: Complications of tube thoracostomy placement in the emergency department. *J Emerg Med* 2011; 40:14-20.
46. Givens ML, Ayotte K, Manifold C: Needle thoracostomy: Implications of computed tomography chest wall thickness. *Acad Emerg Med* 2004; 11:211-213.
47. Inaba K, et al: Optimal positioning for emergent needle thoracostomy: A cadaver-based study. *J Trauma* 2011; 71:1099-1103.
48. Luchette FA, et al: Practice management guidelines for prophylactic antibiotic use in tube thoracostomy for traumatic hemopneumothorax: The EAST Practice Management Guidelines Work Group. Eastern Association for Trauma. *J Trauma* 2000; 48:753.
49. Eckstein M, Suyehara D: Needle thoracostomy in the prehospital setting. *Prehosp Emerg Care* 1998; 2:132.
50. Meyer DM: Hemothorax related to trauma. *Thorac Surg Clin* 2007; 7:47.
51. Working Group, Ad Hoc Subcommittee on Outcomes, American College of Surgeons Committee on Trauma: Practice management guidelines for emergency department thoracotomy. *J Am Coll Surg* 2001; 193:303.
52. Stafford RE, Linn J, Washington L: Incidence and management of occult hemothoraces. *Am J Surg* 2006; 192:722.
53. Landay M, et al: Lung penetration by thoracostomy tubes: Imaging findings on CT. *J Thoracic Imaging* 2006; 21:197.
54. Casos SR, Richardson JD: Role of thoracoscopy in acute management of chest injury. *Curr Opin Crit Care* 2006; 12:584.
55. Paci M, et al: The role of diagnostic VATS in penetrating thoracic injuries. *World J Emerg Surg* 2006; 1:3.
56. Manlulu AV, Lee TW, Thung KH, Wong R, Yim AP: Current indications and results of VATS in the evaluation and management of hemodynamically stable thoracic injuries. *Eur J Cardiothorac Surg* 2004; 25:1048.
57. Kiser AC, O'Brien SM, Detterbeck FC: Blunt tracheobronchial injuries: Treatment and outcomes. *Ann Thorac Surg* 2001; 71:2059.
58. Balci AE, Eren N, Eren S, Ulku R: Surgical treatment of post-traumatic tracheobronchial injuries: 14-year experience. *Eur J Cardiothorac Surg* 2002; 22:984.
59. Gómez-Caro A, et al: Role of conservative medical management of tracheobronchial injuries. *J Trauma* 2006; 61:1426.
60. Scaglione M, et al: Acute tracheobronchial injuries: Impact of imaging on diagnosis and management implications. *Eur J Radiol* 2006; 59:336.
61. Hanna WC, Ferri LE: Acute traumatic diaphragmatic injury. *Thoracic Surg Clin* 2009; 19:485-489.

www.ketabpezeshki.com 66485457-66963820

62. Leppaniemi A, Haapiainen R: Occult diaphragmatic injuries caused by stab wounds. *J Trauma* 2003; 55:646.
63. Reber PU, et al: Missed diaphragmatic injuries and their long term sequelae. *J Trauma* 1998; 44:183.
64. Eren S, Kantarci M, Okur A: Imaging of diaphragmatic rupture after trauma. *Clin Radiol* 2006; 61:467.
65. Sadeghi N, Nicaise N, DeBacker D, Struyven J, Van Gansbeke D: Right diaphragmatic rupture and hepatic hernia: An indirect sign on computed tomography. *Eur J Radiol* 1999; 9:972.
66. Madden MR, et al: Occult diaphragmatic injury from stab wounds to the lower chest and abdomen. *J Trauma* 1989; 29:292.
67. Murray JA, et al: Occult injuries to the diaphragm: Prospective evaluation of laparoscopy in penetrating injuries to the left lower chest. *J Am Coll Surg* 1998; 187:626.
68. Friese RS, Coln EC, Gentilello LM: Laparoscopy is sufficient to exclude occult diaphragm injury after penetrating abdominal trauma. *J Trauma* 2005; 58:789.
69. Bright EF, Beck CS: Nonpenetrating wounds of the heart: A clinical and experimental study. *Am Heart J* 1935; 10:293.
70. Rudusky BM: Classification of myocardial contusion and blunt cardiac trauma. *Angiology* 2007; 57:610.
71. Koehler SA, et al: Cardiac concussion: Definition, differential diagnosis, and cases presentation and the legal ramification of a misdiagnosis. *Am J Forensic Med* 2004; 25:205.
72. Maron BJ, Gohman TE, Kyle SB, Estes NA 3rd, Link MS: Clinical profile and spectrum of commotio cordis. *JAMA* 2002; 287:1142.
73. Elie MC: Blunt cardiac injury. *Mount Sinai J Med* 2006; 73:542.
74. Sybrandy KC, Cramer MJ, Burgersdijk C: Diagnosing cardiac contusion: Old wisdom and new insights. *Heart* 2003; 89:485.
75. Lindstaedt M, et al: Acute and long-term clinical significance of myocardial contusion following blunt thoracic trauma: Results of a prospective study. *J Trauma* 2002; 52:479.
76. Ismailov RM, Ness RB, Redmond CK, Talbott EO, Weiss HB: Trauma associated with cardiac dysrhythmias: Results from a large matched case-control study. *J Trauma* 2007; 62:1186.
77. Nagy KK, et al: Determining which patients require evaluation for blunt cardiac injury following blunt chest trauma. *World J Surg* 2001; 25:108.
78. Walsh P, et al: Use of V4R in patients who sustain blunt chest trauma. *J Trauma* 2001; 51:60.
79. Swaanenburg JC, Klaase JM, DeJongste MJ, Zimmerman KW, ten Duis HJi: Troponin I, troponin T, CKMB-activity and CKMB-mass as markers for the detection of myocardial contusion in patients who experienced blunt trauma. *Clin Chim Acta* 1998; 272:171.
80. Edouard AR, et al: Incidence and significance of cardiac troponin I release in severe trauma patients. *Anesthesiology* 2004; 101:1262.
81. Velmahos GC, et al: Normal electrocardiography and serum troponin I levels preclude the presence of clinically significant blunt cardiac injury. *J Trauma* 2003; 54:45.
82. American Heart Association: *2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care*. Chicago: American Heart Association; 2010.
83. Brathwaite CE, Rodriguez A, Turney SZ, Dunham CM, Cowley R: Blunt traumatic cardiac rupture: A 5-year experience. *Ann Surg* 1990; 212:701.
84. DesForges G, Ridder WP, Lenoci RJ: Successful suture of ruptured myocardium after nonpenetrating injury. *N Engl J Med* 1955; 252:567.
85. Lu LH, et al: Blunt cardiac rupture with prehospital pulseless electrical activity: A rare successful experience. *J Trauma* 2005; 59:1489.
86. Namai A, Sakurai M, Fujiwara H: Five cases of blunt traumatic cardiac rupture: Success and failure in surgical management. *Gen Thorac Cardiovasc Surg* 2007; 5:200.
87. Teixeira PG, et al: Blunt cardiac rupture: A 5-year NTDB analysis. *J Trauma* 2009; 67:788-791.
88. O'Connor J, Ditillo M, Scalea T: Penetrating cardiac injury. *J R Army Med Corps* 2009; 155:185-190.
89. Asensio JA, et al: One hundred five penetrating cardiac injuries: A 2-year prospective evaluation. *J Trauma* 1998; 44:1073.
90. Asensio JA, et al: Penetrating thoracoabdominal injuries: Ongoing dilemma—which cavity and when? *World J Surg* 2002; 26:539.
91. Kirkpatrick AW, Ball CG, D'Amours SK: Acute resuscitation of the unstable adult trauma patient: Bedside diagnosis and therapy. *Can J Surg* 2008; 51:57.
92. Ma OJ, et al: Prospective analysis of a rapid trauma ultrasound examination performed by emergency physicians. *J Trauma* 1995; 38:879.
93. Beck CS: Acute and chronic compression of the heart. *Am Heart J* 1937; 14:515.
94. Ciccone TJ, Grossman SA: Cardiac ultrasound. *Emerg Med Clin North Am* 2004; 22:621.
95. Asensio JA, et al: Penetrating cardiac injuries. *Surg Clin North Am* 1996; 76:685.
96. Toda K, Yoshitatsu M, Izutani H, Ihara K: Surgical management of penetrating cardiac injuries using a fibrin glue sheet. *Interact Cardiovasc Thorac Surg* 2007; 6:577.
97. Evans BJ, Homick P: Use of a skin stapler to repair penetrating cardiac injury. *Ann R Coll Surg Engl* 2006; 88:413.
98. Eckstein M: Termination of resuscitative efforts: Medical futility for the trauma patient. *Curr Opin Crit Care* 2001; 7:450.
99. Hopson LR, et al: Guidelines for withholding or termination of resuscitation in prehospital traumatic cardiopulmonary arrest. *J Am Coll Surg* 2003; 196:475-481.
100. Kortbeek JB, et al: Advanced trauma life support, 8th edition, the evidence for change. *J Trauma* 2008; 6:1638-1650.
101. Moore EE, et al: Defining the limits of resuscitative emergency department thoracotomy: A contemporary Western Trauma Association perspective. *J Trauma* 2011; 70:334-339.
102. Seamon MJ, et al: Emergency department thoracotomy: Survival of the least expected. *World J Surg* 2008; 32:604-612.
103. Schnuriger B, et al: Organ donation: An important outcome after resuscitative thoracotomy. *J Am Coll Surg* 2010; 211:450-455.
104. Stratton SJ, Brikett K, Crammer T: Prehospital pulseless, unconscious penetrating trauma victims: Field assessments associated with survival. *J Trauma* 1998; 45:96.
105. Rhee PM, et al: Survival after emergency department thoracotomy: Review of published data from the past 25 years. *J Am Coll Surg* 2000; 190:288.
106. Soreide K, Petrone P, Asensio JA: Emergency thoracotomy in trauma: Rationale, risks, and realities. *Scand J Surg* 2007; 96:4.
107. Parmley LF, Mattingly TW, Manion WC, Jahnke EJ Jr: Nonpenetrating traumatic injury of the aorta. *Circulation* 1958; 17:1086.
108. Fabian TC, et al: Prospective study of blunt aortic injury: Multicenter trial of the American Association for the Surgery of Trauma. *J Trauma* 1997; 42:374.
109. Schulman CI, et al: Incidence and crash mechanisms of aortic injury during the past decade. *J Trauma* 2007; 62:664.
110. Conroy C, et al: Motor vehicle-related cardiac and aortic injuries differ from other thoracic injuries. *J Trauma* 2007; 62:1462.
111. Neschis DG, Scalea TM, Flinn WR, Griffith BP: Blunt aortic injury. *N Engl J Med* 2008; 359:1708-1716.
112. Duwayri Y, Abbas J, Cerilli G, Chan E, Nazzal M: Outcome after thoracic aortic injury: Experience in a level-1 trauma center. *Ann Vasc Surg* 2008; 22:309.
113. Lee FT Jr, et al: Reevaluation of plain radiographic findings in the diagnosis of aortic rupture: The role of inspiration and positioning on mediastinal width. *J Emerg Med* 1993; 11:289.
114. Woodring JH, King JG: Determination of normal transverse mediastinal width and mediastinal-width to chest-width ratio in control subjects. *J Trauma* 1989; 29:1268.
115. Mirvis SE, et al: Value of chest radiography in excluding traumatic aortic rupture. *Radiology* 1987; 163:47.
116. Heystraten FM, et al: Chest radiography in acute traumatic rupture of the thoracic aorta. *Acta Radiol* 1988; 29:411.
117. Demetriades D, et al: Routine helical computed tomographic evaluation of the mediastinum in high-risk blunt trauma patients. *Arch Surg* 1998; 133:1084.
118. Nagy K, et al: Guidelines for the diagnosis and management of blunt aortic injury: An EAST Practice Management Guidelines Work Group. *J Trauma* 2000; 48:1128.
119. Bruckner BA, et al: Critical evaluation of chest computed tomography scans for blunt descending thoracic aortic injury. *Ann Thorac Surg* 2006; 81:1339.
120. Plurad D, Green D, Demetriades D, Rhee P: The increasing use of chest computed tomography for trauma: Is it being overutilized? *J Trauma* 2007; 62:631-635.
121. Chen MY, et al: The trend of using computed tomography in the detection of acute thoracic aortic and branch vessel injury after blunt thoracic trauma: Single-center experience over 13 years. *J Trauma* 2004; 56:783.
122. Melton SM, et al: The evolution of chest computed tomography for the definitive diagnosis of blunt aortic injury: A single-center experience. *J Trauma* 2004; 56:243.
123. Malhotra AK, et al: Minimal aortic injury: A lesion associated with advancing diagnostic techniques. *J Trauma* 2001; 51:1042.
124. Goarin JP, et al: Evaluation of transesophageal echocardiography for diagnosis of traumatic aortic injury. *Anesthesiology* 2000; 93:1373.

www.ketabpezeshki.com 66485457-66963820

125. Cinnella G, Dambrosio M, Brienza N, Tullo L, Fiore T: Transesophageal echocardiography for diagnosis of traumatic aortic injury: An appraisal of the evidence. *J Trauma* 2004; 57:1246.
126. Vignon P, et al: Comparison of multiplane transesophageal echocardiography and contrast-enhanced helical CT in the diagnosis of blunt traumatic cardiovascular injuries. *Anesthesiology* 2001; 94:615.
127. Patel NH, Hahn D, Comess KA: Blunt chest trauma victims: Role of intravascular ultrasound and transesophageal echocardiography. *J Trauma* 2003; 55:330.
128. Azizzadeh A, et al: The utility of intravascular ultrasound compared to angiography in the diagnosis of blunt aortic injury. *J Vasc Surg* 2011; 53:608-619.
129. Fishman JE: Imaging of blunt aortic and great vessel trauma. *J Thorac Imaging* 2000; 15:97.
130. Fabian TC, et al: Prospective study of blunt aortic injury: Helical CT is diagnostic and antihypertensive therapy reduces rupture. *Ann Surg* 1998; 227:666.
131. Passaro E Jr, Pace WC: Traumatic rupture of the aorta. *Surgery* 1959; 46:787.
132. Miller PR, et al: Complex blunt aortic injury or repair: Beneficial effects of cardiopulmonary bypass use. *Ann Surg* 2003; 237:877.
133. Carter Y, et al: Anatomical considerations in the surgical management of blunt thoracic aortic injury. *J Vasc Surg* 2001; 34:628.
134. Nzewi O, Slight RD, Zamvar V: Management of blunt thoracic aortic injury. *Eur J Vasc Endovasc Surg* 2006; 31:18-27.
135. Whitson BA, Nath DS, Knudtson JR, McGonigal MD, Shumway SJ: Is distal aortic perfusion in traumatic thoracic aortic injuries necessary to avoid paraplegic postoperative outcomes? *J Trauma* 2008; 64:115.
136. Crestanello JA, et al: The effect of perfusion techniques on the incidence of paraplegia after the repair of traumatic thoracic aortic transections. *Mayo Clin Proc* 2006; 81:625.
137. Agostinelli A, et al: Immediate endovascular treatment of blunt aortic injury: Our therapeutic strategy. *J Thorac Cardiovasc Surg* 2006; 131:1053.
138. Kasirajan K, Hefferman D, Langsfeld M: Acute thoracic aortic trauma: A comparison of endoluminal stent grafts with open repair and nonoperative management. *Ann Vasc Surg* 2003; 17:589.
139. Orford VP, et al: Blunt traumatic aortic transection: The endovascular experience. *Ann Thorac Surg* 2003; 75:106.
140. Dunham MB, et al: Endovascular stent grafts for acute blunt aortic injury. *J Trauma* 2004; 56:1173.
141. Kato M, Yatsu S, Sato H, Kyo S: Endovascular stent-graft treatment for blunt aortic injury. *Circ J* 2004; 68:553.
142. Bent CL, et al: Endovascular management of acute blunt traumatic thoracic aortic injury: A single center experience. *J Vasc Surg* 2007; 46:920.
143. Riesenman PJ, et al: Outcomes of surgical and endovascular treatment of acute traumatic thoracic aortic injury. *J Vasc Surg* 2007; 46:934.
144. Patel HJ, Hemmila MR, Williams DM, Diener AC, Deeb GM: Late outcomes following open and endovascular repair of blunt thoracic aortic injury. *J Vasc Surg* 2011; 53:615-621.
145. Starnes BW: Treating blunt aortic injuries with endografts: Pros and cons of a meta-analysis. *Semin Vasc Surg* 2010; 23:176-181.
146. Propper BW, Clouse WD: Thoracic aortic endografting for trauma: A current appraisal. *Arch Surg* 2010; 145:1006-1011.
147. Neschis DG, Scalea TM: Endovascular repair of traumatic aortic injuries. *Adv Surg* 2010; 44:281-292.
148. Barnard J, Humphreys J, Bittar MN: Endovascular versus open surgical repair for blunt thoracic aortic injury. *Interact Cardiovasc Thorac Surg* 2009; 9:506-509.
149. Brinster CJ, et al: Evolving options in the management of esophageal perforation. *Ann Thorac Surg* 2004; 77:1475.
150. Derbes VS, Mitchell RE Jr: Hermann Boerhaave's Atrocis, nec descripti prius, morbi historia, the first translation of the classic case report of rupture of the esophagus, with annotations. *Bull Med Libr Assoc* 1944; 43:217.
151. Wang HE, Mann NC, Mears G, Jacobson K, Yealy DM: Out-of-hospital airway management in the United States. *Resuscitation* 2011; 82:378-385.
152. Wu JT, Mattox KL, Wall MJ: Esophageal perforations: New perspectives and treatment paradigms. *J Trauma* 2007; 63:1173.
153. Gander JW, Berdon WE, Cowles RA: Iatrogenic esophageal perforation in children. *Ped Surg Int* 2009; 25:395-401.
154. Domino KB, Posner KL, Caplan RA, Cheney FW: Airway injury during anesthesia: A closed claims analysis. *Anesthesiology* 1991; 91:1703.
155. Weissberg D, Refaely Y: Foreign bodies in the esophagus. *Ann Thorac Surg* 2007; 84:1854.
156. Loop FD, Groves LK: Esophageal perforations: Collective review. *Ann Thorac Surg* 1970; 10:571.
157. Mamede RCM, De Mello Filho FV: Treatment of caustic ingestion: An analysis of 239 cases. *Dis Esophagus* 2002; 15:210.
158. Swann LA, Munter DW: Esophageal emergencies. *Emerg Med Clin North Am* 1996; 14:557.
159. Lamireau T: Accidental caustic ingestion in children: Is endoscopy always mandatory? *J Pediatr Gastroenterol* 2001; 33:81.
160. Vassiliu P, Baker J, Henderson SO, et al: Aerodigestive injuries of the neck. *Am Surg* 2001; 67:75.
161. Pineau BC, Ott DJ: Isolated proximal esophageal injury from blunt trauma: Endoscopic stricture dilatation. *Dysphagia* 2003; 18:263.
162. Ahmed N, Massier C, Tassie J, Whalen J, Chung R: Diagnosis of penetrating injuries of the pharynx and esophagus in the severely injured patient. *J Trauma* 2009; 67:152-154.
163. Vallbohmer D, Holscher AH, Holscher M: Options in the management of esophageal perforation: Analysis over a 12-year period. *Dis Esophagus* 2010; 23:185-190.
164. Srinivasan R, et al: Role of flexible endoscopy in the evaluation of possible esophageal trauma after penetrating injuries. *Am J Gastroenterol* 2000; 95:1725.
165. Plott E, Jones D, McDermott D, Levoyer T: A state of the art review of esophageal trauma: Where do we stand? *Dis Esophagus* 2007; 20:279.

www.ketabpezeshki.com 66485457-66963820

Chapter 46

Abdominal Trauma

Michael A. Puskarich and John A. Marx

PERSPECTIVE

Background

The management of abdominal trauma should be approached in an organized, vigilant, and knowledgeable manner. Reliance on key clinical features and the timely use of diagnostic procedures tremendously alter morbidity and mortality. Advancements in imaging have helped to decrease missed or delayed diagnoses, yet they remain the most serious pitfalls in the management of abdominal injuries.[1]

Penetrating Abdominal Trauma

Whether by accident or intention, penetrating trauma can result from a wide variety of weapons or instruments, and certain elements of therapy vary accordingly. The management of patients with penetrating trauma has changed dramatically since 1960, when Shaftan introduced the concept of selective laparotomy and serial observations.[2] Before that time, surgery was mandatory. The careful integration of physical examination and certain diagnostic procedures, notably local wound exploration (LWE), ultrasonography, computed tomography (CT), laparoscopy, and in rare instances, diagnostic peritoneal lavage (DPL), now provides the emergency physician and trauma surgeon with an accurate means of determining whether laparotomy should be undertaken. The approach varies according to the clinical status of the patient, the instrument responsible for injury, and the site of penetration. Nonoperative management has gained favor predominantly for stab wounds, though also for carefully selected gunshot wounds (GSWs), with the intent to reduce the incidence of and morbidity from nontherapeutic laparotomies.[3,4]

Blunt Abdominal Trauma

Blunt trauma to the abdomen is a supreme challenge to the emergency specialist's clinical acumen. Historical data may be incomplete, absent, or presumptive. The symptoms and signs can be unreliable and obfuscated by head injury, alcohol, or other toxins. The likelihood of extra-abdominal systems trauma adds further complexity, underscoring the need for a carefully organized approach.

Epidemiology

Blunt injuries carry a greater risk of mortality than penetrating injuries because they are more difficult to diagnose and are commonly associated with severe trauma to multiple intraperitoneal organs and extra-abdominal systems.

Penetrating Abdominal Trauma

Wounds from stabbing implements occur nearly three times more often than wounds from firearms, but the latter have a significantly greater mortality rate and are responsible for 90% of penetrating trauma mortality.[5] The small intestine, colon, and liver are, successively, the most likely organs to sustain injury after penetrating trauma.[5] The highest risk of death from penetrating abdominal injury occurs among African Americans in the 15- to 34-year-old age range, followed by Hispanic persons in that same age group. The rate for non-Hispanic whites is greatest at 75 years of age and older. The predominant intent is homicide among African Americans and suicide among non-Hispanic whites.[6]

The use of firearms in the United States contributes heavily to the morbidity and mortality of trauma. The current U.S. civilian population is the most heavily armed in history. Over 42 million U.S. households have firearms, and there are more than 57 million gun owners.[7] The number of homicides committed with firearms exceeds the number of homicides resulting from all other forms of violence combined. More than 850,000 American civilians were killed by bullets in the 20th century, and mortality from GSWs accounts for 12 per 100,000 deaths in urban areas.[8]

Blunt Abdominal Trauma

The spleen is the organ most often injured, and in nearly two thirds of these cases it is the only damaged intraperitoneal structure. The liver is the second most commonly injured intra-abdominal organ, and the intestine is the most likely hollow viscus to be damaged.

The automobile is the major cause of blunt abdominal trauma (BAT). Motor vehicle collisions (MVCs) and auto-pedestrian crashes have been cited as causes in 50 to 75% of cases, blows to the abdomen in approximately 15% of cases, and falls in 6 to 9%.[9]

Pediatrics

Each year in this country, trauma results in approximately 22,000 deaths and accounts for $160 billion of health care expenditures for children to the age of 16 years. Nearly 13% of children admitted to pediatric trauma centers are proven to have abdominal injury, and this category follows only head, neck, and thoracic trauma as the cause of injury-related death.[10] Blunt mechanism causes approximately 85% of pediatric injury, although penetrating violence is becoming a greater concern. As is true with adults, MVCs are responsible for most of the morbidity and mortality in cases of trauma in children.[8] Auto-pedestrian accidents and falls out of cars cause a significant percentage of these injuries.

www.ketabpezeshki.com 66485457-66963820

Child abuse continues to gain attention, and deservedly so. It is both common and extremely harmful. Soft tissue, skeletal, and intracranial injuries are most likely, but abdominal injuries occur occasionally and are second only to head injuries as the cause of death. Children in the preverbal stage, generally those younger than 2 years of age, are at greatest risk. The history of trauma is extremely difficult to obtain because of the inability or fear of the child to communicate and the reluctance of parents to divulge information. Injuries inconsistent with the history provided or not in keeping with the child's level of physical maturity should alert the physician to the possibility of child abuse.

PRINCIPLES OF DISEASE

Anatomy and Physiology

The abdominal cavity and its contents can be reached not only through the anterior abdominal wall and lower chest but also through the flank, back, and buttocks. Missiles can also lodge intraperitoneally after traversing proximal extremities. The *anterior abdomen* is defined as that region between the anterior axillary lines from the anterior costal margins to the groin creases. The *low chest* begins at the nipple line or fourth intercostal space anteriorly and the inferior scapular tip or seventh intercostal space posteriorly, and then extends down to the inferior costal margins. The *flank* is between the anterior and posterior axillary lines bilaterally from the inferior scapular tip to the iliac crest. The *back* is between the posterior axillary lines, beginning at the inferior scapular tip and extending down to the iliac crest. The intraperitoneal cavity is vulnerable when penetration occurs as high as the fourth intercostal space anteriorly and the sixth or seventh laterally and posteriorly because the diaphragm can ascend to this level during expiration. Likewise, simultaneous thoracic abdominal penetration has been found in 20 to 40% of cases of abdominal thoracic trauma.[11] Scrutiny of entrance and exit sites, as well as wound tracts, is imperative.

Pathophysiology

Penetrating Abdominal Trauma

The instruments responsible for penetrating injuries of the abdomen are varied. Knives, handguns, rifles, and shotguns are at the fore, but certain impalement injuries caused by fences, stakes, or similar objects can be treated as stab wounds. Likewise, various propelled missiles from lawn mowers, chain saws, and other machinery or resulting from violent weather should be managed as GSWs.

Fragmentation injuries produced by grenades and bombs are rare in this country, but industrial explosions can produce similar injuries, which are best categorized as shotgun-type wounds. BAT from blast effect can coexist in this setting. With more widespread terrorism, an increased number of these injuries can be predicted.

The liver, followed by the small bowel, is the organ most often damaged by stab wounds, in keeping with the surface area each of these structures presents.[4] The frequency of organ injury caused by GSWs is greatest for small bowel, followed by the colon and then the liver.[5] Typically, multiple organ injuries are sustained, notably perforations to bowel. This same pattern is seen in the pediatric patient.

Stab Wounds. Knives are not the sole implements used in stabbings. Ice picks, pens, coat hangers, screwdrivers, and broken bottles, to name a few, have been used by assailants. Stab wounds of the abdomen occur most commonly in the upper quadrants, the left more commonly than the right. They are multiple in 20% of cases and involve the chest in up to 10% of cases. Most stab wounds do not cause an intraperitoneal injury, and the incidence varies with the direction of entry into the peritoneal cavity. Anterior stab wounds penetrate the peritoneum in approximately 70% of cases but inflict a visceral injury in only half of these.[4] Left lower chest wounds are associated with a 17% incidence of intraperitoneal damage in addition to the expected high rate of thoracic and diaphragmatic injuries. Right lower chest wounds have a much lower incidence of 0% to 4%.[12] Abdominal entries from the flank and back have reported incidences of up to 44% and 15%, respectively.[13,14] The organ injured cannot be well predicted by the site of entry in the abdominal wall. The liver and spleen are the viscera most commonly damaged in cases of back and flank wounds.

Gunshot Wounds—Ballistics. The science of ballistics is complex, but a few basic principles are helpful in understanding the pathophysiologic processes of these injuries. The magnitude of the injury is proportional to the amount of kinetic energy imparted by the bullet to the victim, according to the following equation:

$$E = \frac{7000mv^2}{2g}$$

where E is the kinetic energy (in foot-pounds), m is the mass of the bullet, v is the velocity of the bullet (in ft/s), and g is gravitational acceleration (in ft/s). In other words, the degree of injury depends on the mass of the bullet and the square of its velocity.[15] Additional factors that affect injury created by a missile include the resistance and viscoelastic properties of the tissue through which it passes, as well as the stability of the missile in this medium. Missile velocities are categorized as low (slower than 1100 ft/s), medium (1100-2000 ft/s), and high (faster than 2000-2500 ft/s); the impact velocity is the most important determinant of wounding capability. The impact velocity depends on the distance between the firearm and the victim, the muzzle velocity, and various characteristics of the missile. At medium and high velocities, the missile has an explosive effect and creates a temporary passage in the tissue along its course. The size of this passage is directly proportional to the specific gravity of the penetrated tissue. This sudden formation of a tract displaces nearby organs and vascular structures, and bone and viscera may be fractured or torn without being directly struck by the missile. Several cases of an intraperitoneal injury caused by a bullet that remained extraperitoneal throughout its entire course have been reported.[16] Solid viscera, such as the liver and spleen, are more vulnerable to this effect.

High-Velocity Missiles. Wounds from high-velocity missiles involve additional problems. First, external contaminants tend to be dragged into the wound. Second, the closure of the tract immediately after the bullet's passage may lead to an underestimation of tissue damage. Finally, high-velocity bullets can fragment internally. In fact, a missile at any velocity can fragment after contact with bone and cause additional multiple trajectories and injuries. Civilian wounds have usually resulted from low-velocity handguns, but unfortunately a trend toward more destructive weapons, such as the .38 and .357, may be occurring.

Shotgun Wounds. The shotgun was designed to strike a small, fast-moving target at close range. Because of the ballistic shape of the individual pellets, a rapid falloff in velocity occurs, making this weapon ineffective in producing severe wounds at long distances. An initial muzzle velocity of 1300 ft/s drops to 950 ft/s within 20 yards, a decrease of 25%. At close range (<15 yards), however, the shotgun is extremely lethal.

The kinetic energy imparted to the victim depends on the pellet's size, the number of striking pellets, the type and amount of powder, and the barrel choke (constriction). The most important variable is the distance between the shotgun and the victim. At a distance of 10 yards, 19% of the pellets cluster in a 9-inch diameter

www.ketabpezeshki.com 66485457-66963820

circle if fired from a full choke (maximum constriction) barrel. At a distance of 20 yards, the circle is approximately double that diameter. Because the kinetic energy is proportional to the square of the velocity, a 25% loss of velocity at 20 yards results in a significant decrease in the damage produced by the blast.

Shotgun wounds have been previously classified in three groups according to the range and pattern of distribution. More recently, classification has been according to the pattern of injury on the victim. Based on distance from the weapon to the victim, type I wounds involve a long range (>7 yards) and a penetration of subcutaneous tissue and deep fascia only. Type II wounds occur at a distance of 3 to 7 yards and may create a large number of perforated structures. Type III wounds occur at point-blank range (<3 yards) and involve a massive destruction of tissue. When categorized by pattern, type I wounds produce a spread greater than 25 cm in diameter; type II, 10 to 25 cm in diameter; and type III, less than 10 cm in diameter.[17] The tissue damage is proportional to the specific gravity and inversely proportional to the elastic properties of the affected organ. Thus the liver is more vulnerable than the lungs to this injury. Close-range shotgun wounds, in addition to the shot, force external contaminants (e.g., clothing and parts of the shell wadding) into the wounds. Type III wounds carry a substantial mortality risk.

Blunt Abdominal Trauma

Several pathophysiologic mechanisms have been described to occur in patients with BAT. First, sudden and pronounced rises in intra-abdominal pressures created by outward forces can cause rupture or burst injury of a hollow organ. Lap-belt–only restraints produce such a mechanism. Second, the compression of abdominal viscera between the applied force to the anterior wall and the posterior thoracic cage or vertebral column produces a crushing effect. Solid viscera are especially vulnerable to this injury, helping account for the high incidence of liver and spleen injuries in cases of BAT. Crush injuries are more likely to occur with the lax abdominal wall characteristic of elderly and alcoholic patients. Finally, acceleration and deceleration forces affecting both hollow and solid viscera cause organs and vascular pedicles to shear, especially at relatively fixed points of attachment.

Seatbelt Injuries. Unrestrained front and rear seat passengers are at unequivocally greater risk of intra-abdominal injury than their restrained counterparts.[18] The three-point shoulder-lap belt is the most effective restraining system and is associated with the lowest incidence of abdominal injuries, compared with older systems. However, abdominal injuries are still ascribed to combined shoulder-lap and lap-belt systems. The shoulder belt component can lead to right-sided and left-sided rib fractures for the driver and front seat passenger, respectively, with potential for injury to underlying abdominal viscera. Improper underarm usage of the shoulder belt increases compressive forces to the upper abdomen, particularly in the event of a front-end crash.

Injuries resulting from solitary lap belts are most often to the abdomen. This is true of nearly half the injuries caused by lap belts. The pathogenesis is usually the compression of bowel between the belt and the vertebral column. Occasionally, an acute, short, closed-loop obstruction occurs along with perforation secondary to the sudden generation of high intraluminal pressures. The resultant injury is primarily a contusion or perforation of the intestines or a tear of the mesentery.

Clinically, two symptom patterns emerge. Approximately one fourth of these patients develop evidence of a hemoperitoneum secondary to mesenteric lacerations. In the remainder, the intestinal injury most commonly involves the jejunum, and the initial signs and symptoms are often absent or considered insignificant. Subsequent delays in diagnosis of up to 8 weeks have rarely been reported. The "seatbelt sign," contusion or abrasion across the lower abdomen, is found in less than one third of patients with abdominal injuries caused by lap belts. Its presence, however, is highly correlated with intraperitoneal pathologic lesions.[19] Rupture of the diaphragm can also occur. Rare cases of acute abdominal aortic dissection with incomplete or complete occlusion have also been described, and injuries to the lumbar spine are not uncommon.[20]

Iatrogenic Injuries. Although well intentioned, diagnostic and therapeutic efforts in patient care are not risk-free. Abdominal injuries may be sequelae of various medical procedures and in certain instances not only are extremely difficult to recognize but may contribute to or cause pronounced morbidity or death. Numerous procedures may cause an iatrogenic injury.

Artificial ventilation can lead to gastric distention, particularly in children. Besides compromising ventilation and increasing the risk of vomiting and aspiration, a significant distention may lead to an esophageal or gastric laceration and perforation. These may occur with bag-mask ventilations, an inadvertent esophageal intubation with a nasotracheal or endotracheal tube, or the mistaken connection of the nasogastric tube to oxygen rather than suction. Esophageal, gastroesophageal junction, and gastric lacerations are evidenced by bloody emesis or nasogastric return. If a gastric perforation occurs and positive-pressure breathing is maintained, a tension pneumoperitoneum or abdominal compartment syndrome may ensue with inferior vena cava compression and decreased cardiac output. External cardiac compressions have produced splenic, hepatic, and gastric injuries. Manual thrusts to clear an airway obstruction, as taught in basic life support courses, and the Heimlich maneuver have caused rib fractures with lacerations and the rupture of abdominal viscera. In cases of a cardiac arrest, these injuries may be occult but life-threatening. If hypotension occurs after cardiopulmonary resuscitation, an abdominal injury and hemorrhage are considered along with cardiogenic shock.[21]

Tube thoracostomy has resulted in injury to the liver and spleen. These injuries may result from an unrecognized elevation of the diaphragm on the side of the thoracostomy or the placement of the tube too low in the chest, with resulting intra-abdominal penetration. Peritoneal lavage, paracentesis, and peritoneal dialysis have caused a series of complications, especially vascular penetration and bowel perforation. Signs of blood loss from a hemoperitoneum in the former case and peritonitis in the latter will evolve.

A liver biopsy can lead to a hemoperitoneum or hemobilia. Endoscopic procedures of the bowel may cause a hollow viscus perforation and peritonitis, particularly when a biopsy is performed, although they can result from rapid retraction of the endoscope without biopsy, as well.[22] Peritoneoscopy has been reported to cause small bowel perforations and iliac vessel lacerations. Barium enemas have an extremely low incidence of perforation but can be another cause of unexplained peritonitis and pneumoperitoneum.

Pediatrics. Congenital anomalies and intra-abdominal neoplasms may be first discovered after a history of blunt trauma. Coagulopathies (e.g., hemophilia) can contribute to the pathologic condition and complicate therapy after apparent minor trauma to the abdomen.

A child's abdomen has poorly developed musculature and a relatively smaller anteroposterior diameter. These factors increase the vulnerability of abdominal contents to compression between a blunt anterior force and the solid posterior vertebrae. The rib cage is extremely compliant in children and less prone to fractures but nonetheless provides only partial protection against splenic and hepatic injuries. Finally, the bladder is less protected by the pelvis in children, exposing it to greater risk of injury.

The liver, spleen, and kidney are the organs most commonly damaged by blunt mechanism of all varieties, and the incidence of injury for each of these three solid viscera is roughly the same. Gastrointestinal tract perforation is not uncommon with blunt

www.ketabpezeshki.com 66485457-66963820

trauma, and these injuries may be isolated. In cases of nonaccidental trauma, those injuries seen most commonly are duodenal and small bowel hematomas and perforations, pancreatic contusions, lacerations and pseudocysts, lacerations and rupture of the liver and spleen, and lacerations of mesenteric vessels.

CLINICAL FEATURES

History

The patient's history may be unobtainable, elusive, or temporarily deferred while resuscitative measures are carried out. When the situation permits and a reliable source is available, certain information is valuable.

The patient's ability to relate the course of events may be compromised by head or spinal cord injury, alcohol intoxication, developmental delay, psychiatric illness, and any number of toxins. At times, the trauma may have preceded the onset of symptoms by days or weeks and may have been forgotten or considered trivial by the patient. Witnesses at the scene, particularly paramedical personnel, often provide the most reliable data.

Knowledge of substance exposure or events that could interfere with the clinical evaluation of the patient is helpful. Alcohol or drug use, a head or spinal cord injury, and psychiatric problems are the most common among these factors. Appreciation of comorbid medical conditions, particularly cardiovascular disease and coagulopathies, optimizes fluid and blood component therapy. Finally, when a prehospital care team or transferring hospital is involved, the vital signs, physical assessment, prehospital course, and response to therapy should be obtained. Clinical records and laboratory and radiologic studies obtained at an outlying hospital should be carefully reviewed. The symptomatology in cases of abdominal trauma is twofold. Volume loss may produce orthostatic or frank dizziness, light-headedness, and confusion. A hematic, infectious, acidic, or enzymatic irritation of the peritoneum produces pain. The pain may be clearly present at the outset or delayed for hours to days.

The patient's communication may be dulled or ineffectual, or the subjective sensation of pain may be impaired by a spinal cord injury or an underlying medical problem such as diabetes. Occasionally, intense, competing pain at another body site dominates and distracts both the patient and physician away from the abdomen. Abdominal pain can be localized, as it sometimes is in the left upper quadrant with a splenic injury, or diffuse, as in septic peritonitis subsequent to bowel perforation. Referred pain to the right and left shoulder tips or neck can occur with hemoperitoneum, particularly when the patient has been in the Trendelenburg position, allowing the blood to irritate the diaphragm; this most often occurs with hepatic and splenic injuries. Pain referred to the testicle is compatible with a retroperitoneal injury and is seen most commonly with urogenital and duodenal trauma.

Nausea and vomiting can accompany peritoneal irritation or hypovolemia. These can also be caused by an obstruction, as can occur with a duodenal hematoma. Dyspnea sometimes occurs with gastric distention or diaphragmatic irritation or when abdominal contents herniate into the chest, impairing respiratory dynamics.

Penetrating Abdominal Trauma

Stab Wounds. It is helpful to obtain information regarding the mode of injury from the patient, paramedic, or witnesses. The number of stabs inflicted, type and size of the instrument, posture of the victim relative to the direction of assault, estimated blood loss at the scene, time of injury, and response to fluids should be sought. However, a significant proportion of victims of stab wounds are found under the influence of alcohol or another drug. This state can make obtaining an accurate history a futile effort and further compromises the validity of symptoms and signs.

Gunshot Wounds. As initial stabilization measures are instituted in the emergency department, the emergency physician can elicit certain facts that can contribute greatly to the evaluation of the patient. These include the weapon used, its distance from the victim when shot, the position of the victim in relationship to the weapon when fired, the suspected number of shots, the blood loss at the scene, the amount and type of field fluids administered, and the vital signs during the prehospital course.

Blunt Abdominal Trauma

With blunt injuries, specifically those resulting from vehicular trauma, inquiries should be made regarding the extent of damage to the car; the patient's location within the car; whether the patient struck the steering wheel; whether seat belts were used and, if so, what type; and whether front or side air bags were deployed. The magnitude of injury to pedestrians varies with the speed and size of the striking vehicle. A triad of injuries to the torso, cranium, and lower aspect of the lower extremity has been well described, and pathologic lesions discovered in two of these sites should prompt careful attention to the third. Motorcycle crashes can be placed in one of four categories: frontal, lateral or angular, ejection, or "laying the bike down." Different pathologic lesions can be projected based on the offending mechanism.

Pediatrics

Assessment and management of abdominal injuries in children are based on the same principles as in adults. The symptoms and signs are similar and in alert, cooperative patients are valuable. Age-related difficulties in communication, fear-induced uncooperative behavior, or a concomitant head injury, however, make the clinical examination less reliable. In cases of unexplained abdominal tenderness or peritonitis, it is important to inquire about vaginal bleeding or discharge and rectal bleeding and to examine the rectum and vagina for foreign bodies. Such objects may be inserted by inquisitive children or by adults during acts of child molestation.

Physical Examination

Abdominal trauma provokes a wide spectrum of presentations that range from seemingly insignificant symptoms and signs to severe shock and coma. Evidence of abdominal tenderness, peritoneal irritation, gastrointestinal hemorrhage, and hypovolemia not attributable to extra-abdominal causes represents most of the signs suggestive of an intraperitoneal injury. These signs may be initially absent or obscure but may emerge during serial examinations.

The physical examination of a hemodynamically unstable patient is performed coincident with therapy, but care and thoroughness are not precluded by these circumstances. When an obvious intracranial, thoracic, or orthopedic injury is present, abdominal symptoms or findings may be obscured, and abdominal injury should be considered. Chest trauma itself is a risk factor for coincident intraperitoneal pathology. This is particularly true in cases of suspected multiple blunt trauma accompanied by a head injury, coma, or obtunded mental status resulting from drugs or alcohol.

The abdomen, then, should neither be ignored nor be the sole focus of the evaluation. All of the patient's clothing should be removed, and a careful inspection of the patient's body should be conducted, to include the scalp, perineum, skin folds, and beneath the hair. Wounds from penetrating trauma can be exceptionally small, difficult to find, and yet lethal.

www.ketabpezeshki.com 66485457-66963820

Hypotension in the acute stage results from hemorrhage that is most often from a solid visceral or vascular injury. Traumatic pancreatitis may produce significant third-space fluid loss, but hours to days are usually required for this to appear, and shock is an uncommon presentation.[23] When hypotension accompanies significant multiple blunt trauma and is unexplained, one should assume the presence of intraperitoneal hemorrhage until it is excluded. However, a known extra-abdominal source of hemorrhage does not mitigate the need to evaluate the peritoneal cavity. A head injury alone does not explain shock except in cases of profound head injury or in the very small infant, in whom traumatic intracranial or extracranial (e.g., cephalohematoma) blood loss may be proportionally substantial.[24]

In cases of penetrating trauma, inspecting the abdomen for entrance and exit wounds may help determine the path of injury. Distention can occur as a result of pneumoperitoneum, gastric dilation, or ileus produced by peritoneal irritation. An ecchymotic discoloration of the flanks (Gray-Turner sign) or umbilicus (Cullen's sign) indicates retroperitoneal hemorrhage, but these signs are usually delayed for 12 hours to several days. Abdominal contusions can result from various implements, and when caused by lap-seat belts, they herald abdominal injuries in one third of cases.

Markedly decreased or absent bowel sounds have traditionally been considered one of the more reliable clinical parameters of intraperitoneal injuries. However, the presence of audible peristalsis, although uncommon, does not rule out ileus or serious injury. In such instances, coexisting electrolyte disturbances or thoracolumbar vertebral body or transverse process fractures may be responsible for the ileus.

Palpation elicits local or generalized tenderness in approximately 90% of alert patients with an intra-abdominal visceral injury. Local and generalized rebound tenderness and rigidity can be signs of peritoneal irritation and occur less commonly. These signs lack specificity, however, and can be found with lower rib fractures and contusions of the thoracoabdominal wall. These findings or, more important, their absence, are more reliable in alert patients. However, false-positive and false-negative abdominal manifestations have been well demonstrated even in conscious, responsive patients.[25,26]

Rarely, encapsulated bleeding into regions walled off by blood clots or adhesions can form palpable intra-abdominal masses; these usually appear at least several hours later. Severe contusions of the abdominal wall can cause tenderness and voluntary guarding that is localized and usually exacerbated by use of the affected muscle. A palpated mass can represent a rectus hematoma or ventral hernia.

A rectal examination rarely reveals blood or subcutaneous emphysema, but the presence of either is highly correlated with abdominal injuries. The rectal examination is now considered less helpful than clinical indicators such as blood at the meatus or scrotal hematoma in urethral injuries, or evidence of paralysis. The rectal examination can be eliminated or deferred in many patients, as the clinical indicators noted earlier appear to be more sensitive than the rectal examination.[27-29] Notable exceptions may include suspected cauda equina syndrome or penetrating trauma to the perirectal area.

In patients who are intubated, who have a distended abdomen, or in whom there is a high concern for stomach or duodenal injury, a nasogastric tube should be placed in the absence of severe maxillofacial trauma to decompress the abdomen, decrease the likelihood of aspiration, and determine whether blood is present. Caution is advised with placement of nasogastric tubes when a cribriform plate fracture or unstable midface fractures are suspected, as rare cases of intracranial insertion have been reported. Foley catheters are useful in unstable patients for following renal output and rapidly obtaining urine samples to search for blood, myoglobin, and toxins.

Thus a number of signs are valuable in assessing the patient with abdominal trauma. Although the presence of physical findings makes intraperitoneal injury more likely, their absence does not preclude serious pathology, and none is exclusively diagnostic of a specific injury. Extensive observation and the use of certain laboratory procedures greatly help prevent erroneous or missed diagnoses.

Penetrating Abdominal Trauma

Stab Wounds. Serial physical examinations performed by the same observer are gaining acceptance in certain centers where these have been found useful, particularly with patients who are alert, communicative, and neurologically intact. The presence of intoxicants does not necessarily preclude reliance on examination but may undermine its value.[30] In other series, patients with impressive physical findings after penetrating trauma to the abdomen have undergone exploratory laparotomy, with negative results in 14 to 28% of cases.[31] Moreover, up to one third of patients with significant intra-abdominal injuries have no suggestive physical signs, particularly when a retroperitoneal injury has occurred.[32] Therefore serial clinical evaluations typically involve physical examinations to include trending of vital signs, laboratory testing including serial hemoglobin measurement, and repeated focused assessment with sonography in trauma (FAST) examinations.

Gunshot Wounds. As with blunt or other modes of penetrating trauma, there is dispute regarding the value of the physical examination of patients with abdominal GSWs. In various series, 20% of patients with a documented intraperitoneal injury had no peritoneal signs before exploration.[32] Moreover, objective physical findings suggestive of intra-abdominal damage have been misleading and falsely positive in 15% of patients in whom laparotomy revealed no injury. Other authors contend that selective management can be undertaken safely when physical examination is the fundamental evaluative measure.[30]

Blunt Abdominal Trauma

Overall, the accuracy of the physical examination in patients with BAT is 55 to 65%.[25] The initial presentation may be exceptionally benign in cases of blunt intra-abdominal injury. The most reliable symptoms and signs in alert patients are pain, tenderness, and peritoneal findings, particularly when risk factors for abdominal injury are present. When altered sensorium intercedes, the physical signs become less reliable. Frequent evaluations by the same examiner are indicated even in alert patients, but especially in sensorium-altered patients, particularly as their mental status and sensorium normalize.

DIAGNOSTIC STRATEGIES

Laboratory

Hematologic and chemical values are of limited use in the management of the acutely traumatized patient.[33] They should be considered adjuncts to diagnosis and not substitutes for clinical assessment.

Hematology

Hematocrit. The hematocrit reflects baseline value, extent of and time from hemorrhage, exogenous fluid administration, and endogenous plasma refill. The last of these is a physiologic compensatory shift of extracellular fluid into the intravascular space, the intent of which is to restore the original blood volume. Based

www.ketabpezeshki.com 66485457-66963820

on a study of volunteers sustaining a 10 to 20% blood loss, this restoration proceeds at a rate of only 40 to 90 mL/hr for the first 10 hours and requires 30 to 40 hours for completion.[34] However, patients evidencing hemorrhagic shock with a blood loss of at least 40% demonstrate much faster plasma refill rates, estimated as high as 1500 mL in the first 90 minutes after injury, with significant decreases in hematocrit within this period. Although the hematocrit is an easily acquired measure, it is often a conundrum when viewed in isolation, and serial determinations are more helpful.

White Blood Cell Count. The white blood cell (WBC) count has little discriminatory value in cases of abdominal trauma, particularly its acute phase.[33] The WBC count may be normal or may show a modest leukocytosis (12,000 to 20,000/mm^3 with or without left shift), which can occur in the setting of multisystem trauma as a result of stress-induced demargination in the absence of any intra-abdominal process, or as a result of tissue injury, acute hemorrhage, or peritoneal irritation.

Chemical

Pancreatic Enzymes. Neither serum amylase nor lipase is useful in the evaluation of acute abdominal trauma. Normal levels do not exclude a major pancreatic injury, and elevated values may be caused by any of an assortment of reasons in addition to an injured pancreas. The use of serum amylase isoenzymes has not appreciably improved accuracy. Nontraumatic causes of hyperamylasemia include several diseases and the use of alcohol, opioids, and various other drugs. Amylase or lipase may also be elevated with pancreatic ischemia produced by the systemic hypotension that often accompanies trauma. Clearly, these enzymes are neither highly specific nor sensitive for pancreatic injuries. Elevated or rising levels may indicate damage but in themselves are not conclusive.[35] In these cases, clinical correlation and further investigation are indicated.

Base Deficit. Metabolic acidosis in the setting of trauma can suggest the presence of hemorrhagic shock. This can be witnessed chemically as a decreased serum bicarbonate level, increased base deficit, or elevated serum lactate level. Although normal values do not exclude abdominal injury, substantive abnormalities, such as a base deficit greater than or equal to 6, may be predictive. These findings should be considered in clinical context, because the resolution of the laboratory findings will lag behind the clinical improvement of the patient.

Liver Function Tests. Elevated serum transaminases can result from hepatic trauma but do not distinguish minor contusions from severe injury.[36] Alternatively, these may be symptomatic of alcohol-induced liver damage. Elevated liver transaminase levels may be useful for screening pediatric patients for intentional trauma (see Chapter 38). They may also play a role in pediatric patients in combination with a FAST examination as a screening tool to decrease the use of CT scanning, although serial physical examination is still required.[37]

Toxicology Analysis. Screens for ethanol and drugs are often used in trauma centers. Their utility in the management of abdominal trauma, per se, has not been established, particularly in patients with normal mental status.[38] Positive study findings may prompt the emergency physician to interdict and the patient to decrease the recidivistic use of ethanol or drugs, and physician intervention during this "teaching moment" has been shown to be effective.

Radiology

Resuscitation and initial stabilization measures precede abdominal radiographic studies. Basic plain radiography in the trauma bay is of limited value, although a chest x-ray examination to screen for significant hemothorax or pneumothorax before the patient is transferred to the CT scanner facilitates early stabilization of these injuries. Hemodynamically stable patients who will undergo abdominopelvic CT can forego pelvic radiographs in the trauma bay. Any potential cervical or lower spinal injury is presumed present based on the mechanism of the trauma, the patient's symptoms, and physical examination findings. A portable cross-table radiograph in the trauma bay is insufficient to exclude any such injury. In the hemodynamically stable patient, depending on physical findings and whether the patient is able to convey pain, pelvic radiographs may be deferred to the radiology suite or omitted entirely (see later). In patients whose symptoms and signs demonstrate a likely need for exploratory laparotomy, delay in operation because of radiologic diagnostics is permissible only when the patient has been stabilized and only if studies might aid in determining management. Adequate radiographic detail cannot be achieved in an uncooperative patient. Trained personnel should accompany any patient who has potential to deteriorate precipitously. Moving the patient from the relative security of the trauma resuscitation room to the radiology suite creates increased risk for the patient because of the relative decrement in monitoring and personnel in attendance.

Plain Radiographs

The chest radiograph and anteroposterior pelvic films can be invaluable in some cases of penetrating and blunt trauma, depending on the presentation and results of initial evaluation. Plain abdominal films can demonstrate the location or track of the missile(s) in gunshot and shotgun injury but are of little value in blunt trauma or nonprojectile penetrating trauma, particularly if CT imaging of the abdomen is anticipated. If plain radiography of the abdomen is done, the finding of rib, pelvic, vertebral body, or transverse spinous process fractures in the blunt trauma patient warrants special consideration for nearby visceral damage.

Very small quantities of readily detectable free intraperitoneal air are present in most patients with gastric, duodenal bulb, and colonic perforations but in fewer than one fourth of those with jejunal and ileal perforation. These are seen more readily on CT than plain films. Free intraperitoneal air uncommonly can be generated by mediastinal or pulmonary injury, as well as by barotrauma, and thus its presence is not pathognomonic of hollow viscus perforation. Intraperitoneal air is mobile, and to maximize visualization the patient should be kept in the appropriate upright or decubitus position for 10 to 15 minutes, if this is tolerable, before upright chest or decubitus abdominal radiographs are obtained. In upright films, air is located under the diaphragm or the central tendon of the diaphragm anteriorly. In supine films, air tracks under peritoneal attachments, such as the falciform ligament and urachus, up to the anterior abdominal wall. On films in which the patient is in a lateral decubitus position, air is located in the superior flank and outlines the lateral liver edge (Fig. 46-1). In cases of gastric perforations, air may be limited to the lesser sac. A rupture of a retroperitoneal hollow viscus can be detected by a stippling pattern outlining the duodenum, kidney, or psoas muscle (Fig. 46-2). Extraperitoneal colonic perforations may extravasate air, which outlines the psoas muscle and perinephric region. All of these injuries are much more readily identified and localized on abdominal CT.

Foreign bodies and missiles are easily identified on abdominal films. Therefore their absence without a known exit wound warrants further search of other body cavities (e.g., the chest, upper thighs, buttocks). A ricochet off the spine or pelvis into the chest or proximal extremities can occur. An entry into the vascular system may carry the object toward and into the right side of the heart or peripherally into the arterial tree. It may also find its way into the gastrointestinal tract and either produce obstruction or pass through unnoticed.

www.ketabpezeshki.com 66485457-66963820

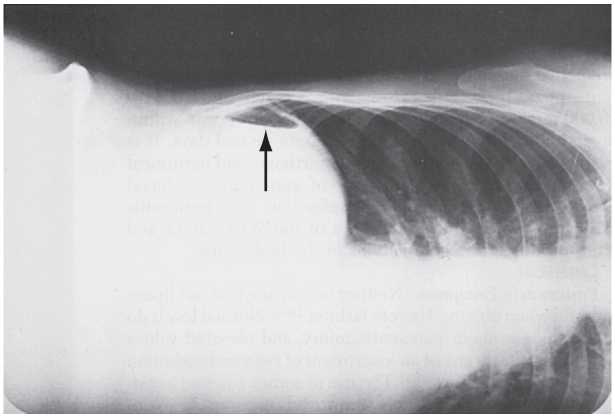


Figure 46-1. Demonstration of free intraperitoneal air on left lateral decubitus film (*arrow*). This is the preferred decubitus position because it avoids confusion with the gastric bubble and splenic flexure.

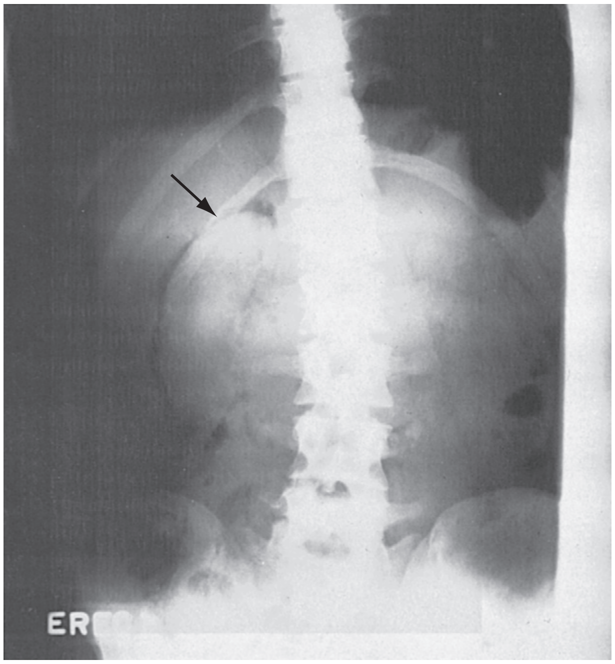


Figure 46-2. Erect film demonstrates the soap bubble appearance of retroperitoneal air outlining the right kidney (*arrow*). Duodenal perforation is the responsible pathologic condition.

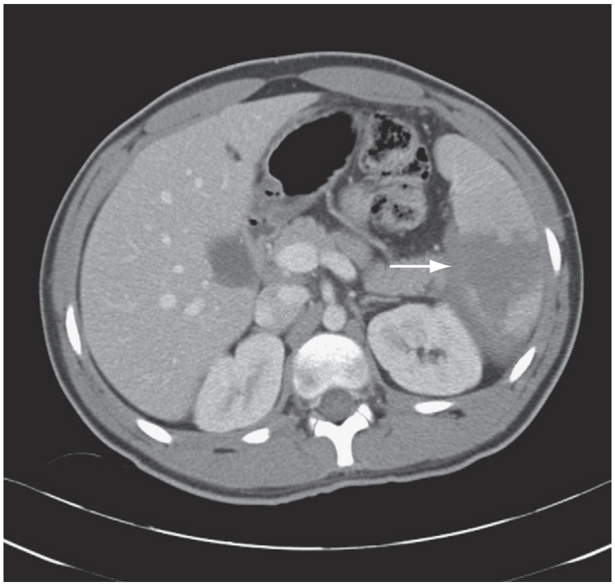


Figure 46-3. Grade 4 splenic laceration.

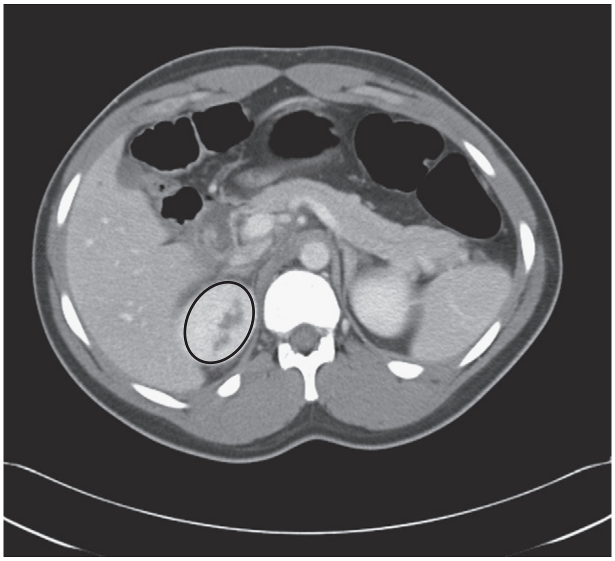


Figure 46-4. Grade 3 right renal laceration (encircled).

Computed Tomography

Over the last 35 years, CT scanning has continued to advance its place among diagnostics for trauma. Evolution to higher multislice helical and spiral scanners has improved resolution and greatly decreased the time required for the scan itself.[39]

Advantages. In most situations, CT scanning has supplanted DPL because of its higher predictive ability for operative lesions and because it is noninvasive. CT scanning can define the injured organ and the extent of the injury. It is most accurate for solid visceral lesions and accurately discerns the presence, source, and approximate quantity of intraperitoneal hemorrhage (Fig. 46-3). It can demonstrate active bleeding from the liver or spleen and can be used to determine whether therapeutic angiographic embolization is indicated.[40] CT scanning also evaluates the retroperitoneum (Fig. 46-4), an area not sampled by DPL, as well as the vertebral column, and can be readily extended above or below the abdomen to visualize the thorax or pelvis.[41] CT scanning also provides definitive evaluation for most possible injuries to the urinary tract, including renal artery injury.[42] It can also detect other vascular hemorrhage and obviate the need for angiography in some patients.[43] CT scanning is particularly helpful in guiding nonoperative management of solid organ damage.[44,45] This includes as-needed follow-up studies of convalescing patients with these injuries. It has also proven effective when incorporated in delayed fashion for patients with decreasing hematocrit, increasing base deficit, or subtle examination changes. By minimizing the incidence of nontherapeutic laparotomies for self-limited injury to the liver or spleen, it decreases morbidity and cost attendant to this operation.[46] Increasingly, trauma centers are using CT with intravenous contrast only, as it has been shown that little additional information is provided by the addition of oral contrast, which delays scanning and may pose an aspiration risk for the patient.[47,48]

Disadvantages. Disadvantages of CT scanning include relative insensitivity for injury of the pancreas, diaphragm, small bowel,

www.ketabpezeshki.com 66485457-66963820

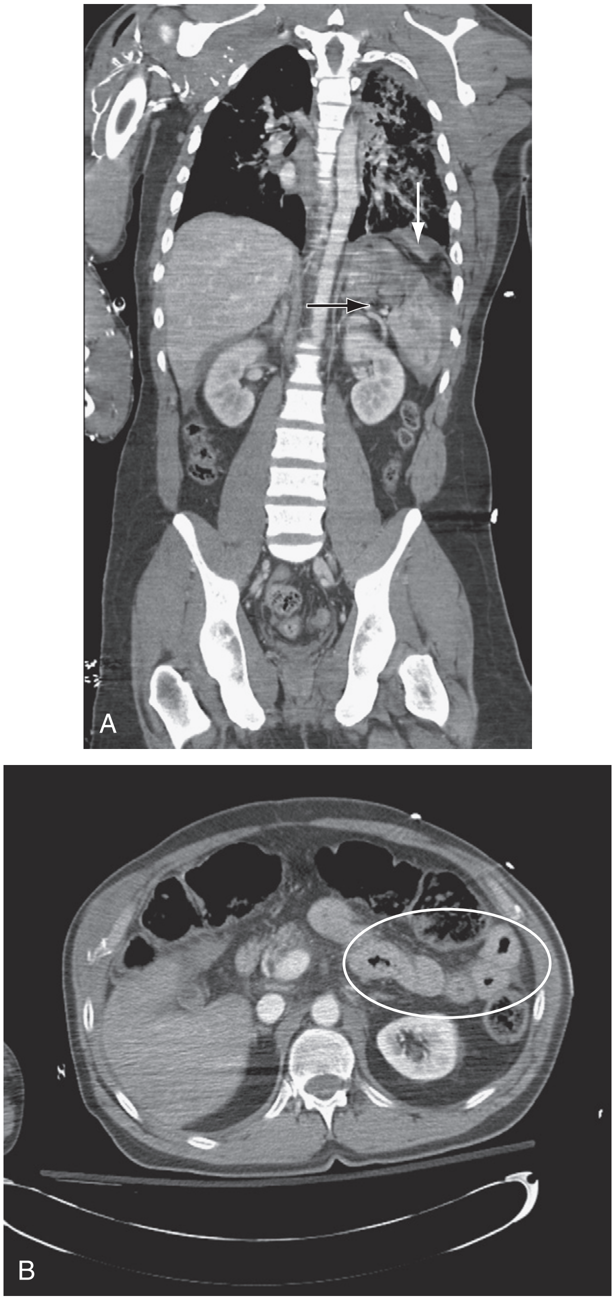


Figure 46-5. **A**, Grade 4 splenic laceration *(black arrow)* with diaphragmatic rupture *(white arrow)*. **B**, Small bowel edema concerning for hollow viscus injury *(encircled)*.

and mesentery, although detection of these injuries is improving[47,48] (Fig. 46-5). The last two are particularly worrisome because isolated coincidental hollow viscus injury in patients with blunt trauma, although uncommon, is not rare, and increased morbidity and death can ensue if diagnosis is missed or the condition goes undetected for a prolonged period. Findings on CT scans, including the suspected quantity of hemoperitoneum or the presence of isolated free fluid, are not able to forecast well the need for operative intervention.[49] Complications can result from intravenous contrast administration or uncommonly from contrast material administered orally. Moreover, oral contrast delivery to opacify bowel is infrequently useful and typically omitted.[47,50] Finally, patients must be temporarily removed from the resuscitation area for the study to be accomplished, which can put the patient at risk in the case of rapid clinical deterioration. However,

Table 46-1 Preferred Site of Diagnostic Peritoneal Lavage

CLINICAL CIRCUMSTANCE	SITE	METHOD
Standard adult	Infraumbilical midline	C or SO
Standard pediatric	Infraumbilical midline	C or SO
Second- and third-trimester pregnancy	Suprauterine	FO
Midline scarring	Left lower quadrant	FO
Pelvic fracture	Supraumbilical	FO
Penetrating trauma	Infraumbilical midline*	C or SO

Adapted from Runyon, M, Marx JA: Peritoneal procedures. In Roberts JR, Hedges JR (eds): Clinical Procedures in Emergency Medicine, 5th ed. Philadelphia, WB Saunders, 2009.
C, closed (percutaneous Seldinger technique); *FO,* fully open; *SO,* semiopen.
*The stab wound or gunshot wound site should be avoided.

CT scanning remains the cornerstone of diagnosis. In cases with equivocal CT scan results, such as more than physiologic fluid, or a worrisome history and physical examination findings, serial examinations or further diagnostic testing should be strongly considered, including DPL, particularly to evaluate for missed hollow viscus injury (Table 46-1).

Radiation Risk. Increasingly, there is concern regarding the negative long-term effects from exposure to ionizing radiation resulting from medical imaging. Over 62 million CT scans are performed per year in the United States, including over 4 million in children,[51] and the number of scans performed per patient after trauma is increasing.[52] Based on data from survivors of the atomic bombs dropped on Japan and average radiation exposure from various types of CT scans, it has been estimated that 0.4% of all cancers in the United States have been caused by exposure to medical radiation, and that number may be increasing to 1 to 2%. Children are especially at risk, and even a single CT scan may increase the lifetime risk of cancer.[51] Although direct evidence of increased cancer risk from CT scans has not yet been demonstrated, several methods are becoming available to reduce radiation exposure. Some groups have attempted to define decision rules to help avoid unnecessary CT scans in very low-risk patients, though their role in clinical practice has yet to be defined.[37,53,54] For very low-risk, hemodynamically stable patients, special consideration should be given to patients with large numbers of negative CT scans in the past, and observation may be preferable to repeat radiation exposure. Adjustment of scanning techniques for children and body habitus on an institutional level through use of "as low as reasonably achievable" (ALARA) principles, developed in conjunction with the department of radiology, can decrease excessive radiation exposure if CT scanning is clinically indicated. If a patient is to be transferred to another facility, attempts should be made to convey hard copy or digital images to the accepting facility, as CT scans are not infrequently repeated at the receiving hospital.[55] These repeat CT scans are unlikely to change management without a concurrent change in clinical picture.[56] A balance between minimizing radiation exposure and simultaneously minimizing the number of missed injuries is a challenge for the emergency physician evaluating a patient with abdominal trauma.

Technique. The technique for CT scanning is reasonably standardized, but certain conventions are debated. The studies should begin in the low chest and be taken through the pelvis. If chest scanning is also required, a single continuous scan is obtained from the root of the neck to the floor of the pelvis. "Quick look" but less thorough studies are problematic and should be avoided; preliminary reads from the CT control room do not have the added accuracy of reconstituted scans and may therefore miss subtle injuries, such as intimal tears of the thoracic aorta. Most

www.ketabpezeshki.com 66485457-66963820

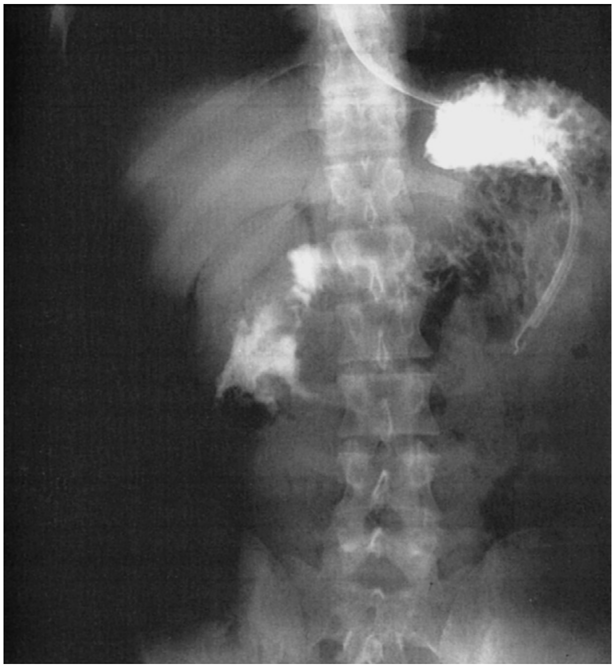


Figure 46-6. Gastrografin study demonstrating rupture of the second portion of the duodenum with extravasation of contrast material.

centers perform enhanced (intravenous contrast) and nonenhanced scans because the latter alone may not demonstrate intraparenchymal hematomas well. Other practitioners believe that the noncontrast portion contributes little other than time to the procedure. In patients who undergo chest and abdominopelvic CTs, reconstituted images can be obtained of the thoracolumbar spine, sparing the need for additional studies and associated ionizing radiation. Except in certain unusual circumstances, single scans through the areas of interest with intravenous contrast only are recommended.

Contrast Studies

Contrast studies with a water-soluble medium (e.g., Gastrografin) can be helpful in cases of suspected gastric, duodenal, and rectal perforations (Fig. 46-6). Barium mixtures should be used to visualize intramural duodenal hematomas.[57] However, a CT scan should be able to discern duodenal hematomas and can distinguish these from perforations.[58]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is usually impractical and sometimes impossible to perform in the acute phase of multiple blunt trauma. Currently, in acutely injured trauma patients, MRI should be reserved for the evaluation of spinal cord injuries and elusive diaphragmatic defects.

Therapeutic Angioembolization

Therapeutic angiography, a time-consuming procedure, is usually reserved for the unstable patient with blunt trauma and pelvic fracture in whom it can be used to embolize bleeding vessels (Fig. 46-7). It can also be a means of staunching solid visceral hemorrhage from blunt trauma, notably of the spleen.[40] Nonoperative management has become standard in management of splenic injuries but is associated with increasing failure rates with increasing grades of injury, up to 44% with the highest-grade injuries. Successful nonoperative management has been demonstrated to

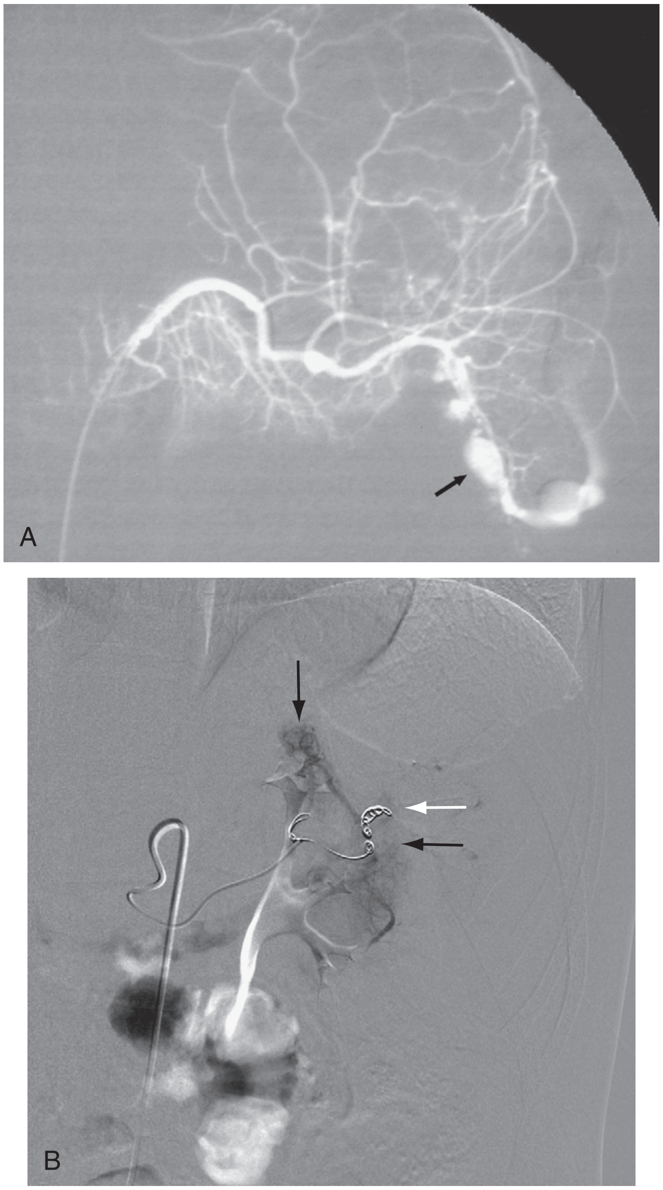


Figure 46-7. A, Angiography of splenic laceration. Note the blush representing active hemorrhage *(black arrow)*. B, Angioembolization of renal laceration. Note coil in the splenic artery *(white arrow)* and blush representing active hemorrhage stemming from two branches *(black arrows)*. (A from Mauro MA: Image Guided Interventions. Philadelphia, Elsevier Health Sciences, 835, 2008.)

increase significantly with the use of angioembolization therapy,[59] though higher-grade injuries are still more likely to fail nonoperative management than lower-grade injuries.[60] Angioembolization also may have the added benefit over splenectomy of preserved splenic immunity in many cases, though further data are needed on the topic.[59] The angioembolization catheter should be inserted as close as possible to the hemorrhaging lesion to minimize infarction of viable tissue. Finally, angioembolization also has been used rarely for intraperitoneal and retroperitoneal hemorrhage after trauma by a penetrating mechanism.

Bedside Procedures

Ultrasonography

Ultrasonography's primary role is detecting free intraperitoneal blood after blunt trauma. This is accomplished by a FAST

www.ketabpezeshki.com 66485457-66963820

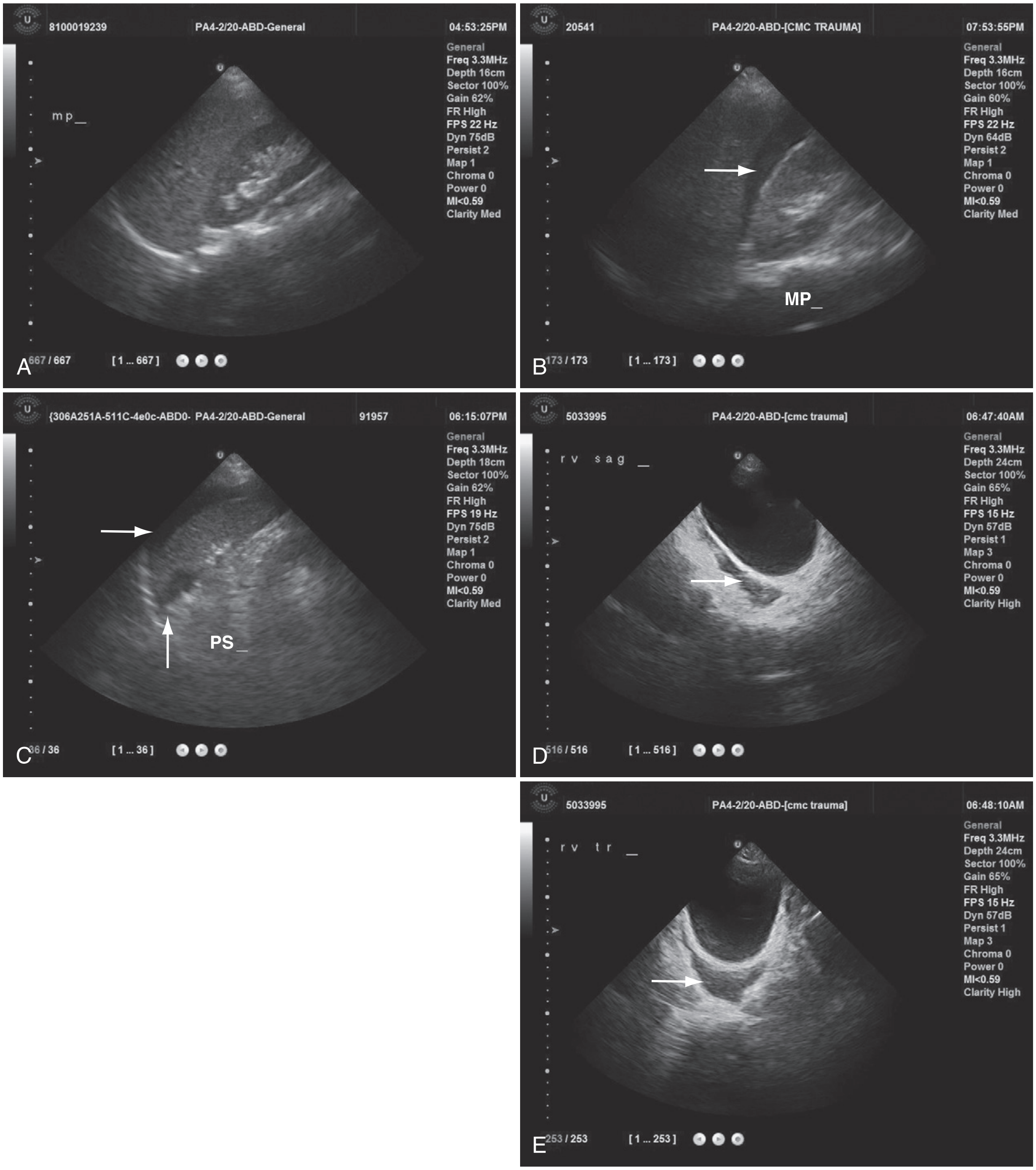


Figure 46-8. **A,** Normal Morrison's pouch view. Note absence of an anechoic stripe, which would represent a fluid collection between the liver and kidney. **B,** Positive Morrison's pouch view. Note presence of an anechoic stripe representing a fluid collection between the liver and kidney *(solid arrow).* **C,** Positive perisplenic view. Note anechoic fluid around spleen *(solid arrows).* **D,** Positive fluid in the sagittal retrovesicular view *(arrow).* Note anechoic stripe indicative of retroperitoneal fluid. **E,** Positive transverse retrovesicular view. Note anechoic area indicative of retroperitoneal fluid *(arrow).*

ultrasound examination of Morrison's pouch, the splenorenal recess, and the pouch of Douglas, which are dependent portions of the intraperitoneal cavity where blood is likely to accumulate (Fig. 46-8). Anechoic areas caused by the presence of blood are best visualized when contrasted against solid organs (e.g., liver, spleen, and kidneys). With penetrating mechanisms, an extended FAST (E-FAST) ultrasound adding visualization of the pleura and pericardial and intraperitoneal spaces can also detect pneumothorax, hemothorax, and pericardial tamponade.[61]

Advantages. Ultrasonography carries a host of advantages. It is a portable instrument that can be brought to the bedside in the trauma resuscitation area. Studies of the pericardial, intraperitoneal, and thoracic spaces can be accomplished in less than 5 minutes. FAST ultrasound has a sensitivity in detecting as little as 100 mL and, more typically, 500 mL of intraperitoneal fluid that ranges from 60 to 95% in most recent studies, and specificity for hemoperitoneum is excellent.[62] Therefore when time is precious in the patient in critical condition, the FAST can provide a rapid answer to the key question in the decision matrix, which is whether hemoperitoneum is present. Unlike DPL, the FAST can evaluate intrathoracic structures, is noninvasive, and can be performed serially and by multiple technicians. Unlike CT scanning,

www.ketabpezeshki.com 66485457-66963820

it is not a potential radiation hazard and does not require administration of contrast agents. Accuracy correlates with length of training and experience, but expertise can be readily achieved in emergency medicine and surgical training programs.[63] Serially performed FAST increases its diagnostic accuracy for organ injury in patients with BAT.[64,65] Furthermore, E-FAST adds thoracic windows to detect the presence of pneumothorax in patients who have sustained penetrating abdominal trauma (PAT) or BAT. These additional views detect pneumothorax with a sensitivity of almost 60% and a specificity of up to 99% when compared with CT, but more important, the E-FAST is three times as sensitive as a portable supine chest x-ray examination done in the trauma bay, which has a sensitivity of only 20%.[66] Overall, ultrasonography can serve as an accurate, rapid, and less expensive diagnostic screening tool than DPL or CT.[67-69]

Disadvantages. The FAST study does not image solid parenchymal damage, the retroperitoneum, or diaphragmatic defects well. It is technically compromised by the uncooperative, agitated patient, as well as by obesity, substantial bowel gas, and subcutaneous air. Indeterminate studies require follow-up attempts or alternative diagnostic tests.[65] It is less sensitive and more operator dependent than DPL in revealing hemoperitoneum and cannot distinguish blood from ascites or uroperitoneum. For unclear reasons, ultrasound has a high (31%) false-negative rate in detecting hemoperitoneum in the presence of pelvic fracture.[70] The FAST study, like DPL, will not detect the presence of solid parenchymal damage if free intraperitoneal blood is absent, as in subcapsular splenic injury.[70,71] Finally, ultrasonography is poor at recognizing bowel injury in which hemorrhage tends to be inconsequential, and failure to diagnose hollow viscus perforation in a timely manner can have catastrophic results.[72] Because of these limitations, reliance on a single negative FAST examination performed within minutes of the injury is ill-advised. Serial FAST examinations may help to determine progressive hemorrhage, however.

Diagnostic Peritoneal Lavage

Although largely supplanted by the FAST examination and CT scanning, DPL (and more commonly aspiration) still has a role in certain cases. DPL comprises two interrelated steps. The first is the attempted aspiration of free peritoneal blood. The recovery of 10 or more mL of frank blood from the peritoneum is a strong predictor of intraperitoneal injury, and the procedure is then terminated. If aspiration findings are negative, lavage is conducted in which the peritoneal cavity is washed with saline. This fluid is introduced by catheter, recovered by gravity drainage, and analyzed. The sole absolute contraindication to DPL is the established need for laparotomy. Relative contraindications include prior abdominal surgery or infections, coagulopathy, obesity, and second- or third-trimester pregnancy.

Advantages. In cases of blunt trauma, DPL's primary remaining use is in the triage of the patient who is hemodynamically unstable and has multiple injuries with an equivocal FAST examination or in the patient in whom FAST cannot be obtained owing to the absence of equipment or competent personnel.[73] In such complex scenarios, DPL can promptly reveal or exclude the presence of intraperitoneal hemorrhage and can serve as an indication for laparotomy. Rarely, DPL is used to discern potentially serious bowel perforations in patients who are poor candidates for serial clinical observations (e.g., coma) and for which other diagnostic methods can be unreliable.[74]

Disadvantages. The morbidity associated with DPL occurs at a low rate and can be categorized as local or systemic infection, intraperitoneal injury, and technical failure. Wound complications, including hematoma and infection, occurred in 0.3% of cases in two large reviews.[75] Technical failure can result in an inaccurate study and difficulty with fluid collection. In addition, DPL is exquisitely sensitive for hemoperitoneum and in a hemodynamically stable patient can lead to unnecessary laparotomy. False-negative interpretations can result from the failure to recover lavage fluid.

Table 46-2 Diagnostic Peritoneal Lavage Red Blood Cell Criteria (per mm^3)

	POSITIVE	INDETERMINATE
Blunt trauma	100,000*	20,000-100,000
Stab wound		
Anterior abdomen	100,000	20,000-100,000
Flank	100,000	20,000-100,000
Back	100,000	20,000-100,000
Low chest	5000-10,000	1000-5000
Gunshot wound	5000-10,000	1000-5000

*In a hemodynamically stable patient with pelvic fracture and positive or equivocal red blood cell count, computed tomography should be obtained to corroborate or refute intraperitoneal injury.

Results. In cases of blunt trauma, the aspiration of 10 mL or more of blood has a positive predictive value of greater than 90% for intraperitoneal injury, predictably solid visceral or vascular, and is responsible for approximately 80% of true positive DPL findings in blunt trauma.[75] The red blood cell (RBC) count of the lavage fluid is the next most widely used and accurate parameter (Table 46-2). In cases of blunt trauma, an RBC count exceeding 100,000/mm^3 is considered positive and generally specific for injury. However, while sensitive to the presence of injury, it may detect self-limited pathology for which laparotomy is unnecessary.

There is a well-known association between false-positive peritoneal lavage in the setting of retroperitoneal hematoma and pelvic fracture.[76] CT scanning is the standard method by which pelvic fracture with possible retroperitoneal or intraperitoneal hemorrhage is evaluated.[77]

With anterior abdominal stab wounds, aspiration of 10 mL of gross blood or the return of lavage fluid with an RBC count greater than 100,000/mm^3 carries a sensitivity exceeding 90% (see Table 46-2).[78] It is recommended that patients with equivocal RBC counts be carefully observed for 12 to 24 hours.[79] Most injuries associated with RBC counts less than 100,000/mm^3 are to hollow viscera, and clinical manifestations of these should develop within this observation period. With lower chest stab wounds, a positive RBC count of 5000 to 10,000/mm^3 should be considered to be evidence of diaphragmatic injury. Because of the more serious nature and greater likelihood of an injury with abdominal GSWs, RBC counts of 5000/mm^3 are advocated as the cutoff, as these will signal peritoneal penetration, if not injury.[75] However, laparoscopy has supplanted DPL for the purpose of identifying or excluding diaphragmatic injury in lower chest penetrating trauma.

Local Wound Exploration

Because stab wounds do not reach the peritoneum in a significant number of cases, LWE is useful in determining the depth of penetration. The wound should be infiltrated with a local anesthetic containing epinephrine and thoroughly prepared for exploration. The stab wound may be extended if required and then carefully visualized through each successive layer of tissue. Blind probing with digits, instruments, or cotton-tipped swabs is inaccurate, unless the peritoneal cavity is obviously freely entered. Blind probing of chest injuries adds no potential additional information and may be hazardous. If LWE indicates that the peritoneum is violated, further diagnostics are indicated. Likewise, when the end of the wound tract cannot be determined clearly, peritoneal entry

www.ketabpezeshki.com 66485457-66963820

is presumed. When the stab wound is documented to be superficial to the abdominal cavity, the patient can be safely discharged home after appropriate wound care.[80]

LWE is generally advocated in cases of anterior abdominal stab wounds, but in other areas the decision is less clear. Abdominal, flank, and back wounds have been evaluated with this method, particularly when the entry is more superficial.[13,14,81] The flesh of obese or heavily muscled patients in particular can present technical problems and decrease the reliability of exploration while increasing its risk. Wound explorations in patients with multiple entrances are not economical and require extensive effort, and it may be wiser to assume peritoneal penetration. Deep exploration over the thoracic cage is precluded by attendant complications to neurovascular structures and pleura. However, careful inspection of superficial chest wounds (e.g., slash wound) is safe and can provide valuable data. CT, laparoscopy, or thoracoscopy is occasionally used in lieu of LWE.

Special Procedures

Laparoscopy

Laparoscopy is increasingly finding a role in some trauma centers. General anesthesia in an operating suite is required. Laparoscopy has been most useful in assessing penetrating trauma, especially for injury to the diaphragm and intrathoracic abdominal organs.[82] It has a reported sensitivity of 87.5% and specificity of 100% for detection of diaphragmatic injury after PAT, with a positive predictive value of 100% and negative predictive value of almost 97%.[83] Organs repaired via the laparoscope include the diaphragm, solid intraperitoneal viscera, stomach, and small bowel. Wound tracts have been assessed as accurately as by LWE. Very little experience in blunt trauma has been documented thus far.

Drawbacks of laparoscopy include poor sensitivity for hollow visceral injury, notably to the small bowel, and difficulty in assessing the retroperitoneum and extent of damage to the liver and spleen.[83] Complications can result from trocar misplacement. If the diaphragm has been violated by the original trauma, pneumothorax or tension pneumothorax can occur during the insufflation phase. At this time the greatest value of laparoscopy is in the evaluation and management of equivocal penetrating wounds to the thoracoabdominal region of stable patients. This approach can realize a reduced incidence of nontherapeutic laparotomy.[84,85]

DIFFERENTIAL CONSIDERATIONS

Trauma versus Medical Condition

Medical and traumatic pathologic conditions can be coincident or lead one to the other. For instance, hypoglycemia or a generalized convulsive seizure may precipitate an MVC, and the patient's altered mental status may incorrectly be ascribed to closed head injury, delaying diagnosis of the medical condition. Patients with infectious mononucleosis can experience splenic rupture after relatively trivial trauma, and presentation may be delayed. Finally, patients with premorbid coagulopathy or who are on therapeutic anticoagulation may sustain serious intracranial hemorrhage from otherwise unconcerning head trauma.

Single versus Multisystem Trauma

Emergency physicians should be wary and not miss the proverbial forest for the trees. For instance, the pedestrian struck by a car who has an alleged isolated tibial-fibular fracture may well harbor significant intra-abdominal pathology, irrespective of a nontender abdomen.

Single versus Multiple Intraperitoneal Organ Injury

There has been an increasing trend toward nonoperative management of known intraperitoneal solid organ injury, specifically of the spleen and liver. It must be remembered, however, that coincident hollow viscus pathologic lesions may exist but not be discernible initially on clinical examination or certain diagnostic studies. In addition, patients without solid organ pathology who have increased amounts of free peritoneal fluid warrant careful consideration for hollow viscus damage.

Intraperitoneal Injury versus Necessary Laparotomy

Formerly, suspicion or knowledge of any intraperitoneal injury mandated laparotomy. Now, diagnostic effort is appropriately aimed at determining whether surgery is necessary or whether the injury is self-limited and does not require repair measures.

MANAGEMENT

General Measures

Prehospital

The field approach to multiple or serious trauma focuses on rapid transportation to a capable receiving emergency department. The initial measures taken vary with the need for active airway management, the presence of concomitant injuries, and the skills of the prehospital personnel. Hemorrhage is the major life threat in cases of PAT or BAT, and two large-bore intravenous lines should be inserted in transit when possible,[86] though delay at the scene for insertion of intravenous lines should not occur unless extrication is prolonged. Penetrating wounds and eviscerations in particular should be covered with sterile dressings. Contact should be made with the base-station physician to communicate pertinent matters of the history, vital signs, treatment measures and their effects, and estimated time of arrival. Certain authors advocate for direct transport to high-level trauma centers unless airway management is a concern.[87]

Emergency Department

The general principles of trauma care apply (see Chapter 36). The use of diagnostic aids for abdominal trauma should be carefully restricted according to the patient's stability and the usefulness of the information sought in guiding management. Patients who do not require immediate laparotomy will likely undergo one or more diagnostic procedures to determine whether abdominal injury exists and, if so, whether operative intervention is necessary.

Thoracotomy. Thoracotomy and subsequent cross-clamping of the descending aorta have been used to stabilize patients with thoracoabdominal injuries and profound hypovolemic shock. However, it is rarely lifesaving in the emergency department (see Chapter 45).

In a patient with massive abdominal injuries and hypotension secondary to a hemoperitoneum, the primary purpose of aortic cross-clamping is to shunt available blood into the coronary and cerebral circulation during resuscitation. Second, it is helpful in providing proximal bleeding control of certain vascular and parenchymal injuries, although continued bleeding can occur via collateral flow, until direct clamping, packing, or repair is achieved. Third, it can allow direct atrial access for rapid fluid administration. Finally, it has been advocated as a prophylactic measure in the operating room before laparotomy is performed for a massive hemoperitoneum. In certain instances, abdominal decompression,

www.ketabpezeshki.com 66485457-66963820

particularly in the face of a vascular injury, may result in worsening shock and death.

Antibiotics. An intestinal perforation and spillage can occur after blunt or, more commonly, penetrating trauma to the abdomen. Anaerobes and coliforms are the predominant organisms found. Antibiotics given prophylactically have been demonstrated to be effective in decreasing the incidence of intra-abdominal sepsis and should be given as soon as such an injury is suspected. A single preoperative dose of a broad-spectrum antibiotic or combination of antibiotics that covers both aerobic and anaerobic organisms, such as piperacillin-tazobactam 3.375 g intravenously, is recommended.[88]

Penetrating Abdominal Trauma: Stab Wounds

Diagnostic Studies

The purpose of diagnostic studies is to determine whether the peritoneal cavity has been violated or whether there is intraperitoneal injury requiring operative repair. Tests used for the former purpose include plain films, LWE, ultrasonography, and laparoscopy. Those most commonly used with the latter intent are serial physical examinations, CT scans, FAST, DPL, and laparoscopy. These modalities are undertaken only if clinical determinants that would indicate the need for emergent laparotomy are not present.

Management

Selective management of abdominal stab wounds is now well accepted because of the relatively low incidence of intraperitoneal injuries coupled with the success of various diagnostic strategies.[89,90] The appropriateness of these strategies is predicated on the site of penetration, the clinical status of the patient, and the experience and preference of an institution and its personnel. Formerly, the goal of mandatory exploration of all stab wounds was to eliminate missed injuries. Currently, selective management has resulted in a tremendous reduction in unnecessary laparotomies and their associated morbidity, with minimal and acceptable loss in sensitivity for significant intraperitoneal injury.[90] Although certain authors promote the relative safety of nontherapeutic operations, others cite considerable immediate and delayed hazards, as well as increased cost.[80] It is generally preferred that the nondiagnostic laparotomy rate be less than 15%.

Anterior Abdomen. In approaching the management of stab wounds to the anterior abdomen, the clinician is faced with three fundamental tasks. The first and most important is to determine whether clinical indications exist for laparotomy. The presence of one or more of these indications, particularly in the context of an unstable patient, sets the course to exigent operation. If none is found, however, the clinician may address the second issue of whether the peritoneal cavity has been violated. If it can be definitively demonstrated that it has not, no further diagnostic evaluation is required, and the patient can be discharged after appropriate wound care. If the cavity has been violated, or if it cannot be determined that the cavity has not been violated, the third question is pursued: does injury exist and, if so, is laparotomy required? One general approach to abdominal stab wounds founded on these three queries is summarized in Figure 46-9. This algorithm is largely based on clinical indicators of injury, LWE, CT, and other radiologic modalities. In centers without such resources, diagnostic peritoneal aspiration and lavage may still have a limited role. Other strategies rely more heavily on other techniques, such as serial abdominal examinations or laparoscopy.[91-94]

Step I: Clinical Indications for Laparotomy. Seven clinical determinants are used to predict the need for laparotomy after stab wounds to the abdomen (Table 46-3). Although there is

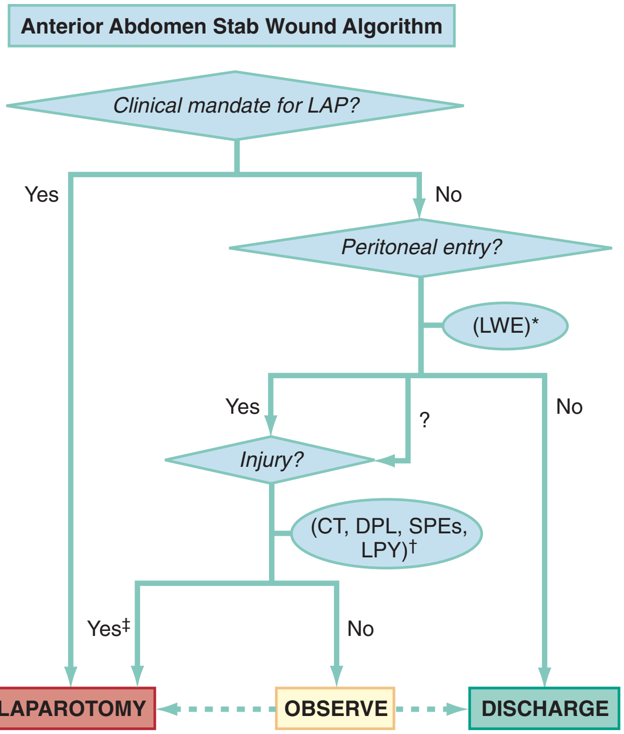


Figure 46-9. Anterior abdomen stab wound algorithm. *LAP,* laparotomy; *LWE,* local wound exploration.
*Plain films, focused assessment with sonography in trauma (FAST), laparoscopy (LPY), and computed tomography (CT) can also assess peritoneal entry.
†CT, diagnostic peritoneal lavage (DPL), serial physical examinations (SPEs), or LPY can be used in singular or complementary fashion, depending on the clinical scenario.
‡Expectant management of injuries is infrequently attempted.

Table 46-3 Clinical Indications for Laparotomy Following Penetrating Trauma

MANIFESTATION	PREMISE	PITFALL
Hemodynamic instability	Major solid visceral or vascular injury	Thorax or mediastinum, causal or contributory
Peritoneal signs	Intraperitoneal injury	Unreliable, especially immediately postinjury
Evisceration	Additional bowel, other injury	No injury in one fourth to one third of stab wound cases
Diaphragmatic injury	Diaphragm	Rare clinical, radiographic findings
Gastrointestinal hemorrhage	Proximal gut	Uncommon, unknown accuracy
Implement in situ	Vascular impalement	Comorbid disease or pregnancy creates high operative risk
Intraperitoneal air	Hollow viscus perforation	Insensitive; may be caused by intraperitoneal entry only or may have cardiopulmonary source

Modified from Marx JA: Diagnostic peritoneal lavage. In Ivatury RR, Cayten CG (eds): The Textbook of Penetrating Trauma. Baltimore, Williams & Wilkins, 1996.

www.ketabpezeshki.com 66485457-66963820

general consensus regarding the reliability of some of these, each has suboptimal predictive value.

1. *Hemodynamic compromise.* This is the preeminent indication of the need for laparotomy and is the most likely reason that a patient will be taken urgently to the operating room without preliminary diagnostic studies. This is typically an appropriate approach after middle and lower abdominal penetration.[94-96] However, stab wounds to the upper abdomen and lower chest may produce hemodynamic instability because of intrathoracic hemorrhage, pneumothorax, or pericardial tamponade.
2. *Peritoneal signs.* There is considerable debate over the reliability of peritoneal signs, particularly in the early postinjury period. Among physical examination findings, unequivocal peritoneal signs have the highest positive predictive value, whereas an entirely normal examination even in the presence of mild to moderate intoxication has the greatest negative predictive value for therapeutic laparotomy.[95,96]
3. *Evisceration.* With isolated omental evisceration, both a selective and a mandatory operating approach have been espoused. Omentum has been successfully ligated, excised, and restored to the peritoneal cavity.[94,95] However, patients with viscus or omental evisceration sustain up to an 80% incidence of major intraperitoneal injury, rendering laparotomy a reasonable next step in management.[12]
4. *Left-sided diaphragmatic injury.* In contradistinction to blunt mechanisms, penetrating trauma to the diaphragm produces small tears and evanescent clinical clues to their presence. Thus clinical examination and plain chest films are rarely diagnostic of injury. Left-sided tears in the diaphragm can lead to herniation of bowel into the thorax weeks to decades later, leading to obstruction, strangulation, infarction, perforation, and death. For right-sided diaphragmatic injury, the liver affords considerable protection against herniation. Other diagnostic measures, such as DPL or laparoscopy, or a mandatory laparotomy approach are necessary to determine whether the diaphragm has been violated.[97]
5. *Gastrointestinal hemorrhage.* Recovery of blood via a nasogastric tube or emesis may reflect a violation of the stomach or duodenum but is an unusual occurrence.[80,94,96] Likewise, examination of the rectum or vagina may reveal hemorrhage that is the result of intraperitoneal or retroperitoneal trauma, but there are often external signs of hemorrhage. Care should be taken in performing a vaginal examination in a woman with pelvic fractures to avoid injury to the examiner's hand.
6. *Implements in situ.* The conservative and widely held maxim is to remove implements in situ of the torso in the operating room. This is to ensure expeditious control of hemorrhage should the implement reside within a vascular space or highly vascularized organ. Although implements in situ are most safely removed in the operating room, exceptions to this practice exist. These include situations in which emergency department resuscitation is impeded by the presence of the implement or the patient is at high risk of significant morbidity from nontherapeutic laparotomy because of severe comorbid conditions or pregnancy, for example.
7. *Intraperitoneal air.* The presence of free intraperitoneal air is often not sought because of the insensitivity and nonspecificity of this finding. Free intraperitoneal air can impute communication of the knife with the intraperitoneal space or the presence of pulmonary or mediastinal injury. Therefore it does not necessarily indicate hollow visceral perforation and should not be used in isolation as an indicator for operation.

Step II: Peritoneal Violation. If clinical indications for laparotomy are absent, a logical next step is assessing the wound tract itself. The presence of peritoneal violation can be determined by a variety of means. There is great value in establishing that a wound tract is superficial to the peritoneal, retroperitoneal, intrathoracic, and pericardial cavities. In this event, the patient can be discharged from the emergency department after receiving appropriate wound care.[91,95] If a study is inconclusive, it should be assumed that one or more of these cavities has been violated and further means of assessment are required. The five methods of assessing the intactness of the peritoneum are as follows:

1. *Evisceration.* Evisceration of bowel or omentum is clear evidence of peritoneal entry. These situations are usually handled by mandatory laparotomy. In certain centers, however, these eviscerations are reduced in the emergency department and further diagnostics pursued.[61,96]
2. *Intraperitoneal air.* A finding of intraperitoneal free air on an upright chest or a lateral decubitus abdominal radiograph generally establishes that the knife has entered the peritoneal cavity and drawn air in with it, has disrupted a hollow viscus, or both. Rarely, a false-positive determination of peritoneal entry can be made when the actual source of intraperitoneal free air is the pulmonary tract.
3. *LWE.* This has been demonstrated to be an effective tool in determining the depth of the stab wound tract.
4. *Ultrasonography.* Ultrasonography demonstrating hemoperitoneum, pneumoperitoneum, or pericardial effusion identifies peritoneal penetration or cardiac injury.[98] However, its reliability as a sole indicator for injury is not as dependable as that in BAT, and it carries a 15% negative laparotomy rate when used as such. In addition, a negative FAST does not rule out peritoneal violation.[99] Ultrasonography may also be used as an adjuvant to LWE to determine intactness of fascia. Although a small study demonstrated that it can positively rule in fascial penetration, it is unreliable to rule this out.[81] Experience with ultrasonography for this purpose has been successful but very limited.
5. *Laparoscopy.* This has compared favorably with LWE in assessing the wound tract but requires far more expertise and carries a far greater risk of complications. It is the most invasive and costly means of evaluating the integrity of the peritoneum. However, laparoscopy may also discover and serve as the mode of repair of certain diaphragmatic or organ injuries or both,[12,83,84] and some postulate that its use in experienced centers actually decreases length of stay and therefore cost.[94]

Step III: Injury Requiring Laparotomy. In this algorithm, patients requiring an operation on clinical grounds have proceeded to laparotomy, and those in whom peritoneal, retroperitoneal, intrathoracic, and pericardial cavity violations have been excluded are discharged home. The patients remaining have presumed or known peritoneal violation. The next consideration is whether injury exists that dictates operative repair, because organ injury is present in only just over 60% of patients with peritoneal violation.[4,92] In any case, patients who reach this stage of evaluation should be observed for at least 12 to 24 hours.[75]

Historically, the diagnostic standard to address the issue of intraperitoneal injury was DPL. Its role was especially valuable as a rapid means of determining hemoperitoneum in the patient in critical condition and for the discovery of occult hollow viscus perforation and isolated diaphragmatic injury.[97,100] However, it is invasive, and thus the vast majority of centers advocate other, less

www.ketabpezeshki.com 66485457-66963820

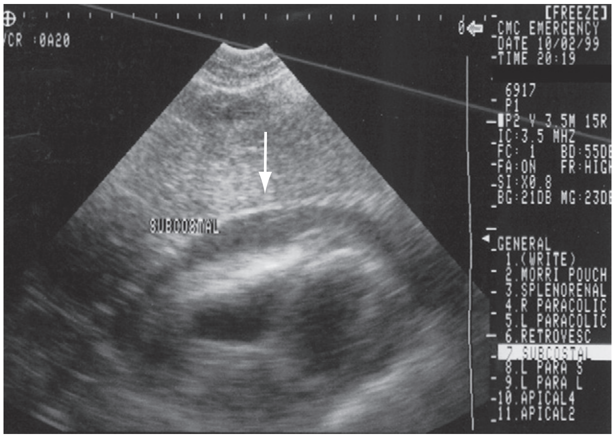


Figure 46-10. Pericardial effusion seen on subcostal view *(arrow).* The white line is the pericardium, and the anechoic space below represents a fluid collection in the pericardial space.

invasive adjuvant testing coupled with serial physical examinations as the next step in management.

Ultrasonography may be somewhat less accurate than DPL in establishing the presence or absence of hemoperitoneum, but it can simultaneously ascertain hemopericardium (Fig. 46-10). In most centers ultrasonography can be accomplished as quickly or more quickly than peritoneal aspiration. Emphasis on serial examinations with selective use of other studies on an as-needed basis can be successful when an adequate number of experienced clinicians are available.[98,101,102]

CT has been particularly useful for potential colorectal trauma or further assessment of patients submitted to serial examination alone. However, some centers routinely perform CT in these cases and not simply for possible colorectal trauma.[103] Most use triple contrast (oral, rectal, and intravenous), although some newer studies cite equal accuracy with intravenous contrast only.[104] Hollow viscus and occult diaphragmatic injuries remain the most frequently missed injuries on CT (even with use of triple contrast), although with the advent of multidetector CT scanners this is decreasing.[11,83]

Laparoscopy works best in experienced hands for restricted indications. However, its routine use is gaining favor in some institutions. Benefits include the ability to detect organ injury (including diaphragmatic injury) and simultaneously repair some injuries, thus decreasing negative and nontherapeutic laparotomy rates.[11,81,84]

Thoracoabdominal. Even a single stab wound to the low chest can violate the mediastinum, thoracic cavity, diaphragm, peritoneal cavity, and retroperitoneum. The risk of diaphragmatic penetration from a left thoracoabdominal stab wound has been measured at 17%.[12] When all thoracoabdominal wounds are considered, the risk of occult injury is 7%.[105] Ultrasonography can be extremely useful by permitting quick assessment for hemopericardium and hemoperitoneum in the marginally stable patient, if thoracotomy or laparotomy is not already clinically indicated.[75] LWE of slash-type wounds may obviate the need for further evaluation. However, the depth of investigation cannot be taken beyond the anterior rib margin to maximize safety and accuracy. Further assessment for intraperitoneal and diaphragmatic injury can be made by DPL. The RBC criterion is lowered to 5000 to 10,000/mm^3 to optimize sensitivity for isolated diaphragmatic injury.[104] Laparoscopy or thoracoscopy can visualize and potentially be used to repair the diaphragm and other organs. Newer multidetector CT scanning and MRI show promise in excluding diaphragmatic injury. CT has a sensitivity of 94% and specificity of almost 96% for detecting diaphragmatic injury. However, equivocal scans should be followed up with more definitive management, such as DPL, exploratory laparotomy, or laparoscopy.[13] A very conservative approach to the left lower chest stab wound, in particular, is mandatory exploration. This approach avoids any opportunity for missed diaphragmatic rents and their delayed consequences but results in an exceptionally high incidence of nontherapeutic operation. Rapid slice helical CT and MRI may provide a solution to this vexing concern, but data are limited to date.

Flank and Back. The incidence of retroperitoneal injuries after stab wounds to the flank and back is greater than with injury to the anterior wall. However, risk of intraperitoneal organ injury is significant, ranging from 15 to 40%.[14] Again, LWE can be a useful first step. However, the paraspinal muscles are quite thick, rendering the procedure more difficult. Triple-contrast CT scan is becoming the preferred method of evaluation in hemodynamically stable patients and coupled with observation may safely allow nonoperative management of these patients.[32,97]

Implement in Situ. It is routinely advised that foreign bodies in situ of the torso be removed under operating conditions. This is considered safest in the event that the implement is intravascular or in a highly vascularized organ. Plain films are generally all that is required. A CT scan may be indicated in stable patients if plain films suggest impalement of major vascular structures. Angiography may also be necessary. For pregnant patients or those with severe comorbid illness in whom unnecessary laparotomy is preferably avoided, a CT scan may be able to discern the depth of entry and extent of injury, though the risk of radiation to the fetus must be weighed against the risk of operative intervention. In these cases the foreign body may be removed safely outside of the operating room.

Penetrating Abdominal Trauma: Gunshot Wounds

Diagnostic Studies

Diagnostic studies are used in a fashion similar to that for stab wounds. Moreover, the same diagnostic agents are applied, although in more restricted circumstances. The principal uses of diagnostic studies are to determine whether the missile has entered the peritoneal cavity and whether injury requiring operative intervention has occurred.

Management

Like stab wounds, GSWs typically produce multiple organ injuries and a high incidence of hollow visceral injury. However, the risk of mortality is significantly greater, especially if vascular structures are involved. Missiles striking the low chest commonly penetrate both intrathoracic and abdominal structures, including the diaphragm.

Abdominal GSWs enter the peritoneal cavity in approximately 80% of cases, and in more than 90% of those involving penetration, there is intraperitoneal damage.[30] These statistics significantly exceed the figures for stab wounds, and most trauma surgeons adjust their management to a conservative bent accordingly. We promote the principle that although selective management is widely accepted for stab wounds, its application in the management of GSWs is more limited, and therefore conservative clinical criteria for mandatory laparotomy should be applied. Other authors argue, however, that although peritoneal penetration and intraperitoneal injury are far more likely to result from GSWs, damage requiring operative repair should be the instrumental concern, and this may be less common than previously stated. More recent series report intra-abdominal injury in only 70 to 80% of cases, supporting the contention that nonoperative management could be appropriate for a substantial percentage of patients.[3,30,103]

www.ketabpezeshki.com 66485457-66963820

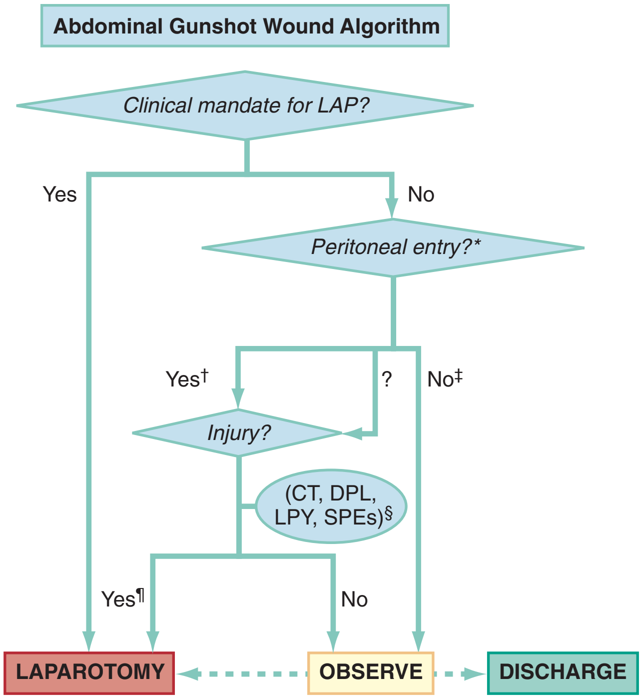


Figure 46-11. Abdominal gunshot wound algorithm. *LAP,* laparotomy. *Can be assessed by missile path, plain films, local wound exploration, ultrasonography, and laparoscopy.
†Most centers proceed to laparotomy if peritoneal entry is suspected.
‡Patients with documented superficial and low-velocity injuries can be discharged; unknown-depth or high-velocity injuries require further tests or observation.
§Computed tomography (CT), diagnostic peritoneal lavage (DPL), laparoscopy (LPY), or serial physical examinations (SPEs) can be used in singular or complementary fashion, depending on the clinical scenario.
¶Expectant management of injuries caused by gunshot wounds is rarely attempted.

A prudent approach to GSWs to the abdomen can follow the same sequential three-step algorithm as for stab wounds (Fig. 46-11). First and foremost, are there clinical grounds for operation? Second, if none exists, has peritoneal violation occurred? Third, does injury requiring laparotomy exist? Centers that adhere to the tenet that known or suspected peritoneal violation imputes high likelihood of intraperitoneal injury will proceed to laparotomy if the second question is answered affirmatively. Those in which it is believed that there is a lower incidence of significant organ damage use other diagnostic agents, including serial physical examination, irrespective of whether the peritoneal cavity has been violated.

Step I: Clinical Indications for Laparotomy. These clinical demands are similar to those proposed for stab wounds (see Table 46-3).

Step II: Peritoneal Violation. Six methods are used to determine whether the missile has entered or traversed the peritoneal cavity. This question is most germane for centers that perform laparotomy based on peritoneal violation alone.

1. *Missile path.* Clear entrance and exit wounds allow for a reasonably reliable estimate of the missile path. However, many GSWs ricochet. Even a single GSW can ricochet, and the tendency of low-velocity missiles to follow fascial planes of lower resistance can render this approach misleading.
2. *Plain radiographs.* An anteroposterior and lateral projection of the abdomen can assist in placing the missile in the peritoneal cavity, but such estimations are imprecise and are largely unhelpful in patients with through-and-through or multiple GSWs.
3. *LWE.* Because GSWs produce considerably more tissue damage than stab wounds, LWE is a less useful tool for GSWs of the abdomen, flank, and back. Its role should likely be restricted to low-velocity projectiles with suspected superficial entry. Because of the much greater technical difficulty and hazard in visualizing these extensive missile tracts, there is a tendency to underestimate the degree of damage.[30]
4. *Ultrasonography.* The experience with ultrasonography in coincidentally assessing wound tracts and the mediastinum for low chest and upper abdominal penetration has been successful but very limited.
5. *Laparoscopy.* Laparoscopy is the most invasive and costly means of evaluating the integrity of the peritoneum. However, it may also discover and serve as the mode for repair of certain diaphragmatic or organ injuries or both.[82,84,102]
6. *CT.* CT has been helpful when trajectory is indeterminate and has shown a sensitivity and specificity of 90.5% and 96%, respectively, for identifying intra-abdominal injury. It can also identify the wound track and indicate vascular structures at risk for injury, although this is more useful in neck wounds.[30,103]

Step III: Injury Requiring Laparotomy. In most institutions, the algorithm terminates after the second step, in which determination or strong suspicion of peritoneal violation presupposes the need for laparotomy. At more liberal centers, these facts are deemed insufficient, and additional diagnostics are undertaken.

1. *Serial examinations.* Patients with normal examination findings or localized wound tenderness can be observed only if clinical circumstances and institutional policy allow. Physical examination may be more reliable than previously suspected in the presence of alcohol or illicit drug intoxication.[75]
2. *DPL.* DPL has been highly successful in determining or excluding intraperitoneal injury. When DPL is used, all criteria for positivity remain the same with the exception of the RBC count, which is lowered to 5000 to 10,000 RBCs/mm^3 to maximize sensitivity.[30,103]
3. *CT.* Higher-resolution scanners may augment the ability of CT to identify hollow visceral damage in addition to solid organ and vascular pathologic lesions.[30]
4. *Laparoscopy.* The greatest use for laparoscopy is in the evaluation of the diaphragm in patients with left thoracoabdominal GSWs who do not have indications for standard operative intervention.[89]

Thoracoabdominal. Patients with GSWs to the low chest have intraperitoneal injuries reported in 45% of cases. Clinical indications for laparotomy are unchanged. DPL is particularly helpful in these cases to discern diaphragm injury, and the RBC threshold of 5000 to 10,000/mm^3 produces excellent sensitivity, but a combination of CT scanning and serial examinations is more commonly used.

Flank and Back. In the past, operative exploration was generally recommended because of the increased likelihood of a serious injury and the greater fallibility of both the physical examination and DPL in cases of retroperitoneal injuries. However, as multidetector CT scanners have evolved, an intravenous contrast CT scan to delineate retroperitoneal pathologic lesions is typically the initial diagnostic test of choice in a stable patient.[95,102] As with stab wounds, laparoscopy or observation alone can be attempted in selected circumstances.[106]

Shotgun Wounds. Type I injuries can be effectively managed by reserving laparotomy for patients with clear peritoneal signs or progressive abdominal tenderness. Certain authors advocate an expectant approach to type II injuries, stating that small punctures of the bowel cause no wound eversion and no peritoneal

www.ketabpezeshki.com 66485457-66963820

leakage and will spontaneously close.[107] A more prudent approach is to perform laparotomy in cases of these penetrating wounds, especially if there are signs of peritonitis. Reconstruction of abdominal wall defects may be required. Type III injuries are commonly associated with multiple organ injuries, shock, and pronounced tissue destruction, requiring hemostasis and extensive débridement.

Blunt Abdominal Trauma

Diagnostic Studies

Most centers assimilate physical examination, bedside ultrasonography, CT, and, in rare instances, DPL into a clinical algorithm.[25] Other tests, such as angiography, may be indicated. To reiterate, a clinical assessment of an alert patient that depends on abdominal findings alone is reasonably accurate but is accompanied by both false-positive and false-negative errors.[67,108-110] Such an assessment is more hazardous for a patient who is under the influence of a variety of toxins or whose examination is compromised by a head injury, spinal injury, or difficulty in communication resulting from developmental delay, psychiatric illness, a language barrier, or age.

The purpose of diagnostic studies in patients with BAT is twofold (Table 46-4): to discern or eliminate the presence of hemoperitoneum in the patient whose condition is critical and unstable to properly sequence management and, in less urgent circumstances, to demonstrate organ injury that requires operative repair.

Determining Hemoperitoneum

FAST Ultrasonography. The FAST examination has a safety advantage in that it can be performed rapidly and conducted in the resuscitation suite in the emergency department. In contradistinction to DPL, the FAST is hazard-free, and serial examinations can be undertaken with ease in any patient. In hypotensive patients the FAST has excellent sensitivity for hemoperitoneum requiring surgical intervention, and most centers proceed to exploratory laparotomy in these patients.[107,111] However, in those with a negative FAST, intra-abdominal injury requiring operative repair cannot be excluded.[112,113]

Diagnostic Peritoneal Lavage. DPL is exceptionally sensitive in discovering hemoperitoneum, with a false-negative rate of less than 2%. This procedure can be performed in virtually any patient by varying the site and technical method. Aspiration of the peritoneum generally requires less than 5 minutes. Given advances in other diagnostic modalities, however, its role is now predominantly at centers without access to ultrasound in hemodynamically unstable patients.

Computed Tomography. Although a CT scan can both visualize and estimate the quantity of hemoperitoneum, the time required to accomplish the procedure, including transport of the patient and setup, can be problematic, depending in part on the location of the scanner. Moreover, the ability to carry out CT scanning in a safe manner depends on the availability and expertise of personnel to monitor the patient while he or she is in the CT scanner.

Demonstrating Organ Injury That Requires Laparotomy.

Indications for the respective studies will vary with clinical need and with the experience, resources, and attitudes of individual institutions.

Ultrasonography and Diagnostic Peritoneal Lavage. Prompt FAST (or, less commonly, DPL) is clearly warranted in the acutely injured and unstable patient with multiple trauma.

The primary value of the FAST is in the search for hemoperitoneum. It is far less reliable in specifying organ pathology, with the exception of traumatic pancreatic pseudocysts.

Computed Tomography. A CT scan alone is sufficient and appropriate in the patient who is hemodynamically stable and has no obfuscating clinical factors. The great advantage of the CT scan is its ability to distinguish intraperitoneal organ injury and simultaneously evaluate the retroperitoneum. It is the most capable instrument in diagnosing liver and spleen pathologic lesions, and it allows visualization and semiquantitation of hemoperitoneum.

Laparoscopy. At this time, the role of laparoscopy in trauma cases is relegated mostly to injuries with a penetrating mechanism.

Table 46-4 Diagnostic Studies in Blunt Abdominal Trauma

STUDY SCENARIO	PRIMARY PURPOSE	STUDY	COMPENSATORY
Hemodynamically Unstable			
General	IPH	FAST, DPA	—
Pelvic fracture	IPH	FAST, DPA*	—
Hemodynamically Stable			
General	OI[†,‡]	FAST, CT	DPL, SPEs
Nonoperative management[§]	OI	FAST, CT[‖]	DPL,[¶] SPEs
CHI	OI, HVI	FAST, CT[‖]	SPEs[#]
BAI	IPH	FAST, DPA	CT**

BAI, blunt aortic injury; *CHI,* closed head injury; *CT,* computed tomography; *DPA,* diagnostic peritoneal aspiration; *DPL,* diagnostic peritoneal lavage; *FAST,* focused assessment with sonography in trauma; *HVI,* hollow viscus injury; *IPH,* intraperitoneal hemorrhage; *OI,* organ injury; *SPEs,* serial physical examinations.
*Positive peritoneal aspirate necessitates laparotomy, positive red blood cell count only, and warrants attention to pelvic fracture.
†To discover fluid or blood suggesting injury.
‡FAST for OI much less reliable than for IPH.
§Institutional capability should be carefully considered.
‖CT less reliable for HVI than for solid visceral injury.
¶Complementary to CT if HVI suspected.
#SPEs are unreliable in the patient with CHI.
**May be more appropriate if helical CT is primary study for blunt abdominal injury or can be rapidly acquired.

Management

In cases of blunt trauma, it is the exception when a patient undergoes laparotomy based on clinical grounds alone. Far more typically, one or a complementary battery of diagnostic tests are performed. The choice of these tests is influenced by the patient's hemodynamic status, the clinical scenario, and the institution's resources and preferences (Fig. 46-12).

Clinical Indications for Laparotomy. The decision to perform immediate laparotomy after injury from a blunt mechanism is rarely determined solely by clinical parameters. Potential indications are any of the following (Table 46-5):

1. Unexplained signs of blood loss or hypotension in a patient who cannot be stabilized and in whom intra-abdominal injury is very strongly suspected
2. Clear and persistent signs of peritoneal irritation
3. Radiologic evidence of pneumoperitoneum consistent with a viscus rupture
4. Evidence of a diaphragmatic rupture
5. Persistent, significant gastrointestinal bleeding seen in the nasogastric return or in vomitus

Establishing the need for urgent laparotomy on clinical grounds is particularly problematic in the patient with multiple blunt injuries. Numerous extra-abdominal potential sources of hypotension exist. In addition, there is often coincident head injury or intoxication to further impair the reliability of examination. A

www.ketabpezeshki.com 66485457-66963820

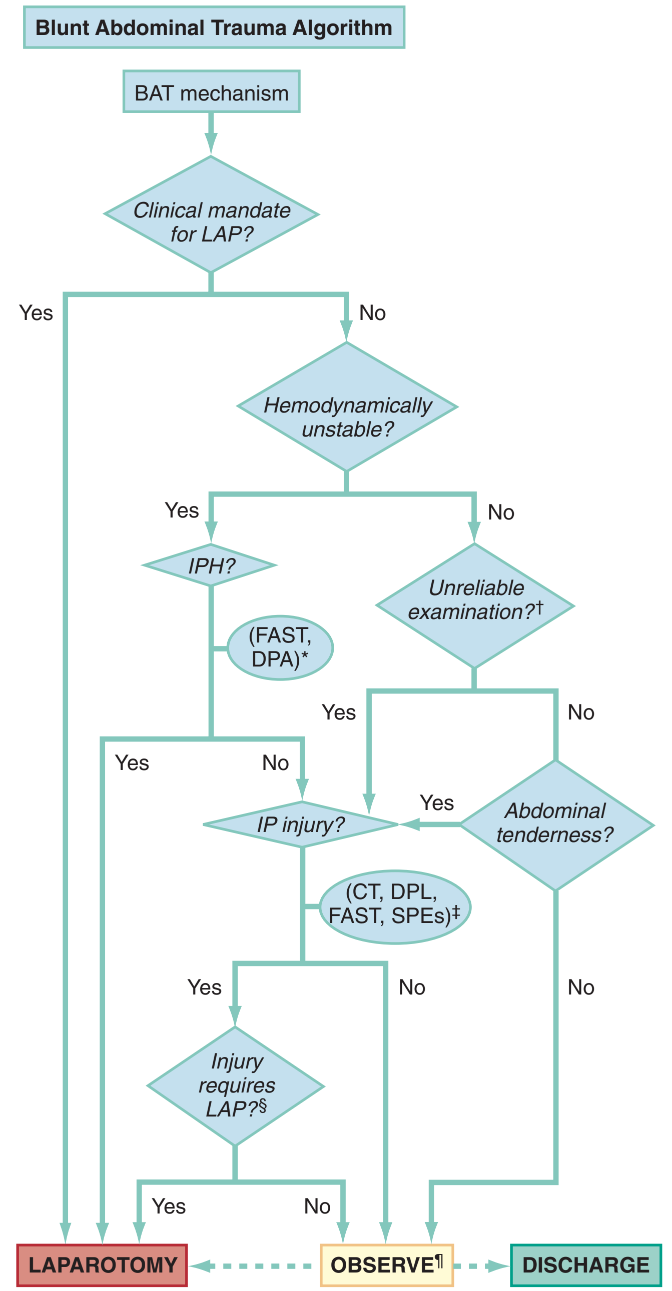


Figure 46-12. Blunt abdominal trauma (BAT) algorithm. *CT,* computed tomography; *DPL,* diagnostic peritoneal lavage; *FAST,* focused assessment with sonography in trauma; *IP,* intraperitoneal; *IPH,* intraperitoneal hemorrhage; *LAP,* laparotomy; *SPEs,* serial physical examinations.
*Determined by unequivocal free intraperitoneal fluid on FAST or positive aspiration of blood on diagnostic peritoneal aspiration (DPA).
†Can be unreliable because of closed head injury, intoxicants, distracting injury, or spinal cord injury.
‡One or more studies may be indicated.
§Need for laparotomy is based on clinical scenario, diagnostic studies, and institutional resources.
¶Duration of observation should be 6 to 24 hours depending on whether diagnostic tests have been performed, the results of the tests, and clinical circumstances, including the absence of factors rendering the examination unreliable.

nontherapeutic laparotomy may imperil the patient, not so much because of the potential morbidity of the procedure but rather because more vital diagnostic and therapeutic steps are delayed. When confusion exists, corroborative diagnostic tests are strongly preferred.

Table 46-5 Clinical Indications for Laparotomy after Blunt Trauma

MANIFESTATION	PITFALL
Unstable vital signs with strongly suspected abdominal injury	Alternate sources of shock
Unequivocal peritoneal irritation	Potentially unreliable
Pneumoperitoneum	Insensitive; may be caused by cardiopulmonary source or invasive procedures (diagnostic peritoneal lavage, laparoscopy)
Evidence of diaphragmatic injury	Nonspecific and insensitive, especially in penetrating trauma
Significant gastrointestinal bleeding	Uncommon, unknown accuracy

Hemodynamically Unstable Patients. In the patient with multiple blunt injuries who is threatened by shock, three cavities are immediately targeted. Chest and pelvic radiographs seek blood loss in the thoracic and retroperitoneal spaces, respectively. FAST or peritoneal aspiration is undertaken to reveal or exclude the presence of blood in the peritoneal cavity. Hemoperitoneum in a clinically unstable patient necessitates laparotomy.

Hemodynamically Stable Patients. In patients who are hemodynamically stable, CT scanning is the widely preferred diagnostic modality because of its ability to specify organ pathology, semiquantitate hemoperitoneum, and study nonabdominal body regions. Its potential drawbacks in certain clinical circumstances must be understood, however. Ultrasonography, DPL, and, very uncommonly, laparoscopy can be used in a complementary or primary mode.

Operative versus Nonoperative Management. Patients with certain intraperitoneal injuries can be watched expectantly and need not be subjected to laparotomy. Specifically, this has been successful with even moderate- to high-grade liver or spleen trauma. Failures, including deaths, have occurred with this approach. Thus, although it is preferable to avoid unnecessary laparotomy, it is imperative to prevent significant morbidity or mortality by waiting too long. The patient with normal sensorium and minor to intermediate severity of mechanism is a superior candidate for expectant management. It is critical that an institution appraise its ability to manage such patients. This includes having experienced nursing staff, trauma surgeons, adequate blood resources, and radiologists and the ability to take a patient to undergo laparotomy urgently if the need arises.

Several pitfalls in the expectant approach are noteworthy. First, multiple injuries of intraperitoneal organs, including hollow viscera, are common.[72] Operative management of hollow visceral injury is necessary, and delay can have severe consequences.[114] The ability of the CT scan to detect coincident injury to these structures is discussed earlier. The patient with multisystem injury and, specifically, closed head trauma is most vulnerable to having delayed diagnosis of perforated intestinal injury.[72,74] Second, expectant management may lead to increased use of blood products. Finally, this management approach will fail in those patients whose hemorrhage is not amenable to therapeutic angiography and embolization and will not abate because of misperceived injury of solid organs. In such cases, the lag time from injury to operation may increase morbidity and mortality.[115]

Pelvic Fracture. In the setting of pelvic fracture, the clinical triage determinant is the presence or absence of hemoperitoneum (Fig. 46-13). Although the sensitivity of FAST in patients with pelvic fractures is decreased, it still serves as a tool to triage the patient to the next intervention. In an unstable patient, a negative

www.ketabpezeshki.com 66485457-66963820

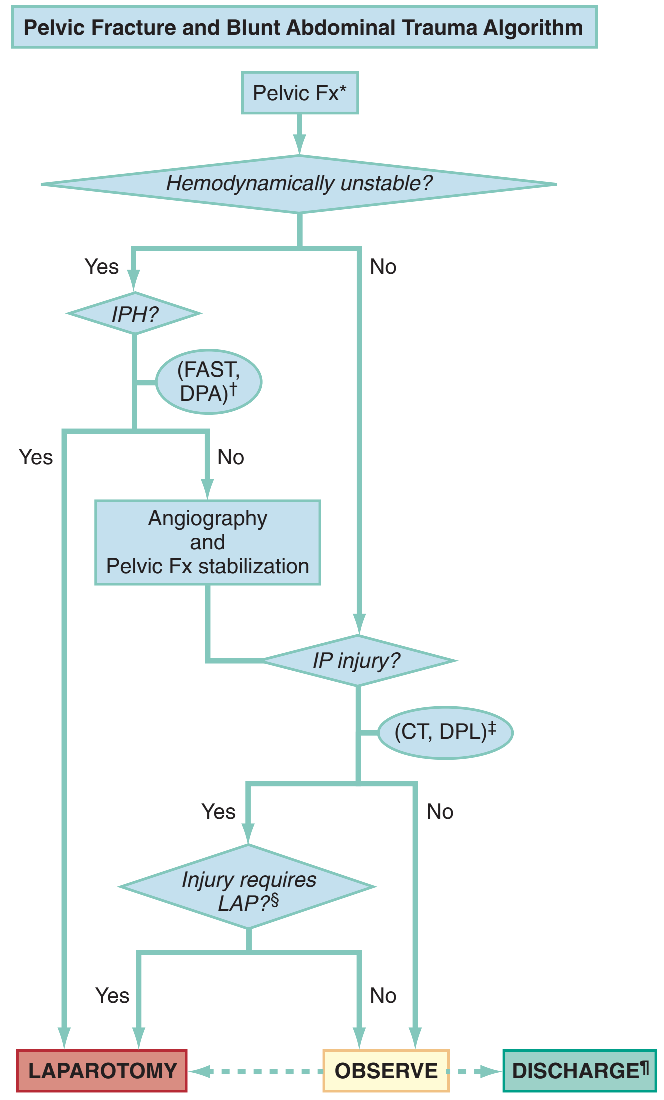


Figure 46-13. Pelvic fracture (Fx) and blunt abdominal trauma algorithm. *CT,* computed tomography; *DPL,* diagnostic peritoneal lavage; *FAST,* focused assessment with sonography in trauma; *IP,* intraperitoneal; *IPH,* intraperitoneal hemorrhage; *LAP,* laparotomy.
*Certain pelvic fractures are more likely to cause pelvic vascular disruption and subsequent retroperitoneal hemorrhage.
†Determined by unequivocal free intraperitoneal fluid on focused assessment with sonography in trauma (FAST) or positive peritoneal aspiration on diagnostic peritoneal aspiration (DPA).
‡One or more studies may be indicated. Serial physical examinations are generally considered unreliable owing to the presence of pelvic fracture.
§Need for laparotomy is based on clinical scenario, diagnostic studies, and institutional resources.
¶Discharge from the perspective of need for further consideration for laparotomy.

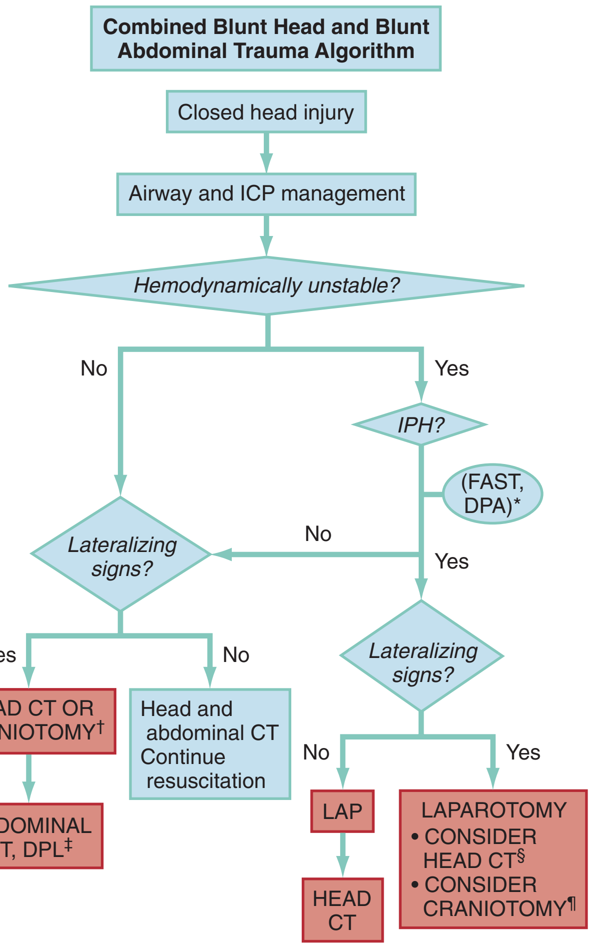


Figure 46-14. Combined blunt head and blunt abdominal trauma algorithm. *CT,* computed tomography; *ICP,* intracranial pressure; *IPH,* intraperitoneal hemorrhage.
*Determined by unequivocal free intraperitoneal fluid on focused assessment with sonography in trauma (FAST) or positive peritoneal aspiration on diagnostic peritoneal aspiration (DPA).
†Craniotomy or burr holes based on clinical picture and unavailability of computed tomography (CT).
‡Diagnostic peritoneal lavage (DPL) can be complementary to CT in determining hollow viscus injury.
§Consider prelaparotomy (LAP) head CT based on clinical picture and availability of CT.
¶Consider craniotomy or burr holes simultaneous with laparotomy.

FAST is followed by a supraumbilical peritoneal aspirate, to avoid potential false positives caused by retroperitoneal blood moving to the anterior infraumbilical space. If this reveals 10 mL or more of blood, then the patient should expeditiously be moved to laparotomy. If instead urine or other fluid is aspirated, then the patient should undergo pelvic angiography before laparotomy. If the FAST is negative, then the patient should proceed to therapeutic angiography with the presumed diagnosis of a life-threatening retroperitoneal bleed. In stable patients, early mechanical pelvic stabilization is advised (see Chapter 55), and CT scan followed by pelvic angiography and embolization are undertaken as early as possible in the context of the multiple injuries.

Multiple System Injury. Management of the abdominal trauma patient with more than one life-threatening injury cannot be dogmatic. It is not unusual to confront intraperitoneal hemorrhage in a patient with apparent closed head injury or suspected blunt aortic disruption or both. Repair of the abdomen is said to take precedence over that of the head and chest. However, these situations are highly complex, and decision-making is influenced by numerous and dynamic variables. The key tenet is that a patient with known hemoperitoneum whose vital signs cannot be stabilized should undergo laparotomy or face imminent exsanguination.

Closed head Injury. In general, patients with coincident severe closed head injury but without frank coma or lateralizing signs do not have intracranial lesions that require craniotomy. When lateralizing features do exist, the clinician must choose between a rapid prelaparotomy CT scan of the head or preemptive burr holes at laparotomy. This judgment rests mostly on the clinical state of the patient with particular regard to his or her response to resuscitative measures and the timely availability of CT.[116] An approach to this scenario is presented in Figure 46-14.

www.ketabpezeshki.com 66485457-66963820

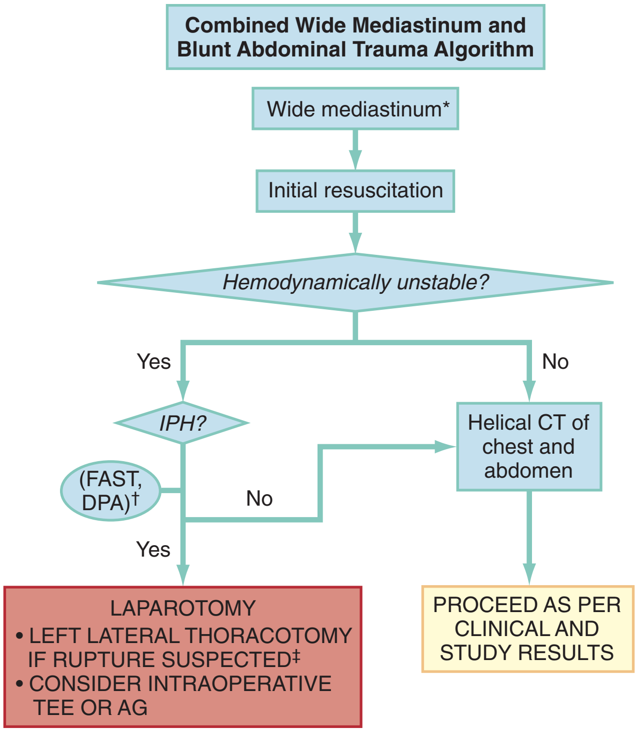


Figure 46-15. Combined wide mediastinum and blunt abdominal trauma algorithm. *AG,* aortogram; *CT,* computed tomography; *FAST,* focused assessment with sonography in trauma; *IPH,* intraperitoneal hemorrhage; *TEE,* transesophageal echocardiogram.
*Preferably based on upright posteroanterior film and mechanism of injury; other radiographic signs or mechanism alone may signal need for evaluation.
†Determined by unequivocal free intraperitoneal fluid on FAST or positive finding on diagnostic peritoneal aspiration (DPA).
‡Allows surgical access to majority of aortic disruption sites.

Blunt Aortic Injury. Clinical or radiographic features that portend great vessel injury, notably a widened mediastinum on a supine anteroposterior chest radiograph, have variable sensitivity and specificity. In addition, although the course of any single aortic lesion is unpredictable, there is more likely than not a lag of at least several hours before rupture. Therefore exigent laparotomy should precede great vessel diagnostics. Should the patient's condition precipitously deteriorate, left lateral thoracotomy allows aortic cross-clamp with its circulatory benefits and, in general, affords access to the injured portion of the vessel (Fig. 46-15).

Pediatrics. Children are prone to aerophagia, and decompressive nasogastric tubes are particularly important to help prevent compromised lung function and aid in the abdominal examination. Care is taken in fluid resuscitation and drug administration, with attention being paid to the patient's size and with surface area or body weight used as a guide. Because of their size and relatively larger surface area, children are more susceptible to hypothermia resulting from the administration of unwarmed fluids and blood products. The use of overhead heat lamps, blood warmers, and prewarmed intravenous fluids helps obviate this condition.

Children with major injuries may cause fear and anxiety in even the most experienced emergency physician or surgeon. It is imperative to maintain careful vigilance and overcome any tendency to avoid indicated procedures.

For physiologic reasons, the expectant management of blunt hepatic or splenic injury has better success in the child than in the adult patient.[117-119] If stability exists, nonoperative management can ensue if capable personnel and resources are present.[120] CT scanning is the primary diagnostic agent in both the initial and the convalescent periods to define and grade solid organ injury. As for adults, this modality is insensitive for the discovery of hollow viscus and, to a lesser degree, pancreatic pathologic conditions.[71]

FAST has been found to be useful for the detection of free fluid and can be used in triage to send the unstable child with visualized hemoperitoneum for laparotomy.[121] However, FAST appears to have less sensitivity when compared with the adult experience. DPL, specifically peritoneal aspiration, can also uncover hemoperitoneum in the initial management of the critically, multiply injured child. Reliance on cell count alone has prompted significant nontherapeutic laparotomy rates.

In the course of expectant treatment, the child should undergo laparotomy if instability develops, transfusion requirements are excessive, peritoneal signs are unequivocal, or observation is not feasible because of associated injuries or lack of institutional resources. Closed head injury need not preclude nonoperative management of known solid parenchymal injury, but the risk associated with undiscovered and coincident hollow viscus perforation is greatly increased. The diagnostic approach to penetrating trauma in children is the same as that in adults.

Transfer. Trauma patients in rural settings may require a stabilizing damage control laparotomy by a general surgeon before being transferred to a trauma center for definitive care.

KEY CONCEPTS

- The accuracy of physical examination is limited in cases of blunt and penetrating trauma. It is rendered less reliable by distracting injury, altered sensorium (e.g., head trauma, alcohol or drug intoxication, developmental delay, psychiatric illness), and spinal cord injury.
- Implements and missiles frequently violate the lung parenchyma, diaphragm, mediastinum, intraperitoneal cavity, and retroperitoneum in some combination.
- The choice of diagnostic studies for abdominal trauma is based on clinical need first and foremost, as well as study availability and the accuracy of that study in a respective center.
- FAST and peritoneal aspiration are rapid methods of determining or excluding the presence of hemoperitoneum in the critically ill blunt or penetrating trauma patient. DPL is more sensitive but is invasive and therefore rarely used. FAST is noninvasive and can simultaneously evaluate for hemopericardium and pneumothorax and hemothorax.
- Clinical indications for laparotomy are more dependable in and more frequently applicable to cases of penetrating trauma than cases of blunt trauma.
- The critical determinant in hemodynamically unstable patients with pelvic fracture is the existence of active intraperitoneal hemorrhage. Discovery of this by FAST, CT scan, or peritoneal aspiration is an indication for laparotomy, whereas its absence prompts diagnostic and potentially therapeutic angiography.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Lawson CM, Daley BJ, Ormsby CB, Enderson B: Missed injuries in the era of the trauma scan. *J Trauma* 2011; 70:452.
2. Shaftan GW: Indications for operation in abdominal trauma. *Am J Surg* 1960; 99:657.
3. Velmahos GC, et al: Selective nonoperative management in 1,856 patients with abdominal gunshot wounds: Should routine laparotomy still be the standard of care? *Ann Emerg Med* 2001; 234:395.
4. Biffl W, Moore EE: Management guidelines for penetrating abdominal trauma. *Curr Opin Crit Care* 2010; 16:609.
5. Nicholas JM, et al: Changing patterns in the management of penetrating abdominal trauma: The more things change, the more they stay the same. *J Trauma* 2003; 55:1095.
6. Bernard SJ, Paulozzi LJ, Wallace DL; Centers for Disease Control and Prevention (CDC): Fatal injuries among children by race and ethnicity—United States, 1999-2002. *MMWR Surveill Summ* 2007; 56:1.
7. Hepburn L, Miller M, Azrael D, Hemenway D: The U.S. gun stock: Results from the 2004 national firearms survey. *Inj Prev* 2007; 13:15.
8. Centers for Disease Control and Prevention (CDC): *About Compressed Mortality, 1999-2007*. CDC WONDER online database. Available at http://wonder.cdc.gov/cmf-icd10.html. Accessed March 14, 2011.
9. Demetriades D, et al: High-level falls: Type and severity of injuries and survival outcome according to age. *J Trauma* 2005; 58:342.
10. Nance ML, ed: *National Trauma Data Bank 2011: Pediatric Report*. 2011, American College of Surgeons. Available at www.facs.org/trauma/ntdb/pdf/ntdbpediatricreport2011.pdf. Accessed February 13, 2012.
11. Friese RS, Coln E, Gentilello LM: Laparoscopy is sufficient to exclude occult diaphragm injury after penetrating abdominal wounds. *J Trauma* 2005; 58:789.
12. Leppäniemi A, Haapiainen R: Occult diaphragmatic injuries caused by stab wounds. *J Trauma* 2003; 55:646.
13. McCarthy MC, Lowdermilk GA, Canal DF, Broadie TA: Prediction of injury caused by penetrating wounds to the abdomen, flank and back. *Arch Surg* 1991; 128:926.
14. Boyle EM Jr, et al: Diagnosis of injuries after stab wounds to the back and flank. *J Trauma* 1997; 42:260.
15. DeMuth WE Jr: Bullet velocity and design as determinants of wounding capability: An experimental study. *J Trauma* 1966; 6:222.
16. Velitchkov NG, et al: Delayed small bowel injury as a result of penetrating extraperitoneal high-velocity ballistic trauma to the abdomen. *J Trauma* 2000; 48:169.
17. Cairns BA, et al: Management and outcome of abdominal shotgun wounds trauma score and the role of exploratory laparotomy. *Ann Surg* 1995; 221:272.
18. Rivara FP, Koepsell TD, Grossman DC, Mock C: Effectiveness of automatic shoulder belt systems in motor vehicle crashes. *JAMA* 2000; 283:2826.
19. Velmahos GC, Tatevossian R, Demetriades D: The "seat belt mark" sign: A call for increased vigilance among physicians treating victims of motor vehicle accidents. *Am Surg* 65:181, 1999.
20. Prince JS, LoSasso BE, Senac MO Jr: Unusual seat-belt injuries in children. *J Trauma* 2004; 56:420.
21. Spoormans I, Van Hoorenbeeck K, Balliu L, Jorens PG: Gastric perforation after cardiopulmonary resuscitation: Review of the literature. *Resuscitation* 2010; 81:272.
22. Ko CW, Dominitz, JA: Complications of colonoscopy: Magnitude and management. *Gastrointest Endosc Clin N Am* 2010; 20:659.
23. Lin BC, et al: Management of blunt major pancreatic injury. *J Trauma* 2004; 56:774.
24. Mahoney EJ, Biffl WL, Harrington DT, Cioffi WG: Isolated brain injury as a cause of hypotension in the blunt trauma patient. *J Trauma* 2003; 55:1065.
25. Brown CK, Dunn KA, Wilson K: Diagnostic evaluation of patients with blunt abdominal trauma: A decision analysis. *Acad Emerg Med* 2000; 7:385.
26. Gonzalez RP, Dziurzynski K, Maunu M: Emergent extra-abdominal trauma surgery: Is abdominal screening necessary? *J Trauma* 2000; 49:195.
27. Shlamovitz GZ, et al: Poor test characteristics for the digital rectal examination in trauma patients. *Ann Emerg Med* 2007; 50:25.
28. Esposito TJ, et al: Reasons to omit digital rectal exam in trauma patients: No fingers, no rectum, no useful additional information. *J Trauma* 2005; 59:1314.
29. Ball CG, et al: Traumatic urethral injuries: Does the digital rectal examination really help us? *Injury* 2009; 40:984.
30. Pryor JP, Reilly PM, Dabrowski GP, Grossman MD, Schwab CW: Nonoperative management of abdominal gunshot wounds. *Ann Emerg Med* 2004; 43:344.
31. Thal ER: Evaluation of peritoneal lavage and local exploration in lower chest and abdominal stab wounds. *J Trauma* 1977; 17:642.
32. Moore EE, Marx JA: Penetrating abdominal wounds. Rationale for exploratory laparotomy. *JAMA* 1985; 253:2705.
33. Asimos AW, et al: Value of point-of-care blood testing in emergent trauma management. *J Trauma* 2000; 48:1101.
34. Moore FD: The effects of hemorrhage on body composition. *N Engl J Med* 1965; 273:567.
35. Herman R, Guire KE, Burd RS, Mooney DP, Ehlrich PF: Utility of amylase and lipase as predictors of grade of injury or outcomes in pediatric patients with pancreatic trauma. *J Pediatr Surg* 2011; 46:923.
36. Holmes JF, et al: Identification of children with intra-abdominal injuries after blunt trauma. *Ann Emerg Med* 2002; 39:500.
37. Sola JE, et al: Pediatric FAST and elevated liver transaminases: An effective screening tool in blunt abdominal trauma. *J Surg Res* 2009; 157:103.
38. Langdorf MI, et al: Decision rule and utility of routine urine toxicology screening of trauma patients. *Eur J Emerg Med* 9:115, 2002.
39. Miller LA, Shanmuganathan K: Multidetector CT evaluation of abdominal trauma. *Radiol Clin North Am* 2005; 43:1079.
40. Haan JM, et al: Splenic embolization revisited: A multicenter review. *J Trauma* 2004; 56:542.
41. Hauser CJ, et al: Prospective Validation of computed tomographic screening of the thoracolumbar spine in trauma. *J Trauma* 2003; 55:228.
42. Charbit J, et al: What are the specific computed tomography scan criteria that can predict or exclude the need for renal angioembolization after high-grade renal trauma in a conservation management strategy? *J Trauma* 2011; 70:1219.
43. Maturen KE, et al: Contrast-enhanced CT accurately detects hemorrhage in torso trauma: Direct comparison with angiography. *J Trauma* 2007; 62:740.
44. Lee SK, Carrillo EH: Advances and changes in the management of liver injuries. *Am Surg* 2007; 73:201.
45. Harbrecht BG, et al: Evaluation of a 15-year experience with splenic injuries in a state trauma system. *Surgery* 2007; 141:229.
46. Weninger P, et al: Emergency room management of patients with blunt major trauma: Evaluation of the multislice computed tomography protocol exemplified by an urban trauma center. *J Trauma* 2007; 62:584.
47. Elton C, et al: Accuracy of computed tomography in the detection of blunt bowel and mesenteric injuries. *Br J Surg* 2005; 92:1024.
48. Stuhlfaut JW, et al: Blunt abdominal trauma: Performance of CT without oral contrast material. *Radiology* 2004; 233:689.
49. Marx JA: So what's a little free fluid? *Acad Emerg Med* 2000; 7:383.
50. Stuhlfaut JW, Lucey BC, Varghese JC, Soto JA: Blunt abdominal trauma: Utility of 5-minute delayed CT with a reduced radiation dose. *Radiology* 2006; 238:473.
51. Brenner DJ, Hall EJ: Computed tomography—an increasing source of radiation exposure. *N Engl J Med* 2007; 357:2277.
52. Salottolo K, et al: Current utilization and radiation dose from computed tomography in patients with trauma. *Crit Care Med* 2009; 37:1336.
53. Holmes JF, Wisner DH, McGahan JP, Mower WR, Kuppermann N: Clinical prediction rules for identifying adults at very low risk for intra-abdominal injuries after blunt trauma. *Ann Emerg Med* 2009; 54:575.
54. Holmes JF, et al: Validation of a prediction rule for the identification of children with intra-abdominal injuries after blunt torso trauma. *Ann Emerg Med* 2009; 54:528.
55. Gupta R, Greer SE, Martin ED: Inefficiencies in a rural trauma system: The burden of repeat imaging in interfacility transfers. *J Trauma* 2010; 69:253.
56. Cook SH, Fielding JR, Phillips JD: Repeat abdominal computed tomography scans after pediatric blunt abdominal trauma: Missed injuries, extra costs, and unnecessary radiation exposure. *J Pediatr Surg* 2010; 45:2019.
57. Timaran CH, Daley BJ, Enderson BL: Role of blunt abdominal trauma in the diagnosis of blunt duodenal injury. *J Trauma* 2001; 51:648.
58. Antoniou D, Zarifi M, Gentimi F, Christopoulos-Geroulanos G: Sonographic diagnosis and monitoring of an intramural duodenal hematoma following upper endoscopic biopsy in a child. *J Clin Ultrasound* 2009; 37:534.

www.ketabpezeshki.com 66485457-66963820

59. Raikhlin A, Baerlocher MO, Asch MR, Myers A: Imaging and transcatheter arterial embolization for traumatic splenic injuries: Review of the literature. *Can J Surg* 2008; 51:464.
60. Duchesne JC, Simmons JD, Schmieg RE Jr, McSwain NE Jr, Bellows CF: Proximal splenic angioembolization does not improve outcomes in treating blunt splenic injuries compared with splenectomy: A cohort analysis. *J Trauma* 2008; 65:1346.
61. Boulanger BR, Kearney PA, Tsuei B, Ochoa JB: The routine use of sonography in penetrating torso injury is beneficial. *J Trauma* 2001; 51:320.
62. Dolich MO, et al: 2576 ultrasounds for blunt abdominal trauma. *J Trauma* 2001; 50:108.
63. Hyacinthe AC, et al: Diagnostic accuracy of ultrasonography in the acute assessment of common thoracic lesions after trauma. *Chest* 2012; 141:1177-1183.
64. Blackbourne LH, et al: Secondary ultrasound examination increases the sensitivity of the FAST exam in blunt trauma. *J Trauma* 2004; 57:934.
65. Henderson SO, Sung J, Mandavia D: Serial abdominal ultrasound in the setting of trauma. *J Emerg Med* 2000; 18:79.
66. Kirkpatrick AW, et al: Hand-held thoracic sonography for detecting post-traumatic pneumothoraces: The extended focused assessment with sonography for trauma (E-FAST). *J Trauma* 2004; 57:288.
67. Ollerton JE, et al: Prospective study to evaluate the influence of FAST on trauma patient management. *J Trauma* 2006; 60:785.
68. Melniker LA, et al: Randomized controlled clinical trial of point-of-care, limited ultrasonography for trauma in the emergency department: The first sonography outcomes assessment program trial. *Ann Emerg Med* 2006; 48:227.
69. Lee BC, Ormsby EL, McGahan JP, Melendres GM, Richards JR: The utility of sonography for the triage of blunt abdominal trauma patients to exploratory laparotomy. *AJR Am J Roentgenol* 2007; 188:415.
70. Miller MT, Pasquale MD, Bromberg WJ, Wasser TE, Cox J: Not so FAST. *J Trauma* 2003; 54:52.
71. Goodwin H, Holmes JF, Wisner DH: Abdominal ultrasound examination in pregnant blunt trauma patients. *J Trauma* 2001; 50:689.
72. Fakhry SM, Brownstein M, Watts DD, Baker CC, Oller D: Relatively short diagnostic delays (<8 hours) produce morbidity and mortality in blunt small bowel injury: An analysis of time to operative intervention in 198 patients from a multicenter experience. *J Trauma* 2000; 48:408.
73. Cha JY, et al: Diagnostic peritoneal lavage remains a valuable adjunct to modern imaging techniques. *J Trauma* 2009; 67:330.
74. Williams MD, Watts D, Fakhry S: Colon injury after blunt abdominal trauma: Results of the EAST Multi-Institutional Hollow Viscus Injury Study. *J Trauma* 2003; 55:906.
75. Nagy KK, et al: Experience with over 2500 diagnostic peritoneal lavages. *Injury* 2000; 31:479.
76. Henneman PL, Marx JA, Moore EE, Cantrill SV, Ammons LA: Diagnostic peritoneal lavage: Accuracy in predicting necessary laparotomy following blunt and penetrating trauma. *J Trauma* 1990; 30:1345.
77. Smith CB, et al: Prediction of blunt traumatic injury in high-acuity patients: Bedside examination vs computed tomography. *Am J Emerg Med* 2011; 29:1.
78. Thacker LK, Parks J, Thal ER: Diagnostic peritoneal lavage: Is 100,000 RBCs a valid figure for penetrating abdominal trauma? *J Trauma* 2007; 62:853.
79. Gonzalez RP, Turk B, Falimirski ME, Holevar MR: Abdominal stab wounds: Diagnostic peritoneal lavage criteria for emergency room discharge. *J Trauma* 2001; 51:939.
80. Sugrue M, et al: Guidelines for the management of haemodynamically stable patients with stab wounds to the anterior abdomen. *ANZ J Surg* 2007; 77:614.
81. Leppäniemi A, Haapiainen R: Diagnostic laparoscopy in abdominal stab wounds: A prospective, randomized study. *J Trauma* 2003; 55:636.
82. Kawahara NT, Alster C, Fujimura I, et al: Standard examination system for laparoscopy in penetrating abdominal trauma. *J Trauma* 2009; 67:589-595.
83. Simon RJ, Rabin J, Kuhls D: Impact of increased use of laparoscopy on negative laparotomy rates after penetrating trauma. *J Trauma* 2002; 53:297.
84. Ahmed N, Whelan J, Brownlee J, Chari V, Chung R: The contribution of laparoscopy in evaluation of penetrating abdominal wounds. *J Am Coll Surg* 2005; 201:213.
85. Cotton BA, et al: Guidelines for prehospital fluid resuscitation in the injured patient. *J Trauma* 2009; 67:389.
86. Cudnik MT, Newgard CD, Sayre MR, Steinberg SM: Level I versus Level II trauma centers: An outcomes-based assessment. *J Trauma* 2009; 66:1321.
87. Luchette FA, et al: Practice management guidelines for prophylactic antibiotic use in penetrating abdominal trauma: The EAST Practice Management Guidelines Work Group. *J Trauma* 2000; 48:508.
88. Gilbert DN, et al: *The Sanford Guide to Antimicrobial Therapy*. Sperryville, VA: Antimicrobial Therapy Inc.; 2008.
89. Conrad MF, Patton JH Jr, Parikshak M, Kralovich KA: Selective management of penetrating truncal injuries: Is emergency department discharge a reasonable goal? *Am Surg* 2003; 69:266.
90. Plackett TP, Fleurat J, Putty B, Demetriades D, Plurad D: Selective nonoperative management of anterior abdominal stab wounds: 1992-2008. *J Trauma* 2011; 70:408.
91. Mitra B, Gocentas R, O'Reilly G, Cameron PA, Atkin C: Management of haemodynamically stable patients with abdominal stab wounds. *Emerg Med Australas* 2007; 19:269.
92. Alzamel HA, Cohn SM: When is it safe to discharge asymptomatic patients with abdominal stab wounds? *J Trauma* 2005; 58:523.
93. Demetriades D, et al: Selective nonoperative management of penetrating abdominal solid organ injuries. *Ann Surg* 2006; 244:620.
94. Leppäniemi AK, Voutilainen PE, Haapiainen RK: Indications for early mandatory laparotomy in abdominal stab wounds. *Br J Surg* 1999; 86:76.
95. Nagy K, Roberts R, Joseph K, An G, Barrett J: Evisceration after abdominal stab wounds: Is laparotomy required? *J Trauma* 1999; 47:622.
96. Arikan S, Kocakusak A, Yucel AF, Adas G: A prospective comparison of the selective observation and routine exploration methods for penetrating abdominal stab wounds with organ or omentum evisceration. *J Trauma* 2005; 58:526.
97. Ertekin C, Yanar H, Taviloglu K, Güloglu R, Alimoglu O: Unnecessary laparotomy by using physical examination and different diagnostic modalities for penetrating abdominal stab wounds. *Emerg Med J* 2005; 22:790.
98. Udobi KF, Rodriguez A, Chiu WC, Scalea TM: Role of ultrasonography in penetrating abdominal trauma: A prospective clinical study. *J Trauma* 2001; 50:475.
99. Murphy JT, Hall J, Provost D: Fascial ultrasound for evaluation of anterior abdominal stab wound injury. *J Trauma* 2005; 59:843.
100. Sriussadaporn S, et al: Clinical uses of diagnostic peritoneal lavage in stab wounds of the anterior abdomen: A prospective study. *Eur J Surg* 2002; 168:490.
101. Shanmuganathan K, et al: Penetrating torso trauma: Triple-contrast helical CT in peritoneal violation and organ injury—a prospective study in 200 patients. *Radiology* 2004; 231:775.
102. Chiu WC, Shanmuganathan K, Mirvis SE, Scalea TM: Determining the need for laparotomy in penetrating torso trauma: A prospective study using triple contrast enhanced abdominopelvic computed tomography. *J Trauma* 2001; 51:860.
103. Velmahos GC, et al: Abdominal computed tomographic scan for patients with gunshot wounds to the abdomen selected for nonoperative management. *J Trauma* 2005; 59:1155.
104. Stein DM, et al: Accuracy of computed tomography (CT) scan in the detection of penetrating diaphragm injury. *J Trauma* 2007; 63:538.
105. Tayal VS, Beatty MA, Marx JA, Tomaszewski CA, Thomason MH: FAST accurate for cardiac and intraperitoneal injury in penetrating chest trauma. *Acad Emerg Med* 2000; 7:493.
106. Brakenridge SC, et al: Detection of intra-abdominal injury using diagnostic peritoneal lavage after shotgun wound to abdomen. *J Trauma* 2003; 54:329.
107. Bode PJ, Edwards MJ, Kruit MC, van Vugt AB: Sonography in clinical algorithm for early evaluation of 1671 patients with blunt abdominal trauma. *AJR Am J Roentgenol* 1999; 172:905.
108. Salim A, et al: Whole body imaging in blunt multisystem trauma patients without obvious signs of injury: Results of a prospective study. *Arch Surg* 2006; 141:468.
109. Poletti PA, et al: Blunt abdominal trauma patients: Can organ injury be excluded without performing computed tomography? *J Trauma* 2004; 57:1072.
110. Gonzalez RP, Han M, Turk B, Luterman A: Screening for abdominal injury prior to emergent extra-abdominal trauma surgery: A prospective study. *J Trauma* 2004; 57:739.
111. Farahmand N, et al: Hypotensive patients with blunt abdominal trauma: Performance of screening US. *Radiology* 2005; 235:436.
112. Runyon M, Marx JA: *Peritoneal procedures*. In: Roberts JR, Hedges JR, eds. *Clinical Procedures in Emergency Medicine*, 5th ed. Philadelphia: WB Saunders; 2009.
113. Holmes JF, Harris D, Battistella FD: Performance of abdominal ultrasonography in blunt trauma patients with out of hospital or emergency department hypotension. *Ann Emerg Med* 2004; 43:354.

www.ketabpezeshki.com 66485457-66963820

114. Rathore MA, Andrabi SI, Najfi SM, Chaudhry Z, Chaudhry AM: Injuries to the duodenum—prognosis correlates with body Injury Severity Score: A prospective study. *Int J Surg* 2007; 5:388.
115. Tayal VS, et al: Accuracy of trauma ultrasound in major pelvic injury. *J Trauma* 2006; 61:1453.
116. Nwomeh BC, et al: Contrast extravasation predicts the need for operative intervention in children with blunt splenic trauma. *J Trauma* 2004; 56:537.
117. St Peter SD, Keckler SJ, Spilde TL, Holcomb GW 3rd, Ostlie DJ: Justification for an abbreviated protocol in the management of blunt spleen and liver injury in children. *J Pediatr Surg* 2008; 43:191.
118. Davis DH, Localio AR, Stafford PW, Helfaer MA, Durbin DR: Trends in operative management of pediatric splenic injury in a regional trauma system. *Pediatrics* 2005; 115:89.
119. Eppich WJ, Zonfrillo MR: Emergency department evaluation and management of blunt abdominal trauma in children. *Curr Opin Pediatr* 2007; 19:265.
120. Mattix KD, et al: Pediatric pancreatic trauma: Predictors of nonoperative management failure and associated outcomes. *J Pediatr Surg* 2007; 42:340.
121. Weinberg JA, et al: Trauma laparotomy in a rural setting before transfer to a regional center: Does it save lives? *J Trauma* 2003; 54:823.

www.ketabpezeshki.com 66485457-66963820

Chapter 47

Genitourinary System

Michael S. Runyon

PERSPECTIVE

Despite considerable advances in the initial evaluation and management of the severely injured patient, confusion remains regarding the recognition and subsequent management of genitourinary trauma. Only major renovascular injuries or a severely shattered kidney, both of which are rare, portend a rapid death. Thus most genitourinary injuries pale in comparison with the potential immediate life threats posed by concomitant injuries to the head, chest, and abdomen. The urinary tract as an anatomically injured system is by necessity relegated to a position of secondary importance. Nevertheless, to maintain clinical excellence and expertise in the overall treatment of all injured patients, the emergency physician should have a thorough understanding of the global spectrum of genitourinary injury and how it can affect patient outcomes.

Genitourinary trauma is frequently a covert entity and is associated with a wide array of injury. Approximately 10% of all multiply injured patients have some manifestation of genitourinary involvement.[1] Because of its relatively infrequent occurrence and often subtle presentation, it may be overlooked in the initial evaluation of the multiply injured patient. Prompt identification and appropriate management of genitourinary injuries can minimize potential long-term complications, including renal insufficiency, chronic hypertension, incontinence, and sexual dysfunction. The astute emergency physician can accomplish these goals by a stepwise evaluation that considers the mechanism of injury, pertinent physical examination findings, urinalysis, and adjunctive diagnostic imaging.

For the stable patient, the urinary tract is unique in that diagnostic evaluation is done in a retrograde fashion—that is, clinical suggestion and elimination of urethral injury before bladder injury before ureteral or renal injury. Adherence to this axiom enables the discovery of virtually any important urinary tract injury. Deviations from this practice may be necessary when life-threatening renal injuries are suspected.

Definitions

For purposes of investigation and staging of urologic injuries, genitourinary trauma is divided into lower tract (bladder or urethral injury), upper tract (renal or ureteral injury), and external genitalia (penile, scrotal, testicular, and vulvar injury). Each category is further subdivided on the basis of a blunt or penetrating mechanism of injury.

Historical Perspective

The basic tenets of lower urinary tract injury have not changed appreciably in recent decades. A thoroughly performed physical examination, pelvic radiography, and the recognition of gross hematuria or blood at the urethral meatus identify virtually all significant lower urinary tract injuries. Major advances in the identification of significant upper tract genitourinary injuries, their clinical markers, and ultimate staging procedures have come to the forefront over the last few decades. Before 1985, all trauma patients with any amount of microhematuria were labeled "at risk" for genitourinary injury and underwent intravenous pyelography. This was neither diagnostically definitive nor cost-effective and simply perpetuated the existing confusion and controversy. In 1985, Nicolaisen and colleagues published the first of a series of articles that established guidelines for identifying significant upper tract genitourinary injuries, their markers, and the diagnostic studies that define the exact extent of these injuries and aid in subsequent patient management.[2] In addition, the advent of ultrasonography has greatly simplified the diagnosis and management of external genitalia trauma.

CLINICAL FEATURES

The symptoms, signs, and examination findings of genitourinary trauma are varied and nonspecific. Acutely, these may include flank, abdominal, rib, back, pelvic, or scrotal pain; urinary retention; penile or scrotal ecchymosis or hematoma; and blood at the urethral meatus. Renovascular hypertension, incontinence, or sexual dysfunction may be the only findings weeks to months after injury.

Physical Examination

Examination of the torso and pelvis during the secondary survey is the first step in the evaluation for urologic injury. Any evidence of abdominal tenderness or low anterior pelvic injury should alert the examining physician to the possibility of a bladder rupture in addition to other intra-abdominal injuries. This likelihood increases significantly in the presence of a pelvic fracture. Tenderness elicited by pelvic compression or palpation of the pelvic girdle or pubic symphysis supports the diagnosis of a potential pelvic fracture and the possibility of lower urinary tract injury.

Examination of the genitalia can be informative. The emergency physician should examine for evidence of hematoma or

www.ketabpezeshki.com 66485457-66963820

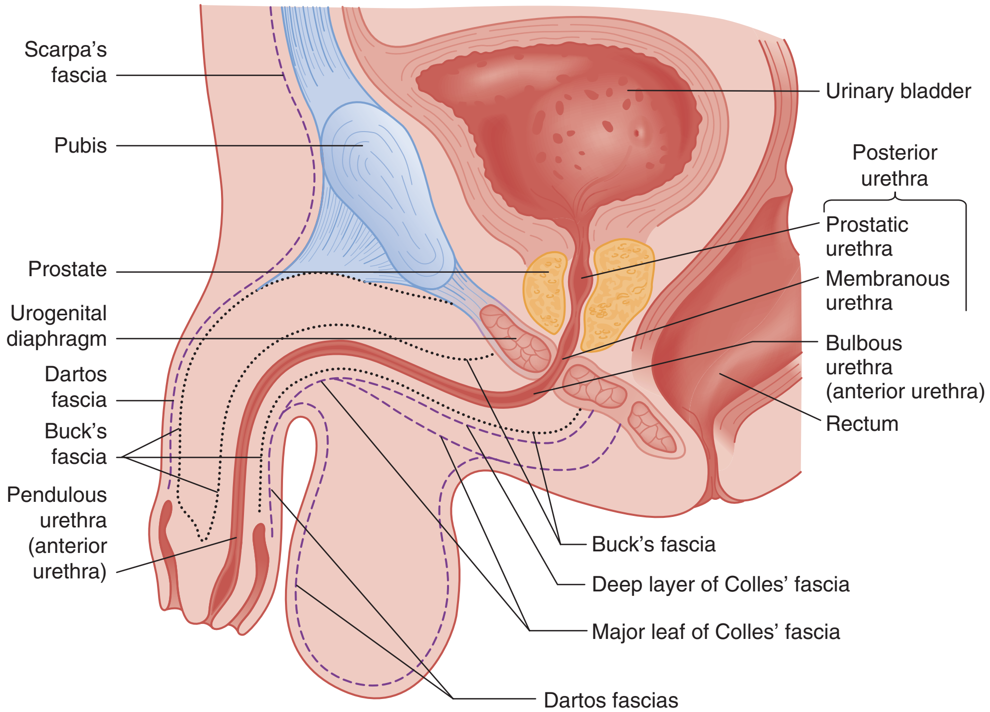


Figure 47-1. Anatomy of male genitalia.

ecchymosis of the penile shaft, scrotal skin, or perineum. Gross blood at the urethral meatus is suggestive of a urethral injury and suggests the need for retrograde urethrography. In circumstances in which emergency surgical exploration for life-threatening injuries is indicated, retrograde urethrography can be performed in the operating room or after the operative procedure. For the male patient, classic teaching dictates that a Foley catheter should never be introduced when urethral injury is possible without prior evaluation of urethral integrity by retrograde urethrography. The concern is that trauma from the catheter placement may convert a partial urethral tear into a complete disruption. Although the literature on this topic is sorely lacking, one small retrospective review of 13 cases of urethral injury demonstrated no evidence that a careful blind attempt to insert a urinary catheter worsened the initial injury.[3]

Careful inspection for blood at the vaginal introitus is particularly important in the female patient known to have a pelvic fracture. A vaginal examination can discern vaginal lacerations or urethral disruption caused by displaced bony pelvic fracture fragments. This examination should be conducted carefully so as to protect the hands of the examiner from injury as well as to prevent worsening of the injuries themselves. Urethral injuries are uncommon in female patients owing to the short length and increased mobility of the female urethra and the relative protection from injury afforded by the symphysis pubis. Unlike with male urethral injuries, urethrography is technically difficult and not routinely recommended in females with suspected urethral injury. The inability to pass a Foley catheter in a premenopausal female patient with a pelvic fracture signifies the potential for urethral injury and possible need for suprapubic urinary drainage. Successful passage of a Foley catheter in a patient with blood at the vaginal introitus does not exclude urethral injury, however, and these worrisome physical examination findings are conveyed to the urologist, who can plan subsequent endoscopic or radiographic urethral evaluation accordingly.[4-6] In an older postmenopausal female trauma patient, urethral injury is distinguished from a superiorly retracted urethral meatus and accompanying meatal stenosis. These preexisting conditions are common in an atrophic vaginal setting, and a 12- or 14-Fr coudé or Foley catheter usually is required to achieve successful bladder access.

The digital rectal examination evaluates sphincter tone, bowel wall integrity, the presence or absence of gross blood, and the position of the prostate. Normally the posterior lobe of the prostate is palpable and well defined (Fig. 47-1). A pelvic fracture may disrupt the puboprostatic ligaments and the prostatomembranous urethra, resulting in significant retropubic venous bleeding. This may produce a large pelvic hematoma that can displace the prostate superiorly, resulting in a boggy, ill-defined mass on rectal examination (Fig. 47-2). Although it has long been recommended as part of the routine evaluation of all trauma patients, multiple studies have questioned the utility of the rectal examination in this setting and have specifically demonstrated that a palpably abnormal prostate is an insensitive indicator of urethral injury.[7-10] Thus the decision to evaluate for urethral injury should consider additional clinical features, especially the presence or absence of gross hematuria or blood at the urethral meatus, and not rely on the findings of the rectal examination.

Foley Catheter

In any significantly injured trauma patient with a major mechanism of injury and the absence of any findings suggestive of urethral injury, a Foley catheter should be passed into the bladder. The initial bladder effluent should be observed by the physician. Because of its importance in dictating subsequent patient evaluation, gross hematuria is conservatively defined as any color to the urine other than clear or yellow. The presence of gross hematuria indicates urologic injury until proven otherwise. Rarely, severe rhabdomyolysis produces large quantities of urine myoglobin, the gross appearance of which can be confused with gross hematuria. In these cases, urinalysis documents the absence of red blood cells (RBCs) consistent with myoglobinuria. Most significant lower urinary tract injuries are accompanied by a pelvic fracture, blood at the urethral meatus, or gross hematuria on spontaneous voiding or Foley catheter placement. However, injuries to the upper tract tend to be more subtle. They are often coincident with

www.ketabpezeshki.com 66485457-66963820

nonurologic organ disruption, the bleeding from which can be life-threatening. These events may dictate rapid volume resuscitation that can clear gross hematuria quickly. Moreover, some significant upper tract injuries, including blunt injury to the renovascular pedicle or penetrating ureteral injury, may not produce gross or even microscopic hematuria.

LOWER URINARY TRACT

URETHRAL TRAUMA

Anatomy

The urogenital diaphragm divides the anterior (bulbous and pendulous) urethra from the posterior (membranous and prostatic) urethra. Contrary to early descriptions, the urogenital diaphragm does not completely encircle the membranous urethra, but rather forms an incomplete sling that offers posterior and lateral support.[5] The prostatic urethra is attached to the posterior symphysis pubis by the puboprostatic ligaments. A fracture of the pelvis with displacement of the symphysis may result in a laceration or avulsion of the prostatic urethra because of the shearing force on the fixed prostatic and membranous urethra. Injuries to the anterior and posterior urethra are caused by different mechanisms, involve different symptoms, and are treated differently.

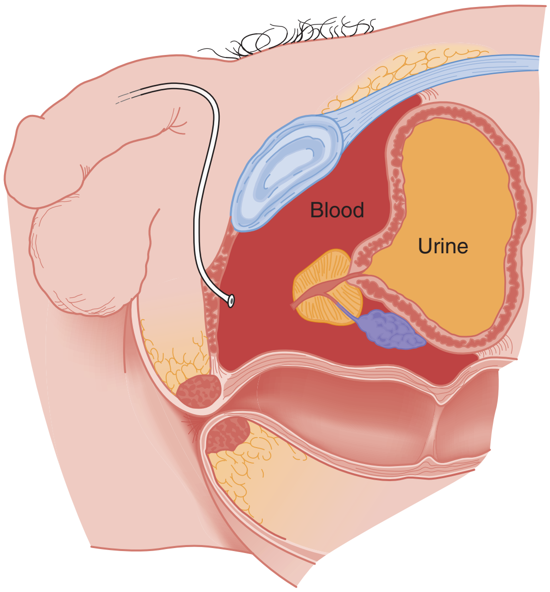


Figure 47-2. Injury to the posterior (membranous) urethra. The prostate has been avulsed from the membranous urethra secondary to fracture of the pelvis. Extravasation occurs above the triangular ligament and is periprostatic and perivesical. (From McAninch JW: Injuries to the Genitourinary Tract. In Tanagho EA, McAninch JW [eds]: Smith's General Urology, 14th ed. Norwalk, Conn, Appleton & Lange, 1995.)

Pathophysiology

Urethral disruption is the most significant injury to be identified. Failure to do so may lead to significant morbidity. Overly aggressive urethral manipulation can convert a partial urethral tear into a complete tear, thus precluding accurate assessment of urinary output and subsequently potentiating the long-term complications of urethral trauma (e.g., urethral stricture formation and urinary incontinence). Anterior urethral injuries are most often caused by straddle injuries, falls, gunshot wounds, and self-instrumentation (Fig. 47-3).

Pelvic fractures account for most posterior urethral injuries (see Fig. 47-2). The risk of urethral injury varies with the specific type of pelvic fracture. High-risk fractures include the straddle fracture, in which all four pubic rami are involved, and the Malgaigne fracture, which involves fracture and displacement of the hemipelvis—that is, both ischiopubic rami anteriorly and the ipsilateral sacrum, sacroiliac joint, or ilium posteriorly. Urethral injuries are rarely associated with fractures that do not involve the ischiopubic rami.[5,11] In a prospective, single-center study of 203 consecutive male patients with pelvic fractures, 51 sustained urethral injuries. Malgaigne and straddle fractures were significantly associated with urethral injuries, with odds ratios of 3.4 and 3.85, respectively. In the same series, the highest risk for urethral injury was seen in patients sustaining a straddle fracture with concurrent sacroiliac diastasis (odds ratio 24). Among those sustaining fractures not involving the anterior pelvic arch, none had urinary tract injury.[11]

Clinical Features

During the secondary survey, examination of the lower abdomen, pelvis, and genitalia provides both direct and indirect evidence to support or refute urethral injury. Urethral integrity is supported by lack of pelvic and suprapubic tenderness; absence of penile,

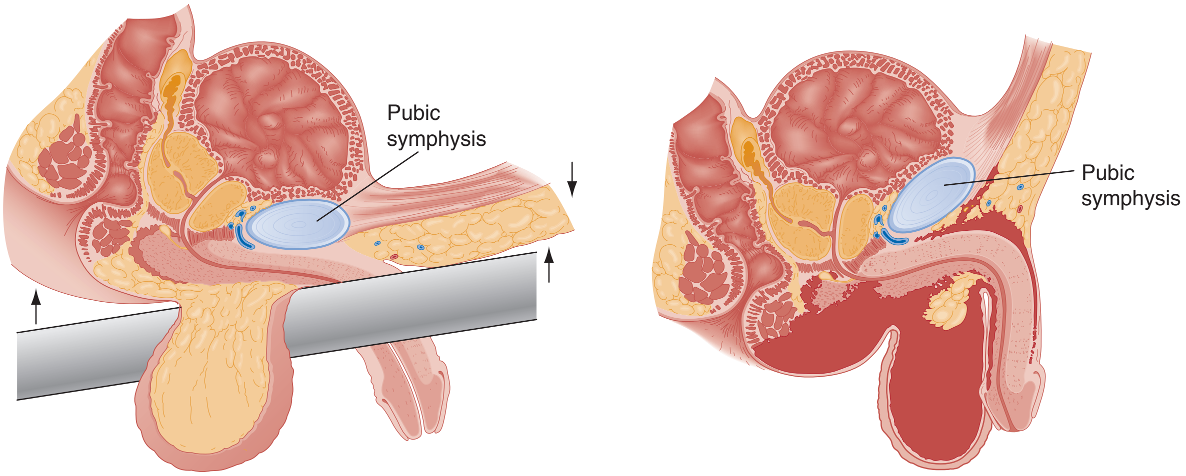


Figure 47-3. Injury to the bulbous urethra. *Left:* Mechanism: Usually a perineal blow or fall astride an object, crushing the urethra against inferior edge of pubic symphysis. *Right:* Extravasation of blood and urine enclosed within Colles' fascia. (From McAninch JW: Injuries to the Genitourinary Tract. In Tanagho EA, McAninch JW [eds]: Smith's General Urology, 14th ed. Norwalk, Conn, Appleton & Lange, 1995.)

www.ketabpezeshki.com 66485457-66963820

scrotal, or perineal hematoma; and lack of blood at the urethral meatus. These physical findings permit the safe passage of a 14- or 16-Fr Foley catheter into the bladder if the patient is unable to void and provide a suitable specimen for evaluation.

Diagnostic Strategies

Catheter Placement

The following technique for catheter placement assumes a normal urethra and includes the use of sterile technique, proper control of the foreskin, the use of copious amounts of lubricating jelly, and the gentle passage of a 14- or 16-Fr Foley or coudé catheter into the bladder. In all uncircumcised patients, continuous foreskin retraction with a folded 4 × 4-inch gauze pad is necessary to control the foreskin during catheter placement (Fig. 47-4). Without

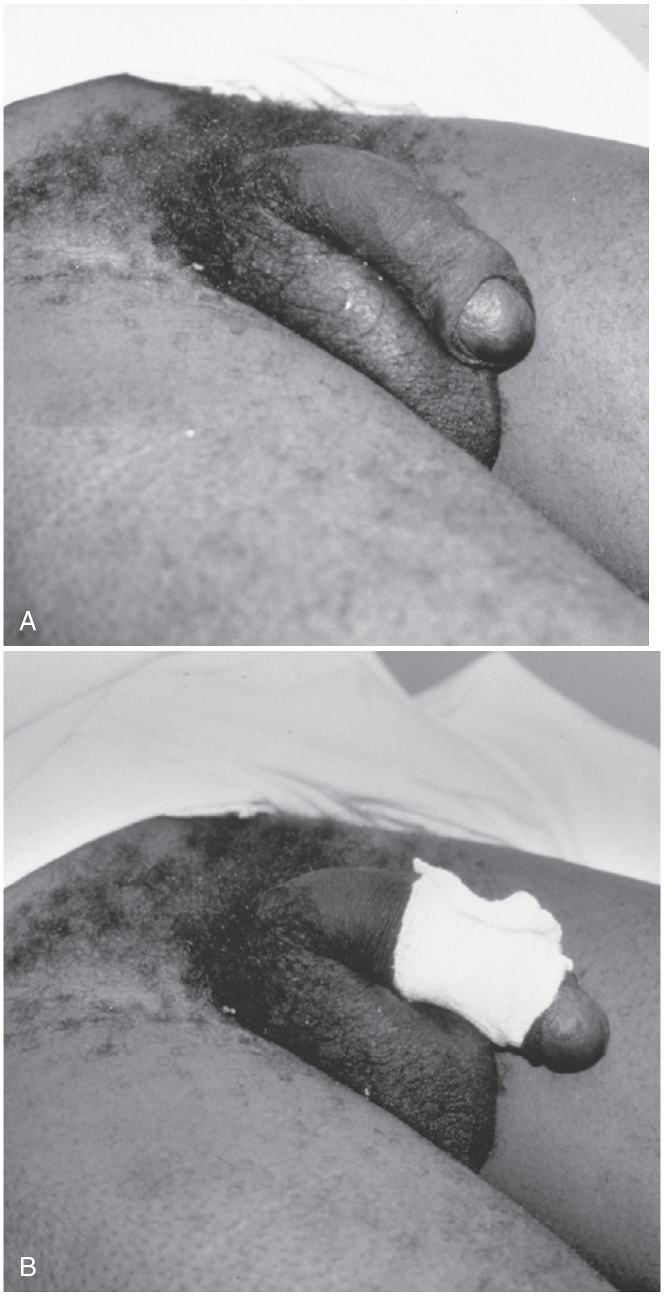


Figure 47-4. **A,** A normal uncircumcised man. **B,** Foreskin has been retracted and a folded 4 × 4-inch gauge sponge wrapped around it to prevent foreskin reduction during instrumentation.

this maneuver, the foreskin tends to repeatedly reduce itself over the glans penis, which contaminates the field and complicates the catheterization attempt. Slight resistance to the advancing catheter should be expected secondary to voluntary contraction of the external sphincter. This is more apt to occur in a combative, anxious trauma patient than in a cooperative or unconscious patient. When this occurs, the patient should be reassured and asked to relax the perineum and rectal area while gentle advancing pressure is applied to the catheter. This combined approach allows the catheter to navigate the external sphincter successfully and pass easily into the bladder. If reassurance and relaxation do not allow easy passage of the catheter in a male patient with clinical features suggestive of urethral injury, it should be removed and retrograde urethrography performed. The catheter is passed to its fullest extent to ensure that the balloon is completely in the bladder when inflated, The catheter is then withdrawn to the point of balloon approximation with the bladder neck, secured to the patient's leg to prevent accidental dislodgement, and left to drain. Inflation of the catheter balloon under any other circumstances may result in iatrogenic urethral trauma.

Successful passage of a Foley catheter precludes a complete urethral disruption. Nonetheless, the possibility of a partial urethral injury not manifested by history, mechanism of injury, or physical examination does exist. If a possible urethral injury is suggested by physical examination findings before the placement of a Foley catheter, a retrograde urethrogram should be obtained. The presence of urethral extravasation together with contrast material filling the bladder is diagnostic of a partial urethral injury (Fig. 47-5). Identification of a partial urethral injury enables one careful attempt at urethral placement of a 12- or 14-Fr Foley or coudé catheter, depending on the size of the patient.[6] If any difficulty is encountered, the catheter should be removed and a urologist consulted. If a partial urethral tear is suggested subsequent to successful passage of a Foley catheter, a small feeding tube can be placed alongside the urethral catheter and a modified retrograde urethrogram obtained. In this circumstance the urethrogram is for documentation and subsequent management purposes only because appropriate therapy (Foley catheter drainage) has already been instituted.

Radiology

In male patients with possible urethral injury, retrograde urethrography is the diagnostic procedure of choice. Retrograde

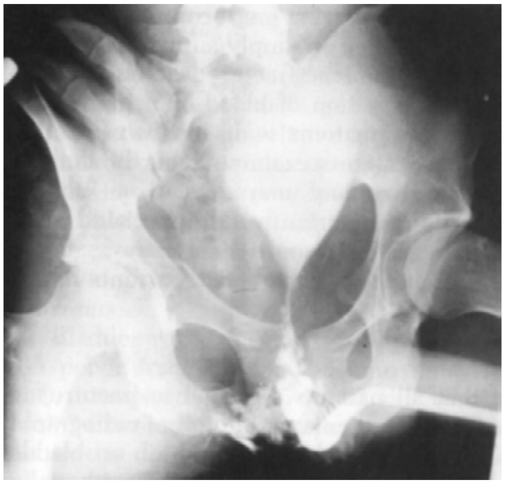


Figure 47-5. Retrograde urethrogram demonstrates a partial urethral disruption. Note the elongation of the posterior urethra with filling of the bladder. (From Spirnak JP: Pelvic fracture and injury to the lower urinary tract. Surg Clin North Am 68:1057, 1988.)

www.ketabpezeshki.com 66485457-66963820

urethrography is not an emergency procedure and should follow more critical diagnostic and resuscitative measures.

In a patient with a pelvic fracture, the entire retrograde urethrogram should be obtained with the patient in the supine position. Although some authors recommend oblique films for portions of the retrograde urethrogram to enhance urethral definition, these views add little information to a good supine study. More important, pelvic fractures are often associated with significant venous bleeding and hematoma formation. Maintenance of this stable hematoma can be crucial in the initial hemodynamic resuscitation of the patient. Any patient movement from the supine to the oblique position has the potential to disrupt the organized hematoma with resultant significant and potentially lethal rebleeding. The integrity of the entire urethral length can be defined with the patient in the supine position throughout the examination, aided by oblique stretching of the penis over the left or right thigh to promote necessary urethral unfolding.

A preinjection kidney, ureter, and bladder (KUB) film is first obtained. In uncircumcised patients, the penile foreskin is retracted and secured with a folded 4 × 4-inch gauze pad (see Fig. 47-4). The penis should be held between the long and ring fingers of the nondominant hand. A simple Christmas tree adapter, a Cooke adapter placed on the end of a 60-mL Toomey syringe, or a Toomey syringe alone is gently passed into the urethral meatus until a snug fit inside the meatus is confirmed. The distal end of the syringe is secured with the thumb and index fingers of the nondominant hand (Fig. 47-6). Some authors have recommended inflation of a Foley catheter balloon just proximal to the fossa navicularis or the use of other cumbersome adjuncts to facilitate injection of contrast media. These techniques should be avoided, however, because they promote leakage of contrast material around the penis, which can simulate extravasation on the urethrogram and promote a spurious examination. Next, 60 mL (or 0.6 mL/kg in children) of full-strength or half-strength water-soluble contrast medium is injected slowly over 30 to 60 seconds. Overly forceful injection may result in intravasation of contrast material into the urethral venous plexus. A radiograph is taken during the injection of the last 10 mL of contrast material. Retrograde flow through the urethra and into the bladder without extravasation ensures continuity of the urethra and absence of urethral injury (Fig. 47-7). Extravasation of contrast material outside the urethra with concomitant evidence of bladder filling distinguishes a partial urethral injury (see Fig. 47-5) from a complete urethral disruption, in which contrast material will be absent from inside the bladder (Fig. 47-8). The latter situation requires urologic consultation for appropriate management, the timing and specifics of which remain controversial and depend on the location and mechanism of injury.[6,12,13] In the interim, if measurement of urinary output is essential, the bladder should be accessed by the suprapubic placement of a peel-away sheath and Foley catheter through use of the Seldinger technique (Fig. 47-9). When venous intravasation of contrast is suggested, a postvoid film demonstrates clearing of any intravasated material while extravasated contrast from a urethral injury remains. Retrograde urethrography should be deferred if pelvic angiography is indicated, as extravasated contrast material from a urethral injury may obscure computed tomography (CT) scans and angiographic images and

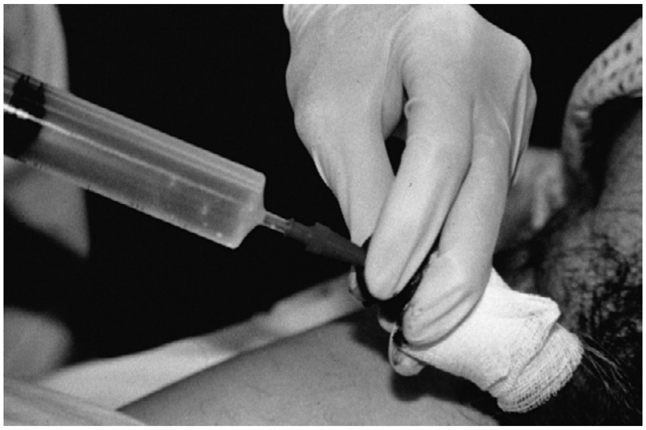


Figure 47-6. Christmas tree adapter on the end of a 60-mL syringe has been gently placed inside the fossa navicularis in preparation for retrograde urethrography.

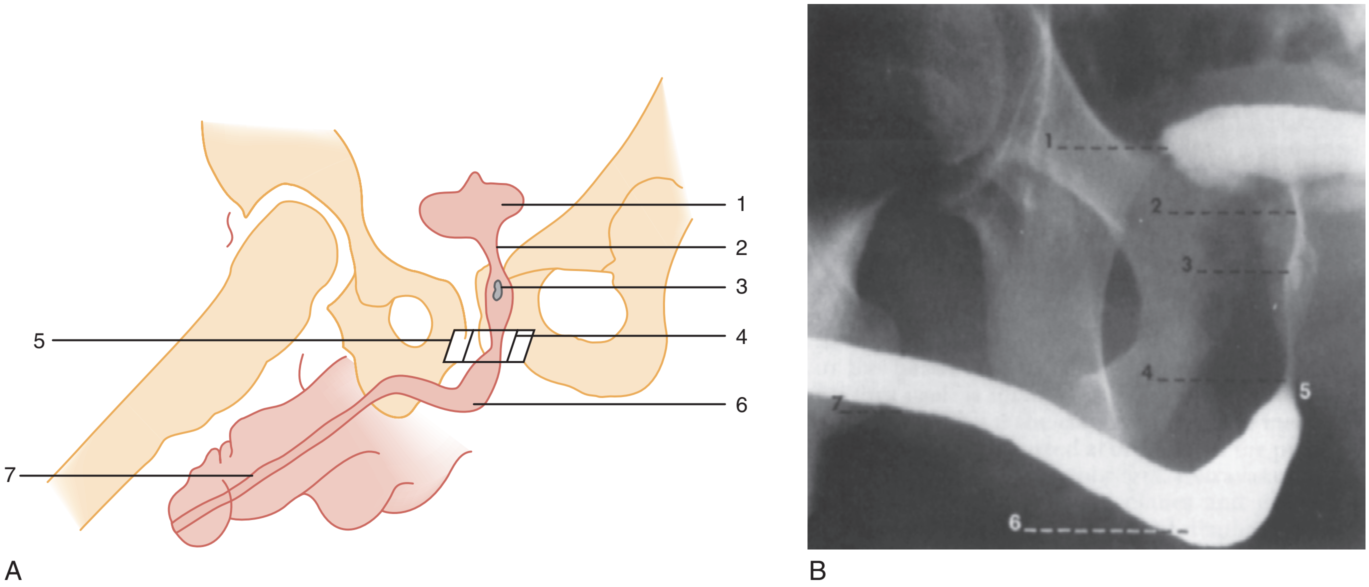


Figure 47-7. Normal anatomy is demonstrated by a line drawing (**A**) and by dynamic retrograde urethrography (**B**). *1,* Bladder; *2,* prostatic urethra; *3,* verumontanum; *4,* membranous urethra; *5,* position of the urogenital diaphragm; *6,* bulbous urethra; and *7,* penile urethra. The penile and bulbous urethra together are considered the anterior urethra; the prostatic and membranous urethra constitute the posterior urethra. (Adapted from McCallum RW, Colapinto V: Urological Radiology of the Adult Male Lower Urinary Tract. Springfield, Ill, Charles C Thomas, 1976.)

www.ketabpezeshki.com 66485457-66963820

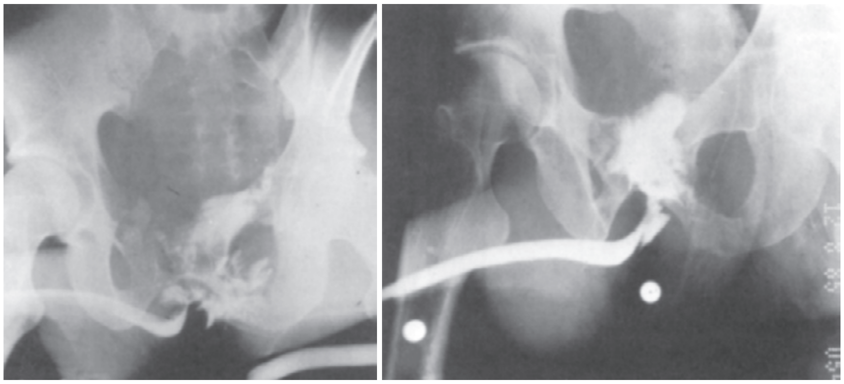


Figure 47-8. Retrograde urethrograms from two patients, each demonstrating complete urethral disruption. Note the absence of bladder filling, a finding diagnostic of complete disruption. (From Spirnak JP: Pelvic fracture and injury to the lower urinary tract. Surg Clin North Am 68:1057, 1988.)

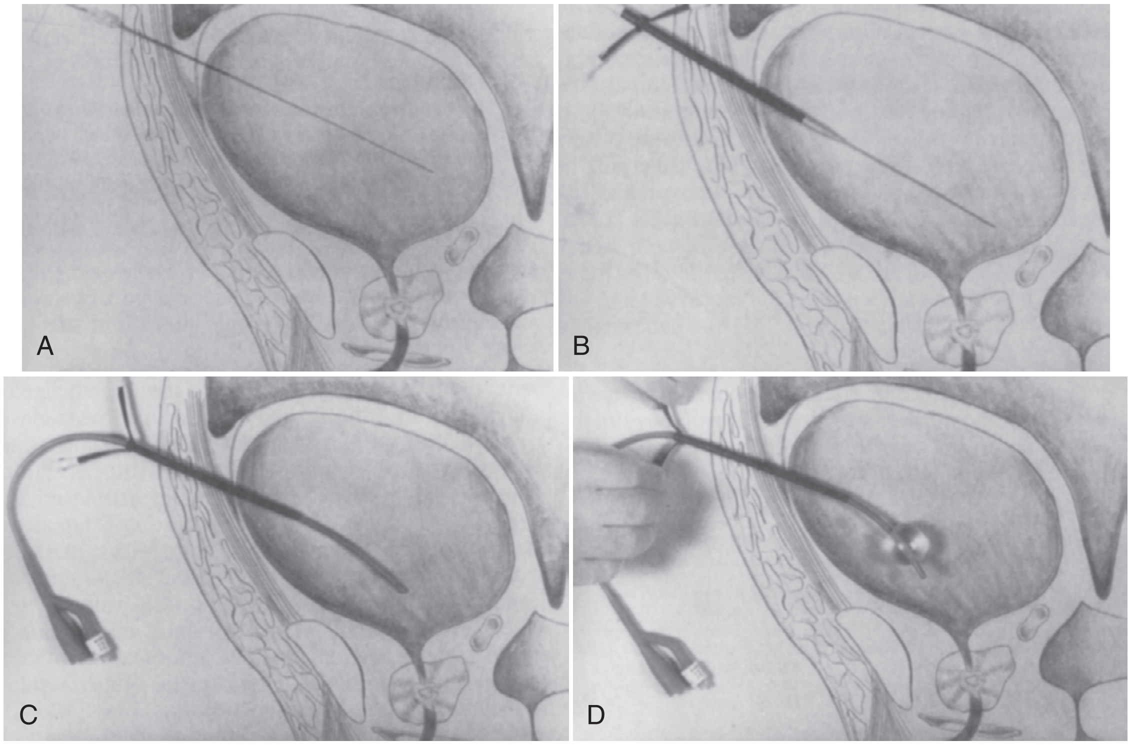


Figure 47-9. Percutaneous placement of a suprapubic tube with peel-away sheath introducer. **A,** An 18-gauge needle is in the bladder. A guidewire is advanced through the needle. **B,** A dilator and peel-away sheath are advanced over the guidewire. **C,** The dilator and guidewire are removed. Through the peel-away sheath, an appropriately sized catheter can be introduced into the bladder. **D,** The balloon is inflated, and the sheath is pulled back and peeled away. (From O'Brien WM: Percutaneous placement of suprapubic with peel away sheath introducer. J Urol 145:1015, 1991.)

complicate attempts to control significant pelvic hemorrhage by vascular embolization.[14]

Management

If the clinical features of urethral injury are absent or the urethrogram is normal, the urethra is intact and a Foley catheter can be passed into the bladder. If a partial urethral disruption is identified, one careful attempt to pass a 12- or 14-Fr Foley or coudé catheter can be undertaken. If this is unsuccessful or if a complete urethral tear is detected, placement of a suprapubic catheter for measurement of urinary outflow and volume requirements is often needed, especially if the patient is in shock or requires osmotic therapy for a severe head injury.

The optimal definitive management of urethral injuries remains a subject of controversy in the urologic literature.[6,12,13] Pertinent variables include the location of the injury (anterior vs. posterior), extent of the disruption (partial vs. complete), mechanism of injury, hemodynamic stability of the patient, and presence of associated injuries. Treatment options vary from allowing a partial disruption to heal over a stenting urethral catheter to early or delayed, open or endoscopic repair. Adjunctive suprapubic urinary drainage is frequently indicated. Regardless of the specific management plan, the ultimate goals are the preservation of urinary continence and sexual function and avoidance of the disruption of any pelvic hematoma.

In female patients, proximal urethral injuries are managed by immediate surgical exploration and repair, as conservative management with proximal urinary diversion alone is associated with an increased risk of urethrovaginal fistulae or obliterative urethral strictures. Distal injuries may be managed by urethral catheterization. Regardless of the location of the urethral injury, associated

www.ketabpezeshki.com 66485457-66963820

vaginal lacerations require transvaginal repair to reduce the incidence of fistula formation.[6]

BLADDER TRAUMA

Anatomy

When empty, the bladder lies almost entirely within the bony pelvis. It rests on the pubis and adjacent pelvic floor parts. When full, the bladder can extend up to the level of the umbilicus, where it is most vulnerable to blunt and penetrating trauma. The bladder consists of an inner longitudinal, a middle circular, and an outer longitudinal muscle layer. These three layers constitute the detrusor muscle, which contracts to propel urine out the urethra. Blood is supplied to the bladder by the internal iliac artery and vein. The nerve supply comes from the lumbar and sacral segments of the spinal cord. It includes parasympathetic motor fibers to the detrusor muscle and sensory fibers to the detrusor that give rise to the sensation of fullness and urgency when the detrusor is stretched. Sympathetic fibers innervate the blood vessels of the bladder and the bladder neck musculature.

Pathophysiology

More than two thirds of bladder injuries result from blunt trauma. Approximately 90% result from motor vehicle collisions (MVCs) as a result of trauma sustained during ejection from the vehicle or the compressive force of the seat belt on a distended bladder. Approximately 80% of blunt bladder injuries are associated with fractures of the bony pelvis.[15] Additional life-threatening, nonurologic injuries are common and confer a significant mortality risk.[15,16] Penetrating injuries may be inflicted by gunshot wounds, stab wounds, or impalement injuries. The diagnostic evaluation of the bladder, like that of the urethra, can be accomplished quickly without elaborate radiographic equipment or can be part of the CT evaluation performed for the evaluation of nonurologic injuries.

Bladder injuries are classified as contusions, intraperitoneal ruptures, extraperitoneal ruptures, or a combination of intraperitoneal and extraperitoneal ruptures. Proper classification is important because treatment options differ with injury type. Intraperitoneal bladder rupture results from blunt lower abdominal trauma in a patient with a distended bladder. These blunt forces are directed to the dome of the bladder where the urachus originates during embryonic life. Because of this developmental hiatus, the dome is thinner and represents the anatomic area most susceptible to rupture from the sudden rise in intravesical pressure associated with blunt trauma. The dome also is unique in its isolated peritoneal reflection so that rupture in this area most likely results in intraperitoneal urinary contamination.

Extraperitoneal rupture occurs almost exclusively with pelvic fractures when the associated shearing forces result in tearing of the anterolateral bladder wall at its fascial attachments. Occasionally, extraperitoneal rupture results from bladder laceration by a bone spicule from the fractured pelvis.[15] Extravasated urine may be confined to the perivesical space or may dissect along tissue planes and extend to the penis, scrotum, thigh, anterior abdominal wall, obturator foramen, or retroperitoneum.[15,17,18]

Clinical Features

Lower abdominal or suprapubic pain, pelvic fracture, the inability to urinate, gross hematuria, or the presence of blood at the urethral meatus may alert the physician to the possibility of bladder injury.

Diagnostic Strategies

Laboratory

Gross hematuria is the cardinal sign of bladder injury and is present in more than 95% of cases.[15,19,20] In the setting of pelvic fracture, gross hematuria indicates the need to investigate for bladder injury. Relative indications for bladder imaging include gross hematuria without pelvic fracture and microhematuria in the setting of pelvic fracture.[15] Grossly clear urine in a blunt trauma patient without a pelvic fracture virtually eliminates the possibility of bladder rupture.

Radiology

Conventional retrograde cystography and retrograde CT cystography are the diagnostic procedures of choice for suggested bladder injury.[21-23] It is key that these studies *not* be done in an antegrade fashion, as such studies (e.g., injecting intravenous contrast material, clamping the Foley catheter, and allowing the examination to depend on antegrade filling of the bladder from renal excretion of progressively dilute contrast material) may produce incomplete and spurious findings owing to inadequate distention of the bladder.

Conventional Retrograde Cystogram. Performance of either conventional plain film retrograde cystography or CT retrograde cystography assumes prior evaluation of urethral integrity and the presence of an indwelling Foley catheter in the bladder. A Toomey syringe alone without its central piston is used for gravity instillation of contrast material (Fig. 47-10). Allowing the contrast material to freely infuse from a hanging bottle connected to an indwelling Foley catheter runs the risk of the tubing becoming disconnected, with contrast material subsequently leaking onto the examination table (Fig. 47-11A and B). This promotes an inaccurate examination that may result in an unnecessary operative procedure (Fig. 47-11C). In the setting of pelvic fracture, it is imperative that the patient remain supine throughout the examination. This lessens the potential for rebleeding from an organized retropubic hematoma.

A preliminary KUB or scout film is obtained to provide a baseline evaluation of the pelvis, abdomen, and surrounding bony structures. It will become the film of reference for the postevacuation radiograph obtained after completion of the cystogram. Potential areas of extravasation on the postevacuation film will be confirmed when compared with the preliminary KUB film (Fig. 47-12). Contrast material should not be instilled into the bladder

Figure 47-10. Retrograde cystogram. A Toomey syringe without its central piston is connected to the catheter and held by the examiner while gravity-instilled contrast material fills the bladder.

www.ketabpezeshki.com 66485457-66963820

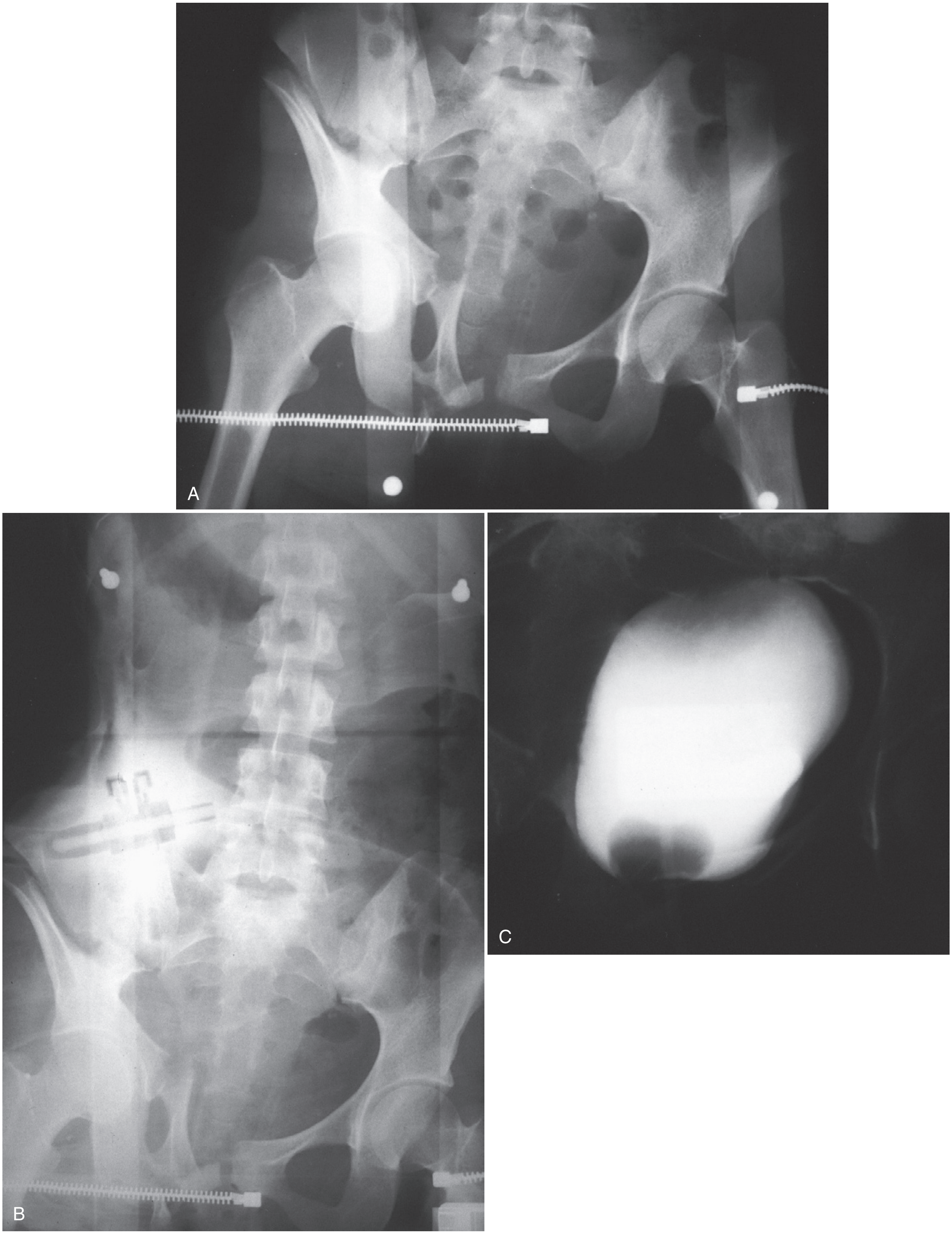


Figure 47-11. Spurious retrograde cystogram. This examination resulted when the tubing from the contrast bottle became disconnected from the Foley catheter after both were placed on the examination table, and bladder filling was completed without direct supervision. **A,** Kidney, bladder, ureter (KUB) film. **B,** Postinfusion KUB film interpreted as intraperitoneal bladder perforation. **C,** Intraoperative retrograde cystogram showing no evidence of extravasation.

www.ketabpezeshki.com 66485457-66963820

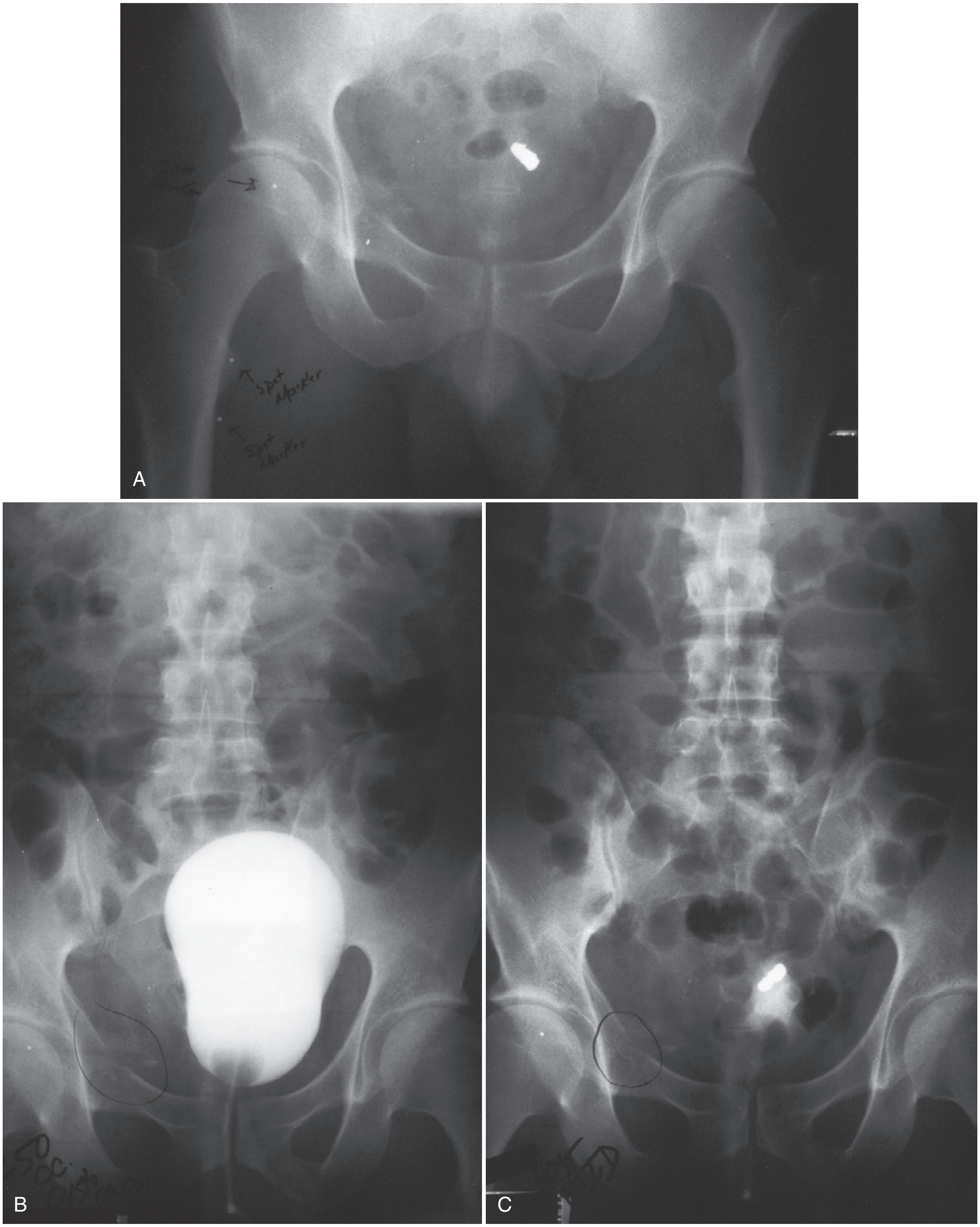


Figure 47-12. Retrograde cystogram. **A,** Preliminary kidney, bladder, ureter (KUB) film. **B,** Film of filled bladder. **C,** Postevacuation film comparing posterior extravasation with the preliminary KUB film.

until the quality and anatomic information on the preliminary KUB film have been confirmed.

Full-strength water-soluble contrast medium is instilled under gravity filling to one of three endpoints:

1. Instillation of 100 mL with immediate fluoroscopic evidence of gross extravasation.
2. A total instillation of 300 to 400 mL in any patient 11 years of age or older; in patients younger than 11 years, the correct amount of contrast medium is determined by the following formula: (age in years divided by 2) × 30.
3. The instillation of a lesser amount than 100 mL that initiates a bladder contraction. This becomes evident by

www.ketabpezeshki.com 66485457-66963820

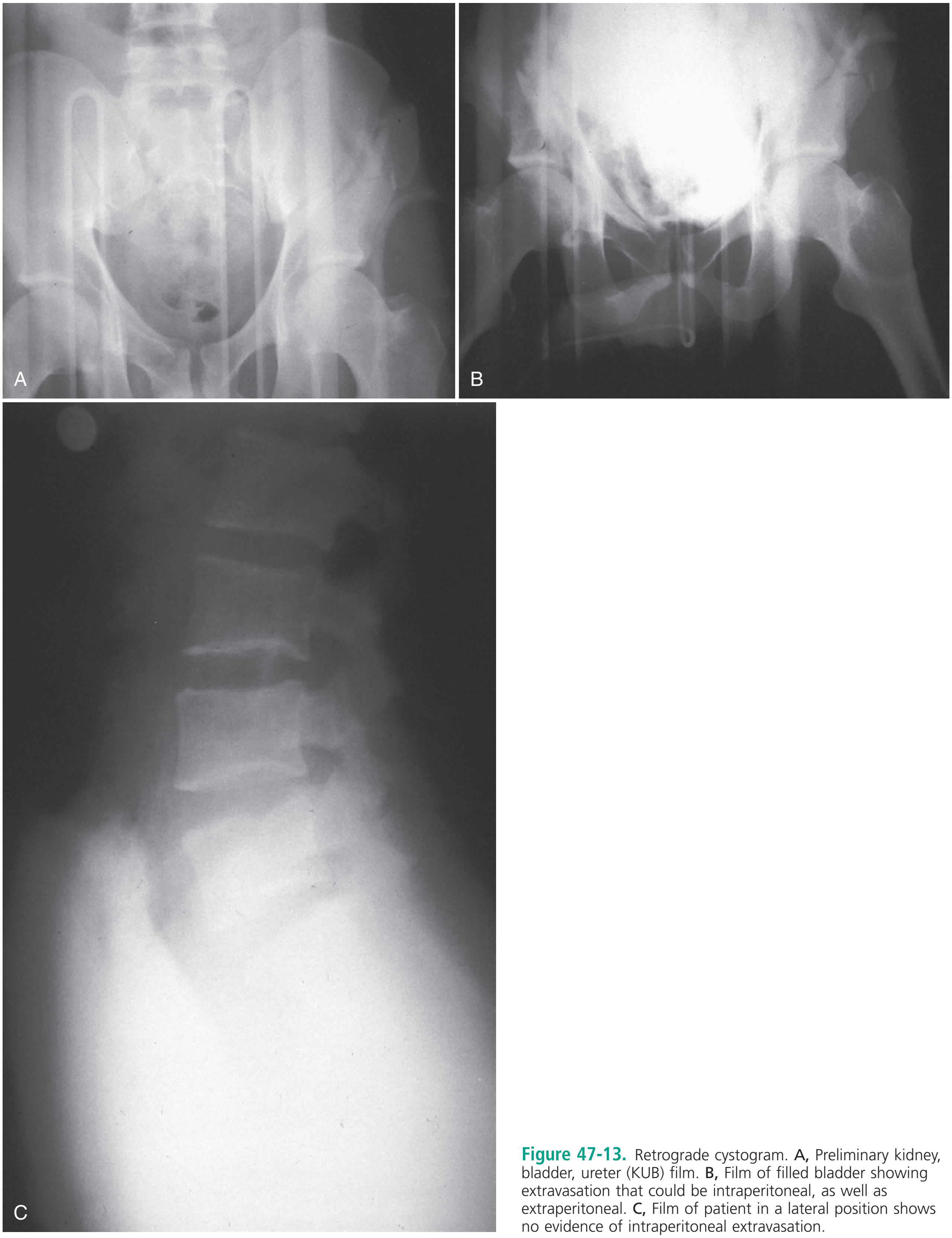


Figure 47-13. Retrograde cystogram. **A,** Preliminary kidney, bladder, ureter (KUB) film. **B,** Film of filled bladder showing extravasation that could be intraperitoneal, as well as extraperitoneal. **C,** Film of patient in a lateral position shows no evidence of intraperitoneal extravasation.

the retrograde filling of the Toomey syringe with bladder contents.

After a few minutes, the original contrast material can again be instilled to the point of stimulating a bladder contraction, at which time an additional 50 mL of full-strength contrast material should be injected slowly but forcefully into the bladder. The Foley catheter is clamped, and an anteroposterior radiograph is taken of the filled bladder (Fig. 47-13A and B). A lateral film may help clarify any areas in question (Fig. 47-13C). After the film of the filled bladder meets standards for quality and detail, the bladder should be completely evacuated into a large basin or, preferably, into an available bedside drainage bag. Any spillage

www.ketabpezeshki.com 66485457-66963820

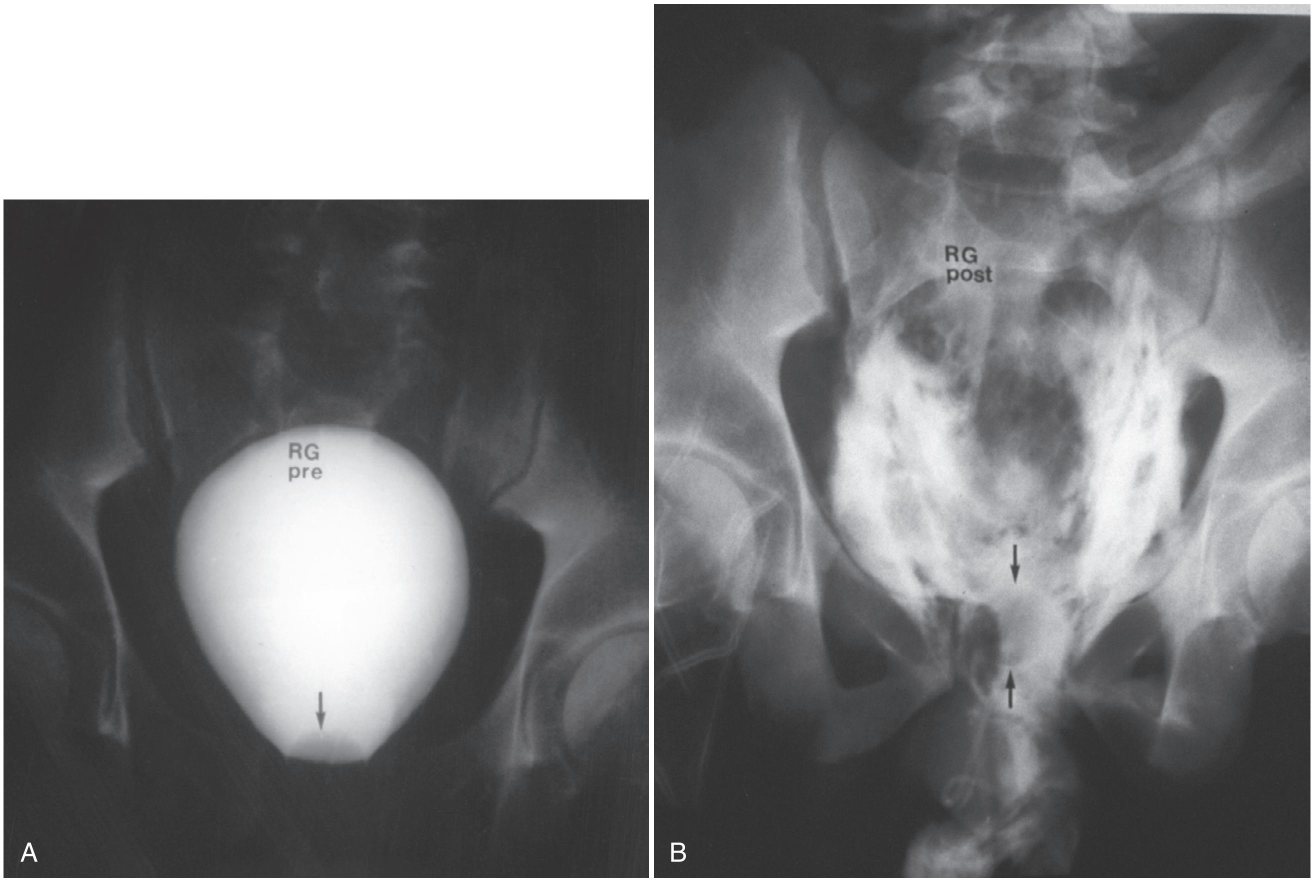


Figure 47-14. Retrograde cystogram. **A,** Film of filled bladder. **B,** Postevacuation film showing extensive extraperitoneal extravasation. Arrows point to the Foley catheter balloon.

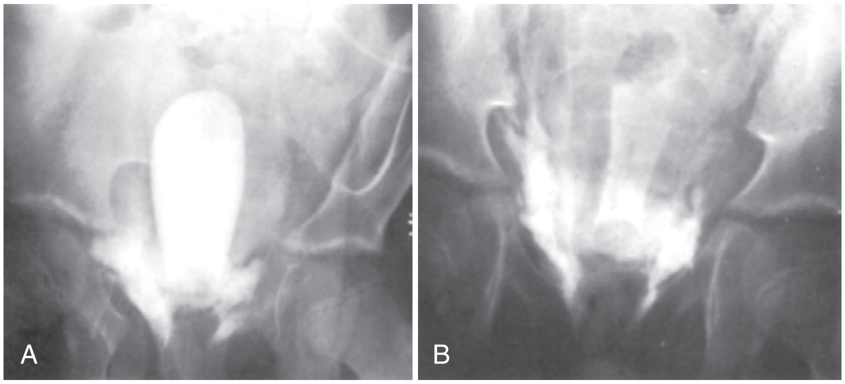


Figure 47-15. Cystographic appearance of extraperitoneal bladder perforation. Note the teardrop deformity caused by extrinsic compression by the pelvic hematoma and the flamelike wisps of extravasation confined by the pelvis. The bladder itself is elongated by a collection of perivesicular fluid. (From Spirnak JP: Pelvic fracture and injury to the lower urinary tract. Surg Clin North Am 68:1057, 1988.)

of contrast material onto the pelvic genitalia or examination table may lead to false-positive findings on the postevacuation radiograph. The postevacuation film may disclose evidence of posterior bladder wall or extraperitoneal extravasation not seen on the anteroposterior radiograph of the filled bladder (Figs. 47-12 and 47-14).

In cases of extraperitoneal bladder perforation, contrast material is evident in the area of the pubic symphysis and pelvic outlet (Fig. 47-15). With intraperitoneal perforation, contrast material outlines intraperitoneal structures (e.g., loops of bowel, the liver, and spleen) (Fig. 47-16).

Several studies have documented that false-negative results are associated with the use of less than 300 to 400 mL, or an age-inappropriate amount, of contrast material for cystography.[17] This has been seen primarily in penetrating bladder injuries in which the perforation from a small-caliber gunshot wound or a thin-blade stab wound can be missed. The anatomically interlacing bladder wall muscle fibers are arranged such that these wounds lend themselves to immediate muscle fiber reapproximation and tenuous sealing of the wound by covering peritoneum and intra-abdominal mesentery. Unless an adequate amount of full-strength contrast material is used to fully distend or even overdistend the bladder, extravasation will not be evident, the injury will be missed, and there will be potential for significant morbidity.

Computed Tomography Retrograde Cystogram. The same anatomic information regarding bladder injury may be obtained with retrograde CT cystography rather than routine plain film radiography.[21-23] CT cystography is best performed in trauma patients who are undergoing CT evaluation for other possible injuries.

www.ketabpezeshki.com 66485457-66963820

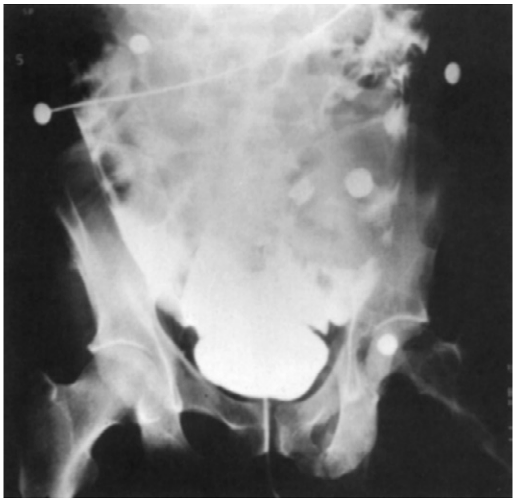


Figure 47-16. Cystographic appearance of intraperitoneal bladder perforation. Cystogram reveals massive intraperitoneal perforation and extravasation. (From Spirnak JP: Pelvic fracture and injury to the lower urinary tract. Surg Clin North Am 68:1057, 1988.)

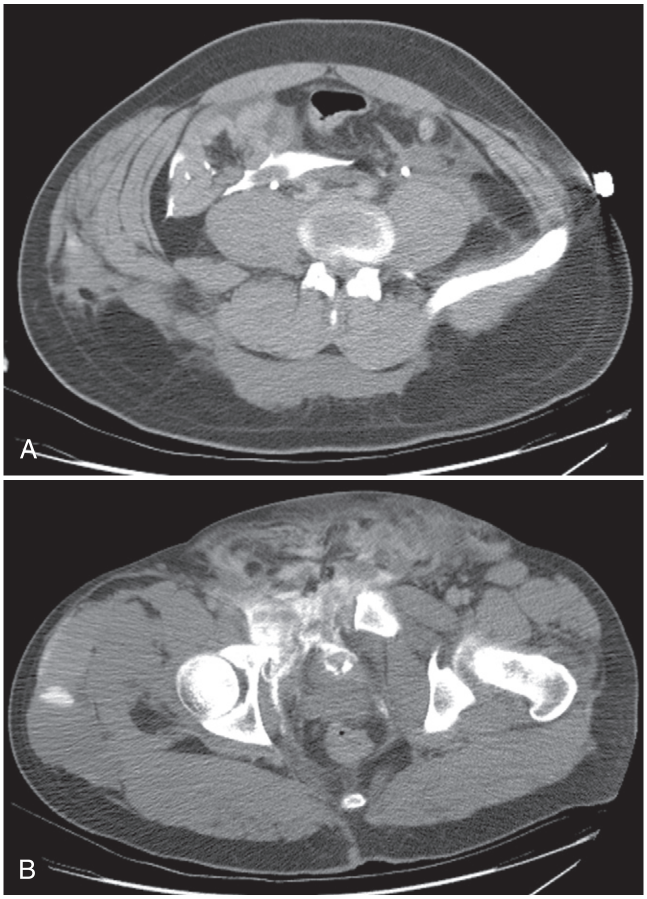


Figure 47-17. Bladder rupture. A, Intraperitoneal rupture shows contrast material extravasated from the bladder outlining loops of bowel in the lower abdomen. B, Extraperitoneal rupture shows contrast material extravasating into the disrupted soft tissue plains of the anterior and left pelvic side wall. (Courtesy Charlotte Radiology, Emergency Radiology Section, Charlotte, North Carolina.)

Following standard CT imaging of the abdomen and pelvis to evaluate for injury, the bladder is filled with water-soluble contrast medium in the same manner as for the retrograde cytogram, and additional CT images are obtained. Postvoid images are not necessary given the additional detail evident on CT imaging. Intraperitoneal rupture is diagnosed on helical CT scan by the presence of extravasated contrast material throughout the abdominal cavity (i.e., contrast ascites). Extraperitoneal extravasation is more difficult to visualize but can be appreciated on images taken through the area of the bladder neck and lower pelvis (Fig. 47-17A and B).

Management

In cases of bladder contusions, there is no evidence of extravasation on retrograde cystography. For these injuries, expectant management with or without Foley catheter drainage is standard practice.[15,24] Most uncomplicated extraperitoneal bladder ruptures heal spontaneously with urinary catheter drainage alone. Indications for operative repair of extraperitoneal ruptures include the presence of concomitant injury to the rectum or vagina, injury involving the bladder neck, or situations in which laparotomy is required for other injuries. Intraperitoneal bladder rupture requires surgical repair. Without operative intervention, lower urinary tract contamination will infect initially sterile urine and promote the development of subsequent bacterial peritonitis. Bladder repairs are never emergencies and normally follow operative repair of life-threatening injuries. Prompt urology consultation is indicated to allow for coordination between surgeons and determination of the optimal timing of the repair.

UPPER TRACT

RENAL TRAUMA

Perspective

Renal trauma rarely occurs in isolation. Concomitant nonurologic injuries may result in hemodynamic instability, necessitating prompt intervention and relegating the search for renal injury to a position of secondary importance. Significant renal injuries define a small subset of the trauma population at large, and mortality from renal trauma accounts for less than 0.1% of trauma deaths.[25] This fact may lead to complacency and causes some of these injuries to be overlooked initially. Renal injuries are graded 1 through 5 according to the American Association for the Surgery of Trauma Organ Injury Scaling Committee guidelines, which identify most injuries requiring operative intervention.[26,27]

Complications

Urinary extravasation is the most common complication of renal trauma, occurring in 10 to 30% of penetrating trauma and 2 to 18% of blunt injuries.[25] There is considerable controversy in the urologic literature regarding the incidence of hypertension after renal trauma, with reported rates varying greatly from as little as 0.2% to as much as 55%.[25,28] Many experts currently believe the overall risk of hypertension after most renal injuries to be quite low.[25,28,29] Factors affecting the risk of hypertension after renal trauma include the specific injury type and severity. Renal artery occlusion, although rare, imparts a risk of hypertension of up to 50%.[25,29]

Anatomy and Physiology

The kidneys are located in the retroperitoneal space, are surrounded by adipose tissue and loose areolar connective tissue, and lie along the lower two thoracic vertebrae and the first four lumbar vertebrae (Fig. 47-18). The kidneys are not fixed. They move with the diaphragm and are supported by their renal arteries, veins, and adipose tissue, which is connected to a layer of fibrous tissue called the *renal fascia* or *Gerota's fascia*.

www.ketabpezeshki.com 66485457-66963820

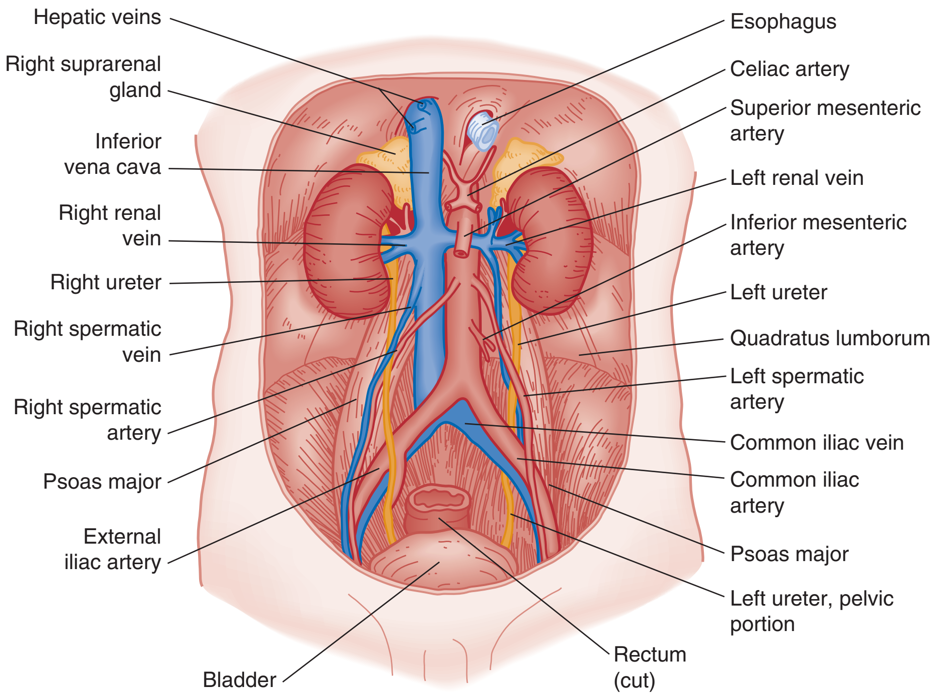


Figure 47-18. Dissection of abdomen showing kidneys and ureters and their relationship to other anatomic features in the retroperitoneal space.

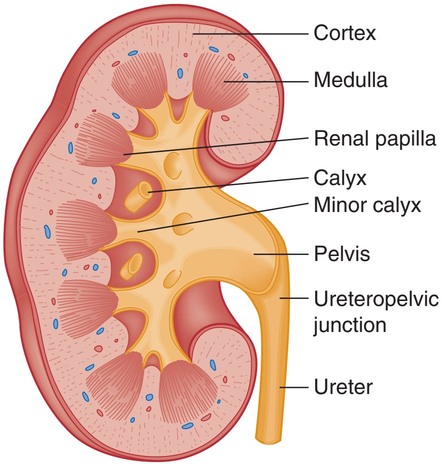


Figure 47-19. Longitudinal section of kidney.

The indented medial border of the kidney is called the *hilum.* The major renal vessels and ureter make up the renal pedicle and enter and exit at the hilum. The longitudinal section of the kidney (Fig. 47-19) shows an outer renal cortex and an inner renal medulla with its columns of Bertin. Each column of Bertin forms a papilla that empties into the renal pelvis. The renal pelvis is a funnel-shaped sac with cup-shaped extensions called *calyces,* which receive urine from each papilla and are the important decompression areas for rises in intrapelvic pressure.

The kidneys are perfused by 1200 mL of blood per minute, or 20 to 25% of cardiac output. Of this, 90% goes to the cortex and 10% to the medulla. Reduced blood flow to the kidney, whether from blunt or penetrating injury, causes renin to be released from the juxtaglomerular cells. Renin enters the bloodstream and combines with a plasma protein to form angiotensin. Angiotensin raises blood pressure by causing arteriolar vasoconstriction and acting on the adrenal cortex to augment aldosterone secretion. Aldosterone acts on the renal tubules to promote sodium reabsorption. Water follows passively with subsequent increase in blood volume. These changes increase blood flow to the kidney and other organs. The body requires only one third of normal renal function to sustain life. It is unusual in cases of genitourinary trauma to lose total renal function unless the patient had only one kidney prior to injury, which carries a 1 in 1000 to 1 in 5000 incidence.[30]

Epidemiology

Renal injury occurs in 1 to 5% of hospitalized trauma patients and represents the most common of all genitourinary injuries.[13,29] Associated organ injuries occur in 61 to 100% of penetrating trauma and 35 to 55% of blunt injuries.[25] Blunt trauma accounts for approximately 90% of injuries and occurs most often after MVCs, falls from heights, or direct blows to the flank. The pathophysiologic mechanisms include rapid deceleration, displacement, and, rarely, an explosion-type injury of the ureteropelvic junction. Penetrating injuries tend to be more severe and are associated with a higher nephrectomy rate.[13]

Renal vein injuries are more common than renal artery avulsions or intimal tears. Both injuries are often associated with rapid deceleration events. Most venous injuries tend to be partial rather than complete tears. As expected, a venous injury can potentially contribute more to a patient's unstable hemodynamic status than an arterial injury, as the protective secondary vasospasm that occurs after arterial transection does not occur with venous injuries. Intravenous contrast-enhanced helical CT identifies most renal artery disruptions, whereas renal vein injuries must be indirectly diagnosed by the presence of a normal-appearing kidney in association with a large hematoma disproportionate to the rest of the radiographic study.

Diagnostic Strategies

Laboratory

Hematuria. The presence, absence, or degree of hematuria correlates poorly with the severity of renal injury. This is especially true in the setting of penetrating trauma. In select cases of blunt

www.ketabpezeshki.com 66485457-66963820

trauma, the distinction between gross and microscopic hematuria can be used to guide clinical decision-making when considered along with the patient's hemodynamic status and the mechanism and severity of injury.[13,29,31,32] Formerly, a trauma patient who exhibited gross or microscopic hematuria was labeled "at risk" for urologic injury and underwent intravenous pyelography. Experience has shown that most of the identifiable injuries were renal contusions that could be managed expectantly. Moreover, in a significant number of severely traumatized patients, vigorous initial fluid resuscitation precluded satisfactory contrast concentration in the kidney, yielding an incomplete, nondiagnostic initial radiographic examination.

In 1989, Mee and associates published the hallmark article that established guidelines for the evaluation and treatment of renal trauma. Their 10-year prospective study of 1146 consecutive patients with blunt (88%) and penetrating renal trauma established that clinically significant blunt renal injuries are associated with gross hematuria, microscopic hematuria with shock (any systolic blood pressure less than 90 mm Hg), or, rarely but importantly, a history of sudden deceleration injury without hematuria or shock. In the same series, there was no correlation between the presence or absence of hematuria and the extent of renal injury among 139 cases of penetrating trauma.[32]

Pediatrics. In children the kidney is the most commonly injured genitourinary organ.[33] Controversy exists in the urologic literature as to whether the adult criteria for renal imaging after blunt trauma can be safely applied to the pediatric population.[29,34,35] Owing to significant differences in physiology, hypotension is a late and unreliable indicator of shock in children.[13,29] In addition, unlike in adults, major blunt renal injuries can occur in the presence of microhematuria. The literature has defined 50 RBCs per high-power field (hpf) as the threshold below which imaging could be confidently deferred without missing significant injuries in children.[35,36] Current guidelines support imaging for pediatric (16 years or younger) patients with blunt renal trauma in the presence of gross hematuria, with microhematuria greater than 50 RBCs/hpf, or with significant deceleration injuries.[29,37] As with adults, intravenous contrast-enhanced helical CT scanning is the diagnostic imaging technique of choice.

Radiology

Computed Tomography. Intravenous contrast-enhanced helical CT is the diagnostic radiographic procedure of choice in evaluating significant upper tract renal trauma.[13,29,31,38] CT detects renal contusions, lacerations, renal pedicle injuries, devitalized segments, and urinary extravasation (Fig. 47-20). It allows for grading of renal injuries and provides important information about concomitant nonurologic injuries to abdominal and pelvic structures. Additional images obtained 10 minutes after contrast injection enable the detection of delayed extravasation and increase diagnostic accuracy.

Angiography. Angiography may be a useful adjunct to CT imaging in the stable trauma patient with suggested renovascular injury, such as renal artery thrombosis, laceration, or pseudoaneurysm, and may be therapeutic in cases in which stenting or embolization is indicated.[21,31,38]

Intravenous Pyelography. Formerly, intravenous pyelography was the most common imaging modality used in the evaluation of renal trauma. It has been shown to be less accurate than CT, is time-consuming and labor-intensive, and images only the urinary tract.[31] Despite these significant limitations, it may play a limited role in the initial evaluation of suspected renal trauma when CT is not readily available. In patients requiring immediate surgical intervention for other indications, a "one-shot intravenous pyelogram" (IVP) obtained in the emergency department or, more commonly, on the operating table may provide limited information to help the surgeon stage upper tract injuries and confirm bilateral renal function. This test is performed by obtaining a single KUB film 10 minutes after the injection of 2 mL of intravenous contrast per kilogram (maximum 150 mL).[30]

Ultrasound. Ultrasound is not sufficiently sensitive to rule out possible renal trauma, as it has been shown to miss up to 78% of known renal injuries.[31,38] In the multiply injured trauma patient, ultrasound is useful in the evaluation for free fluid in the abdomen and pelvis, which may herald other significant nonrenal injuries; however, this modality cannot reliably distinguish blood from other types of fluid such as ascites or extravasated urine.[39] Moreover, free intraperitoneal fluid may be absent in up to 65% of isolated renal injuries.[21,38]

Management

Blunt Injury

In the absence of a significant deceleration mechanism, adult blunt trauma patients without gross hematuria or shock (any systolic blood pressure <90 mm Hg) and pediatric blunt trauma patients with microhematuria of 50 RBCs or fewer per high-power field can be confidently discharged from the emergency department if hospital admission is not otherwise indicated. Outpatient urology follow-up until microhematuria has cleared is advisable to be certain it does not represent another more serious underlying condition.

The optimal management of blunt renal trauma depends on the type and severity of injury (Figs. 47-21 and 47-22), the patient's hemodynamic status, and the management plan for any associated nonurologic injuries. The American Association for the Surgery of Trauma organ injury severity scale for the kidney stratifies injuries and has been shown to correlate with the need for surgical intervention and the rate of nephrectomy.[26] Grade I injuries include simple contusions and subcapsular, nonexpanding hematomas without parenchymal laceration. Grade II injuries are parenchymal lacerations less than 1 cm in depth without urinary extravasation and a stable, nonexpanding hematoma. Grade III injuries are parenchymal lacerations greater than 1 cm in depth without urinary extravasation. Grade IV injuries involve lacerations extending through the cortex, medulla, and collecting system or main renal artery or vein injuries with contained hemorrhage. Grade V injuries involve completely shattered kidneys or avulsion of the renal hilum and devascularization of the kidney.[26] In one large retrospective review of 2467 patients with renal injury, the need for surgery increased from 0% of grade I injuries to 93% of grade V injuries. Likewise, the nephrectomy rate increased from 0% of grade I and II injuries to 86% of grade V injuries. Given that 80 to 90% are grade I or II, most blunt renal injuries can be managed nonoperatively with bed rest until any gross hematuria clears and with periodic follow-up imaging to assess for injury resolution and to document renal function.

Immediate operative intervention is indicated for persistent life-threatening hemorrhage of possible renal origin. Restoration of normal renal function is unlikely after main renal artery injury, and nephrectomy may be required, especially in the presence of longer than 2 to 3 hours of complete or 6 hours of partial renal ischemia.[29,40] In select patients, arteriography with hemorrhage control by embolization is a reasonable alternative to laparotomy.[13] Of note, arterial embolization results in infarction of the affected renal segment, imparting a risk of infection and posttraumatic hypertension. These risks can be minimized by superselective catheterization and embolization of peripheral branches of the renal artery when possible, based in the specific injury and expertise of the interventionalist. When laparotomy is required

www.ketabpezeshki.com 66485457-66963820

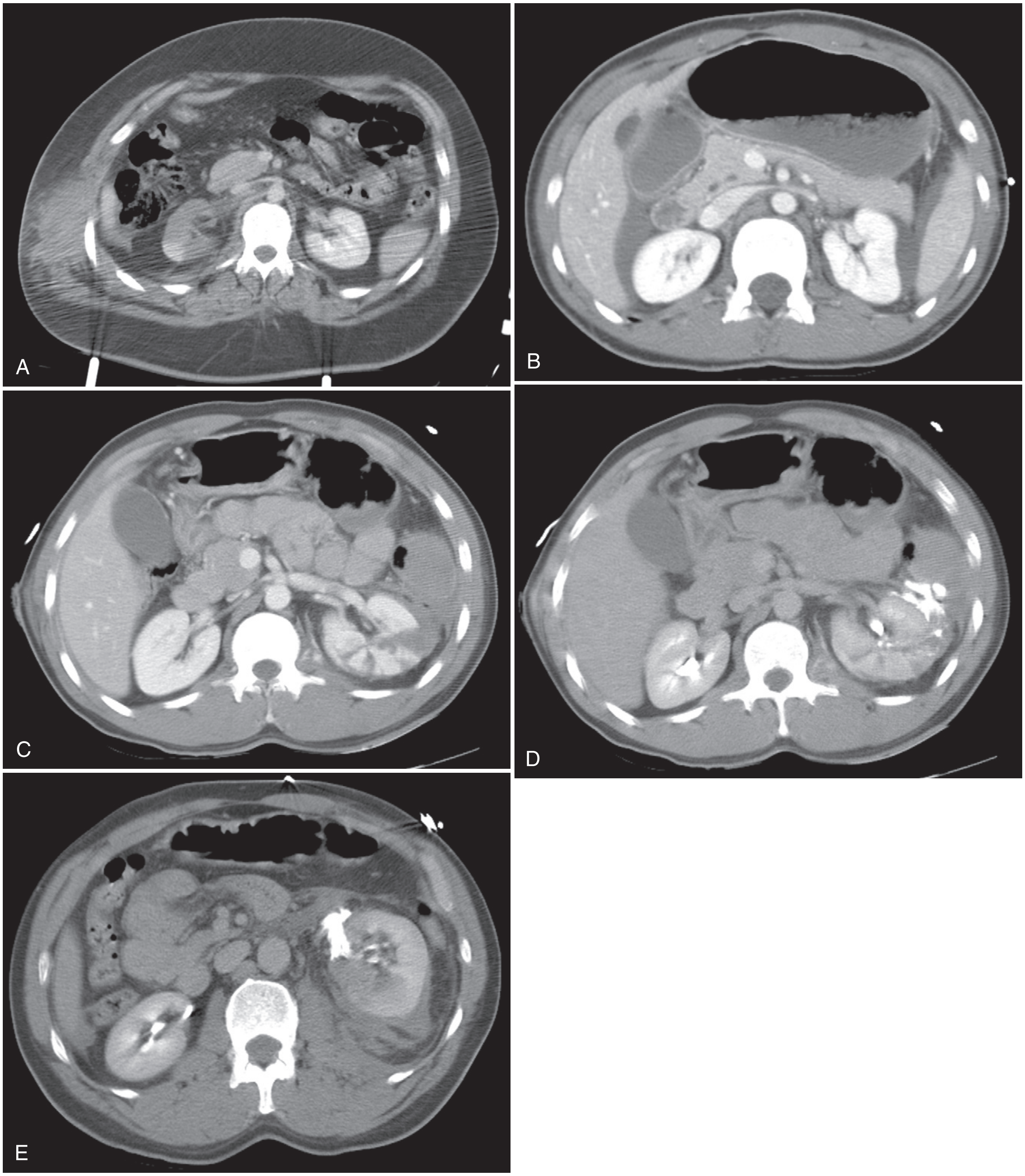


Figure 47-20. A, Renal artery injury. The right kidney demonstrates almost complete acute devascularization. (Note the right flank hematoma.) B, Subcapsular hematoma. Deforming renal parenchyma on the left. C and D, Renal laceration. These two images are of the same patient separated by several minutes of delay. The wedge-shaped hypodensities in the left kidney on the first scan (C) indicate the lacerations. The delayed scan (D) shows extravasation of contrast material from the lacerated kidney. E, Collecting system injury. Extravasation of contrast material from the lacerated left renal pelvis. (Hypodense areas of the kidney represent contusion.) (Courtesy Charlotte Radiology, Emergency Radiology Section, Charlotte, North Carolina.)

for other injuries before adequate radiographic evaluation, blunt renal trauma may be surgically staged. In this setting, renal exploration is indicated in the presence of an expanding, pulsatile, or uncontained retroperitoneal hematoma that is thought to indicate renal pedicle avulsion or when the injured kidney is not visualized on the one-shot IVP.[31]

Penetrating Injury

In cases of penetrating renal trauma, the presence or absence of hematuria is of no consequence in predicting upper urinary tract injury. The location of the penetrating injury in relation to the urinary tract is the most important determining factor in deciding

www.ketabpezeshki.com 66485457-66963820

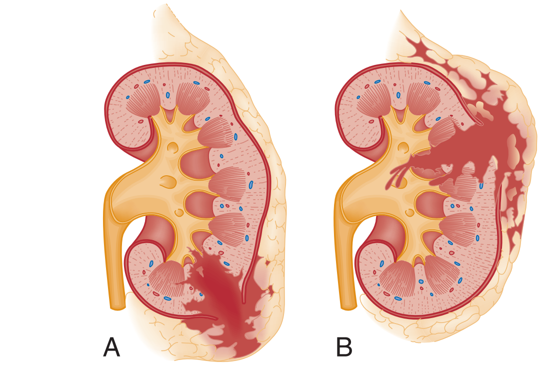


Figure 47-21. Major renal lacerations. **A,** Deep medullary laceration. **B,** Laceration into collecting system. (From Nicolaisen GS, et al: Renal trauma: Re-evaluation of the indications for radiographic assessment. J Urol 133:183, 1985.)

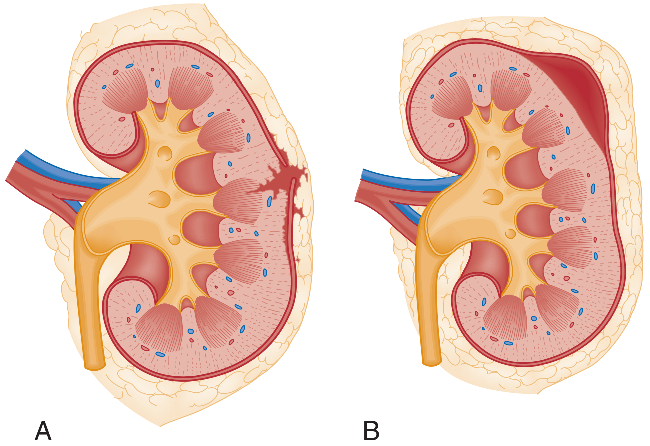


Figure 47-22. Minor renal injuries. **A,** Minor renal laceration. **B,** Renal contusion. (From Nicolaisen GS, et al: Renal trauma: Re-evaluation of the indications for radiographic assessment. J Urol 133:183, 1985.)

the need for radiographic investigation. Therefore the absence of hematuria in a patient with a gunshot or stab wound in proximity to the urinary tract does not eliminate the need for intravenous contrast-enhanced CT as the initial diagnostic examination. Significant injuries to the kidney and ureter may occur in penetrating trauma *without* hematuria.[13,29,32] Additional images obtained at 10 minutes after contrast injection are indicated to evaluate for delayed contrast extravasation and maximize the sensitivity of the study. The majority of penetrating renal injuries require surgical intervention.

URETERAL TRAUMA

Pathophysiology

Approximately 80% of ureteral injuries are iatrogenic, resulting from complications of abdominal or pelvic surgery, with the remainder caused by external trauma. The ureters are relatively protected from injury by the bony pelvis, vertebral column, and psoas muscle. Thus ureteral trauma is rare, present in approximately 3 per 10,000 trauma admissions.[41] Gunshot wounds are the most frequently reported mechanism, with ureteral injuries complicating 2 to 3% of abdominal gunshot wounds.[42,43]

Blunt force trauma causes ureteral injury when a significant decelerating force results in avulsion of the ureter from its fixed points at the ureteropelvic junction or, less commonly, the ureterovesicular junction. Owing to the significant force required for ureteral injury, concomitant major organ injury occurs in approximately 90% of cases, and hypotension is present in more than 50%.[44]

Clinical Features

There are no reliable signs and symptoms of ureteral injury in the acutely injured patient. Hematuria (gross or microscopic) is frequently present but may be absent in more than 25% of patients, and thus its absence alone cannot be relied on to exclude the diagnosis.[44] After blunt trauma, ureteral injury should be considered in patients with a significant decelerating mechanism, gross hematuria, or microscopic hematuria with hypotension. With penetrating mechanisms, ureteral injury should be considered when the injuring force occurs in proximity to the anatomic course of the ureter. Missed ureteral injury may manifest in a delayed fashion with a variety of signs and symptoms, including fever, nausea and vomiting, hematuria, flank pain, and a palpable flank mass.

Diagnostic Strategies

Intravenous contrast-enhanced CT of the abdomen and pelvis is highly sensitive for visualization of upper tract injuries and is often indicated for the investigation of associated nonurologic injuries. Additional images obtained 10 minutes after contrast injection enable the detection of delayed extravasation and increase diagnostic accuracy.[21]

Retrograde pyelography (Fig. 47-23) is slightly more sensitive than intravenous contrast-enhanced CT for the evaluation of ureteral injury, but its performance is frequently impractical in the multiply injured patient and it is rarely undertaken in lieu of CT. Likewise, a formal IVP, although sensitive, is of limited usefulness owing to the significant time required for study completion.[44] In patients requiring immediate surgical intervention for other indications, a one-shot IVP performed in the emergency department or, more commonly, on the operating table may provide limited information to help the surgeon stage upper tract injuries and confirm bilateral renal function. This test is performed by obtaining a single KUB film 10 minutes after the injection of 2 mL/kg of intravenous contrast (maximum 150 mL). The presence or absence of ureteral injury is subsequently confirmed during operative exploration.

Management

Operative repair is indicated for all ureteral injuries. With early diagnosis and appropriate treatment, the kidney and ureter can be saved in most cases. The complications of missed ureteral injuries are significant and include extended hospital stays, persistent urinoma, sepsis, loss of renal function, and death.[45,46]

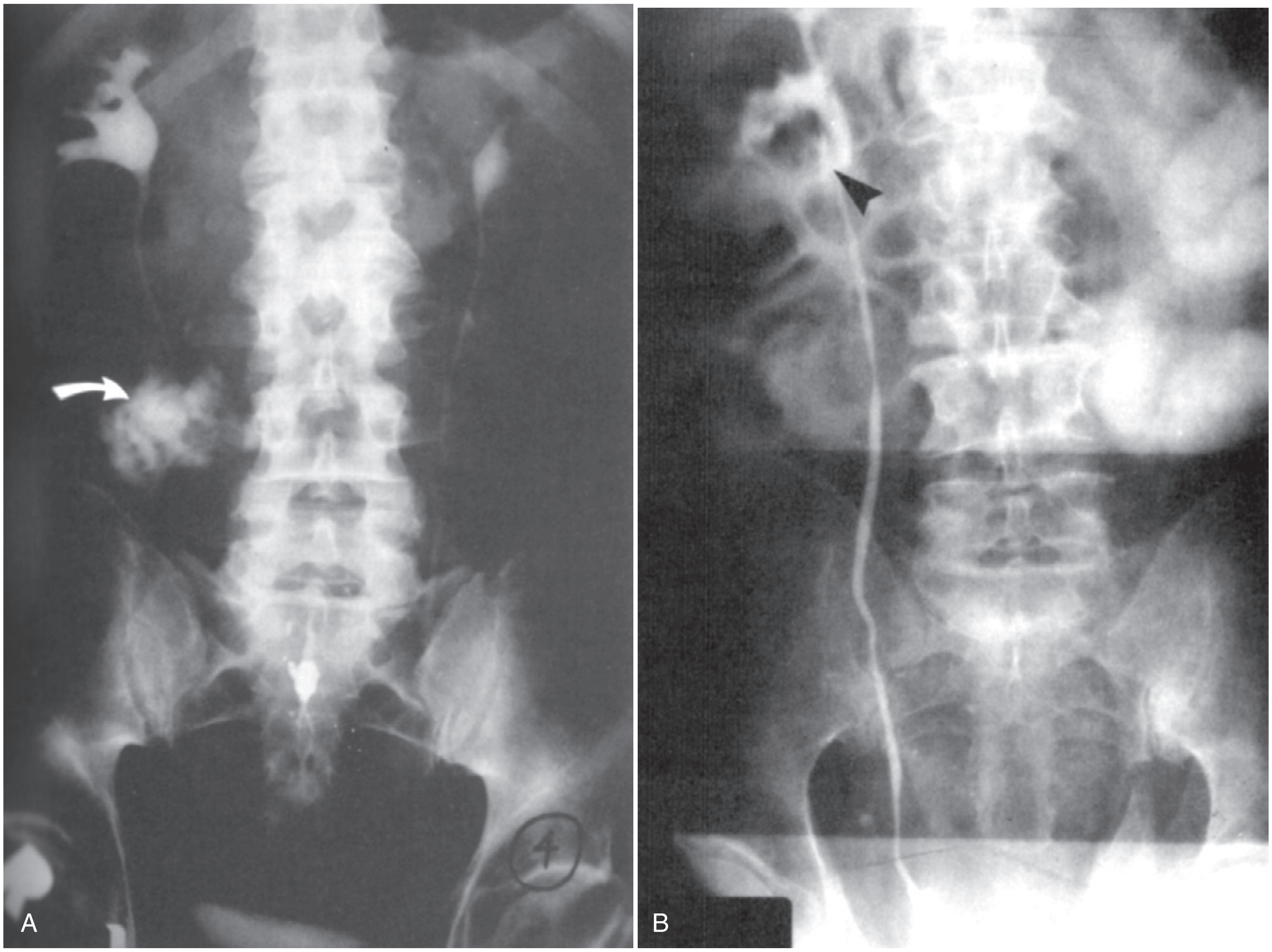
EXTERNAL GENITALIA

PENILE TRAUMA

Anatomy

The penis contains three masses of erectile tissue (Fig. 47-24). The two corpora cavernosa constitute the main bulk and lie in the center of the penis. The smaller corpus spongiosum lies on the ventral surface of the penis, encases the urethra, and expands at the penile tip to form the glans penis. Blood is supplied by arteries lying in each of the three erectile masses and by the two dorsal penile arteries. A single dorsal vein drains most of the penis. The tunica albuginea is a dense fibrous envelope that surrounds the corpus spongiosum and each corpus cavernosum. Buck's fascia

www.ketabpezeshki.com 66485457-66963820



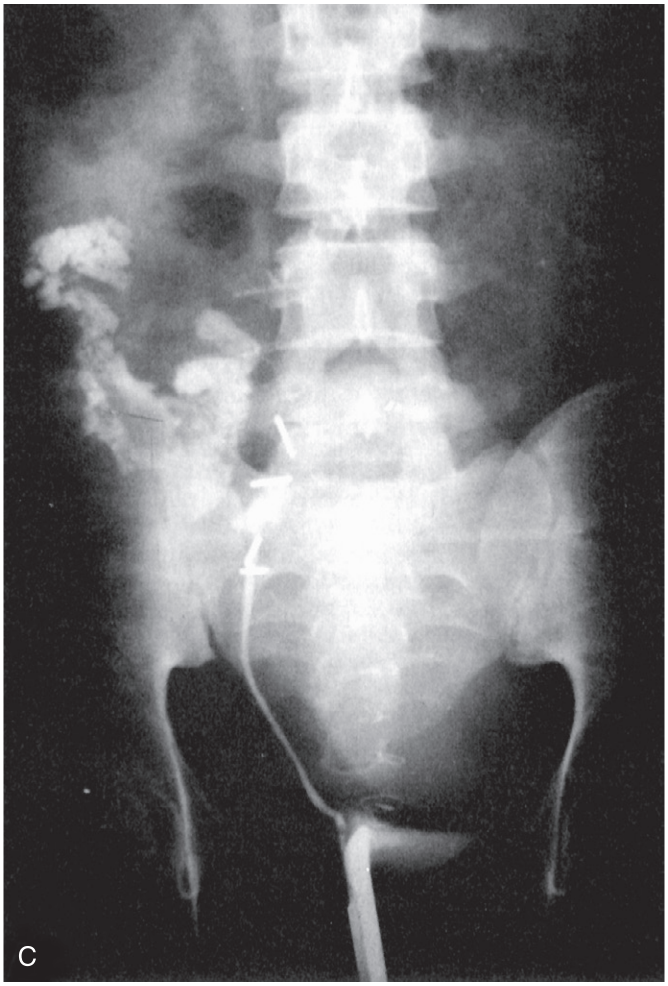


Figure 47-23. Ureteral injuries. **A,** Intravenous pyelography (IVP) of patient with upper ureteral injury demonstrating extravasation *(white arrow).* **B,** Retrograde pyelogram demonstrating extravasation at the ureteropelvic junction *(black arrowhead).* **C,** Retrograde pyelogram demonstrating extravasation into a urinoma in a patient with delayed diagnosis. (From Presti JC Jr, Carroll PR, McAninch JW: Ureteral and renal pelvic injuries from external trauma: Diagnosis and management. J Trauma 29:370, 1989.)

www.ketabpezeshki.com 66485457-66963820

overlies the tunica albuginea, enclosing all three of the erectile masses, the dorsal arteries, dorsal nerve, and deep dorsal vein within a common compartment.

Clinical Features

Important historical factors to ascertain include the mechanism of injury and the state of the penis, flaccid or erect, at the time the injuring force was inflicted, as well as tetanus immunization status. Penile injuries range from small lacerations or contusions to skin degloving or amputation. Strangulation injuries of the penile shaft inflicted by an encircling piece of string or hair may be seen in children (Fig. 47-25). Adolescents and adults may have various objects of penile incarceration such as bottles, washers, and metal rings (Fig. 47-26). These objects are often used to facilitate masturbation, prevent detumescence, and heighten sexual pleasure. Prolonged application of these devices may result in loss of superficial skin, deep urethral necrosis, or eventual need for penile amputation.[47]

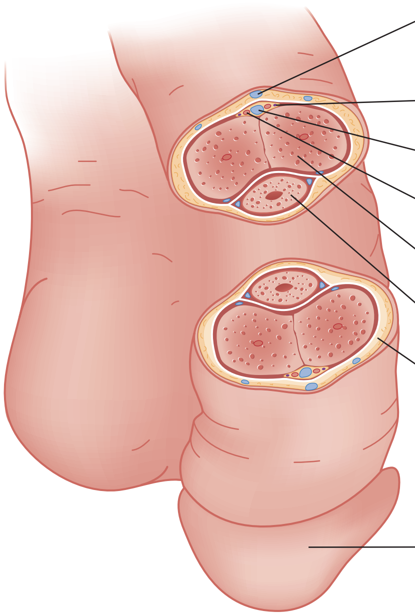


Figure 47-24. Cross-sectional view of the penis.

The pendulous nature of the flaccid penis provides a measure of protection from blunt injury. By contrast, forceful bending of the erect penis may result in traumatic rupture of the corpus cavernosum, or penile fracture, owing to tearing of the tunica albuginea. This injury may occur during vigorous sexual intercourse or masturbation.[48] The patient often reports hearing a snapping sound followed by immediate pain, detumescence, and a slowly progressive penile hematoma (Fig. 47-27). In the majority of cases, the swelling and ecchymosis are localized to the penile shaft and contained by Buck's fascia. The resultant appearance has been described as an "eggplant deformity." If Buck's fascia is torn, blood may track along fascial planes to the scrotum, perineum, and pubis. The corporal defect may be palpable on physical examination. Urethral injury occurs in 10 to 38% of penile fractures.[47] The diagnosis is suggested by the presence of gross hematuria, blood at the urethral meatus, or the inability to void, but may be possible even in the absence of these clinical findings. Urethral injury is present in up to 50% of all penetrating penile injuries.[21]

Penetrating trauma to the external genitalia may be inflicted by stab wounds or gunshot wounds. These injuries are frequently associated with concomitant injuries to the bladder, urethra, rectum, testis, and iliac and femoral vasculature.[47] Penile amputation may result from interpersonal violence or be self-induced as a result of severe psychiatric disease.

The testicles are vulnerable to injury because of their location but are relatively protected by the mobility of the scrotum, the tough tunica albuginea that surrounds the testes, and the cremasteric reflex. Eighty-five percent of testicular injuries are inflicted by blunt trauma, most commonly during sporting endeavors.[49] Mechanisms include falls, kicks, and direct strikes by thrown

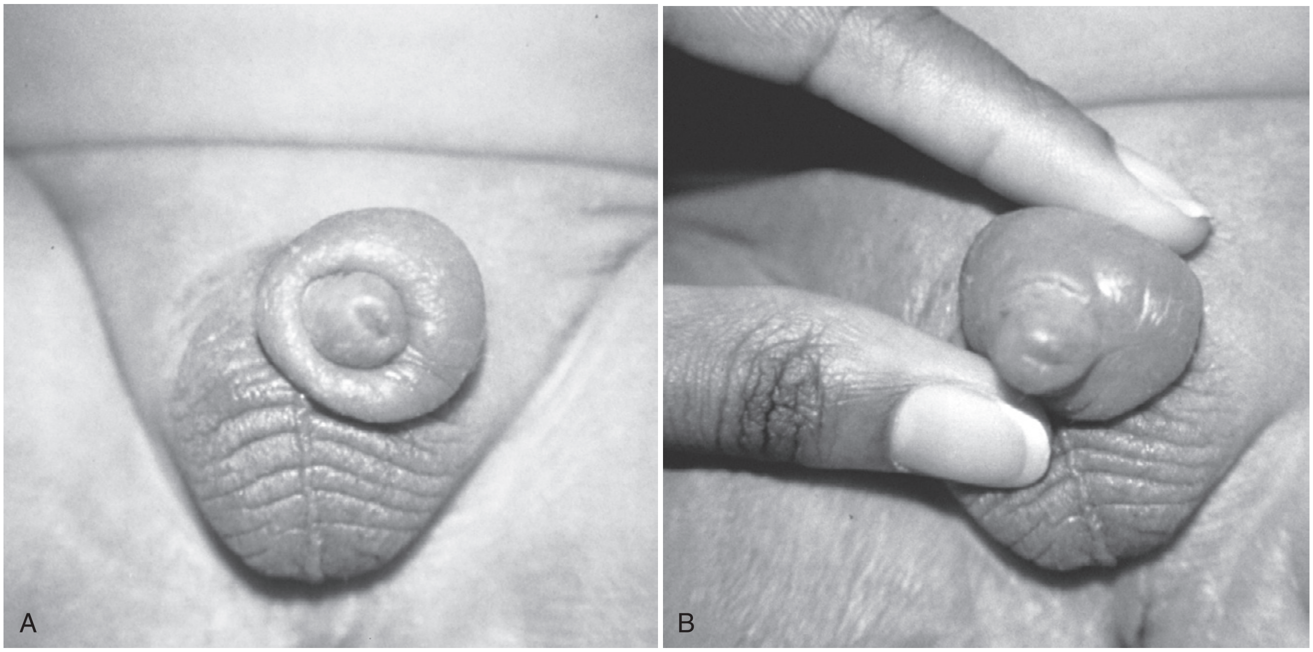


Figure 47-25. Idiopathic foreskin edema. **A,** This is the same picture that can be seen with penile strangulation injuries in children. **B,** The edematous foreskin is retracted proximally and distally, and encircling hair, string, or other objects that may lead to vascular compromise are sought.

www.ketabpezeshki.com 66485457-66963820

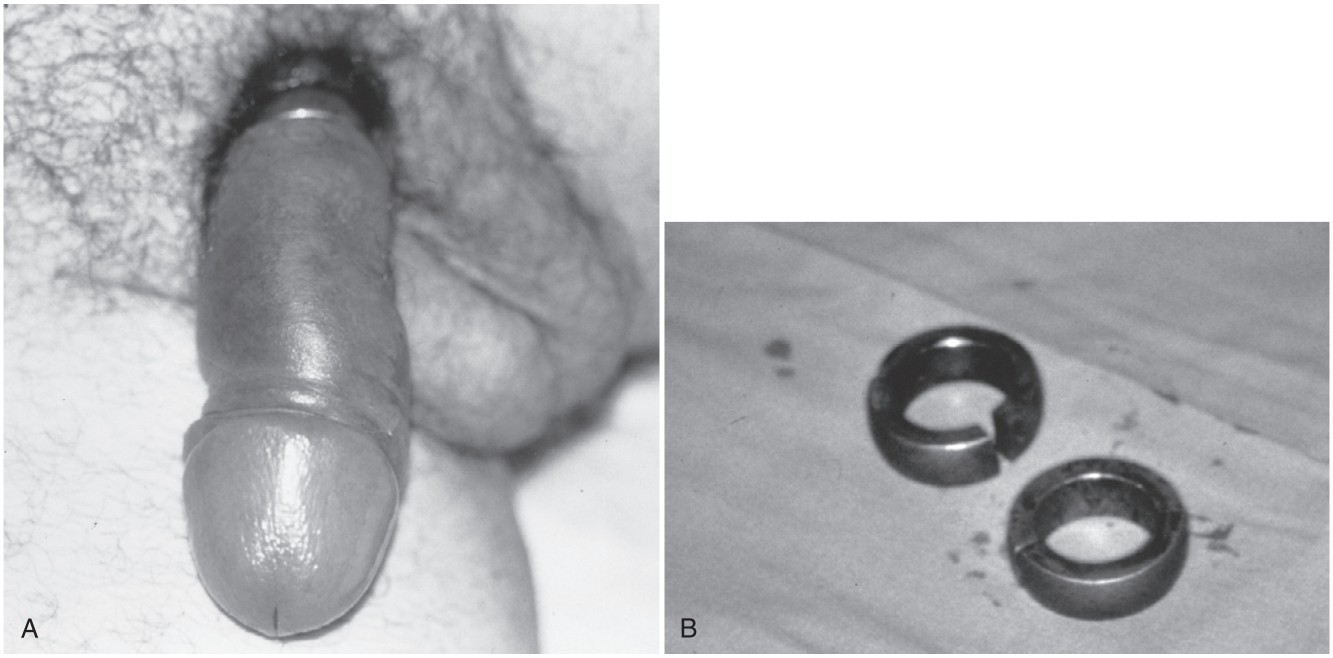


Figure 47-26. A, Self-induced priapism. This patient placed two steel washers (B) around the base of his penis to prolong his erection. Subsequent priapism developed, and the incarceration necessitated emergency intraoperative removal with a pneumatic orthopedic drill.

Figure 47-27. Fracture of the penis. Traumatic rupture of the corpus cavernosum, usually associated with sexual activity, results in a profound penile hematoma, most often requiring operative repair.

objects. Testicular rupture occurs in more than 40% of blunt scrotal trauma in patients who come to the hospital.[13,50] Additional injuries include scrotal hematoma, hematocele, intratesticular hematoma, traumatic testicular torsion, testicular avulsion, testicular displacement, and epididymal injury. Symptoms include severe pain, faintness, nausea, vomiting, and occasionally urinary retention secondary to pain. Physical examination is often inadequate owing to significant pain and swelling.[50]

Genital bite wounds may be inflicted by humans during sexual activity or by animals. The predominant human oral bacterial organism in genital bite wounds is *Eikenella corrodens;* however, transmission of viral infections, including hepatitis and human immunodeficiency virus (HIV), is possible.[47] Dog and cat bites may lead to pathogenic infections with *Pasteurella multocida* and anaerobic organisms. With certain animal bites, the possibility of rabies transmission is considered.

Injuries to the female external genitalia may result from pelvic fractures, sexual assault, or straddle-type mechanisms. Hematomas and lacerations are the most common injuries. Physical examination includes evaluation for associated injuries of the vagina, urethra, bladder, and rectum. Screening for interpersonal violence should be considered in all women with injuries to the external genitalia.

In children, blunt or penetrating injury to the external genitalia may be inflicted by straddle-type injuries or falls onto sharp objects. Child abuse should be considered and investigated when the explanation given for the event does not match the type of injury and objective physical findings. Examples include bruises that look like pinches, cigarette burns, or a penile injury reportedly caused by a falling toilet seat in a child who is too small to stand unsupported.

Diagnostic Strategies

A careful physical examination is usually sufficient to diagnose most blunt penile injuries. Retrograde urethrography is indicated in cases of suggested urethral injury, which should be considered in the presence of concomitant penile or scrotal hematoma, gross hematuria, or blood at the urethral meatus. Rarely, atypical presentations of penile fracture may require adjunctive imaging. Corpus cavernosography, ultrasound, and magnetic resonance imaging have all been advocated for this indication.[47,51,52] The acquisition of penile imaging should occur in consultation with the treating urologist.

Unlike with penile injuries, physical examination is frequently inadequate for the assessment of blunt scrotal trauma. Ultrasound is the test of choice owing to its higher than 95% sensitivity for testicular rupture when the diagnosis is based on the finding of a heterogeneous echo pattern of the testicular parenchyma with a loss of contour definition (Fig. 47-28).[50,53] Scrotal imaging is rarely indicated after penetrating trauma because surgical exploration is usually warranted.

www.ketabpezeshki.com 66485457-66963820

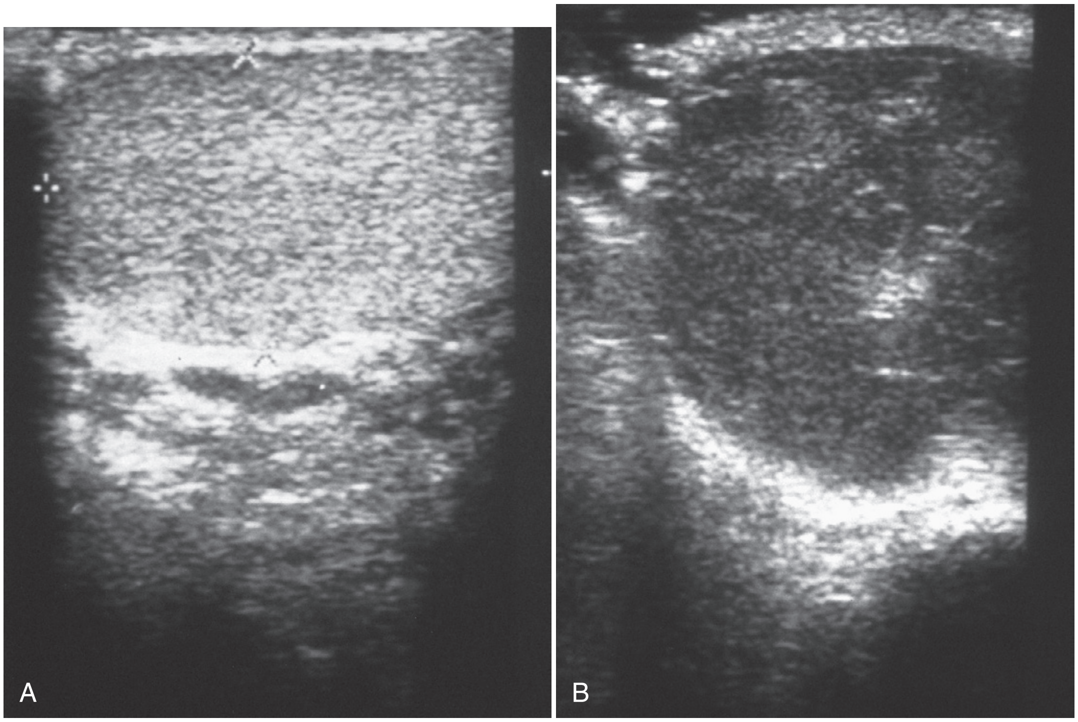


Figure 47-28. Testicular rupture. **A,** Testicular ultrasonogram demonstrates the normal homogeneous testicular pattern. **B,** The heterogeneous pattern of injury, tumor, or disruption.

Management

Constricting devices are promptly identified and removed, a procedure that can test the ingenuity of even the most experienced emergency physician (see Fig. 47-26). Various creative techniques with saws, metal cutters, or emery wheels may be necessary to remove some metal objects. Reconstructive surgery of the penis may eventually be needed but is usually delayed until penile tissue viability has been determined. Fortunately, each corpora body has a separate blood supply and may be preserved even though the penile skin may slough, necessitating skin grafting.

Superficial penile hematomas without rupture of the tunica albuginea and with no immediate detumescence of the erect penis may be treated conservatively with the local application of ice and administration of nonsteroidal anti-inflammatory drugs (NSAIDs).[13] Superficial lacerations of the penile and scrotal skin may be primarily approximated with 4-0 chromic or Vicryl absorbable suture. Patients with degloving penile injuries and scrotal skin loss should be treated by a urologist and plastic surgeon in the operating room with irrigation, débridement, and skin flaps or skin grafts.

With penile fracture, early surgical repair of the tunica albuginea defect (within 24-36 hours after injury) is indicated to maximize functional outcomes.[13,49,51] Early surgical exploration and repair are recommended for most penetrating injuries to the penis.[54] Penile amputation may be managed by reimplantation or local reshaping. Successful reimplantation may be achieved even up to 24 hours after amputation.[47,49] The recovered amputated penis should be carefully wrapped in sterile, saline-moistened gauze and placed in a plastic bag. That bag is then placed in a second plastic bag containing ice. Hemostasis of a bleeding penile stump can usually be achieved with direct pressure.

After blunt scrotal trauma, surgical exploration is indicated for treatment of testicular rupture, large hematocele, traumatic torsion, and testicular dislocation. Testicular salvage rates are 80 to 90% when surgical exploration occurs within 72 hours and less than 50% when exploration is delayed beyond 72 hours.[49] In patients with a sonographically normal, homogenous-appearing testicle, exploration is not necessary.[50] Testicular contusions are treated with bed rest, ice packs, NSAIDs, and urologic follow-up. Surgical exploration is indicated in nearly all cases of penetrating scrotal trauma.[50,54]

Patients with simple bite wounds within 6 to 12 hours after injury without gross contamination can be treated with irrigation and primary closure.[47,49] Broad-spectrum antibiotic coverage with an agent such as amoxicillin-clavulanate is indicated. Grossly contaminated or infected wounds should be irrigated, covered with a sterile dressing, and managed in conjunction with the consulting urologist.

Human bite wounds can cause a potentially serious polymicrobial infection. When cellulitis is present, immunocompromised patients should be admitted to the hospital for broad-spectrum intravenous antibiotic coverage for both aerobic and anaerobic organisms with an agent such as piperacillin-tazobactam. Immunocompetent hosts may be treated in the outpatient setting with broad-spectrum oral antibiotics, NSAIDs, and reevaluation in 48 hours.

www.ketabpezeshki.com 66485457-66963820

KEY CONCEPTS

- Diagnostic evaluation of the urinary tract is generally undertaken in retrograde fashion, that is, suggestion and elimination of urethral injury before bladder injury before ureteral or renal injury.
- Urethral injury is suggested by the presence of a pelvic fracture, blood at the urethral meatus, or evidence of a perineal, scrotal, or penile hematoma.
- Gross hematuria alone or in conjunction with a pelvic fracture is the absolute marker for significant bladder injury. Grossly clear urine in a trauma patient without a pelvic fracture virtually eliminates the possibility of bladder rupture.
- Bladder injury should be ruled out by retrograde cystography, which is more accurate than methods that use anterograde contrast administration.
- Adults at risk for significant blunt renal injury have gross hematuria, microhematuria with shock, or a history of sudden deceleration. Children at risk for significant blunt renal injury have hematuria with more than 50 RBCs/hpf or a history of significant deceleration.
- Intravenous contrast-enhanced helical CT with delayed images at 10 minutes after contrast injection is the imaging modality of choice for suggested upper tract injury.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. McAninch JW: *Injuries to the genitourinary tract*. In: Tanagho EA, McAninch JW, eds: *Smith's General Urology*, 18th ed. New York: McGraw-Hill; 2008.
2. Nicolaisen GS: Re-evaluation of the indications for radiological assessment. *J Urol* 1985; 133:183.
3. Shlamovitz GZ, McCullough L: Blind urethral catheterization in trauma patients suffering from lower urinary tract injuries. *J Trauma* 2007; 62:330.
4. Perry MO, Husmann DA: Urethral injuries in female subjects following pelvic fractures. *J Urol* 1992; 147:139.
5. Rosenstein DI, Alsikafi NF: Diagnosis and classification of urethral injuries. *Urol Clin North Am* 2006; 33:73.
6. Brandes S: Initial management of anterior and posterior urethral injuries. *Urol Clin North Am* 2006; 33:87.
7. Shlamovitz GZ, et al: Poor test characteristics for the digital rectal examination in trauma patients. *Ann Emerg Med* 2007; 50:25.
8. Ziran BH, Chamberlin E, Shuler FD, Shah M: Delays and difficulties in the diagnosis of lower urologic injuries in the context of pelvic fractures. *J Trauma* 2005; 58:533.
9. Esposito TJ, et al: Reasons to omit digital rectal exam in trauma patients: No fingers, no rectum, no useful additional information. *J Trauma* 2005; 59:1314.
10. Ball CG, et al: Traumatic urethral injuries: Does the digital rectal examination really help us? *Injury* 2009; 40:984.
11. Koraitim MM, Marzouk ME, Atta MA, Orabi SS: Risk factors and mechanism of urethral injury in pelvic fractures. *Br J Urol* 1996; 77:876.
12. Chapple C, et al: Consensus statement on urethral trauma. *BJU Int* 2004; 93:1195.
13. Lynch TH, et al: EAU guidelines on urological trauma. *Eur Urol* 2005; 47:1.
14. Spencer Netto FA, et al: Retrograde urethrocystography impairs computed tomography diagnosis of pelvic arterial hemorrhage in the presence of a lower urologic tract injury. *J Am Coll Surg* 2008; 206:322.
15. Gomez RG, et al: Consensus statement on bladder injuries. *BJU Int* 2004; 94:27.
16. Cass AS, Luxenberg M: Features of 164 bladder ruptures. *J Urol* 1987; 138:743.
17. Corriere JN, Sandler CM: Mechanisms of injury, patterns of extravasations and management of extraperitoneal bladder rupture due to blunt trauma. *J Urol* 1988; 139:43.
18. Andrich DE, Mundy AR: The nature of urethral injury in cases of pelvic fracture urethral trauma. *J Urol* 2001; 165:1492.
19. Brewer ME, Wilmoth RJ, Enderson BL, Daley BJ: Prospective comparison of microscopic and gross hematuria as predictors of bladder injury in blunt trauma. *Urology* 2007; 69:1086.
20. Morey AF, et al: Bladder rupture after blunt trauma: Guidelines for diagnostic imaging. *J Trauma* 2001; 51:683.
21. Jankowski JT, Spirnak JP: Current recommendations for imaging in the management of urologic traumas. *Urol Clin North Am* 2006; 33:365.
22. Deck AJ, Shaves S, Talner L, Porter JR: Computerized tomography cystography for the diagnosis of traumatic bladder rupture. *J Urol* 2000; 164:43.
23. Vaccaro JP, Brody JM: CT cystography in the evaluation of major bladder trauma. *Radiographics* 2000; 20:1373.
24. Corriere JN Jr, Sandler CM: Diagnosis and management of bladder injuries. *Urol Clin North Am* 2006; 33:67.
25. Al-Qudah HS, Santucci RA: Complications of renal trauma. *Urol Clin North Am* 2006; 33:41.
26. Santucci RA, et al: Validation of the American Association for the Surgery of Trauma organ injury severity scale for the kidney. *J Trauma* 2001; 50:195.
27. Moore EE, et al: Organ injury scaling: Spleen, liver, and kidney. *J Trauma* 1989; 29:1664.
28. Broghammer JA, Fisher MB, Santucci RA: Conservative management of renal trauma: A review. *Urology* 2007; 70:623.
29. Santucci RA, et al: Evaluation and management of renal injuries: Consensus statement of the renal trauma subcommittee. *BJU Int* 2004; 93:937.
30. Morey AF, McAninch JW, Tiller BK, Duckett CP, Carroll PR: Single shot intraoperative excretory urography for the immediate evaluation of renal trauma. *J Urol* 1999; 161:1088.
31. Alsikafi NF, Rosenstein DI: Staging, evaluation, and nonoperative management of renal injuries. *Urol Clin North Am* 2006; 33:13.
32. Mee SL, McAninch JW, Robinson AL, Auerbach PS, Carroll PR: Radiographic assessment of renal trauma: A 10-year prospective study of patient selection. *J Urol* 1989; 141:1095.
33. Brown SL, Elder JS, Spirnak JP: Are pediatric patients more susceptible to major renal injury from blunt trauma? A comparative study. *J Urol* 1998; 160:138.
34. Santucci RA, Langenburg SE, Zachareas MJ: Traumatic hematuria in children can be evaluated as in adults. *J Urol* 2004; 171:822.
35. Morey AF, Bruce JE, McAninch JW: Efficacy of radiographic imaging in pediatric blunt renal trauma. *J Urol* 1996; 156:2014.
36. Buckley JC, McAninch JW: Pediatric renal injuries: Management guidelines from a 25-year experience. *J Urol* 2004; 172:687.
37. Buckley JC, McAninch JW: The diagnosis, management, and outcomes of pediatric renal injuries. *Urol Clin North Am* 2006; 33:33.
38. Smith JK, Kenney PJ: Imaging of renal trauma. *Radiol Clin North Am* 2003; 41:1019.
39. Jones AE, Mason PE, Tayal VS, Gibbs MA: Sonographic intraperitoneal fluid in patients with pelvic fracture: Two cases of traumatic intraperitoneal bladder rupture. *J Emerg Med* 2003; 25:373.
40. Master VA, McAninch JW: Operative management of renal injuries: Parenchymal and vascular. *Urol Clin North Am* 2006; 33:21.
41. Siram SM, et al: Ureteral trauma: Patterns and mechanisms of injury in an uncommon condition. *Am J Surg* 2010; 199:566.
42. Elliott SP, McAninch JW: Ureteral injuries from external violence: The 25-year experience at San Francisco General Hospital. *J Urol* 2003; 170:1213.
43. Perez-Brayfield MR, et al: Gunshot wounds to the ureter: A 40-year experience at Grady Memorial Hospital. *J Urol* 2001; 166:119.
44. Elliott SP, McAninch JW: Ureteral injuries: External and iatrogenic. *Urol Clin North Am* 2006; 33:55.
45. Kunkle DA, Kansas BT, Pathak A, Goldberg AJ, Mydlo JH: Delayed diagnosis of traumatic ureteral injuries. *J Urol* 2006; 176:2503.
46. Carver BS, Bozeman CB, Venable DD: Ureteral injury due to penetrating trauma. *South Med J* 2004; 97:462.
47. Wessells H, Long L: Penile and genital injuries. *Urol Clin North Am* 2006; 33:117.
48. Koifman L, Barros R, Júnior RA, Cavalcanti AG, Favorito LA: Penile fracture: Diagnosis, treatment and outcomes of 150 patients. *Urology* 2010; 76:1488.
49. Morey AF, Metro MJ, Carney KJ, Miller KS, McAninch JW: Consensus on genitourinary trauma: External genitalia. *BJU Int* 2004; 94:507.
50. Buckley JC, McAninch JW: Diagnosis and management of testicular ruptures. *Urol Clin North Am* 2006; 33:111.
51. Lee SH, et al: Trauma to male genital organs: A 10-year review of 156 patients, including 118 treated by surgery. *BJU Int* 2008; 101:211.
52. Bhatt S, Kocakoc E, Rubens DJ, Seftel AD, Dogra VS: Sonographic evaluation of penile trauma. *J Ultrasound Med* 2005; 24:993.
53. Guichard G, et al: Accuracy of ultrasonography in diagnosis of testicular rupture after blunt scrotal trauma. *Urology* 2008; 71:52.
54. Cline KJ, Mata JA, Venable DD, Eastham JA: Penetrating trauma to the male external genitalia. *J Trauma* 1998; 44:492.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 48

Peripheral Vascular Injury

Edward J. Newton and Sanjay Arora

PERSPECTIVE

Injury to the major peripheral arteries or veins is often life-threatening but invariably poses a threat to the viability of the affected limb. Historically, because of rapid blood loss, injury to major vessels was often quickly fatal in the field. Most patients who survived to reach a hospital had relatively minor vascular injuries. However, with the advent of modern emergency medical services systems with advanced extrication methods and rapid transport, more patients with major vascular injury reach the hospital alive.[1] In addition, the incidence of penetrating civilian injuries from interpersonal violence and blunt injuries from motor vehicle–related trauma in the United States has increased dramatically during the past 50 years. Consequently, emergency physicians are frequently confronted with critically ill patients harboring overt or occult vascular injuries. Management of vascular injuries has evolved with advances in diagnostic methods and surgical techniques. Treatment of vascular injuries before and during World War II was simple ligation of the peripheral artery or vein involved. This approach resulted in limb amputation rates ranging from 40% for axillary artery injuries to 72% for popliteal artery injuries. During the Korean War, routine attempts to repair injured arteries decreased the amputation rate for popliteal injuries to 32%.[2,3] During the Vietnam War, repair of penetrating axillary and popliteal artery injuries with routine angiography and improved surgical techniques resulted in decreases in the amputation rate to as low as 5 and 15%, respectively, which approach the current rates of amputation for civilian injuries.[2,3] Owing to the nature of the munitions and the extensive use of body armor in the Iraq and Afghanistan wars, the proportion of severe wounds of the extremities has increased. The amputation rates thus far are 5% for upper extremity and 21% for lower extremity vascular injuries.[2] However, extrapolation of high-velocity military wound data to low-velocity civilian gunshot wounds may not be valid, and even lower rates might be expected with civilian wounds.

Tremendous progress has been achieved in diagnostic and therapeutic techniques for dealing with peripheral vascular injuries, and several noninvasive diagnostic modalities have emerged as accurate alternatives to surgical exploration or angiography. These techniques are easily used in the emergency department, and the goal of timely detection and repair of serious vascular injuries is achievable in the vast majority of cases.

Epidemiology

Throughout the world, the causes of peripheral vascular injuries are divided almost equally between blunt and penetrating mechanisms. In the United States, 56 to 90% of these injuries are a result of penetrating wounds, mainly because of the high rate of penetrating trauma in inner-city urban areas.[4-7] Although the incidence of low-velocity gunshot wounds has decreased during the past decade, gunshot wounds remain the second leading cause of death in the 15- to 34-year-old age group in the United States.[8] Major venous injuries are present in 13 to 51% of all cases, but more than 80% of these are associated with arterial injury as well.[9] Approximately 90% of patients with vascular injury are male, and most are younger than age 40 years.[5] Because of the increased use of percutaneous endovascular diagnostic and therapeutic procedures, the incidence of iatrogenic vascular injuries has increased and accounts for up to one third of all cases in some series.[10,11]

PRINCIPLES OF DISEASE

Pathophysiology

Blunt and penetrating types of trauma result in a similar spectrum of vascular injuries, although the mechanisms of injury differ. Although blunt vascular injuries are less common than penetrating injuries, they are often more severe and more commonly result in amputation because of associated injuries to nerves, bone, and soft tissue. Certain mechanisms of injury, such as animal bites that crush and lacerate vessels, combine penetrating and blunt mechanisms.

Penetrating Trauma

Penetrating trauma from gunshot wounds results in the formation of a temporary cavity within distensible soft tissues with almost immediate recoil of these tissues. The size of the cavity and hence the degree of soft tissue injury depend principally on the velocity of the missile, as well as the tumble and yaw of the bullet. Consequently, gunshot wounds can cause direct arterial laceration or transection in addition to concussive injury at some distance from the track of the bullet. The latter injuries tend to be tears in the intima of an artery with subsequent thrombosis that may not become apparent for hours to months after the injury. Ricochet of bullets that are deflected by bone make predicting the trajectory less accurate that with stab wounds.

Stab wounds can cause vascular injury by complete or partial transection of vessels. Partial laceration of an artery may produce few symptoms of arterial insufficiency on initial evaluation but commonly results in delayed complications. The vascular structures at risk can be predicted more reliably with stab wounds than with gunshot wounds by taking into consideration the anatomic location, the depth and direction of the wound, and the implement involved.

Shotgun wounds are less common than gunshot or stab wounds and cause injuries varying from minor soft tissue wounds to

www.ketabpezeshki.com 66485457-66963820

massive destruction of soft tissue and bone, depending primarily on the range from which the shotgun was fired. The presence of multiple missiles ranging from 9 or 10 (buckshot) to dozens (birdshot) also complicates the evaluation of these injuries because of the many potential sites for vascular injury to occur. In addition, close-range shotgun wounds (<3 yards) can cause significant blunt trauma to blood vessels as well as a higher rate of bone and nerve injury than occurs with gunshot wounds. Migration of pellets or bullets proximally through the venous system to the heart or migration through an artery with subsequent distal occlusion has been reported frequently as a delayed complication.

Blunt Trauma

Blunt injury involves avulsion forces that can stretch vessels beyond their capacity or direct crushing injury that disrupts the vessel wall. Fracture fragments resulting from blunt extremity trauma can lacerate or entrap vessels. Vascular injury can range from small intimal tears to complete avulsion of arteries and nerves. Open avulsion injury of a limb is particularly severe because the skin is the final structure to tear, and once such tearing has occurred, it is inevitable that vessels and nerves will be torn as well. Vascular injury also should be suspected in patients with massive soft tissue avulsion or crush injury, displaced long bone fractures, electrical or lightning injuries, and severe burns, as well as in those with compartment syndrome from trauma or prolonged immobilization as a result of stroke, coma, drug overdose, or other causes.[12-15] Bites that are inflicted by large animals, such as dogs used by law enforcement, are particularly prone to arterial injury and wound complications.[12,13] Collateral circulation may continue to perfuse the limb adequately, but injuries that occur proximal to the collateral branch point or that involve both the main trunk and collateral branches will preclude adequate flow.

Distal ischemia results from the inability of tissues to continue aerobic metabolism. Eventually, anaerobic metabolism consumes all substrate, thereby resulting in the accumulation of lactic acid. As ischemia progresses, cellular integrity is lost and irreversible cell death occurs. A vicious cycle of tissue edema and further impairment of the blood supply occurs.

When no specific measures are taken to cool the limb, it is said that the limb is undergoing “warm ischemia” at room temperature. Although the time in individuals may vary, 6 hours of complete warm ischemia is generally considered the point at which irreversible nerve and muscle damage begins to occur. After 6 hours of warm ischemia, 10% of patients will have irreversible damage; by 12 hours, 90% will have irreversible damage. Artificially cooling the limb to just higher than freezing temperature (cold ischemia) will reduce the metabolic demands of unperfused tissues and greatly prolong the tissue’s tolerance of ischemia to 24 hours or more. Animal studies suggest that hyperbaric therapy may be useful in repaired limbs that have undergone prolonged warm ischemia.[16]

Two main types of vascular injury can result from trauma: *occlusive injury* (transection, thrombosis, and reversible spasm), in which all effective perfusion distal to the occlusion is lost, and *nonocclusive injury* (intimal flap, dissection, arteriovenous fistula [AVF], and pseudoaneurysm), in which some arterial flow continues past the injury.

Complete Occlusive Injury

Transection. The most common vascular injury is complete transection in which distal flow is effectively eliminated. Cleanly transected arteries will often retract and undergo spasm so that blood loss is minimized. With longitudinal arterial lacerations and venous injuries, blood loss cannot be limited by this means, and such injuries tend to result in greater blood loss. Pulsatile bleeding may lead to exsanguinating hemorrhage and shock.

Figure 48-1. Complete thrombosis of the distal brachial artery after reduction of a posterior elbow dislocation. (Courtesy D. Demetreades, MD.)

Thrombosis. Intraluminal thrombosis (Fig. 48-1) may occur in an injured artery acutely (within 24 hours) or may be delayed for many months. Acute thrombosis is initiated by stasis resulting from compression of the artery or from a disruption in the intima of an artery that becomes a nidus for thrombus formation. As the thrombus propagates, complete occlusion of the vessel can occur. Delayed thrombosis can occur months to years after injury if the injured vessel heals with stricture formation and decreased blood flow distally, followed by stasis and clot formation.

Reversible Arterial Spasm. The precise cause and incidence of significant reversible arterial spasm after trauma are unknown. In the case of arterial transection, arterial spasm is beneficial and limits hemorrhage. In other cases, however, the segmental arterial spasm occurs at some distance from the site of traumatic injury and can produce severe distal ischemia. Arterial spasm is particularly common in children. The spasm usually reverses with conservative treatment (topical warm saline or topical nitroglycerin paste), but prolonged spasm may require infusion of vasodilators such as nitroglycerin, calcium channel blockers, alpha-blockers, nitroprusside, specific prostaglandin inhibitors, or warm saline.[17] In many series, segmental arterial spasm is the most common arteriographic finding. However, it should never be assumed on clinical grounds that symptoms of ischemia are a result of arterial spasm; that diagnosis is based on arteriographic results only.

Nonocclusive Injuries

Intimal Flap. An intimal flap occurs when there is a break in the intima of a vessel, generally from excessive stretch or concussive forces. Although flow is not altered by small flaps and the associated soft tissue wounds often appear benign initially, these intimal flaps may become a nidus for thrombosis that can occur hours to months after the initial injury. However, most intimal flaps heal spontaneously, and asymptomatic injuries that do not disrupt perfusion of the limb can be treated conservatively with antiplatelet agents such as clopidogrel.

www.ketabpezeshki.com 66485457-66963820

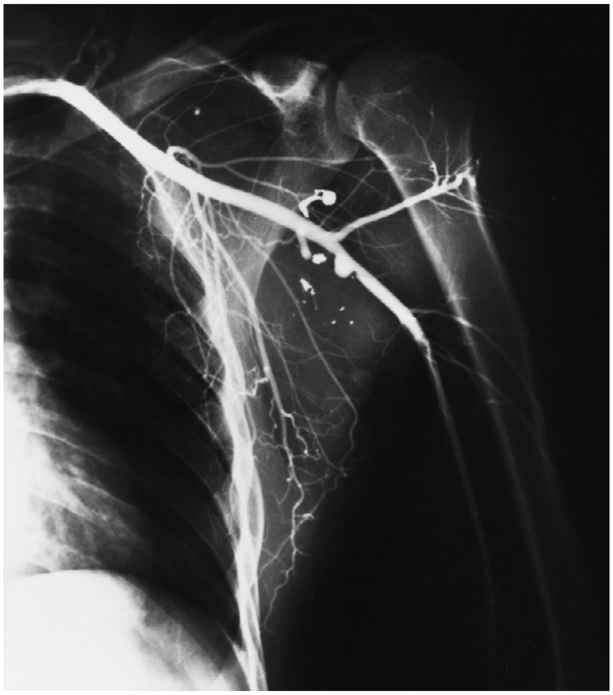


Figure 48-2. Multiple small pseudoaneurysms of the axillary artery after penetrating injury. (Courtesy D. Demetreades, MD.)

Pseudoaneurysm. A true aneurysm contains all three layers of the vessel wall (intima, media, and adventitia) and rarely is caused by trauma. A pseudoaneurysm is formed following a tear in a vessel wherein the hemorrhage is contained by surrounding fascia and the resulting hematoma is gradually encased by a capsule of fibrous tissue, analogous in consistency to the adventitia of a normal vessel (Fig. 48-2). Because it is relatively thin walled, rupture of a pseudoaneurysm is a distinct possibility. In addition, because its diameter inevitably expands under arterial pressure over days to months, compression of adjacent tissue may result in neuropathy, venous obstruction with resultant peripheral edema and venous thrombosis, and even erosion into adjacent bone.[18] The cavity of a pseudoaneurysm is in direct communication with the lumen of the vessel, so embolization of mural clots may produce distal arterial occlusion. Patients with pseudoaneurysm are commonly seen months to years later with symptoms of compression neuropathy or peripheral arterial embolism or for investigation of a soft tissue "tumor" that represents the growing aneurysm.

Arteriovenous Fistula. An AVF is formed when both the artery and an adjacent vein are injured. Higher-pressure arterial flow is directed into the lower-pressure vein, thereby diverting the blood supply to distal tissues and engorging the distal veins. Because the aperture of the fistula is often relatively narrow and thus results in turbulent flow, a bruit and palpable thrill are common diagnostic findings. Symptoms are primarily those of distal ischemia, but rarely, high-output congestive heart failure may occur when large central vessels are involved. Symptoms are often delayed for months because it takes time for the fistula to mature.

Compartment Syndrome. Compartment syndrome is most common after crush injury or a long bone fracture but may also be seen after reperfusion of an ischemic limb. Initially, blood flow is diminished and the injury can be considered nonocclusive. Progressive edema elevates tissue pressure above capillary pressure, thus ending arterial perfusion and initiating a cascade of events that results in compartment syndrome. The risk for this complication is increased when ischemia time is prolonged; in the presence of combined arterial and venous injury; after ligation or repair of a major artery or vein; or in the presence of significant soft tissue injury, frequently concomitant with a long bone fracture.[5] Smaller caliber vessels are compressed first, whereas larger vessels remain relatively patent and compartment pressure rarely exceeds arterial pressure, so pulses may be palpable until very late in the course. If the condition is allowed to progress, however, all blood flow may end and the injury is then an occlusive one. After restoration of arterial flow to a previously ischemic limb, a cascade of reperfusion injury has been identified that results from release of oxygen free radicals, lipid peroxidation, and influx of intracellular calcium. These mediators give rise to progressive cellular damage, edema, and necrosis, thereby propagating the vicious cycle that increases compartment pressure.[19] Consequently, frequent reexamination of the limb is indicated to assess compartment pressure after arterial repair or in the high-risk circumstances listed earlier.

CLINICAL FEATURES

Detection and treatment of vascular injuries takes place within the context of the overall resuscitation of the patient according to established principles of trauma care.[20] If the source of bleeding is readily identifiable, it is compressed with digital pressure. While control of active bleeding is being achieved in this manner, detection and treatment of other life-threatening injuries proceed concurrently. Peripheral vascular injury can occur coincident with other life-threatening trauma, which may take higher priority in resuscitating the patient. In other cases, peripheral vascular injury may be the most serious or only injury, and evaluation and management of this type of injury can proceed directly. Despite rapid transport to a hospital through a modern emergency medical service, injury to large central arteries and veins is still often fatal, and many of these deaths occur before medical contact. Patients who survive to reach the hospital may have obvious exsanguinating hemorrhage or only very subtle signs of vascular injury. Many patients have no evidence of injury but are considered at risk for vascular injury because of penetrating wounds that traverse the course of major neurovascular bundles or because they have sustained high-risk injuries such as posterior knee dislocation. Patients who remain hypotensive after an initial fluid challenge may harbor an occult vascular injury if no other cause is found. In addition, patients with symptoms of intermittent claudication or with unexplained peripheral embolization and a history of previous trauma to the limb should be suspected of having occult arterial injury.

Peripheral vascular injury can be divided into three categories by physical examination: hard findings, soft findings, and asymptomatic high-risk wounds based on the mechanism of injury.

Hard Findings of Vascular Injury

Many patients have the classic "hard" findings of arterial injury, including pulsatile bleeding, loss of distal pulses, an audible bruit or palpable thrill indicative of an AVF, or an expanding or pulsatile hematoma.[21] In addition, pallor or cyanosis and decreased temperature are common in a poorly perfused extremity, and massive distention of distal superficial veins may indicate an AVF as arterial flow is directed into distensible veins. The incidence of arterial injury in patients with any hard finding is consistently greater than 90%,[22,23] and the presence of these findings requires further investigation by emergency angiography or, more commonly, immediate surgical intervention, depending on the duration of warm ischemia and the overall status of the patient.

Soft Findings of Vascular Injury

An additional group of patients have "soft findings" of vascular injury, including a palpable but diminished pulse in comparison

www.ketabpezeshki.com 66485457-66963820

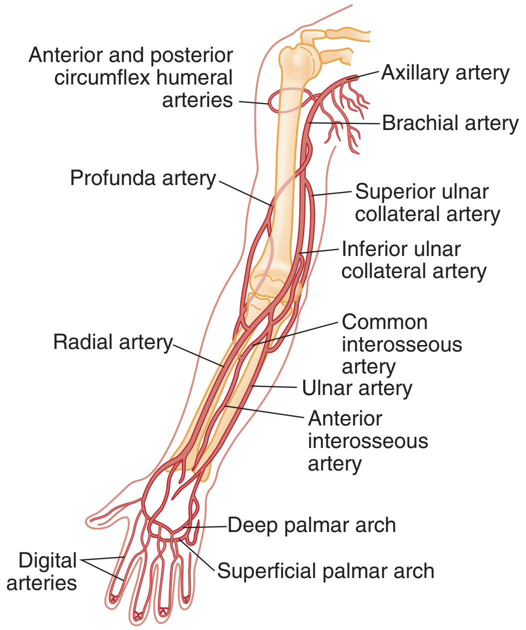


Figure 48-3. Major arteries of the upper limb. (From Snell R, Smith M [eds]: Clinical Anatomy for Emergency Medicine. St Louis, Mosby, 1993.)

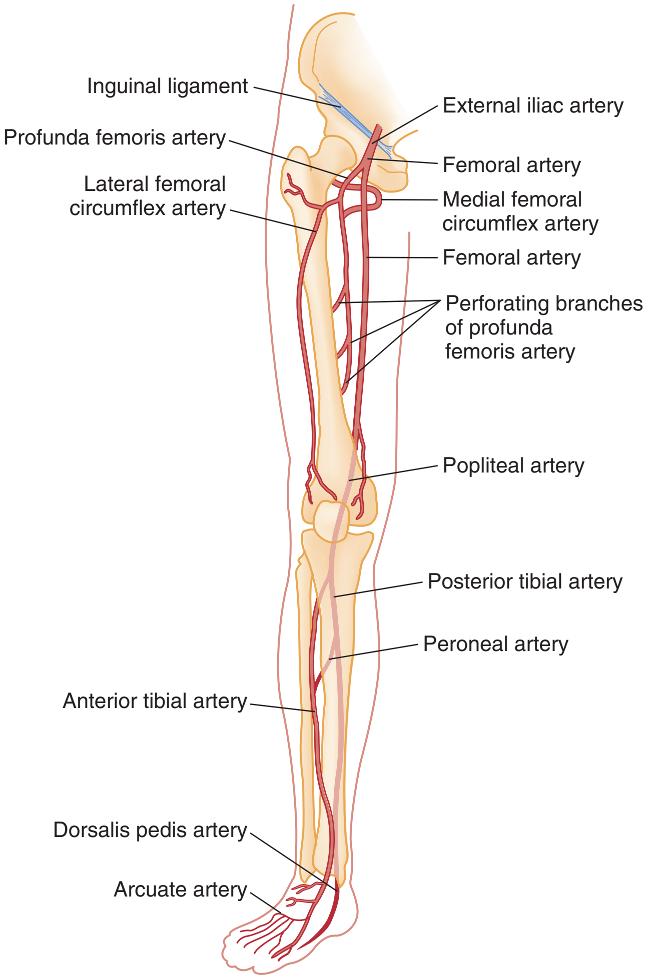


Figure 48-4. Major arteries of the lower limb. (From Snell R, Smith M [eds]: Clinical Anatomy for Emergency Medicine. St Louis, Mosby, 1993.)

with the uninjured extremity, isolated peripheral nerve injury, history of severe hemorrhage in the field, unexplained hypotension, or a large nonpulsatile hematoma.[21-24] The significance of prolonged capillary refill is controversial; some experts find it to be a reliable sign of vascular injury (when combined with a pulse deficit) and consider delayed capillary refill to be a valid "soft sign" of vascular injury. Others have found this sign to be a nonspecific and unreliable predictor of arterial injury.[5] Delayed capillary refill by itself is insufficient to diagnose arterial injury, but in combination with other physical signs it supports the diagnosis.

Isolated penetrating injury to a peripheral nerve is commonly associated with vascular injury because of the close proximity of these structures within the neurovascular bundles. Vascular injury occurs in 8 to 45% of cases of penetrating peripheral nerve injury.[25,26] Conversely, vascular injuries have associated peripheral nerve injury in almost half of cases. It is sometimes difficult to distinguish whether the pain, paresthesias, or paralysis is caused by a primary nerve injury, an associated vascular injury causing compression of the nerve, or compartment syndrome. In general, primary nerve injury occurs immediately at the time of injury, whereas vascular neuropathy occurs over minutes to hours after the injury. Up to 35% of patients with "soft" findings of vascular injury have positive angiographic studies, although only a small proportion of these injuries require emergency repair.[21,26,27]

High-Risk Injuries

The proximity of a penetrating wound to a neurovascular bundle is defined imprecisely. Various definitions include 1 cm, 1 inch, or 5 cm as constituting "proximity." Certainly, penetrating wounds that occur within 1 cm of a major neurovascular bundle or whose presumed trajectory has crossed such a bundle ("proximity wounds") are more likely to produce an occult vascular injury. Major neurovascular bundles include large limb arteries proximal to critical branch points, such as the axillary, brachial, common femoral, and popliteal arteries (Figs. 48-3 and 48-4).[28] In addition, a small minority of patients with high-risk injuries, such as bites from large dogs or other animals, shotgun wounds, severely displaced fractures, crush injuries, or major joint dislocations (especially knee dislocation), will initially have occult vascular injury that may not be detected on physical examination.[29] The risk of missing such injuries is that the traditional 6-hour window of warm ischemia time will be exceeded or the patient will experience delayed complications resulting in loss of the limb. For example, patients with intimal flaps may be completely asymptomatic initially but can subsequently develop arterial thrombosis. Similarly, pseudoaneurysms progressively enlarge to produce compression of adjacent structures but may be very small and undetectable on initial physical examination. Consequently, some centers routinely perform radiographic confirmation of arterial patency in these cases, although in most large-volume trauma centers current practice does not consider proximity alone as an indication for imaging.

History

In patients who achieve and maintain hemodynamic stability, a more comprehensive history can be obtained. Important historical points to note include the exact time and mechanism of the injury. The time of injury is important because of the significant morbidity that results from prolonged warm ischemia time. The mechanism is of clinical and often forensic importance in that the injury is frequently inflicted during an assault or other violent crime, in the context of domestic violence or physical abuse, or in association with work. Various mechanisms of injury may mandate special reporting and may alter the patient's ultimate disposition. Certain types of injuries, such as crush or bite wounds, are

www.ketabpezeshki.com 66485457-66963820

particularly prone to complications. The occupation, avocation, and hand dominance of the patient are pertinent because a more aggressive strategy may be indicated in certain cases. Medical conditions that pose a risk of complications are important to note. Patients who are immunocompromised because of diabetes, acquired immunodeficiency syndrome, asplenia, cancer, or steroid use are at increased risk for infection and impaired wound healing. Patients with previous vascular insufficiency have more tenuous perfusion, are more susceptible to ischemia from elevated compartment pressure, and have a higher incidence of complications. As with most aspects of trauma care, patients whose sensorium is altered by head injury or intoxication, patients with spinal cord injury who cannot perceive pain, and those with significant painful distracting injuries will not reliably be able to report pain or paresthesias suggesting vascular insufficiency, so extra caution is exercised in these cases.

Physical Examination

Surprisingly, in this era of increased reliance on technology, meticulous physical examination in combination with comparison of blood pressures in the affected and unaffected limbs has reemerged as the mainstay of diagnosis of vascular injury.[22] Physical examination is directed at discovering evidence of local wound complications and distal ischemia suggestive of vascular injury. Palpation of pulses in the affected extremities is the initial step. A comparison of the strength and quality of the pulses between the injured limb and its uninjured counterpart is then made. Isolated detection of a diminished pulse distal to the site of injury is a finding that merits further investigation rather than immediate surgery because palpation of pulses is a relatively inaccurate means of predicting arterial injury. False-positive findings of a pulse deficit may occur because of shock, in which all pulses are diminished; congenital absence of a pulse in one extremity; preexisting vascular disease; or arterial spasm or compression. A false-positive finding of a pulse deficit occurs in 10 to 27% of cases.[5,22,23] False-negative findings can occur with transmission of the pulse through a "soft clot," past an intimal flap, or through collateral circulation. Distal pulses can persist in 6 to 42% of patients despite significant arterial injury.[30] Compression of an artery by casts, splints, or dressings may produce a pulseless extremity, and these should be removed if evidence of ischemia occurs. Finally, although the pulse may be absent, the limb may be well perfused by collateral arterial supply, thus making immediate repair of the arterial injury less compelling. Simultaneous palpation of the injured and unaffected limbs can detect relatively small differences in skin temperature that may suggest hypoperfusion. Testing two-point discrimination on the injured and unaffected limbs is similarly an effective means of detecting sensory deficits. Auscultation over the site of injury is an often-ignored examination that may reveal a bruit suggestive of an AVF. A bruit is audible in more than half of patients with an AVF.[31] Repeated examination of the hematoma adjacent to the wound is indicated during the first 24 hours to determine whether it is expanding or pulsatile.

Despite the limitations just noted, reliance on the history and physical examination to triage patients into immediate surgery, imaging studies, and observation groups has been found to be relatively dependable, with a sensitivity of 92% and a specificity of 95%.[22] However, studies of military casualties injured by blast injury or high-velocity gunshot wounds have found physical examination to be less reliable than in studies of civilian casualties.[32]

DIAGNOSTIC STRATEGIES

The diagnostic strategy for detection of peripheral vascular injury is tailored to the clinical situation. Patients with clearly evident major arterial injury (e.g., pulsatile hemorrhage from a penetrating wound with a cold, pulseless distal end of the extremity) may require emergency operative intervention without the potential benefit of any ancillary confirmation of their injury. Occasionally the use of an intraoperative angiogram may be helpful in delineating the exact location and nature of the injury in patients taken directly to the operating room, especially if there are multiple potential sites of injury. However, delaying definitive treatment of an obvious arterial injury that is approaching the 6-hour limit of warm ischemia time to obtain an angiogram is ill advised.

Plain Radiography

Plain radiographs of the affected extremity are indicated to detect fractures, joint penetration, and foreign bodies. With gunshot wounds, the sum of the number of intact bullets seen on radiographs and the number of entrance and exit wounds in the body should be an even number. Failure to locate a bullet can result in unexpected complications. Rarely, bullets or shotgun pellets can migrate distally and produce vascular occlusion or migrate proximally through the venous system to the heart. These emboli are readily detected on plain radiographs if the search is vigilant.[33,34] Lead bullets retained within a synovial joint can result in systemic absorption and elevated lead levels and should be removed electively.[35-41]

Pulse Oximetry

Several relatively simple noninvasive maneuvers can be performed at the bedside to elicit evidence of arterial injury. The use of pulse oximetry has been suggested as a means of identifying limb ischemia after trauma, but it has been found to be relatively insensitive for this purpose. Clearly, in the absence of a pulse, no reading can be obtained. As the technology of transcutaneous measurement of physiologic indices advances, measurement of tissue oxygenation by near-infrared spectroscopy (NIRS) to quantify muscle oxyhemoglobin may prove more useful in detecting vascular injury because these devices are portable, noninvasive, and simple to use and appear to provide more accurate information than pulse oximetry.[42-47] Thus far, however, small clinical studies have found contradictory results in use of NIRS for this indication.[48,49]

Hand-held Doppler

An inability to palpate pulses in an injured extremity should be verified by auscultation with a hand-held Doppler unit. Apart from the absence of any signal, arterial injury may be suggested by a change in the usual triphasic quality of the Doppler pulse to a biphasic or monophasic waveform as the pulse is "damped" by partial occlusion. Although Doppler is more sensitive, auscultation of the pulse by this method is subject to the same types of limitations as is palpation of the pulse.

Ankle-Brachial Index and Arterial Pressure Index

In an effort to improve on the accuracy of physical examination without relying on expensive and invasive tests such as arteriography, the use of blood pressure in the injured versus the uninjured extremity (arterial pressure index [API]) or the blood pressure in an injured leg at the ankle compared with brachial artery pressure (ankle-brachial index [ABI]) was developed and validated in numerous studies as an accurate means of detecting vascular injury. Systolic pressure is measured by inflating a standard blood pressure cuff proximal to the injury and recording hand-held Doppler systolic pressure distal to the injury. The

www.ketabpezeshki.com 66485457-66963820

process is repeated on the uninjured limb, and a ratio of injured to uninjured systolic pressure is calculated (API). In general, a ratio less than 0.90 is considered abnormal and is an indication for further investigation. In several studies, an API less than 0.90 yielded a sensitivity of 95%, specificity of 97%, positive predictive value of 100%, and negative predictive value of 95%.[5,21,50-52] However, a few studies have found API to be less accurate, including one in which a cutoff of 0.90 resulted in a false-negative rate of nearly 40%; nevertheless, the use of an API ratio less than 0.90 can eliminate a large number of unnecessary angiograms for proximity wounds and increase the diagnostic efficiency of angiography or computed tomographic angiography (CTA) by limiting its use to high-yield cases.

Patients with an API of 0.90 to 0.99 merit observation for 12 to 24 hours for repeated physical examination and API measurements to detect evolving injury. Patients with normal physical examination findings and a completely normal (>0.99) ABI can be safely discharged from the emergency department provided there are no other injuries requiring admission.[52]

Exclusive reliance on API to screen for arterial injury has significant limitations. Comparisons cannot be made when both limbs are injured or when severe soft tissue mangling precludes placement of a blood pressure tourniquet or location of the artery to be measured with the Doppler unit.[21] As with physical examination, the sensitivity of API is limited when an intimal flap allows near-normal flow or when collateral circulation is sufficient to produce near-normal systolic pressure, as in proximal injuries to the subclavian or iliac vessels. Certain arteries (e.g., the profunda femoris, profunda brachii, and peroneal arteries) normally do not produce palpable pulses, and API is of limited usefulness in these injuries. Shotgun wounds often are associated with normal APIs despite multiple small arterial wounds; catheter-based angiography is the preferred diagnostic modality in this group. As with formal angiography, API cannot detect venous injuries.

Despite the limitations previously noted, API has proved effective in screening patients with proximity wounds. The vast majority of injuries missed by API heal spontaneously. Those that do not heal are generally seen within 3 months with signs of arterial injury and can be repaired electively.

Ultrasound

The development of relatively small portable ultrasound (US) units has made possible direct visualization of both arterial and venous flow in major vessels. There are several different types of US that can detect vascular injury, and newer, more accurate techniques are being developed rapidly. B-mode (real-time) US is the most readily available form of US in portable units. It can easily visualize arterial pulsation in major vessels. Loss of pulsation distal to an obstruction or thrombosis is readily apparent. However, B-mode US cannot visualize certain anatomic areas accurately (subclavian and iliac vessels) because of overlying pulmonary tissue, and it is unreliable in detecting a fresh, relatively nonechogenic thrombosis or hematoma. As blood liquefies within a hematoma, it becomes echolucent and more readily distinguishable from surrounding tissues.

Doppler US interprets sound moving toward or away from the transducer as flow. Venous flow is heard as a low-pitched hum, whereas arterial flow has a higher-pitched triphasic quality. The combination of B-mode and Doppler US is called *duplex US* and has enhanced accuracy in examining blood vessels. Duplex scans showing a focal increase in peak systolic velocity suggest partial obstruction of the vessel. However, duplex scanning is slightly less accurate in detecting injuries that do not decrease flow, such as small pseudoaneurysms, AVF, and intimal flaps.[53] Also, it is technically limited in examining certain anatomic areas, such as the profunda femoris and profunda brachii arteries and the iliac and subclavian vessels. Duplex US findings may be subtle, and as with other applications of US, its accuracy is highly operator dependent. Despite these limitations, the sensitivity of duplex US in comparison with standard angiography ranges from 83 to 100%, with a specificity of 99 to 100% and an accuracy of 96 to 100%.[21,53,54]

Color flow Doppler converts Doppler echoes into quantitated visual signals. Flow toward the transducer is seen as red, and flow away from the transducer is seen as blue. The intensity of the color (the number of pixels on the screen) is proportional to flow through the vessel. Small prospective studies have indicated a high rate of accuracy in detecting arterial injury.[53,54] Absence of flow is readily apparent, but more subtle injuries, such as intimal flaps and small pseudoaneurysms, are more difficult to identify. In addition, color flow Doppler is more accurate than standard venography in detecting major venous injuries. The overall sensitivity of color flow Doppler in detecting arterial injury is 50 to 90%, with a specificity of 95 to 99%. The sensitivity for detecting injuries requiring surgical repair is greater than 90%.[23,53,54] The use of intravascular US for examination of abdominal aortic aneurysms has been well documented. Although not yet applicable to smaller peripheral vessels, with further reduction in size of the transducers, this technique may eventually be applicable for peripheral vascular injury as well.

Computed Tomography and Magnetic Resonance Imaging

With a few important exceptions, computed tomography (CT) with contrast enhancement (CTA) has largely replaced catheter-based angiography for the detection of peripheral vascular injury in most trauma centers. Multidetector helical CT (MDCT) scanners have proven very accurate for diagnosis of peripheral vascular injury in multiple series with a sensitivity of 93 to 100% and specificity of 87 to 100% compared with catheter-based angiography.[2,55-72] The advantages of CTA over catheter-based angiography are that it is noninvasive, readily available, and less costly and provides information on other injuries in the region being studied. However, there are several pitfalls to the use of MDCT angiography. Metallic artifact from bullets, orthopedic hardware, or other penetrating objects may obscure visualization of parts of a vessel, although with image reconstruction techniques, this problem can be largely overcome.[62] Venous injuries may be missed depending on the phase of the contrast.[62] The rapid image acquisition of current CT scanners makes timing of the contrast bolus more critical, and out-of-phase images may miss arterial injury. In practical terms, though, CTA is very useful in that it can be integrated into an overall plan for diagnostic imaging, including CT of the head and trunk, all of which can be accomplished rapidly.[69] Because of the enhanced detail, accuracy, and speed of image acquisition with 64- to 256-slice CT scanners and the ability to perform three-dimensional reconstructions, this modality has become the standard imaging technique for suspected vascular injury. Magnetic resonance angiography (MRA) has been described and accurately detects vascular injuries but has yet to prove clinically useful.[73] MRI is also contraindicated in the presence of iron-containing metallic foreign bodies.

Arteriography

The policy of routinely exploring proximity wounds greatly improved the preservation of injured limbs in World War II. With the advent of arteriography and digital subtraction angiography (DSA), it became apparent that many negative wound explorations could be avoided with routine arteriography. In a study using routine arteriography, the negative surgical exploration rate

www.ketabpezeshki.com 66485457-66963820

in patients with soft signs of arterial injury or with proximity wounds decreased from 84 to 2%.[74] As a result, until recently, catheter-based contrast angiography has been the gold standard for diagnosing peripheral arterial injury, with a sensitivity of 99% and specificity of 97%.[21]

Beginning in the 1980s, the number of civilian penetrating wounds increased dramatically. Because of high cost, limited availability at all hours, and poor reimbursement rates, the policy of routine arteriography for proximity wounds has been questioned. From a practical perspective, the time required to mobilize the angiography team and perform the study may be several hours, thus making this option less desirable when dealing with the time limitations posed by arterial injury. In addition, arteriography has a small but measurable complication rate, including allergic reactions to contrast media, renal complications, hematoma formation, and false aneurysm formation at the site of cannulation. Finally, the clinical usefulness of the information provided by arteriography has become increasingly suspect in recent years as more of these injuries have been managed expectantly. Routine "exclusion" arteriography for proximity wounds detects unsuspected arterial injury in 0 to 21% of cases.[27,75-77] However, relatively few of these patients require emergency surgery. In a series of 284 patients who underwent routine angiography for proximity wounds, 17% had unsuspected arterial injury detected, but only 1.8% (five patients) required emergency surgical repair.[76] In other series reporting on a total of 483 patients who underwent angiography for proximity wounds, only one arterial injury that required emergency repair was discovered.[74-78] In the presence of soft signs of injury other than proximity, the yield for angiograms increases to 29 to 35%, but many of these injuries do not require emergency repair and can be detected by noninvasive means.[76] In addition, angiography results in an approximately 5% false-positive and false-negative rate compared with surgical exploration. Many of the injuries detected on angiography are caused by reversible vasospasm or very small intimal defects that generally heal spontaneously. Consequently, angiography for proximity wounds can detect injury in up to 21% of cases but results in acute surgical intervention in only 0 to 4.4% of cases.[74] Many centers now successfully manage proximity wounds by repeated physical examination over a 24-hour period and reserve CTA for those with abnormal physical findings or an ABI less than 0.9.[78-82] Angiography is also limited in that it cannot detect major venous injuries, which are increasingly being repaired surgically. The use of angiography is difficult in children because of the small caliber of their vessels and a propensity for vasospasm induced by angiography. Consequently, physical examination and noninvasive methods are preferred for detection of vascular injury in young children.[77]

DSA has been used for detecting vascular injuries as well. DSA has been found to be more accurate than standard angiography for detection of extravasation and has the advantage of requiring the administration of a smaller load of contrast material. However, the field of view is much smaller with DSA than with standard angiography, thus making it technically difficult to study the entire course of a limb artery with DSA. Standard angiography is also more accurate than DSA in detecting intimal flaps and dissection. Traditional catheter-based angiography has the advantage over other diagnostic techniques in that it can also be used to treat many lesions. Embolization of pseudoaneurysms, endovascular stent insertion to bypass a dissection or AVF, and injection of thrombolytic agents to dissolve thrombus are routinely performed via intra-arterial catheter. Because of increased reliance on endovascular treatment, many of the lesions detected by other means ultimately still require angiography.[69] Intraoperative angiography is often used as a primary study in patients with hard findings of vascular injury to delineate the extent of the damage to the vessel and plan operative repair.

TREATMENT

Initial treatment is directed at ensuring a patent airway and adequate air exchange before assessing the circulation. Once this has been accomplished, active hemorrhage is controlled by direct digital pressure. Blind clamping of a bleeding vessel is not recommended because of the risk of crushing adjacent nerves; however, clamping a clearly visible vessel can be effective. The use of tourniquets has been generally discouraged because of compression nerve palsies, occlusion of veins resulting in increased compartment pressure, and an increased risk of venous thrombosis.[5] However, recent reports in the military literature state that the use of tourniquets for up to 6 hours is safe, effective, and lifesaving in some cases.[83] Tourniquets should be applied if direct pressure is insufficient to control bleeding and left in place until definitive surgical control can be achieved. In the military studies, there were few complications associated with the use of tourniquets, and almost all of these were transient. In cases in which proximal and distal control of large-vessel injuries cannot be readily achieved in the emergency department, insertion of a Foley catheter into the wound and inflation of the balloon with sterile water can temporarily tamponade the bleeding. Intravenous lines should not be started in the injured extremity because they may be ineffective in delivering resuscitation fluid or medication and because extravasation from an injured vein may increase compartment pressure. Serial hemoglobin determinations may indicate unexpected blood loss from occult vascular injury. Patients with significant blood loss should have blood typed and crossmatched and may require immediate transfusion for stabilization. Patients with significant vascular injury often remain hypotensive despite such infusion and require further volume infusion or blood transfusion. Moribund patients with multiple severe injuries may require urgent amputation as part of their overall stabilization or extrication from wrecked automobiles or collapsed buildings. Between 50 and 70% of patients with severely mangled limbs require urgent amputation, especially if they have multisystem trauma.[84]

The issue of "hypotensive resuscitation" is controversial with regard to major vascular injuries. A tenuous clot can form in injured arteries and prevent further blood loss as long as the patient remains hypotensive. Once arterial pressure reaches a critical but variable point, the clot may be expelled and massive blood loss can ensue. Therefore when the arterial injury is inaccessible for occlusion by direct pressure, the target blood pressure for resuscitation should be lowered to a systolic pressure of approximately 90 mm Hg. Overly aggressive and rapid fluid administration in the field or in the emergency department can produce transient intravascular hypervolemia and may ultimately increase the rate of blood loss. Close monitoring of vital signs and the total volume of fluid infused is indicated in these situations.[85]

Once a vascular injury has been identified, a specific diagnostic and therapeutic strategy can be developed that is consistent with the severity of the injury, the presence of other injuries, and the resources available. In hospitals without the ability to perform vascular repair, transfer to a trauma center should be initiated early. In cases in which the transfer will involve a delay of several hours, cooling the ischemic limb will avoid exceeding the critical 6-hour cutoff for warm ischemia. For this to be accomplished, the limb is wrapped in towels, and ice in plastic bags is applied around the limb, avoiding direct contact of the ice to the limb, which can result in frostbite.

Major Vascular Injuries

Major vascular injuries that compromise the viability of a limb should be repaired within 6 hours to avoid irreversible ischemic neuropathy and myonecrosis.[5] Treatment of vascular injury has changed dramatically in the past 10 years. Endovascular treatment

www.ketabpezeshki.com 66485457-66963820

with self-expanding stents is currently the preferred technique for repair of these injuries in stable patients, and the majority of arterial repairs in the United States are now done with this technique.[86-88] In hemodynamically unstable patients, open surgical repair is still preferred. If other life-threatening injuries must be repaired first, a temporary polytetrafluoroethylene (PTFE) vascular shunt can be placed in the operating room to restore perfusion to a limb.[89] These temporary PTFE shunts can be left in place for up to 24 hours before thrombosis begins to occur within the shunt. Major arterial transection or thrombosis is ideally repaired by end-to-end reanastomosis, if possible, without placing undue tension on the suture line. If a larger segment of the artery is destroyed, interposition of a reverse saphenous vein graft is the preferred technique. PTFE grafts are suitable for grafting larger arteries if necessary, but they tend to occlude when used in smaller arteries (e.g., distal to the femoral or brachial arteries). Before completion of the reanastomosis, a Fogarty catheter is passed through both ends of the repair to extract any thrombi that may have formed. The distal circulation is flushed with a dilute 1:10 solution of heparin or enoxaparin to prevent early clot formation. Systemic administration of heparin is usually contraindicated in patients with major trauma. Assessment of distal perfusion and, in particular, compartment pressures is indicated frequently after repair and reperfusion of the limb. The use of broad-spectrum antibiotics is recommended before commencement of vascular repair.

Apart from excision of the affected arterial segment and repair of the vessel, less invasive techniques have been developed to manage pseudoaneurysms. Percutaneous embolization with Silastic beads, gel clot emboli, or thrombogenic coils is often successful in excluding the pseudoaneurysm.[90] Placement of an endovascular stent can exclude the aneurysm and is also a successful alternative to open repair.[91] Similarly, repair of an AVF can be undertaken through open surgical ligation of the fistulous connection, by endovascular placement of a stent to exclude the fistula, or by percutaneous embolization of the fistulous tract.[90]

Late Complications

Despite timely optimal repair of arterial injuries, approximately 21% of patients experience delayed complications requiring further surgical intervention, including delayed amputation. The most common of such complications is delayed thrombosis, which often occurs after many months as stenosis at the repair site progresses. Other complications include intermittent claudication, chronic pain or edema of the limb, and aneurysm formation in the graft.[92]

Venous Injuries

Venous injuries may be primarily ligated if the condition of the patient cannot tolerate prolongation of surgery. However, the current trend is to repair major venous injuries if possible, particularly in the lower extremity, because wound healing is improved and the incidence of compartment syndrome, venous thrombosis, pulmonary embolism, and chronic edema is decreased.[92-95] Extensive venous collaterals in the upper extremity make surgical repair less compelling.

The timing of repair of a vascular injury when associated with complex fractures requiring fixation is controversial. Historically, the fracture was repaired first to give a more accurate measurement of limb length and the length of graft required for vascular repair and because of fear that manipulation of long bones during reduction might damage the vascular repair. However, the need for postoperative fasciotomy is higher in these patients than in those who undergo vascular repair first (80% vs. 36%), and vascular repair is limited by warm ischemic time.[96] Currently in most centers, vascular repair is prioritized over orthopedic repair, although temporizing PTFE shunts may be used to restore perfusion during fracture repair.

Minor Vascular Injuries

Increasingly, minor nonocclusive vascular injuries are being treated expectantly. Criteria for observation of vascular injuries include low-velocity missile wounds, intact distal circulation, absence of active hemorrhage, and minimal arterial wall disruption on angiography if performed. Angiographic or CTA findings meeting these criteria include intimal flaps extending less than 5 mm and pseudoaneurysms smaller than 5 mm in diameter.[5] Follow-up of these injuries with repeat angiography or US reveals that approximately 85% resolve spontaneously.[68] Patients meeting these criteria can be monitored as outpatients for 3 months, with repeat physical examination and US to detect delayed complications.[27,76,97] However, almost all pseudoaneurysms ultimately require repair and, once discovered, should be repaired electively rather than undergoing continued observation. Failure to detect and repair occult arterial injuries in children often results in severe differential limb growth, and thus a more aggressive policy of repairing any arterial injury that causes even a relatively minor decrease in blood flow to a child's growing limb may be justified.

SPECIFIC INJURIES

Upper Extremity

Subclavian Artery and Vein

Subclavian artery injuries are uncommon and represent 1 or 2% of all vascular trauma.[98] Isolated injury to the subclavian vein is more common than isolated arterial injury, but in almost half the cases both the vein and the artery are injured.[99] The vast majority (95-99%) are penetrating wounds, and because of massive hemorrhage, these injuries are often lethal before arrival at a hospital. Mortality in those who reach the hospital alive averages 15%, but overall mortality as high as 75% has been reported.[100-104] It is interesting to note that morbidity is higher with a blunt mechanism, whereas mortality is higher with penetrating wounds.[101] The right subclavian artery arises from the brachiocephalic artery, and the left arises from the arch of the aorta. From their origin, they course posterior and inferior to the clavicles to the outer margins of the first ribs, where they become the axillary artery and vein. The left subclavian artery rises higher than the right and extends into the root of the neck.[28]

The clinical manifestation is that of hemorrhagic shock in 77% of cases. Occasionally, unsuspected subclavian vascular injury is discovered at thoracotomy performed for excessive blood loss from a chest tube.[99] Approximately 60% have an associated pneumothorax or hemothorax, and additional injury to mediastinal and spinal structures is relatively common.[98] Symptoms of limb ischemia may be apparent with absent radial and brachial pulses. However, pulses are completely absent in only 33% of cases because collateral flow from the thyrocervical trunk may provide sufficient perfusion to avoid the symptoms and signs of ischemia.[99] Neurologic deficits in the upper extremity occur in more than half of patients. The most severe of these injuries is damage to the brachial plexus, which occurs in almost 50% of patients with blunt injury.[99]

In a series of 100 cases of subclavian artery injury, the combination of physical examination and chest x-ray findings suggestive of subclavian injury (hemothorax, pneumothorax, apical pleural cap, or wide mediastinum) was 100% sensitive and could have eliminated the need for 69% of the arteriograms obtained.[101] If the patient's clinical condition permits, however, angiography can

www.ketabpezeshki.com 66485457-66963820

provide an accurate diagnosis and can locate the injury precisely. APIs are relatively inaccurate with proximal thoracic outlet injuries because of collateral arterial flow. US techniques are also relatively inaccurate in detecting subclavian injuries because of interference by overlying gas-filled lung tissue. Therefore in cases in which the clinical diagnosis is equivocal (soft signs of injury or proximity wounds), arteriography (CTA or catheter based) is required to detect the injury. Immediate proximal and distal control of the subclavian artery is very difficult. An incision along the course of the clavicle is recommended but often needs to be extended to a sternotomy.[67] If primary reanastomosis is not possible, synthetic grafts are usually successful but have a tendency to fracture over time owing to the wide range of motion at the shoulder and resultant compression of the graft by the first rib and clavicle.[105]

Blunt subclavian injuries are often associated with clavicular fracture or dislocation. Isolated first rib fracture is rarely combined with vascular injury unless posterior displacement occurs. However, first rib fracture in association with other major injuries, such as a wide mediastinum on the chest radiograph, an expanding hematoma, an upper extremity pulse deficit, or a brachial plexus injury, is accompanied by arterial injury in 24% of cases and merits investigation by angiography or CTA.[106] Several cases of shear injury of the subclavian artery have been reported to result from a loose shoulder restraint of a seat belt during a motor vehicle collision (MVC). Overall, blunt subclavian artery injuries have a higher morbidity than penetrating injuries because of higher rates of limb amputation and associated brachial plexus injury.[98]

Subclavian vein injuries are even more lethal than those to the artery. In addition to massive blood loss, there is a relatively high risk of massive air embolism, which is frequently fatal in association with penetrating subclavian vein injuries. Patients with known or suspected subclavian vein injury should be placed in Trendelenburg's and left lateral decubitus position to reduce the incidence of this complication.

Axillary Artery and Vein

Injury to the axillary vessels constitutes 3 to 9% of all vascular injuries, with penetrating mechanisms predominant.[107] Blunt injuries are associated with proximal humerus fracture or forceful reduction of a dislocated shoulder, particularly if chronically dislocated.[108] The axillary artery courses from the lateral border of the first rib to the inferior border of the teres major muscle, where it becomes the brachial artery. The axillary vein runs medial to the artery. The extensive anastomotic arterial connections around the shoulder joint usually permit good collateral flow,[28,99] and up to half of these patients will have palpable pulses as a result of collateral circulation.[109] Because of the close proximity of the brachial plexus and the axillary vessels, significant denervation of the upper extremity can occur. Near-avulsion injuries resulting in scapulothoracic dissociation invariably produce severe disruption of the brachial plexus and often ultimately result in amputation despite successful vascular repair. There is a high rate of amputation for the combination of axillary vascular and brachial plexus injury, mainly because the presence of a flail limb results in amputation for placement of a prosthesis.

Brachial Artery

The brachial artery continues from the lower border of the teres major muscle and divides into the radial and ulnar arteries at the level of the proximal aspect of the radial head. The median and ulnar nerves and the basilic vein are in close proximity to the brachial artery. The profunda brachii artery is a major branch that arises slightly after the origin of the brachial artery and often contributes good collateral flow if the brachial artery is injured distal to this branch point.[28,99] Brachial artery injuries occur as a result of penetrating trauma, humeral shaft fracture, elbow dislocation, or animal bites.[100] They are the most common major vascular injuries in the upper extremity. In 75% of cases the radial pulse is absent.[30] Studies have shown that limb salvage rates have improved to nearly 100% owing to efficient out-of-hospital transport, improved surgical techniques, and shorter time to first antibiotic dose.[110] Repair is indicated in all cases because the amputation rate is high with ligation.

Forearm Arteries

The radial artery begins in the cubital fossa and runs superficially to the distal end of the radius, where it ultimately joins the deep branch of the ulnar artery to form the deep palmar arch of the hand. The ulnar artery begins in the cubital fossa and runs with the ulnar nerve anterior to the flexor retinaculum, at which point it joins the radial artery to form the superficial palmar arch of the hand.

Injuries detected by arteriography or US that are below the bifurcation of the arterial supply in the upper extremity do not need to be repaired unless there are signs of ischemia in the hand; "hard signs" of arterial injury such as an expanding hematoma, pseudoaneurysm, or AVF; or injury to both radial and ulnar arteries. However, some authors recommend repairing all these injuries because of the risk of intermittent claudication or cold intolerance in patients who have one artery ligated. Certain patients are almost exclusively dependent on the ulnar arterial supply to the hand because of an underdeveloped deep palmar arch. Clearly, ulnar artery injuries should be repaired in these patients. Compartment syndrome in the forearm is common after repair of proximal arteries and veins and may require fasciotomy.

Lower Extremity

Iliac Artery and Vein

Given the intra-abdominal course of the iliac vessels, virtually all iliac artery and vein injuries have associated trauma to the small or large intestine, bladder, solid viscera, or bony pelvis. The common and external iliac arteries are injured with equal frequency and more often than the internal iliac vessels.[111] Approximately 80% of iliac vessel injuries are caused by penetrating trauma, and the remainder are mainly associated with pelvic fracture.[112] Trauma to the iliac veins is responsible for massive bleeding in displaced pelvic fractures and often requires angiographic embolization for control (see Chapter 55). In moribund patients, an initial "damage control" laparotomy with temporary vascular shunting of the iliac vessels is often necessary as resuscitation continues. After the patient has overcome lactic acidosis, hypothermia, and coagulopathy, a second definitive repair can be undertaken. It is surprising to note that the incidence of infection of synthetic or autologous grafts is rather low despite the high degree of bacterial contamination associated with perforation of a hollow viscus. Distal ischemic complications occur with approximately one third of repaired iliac arteries, and subsequent amputations are required in up to 18%.[111]

Femoral Artery and Vein

The external iliac vessels become the common femoral vessels at the inguinal ligament. After giving off the profunda femoris artery in the femoral triangle, the femoral artery continues as the superficial femoral artery almost vertically to the adductor tubercle of the femur and enters the popliteal fossa as the popliteal artery. There are extensive proximal collaterals around the hip joint,

www.ketabpezeshki.com 66485457-66963820

including the gluteal, obturator, and pudendal branches of the iliac artery.[28]

Femoral artery and vein injuries are the most common vascular injuries seen in major trauma centers. Common femoral artery injury occurs as a result of intertrochanteric hip fracture, hip dislocation, and iatrogenic injury from the placement of arterial catheters or from hip replacement surgery, although 86% of femoral artery injuries are caused by penetrating wounds.[113] Ligation of the common femoral artery culminates in amputation of the lower extremity in 80% of cases, so repair should be attempted in all cases. Penetrating wounds of the thigh result in femoral artery injury in 6.2% of cases, and up to 40% of these injuries are clinically occult. A medial or anteromedial wound track is present in virtually all these cases, and CTA has proven highly accurate in diagnosing these injuries and has largely replaced other imaging techniques.[114-116]

Popliteal Artery and Vein

The popliteal artery gives off the genicular branches in the popliteal fossa and then divides into the anterior and posterior tibial arteries at the lower border of the popliteus muscle. The peroneal artery arises from the posterior tibial artery slightly after its origin. The anterior and posterior tibial arteries and the peroneal artery form the trifurcation of the popliteal artery, and each runs with a corresponding vein and nerve in different compartments of the leg.[28]

The most common cause of popliteal artery injury is posterior knee dislocation in which bony elements directly lacerate or cause thrombosis of the artery. Displaced fractures of the knee, particularly tibial plateau fractures, may also result in popliteal artery injury. Anterior knee dislocations may cause excessive stretch on the popliteal vessels that can culminate in arterial thrombosis, but this injury is relatively rare. Overall, knee dislocation results in popliteal artery injury in 25 to 33% of cases.[117] Up to 40% of these injuries may be clinically occult, and diagnosis is delayed in up to 40% of cases,[2] although other series note that more than two hard signs of ischemia occur immediately in 71 to 94%.[4,5] Twenty-five percent of cases have an associated injury to the peroneal and posterior tibial nerves. In half the cases, the knee dislocation may reduce spontaneously, leaving little evidence of the original trauma, particularly in obtunded patients.[101] Patients showing complete ligamentous disruption of the knee on physical examination should be suspected of having a spontaneously reduced knee dislocation. Hemarthrosis may also be absent if the joint capsule is torn because blood can track into the fascial planes of the leg.

No consensus has been reached on the diagnostic approach to detect popliteal artery injury resulting from documented or suspected knee dislocation. There are three possible strategies, and each has proponents and detractors. The first option is to perform routine arteriography on every case of knee dislocation.[118,121] The second is to perform CTA or arteriography on selected cases in which vascular injury is not certain despite the combination of physical signs, abnormal ABI measurement, or findings on noninvasive tests such as color flow Doppler or duplex scan.[121] The third option is to rely completely on these physical findings and ABI to exclude arterial injury. If both these findings are normal, advocates of this approach claim 100% negative predictive value for vascular injury that requires surgery.[51,80,82,122,123] The choice of these options is institution specific, but most centers continue to use angiography in selected cases. Abnormal ABI and US (duplex and color flow Doppler) have been found to be very accurate in detecting popliteal injuries, and many centers reserve angiography or CTA for cases in which noninvasive tests result in equivocal findings. As a general rule, high-energy mechanisms of trauma (e.g., auto vs. pedestrian and MVC) and posterior knee dislocations are more likely to produce popliteal artery injury than are low-energy mechanisms (e.g., sports injuries), and a more aggressive diagnostic approach (i.e., angiography or CTA) may be warranted in such cases. However, patients with *penetrating* trauma and more than one hard sign of popliteal artery injury can be taken directly to the operating room for repair because delaying these cases to obtain an angiogram is "superfluous, unnecessary, costly, and potentially dangerous."[106] Patients with *blunt* trauma can have false-positive hard findings generated by soft tissue swelling and external arterial compression, and these patients should undergo diagnostic testing first to confirm arterial injury. The amputation rate for popliteal injuries was as high as 40% in the past, but current rates are lower. In one large series, the amputation rate was 20%, but a high rate of permanent disability was found at 2-year follow-up.[124] Another series reported no amputations with modern diagnostic and repair techniques.[5,106] Factors that place patients at higher risk of amputation include severe mangling of the extremity, the presence of multiple fractures, major venous repair, or delay in repair exceeding 6 hours of warm ischemia time.[119] Because of the high incidence of compartment syndrome with lower leg injuries, fasciotomy is required in 49% of cases, and some centers routinely perform fasciotomy in all such cases.[125] Approximately two thirds of patients with popliteal artery injury will have persistent deficits caused by peripheral nerve injury, chronic ischemia, or amputation.

Lower Leg Arteries

The popliteal artery divides into three branches—the anterior and posterior tibial and the peroneal arteries at the inferior margin of the popliteal fossa. Injuries below the trifurcation at the knee may need repair if hard signs of arterial injury are apparent in the foot or if two of the three arteries are occluded on angiography.[27] However, vascular injuries in the lower part of the leg are notorious for causing compartment syndrome and need to be monitored closely. Amputation is usually a result of a combination of soft tissue, nerve, and bone injuries. If significant injury to all three of these tissues is present, the amputation rate may reach 54%.[27,126] The combination of orthopedic and vascular injury, particularly as a result of crush injury, and shock on initial evaluation culminates in amputation in 35% of cases and should be considered a poor prognostic sign for limb viability.[110]

DISPOSITION

Patients with confirmed injury to major vessels, equivocal findings on diagnostic tests, or symptoms of limb ischemia are admitted to the hospital for further investigation or observation. Consultation with a vascular surgeon is indicated as soon as vascular injury is strongly suspected or the need for emergency operative repair established. Patients who are unstable because of vascular or other injuries may undergo further investigation or exploration in the operating room. If the treating hospital is incapable of performing vascular surgery or appropriate investigations, transfer to a trauma center should be initiated. Delaying transfer for angiograms of proximity wounds in centers that are incapable of acting on positive results is unwise because it often delays definitive care beyond the safe limits of warm ischemia time.

www.ketabpezeshki.com 66485457-66963820

KEY CONCEPTS

- The overall condition of the patient determines the extent of diagnostic study and stabilization in the emergency department. Critically injured patients may require immediate surgery, which should not be delayed for confirmatory study of obvious vascular injury.
- Arterial injury may be readily apparent or clinically occult. Up to 21% of proximity wounds show arterial injury only on angiography, although few of these require emergent surgery. Similarly, various US modalities and abnormal APIs frequently detect clinically unapparent vascular injuries.
- Symptoms of arterial injury may be delayed by hours to months after the initial injury. Late onset of symptoms suggests delayed thrombosis, pseudoaneurysm or AVF formation, compartment syndrome, or intermittent claudication resulting from stenosis or reliance on small-caliber collateral vessels for arterial perfusion.
- Reperfusion injury can occur after restoration of arterial flow and result in compartment syndrome. Frequent reexamination of the reperfused limb is indicated in the postoperative period.
- Compartment syndrome frequently develops in limbs with arterial injury, and fasciotomy is often required.
- CT angiography is playing an increasing role in the diagnosis of vascular injury and essentially replaced catheter-based angiography for all but a few indications.
- Many vascular injuries are amenable to endovascular treatment with self-expanding stents. This results in fewer complications, lower cost, and earlier discharge from the hospital.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Fowler R, Pepe PE: Prehospital care of the patient with major trauma. *Emerg Med Clin North Am* 2002; 20:953.
2. Sohn VY, Arthurs ZM, Herbert GS, Beekley AC, Sebesta JA: Demographics, treatment, and early outcomes in penetrating vascular combat trauma. *Arch Surg* 2008; 143:783-787.
3. Weber MA, et al: Upper extremity arterial combat injury management. *Perspect Vasc Surg Endovasc Ther* 2006; 18:141-145.
4. Mullenix PS, et al: Limb salvage and outcomes among patients with traumatic popliteal vascular injury: An analysis of the National Trauma Data Bank. *J Vasc Surg* 2006; 44:94.
5. Modrall JG, Weaver FA, Yellin AE: Diagnosis and management of penetrating vascular trauma and the injured extremity. *Emerg Med Clin North Am* 1998; 16:129.
6. Hafez HM, Woolgar J, Robbs JV: Lower extremity arterial injury: Results of 550 cases and review of risk factors associated with limb loss. *J Vasc Surg* 2001; 33:1212.
7. Franz RW, et al: A 5-year review of management of lower extremity arterial injuries at an urban level I trauma center. *J Vasc Surg* 2011; 53:1604-1610.
8. Vyrosek SB, Annest JL, Ryan GW: Surveillance for fatal and nonfatal injuries—United States, 2001. *MMWR Surveill Summ* 2004; 53:1.
9. Zamir G, Berlatzky Y, Rivkind A, Anner H, Wolf YG: Results of reconstruction in major pelvic and extremity venous injuries. *J Vasc Surg* 1998; 28:901.
10. Giswold ME, Landry GJ, Taylor LM, Moneta GL: Iatrogenic arterial injury is an increasingly important cause of arterial trauma. *Am J Surg* 2004; 187:590.
11. Wilson JS, et al: Vascular injuries associated with elective orthopedic procedures. *Ann Vasc Surg* 2003; 17:641.
12. Calkins CM, Bensard DD, Partrick DA, Karrer FM: Life-threatening dog attacks: A devastating combination of blunt and penetrating injuries. *J Pediatr Surg* 2001; 36:1115.
13. Benfield R, et al: The epidemiology of dog attacks in an urban environment and the risk of vascular injury. *Am Surg* 2010; 76:203-205.
14. Fish RM: Electrical injury. Part II: Specific injuries. *J Emerg Med* 2000; 18:27.
15. Franc-Law JM, Rossignol M, Vernec A, Somogyi D, Shrier I: Poisoning-induced acute atraumatic compartment syndrome. *Am J Emerg Med* 2000; 18:616.
16. Salgado CJ, et al: Effects of hyperbaric oxygen on the replanted extremity subjected to prolonged warm ischaemia. *J Plast Reconstr Aesthet Surg* 2010; 63:532-537.
17. Attaran S, Lindsay J, El-Gamel A: Clinical and potential use of pharmacological agents to reduce radial artery spasm in coronary artery surgery. *Ann Thorac Surg* 2008; 85:1483.
18. Kalapatapu VR, Shelton KR, Ali AT, Moursi MM, Eidt JF: Pseudoaneurysm: A review. *Curr Treat Options Cardiovasc Med* 2008; 10:173.
19. Carden DL, Granger DN: Pathophysiology of ischaemia-reperfusion injury. *J Pathol* 2000; 190:255.
20. American College of Surgeons: *ATLS: Advanced Trauma Life Support Program for Doctors*, 8th ed. Chicago: American College of Surgeons; 2008.
21. Manthey DE, Nicks BA: Penetrating trauma to the extremity. *J Emerg Med* 2008; 34:187.
22. Inaba K, et al: Prospective evaluation of multidetector computed tomography for extremity vascular trauma. *J Trauma* 2011; 70:808-815.
23. Halvorson JJ, et al: Vascular injury associated with extremity trauma: Initial diagnosis and management. *J Am Acad Orthop Surg* 2011; 19:495-504.
24. Levy BA, Zlowodzki MP, Graves M, Cole PA: Screening for extremity arterial injury with the arterial pressure index. *Am J Emerg Med* 2005; 23:689.
25. Howlett DC, Holemans JA, Downes MO: Case report: The role of arteriography in patients with isolated neurological deficit following a penetrating upper limb injury. *Br J Radiol* 1995; 68:674.
26. Zellweger R, et al: An analysis of 124 surgically managed brachial artery injuries. *Am J Surg* 2004; 188:240.
27. Britt LD, Weireter LJ, Cole FJ: Newer diagnostic modalities for vascular injuries: The way we were, the way we are. *Surg Clin North Am* 2001; 81:1263.
28. Snell R, Smith M, eds: *Clinical Anatomy for Emergency Medicine*. St Louis: Mosby; 1993.
29. Pillay WR, Pillay B, Mulaudzi TV, Mohamed GS, Robbs JV: Fluctuating pulse deficits associated with intimal arterial injury following gunshot wounds of the extremity—a sign not to be missed. *S Afr J Surg* 2005; 43:22-24.
30. Fields EF, Latifi R, Ivatury RR: Brachial and forearm vessel injuries. *Surg Clin North Am* 2002; 82:105.
31. Ilijevski N, et al: Emergency surgery of acute arteriovenous fistulas. *Cardiovasc Surg* 2000; 8:181.
32. Johnson ON, et al: Arteriography in the delayed evaluation of wartime extremity injuries. *Vasc Endovasc Surg* 2007; 41:217-224.
33. da Costa LB, Wallace MC, Montanera W: Shotgun pellet embolization to the posterior circulation. *Am J Neuroradiol* 2006; 27:261.
34. Raghavendran K, Evans JT: Bullet migration within the inferior vena cava. *South Med J* 2003; 96:96.
35. Nguyen A, et al: Elevation of blood lead levels in emergency department patients with extra-articular retained missiles. *J Trauma* 2005; 58:289.
36. McQuirter JL, Rothenberg SJ: Changes in blood lead levels caused by retained bullets from gunshot wounds. *Am J Epidemiol* 2004; 159:683.
37. DeMartini J, Wilson A, Powell JS, Powell CS: Lead arthropathy and systemic lead poisoning from an intraarticular bullet. *AJR Am J Roentgenol* 2001; 176:1144.
38. Bors V, et al: Bullet embolization from the left brachiocephalic vein to the right ventricle. *J Card Surg* 2008; 23:176.
39. Bertoldo U, et al: Retrograde bullet embolization: A rare occurrence—a case report and literature review. *Forensic Sci Int* 2004; 57:187.
40. Harirchi I, Salehi M, Ghazisoltani M, Sanatkar-Far M, Satarzadeh R: Gunshot wound of the heart with embolism to the right axillary artery. *Int Surg* 2004; 89:176.
41. Sokolowski MJ, Sisson G Jr: Systemic lead poisoning due to an intra-articular bullet. *Orthopedics* 2005; 28:411.
42. Cohn SM, Crookes BA, Proctor KG: Near-infrared spectroscopy in resuscitation. *J Trauma* 2003; 54:S199.
43. Gentilello LM, Sanzone A, Wang L, Liu PY, Robinson L: Near infrared spectroscopy versus compartment pressure for the diagnosis of the lower extremity compartmental syndrome using electromyography-determined measurements of neuromuscular function. *J Trauma* 2001; 51:1.
44. Gianotti G, et al: Utility of near-infrared spectroscopy in the diagnosis of lower extremity compartment syndrome. *J Trauma* 2000; 48:396.
45. Velmahos GC, Toutouzas KG: Vascular trauma and compartment syndromes. *Surg Clin North Am* 2002; 82:125.
46. Mathieu D, Mani R: A review of the clinical significance of tissue hypoxia measurements in lower extremity wound management. *Int J Low Extrem Wounds* 2007; 6:273.
47. Ward KR, et al: Near infrared spectroscopy for the evaluation of the trauma patient. *Resuscitation* 2006; 68:27.
48. Shuler MS, et al: Correlation between muscle oxygenation and compartment pressures in acute compartment syndrome of the leg. *J Bone Joint Surg Am* 2010; 92:863-870.
49. Bariteau JT, Beutel BG, Kamal R, Hayda R, Born C: The use of near-infrared spectrometry for the diagnosis of lower-extremity compartment syndrome. *Orthopedics* 2011; 34:178.
50. Feliciano DV: Management of peripheral arterial injury. *Curr Opin Crit Care* 2010; 16:602-608.
51. Mills WJ, Barei DP, McNair P: The value of the ankle-brachial index for diagnosing arterial injury after knee dislocation: A prospective study. *J Trauma* 2004; 56:1261.
52. Conrad MF, Patton JH Jr, Parikshak M, Kralovich KA: Evaluation of vascular injury in penetrating extremity trauma: Angiographers stay home. *Am Surg* 2002; 68:269.
53. Gaitini D, Razi NB, Ghersin E, Ofer A, Soudack M: Sonographic evaluation of vascular injuries. *J Ultrasound Med* 2008; 27:95-107.
54. Kuzniec S, Kauffman P, Molnár LJ, Aun R, Puech-Leão P: Diagnosis of limbs and neck arterial trauma using duplex ultrasonography. *Cardiovasc Surg* 1998; 6:358.
55. Peng PD, et al: CT angiography effectively evaluates extremity vascular trauma. *Am Surg* 2008; 741:103.
56. Fishman EK, Horton KM, Johnson PT: Multidetector CT and three-dimensional CT angiography for suspected vascular trauma of the extremities. *Radiographics* 2008; 28:653.
57. Fleiter TR, Mervis S: The role of 3D-CTA in the assessment of peripheral vascular lesions in trauma patients. *Eur J Radiol* 2007; 64:92.
58. Foster BR, Anderson SW, Soto JA: CT angiography of extremity trauma. *Tech Vasc Interv Radiol* 2006; 9:156.
59. Soto JA, et al: Focal arterial injuries of the proximal extremities: Helical CT arteriography as the initial method of diagnosis. *Radiology* 2001; 18:188.
60. Inaba K, Munera F, Rivas L, Ginzburg E, McKenney M: Computed tomographic angiography in the initial assessment of penetrating extremity injuries. *J Trauma* 2007; 62:520.

www.ketabpezeshki.com 66485457-66963820

61. Rieger M, Mallouhi A, Tauscher T, Lutz M, Jaschke WR: Traumatic arterial injuries of the extremities: Initial evaluation with MDCT angiography. *AJR Am J Roentgenol* 2006; 186:656.
62. Miller-Thomas M, West OC, Cohen AM: Diagnosing traumatic arterial injury in the extremities with CT angiography: Pearls and pitfalls. *Radiographics* 2005; 25:S133.
63. Staller B, Mùnera F, Sanchez A, Nuñez DB Jr: Helical and multislice CTA following penetrating trauma to the subclavian and axillary arteries. *Emerg Radiol* 2005; 11:336.
64. Hiatt MD, Fleischmann D, Hellinger JC, Rubin GD: Angiographic imaging of the lower extremities with multidetector CT. *Radiol Clin North Am* 2005; 43:1119.
65. Iezzi R, Cotroneo AR, Pascali D, Merlino B, Storto ML: Multi-slice CT (MSCT) angiography for assessment of traumatic lesions of lower limbs peripheral arteries. *Emerg Radiol* 2007; 14:389.
66. Busquéts AR, Acosta JA, Colón E, Alejandro KV, Rodríguez P: Helical computed tomographic angiography for the diagnosis of traumatic arterial injury of the extremities. *J Trauma* 2004; 56:625.
67. Hogan AR, et al: Value of computed tomographic angiography in neck and extremity pediatric vascular trauma. *J Ped Surg* 2009; 44:1236-1241.
68. White PW, et al: Sixty-four slice multidetector computed tomographic angiography in the evaluation of vascular trauma. *J Trauma* 2010; 68:96-102.
69. Uyeda JW, Anderson SW, Sakai O, Soto JA: CT angiography in trauma. *Radiol Clin North Am* 2010; 48:423-438.
70. Shah N, et al: Extremity CT angiography: Application to trauma using 64-MDCT. *Emerg Radiol* 2009; 16:425-432.
71. Seamon MJ, et al: A prospective validation of a current practice: The detection of extremity vascular injury with CT angiography. *J Trauma* 2009; 67:238-243.
72. Grainger ML, Wilson CH, Augustine SJ, Griffiths HJ: Radiologic case study: Traumatic dislocation of the knee. *Orthopedics* 2003; 26:280, 351-354.
73. Tocci SL, Heard WM, Fadale PD, Brody JM, Born C: Magnetic resonance angiography for the evaluation of vascular injury in knee dislocations. *J Knee Surg* 2010; 23:201-207.
74. Reid JD, Weigelt JA, Thal ER, Francis H 3rd: Assessment of proximity of a wound to major vascular structures as an indication for arteriography. *Arch Surg* 1988; 123:942.
75. Dennis JW, Frykberg ER, Crump JM, Vines FS, Alexander RH: New perspectives on the management of penetrating trauma in proximity to major limb arteries. *J Vasc Surg* 1990; 11:85.
76. Weaver FA, et al: Is arterial proximity a valid indication for arteriography in penetrating extremity trauma? A prospective analysis. *Arch Surg* 1990; 125:1256.
77. Gillespie DL, et al: Role of arteriography for blunt or penetrating injuries in proximity to major vascular structures: An evolution in management. *Ann Vasc Surg* 1993; 7:145.
78. Sadjadi J, Cureton EL, Dozier KC, Kwan RO, Victorino GP: Expedited treatment of lower extremity gunshot wounds. *J Am Coll Surg* 2009; 209:740-745.
79. Rose SC, Moore EE: Trauma angiography: The use of clinical findings to improve patient selection and case preparation. *J Trauma* 1988; 28:240.
80. Stannard JP, et al: Vascular injuries in knee dislocations: The role of physical examination in determining the need for arteriography. *J Bone Joint Surg Am* 2004; 86:910-915.
81. Hollis JD, Daley BJ: 10-Year review of knee dislocations: Is arteriography always necessary? *J Trauma* 2005; 59:672.
82. Klineberg EO, Crites BM, Flinn WR, Archibald JD, Moorman CT 3rd: The role of angiography in assessing popliteal artery injury in knee dislocations. *J Trauma* 2004; 56:786.
83. Beekley AC, et al: Prehospital tourniquet use in Operation Iraqi Freedom: Effect on hemorrhage control and outcomes. *J Trauma* 2008; 64:S28.
84. Newton E, Love J: Emergency department management of selected orthopedic injuries. *Emerg Med Clin North Am* 2007; 25:763.
85. Morrison CA, et al: Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: Preliminary results of a randomized controlled trial. *J Trauma* 2011; 70:652-653.
86. Reuben BC, Whitten MG, Sarfati M, Kraiss LW: Increasing use of endovascular therapy in acute arterial injuries: Analysis of the National Trauma Data Bank. *J Vasc Surg* 2007; 46:1222.
87. Arthurs ZM, Sohn VY, Starnes BW: Vascular trauma: Endovascular management and techniques. *Surg Clin North Am* 2007; 87:1179.
88. Lyden SP, Srivastava SD, Waldman DL, Green RM: Common iliac artery dissection after blunt trauma: Case report of endovascular repair and literature review. *J Trauma* 2001; 50:339.
89. Bechara C, Nuynh TT, Lin PH: Management of lower extremity arterial injuries. *J Cardiovasc Surg (Torino)* 2007; 48:567.
90. Naidoo NM, Corr PD, Robbs JV, Maharaj J, Nair R: Angiographic embolisation in arterial trauma. *Eur J Vasc Endovasc Surg* 2000; 19:77.
91. Criado E, Marston WA, Ligush J, Mauro MA, Keagy BA: Endovascular repair of peripheral aneurysms, pseudoaneurysms and arteriovenous fistulas. *Ann Vasc Surg* 1997; 11:256.
92. Rich NM: Complications of vascular injury management. *Surg Clin North Am* 2002; 82:143.
93. Quan RW, et al: The management of trauma venous injury: Civilian and wartime experiences. *Perspect Vasc Surg Endovasc Ther* 2006; 18:149.
94. Quan RW, et al: The effect of vein repair on the risk of venous thromboembolic events: A review of more than 100 traumatic military venous injuries. *J Vasc Surg* 2008; 47:571.
95. Kuralay E, et al: A quantitative approach to lower extremity vein repair. *J Vasc Surg* 2002; 36:1213.
96. McHenry TP, Holcomb JB, Aoki N, Lindsey RW: Fractures with major vascular injuries from gunshot wounds: Implications of surgical sequence. *J Trauma* 2002; 53:717.
97. Dennis JW, Frykberg ER, Veldenz HC, Huffman S, Menawat SS: Validation of nonoperative management of occult vascular injuries and accuracy of physical examination alone in penetrating extremity trauma: 5- to 10-year follow-up. *J Trauma* 1998; 44:243.
98. Cox CS Jr, et al: Blunt versus penetrating subclavian artery injury: Presentation, injury pattern, and outcome. *J Trauma* 1999; 46:445.
99. Demetriades D, et al: Penetrating injuries to the subclavian and axillary vessels. *J Am Coll Surg* 1999; 188:290.
100. Martin DJ, Fazzi UG, Leach WJ: Brachial artery transection associated with closed and open dislocation of the elbow. *Eur J Emerg Med* 2005; 12:30-33.
101. Gasparri MG, Lorelli DR, Kralovich KA, Patton JH Jr: Physical examination plus chest radiography in penetrating periclavicular trauma: The appropriate trigger for angiography. *J Trauma* 2000; 49:1029.
102. McKinley AG, Carrim ATO, Robbs JV: Management of proximal axillary and subclavian artery injuries. *Br J Surg* 2000; 87:175.
103. Katras T, et al: Subclavian arterial injury associated with blunt trauma. *Vasc Surg* 2001; 35:43-50.
104. Aksoy M, et al: Traumatic injuries to the subclavian and axillary arteries: A 13-year review. *Surg Today* 2005; 35;561-565.
105. du Toit DF, Lambrechts AV, Stark H, Warren BL: Long term results of stent graft treatment of subclavian artery injuries: Management of choice for stable patients? *J Vasc Surg* 2008; 47:739.
106. Gupta A, Jamshidi M, Rubin JR: Traumatic first rib fracture: Is angiography necessary? *Cardiovasc Surg* 1997; 5:48.
107. Gill H, et al: Civilian penetrating axillary artery injuries. *World J Surg* 2011; 35:962-966.
108. Mouzopoulos G, Lassanianos N, Mouzopoulos D, Tzurbakis M, Georgilas I: Axillary artery injury associated with proximal humerus fractures. *Vasa* 2008; 37:274-277.
109. Gonzalez RP, Falimirski ME: The role of angiography in periclavicular penetrating trauma. *Am Surg* 1999; 65:711.
110. Shanmugam V, Velu RB, Subramaniyan SR, Hussain SA, Sekar N: Management of upper limb arterial injury without angiography—Chennai experience. *Injury* 2001; 35:61.
111. Woodman G, Croce MA, Fabian TC: Iliac artery ischemia: Analysis of risks for ischemic complications. *Am Surg* 1998; 64:833.
112. Baker WE, Wasserman J: Unsuspected vascular trauma: Blunt arterial injuries. *Emerg Med Clin North Am* 2004; 22:1081-1098.
113. Asensio JA, Kuncir EJ, García-Núñez LM, Petrone P: Femoral vessel injuries: Analysis of factors predictive of outcomes. *J Am Coll Surg* 2006; 203:512.
114. Inaba K, et al: Multi-slice CT angiography for arterial evaluation in the injured lower extremity. *J Trauma* 2006; 60:502-506.
115. Foley WD, Stonely T: CT angiography of the lower extremities. *Radiol Clin North Am* 2010; 48:367-396.
116. Redmond JM, Levy BA, Dajani KA, Cass JR, Cole PA: Detecting vascular injury in lower extremity orthopedic trauma: The role of CT angiography. *Orthopedics* 2008; 31:761-767.
117. Ergunes K, et al: Traumatic brachial artery injuries. *Texas Heart Inst J* 2006; 33:31.
118. Barnes CJ, Pietrobon R, Higgins LD: Does the pulse examination in patients with traumatic knee dislocation predict a surgical arterial injury? A meta-analysis. *J Trauma* 2002; 53:1109.

www.ketabpezeshki.com 66485457-66963820

119. Wascher DC: High-velocity knee dislocation with vascular injury. *Clin Sports Med* 2000; 19:457.
120. Robertson A, Nutton RW, Keating JF: Dislocation of the knee. *J Bone Joint Surg Br* 2006; 88:706.
121. Abou-Sayed H, Berger DL: Blunt lower-extremity trauma and popliteal injuries: Revisiting the case for selective arteriography. *Arch Surg* 2002; 137:585.
122. Miranda FE, Dennis JW, Veldenz HC, Dovgan PS, Frykberg ER: Confirmation of the safety of physical examination in the evaluation of knee dislocation for injury of the popliteal artery: A prospective study. *J Trauma* 2002; 52:247.
123. Frykberg ER: Popliteal vascular injuries. *Surg Clin North Am* 2002; 82:67.
124. Patterson BM, et al: Knee dislocations with vascular injury: Outcomes in the Lower Extremity Assessment Project (LEAP) study. *J Trauma* 2007; 63:855.
125. Grossman MD, Reilly P, McMahan D, Kauder D, Schwab CW: Gunshot wounds below the popliteal fossa: A contemporary review. *Am Surg* 1999; 65:360.
126. Rowe VL, Salim A, Lipham J, Asensio JA: Shank vessel injuries. *Surg Clin North Am* 2002; 82:91.

www.ketabpezeshki.com 66485457-66963820

Chapter 49

General Principles of Orthopedic Injuries

Joel M. Geiderman and Dan Katz

MANAGEMENT PRINCIPLES

Patients with orthopedic injuries and nontraumatic musculoskeletal disorders compose a large portion of the more than 100 million patients who come to U.S. emergency departments (EDs) annually. Although only rarely life-threatening, orthopedic injuries may threaten a limb or its function, and accurate early diagnosis and treatment can avert long-term complications. Many of these injuries can and should be treated definitively by the emergency physician. Consultation with an orthopedist should be sought for the treatment of most long bone fractures, open fractures, injuries with joint violation, and injuries with neurovascular compromise and for follow-up of certain patients initially treated in the ED.

Orthopedic injuries often occur as a result of accidents (industrial or otherwise) and frequently involve young, otherwise healthy, working individuals. Accurate initial diagnosis, treatment, and documentation assume great importance medically and economically. Many problems can be avoided if the following 10 general principles are kept in mind:

1. Most orthopedic injuries can be predicted by understanding the chief complaint, the age of the patient, the mechanism of injury, and an estimate of the amount of energy delivered.
2. A careful history and physical examination predict radiographic findings with a high degree of accuracy. A presumptive diagnosis before a radiographic study may prompt the physician to order special views necessary to correctly diagnose an injury. Many fractures were accurately described before the advent of roentgenology (Table 49-1).
3. If a fracture is suggested clinically, but radiographic films appear negative, the patient should initially be treated with immobilization as though a fracture were present.
4. Criteria for adequate radiographic studies exist; inadequate studies should not be accepted.
5. Radiographic studies should be performed before most reductions are attempted, except when a delay could be potentially harmful to the patient or in some field situations.
6. Neurovascular competence should be checked and recorded before and after all reductions and after application of immobilization.
7. Patients must be checked for the ability to safely ambulate before discharge from the ED and should not be discharged unless this can be established.
8. Patients should receive explicit aftercare instructions before leaving the ED, covering such areas as monitoring for signs of neurovascular compromise or increasing compartment pressure, cast care, weightbearing, crutch use, and an explicit plan and timing for follow-up.
9. In a patient with multiple trauma, noncritical orthopedic injuries should be diagnosed and treated only after more threatening injuries have been addressed.
10. All orthopedic injuries should be described precisely and according to established conventions. When communicating with an orthopedic consultant, this may affect decisions regarding disposition of a patient and operative versus nonoperative management.

FRACTURES

Fracture Nomenclature

Describing orthopedic injuries with precise language according to established convention enables accurate, clear communication with other parties. Terms commonly used to describe a fracture are listed in Box 49-1. A fracture is a break in the continuity of bone or cartilage. Clinically, a history of loss of function, pain, tenderness, swelling, abnormal motion, and deformity suggests a fracture. Radiographic studies are the mainstay of diagnosis and are usually, although not always, confirmatory. At times, use of special views, radionuclide bone scans, computed tomography (CT), or magnetic resonance imaging (MRI) is necessary to confirm a clinical impression. These studies should be considered when the clinical evidence is at odds with the findings of routine radiography.

General Descriptors

Description of a fracture should begin by stating whether the fracture is *closed* or *open* (less desirable terms are *simple* or *compound*). In a closed fracture the skin and soft tissue overlying the fracture site are intact. The fracture is open if it is exposed to the outside environment in any manner. This exposure may be as obscure as a puncture wound or as gross as splintered bone protruding through the skin. It is sometimes difficult to determine whether a small wound in proximity to a fracture actually communicates with that fracture. Some physicians advocate probing such a wound with a blunt sterile swab to establish a relationship; no study has established the safety, benefit, or accuracy of this maneuver. If doubt exists, an open fracture should be assumed to be present.

The next item that should be noted in the description of a fracture is the exact anatomic location, including the name of the bone, left or right, and standard reference points along the bone, for example, the *humeral neck* or *posterior tibial tubercle.* Long bones can be divided into thirds—proximal, middle, or

www.ketabpezeshki.com 66485457-66963820

Table 49-1 Common Fracture Names and Their Origins

FRACTURE EPONYM OR NAME	DESCRIPTION	COMMENT
Aviator's	Vertical fracture of the neck of the talus with subtalar dislocation and backward displacement of the body.	First described in flyers during World War I. Arises from forced dorsiflexion of the foot in flying accidents and in traffic accidents after a head-on collision.
Barton's	Intra-articular fracture-dislocation of the wrist.	Considered complicated and unstable. Requires surgical reduction in most cases. Described by Barton in 1838 before the advent of radiography.
Dorsal Barton's	Oblique intra-articular fracture of the dorsal rim of the distal radius with displacement of the carpus along with the fracture fragment.	Results from high-velocity impact across the articular surface of the radiocarpal joint, with the wrist in dorsiflexion at the moment of impact.
Volar Barton's	Wedge-shaped articular fragment sheared off the volar surface of the radius (volar rim fracture), displaced volarly along with the carpus.	Similar mechanism as dorsal Barton's but with wrist in volar flexion at time of injury. Also referred to as *reverse Barton's fracture.* Much rarer than dorsal Barton's fracture.
Bennett's	Oblique fracture through base of the first metacarpal with dislocation of the radial portion of the articular surface.	Usually produced by direct force applied to the end of the metacarpal. Dorsal capsular structures disrupted by the dislocation. Marked tenderness along medial base of thumb.
Bosworth	Fracture-dislocation of the ankle resulting in the fibula being entrapped behind the tibia.	Rare injury, produced by a severe external rotation force applied to the foot. Physical examination reveals foot severely externally rotated in relation to the tibia.
Boxer's	Fracture of the neck of the fourth or fifth metacarpal.	Results from striking a clenched fist into an unyielding object, usually during an altercation, or against a wall, out of frustration or anger.
Chance's	Vertebral fracture, usually lumbar, involving the posterior spinous process, pedicles, and vertebral body.	Caused by simultaneous flexion and distraction forces on the spinal column, usually associated with use of lap seat belts. Anterior column fails in tension along with the middle and posterior columns. May be misdiagnosed as a compression fracture.
Chauffeur's	Solitary fracture of radial styloid.	Occurs from tension forces sustained during ulnar deviation and supination of the wrist. Name derives from occurrence in chauffeurs who suffered violent, direct blows to the radius incurred while turning the crank on a car, only to have it snap back, during previous eras.
Clay shoveler's	Fracture of the tip of the spinous process of the sixth or seventh cervical vertebra.	First described in Australian clay shovelers who sustained a fracture of the spinous process by traction as they lifted heavy loads of clay.
Colles'	Fracture of the distal radius with dorsal displacement and volar angulation, with or without an ulnar styloid fracture.	Most common wrist fracture in adults, especially in the elderly. Results from fall on an outstretched hand. Also known as *silver fork deformity,* which accurately describes the gross appearance in the lateral view. First described by Colles in 1814, before the advent of radiography.
Cotton's	Trimalleolar fracture.	Fracture of the lateral malleolus, fracture of the posterior malleolus, and either a fracture of the medial malleolus or a disruption of the deltoid ligament with visible widening of the mortise on ankle radiograph.
Dashboard fracture	Fracture of the posterior rim of the acetabulum.	Named for mechanism of injury: a seated passenger striking the knee on a dashboard, driving the head of the femur into the acetabulum.
Dupuytren's	Fracture-dislocation of the ankle.	Results from a similar mechanism as the better known Maisonneuve fracture (i.e., external rotation of the ankle), resulting in either deltoid ligament rupture or medial malleolus fracture, diastasis of the inferior tibiofibular joint, and indirect fracture of the fibular shaft. Maisonneuve was the student of Dupuytren.
Essex-Lopresti	Fracture of radial head with dislocation of distal radioulnar joint.	Results from longitudinal (axial) compression of the forearm.
Galeazzi's	Fracture of the shaft of the radius with dislocation of the distal radioulnar joint. Ligaments of inferior radioulnar joint are ruptured and head of ulna displaced from ulnar notch of the radius.	Results from fall on outstretched hand, with the wrist in extension and the forearm forcibly pronated. Inherently unstable with tendency to redisplace after reduction.
Hangman's	Fracture-dislocation of atlas and axis, specifically of pars interarticularis of C2 and disruption of C2-3 junction. Separation occurs between second and third vertebral bodies from anterior to posterior side.	Results from extreme hyperextension during abrupt deceleration. Most common cause is the forehead striking the windshield of a car during a collision. A bit of a misnomer in that hanging usually produces death by strangulation rather than cord damage.

www.ketabpezeshki.com 66485457-66963820

Table 49-1 Common Fracture Names and Their Origins—cont'd

FRACTURE EPONYM OR NAME	DESCRIPTION	COMMENT
Hume's	Fracture of the proximal ulna associated with forward dislocation of the head of the radius.	Essentially high Monteggia's injury.
Jefferson's	Burst fracture of ring of C1, or atlas.	Axial loading results in a shattering of the ring of the atlas. Decompressive type of injury. Associated with disruption of transverse ligament; an unstable injury.
Jones	Transverse fracture of the metatarsal base, occurring at least 15 mm distal to the proximal end of the bone, distal to the insertion of the peroneus brevis.	Should not be confused with the more common avulsion fracture of fifth metatarsal styloid, produced by avulsion at the insertion of the peroneus brevis. Jones described the fracture that bears his name in 1902, after sustaining the injury himself while dancing.
Le Fort	Maxillary fracture.	Types I, II, and III (see Chapter 42).
Le Fort-Wagstaffe	Avulsion fracture of the anterior cortex of the lateral malleolus.	Rare pull-off injury of the fibular attachment of the anterior tibiofibular ligament.
Lisfranc's	Fracture located around the tarsometatarsal (Lisfranc's) joint, usually associated with dislocation of this joint.	Lisfranc, a field surgeon in Napoleon's army, described an amputation performed through the tarsometatarsal joint in a soldier who caught his foot in a stirrup when he fell off his horse. Since then, the joint has borne his name.
Maisonneuve	Fracture of proximal third of fibula associated with rupture of the deltoid ligament or fracture of the medial malleolus and disruption of the syndesmosis.	Results from external rotation of the ankle with transmission of forces through syndesmosis; proximally the force is relieved by fracture of the fibula. Described experimentally in 1840, before radiography.
Malgaigne's	Fracture of the ilium near the sacroiliac joint with displacement of the symphysis, or a dislocation of the sacroiliac joint with fracture of both ipsilateral pubic rami.	Resultant pelvic injury is unstable. Described by Malgaigne, based on clinical findings, in 1847.
March	Fatigue, or stress, fracture of the metatarsal.	Arises from long marches or other repetitive use trauma (e.g., marathon running) or less commonly from single stumbling movements.
Monteggia's	Fracture of the junction of the proximal and middle thirds of the ulna associated with anterior dislocation of the radial head.	Usually caused by fall on outstretched hand along with forced pronation of forearm or by a direct blow on the posterior aspect of the ulna. Reported by Monteggia in 1814.
Nightstick	Fracture of either ulna or radius, or both.	Name derived from a citizen's attempt to protect himself from a police officer's baton or "nightstick" by offering the forearm.
Piedmont	Closed fracture of the radius at the middle third–distal third junction, without associated ulnar fracture.	Named for a series of cases presented at the Piedmont Orthopaedic Society of Durham, North Carolina.
Pott's	Definitions vary (see comment); most commonly a bimalleolar fracture or a fracture of the distal fibula, 4-7 cm above the lateral malleolus.	The exact fracture Pott described in 1769 is uncertain; clearly it referred to a fracture of the lower fibula, usually associated with other fractures or dislocations about the ankle.
Rolando's	Intra-articular fracture at base of metacarpal. Frequently Y- or T-shaped, or may be severely comminuted.	Produced by an axial load with the metacarpal in partial flexion. Worse prognosis than a Bennett's fracture and, fortunately, rarer.
Salter-Harris	An epiphyseal fracture occurring in children or adolescents.	Graded I-V, depending on degree of involvement and/or displacement of epiphysis and metaphysis (see text dealing with Salter-Harris fractures and also Figure 46-1).
Smith's	Extra-articular fracture of the distal radius with volar displacement of distal fragment.	Reverse of the Colles' fracture but much more uncommon. Sometimes referred to as a "garden spade" deformity. Usually results from fall with force to back of hand. First described by Smith in 1847.
Stener	Avulsion of the ulnar corner of the base of the proximal phalanx of the thumb.	Bony equivalent of rupture of the ulnar collateral ligament, or "gamekeeper's thumb."
Teardrop	Wedge-shaped fracture of the anteroinferior portion of the vertebral body, displaced anteriorly.	Commonly involves a ligamentous injury and may produce neurologic injury.
Thurston Holland's fragment	Triangular metaphyseal fragment that accompanies the epiphysis in Salter-Harris type II fractures.	Described by Thurston Holland in 1929. The name is commonly hyphenated, although technically it should not be.
Tillaux	Isolated avulsion fracture of the anterolateral aspect of the distal tibial epiphysis.	Occurs in older adolescents (12-15 years) after the medial parts of the epiphyseal plates close but before the lateral part closes. External rotation force places stress on anterior talofibular ligament. Described by Tillaux in 1872.

www.ketabpezeshki.com 66485457-66963820

distal—and these thirds or the junction of any two of them (e.g., the junction of the middle and distal third of the tibia) are used to describe fractures. The most descriptive language possible should be used. It is better to say "closed fracture of the right ulnar styloid" than "closed fracture of the right distal ulna" because the former conveys more precise anatomic information.

An additional modifier describes the direction of the fracture line in relation to the long axis of the bone in question. A *transverse* fracture occurs at a right angle to the long axis of the bone (Fig. 49-1A), whereas an *oblique* fracture runs oblique to the long axis of the bone (Fig. 49-1B). A *spiral* fracture results from a rotational force and encircles the shaft of a long bone in a spiral fashion (Fig. 49-1C). A fracture with more than two fragments is termed *comminuted* (Fig. 49-1D).

The position and alignment of the fracture fragments (i.e., their relationship to one another) should be described. Fragments are described relative to their normal position, and any deviation from normal is termed *displacement.* By convention, the position of the distal fragment is described relative to the proximal one. Displacement may be described as a quantitative measurement (i.e., in millimeters) or as a percentage of the bone width. Figure 49-2 shows a dorsal displacement of the fractured radius, and Figure 49-3 shows lateral, or valgus, displacement of the distal tibia and fibula.

The terms *valgus* and *varus* are sometimes confusing. *Valgus* denotes a deformity in which the described part is angled away from the midline of the body. Conversely, *varus* denotes a deformity in which the angulation of the part is toward the midline. *Alignment* refers to the relationship of the longitudinal axis of one fragment to another; deviation from the normal alignment is termed *angulation.* The direction of angulation is determined by the direction of the apex of an angle formed by the two fracture fragments (Fig. 49-4). This angle is opposite to the direction of displacement of the distal fragment. The relative position or angulation of the distal fragment of a fracture may also be described with terms such as *radial* or *ulnar, dorsal* or *volar, anterior* or *posterior,* and *lateral* or *medial.* One should also be aware of rotational deformity, present when the distal fragment of a fracture is rotated to some degree along the axis of the bone itself. Especially in the digits of the hand, radial or ulnar deviation of a flexed finger can occur, and radiographs often underestimate the degree of clinical deformity and rotation present.

Descriptive Modifiers

A fracture is termed *complete* if it interrupts both cortices of the bone and *incomplete* if it involves only one. It should be noted whether a fracture extends into and involves an *articular surface.* Frequently the percentage of articular surface involved can only be estimated; in some cases the percentage that is actually involved dictates the need to perform a surgical reduction. In general, it is important that the articular surface be restored to anatomic integrity to prevent consequent traumatic arthropathy.

Avulsion fracture refers to a bone fragment that is pulled away from its normal position by either the forceful contraction of a muscle (Fig. 49-5A) or the resistance of a tendon or ligament to a force in the opposite direction (Fig. 49-5B). *Impaction* refers to the

Box 49-1 Fracture Description

Identification
Open versus closed
Exact anatomic location
Direction of fracture line
Simple, comminuted
Position (displacement, alignment)

Additional Modifiers
Complete versus incomplete
Involvement of articular surface (%)
Avulsion
Impaction
  Depression
  Compression

Special Situations
Pathologic
Stress

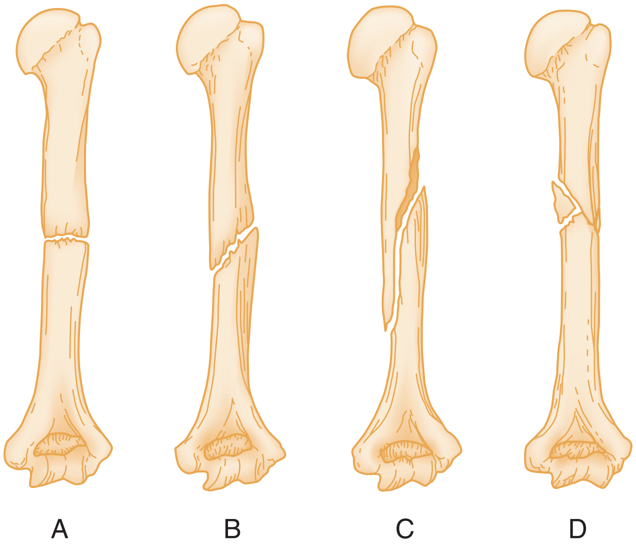


Figure 49-1. Types of fractures. **A,** Transverse. **B,** Oblique. **C,** Spiral. **D,** Comminuted.

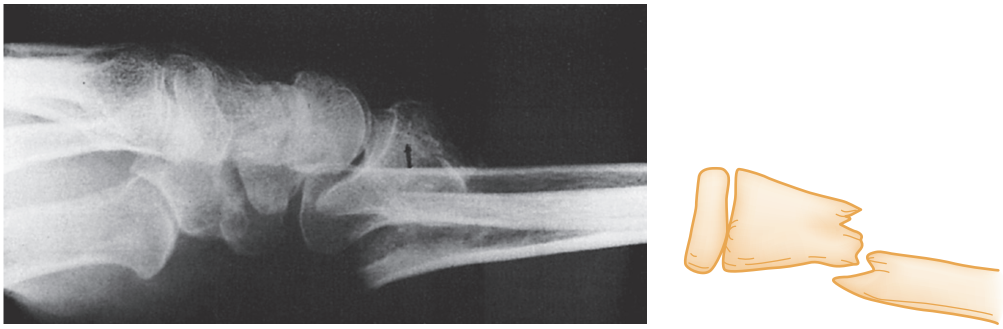


Figure 49-2. Dorsal displacement of distal radius.

www.ketabpezeshki.com 66485457-66963820

forceful collapse of one fragment of bone into or onto another. In the proximal humerus, this collapse typically occurs in a telescoping manner, particularly in elderly patients, whose bones are soft and brittle. In the tibial plateau, impaction occurs frequently in the form of a depression (Fig. 49-6A and B), and in the vertebral bodies, impaction frequently occurs in the form of compression (Fig. 49-6C).

A fracture that occurs through abnormal bone is termed *pathologic*. A pathologic fracture is suggested whenever a fracture occurs from seemingly trivial trauma. Diseases that cause structural weakness predisposing to injury include primary or metastatic malignancies, cysts, enchondromata, and giant-cell tumors. In addition, osteomalacia, osteogenesis imperfecta, scurvy, rickets, and Paget's disease all weaken bones, making them susceptible to fracture. The term *pathologic* also is applied to fractures through osteoporotic bone when the demineralization is a result of disease, as in polio. Fractures through osteoporotic bone of the elderly usually are not described as pathologic. When fractures occur in normal bones and a history of "trivial trauma" is elicited, violence or battering should be suspected. Repeated low-intensity forces may lead to resorption of normal bone, resulting in a stress fracture. Other names for this condition are *fatigue fracture* and *march fracture* (see Table 49-1). Most stress fractures occur in the lower extremities and commonly affect individuals involved in activities such as running, basketball, aerobics, and dancing. Extrinsic factors such as training regimens, type of equipment used, and nutrition habits, as well as intrinsic factors such as anatomic variation, muscle endurance, and hormonal factors have all been associated with stress fractures. These injuries may not be recognizable on initial plain films; therefore management should be based on clinical diagnosis.[1] The tibia, fibula, metatarsals, navicular, cuneiform, calcaneus, femoral neck, or femoral shaft may be involved.[2,3]

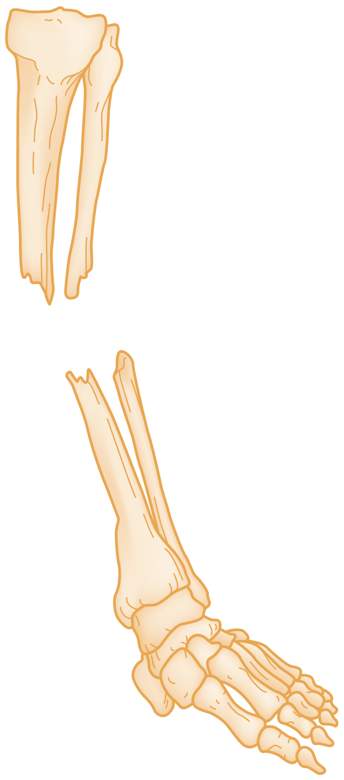


Figure 49-3. Valgus displacement of the distal tibia and fibula. The distal segment is angled away from the midline of the body.

Fracture Eponyms

Many fractures were described before the advent of radiography and are described by an eponym rather than the exact bony injury. These eponyms reflect the rich history of orthopedic care and, despite the objections of some, are still commonly used to describe orthopedic injuries (see Table 49-1).

Fracture Healing

Specific fractures are discussed in subsequent chapters. In general, the goal is to realign bony fragments so that healing or union can take place and normal function is restored. The process from fracture to union begins with a hematoma, caused by rupture of vessels crossing the fracture line. The hematoma bridges the fragments and is followed by an inflammatory phase when granulation tissue forms on the fracture surfaces. Resorption of the hematoma provides the first continuity between the fragments; however, this procallus provides no structural rigidity for bearing stress. With remodeling, callus subsequently is formed on the periosteal and endosteal surfaces of the bone, acting as a biologic splint. This area first becomes mineralized by deposition of calcium phosphate and then undergoes osseous metaplasia. Callus is resorbed as the original fracture surfaces develop firm bony union. In some bones, such as the skull and the neck of the femur, where periosteum is deficient, there may be virtually no callus formation.

Radiographic studies conducted 10 to 14 days after injury show the bone surrounding the fracture line becoming less dense because of localized bone resorption and hyperemia associated with the formation of granulation tissue. As a result, the fracture becomes considerably easier to visualize radiographically about 10 days after injury. After 2 to 3 weeks, soft tissue swelling has regressed, and callus first becomes visible, initially in a mottled pattern and then taking on a dense appearance. The callus undergoes organization, with peripheral margins becoming smooth as physically unstressed portions are resorbed.

Figure 49-4. Volar angulation of a fractured radius.

www.ketabpezeshki.com 66485457-66963820

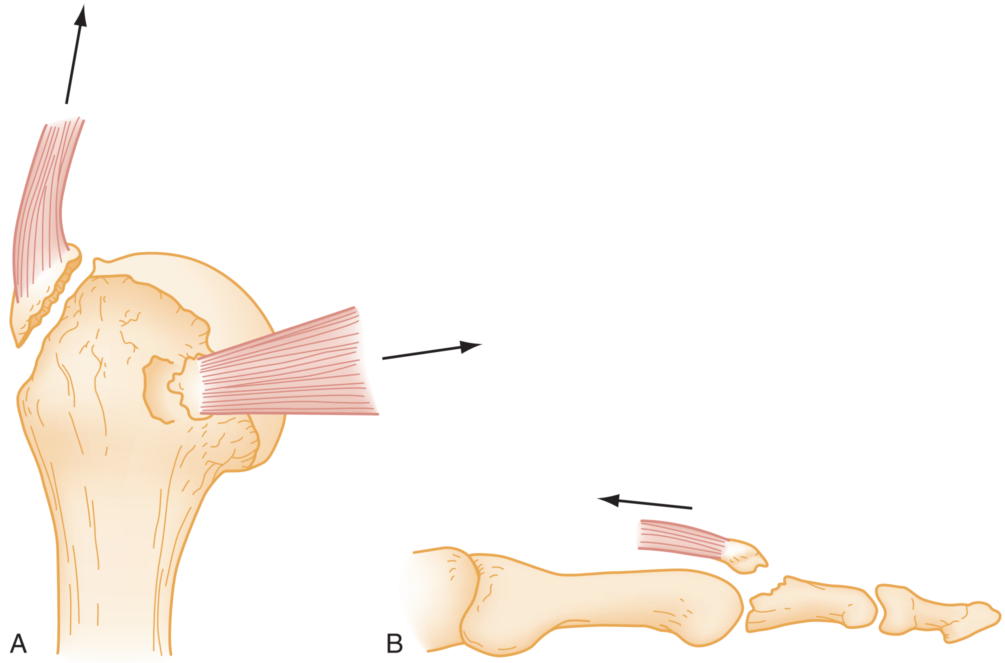


Figure 49-5. Avulsion fractures. **A,** Musculotendinous avulsions of small bone fragments from the head of the humerus. **B,** Extensor tendon avulsion of bone from the base of the middle phalanx.

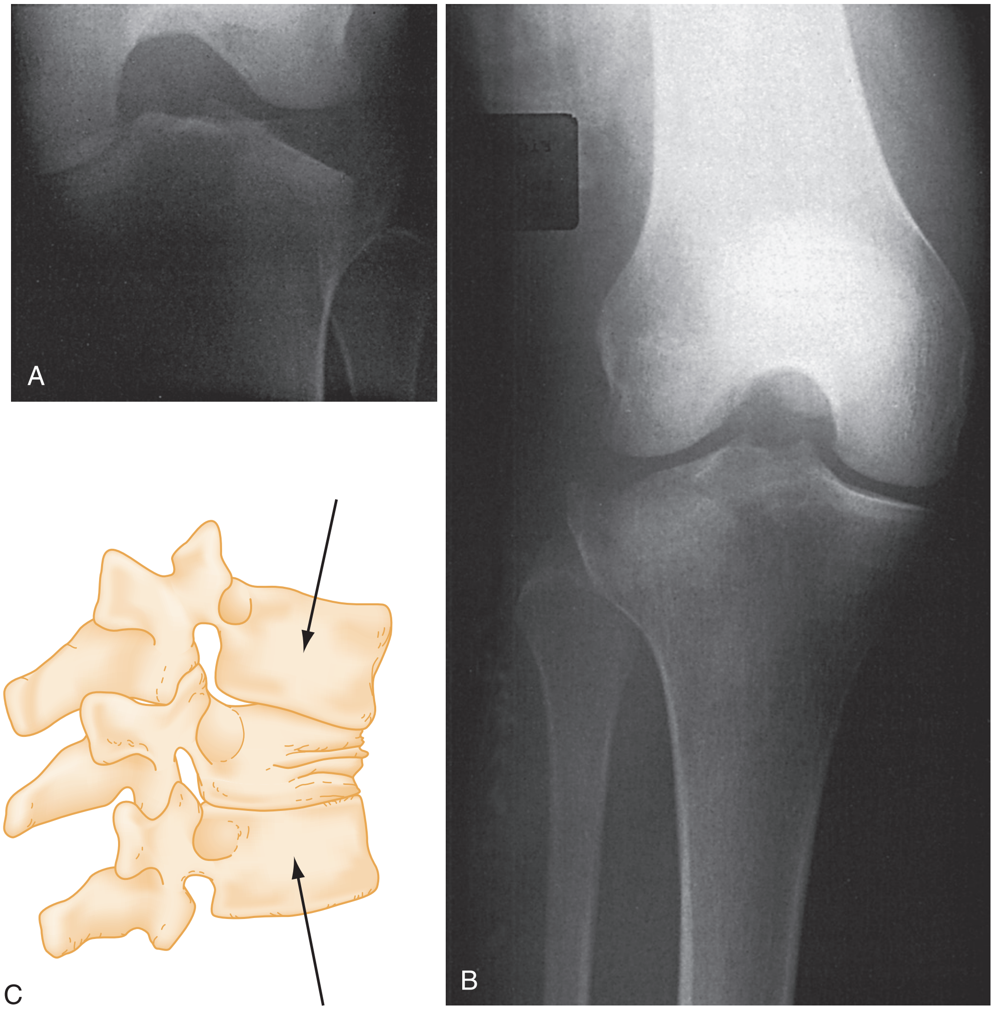


Figure 49-6. A and B, Tibial plateau fracture. C, Vertebral body compression fracture.

www.ketabpezeshki.com 66485457-66963820

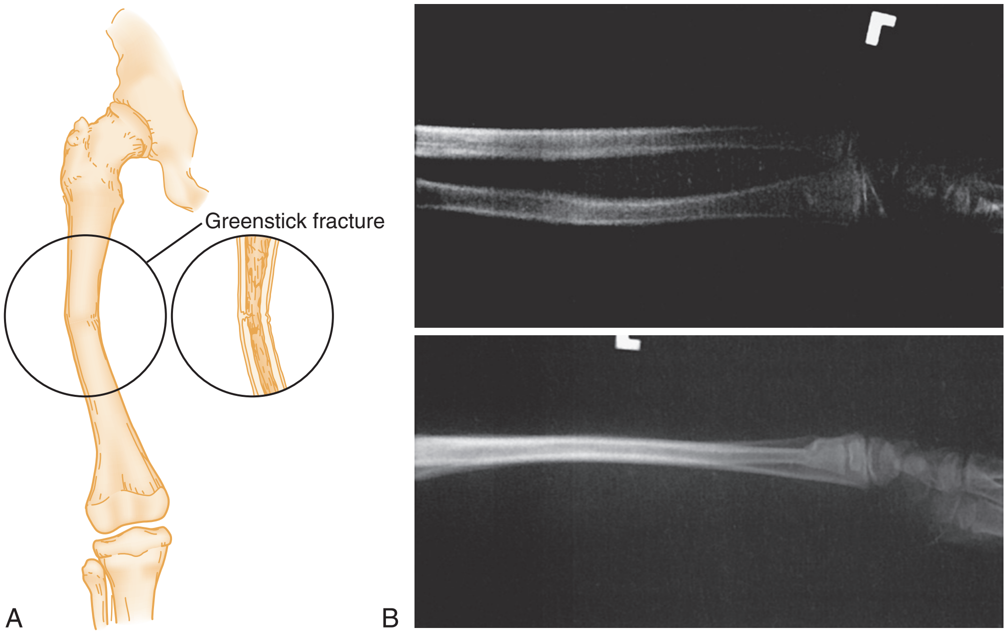


Figure 49-7. A, Greenstick fracture of midshaft of femur. B, Torus fracture of distal third of radius.

In a healthy adult the whole process from injury to consolidation takes about 2 months for the humerus and about 4 months for a large bone such as the femur. Oblique fractures tend to heal more quickly than transverse fractures. Healing is quicker in children and slower in the elderly. The rate of fracture healing is affected by many factors, including the type of bone (cancellous bone heals faster than cortical bone); degree of fracture and opposition; and systemic states, such as hyperthyroidism or illness requiring ongoing cortiscosteroid treatment. Exercise speeds healing, whereas chronic hypoxia has been known to slow repair.

The presence of abundant callus seen on radiograph that is beginning to organize is usually associated with clinical union. If any suggestion of movement at the fracture site is noted on clinical examination, union is regarded as inadequate. Several terms are used to denote abnormal union. *Delayed union* is union that takes longer than usual for a particular fracture location. *Malunion* occurs when a residual deformity exists. *Nonunion* is the failure of a fracture to unite. When nonunion results in a false joint, it is termed a *pseudarthrosis.*

If the ends of the bone have remained constant on serial films and an adequate surrounding sheath of organizing callus can be seen, it is permissible for the patient to return to limited active use, even if the original fracture remains visible. The final process of consolidation develops later.

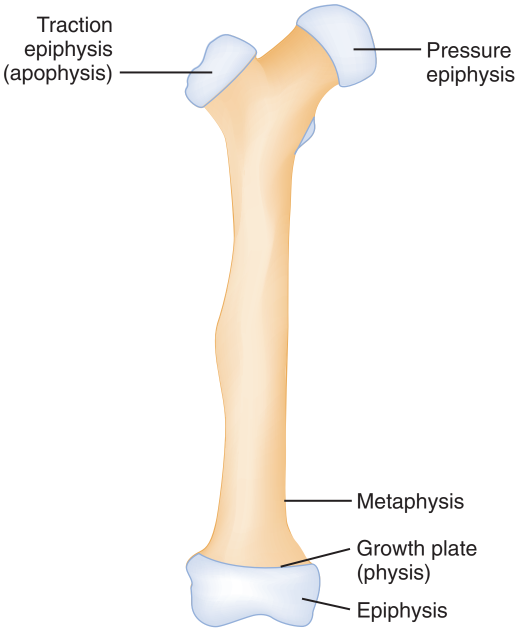


Figure 49-8. Anatomy of growing bone.

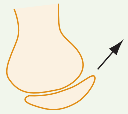
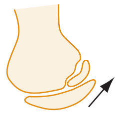
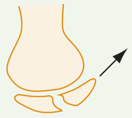
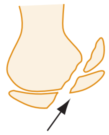
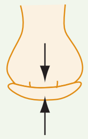
Fractures in Children

Certain features of children's bones distinguish pediatric fractures from adult fractures. Bones of children are necessarily soft and resilient and sustain numerous incomplete fractures. *Greenstick* fractures are incomplete angulated fractures of long bones. The resultant bowing of the bone causes an appearance resembling a moist, immature branch that breaks in a similar fashion when bent (Fig. 49-7A). A *torus* fracture is another form of incomplete fracture, characterized by a wrinkling or buckling of the cortex. In Greek architecture a torus is a bump at the base of a column, and these fractures, occurring at the end of long bones, take on such an appearance. These fractures may be extremely subtle on radiographs (Fig. 49-7B).

Another feature of growing long bones that is a frequent source of trouble and confusion is the presence of epiphyses, cartilaginous centers at or near the ends of bone that give rise to growth of the bone. Figure 49-8 is a schematic review of the anatomy of a growing bone. Because cartilage is radiolucent, the cartilaginous portion of an epiphysis is not visualized on radiographs. A tendency exists to consider only the ossified nucleus and to ignore the cartilaginous structure that bridges to the metaphysis. Cartilage is present even before an ossified nucleus is seen. Because the epiphyseal growth plate is represented by a radiolucent line, confusion may exist as to whether a fracture line is present. These complexities in interpreting radiographs in children sometimes, but not always, require comparison radiographic views of the uninjured side. Injuries to the epiphyses may result from either compressive or shearing forces. These injuries are relatively common during childhood as opposed to sprains or shaft fractures and should be considered in children with a "sprained

www.ketabpezeshki.com 66485457-66963820

Table 49-2 Salter-Harris Classification

	DESCRIPTION	DIAGRAM
Type I	Fracture extends through the epiphyseal plate, resulting in displacement of the epiphysis (this may appear merely as widening of the radiolucent area representing the growth plate).	
Type II	As above; in addition, a triangular segment of metaphysis is fractured.	
Type III	Fracture line runs from the joint surface through epiphyseal plate and epiphysis.	
Type IV	Fracture line occurs as in type III but also passes through adjacent metaphysis.	
Type V	This is a crush injury of the epiphysis; it may be difficult to determine by radiographic examination.	

ankle" because of the relative weakness of the cartilaginous growth zone, which separates before stronger ligaments and bones are torn or broken. Epiphyseal injuries should be described according to the Salter-Harris classification (Table 49-2).

Type I injuries involve only a slip of the zone of provisional calcification. Comparison radiographs are usually necessary to detect small slips. Swelling and tenderness over an epiphysis (e.g., of the lateral ankle) and a negative radiograph suggest an epiphyseal injury rather than a sprain, because the epiphysis is weaker than the overlying ligaments.

Type II injuries are similar to type I injuries, with a fracture extending into the metaphysis. The triangular metaphyseal fragment sometimes is referred to as the *Thurston Holland sign* (see Table 49-1). Type II injuries account for approximately three fourths of all epiphyseal fractures. Because the germinal layer is not involved, growth disturbance usually does not occur with type I and II injuries. These injuries are amenable to closed reduction and immobilization without internal fixation.

Type III injuries are composed of a slip of the growth plate plus a fracture through the epiphysis, involving the articular surface. Because this fracture involves the germinal layer, growth may be disrupted. Anatomic reduction does not eliminate the possibility of growth disturbance. Type IV fractures are similar to type III fractures, with the additional involvement of a metaphyseal fracture. Open reduction and internal fixation are usually required to obtain anatomic alignment of the physis and articular surface. Growth disturbance occurs in a high proportion of patients.

Type V fractures are crush injuries of the epiphyseal plate, usually produced by a compressive force.[3] This type of injury usually occurs in joints that move in one plane, most commonly the knee and ankle. Because this injury occurs in a radiolucent area, the injury may be difficult to diagnose on radiograph, but it is suggested by mechanism of injury and pain over the epiphysis. The diagnosis can be established by MRI if hemorrhage or a hematoma is identified within the growth plate immediately after injury.[3-5] Also reported is loss of MRI signal from the cartilage.[6] Rarely are type V injuries diagnosed acutely, and growth arrest manifested by shortening or angulation is the rule with this injury.

Physeal injuries occur twice as often in boys as in girls and are most common in boys aged 12 to 15 years and in girls aged 9 to 12 years.[7] Distal physes are injured more often than proximal physes, and the most common anatomic locations include the distal radius, phalanges, and distal tibia. Distal radius fractures account for two thirds of fractures in pediatric patients in the ED.[8] The incidence of these fractures has increased by 40% over the past three decades, possibly because of a change in recreational activities, such as increased skiing and skating among boys and increased basketball, soccer, and skating among girls.[9] Most distal radius type I and II fractures can be treated through closed reduction, though this may be more technically difficult with completely displaced both-bone fractures. Similar practice has been applied to distal tibia type I and II fractures, though the incidence of premature physeal closure was shown to be 3.5 times higher if the residual fracture displacement was greater than 3 mm in postreduction radiographs.[10] Growth arrest as a complication of physeal fracture is most likely to be seen at the distal femur, distal and proximal tibia, and distal radius.[7]

Diagnostic Modalities for Fracture Diagnosis

Plain Radiography

Conventional radiography is the mainstay in diagnosing fractures. In addition to confirming or excluding fractures, it can identify other pathologic conditions. With penetrating trauma, foreign bodies, air, and gas also may be detected. With minor trauma and when good follow-up monitoring is ensured, it is acceptable to delay radiography. Delay cannot be permitted, however, when the suggested injury is one that might be made worse by delayed diagnosis, such as a nondisplaced hip fracture.

Biplanar radiographs of an injured extremity should be obtained to fully delineate the bony injury. Conventional radiographic evaluation of long bones include at least two orthogonal views, and an oblique view is also usually obtained. In certain locations, such as the phalanges, oblique views are necessary. If doubt still exists, the clinician should ask for more views in various degrees of obliquity to the other films. A fracture line is most visible when it is parallel to the x-ray beam and is invisible when it is exactly 90 degrees to the beam. *The clinician should never accept a study that examines the bone in only one plane.* When a long bone is found to be fractured, it is imperative that the bone be viewed radiographically in its entire length.

Each film is examined to ensure that proper technique has been used and that no important area is omitted from the film. Overexposed films may fail to reveal an abnormality. Although some fine detail is lost on portable films, these are acceptable in unstable patients, in whom the risk of moving the patient does not outweigh the benefit of the more detailed study. Even with good technique, some fractures are not visible initially and do not appear until the margins of the fracture absorb. Absorption widens the radiolucent line, and a defect appears in 7 to 10 days. At that time, new bone produced beneath the periosteum at the margins of the fracture accentuates the fracture. Accordingly, if a fracture is suggested but not visible at the initial visit, the injury should be treated as a fracture and reexamined clinically and radiographically in 7 to 10 days, and the patient should be informed of the rationale for this regimen.

Stress views of joints are used in some instances to evaluate the degree of ligamentous injury. Some authors argue against the use of stress views, citing a risk of further injuring an already traumatized structure, additional radiation exposure to the patient and

www.ketabpezeshki.com 66485457-66963820

the technologist, and the possibility that pain may not allow sufficient stress to be applied. For these reasons, stress views should be used judiciously in circumstances when other methods of evaluating ligamentous injuries are not available. *Comparison views* are useful in selected situations but should not routinely be performed in all pediatric examinations.[11] If a fracture is definitely present on the affected side, the comparison view exposes the child to radiation and adds expense with no benefit. Similarly, an experienced physician generally is able to read a normal film with reasonable certainty. It is reasonable to use comparison views in instances when radiographs are inconclusive and when the confusion arises specifically out of the need to distinguish between a possible fracture and normal developmental anatomy. Obtaining a wide field of the affected extremity is more useful than routine comparison views for a young child because the child often does not localize the pain well; this is especially true with regard to complaints of knee pain in cases of hip injury or wrist complaints in forearm and elbow injury. Comparison views sometimes are helpful in adults when a question of accessory ossicles or nonfused bones (e.g., bipartite patella) exists because these anomalies are usually bilateral. The bleeding that inevitably accompanies fractures may produce soft tissue swelling, which may impinge on or obliterate overlying muscle planes. Fat pads, such as in the elbow, may be displaced. Another useful sign is the fat-fluid level, which may accompany fractures extending into the knee joint. The fat-fluid level is visible, however, only if the cross-table technique is used.

The bones themselves should be examined systematically. Normal adult bones possess a smooth unbroken contour. A distinct angle is highly suggestive of a fracture. In an adult the typical fracture is represented by a lucent line that interrupts the smooth contour and usually extends to the opposite side. Nutrient arteries may be confused with fractures but have different radiographic characteristics: They are fine, are sharply marginated, extend obliquely through the cortex, and are less radiolucent than fractures. *Pseudofractures* can be created by soft tissue folds, bandages or other overlying material, or a radiographic artifact called the *Mach effect*. If lucencies extend beyond the bones, the line is highly unlikely to represent a fracture. Anomalous bones and calcified soft tissue likewise may be mistaken for fractures. Avulsions and small fracture fragments have an irregular surface that lacks well-corticated margins and a defect in the adjacent bone is present, whereas anomalous ossification centers (accessory ossicles) and sesamoids are characterized by smooth cortical margins. Reference texts are useful in identifying and confirming these anomalies because they tend to occur in predictable locations.[12] Compression fractures are represented by increased density rather than a lucency. Finally, the most commonly missed fracture is the second fracture. One should be diligent in searching for additional fractures after discovering the first fracture on a study. In particular, certain paired fractures, such as the distal tibia and proximal fibula, should be sought out.

Special Imaging Techniques

Radionuclide Bone Scanning. In the past, radionuclide bone scanning was used to detect skeletal abnormalities not radiographically evident in children and adults.[13] Occult lesions, especially stress fractures, acute osteomyelitis, and tumors, can be detected on these scans, although there are problems with specificity and sensitivity. This modality has been largely supplanted by CT and MRI and now is seldom used.

Computed Tomography. Computed (digital) radiography is now in widespread use. Although conventional radiography remains the initial imaging study of choice for skeletal trauma, CT offers a more detailed and diagnostically sensitive evaluation of bones and joints. With improved resolution and speed, multidetector-row CT captures large volumetric data sets from which two- and three-dimensional images can be created.[14,15] Workstation post-processing has become an integral part of the examination. Two-dimensional multiplanar reconstruction in any chosen plane, and three-dimensional surface rendering techniques provide images with unprecedented quality, even in the presence of metallic implants or fixation devices.[16]

CT is used to confirm possible fractures or to better define displacement, alignment, or fragmentation of fractures. It is also useful in trauma to rule out cervical spine fracture when plain films are equivocal and in noncompressive vertebral fractures to assess the number of fragments and their spatial relationship to the spinal canal. CT is used frequently to define the integrity of articular surfaces in the acetabulum, knee, wrist, or ankle and in Salter-Harris type IV fractures.[4] In the multiple trauma patient requiring thoracic, abdominal, and pelvic CT imaging to rule out visceral injury, the soft tissue protocols may be adapted to acquire diagnostic bone images, as well.[17] During imaging of the chest, abdomen, or pelvis, data sets are created from which the thoracolumbar spine and bony pelvis can be derived.

Magnetic Resonance Imaging. MRI constitutes the most advanced noninvasive examination of orthopedic structures, delineating lesions of bone, cartilage, ligaments, and other structures, such as menisci, disks, and epiphyseal structures. MRI is expensive and time-consuming and should be reserved for instances in which the diagnosis is in doubt and specific findings would alter the treatment.

Ultrasound Imaging. Point-of-care ultrasound may be an effective tool for the diagnosis of fractures when conventional radiography is unavailable. Through use of bedside ultrasonography, fractures are visualized as an interruption of the linear bony cortex and may be clinically correlated during the physical examination of the affected area. Ultrasound can be effective in the diagnosis of long bone fractures, orbital floor fractures, rib fractures, and occult fractures of the foot and ankle.[18] Ultrasound can be used in "real-time" during fracture reduction to confirm proper reduction and alignment of bony fragments.[19]

Complications of Fractures

Infection (Osteomyelitis)

Any fracture communicating with the surface of the skin is termed an *open fracture*. Open fractures are treated as true orthopedic emergencies because of the risk of infection; the dreadful nature of the complication of osteomyelitis dictates that no time should be wasted in initiating therapy (Box 49-2). Wounds should be irrigated of gross debris and covered with a sterile dressing, and parenteral antibiotics should be instituted as early as possible.[20]

Currently, suggested therapy includes a first-generation cephalosporin, such as cefazolin, for all open fractures, with the addition of an aminoglycoside for grade II or III fractures.[21,22] Early versus delayed treatment of open fractures and its subsequent effect on rates of infection has been a source of debate. Historic guidelines recommending débridement of open fracture wounds within 6 hours of injury were based on animal experiments conducted in the 1890s.[23] Current human studies suggest no clear advantage to performing surgical débridement within 6 hours of injury. The timing of débridement—less than 6 hours versus more than 6 hours after injury—had no effect on clinical or functional outcome in a prospective multicenter study of severe lower-extremity fractures.[24] Other retrospective studies and literature reviews advocate early débridement and irrigation of the wound within the first 24 hours of injury to prevent infection.

Certain open fractures of the finger present a notable exception to the previous recommendation. Such injuries, especially an open distal tuft fracture, are common when the phalanx of a finger is

www.ketabpezeshki.com 66485457-66963820

subject to crush injury (e.g., by a door) and there exists a skin defect overlying a fractured bone. In a prospective randomized, placebo-controlled study of 193 patients with open fracture of the finger, flucloxacillin or placebo was administered to randomized patients with open phalangeal fractures, and both groups were treated with aggressive surgical irrigation and débridement. No significant difference was found in the infection rate between the groups, and no patient developed osteomyelitis. The data suggest that vigorous irrigation and débridement are adequate primary treatment for open phalangeal fractures in fingers with intact digital arteries.[25] Such injuries might be repaired by the emergency physician without consultation.

Hemorrhage

Because of the rich blood supply to the skeleton, fractures can result in large amounts of blood loss, shock, and death from exsanguination. In particular, certain pelvic fractures can cause great blood loss as adequate tamponade is not possible. In adults, blood loss can range from 100 mL from a forearm fracture to 3 L from a pelvic fracture (Table 49-3).

Vascular Injuries

Vascular injuries characteristically are associated with certain fractures and may be limb-threatening. Fractures and dislocations (at the femorotibial articulation) of the knee result from tremendous force that often injures the popliteal artery. Fracture of the femoral neck requires emergent reduction and fixation to protect the blood supply to the femoral head.[23] In the extremities, assessment of vascular injuries may be difficult. The initial survey should note the presence or absence of pulses and the state of capillary filling. If an end artery is completely disrupted, the tissue distal to the injury may exhibit the classic five *P*s: pain, pallor, pulselessness, paresthesias, and paralysis. Incomplete and subclinical injuries occasionally occur that initially may be asymptomatic and undetectable. Likewise, in an unconscious, multiply injured patient, major vascular injuries may not be obvious. The mechanism of injury and anatomy dictate the need to assess the possibility of an injured vessel. If pulses cannot be palpated, a Doppler stethoscope should be used to listen for blood flow. Even palpable pulses may be misleading, however, because it has been shown that in 10 to 20% of significant arterial injuries, distal pulses may initially be normal. When pulses are present but the mechanism of injury suggests the possibility of vascular injury, additional diagnostic studies or surgical exploration may be necessary. If a limb is clearly not perfused, operative vascular exploration and repair should take place promptly. Late complications of undiagnosed vascular injuries include thrombosis, arteriovenous fistulae, aneurysm, false aneurysm, and tissue ischemia with limb dysfunction. Delay of vascular injury repair is a risk factor for consequent amputation.[26]

Traditionally, conventional arteriography has been the diagnostic modality of choice in evaluating vascular injuries; however, it is invasive and costly. Alternative methods of vascular assessment include arterial pressure indices and serial physical examinations. Recent advances in computed tomographic angiography have proven it an effective alternative to conventional arteriography, and its advantages include immediate availability and noninvasiveness.[27]

Nerve Injuries

Nerves can be injured by either blunt or penetrating trauma. *Neurapraxia* is the contusion of a nerve, with disruption of the ability to transmit impulses. Paralysis, if present, is transient, and sensory loss is slight. Normal function usually returns to a neurapraxic nerve in weeks to months. *Axonotmesis* is a more severe crush injury to a nerve. The injury to nerve fibers occurs within their sheaths. Because the Schwann tubes remain in continuity, spontaneous healing is possible but slow. *Neurotmesis* is the severing of a nerve, usually requiring surgical repair. Age, site, injured nerve, and delay between injury and repair have all been shown to influence prognosis after microsurgical repair.[28] Because of proximity, specific nerve injuries characteristically accompany certain fractures (Table 49-4). For example, in the upper extremity,

Box 49-2 Classification and Emergency Management of Open Fractures

Grades

Grade I: Wound less than 1 cm long, punctured from below
Grade II: Laceration 5 cm long; no contamination or crush; no excessive soft tissue loss, flaps, or avulsion
Grade III: Large laceration, associated contamination or crush; frequently includes a segmental fracture
- IIIA: Involves extensive soft tissue stripping of bone
- IIIB: Periosteal stripping has occurred
- IIC: Major vascular injury present

Management

1. Control hemorrhage in field with sterile pressure dressing after carefully removing gross debris (e.g., wood, clothing, leaves).
2. Splint without reduction, unless vascular compromise is present.
3. Irrigate with saline and cover with saline-soaked sponges after arrival in the emergency department.
4. Begin intravenous antibiotic prophylaxis, usually a first-generation cephalosporin for grade I, with the addition of an aminoglycoside for grades II and III.
5. Administer tetanus prophylaxis, including tetanus immune globulin, for large crush wounds.

Table 49-3 Blood Loss Associated with Fracture in Adults

FRACTURE SITE	AMOUNT OF BLOOD LOSS (mL)
Radius and ulna	150-250
Humerus	250
Tibia and fibula	500
Femur	1000
Pelvis	1500-3000

Table 49-4 Nerve Injuries Accompanying Orthopedic Injuries

ORTHOPEDIC INJURY	NERVE INJURY
Distal radius	Median nerve
Elbow injury	Median or ulnar
Shoulder dislocation	Axillary
Sacral fracture	Cauda equina
Acetabulum fracture	Sciatic
Hip dislocation	Femoral nerve
Femoral shaft fracture	Peroneal
Knee dislocation	Tibial or peroneal
Lateral tibial plateau fracture	Peroneal

www.ketabpezeshki.com 66485457-66963820

Table 49-5 Life-Threatening or Limb-Threatening Emergencies

CONDITION	POSSIBLE ADVERSE OUTCOME
Open fracture	Osteomyelitis
Fracture or dislocation with major vascular disruption (especially popliteal)	Amputation
Major pelvic fracture	Exsanguination
Hip dislocation	Avascular necrosis of femoral head
Compartment syndrome	Ischemic contracture; myoglobinuria, renal failure

a distal radius fracture caused by a high-energy insult can be associated with acute dysfunction of the median nerve. Deteriorating neurologic function may necessitate temporary or definitive stabilization of a fracture.

When the nerve is completely severed, all functions are absent, including superficial sensation to touch, pain, and temperature; deep sensation to muscle and joint movements, position, deep pressure, and vibration; motor supply and deep tendon reflexes (to distally innervated muscle groups); and response to electrical stimulation. For less severe injuries, any subjective change in sensation should be noted. Light touch is a good screening test. Two-point discrimination is a more sensitive examination and should be used routinely in evaluating digital nerves. Separating the ends of a paper clip a few millimeters apart and asking the patient to discriminate between one or two points may easily accomplish this. The discrimination on the injured digit is then compared with the uninjured ones. Two-point discrimination may be of limited value in children in whom a subjective response may be misleading; this is also true in patients with calloused fingertips and in patients who are uncooperative, comatose, in severe pain, or intoxicated. Testing for sympathetic nerve function with the O'Riain wrinkle test may be helpful.[29,30] Soaking the normally innervated digits in warm saline for 20 minutes causes the digital pulps to wrinkle through a mechanism that is not understood. The presence of wrinkling probably indicates the nerve is intact, whereas absence of wrinkling may be more difficult to interpret. The Ninhydrin test, another sudomotor test used to assess peripheral nerve integrity, is reportedly more reliable than the O'Riain test but is not practical to perform in the ED.

Compartment Syndrome

Compartment syndrome is a serious acute emergency complication that should be considered whenever pain and paresthesias occur in an extremity after a fracture within an enclosed osseofascial space (Table 49-5). The immediate threat is to the viability of nerve and muscle tissue within the involved compartment, but infection, gangrene, myoglobinuria, and renal failure also may ensue. Compartment syndrome is associated most commonly with a closed long bone fracture of the tibia, but it also is well described in the thigh, forearm, arm, hand, and foot.[31-35] In addition, compartment syndrome can occur with soft tissue trauma alone and even with open fractures. It also has been described in a host of unusual situations, including prolonged procedures in the lithotomy position, the tuck position (knees tucked to the chest for lumbar surgery), coma, spontaneous hemorrhage, intravenous injections, and the application of excessive traction in treatment of a fracture.[36,37] Acute surgical stabilization of a fracture is also associated with higher rates of compartment syndrome in the postoperative period.[38]

Pathophysiology. Increased pressure in a closed nonexpandable compartment essentially represents a mismatch between the volume of that space and its contents. As such, it may arise from one of three circumstances: (1) increased compartment contents, (2) decreased compartment volume, or (3) external pressure (Box 49-3). As tissue pressure increases, so does venous pressure, resulting in compromise of the local circulation and tissue hypoxia; this is believed to occur at pressures that are above normal diastolic pressure but below systemic arterial pressure because of a reduced arteriovenous gradient at the tissue level. The body responds by releasing histamine in an attempt to dilate capillaries and increase blood flow to the affected area. Histamine also increases capillary membrane permeability, resulting in a leak of proteins and fluid into the surrounding tissue, further increasing compartment pressure.

Box 49-3 Causes of Compartment Syndrome

Increased Compartment Content

- Bleeding
  - Major vascular injury
  - Coagulation disorder
  - Anticoagulant therapy
- Increased capillary filtration
  - Reperfusion after ischemia
    - Arterial bypass grafting
    - Embolectomy
    - Ergotamine ingestion
    - Cardiac catheterization
    - Lying on limb
  - Trauma
    - Fracture
    - Convulsion
  - Intensive use of muscle
    - Exercise
    - Seizures
    - Eclampsia
    - Tetany
  - Burns
    - Thermal
    - Electrical
  - Intra-arterial drug injection
  - Orthopedic surgery
    - Tibial osteotomy
    - Hauser's procedure
    - Reduction and internal fixation of fractures
  - Snakebite
- Increased capillary pressure
  - Intensive use of muscles
  - Venous obstruction
    - Phlegmasia cerulea dolens (i.e., acute inflammation and edema of the legs)
    - Ill-fitting leg brace
    - Venous ligation
  - Diminished serum osmolarity (i.e., nephrotic syndrome)

Decreased Compartment Volume

- Closure of fascial defects
- Excessive traction on fractured limbs

Miscellaneous

- Infiltrated infusion
- Pressure transfusion
- Leaky dialysis cannula
- Muscle hypertrophy
- Popliteal cyst

External Pressure

- Tight casts, dressings, or air splints
- Lying on limb

From Matsen FA III: Compartmental Syndromes. New York, Grune & Stratton, 1980.

www.ketabpezeshki.com 66485457-66963820

As tissue pressure continues to increase, venous blood flow is impaired as capillary perfusion pressure is exceeded. Finally, arterial capillary blood flow falls to a point at which the basic metabolic needs are no longer met, leading to ischemic necrosis of muscles and nerves within the compartment. An important concept in the management of compartment syndrome is that because local venous pressure cannot be significantly below local tissue pressure, and because elevation of a dependent limb decreases local arterial pressure by 0.8 mm Hg for each 1 cm of limb elevation, elevation of a limb with resultant reduction in the local arteriovenous gradient may be counterproductive and may exacerbate compartment syndrome. Vascular spasm seems to play an insignificant or minimal role in the development of compartment syndrome, as evidenced angiographically, where spasm has never been shown, and clinically, where it is observed that distal pulses usually are maintained until late in the course.

Normal compartment pressure is 0 mm Hg. Microcirculation generally is impaired when tissue pressures reach 30 mm Hg or more; however, some patients can tolerate much higher compartment pressures without development of compartment syndrome. Controversy exists over attempts to define compartment syndromes on the basis of specific tissue pressure. The tolerance to tissue ischemia varies among individuals because of shock, compensatory hypertension, altered tone in resistance vessels, preexisting vascular disease, and other unknown factors. Inadequate perfusion and relative ischemia begin when tissue pressure within a closed compartment increases to within 20 mm Hg of a patient's diastolic pressure or, more accurately, within 30 mm Hg of the mean arterial pressure.[39] When tissue pressure equals or exceeds the patient's diastolic pressure, tissue perfusion effectively ceases. The development of muscle ischemia depends not only on the magnitude but also on the duration of elevated pressure. Intracompartmental pressures do not measure muscle and nerve ischemia but rather suggest the existence of the proper setting for compartment syndrome.

Anatomic Considerations and Risk Factors. Compartment syndrome theoretically can develop in any location where neuromuscular tissue is contained in a limiting envelope. The condition has been reported in the leg, thigh, buttock, arm, forearm, and hand (Box 49-4). By virtue of its location and higher likelihood of sustaining high-energy trauma, the leg, particularly the anterior compartment, is most commonly involved. Higher rates of compartment syndrome are seen with open fractures than with closed fractures, despite the fascial rents that accompany open fractures. The higher energy of injury observed with open fractures, with resultant tissue trauma, swelling, and bleeding, may account for this observation.

In a study of 164 patients treated over an 8-year period in the United Kingdom, a fracture was present in 69%, and half of these involved the tibial shaft.[31] Perhaps more significant is that 31% of patients had only soft tissue injury *without* fracture. Most patients were men younger than age 35. Ten percent of patients either had a bleeding disorder or were taking anticoagulants. Traffic accidents and sports activities were the most common mechanisms of injury.

Clinical Presentation. Compartment syndrome is a clinical diagnosis. In a conscious and fully oriented patient, pain that is disproportionate to the injury or physical findings is a hallmark finding in compartment syndrome. Pain often is characterized as deep, burning, and unrelenting and is difficult to localize. The need for increasing amounts of analgesics should not lead the clinician automatically to the conclusion that the patient is drug-seeking; rather, it should serve as a prompt to the possibility that a compartment syndrome is developing or is present.

Pain on passive stretching of the muscle groups in the suggestive compartment is an important finding. In addition, active flexion of involved muscles may produce pain. Other reliable suggestive signs and symptoms are hypoesthesias and paresthesias in the distribution of nerves crossing the compartment or tenderness, tenseness, or the sensation of tightness of the compartment.

Skin color, temperature, capillary refill, and distal pulses all are unreliable monitors for compartment syndrome because the pressure necessary to produce compartment syndrome is well below arterial pressure. Pallor and loss of pulses are late and ominous signs. Diminished pulses should suggest concomitant pathologic conditions responsible for reduced arterial flow. Although it is still frequently taught that the five *P*s (pain, pallor, pulselessness, paresthesias, and paralysis) are signs and symptoms of compartment syndrome, this is generally not true. Rather, they are the signs of acute disruption of arterial flow. Subjective complaints are an important indicator of compartment syndrome. Patients who are not fully alert or cooperative are assessed with particular care.

Diagnostic Tests. If the history and examination suggest compartment syndrome, compartment pressures should be measured with any of the commercially available monitors (Fig. 49-9).[40,41] The two most common methods of determining compartment pressures are the slit-catheter techniques and the side-port needle. The Stryker Intra-Compartmental Pressure Monitor system is a hand-held digital device that is easy to use with minimal training. Care should be taken to zero the monitor in on the plane in which it will be inserted to account for the effects of gravity. It is also paramount that the appropriate compartment be measured. Pressures of less than 30 mm Hg generally do not produce compartment syndrome. Pressures exceeding 30 mm Hg or within 30 mm Hg of the patient's mean arterial pressure are an indication for fasciotomy. Serial or continuous pressure measurements should be performed in cases that are not clear-cut. A rising or sustained elevated compartment pressure is superior to a single measurement as an indicator of acute compartment syndrome or the need for fasciotomy. Compartment syndrome can occur at pressures significantly below systemic pressure. Doppler ultrasound is not useful in evaluating these patients because excellent arterial blood flow may be documented even in the presence of a significant compartment syndrome. Newer devices based on near-infrared spectroscopy (NIRS) measurement of tissue oxygenation have proven effective experimentally in detecting compartment syndrome but will require validation in the clinical setting before widespread application.[42,43]

Box 49-4 Reported Anatomic Locations of Compartment Syndromes

Lower Extremity

Leg
Anterior compartment
Lateral compartment
Deep posterior compartment
Superficial posterior compartment

Thigh
Quadriceps compartment

Buttock
Gluteal compartment

Upper Extremity

Hand
Interosseous compartment

Forearm
Dorsal compartment
Volar compartment

Arm
Deltoid compartment
Biceps compartment

www.ketabpezeshki.com 66485457-66963820

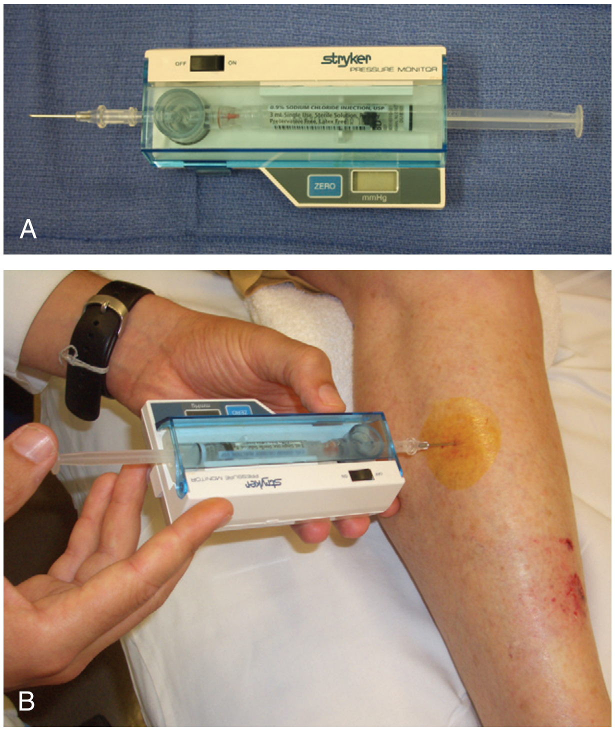


Figure 49-9. A, Hand-held device for measuring compartment pressure. B, Device is inserted perpendicular to skin.

Treatment, Complications, and Disposition. Complete fasciotomy is the only treatment that can reliably normalize elevated compartment pressure. Preparation for surgery is done as quickly as possible. Delaying fasciotomy for more than 12 hours often results in irreversible myonecrosis and nerve damage. While the patient is awaiting definitive treatment, the affected part should *not* be elevated above the level of the heart because this maneuver does not improve venous outflow and reduces arterial inflow. Slight dependency has been suggested to maximize the pressure head in the extremity.

Because tissue compartments are more pliable soon after injury, the rate of extremity swelling is greater in the immediate postinjury period, and tends to peak at 36 to 48 hours after injury.[44] Extremity swelling decreases over a similar duration. Rhabdomyolysis, hyperkalemia, and myoglobinuria may occur and should be managed aggressively to avoid renal failure. Lactic acid also is released from necrotic muscle tissue. Other complications include infection and tissue loss.

Delayed treatment results in loss of nerve and muscle function and eventual contracture formation. The magnitude of these disasters may be measured by the fact that in 2004, the average indemnity award in cases of missed compartment syndrome was nearly $426,000. Awards were proportional to the delay beyond 8 hours in performing fasciotomy and the number of the five *P*s indicating ischemia that were present during the initial missed diagnosis.[45] For these reasons, when the diagnosis of compartment syndrome is confirmed, fasciotomy should be done without delay.

Avascular Necrosis

Because of their blood supply, certain bones may undergo avascular necrosis after fracture, especially if fractures are comminuted and go untreated for any length of time. The femoral head, talus, scaphoid, lunate, and capitate are particularly prone to this complication.[46-49] These injuries are described in subsequent chapters.

Complex Regional Pain Syndromes (Reflex Sympathetic Dystrophy and Causalgia)

Definitions. The terms *reflex sympathetic dystrophy* (RSD) and *causalgia* have been used to describe pain syndromes that sometimes follow fractures, orthopedic surgery, soft tissue injuries, and other unrecognized trauma to the limbs and their appendages. Other names previously used for this spectrum of post-traumatic injuries include *Sudeck's atrophy, shoulder-hand syndrome,* and *postinfarction sclerodactyly.* In an attempt to reduce misunderstanding about their etiology and treatment, the International Association for the Study of Pain (IASP) issued a consensus statement renaming the syndromes formerly called *reflex sympathetic dystrophy* and *causalgia.*[50,51] *Complex regional pain syndrome type 1* (CRPS-1), replacing the term *reflex sympathetic dystrophy,* is a pain syndrome that develops after an initiating noxious event, extends beyond the distribution of a single peripheral nerve, and is usually disproportionate to the inciting event. The site is most often the distal end of the affected extremity, with a distal-to-proximal gradient. It is associated with edema, changes in blood flow to the skin, abnormal sudomotor activity in the region of the pain, allodynia (pain resulting from non-noxious stimulation to the skin), hyperpathia (pain persisting or increasing after mild or light pressure), or hyperalgesia. The presence of a condition that otherwise would explain the degree of pain and dysfunction excludes the diagnosis of CRPS-1. Because so much of the literature still refers to RSD, this chapter still uses the terms *RSD* and *CRPS-1* interchangeably. The definition of *CRPS-2* is the same as for CRPS-1 except that there is demonstrable peripheral nerve injury. This term replaces *causalgia* under the IASP taxonomy.

Pathogenesis and Etiology. The pathogenesis of CRPS-1 has not been elucidated. Current research suggests that central and peripheral sensitization after a noxious event, inflammation, alteration of sympathetic and catecholaminergic function, altered limb representation in the somatosensory cortex, genetic factors, and psychophysiologic interactions may all play a role.[52] Cases of CRPS-1 have been reported after fractures and as iatrogenic complications of surgery or after minor procedures, including subcutaneous excision and intravenous injection. Forceful manipulations and tight casts also are alleged to have produced the syndrome. In 10 to 26% of patients, no inciting event is identified.[53,54]

Although malingering and secondary gain are suspected in some patients, they are not the causes in most patients, as evidenced by pathologic tissue changes in patients who actually have CRPS-1.[55] CRPS-1 occurs in children and adolescents.[56] Girls are affected three times as often as boys, and the median age is 12 years. The lower limb is affected twice as often as the upper, and history of inciting trauma can be identified in only half the children with the disorder.

Diagnosis. No correlation exists between the severity of the original trauma and the incidence, severity, and cause of the symptoms, making early diagnosis a challenge, especially after trivial injury. Early diagnosis is crucial because the earlier treatment is initiated, the better the response. Although consensus-based diagnostic criteria were proposed by the IASP in 1994, because of their low specificity, there is no agreement on the best method for diagnosis of CRPS, and several sets of diagnostic criteria exist.[57] Bruehl's and Veldman's criteria sought to improve the IASP criteria, but there is no reason to recommend one set of criteria over another (Table 49-6).[57]

Treatment. Treatment of CRPS is controversial. Debate arises because published randomized controlled trials provide limited evidence to formulate treatment recommendations; individual response to treatment varies; and experts disagree regarding the pathogenesis of the disease. A multidisciplinary approach, including physical therapy and psychological counseling, is often necessary for treatment of CRPS.[58] For some patients, definitive

www.ketabpezeshki.com 66485457-66963820

Table 49-6 Diagnostic Criteria for Complex Regional Pain Syndrome (CRPS) Type 1*

NAME	CRITERIA
IASP 1994 consensus criteria	Criteria 2, 3 and 4 are necessary for a diagnosis of CRPS type 1. 1. Type I is a syndrome that develops after an initiating noxious event. 2. Spontaneous occurrence of pain in the absence of an external stimulus, allodynia (pain caused by a mechanical or thermal stimulus that normally does not provoke pain), or hyperalgesia (exaggerated response to a stimulus that is normally painful) that is not limited to the territory of a single peripheral nerve and is disproportionate to the inciting event. 3. There is or has been evidence of edema, skin blood flow abnormality, or abnormal sudomotor activity (sweating) in the region of the pain since the inciting event. 4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.
Bruehl's criteria: IASP-family	1. Continuing pain disproportionate to any inciting event. 2. Patient must report at least one symptom in each of the following categories: a. Sensory: reports of hyperesthesia b. Vasomotor: reports of temperature asymmetry or skin color changes or skin color asymmetry c. Sudomotor or edema: reports of edema or sweating changes or sweating asymmetry d. Motor or trophic: reports of decreased range of motion or motor dysfunction (weakness, tremor, dystonia) or trophic changes (hair, nail, skin) 3. Must display at least one sign in two or more of the following categories: e. Sensory: evidence of hyperalgesia (to pinprick) or allodynia (to light touch) f. Vasomotor: evidence of temperature asymmetry or skin color changes or asymmetry g. Sudomotor or edema: evidence of edema or sweating changes or sweating asymmetry h. Motor or trophic: evidence of decreased range of motion or motor dysfunction (weakness, tremor, dystonia) or trophic changes (hair, nail, skin)
Veldman's criteria	1. Presence of four out of five symptoms: a. Diffuse pain during exercise b. Temperature difference between affected and unaffected extremity c. Color differences between affected and unaffected extremity d. Volume differences between affected and unaffected extremity e. Limitations in active range of movement of the affected extremity 2. Occurrence or increase of symptoms during or after use. 3. Symptoms in an area larger than the area of the primary injury.

From Quisel A, Gill JM, Witherell P: Complex regional pain syndrome underdiagnosed. J Fam Pract 54:524-532, 2005.
IASP, International Association for the Study of Pain.
*IASP definition of CRPS-1: A variety of painful conditions following injury that appear regionally, having a distal predominance of abnormal findings, exceeding in both magnitude and duration the expected clinical course of the inciting event and often resulting in significant impairment of motor function, and showing variable progression over time. (All three criteria sets use this definition).

treatment involves sympathetic blockade, usually with regional anesthesia and occasionally by surgical sympathectomy. Oral medications, including bisphosphonates, calcitonin, indomethacin, corticosteroids, tricyclic antidepressants, gabapentin, acupuncture, spinal cord stimulation, regional nerve blocks, and other medications and methods, have been used to treat RSD with variable success.[59,60] In one study, vitamin C was shown to reduce the incidence of RSD after wrist fracture.[61]

Fat Embolism Syndrome

Fat embolism refers to the presence of fat globules in the lung parenchyma and peripheral circulation after a long bone fracture or major trauma.[62] The phenomenon of fat embolization is probably common as a subclinical event after long bone fracture. Intravascular fat droplets appear in nearly one of five patients admitted with major trauma, although not all patients are symptomatic or require treatment.

Fat embolism syndrome is a serious manifestation of fat embolism, occurring most commonly after long bone fractures (usually tibia and fibula) in young adults and after hip fractures in elderly patients. Symptoms usually appear 1 to 2 days after an acute injury or after intramedullary nailing. Respiratory distress and hypoxemia are the earliest, most common manifestations. Acute respiratory distress syndrome (ARDS) may occur and is the usual cause of death. Neurologic involvement, manifesting as restlessness, confusion, or deteriorating mental status, also is an early sign, as are thrombocytopenia and a petechial rash. Fever, tachycardia, jaundice, retinal changes, and renal involvement may occur. Fat is seen in the urine in 50% of patients within 3 days of the injury. The incidence of full-blown fat embolism syndrome varies from 0.5 to 2% in patients with isolated long bone fractures to 5 to 10% in patients with multiple fractures. Management of fat embolism syndrome is primarily supportive, usually in an intensive care unit. The mortality rate is 20%, but most patients recover without severe sequelae.[63] No specific therapy has shown benefit.

Fracture Blisters

Fracture blisters are tense blisters or bullae that accompany high-energy injuries in areas of relatively little skin coverage over a fracture site. The ankle, elbow, foot, and knee (in that order) are the most common sites; all of these contain fewer hair follicles and sweat glands to anchor together the epidermal-dermal junction than do other limb locations.[64] Fracture blisters are believed, in many cases, to occur in the setting of increased underlying tissue pressure and may be a harbinger of compartment syndrome.

Early surgical intervention reduces the incidence of fracture blister formation.[64] In addition, the presence of a fracture blister requires an alteration of the surgical approach or a delay in surgery. Most experts discourage incisions through a fracture blister because such incisions seem to increase infection and skin breakdown. Measures to perform early surgery after high-energy

www.ketabpezeshki.com 66485457-66963820

injuries and to minimize increases in tissue pressures might reduce the incidence of this complication. Intact blisters should be covered with povidone-iodine solution and a sterile dressing. Unroofing the blister and applying coverage with silver sulfadiazine paste has been reported to decrease the incidence of complications.[64]

Complications of Immobilization

Fractures frequently result in long periods of immobilization. Immobility may lead to multiple medical problems, especially in elderly patients, including pneumonia, deep venous thrombophlebitis, pulmonary embolism, urinary tract infection, wound infection, decubitus ulcers, muscle atrophy, stress ulcers, gastrointestinal hemorrhage, and psychiatric disorders (Box 49-5). Early ambulation is a major goal of optimal orthopedic care.

Damage Control Orthopedic Surgery

Over the past few decades, the management of the multiply injured trauma patient has changed considerably. Historically, patients with multiple injuries were treated nonoperatively as it was believed they were too ill to tolerate surgery. In the 1970s, literature began to appear suggesting adverse outcomes as a result of prolonged recumbency. In addition, operative fracture fixation techniques were evolving, and this lead to the advent of early fracture stabilization and the notion of early total care of the polytrauma patient.[65] During the 1990s, the concept of damage control surgery came to the forefront of trauma surgical care. In a landmark paper, Rotondo and colleagues reported on the successful use of an abbreviated operation in patients with penetrating abdominal trauma to avoid the lethal triad of hypothermia, acidosis, and coagulopathy, and coined the phrase "damage control."[66] Similar principles were found to be applicable to the management of pelvic and long bone fractures in the polytrauma patient. Early total care with immediate definitive fixation of all major fractures saw a gradual move toward early temporary fracture stabilization, resuscitation of the patient to a stable physiologic state, then definitive fixation at a later time once the patient's physiology had been stabilized.[65] Temporary fracture stabilization is usually accomplished by application of external fixation devices to aid in hemorrhage control and tissue oxygenation, but the timing and optimal type of fracture surgery in the multiply injured trauma patient are still subjects of research.[67]

Box 49-5 Complications of Fractures and Immobility

Fractures
- Hemorrhage
- Vascular injuries
- Nerve injuries
- Compartment syndrome
- Volkmann's ischemic contracture
- Avascular necrosis
- Reflex dystrophy
- Fat embolism syndrome

Immobility
- Pneumonia
- Deep venous thrombosis
- Pulmonary embolism
- Urinary tract infection
- Wound infection
- Decubitus ulcers
- Muscle atrophy
- Stress ulcers

SUBLUXATION AND DISLOCATIONS

Nomenclature

Abnormal forces applied to joints may result in the loss of continuity between two articulating surfaces. Partial loss of continuity is termed *subluxation,* and complete loss is termed *dislocation*. In general, dislocations are named for the major joint involved, as in a dislocated shoulder or hip. In three-bone joints, the injury is named for the joint involved if the disturbance involves the two major bones, or, if the lesser bone is involved, the disturbance is named for that bone. Separation of the femur from the tibia is termed *dislocation of the knee,* whereas displacement of the patella from its normal articulation is termed *dislocation of the patella* (Fig. 49-10). At the elbow, separation of the olecranon from the humerus is a *dislocation of the elbow,* whereas separation of the radius from the humerus is termed *radial head dislocation.*

Dislocations and subluxations should be described according to the direction of the distal segment relative to the proximal segment or of the displaced bone relative to the normal structures. The injury shown in Figure 49-11 is termed *dorsal dislocation of the interphalangeal joint of the thumb.* Disruption of articulation also may occur in combination with a fracture. The term *fracture-dislocation* is used to describe this combination. If the overlying skin is broken in any way, dislocations, subluxations, or fracture-dislocations are described as *open* and constitute the same emergency as does an open fracture alone.

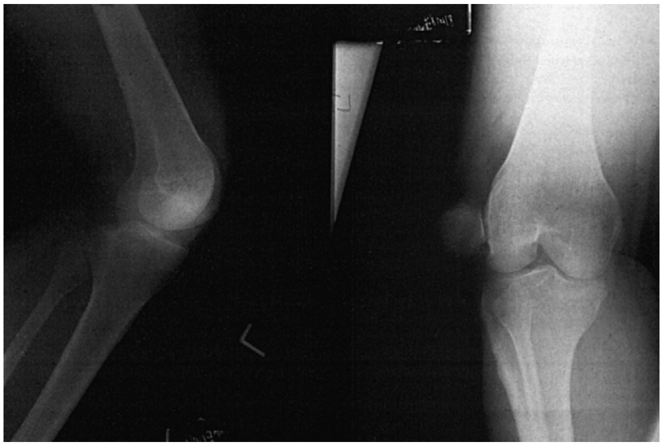


Figure 49-10. Dislocation of the patella.

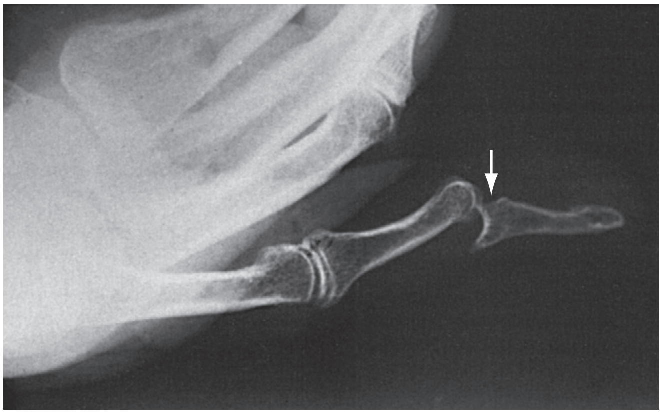


Figure 49-11. Dorsal dislocation of the distal phalanx of the thumb.

www.ketabpezeshki.com 66485457-66963820

Assessment

In most cases of dislocation, severe to excruciating pain is present because the joint capsule is stretched or torn. Movement of the joint exacerbates the pain. This useful sign is lost in an obtunded, intoxicated, or unconscious patient and may result in a missed diagnosis if a careful survey is not performed. Some dislocations, such as anterior shoulder dislocation, cause an obvious deformity, whereas others, such as posterior shoulder dislocation, may be subtle. Swelling of soft tissues also may obscure the diagnosis, such as in the tarsal-metatarsal region. Gentle passive testing of range of motion should be performed but never forced. Assessment for neurovascular function is similar to that for fracture. Certain dislocations (e.g., knee) are so commonly associated with vascular injuries that a careful assessment of blood flow is important in evaluating these injuries.

Plain radiographic studies detect most dislocations, provided that the correct views are ordered. Radiographs should be performed before and after attempts at reduction of first-time or complicated dislocations, unless there is neurovascular compromise. This confirms the diagnosis and ensures that associated fractures are documented before treatment is undertaken.

Treatment

Methods of relocating specific joints are reviewed in subsequent chapters, but a few principles apply. In general, the sooner a joint is relocated, the better. Later, swelling and muscle spasm make reduction more difficult. Also, pain is not adequately relieved until the dislocation is reduced. In the hip, early reduction is mandatory to restore vascular supply and to avert the complication of avascular necrosis. Before relocation is attempted, adequate analgesia or conscious sedation should be used. Nerve blocks are especially useful on the digits. The general principle of reducing a dislocation is to re-create and reverse the mechanism of injury, pulling the proximal end of the dislocated bone out and away from whatever is trapping it in its final resting place. This technique helps prevent interposition of soft tissues in the joint that can preclude reduction. As this maneuver is accomplished, the disarticulated surface is manipulated back or may snap back spontaneously toward its normal anatomic position. If the reduction is difficult, it should not be forced. A single good attempt is better than repeated attempts in an inadequately relaxed patient. Some joints cannot be reduced in the ED because (1) the opposing muscles are contracting too forcefully and general anesthesia is necessary to overcome these forces or (2) mechanical obstruction by a bony fragment or a torn piece of cartilage, tendon, joint capsule, or skin requires surgical removal for reduction to occur.[68]

SOFT TISSUE INJURIES

Sprains

Nomenclature

Ligamentous injuries resulting from an abnormal motion of a joint are termed *sprains.* A sprain is injury to the fibers of a supporting ligament of a joint. Sprains may be graded according to the severity of pathologic findings; clinically, however, the grades are often indistinct. *First-degree* sprains are characterized by minor tearing of ligamentous fibers with resultant mild hemorrhage and swelling. Minimal point tenderness can be elicited. Stressing the ligament produces some pain, but there is no opening or abnormal joint motion.

A *second-degree* sprain is a partial tear of a ligament, meaning more fibers are torn than in the first-degree injury. Clinical findings include moderate hemorrhage and swelling, tenderness, painful motion, abnormal motion, and loss of function. There may be a tendency toward persistent instability and recurrence, and prevention of these complications is a major goal of treatment.

A *third-degree* sprain describes the complete tearing of a ligament. Signs include a further exaggeration of the signs mentioned for second-degree sprain. In addition, stressing the joint reveals grossly abnormal joint motion, provided that this is not limited by pain or swelling. Analgesia and the evacuation of a hemarthrosis may be used to allow a more complete diagnosis of these injuries. Chronic joint instability is the rule if severe ligamentous injuries do not heal properly.

Assessment

The clinical presentation of a sprain of the extremity may be indistinguishable from that of a fracture. The injury frequently occurs during vigorous athletic activity when forces applied in opposite directions result in a joint being stressed in an abnormal or exaggerated direction. The patient may complain of hearing a "snap" or a "pop" at the moment of injury and conclude that a fracture is present. Other patients report "seeing stars" or "almost passing out" at the moment the injury occurred and may still be in extreme pain, appearing pale and diaphoretic if seen shortly after the injury. Analgesia should be provided to these patients. Evaluation should include a careful history of the exact sequence of events at the time of the injury and ascertaining the position of the extremity and the forces applied to it at that moment. A history of any sounds that accompanied the injury should be elicited. Examination of the joint should include stressing it to show abnormal motion. If radiographs are planned to rule out a fracture anyway or if exquisite pain is produced by mild attempts to apply stress, it is probably better to delay stressing until films have verified the absence of a significant fracture. Plain radiography is indicated in some, but not all, cases to rule out a fracture. It has been well demonstrated that clinical decision rules can reduce the number of radiographic studies without missing significant fractures.[69-72]

Avulsion fractures may occur concomitantly with sprains. In children, epiphyseal fractures occur more commonly than ligamentous disruption because of the relative ligamentous strength compared with the ease of disrupting the epiphyses. Arthroscopy or MRI is indicated in the follow-up evaluation of some of these injuries (e.g., for suspected cruciate ligament tears) when significant pain or disability is present.[73-75]

Treatment and Disposition

Specific management of sprains varis depending on the location and severity of the injury. In general, initial measures should include the traditional recommendations of ice, elevation, and analgesia. Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective analgesics in many patients. Several studies have found a more rapid decrease in swelling, increased exercise endurance, and earlier return to work with use of NSAIDs.[76]

Immobilization through use of one of the following methods provides protection and comfort in the initial management of most injuries. Because the severity of injury is sometimes difficult to establish at the first visit, it is reasonable to immobilize the affected joint for the first 48 to 72 hours, after which the extent of injury can be better determined. At that time, early mobilization is often desirable, particularly in lateral ankle injuries because this leads to earlier return to work and athletic activities and better preservation of proprioceptive neuromuscular function.[77] Use of an inflatable "air cast" alone or in conjunction with an elastic ankle wrap has been shown to be effective in decreasing the symptomatic period.[78] For lower extremity injuries, protected weightbearing with crutches provides patients with comfort and avoids

www.ketabpezeshki.com 66485457-66963820

motion of the impaired part. In elderly patients, safe ambulation sometimes cannot be accomplished, and a short hospitalization or admission to a skilled nursing facility may be necessary.

For complete or nearly complete ligamentous disruption, urgent orthopedic consultation is usually mandatory. Less severe injuries can be followed up 3 to 7 days postinjury when acute swelling has subsided. Copies of plain films ordered in the ED should be sent with the patient if possible. Physical therapy and rehabilitative exercises sometimes are begun at these visits and carried on for several weeks. Because ligaments are relatively avascular, healing is slow, and patients with significant sprains should be informed of this. Sprains should be diagnosed as precisely as possible and should not be trivialized. Too often after radiographs have ruled out fracture of an affected extremity, the term *sprain* is applied indiscriminately or the patient is told that the injury is *only* a sprain, a misleading expression that should be avoided. Aside from creating false expectations regarding recovery, thoughtless mislabeling of injuries not in evidence may lead to missed occult fractures in adults or epiphyseal injuries in children.

Strains

Nomenclature

A *strain* is an injury to a musculotendinous unit resulting from violent contraction or excessive forcible stretch. The term *pulled muscle* sometimes is used interchangeably with muscle strain. These injuries are graded in a manner similar to sprains.

A *first-degree* (mild) strain is a minor tearing of the musculotendinous unit, characterized by minor swelling, local tenderness, and minimal restriction of movement. Findings increase along a continuum such that in a *second-degree* (moderate) strain, more fibers are torn, but without complete disruption; swelling, ecchymosis, and loss of strength are more marked. In a *third-degree* (severe) strain, the muscle or tendon is completely disrupted, with resultant separation of muscle from muscle, muscle from tendon, or tendon from bone.[79] An accompanying avulsion fracture may be present on radiographs in either second- or third-degree injuries.

Assessment

Signs and symptoms include pain, ecchymosis, swelling, and loss of function. A force applied to the muscle, either passive stress or active contraction, produces sharp pain at the site of injury even as the injured muscle may be relatively comfortable at rest. A palpable defect sometimes is present at the site of a complete rupture, which usually involves the region of the muscle-tendon junction, or a bunching up of the muscle may be appreciated. Ultrasound is increasingly being used to diagnose an assortment of soft tissue injuries, including rotator cuff tears, tendon ruptures, and muscle tears.[80,81] Among nonathletes, strains commonly are seen in patients who have either overstressed a muscle group or tried to generate excessive force in an unconditioned muscle. Examples are the weekend gardener or mover who experiences lower back strain on Monday morning, the aerobics student who strains the rectus muscles, and the weightlifter with chest wall pain resulting from pectoralis major strain. These are usually first-degree injuries, and the onset is slow. Rapid acceleration (e.g., in a tennis player) may result in a third-degree gastrocnemius or plantaris tear, whereas pushing off to jump is a common cause of ruptures of the Achilles tendon in a basketball player. A sudden violent attempt at lifting in an older individual can result in a complete biceps brachii disruption. Sudden generation of forces of which the thighs are capable results in second-degree strain of the hamstrings, quadriceps, or thigh abductor muscles.

In athletes, generation of tremendous contraction forces coupled with excessive forcible stretching (while the body may be either accelerating or "planting") results in severe strains. Involvement of almost any muscle group is possible, and the onset of such injuries is usually acute. Immediate removal from activity, application of ice, and rest of the affected limb for 48 to 72 hours usually are advised for prevention of further injury. A competitive athlete usually is unable to continue anyway because of the accompanying loss of function. After a brief rest period, however, early mobilization and rehabilitation should be encouraged.

Treatment and Disposition

Treatment depends on the degree of disruption, location, and functional loss. Most first-degree injuries respond in a few days to rest, application of ice, and, for some patients, analgesics. NSAIDs commonly are recommended and prescribed, although their efficacy for other than analgesic purposes is unproven. Second-degree strains are treated similarly, with protection against aggravating activity required for longer periods. Third-degree strains receive similar initial treatment in the ED plus early orthopedic consultation. Some of these injuries are amenable to surgical repair, whereas others may be treated with immobilization. The muscle affected and the age, occupation, and activity level of the patient all are factors in deciding whether surgical intervention is appropriate. Early mobilization is an important tenet in the treatment of muscle strains; its timing may be based on the ability to stretch the injured muscle as much as the uninjured contralateral muscle, and the use of the injured muscle without pain during basic movements.[79] Many athletes and their trainers believe, and it is universally espoused, that many strains can be prevented by proper preseason conditioning, warm-up, stretching exercises, and avoidance of overexertion, although limited scientific data exist to support these recommendations.[82]

Tendinitis and Tendinosis

Tendinitis is classically described as an inflammatory condition characterized by pain at tendinous insertions into bone, occurring in the setting of overuse.[83,84] It is now believed that the pathophysiology of this condition is more complex than mere overuse, with the roles of load and use affecting cell-matrix interaction.[85] Causative factors are believed to include aging, with decreased blood supply and decreased tensile strength; muscle weakness and imbalance; insufficient flexibility; male gender; obesity (in weight-bearing joints); smoking; malalignments; training errors; and improper equipment.[86,87] In addition, certain systemic diseases, including diabetes mellitus, chronic renal failure, rheumatoid arthritis, and systemic lupus erythematosus; steroid use; and occasionally fluoroquinolone use are associated with the development of tendinopathy.[88]

The histopathology of tendinitis is characterized by degeneration and disorganization of collagen fibers; infiltration by macrophages, plasma cells, and lymphocytes rather than leukocytes; and increased vascularity. Inflammatory changes are not a principal finding in tendinitis.[89] This evolving understanding of tendinitis in the future should allow for more logical treatment of these injuries aimed at the underlying pathophysiology. It also has led some authors to propose that chronic painful conditions of the tendon should be referred to as *tendinosis* rather than *tendinitis* or other terms previously used to describe this condition, including *tendonitis, degenerative changes, chronic tendinopathy,* or *partial rupture*.[86,90] In this chapter, *tendinitis* and *tendinosis* are used interchangeably.

Common sites for tendinitis are the rotator cuff of the shoulder, the Achilles tendon, the radial aspect of the wrist (de Quervain's tenosynovitis), and the insertion of the hand extensors on the

www.ketabpezeshki.com 66485457-66963820

lateral humeral epicondyle (tennis elbow). Also commonly involved in athletes are the patellar tendon, particularly in athletes engaged in jumping sports; the biceps femoris, semitendinosus, and semimembranosus (hamstring syndrome); the posterior tibial tendon (shin splint syndrome); the iliotibial band; and the common wrist flexors (medial epicondylitis) (involvement is seen in little league pitchers and golfers).[85] In some locations, most commonly the shoulder, calcium deposition occurs along the course of the tendon, resulting in a painful condition termed *calcific tendinitis*. This condition also may occur in the wrist, hand, neck, hip, knee, ankle, or foot.[91]

Physical examination reveals pain with motion and limitation of function and may include point tenderness and palpable crepitus over the involved tendon with motion. In general, a clinical test can be performed by forcible flexion of the involved muscle while keeping the point of insertion fixed or by operating the involved muscle against resistance. Either test should intensify the discomfort. Radiographs are usually negative. A small fleck of bone may suggest an avulsion, or the surface of the bone at the attachment may be roughened, indicating periostitis. As mentioned, there also may be calcium deposits along the course of the tendon, which should not be confused with an avulsion fracture. Ultrasound is sometimes useful in confirming the diagnosis of tendinitis. Although a normal tendon is characterized by a relatively homogeneous pattern, tendinitis is characterized by one or more of the following features: loss of the fibrillar echotexture, focal tendon thickening, diffuse thickening, focal hypoechoic area, irregular or ill-defined borders, or microruptures.[92]

There is little evidence to support any specific treatment for tendinosis. The classic approach consists of rest, ice, and NSAIDs initially, followed by rehabilitation and training and control of force loads to prevent recurrences. Although NSAIDs may be useful for a brief period at the onset of symptoms for their analgesic effects, no evidence exists that they significantly alter the pathophysiology of this condition, and no rationale exists for ordering them in patients at any risk for complications from this class of drugs.[93,94] Peritendinous local infiltrations of anesthetics and corticosteroids may be useful but should not be repeated too often because tendon rupture may occur. Injection therapy is especially useful in calcific tendinitis around the shoulder. Injection of steroids directly into the Achilles tendon should be avoided because of reports of partial or complete rupture after even a single injection. Some cases of calcific tendinitis that do not respond to conservative therapy may require either arthroscopic or open surgery.[95]

Bursitis

Bursitis is a painful inflammation of the bursa that may be traumatic, infectious, or related to systemic illness. Commonly involved sites include the olecranon, the greater trochanter of the femur, and the prepatellar and anserine bursae around the knee. Physical findings are tenderness and swelling over the involved bursa, whereas warmth and overlying erythema may signal infection. If infection is suggested, aspiration of the bursal fluid and Gram's staining and culture are recommended. Otherwise, treatment may be conservative and is similar to treatment for tendinitis, with ice, NSAIDs, or steroid injections. Most patients can be treated as outpatients.[96]

TREATMENT MODALITIES

Splinting and Bandaging

Suggested or confirmed fractures or dislocations should be splinted to avoid damage to muscles, nerves, vessels, and the skin. Splinting also may restore blood flow to ischemic tissue by removing pressure caused by a bone fragment resting against a blood vessel. In addition, splinting may relieve the pain associated with movement of fracture fragments.

Field Care

Splinting should begin in the field because it reduces the risk of further neurovascular compromise, prevents a closed injury from potentially being converted to an open one during transport, reduces the patient's pain, and facilitates subsequent ED assessment and imaging. Numerous commercial devices are available, and most ambulances carry an assortment of immobilization devices (Fig. 49-12). Minimal equipment includes long and short backboards, cervical collars, sandbags, and extremity splints. A half-ring traction splint also is essential. Inflatable air splints are favored by some authors because they are convenient, easy to apply, transparent, and radiolucent and because they tamponade low-pressure bleeding. Other authors prefer to avoid these devices because theoretically they could contribute to the development of a compartment syndrome. If used, inflatable splints should be inflated only by mouth and to the point that still permits indentation by gentle finger pressure.

Field personnel should splint possible fractures before the patient is moved. Severely angulated long bone fractures should be straightened in the field before they are splinted. Splints should

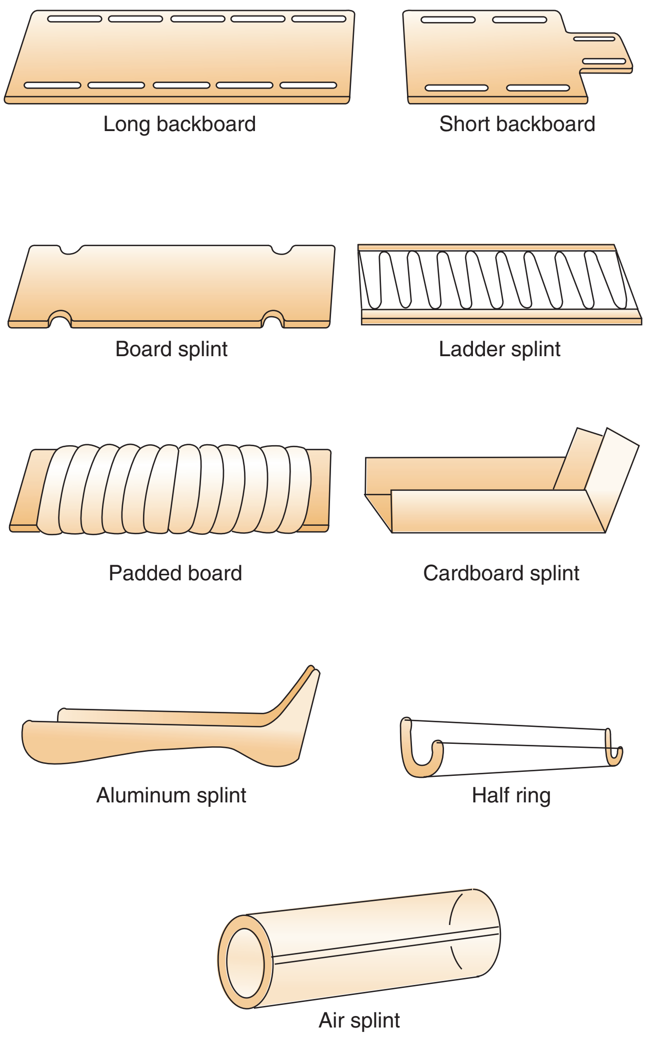


Figure 49-12. Commercial splints.

www.ketabpezeshki.com 66485457-66963820

be applied in such a way as to immobilize the joints above and below the fracture site to avoid motion of the involved bone. The skin should be padded to avoid local necrosis, and the splint should be secured by use of a circumferential wrapping material. This material should allow for some expansion and should not be applied in a constricting manner.

Emergency Department Care

In the ED, the indications for splinting are the same as in the field. All splints should be checked and if properly applied need not be changed. Hare traction should be removed in the ED because it may angulate femur fractures. Splinting or other immobilization is also used after diagnosis and treatment of injuries. In some cases a splint is all that is needed for definitive treatment. Injuries other than sprains and fractures (e.g., inflammatory and infectious processes, bites, burns, and repaired injuries of muscle bellies or tendons) also benefit from immobilization. Splints also can be used to improve function, such as with wristdrop that accompanies radial nerve palsy. When the injury is immobilized, it is important to stress elevation of the affected part to avoid edema formation. Many different devices and materials are available. Some devices that are commonly used are described next.

Upper Extremity

Sling-and-Swathe and Velpeau Bandages. Sling-and-swathe and Velpeau bandages are useful in immobilizing the shoulder, humerus, and elbow. They are commonly used after reduction of dislocated shoulders and to treat impacted fractures of the humeral neck. The axillae should be padded and powdered to avoid skin maceration. A commercial shoulder immobilizer also is available and is useful after reduction of a shoulder dislocation. Its advantages are ease of application and ease of removal and reapplication by the patient for bathing.

Clavicle Splint. Historically, middle third fractures of the clavicle routinely were initially treated with a figure-of-eight clavicle strap with or without the addition of a sling. This device is commercially available or can be fashioned from tubular stockinette. If used, a clavicle splint should be applied snugly enough to keep the shoulders back in the "at-attention" position, but not so tight as to compress the axillary artery or brachial plexus. Chafing of the skin can be avoided by padding and powdering the axillae. Superiority of the figure-of-eight clavicle strap over a simple sling has not been shown.

Plaster and Fiberglass Splints. Well-fitting, customized plaster splints can be fashioned easily to immobilize the elbow, forearm, wrist, and hand. The advantage of these splints is the ability to mold them to an exact size and shape (e.g., along the ulnar side of the forearm and hand to immobilize a midshaft fourth or fifth metacarpal fracture, the so-called "gutter splint"). Several commercially available products consist of multiple layers of plaster or fiberglass strips, inside a covering of foam and flannel, on a continuous roll that can be applied to any length. While the splint is still wet, a bandage is wrapped over it, and the splint is molded and held in the desired position as the plaster or fiberglass resin hardens.

Forearm and Wrist Splints. Numerous preformed splints are available for splinting fractures of the distal forearm and wrist. They are lightweight, neat, and easy to apply and are easily removed and replaced by the patient (Fig. 49-13).

Figure 49-13. Wrist splints.

Lower Extremity

Femur and Hip. Fractures of the femoral shaft can be immobilized with a traction device, such as the Hare traction splint or a similar appliance (Fig. 49-14). These devices should be applied in the field if possible; most ambulances carry them. The principle is that a proximal ring engages the ischial tuberosity for countertraction while the longitudinal traction is applied through the ankle by means of an ankle hitch. A commercial ankle hitch is recommended, but if one is not available, an improvised hitch can be fashioned with a triangular bandage or a wide piece of cloth tied in a Collins hitch. The patient's ankle bones, Achilles tendon, and arch of the foot should be padded, and the circulation should be checked to ensure it is intact. A properly applied splinting device relieves pain from a fracture rather than exacerbating it.

The Sager splint might offer advantages over other appliances in that it is applied to the medial and lateral aspect of the thigh rather than having a half-ring posteriorly (Fig. 49-15). The Sager splint is more acceptable for use in the presence of pelvic fractures and avoids compression of the sciatic nerve. Because the half-ring devices may produce angulation at the fracture site, the Sager device is purported to result in better alignment, although this has never been measured. The Sager splint is shorter and more compact than the Hare traction splint, rendering it more acceptable for certain transport helicopters and body scanners. Also, the amount of traction is metered at the ankle, and overtraction can be avoided.

Knee. Commercially available knee immobilizers can be used after acute injuries to provide firm but not rigid stabilization of the knee. The device is essentially a foam cylinder with medial and lateral aluminum stays, attached by Velcro straps, and spanning the upper thigh to upper ankle. This device is commonly used after trauma to let the knee "cool off" until a better physical examination or diagnostic study can be performed in a few days.

Another dressing that may be applied at the knee is the Jones "compression" dressing. Some authors believe the word *compression* should not be used here, to discourage application that is too tight. The Jones dressing is a bulky dressing that is used by some clinicians in situations when swelling is expected, including internal fixation procedures. The ability to flex and extend at the knee is maintained. The dressing consists of a thick layer of

www.ketabpezeshki.com 66485457-66963820

Figure 49-14. A, Hare traction splint. B, The commercial hitch is designed to protect the ankle and heel during traction.

Figure 49-15. A, Sager splint. B, Detail of distal Sager splint end with 10 pounds of traction applied.

absorbent cotton bandage (Webril) wrapped with an elastic bandage, followed by another layer of cotton bandage, followed by an additional elastic wrap. If more stability is required, slabs of plaster can be placed on the medial and lateral side of the limb, just under the last bandage. Caution is exercised because burns have been reported with this type of dressing when too many layers of plaster are used. A similar type of bulky dressing may be used for some injuries of the ankle and fractures of the calcaneus. In general, commercial knee immobilizers have replaced the Jones dressing in the treatment of acute knee injuries.

Ankle. Immobilization of the ankle can be accomplished by numerous means. Plaster splints can be used temporarily for the treatment of nondisplaced ankle fractures or for the treatment of severe sprains. These can be fashioned in the same manner as described for the upper extremity. An alternative method is to apply a full circular cast, bivalve it on either side, discard the anterior piece, and affix the posterior mold with an elastic bandage or bias-cut stockinette. Most ankle injuries should be splinted with the patient's ankle in neutral position. Injuries to the Achilles tendon, plantaris muscle, or gastrocnemius muscle initially should be treated with the foot held in slight equinus (plantar flexion) for comfort. The toes should be free to move distal to the metatarsophalangeal joints, and the proximal border should end below the tibial tubercle to avoid pressure on the peroneal nerve.

Adhesive strapping is an alternative method of ankle immobilization that provides good support and limitation of motion. Taping reportedly loses its "protective properties" with cyclic loading and sweating; although this is cited as a disadvantage, it may actually be helpful in encouraging and allowing early mobilization. This method is lightweight and not bulky, and a shoe can be worn over the material. Tape is applied in a noncontinuous manner, which allows for swelling and avoids constriction. First, the hair is shaved. Next, strips of tape are measured and torn off; 1½-inch or 2-inch cloth-backed adhesive tape or Elastoplast is used. Elastoplast is an elastic-backed tape, constructed to stretch only in the longitudinal direction; this serves to spring the foot back automatically to a neutral position if the foot is plantarflexed for any reason. The tape should be applied directly to the skin after a skin adherent, such as tincture of benzoin, is applied. The tape should lie flat because wrinkles may damage the skin (Fig. 49-16). The use of tape is associated with dermatologic complications, including itching or contact dermatitis, owing to adhesion of the tape to the skin.

For mild-to-moderate sprains, functional treatment options including elastic bandaging, soft cast, taping, or orthoses were found to be statistically better than immobilization for multiple outcome measures.[97] Lace-up supports may be more effective than elastic bandaging and result in less persistent swelling in the short

www.ketabpezeshki.com 66485457-66963820

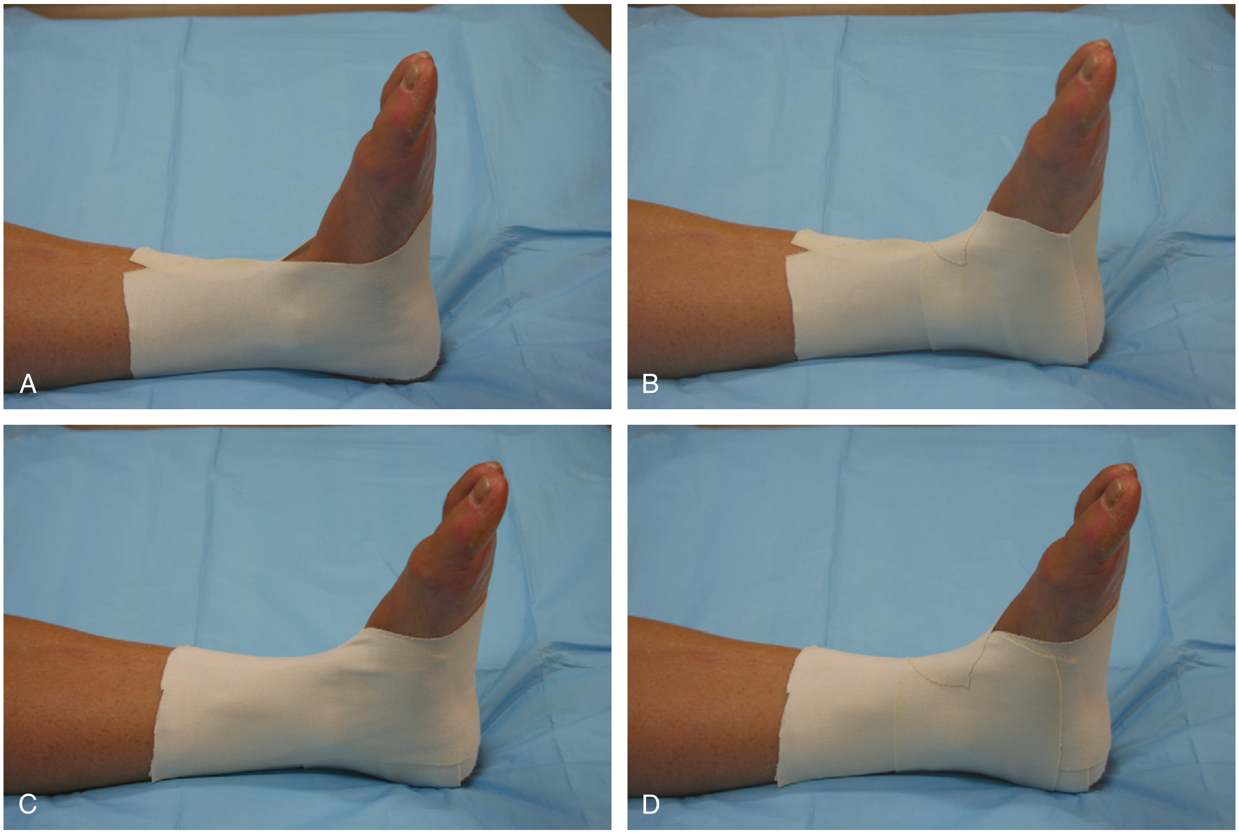


Figure 49-16. Application of adhesive strips to immobilize the ankle.

term as compared with semirigid ankle supports, elastic bandaging, and tape.[98]

For moderate-to-severe lateral ankle sprains, a commercial mechanical support composed of molded plastic with Velcro straps (e.g., AirCast Air-Stirrup) is more effective than elastic bandaging alone (Fig. 49-17).[77,99] This product may be worn in the patient's shoe and permits early weightbearing and return to activity. It is designed to permit dorsiflexion and plantar flexion but to limit inversion and eversion, a concept referred to as *functional bracing.* Some authors also find this device useful for athletic activities instead of adhesive taping to prevent recurrences.[78,100] Although these orthoses are relatively expensive, the cost might be more than offset by their ease of application, their reusability, and the benefit derived from earlier return to work.

Severe ankle sprains also may benefit from immobilization in a Cam Walker, which is a commercial appliance consisting of a layer of padding extending from the tibial tubercle to the metatarsal heads, supported by metal plates along the length of the lower leg. These plates articulate with a molded hard plastic boot at the ankle. The position of the foot can be adjusted as desired, and when set, the ankle is kept firmly immobile. The rounded undersurface of the boot allows for ambulation without movement of the ankle joint.

Casts

Plaster or synthetic (fiberglass) casts perform a function similar to splints in that they provide stability and pain relief. Casts are not mandatory for all fractures, and in situations in which they are, application is usually not an immediate necessity. Because they are circumferential, casts provide more effective immobilization of a fracture, but they require more skill and time to apply. Swelling and subsequent pressure under the cast are highest during the first 24 hours after injury. Complications of casting include compartment syndrome, thermal injury, pressure sores, bacterial and fungal infections (especially if a wound is present under the casted area), and pruritic dermatitis.[101] Plaster is applied as strips or rolls of cloth that are impregnated with a hemihydrate of calcium sulfate. When this cloth is dipped in lukewarm water, a creamy paste is formed that can be molded into a cast. An exothermic reaction takes place that causes the plaster to harden and can burn the skin.[102] Factors that have been shown experimentally to increase skin temperatures during plaster application are dip-water temperatures greater than 24° C, cast thickness greater than eight plies, and inadequate ventilation of the newly applied cast.[103] Immersing the plaster in water for too short a time or squeezing too much water out also may lead to generation of excess heat. To avoid pressure on the skin and over bony prominences, stockinette and layers of cotton sheet wadding (Webril) are snugly applied first. Padding that migrates under a formed cast can be uncomfortable and result in pressure sores. Padding alone does not prevent burns.

Variations of the basic cast exist. A window may be placed in the cast, and the cutout area may be used for access to skin wounds that require care during immobilization. Walking heels may be worked onto a lower extremity cast and should be placed in the center of the foot. Synthetic casts (fiberglass and other materials) are lightweight, durable, and water-resistant.[104] In addition, their setting temperatures are significantly lower, and they are less likely to produce burns. However, they are more expensive and more difficult to apply.

Patients with casts may visit the ED for complaints related to their casts; these usually are pain, local irritation, swelling, or numbness of the distal part. A cast that is too tight results in swelling, pain, coolness, and change in skin color of the distal parts. Pain also may be caused by the initial injury or by local pressure,

www.ketabpezeshki.com 66485457-66963820

Figure 49-17. Air cast ankle support. **A,** Lateral view. **B,** Anterior view.

or it may be a result of a developing compartment syndrome or wound infection. When a patient complains of pain, it is prudent to bivalve the cast and inspect the extremity. This is done by cutting the plaster and the padding on each side and removing half the cast at a time, with the other half used as a mold to keep the extremity immobile. Afterward, the bivalved cast can be held together with bias-cut stockinette or elastic wrap until a new cast is applied. If relieving external pressure does not alleviate symptoms, the diagnosis of compartment syndrome should be seriously considered. Casts may obscure wound infections, sources of sepsis, and even the source of tetanus. The clinician should not hesitate to bivalve the cast and inspect the extremity.

The need for mandatory routine cast checks 1 day after initial application has been questioned.[105] In a retrospective study of 250 patients, none experienced problems from neurovascular compression, although 24% required some alteration of the cast. In the study, it may be simply that the casts were applied incorrectly in the first place. It is probably advisable to continue routine cast checks if casts are applied in the ED.

Thermal Therapy

Some confusion exists as to the role of cryotherapy versus heat therapy in the treatment of acute orthopedic injuries. Part of this confusion arises because heat may be more soothing to the patient. Cold causes vasoconstriction, limiting blood flow and hemorrhage into the traumatized area. Metabolic requirements are reduced in cooled tissues, as is histamine, and less capillary breakdown occurs as a result. The sooner postinjury ice therapy is initiated, the more beneficial the reduction in metabolism will be.[106] Reduced blood flow also limits edema formation. Lower extravascular fluid pressure allows for better lymphatic drainage of injured areas. Cryotherapy produces three, and perhaps four, stages of sensation of which the physician and the patient should be aware. In the first stage, a cold sensation is noted for 1 to 3 minutes. The second stage consists of a burning or aching sensation for 2 to 7 minutes after the application of cold. This stage is uncomfortable but needs to be endured if the benefits of the next two stages are to be received. Heat therapy, by contrast, is soothing, and patients are likely to prefer this to the second stage of cryotherapy. The third stage begins 5 to 12 minutes after the application of ice and produces local numbness or anesthesia. The pain-spasm cycle is interrupted. While the patient is under this anesthetic effect, passive exercise may be desirable. This exercise helps to prevent atrophy, mobilize edema, clear injury debris, and reduce adhesions. However, several reviews of cryotherapy for soft tissue injury all reflect the lack of adequate science in establishing recommendations for cryotherapy. Application of ice appears to be effective in reducing pain, but there is no credible evidence that it accelerates healing.[107-109]

A fourth stage sometimes occurs 12 to 15 minutes after intense cryotherapy is begun, consisting of reflex deep tissue vasodilation without a corresponding increase in metabolism (reminiscent of the situation in rewarming shock). Because of this, a maximum of 10 to 15 minutes of cold application per treatment usually is advised. A systematic review of small, limited-quality studies assessed cryotherapy in the management of soft tissue injuries noted wide variation on the optimal mode, duration, and frequency of ice application.[109] Therefore recommendations for an optimal cryotherapy protocol cannot be made.

Absolute contraindications to cryotherapy include severe cold allergy (with hives and joint pain) and Raynaud's phenomenon and disease. Relative contraindications include some rheumatoid conditions and paroxysmal cold hemoglobinuria with renal dysfunction and secondary hypertension. Anesthetic skin in a paralyzed or comatose patient is at risk with ice therapy. Complications

www.ketabpezeshki.com 66485457-66963820

of cryotherapy can include skin burns and nerve damage but are rare, especially in the athletic population most at risk for serious injuries. Heat increases blood flow and the inflammatory response and edema. Warm tissues and cells have a higher metabolic rate and increased requirements of nutrients and oxygen. Ice, rather than heat, is the method of choice of most authorities in the acute treatment and rehabilitation of acute orthopedic injuries and should be initiated as soon as possible for maximum benefit.

Autologous Blood Product and Growth Factors

In recent years, growth factors have been used for the management of soft tissue injury related to acute trauma and overuse injury. Platelets contain growth factors in their alpha-granules, including insulinlike growth factor-1, basic fibroblast growth factor, platelet-derived growth factor, epidermal growth factor, vascular endothelial growth factor, and transforming growth factor-β_1, and these are thought to help the regeneration of tissues that otherwise have low healing potential.[110,111] Growth factors can be delivered as a preparation of platelet rich plasma (PRP), autologous blood injection, and autologous conditioned serum. PRP injections have been described in patients with patellar and elbow tendinosis, Achilles tendon injury, and acute ligamentous and muscle injuries, and they have also been administered intraoperatively during anterior cruciate ligament reconstruction and rotator cuff repair.[112-114] Theoretic advantages to the use of PRP include faster recovery and improved functional outcome, but evidence supporting the use of PRP in different tissues is limited and further studies are required before conclusions are drawn.

KEY CONCEPTS

- Consultation with an orthopedist should be sought for the treatment of most long bone fractures, open fractures, injuries with joint violation, and injuries with neurovascular compromise.
- Compartment syndrome is associated most commonly with a closed long bone fracture of the tibia but also is well described in the thigh, forearm, arm, hand, and foot and can occur with soft tissue trauma alone. Elevation of a limb with resultant reduction in the local arteriovenous gradient may be counterproductive and may exacerbate compartment syndrome.
- Because of their blood supply, certain bones may undergo avascular necrosis after fracture, especially if fractures are comminuted and go untreated for any length of time. The femoral head, talus, scaphoid, and capitate are particularly prone to this complication.
- Fat embolism syndrome is a serious manifestation of fat embolism, occurring most commonly after long bone fractures in young adults (usually tibia and fibula) and after hip fractures in elderly patients. ARDS is the earliest, most common, and serious manifestation. Neurologic involvement, manifesting as restlessness, confusion, or deteriorating mental status, is also an early sign, as are thrombocytopenia and a petechial rash.
- In children, epiphyseal fractures occur more commonly than ligamentous disruption because of the relative ligamentous strength compared with the ease of disrupting the epiphyses.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Raasch WG, Hergan DJ: Treatment of stress fractures: The fundamentals. *Clin Sports Med* 2006; 25:29.
2. Dugan SA, Weber KM: Stress fractures and rehabilitation. *Phys Med Rehabil Clin North Am* 2007; 18:401.
3. Datir AP: Stress related bone injury with emphasis on MRI. *Clin Radiol* 2007; 62:828.
4. de Sancis N, Della Corte S, Pempinello C: Orthopaedics distal tibial and fibular epiphyseal fractures in children: Prognostic criteria and long-term results in 158 patients. *J Pediatr Orthop* 2000; 9:40.
5. Sferopoulos NK: Type V physeal injury. *J Trauma* 2007; 63:E121.
6. Close BJ, Strouse PJ: MR of physeal fractures of the adolescent knee. *Pediatr Radiol* 2000; 30:756.
7. Green NE, Swiontkowski MF: *Skeletal Trauma in Children*, 4th ed. Philadelphia: Elsevier; 2009.
8. Laine JC, Kaiser SP, Diab M: High-risk pediatric orthopedic pitfalls. *Emerg Med Clin North Am* 2010; 28:85-102.
9. Khosla S, et al: Incidence of childhood distal forearm fractures over 30 years: A population based study. *JAMA* 2003; 290:1479-1485.
10. Barmada A, Gaynor T, Mubarak SJ: Premature physeal closure following distal tibia physeal fractures: A new radiographic predictor. *J Pediatr Orthop* 2003; 23:733-739.
11. Dowling S, Farion K, Clifford T: Comparison views to diagnose elbow injuries in children: A survey of Canadian non-pediatric emergency physicians. *CJEM* 2005; 7:237.
12. Keats TE, Anderson MW: *Atlas of Normal Roentgen Variants That May Simulate Disease*, 7th ed. St Louis: Mosby; 2001.
13. Diagnostic imaging of child abuse. *Pediatrics* 2000; 105:1345.
14. El-Khoury GY, Bennet DL, Ondr GJ: Multidetector-row computed tomography. *J Am Acad Orthop Surg* 2004; 12:1-5.
15. Buckwalter KA, Rydberg J, Kopecky KK, Crow K, Yang EL: Musculoskeletal imaging with multislice CT. *AJR Am J Roentgenol* 2001; 176:979-986.
16. You JS, et al: The usefulness of CT for patients with carpal bone fractures in the emergency department. *Emerg Med J* 2007; 24: 248-250.
17. Watura R, Cobby M, Taylor J: Multislice CT in imaging of trauma of the spine, pelvis and complex foot injuries. *Br J Radiol* 2004; 77:S46-S63.
18. Legome E, Pancu D: Future applications for emergency ultrasound. *Emerg Med Clin North Am* 2004; 22:817-827.
19. McManus JG, et al: Use of ultrasound to assess acute fracture reduction in emergency care settings. *Am J Disaster Med* 2008; 3:241-247.
20. Gosselin RA, Roberts I, Gillespie WJ: Antibiotics for preventing infection in open limb fractures. *Cochrane Database Syst Rev* 2004; 1:CD003764.
21. Sorger JI, et al: Once daily, high dose versus divided, low dose gentamicin for open fractures. *Clin Orthop Relat Res* 1999; 366:197.
22. Stewart DG Jr, Kay RM, Skaggs DL: Open fractures in children. Principles of evaluation and management. *J Bone Joint Surg Am* 2005; 87:2784-2798.
23. Schmidt AH, Anglen J, Nana AD, Varecka TF: Adult trauma: Getting through the night. *J Bone Joint Surg Am* 2010; 92:490-505.
24. Webb LX, Bosse MJ, Castillo RC; LEAP Study Group: Analysis of surgeon-controlled variables in the treatment of limb-threatening type-III open tibial diaphyseal fractures. *J Bone Joint Surg Am* 2007; 89:923-928.
25. Stevenson J, McNaughton G, Riley J: The use of prophylactic flucloxacillin in the treatment of open fractures of the distal phalanx within an accident and emergency department: A double-blind randomized placebo controlled trial. *J Hand Surg Br* 2003; 28:388.
26. Hollis JD, Daley BJ: 10-year review of knee dislocations: Is arteriography always necessary? *J Trauma* 2005; 59:672-675.
27. Peng PD, et al: CT angiography effectively evaluates extremity vascular trauma. *Am Surg* 2008; 74:10.
28. Ruijs AC, Jaquet JB, Kalmijn S, Giele H, Hovius SE: Median and ulnar nerve injuries: A meta-analysis of predictors of motor and sensory recovery after modern microsurgical nerve repair. *Plast Reconstr Surg* 2005; 116:484.
29. Tindall A, Dawood R, Povlsen B: Case of the month: The skin wrinkle test: A simple nerve injury test for paediatric and uncooperative patients. *Emerg Med J* 2006; 23:883-886.
30. Vasudevan TM, van Rij AM, Nukada H, Taylor PK: Skin wrinkling for the assessment of sympathetic function in the limbs. *Aust N Z J Surg* 2000; 70:57-59.
31. McQueen MM, Gaston P, Court-Brown CM: Acute compartment syndrome. Who is at risk? *J Bone Joint Surg Br* 2000; 82:200-203.
32. Konstantakos EK, Dalstrom DJ, Nelles ME, Laughlin RT, Prayson MJ: Diagnosis and management of extremity compartment syndromes: An orthopaedic perspective. *Am Surg* 2007; 73:1199.
33. Rozycki GS, Tremblay LN, Feliciano DV, McClelland WB: Blunt vascular trauma in the extremity: Diagnosis, management and outcome. *J Trauma* 2003; 55:814.
34. Andermahr J, Helling HJ, Tsironis K, Rehm KE, Koebke J: Compartment syndrome of the foot. *Clin Anat* 2001; 14:184.
35. King TW, Lerman OZ, Carter JJ, Warren SM: Exertional compartment syndrome of the thigh: A rare diagnosis and literature review. *J Emerg Med* 2010; 39:93-99.
36. Newton EJ, Love J: Acute complications of extremity trauma. *Emerg Med Clin North Am* 2007; 25:751.
37. Dua RS, Bankes MJ, Down GS, Lewis AA: Compartment syndrome following pelvic surgery in the lithotomy position. *Ann R Coll Surg Engl* 2002; 84:170-171.
38. Nassif JM, Gorczyca JT, Cole JK, Pugh KJ, Pienkowski D: Effect of acute reamed versus unreamed intramedullary nailing on compartment pressure when treating closed tibial shaft fractures: A randomized prospective study. *J Orthop Trauma* 2000; 14:554-558.
39. Olson SA, Glasgow RR: Acute compartment syndrome in lower extremity musculoskeletal trauma. *J Am Acad Orthop Surg* 2005; 13:436.
40. Elliott KG, Johnstone AJ: Diagnosing acute compartment syndrome. *J Bone Joint Surg Br* 2003; 85:625-632.
41. Perron AD, Brady WJ, Keats TE: Orthopedic pitfalls in the ED: acute compartment syndrome. *Am J Emerg Med* 2001; 19;413-416.
42. Boody AR, Wongworawat MD: Accuracy in the measurement of compartment pressures: A comparison of three commonly used devices. *J Bone Joint Surg Am* 2005; 87:2415-2422.
43. Tobias JD, Hoernschyer DG: Near infrared spectroscopy identifies compartment syndrome in an infant. *J Pediatr Orthop* 2007; 27:311.
44. Tull F, Borrelli J Jr: Soft-tissue injury associated with closed fractures: Evaluation and management. *J Am Acad Orthop Surg* 2003; 11:431-438.
45. Battcharya T, Vrahas MS: The medical legal aspects of compartment syndrome. *J Bone Joint Surg Am* 2004; 86:864.
46. Lauder AJ, Trumble TE: Idiopathic avascular necrosis of the scaphoid: Preiser's disease. *Hand Clin* 2006; 22:475.
47. Kerachian MA, Harvey EJ, Cournoyer D, Chow TY, Séguin C: Avascular necrosis of the femoral head: Vascular hypotheses. *Endothelium* 2006; 13:237.
48. Rammelt S, Winkler J, Grass R, Zwipp H: Reconstruction after talar fractures. *Foot Ankle Clin* 2006; 11:61.
49. Niesten JA, Verhaar JA: Idiopathic avascular necrosis of the capitate—a case report and review of the literature. *Hand Surg* 2002; 7:159.
50. Stanton-Hicks M, et al: Reflex sympathetic dystrophy: Changing concepts and taxonomy. *Pain* 1995; 63:127-133.
51. Albazaz R, Wong YT, Homer-Vanniasinkam S: Complex regional pain syndrome: A review. *Ann Vasc Surg* 2008; 22:297.
52. Bruehl S: Modifying diagnostic criteria for complex regional pain syndrome. *Pain* 2010; 150:217-218.
53. Marinus J, et al: Clinical features and pathophysiology of complex regional pain syndrome. *Lancet Neurol* 2011; 10:637-648.
54. Schott GD: Complex? Regional? Pain? Syndrome? *Pract Neurol* 2007; 7:145-157.
55. Bruehl S: An update on the pathophysiology of complex regional pain syndrome. *Anesthesiology* 2010; 113:713-725.
56. Low AK, Ward K, Wines AP: Pediatric complex regional pain syndrome. *J Pediatr Orthop* 2007; 27:567-572.
57. Quisel A, Gill JM, Witherell P: Complex regional pain syndrome underdiagnosed. *J Fam Pract* 2005; 54:524-532.
58. Oerlemans HM, Oosteodorp RA, de Boo T, Goris RJ: Pain and reduced mobility in complex regional pain syndrome I: Outcome of a prospective randomized, controlled clinical trial of adjuvant physical therapy versus occupational therapy. *Pain* 1999; 83:77.
59. Perez RS, et al: Evidence based guidelines for complex regional pain syndrome type 1. *BMC Neurol* 2010; 10:20.
60. van de Vusse AC, Stomp-van den Berg SG, Kessels AH, Weber WE: Randomised controlled trial of gabapentin in complex regional pain syndrome type 1. *BMC Neurol* 2004; 4:13.
61. Zollinger PE, Tuinebreijer WE, Kreis RW, Breederveld RS: Effect of vitamin C on frequency of reflex sympathetic dystrophy in wrist fractures: A randomised trial. *Lancet* 1999; 354:2025.
62. Imberti R, Scagnelli P, Amatu A: Post-traumatic pulmonary and cerebral fat embolism. *Anaesth Int Care* 2008; 36:619.
63. Memtsoukis SG, Rosenberger P, Walz JM: Critical care issues in the patient after major joint replacement. *J Int Care Med* 2007; 22:92.

www.ketabpezeshki.com 66485457-66963820

64. Strauss EJ, Petrucelli G, Bong M, Koval KJ, Egol KA: Blisters associated with lower extremity fracture: Results of a prospective treatment protocol. *J Orthop Trauma* 2006; 20:618.
65. Bose D, Tejwani NC: Evolving trends in the care of polytrauma patients. *Injury* 2006; 37:20-28.
66. Rotondo MF, et al: 'Damage control': An approach for improved survival in exsanguinating penetrating abdominal injury. *J Trauma* 1993; 35:375-383.
67. Pape HC, Giannoudis P, Krettek C: The timing of fracture treatment in polytrauma patients: Relevance of damage control orthopedic surgery. *Am J Surg* 2002; 183:622-629.
68. Worth C, Harris A: Non-reducible hip dislocation in the ED. *Emerg Med J* 2009; 26:42.
69. Stiell IG, et al: A study to develop clinical decision rules for the use of radiography in acute ankle injuries. *Ann Emerg Med* 1992; 21:384.
70. Stiell IG, et al: Decision rules for the use of radiography in acute ankle injuries: Refinement and prospective validation. *JAMA* 1993; 269:1127.
71. Stiell IG, et al: Implementation of the Ottawa ankle rules. *JAMA* 1994; 271:827.
72. Bachmann LM, Kolb E, Koller MT, Steurer J, ter Riet G: Accuracy of Ottawa ankle rules to exclude fractures of the ankle and mid-foot: Systematic review. *BMJ* 2003; 326:417.
73. Anderson SJ: Lower extremity injuries in youth sports. *Pediatr Clin North Am* 2002; 49:627-641.
74. Schub D, Saluan P: Anterior cruciate ligament injuries in the young athlete: Evaluation and treatment. *Sports Med Arthrosc* 2011; 19:34-43.
75. Emery KH: Imaging of sports injuries of the upper extremity in children. *Clin Sports Med* 2006; 25:543-568, viii.
76. Ivins D: Acute ankle sprain: An update. *Am Fam Physician* 2006; 15:1714.
77. Jones MH, Amendola AS: Acute treatment of inversion ankle sprains: Immobilization versus functional treatment. *Clin Orthop Relat Res* 2007; 455:169.
78. Boyce SH, Quigley MA, Campbell S: Management of ankle sprains: A randomized controlled trial of the treatment of inversion injuries using an elastic support bandage or an Aircast ankle brace. *Br J Sports Med* 2005; 39:91.
79. Järvinen TA, Kääriäinen M, Järvinen M, Kalimo H: Muscle strain injuries. *Curr Opin Rheumatol* 2000; 12:155-161.
80. Lew HL, Chen CP, Wang TG, Chew KT: Introduction to musculoskeletal diagnostic ultrasound: Examination of the upper limb. *Am J Phys Med Rehabil* 2007; 86:310.
81. Bianchi S, Poletti PA, Martinoli C, Abdelwahab IF: Ultrasound appearance of tendon tears. Part 2: Lower extremity and myotendinous tears. *Skeletal Radiol* 2006; 35:63.
82. Heidt RS Jr, Sweeterman LM, Carlonas RL, Traub JA, Tekulve FX: Avoidance of soccer injuries with preseason conditioning. *Am J Sports Med* 2000; 28:659-662.
83. Rettig AC: Wrist and hand overuse syndromes. *Clin Sports Med* 2001; 20:591.
84. Sharma P, Maffuli N: Biology of tendon injury: Healing, modeling and remodeling. *J Musculoskelet Neuronal Interact* 2006; 6:1818.
85. Scott A, Ashe MC: Common tendinopathies in the upper and lower extremities. *Curr Sports Med Rep* 2006; 5:233.
86. Alfredson A, Lorentzon R: Chronic Achilles tendinosis: Recommendations for treatment and prevention. *Sports Med* 2000; 29:135.
87. Fenwick SA, Hazleman BL, Graham PR: The vasculature and its role in the damaged and healing tendon. *Arthritis Res* 2002; 4:252.
88. Corrao G, et al: Evidence of tendinitis provoked by fluoroquinolone treatment: A case-control study. *Drug Saf* 2006; 8:889.
89. Khan KM, Cook JL, Bonar F, Harcourt P, Astrom M: Histopathology of common tendinopathies. Update and implications for clinical management. *Sports Med* 1999; 27:393-408.
90. Maffulli N, Wong J, Almekinders LC: Types and epidemiology of tendinopathy. *Clin Sports Med* 2003; 22:675.
91. Harvie P, Pollard TC, Carr AJ: Calcific tendinitis: Natural history and association with endocrine disorders. *J Shoulder Elbow Surg* 2007; 16:169.
92. Grassi W: Sonographic imaging of tendons. *Arthritis Rheum* 2000; 43:969.
93. Andres BM, Murrell GA: Treatment of tendinopathy: What works, what does not and what is on the horizon. *Clin Orthop Relat Res* 2008; 466:1539.
94. Feucht CL, Patel D: Analgesics and anti-inflammatory medications in sports: Use and abuse. *Pediatr Clin North Am* 2010; 57:751-774.
95. Shrier I, Matheson GO, Kohl HW: Achilles tendonitis: Are corticosteroid injections useful or harmful? *Clin J Sports Med* 1996; 6:245-250.
96. Stell I: Management of acute bursitis: Outcome study of a structured approach. *J R Soc Med* 1999; 92:5216.
97. Seah R, Mani-Babu S: Managing ankle sprains in primary care: What is best practice? A systematic review of the last 10 years of evidence. *Br Med Bull* 2011; 97:105-135.
98. Kerkhoffs GM, et al: Functional treatments for acute ruptures of the lateral ankle ligament: A systematic review. *Acta Orthop Scand* 2003; 74:69-77.
99. Lamb SE, et al: Mechanical supports for acute, severe ankle sprain: A pragmatic, multicentre, randomised controlled trial. *Lancet* 2009; 373:575-581.
100. Handoll HH, Rowe BH, Quinn KM, de Bie R: Interventions for preventing ankle ligament injuries. *Cochrane Database Syst Rev* 2001; 3:CD000018.
101. Boyd AS, Benjamin HJ, Asplund C: Principles of casting and splinting. *Am Fam Physician* 2009; 79:16-22.
102. Unal S, Aksoy A, Yilmaz C, Arslan E, Demirkan F: Third-degree burn after plaster of Paris brace. *Plast Reconstr Surg* 2004; 114:1686.
103. Halanski MA, Halanski AD, Oza A: Thermal injury with contemporary cast-application techniques and methods to circumvent morbidity. *J Bone Joint Surg Am* 2007; 89:2369-2377.
104. Smith GD, Hart RG, Tsai TM: Fiberglass cast application. *Am J Emerg Med* 2005; 23:347-360.
105. Riding G, Edgel M, James M: Plaster checks: A waste of resources? *J Accid Emerg Med* 1994; 11:266.
106. Knight KL, et al: Muscle injury management with cryotherapy. *Athl Ther Today* 2000; 5:26-30.
107. Hubbard TJ, Denegar CR: Does cryotherapy improve outcomes with soft tissue injury? *J Athlet Train* 2004; 39:278.
108. Collins NC: Is ice right? Does cryotherapy improve outcome for acute soft tissue injury? *Emerg Med J* 2008; 25:65.
109. Bleakley C, McDonough S, McCauley D: The use of ice in the treatment of acute soft-tissue injury: A systematic review of randomized controlled trials. *Am J Sports Med* 2004; 32:251.
110. Creaney L, Hamilton B: Growth factor delivery methods in the management of sports injuries: The state of play. *Br J Sports Med* 2008; 42:314-320.
111. Taylor DW, Petrera M, Hendry M, Theodoropoulos JS: A systematic review of the use of platelet-rich plasma in sports medicine as a new treatment for tendon and ligament injuries. *Clin J Sport Med* 2011; 21:344-352.
112. Mishra A, Pavelko T: Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. *Am J Sports Med* 2006; 34:1774-1778.
113. Mishra A, Woodall J Jr, Vieira A: Treatment of tendon and muscle using platelet-rich plasma. *Clin Sports Med* 2009; 28:113-125.
114. Sánchez M, et al: Comparison of surgically repaired Achilles tendon tears using platelet-rich fibrin matrices. *Am J Sports Med* 2007; 35:245-251.

www.ketabpezeshki.com 66485457-66963820

Chapter 50

Hand

Thomas Mailhot and Everett T. Lyn

PERSPECTIVE

The hand is intricate, dynamic, and unique in function. It combines extreme mobility, precision, power, and sensation and is used to express and execute. Because the hands are used more to manipulate the environment than the rest of the body, they are commonly injured. Function depends on intact relationships among intrinsic structural components, musculotendinous units originating from more proximal areas, and motor and sensory connections with the central nervous system. Restoration of function rather than appearance is the primary goal in management of hand injuries and infections. Early recognition and timely initiation of therapy for limb-threatening conditions are essential to an optimal outcome. The fate of the injured hand depends largely on the physician who provides initial care. Mismanagement may result in unnecessary functional loss that may not be recoverable, even with the best convalescent care. An understanding of the functional anatomy of the hand is necessary for the appropriate evaluation and management of these disorders.

Epidemiology

Overall, hand injuries are reported to represent 5 to 10% of visits to an emergency department (ED), and approximately 6% of the patients have deep, significant injuries.[1] Injuries have environmental, occupational, and recreational causes and are seen in all age groups. The spectrum of injury includes infections, lacerations, fractures, crush wounds, amputations, and burns. It is estimated that 10% of all patients with hand injuries require referral to a hand specialist, and most patients referred from EDs have fractures.[2] The disability potential of hand injuries generally is high; such disability may involve loss of strength, flexibility, or sensation. According to available data, hand injuries account for 19% of lost-time injuries and for 9% of worker compensation cases.[3] Approximately 3 to 4 million working days are lost each year as a result of hand injuries.[4] Overall, hand and fingers are the most frequent body parts injured in the workplace and cared for in EDs.[5]

PRINCIPLES OF DISEASE, FUNCTIONAL ANATOMY, PHYSIOLOGY, AND EXAMINATION OF THE HAND

Terminology

To avoid confusion, it is important that standard terminology for the surface anatomy of the hand be used (Fig. 50-1). The back of the hand and fingers is called the *dorsal surface,* and the palm side is called either the *palmar* or the *volar surface*. The borders of the hand are *radial* and *ulnar.* The five digits often are designated by numerals, but common names are preferable: I (thumb), II (index finger), III (long or middle finger), IV (ring finger), and V (little finger). Each finger has three joints: the metacarpophalangeal (MCP), the proximal interphalangeal (PIP), and the distal interphalangeal (DIP) joints. The thumb has an MCP joint and only one interphalangeal (IP) joint. There are proximal, middle, and distal phalanges in the fingers and only a proximal and a distal phalanx in the thumb. The *thenar mass* or *eminence* refers to the muscular area on the palmar surface overlying the thumb metacarpal. The *hypothenar eminence* is the muscle mass on the palmar surface overlying the little finger metacarpal.

Hand and digit motion has been standardized and is illustrated in Figures 50-2 through 50-6. The carpometacarpal (CMC) joint is more mobile in the thumb than in the other fingers and is the key to the grasp and dexterity that characterize the human hand. Motions of this joint include *palmar abduction* (also called *flexion*), *radial abduction, retroposition (extension), adduction,* and *opposition* (see Fig. 50-6). The IP joints are essentially hinge joints and are capable of only two motions: flexion and extension.

Structural Framework

Skin Cover

The hand has two skin surfaces, each with different functions. The skin of the palm is thick compared with the dorsal skin and is stabilized by fibrous connections on its deep surface. The skin creases in the palmar aspect of the hand are largely transverse and represent adherence between skin and underlying fascia, without intervening adipose tissue. These features facilitate flexion and limit the development of inflammatory edema in the palm.[6] The other noteworthy characteristic of the palmar skin is the unique arrangement of epithelial ridges of the dermis that form cutaneous striations. These ridges have forensic importance in the pulp as "fingerprints" and play an important role in increasing friction for grasping objects.[7]

The dorsal skin is relatively thin and mobile, permitting motion of the various joints. As a path of least resistance, the dorsum of the hand also swells easily after inflammation or trauma, which may limit flexion of the MCP joints.[7] In addition, infection in the palmar aspect of the hand may cause dorsal swelling; this finding can be misleading without a careful physical examination.

Skeleton

The hand and wrist contain 27 bones: 14 phalangeal bones, 5 metacarpal bones, and 8 carpal bones (Fig. 50-7). The eight small

www.ketabpezeshki.com 66485457-66963820

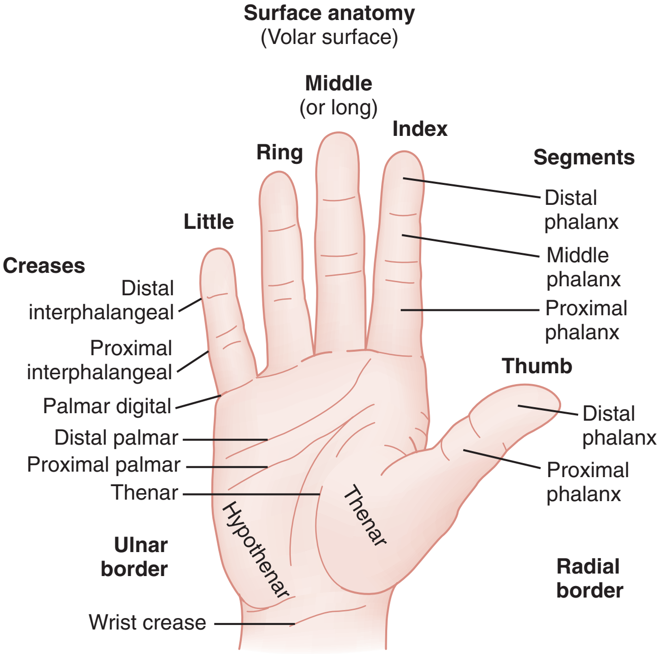


Figure 50-1. Surface anatomy of the hand. (From Burton RI, et al: The Hand: Examination and Diagnosis, 3rd ed. New York, Churchill Livingstone, 1990, p 6.)

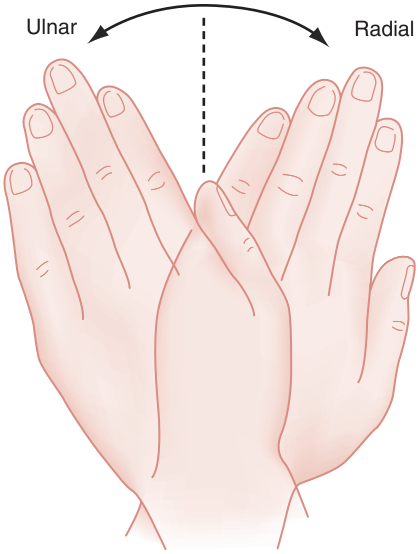


Figure 50-3. Ulnar and radial deviation of the hand.

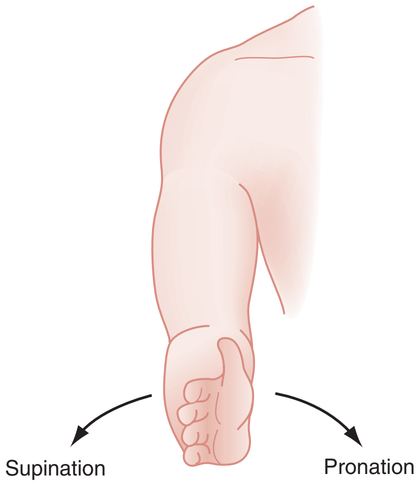


Figure 50-2. Supination and pronation of the hand.

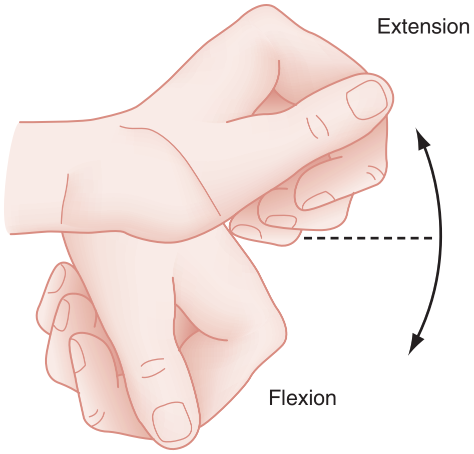


Figure 50-4. Wrist extension and flexion.

carpal bones in the region of the wrist are strongly united to one another by ligaments. These bones form synovial joints and are arranged in two rows, proximal and distal, with four bones in each row. Together the bones of the carpus present a concavity on their volar surface, which is bridged by a strong membranous band, the flexor retinaculum. In this way, the bridge and the bones form a tunnel, known as the *carpal tunnel,* through which pass the median nerve and the long flexor tendons of the fingers. The IP joints are inherently more stable than the MCP joint by virtue of their bicondylar configuration, which gives a modified tongue-in-groove appearance (Fig. 50-8).

The soft tissue supporting these joints includes the capsular ligamentous structures, which afford stability, and the tendinous structures, which generate mobility. The metacarpal and IP joints are stabilized on both sides by collateral ligaments and anteriorly by a palmar fibrocartilaginous "volar plate." Because of anatomic

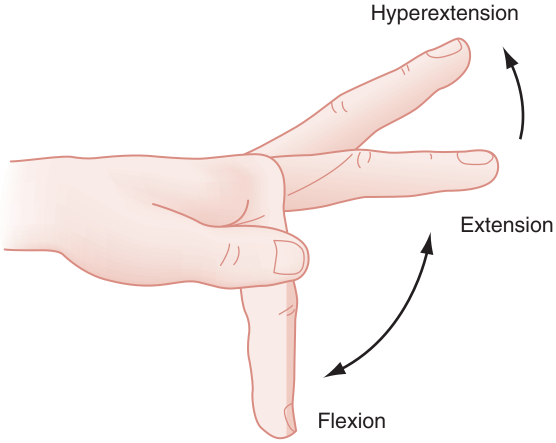


Figure 50-5. Finger flexion is volar and occurs at the metacarpophalangeal joint; extension and hyperextension are as shown.

www.ketabpezeshki.com 66485457-66963820

differences between the metacarpals and phalanges, the IP collaterals are tight throughout the entire range of motion, whereas the collaterals of the MCP joint are tightest in flexion (Fig. 50-9). The IP joints are hinges, but the MCP joint has additional side-to-side mobility and rotational movement to facilitate efficient grasp.[7] The clinical importance of these differences is that for minimization of the development of contractures after joint injuries, the preferred position of immobilization of the PIP joints is extension, whereas the MCP joints are more properly placed in flexion.

The structure and arrangement of the metacarpals are noteworthy. The metacarpals participate in three arches: the proximal (carpal) and distal (metacarpal) transverse arches and the longitudinal arch[6] (Fig. 50-10). The index and long finger metacarpals form a fairly immobile segment because of their ridged articulation with the carpals. The adjacent metacarpals are more mobile. This unique anatomy gives the human palm a longitudinal and transverse concavity when the thumb is alongside the index finger; however, this changes to an oblique gutter when the thumb is extended.

The small bones of the child's hand differ significantly from the bones of the adult and from other long bones because of the presence of an epiphysis or growth plate at one end of the bone. The phalangeal epiphyses and the thumb metacarpal epiphysis are located at the proximal end, and the finger metacarpal epiphyses are located at the distal end of the bone (Fig. 50-11). In boys the proximal phalangeal epiphysis appears at 15 to 24 months and fuses at 16 years. In girls it appears at 10 to 15 months and fuses at 14 years.[8] The time of appearance and fusion is related to skeletal maturity and can be judged accurately until puberty from hand and wrist radiographs, because the sequence of development is age-specific.[9]

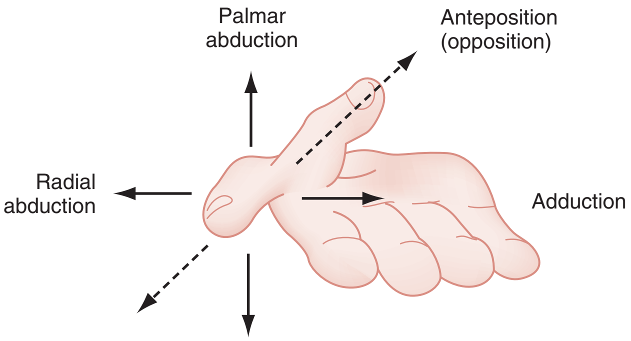


Figure 50-6. Perpendicular view of thumb mobility.

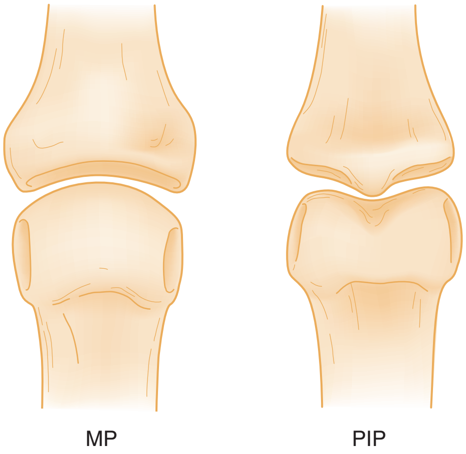


Figure 50-8. The metacarpophalangeal *(MP)* and proximal interphalangeal *(PIP)* joints are quite different structurally. The PIP joint has a bicondylar configuration, making it inherently more stable than the globular MP joint. (From DeLee JC, Drez D Jr: Orthopedic Sports Medicine: Principles and Practice, 2nd ed. Philadelphia, Saunders, 2003.)

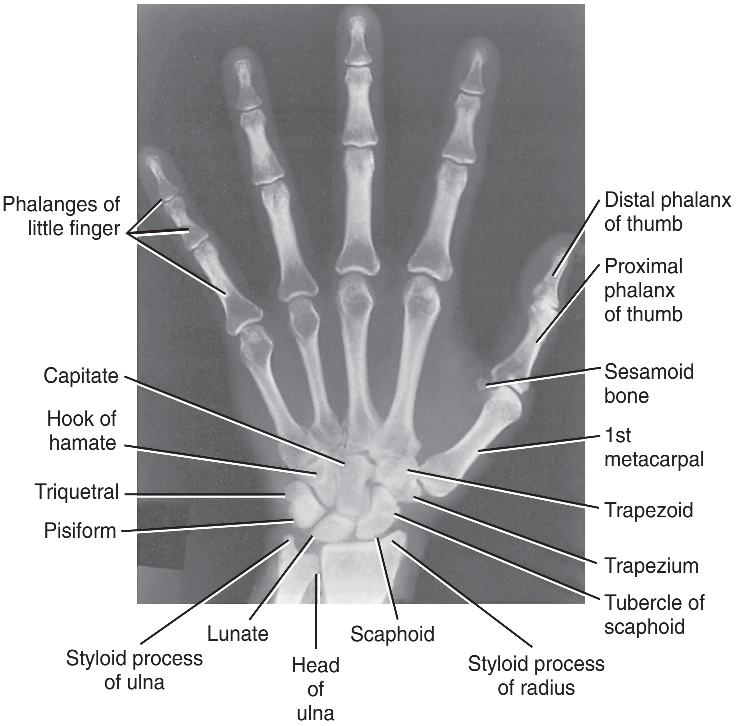


Figure 50-7. Posteroanterior radiograph of the wrist and hand with the forearm pronated. (From Snell RS, Smith MS: Clinical Anatomy for Emergency Medicine. St. Louis, Mosby, 1993, p 650.)

www.ketabpezeshki.com 66485457-66963820

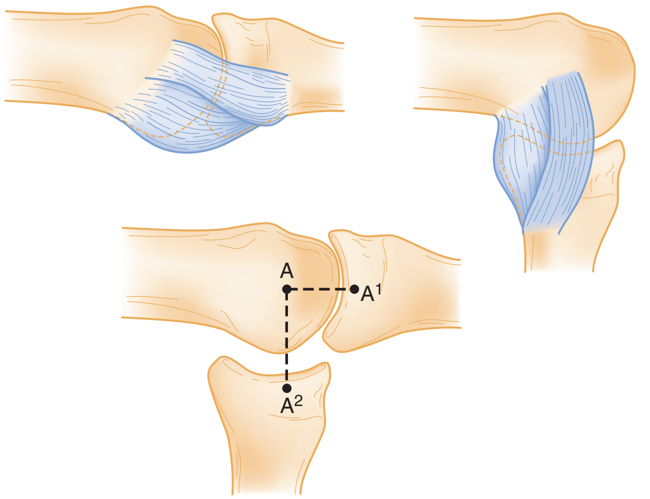


Figure 50-9. The shape of the metacarpal head is eccentric, resulting in a cam effect that makes the collateral ligaments more taut in flexion than in extension. Distance A-A^1 is less than A-A^2. The cam effect is not present in the proximal interphalangeal joint. (From DeLee JC, Drez D Jr: Orthopedic Sports Medicine: Principles and Practice, 2nd ed. Philadelphia, Saunders, 2003.)

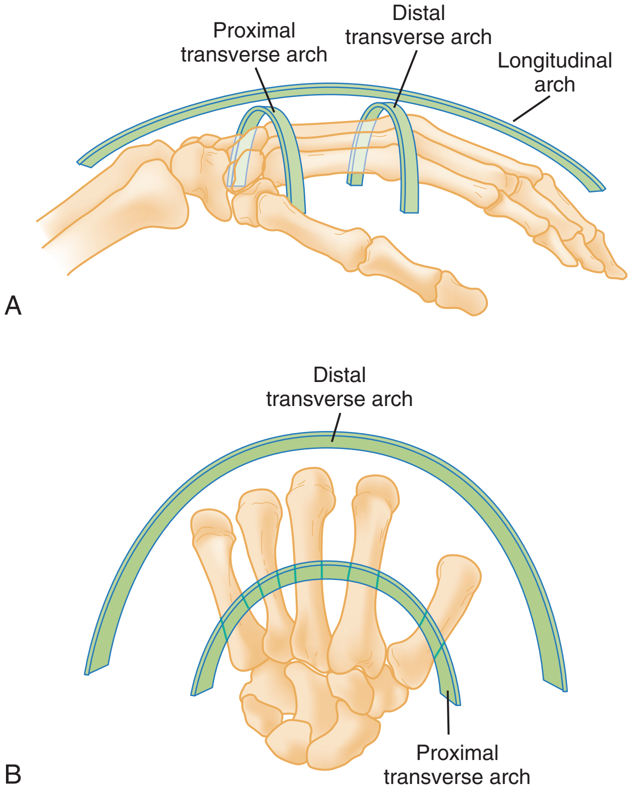


Figure 50-10. The three arches of the metacarpals. **A,** Sagittal view. **B,** Transverse view. (From American Society for Surgery of the Hand: Regional Review Course in Hand Surgery Syllabus, 10th ed. Aurora, Colo, ASSH, 1990.)

Figure 50-11. Normal location of the epiphysis of the hand. All of the phalangeal epiphyses are located at the proximal end. The metacarpophalangeal epiphyses all are distally situated, however, except for that of the thumb, which is proximal. (From Harris WH, Harris CC: The Radiology of Emergency Medicine. Baltimore, Williams & Wilkins, 1993, p 440.)

Muscle and Tendon Function

The muscles that power the hand may be divided into extrinsic and intrinsic muscles. The intrinsic muscles have their origins and insertions within the hand. The extrinsic muscles have origins in muscle bellies in the forearm and tendinous insertions on bones in the hand. They are divided further into extrinsic flexor and extensor muscles. The flexors of the digits in the hand lie on the volar surface of the forearm; the extensors are on the dorsal surface.

Intrinsic Musculature. The intrinsic muscles of the hand include the muscles of the thenar and hypothenar eminences, the adductor pollicis, the interossei, and the lumbricals (Fig. 50-12). The thenar muscles cover the thumb metacarpal. This group includes the abductor pollicis brevis, opponens pollicis, and flexor pollicis brevis. These muscles originate in the flexor retinaculum and on the carpal bones and insert at the base of the first metacarpal and first proximal phalanx. They act in concert with the long flexors and extensors to carry the thumb through its intricate range of motion. The muscles are evaluated by palpation of the thenar eminence for contraction as the patient brings together the tips of the thumb and little finger. They also can be tested by asking the patient to place the dorsum of the hand on a flat surface and to raise the thumb up straight to form a 90-degree angle with the palm. The thenar muscles usually are innervated by the motor branch of the median nerve. In some cases they may be partially innervated by the ulnar nerve.

The adductor pollicis arises from the index and middle finger metacarpals and inserts on the first proximal phalanx. This muscle is innervated by the ulnar nerve. Thumb adduction is tested separately by having the patient forcibly hold a piece of paper between the thumb and radial side of the index proximal phalanx. If the adductor pollicis is weak or nonfunctioning, the thumb IP joint flexes with this maneuver (Froment's paper sign).[10] In this evaluation, the two hands should be compared.

The lumbrical muscles arise from the sides of the flexor digitorum profundus (FDP) tendons; the interossei muscles lie between the metacarpal bones and originate from them. Both of these muscle groups insert in the extensor expansions of the index, middle, ring and little fingers and act on the fingers to flex the

www.ketabpezeshki.com 66485457-66963820

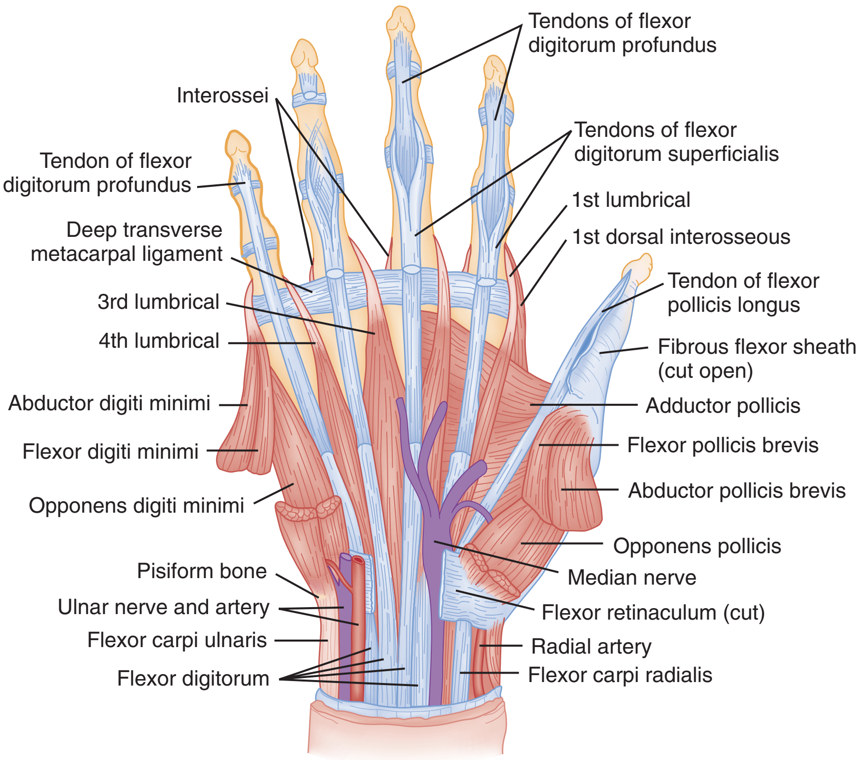


Figure 50-12. Anterior view of the palm of the hand. The palmar aponeurosis and the greater part of the flexor retinaculum have been removed to display the median nerve, the long flexor tendons, and the lumbrical muscles. Segments of the tendons of the flexor digitorum superficialis muscle have been removed to show underlying tendons of the flexor digitorum profundus muscles. (From Snell RS, Smith MS: Clinical Anatomy for Emergency Medicine. St. Louis, Mosby, 1993, p 641.)

MCP joints and extend the IP joints. The radial two lumbricals are innervated by the median nerve, and the ulnar two are innervated by the ulnar nerve. The seven interossei (three palmar and four dorsal) can be considered together. They lie on either side of the finger metacarpals and are innervated by the ulnar nerve. The dorsal interossei abduct the fingers away from the midline; the volar muscles adduct the fingers. For an accurate test that isolates their function from the extrinsic muscles, the patient should place the palm flat on a table, extend the digit, and move it from side to side.

The hypothenar group of intrinsic muscles includes the opponens digiti minimi, the flexor digiti minimi, and the abductor digiti minimi. These muscles arise from the carpal bones and in the flexor retinaculum and insert on the proximal phalanx and metacarpal of the little finger. The flexor digiti minimi and abductor digiti minimi flex the proximal phalanx and abduct the little finger respectively. The three muscles are evaluated as a group by having the patient place the wrist in a neutral position and abduct the little finger (move it away from the other fingers) against resistance. This muscle mass is palpated at that time, and a dimpling of the hypothenar skin is noted. All of the intrinsic muscles of the little finger are innervated by the ulnar nerve.

Extensor Tendons. The extensor tendons are on the dorsal side of the forearm, wrist, and hand. The nine extensor tendons cross the wrist joint dorsal to its axis of rotation, pass under the extensor retinaculum, and are separated on the dorsum of the hand by a series of six fibro-osseous canals or compartments. Figure 50-13 outlines the compartments and their contents. The fibrous roof of these compartments prevents the tendons from bowstringing dorsally during active finger extension, particularly when the wrist also is extended.

The first dorsal wrist compartment contains the tendons of the abductor pollicis longus, which inserts at the dorsal base of the thumb metacarpal, and the extensor pollicis brevis, which inserts on the proximal phalanx of the thumb. The abductor pollicis longus serves to abduct the thumb ray, or thumb digit and metacarpal bone, radially, and the extensor pollicis brevis acts primarily to extend the thumb ray at the MCP joint. These tendons are evaluated by having the patient abduct and extend the thumb with resistance applied to the thumb; they can be palpated on the radial side of the wrist during this maneuver.

Two tendons lie in the second compartment: the extensor carpi radialis longus and brevis. These tendons insert at the dorsal base of the index and middle metacarpals. They act primarily to extend and deviate the wrist radially. These tendons can be palpated by having the patient extend the wrist against resistance while making a fist.

In the third compartment, a single tendon, the extensor pollicis longus, arises from the deep muscles of the midforearm, passes around a bony prominence on the dorsum of the wrist termed *Lister's tubercle,* and inserts on the base of the distal phalanx of the thumb. This tubercle can be palpated just proximal to the wrist joint. The extensor pollicis longus forms the dorsal border of the anatomic snuffbox, and the abductor pollicis longus forms the volar border (Fig. 50-14). The floor of this area contains the radial artery and two carpal bones, the scaphoid and trapezium. The extensor pollicis longus functions to extend and adduct the entire first ray and extend and hyperextend the IP joint of the thumb. This muscle is evaluated by placing the hand flat on a table and having the patient lift only the thumb off the surface. Because the abductor pollicis brevis and the adductor pollicis add terminal extension, complete laceration of the extensor pollicis longus tendon may not eliminate the patient's ability to extend the thumb.[11]

The tendons that extend the fingers—the extensor indicis proprius and the extensor digitorum communis—are in the fourth compartment. The extensor digitorum muscle divides into four tendons proximal to the wrist. In the dorsum of the hand, these tendons are joined distally by fibrous interconnections called *juncturae tendinum* which help stabilize them to their insertions in the extensor expansions of the index, middle, ring, and little fingers. The extensor digiti minimi is contained in the fifth dorsal compartment. Both the extensor indicis proprius and the extensor digiti minimi typically lie ulnar to their respective common

www.ketabpezeshki.com 66485457-66963820

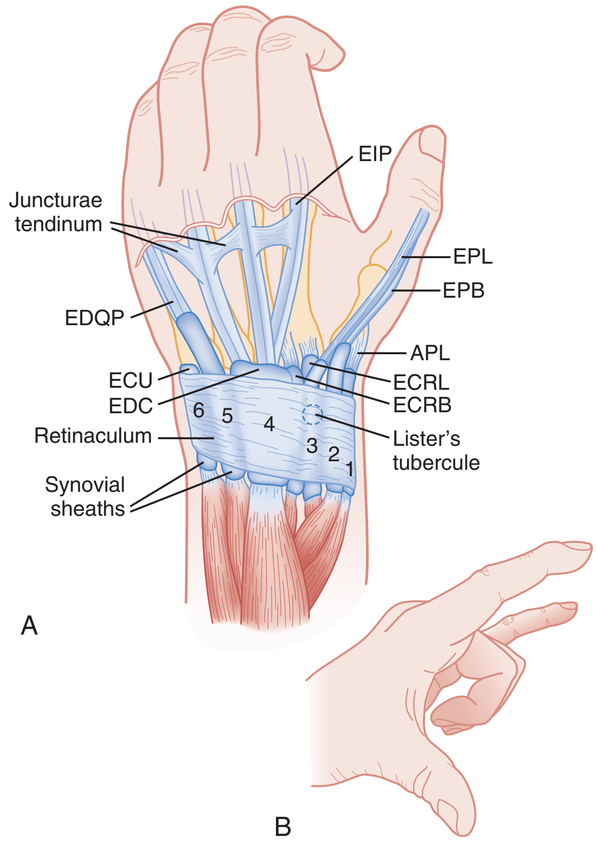


Figure 50-13. A, The extensor tendons gain entrance to the hand from the forearm through a series of six canals, five fibro-osseous and one fibrous (the sixth dorsal compartment, which contains the extensor digiti quinti proprius *[EDQP]*). The first compartment contains the abductor pollicis longus *(APL)* and extensor pollicis brevis *(EPB);* the second, the radial wrist extensors; the third, the extensor pollicis longus *(EPL),* which angles around Lister's tubercle; the fourth, the extensor digitorum communis *(EDC)* to the fingers and the extensor indicis proprius *(EIP);* the fifth, the EDQP; and the sixth, the extensor carpi ulnaris *(ECU).* The communis tendons are joined distally near the metacarpophalangeal joints by fibrous connections called *juncturae tendinum.* Beneath the retinaculum, the extensor tendons are covered with a synovial sheath. **B,** The proprius tendons to the index and little fingers are capable of independent extension, and their function may be evaluated as depicted. With the middle and ring fingers flexed into the palm, the proprius tendons can extend the ring and little fingers. *ECRB,* extensor carpi radialis brevis; *ECRL,* extensor carpi radialis longus; *EDQP,* extensor digiti quintus proprius. (From Doyle JR: Extensor tendons-acute injuries. In Green DP [ed]: Operative Hand Surgery. New York, Churchill Livingstone, 1993, p 1927.)

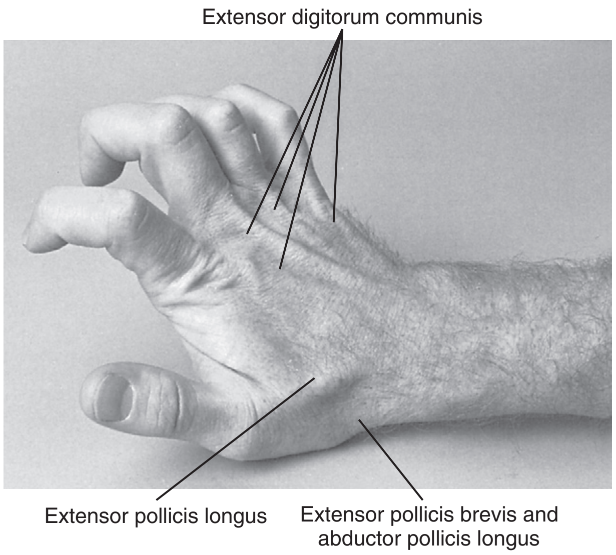


Figure 50-14. Surface anatomy of the wrist and hand. The tendons that are palpated with the thumb abducted and extended form an anatomic snuffbox.

extensor tendons. The dual extensor system for the index and small fingers gives these two digits extension independent of the other digits. The middle finger and especially the ring finger have considerably limited independent extension. The motion restriction is because of the juncturae, which also prevents retraction of the proximal tendon end after distal transection of an extensor. Complete severance of an extensor proximal to the juncturae can be associated with normal MCP joint extension.[7] This extension occurs through the juncturae connections. The extensor digitorum communis tendons can be evaluated by asking the patient to straighten out all of the fingers. The function of the extensor indicis proprius can be isolated from the common extensors by asking the patient to make a fist and then to point the index finger. The extensor digiti minimi is examined by having the patient straighten the little finger while the hand is closed into a fist.

The extensor mechanism of each digit is a complex interrelationship of muscle-tendon units of the long extrinsic extensor tendons and the intrinsic system (Fig. 50-15). The extensor expansion divides into a central slip that attaches to the middle phalanx and two lateral bands that join with the tendons of the lumbrical and interosseous muscles and attach to the base of each distal phalanx. The interossei and lumbrical muscles insert in the lateral aspects of the dorsal hood. Most of the power of the common extensors serves to extend the MCP joint. Distal digit extension is provided by continuation of the lateral band mechanism and the oblique retinacular ligament. Because of this complex anatomy, injuries involving the extensor mechanism require meticulous repair.

The sixth compartment contains the extensor carpi ulnaris. This tendon passes distal to the head of the ulna on the ulnar aspect of the wrist and inserts on the base of the little finger metacarpal. The extensor carpi ulnaris functions to extend and deviate the wrist ulnarly. This tendon is evaluated by having the patient extend and push the hand to the ulnar side against resistance; the tendon can be palpated distal to the ulnar styloid process.

Flexor Tendons. The flexor tendons reside on the volar side of the forearm and cross the wrist joint volar to its axis. In general, 12 tendons function to flex the wrist and digits; three of them—the flexor carpi radialis, flexor carpi ulnaris, and palmaris longus—primarily flex the wrist and deviate the wrist radially or ulnarly (Fig. 50-16). The remaining tendons pass into the digits through the carpal tunnel. A single tendon, the flexor pollicis longus, inserts on the distal phalanx of the thumb, and two flexor tendons go to each remaining finger. The flexor digitorum superficialis (FDS) tendons bifurcate near the base of the proximal phalanges and surround the tendons of the FDP before inserting on the middle phalanges of the index, middle, ring, and little fingers (Fig. 50-17). The FDS flexes all the joints it crosses, including the wrist, PIP joints, and MCP joints. The profundus tendons lie deep to the superficialis tendons over most of their course in the forearm. At the level of the MCP joint, they perforate the superficialis tendon to emerge to a superficial position. They insert at the base of the distal phalanx and act primarily to flex the DIP joint and all joints flexed by the FDS. From the level of the MCP joint distally, the two flexor tendons become enclosed in a fibrous flexor sheath lined by synovium. Regions of thickening in this sheath form pulleys that help prevent bowstringing of the flexor tendons across the joint and assist smooth, effective flexion (Fig. 50-18).

www.ketabpezeshki.com 66485457-66963820

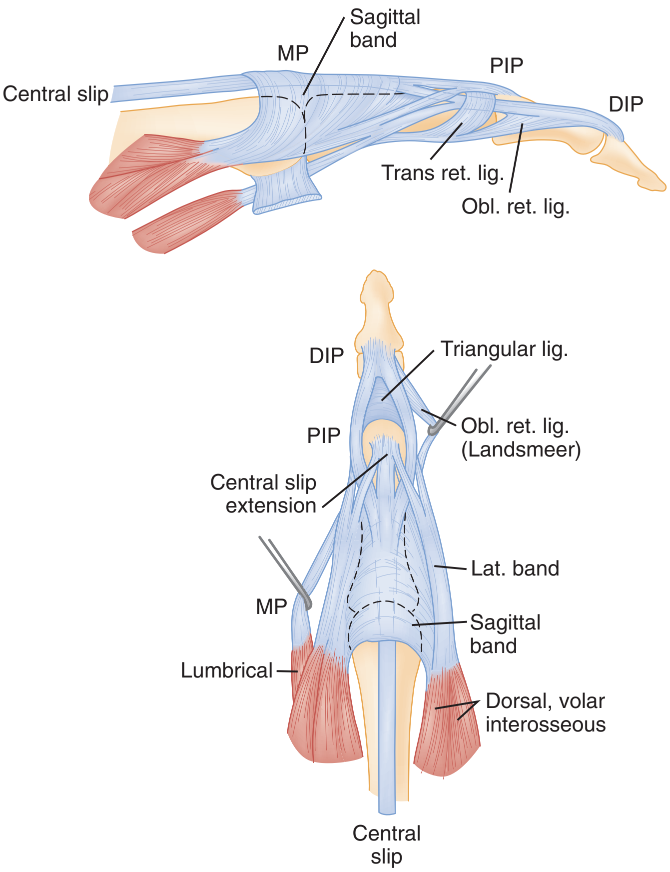


Figure 50-15. The extensor tendon at the metacarpophalangeal *(MP)* joint level is held in place by the transverse lamina or sagittal band, which tethers and centers the extensor tendons over the joint. This sagittal band arises from the volar plate and the intermetacarpal ligaments at the neck of the metacarpals. Any injury to the extensor hood or expansion may result in subluxation or dislocation of the extensor tendon. The intrinsic tendons from the lumbrical and interosseous muscles join the extensor mechanism at approximately the level of the proximal and middle portion of the proximal phalanx and continue distally to the distal interphalangeal *(DIP)* joint of the finger. The extensor mechanism at the proximal interphalangeal *(PIP)* joint is best described as a trifurcation of the extensor tendon into the central slip, which attaches to the dorsal base of the middle phalanx and the two lateral bands. These lateral bands continue distally to insert at the dorsal base of the distal phalanx. The extensor mechanism is maintained in place over the PIP joint by the transverse retinacular ligaments. (From Doyle JR: Extensor tendons-acute injuries. In Green DP [ed]: Operative Hand Surgery. New York, Churchill Livingstone, 1993, p 1928.)

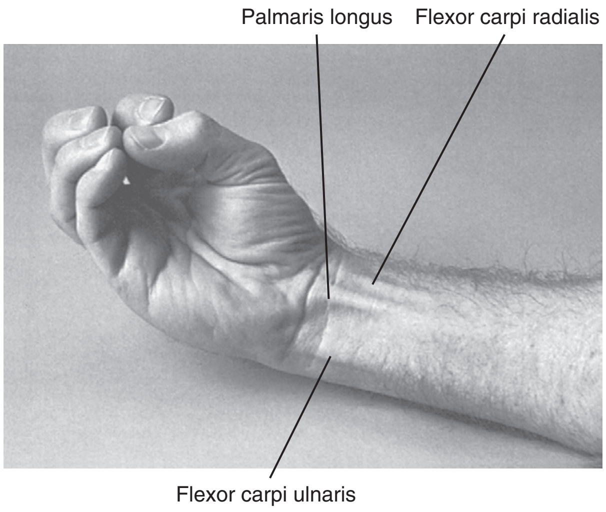


Figure 50-16. Palmaris longus accentuation.

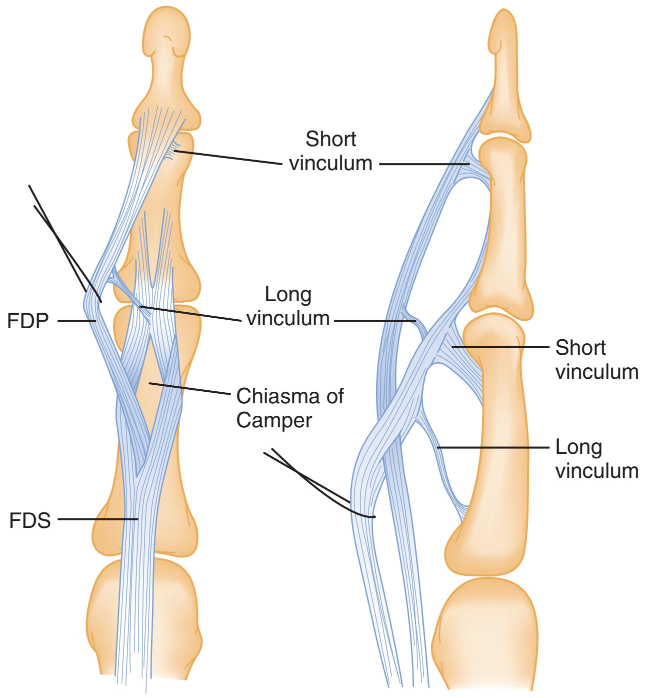


Figure 50-17. Anatomy of flexor digitorum superficialis *(FDS)* and profundus *(FDP)* in the finger. (From Schneider LH: Flexor Tendon Injuries. Boston, Little, Brown, 1985.)

After observation, each muscle-tendon unit is tested with a functional examination. The flexor carpi radialis, palmaris longus, and flexor carpi ulnaris are tested together by having the patient flex the wrist against resistance while the examiner palpates the individual tendons. The tendon of the flexor pollicis longus attaches to the base of the distal phalanx of the thumb and flexes the thumb MCP and IP joints. This tendon is tested by having the patient bend the tip of the thumb against resistance. FDP function can be tested by having the patient flex the distal phalanx of each finger while the PIP is stabilized in extension by the examiner (Fig. 50-19). The FDS is tested individually by asking the patient to flex the PIP joint while the other fingers are held in extension to block the flexion produced by the profundus tendons (Fig. 50-20). This is a subtle but important distinction, because lacerations of the digital creases can easily damage one or more of the tendons or adjacent neurovascular bundles. The FDP is more commonly lacerated in the finger because of its paradoxically superficial position.

If movement against resistance is intact but accompanied by pain or diminished strength, the involved tendon may be partially disrupted. Pathologic nodular swelling of one of the long flexor tendons may result in intermittent catching, or "triggering," on a thickened flexor sheath anterior to the MCP joint. In this condition, known as *trigger finger,* a palpable and sometimes audible snapping can be appreciated when the patient is asked to flex and extend the fingers. On occasion, the patient may need to break the triggering effect by directly palpating the affected joint with the opposite hand.

Synovial Spaces. Bursae are synovial sheaths that cover tendons as they pass through osseofibrous tunnels. They contain synovial fluid and serve two essential functions: They decrease friction during tendon movement, and they help supply nutrients to the

www.ketabpezeshki.com 66485457-66963820

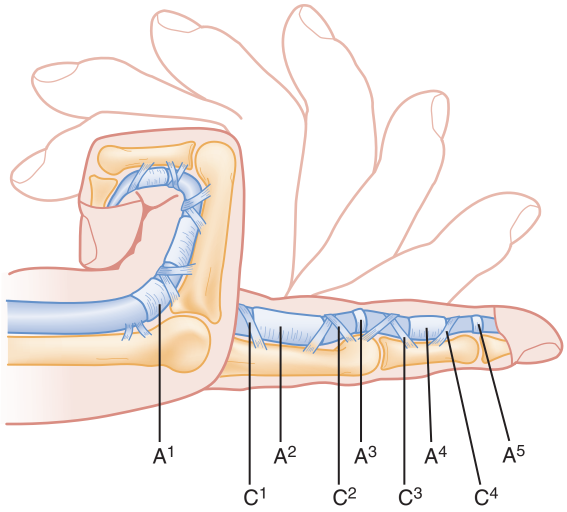


Figure 50-18. The flexor pulley system. The pulleys are thickenings in the fibrous flexor sheath. There are five annular pulleys (transversely oriented fibers) (A^1 to A^5). There are four cruciate pulleys (oblique with some crisscrossing fibers) (C^1 to C^4). (Courtesy Kleinert, Kutz and Associates Hand Care Center.)

Figure 50-19. To test for an intact profundus tendon, the examiner maintains the digit in extension while the patient attempts to flex the terminal phalanx.

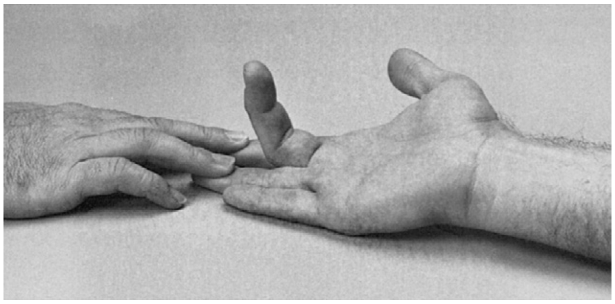


Figure 50-20. Examination to assess function of the flexor digitorum superficialis.

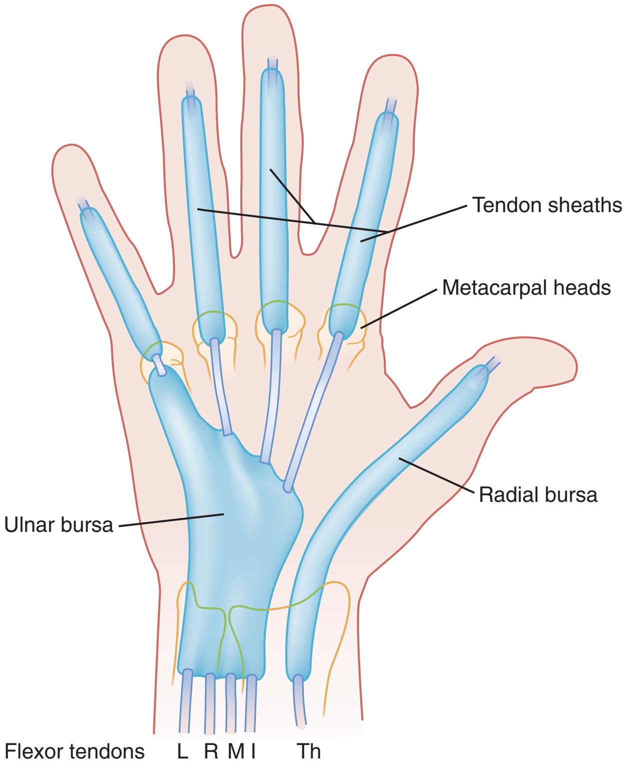


Figure 50-21. Radial and ulnar bursae and their relation to flexor tendons and to each other. *I,* index finger; *L,* little finger; *M,* middle finger; *R,* ring finger; *Th,* thumb. (From Siegel DB, Gelberman RH: Infections of the hand. Orthop Clin North Am 19:779, 1988.)

relatively avascular tendons (Fig. 50-21). These sheaths also can provide pathways for spread of infection. Extensor tendons do not lie within definite sheaths and are afforded a greater resistance to infections. The synovial sheaths of the flexors in the index, middle, and ring fingers are enclosed from their insertion to approximately the level of the distal palmar crease. The sheath of the flexor pollicis longus extends from the tip of the thumb to the proximal volar wrist crease, where it communicates with the radial bursa in the palm and carpal tunnel. Similarly, the synovial sheath of the little finger communicates with the ulnar bursa. Clinical features of flexor tenosynovitis are caused by inflammation and distention of these synovial sheaths. Kanavel[12] described the classic signs: a semiflexed posture of the digit, pain on passive extension of the digit, fusiform swelling, and tenderness of the synovial sheath.

Blood Supply

Arterial System. The hands and the digits have a dual blood supply (Fig. 50-22). The major blood supply to the hand is from the radial and ulnar arteries. The radial artery lies on the anterior aspect of the radius in the distal part of the forearm. It continues around the lateral side of the wrist onto the dorsum of the hand by passing deep to the tendons of the abductor pollicis longus and the extensor pollicis brevis. On entering the palm, the radial artery terminates as the deep palmar arch. The ulnar artery enters the hand anterior to the flexor retinaculum on the radial side of the ulnar nerve and pisiform bone. The artery gives off a deep branch and then continues into the palm as the superficial palmar arch. This complex arterial arch system anastomoses and sends branches to the individual digits and the deep palmar spaces. Because of extensive collateralization, the hand usually survives even if both vessels are transected at the wrist.[13] The circulation of the hand is evaluated by palpation of the radial and ulnar arteries on the volar aspect of the wrist, by assessment of the color and warmth of the skin, and by testing of capillary refill. Because "normal" findings vary among patients, the injured hand should be compared with the unaffected side.

Although Allen's test is an imperfect predictor of vascular compromise, it is commonly used to determine the patency of the arteries supplying the hand and the contributions to the circulation of the hand derived from each of the major vessels. The radial and ulnar arteries are compressed by the examiner at the wrist (Fig. 50-23). The patient opens and closes the hand repeatedly to

www.ketabpezeshki.com 66485457-66963820

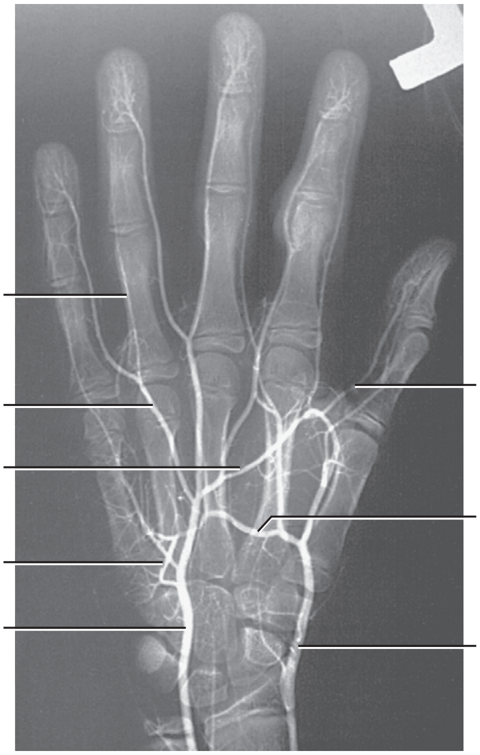


Figure 50-22. Arteriogram of the hand. The ulnar artery is the principal contributor to the superficial palmar arch. (Courtesy Dr. D. Armstrong, Associate Professor of Radiology, University of Toronto, Ontario, Canada.)

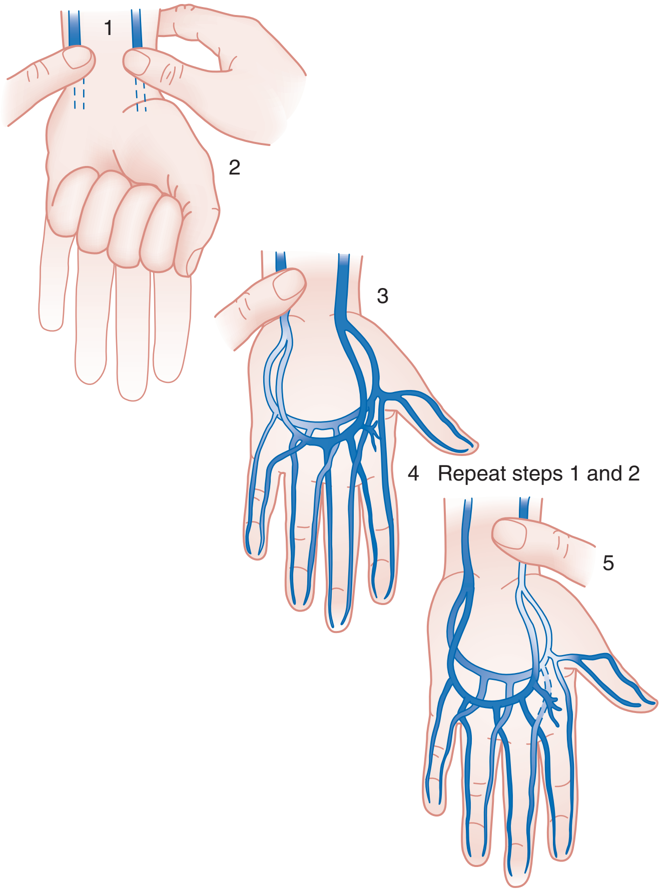


Figure 50-23. Allen's test. (From American Society for Surgery of the Hand: The Hand: Examination and Diagnosis, 3rd ed. New York, Churchill Livingstone, 1990, p 46.)

exsanguinate it and then maintains a relaxed position. The radial artery is released. If the palm and fingers fill immediately with blood, the radial artery is patent, with good collateral flow into the ulnar artery system. To evaluate the ulnar artery, the same steps are repeated, but the ulnar artery is released. This method also can be used on a single digit to help evaluate the patency of each digital artery to that finger. Unilateral digital artery injuries may be well tolerated owing to adequate collateral circulation from the uninjured side. Bilateral digital artery injuries, although rare, tend to have poor outcomes.[13,13a,13b]

Venous and Lymphatic Systems. The veins generally follow the arterial pattern in the deep system. The abundant dorsal, superficial veins are more extensive than the deep system and drain most of the blood from this region. The lymphatic vessels essentially follow the veins, with most lymph flowing into channels in the dorsal subcutaneous space. This vascular anatomy and the laxity of the dorsal skin account for palmar infections causing swelling on the dorsum rather than on the palmar surface of the hand.

Nerve Supply

The nerve supply to the hand comes from the radial, ulnar, and median nerves. All three nerves control movement of the wrist, fingers, and thumb. In the hand, the ulnar and median nerves are mixed motor and sensory nerves, whereas the radial nerve is purely sensory. Each of the three major nerves passes through a muscle in the forearm, and each passes points of potential entrapment en route to the hand.

Motor Innervation. The radial nerve (formed from nerve roots C6 through C8) passes through the supinator muscle and enters the dorsal aspect of the wrist between the radial styloid and Lister's tubercle. At this level, the nerve has a purely sensory function. Its important motor function is to innervate the dorsal extrinsic muscles in the forearm, which extend the wrist and MCP joints and abduct and extend the thumb. No intrinsic muscles in the

www.ketabpezeshki.com 66485457-66963820

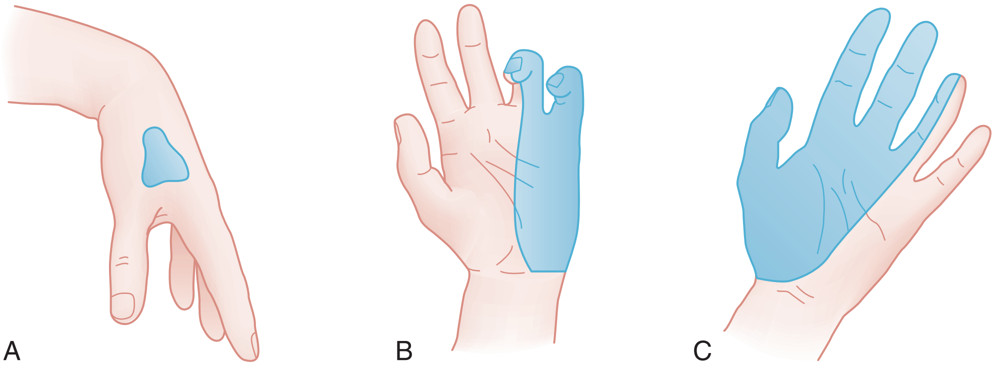


Figure 50-24. Deformities of the hand. **A,** Radial palsy—wristdrop. **B,** Ulnar nerve palsy—*main en griffe* (clawhand). **C,** Median nerve palsy—*main en singe* ("monkey hand"). The shaded areas represent the usual distribution of anesthesia. (From Ellis H: Clinical Anatomy: A Revision and Applied Anatomy for Clinical Students, 7th ed. Oxford, UK, Blackwell Scientific, 1983.)

hand are innervated by the radial nerve. Motor function in this nerve is tested by having the patient extend the wrist against resistance. Proximal injury to the radial nerve causes a condition known as *wristdrop:* The fingers are held in flexion at the MCP joints, and the thumb is adducted (Fig. 50-24A).

The ulnar nerve (C7, C8, and T1) passes through the flexor carpi ulnaris muscle in the forearm and lies ulnar to the artery and superficial to the flexor retinaculum. It enters the hand at the wrist through the ulnar tunnel, or Guyon's canal. The ulnar nerve innervates the hypothenar muscles, the seven interosseous muscles, the lumbrical muscles to the ring and little fingers, and the adductor pollicis. Innervation of the flexor pollicis brevis is variable. In the forearm, the flexor carpi ulnaris and the ulnar half of the FDP also are innervated by the ulnar nerve. Loss of motor function of the ulnar nerve results in inability to pinch a piece of paper tightly between the thumb and the index finger. A late characteristic of distal ulnar damage is Duchenne's sign, manifested by clawing of the ring and little fingers (see Fig. 50-24B). The ring and little fingers are hyperextended at the MCP joints by the extensor digitorum communis (radial nerve) and flexed at the IP joints by the FDP (intact proximal ulnar nerve). In addition, the interosseous and hypothenar muscles are atrophied.

The median nerve enters the forearm through the pronator teres muscle. At that level, it innervates that muscle, the flexor carpi radialis, the FDS, the radial part of the FDP, the flexor pollicis longus, and the pronator quadratus. The branch of the median nerve that innervates the last three muscles is called the *anterior interosseous nerve.* The median nerve enters the hand through the carpal tunnel accompanied by the nine extrinsic flexor tendons of the digits. The thenar motor branch (recurrent median nerve) innervates the abductor pollicis brevis, the opponens pollicis variably, and the flexor pollicis brevis. Common digital branches innervate the lumbrical muscles to the index and long fingers. Injury to this nerve occurs most commonly at the level of the wrist, by laceration or by compression in the carpal tunnel. Motor function is tested by having the patient appose the thumb to the index digit. Injury to the median nerve in the upper forearm or at the elbow usually results in weakness or absence of flexion of the index finger distal phalanx, the middle phalanx, and the thumb and weakness of thumb abduction and opposition. With passage of time, the muscles of the thenar eminence atrophy, leaving the hand with a flattened and "apelike" appearance (see Fig. 50-24C).

Sensory Innervation. The typical distribution of the sensory nerves to the hand is shown in Figure 50-25. Because some overlap occurs between various sensory nerves, it is preferable to test sensation in the areas least likely to have dual innervation. The anatomic area of least ulnar variation and overlap is the volar tip of the little finger. The median nerve exclusively innervates the volar tip of the index finger. The dorsal first web space is entirely within the radial nerve distribution.

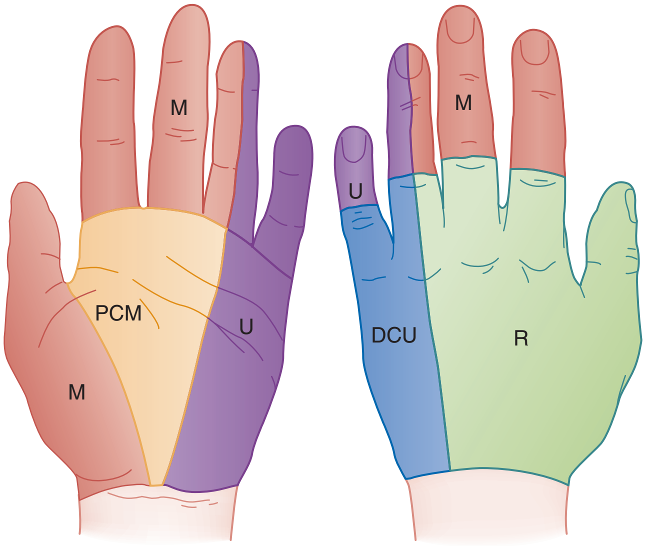


Figure 50-25. The cutaneous nerve supply in the hand. *Left*, Palmar aspect; *right*, dorsal aspect. *DCU,* dorsal cutaneous branch of ulnar nerve; *M,* median; *PCM,* palmar cutaneous branch of median nerve; *R,* radial; *U,* ulnar. (Courtesy Kleinert, Kutz and Associates Hand Care Center.)

Several methods exist to assess sensation. Two-point discrimination is one such method, although both the accuracy and objectivity of this test have been called into question.[14] An uninjured hand is able to distinguish two points that are 2 to 5 mm apart at the fingertips and 7 to 10 mm apart at the base of the palm. The dorsum of the hand is the least sensitive region, with a normal threshold at 7 to 12 mm. Two-point threshold distances wider than these ranges indicate impaired sensory function.[14] The threshold and two-point discrimination tests may be of limited value in children, patients with heavily calloused fingertips, uncooperative patients, comatose patients, patients in severe pain, or suspected malingerers. In such patients, submerging the hand in water and observing the skin for the development of wrinkles has been offered as a way to diagnose nerve impairment because denervated skin will not wrinkle.[15]

Fingertip

The fingertip generally is defined as the area distal to the insertion of the flexor profundus and extensor tendons (Fig. 50-26). The

www.ketabpezeshki.com 66485457-66963820

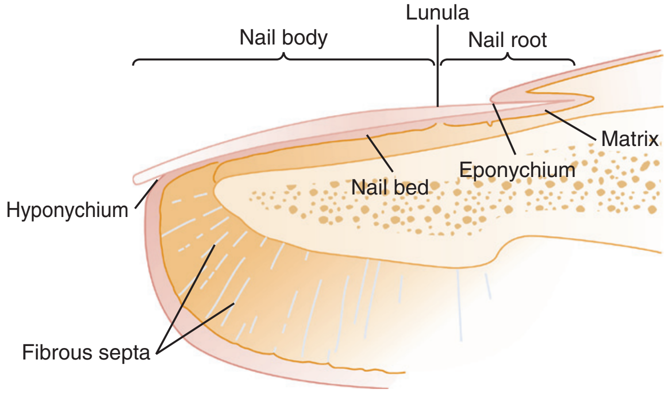


Figure 50-26. Sagittal section of the distal finger, showing structures of the fingertip. (From Siegel DB, Gelberman RH: Infections of the hand. Orthop Clin North Am 19:779, 1988.)

pulp is the tissue of the fingertip between the volar skin and the distal phalangeal bone. The fingertip is well padded by adipose tissue and is covered by highly innervated skin that is tethered to the distal phalanx by a series of fibrosepta. The dorsal skin is thinner and less vascularized than the volar skin. Sensation is supplied by nerves that travel with arteries bilaterally along the radial and ulnar aspects of the fingers. The arteries branch to form volar anastomoses or arches similar to those in the palm. Dorsal branches supply the nail bed and matrix.

Nail

The nail (or nail plate) consists of compacted scales that originate from cornified epithelial cells. The proximal part of the nail is called the *root;* it emerges from a groove in the skin to form the body of the nail, which is exposed. The root of the nail is covered by a fold in the skin called the *proximal nail fold.* A small portion of the epidermis of the nail fold extends out over the proximal body of the nail to form the cuticle, or *eponychium.* The floor of the nail plate or nail bed is composed of tissue known as the *nail matrix.* The distal skin of the nail bed complex is called the *hyponychium.* The skin overlying the nail laterally is called the *perionychium.* The semicircular white crescent region near the nail fold is called the *lunula.*

The nail bed complex is important in providing additional stabilization of the palmar soft tissues against compression and shear forces. The nail grows from the nail matrix along the nail bed and is firmly adherent to the bed. It is now believed that the entire nail bed is active in the generation and migration of the nail. As new nail forms, it glides forward over the nail bed at a rate of approximately 0.5 to 1.2 mm per week (toenails grow much more slowly). The nail itself is a hard, firm, and relatively translucent structure; the underlying vascular tissue showing through gives the nail its pink appearance. A smooth nail bed is essential to normal function. If the nail bed sustains injury that is not repaired accurately, granulation tissue forms scar that impedes normal nail production and growth. The result may be a split or absent nail that is cosmetically unappealing and sometimes functionally debilitating.[16]

CLINICAL FEATURES: SIGNS AND SYMPTOMS

The initial evaluation of an acutely injured hand is crucial because it affords the best opportunity for accurate assessment of the extent of damage and for restoration of altered anatomy.[17] Evaluation of any hand injury should begin by obtaining the historical

Box 50-1 General Physical Examination of the Hand

- I. General appearance
  - A. Active hemorrhage
  - B. Amputations or avulsions
  - C. Position at rest
- II. Skin
  - A. Integrity
  - B. Moisture
  - C. Swelling or edema
  - D. Discoloration
  - E. Inflammation
  - F. Scars
- III. Vascular
  - A. Color and warmth
  - B. Pulses
  - C. Capillary refill
  - D. Allen's test
- IV. Neurologic
  - A. Motor function
    1. Ulnar nerve—finger abduction and adduction
    2. Radial nerve—wrist extension
    3. Median nerve—flexion of digits I, II, and III; thumb opposition
  - B. Sensory function
    1. Ulnar nerve—tip of digit V
    2. Median nerve—tip of digit II
    3. Radial nerve—dorsal first web space
- V. Bone and joint
  - A. Deformity
  - B. Local tenderness
  - C. Pain with axial compression
  - D. Joint range of motion
  - E. Ligamentous stability: distal interphalangeal, proximal interphalangeal, and metacarpophalangeal joints
- VI. Musculotendinous
  - A. Function of each muscle-tendon group
  - B. Strength against resistance
  - C. Pain with motion

facts of the patient's age, occupation, hand dominance, and previous hand impairment or injury. In traumatic injuries, elapsed time since the injury, mechanism of injury, posture of the hand at the time of injury, and treatment before arrival in the ED all are useful data. In nontraumatic problems, pain, swelling, sensory change, contracture, timing of symptoms, presence of similar symptoms in other extremities, aggravating or alleviating factors, and functional impairment are useful historical points. A review of the medical history and a review of systems complete the evaluation.

After a detailed history is taken, the entire extremity should be exposed and evaluated when the hand is examined. A system of priorities, based primarily on threat to ultimate function, should direct the sequence of the examination. In order of priority, the examination includes evaluation of vascular and neurologic integrity, skin cover, skeletal stability, and joint and tendon function (Box 50-1). The general appearance of the hand should be noted, with focus on its color, presence of swelling or edema, and any abnormal posture or position. In traumatic injuries, the precise area of maximal tenderness should be localized. Rotational, angular, and shortening deformities should be noted with regard to direction and extent. Angular deformity may be seen best with the fingers in full extension. Rotational deformity is best observed during digital flexion. Digital or wrist block anesthesia may be helpful in some cases to accurately assess fracture deformity and stability during digital motion and, if necessary, stress testing. Open wounds should be assessed with regard to location, relationship to skin creases, direction and viability of skin flaps, extent of skin loss, degree of contamination of the wound, and extent of

www.ketabpezeshki.com 66485457-66963820

soft tissue injury. The examiner should have good light, adequate exposure, and a nearly bloodless field for a thorough evaluation. The complete examination also may require an evaluation of active shoulder motion, elbow motion, and pronation and supination of the forearm and assessment of the contralateral hand.

DIAGNOSTIC STRATEGIES: RADIOLOGY

Despite the development of numerous new and sophisticated imaging techniques, plain radiography remains the most important imaging modality for the hand and wrist. The standard radiographic series of the hand should include a posteroanterior, a true lateral, and an oblique projection (Fig. 50-27). With correct positioning, the bones do not overlap on the film, allowing complete evaluation of each area for visualization of fractures, subluxation, dislocation, deformities, and retained radiopaque foreign bodies.[18] On a hand series, the wrist is not properly positioned for radiographic examination, and vice versa; if the patient has injuries to the hand and wrist, separate radiographic series should be obtained.

For an adequate posteroanterior view, the forearm and hand should be fully pronated so that the palm rests flat on the film. This view forms the basis for all assessments but is poor at showing fractures of the articular surface of the metacarpal head. The lateral view normally is a radioulnar projection and is made by positioning the palm and forearm at 90 degrees to the film with the fingers splayed. This view is essential to show displacement of

Figure 50-27. Normal hand radiographs. **A,** Anteroposterior view. **B,** Lateral view. **C,** Oblique view. The hand is routinely examined in three different planes to identify fractures that may escape detection on the usual anteroposterior and lateral views because of overlapping bony structures. (From Rosen P, et al: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1992, p 179.)

www.ketabpezeshki.com 66485457-66963820

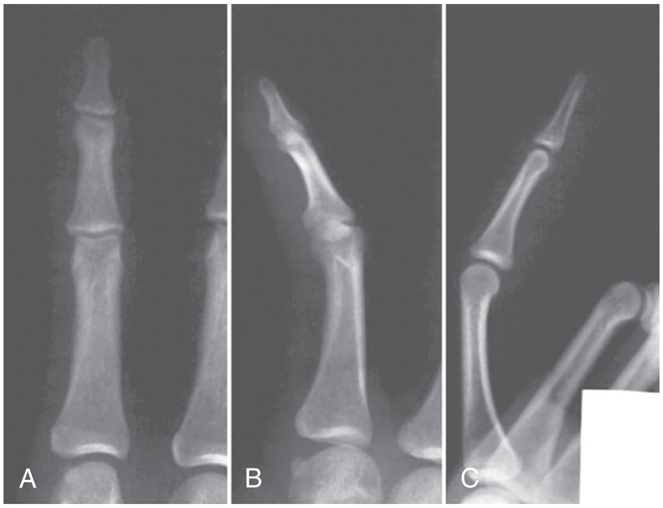


Figure 50-28. Normal radiographic appearance of fingers of three different patients.

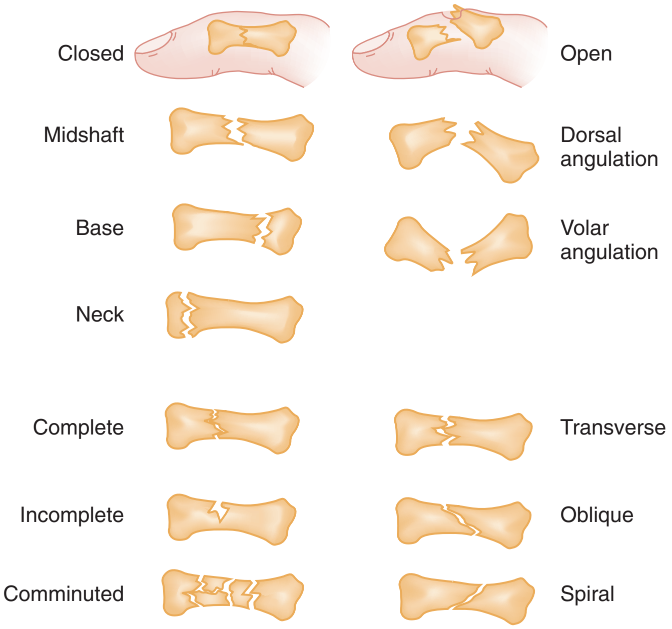


Figure 50-29. Fracture terminology. (From Idler RS, et al [eds]: The Hand: Examination and Diagnosis, 3rd ed. New York, American Society for Surgery of the Hand, 1990, p 64.)

fracture fragments and joint dislocations. If the projection is not a true lateral view, joint dislocation, avulsion fractures, or fractures through the articular surface of the base of the phalanx may be overlooked. The oblique view is obtained with the hand and forearm pronated at 45 degrees to the film. It is particularly useful for assessing dislocation of the MCP and CMC joints and fractures at the base of the metacarpal bones. When injury is confined to the distal end of a single digit, radiologic evaluation should be limited to that digit, but the same projections are used (Fig. 50-28).

Special views are used to diagnose specific injuries. The standard views of the hand do not give true posteroanterior and lateral projections of the thumb because the plane of the thumb is at 90 degrees to that of the fingers. Separate posteroanterior and lateral views of the thumb should be requested. The posteroanterior projection of the thumb is obtained with the hand and forearm hyperpronated so that the dorsal surface of the thumb and the thumb metacarpal rests flat on the film. The lateral view is obtained by pronating the hand and forearm to allow the lateral surface of the thumb to lie on the film. Stress views are used most often to rule out ligamentous injury to the first MCP joint. Localized widening of the joint space or subluxation may indicate a significant collateral ligament injury. Plain radiographs taken in multiple projections can help detect and localize soft tissue foreign bodies. Whether an object can be visualized will depend on its composition, configuration, size, and orientation. Many foreign bodies encountered in the ED, including almost all glass, are more dense than soft tissue and can be readily seen on plain radiographs.[19] Plastic and wood foreign bodies are notable exceptions, with many of these objects being radiolucent.

MECHANISMS OF INJURY AND MANAGEMENT

Trauma

The bones of the hand are the most commonly fractured bones in the body. Radiologic evaluation of significant hand injuries is mandatory. Any hand injury that causes swelling should be evaluated radiographically with a minimum of three views. Although the classification of hand fractures is difficult and at times confusing, it generally is done according to the nature and site of the fracture line and whether the fracture is open or closed (Fig. 50-29).

A fracture is unstable if it cannot be reduced or maintained in an anatomic or near-anatomic position without fixation when the hand is placed in the "safe" or functional position. The four principal determinants of fracture stability or instability are (1) fracture configuration, (2) integrity of the periosteal sleeve and surrounding soft tissues, (3) muscle balance or imbalance, and (4) external forces.

In general, transverse fractures have a stable configuration. Spiral, oblique, and comminuted fractures are unstable. The degree of displacement also is an indicator of potential fracture instability. Fractures of inherently unstable configuration may be stable if they are nondisplaced or only minimally displaced because the periosteum is undamaged or minimally disrupted. Displacement is defined by the deformity it creates and can result in rotation, angulation, shortening, or a combination of these fractures. Although shortening has an adverse effect on muscle tension, the hand accommodates more easily to this component of deformity than to others.[18]

Definitive management of many hand fractures is controversial and beyond the scope of this discussion. The emphasis here is on appropriate initial interventions, including proper splinting techniques to minimize morbidity, and recognition of which fractures may require operative fixation and their potential complications. Most closed injuries may be treated initially in the ED. Most open, intra-articular, periarticular, and unstable fractures require operative management by a hand surgeon.

Distal Phalanx Fractures

Pathophysiology and Clinical Features

Fractures of the distal phalanx are the most common fractures of the hand. They occur most often as a result of crush or shearing forces, usually as a sports-related injury in children and adolescents, industrial accidents in adults, or accidental falls in elderly persons.[20] Distal phalangeal fractures are classified as extra-articular fractures (longitudinal, transverse, and comminuted) or intra-articular fractures. The most common location for these

www.ketabpezeshki.com 66485457-66963820

Figure 50-30. Tuft fracture of the distal phalanx of the thumb, anteroposterior view. This radiograph reveals the comminuted displaced fracture fragments and some radiopaque foreign material on the substance of the nail. (From Rosen P, et al: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1992, p 180.)

fractures is the distal tuft (Fig. 50-30). Because the mechanism of injury is usually direct trauma, tuft fractures often are comminuted and usually are associated with soft tissue injury to the nail, nail bed, and nail matrix.[21] Supporting fibrous septa that radiate from the bone to the skin prevent displacement of fracture fragments and act to contain soft tissue swelling, contributing to the severe pain that can accompany these fractures. Examination typically reveals tenderness and swelling over the distal phalanx, including the pulp.

Fractures at the base of the distal phalanx may be associated with tendon avulsion. The flexor profundus tendon attaches to the volar aspect of the index, middle, ring, and little fingers, and the terminal slip of the extensor tendon attaches on the dorsal surface of the distal phalanx. In the distal phalanx of the thumb, the flexor pollicis longus inserts on the volar base, and the extensor pollicis longus inserts on the dorsal base. These tendons can avulse when subjected to excessive stress. Clinically, loss of function is evident, and small avulsion fractures along the dorsal or volar surface may be seen on radiographs. These fractures are considered intra-articular, and their management is as for other tendon injuries.

Management

Treatment of most fractures of the distal phalanges is directed toward the accompanying soft tissue injury. Closed tuft fractures need only symptomatic treatment with elevation (to reduce swelling) and analgesics. Fracture immobilization is rarely necessary; however, a short volar splint or hairpin splint (Fig. 50-31) is recommended for 2 to 3 days to protect the tip of the finger from further trauma and allow swelling without constriction. Immobilization should not include the PIP joint. Transverse shaft fractures with angulation or displacement may be irreducible because of interposition of soft tissue. Closed reduction may be attempted

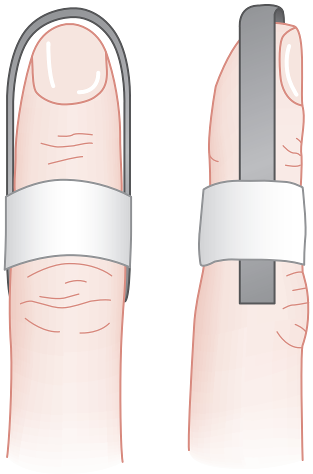


Figure 50-31. The hairpin splint used for distal phalangeal fractures. (From Simon RR, Koenigsknecht SJ: The hand. In Simon RR [ed]: Emergency Orthopedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1995, p 59.)

with dorsal traction on the distal fragment followed by immobilization with a volar splint and repeat radiographs for documentation of position. If this approach is unsuccessful, referral to a hand surgeon is indicated for Kirschner wire fixation.[21]

Distal phalangeal fractures associated with nail bed laceration are considered open fractures. This may be obvious if the nail has been avulsed or torn, but recognition of nail bed laceration is more difficult in closed tuft fractures with an intact nail despite presence of a subungual hematoma. Subungual hematomas often are associated with occult lacerations of the nail bed, and in such cases removal of the nail for accurate assessment and laceration repair uncommonly may be required.

Complications

Distal phalanx fractures generally are uncomplicated; however, distal phalanx fractures that appear innocuous can result in prolonged morbidity, especially if associated with soft tissue crush injury. In a long-term follow-up series, DaCruz and associates[22] showed that at 6 months 31% of tuft fractures had not healed radiographically and 70% of all patients had bothersome symptoms, including numbness, hyperesthesia, and cold sensitivity. Trauma to the nail bed may result in abnormal nail growth despite exact tissue approximation. Failure to recognize and extricate an entrapped nail bed in the fracture site may result in nonunion of the fracture. Osteomyelitis from open fractures is a rare but potentially serious complication.

Proximal and Middle Phalangeal Fractures

Pathophysiology and Clinical Features

Because the anatomy, mechanism of injury, and treatment for proximal and middle phalangeal fractures are similar, these fractures are discussed together. The proximal phalanx has no tendinous attachments. Fractures in this region have a typical volar angulation resulting from forces exerted from the extensors and the interosseous muscles. The middle phalanx has two important insertions. The tendon of the FDS divides and inserts along nearly the entire volar surface of the phalanx, and the extensor tendon inserts on the proximal dorsal base of the middle phalanx. Because of this alignment, fractures at the base of the middle phalanx usually result in dorsal angulation, and fractures at the neck of the

www.ketabpezeshki.com 66485457-66963820

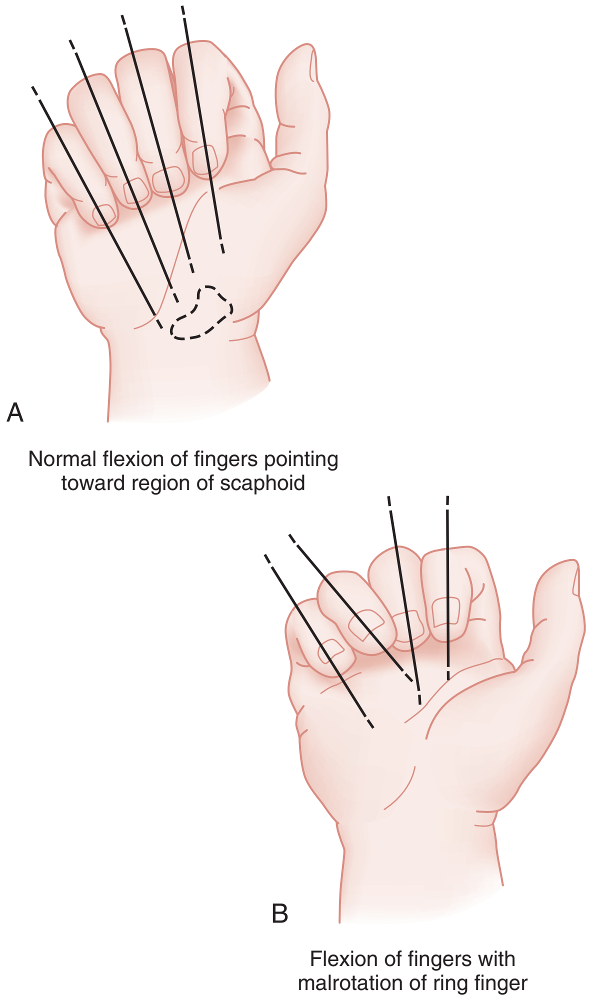


Figure 50-32. Any malrotation of a metacarpal or phalangeal fracture should be corrected. **A,** Normally all fingers point toward the region of the scaphoid when a fist is made. **B,** Malrotation at fracture causes the affected finger to deviate. (From Jobe MT, Calandruccio JH: Fractures, dislocations and ligamentous injuries. In Canale ST [ed]: Campbell's Operative Orthopedics, 10th ed. St. Louis, Mosby, 2003, p 3484.)

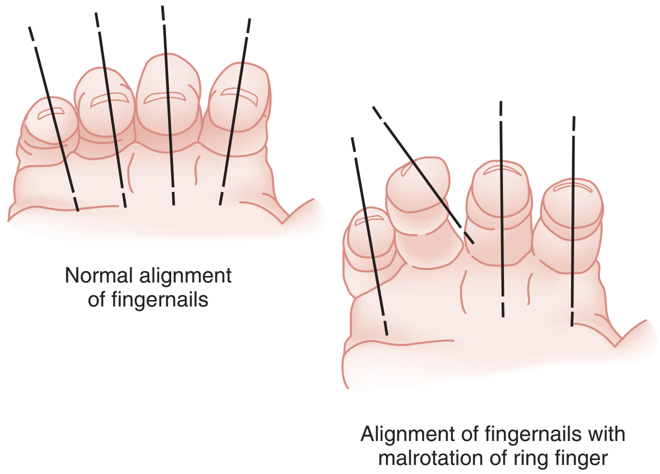


Figure 50-33. Observing the plane of the fingernails helps detect any malrotation at the fracture. (From Jobe MT, Calandruccio JH: Fractures, dislocations and ligamentous injuries. In Canale ST [ed]: Campbell's Operative Orthopedics, 10th ed. St. Louis, Mosby, 2003, p 3484.)

middle phalanx usually result in volar angulation.[23] The mechanism of injury often determines the nature of the fracture; a direct blow is more likely to cause a transverse or comminuted fracture, whereas a twisting injury more often results in an oblique or spiral fracture. Associated injuries may include contusion or transection of digital nerves, vascular disruption, and tendon rupture.

Intra-articular fractures include condylar fractures; comminuted fractures; dorsal, volar, or lateral base fractures; fracture-dislocations; and shaft fractures involving the joint. Extra-articular fractures involve the neck, shaft, or base of the phalanx. Although most phalangeal fractures may be easily seen, condylar fractures and displaced neck fractures are not always apparent on anteroposterior radiographs; oblique views may be needed to identify them.[24] Rotational deformities are difficult to determine by radiologic study but may appear on the lateral view as discrepancies in the diameter of the shaft at the fracture site.

Skeletal alignment can be assessed radiographically, but rotational alignment should be judged clinically by the relationship of the finger to adjacent normal fingers (Fig. 50-32). Symmetrical flexion of adjacent injured and normal fingers at their MCP and PIP joints is the best possible guide to accurate rotational alignment of the injured segment.[23] Normally, all of the fingers of the closed fist except the thumb should point to the scaphoid. Alternatively, when the fingers are loosely flexed, the nails of opposing digits should lie in the same parallel plane (Fig. 50-33). The uninjured hand should be used for comparison.

Management

Similar to metacarpal fractures, phalangeal fractures require precise anatomic alignment to ensure a good result because of the intimate relationship of the flexor and extensor tendons to the phalanx.[23] Appropriate treatment selection depends on accurate assessment of fracture stability. The angle of the fracture is an important factor in determining this stability. Transverse fractures usually are stable, whereas oblique fractures are inherently unstable. It also is important to ascertain whether the fracture has been impacted or displaced and what deforming forces are acting on it. If there is any question of the fracture's stability, the digit should be anesthetized, and stress should be applied. Reduction of phalangeal fractures usually is not necessary because most are stable and nondisplaced.[17] Patients with such fractures should be started on early protected motion as soon as pain subsides (within the first 3 to 5 days). Protection is provided by taping the injured digit to an adjacent, larger normal finger proximally, a form of *dynamic splinting.* This technique, known as "buddy-taping," encourages the patient to move the finger and use the hand as normally as possible while the fracture heals (Fig. 50-34).

If the fracture is displaced or unstable, it is not suitable for dynamic splinting. In general, treatment depends on the type of trauma and the ability to achieve a stable reduction. Phalangeal fractures that are satisfactorily managed by closed reduction can be immobilized by several methods. In such cases it is advisable to immobilize the wrist and the injured finger. Specific types of immobilization include circular cast, the Böhler method of incorporating a cast with an outrigger, gutter splints, and anterior and posterior splints (Fig. 50-35). The period of immobilization of phalangeal fractures should not exceed 3 weeks, to prevent stiffness and to minimize disability. In addition to temporary immobilization, ED management includes ice for comfort, elevation, analgesics, and referral for follow-up care. Repeat radiographs in 7 to 10 days are recommended to ensure that no delayed displacement has occurred.

Unstable fractures that cannot be reduced by closed manipulation and maintained with external splinting require internal fixation. Midshaft transverse fractures tend not to be amenable to closed reduction; similarly, spiral oblique fractures and

www.ketabpezeshki.com 66485457-66963820

intra-articular fractures are inherently unstable and require surgical fixation if a significant portion of the articular surface is involved.[25] Intra-articular fractures of the proximal metaphysis of the middle phalanx that have extreme comminution may require treatment in static or dynamic traction or external fixation with or without ancillary Kirschner wire fixation.[25]

Complications

Malunion is the most common bony complication of phalangeal fractures and may result from malrotation, volar or lateral angulation, or shortening. Malrotation usually is seen after oblique or spiral fractures of the proximal and middle phalanges and may require osteotomy through the phalanx or metacarpal for correction. Volar angulation of proximal phalangeal fractures greater than 25 to 30 degrees results in pseudoclawing. This deformity makes use of the hand awkward and is esthetically unacceptable. Other potential complications include diminished motion resulting from tendon adhesions and stiffness of the PIP joint after intra-articular fractures with incongruity.[23]

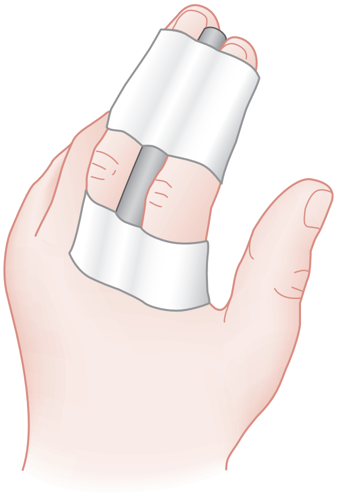


Figure 50-34. The injured finger is splinted to the adjacent normal finger. This splint provides support for the injured digit while permitting motion of the metacarpophalangeal joint and some motion at the interphalangeal joint. A piece of felt cut to the proper size is inserted between the fingers, and the two digits are taped together as shown. (From Simon RR, Koenigsknecht SJ: The hand. In Simon RR [ed]: Emergency Orthopedics: The Extremities, 3rd ed. Norwalk, Conn, Appleton & Lange, 1995, p 518.)

Metacarpal Fractures

Metacarpal fractures generally are divided into two groups: fractures involving the thumb metacarpal and fractures involving metacarpals of the index, middle, ring, and little fingers. This distinction is based on the fact that the base of the thumb metacarpal is biomechanically distinct from the remaining metacarpals because of its high degree of mobility. For this reason, these two groups are discussed separately.

Metacarpal Fractures of the Index, Middle, Ring, and Little Fingers

The hand can adjust functionally to dorsal angulation in the metacarpal equal to its motion at the CMC joint, plus 10 to 15 degrees in some patients. Because the index and middle fingers are immobile at their CMC joints, they may accommodate only 10 to 15 degrees of dorsal angulation. The ring finger usually has 20 to 30 degrees of mobility at its CMC joint and may accommodate 40 to 45 degrees of dorsal angulation. The small finger generally has 30 to 50 degrees of motion at its base and may accommodate 50 to 70 degrees of dorsal angulation. Finger metacarpals may tolerate 10 to 15 degrees of lateral angulation and 3 to 4 mm of shortening. Rotational deformity, most commonly seen in spiral and oblique fractures, is poorly tolerated. A small amount of rotational deformity can translate into a substantial digital overlap when the fingers are closed to form a fist. Just 10 degrees of malrotation may cause as much as 2 cm of overlapping (scissoring) of the fingers during flexion.[17] Surgical intervention is indicated with 2 to 3 mm of shortening, 1 mm of articular surface step-off, greater than 25% articular involvement, or any degree of malrotation.[23]

Metacarpal Head Fractures

Pathophysiology. Fractures of the metacarpal head are rare. They usually occur as a result of direct trauma or crush injury and typically are comminuted.[21] These fractures occur distal to the attachment of the collateral ligaments. Physical examination reveals tenderness and swelling over the involved MCP joint. Pain is increased if axial compression is applied along the extended digit. The presence of lacerations over the metacarpal heads is significant and suggests the possibility of an open fracture potentially caused by human bite injury.

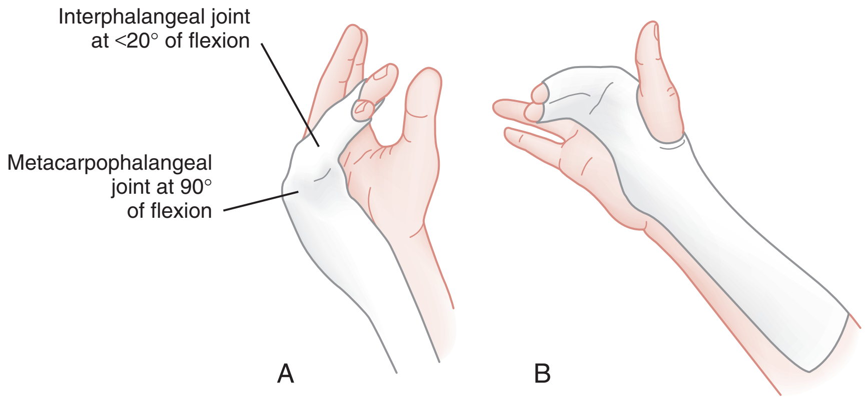


Figure 50-35. Gutter splints are used for the treatment of phalangeal and metacarpal fractures. **A,** Fractures of the ring and little fingers are immobilized in an ulnar gutter splint. **B,** Fractures involving the index finger and the long finger are immobilized in a radial splint. The splint is made with plaster sheets cut to the proper size. The measurement should be from the tip of the finger to a point two thirds of the way up the forearm. (From Simon RR, Koenigsknecht SJ: The hand. In Simon RR [ed]: Emergency Orthopedics: The Extremities, 3rd ed. Norwalk, Conn, Appleton & Lange, 1995, p 519.)

www.ketabpezeshki.com 66485457-66963820

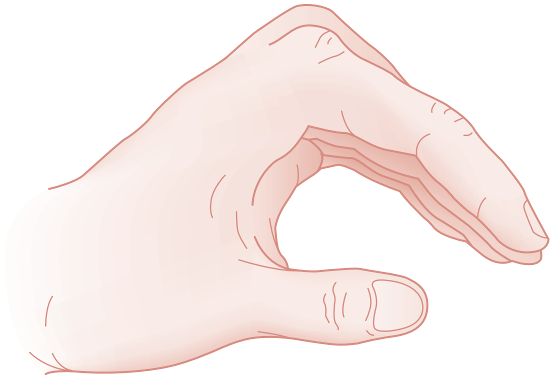


Figure 50-36. The "safe" position described by James. (Adapted from Stern PJ: Fractures of the metacarpals and phalanges. In Green DP [ed]: Green's Operative Hand Surgery, 4th ed. New York, Churchill Livingstone, 1999.)

Diagnostic Strategies: Radiology. Although routine radiographic imaging of the injured hand reveals most fractures, the metacarpal heads can be difficult to assess because of overlap on the lateral view. In such cases in which clinical suspicion of a fracture exists and the initial radiographic appearance is normal, the Brewerton "ball-catcher's" view may be helpful.[26] This view is obtained with the digits in 65 degrees of flexion at the MCP joints and the x-ray beam angled 15 degrees radially, projecting the metacarpal heads in profile. Occasionally, computed tomography also may be required to evaluate accurately the degree of displacement of intra-articular fractures at the MCP level.

Management. Emergency management of closed metacarpal head fractures consists of elevation, ice for comfort, analgesics, and immobilization of the hand in the "safe" or functional position, which balances the forces of the intrinsic muscles. In this position, shown in Figure 50-36, the wrist is extended 20 degrees, the MCP joints are flexed to 90 degrees, and the PIP and the DIP joints are extended. Referral to a hand surgeon for management and follow-up evaluation is required in all cases. Because these are intra-articular fractures, displacement by more than 1 to 2 mm predisposes the patient to a poor result; however, little consensus has been reached regarding optimal definitive treatment.[27]

Lacerations or puncture wounds over the dorsum of the MCP joint associated with a metacarpal head fracture should be considered open until proven otherwise. Such injuries often are caused by a clenched-fist injury and are highly contaminated wounds. Emergent consultation with a hand surgeon for operative débridement and irrigation is recommended. Prophylactic coverage with a cephalosporin is routinely recommended, although patients with highly contaminated wounds should receive penicillin with a β-lactamase inhibitor and an aminoglycoside.[28] Several studies have found preoperative wound cultures to be of no value in predicting the risk of infection or identifying the likely pathogen, and some clinicians have abandoned their use.[29,30]

Complications. Metacarpal head fractures may be associated with debilitating hand complications, including avascular necrosis, rotational malalignment, interosseous muscle fibrosis, extensor tendon injury or fibrosis, and chronic stiffness of the MCP joint. Many of these fractures also may require late arthroplasty.[21]

Metacarpal Neck Fractures

Pathophysiology. Fractures of the metacarpal neck are among the most common fractures in the hand. The mechanism of injury is a direct impaction force (e.g., a punch with a closed fist). A *boxer's fracture* is a fracture of the neck of the little finger metacarpal (Fig. 50-37). Most metacarpal neck fractures have a typical apex dorsal angulation. They are inherently unstable because of the deforming muscle forces and frequent comminution of the volar cortex. Management generally is difficult because of this instability and the difficulty in maintaining reduction.

Figure 50-37. Boxer's fracture *(arrow)*. (From Harris JH Jr, et al: The Radiology of Emergency Medicine. Baltimore, Williams & Wilkins, 1993, p 444.)

Management. For treatment purposes, metacarpal neck fractures are divided into two groups: fractures involving the ring and little finger metacarpals and fractures involving the index and long finger metacarpals. There is considerably more mobility of the metacarpals of the ring and little fingers compared with the index and long fingers. This greater mobility makes them more prone to fracture, and the relative immobility of the index and long finger metacarpals increases the need for accurate alignment after reduction. In general, less than 15 degrees is allowed in the index and long finger metacarpals; in the ring and little finger metacarpals, 35 degrees and 45 degrees of angulation, respectively, are allowed. Any rotational malalignment should be completely corrected.

Nondisplaced ring and little finger metacarpal fractures without angulation deformity can be treated initially with ice, limb elevation, analgesia, and immobilization in a gutter splint. Nondisplaced, nonangulated metacarpal fractures of the index and long finger metacarpals are treated similarly. The splint should be in standard position of function and extend from below the elbow up to, but not including, the PIP joint. In general, it is recommended to begin PIP and DIP motion without delay. Protected MCP motion can begin in 3 to 4 weeks.[21] For isolated fractures of the little finger metacarpal neck, some clinicians advocate immediate mobilization of fractures regardless of the degree of angulation. Results with this approach include excellent function, with only minor cosmetic deformity, and early return to work. Early follow-up evaluation is advised to exclude residual angulation, rotational deformity, and delayed displacement.[31]

Reduction of ring and little finger metacarpal neck fractures with significant angulation or deformity may be attempted in the

www.ketabpezeshki.com 66485457-66963820

Figure 50-38. The 90-90 method for metacarpal neck fracture reduction.

Figure 50-39. This radiograph shows the typical dorsal angulation of fractures of the metacarpal shafts. These fractures usually are the result of a direct blow and generally angulate dorsally because of the volar force exerted by the interosseous muscles. (From Green DP, Rowland SA: Fractures and dislocations in the hand. In Rockwood CA Jr, Green DP [eds]: Fractures in Adults. Philadelphia, JB Lippincott, 1991, p 490.)

ED. After appropriate anesthesia is obtained, usually with a hematoma block or an ulnar nerve block, traction is applied on the metacarpal to disimpact the fracture. The MCP joints and IP joints are flexed at 90 degrees, and simultaneous pressure is applied in a volar direction over the metacarpal shaft and in a dorsal direction over the flexed PIP joint (Fig. 50-38). This maneuver is termed the *90-90 method* and should complete reduction. A gutter splint in position of function should be applied. Postreduction radiographs should be obtained immediately and after 1 week to ensure that reduction has not been lost. If closed reduction cannot be achieved or maintained, pin fixation by a hand surgeon is necessary, and early referral is indicated.

Displaced or angulated index or long finger metacarpal neck fractures commonly require anatomic reduction and surgical fixation. ED management consists of ice, limb elevation, and the application of a volar splint. Prompt referral to a hand surgeon is necessary.

Complications. Metacarpal neck fractures may have an associated rotational component that can impair function and result in overlapping of the affected finger over an adjacent finger. If excessive angulation is not corrected, the patient may experience forced hyperextension of the MCP joint and flexion of the PIP joint when extending the finger and pain when tightly grasping objects. Other complications include extensor tendon injury and collateral ligament damage. Nonunion is rare after closed metacarpal fractures.

Metacarpal Shaft Fractures

Pathophysiology. There are three types of metacarpal shaft fractures: transverse, oblique or spiral, and comminuted. Transverse and comminuted fractures usually result from a direct blow and commonly exhibit dorsal angulation (Fig. 50-39). Indirect trauma or rotational torque applied to the finger may result in a spiral shaft fracture. These fracture fragments tend to shorten and rotate rather than angulate.

Management. Metacarpal shaft fractures are treated differently than fractures involving the neck because rotational deformity and shortening are more likely and less angular deformity is acceptable. In general, any rotational deformity should be corrected. Angulation deformities are unacceptable in the index and long finger metacarpals, whereas a small amount of angulation may be compensated for in the ring and little finger metacarpals. Acceptable reduction is less than 10 degrees of angulation in the former and less than 20 degrees in the latter, with less than 3 mm of shortening and normal rotational alignment.[21]

Most metacarpal shaft fractures can be managed initially with ice, limb elevation, analgesia, and immobilization in a gutter splint. The splint should include the wrist and the entire metacarpal shaft, but not the MCP joint if the fracture is proximal to the neck. Repeat radiographic examination and referral to a hand surgeon are recommended. If manipulative reduction is necessary, operative fixation usually is indicated. Multiple displaced metacarpal shaft fractures, oblique or spiral fractures with rotational deformity, irreducible transverse fractures, and displaced open fractures require internal fixation.[31]

Complications.

Complications seen in metacarpal shaft fractures are similar to the complications described for other metacarpal fractures. In addition to malrotation, which can cause a chronic painful grip, limitation of extensor function and interosseous muscle fibrosis may develop.

Metacarpal Base Fractures

Clinical Features. Fractures of the metacarpal base generally are stable and occur infrequently. They may result from either a direct blow over the base of the metacarpal or an axial force or torque applied along the digit. Examination reveals tenderness and swelling at the base of the involved metacarpal, and a significant degree of rotational deformity may be evident. Fractures at the base of the ring or little finger metacarpals may cause injury to the motor branch of the ulnar nerve, resulting in paralysis of the intrinsic hand muscles. In addition, they may be associated with a carpal bone fracture.

www.ketabpezeshki.com 66485457-66963820

Management. Initial management in the ED consists of ice, limb elevation, analgesia, and immobilization in a bulky compressive dressing or volar splint with referral to a hand surgeon for definitive management.

Complications. Metacarpal base fractures may be associated with extensor or flexor tendon damage and significant rotational malalignment. Chronic CMC joint stiffness often is associated with intra-articular fractures and may necessitate arthrodesis or arthroplasty.

Thumb Metacarpal Fractures

Fractures of the thumb metacarpal are relatively uncommon because of its high degree of mobility. Although the shaft occasionally may be involved, most fractures involve the base of the metacarpal. These fractures are classified into two groups: extra-articular and intra-articular. The two common types of intra-articular fractures of the thumb are Bennett's and Rolando's fractures.

Extra-articular Fractures. Extra-articular fractures are seen more commonly than intra-articular fractures and usually result from direct trauma or impaction. The three types of extra-articular fractures are transverse, oblique, and, in children, epiphyseal. Examination reveals localized pain and swelling over the fracture site.

Mobility of the thumb metacarpal allows 20 to 30 degrees of angular deformity without functional impairment. Patients with extra-articular fractures with a greater degree of angulation should undergo closed reduction, postreduction radiographic evaluation, and immobilization of the thumb in abduction with its IP joint extended with a thumb spica cast for 4 weeks. Transverse fractures usually are stable and can be managed with closed reduction and immobilization. If the fracture is oblique, it may require Kirschner wire fixation because of instability and a propensity for rotational deformity.[21]

Intra-articular Fractures

Bennett's Fracture. Bennett's fracture is an intra-articular fracture at the base of the thumb metacarpal combined with a dislocation or subluxation of the CMC joint. The ulnar portion of the metacarpal remains in place, and the larger fragment subluxates dorsally because of the pulling force of the abductor pollicis longus and adductor pollicis muscles (Fig. 50-40). There is complete disruption of the ligaments around the CMC joint. Because stability is conferred mostly by the dorsal ligament (posterior oblique CMC ligament), dislocation ensues. The mechanism of injury usually involves an axial force acting on a partially flexed metacarpal (e.g., striking a rigid object with a closed fist). This is the most common fracture of the thumb base.[32]

Bennett's fracture requires an anatomic reduction. Treatment goals are to achieve stability of the CMC joint by rejoining the volar lip fragment to the first metacarpal and to restore articular congruity. Initial management consists of immobilization in a thumb spica splint, ice, limb elevation, and analgesia. Early referral to a hand surgeon is warranted because although closed reduction can be achieved, the fragments are difficult to hold in position as a result of the pulling forces of the abductor pollicis longus and adductor pollicis muscles. Definitive treatment consists of conservative management, closed reduction with percutaneous pinning, or, if anatomic reduction fails or the fracture fragment represents more than 20% of the articular surface, open reduction and internal fixation.[23]

Rolando's Fracture. *Rolando's fracture* is a comminuted fracture of the base of the thumb metacarpal. Various degrees of comminution occur, but the typical configuration is in a Y- or T-shaped pattern. The severity of comminution often is underrepresented on radiographic studies. The mechanism of injury is the same as in Bennett's fracture, but Rolando's fracture occurs much less commonly and generally carries a much worse prognosis.

Figure 50-40. Bennett's fracture, anteroposterior view. Avulsion fracture of the articular surface of the first metacarpal with subluxation at the carpometacarpal joint *(arrow).* This fracture should be differentiated from Rolando's fracture and the more common extra-articular varieties. (From Rosen P, et al: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1992, p 181.)

ED management of Rolando's fracture consists of immobilization in a thumb spica splint, ice, limb elevation, analgesia, and early referral to a hand surgeon for surgical reduction. Definitive treatment is controversial and depends on the severity of comminution at the base of the thumb and the degree of displacement. If open reduction is indicated, a plate often is placed dorsally to maintain the reconstruction; with severe comminution, Kirschner wire fixation, bone graft placement, and external fixation may be used for continued distraction until healing occurs.[33]

Complications. Complications include joint stiffness, degenerative arthritis, and malunion. Malunion is the most common late complication but usually is well tolerated at the thumb CMC joint.[34] Post-traumatic arthritis is more common after Rolando's fracture and may require arthrodesis or resection hemiarthroplasty. Nonunion is rare.

Pediatric Fractures of the Hand

Pathophysiology and Assessment

The hand is frequently injured in children, with phalanx and metacarpal fractures representing the most commonly fractured bones.[35] In young children, the most common hand fracture involves a crush injury of the fingertip with an open fracture of the distal tuft.[36] The most distinctive feature of the immature skeleton is the presence of epiphyseal growth centers. Although the cartilaginous epiphysis is believed to be a weak link in the immature skeleton, injuries involving this region reportedly account for only 18% of pediatric fractures.[37]

The Salter-Harris classification of epiphyseal fractures is used to direct treatment and predict outcome. The injuries are classified

www.ketabpezeshki.com 66485457-66963820

numerically I through V, with higher numbers corresponding to an increased risk for growth disturbance.[38] The proximal phalanx is the most frequently fractured bone among the phalanges.[39] The most common epiphyseal fracture in the hand is a Salter-Harris type II fracture of the proximal phalanx.[40] It usually results from a twisting or hyperextension mechanism and most often involves the ring and little fingers and the thumb. Although lack of cooperation in this age group may make examination difficult, the clinician should look for swelling, ecchymosis, and deformity. In addition, the examiner should palpate for bony tenderness and for tenderness over the collateral ligaments. Persistent limitation of motion in a young child usually implies a significant injury of the bones or joints of the digit.

Radiologic studies should be obtained and should include the same views that are obtained in an adult. In addition, comparison views may be helpful, particularly in subtle fractures. Epiphyseal fractures may be particularly difficult because pediatric growth plates appear differently at different ages, and their varied radiographic appearance may be mistaken for fractures.

Management

Most pediatric hand fractures can be readily treated with either simple splinting or closed reduction, followed by brief immobilization, usually for no longer than 3 weeks. A plaster or fiberglass gutter splint incorporating the adjacent uninjured finger and including the wrist is the best means of immobilizing a child's finger fracture. The previously mentioned safe position still should be used whenever possible. Some clinicians advocate that in children, even stable injuries that ordinarily would be treated by buddy-splinting in an adult should be protected with full splinting for several weeks to prevent further injury. Open reduction and surgical fixation may be necessary for displaced intra-articular fractures, displaced Salter-Harris type III or IV fractures, and unstable fractures that cannot be maintained by closed methods.[41]

Complications

Pediatric hand fractures heal more quickly compared with similar injuries in adults. In addition, remodeling allows correction of some step-offs or angular deformities in younger children but does not correct rotational deformities. The ability of bone to correct angular deformities by remodeling is diminished with age and cannot be relied on for adequate correction in adolescents and adults. Residual deformity is the most commonly reported complication. Other complications, including joint stiffness, tendon adherence, and nonunion, are rarely seen.

Soft Tissue Injuries

Soft tissue injuries of the hand are extremely common ED presentations.[42] Trauma accounts for most of these injuries to the tendons, ligaments, and cartilage. Although such injuries are not life-threatening, they may result in potentially disabling complications, including deep space infection, osteomyelitis, compartment syndrome, joint laxity, loss of motion, chronic pain, swelling, and deformity.

Dislocations and Ligamentous Injuries

Ligamentous injuries to the hand are common and often missed. Injury may range from mild sprain to complete rupture and may produce various degrees of joint instability. Purely ligamentous injuries may be "tears in continuity" (grade I), partial tears (grade II), or complete tears (grade III). The disruption of joints may be complete, with the articular surfaces completely separated (a dislocation), or incomplete, leaving the articular surfaces in partial communication (a subluxation).

Because the goal of treatment is to restore functional stability, it is essential to perform a systematic evaluation of joint stability. Functionally, stability may be determined through use of a two-phase test of the IP and MCP joints of the hand. Because range of motion is heavily influenced by pain, accurate assessment generally requires digital or wrist block anesthesia in even the most cooperative patients. Active stability is tested by allowing the patient to move the digit through the normal range of motion. Completion of a full range without displacement indicates that adequate joint stability remains. Passive stability is assessed by applying gentle radial and ulnar stress to each collateral ligament and posteroanterior stress to assess volar plate integrity. Stress testing should be done in extended and moderately flexed positions to avoid the stabilizing effect of the volar plate. Comparisons with the same joint of the uninvolved hand may assist in the diagnosis. Supplemental stress radiographs also may be helpful in evaluating difficult cases.[43]

The diagnosis of incomplete or partial ligamentous injuries is made when the joint is stable to active and passive stress but is significantly swollen, with pain elicited on stress and palpation of the involved ligament systems. The examiner should attempt to ascertain whether the most tender area is over the central slip (dorsal), collateral ligaments (radial and ulnar), or volar plate (volar). Grade I and II injuries exhibit stability with pain on stress testing. Grade III injuries show instability on stress testing. Stability of the joint provides strong evidence that optimal functional recovery would result from short-term immobilization rather than surgical intervention. Because of the three-dimensional boxlike configuration that the collateral ligaments and volar plate form around the joint, wide displacement indicates that at least two components of the ligament box complex are disrupted[21,42] (Fig. 50-41). Joints with demonstrable instability should be immobilized in a gutter splint and the patient referred to a hand surgeon to determine whether surgical repair is necessary. Immobilization should be done with the IP joints splinted at 30 degrees of flexion and the MCP joints splinted at 45 to 50 degrees of flexion; when the thumb MCP is involved, it should be splinted in 30 degrees of flexion. Because the long-term effects of joint injuries are almost always joint stiffness and loss of flexion rather than persistent instability, the immobilization period usually is brief (2 to 3 weeks) and should be followed by a gradual procession of active range-of-motion exercises.[21]

Interphalangeal Joint Injuries

Distal Interphalangeal Joint. The DIP joint structure is analogous to that of the PIP joint. Additional stability is provided by the adjacent insertions of the flexor and extensor tendons, and dislocations are uncommon. Most dislocations are dorsal and usually are associated with an open wound (Fig. 50-42). The distal phalanx

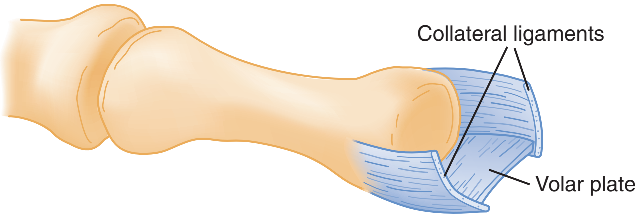


Figure 50-41. The collateral ligaments on either side of the joint and the volar plate form a boxlike support around the joint. (From Simon RR, Koenigsknecht SJ: The hand. In Simon RR [ed]: Emergency Orthopedics: The Extremities, 3rd ed. Norwalk, Conn, Appleton & Lange, 1995.)

www.ketabpezeshki.com 66485457-66963820

Figure 50-42. Dorsal dislocation of the distal interphalangeal joint without associated fracture. (From Harris JH Jr, et al: The Radiology of Emergency Medicine. Baltimore, Williams & Wilkins, 1993, p 446.)

is said to be "bayonet-apposed"—the shafts of distal and middle phalanges lie adjacent to each other, but no bony contact occurs end-to-end at the articular surfaces. Routine radiographs are used more often to rule out associated fractures than to confirm a suspected diagnosis. Treatment consists of closed reduction performed under digital or wrist block anesthesia, followed by active and passive stability testing. Reduction usually is accomplished easily by longitudinal traction and hyperextension to distract the bayonet-apposed distal phalanx followed by direct application of dorsal pressure to the base of the distal phalanx. Irreducible fractures require surgery for open reduction. The irreducibility may be a result of interposition of an avulsed fracture fragment in the joint, entrapment of the profundus tendon, or buttonhole tear through the volar plate.[44]

If the dislocation is open, the joint is contaminated, and treatment should include débridement and copious wound irrigation. The skin should be sutured and the joint splinted in slight flexion with a dorsal splint for 3 weeks. Most authorities recommend prophylactic antibiotics.[44]

Proximal Interphalangeal Joint. Dislocations of the PIP joint are the most common ligament injuries in the hand. Stability is derived from the strong conjoined attachments of the paired collateral ligaments and the volar plate. Three types of displacement of the PIP joint may occur: dorsal, lateral, and volar. The mechanism of injury usually is sports related, with a high-velocity blow to the end of the finger, which causes an axial load and hyperextension. Simple dorsal dislocations result when the volar plate ruptures and the middle phalanx assumes the position of bayonet apposition. Alternatively, a lateral dislocation may result from a radially or ulnarly directed force on the joint that leads to rupture of one collateral ligament and at least partial avulsion of the volar plate from the middle phalanx. In lateral dislocations, the ratio of radial-to-ulnar collateral ligament (UCL) rupture is 6:1, and the digit usually is ulnarly deviated. Volar dislocation of the PIP joint is rare. The most common mechanism of injury is a rotary longitudinal compression force on a semiflexed middle phalanx that results in unilateral disruption of a collateral ligament and partial avulsion of the volar plate. Physical examination reveals swelling and tenderness over the PIP joint and inability to extend the joint. Routine radiographs of the injured digit reveal the type of dislocation and any associated avulsion fractures.

Management. Small bone fragments at attachment sites seen on radiographs are associated with avulsions of minor ligamentous attachment points and do not indicate the need for open repair. Avulsion fractures involving 33% or more of the articular surface usually are unstable and require surgery.[45]

Most closed dorsal and lateral PIP dislocations are treated nonoperatively.[44] Reduction is facilitated by digital nerve block and usually can be accomplished by longitudinal traction and mild hyperextension followed by firm dorsal pressure on the proximal aspect of the middle phalanx. When reduction has been achieved, active motion is tested. Reduction is stable if no displacement occurs during active range of motion and passive stressing of the joint. More than 20 degrees of deformity and instability with lateral testing indicate a complete ligamentous injury.[46] If stability is maintained during active range of motion, treatment consists of 3 weeks of immobilization in 20 to 30 degrees of flexion, followed by active exercises. Although stiffness, pain, and swelling are likely to persist for months, the long-term prognosis is good, and subluxation usually does not recur unless the finger is hyperextended again.[44] If the dislocation is irreducible or there is evidence of complete ligamentous disruption with dislocation on active range of motion, operative repair is required.

The management of volar dislocations of the PIP joint is controversial. The dislocation has been described as irreducible and requiring open reduction; however, some authorities state that most volar dislocations can be reduced by a closed technique of applying gentle traction with MCP and PIP joints flexed.[44] A stable reduction with repair of the soft tissue structures and transarticular pinning in the fully extended position also has been recommended.[44]

Injury to the Metacarpophalangeal Joints of the Fingers

Pathophysiology. MCP dislocations are considerably less common than dislocations of the PIP joint. The MCP joints of the fingers are resistant to ligamentous injury and dislocation because of their inherent ligamentous structure, their surrounding supporting structures, and their protected position at the base of the fingers. Like the DIP and PIP joints, each MCP joint has two collateral ligaments and a volar fibrocartilaginous plate; however, the MCP joints are condyloid joints and permit, in addition to flexion and extension, 30 degrees of lateral motion while the joint is extended. Because of the shape of this articulation, the joint is more stable in flexion when the collateral ligaments are stretched than when they are in extension. They are most vulnerable to injury from forces directed ulnarly and dorsally.

Isolated injury to the collateral ligaments and volar plate of the MCP joint is rare. These injuries usually occur with hyperextension stress applied to the MCP joint with the finger extended. The patient has ecchymosis and swelling of the joint. Examination reveals tenderness along the joint and varying degrees of instability. The radiographic appearance usually is normal on routine views, but some clinicians recommend a Brewerton view to show any evidence of avulsed bone fragments.[47] Treatment for most of these injuries consists of application of a gentle compression dressing with light plaster reinforcement and early orthopedic referral.

Dislocations of the MCP joints of the fingers are relatively rare injuries and usually are dorsal. The most common digit involved is the index finger, followed by the little finger. These dislocations result from hyperextension forces that rupture the proximal volar plate and are divided into simple and complex types. In the simple dislocation (subluxation), the joint appears to be hyperextended to 60 to 90 degrees, and the articular surfaces are in contact without interposed soft tissue. With complex (complete) dislocations, the MCP joint is in moderate hyperextension and angulated, the metacarpal head is prominent in the palm, and the distended palmar skin is dimpled. Complex dislocations have a less striking

www.ketabpezeshki.com 66485457-66963820

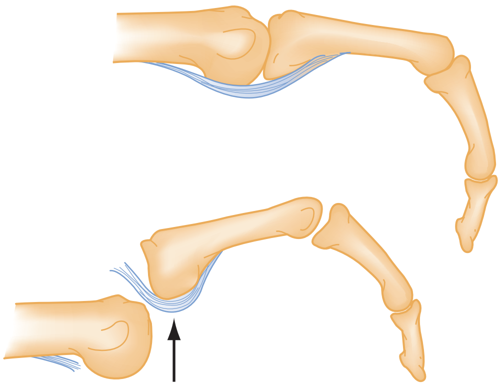


Figure 50-43. The most important element preventing reduction in a complex metacarpophalangeal dislocation is interposition of the volar plate within the joint space *(arrow).* It typically requires surgical extrication. (From Green DP, Rowland SA: Fractures and dislocations in the hand. In Rockwood CA Jr, Green DP [eds]: Fractures in Adults. Philadelphia, JB Lippincott, 1991, p 521.)

Figure 50-44. A pathognomonic radiographic sign of complex metacarpophalangeal dislocation is the presence of a sesamoid bone in the widened joint space, indicative of interposition of the entrapped volar plate. (From DeLee JC, Drez D Jr, Miller MD: Orthopedic Sports Medicine: Principles and Practice, 2nd ed, vol 2. Philadelphia, Saunders, 2003, p 1387.)

presentation but represent a more severe injury; the volar plate is interposed in the MCP joint space, and closed reduction is not possible (Fig. 50-43). Radiographic examination shows an obvious dislocation on the lateral view. Posteroanterior views reveal widening of the joint space in complex dislocations. In addition, sesamoid bones may be seen in the joint; this finding is pathognomonic for this injury (Fig. 50-44).

Management. After appropriate anesthesia is obtained, simple dorsal dislocations should be reduced in a way that prevents entrapment of the volar plate in the joint. Reduction is accomplished by flexing the wrist to relax the flexor tendons and

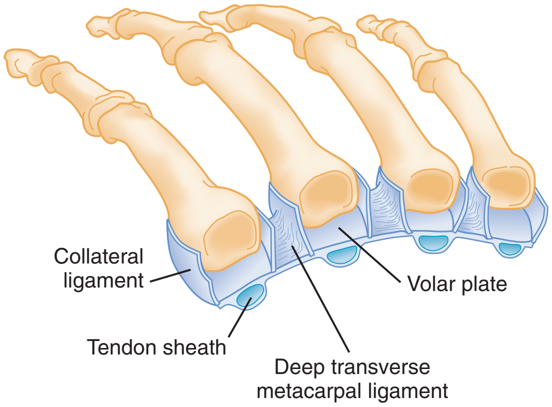


Figure 50-45. The volar plates of four palmar metacarpals are held together firmly by the deep transverse metacarpal ligament, which is continuous with the volar plate. Eaton calls this the "intervolar plate ligament." (From Green DP, Rowland SA: Fractures and dislocations in the hand. In Rockwood CA Jr, Green DP [eds]: Fractures in Adults. Philadelphia, JB Lippincott, 1991, p 518.)

applying firm pressure over the dorsum of the proximal phalanx in a distal and volar direction. Excessive hyperextension or longitudinal traction should be avoided. The MCP joints should be splinted in flexion, and referral to a hand surgeon is necessary. Complex dorsal dislocations do not reduce with closed methods and require operative reduction. Volar dislocations are rare and generally require operative reduction.

Injury to the Carpometacarpal Joints of the Fingers

Pathophysiology. The CMC joints of the digit form the base of the transverse metacarpal arch of the hand. The metacarpal bases articulate with one another and with the distal carpal row in a complex interlocking structural arrangement. The joints are supported by strong dorsal, volar, and interosseous ligaments and are reinforced by the broad insertions of the wrist flexors and extensors (Fig. 50-45). Dislocations of the CMC joints are uncommon and often are missed.[48] Overall, the most commonly injured CMC joint is the little finger, and most of these injuries are dorsal fracture-dislocations.[49] The injury occurs as a result of motor vehicle collisions, falls, crushes, and closed-fist trauma.

Clinical Features and Diagnostic Strategies. Clinically, the patient has swelling on the dorsum of the hand and tenderness over the involved CMC joints. Routine radiographs should be viewed carefully because fracture lines may be subtle, and the metacarpals may be obscured by superimposition. Other radiographic views that may be helpful include multiple oblique, forearm in 30-degree pronation, and Brewerton views.[49]

Management. Initial treatment consists of ice for comfort, limb elevation, and analgesia. Closed reduction of the dorsal fracture-dislocation may be attempted after adequate regional anesthesia has been obtained. Traction and flexion with simultaneous longitudinal pressure on the metacarpal base, followed by extension of the metacarpal head when length has been restored, generally result in reduction. Even in cases in which reduction is achieved by closed means, early referral to a hand surgeon is needed because Kirschner wire fixation is advisable to ensure adequate stability. The late sequelae of fracture-dislocations include pain and weakness from traumatic arthritis secondary to imprecise alignment or chronic dislocation of the CMC joints.

Injury to the Interphalangeal Joint of the Thumb

The IP joint of the thumb is similar to a finger DIP joint except that the phalanges of the thumb typically are larger and stronger

www.ketabpezeshki.com 66485457-66963820

than the phalanges of the fingers. Even with the thumb's vulnerable position, IP dislocation is uncommon. Most dislocations are dorsal, and they often are associated with open injuries. Reduction usually is simple after a median nerve block. The joint usually remains stable because the volar plate remains attached to the distal phalanx, and immobilization in mild flexion for 3 weeks usually suffices for successful management.

Injury to the Metacarpophalangeal Joint of the Thumb

The MCP joint of the thumb is a condyloid joint that allows mainly flexion and extension; however, it also permits some degree of abduction, adduction, and rotation. Its volar plate and collateral ligaments are stronger than in other MCP joints, but its vulnerable position leads to frequent traumatic injury. Overall, injury to the MCP joint of the thumb accounts for five times the number of injuries of all other MCP joints combined.

Most dislocations of thumb MCP joints are dorsal and result from a hyperextension force that ruptures the volar plate, joint capsule, and at least part of the collateral ligament. As with other dorsal MCP dislocations, displacement ranges in extent from subluxation of the phalanx to a complex dislocation with the proximal phalanx resting over the metacarpal head. The complex dislocation is not easily reduced because of volar plate entrapment in the joint. Clinically, the complex dislocation may show a dimple over the thenar eminence. Radiographic studies confirm the dorsal dislocation and reveal the sesamoids in close proximity to the proximal phalanx.

Management. Closed reduction may be attempted after radial and median nerve wrist block anesthesia has been achieved. Pressure is directed distally on the base of the proximal phalanx, with the metacarpal flexed and adducted. If reduction is difficult, the IP joint and wrist can be flexed to relax the entrapped flexor pollicis longus tendon. When restoration of anatomic position has been accomplished, the collateral ligaments should be tested, and reduction should be confirmed by radiographic assessment. Stability to active range of motion and stress testing suggests that immobilization in a thumb spica splint with the MCP joint in 20 degrees of flexion for 4 weeks constitutes adequate treatment. Nonreducible (complex) dislocations or dislocations with significant lateral instability require open reduction and operative repair. Hyperextension, instability, and chronic pain on pinching may occur after these injuries.

Ulnar Collateral Ligament Injuries (Gamekeeper's Thumb, Skier's Thumb)

Pathophysiology. Injury to the UCL was first described as an occupational hazard of Scottish gamekeepers, who damaged their thumbs by a repeated maneuver involving twisting the necks of hares.[50] Skiing is now the most common cause of acute and chronic injury to the UCL.[51] *Skier's thumb* is the most common upper extremity injury in skiing and results from interference with release of the pole at the moment of impact during a fall. UCL rupture occurs 10 times more often than radial collateral ligament injury.[52] The mechanism of injury is forced radial deviation (abduction), and the subsequent tear usually occurs at the insertion into the proximal phalanx. Stener[53] showed that in nearly two thirds of cases of complete UCL rupture, the adductor pollicis becomes interposed between the superficial proximal portion and the deep distal portion of the ligament (see Fig. 50-45). Besides the collateral ligament injury, associated injuries of the dorsal capsule and volar plate are common.

Clinical Features. Physical examination reveals swelling and localized tenderness over the ulnar border of the joint and weakness of pinch. Complete and partial ruptures usually can be differentiated by clinical examination. Valgus stress testing of the UCLs is required and should be performed with the joint in full extension and in 30 degrees of flexion to avoid the stabilizing effect of the volar plate. If the examination elicits pain and guarding, the test should be done after median and radial nerve block at the wrist or with use of local infiltration anesthesia. More than 35 degrees of joint laxity or 15 degrees of laxity beyond that present in the uninjured thumb is consistent with complete UCL rupture.[54] Routine radiographs should be obtained before the joint is stressed and may reveal a bony avulsion from the insertion of the UCL into the proximal phalanx or an associated condylar fracture. Radiographic findings of proximal phalanx volar subluxation and radial deviation may indicate complete UCL rupture.[55] Because of the difficulty in diagnosing complete rupture, it is commonly misdiagnosed as a simple sprain in the ED, potentially resulting in chronic disability.[56]

Management. Acute partial ruptures of the UCL can be treated effectively with a 4-week period of immobilization in a thumb spica cast; full recovery is the rule. Complete ligament tears require surgical repair because a high percentage are associated with soft tissue interposition from the adductor aponeurosis (Stener's lesion), with limited predicted healing potential. Anatomic repair within 3 weeks of injury achieves good or excellent results in 90% of affected patients.[57] Long-term complications include chronic pain and instability with the loss of pinch strength, which may necessitate arthrodesis.

Radial Collateral Ligament Injuries

Radial collateral ligament injuries of the MCP joint of the thumb are less common but equally debilitating.[52] The usual mechanism is forced adduction with or without hyperextension. Diagnosis and treatment generally are similar to those for UCL injuries. There have been isolated case reports of a Stener-like lesion on the radial side, with some authors advocating for the role of surgical repair.[58]

Injuries to the Carpometacarpal Joint of the Thumb

Injuries of the volar ligament of the thumb CMC joint, similar to those of other joints of the hand, may be complete or partial. Complete rupture permits the entire thumb metacarpal to dislocate dorsally. Controversy exists regarding the ligament most responsible for stability of the thumb CMC joint, although most recent evidence implicates the dorsoradial ligament in dislocations at this joint.[59] These dislocations are reduced easily but are unstable after reduction. Initial management consists of ice, analgesia, limb elevation, and application of a thumb spica splint. The patient should be promptly referred to a hand surgeon for possible operative repair of the ligament. If the capsule is allowed to heal with imperfect metacarpal reduction, joint instability may result, with progressive degenerative changes leading to chronic pain.

Tendon Injuries

Tendon injuries may involve one or more of the extensor or flexor tendons in the hand and encompass a spectrum of abnormalities, ranging from simple stretching of the fibers to complete tendon rupture with or without an associated avulsion fracture. The most common mechanisms of injury of tendons are lacerations, avulsions, and crush injuries. In a normal resting position, the fingers are flexed, with the little finger having the greatest degree of flexion and the index finger having the least. In the resting hand, a finger with a greater or lesser degree of flexion than that of the opposite hand often indicates a tendon injury. This observation may be especially useful in an uncooperative or pediatric patient. If the patient can move a joint, but active flexion or extension is limited

www.ketabpezeshki.com 66485457-66963820

or painful, a partial tendon laceration may be present. To assess the tendons adequately, motion should be tested against resistance. This testing may cause a partially ruptured tendon to rupture but identifies a lesion that needs surgical repair. The tendon should be placed in maximal stretch before testing to provide for the greatest strength during contraction. As a general rule, extensor injury causes greater impairment of motion than a similar flexor injury. Vessels and nerves travel closely with flexor tendons, particularly in the fingers. Damage to one of these structures is likely to be associated with damage to the other two.

The position the hand was in when the injury occurred is important. When trauma occurs while the hand is held in flexion, the flexor tendons may be transected, and the distal tendon stump would retract distal to the overlying skin wound. If the hand is in the extended position, however, the tendon stumps would lie at the wound edges. When the tendons are injured by a direct blow to the hand or the fingers, the closed injury may hide significant tissue damage. Partial tendon lacerations may be associated with small surface wounds. To help exclude injury, wounds and visible tendons should be inspected while the joints are taken through a full range of motion.

Extensor Tendon Injuries

The most common site of tendon injury is the extensors over the dorsum of the hand. The extensors are predisposed to laceration because of their superficial location on the dorsum of the hand and the minimal amount of subcutaneous tissue between the tendon and overlying skin. This anatomic arrangement also predisposes the extensor mechanism to more complex tendon injuries, including abrasion, crush, and avulsion. Because the extensor tendons are not constrained in tight fibro-osseous canals except in the wrist, they also are easily located and repaired.

Injuries to the extensor tendons have been grouped into anatomic zones for easy understanding and classification. Different systems for assigning zones have been described, but the most widely accepted is that of Verdan[60] (Fig. 50-46). This system defines eight zones, from zone I at the DIP joint level to zone VIII at the distal forearm level. The use of zones is convenient for assessing injury patterns, repair techniques, and rehabilitation.

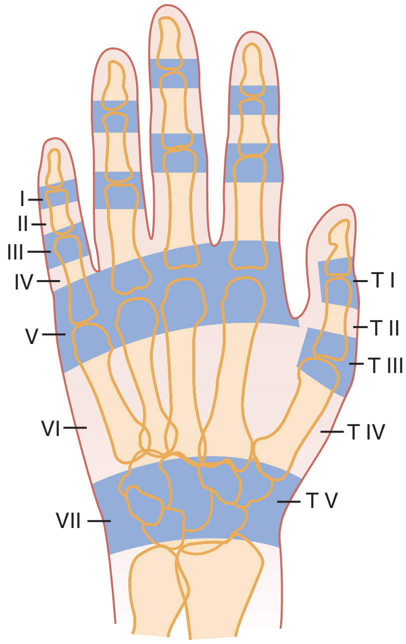


Figure 50-46. Zone classification for extensor tendon injuries. (From Kleinert HE, et al: Flexor tendon injuries. Surg Clin North Am 61:267, 1981.)

Zone I Injuries

Pathophysiology. Zone I is the area over the distal phalanx and DIP joint. In this region, the conjoint extensor tendon is well defined and dorsally positioned. Injuries that occur here disrupt the terminal extensor tendon; they may be open or closed and may occur with or without a fracture. Complete laceration of the conjoint tendon results in a flexed posture of approximately 40 degrees at the DIP joint. Partial transection results in a lesser extension lag and a decrease in the strength of extension against resistance from a flexed position. The extension lag may increase if the partial injury is not treated appropriately. For this reason, exploration of dorsal lacerations near the DIP joint is important.

Mallet finger is the most common injury in zone I and refers to a closed disruption of the distal extensor apparatus.[21] As a result of loss of extensor tendon continuity to the distal phalanx, there is a flexion deformity of the DIP joint. The injury can be seen in any finger but is most common in the long, ring, and little fingers. Overall, mallet finger represents the most common tendon injury in the hand seen in athletes.[61] The mechanism of injury often is sudden forceful flexion of an extended finger when an object, such as a ball, strikes the tip of the finger. This mechanism is commonly encountered in athletes and often is described as "jamming" the finger. Other mechanisms include hyperextension with axial compression and direct crush injury at the DIP joint. Four types of injury patterns are recognized, with type 1 injuries being the most common (Fig. 50-47 and Box 50-2). Fracture fragments of

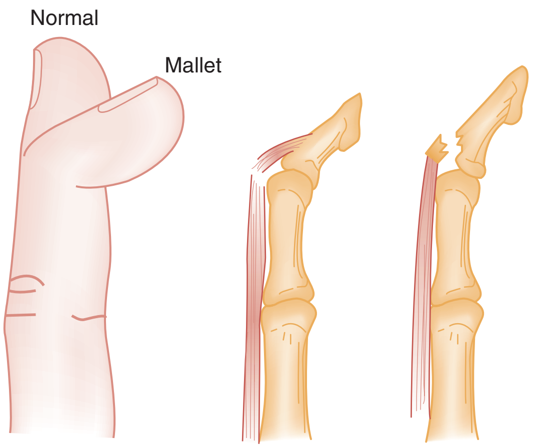


Figure 50-47. Mallet finger occurs with loss of extensor function to the distal phalanx. This may be caused by a tear of the tendon itself or an avulsion fracture of the dorsal base of the distal phalanx.

Box 50-2 Classification of Mallet Fingers (Doyle)

Type I—Closed tendon rupture, with or without small dorsal avulsion fracture
Type II—Open tendon laceration
Type III—Open tendon injury with skin and subcutaneous tissue loss
Type IV—Mallet fracture
- A. Transepiphyseal plate fracture in children
- B. Hyperflexion injury with fracture of articular surface of 20 to 50%
- C. Hyperextension injury with fracture of the articular surface >50% and with early or late volar subluxation of distal phalanx

From Strauch RJ: Extensor tendon injury. In Wolfe SW, Hotchkiss RN, Pederson WC, Kozin SH [eds]: Green's Operative Hand Surgery, 6th ed. Philadelphia, Churchill Livingstone, 2011, p 169.

www.ketabpezeshki.com 66485457-66963820

Figure 50-48. Mallet finger fracture, lateral view. This is an intra-articular avulsion of the dorsal surface of the distal phalanx *(arrow)*. (From Rosen P, et al: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1992, p 181.)

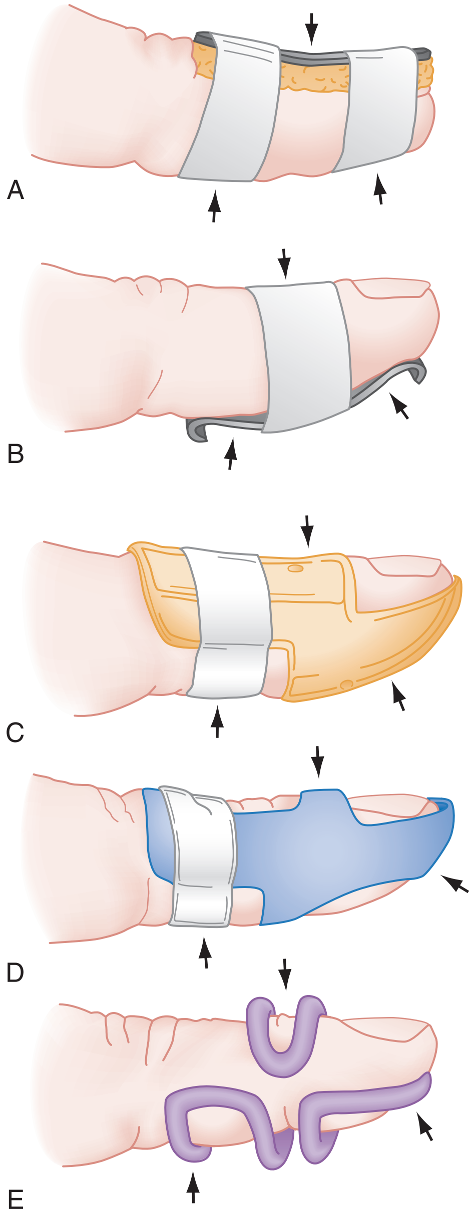


Figure 50-49. Only the distal interphalangeal joint is immobilized in treating mallet fingers. This may be done with a dorsal padded aluminum splint **(A)**, a volar unpadded aluminum splint **(B)**, a Stack splint **(C)**, a modified Stack splint **(D)**, or an Abouna splint **(E)**. Each of these splints uses a three-point *(arrows)* fixation principle. (From Green DP, Rowland SA: Fractures and dislocations in the hand. In Rockwood CA Jr, Green DP [eds]: Fractures in Adults. Philadelphia, JB Lippincott, 1991, p 450.)

variable size are seen in one fourth to one third of cases (Fig. 50-48). Small avulsion fractures usually are the result of hyperflexion injuries, whereas large fracture fragments usually result from a hyperextension mechanism.[62]

Clinical Features. In the acute injury, clinical findings include swelling, pain, and tenderness over the DIP joint. The distal phalanx is flexed because of the unopposed action of the FDP. There is usually complete passive but incomplete active extension at the DIP joint. Although the diagnosis is easily made, the patient often seeks treatment late because the functional disability is not great.

Management. Although various treatment protocols have been proposed, splinting of the IP joint for 6 to 8 weeks has yielded good results while minimizing morbidity in a majority of patients. The primary goal of treatment is the maintenance of continuous DIP joint extension until tendon healing occurs. Treatment of closed (type I) injuries is nonoperative. Immobilization can be accomplished with either a volar or a dorsal splint made from a variety of materials, including aluminum and plastic (Fig. 50-49). The DIP joint is immobilized in slight hyperextension for 6 to 8 weeks, but the PIP and MCP joints are allowed to move freely.[21] An excessive degree of hyperextension should be avoided because this can lead to skin necrosis on the dorsal surface of the DIP joint.[63]

Open zone I injuries that divide the extensor tendon (mallet finger types II and III) are treated by suturing the cut ends (Fig. 50-50). Partial and compete lacerations are repaired with either a roll suture or figure-of-eight stitch with 5-0 nonabsorbable sutures. This repair should be followed by continuous splinting of the DIP joint in full extension for a minimum of 6 weeks.[60]

Definitive treatment of a type IV injury is controversial. Some authorities recommend operative repair; others recommend conservative management with uninterrupted splinting of the digit.[60]

Prognosis. More than 80% of patients who receive conservative treatment for mallet finger report successful outcomes; however, most patients do not regain full mobility at the DIP joint.[64] Possible delayed complications include dorsal deformity, cold intolerance, pain, and the so-called *swan neck deformity* (Fig. 50-51). This abnormality develops when the lateral bands displace proximally and dorsally, resulting in increased extension forces on the PIP joint. Secondarily, the extensor lag at the DIP joint increases because the force of the FDP tendon is unopposed. The swan neck deformity is not seen acutely unless the injured finger has a normally hyperextended PIP joint. Classically, this deformity occurs as a complication of a chronic untreated mallet finger.[60]

www.ketabpezeshki.com 66485457-66963820

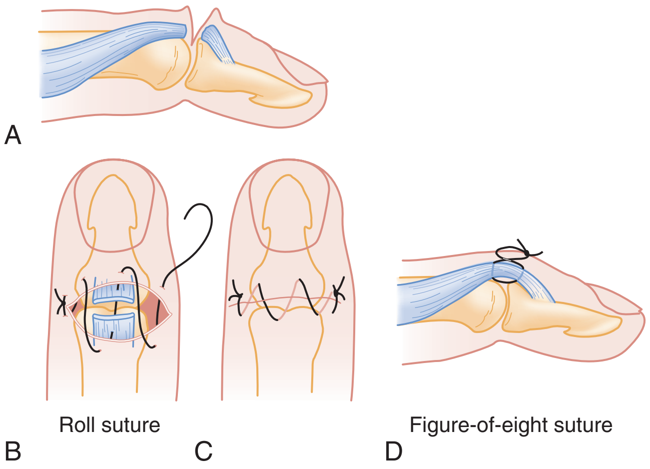


Figure 50-50. Lacerations of the extensor mechanism over the distal joint with mallet finger deformity **(A)** can be repaired by a roll-type suture, which simultaneously approximates skin and tendon (**B** and **C**). A small dressing is applied with a splint to maintain the joint in full extension. Sutures are removed at 10 to 12 days. A figure-of-eight vertical suture **(D)** also may be used, which simultaneously closes the defect in tendon and skin. Splinting is mandatory for 6 weeks. (From Doyle JR: Extensor tendons-acute injuries. In Green DP [ed]: Operative Hand Surgery. New York, Churchill Livingstone, 1993, p 1939.)

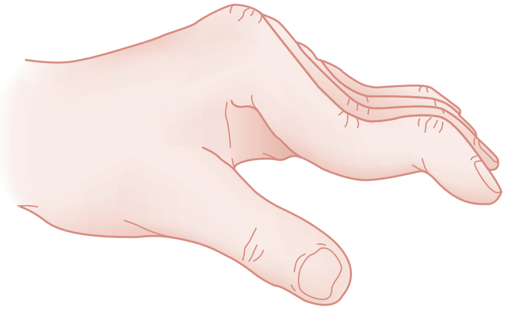


Figure 50-51. Swan neck deformity of the fingers.

Zone II Injuries. Zone II is the area over the middle phalanx. As the lateral bands blend dorsally to form the conjoint tendon, they are thin and oriented around the dorsal half of the middle phalanx. Injuries here usually are the result of a simple laceration, which seldom transects all of the dorsal apparatus. Examination reveals a typical mallet deformity. The treatment is identical to that for open zone I injuries.

Zone III Injuries

Pathophysiology. Zone III is the area over the PIP joint. The central tendon is the most commonly injured structure in this zone; such injuries are the second most common closed tendon injury in athletes.[61] The mechanisms for closed rupture include forced flexion of an actively extended finger, a direct blow to the dorsum of the PIP joint, and hyperextension with volar dislocation of the PIP joint. It often results from a “jamming” injury. Lacerations that occur just distal to the PIP joint also may divide the central tendon and readily extend into the joint. Wounds are carefully explored to define the status of the PIP joint capsule.

Disruption of the central tendon causes an imbalance in the extensor mechanism. The FDS is now unopposed and flexes the PIP joint. The lateral bands displace volarly to the axis of the PIP joint and become flexors of the joint. In addition, the extensor hood retracts proximally, causing extension of the MCP and DIP joints. The resulting tendon imbalance leads to the so-called *boutonnière* (buttonhole) deformity, with flexion of the PIP joint

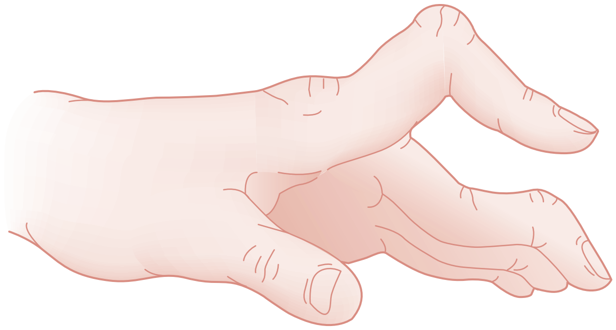


Figure 50-52. Buttonhole (boutonnière) deformity of the index finger, with swan neck deformity of the other fingers.

and hyperextension of the DIP and MP joints (Fig. 50-52). Although open injuries of the central tendon may cause an acute boutonnière deformity, this usually is delayed several weeks after a closed athletic injury.

Clinical Features. Early diagnosis of a closed central tendon rupture or avulsion is difficult before the boutonnière deformity has developed. The patient typically has a history of trauma to the involved digit and a painful, swollen PIP joint. The finger is held in slight flexion at the PIP joint and slight extension at the DIP joint. Rupture of the central tendon may be differentiated from the more common injury to the collateral ligament by the location of the maximal area of tenderness on the dorsum rather than on the sides of the joint, and by the patient’s inability to extend the PIP joint actively. PIP joint extension can be tested by having the patient attempt to extend the fingers against slight resistance with the hand flat on the table and the PIP joint flexed 90 degrees over an edge of a table (Elson’s test). A positive Elson’s test result, indicative of rupture of the central tendon slip, occurs when the DIP joint is held in fixed extension or hyperextension, with the absence of PIP joint extension.[65] During the acute phase of an injury, a digital block may be necessary to facilitate performance of the Elson test.[60] The radiographic appearance of a central tendon rupture typically is normal but may be diagnostic if an avulsion fracture of the volar base of the middle phalanx is visualized on the lateral view.

Management. Patients with suspected closed central tendon injuries should be managed with splinting of the PIP joint in full extension for 5 to 6 weeks. Only the PIP joint should be immobilized, and passive and active DIP joint flexion is encouraged from the outset. Operative repair may be required for an acute closed boutonnière injury associated with a displaced avulsion fracture and injury with volar PIP joint dislocation. Early referral to a hand surgeon is advised.

When an acute boutonnière deformity is caused by an open injury, exploration of the central slip is mandatory and a hand surgeon should be consulted immediately. Primary repair of the tendon and Kirschner wire fixation of the PIP joint often are performed. If the joint capsule has been violated, the joint should be thoroughly débrided and irrigated, and the use of prophylactic antibiotics is recommended.

Zone IV Injuries. Zone IV includes the area over the proximal phalanx. The clinical findings are similar to those with zone III injury but are less severe because the PIP joint and lateral bands are intact. The resulting injury usually is partial, and the tendon ends usually do not retract appreciably. These injuries are treated with primary or delayed primary repair and appropriate splinting for 3 to 6 weeks. Simple injuries in this zone can be well approximated with 5-0 nonabsorbable sutures with buried knots. Immobilization should be done with maintenance of the wrist in extension and the MCP joints in approximately 15 degrees of

www.ketabpezeshki.com 66485457-66963820

flexion. Tendon adhesions are common in this zone because of associated damage to the periosteum.

Zone V Injuries. Zone V injuries involve the areas over the MCP joint and should be presumed to be the result of a human bite until proven otherwise. These injuries occur most commonly over the MCP joints of the long and ring fingers. Radiographs are mandatory and may include Brewerton views to assess the metacarpal head closely for injury. The clinical findings with injuries to the extensor tendon at this level are flexion of the MCP joint and inability to extend the joint fully.

In an open joint injury caused by a human bite, the potential for mixed aerobic and anaerobic infections is high. Operative exploration, débridement, and irrigation are necessary. A combination of a β-lactam and a β-lactamase inhibitor drug is recommended empirically for infections related to human bites.[28] In penicillin-allergic patients, clindamycin in combination with a fluoroquinolone may be given.[28] The wound is left open and may be closed at 4 to 5 days if free from infection. The resultant tendon injury usually is only a partial laceration, which may be managed with primary or delayed primary repair.

For simple lacerations at this level caused by a sharp, clean object, primary repair is indicated. The involved tendon ends do not retract and can be approximated with 4-0 nonabsorbable sutures. Sagittal bands also should be repaired if injured to prevent loss of extension or subluxation. The wrist and MCP joints should be immobilized. Early referral to a hand surgeon is advised.

Zone VI Injuries. Zone VI includes the area of the dorsum of the hand. Although these injuries may be similar in clinical appearance to zone V injuries, the joint is not involved, and these injuries generally are not as severe. Because the extensor tendons are superficial at this level, a relatively trivial-appearing skin laceration may be associated with one or more tendon lacerations. If the injury is proximal to the juncturae tendinum, the patient may be able to extend the involved MCP joint because weak extensor forces are transmitted to the junctura from adjacent extensor tendons.

The tendons in this area are round or oval and easily exposed. Primary repair with a modified Kessler stitch with a 4-0 nonabsorbable material or a figure-of-eight stitch with a buried knot on the deep, palmar surface of the tendon suffices. This repair is followed by immobilization of the wrist at 30 degrees of extension and the MCP joint in neutral position. Referral to a hand surgeon for delayed primary repair also is appropriate.

Zone VII and VIII Injuries. Zone VII and VIII injuries involve the wrist and forearm. Management follows basic principles for tendon injuries.

Flexor Tendon Injuries

Pathophysiology. Flexor tendon injuries are not as common as injuries to the extensor complex and often have a subtle clinical presentation. The most common mechanism of injury is laceration, but closed traumatic disruption also may occur. FDP avulsion is the third most common tendon rupture in the hand in athletes.[61] This injury usually is sports-related and involves a hyperextension force applied to an actively flexing digit; the classic example is that of an injured digit in a football player who grabs the clothing of an opponent who is breaking free from a tackle. Most of these injuries involve the ring finger, possibly because the ring finger becomes the most prominent finger with the fingers held in a partially flexed position.[66] Because of the closed nature of these injuries, the patient may not seek immediate care, or the condition initially may be misdiagnosed.

Clinical Features. Careful assessment is necessary to diagnose flexor tendon disruption and associated neurovascular injury. With the normal hand at rest, there is a cascade of flexion of the digits, beginning with less flexion at the index finger and progressing to more flexion toward the little finger. An injury to a flexor tendon may be evident if the involved finger does not assume a naturally flexed position. Complete disruption of the profundus tendon results in an extended position of the DIP joint as a result of unopposed extensor forces. If the FDS is completely severed, or a partial tendon injury has occurred, the digit rests in less flexion than normal. An abnormal posture of the injured digit may suggest a flexor tendon injury; this usually is confirmed by a functional examination. The FDP and the FDS should be tested separately as previously described. This examination requires careful observation: The patient may flex the distal tip with an intact profundus, but an injury to the FDS precludes flexion at the PIP joint. Disruption of the FDP tendon leads to loss of flexion at the DIP joint, instability in pinch, and loss of grip strength. FDP avulsions can be classified into three types. Type I injuries involve retraction of the avulsed FDP tendon into the palm, damaging the blood supply to the tendon and causing hematoma formation in the process. Because of the damaged vasculature, these injuries should be repaired urgently to prevent ischemic tendon damage.[67] Types II and III injuries cause lesser degrees of retraction of the FDP tendon. Accordingly, these injuries result in less compromise of the tendon's blood supply and have more favorable outcomes.[67] FDP injuries may be present if the patient complains of subjective weakness or if an abnormal position of the hand is observed at rest. Clinically, injuries are associated with pain and weakness with flexion against resistance. Despite these findings, it may not be possible to arrive at a complete and accurate diagnosis until the wound is surgically explored. The palmaris longus, which is not present in approximately 15% of people, is not a functionally significant wrist flexor. Palmaris longus lacerations have tremendous diagnostic significance, however, because most of these injuries (80 to 90%) are associated with concomitant partial or complete median nerve lacerations. For this reason, all patients with palmaris longus lacerations should be assumed to have median nerve laceration until such injury has been ruled out clinically or by direct examination.[68]

Management. Flexor tendon repairs require the expertise of a hand surgeon and generally are not repaired by emergency physicians. Immediate or delayed primary repair is now advocated for most acute flexor tendon injuries, including avulsions of the FDP and injuries involving the so-called "no man's land," which extends from the distal palmar crease to the midportion of the middle phalanx. The term "no man's land" refers to the high frequency of tendon adhesion after injury in this area. The advantages of primary repair with surgical reapproximation over secondary grafting for treatment of acute injuries have been well described in the literature.[69] Emergent repair of lacerated flexor tendons is indicated in the setting of diminished circulation to the digit requiring vascular repair. Otherwise, early definitive repair can be undertaken within days of the injury.[69] Secondary repair of flexor tendons may be performed 4 weeks after injury, but repair is considered late after that. In general, the results of primary, delayed primary, and early secondary repair are approximately equal. Treatment of partial flexor tendon lacerations is controversial, but referral to a hand surgeon for further exploration and possible repair is prudent.

If a hand surgeon is not immediately available, open wounds should be copiously irrigated and closed with 5-0 nylon and the hand splinted with the wrist in 30 degrees of flexion—the MCP joints flexed approximately 70 degrees and the IP joint flexed 10 to 15 degrees. This flexion ensures that no further damage occurs to the tendon and that the tendon will not contract further on movement. The patient also should receive tetanus immunization as indicated, and most authorities recommend empirical use of broad-spectrum antibiotics. Most closed tendon injuries require referral to a hand surgeon because of the risk of long-term disability.

www.ketabpezeshki.com 66485457-66963820

Complications. With optimal management, most patients with flexor tendon injuries have good to excellent outcomes.[70] With injuries involving the no man's land, results may be poor, and tendon grafting occasionally is required. Overall, adhesions remain the most significant problem after operative repair. Other complications include triggering, bowstringing, and intratendinous epidermoid cyst formation.[71]

Mutilating Injuries

Mutilating injuries to the hand are encountered frequently in the ED. These are severe multistructural injuries that destroy the anatomy and functional integrity of the hand. Initial evaluation should focus on preservation of vital structures, analgesics, early consultation, wound care with débridement of devitalized tissue, and antibiotics. Evolving over recent years is a more aggressive push with respect to procedure timing, whether a single-stage or multistage strategy is used.[72] Successful long-term clinical and socioeconomic outcomes have brought focused attention on procedure timing. The concept of early primary reconstruction with fast rehabilitation should be pursued based on case profile.[72] One such type is snowblower-, wood chipper–, or lawnmower-associated hand injuries, which can result in substantial deformity and disability. Snowblower injuries typically occur in clusters and are responsible for approximately 1000 amputations and 5000 ED visits annually.[73] The dominant hand is involved approximately 68% of the time, with middle and index fingers most commonly injured. Phalangeal fractures are the most common type of injury.[74] Snowblower injuries often are managed as open fractures with intravenous antibiotics, irrigation, and débridement and repair of bone, soft tissue, and nail bed structures.[74] Irreparable devascularization currently is considered the only absolute indication for immediate or early digital amputation after injury.[75] The concept and techniques for reimplantation and revascularization in mutilating injuries in children are similar to those in adults.[76]

Fingertip Injuries

Fingertip injuries may involve any structures distal to the DIP joint, including the skin, volar pulp tissue, distal phalanx, nail, nail bed, and related structures. These are among the most common injuries of the upper extremity and, although usually minor, may have significant long-term consequences. The goals of management are to maintain finger length and to achieve good tissue coverage, near-normal sensibility, and early functional recovery.

Fingertip Amputations

Classification. Fingertip amputations are the most common type of amputation of the upper extremity. In zone I injuries (Fig. 50-53), the proximal two thirds of the nail bed is preserved. In zone II injuries, bone is exposed, and in zone III injuries, the entire nail bed is lost. Radiographic studies are indicated if bony avulsion injury or fracture cannot be excluded. Most of these fingertip injuries can be managed on an outpatient basis.

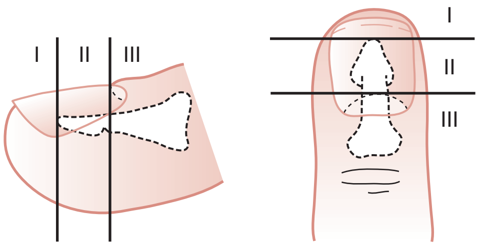


Figure 50-53. Classification of nail bed and fingernail injuries: zone I, distal to the bony phalanx; zone II, distal to lunula (between distal end of lunula and end of phalanx); zone III, proximal to distal end of lunula. (From Rosenthal EA: Treatment of fingertip and nail bed injuries. Orthop Clin North Am 14:675, 1983.)

Management. Treatment of distal fingertip injuries is controversial; consequently, management should be individualized, and few guidelines are available. In general, most hand surgeons try to maintain length of the thumb by whatever means possible.[77] The index finger is considered next before the other fingers. An intact pulp-to-pulp pinch mechanism is the principal goal. Other factors to consider include the patient's age, health, occupation, and handedness.

In most fingertip amputations distal to the DIP joint, adequate care can be provided with conservative wound management. The simplest and often best method for managing a fingertip amputation is allowing the wound to heal by secondary intention. This method generally is effective and produces good results if the wound is less than 1 cm. Large dorsal wounds also heal well by this method. It is the treatment of choice in childhood fingertip amputations, particularly when no bone is exposed. In cases in which a small protuberance of phalangeal bone (extending no more than 0.5 cm) is exposed, it may be trimmed back with a rongeur to just below skin level and the wound allowed to heal by secondary intention; if the bone is left exposed without soft tissue coverage, the patient will need an operative procedure. In most cases the wound heals through a process of granulation, wound contracture, and reepithelialization within a few weeks. Initial management should include careful and meticulous wound cleansing, a nonadherent dressing, appropriate tetanus prophylaxis, and splinting to protect the tip. Amputations that involve the distal phalanx usually are treated as contaminated open fractures with an initial intravenous dose of a cephalosporin followed by an oral course. Patients should have appropriate follow-up care to ensure adequate healing and recovery.

Management of fingertip injuries involving significant soft tissue (especially volar) or bone loss usually requires the expertise of a hand surgeon. Surgical management may include primary closure, full-thickness or partial-thickness skin grafts, composite grafts, adjacent flaps, regional flaps from the hand, distant flaps, and reimplantation. With most of these operative techniques, repair is best performed as a primary procedure under ideal circumstances or as a delayed procedure when necessary. A flap may be used to cover exposed bone or soft tissue avulsion and to add bulk to the tip. The nail bed tissues should be preserved because the presence of a nail affects the cosmetic result. At least 5 mm of healthy nail bed distal to the lunula is needed for nail adherence. Skin grafting is a common method for treating fingertip amputations with significant avulsed tissue and can provide a functional and an esthetic reconstruction.

Complications. These injuries commonly leave the patient with a painful, cold-intolerant fingertip; this complication has been described after primary closure, coverage with grafts or flaps, and healing by secondary intention. Skin grafting may result in induration, fissuring, and diminished sensibility. Nail deformity is common, particularly with considerable volar loss of tissue.[78]

Acute Nail Bed Injuries

Injuries of the nail bed most commonly result from localized trauma to the nail with subsequent compression of the nail bed. The most common type of injury is simple laceration followed by stellate laceration, crush, and avulsion.[79] The middle and distal thirds of the nail bed are the most common sites of injury, and 50% of these injuries involve fractures of the distal phalanx or tuft.[79] Radiographs are required in most cases to show occult fractures and foreign bodies.

Subungual Hematoma. Subungual hematomas result from crush injury or blunt trauma to the nail bed with bleeding from

www.ketabpezeshki.com 66485457-66963820

the rich vascular bed. The nail bed is predisposed to injury because it is interposed between the firm nail and the distal phalanx. The injury is manifested by pain and dark red to black discoloration of the nail bed and is classified by the percentage of area beneath the nail that is involved. When the fingertip is unstable or the mechanism of injury suggests a significant distal phalanx fracture, a radiograph should be obtained to identify associated fracture.

Management. Small subungual hematomas do not require drainage; the blood is incorporated into the nail and eventually removed with the free edge. Large (>50% of the nail) hematomas cause significant discomfort and should be removed by nail trephination with a heated paper clip or a hot microcautery unit. Some clinicians recommend a surgical scrub of the finger before perforation of the nail to prevent contamination of the subungual area and the subsequent risk of infection and potential osteomyelitis, but this generally is unnecessary. Anesthesia is not necessary, and pain relief is immediate with decompression. If a significant fracture is present, the digit should be splinted. Although a distal phalangeal fracture with a subungual hematoma is technically an open fracture, such injuries usually heal without problems. Ungual tuft fractures are not associated with osteomyelitis. The risk of infection with an open fracture of the phalanx proper should be considered, and a broad-spectrum antibiotic and close follow-up monitoring are recommended. Otherwise, antibiotics are not necessary. Patients with significant hematomas should be informed that they may lose the nail.

Some authorities recommend nail removal and nail bed repair if the size of the subungual hematoma is greater than 50% of the nail area. Simon and Wolgin[80] attempted to correlate the association between subungual hematoma size, digital phalanx fractures, and occult nail bed lacerations. In their series, patients with a subungual hematoma greater than half the size of the nail had a 60% incidence of nail bed laceration requiring repair, and if an associated fracture of the distal phalanx was present, the incidence was 95%. If more than 50% of the visible portion of the nail is undermined by hematoma, some clinicians recommend removal of the nail, inspection of the nail bed, and repair of injuries. However, several studies have found no notable differences in outcome between nail trephination alone and formal nail bed repair regardless of hematoma size in cases with an intact nail and nail margins.[81-83] As a result, many authorities now recommend nail removal and repair of the nail bed only if the nail is broken or the nail edges are disrupted.[79]

Nail Bed Lacerations. Lacerations of the nail bed should be repaired to minimize esthetic deformity and the duration of functional impairment. These injuries generally do well after primary repair, but late reconstruction of the nail bed is unpredictable, and usually little improvement is obtained.

Simple and crushing lacerations should be repaired accurately with 5-0 or 6-0 absorbable suture, ideally under loupe magnification. The results with both injuries should be satisfactory in the majority of cases.[79] After the nail bed is accurately approximated, a hole is burned through the nail to allow drainage of blood from the subungual area after the nail is reinserted into the nail fold. The avulsed nail may be sutured in place or secured with tape. A single thickness of nail-shaped Adaptic or other nonadherent gauze may be placed in the nail fold if the nail is unavailable. The replaced nail or gauze is used as a temporary splint to help protect the integrity of the underlying nail bed and maintain the fold for new nail growth and to help prevent synechiae and subsequent nail deformity. Complete nail growth takes 70 to 160 days, but after the injury the growth pattern often is changed.

Nail bed avulsion commonly leaves fragments of nail bed attached to the undersurface of the avulsed nail.[84] In these cases it is advisable to replace the nail as accurately as possible onto the avulsion site. Repair should be done with mattress sutures without attempting to separate the nail from the nail bed. If the tissue is not available and the defect is small, effective healing occurs by secondary intention.

Clenched-Fist Injuries

All human bites should be considered serious in nature and at risk for significant complications. Clenched-fist injuries, also called “fight bites,” are notorious for being the worst human bites. Inadequate initial management leads to significant morbidity. Misleading history, innocuous wound appearance, intoxication and lack of cooperation of the patient leading to inadequate examination, patient reluctance to admit the nature of the injury, delayed presentation, and inadequate exploration all may lead to mismanagement. Clenched-fist injuries are associated with the highest incidence of complications of any closed-fist injury and of any type of bite wound.[85]

Clinical Features

The classic injury is a bite wound over the third MCP joint, but injury can occur over any joint. Soft tissue injury is apparent with possible extensor tendon injury and violation of the joint capsule. When the fist is subsequently opened, the bacterial inoculum is dragged with the extensor tendon and soft tissue proximally into the dorsum of the hand.[85] Presentation may be acute or delayed. Swelling, limited range of motion, erythema, and pain out of proportion to the apparent severity of injury are typical findings. Pain is more severe with range of motion.

Management

Aggressive management is indicated with these injuries. Immediate consultation with a hand surgeon is advised. Analgesics, irrigation, tetanus, cultures, intravenous antibiotics, appropriate wound care, elevation of the affected limb, and hospital admission should be considered for all patients. Foreign bodies are excluded with radiologic studies and possibly exploration. Tendon injuries are ruled out with careful exploration. The hand should be splinted in the position of function. Pathogens usually are polymicrobial, with *Staphylococcus aureus,* streptococci, and anaerobes the predominant species. Multiple-drug regimens are recommended; amoxicillin-clavulanic acid or penicillin with a first-generation cephalosporin is commonly used.

High-Pressure Injection Injuries

Epidemiology

High-pressure injection injuries to the hand are uncommon, and most are occupation related. The usual cause is an accident involving industrial equipment, with machinery such as grease guns, spray guns, and diesel engine injectors accounting for most of these injuries.[86] A wide variety of materials, including paint, paint thinner, grease, oil, hydraulic fluid, plastic, wax, water, and semifluid cement, have been reported to be injected. In general, substances that are highly viscous (e.g., grease) require higher forces to produce injury than do paint, oil, and solvents. The high pressures involved are sufficient to penetrate skin from a distance, and contact of the device with the hand is not a prerequisite for injury to occur. High-pressure injection injuries have been associated with amputation rates as high as 48%.[87] Recent data suggest amputation rates of 30%, which may be a result of higher vigilance and early recognition of tissue injury.[88] Early recognition and intervention are essential. Even with early intervention, the injury leads to significant impairment, with delays in débridement associated with higher rates of amputation.[87]

www.ketabpezeshki.com 66485457-66963820

Pathophysiology

Patient characteristics and injury circumstances often are similar in high-pressure injection injuries. The patient generally has a history of coming into close proximity to the jet stream during cleaning of the nozzle or testing or operation of the equipment. The patient usually is an inexperienced worker, and the nondominant hand most commonly is involved, with the index finger the most common site.

Tissue injury from high-pressure injection generally depends on physical, chemical, and biologic factors. Of particular importance are the type, amount, and velocity of injected material and the anatomic location of the injury. The most important factor is the type of material injected, which determines the likely tissue inflammatory response and the resulting fibrosis that develops during healing. Paint and paint thinner produce a large, early inflammatory response, resulting in a high percentage of amputations.[89] By contrast, grease injuries cause a small inflammatory response and carry a lower amputation rate but are associated with oleogranuloma and fistula formation, scarring, and loss of digit function.[89] The amount of material injected into the confined space of the digits or palm determines the degree of mechanical distention and the potential for vascular compromise. The velocity of the injected material and the site of tissue penetration determine dispersion, which may include the digit, hand, and forearm. Injection injuries at distal sites (e.g., tips of fingers) carry a worse prognosis than proximal injections.[87]

Clinical Features

The patient who seeks treatment early after injury may have minimal symptoms with either an innocuous entrance wound or no visible break in the skin. Fusiform swelling resulting from mechanical distention of the tissue by the injectant may not be apparent. Several hours later, the involved digit or palm becomes extremely painful, swollen, and pale because of vascular compromise and tissue necrosis. Careful examination is necessary to document the extent of injury and associated neurovascular function. Radiographs of the involved hand can help determine the spread of material and the amount of débridement necessary, because certain injected materials are radiopaque. In addition, they may reveal subcutaneous emphysema.

Management

Initial ED management includes splinting, elevation of the affected limb, tetanus prophylaxis, analgesia, and broad-spectrum antibiotics. Digital blocks are contraindicated because of the potential for increased tissue pressure, which may aggravate vascular compromise. The keystone in treatment of these injuries is prompt recognition of the severe nature of the injury despite the often innocuous appearance of the wound. Emergent hand surgery consultation is warranted because most cases require early extensive surgical decompression and débridement.

Complications

Early recognition and treatment, including operative decompression and débridement, greatly influence outcome. Early surgical amputation should be considered in cases in which the affected digit is initially cool or poorly perfused.[90] In most other cases, joint stiffness is a late sequela.

Amputations and Ring Avulsion Injuries

Few epidemiologic studies have been done on amputation injuries. Traumatic amputations have been reported to constitute 0.1 to 1% of all hand injuries.[2] Amputation may be complete or partial. Injuries with interconnecting tissue between the distal and the proximal portions are considered incomplete, or partial, amputations. Complete amputations will necessitate replantation, whereas with partial amputations, revascularization is attempted. Traumatic amputations most commonly result from local crush injuries and occur infrequently from a sharp guillotine mechanism. Partial and complete amputations reportedly occur with equal frequency. The former are often related to the use of power saws and lawnmowers.

Ring avulsions include a spectrum of injuries from partial degloving of the skin of a finger to loss of the entire digit and entire length of a flexor tendon. These injuries usually occur when a ring on a finger catches on an object during a fall. In addition to neurologic and arterial injuries, there may be complete disruption of the venous return of the finger. In general, these injuries represent complex management problems, and treatment may range from primary amputation to microvascular repair with replantation and free tissue transfer in addition to local flap, pedicle flap, or graft coverage.[91]

The initial care and treatment for the patient who has had a body part amputated are the same as for any trauma patient. After the initial primary assessment and stabilization of the patient, the injured extremity should be examined carefully with documentation of neurologic, vascular, and musculotendinous function. Subsequent care should be directed toward preservation of the limb and its components. General management goals include the following: (1) provide supportive care, such as control of hemorrhage with direct pressure and elevation; (2) prolong the time that the amputated tissues remain viable; (3) protect wounds from further injury; and (4) arrange expeditious consultation by a surgical subspecialist. With few exceptions, all completely amputated parts should be considered for replantation, and all partially amputated parts should be considered for revascularization.

In complete amputations, the proximal stump and the amputated part should be examined for degree of tissue injury, contamination, and associated injuries. Gross contaminants can be removed by irrigation with normal saline. Local antiseptics, especially hydrogen peroxide or alcohol, should not be used because they may damage viable tissues. The wound should not be manipulated, clamped, tagged, or traumatized further in any way. The stump should be covered with a saline-moistened sterile dressing to prevent further contamination and desiccation, and the limb should be elevated to help reduce edema and control bleeding. The amputated part requires minimal handling and should be cooled as soon as possible. After being wrapped in saline-moistened gauze, the part is sealed in a dry plastic bag, which is placed in ice water. Ice should not come in direct contact with the tissue because this can cause tissue freezing. Amputated parts should not be discarded or sent to the pathology department because even if they cannot be replanted, they may serve as a donor source for skin, bone, or vessel grafts. Radiographs of the amputated part and proximal stump should be obtained. The use of analgesic medications will likely be necessary, and appropriate tetanus prophylaxis can be administered. The use of prophylactic antibiotics is indicated in amputation injuries because significant devitalized tissue often is present. Most authorities recommend empirical coverage for *S. aureus* with a combination of penicillin G and an antistaphylococcal antibiotic or first-generation cephalosporin.

Treatment for partial amputations with vascular compromise is the same as that just described. The wound should be cleaned with normal saline irrigation, and the injured part wrapped in a sterile moist dressing and splinted to protect it from further injury. Cold packs are applied to the dressings to prevent warm ischemia.

The time for which an amputated part can survive before replantation has not been determined. As a general rule, the more proximal the amputation, the less ischemia time the amputated

www.ketabpezeshki.com 66485457-66963820

part can tolerate. Attempts to extend viability during ischemia have shown that the most important controllable factor is the temperature of the amputated part. Warm ischemia may be tolerated for 6 to 8 hours; cooling the part to 4° C extends this time to approximately 12 to 24 hours with distal amputations. Successful replantation of digits after 40 hours of warm ischemia has been reported.[92]

The decision of whether to attempt replantation should be made by the surgeon who is responsible for performing the procedure. On occasion, final judgment regarding replantation may be delayed until after microscopic inspection of vessels and nerves has been completed.[93] Patient selection generally is based on the nature and level of the injury and patient age and health-related factors. The classic indications for and contraindications to replantation are listed in Box 50-3. The thumb is needed to preserve the function of opposition, and all such traumatic amputations should be considered for microvascular salvage regardless of the level of amputation or mechanism of injury. Loss of the thumb is equivalent to a 40% loss of function of the hand.[94] Similarly, all amputations in children should be considered for replantation. In replantation of digits amputated distal to the insertion of the FDS between the PIP joint and the DIP joint, good motor and sensory function often is achieved. If the amputated part is crushed, mangled, or amputated at multiple levels, however, replantation usually is contraindicated. With digits that cannot be replanted, skin coverage by flaps or ray resection will be required.

Complications

Replanted fingers and hands never regain premorbid function. Replanted and revascularized parts may develop cold intolerance, stiffness, loss of sensation, pain, malunions, and nonunions. Even successful replantations may require repeated operative procedures and involve prolonged disability. Necrosis is an obvious sign of failure.

Vascular Injuries

Significant vascular disorders of the hand are uncommon compared with other problems of the hand. The vascular supply to the hand and digits is duplicated so that isolated arterial injuries to either side seldom result in ischemia. Lacerations of the arteries of the hand may stop bleeding by the time the patient is evaluated; in these situations, a history of pulsatile bleeding is highly suggestive of an arterial injury. Although most arterial injuries are the result of penetrating trauma, blunt trauma to the hand occasionally can result in arterial thrombosis or a false aneurysm.[13] In addition, associated injuries should not be overlooked. Because digital nerves invariably cross with and are superficial to the digital artery, an arterial lesion should raise the possibility of an accompanying nerve injury.

Circulatory status is assessed as previously described by observation for cyanosis or pallor, palpation of radial or ulnar pulses at the wrist, assessment of capillary refill, and the use of Allen's test. Ischemic pain is the most common initial complaint of patients with vascular insufficiency, along with physical manifestations of pallor and gangrene. The presence of a mass, with or without pain and tenderness, is the second most common initial complaint.

Management

Lacerations or amputations of the upper limb rarely cause life-threatening hemorrhage. Even a major vessel that is completely transected usually retracts, constricts, and clots. Major vessels often continue to bleed briskly, however, from partial transections with life-threatening hemorrhage. Usually hemorrhage can be adequately controlled with direct pressure and limb elevation. If necessary, a proximally placed blood pressure cuff inflated to 30 mm Hg above systolic pressure can be used for short periods (<30 minutes) to control severe bleeding. Vascular clamps and hemostats should not be used in the ED to control bleeding in the hand because of the danger of inadvertently crushing nerves and tendons. Lacerated arteries should be repaired if symptoms of ischemia or an associated nerve injury are present. Arterial repair is not mandatory in isolated arterial injuries with good distal vascularity because there is a high rate of thrombosis after reanastomosis. If the decision is made not to repair a lacerated artery, both stumps should be ligated to prevent further bleeding. Palmar arch lacerations may be difficult to visualize in the ED and usually require surgical exploration to control bleeding.

Compartment Syndrome in the Hand

A *compartment syndrome* develops when elevated pressure within a closed fascial space reduces perfusion to the point of muscle and nerve dysfunction. In the hand, 10 compartments are evident on cross section through the palm (Fig. 50-54). In addition, the

Box 50-3 Classic Indications for and Contraindications to Replantation

Indications
- Multiple digits
- Thumb
- Wrist and forearm
- Sharp amputations with minimal to moderate avulsion proximal to the elbow
- Single digits amputated between proximal interphalangeal joint and distal interphalangeal joint (distal to flexor digitorum superficialis insertion)
- All pediatric amputations

Contraindications
- Amputations in unstable patients secondary to other life-threatening injuries
- Multiple-level amputations
- Self-inflicted amputations
- Single-digit amputations proximal to the flexor digitorum superficialis insertion
- Serious underlying disease, such as vascular disease, complicated diabetes mellitus, or congestive heart failure
- Extremes of age

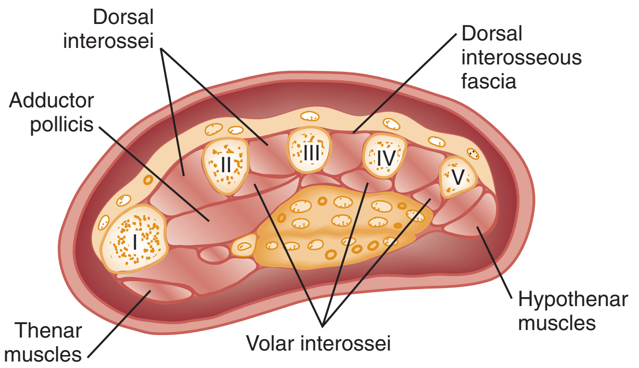


Figure 50-54. Cross section through the palm showing structures involved in forming the compartments of the hand. (From Rowland SA: Fasciotomy: The treatment of compartment syndrome. In Green DP [ed]: Operative Hand Surgery, 3rd ed. New York, Churchill Livingstone, 1993, p 670.)

www.ketabpezeshki.com 66485457-66963820

fingers are compartmentalized by fascia and skin at flexor creases. Because these compartments are not interconnected, each additional compartment should be surgically decompressed if muscle ischemia is suspected.[13,95]

Nerve Injuries

Nerve injuries may result from a direct blow, puncture or laceration, crush injury, injection injury, or amputation. These injuries are divided into three main groups: neurapraxia, axonotmesis, and neurotmesis. In *neurapraxia,* there is loss of function of the nerve, but the axon, Schwann's sheath, and endoneurium remain intact. Recovery in these cases is usually complete within days. In *axonotmesis,* the axon is severed within an intact endoneurial tube. The distal axon degenerates and is absorbed after disruption. The proximal portion of the severed axonal stump can regenerate along the intact endoneurial tube at a rate of approximately 1 to 3 mm/day with ultimate return of function. *Neurotmesis* refers to complete disruption of all nerve elements. Regrowth of the proximal axonal endings does not occur along the endoneurial tubes, unless the severed nerve endings are reapproximated.[96]

Peripheral nerve injuries are diagnosed by physical examination showing loss of motor or sensory function. Specific nerves at risk should be examined as previously outlined. Injury most commonly involves one of the digital nerves but also may be localized to the median, radial, or ulnar nerve.

Management

Identification of the injury and appropriate referral are important aspects in the initial management of patients with nerve injuries in the hand. Patients with closed nerve injuries not associated with compartment syndromes should be referred to a hand specialist for serial examinations. All digits that have lost function as a result of a nerve injury should be splinted to prevent further inadvertent injury. If function does not return within 3 weeks, electromyograms and nerve conduction studies can help differentiate neurotmesis from axonotmesis and determine the need for surgical exploration.[96]

Lacerated nerves require reapproximation by hand surgeons. In general, all motor branches of the ulnar and median nerves should be repaired. In addition, digital nerve injuries proximal to the DIP crease on the radial aspect of the index finger, the ulnar aspect of the little finger, and both sides of the thumb should be considered for repair.[97] Clean, single-nerve lacerations should be repaired primarily when feasible. Complex nerve injuries may involve wound contamination or extensive tissue damage and usually are managed by delayed repair to allow for improved soft tissue conditions. Although the functional recovery is never complete, a good outcome can result from primary and delayed repair. In general, sensory recovery returns more often than does motor function.

Complications

Complications of nerve injuries include motor and sensory loss, atrophy from denervation, chronic paresthesias, regrowth of painful neuromas, and sympathetic dystrophy.

Infections of the Hand

The unique anatomic structures of the hand affect the nature of infections in this region of the body. In general, hand infections can be divided into infections involving the skin, subcutaneous tissues, fascial spaces, tendon, joint, and bone. Fibrous compartments of the distal fingertips contain the spread of infection, whereas flexor tendon sheaths allow infection to travel considerable distances along the lengths of the tendons from the original site. Infections in the deep spaces of the palm usually manifest on the dorsal surface of the hand.

Paronychia

Pathophysiology. A *paronychia* is a localized superficial infection or abscess involving the lateral nail fold. It is the most common infection in the hand and is thought to be caused by frequent trauma to the delicate skin around the fingernail and cuticle. Clinically, swelling and tenderness of the soft tissue along one or both sides of the lateral nail fold are evident. A paronychia begins as a cellulitis, but a frank abscess may form, and occasional extension to the overlying proximal nail (termed an *eponychia*) may be seen. *S. aureus* is the most common isolate, followed by streptococci.[98] Paronychias in children often are caused by anaerobes, presumably because of finger sucking and nail biting common in this age group.[99] Atypical mycobacteria, *Candida albicans,* and other fungi should be considered as causative agents in chronic cases unresponsive to standard treatment.[100]

Management. In the early cellulitis phase, management consists of frequent warm soaks, elevation of the affected limb, and administration of an oral antistaphylococcal antibiotic, such as dicloxacillin or cephalexin. When the area becomes fluctuant, drainage is necessary and usually is curative. Adequate drainage often can be obtained by lifting the skin edge off the nail to allow the pus to drain (Fig. 50-55). This can be accomplished without anesthesia in selected patients, but drainage for more extensive lesions is best carried out under digital block anesthesia. After the eponychium has been softened by soaking, a No. 11 blade scalpel or an 18-gauge needle may be advanced parallel to the nail and under the eponychium at the site of maximal swelling.[98] If the infection is more extensive, the lateral one fourth of the nail may be bluntly dissected from the underlying nail bed and germinal matrix, and the lateral nail plate excised. After the cavity is irrigated, a small piece of packing gauze may be slipped under the eponychium for 24 hours to provide continual drainage. Cultures are not indicated. Antibiotics are commonly prescribed, although this is not necessary if drainage is complete or if the surrounding area of cellulitis is minimal. Most paronychias resolve in 5 to 10 days, and patients are advised to obtain primary care follow-up evaluation. A well-known complication of even a properly drained paronychia is osteomyelitis of the distal phalanx. Patients with a chronic,

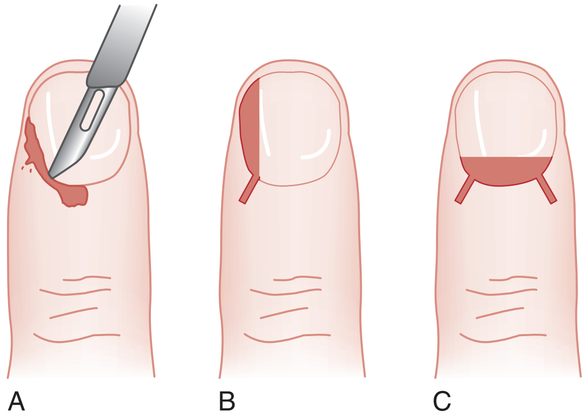


Figure 50-55. Drainage of paronychia. **A,** Eponychial fold is elevated from the nail for a simple paronychium. **B,** Lateral nail is removed if pus tracks under it. A small eponychial incision may be necessary. **C,** Proximal nail is removed if pus tracks under it. Two incisions are needed to remove the proximal nail. (From Moran GJ, Talan DA: Hand infections. Emerg Med Clin North Am 11:601, 1993.)

www.ketabpezeshki.com 66485457-66963820

indolent infection of the perionychium seldom respond to ED intervention. These patients should be referred to a dermatologist or hand surgeon because of the prolonged treatment required.

Felon

Pathophysiology. A *felon* is an infection of the pulp of the distal finger or thumb. It differs from other types of subcutaneous abscesses because of the presence of multiple vertical septa that divide the pulp into small fascial compartments. The usual cause is penetrating trauma with secondary bacterial invasion. The most common pathogen is *S. aureus,* although gram-negative organisms and polymicrobial infections also have been described.[100] Although the septa may facilitate an infection in the pulp and inhibit drainage after incomplete surgical decompression, they provide a barrier that protects the joint space and the tendon sheath by limiting the proximal spread of infection. Clinically, a felon begins as an area of cellulitis and inflammation that progresses rapidly to severe throbbing, pain, swelling, and increased pressure in the distal pulp space.

Management. Traditional management of felons emphasizes the need for early and complete incision through the septa to provide adequate drainage and to relieve pressure in septal compartments. Most felons can be drained by a single lateral incision.[100] The incision should be made along the ulnar aspect of the index, middle, and ring fingers and the radial aspects of the thumb and little finger, avoiding pincher surfaces. The incision is begun approximately 0.5 cm distal to the DIP joint crease and dorsal to the neurovascular bundle of the fingertip. The incision is extended to the free edge of the nail (Fig. 50-56). The wound should be irrigated and loosely packed with gauze, and the affected finger splinted. The packing is removed in 48 to 72 hours, and the wound is left to close secondarily. Most felons are treated empirically with an antistaphylococcal oral antibiotic for at least 5 days pending culture results. Some authorities recommend draining this abscess where it "points," with use of a volar midline incision that does not cross the distal flexion crease.[101]

Complications. If untreated, the expanding abscess can extend toward the phalanx, producing an osteitis or osteomyelitis, or toward the skin, resulting in necrosis and formation of a sinus tract on the palmar surface of the digital pulp. Other complications include soft tissue and bony tuft necrosis, osteomyelitis, septic arthritis of the DIP joint, and flexor tenosynovitis from proximal extension. The lateral incision used to drain felons commonly leaves unstable finger pads or may result in painful neuromas or anesthetic fingertips. "Fishmouth" incisions may destroy the blood supply to the fingertip.[100] Longitudinal midline incisions on the volar surface may leave scars over an important area for sensation but do not have the other disadvantages of lateral incisions. Any incision that is made too deeply and proximally can injure the flexor tendon sheath, initiating a tenosynovitis.

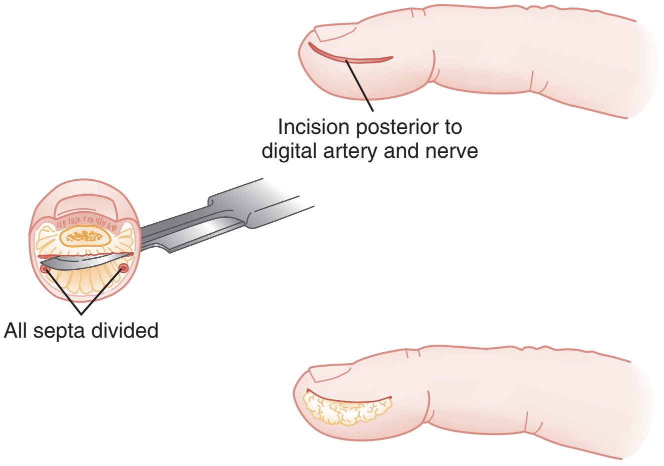


Figure 50-56. Incision and drainage of felon with the unilateral longitudinal approach. Most felons should be drained via this incision. (From Wright PE: Hand infections. In Canale ST [ed]: Campbell's Operative Orthopaedics, 11th ed. St. Louis, Mosby, 2008.)

Herpetic Whitlow

Epidemiology and Pathophysiology. Herpetic whitlow is a self-limited herpes simplex viral infection of the distal finger. It is the most common viral infection of the hand. Infection by human herpes simplex virus type 1 or 2 is clinically indistinguishable.[102] Direct inoculation of the virus into an open wound or broken skin is the usual mechanism of primary infection. Herpetic whitlow commonly is reported in adult women with genital herpes and children with coexistent herpetic gingivostomatitis. Health care workers are at increased risk for development of this infection as an occupational hazard secondary to exposure to orotracheal secretions; however, a review of herpes infection in the hand found that only 14% of adult cases occur in health care workers.[103] The overall incidence has decreased, probably as a result of heightened awareness of the condition and strict infection control precautions.

Clinical Features. The infection usually involves a single finger and begins with localized pain, pruritus, and swelling, followed by the appearance of clear vesicles. Systemic symptoms usually are absent; however, secondary infection of the vesicles can occur.[102] More typically, the vesicles coalesce over 2 weeks to form an ulcer, which may develop a hemorrhagic base. At this stage, it may be difficult to distinguish herpes simplex infection of the hand from more common bacterial infections, such as felon or paronychia. The distinction is important because drainage of the herpetic lesions is contraindicated and may lead to viral dissemination and secondary bacterial infection. A careful history is important to determine risk of a possible herpetic cause. On examination, tenderness is present but is noticeably less than that typical for bacterial infections. In addition, the pulp space remains soft and does not become tense, as it does in a bacterial felon.[104]

Diagnostic Strategies. The diagnosis usually is made clinically on the basis of the appearance of the lesion and the history of recurrence or potential sources of inoculation. The diagnosis may be confirmed by polymerase chain reaction (PCR), viral culture, or a Tzanck smear showing multinucleated giant cells in a scraping taken from the base of an unroofed vesicle.[102,105]

Management. Herpetic whitlow usually resolves spontaneously in 3 to 4 weeks, although recurrence is common, occurring in up to 20% of cases. The main goals of treatment are to prevent oral inoculation or transmission of the infection and to provide symptomatic relief. The involved digit should be kept covered with a dry dressing. Oral acyclovir has a role in treatment for immunocompromised patients and patients with frequently recurring infections, but its role in immunocompetent patients is less clear.[105] Topical acyclovir has not been shown to be effective in either the treatment of or the prophylaxis for this disorder.

Tenosynovitis

Pathophysiology. Acute synovial space infections in the hand usually involve the flexor tendon sheaths and the radial and ulnar bursae. The tendon sheaths are double-walled, with a visceral layer adherent to the tendon and a parietal layer extending from the midpalmar crease to just proximal to the DIP joint. The flexor tendon sheath of the thumb is continuous with the radial bursa of the palm, and the small finger sheath is continuous with the

www.ketabpezeshki.com 66485457-66963820

ulnar palmar bursae. The ulnar bursa surrounds the superficial and deep flexor tendons, and the radial bursa surrounds the flexor pollicis longus. These two bursae communicate in 80% of persons; in most instances, however, the tenosynovial coverings of the index, middle, and ring fingers do not communicate. Infections in the synovial spaces in the hand tend to spread along the course of the flexor tendon sheaths and may spread to the midpalmar, thenar, and lumbrical compartments. Infections usually are caused by penetrating trauma to the sheath, but they occasionally result from hematogenous spread. The most commonly isolated organisms are *S. aureus* and streptococci, followed by gram-negative organisms and enterococci.[106]

Clinical Features. Four cardinal signs of acute flexor tenosynovitis usually are present and help differentiate tenosynovitis from other soft tissue infections in the hand: (1) tenderness along the course of the flexor tendon, (2) symmetrical swelling of the finger, (3) pain on passive extension, and (4) a flexed posture of the finger.[60] All four signs may not be present early in the course of infection. The third sign may be the most important. Early recognition and treatment are essential because elevated pressure within the enclosure of the flexor tendon sheath can occlude the already tenuous circulation to the tendon, resulting in necrosis and proximal spread.

Management. All patients with flexor tenosynovitis require hospital admission and prompt consultation with a hand surgeon to determine whether open drainage or closed tendon sheath irrigation is indicated. In early cases or uncertain diagnoses, the hand should be splinted in a bulky dressing and elevated, and intravenous antibiotics should be initiated. Infections secondary to penetrating trauma should be treated with a penicillinase-resistant antistaphylococcal penicillin or first-generation cephalosporin. Disseminated gonorrhea should be considered in all sexually active persons, especially if a traumatic cause for the infection is not apparent. In such cases, some authorities recommend empirical treatment with ceftriaxone until results of final cultures (including mucosal sites) are available.[106,107] Surgical treatment is indicated for established cases or when improvement is not evident within 24 hours.

Deep Space Infections

Anatomy and Pathophysiology. The deep fascial or palmar spaces of the hand include the midpalmar space, the hypothenar space, and the thenar space. Three additional, more superficial spaces of the hand are the dorsal subcutaneous space, the dorsal subaponeurotic space, and the interdigital web space[108] (Fig. 50-57). Although anatomically distinct from the deep spaces owing to their lack of well-defined anatomic borders, superficial spaces can harbor infections that manifest similarly to deep space infections.[108] The fascial spaces are potential rather than actual spaces in a normal hand.[109] These closed compartments are susceptible to infection from direct penetrating trauma, infection in contiguous compartments, or hematogenous seeding. The most commonly isolated pathogens are *S. aureus*, streptococci, and coliforms.

Clinical Features. The unique anatomic features of the deep fascial spaces lead to characteristic clinical findings when these regions are involved with pyogenic infection. The dorsal subaponeurotic abscess causes swelling and erythema on the dorsum of the hand. Pain with passive movement of the extensor tendons often is present, but it may be difficult to distinguish clinically from simple cellulitis on the dorsum of the hand. Subfascial web space infections commonly result when palmar blisters become secondarily infected. The infection tends to spread dorsally into the interdigital space and produce a characteristic hourglass configuration, or the so-called "collar-button abscess" (Fig. 50-58). Thenar space infections are characterized by pain and swelling of the thenar eminence and the first web space; the thumb is held in abducted and flexed position.[109] In midpalmar infections, clinical features include loss of the normal hand concavity and tenderness of the central palm; movement of the middle and ring fingers is painful. Suppurative tenosynovitis of the second digit can rupture proximally into the thenar space, with subsequent abscess formation. Tenosynovitis of digits III, IV, and V may be responsible for a midpalmar space infection.

Management. Treatment of all deep fascial space infections involves intravenous antibiotics and operative exploration and drainage by experienced surgeons. The most common practice is to use broad-spectrum empirical coverage with a β-lactamase–resistant penicillin or a first-generation cephalosporin. Based on local bacteriologic data, it may be necessary to begin empirical coverage against methicillin-resistant *S. aureus* (MRSA).[110]

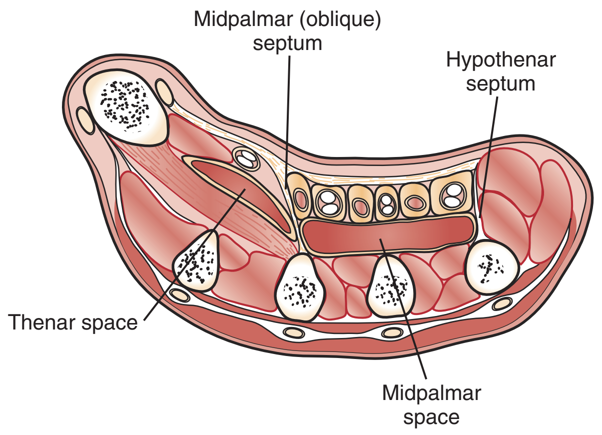


Figure 50-57. Potential midpalmar spaces. (From Stevanovic MV, Sharpe F: Acute infections. In Wolfe SW, Hotchkiss RN, Pederson WC, Kozin SH [eds]: Green's Operative Hand Surgery 6th ed. New York, Churchill Livingstone, 2011, p 59.)

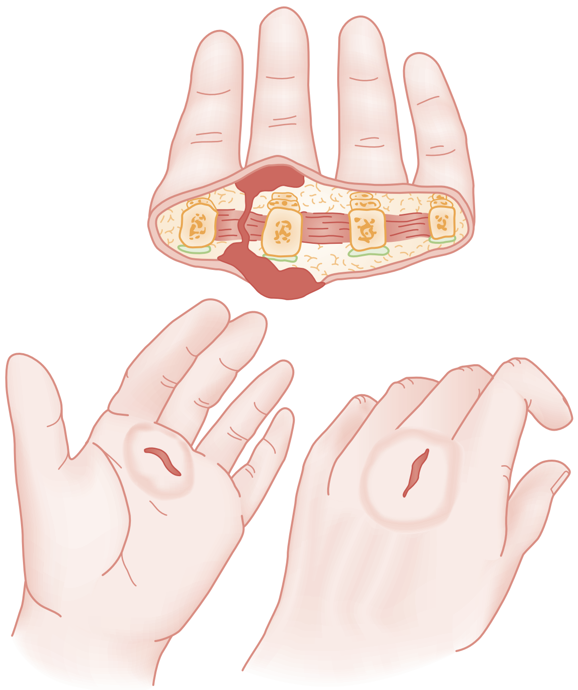


Figure 50-58. Collar-button abscess. The palmar space infection has spread to the dorsum of the hand. (From Lewis RC Jr: Infections of the hand. Emerg Med Clin North Am 3:263, 1985.)

www.ketabpezeshki.com 66485457-66963820

Septic Arthritis

Pathophysiology. Septic arthritis in the hand may involve the IP, MCP, CMC, or radiocarpal joints. These joints usually are infected by direct inoculation of bacteria from penetrating trauma or by spread from a contiguous infective process, such as a felon or tenosynovitis. Hematogenous spread may occur but is less common than in other joints of the body. *S. aureus* is the most common cause; streptococci, *Haemophilus influenzae, Pseudomonas aeruginosa,* and coliforms are involved much less commonly.[111] A survey at a large county hospital found that the most commonly isolated organisms were staphylococci and streptococci in nearly equal numbers, with enterococci, corynebacteria, and anaerobes encountered rarely.[112] Monarticular nontraumatic septic arthritis also may be caused by *Neisseria gonorrhoeae.*

Clinical Features. Clinically the involved joint appears red and swollen and is extremely tender; an overlying puncture wound may be visible. The joint is held in a position that maximizes its volume (slight flexion for MCP and IP joints), and passive motion of the joint, however slight, is painful. In contrast with flexor tenosynovitis, tenderness is localized to the involved joint.[108] Pain also may be elicited by axial compression of the joint. The diagnosis is made by arthrocentesis.

Management. Treatment includes parenteral antibiotics with a semisynthetic antistaphylococcal penicillin and emergent drainage of the joint. Most infected joints require open drainage, but some hand surgeons may choose to manage certain cases with closed joint catheter irrigation and repeated aspiration.

Osteomyelitis

Osteomyelitis in the hand occurs most commonly with open fractures or with secondary involvement of bone from soft tissue infections. The incidence of infection in open fractures of the hand is much lower than in open long bone fractures and is reported to be 1 to 11%. McLain and colleagues[30] found that injuries with severe skeletal trauma, gross contamination, and significant soft tissue injury have the highest risks for infection. The presentation of osteomyelitis is seldom rapid and fulminant, unless associated with septic arthritis or other deep space infection of the hand. Physical signs may include fever, localized redness, swelling, warmth, and tenderness. Children with osteomyelitis may have pseudoparalysis, manifesting as refusal to use the affected limb.[114] Radiographs may show bone destruction or periosteal elevation. Treatment includes débridement of infected bone and sequestra and parenteral antibiotics.

Nontraumatic Disorders of the Hand

Stenosing Tenosynovitis

The most common type of stenosing tenosynovitis in the hand involves the flexor tendons at the level of the MCP joint where the tendon passes through the pulley systems. Repetitive strain can result in tendon and pulley hypertrophy with localized tenderness. When painful blocking of flexion and extension is noted at the involved joint, the condition is called *trigger finger,* as noted earlier. The ring and long fingers are the most commonly involved digits. Injection therapy is recommended and works well in most patients.[115] A mixture of 1% lidocaine and steroid suspension (for a total volume of 0.5-1 mL) is given over the nodule and into the tendon sheath.[116,117] After the injection, extension of the finger usually is possible. The finger should be splinted in extension, and referral to a hand surgeon is advised because multiple injections or surgical release may be required.[118]

Ganglion

A ganglion is the most common soft tissue tumor of the hand and consists of a synovial cyst from either a joint or the synovial lining of a tendon that has herniated. Ganglia contain a gelatinous fluid that is secreted by the synovial tissue. They are common in the wrist and the flexor tendon sheaths of the fingers and usually have an insidious onset. Patients rarely recall a specific inciting traumatic event.[119] Patients commonly complain of a dull ache or mild pain over the ganglion. Reassurance is important, and the patient should be informed of the benign nature of the lesion. A large or troublesome ganglion can be aspirated. Because of the high rate of recurrence, definitive treatment is operative excision, which is done on an elective basis.[119]

Foreign Bodies in the Hand

Penetrating trauma to the hand may result in a foreign body becoming lodged in the soft tissues. The presence of a foreign body should be considered in any wound regardless of its size. A detailed and accurate history of the injury should be obtained because the mechanism often gives clues to the possibility of a foreign body.[120] The most common foreign bodies are pieces of wood, glass, or metal. Useful signs of occult foreign bodies include sharp pain with deep palpation over a puncture wound, pain associated with a mass, and failure of a wound to heal or persistence of pain with movement.[19]

Initial examination of hand wounds should include local exploration with sterile technique in a bloodless field. After exploration and removal of easily accessible foreign bodies, radiographs should be taken using soft tissue technique with multiple views. Radiographs are the best method for detecting radiopaque foreign bodies and detect metals, most glass, many plastics, gravel, and sand.[19] Wooden foreign bodies are difficult to visualize radiographically.[121] Whether an object shows on plain radiographs depends on its composition, configuration, size, and orientation. When a foreign body is clinically suspected and the initial radiographic appearance is normal, other imaging methods should be considered. The identification of nonmetallic objects such as splinters may be improved by the use of modalities including computed tomography, magnetic resonance imaging, and ultrasound studies.[19,121,122]

Management

Removal of embedded foreign bodies can be difficult and time-consuming, and potential damage to tissues caused by the procedure is weighed against the risk posed by the specific foreign body. Generally, if a foreign body contaminating a wound is clearly visible and likely to be easily extractable during local exploration, it should be removed in the ED. In some cases, the entrance wound may need to be enlarged with a small skin incision. In general, foreign bodies should be removed only under direct vision. When the object is buried within the intricate anatomy of the hand, this procedure should be deferred to a hand specialist.

Decisions regarding the necessity and timeliness of removal of a foreign body are based on the size and the reactivity of the foreign body, proximity to vital structures, degree of wound contamination, and presence or absence of symptoms.[19] Foreign bodies that cause continued pain, interfere with hand function because of their size or their position, or cause local or systemic toxicity (e.g., paints or mercury) should be removed. In removing foreign bodies, traction should be applied along the long axis of the foreign body in order to allow easier extraction, as well as to avoid breakage into two or more pieces. With foreign bodies

www.ketabpezeshki.com 66485457-66963820

associated with fractures, prompt surgical débridement is necessary to prevent osteomyelitis.[123] Wounds that are grossly contaminated with soil or organic material require immediate removal of the foreign body, débridement, and irrigation. Foreign bodies near tendons, nerves, and vessels and foreign bodies causing ischemia or hemorrhage require cautious removal under optimal conditions.

Patients who do not require immediate removal of the foreign body may be referred to a hand surgeon for delayed surgical exploration. If the hand specialist plans to remove the object within 3 to 4 days after injury, and if bacterial contamination is minimal, the wound may be closed primarily. Initial treatment also should include tetanus prophylaxis and an appropriate wound dressing. The patient should be informed about the presence of the foreign body and the reason for delayed removal. If no removal is planned, the physician should explain to the patient that the dangers of removal outweigh the benefits.

Complications.

Foreign bodies can damage soft tissues, provoke excessive inflammation with granuloma formation, predispose the patient to infection, and cause systemic toxicity. Iatrogenic damage to tissue can result from blind probing or excessively aggressive searches for foreign bodies; such maneuvers should be avoided, particularly in the hand.

KEY CONCEPTS

- Injuries and infections of the hand are among the most commonly encountered problems in the ED.
- An accurate history and carefully performed physical examination of the hand have a central role in evaluation and treatment. Hand radiographs should be obtained if suggestive signs are present. High-technology diagnostic modalities are rarely indicated.
- The best functional outcomes of hand injuries usually are achieved by accurate initial evaluation and treatment.
- A key factor in the evaluation of hand injuries is determining which entities require specialty referral or urgent consultation.
- Management of the injured hand should focus on restoring function and minimizing long-term disability.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Overton DT, Uehara DT: Evaluation of the injured hand. *Emerg Med Clin North Am* 1993; 11:585.
2. Atroshi I, Rosenberg H: Epidemiology of amputations and severe injuries of the hand. *Hand Clin* 2001; 17:343.
3. Altman RS, Harris GD, Knuth CJ: Initial management of hand injuries in the emergency patient. *Am J Emerg Med* 1987; 5:400.
4. Chung K, Spilson S: The frequency and epidemiology of hand and forearm fractures in the United States. *J Hand Surg Am* 2001; 26:908.
5. Sorock G, et al: Acute traumatic occupational hand injuries: Type, location, and severity. *J Occup Environ Med* 2002; 44:345.
6. Pratt NE: *Anatomy and kinesiology of the hand*. In: Skirven TM, eds: *Rehabilitation of the Hand and Upper Extremity*, 6th ed. Philadelphia: Mosby; 2011:3-17.
7. Belliappa PP, Scheker LR: Functional anatomy of the hand. *Emerg Med Clin North Am* 1993; 11:557.
8. Kozin SH, Waters PM: *Fractures and dislocations of the hand and carpus in children*. In: Beaty JH, Kasser JR, eds: *Rockwood and Wilkins Fractures in Children*, 7th ed. Philadelphia: Lippincott, Williams & Wilkins; 2010:225-291.
9. Hodgkinson DW, Kurdy N, Nicholson DA, Driscoll PA: The hand: ABC of emergency radiology. *BMJ* 1994; 308:401.
10. Froment J: La préhension dans les paralysies du nerf cubital et le signe du pouce. *Presse Med* 1915; 23:409.
11. Wright PE: *Flexor and extensor tendon injuries*. In: Canale ST, Beaty JH, eds: *Campbell's Operative Orthopaedics*, vol 4, 11th ed. St Louis: Mosby; 2008.
12. Kanavel AB: *Infections of the Hand*, 6th ed. Philadelphia: Lea & Febiger; 1993.
13. Koman LA, et al: *Vascular disorders*. In: Wolfe SW, Hotchkiss RN, Pederson WC, Kozin SH, eds: *Green's Operative Hand Surgery*, 6th ed. Philadelphia: Churchill Livingstone; 2011:2197.

13a. Luczak BP, et al: Closed digital artery injury. *Ochsner J* 2011; 11:139-142.

13b. Al-Qattan MM: Phalangeal neck fractures with concomitant vascular injury. *J Hand Surg Eur Vol* 2009; 34:104-109.

14. Lundborg G, Rosen B: The two-point discrimination test—time for a reappraisal? *J Hand Surg Br* 2004; 29:418.
15. Tindall A, Dawood R, Povlsen B: The skin wrinkle test: A simple nerve injury test for paediatric and uncooperative patients. *Emerg Med J* 2006; 23:883.
16. Zook EG: Reconstruction of a functional and aesthetic nail. *Hand Clin* 2002; 18:577.
17. Henry MH: *Hand fractures and dislocations*. In: Bucholz RW, et al, eds: *Rockwood and Green's Fractures in Adults*, 7th ed. Philadelphia: Lippincott, Williams & Wilkins; 2010:710.
18. Wilks M, Meldon S: *The hand*. In: Schwartz DT, Reisdorff EJ, eds: *Emergency Radiology*. New York: McGraw-Hill; 2000.
19. Stone DB, Levine MR: *Foreign body removal*. In: Roberts JR, Hedges JR, eds: *Clinical Procedures in Emergency Medicine*. Philadelphia: Saunders; 2009.
20. De Jonge JJ, Kingma J, van der Lei B, Klasen HJ: Phalangeal fractures of the hand: An analysis of gender and age-related incidence and aetiology. *J Hand Surg Br* 1994; 19:168.
21. Simon RR, Sherman SC, Koenigsknecht SJ: *Emergency Orthopedics: The Extremities*, 5th ed. New York: McGraw-Hill; 2007.
22. DaCruz DJ, Slade RJ, Malone W: Fractures of the distal phalanges. *J Hand Surg Br* 1988; 13:350.
23. Freeland AE, Lindley SG: Malunions of the finger metacarpals and phalanges. *Hand Clin* 2006; 22:341.
24. Wayne PH: Radiology of the occupationally injured hand. *Hand Clin* 1986; 2:467.
25. Stern PJ, Roman RJ, Kiefhaber TR, McDonough JJ: Pilon fractures of the proximal interphalangeal joint. *J Hand Surg Am* 1991; 16:844.
26. Stapczynski JS: Fracture of the base of the little finger metacarpal: Importance of the "ball-catcher" radiographic view. *J Emerg Med* 1991; 9:145.
27. Light TR, Bednar MS: Management of intra-articular fractures of the metacarpophalangeal joint. *Hand Clin* 1994; 10:303.
28. Talan DA, et al: Clinical presentation and bacteriologic analysis of infected human bites in patients presenting to emergency departments. *Clin Infect Dis* 2003; 37:1481.
29. Wolfe SW, Dick HM: Articular fractures of the hand: Part I. Guidelines for assessment. *Orthop Rev* 1991; 20:27.
30. McLain RF, Steyers C, Stoddard M: Infections in open fractures of the hand. *J Hand Surg Am* 1991; 16:108.
31. Lee SG, Jupiter JB: Phalangeal and metacarpal fractures of the hand. *Hand Clin* 2000; 16:323.
32. Peterson JJ, Bancroft LW: Injuries of the fingers and thumb in the athlete. *Clin Sports Med* 2006; 25:527.
33. Soyer AD: Fractures of the base of the first metacarpal: Current treatment options. *J Am Acad Orthop Surg* 1999; 7:403.
34. Foster RJ, Hastings H II: Treatment of Bennett, Rolando, and vertical intraarticular trapezial fractures. *Clin Orthop Relat Res* 1987; 214:121.
35. Landin LA: Epidemiology of children's fractures. *J Pediatr Orthop B* 1997; 6:79.
36. Papadonikolakis A, Li Z, Smith BP, Koman LA: Fractures of the phalanges and interphalangeal joints in children. *Hand Clin* 2006; 22:11.
37. Della-Guistina K, Della-Guistina DA: Emergency department evaluation and treatment of pediatric orthopedic injuries. *Emerg Med Clin North Am* 1999; 17:895.
38. Salter RB, Harris WR: Injuries involving the epiphyseal plate. *J Bone Joint Surg Am* 1963; 45:587.
39. Vadivelu R, Dias JJ, Burke FD, Stanton J: Hand injuries in children. *J Pediatr Orthop* 2006; 26:29.
40. Mahabir RC, Kazemi AR, Cannon WG, Courtemanche DJ: Pediatric hand fractures: A review. *Pediatr Emerg Care* 2001; 17:153.
41. Stahl S, Jupitur JB: Salter-Harris types III and IV epiphyseal fractures in the hand treated with tension-band wiring. *J Pediatr Orthop* 1999; 19:233.
42. Clark DP, Scott RN, Anderson IWR: Hand problems in an accident and emergency department. *J Hand Surg* 1985; 10:297.
43. Musharafieh RS, Bassim YR, Atiyeh BS: Ulnar collateral ligament rupture of the first metacarpophalangeal joint: A frequently missed injury in the emergency department. *J Emerg Med* 1997; 15:193.
44. Merrell G, Slade JF: *Dislocations and ligament injuries in the digits*. In: Wolfe SW, Hotchkiss RN, Pederson WC, Kozin SH, eds: *Green's Operative Hand Surgery*, 6th ed. Philadelphia: Churchill Livingstone; 2011:291.
45. Kahler D, McCue F: Metacarpophalangeal and proximal interphalangeal joint injuries of the hand, including the thumb. *Clin Sports Med* 1992; 11:57.
46. Kiefhaber TR, Stern PH, Grood ES: Lateral stability of the proximal interphalangeal joint. *J Hand Surg Am* 1986; 11:661.
47. Wilson RL, Liechty BW: Complications following small joint injuries. *Hand Clin* 1986; 2:329.
48. Henderson JJ, Arafa MA: Carpometacarpal dislocation: An easily missed diagnosis. *J Bone Joint Surg Br* 1987; 69:212.
49. Gurland M: Carpometacarpal joint injuries of the fingers. *Hand Clin* 1992; 8:733.
50. Campbell CS: Gamekeeper's thumb. *J Bone Joint Surg Br* 1955; 37:148.
51. Gerber C, Senn E, Matter P: Skier's thumb. Surgical treatment of recent injuries to the ulnar collateral ligament of the metacarpophalangeal joint. *Am J Sports Med* 1981; 9:171.
52. Edelstein DM, Kardashian G, Lee SK: Radial collateral ligaments injuries of the thumb. *J Hand Surg Am* 2008; 33:760.
53. Stener B: Displacement of the ruptured ulnar collateral ligament of the metacarpophalangeal joint of the thumb. *J Bone Joint Surg* 1962; 44:869.
54. Tang P: Collateral ligament injuries of the thumb metacarpophalangeal joint. *J Am Acad Orthop Surg* 2011; 19:287.
55. Patel S, Potty A, Taylor EJ, Sorene ED: Collateral ligament injuries of the metacarpophalangeal joint of the thumb: A treatment algorithm. *Strategies Trauma Limb Reconstr* 2010; 5:1.
56. Heyman P: Injuries to the ulnar collateral ligament of the thumb: Metacarpophalangeal joint. *J Am Acad Orthop Surg* 1997; 5:224.
57. Chuter GS, Muwanga CL, Irwin LR: Ulnar collateral ligament injuries of the thumb: 10 years of surgical experience. *Injury* 2009; 40:652.
58. Doty JF, Rudd JN, Jemison M: Radial collateral ligament injury of the thumb with a Stener-like lesion. *Orthopedics* 2010; 33:925.
59. Bosmans B, Verhofstad MH, Gosens T: Traumatic thumb carpometacarpal joint dislocations. *J Hand Surg Am* 2008; 33:438.
60. Strauch RJ: *Extensor tendon injury*. In: Wolfe SW, Hotchkiss RN, Pederson WC, Kozin SH, eds: *Green's Operative Hand Surgery*, 6th ed. Philadelphia: Churchill Livingstone; 2011:159.
61. Pyne JI, Adams BD: Hand tendon injuries in athletics. *Clin Sports Med* 1992; 11:833.
62. Hanz KR, Saint-Cyr M, Semmler MJ, Rohrich RJ: Extensor tendon injuries: Acute management and secondary reconstruction. *Plast Reconstr Surg* 2008; 121:109e.

www.ketabpezeshki.com 66485457-66963820

63. Rayan GM, Mullins PT: Skin necrosis complicating mallet finger splinting and vascularity of the distal interphalangeal joint overlying skin. *J Hand Surg Am* 1987; 12:548.
64. Geyman JP, Fink K, Sullivan SD: Conservative versus surgical treatment of mallet finger: A pooled quantitative literature evaluation. *J Am Board Fam Pract* 1998; 11:382.
65. Elson RA: Rupture of the central slip of the extensor hood of the finger. A test for early diagnosis. *J Bone Joint Surg Br* 1986; 68:229.
66. Bynum DK, Gilbert JA: Avulsion of the flexor digitorum profundus: Anatomic and biomechanical considerations. *J Hand Surg* 1988; 13A:222.
67. Murphy BA, Mass DP: Zone I flexor tendon injuries. *Hand Clin* 2005; 21:167.
68. Ablove RH, Moy OJ, Peimer CA: Pediatric hand disease diagnosis and treatment. *Pediatr Clin North Am* 1998; 45:1507.
69. Seiler JG III: *Flexor tendon injury: Acute injuries*. In: Wolfe SW, Hotchkiss RN, Pederson WC, Kozin SH, eds: *Green's Operative Hand Surgery*, 6th ed. Philadelphia: Churchill Livingstone; 2011:189.
70. Taras JS, Kaufmann RA: *Flexor tendon injury: Flexor tendon reconstruction*. In: Wolfe SW, Hotchkiss RN, Pederson WC, Kozin SH, eds: *Green's Operative Hand Surgery*, 6th ed. Philadelphia: Churchill Livingstone; 2011:207.
71. O'Hara JJ, Stone JH: An intratendinous epidermoid cyst after trauma. *J Hand Surg Am* 1990; 15:477.
72. Geissler GA, Erdmann D, Germann G: Soft tissue coverage in devastating hand injuries. *Hand Clin* 2003; 19:63.
73. Hammig B, Jones C: Injuries related to snow blowers in the United States: 2002 through 2008. *Acad Emerg Med* 2010; 17:566.
74. Chin G, Weinzweig N, Weinzweig J, Geldner P, Gonzalez M: Snowblower injuries to the hand. *Ann Plast Surg* 1998; 41:390.
75. Arellano A, Wegener E, Freeland A: Mutilating injuries to the hand: Early amputation or repair and reconstruction? *Orthopedics* 1999; 22:683.
76. Buncke G, Buntic R, Romeo O: Pediatric mutilating hand injuries. *Hand Clin* 2003; 19:121.
77. Jebson PJ, Louis DS, Bagg M: *Amputations*. In: Wolfe SW, Hotchkiss RN, Pederson WC, Kozin SH, eds: *Green's Operative Hand Surgery*, 6th ed. Philadelphia: Churchill Livingstone; 2011:1885.
78. Dautel G, Barbary S: Mini replants: Fingertip replant distal to the IP or DIP joint. *J Plast Reconstr Aesthet Surg* 2007; 60:811.
79. Sommer NZ, Brown RE: *The perionychium*. In: Wolfe SW, ed: *Green's Operative Hand Surgery*, 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2011:333.
80. Simon RR, Wolgin M: Subungual hematoma: Association with occult laceration requiring repair. *Am J Emerg Med* 1987; 5:302-304.
81. Meek S, White M: Subungual hematomas: Is simple trephining enough? *J Accid Emerg Med* 1998; 15:269.
82. Seaberg DC, Angelos WJ, Paris PM: Treatment of subungual hematomas with nail trephination: A prospective study. *Am J Emerg Med* 1991; 9:209.
83. Roser SE, Gellman H: Comparison of nail bed repair versus nail trephination for subungual hematomas in children. *J Hand Surg Am* 1999; 24:1166.
84. Shepard G: Perionychial grafts in trauma and reconstruction. *Hand Clin* 2002; 18:595.
85. Perron A, Miller M, Brady W: Orthopedic pitfalls in the ED: Fight bite. *Am J Emerg Med* 2002; 20:114.
86. Bekler H, Gokce A, Beyzadeoglu T, Parmaksizoglu F: The surgical treatment and outcomes of high-pressure injection injuries of the hand. *J Hand Surg Br* 2007; 32:394.
87. Neal NC, Burke FD: High-pressure injection injuries. *Injury* 1991; 22:467.
88. Hogan CJ, Ruland RT: High-pressure injection injuries to the upper extremity: A review of the literature. *J Orthop Trauma* 2006; 20:503.
89. Wong TC, Ip FK, Wu WC: High-pressure injection injuries of the hand in a Chinese population. *J Hand Surg Br* 2005; 30:588.
90. Lewis HG, Clarke P, Kneafsey B, Brennen MD: A 10-year review of high-pressure injection injuries to the hand. *J Hand Surg Br* 1998; 23:479.
91. Kay S, Werntz J, Wolff TW: Ring avulsion injuries: Classification and prognosis. *J Hand Surg Am* 1989; 14:204.
92. Baek SM, Kim SS: Successful digital replantation after 42 hours of warm ischemia. *J Reconstr Microsurg* 1992; 8:455.
93. Morrison WA, McCombe D: Digital replantation. *Hand Clin* 2007; 23:1.
94. Neumeister M, Brown R: Mutilating hand injuries: Principles and management. *Hand Clin* 2003; 19:1.
95. Gulgonen A, Ozer K: *Compartment syndrome*. In: Wolfe SW, ed: *Green's Operative Hand Surgery*, 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2011:1929.
96. Isaacs J: Treatment of acute peripheral nerve injuries: Current concepts. *J Hand Surg* 2010; 35A:291.
97. Harrison BP, Hilliard MW: Emergency department evaluation and treatment of hand injuries. *Emerg Med Clin North Am* 1999; 17:793.
98. Jebson PJ: Infections of the fingertip: Paronychias and felons. *Hand Clin* 1998; 14:547.
99. Brook I: Bacteriologic study of paronychia in children. *Am J Surg* 1981; 141:703.
100. Wright PE: *Hand infections*. In: Canale ST, Beaty JH, eds: *Campbell's Operative Orthopaedics*, 11th ed, vol 4. St Louis: Mosby; 2008.
101. Kilgore ES Jr, Brown LG, Newmeyer WL, Graham WP 3rd, Davis TS: Treatment of felons. *Am J Surg* 1975; 130:194.
102. Wu IB, Schwartz RA: Herpetic whitlow. *Cutis* 2007; 79:193.
103. Gill MJ, Arlette J, Buchan K: Herpes simplex virus infection of hand: A profile of 79 cases. *Am J Med* 1988; 84:89.
104. Mann RJ, Hoffeld TA, Farmer CB: Human bites of the hand: Twenty years of experience. *J Hand Surg Am* 1985; 2:97.
105. Habif TP: *Clinical Dermatology: A Color Guide to Diagnosis and Therapy*, 4th ed. Edinburgh: Mosby/Elsevier; 2010.
106. Small LN, Ross JJ: Suppurative tenosynovitis and septic bursitis. *Infect Dis Clin North Am* 2005; 19:991.
107. Garcia-De La Torre I, Nava-Zavala A: Gonococcal and nongonococcal arthritis. *Rheum Dis Clin North Am* 2009; 35:63-73.
108. Stevanovic MV, Sharpe F: *Acute infections of the hand*. In: Wolfe SW, ed: *Green's Operative Hand Surgery*, 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2011:41.
109. Jebson PJ: Deep subfascial space infections. *Hand Clin* 1998; 14:557.
110. Wilson PC, Rinker B: The incidence of methicillin-resistant *Staphylococcus aureus* in community-acquired hand infections. *Ann Plast Surg* 2009; 62:513.
111. Murray PM: Septic arthritis of the hand and wrist. *Hand Clin* 1998; 14:579.
112. Weinzweig N, Gonzalez M: Surgical infections of the hand and upper extremity: A county hospital experience. *Ann Plast Surg* 2002; 49:621.
113. Reference deleted in proofs.
114. McLario DJ, Burton LJ, Bruce RW, Whipple TJ, Simon HK: Pseudoparalysis of the lower extremity in an infant. *Pediatr Emerg Care* 1998; 14:277.
115. Nimigan AS, Ross DC, Gan BS: Steroid injections in the management of trigger fingers. *Am J Phys Med Rehabil* 2006; 85:36.
116. Saunders S, Longworth S: *Injection Techniques in Orthopaedics and Sports Medicine*. Edinburgh: Churchill Livingstone; 2006.
117. Peters-Veluthamaningal C, van der Windt DA, Winters JC, Meyboom-de Jong B: Corticosteroid injection for trigger finger in adults. *Cochrane Database Syst Rev* 2009; 1:CD005617.
118. Zyluk A, Jagielski G: Percutaneous A1 pulley release vs steroid injection for trigger digit: The results of a prospective, randomized trial. *J Hand Surg Eur Vol* 2011; 36:53.
119. Abe Y, Watson HK, Renaud S: Flexor tendon sheath ganglion: Analysis of 128 cases. *Hand Surg* 2004; 9:1.
120. Steele MT, Tran LV, Watson WA, Muelleman RL: Retained glass foreign bodies in wounds. *Am J Emerg Med* 1998; 16:627.
121. Blankenship RB, Baker T: Imaging modalities in wounds and superficial skin infections. *Emerg Med Clin North Am* 2007; 25:223.
122. Allen GM, Drakonaki EE, Tan ML, Dhillon M, Rajaratnam V: High resolution ultrasound in the diagnosis of upper limb disorders: A tertiary referral centre experience. *Ann Plast Surg* 2008; 61:259.
123. Stein F: Foreign body injuries of the hand. *Emerg Med Clin North Am* 1985; 3:383.

www.ketabpezeshki.com 66485457-66963820

Chapter 51

Wrist and Forearm

David T. Williams and Hyung T. Kim

WRIST

PERSPECTIVE

The wrist joint is broadly defined as the anatomic area from the distal radius and ulna bones of the forearm to the carpometacarpal junctions of the hand. It is anatomically and biomechanically complex, allowing for diverse functional capabilities. In the setting of trauma, this area is exposed, mobile, and at high risk of injury. Detailed knowledge of relevant anatomy, mechanism of injury, accurate clinical assessment, and radiograph interpretation are essential for proper emergent diagnosis and treatment.

Anatomy

The wrist is composed of many complex articulations, including the radiocarpal, midcarpal and distal radial ulnar joints (DRUJs), allowing for flexion, extension, abduction (radial deviation), adduction (ulnar deviation), and circumduction movements. Pronation and supination of the hand are primarily movements of the forearm occurring at the proximal and DRUJs.

The wrist includes the distal radius, ulna, and eight carpal bones, which are arranged in two transverse rows and commonly referred to as the *carpus* (Fig. 51-1). Each carpal row contains four bones. The more mobile, proximal row, listed radial to ulnar, consists of the scaphoid, lunate, triquetrum, and pisiform, whereas the distal row consists of the trapezium, trapezoid, capitate, and hamate bones.

The radius has three articular surfaces at the wrist: the radiocarpal joint, the DRUJ, and an interface with the triangular fibrocartilage complex (TFCC), also known as the *articular disk*. Only the distal radius articulates directly with the carpus via the scaphoid and lunate bones, forming the radiographic joint, commonly referred to as the "wrist joint." The ulna is separated from direct articulation with the proximal carpal row by the TFCC. This articular disk binds the distal ends of the radius, ulna, lunate, and triquetrum together. The DRUJ is a synovial pivot where the distal radius articulates and rotates around the relatively fixed ulna, and this joint is primarily stabilized by the TFCC.

Aside from the pisiform, which is considered to be a sesamoid bone embedded within the flexor carpi ulnaris (FCU) tendon, the carpus bones are lined by synovium that creates a continuous capsule throughout the intercarpal joints and distally to the metacarpal articulations. The only muscular insertions that occur throughout the carpus are the origin of the abductor digiti minimi from the pisiform and the point at which the FCU tendon inserts onto the hook of the hamate. As a result, nearly all carpal bone movements are passive based on muscular insertions on the distal radius, ulna, and metacarpal bases.

The stabilizing ligaments of the wrist joint are divided into two major groups: the intrinsic ligaments and the extrinsic ligaments. The *intrinsic* ligaments interconnect the individual carpal bones, and the *extrinsic* ligaments link the carpal bones to the distal radius, the ulna, and the metacarpals. The intrinsics are named for the adjacent bones they connect, and the most important for maintaining carpal stability are the scapholunate and lunotriquetral ligaments. The extrinsics are divided into a volar and dorsal group. The volar extrinsic ligaments are divided into two V-shaped ligamentous bands called the *proximal* and *distal arcades*, which generally are thicker and stronger than the dorsal extrinsic ligaments and are the most important in providing stability to the wrist. Between these volar arcades is an area relatively devoid of ligamentous support called the *space of Poirier*. This space enlarges when the wrist is dorsiflexed, and an injury to the joint capsule in this region can result in significant carpal instability (Fig. 51-2).

Most structures that cross the wrist joint are contained within individual compartments formed by the deep fascia of the wrist. On the dorsal surface of the wrist, the extensor tendons are divided by the extensor retinaculum into six compartments, each having a separate synovial sheath that extends proximal and distal to the retinaculum. On the volar surface of the wrist, the flexors of the digits and the median nerve are contained within the carpal tunnel, which is formed by the flexor retinaculum superficially and its attachments to the carpal bones. Radially, the flexor retinaculum attaches to the scaphoid tubercle and the ridge of the trapezium. On the ulnar side, it attaches to the pisiform and the hook of the hamate. The floor of the carpal tunnel is formed by both the trapezoid and capitate bones. Radial and superficial to the carpal tunnel, the flexor carpi radialis tendon crosses the wrist joint in its own compartment.

The vascular supply to the wrist is provided by the radial and ulnar arteries, which join in a series of dorsal and palmar arches to supply the bones of the carpus. The intrinsic blood supply to most carpal bones enters the distal portion of the bone, leaving the proximal portion at risk for devascularization and avascular necrosis (AVN) when fractured. This is particularly true for the scaphoid, capitate, and lunate, because they each receive their blood supply from a single distal vessel (Fig. 51-3).

The innervation of the wrist and hand is by the radial, median, and ulnar nerves. The radial nerve and the dorsal sensory branch of the ulnar nerve cross the dorsum of the wrist near the radial and ulnar styloids, respectively. The median nerve crosses within the carpal tunnel on the volar aspect of the wrist just radial and deep to the palmaris longus tendon. The ulnar nerve is within Guyon's canal between the pisiform and the hook of the hamate (see Fig. 51-3). In the setting of trauma, motor and sensory function of the radial, median, and ulnar nerves may be assessed

www.ketabpezeshki.com 66485457-66963820

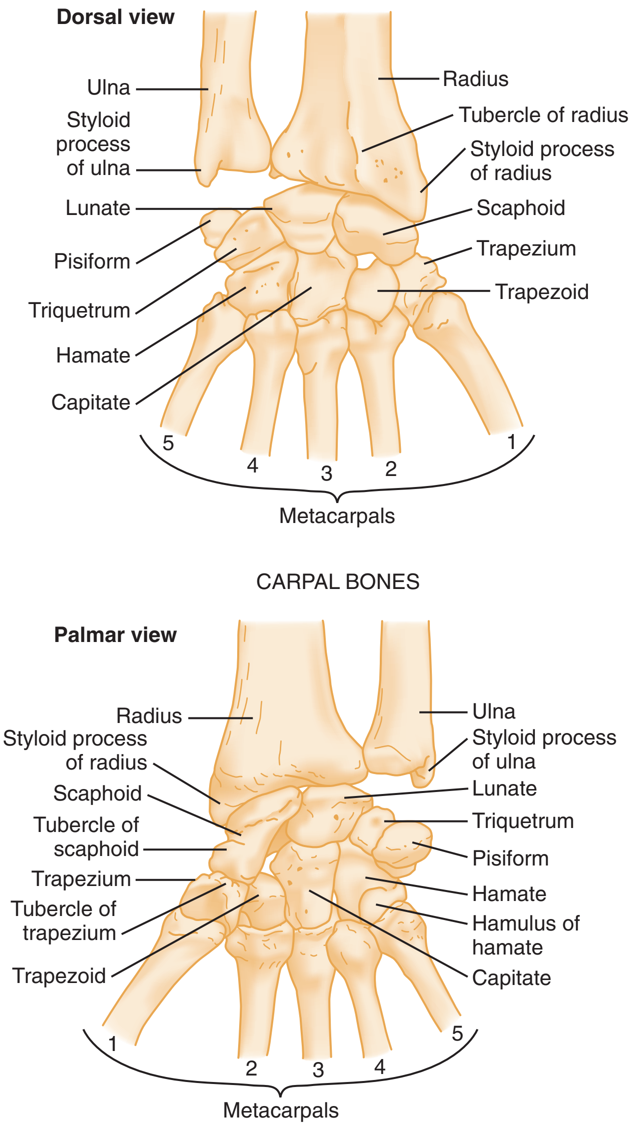


Figure 51-1. Bones of the wrist. The wrist joint includes the distal articular surfaces of the radius and ulna and the proximal and distal carpal rows. (Redrawn from Netter FH: Atlas of Human Anatomy, 3rd ed. Teterboro, NJ, Icon, 2003.)

at the wrist and distally based on common clinical examinations (Table 51-1).

CLINICAL FEATURES

The clinical examination of the patient with a wrist injury begins with a complete history, including the mechanism of injury and the site of maximal pain or tenderness. Most wrist injuries are caused by a fall on the outstretched hand. The physical examination begins with inspection of the wrist, with the opposite uninjured wrist used as the "normal" reference, and includes an assessment of the presence of swelling, discoloration, or obvious deformity and the ability of the patient to move the joint through a normal range of motion.

On palpation, several bony prominences serve as useful landmarks, and the locations of these are best described in relation to the two major lateral and medial reference points in the wrist, the radial and ulnar styloids, respectively. Just distal to the radial styloid is the anatomic snuffbox, bordered radially by the abductor pollicis longus (APL) and extensor pollicis brevis (EPB) tendons and ulnarly by the extensor pollicis longus tendon. The body of the scaphoid is palpable within the snuffbox and is more prominent with the wrist in ulnar deviation.[1] Lister's tubercle can be palpated on the dorsum of the wrist just ulnar to the radial styloid. This is an important landmark because, notably, just distal to the tubercle lies the scapholunate joint, a common site of ligamentous injury in the wrist. With the wrist in neutral position, the capitate is palpable in a small depression found midway between the base of the middle metacarpal and Lister's tubercle. Bringing the wrist into flexion can bring the lunate forward into a palpable position at this same site. Lister's tubercle divides the second and third dorsal extensor compartments of the wrist and is also used as a primary landmark for radiocarpal arthrocentesis. Further ulnar on the dorsal side of the wrist from Lister's tubercle is the DRUJ. The triquetrum is palpable just distal to the ulnar styloid in the proximal carpal row and can be made more prominent with radial deviation of the wrist.

On the volar aspect of the wrist, the scaphoid tubercle is palpable just distal and palmar to the radial styloid. It is felt as a rounded prominence at the base of the thenar muscles and is especially prominent when the wrist is extended. On the ulnar border of the wrist, the pisiform is palpable at the base of the hypothenar muscles, just distal to the distal wrist crease. In addition, approximately 1 cm distal and radial to this point, the prominence formed by the hook of the hamate can be palpated.

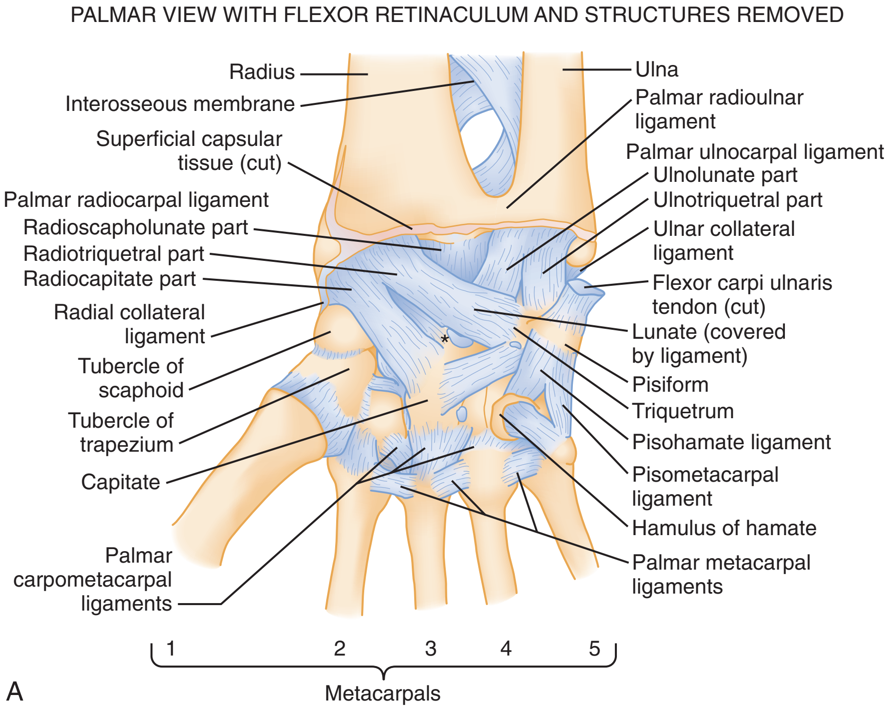
The clinical examination also includes an assessment of the neurovascular status. Radial and ulnar pulses are easily palpable on the volar surface of the wrist, and the presence of pulses should be evaluated in all injuries to the wrist.

DIAGNOSTIC STRATEGIES: RADIOLOGY

Plain radiographs remain the cornerstone of emergent diagnosis of fractures and dislocations of the wrist. Routine radiographic views include the posteroanterior (PA), lateral, and oblique projections, each obtained with the wrist in neutral position. Accurate interpretation of these views requires knowledge of the normal appearance and anatomic relationships of the distal radius, ulna, and carpal bones.

On a correctly positioned PA view of the wrist, the ulnar styloid arises from the lateral aspect of the distal ulna, and the extensor carpi ulnaris (ECU) tendon groove should be visualized at, or radial to, its base. The radial styloid process extends beyond the end of the articular surface of the ulna by a normal distance of 9 to 12 mm. This normal difference in length is called the *radial length measurement* (Fig. 51-4). There may be some degree of *ulnar variance* that affects the radial length measurement on a PA radiograph. The distal articular surface of the ulna may terminate before, at, or distal to the radiolunate articulation as a result of wrist rotation, flexion, extension, anatomic variation, or injury. Neutral ulnar variance (as seen in Fig. 51-4) is described when both the distal ulnar and radiolunate articular surfaces terminate at the same point distally. A positive ulnar variance (ulnar articulation is more distal) or negative ulnar variance (ulnar articulation is more distal) or negative ulnar variance (ulnar articulation is more proximal) is independent of styloid size and may be associated with wrist pathology (e.g., ulnar impaction syndrome and Kienbock's disease, respectively). The ulnar slant of the articular surface of the radius, referred to as *radial inclination,* is visible on the PA view and normally measures 15 to 25 degrees (see Fig. 51-4). Both of these measurements are important in assessing the degree of radial shortening seen in association with some fractures of the distal radius.[2] The normal appearance of the carpus on the PA view shows an approximately equal distance (usually 1 to 2 mm) between each of the carpal bones, and opposing articular surfaces are parallel to one another (an arrangement known as *parallelism*). On radiographs, three smooth curves normally can

www.ketabpezeshki.com 66485457-66963820



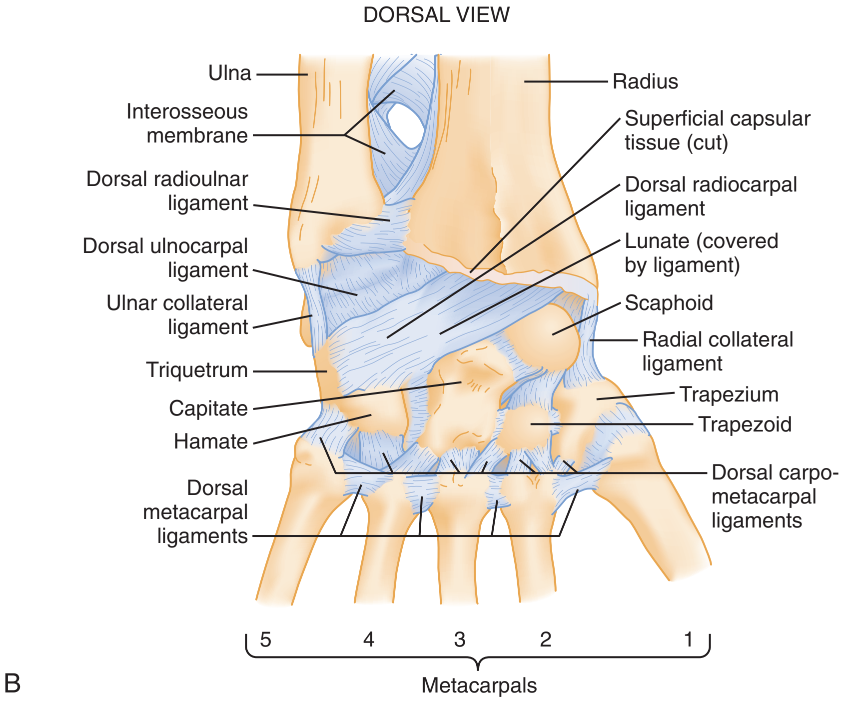


Figure 51-2. Ligaments of the wrist. **A,** The volar extrinsic ligaments are most important in providing stability to the wrist and include the radial collateral, radiocapitate, radioscaphoid, radiotriquetral, ulnotriquetral, capitotriquetral, and ulnar collateral ligaments. The space of Poirier (*) is a gap in the volar ligaments and the site of potential weakness. **B,** The intrinsic (intercarpal) ligaments connect the individual carpal bones. The most important of these are the scapholunate and the lunotriquetral ligaments. (Redrawn from Netter FH: Atlas of Human Anatomy, 3rd ed. Teterboro, NJ, Icon, 2003.)

www.ketabpezeshki.com 66485457-66963820

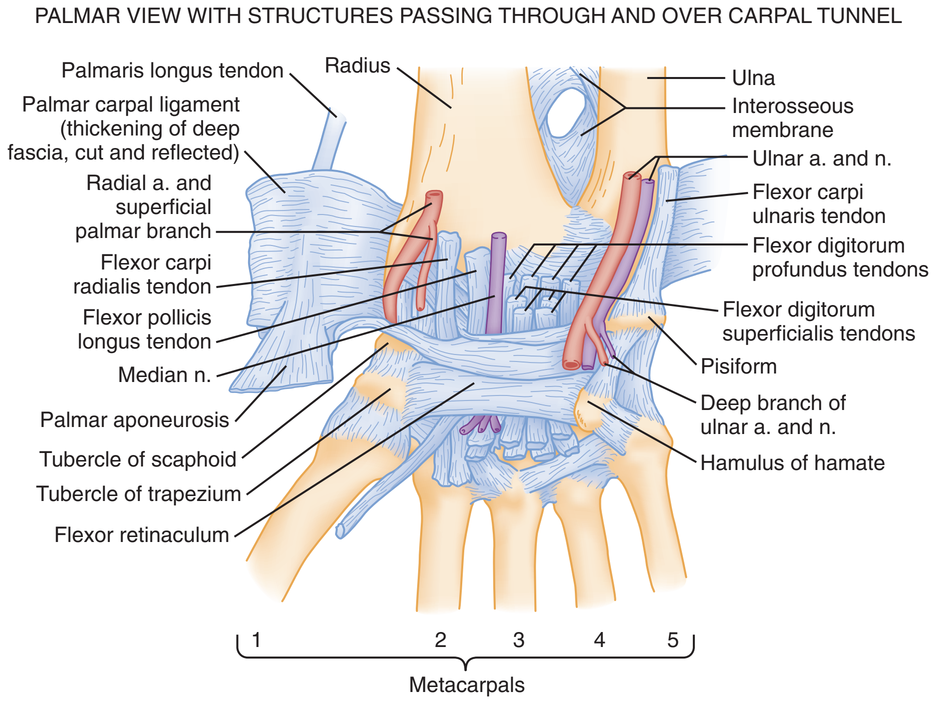
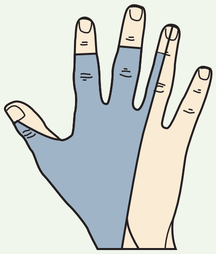
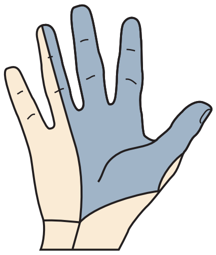
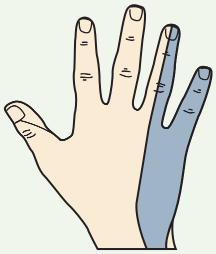
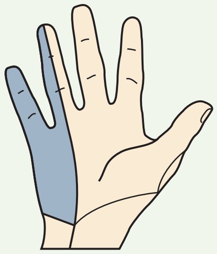


Figure 51-3. Vascular supply to the wrist. Note the relationship of the ligaments to the neurovascular supply to the wrist. (Redrawn from Netter FH: Atlas of Human Anatomy, 3rd ed. Teterboro, NJ, Icon, 2003.)

Table 51-1 Radial, Median, and Ulnar Nerve Innervations and Clinical Examination

NERVE	MOTOR	SENSORY	CLINICAL EXAMINATION
Radial	Brachioradialis Extensor carpi radialis longus Extensor carpi radialis brevis Supinator Extensor digitorum Extensor digiti minimi Extensor carpi ulnaris Abductor pollicis longus Extensor pollicis brevis Extensor pollicis longus Extensor indicis	 Dorsal	Wrist extension Finger Extension Supination “Thumbs up” sign Sensation: first dorsal web space
Median	Pronator teres Flexor carpi radialis Palmaris longus Flexor digitorum superficialis Flexor digitorum profundus Flexor pollicis longus Pronator quadratus	 Ventral	Thumb opposition Pincer function (thumb and index finger) Pronation “A-OK” sign Sensation: index finger volar tip
Ulnar	Flexor carpi ulnaris Flexor digitorum profundus Opponens digiti minimi Abductor digiti minimi Flexor digiti minimi Lumbricales 3 and 4 Dorsal interossei Palmar interossei Adductor pollicis Palmaris brevis	 	Finger abduction Finger adduction Sensation: little finger volar tip

www.ketabpezeshki.com 66485457-66963820

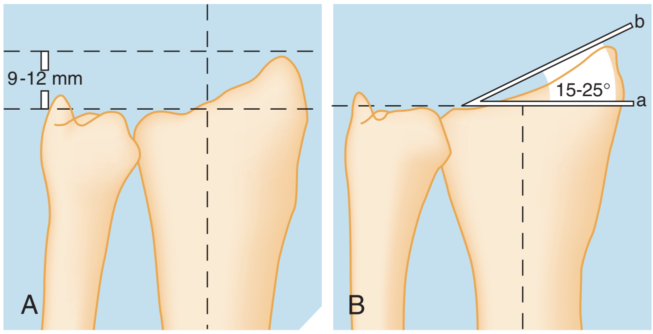


Figure 51-4. Normal radiographic appearance of the wrist on a posteroanterior view. The ulnar styloid arises from the lateral aspect of the distal ulna, and the tendon groove for the extensor carpi ulnaris should be visualized at, or radial to, its base. **A,** Radial length measurement with neutral ulnar variance. The radial styloid extends 9 to 12 mm beyond the articular surface of the distal ulna. The ulna may terminate distal, at, or proximal to the radiolunate articulation affecting radial length measurement with a positive, neutral, or negative variance, respectively. **B,** The ulnar slant of the distal radius normally measures 15 to 25 degrees. (From Greenspan A: Orthopedic Radiology: A Practical Approach, 2nd ed. New York, Gower Medical Publishing, 1992.)

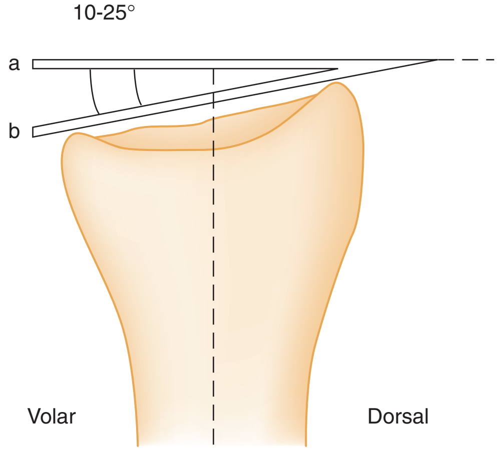


Figure 51-6. Normal radiographic appearance of the wrist on a lateral view. The distal radius has a normal volar tilt of 10 to 25 degrees. (From Greenspan A: Orthopedic Radiology: A Practical Approach, 2nd ed. New York, Gower Medical Publishing, 1992.)

Figure 51-5. Carpal (Gilula's) arcs. On a posteroanterior radiograph of the wrist, three arcuate lines (*1* to *3*) can be drawn along the articular surfaces. Although small indentations at joint lines may occur, a step-off or "broken arc" suggests fracture, ligamentous instability, or disruption of the wrist.

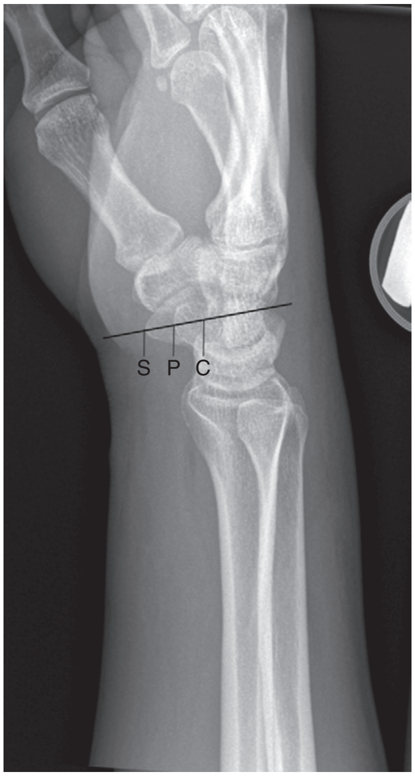


Figure 51-7. Normal S-P-C (scaphoid-pisiform-capitate) lateral view of the wrist. The palmar cortex of the pisiform *(P)* is shown bisecting the line between the palmar aspect of the scaphoid *(S)* and capitate *(C)* bones.

be drawn along the carpal articular surfaces, known as *carpal* or *Gilula's arcs* (Fig. 51-5). Disruption of these curves or widening of the carpal spaces is an indication of carpal ligament disruption, instability, or fracture.[3]

The normal volar tilt of the distal radial articular surface is visible on the lateral view of the wrist and normally measures 10 to 25 degrees (Fig. 51-6). Adequacy of a lateral view of the wrist is assessed based on the relationship among the scaphoid, pisiform, and capitate projections. The palmar cortex of the pisiform should project midway between the palmar margins of the distal pole of the scaphoid and the capitate head, forming the S-P-C lateral (Fig. 51-7). The normal alignment of the distal radius with the lunate and capitate also is seen on the lateral view, which will show two concentric cups, the cup of the distal radius containing the lunate and the cup of the distal lunate containing the capitate. Ideally, the long axis of the radius, lunate, capitate, and third metacarpal should appear as a straight line on the lateral view, although the "normal" alignment usually is within 10 degrees of this line (Fig. 51-8). The carpal alignment on the lateral view is defined further by the scapholunate angle, which normally

www.ketabpezeshki.com 66485457-66963820

measures 30 to 60 degrees, and the capitolunate angle, which normally is 0 to 30 degrees (Fig. 51-9). Abnormalities in these angles are seen in patients with carpal ligament injuries and carpal instability.

The soft tissues of the wrist also offer valuable clues to the presence of underlying bony injuries. It is estimated that on 90% of normal lateral radiographs of the wrist, the pronator quadratus line is visible as a linear, lucent, fat collection in the volar soft tissues just anterior to the distal radius and ulna (Fig. 51-10). Fractures of the distal radius or the ulna result in volar displacement, anterior bowing, or complete obliteration of this line. Although this pronator quadratus sign may suggest fracture, a wide range of sensitivities has been quoted—26 to 98%—so its absence does not exclude a fracture. A positive pronator quadratus sign has also been observed in soft tissue injuries and infectious and inflammatory medical conditions.[4]

Additional radiographic imaging of the wrist may be indicated based on chief complaint, mechanism of injury, or physical examination findings, including specific areas of tenderness. In addition to the standard PA, lateral and oblique wrist radiographs, adjunct imaging may include views with ulnar and radial deviation, maximal flexion, extension, a carpal tunnel view, reverse (supinated) oblique, clenched fist PA, or anteroposterior (AP) views. Patient-specific imaging helps to further delineate otherwise occult fracture or abnormal motion of the carpus resulting from ligamentous injuries. Specific scaphoid views, obtained with the wrist pronated and in ulnar deviation, allow for better visualization of the scaphoid along its long axis. The carpal tunnel view is performed with the wrist hyperextended and provides an axial image of the bony margins of the carpal tunnel. This view and the reverse (supinated) oblique view help identify fractures, especially involving the hook of the hamate and the pisiform.[5] The clenched fist, both PA and AP views, drive the capitate proximally as a wedge causing diastasis within the scapholunate joint, highlighting ligamentous instability (Table 51-2). Although scapholunate width may be exaggerated on the AP view, instability is suspected when either view shows a distance of 3 mm or greater.

Given the high incidence of occult fractures of the wrist, when radiographs are negative and pain persists, immobilization is

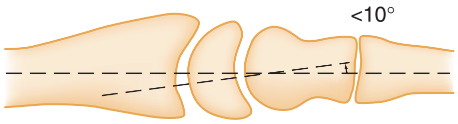


Figure 51-8. Normal relationship of carpal bones on a lateral radiographic view. Concavity of radius and lunate and convexity of capitate form three C-shaped areas *(stippled)* along a straight line that runs through the central axis of these bones.

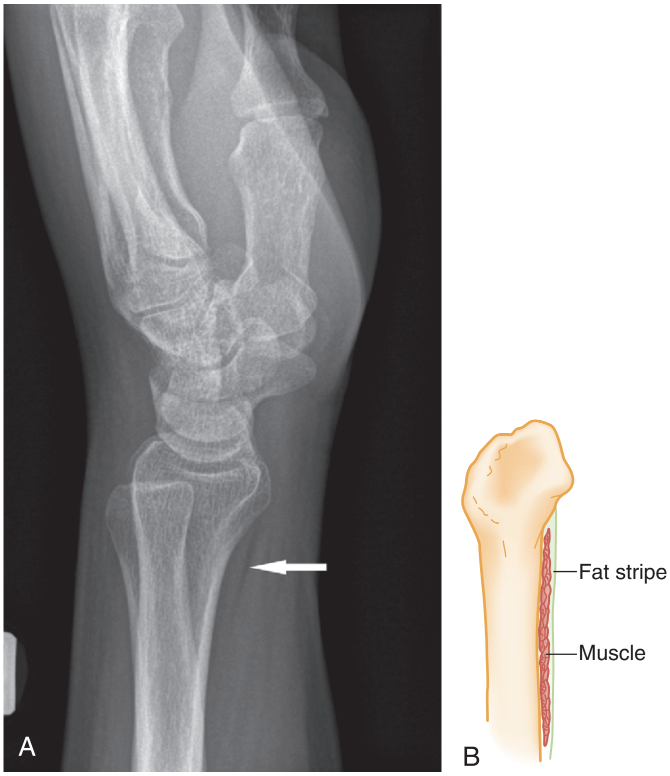


Figure 51-10. The pronator quadratus fat pad. Narrow fat stripe *(arrow)* located on the volar surface of the radius is seen on the lateral view of the wrist. Although not highly sensitive, volar displacements, anterior bowing, or complete obliteration of this line caused by hematoma in the setting of trauma is suggestive of wrist injury or fracture.

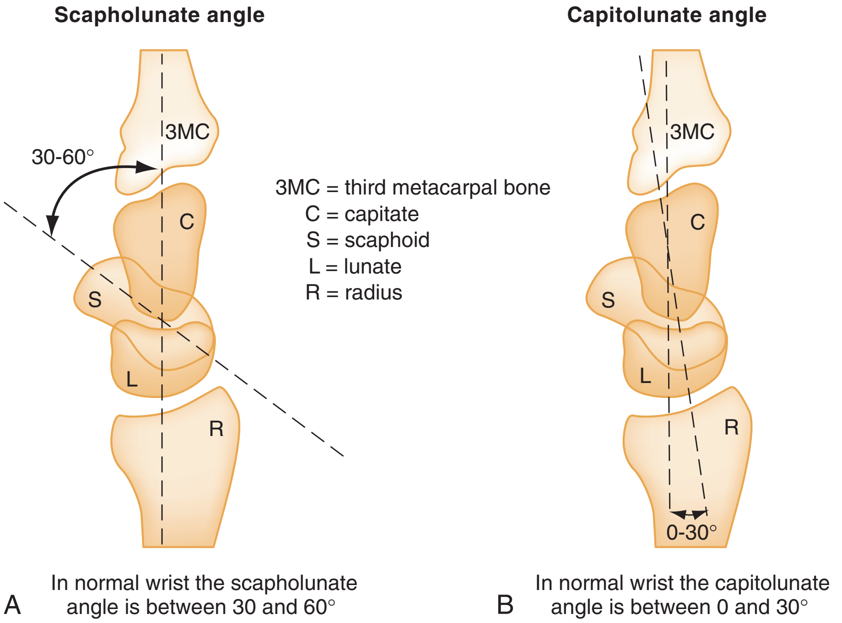


Figure 51-9. A, The normal scapholunate angle is formed by the intersection of the longitudinal axes of the scaphoid and lunate and normally measures 30 to 60 degrees. B, The normal capitolunate angle is formed by the intersection of the capitate and lunate central long axes and normally measures 0 to 30 degrees. (From Greenspan A: Orthopedic Radiology: A Practical Approach, 2nd ed. New York, Gower Medical Publishing, 1992.)

www.ketabpezeshki.com 66485457-66963820

Table 51-2 Additional Radiographic Wrist Views

RADIOGRAPHIC VIEW	BENEFIT
Clenched fist view (PA or AP with clenched fist)	Exposes scapholunate ligament injury; pushes capitate into proximal carpal row
Scaphoid view (PA with ulnar deviation)	Elongates scaphoid; exposes wrist fractures
Carpal tunnel and reverse supinated oblique view	Identifies fractures involving hamate and pisiform; identifies bony encroachment onto carpal tunnel

AP, anteroposterior; *PA*, posteroanterior.

recommended. A thumb spica is usually added in the setting of suspected scaphoid and other carpal fractures, which is discussed in more detail below. In general, repeat physical examination, radiographs, or advanced imaging protocols are pursued urgently or after a period of observation. Although many studies regarding magnetic resonance imaging (MRI) and computed tomography (CT) protocols have already concluded that emergent advanced imaging is appropriate, more prospective and conclusive data are needed. The best data exists for scaphoid fractures and includes economic arguments. Although it is tempting to extend those conclusions to other carpus fractures, this would be premature, especially in view of the fact that these other injuries have less severe consequences and are more rare. In addition, highly sensitive emergent advanced imaging protocols are not readily available in many emergency departments (EDs), and as a result changes in management will likely be institution dependent.

Figure 51-11. Scaphoid waist fracture. A posteroanterior view of the wrist in ulnar deviation (scaphoid view) illustrates a nondisplaced fracture of the scaphoid waist *(arrow)*.

CARPAL INJURIES

Scaphoid Fractures

The scaphoid is the most commonly fractured bone of the carpus.[6] It accounts for approximately 70% of all carpal fractures. Typically seen in individuals 15 to 40 years of age, scaphoid fractures most commonly occur after a fall on the outstretched hand or as a sports-related injury.[7,8] Scaphoid fractures are rare in skeletally immature patients because the carpus is composed entirely of cartilage at birth and remains predominantly cartilaginous until late childhood and the adolescent years.[9] In pediatric patients, although the physis of the radius is likely to fail first, scaphoid fractures with and without this injury pattern have been observed.[9] In the elderly, a distal radius metaphysis fracture is more likely to occur than a scaphoid fracture.[8] Scaphoid fractures are classified by their anatomic location and may be divided into three groups: fractures of the tuberosity and distal pole, the waist, and the proximal pole. Of these three patterns, fractures through the waist of the scaphoid are the most common, accounting for approximately 70 to 80% (Fig. 51-11).[8]

Patients typically report dorsal radial wrist pain, distal to the radial styloid, with limited range of motion of the wrist and thumb. Classically, physical examination reveals tenderness on palpation of the scaphoid and swelling within the anatomic snuffbox. Increased sensitivities have been suggested for snuffbox tenderness with ulnar or radial deviation of the wrist with pronation. Pain also may be elicited with palpation of the scaphoid tubercle volarly, Watson's scaphoid shift test, axial compression of the first metacarpal, and pain on thumb–index finger pinch.[10] In an effort to not miss occult scaphoid fractures, the combination of clinical examination methods of tenderness in the anatomic snuffbox, on the scaphoid tubercle, and with first metacarpal compression has been suggested and may approach 100% sensitivity for disease.[10] When routine radiography is negative, a combination of these clinical examinations is used for maintaining a high sensitivity for identification of occult fracture, despite a low specificity (40-80%).[10-12]

Radiographic diagnosis of scaphoid fractures often is difficult, and special scaphoid views should be requested when a fracture is suspected based on clinical findings. A visible fracture lucency may be absent, and a more subtle change, such as obliteration or displacement of the scaphoid fat pad, may be the only clue to the presence of a fracture, although these signs are not reliably present.[13] Plain radiographs taken soon after injury fail to detect approximately 15% of scaphoid fractures.[14,15] In addition, because of the associated risk of nonunion, when diagnosis and immobilization are delayed, patients clinically suspected of having a scaphoid fracture are often treated with splint immobilization and repeat clinical evaluation, and radiographic imaging after 7 to 10 days.[16] Recent evidence has called into question the practice of immobilizing the wrist in all patients with suspected scaphoid injuries and has suggested that the use of more advanced imaging modalities is both accurate and cost-effective and should be performed earlier rather than later. The cost of time off from work, serial casting, repeat physician evaluation, and office visits easily exceed that of MRI, bone or CT scans for definitive diagnosis where these imaging modalities are readily available.[17,18] In addition to advanced imaging, clinical risk assessments and decision rules are being developed to help further risk stratify patients.[10]

MRI and CT imaging allows clinicians to diagnose the majority of radiographically occult scaphoid fractures and offer alternative diagnoses for wrist pain.[10,15] Macroradiography and ultrasound, including high-resolution sonography, have not approached the sensitivities and specificities observed with bone scintigraphy, MRI, and CT imaging. Despite extensive study, the optimal imaging modality and the sensitivity and timing of these studies in diagnosis of occult scaphoid fracture remain controversial.[10,19] As a result, these imaging modalities are not emergently performed on a routine basis.

www.ketabpezeshki.com 66485457-66963820

Figure 51-12. Short arm thumb spica splint. Common immobilization technique used for occult fractures of the scaphoid bone seen in volar view. Note the optimal 10 degrees of wrist flexion and radial deviation, which assists in scaphoid immobilization.

Figure 51-13. Avascular necrosis of scaphoid bone. A common complication of scaphoid fractures is avascular necrosis as a result of the distal to proximal osseous blood supply, displacement, or nonunion, resulting in chronic wrist pain and arthritis.

Historically, bone scans were used 72 to 96 hours after injury to detect scaphoid fractures. Although high sensitivities are quoted (97%), lower specificities, many false positives, decreased effectiveness in the elderly, and limited availability have tempered their use.[10,20,21] CT is excellent for detailed bone imaging, and it reveals the complications of fracture fragment displacement, malunion, and nonunion.[22] However, CT has not had the sensitivity required (93%) for diagnosing occult fractures in the emergent setting. Despite increased costs and more limited availability, MRI protocols have the advantage of allowing diagnosis of alternative soft tissue injuries and are being used to detect these radiographically occult fractures with sensitivity rates approaching 100%.[10,21,23-26] More prospective data on the optimal emergent and urgent diagnostic imaging modalities for occult scaphoid fractures are needed.

The definitive treatment for uncomplicated, nondisplaced scaphoid fractures is debated among orthopedic specialists, although trends toward screw fixation over cast immobilization are evident.[10] Emergency management typically involves immobilization in a thumb spica splint (Fig. 51-12). Immobilization with the wrist in 10 degrees of flexion with radial deviation is used to immobilize the fracture fragments of the scaphoid, and the majority of surgeons terminate the thumb spica at the interphalangeal joint line. Some specialists prefer a long arm (above the elbow) cast or splint, which prevents pronation and supination for the first few weeks. In addition to flexion and extension, pronation and supination have been suggested to produce fracture displacement in the proximal carpal row. Eventual replacement with a short arm cast for the remainder of the immobilization period may be acceptable. The duration of immobilization varies relative to the location of the fracture, but 6 to 12 weeks is common. More proximal fractures commonly require longer durations to ensure adequate healing. Variability in healing time is related directly to the pattern of blood supply to the scaphoid, which flows from the distal to the proximal portion of the bone through the scaphoid tuberosity. This pattern of blood flow also accounts for the higher incidence of AVN and nonunion in the more proximal fractures (Fig. 51-13). AVN is seen in approximately 13 to 40% and nonunion in 5 to 12% of scaphoid fractures, with the risk of complications being greatest in fractures of the proximal pole.[27-29] Because of the increased risk of AVN or nonunion, scaphoid fractures, especially those that are unstable, are displaced more than 1 mm, are associated with other fractures, or have an increased scapholunate or capitolunate angle, require urgent orthopedic referral for consideration of operative treatment.

Lunate Fractures

Fractures of the lunate are relatively uncommon and represent approximately 1 to 4% of all carpal fractures.[6,8,30,31] This injury occurs more commonly in persons with a congenitally short ulna, perhaps as a result of a compromised support for the TFCC. The usual mechanism of injury involves a fall on the outstretched hand, causing extreme dorsiflexion, with transmittal of the resultant force from the capitate to the lunate. Patients have pain over the dorsum of the wrist, which is exacerbated by axial loading of the long finger metacarpal. On physical examination, tenderness may be elicited by palpation over the dorsum of the wrist in the depression felt just distal to Lister's tubercle.

Fractures of the lunate may be difficult to see on plain radiographs because of overlap of the distal radius, ulna, and other carpal bones. For this reason, and because of the risk of AVN in missed injuries, clinically suspected lunate fractures should be immobilized. Nondisplaced lunate fractures are treated with immobilization in a short arm splint with a thumb spica, and patients are given orthopedic referral in 7 to 10 days. Displaced fractures should be reduced, and urgent orthopedic referral is warranted. Complications include progression to carpal instability, nonunion, and AVN. Lunate and perilunate dislocations are discussed later in the section on carpal instability. Post-traumatic AVN is a sequela in 20% of fractures and is presumed to be the cause of Kienbock's disease. In well-established cases of Kienbock's disease, the lunate appears sclerotic and fragmented on radiographic examination, and ultimately the bone collapses with resultant proximal migration of the capitate (Fig. 51-14). These changes cause secondary osteoarthritis of the radiocarpal joint and chronic wrist pain. Treatment involves operative intervention, with correction of the articular abnormalities either by lengthening the ulna or by shortening the radius. In more advanced cases, excision and prosthetic replacement of the lunate or arthrodesis may be necessary.[32]

www.ketabpezeshki.com 66485457-66963820

Figure 51-14. Avascular necrosis of the lunate bone *(circle),* also known as *Kienbock's disease,* is formally of unknown cause; however, prevailing theories support fracture of the lunate bone or compromised circulation as the most likely cause of disease.

Figure 51-15. Triquetral avulsion fracture. A minimally displaced triquetral avulsion or dorsal chip fracture *(arrow)* is seen on this lateral radiograph of the wrist.

Triquetral Fractures

Triquetrum injuries, second only to the scaphoid in incidence, account for approximately 15% of carpal fractures.[8] They usually result either from a direct blow to the bone, causing a fracture of the body, or much more commonly from a fall on the outstretched hand. In the former scenario, triquetrum body fractures are commonly associated with perilunate and lunate dislocations, and therefore ligamentous injury should be considered. A fracture to the triquetral body is best seen on the AP radiograph, and urgent orthopedic referral is suggested. In the latter scenario, the mechanism of fracture is believed to be impact of the ulnar styloid or proximal hamate against the triquetrum, which results in a dorsal avulsion fracture.[31,33] Patients have localized tenderness over the dorsum of the wrist just distal to the ulnar styloid. On physical examination, swelling may be noted in this same area, and wrist motion is limited secondary to pain. The fracture is best seen on the standard lateral view of the wrist as a small dorsal avulsion fragment, although, a more oblique pronated view may be necessary for visualization (Fig. 51-15). Treatment is with immobilization in a short arm splint or ulnar gutter with more routine orthopedic referral (1-2 weeks). Definitive treatment in a short arm cast usually results in an uncomplicated course, with prompt fracture healing over 4 to 6 weeks.

Pisiform Fractures

The pisiform is unique in the carpus because it is the only sesamoid bone and lies within the FCU tendon, articulating on its dorsal surface with the triquetrum. Although pisiform fractures are extremely rare, occurring in less than 1% of all carpal fractures, given the important role of the pisiform in forming the lateral wall of Guyon's canal, ulnar arterial damage and neurapraxias may be associated. Fractures of the pisiform usually occur from a fall on the outstretched hand but also may be seen after direct blows to the hypothenar eminence. Commonly this occurs from repetitive trauma when the palm of the hand is used in a hammer-like manner. On clinical examination, there is tenderness over the ulnar aspect of the wrist just distal to the volar crease. Pain may be exacerbated with wrist flexion and ulnar deviation. Paresthesias in the distribution of the ulnar nerve and hand clumsiness from intrinsic muscle dysfunction can occur. Pisiform fractures are poorly seen on routine wrist radiographs and are therefore likely under-reported, so special views should be requested. A reverse (supinated) oblique and the carpal tunnel view allow for better visualization of these fractures (Fig. 51-16).[4]

Fractures of the pisiform generally carry an excellent prognosis and are treated conservatively with immobilization in a short arm splint or ulnar gutter with orthopedic referral in 1 to 2 weeks. Definitive treatment is with a short arm cast for 3 to 4 weeks. Most pisiform fractures with evidence of ulnar nerve compromise, will resolve on their own; however, urgent orthopedic referral for consideration of surgical decompression is indicated. Pisiform fractures that are complicated by nonunion and pain may also require excision.

Hamate Fractures

Hamate fractures are rare and account for approximately 2 to 6% of all carpal bone fractures.[8] The hook or hamulus is the most common site of fracture, although articular surfaces and body fractures are also seen. Fracture of the hook usually occurs from a fall on the outstretched hand or from a direct blow to the palm. Classically, hook of the hamate fractures occur from those participating in racquet or club sports (e.g., tennis, golf, baseball). The use of hammers and vibration equipment (e.g., jack hammers) is

www.ketabpezeshki.com 66485457-66963820

Figure 51-16. Pisiform fracture. Reverse supinated oblique radiograph of the wrist profiling the pisotriquetral joint demonstrates minimally displaced pisiform fracture *(arrow)* not typically seen on traditional posteroanterior, lateral, and oblique views.

Figure 51-17. Hamate fracture. Fracture of the articular surface of the hamate bone *(arrow)* is seen on this posteroanterior radiograph of the wrist.

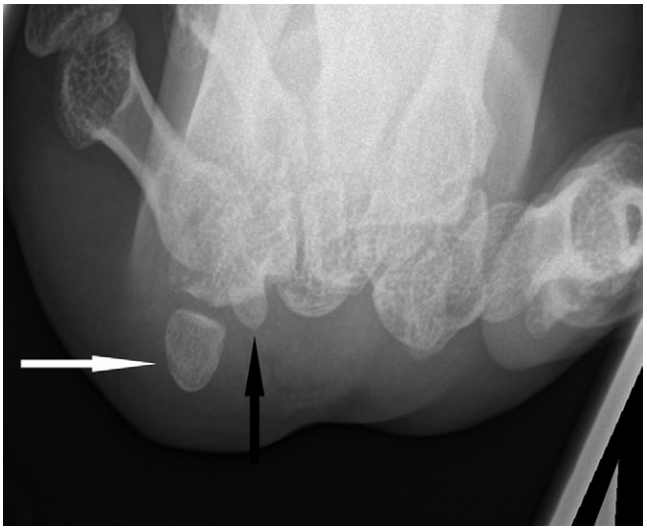


Figure 51-18. Carpal tunnel view of wrist. Pisiform *(white arrow)* and hook of hamate or hamulus *(black arrow)* are better visualized on carpal tunnel views of the wrist when clinical hypothenar palmar wrist pain is present and fracture is suspected.

also a common mechanism, which can predispose workers to hamate fractures, ulnar canal and hypothenar hammer syndrome.[34] Patients may have isolated pain over the hypothenar eminence, associated decreased grip strength, or compromised distal perfusion. Pain may be localized directly on palpation of the hamate, 1 cm distal and radial to the pisiform. Hamate body and articular surface fractures are usually caused by increased load to the ring and little finger metacarpals. These fracture patterns are best seen on PA views of the wrist (Fig. 51-17). Fractures of the hook are more easily seen on the reverse supinated oblique and carpal tunnel views (Fig. 51-18).[4] Because low sensitivities have been quoted for hook of the hamate fractures (40-70%), when radiographs are inconclusive and pathology is still suspected, CT scanning may be considered given its increased sensitivity, the complications of missed fracture, and changes in clinical management. The timing of CT scanning is debatable, and empirical treatment may be warranted. However, confirmed hook of hamate fractures should be splint immobilized with ulnar outrigger and thumb spica to limit traction from the transverse carpal ligament. Missed injury may result in complications, including delayed flexor tendon rupture affecting the little finger.[5,35] Fractures of the hook of the hamate may also be complicated by associated ulnar neurapraxia, which would warrant urgent orthopedic referral and is an indication for operative intervention with excision of the hook at the fracture site to restore function.[5] Vascular compromise or distal ischemia would warrant emergent orthopedic consultation.[36] Hamate body and articular fractures typically require closed or open reduction and internal fixation.

Trapezium Fractures

Fractures of the trapezium are also uncommon and represent approximately 3% of all carpal fractures.[8] There are two main types of fractures, those involving the body and the trapezial ridge. A direct blow to the adducted thumb causes fracture through the body of the trapezium, with transmittal of the force by the base of the thumb metacarpal. Avulsion fractures of the trapezial ridge occur with forceful radial deviation or rotation of the wrist. On examination, patients report pain with movement of the thumb and on direct palpation of the trapezium just distal to the scaphoid in the anatomic snuffbox. Although trapezium fractures may be seen on the AP view of the wrist, they are typically better visualized on oblique views (Fig. 51-19) and unfortunately are also commonly occult.[35] These injuries are treated with immobilization in a thumb spica splint, and patients are given orthopedic referral. Nondisplaced fractures are held in a cast for 6 weeks, whereas

www.ketabpezeshki.com 66485457-66963820

Figure 51-19. Trapezium fracture. An oblique view of the wrist shows an isolated, comminuted, intra-articular fracture of the trapezium body *(arrow).*

displacement or involvement of the carpometacarpal joint warrants urgent orthopedic referral for ORIF.

Capitate Fractures

The capitate lies in a central position in the distal carpal row, and because of this protected location, it is rarely fractured. When fracture does occur, the mechanism generally is a direct blow to the dorsum of the wrist. Fracture also may be seen in association with a perilunate dislocation after a fall on the outstretched dorsiflexed hand. Clinical examination reveals dorsal wrist pain and swelling, with localized tenderness on palpation of the capitate. Fractures usually are visible on the standard PA view of the wrist, although the lateral view may be helpful in determining the presence of rotation or displacement of the fracture fragment.

Nondisplaced isolated fractures of the capitate may be managed with immobilization in a short arm splint with thumb spica, with the patient given orthopedic referral. Urgent orthopedic referral is indicated for fractures with displacement, and emergency consultation for associated carpal dislocation. Complications of nonunion and AVN of the proximal fragment are rare but do occur because the capitate receives its blood supply through its distal half.

Trapezoid Fractures

Trapezoid fractures are rare, most commonly seen in association with other carpal injuries, and account for only approximately 1% of all carpal fractures.[5] The typical mechanism of injury is a direct blow down the long axis of the index metacarpal, which may result in isolated fracture to the trapezoid or cause a dorsal fracture-dislocation. On clinical examination, pain and tenderness are localized over the dorsum of the wrist at the base of the second metacarpal. The fracture may be visible on routine PA views of

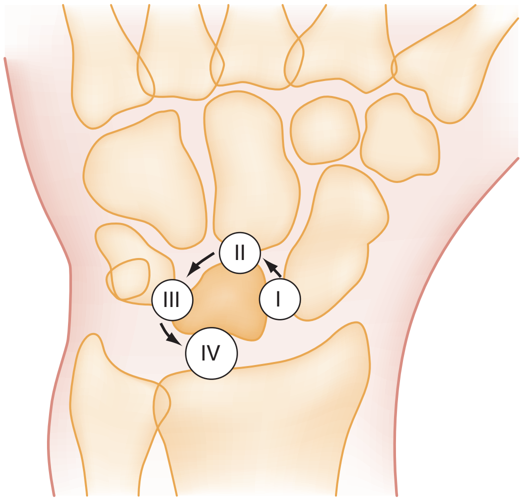


Figure 51-20. Sequential stages of carpal dislocation. Each of four stages represents a sequential intercarpal ligament injury proceeding around the lunate. (From Greenspan A: Orthopedic Radiology: A Practical Approach, 2nd ed. New York, Gower Medical Publishing, 1992.)

the wrist; however, oblique views may be superior for visualization of the injury. Nondisplaced trapezoid fractures should be immobilized with a short arm splint and thumb spica, and patients are given an orthopedic referral in 1 to 2 weeks. However, displaced fractures warrant urgent orthopedic referral for reduction and fixation.

Carpal Instability

Mayfield and associates described a progressive pattern of carpal ligamentous injury caused by wrist hyperextension, ulnar deviation, and intercarpal supination.[37] Their studies of the pathomechanics of these injuries led to the classification of carpal instability into four distinct stages. Each stage represents a sequential intercarpal injury beginning with scapholunate joint disruption and proceeding around the lunate, creating progressive carpal instability (Fig. 51-20). Each stage also may be associated with specific bony fractures, which, if present, should alert the physician to the possibility of an occult perilunate ligamentous injury. These associated injury patterns include fractures of the radial styloid, scaphoid, capitate, and triquetrum.

A *stage I injury,* or scapholunate dissociation, results in a characteristic widening of the scapholunate joint on the PA view, which has been called the "Terry Thomas sign," after the British comedian with a gap between his front teeth.[38] This radiographic sign has been updated to reference more current celebrity figures and is also referred to as the "Madonna sign" or the "David Letterman sign." This injury pattern may be associated with a rotary subluxation of the scaphoid. Radiographically the scaphoid is seen end on, with the cortex of the distal pole appearing as a ring shadow, referred to as the "signet ring sign" (Fig. 51-21). Scapholunate dissociation may not be demonstrated on routine radiographs, so when clinical examination reveals tenderness to palpation, suggesting ligamentous injury, additional stress views could be considered. Radiographs taken with a clenched fist and with ulnar deviation (the clenched-fist AP view) accentuate widening of the scapholunate joint and are suggestive of disease when a gap greater than 3 mm is observed.

A stage *II injury,* or perilunate dislocation, is seen best on the lateral view of the wrist. Although the lunate remains articulated to the distal radius, the capitate is dorsally dislocated. The PA view shows overlap of the distal and proximal carpal rows and also may

www.ketabpezeshki.com 66485457-66963820

show an associated scaphoid, radial styloid, or capitate fracture (Fig. 51-22).[39]

A *stage III injury* appears identical to a stage II injury but includes a dislocation of the triquetrum that is seen best on the PA view, with overlap of the triquetrum on the lunate or hamate. This injury may be associated with a volar triquetral fracture.

A *stage IV injury,* or lunate dislocation, results in a characteristic triangular appearance of the lunate on the PA view that is caused by the rotation of the lunate in a volar direction. This triangular appearance is known as the "piece of pie sign." This rotation also is visible on the lateral view of the wrist, in which the lunate looks like a cup tipped forward and spilling its contents, referred to as the "spilled teacup sign." On the lateral view, the capitate is seen to lie posterior to the lunate and often has migrated proximally to contact the distal radius (Fig. 51-23).

Patients with these carpal dislocation injuries typically have a history of a fall on the outstretched hand. They complain of pain and swelling over the dorsum of the wrist, with limited range of motion. On physical examination, tenderness to palpation is noted over the dorsum of the wrist, particularly in the region of the scapholunate ligament. Scapholunate instability may be clinically elicited by a provocative maneuver, such as Watson's scaphoid shift test, which will increase pain and produce a clunk or snap.[40] This test is performed by placing upward pressure on the scaphoid tuberosity while the hand is in ulnar deviation. In scapholunate instability, this action will cause the scaphoid to ride out of the radial fossa over the dorsal rim, and as the hand is moved back radially, a painful snap is produced.[41,42] In the setting of acute trauma, unfortunately, this test frequently proves to be too painful to perform. With perilunate and lunate dislocations, visible deformity of the wrist also is apparent, and two-point sensation in the

Figure 51-21. Scapholunate dissociation with scaphoid subluxation. Posteroanterior view of the wrist shows characteristic widening of the scapholunate joint *(black arrow),* known as the "Terry Thomas sign," and a ring shadow over the scaphoid *(white arrow)* secondary to subluxation and known as the *signet ring sign.*

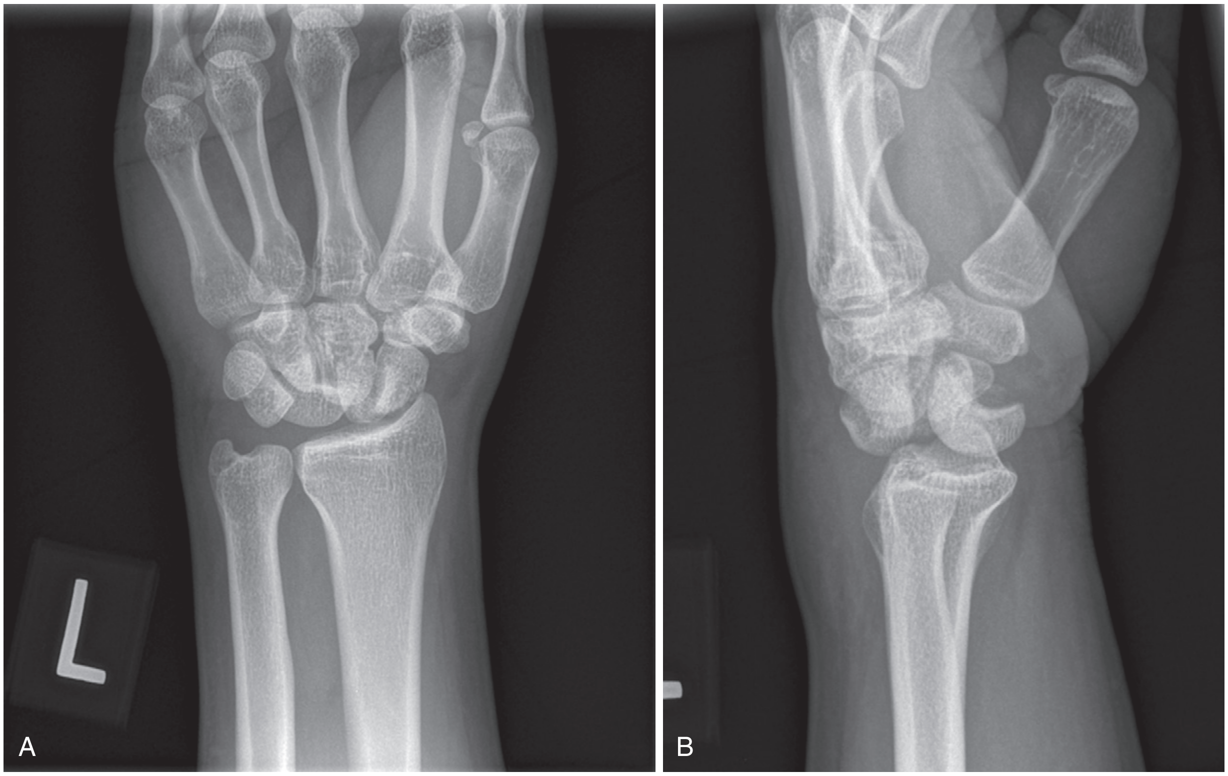


Figure 51-22. Perilunate dislocation. **A,** This posteroanterior view of the wrist shows an abnormal appearing lunate bone, obvious disruption of the normal carpal arcs, and the commonly associated, and in this instance, displaced scaphoid fracture. **B,** Lateral view shows a dislocated and dorsally displaced capitate bone in relation to the lunate. Of note, the lunate maintains its articular connection and alignment with the radius, suggesting perilunate dislocation.

www.ketabpezeshki.com 66485457-66963820

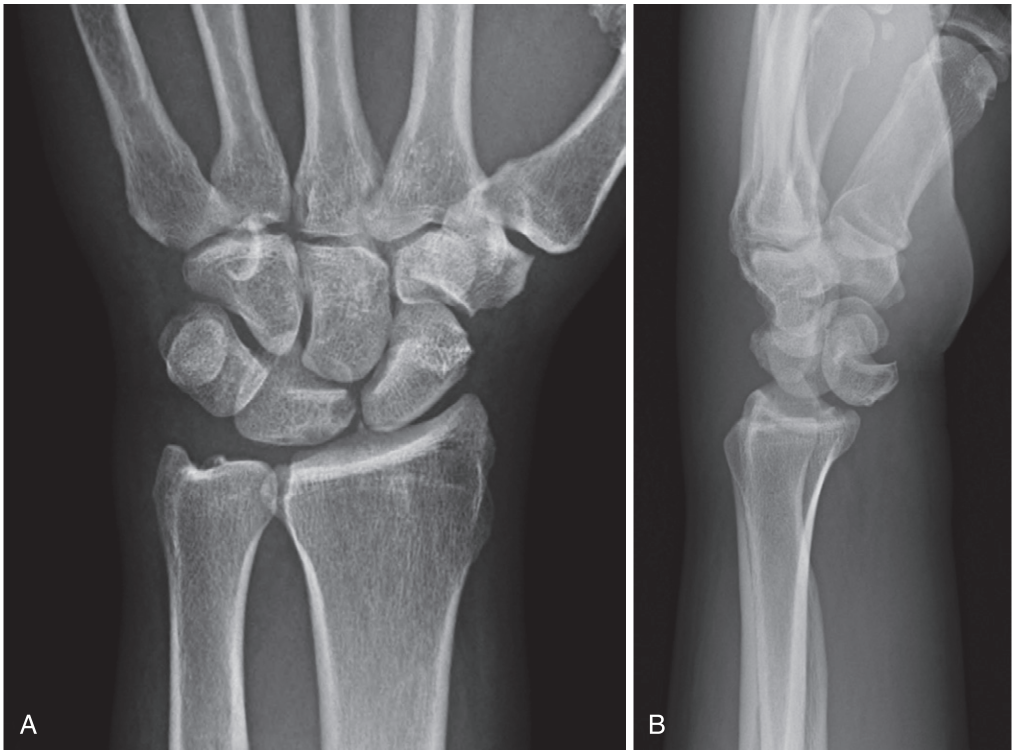


Figure 51-23. Lunate dislocation. **A**, This posteroanterior view shows the characteristic triangular shape of the lunate bone during dislocation. **B**, Volar displacement of the lunate resembles a spilled teacup on the lateral view. Note the disrupted articulation between the lunate and distal radius and realignment of radius, capitate, and metacarpals, suggesting lunate dislocation.

median nerve distribution often is diminished. Complications of carpal dislocation injuries include median nerve injury and chronic carpal instability with resultant degenerative arthritis.

MRI has been shown to have relatively low sensitivity (63%) and specificity (86%) for the diagnosis of scapholunate injury.[43,44] Arthroscopy remains the "gold standard" modality for identifying and grading scapholunate injuries. It allows superior detection of internal derangement of wrist ligaments and a more accurate visualization of the articular surfaces.[41]

Carpal dislocation injuries need emergent orthopedic consultation in the ED for reduction and stabilization. Either arthroscopically guided reduction with pinning or ligament repair can be considered in management of these acute injuries.

Midcarpal and Intercalated Segment Instability

Clinically significant abnormal wrist kinematics may be seen in the ED as midcarpal instability (MCI), including dorsal intercalated segment instability (DISI) and volar intercalated segment instability (VISI).[45,46] The midcarpal joint lies between the proximal and distal carpal rows. The proximal row of carpus bones is known as the *intercalated segment* and moves passively with no direct muscular insertions. Clinically, patients have chronic pain, weakness, and limited range of motion and may report wrist clicking. On physical examination, point tenderness may be elicited over the area of primary injury, usually the scapholunate or lunotriquetral joints. Gross deformity of the wrist, resulting from subluxation, also may be apparent on comparison with the unaffected "normal" wrist.

When ligamentous injury is present, MCI, DISI, and VISI patterns of carpal instability may be recognized radiographically by specific deformities on the lateral view of the wrist (Fig. 51-24). Although the radiographic angles appear complex, a simple approach to diagnose DISI and VISI carpal instability is to locate the lunate, which is one of the easiest carpal bones to visualize on the lateral radiograph. If the lunate is tilted dorsally with respect to the radius, a DISI pattern is suspected; conversely, if the lunate is tilted volarly, a VISI pattern is suspected. A DISI pattern of instability is identified by an increase in both the scapholunate and capitolunate angles, whereas the VISI pattern has a decrease in the scapholunate angle and an increase in the capitolunate angle. DISI is the most common pattern of carpal instability and may occur after scapholunate dissociation or with scaphoid fractures with or without associated perilunate dislocation. VISI occurs after lunotriquetral or triquetrohamate joint disruption.[47] Either pattern may be seen in association with radiocarpal joint malalignment, as is seen in lunate collapse with Kienbock's disease, rheumatoid arthritis, or congenital carpal ligamentous laxity.[42,45] Patients should be splinted and referred to an orthopedic surgeon for definitive stress view radiographs, videofluoroscopy, and advanced CT and MRI imaging for treatment of these injuries. The optimal treatments, which may be surgical reduction, stabilization, and ligamentous repair, are debated in the orthopedic literature.[48]

Radiocarpal Instability

Although radiocarpal dislocations and fracture-dislocations are considered extremely rare, representing only 0.2% of all dislocations, some consider this diagnosis to be under-reported.[49,50] High-energy trauma is the mechanism of injury; patients usually have many additional injuries and are commonly involved in polytrauma scenarios. Dislocations may be volar or dorsal, and ulnar translation of the carpal bones is much more common than radial. Emergent reduction of these injuries is paramount because of the extensive soft tissue damage and commonly associated distal

www.ketabpezeshki.com 66485457-66963820

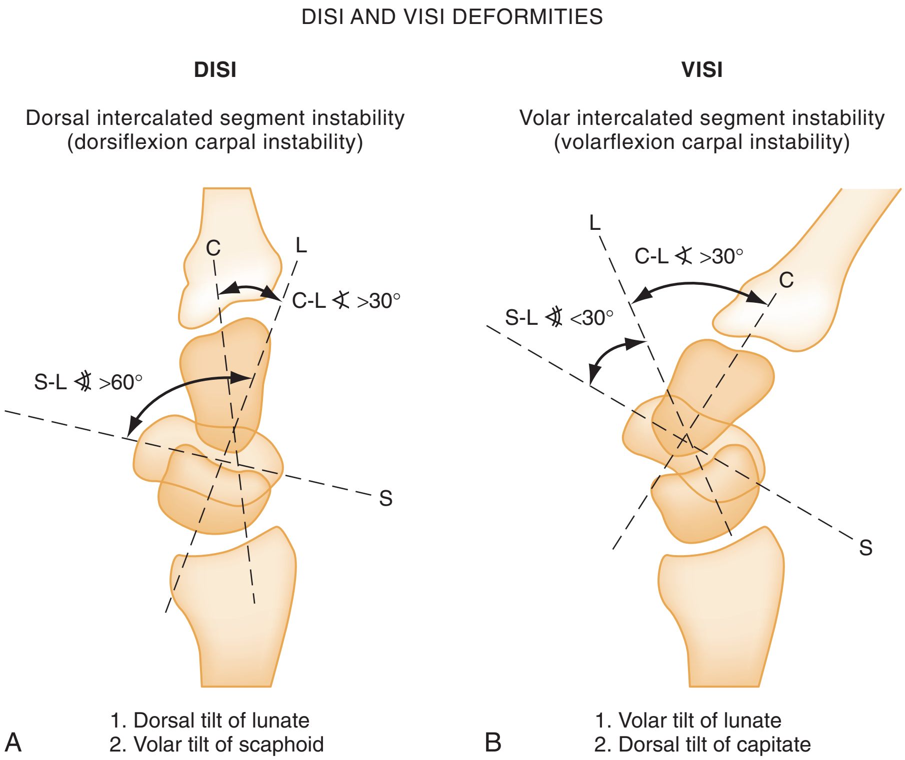


Figure 51-24. Scaphoid (*S*), lunate (*L*), and capitate (*C*) angles in dorsal intercalated segment instability (*DISI*) and volar intercalated segment instability (*VISI*) deformities. **A,** DISI. In this pattern of carpal instability, the scapholunate angle measures more than 60 degrees, and the capitolunate angle measures more than 30 degrees. **B,** VISI. In this pattern of carpal instability, the scapholunate angle measures less than 30 degrees, and the capitolunate angle measures more than 30 degrees. (From Propp DA, Chin H: Forearm and wrist radiology—Part I. J Emerg Med 7:393, 1989.)

neurovascular compromise.[51] Reduction is, however, commonly difficult to maintain in these complex and unstable injuries, which usually require ORIF. Emergent orthopedic consultation in the ED is indicated.

DISTAL RADIUS AND ULNA INJURIES

Distal radius and ulna fractures remain some of the most common injuries seen in EDs worldwide. Women older than 50 years, who are most vulnerable, can carry a 15% lifetime risk of this injury pattern. Occurring, in general, from a fall on the outstretched hand in older patients and from high-energy trauma in younger patients, these injuries are commonly closed, may have intra-articular involvement and displacement, and frequently require closed reduction, splinting, and outpatient orthopedic referral. Numerous classification patterns have been devised, and the most commonly encountered fractures are discussed in the following sections.[52]

Colles' Fracture

Colles' fracture, first described in 1814, is the most common wrist fracture seen in adults.[53] It is a transverse fracture of the distal radial metaphysis, which is dorsally displaced and angulated, causing the classic "dinner fork" deformity seen on physical examination. The fracture usually is located within 2 cm of the radial articular surface and may be associated with comminution and intra-articular extension into the radiocarpal or radioulnar joints. There is commonly an associated fracture of the ulnar styloid in 60 to 70% of cases, which may suggest concomitant injury to the TFCC.[54] A neurovascular examination should be performed to exclude any neurapraxia or vascular compromise caused by the deformity or fracture fragments.

The PA and lateral views of the wrist show the fracture through the radial metaphysis. The PA view may show extension of the fracture into the radioulnar or radiocarpal joints and the amount of intra-articular step-off and radial shortening present. The degree of dorsal displacement and angulation is best seen on the lateral view, with loss of the normal volar tilt of the distal radial articular surface (Fig. 51-25).

Many Colles' fractures require early anatomic reduction with restoration of radial length and correction of the dorsal angulation either to a neutral position or ideally restoring the normal volar tilt.[54] This procedure is often performed by emergency physicians. Closed reduction may be assisted by intravenous analgesia, local or regional anesthesia, or procedural sedation and is followed by sugar-tong splint immobilization. This treatment may be definitive and, if successful, allows for outpatient orthopedic referral in the majority of cases. Methods of local and regional anesthesia for distal radial fracture reduction include the classic hematoma block; intravenous regional anesthesia, known as the *Bier block*, which is not routinely taught to emergency physicians today; and regional nerve blocks, including radial, median, ulnar, or brachial plexus approaches.[54] The hematoma block remains an effective method of anesthesia and is performed by placing a 22-gauge needle in the dorsum of the distal radius, withdrawing until a fracture hematoma is encountered, then instilling 5 to 10 mL of 2% lidocaine (Fig. 51-26). Use of finger traps also is an effective means of obtaining the reduction to allow positioning for splinting (Fig. 51-27). The more comminuted and displaced the fracture, the higher the likelihood that operative reduction will be necessary. Common emergent indications for Colles fracture reductions include any neurovascular compromise, significant soft tissue tension, or tenting of the skin. More debatable indications for emergent or urgent reduction include a loss of volar tilt with significant dorsal angulation (>10-20 degrees), radial shortening or a positive ulnar variance greater than 2 mm. An intra-articular

www.ketabpezeshki.com 66485457-66963820

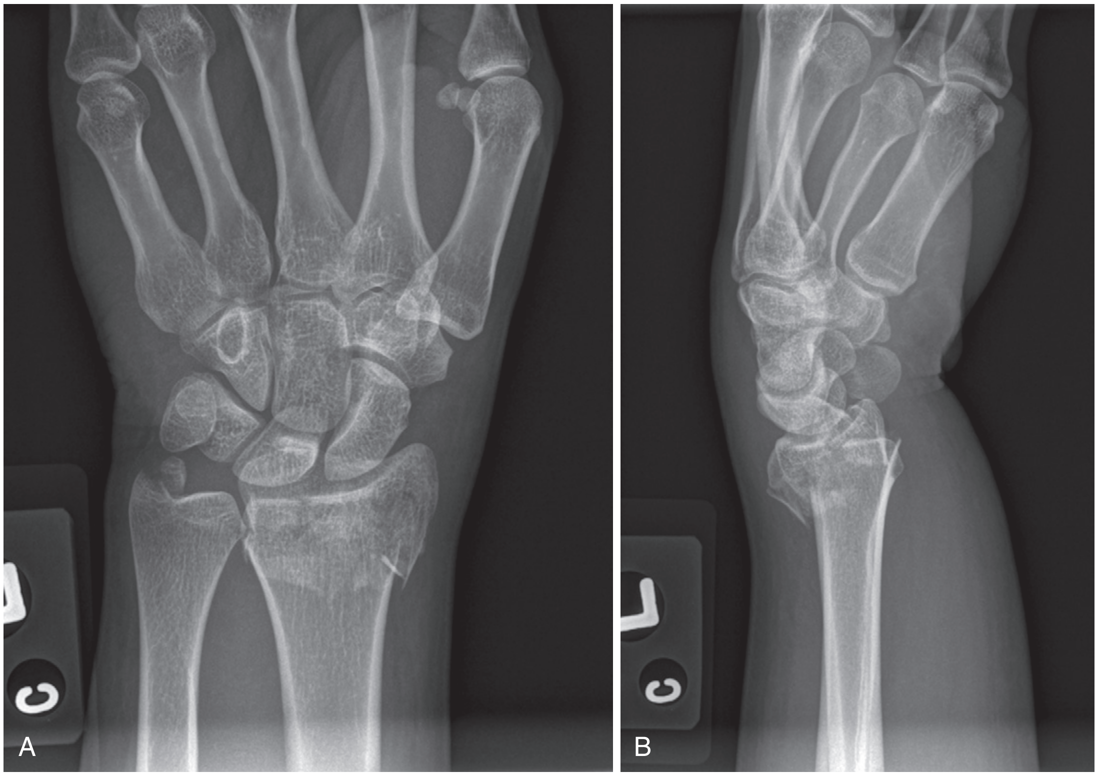


Figure 51-25. Colles' fracture. **A,** Posteroanterior view shows fracture and shortening of the radius, intra-articular extension, and associated ulnar styloid fracture. **B,** Lateral view shows typical dorsal displacement and angulation of the radial fracture known as the *dinner-fork deformity.*

Figure 51-26. Hematoma block. Sterile preparation of the fracture area is performed, and local anesthetic is then introduced to the hematoma that surrounds the fracture site to assist with pain control during reduction.

step-off less than 1 to 2 mm and radial inclination less than 15 degrees are also considered optimal in younger patients but difficult to affect with closed reduction.[54,55] Loss of reduction will occur in many of these patients before follow-up, especially the elderly, in whom the long-term benefits of anatomic restoration are questioned.[56] Emergent orthopedic consultation should be considered if initial attempts at closed reduction are unsuccessful and there is associated neurovascular compromise, clinical compartment syndrome, or if the fracture is open.

Complications of Colles' fracture are seen most often in elderly patients and those with inadequate fracture reduction.[54-57] Although radial and ulnar nerves may be compromised, median nerve injury is most common and may occur acutely from contusion, traction from displacement, transection from fracture fragments, nerve compression after closed reduction, overlying cast pressure, or secondary to acute carpal tunnel syndrome (CTS; discussed later).[57] Overlying skin and soft tissues are at risk, and tendon injury has been reported. For this reason, it is important to evaluate neurologic function before and after fracture reduction.

Smith's Fracture

Smith's fracture is a transverse fracture of the metaphysis of the distal radius, with associated volar displacement and angulation. In some cases, the fracture may extend into the radiocarpal joint. On physical examination it is known as the *garden spade deformity* but because displacement is opposite to that seen in Colles' fracture, Smith's fracture often is called a *reverse Colles' fracture.* The typical mechanism of injury involves a direct blow to the dorsum of the wrist or a fall onto the dorsum of the hand resulting in extreme palmar flexion. The fracture also may be seen after a fall backward on an outstretched hand with the forearm in supination. The patient has a swollen, painful wrist, which is deformed, with fullness visible on the volar aspect. The fracture is visible on PA and lateral radiographs of the wrist, but the lateral view best shows the degree of volar displacement and angulation (Fig. 51-28).

Treatment of this fracture involves closed reduction and immobilization in a sugar-tong splint as discussed earlier. Unlike Colles' fracture, however, Smith's fracture is much more likely to be unstable and to require operative repair and splint reduction, and has an increased tendency to cause neurovascular compromise, specifically median nerve compression. Urgent orthopedic referral or emergent consultation is indicated based on the severity of angulation, neurovascular compromise, or associated soft tissue complications. Similarly, prognosis is most favorable in patients with successful reduction and restoration of the normal radial length and volar tilt.[54,58]

Barton's Fracture

Barton's fracture is an oblique intra-articular fracture of the rim of the distal radius, with displacement and dislocation of the

www.ketabpezeshki.com 66485457-66963820

carpus along with the fracture fragment. The fracture may involve the dorsal rim of the radius with dorsal carpal subluxation (classic Barton's fracture), or it may involve the volar rim with volar carpal subluxation (volar Barton's fracture). These fractures are rare and account for only 1% of all distal radius fractures.[59] The volar-anterior margin fracture is seen more often than the dorsal-posterior margin fracture.

The mechanism of injury for these fractures is a high-velocity impact across the articular surface of the radiocarpal joint, with the wrist in either volar flexion (causing a volar rim fracture) or dorsiflexion (causing a dorsal rim fracture). Volar and dorsal rim fractures are easily visible on PA and lateral wrist radiographs; however, the lateral view best shows the degree of articular surface involvement and the amount of associated fracture displacement (Fig. 51-29).

Treatment of these fractures requires emergent orthopedic consultation for reduction and stabilization. Closed reduction occasionally may be successful. Most authorities now advocate early operative management with either closed reduction performed under fluoroscopy, followed by percutaneous pinning or ORIF to accurately restore the articular surface of the radius and stabilize the carpus.[59] Complications include post-traumatic arthritis of the radiocarpal joint and delayed carpal instability. Both complications are seen more commonly when reduction fails to achieve or maintain anatomic realignment of the radiocarpal joint surface.

Hutchinson's Fracture

Hutchinson's fracture, or chauffeur's fracture, is an intra-articular fracture of the radial styloid. The mechanism of injury is usually a direct blow or fall resulting in trauma to the radial side of the wrist. The term *chauffeur's fracture* originated in the era of hand-cranked automobiles, when this injury occurred because of direct

Figure 51-27. Finger traps. Distal radius reduction method typically involves traction followed by manipulation facilitated by the finger traps. Ten pounds of weight are hung from the elbow at 90 degrees of flexion for approximately 10 minutes before the reduction attempt.

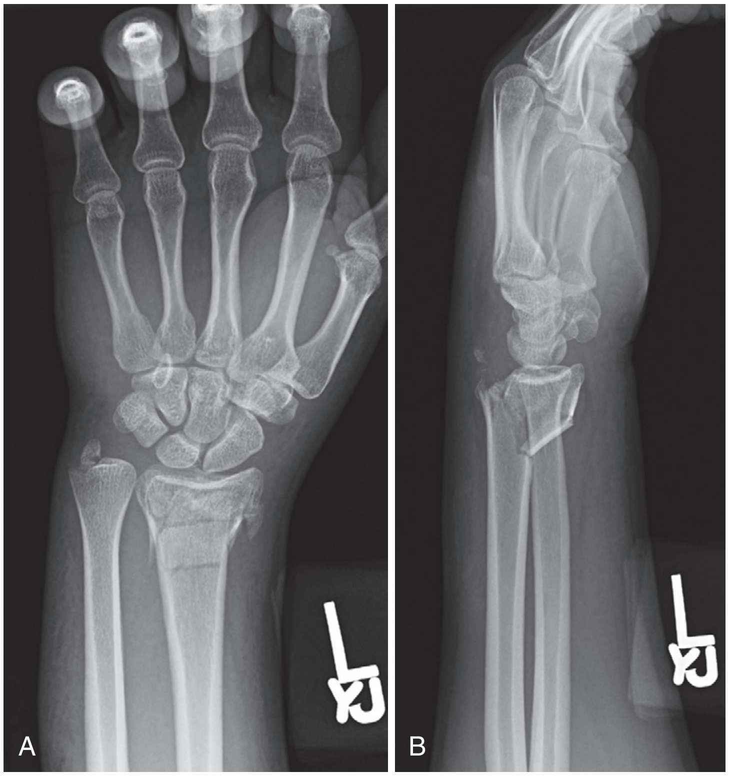


Figure 51-28. Smith's fracture. **A,** Posteroanterior view shows a metaphyseal fracture of the radius with shortening and associated ulnar styloid base fracture. **B,** Lateral view shows volar displacement of the distal fracture fragment along with the carpus.

www.ketabpezeshki.com 66485457-66963820

Figure 51-29. Volar Barton's fracture. Lateral radiograph of the wrist shows typical oblique intra-articular fracture of the volar rim of the radius with associated displacement of the distal radial fragment and carpus dislocation.

trauma to the radial side of the wrist from the recoil of the motor crank. The fracture is seen best on the PA view of the wrist as a transverse fracture of the radial metaphysis with extension through the radial styloid into the radiocarpal joint.

Nondisplaced fractures may be immobilized in a sugar-tong splint, with the patient given urgent orthopedic referral; definitive treatment is in a short arm cast. However, displaced fractures, which are frequently associated with scapholunate ligament disruption, require open or closed reduction and fixation (Fig. 51-30). Because the radial styloid is the primary site of attachment for many of the ligaments of the wrist, accurate fracture reduction and union are crucial for wrist function.[60] Post-traumatic arthritis is a common complication of radial styloid fractures and more common with displacement and scapholunate ligament disruption.

Distal Radioulnar Joint Disruption

Acute dislocation of the DRUJ can occur as an isolated injury, which is rare, or in association with a fracture to the distal radius (Colles' fracture), radial diaphysis (Galeazzi's fracture), or radial head (Essex-Lopresti injury).[61,62] Diagnosis often is difficult because when the injury occurs in isolation or is not suspected, plain radiographs commonly are reported as normal in appearance. Certain characteristic findings on clinical examination may constitute the only clue to the presence of this injury.

The typical mechanism of injury is a fall on the outstretched hand with either hyperpronation, resulting in dorsal dislocation, or hypersupination, causing volar dislocation of the ulna. Dorsal ulna dislocations are more common than volar dislocations.[6,62] Another mechanism known to cause DRUJ dislocation is the catching of the hand in rotating machinery, resulting in the same forcible hyperpronation or supination. This forcible rotation of

Figure 51-30. Hutchinson's fracture. Posteroanterior radiographic view shows intra-articular fracture of the radial styloid with displacement and scapholunate dissociation, a common complication of untreated Hutchinson's fracture.

the wrist causes disruption of the TFCC, the major stabilizer of the DRUJ, and may result in an associated avulsion fracture of the ulnar styloid.

Patients with this injury have a history of sudden onset of pain with a "snapping" sensation in the wrist, swelling, and limited range of motion. On examination, tenderness is present over the ulnar aspect of the wrist, with palpable crepitus on supination and pronation. With a dorsal dislocation of the ulna, the ulnar styloid appears more prominent than on the unaffected side, and significant pain and limitation of movement are noted on supination of the wrist. With a volar dislocation of the ulna, there is loss of the normal ulnar styloid prominence, with pain and limitation of movement on pronation. These characteristic clinical findings should alert the physician to the possibility of DRUJ disruption and prompt the appropriate investigations to confirm the presence or absence of this injury.[63]

Well-positioned lateral radiographs of the wrist may show the presence of a DRUJ dislocation with more than 20 degrees of dorsal angulation or volar displacement, but pain and inability of the patient to rotate the wrist fully may cause a false-negative result because a true lateral view cannot be obtained.[64] Fractures of the ulnar styloid base should increase suspicion regarding a DRUJ disruption. It also is important to assess for radial head fractures because this injury is commonly associated with DRUJ disruption and interosseous membrane rupture (Essex-Lopresti injury).[65] A DRUJ dislocation is seen on the PA view of the wrist showing significant overlap or widening of the distal radius and ulna (Fig. 51-31). If there is significant clinical suspicion of injury and the radiographic appearance is normal, a CT scan may assist in the diagnosis.[66,67]

Treatment of these injuries commonly requires orthopedic consultation for reduction and stabilization. Closed reduction with the forearm in supination followed by application of a long arm cast often is successful. Alternatively, open reduction frequently is necessary with volar dislocations because the ulnar head often is locked on the distal radius. Operative reduction also is necessary in dorsal dislocations to repair the associated injury to

www.ketabpezeshki.com 66485457-66963820

Figure 51-31. Distal radioulnar joint dislocation. Posteroanterior radiographic view shows ulnar styloid base fracture suggestive of triangular fibrocartilage complex disruption and widening of the radius and ulna consistent with distal radioulnar dislocation.

the TFCC. Immobilization in a long arm cast usually is maintained for 6 weeks.

Pediatric Fractures of the Distal Radius

Fractures of the distal radius in children may be divided into two types: fractures involving the distal radial metaphysis and fractures involving the growth plate. They usually occur as a result of a fall on an outstretched hand with the wrist forcibly dorsiflexed. Fractures of the radial metaphysis are of three types: torus fractures, greenstick fractures, and complete fractures.

The periosteum of growing immature pediatric bone is strong but more pliable than completely matured adult bone, often leading to bowing injuries of the radial metaphysis rather than the typical fracture patterns seen in adults. The torus fracture is the most common of these radial metaphyseal fractures and results in a buckling of the radial cortex, which occurs without significant displacement (Fig. 51-32).[68] These fractures are treated with immobilization in a short arm splint with orthopedic referral and follow-up evaluation.[69,70] Healing usually occurs over 2 to 3 weeks, and complications are rarely seen.[71] Mild angulation remodels well in children, allowing for acceptance of the fracture "as it lies" in many cases. As a result, studies now debate the need for definitive casting and orthopedic evaluation for simple nondisplaced torus fractures of the distal radius.

Greenstick fractures also are incomplete metaphyseal fractures, with disruption of the cortex on one side and angulation or bowing on the opposite side (Fig. 51-33). Commonly, these fractures are displaced and require reduction if angulated more than 10 degrees. Angulations of less than 10 degrees usually remodel. Short arm splint immobilization is recommended, with close orthopedic follow-up to ensure maintenance of reduction.

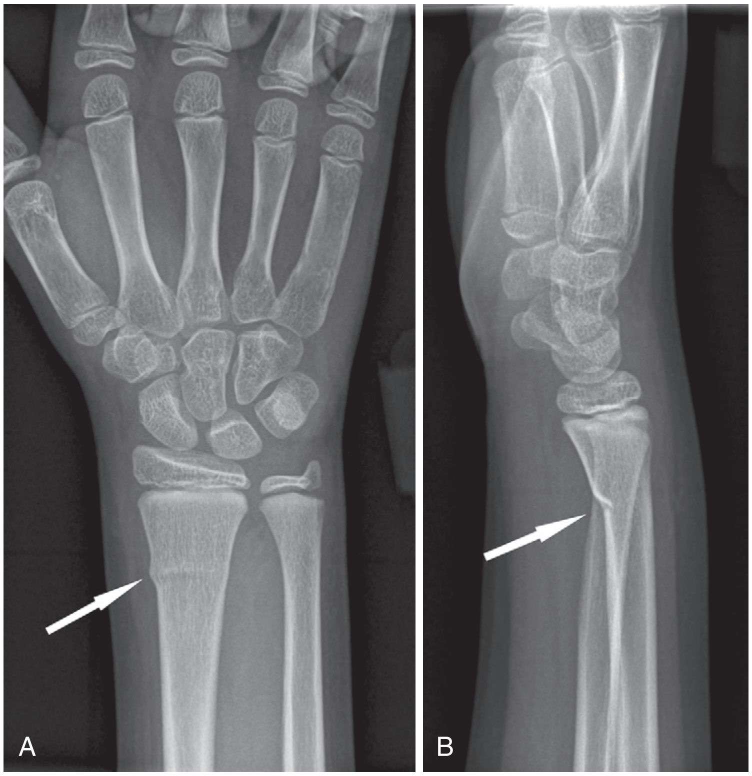


Figure 51-32. Torus fracture of the distal radius. **A,** Anteroposterior and **B,** lateral radiographic views of the wrist show a distal radial torus fracture with buckling of the cortex *(arrows).*

www.ketabpezeshki.com 66485457-66963820

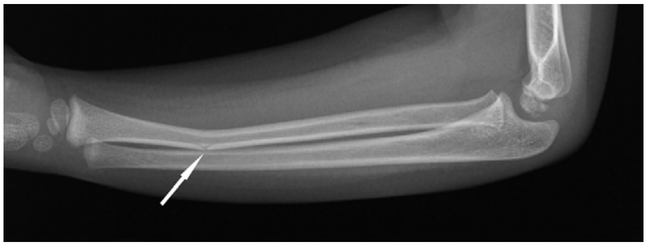


Figure 51-33. Greenstick fracture. Angulation and bowing of the distal radius with a greenstick-type pediatric fracture *(arrow)* is pictured in this lateral view of the forearm.

Complete fractures of the radial metaphysis involve disruption of both cortices of bone and usually result in significant displacement and angulation. These injuries also may be associated with a fracture of the distal ulna. Closed reduction may be successful; however, if the fracture is unstable or open, if there is neurovascular compromise, or if compartment syndrome is a concern (discussed later), emergent orthopedic consultation is indicated.[72]

In 1963, Salter and Harris classified growth plate injuries in children.[73] A discussion and descriptive table of the Salter-Harris I to V classification system may be found in Chapter 176. Growth plate, or physeal fractures, of the distal radius are usually Salter-Harris type I or II. Although these injuries result in disruption of the growth plate, they rarely result in growth disturbance.[68,73] Type I injuries cause pain and palpable tenderness over the distal radial physis. There may be no radiographic abnormality, or subtle volar displacement of the pronator quadratus fat pad may be observed. Type II injuries involve a fracture through the radial metaphysis and the physis and are visible on routine wrist radiographs as a triangular metaphyseal fragment on the dorsal surface of the radius. These fractures may be complicated by displacement of the radial epiphysis or by an associated fracture of the distal ulna (Fig. 51-34). These injuries may be treated with short arm splint immobilization and given orthopedic follow-up evaluation within 1 week of the injury. Immobilization or closed reduction may be sufficient; however, operative fixation may be necessary if adequate alignment cannot be achieved or maintained with casting.

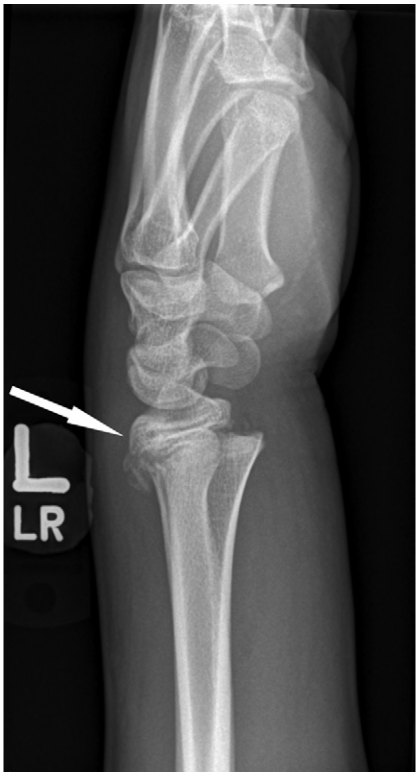


Figure 51-34. Salter-Harris type II distal radius fracture. A Salter-Harris type II distal radial fracture with triangular metaphyseal fragment and dorsal displacement *(arrow)* is pictured in this lateral view of the pediatric wrist.

SOFT TISSUE INJURIES OF THE WRIST

Carpal Tunnel Syndrome

CTS is the most common entrapment neuropathy that occurs at the wrist as a result of compression of the median nerve. CTS has an overall lifetime incidence ranging from 3 to 6%, with a female preponderance.[74,75] The transverse carpal ligament and the volar surfaces of the carpal bones form the carpal tunnel. It is a rigid compartment that contains nine flexor tendons (the flexor pollicis longus tendon, four flexor digitorum superficialis tendons, and four flexor digitorum profundus tendons) and the median nerve. Any process, local or systemic, that results in an increase in pressure within this compartment may produce CTS.

The most common causes of CTS are distal radius fractures and repetitive strain. CTS also can be associated with numerous systemic conditions, such as rheumatoid arthritis, hypothyroidism, diabetes mellitus, renal failure, congestive heart failure, acromegaly, and collagen vascular diseases.[76] Each of these systemic diseases is thought to produce an increase in pressure within the carpal tunnel from thickening of the flexor synovia or transverse carpal ligament. Hormonal changes associated with pregnancy and menopause also are known to cause CTS, probably from retention of fluid in the soft tissues about the wrist.[75,77]

Figure 51-35. Phalen's test.

The classic symptoms include a gradual onset of numbness, paresthesia, and pain in the thumb, index, and long fingers. These symptoms often are bilateral and are worse during the night and after strenuous activities. Typically, patients report numbness and paresthesias on awakening that lessen when the hands are shaken or held in a dependent position. The paresthesias are in the classic median nerve distribution and can be seen in a Katz diagram (see Table 51-1).

Examination of the neck and chest is important to detect cervical radiculopathy or thoracic outlet syndrome, which can mimic CTS. The most common provocative test is the wrist flexion or Phalen's test (sensitivity of 76% and specificity of 80%) (Fig. 51-35).[78] This test is performed by asking the patient to flex the wrists fully for 60 seconds while holding the forearms in a vertical

www.ketabpezeshki.com 66485457-66963820

position. The test result is positive if paresthesia or numbness develops in the median nerve distribution.

Another test for CTS is Tinel's sign, which demonstrates pain or paresthesias in the median nerve distribution elicited by light tapping or percussion over the median nerve at the wrist. Analysis of the literature suggests, however, that Tinel's sign (sensitivity of 42 to 85%; specificity of 54 to 98%) is not as powerful as Phalen's test in detecting median nerve compression.[79] An additional test, Durkan's or the median nerve compression test, which consists of application of pressure directly over the median nerve at the carpal tunnel, has a sensitivity of 87% and specificity of 90%.[80]

Because none of these physical tests is completely reliable in making the diagnosis of CTS, nerve conduction studies have been used to confirm the diagnosis, with reports of 85 to 90% sensitivity.[79] MRI and high-resolution ultrasound studies occasionally are used for confirmation, but the diagnosis of CTS is primarily clinical.[80]

Conservative (nonoperative) treatment for CTS yields variable results. Specific measures include splinting the wrist in a neutral position and administering cortisone injections in the carpal tunnel. Splinting initially may be prescribed full time and then reduced to splinting at night only. Kaplan identified five important factors that lessen the likelihood of successful nonoperative treatment: (1) age older than 50 years, (2) duration longer than 10 months, (3) constant paresthesias, (4) stenosing flexor tenosynovitis, and (5) positive Phalen's test result at less than 30 seconds. Two thirds of patients in his series were cured by medical treatment when none of these factors were present. However, 59.6% with one factor, 83.3% with two factors, and 93.2% with three factors did not improve. No patient with four or five factors was cured by medical management.[81] Nonsteroidal anti-inflammatory drugs (NSAIDs) have proved to be of little benefit. Surgical release of the flexor retinaculum to unroof the carpal tunnel is indicated when medical management fails.[82]

Acute carpal tunnel syndrome (ACTS), which occurs over hours rather than weeks, months, or years, is much less common than the chronic, gradually progressive presentations of CTS requiring symptomatic relief, appropriate referral, and patient education. ACTS is more often directly related to fractures, fracture-dislocations, hemorrhagic conditions, infections, vascular disorders, and edema involving the wrist.[83] Although the carpal tunnel is open at both ends, it has the physiologic properties of a closed compartment.[84] Distal radius fractures are likely the most common cause of ACTS; however, lunate and perilunate dislocations are associated, and even isolated carpal fractures and rupture of the extensor pollicis longus (EPL) tendon have been documented as rare causes. No reliable clinical method currently exists for differentiating acute median nerve compression in ACTS from concussive insult. In the absence of trauma, ACTS has occurred secondary to hemorrhagic, vascular, and bleeding disorders and anticoagulant use. When ACTS has been diagnosed, orthopedic consultation is recommended for immediate surgical decompression and release of the transverse carpal ligament. This may preserve nerve function and prevent post-traumatic complex regional pain syndromes.[83,85,86]

de Quervain's Disease and Intersection Syndrome

de Quervain's disease and intersection syndrome, like CTS, have been grouped into the overuse or repetitive strain injury pattern category, sometimes referred to as *work-related cumulative trauma* in the occupational medical literature. The APL and EPB, both within the first dorsal extensor compartment of the wrist, are the tendons affected in de Quervain's disease. Traditionally known as a stenosing tenosynovitis, tendonitis, or tendovaginitis of the wrist, de Quervain's disease involves enlarged tendons, which may reach five times their original size, creating a stenosing tendinopathy. Clinically, patients report pain on the radial side of the wrist, with ulnar deviation, thumb movements, weakened grip strength, or a combination of these symptoms. Onset is gradual and typically the result of increased use. There are no large epidemiologic studies, but de Quervain's disease is thought to be common, affecting women six times more frequently than men, and typically at an age older than 40 years. Radiographs are useful in ruling out bony pathology, but the diagnosis may be made with physical examination only.

Originally described in 1930, Finkelstein's test has long been considered to be a pathognomonic sign of de Quervain's disease. The test is named after the Swiss surgeon Fritz Finkelstein, who said, "On grasping the patient's thumb and quickly abducting the hand ulnarward, the pain over the styloid tip is excruciating. This is probably the most pathognomonic objective sign."[87]

There are surprisingly few prospective randomized controlled studies with good methodological quality regarding treatment of de Quervain's disease. Conservative interventions of rest, splinting, NSAIDs, and corticosteroid injections of the dorsal extensor compartment of the wrist are the first-line treatments for mild to moderate disease. Wrist splints with thumb spicas effectively immobilize the APL and EPB, but pain may return when inciting activity is resumed. Use of corticosteroid preparations with local anesthetic has been reported to be successful. Patients with refractory or severe cases of de Quervain's disease that interfere with the activities of daily living undergo surgical release of the first dorsal extensor compartment of the wrist with decompression of the APL and EPB tendons.[88]

Intersection syndrome is another overuse tendinopathy that clinically manifests with pain on the radial side of the wrist approximately 4 to 8 cm proximal to the site of de Quervain's disease. The condition is also known as *peritendinitis crepitans* or *crossover* or *oarsman's syndrome.* The mechanism of injury is secondary to rowing, weightlifting, or a repetitively resisted pulling action. Pathophysiologically, intersection syndrome occurs secondary to inflammation where the muscle bellies of the APL and EPB cross over the muscle bellies of the extensor carpi radialis longus and brevis proximal to the retinaculum. Physical examination findings include significant pain, soft tissue swelling, and crepitus with movement in more severe cases. Ultrasound findings may include thickened tendons or effusion, and radiographs are negative. The treatment for this disease is immobilization with a wrist splint and anti-inflammatory medication. Although surgical treatments have been described, this syndrome is typically self-limited.[89]

FOREARM

PERSPECTIVE

Forearm injuries are one of the common encounters in the ED. In children, forearm fractures account for almost half of the all pediatric fractures.[90] Mechanisms of injury include falls on outstretched hands, direct blows to the area, or involvement in motor vehicle collisions. Evaluation of forearm injuries requires understanding of the interdependent biomechanical relationship between the radius and ulna. These two bones articulate at both the proximal and distal ends, which allows the radius to rotate around the ulna to provide pronation and supination. As the fracture of either radius or ulna can result in dislocation at the wrist or elbow, emergency physicians should be vigilant when treating forearm fractures. Early diagnosis and prompt treatment of these injuries are critical if full function of the forearm is to be retained.

www.ketabpezeshki.com 66485457-66963820

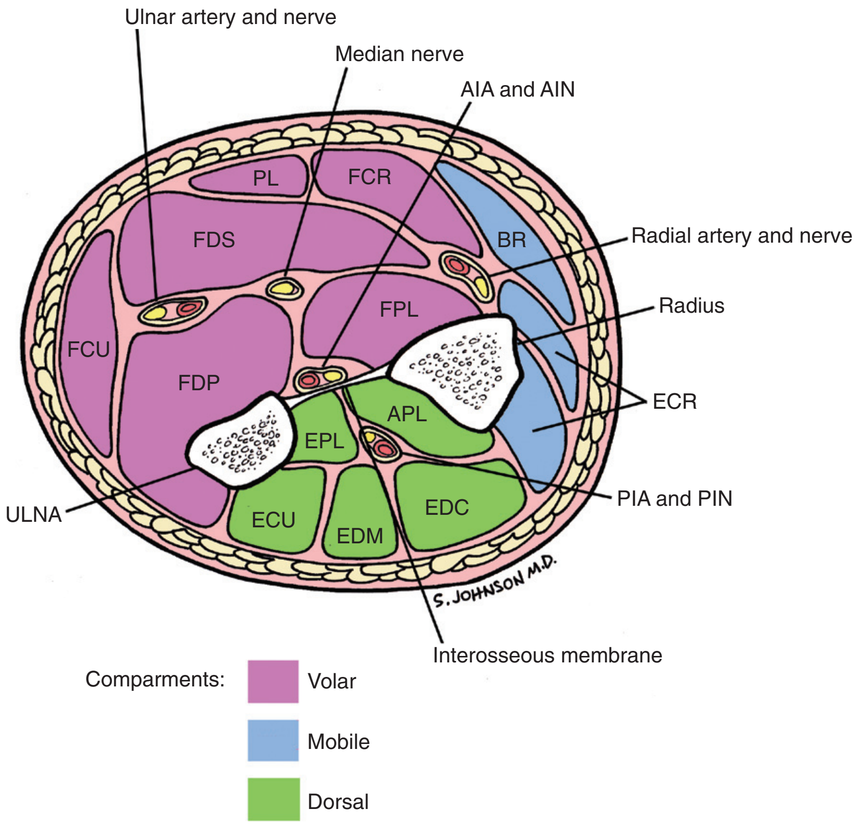


Figure 51-36. Cross section of the forearm demonstrating the compartments and the neurovascular structures. The volar compartment contains the flexor of hands and wrist, including the policis longus (*PL*), the flexor digitorum superficialis *(FDS),* flexor carpi radialis *(FCR),* flexor pollicis longus *(FPL),* flexor digitorum profundus *(FDP),* and flexor carpi ulnaris *(FCU),* as well as the ulnar nerve, ulnar artery, median nerve, radial artery, superficial branch of the radial nerve, anterior interosseous artery *(AIA),* and anterior interosseous nerve *(AIN).* The dorsal and volar compartments are bordered by the interosseous membrane. The dorsal compartment contains finger extensors and the long thumb abductor as well as the posterior interosseous artery *(PIA),* posterior interosseous nerve *(PIN),* the abductor pollicis longus (*APL*), the extensor digiti minimi (*EDM*), extensor carpi ulnaris *(ECU),* extensor pollicis longus *(EPL),* and extensor digitorum communis *(EDC).* The mobile wad, which is often considered to be a third compartment, is composed of the extensor carpi radialis brevis and longus muscles *(ECR)* and the brachioradialis *(BR).* (Courtesy Sonia Johnson, MD.)

Anatomy

The forearm is a unique two-bone structure with the radius and ulna being bound at both ends by a ligamento-capsular structure. The proximal radioulnar joint (PRUJ) is made up of an articulation between the radial head and ulna. The radial head, the primary stabilizer of the forearm combined with the annular, quadrate, radial, and ulnar ligaments, provides strong support at the PRUJ. At the DRUJ, the TFCC and the anterior and posterior radioulnar ligaments support the articulation of the distal radius and ulna.[91] The interosseous membrane further stabilizes the forearm by providing a strong interconnection between the radius and ulna. The ulna is relatively straight and provides the rotational axis for the bowed radius to rotate around through various planes of motion. The supinator, pronator teres, and pronator quadratus muscles insert along the shaft of the radius and ulna to provide their named function, but they also are responsible for the deforming forces in forearm fractures.

The forearm is typically divided into three compartments: volar, dorsal, and mobile wad.[92] The interosseous membrane divides the volar and the dorsal compartments, and the mobile wad is located laterally (Fig. 51-36). The volar compartment, which can be further divided into superficial and deep layers, contains the pronators and flexor muscles of the hands. The radial, ulnar, and anterior interosseus arteries and median, ulnar, and superficial radial nerves are also contained within the volar compartment. The dorsal compartment consists of the extensor muscles of the hand and the posterior interosseous artery and nerve. The mobile wad is located in the proximal lateral aspect of the forearm and contains the brachioradialis, the extensor carpi radialis longus, and the extensor carpi radialis brevis.

CLINICAL FEATURES

Obtaining the history of the mechanism of injury is crucial in the initial assessment of a forearm injury. Physical examination of the forearm injury begins with visual inspection evaluating for swelling along the injured area, obvious deformity, and evidence of lacerations. Gentle palpation of the injured area can assist in localization, reveal crepitus in grossly unstable fractures, and allow assessment of skin turgor in the evaluation of compartment pressure. Significant swelling as well as disproportionate pain, paresthesia, and paleness of skin should alarm physicians regarding development of compartment syndrome. Neurologic evaluation should include careful examination of motor and sensory function of the radial, ulnar, and median nerves. Assessment of the brachial, radial, and ulnar arteries should be part of the vascular examination.

DIAGNOSTIC STRATEGIES: RADIOLOGY

The radiologic evaluation of the forearm injury should begin with the AP and lateral views. It is essential to include both wrist and

www.ketabpezeshki.com 66485457-66963820

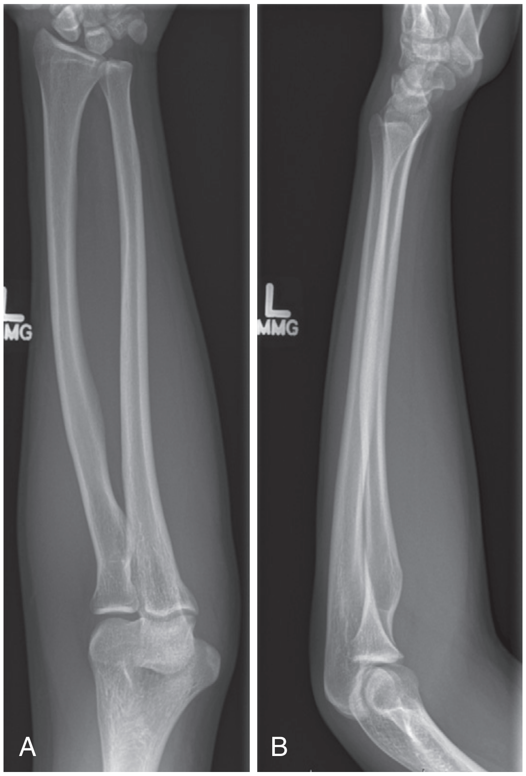


Figure 51-37. Normal anteroposterior **(A)** and lateral **(B)** radiographic views of the forearm. Both bones should be visible for their entire length, and the radiograph should include the wrist and elbow joints.

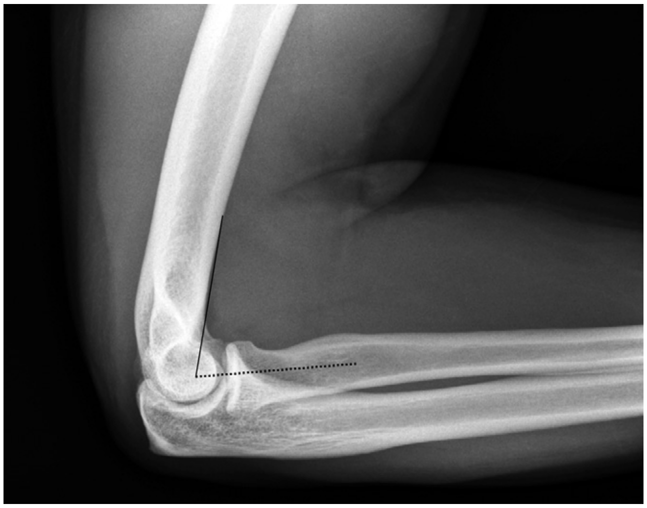


Figure 51-38. Lateral radiographic view of a normal elbow. A line *(dotted)* bisecting the proximal radial shaft also bisects the capitellum.

elbow in the x-ray examination of the forearm to exclude any concomitant injuries to either the DRUJ or PRUJ.

On the normal AP view of the forearm, a medially pointing radial styloid and laterally projecting biceps tuberosity of the proximal radius are visible. On the lateral view, the coronoid process of the proximal ulna points volarly and the ulnar styloid lies dorsally (Fig. 51-37). Any deviation suggests an abnormal rotational or axial deformity. The normal radiologic findings of the forearm, including radiocarpal articulation angle, relationship between radial styloid and ulnar styloid, and normal volar tilt of the radius, are described in the section on radiology of the wrist (earlier).

Injury to the radial head can be evaluated by drawing a mid-axis line through the radial shaft, neck, and head. This radial mid-axis line should intersect the center of capitellum of the elbow on any radiologic view. Any variance from this alignment should raise suspicion regarding radial head dislocation (Fig. 51-38).

CT scans can be useful when there is a suspicion of extension of the fracture into the DRUJ or PRUJ on plain radiography. MRI is the study of choice for evaluation of soft tissues (muscle, tendon, and ligament) of the forearm, including the interosseous membrane. Ultrasound images can also help with evaluation of interosseous membrane injury.[93]

FOREARM FRACTURES

Shaft Fractures of Radius and Ulna

Fractures involving both the radius and the ulna, also known as "both-bone" fractures, are common forearm injuries. Patients often have pain and obvious deformity of the forearm as a result of either minor or major trauma. Careful physical examination is warranted to exclude any associated neurovascular injuries or open fracture. Compartment syndrome should be considered in all patients with this type of injury. Initial radiologic evaluation should include not only AP and lateral radiographs of the forearm, but dedicated wrist and elbow radiographs as well.

After initial evaluation, any open fractures should be immediately irrigated with sterile normal saline to decrease contamination, and a sterile dressing should be applied while operative management is awaited. Any grossly displaced fracture-dislocation should be reduced to improve alignment and prevent impending or ongoing neurovascular injury. Application of a sugar-tong forearm splint should be made with an urgent referral to an orthopedist as long as there is no evidence of open fracture or neurovascular compromise.[94] Because nondisplaced radius and ulna fractures are extremely uncommon, most both-bone fractures of the forearm will eventually require operative management. Common complications of combined radius and ulna fractures are nonunion, malunion, infection, and neurovascular injury.[94]

Ulna Shaft Fractures

Isolated fractures of the ulna shaft, known as "nightstick fractures," are seen frequently in the ED. Patients often have pain and swelling over the medial aspect of the forearm, as the usual mechanism involves raising the arm overhead to protect from a direct traumatic impact. Careful inspection of the skin is necessary; many patients have open fractures, given the superficial position of the ulna directly under the subcutaneous skin. Complete examination should include wrist and elbow examinations to exclude any associated injuries involving the PRUJ or DRUJ. The practitioner should be aware of potential instability at either articulation associated with fractures involving the proximal or distal third of the ulna.

Diagnosis of an ulna fracture is made through the findings on AP and lateral radiographs of the full-length forearm. (Fig. 51-39) Although most isolated ulna fractures are considered stable, those with more than 50% displacement, more than 10 degrees of angulation, involvement of the proximal one third of the ulna, or instability at either the DRUJ or PRUJ are considered unstable fractures.[95] There are no absolute indications for operative management of isolated ulna shaft fracture; however, unstable fractures should be referred to an orthopedist urgently for possible ORIF, as they carry a high risk of function loss, nonunion, malunion, and radioulnar synostosis.[96]

www.ketabpezeshki.com 66485457-66963820

Figure 51-39. Isolated ulna fracture (nightstick fracture). Anteroposterior **(A)** and lateral **(B)** radiographic images show isolated ulnar fracture.

Most stable ulna fractures heal without significant clinical sequelae. Stable fractures can be managed with 6 to 8 weeks of short arm, below-elbow immobilization with interosseous molding to limit radial angulation and prevent forearm rotation. Above-elbow immobilization or long arm casting may be detrimental to the healing process, and they have been associated with nonunion and delayed union.[96]

Monteggia's Fracture

The ulna fractures associated with radial head dislocation are commonly known as *Monteggia's fractures* and account for 1 to 2% of all forearm fractures.[97] In 1814, Giovanni Battista Monteggia specifically described a traumatic lesion involving the fracture of the proximal third of the ulna and anterior dislocation of the radius. In 1974, Bado redefined Monteggia's lesion and classified it to encompass various ulna fractures with concomitant radial head dislocation. The Bado classification divides the injury into four types depending on the location and the angulation of the ulna fracture along with the direction of the radial head dislocation.[98]

Patients with Monteggia's fracture often have fallen on an outstretched hand, resulting in hyperpronation. Direct posterior force on the ulna or a fall on the flexed elbow has been implicated in the mechanism of the injury as well. Typically, patients have edema and tenderness along the fracture site accompanied by a limited range of motion at the elbow and pain with pronation of the forearm. A dislocated radial head may be appreciated on

Figure 51-40. Monteggia's fracture-dislocation. A fracture of the ulna diaphysis with anterior dislocation of the radial head *(arrow)* is shown in this lateral view of the forearm.

palpation. Initial assessment of Monteggia's fracture should include complete neurologic examination because the posterior interosseous nerve (PIN), a deep branch of the radial nerve, can be injured. Because the PIN innervates the finger extensors along with the supinator, PIN injury is often manifested by weakness or paralysis of the thumb and/or finger extension.[99]

The radiograph of the forearm reveals the obvious ulna fracture that often overshadows the subtle radial head dislocation (Fig. 51-40). A chronic, irreducible radial head dislocation can occur as a result of delay in diagnosis. Drawing of the radiocapitellar line through the head of the capitellum can prevent the overlooking of a proximal dislocation. The line should intersect the distal third of the capitellum on all views and confirm correct alignment.

Treatment of Monteggia's fracture depends on the age of the patient. Pediatric patients with this type of injury can be treated conservatively with long arm casting in supination with acceptable reduction. However, most adult patients with this type of fracture should be referred to an orthopedic surgeon urgently for ORIF. Complications of Monteggia's fracture include malunion, nonunion, synostosis, stiffness, and nerve palsy. Early diagnosis and treatment of Monteggia's fracture are crucial in achieving good outcomes.[97]

Galeazzi's Fracture

Galeazzi's fracture refers to a fracture of the middle to distal third of the radius associated with injury to and dislocation of the DRUJ. It accounts for 3 to 7% of all forearm fractures.[100] Typically, Galeazzi's fracture results from a fall or motor vehicle collision as the patient attempts to brace for impact by outstretching the hand in pronation. A direct blow to the dorsolateral aspect of the forearm is less common but well recognized as a mechanism of injury for Galeazzi's fracture as well. Galeazzi's fracture is often overlooked as a simple radius fracture, yet it often results in diminished forearm range of motion, weakness, and chronic pain.

In addition to the radiographic imaging, history and clinical examination play a crucial role in diagnosis of Galeazzi's fracture, as injuries to the DRUJ may not be obvious. Patients with Galeazzi's fracture have deformity at the site of the fracture associated with swelling and tenderness. Meticulous attention is required in examining the wrist to evaluate for stability of the DRUJ. Instability of the DRUJ can range from obvious prominence of the ulnar head (associated with the subluxation or dislocation) to tenderness elicited at the wrist, which can be a subtle sign of DRUJ ligament injury.

AP and lateral radiographs of the entire forearm and wrist are essential to diagnose Galeazzi's fracture. Besides the obvious fracture of the radius at the middle to distal third, there will be other radiographic findings. On the AP view of the forearm, the space

www.ketabpezeshki.com 66485457-66963820

Figure 51-41. Galeazzi's fracture-dislocation. The anteroposterior **(A)** and lateral **(B)** views of the forearm show an obvious fracture of the distal third of the radius with severe displacement and an associated dislocation of the distal radioulnar joint *(arrow)*.

between the distal radius and ulna is widened (greater than 2 mm) and the radius appears relatively shortened. In the lateral view, the dorsally angulated fracture of the radius can cause a dorsal displacement of the ulnar head. A fracture at the base of the ulnar styloid should raise the suspicion for DRUJ interruption (Fig. 51-41). Although not all radius shaft fractures are associated with DRUJ injury, Ring and colleagues showed that at least 25% of all patients with radius fractures had DRUJ dislocation.[100] Therefore patients with radius shaft fracture should be referred to an orthopedist for close follow-up.

Conservative management of Galeazzi's fracture in adults has been associated with poor outcomes. Because of the deforming forces from different forearm muscles and loss of stability at the DRUJ, displacement of the alignment in the cast occurs despite successful initial reduction. Galeazzi's fracture has been termed a "fracture of necessity" to imply that surgical intervention is crucial for achievement of an ideal anatomic position and acceptable functional outcomes.[101,102] Any patient with this fracture should be referred to an orthopedist urgently for ORIF of the radius and associated repair of DRUJ. In contrast, conservative treatment with closed reduction and long arm casting has been successful in children and rarely requires surgical intervention.[103] Along with the common complications associated with forearm fractures such as malunion and nonunion, the occurrence of subluxation and dislocation of the DRUJ can result in limited motion and chronic pain.[104]

Essex-Lopresti Lesion

The *Essex-Lopresti lesion,* or longitudinal radioulnar disassociation, refers to an unstable forearm as a result of a triad of injuries to the radial head, disruption of the interosseous membrane, and violation of the DRUJ. The patient often has fallen on an outstretched hand, resulting in transmission of a large axial loading force from the wrist to the elbow. Consequently, the radial head, the primary forearm stabilizer, is fractured and displaced proximally. Disruption of the interosseous membrane and DRUJ also occurs and compromises the stability of the forearm.[105] In addition to localized pain along the elbow from radial head fracture, patients with the Essex-Lopresti injury have wrist and forearm pain along with grip and pronation weakness. The diagnosis of the Essex-Lopresti lesion remains elusive, as the standard AP and lateral views of the forearm often reveal only isolated radial head fracture. The integrity of the interosseous membrane is difficult to assess based on the plain film. Subtle findings of positive ulna variance and a widened DRUJ are suggestive of longitudinal radioulnar dissociation. Obtaining a grip view and comparing the injured wrist with the contralateral wrist can be helpful in diagnosing an Essex-Lopresti injury. MRI is the study of choice when clinical suspicion for Essex-Lopresti injury is high; however, ultrasound has been used more frequently recently to evaluate the integrity of the interosseous membrane.[93,106]

Once the diagnosis of Essex-Lopresti injury has been made, the patient should be referred to an orthopedic surgeon for further surgical intervention. Many strategies have been proposed to repair Essex-Lopresti lesions, and the treatment option varies depending on the chronicity of the injury. Radioulnar synostosis and loss of forearm rotation can result from longitudinal disassociation.[106]

Pediatric Forearm Fractures

Forearm fractures are the most common orthopedic injuries in children.[107] Many patients have a painful, swollen, and possibly deformed forearm after having fallen onto the outstretched hand. In general, forearm fractures are divided into three categories: greenstick (or incomplete fractures), complete fractures, and plastic deformation. Depending on the growth plate maturity, fracture pattern, anatomic location of the fracture, degree of angulation, and displacement, treatment options vary.[108]

The principal goal in treating pediatric forearm fracture is to achieve bony healing and preservation of function while avoiding surgery and minimizing complications. Any fracture with deformity in a pediatric patient should be reduced to anatomical alignment, but a clinician should also consider the potential correction of the bone remodeling. Usually, younger patients (younger than 10 years) with fractures near the physis have the greatest potential for remodeling. These principles govern the acceptability of fracture reduction, and in general, an angulation of less than 10 degrees is often considered acceptable.[109]

Greenstick fractures or incomplete fractures usually result from torsional mechanisms resulting in disruption on one side of the cortex and traumatic bowing. Although the utility of completing the greenstick fracture at the site of bowing remains controversial, patients with greenstick fracture should be referred to an orthopedic surgeon for closed reduction under adequate anesthesia.[90,110]

A complete fracture is complete disruption of the cortex and requires an orthopedic referral for closed reduction (Fig. 51-42). Surgical indications for forearm fractures include open fractures, injuries resulting in neurovascular compromise, and irreducible or unstable fractures. After application of a long arm cast for immobilization, serial radiographs are obtained to ensure adequate reduction. Common complications of forearm fractures, such as malunion and nonunion, are uncommon owing to rapid healing among the pediatric population, but there is an increase in risk of refracture within the first 12 months.

Plastic deformation refers to bending of the bone, resulting in traumatic bowing without obvious fracture (Fig. 51-43). Initially,

www.ketabpezeshki.com 66485457-66963820

Figure 51-42. Pediatric forearm fracture. Anteroposterior **(A)** and lateral **(B)** radiographic views show radial and ulnar shaft fractures with dorsal angulation.

Figure 51-43. Plastic deformation. Lateral radiograph of the forearm shows severe plastic deformation of radial and diaphyseal fracture of the ulna.

plastic deformation was described exclusively in children, but adults with such injury pattern have been recognized.[111] Typically, patients with plastic deformation are younger than 10 years of age and have little deformity, localized tenderness and swelling, and reduced pronation and supination range of motion. The radiograph may show subtle abnormal bowing of the radius or ulna shaft with narrowing of the interosseous space. Patients with plastic deformation should be promptly referred to an orthopedist for closed reduction and long arm casting. Although most will achieve a good functional outcome, some may require surgery if the bowing remains excessive.

Compartment Syndrome

Acute compartment syndrome of the forearm has been associated with multiple causes. In the pediatric population, subcondylar fractures have been commonly linked to compartment syndrome of the forearm, whereas distal radius fracture remains the most common cause in adults.[112] If the entity is not recognized early and is left untreated, it can result in permanent contracture of the hand and wrist, known as *Volkmann's ischemic contracture.*

There are many theories on the exact mechanisms of the compartment syndrome, but tissue hypoperfusion and damage to the muscles and nerves are its end results. Classically, patients may have a tense edema of the forearm with blisters associated with the traditional five *P*s of compartment syndrome: pain, pallor, pulselessness, paralysis, and paresthesia.[113] However, absence of pulse is a late finding of the compartment syndrome, and a practitioner should not wait for presence of all five *P*s before suspecting compartment syndrome. One should have a low threshold for obtaining compartment pressures when this syndrome is suspected. If the compartment pressure is greater than 30 mm Hg or within 20 mm Hg of the diastolic pressure in the presence of other characteristic clinical findings, emergency surgical consultation is mandatory for surgical decompression.[114] Early diagnosis of compartment syndrome and prompt fasciotomy have been associated with good functional outcomes.

KEY CONCEPTS

- In the setting of acute trauma, there is a high incidence of occult fractures of the wrist. For instance, plain radiographs fail to detect 15% of scaphoid fractures. Because of the associated risk of malunion, nonunion, and AVN when diagnosis is delayed, when radiographs are negative and pain persists, immobilization is recommended. A thumb spica is usually added in the setting of suspected scaphoid and other carpal fractures. Repeat physical examination, radiographs, or advanced imaging (e.g., MRI, CT, or ban scan) is indicated if symptoms persist.
- Triquetral fracture is best seen on the standard lateral view of the wrist as a small dorsal avulsion fragment, although a more oblique pronated lateral view may be necessary to visualize it.
- Lunate dislocation results in a characteristic triangular appearance of the lunate on the PA view ("piece of pie sign") owing to the rotation of the lunate in a volar direction. This rotation also is visible on the lateral view of the wrist, on which the lunate looks like a cup tipped forward and spilling its contents into the palm ("spilled teacup sign").
- On the PA radiograph of the wrist, three arcs, known as *Gilula's lines,* and equal spacing between carpus bones (1-2 mm), known as *parallelism,* assist in the radiographic diagnosis of carpus injury.

www.ketabpezeshki.com 66485457-66963820

- Colles' fracture reduction attempts to restore radial length and ulnar variance (<2 mm) and correct dorsal angulation to the normal volar tilt (0-20 degrees). Closed reduction is commonly performed with use of pain control, local analgesia (hematoma block), regional anesthesia, or procedural sedation.
- Anteroposterior and lateral views of the forearm must include the wrist and elbow joints because radial and ulnar forearm fractures may be associated with proximal, radial, or DRUJ dislocations.

ACKNOWLEDGMENT

We would like to thank the previous authors, Karen G. H. Woolfrey, Michael Woolfrey, and Mary A. Eisenhauer, for their work and contributions to this chapter.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Watson HK, Weinzweig J: Physical examination of the wrist. *Hand Clin* 1997; 13:17.
2. Greenspan A: *Orthopedic Radiology: A Practical Approach*, 2nd ed. New York: Gower Medical Publishing; 1992.
3. Schreibman KL, Freeland A, Gilula LA, Yin Y: Imaging of the hand and wrist. *Orthop Clin North Am* 1997; 28:537.
4. Moosikasuwan JB: The pronator quadratus sign. *Radiology* 2007; 244:927.
5. Lacey JD, Hodge JC: Pisiform and hamulus fractures: Easily missed wrist fractures diagnosed on a reverse oblique radiograph. *J Emerg Med* 1998; 16:445.
6. Abraham MK, Scott S: The emergent evaluation and treatment of hand and wrist injuries. *Emerg Med Clin North Am* 2010; 28:789.
7. Vigler M, Aviles A, Lee SK: Carpal fractures excluding the scaphoid. *Hand Clin* 2006; 22:501.
8. Gaebler C, McQueen MM: *Carpus fractures and dislocations*. In: Bucholz RW, et al, eds. *Rockwood and Green's Fractures in Adults*, 7th ed. Philadelphia: Lippincott, Williams & Wilkins; 2010:782-828.
9. Evenski AJ, Adamczyk MJ, Steiner RP, Morscher MA, Riley PM: Clinically suspected scaphoid fractures in children *J Pediatr Orthop* 2009; 29:352-355.
10. Duckworth AD, Ring D, McQueen MM: Assessment of the suspected fracture of the scaphoid. *J Bone Joint Surg Br* 2011; 93:713-719
11. Grover R: Clinical assessment of scaphoid injuries and detection of fractures. *J Hand Surg Br* 1996; 21:341.
12. Adams J, Steinmann S: Acute scaphoid fractures. *Orthop Clin North Am* 2007; 38:229.
13. Kirk M, Orlinsky M, Goldberg R: The validity and variability of the navicular fat stripe as a screening test for the detection of navicular fractures. *Ann Emerg Med* 1990; 19:1371.
14. Phillips TG, Reibach AM, Slomiany WP: Diagnosis and management of scaphoid fractures. *Am Fam Physician* 2004; 70:879.
15. Germann CA, Perron AD: Risk management and avoiding legal pitfalls in the emergency treatment of high-risk orthopedic injuries. *Emerg Med Clin North Am* 2010; 28:969.
16. Gäbler C, Kukla C, Breitenseher MJ, Trattnig S, Vécsei V: Diagnosis of occult scaphoid fractures and other wrist injuries: Are repeated clinical examinations and plain radiographs still state of the art? *Langenbecks Arch Surg* 2001; 386:150.
17. Pillai A, Jain M: Management of clinical fractures of the scaphoid: Results of an audit and literature review. *Eur J Emerg Med* 2005; 12:47.
18. Amrami KK: Diagnosing radiographically occult scaphoid fractures: What's the second best test? *J Am Soc Surg Hand* 2005; 5:134.
19. Mitchell S: Commentary on an article by Wouter Mallee, MSc, et al: "Comparison of CT and MRI for diagnosis of suspected scaphoid fractures." *J Bone Joint Surg Am* 2011; 93:e31.
20. Woolfrey K, et al: Accuracy of day four bone scans and efficacy of clinical findings in the assessment of patient with clinical scaphoid fractures. *Ann Emerg Med* 1999; 34:544.
21. Beeres FJ, et al: Early magnetic resonance imaging compared with bone scintigraphy in suspected scaphoid fractures. *J Bone Joint Surg Br* 2008; 90:1205-1209.
22. Adey L, et al: Computed tomography of suspected scaphoid fractures. *J Hand Surg Am* 2007 32:61.
23. Memarsadeghi M, et al: Occult scaphoid fractures: Comparison of multidetector CT and MR imaging—initial experience. *Radiology* 2006; 240:169.
24. Mallee W, et al: Comparison of CT and MRI for diagnosis of suspected scaphoid fractures. *J Bone Joint Surg Am* 2011; 93:20.
25. Yin ZG, Zhang JB, Kan SL, Wang XG: Diagnosing suspected scaphoid fractures: A systematic review and meta-analysis. *Clin Orthop Relat Res* 2010; 468:723.
26. Ring D, Lozano-Calderón S: Imaging for suspected scaphoid fracture. *J Hand Surg Am* 2008; 33:954.
27. Fowler C, Sullivan B, Williams LA: A comparison of bone scintigraphy and MRI in the early diagnosis of the occult scaphoid waist fracture. *Skeletal Radiol* 1998; 28:683.
28. Pao V, Chang J: Scaphoid nonunion: Diagnosis and treatment. *Plast Reconstr Surg* 2003; 112:1666.
29. Botte MJ, Pacelli LL, Gelberman RH: Vascularity and osteonecrosis of the wrist. *Orthop Clin North Am* 2004; 35:405.
30. Brach P, Goitz R: An update on the management of carpal fractures. *J Hand Surg* 2003; 16:152.
31. Marchessault J, Conti M, Baratz ME: Carpal fractures in athletes excluding the scaphoid. *Hand Clin* 2009; 25:371.
32. Salmon J, Stanley JK, Trail IA: Keinbock's disease: Conservative management versus radial shortening. *J Bone Joint Surg Br* 2003; 82:820.
33. Papp S: Carpal bone fractures. *Orthop Clin North Am* 2007; 38:251.
34. McCready RA, Bryant MA, Divelbiss JL: Combined thenar and hypothenar hammer syndromes: Case report and review of the literature. *J Vasc Surg* 2008; 48:741.
35. Welling RD, et al: MDCT and radiography of wrist fractures: Radiographic sensitivity and fracture patterns. *AJR Am J Roentgenol* 2008; 190:10-16.
36. Yuen JC, Wright E, Johnson LA, Culp WC: Hypothenar hammer syndrome: An update with algorithms for diagnosis and treatment. *Ann Plast Surg* 2011; 67:429-438.
37. Mayfield JK, Johnson RP, Kilcoyne RK: Carpal dislocations: Pathomechanics and progressive perilunar instability. *J Hand Surg Am* 1980; 5:226.
38. Frankel VH: The Terry Thomas sign. *Clin Orthop Relat Res* 1978; 135:311.
39. Herzberg G, et al: Perilunate dislocations and fracture-dislocations: A multicenter study. *J Hand Surg Am* 1993; 18:768.
40. Park MJ: Radiographic observation of the scaphoid shift test. *J Bone Joint Surg Br* 2003; 85:358-362.
41. Manuel J, Moran SL: The diagnosis and treatment of scapholunate instability. *Hand Clin* 2010; 26:129-144.
42. Watson HK, Weinzweig J, Zeppieri J: The natural progression of scaphoid instability. *Hand Clin* 1997; 13:29.
43. Schädel-Höpfner M, et al: MRI versus arthroscopy in the diagnosis of scapholunate ligament injury. *J Hand Surg Br* 2001; 26:17.
44. Morley J, Bidwell J, Bramby-Zachary M: A comparison of the findings of wrist arthroscopy and magnetic resonance imaging in the investigation of wrist pain. *J Hand Surg Br* 2001; 26:544.
45. O'Meeghan CJ, Stuart W, Mamo V, Stanley JK, Trail IA: The natural history of an untreated isolated scapholunate interosseous ligament injury. *J Hand Surg Br* 2003; 28:307.
46. Linscheid RL, Dobyns JH, Beabout JW, Bryan RS: Traumatic instability of the wrist. *J Bone Joint Surg Am* 1972; 54:1612.
47. Lichtman DM, Wroten ES: Understanding midcarpal instability. *J Hand Surg Am* 2006; 31:491.
48. Toms AP, Chojnowski A, Cahir JG: Midcarpal instability: A radiological perspective. *Skeletal Radiol* 2011; 40:533.
49. Grabow RJ, Catalano L 3rd: Carpal dislocations. *Hand Clin* 2006; 22:485.
50. Ilyas AM, Williamson C, Mudgal CS: Radiocarpal dislocation: Is it a rare injury? *J Hand Surg Eur Vol* 2011; 36:164.
51. Ilyas AM, Mudgal CS: Radiocarpal fracture-dislocations. *J Am Acad Orthop Surg* 2008; 16:647.
52. Handoll HH, Madhok R, Dodds C: Anesthesia for treating distal radial fracture in adults. *Cochrane Database Syst Rev* 2002; 3:CD003320.
53. Colles A: On the fracture of the carpal extremity of the radius. *Edinb Med Surg J* 1814; 10:182.
54. Ng CY, McQueen MM: What are the radiological predictors of functional outcome following fractures of the distal radius? *J Bone Joint Surg Br* 2011; 93:145.
55. Ruch DS, McQueen MM: *Distal radius and ulna fractures*. In: Bucholz RW, et al, eds. *Rockwood and Green's Fractures in Adults*, 7th ed. Philadelphia: Lippincott, Williams & Wilkins; 2010:829-880.
56. Egol KA, Walsh M, Romo-Cardoso S, Dorsky S, Paksima N: Distal radial fractures in the elderly: Operative compared with nonoperative treatment. *J Bone Joint Surg Am* 2010; 92:1851-1857.
57. Davis DI, Baratz M: Soft tissue complications of distal radius fractures. *Hand Clin* 2010; 26:229-235.
58. Mehta JA, Bain GI: An overview of distal radius fractures. *Aust J Rural Health* 1999; 7:121.
59. Lozano Calderon SA, Doornberg J, Ring D: Fractures of the dorsal articular margin of the distal part of the radius with dorsal radiocarpal subluxation. *J Bone Joint Surg Am* 2006; 88:1486.
60. Leibovic SJ, Geissler WB: Treatment of complex intra-articular distal radius fractures. *Orthop Clin North Am* 1994; 25:685.
61. Carlsen BT, Dennison DG, Moran SL: Acute dislocations of the distal radioulnar joint and distal ulna fractures. *Hand Clin* 2010; 26:503.
62. Mulford JS, Axelrod TS: Traumatic injuries of the distal radioulnar joint. *Orthop Clin North Am* 2007; 38:289.
63. Tsai PC, Paksima N: The distal radioulnar joint. *Bull NYU Hosp Jt Dis* 2009; 67:90.
64. Amrami KK, Moran SL, Berger RA, Ehman EC, Felmlee JP: Imaging the distal radioulnar joint. *Hand Clin* 2010; 26:467.
65. Dodds SD, Yeh PC, Slade JF III: Essex-Lopresti injuries. *Hand Clin* 2008; 24:125.

www.ketabpezeshki.com 66485457-66963820

66. Adams BD, Divelbiss BJ: Reconstruction of the post traumatic unstable distal radioulnar joint. *Orthop Clin North Am* 2001; 32:353.
67. Adams BD, Berger RA: An anatomic reconstruction of the distal radioulnar ligaments for post-traumatic distal radioulnar joint instability. *J Hand Surg Am* 2002; 27:243.
68. Chasm RM, Swencki SA: Pediatric orthopedic emergencies. *Emerg Med Clin North Am* 2010; 28:907.
69. Sherbino J: How do I treat pediatric wrist fractures? *Ann Emerg Med* 2010; 54:541.
70. Randsborg PH, Siversten EA: Distal radius fractures in children: Substantial difference in stability between buckle and greenstick fractures. *Acta Orthop* 2009; 80:585.
71. Oakley EA, Ooi K, Barnett PL: A randomized clinical trial of 2 methods for immobilizing torus fractures of the distal forearm. *Pediatr Emerg Care* 2008; 24:65.
72. Mehlman CT, Wall EJ: *Injuries to the shafts of the radius and ulna*. In: Beaty JH, Kasser JR, eds. Rockwood and Wilkins' Fractures in Children, 7th ed, vol 3. Philadelphia: Lippincott-Raven; 2010:348-404.
73. Salter RB, Harris WR: Injuries involving the epiphyseal plate. *J Bone Joint Surg Am* 1963; 45:587.
74. Bland JDP: Carpal tunnel syndrome. *Curr Opin Neurol* 2005; 18:581.
75. Leblanc KE, Cestia W: Carpal tunnel syndrome. *Am Fam Physician* 2011; 83:952.
76. Katz JN, Simmons BP: Clinical practice. Carpal tunnel syndrome. *N Engl J Med* 2002; 346:1807.
77. Cranford CS, Ho JY, Kalainov DM, Hartigan BJ: Carpal tunnel syndrome. *J Acad Orthop Surg* 2007; 15:537.
78. Amirfeyz R, et al: Clinical tests for carpal tunnel syndrome in contemporary practice. *Arch Orthop Trauma Surg* 2011; 131:471-474.
79. Wilder-Smith EP, Seet RC, Lim EC: Diagnosing carpal tunnel syndrome—clinical criteria and ancillary tests. *Nat Clin Pract Neurol* 2006; 2:366.
80. Wiesler ER, et al: The use of diagnostic ultrasound in carpal tunnel syndrome. *J Hand Surg Am* 2006; 31:726.
81. Kaplan SJ, Glickel SZ, Eaton RG: Predictive factors in the non-surgical treatment of carpal tunnel syndrome. *J Hand Surg Br* 1990; 15:106.
82. Bland JD: Treatment of carpal tunnel syndrome. *Muscle Nerve* 2005; 32:527.
83. Schnetzler KA: Acute carpal tunnel syndrome. *J Am Acad Orthop Surg* 2008; 16:276.
84. Szabo RM: Acute carpal tunnel syndrome. *Hand Clin* 1998; 14:419.
85. Wolf JM, Athwal GS, Shin AY, Dennison DG: Acute trauma to the upper extremity: What to do and when to do it. *J Bone Joint Surg Am* 2009; 91:1240.
86. Henry M, Stutz C: A prospective plan to minimize median nerve related complications associated with operatively treated distal radius fractures. *Hand Surg* 2007; 12:199.
87. Dawson C, Mudgal CS: Staged description of the Finkelstein test. *J Hand Surg Am* 2010; 35:1513-1515.
88. Ilyas AM, Ast M, Schaffer AA, Thoder J: de Quervain tenosynovitis of the wrist. *J Am Acad Orthop Surg* 2007; 15:757.
89. Hanlon DP, Luellen JR: Intersection syndrome: A case report and review of the literature. *J Emerg Med* 1999; 17:969.
90. Rodríguez-Merchán EC: Pediatric fractures of forearm. *Clin Orthop Relat Res* 2005; 432:65.
91. Huang JI, Hanel DP: Anatomy and biomechanics of the distal radioulnar joint. *Hand Clin* 2012; 28:157.
92. Soubeyrand M, et al: The "muscular hernia sign": An original ultrasonographic sign to detect lesions of the forearm's interosseous membrane. *Surg Radiol Anat* 2006; 28:372.
93. Moss J, Bynum D: Diaphyseal fractures of the radius and ulna in adults. *Hand Clin* 2007; 23:143.
94. Falcon-Chevere JL, Mathew D, Cabanas JG, Labat E: Management and treatment of elbow and forearm injuries. *Emerg Med Clin North Am* 2010; 28:765.
95. Sauder D, Athwal G: Management of isolated ulnar shaft fractures. *Hand Clin* 2007; 23:179.
96. Eathiraju S, Mudgal CS, Jupiter JB: Monteggia fracture-dislocations. *Hand Clin* 2007; 23:165.
97. Guitton TG, Ring D, Kloen P: Long-term evaluation of surgically treated anterior Monteggia fractures in skeletally mature patients. *J Hand Surg* 2009; 34:1618.
98. Perron AD, Brady WJ : Evaluation and management of the high-risk orthopedic emergency. *Emerg Med Clin North Am* 2003; 21:159.
99. Faierman EJ, Jupiter JN: The management of acute fractures involving distal radioulnar joint and distal ulna. *Hand Clin* 1998; 12:213.
100. Ring D, Rhim R, Carpenter C, Jupiter JB: Isolated radial shaft fractures are more common than Galeazzi fractures. *J Hand Surg* 2006; 31:17.
101. Sebastin SJ, Chung KC: A historical report on Riccardo Galeazzi and the management of Galeazzi fractures. *J Hand Surg* 2010; 35:1870.
102. Eberl R, Singer G, Schalamon J, Petnehazy T, Hoellwarth ME: Galeazzi lesions in children and adolescents: Treatment and outcome. *Clin Orthop Relat Res* 2008; 466:1705.
103. Giannoulis F, Sotereanos D: Galeazzi fractures and dislocations. *Hand Clin* 2007; 23:153.
104. Green JB, Zelouf DS: Forearm instability. *J Hand Surg* 2009; 34:953.
105. Marcotte A, Osterman A: Longitudinal radioulnar dissociation: Identification and treatment of acute and chronic injuries. *Hand Clin* 2007; 23:195.
106. Guitton TG, Van Dijk NC, Raaymakers EL, Ring D: Isolated diaphyseal fractures of the radius in skeletally immature patients. *Hand (N Y)* 2009; 5:251.
107. Bae D: Pediatric distal radius and forearm fractures. *J Hand Surg* 2008; 33:1911.
108. Bowman EN, Mehlman CT, Lindsell CJ, Tamai J: Nonoperative treatment of both-bone forearm shaft fractures in children: Predictors of early radiographic failure. *J Pediatr Orthop* 2011; 31:23.
109. Kropman RH, Bemelman M, Segers MJ, Hammacher ER: Treatment of impacted greenstick forearm fractures in children using bandage or cast therapy: A prospective randomized trial. *J Trauma* 2010; 68:425.
110. Moon ES, Howlett J, Wiater BP, Trumble TE: Treatment of plastic deformation of the forearm in young adults with double-level osteotomies: Case reports. *J Hand Surg* 2010; 36:639.
111. Kalyani BS, Fisher BE, Roberts CS, Giannoudis PV: Compartment syndrome of the forearm: A systematic review. *J Hand Surg* 2011; 36:535.
112. Newton EJ, Love J: Acute complications of extremity trauma. *Emerg Med Clin North Am* 2007; 25:751.
113. Friedrich J, Shin A: Management of forearm compartment syndrome. *Hand Clin* 2007; 23:245.
114. Botte MJ, Gilberman RH: Acute compartment syndrome of the forearm. *Hand Clin* 1998; 14:391.

www.ketabpezeshki.com 66485457-66963820

Chapter 52

Humerus and Elbow

Thom A. Mayer

PERSPECTIVE

Because injuries in the region of the elbow have a high potential for complications and residual disability, early recognition of neurovascular and soft tissue complications improves the outcome in many of these injuries. Coordination between the emergency physician and the treating orthopedist is essential, particularly because new options are emerging for many of these injuries.

Anatomy

The humerus is a long bone that articulates proximally at the shoulder with the glenoid of the scapula to form the glenohumeral joint and distally with the radius and ulna to form the three-way elbow joint. The upper end of the humerus, the humeral head, is shaped like a near hemisphere. Adjacent to the humeral head are two bony prominences, the greater and lesser tuberosities. Between these, on the anterolateral aspect of the humerus, runs the bicipital groove. The shaft of the humerus extends from the upper border of the insertion of the pectoralis major muscle superiorly to the supracondylar ridges inferiorly. The shaft is cylindrical on cross section in the upper half and tends to become flat in the distal portion in an anteroposterior direction. Three surfaces are described. The anterolateral surface presents the deltoid tuberosity for the insertion of the deltoid muscle, and below this is the radial soleus, which transmits the radial nerve and profunda artery. The anteromedial surface forms the floor of the intertubercular groove, but it normally has no outstanding surface markings. The posterior surface is the origin for the triceps and contains the spiral groove.

The bony anatomy of the distal humerus and elbow is diagrammed in Figure 52-1. The distal end of the humerus tapers into two columns of bone, the medial and lateral condyles. Between the condyles, the bone thins, and the recess created is the coronoid fossa. The more proximal nonarticular portions of the condyles are the epicondyles. Just proximal to the epicondyles, the supracondylar ridges run up each side of the humerus. Collectively, these areas serve as points of origin for the muscles of the forearm. The wrist flexors originate from the medial epicondyle, and the wrist extensors originate from the lateral epicondyle. Fractures of the distal humerus often result in fragment displacement because of the pull of these strong forearm muscles on attachment sites.

The bony anatomy of the elbow allows for two complex motions: flexion-extension and pronation-supination. The elbow is composed of three articulations within a common joint cavity. The trochlea is the articular surface of the medial condyle and articulates with the deep trochlear notch of the ulna formed by the olecranon inferiorly and posteriorly and by the coronoid process anteriorly. This articulation permits hinged flexion and extension at the elbow. The articular surface of the lateral condyle is the capitellum, which permits the radius to hinge on the elbow. The proximal radius consists of a disklike head supported by the smooth narrow radial neck. The radial head articulates with the capitellum of the humerus and with the radial notch of the ulna.

Four ligamentous structures are important in evaluating elbow injuries (Fig. 52-2). The radial head is held in place by the annular ligament and the adjacent radial collateral ligament. Rotation of the radial head within the confines of the fibrous annular ligament permits pronation and supination. In addition, the ulnar collateral ligament and anterior capsule add stability to the joint. Fracture or dislocation of the joint may severely damage the ligamentous structures.

The soft tissues of the upper arm are divided into two compartments: anterior and posterior. The anterior compartment contains three muscles—the biceps brachii, the brachialis, and the coracobrachialis—and the brachial artery, median nerve, musculocutaneous nerve, and ulnar nerve. The only two structures contained in the posterior compartment are the triceps brachii muscle and the radial nerve.

The neurovascular structures of this area are shown in Figure 52-3. The brachial artery, which is the continuation of the axillary artery, travels with the median nerve in the anterior compartment of the upper arm. It enters the antecubital fossa and bifurcates into the radial and ulnar arteries.

One important anatomic variation is the presence of a supracondylar process (in approximately 2.5% of cases) just proximal to the medial epicondyle (Fig. 52-4). When the supracondylar process is present, the median nerve and brachial artery must traverse behind this process, then forward between a fibrous band connecting the process to the epicondyle. Median nerve symptoms may develop if this process is fractured or if an injury causes swelling in the vicinity of the supracondylar process.

The radial nerve leaves the axilla and spirals posteriorly around the humerus between the heads of the triceps in the radial groove. It reenters the anterior compartment of the arm laterally, crossing the elbow anterior to the lateral epicondyle to innervate the extensors of the wrist and fingers. Because of its close relationship to the shaft of the humerus, the radial nerve is particularly susceptible to injury with midshaft humeral fractures. Fixed in position by the intermuscular septum, the nerve may become trapped between fracture fragments, particularly when reduction is attempted.

The ulnar nerve runs parallel to the median nerve. Halfway down the arm, it penetrates the intermuscular septum to run along the medial aspect of the triceps muscle in the posterior compartment. It enters the forearm by passing behind the medial condyle. Fractures in the vicinity of the medial condyle place this nerve at considerable risk for injury.

www.ketabpezeshki.com 66485457-66963820

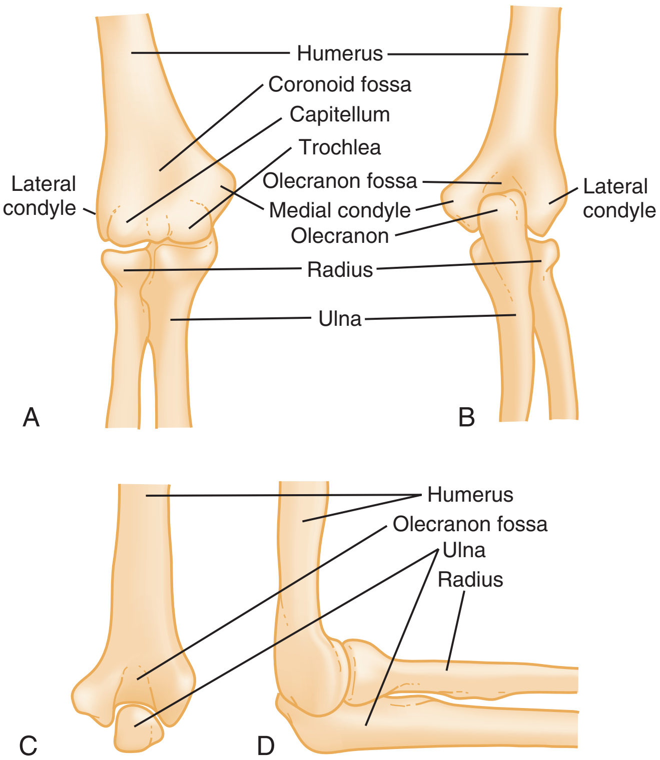


Figure 52-1. Bony anatomy of distal humerus and elbow region. **A,** Anterior view. **B,** Posterior view. **C,** Posterior view, 90 degrees flexion. **D,** Lateral view. Right elbow is shown. (Adapted from Connolly JF: DePalma's Management of Fractures and Dislocations. Philadelphia, WB Saunders, 1981.)

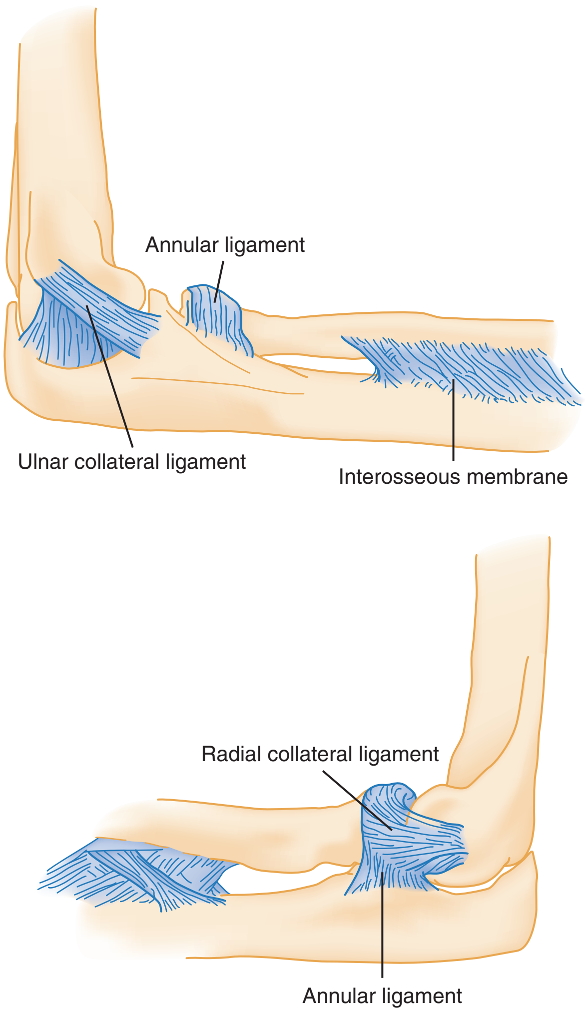


Figure 52-2. Ligamentous structures of elbow. (From Simon R, Koenigsknecht S: Emergency Orthopaedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

Three elbow bursae are clinically important. The olecranon bursa is located between the olecranon and the skin posterior to the joint. This bursa provides protective padding and allows smooth movement of the skin over the olecranon. Because of its position, it is often a site of traumatic or infectious bursitis. The radiohumeral bursa provides for smooth movement over the radial head with supination and pronation. A third bursa cushions the biceps tendon from the radius during flexion of the elbow. As evident by the descriptions of these structures, all are vulnerable when significant skeletal injury occurs in this region.

CLINICAL FEATURES

History

A history detailing musculoskeletal complaints includes a description of any pain in terms of quality, duration, location, palliative and provocative activities, severity, and radiation. Past medical history and occupational factors are important in chronic problems. For traumatic injuries, a detailed account of the incident is important because it provides information about the mechanism of injury and some estimate of the energy delivered. Subjective complaints of numbness or weakness distal to the injury are important clues to possible neurovascular injury. In dealing with injuries in children, the possibility of nonaccidental trauma needs to be considered.

Physical Examination

Inspection of the upper extremity is important, but manipulation of the painful extremity should be minimized and postponed to the end of the examination whenever possible. This is especially important with children. A great deal of useful information can

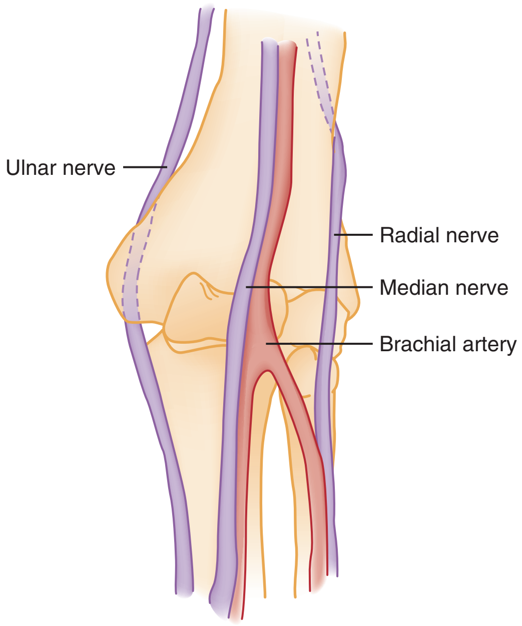


Figure 52-3. Neurovascular structures of elbow region. Volar surface of left elbow is shown.

www.ketabpezeshki.com 66485457-66963820

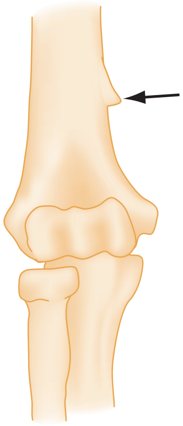


Figure 52-4. Supracondylar process of the humerus *(arrow)*. Volar surface of right elbow is shown.

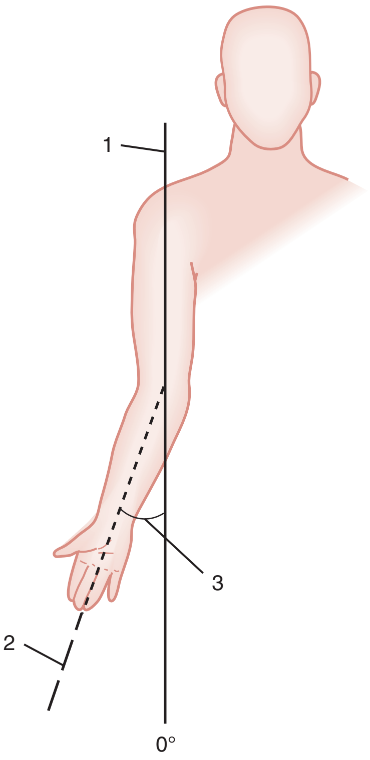


Figure 52-5. Carrying angle *(3)* is formed by intersection of lines drawn parallel to long axis of humerus *(1)* and ulna *(2)*. (Adapted from Ruiz E, Cicero J: Emergency Management of Skeletal Injuries. St Louis: Mosby; 1995.)

be gathered by simple inspection and comparison with the contralateral limb. The position in which the extremity is held should be noted. In children with extension-type supracondylar fractures, the arm is held at the side and has a characteristic S-shaped configuration, whereas with flexion-type supracondylar fractures, the forearm is supported with the opposite hand with the elbow flexed to 90 degrees. Patients with radial head subluxation have the elbow only slightly flexed and hold the forearm in pronation.

Deformity is evidence not only of significant injury, but also of the type of injury. Increased prominence of the olecranon suggests a posterior dislocation of the elbow or extension supracondylar fracture, whereas loss of the normal olecranon prominence indicates anterior dislocation or flexion supracondylar fracture. The extremity also should be inspected for wounds that may indicate an open fracture, evidence of swelling, and change in color of the distal extremity.

One special aspect of the elbow examination is the determination of the carrying angle, the normal outward angulation of the extended forearm at the elbow. This angle allows the long axes of the humerus and forearm to become superimposed when the elbow is flexed (Fig. 52-5). This angle varies from 5 to 20 degrees in adults, with men having less angulation than women. Measurement of the carrying angle is helpful in assessing subtle supracondylar fractures in children. As shown in Figure 52-6, lines drawn parallel to the shafts of the humerus and ulna intersect to form an angle with a mean measurement in children of 13 degrees, although this angle varies widely.[1] A difference in carrying angles of greater than 12 degrees (from one side to the other for a particular individual) is associated with fractures. However, the carrying angle is used primarily for assessing the adequacy of reduction or the results of fracture healing rather than for acute diagnosis, because it is difficult for children to fully extend the arm during the initial evaluation for this measurement to be obtained.

The vascular status of the extremity is of highest priority. Brachial, radial, and ulnar pulses should be palpated and documented. The ulnar pulse is not palpable in some normal people. Although brisk capillary refill suggests adequate tissue perfusion, a handheld Doppler device often is required to evaluate major vessel flow if significant swelling is present or if the pulses are not palpable. Any suggestion of arterial injury requires immediate investigation. Poor perfusion may result from direct arterial injury, compression or kinking in the instance of significant displacement from a fracture or dislocation, or compartment syndrome. Passive extension of the fingers produces severe pain in the forearm in the presence of flexor (volar) compartment ischemia. Of the five *Ps* associated with arterial occlusion (pain, paresthesia, pallor, pulselessness, and paralysis), pain is the only dependable early sign of compartment syndrome. Orthopedic consultation and measurement of compartment pressures should be considered for patients who have pain disproportionate to their injury. Other modalities used to evaluate vascular status while the orthopedist is being called in include measurement of the ankle-brachial index and color flow Doppler.

Neurologic evaluation includes assessment of the radial, median, and ulnar nerves. After evaluation of neurovascular function, all bony prominences are palpated, and areas of tenderness are noted carefully and documented. Crepitus and bony deformities are unusual in the absence of fracture or dislocation. Bony crepitus associated with pain in an acutely injured limb is virtually diagnostic of a fracture. The radial head specifically should be palpated for tenderness, and any noticeable effusion should be noted.

The range of motion of the elbow in all planes (i.e., flexion-extension and pronation-supination) should be determined and documented. With the forearm supinated, the normal range of motion is 0 degrees in full extension to 150 degrees in full flexion. A mild degree of hyperextension is normal in some individuals and should be symmetrical. With the elbow flexed at 90 degrees and the thumb facing up, the forearm normally supinates and pronates 90 degrees. Range-of-motion testing may be impossible with severe injuries and can be postponed until after radiographic evaluation, avoiding manipulating fractures and dislocations. Any manipulation of the extremity is followed by reexamination because neurovascular injury has been reported with nearly every therapeutic procedure.

Radiographic Findings

Whereas most elbow and humerus injuries are evaluated radiographically, occasionally history and clinical examination alone are sufficient (e.g., radial head subluxations). Although clinical

www.ketabpezeshki.com 66485457-66963820

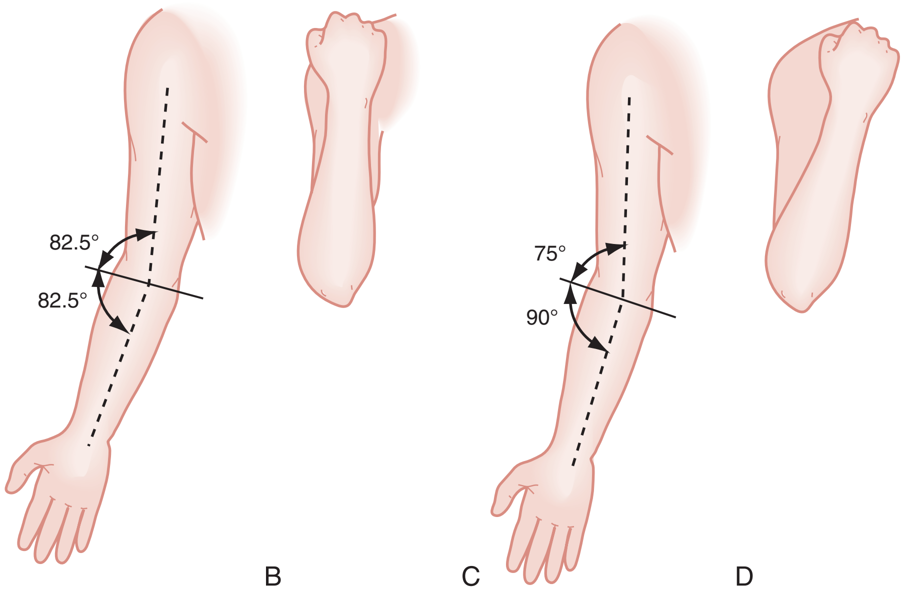


Figure 52-6. **A,** The axis of the elbow joint bisects the angle formed by the long axes of the humerus and forearm. **B,** This allows these axes to become superimposed when the elbow is flexed. **C,** If the axis of the elbow joint was perpendicular to the long axis of the forearm, the respective axes would diverge when the elbow was flexed, as shown in **D.**

decision rules for the elbow have not been validated, it is reasonable to perform radiography when there is significant limitation in range of motion, obvious deformity, joint effusion, or significant tenderness over any of the bony prominences or the radial head. In the absence of these, radiographic studies are optional. The threshold for radiography should be much lower in pediatric populations owing to the presence of open growth plates and limitation in the physical examination with the exception of children with obvious nursemaid's elbow (radial head subluxation).

Routine views of the elbow include at least the anteroposterior and lateral views, with consideration given to obtaining oblique views for certain injuries. Anteroposterior and oblique views are taken with the elbow extended. The lateral view is taken with the elbow in 90 degrees of flexion and the thumb pointing upward. Positioning of the elbow is important because anything but a true lateral view makes accurate interpretation of soft tissue findings and alignment difficult. Corresponding views of the opposite extremity may be helpful, especially for children, but should not be ordered routinely.

Many fractures in the elbow region are obvious on plain film, with cortical disruption, angulation, or displacement of fragments. Minor fractures can be subtle and may be missed. Special attention to the contour of the radial head and the fat pads reduces the risk of missing fractures. The normal cortex of the radius is smooth and has a gentle continuous concave sweep. If consistent with history and physical findings, any disruption of this smooth arc is considered evidence of fracture. Abnormalities within the soft tissues on elbow films are particularly important and may be the only radiographic sign of a fracture. Normally, fat surrounding the proximal elbow joint is hidden in the concavity of the olecranon and coronoid fossae. The normal elbow has only a narrow strip of lucency anteriorly (the anterior fat pad), and a posterior fat pad is not visible on radiographs. Injuries that produce intra-articular hemorrhage cause distention of the synovium and displace the fat out of the fossa, making the posterior fat pad visible on lateral radiographic views. The anterior fat pad also is altered by this swelling, becoming more prominent and taking the shape of a spinnaker sail from a boat: "sail sign" (Fig. 52-7). In the setting of trauma, more than 95% of patients with the "posterior fat pad" sign have intra-articular skeletal injury. These soft tissue findings occur even with subtle fractures, and when they are present in the setting of trauma, an occult fracture is considered to be present even when not visible on radiographs. In adults, a radial head fracture is implied, whereas in children a supracondylar fracture is the more likely underlying injury. In the absence of trauma, the presence of a fat pad suggests other causes of effusion (e.g., gout, infection, bursitis). The fat pad signs may be absent in fractures where the injury is severe enough to rupture the capsule.

The anterior humeral line is a line drawn on a lateral radiograph along the anterior surface of the humerus through the elbow. Normally, this line transects the middle third of the capitellum (Fig. 52-8). With an extension supracondylar fracture, this line either transects the anterior third of the capitellum or passes entirely anterior to it. The abnormal relationship between the anterior-humeral line and capitellum may be the only evidence of a minimally displaced supracondylar fracture and is a presumptive finding of a fracture.

Another diagnostic aid in evaluating radiographs of possible supracondylar fractures in children is the determination of Baumann's angle. As shown in Figure 52-9, the intersection of a line drawn on the anteroposterior film through the midshaft of the humerus and the growth plate of the capitellum defines an angle of approximately 75 degrees. In normal children, Baumann's angle is the same in both elbows, and it has been suggested that a comparison between the injured and uninjured sides be used to assess the accuracy of reduction. An increase in Baumann's angle indicates medial tilting of the distal fragment. Alteration in Baumann's angle is thought to predict the final carrying angle when the fracture heals, although there is controversy regarding its reliability.[2]

Radiographic evaluation of the elbow in children is difficult because of the presence of multiple ossification centers (Fig. 52-10). Table 52-1 lists the typical age of first appearance and fusion of ossification centers, which gives rise to the *CRITOE* acronym:

- Capitellum
- Radial head
- Internal (medial) epicondyle
- Trochlea
- Olecranon
- External (lateral) epicondyle

www.ketabpezeshki.com 66485457-66963820

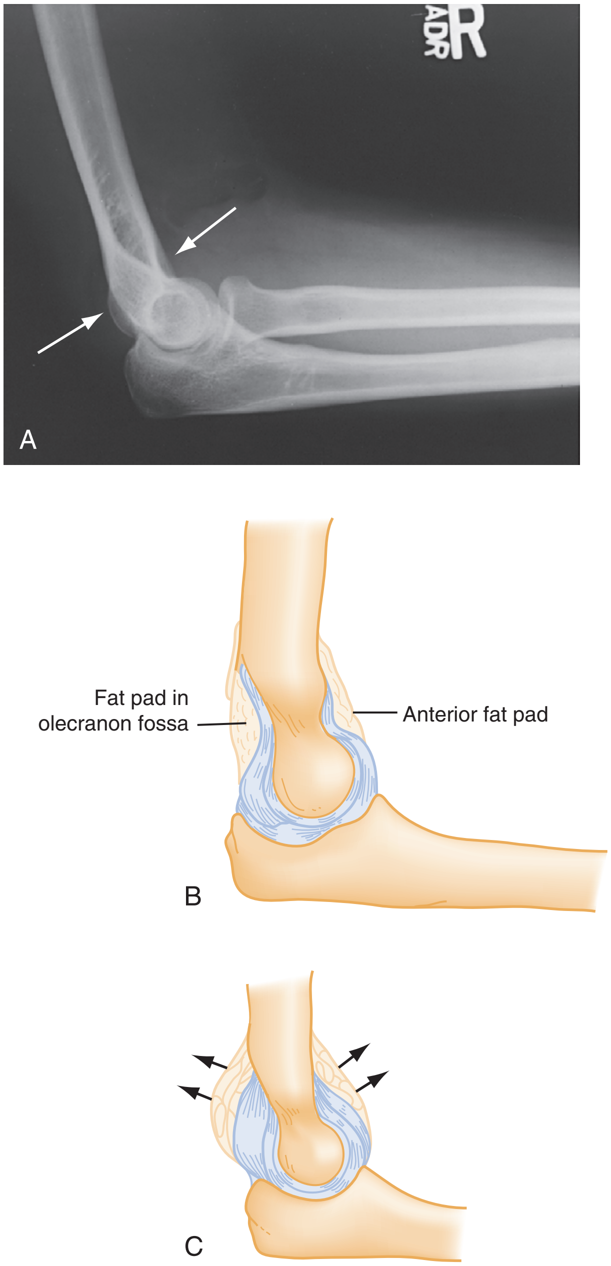


Figure 52-7. **A,** Anterior and posterior fat pads on lateral study *(arrows).* **B,** The anterior fat pad is normally a thin radiolucent stripe; the posterior fat pad is now visible. **C,** An effusion displaces both fat pads. This posterior fat pad is now visible.

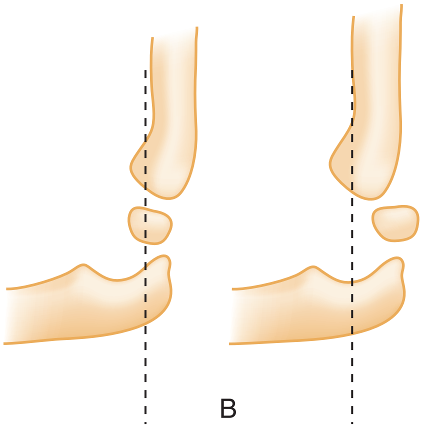


Figure 52-8. **A,** A line drawn down the anterior surface of the humerus on a lateral film should transect the middle of the capitellum. **B,** With an extension supracondylar fracture, the line passes more anteriorly. (From Simon R, Koenigsknecht S: Emergency Orthopaedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

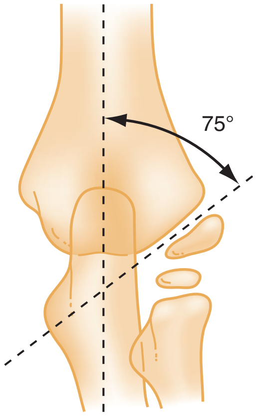


Figure 52-9. Baumann's angle as measured on anteroposterior film. (From Worlock P: Supracondylar fractures of the humerus. J Bone Joint Surg [Br] 68:755, 1986.)

Table 52-1 Ossification Centers of the Elbow: CRITOE

OSSIFICATION CENTERS	AGE OF APPEARANCE
Capitellum	1-2
Radial head	4-5
Internal (medial) epicondyle	4-5
Trochlea	8-10
Olecranon	8-9
External (lateral) epicondyle	10-11

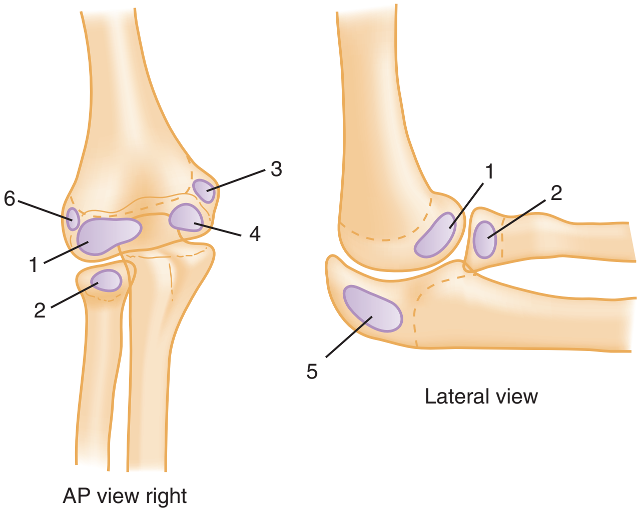


Figure 52-10. Secondary growth centers of the elbow. *(1)* Capitellum; *(2)* radial head; *(3)* medial epicondyle; *(4)* trochlea; *(5)* olecranon; *(6)* lateral epicondyle. (From Townsend DJ, Bassett GS: Common elbow fractures in children. Am Fam Physician 53:2031, 1996.)

www.ketabpezeshki.com 66485457-66963820

Box 52-1 Classification of Fractures

I. Humerus fracture
  A. Shaft of the humerus fractures
  B. Distal humerus fractures
    1. Supracondylar
      a. Extension
      b. Flexion
    2. Transcondylar
      a. Extension
      b. Flexion
    3. Intercondylar
      a. Nondisplaced
      b. Separated
      c. Separated and rotated
      d. Combination with articular surfaces
    4. Condylar
      a. Medial
      b. Lateral
    5. Articular surface
      a. Capitellum
      b. Trochlea
    6. Epicondylar
      a. Medial
      b. Lateral
II. Radial head fracture
  A. Nondisplaced
  B. Displaced
  C. Comminuted
III. Ulnar fracture
  A. Olecranon fracture
  B. Coronoid fracture

Comparison views of the uninjured elbow are often helpful in distinguishing fractures from the normal epiphyses and ossification centers.

Management

General management principles for humerus and elbow injuries are similar to those for other orthopedic injuries. Limb-threatening conditions, such as vascular injury, are addressed immediately by reduction of fractures or surgical exploration. The limb should be splinted in a position of comfort, and appropriate analgesia should be provided. Antibiotics are administered for suggested open fractures. Prolonged immobilization of the elbow frequently results in stiffness of the joint that requires extensive physiotherapy to restore normal function. For this reason, range-of-motion exercises are begun early in the convalescent period, often before a fracture has healed completely.

FRACTURES

Injuries in the region of the shaft of the humerus and about the elbow fall into several categories (Box 52-1). Emergency department (ED) management varies with location and type of fracture or dislocation. Supracondylar fractures of the humerus in children are usually described according to the Gartland classification (Box 52-2).

Box 52-2 Gartland Classification for Supracondylar Fractures in Children

Type I—Minimal or no displacement
Type II—Displacement of the fracture, but with the posterior cortex intact
Type III—Displaced, no cortical contact
Type IIIA—No rotation of the fracture
Type IIIB—Rotation present

Fractures of the Shaft of the Humerus

Pathophysiology

Fractures of the humeral shaft commonly result from a direct blow to the arm, such as occurs during a fall or motor vehicle collision. Severe twisting of the arm or a fall on an outstretched hand can also produce this type of fracture. Fractures produced by violent muscle contraction, such as occurs when a javelin or baseball is thrown, also are reported.[3] Motion of the humerus is controlled by several muscle groups, which also influence the fracture pattern of the humeral shaft. If the fracture is located proximal to the attachment of the pectoralis major, the proximal fragment of the humerus abducts and rotates internally owing to the action of the rotator cuff, whereas the distal fragment is displaced medially by the pectoralis major (Fig. 52-11A). If the fracture occurs below the pectoralis major insertion but above the deltoid insertion, the distal fragment is displaced laterally by the deltoid muscle, and the proximal fragment is displaced medially by the pull of the pectoralis major, latissimus dorsi, and teres major muscles (Fig. 52-11B). In fractures occurring distal to the deltoid insertion, the proximal fragment is abducted by the deltoid, and the distal fragment is proximally displaced (Fig. 52-11C). The shaft of the humerus most commonly fractures in the middle third in a transverse fashion (Fig. 52-12).

Clinical Features

The patient reports localized pain, often severe in nature. The arm is visibly swollen and cannot be used. When a fracture is complete, bony crepitus is felt in the shaft of the humerus with any manipulation of the arm. The arm may be shortened or rotated, depending on the displacement of the fracture fragments. When the fracture is incomplete, the skeleton is tender to palpation and swollen, but not otherwise deformed. A complete neurovascular examination is indicated. Attention should be directed to radial nerve function because injury to this nerve is the most common complication associated with humeral shaft fractures.

Radiographic findings are confirmatory. Studies routinely should include the shoulder and elbow joints. The humerus is a common site for benign tumors, unicameral cysts, and primary bone malignancies. The humeral shaft also is a common site for metastatic disease. Thinning of the cortex and abnormal osteoblastic or osteoclastic activity are evidence of a pathologic fracture (see Fig. 52-12). These fractures do not heal without concomitant treatment of the underlying pathologic condition.

Management

Closed fractures that are isolated injuries are treated conservatively with a high degree of success. Elaborate attempts at fracture reduction and external immobilization are unnecessary and sometimes detrimental to healing. Humeral shaft fractures remain surrounded by a richly vascularized envelope of muscle so that fracture reduction is accomplished most easily with the aid of gravity and muscle balance. Fractures that are nondisplaced or minimally displaced are immobilized by adding a coaptation, or "sugar-tong," splint, to the sling and swathe (Fig. 52-13). This is accomplished by first padding the extremity, then carrying a long plaster splint from the lateral side of the shoulder, down the lateral aspect of the upper arm, around the elbow with the elbow flexed, and then up the inner aspect of the arm to the axilla. The sugar tong is wrapped in an elastic bandage, and a sling is used to support the arm in 90 degrees or less of flexion. The weight of the

www.ketabpezeshki.com 66485457-66963820

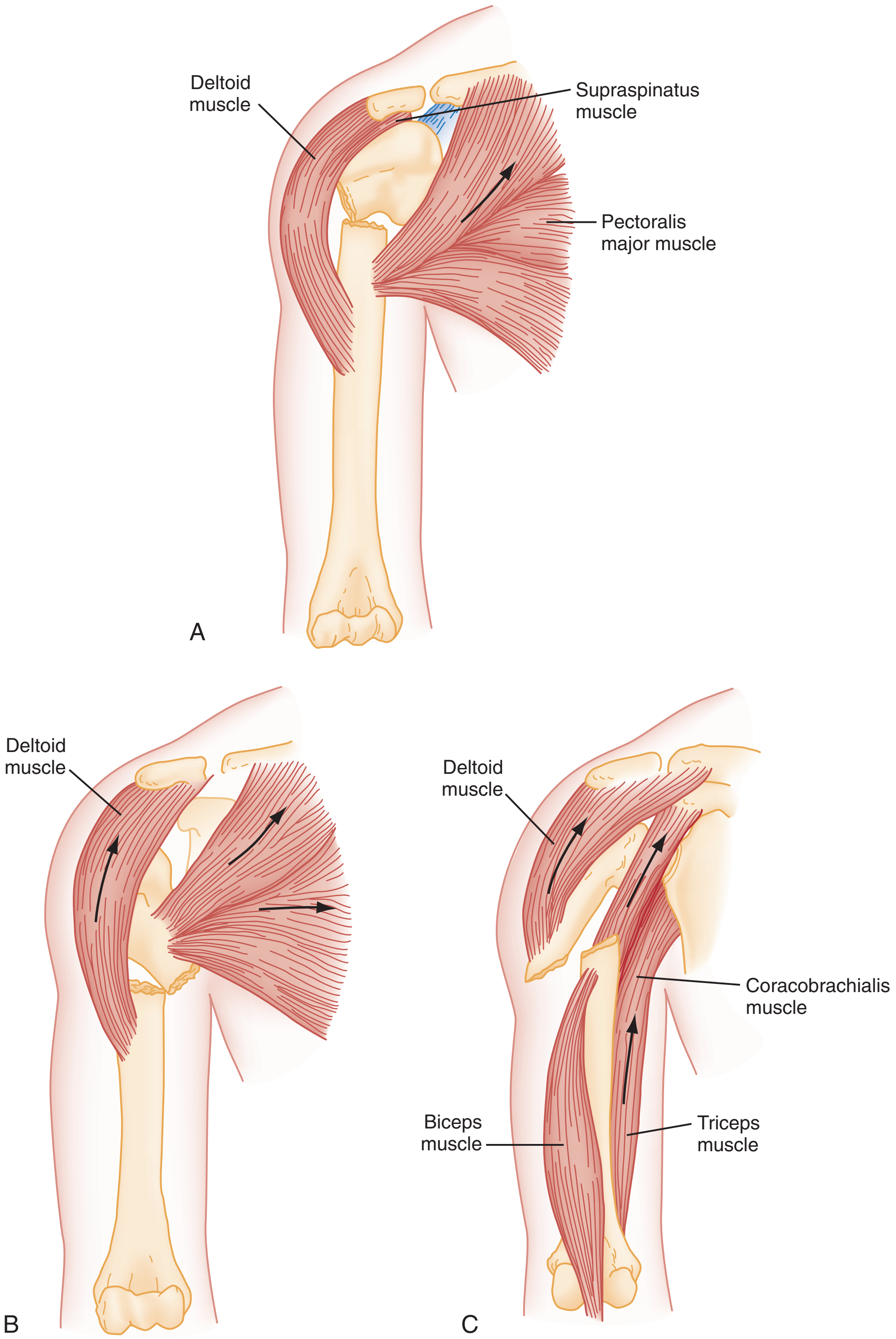


Figure 52-11. Influence of muscles on displacement of humeral shaft fractures based on fracture location. **A,** Fracture is proximal to the attachment of the pectoralis major muscle. **B,** Fracture is between insertion of the pectoralis major and deltoid muscles. **C,** Fracture is distal to the deltoid insertion.

splint aided by gravity applies traction while it immobilizes the fracture. Some authorities use the coaptation splint for only the first 10 to 14 days of treatment, followed by a functional brace.

If the fracture is grossly displaced or comminuted, the hanging cast technique sometimes is used. This technique is especially effective with spiral fractures. The cast is lightweight, applied at least 1 inch proximal to the fracture site, and extends to the distal palmar crease of the hand. The elbow is flexed 90 degrees, and the wrist is placed in the neutral position. The sling is attached through a loop at the wrist. Angulation is corrected by placing the plaster loop on the dorsal aspect of the cast (to reduce lateral angulation) or on the volar side of the cast (to reduce medial angulation). Anterior or posterior angulation is corrected by altering the length of the sling apparatus (Fig. 52-14). Care is taken not to make the cast too heavy because this would distract fracture fragments. The hanging cast has the disadvantage of requiring gravity for traction and requires that the patient remain upright at all times, including during sleep, a situation that many patients find intolerable.

www.ketabpezeshki.com 66485457-66963820

Figure 52-12. Pathologic fracture of proximal humerus.

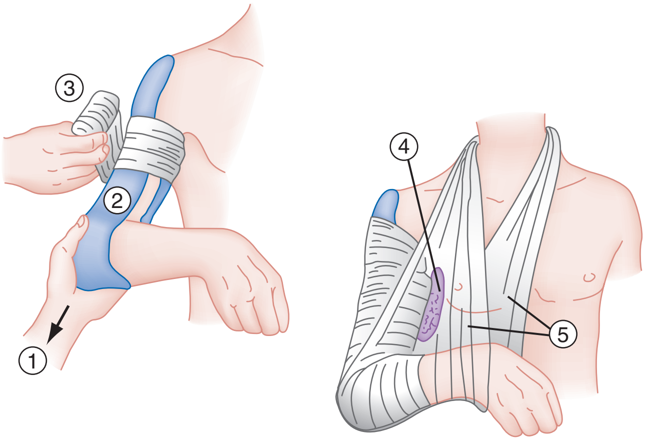


Figure 52-13. Sugar-tong splint for humeral shaft fractures. Gentle traction is applied *(1)* as the splint is placed *(2)* from over the deltoid laterally, under the elbow, and up into the axilla. An elastic wrap holds the splint in place *(3)*. The axilla must be padded *(4),* and a sling is used *(5)*. (Adapted from Connolly JF: DePalma's Management of Fractures and Dislocations. Philadelphia, WB Saunders, 1981.)

Neurovascular examination should be repeated and documented after the application of any splint or cast, because loss of nerve function from entrapment of the nerve between fragments can occur after these interventions.

The use of open reduction and internal fixation (Fig. 52-15) has been more frequent recently and is necessary in certain circumstances, including open fractures, presence of multiple injuries that preclude mobilization, bilateral fractures, poor reduction, poor patient compliance, failure of closed treatment, and fractures through pathologic bone.[4,5] Isolated radial nerve palsy usually is assumed to be a neurapraxia and is managed nonoperatively. Exploration and internal fixation are indicated, however, if the radial nerve palsy develops after manipulation because this is highly suggestive of nerve entrapment.[4]

All patients with humeral shaft fractures should be referred to an orthopedic surgeon for close follow-up monitoring. When

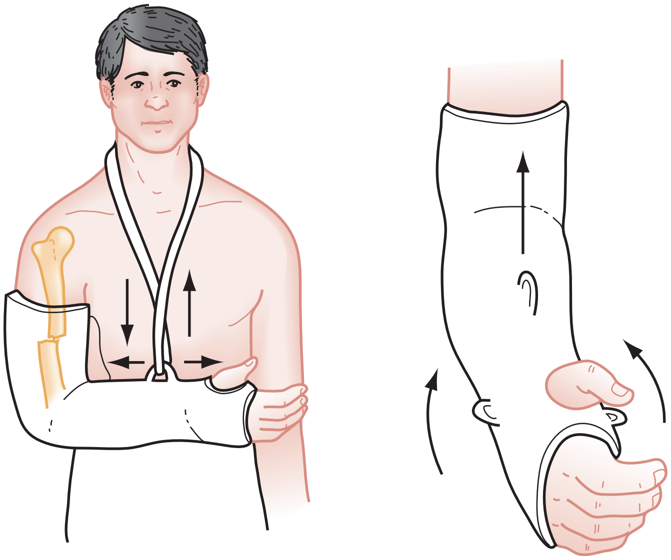


Figure 52-14. Hanging cast technique.

dependency casting is used, follow-up evaluation within 24 to 48 hours is recommended to be certain that the alignment has been maintained. Emergent referral to an orthopedist is recommended for patients with evidence of radial nerve injury, severely displaced or comminuted fractures, open fractures, or fractures associated with forearm fractures in the same extremity.

Complications

The most common complication, radial nerve injury, occurs in 20% of humerus fractures. This nerve injury is most often a benign neurapraxia that resolves spontaneously in most patients, although recovery may take several months. Patients should be advised of this possible complication, with instructions to contact their orthopedist or return to the ED for evaluation if this occurs. Radial nerve injuries associated with penetrating trauma or open fractures are likely to be permanent and usually warrant operative exploration. Median and ulnar nerve injuries are rarely seen, usually in the presence of penetrating trauma. Injuries to the brachial artery occur rarely, and, if clinically suggested, angiography or other vascular studies should be considered.

Fractures of the Distal Humerus

Supracondylar Fractures

Distal humerus fractures that occur proximal to the epicondyles are called *supracondylar fractures.* This type of fracture is almost exclusively an injury of the immature skeleton, with a peak incidence in children 5 to 10 years old[6] This injury rarely occurs after age 15 and accounts for approximately one half of all elbow fractures and one third of pediatric limb fractures. In children, the tensile strength of the collateral ligaments and joint capsule of the elbow is greater than that of bone. In adults, the reverse is true, and a posterior elbow dislocation is sustained instead. Supracondylar fractures are classified as either extension or flexion fractures, depending on the mechanism of injury and the displacement of the distal fragment. Of these injuries, 98% are of the extension type.

Extension Supracondylar Fractures

Pathophysiology. Extension supracondylar fractures occur as a consequence of a fall on the outstretched arm when the elbow is either fully extended or hyperextended (e.g., a fall off the

www.ketabpezeshki.com 66485457-66963820

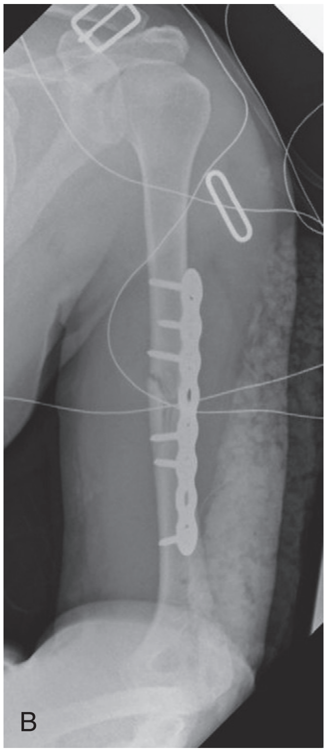


Figure 52-15. Midshaft humerus fracture: **A**, before and **B**, after open reduction and internal fixation.

“monkey bars”). The elbow is likely to be in the latter position at the time of the fall because ligamentous laxity, with hyperextension of the joints, is a normal phenomenon in younger children. With the forearm acting as a lever,[7] the ground reaction produces a moment of force at the elbow (Fig. 52-16). Ultimately the distal humerus fails anteriorly in the supracondylar area. The strong action of the triceps tends to pull and displace the distal fragment in a posterior and proximal direction. There may be anterior angulation of the sharp distal end of the proximal fragment into the antecubital fossa, endangering the brachial artery and median nerve (Fig. 52-17). In most cases, however, the brachialis muscle protects the anterior neurovascular structures from injury.

Clinical Features. A child with a complete fracture comes to the ED holding the upper extremity immobile in extension to the side, with a typical S-shaped configuration and tenderness and swelling in the region of the elbow. Prominence of the olecranon attached to the posteriorly displaced distal fragment is similar to that seen with posterior dislocation of the elbow. When an incomplete supracondylar fracture exists, the diagnosis may be less obvious, with an elbow effusion as the only clinical sign. A careful neurovascular examination is essential. Although palpation is useful in determining the site of injury, the examining physician should avoid manipulation of the injury to elicit crepitus because movement can cause further neurovascular damage. Alleviating pain often facilitates the examination.

Diagnostic Strategies. On radiographic examination, the distal fragment is often displaced on the lateral view. This displacement is most likely to occur with a complete fracture wherein the muscle activity results in proximal migration of the distal fragment. Because this fracture occurs in children, 25% of supracondylar fractures are of the greenstick variety, with the posterior cortex remaining intact. Subtle changes (e.g., the presence of a posterior fat pad or an abnormal anterior humeral line) may be the only radiographic clues to the presence of a fracture (Fig. 52-18). In displaced fractures on the anteroposterior view, the distal fragments may be displaced either medially or laterally in relationship to the humerus. Often, with minimally displaced fractures, the fracture line is transverse and not visible on the anteroposterior view. Based on radiographic findings, extension supracondylar fractures are classified into three types: type I, minimal or no displacement; type II, displaced fracture, posterior cortex intact; and type III, totally displaced fracture, anterior and posterior cortex disrupted.

Management. Nondisplaced fractures (type I) are immobilized primarily for comfort and protection because they are inherently stable. They are treated in a splint or cast flexed to 90 degrees with the forearm in neutral rotation. Protected active range of motion is begun in approximately 3 weeks. Even without definite radiographic findings, a child with localized tenderness consistent with a supracondylar fracture should be splinted and referred for follow-up examination within 24 to 48 hours. A radiographic study performed a few weeks after the injury may reveal periosteal new bone formation in the supracondylar region.

Minimally displaced (type II) fractures that are stable after reduction can be treated with splinting or casting with the elbow flexed. Some authors recommend flexion to 110 to 120 degrees for this injury.[6,8,9] This position uses the intact posterior periosteum as a tension band to hold the reduction; however, if swelling or circulatory obstruction prevents this much flexion, it cannot and should not be used. The greater the flexion at the elbow, the greater is the chance of vascular impairment. When swelling peaks at 24 to 48 hours, the risk of vascular obstruction and compartment syndrome is the greatest. Occasionally, these injuries must be pinned percutaneously to maintain stability, especially if a significant rotational component is present. Percutaneous pinning of fractures after reduction has grown in popularity in recent years.[10]

Type III totally displaced fractures generally are the result of more severe injuries that produce more swelling than type I or type II injuries. Displacement necessitates the reestablishment of length, increases the chance of varus deformity, and increases the chances of interposed soft tissues and neurovascular injury. For all these reasons, patients with type III fractures require immediate orthopedic consultation in the ED and should be admitted to the hospital for frequent neurovascular checks and closed versus open fixation and percutaneous pinning.

www.ketabpezeshki.com 66485457-66963820

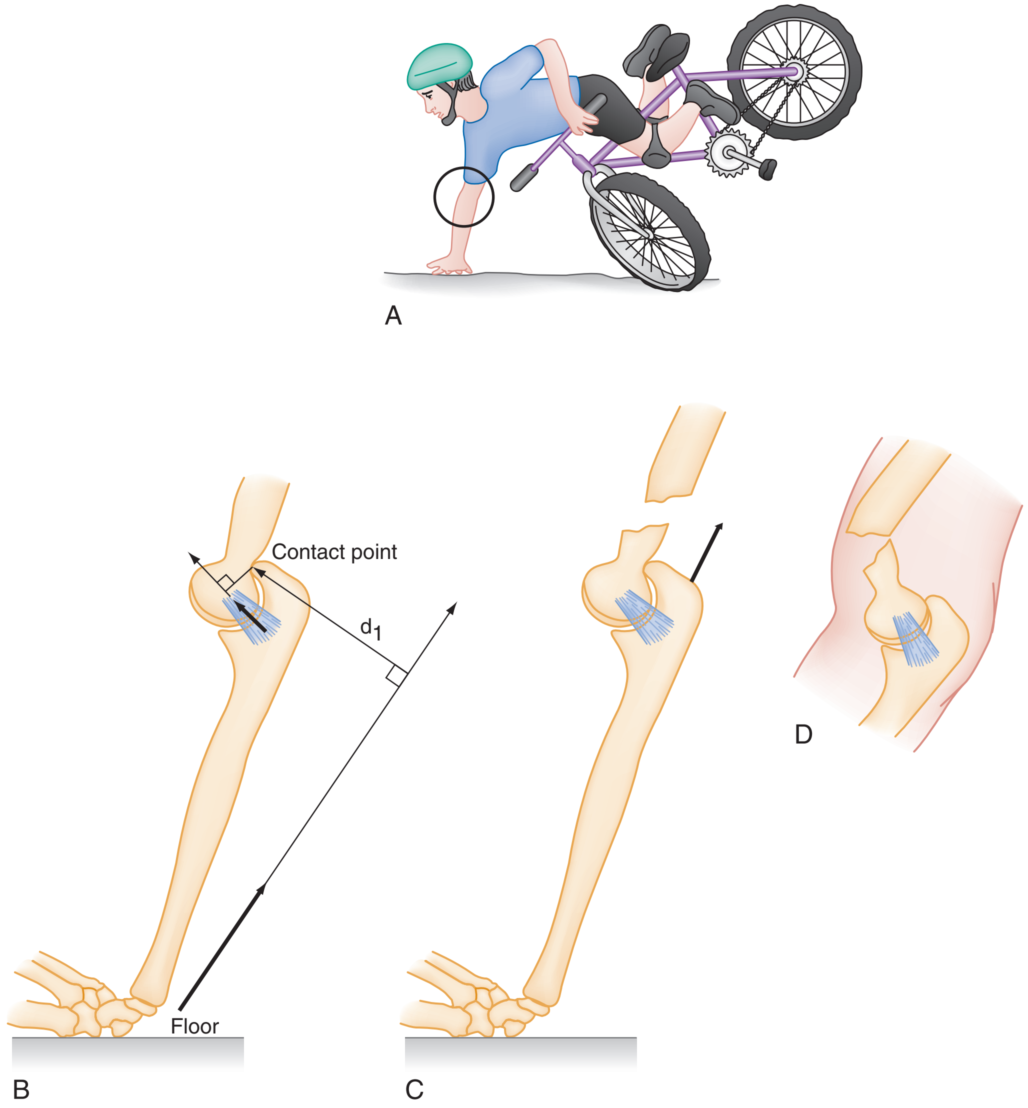


Figure 52-16. Mechanism of injury, extension supracondylar fractures. **A,** Fall on outstretched arm produces hyperextension of elbow. **B,** Ulna levers against distal humerus. **C,** Humerus fails, triceps exerts unopposed force. **D,** Distal fragment displaces.

These general principles should be adhered to in treating these injuries: (1) achieving adequate reduction, (2) properly assessing reduction, and (3) maintaining the reduction. Closed reduction is attempted with the patient under anesthesia. If closed reduction is not possible or if the brachial artery seems to be trapped in the fracture site, open reduction may be necessary. When adequate reduction has been achieved, most authorities recommend percutaneous pin fixation to maintain the reduction.[7,11,12]

Reduction in the ED is indicated only when the displaced fracture is associated with vascular compromise that threatens the viability of the extremity. Under these conditions, closed reduction should be attempted. After appropriate procedural sedation, an assistant fixes the arm of the patient. The physician grasps the patient's wrist and applies steady, firm traction in line with the long axis of the limb (Fig. 52-19A). The forearm is kept in the neutral, thumb-up position. While traction is maintained, correction of any medial or lateral displacement is accomplished with the other hand at the elbow (Fig. 52-19B). If the distal fragment is displaced laterally, it is pushed inward; if it is displaced medially, it is pushed outward.

After length has been restored and the angular deformity has been corrected, the thumb of the free hand is placed over the anterior surface of the proximal fragment with the fingers behind the olecranon. While traction is maintained, the elbow is gently flexed to just beyond 90 degrees (Fig. 52-19C). Angulation is corrected to a normal carrying angle.

Medially displaced supracondylar fractures are most prone to tilt into cubitus varus and are immobilized with the forearm pronated to tighten the brachioradialis and common extensor muscles. This procedure closes the fracture laterally. The less common laterally displaced fracture is immobilized in supination to close the fracture medially.

Only one attempt should be made at manipulation. Multiple attempts increase the likelihood of neurovascular injury and swelling. If reduction is unsuccessful, simple traction on the extended elbow may restore vascular supply. When reduction is performed, follow-up radiographs are obtained to ensure adequate reduction. Neurovascular function is checked at frequent intervals. Cylinder casts are not applied initially because they increase the risk of forearm ischemia; a posterior plaster splint provides safe and adequate immobilization.

Patients with type I fractures can be discharged safely from the ED with instructions to elevate the extremity, apply ice, and have a follow-up evaluation in 1 to 2 days. Fractures that require manipulation usually warrant admission to the hospital to ensure compliance and for neurovascular monitoring.

www.ketabpezeshki.com 66485457-66963820

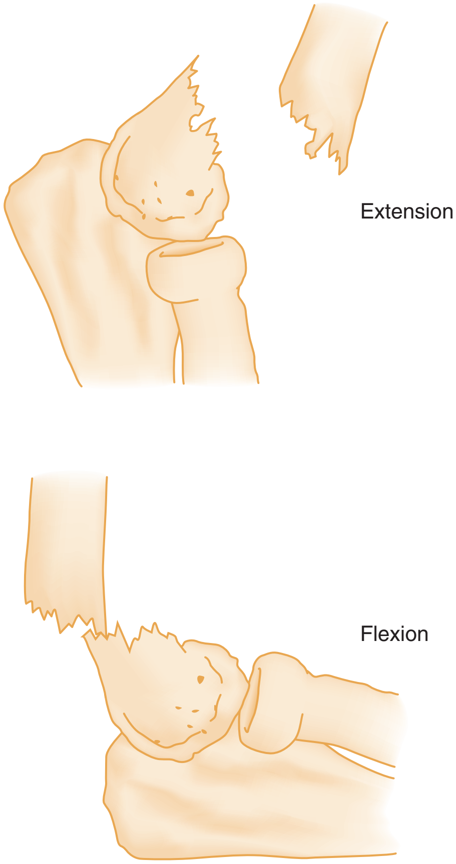


Figure 52-17. Supracondylar fractures, extension and flexion. (Adapted from Simon R, Koenigsknecht S: Emergency Orthopaedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

Figure 52-18. Supracondylar fracture *(arrow)* with anterior and posterior fat pads visible.

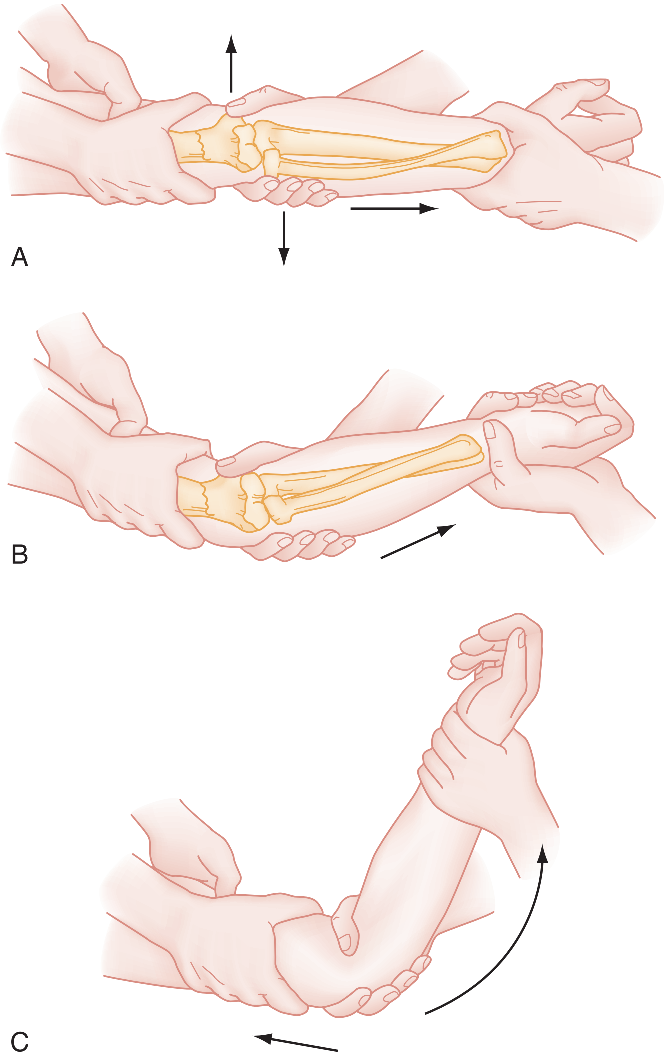


Figure 52-19. Steps in reduction of displaced supracondylar fracture (see text).

Complications. Ten percent of children lose the radial pulse temporarily, most often as a result of swelling and not direct brachial artery injury. Reducing the fracture, avoiding flexing the elbow more than 90 degrees, and elevating the arm help prevent secondary obstruction to arterial flow. Compartment syndrome, or Volkmann's ischemic contracture, as a result of prolonged ischemia of the forearm is a dreaded complication but is rare in this era (reported incidence <0.5%).[10]

The most common complication is the loss of the carrying angle, resulting in a cubitus varus, or "gunstock," deformity. Measurement of Baumann's angle after reduction is predictive of the final carrying angle. Cubitus varus has been reported previously in 25 to 60% of patients, depending on the treatment method used.[2,13] This incidence has decreased significantly (<10%) with the use of percutaneous pinning. The distal humerus has little capacity to remodel because only 20% of the growth of the bone derives from the distal physis. A small amount of extension or flexion deformity produces little disability, has the greatest chance of remodeling, and is not a major cosmetic concern. Valgus or varus deformities, being in the coronal plane, have little or no chance of remodeling. Although cubitus varus is not a significant functional disability, it presents a significant cosmetic problem. In most cases this complication can be corrected at a later time by an osteotomy.

Nerve injuries occurred in 7% of 4520 fractures compiled from 31 major reported series. The incidence increases to a range of 19 to 49% with increasing severity of fracture displacement.[14] The interosseous nerve is the most commonly injured, followed by the radial, median, and ulnar nerves. Most deficits seen at the time of injury are neurapraxias that resolve with conservative

www.ketabpezeshki.com 66485457-66963820

management. Motor function returns within 7 to 12 weeks, whereas recovery of sensation may take more than 6 months.[15]

Flexion Supracondylar Fractures

Pathophysiology. Flexion-type injuries are much less common, with a reported frequency of 1 to 10%, accounting for 2% of all supracondylar fractures in a large pooled series of patients.[16] The mechanism of injury is a direct blow to the flexed elbow. Energy is transferred from the posterior aspect of the proximal ulna to the distal humerus, resulting in a supracondylar fracture with anterior displacement of the distal fragment. As the fragment displaces, the periosteum is torn posteriorly.

Clinical and Radiographic Features. The elbow is usually held in flexion rather than with the extremity in the S-shaped configuration seen in extension-type injuries. In displaced fractures, the normal olecranon process is not palpable, in contrast to the increased prominence of the olecranon seen with extension injuries.

Radiographically, these injuries can be classified into three types, similar to extension injuries:

- Type I fracture—undisplaced or minimally displaced
- Type II fracture—incomplete fracture; anterior cortex intact
- Type III fracture—completely displaced; distal fragment migrates proximally and anteriorly

Plain films may reveal a simple increase in the anterior angulation of the distal supracondylar fragment or gross displacement of the distal fragment proximal and anterior to the distal end of the proximal fragment. In the latter case, the distal end of the proximal fragment protrudes posteriorly. A line down the anterior humeral shaft intersects the capitellum either normally or posteriorly in these fractures, depending on whether there is anterior displacement.[17]

Management. When the posterior periosteum is torn, the anterior periosteum functions as a tension band with the arm in extension. In type I fracture, the periosteum is minimally displaced. These injuries do not need to be immobilized in extension. The elbow can be comfortably flexed and should be immobilized in a splint as with extension injuries. Type II and III injuries should be referred to an orthopedist emergently. Type II injuries are manipulated into extension, then held either in a long arm cast or with percutaneous pins. Type III injuries often require open reduction (Fig. 52-20).

Complications. The most common complication is injury to the ulnar nerve by posterior displacement of the proximal fragment. The radial and median nerves are rarely injured. Stiffness of the elbow also may occur, especially after open reduction. Cubitus valgus may occur but is not as cosmetically problematic as cubitus varus.

Figure 52-20. Type III supracondylar fracture with significant displacement of distal fragment.

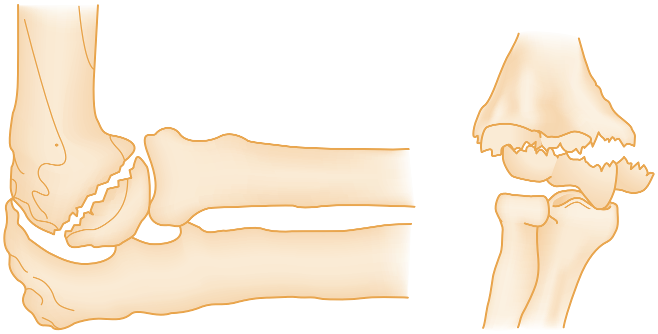


Figure 52-21. Transcondylar fracture of distal humerus. (*Left* from Ruiz E, Cicero J: Emergency Management of Skeletal Injuries. St Louis, Mosby, 1995. *Right* adapted from Simon R, Koenigsknecht S: Emergency Orthopaedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

Transcondylar Fractures

Transcondylar (or dicondylar) fractures have a fracture line, either transverse or crescent shaped, that passes through both condyles within the joint capsule just proximal to the articular surface (Fig. 52-21). As with supracondylar fractures, two types have been described—extension and flexion—based on the position of the elbow when fractured. Extension types are the most common. The mechanism of injury is similar to that for supracondylar injuries. In contrast to supracondylar fractures, however, the injury is more common in elderly individuals with fragile, osteoporotic bone. These fractures generally are difficult to treat because the small distal fragment possesses little extra-articular bone, and only a small amount of bone contact is available for union.[17] During healing, excessive callus may form in the olecranon or coronoid fossae with residual loss of motion. Orthopedic consultation should be immediately obtained for these injuries.

Intercondylar Fractures

Intercondylar fractures are usually T-shaped or Y-shaped fractures with variable degrees of separation of the condyles from each other and from the proximal humerus fragment (Fig. 52-22). The distal portion of the fracture extends to the articular surface of the distal humerus. These injuries are rare and generally are seen in adults in their 50s and 60s.[18] The usual mechanism of injury is direct trauma to the elbow that drives the olecranon against the humeral articular surface and splits the distal end.

Clinical and Radiographic Features. Patients with intercondylar fractures complain of pain at the elbow, which on examination is tender to palpation. Good-quality anteroposterior and lateral radiographic views are essential in evaluating fracture displacement and comminution (Fig. 52-23). Computed tomography may be used to delineate fracture patterns further. Neurovascular complications are not common with these injuries.

www.ketabpezeshki.com 66485457-66963820

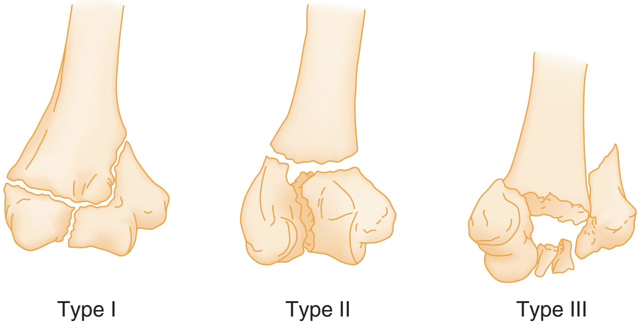


Figure 52-22. Intercondylar T fractures, types I, II, and III. (From Connolly JF: DePalma's Management of Fractures and Dislocations. Philadelphia, WB Saunders, 1981.)

Management. Treatment of intercondylar fractures is difficult and complicated.[16,19] The goal of treatment is to reestablish articular congruity and alignment and to begin active motion as soon as possible, most often through open reduction with rigid internal fixation. Closed treatment is typically restricted to elderly patients, patients with medical conditions that prohibit surgery, and certain patients with nondisplaced fractures. These injuries all should be referred to an orthopedic surgeon emergently. As with supracondylar fractures, manipulation should be avoided unless limb-threatening ischemia is present. Traction across the elbow with the arm extended is helpful in restoring blood flow to an ischemic forearm.

Complications. Historically, loss of elbow joint function is the most common complication reported, although this now can be largely avoided with optimal surgical technique.[16] Any method of treatment that requires prolonged immobilization is likely to result in fibrosis or ankylosis of the joint. Neurovascular complications are rare.

Lateral Condyle Fractures in Children

Lateral condyle fractures are the second most common fractures involving the elbow in children, after supracondylar fractures.[20] The fracture has an age distribution similar to that of supracondylar fracture and occurs after a fall on the outstretched hand, with a varus stress applied to the extended arm.

Clinical and Radiographic Features. Tenderness and swelling are noted over the lateral aspect of the elbow. In general, children exhibit less swelling than with supracondylar fractures, and neurovascular compromise is uncommon. Diagnosis is usually made on standard anteroposterior and lateral views, although an oblique view also may be helpful. These fractures are notoriously difficult to diagnose because fractures with minimal displacement are difficult to see radiographically and are often misdiagnosed as supracondylar humerus fractures.

Management. Nondisplaced fractures are treated nonoperatively with a cast, whereas fractures with any displacement require closed or open reduction with percutaneous pin fixation for 3 to 4 weeks.[20,21]

Complications. The risk of neurovascular compromise is much lower than with supracondylar humerus fractures. Fractures diagnosed and treated in a timely manner should have few complications, although historically, nonunion, cubitus varus or valgus, and fishtail deformity (avascular necrosis) have been reported.[22]

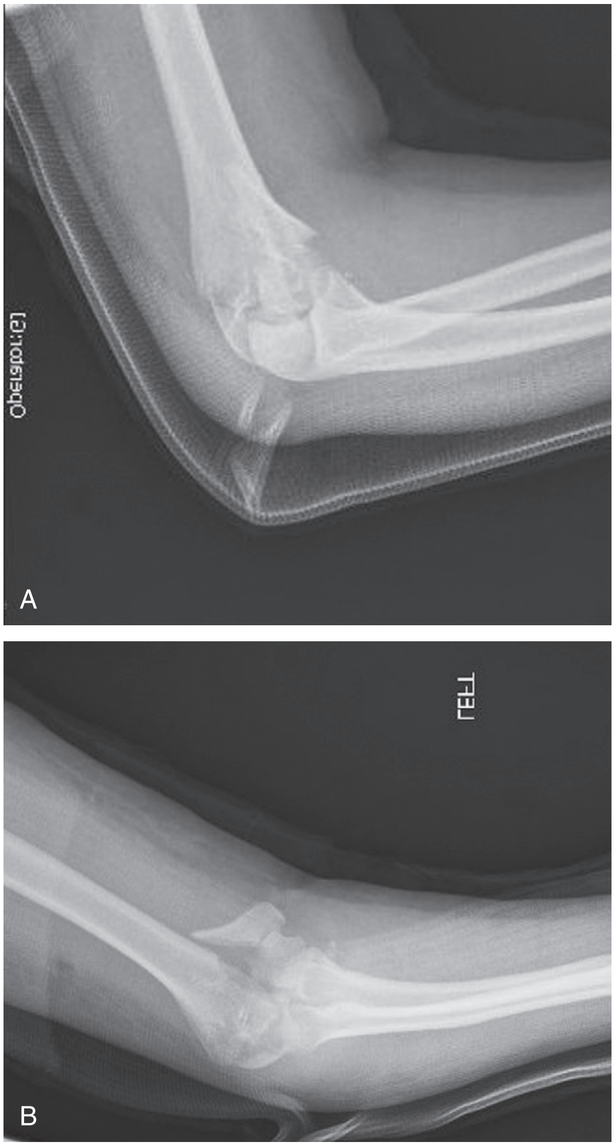


Figure 52-23. Intercondylar fracture, type III. **A,** Lateral and **B,** anteroposterior views.

Medial Condyle Fractures in Children

Medial condyle fractures are rare, comprising 1 to 2% of pediatric elbow fractures.[23] These fractures are type IV Salter-Harris injuries with physeal injury a possible outcome. The mechanism of injury is believed to be a valgus force on the extended elbow.

Clinical and Radiographic Features. The patient has tenderness and swelling over the medial aspect of the elbow. Anteroposterior, lateral, and oblique films may show the fracture in older children, but because the trochlea does not ossify until about age 9, plain films in younger children do not show the fracture. Magnetic resonance imaging (MRI) may be necessary to confirm the diagnosis in these patients.

Management. Operative treatment is indicated if displacement is greater than 2 mm; otherwise, conservative treatment is sufficient.

Complications. A study of 21 patients with medial condyle fractures revealed a 33% complication rate.[23] Complications included loss of reduction requiring reoperation, avascular necrosis, nonunion, and cubitus varus. Most minimally displaced fractures healed uneventfully.

www.ketabpezeshki.com 66485457-66963820

Condylar Fractures in Adults

Condylar fractures are rare in adults and typically involve the articular surface and the nonarticular portion of the distal humerus, including the epicondyle (Fig. 52-24). The status of the lateral trochlear ridge is the key to analyzing humeral condyle fractures. It may be involved with either medial or lateral condylar fractures and, when incorporated into the distal fragment, is far more likely to result in instability.

Pathophysiology. Lateral condylar fractures are uncommon, although more common than fractures of the medial condyle. The mechanism of injury is either a direct blow to the lateral aspect of the flexed elbow or a force that results in adduction and hyperextension with avulsion of the lateral condyle. Medial condylar fractures are rare and result from either a direct blow to the apex of the flexed elbow or a fall on the outstretched arm with the elbow forced into varus.

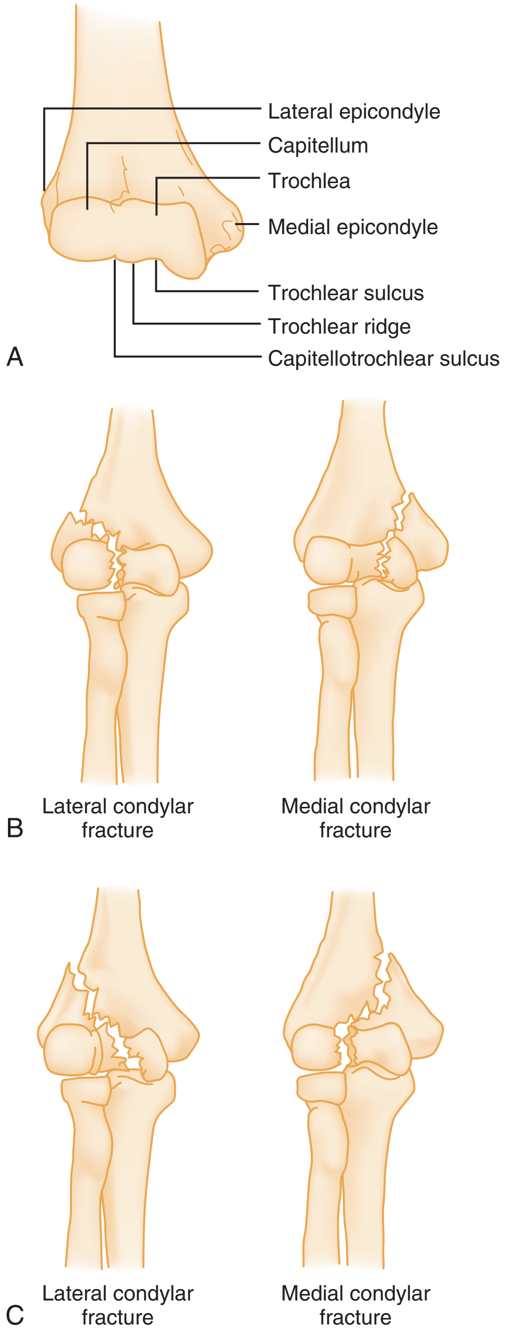


Figure 52-24. Condylar fractures. **A,** Normal anatomy. **B,** Lateral trochlear ridge not in fracture fragment (stable). **C,** Lateral trochlear ridge included with fracture fragment (unstable). (Adapted from Simon R, Koenigsknecht S: Emergency Orthopaedics: The Extremities, 2nd ed. Norwalk: Conn, Appleton & Lange; 1987.)

Clinical and Radiographic Features. The presentation of condylar fractures is similar to that of other distal humerus fractures, with swelling, tenderness, and crepitus localized over either the medial or the lateral elbow. On palpation, independent motion of the involved condyle may be appreciated. In lateral condylar fractures, findings may be accentuated with movement of the radius. On radiographic examination, lateral condylar fractures show a widening of the intercondylar distance. The distal fragment is often displaced, most commonly posteriorly and inferiorly. Because of the location of the ulnar nerve, it is imperative to test its function when this fracture is present. Medial condylar fractures are associated with tenderness over the medial condyle and pain with flexion of the wrist against resistance. On radiographic examination, displaced distal fragments tend to be anterior and inferior because of the pull of the forearm flexors.

Management. Immediate treatment depends on radiographic findings. For undisplaced or minimally displaced condylar fractures, immobilization of the flexed elbow in a long arm posterior plaster splint is sufficient. For lateral condylar fractures, the forearm should be supinated and the wrist extended to relieve the tension on the extensor muscle attachments. For medial condylar fractures, the reverse is true (i.e., the forearm should be pronated and the wrist flexed). For fractures displaced more than 3 mm, surgical fixation is required.

Complications. Complications include nonunion, restricted range of motion, joint instability, cubitus valgus or varus deformity, arthritis, and ulnar neuropathy. Because of the high rate of complications, orthopedic consultation should be sought for all condylar fractures.

Articular Surface Fractures

Capitellum Fractures

Pathophysiology. Fractures of the capitellum and trochlea typically occur together, usually as a result of posterior dislocation of the elbow, with isolated fractures being rarer. Injury to the capitellum occurs when the patient falls on an outstretched hand, jamming the radial head upward, similar to the motion of a piston, shearing off the capitellum into the radial fossa. Because the capitellum has no muscular attachments, the fragment may remain nondisplaced. More often the fragment is displaced (usually anteriorly, but occasionally posteriorly). Because of this mechanism, a radial head fracture also may be present and should be clinically suspected.

Clinical and Radiographic Features. The development of significant signs and symptoms may be delayed with capitellum fractures. Eventually, swelling within the capsule results in severe pain that manifests as well-localized tenderness on examination. Flexion of the elbow increases pain. A true lateral plain film usually shows the fragment lying anterior and proximal to the main portion of the capitellum (Fig. 52-25).

Management. Treatment begins in the ED with a posterior splint, ice packs, elevation, compression, and analgesia. Accurate anatomic alignment, rigid internal fixation, and early mobilization are prerequisites for a good functional result.[24] Fractures of the articular surfaces can be treated nonsurgically only if radiographs show perfect anatomic alignment.

Complications. Complications include post-traumatic arthritis, avascular necrosis of the fracture fragment, and restricted range of motion.

www.ketabpezeshki.com 66485457-66963820

Figure 52-25. Fracture of the capitellum.

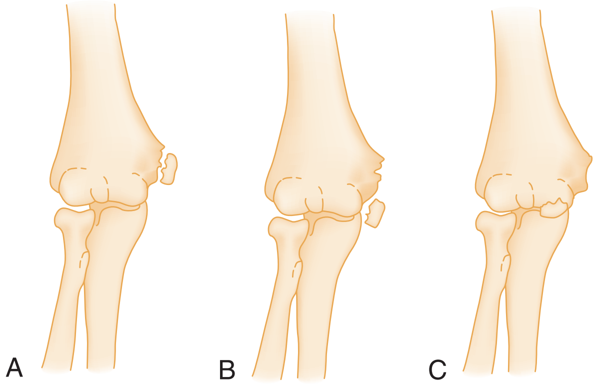


Figure 52-26. Fractures of medial epicondyle. **A,** Minimal displacement. **B,** Marked displacement. **C,** Displacement into joint. (From Connolly JF: DePalma's Management of Fractures and Dislocations. Philadelphia, WB Saunders, 1981.)

Trochlea Fractures

Pathophysiology. Isolated fractures of the trochlea are exceedingly rare because of the structure's protected position deep within the elbow joint. The shearing force of the ulna against the trochlea is associated more commonly with posterior elbow dislocation.

Clinical Features. The elbow is painful, with an effusion and limited range of motion because this is an intra-articular injury. On the radiograph a fragment is visible lying on the medial side of the joint, just distal to the medial epicondyle, and signs of joint effusion are visible. The fracture may extend into the distal portion of the medial epicondyle.

Management. Nondisplaced fractures may be treated with a posterior splint for 3 weeks, followed by early range-of-motion exercises. Displaced fractures should be treated operatively; fragments that can be internally fixed are repaired, whereas small fragments are excised. Immobilization should be minimized to 10 to 14 days.[25]

Epicondyle Fractures

Most epicondylar fractures involve the medial epicondyle. Medial epicondyle fractures are most common in children and adolescents and often involve the apophysis, which is the last ossification center to fuse in the distal humerus, usually after age 15. Fractures through this ossification center usually occur in adolescence and constitute 11% of pediatric elbow fractures.[26] These are not Salter-Harris injuries because the apophysis is involved rather than the physis. Because the lateral epicondyle is almost level with the flattened outer surface of the lateral condyle, it has only minimal exposure to a direct blow, and fracture is extremely rare.

Pathophysiology. Medial epicondyle injuries occur from a variety of mechanisms. First, avulsion fractures are associated with posterior elbow dislocations in patients younger than 20 years in 30 to 55% of cases.[27] Second, repetitive valgus stress (as with throwing a ball) results in eventual avulsion fracture of the epicondyle (Little Leaguer's elbow). Another reported cause of fracture separation of the medial epicondyle, usually in adolescent boys, is arm wrestling.[28] Violent muscular forces associated with a shifting center of gravity during this activity seem to produce an avulsion just before closure of the epiphyseal plate. Finally, a direct blow to the medial epicondyle can cause this injury.

Clinical and Radiographic Features. The elbow is held in flexion, and any movement is resisted. Isolated fractures are associated with focal tenderness over the medial epicondyle. Use of the forearm flexors increases pain because their attachment is along the medial epicondyle. Ulnar nerve function should be evaluated. When the fracture is associated with a posterior dislocation, the examination reveals a prominent olecranon.

Simple fractures of the medial epicondyle are extra-articular injuries with limited soft tissue injury.[20] They generally do not produce a fat pad sign on the lateral radiographic view of the elbow. A posterior fat pad or significant swelling of the joint should suggest concurrent injuries, such as elbow dislocation. Careful radiographic evaluation is especially important because fracture fragments may migrate into the joint space. If the fragment is overlying the joint line on radiographic examination, it should be considered intra-articular (Fig. 52-26). Radiographic detection of the intra-articular fragment is often difficult.[27] Associated ulnar nerve palsy may be present with an entrapped fragment. Fragments may be difficult to see on radiographs, and a true anteroposterior view is difficult to obtain because of severe pain on extension. In an adolescent patient, there is a tendency to confuse the normal radiolucent epiphyseal growth plate with a fracture. In addition, minimally displaced fractures may be difficult to appreciate with radiographs. Comparison films of the uninjured elbow may be necessary. If dislocation is present, repeat radiographs taken after reduction should be evaluated for fragment location.

Management. If the fracture fragment is minimally displaced (<5 mm), treatment with a posterior splint is appropriate. To minimize distraction of the fragment by the forearm flexors, the elbow and wrist are flexed with the forearm pronated.

Treatment of displaced fractures is controversial. In the past, the amount of displacement often dictated the need for surgery. Results of operative and nonoperative treatment seem to be good, however, regardless of the degree of displacement.[29] Some experts advocate surgery for patients who participate in high-performance athletic activities that involve the injured extremity, but controlled studies are lacking.[20] Intra-articular fragments that cannot be removed from the joint by manipulation are an indication for surgery.[29] Immediate orthopedic consultation should be sought for these injuries. The rare lateral epicondylar fracture in adults was previously treated with immobilization, but more recent experience indicates that operative management is more successful.[30]

www.ketabpezeshki.com 66485457-66963820

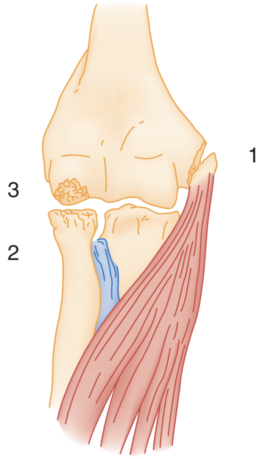


Figure 52-27. Little Leaguer's elbow. Avulsion fracture of medial epicondyle *(1)*. Compression fractures of the radial head *(2)* and capitellum *(3)*. (From Connolly JF: DePalma's Management of Fractures and Dislocations. Philadelphia, WB Saunders, 1981.)

Table 52-2 Little League Baseball Pitch Count Regulations

AGE (YR)	MAXIMUM PITCHES PER GAME
7-8	50
9-10	75
11-12	85
13-16	95
17-18	105

Table 52-3 Little League Baseball Rest Requirements for Pitchers Age 16 and Older

PITCHES	DAYS REST
1-20	0
21-40	1 calendar day
41-60	2 calendar days
>61	3 calendar days

Little Leaguer's Elbow

Little Leaguer's elbow warrants special mention. An adolescent pitcher traumatizes immature epiphyses by repetitive throwing. Throwing the curve ball or breaking ball was previously implicated as a particular culprit, although the most important factor appears to be the total number of pitches per game.[31] It has been shown in a group of highly competitive young baseball players that this injury is also common in catchers and fielders.[32] The adolescent bone structure cannot withstand the extreme loading produced by repetitive hard throwing. Avulsion of the medial epicondyle or compression fracture of the subchondral bone of the lateral condyle or radial head may result (Fig. 52-27). This diagnosis should be sought in an athletic adolescent with medial epicondyle or radial head pain in the absence of acute injury by history. Adolescents with this condition should be forced to rest the elbow if throwing causes pain. After healing occurs, the amount of throwing and technique should be monitored carefully. The Committee on Sports Medicine and Fitness of the American Academy of Pediatrics and Little League Baseball recommend preventive measures to avoid these injuries, with guidelines for both pitch counts per game and mandated rest periods (Tables 52-2 and 52-3). The latest updates on new rules set forth by Little League Baseball can be found at www.littleleague.org.

Olecranon Fractures

Pathophysiology. Fractures of the olecranon may result from one of several mechanisms. Most commonly, a direct blow as a result of a fall, a motor vehicle or motorcycle crash, or an assault produces this injury. Such injuries are frequently comminuted. Less commonly, indirect force applied by forceful contraction of the triceps while the elbow is flexed during a fall can cause a transverse or oblique fracture through the olecranon. A combination of direct and indirect forces is believed also to cause some of these fractures. Olecranon fractures occur in adults and less commonly in children. The anatomic integrity of the olecranon is essential for triceps strength and normal function of the elbow, similar to the way intact patellar function is necessary for extension of the knee.

Clinical Features. Physical findings may include tenderness and pain over the olecranon, a palpable separation at the fracture site, or the inability to extend the elbow against force. This last finding indicates complete discontinuity of the pulling mechanism and the consequent failure of triceps function. The neurovascular status should be examined, with special attention given to the ulnar nerve distribution, because this structure is most vulnerable to injury in this location. Loss of sensation over the palmar aspect of the fifth digit and hypothenar eminence or motor weakness in the interossei muscles of the hand suggests ulnar nerve injury.

Diagnostic Strategies. Lateral radiographic views are most helpful. In addition to the fracture, the degree of comminution, the extent of articular surface disruption, and the amount of displacement in the 90-degree flexion position should be noted. Nondisplacement in this position indicates that the triceps aponeurosis is intact, and prolonged immobilization is unnecessary. Displacement of more than 2 mm is considered an indication for surgery (Fig. 52-28A). A fracture line that increases in separation with flexion of the elbow also is considered a displaced fracture. When this fracture is associated with elbow dislocation, the plane of instability is located through the fracture site and the radiohumeral joint, resulting in posterior displacement of the proximal fragment of the ulna and anterior dislocation of the radius and ulna as a unit (Fig. 52-28B).

Management. Undisplaced fractures can be treated conservatively on an outpatient basis with ice, compression, immobilization in 45 to 90 degrees of flexion, and analgesia. Follow-up films should be done at frequent intervals to ensure that subsequent displacement does not occur. Range-of-motion exercises can be started within 3 weeks in many cases.

Displaced fractures or fracture-dislocations require open reduction and internal fixation, and patients should be referred immediately to an orthopedic consultant. Displaced fractures in elderly patients sometimes are treated conservatively, but this should be left to the discretion of the consultant. Orthopedic referral also is necessary when ulnar nerve symptoms are present. These symptoms occur in 10% of patients, and in most cases the injury is an ulnar contusion that resolves spontaneously. The long-term outcome of treated olecranon fractures in adults is usually favorable with a low incidence of subsequent arthritis.[32]

Radial Head and Neck Fractures

Pathophysiology. Radial head and neck fractures, in general, are produced by an indirect mechanism, typically a fall on an outstretched hand. The radius transmits the force upward, driving the

www.ketabpezeshki.com 66485457-66963820

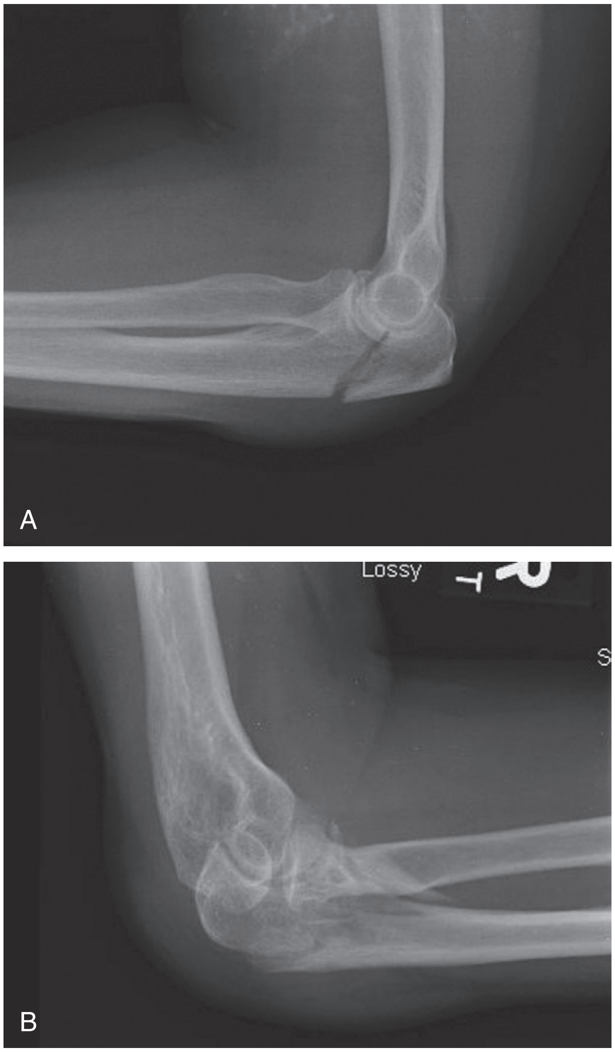


Figure 52-28. A, Olecranon fracture with displacement, B, Fracture accompanied by radial head dislocation.

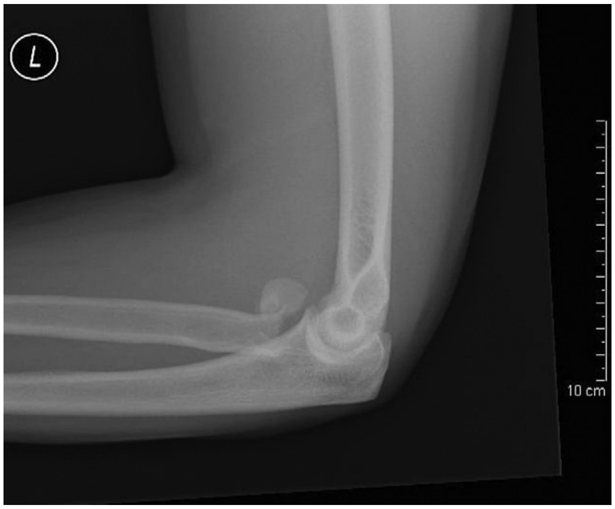


Figure 52-29. Radial head fracture with displacement.

radial head against the capitellum and resulting in fracture of the weaker radial head or neck. Although the fracture of the radial head may be the only radiographic finding, damage to the articular surface of the capitellum and injury to the collateral ligament commonly occur. Displacement of the radial head fragment suggests considerable force and significant soft tissue injury. This injury is characterized by localized tenderness over the radial head or pain with passive rotation of the forearm.

Diagnostic Strategies. Radiographic findings range from a subtle disruption of the usual gradual sweep of the radial neck and head surface to an obvious displaced or comminuted fracture (Fig. 52-29). Undisplaced fractures are notoriously difficult to see on radiographs. Tenderness coupled with a positive fat pad sign on the radiograph indicate that the injury should be treated as a radial head fracture even in the absence of a visible fracture. Radial head fractures are classified into four types:

- Type I—undisplaced fractures
- Type II—marginal fractures (involving <30% of the articular surface) with more than 2 mm displacement, including impaction or angulation
- Type III—comminuted fractures of the entire radial head
- Type IV—any of the previous types with elbow dislocation[33]

Management. Type I nondisplaced fractures are treated symptomatically with a brief period of sling support and early range-of-motion exercises (within 24-48 hours). Aspiration of the hemarthrosis and injection of 0.5% bupivacaine into the joint space may give dramatic relief of pain and improve the range of motion.[35] However, a recent prospective randomized study found no benefit to bupivacaine instillation compared with simple aspiration.[1] Most patients with this injury recover well in 2 to 3 months. A few do poorly, however, with long-term pain, contracture, or inflammation.

Type II injuries usually are treated similarly, with aspiration, instillation of bupivacaine, and immobilization in the ED, followed by a trial period of range-of-motion exercises. In these cases, aspiration of the joint and instillation of bupivacaine not only relieve pain but also allow testing of the range of motion to identify entrapped fragments. Radial head excision sometimes is performed later if the patient fails to improve. Early excision is advised for type II fractures when a mechanical block is present and for most type III fractures. Long-term functional results after radial head excision are acceptable in most patients, although a few have some functional disability after this procedure.[34] Type IV injuries are treated for the elbow dislocation as described next and for the specific radial head lesion.

DISLOCATION AND SUBLUXATION

Elbow Dislocation

Because of its anatomic structure, the elbow is inherently subject to mechanical instability, and dislocations are common. The elbow is second only to the shoulder as the most commonly dislocated large joint. *Elbow dislocation* is a term usually used to describe a disruption of the relationship between the humerus and the olecranon. In general, the radius and ulna, bound together firmly by the annular ligament and interosseous membrane, displace as a unit. Most classifications refer to the abnormal position of the ulna relative to the humerus. The elbow most often dislocates posteriorly, although it may dislocate anteriorly, medially, or laterally (Fig. 52-30). A dislocation also may occur between the radius and ulna, and such dislocations rarely occur concurrently with the ulnohumeral type. The latter are termed *divergent* dislocations.

Dislocation of the elbow requires considerable energy, and it is not surprising that a significant number of dislocations are associated with fractures of adjacent bony structures. A

www.ketabpezeshki.com 66485457-66963820

Figure 52-30. Elbow dislocation, posterior and anterior. (Adapted from Simon R, Koenigsknecht S: Emergency Orthopaedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

fracture-dislocation injury is referred to as a *complex elbow dislocation.* Immediate reduction of these dislocations is imperative to relieve pain and to prevent circulatory embarrassment or cartilaginous damage.

Posterior Elbow Dislocation

Pathophysiology. The mechanism of injury is a fall on the outstretched hand or wrist, the elbow being either extended or hyperextended at the time of impact. A valgus stress usually also occurs. The resultant forces lever the ulna from the trochlea and produce the dislocation.

Clinical and Radiographic Features. Patients hold the elbow in flexion at approximately 45 degrees and have marked prominence of the olecranon. Some elbow dislocations reduce before examination in the ED, presenting a confusing picture. In any case, significant diffuse tenderness and swelling are present. Neurovascular status is checked because brachial artery and median nerve injuries have been described. Neurovascular injury may occur from numerous mechanisms, including the initial traction, local swelling, and entrapment during reduction. Repeat examinations are mandatory.

A radiographic example of elbow dislocation before reduction is provided in Figure 52-31. Radiographic evaluation is crucial before manipulation to rule out fractures that can mimic dislocation on examination. Also, several fractures commonly occur in conjunction with dislocation, and these need to be identified and treated when present. These include fractures of the distal humerus, radial head, and coronoid process.

Management. Orthopedic consultation is usually not necessary to proceed. Reduction should be attempted immediately, especially if there is neurovascular compromise. Intra-articular injection of local anesthetic may provide adequate analgesia to allow for closed reduction. Procedural sedation is very helpful and often required to facilitate reduction. Rarely is a regional block or general anesthesia needed. Posterior dislocations are reduced with an assistant immobilizing the humerus and applying countertraction while traction is applied to the distal forearm. The ideal position is for the elbow to be flexed at 30 degrees with the forearm supinated while distal traction is applied. When the capitellum slides over the coronoid process, a coupling sound occurs as the articular surfaces mesh. If reduction is unsuccessful with this technique, the physician should apply downward pressure at the proximal forearm and apply pressure behind the olecranon while maintaining in-line traction. This downward force may help "unlock" the coronoid process, which may be trapped in the olecranon fossa. The joint is gently moved through its normal range of motion to check stability. If stable, the elbow is flexed to approximately 90 degrees and immobilized with a posterior plaster mold. The neurovascular status should be rechecked. Postreduction radiographs are important to avoid missing concomitant fractures of the coronoid process or radial head or, in children, separation of the medial epicondylar apophysis.

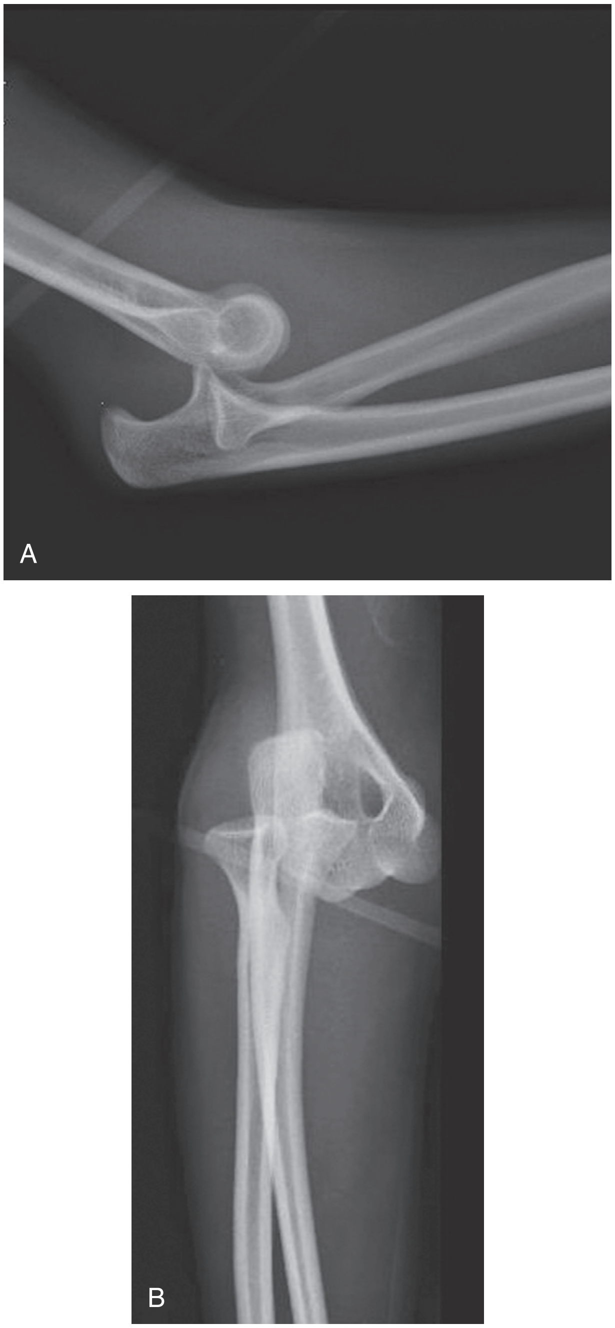


Figure 52-31. Characteristic posterior dislocation of elbow, lateral **(A)** and anteroposterior **(B)** views.

Postreduction management includes immobilization in a posterior splint with the elbow in as much flexion as circulation allows. The arm is suspended in a sling. Circular casting should be avoided initially. Patients can be discharged with instructions to apply ice, elevate, and watch for signs of vascular impairment. Patients should not be discharged until and unless they can follow such instructions. If the elbow is stable after reduction, gentle range-of-motion exercises may be initiated in 3 to 5 days. Unstable joints may require either prolonged immobilization in

www.ketabpezeshki.com 66485457-66963820

the presence of ligamentous instability or internal fixation for instability associated with fracture.[36]

Complications. The most serious complication of elbow dislocation is vascular compromise. Severe disruption results in injury to the brachial artery in 5 to 13% of cases.[37] Vascular injury should be sought when a wide opening between the tip of the olecranon and the distal humerus is palpated or seen on a radiograph. The presence of distal pulses is not proof of an intact artery, and if a question of vascular compromise exists, emergent vascular studies or consultation is indicated. Median nerve traction injuries and entrapment also have been reported. Loss of median nerve function after reduction should prompt immediate orthopedic consultation. Recurrent dislocation of the elbow is rare.

Medial and Lateral Dislocations

Medial and lateral elbow dislocations are produced by a mechanism similar to that in posterior dislocations, with a vector of force displacing the ulna and radius as a unit either medially or laterally. The anteroposterior view is the key to determining these dislocations. Reduction is carried out with the arm in slight extension but otherwise is similar to that for posterior dislocation. Care should be taken not to convert these to posterior dislocations during reduction. Complications and aftercare are the same as for posterior dislocations.

Anterior Elbow Dislocation

Pathophysiology. Anterior dislocations are rare and occur as a result of a blow from behind to the olecranon while the elbow is in the flexed position. Severe associated soft tissue trauma is present, including avulsion of the triceps mechanism or vascular disruption. These dislocations are frequently open.

Clinical Features. The upper arm appears shortened and the forearm elongated. The elbow is fully extended, and the forearm is supinated. The olecranon fossa is palpable posteriorly.

Management. Reduction of closed injuries is performed with distal traction of the wrist and a backward pressure on the forearm while the distal humerus is grasped. A click usually indicates that reduction has been achieved. These injuries have a higher incidence of vascular impairment than the more common posterior dislocation, but ulnar nerve injuries are unusual.[38] Emergent orthopedic referral is advised and is mandatory for open injuries or when vascular disruption is suggested.

Radial Head Subluxation

Pathophysiology

Subluxation of the radial head is a common injury, representing more than 20% of upper extremity injuries in children. Children aged 1 to 4 years are most often affected, although cases have been reported in children 6 months to 15 years of age. Girls are affected more commonly than boys, and the left arm is more commonly affected than the right.[39] This injury is called *nursemaid's elbow* because it results from a sudden longitudinal pull on the forearm while the child's arm is in pronation. Stretching of the annular ligament allows fibers to slip between the capitellum and the head of the radius, resulting in an inability of the child to supinate the arm. By the age of 5, the annular ligament becomes thick and strong and thus is far less likely to tear or be displaced.

Clinical and Radiographic Features

The classic history, present approximately half of the time,[40] is that of the forearm being pulled while in pronation with the elbow extended. Other mechanisms include direct trauma to the elbow or a twisting motion of the arm. In children younger than 6 months, the mechanism of subluxation involves rolling over in bed, which may trap the involved forearm under the body with resulting longitudinal traction on the joint. Clinically, the arm is held in passive pronation, with slight flexion at the elbow. The child is unable or unwilling to move the arm. Resistance to supination and tenderness on direct palpation over the head of the radius are present. Swelling, ecchymosis, and deformity are absent. Examination should include inspection and palpation of the entire extremity, including the clavicle.

When the history is suggestive of radial head subluxation, radiographs are not necessary and are rarely positive. If there is swelling or deformity, if there is an uncharacteristic history, if the child does not resume use of the arm after reduction, or if there is a possibility of nonaccidental trauma, appropriate radiographic studies are recommended. If palpation of the forearm, wrist, or humerus away from the elbow elicits reproducible tenderness, radiographs should be taken to exclude other diagnoses.

Management

Reduction may be attempted in children with typical presentations and is safe even when the classic history is absent. Supination-flexion is the method most commonly used in the past. Reduction is achieved by supination of the forearm while slight pressure on the radial head is applied with the examiner's thumb. In one continuous motion, the elbow is supinated and flexed with gentle traction applied. A click often, but not always, is felt as the radial head reduces (Fig. 52-32). A second technique of reduction, hyperpronation, has a significantly higher reported success rate of reduction on the first attempt.[41] With the hyperpronation method, the child's elbow is supported with moderate pressure applied to the radial head. The examiner then grips the child's distal forearm and hyperpronates the forearm, resulting in a click felt over the radial head (Fig. 52-33).

Many patients are asymptomatic within 5 to 10 minutes; 90% of patients regain use of the arm within 30 minutes. Hearing or palpating a click is associated with success. It is a good idea for the physician to leave the room and for parents to distract the child to show return of normal function. A fearful child often does not use even the successfully reduced limb. If function does not return within 24 hours, the patient should be reevaluated. After successful reduction, no additional treatment, immobilization, or activity reduction is necessary. Parents and caregivers should be instructed to avoid excessive traction on the child's forearm to prevent recurrent radial head subluxation. The recurrent radial head subluxation rate is approximately 20%.[42] Most of these injuries are unintentional on the part of the caregiver, but inflicted injury should be considered in suggestive cases.

SOFT TISSUE DISORDERS

Epicondylitis (Tennis Elbow)

Pathophysiology

Tennis elbow is a term first introduced in the 1880s to describe an inflammatory process that involves the radiohumeral joint or lateral epicondyle of the humerus. It is a common exercise-related syndrome, and the mechanism is thought to be repetitive pronation and supination of the forearm. The actual pathologic nature of this syndrome is unclear. Radiohumeral bursitis or synovitis, tendinitis of the common extensor tendon, periostitis of the lateral epicondyle, and entrapment by scar tissue of the radial nerve all have been suggested as culprits in this syndrome. Histologically, the abnormality has been described as *angiofibroblastic*

www.ketabpezeshki.com 66485457-66963820

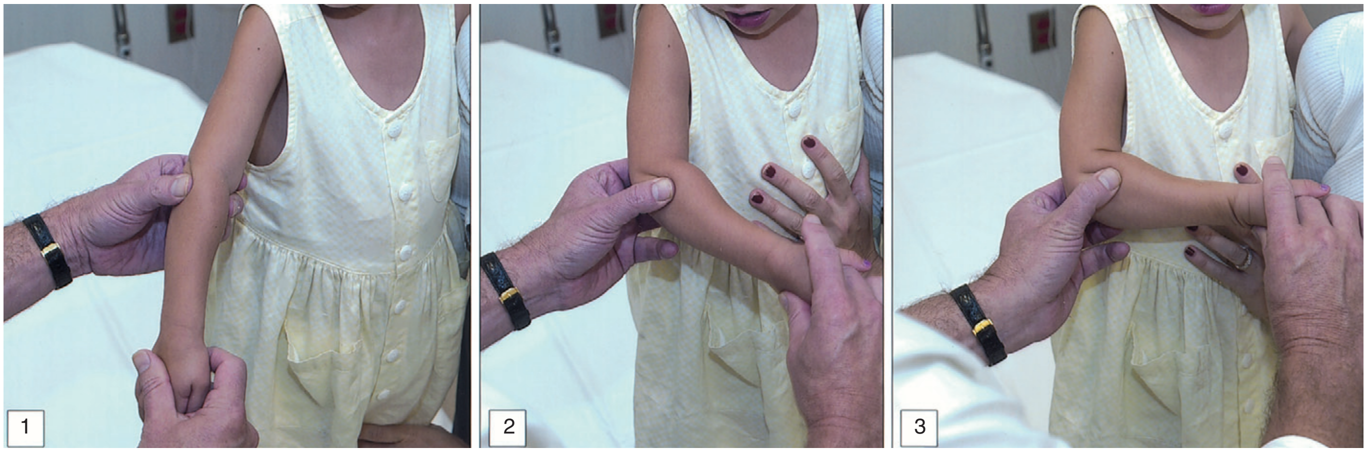


Figure 52-32. Subluxation of the radial head. Method of reduction: *(1)* Apply pressure to radial head, *(2)* supinate the forearm, and *(3)* flex elbow, in one continuous motion.

hyperplasia, a term subsequently modified to *angiofibroblastic tendinosis.* The cause has been theorized to be a degenerative process because of the paucity of acute inflammatory cells seen histologically.[43] Medial tennis elbow and posterior tennis elbow have been reported, the former involving the pronator teres and flexor carpi radialis insertions and the latter involving the triceps tendon. The following discussion pertains to lateral tennis elbow.

Clinical and Radiographic Features

Whatever the cause, the onset is usually gradual. Patients report dull pain over the lateral aspect of the elbow, increased by grasping or twisting motions. Tenderness is located over the lateral epicondyle or radiohumeral joint. Supination and pronation against resistance may be painful. Pain can be shown by stretching the wrist extensors. To test this, the elbow is extended, the forearm pronated, and the wrist fully dorsiflexed.

Radiographic findings may be normal, although with chronicity, calcifications may be present over the lateral epicondyle. Characteristic MRI findings also have been described, although MRI is not indicated emergently.

Management

Traditional treatment includes protection, rest, ice, compression, elevation, and medication. Initial therapy includes avoidance of the inciting activity and immobilization with a sling. Nonsteroidal anti-inflammatory drugs are often used, but their efficacy probably is limited to their analgesic rather than their anti-inflammatory properties. Injection of a corticosteroid at the point of tenderness provides some pain relief in most patients.[43,44] Because corticosteroids weaken collagen, premature resumption of heavy loading of the tendon at the lesion should be avoided, as should injection directly into the tendon. Patients with pain that persists despite treatment and a rehabilitation program should be referred for possible surgery.[45] Modification of athletic technique is recommended after the symptoms subside.

Olecranon Bursitis

Pathophysiology

Although several bursae are located in the elbow region, the olecranon bursa is the one most often involved in an isolated pathologic process. Olecranon bursitis commonly is caused by repetitive

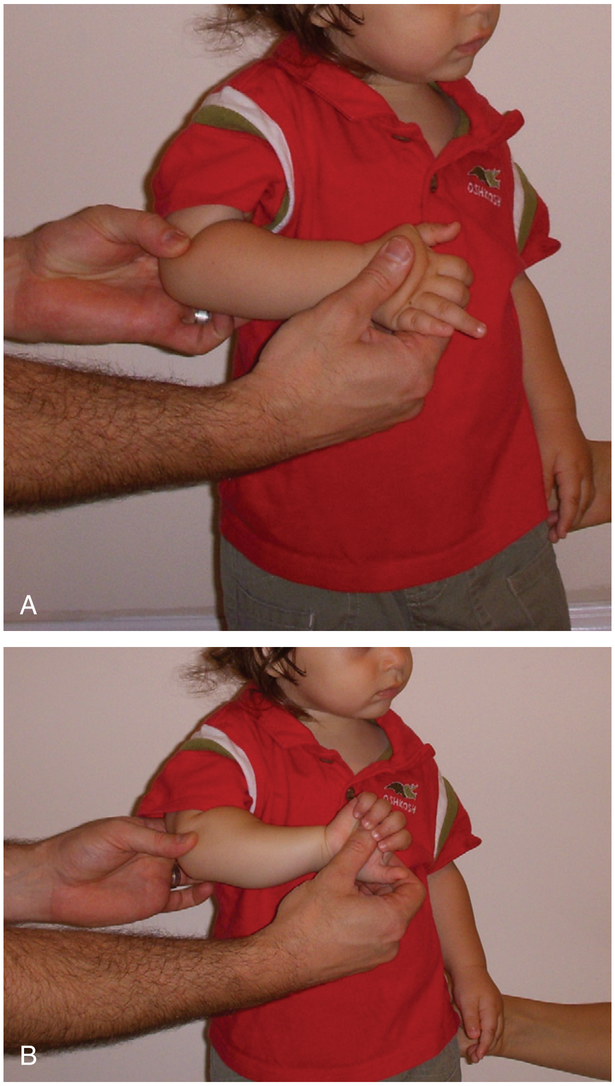


Figure 52-33. Hyperpronation method of radial head subluxation reduction: **A,** Support elbow with pressure to radial head, then hyperpronate the arm distally **(B)**.

www.ketabpezeshki.com 66485457-66963820

minor trauma, such as leaning on the elbow during work activities. It also may result from an inflammatory process, such as gout or an infectious process within the bursa (septic bursitis). Septic olecranon bursitis occurs most commonly in patients engaged in work that predisposes to repetitive trauma to the elbow, such as gardening or plumbing.

Clinical Features

Patients usually have progressive pain, tenderness, and swelling over the olecranon. Some patients with septic bursitis have an abrupt onset instead, with a rapid increase in pain over a few hours. On examination, the septic bursa is typically swollen, hot, erythematous, and tender. Flexion often is limited by pain brought on by tightening of the skin over the inflamed bursa. Minor breaks in the skin, frank abrasions, or healing lacerations over the bursa may be present. Noninfectious bursitis usually manifests with less warmth and erythema. The skin is intact, and swelling may be the only finding. The most important aspect of evaluation is the differentiation of a septic process from a benign inflammatory one. This differentiation may be difficult on clinical grounds because considerable overlap exists in the histories and physical findings.

Diagnostic Strategies

If doubt exists, aspiration of the bursa should be performed and the aspirate sent for crystals, white blood cell count, Gram's stain, and cultures. Unless the aspirate is frankly bloody, traumatic nonseptic olecranon bursitis usually has a leukocyte count lower than 1000 cells/mm^3, whereas septic bursal fluid usually has a count higher than 10,000 white blood cells/mm^3.

Management

Aspiration is diagnostic and therapeutic because relief of pressure relieves some of the pain. In cases of purulent bursitis, the bursa should be drained, and appropriate antibiotics should be begun in the ED. Pending culture results, empirical antibiotics should include coverage for routine skin organisms as well as methicillin-resistant *Staphylococcus aureus* (MRSA). Bursitis refractory to aspiration and appropriate antibiotics may require incision and drainage. Noninfectious bursitis can be managed with a compression dressing, ice, nonsteroidal anti-inflammatory medications, and avoidance of the inciting activity. Patients who have had their bursa aspirated should be rechecked within 24 to 48 hours to verify culture results and monitor their response to treatment.

Biceps Tendon Rupture

Pathophysiology

Biceps tendon rupture occurs most commonly in the proximal portion of the long head of the biceps. It is most common in middle-aged athletes or physical laborers who sustain repetitive microtrauma to the tendon. Patients experience a snapping sound and pain in the anterior shoulder during strenuous activities that produce rapid loading of the muscle. Rupture also occurs distally, usually as an avulsion from the insertion on the radial tuberosity, although ruptures at the musculotendinous junction occasionally occur. Rupture of the distal biceps tendon occurs almost exclusively in men, most commonly between the ages of 40 and 60, and most often involves the dominant arm.[46-47] The inciting event is usually an unexpected extension force applied to the arm flexed at 90 degrees. The pathophysiology of tendon rupture is poorly understood, although tendon rupture generally occurs in the setting of underlying tendinosis. Biceps tendon tears are becoming more common in players in the National Football League (NFL), most commonly in offensive linemen.[48] Diabetes, chronic renal failure, systemic lupus erythematosus, rheumatoid arthritis, and steroid or fluoroquinolone therapy all may result in tendinosis. Smoking has been shown to be strongly associated with distal biceps tendon rupture.[49]

Clinical Features

The diagnosis is usually obvious. In proximal tendon rupture, the patient usually has a visible defect at the top of the bicipital groove with bunching of the muscle distally. Flexing of the elbow produces pain at the proximal insertion. Flexion remains intact, however, because the short head of the biceps usually maintains its integrity. With distal ruptures the patient reports pain and tearing in the antecubital region. Visible deformity and a palpable defect of the biceps muscle belly are present with weakness of elbow flexion and supination. If the tendon is completely ruptured, there is a bunching up of the muscle, and this effect is accentuated when the patient attempts flexion. Radiographs are not revealing and usually not necessary. MRI may be useful when a partial rupture is suggested.

Management

All patients require urgent referral to an orthopedist. Early anatomic repair of complete ruptures usually is recommended. Partial ruptures occasionally respond to conservative treatment but also may require surgical repair. The arm should be splinted and the patient advised to apply ice and be given analgesics while awaiting orthopedic consultation.

KEY CONCEPTS

- Clinical decision rules for the elbow joint have not been validated. Radiographs should be obtained when there is limitation in range of motion, obvious deformity, joint effusion, or significant tenderness or crepitus over any of the bony prominences or the radial head. In the absence of these, it would seem appropriate to omit radiographs in adults. The threshold for imaging should be lower in pediatric patients owing to the presence of open growth plates and limitations to the physical examination.
- In children with wrist pain and traumatic mechanism of injury, the absence of a clear-cut explanation for the pain (e.g., no abnormal radiographic findings) should prompt consideration of an elbow injury causing referred pain to the wrist.
- In the setting of trauma, more than 90% of patients with the posterior fat pad sign of the elbow have intra-articular skeletal injury. In adults, a radial head fracture is implied, whereas in children, a supracondylar fracture is the probable underlying injury. In the absence of trauma, other causes of effusion (e.g., gout, infection, or bursitis) should be considered.
- The most common complication, radial nerve injury, occurs in 20% of humerus fractures. This is most often a benign neurapraxia that resolves spontaneously in most patients, although recovery may take several months. Radial nerve injuries associated with penetrating trauma or open fractures are likely to be permanent and usually warrant operative exploration.
- Generally the radius and ulna, bound together firmly by the annular ligament and interosseous membrane, displace as a unit and typically dislocate posteriorly, although anterior, medial, or lateral dislocations may occur.
- Radiographic studies are not required when the history suggests radial head dislocation (nursemaid's elbow). If there

www.ketabpezeshki.com 66485457-66963820

is swelling or deformity, if there is an uncharacteristic history, if the child does not resume use of the arm after reduction, or if there is a suggestion of child abuse, appropriate radiographic studies should be obtained.

- Biceps tendon rupture occurs almost exclusively in men, most commonly between ages 40 to 60, most often involving the dominant arm, and usually subsequent to an unexpected extension force applied to the arm flexed at 90 degrees. Smoking, diabetes, chronic renal failure, systemic lupus erythematosus, rheumatoid arthritis, and steroid or fluoroquinolone therapy may predispose to this injury. This injury is increasing in frequency in NFL players, usually in offensive linemen, and may become more common in college athletes as well.

ACKNOWLEDGMENT

We would like to thank Drs. Joel M. Geiderman and Sam S. Torbabi for their work on this chapter in previous editions.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Paraskevas G, et al: Study of the carrying angle of the human elbow joint in full extension: A morphometric analysis. *Surg Radiol Anat* 2004; 26:19.
2. Silva M, et al: Inter- and intra-observer reliability of the Baumann angle of the humerus in children with supracondylar humeral fractures. *Int Orthop* 2010; 34:553-557.
3. Chen FS, Diaz VA, Loebenberg M, Rosen JE: Shoulder and elbow injuries in the skeletally immature athlete. *J Am Acad Orthop Surg* 2005; 13:172.
4. Shao YC, Harwood P, Grotz MR, Limb D, Giannoudis PV: Radial nerve palsy associated with fractures of the shaft of the humerus: A systematic review. *J Bone Joint Surg Br* 2005; 87:1647-1652.
5. Hobgood ER, Khan SO, Field LD: Acute dislocations of the elbow. *Hand Clin* 2008; 24:10.
6. Beaty JA, Kasser JR: *The elbow region: General concepts in the pediatric patient*. In: Beaty JA, Kasser JR, eds. *Rockwood and Wilkins' Fractures in Children*, 5th ed. Philadelphia: Lippincott, Williams and Wilkins, 2005:563-576.
7. Ilyas AM, Jupiter JB: Treatment of distal humerus fractures. *Acta Chir Orthop Traumatol Cech* 2008; 75:6.
8. Gadgil A, Hayhurst C, Maffulli N, Dwyer JS: Elevated-straight arm traction for supracondylar fractures of the humerus in children. *J Bone Joint Surg Br* 2005; 87:82.
9. Pollock JW, Faber KJ, Athwal GS: Distal humerus fractures. *Orthop Clin North Am* 2008; 39:187.
10. Omid R, Choi PD, Skaggs DL: Supracondylar humeral fractures in children. *J Bone Joint Sur Am* 2008; 90:1121.
11. Slongo T, Schmid T, Wilkins K, Joeris A: Lateral external fixation—a new surgical technique for displaced unreducible supracondylar humeral fractures in children. *J Bone Joint Surg Am* 2008; 90:1690.
12. Skaggs DL, et al: Operative treatment of supracondylar fractures of the humerus in children: The consequences of pin placement. *J Bone Joint Surg Am* 2001; 83:735.
13. Weiland AJ, Meyer S, Tolo VT, Berg HL, Mueller J: Surgical treatment of displaced supracondylar fractures of the humerus in children. Analysis of fifty-two cases followed for five to fifteen years. *J Bone Joint Surg Am* 1978; 60:657.
14. Hodge D 3rd, Gregg J, Christofersen M, Wong J: Trauma to elbows, knees, and ankles. *Pediatr Emerg Care* 1991; 7:188.
15. Ramachandran M, Birch R, Eastwood DM: Clinical outcome of nerve injuries associated with supracondylar fractures of the humerus in children. *J Bone Joint Surg Br* 2006; 88:90.
16. Wong AS, Baratz ME: Elbow fractures: Distal humerus. *J Hand Surg Am* 2009; 34:176-190.
17. Gupta R, Khanchandrani P: Intercondylar fractures of the distal humerus in adults: A critical review of 55 cases. *Injury* 2002; 33:511.
18. Robinson CM, Hill RM, Jacobs N, Dall G, Court-Brown CM: Adult distal humeral metaphyseal fractures: Epidemiology and results of treatment. *J Orthop Trauma* 2003; 17:38-47.
19. Ring D: *Elbow fractures and dislocations*. In: Bucholz RW, et al, eds. *Rockwood and Greene's Fractures in Adults*, 7th ed. Philadelphia: Lippincott, Williams, and Wilkins, 2010.
20. Kramer DE: Elbow pain and injury in young athletes. *J Pediatr Orthop* 2010; 30:S7.
21. Shrader MW: Pediatric supracondylar fractures and pediatric physeal elbow fractures. *Orthop Clin North Am* 2008; 39:163.
22. Weiss JM, et al: A new classification system predictive of complications in surgically-treated pediatric humeral lateral condyle fractures. *J Pediatr Orthop* 2009; 29:602-605.
23. Leet AI, Young C, Hoffer M: Medial condyle fractures of the humerus in children. *J Pediatr Orthop* 2002; 22:2.
24. Dubberley JH, Faber KJ, Macdermid JC, Patterson SD, King GJ: Outcome after open reduction and internal fixation of capitellar and trochlear fractures. *J Bone Joint Surg Am* 2006; 88:46.
25. Faber KJ: Coronal shear fractures of the distal humerus: The capitellum and trochlea. *Hand Clin* 2004; 20:455-464.
26. Farsetti P, Potenza V, Caterini R, Ippolito E: Long-term results of treatment of fractures of the medial humeral epicondyle in children. *J Bone Joint Surg Am* 2001; 83:1299.
27. Louahem DM, et al: Displaced medial epicondyle fractures of the humerus: Surgical treatment and results. A report of 139 cases. *Arch Orthop Trauma Surg* 2010; 130:649-655.
28. Khashaba A: Broken arm wrestler. *Br J Sports Med* 2000; 34:461-462.
29. Micheli LJ, Luke AC, Mintzer CM, Waters PM: Elbow arthroscopy in the pediatric and adolescent population. *Arthroscopy* 2001; 17:694.
30. Ring D, Jupiter J, Gulotta L: Articular fractures of the distal part of the humerus. *J Bone Joint Surg Am* 2003; 85:232-238.
31. Olsen SJ 2nd, Fleisig GS, Dun S, Loftice J, Andrews JR: Risk factors for shoulder and elbow injuries in adolescent baseball pitchers. *Am J Sports Med* 2006; 34:905.
32. Hang DW, Chao, CM, Hang YS: A clinical and roentgenographic study of Little League elbow. *Am J Sports Med* 2004; 32:79.
33. Kaas L, et al: Management of radial head fractures: Current concepts. *J Shoulder Elbow Surg* 2011; 3:34-40.
34. Karlsson MK, Hasserius R, Karlsson C, Besjakov J, Josefsson PO: Fractures of the olecranon: A 15- to 25-year followup of 73 patients. *Clin Orthop Relat Res* 2002; 403:205.
35. Chalidis BE, Papadopoulos PP, Sachinis NC, Dimitriou CG: Aspiration alone versus aspiration and bupivacaine injection in the treatment of undisplaced radial head fractures: A prospective randomized study. *J Shoulder Elbow Surg* 2009; 18:676-679.
36. Karlsson MK, et al: Comminuted fractures of the radial head. *Acta Orthop* 2010; 81:224-227.
37. Phillips CS, Segalman KA: Diagnosis and treatment of post-traumatic medial and lateral elbow ligament incompetence. *Hand Clin* 2002; 18:149.
38. Carter SJ, Germann CA, Dacus AA, Sweeney TW, Perron AD: Orthopedic pitfalls in the ED: Neurovascular injury associated with posterior elbow dislocations. *Am J Emerg Med* 2009; 28:960-965.
39. Carson S, Woolridge DP, Colletti J, Kilgore K: Pediatric upper extremity injuries. *Pediatr Clin North Am* 2006; 53:41.
40. Chasm RM, Swencki SA: Pediatric orthopedic emergencies. *Emerg Med Clin North Am* 2010; 28: 907.
41. Bek D, Yildiz C, Köse O, Sehirlioğlu A, Başbozkurt M: Pronation versus supination maneuvers for the reduction of 'pulled elbow': A randomized clinical trial. *Eur J Emerg Med* 2009; 16:135-138.
42. Kim MC, Eckhardt BP, Craig C, Kuhns LR: Ultrasonography of the annular ligament partial tear and recurrent "pulled elbow". *Pediatr Radiol* 2004; 34:999-1004.
43. Van Hofwegen C, Baker CL 3rd, Baker CL Jr: Epicondylitis in the athlete's elbow. *Clin Sports Med* 2010; 29:577-597.
44. Rinner CA, Ruch DS: Elbow tendinopathy and tendon ruptures: Epicondylitis. *J Hand Surg* 2009; 34:566.
45. Hay EM, Paterson SM, Lewis M, Hosie G, Croft P: Pragmatic randomised controlled trial of local corticosteroid injection and naproxen for treatment of lateral epicondylitis of elbow in primary care. *BMJ* 1999; 319:964.
46. Mariscalco MW, Saluan P: Upper extremity injuries in the adolescent athlete. *Sports Med Athrosc* 2011; 19:17.
47. Sutton KM, Dodds SD, Ahmad CS, Sethi PM: Surgical treatment of distal biceps rupture. *J Acad Orthop Surg* 2010; 18:139-148.
48. Anderson R: Biceps tendon rupture in NFL athletes. Presented to the NFL Physicians Society National Meeting, Indianapolis, Ind, February 25, 2011.
49. Safran M, Graham SM: Distal biceps tendon ruptures: Incidence, demographics, and the effect of smoking. *Clin Orthop Relat Res* 2002; 404:275.

www.ketabpezeshki.com 66485457-66963820

Chapter 53

Shoulder

Mohamud R. Daya and Rachel R. Bengtzen

PERSPECTIVE

The shoulder joint is a unique and complex articulation unit. It has the largest range of motion of any appendicular joint in the body and can be moved through a space that exceeds a hemisphere in extent. The nature of shoulder injuries has been long recognized: Wall paintings in Egyptian tombs from 3000 BCE show accurate drawings of manipulations (similar to the Kocher technique) used to reduce shoulder dislocations.[1] Hippocrates outlined the oldest known method for reduction of shoulder dislocations.[2]

Shoulder injuries are commonly encountered in emergency medicine. Statistical studies show that 8 to 13% of all athletic injuries involve the shoulder and that shoulder dislocations account for more than 50% of all major joint dislocations seen in the emergency department (ED). Almost every major sport or athletic activity involves use of the shoulder joint in one way or another. The shoulder can be injured by trauma (indirect or direct) or by overuse. Traumatic injuries tend to occur in contact sports such as football and ice hockey, whereas overuse injuries (impingement syndromes) are more common in swimming and baseball. Shoulder injuries also are common in wrestling, tennis, volleyball, and javelin throwing.[3]

In general, children are vulnerable to the same injuries as those incurred by adults; however, the presence of the epiphysis and its growth plate changes the pattern of injuries.[4] The strength of the joint capsule and its ligaments is two to five times greater than that of the epiphyseal plate. An injury that produces a sprain or dislocation in an adult often causes a fracture through the hypertrophic zone of the growth plate in a child. The shoulder girdle has epiphyseal plates at the acromion process, proximal humeral head, coracoid process, glenoid cavity, and medial end of the clavicle. Complete or greenstick fractures of the clavicle and fractures of the proximal humeral epiphysis are encountered more commonly in the pediatric population. Most shoulder injuries in children can be treated conservatively, with a good prognosis for full return of function.[4]

PRINCIPLES OF DISEASE

Anatomy

The shoulder girdle connects the upper extremity to the axial skeleton (Fig. 53-1). It consists of three bones, the *clavicle, humerus,* and *scapula;* three joints, the *acromioclavicular, glenohumeral,* and *sternoclavicular* joints; and one pseudoarticulation, the *scapulothoracic* pseudoarticulation.

The sternoclavicular joint (SCJ) represents the only true articulation between the upper extremity and the axial skeleton (Fig. 53-2). Stabilizers of this diarthrodial joint include the anterior and posterior sternoclavicular ligaments, the interclavicular ligament, and the costoclavicular ligament. The costoclavicular ligament opposes the pull of the sternocleidomastoid and is considered the most important stabilizing ligament.[5] The SCJ participates in all movements of the upper extremity and is the most moved joint in the body. The superior mediastinum with its great vessels, trachea, esophagus, thoracic duct, lung apices, and other important structures is immediately posterior to the joint.

The clavicle is an S-shaped bone that acts as a strut to support the upper extremity and keep it away from the chest wall. It articulates medially with the sternum and laterally with the acromion process. The clavicle provides the neck with an acceptable cosmetic appearance and protects the subclavian vessels and brachial plexus. Its middle third, which is thin and untethered, is the most commonly fractured segment.[6]

The acromioclavicular joint (ACJ) connects the lateral end of the clavicle with the medial aspect of the acromion process (Fig. 53-3). The diarthrodial ACJ has little or no bony stability and is dependent on the associated ligaments and muscles for support.[7] The weak acromioclavicular ligaments provide posterior support while the clavicular and acromial attachments of the deltoid and trapezius muscles provide static and dynamic support for the superior aspect of the joint. The most important stabilizers are the coracoclavicular ligaments (conoid and trapezoid), which provide vertical and anterior support.

The scapula is a flat triangular bone that forms the posterior aspect of the shoulder girdle. The thin body of the scapula lies flat against the posterior thorax and widens laterally to form the glenoid fossa. The scapula's thickened borders are the attachment sites for 18 muscle origins and insertions.[8] The thick muscle coat and ability to recoil along the posterior chest wall protect the scapula from both direct and indirect trauma.

A synovial membrane extends from the glenoid fossa to the humeral head. The membrane is large and redundant inferiorly to accommodate the extensive range of movement. Overlying the synovial membrane is a loose and redundant fibrous capsule. Anteriorly, the capsule is thickened to form the superior, middle, and inferior glenohumeral ligaments. The anterior band of the inferior glenohumeral ligament is the most important restraint to anterior glenohumeral dislocations.[9]

The glenohumeral articulation is a ball-and-socket–type joint that depends largely on associated capsule, muscles, and ligaments for stability (Fig. 53-4). A negative intracapsular pressure completes the stabilization mechanism.[9,10] The absence of bony stability permits a range of motion, however, that is greater than that of any other joint in the body.

The proximal humerus articulates with the glenoid fossa and provides for the attachment of many important muscles. The

www.ketabpezeshki.com 66485457-66963820

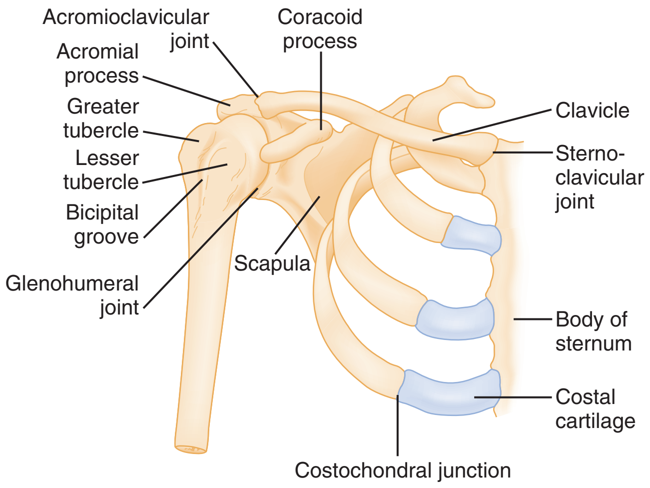


Figure 53-1. Anatomy of the shoulder girdle. (From Roy S, Irwin R: Sports Medicine: Prevention, Evaluation, Management and Rehabilitation. Englewood Cliffs, NJ, Prentice Hall, 1983.)

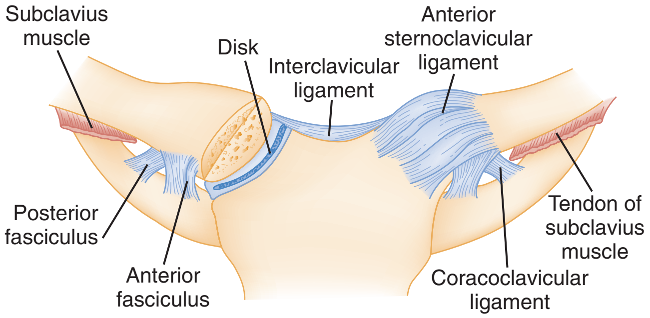


Figure 53-2. Ligaments and the interarticular disk of the sternoclavicular joint. (Redrawn from DePalma AF: Surgery of the Shoulder, 3rd ed. Philadelphia, JB Lippincott, 1983.)

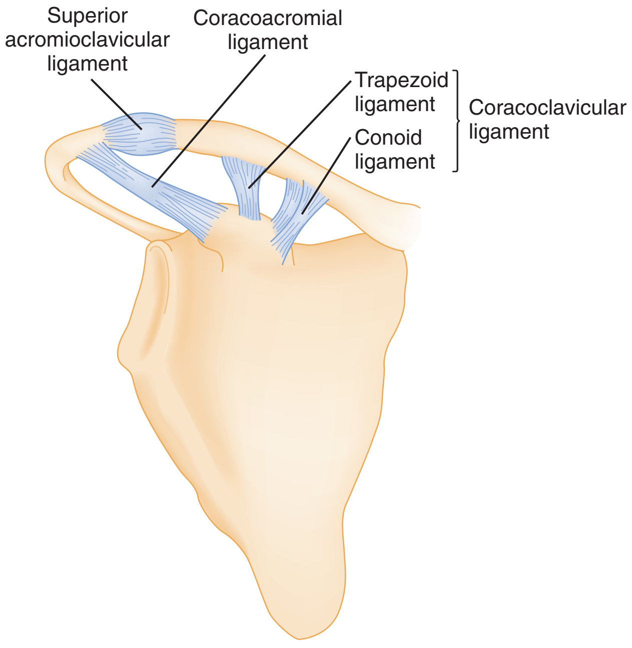


Figure 53-3. Ligaments of the acromioclavicular joint. (Redrawn from DePalma AF: Surgery of the Shoulder, 3rd ed. Philadelphia, JB Lippincott, 1983.)

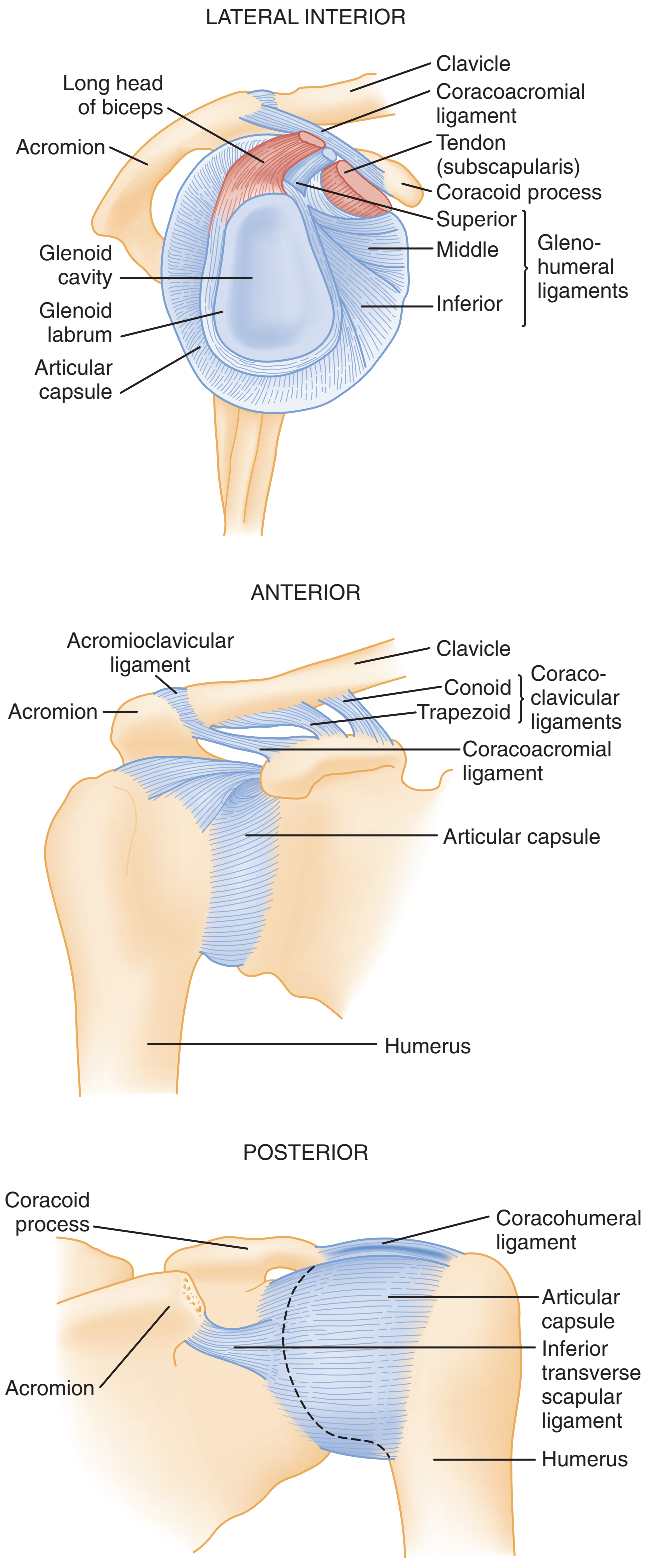


Figure 53-4. Anatomy of the glenohumeral joint.

supraspinatus, infraspinatus, and teres minor insert onto facets of the greater tuberosity, whereas the subscapularis inserts onto the lesser tuberosity. Together, this group of muscles forms the rotator cuff, which helps stabilize the humeral head within the glenohumeral joint (Fig. 53-5). The long head of the biceps tendon originates from the supraglenoid tubercle and ascends over the humeral head to enter the arm via the bicipital groove. The long head acts as an additional stabilizer for the superior

www.ketabpezeshki.com 66485457-66963820

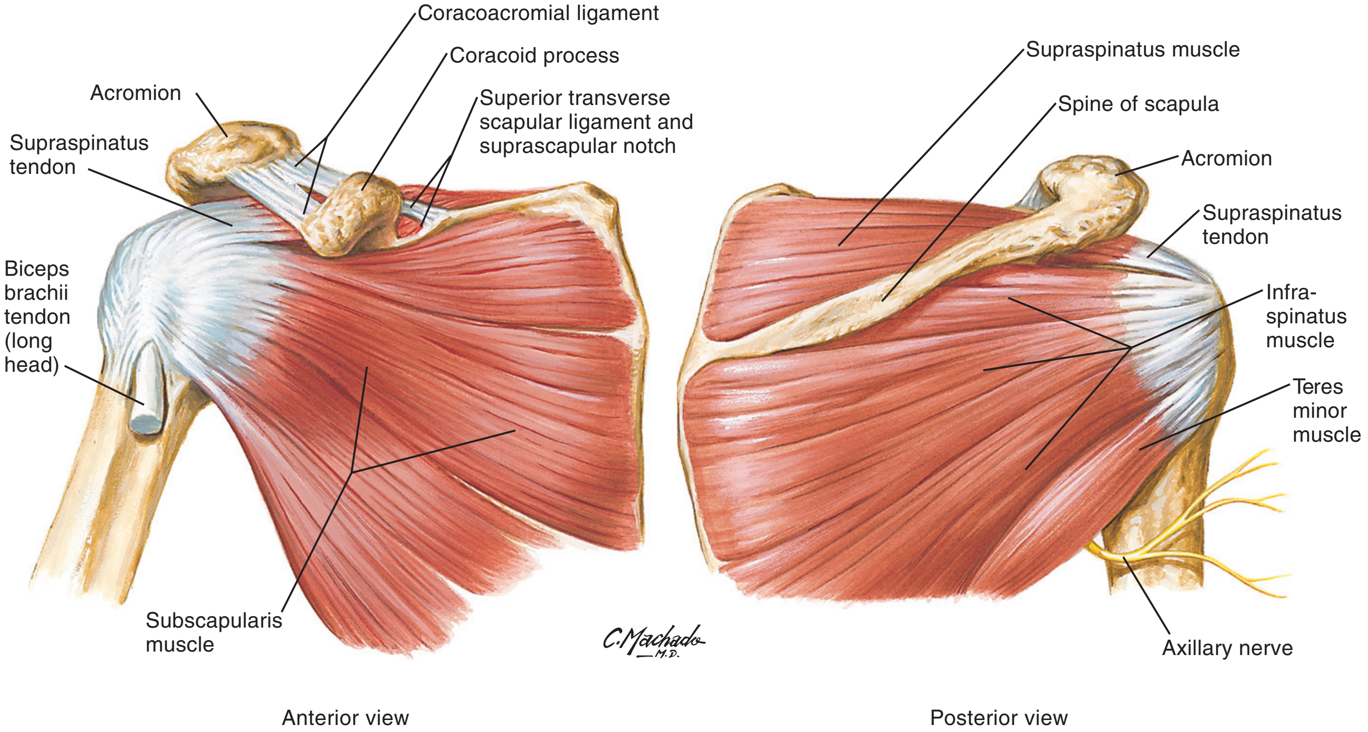


Figure 53-5. The rotator cuff: anterior view, posterior view, and the four muscles—subscapularis, supraspinatus, infraspinatus, teres minor. (Netter illustration from www.netterimages.com. Copyright Elsevier Inc. All rights reserved.)

and anterior aspects of the glenohumeral joint (see Fig. 53-5). Long muscles that cross the articulation are involved primarily in movements of the glenohumeral joint. The pectoralis major, latissimus dorsi, and teres major muscles all insert into the humeral intertubercular groove. Displacements encountered with fractures of the humerus usually reflect the pull of these attached muscle groups. The proximal humerus is composed primarily of trabecular bone with a thin cortical shell. Changes in bone density with age (osteoporosis) greatly increase the risk of fractures in this area.[6]

The brachial plexus and subclavian vessels enter the shoulder girdle complex superiorly between the clavicle and the first rib, traverse under the coracoid process, and exit anterior to the inferior aspect of the glenohumeral joint as the median, ulnar, and radial nerves and axillary vessels. These nerves represent the final branches of the upper brachial plexus (nerve roots C5 to C8), and injuries to the brachial plexus invariably result in significant shoulder dysfunction.

CLINICAL FEATURES

History

Most complaints usually involve some combination of pain, stiffness, instability, and weakness. Pain can result from many different conditions extrinsic and intrinsic to the shoulder. Extrinsic sources of shoulder pain include disorders of the cervical spine, thoracic outlet syndromes, and Pancoast tumors. In addition, pain can be referred to the shoulder from myocardial processes, diaphragmatic irritation (e.g., subphrenic abscess, lower lobe pneumonia, splenic hematoma, ruptured ectopic pregnancy, gallbladder disease), and gastric or pancreatic diseases.

Acute intrinsic pain usually is associated with a traumatic event. The most important factors to determine are the time and mechanism of injury, its precise location, the intensity of the pain, and associated sensorimotor complaints. Occasionally, the patient may have acute pain in the absence of associated trauma (e.g., with calcific tendinitis). Shoulder pain also can manifest in an insidious manner, unrelated to any precipitating factor. In these instances, the duration, location, character, and aggravating and alleviating factors of the pain should be noted. Intrinsic shoulder pain in general does not radiate past the elbow.

Stiffness usually signifies a restricted range of motion resulting from an underlying painful condition of the shoulder. Instability can be seen in the form of an obvious subluxation or dislocation. Alternatively, the patient may describe the sensation of the shoulder's almost "going out." A rotator cuff tear or an underlying nerve lesion usually causes significant shoulder weakness.

Physical Examination

The shoulder should be inspected from the anterior, posterior, and lateral positions. Any obvious deformity, ecchymosis, laceration, swelling, or hematoma should be noted. The masses of the trapezius, deltoid, infraspinatus, and supraspinatus muscles should be compared with the unaffected side to detect any atrophy.

Palpation of the shoulder should be performed systematically, beginning at the SCJ and moving laterally along the clavicle to the ACJ. Next, the scapula, glenohumeral joint, and humerus are palpated. Any point tenderness, crepitus, swelling, or deformity should be noted.

Active and passive ranges of motion should be tested. Active range of motion is best determined with the patient in the sitting position, which eliminates the contributions of the lumbar spine and lower extremity joints. Passive range of motion is best evaluated with the patient in the supine position. The degrees of abduction, forward flexion, extension, and internal and external rotation should be recorded and compared with those for the unaffected extremity. In addition, the motion of the scapulothoracic articulation should be observed carefully in all cases. After 45 degrees of abduction, the scapula moves approximately 1 degree for every 2 degrees of glenohumeral motion.

www.ketabpezeshki.com 66485457-66963820

The examination is completed with an assessment of the neurovascular function. A complete sensory (light touch and pinprick) and full motor examination of the brachial plexus should be performed. This examination is best performed by assessing the myotomes and dermatomes (Table 53-1) pertinent to each nerve root within the brachial plexus. The radial pulse should also be checked, although collateral circulation may preserve this in the presence of a vascular injury. The presence of pallor, paresthesias, or an expanding hematoma should raise suspicion for a vascular injury. The neurovascular examination should be repeated after any manipulation in the ED, and the findings recorded.

DIAGNOSTIC STRATEGIES

Radiology

The initial assessment of traumatic injuries includes a three-view series of radiographs consisting of true anteroposterior (AP) (45-degree lateral), transscapular lateral ("Y" view), and axillary lateral views (Figs. 53-6 and 53-7). The true AP view (see Fig. 53-7B) is preferred over standard AP views because it shows the glenohumeral joint without any bony overlap. Standard AP views taken with the joint in internal and external rotation profile the lesser and greater tuberosity and are more useful in the evaluation of soft tissue conditions.

Table 53-1 Sensory and Motor Components of the Brachial Plexus

SPINAL LEVEL	SENSORY AREA	MUSCLE
C2-4	—	Trapezius
C5	Lateral arm	Deltoid
C6	Lateral forearm and thumb	Biceps
C7	Tip of long finger	Thumb extensors
C8	Tip of little finger and medial forearm	Finger flexors
T1	Medial arm	Hand interossei

Acceptable orthogonal views include the axillary lateral, transscapular lateral, and apical oblique.[11] The preferred view is the axillary lateral (see Fig. 53-7A), which projects the glenohumeral joint in a cephalocaudal plane. This view is particularly useful for defining the relationship of the humeral head with the glenoid fossa and in identifying lesions of the coracoid process, humeral head, and glenoid rim. Some degree of abduction is required for the axillary view, and patient cooperation with this position may be limited by pain. The difficulty in obtaining this view has led to the popularity of the transscapular view (see Fig. 53-7B). Advantages of this projection include its simplicity and reproducibility and a clear delineation of anatomic structures. In this view the scapula is projected as a Y, with the body forming the lower limb and the coracoid and acromion processes forming the upper limbs. The humeral head normally is superimposed over the glenoid, which is located at the junction of the three limbs. This view is particularly useful in identifying anterior and posterior glenohumeral dislocations. The apical oblique view (obtained by having the patient stand bending forward, and angling the central ray 45 degrees caudally) shows the glenohumeral joint in a unique coronal projection. This view can be obtained easily and painlessly and has been found to be useful in evaluating for Hill-Sachs lesions in shoulder dislocations, and displacement and angulation of proximal humerus fractures.[11]

Plain radiographs are the mainstay of the radiologic examination in the ED, but in selected circumstances, additional bone and soft tissue details may be obtained via computed tomography (CT) or magnetic resonance imaging (MRI). Bedside ultrasonography is emerging as a reliable screening and diagnostic imaging modality for selected injuries, in particular fractures of the clavicle.[5,12]

SPECIFIC INJURIES

Fractures

Clavicle

Pathophysiology. The clavicle accounts for 5% of all fractures and is the most commonly fractured bone in children. Epidemiologic

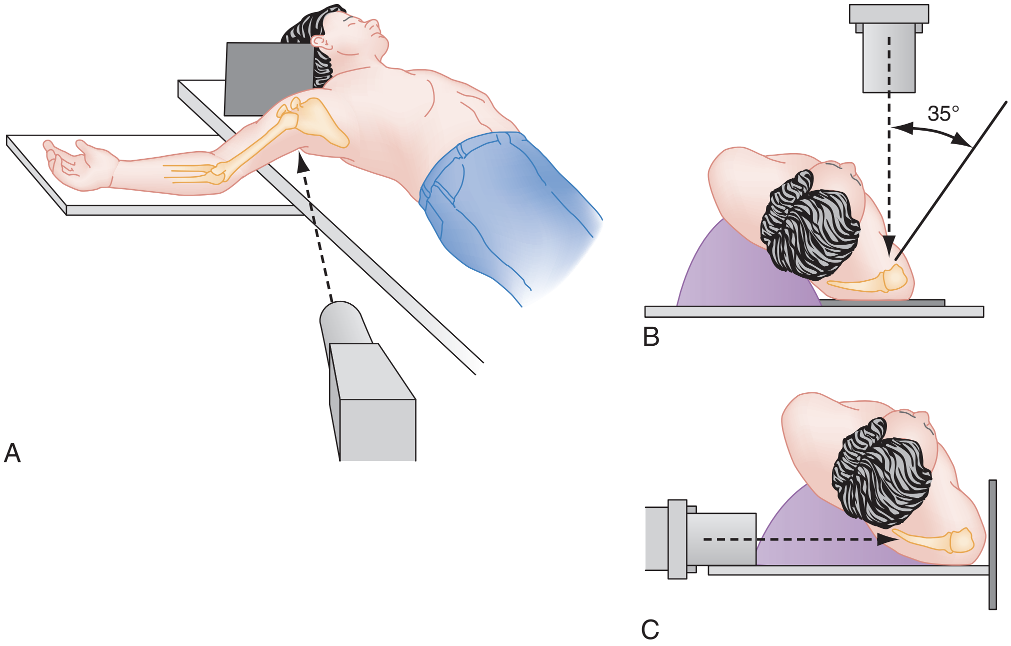


Figure 53-6. Positions for the trauma series of shoulder radiographs. **A,** Axillary view. **B,** True anteroposterior (35-degree oblique) view. **C,** Transscapular lateral "Y" view.

www.ketabpezeshki.com 66485457-66963820

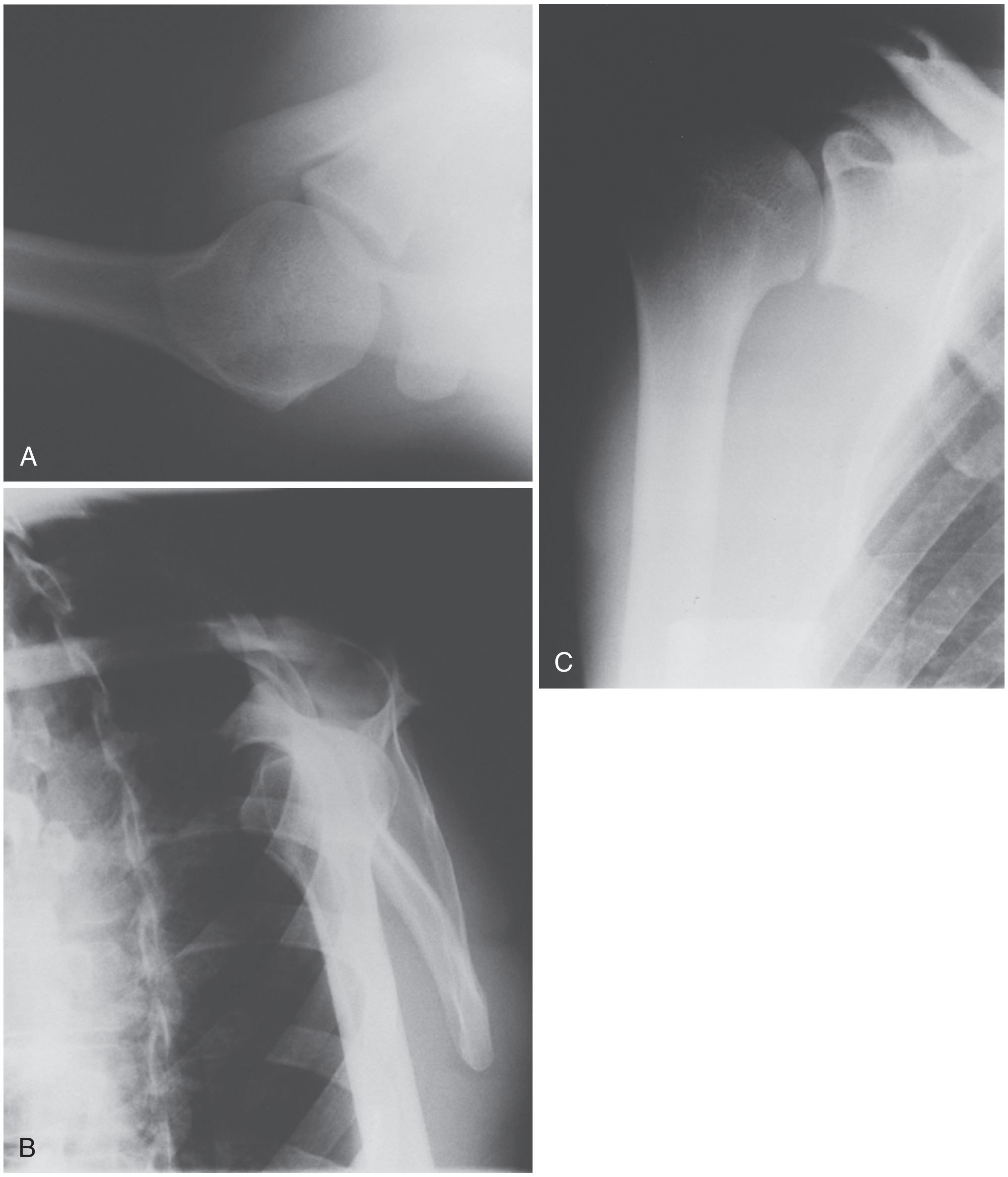


Figure 53-7. Normal: axillary **(A)**, true anteroposterior **(B)**, and transscapular lateral **(C)** radiographic views (i.e., trauma series) of the shoulder.

studies in adults have documented an annual incidence rate of 29 to 64 per 100,000 population, with a 2:1 male-to-female ratio.[13] Clavicular fractures are classified anatomically and mechanistically into three groups. Fractures of the medial third are uncommon (5%) and occur as a result of a direct blow to the anterior chest. Fractures of the middle third are the most frequent (Fig. 53-8), accounting for 80% of all injuries. The usual mechanism of injury involves a direct force applied to the lateral aspect of the shoulder as a result of a fall, sporting injury, or motor vehicle collision (MVC). Fractures of the lateral third (15%) result from a direct blow to the top of the shoulder and are classified further into three subtypes.[13] Type I fractures are stable and minimally displaced because the coracoclavicular ligament remains intact. Type II fractures are associated with a torn coracoclavicular ligament and have a tendency to displace because the proximal fragment lacks any stabilizing forces. Type III injuries involve the articular surface (Fig. 53-9).

Clinical Features. The patient has pain over the fracture site, and the affected extremity is held close to the body. With fractures of the middle third, the shoulder typically is slumped downward, forward, and inward. This positioning is a result of the effect of gravity and the pull of the pectoralis major and latissimus dorsi on the distal fragment. The proximal fragment often is displaced upward by the action of the sternocleidomastoid. The head is often tilted toward the injured side in an attempt to relax the effects of these displacing muscular forces. Ecchymosis, crepitus, and a palpable or visible deformity may be noted over the fracture site.

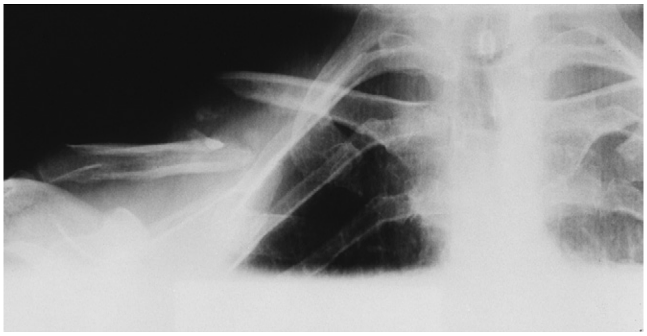


Figure 53-8. Displaced midclavicular fracture.

www.ketabpezeshki.com 66485457-66963820

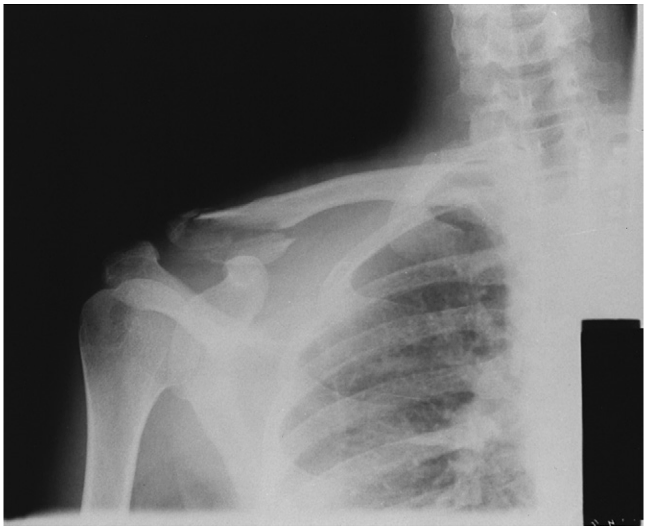


Figure 53-9. Type III lateral clavicular fracture (intra-articular). (Courtesy David Nelson, MD.)

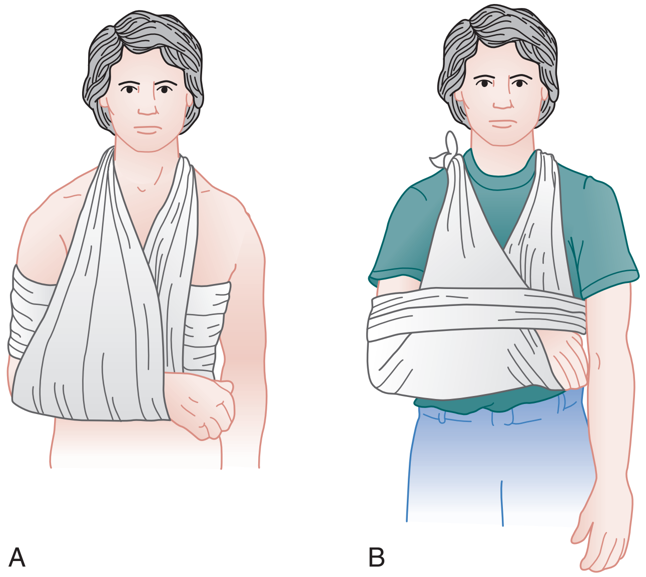


Figure 53-11. Shoulder immobilization. **A,** Sling over swathe. **B,** Velpeau sling immobilization.

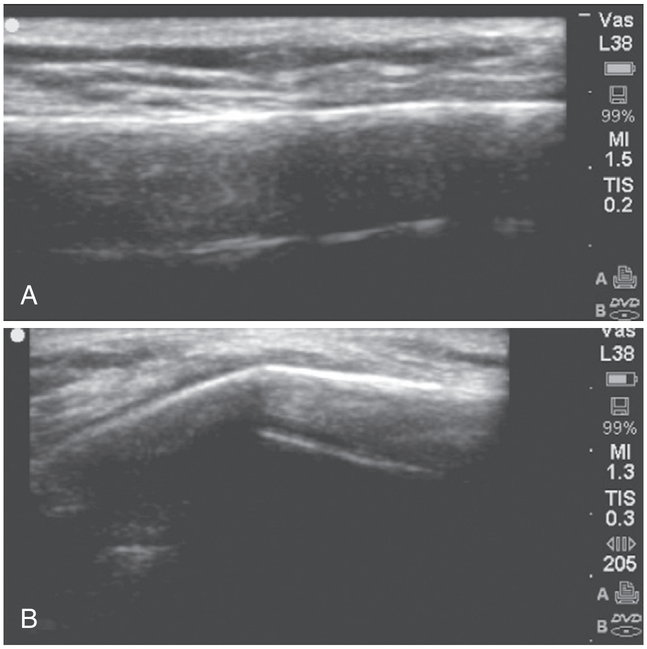


Figure 53-10. Ultrasound images of the clavicle. **A,** Normal. **B,** Midclavicular fracture. (Courtesy Keith Cross, MD.)

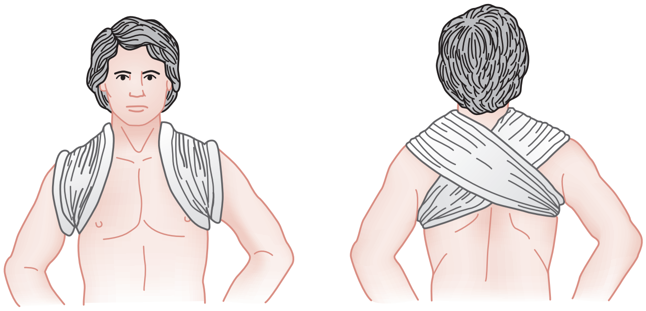


Figure 53-12. Clavicular or figure-of-eight splint.

Examine thoroughly for any tenting of the skin, as this can cause pressure necrosis and progression to an open fracture. Although associated neurovascular injury is rare, the close proximity of the subclavian vessels and brachial plexus demands a thorough assessment. Associated pneumothorax and pulmonary injuries are also rare unless an open or medial third fracture is present.[14] Clavicle-specific plain radiographs should be obtained to confirm the presence of a fracture.[12] The newborn clavicle fracture sustained during birth classically manifests as an uneventful "lump," representing the area of subsequent callus formation, in a child brought in by a concerned parent. Fractures in children, especially neonates, can also be reliably diagnosed or ruled out by bedside ultrasound, sparing the infant exposure to radiation (Fig. 53-10).

Management. Principles of initial management include pain control, immobilization, and proper follow-up care. Fractures of the clavicle can be immobilized with supportive devices, such as a simple sling or sling and swathe (Fig. 53-11). Another immobilization technique for midclavicular fractures still recommended in the orthopedic literature, although its efficacy is not supported by evidence, is the clavicular (figure-of-eight) splint (Fig. 53-12). This splint is applied after closed reduction of the fracture, which is accomplished by pulling the shoulders up and back. Such reductions are difficult to maintain and may be associated with increased discomfort at the fracture site. Use of clavicular splints also can lead to skin irritation and compression of the neurovascular bundle in the axilla. Because some degrees of malunion and shortening are associated with an acceptable functional and cosmetic outcome, treatment with a simple sling is a valid and appropriate alternative to the clavicular splint in the ED.

Disposition. Immediate orthopedic consultation should be sought for open fractures or fractures associated with neurovascular injuries, skin tenting, or interposition of soft tissues. More urgent orthopedic consultation (before 72 hours) is recommended for type II lateral clavicle fractures because these fractures have up to a 30% incidence of nonunion and may require surgical repair.[13] Severely comminuted or displaced fractures of the middle third (defined as over 20 mm of initial shortening) may also benefit from early orthopedic referral for consideration of operative reduction, because these have been associated with a higher incidence of nonunion and long-term functional deficits.[14,15] Additional risk factors that have been associated with nonunion in midclavicular fractures include female gender and advancing age.[16]

www.ketabpezeshki.com 66485457-66963820

Greenstick fractures of the midclavicle are common in children (Fig. 53-13). Most of these fractures are nondisplaced and heal uneventfully. Initial radiographs may appear normal despite suggestive clinical findings. In these instances, the arm should be immobilized in a simple sling and the radiographic evaluation repeated in 7 to 10 days if pain persists, to evaluate for early callus formation.

Most fractures of the clavicle heal uneventfully, and follow-up can be provided by a primary care physician. A sling should be worn until repeat radiographs show callus formation and healing across the fracture site. Early passive shoulder range-of-motion exercises (Fig. 53-14) are encouraged to reduce the risk of adhesive capsulitis (so-called "frozen shoulder"). Younger children generally require shorter periods of immobilization (2 to 4 weeks) than adolescents and adults (4 to 8 weeks). Vigorous competitive play should be avoided until the bone healing is solid. Full range of motion of the shoulder and an absence of pain are two good clinical signs that the fracture has healed.

Figure 53-13. Greenstick fracture of the clavicle *(arrow)*.

Complications. The most common complications are delayed union, nonunion, and symptomatic malunion.[13,17] Displaced fractures of the middle third have a 15 to 20% rate of nonunion and up to 25% rate of symptomatic malunion.[15] Vascular complications after fractures of the medial third can resemble those associated with posterior sternoclavicular dislocations. Articular surface injuries (type III lateral clavicle fractures) can lead to subsequent osteoarthritis of the ACJ.

An uncommon but important association is that between clavicle fractures and atlantoaxial rotatory displacement (AARD). Most cases occur in girls younger than 10 years. The pathophysiology may involve a lax or disrupted alar ligament along with sternocleidomastoid spasm. Early diagnosis is important because delayed diagnosis can lead to a chronic deformity requiring surgical correction. AARD should be suspected if the child has a clavicle fracture and demonstrates a "cocked-robin" position with the head bent toward the fractured side but rotated in the opposite direction. The injury is best demonstrated by CT and, if recognized early, can be treated with a soft cervical collar or halo traction.[18]

Scapula

Pathophysiology. Fractures of the scapula are rare, with an annual incidence of 10 to 12 per 100,000 population.[19] They account for 1% of all fractures and occur primarily in men 30 to 40 years old.[8] In general, considerable force and energy are required to

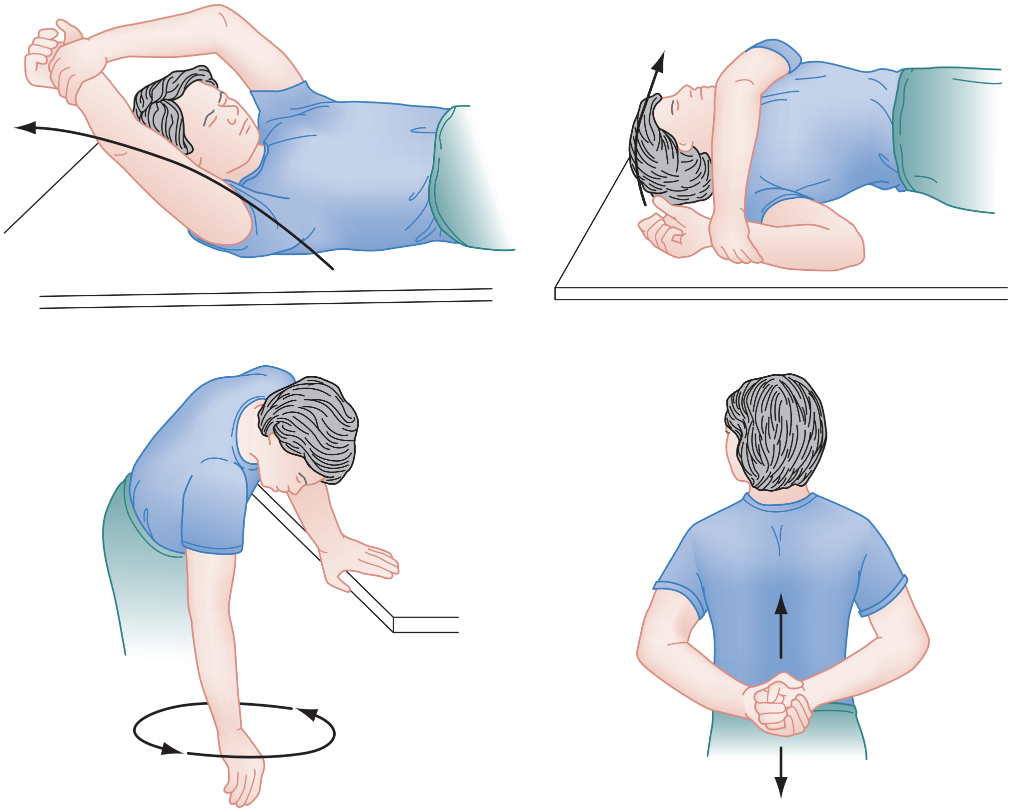


Figure 53-14. Types of active and passive shoulder exercises. *Top left,* active flexion; *top right,* active external rotation; *bottom left,* pendular; and, *bottom right,* active internal rotation.

www.ketabpezeshki.com 66485457-66963820

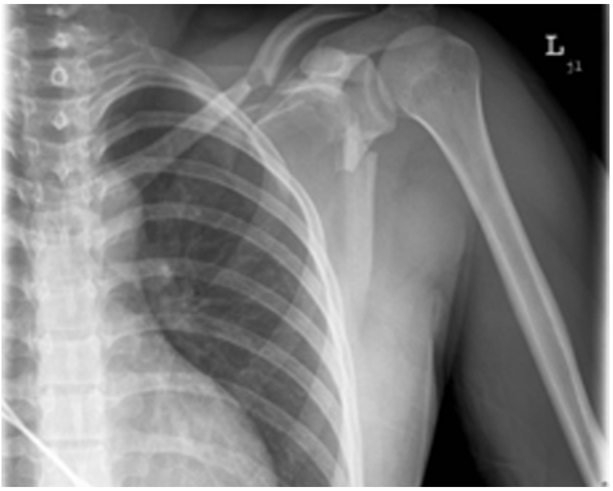


Figure 53-15. Type II scapular fracture involving the neck of the scapula. Note the associated midclavicular fracture.

fracture the body and neck of the scapula. Common mechanisms of injury include high-speed MVCs and falls from height.[20] Coracoid process fractures are usually avulsive, and glenoid rim fractures are commonly associated with anterior glenohumeral dislocations. Acromial or spinous process fractures result from blunt trauma to the top of the shoulder.[21]

The most important aspect of scapular fractures is the high incidence (75-98%) of associated injuries to the ipsilateral lung, chest wall, and shoulder girdle complex.[8,20] The most common associated orthopedic injuries are fractures of the ribs, proximal humerus, and clavicle. Associated lung injuries, including pneumothorax, hemothorax, and pulmonary contusion, usually occur acutely but may manifest in delayed fashion, 2 to 3 days after the initial injury. Associated injuries of the head, spinal cord, brachial plexus, and subclavian or axillary vessels are more significant but less common.[8,20] Of note, in a large series of blunt trauma admissions, the prevalence of aortic injury was similar in patients with or without a fractured scapula.[20]

Fractures of the scapula have traditionally been classified according to their anatomic location. Fractures can involve the acromion process, scapular spine, or coracoid process. Fractures can also involve the scapular neck (Fig. 53-15), glenoid fossa (intra-articular), and scapula body. Recently the Orthopaedic Trauma Association proposed a more comprehensive classification system that allows for a better understanding of severity and prognosis associated with these fractures. Fractures are divided into two main types: extra-articular and intra-articular (with partial or total glenoid involvement).[22]

Clinical Features. In a conscious patient, the shoulder is adducted and the arm is held close to the body. Any attempts at movement result in significant pain. Associated tenderness, crepitus, or hematoma may be noted over the fracture site. The clinical findings occasionally mimic those with a rotator cuff tear. Hemorrhage into the rotator cuff associated with the scapula fracture can result in spasm and a temporary reflex inhibition of function (pseudorupture).[21] The presence of a scapula fracture should prompt a thorough search for associated thoracic, intracranial, orthopedic, and neurovascular injuries.

Diagnostic Strategies: Radiology. The three-view trauma shoulder series will reveal most scapular fractures, as will careful examination of the scapula on the trauma chest radiograph. The true AP view best evaluates the glenohumeral joint, glenoid neck, and scapular body. The transscapular lateral view may demonstrate displacement of the glenoid and scapular body. The axillary lateral view is especially useful in evaluating fractures of the glenoid fossa and the acromion or coracoid process.[8,21] An os acromiale (unfused acromial process epiphysis) is present in 3% of the population and should not be confused with a fracture of the acromion.[6] A comparison film can be useful because the abnormality is present bilaterally in 60% of cases. In many patients, fractures of the scapula initially are overlooked despite being readily apparent on the initial supine trauma chest radiograph because of the life-threatening nature of the associated injuries.[8] Although additional dedicated scapula views can be obtained in the ED, the presence as well as the extent of scapular injury is best determined by CT. In the event that a trauma chest CT scan has been obtained to search for associated injuries, a three-dimensional reconstruction of the scapula should be requested to further define the nature and extent of the injury.[21,23]

Management. Most fractures, including fractures with severe comminution and displacement, heal rapidly with conservative therapy.[8,22] Initial therapy consists of analgesia and immobilization in a sling to support the ipsilateral upper extremity. Passive (see Fig. 53-14) followed by active range-of-motion shoulder exercises should be initiated as soon as discomfort subsides, to reduce the risk of adhesive capsulitis. Most patients require a sling for 2 to 4 weeks and close radiographic follow-up for assessment for delayed displacement.[21]

Fractures of the body and spine usually require no further therapy. Nondisplaced fractures of the acromion process also respond well to conservative therapy. Displaced acromial fractures that impinge on the glenohumeral joint require surgical management. Rarely, the acromion is fractured as part of a superior dislocation of the humeral head. In these instances, an accompanying tear of the rotator cuff is invariably present and requires surgical repair. If the coracoclavicular ligaments remain intact, fractures of the coracoid process respond well to conservative therapy. Severely displaced coracoid fractures with ruptured coracoclavicular ligaments usually require open reduction and internal fixation. Scapular neck and glenoid fossa fractures present the most difficult management issues. Although most of these injuries also do well with conservative therapy, open reduction and internal fixation may be recommended for severely displaced or angulated fractures.[21]

In a review of 520 scapula fractures from 22 case series, Zlowodzki and co-workers reported that 80% of all fractures with glenoid involvement were treated operatively, whereas 83% of all neck injuries and 99% of all isolated scapula body fractures were treated nonoperatively.[19]

Complications. Associated injuries of the ipsilateral lung, chest wall, and shoulder girdle account for most complications after fractures of the scapula. A shear-type brachial plexus injury has been associated with fractures of the acromion process. Neurovascular (brachial plexus, axillary artery) injuries also have been reported with fractures of the coracoid process, scapular neck, body, or spine fractures that extend into the suprascapular notch to injure the suprascapular nerve. The most common presenting symptom of a suprascapular nerve injury is dull posterior shoulder pain that is worsened by activity. The characteristic examination finding is atrophy of the scapular muscles along with weakness in abduction and external rotation Delayed complications include adhesive capsulitis and rotator cuff dysfunction.

Proximal Humerus

Pathophysiology. Fractures of the proximal humerus are common and account for 4 to 5% of all fractures.[24] An epidemiologic Swedish study reported an incidence of 14 to 60 per 100,000 per year, with a mean age at occurrence of 63 years and a female-to-male ratio of 1.5 : 1.[25] These fractures occur primarily in the older population, in whom structural changes associated with aging (osteoporosis) weaken the proximal humerus, predisposing it to

www.ketabpezeshki.com 66485457-66963820

injury. Although most of these injuries involve minimal displacement and are adequately managed with conservative therapy, significantly displaced fractures may require operative intervention. Displacements encountered with fractures of the humerus usually reflect the pull of the attached muscle group.

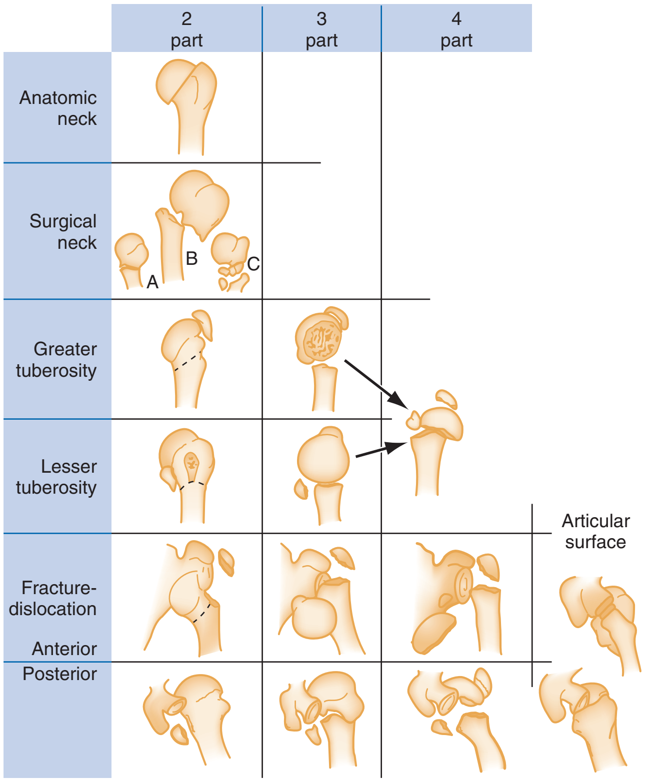


Figure 53-16. Neer's classification of proximal humeral fractures. (From Neer CS: Displaced proximal humeral fractures: Part 1. Classification and evaluation. J Bone Joint Surg Am 52:1077, 1979.)

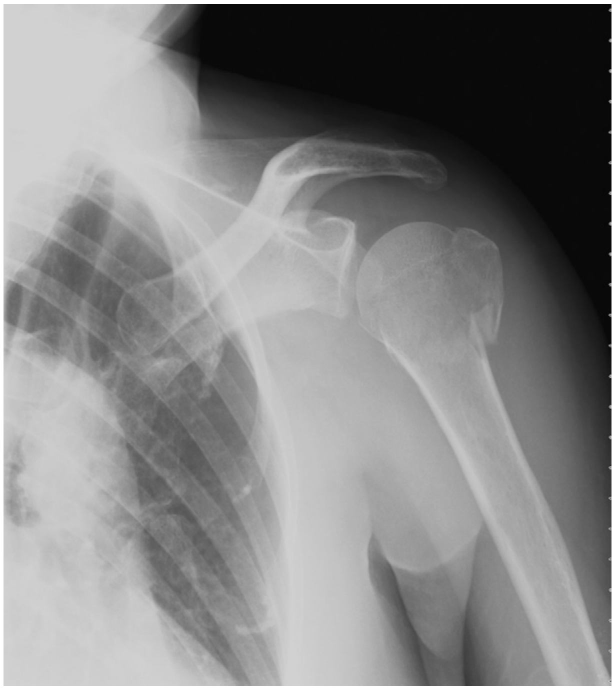


Figure 53-17. Three-part minimally displaced fracture of the proximal humerus involving the greater and lesser tuberosities.

Fractures of the proximal humerus separate along old epiphyseal lines, producing four distinct segments consisting of the articular surface (anatomic neck), greater tuberosity, lesser tuberosity, and humeral shaft (surgical neck). Neer's classification system (Fig. 53-16) is based on the relationship of these fracture fragments.[24] In this system, a segment is considered displaced if it is angled more than 45 degrees or separated more than 1 cm from the neighboring segment. Because this classification system considers only displacement, the number of fracture lines is irrelevant. There are four major categories of fracture: minimal displacement (Fig. 53-17), two-part displacement (Fig. 53-18), three-part displacement, and four-part displacement. When present, anterior and posterior dislocations are included as part of the classification. Impaction and head-splitting fractures are classified separately.

The classic mechanism of injury involves a fall on an outstretched abducted arm. Concurrent pronation limits further abduction and levers the humerus against the acromial process; this produces a fracture or dislocation, depending on the tensile strengths of the bone and surrounding ligaments. Older patients are prone to fracture, whereas younger persons are apt to have dislocations. The combined injury (fracture and dislocation) may be seen in middle-aged patients. Proximal humerus fractures also may result from a direct blow to the lateral side of the arm or from an axial load transmitted through the elbow. High-energy mechanisms and polytrauma are more common in younger persons.

Clinical Features. The affected arm is held close to the body, and movement is restricted by pain. Tenderness, hematoma, ecchymosis, deformity, or crepitus may be noted over the fracture site. A

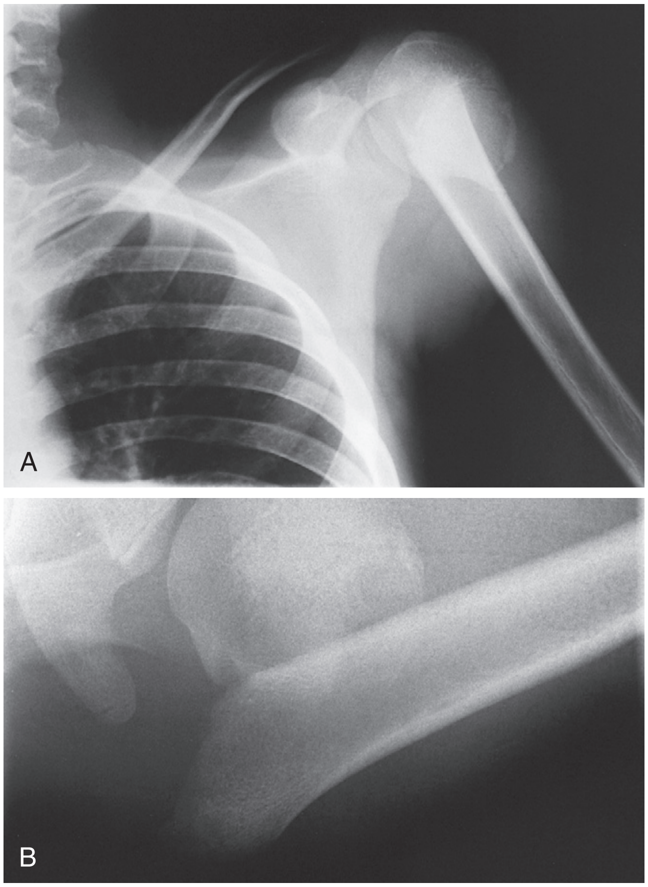


Figure 53-18. Anteroposterior (A) and axillary (B) radiographic views of a two-part displaced fracture of the proximal humerus. The degree of displacement often is better visualized on the axillary view. (Courtesy David Nelson, MD.)

www.ketabpezeshki.com 66485457-66963820

thorough neurovascular examination is essential to identify associated injuries of the axillary nerve, brachial plexus, or axillary artery (see Table 53-1). The three-view trauma series of shoulder radiographs will allow for assessment of the number of fracture fragments and degree of displacement or angulation.

Management. Minimally displaced fractures (see Fig. 53-17) constitute 80 to 85% of all cases. In these instances, limited displacement or angulation is present, and the fracture segments are held together by the capsule, periosteum, and surrounding muscles. Initial treatment consists of adequate analgesia and immobilization with a sling or sling and swathe device. The former is more comfortable, and a Cochrane review of 16 randomized trials found only limited evidence that use of special bandage immobilization affected time to fracture union or functional outcome.[26] Traditionally, it has been recommended that immobilization be continued until clinical union is achieved (head and shaft are seen to move together). The Cochrane review also noted that immediate or earlier commencement of physiotherapy (within 1 week) resulted in less pain and did not compromise long-term outcome. Initial passive exercises (see Fig. 53-14) are gradually replaced by more active and resistive exercises. Most nondisplaced fractures heal over 4 to 6 weeks.

The treatment of two-part, three-part, and four-part displaced fractures is beyond the scope of this discussion. An orthopedic surgeon should be consulted, because many of these injuries require operative repair.[24] Prospective and retrospective observational studies, however, have failed to show a significant functional difference between operative and nonoperative treatment of displaced two-part and three-part fractures in elderly patients. Current literature continues to support operative treatment of four-part fractures in the elderly; the procedure of choice is hemiarthroplasty.[26]

Fracture-dislocation injuries (Fig. 53-19) are best managed in consultation with an orthopedic surgeon before attempts at reduction (except in cases of neurovascular compromise or unavailability of an orthopedic surgeon). Of note, reductions of these injuries in the ED often are unsuccessful, and these manipulations can cause separation of previously undisplaced segments. Closed reduction under radiologic control and general anesthesia may be preferable.

Posterior glenohumeral dislocations usually are associated with anteromedial impression fractures of the articular surface. A similar fracture of the posterolateral aspect of the humeral head is present with anterior dislocations (Hill-Sachs deformity). Impression fractures involving less than 20% of the articular surface usually are stable. With more than 20% involvement, the reduction usually is unstable and requires surgical repair.

Complications. The most common complication of proximal humeral fractures is adhesive capsulitis. This complication can be prevented by the early initiation of pendular shoulder exercise, along with a thorough rehabilitation program. One of the most devastating complications is avascular necrosis (AVN) of the humeral head. The highest rate of AVN (up to 90%) has been documented for four-part fractures.[27] Repeated forceful attempts at reduction of fracture-dislocations may be associated with subsequent heterotopic bone formation (myositis ossificans). Neurovascular injuries (axillary nerve, brachial plexus, and axillary artery) may be encountered with displaced surgical neck fractures and fracture-dislocations.

Proximal Humeral Epiphysis

Pathophysiology. Fractures of the proximal humeral epiphysis are uncommon and account for less than 1% of all pediatric fractures.[28] The injury can occur at any age while the epiphysis remains open but is most common in adolescent boys. The most common mechanism of injury involves a fall onto the outstretched hand, and the fracture typically occurs through the zone of hypertrophy in the epiphyseal plate. Injuries can be classified according to their location (Salter system), stability, and degree of displacement.

Clinical Features. The patient holds the injured arm tightly against the body by the opposite hand. The area over the proximal humerus is swollen and extremely tender to palpation. Radiographs obtained at 90 degrees to each other confirm the diagnosis.

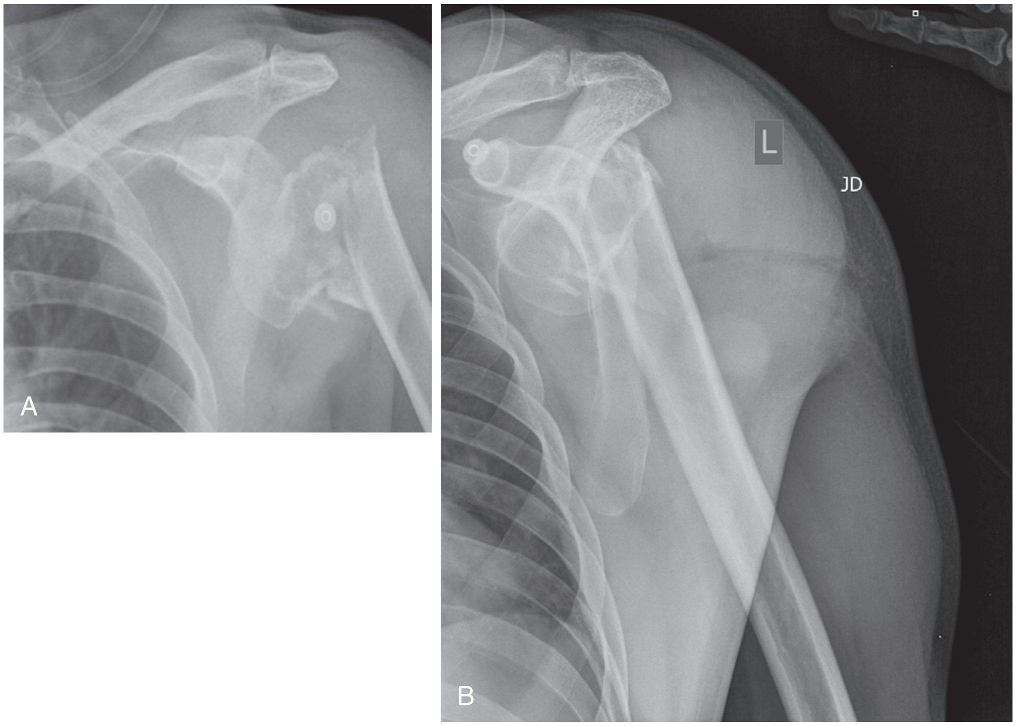


Figure 53-19. Two-part fracture and dislocation of the proximal humerus; anteroposterior (A) and transscapular lateral (B) radiographic views.

www.ketabpezeshki.com 66485457-66963820

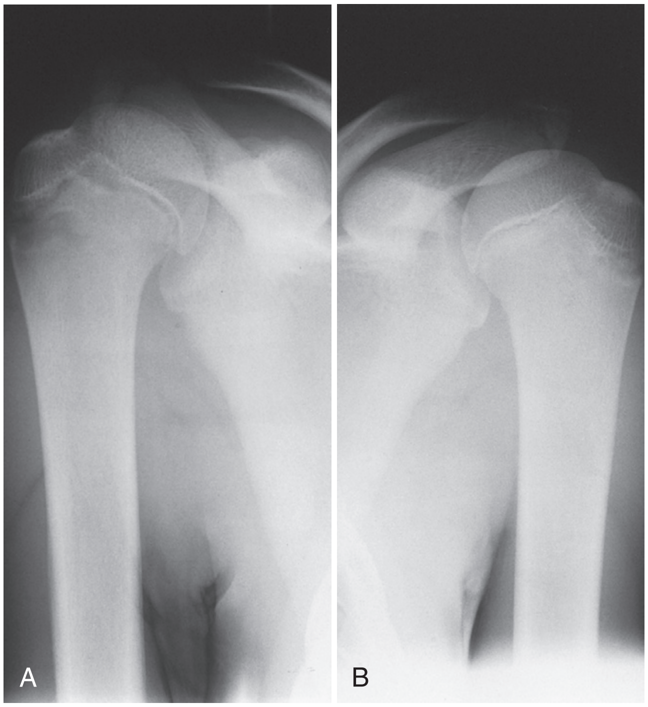


Figure 53-20. **A,** Salter I injury of the right proximal humeral epiphysis. **B,** Normal left side is included for comparison.

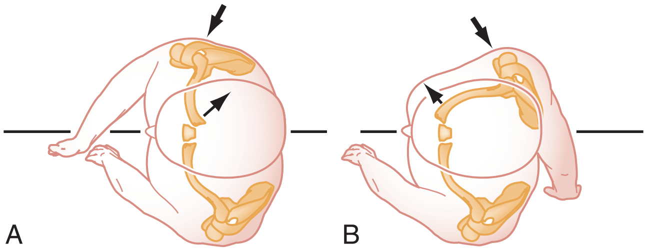


Figure 53-21. Mechanisms that produce anterior and posterior displacements of the sternoclavicular joint. **A,** When the patient is lying on the ground and a compression force *(upper arrow)* is applied to the posterolateral aspect of the shoulder, the medial end of the clavicle is displaced posteriorly *(lower arrow).* **B,** When the lateral compression force *(upper arrow)* is directed from the anterior position, the medial end of the clavicle is dislocated anteriorly *(lower arrow).* The same mechanism could apply with any type of lateral compression injury of the shoulder. (From Neer CS, Rockwood CA: Fractures and dislocations of the shoulder. In Rockwood CA, Green DP (eds). Fractures in Adults, 4th ed. Philadelphia, JB Lippincott, 1984.)

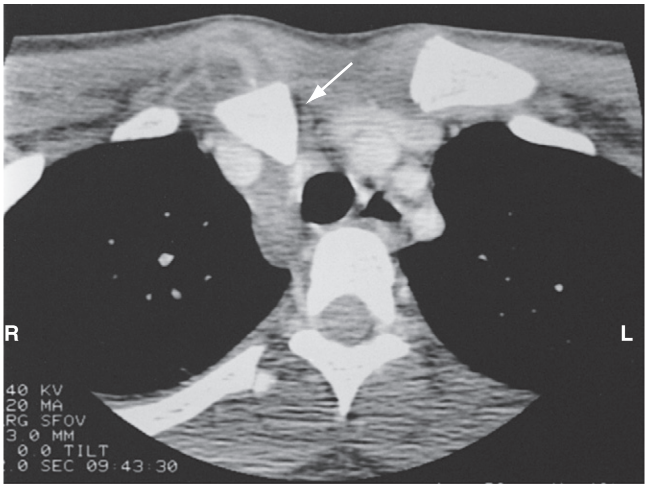


Figure 53-22. This computed tomography scan shows posterior dislocation of the right sternoclavicular joint *(arrow)* with compression of the superior mediastinum. (Courtesy Donald Sauser, MD.)

Comparison views may be helpful with minimally displaced fractures. Bedside ultrasound has also been shown to detect these injuries. In one series of 100 shoulder injury subjects, all three cases of proximal humerus fractures were detected by ultrasound imaging (sensitivity 83-93%) before shoulder radiographs had been obtained.[12]

Management. Fractures of the proximal humeral epiphysis should not be taken lightly, because the physis accounts for 80% of the growth of the bone. The active healing process at the site of an epiphyseal injury makes delayed reduction extremely difficult. Early orthopedic consultation should be obtained for all such injuries. Children younger than 6 years usually have Salter I epiphyseal injuries (Fig. 53-20), which can be treated conservatively with sling and swathe immobilization and analgesic agents. Children older than 6 years usually have a Salter II epiphyseal injury. Salter II injuries with more than 20 degrees of angulation may benefit from reduction, which is accomplished by reversing the mechanism of injury.[28] Imperfect reductions often are acceptable because growth and remodeling correct the deformity with time. After reduction, unstable injuries should be immobilized in a shoulder spica cast, whereas stable lesions can be immobilized with a sling and swathe. Fractures of the proximal humeral epiphyses generally heal in 3 to 5 weeks.[28]

Complications. Complications are rare and include malunion, growth plate disturbances, and injuries to the neurovascular bundle. Markedly displaced or angulated fractures are more likely to result in a residual loss of mobility.

Dislocations

Sternoclavicular

Pathophysiology. SCJ dislocations are infrequent and account for less than 1% of all dislocations.[29] Significant forces are required to disrupt the strong ligamentous stabilizers of this joint. The most common causes are MVCs and injuries sustained in contact sports. The SCJ can dislocate in an anterior or a posterior direction. Anterior dislocations, which result from indirect forces, are more common (9:1 ratio).[5] The usual mechanism of injury (Fig. 53-21) involves an anterolateral force to the shoulder, followed by backward rolling, which levers the medial clavicle out of its articulation. Posterior dislocations (Fig. 53-22) can result from a direct blow to the medial clavicle (30%) or from delivery of a posterolateral force to the shoulder, followed by inward rolling (70%). Posterior dislocations can be associated with life-threatening injuries within the superior mediastinum, including acute airway compression.

Injuries to the SCJ can be graded into three types.[5] A grade I injury is a mild sprain secondary to stretching of the sternoclavicular and costoclavicular ligaments. A grade II injury is associated with subluxation of the joint (anterior or posterior) secondary to rupture of the sternoclavicular ligament. The costoclavicular ligament remains intact. Complete rupture of the sternoclavicular and costoclavicular ligaments results in a grade III injury (dislocation). In patients younger than 25 years, these actually represent Salter type I injuries, because the medial epiphysis of the clavicle has not yet fused.[30]

Clinical Features. Clinical suspicion is the most important factor in diagnosing these injuries, and prompt diagnosis is vital because

www.ketabpezeshki.com 66485457-66963820

it is associated with a better prognosis. The injured extremity is flexed at the elbow and supported across the trunk by the opposite arm. Pain results from any movement of the upper extremity or lateral compression of the shoulders. The SCJ may be mildly swollen and tender to palpation. With an anterior dislocation, the displaced medial end of the clavicle may be palpable. Posterior dislocations are associated with more severe pain, and the neck is often flexed toward the injured side.[30] The clavicular notch of the sternum may be palpable, and complaints of hoarseness, dysphagia, dyspnea, and weakness or paresthesias in the upper extremities have been documented. Rarely, airway complications caused by tracheal injury may be present. If present, airway compromise should be attended to promptly. These patients should also be examined thoroughly to identify any injuries to superior mediastinal or intrathoracic structures. The presence of cyanosis and venous congestion of the neck and arm is typical of an innominate vein injury.[30] When necessary, appropriate consultation should be obtained.

Diagnostic Strategies: Radiology. Although the diagnosis of sternoclavicular dislocation can be made clinically, it should be confirmed radiologically. Findings on standard AP, oblique, and specialized (40-degree cephalic tilt) views often are difficult to interpret because of overlapping rib, sternum, and vertebral shadows. These dislocations and associated injuries are best visualized by CT (see Fig. 53-22). Ultrasound imaging also may be a useful adjunct in some circumstances.[5]

Management. Treatment of grade I injuries includes immobilization (simple sling), adequate analgesia, and primary care follow-up. Immobilization generally is maintained (1-2 weeks) until full painless motion is restored. Grade II injuries should be immobilized with a sling or soft clavicular (figure-of-eight) splint (see Fig. 53-12) and the patient referred for orthopedic follow-up care. The figure-of-eight splint is preferred because it maintains the clavicle in a more anatomic position and permits ligament healing. Grade II injuries require a longer course of immobilization (3-6 weeks) and are more likely to be associated with persistent pain.[5] All grade III injuries should be managed by closed reduction.

Anterior dislocations may be reduced in the ED after orthopedic consultation and intravenous analgesia (Fig. 53-23). A rolled sheet is placed posteriorly between the shoulder blades to elevate both shoulders approximately 5 cm above the table. Traction is applied to the arm in an extended (10- to 15-degree) and abducted (90-degree) position. If reduction does not occur, an assistant can add inward pressure on the medial end of the clavicle. Stable reductions should be maintained in a clavicular splint, and the patient referred for orthopedic follow-up care.[30] Most reductions are unstable. Because the deformity is primarily cosmetic and not functional, the current treatment of choice for recurrent anterior dislocations is benign neglect.

Posterior dislocations constitute true orthopedic emergencies and should be reduced expeditiously.[5,30] Ideally, reduction of posterior dislocations should be attempted in the operating room with the patient under general anesthesia, although it can be attempted in the ED with use of procedural sedation. Emergency reduction may be required for patients with airway obstruction or vascular compromise. The patient is positioned as described previously, and traction is applied in an extended and abducted position. If traction alone does not reduce the dislocation, concurrent clavicular manipulation may be helpful. After sterile preparation of the skin and administration of local anesthesia, the clavicle shaft is grasped with a sterile towel clip and pulled out anterolaterally. Once reduced, these injuries generally are stable and can be immobilized with a clavicular splint. An alternate method of reduction involves traction to the adducted injured arm while both shoulders simultaneously are forced posteriorly with direct pressure.[31] This technique levers the clavicle into place and requires much less force than the traditional abduction-extension method.

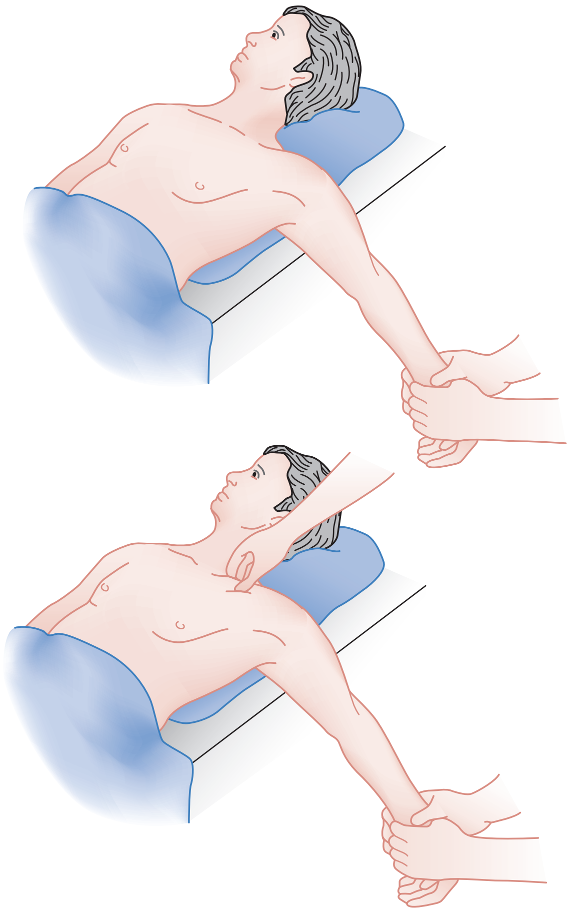


Figure 53-23. Reduction of dislocated sternoclavicular joints. (From Simon RR, Koenigsknecht SJ: Emergency Orthopedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

Complications. Complications of anterior injuries are primarily cosmetic. By contrast, 30% of posterior dislocations may be complicated by life-threatening injuries to intrathoracic and superior mediastinal structures.[30] Complications include compression or laceration of the great vessels, tracheoesophageal fistula, tracheal compression, pneumothorax, thoracic outlet syndrome, and brachial plexus injuries. These injuries are best visualized though a chest CT angiogram. A potential long-term complication of both anterior and posterior injuries is degenerative osteoarthritis, which manifests with pain and swelling over the joint or pain on shoulder movement.

Acromioclavicular Joint

Pathophysiology. Injuries of the ACJ occur primarily in young men as a result of participation in contact sports, such as football, rugby, ice hockey, and wrestling. A small percentage of injuries are caused by MVCs and falls.

The most common mechanism of injury involves a fall or direct blow to the point of the shoulder with the arm adducted. The resultant force drives the scapula downward and medially to produce the injury. The weak acromioclavicular ligaments rupture first. With increasing force, the coracoclavicular ligament ruptures, and the attachments of the deltoid and trapezius muscles are torn from the distal clavicle. The ACJ also can be injured after a fall onto the outstretched hand. In this instance, the force is

www.ketabpezeshki.com 66485457-66963820

transmitted to the acromioclavicular ligaments only, and the coracoclavicular ligament, which is relaxed, remains uninjured.

Classification is based on the degree of damage sustained by the acromioclavicular and coracoclavicular ligaments (Fig. 53-24). The most commonly used system is that modified by Rockwood.[32] Type I injuries are sprains of the acromioclavicular ligaments with no separation of the acromion and clavicle. Type II injuries are associated with disruption of the acromioclavicular ligaments. The joint space is widened, and the clavicle is displaced slightly upward. There are minor tears in the attachments of the deltoid and trapezius muscles, but the coracoclavicular ligament remains intact, and the coracoclavicular distance is maintained. A type III injury is characterized by complete disruption of the acromioclavicular ligaments, coracoclavicular ligament, and muscle attachments. The joint space is widened, and the coracoclavicular distance is increased by 25 to 100%. The clavicle is displaced upward by the pull of the trapezius, and the shoulder is displaced downward by the effect of gravity. In type IV and V injuries, the ligamentous and muscle disruptions are similar to the disruptions encountered in type III injuries, but the clavicle is displaced either posteriorly into the trapezius (type IV) or superiorly in an exaggerated fashion (coracoclavicular distance increased 100 to 300%; type V). In the rare type VI injury, the clavicle is displaced inferiorly.

Clinical Features. Patients should be examined while they are in the sitting or standing position because the supine position can mask ACJ instability. It is helpful to visualize both shoulders simultaneously to assess for symmetry. Type I and type II injuries are associated with mild tenderness and swelling over the ACJ margin, with minimal deformity. A full range of motion often is possible, although painful. Patients with type III, IV, V, and VI injuries usually have severe pain and hold the arm tightly adducted to reduce traction stress across the joint. In type III injuries, the shoulder hangs downward and the clavicle rides high, producing a characteristic clinical deformity. In type IV injuries, the clavicle may be palpable posteriorly, and in type V injuries, the clavicle may be palpable subcutaneously above the acromion. In type VI injuries, the shoulder assumes a flattened clinical appearance as seen from the side.

Diagnostic Strategies: Radiology. The energy settings used for the three-view shoulder trauma series usually overpenetrate the ACJ. Specific ACJ views that use one-third to two-thirds less intensity should be ordered. The recommended projections include an AP view of both joints on a single wide film, an axillary lateral view, and a 15-degree cephalic tilt view.[32] The axillary lateral view is useful for identifying associated fractures and posterior dislocation of the clavicle. The normal coracoclavicular distance ranges from 11 to 13 mm. A difference of more than 5 mm between the injured and uninjured sides is diagnostic of a complete coracoclavicular disruption. With type I injuries, the radiographic appearance is essentially normal. With type II injuries, radiographs show widening of the joint and a slight upward or posterior displacement of the clavicle but a normal coracoclavicular distance. Type II injuries are often subtle and can be easily overlooked. With type III, IV, and V injuries, radiographic features include a widened joint, an increased coracoclavicular distance, and either superior or posterior displacement of the clavicle (Fig. 53-25). Historically, stress views of the ACJ have been recommended to differentiate between type II and type III injuries. Such views lack efficacy for this purpose, and their routine use is unnecessary.[33]

Management. Type I and II injuries should be immobilized in a sling for comfort and to protect against further injury. Patients with these injuries should be referred for follow-up with their primary care physician. When pain has subsided (1 to 3 weeks), range-of-motion and strengthening exercises can begin, with a return to sports when pain-free function has been achieved.

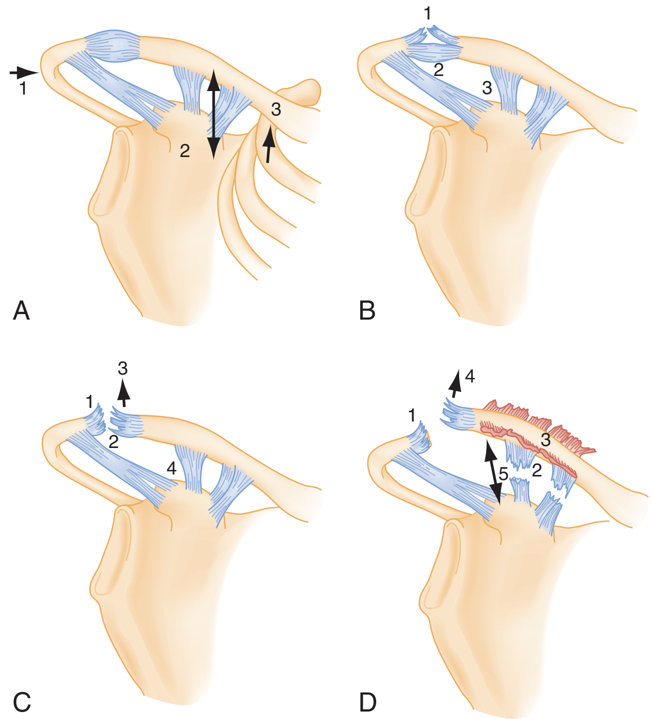


Figure 53-24. Mechanism of injury and classification of acromioclavicular joint injuries. Arrows indicate direction of applied force and relevant movement. **A,** The direct force is applied to the point of the shoulder *(1);* the scapula and attached clavicle are forced downward and medially; the clavicle approaches the first rib *(2).* If the force continues, the first rib abuts the clavicle, producing a counterforce *(3).* Depending on the magnitude of the force, a grade I, II, or III sprain may occur. **B,** Grade I sprain. A few fibers of the acromioclavicular ligament stretch, and a few tear *(1);* the acromioclavicular joint is stable *(2);* the coracoclavicular ligament is intact *(3).* **C,** Grade II sprain (subluxation). The capsule and the acromioclavicular ligament rupture *(1);* the joint is lax and unstable *(2);* the end of the clavicle rides upward, with displacement usually less than half of the width of the end of the clavicle *(3);* the coracoclavicular ligament remains intact *(4);* the attachments to the trapezius and deltoid remain intact. **D,** Grade III sprain (dislocation). The capsule and acromioclavicular ligaments rupture *(1);* the coracoclavicular ligament ruptures *(2);* the insertions of the trapezius and deltoid tear away *(3);* the clavicle rides upward *(4);* the interval between the clavicle and the coracoid process is greatly increased *(5).* (From DePalma AF: Surgery of the Shoulder, 3rd ed. Philadelphia, JB Lippincott, 1983.)

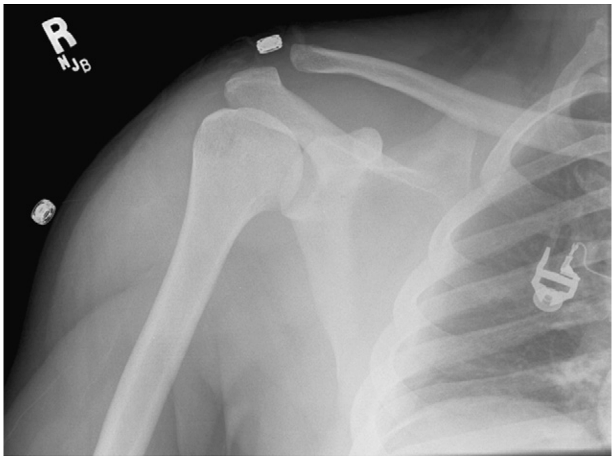


Figure 53-25. Third-degree sprain of the acromioclavicular joint. The coracoclavicular distance is increased.

www.ketabpezeshki.com 66485457-66963820

Type IV, V, and VI injuries require early surgical treatment. The management of type III injuries has changed dramatically since the 1980s. Most studies have concluded that conservative treatment provides functional results equivalent to or, in some cases, better than those obtained with surgical intervention. In addition, surgical patients have longer recovery times and higher complication rates.[7] The main complications of conservative therapy are the persistence of nuisance symptoms (clicking or minor pain) and a cosmetic deformity. Selected patients who are young, have severe displacement (more than 2 cm), and perform repetitive overhead activities may be candidates for surgical intervention.[7] Treatment of type III injuries in the ED should consist of sling immobilization and early orthopedic referral (within 72 hours) if the patient is deemed to be a potential surgical candidate. The initial therapy in all cases should include adequate analgesia.

Complications. The most common concurrent injuries are associated fractures of the clavicle and coracoid process. The most common complications of ACJ injuries are residual symptomatic instability and tenderness over the joint caused by secondary degenerative changes.[7,33] Acromioclavicular arthritis typically manifests as an impingement syndrome with shoulder pain between 120 and 180 degrees of abduction.

Glenohumeral Dislocations

Perspective. The glenohumeral joint is the most commonly dislocated major joint in the body. The lack of intrinsic bone stability in conjunction with its wide range of motion predisposes the joint to dislocations. The annual incidence is 17 per 100,000, and two distinct age peaks are recognized, the first in men 20 to 30 years of age and the second in older women.[34] The glenohumeral joint can dislocate anteriorly, posteriorly, inferiorly, or superiorly. Anterior dislocations account for 95 to 97% of all glenohumeral dislocations. Posterior dislocations account for most of the remainder, whereas inferior and superior dislocations are rare.

Anterior Dislocations

Pathophysiology. Anterior dislocations can result from indirect or direct forces. The most common mechanism of injury consists of an indirect force transferred to the anterior capsule from a combination of abduction, extension, and external rotation. In younger persons, the injury usually is sustained during athletic activities involving rapid movements, and a characteristic pathologic feature is avulsion of the anteroinferior glenohumeral ligament with capsulolabral detachment (Bankart's lesion).[34] In older patients, a fall onto the outstretched arm is the more common mechanism of injury, and an accompanying rotator cuff tear is common.[34] Rarely, a direct force applied to the posterolateral aspect of the shoulder can force the humeral head out of the glenoid fossa anteriorly.

Anterior dislocations can be classified according to their cause (traumatic or nontraumatic), their frequency (primary or recurrent), and the anatomic position of the dislocated humeral head. After dislocation the humeral head can assume a subcoracoid, subglenoid, subclavicular, or intrathoracic position (Fig. 53-26). The subcoracoid is the most common type of anterior dislocation. The head is displaced anteriorly and rests on the scapular neck inferior to the coracoid process. The next most common type is the subglenoid dislocation, in which the head is anterior and inferior to the glenoid fossa. Together, the subcoracoid and subglenoid types account for 99% of all anterior dislocations. Subclavicular and intrathoracic dislocations are extremely rare and involve the addition of strong lateral to medial forces that push the humeral head medially.

Clinical Features. The patient is in severe pain, with the dislocated arm held in slight abduction and external rotation by the opposite extremity. The lateral edge of the acromion process is prominent, and the normally rounded shoulder assumes a

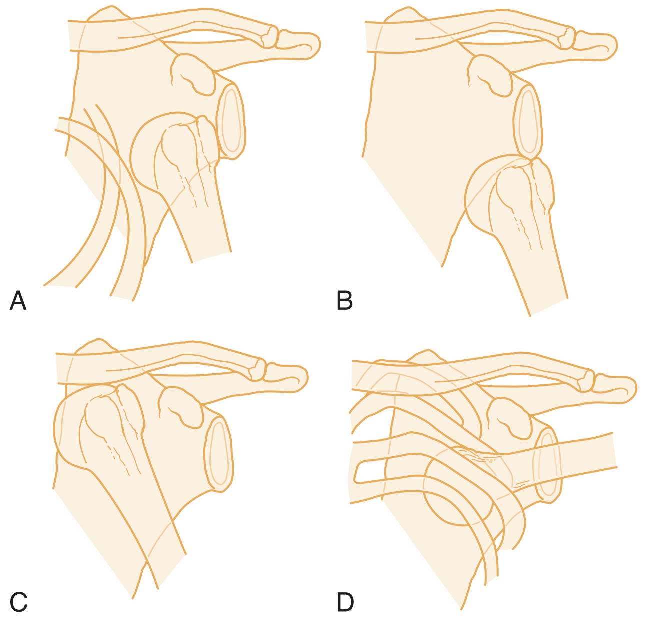


Figure 53-26. Types of anterior dislocation. **A,** Subcoracoid. **B,** Subglenoid. **C,** Subclavicular. **D,** Intrathoracic. (From DePalma AF: Surgery of the Shoulder, 3rd ed. Philadelphia, JB Lippincott, 1983.)

"squared-off" appearance. The coracoid process is indistinct, and the anterior shoulder appears full. The patient leans away from the injured side and cannot adduct or internally rotate the shoulder even slightly without severe pain. A neurovascular examination is performed to identify associated injuries of the brachial plexus, axillary nerve, radial nerve, or axillary artery. The reported incidence of axillary nerve injuries after anterior glenohumeral dislocation ranges from 5 to 54%, and they are more frequent in patients older than 50 years.[35,36] Axillary nerve function can be assessed by testing for sensation over the lateral aspect of the shoulder and by testing motor function of the teres minor and deltoid muscles. Deltoid function is tested by having the patient attempt shoulder abduction while the examiner feels for muscle contraction. Motor testing is more accurate because sensory testing can be misleading owing to the presence of overlapping cutaneous nerve root dermatomes.

Diagnostic Strategies: Radiology. The trauma series of radiographs will confirm the clinical diagnosis and identify the position of the humeral head (Fig. 53-27). Associated fractures may be present in 50% of cases. The most common of these is a compression fracture of the posterolateral aspect of the humeral head caused by forceful impingement against the anterior rim of the glenoid fossa. This defect in the humeral head, or Hill-Sachs deformity (see Fig. 53-27), is reported to be present in 11 to 50% of all anterior dislocations. The actual incidence is probably much higher, because minor compression fractures are difficult to visualize on plain radiographs. The defect is best visualized on an internal rotation AP view of the glenohumeral joint. Although common, Hill-Sachs fractures are of limited clinical significance unless they are large enough to cause recurrent shoulder instability or painful clicking or catching, in which case surgical repair may be necessary. A corresponding fracture of the anterior glenoid rim (Bankart's fracture) is present in approximately 5% of cases.[9] Avulsion fractures of the greater tuberosity are present in 10 to 15% of cases.[9,35]

Management. Reduction of the dislocation should be accomplished expeditiously, because the incidence of neurovascular complications increases with time.[36] Radiographic documentation of the type of dislocation and any associated fractures should

www.ketabpezeshki.com 66485457-66963820

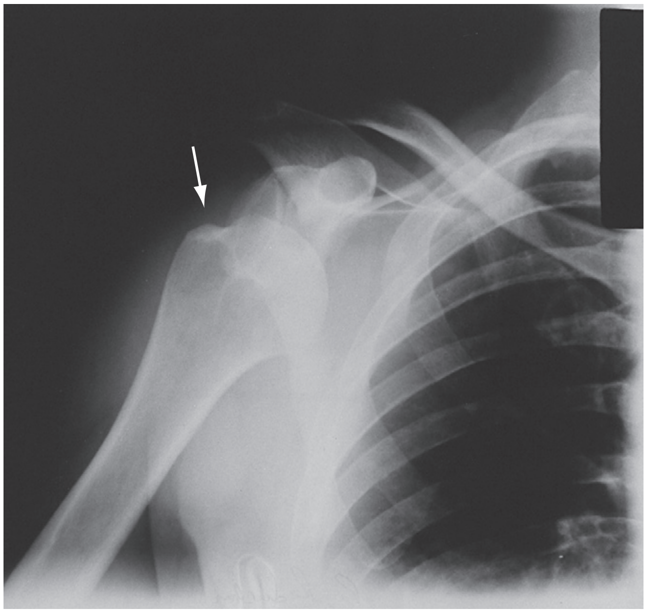


Figure 53-27. Recurrent anterior subcoracoid dislocation with Hill-Sachs deformity of the humeral head *(arrow).*

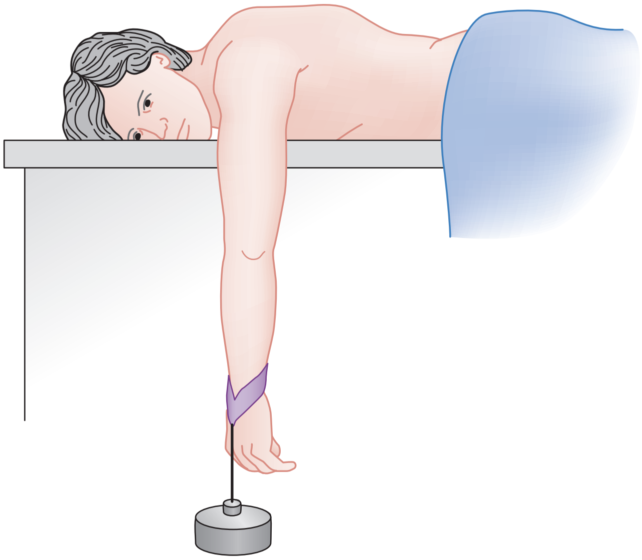


Figure 53-28. Stimson or hanging weight method of reduction for anterior shoulder dislocations.

generally be obtained *before* reduction is attempted. Reduction can be accomplished with various techniques, most of which involve traction, leverage, or scapular manipulation principles.[37] The ideal method should be simple, quick, and effective; require little assistance; and cause no additional injury to the shoulder. It is wise to be familiar with several techniques of reduction, because none is uniformly successful.

Analgesia and muscle relaxation through procedural sedation are often used to facilitate reduction in the ED. Muscle relaxation and analgesia also can be provided through intra-articular injection of a local anesthetic agent. This technique is especially useful when procedural sedation is contraindicated. Under sterile technique, the joint is entered 2 cm inferior to the lateral edge of the acromion with an 18-gauge or 20-gauge needle. Any associated hemarthrosis is aspirated; then 20 mL of 1% lidocaine is injected over 30 seconds. The patient is allowed to relax for 15 minutes before reduction is attempted. The published studies to date all have used lidocaine, although it would be reasonable to expect similar results with other local anesthetic agents such as bupivacaine.

Fitch and Kuhn recently reviewed six randomized controlled trials comparing intravenous sedation and intra-articular lidocaine.[38] Outcomes in these studies included success rates, complications, and time spent in the ED. Although the reduction techniques were not controlled in these studies, none showed a statistical difference in the reduction success rates, which averaged 92% for both the intra-articular lidocaine and intravenous sedation groups. Complication rates were quite different, however, averaging 0.67% in the intra-articular lidocaine group and 13.3% in the intravenous sedation group. The most common in the lidocaine group was "psychological agitation," whereas the sedation group experienced nausea, vomiting, and respiratory depression. Time spent in the ED was significantly less for the intra-articular lidocaine group.[38] Depending on the duration of the dislocation, nature (primary vs. recurrent) and technique, reduction can also be attempted and accomplished successfully without the use of any analgesia or muscle relaxation.[2,37,39]

There are many techniques that can be used for reduction of an anterior shoulder dislocation, some of which are highlighted here.

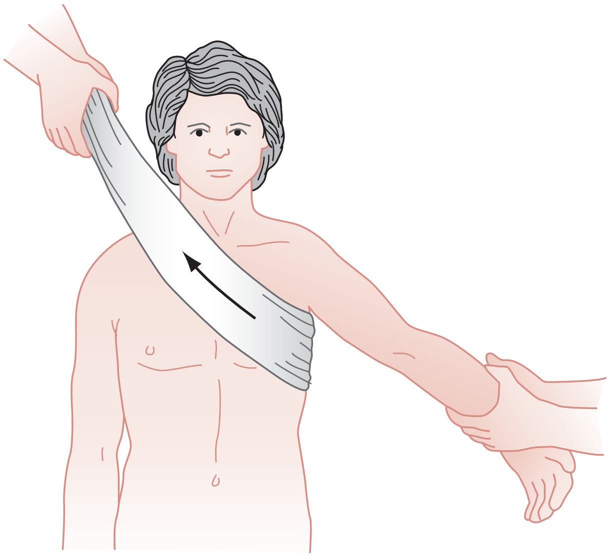


Figure 53-29. Traction-countertraction method for reducing anterior shoulder dislocations.

Most of these techniques are quite effective, but approximately 5 to 10% of dislocations cannot be reduced in the ED.[37] Traction techniques use steady force applied in various directions (forward flexion, abduction, overhead, lateral) to overcome the muscle spasm that holds the humeral head in its dislocated position. In the *Stimson* or *hanging weight technique* (Fig. 53-28), the patient is placed prone with the dislocated arm hanging over the edge of the examining table. A 10- or 15-pound weight attached to the wrist or lower forearm provides traction in forward flexion. Reduction usually occurs over 20 to 30 minutes. In the *traction-countertraction method* (Fig. 53-29), traction is applied along the abducted arm while an assistant using a folded sheet wrapped across the chest applies countertraction. Another simple and effective traction technique is the *Snowbird technique,* which has a reported success rate of 97%.[37] In this method, the patient is seated in a chair and the affected arm is supported by the patient's unaffected extremity. A 3-foot loop of 4-inch cast stockinette is placed

www.ketabpezeshki.com 66485457-66963820

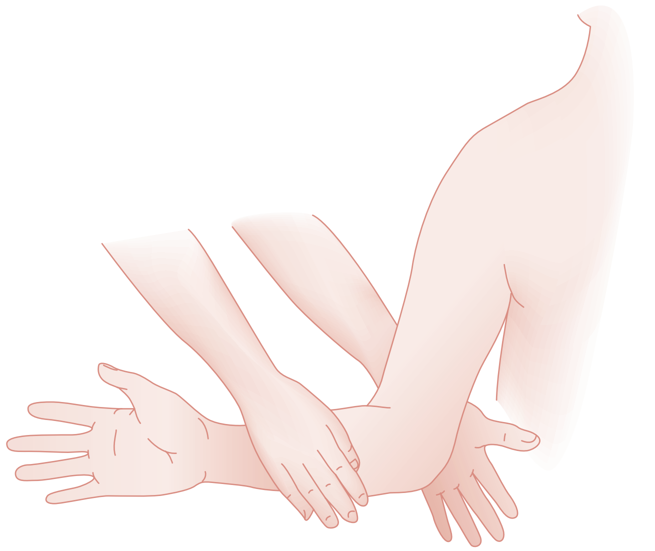


Figure 53-30. External rotation technique for reducing anterior shoulder dislocations. The involved arm is slowly adducted to the patient's side, and the elbow is flexed 90 degrees. Gentle external rotation is applied to the forearm to achieve reduction. (From Simon RR, Koenigsknecht SJ: Emergency Orthopedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

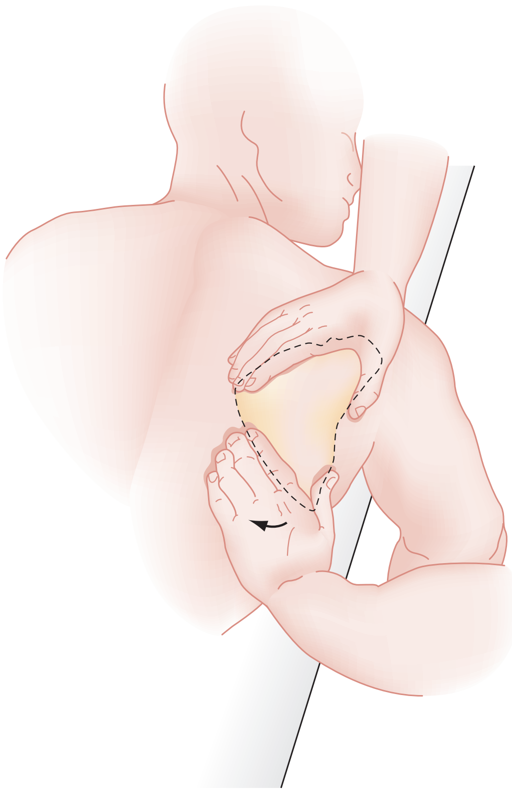


Figure 53-31. Proper hand position and direction of rotation during shoulder relocation via the scapular manipulation technique. Arrow indicates direction of applied force. (From Kothari RU, Dronen SC: The scapular manipulation technique for the reduction of acute anterior shoulder dislocations. J Emerg Med 8:625, 1990.)

along the proximal forearm of the involved extremity with the elbow at 90 degrees. The patient is assisted or instructed to sit up, and the physician's foot is placed in the stockinette loop to provide firm downward traction. The physician's hands remain free to apply any gentle external pressure or rotation as needed until reduction is accomplished.

The most commonly recommended leverage technique is the *external rotation method of Leidelmeyer*.[40] With the patient in the supine position, the involved arm is slowly and gently adducted to the side. The elbow is flexed to 90 degrees, and slow, gentle external rotation is applied to achieve reduction (Fig. 53-30). Success rates with this method range from 80 to 90%.[31] With the *Milch technique*, the patient is placed supine on the gurney and the head of the bed is elevated 20 to 30 degrees. The affected arm is held by the wrist and slowly abducted and externally rotated. The operator stops whenever resistance to motion is encountered and continues when the patient is relaxed. If the humerus has not reduced by the time 90 degrees of abduction and 90 degrees of external rotation have been reached, gentle longitudinal traction is applied along the humerus while the free hand is used to exert lateral and superior pressure on the humeral head to complete the maneuver.[2] Reduction usually takes 5 to 10 minutes and can be accomplished without an assistant or procedural sedation. O'Connor and colleagues[2] recently reported a 100% success rate on first attempt with the Milch technique. The effectiveness of this method has been attributed in part to more conical symmetry of the muscle forces acting across the glenohumeral joint. Several variants of the Milch technique have been reported in the literature.[37,39]

Scapular manipulation accomplishes reduction by repositioning the glenoid fossa rather than the humeral head and can be successful with minimal analgesia or muscle relaxation. Manipulation can be combined with the Stimson or traction-countertraction techniques. After the application of traction (manual or hanging weights), the scapula is manipulated by rotation of the inferior tip medially (Fig. 53-31) while the superior and medial edges are stabilized with the opposite hand. Scapular manipulation can also be used in a seated position in which a second operator applies traction in the forward horizontal position.[31,37] Scapular manipulation can be difficult in heavyset patients, in whom it is difficult to palpate and grasp the inferior tip of the scapula.

More traditional techniques, such as the Hippocratic method (traction with the foot in the axilla) and the Kocher maneuver (leverage, adduction, and internal rotation), are no longer recommended because of a high incidence of associated complications (axillary nerve injury, humeral shaft and neck fractures, capsular damage). Comparative studies of the efficacy, safety, and reliability of reduction techniques are limited. In a recent randomized study, a variation of the Milch technique called FARES (*FA*st, *RE*liable, and *S*afe) was found to be more effective, faster, and less painful than the traction-countertraction and Kocher methods. FARES adds oscillation in a vertical direction while the affected arm is abducted. In this study, reductions were performed by junior residents without any anesthesia, sedation, or analgesia.[39]

The neurovascular examination should ideally be repeated and findings recorded after any attempt at reduction.

Traditional teaching has been to obtain prereduction and postreduction radiographs. Shuster and colleagues investigated the need for prereduction radiographs.[41] In one study, they found that when the emergency physician was clinically confident of the diagnosis, the radiographs were 100% accurate.[41] In a follow-up study, the researchers demonstrated that implementation of voluntary guidelines based on physician certainty allowed for the elimination of prereduction radiographs in 88.9% of cases.[42] It also is generally recommended that radiographic studies be performed after reduction to confirm reduction and identify any associated fractures. Some studies have questioned the need for and cost-effectiveness of routine postreduction radiographs.[43,44] These investigators did not find any new clinically significant fractures on postreduction radiographs and argued that in most instances

www.ketabpezeshki.com 66485457-66963820

a successful reduction can be determined clinically by the presence of a palpable clunk, decrease in pain, and improvement in the range of motion. Reduction in the number of postreduction radiographs also decreases costs and shortens the ED throughput times.[44] The findings on most of these studies are very subjective, however, and one cannot assume that all practitioners will have the same clinical acumen. Other studies show that as many as 7.5% of fractures initially were detected only on postreduction films.[45] Plain radiography of the shoulder is readily available and presents little or no risk to the patient. Unfortunately, failure to confirm reduction with radiographs and failure to diagnose all associated fractures could lead to malpractice claims. For these reasons, imaging of suspected shoulder dislocations remains advisable in most cases, with the possible exception of some patients with a history of recurrent dislocations in the absence of trauma. In these cases, prereduction films may not be necessary; however, a postreduction film may be advisable. In addition, imaging can also identify Bankart's lesions (avulsion of the anteroinferior glenohumeral ligament with capsulolabral detachment), which are an indication for surgery, as well as Hill-Sachs deformities, which when large can be associated with subsequent shoulder instability.

After reduction, the affected extremity is immobilized with a sling and swathe bandage or a Velpeau sling (see Fig. 53-11). Patients should be discharged with adequate analgesia and appropriate follow-up referral. Primary dislocations and complicated cases (associated fracture, rotator cuff tear, axillary nerve injury) should receive orthopedic follow-up care. Conventionally, the shoulder is immobilized for 3 to 6 weeks in younger patients and for 1 to 2 weeks in those older than 40 years.[9] A recent meta-analysis, however, found no added benefit from more prolonged immobilization in younger populations.[46]

The traditional position of immobilization is with the shoulder in internal rotation. Studies suggest that this positioning may delay healing and is associated with a higher recurrence rate.[47] External rotation may allow for better alignment of injured soft tissues (Fig. 53-32). In a randomized clinical trial with a minimum follow-up of 2 years, Itoi and colleagues[48] found that 3 weeks of immobilization in 10 degrees of external rotation was associated with a 26% recurrence rate, compared with a 42% recurrence rate with sling immobilization in internal rotation. Similar findings were reported in a recent systematic review of the literature on immobilization position.[46] Other investigators, however, have failed to confirm this finding, and so the optimal postreduction immobilization position remains unclear.[49] Early initiation of shoulder exercises (see Fig. 53-14) helps reduce the risk of adhesive capsulitis. A meticulous rehabilitation program aimed at restoring the static and dynamic stabilizers of the glenohumeral joint follows the period of immobilization.[9]

Complications. Complications include the aforementioned fractures and neurovascular injuries. Most axillary nerve injuries are neurapraxic, management is expectant, and the prognosis for recovery of function is good.[36] Rotator cuff tears may be present in 10 to 15% of cases.[50] Rotator cuff tears are especially common in primary dislocations in patients older than 40 years. In this setting, failure to abduct the arm often is misdiagnosed initially as an axillary nerve injury. Most of these patients require tendon and capsular repair to restore shoulder stability.[50] Recurrence also is a common complication after anterior dislocation, and patients younger than 30 years have a reported recurrence rate of 79 to 100%. A Hill-Sachs deformity, Bankart's lesion, or a glenoid rim fracture are all associated with increased risk of recurrence.[9] Recent studies suggest that the traditional method of treatment (immobilization followed by physical therapy) is ineffective in preventing redislocation in young, highly athletic persons. Arthroscopic studies of primary anterior dislocations in such patients have detected a high incidence of anterior-inferior capsulolabral avulsions (Bankart's lesion) from the glenoid rim. This avulsion is believed to be the primary predisposing factor for recurrence, and affected patients seem to benefit from early arthroscopic repair of the lesion.[51] Recurrence rates decline with increasing age and in the presence of a greater tuberosity fracture, and possibly immobilization in external rotation.[46,48]

Anterior Subluxation. Transient anterior subluxation of the shoulder is encountered often in young athletic adults. The patient reports sudden sharp shoulder pain and weakness ("dead arm syndrome") that occurred while performing an abduction and external rotation maneuver. The patient also may relate a sensation of the shoulder's slipping in and out. The radiographic appearance usually is normal, and presence of an apprehension sign confirms the diagnosis. For this sign to be elicited, the injury motion (abduction and external rotation of the arm) is gently reproduced while an anterior force is applied to the posterior shoulder (Fig. 53-33). This maneuver increases the pain and may cause anterior displacement of the humeral head. With a positive test result, the patient will actively resist further external rotation and appear apprehensive. A lax or redundant anterior capsule is thought to be responsible for this syndrome, and recurrent episodes are common. These patients should be referred for orthopedic follow-up care because definitive therapy (capsulorrhaphy) is surgical.

Figure 53-32. Postreduction immobilization with an external rotation splint

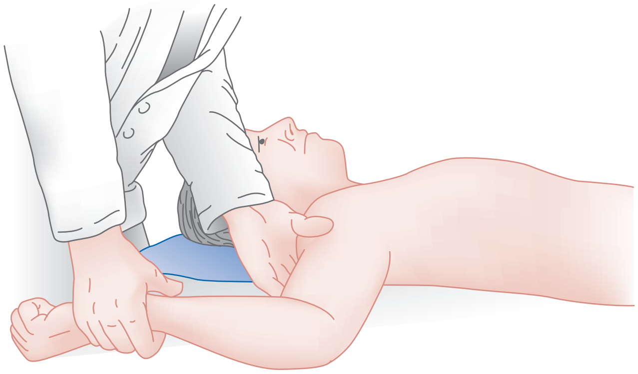


Figure 53-33. Technique for performing the shoulder apprehension test. (From Simon RR, Koenigsknecht SJ: Emergency Orthopedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

www.ketabpezeshki.com 66485457-66963820

Posterior Dislocation

Pathophysiology. Posterior dislocations are rare and account for 2 to 5% of all glenohumeral dislocations.[52] This rarity is explained partly by the anatomy of the shoulder girdle. The 45-degree angulation of the scapula on the thoracic cage positions the glenoid fossa posterior to the humeral head, which serves as a partial buttress against posterior dislocation. More than 50% of posterior dislocations are missed on initial evaluation, and many remain unrecognized ("locked posterior dislocations") for weeks or months.[52,53]

A posterior dislocation can result from several distinct mechanisms of injury. Convulsive seizures (epileptic or after electrical shock) have been associated with unilateral or bilateral posterior dislocations. In this instance, the larger and stronger internal rotator muscles (latissimus dorsi, pectoralis major, teres major, subscapularis) overpower the weaker external rotators (teres minor, infraspinatus) to produce the injury with or without associated trauma.[52] A posterior dislocation also can occur after a fall onto the outstretched hand with the arm held in flexion, adduction, and internal rotation or after a direct blow to the anterior aspect of the shoulder. A seizure disorder should be suspected in cases of unexplained nocturnal posterior dislocations. Acute posterior dislocations are anatomically classified into three types—subacromial (most common), subglenoid, and subspinous—based on the final resting position of the humeral head.[52]

Clinical Features. Early diagnosis is essential to prevent long-term functional and therapeutic complications. As mentioned, the initial examining physician misses the diagnosis with some regularity, in part because of an over-reliance on radiologic findings and an under-reliance on the clinical examination. The most common misdiagnosis is adhesive capsulitis.[52] The patient holds the affected arm across the chest in adduction and internal rotation. Although usually painful, the injury can be relatively painless. The normal shoulder contour is replaced by a flat, squared-off appearance, and the coracoid process is prominent and easily palpated. The humeral head may be palpable posteriorly beneath the acromion process. Abduction is severely limited, and external rotation is completely blocked because the humeral head remains impacted against the posterior glenoid rim.

Diagnostic Strategies: Radiology. True or standard AP radiographs can appear deceptively normal with posterior dislocations. The common difficulty with identifying posterior dislocation in the frontal plane has led to the description of several characteristic radiographic features. Standard AP films show loss of the half-moon elliptic overlap of the humeral head and glenoid fossa. In addition, the distance between the anterior glenoid rim and the articular surface of the humeral head is increased (the rim sign). The humeral head is profiled in internal rotation and takes on a "lightbulb" or "drumstick" appearance (Fig. 53-34). A true AP film shows abnormal overlap of the glenoid fossa with the humeral head (Fig. 53-35). Finally, an impaction fracture of the anteromedial humeral head (reverse Hill-Sachs deformity) is invariably present (see Fig. 53-35). This fracture may produce a curvilinear density on the frontal projection parallel to the articular cortex of the humeral head (the trough sign). An orthogonal view, such as an axillary lateral, transscapular Y (see Fig. 53-34), or apical oblique view, confirms the diagnosis. The axillary lateral view or apical oblique view also identifies associated fractures of the humeral head and posterior glenoid rim. If an adequate orthogonal view cannot be obtained, shoulder CT should be considered.[52,54]

Management. Closed reduction may be attempted in the ED with procedural sedation. The technique of reduction incorporates internal rotation and lateral traction to disimpact the humeral head from the glenoid rim. The humeral head can also be disimpacted with use of the "lever principle"—adducting the arm as much as possible, pulling the forearm in internal rotation to the opposite side of body while simultaneously pushing the medial side of the proximal arm laterally.[55] Once the humeral head is disimpacted, reduction can be accomplished with slow external rotation in conjunction with gentle pressure on the posteriorly displaced head. If this technique fails, reduction with the patient under general anesthesia is indicated. After reduction the shoulder should be immobilized in external rotation with slight abduction.[53] Cases that were missed initially and manifest as chronic or "locked" posterior dislocations should be discussed with the

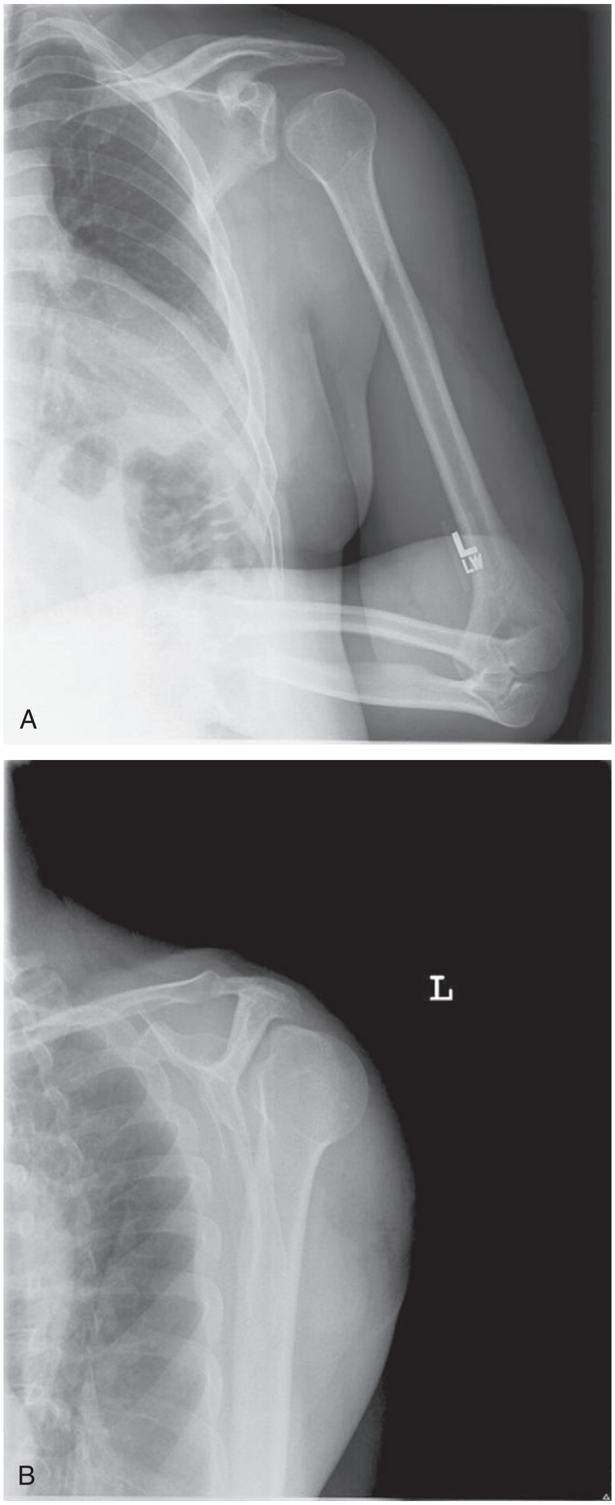
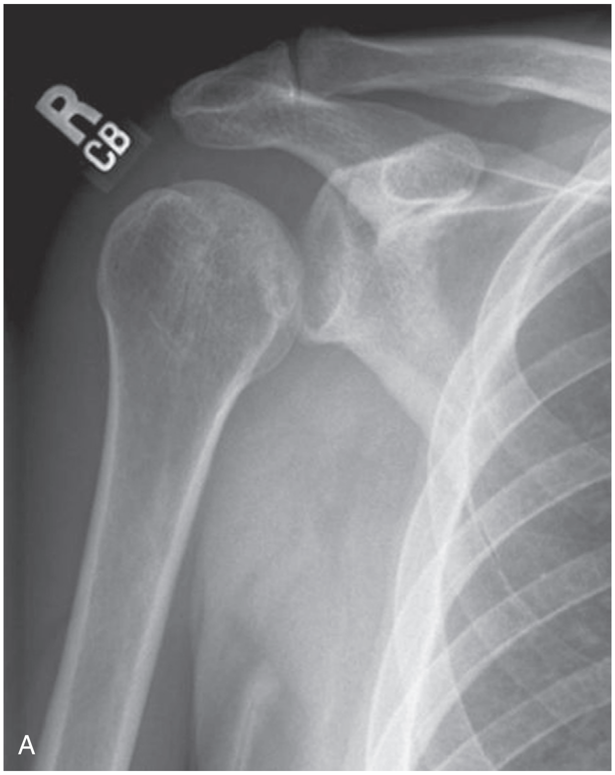


Figure 53-34. Anteroposterior (A) and transscapular (B) radiographic views of a posterior glenohumeral dislocation. Note the "lightbulb" or "drumstick" appearance of the humeral head.

www.ketabpezeshki.com 66485457-66963820



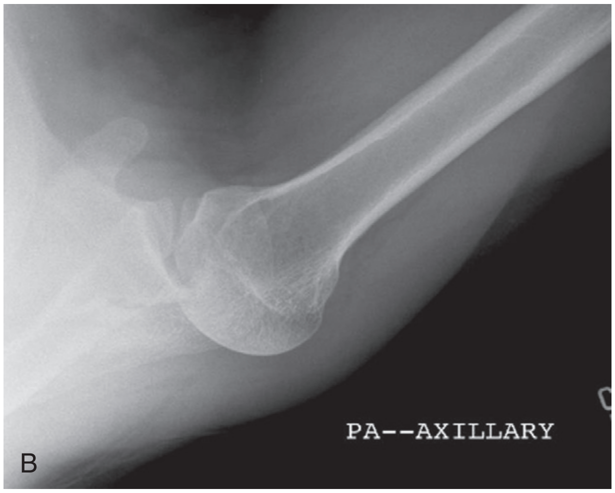


Figure 53-35. True anteroposterior **(A)** and axillary **(B)** radiographic views of a posterior glenohumeral dislocation. Note the abnormal overlap of the glenoid rim and humeral head and the impaction fracture of the anteromedial humeral head (reverse Hill-Sachs deformity).

orthopedist because they often require semielective open reduction and internal fixation or arthroplasty.[53,54]

Complications. Fractures of the glenoid rim, greater tuberosity, lesser tuberosity, and humeral head account for most associated injuries. The subscapularis muscle rarely may be avulsed from its insertion site on the lesser tuberosity. Neurovascular injuries are uncommon because the anterior location of the neurovascular bundle protects it from injury. Recurrent posterior dislocations occur in 30% of patients and predispose the joint to degenerative changes.

Inferior Glenohumeral Dislocation (Luxatio Erecta)

Pathophysiology. Luxatio erecta is a rare type of glenohumeral dislocation in which the superior aspect of the humeral head is forced below the inferior rim of the glenoid fossa. Less than 0.5% of all shoulder dislocations are of this variety, and the mechanism of injury involves either indirect or direct forces.[56] Most inferior dislocations result from indirect forces that hyperabduct the affected extremity. This causes impingement of the humeral head against the acromion process. Further levering of the humeral shaft against the acromion ruptures the capsule and dislocates the head inferiorly (Fig. 53-36). Application of a direct axial load to an abducted shoulder also can disrupt the weak inferior glenohumeral ligament and drive the humeral head downward.

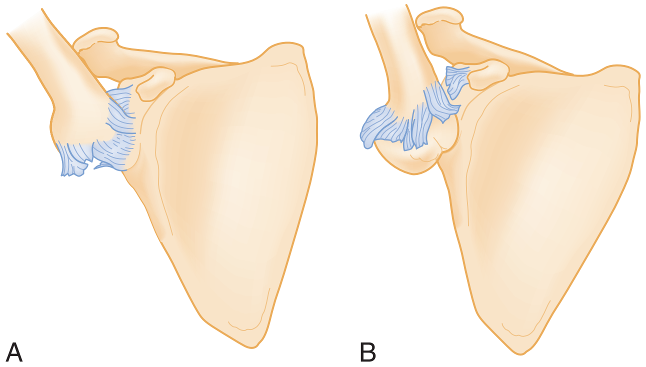


Figure 53-36. Luxatio erecta. **A,** The mechanism by which this injury occurs in hyperabduction. **B,** This is always accompanied by disruption of the rotator cuff and tear through the inferior capsule. (From Simon RR, Koenigsknecht SJ: Emergency Orthopedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

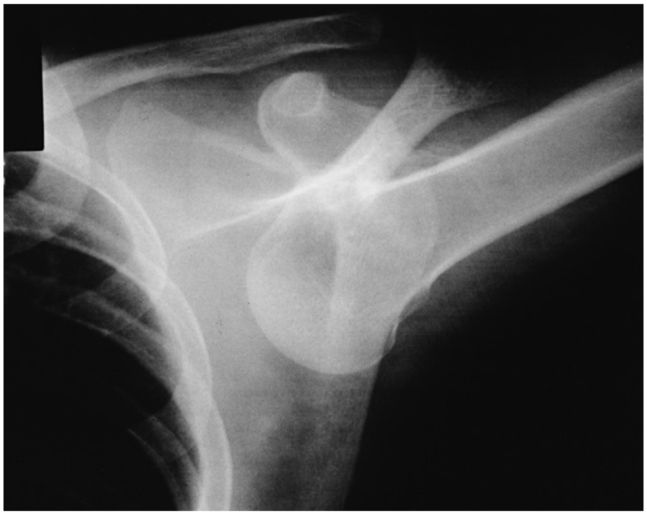


Figure 53-37. Anteroposterior radiographic view of an inferior glenohumeral dislocation. The humeral shaft lies parallel to the spine of the scapula.

Clinical Features. Clinically, the patient has the arm locked overhead in 110 to 160 degrees of abduction. The elbow usually is flexed, and the forearm typically rests on top of the head. The shoulder is fixed in this position, and any attempts at movement result in significant pain. The inferiorly displaced humeral head may be palpable along the lateral chest wall. A thorough neurovascular examination is essential to evaluate for associated injuries.

Diagnostic Strategies: Radiology. Many cases of luxatio erecta are mistakenly diagnosed and treated as subglenoid anterior dislocations because the radiographic features of these two clinical entities are remarkably similar. Standard AP radiographs show the superior articular surface inferior to the glenoid fossa (Fig. 53-37). In addition, the humeral shaft characteristically lies parallel to the

www.ketabpezeshki.com 66485457-66963820

spine of the scapula on the AP view. This radiographic feature is useful in distinguishing luxatio erecta from a subglenoid anterior dislocation: in the latter the humeral shaft lies parallel to the chest wall. Associated fractures of the acromion, coracoid, clavicle, greater tuberosity, humeral head, and glenoid rim are common.

Management. Reduction usually can be accomplished by traction-countertraction maneuvers under procedural sedation. The operator applies traction in line with the humeral shaft while an assistant applies countertraction across the shoulder (Fig. 53-38). Gentle abduction usually reduces the dislocation, and the arm is brought down into an adducted position. Multiple attempts may be necessary; occasionally, "buttonholing" of the capsule will prevent closed reduction, necessitating an orthopedic consultation for open reduction. An alternative approach is the two-step closed reduction maneuver, in which the inferior dislocation is first converted into an anterior dislocation before being reduced.[57] Initially, one hand is placed on the shaft of the dislocated humerus and the other hand on its medial condyle. The hand on the shaft initiates an anteriorly directed force rotating the humeral head from an inferior to an anterior position. The adducted humerus can then be externally rotated to reduce the head into the glenoid fossa. The reported advantages of the two-step maneuver are that it requires a single operator, fewer attempts, minimal force, and only local analgesia or minimal procedural sedation.[57]

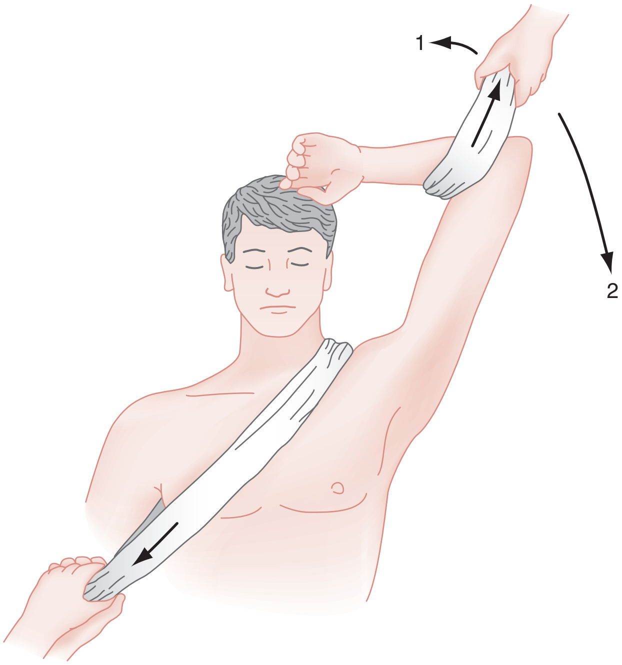


Figure 53-38. Traction-countertraction method for reduction of luxatio erecta humeri. Arrows indicate direction of applied force and relevant movement. The initial maneuver *(1)* includes steady axial traction in line with the humeral shaft position, followed by gentle abduction. This reduces the glenohumeral dislocation. At this point *(2),* the arm is brought down to a position of adduction and internal rotation. (Redrawn from Davids JR, Talbott RD: Luxatio erecta humeri. A case report. Clin Orthop Relat Res 252:144, 1990.)

Complications. Neurapraxic lesions of the brachial plexus are common, and thrombosis of the axillary artery has also been associated with luxatio erecta.[56] Other associated injuries include tears of the rotator cuff, damage to the glenoid labrum, and avulsion fractures of the greater tuberosity.

Scapulothoracic Dislocation

Scapulothoracic dissociation is a rare and severe injury characterized by complete disruption of the scapulothoracic articulation and may be thought of as a partial or complete internal forequarter amputation.[58] The mechanism of injury involves a massive blunt force directed over the shoulder or severe traction force applied to the upper extremity. Approximately 50% of the reported cases involve motorcycle accidents, with the injury occurring when the motorcyclist hangs onto the handlebars while the body is forced away.[59] The diagnosis is based on history, clinical findings, and radiologic studies. The injury often is overlooked at first, because most patients have multiple injuries that distract the treating physician.[59] Massive local soft tissue swelling of the shoulder, along with more than 1 cm of lateral displacement of the scapula on the AP chest radiograph, is pathognomonic for scapulothoracic dissociation (Fig. 53-39). Associated osseous injuries include acromioclavicular separation, displaced fractures of the clavicle, and dislocations of the SCJ. Vascular lesions have been reported in 88% of patients and severe neurologic injuries in 94%, so a thorough assessment for these injuries is essential.[58] Acute limb ischemia is rare because of the extensive collateral network in the shoulder. Vascular and neurologic injuries can be confirmed through angiography and MRI. Outcomes generally are poor, with death in 10% of cases and a flail anesthetic upper extremity in complete brachial plexus injuries. Many of these latter cases eventuate in upper extremity amputation.[58]

Soft Tissue Conditions

Impingement Syndromes: Rotator Cuff Tendinitis, Subacromial Bursitis

Pathophysiology. Rotator cuff tendinitis and subacromial bursitis can be considered part of a pathophysiologic continuum whose

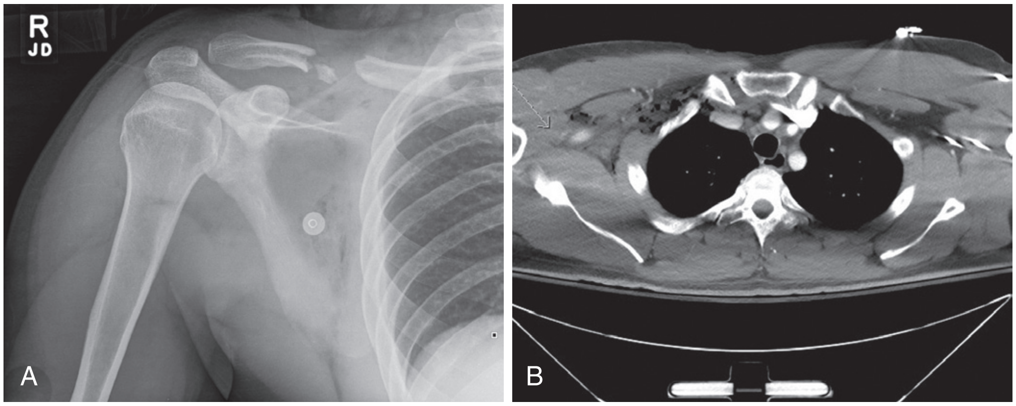


Figure 53-39. Scapulothoracic dissociation with associated clavicle fracture **(A)**, and CT scan of associated axillary artery injury **(B)**.

www.ketabpezeshki.com 66485457-66963820

endpoint is represented by complete rupture of the rotator cuff. These two conditions are common causes of shoulder pain and have similar clinical presentations.[60] A key clinical feature is the presence of a painful arc sign (Fig. 53-40).

The subacromial space is the area between the coracoacromial arch and the greater tuberosity of the humerus. This space, which is only a few millimeters wide, contains the long head of the biceps, the rotator cuff, and the subacromial bursa. The bursa provides the gliding mechanism between the musculotendinous cuff and the coracoacromial arch. The functional arc of shoulder elevation is forward, which normally leads to impingement of the cuff and bursa under the anterior third of the coracoacromial arch. Similar impingement also occurs at 60 to 120 degrees of abduction and with the extremes of adduction. The critical wear from impingement is centered on the supraspinatus tendon, near its insertion on the greater tuberosity. Micro-opaque injection studies also have shown a relative avascularity within this "critical" area. The hypovascularity, in conjunction with repeated wear and age-related degenerative changes, ultimately results in rotator cuff tendinitis. Narrowing of the subacromial space (anatomic variants of anterior acromion) and occupations that require excessive overhead activity accelerate the entire process. With time, the inflammatory reaction spreads to involve the adjacent bursa. This inflammation leads to edema, thickening, and fibrosis, further narrowing the subacromial space (secondary impingement); this is eventually followed by attritional changes within the rotator cuff. Because the rotator cuff is a primary humeral head depressor, loss of function adds to the secondary impingement process.[60]

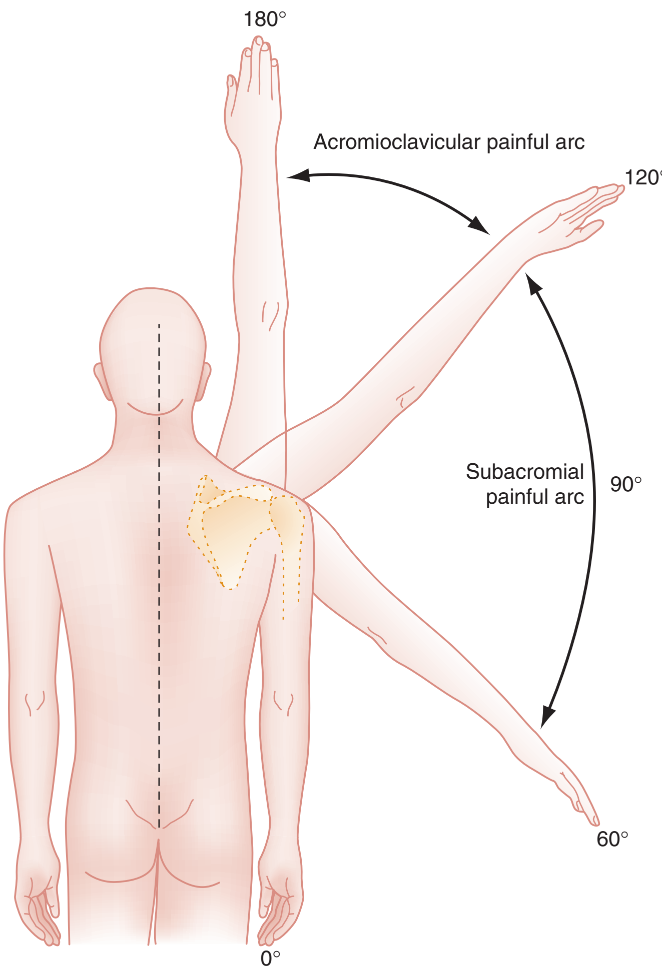


Figure 53-40. Arcs of painful abduction: subacromial painful arc, 60 to 120 degrees; acromioclavicular painful arc, 120 to 180 degrees. (From DePalma AF: Surgery of the Shoulder, 3rd ed. Philadelphia, JB Lippincott, 1983.)

The impingement process also may involve the long head of the biceps. In such cases, bicipital tendinitis, degeneration, or rupture may be present. If osteoarthritis of the ACJ has narrowed the subacromial space, the pathologic process can be accelerated. Impingement in this context occurs at 120 to 180 degrees of abduction (see Fig. 53-40).

Clinical Features. The spectrum of illness is marked by a progression of symptoms.[31] Neer classified the progressive pathologic processes into three stages (Table 53-2).[61] Patients in stage 1 report a dull ache around the deltoid area after strenuous activity. On examination, tenderness can be elicited over the supraspinatus and anterior acromion. A painful arc of abduction at 60 to 120 degrees is characteristic. The Neer impingement sign (Fig. 53-41) has a sensitivity of 68% for all three stages. Several other tests have been described for the diagnosis of impingement syndrome. The combination of the Hawkins-Kennedy impingement sign (arm placed into 90 degrees of flexion followed by internal rotation), the painful arc sign, and the infraspinatus muscle test (resistance to internal rotation with arm adducted and elbow flexed to 90 degrees) provided the best post-test probability (95%) in one large clinical study.[62]

Stage 2 is characterized by more persistent pain that is particularly severe at night. The inflammatory process within the bursa and tendons leads to the formation of minor adhesions. Disruption of these adhesions is thought to account for the nighttime pain. Physical findings are similar to those in stage 1. In addition, bursal thickening leads to increased soft tissue crepitus within the glenohumeral joint.

The hallmark of stage 3 is significant tendon degeneration after a prolonged history of tendinitis and bursitis. Findings in this stage are discussed in the subsequent section on tears of the rotator cuff. The radiographic appearance usually is normal in stages 1 and 2. Findings in stage 3 are similar to those with complete tears of the rotator cuff.

The differential diagnosis of impingement syndrome is extensive and includes intrinsic and extrinsic causes of shoulder pain. Extrinsic sources include the cervical spine, lung, heart, and diaphragm. Intrinsic conditions include acromioclavicular arthritis, adhesive capsulitis, calcific tendinitis, and traumatic anterior subluxation. A Neer impingement sign may be present in many of these other conditions. Relief of pain after the subacromial injection of 10 mL of 1% lidocaine (impingement test; see Fig. 53-41) helps localize the condition to the subacromial space.

Table 53-2 Three Progressive Stages of Impingement Lesions

STAGE	PATHOLOGIC FINDINGS	AGE (yr)	COURSE	TREATMENT
1	Edema, hemorrhage	<25	Reversible	Conservative
2	Fibrosis, tendinitis	25-40	Recurrent pain with activity	Conservative, surgical
3	Bone spurs, tendon rupture	>40	Progressive disability	Surgical

www.ketabpezeshki.com 66485457-66963820

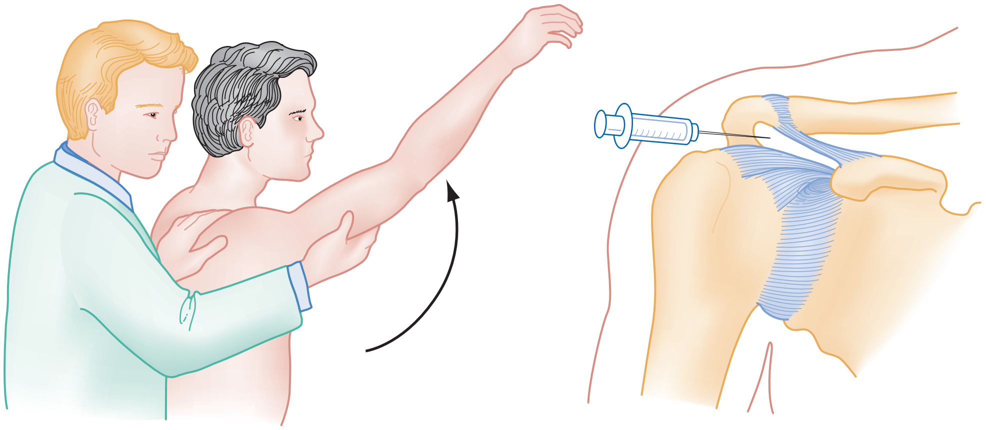


Figure 53-41. Impingement injection test. The impingement sign is elicited with the patient seated or standing and the examiner standing. Scapular rotation is prevented with one hand while the other hand raises the arm in forced forward elevation *(arrow),* causing the greater tuberosity to impinge against the acromion. This maneuver produces pain in patients with impingement lesions of all stages. It also causes pain in many other shoulder conditions. In the case of impingement lesions, the pain caused by this maneuver is relieved by the injection of 10 mL of 1% lidocaine beneath the anterior acromion. This test is useful in separating impingement lesions of all stages from other causes of shoulder pain. (Redrawn from Neer CS 2nd: Impingement lesions. Clin Orthop 173:70, 1983.)

Table 53-3 Potency, Duration of Action, and Recommended Dose of Commonly Used Corticosteroid Preparations

PREPARATION (TRADE NAME)	RELATIVE POTENCY	DURATION OF ACTION	SUBACROMIAL DOSE (mg)
Hydrocortisone acetate (Hydrocortone)	1	Short	25-37.5
Betamethasone sodium phosphate and acetate (Celestone Soluspan)	25	Short/long	6
Methylprednisolone acetate (Depo-Medrol)	5	Long	40-80
Triamcinolone acetonide (Kenalog-10)	5	Long	10-20
Triamcinolone hexacetonide (Aristospan)	5	Long	20
Triamcinolone diacetate (Aristocort)	5	Long	25
Dexamethasone acetate (Decadron-LA)	25	Long	4-16

Management. Initial treatment in stage 1 impingement syndrome is conservative and consists of rest, nonsteroidal anti-inflammatory drugs (NSAIDs), and modification of activities that produce impingement. In stage 2, emphasis is on maintaining flexibility and range of motion through physiotherapy and rotator cuff strengthening exercises. Patients with stage 1 and 2 disease in the ED with reports of treatment failure with NSAIDs may benefit from a subacromial injection of a local anesthetic (lidocaine or bupivacaine) and corticosteroid preparation (Table 53-3), along with referral to a primary care sports medicine physician. Corticosteroid injections take 3 to 4 days to achieve their full effect and need to be injected accurately into the subacromial bursa.[63] Patients with treatment-refractory stage 2 and stage 3 disease may require decompression surgery to control pain. Patients with stage 2 and stage 3 disease may benefit from referral to an orthopedist for more detailed evaluation and treatment.

Rotator Cuff Tears

Pathophysiology. The rotator cuff acts as a dynamic stabilizer of the glenohumeral joint. Its primary function is to hold the humeral head in place throughout the full range of motion (see Fig. 53-5). In addition, it contributes power in all directions and is responsible for specific movements. The infraspinatus and teres minor act as external rotators, whereas the subscapularis is an internal rotator. The supraspinatus is essential for the first 30 degrees of shoulder abduction.

The tenuous blood supply of the rotator cuff, abusive tensile overload, and chronic wear under the coracoacromial arch predispose it to age-related degenerative changes. The advanced stage of this process is characterized by complete rupture of the rotator cuff.

The role of impingement in the development of rotator cuff tears is controversial. Primary impingement (e.g., impingement related to variation in acromion anatomy) is uncommon but when present accelerates the degenerative process. More often, weakening or rupture of the cuff with age allows for superior migration of the humeral head, which results in secondary impingement. This impingement produces secondary changes within the subacromial space and symptoms characteristic of the impingement syndrome.

Rotator cuff tears typically involve the dominant arm and occur in men older than 40 years. The occupational history is significant for strenuous work requiring overhead activity. Most tears occur near the attachment of the supraspinatus and can extend anteriorly into the subscapularis or posteriorly into the infraspinatus. Tears can be classified according to their size, completeness, pattern location, or duration. A clinically useful system is to divide tears into acute or chronic types. Acute tears (10%) usually are associated with a specific traumatic event. Often, no history of previous shoulder problems can be identified. The most common mechanism of injury is forced abduction associated with significant resistance; this usually occurs when the patient attempts to break a fall with an outstretched hand. Alternatively, the tendon

www.ketabpezeshki.com 66485457-66963820

rupture may occur with attempts to lift a heavy object or with a fall directly onto an immovable object.[64]

Clinical Features. With acute tears, patients typically report a sudden tearing sensation in the shoulder followed by severe pain that radiates into the arm. Pain and secondary muscle spasm limit shoulder motion. Physical findings depend on the completeness, size, and location of the tear. Point tenderness is usually present over the site of rupture (greater tuberosity). A palpable defect also may be present. Subacromial injection of 10 mL of 1% lidocaine eliminates pain and allows for proper evaluation of motor function. The patient with a large tear cannot initiate shoulder abduction. A discrepancy between active and passive range of motion is highly suggestive of a rotator cuff tear.[64] The drop-arm test, performed by passively abducting the arm to 90 degrees and asking the patient to hold the arm in this position, is positive with significant tears. Slight pressure on the distal forearm or wrist causes the patient to drop the arm suddenly. The acute pain resulting from hemorrhage and spasm subsides over a few days. Repeat examination at this point confirms the loss of function in significant tears.

Chronic tears account for approximately 90% of all lesions. Chronic tears are attritional and more insidious in their presentation. Early findings include the painful arc sign as a result of secondary impingement. The pain is worse at night and interferes with sleep. Worsening pain is followed by the gradual onset of weakness in the arm. Flexion and abduction are affected first. The patient attempts to initiate abduction with scapulothoracic movement. Internal rotation is weakened by anterior extension of the tear. Posterior extension compromises external rotation. The drop-arm test result is positive with large tears, and atrophy of the supraspinatus and infraspinatus muscles may be seen. In a large clinical study, the combination of the painful arc sign, positive drop-arm test result, and positive infraspinatus muscle test result produced the best post-test probability (91%) for full-thickness rotator cuff tears.[62]

Diagnostic Strategies: Radiology. Radiographs may be normal in acute and chronic tears, but more often they show evidence of nonspecific degenerative changes within the glenohumeral joint and subacromial space. The greater tuberosity can have a sclerotic or cystic appearance. Osteophytic spurs and sclerosis of the undersurface of the acromion may narrow the subacromial space. The hallmark of a complete tear is superior displacement of the humeral head. This displacement is best seen on an external rotation view. The normal distance from the superior aspect of the humerus to the undersurface of the acromion ranges from 7 to 14 mm. A distance of less than 6 mm is highly suggestive of a complete tear. Outpatient ultrasound examination, MRI, or an arthrogram can confirm the diagnosis. Ultrasound appears to be an excellent initial screening test, and in one study the overall accuracy of ultrasonography in the detection of partial- and full-thickness rotator cuff tears was 87%, with arthroscopy used as the "gold standard" diagnostic modality.[65]

Management. Acute tears should be immobilized in a sling and the patient referred promptly for orthopedic follow-up care. Early surgical repair (before 3 weeks) is preferred in these instances, especially for a young or active person. The management of chronic tears includes pain control and a shoulder rehabilitation program. Painful arc symptoms may respond to subacromial injection of a corticosteroid (see Table 53-3). Orthopedic follow-up care is essential because patients with persistent pain and weakness may require surgical repair.

Lesions of the Biceps Muscle

The biceps is composed of two heads. The long head originates from the supraglenoid tubercle and glenoid labrum and ascends over the humeral head to enter the arm by way of the bicipital groove. The long head is covered by a synovial sheath and is held in place within the groove by the coracohumeral and transverse humeral ligaments. The short head of the biceps originates from the coracoid process and inserts with the long head onto the tuberosity of the radius. The biceps is responsible for flexion as well as supination at the elbow and serves as a stabilizer for the glenohumeral joint.

Bicipital Tendinitis

Pathophysiology. Anatomically, the long head of the biceps is subject to the same stresses as those incurred by the rotator cuff within the subacromial space. Irritation and microtrauma as a result of repetitive elevation or abduction of the shoulder produce an inflammatory reaction within the synovial sheath. Bicipital tendinitis usually is associated with other acromial arch impingement conditions (e.g., subacromial bursitis, rotator cuff tendinitis).[66]

The typical patient is middle-aged and involved in an occupation or recreational activity that requires overhead movement. The presenting complaint is pain in the anterior part of the shoulder along the bicipital groove that radiates into the upper arm. There is usually no history of trauma. Pain increases with activity and decreases with rest. Abduction and external rotation in particular are painful. Pain is worse at night and may interfere with sleep.

Primary bicipital tendinitis (inflammation without other underlying pathology) is rare (5% of cases) and affects younger individuals.[66]

Clinical Features. On examination, point tenderness can be elicited over the biceps tendon as it passes through the bicipital groove. This is best shown with the arm in 10 degrees of internal rotation. Active range of motion is limited by pain, but the passive range remains intact. Supination against resistance—the Yergason test—with the arm adducted and the elbow flexed to 90 degrees reproduces the pain in 50% of cases (Fig. 53-42).[66] Another proactive test is the biceps resistance test (Speed test), in which forward flexion of the shoulder (elbow extended and forearm supinated) carried out against resistance produces pain in the bicipital groove. The specificity of these tests is limited in the presence of impingement and rotator cuff disease.

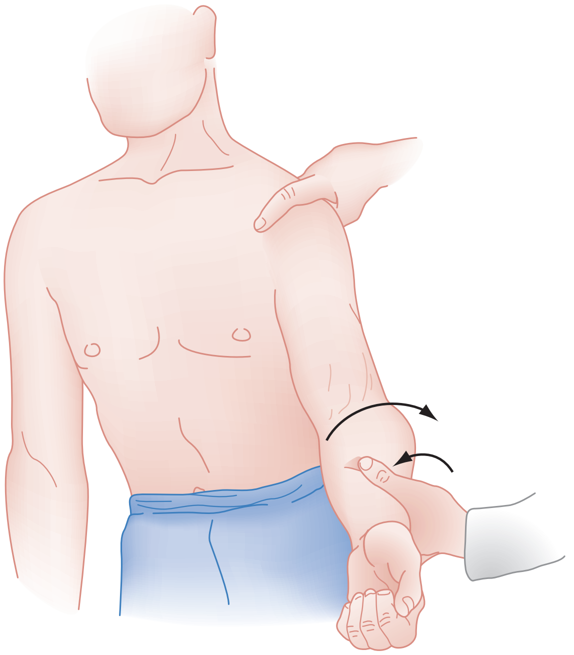


Figure 53-42. Yergason's test. With the elbow flexed, supination of the forearm *(arrows)* against resistance causes pain in the anterior and inner aspect of the shoulder. (From DePalma AF: Surgery of the Shoulder, 3rd ed. Philadelphia, JB Lippincott, 1983.)

www.ketabpezeshki.com 66485457-66963820

Diagnostic Strategies: Radiology. Radiographs are usually normal but may show evidence of subacromial space impingement by associated acromioclavicular arthritis and osteophytic spurs. The preferred imaging modality is MRI.[67]

Management. Emergency treatment consists of rest (immobilization in a sling), application of ice, and an NSAID regimen. Gentle stretching exercises are encouraged as symptoms subside. Refractory or progressive cases should be referred to an orthopedic surgeon. Although the bicipital sheath can be injected with a corticosteroid preparation, the procedure is technically difficult, and inadvertent direct tendon injection can lead to tendon rupture. An alternative option is iontophoresis with a topical steroid over the bicipital groove.[67] Surgery may be necessary in patients who fail to respond to conservative therapy.

Ruptures of the Biceps Tendon

Pathophysiology. Ruptures of the biceps tendon can be classified into proximal and distal types. Distal ruptures are rare and are not discussed here. Proximally, microtears and other age-related attritional changes within the long head predispose it to rupture.[64] The rupture can be spontaneous or may follow a traumatic event involving either forced extension or resisted supination and flexion.

Clinical Features. The classic history of an acute rupture is that of a sudden snap or pop, followed by pain and ecchymosis along the arm. The tendon usually ruptures at its weakest point, which is just distal to the exit from the glenohumeral joint cavity. With a complete rupture, distal retraction of the muscle results in a "Popeye" appearance of the arm. A difference in muscle contour (Ludington sign) also may be seen when both arms are placed behind the head and the biceps muscles are contracted. Functionally, forearm supination is weakened, but elbow flexion stays strong because the coracobrachialis and short head of the biceps remain intact. Most bicep tendon ruptures are associated with the impingement syndrome and a rotator cuff tear.

Diagnostic Strategies: Radiology. Radiographic findings usually are unremarkable, and the confirmatory test of choice is MRI.

Management. The injured arm should be immobilized in a sling with the elbow in 90 degrees of flexion. The local application of ice may provide temporary relief. Analgesia should be provided, and the patient should be referred to an orthopedic surgeon for further evaluation and treatment within 72 hours. Surgical repair is a consideration in young, active persons. In older patients, conservative therapy (range-of-motion and strengthening exercise) is preferred because the cosmetic deformity is minimal and the mild functional loss usually is acceptable.

Subluxations and Dislocations of the Biceps Tendon. Subluxations and dislocations of the biceps tendon usually are associated with a congenitally shallow bicipital groove or atraumatic (attritional) tears of the coracohumeral and transverse humeral ligaments. The patient reports a snapping sensation in the upper arm with abduction and external rotation. External and internal rotation of the abducted shoulder shows dislocation and relocation of the tendon. With complete dislocation, the arm may reflexively drop to relocate the tendon. These conditions may require operative repair and should be referred to an orthopedist.

Calcific Tendinitis

Pathophysiology. Shoulder calcific tendinitis affects up to 10% of the population and frequently is encountered in the ED. The condition affects people aged 30 to 50 years and is painful in 50% of patients.[68] Calcific deposits occur primarily in the supraspinatus tendon near its attachment to the greater tuberosity. Deposits also may involve the infraspinatus, teres minor, or subscapularis tendons. Women are more often affected than men, and 10% of the patients have bilateral deposits. In the precalcific stage, the tendon undergoes fibrocartilaginous transformation. The precipitating factors for this change remain unclear and may involve hypoxia- or stress-related degenerative changes within the tendon.[69] Calcium hydroxyapatite crystals are deposited and coalesce within the matrix of the tendon. Subsequent invasion of vascular channels into the deposit allows for the influx of neutrophils and macrophages (inflammatory response), which remove the calcification through phagocytosis. Finally, fibroblasts form collagen to create a postcalcification scar.[69]

Clinical Features. The clinical presentation can be divided into silent, subacute, and acute phases based on the physical characteristics of the calcific deposits and the nature of the inflammatory response within the tendon and subacromial bursa. The silent phase consists of a dry, powdery deposit with no surrounding inflammatory reaction. It usually is an incidental diagnosis when shoulder radiographs are obtained for other purposes. The deposits may remain painless and eventually reabsorb.

The painful arc syndrome is a hallmark of the subacute phase of calcific tendinitis. Enlargement and softening of the deposit lead to narrowing of the subacromial space, resulting in impingement under the acromial arch. Pain experienced at 60 to 120 degrees of abduction (see Fig. 53-40) is characteristic.

A severe inflammatory reaction within and around the deposit produces the acute phase of calcific tendinitis. The deposit becomes milky and has the appearance of an acute abscess. The patient is in severe pain and holds the arm close to the chest. Active and passive range of motion is severely limited. The shoulder is warm and extremely tender to the touch. Severe pain is related to increased intratendinous pressure, and spontaneous rupture of the deposit into the subacromial bursa can be associated with dramatic relief of symptoms.

Diagnostic Strategies: Radiology. Radiographs show calcific deposits in the involved tendon (Fig. 53-43). For the supraspinatus, calcific deposits are best seen on the internal and external rotation AP views. The axillary view is useful for showing calcification within the other tendons of the rotator cuff.

Management. Subacute symptoms usually respond to NSAIDs and measures to limit any offending activity. The acute phase should be treated with sling immobilization, NSAIDs, and analgesia. Subacromial injection of a local anesthetic may provide dramatic temporary relief in the ED. Needle lavage (puncturing of the calcific deposits to decrease intratendinous pressure) under ultrasound or fluoroscopy guidance also has been described as an effective treatment during the acute phase.[69] The subacromial injection of corticosteroids for impingement symptoms is controversial because these agents may delay the process of calcium resorption, thereby interfering with the natural course of the condition. Patients with chronic symptoms may benefit from surgical removal or extracorporeal shock wave therapy to produce

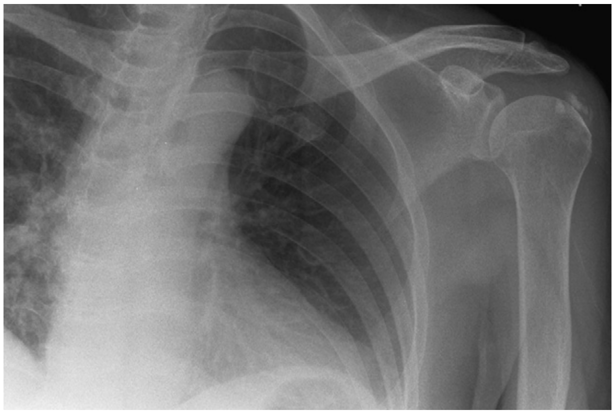


Figure 53-43. Rotator cuff calcific tendinitis.

www.ketabpezeshki.com 66485457-66963820

fragmentation of the calcific deposits.[68,69] Early shoulder range-of-motion exercises should be encouraged in all patients to minimize the risk of adhesive capsulitis. All symptomatic patients should be referred for orthopedic follow-up care.

Adhesive Capsulitis

Pathophysiology. Adhesive capsulitis ("frozen shoulder") is a specific diagnostic entity characterized by an idiopathic inflammatory reaction within the capsule and synovium of the glenohumeral joint. The inflammatory reaction results in the formation of adhesions within the capsule and inferior axillary fold, leading to restricted active and passive range of motion. The prevalence rate is 2 to 5%, with a female predominance.[70] Adhesive capsulitis is more common in diabetic patients. Adhesive capsulitis should be differentiated from other, more common causes of the painful stiff shoulder; this distinction is important because any painful condition of the shoulder (e.g., calcific tendinitis, rotator cuff tear, osteoarthritis, or trauma) may be associated with decreased range of motion.[70] Although the cause of adhesive capsulitis remains unknown, any condition associated with prolonged disuse of the arm can result in capsular contraction, including voluntary immobilization after calcific tendinitis, rotator cuff injury, mastectomy, or a distal upper extremity injury (Colles' fracture).

Clinical Features. The typical patient is a diabetic woman 40 to 60 years of age. The nondominant arm usually is affected, and the patient has trouble with the activities of daily living. The pain often is severe at night and localized over the deltoid area. As the condition progresses, there is uniform limitation of all glenohumeral movement, including flexion, abduction, and rotation. On passive testing, a sense of mechanical restriction of joint motion can often be appreciated. Shoulder radiographs usually are normal in appearance if no associated pathologic condition is present.

Management. The best form of therapy is preventive in nature. Prolonged shoulder immobilization is avoided, and early motion is encouraged in all instances (see Fig. 53-14). Treatment of adhesive capsulitis in the ED consists of NSAIDs and referral to an orthopedic surgeon. Initial therapy usually is conservative and consists of a gentle assisted exercise program along with intra-articular steroid injection. Surgical treatment, including manipulation under anesthesia and arthroscopic capsular release, is reserved for patients in whom nonoperative treatment for at least 6 months has failed to produce improvement.[70]

Injection Therapy. The local injection of corticosteroid preparations can be useful in many painful conditions that affect the shoulder, including rotator cuff tendinitis and subacromial bursitis. Evidence-based research that supports or refutes the use of injection corticosteroid therapy is limited and conflicting.[71] Potential explanations for discordant results of randomized controlled studies include differing outcome definitions and the observation that subacromial injections are difficult to give.[72] The accuracy of needle placement for subacromial injections has been reported to be 70%.[63] Although useful for relieving the inflammatory reaction, corticosteroid injections in general do not alter the underlying disease process. Corticosteroids inhibit all phases of the inflammatory response, including leukocyte migration, edema formation, mediator release, vascular permeability, collagen deposition, and fibroblast proliferation. Systemic complications are rare after local injection therapy. Site-specific complications include articular cartilage damage, tendon weakening or rupture, and subcutaneous atrophy. The incidence of local complications correlates with the injection technique, dose used, and frequency of administration. Direct tendon injection is avoided at all times, and the number of steroid injections should be limited to two per shoulder since a high failure rate for rotator cuff repairs has been reported in patients who have received more than three preoperative subacromial injections.[63]

Numerous corticosteroid preparations are available (see Table 53-3). Injection of a long-acting agent or a combination of a short-acting and a long-acting agent is preferred. The dose used depends on the size of the joint or bursa and the response of the individual patient. With concurrent use of a local anesthetic agent for acute pain relief, better diffusion of the steroid preparation may be obtained.

After injection, the shoulder should be immobilized and activity should be limited for several days to protect against further injury. Improvement usually begins within 1 to 7 days and can last weeks to months, depending on the preparation and underlying condition. Local anesthetic injection may result in dramatic temporary relief of symptoms in the ED.

KEY CONCEPTS

- A thorough neurovascular examination is essential and is performed before and repeated after any manipulation.
- Axillary nerve function is best evaluated by testing the motor function of the deltoid muscle.
- The three-view trauma series of the shoulder (true AP, scapular Y, and axillary views) leads to an accurate radiographic diagnosis of most fractures and dislocations, although specialized views are necessary in some instances. The presence of unfused epiphyses in adolescents and young adults is an important consideration, and comparison films may be indicated on a selective basis.
- Most fractures can be treated conservatively with good functional outcomes.
- The most important aspect of scapular fractures is the high incidence of associated injuries to the ipsilateral lung, chest wall, and shoulder girdle complex.
- Posterior SCJ dislocations can be associated with life-threatening injuries within the superior mediastinum, which are best visualized with a chest CT angiogram.
- If the coracoclavicular distance exceeds 10 to 13 mm, or if a difference of more than 5 mm in this distance is observed between the injured and the uninjured sides, a grade III ACJ dislocation should be suspected.
- Most studies have concluded that conservative treatment of type III ACJ dislocations achieves functional results equal to or in some cases better than those achieved with surgical intervention.
- A compression fracture of the posterolateral aspect of the humeral head (Hill-Sachs deformity) is present in a large percentage of anterior glenohumeral dislocations.
- Recurrence is a common complication after anterior dislocation, especially in male patients younger than 30 years, and such patients may benefit from surgical repair.
- Posterior dislocation should be included in the differential diagnosis of any shoulder injury. A posterior dislocation should be suspected in any patient who reports shoulder pain or discomfort after a convulsive episode and in the presence of a lesser tuberosity fracture.
- It is important to evaluate the relationship between the spine of the scapula and the longitudinal axis of the humerus to avoid missing an inferior glenohumeral dislocation.
- Early initiation of passive shoulder range-of-motion exercises helps reduce the risk of adhesive capsulitis when the shoulder is immobilized for any reason.
- It is important to be familiar with several techniques for the reduction of anterior shoulder dislocations.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Hussein MK: Kocher's method is 3,000 years old. *J Bone Joint Surg Br* 1968; 50:669.
2. O'Connor DR, Schwarze D, Fragomen AT, Perdomo M: Painless reduction of acute anterior shoulder dislocations without anesthesia. *Orthopedics* 2006; 29:528.
3. Simon RR, Koenigsknecht SJ: *Emergency Orthopedics: The Extremities*, 4th ed. Norwalk, Conn: McGraw-Hill; 2001.
4. Carson S, Woolridge DP, Colletti J, Kilgore K: Pediatric upper extremity injuries. *Pediatr Clin North Am* 2006; 53:41.
5. Yeh GL, Williams GR: Conservative management of sternoclavicular injuries. *Orthop Clin North Am* 2000; 31:189.
6. McKoy BE, Bensen CV, Hartsock LA: Fractures about the shoulder: Conservative management. *Orthop Clin North Am* 2000; 31:205.
7. Clarke HD, McCann PD: Acromioclavicular joint injuries. *Orthop Clin North Am* 2000; 31:177.
8. Cole PA: Scapular fractures. *Orthop Clin North Am* 2002; 33:1.
9. Wen DY: Current concepts in the treatment of anterior shoulder dislocations. *Am J Emerg Med* 1999; 17:410.
10. Cleeman E, Flatow EL: Shoulder dislocation in the young patient. *Orthop Clin North Am* 2000; 31:217.
11. Geusens E, Pans S, Verhulst D, Brys P: The modified axillary view of the shoulder: A painless alternative. *Emerg Radiol* 2006; 12:227.
12. Cross KP, Warkentine FH, Kim IK, Gracely E, Paul RI: Bedside ultrasound diagnosis of clavicle fractures in the pediatric emergency department. *Acad Emerg Med* 2010; 17:687.
13. Kim W, McKee MD: Management of acute clavicle fractures. *Orthop Clin North Am* 2008; 39:491.
14. Bahk MS, Kuhn JE, Galatz LM, Connor PM, Williams GR Jr: Acromioclavicular and sternoclavicular injuries and clavicular, glenoid, and scapular fractures. *J Bone Joint Surg Am* 2009; 91:2492.
15. McKee MD: Clavicle fractures in 2010: Sling/swathe or open reduction and internal fixation? *Orthop Clin North Am* 2010; 41:225.
16. Zlowodzki M, et al: Treatment of acute midshaft clavicle fractures: Systematic review of 2144 fractures: On behalf of the Evidence-Based Orthopaedic Trauma Working Group. *J Orthop Trauma* 2005; 19:504.
17. Nowak J, Holgersson M, Larsson S: Sequelae from clavicular fractures are common: A prospective study of 222 patients. *Acta Orthop* 2005; 76:496.
18. Bowen RE, Mah JY, Otsuka NY: Midshaft clavicle fractures associated with atlantoaxial rotatory displacement: A report of two cases. *J Orthop Trauma* 2003; 17:444.
19. Zlowodzki M, Bhandari M, Zelle BA, Kregor PJ, Cole PA: Treatment of scapula fractures: Systematic review of 520 fractures in 22 case series. *J Orthop Trauma* 2006; 20:230.
20. Brown CV, et al: Association of scapular fractures and blunt thoracic aortic injury: Fact or fiction? *Am Surg* 2005; 71:54.
21. Lapner PC, Uhthoff HK, Papp S: Scapula fractures. *Orthop Clin North Am* 2008; 39:459.
22. Südkamp NP, Jaeger N, Bornebusch L, Maier D, Izadpanah K: Fractures of the scapula. *Acta Chir Orthop Traumatol Cech* 2011; 78:297.
23. Tadros AM, Lunsjo K, Czechowski J, Corr P, Abu-Zidan FM: Usefulness of different imaging modalities in the assessment of scapular fractures caused by blunt trauma. *Acta Radiol* 2007; 1:71.
24. Murray IR, Amin AK, White TO, Robinson CM: Proximal humeral fractures: Current concepts in classification, treatment and outcomes. *J Bone Joint Surg Br* 2011; 93:1.
25. Ekholm R, et al: Fractures of the shaft of the humerus. An epidemiological study of 401 fractures. *J Bone Joint Surg Br* 2006; 88:1469.
26. Handoll HH, Gibson JN, Madhok R: Interventions for treating proximal humeral fractures in adults. *Cochrane Database Syst Rev* 2010; 4:CD000434.
27. McLaurin TM: Proximal humerus fractures in the elderly: Are we operating on too many? *Bull Hosp Jt Dis* 2004; 62:24.
28. Di Gennaro GL, Spina M, Lampasi M, Libri R, Donzelli O: Fractures of the proximal humerus in children. *Chir Organi Mov* 2008; 92:89.
29. Ferrera PC, Wheeling HM: Sternoclavicular joint injuries. *Am J Emerg Med* 2000; 18:58.
30. Jaggard MK, Gupte CM, Gulati V, Reilly P: A comprehensive review of trauma and disruption to the sternoclavicular joint with the proposal of a new classification system. *J Trauma* 2009; 66:576.
31. Malik S, Chiampas G, Leonard H: Emergent evaluation of injuries to the shoulder, clavicle and humerus. *Emerg Med Clin North Am* 2010; 28:739.
32. Garretson RB, Williams GR: Clinical evaluation of injuries to the acromioclavicular and sternoclavicular joints. *Clin Sports Med* 2003; 22:239.
33. Clavert P, Moulinoux P, Kempf JF: Technique of stabilization in acromioclavicular joint dislocation. *Tech Shoulder Elbow Surg* 2005; 6:1.
34. Chalidis B, et al: Has the management of shoulder dislocation changed over time? *Int Orthop* 2007; 31:385.
35. Perron AD, Ingerski MS, Brady WJ, Erling BF, Ullman EA: Acute complications associated with shoulder dislocation at an academic emergency department. *J Emerg Med* 2003; 24:141.
36. Perlmutter GS: Axillary nerve injury. *Clin Orthop Relat Res* 1999; 368:28.
37. Ufberg JW, Vilke GM, Chan TC, Harrigan RA: Anterior shoulder dislocations: Beyond traction-countertraction. *J Emerg Med* 2004; 27:301.
38. Fitch RW, Kuhn JE: Intraarticular lidocaine versus intravenous procedural sedation with narcotics and benzodiazepines for reduction of the dislocated shoulder: A systematic review. *Acad Emerg Med* 2008; 15:703.
39. Sayegh FE, et al: Reduction of acute anterior dislocations: A prospective randomized study comparing a new technique with the Hippocratic and Kocher methods. *J Bone Joint Surg Am* 2009; 91:2775.
40. Eachempati KK, Dua A, Malhotra R, Bhan S, Bera JR: The external rotation method for reduction of acute anterior dislocations and fracture-dislocations of the shoulder. *J Bone Joint Surg Am* 2004; 86:2431.
41. Shuster M, Abu-Laban RB, Boyd J: Prereduction radiographs in clinically evident anterior shoulder dislocation. *Am J Emerg Med* 1999; 17:653.
42. Shuster M, et al: Prospective evaluation of a guideline for the selective elimination of pre-reduction radiographs in clinically obvious anterior shoulder dislocation. *CJEM* 2002; 4:257.
43. Hendey GW: Necessity of radiographs in the emergency department management of shoulder dislocations. *Ann Emerg Med* 2000; 36:108.
44. Hendey GW, Chally MK, Stewart VB: Selective radiography in 100 patients with suspected shoulder dislocation. *J Emerg Med* 2006; 31:23.
45. Kahn JH, Mehta SI: The role of post-reduction radiographs after shoulder dislocation. *J Emerg Med* 2007; 33:169.
46. Paterson WH, Throckmorton TW, Koester M, Azar FM, Kuhn JE: Position and duration of immobilization after primary anterior shoulder dislocation: A systematic review and meta-analysis of the literature. *J Bone Joint Surg Am* 2010; 92:2924.
47. Murrell GC: Treatment of shoulder dislocation: Is a sling appropriate? *Med J Aust* 2003; 179:370.
48. Itoi E, et al: Immobilization in external rotation after shoulder dislocation reduces the risk of recurrence. A randomized controlled trial. *J Bone Joint Surg Am* 2007; 89:2124.
49. Liavaag S, et al: Immobilization in external rotation after primary shoulder dislocation did not reduce the risk of recurrence: A randomized controlled trial. *J Bone Joint Surg Am* 2011; 93:897.
50. Simank HG, Dauer G, Schneider S, Loew M: Incidence of rotator cuff tears in shoulder dislocations and results of therapy in older patients. *Arch Orthop Trauma Surg* 2006; 126:235.
51. Bedi A, Ryu RK: The treatment of primary anterior shoulder dislocations. *Instr Course Lect* 2009; 58:293.
52. Kowalsky MS, Levine WN: Traumatic posterior glenohumeral dislocation: Classification, pathoanatomy, diagnosis, and treatment. *Orthop Clin North Am* 2008; 39:519.
53. Perron AD, Jones RL: Posterior shoulder dislocation: Avoiding a missed diagnosis. *Am J Emerg Med* 2000; 18:189.
54. Cicak N: Posterior dislocation of the shoulder. *J Bone Joint Surg Br* 2004; 86:324.
55. Mimura T, et al: Closed reduction for traumatic posterior dislocation of the shoulder using the 'lever principle': Two case reports and a review of the literature. *J Orthop Surg (Hong Kong)* 2006; 14:336.
56. Grate I Jr: Luxatio erecta: A rarely seen, but often missed shoulder dislocation. *Am J Emerg Med* 2000; 18:317.
57. Nho SJ, et al: The two-step maneuver for closed reduction of inferior glenohumeral dislocation (luxatio erecta to anterior dislocation to reduction). *J Orthop Trauma* 2006; 20:354.
58. Althausen PL, Lee MA, Finkemeier CG: Scapulothoracic dissociation: Diagnosis and treatment. *Clin Orthop Relat Res* 2003; 416:237.
59. Brucker PU, Gruen GS, Kaufmann RA: Scapulothoracic dissociation: Evaluation and management. *Injury* 2005; 36:1147.
60. Morrison DS, Greenbaum BS, Einhorn A: Shoulder impingement. *Orthop Clin North Am* 2000; 31:285.
61. Neer CS 2nd: Impingement lesions. *Clin Orthop Relat Res* 1983; 173:70.
62. Park HB, Yokota A, Gill HS, El Rassi G, McFarland EG: Diagnostic accuracy of clinical tests for the different degrees of subacromial impingement syndrome. *J Bone Joint Surg Am* 2005; 87:1446.
63. Codsi MJ: The painful shoulder: When to inject and when to refer. *Cleve Clin J Med* 2007; 74:473.

www.ketabpezeshki.com 66485457-66963820

64. Brunelli MP, Gill TJ: Fractures and tendon injuries of the athletic shoulder. *Orthop Clin North Am* 2002; 33:497.
65. Teefey SA, et al: Detection and quantification of rotator cuff tears: Comparison of ultrasonographic, magnetic resonance imaging, and arthroscopic findings in seventy-one consecutive cases. *J Bone Joint Surg Am* 2004; 86:708.
66. Patton WC, McCluskey GM: Biceps tendinitis and subluxation. *Clin Sports Med* 2001; 20:505.
67. Friedman DJ, Dunn JC, Higgins LD, Warner JJ: Proximal biceps tendon: Injuries and management. *Sports Med Arthrosc* 2008; 16:162.
68. Mouzopoulos G, Stamatakos M, Mouzopoulos D, Tzurbakis M: Extracorporeal shock wave treatment for shoulder calcific tendonitis: A systematic review. *Skeletal Radiol* 2007; 36:803.
69. Gosens T, Hofstee DJ: Calcifying tendinitis of the shoulder: Advances in imaging and management. *Curr Rheumatol Rep* 2009; 11:129.
70. Neviaser AS, Hannafin JA: Adhesive capsulitis: A review of current treatment. *Am J Sports Med* 2010; 38:2346.
71. Buchbinder R, Green S, Youd JM: Corticosteroid injections for shoulder pain. *Cochrane Database Syst Rev* 2003; 1:CD004016.
72. Arroll B, Goodyear-Smith F: Corticosteroid injections for painful shoulder: A meta-analysis. *Br J Gen Pract* 2005; 55:224.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 54

MUSCULOSKELETAL BACK PAIN

Michelle Lin and Bory Kea

LOW BACK PAIN

PERSPECTIVE

Background

Approximately 70 to 90% of adults during their lifetime experience *acute low back pain,* defined as pain lasting less than 6 weeks in duration.[1,2] The cause of the back pain remains unknown in 85% of affected persons after appropriate initial investigation—a situation frustrating for both physician and patient.[3] Frequent diagnoses in such cases include "acute lumbosacral strain," "lumbago," and "mechanical back pain." These nonspecific, catch-all terms reflect the diagnostic challenge and lack of pathognomonic tests for low back pain. More accurately, these patients should be diagnosed with *idiopathic low back pain.* Regardless, most cases resolve spontaneously within 6 weeks. In recent studies on the management of acute low back pain, the most significant discovery—contradictory to traditional teaching from the 1980s—is the need for these patients, including those with sciatica symptoms, to avoid bed rest.[4,5] Management recommendations for chronic back pain remain controversial, however, and the condition accounts for a significant proportion of costs to the health care system.

Epidemiology

In the ambulatory care setting the medical complaint of back pain is the fifth most common reason for a visit to a physician's office, with 15 million annual visits in the United States, of which 7.3 million are to the emergency department (ED) at an average of 20,000 visits per day in 2008.[6,7] Back pain was the leading cause of pain as reported in the 2010 National Health Interview Survey (NHIS), with 28.8% of the respondents reporting back pain lasting at least 1 day within the previous 3 months.[8] Back pain primarily affects adults 30 to 60 years of age and has a tremendous impact on worker productivity, with significant economic consequences. It is the second leading cause of pain resulting in lost productive time from work, following headache.[9] For aggregate hospitalization costs alone, it was the ninth most expensive condition in 2008 at more than $9.5 billion.[7] Overall, patients with back pain account for billions of dollars in total direct and indirect costs in the United States.[1,2,10]

The natural history of most cases of low back pain follows a benign and self-limited course. In a large pooled analysis, patients reported a decrease in back pain by 58% within 1 month. If the pain did not resolve within 3 months, however, it was unlikely to resolve after 12 months. The recurrence rate for pain was 66 to 84% within the first 12 months.[11]

Risk factors for low back pain are continually being investigated. In a large systematic review, the presence of nonorganic signs of pain, poor pain-coping behaviors, great functional impairment, poor general health, and known psychiatric disease seem to predict patients who would develop chronic, disabling back pain in the future.[12] Early evidence also points to a genetic predisposition to lumbar disk disease.[13] Multiple other factors have been investigated, including body habitus, various occupations, deconditioning, tobacco smoking, stress levels, and psychological profile, with conflicting results.[13-19]

PRINCIPLES OF DISEASE

Anatomy and Physiology

The lumbosacral spine consists of five lumbar vertebrae and the sacrum. Moving from anterior to posterior, each vertebra can be divided into the cylindrical vertebral body, two pedicles, two transverse processes, two overarching laminae, and a spinous process. These structures surround the neural canal, which houses the spinal cord and nerve roots and has a midsagittal anteroposterior diameter of 15 to 23 mm. The paired superior and inferior articulating processes join the articulating processes one vertebral level above and below. Each articulation site is called a *facet joint.* Intervertebral disks interpose between vertebral bodies, providing elasticity and stability to the vertebral column. Each disk consists of an inner colloidal gelatinous substance, the *nucleus pulposus,* and an outer capsule, the *annulus fibrosus,* which is thinner posteriorly than anteriorly (Fig. 54-1).

Various ligaments and muscles also provide stability to the lumbosacral spine. The anterior and posterior longitudinal ligaments course along the anterior and posterior surfaces of the vertebral bodies. The posterior longitudinal ligament forms a border between the intervertebral disks and the neural canal. As expected, because this ligament thins as it runs inferiorly from L1 to S1, 95% of lumbar disk herniations occur at the L4-5 and L5-S1 levels, causing pain and neurologic deficit in the L5 and S1 distribution. Most herniations extrude posterolaterally to impinge on a nerve root asymmetrically.[20] The ligamentum flavum courses just anterior to the laminae within the neural canal. With age, this ligament can thicken, potentially causing spinal stenosis.

The spinal cord ends at the L1-2 interspace, and the lower cauda equina nerve roots extend inferiorly, exiting the sacral foramina as peripheral nerves to the lower extremity. Pain fibers supplying structures in the lumbosacral region primarily arise from the posterior rami and sinuvertebral nerves at each lumbar vertebral level. The nucleus pulposus and inner annular fibers of the intervertebral disk are unique in their lack of any pain fibers.[21] This

www.ketabpezeshki.com 66485457-66963820

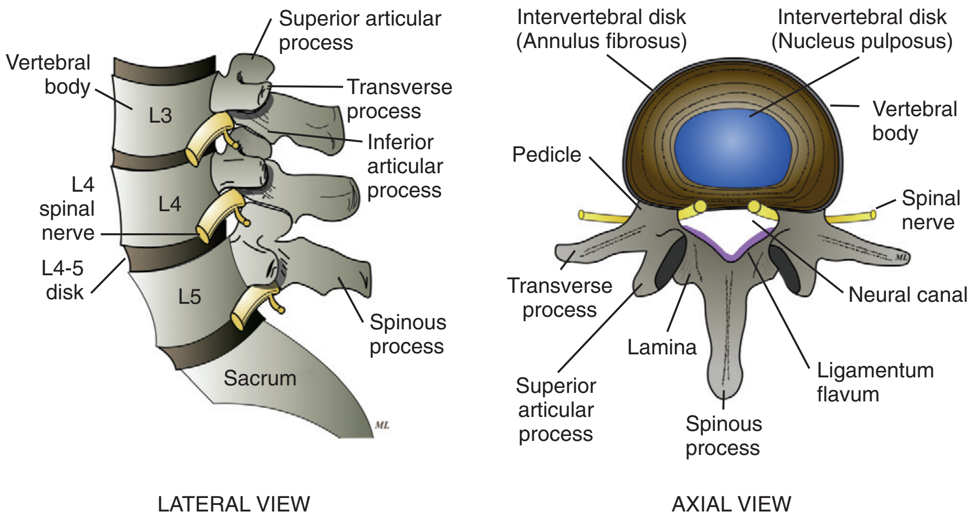


Figure 54-1. Lateral and axial views of lumbar vertebral anatomy.

anatomic feature correlates consistently with magnetic resonance imaging (MRI) evidence of disk pathology in as many as 31% of asymptomatic patients. On follow-up, one study showed that abnormal disk findings in asymptomatic individuals did not predict the future development of back pain after 7 years.[21,22]

Pathophysiology

Most conditions of low back pain have no proven cause. It is estimated that 85% of patients have no definitive diagnosis and are presumed to have pain originating from the soft tissue, including the muscles and ligaments.[10,20] In the other 15% of patients with a known cause, the pain may originate in the nerve root, the articular facets, or the bone itself.

In low back pain of *nerve root origin,* a spinal nerve root can become inflamed and painful with external impingement. Disk herniation, usually at the L4-5 and L5-S1 levels, is the most common cause of *sciatica* (i.e., pain radiating down the posterior leg from sciatic nerve root irritation). As the disk starts to desiccate and degenerate, starting in their 30s, patients are at increased risk for outward herniation of the nucleus pulposus with consequent nerve root impingement. With further aging, these disks progressively shrink in size. In keeping with these findings, symptomatic disk herniations typically are found in patients 30 to 50 years of age. Local nerve ischemia from physical compression also may contribute to the inflammation and pain. Studies also show that exposure of the nucleus pulposus during disk herniation may result in local neural inflammation, leading to pain.[23] Nerve root impingement also can occur with spinal stenosis, a narrowing of the neural canal from congenital narrowing or, more often, from degenerative or hypertrophic changes of the disks, vertebrae, facet joints, and ligamentum flavum.[24]

The two most critical conditions that cause nerve irritation are cauda equina syndrome and a spinal epidural abscess. Cauda equina syndrome is most commonly a result of a massive central disk herniation, usually compressing multiple, bilateral nerve roots and causing back pain radiating to both legs, saddle anesthesia, and impaired bowel and bladder function (i.e., diminished rectal tone and urinary retention, respectively). Emergent surgical decompression is indicated to preserve neurologic function. An epidural abscess similarly results in nerve root impingement, commonly with spinal cord involvement, causing significant back pain and ultimately neurologic deficits. These rare infections develop most commonly from the hematogenous spread of both methicillin-sensitive and methicillin-resistant *Staphylococcus aureus.*[20]

Congenital and developmental spinal abnormalities also may cause back pain by nerve root inflammation in some cases, but much less frequently than was thought previously. Conditions such as kyphosis and scoliosis usually do not cause pain unless the degree of vertebral column misalignment is pronounced.[25] Similarly, spondylolisthesis (slippage of one vertebral body on another) does not usually cause pain if the slippage is less than 25% of the vertebral body width. Even in patients with higher grades of anterior slippage (anterolisthesis), the development of severe back pain is rare. Although it is one third as common as anterolisthesis, backward slippage (retrolisthesis) is almost always associated with back pain. Multifactorial causes of spondylolisthesis include degenerative changes and trauma. Degenerative lumbar spondylolisthesis in older patients occurs most often at the L4-5 level (7.4% overall population prevalence), followed by the L5-S1 level (1.9%) and the L3-4 level (1.7%).[26] Spondylolisthesis often is associated with bilateral pars interarticularis defects in the affected vertebra (spondylolysis).

In low back pain of *articular facet origin,* as with any other joint in the body, degenerative changes in the synovial articular facets in the lumbosacral spine occur with age. Although the exact role and significance of articular facet joints in back pain are unclear, facet pathology has been suggested to contribute to 15 to 45% of chronic back pain cases.[27]

In low back pain *originating from bone,* direct irritation of the vertebral bone and its periosteum can cause back pain. The causes of spondylitis (osteomyelitis of the axial skeleton) can range from a slowly progressing tuberculosis infection (Pott's disease) to a more acute bacterial infection. Typically, bacteria seed the bone from a hematogenous source, such as from a skin wound or urinary tract infection, or directly from intravenous drug use. The most common bacterial culprit is *S. aureus.* Primary and metastatic bone neoplasms can cause back pain from tumor infiltration into the bone. Primary bone tumors, such as multiple myeloma, chordoma, Ewing's sarcoma, and osteosarcoma, occur 25 times less frequently than metastatic disease.[28] Of the neoplasms, breast, lung, prostate, thyroid, and kidney cancers and lymphoma are the most likely to metastasize to bone. Inflammatory conditions, such as ankylosing spondylitis, other arthropathies, and osteoporosis also can cause back pain. In osteoporosis the generalized decrease in bone mineralization can cause pain from microfractures of the vertebral column.

www.ketabpezeshki.com 66485457-66963820

Referred pain, most commonly from intraperitoneal and retroperitoneal abdominal pathology, also is considered in patients with back pain. Chronic back pain is complex and multifactorial. Not only are the structural causes unclear, but the nonphysical factors are variable and difficult to determine. Functional factors range from fear, depression, and personality disorders to financial motivation. Although it is likely that many of these patients do experience some kind of chronic pain, it is unknown why their pain then triggers depression, drug dependence, and malingering in some people but not in others. One difference may be the degree of disruption that the condition causes in the patient's lifestyle. A normally active and athletic person who is incapacitated is more profoundly affected than someone who is habitually sedentary. Psychological factors and potential compensation play a large role in the behavior of many patients with chronic back pain.[12,17,29,30]

It has traditionally been taught that pediatric back pain results in a diagnosis more often than adult pain; however, this axiom has been called into question as multiple studies have shown an increasing number of children being diagnosed with nonspecific back pain, accounting for at least 50% of cases, paralleling adults in pathophysiology.[31-34] Children complaining of back pain require appropriate investigation. They may turn out to have spondylolysis with a variable degree of spondylolisthesis, Scheuermann's disease (kyphosis and osteochondritis of the vertebral endplates), an infectious disease, or a neoplastic process. Disk herniation in children is comparatively rare, but when it does occur, the presentation is similar to that in adults.[31]

CLINICAL FEATURES

Signs and Symptoms

A thorough history and physical examination are crucial in evaluating all patients with acute low back pain. The classic historical (Table 54-1) and physical findings with various entities associated with low back pain are reviewed in this section. Although most of these causative disorders are benign, four such disorders have been identified by the Agency for Healthcare Research and Quality (AHQR) as "cannot miss" or "red flag" diagnoses: spinal fracture, cauda equina syndrome, spinal infection, and malignancy.[5] A methodical and focused approach to the history and physical examination can help assess the patient's pretest probability for each of these disease entities and determine whether further tests should be ordered.

Table 54-1 Historical Clues to the Cause of Low Back Pain

QUESTIONS FOR PATIENT	POTENTIAL DIAGNOSIS
Does the back pain radiate down past the knees?	Radiculopathy and likely a herniated disk
Is the pain worse with walking and better with bending forward and sitting?	Spinal stenosis
Do you have morning back stiffness that improves with exercise?	Ankylosing spondylitis
Are you older than 50 years?	Osteoporotic fracture, spinal malignancy
Has there been any recent history of blunt trauma?	Fracture
Do you take long-term corticosteroids?	Fracture, spinal infection
Do you have a history of cancer?	Spinal metastatic malignancy
Does your pain persist at rest?	Spinal malignancy, spinal infection
Has there been persistent pain for longer than 6 weeks?	Spinal malignancy
Has there been unexplained weight loss?	Spinal malignancy
Is the pain worse at night?	Spinal malignancy, spinal infection
Are you immunocompromised (e.g., HIV infection, alcoholism, diabetes)?	Spinal infection
Have you had fevers or chills?	Spinal infection
Do you have pain, weakness, or numbness in both legs?	Cauda equina syndrome
Do you have bladder or bowel control problems?	Cauda equina syndrome

HIV, human immunodeficiency virus.

Uncomplicated Musculoskeletal Back Pain

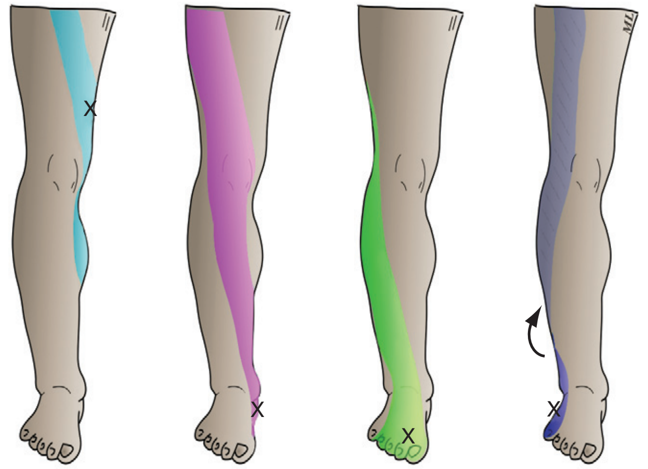
Most patients with back pain can be classified in the category of those with uncomplicated musculoskeletal back pain. These patients have no red flag findings in their history and on physical examination. Often, patients are unable to recall an inciting incident. The pain usually is characterized as an "ache" or "spasm" and is localized asymmetrically in the lumbar paraspinous muscle, with radiation to the buttock or posterior thigh proximal to the knee. Movement exacerbates the pain, and rest relieves it. No associated deficit in sensation, strength, or bowel or bladder sphincter tone is identified in the history or on the clinical examination. The sole physical findings may be regional lumbosacral tenderness and a limited range of motion of the lower back.

Radiculopathy

Approximately 1% of all patients with low back pain exhibit signs of lumbar radiculopathy (i.e., nerve root irritation).[35] The most common causative process is herniation of a lumbar disk; other causes include spinal stenosis, malignancy, and infection. The most common type of lumbar radiculopathy is an L5 or S1 radiculopathy causing sciatica symptoms. Patients with sciatica describe their pain as radiating from the low back to the legs, distal to the knee. Such pain is characterized as "shooting," "lancing," "sharp," or "burning." Associated symptoms include focal numbness or weakness in one of the lower extremities. Exacerbating triggers include sitting, bending, coughing, and straining; relieving factors include lying supine and still.

On physical examination the patient frequently exhibits tenderness to palpation in the sciatic notch. The *straight leg raise* (SLR) *test* is a fairly sensitive assessment tool to determine if the patient has sciatica. The SLR test is done with the patient supine and the legs extended. The symptomatic leg is passively raised while the knee is kept straight. The presence of back pain, which radiates past the knee when the leg is elevated 30 to 70 degrees, suggests an L5 or S1 radiculopathy. If the SLR test results in isolated low back pain without radiation symptoms to the legs, however, it is considered to be a *negative* finding. Through pooled analysis, the SLR test has a sensitivity of 91% but a low specificity of 26%, meaning that a negative result is fairly accurate in ruling out sciatica.[36] Corroborative tests for sciatica include the "bowstring sign" (reproduction of pain with deep palpation of the taut "bowstring" posterior tibial nerve in the midline popliteal fossa) and reproduction of pain with foot dorsiflexion when the leg is elevated just short of the pain threshold during the SLR test. As an alternative to the SLR test, with the patient in a seated position, the knee can be extended ("flip test"), which also should stretch the sciatic nerve. Reproduction of the pain often causes the patient

www.ketabpezeshki.com 66485457-66963820



Nerve root level	L3	L4	L5	S1
Pain location				
Stress test	R-SLR	R-SLR	SLR, C-SLR	SLR, C-SLR
Sensation (“X”)	Medial thigh	Medial foot	Between 1st and 2nd toe	Lateral foot
Strength	Hip flexion	Knee extension	Big toe/ankle dorsiflexion	Ankle plantar flexion
Reflex	—	Patellar	—	Achilles

Figure 54-2. Physical examination findings for L3-S1 radiculopathy. The X marks the ideal location to test for sensation for each nerve root. *C-SLR,* crossed straight leg raise; *R-SLR,* reverse straight leg raise; *SLR,* straight leg raise.

to lean backward reflexively from the pain, almost “flipping” back into a supine position.

A *crossed SLR test* is done by passively raising the patient’s asymptomatic leg while keeping the knee straight. The presence of pain radiating from the back to the opposite affected leg has a sensitivity of only 29% but a high specificity of 88% for sciatica, meaning that a positive result on crossed SLR testing is almost pathognomonic for sciatica, whereas a negative result is nondiagnostic.[36]

A *reverse SLR test* is performed to detect L3 or L4 radiculopathy. With the patient prone, each hip is passively extended. If there is irritation of the L3 or L4 nerve root, pain is elicited.

In addition to stressing lumbar nerve roots, a thorough examination of the lower extremities detects subtle abnormalities associated with radiculopathies. This examination includes mapping the distribution of pain and assessing individual nerve root function, specifically strength, sensation, and reflexes. For the sensory examination, the earliest deficit can be detected by examining the most distal aspect of the dermatome. Specifically, light touch and pinprick sensation should be tested on the medial foot (L4), in the area between the great and second toes (L5), and on the lateral foot (S1) (Fig. 54-2).

Herniated Disk

Patients with symptomatic herniated lumbar disks usually are 30 to 50 years of age and often have a long history of recurrent nonradicular low back pain, theoretically from irritation of the outer annular fibers of the disk. When the nucleus pulposus of the disk prolapses through the annulus fibrosus, local nerve root inflammation and radiculopathy result. Coughing, sitting, and any movement in general exacerbate the patient’s pain and radiculopathy symptoms. The severity of leg pain from radiculopathy often overshadows the back pain. Sciatica findings have a sensitivity of 95% for lumbar disk herniation, meaning that herniation is extremely unlikely in the absence of sciatica.

The physical examination should focus on lower extremity neurologic function and signs of radiculopathy. Weakness of ankle dorsiflexion, great toe extension, ankle plantar flexion, and knee extension is associated with respective specificities of 70%, 70%, 95%, and 99% for lumbar disk herniation.[20]

Spinal Stenosis

Patients with spinal stenosis are typically older (mean age of 55 years) and constitute only 3% of all patients with low back pain.[4,37] The classic history, identified in 60 to 75% of patients with spinal stenosis, is one of subacute or chronic pain and lower extremity radiculopathy that occurs with walking and is relieved with rest and, uniquely, bending forward at the waist.[38] Because these symptoms mimic peripheral vascular claudication symptoms, pain from spinal stenosis is termed *pseudoclaudication.* Typically, vascular claudication lasts 5 minutes after resting, whereas pseudoclaudication lasts 10 to 15 minutes. Patients with spinal stenosis obtain symptom relief with spine flexion and bending forward, because these maneuvers increase spinal canal diameter and reduce spinal cord tension. Similarly, sitting also helps to relieve the symptoms in these patients, in contrast with patients with herniated disks. A typical patient describes walking uphill without pain but experiencing pain on walking downhill, when the back is extended.

On physical examination, most patients are found to have a lumbar radiculopathy at one or multiple levels and increased back pain with extension.[38] Classically, patients with spinal stenosis walk with a slightly bent-forward position. To help differentiate spinal stenosis from vascular claudication, peripheral pedal pulses and ankle-brachial indices should be checked.

Degenerative Spondylolisthesis

Most cases of spondylolisthesis, forward displacement of one vertebral body over another, are caused by degenerative changes. This condition is most prevalent in adults older than age 50 and occurs most commonly at the L4-5 and L5-S1 junctions. Two thirds of older patients with radiographically documented degenerative spondylolisthesis are asymptomatic.[39] For patients with pain,

www.ketabpezeshki.com 66485457-66963820

bending, twisting, and lifting activities aggravate the symptoms. Radiculopathies, spinal stenosis symptoms, or both may coexist. On physical examination, clinical findings may include a loss of lumbar lordosis causing a change in posture, a step-off along the midline spine if the spondylolisthesis is severe, tight hamstrings resulting in decreased mobility of the hamstrings and subsequent "waddling" gait, or a radiculopathy.

Arthropathies

Inflammatory arthropathies, such as ankylosing spondylitis, rheumatoid arthritis, and psoriatic arthritis, all are associated with subacute and chronic low back pain. Patients with these conditions exhibit a decreased range of spinal flexibility. Commonly with ankylosing spondylitis, patients report morning back stiffness and pain relief with exercise. On physical examination, patients with an inflammatory arthropathy may have nonspecific manifestations, such as decreased spinal mobility, sacroiliac joint tenderness, and decreased chest expansion.

Red Flag Diagnosis: Fracture

In all patients who have experienced significant blunt trauma to the back or only minimal trauma in the setting of osteoporosis, fractures of the spinal column are considered. Chronic corticosteroid users deserve special attention, because they typically have developed some degree of osteoporosis. In a 20-year observation study of 2631 collagen vascular patients, vertebral fractures occurred in 23.9% of patients on high-dose corticosteroids as compared with only 2.6% of patients on no corticosteroids.[40] Thus providers should have a low threshold to assess this unique patient population for a fracture despite the absence of trauma.

Red Flag Diagnosis: Cauda Equina Syndrome

Cauda equina syndrome results from a sudden compression of multiple lumbar and sacral nerve roots. Although it is an extremely rare presentation of back pain, it constitutes a neurosurgical emergency. The usual cause is a massive central disk herniation, but other potential causative disorders include spinal epidural abscess, hematoma, trauma, and malignancy. Patients with cauda equina syndrome have back pain and multiple-level radiculopathies, often involving both legs. Difficulty with bladder or bowel function, specifically urinary retention or decreased rectal tone, respectively, also may be a feature. Diagnostic dilemmas arise because the presentation can be atypical with equivocal neurologic compromise and only mild to moderate pain.

The most consistent examination finding in cauda equina syndrome is urinary retention. Patients often complain of overflow incontinence owing to a neurogenic bladder. Given the high sensitivity of urinary retention of 90% and a negative predictive value of 99.99%, this disease process is extremely unlikely if the patient's postvoid residual urine volume is less than 100 to 200 mL. This can be measured by urethral catheterization or estimated by ultrasonography.[41] Saddle anesthesia—sensory deficit over the buttocks, upper posterior thighs, and perineal area—frequently is an associated finding, with a sensitivity of 75%. In 60 to 80% of cases, the rectal examination reveals decreased sphincter tone.[20]

Red Flag Diagnosis: Spinal Infection

Epidural abscess and spondylitis (osteomyelitis of the vertebral bone) are two types of dangerous spinal infections. Patients at higher risk include injection drug users, alcoholics, immunocompromised patients (e.g., patients with human immunodeficiency virus, diabetes mellitus, chronic renal failure, or long-term corticosteroid use), the elderly, patients who have sustained blunt trauma to the back, patients with an indwelling catheter or who have undergone recent dental instrumentation or instrumentation of the gastrointestinal or genitourinary tract or the spine, and patients with a recent bacterial infection.[42-45] With spinal epidural abscess, however, approximately 20% of patients have no comorbid illnesses or risk factors. The most common bacterial culprit is *S. aureus,* spreading hematogenously from a remote site or from direct extension of a local infection, such as spondylitis or disk space infection. Less common culprits are streptococcal strains and enteric gram-negative bacilli. Patient history reveals back pain even at rest and subjective fevers. On physical examination, there is often tenderness to percussion over the spinous process near the abscess location. Spinal epidural abscess remains a diagnostic challenge despite the "triad" of fever, focal back pain, and neurologic deficit, because approximately 50% of the patients have no neurologic deficits, and 50% may be afebrile on initial presentation.[46] With this subtle and often chronic presentation, many cases are misdiagnosed on initial presentation. Thus an awareness of this entity as a possible cause of low back pain is important for prompt diagnosis of this neurosurgical emergency, which carries a mortality rate as high as 15%.[46-48]

With spondylitis, infection often begins as a subtle hematogenous seeding of the disk space, causing diskitis. Subsequent contiguous spread of the disk space infection causes vertebral endplate erosion, leading to spondylitis. As with a spinal epidural abscess, the most common bacterial culprit is *S. aureus.* Less commonly, enteric gram-negative bacilli and *Mycobacterium tuberculosis* (in Pott's disease) are the infecting organisms. Injection drug users also are at risk for *Pseudomonas* spondylitis. The history typically reveals a more indolent course of back pain, with subjective fevers. The physical examination findings can range from nonspecific tenderness of the spine to radiculopathy and cauda equina syndrome. Similarly nondiagnostic, the presence of fever has a sensitivity of only 27 to 50% for spondylitis.[20]

Red Flag Diagnosis: Malignancy

Vertebral infiltration with a tumor can be caused by either a primary or, more commonly, a metastatic malignancy. Classically, affected patients generally are older than 50 years and often complain of subacute or chronic back pain that is worse at night. In a systematic review, a history of known cancer, a moderately elevated erythrocyte sedimentation rate (ESR) (≥50 mm/hr), a significantly elevated ESR (≥100 mm/hr), hematocrit less than 30%, and clinical judgment yielded positive likelihood ratios for a vertebral malignancy of 23.7, 18.0, 55.6, 18.2, and 12.1.[49,50] On examination, patients typically have mild to moderate spinal tenderness. Examination of the organs in which tumors are most likely to metastasize to bone, including breast, prostate, and lung, is indicated.

Referred Back Pain

Referred pain often is difficult to differentiate from pain originating from the lumbosacral structures. It is vital, however, to make the distinction. A sudden onset of severe, "tearing" back pain is classically an aortic dissection. Abdominal pain radiating to the back may be caused by a ruptured abdominal aortic aneurysm in an elderly patient with atherosclerotic disease. Alternatively, abdominal pain radiating to the back could be from pancreatitis in a chronic alcoholic. Unilateral paraspinal pain associated with fever and nausea in a young woman could indicate pyelonephritis. Other examples of conditions radiating to the back include biliary diseases, pneumonia, pulmonary embolism, renal colic, and retroperitoneal hemorrhage. In all such cases, a thorough examination of the abdomen, genitourinary system, and cardiovascular

www.ketabpezeshki.com 66485457-66963820

system is essential. Pinpointing the primary cause of the pain may radically alter the therapy for the patient.

Functional Back Pain

Distinguishing functional pain from "real" pain often is difficult, but several clues can be elicited from the history. A prolonged history of nonanatomic pain complaints, vague pain descriptions without localization, multiple lawsuits over similar problems, multiple prescriptions for narcotics from different providers, and lack of coordinated care for a problem that otherwise seems to dominate the patient's life all suggest that a search for a physical cause would be fruitless. In such cases, secondary gain for the patient's complaints often is likely.

On physical examination, maneuvers can be performed to try to detect functional back pain, if a psychological overlay is suspected. The first recommended maneuver is performing the SLR test from the sitting instead of the supine position. Seemingly focused on the knee examination, the physician extends the patient's knee; this physiologically reproduces the SLR by stretching the L5 and S1 nerve roots. A positive response includes reproduction of the patient's pain and extension of the back while seated to decrease traction on the sciatic nerve. A positive result on SLR testing in the supine position but a negative result in the seated position, and vice versa, suggests a nonphysiologic cause for the pain.

A second sign is apparent superficial tenderness. Some patients, to impress the physician with their degree of pain, respond dramatically to superficial palpation. This response is atypical for patients with genuine back pain. Nondermatomal sensory loss and widespread nondermatomal pain complaints also are unlikely to be caused by nonphysiologic processes.

Third, back pain should not be elicited by pushing down on the patient's scalp against the cervical spine. This maneuver axially loads only the cervical and not the lumbar spine.

Fourth, a patient who generally overreacts during the examination probably is not giving a true reflection of the actual discomfort. All of these signs are believed to correlate well with psychopathology but have poor prognostic value. They are suggestive of malingering and functional complaints but are neither sensitive nor specific enough to rule out organic pathology.[51,52]

Back Pain in the Elderly

In elderly persons with back pain, musculoskeletal processes and disk herniation are less likely causative disorders. Instead, spinal stenosis and degenerative spondylolisthesis should be considered. Also, the incidence of more worrisome diagnoses, such as an osteoporotic fracture, spinal infection, and malignancy, is much greater in this patient population. Consequently, in these cases the threshold for further investigation should be much lower.

Back Pain in Children

The likelihood of a congenital cause for back pain, such as leg-length discrepancy and spondylolisthesis, is greater for children than for adults. Spondylolisthesis is diagnosed most often in patients older than 10 years who are involved heavily in sports and complain of low back pain worsened with activity. In a retrospective study in an urban pediatric ED over a 1-year period, the most common causative disorders in patients with back pain complaints included direct trauma (25%), muscular strain (24%), sickle cell crisis (13%), idiopathic causes (13%), urinary tract infection (5%), and viral syndrome (4%).[31] A history suggesting infection or malignancy in children is similar to that in adults. Radicular symptoms are relatively rare in children. Functional processes are suggested when the pain is present only with certain undesired activities, such as housework or chores.

DIAGNOSTIC STRATEGIES

Laboratory Evaluation

In the absence of historical and physical findings suggesting red flag diagnoses for low back pain, laboratory evaluation is unnecessary. When a patient's back pain is suggestive of a spinal infection or malignancy, however, laboratory studies may help with risk stratification. Specifically, a complete blood cell count, ESR, and urinalysis should be performed. Additional laboratory studies should be tailored to the patient's history and physical examination findings. Liver function testing and determination of amylase or lipase level may be indicated to investigate abdominal complaints.

For a spinal infection, an ESR greater than 20 mm/hr has a sensitivity of 98%, and if the patient also has a spinal epidural abscess risk factor (e.g., diabetes, intravenous drug use history, chronic liver or kidney disease, recent spine procedure or indwelling spinal hardware, recent spine fracture, indwelling vascular catheter, immunocompromised state), then the sensitivity becomes 100% with a specificity of 67%.[53] The serum white blood cell (WBC) count, in contrast, may or may not be elevated.[54,55] In one study, 13 of 40 (33%) patients with a spinal epidural abscess had a falsely reassuring WBC count of less than 11,000/μL.[47] Thrombocytopenia (<100,000/μL), an extremely high ESR (≥110 mm/hr), and cervical spine epidural abscess are poor prognostic indicators and predictive of relapses and death.[56] When patients are diagnosed with a spinal infection, blood should be drawn for cultures because a single strain, most commonly *S. aureus,* can be isolated in 63 to 78% of the cases.[47,55,57] Performing a lumbar puncture to evaluate the cerebrospinal fluid is unnecessary and is relatively contraindicated because of the risk of seeding the fluid with bacteria.

With a bony malignancy the ESR also usually is elevated, whereas the WBC count may be equivocal. The hematocrit may be low secondary to anemia of chronic disease. Other additional helpful laboratory tests include measurement of alkaline phosphatase, prostate-specific antigen assay, and serum immunoelectrophoresis and urine testing for light chains (for multiple myeloma).

Radiology

Plain Radiography

The utility of "screening" lumbosacral plain radiographs for all patients with acute low back pain is extremely low; however, approximately one third of all patients with back pain–related disorders receive plain films, with increasing trends toward advanced imaging, including computed tomography (CT) and MRI.[58] Plain radiographs contribute little to patient management in the absence of concerning red flag findings and needlessly expose the patient to radiation.[59] Most patients with back pain do not need radiographs. In those cases in which radiographs have been obtained, normal findings are usual, but incidental findings, which may or may not be the true cause of the patient's pain, also are relatively common and may include spondylolisthesis, abnormal spinal curvature, disk space wedging, or degenerative changes.[10] Currently accepted indications for radiographs in patients with back pain are listed in Box 54-1.

Patients with radicular symptoms suggesting a herniated disk do not require radiographs. In addition to being undetectable on plain radiographs, disk herniations resolve with conservative management in most cases.

www.ketabpezeshki.com 66485457-66963820

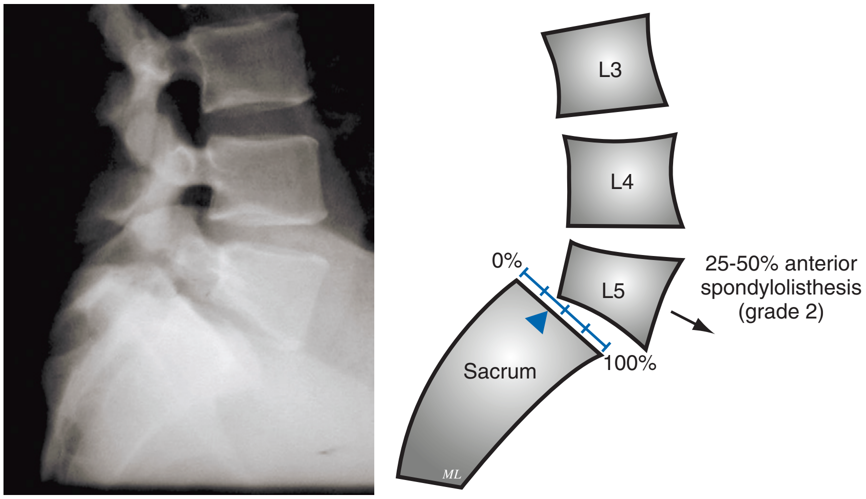


Figure 54-3. Lateral plain radiograph and schematic diagram of grade 2 anterior spondylolisthesis of L5 on S1. Grading is based on the percentage of slippage, with 0 to 25%, 25 to 50%, 50 to 75%, and greater than 75% corresponding to grades 1 to 4, respectively.

Box 54-1 Indications for Plain Lumbosacral Radiographs in Patients with Low Back Pain

- Age younger than 18 or older than 50 years
- Any history of malignancy or unexplained weight loss
- Any history of fever, immunocompromised state, or injection drug use
- Recent trauma, other than simple lifting
- Progressive neurologic deficits or other findings consistent with cauda equina syndrome
- Prolonged duration of symptoms beyond 4 to 6 weeks

If radiographs are obtained, anteroposterior and lateral views usually are sufficient in the ED, although many centers also prefer to obtain a cone-down lateral sacral view to improve visualization of the lumbosacral joint. Oblique views are not necessary except in children, in whom spondylolysis and spondylolisthesis may be more prevalent.[60]

On plain radiographs, spondylolisthesis, vertebral osteomyelitis, and vertebral metastatic disease have classic appearances. Spondylolisthesis (Fig. 54-3) is classified into grade 1 through grade 4 based on the severity of the anterior slippage of one vertebral body over another. Grade 1, which is often asymptomatic, involves less than 25% slippage. Grades 2, 3, and 4 involve 25 to 50%, 50 to 75%, and at least 75% slippage, respectively.

Spondylitis (Fig. 54-4) is characterized by erosion of contiguous vertebral endplates and a shortened disk space height, best seen on the lateral view. Because the anterior subchondral vertebral bone and disk space are highly vascular, it follows that spondylitis has a predilection for these areas because of the hematogenous spread of infection. With more advanced disease, vertebral bone erosion and collapse may occur.

Vertebral metastatic disease (Fig. 54-5) can manifest as either a blastic (hyperdense) or a lytic (hypodense) lesion and has a predilection for the vertebral body and pedicles. In contrast to osteomyelitis, in vertebral metastatic disease, the intervertebral disk space is spared.

If a red flag diagnosis is of concern, a plain radiograph may screen for a fracture but may not adequately rule out other pathologic processes, such as cauda equina syndrome, spinal infection, and malignancy. For cauda equina syndrome, patients more often have normal or nonspecific plain film findings because the most common cause is a central disk herniation. For spinal infection and vertebral malignancy, the sensitivity of a plain radiograph is only fair at 82% and 60%, respectively.[59] In these cases, the patient subsequently should undergo MRI if the there is a high clinical suspicion.

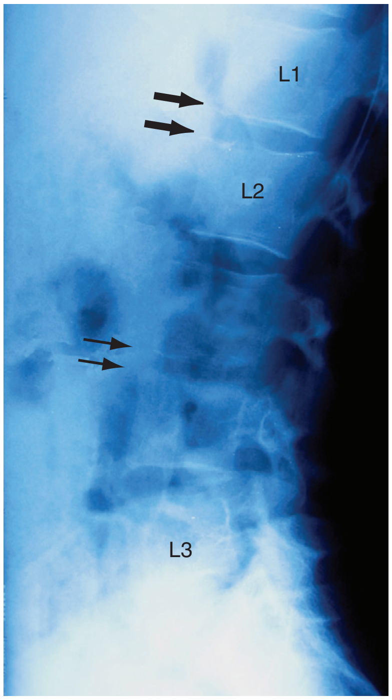


Figure 54-4. Lateral plain radiograph shows *Staphylococcus aureus* spondylitis of L3 and L4. There is narrowing of the L3-4 disk space and erosion of the vertebral endplates of L3 and L4 *(small arrows)*. Note the distinct vertebral endplate margins in unaffected areas *(large arrows)*.

Ultrasonography

In suspected cases of cauda equina syndrome, one should consider use of bedside ultrasonography to assess the postvoid residual volume of the bladder to help with risk stratification. An estimate of the postvoid residual can be obtained by measuring the bladder with ultrasound with the following formula: Volume (mL) = 0.52 × height (cm) × width (cm) × depth (cm).[41]

Computed Tomography and Magnetic Resonance Imaging

For assessment of fractures of the vertebral column, CT is superior to MRI. In the case of a fracture, CT helps to elucidate the integrity of the spinal canal and the risk for spinal cord impingement. For all other red flag diagnoses—cauda equina, spinal infection, and

www.ketabpezeshki.com 66485457-66963820

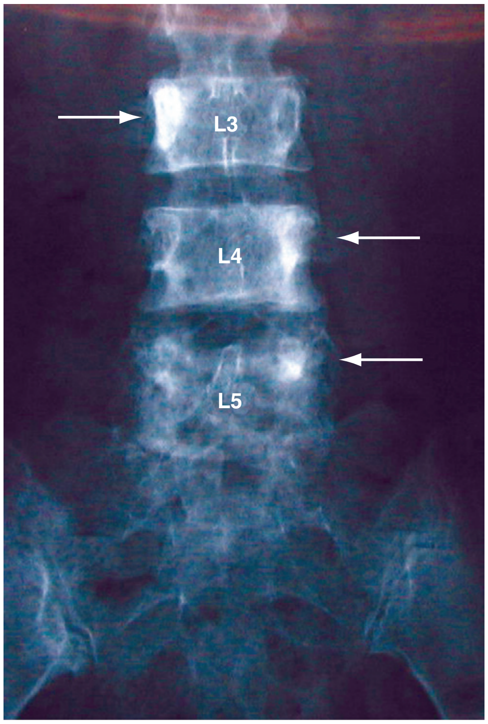


Figure 54-5. Anteroposterior plain radiograph shows blastic infiltration of metastatic breast cancer to the pedicles of L3 to L5 *(arrows)*.

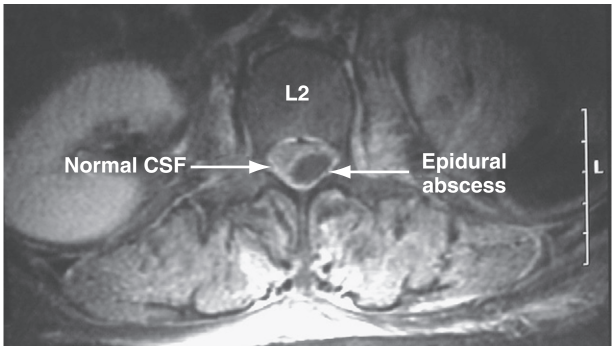


Figure 54-6. Axial T2-weighted magnetic resonance imaging of *Staphylococcus aureus* L2 epidural abscess impinging on the dorsolateral aspect of the spinal canal. *CSF,* cerebrospinal fluid. (Image contributed by Dr. Stephen Bretz.)

malignancy—MRI is the definitive investigative modality. Its superior tissue resolution, especially of the spinal cord and intervertebral disks, and its capability of generating more accurate sagittal reconstructions make MRI the ideal imaging modality. MRI is able to differentiate and detect subtle soft tissue pathology, such as a spinal epidural abscess (Fig. 54-6). No ionizing radiation exposure is incurred with MRI, whereas one CT scan of the entire spine exposes the patient to the equivalent of approximately 18.8 years of natural background radiation—cervical spine, 2 years; thoracic spine, 8.8 years; and lumbar spine, 8 years.[61] For patients who have contraindications to MRI (e.g., pacemaker, metallic implants), a CT myelogram can be performed to assess for spinal cord impingement, cauda equina syndrome, and spinal epidural abscess. A spine CT scan can be performed to assess for vertebral bone infiltration by malignancies.

Although disk herniation is easily visualized on MRI, patients with findings consistent with an uncomplicated disk herniation (i.e., without objective findings of motor or sensory deficit on examination) should not routinely undergo MRI imaging because of the self-limited nature of the disease in most cases. Overimaging in patients with lumbar radiculopathy is costly and may lead to an overdiagnosis of disk herniations because incidental MRI-documented herniations have been shown to be present in 28 to 33% of asymptomatic patients. The result may be unnecessary surgical intervention.[10,22,62]

Special Investigations

Most cases of back pain in the ED do not require any diagnostic tests. Additional workup is warranted only when red flag conditions are suspected. Radionuclide scans have been used for locating suspected malignancy, infectious foci, and occult fractures as in spondylolysis. Nuclear medicine scans are regarded as sensitive but nonspecific.

DIFFERENTIAL CONSIDERATIONS

Nonspecific low back pain is in many ways a diagnosis of exclusion. In a typical patient, within the 18- to 50-year age range with acute low back pain and with no radiculopathy, previous malignancy, weight loss, risk factors for spinal infection, or fever, the diagnosis is almost certainly uncomplicated musculoskeletal back pain. When the patient falls outside of the aforementioned parameters, a wide variety of diagnostic possibilities should be entertained.

Almost anything can cause low back pain. Box 54-2 presents an extensive list of diagnostic considerations, but it is useful to look at the most common and most serious causes of low back pain other than musculoskeletal lumbosacral pain. One of the most life-threatening causes of referred back pain is a leaking or ruptured abdominal aortic aneurysm. The reader is referred to appropriate chapters for further discussion of specific problems.

MANAGEMENT

Because most patients with acute low back pain without objective sensory or motor loss on examination experience symptomatic resolution within 4 to 6 weeks, only conservative management is needed. In general, MRI and surgery are reserved for the few patients who have worrisome systemic signs and patients with refractory, debilitating back pain. Over the past few decades, the accepted practice has shifted 180 degrees, from an overaggressive recommendation for invasive surgical intervention to the minimalistic recommendation of symptomatic pain control and early return to activity. In one large prospective study, the randomized intention-to-treat analysis found no significant difference in the outcomes of surgical versus nonsurgical treatment of degenerative spondylolisthesis.[63] Thus the recommended role of the emergency physician in back pain management is to arrive at a correct diagnosis, rule out significant pathology, avoid excessive investigation, provide analgesia, and educate the patient.[64] The management for various etiologic categories of disorders that may cause low back pain is summarized in Figure 54-7. For management of fractures and referred pain, the reader is referred to the appropriate chapters.

Uncomplicated Musculoskeletal Back Pain

Besides a thorough history and physical examination, no further investigations are required for uncomplicated low back pain. Only pain control and patient education are indicated. Aside from an initial parenteral opioid or nonsteroidal anti-inflammatory drug (NSAID), most patients can be managed with oral nonsteroidal medications. Ibuprofen is an ideal choice because it is inexpensive, but various NSAIDs can alternatively be used because they

www.ketabpezeshki.com 66485457-66963820

Box 54-2 Differential Diagnosis for Low Back Pain

Localized and Common
Uncomplicated musculoskeletal back pain
Intervertebral disk herniation
Spinal stenosis
Spondylolisthesis
Osteoarthritis
Fracture

Localized and Uncommon
Infection
Spondylitis
Epidural abscess
Diskitis
Herpes zoster

Malignancy
Metastatic
- Breast
- Lung
- Prostate
- Kidney, thyroid, colon (less common)

Primary
- Multiple myeloma
- Lymphoma
- Leukemia
- Primary cord or extradural tumors
- Osteoid osteoma
- Other primary bone tumors

Pediatric
Spondylolisthesis, spondylolysis
Severe scoliosis
Scheuermann's disease

Rheumatologic
Ankylosing spondylitis
Psoriatic arthritis
Polymyalgia rheumatica
Reiter's syndrome

Vascular
Arteriovenous malformation of spinal cord
Epidural hematoma

Life-Threatening Referred Pain
Abdominal aortic aneurysm

Gastrointestinal System
Biliary pathology
Pancreatitis
Peptic ulcer disease
Diverticulitis

Genitourinary System
Renal colic
Pyelonephritis
Prostatitis
Cystitis

Gynecologic System
Menstrual cramps
Spontaneous abortion
Labor
Ectopic pregnancy
Pelvic inflammatory disease
Endometriosis
Ovarian cyst
Ovarian torsion

Hematologic System
Sickle cell crisis

Functional
Somatization disorder
Depression
Fibrositis
Malingering

have been shown to have similar efficacy. It is unclear whether NSAIDs are superior to acetaminophen, but it is known that acetaminophen has fewer side effects than NSAIDs.[65,66] Selective cyclooxygenase-2 (COX-2) inhibitors are equally effective compared with NSAIDs, with fewer side effects than traditional NSAIDs; however, COX-2 inhibitors now are rarely used because of recent studies showing an increased cardiovascular risk in certain populations.[66] Short-term opioids also occasionally are needed for breakthrough pain in the acute setting. Various other medications have been advocated, including benzodiazepines and other muscle relaxants. Based on the current conflicting literature, these medications probably do not provide a significant added benefit, but they do increase the incidence of side effects such as drowsiness, falls, accidents, and drug dependence.[67] Corticosteroids are not significantly beneficial in the treatment of uncomplicated low back pain.[68,69]

In terms of patient education, one of the outdated practices of back pain management was that physicians convinced patients that they were sick. This was done by excessively investigating and overtreating patients, restricting patients to strict bed rest, and taking them off work. It now has been shown convincingly and repeatedly that all of those interventions are unnecessary. Instead, patients should be educated about why they are not undergoing radiographic studies of their lumbosacral spine or laboratory tests and should be reassured of the likely benign course of the pain. Most patients can be convinced by education and an explanation of radiation dosage. A typical lumbosacral spine series involves as much gonadal irradiation as that incurred with a daily chest radiograph for 5 to 6 years.[70] Patients also are discouraged from the outdated recommendation of strict bed rest. Compared with patients who are prescribed strict bed rest, patients with acute back pain who remain active experience earlier resolution of pain and return to work sooner.[4] Patients should be made aware, however, that the back pain has a 66 to 84% likelihood of recurring within 12 months.[11]

Other supplemental treatment modalities have been shown to be of debatable efficacy in the management of acute and chronic low back pain. These include acupuncture, physiotherapy, chiropractic manipulation, massage, ultrasound, traction, and transcutaneous nerve stimulation.[10,71-74]

Lumbar Disk Herniation

Like patients with uncomplicated low back pain, patients with disk herniations and radiculopathy do not benefit from strict bed rest.[5,64] In the acute setting, these patients should receive analgesics. Further investigation with laboratory tests and radiographs is not necessary. Most of these patients experience symptomatic resolution within 6 weeks with conservative, nonsurgical management.[75,76]

Corticosteroid injections into the epidural space have been advocated for sciatica in the belief that this treatment helps to relieve some of the inflammation associated with disk herniation. Although some reduction of symptoms may be obtained initially, no long-term benefit or reduction in the need for later surgery has been documented.[77-79] The use of systemic steroids in back pain

www.ketabpezeshki.com 66485457-66963820

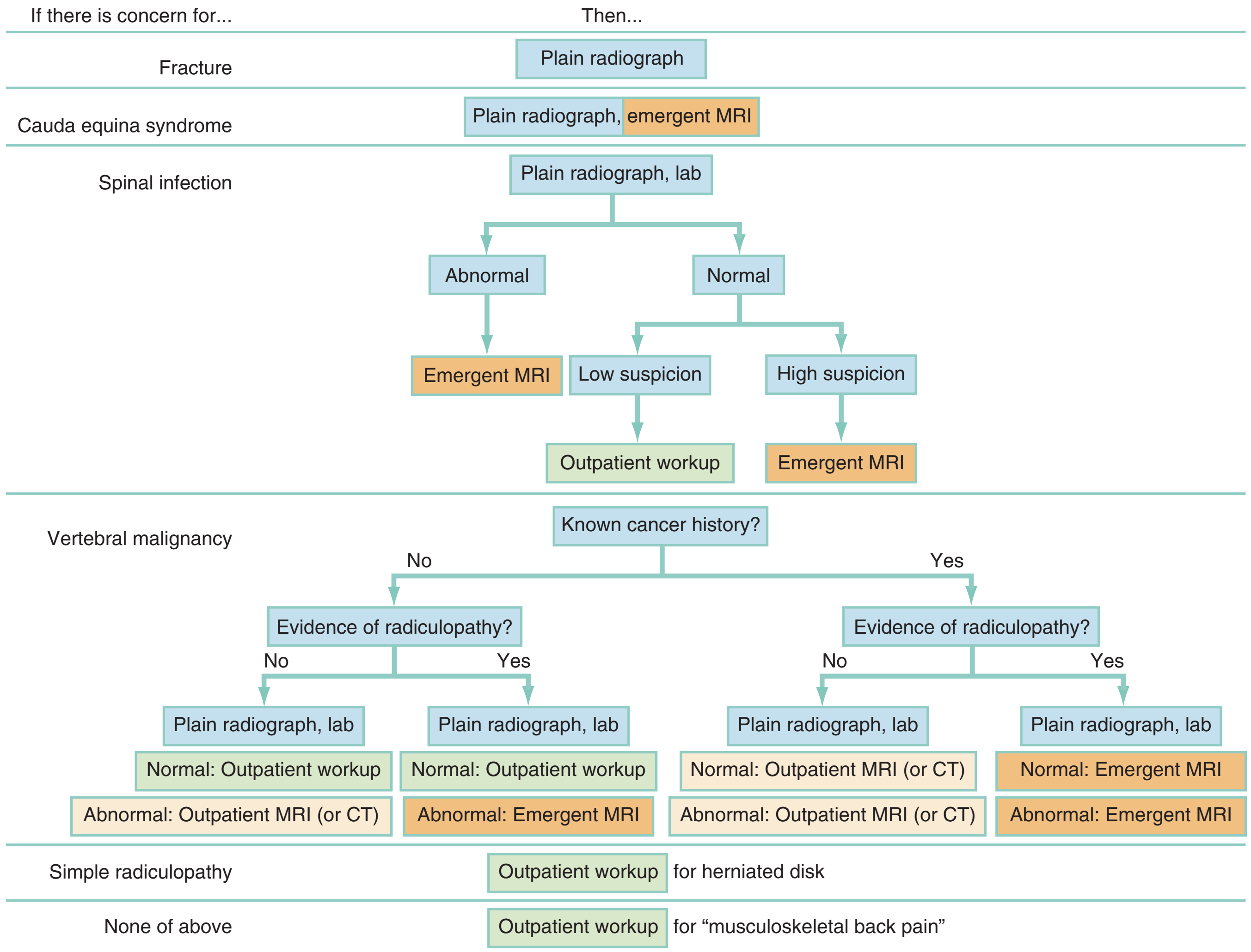


Figure 54-7. Algorithm for management of low back pain. The patient’s history may be concerning for more than one red flag diagnosis. *CT,* computed tomography; *MRI,* magnetic resonance imaging.

and disk herniation remains controversial. Although there is no proven benefit, the anti-inflammatory effects make empirical sense in the context of radiculopathy. A large retrospective review showed no definite benefit of systemic steroids in either presentation, but the definitive trial is yet to be done.[67] When the pain from disk herniation persists for longer than 4 to 6 weeks, outpatient MRI is indicated. With a documented herniation, these patients may benefit from surgical diskectomy, although this remains controversial compared with conservative management.[80] Other potential indications for surgery include intractable pain and worsening motor or sensory deficit. Although surgical patients tend to have earlier relief of pain compared with nonsurgical patients, the 4- and 10-year results are the same. Microsurgery techniques and laser therapy have not been shown to confer any advantage over conventional techniques.[81]

Spinal Stenosis

Patients with spinal stenosis should be managed conservatively with pain medications. In the absence of alarming red flag findings, these patients do not require laboratory or radiographic studies in the ED. These patients may be candidates for surgery if they show any of the following conditions: progressive neurologic deficit, progressive reduction in ability to walk secondary to pseudoclaudication, evidence of cauda equina syndrome, or intractable pain. Elective surgical decompression is more controversial. A 10-year longitudinal study showed that no findings predicted which patients would benefit more from surgery than from conservative management.[82] The benefits of surgery also are weighed against the risks of surgery itself, because these patients usually are elderly.

Degenerative Spondylolisthesis

Patients with symptomatic degenerative spondylolisthesis are managed conservatively with analgesia and lifestyle changes, which include the avoidance of repetitive bending, heavy lifting, and twisting at the waist. For patients with refractory or severe back pain, outpatient MRI and neurosurgical referral for possible operative decompression are recommended.

Red Flag Diagnosis: Fracture

See Chapter 43, Spinal Injuries.

Red Flag Diagnosis: Cauda Equina Syndrome

Cauda equina syndrome is a neurosurgical emergency that requires urgent operative decompression to help preserve distal neurologic function. All patients with concerning findings, such as saddle anesthesia or a large postvoid residual volume, require emergent

www.ketabpezeshki.com 66485457-66963820

MRI. On average, outcome is improved if decompression takes place within 48 hours of symptom onset.[83] Although the standard of care is for emergent decompression, preliminary evidence suggests that delayed operative decompression for selected patients in a more controlled setting may be performed without any adverse effects, particularly in patients who have overflow urinary incontinence.[84]

Red Flag Diagnosis: Spinal Infection

If findings on the history or physical examination are worrisome for a spinal infection, further investigation is of paramount importance. In low-risk patients, normal results on serum WBC count, ESR, and lumbosacral plain radiograph can safely rule out infection. In patients with a moderate to high pretest probability for a spinal infection, the next step is to perform emergent MRI.

Pyogenic spinal infections should be treated with neurosurgical drainage and decompression, in addition to broad-spectrum intravenous antibiotics that cover at least for *S. aureus* and gram-negative bacilli until blood culture results return. Vancomycin should be included in the antibiotic regimen, given the increased prevalence of methicillin-resistant *S. aureus.* In a case series from 2003 to 2008, *S. aureus* accounted for 67% of the 45 cases of adult spinal epidural abscesses. Of this group, 41% were oxacillin/methicillin-resistant strains.[85] For injection drug users, antibiotic coverage for *Pseudomonas* is necessary. The recent literature suggests that a nonsurgical management approach may be acceptable for a select group of patients at lower risk, such as those who are hemodynamically stable and neurologically intact.[85]

Red Flag Diagnosis: Malignancy

Patients with a known malignancy who report back pain and have an associated neurologic deficit require emergent MRI to rule out spinal cord compression. However, patients who have no myelopathic findings pose a greater diagnostic challenge. A suggested algorithmic guideline in the diagnostic evaluation of back pain that is worrisome for malignancy involves subdividing patients into two categories: patients with and patients without a history of previous cancer. Development of spinal metastasis has been reported in 20 to 85% of patients with cancer.[86,87] These patients are subdivided further into those with and those without evidence of a radiculopathy.

Most patients fall into the classification of *back pain without a history of cancer and without a radiculopathy.* They have a history that is only suggestive of a malignancy, such as unexplained weight loss or back pain that is worse at night. These patients require further risk stratification with plain radiographs (or a spine CT scan for patients with a high pretest probability for malignancy) and laboratory tests, including a complete blood cell count and ESR. With normal results, these patients can be referred to their primary care physician for further workup. The physician should not feel completely reassured that malignancy has been ruled out with plain films, however, because they have a false-negative rate of 10 to 17% for vertebral bone metastasis. This false-negative rate is likely a result of the fact that a cancer needs to erode at least 50% of the bone before becoming radiographically apparent on plain films.[88] With abnormal results, such as a bone lesion or an extremely elevated ESR level (above 100 mm/hr), an urgent CT scan or MRI should be performed on an outpatient basis within the following 3 to 7 days, assuming that there are no neurologic deficits.

For patients *without a history of cancer but with signs of radiculopathy,* the workup also includes a plain radiograph, complete blood cell count, and ESR. If the test results are normal, the patient should be referred to his or her primary care physician for further evaluation for malignancy and other potential causes of radiculopathy, including spinal stenosis and disk herniation. If the workup shows a bone lesion on plain radiographs or an extremely elevated ESR level (greater than 100 mm/hr), the patient should undergo emergent MRI because (1) the presence of radiculopathy may be an early harbinger of impending spinal cord compression from a mass effect and (2) it often is difficult on plain radiography to distinguish between a neoplasm from early spondylitis (especially tuberculous osteomyelitis) and an osteoporotic fracture causing a vertebral collapse.[89] If MRI is unavailable, multidetector CT imaging can be performed initially to screen for the presence of malignant bone infiltration, although definitive spinal cord and nerve root imaging will require MRI. The presence of a vertebral mass lesion on CT images suggests nerve root compression as a cause of the pain.

For patients *with a history of previous cancer and low back pain,* advanced imaging is indicated, either emergently or urgently within 3 to 7 days. In the absence of clinical manifestations of radiculopathy, these patients should undergo outpatient MRI (or CT, if MRI is not available or is contraindicated) regardless of plain radiography findings and laboratory results. Plain radiography is too insensitive to rule out a vertebral neoplastic process definitively. If a radiculopathy is present, however, these patients require emergent MRI regardless of plain radiography findings because of the concern for spinal cord compression. In a study of patients with a known diagnosis of cancer who had back pain and radiculopathy, the risk of epidural spinal cord compression was 25% despite normal radiographic findings, and 88% with radiographic evidence of vertebral metastasis.[90]

In all patients undergoing emergent MRI to evaluate for vertebral malignancy and spinal cord compression or cauda equina syndrome, dexamethasone should be administered as soon as these conditions are suspected to reduce the potential mass effect. In the setting of a diagnosed neoplasm causing spinal cord compression or cauda equina syndrome, emergent radiation therapy and potentially spinal surgery should be arranged.

Pediatric Back Pain

Management of back pain in children is similar to management in adults and depends on the underlying causative disorder. Spondylolisthesis is managed by observation, with only 4 to 5% of cases worsening. Progression usually stops as skeletal maturity is achieved in the late teens. Current recommendations are for limited contact sports in children with less than 30 to 50% slippage who are asymptomatic with conservative therapy (activity, rest, physiotherapy, and brace) and avoidance of loading the spine in a hyperextended position. Surgical stabilization for children may be indicated with slippage greater than 30 to 50%. Treatment becomes more aggressive if the child is symptomatic or if radiologic evidence of further displacement is present.[91]

Chronic Back Pain

Patients with chronic back pain often are regarded as the most challenging of all patients with back pain. The cause of chronic back pain is complex and multifactorial and usually requires a multidisciplinary approach for the greatest chance of success. Psychosocial factors, including depression, drug dependence, and financial gain, undoubtedly play a significant role in the behavior of many of these patients, making proper assessment and treatment extremely challenging in the ED.

After appropriate evaluation has ruled out a red flag cause for the back pain, ED management involves analgesia and referral for follow-up care. The main decision usually centers on the use of narcotics, which should be individualized in accordance with the physician's assessment of the clinical scenario. Patients exhibiting

www.ketabpezeshki.com 66485457-66963820

drug-seeking behavior classically are from out of town, have a primary care physician who cannot be contacted, or are reportedly allergic to all nonopioid medications.

DISPOSITION

Almost all patients with uncomplicated back pain can be discharged from the ED with follow-up with their primary care physician. In rare circumstances, severe pain or inadequate support for convalescence at home may preclude discharge. For patients who have a red flag diagnosis of spinal cord compression or cauda equina syndrome or spinal epidural abscess, immediate neurosurgical consultation is required for emergent surgical decompression. Although less emergently, consultation with a neurosurgeon or orthopedic spine specialist is necessary for patients with spine fractures, spondylitis, or a new vertebral malignancy in the absence of spinal cord or cauda equina involvement. Most patients with a spine fracture require hospitalization for pain control, fracture stabilization, and/or assessment of concurrent injuries. Some patients with stable fractures (e.g., small wedge fracture of the vertebral body) and tolerable pain can be managed on an outpatient basis. For patients with spondylitis, hospitalization will be necessary for administration of intravenous antibiotics. For patients with a vertebral malignancy, the decision to hospitalize the patient for pain control, administration of high-dose corticosteroids, and radiation therapy should be made in conjunction with a neurosurgeon, an oncologist, and a radiation therapist.

One of the most important aspects of management of low back pain is the discharge instructions for the patient. Not only are clear and simple directions useful to the patient, but they also constitute a medicolegal necessity for the physician. Physicians are advised to avoid use of purely medical terms. The discharge instruction should include the following:

1. *Diagnosis*: Distinguish between uncomplicated (musculoskeletal) back pain and diskogenic radiculopathy.
2. *Activity*: Recommend maintaining active mobility as limited only by pain, avoiding heavy lifting until symptoms resolve, and getting back to full activity as soon as possible. Also teach patients how to properly lift heavy objects in the future. This includes positioning the object closer to the body, standing with feet shoulder-width apart, keeping the back straight, tightening the abdominal muscles, and lifting with the knees.
3. *Reassurance*: Educate patients about the likely benign nature of the causative condition responsible for the pain.
4. *Warnings:* Instruct patients to return to the ED immediately if they experience any of the following: fever; loss of bladder or bowel control; numbness or tingling around the anus, vagina, or penis; or new pain or weakness down one or both legs.

In patients with pain secondary to spondylolisthesis, activity restrictions should be made in conjunction with an orthopedic surgeon. ED disposition for a patient with chronic back pain is relatively simple: pain management with nonopioids, when possible, and referral to a primary care physician for follow-up care. The prognosis is guarded because patients who are off work for 6 months usually are still off work after 2 years.[29] Pediatric patients with back pain require the same discharge instructions as adults.

UPPER BACK PAIN

PERSPECTIVE

Background

Thoracic pain is far less common than low back pain. Thoracic pain usually has a musculoskeletal origin, but other, more emergent causes are considered first, including thoracic aortic dissection, pulmonary embolism, and esophageal disease. Compared with lumbar disk herniation, which is fairly common, thoracic disk disease is extremely rare, difficult to diagnose, and difficult to treat.

Epidemiology

The actual incidence of thoracic pain is unknown. The incidence of symptomatic thoracic disk disease is low, with estimates at 1 in 1 million.[92] The average age is in the 40s with equal gender distribution. Surgery for thoracic disks accounts for less than 4% of all disk operations.[93] Metastases are more common in the thoracic spine than in the lumbar spine, with 60 to 70% of spinal metastases localizing there.[10,94]

PRINCIPLES OF DISEASE

Anatomy and Physiology

The thoracic vertebral column can be regarded as an extension of the cervical column with the addition of ribs. There are 12 thoracic vertebrae, connected by the anterior and posterior longitudinal ligaments and the ligamentum flavum, similar to the lumbar vertebrae. Also similarly, intervertebral disks provide elasticity and stability to the thoracic column. The spinal canal diameter remains unchanged through the thoracic and lumbar levels, but at the thoracic level, the space around the spinal cord is smaller than at the lumbar level. Because lumbar nerve fibers have not yet branched off from the spinal cord, the thoracic cord is thicker than the lumbar cord. Significant neurologic abnormalities may result from minimal spinal canal impingement at the thoracic level.

Pathophysiology

Common thoracic soft tissue pain is likely to be a combination of sprain and muscle inflammation. As in the lower back, innervation of the paravertebral area is provided by the sinuvertebral nerve, and any anatomic disruption of surrounding structures results in nonspecific pain. Thoracic disk herniations, which most commonly occur in the midthoracic to lower thoracic spine, cause pain and neurologic symptoms in much the same way as for lumbar disks. It is not clear why the clinical presentation is so varied, although a possible cause is a higher number of centrally herniated disks, resulting in much more frequent myelopathic symptoms.[93]

CLINICAL FEATURES

Symptoms and Signs

History

Nondiskogenic thoracic back pain usually manifests as paraspinal discomfort. A history of trauma or recent unusual activity may or may not precede the onset of pain. Complaints with thoracic disk herniations are variable but usually are associated with long-standing pain, neurologic symptoms, or both. Pain may be localized to one part of the thoracic vertebrae, it may radiate down to the sacrum, or it may have a radicular component along the ribs. Central disk herniation can manifest as diffuse abdominal and back pain or a burning sensation in the lower extremities. Associated findings may include mild weakness, spasticity, gait disturbance, bowel or bladder dysfunction, and paraplegia. These usually progress until the condition is diagnosed. Because of the variable and often subtle signs and symptoms, thoracic disk disease typically is not diagnosed until 20 months after the first clinical presentation. Pain from other causes should be sought in the initial assessment. A history of trauma, fever, previous malignancy, cardiovascular disease, or gastrointestinal problems may indicate more worrisome conditions or those originating from outside the thoracic spine and may warrant further investigation.

www.ketabpezeshki.com 66485457-66963820

Physical Examination

In patients with benign musculoskeletal pain, the physical examination fails to disclose evidence of a pathologic process. These patients may experience mild to moderate paraspinal tenderness to palpation, pain with motion, and even discomfort from chest wall expansion with respirations, but objective findings are minimal.

Physical findings in patients with thoracic disk herniation will vary with the location and degree of herniation. Objective findings may range from a normal-looking spine to loss of posterior column function (position, touch, vibration) or unilateral or bilateral weakness. Gait and sensory abnormalities are common. Hypotonic abdominal reflexes, elicited by scraping the skin tangential to the umbilicus in a particular quadrant, causing contraction of abdominal muscles in that quadrant, may be present with distal hyperreflexia. Babinski's response may be present. Myelopathy may result in urinary retention. Muscle wasting may be present with chronic symptoms. The possibility of other pathologic conditions should be kept in mind during the physical examination, with appropriate assessment tailored to the presentation and level of clinical suspicion.

DIAGNOSTIC STRATEGIES

Laboratory Evaluation

In the face of unremarkable history and physical examination findings, the likelihood that laboratory evaluation will yield useful results is extremely small. In appropriate clinical circumstances, assessment for malignancy, infection, and inflammation should be undertaken.

Radiology

The usefulness of radiologic assessment is dubious in a patient with acute atraumatic thoracic back pain in whom preexisting illness or neurologic abnormalities are absent. As a general guide, however, the following factors should prompt basic radiologic studies and appropriate further investigations: clinical suspicion for presence of other conditions; unexplainable symptoms; extremes of age; concern for trauma, tumor, infection, gastrointestinal pathology, or vascular pathology; and prolonged symptoms. Like patients with lower back pain, patients with a history of cancer and upper back pain should undergo plain radiography (or CT or MRI for high-suspicion cases) to assess for vertebral metastatic disease, especially because metastases have a predilection for the thoracic spine.

MRI has become the modality of choice for evaluating a herniated thoracic disk. The incidence of asymptomatic disk herniations seen on MRI is 37%. Most herniated thoracic disks, whether symptomatic or not, have been reported to recede spontaneously.[92]

DIFFERENTIAL CONSIDERATIONS

Although muscular back pain is extremely common, Box 54-3 summarizes the important considerations in the expansive differential diagnosis for thoracic back pain.

Box 54-3 Differential Diagnosis for Thoracic Back Pain

- Uncomplicated musculoskeletal back pain
- Spinal cord and nerve root pathology (e.g., disk herniation, tumor, hematoma)
- Vertebral column disease (e.g., primary or metastatic malignancy, osteomyelitis)
- Disk infection
- Primary neurologic disease
- Degenerative and autoimmune arthropathies
- Herpes zoster
- Vascular disease (e.g., thoracic aortic dissection, acute coronary syndrome, pulmonary embolism)
- Thoracic cavity pathology (e.g., pleuritis, pericarditis, pneumonia, esophageal pathology)
- Intraperitoneal and retroperitoneal abdominal pathology (e.g., peptic ulcer disease, pancreatitis, hepatobiliary disease)

MANAGEMENT

Commonly, thoracic musculoskeletal pain is managed with analgesia. No studies have shown the need for any difference in management from that for musculoskeletal back pain.

Thoracic disk disease is difficult to diagnose and manage. Symptomatic pain management and outpatient follow-up care are recommended. In view of the limited space in the spinal canal at the thoracic level compared with the lumbar level, spinal cord compression from a herniated disk is more likely at the thoracic level. Any disk herniation that precipitates an acute neurologic deficit warrants MRI and early neurosurgical evaluation.

DISPOSITION

Patients with benign back pain in any part of the thoracic vertebral column can be discharged with referral for follow-up care by the primary care physician. Patients with a suspected thoracic disk herniation require close outpatient follow-up. Most cases of subjective discomfort resulting from thoracic disk disease without objective neurologic findings resolve spontaneously, with one study showing a 77% improvement rate.[92] Although clear guidelines are lacking for when emergent neurosurgical consultation is required for thoracic disk herniation, patients with significant pain or neurologic compromise should be assessed rapidly.

KEY CONCEPTS

- The key to differentiating between benign and serious pathology in low back pain is a focused and thorough history and physical examination.
- The absence of sciatica findings practically rules out a lumbar disk herniation.
- Screening laboratory tests and plain radiographs are not indicated for patients with uncomplicated low back pain or a simple disk herniation.
- The best treatment for uncomplicated back pain and disk herniation is analgesia and resumption of normal activities—not bed rest.
- Age younger than 18 or older than 50 years, fever, injection drug use, immunocompromised status, symptoms lasting more than 4 to 6 weeks, night pain, and previous malignancy all are red flag warnings of potentially serious causes of back pain and should be heeded and evaluated accordingly.
- Although thoracic disk herniation can result in significant upper back pain, other, more dangerous causative disorders, such as aortic dissection, pulmonary embolism, and acute coronary syndrome, are considered first.
- The associated findings on the neurologic examination with thoracic disk herniations can be extremely variable, ranging from nonspecific paresthesias to significant upper motor neuron weakness.
- The incidence of vertebral metastatic malignancy is higher in the thoracic spine than in the lumbar spine.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Luo X, Pietrobon R, Sun SX, Liu GG, Hey L: Estimates and patterns of direct health care expenditures among individuals with back pain in the United States. *Spine (Phila Pa 1976)* 2004; 29:79.
2. Dagenais S, Caro J, Haldeman S: A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J* 2008; 8:8.
3. Deyo RA, Weinstein JN: Low back pain. *N Engl J Med* 2001; 344:363.
4. Dahm KT, Brurberg KG, Jamtvedt G, Hagen KB: Advice to rest in bed versus advice to stay active for acute low-back pain and sciatica. *Cochrane Database Syst Rev* 2010; 6:CD007612.
5. Chou R, et al: Diagnosis and treatment of low back pain: A joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med* 2007; 147:478.
6. Friedly J, Standaert C, Chan L: Epidemiology of spine care: The back pain dilemma. *Phys Med Rehabil Clin N Am* 2010; 21:659.
7. Owens PL, Woeltje M, Mutter R: *Emergency department visits and inpatient stays related to back problems, 2008: statistical brief #105. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs [Internet]*. Rockville (MD): Agency for Health Care Policy and Research (US); 2006-2011 Feb. Available from http://www.ncbi.nlm.nih.gov/books/NBK53197/.
8. Schiller JS, Lucas JW, Ward BW, Peregoy JA: Summary health statistics for U.S. adults: National Health Interview Survey, 2010. *Vital Health Stat* 2012; 10(252):1-207.
9. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R: Lost productive time and cost due to common pain conditions in the U.S. workforce. *JAMA* 2003; 290:2443.
10. Martin BI, et al: Expenditures and health status among adults with back and neck problems. *JAMA* 2008; 299:656.
11. Pengel LH, Herbert RD, Maher CG, Refshauge KM: Acute low back pain: Systematic review of its prognosis. *BMJ* 2003; 327:323.
12. Chou R, Shekelle P: Will this patient develop persistent disabling low back pain? *JAMA* 2010; 303:1295.
13. Livshits G, et al: Lumbar disc degeneration and genetic factors are the main risk factors for low back pain in women: The UK twin spine study. *Ann Rheum Dis* 2011; 70:1740.
14. Rivinoja AE, et al: Sports, smoking, and overweight during adolescence as predictors of sciatica in adulthood: A 28-year follow-up study of a birth cohort. *Am J Epidemiol* 2011; 173:890.
15. Shaw WS, Pransky G, Winters T: The back disability risk questionnaire for work-related, acute back pain: Prediction of unresolved problems at 3-month follow-up. *J Occup Environ Med* 2009; 51:185.
16. van Oostrom SH, Verschuren M, de Vet HC, Boshuizen HC, Picavet HS: Longitudinal associations between physical load and chronic low back pain in the general population: The Doetinchem Cohort Study. *Spine (Phila Pa 1976)* 2012; 37:788.
17. Rainville J, et al: Fear-avoidance beliefs and pain avoidance in low back pain—translating research into clinical practice. *Spine J* 2011; 11:895.
18. Verbunt JA, Smeets RJ, Wittink HM: Cause or effect? Deconditioning and chronic low back pain. *Pain* 2010; 149:428.
19. Alkherayf F, Agbi C: Cigarette smoking and chronic low back pain in the adult population. *Clin Invest Med* 2009; 32:E360.
20. De Luigi AJ, Fitzpatrick KF: Physical examination in radiculopathy. *Phys Med Rehabil Clin N Am* 2011; 22:7.
21. McCall IW: Lumbar herniated disks. *Radiol Clin North Am* 2000; 38:1293.
22. Borenstein DG, et al: The value of magnetic resonance imaging of the lumbar spine to predict low-back pain in asymptomatic subjects: A seven-year follow-up study. *J Bone Joint Surg Am* 2001; 83:1306.
23. Olmarker K, Rydevik B: Selective inhibition of tumor necrosis factor-alpha prevents nucleus pulposus-induced thrombus formation, intraneural edema, and reduction of nerve conduction velocity: Possible implications for future pharmacologic treatment strategies of sciatica. *Spine (Phila Pa 1976)* 2001; 26:863.
24. Thomas SA: Spinal stenosis: History and physical examination. *Phys Med Rehabil Clin N Am* 2003; 14:29.
25. Fabry G: Clinical practice: The spine from birth to adolescence. *Eur J Pediatr* 2009; 168:1415.
26. Jacobsen S, Sonne-Holm S, Rovsing H, Monrad H, Gebuhr P: Degenerative lumbar spondylolisthesis: An epidemiological perspective: The Copenhagen osteoarthritis study. *Spine (Phila Pa 1976)* 2007; 32:120.
27. Manchikanti L, et al: Role of facet joints in chronic low back pain in the elderly: A controlled comparative prevalence study. *Pain Pract* 2001; 1:332.
28. Winters ME, Kluetz P, Zilberstein J: Back pain emergencies. *Med Clin North Am* 2006; 90:505.
29. Pincus T, Burton AK, Vogel S, Field AP: A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. *Spine (Phila Pa 1976)* 2002; 27:E109.
30. Heneweer H, et al: Psychosocial variables in patients with (sub)acute low back pain: An inception cohort in primary care physical therapy in the Netherlands. *Spine (Phila Pa 1976)* 2007; 32:586.
31. Malleson P, Clinch J: Pain syndromes in children. *Curr Opin Rheumatol* 2003; 15:572.
32. Houghton KM: Review for the generalist: Evaluation of low back pain in children and adolescents. *Pediatr Rheumatol Online J* 2010; 8:28.
33. Bhatia NN, Chow G, Timon SJ, Watts HG: Diagnostic modalities for the evaluation of pediatric back pain: A prospective study. *J Pediatr Orthop* 2008; 28:230.
34. Feldman DS, Hedden DM, Wright JG: The use of bone scan to investigate back pain in children and adolescents. *J Pediatr Orthop* 2000; 20:790.
35. Frymoyer JW: Back pain and sciatica. *N Engl J Med* 1988; 318:291.
36. Devillé WL, van der Windt DA, Dzaferagić A, Bezemer PD, Bouter LM: The test of Lasègue: Systematic review of the accuracy in diagnosing herniated discs. *Spine (Phila Pa 1976)* 2000; 25:1140.
37. Atlas SJ, Delitto A: Spinal stenosis: Surgical versus nonsurgical treatment. *Clin Orthop Relat Res* 2006; 443:198.
38. Radu AS, Menkès CJ: Update on lumbar spinal stenosis. Retrospective study of 62 patients and review of the literature. *Rev Rhum Engl Ed* 1998; 65:337.
39. Kauppila LI, Eustace S, Kiel DP, Felson DT, Wright AM: Degenerative displacement of lumbar vertebrae. A 25-year follow-up study in Framingham. *Spine (Phila Pa 1976)* 1998; 23:1868.
40. Tatsuno I, et al: Age dependence of early symptomatic vertebral fracture with high-dose glucocorticoid treatment for collagen vascular diseases. *J Clin Endocrinol Metab* 2009; 94:1671.
41. Dicuio M, et al: Measurements of urinary bladder volume: Comparison of five ultrasound calculation methods in volunteers. *Arch Ital Urol Androl* 2005; 77:60.
42. Nolla JM, et al: Spontaneous pyogenic vertebral osteomyelitis in nondrug users. *Semin Arthritis Rheum* 2002; 31:271.
43. Walters HL, Measley R: Two cases of pseudomonas aeruginosa epidural abscesses and cervical osteomyelitis after dental extractions. *Spine (Phila Pa 1976)* 2008; 33:E293.
44. Ewald C, Kuhn S, Kalff R: Pyogenic infections of the central nervous system secondary to dental affections—a report of six cases. *Neurosurg Rev* 2006; 29:163.
45. Burgess BJ: Epidural abscess after dental extraction. *Emerg Med J* 2001; 18:231.
46. Joshi SM, Hatfield RH, Martin J, Taylor W: Spinal epidural abscess: A diagnostic challenge. *Br J Neurosurg* 2003; 17:160.
47. Darouiche RO: Spinal epidural abscess. *N Engl J Med* 2006; 355:2012.
48. Reihsaus E, Waldbaur H, Seeling W: Spinal epidural abscess: A meta-analysis of 915 patients. *Neurosurg Rev* 2000; 23:175.
49. Perrin RG, Laxton AW: Metastatic spine disease: Epidemiology, pathophysiology, and evaluation of patients. *Neurosurg Clin N Am* 2004; 15:365.
50. Henschke N, Maher CG, Refshauge KM: Screening for malignancy in low back pain patients: A systematic review. *Eur Spine J* 2007; 16:1673.
51. Polatin PB, Cox B, Gatchel RJ, Mayer TG: A prospective study of Waddell signs in patients with chronic low back pain. When they may not be predictive. *Spine (Phila Pa 1976)* 1997; 22:1618.
52. Main CJ, Waddell G: Behavioral responses to examination. A reappraisal of the interpretation of "nonorganic signs." *Spine (Phila Pa 1976)* 1998; 23:2367.
53. Davis DP, Salazar A, Chan TC, Vilke GM: Prospective evaluation of a clinical decision guideline to diagnose spinal epidural abscess in patients who present to the emergency department with spine pain. *J Neurosurg Spine* 2011; 14:765.
54. Davis DP, et al: The clinical presentation and impact of diagnostic delays on emergency department patients with spinal epidural abscess. *J Emerg Med* 2004; 26:285.
55. Curry WT Jr, Hoh BL, Amin-Hanjani S, Eskandar EN: Spinal epidural abscess: Clinical presentation, management, and outcome. *Surg Neurol* 2005; 63:364.
56. Tang HJ, Lin HJ, Liu YC, Li CM: Spinal epidural abscess—experience with 46 patients and evaluation of prognostic factors. *J Infect* 2002; 45:76.

www.ketabpezeshki.com 66485457-66963820

57. Savage K, Holtom PD, Zalavras CG: Spinal epidural abscess: Early clinical outcome in patients treated medically. *Clin Orthop Relat Res* 2005; 439:56.
58. Friedman BW, Chilstrom M, Bijur PE, Gallagher EJ: Diagnostic testing and treatment of low back pain in United States emergency departments: A national perspective. *Spine (Phila Pa 1976)* 2010; 35:E1406.
59. Jarvik JG, Deyo RA: Diagnostic evaluation of low back pain with emphasis on imaging. *Ann Intern Med* 2002; 137:586.
60. Boos N, Hodler J: What help and what confusion can imaging provide? *Baillieres Clin Rheumatol* 1998; 12:115.
61. Biswas D, et al: Radiation exposure from musculoskeletal computerized tomographic scans. *J Bone Joint Surg Am* 2009; 91:1882.
62. Jarvik JG, et al: Rapid magnetic resonance imaging vs radiographs for patients with low back pain: A randomized controlled trial. *JAMA* 2003; 289:2810.
63. Weinstein JN, et al: Surgical versus nonsurgical treatment for lumbar degenerative spondylolisthesis. *N Engl J Med* 2007; 356:2257.
64. Hagen KB, Jamtvedt G, Hilde G, Winnem MF: The updated Cochrane review of bed rest for low back pain and sciatica. *Spine (Phila Pa 1976)* 2005; 30:542.
65. van Tulder MW, Scholten RJ, Koes BW, Deyo RA: Nonsteroidal anti-inflammatory drugs for low back pain: A systematic review within the framework of the Cochrane Collaboration Back Review Group. *Spine (Phila Pa 1976)* 2000; 25:2501.
66. Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW: Non-steroidal anti-inflammatory drugs for low back pain. *Cochrane Database Syst Rev* 2008; 1:CD000396.
67. Machado LA, Kamper SJ, Herbert RD, Maher CG, McAuley JH: Analgesic effects of treatments for non-specific low back pain: A meta-analysis of placebo-controlled randomized trials. *Rheumatology (Oxford)* 2009; 48:520.
68. Friedman BW, et al: A randomized placebo-controlled trial of single-dose IM corticosteroid for radicular low back pain. *Spine (Phila Pa 1976)* 2008; 33:E624.
69. Friedman BW, et al: Parenteral corticosteroids for emergency department patients with non-radicular low back pain. *J Emerg Med* 2006; 31:365.
70. Jarvik JG: Imaging of adults with low back pain in the primary care setting. *Neuroimaging Clin N Am* 2003; 13:293.
71. Friedrich M, Gittler G, Arendasy M, Friedrich KM: Long-term effect of a combined exercise and motivational program on the level of disability of patients with chronic low back pain. *Spine (Phila Pa 1976)* 2005; 30:995.
72. Cherkin DC, Sherman KJ, Deyo RA, Shekelle PG: A review of the evidence for the effectiveness, safety, and cost of acupuncture, massage therapy, and spinal manipulation for back pain. *Ann Intern Med* 2003; 138:898.
73. Furlan AD, Imamura M, Dryden T, Irvin E: Massage for low-back pain. *Cochrane Database Syst Rev* 2008; 4:CD001929.
74. Furlan AD, et al: A systematic review and meta-analysis of efficacy, cost-effectiveness, and safety of selected complementary and alternative medicine for neck and low-back pain. *Evid Based Complement Alternat Med* 2012; 2012:953139.
75. Vroomen PC, de Krom MC, Slofstra PD, Knottnerus JA: Conservative treatment of sciatica: A systematic review. *J Spinal Disord* 2000; 13:463.
76. Benoist M: The natural history of lumbar disc herniation and radiculopathy. *Joint Bone Spine* 2002; 69:155.
77. Carette S, et al: Epidural corticosteroid injections for sciatica due to herniated nucleus pulposus. *N Engl J Med* 1997; 336:1634.
78. Ghahreman A, Ferch R, Bogduk N: The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. *Pain Med* 2010; 11:1149.
79. Stout A: Epidural steroid injections for low back pain. *Phys Med Rehabil Clin N Am* 2010; 21:825.
80. Weinstein JN, et al: Surgical vs nonoperative treatment for lumbar disk herniation: The spine patient outcomes research trial (sport): A randomized trial. *JAMA* 2006; 296:2441.
81. Gibson JN, Grant IC, Waddell G: The Cochrane review of surgery for lumbar disc prolapse and degenerative lumbar spondylosis. *Spine (Phila Pa 1976)* 1999; 24:1820.
82. Amundsen T, et al: Lumbar spinal stenosis: Conservative or surgical management?: A prospective 10-year study. *Spine (Phila Pa 1976)* 2000; 25:1424.
83. Ahn UM, et al: Cauda equina syndrome secondary to lumbar disc herniation: A meta-analysis of surgical outcomes. *Spine (Phila Pa 1976)* 2000; 25:1515.
84. Gleave JR, Macfarlane R: Cauda equina syndrome: What is the relationship between timing of surgery and outcome? *Br J Neurosurg* 2002; 16:325.
85. Chen SH, et al: The clinical characteristics, therapeutic outcome, and prognostic factors of non-tuberculous bacterial spinal epidural abscess in adults: A hospital-based study. *Acta Neurol Taiwan* 2011; 20:107.
86. Weigel B, et al: Surgical management of symptomatic spinal metastases. Postoperative outcome and quality of life. *Spine (Phila Pa 1976)* 1999; 24:2240.
87. Antunes NL, De Angelis LM: Neurologic consultations in children with systemic cancer. *Pediatr Neurol* 1999; 20:121.
88. Schiff D: Spinal cord compression. *Neurol Clin* 2003; 21:67.
89. Laredo JD, el Quessar A, Bossard P, Vuillemin-Bodaghi V: Vertebral tumors and pseudotumors. *Radiol Clin North Am* 2001; 39:137.
90. Byrne TN: Spinal cord compression from epidural metastases. *N Engl J Med* 1992; 327:614.
91. Tsirikosi AI, Garrido EG: Spondylolysis and spondylolisthesis in children and adolescents. *J Bone Joint Surg Br* 2010; 92:751.
92. Wood KB, et al: The natural history of asymptomatic thoracic disc herniations. *Spine (Phila Pa 1976)* 1997; 22:525.
93. Stillerman CB, Chen TC, Couldwell WT, Zhang W, Weiss MH: Experience in the surgical management of 82 symptomatic herniated thoracic discs and review of the literature. *J Neurosurg* 1998; 88:623.
94. Jenis LG, Dunn EJ, An HS: Metastatic disease of the cervical spine. A review. *Clin Orthop Relat Res* 1999; 359:89.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 55

Pelvic Trauma

Stephen B. Choi and A. Adam Cwinn

PERSPECTIVE

Background

Patients with traumatic pelvic ring injury may represent an immense challenge for the emergency physician. First, patients with pelvic ring fractures are at risk for exsanguinating pelvic hemorrhage. Furthermore, the profound magnitude of force required to disrupt the pelvic ring frequently causes severe injuries to other organ systems. The resuscitation from hemorrhagic shock, rapid identification of other major injuries and sites of blood loss, and the coordination of definitive angiographic and surgical treatments are paramount to achieving good clinical outcomes.

Epidemiology

Based on data from trauma registries, the majority of high-energy pelvic ring injuries are caused by motor vehicle collisions (MVCs), motorcycle crashes, and pedestrians being struck by motor vehicles, together accounting for 80 to 84% of pelvic fractures; and falls from height, which account for 5 to 12%[1-5] of pelvic fractures. The mortality rates reported in the literature associated with pelvic fracture range from 9 to 22%[1-5]; in studies of large cohorts of trauma patients, the presence of pelvic fracture has been consistently shown to be an independent risk factor for death compared with trauma patients without pelvic fracture.[6-8] Patients with pelvic fractures and with shock on arrival to the hospital have mortality rates of 33 to 57%.[3,4] Increased age, shock on arrival at the hospital, high injury severity and revised trauma scores (which generally reflect the presence of multisystem injuries), and the need for transfusion have all been shown to increase the risk of death.[3-5,9,10] The mortality rate among pedestrians struck by motor vehicles who sustain pelvic injury has been shown to be 23%.[11]

Despite advances in motor vehicle safety design, MVCs continue to be a major cause of pelvic fracture. Rates of pelvic fracture secondary to MVC range from 10 to 28%.[9,12,13] Lateral impact remains the most prevalent mechanism for pelvic trauma in collisions, for which the widespread advent of front airbags has little effect. Some have speculated that the increased popularity of sport-utility vehicles in past decades is contributing to the severity of side-impact injuries, specifically as a result of the higher bumper in these vehicles striking the side of lower cars.[9,12,14]

PRINCIPLES OF DISEASE

Anatomy

Detailed descriptions of pelvic anatomy may be found in standard anatomy texts. This section focuses on the relevant anatomy essential to understanding pelvic injuries.

Bony and Ligamentous Anatomy

The pelvic ring is made up of right and left innominate bones and the sacrum. The innominate bones consist of the pubis, ischium, and ilium (Fig. 55-1). The bony pelvis provides protection for its visceral contents, serves as attachment points for muscles, and transmits weight from the trunk to the lower limbs. The main weight-bearing forces are transmitted through the posterior wall of the pelvis, called the *posterior arch*, which is composed of thick bone and ligaments. The rich network of major arteries, veins, and nerves that course in front of the posterior arch may be injured concomitantly with forces causing bony injuries of this arch.

Knowledge of the ligamentous attachments of the pelvic ring is crucial to understanding how stability is maintained or disrupted in pelvic injury. The stability of the pelvis is maintained by ligaments, as well as the muscles and fascia that make up the pelvic floor. Anteriorly, the symphysis pubis provides the major mechanical stability. Posteriorly, a complex of strong ligaments—the sacrospinous, sacrotuberous, iliolumbar, and anterior and posterior sacroiliac (SI) ligaments—maintains the integrity of the posterior arch (Fig. 55-2). It is important to appreciate that mechanically unstable pelvic fractures are unstable primarily because of the disruption of these posterior ligaments.

Vascular Anatomy

Most of the blood supply to the pelvis comes from the left and right internal iliac arteries. The internal iliac arteries course at the level of the SI joints. The various arteries that derive from the internal iliac arteries initially run in close proximity to the posterior pelvic arch and eventually anastomose extensively with one another, forming a rich collateral network (Fig. 55-3). The superior gluteal artery is the largest branch and is commonly injured in fractures of the posterior pelvic arch. The obturator and internal pudendal branches are often injured in fractures involving the pubic rami.

www.ketabpezeshki.com 66485457-66963820

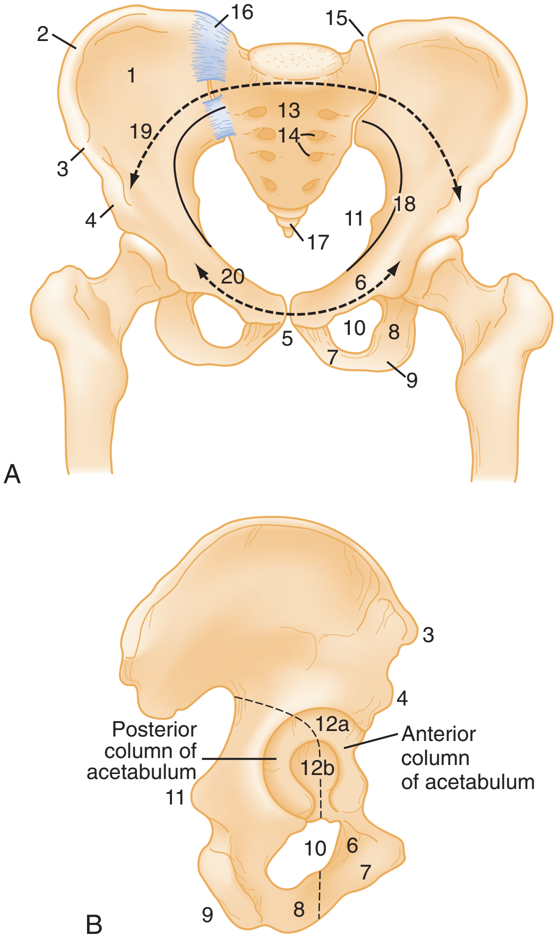


Figure 55-1. Bony pelvic anatomy. **A,** Anterior view of pelvis. **B,** Lateral view of right innominate bone. *(1)* Iliac fossa, *(2)* iliac crest, *(3)* anterior superior iliac spine, *(4)* anterior inferior iliac spine, *(5)* symphysis pubis, *(6)* superior ramus of pubis, *(7)* inferior ramus of pubis, *(8)* ramus of ischium, *(9)* ischial tuberosity, *(10)* obturator foramen, *(11)* ischial spine, *(12)* acetabulum (*[12a]* articular surface, *[12b]* fossa), *(13)* sacrum, *(14)* anterior sacral foramina, *(15)* sacroiliac joint, *(16)* anterior sacroiliac ligament, *(17)* coccyx, *(18)* arcuate line, *(19)* posterior or femorosacral arch, through which main weight-bearing forces are transmitted, *(20)* anterior arch.

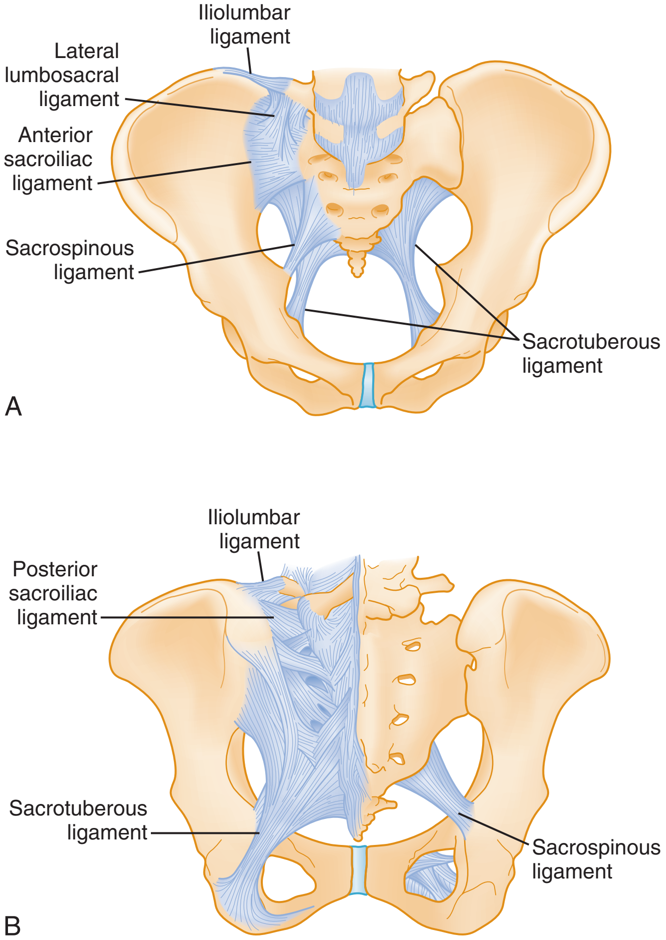


Figure 55-2. **A,** Anteroposterior view of the pelvis indicates that the sacrospinous ligament is a triangular strong ligament lying anterior to the sacrotuberous ligament, which is a strong broad band extending from the lateral portion of the dorsum of the sacrum to the ischial tuberosity. **B,** The major posterior stabilizing structures of the pelvic ring, that is, the posterior tension band of the pelvis, include the iliolumbar ligament, posterior sacroiliac ligaments, sacrospinous ligaments, and sacrotuberous ligaments.

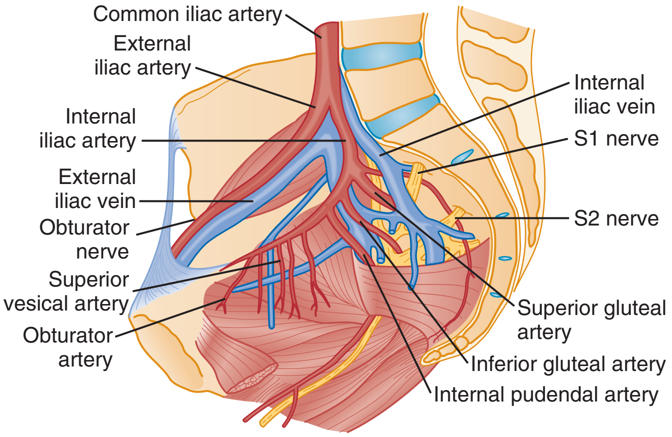


Figure 55-3. The internal iliac plexus of arteries and veins. (From Tile M: Fractures of the Pelvis and Acetabulum, 3rd ed. Philadelphia, Lippincott, Williams & Wilkins, 2003.)

The venous system also has many collateral branches and is without valves, allowing bidirectional flow. The veins are arranged in a plexus that adheres closely to the pelvic walls. Because these veins are thin-walled, they do not have the ability to constrict in response to damage. This anatomic arrangement of the arteries and veins accounts for the hemorrhage often seen with pelvic fractures.

Neurologic Anatomy

The cauda equina courses through the sacral spinal canal and exits through the sacral neural foramina to form the lumbar and sacral plexus. Injury to the posterior bony pelvis and sacrum may result in neurologic deficits in the lower extremities and autonomic dysfunction involving the bowel, bladder, and genitalia.

Pathophysiology and Key Patterns of Pelvic Fracture

Numerous classification schemes exist for pelvic fractures. Two widely used schemes for pelvic injury are presented here. The classification by Tile stresses the biomechanical stability of the pelvic ring[15] (Box 55-1). The Young-Burgess classification emphasizes the mechanisms of injury[16] (Box 55-2). From a practical viewpoint, it is highly useful to consider both of these elements in the assessment of a pelvic ring fracture. Within both classification systems exist numerous subtypes of injuries, the interobserver

www.ketabpezeshki.com 66485457-66963820

Box 55-1 Tile's Classification of Pelvic Fractures

Type A—Stable, posterior arch intact
Includes avulsion fractures, isolated iliac wing fracture, pubic rami fractures, minimally displaced ring fracture, transverse fractures of the sacrum or coccyx.
Type B—Partially stable, incomplete disruption of the posterior arch
Includes anteroposterior injuries (open book) and lateral compression injuries. May be unilateral or bilateral. These injuries are rotationally unstable but vertically stable.
Type C—Unstable, complete disruption of the posterior arch
Includes iliac, sacroiliac, and vertical sacral injuries that result from vertical shearing forces. May be unilateral or bilateral. These injuries are both rotationally and vertically unstable.

From Tile M: Fractures of the Pelvis and Acetabulum, 3rd ed. Philadelphia, Lippincott, Williams & Wilkins, 2003.

Box 55-2 Young-Burgess Classification of Pelvic Fractures

Anteroposterior Compression
I. Symphysis diastasis <2.5 cm
II. Symphysis diastasis >2.5 cm, sacrospinous and anterior SI ligament disruption, results in rotational instability
III. Symphysis diastasis >2.5 cm, with complete disruption of the anterior and posterior SI ligament, results in complete rotational and vertical instability

Lateral Compression
I. Sacral crush injury on ipsilateral side
II. Sacral crush injury with disruption of posterior SI ligaments; iliac wing fracture may be present (crescent fracture); rotationally unstable
III. Severe internal rotation of ipsilateral hemipelvis with external rotation of contralateral side ("windswept" pelvis), rotationally unstable

Vertical Shear
Vertical displacement of symphysis and sacroiliac joints resulting in complete rotational and vertical instability

Combined Mechanisms
Any combination of the above mechanisms

From Burgess AR, Eastridge BJ, Young JW, et al: Pelvic ring disruptions: Effective classification system and treatment protocols. J Trauma 30:848, 1990.
SI, sacroiliac.

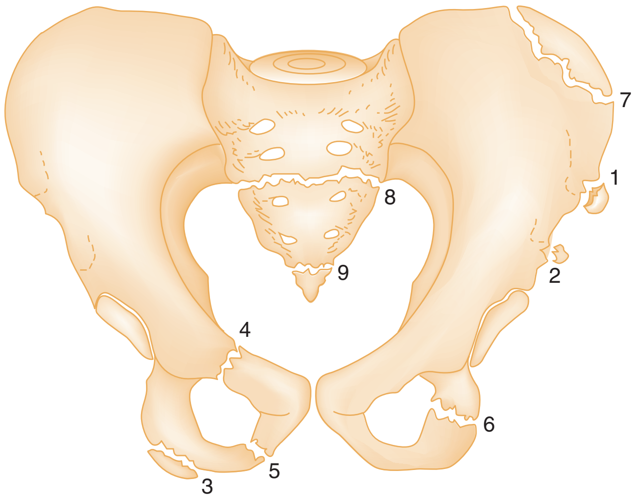


Figure 55-4. Fractures of individual pelvic bones. *(1)* Avulsion of anterosuperior iliac spine, *(2)* avulsion of anteroinferior iliac spine, *(3)* avulsion of ischial tuberosity, *(4)* fracture of superior pubic ramus, *(5)* fracture of inferior pubic ramus, *(6)* fracture of ischial ramus, *(7)* fracture of iliac wing, *(8)* transverse fracture of sacrum, *(9)* fracture of coccyx. (From Tile M: Fractures of the Pelvis and Acetabulum, 3rd ed. Philadelphia, Lippincott, Williams & Wilkins, 2003.)

reliability of which has been questioned.[17,18] For the emergency physician, a good understanding of both the underlying principles of pelvic stability and mechanisms of injury is far more important than a detailed knowledge of the numerous subtypes of injury that exist within the classification schemes. The broad distinction of mechanically stable from unstable fractures of the pelvic ring is clinically useful to bear in mind in assessing patients, as it has been demonstrated consistently over time that those with unstable injuries have higher mortality and greater transfusion requirements.[16,19,20]

Stable Injuries (Tile Type A)

Fractures of individual bones without involvement of the pelvic ring represent one third of all pelvic fractures. In general, most stable pelvic fractures heal well with rest and analgesic drugs for pain control (Fig. 55-4).[15]

Undisplaced or Minimally Displaced Fractures of the Pelvic Ring. The normal pelvis is not totally rigid because of the slight mobility at the SI joints and symphysis pubis and the inherent elasticity of bone. A single break in the ring is possible. Nevertheless, the pelvis is not totally forgiving, and identification of a single break in the ring should prompt a search for a second disruption.

An isolated fracture of the superior or inferior pubic ramus is the most common pelvic fracture. These fractures are stable. They are common fractures in elderly people after a fall and should be considered in the evaluation of an acutely painful hip. Fracture of the body of the ischium is a rare injury that may result from a fall in the sitting position. These fractures around the obturator foramen are treated conservatively with bed rest, analgesia, and early mobilization.

Fracture of the superior and inferior pubic rami on the same side is a commonly encountered injury after a fall or MVC. These are generally stable fractures and are treated conservatively. However, the presence of significant displacement at the fracture site indicates a second disruption elsewhere in the pelvic ring that should be diagnosed. Alternatively, fractures of both rami on the same side may be associated with an unrecognized impaction fracture of the posterior pelvis.

If the patient with a ramus fracture reports posterior pelvic pain and plain radiographs do not reveal posterior injury, further investigations may reveal occult posterior fractures. A study performed more than 35 years ago found that patients who sustained apparently isolated pubic ramus fractures showed increased uptake of radionuclides on bone scans in the acetabulum and SI joint, suggesting that occult bony or ligamentous injury accounted for the pain.[21] More recently, a study that prospectively evaluated elderly patients who were diagnosed with isolated ramus fractures on plain films found that 95% had sacral fracture detected by magnetic resonance imaging (MRI).[22] This study does not imply a need to perform MRI on all elderly patients with ramus fractures in the ED; rather, it enhances our understanding of the pathophysiology of ramus fractures and underscores the importance of adequate analgesia in these patients. The lateral compression type I fracture described by Young and Burgess (Fig. 55-5)—characterized by pubic ramus fracture with ipsilateral sacral compression—bears special consideration among the mechanically stable pelvic fractures, as it has been shown to be associated with a mortality rate of 8% with a high incidence of associated injuries.[20,23,24]

Also termed a *straddle fracture*, four-pillar injuries involve fractures of both pubic rami on both sides of the symphysis pubis,

www.ketabpezeshki.com 66485457-66963820

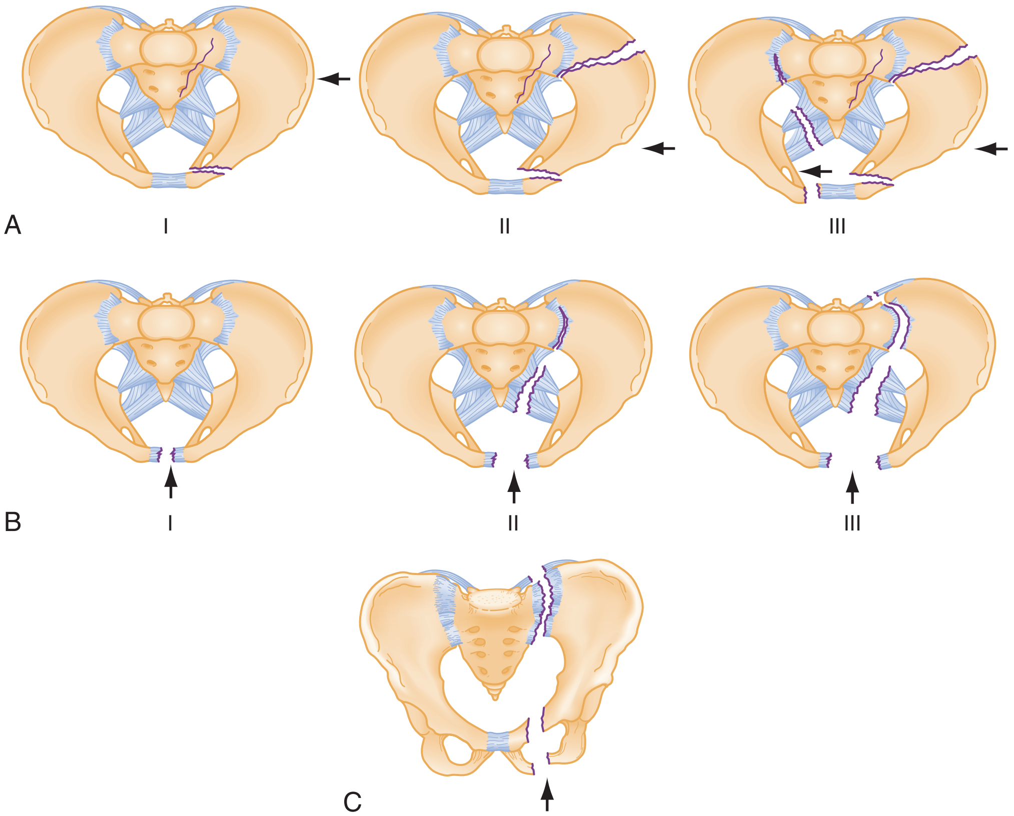


Figure 55-5. Young-Burgess classification. **A,** Lateral compression. Type I: A posteriorly directed force causing a sacral crushing injury and horizontal pubic ramus fractures ipsilaterally. Type II: A more anteriorly directed force causing horizontal pubic ramus fractures with an anterior sacral crushing injury and either disruption of the posterior sacroiliac joints or fractures through the iliac wing. Type III: An anteriorly directed force that is continued, causing external rotation of the contralateral side; the sacroiliac joint is opened posteriorly, and the sacrotuberous and spinous ligaments are disrupted. **B,** Anteroposterior (AP) compression. Type I: Symphysis disrupted but with intact posterior ligamentous structures. Type II: Continuation of a type I fracture with disruption of the sacrospinous and potentially the sacrotuberous ligaments and an anterior sacroiliac joint opening. Type III: Continuation force disrupts the sacroiliac ligaments. **C,** Vertical shear. Vertical fractures in the rami and disruption of all posterior ligaments. This injury is equivalent to an AP type III or a completely unstable and rotationally unstable fracture. Arrow indicates the direction of force. (Redrawn from Young JWR, Burgess AR: Radiologic Management of Pelvic Ring Fractures. Baltimore, Munich, Urban & Schwarzenberg, 1987. Browner BD: Skeletal Trauma: Basic Science, Management, and Reconstruction, 3rd ed. Copyright © 2003 Saunders, an imprint of Elsevier.)

causing the so-called “butterfly segment” (Fig. 55-6). The injury is produced by a direct blow with a straddle mechanism. Although these fractures may occur without posterior arch disruption, four-pillar injuries are also commonly associated with lateral compression or vertical shear forces that may cause concomitant injuries to the posterior pelvic arch. CT of the pelvis is required in cases of four-pillar injuries to detect and classify precisely the posterior arch injury and plan orthopedic treatment.[15] The genitourinary tract frequently is injured concomitantly with this type of pelvic fracture and should be evaluated carefully (see Fig. 55-6).

Isolated fracture of the iliac wing was described by Duverney in 1751 and now bears his name. It is caused by direct trauma to the iliac crest, usually by lateral compression forces. Although displacement is usually minimal because of the arrangement of the muscle attachments of the abdominal wall, orthopedic consultation is recommended. The fracture may extend into the acetabulum, altering the treatment and prognosis. Severely displaced fractures of the iliac wing require open reduction and internal fixation.[15] It is worth noting that a high incidence of major associated nonpelvic injuries among patients with isolated iliac wing fracture has been reported.[23]

Transverse Fractures of the Sacrum. Transverse fractures of the sacrum do not compromise the pelvic ring. Transverse fractures at or below S4 are unlikely to be accompanied by neurologic injury.[25] An upper sacral transverse fracture is the result of a flexion injury, such as being struck on the lower back by a heavy load while bending over, or by direct forces to the sacrum, as in a fall from a great height.[25] The patient reports pain in the buttocks, perirectal area, and posterior thighs. There may be local pain, swelling, and bruising overlying the sacrum, and on gentle bimanual rectal examination, severe pain, abnormal motion, and palpable hematoma may be elicited. Radiographically, the fracture may be difficult to visualize on anteroposterior (AP) and lateral projections, in which case a pelvic outlet view may be helpful. Simple transverse fractures at or below S4 are treated conservatively. Above S4, neurologic injuries are common, necessitating careful clinical evaluation and surgery when neurologic compromise is present.

Avulsion Fractures. These usually occur during athletic activities and are the result of a sudden, forceful muscular contraction or excessive muscle stretch. They are seen more commonly in older children and teenagers before closure of the corresponding physis occurs; adults may have the same symptoms from ligamentous injury at these sites without radiographic abnormality.

The ischial tuberosity may be avulsed during strenuous contraction of the hamstrings. There is pain on palpation of the involved tuberosity, and this pain is increased by flexion of the hip with the knee in extension (hamstrings stretched), but not with the knee flexed (hamstrings relaxed). Ischial tuberosity avulsion also may cause chronic discomfort with no history of acute injury.

A portion of the iliac crest epiphysis may be avulsed by contraction of the abdominal muscles. Similarly, the anterior superior

www.ketabpezeshki.com 66485457-66963820

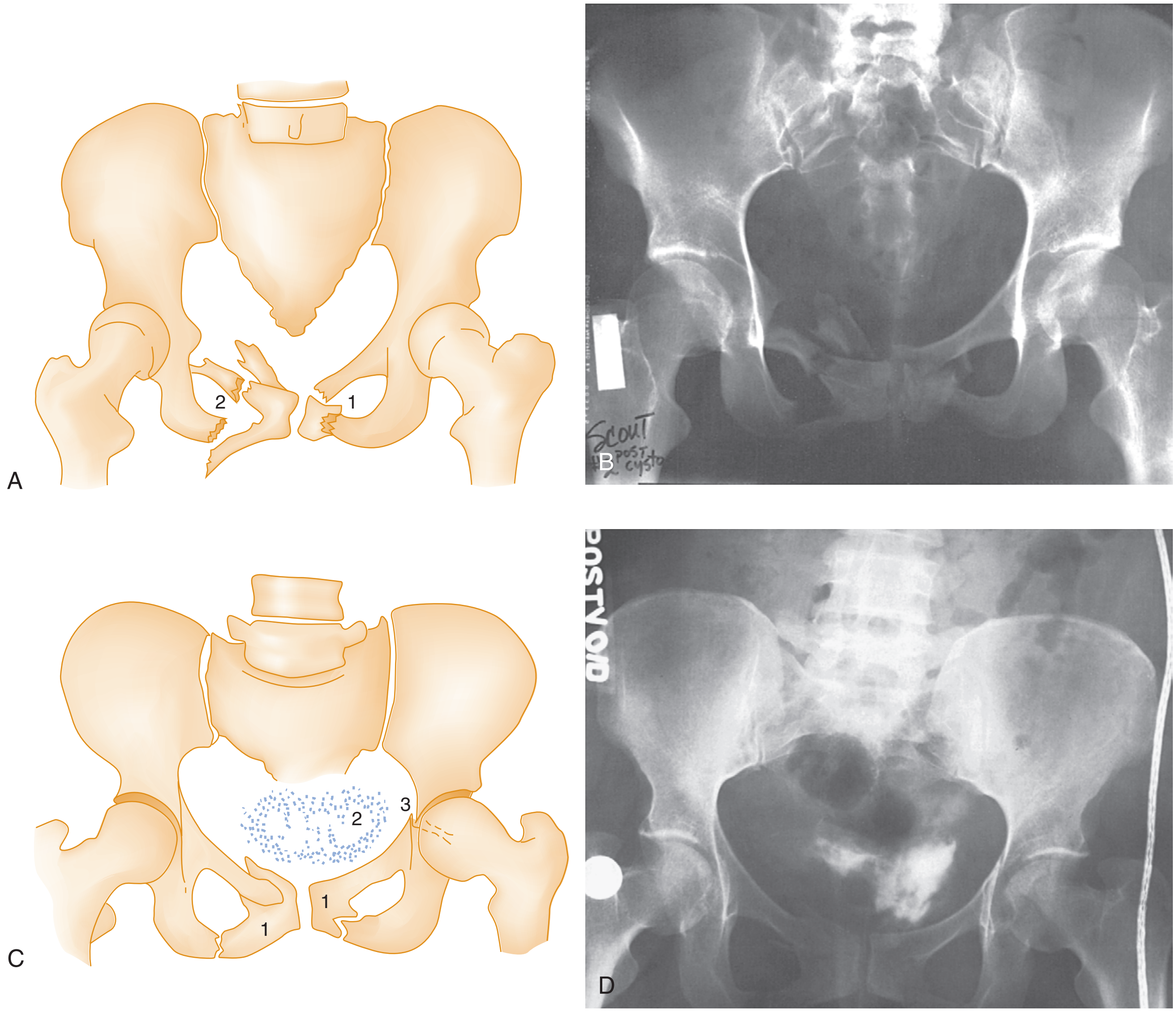


Figure 55-6. Four-pillar (straddle) fracture. A and B, Partial inlet view of pelvis shows straddle fracture. *(1)* and *(2)* Marked comminution of left pubic bone and comminuted right superior and inferior rami. This partial inlet projection shows displacement of fragments into the pelvis, which is not evident on the anteroposterior view of the same patient in C and D. A true inlet projection and computed tomography scan (not available) would provide further information about the posterior arch, which is injured frequently in straddle fractures and should be imaged (see text). C and D, Postvoid cystogram of the same patient with anteroposterior pelvis. *(1)* Fractures of pubic rami are seen again but do not appear to be as displaced compared with A and B because this projection is an anteroposterior view. Even minor degrees of angulation of the x-ray beam can change the appearance of pelvic fracture displacement. *(2)* Extravascular contrast indicates bladder rupture; *(3)* left acetabular fracture is seen in this projection but not in B because of the difference in projection. The acetabular fracture disrupts the ilioischial line (see also Fig. 55-13) and is a posterior column fracture.

iliac spine may be avulsed by forcible contraction of the sartorius muscle. Forceful contraction of the rectus femoris (as in kicking a ball) can result in the less common injury of anterior inferior iliac spine avulsion; however, this radiographic finding should be distinguished from a normal variant, the os acetabuli, which is a secondary center of ossification at the superolateral margin of the acetabulum.[26] Clinical examination is similar in these injuries and reveals local pain, swelling, and limitation of motion.

Conservative treatment, including analgesia and bed rest in a position that avoids tension on the affected muscles, is generally all that is required for avulsion injuries; surgical treatment is rarely necessary. Orthopedic consultation is advised for follow-up care.

Stress Fractures. Stress fractures occur with vigorous athletic or military training and in the last trimester of pregnancy.[27] The diagnosis of stress fractures is based on the clinical evaluation and can be confirmed, if required, by radionuclide bone scan, although MRI has been shown to be a superior method for detecting these injuries.[28]

Pathologic and Insufficiency Fractures. Pathologic fracture related to neoplasm, Paget's disease, or dietary osteomalacia is included in the differential diagnosis. Radiation therapy has also been shown to increase the risk of pelvic fracture.

Partially Stable and Unstable Injuries (Tile Types B and C)

Partially stable and unstable injuries are caused by high-energy impacts. The forces applied to the pelvis determine the types of injuries that occur. Broadly, forces may be applied to the pelvic ring in AP, lateral, or vertical directions that result in characteristic injury patterns; combinations of forces result in

www.ketabpezeshki.com 66485457-66963820

more complex injuries. The terms *unstable fracture* (referring to mechanical stability) and *unstable patient* (referring to hemodynamic status) should not be confused, although a cause-and-effect relationship often exists.

Anteroposterior Compression. Severe AP compression forces result in disruption at or near the symphysis pubis. Symphysis widening of less than 2.5 cm is considered a stable injury (the symphysis should normally be ≤0.5 cm in an adult but can increase 2-3 mm during or after pregnancy); however, with continued force in the AP direction, the hemipelvis externally rotates, tearing the sacrospinous, sacrotuberous, and anterior SI ligaments. The SI joint opens and hinges on the intact posterior SI ligaments. The resulting injury is aptly described as an "open-book" fracture. The pelvis is rotationally unstable in the horizontal plane, but the intact posterior SI ligaments maintain vertical stability.[15,16]

When diastasis of the pubic symphysis is greater than 2.5 cm on the AP radiograph, the posterior injury is usually seen as widening of the SI joint and occasionally as a sacral or iliac fracture (see Fig. 55-5).[15] If the injurious forces continue, they may separate the hemipelvis, and the SI joint is seen as widely separated on the plain AP radiograph (Fig. 55-7) and the CT scan.[15] The AP radiograph may be misleading in suggesting a pure open-book fracture in cases with symphysis disruptions greater than 2.5 cm. These cases commonly are associated with vertical shear fractures, and careful clinical and computed tomography (CT) assessment for vertical instability is essential to classify the fracture properly and plan treatment.[15]

These same forces also may injure the neurologic and vascular structures at the posterior arch; the overall volume of the pelvis is increased in the open-book injury, facilitating the expansion of a retroperitoneal hematoma. Several studies have demonstrated that patients with severe grades of AP compression injuries have the highest crystalloid and blood requirements.[16,19]

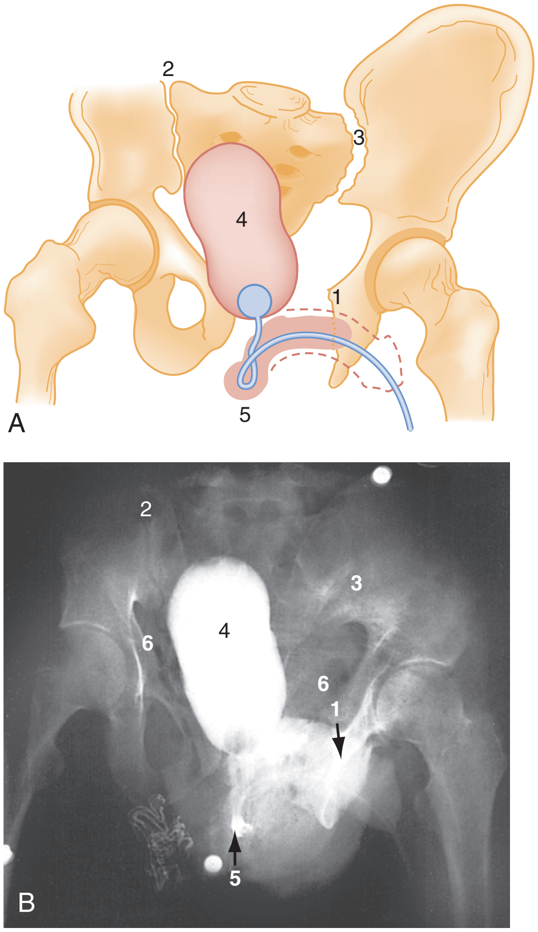


Figure 55-7. Interpretive drawing **(A)** and radiograph **(B)**. Severe unilateral open-book fracture from anteroposterior compression forces that is also open (compound). *(1)* Separated pubic symphysis with asymmetry of hemipelvis, *(2)* normal sacroiliac joint, *(3)* separated sacroiliac joint, *(4)* cystogram with displacement and abnormally elongated shape of bladder caused by retroperitoneal hematoma associated with separated left sacroiliac joint, which has pushed the bladder to the right, *(5)* extravasated contrast into perineum from urethral rupture, *(6)* soft tissue air indicating an open fracture.

Lateral Compression. Lateral compression of the pelvic ring results in varying degrees of internal rotation of the affected hemipelvis. Initially, this causes buckling of the sacrum and horizontal pubic rami fractures. Rami fractures may occur on the ipsilateral or contralateral side, the latter being referred to as the "bucket-handle" fracture (Fig. 55-8).

As the magnitude of force increases, the symphysis may disrupt, causing overlapping of the pubic bones. Note that on plain radiographs, evidence of injury to the sacrum may be subtle; overlapping pubic bones with any significant displacement should prompt a search for a posterior injury.

Similar to the AP injury, with increasing disruption of the posterior ligaments comes increasing rotational instability. In the most severe lateral compression trauma, the ipsilateral pelvis internally rotates to such a degree that the contralateral pelvis may externally rotate. This is referred to as the "windswept" pelvis. Lateral compressive injuries result in varying degrees of horizontal rotational instability; however, the vertical stability of the pelvis is maintained (see Fig. 55-8).

As internal rotation causes the pelvic volume to decrease, lateral compressive injuries are generally associated with lesser degrees of blood loss than are AP injuries.

Vertical Shear. Vertical shear injuries represent the most unstable injuries to the pelvic ring and are associated with violent axial loading of the hemipelvis (e.g., fall from height, "submarining" underneath a dashboard). Fractures occur in vertical planes. Anteriorly, the symphysis and rami may be disrupted. Posteriorly, gross displacement and instability in the rotational and vertical planes may be present through the sacrum, the SI joint, or the ilium such that the hemipelvis may displace posteriorly and cephalad[15,16] (see Fig. 55-9).

Avulsion of the ischial spine, the lower lateral lip of the sacrum, and the transverse process of the fifth lumbar vertebra (sites of insertion of ligaments) (Fig. 55-9 and Box 55-3) are important clues to the presence of vertical shear fractures.[15] The vertical shearing forces transmitted through the bony pelvis are also transmitted through the rich vascular network and nerve plexus that are directly adjacent to the bone. This activity accounts for the major hemorrhage and neurologic injuries associated with vertical shear fractures.

Vertical Sacral Fractures. A crucial distinction in considering sacral fractures is that transverse fractures do not involve the pelvic ring, but vertical fractures do. Vertical sacral fractures are caused by high-energy injuries and were classified by Denis into three groups according to whether the fracture line extends (1) laterally to the sacral foramina, (2) through the foramina, or (3) medially to the foramina, involving the central spinal canal[29] (Fig. 55-10). The radiographic diagnosis of this fracture hinges on careful examination of the symmetrical cortical lines that are normally present at the superior margins of the sacral foramina on the AP view. Disruption, distortion, or asymmetry of these lines is an important marker of sacral fractures.[26]

There is a high risk of neurologic complications associated with these injuries: 6% when lateral to the foramina, 28% when through the foramina, and 58% when medial to the foramina.[29] Neurologic dysfunction correlates to the nerve roots involved but may include any bowel, bladder, or sexual dysfunction. Surgery is commonly

www.ketabpezeshki.com 66485457-66963820

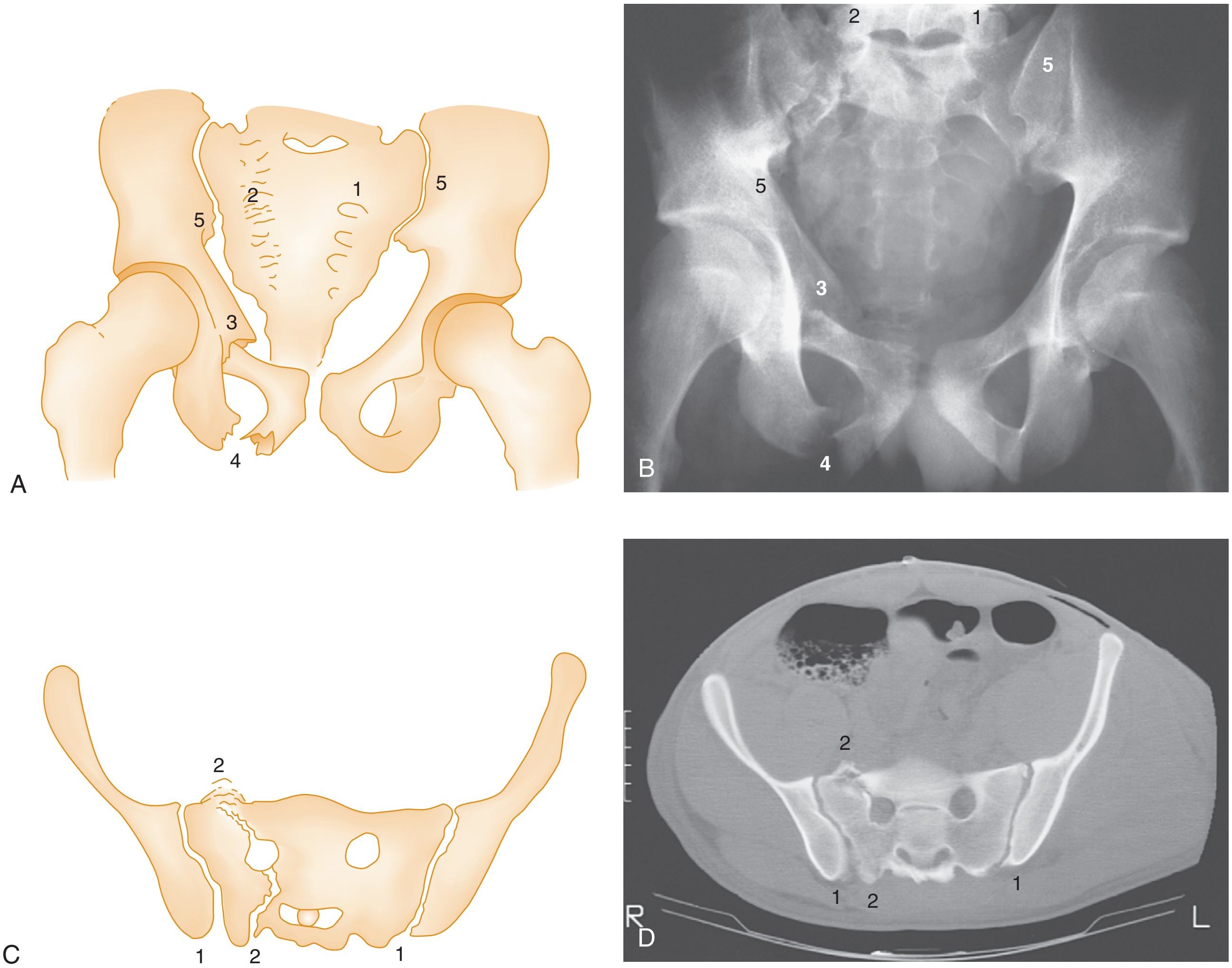


Figure 55-8. Lateral compression fracture. A and B, Anteroposterior view of the pelvis. *(1)* Normal sacral foraminal lines on the left; *(2)* sacral foraminal lines on the right are indistinct and do not mirror the normal side, indicating the subtle second break in the pelvic ring; *(3)* and *(4)* fractures of the superior and inferior pubic rami are overriding and displaced, indicating the lateral compression forces (there must be a second break in the pelvic ring); *(4)* is the "bucket-handle" fracture; *(5)* normal sacroiliac joints. C and D, Computed tomography scan of same pelvis. *(1)* Normal sacroiliac joints, *(2)* compression fracture of the sacrum through the foramen corresponding to the loss of definition of the foraminal lines in A and B.

performed for fractures associated with neurologic dysfunction, with the goals of bony fixation of the sacrum and decompression of affected nerve roots.

Open Pelvic Fractures

An open pelvic fracture is present when there is direct communication between the fracture site and a skin, rectal, or vaginal wound. These are potentially lethal injuries, especially if the open nature is not recognized: hemorrhage accounts for early mortality, but infection, sepsis, acute respiratory distress syndrome, and multisystem organ failure are all causes of delayed death.[24,30] The majority of case series before 1991 reported mortality rates greater than 50%; rates reported from 1991 to 1999 ranged from 5 to 30%,[30] although a recent series reported a 45% mortality rate.[31]

The skin over the posterior pelvis and gluteal area and perineum is inspected carefully for wounds. Some fractures are open only by virtue of a bone spicule penetrating the vagina or rectum and are identified by careful digital rectal examination (DRE) and vaginal examination. Hemorrhage from a large open laceration should be treated by direct manual pressure or pressure dressing. Pelvic fractures communicating with the rectum have traditionally mandated a diverting colostomy; however, a systematic review of the literature on this topic found no difference in infection rates between patients treated with colostomy and those treated without.[32]

Penetrating Pelvic Trauma

Because of the complex anatomy of the viscera, blood vessels, and nerves within the pelvis, penetrating trauma to this area presents a major challenge. Overall mortality in this group of patients has been reported to be 6 to 12%, but the mortality rate of patients in shock is 50%.[33,34] Vascular injuries singly and in combination may involve the aorta; common iliac artery; and external, internal, and common iliac veins. Injuries to genitourinary structures and hollow viscera may occur, with fecal contamination from colorectal injury being a major concern. When present, the finding of blood on DRE is an important clue that rectal injury has occurred. Emergent surgical consultation is required in all cases of penetrating pelvic trauma.

www.ketabpezeshki.com 66485457-66963820

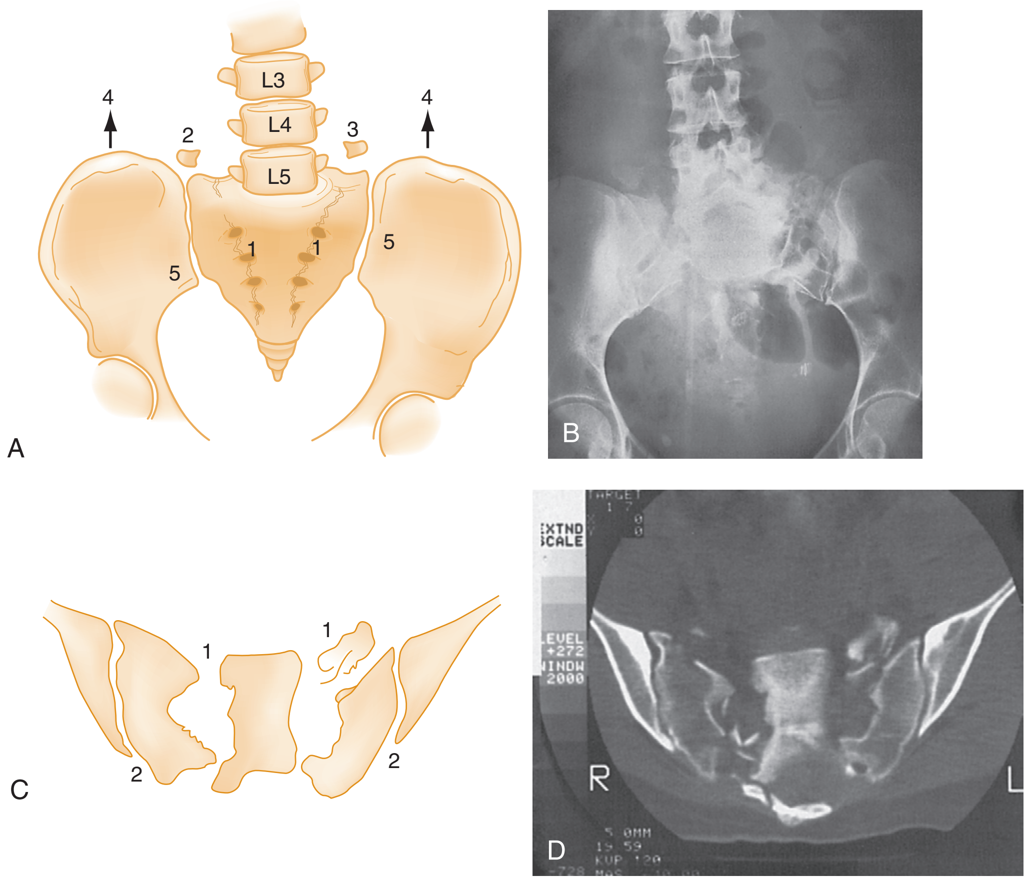


Figure 55-9. **A** and **B,** Vertical shear fractures bilaterally. At first glance the pelvis appears normal because of the smooth, uninterrupted arcuate line, but careful interpretation reveals the extremely critical nature of the injuries. *(1)* Fractures through the sacrum—note loss of definition and symmetry of sacral foramina, indicating vertical fractures through both sides of the sacrum (see computed tomography scan in **D**). *(2)* Transverse process fragment from right L5 (iliolumbar ligament attachment) is pathognomonic for a vertical shear fracture through the right sacrum. *(3)* Transverse process fragment from left L5, pathognomonic for a vertical shear fracture through the left sacrum. *(4)* Both hemipelves are dislocated cephalad because of the double-ring fractures through each side of the sacrum. This dislocation explains why the L5 transverse processes appear so close to the iliac crests (the body of L5 is obscured because of rotational dislocation of the central free sacral fragment posteriorly and because of technique). *(5)* Normal sacroiliac joints. **C** and **D,** Computed tomography scan of same pelvis. *(1)* Bilateral comminuted fractures of sacrum with lateral displacement of both hemipelves, *(2)* normal sacroiliac joints.

Box 55-3 Radiographic Clues to Posterior Arch Fractures

Avulsion of L5 transverse process*
Avulsion of ischial spine*
Avulsion of lower lateral lip of the sacrum (sacrotuberous ligament)*
Displacement at the site of a pubic ramus fracture
Asymmetry or lack of definition of bone cortex at superior aspect of the sacral foramina

*Indicates mechanical instability.

CLINICAL FEATURES

History

Understanding the mechanism of injury is an important means of determining a patient's risk of having a pelvic fracture and, if present, the pattern and severity of the fracture. Low-energy injuries (e.g., fall on level ground) typically cause stable injuries to the pelvis; patients who have sustained high-energy injuries (e.g., MVCs, falls from heights) are at risk for unstable fracture patterns of the pelvis as well as associated injuries to other organ systems.

Determining the direction of forces applied to the pelvis can also give important clues to the types of injury sustained. AP forces (e.g., head-on MVCs) may cause open-book injuries to the pelvis. Lateral forces to the pelvis (e.g., side-impact collisions) may disrupt the posterior ligaments; however, the pelvic floor generally remains intact. Vertical shear injuries (e.g., falls from height) may disrupt the posterior ligaments and pelvic floor, causing gross instability of the pelvis.

Age is an important consideration in patients with pelvic fracture. Osteopenic bone may be disrupted by lesser forces. Furthermore, studies consistently demonstrate higher morbidity and mortality among elderly patients with pelvic fracture. Although pelvic hemorrhage remains an important consideration among elderly patients with pelvic fracture, higher mortality rates are further influenced by a greater prevalence of preexisting medical conditions in this population that increase the risk of death from multisystem organ failure.[35,36] Decreased physiologic reserves in older patients may limit success in the acute resuscitation and definitive treatment of injuries.

Injuries to other organ systems are extremely common in patients with pelvic fracture.[2,4,5] It is important to identify all major injuries to other organ systems to prioritize definitive surgical treatment for the multiply traumatized patient. In women, it is important to consider the possibility of pregnancy and to test for pregnancy whenever appropriate.

www.ketabpezeshki.com 66485457-66963820

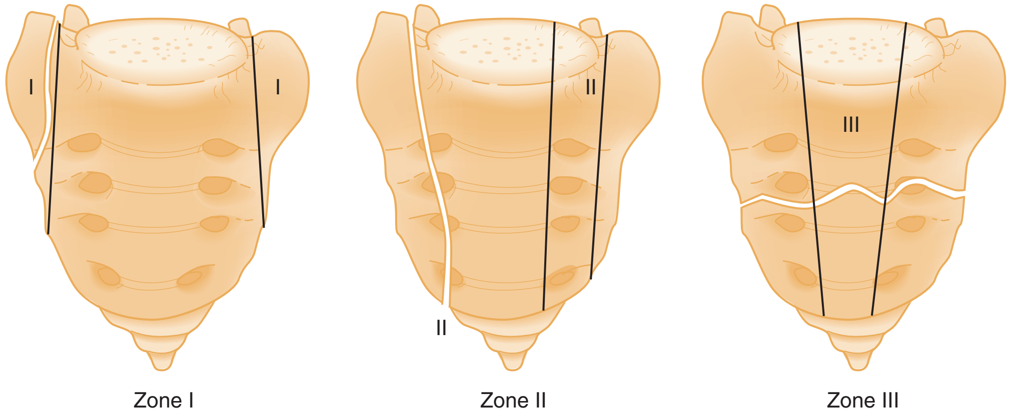


Figure 55-10. The Denis classification of vertical sacral fracture. Zone I is lateral to the sacral foramina (known as the *sacral ala*). Zone II is transforaminal. Zone III is the central sacrum medial to the foramina.

Physical Examination

On inspection, rotation of the iliac crests indicates a serious pelvic fracture. Leg-length discrepancy may suggest a hip injury or cephalad migration of an unstable hemipelvis. Careful inspection of the skin and skin folds is necessary to identify open fractures. Perineal or genital ecchymosis or hematoma may be observed, and in cases in which many hours have elapsed since the injury, ecchymosis in the periumbilical area (Cullen's sign) or flanks (Grey Turner's sign) from retroperitoneal hemorrhage may be present. Careful palpation of the pelvic ring to seek the presence of point tenderness is imperative; palpation starts at the symphysis anteriorly and proceeds to both pubic rami, the iliac spines and crests, and finally to the sacrum and SI joints posteriorly. The presence of tenderness in any of these locations is an important indicator of pelvic ring injury in alert patients without distracting injury.[37]

Manipulation of the pelvis during physical examination should be gentle and kept to a minimum. "Springboarding" of the pelvis (i.e., vigorous downward pressure on the anterior superior iliac spines) to assess the rotational stability of the pelvic ring should be strictly avoided, as this maneuver has the potential to disrupt any tenuous blood clotting that may have occurred around a fracture site and may therefore worsen hemorrhage.

The penis should be milked to examine for blood at the meatus. Although the value of the DRE has been questioned in the literature with claims that it has extremely low sensitivity as a diagnostic test, it remains useful as a screening tool.[38] The DRE should evaluate sensation, sphincter tone, position and consistency of the prostate, presence of a presacral hematoma, bony contour of the sacrum and coccyx, mucosal penetration of bony spicules, and presence of frank or occult blood. In the setting of a pelvic fracture, female patients should undergo a vaginal examination to diagnose an open fracture. Because it is possible to create an open fracture iatrogenically through the vaginal or rectal wall, DRE and vaginal examination should be performed carefully, especially in an unconscious patient who cannot localize pain. The examiner should be mindful when performing these examinations that bony spicules can lacerate the examining finger. Extravasated urine may be detected in the scrotum or the subcutaneous tissues of the penis, vulva, or abdominal wall. The presence and quality of pulses in the lower limb should be assessed, as should sensation, strength, and deep tendon reflexes.

Associated Pelvic Injuries

Urologic Injury

The overall incidence of bladder or urethral disruption associated with any pelvic fracture is approximately 4 to 6%, with increased risk among those with severe pelvic injuries.[2] Because the urethra is far less exposed in women than in men, injury to the urethra in women with pelvic fracture is rare.[39,40]

A review of 721 patients with pelvic fracture revealed an incidence of bladder rupture in 5% of patients. Those with fractures of the anterior arch of the pelvis are at greatest risk for bladder injury: diastasis of the symphysis more than 1 cm and fracture around the obturator ring with displacement greater than 1 cm were associated with a tenfold and threefold increased risk of bladder rupture, respectively.[41]

The presence of gross hematuria indicates injury of the lower urinary tract. Blood at the urethral meatus necessitates a retrograde urethrogram followed by a cystogram. Gross hematuria is investigated with a combination of urethrography, intravenous pyelography, cystography, and CT. The sequence and types of examinations are individualized for each patient. Fracture to the inferomedial pubic ramus and increasing symphyseal diastasis have both been shown to be predictive of urethral injury.[42] Of note, it has been reported that retrograde urethrocystography done before CT of the pelvis may impair the ability of CT to detect extravasation of contrast that would indicate active pelvic bleeding.[43] Therefore if CT is to be performed, it should be done before retrograde urethrocystography.

Sexual dysfunction in both men and women is a recognized complication of pelvic trauma. The incidence of impotence associated with urethral rupture is significant. In the absence of urethral injury, sexual dysfunction in men still may occur secondary to neurovascular disruption associated with the pelvic fracture.[38]

Neurologic Injury

The risk of neurologic injury has been shown to correlate with instability of the pelvic injury, with a reported incidence of neurologic dysfunction of 1.5, 3.8, and 14% in Tile type A, B, and C fractures, respectively; acetabular fractures were associated with a 10% incidence of neurologic dysfunction.[45] Neurologic injury occurs commonly in patients with vertical sacral fractures or transverse fractures above the S4 level. Among patients with vertical fractures that involve the foramina, 28% have associated neurologic deficits. In patients with fractures medial to the foramina involving the spinal canal, 57% have neurologic deficits.[29]

Cauda equina syndrome and various plexopathies and radiculopathies may occur as follows. Injury to the L5 root may cause weakness of muscles in the anterior tibial compartment and sensory deficits in the dorsum of the foot and lateral calf. Injury to S1 and S2 roots may cause weakness of hip extension, knee flexion, and plantar flexion and sensory deficits on the posterior

www.ketabpezeshki.com 66485457-66963820

aspect of the leg, sole and lateral foot, and genitalia. Injury to S2-5 roots and distal afferent, efferent, and autonomic fibers causes sensory deficits in the perineum, sexual dysfunction, and bowel and bladder dysfunction. Cauda equina syndrome may be fully or partially present with sacral fractures. Hyperesthesia and later anesthesia occur in a saddle-shaped distribution in the groin; in addition, weakness of ankle plantar flexion, hamstrings, and gluteus muscles and decreased or absent ankle jerk are present. With involvement of the lower sacral roots, a neurogenic bladder with overflow incontinence, motor and sensory deficits in the lower extremities, anal sphincter dysfunction, and sexual dysfunction may occur. All patients with neurologic deficits from sacral fractures require orthopedic or neurosurgical consultation.

Gynecologic Injury

Blood at the introitus may indicate a urethral injury, open pelvic fracture, or local laceration without communication with the bony pelvis. Delayed urologic and sexual dysfunction and complications with pregnancy are common after pelvic injury.[46] Gynecology consultation is indicated when there is injury to the female reproductive tract in association with a pelvic fracture and for all pregnant women who sustain pelvic fracture of any kind.

Associated Nonpelvic Injuries

The magnitude of force required to disrupt the pelvis commonly results in severe injuries to other organ systems. Among those patients who die with pelvic fracture, it is rare that the pelvic fracture is an isolated injury.[1,2,19,47,48] Furthermore, associated injuries among trauma patients with pelvic fracture may contribute more to mortality than the pelvic injury itself.[10]

Some authors have described patterns of associated nonpelvic injuries with certain patterns of pelvic fracture; however, these findings have not been consistently reproduced in the literature.[19,49] Severe injuries to head, spine, thorax, and abdomen may occur with both stable and unstable pelvic fractures; they may all occur with all major mechanisms of pelvic injury. One associated injury that reflects the dispersion of enormous forces throughout the body is the rupture of the thoracic aorta; albeit uncommon in blunt trauma, it is five to eight times more likely in older patients with pelvic fracture.[2,50] Therefore the diagnosis of a pelvic fracture should prompt a careful evaluation for other system injuries.

DIAGNOSTIC STRATEGY

Radiology

Plain Radiography

Routine radiographs of the pelvis are not necessary in cases of blunt trauma if the patient is asymptomatic, awake, and alert and has normal findings on physical examination of the pelvis.[51-54] However, routine AP plain radiography of the pelvis (PXR) is advised by the Advanced Trauma Life Support (ATLS) guidelines for patients with severe mechanisms of injury who are symptomatic or whose examination is compromised by either decreased level of consciousness or distracting injuries.

On the AP radiograph, the symphysis pubis is normally no more than 5 mm wide, and a small (1- or 2-mm) vertical offset of the left and right pubic rami is normal.[26] Overlapping at the symphysis pubis is abnormal and is the result of a severe crushing injury. Normally the SI joint is approximately 2 to 4 mm wide.[26]

On the AP view, the physician may judge the degree of pelvic rotation caused by technique and positioning by the presence of asymmetry in the size and shape of the left and right obturator foramina and iliac wings. Diastasis of the SI joint also causes an asymmetrical appearance of the obturator foramina and the iliac wings: If there is displacement into external rotation, the affected iliac wing appears broader, and the anterior iliac spine appears more prominent.[26] Avulsion fracture of the fifth lumbar transverse process by the iliolumbar ligament often accompanies an SI joint disruption or a vertical sacral fracture and is a valuable clue to posterior arch injuries[26] (see Fig. 55-9 and Box 55-3).

The reliability of the single AP PXR to detect pelvic fractures has been questioned in the literature. Two case series have reported sensitivities of only 64 and 68% with specificities of 90 and 98%, respectively, thus prompting the question of whether PXR is necessary at all when patients are to undergo immediate abdominopelvic CT evaluation.[55,56] In particular, sacral fractures and SI joint disruptions are not well visualized on the AP view.[57] However, the addition of inlet and outlet views of the pelvis has been shown to increase the sensitivity and specificity of plain radiographs in detecting significant pelvic fracture (Fig. 55-11) and SI joint disruption and should be considered in all patients with presumed stable anterior pelvic ring injuries with any complaints of posterior pelvic pain.[58]

When patients are too unstable to undergo CT investigation, the AP PXR is useful in screening for pelvic injuries that are most associated with major blood loss and potentially require urgent intervention.[59,60] That is, although PXR may miss many fractures, a very abnormal PXR is predictive. Findings that predict the need for transfusion include open-book fracture or displacement of 0.5 cm or more at any fracture site in the pelvic ring and displaced symphysis pubis, displaced obturator ring fracture, or obvious vertical displacement in the posterior pelvis.[61,62] It is important to note that all of these signs may be associated with posterior pelvic injury. Therefore the PXR remains a vital test when CT cannot be immediately performed and should be used to alert both surgeons and angiographers of the potential need for definitive management of pelvic hemorrhage.[63]

Computed Tomography

CT is the imaging test of choice for evaluating the injured pelvis. CT provides detailed information about the posterior arch and rotational deformities that indicate the relative stability of the pelvic ring; furthermore, the acetabulum, which may be difficult to assess with plain radiographs, can be well visualized with CT. CT has demonstrated a much higher sensitivity and specificity than plain radiography in detecting pelvic fracture.[55,56] Furthermore, abdominopelvic CT provides detailed information about concomitant injury to abdominal organs that aids in the planning of laparotomy, external fixation of the pelvis, angiography, and definitive orthopedic management of the pelvic injury. Finally, it has been demonstrated that selective CT scanning of the chest, abdomen, and pelvis in patients who sustain high-energy trauma results in a high miss rate of important diagnoses that alter treatments plans versus "pan" CT scanning (i.e., including all of the head, neck, chest, abdomen, and pelvis).[64,65] It should be noted that the decision to "pan" CT scan should be based on a combination of factors, such as abnormal vital signs, neurologic status, the detection of injuries on clinical examination, and the patient's mechanism of injury. Clinical judgment should guide the decision, to avoid wasting resources and unnecessarily exposing patients to radiation.

Given the speed with which current CT scanners are able to obtain images, unless patients require immediate lifesaving surgical treatment in the operating room, it is recommended that all patients with high-energy mechanisms of injury with suspected pelvic fracture or pelvic fracture confirmed by PXR undergo CT investigation.

www.ketabpezeshki.com 66485457-66963820

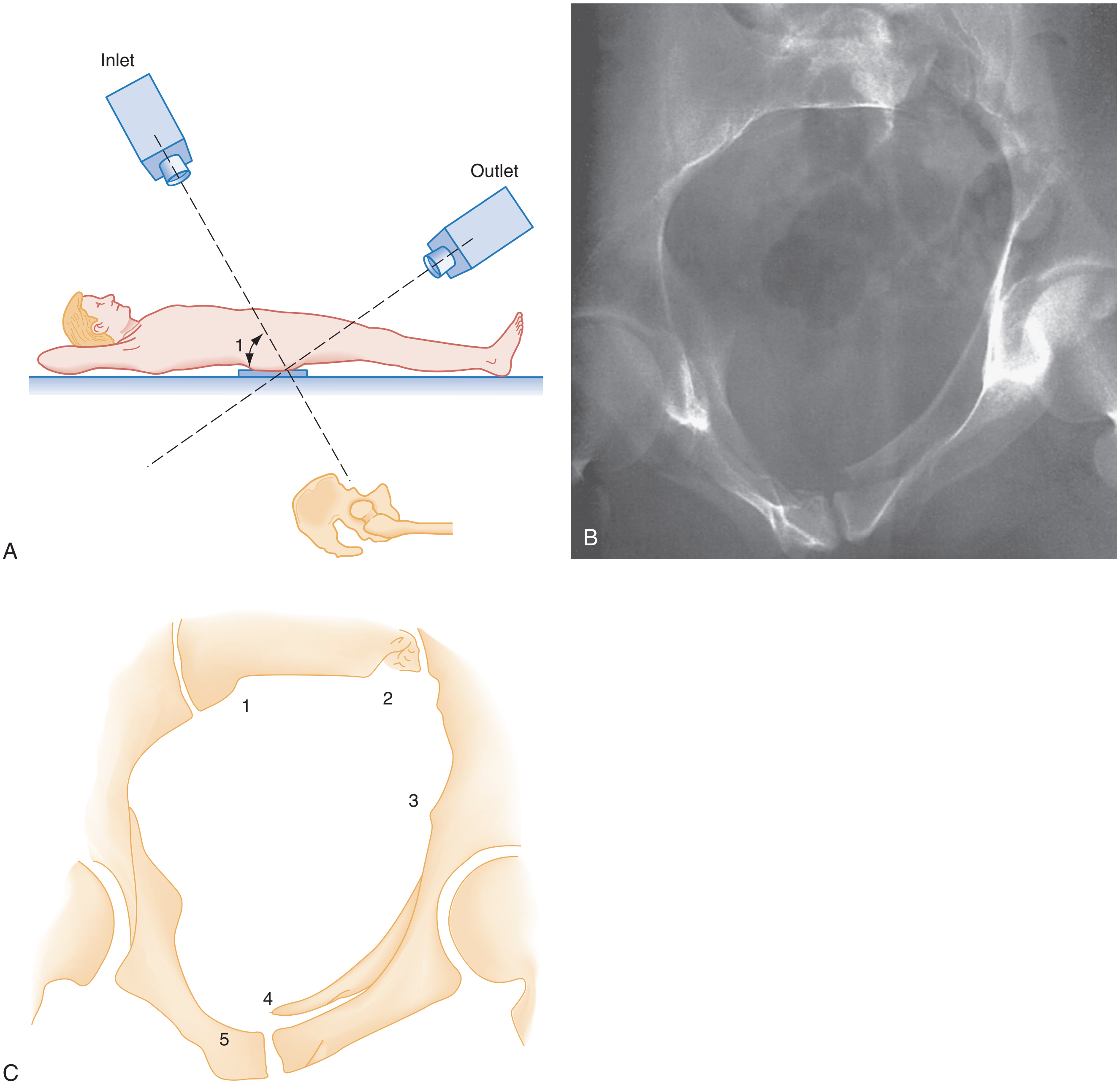


Figure 55-11. **A,** The inlet and outlet views. The inlet view is angled 60 degrees to the plate from head to feet; the outlet view is angled 30 degrees in the opposite direction. Both views can be obtained with a portable machine if necessary. Injuries to the sacrum and sacroiliac joint are commonly difficult to visualize with the anteroposterior view only. The combination of all three views allows the identification of virtually all significant injuries to the bony pelvis. **B,** Inlet of pelvis is well demonstrated in this radiograph of a unilateral vertical shear fracture with cephalad and posterior displacement of the left hemipelvis. **C,** Schematic of unilateral vertical shear fracture. *(1)* Normal sacral ala on the right side, *(2)* left sacral ala is indistinct because of a vertical fracture, and the cephalad and posterior displacement of this hemipelvis is shown by this inlet projection, *(3)* ischial spine on the left is partially obscured by bowel gas, but it is located more cephalad compared with the right spine because of cephalad displacement of the left hemipelvis, *(4)* fractured left superior pubic ramus with displacement cephalad, *(5)* the inlet view is taken looking through the superior and inferior pubic rami, which are superimposed so that the obturator foramina are not seen.

Evaluation of Hemorrhage

Hemorrhage is the most devastating direct complication of pelvic fracture. In the original series of high-energy pelvic injuries used to formulate their classification system, Burgess and colleagues analyzed blood transfusions and found that an average of 14.8 units were required in the AP compression group, 9.2 units in the vertical shear group, and 3.6 units in the lateral compression group.[16] The correlation between transfusion requirements and type of pelvic fracture has been confirmed in more recent studies that demonstrate that unstable fracture patterns increase the need for transfusion and risk of mortality,[63] with one series reporting a median of 10 units of blood required (range 1-70 units).[3]

Major pelvic hemorrhage results from lacerations of the rich vascular network supplying the pelvis in the retroperitoneal space. Pelvic hemorrhage is commonly venous in origin and may be contained and tamponaded retroperitoneally by an intact peritoneum. However, it is possible for bleeding to extend beyond the retroperitoneum and dissect into the anterior abdominal wall (to the chagrin of the unwary clinician who introduces a scalpel or peritoneal dialysis catheter) or through the peritoneum into the

www.ketabpezeshki.com 66485457-66963820

abdominal cavity (see later). Bleeding also may occur from the marrow at the fracture sites.[66] Finally, coagulopathy is another cause of persistent retroperitoneal bleeding and should be considered when the patient does not respond to fluid and blood replacement.

The combination of both pelvic and intra-abdominal bleeding is associated with devastating outcomes.[63] In one large series, major pelvic injury was associated with intra-abdominal injuries in 31% of cases; the liver and spleen were injured in 10 and 6% of these cases, respectively.[2] In the patient with pelvic fracture who is in shock, it is important to establish early whether there is hemorrhage within the abdominal cavity necessitating laparotomy. Diagnostic strategies for evaluation of pelvic fracture–associated hemorrhage include diagnostic peritoneal lavage (DPL), ultrasound, and CT. Regardless of the modality of evaluation, it is crucial to avoid unnecessary laparotomy because of the higher mortality rate for hemodynamically unstable patients with pelvic fractures who undergo a negative abdominal exploration.

Diagnostic Peritoneal Lavage

DPL is a widely accepted, rapid, and accurate means of establishing the presence of intra-abdominal hemorrhage. Although it has been largely supplanted in many centers by ultrasound and CT, DPL nevertheless remains an effective tool to assist with difficult triage decisions in the trauma patient. A pelvic fracture presents a special situation for DPL because of the possibility that a retroperitoneal hematoma may dissect into the anterior abdominal wall. However, when a fully open technique is used (i.e., the peritoneum is entered under direct visual control), the false-positive and false-negative rates are each 0.7%.[67]

DPL may be performed in the infraumbilical location in most patients; however, the supraumbilical location should be used if any of the following conditions are present: prior abdominal scars, time delay since the injury of more than 1 hour, or a hematoma encountered during the procedure.[67]

A negative peritoneal aspirate indicates that the peritoneal cavity is not a major source of bleeding or a significant contributor to hemorrhagic shock. If external and thoracic sources of blood loss and spinal cord injury have been eliminated as causes of hemodynamic instability, a negative peritoneal aspirate in a patient with a major pelvic fracture indicates pelvic hemorrhage. A combination of angiography with rapid therapeutic embolization, surgical packing of the pelvis, and mechanical fracture stabilization should be pursued.

Gross aspiration of blood indicates possible major intra-abdominal hemorrhage, and laparotomy is recommended at the earliest opportunity for hemodynamically unstable patients.[47] The lavage that is positive by cell count criteria alone is a special situation. If these patients are hemodynamically unstable, it is advisable to perform angiography with therapeutic embolization and external pelvic fixation before laparotomy.[66,67]

Ultrasound

Focused assessment with sonography in trauma (FAST) is widely used to identify free intraperitoneal fluid in the trauma patient. An important caveat to note is that FAST is not helpful for evaluating the retroperitoneal space where pelvic hemorrhage occurs. Although a positive FAST study that shows free fluid is widely used as a triage point to decide on laparotomy in a hemodynamically unstable patient, its reliability in patients with major pelvic injury has been questioned. Sensitivities ranging from 24 to 81% and specificities ranging from 87 to 96% for the detection of hemoperitoneum have been reported[68,69] in patients with pelvic fracture; the presence of pelvic fracture has been reported to be a predictor of a false-negative FAST examination, with an odds ratio of 3.5 (95% confidence interval 1.3-9.2).[70]

Although these reports come from retrospective case series—and therefore do not necessarily represent the highest levels of evidence—the high incidence of false-negative FAST examinations reported in the literature in patients with pelvic injury is nonetheless cause for concern. This is because pelvic and intra-abdominal hemorrhages are highly associated and in combination result in major blood loss.[63]

Computed Tomography

CT is unquestionably the diagnostic test of choice for detecting pelvic and intra-abdominal injuries. It reveals bleeding in both the peritoneal and retroperitoneal spaces. CT with intravenous contrast often can distinguish a stable hematoma from ongoing bleeding from pelvic arteries. The presence or absence of extravasated intravenous contrast material on CT scan of the pelvis is useful in predicting which patients will require therapeutic angiography[71]; however, its absence does not rule out ongoing pelvic bleeding: One series found the sensitivity for the detection of arterial bleeding by CT to be only 66% in patients who also underwent angiography.[72] It is worth noting that with improving CT technology, its use will continue to evolve for patients with pelvic hemorrhage. Specifically, pelvic CT angiography (CTA) has been reported to not only localize active pelvic bleeding but also distinguish bleeding from an arterial versus a venous source.[73,74] This is a distinction that could have great impact on the decision to perform therapeutic angiography for active arterial bleeding. Advancing CT technology will require further study to define its role in patients with pelvic hemorrhage, but it is likely that it will also be concurrently incorporated into clinical practice.

MANAGEMENT

Resuscitation

The mortality rate in patients with blunt trauma who have the combination of pelvic ring fractures and hemorrhagic shock is approximately 50%.[1,2] ATLS guidelines advocate the initial use of crystalloid solutions to stabilize vital signs in the trauma patient. However, when severe hypotension is present in patients with severe pelvic fracture, transfusion of blood products (including packed red blood cells, plasma, platelets, and occasionally cryoprecipitate) is crucial early in the resuscitation. Some patients appear to achieve hemodynamic stability after minimal volume infusion only to decompensate precipitously. It is important to note that case series commonly report patients with severe pelvic injury who require transfusion of packed red blood cells on the order of 10 to 20 units within the first 24 to 48 hours.

The endpoint for fluid resuscitation should be evidence of end-organ perfusion. A large body of evidence from animal studies suggests that standard volumes of crystalloid fluids typically used in traumatic hemorrhagic shock to restore normal heart rate and blood pressure lead to greater volumes of blood loss compared with low-volume resuscitation strategies that accept lower systemic blood pressures.[75,76] Furthermore, in a landmark human study of hypotensive patients with penetrating chest injury, it was shown that delaying fluid resuscitation (despite systolic blood pressure below 90 mm Hg) resulted in a higher rate of discharge from the hospital than did immediate fluid resuscitation.[76a]

For patients with pelvic fracture, attempts to achieve a normal pulse and blood pressure with fluid resuscitation in the ED are unrealistic and should not delay more definitive treatments to halt the hemorrhagic process.

www.ketabpezeshki.com 66485457-66963820

Lower limb intravenous sites should be avoided in patients with severe pelvic fractures because the infused products may be delivered to the retroperitoneal space.

Box 55-4 details the methods for controlling hemorrhage in the ED phase of the care of patients with pelvic fractures.

Control of Hemorrhage

In addition to blood transfusion, two important therapeutic modalities for control of hemorrhage are mechanical stabilization of the pelvis and angiographic embolization. There has been some debate as to which of these modalities should take precedence, and this has been predicated on institutional availability. As a general rule, angiography with therapeutic embolization of bleeding arteries is more effective than and takes precedence over invasive external fixation.[77,78]

Box 55-4 Pelvic Fracture–Related Hemorrhage: Goals in the Emergency Department

1. *Resuscitation:* Recognize the patient who is in hemorrhagic shock, and initiate blood transfusion early in the resuscitation.
2. *Recognition:* Realize that patients with posterior arch injuries are at higher risk for pelvic hemorrhage.
3. *Evaluation:* Identify associated nonpelvic injuries (especially head, chest, and intra-abdominal) that contribute immensely to increase in mortality in patients with pelvic fracture.
4. *Stabilization:* Wrapping the pelvis in a sheet and towel clamps is the easiest way to immobilize the pelvis in the emergency department. Stabilization by external fixation or pelvic C-clamp should be performed by orthopedic surgeons.
5. *Control of pelvic bleeding:* Angiography is highly effective in treating pelvic arterial hemorrhage. Pelvic packing during laparotomy is another way of controlling bleeding. Institutional practices determine if one or both techniques are used.

Stabilizing the Pelvis

Noninvasive Techniques. The most readily available means to quickly stabilize the pelvis in the ED may be realized with a simple sheet and towel clamps. Wrapping the pelvis tightly with a sheet and securing this with towel clamps has been shown to be effective in reducing an open-book pelvic injury (Fig. 55-12),[79,80] thereby reducing the potential volume in the pelvis for blood loss. A technique of taping the lower extremities in internal rotation has also been described as a means of achieving a closed pelvic reduction in the presence of symphyseal diastasis.[81]

Other commercial circumferential compression devices have been developed to facilitate noninvasive stabilization of the pelvis. Generally speaking, in cadaveric studies, it appears these devices are effective at reducing the open-book pelvis.[82,83] One retrospective comparison of patients with exsanguinating pelvic hemorrhage found that patients treated with a noninvasive splinting device had substantially lower transfusion requirements than those who had formal external fixation of the pelvis performed emergently (4.9 units vs. 17.1 units in the first 24 hours, $P = .008$). However, there was no statistically significant change in mortality between the two groups (26% vs. 37%, $P = .11$).[84]

Patients who have sustained AP open-book injuries are likely to derive the most benefit from tight wrapping of the pelvis. This maneuver may not be desirable when lateral compression forces have already internally rotated the hemipelvis because indiscriminately forceful wrapping may, in fact, worsen the degree of displacement. Here, some judgment is required to discern whether one is wrapping the pelvis to *reduce* the volume of an externally rotated pelvis versus *splinting* a pelvis to minimize pelvic movement that may occur, especially when the patient is transferred.

Invasive Fixation. External fixation of the pelvis is performed by orthopedic surgeons. The goal of fixation is to prevent movement at pelvic fracture sites and attendant bleeding.[15] Although the acute application of an external fixator has not been proved to

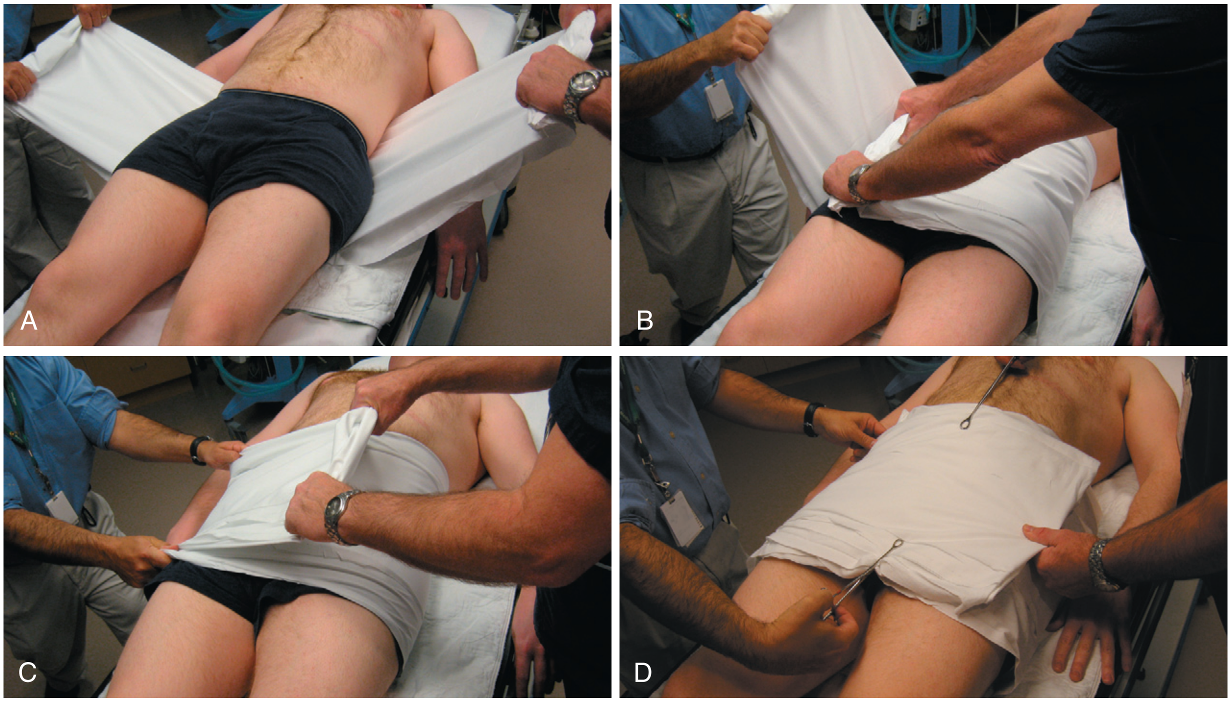


Figure 55-12. **A,** Circumferential pelvic antishock sheeting is applied in this example patient. The patient's clothing should be removed before application. The sheet is positioned beneath the patient's pelvis smoothly. The ends of the sheet are crossed in an overlapping manner anteriorly **(B)** and are pulled taut **(C)**. Clamps secure the smooth and snug sheet **(D)**.

www.ketabpezeshki.com 66485457-66963820

decrease morbidity or mortality in a prospective study, there is evidence that this technique improves clinical outcome by limiting hemorrhage and restoring mechanical integrity.[66] Application of the fixator is time-consuming; therefore it should not delay more definitive treatment of pelvic bleeding by angiography or the treatment of other sources of severe blood loss. The timing of the application of the external fixator requires coordination among the trauma surgeon, orthopedic surgeon, and interventional radiologist. Early surgical consultation is vital to efficient planning and prioritization of surgical management.

Many stable AP and lateral compression fractures can be treated definitively by the external fixator.[15] When the pelvis is vertically displaced, traction combined with external fixation is necessary to reduce the pelvis pending definitive open surgical repair.[15] Most fixators can be constructed to allow convenient surgical access to the abdomen and groin.

The pelvic C-clamp is one type of external fixation device that can theoretically be applied rapidly by the orthopedic surgeon in the ED to externally stabilize the posterior pelvic arch on an emergency basis.[85] It is likely more effective in reducing AP than vertical injuries.[86] Institutional practices may influence the use of C-clamp over standard external fixation. Although the C-clamp may aid in stabilizing blood loss, its application does not obviate the need for angiography.[87] It is unclear whether the C-clamp offers any additional advantage over wrapping the pelvis with a sheet during initial resuscitation efforts.

The specific mode of invasive fixation will be institution specific and will rely heavily on the experience of the treating orthopedic surgeons.

Angiography and Embolization

Arteriography and venography have been investigated for managing hemorrhage associated with pelvic fractures. Although pelvic bleeding is commonly venous in origin, venography is not useful in managing these cases; the extensive anastomoses and valveless collateral flow make embolization ineffective. In contrast, arteriography is excellent at both diagnosing and managing arterial bleeding.

Arteriography is performed with the contrast material injected through the femoral artery on the less-injured side or via the upper extremity. The examination starts above the level of the aortic bifurcation and proceeds to selective branches of the internal iliac (hypogastric) artery. Transcatheter embolization with thrombogenic coils, foam, or spherules is used to stop the hemorrhage from the branches of the internal iliac artery.

Embolization is highly effective for controlling arterial bleeding. One case series of 556 patients undergoing pelvic angiography reported that repeat angiography was necessary in only 7.5% of patients as a result of ongoing bleeding. These authors found that hypotension, a need for more than 2 units of packed red cells, symphysis widening, and more than two arteries embolized at the first angiogram predicted the need for repeat angiography.[88]

Angiography is indicated when hypovolemia persists in a patient with a major pelvic fracture despite control of hemorrhage from other sources. Although it is impossible to determine whether bleeding is venous or arterial in origin until angiography is performed, one study found that inadequate response to initial resuscitation (defined as failure to maintain a systolic blood pressure above 90 mm Hg after the administration of 2 or more units of packed red cells or less) and the presence of contrast extravasation on admission CT were both indicative of active arterial bleeding.[77] Although the presence of contrast extravasation on CT is an indication for angiography, the absence of contrast blush on CT is not sufficient to rule out serious pelvic bleeding.[77] SI joint disruption, persistent systolic blood pressure below 100 mm Hg, and female gender were shown to be predictors of need for embolization at the time of angiography.[89]

The timing of angiography is individualized for each patient depending on priorities for treatment of concomitant injuries. Posterior arch disruptions are associated with the most severe hemorrhage; angiography should be considered at an early stage for these patients. Whether patients undergo angiography immediately from the ED or angiography immediately precedes laparotomy, it is important to be mindful of the logistical delay that often occurs in mobilizing the angiography team, so this intervention should be anticipated as early as possible. The transfer of the patient to the angiography suite also requires orchestrating the necessary personnel and equipment to care for the critically injured patient there. The feasibility of use of mobile angiography equipment in the ED for acutely controlling pelvic hemorrhage has been reported; this removes the usual logistic delays while ensuring a greater degree of safety in monitoring patients during the procedure.[90]

Hemodynamically Unstable Patients with Pelvic and Intra-abdominal Hemorrhage

Patients who hemorrhage from both the pelvis and the abdomen have mortality rates above 40% and deserve special consideration. These patients may be too unstable to undergo CT imaging. Prioritizing the need for laparotomy versus angiography in these patients may be challenging when the need for laparotomy is based on the detection of intra-abdominal fluid by FAST or DPL. Unnecessary laparotomy performed in patients who are hemodynamically unstable with pelvic fracture has been shown to contribute to high mortality rates.[91] Therefore in these cases, it is crucial that the efforts of the general surgeon, orthopedic surgeon, and interventional radiologist be coordinated to optimize the timing of necessary procedures.

Gross aspirates of blood on DPL are strong indicators for prompt laparotomy. Given the high rates of false-negative FAST examinations in pelvic trauma, caution should be used in making difficult triage decisions regarding laparotomy versus angiography on the basis of FAST findings in this setting. However, when the FAST examination does reveal hemoperitoneum, it is generally accepted that laparotomy be pursued first.[92] When concurrent pelvic bleeding is highly suggested (e.g., severe open-book pelvis), it is advisable that angiography promptly follow laparotomy.

At the time of laparotomy, it may be appropriate for the orthopedic surgeon to place either an external fixator or a pelvic C-clamp. Packing of the pelvis at the time of laparotomy has been reported as a means to obtain hemostasis in pelvic hemorrhage.[93,94] Although there is limited evidence from clinical studies to support packing, it has become a mainstay of treating pelvic hemorrhage at some centers, especially in Europe. Part of the rationale for use of packing rather than angiography is the fact that pelvic bleeding is commonly venous in origin, for which arteriography is useless. In contrast, packing may aid in tamponading bleeding from the posterior venous plexus. It is recommended that the pelvis be stabilized before packing to provide solid structural support against which packing may be performed.[94] Intraperitoneal, retroperitoneal, and extraperitoneal techniques of packing have been described, with authors reporting retroperitoneal and extraperitoneal approaches being rapidly done even in the ED setting.[94,95] A systematic review of pelvic packing concluded that for patients with hemodynamic instability caused by pelvic hemorrhage, packing could be used as a temporizing measure for control of bleeding until more selective treatments could be performed.[96]

When FAST or DPL does not reveal hemoperitoneum in the presence of severe pelvic fracture, emergent angiography should

www.ketabpezeshki.com 66485457-66963820

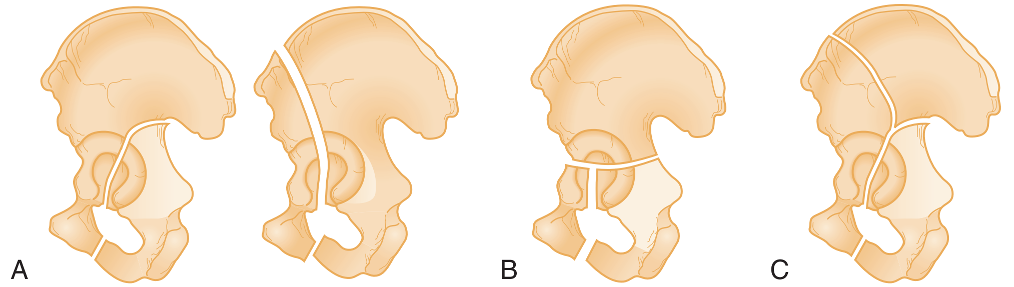


Figure 55-13. Universal classification of acetabular fractures. **A,** Type A: Fractures of one column or one wall, for example, posterior column *(left)* and anterior *(right)* column. **B,** Transverse or T-type fractures involving both columns but by definition leaving a fragment of articular cartilage attached to the proximal ilium and, thus, to the axial skeleton. **C,** Type C: Two-column fracture of the acetabulum. By definition, no portion of the articular surface remains attached to the axial skeleton because fracture of both columns of the ilium is proximal to the joint. (From Tile M: Fractures of the Pelvis and Acetabulum, 3rd ed. Philadelphia, Lippincott, Williams & Wilkins, 2003.)

Box 55-5 Classification of Acetabular Fractures

Type A
Fractures of one column of the acetabulum (anterior or posterior column).

Type B
Transverse (T-type) fractures through both anterior and posterior columns; portion of acetabulum remains attached to proximal ilium.

Type C
Transverse (T-type) fractures through both anterior and posterior columns; no portion of acetabulum remains attached to axial skeleton.

From Tile M: Fractures of the Pelvis and Acetabulum, 3rd ed. Philadelphia, Lippincott, Williams & Wilkins, 2003.

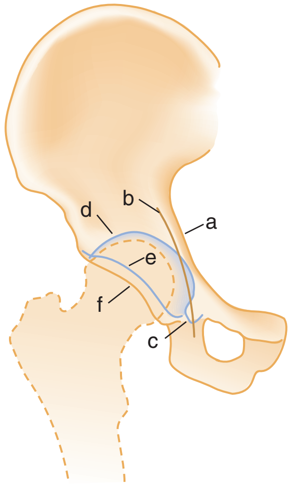


Figure 55-14. Schematic drawing of radiographic anatomy of acetabulum in anteroposterior pelvis projection. *(a)* Arcuate (iliopubic) line. *(b)* Ilioischial line. *(c)* Radiographic U, or teardrop, caused by superimposition of parasagittal surface of ilium onto anteroinferior portion of acetabulum. *(d)* Acetabular roof. *(e)* Anterior lip of acetabulum. *(f)* Posterior lip of acetabulum. (Redrawn from Rogers LF, Novy SB, Harris NF: Occult central fractures of the acetabulum. AJR Am J Roentgenol 124:98, 1975.)

be arranged. If pelvic bleeding continues despite angiography (i.e., secondary to venous bleeding), open stabilization and packing should be considered as the next step.

For any trauma center, planning for challenging clinical situations by emergency physicians, trauma surgeons, and angiographers and the creation of protocols for care may be useful in optimizing a timely and coordinated response.[78,97,98]

Acetabular Fractures

Many pelvic fractures in adults involve the acetabulum. Pain and inability to bear weight are the hallmark complaints associated with acetabular fractures. On clinical examination, tenderness with percussion of the heel of the foot or medial pressure on the greater trochanter is an important clue to the presence of an acetabular fracture. It is important to note the presence of neurologic deficit, as the sciatic nerve is commonly injured. A common mechanism of acetabular injury is the so-called "dashboard" injury whereby the knee of a person seated in the front seat of a car strikes the dashboard in sudden deceleration, driving the head of the femur into the acetabulum; as a result, concurrent fracture or dislocation of the patella (or both) are common.

Acetabular fractures are broadly classified into three types[15] (Fig. 55-13 and Box 55-5).

Type A fractures may be subdivided into anterior and posterior column injuries. Posterior wall fractures are the most common acetabular injuries and are generally caused by a forceful impact to a flexed knee (e.g., dashboard injury)—the force is transmitted up through the femur through the posterior acetabulum. An associated posterior dislocation of the hip is frequently associated with posterior rim fracture of the acetabulum and may result in an unstable hip joint and recurrent dislocation. Posterior hip dislocation is commonly associated with secondary sciatic nerve injury. The anterior column of the acetabulum is commonly injured when a superior ramus fracture extends into the low anterior column.

Type B fractures involve both anterior and posterior columns, but a portion of the acetabulum remains attached to the ilium. When the columns are split, this is referred to as a *T fracture.* The T fracture is associated with the worst prognosis, owing to the difficulty in obtaining open anatomic reduction.

Type C fractures are readily apparent on plain radiographs as a result of disruption of the ilium.

Assessment of the AP pelvic radiograph should focus on the disruption of the ilioischial and iliopectineal lines as well as the anterior and posterior lips of the acetabulum (Fig. 55-14). Ramus fractures should be evaluated for possible extension into the acetabulum. Oblique views of the acetabulum (Judet views) can aid in visualizing the anterior and posterior columns. CT is, without question, the imaging test of choice for visualizing acetabular fractures and planning for possible surgical repair. It is important to note that because fracture of the acetabulum often occurs with a high-energy mechanism, even patients with isolated acetabular fractures may have significant hemorrhage necessitating blood

www.ketabpezeshki.com 66485457-66963820

transfusion.[99] All patients with acetabular fracture require orthopedic referral in the emergency department.

Coccyx Fractures

Fractures of the coccyx occur frequently after a fall in the sitting position or a kick. Fracture and injury also may occur during parturition. Physical examination reveals local tenderness to palpation in the gluteal crease, with pain and sometimes abnormal motion of the coccyx during palpation on DRE. Normally, the tip of the coccyx moves 30 degrees anteriorly and 1 cm laterally.[100] Displacement also is diagnosed on rectal examination, but attempts at reduction are not recommended.

Radiographic confirmation of a coccygeal fracture is not always necessary. Displaced fractures often are seen on the lateral view, but the diagnosis is evident on rectal examination. Undisplaced fractures may be difficult to show radiographically. The physician must decide whether the knowledge gleaned from radiographic studies would alter the therapy to a degree that warrants radiation exposure to the pelvis, especially considering that most of these fractures occur in women.

Treatment of coccygeal fracture consists of bed rest, stool softeners, analgesia, and sitz baths to relieve muscle spasm. As activity is increased, maneuvers that may minimize discomfort include use of an inflatable rubber donut cushion, alternate sitting on the side of each buttock, slouching to displace body weight more proximally, and sitting on a hard chair rather than a soft one (sinking into a soft chair may distribute weight onto the coccyx).[100] Because of muscle action on the fragment, healing is slow and patients should be cautioned that discomfort may be prolonged. In the case of persistent severe disability, an orthopedic consultation is indicated for considerations of local steroid injection or possible coccygectomy.[101] Other causes of coccydynia (besides fracture) include trauma during parturition; faulty posture; midline disk herniations (caused by nonsegmental referral of pain from irritation of the dura); lumbar facet arthropathy; compression of the first, fourth, and fifth sacral roots; neuralgia from sacral plexopathy or sacrococcygeal neuropathy; infections; and local tumors.[100]

KEY CONCEPTS

- The most serious pelvic ring injuries caused by high-energy impact include (1) AP compression fractures (open book), (2) vertical shear fractures, and (3) any fractures that involve significant displacement. These are associated with major blood loss and transfusion requirements.
- Pelvic injury is a marker for serious injury of other organ systems. The vast majority of patients who die with pelvic fracture are those who have sustained multiple trauma.
- Careful examination of the skin in the perineum and buttocks and digital rectal and vaginal examinations are necessary to diagnose open fractures because these are associated with the highest mortality rates.
- CT is the imaging test of choice to diagnose pelvic fracture and concurrent intra-abdominal injuries for patients stable enough to undergo CT. CT aids in establishing surgical priorities and planning of definitive orthopedic care. The presence of contrast extravasation with modern CT imaging is a subject of ongoing research with respect to localizing pelvic bleeding and distinguishing between arterial and venous sources.
- In the hemodynamically unstable patient who cannot undergo CT imaging, the AP radiograph usually reveals serious pelvic fractures that result in major pelvic bleeding. Inlet and outlet radiographs improve the sensitivity and specificity of pelvic plain radiography.
- The combination of posterior arch fracture plus hypotension is associated with a mortality rate of approximately 50%. Early fluid resuscitation with blood products is recommended for patients suspected to have active pelvic bleeding.
- Trauma hospitals should have institutional guidelines and mechanisms to facilitate early decisions regarding the treatment for pelvic hemorrhage that may include angiography and embolization, pelvic packing, invasive fixation, or any combination of these.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Balogh Z, et al: The epidemiology of pelvic ring fractures: A population-based study. *J Trauma* 2007; 63:1066.
2. Demetriades D, et al: Pelvic fractures: Epidemiology and predictors of associated abdominal injuries and outcomes. *J Am Coll Surg* 2002; 195:1.
3. O'Sullivan RE, White TO, Keating JF: Major pelvic fractures: Identification of patients at high risk. *J Bone Joint Surg Br* 2005; 87:530.
4. Starr AJ, et al: Pelvic ring disruptions: Prediction of associated injuries, transfusion requirement, pelvic arteriography, complications, and mortality. *J Orthop Trauma* 2002; 16:553.
5. Smith W, et al: Early predictors of mortality in hemodynamically unstable pelvis fractures. *J Orthop Trauma* 2007; 21:31.
6. Giannoudis PV, et al: Prevalence of pelvic fractures, associated injuries, and mortality: The United Kingdom perspective. *J Trauma* 2007; 63:875-883.
7. Sathy AK, Starr AJ, Smith WR: The effect of pelvic fracture on mortality after trauma: An analysis of 63,000 trauma patients. *J Bone Joint Surg Am* 2009; 91:2803-2810.
8. Schulman JE, et al: Pelvic ring fractures are an independent risk factor for death after blunt trauma. *J Trauma* 2010; 68:930-934.
9. Henry SM, Pollak AN, Jones AL, Boswell S, Scalea TM: Pelvic fracture in geriatric patients: A distinct clinical entity. *J Trauma* 2002; 53:15.
10. Hauschild O, et al: Mortality in patients with pelvic fractures: Results from the German pelvic injury register. *J Trauma* 2008; 64:449-455.
11. Eastridge BJ, Burgess AR: Pedestrian pelvic fractures: 5-year experience of a major urban trauma center. *J Trauma* 1997; 42:695.
12. Rowe SA, Sochor MS, Staples KS, Wahl WL, Wang SC: Pelvic ring fractures: Implications of vehicle design, crash type, and occupant characteristics. *Surgery* 2004; 136:842.
13. Stein DM, et al: Risk factors associated with pelvic fractures sustained in motor vehicle collisions involving newer vehicles. *J Trauma* 2006; 61:21.
14. Inaba K, Sharkey PW, Stephen DJ, Redelmeier DA, Brenneman FD: The increasing incidence of severe pelvic injury in motor vehicle collisions. *Injury* 2004; 35:759.
15. Tile M: *Fractures of the Pelvis and Acetabulum*, 3rd ed. Philadelphia: Lippincott, Williams & Wilkins; 2003.
16. Burgess AR, et al: Pelvic ring disruptions: Effective classification system and treatment protocols. *J Trauma* 1990; 30:848.
17. Furey AJ, et al: Classification of pelvic fractures: Analysis of inter- and intraobserver variability using the Young-Burgess and Tile classification systems. *Orthopedics* 2009; 32:401.
18. Koo H, et al: Interobserver reliability of the Young-Burgess and Tile classification systems for fractures of the pelvic ring. *J Orthop Trauma* 2008; 22:379-384.
19. Dalal SA, et al: Pelvic fracture in multiple trauma: Classification by mechanism is key to pattern of organ injury, resuscitative requirements, and outcome. *J Trauma* 1989; 29:781; discussion 1000.
20. Manson T, et al: Young-Burgess classification of pelvic ring fractures: Does it predict mortality, transfusion requirements, and non-orthopaedic injuries? *J Orthop Trauma* 2010; 24:603-609.
21. Gertzbein SD, Chenoweth DR: Occult injuries of the pelvic ring. *Clin Orthop Relat Res* 1977; 128:202.
22. Cosker TD, Ghandour A, Gupta SK, Tayton KJ: Pelvic ramus fractures in the elderly: 50 patients studied with MRI. *Acta Orthop* 2005; 76:513.
23. Abrassart S, Stern R, Peter R: Morbidity associated with isolated iliac wing fractures. *J Trauma* 2009; 66:200-203.
24. Duchesne JC, et al: Open-book pelvic fractures with perineal open wounds: A significant morbid combination. *Am Surg* 2009; 75:1227-1233.
25. Gibbons KJ, Soloniuk DS, Razazk N: Neurologic injury and patterns of sacral fractures. *J Neurosurg* 1990; 72:889.
26. Rogers LF, Bradd FJ, Kennedy W: *Radiology of Skeletal Trauma*. New York: Churchill Livingstone; 1992.
27. Mattila VM, Niva M, Kiuru M, Pihlajamäki H: Risk factors for bone stress injuries: A follow-up study of 102,515 person-years. *Med Sci Sports Exerc* 2007; 39:1061.
28. Kiuru MJ, Pihlajamaki HK, Hietanen HJ, Ahovuo JA: MR imaging, bone scintigraphy, and radiography in bone stress injuries of the pelvis and the lower extremity. *Acta Radiol* 2002; 43:207.
29. Denis F, Davis S, Comfort T: Sacral fractures: An important problem. *Clin Orthop Relat Res* 1988; 227:67.
30. Grotz MR, et al: Open pelvic fractures: Epidemiology, current concepts of management and outcome. *Injury* 2005; 36:1.
31. Dente CJ, et al: The outcome of open pelvic fractures in the modern era. *Am J Surg* 2005; 190:830.
32. Lunsjo K, Abu-Zidan FM: Does colostomy prevent infection in open blunt pelvic fractures? A systematic review. *J Trauma* 2006; 60:1145.
33. Duncan AO, et al: Management of transpelvic gunshot wounds. *J Trauma* 1989; 29:1335.
34. Malangoni MA, Miller FB, Cryer HM, Mullins RJ, Richardson JD: The management of penetrating pelvic trauma. *Am Surg* 1990; 56:61.
35. O'brien DP, et al: Pelvic fracture in the elderly is associated with increased mortality. *Surgery* 2002; 132:710.
36. Dechert TA, Duane TM, Frykberg BP: Elderly patients with pelvic fracture: Interventions and outcomes. *Am Surg* 2009; 75:291-295.
37. McCormick JP, Morgan SJ, Smith WR: Clinical effectiveness of the physical examination in diagnosis of posterior pelvic ring injuries. *J Orthop Trauma* 2003; 17:257.
38. Metze M, Tiemann AH, Josten C: Male sexual dysfunction after pelvic fracture. *J Trauma* 2007; 63:394-401.
39. Black PC, Miller EA, Porter JR, Wessells H: Urethral and bladder neck injury associated with pelvic fracture in 25 female patients. *J Urol* 2006; 175:2140.
40. Carter CT, Schafer N: Incidence of urethral disruption in females with traumatic pelvic fractures. *Am J Emerg Med* 1993; 11:218.
41. Avey G, Blackmore CC, Wessells H, Wright JL, Talner LB: Radiographic and clinical predictors of bladder rupture in blunt trauma patients with pelvic fracture. *Acad Radiol* 2006; 13:573.
42. Basta AM, Blackmore CC, Wessells H: Predicting urethral injury from pelvic fracture patterns in male patients with blunt trauma. *J Urol* 2007; 177:571-575.
43. Spencer Netto FA, et al: Retrograde urethrocystography impairs computed tomography diagnosis of pelvic arterial hemorrhage in the presence of a lower urologic tract injury. *J Am Coll Surg* 2008; 206:322-327.
44. Reference deleted in proofs.
45. Schmal H, Hauschild O, Culemann U: Identification of risk factors for neurological deficits in patients with pelvic fractures. *Orthopedics* 2010; 33:8.
46. Copeland CE, et al: Effect of trauma and pelvic fracture on female genitourinary, sexual, and reproductive function. *J Orthop Trauma* 1997; 11:73.
47. Papadopoulos IN, et al: Auditing 655 fatalities with pelvic fractures by autopsy as a basis to evaluate trauma care. *J Am Coll Surg* 2006; 203:30.
48. Lunsjo K, et al: Associated injuries and not fracture instability predict mortality in pelvic fractures: A prospective study of 100 patients. *J Trauma* 2007; 62:687.
49. Gustavo Parreira J, et al: The role of associated injuries on outcome of blunt trauma patients sustaining pelvic fractures. *Injury* 2000; 31:677.
50. Ochsner MG Jr, et al: Associated aortic rupture-pelvic fracture: An alert for orthopedic and general surgeons. *J Trauma* 1992; 33:429.
51. Gonzalez RP, Fried PQ, Bukhalo M: The utility of clinical examination in screening for pelvic fractures in blunt trauma. *J Am Coll Surg* 2002; 194:121.
52. Salvino CK, et al: Routine pelvic x-ray studies in awake blunt trauma patients: A sensible policy? *J Trauma* 1992; 33:413.
53. Koury HI, Peschiera JL, Welling RE: Selective use of pelvic roentgenograms in blunt trauma patients. *J Trauma* 1993; 34:236.
54. Duane TM, Dechert T, Wolfe LG: Clinical examination is superior to plain films to diagnose pelvic fractures compared to CT. *Am Surg* 2008; 74:476-479.
55. Kessel B, et al: Is routine portable pelvic x-ray in stable multiple trauma patients always justified in a high technology era? *Injury* 2007; 38:559.
56. Guillamondegui OD, et al: Pelvic radiography in blunt trauma resuscitation: A diminishing role. *J Trauma* 2002; 53:1043.
57. Lunsjo K, Tadros AM, Hauggaard A: Acute plain anterioposterior radiograph of the pelvis is not useful in detecting fractures of iliac wing and os sacrum: A prospective study of 73 patients using CT as gold standard. *Australas Radiol* 2007; 51:147-149.
58. Resnik CS, Stackhouse DJ, Shanmuganathan K, Young JW: Diagnosis of pelvic fractures in patients with acute pelvic trauma: Efficacy of plain radiographs. *AJR Am J Roentgenol* 1992; 158:109.
59. Dormagen JB, Tötterman A, Røise O, Sandvik L, Kløw NE: Efficacy of plain radiography and computer tomography in localizing the site of pelvic arterial bleeding in trauma patients. *Acta Radiol* 2010; 51:107-116.
60. Fu CY, Wu SC, Chen RJ: Evaluation of pelvic fracture stability and the need for angioembolization: Pelvic instabilities on plain film have an increased probability of requiring angioembolization. *Am J Emerg Med* 2009; 27:792-796.

www.ketabpezeshki.com 66485457-66963820

61. Cryer HM, Miller FB, Evers BM, Rouben LR, Seligson DL: Pelvic fracture classification: Correlation with hemorrhage. *J Trauma* 1988; 28:973.
62. Blackmore CC, et al: Predicting major hemorrhage in patients with pelvic fracture. *J Trauma* 2006; 61:346.
63. Eastridge BJ, Starr A, Minei JP, O'Keefe GE, Scalea TM: The importance of fracture pattern in guiding therapeutic decision-making in patients with hemorrhagic shock and pelvic ring disruptions. *J Trauma* 2002; 53:446; discussion 450.
64. Deunk J, Dekker HM, Brink M: The value of indicated computed tomography scan of the chest and abdomen in addition to the conventional radiologic work-up for blunt trauma patients. *J Trauma* 2007; 63:757-763.
65. Deunk J, Brink M, Dekker HM: Routine versus selective computed tomography of the abdomen, pelvis, and lumbar spine in blunt trauma: A prospective evaluation. *J Trauma* 2009; 66:1108-1117.
66. Dyer GS, Vrahas MS: Review of the pathophysiology and acute management of haemorrhage in pelvic fracture. *Injury* 2006; 37:602.
67. Mendez C, Gubler KD, Maier RV: Diagnostic accuracy of peritoneal lavage in patients with pelvic fractures. *Arch Surg* 1994; 129:477.
68. Friese RS, Malekzadeh S, Shafi S, Gentilello LM, Starr A: Abdominal ultrasound is an unreliable modality for the detection of hemoperitoneum in patients with pelvic fracture. *J Trauma* 2007; 63:97.
69. Tayal VS, et al: Accuracy of trauma ultrasound in major pelvic injury. *J Trauma* 2006; 61:1453.
70. Hoffman L, Pierce D, Puumala S: Clinical predictors of injuries not identified by focused abdominal sonogram for trauma (FAST) examinations. *J Emerg Med* 2009; 36:271-279.
71. Brasel KJ, Pham K, Yang H, Christensen R, Weigelt JA: Significance of contrast extravasation in patients with pelvic fracture. *J Trauma* 2007; 62:1149.
72. Hagiwara A, et al: Predictors of death in patients with life-threatening pelvic hemorrhage after successful transcatheter arterial embolization. *J Trauma* 2003; 55:696.
73. Uyeda J, Anderson SW, Kertesz J: Pelvic CT angiography: Application to blunt trauma using 64MDCT. *Emerg Radiol* 2010; 17:131-137.
74. Uyeda JW, Anderson SW, Sakai O: CT angiography in trauma. *Radiol Clin North Am* 2010; 48:423-438, ix-x.
75. Stern SA: Low-volume fluid resuscitation for presumed hemorrhagic shock: Helpful or harmful? *Curr Opin Crit Care* 2001; 7:422.
76. Revell M, Greaves I, Porter K: Endpoints for fluid resuscitation in hemorrhagic shock. *J Trauma* 2003; 54(5 Suppl):S63.
76a. Bickell WH, Wall MJ, Pepe PE: Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med* 1994; 331:1105-1109.
77. Miller PR, Moore PS, Mansell E, Meredith JW, Chang MC: External fixation or arteriogram in bleeding pelvic fracture: Initial therapy guided by markers of arterial hemorrhage. *J Trauma* 2003; 54:437.
78. Biffl WL, et al: Evolution of a multidisciplinary clinical pathway for the management of unstable patients with pelvic fractures. *Ann Surg* 2001; 233:843.
79. Routt ML Jr, Falicov A, Woodhouse E, Schildhauer TA: Circumferential pelvic antishock sheeting: A temporary resuscitation aid. *J Orthop Trauma* 2006; 20(1 Suppl):S3.
80. Nunn T, Cosker TD, Bose D, Pallister I: Immediate application of improvised pelvic binder as first step in extended resuscitation from life-threatening hypovolaemic shock in conscious patients with unstable pelvic injuries. *Injury* 2007; 38:125.
81. Gardner MJ, Parada S, Chip Routt ML Jr: Internal rotation and taping of the lower extremities for closed pelvic reduction. *J Orthop Trauma* 2009; 23:361-364.
82. Knops SP, Schep NW, Spoor CW: Comparison of three different pelvic circumferential compression devices: A biomechanical cadaver study. *J Bone Joint Surg Am* 2011; 93:230-240.
83. DeAngelis NA, Wixted JJ, Drew J: Use of the trauma pelvic orthotic device (T-POD) for provisional stabilisation of anterior-posterior compression type pelvic fractures: A cadaveric study. *Injury* 2008; 39:903-906.
84. Croce MA, Magnotti LJ, Savage SA, Wood GW 2nd, Fabian TC: Emergent pelvic fixation in patients with exsanguinating pelvic fractures. *J Am Coll Surg* 2007; 204:935.
85. Archdeacon MT, Hiratzka J: The trochanteric C-clamp for provisional pelvic stability. *J Orthop Trauma* 2006; 20:47.
86. Archdeacon MT, Safian C, Le TT: A cadaver study of the trochanteric pelvic clamp for pelvic reduction. *J Orthop Trauma* 2007; 21:38.
87. Sadri H, Nguyen-Tang T, Stern R, Hoffmeyer P, Peter R: Control of severe hemorrhage using C-clamp and arterial embolization in hemodynamically unstable patients with pelvic ring disruption. *Arch Orthop Trauma Surg* 2005; 125:443.
88. Gourlay D, Hoffer E, Routt M, Bulger E: Pelvic angiography for recurrent traumatic pelvic arterial hemorrhage. *J Trauma* 2005; 59:1168; discussion 1173.
89. Salim A, Teixeira PG, DuBose J: Predictors of positive angiography in pelvic fractures: A prospective study. *J Am Coll Surg* 2008; 207:656-662.
90. Morozumi J, Homma H, Ohta S: Impact of mobile angiography in the emergency department for controlling pelvic fracture hemorrhage with hemodynamic instability. *J Trauma* 2010; 68:90-95.
91. Verbeek D, Sugrue M, Balogh Z: Acute management of hemodynamically unstable pelvic trauma patients: Time for a change? Multicenter review of recent practice. *World J Surg* 2008; 32:1874-1882.
92. Heetveld MJ, Harris I, Schlaphoff G, Sugrue M: Guidelines for the management of haemodynamically unstable pelvic fracture patients. *ANZ J Surg* 2004; 74:520.
93. Cothren CC, et al: Preperitonal pelvic packing for hemodynamically unstable pelvic fractures: A paradigm shift. *J Trauma* 2007; 62:834; discussion 839.
94. Tötterman A, Madsen JE, Skaga NO, Røise O: Extraperitoneal pelvic packing: A salvage procedure to control massive traumatic pelvic hemorrhage. *J Trauma* 2007; 62:843.
95. Suzuki T, Smith WR, Moore EE: Pelvic packing or angiography: Competitive or complementary? *Injury* 2009; 40:343-353.
96. Papakostidis C, Giannoudis PV: Pelvic ring injuries with haemodynamic instability: Efficacy of pelvic packing, a systematic review. *Injury* 2009; 40(Suppl 4):S53-S61.
97. Jeske HC, Larndorfer R, Krappinger D: Management of hemorrhage in severe pelvic injuries. *J Trauma* 2010; 68:415-420.
98. Davis JW, Moore FA, McIntyre RC Jr: Western trauma association critical decisions in trauma: Management of pelvic fracture with hemodynamic instability. *J Trauma* 2008; 65:1012-1015.
99. Magnussen RA, Tressler MA: Predicting blood loss in isolated pelvic and acetabular high-energy trauma. *J Orthop Trauma* 2007; 21:603-607.
100. Traycoff RB, Crayton H, Dodson R: Sacrococcygeal pain syndromes: Diagnosis and treatment. *Orthopedics* 1989; 12:1373.
101. Maigne JY, Lagauche D, Doursounian L: Instability of the coccyx in coccydynia. *J Bone Joint Surg Br* 2000; 82:1038.

www.ketabpezeshki.com 66485457-66963820

Chapter 56

Femur and Hip

Brittany L. Murray

PERSPECTIVE

Background

Ancient Egyptian and Greek drawings depict persons with hip deformities ambulating with assistive crutches. The first available written description of a hip fracture was by the 16th-century French surgeon Ambroise Paré.[1] In 1850, von Langenbeck was the first to attempt repair of a hip fracture with a nail for internal fixation. Later, Davis used ordinary wood screws in an attempt to aid the healing of femoral neck fractures.[2] With the advent of radiography in the 19th century, the types of fractures and dislocations became easily identifiable, thus allowing discussion and investigation of management strategies, classification systems, and prognosis.

Epidemiology

Both age and gender are important predisposing factors for specific injury patterns and pathologic conditions found in the hip, femur, and thigh.

Approximately 10 million adults in the United States have osteoporosis, and an additional 33.6 million have low bone density of the hip, both of which predispose to hip fracture.[3] The annual incidence of hip fracture continues to grow as our population ages. During the late 1990s, approximately 250,000 patients a year sought treatment in emergency departments (EDs) after sustaining hip fractures.[4] In 2005 alone, this number exceeded 290,600 patients.[5] It is estimated that this number will surpass half a million patients a year by 2025.[5] Although hip fractures represent only 14% of all fractures in adults, they account for 72% of medical costs related to fractures.[5] Femoral neck fractures have a female to male ratio of 4 : 1 and typically occur in elderly patients with osteoporosis.[6] There is an increasing incidence of intertrochanteric fractures with advancing age, and women are affected six times more often than men.[3,7] Overall, more than three quarters of all hip fractures occur in postmenopausal women older than 50 years.[3]

Among the elderly segment of society, nontraumatic hip pathology is also very common. Osteoarthritis of the hip can severely limit the affected person's ability to perform activities of daily living.

The elderly are not the only population affected by hip and femur pathology. Perthes' disease—avascular necrosis (AVN) of the femoral head—occurs from 2 to 14 years of age, with a peak age of onset of 5 years, and it is five times more common in boys than in girls.[8] Slipped capital femoral epiphysis (SCFE) peaks at 13.5 years of age among boys and 12 years among girls, in association with the onset of puberty, and is nearly twice as common in boys.[9]

PRINCIPLES OF DISEASE

Anatomy of the Hip and Femur

Skeletal Anatomy

The femoral head is firmly seated in the acetabulum, which is reinforced by labral cartilage. The well-developed capsule, overlying ligaments, and proximal musculature of the lower extremity add strength to the joint (Fig. 56-1). The nearly spherical femoral head articulates with the acetabular cup in a variation of the ball-and-socket joint.

The femur is the longest and strongest bone in the human body and is routinely subjected to substantial forces produced during powerful muscle contraction and weight transmission. In an anatomic position, the two femurs extend obliquely from the pelvis medially to the knee and bring the legs closer to the midline, where they can best support the body. Structurally, the femoral neck serves as an oblique strut between the pelvis (the horizontal beam) and the shaft of the femur (the vertical beam) (Fig. 56-2). The length, angle, and narrow circumference of the femoral neck permit substantial range of motion at the hip, but these same characteristics subject the neck to incredible shearing forces. A fracture results when these forces exceed the strength of the bone. As drawn on an anteroposterior (AP) radiograph, the intertrochanteric line, an oblique line connecting the greater and lesser trochanters, marks the junction of the femoral neck and its shaft.

The bone in the femoral head, neck, and intertrochanteric region is predominantly cancellous, which is less resistant to torsional forces. Distal to the intertrochanteric region, including both the subtrochanteric region and femoral shaft, the bone is cortical, requiring great forces to break. At the distal metaphysis, the femur widens and the cortical bone thins, lessening its resistance to stress.

Musculature

The musculature of the hip and thigh is the largest and most powerful in the human body. The muscles in this region of the body are located within three different compartments, each containing associated nerves and vessels (Table 56-1). The muscles also are grouped according to their primary action at the hip. Knowledge of the major muscle actions offers insight into the injury patterns and deformities commonly seen (Fig. 56-3).

www.ketabpezeshki.com 66485457-66963820

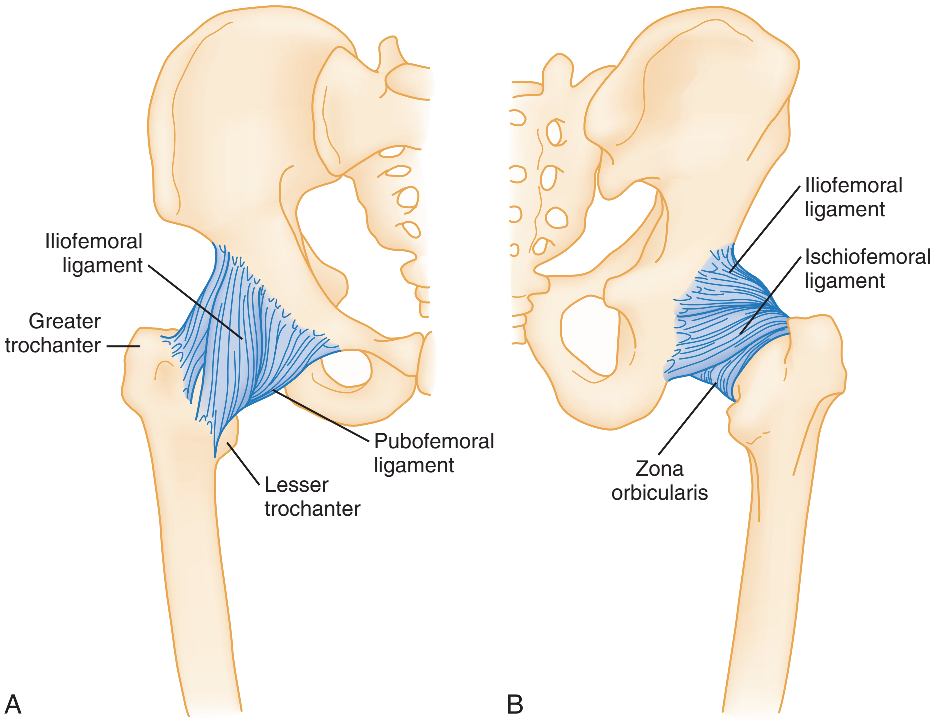


Figure 56-1. The ligaments of the hip combine to form a tough joint capsule, as seen on both anterior **(A)** and posterior **(B)** views.

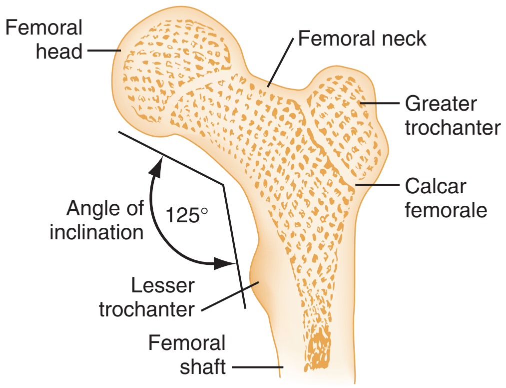


Figure 56-2. Bony architecture of proximal end of the femur.

Vascular Anatomy

Arterial Supply

The arterial supply to the femoral head arises from two main sources (Fig. 56-4). The major source is the ascending cervical arteries as they branch off the extracapsular ring and run along the femoral neck beneath the synovium. Some blood is supplied to the femoral head from the second source, within the marrow spaces—the intraosseous cervical vessels. A third and minor source is the foveal artery, which lies within the ligamentum teres.

As the external iliac artery passes beneath the inguinal ligament, it becomes the common femoral artery.[10] At this point the artery is located midway between the anterior superior iliac spine (ASIS) and the symphysis pubis. Approximately 3 to 4 cm distal to the inguinal ligament, the common femoral artery branches to form the superficial and deep femoral arteries. The larger superficial femoral artery passes along the anteromedial aspect of the thigh and terminates at the junction of the middle third and lower third of the thigh. Here, the superficial femoral artery passes through the adductor hiatus and becomes the popliteal artery. The deep femoral artery runs posterolaterally to the superficial femoral artery, supplies the hamstrings, and terminates in the distal third of the thigh as small branches piercing the belly of the adductor magnus. These perforating branches constitute an additional site of potential injury. The abundant muscle coverage and blood supply of the thigh aid in healing fractures of the femoral shaft.

Venous System

In the proximal two thirds of the thigh, the common and superficial femoral veins lie adjacent to the common and superficial femoral arteries. At the inguinal ligament, the common femoral vein is posterior and medial to the common femoral artery and moves to the lateral position as it passes distally. The deep femoral vein and the greater saphenous vein are the two main tributaries to the common and superficial femoral veins. The deep femoral vein and artery run in parallel as the vein joins the superficial femoral vein just distal to the inguinal ligament. The greater saphenous vein arises in the dorsum of the foot and ascends anterior to the medial malleolus. This vein is relatively superficial as it passes up the medial aspect of the leg to join the common femoral vein distal to the inguinal ligament.[10]

Nerves

The femoral and sciatic nerves are the major nerves within the thigh. The femoral nerve is the largest branch of the lumbar plexus; it passes under the inguinal ligament lateral to the femoral artery and divides into anterior and posterior branches soon after entering the thigh. The sensory divisions of the anterior branch, the intermediate and medial cutaneous nerves, supply sensation to the anteromedial aspect of the thigh. The motor division of the anterior branch innervates the pectineus and sartorius muscles. The posterior femoral branch gives off the saphenous nerve, which supplies sensation to the skin along the medial aspect of the lower

www.ketabpezeshki.com 66485457-66963820

Table 56-1 Structures within Compartments of the Thigh

COMPARTMENT	MUSCLES	NERVES	VESSELS
Anterior	Quadriceps femoris, sartorius, iliacus, psoas, pectineus	Lateral femoral cutaneous	Femoral artery and vein
Medial	Gracilis, adductor longus and magnus, obturator externus	Obturator	Profundus femoris artery, obturator artery and vein
Posterior	Biceps femoris, semitendinosus, semimembranosus, adductor magnus	Sciatic, posterior femoral cutaneous	Profundus femoris artery branches

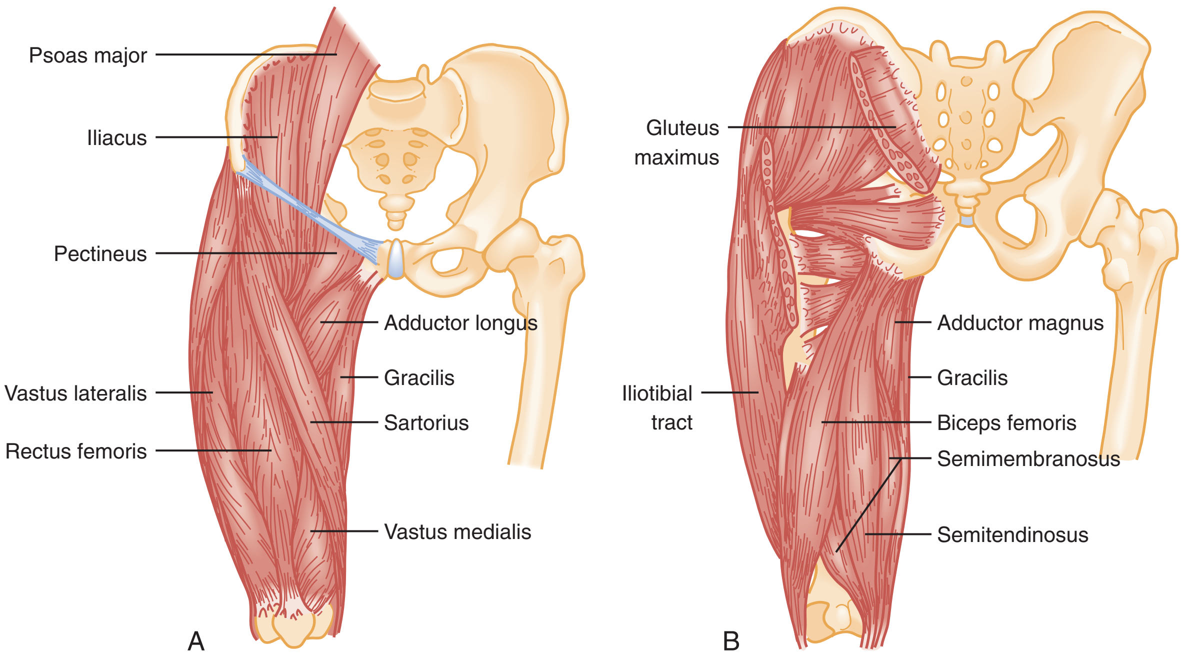


Figure 56-3. Anatomic illustrations of the major muscles acting about the hip and thigh.

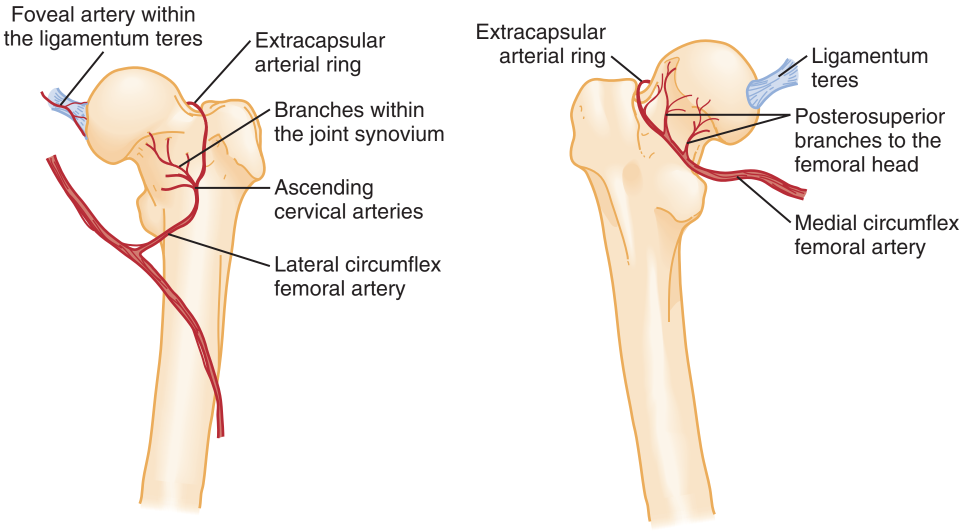


Figure 56-4. The arterial blood supply of the femoral neck and head is provided to varying degrees by three sources: the ascending cervical arteries, the arterial branches within the marrow *(not illustrated),* and the foveal artery within the ligamentum teres.

www.ketabpezeshki.com 66485457-66963820

Figure 56-5. Radiographic evidence of the development of osteoarthritis or degenerative joint disease of the hip is demonstrated with serial radiographs in the same patient over several years. **A,** The symptoms initially are more dramatic than would be expected with the radiographic findings of increased sclerosis along the weight-bearing surface of the superior acetabulum. **B,** The joint space is lost. **C,** Erosion of the head and acetabular surfaces and reactive bony cystic changes are now evident.

part of the leg. The posterior branch also supplies motor function to the muscles of the quadriceps femoris group.[10]

The sciatic nerve is the largest peripheral nerve in the body. It arises from the sacral plexus. The sciatic nerve exits the pelvis through the greater sciatic foramen and travels through the posterior thigh; it extends from the inferior border of the piriformis to the distal third of the thigh. The sciatic nerve gives off articular branches that supply the hip joint. In the thigh, muscular branches innervate the adductor magnus and hamstring muscles. Just proximal to the popliteal fossa, the sciatic nerve divides to form the tibial and common peroneal nerves.[10]

Pathophysiology

Fractures and Trauma of the Femur and Hip

The pathophysiology of specific femur and hip fractures is discussed later in this chapter. The vast majority of hip fractures occur in elderly patients with preexisting bone disease and result from relatively low-energy trauma, usually a ground-level fall. In young healthy individuals, major trauma, such as a motor vehicle collision (MVC) or a fall from a significant height, is responsible for the majority of fractures.

Osteoporosis of the Femur

Osteoporosis is the leading cause of hip fracture. Osteoporosis currently affects more than 10 million people in the United States and is projected to affect approximately 14 million adults older than 50 years by the year 2020. The number of hip fractures attributable to osteoporosis is expected to be 6.3 million by the year 2050, although the incidence in women has been decreasing in recent years, probably because of an increased awareness and more aggressive treatment of osteoporosis.[3,11] Hip fractures can have a devastating impact. One in five patients dies during the first year after a hip fracture, mostly from causes other than the fracture itself; one third require nursing home placement after hospital discharge; and less than one third regain their prefracture level of physical function.[12] The economic impact of these fractures is enormous.

The pathophysiology of osteoporosis is not completely understood, but strong associations with hormonal changes related to aging, genetic predisposition, vitamin D deficiency, lack of physical activity, and smoking have been recognized.[13] Severe osteoporosis and hip fractures are most common in elderly white women; however, a decrease in bone density after age 30 is seen across all demographic groups. Radiography of the head of the femur can quantify the degree of osteoporosis, even in the nonfractured hip. The trabeculae of the femoral head and neck strengthen the bone and support the large mechanical forces produced across the hip joint. As osteoporosis begins and then progresses, these trabeculae disappear. This loss of trabeculae weakens the bone and increases the risk of fracture.

Osteoarthritis of the Hip

As the population ages, a greater percentage of the population will develop chronic pain from degenerative osteoarthritis of the hip. Overall, osteoarthritis ranks fifth in health impact (measured in years lost to disability) in high-income countries and ninth in low- and middle-income countries.[14] Disability often results from persistent pain and limited physical mobility. The progression of osteoarthritis can be demonstrated with serial radiographs of the affected hip (Fig. 56-5); however, radiographic findings do not necessarily correlate with symptoms.[15]

Avascular Necrosis

When a patient has an increasingly painful hip, buttock, thigh, or knee and no history of recent trauma, AVN of the femoral head should be considered. AVN has been referred to as *aseptic necrosis, ischemic necrosis,* and *osteonecrosis.* It is the result of ischemic bone death of the femoral head after compromise of its blood supply (Fig. 56-6). AVN is bilateral in 40 to 80% of patients. It is common in relatively young patients, the mean age at diagnosis being 38 years.[16] Although a specific causative disorder is not identified in 20% of the cases, known atraumatic causes include chronic corticosteroid therapy, chronic alcoholism, hemoglobinopathy (e.g., sickle cell anemia), dysbarism, and chronic pancreatitis.[16,17] AVN also is an emerging complication associated with human immunodeficiency virus (HIV) infection. It is unclear whether the virus itself or the treatments are the pathogenic agents.[17]

Traumatic AVN is a subacute manifestation after hip dislocation or femoral neck fracture. It is a direct result of disruption of the blood supply to the femoral head. It is more common in males and African Americans. The incidence of AVN as a subacute complication is clearly related to both the initial degree of trauma and the amount of time the femoral head remains out of joint. Reduction of the hip within 6 hours after dislocation significantly decreases the incidence of AVN.[18] Multiple studies have shown that there is relationship between the length of time the hip is dislocated and the rates of AVN, with as few as 4.8% of patients

www.ketabpezeshki.com 66485457-66963820

Figure 56-6. Avascular necrosis of the left femoral head. Note the asymmetry of the joint and the collapse of the femoral head.

developing AVN with reduction within 6 hours, and as many as 58.8% developing AVN with reduction after more than 12 hours. For this reason, hip dislocation should be considered an orthopedic emergency. The emergency physician should perform reduction of the hip if there is any delay in orthopedic consultation.

Even with optimal treatment, femoral neck fractures are complicated by AVN in 11 to 19% of cases. For all practical purposes, femoral neck fractures are effectively intra-articular fractures. Acutely, bleeding from the fracture site may cause high intracapsular pressure and a tamponade effect on the femoral head, thereby further impairing the blood supply to it.[19] In addition, if the bone fragments are not impacted, synovial fluid will lyse the blood clot. Such lysis prevents the development of capillary buds and the scaffolding needed for osseous repair. These factors all contribute to make AVN of the femoral head a common complication. Conversely, intertrochanteric and subtrochanteric fractures are located in an area of rich blood supply provided by an extracapsular arterial supply. AVN rarely complicates these fractures.

Treatment of AVN should be directed at reversing the underlying cause. Supportive treatment is the mainstay, with total hip replacement reserved for severe cases.

Myositis Ossificans

Myositis ossificans (heterotrophic ossification) is pathologic bone formation at a site where bone is not normally found. Traumatic myositis ossificans results most commonly from a direct blow to muscle. The thigh and hip muscles are often involved. The incidence of myositis has been reported as up to 17% of patients undergoing medical evaluation of thigh contusions, and the condition is thought to be related to the severity of the injury.[20-22] The incidence of myositis ossificans after hip surgery is approximately 2%, but these lesions are clinically significant in only 10 to 20% of cases.[21] Increased susceptibility to myositis ossificans has been described in persons with hemophilia or other bleeding disorders in conjunction with soft tissue injury.[21]

Bleeding into the muscle after trauma produces a local hematoma with subsequent new bone formation within the hematoma. This inappropriate response may also result from repeated minor trauma. The ossific mass may be palpable and may limit motion, depending on its location.

Radiographically, myositis ossificans appears as irregularly shaped masses of heterogeneous bone in the soft tissues around the joint or along fascial planes (Fig. 56-7). It may be seen as early

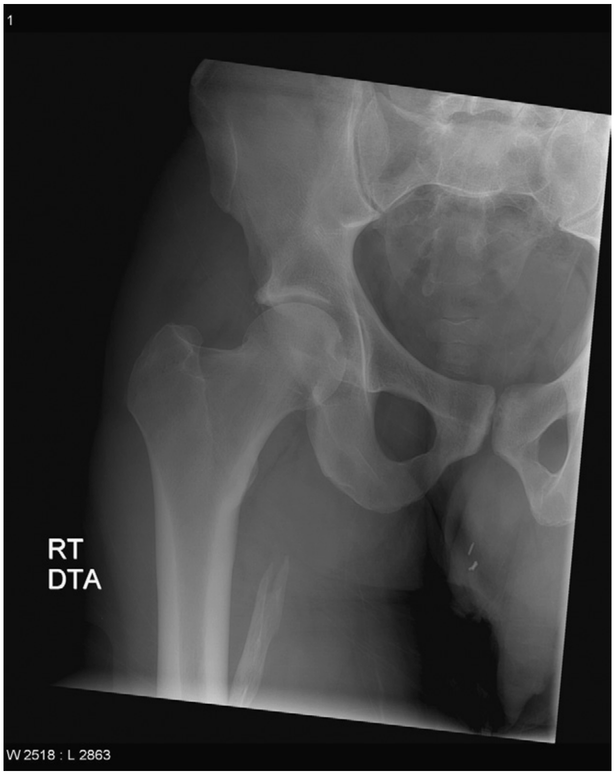


Figure 56-7. Myositis ossificans of the proximal end of the femur. Lesions may be immature or mature such as this one, with well-organized calcifications.

as 10 to 21 days after injury, but radiographic evidence typically lags behind onset of symptoms by weeks.[20] Its appearance may simulate primary bone neoplasm, especially when the periosteum is involved. Osteosarcoma and periosteal osteogenic sarcoma should be considered in the differential diagnosis. Computed tomography (CT) scan can sometimes be helpful in distinguishing between neoplasm and myositis ossificans, as the lesions of myositis ossificans begin to calcify at the periphery and progress toward the center, and those of osteosarcoma begin to calcify at the center first. Orthopedic follow-up should be arranged for these patients.

Initial treatment of contusions is aimed at preventing myositis ossificans by use of the RICE principle of rest, ice, compression, and elevation. Immobilization of the extremity may prevent retraction of ruptured muscle and increasing size of hematoma formation but should be limited to less than 48 hours. Once a stable scar has formed, range of motion within limits of pain should be initiated. If myositis ossificans has already formed, the mainstay of treatment is supportive with rest, slow return to normal activity, and physical therapy. Although indomethacin is commonly used to prevent heterotopic ossification after surgery, it has not been validated for the prevention as well as the treatment of myositis ossificans.[20,21] Its use based on the principle of inhibition of bone formation does not seem to be contraindicated.[20] Operative removal of a mature lesion may be indicated if the lesion is near a joint or is causing permanent impairment or pain.

Calcific Bursitis and Calcifying Peritendinitis

Calcification surrounding tendons and bursae or occurring in the joint capsule is referred to as *calcific bursitis* or *calcifying peritendinitis*. The cause of these lesions is unknown. No relationship has been documented between the radiographic findings and acute

www.ketabpezeshki.com 66485457-66963820

symptoms. Calcific bursitis of the hip is uncommon, but when it does occur, it most frequently affects the trochanteric bursa (Fig. 56-8). Other possible affected areas include gluteal muscles and the hip flexors and adductors. The bursal calcification is seen on radiographs as an amorphous, poorly marginated line that is clearly separate from the cortex of the femur. Treatment should focus on stretching and strengthening of the hip.

Neoplastic Disease in the Hip

The most common neoplastic disease of bone is metastatic, generally from breast, kidney, lung, thyroid, or prostate tumors. Primary bone lesions also occur, with the most common being osteoid osteoma (Fig. 56-9). Bone lesions may be osteoblastic or osteolytic. Patients may come to the ED with significant bone pain or a large bothersome mass, such as a solitary osteochondroma (Fig. 56-10). Neoplasms place the patient at higher risk for pathologic fracture, especially if the lesions are large or lytic or have eroded the cortex.

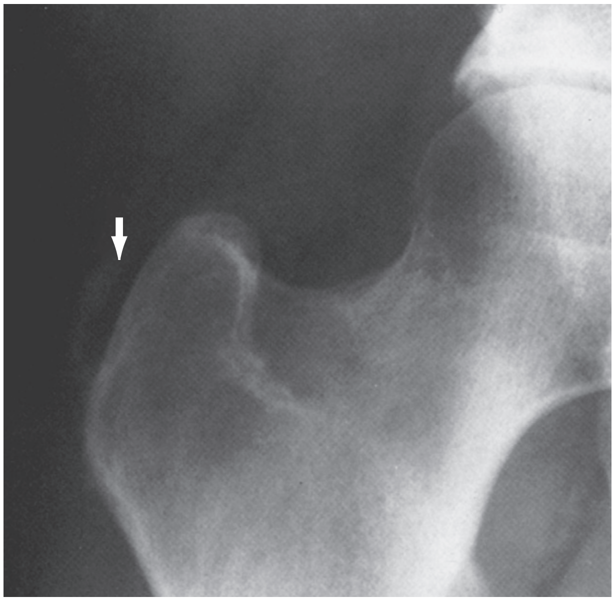


Figure 56-8. Calcific trochanteric bursitis. Faint calcification *(arrow)* in the region of the trochanteric bursa is visible along the lateral cortex of the greater trochanter. (From Harris JH, Harris WH, Novelline RA: The Radiology of Emergency Medicine, 3rd ed. Baltimore, Williams & Wilkins, 1993.)

CLINICAL FEATURES

History

Age and gender are predisposing factors for certain injuries. A detailed description of any antecedent trauma or other precipitating events is often helpful. With trauma, details of the mechanism of injury may aid in predicting injury patterns. With stress fractures, an alteration in physical activity or exercise routine provides a clue to the diagnosis. Systemic illnesses or known metabolic disorders should be noted. Previous cancer, irradiation, and chemotherapy are clues to pathologic fractures. Any past steroid use, including inhaled steroids, is important to identify because it predisposes patients to AVN of the femoral head. A linear relationship has been recognized between the cumulative steroid dose and the incidence and severity of osteoporosis and hip fracture.[23]

Ascertainment of the location of the patient's pain is paramount; true hip joint pain is often groin pain. However, pediatric patients with hip pathology often have knee pain as the sole presenting complaint. A review of systems should include information that may help in ascertaining hip or femur pathology versus another cause. Atypical pain may be the result of nephrolithiasis, pelvic inflammation, infection or tumor, inguinal and femoral hernia, or adenopathy from genital or cutaneous infection. A history of low back pain may suggest radiculopathy as the cause of the patient's pain. A differential diagnosis of hip pain without obvious fracture on radiographs is listed in Box 56-1.

The history should also focus on comorbid conditions and injuries. Elderly patients with a hip fracture sustained in a fall at home may be unable to summon help for hours to days. They often have severe dehydration, electrolyte abnormalities, rhabdomyolysis, and renal insufficiency and require a thorough evaluation of these metabolic parameters before surgery is considered.[24]

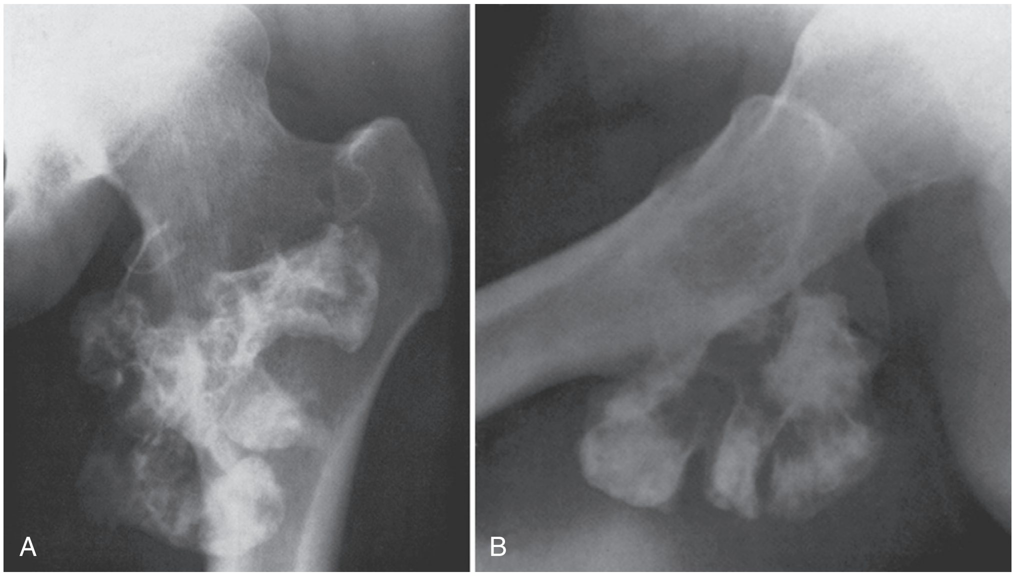


Figure 56-9. Classic radiographic appearance of a solitary osteochondroma of the femur as seen in the anteroposterior **(A)** and frogleg lateral **(B)** views. This lesion is a cartilage-capped bony excrescence, typically arising from the cortex of long tubular bones. (From Harris JH, Harris WH, Novelline RA: The Radiology of Emergency Medicine, 3rd ed. Baltimore, Williams & Wilkins, 1993.)

www.ketabpezeshki.com 66485457-66963820

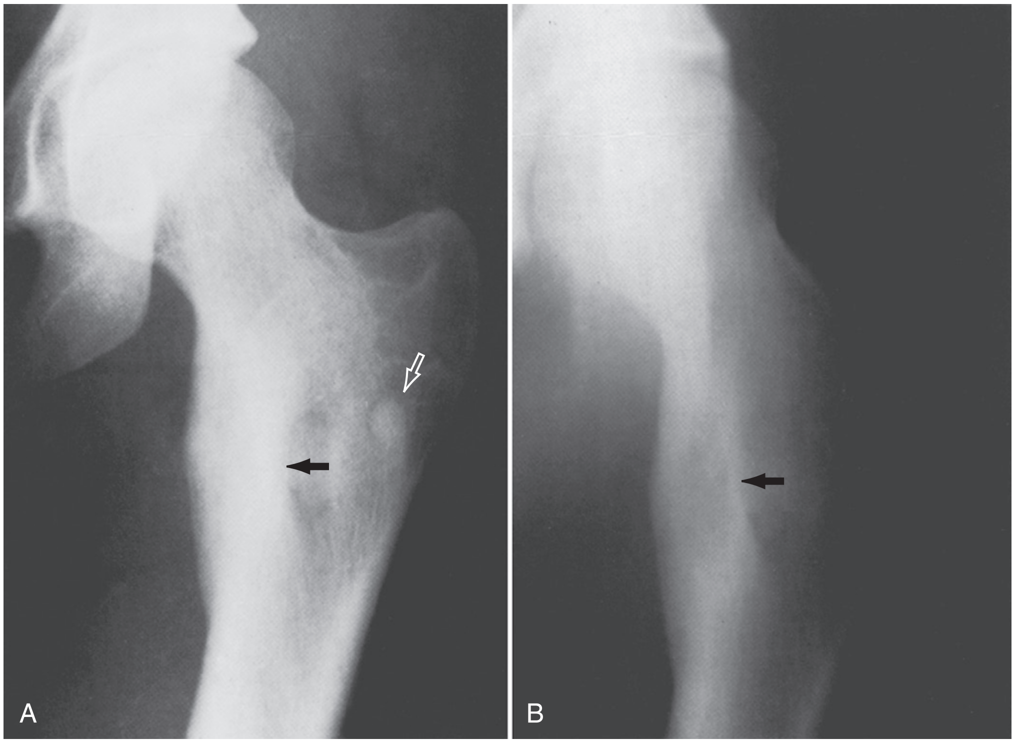


Figure 56-10. Osteoid osteoma of the femur *(solid black arrow)*. **A,** A large focal area of greater density than that of the surrounding femur represents both cortical and endosteal proliferation. The new cortical bone is smooth and sharply delineated, indicative of a nonaggressive process. The open arrow represents a bone island. **B,** A frontal-view tomogram demonstrates an oval central radiolucent nidus *(solid black arrow)*. (From Harris JH, Harris WH, Novelline RA: The Radiology of Emergency Medicine, 3rd ed. Baltimore, Williams & Wilkins, 1993.)

Box 56-1 Differential Diagnosis of a Painful Hip without Obvious Fracture

Referred pain (lumbar spine, hip, or knee)
Avascular necrosis of the femoral head
Degenerative joint disease or osteoarthritis
Herniation of a lumbar disk
Diskitis
Transient synovitis of the hip
Septic arthritis
Bursitis
Tendonitis
Ligamentous injuries of the knee or hip
Occult fracture
Slipped capital femoral epiphysis
Perthes' disease
Tumor (lymphoma)
Deep venous thrombosis
Arterial insufficiency
Osteomyelitis
Iliopsoas abscess
Retroperitoneal hematoma
Inguinal hernia
Inguinal lymphadenopathy
Genitourinary complaints
Sports-related hernia

In addition, the reason for the fall should be determined, as it may reveal other comorbid conditions (e.g., syncope, cardiac dysrhythmias, polypharmacy, alcoholism). Sedative or antihypertensive medications predispose elderly patients to falling and should be prescribed carefully. In a fall, elderly patients may have sustained additional injuries; most commonly, these injuries involve fracture of a vertebral body or wrist. Cervical spine and intracranial injuries also are considered. Young patients with a hip fracture resulting from high-energy mechanisms have concomitant injuries in 40 to 75% of cases.[18]

Physical Examination

Management principles for injuries of the hip and femur are the same as those for traumatic injuries elsewhere in the body.

Hypotension is a problem commonly encountered during the initial resuscitation of a multitrauma patient. Although hypotension might result from the loss of up to 3 units of blood into the thigh with a femoral fracture, other conditions (cardiac, pulmonary, intra-abdominal, and pelvic trauma) must be considered. Hemorrhagic shock from an isolated femoral fracture should be a diagnosis of exclusion. Hypotension, neurovascular compromise, or suspicion for multiple injuries will necessitate consideration of transfer to a trauma center.

After life-threatening conditions have been addressed, the injured extremity should be carefully evaluated. Visual inspection will reveal any pallor, ecchymosis, asymmetry, or deformity. Abrasions, lacerations, and open wounds are critical because their presence alters the management of concomitant fractures. The position that the leg assumes offers a clue to what may be found radiographically. In the presence of a displaced femoral neck fracture, the leg classically assumes the position of external rotation, abduction, and shortening. In intertrochanteric fractures, the leg is found in external rotation with shortening. Shortening or a limb-length discrepancy is found with fractures, dislocations, and osteoarthritis. Nondisplaced fractures, including stress fractures, will not produce limb shortening or rotation but will be painful on passive range of motion, particularly internal and external rotation. These fractures also will prevent the patient from being able to perform a straight leg raise. In patients with obvious deformities, range of motion should be deferred until after radiographs have been obtained.

www.ketabpezeshki.com 66485457-66963820

Systematic examination of the injured extremity will reveal any focal tenderness or warmth that may indicate injury or infection. Active and passive range of motion, and muscle strength, though offering important information, are frequently limited by pain. Detailed neurovascular assessment is vital. Femoral nerve and arterial injury often occur with subtrochanteric and femoral shaft fractures or anterior hip dislocation. The sciatic nerve can be injured with a hip fracture or posterior hip dislocation. Neurologic examination includes evaluation of light touch and pinprick sensation. Femoral, popliteal, dorsalis pedis, and posterior tibial pulses are assessed. Comparative blood pressures obtained by Doppler examination in the injured and uninjured extremities (arterial pressure index) may be useful in diagnosing occult femoral arterial injuries. If the systolic pressure in the affected extremity is 90% or less (ratio less than 0.9) than that in the unaffected extremity, additional diagnostic studies should be undertaken. Additional diagnostic studies include Doppler flow ultrasound imaging, CT angiography, or angiography alone. The ankle-brachial index (ABI) also can be similarly determined by comparing the systolic pressures of the affected extremity and of the ipsilateral arm. An index less than 0.9 necessitates further diagnostic studies.[25,26]

DIAGNOSTIC STRATEGIES

Radiographic Anatomy and Evaluation

Normal radiographic and skeletal anatomy is familiar to emergency physicians (Fig. 56-11).

True AP and lateral radiographs of the femur are usually adequate for the evaluation of potential fractures. The femur should be in as much internal rotation as possible. Fracture lines may be very subtle, particularly with femoral neck fractures. Experts have found three methods useful for identifying inconspicuous fractures. The use of Shenton's line is described in a subsequent section on hip dislocations. (A second method is illustrated in Fig. 56-15.) In searching for a fracture of the femoral neck, both the medial and lateral cortical margins of the femoral head and neck should be carefully examined for the normal S and reverse S curves seen on radiographs of nonfractured hips. The convex outline of a normal femoral head smoothly joins the concave outline of the femoral neck when in anatomic position. This produces an S curve and a reverse S curve, regardless of the orientation of the radiographic projection. A fracture produces a tangential or sharp angle, indicative of disruption of the normal anatomic relationship. A third method, useful in the evaluation of seemingly unremarkable hip radiographs, is to trace the trabecular lines as they pass from the femoral shaft to the femoral head. These lines will be disrupted as they pass through the fracture site, and such disruption often provides the only, albeit subtle, clue. If a fracture is found, radiographs of the knee should be obtained as well. It is a basic orthopedic principle to image the joint above and below any fracture.[25]

One common inaccuracy in hip radiography merits clarification: The soft tissue linear radiolucencies superolateral and inferomedial to the femoral head and neck do not represent the hip capsule, as is commonly believed. Instead, they represent the fat within the fascial plane covering the gluteus minimus superiorly and the tendon of the iliopsoas muscle inferiorly.[27] Comparison of these lines on the symptomatic side with those on the unaffected side should not be used to determine whether an effusion of the hip is present.

Occult Hip Fracture

If radiographs do not show a fracture, or suggestion of injury, ambulation may be attempted. Inability to ambulate or difficulty in ambulation heightens the suspicion of occult fracture. Approximately 2 to 10% of all hip fractures are radiographically "occult" on plain films.[28] Failure to detect these injuries results in increased mortality, risk of subsequent displacement of the fracture, and a higher incidence of AVN.[29,30] When a painful hip prevents ambulation and plain radiographs do not reveal a fracture, magnetic resonance imaging (MRI) should be performed.[28,29] In addition, elderly patients with unexplained chronic hip pain for more than 3 weeks may harbor an occult fracture even if they continue to ambulate. T1-weighted MRI will reveal a fracture that was imperceptible at the time of injury with 100% accuracy and has been found to be cost-effective when compared with other strategies.[29] A small study comparing CT scans with MRI in the diagnosis of occult hip fractures revealed a 66% misdiagnosis rate for CT scans.[29] MRI remains the "gold standard" modality for diagnosing occult hip fractures and helps determine the treatment of these fractures (Fig. 56-12).

Bone scans have been useful in these patients, yet such scans lack adequate sensitivity. To identify most occult fractures, the

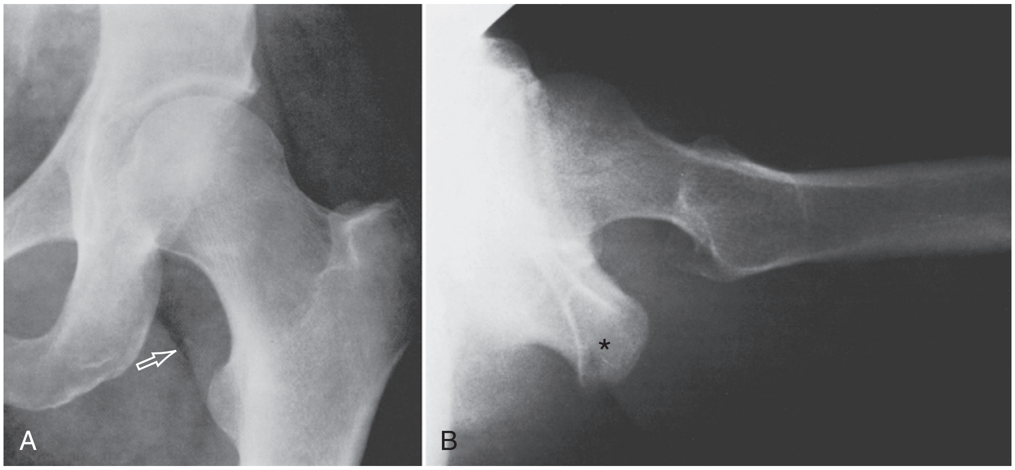


Figure 56-11. Normal radiographic anatomy of the hip. **A,** Anteroposterior view of the normal adult hip. The open arrow indicates the edge of the iliopsoas muscle shadow. This muscle lies immediately on the capsule of the hip joint. The small concavity in the center of the femoral head is for the attachment of the ligamentum teres. **B,** Cross-table lateral view of the hip demonstrating the normal relationship of the femoral head to the neck. The asterisk indicates the ischial tuberosity. (From Harris JH, Harris WH, Novelline RA: The Radiology of Emergency Medicine, 3rd ed. Baltimore, Williams & Wilkins, 1993.)

www.ketabpezeshki.com 66485457-66963820

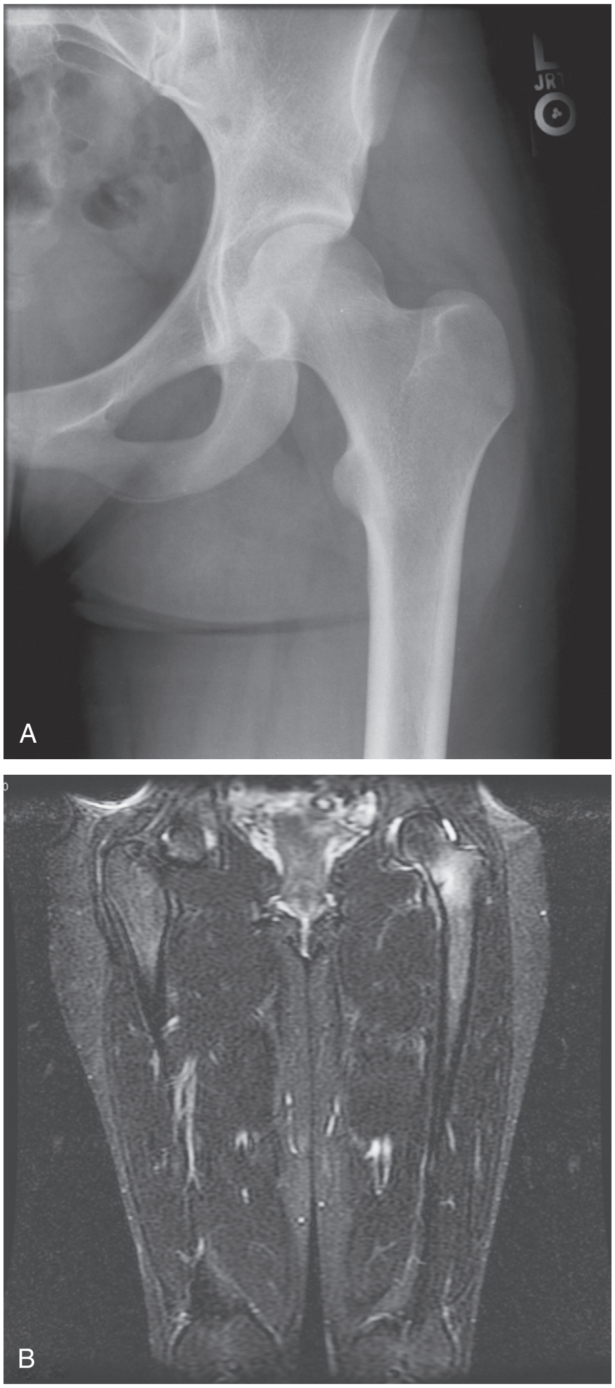


Figure 56-12. The patient reported hip pain and could not ambulate. **A,** Initial radiographs failed to demonstrate a fracture. **B,** A magnetic resonance image revealed a femoral neck fracture through the compressive trabecular fibers.

scan should be delayed 72 hours after the injury. The intervening 3 days of bed rest and hospitalization until a bone scan can be performed are costly and not without risk. Various measures should be implemented to diminish the likelihood of deep vein thrombosis.

MANAGEMENT

Patients with traumatic fracture of the hip or femur should have blood typed and crossmatched for at least 2 units of blood. The potential for significant blood loss and the multiple common associated injuries constitute important justification for this recommendation. Hemodynamic instability may result from dehydration and blood loss of up to 3 units into the fracture site. Currently, treatment of these fractures is hemiarthroplasty or open reduction and internal fixation for femoral neck fractures. Internal fixation with a sliding compression screw generally is used to treat intertrochanteric fractures. The goal is to promote immediate postoperative mobilization. It has become widely accepted that the risks of surgery in elderly patients are minimal when compared with the risks of prolonged bed rest, deep vein thrombosis, pulmonary embolism, pneumonia, and urosepsis from an indwelling Foley catheter. If possible, the repair is conducted with use of spinal anesthesia to decrease the operative risk. Operative repair should be performed after the patient is resuscitated and is in optimal preoperative condition. Care of an elderly patient with a hip fracture requires a multidisciplinary approach and often involves coordination of the efforts of the emergency physician, orthopedist, internist, neurologist, and cardiologist to stabilize the patient before surgery. Comprehensive hip fracture programs for the elderly that include comanagement by geriatricians and orthopedic surgeons have been shown to improve short-term outcomes and may even lower mortality, highlighting the importance of medical management of these complex patients.[31,32]

Traction and Immobilization

Emergency rescue personnel often place a Hare splint, Sager splint, or similar device that applies traction to the leg before transport if they suspect a femoral fracture. This management strategy is popular as it provides pain relief and immobilization and limits blood loss. However, great care should be taken to ensure the proper use of these devices. Prolonged traction during the assessment and management of other injuries can cause or worsen serious neurologic injury in the thigh. The traction used in the field for transport may cause skin breakdown at pressure points and may produce potentially damaging tension on the nerve. The femoral and sciatic nerves are more likely to be injured from traction or during surgery than from a femoral fracture.

Contraindications to the use of traction splints include pelvic fractures, patellar fractures, ligamentous knee injuries, and tibia or fibula fractures. Traction in the prehospital setting should not be applied to any open fracture that has exposed bone. Such reduction pulls grossly contaminated bone fragments back into the wound before adequate débridement can be undertaken in the operating room. A study that evaluated patients with multisystem trauma in whom traction splints were placed in the field for femur fractures showed that up to 38% of the cases had contraindications to the splints that were placed.[33]

With or without traction, the injured extremity should be immobilized when the patient is moved, to prevent further damage from mobile bone fragments. This can be done with simple splinting in the prehospital setting. In the ED, maintaining the leg in slight flexion at the hip reduces intracapsular pressure, whereas extension of the leg increases pressure and potential for ischemic necrosis of the femoral head. Therefore traction for proximal femur fractures may be discontinued once the patient has arrived in the ED. The leg may be supported in a position of comfort with a pillow placed under the thigh. The theoretic advantages for continuation of traction in the ED are pain control and fracture reduction, making operations easier to perform. This is likely true in femoral shaft fractures; however, a Cochrane systematic review looking at preoperative traction for fractures of the proximal femur in adults found no evidence to support these proposed advantages.[34]

www.ketabpezeshki.com 66485457-66963820

Table 56-2 Classification of Open Fractures

CRITERION	TYPE I	TYPE II	TYPE III
Wound size	<1 cm	1-10 cm	>10 cm
Soft tissue damage	Minimal, if any	Moderate, without nerve, arterial, or periosteal stripping	Extensive muscle devitalization; nerve and arterial involvement often classified as type IIIb
Mechanism of injury	Bone edge pierces outward	Variable	High-energy shotgun blast, high-velocity gunshots

From Hoff WS, Bonadies JA, Cachecho R, Dorlac W: East Practice Management Guidelines Work Group: update to practice management guidelines for prophylactic antibiotic use in open fractures. J Trauma 70:751-754, 2011.

Open Fracture Care

By definition, an *open fracture* is any fracture in which a break in the integrity of the skin and soft tissue allows communication with the fracture and its hematoma. Any nearby wound or break in the skin must be considered to communicate with the fracture. Open fractures are divided into three categories (Table 56-2). A bone piercing from the inside outward often causes only a small wound. The contaminated bone tip may then slip deceptively back into the soft tissue; therefore any break in the integrity of the skin makes the fracture an open one. Open wounds should be irrigated and then covered with sterile saline-moistened gauze.

For all type I open fractures, a first-generation cephalosporin should be administered intravenously. Types II and III may require additional gram-negative coverage because of the amount of devitalized tissue and increased gram-negative skin flora found in the groin.[35] This additional coverage could be provided by an aminoglycoside such as gentamicin or tobramycin. The use of perioperative first-generation cephalosporins has been shown to reduce postoperative infection even in closed fractures in patients who are to undergo surgery.[35]

Great care should be taken to identify tetanus-prone wounds so that appropriate prophylaxis can be provided with tetanus immune globulin when indicated. Immunization status should be verified in all patients and immunizations updated as needed.

Compartment Syndrome

Because of the thigh's larger volume, compartment syndrome within the thigh is far less common than in the lower part of the leg. A large amount of bleeding into the compartment is required before the pressure rises above capillary perfusion pressure. When compartment syndrome does occur in the thigh, only 50% of the cases are associated with a femur fracture.[36] It is difficult to clinically differentiate the expected swelling after an injury from early compartment syndrome. Clinical examination and the use of direct compartment pressure measurements can detect the development of compartment syndrome at an early stage.

Pain Management

Systemic Analgesia

It is well known that control of pain in EDs is often inadequate.[37] In the case of femoral fractures, narcotic analgesia is often indicated in combination with other pain-relief strategies including immobilization of the injured extremity, placement of the injured extremity in a position of comfort, and the consideration of local analgesia in the form of nerve blocks.

Femoral Nerve Block

Femoral nerve blocks have been used to treat femoral shaft fractures for more than 50 years. Despite proven effectiveness and a low complication rate, this technique has not been widely embraced by emergency physicians or surgeons.[38] The femoral nerve block is an excellent option as an adjunct or alternative to systemic analgesics in patients at risk for hypotension. It has been shown to significantly decrease time to lowest pain score as compared with intravenous narcotics, and patients have been found to require significantly lower doses of narcotics in conjunction with femoral nerve blocks.[38,39] The block can be performed with the assistance of a peripheral nerve stimulator to localize the nerve, or bedside ultrasound to directly visualize the nerve before anesthetic injection.[40] Femoral nerve blocks have been shown to be effective when performed by newly trained emergency physicians without the assistance of peripheral nerve stimulators or ultrasound.[39] If a long-acting anesthetic such as bupivacaine is used, the expected onset of analgesia is within 30 minutes, and its duration is 6 to 8 hours.[41]

Careful neurovascular examination should be undertaken and documented before the femoral nerve block is performed. After the nerve block procedure, continued assessment of the femoral muscular compartments is advisable to check for the development of compartment syndrome. If an injury is considered at especially high risk for compartment syndrome, orthopedic surgery consultation should be obtained before the block, and there should be consideration of measurement of compartment pressures after the block. As the sciatic nerve innervates the compartments of the lower limb, a femoral nerve block should not mask the clinical presentation of compartment syndrome in the lower leg.

Hip Arthroplasty

Background and Epidemiology

Sir John Charnley first described the modern form of total hip arthroplasty (THA) in 1961. Despite many changes in both the design and materials used, Charnley's essential design has been established as the standard.[42] The number of THA procedures performed annually in the United States rose from 65,000 in 1982 to more than 230,000 in 2007.[43] The most common indication for THA is joint failure resulting from severe osteoarthritis. Other indications include rheumatoid arthritis, certain types of hip fracture, AVN, and certain tumors. Arthritis associated with Paget's disease, trauma, ankylosing spondylitis, and juvenile rheumatoid arthritis are also relative indications for THA or partial hip arthroplasty.

Outcomes and Complications

THA provides an immediate, substantial reduction of pain and improvement in functional ability and overall quality of life. A 10-year follow-up study of patient outcomes, including gait, perception of pain, physical mobility, sleep patterns, and energy scores, showed positive results in more than 90% of cases.[44] Despite the tremendous success of THA, numerous complications have been reported. Aseptic loosening of the prosthesis is the most common. Other complications include component wear, infection, adjacent femoral fractures, deep vein thrombosis, and postoperative dislocation of the femoral component. In general, flexion past 90 degrees, adduction, and internal rotation place the hip at risk for dislocation. This combination can occur when patients bend at the waist (e.g., to sit on a normal low toilet or to get out of a chair) or cross the legs[45] (Fig. 56-13).

www.ketabpezeshki.com 66485457-66963820

Figure 56-13. Dislocation of the femoral prosthesis in a patient who had undergone a total hip arthroplasty. The femoral head often becomes caught on the rim of the acetabular cup, thereby preventing reduction. Reduction may disrupt or dislocate the acetabular cup.

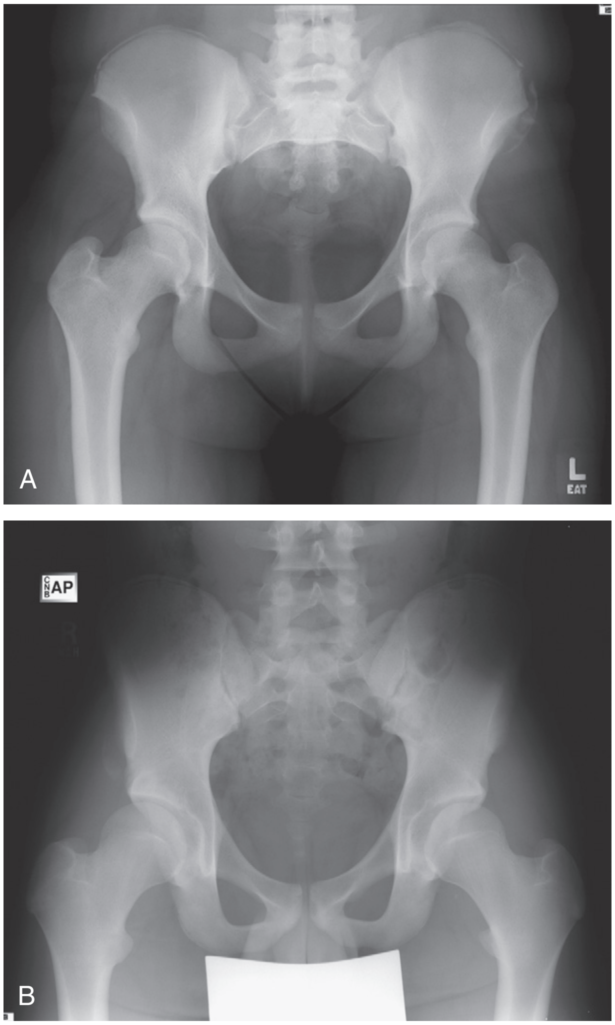


Figure 56-14. **A,** Avulsion fracture of the anterior superior iliac spine by the sartorius muscle. **B,** Avulsion fracture of the anterior inferior iliac spine by the rectus femoris.

SPECIFIC INJURY PATTERNS

Fractures of the Hip and Femur

Avulsion Fractures

The pain of avulsion injuries of the hip may manifest as referred pain to the thigh; these fractures are most common in adolescents and young adult athletes. The incidence of avulsion fractures is increasing as a result of the growth of competitive sports participation, especially in teenage athletes.[46,47] The muscular origin of this type of injury commonly involves the pelvic apophyses, which may not fully ossify until age 25. Avulsion at the site of the growth plate is the result of sudden maximal muscular exertion. It may occur with rapid acceleration or sudden changes in speed or direction. The athlete classically experiences a sudden piercing pain at the site of injury, along with a “snapping” or “popping,” and frequently falls to the ground because of the intensity of this pain. As depicted in Figure 56-14, avulsion at the ASIS involves the separation of a thin piece of bone as the sartorius muscle suddenly contracts (see Fig. 56-14A). The anterior inferior iliac spine (AIIS) is avulsed by the rectus femoris, and the hamstring group may pull off the ischial tuberosity (see Fig. 56-14B). Avulsion fractures of the ASIS and AIIS are managed nonoperatively with conservative treatment. Treatment of avulsion fractures of the ischial tuberosity is more controversial. Most experts recommend conservative treatment for avulsion injuries with less than 2 cm of displacement. Fractures with more than 2 cm of displacement may benefit from operative fixation to prevent nonunion, as well as union with exuberant callus formation.[47,48]

Proximal Femoral Fractures

Classification Systems. Fractures of the proximal end of the femur have been classified on the basis of their relationship to the hip capsule (e.g., intracapsular and extracapsular), anatomic location (neck, trochanteric, intertrochanteric, subtrochanteric, and shaft fractures), and degree of displacement. A working knowledge of the classification system will allow the emergency physician to communicate with the consulting orthopedist regarding the fracture’s pattern and stability and treatment options.

Femoral Neck Fractures

Pathophysiology. Many experts now refer to femoral neck fractures as *insufficiency fractures* in acknowledgment of the major role played by osteoporosis. Age-related bone loss is believed to be the most important etiologic factor in femoral neck fractures.[49] The theory that these fractures result from primary skeletal pathology is supported by the fact that minimal or no injury is associated with most of these fractures. Pathologic fractures from metastatic carcinoma are also well described.

Classification. Although several classification systems were formerly used to describe these fractures, they have been abandoned because of poor inter-rater reliability and limited clinical utility.

www.ketabpezeshki.com 66485457-66963820

Currently, femoral neck fractures should be classified as either nondisplaced or displaced fractures.

From 15 to 20% of all femoral neck fractures are *nondisplaced fractures*. The fracture line often may be very subtle. Techniques described for detection of subtle fracture lines may be useful for this reason. Evaluation of the continuity of the subcapital cortical lines, search for an indistinct broad band of increased subcapital density, and identification of the S and reverse S curves (Fig. 56-15) will lead to the correct diagnosis in most cases. In impacted femoral neck fractures, the neck cortex is driven into the cancellous femoral head. Bone impaction lends a certain inherent stability (Fig. 56-16). Because of this inherent stability, two different management approaches have been advocated: early ambulation and internal fixation. Internal fixation has been associated with a reduced length of hospital stay and improved rehabilitation and has become the preferred treatment modality. Without impaction, a nondisplaced femoral neck fracture is unstable and will become displaced without internal fixation.

On initial evaluation, a patient with a *displaced fracture* of the femoral neck lies with the limb externally rotated, abducted, and slightly shortened. The diagnosis is confirmed with plain hip films. To avoid further disruption of the blood supply to the femoral head, range-of-motion assessment should be deferred unless radiographs fail to reveal a fracture. Treatment of these displaced fractures consists of open reduction with internal fixation, hemiarthroplasty, or THA. In all displaced femoral neck fractures, the femoral head is rendered largely avascular, and signs of AVN and collapse may develop over the ensuing several years.

Outcome and Complications. The mortality rate during the first year after a femoral neck fracture is 14%, as compared with 9% for the control population. Factors affecting mortality include age, male sex, psychiatric illness, end-stage renal disease, and congestive heart failure.[50] Institutionalized patients have a death rate up to three times higher than noninstitutionalized patients.[51] Complications can be minimized by early reduction, stable internal fixation, early ambulation, and close attention to medical comorbidities.

AVN and nonunion are the two major complications of femoral neck fractures. AVN is the most common complication, despite optimal treatment, because of the complex arterial anatomy.

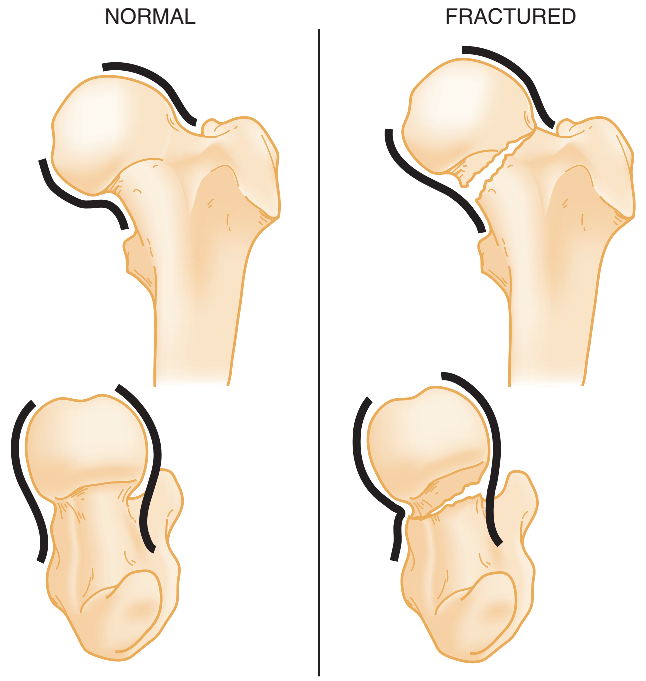


Figure 56-15. The normal anatomic appearance of the femoral head as smooth S and reversed S lines is drawn above. The concave outline of the femoral neck meets the convex outline of the femoral head as shown here in various views. Any tangential angle suggests a fracture.

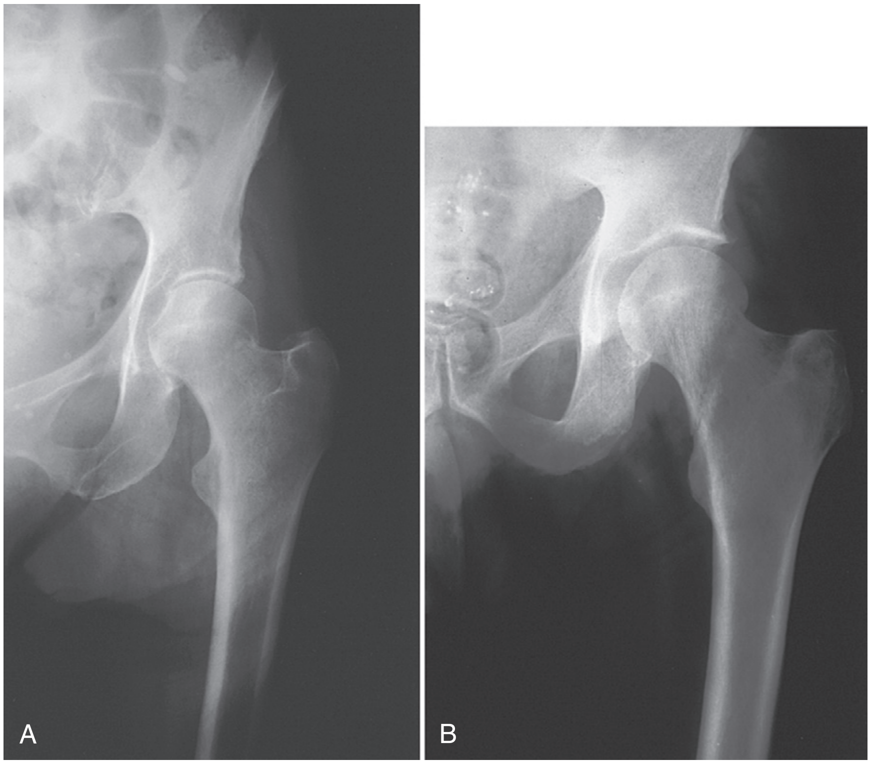


Figure 56-16. A, Subtle nondisplaced impacted femoral neck fracture. Use of S curves aids in identification. B, A nondisplaced femoral neck fracture possesses no stability without impaction.

www.ketabpezeshki.com 66485457-66963820

Deep infection in the form of osteomyelitis or septic arthritis is more common with femoral neck fractures because the fracture line extends into the joint. The rate of infection has been dramatically reduced with the use of perioperative antibiotics. Pulmonary embolism is another significant complication and is the leading cause of death 7 days after fracture in orthopedic patients. Anticoagulation is recommended for at least 10 days after any hip surgery in patients without significant contraindications. Fondaparinux has been shown to be an effective anticoagulant in this setting.[52]

Intertrochanteric Fractures

Anatomy. The fracture line of intertrochanteric fractures extends between the greater and lesser trochanters of the femur. These injuries are considered to be extracapsular fractures. The fracture line extends through cancellous bone, which has an excellent blood supply. The hip's short external rotators remain attached to the distal fracture fragment, and the internal rotators are attached to the proximal fracture fragment. Owing to the strong action of the iliopsoas muscle, the leg is shortened and externally rotated.

Pathophysiology. An intertrochanteric fracture in younger adults usually is the result of high-speed collisions or high-energy trauma, such as falls from heights. An elderly person may sustain this injury during a fall from any height. The fracture lines are the result of both direct and indirect forces. The direct forces act along the axis of the femur and on the greater trochanter as it strikes the ground. Indirect forces are produced as the iliopsoas pulls the lesser trochanter and the abductors pull the greater trochanter; these forces often cause fractures at the site of insertion.

Classification. A large number of classification systems for intertrochanteric fractures have been proposed to predict the possibility of achieving and maintaining stable reduction.[53] A useful system designates the fracture according to the number of separate bone fragments produced (Fig. 56-17).

Management. Intertrochanteric fractures carry particular management pitfalls for the emergency physician. Great care must be taken to maintain focus on the entire patient and not on the fracture alone. Hemodynamic instability may result from blood loss of up to 3 units into the fracture site.[54] Poor nutrition before the fall, chronic diuretic use, and decreased oral intake in patients who have to wait until they are found will contribute to the level of dehydration. Up to 70% of these patients are under-resuscitated.[24] Associated distal radius fractures, proximal humerus fractures, rib fractures, and compression fractures of the lumbar and thoracic spine often are overlooked because the femoral fracture distracts the attention of both patient and physician.

A substantial majority of intertrochanteric fractures will require some type of internal fixation. Such fixation allows rapid mobilization, decreased hospital length of stay, reduced mortality, and improved function.[25] The procedure should be performed on an urgent rather than an emergent basis. Mortality is increased when the patient is taken to the operating room on the day of injury; however, early repair within 24 to 48 hours is associated with a 1-year mortality reduction.[55] Preoperative medical optimization by multidisciplinary medical teams may decrease the incidence of 1-year mortality in these patients.[32]

Outcomes. Intertrochanteric fractures have an associated mortality rate of 10 to 30% in the first year.[32] Life expectancy returns to normal among patients who survive that year. Survival is most commonly related to the patient's age and preexisting medical conditions. Additional risks associated with operative treatment include mechanical failure (1-16%), implant migration (2-10%), and infection (2-8%).[56] Mechanical failure and nonunion are much more common in unstable fractures and those that were not adequately reduced. Approximately half of patients sustaining these fractures are eventually able to regain their original level of ambulation. Yearly infusion of zoledronic acid (a bisphosphonate) beginning within 90 days of hip fracture repair reduces the incidence of new fractures and decreases mortality.[49,57]

Pathologic Intertrochanteric Fractures

Aggressive treatment is indicated for patients who have pathologic intertrochanteric fractures or impending fractures if their life expectancy is more than a few months. Such treatment with subsequent radiation therapy improves the patient's quality of life, decreases pain, and improves mobility.

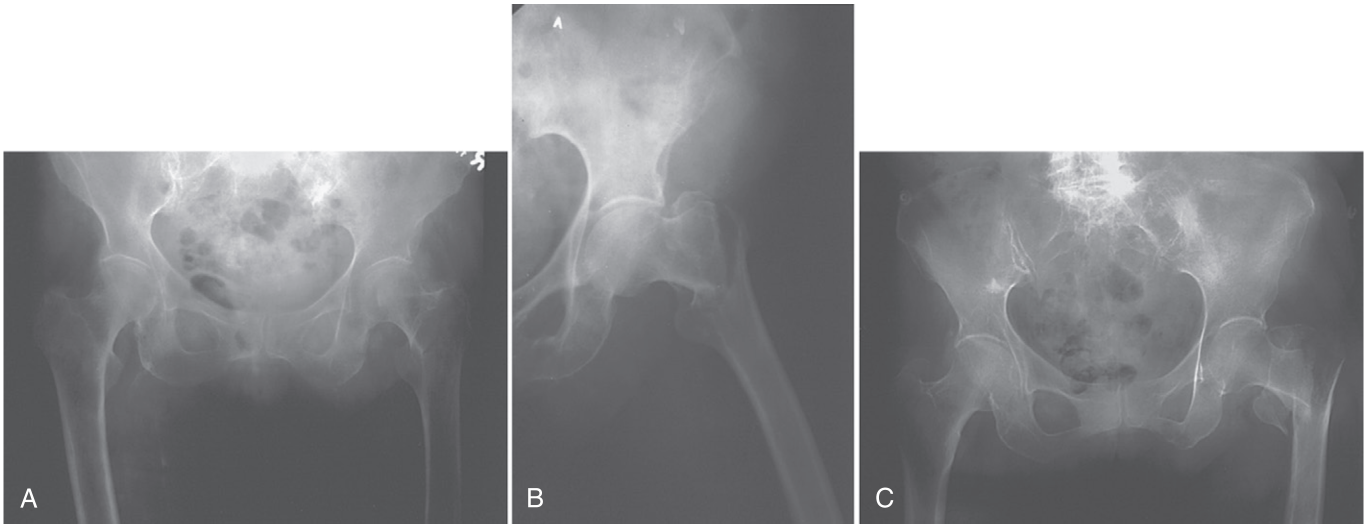


Figure 56-17. The number of parts that the fracture produced classifies intertrochanteric fractures. **A,** Two-part fractures have one part connected to the femoral head and a second part attached to the shaft. **B,** The greater or lesser trochanter also is fractured with three-part fractures. A greater degree of instability is produced because the attached muscles continue to act on the fractured trochanter. **C,** Four-part intertrochanteric fractures involve both trochanters.

www.ketabpezeshki.com 66485457-66963820

Figure 56-18. Isolated fracture of the greater trochanter. Note that the trochanter is displaced in the typical posterior and superior direction.

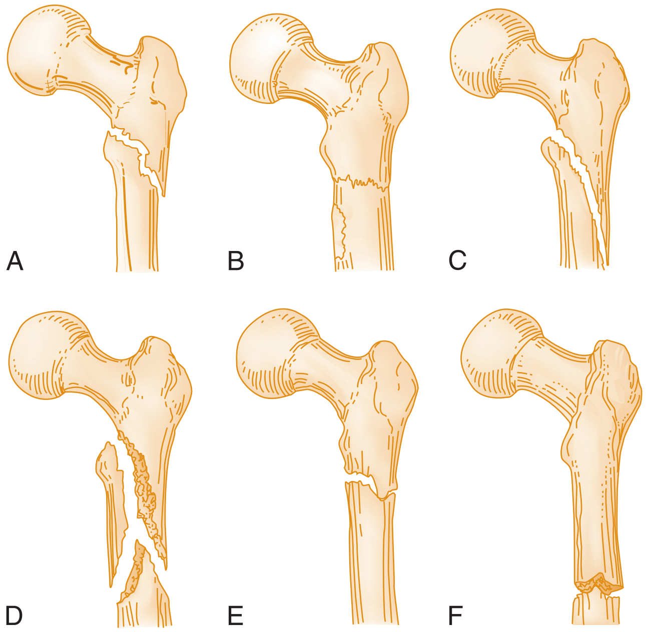


Figure 56-19. Variants of subtrochanteric fractures. **A,** Short oblique fracture. **B,** Short oblique fracture with comminution. **C,** Long oblique fracture. **D,** Long oblique fracture with comminution. **E,** High transverse fracture. **F,** Low transverse fracture.

Isolated Fractures of the Greater or Lesser Trochanter

Fractures of the greater or lesser trochanter are rare. They occur in women more often than in men and are the result of a fall directly onto the trochanter or avulsion by the iliopsoas muscle. There may be a comminuted fracture involving only part of the greater trochanter or more subtle impaction of the lateral cortex. If avulsed, the fragments are displaced superiorly and posteriorly[25] (Fig. 56-18).

Treatment consists of pain control and early mobilization with crutches; weightbearing is allowed as pain is tolerated. Outpatient management of this injury is possible with satisfactory support for home convalescence. The prognosis is good, and healing generally is excellent.

Subtrochanteric Fractures

Anatomy and Pathophysiology. Subtrochanteric fractures occur between the lesser trochanter and the proximal 5 cm of the femoral shaft. They may accompany intertrochanteric fractures. The subtrochanteric region is composed almost entirely of cortical bone, which lacks the vascularity important to new bone growth and repair. When fractured, it is more likely to be comminuted than bone with a higher cancellous content. In addition, the greater portion of the biomechanical forces of the femur is transmitted down the curved medial cortex of the femoral shaft. If this cortex is disrupted, the metal hardware undergoes the majority of the stress. This mechanism accounts for the increased incidence of hardware failure when the medial cortex is largely involved.

These fractures characteristically are deformed because of the unbalanced muscle forces. In displaced fractures the attachments of the iliopsoas, gluteal, and external rotator muscles consistently produce flexion, abduction, and external rotation of the proximal fragment.

Epidemiology. Subtrochanteric fractures account for 11% of all fractures of the proximal end of the femur. Although 10% of these fractures are caused by gunshots, the usual mechanism of injury is direct blunt trauma.[58] A bimodal distribution for these injuries has been recognized. The first group consists of elderly patients who experience a fall, in whom the fracture occurs through an area of weakened cortical bone. Pathologic fractures from metastatic lesions, Paget's disease, renal osteodystrophy, osteogenesis imperfecta, and osteomalacia are well-recognized clinical entities in these patients. The second group comprises victims of extreme high-energy trauma. In these patients, the subtrochanteric fracture is rarely an isolated injury because of the tremendous force required to produce it. Associated thoracic and abdominal injuries are common and should be aggressively sought to ensure adequate management. From 30 to 50% of patients with subtrochanteric fractures have associated fractures of the pelvis, spine, or other long bones. Stress fractures can occur in this region but are extremely uncommon.

Classification. Various classification systems for these fractures have been proposed, although none is widely accepted.[53] From a practical standpoint, it is best to define and describe these fractures by location (*proximal* or *distal*), angle (*transverse, oblique*), and the presence of comminution (Fig. 56-19).

Management. Hemodynamic instability may result from blood loss of up to 3 units into the fracture site.[54] Although such blood loss can lead to hypovolemic shock, other causes of hypotension in a trauma patient need to be considered. Open fractures are rare and when present are accompanied by significant soft tissue injury. Vascular and neurologic injuries are also uncommon.

Definitive management of subtrochanteric fractures is a complex issue. Maintaining limb length and controlling rotation are difficult. Open reduction with internal fixation generally is the treatment of choice. However, in the rare case with severe comminution or an open, grossly contaminated fracture, nonoperative

www.ketabpezeshki.com 66485457-66963820

management may be preferable.[59] Children younger than 10 years also may be managed nonoperatively. The amount of remodeling and growth stimulation occurring in children of this age usually ensures good results without internal fixation.

Outcomes. The bone in the subtrochanteric region is largely cortical and relatively avascular when compared with the cancellous intertrochanteric region. It logically follows that healing is comparatively slow. Comminution is common and increases the likelihood of nonunion. Comminuted and distal subtrochanteric fractures carry a worse prognosis.

Complications include fat embolism in patients of all ages, and the adverse effects of prolonged immobilization in the elderly. Reported mortality rates from subtrochanteric fractures range from 9.6 to 13.3%.[59] The violent force and common associated injuries contribute to the high mortality among patients who sustain these fractures.

Femoral Shaft Fractures

Pathophysiology. Femoral shaft fractures are common injuries in young adults after high-energy trauma. As is the case with other femoral cortical fractures, considerable violent force is required to produce a fracture in a normal shaft. Automobile and motorcycle accidents, falls, and pedestrian accidents account for a majority of femoral shaft fractures. The femoral shaft usually fails under tensile strain, and a transverse fracture results. Higher forces produce varying degrees of segmentation or comminution. Open fractures of the femoral shaft are less frequent and are often the result of a gunshot wound. Pathologic fractures occur from a low-mechanism force that may produce torsion and spiral fractures.[60]

Classification. There is no commonly accepted or easily remembered classification for femoral shaft fractures. Location and geometry of the fracture line should be used to describe these fractures. Transverse, oblique, spiral, wedge, and *comminuted* are useful terms for describing these fractures.

Clinical Features. Patients often arrive in the ED with the injured extremity immobilized by traction devices, which should be removed while immobilization of the limb is maintained. Neurovascular injuries are rarely associated with closed femoral shaft fractures.[61] Significant hemorrhage into the thigh can occur with a femoral shaft fracture, just as it can with intertrochanteric and subtrochanteric fractures. Injuries commonly occurring in the presence of femoral shaft fractures include hip fractures, fracture-dislocations, femoral neck fractures, supracondylar femoral fractures, and patellar fractures.[62] Almost half of femoral shaft fractures have associated ligamentous damage in the knee. If the patient has a femoral fracture, pain often prevents adequate evaluation of knee stability. Any attempt to evaluate the stability of the knee acutely will result in additional pain and hemorrhage without providing useful, reliable information.

Management. Internal fixation with intramedullary rods has been demonstrated to shorten both hospitalization and total disability time with most femoral shaft fractures. The vast majority of femoral shaft fractures heal well in time, regardless of the mode of treatment. Severely comminuted fractures are more likely to be treated by closed reduction.

Outcomes. Femoral shaft fractures have close to a 100% union rate, and most patients are able to return to work after approximately 6 months. Even a minor degree of limb shortening or malalignment can result in arthritis of the hip or knee or chronic back pain.[63] Refracture is a rare occurrence that is most likely at two times during the healing process: during early healing and callus formation or during the brief period after the hardware is removed. After the hardware removal, the unsupported bone is required to bear the entire weight of axial loading and is at risk for refracture.

Fractures with Minimal or No Trauma

Most patients who arrive in the ED with hip or thigh pain will provide a clear history of a traumatic event. Hip or knee pain in the young, in athletes, and in the elderly deserves investigation, even when minimal or no trauma has been reported. This patient population commonly has occult hip pathology and occasionally femoral pathology. Although senile osteoporosis is the leading cause of femoral neck fractures after minor trauma, pathologic fractures of the femur may result from metastatic, metabolic, or endocrine disease.[64]

Stress Fractures

Pathophysiology. Stress fracture of the femoral neck was first reported in 1905 by Blecher.[65] Stress fractures occur when normal bone is repeatedly subjected to submaximal forces. This recurring stress stimulates the bones to remodel and strengthen. In a stress fracture, osteoblasts are unable to lay down new bone and remodel fast enough, so the bone fails. Stress fractures can also occur in diseased bone when it is subjected to repeated minimal stress.[66]

Clinical Features. The symptoms of a stress fracture of the femoral neck often are so subtle that they may be mistaken for muscle strain or an overuse injury. Early symptoms frequently include morning stiffness and aching in the hip on the first steps after a period of rest. The pain gradually increases during prolonged exercise and may reach the point at which bearing weight becomes impossible. Pain is felt in the groin or along the medial aspect of the thigh toward the knee.

On examination, a painful limp is obvious. This painful or *antalgic* gait is characterized by shortening of the stance phase of the injured extremity. No obvious external rotation or shortening of the leg is seen; the patient experiences only minor discomfort with active or passive motion, except at the extremes of flexion and internal rotation. Tenderness is minimal because of the large amount of soft tissue coverage at the femoral neck.

Diagnostic Strategies. Radiographs are helpful if they demonstrate a fracture, but findings often are negative until 10 to 14 days after the injury.[25] Endosteal or subperiosteal callus develops at the fracture site during this period. In addition to the standard AP and lateral views of the hip, oblique views may delineate the fracture line. Close attention should be paid to the trabecular fibers of the femoral neck. A stress fracture often can be identified as an isolated disruption of either the tensile (lateral aspect of the femoral neck) (Fig. 56-20A) or the compressive (medial aspect of the femoral neck) (Fig. 56-20B) trabecular fibers. If a fracture is

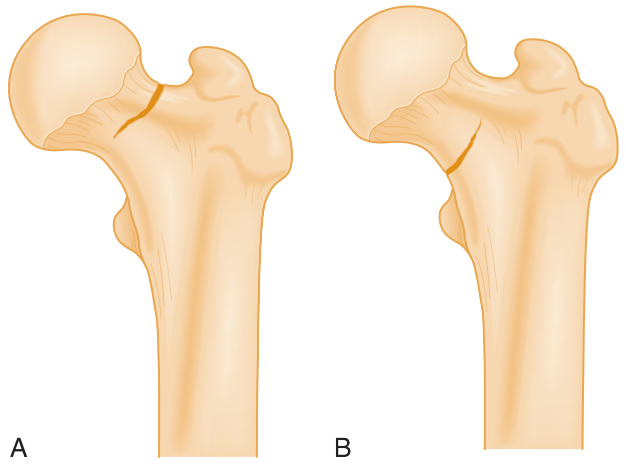


Figure 56-20. Schematic illustrating femoral neck fractures through the tensile (A) and compressive (B) trabecular fibers.

www.ketabpezeshki.com 66485457-66963820

suspected clinically but radiographic findings are negative, the next step is MRI.[30] If a fracture is found, the contralateral hip should be extensively evaluated because of the significant incidence of bilateral stress fractures.

Management. Treatment of stress fractures of the femoral neck is determined by the involvement of the compressive or tensile aspect. Compressive-side fractures involving less than half of the cortex are inherently stable and can be treated conservatively with partial weightbearing with crutches. Tension-side fractures and compressive-side fractures involving more than half the cortex are considered unstable and at risk for displacement. These fractures should be treated operatively with screw fixation.[67]

Other Causes of Pain

Considerations in the diagnosis of atraumatic pain of the hip and thigh are listed in Box 56-1.

Dislocations and Fracture-Dislocations of the Hip and Femur

Injury Patterns

Epidemiologists have identified injury patterns in victims according to the mechanism of injury.[68] Pedestrians who are struck by a car may have head, chest, pelvic, arm, and femur injuries. Motorcyclists tend to sustain pelvic and ipsilateral leg injuries. A person who stumbles and falls seldom has major associated injuries unless there is underlying bone pathology (e.g., osteogenesis imperfecta, osteoporosis). Each of these main categories of injury is discussed next.

Hip Dislocations

Dislocations and fracture-dislocations of the hip are two true orthopedic emergencies. The hip joint possesses impressive inherent strength and stability; therefore considerable force is required to produce these injuries. With this understanding, a hip dislocation serves as a "red flag" for multisystem injury and should prompt a diligent search for other occult injuries. Serious associated injuries are found in up to 95% of patients with a dislocated hip. There is an associated acetabular fracture in up to 70% of cases. Knee fractures, ligamentous injuries, and dislocations are present in up to 30% of patients sustaining a hip dislocation.[69] It is highly recommended that in the presence of this type of injury, patients be managed as major trauma victims.

Mechanism and Biomechanics. Traumatic hip dislocations occur primarily in patients sustaining severe multisystem trauma, most often as a result of a high-speed MVC. Failure to use seat belts is a significant risk factor. Less common mechanisms include falls, sports injuries, and pedestrians struck by automobiles.

Posterior dislocations are almost always the result of MVCs. A seated vehicle occupant typically has the hip adducted, flexed, and internally rotated at the time of impact. As the knee strikes the dashboard, the force is transmitted through the femoral shaft to the femoral head. With sufficient force, the femoral head dislocates posteriorly. Anterior dislocations result from forceful extension, abduction, and external rotation of the femoral head. These forces lever the head up out of the acetabular cup. Such dislocation most often occurs after an MVC when the occupant has the hip abducted and externally rotated at the time of impact. It may also result from a fall or sports injury when the hip is forcefully hyperextended.

Classification. The relationship of the femoral head to the acetabulum is used to classify dislocations into anterior, posterior, central, and inferior types. A fracture-dislocation includes an associated fracture of the acetabulum or femoral head. Posterior

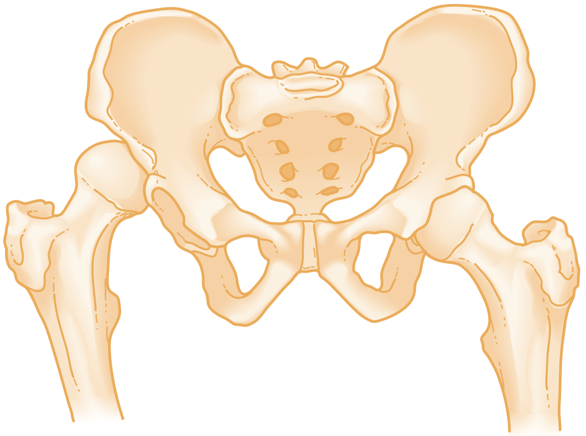


Figure 56-21. In a posterior dislocation, the hip is internally rotated[70] and the lesser trochanter is superimposed on the femoral shaft. Failure to visualize the lesser trochanter on the anteroposterior projection identifies a posterior dislocation.

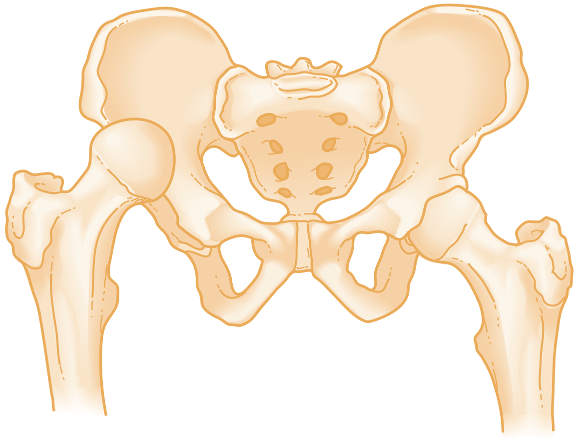


Figure 56-22. In an anterior dislocation, the hip is externally rotated and the lesser trochanter appears in profile. The hip is farther from the x-ray cassette than the unaffected side and may appear larger because of the beam's projection.

dislocations (Fig. 56-21) account for 80 to 90% of dislocations. Anterior dislocations (Fig. 56-22) are seen in 10 to 15% of patients. In anterior dislocations the femoral head may dislocate medially toward the obturator foramen (obturator dislocation) (Fig. 56-23) or laterally toward the pubis (pubic dislocation), or toward the iliac crest. Central dislocations, which occur in 2 to 4% of cases, are not true dislocations because the entire femoral head is forced centrally through a comminuted fracture of the acetabulum. Inferior dislocation of the hip associated with inversion of the femoral shaft (luxatio erecta femoris) is a very rare condition that may occur with or without associated trochanteric fracture.[70]

Clinical Features. The position of the injured extremity may provide valuable clues in the evaluation of a hip dislocation. A patient with a posterior dislocation typically holds the hip flexed, adducted, and internally rotated. The knee of the affected extremity rests on the opposite thigh. The extremity generally is shortened, and the greater trochanter and buttock may be unusually prominent. By contrast, a patient with an anterior dislocation holds the hip in abduction, slight flexion, and external rotation, and the leg may appear lengthened. These physical findings may be absent in patients with an associated ipsilateral femoral shaft fracture.

www.ketabpezeshki.com 66485457-66963820

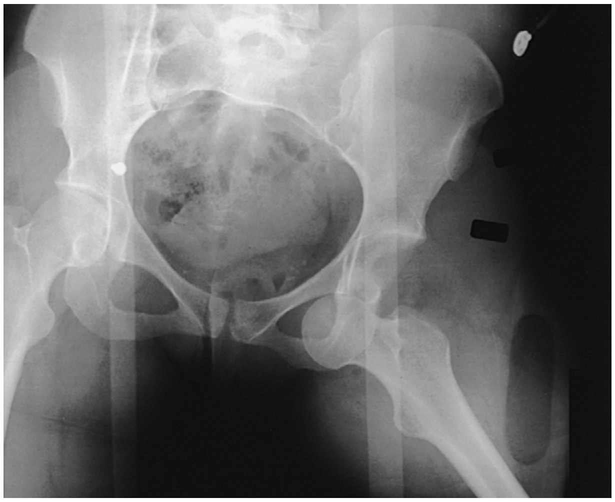


Figure 56-23. Radiograph of obturator dislocation.

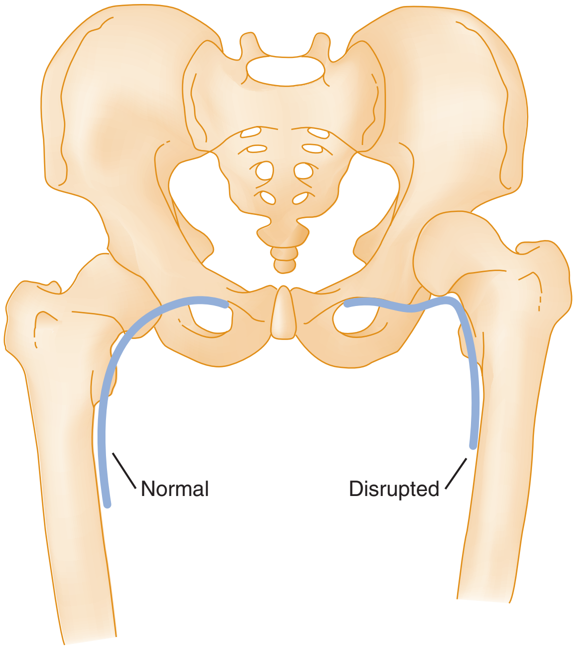


Figure 56-24. Shenton's line is a smooth curved line drawn along the superior border of the obturator foramen and medial aspect of the femoral metaphysis. Disruption of this line should raise suspicion of a femoral neck fracture or hip dislocation.

The neurovascular examination should focus on the sciatic nerve and femoral vessels. Sciatic palsy is present in approximately 10% of patients with hip dislocation and most commonly involves the peroneal nerve branch. The most sensitive clinical sign of peroneal nerve palsy is weakness of the extensor hallucis longus; other signs include weakness of dorsiflexion and numbness or tingling over the dorsum of the foot. The femoral vessels and nerve are particularly prone to injury after an anterior dislocation.[71]

Diagnostic Strategies. Radiologic investigation begins with an AP view of the pelvis. This view alone will identify a majority of hip dislocations. An AP pelvis film should be obtained in all trauma patients with the aforementioned deformities. The AP radiograph should include the entire pelvis and the proximal third of the femur to allow comparison of both hips. When a dislocation is found or suspected, a lateral view of the hip will provide additional definition of the injury.

Although most hip dislocations are seen clearly with these two views, several more subtle radiographic signs may assist physicians in making a confident diagnosis. The first indicator involves the position of the lesser trochanter. Because a posteriorly dislocated hip is internally rotated, the lesser trochanter is superimposed on the femoral shaft and is not seen on the AP projection. By contrast, an anteriorly dislocated hip is externally rotated, and the lesser trochanter appears in profile. The second clue is found in the size of the femoral head. Because a posteriorly dislocated hip is closer than the unaffected side to the x-ray cassette, it appears smaller. The converse is true in anterior dislocations, in which the hip is farther from the x-ray cassette than the contralateral side is and thus appears larger. The third finding relates to the integrity of Shenton's line (Fig. 56-24). This line is a smooth, curved line drawn on the radiograph along the superior border of the obturator foramen and medial aspect of the femoral metaphysis. Disruption of this line should raise suspicion for a femoral neck fracture or hip dislocation.[72]

An obvious dislocation may distract the emergency physician from a search for concomitant fractures. Examination of the trabecular pattern can identify associated fractures of the acetabulum and femoral head, neck, or shaft. It is important to identify acetabular fractures before closed reduction is attempted because intra-articular bone fragments may interfere with effective reduction.[73] Although these fractures may make the reduction more difficult, their presence is not a contraindication to reduction.

Management. Hip dislocations constitute a true orthopedic emergency, and reduction should be performed within 6 hours. The earlier the reduction, the better the results. The incidence of AVN, traumatic arthritis, permanent sciatic nerve palsy, and joint instability logarithmically increases with the length of time for which the hip remains dislocated.[73,74]

The timing and method of reduction are dependent on the overall condition of the patient, the type of dislocation, and the presence or absence of associated fractures. In cases of simple dislocation, closed reduction should be attempted first. Although some clinicians recommend that this procedure be performed with the patient under general anesthesia, this delay, with its associated increase in the rate of AVN, is not warranted when moderate or deep sedation in the ED is readily available. If the emergency physician chooses to attempt closed reduction, the principles of procedural sedation and monitoring should be followed. The primary relative contraindication to closed reduction is the presence of a femoral neck fracture. Another relative contraindication is the presence of fractures in the dislocated extremity because such fractures preclude application of traction to the limb. Techniques of closed reduction are described next.

Reduction Techniques. Stimson's technique and the Allis technique are the methods most commonly used for reduction of posterior hip dislocations[25] (Fig. 56-25). The Allis technique usually is effective for both posterior and obturator dislocations (Fig. 56-26). It is perhaps the most commonly used method for hip reductions in the ED.

Allis technique for reduction of posterior hip dislocation:

1. The patient is placed in the supine position, and the pelvis is stabilized by an assistant.
2. With the knee flexed, the operator applies steady traction in line with the deformity.
3. The hip is slowly brought to 90 degrees of flexion while steady upward traction and gentle rotation are applied.
4. The assistant pushes the greater trochanter forward toward the acetabulum.
5. Once reduction has been achieved, the hip is brought to the extended position while traction is maintained.

Stimson's technique (Fig. 56-27) uses the weight of the limb and the force of gravity to reduce the dislocation and is relatively atraumatic. Although Stimson's technique generally is effective,

www.ketabpezeshki.com 66485457-66963820

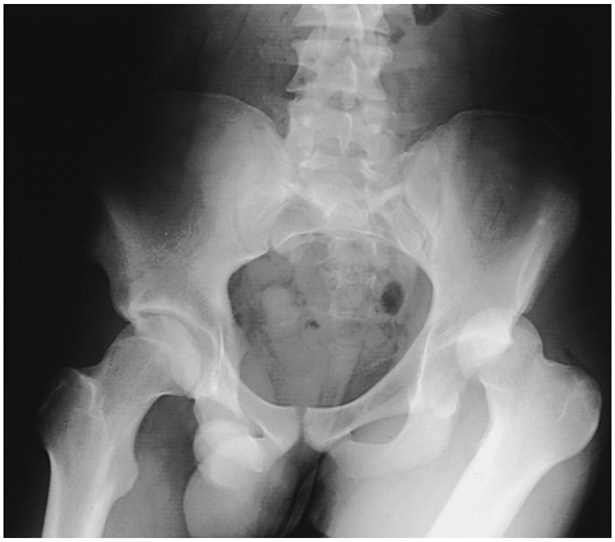


Figure 56-25. Radiograph of posterior dislocation identified by loss of the lesser trochanter on the anteroposterior view.

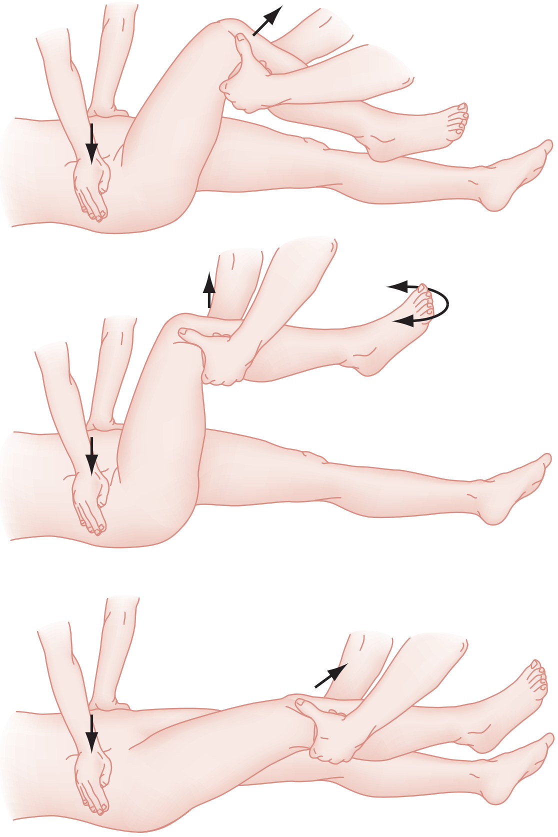


Figure 56-26. The Allis technique for hip reduction. See text for a description of this method.

placing an acutely and often multiply injured trauma patient in the required prone position may be a challenge. Adequate radiographic clearance of the spine usually has not yet been accomplished, and the administration of sedatives and analgesics in a prone patient has inherent risks.

Stimson's technique for reduction of posterior hip dislocation:

1. The patient is placed in a prone position, with the leg hanging over the edge of the bed. The hip and knee are flexed at 90 degrees.

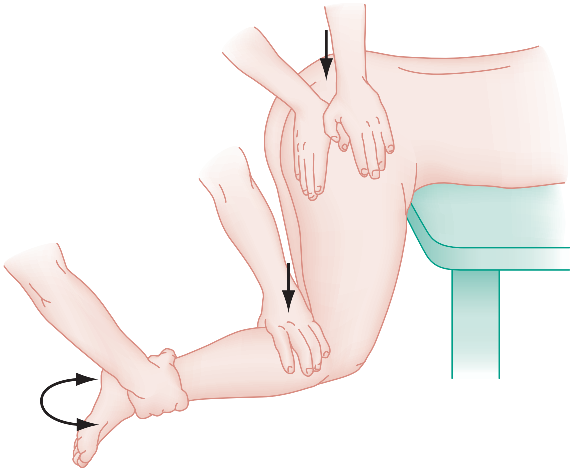


Figure 56-27. Stimson's technique for hip reduction. See text for a description of this method.

2. An assistant stabilizes the pelvis.
3. The operator applies steady downward traction in line with the femur.
4. The femoral head is gently rotated, and the assistant pushes the greater trochanter anteriorly toward the acetabulum.
5. Once reduction has been achieved, the hip is brought to the extended position while traction is maintained.

Other techniques for closed reduction of posterior hip dislocations include the Rochester method,[75] the Whistler method,[76] and the traction-countertraction technique.[77]

Closed reduction of a pubic dislocation can be quite difficult. The anterior position of the femoral head will resist flexion, making the Allis technique impossible. The following sequence of maneuvers is recommended:

Technique for reduction of pubic dislocation:

1. The patient is placed in the supine position.
2. Longitudinal traction is applied in line with the deformity.
3. The hip is hyperextended and internally rotated as an assistant applies downward pressure on the femoral head.

Although prompt anatomic reduction is clearly desirable, multiple attempts at reduction in the ED should be avoided because of potential damage to the articular surface and because the incidence of osteonecrosis increases with the number of attempts at reduction as well as the duration of the dislocation. Difficulty with reduction is usually the result of incarceration of a tendon, a capsular structure, or an osteochondral fragment that is blocking reduction. In the case of an irreducible dislocation, closed reduction with the patient under general anesthesia or an open reduction procedure often is required.

Postreduction Management. After closed reduction, the hip should be tested for stability, which is accomplished by gently taking it through a full range of motion to see whether it will redislocate. After testing has ensured stability, the injured extremity should be placed in a knee immobilizer and an abduction pillow should be applied to prevent repeat dislocation. An AP radiograph of the pelvis should be obtained to verify the adequacy of reduction. The radiograph should be carefully inspected to verify that the femoral head is in the acetabulum, the shaft of the femur is in neutral position, Shenton's line is intact, and the profile of the lesser trochanter is well visualized. The intra-articular space should be symmetrical and, when measured, of the same depth as in the unaffected joint. Asymmetry signals an entrapped intra-articular fragment and is an indication for CT scanning (Fig. 56-28).

www.ketabpezeshki.com 66485457-66963820

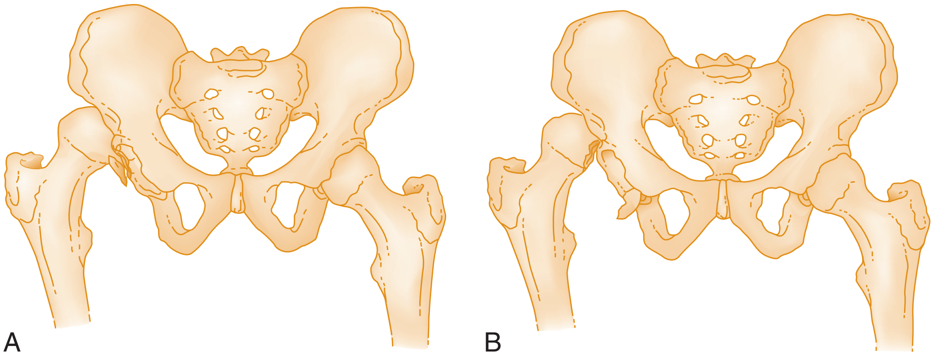


Figure 56-28. **A,** A fracture through the femoral head is seen with this anterior hip dislocation. **B,** Incomplete reduction is identified by examination of the joint space. This space should be the same width as in the unaffected joint. Asymmetry signals an entrapped intra-articular fragment, which should be verified by computed tomography scan.

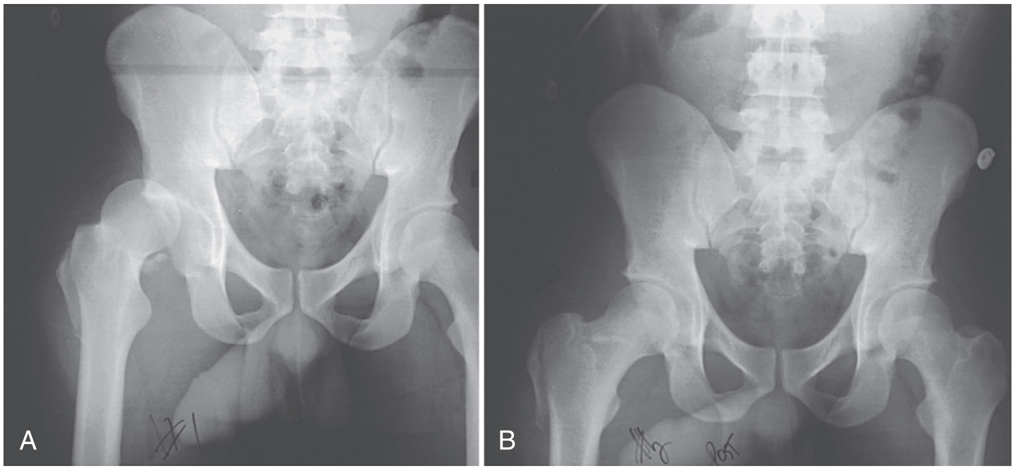


Figure 56-29. **A,** Anterior hip dislocation is identified as the lesser trochanter is brought into profile. Note the fracture of the lateral aspect of the greater trochanter. **B,** A postreduction radiograph demonstrates adequate reduction with symmetrical joint spaces.

Outcomes. The precarious blood supply to the femoral head is particularly important with regard to the long-term consequence of hip dislocations. The development of AVN of the femoral head has been reported in 1 to 17% of dislocations.[74] Other risk factors for the development of AVN include the total dislocation time, the severity of the injury, the number of reduction attempts, and the presence of comorbid conditions.

Fracture-Dislocation of the Femoral Head

Epidemiology and Mechanism. Hip dislocations may be associated with fractures of the femoral head (Fig. 56-29A). Femoral head fracture occurs in 35 to 55% of anterior hip dislocations and in 10 to 16% of posterior hip dislocations.[78] These injuries are almost always the result of high-speed vehicular trauma. Because of the tremendous force required to produce this injury pattern, coexistent multisystem trauma is the rule.

When a femoral head fracture and hip dislocation coexist, patients assume the position typical for the dislocation. Hip mobility is markedly reduced, and pain usually is severe. After initial stabilization, the involved extremity should be carefully examined for associated fractures of the femoral shaft and knee. The neurovascular examination should assess for femoral or sciatic nerve injury. Radiographs should be evaluated carefully for any femoral head fracture in all patients with hip dislocations. Evidence for fracture of the femoral head can be subtle. These fractures may be detected on radiographs by following the curve of the dislocated head and the acetabular cup to search for a small fragment that may otherwise be overlooked. Known or suspected injuries can be further defined by CT or MRI.[73,78]

In most cases, satisfactory results can be obtained with closed reduction (see Fig. 56-29B).[73] Several experts recommend obtaining a CT scan of the hip before closed reduction to further define the injury and locate fracture fragments.[73] If the hip cannot be reduced by manipulation or if reduction of the femoral head fragment is unsatisfactory, open reduction will be required.

Dislocation of Hip Prosthetics

An increasing number of patients have undergone hip arthroplasty. In addition to those procedures performed for treatment of femoral neck fractures, more than 230,000 patients undergo elective primary THA each year.[79] Postoperative dislocation may occur in 0.5 to 3% of patients with primary THA and in 5 to 27% of patients with a revised THA.[80] Although most dislocations take place within 3 months of surgery, "late dislocations" have been reported up to 10 years after the operative procedure; such dislocations can result from major trauma or from trivial events (e.g., rising from a seated position). Posterior dislocations account for 75 to 90% of cases (see Fig. 56-13).[79] Reduction techniques for prosthetic hip dislocations are identical to those described earlier. Consultation with an orthopedic surgeon is essential for safe reduction and development of a long-term treatment plan for the patient. Reduction of the prosthesis does not carry the same

www.ketabpezeshki.com 66485457-66963820

urgency as for reduction of a dislocated native hip because there is no risk for the development of AVN once the femoral head has been replaced. Traction on the sciatic nerve can occur, however, making early reduction more compelling. In addition, the reduction itself carries the unique dangers of loosening of the components, fracturing of the surrounding bone, and movement of the acetabular cup. Reduction is best performed with an orthopedic consultant.

Soft Tissue Injuries

Soft tissues may be subject to muscle or tendon strain or contusions from misuse, overuse, or accidental trauma. Rupture, hemorrhage, or myositis ossificans may develop in muscles.

Muscular Injuries

Strenuous exercise in a poorly conditioned person, sudden exertion, and direct trauma all may traumatize soft tissues. Cold temperature, vascular or infectious disease, fatigue, and poor training are known predisposing conditions for muscular injury.[81]

A detailed classification system of muscular injuries has been devised, but it is of little clinical significance for the emergency physician. Classification of complete and partial tears is reasonable and of greater clinical utility. Partial tears are reversible injuries that are aggravated by movement or tension. Mild spasm, swelling, ecchymosis, and tenderness cause minor loss of function and strength. Complete tears produce a palpable depression, and the torn muscle edge also is often palpable. Other possible findings include severe spasm, swelling, ecchymosis, tenderness, and loss of muscle function. In significant muscle strains, radiographs are needed to evaluate for the possibility of an accompanying bone avulsion injury.

Initial management of incomplete tears traditionally includes the local application of ice for the first 48 hours, followed by heat.

Compressive wraps cause distal venostasis with the potential for distal venous clot formation and do not significantly decrease recovery time. A regimen of nonsteroidal anti-inflammatory agents to achieve sufficient analgesia is important for recovery and patient satisfaction. Muscle relaxants may be useful when the injury is accompanied by muscular spasm. In general, complete rest of the affected muscle should be maintained, with the recommendation of "weightbearing as pain tolerated." This progressive muscle loading can be started within 3 to 5 days once sufficient scar has formed. In order to prevent reinjury, the muscle loading should be limited by the patient's pain. Any patient with significant injury should be referred for physical therapy.

A complete muscle tear is a serious condition. Consultation plus follow-up care with an orthopedic surgeon or sports medicine specialist is vital for these patients.

Sports Injury Patterns. Athletes commonly experience muscular injury from accidents and overtraining. The two most common injuries involve the hamstrings and the quadriceps.

The Hamstrings. Hamstring muscle strains are common in sports involving running and sudden acceleration. The injury is accompanied by sudden intense pain in the posterior aspect of the thigh. Any active or passive motion at the hip is poorly tolerated because of the intense pain that movement causes. Ischial avulsion fractures can occur, and pelvic radiographs should be obtained if the examination reveals bony tenderness. Crutches and toe-touch weightbearing are recommended until the patient is evaluated by a physician trained in sports medicine. *Toe-touch weightbearing* refers to walking with crutches while the toes of the injured extremity rest on the ground without placing any weight on it. Appropriate weight-training programs have been shown to speed rehabilitation of this injury. Complete recovery from a hamstring muscle strain may take weeks to months.

The Quadriceps. The quadriceps is the most common muscular group to sustain complete tears. This injury occurs when the muscles are contracted suddenly against the body's weight, as may occur when an athlete slips or stumbles and attempts to avoid a fall. Ambulation is significantly affected. There is pain with active and passive knee extension. In significant tears, the patient may be unable to actively extend the knee or maintain its extension against gravity. A palpable depression just proximal to the superior pole of the patella suggests a complete tear. It is imperative to document an intact patellar mechanism on examination because a complete tear of the quadriceps most often requires surgical repair and extensive rehabilitation.

Iliopsoas Strain. Gymnasts and dancers are the group of athletes most likely to experience an injury to the iliopsoas as a result of sudden forceful hip flexion against resistance. Severe pain often is experienced in the groin, thigh, or low back region. Severe intra-abdominal pain is common at the muscle origin and may dominate the clinical picture. Examination reveals groin tenderness and pain with active hip flexion. Radiographs of the femur should be obtained to identify an avulsion fracture of the lesser trochanter. CT frequently will demonstrate a large hematoma. Bed rest with partial flexion at the knee and hip generally is required for 7 to 10 days. With severe strains, symptoms may persist for 2 to 3 months.

Hip Adductor Strain. Injury to the hip adductors occurs as the thigh is forcefully abducted, as in a straddle injury. The patient reports pain in the groin, the pubic region, and the medial proximal aspect of the thigh. Abduction and adduction often are limited because of pain. Swelling and skin discoloration may confirm presence of the tear. If the tear is complete, a defect in the muscle may be felt by the examiner along the medial aspect of the thigh near the groin. Treatment is conservative, with patients initially benefiting from rest, with gradual progression in a stretching and strengthening program.

Gluteus Muscle Strain. The gluteus muscles may be injured with vigorous or forced hip extension, as seen in track-and-field jumping events. The pain typically is less severe than that associated with injuries to other muscle groups. The hip is tender when extended or abducted.

Tendon Injuries

Clinically, tendon strains tend to have a more insidious onset than that typical for muscle strains. These strains may occur at the attachment of the muscles to the superior or inferior pubic ramus, the pubic symphysis, the ischium, and the femur.

A *groin pull* is the lay term for an injury to the tendons of the hip adductors. One study found adductor strains to be the most common groin injury in athletes, with 62% of the cases involving the adductor longus muscle.[81] The adductor magnus and brevis and the pectineus often are involved as well.[82] This injury commonly occurs in skaters and cross-country skiers when an accidental stress abducts the thigh during a powerful contraction of the adductors. These muscles also may be injured from overuse in an unconditioned patient. Local pain is noted at the inferior pubic ramus and the ischial tuberosity. Extension, abduction, and adduction of the hip are painful. The pain may radiate to the back of the thigh.

Pain over the greater trochanter may represent tendon strain of the attachments of the gluteus medius, gluteus minimus, tensor fasciae latae, or piriformis. The pain is aggravated by resisted abduction. Tenderness in the groin and painful hip movement suggest a strain of the iliopsoas tendon at its attachment to the lesser trochanter. Trochanteric bursitis, peritendinitis, AVN, neoplasm, and other possible causes should be considered.

Treatment of a tendon strain is similar to that for other soft tissue injuries. The use of crutches with weightbearing as tolerated

www.ketabpezeshki.com 66485457-66963820

Figure 56-30. Plain radiograph showing irregular articular surfaces and periarticular sclerosis consistent with osteitis pubis.

(i.e., as pain permits) is helpful for the first 2 weeks. Opioid analgesics and a short course of anti-inflammatory agents should be given. Complete tendon disruption may require surgical repair.

Osteitis Pubis

Osteitis pubis is a poorly understood disorder. It is characterized by pubic symphysis pain and joint disruption and is most common in distance runners and soccer players.[83] The adductor muscles act as a "compression strut," displacing forces across the hip. The most likely mechanism is repetitive pulling of the adductor muscles, causing increased shearing at the pubic symphysis.

Clinically, patients have groin pain of insidious onset, with most reporting pain at the symphysis and adductor muscles.[84] Pain usually can be elicited on palpation of the symphysis and also can be provoked by adduction of the hip or by sit-ups. Plain radiographs show widening of the symphysis, irregular contour of the articular surfaces, or periarticular sclerosis (a late finding) (Fig. 56-30). These features are not specific and in one study were seen in 76% of asymptomatic soccer players. MRI is the imaging study of choice and will show marrow edema on T2 images early in disease. Osteitis pubis has been associated with spontaneous cases of pubic symphysis osteomyelitis, and this should be considered in the differential diagnosis.[84]

Treatment is conservative, and in most cases the process is self-limited. Patients benefit from activity modification, good shoe wear, and therapy addressing flexibility and strength of the pelvic and hip musculature. Average time to heal has been reported to be 9 months. Owing to the length of healing associated with these injuries, follow-up care should be arranged at the time of initial injury to prevent unnecessary ED visits.

Vascular Injuries

Hip dislocations and femoral fractures may have associated arterial injury. The vessel may be partially lacerated, dissected, completely severed, or thrombosed. Lack of distal arterial flow may also represent a stretched vessel in spasm. The superficial femoral artery is most commonly injured with trauma to the hip and thigh. The common and the deep femoral arteries are less frequently injured. In the acute setting, penetrating trauma is the usual mechanism of injury. Arterial injury with femoral shaft fractures is rare. Anterior- and superior-type dislocations may produce femoral artery injury.[25]

Comparative blood pressures obtained by Doppler examination in the injured and uninjured extremities at the ankle may be useful in suspected arterial injuries. If the systolic pressure in the affected extremity is 90% or less (index less than 0.9) than that in the unaffected extremity, additional diagnostic studies should be undertaken. The ABI also can be similarly determined by comparing the systolic pressures of the affected extremity and of the ipsilateral arm. An index less than 0.9 necessitates further diagnostic studies.[23] Additional diagnostic studies include Doppler flow ultrasound imaging, CT angiography, and angiography alone. CT angiography, however, is becoming more prevalent, with recent studies showing 96 and 97% sensitivity and specificity, respectively, when compared with conventional radiography.[85]

Diagnostic evaluation must not delay surgical exploration when clinical signs and symptoms of vascular injury are obvious. These hard signs and symptoms of injury include active or pulsatile hemorrhaging, expanding or pulsatile hematoma, diminished or absent pulses, auscultated bruit or palpable thrill, and evidence of limb ischemia. Early restoration of blood flow is essential to prevent ischemic damage to the leg.

Neurologic Injuries

Peripheral nerve injury can be caused by trauma, infectious agents, and degenerative disease. In trauma, nerves may be injured by a blunt object that causes a contusion, by a sharp penetrating object that produces a partial or complete tear, or by stretch. Nerves are particularly vulnerable to prolonged ischemia, which can lead to necrosis. Compression of the nerve from a hematoma or a dislocated femoral head may also appear as a neurapraxia manifested by transient loss of conductivity. The femoral and sciatic nerves are rarely injured with femoral shaft fractures because they are encased in muscle throughout the length of the thigh.

Treatment of neurovascular compromise from a hip dislocation or a displaced femoral fracture consists of immediate reduction to ensure limb viability. Whenever possible, reduction should be accomplished before transfer of the patient to another treatment center.

Femoral Nerve. When the femoral nerve is injured, the iliac and femoral arteries are commonly involved because of their anatomic proximity. The femoral nerve is most often traumatized in penetrating trauma of the pelvis, groin, or thigh. Femoral neuropathy can occasionally result from compression by a hematoma within the abdominal wall or the iliopsoas as a complication of hemophilia, anticoagulant therapy, or severe trauma.[86]

The motor deficit in complete femoral neuropathy manifests as marked weakness of knee extension. The patient is able to walk on level ground yet has extreme difficulty walking up stairs or an incline. Patients cannot rise from a sitting position because of significant proximal muscle weakness. The sensory deficit varies but is localized along the anterior aspect of the thigh and medial lower aspect of the leg. The most reliable spot for testing for a sensory deficit is just superior and medial to the patella. The deep tendon reflex of the knee will be diminished or absent with such deficits.

If a traumatic neuropathy is suspected, immediate orthopedic consultation should be obtained. Nerve exploration and repair generally are preferred for penetrating trauma and when direct impingement on the nerve by bone fragments or hematoma is suspected. Surgical exploration and drainage of a hematoma that is impinging on the femoral nerve are appropriate.

www.ketabpezeshki.com 66485457-66963820

Figure 56-31. Development of the femoral head and neck with its growth plates and two primary ossification centers.

Progressive nontraumatic neuropathies warrant urgent neurology consultation. With a chronic neuropathy, atrophy of the anterior aspect of the thigh will already have developed. The motor deficits were discussed previously.

Sciatic Nerve. Sciatic injury is rare with femur fractures, but occasionally it may be the result of traction used to stabilize the fracture during the initial management period. Complete traumatic injury may result from a deep penetrating wound in the hip, thigh, or buttock. Posterior hip dislocations and fracture-dislocations produce sciatic neurapraxia in 10 to 14% of these injuries.[25,71] Patients with complete sciatic neuropathy have paralysis of the hamstring muscles and all muscles below the knee. With partial injury, a peroneal palsy with weakness of the extensor hallucis longus muscle is the most sensitive clinical sign. There is sensory loss below the knee and along the posterior aspect of the thigh. The deep tendon reflex at the ankle is absent or diminished. Sciatic nerve palsy from inadvertent injection into the nerve or secondary to intraneural or extraneural hemorrhage in patients taking anticoagulants has been described.

Sciatic injury from posterior dislocations often consists of only transient loss of conductivity, particularly in motor fibers. Unfortunately, the other patterns of injury to the sciatic nerve carry the worst prognosis of all peripheral nerve injuries. The prognosis is poorest when the injury is proximal and complete. Even with optimal repair, recovery often is inadequate. Sciatic neuropathy is a disabling problem. Obvious atrophy of the lower part of the leg and foot develops, followed by ulceration of the sole of the foot and infection. A below-the-knee amputation frequently is necessary in these cases.

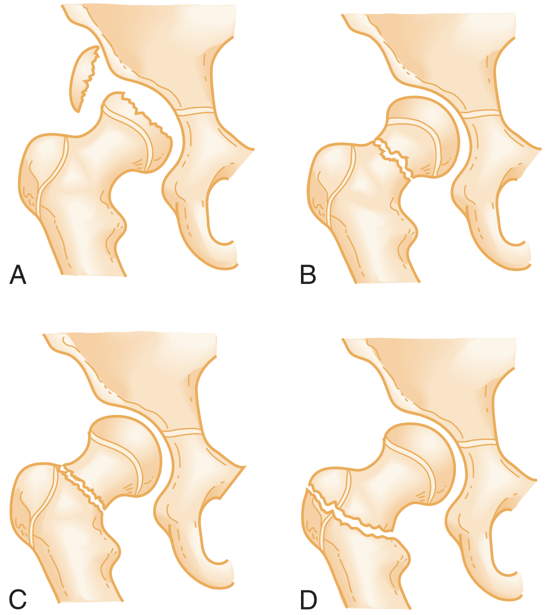


Figure 56-32. Pediatric proximal femoral fractures are classified by a system that separates fractures in the physis **(A)**, the transcervical area **(B)**, the cervicotrochanteric area **(C)**, and the intertrochanteric region **(D)**. (From Canale ST, Beaty JH: Fractures of the pelvis. In Rockwood JC Jr, Green DP, Bucholz RW (eds): Rockwood and Green's Fractures in Children, 5th ed, vol. 3. Philadelphia, JB Lippincott, 2001, pp 883-911.)

SPECIAL PEDIATRIC CONSIDERATIONS

Anatomy

Development of the femoral head and neck with its growth plates and two primary ossification centers is illustrated in Figure 56-31. A significant proportion of the pediatric hip is cartilage and developing new bone. For this reason, almost any type of trauma in this location carries the potential for premature growth arrest. Recognition that large portions of the pediatric hip are radiolucent will counter the tendency to focus attention on the ossified elements only.

Hip Dislocation

The incidence of hip fractures and dislocations is increasing in young patients, often as a result of high-energy trauma. Up to 50% of children with a hip dislocation also will have fractures elsewhere. In small children, dislocation of the hip is more common than femoral neck fractures. The force required to dislocate a pediatric hip is much less than that required in an adult because the acetabulum is less completely developed than in adults. Seemingly negligible trauma, such as tripping or a minor fall, may dislocate the femoral head in a young child. In a school-age child, athletic injuries are the major cause of traumatic hip dislocation. In the teenage years, MVCs predominate as the cause of hip dislocations.

Hip and Femur Fractures

The vast majority of pediatric hip fractures result from high-energy violent trauma. These fractures usually are the result of falling from heights, jumping out of a swing, being struck by a car, or a having a bicycle accident. Whereas a car commonly strikes an adult pedestrian at the tibial level, a smaller child most often is hit at the level of the hip, which results in a fracture there.

The Salter-Harris classification of fractures in the pediatric population is not used for hip fractures. The Delbet classification is a well-accepted system used for pediatric femoral fractures.[87] This system separates fractures through the physis and the transcervical, cervicotrochanteric, and intertrochanteric regions (Fig. 56-32).

www.ketabpezeshki.com 66485457-66963820

Spiral Shaft Fractures

If seemingly trivial trauma has resulted in a spiral femoral shaft fracture in a child, nonaccidental trauma and pathologic fracture should be considered.[88,89] Common causes of pathologic fracture include unicameral bone cysts, fibrous dysplasia, osteogenesis imperfecta, and malignancy.[89]

Management. Although these pediatric injuries are extremely rare, their complications are significant. Unlike in an adult, a child's femur has growth potential, and any disruption carries the possibility of lifetime disability. Treatment of femoral shaft fractures in adults is aimed at prevention of the complications of prolonged immobilization. Unlike adults, children tolerate bed rest well, which allows more treatment options. The primary goal in children is prevention of the many complications common with femoral fractures. Premature closure of the physeal plate results in a valgus deformity of the hip. AVN, malunion, nonunion, and limb-length discrepancy all are complications frequently seen with pediatric femoral fractures. For these reasons, referral to a pediatric orthopedist is recommended.[87]

Child with a Limp

A child who comes to the ED with a limp presents a diagnostic challenge. Both life-threatening and benign disease processes can produce a limp. When the child is too young to give an adequate history, the cause becomes more elusive. The emergency physician should inquire about the chronology of the symptoms, the child's development (i.e., social milestones, weight gain, physical development), and diet. Associated illness and a family history may be helpful. Although identification of a specific causative disorder is challenging, the history and physical examination, combined with appropriate diagnostic modalities, will allow definitive diagnosis in most patients. An important point is that in the pediatric population, the knee is a common site for referred hip pain. Proper follow-up care is crucial to prevent additional morbidity in these children.

Evaluation of the Child's Gait

Gait is a learned, complex combination of motions produced through coordination of the musculoskeletal, peripheral, and central nervous systems. A limp is produced by anything that alters this process; the numerous clinical entities that may be associated with a limp can be divided into categories according to the underlying abnormality. Pain, muscle weakness, structural alteration, peripheral sensory deficit, and cerebellar or vestibular imbalance are major categories. A limp caused by pain is referred to as an "antalgic" gait. Conditions that disturb the biomechanics of the hip or cause the child pain may affect any of the elements of gait. Other conditions, such as cerebellar pathology or disease of the knee or foot, are discussed in their respective chapters.

Etiology of the Limp

Inflammation and Infection. Inflammation of the articular surface, the intra-articular synovium, or the joint capsule creates pain. Weightbearing increases the pain. The child limps in an attempt to limit the time during which the affected hip bears the body's weight.

Transient synovitis (also known as *toxic synovitis*) is a common nonbacterial inflammatory clinical entity that can cause a limp. Little is known about its cause. It develops most frequently in boys 3 to 10 years of age. Clinically, the synovitis manifests as pain in the hip or knee. An antalgic gait is present, with minimal systemic symptoms. There is restriction of hip motion and associated muscle spasm, and the child often will refuse to bear weight on the hip. As the disease progresses, the joint capsule is increasingly stretched, and intra-articular pressure rises. The potential volume of the joint capsule is largest with the hip flexed, abducted, and externally rotated. The child prefers to lie in this position as the capsule begins to bulge, to minimize the tension and intra-articular pressure.

The diagnosis of transient synovitis is one of exclusion of more serious diseases that mimic this condition. Acute joint inflammation and pain may be associated with septic arthritis, juvenile rheumatic arthritis, systemic lupus erythematosus, Perthes' disease, and tuberculous arthritis. Ultrasound imaging of the hip joint will detect an effusion in 78% of cases of transient synovitis but cannot distinguish this condition from septic arthritis.[90] Joint aspiration may be required when the diagnosis is in doubt.

Distinguishing between transient synovitis and septic arthritis can be a diagnostic dilemma. Key predictors may include temperature higher than 38.5° C in the preceding week, non–weight-bearing status (refusal or inability to bear weight even with support), erythrocyte sedimentation rate higher than 40 mm/hr, and a white blood cell count greater than 12,000/mL. These four predictors were developed in a retrospective study and then validated in a prospective study.[91,92] Based on the validation study, the probability of septic arthritis was 2% for zero predictors, 9.5% for one predictor, 35% for two predictors, 73% for three predictors, and 93% for four predictors.[93]

The use of C-reactive protein (CRP) assay is becoming more prevalent in the evaluation of septic arthritis. A positive CRP (defined as a result greater than 2.0 mg/dL) has been identified as a strong independent risk factor for septic arthritis.[94,95] Taken together, all of these predictors should be used in conjunction with clinical assessment.

Acute bacterial infections of the hip and femur require early identification and intervention to minimize subsequent morbidity and disability.[93] Unfortunately, the diagnosis often is missed initially because the child may appear relatively nontoxic in the early phases of infection. Signs and symptoms of systemic illness usually accompany infection of the femur or hip. Fever, malaise, decreased oral intake, a limp, and refusal to bear any weight are common.[96] Whereas osteomyelitis most commonly develops in the metaphysis in adults, the physeal region often is the infected site in children. Septic arthritis (pyarthrosis) may result from hematogenous seeding or direct extension of osteomyelitis. The hip and the knee are the most commonly infected joints.

The causative agent in osteomyelitis and pyarthrosis is nearly always a gram-positive organism, usually *Staphylococcus.* The incidence of *Haemophilus influenzae* infection has fallen as a direct result of addition of that vaccine to the childhood immunization regimen. Neonates, asplenic children, and children with sickle cell anemia are at risk for infection with gram-negative organisms. *Salmonella* infection also is more often seen in patients with sickle cell disease–related osteomyelitis. Viral and rickettsial diseases (e.g., Lyme disease) have been identified in subacute cases.

Identification of acute osteomyelitis on plain radiographs is difficult until 2 to 3 weeks after onset of infection. Pyarthrosis may manifest with widening of the space between the femoral head and the acetabular roof and bulging of the joint capsule and surrounding soft tissues. This is seen as a change in the contour of the gluteus minimus and iliopsoas fat stripes (Fig. 56-33). Care should be taken to identify the normal shadow of the muscles and the joint capsule, as described earlier in this chapter (see Fig. 56-11). Plain radiographs are seldom useful in the initial identification of infection because visualization of a joint effusion has low sensitivity for pyarthrosis. Bone scan, MRI, CT, and ultrasound-guided joint aspiration are appropriate to diagnose a septic joint.

www.ketabpezeshki.com 66485457-66963820

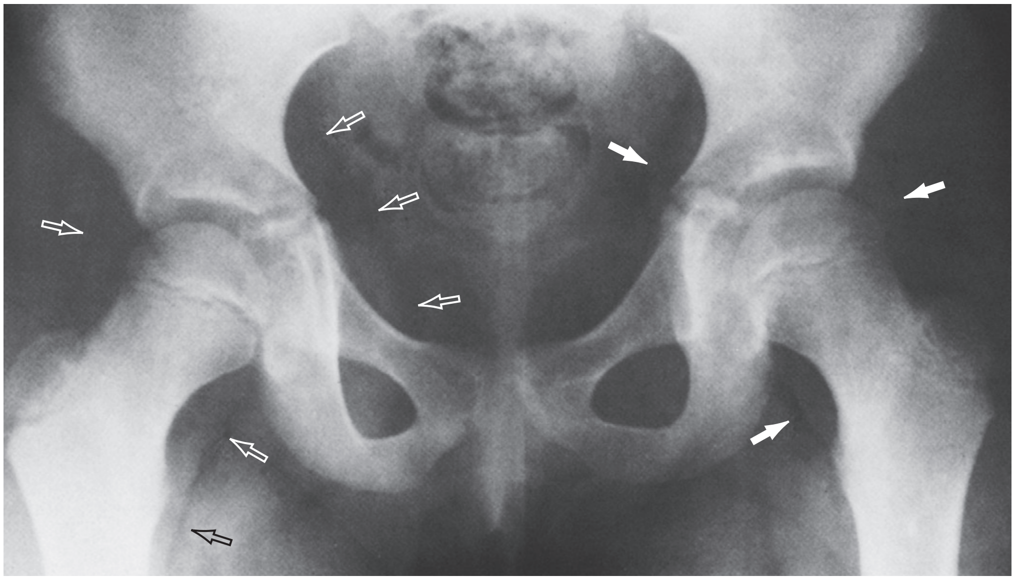


Figure 56-33. Prominence of the soft tissue shadows about the right hip, including bulging of the obturator internus muscle and its aponeurosis *(open arrows),* indicates distention of the joint capsule. The opposite hip shows the normal soft tissue shadows, indicated by the solid arrows. (From Harris JH, Harris WH, Novelline RA: The Radiology of Emergency Medicine, 3rd ed. Baltimore, Williams & Wilkins, 1993.)

The inflammatory process involved in the immune system's attempt to eradicate the intruder in pyarthrosis may also begin to destroy the body's own articular surfaces. Even with treatment, many children experience some arthritic disability.

Slipped Capital Femoral Epiphysis

Anatomy. The capital femoral epiphysis appears during the first year of life. The epiphysis of the greater trochanter appears by the age of 5 years and that of the lesser trochanter during the 13th year of life. All of these structures unite at age 17 to 19 years. The anatomic relationship has been compared with a scoop of ice cream sitting on a cone. This relationship remains symmetrical on both AP and frogleg lateral radiographs (Fig. 56-34A and B). Asymmetry in any view represents either SCFE or a subcapital fracture (Fig. 56-35).

Epidemiology and Pathophysiology. SCFE is the most common hip disorder in adolescents, with an incidence of approximately 5 per 100,000 population per year. From 25 to 50% of the cases are bilateral.[46,97] SCFE occurs twice as frequently in boys as in girls, with the respective peaks of incidence at the ages of 13 and 11 years.

Epidemiologic data have provided clues to the pathophysiology of this injury. SCFE is associated with the onset of puberty and is rare before the age of 10 years. It most commonly is seen in boys 10 to 17 years of age during their period of rapid growth. It is believed to be the result of a structural weakness in physeal cartilage associated with pubescence.[9]

The specific cause of SCFE is not well understood, and most cases are deemed idiopathic. There are likely genetic and environmental factors that influence the development of SCFE. It occurs more frequently in male African Americans than in the Caucasian population and has seasonal and geographic variation.[9] Other risk factors identified are obesity, previous irradiation or chemotherapy, renal osteodystrophy, hypothyroidism, and neglected septic arthritis.[98]

Clinical Features. SCFE is usually an insidious process extending over weeks to months. Initially, the only complaint may be slight discomfort in the groin, thigh, or knee after activity. Shear stress combined with a weaker physeal plate leads to slippage of the epiphysis inferiorly and posteriorly in the direction of weight-bearing force. Pain worsens as slippage progresses, and eventually

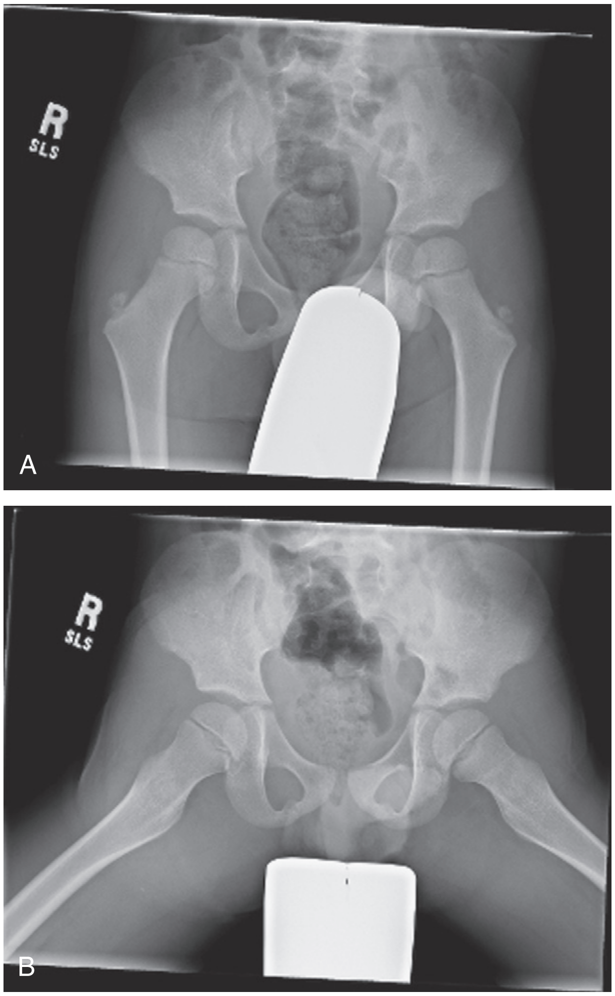


Figure 56-34. Anteroposterior **(A)** and frogleg lateral **(B)** radiographs obtained in a young boy demonstrate the normal anatomic relationship of the capital femoral epiphysis, the proximal physis, the apophysis of the lesser trochanter, and the triradiate synchondrosis.

www.ketabpezeshki.com 66485457-66963820

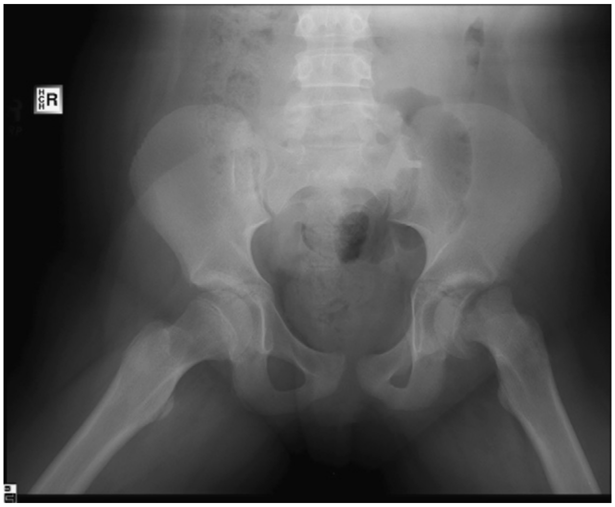


Figure 56-35. Frank slippage of the capital femoral epiphysis of the left hip. The capital femoral epiphysis is displaced medially, inferiorly, and posteriorly.

pain may occur at rest as well. Referred pain to the knee is a classic manifestation, and patients frequently have groin, thigh, or knee pain rather than hip pain. This presentation often causes delay in diagnosis, potentially increasing displacement and worsening the prognosis.[99] Parents often bring the child in for medical evaluation when they notice the child beginning to limp. Physical examination may reveal hip tenderness, decreased hip range of motion, and an abducted, externally rotated thigh.

Diagnostic Strategies and Treatment. Children with unexplained hip or knee pain merit clinical as well as radiographic evaluation. Initially, AP, lateral, and frogleg lateral radiographs of the hip should be obtained. The frogleg lateral projection shows the hip in a plane midway between the AP and lateral views. The earliest radiographic findings are subtle, with the abnormality visualized on only one projection. The most reliable initial finding with SCFE is asymmetry of the femoral epiphysis in relation to the neck. Small amounts of slippage can be detected by examining the epiphyseal edge as it becomes flush with the superior border of the femoral neck. This can be visualized as "the scoop slipping off the ice cream cone." The dome of the epiphysis may be flattened. On the radiograph, a line drawn along the superior margin of the femoral neck (Klein's line) should intersect some part of the normal femoral head. Failure of this line to intersect the head indicates medial and posterior movement of the head on the epiphysis.[97] Comparative views of the two hips are indicated if initial radiographic findings are equivocal. If occult fracture is suspected, MRI or CT should be performed.[27,100] The goal of treatment is to prevent further slippage and subsequent injury to the physis. The patient should be placed on non–weight-bearing status and referred for orthopedic management. Surgery is required to anchor the epiphysis and prevent further slippage.

Perthes' Disease. *Perthes' disease* is the name given to AVN of the pediatric femoral head (Fig. 56-36). It also has been called *Legg-Calvé-Perthes disease* and *Calvé-Perthes disease.* A majority of cases are diagnosed at ages 4 to 8, with the peak incidence at 6 years. It occurs five times more often in boys than in girls and affects both hips 15 to 24% of the time.[101]

Patients classically have a unilateral, often painless limp of insidious onset. As the disease progresses, pain becomes nearly constant and typically is exacerbated by activity and exercise. Treatment is controversial and determined by progression of disease and age at diagnosis.

Isolated Fracture of the Greater or Lesser Trochanter in Children. An isolated fracture of the greater trochanter is a rare injury. In

Figure 56-36. Perthes' disease affecting the left hip. Similar collapse of the femoral head as seen in adults. (From Kocher MS, Tucker R: Pediatric athletic hip disorders. Clin Sports Med 25:241, 2006.)

Figure 56-37. Forceful contraction of the iliopsoas muscle results in avulsion of the lesser trochanter. (From Kocher MS, Tucker R: Pediatric athletic hip disorders. Clin Sports Med 2006; 25:241.)

children, this fracture occurs when the entire greater trochanteric epiphysis is avulsed from the femur. Children and adolescents aged 7 to 17 years are most commonly affected. The mechanism of injury generally is a powerful muscular contraction of the lateral rotators of the hip joint during a twisting fall. If the fragment is large and displaced by more than 1 cm, open reduction and internal fixation may be indicated.

An isolated fracture of the lesser trochanter occurs when a forceful contraction of the iliopsoas muscle avulses the lesser trochanter from the physis during sudden hip flexion (Fig. 56-37). Eighty-five percent of all cases occur in patients younger than 20 years, with a peak incidence in males between aged 13 to 17 years.[102] Marked tenderness can be elicited in the femoral triangle, and hip flexion against resistance is painful. Clinically, the seated patient is unable to lift the foot of the affected leg from the floor. Treatment of an isolated lesser trochanter avulsion fracture usually

www.ketabpezeshki.com 66485457-66963820

involves bed rest and early mobilization. Painless active hip motion is achieved within 3 weeks.

ACKNOWLEDGMENT

We would like to thank Drs. James F. Fiechtl and Robert W. Fitch for their work on this chapter in previous editions.

KEY CONCEPTS

- Hip dislocation is an orthopedic emergency. The likelihood of its complication, AVN, is related to both the initial degree of trauma and the amount of time the femoral head remains out of joint. Reduction of the hip within 6 hours after dislocation significantly decreases the incidence of AVN.
- Postreduction radiographs should be obtained to ensure the adequacy of reduction and assess for other injuries.
- When a painful hip makes ambulation difficult and plain radiographs do not reveal a fracture, CT or MRI should be performed. MRI is the gold standard.
- With intertrochanteric fracture, hemodynamic instability may result from dehydration and blood loss of up to 3 units into the fracture site. Up to 70% of patients with these injuries are under-resuscitated.
- It is important to identify acetabular fractures before closed reduction is attempted because intra-articular bone fragments may interfere with effective reduction.
- Slipped capital femoral epiphysis is most commonly seen in African American boys 10 to 17 years of age; 25% of cases are bilateral. The most reliable initial finding with SCFE is asymmetry of the femoral epiphysis in relation to the neck, wherein small amounts of slippage give the appearance of "the scoop slipping off the ice cream cone."

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Paré A: *The Work of That Famous Chirurgeon, Ambrose Paré,* translated out of Latin and compared with the French by Tho Johnson, book XV. London: T Cotes & R Young; 1634.
2. Von Langenbeck B: Verhandld, Deutch, p 92. Gesellsch F, Chir 1878. As found in Davis GG: The operative treatment of intracapsular fracture of the neck of the femur. *Am J Orthop Surg* 1908-1909; 6:481.
3. National Osteoporosis Foundation: *America's Bone Health: The State of Osteoporosis and Low bone Mass in Our Nation*. Washington, DC: National Osteoporosis Foundation; 2002.
4. Koval KJ, Zuckerman JD: Functional recovery after fracture of the hip. *J Bone Joint Surg Am* 1994; 77:751.
5. Burge R, et al: Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *J Bone Miner Res* 2007; 22:465-475.
6. Dominguez S, Liu P, Roberts C, Mandell M, Richman PB: Prevalence of traumatic hip and pelvic fractures in patients with suspected hip fracture and negative initial standard radiographs—a study of emergency department patients. *Acad Emerg Med* 2005; 12:366-369.
7. Kesmezacar H, Aynan E, Uniu M, Seker A, Karaca S: Predictors of mortality in elderly patients with an intertrochanteric or a femoral neck fracture. *J Trauma* 2010; 68:153-158.
8. Perry DC, Hall AJ: The epidemiology and etiology of Perthes disease. *Orthop Clin North Am* 2011; 42:279-283.
9. Lehmann CL, Arons RR, Loder RT, Vitale MG: The epidemiology of slipped capital femoral epiphysis: An update. *J Pediatr Orthop* 2006; 26:286-290.
10. Gray H: *Anatomy, Descriptive and Surgical*, revised from English, 17th ed. New York: Bounty Books; 1997.
11. Lane NE: Epidemiology, etiology, and diagnosis of osteoporosis. *Am J Obstet Gynecol* 2006; 194:S3.
12. Gehibach SH, Avrunin JS, Puleo E: Trends in hospital care for hip fractures. *Osteoporos Int* 2007; 18:585.
13. Brunner LC, Eshilian-Oates L: Hip fractures in adults. *Am Fam Physician* 2003; 67:537.
14. Mathers C, Fat DM: *The Global Burden of Disease—2004 Update*. Geneva: World Health Organization; 2004.
15. Lane NE: Osteoarthritis of the hip. *N Engl J Med* 2007; 357:1413.
16. Lavernia CJ, Sierra RJ, Grieco FR: Osteonecrosis of the femoral head. *J Am Acad Orthop Surg* 1999; 7:250-261.
17. Mont MA, Jones LC, Hungerford DS: Nontraumatic osteonecrosis of the femoral head: Ten years later. *J Bone Joint Surg Am* 2006; 88:1117-1132.
18. Sahin V, et al: Traumatic dislocation and fracture dislocation of the hip: A long-term follow-up study. *J Trauma* 2003; 54:520.
19. Bachiller FG, Caballer AP, Portal LF: Avascular necrosis of the femoral head after femoral neck fracture. *Clin Orthop Relat Res* 2002; 399:87.
20. Järvinen TA, et al: Muscle injuries: Optimising recovery. *Best Pract Res Clin Rheumatol* 2007; 21:317.
21. Beiner JM, Jokl P: Muscle contusion injury and myositis ossificans traumatica. *Clin Orthop Relat Res* 2002; 403:S110.
22. Muir B: Myositis ossificans traumatica of the deltoid ligament in a 34 year old recreational ice hockey player with a 15 year post-trauma follow-up: A case report and review of the literature. *J Can Chiropr Assoc* 2010; 54:229-242.
23. Vestergaard P, et al: Corticosteroid use and risk of hip fracture: A population-based case-control study in Denmark. *J Intern Med* 2003; 254:486.
24. Koval KJ, Chen AL, Aharonoff GB, Egol KA, Zuckerman JD: Clinical pathway for hip fractures in the elderly: the Hospital for Joint Diseases experience. *Clin Orthop Relat Res* 2004; 425:72.
25. Tornetta P: *Hip dislocations and fractures of the femoral head*. In: Bucholz RW, Heckman JD, Court-Brown JM, Tornetta P, eds. *Rockwood and Green's Fractures in Adults*, 7th ed. Philadelphia: JB Lippincott; 2009.
26. Feliciano DV: Management of peripheral arterial injury. *Curr Opin Crit Care* 2010; 16:602-608.
27. Harris JH, Harris WH, Novelline RA: *The Radiology of Emergency Medicine*, 3rd ed. Baltimore: Williams & Wilkins; 1993.
28. Rizzo PF, Gould ES, Lyden JP, Asnis SE: Diagnosis of occult fractures about the hip: Magnetic resonance imaging compared with bone scanning. *J Bone Joint Surg Am* 1993; 73:395.
29. Lubovsky O, Liebergall M, Mattan Y, Weil Y, Mosheiff R: Early diagnosis of occult hip fractures MRI versus CT scan. *Injury* 2005; 36:788.
30. Perron AD, Miller MD, Brady WJ: Orthopedic pitfalls in the emergency department: Radiographically occult hip fracture. *Am J Emerg Med* 2002; 20:234.
31. Vidán M, Serra JA, Moreno C, Riquelme G, Ortiz J: Efficacy of a comprehensive geriatric intervention in older patients hospitalized for hip fracture: A randomized controlled trial. *J Am Geriatr Soc* 2005; 53:1476-1482.
32. Schnell S, Friedman SM, Mendelson DA, Bingham KW, Kates SL: The 1-year mortality of patients treated in a hip fracture program for elders. *Geriatr Orthop Surg Rehabil* 2010; 1:6-13.
33. Wood SP, Vrahas M, Wedel SK: Femur fracture immobilization with traction splints in multisystem trauma patients. *Prehosp Emerg Care* 2003; 7:241.
34. Parker MJ, Handoll HH: Pre-operative traction for fractures of the proximal femur in adults. *Cochrane Database Syst Rev* 2006; 3:CD000168.
35. Brillman J, Quenzer RW: *Infectious Disease in Emergency Medicine*, 2nd ed. Philadelphia: Lippincott-Raven; 1998.
36. Mithöfer K, Lhowe DW, Vrahas MS, Altman DT, Altman GT: Clinical spectrum of acute compartment syndrome of the thigh and its relation to associated injuries. *Clin Orthop Relat Res* 2004; 425:223.
37. Rupp T, Delaney KA: Inadequate analgesia in emergency medicine. *Ann Emerg Med* 2004; 43:494.
38. Fletcher AK, Rigby AS, Heyes FLP: Three-in-one femoral nerve block as analgesia for fractured neck of the femur in the emergency department: A randomized controlled trial. *Ann Emerg Med* 2003; 41:227.
39. Mutty CE, Jensen EJ, Manka MA Jr, Anders MJ, Bone LB: Femoral nerve block for diaphyseal and distal femoral fractures in the emergency department. *J Bone Joint Surg Am* 2007; 89:2599.
40. Beaudoin FL, Nagdev A, Merchant RC, Becker BM: Ultrasound-guided femoral nerve blocks in elderly patients with hip fractures. *Am J Emerg Med* 2010; 28:76-81.
41. Spektor M, Kelly J: *Nerve blocks of the thorax and extremities*. In: Roberts J, Hedges J, eds. *Clinical Procedures in Emergency Medicine*, 5th ed. Philadelphia: WB Saunders; 2010.
42. Harkness JW: *Arthroplasty of the hip*. In: Canale ST, ed. *Campbell's Operative Orthopaedics*, 9th ed. St Louis: Mosby; 1998.
43. Hall MJ, DeFrances CJ, Williams SN, Golosinkly A, Schwartzman A: National Hospital Discharge Survey: 2007 summary. *Natl Health Stat Report* 2010; 29:1.
44. Liu SS, Della Valle AG, Besculides MC, Gaber LK, Memtsoudis SG: Trends in mortality, complications and demographics for primary hip arthroplasty in the United States. *Int Orthop* 2009; 33:643.
45. Shaw JA, Greer RB: *Complications of total hip replacement*. In: Epps CH Jr, ed. *Complications in Orthopedic Surgery*, 3rd ed. Philadelphia: JB Lippincott; 1994.
46. Kocher JS, Tucker R: Pediatric athlete hip disorders. *Clin Sports Med* 2006; 25:241.
47. Rossi F, Dragoni S: Acute avulsion fractures of the pelvis in adolescent competitive athletes. Prevalence, location, and sports distribution of 203 cases collected. *Skeletal Radiol* 2001; 30:127-131.
48. Gidwani S, Bircher M: Avulsion injuries of the hamstring origin—a series of 12 patients and management algorithm. *Ann R Coll Surg Engl* 2007; 89:394.
49. Johnell O, et al: Predictive value of BMD for hip and other fractures. *J Bone Miner Res* 2005; 20:1185.
50. Dobbs RE, Parvize J, Lewallen DG: Preoperative morbidity and 30-day mortality after intertrochanteric hip fractures treated by internal fixation or arthroplasty. *J Arthroplasty* 2005; 20:963.
51. Ahmad LA, Eckhof DG, Kramer AM: Outcome studies of hip fractures: A functional viewpoint. *Orthop Rev* 1994; 23:19.
52. Shorr AF, et al: Venous thromboembolism after orthopedic surgery: Implications of the choice for prophylaxis. *Thromb Res* 2007; 121:17.
53. De Boeck H: Classification of hip fractures. *Acta Orthop Belg* 1994; 60(Suppl 1):106.
54. Adunsky A, Lichtenstein A, Mizrahi E, Arad M, Heim M: Blood transfusion requirements in elderly hip fracture patients. *Arch Gerontol Geriatr* 2003; 36:75.
55. Huddleston JM, Whitford KJ: Medical care of elderly patients with hip fractures. *Mayo Clin Proc* 2001; 76:295.
56. Stern R: Are there advances in the treatment of extracapsular hip fractures in the elderly? *Injury* 2007; 38(Suppl 3):S77.
57. Lyles KW, et al: Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007; 357:1799.
58. Nork SE, Reilly MC: *Subtrochanteric fractures of the femur*. In: Browner BD, et al, eds. *Skeletal Trauma*. Philadelphia: Saunders; 2008.
59. Craig NJ, Maffuli N: Subtrochanteric fractures: Current management options. *Disabil Rehabil* 2005; 27:1181.

www.ketabpezeshki.com 66485457-66963820

60. Zlowodzki M, Bhandari M, Marek DJ, Cole PA, Kregor PJ: Operative treatment of acute distal femur fractures: Systematic review of 2 comparative studies and 45 case series (1989 to 2005). *J Orthop Trauma* 2006; 20:366-371.
61. Hafez HM, Woolgar J, Robbs JV: Lower extremity vascular injury: Results of 550 cases and review of the risk factors associated with limb loss. *J Vasc Surg* 2001; 33:122.
62. Hau T, et al: Fixation of femoral fractures in multiply-injured patients with combined chest and head injuries. *Aust N Z J Surg* 2003; 73:1018.
63. Nork, SE: *Femoral shaft fractures*. In: Bucholz RW, Heckman JD, Court-Brown JM, Tornetta P, eds. *Rockwood and Green's fractures in adults*, 7th ed. Philadelphia: JB Lippincott; 2009.
64. Stein E, Shane E: Secondary osteoporosis. *Endocrinol Metab Clin North Am* 2003; 32:115.
65. Blecher A: Über den Einfluß des Parademarsches auf der Entstehung der Fußgeschwulst. *Med Klin* 1905; 1:305.
66. DeFranco MJ, Recht M, Schils J, Parker RD: Stress fractures of the femur in athletes. *Clin Sports Med* 2006; 25:89.
67. Harrast MA, Colonno D: Stress fractures in runners. *Clin Sports Med* 2010; 29:399-416.
68. Leung KS, So WS, Lam TP, Leung PC: Treatment of ipsilateral femoral shaft fractures and hip fractures. *Injury* 1993; 24:41.
69. Ferguson KL, Harris V: Inferior hip dislocation in an adult: Does a rare injury now have a common mechanism? *Am J Emerg Med* 2000; 16:117.
70. Kolar MK, Joseph S, McLaren A: Luxatio erecta of the hip. *J Bone Joint Surg Br* 2011; 93:273.
71. Cornwall R, Radomisli TE: Nerve injury in traumatic dislocation of the hip. *Clin Orthop Relat Res* 2000; 377:84.
72. Newton E, Love J: Emergency department management of selected orthopedic injuries. *Emerg Med Clin North Am* 2007; 25:763-793.
73. Brooks RA, Ribbans WJ: Diagnosis and imaging studies of traumatic hip dislocations in the adult. *Clin Orthop Relat Res* 2000; 377:15-23.
74. Yang EC, Cornwall R: Initial treatment of traumatic hip dislocation in the adult. *Clin Orthop Relat Res* 2000; 377:24.
75. Stefanich RJ: Closed reduction of posterior hip dislocation: The Rochester method. *Am J Orthop* 1999; 28:401.
76. Walden PD, Hamer JR: Whistler technique used to reduce traumatic dislocation of the hip in the emergency department setting. *J Emerg Med* 1999; 17:441.
77. Dahner LE, Hundley JD: Reduction of posterior hip dislocations in the lateral position using traction-countertraction: Safer for the surgeon? *J Orthop Trauma* 1999; 13:373.
78. Potter HG, Montgomery KD, Heise CW, Helfet DL: MR imaging of acetabular fractures: Value of detecting femoral head injury, intraarticular fragments, and sciatic nerve injury. *AJR Am J Roentgenol* 1994; 163:881.
79. National Institutes of Health: Total hip replacement. *NIH Consens Statement* 1999; 12:1, 1999.
80. Kosashvili Y, Backstein D, Safir O, Lakstein D, Gross AE: Dislocation and infection after revision of total hip arthroplasty: Comparison between the first and multiply revised total hip arthroplasty. *J Arthroplasty* 2011; 26:1170-1175.
81. Armfield DR, Kim DH, Towers JD, Bradley JP, Robertson DD: Sports-related muscle injury in the lower extremity. *Clin Sports Med* 2006; 25:803.
82. Järvinen TA, Järvinen TL, Kääriäinen M, Kalimo H, Järvinen M: Muscle injuries: Biology and treatment. *Am J Sports Med* 2005; 33:745.
83. Morelli V, Smith V: Groin injuries in athletes. *Am Fam Physician* 2001; 64:1405.
84. Knoeller SM, Uhl M, Herget GW: Osteitis or osteomyelitis of the pubis? A diagnostic and therapeutic challenge: Report of 9 cases and review of the literature. *Acta Orthop Belg* 2006; 72:541.
85. Willmann JK, et al: Aortoiliac and lower extremity arteries assessed with 16-detector row CT angiograpy: Prospective comparison with digital subtraction angiography. *Radiology* 2005; 236:1083.
86. Rathjen KE, Birch JG: *Pathologic fractures associated with tumors and unique conditions of the musculoskeletal system*. In: Beaty JH, Kasser JR, eds. *Rockwood and Green's Fractures in Children*, 7th ed. Philadelphia: JB Lippincott; 2010.
87. Boardman MJ, Herman MJ, Buck B, Pizzutillo PD: Hip fractures in children. *J Am Acad Orthop Surg* 2009; 17:162-173.
88. Arkader A, Friedman JE, Warner WC Jr, Wells L: Complete distal femoral metaphyseal fracture: A harbinger of child abuse before walking age. *J Pediatr Orthop* 2007; 27:751.
89. Coffey C, Haley K, Hayes J, Groner JI: The risk of child abuse in infants and toddlers with lower extremity injuries. *J Pediatr Surg* 2005; 40:120.
90. Kocher MS, Zurakowski D, Kasser JR: Differentiating between septic arthritis and transient synovitis of the hip in children: An evidence-based clinical prediction algorithm. *J Bone Joint Surg Am* 1999; 81:1662.
91. Kocher MS, Mandiga R, Zurakowski D, Barnewolt C, Kasser JR: Validation of a clinical prediction rule for the differentiation between septic arthritis and transient synovitis of the hip in children. *J Bone Joint Surg Am* 2004; 86:1629.
92. Perry DC, Bruce C: Evaluating the child who presents with an acute limp. *BMJ* 2010; 341:c4250.
93. Frank G, Mahoney HM, Eppes SC: Musculoskeletal infections in children. *Pediatr Clin North Am* 2005; 52:1083.
94. Levine MJ, McGuire KJ, McGowan KL, Flynn JM: Assessment of the test characteristics of C-reactive protein for septic arthritis in children. *J Pediatr Orthop* 2003; 23:373.
95. Caird MS, et al: Factors distinguishing septic arthritis from transient synovitis of the hip in children. *J Bone Joint Surg Am* 2006; 88:1251.
96. Choi IH, Yoo WJ, Cho TJ, Chung CY: Operative reconstruction for septic arthritis of the hip. *Orthop Clin North Am* 2006; 37:173.
97. Perron AD, Miller MD, Brady WJ: Orthopedic pitfalls in the emergency department: Slipped capital femoral epiphysis. *Am J Emerg Med* 2002; 20:484.
98. Sink EL, Blaiser D: *Fractures and traumatic dislocations of the hip*. In: Beaty JH, Kasser JR, eds. *Rockwood and Green's Fractures in Children*, 7th ed. Philadelphia: JB Lippincott; 2010.
99. Ankarath S, Ng AB, Giannoudis PV, Scott BW: Delay in diagnosis of slipped upper femoral epiphysis. *J R Soc Med* 2002; 95:356.
100. Tins B, Cassar-Pullicino V, McCall I: The role of pre-treatment MRI in established cases of slipped capital femoral epiphysis. *Eur J Radiol* 2009; 70:570-578.
101. McErlean MA: *The child with a limp*. In: Graff J, ed. *Critical Decisions in Emergency Medicine*. Irving, Texas: American College of Emergency Physicians; 2004.
102. Giacomini S, Di Gennaro GL, Donzelli O: Fracture of the lesser trochanter. *Chir Organi Mov* 2002; 87:255-258.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 57

KNEE AND LOWER LEG

Daniel J. Pallin

KNEE

PERSPECTIVE

More than 1 million knee injuries are treated annually in North American emergency departments (EDs).[1] These injuries range in severity from minor contusions to limb-threatening injuries to the popliteal artery. The knee joins the longest mechanical levers in the body, the femur and tibia, and is therefore subject to high forces. It is the largest and most complex joint in the body and functions through a complicated interaction of flexion, extension, rotation, gliding, and rolling. Its large synovial space frequently is involved in infections and other inflammatory conditions.

The main goal in emergency evaluation of the traumatized knee is to prevent further damage by identifying reparable vascular injuries, reducing dislocations, stabilizing fractures, and administering antibiotics when indicated. Definitive treatment of less urgent problems is deferred to other settings, such as primary care offices for chronic knee pain and orthopedic clinics for ligamentous injuries.

PRINCIPLES OF DISEASE: ANATOMY AND PATHOPHYSIOLOGY

The knee is a modified-hinge diarthrodial synovial joint that consists of the tibiofemoral and patellofemoral joints.[2] The head of the fibula, although not part of this articulation, is closely approximated laterally and provides a site for the attachment of muscles and ligaments. Joint stability is provided by ligaments, although surrounding muscles and the joint capsule contribute as well (Fig. 57-1).

The distal femur terminates in the medial and lateral condyles. A *condyle* is a rounded prominence at the end of a bone, where it interfaces with another bone. An *epicondyle* is a prominence on a condyle, where a ligament or tendon attaches. The femoral condyles protrude anteriorly, leaving a vertical groove between them, forming the femoral trochlea. *Trochlea* is the term for an anatomic structure that resembles a pulley. The patella slides up and down in the groove during knee extension and flexion.

The femoral condyles articulate with the superior surface of the tibia and the tibial condyles. The medial and lateral menisci are cushions between the femoral and tibial condyles.

The tibia is anchored to the femur by four strong ligaments, the anterior and posterior cruciate ligaments (ACL and PCL) and the medial and lateral collateral ligaments (MCL and LCL). The ACL and PCL are located deep within the knee. The ACL arises from the posterior aspect of the femoral intercondylar notch and inserts on the anterior surface of the tibial plateau within the tibial intercondylar notch. It prevents anterior displacement of the tibia relative to the femur. The PCL arises from the anterior aspect of the femoral intercondylar notch and inserts on the posterior surface of the tibial plateau within the tibial intercondylar notch. It prevents posterior displacement of the tibia relative to the femur. The cruciate ligaments have a rich blood supply, and injury typically results in a hemorrhagic knee effusion.

The MCL and the LCL connect the femoral epicondyles to the tibial condyle and the head of the fibula, respectively. The MCL prevents *valgus* deviation. *Valgus deviation* refers to angulation with the apex pointing medially. The LCL prevents *varus* deviation, which is angulation of the tibia relative to the femur with the apex pointing laterally.

Functionally the knee joint can be divided into three compartments: patellofemoral, medial tibiofemoral, and lateral tibiofemoral. These compartments, defined anatomically by the articulation of the bones, are contained within the same joint capsule. The patellofemoral compartment, located anteriorly, contains the quadriceps tendon, which envelops the patella, continues inferiorly as the patellar tendon, and inserts on the tibial tubercle. The fibers of the medial and lateral retinacula are found on either side of the patella, originating from the vastus medialis and vastus lateralis. The patella increases the mechanical advantage of the quadriceps tendon. The quadriceps tendon is a continuation of the quadriceps femoris muscle, which consists of the rectus femoris, vastus medialis, vastus lateralis, and vastus intermedius, which extend the knee.

The medial tibiofemoral compartment is located on the medial aspect of the knee and consists of the medial femoral condyle, concave medial tibial condyle (plateau), medial meniscus, MCL, adductor tubercle, and pes anserinus. The pes anserinus (literally, "goose foot") is a three-pronged tendinous structure that is the conjoined insertion of the sartorius, semitendinosus, and gracilis muscles and is located on the proximal medial tibia.

The lateral tibiofemoral compartment encompasses the lateral half of the knee joint and includes the lateral femoral condyle and epicondyle, lateral tibial condyle (plateau), LCL, lateral meniscus, and popliteus tendon. The fibular head can be palpated posterolaterally and inferiorly to the joint line but is not usually considered a structure of the lateral tibiofemoral compartment.

The knee is surrounded by a thick ligamentous sheath composed largely of tendons and their expansions. The capsule of the knee joint is reinforced at multiple sites: anteriorly, by the ligamentum patellae; medially and laterally, by the medial and lateral patellar retinacula; and posterolaterally, by a combination of structures referred to as the *posterolateral corner.* The posterolateral corner includes the iliotibial (IT) band, biceps femoris tendon,

www.ketabpezeshki.com 66485457-66963820

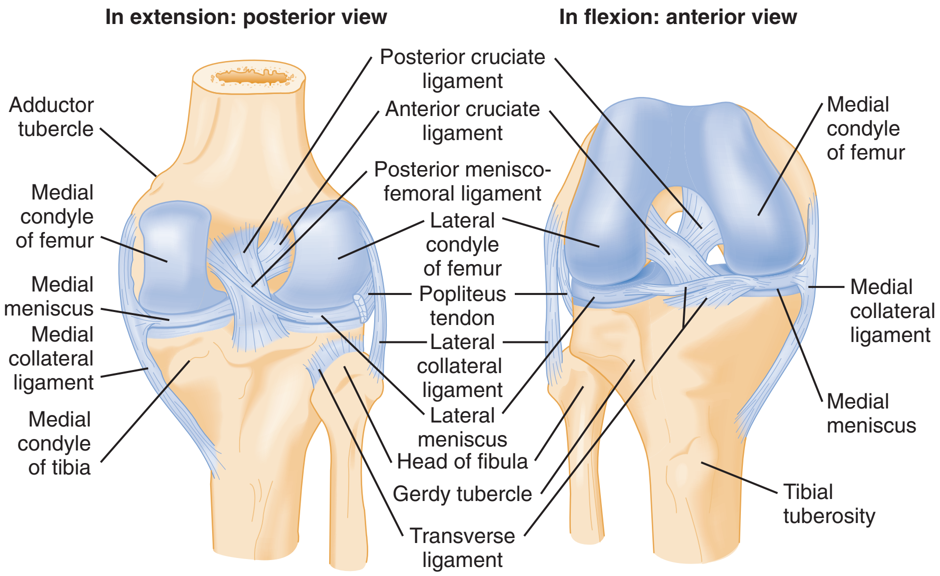


Figure 57-1. Posterior and anterior views of the right knee.

fibular collateral ligament, popliteus complex (tendon, tibial attachment, popliteofibular ligament, lateral meniscal attachments), arcuate complex, fabellofibular ligament, capsular ligament, and joint capsule. The popliteofibular ligament has been identified as an important contributor to posterolateral stability. The synovial capsule of the knee works in unison with the ligamentous structures in strengthening the knee. The tibiofemoral joint communicates with the suprapatellar bursa, which expands in conditions that cause knee effusion. The prepatellar bursa is anterior to the patella and does not communicate with the tibiofemoral joint. It is important not to confuse prepatellar bursitis with knee arthritis.

The popliteal fossa is a rhomboid hollow in the posterior aspect of the knee. It is bounded laterally by the biceps femoris tendon, medially by the semimembranosus and semitendinosus muscles, and inferiorly by the two heads of the gastrocnemius muscle. Found within the popliteal space are the popliteal artery, the popliteal vein, and the peroneal and tibial nerves.

The popliteal artery is the continuation of the femoral artery beyond the adductor hiatus. It descends across the posterior aspect of the knee joint and terminates at the level of the tibial tubercle, where it divides into the anterior and posterior tibial arteries. The peroneal artery then branches from the posterior tibial artery. Together the three arteries are referred to as the *trifurcation of the popliteal artery.* The popliteal artery is anchored firmly at the proximal and distal ends of the popliteal fossa, which explains the high incidence of arterial injury with knee dislocations. Blood supply to the knee joint comes from the popliteal artery by way of the geniculate arteries. Branches of the geniculate arteries interconnect with other vessels, forming a complex anastomosis around the knee. The circumflex fibular artery is a branch from the anterior tibial artery and constitutes the main blood supply to the head of the fibula. Blood supply to the head of the tibia is derived in part from two branches of the anterior tibial artery: the anterior and posterior recurrent tibial arteries.

The tibial nerve, along with one of its branches, the common peroneal nerve, is responsible for innervation of the knee. The tibial nerve joins the artery and vein in the popliteal fossa. The common peroneal nerve wraps around the head of the fibula and continues inferiorly as the deep and superficial peroneal nerves. Common peroneal nerve injury may occur in association with tibiofemoral dislocation or injury to the head of the fibula, or it may be caused by prolonged compression, as when the flexed knee hangs over the edge of a hard surface, such as an operating room table. This causes footdrop, in which dorsiflexion strength at the ankle is reduced.

Depending on the population studied, management of knee and leg fractures commonly requires immobilization, which can result in deep vein thrombosis in up to 19% of patients. Prophylactic treatment with low-molecular-weight heparin reduces this risk.[3]

CLINICAL FEATURES

Presentation

Patients with knee injuries may have pain, tenderness, deformity, limited range of motion, effusion, warmth, or redness. Knee pain without an immediately apparent knee abnormality should prompt a careful evaluation of the entire femur and hip, injuries of which frequently manifest with pain referred to the knee. Patients with radiculopathy of the third, fourth, or fifth lumbar roots also may report knee pain. Children with a slipped capital femoral epiphysis, toxic tenosynovitis, or septic hip frequently complain of knee pain.

A knee effusion may result from infection, hemarthrosis, lipohemarthrosis, or inflammatory arthritis, and arthrocentesis is commonly required for diagnosis.

High-energy trauma without knee swelling should raise suspicion for disruption of the joint capsule with expulsion of synovial fluid and blood into the thigh or lower leg. Lower-energy injuries are more commonly associated with meniscal tears, patella dislocations, and less severe ligament injuries. Activities with twisting and turning are associated with anterior cruciate and meniscal tears. Immediate deformity, hemarthrosis, or instability suggests intra-articular fracture, cruciate ligament injury, or vascular injury. By contrast, a torn meniscus more commonly is associated with delayed onset of swelling over 12 to 24 hours and intermittent locking associated with joint line pain.

Locking of the knee manifests clinically with inability to extend the joint fully. It typically results from either a meniscal tear or trapping of a loose body within the joint, thereby preventing full extension. A complaint of "giving way" may indicate instability or involuntary muscle inhibition secondary to pain. This is a nonspecific symptom and may be reported in association with arthritis or patellofemoral disorders when inhibition of quadriceps

www.ketabpezeshki.com 66485457-66963820

Box 57-1 Examination of the Knee

1. Assess neurovascular integrity of the foot.
2. Determine whether a knee effusion is present, and assess for gross deformity.
3. Identify signs of infection (redness, warmth, and effusion out of proportion to mechanism of injury).
4. Localize tenderness.
5. Assess range of motion and perform stability testing and meniscal evaluation when feasible.

function occurs in association with episodic pain. Although pain remains a helpful indicator of injury, its absence should not be interpreted as proof that only minor injury is present. Complete ligament tears may be less painful than partial tears because the completely disrupted ligament has no tension across injured fibers.

Dislocation is among the most serious of knee injuries, because the popliteal artery is commonly injured. Because many knee dislocations reduce spontaneously before the patient arrives at the ED, normal findings on physical examination and radiographs do not rule out a recent dislocation.[4] If a history of knee dislocation is suspected or when a trauma patient has unexplained vascular insufficiency of the foot, thorough evaluation of the neurovascular status of the feet is an integral part of the secondary trauma survey.

Physical Examination

Proper examination of the knee requires the patient to be supine with both legs exposed. The question of whether knee pain may be the result of hip or spine pathology should be raised early, and the neurovascular integrity of the foot should be assessed. Examination of the knee begins with visual inspection (Box 57-1), followed by palpation (Fig. 57-2). Any obvious deformity, swelling, effusion, or ecchymosis is noted. Localized swelling should be distinguished from the presence of a joint effusion, which may obliterate the normal contour of the knee. If a large effusion is present, the patella is elevated from the femur by fluid, and the patella can be "ballotted" against the femur. Loss of the medial peripatellar concavity may be the only sign of a small knee effusion. A small knee effusion may be accentuated by milking the suprapatellar pouch inferiorly to force fluid into the knee joint. An effusion in the prepatellar bursa is found just beneath the skin anterior to the patella; this should not be confused with a knee effusion.

Palpate areas of suspected tenderness last, to avoid causing anxiety and muscle spasm during the examination. The patella and the extensor mechanism should be palpated with attention to the superior pole. In the absence of trauma, tenderness localized here is consistent with quadriceps tendinitis. Warmth, erythema, and swelling over the anterior patella may result from prepatellar bursitis. Tenderness along the inferior pole of the patella is seen with peripatellar tendinitis. The insertion of the patellar tendon onto the tibial tubercle should be palpated. Pain at this location in an adolescent is the hallmark of Osgood-Schlatter disease. In an adolescent, pain along the femoral or tibial epiphysis after trauma may represent a Salter-Harris type I fracture (i.e., a nondisplaced fracture through the physis). The joint line should be palpated carefully. Pain along the joint line may indicate meniscal pathology. The posterior aspect of the knee should be examined for fullness, which may indicate a Baker's cyst, or popliteal artery pseudoaneurysm. Tenderness over the medial or lateral head of the gastrocnemius may indicate tendinitis or muscle strain.

Accurate diagnosis of soft tissue knee injuries often is impossible in the acute phase because of pain and swelling. In the acute setting the main goals are to relieve pain, stabilize the joint, rule out vascular injury, determine the need for radiography, and identify infections and inflammatory conditions hidden by a history of minor trauma. In the subacute setting (days to weeks after injury), range of motion should be assessed. The normal range is from slight hyperextension to approximately 135 degrees of flexion, but the patient's unaffected knee should be used for comparison. With knee flexion, it is normal for the tibia to glide posteriorly as much as a few millimeters and to rotate internally up to 40 degrees. Similarly, the tibia moves anteriorly and rotates externally during extension. In the extended position, tautness of the ligaments prevents rotary motion. Loss of active extension of the knee and inability to maintain the passively extended knee against gravity are the hallmarks of quadriceps and patellar tendon rupture, which otherwise may be clinically occult.

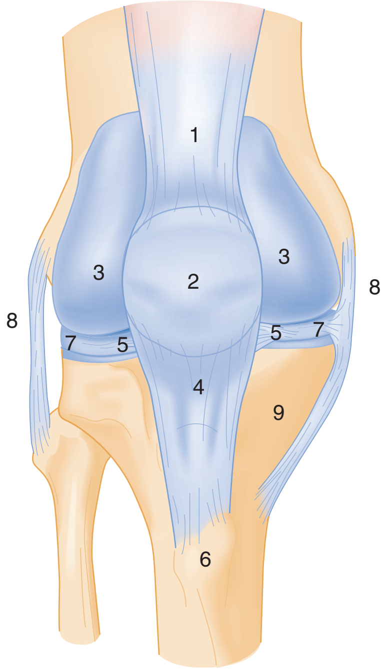


Figure 57-2. Sites for palpation of tenderness in the knee: *1,* quadriceps tendinitis; *2,* prepatellar bursitis, patella pain; *3,* retinacular pain after patella subluxation; *4,* patella tendinitis; *5,* fat pad tenderness; *6,* tibial tubercle pain caused by Osgood-Schlatter disease; *7,* meniscus pain; *8,* collateral ligament pain; *9,* pes anserine tendinitis-bursitis. (Adapted from Cailliet R: Knee pain. In Soft Tissue Pain and Disability, 3rd ed. Philadelphia, FA Davis, 1976, p 411.)

Tests for Specific Injuries and Disturbances

Stability Testing

Although range of motion is important for documentation of disability, it is stability testing that provides the most specific diagnostic information. Stability testing seeks to identify tears of the four major ligaments of the knee—the ACL, PCL, MCL, and LCL. Stability testing in the acute phase is often misleading owing to splinting and effusion and is often not clinically useful in the ED. When the acute phase has passed, the goal of stability testing is to determine whether a patient may benefit from orthopedic referral for evaluation and repair.

Anterior Drawer Test

The anterior drawer test seeks to identify tears of the ACL. A positive test result is defined as greater anterior movement of the tibia

www.ketabpezeshki.com 66485457-66963820

as compared with the other knee. The test is performed with the patient in a supine position, the hip flexed at 45 degrees, and the knee flexed at 90 degrees. The examiner may stabilize the patient's tibia by sitting on the patient's foot. The examiner then determines the amount of step-off between the femoral condyle and the tibial plateau by placing the thumbs over the joint line while exerting a smooth, gentle pull anteriorly on the tibia. The amount of forward displacement is compared with that on the normal side. Significant laxity relative to the contralateral knee is fairly specific for ACL disruption, although a false-positive result can be caused by PCL insufficiency, which allows the tibia to slip back on the femur, with anterior movement as the slack in the PCL is taken up. Sensitivity of the anterior drawer test is poor—10% acutely and only 50% with general anesthesia.[5] False-negative findings may result from an effusion preventing knee flexion to 90 degrees, insufficient force applied during the test, or simply the strength of the knee flexors and extensors preventing abnormal movement.

Lachman's Test

Lachman's test is the most accurate physical test for anterior cruciate ligament damage, with a sensitivity of 80% when performed acutely and 100% when performed with the patient under general anesthesia.[5] Lachman's test is done with the knee flexed 20 to 30 degrees while the examiner uses one hand to grasp the thigh and stabilize it. The tibia is pulled anteriorly, and the examiner notes tibial excursion. The examiner records "firmness" or a "soft endpoint." The endpoint can be graded as 1+ (0-5 mm more displacement than on the normal side), 2+ (5-10 mm), or 3+ (more than 10 mm). The knee should be in a neutral position before manipulation, and the PCL must be intact for the test results to be valid. In an acute injury, any difference in translation or the feeling of a soft or indistinct endpoint may indicate a ligament tear. A PCL injury results in a false-positive test result as the knee is pulled forward. Potential causes of false-negative test results include hamstrings that are very strong or in spasm, meniscal tears, and third-degree MCL tears with posterior medial extension. Partial tears are not detected reliably. Lachman's test is difficult if the examiner's hands are small relative to the patient's thigh.

Pivot Shift Test

The pivot shift test, also called *subluxation provocation* or the *jerk test,* is performed to detect anterolateral rotatory instability associated with an injury to the ACL or lateral capsular structure. This test should be done carefully, if at all, in the acutely injured knee because the test maneuvers can exacerbate the initial injury. Sensitivity in the acute phase is only 27%, but the test is highly specific for ACL tear.[6]

Posterior Drawer Test

The posterior drawer test assesses for PCL injury.[5] The posterior drawer test can be accomplished with the patient's knee flexed at 90 degrees and the foot stabilized by the examiner's thigh. A smooth backward force is applied to the tibia. Posterior displacement of the tibia more than 5 mm, or a "soft endpoint," indicates injury to the PCL. A normal knee should exhibit no significant posterior excursion. The posterior drawer test result may be positive in only 85% of patients with PCL insufficiency documented operatively.

Posterior Sag Sign Test

The posterior sag sign test is a second method of determining PCL integrity. Sensitivity in the acute phase is 79%.[5] The test is done as follows. The patient is placed in a supine position, and a pillow is placed under the distal thigh for support while the heel rests on the stretcher. The knee is flexed to either 45 or 90 degrees, depending on which position provides the greater muscle relaxation. If the tibia sags backward, the test result is considered to be positive, indicating PCL insufficiency. If the posterior sag sign is not appreciated before the different drawer tests are performed, a false-positive result on the anterior drawer test is misinterpreted as an ACL injury. Posterior sag also may be shown by passive elevation of the leg in a fully extended position, with the examiner applying the elevating force at the ankle. As the leg is elevated, the tibia may fall back on the femur if the PCL is ruptured.

The pivot shift test is performed with the patient supine. The knee is examined in full extension. The tibia is internally rotated while the examiner grasps the foot with one hand and applies a mild valgus stress at the level of the knee joint with the other hand. Then, with flexion of the knee to approximately 20 to 30 degrees, a jerk is suddenly felt by the examiner at the anterolateral corner of the proximal tibia. With a positive result, the tibia subluxates when the knee is extended and relocates when it is flexed to 20 to 30 degrees. Grading of the relocation event is as follows: absent (0), rolling (1+), moderate (2+), or momentary locking (3+). Because of pain or spasm, the pivot shift test is unreliable without use of anesthesia.

Instrument Testing

Arthrometers are devices that quantitate anterior displacement of the tibia relative to the femur and are far more accurate in diagnosing ACL tears than the anterior drawer and Lachman's tests, although these devices are rarely used in the ED setting. Studies in which commercially available arthrometers were used indicate that a side-to-side difference exceeding 3 mm of anterior displacement at 20 pounds is predictive of ACL injury with high accuracy.[7]

Collateral Ligament Stress Test

The collateral ligament stress test is used to test the integrity of the MCL and LCL. With the patient lying supine, the examiner applies varus and valgus stress with the knee at 0 and 30 degrees of flexion. *Joint line opening* is the amount of movement (i.e., hinging) produced between the tibia and the femur; this can be palpated and estimated in millimeters. The normal knee should be subjected to the same amount of valgus and varus stress, and the joint line opening is then compared with that in the injured knee. Isolated collateral ligament tears are detected only with the knee in slight flexion, because in extension the cruciate ligaments, capsule, and lesser ligaments of the knee provide significant lateral stability. Laxity in full extension implies complete collateral ligament tear and also injury to the cruciate ligaments or other structures. Laxity may be graded as follows: grade I, some laxity; grade II, marked laxity; and grade III, total laxity.

Assessing for Meniscal Tears

Meniscal tears are difficult to diagnose in the acute setting, and these assessments are best reserved for the convalescent phase. Even then, small meniscal tears can cause significant symptoms but may not be detected on physical examination, and arthroscopic evaluation may be required for diagnosis. However, meniscal tears are likely to limit activity, rather than leading to further damage, so there is less urgency. By contrast, failure to diagnose a nondisplaced fracture can lead to displacement and severe consequences.

McMurray's Test. McMurray's test is used to help identify meniscal tears. The patient is placed in supine position with the knee

www.ketabpezeshki.com 66485457-66963820

hyperflexed. The examiner grasps the foot with one hand and the knee with the other. The examiner flexes and extends the knee while simultaneously internally and externally rotating the tibia on the femur and providing slight varus and valgus stress. A positive test result is the occurrence of clicking palpable along the joint line, or locking of the knee. Internal rotation of the leg tests the posterior segment of the lateral meniscus. External rotation tests the posterior segment of the medial meniscus. In the acute setting, limitation of range of motion may not allow sufficient hyperflexion to perform McMurray's test, and the test result may be falsely negative.

Apley's Test. *Apley's test* also aids in diagnosing meniscal tears. With the patient prone, the knee is flexed 90 degrees, and the leg is internally and externally rotated with pressure applied to the heel. Pain elicited by downward pressure suggests meniscal pathology. The pain should be relieved with distraction of the knee and rotation of the leg back to a neutral position. Although relatively specific, Apley's test is not sensitive.[6]

DIAGNOSTIC STRATEGIES

Radiologic Evaluation

Plain Radiographs

In acute knee trauma, the goal of radiography is to rule out fracture. Because radiographs are not 100% sensitive, knee immobilization and orthopedic referral for reevaluation are options. When suspicion for a fracture is extremely high, computed tomography (CT) can be used; it is more sensitive than plain films. One study found a negative predictive value of only 49% for plain films in diagnosing knee fracture, with CT as the gold standard.[8] Magnetic resonance imaging (MRI) is even more sensitive but is not customarily used in the ED evaluation of knee and leg trauma.

Plain films are useful for diagnosing fracture, effusion, foreign bodies, joint space narrowing, and lipohemarthrosis. Evaluating plain films begins with an assessment of bone anatomy and alignment. Nonobvious fractures are best detected by careful inspection of the cortex of all visualized bones. Any disruption of the continuous line of the cortex should raise suspicion for fracture. Subtle cortical disruptions indicate either nondisplaced fractures or draining cortical veins. The next step is to evaluate for the presence of an effusion, seen as a radiolucent area (of density similar to that of fat) distending the joint capsule. Presence of a linear interface between two different densities within an effusion suggests lipohemarthrosis (see Fig. 57-3), in which the effusion contains not only blood but also fat. This feature results from entry of marrow fat into the joint cavity and is diagnostic of fracture.

The traditional practice was to obtain anteroposterior (AP) and lateral radiographic views of the knee in all cases of acute knee trauma. More recent work has led to validation of clinical decision rules that help decrease unnecessary radiography.[9-11] The Ottawa Knee Rule states that radiography is necessary only if any one of five conditions is present: (1) age older than 55 years, (2) inability to transfer weight from one foot to the next four times at the time of injury and in the ED, (3) inability to flex the knee to 90 degrees, (4) patellar tenderness with no other bone tenderness, or (5) tenderness of the fibular head. Initial tests found that this rule detected 100% of fractures while allowing significantly fewer radiographs to be done.[10,11] The Pittsburgh Knee Rule similarly was found to be 100% sensitive.[12] This decision rule states that radiography is necessary only if the patient fell or sustained blunt trauma to the knee and if either of two conditions is present: (1) age younger than 12 or older than 50 years or (2) inability to walk four full weight-bearing steps in the ED.

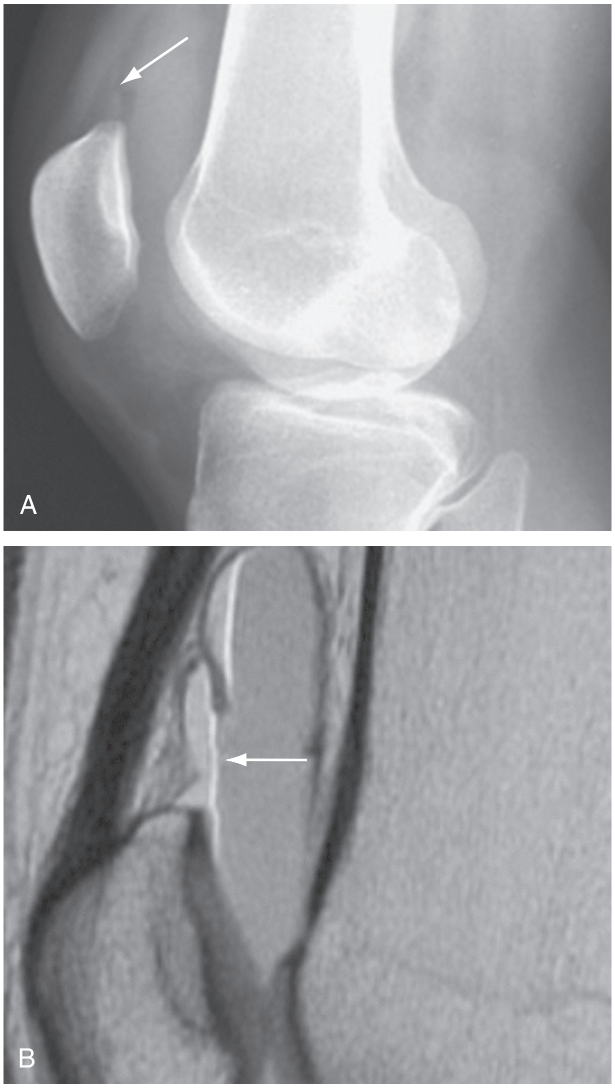


Figure 57-3. Lipohemarthrosis. **A,** A lateral plain film of the knee of a young woman with a nondisplaced patella fracture. The only radiographic abnormality is an effusion that contains a linear interface *(arrow)* between two soft tissue densities, suggesting lipohemarthrosis. **B,** A magnetic resonance image from the same patient shows plainly the presence of blood and fat in the effusion *(arrow)* (the nondisplaced patella fracture is not seen).

In a study comparing these two decision rules, both had good sensitivity, but the Pittsburgh rule was more specific, allowing fewer radiographs to be done without sacrificing sensitivity; in this study, the sensitivity of the Ottawa rule was 97% (95% confidence interval, 90 to 99%) and the sensitivity of the Pittsburgh rule was 99% (95% confidence interval, 94 to 100%).[13] Either rule may be used, but patients should be told that this approach is associated with an approximately 1% chance of a missed fracture and that they should seek reevaluation in the event of persistent or progressive symptoms.

One study validated the Ottawa Knee Rule in children older than 5 years, finding a sensitivity of 100%. The Ottawa Knee Rule permitted a 31% reduction in the number of radiographic evaluations.[14] In another pediatric study of the Ottawa Knee Rule, 1 of 13 fractures was missed, implying a sensitivity of only 92%, so application of the rule in children still requires clinical judgment.[15]

In another approach, investigators asked whether a single lateral radiograph could replace the traditional three-view "knee series"

www.ketabpezeshki.com 66485457-66963820

(AP, lateral, and tunnel views). These investigators found that a single lateral view could detect 100% of fractures identifiable on the full series.[16] This innovative approach merits further study.

Joint space narrowing, as seen in osteoarthritis, is easily discernible on erect standard views. Lateral views may reveal an abnormally low-riding or high-riding patella. Tangential, "sunrise," or "skyline" views are especially good for assessing patella tracking. Oblique films are used when tibial plateau fractures are suspected but not seen on routine views, although MRI is far more sensitive. "Tunnel" views, which image the intercondylar notch, are used to detect tibial spine fractures and loose bodies within the notch. Although most ligamentous injuries cannot be diagnosed by plain radiography, avulsion of the attachment site can be seen occasionally and provides indirect evidence of ligament disruption. Stress radiographs may aid in the diagnosis of collateral ligament disruption but generally are not used in the initial evaluation. In the ED setting, the three-view knee series remains standard: AP, lateral, and tunnel.

Computed Tomography

CT is most useful in detecting and classifying tibial plateau fractures and usually is done when the diagnosis is unclear or if operative intervention is being considered. CT angiography is an excellent tool for detecting injury to the popliteal artery, although its sensitivity relative to traditional angiography has not been quantified in large high-quality studies.[17]

Angiography

In the ED evaluation of trauma to the knee and leg, angiography is used to seek popliteal artery injury after knee dislocation. To obtain an angiogram, a catheter is placed in the femoral artery and contrast is injected while fluoroscopy (video x-ray examination) is performed. Complications occur in about 1.7% of these procedures, and include vascular injury and contrast nephropathy. False-positive results can lead to unnecessary surgical exploration. From a practical standpoint, the patient must be removed from the ED to a radiology suite, where other injuries cannot be addressed, and the angiography team must be mobilized, often resulting in delays in care.[4] Because of these limitations, relatively accurate alternatives, including CT angiography and duplex ultrasound, have been adopted.[17]

Duplex Ultrasonography

Duplex ultrasonography refers to the combination of two-dimensional ultrasound imaging plus color Doppler examination. This method is used for evaluation of the popliteal artery after tibiofemoral dislocation (discussed later). Color Doppler imaging is used to compare the velocity of blood in a narrowed area with the velocity just proximal to the narrowed area. As the lumen narrows, flow accelerates, and the ratio of velocities is an accurate predictor of the degree of stenosis.

Radionuclide Bone Scan

A radionuclide bone scan can be used to detect osteomyelitis or occult bony injuries, such as stress fractures, osteochondritis dissecans, and avascular necrosis.

Magnetic Resonance Imaging

MRI has replaced contrast arthrography in the workup of occult fractures and ligamentous and meniscal injuries. Contrast arthrography involves injection of radiopaque contrast material into the joint, followed by radiography. Double-contrast arthrography involves injection of both air and contrast. These techniques are rarely performed when MRI is available.

MRI is highly accurate for diagnosis of fractures and ligamentous injuries, although it often misses small meniscal tears. It has proved to be superior to other imaging modalities in the evaluation of osteonecrosis, osteochondritis dissecans, occult fractures, and bone contusion.[18] Its advantages are that it is noninvasive and painless and does not involve exposure to ionizing radiation. MRI of the knee is rarely performed on an emergency basis, because immobilization and non–weight-bearing status are the usual procedure, pending outpatient orthopedic evaluation.

Arthroscopy

Arthroscopy of the knee is the most commonly performed orthopedic surgical procedure in the United States. This nonemergent procedure is useful in diagnosis and treatment of knee injuries, including injuries of the meniscus, cruciate ligaments, articular cartilage, capsule, and synovium. The superior diagnostic accuracy of arthroscopy compared with the clinical knee examination has been well documented. In particular, arthroscopy has increased the accuracy of diagnosis of ACL injuries and small capsular tears. It is especially helpful in children, in whom diagnosis can be difficult because developing skeletal changes can obscure pathology. Difficulties in visualization arise when the capsular structures are tight and when meniscal tears are situated posteriorly. Arthroscopy is superior to MRI for diagnosis of meniscal tears and other soft tissue injuries, and the diagnosed problem can be repaired immediately. The need for arthroscopy is established in the convalescent phase of injury and need not be determined in the emergent setting, so long as appropriate referral to an orthopedist is made.[19]

Joint Injection

An open joint is considered a surgical emergency. When violation of the joint capsule is suspected but not obvious, the traditional approach was to inject methylene blue into the joint to see if it emerged from the laceration. Normal saline is now preferred over methylene blue, as the latter can interfere with arthroscopy and cause an inflammatory reaction. The technique is simple. With sterile technique, sterile saline is injected into the knee joint at a location distant from the laceration. If saline emerges from the laceration, an open joint is diagnosed. Historically, 50 mL was the recommended volume, but nearly 200 mL is needed to achieve a sensitivity of 95%.[20] This can be accomplished with intravenous fluid and tubing; maintenance of sterility is crucial.

Arthrocentesis

Aspiration of fluid from the knee joint can be diagnostic and can reduce pain from a tense effusion. Arthrocentesis should be performed if the injured knee is greatly distended with a tight effusion and when the cause of the joint effusion is unknown. Aspiration of the joint and subsequent analysis can differentiate simple effusion, hemarthrosis, lipohemarthrosis, and septic arthritis.

KNEE INJURIES

Dislocation

Anatomy and Pathophysiology

Knee dislocation refers to tibiofemoral dislocation and should not be confused with patellofemoral dislocation, a relatively minor injury. Knee dislocation is a limb-threatening emergency, because popliteal artery injury occurs frequently. Knee dislocation is

www.ketabpezeshki.com 66485457-66963820

uncommon but should be considered in the setting of an appropriate injury mechanism, because one half of all knee dislocations are reduced before the patient arrives at the ED.[21] Reduction before ED arrival does not lessen the likelihood of vascular injury, and vascular injury should be considered in patients with severe ligamentous injuries and high-energy mechanisms.

Knee dislocations are always associated with significant ligamentous injury. The joint capsule is disrupted, with accompanying trauma to the muscles and tendons. Injury to the popliteal artery is the most severe complication and is the primary cause of morbidity and limb loss.[22,23]

The neurovascular bundle, which is composed of the popliteal artery, popliteal vein, and common peroneal nerve, runs posteriorly behind all bony and ligamentous structures in the popliteal fossa. The popliteal artery is fixed in the fibrous tunnel of the adductor magnus hiatus proximally and traverses the fibrous arch of the soleus and interosseous membrane distally. In essence, it is tethered to the femur and the tibia, and its inherent immobility renders it susceptible to injury during dislocation. Because of the parallel course of the popliteal vein and the peroneal nerve, they are vulnerable to simultaneous injury.

Anatomically, dislocations are described according to the displacement of the tibia relative to the femur. They are classified into five types: anterior, posterior, medial, lateral, and rotary. More than half of all dislocations are anterior and result from hyperextension. Posterior dislocations are the second most common type and usually result from high-velocity direct trauma to the flexed knee, often in association with vehicular trauma (dashboard impact).[22]

Clinical Features

The diagnosis of knee dislocation is based on the mechanism of injury and clinical and radiographic findings. When a dislocation is present, it is usually obvious. There may be no effusion after reduction, because the ruptured capsule allows blood and joint fluid to escape into the thigh and leg. Some experts have advocated expanding the definition of knee dislocation to include bicruciate ligament (i.e., ACL and PCL) injuries, even when the knee is reduced on initial presentation.[21] For this reason, patients with grossly unstable knees but no proven dislocation and patients who have a bicruciate ligament injury should be evaluated for concomitant injuries, as with patients with known dislocation.[4]

Vascular injury is a catastrophic complication of knee dislocation, and popliteal artery injury is reported in 4.8 to 65% of these patients, depending on the mechanisms of injury in the population studied.[4,22] The collateral geniculate arteries around the knee also may be damaged directly or secondarily compressed by hematoma formation after the dislocation. Direct arterial injury, decreased collateral circulation, and elevated compartment pressures all may compromise limb perfusion. In addition to being clinically occult, vascular injury in blunt trauma is more difficult to manage because of associated soft tissue injury and edema.

"Hard" signs of vascular injury are absence of pulse, limb ischemia, rapidly expanding hematoma, pulsatile bleeding, and bruit or thrill over the wound, especially in penetrating injuries.[24] Paresthesias in the leg should also lead to suspicion of injury to popliteal structures. When repair of a disrupted popliteal artery is delayed, the amputation rate increases with time, nearing 90% after 8 hours.[23] The posterior tibial and dorsal pedal pulses should be evaluated but will be normal in 5 to 15% of popliteal artery injuries.[25]

Isolated intimal tears are usually managed without surgery, but a vascular surgeon should be consulted when such a tear is identified. Isolated intimal tears are not detectable on physical examination and are seen only angiographically or with duplex ultrasound. These injuries are treated with observation or anticoagulation alone but can result in popliteal artery occlusion during surgery. Injuries to small branches of the popliteal artery can be managed by observation and serial examinations, but vigilance for compartment syndrome is necessary.[21]

Neurologic integrity in the limb also should be assessed. Peroneal nerve injury is the most common major neurologic problem associated with knee dislocation; some degree of dysfunction occurs in 20 to 40% of patients and is permanent in approximately 80% of these.[1,21,26] The peroneal nerve should be evaluated by determining sensation of the dorsum of the foot and by having the patient dorsiflex the ankle. Less commonly, the posterior tibial nerve may be injured, manifesting as diminished plantar sensation and plantar flexion of the foot. Complete nerve palsy in the acute setting is associated with a poor prognosis for recovery.[26,27]

Diagnostic Strategies

The diagnostic workup begins with an understanding of two crucial facts: half of all tibiofemoral dislocations are reduced before presentation, and injury to the popliteal artery is common with tibiofemoral dislocation regardless of whether there is spontaneous reduction or not. Therefore the diagnostic strategy is not applied only to the patient with known knee dislocation, but to any patient with a multiligament knee injury or with known or possible high-force trauma to the knee. The intubated multitrauma patient with ecchymosis around the knee may harbor an occult popliteal injury. The athlete with isolated knee trauma and no dislocation on presentation may end up an amputee.[28]

Until the 1990s the testing for popliteal injury generally involved angiography. But angiography is an invasive procedure that requires canalization of the femoral artery, it involves a large dye load, and it must be performed in a radiology suite, where other injuries cannot be managed. Other approaches to ruling out popliteal artery injury include measurement of the ankle-brachial index (ABI) with serial physical examinations, CT angiography, and duplex ultrasonography.

Serial physical examinations—meaning palpation of the pedal pulses—can detect most popliteal artery injuries, with a sensitivity of 79%, specificity of 91%, positive predictive value of 75%, and negative predictive value of 93%.[24] This has led some authors to suggest physical examination alone as a screening tool. However, a miss rate of 7% is too high for such a devastating injury. Adding measurement of the ABI is thought to improve the sensitivity enough for safe clinical practice.

The ABI is traditional in primary care and vascular surgery clinics, where it is used to monitor arterial narrowing caused by peripheral vascular disease. The index is simply the ratio of the systolic blood pressure measured in the standard humeral location to the systolic pressure measured at the ankle. An ABI of greater than 0.9 has been found to have a negative predictive value for popliteal artery injury of 100% in knee dislocation.[24]

Duplex ultrasonography is thought to be equivalent to angiography as a sensitive tool for detection of traumatic occlusion or disruption of the popliteal artery, though the sensitivity has not been quantified in the setting of knee dislocation.[29] CT angiography is promising, but its sensitivity has not been quantified in this setting.[17,30,31]

The choice of diagnostic strategy depends on the patient's presentation. At one extreme is the patient with obviously impaired leg perfusion. In this case, emergency angiography or surgical exploration are indicated. At the other extreme is the patient with knee trauma but no clear indication that a dislocation even occurred. Figure 57-4 depicts a safe and efficient algorithm.[28] During the secondary survey, the dislocation is reduced, if present on presentation. The feet are examined, and if both are warm and well perfused, dorsalis pedis and posterior tibial pulses are palpable and symmetrical, and, in the awake patient, sensation is

www.ketabpezeshki.com 66485457-66963820

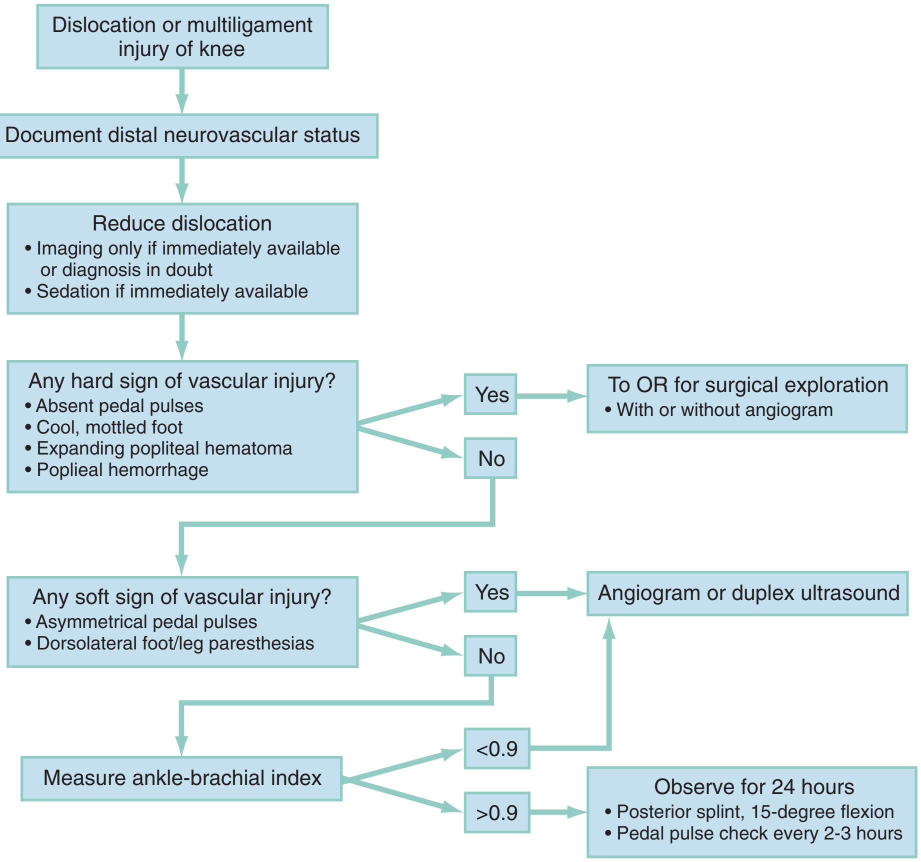


Figure 57-4. Algorithm for management of knee dislocation. (From Nicandri GT, Dunbar RP, Wahl CJ: Are evidence-based protocols which identify vascular injury associated with knee dislocation underutilized? Knee Surg Sports Traumatol Arthrosc 18(8):1005-1012, 2010.)

subjectively and objectively intact, the ABI is measured. If the ABI is above 0.9, the physical examination is repeated every 3 to 4 hours for 24 hours. If no abnormalities attributable to popliteal artery disruption are detected, no further emergent workup is indicated. Before surgery to repair associated injuries, the surgeon may choose to perform duplex ultrasonography to rule out an isolated intimal tear, which, though not important to detect in the ED setting, can lead to complications during surgery. If the pedal pulses are asymmetrical or the ABI is below 0.9, immediate angiography is indicated. If pedal pulses are absent, the foot is cool or otherwise appears poorly perfused, or there is an expansile popliteal hematoma, immediate surgical exploration is indicated, with or without an arteriogram.

Management

The dislocated knee should be reduced immediately and before radiographic confirmation unless the diagnosis is in doubt. Neurovascular status should be documented before and after reduction. For patients being transferred from nontrauma centers to trauma centers, reduction should be attempted before transfer. Reduction usually can be accomplished with simple traction-countertraction, ideally with sedation. Lateral pressure may be required—for example, for an anterior dislocation, the femur can be pushed posteriorly while the tibia is pulled anteriorly—but care should be taken not to apply undue pressure to the popliteal fossa. Posterolateral dislocations may not be reducible because the medial femoral condyle and MCL secure the dislocated joint in place, in which case, emergent open reduction in the operating room is indicated.[27] Because many reductions are unstable, the limb should be immobilized in a long leg posterior splint with the knee in 15 to 20 degrees of flexion, and popliteal artery injury sought, according to the algorithm shown in Figure 57-4.

Loss and disability are minimized by expedient revascularization and primary arterial repair, heparinization when not contraindicated, repair of popliteal venous injury, and aggressive wound débridement. Open joints require prophylactic antibiotics. If the neurovascular structures remain intact after dislocation, the knee joint is reduced and allowed to rest for 2 to 3 days before reconstruction of the torn ligaments is considered.[27,32]

Delayed complications associated with traumatic knee dislocations include deep vein thrombosis, compartment syndrome, pseudoaneurysm, and arterial thrombosis. Compartment syndromes generally develop within 24 to 48 hours of the initial injury. Pseudoaneurysms are rare but may form several hours to months after popliteal artery injury.[32] Heterotopic ossification is a poorly understood syndrome of calcification of the soft tissues of the knee.[33] It has been observed in uninjured knees of patients who have sustained major trauma. In its most severe form, heterotopic ossification can cause dramatic decrease in knee mobility. Almost one half of dislocated knees are found to have subsequent heterotopic ossification, although the most function-limiting form may be limited to patients with a history of severe trauma.[33]

Distal Femur Fractures

Anatomy and Pathophysiology

Distal femur fractures are uncommon, constituting approximately 4% of femur fractures.[32] A high-energy mechanism of injury is required. An isolated fracture of the femoral condyle may occur, or the fracture may extend in a T or Y pattern to include the

www.ketabpezeshki.com 66485457-66963820

intercondylar or supracondylar region of the femur. Condylar fractures are intra-articular and may result in disruption of the articular surface with subsequent arthritis.

Clinical Features

Patients with condylar or intercondylar fractures have pain and swelling in the distal femur and suprapatellar region and often are unable to bear weight. Examination may reveal shortening, rotation, and angulation of the extremity and tenderness to palpation along the medial or lateral joint line. Acute hemarthrosis is common and may be caused by intra-articular extension of the fracture or associated ligamentous injury. Distal neurovascular status should be documented. Any laceration in the region of the fracture represents an open fracture until proven otherwise.

Diagnostic Strategies

Routine AP and lateral views should be obtained and usually show the fracture pattern and any significant displacement of fragments. In high-energy injuries, radiographs of the ipsilateral hip and tibia are required to exclude associated fractures. Occasionally, CT or MRI may be required to diagnose a nondisplaced fracture. MRI is more sensitive, although CT is more readily available. If signs of vascular impairment are present, consultation for angiography or surgical exploration should be obtained emergently.

Management

After the initial examination, the leg should be splinted to prevent excessive motion of the fracture site. Early orthopedic consultation is advised. In a stable patient with an uncomplicated fracture, reduction may be done with skeletal traction, followed by immobilization. Intra-articular fractures generally are treated with open reduction and internal fixation. Distal femur fractures may be associated with thrombophlebitis, fat embolus syndrome, delayed union or malunion if reduction is incomplete or not maintained, intra-articular or quadriceps adhesions if the fracture is intra-articular, angulation deformities, and osteoarthritis, particularly affecting the patellofemoral articulation.

Tibial Plateau Fractures

Anatomy and Pathophysiology

The proximal end of the tibia is expanded into the medial and lateral condyles, the former having the greater surface of the two. Together they make up approximately three quarters of the proximal tibial surface, and their integrity is important for normal knee alignment, stability, and motion. The plateau normally slopes 10 degrees from anterior to posterior; on a straight AP view, the anterior and posterior portions of the plateau may not appear to be at the same level. In addition, the lateral plateau is slightly convex upward, whereas the medial is slightly concave upward.

Tibial plateau fractures often are intra-articular and result in loss of joint congruity. The forces that normally act on the tibial condyles include axial compression and rotation. The most common mechanism of injury is a strong valgus force with axial loading. Severe high-energy tibial plateau fractures occur primarily in younger patients and are often the result of motor vehicle collisions or falls from heights. These fractures occur in concert with many other injuries and may be open. Fatigue stress fractures of the tibial plateau occur mostly in the elderly. These low-energy fractures are the result of compression forces in osteoporotic bones.

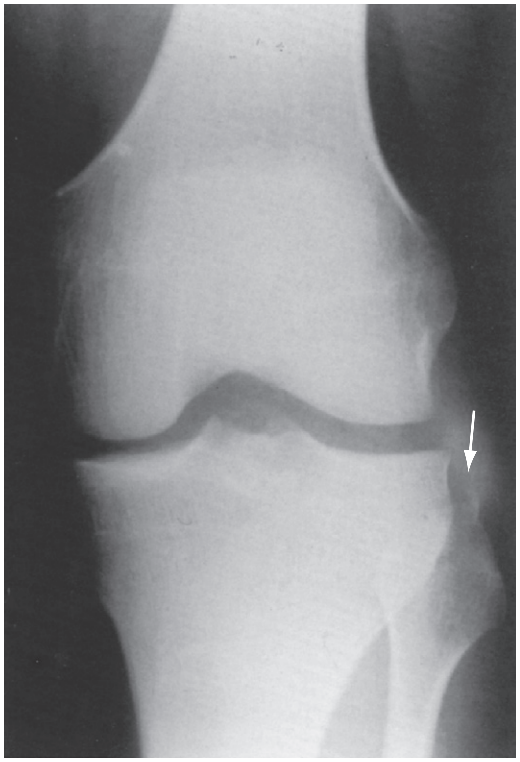


Figure 57-5. Segond fracture. Anteroposterior view of the left knee shows lateral curvilinear avulsion fracture *(arrow)* and joint effusion. (From Kerr HD: Segond fracture, hemarthrosis, and anterior cruciate ligament disruption. J Emerg Med 8:29, 1990.)

Tibial plateau fractures encompass many differing degrees of articular depression and displacement. Because the initial injury mechanism usually is a valgus stress with an abduction force on the leg, 55 to 70% of condylar fractures involve the lateral plateau. Medial plateau fractures typically result from adduction forces on the distal leg and account for 10 to 23% of these fractures; both plateaus are involved in 11 to 31% of cases.[32] If the knee is extended at the time of injury, the fracture tends to be anterior. Posterior condylar fractures usually occur when the knee is flexed at the time of impact.

The Segond fracture represents a bone avulsion of the lateral tibial plateau (Fig. 57-5). The avulsion occurs at the site of attachment of the lateral capsular ligament. On radiographs, an oval-shaped fragment can be seen adjacent to the lateral tibial plateau, which can be confused with an avulsion from the adjacent fibular styloid. Segond fractures are usually accompanied by ACL disruption and anterolateral rotatory instability. Most Segond fractures are caused by sports injuries, and the mechanism is almost always knee flexion with excessive internal rotation and varus stress.

Clinical Features

Knee fractures cause pain, tenderness, ecchymosis, soft tissue swelling, and hemarthrosis when intra-articular. A valgus or varus limb deformity may be present and usually indicates a depressed fracture or concomitant leg fracture. The most important aspect of the initial examination is assessment of neurovascular status. Many tibial plateau fractures cause vascular complications. The popliteal artery is immobile in this region and branches into the anterior and posterior tibial arteries at the upper edge of the interosseous membrane. The popliteal artery may be injured by fragments from bicondylar or comminuted fractures involving the subcondylar area. Vascular impairment may result in distal

www.ketabpezeshki.com 66485457-66963820

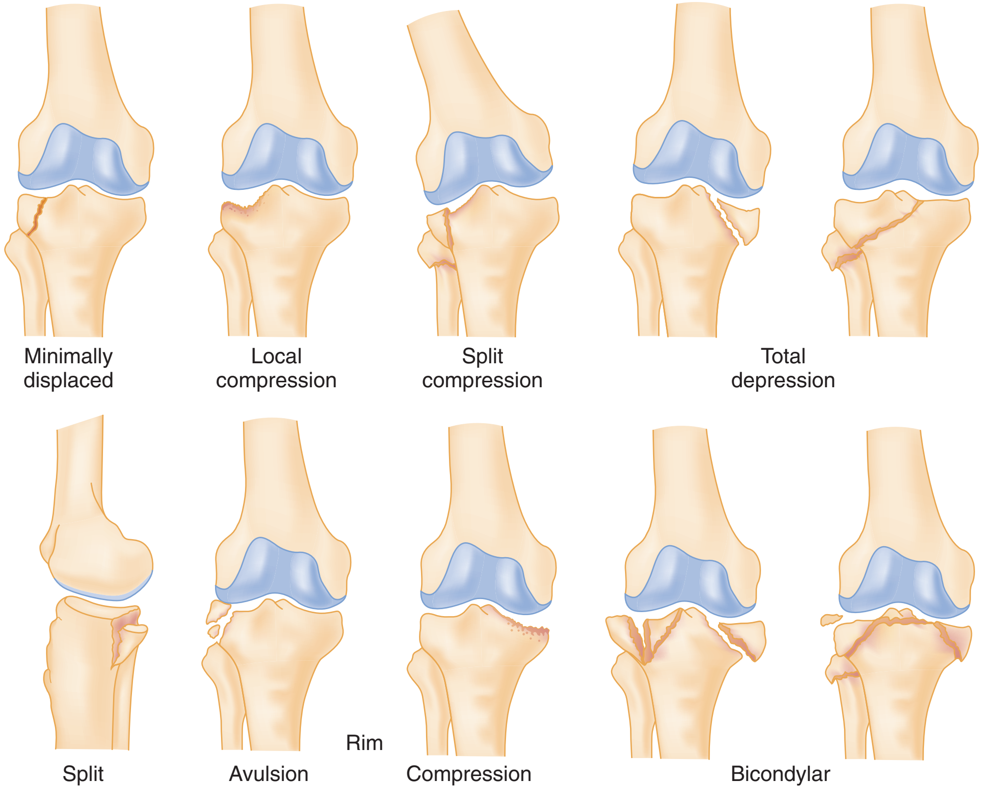


Figure 57-6. Hohl's revised classification of tibial plateau fractures: minimally displaced (accounting for 22% of such fractures), local compression (28%), split compression (18%), total depression (13%), split (3%), rim avulsion or compression (5%), and bicondylar (11%). (Adapted from Watson JT, Wiss AA: Fractures of the proximal tibia and fibula. In Rockwood CA Jr, Green DP (eds): Fractures, 5th ed, vol 3. Philadelphia, JB Lippincott, 2001.)

circulatory compromise. Displaced fractures of the lateral condyle may produce peroneal nerve paralysis in addition to injury to the anterior tibial artery. Stretch of the peroneal nerve is the usual cause of injury.

Soft tissue injuries also may involve the capsuloligamentous structures of the knee. Ligamentous injuries accompany tibial plateau fractures in up to 66% of cases, most often involving the ACL and MCL.[34]

Cruciate ligament injuries associated with tibial plateau fractures are associated with an increased incidence of late traumatic arthritis and a poor prognosis. Regardless of the type of treatment, operative or nonoperative, tibial plateau fractures with significant residual laxity fare poorly in comparison with stable fractures.[35]

Fractures of the tibial plateau generally carry a good prognosis, with good to excellent results reported in 90% of patients more than 20 years after injury; however, high-energy tibial plateau fractures generally are associated with a more guarded prognosis.[36] In high-energy fractures, a large degree of articular depression, multiple displaced condylar fracture lines, and diaphyseal-metaphyseal extension and comminution in association with open injuries or an extensive internal degloving injury are poor prognostic signs.[37]

Diagnostic Strategies

Lipohemarthrosis, seen as a fat-fluid level on a plain film, suggests an occult fracture and is caused by entry of marrow fat into the joint space (see Fig. 57-3).[38] Lipohemarthrosis also is detected when fat globules are found on aspiration of a hemarthrosis. All knee radiographs should be examined closely for bone avulsion fragments from the fibular head, femoral condyles, and intercondylar eminence, because these may indicate ligamentous injury. Widened joint spaces associated with a fracture of the opposite condyle also may indicate concomitant ligamentous injury.

CT and particularly MRI are more sensitive than plain radiography, help localize occult lesions, and help quantify the amount of depression in displaced fractures and the extent of articular surface involvement in comminuted fractures.[34] These studies need not be undertaken emergently, because the knee can be immobilized pending orthopedic consultation.

Several classification systems have been proposed. Most such systems depend on the mechanism of injury (i.e., the location and force with which the femoral condyle is driven into the plateau). The revised Hohl classification is in common although not universal use.[32] As shown in Figure 57-6, this system divides the plateau fractures into two categories: minimally displaced (less than 4 mm of depression or displacement) and displaced. Displaced fractures are subdivided into six distinct types: local compression, split compression, total depression, splint, rim, and bicondylar.

Management

All patients with a tibial plateau fracture should be referred for evaluation by an orthopedist. In the acute phase, the fracture should be immobilized in a noncircumferential splint and the patient should not bear weight on the limb until seen by an orthopedist. The therapeutic goals include precise reconstruction of the articular surfaces, stable fragment fixation, and early knee motion to prevent stiffness. Weightbearing generally is delayed until healing is complete, usually 6 to 8 weeks. Stable nondisplaced fractures may be treated with immobilization alone, but instability or significant depression or disruption of the joint surface will necessitate surgical management.[32]

www.ketabpezeshki.com 66485457-66963820

Early complications of tibial plateau fractures include wound infection, loss of reduction, and development of compartment syndrome. Compartment syndromes most commonly occur with high-energy fractures, typically within the first 24 to 48 hours after injury. Deep vein thrombosis also may occur, and prophylactic anticoagulation should be considered in consultation with an orthopedist. The most common late complication is the development of osteoarthritis in the affected compartment.

Fractures of the Intercondylar Eminence (Tibial Spine)

Anatomy and Pathophysiology

The intercondylar eminence, or tibial spine, is the central portion of the proximal tibial surface. The spine has two prominences: the medial and the lateral tubercle. The medial tubercle is larger and located more anteriorly than the lateral tubercle. Two intercondylar fossae are present on the proximal tibial surface, one anterior to the intercondylar eminence and one posterior to it. The ACL and the anterior horns of the medial and the lateral menisci attach in the anterior intercondylar fossa. The PCL and the posterior horns of the menisci attach in the posterior intercondylar fossa.

Tibial spine fractures are commonly seen in children and adolescents, but a study suggests that these fractures occur more frequently in adults than was previously thought.[39] The injury is more common in children than in adults because the ligaments are stronger than the adjacent physeal plates in the immature skeleton. A fracture of the anterior tibial spine in children usually is associated with an ACL rupture, as is the case in adults.

Most tibial spine fractures occur as a result of violent knee twisting, hyperflexion, hyperextension, or valgus-varus forces generated during motor vehicle collisions or athletic activities. The tibial spines are fractured by twisting knee movements, whereas hyperextension or hyperflexion forces may cause avulsion of the intercondylar eminence or of the cruciate ligaments from their tibial attachments.

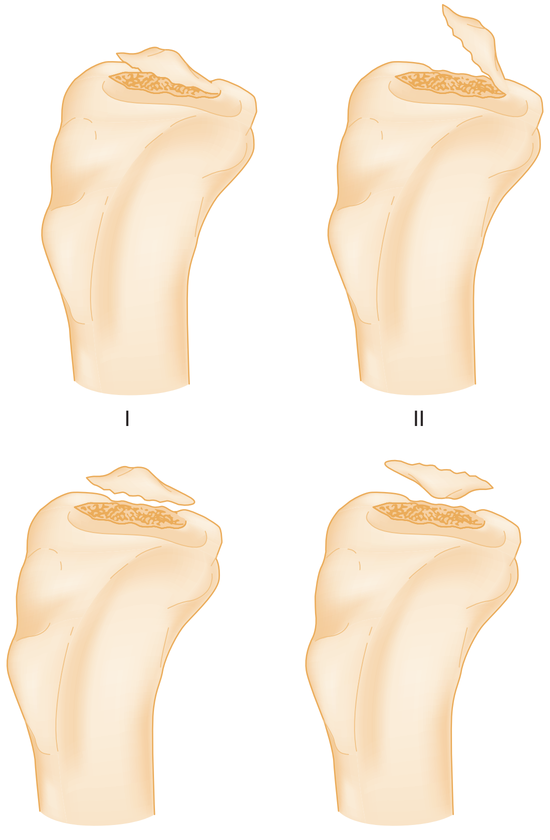


Figure 57-7. Tibial eminence fracture classification. *Type I*: The fracture fragment is elevated anteriorly only slightly; *type II*: the anterior fracture fragment is elevated with only minimal posterior attachment; *type IIIA*: the fracture fragment is completely separated from the tibia; *type IIIB*: the fracture fragment is completely separated and rotated. (Adapted from Meyers MH, McKeever FM: Fracture of the intercondylar eminence of the tibia. J Bone Joint Surg Am 41(2):209-220, 1959.)

Clinical Features

After tibial spine fracture the patient reports pain and swelling of the knee and may be unable to bear weight on the affected extremity. Examination confirms acute hemarthrosis and may reveal a block to full knee extension. Tense effusion may limit range of motion, hinder physical examination, and mask ligament disruption. Definite ACL laxity is associated with this injury, and patients may exhibit an anterior drawer sign, a positive result on Lachman's test, or other signs of ligamentous laxity. In the presence of open physes, tibial spine fractures usually are isolated injuries. Adults are more likely to have an associated tear of the MCL, or intra-articular fracture, which portends a worse prognosis.[39]

Diagnostic Strategies

Radiographic evaluation should include standard AP and lateral views, and a tunnel view provides a clearer look at the intercondylar area and may reveal the diagnosis. Joint margins should be examined closely for evidence of collateral ligament or capsular bone avulsions. CT sometimes is required to show the location and displacement of the fracture. The fabella, present in some patients, is a sesamoid bone located in the lateral head of the gastrocnemius muscle and should not be mistaken for an intra-articular loose body or fracture fragment.

The classification of tibial spine fractures is based on the degree of displacement (Fig. 57-7). Type I involves incomplete avulsion of the tibial spine without displacement. In type II, an incomplete avulsion is associated with minimal displacement of the anterior third of the fracture fragment, but the posterior portion remains adherent. Type III is characterized by complete separation of the fragment from its fracture bed and has a higher associated rate of collateral ligament injuries and peripheral meniscal tears. Type III may be subdivided into type IIIA, fractures with complete displacement, and type IIIB, fractures with displacement and rotation (see Fig. 57-7).

Arthroscopy is useful for diagnosis and treatment of tibial spine fractures. This modality allows drainage of tense hemarthrosis and enables precise diagnosis and classification, especially for children, in whom the diagnosis can be difficult because of developing skeletal changes.

Management

Conservative treatment is effective for all type I injuries. Nondisplaced or incomplete tibial spine fractures generally heal well when treated with cast immobilization in full extension for approximately 6 weeks. Type I and II fractures may require arthroscopy for lavage and accurate classification. If satisfactory closed reduction cannot be obtained or there is associated ligamentous injury, open or arthroscopic reduction and internal fixation should be performed. For restoration of normal function of the ACL, displaced or rotated fragments must be reduced. Type III fractures usually require arthroscopic or open reduction; screws and tension band wiring techniques have yielded excellent results.[32]

www.ketabpezeshki.com 66485457-66963820

With most uncomplicated fractures of the tibial spine, a good result can be expected when the fracture heals and restores function to the avulsed ACL. A poor outcome, with residual pain and instability, may be associated with additional intra-articular fractures and damage to the MCL.

Epiphyseal Fractures

Anatomy and Pathophysiology

The physes, which are present at the end of the long bones, are primarily responsible for longitudinal growth through the process of endochondral ossification. From birth to skeletal maturity, the distal femoral growth plate contributes 70% of the growth of the femur and 37% of the growth of the lower extremity.[40] Likewise, the upper tibial epiphysis accounts for most of the long growth of the tibia.

Biomechanical data and clinical studies in children and adolescents have confirmed that the ligaments and articular capsule are stronger than the bone and epiphyseal plate.[41] As a result, trauma to this region of the maturing skeleton usually injures the cartilaginous epiphyseal plate. In this way, the physis protects the joint surface from the grossly comminuted fractures seen in adults.

Despite data showing that the physis is the weakest link in the immature skeletal unit, only 15 to 20% of all fractures in children occur through the growth plate.[42]

The proximal tibial physis is far more resistant than other physes as a result of the unique anatomic features of this site.[40] The proximal tibial physis has no significant attachments to the collateral ligaments of the knee. The LCL inserts into the head of the fibula and has no tibial attachment, and the MCL has only a minor attachment to the epiphysis. The major portion of this ligament is attached to the tibial shaft well below the epiphysis. Varus or valgus stress is more likely to injure the distal femoral physis or the tibial metaphysis. Fracture-separation of the distal femoral growth plate and proximal tibial epiphysis most often is caused by an indirect mechanism, commonly related to sports injuries.[40] The Salter-Harris classification of epiphyseal injuries is described in Chapter 49.

Clinical Features

Epiphyseal injuries should be suspected in a child or adolescent who has juxta-articular (growth plate) tenderness, limps, or refuses to or cannot bear weight. The degree of discomfort varies, but the pain often is severe. Depending on the mechanism of injury, the overlying soft tissue may be abraded or lacerated. Swelling is usual in the overlying soft tissue, and an effusion may be present. If the separation is displaced, an angular deformity may be noted.

Epiphyseal growth plate fractures in the lower extremity carry a high incidence of associated injury. Physeal fractures in the region of the knee may be associated with ligament injuries, especially to the ACL and MCL, in one half of the patients. The most serious injury associated with a proximal tibial physis fracture is neurovascular trauma. In particular, popliteal artery injuries have been associated with these fractures, especially when posterolateral or posteromedial displacement is a feature. Peroneal nerve injury also has been reported and may range in severity from neurapraxia to complete disruption.[40]

Diagnostic Strategies

Plain radiography remains the primary means for evaluating epiphyseal injuries. Diagnosis is based on epiphyseal displacement, widening of the physis, and obliteration or haziness of the normal sharply defined, fine, sclerotic opposing margins of the metaphysis and epiphysis. The latter may result from angulation at one or both sites. Oblique views may be required to show nondisplaced fractures of the epiphysis. CT or MRI can evaluate more fully or classify injuries that already are established on the basis of plain radiography; in the acute setting, CT is more readily available.

Management

The most common complication of fractures through the proximal tibial physis is growth disturbance.[41] When growth arrest occurs (approximately 1% of cases), it usually is partial and results from formation of a bridge of bone from the metaphysis to the epiphysis, crossing the growth plate. Although shortening or deformity is less well tolerated in the lower extremity because of weightbearing, many of the growth disturbances do not prove to be clinically significant because of the ability of the immature skeleton to remodel; few such cases are reported to be of sufficient severity to interfere with function.

With regard to treatment, important differences exist between fractures in children and fractures in adults. In general, fractures in children heal rapidly. The younger the child, the more rapidly the fracture heals. In newborn infants, callus forms within 1 week after a birth injury. During the first year, callus is established within 2 weeks; callus takes slightly longer to form in toddlers. Fracture modeling also is more extensive in younger children and when the fracture is closer to the end of the bone. Modeling is less perfect in fractures of the mid-diaphysis in older children. Reduction of fractures near the proximal or distal end of the bone need not be perfect.

If a child has juxta-articular tenderness with negative radiographic findings, a growth plate injury (Salter-Harris type I) should be assumed. If it is difficult to determine whether a line on the radiograph is an epiphyseal line or fracture, a comparison view of the contralateral limb should be obtained. Because growth centers ossify at different times, this technique of comparing the uninvolved limb is often of great assistance in confirming a suspected physeal injury. In such cases, when a physeal injury is suspected, the extremity should be immobilized for approximately 2 weeks and reevaluated with at least a plain film, looking for periosteal new bone or physeal thickening. In general, emergency management of most epiphyseal fractures of the distal femur or proximal tibia includes ice, elevation, and immobilization with a long leg posterior splint, with early orthopedic consultation. Anatomic reduction is desirable for displaced fractures of the distal femur and proximal tibial epiphysis. Open reduction usually is required only for patients in whom closed reduction fails.[43]

Late complications include angular deformity, leg length discrepancy, stiffness, quadriceps atrophy, and persistent instability of the knee. Delayed union or nonunion is almost never a problem except in patients with an underlying neuropathy.[32] Because growth inhibition may follow even nondisplaced physeal fractures, long-term orthopedic follow-up care is advisable.

Bone Bruise

Bone bruise is a radiographic diagnosis, involving areas of cancellous bone with high signal intensity on MRI fat suppression sequences. Bone bruise may be present in approximately one half of acutely injured knees.[44] A high proportion of patients with a bone bruise have significant soft tissue injury. Nearly all bone bruises resolve after 1 year.[44]

Osteochondritis Dissecans

Osteochondritis dissecans is a rare orthopedic disorder of unknown cause (Fig. 57-8). The disorder is found mainly in adolescents and results in partial or total separation of a segment of

www.ketabpezeshki.com 66485457-66963820

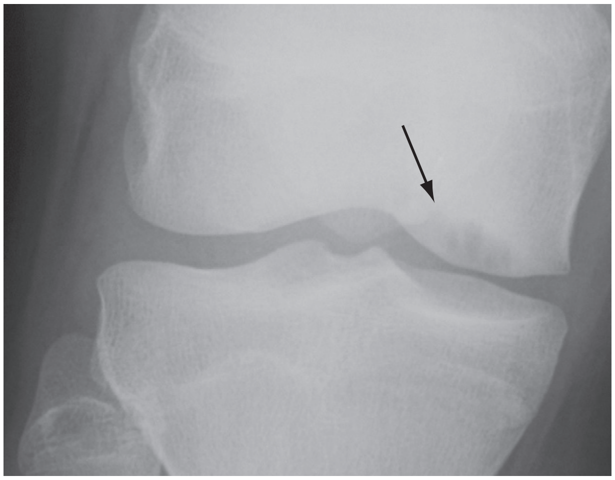


Figure 57-8. Osteochondritis dissecans. The arrow indicates a subcortical radiolucency in the knee of an adolescent female with chronic medial knee pain.

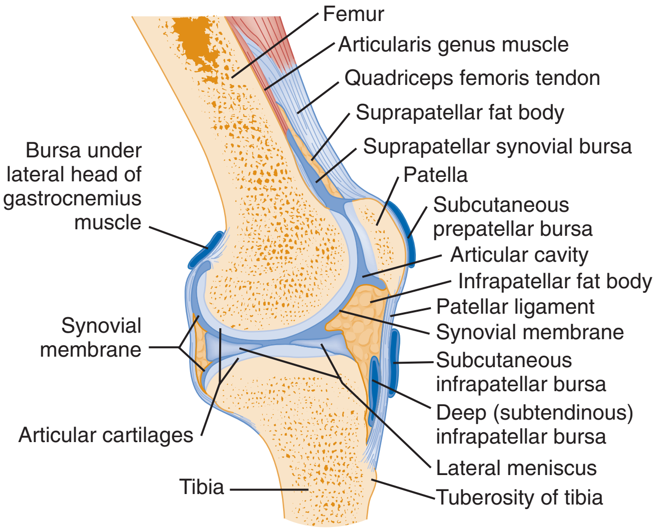


Figure 57-9. Parasagittal section (lateral to midline) of the knee showing extensor mechanisms and relevant structures.

articular cartilage and subchondral bone from the underlying bone. It is commonly unilateral, involving the non–weight-bearing lateral aspect of the medial femoral condyle, and is thought to be related to acute or chronic trauma. Occasionally the lateral femoral condyle or inferior patella pole is involved. Patients often have pain, swelling, and giving-way episodes without a history of trauma. Localized tenderness of the condyle often is the only physical finding. Routine radiographic views usually are diagnostic; a subcortical lucency (see Fig. 57-8) can be appreciated, and an osteochondral fragment may be seen separated from the underlying bone. MRI or CT may aid in determining the exact location and extent of the osteochondrotic lesion. ED patients with suspected osteochondritis dissecans should not bear weight until seen by an orthopedist.

The management of these patients is based on the stability of the osteochondral fragment and the maturity of the skeleton.[45] If the epiphyses are open, conservative treatment with protective weightbearing usually results in healing of the lesion. When the epiphyses are closed, the prognosis for healing is guarded. If the fragments are detached, the loose fragments require surgery for removal or fixation. Protected range of motion with non–weight-bearing activity for 6 to 10 weeks generally is advised.

Osteonecrosis

Osteonecrosis occurs when disruption of the blood supply to the bone causes infarction. The knee is a common site of involvement, particularly the weight-bearing surface of the medial femoral condyle.[46] Spontaneous osteonecrosis usually affects middle-aged and elderly patients, whereas secondary osteonecrosis may occur in younger patients related to corticosteroid therapy or in association with sickle cell disease, lupus, or renal transplantation, among many other risk factors.[46] The exact cause is unknown. A common clinical presentation is spontaneous onset of severe localized knee pain that may be accompanied by an effusion and loss of joint motion. The physical examination reveals point tenderness over the involved femoral condyle or tibial compartment. Radiographs obtained at the onset of symptoms usually are normal in appearance, and the diagnosis is confirmed with technetium bone scanning, which shows increased activity. MRI also is diagnostic of acute osteonecrosis. Subchondral marrow signal abnormality is the earliest change noted; subchondral collapse and fracture may be seen in more advanced cases.[47]

Initially, most patients can be managed with conservative treatment consisting of rest, protected weightbearing, and nonsteroidal anti-inflammatory drugs (NSAIDs). The outcome depends on the percentage of the weight-bearing surface involved with the process. If the lesion is small, no surgical treatment is required. Over the long term, degenerative changes will develop in most patients, but initially the changes are not severe. For more advanced stages of femoral osteonecrosis, various surgical treatments have been proposed, including arthroscopic débridement, proximal tibial osteotomy, prosthetic replacement, and allografting.[46]

Extensor Mechanism Injuries

Anatomy and Pathophysiology

The extensor mechanism consists of the quadriceps muscles, quadriceps tendon, medial and lateral retinacula, patella, patellar tendon, and tibial tubercle (Fig. 57-9). Passive and dynamic stabilization of the patella are aided by the surrounding soft tissue. Although this anatomic complex encompasses the most superficial aspect of the knee, ruptures of the extensor mechanism are infrequent injuries relative to other types of injuries of the knee joint. Disruptions of the extensor mechanism may occur at any level from the quadriceps muscle to the insertion on the tibial tubercle. Injury generally occurs as a result of sudden vigorous contraction of the quadriceps muscle with the knee in a flexed position, laceration, or a direct blow. Rupture of the quadriceps tendon usually occurs at or just proximal to the patellar insertion. Occasionally the rupture may extend into the vastus intermedius tendon or transversely into the retinaculum. Most patellar tendon ruptures occur at the site of origin on the inferior pole of the patella.

Chronic systemic conditions, including rheumatoid arthritis, gout, systemic lupus erythematosus, hyperparathyroidism, and iatrogenic immunosuppression in organ transplant recipients, may render the tendon vulnerable to rupture.[48] Several studies have implicated use of steroids or fluoroquinolones in tendon rupture.[49] In children, quadriceps and patellar tendon ruptures are rare, and muscle tears seem to predominate. In adolescents, patellofemoral dysplasia, chronic tendinitis, and the use of steroids are predisposing factors. Dysplasia may cause extensor mechanism injury by repetitive tensile overloading, and corticosteroids seem to weaken collagen ultrastructure and impair the reparative process.

www.ketabpezeshki.com 66485457-66963820

Clinical Features

Clinical evaluation can elicit the correct diagnosis in most cases of complete disruption of the extensor mechanism.[50] Patients with extensor disruption may have the following signs and symptoms: (1) acute onset of pain, swelling, and ecchymoses over the anterior aspect of the knee and a palpable defect in the patella, quadriceps tendon, or patella tendon; (2) loss or limitation of ability for active leg extension (extension lag usually is seen when extension for the last 10 degrees is performed haltingly or with difficulty); (3) high-riding patella (patella alta) with patellar tendon rupture and superior retraction; and (4) low-riding patella (patella baja) with quadriceps tendon rupture and inferior retraction. Partial disruptions may be difficult to diagnose on clinical examination and may require MRI for confirmation.

Diagnostic Strategies

Standard AP and lateral radiographs should be obtained and may reveal characteristic findings, possibly including obliteration of the quadriceps or patella tendon, a poorly defined suprapatellar or infrapatellar soft tissue mass, soft tissue calcific densities, or a displaced patella (Fig. 57-10). Patella alta may be sought on the lateral radiograph with use of a ratio of patellar length to patellar tendon length (the Insall-Salvati ratio). If this ratio is less than 0.8, patella alta is present.[51,52] The degree of flexion should not affect this ratio, which relies on the inelasticity of the patellar tendon. In patients with quadriceps rupture, degenerative spurring of the patella (tooth sign) commonly is seen on tangential views. Obliteration of the extensor tendons may be caused by a frayed tendon and surrounding hematoma. A soft tissue mass represents proximal or distal retraction of the torn tendon. Calcific densities may represent avulsed bone fragments of the patella or tibial tubercle or dystrophic calcifications in the substance of the tendons. Despite these multiple radiographic signs, the correct diagnosis is infrequently made by plain radiography in cases of incomplete quadriceps tendon rupture. MRI shows the entire extensor mechanism and is the best imaging modality for diagnosing pathology in this system, even in the acute phase. MRI usually is reserved for patients with possible incomplete disruption or for those with a complication of intra-articular derangements.

Management

Treatment of acute extensor mechanism injuries produces a much better clinical outcome if instituted early, within 2 to 6 weeks of the initial injury. Accurate diagnosis at the time of injury is essential. Patients with delayed diagnosis of patellar tendon rupture may experience significant retraction of the patella proximally and subsequent development of quadriceps contractures or adhesions. If the tear is only partial, immobilization with the knee in full extension for 4 to 6 weeks is the treatment of choice.[53] Surgical intervention is required for reattachment of complete tendon ruptures, and repair should be performed as soon as possible after injury for the best results to be achieved. Numerous techniques have been described for early and late repairs, and the choice of procedure depends on several factors, including location of the tear, lag time between injury and repair, and presence or absence of adhesions. After primary repair, the knee is immobilized in full extension with a long leg cast until healing is complete. Gradually progressive active and passive range-of-motion exercises are indicated for optimal results.

Patellar Fractures

Anatomy and Pathophysiology

The patella is the largest sesamoid bone in the body. It is held in place by the quadriceps tendon, the patellar ligament, and the medial and lateral retinacula. As an integral part of the extensor mechanism, the patella increases the effective lever arm of the quadriceps by providing anterior displacement of the quadriceps tendon.[2] All fractures of the patella, except for small avulsion fractures of the rim, are intra-articular.

Patellar fractures constitute approximately 1% of all skeletal injuries and occur in all age groups.[54] Patellar fractures are classified as transverse, stellate, or comminuted; longitudinal or marginal; proximal pole or distal pole; and rarely osteochondral. They

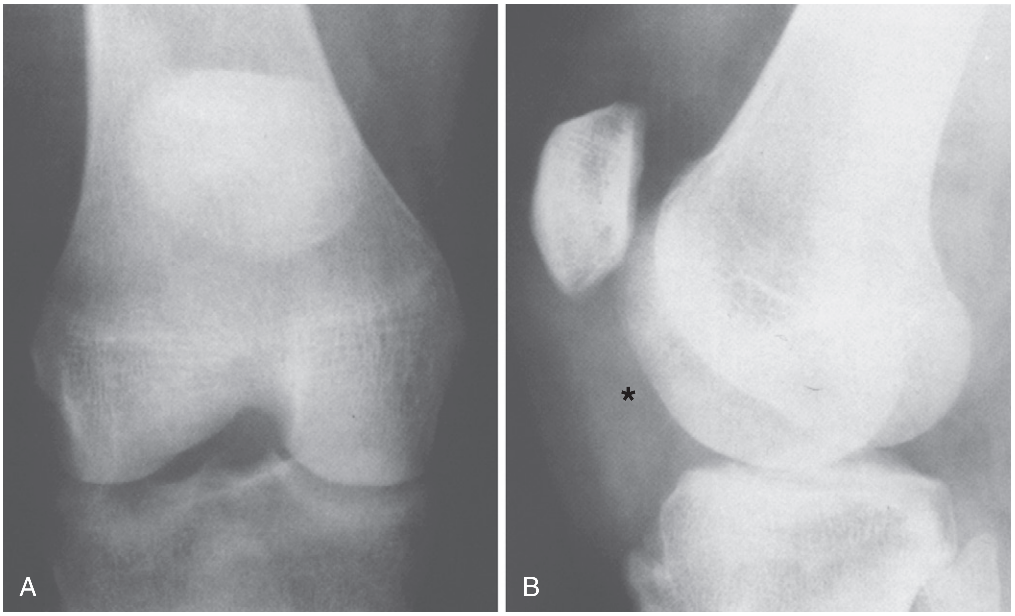


Figure 57-10. Rupture of the patellar tendon, resulting in the high-riding patella in frontal **(A)** and lateral **(B)** projections. In **B,** the normally lucent infrapatellar portion of the joint space is dense *(asterisk),* representing blood within the anterior compartment. (From Harris JH, et al: The Radiology of Emergency Medicine, 3rd ed. Baltimore, Williams & Wilkins, 1993.)

www.ketabpezeshki.com 66485457-66963820

may be either displaced or nondisplaced and occur either from direct or indirect forces or from dislocation. The most common fracture pattern is the *transverse* fracture (accounting for 50-80% of cases).[54] This type often is seen in young adults and usually results from a powerful contractile force transmitted from the quadriceps tendon. This force may pull the superior portion of the patella upward, leading to wide displacement. In such cases the medial and lateral retinacula are usually disrupted, resulting in significant functional disability; active extension is impossible. Nondisplaced transverse patellar fractures usually are caused by a direct blow to the anterior aspect of the patella (e.g., a fall on the knee or a direct blow sustained in vehicular trauma). The retinaculum and extensor mechanism usually remain intact, and the patient retains limited functional ability for active extension. *Stellate* and *comminuted* fractures account for 30 to 35% of all patellar fractures and commonly result from a direct impact.[54] The fracture elements often appear as separated fragments on plain radiographs, but they are held in place and supported by the medial and lateral retinacula and the overlying soft tissues. Small proximal fragments are at risk for avascular necrosis because the patellar blood supply is central and inferior. *Longitudinal* or *marginal* vertical patellar fractures are less common, usually are the result of direct injury, and involve the lateral facet.

Clinical Features

On physical examination, tenderness, swelling, and ecchymosis over the patella and prepatellar bursa are noted. Active extension may be limited or absent, depending on the fracture pattern and amount of fragment displacement. Associated injuries may include fractures of the femoral neck, dislocation of the hip, and acetabulum fractures.

Diagnostic Strategies

Radiologic evaluation of patellar fractures should include standard AP, lateral, and sunrise views. Most patellar fractures are obvious on plain radiographs, but vertical marginal fractures may be difficult to identify; they are obscured by the femur on the AP view and not seen at all on the lateral view.[53,54] Close examination of sunrise (or equivalent) views may reveal an osteochondral avulsion fragment or marginal fracture (Fig. 57-11). Bipartite and multipartite patellae are common normal variants and should not be confused with fractures. Ossification centers are found at the upper outer quadrant of the patella and have smooth cortical margins, but differentiating physeal lines from fractures can be difficult. Comparison radiographs may be helpful because these anatomic anomalies often are bilateral. In some cases, MRI or arthroscopy may be needed to identify occult marginal fractures or free osteochondral fragments.

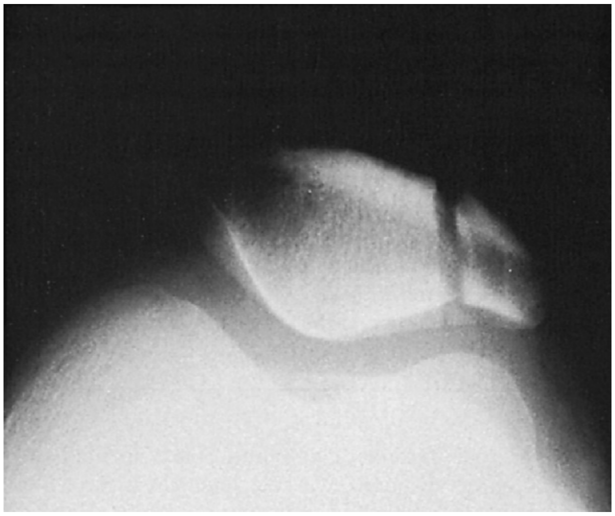


Figure 57-11. Patellar fracture, sunrise view. The sharp nonsclerotic margins identify this as an acute fracture and not a congenital finding. (From Rosen P, et al: Diagnostic Radiology in Emergency Medicine. St Louis, Mosby, 1992, p 196.)

Management

If the patient can actively extend the knee without displacing the fracture, the retinaculum is intact, and the fracture may be treated nonoperatively. Nondisplaced patellar fractures usually are treated with a long leg cast for 4 to 6 weeks, with uniformly good results. Casting the knee in full extension relieves the patella of almost all stress during the healing period. For initial management, a knee immobilizer may be used. Patients should be instructed to use crutches, with partial weightbearing as tolerated, and should be referred for orthopedic or primary care follow-up.

For widely displaced transverse fractures, open reduction and internal fixation are necessary for optimal results. Although operative techniques vary among surgeons, tension band wire and suturing of the retinaculum often are used. A knee immobilizer or long leg posterior splint can be used initially to immobilize the extremity before definitive care is provided. Treatment options for displaced comminuted fractures include open reduction and internal fixation and partial or complete patellectomy.

Fracture fragment separation and dehiscence of the fracture repair are uncommon. They generally result from inadequate internal fixation or, in some cases, an inadequate period of immobilization. Avascular necrosis is rare. Range of motion generally is good after all procedures. Persistent patellofemoral pain and osteoarthritic symptoms are reported as late sequelae of patellar fractures in 56% of patients.[54]

Patellar Dislocation

Anatomy and Pathophysiology

Traumatic patellar dislocation is a relatively common knee injury and can lead to recurrent patellar subluxation and dislocation. It is more common in children than in adults. Most cases are lateral, and the mechanism of injury usually is a direct blow to the anterior or medial surface of the patella. It may occur from an athletic injury caused by a valgus stress combined with flexion and external rotation. In nearly all cases, disruption or sprain in the medial patellar retinaculum results from stretching of this structure as the patella subluxates laterally; subluxation usually indicates a stretched medial retinaculum, and dislocation suggests a tear. Although extra-articular patella dislocations are common, intra-articular dislocations are rare occurrences that are considered in any patient with a locked knee.

The quadriceps angle (Q angle) is measured with the quadriceps contracted. The angle is formed by lines drawn on an AP radiograph from the tibial tubercle to the center of the patella and from the center of the patella to the anterior superior iliac spine. Normally, this angle is 10 degrees or less in men; it may be 15 degrees in women. A Q angle exceeding these dimensions may predispose the patient to patellofemoral problems.[55]

Clinical Features

Patients with lateral patellar dislocation may complain of the knee giving out, accompanied by pain and swelling. Inability to bear weight and inability to flex the knee are common complaints. There may be a history of previous dislocation. Examination

www.ketabpezeshki.com 66485457-66963820

reveals a defect anteriorly with the patella deviated laterally. Tenderness along the medial joint line usually can be elicited by palpation, and an effusion may be present. Acute hemarthrosis is seen most commonly if there is an associated osteochondral fracture. Osteochondral fractures typically occur on the articular surface of the patella and may involve only cartilage (chondral fractures) or include a piece of underlying cortical bone. Patellar dislocations may reduce spontaneously, or the patient may self-reduce the dislocation, usually followed by formation of a large effusion.

The patellar apprehension test is used to aid the clinical identification of patients at risk for patellar dislocation or subluxation. The *apprehension sign* refers to the combination of manifestations of anxiety and anticipatory reactions observed in the patient when the examiner attempts to slide the nondisplaced patella laterally. As a more objective element of this reactive pattern, the patient may forcefully contract the quadriceps femoris muscle in an attempt to prevent such displacement and its associated pain. A positive result on the apprehension test indicates a tendency for patellar subluxation or dislocation. This test has no proven value and is not necessary in a patient with acute patellar dislocation, but it may be useful in establishing the diagnosis in patients who report an "event" that resolved spontaneously.

Diagnostic Strategies

Standard AP and lateral radiographic views generally are adequate for diagnosis. Obtaining a sunrise (skyline) view usually is not possible because of pain and inability to flex the knee. Radiographic findings include lateral deviation of the patella out of the trochlear groove, usually with an effusion. Radiographs should be examined for evidence of avulsion fractures.

Management

After dislocation is diagnosed, closed reduction should be attempted. Force or pressure should be directed anteromedially on the lateral patellar margin while gentle extension of the leg is attempted simultaneously. Uncommonly, patellar reduction may be difficult. Closed reduction can be achieved by applying downward pressure to the lateral aspect of the patella, creating an external rotational force that unlocks the medial patellar facet.[56] Postreduction radiographs are recommended and should reveal the patella in the trochlear grove. Osteochondral avulsion fragments may be visualized radiographically, and postreduction radiographs should be examined carefully for their presence. Radiologically evident intra-articular loose bodies may require arthroscopic removal.

Typically, traumatic patellar dislocations occur with disruption of the medial retinaculum but an intact lateral retinaculum, preventing internal rotation. Dislocations that are irreducible by conventional methods may be associated with significant internal rotation and lateral retinaculum pathology.

After successful reduction, the knee should be immobilized in full extension for 3 to 6 weeks to allow adequate time for the medial retinaculum to heal. Ice, elevation, non–weight-bearing status, and analgesia provide additional benefit in the acute setting. The patient can be discharged with referral for orthopedic or primary care follow-up within 2 weeks. Although the incidence of recurrence may be decreased with appropriate therapy and proper patient selection, up to 44% will experience a recurrent dislocation, and more than one half of all patients with a primary patellar dislocation will continue to have symptoms of instability or anterior knee pain.[57] Patellar dislocations often recur and sometimes require surgery, involving arthroscopic release of the lateral retinaculum.

Soft Tissue Injuries

The knee is the most commonly injured joint. The ligaments of the knee function in conjunction with the joint capsule to limit varus-valgus (medial-lateral) bending of the knee and both anterior-posterior and varus-valgus translations of the knee. Ligament injuries to the knee may involve any or all of the ligaments and may range in severity from mild sprain to complete tears. Collateral ligament injury usually causes tenderness and pain along the joint line. Cruciate injuries pose more of a diagnostic dilemma because they are intra-articular structures.

Cruciate Ligament Injuries

The cruciate ligaments are the primary stabilizers for anterior and posterior displacement of the tibia on the femur. They are so named (Latin *crus* means "cross") because they cross each other between their attachments. The ACL extends obliquely upward, medially, and backward from the anterior intercondylar area of the tibia to the medial aspect of the lateral femoral condyle. The ACL prevents excessive anterior displacement of the tibia on the femur and helps control rotation and hyperextension of the knee during cutting, twisting, and turning activities. It is the most commonly injured major ligament of the knee, with more than 100,000 new ACL tears occurring in the United States annually.[58] The PCL passes upward, laterally, and forward medial to the ACL from the posterior intercondylar area of the tibia to the lateral aspect of the medial condyle of the femur. The PCL prevents excessive posterior displacement of the tibia on the femur, especially during flexion. The PCL is extremely strong, and injuries are relatively uncommon. Cruciate ligament injury is uncommon in children with open physes.

The ACL is commonly injured in sports. Numerous mechanisms of injury produce ACL disruption. Although ACL injuries can be caused by contact, they are more common in noncontact sports, with the plant-and-pivot and stop-and-jump mechanisms predominating. A direct blow to the flexed knee, as may occur in motor vehicle collisions (from the dashboard), and turf injuries with the knee flexed and the ankle plantar-flexed also can result in an ACL injury.

One half of ACL injuries are associated with meniscal tears. The lateral meniscus is torn more commonly than the medial meniscus in acute ACL injuries, but in chronic ACL tears the medial meniscus is more commonly involved. The classic "unhappy triad" of ACL, MCL, and medial meniscus injury may actually be less common than the association of torn ACL, torn MCL, and torn lateral meniscus.

The diagnosis of ACL injury often can be made from the history alone. Pain is the most common complaint with ACL rupture and usually is immediate. An audible "pop" at the time of injury is an important clue and is reported by approximately 70% of patients with ACL rupture. Patients also may report buckling, locking, or collapse of the knee and its inability to bear weight. The anterior drawer test is used to diagnose ACL injuries (see earlier).

PCL injuries are comparatively rare. Mechanisms include a fall onto the ground with the foot plantar-flexed (striking the tibial tubercle), a direct posterior blow to a flexed knee (e.g., a dashboard injury), hyperflexion, hyperextension, severe varus or valgus loads after failure of the collaterals, and knee dislocations. Nearly all PCL injuries are associated with other ligament injuries, including concurrent injuries of the MCL, ACL, or posterolateral complex.[58,59] PCL injuries are classified as partial (grade I or II) or complete (grade III) tears. Pain and swelling are common complaints with isolated PCL tears and with PCL tears having combined capsuloligamentous disruption. Popping or tearing sensations are infrequently noted, and instability usually is not immediately appreciated. Later, the patient may complain of

www.ketabpezeshki.com 66485457-66963820

feeling the femur "fall off" the tibia. The posterior drawer test (see earlier) is commonly done to assess the integrity of the PCL.

Clinical evaluation is moderately sensitive for ACL tears and other intra-articular injuries, with sensitivity for ACL injury ranging from 62 to 100% and 64 to 82% for meniscus injury.[60] The lesions most difficult to diagnose are chondral fractures, tears in the ACL, loose bodies, and fibrotic fat pads.

Collateral Ligament Injuries

The medial stabilizers of the knee are the joint capsule and the MCL. The semimembranosus and pes anserinus are medial dynamic stabilizers. These structures resist valgus laxity and medial rotary instability. The MCL is a two-part structure with both a long superficial and a deep capsular component; the latter attaches to the medial meniscus and acts as a stabilizer for this structure. The MCL usually is injured by a direct blow or impact to the lateral aspect of the knee, which imposes a valgus stress. MCL injury is the most common isolated knee ligament injury, and it is the injury most commonly associated with ACL injury. MCL injury usually does not require surgical treatment.

The lateral stabilizers of the knee are the LCL and the lateral joint capsule. Secondary contributors to lateral stability are supplied by the IT band, biceps tendon, and popliteal arcuate complex in the posterolateral corner of the knee. Resistance to varus stress is provided mainly by the LCL. Fibers descend from the lateral femoral condyle and insert at the fibula head. The lateral ligaments are under tension during standing and walking, when they are at or near maximal extension. The LCL usually is injured by a mechanism of hyperextension with varus stress, commonly accompanied by a direct blow or rotation. Injuries to the LCL are less common but more disabling than injuries of the MCL. The lower incidence of injury is attributed to the greater mobility of the LCL and overall greater stability of the lateral compartment. Varus injury is uncommon because the inner aspect of the knee is protected by the opposite leg. The forces necessary to produce LCL injury usually are greater than the forces required for medial injury, which partially explains the high frequency of associated injuries accompanying LCL injury. The tendon of the biceps femoris muscle attaches to the head of the fibula, just inferior to which the peroneal nerve passes. Because of this relationship, common peroneal nerve injury and biceps femoris tendon injury are considered in patients with LCL injury.

The accuracy of the knee examination for ligamentous damage is enhanced if it is accomplished soon after injury and before the onset of swelling and pain, but the patient may not tolerate the examination in any case, and muscle spasm can obscure findings. In any case, ligamentous injuries are not emergencies and can be diagnosed definitively after the acute phase has passed. Focal tenderness at the origin or insertion sites suggests collateral ligament trauma but also can occur with muscular injury, osseous pathology, or meniscal tear. Range of motion should be documented and stability testing done to assess ligamentous injury as outlined previously.

Diagnostic Strategies. Plain radiography may be used before stress testing in cases of suspected ligamentous injury to rule out the possibility of an associated fracture. Although patients with isolated collateral ligament strain rarely show acute osseous pathology, the yield increases in cases with radiographic evidence of traumatic effusion and in cases in which cruciate ligament injury is suspected. The initial radiographic evaluation should include AP, lateral, intercondylar notch, and sunrise views. Each radiograph should be evaluated for possible osteochondral injuries, loose bodies, or avulsion injuries at the attachment sites of ligaments. The lateral capsular sign, associated with the Segond fracture (see Fig. 57-5) and fracture of the posterior aspect of the lateral tibial plateau, commonly is associated with ACL tear.

Arthroscopy is the gold standard for diagnosis of soft tissue injuries of the knee (ligaments or menisci). MRI is useful but may miss small tears and anatomic abnormalities, and even if findings are normal, arthroscopy may still be necessary if symptoms persist. Moreover, abnormalities discovered at arthroscopy can be repaired. Therefore many orthopedic surgeons recommend arthroscopy rather than imaging for diagnostic workup of knee pain when the causative disorder is not apparent on physical examination.

Management. Isolated collateral ligament injuries of all grades usually are managed nonoperatively, provided that the ACL is intact. The nonoperative approach should focus on controlling pain, restoring range of motion, regaining muscle strength, and protecting the knee from further injury. Appropriate initial therapy includes ice, NSAIDs, and immobilization if needed to control pain. Patients may be placed on a regimen of partial weight-bearing or non–weight-bearing status with use of crutches. Orthopedic or primary care follow-up is advised, and a rehabilitative exercise program for quadriceps and hamstring strengthening may be instituted when the acute injury has resolved.

Management of an ACL tear is controversial, because short-term disability and long-term arthritic sequelae are difficult to predict. Most young patients with a complete ACL tear who are active in sports require reconstructive surgery to stabilize the knee. Surgical repair usually is performed arthroscopically after a delay of 2 to 3 weeks to allow swelling to subside. Older patients and patients who do not participate in active sports may be managed conservatively with muscle strength training. If recurrent functional instability subsequently develops, reconstruction may be considered at a later date.

Isolated PCL injuries are unusual and typically are managed nonoperatively. These injuries often are painful but usually do not lead to instability. Rehabilitation involves quadriceps strengthening and functional bracing. Over 10 to 20 years, degenerative changes of the articular surface may result in stiffness and pain.

Meniscal Injuries

Anatomy and Pathophysiology. The medial and lateral menisci are crescent-shaped fibrocartilaginous cushions that sit on the superior articular surface of the tibia and provide a gliding surface for the femoral condyles. They function as shock absorbers and aid in the distribution of stress across the joint surface by providing a larger area of contact. They also act as secondary stabilizers by deepening the tibial plateau. Normal tibiofemoral articulation and function depend on meniscal integrity; damage or loss leads to osteoarthritis. The medial meniscus is firmly attached anteriorly and posteriorly to the joint capsule. The lateral meniscus is less firmly attached to the capsule and more mobile. The menisci move slightly forward with extension and backward with flexion. Because of its greater mobility, the lateral meniscus is less vulnerable to injury. The meniscus is avascular except at the peripheral third, which has the greatest potential to heal after injury.

Meniscal injury classically manifests with pain and tenderness at the joint line, effusion, and clicking or locking of the knee. Significant hemarthrosis is less likely and suggests cruciate ligament injury. Intermittent locking results from a meniscal fragment blocking joint movement. By contrast, persistently decreased range of motion results from prevention of knee movement by effusion and pain. Injury to the menisci may be from a single traumatic episode, a degenerative process, or a combination. The mechanism usually involves a twisting maneuver on a weight-bearing knee. The force required sometimes can be as slight as arising from a chair while turning. Most meniscal tears are posterior.

Clinical Features. Meniscal injuries are unusual in children but become increasingly more common in adolescents and adults. An

www.ketabpezeshki.com 66485457-66963820

isolated meniscal tear should be suspected in a patient with a history of intermittent locking, effusion, giving way, and pain and physical examination findings of joint line tenderness and a positive result on McMurray's test. Cruciate tears invariably result in immediate hemarthrosis; meniscal tears usually result in development of an effusion over 12 to 24 hours. A second, more common presentation is that of a patient with an unstable knee who has chronic ACL insufficiency and similar history and physical examination findings.

The cardinal sign of a meniscal tear is local pain and tenderness along the joint line. Joint line pain and tenderness are especially apparent with extremes of flexion and extension. Not all tears of the menisci are symptomatic. Degenerative lesions of the posterior horn are relatively common in middle age and later and may be asymptomatic. The differential diagnosis for a torn meniscus is extensive and includes loose bodies, osteochondrotic lesions, tibial spine fractures, patellofemoral pain syndrome, popliteal tendinitis, plica syndromes, inflammatory arthritis, and discoid menisci with or without a tear. Meniscal tears commonly accompany ACL tears.

Diagnostic Strategies. Diagnosis of acute meniscal injury is difficult, and more so in the presence of any acute knee injury, especially ACL tear.[60] Meniscal injury cannot be diagnosed by plain radiography or CT scanning. Arthroscopy is the gold standard for diagnosis, and MRI is an alternative but may miss some meniscal tears.

Management. Definitive treatment of a meniscal injury is not urgent. Unless the knee is locked and cannot be extended or flexed, a patient with a meniscal tear should be managed with analgesics, immobilization, ice, non–weight-bearing status, and referral for orthopedic or primary care follow-up. The locked knee requires acute orthopedic consultation if a knee immobilizer cannot be applied. Surgery is reserved for cases with persistent symptoms that limit activity. Surgery involves arthroscopic exploration. The torn meniscal fragment is reattached if it is well vascularized; otherwise, it is resected.

Overuse Syndromes

Overuse syndromes result from repetitive trauma and inflammation. The typical complaint is knee pain, often localized to one of three particular areas: the medial aspect, the lateral aspect, or the peripatellar region. Medial knee pain may be caused by subluxation of the patella, a stress fracture of the upper third of the tibia, anserine bursitis or tendinitis, and MCL strain related to excessive foot pronation. Lateral knee pain may be caused by IT or popliteal tendinitis, LCL strain, or stress fracture of the fibula. Anterior pain is typical of lateral patellar compression syndrome, peripatellar tendinitis, and patellofemoral syndrome, the most common cause of knee pain.

Patellofemoral Pain Syndrome

Anatomy and Pathophysiology. The *patellofemoral pain syndrome* refers to the clinical presentation of anterior knee pain related to changes in the patellofemoral articulation. *Chondromalacia patellae* describes softening of the articular cartilage. Correlating pathologic changes on the surface of the patella and clinical symptoms has been difficult, and the pain mechanism has not been precisely defined.

Clinical Features. As noted, the patellofemoral pain syndrome is the most common cause of knee pain. Affected patients generally are 10 to 20 years of age and often have difficulty describing their symptoms clearly. The pain usually begins gradually and commonly is not related to trauma. One knee usually is more affected than the other. The knee is more painful with prolonged flexion (e.g., from sitting in a movie theater), and the discomfort typically is accentuated by stair climbing and kneeling. The patient may have instability related to patellar subluxation or dislocation. The syndrome occurs both in athletes and in elderly patients who have arthritis affecting the patellofemoral joint. Considerations in the differential diagnosis include tears of the menisci, plica syndrome, inflammatory or degenerative arthritis, ligament injuries, and overuse syndromes (e.g., prepatellar bursitis, patella tendinitis).

The physical examination should begin with observation. The patient may ambulate with an antalgic gait. A tibiofemoral joint effusion may be present. The patellar facets may be tender. Classically, compression of the patella against the femur with the knee extended causes pain. There may also be apprehension regarding medial or lateral subluxation.

Diagnostic Strategies. Plain films are typically normal, and more advanced studies should be undertaken only if other diagnoses are being considered.

Management. Most patients, regardless of the cause of their condition, respond to a rehabilitation program. Conservative treatment for patellofemoral pain usually is effective, with most patients responding to one or more of four types of treatment: (1) exercises to strengthen the quadriceps, (2) brace support of the patellofemoral mechanism, (3) activity modification limiting flexion, and (4) medications such as NSAIDs for pain. The initial goal is to reduce pain and improve function, with emphasis placed on strengthening the vastus medialis oblique muscle. The patient should receive appropriate referral to ensure that an optimal rehabilitative scheme is designed.

Iliotibial Band Syndrome

The IT band is a strip of fascia lata that extends from the iliac crest to the lateral tibial tubercle. It connects the lateral femoral condyle and the lateral tibia and stabilizes the knee joint in extension. Irritation from overuse can cause inflammation of a bursa underlying the IT band at the lateral femoral epicondyle, resulting in lateral knee pain. The syndrome is most common in distance runners and is more likely in hyperpronators. Physical findings include localized tenderness of the lateral femoral epicondyle and IT tightness or pain, elicited by Ober's or a related test.[61] In Ober's test the patient lies on the side with the unaffected leg down, flexed to 90 degrees at the hip and knee. The affected hip is abducted, the knee is extended, then the hip is allowed to return to neutral adduction with gravity. Failure of the hip to adduct fully with gravity or reproduction of pain at the lateral knee indicates IT tightness or inflammation, respectively. Radiographs are normal in appearance. Considerations in the differential diagnosis include early degenerative joint disease, cystic or torn lateral meniscus, lateral capsular strain, lateral tibial or femoral condyle osteonecrosis, stress reactions, chondromalacia, and popliteus tendinitis. Treatment involves rest, ice, and NSAIDs during the acute phase, followed by an IT band stretching regimen, improved footwear and orthotics when indicated, and gradual return to previous levels of activity. Steroid injections are helpful for refractory cases, and surgical release is uncommonly required.

Peripatellar Tendinitis

Peripatellar tendinitis, or *jumper's knee,* refers to a spectrum of patellar tendon and extensor mechanism abnormalities that result from chronic repetitive stress from jumping, running, or cutting. Microscopic tears occur in the tendon. Treatment involves NSAIDs, rest, and activity modification. Local steroid injections are not recommended. For highly competitive athletes and patients in whom conservative treatment fails to effect improvement, surgery with débridement of abnormal tissue may be performed.

www.ketabpezeshki.com 66485457-66963820

Plica Syndrome

Plicae, or redundant folds of synovium, are normal embryologic structures that persist in the adult knee. Repetitive bouts of synovitis within the plica may result in a tight inelastic band that interferes with knee motion. Patients typically complain of pain over the region of the medial femoral condyle brought on by activity but also occurring after sitting for prolonged periods. A snapping sensation is another commonly reported symptom as the plica sweeps across the femoral condyle. Other nonspecific symptoms include intermittent swelling, locking, weakness, and stiffness. The physical examination often elicits tenderness over the medial femoral condyle but not the medial joint line; the latter finding would be more typical of a medial meniscal lesion. An effusion, crepitus, loss of motion, quadriceps atrophy, and a positive result on McMurray's test may be noted as well.[62]

Plain radiography is necessary to exclude other causes of knee pain but is of no value in diagnosing plica syndrome, for which arthroscopy usually is required. Most plicae are incidental arthroscopic findings unrelated to underlying knee pathology. Medial patella pain is more likely to be related to patellofemoral maltracking than to plica syndrome. Likewise, anteromedial joint line tenderness is more likely to be related to a meniscal tear than to a pathologic plica.

Treatment involves rest and NSAIDs. When the acute symptoms have resolved, a rehabilitation program is instituted to emphasize quadriceps strengthening and stretching. Arthroscopic excision of pathologic plica may be necessary if conservative treatment fails.

Popliteus Tendinitis

The popliteus is a small, flat muscle that originates on the lateral femoral condyle and inserts on the posteromedial tibia, capsule, and lateral meniscus. It passes beneath the lateral head of the gastrocnemius. Its tendon is surrounded by a bursa that separates it from the fibular collateral ligament, femoral condyle, and capsule. Functionally, it prevents external rotation of the tibia and withdraws the lateral meniscus during flexion to prevent impingement between the femur and the tibia. A third function, along with the quadriceps and PCL, is to stabilize the knee by preventing forward displacement of the femur on the tibia. Popliteal tendinitis usually occurs in athletes and often causes localized pain over the posterior or posterolateral aspect of the knee. Running and walking downhill exacerbate symptoms. Usually there is no history of effusion, locking, or giving way.[63]

On physical examination, tenderness is noted at the insertion point of the muscle, medial to the insertion of the lateral head of the gastrocnemius. Because of the close relationship of the popliteus to other soft tissue structures, the diagnosis may be difficult. The Webb test is performed with the patient supine and the knee flexed to 90 degrees. The leg is rotated internally, and the patient is asked to resist the examiner's attempt to externally rotate the leg. Reproduction of symptoms suggests the diagnosis. Considerations in the differential diagnosis for popliteus tendinitis include injury of the biceps femoris insertion, lateral meniscus, lateral gastrocnemius, and IT band.

Treatment involves rest, ice, NSAIDs, and quadriceps strengthening and stretching. Most athletes can gradually return to activity in 10 to 14 days.

Bursitis

The knee has several bursae, which decrease friction between moving structures. They usually are thin but with repeated stress may become thickened and fluid-filled. The *prepatellar bursa* is located between the patella and the skin. The *superficial infrapatellar bursa* is located between the tibial tubercle and the skin. The *deep infrapatellar bursa* is located between the posterior margin of the distal part of the patellar tendon and the anterior aspect of the tibia. The *suprapatellar bursa* is not a true bursa but rather is an extension of the tibiofemoral joint capsule. The *anserine bursa* separates the pes anserinus from the distal portion of the MCL and the medial tibial condyle. As noted previously, *pes anserinus* means "goose foot" and *anserine* means "related to the pes anserinus." The term derives from the fact that the bursa underlies the anserine tendon, a three-forked structure constituting the insertion of the gracilis, sartorius, and semitendinosus muscles.

Bursitis is caused by repeated stress, infection, local trauma, crystal deposition, or systemic inflammatory arthropathy. It is important to differentiate bursitis from a joint effusion. Prepatellar bursitis is characterized by swelling with effusion of the superficial bursa overlying the lower pole of the patella. Passive motion usually is fully preserved, and the pain generally is mild. The disorder usually is caused by pressure from repetitive kneeling on a firm surface ("housemaid's knee"). The prepatellar bursa also is a common site of septic bursitis, and a common error is to confuse this entity with a septic knee (involving the tibiofemoral joint).

Anserine bursitis involves pain and tenderness at the proximal medial tibia, a few centimeters inferior to the medial joint line. It occurs most commonly in obese women in association with osteoarthritis of the knee but also may occur from overuse, especially in runners. It is characterized by a relatively abrupt onset of knee pain with localized tenderness and puffiness at the pes anserinus. It can be confused with a medial meniscal or MCL tear.

Radiographic studies may reveal soft tissue swelling. Ultrasound imaging also may detect the fluid collection. MRI may be helpful but is not required on an urgent basis. With any uncertainty regarding the possibility of infection, the bursa fluid should be aspirated, and Gram staining, culture, cell count, and crystal analysis of the aspirate should be performed.

Septic (bacterial) bursitis requires antibiotic treatment, with operative drainage in refractory cases. Aseptic (inflammatory) bursitis is treated with ice, rest, anti-inflammatories, and injection of bupivacaine and corticosteroids—the last, of course, being contraindicated in the presence of infection. All of the bursae of the knee may be injected with steroids; in the ED, steroid injection of the anserine and prepatellar bursae is most common.

Osteoarthritis

Osteoarthritis is joint inflammation caused by degeneration. The incidence increases with age, obesity, trauma, and meniscectomy. Pain usually is the initial complaint and typically is aggravated by activity and relieved by rest. Locking, giving way, and a sensation of instability may be associated complaints. The physical examination may reveal a gross angular deformity—either genu valgum (knock-knee) or genu varum (bowleg)—and an antalgic gait may be noted. The joint line of the involved compartment usually is tender. Osteoarthritis may involve one or all compartments of the knee.

Standard AP weight-bearing radiographs may reveal narrowing of the joint spaces, peripheral osteophyte formation, subchondral sclerosis, and cyst formation; they also may show angular deformity of the knee. Lateral and oblique views may show the presence of peripheral osteophytes and loose bodies. Tangential sunrise views are needed to evaluate the patellofemoral joint for osteophytes, sclerosis, and maltracking.

Treatment consists of activity modification, NSAIDs, bracing, and strengthening exercises. A cane may be helpful to unload the affected extremity and provide symptomatic relief. If the patient is obese, weight reduction is recommended. Surgical treatment is reserved for severe cases and may involve osteotomy, hemiarthroplasty, or total knee arthroplasty.

www.ketabpezeshki.com 66485457-66963820

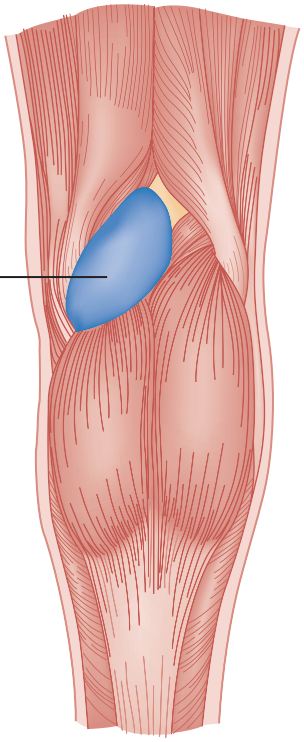


Figure 57-12. Baker's cyst is an extension of the semimembranosus bursa posteriorly. This bursa often is connected with a joint cavity.

Septic Arthritis

The knee is the joint most commonly affected by septic arthritis. Hematogenous seeding is the most common route of spread, but joint trauma also is a frequent cause. Bacterial spread usually affects the vascular synovial membrane and then extends into the joint. *Staphylococcus aureus* is the most common pathogen, but *Neisseria gonorrhoeae* also is a concern because the typical treatment is vancomycin for the former and ceftriaxone for the latter. Moreover, the latter is a reportable disease requiring contact tracing. For prevention of septic arthritis in the ED setting, all open joint injuries should be treated by operative washout and antibiotics, and clinicians should avoid performing arthrocentesis through infected skin, which can seed the joint.

Baker's Cyst

Baker's cyst (popliteal cyst) is a herniation of the synovial membrane through the posterior aspect of the capsule of the knee (Fig. 57-12). It results from an enlarging knee effusion of any cause. A mass is palpable in the posteromedial corner of the knee and often produces pressure, pain, and limitation of range of motion. Rupture of the bursa with resultant escape of fluid into the calf may produce a clinical picture similar to that of deep vein thrombosis or compartment syndrome.[64] In this circumstance, ruptured Baker's cyst is a diagnosis of exclusion (i.e., thrombosis should be ruled out). Treatment is directed at the underlying intra-articular pathology.

LEG

PERSPECTIVE

Anatomically, the leg comprises the tibia, fibula, and associated soft tissues, whereas the thigh comprises the femur and its soft tissues. Bearing the full weight of the body, the leg is subject to enormous stress, and the tibia is the most commonly fractured long bone. Moreover, the tibia is poorly covered by soft tissue anteriorly, making infection and delayed healing common.

PRINCIPLES OF DISEASE: ANATOMY AND PATHOPHYSIOLOGY

The bony structure of the lower leg is relatively simple, consisting of the tibia and fibula. The fibula does not bear weight. The shaft of the tibia is triangular in cross section and poorly covered with soft tissue over its anteromedial aspect. It is the most common long bone to be fractured and to sustain open fracture. The lack of overlying soft tissue results in a tenuous blood supply, which increases the rate of osteomyelitis and contributes to delayed union and nonunion, which are common in tibial fracture.

The distal end of the tibia is expanded and bears an additional surface feature, the fibular notch, for the lower tibiofibular joint. The medial malleolus projects from the distal medial aspect of the tibia and has a posterior groove for the tibialis posterior tendon. The inferior surface of the distal tibia is covered with articular cartilage and forms the tibial plafond, the upper anterior surface of the ankle joint. The fibula, in contrast to the tibia, is covered by soft tissue except at the ankle, where it is subcutaneous and easily palpable. The fibula is composed of the head with its styloid process, the neck, the shaft, and the lateral malleolus of the ankle.

The tibia and fibula are connected by a superior and an inferior tibiofibular joint and a strong interosseous membrane or syndesmotic ligament. The latter is a fibrous band that has particular importance at the distal portion of the lower leg, where it is responsible for keeping the tibia and fibula closely approximated to provide a stable ankle mortise.

The vascular supply of the lower leg derives from the popliteal artery, which trifurcates to form three branches: the anterior tibial artery, the posterior tibial artery, and the peroneal artery. The anterior tibial artery can be assessed by palpating the dorsalis pedis artery pulse over the dorsum of the foot, and the posterior tibial artery pulse can be palpated posterior to the medial malleolus.

The lower leg is divided into compartments by deep partitions of the investing crural fascia. Each compartment has a sensory nerve running through it, an anatomic feature that can be used to help diagnose compartment syndrome. The compartments are anterior, lateral, superficial posterior, and deep posterior. The anterior compartment contains the tibialis anterior, the long toe extensor muscles, the anterior tibial artery, and the deep peroneal nerve, which supplies sensation to the first web space of the foot. The lateral compartment contains two muscles that evert the foot, the peroneus longus and brevis, and the superficial peroneal nerve, which supplies sensation to the dorsum of the foot. The superficial posterior compartment contains the gastrocnemius, plantaris, and soleus muscles and the sural nerve, which supplies the lateral side of the foot and distal calf. The deep posterior compartment contains the tibialis posterior muscle, the long toe flexor muscles, the posterior tibial and peroneal arteries, and the tibial nerve, which supplies sensation to the plantar aspect of the foot.

MECHANISMS OF INJURY AND MANAGEMENT

Proximal Extra-articular Tibial Fractures

Subcondylar Tibial Fractures

Subcondylar tibial fractures usually are associated with tibial plateau fractures, especially bicondylar fractures. Subcondylar fractures involve the proximal tibial metaphysis and typically are

www.ketabpezeshki.com 66485457-66963820

transverse or oblique. The mechanism of injury involves a rotational or angular stress accompanied by vertical compression. Examination reveals tenderness and swelling of the involved area. A hemarthrosis may indicate extension of the fracture into the joint or associated ligamentous injury. Routine radiographic views usually are adequate in showing the fracture line. ED management includes ice and immobilization with a long leg posterior splint. Stable extra-articular nondisplaced transverse fractures usually are treated conservatively with a long leg splint, followed by delayed casting on an outpatient basis (because of the risk of swelling and compartment syndrome). In children, casting (with adequate padding) is sometimes performed acutely. Comminuted fractures or fractures associated with an intra-articular component require open reduction and internal fixation and may be treated in the acute setting.

Tibial Tubercle Fractures

Anatomy and Pathophysiology. The tibial tubercle is located at the proximal anterior border of the tibial shaft and is the insertion point of the patellar ligament. The proximal tibial epiphysis and the tibial tuberosity develop from two separate ossification centers that coalesce during adolescence. Epiphyseal ossification terminates in late adolescence.

Avulsion fractures of the tibial tubercle are uncommon. They occur predominantly in adolescent boys.[65] The injury typically occurs near the end of growth, when endochondral ossification of the physeal cartilage of the tibial tubercle occurs. Avulsion fractures mainly occur as an indirect injury during activity. The mechanism of injury has been described as a violent flexion of the knee against a tightly contracted quadriceps muscle, which also can cause patellar tendon rupture. The Watson-Jones classification describes three grades of injury depending on the extent of displacement (Fig. 57-13). In type I injuries, the tubercle is hinged upward without displacement from the proximal base. The type II injury has a small portion of the tubercle avulsed, but it is retracted proximally; the articular surface is not involved. Type III fractures are more severe and extend across the articular surface; displacement of the fragment and often comminution are features.

Clinical Features. Physical examination reveals acute tenderness and swelling at the anterior aspect of the knee and proximal tibia. Depending on the type of injury, functional disability may range in severity from extensor lag to complete loss of active extension. Hemarthrosis is evident with type III injury because of intra-articular fracture extension across the proximal epiphysis.

Diagnostic Strategies. Plain radiographs usually are adequate for diagnosis. The lateral view shows the avulsion fracture, number of fragments, and amount of displacement. Swelling of the overlying soft tissue is evident. Comparison views may be necessary when a type I injury is suspected.

Management. Treatment depends on the degree of displacement and the presence of joint involvement. Nondisplaced type I avulsions are treated with cast immobilization with the knee in extension until healing results. Minimally displaced type II avulsions may be treated similarly if the displacement can be reduced by external manual maneuvers. Displaced type III fractures are treated by open reduction and internal fixation to restore proper biomechanics and joint congruity. Fixation screw and tension band wiring techniques have yielded excellent results. After a period of immobilization and progressive rehabilitation, most patients are able to return to full activity.

Complications of tibial tubercle fractures are rare and include genu recurvatum (backward curvature of the knee), patella alta, meniscal tears, failure of surgical fixation, and subsequent heterotopic ossification and osteonecrosis of the tubercle.[66] If the involved growth plates are closing at the time of injury, premature physeal closure can rarely result in a significant recurvatum deformity.

Osgood-Schlatter Disease

Anatomy and Pathophysiology

Adolescents are susceptible to the development of Osgood-Schlatter disease, also known as *osteochondritis of the tibial tuberosity* or *apophysitis of the tibial tuberosity.* This common condition results from traction of the distal patellar tendon on the tibial tubercle, causing repetitive microtrauma with subsequent healing of the physis of the tibial tuberosity. This traction apophysitis occurs during the adolescent growth spurt, usually in athletically active children.

Clinical Features

The disease is characterized by painful swelling over the tibial tubercle, which is exacerbated by activity, is relieved by rest, and is usually of several months' duration. The tubercle may appear

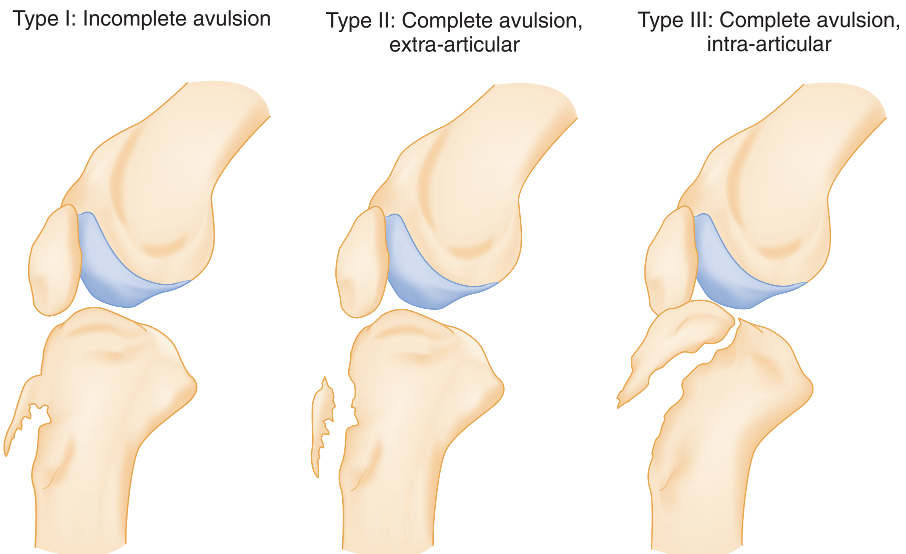


Figure 57-13. Tibial tuberosity fractures.

www.ketabpezeshki.com 66485457-66963820

abnormally prominent, often on both sides. Pain is elicited on resisted extension of the flexed knee, and occasionally an extensor lag may be noted. Tenderness is most pronounced at the insertion of the patellar tendon. Bilateral involvement is noted in 20 to 30% of patients.[67]

Diagnostic Strategies

The diagnosis of Osgood-Schlatter disease is based on clinical signs and symptoms. Plain radiography of the knee may be useful to exclude other pathologic entities (e.g., tumors, infection, avulsion fractures) but generally is not required. Radiographs are normal in appearance or reveal pretibial soft tissue edema or prominence of the tubercle, with no other bone abnormalities.

Management

Treatment varies according to the acuteness of the symptoms and the skeletal age of the patient. Initially, rest, ice, and analgesics are the mainstays of therapy. As symptoms subside, a rehabilitation program that stretches and strengthens the quadriceps should be instituted. Knee orthoses are used to damp the pull of the extensor mechanism on the weakened tibial apophysis. Immobilization is reserved for the unreliable patient who will not or cannot comply with the program of relative rest in which aggravating activities are avoided. For children with severe symptoms, immobilization for 2 to 3 weeks may be used. Surgical repair may be required if the conservative treatment fails, but it cannot be implemented until the epiphysis is closed, at which time the problem usually is resolved.

Tibial Shaft Fractures

Anatomy and Pathophysiology

The tibia and fibula are tightly bound to each other by the syndesmotic ligament. This strong band of tissue can transmit energy such that the tibia and fibula may be fractured at nonadjacent sites. The fibula remains intact in only 15 to 25% of tibial shaft fractures. Tibial shaft factures are associated with a high incidence of infection, delayed union, nonunion, and malunion, in part because of the poor soft tissue coverage of the anterior tibia.

Transverse tibial diaphyseal fractures typically result from high-energy direct trauma. Low-energy rotatory and compressive forces often result in spiral or oblique fractures.

The *toddler's fracture* is a nondisplaced spiral fracture of the distal tibia in a child 9 months to 3 years of age. The classic distal fracture often relates to accidental trauma, as opposed to a midshaft fracture, which suggests abuse.

Tibial fractures also may occur without trauma. Stress fractures occur most commonly in the tibial shaft. Pathologic fractures may be caused by metabolic bone disease, osteomalacia, or neoplasm.

In children, buckle fractures and greenstick fractures are common in the tibia and fibula. A buckle fracture manifests radiographically as an often subtle buckling without angulation, in contrast to the smooth line formed by the normal cortex. A greenstick fracture is a bending fracture, with a break in the periosteum and cortex of the convex side of the angulated bone, while the concave side of the bone is spared. Both of these fractures are stable with an intact periosteum so that swelling, crepitance, and mobility at the fracture site are minimal.

Clinical Features

Tibial shaft fractures cause pain, swelling, and localized deformity, usually angulation or rotation of the foot. Determination of vascular integrity is the priority. Distal dorsalis pedis and posterior tibial pulses should be assessed; however, vascular injury is a rare complication of these fractures. Neurologic injury, by contrast, is common, particularly injury of the peroneal nerve. Motor function of the peroneal nerve is checked by testing active ankle and toe dorsiflexion (deep peroneal nerve) and active foot eversion (superficial peroneal nerve). Sensory function of the peroneal nerve is documented by testing sensation in the first dorsal web space in the foot (deep peroneal nerve distribution) and sensation of the dorsal lateral foot (superficial peroneal nerve distribution). Integrity of the posterior tibial nerve is assessed by checking for the presence or absence of plantar sensation. Significant soft tissue damage also may accompany tibial shaft fractures. Compartment syndrome may be a complication of tibial fractures and usually develops within the first 24 to 48 hours.

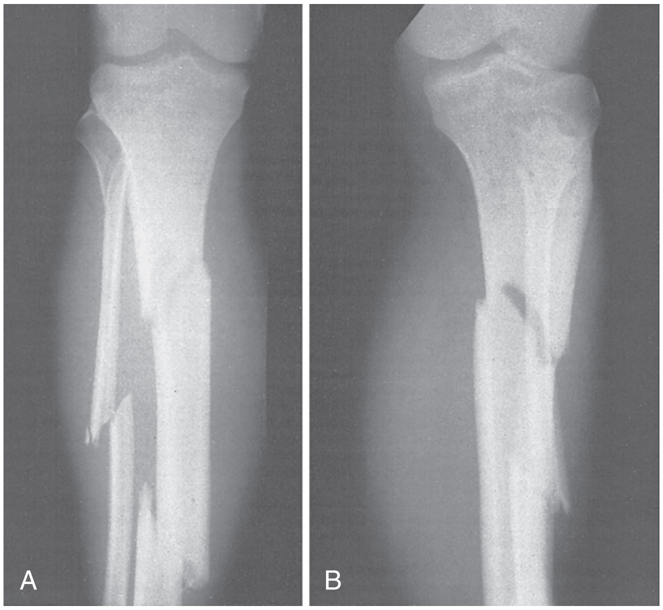


Figure 57-14. Tibiofibular fracture. **A,** Anteroposterior view. Comminuted fractures of the tibial and fibular shafts are present. Note the obliteration of the normal soft tissue planes secondary to edema or hemorrhage. **B,** Lateral view. (From Rosen P, et al: Diagnostic Radiology in Emergency Medicine. St Louis, Mosby, 1992, p 198.)

Diagnostic Strategies

AP and lateral radiographic studies document the fracture, define the fracture pattern, and identify any associated bone loss (Fig. 57-14). The knee and ankle should be included in both views, and radiographs of the pelvis and ipsilateral femur may be required to assess for associated injuries. Postreduction views should be taken after any manipulation of the extremity and should include the knee and ankle joints so that alignment of the proximal and distal joint surfaces can be determined.

Management

The initial management of closed tibial shaft fractures consists of immobilization in a long leg posterior splint applied with the knee in 10 to 20 degrees of flexion. The splinting procedure may require analgesia and sedation. In general, after fractures have been immobilized, pain decreases. If the patient reports continued severe pain after immobilization, a complication such as compartment syndrome, nerve root compression, or limb ischemia should be considered. Circumferential casts generally are avoided in the acute setting because of the risk of compartment syndrome, although

www.ketabpezeshki.com 66485457-66963820

some orthopedists will cast pediatric fractures in the acute phase. Initial hospitalization is indicated for most patients with significant tibial shaft fractures to allow adequate pain control and observation for compartment syndrome.

Open fractures should be covered by a sterile dressing. Antistaphylococcal antibiotics (typically cefazolin) should be given, with consideration of agents active against methicillin-resistant *S. aureus* (MRSA). Gentamicin is added for severely contaminated wounds.[68] Tetanus vaccination status should be updated as indicated. A long leg posterior splint should be applied. (This applies to all open fractures.)

Emergency operative débridement with external or internal fixation is recommended as soon as possible for open tibial fractures with significant soft tissue disruption. Osteomyelitis is more likely with open fracture, significant soft tissue disruption, and longer time from contamination to definitive surgical management.

In general, tibial fractures are slow to heal. The average time to union is approximately 20 weeks for stable tibial shaft fractures caused by a low-energy mechanism and more than 30 weeks for unstable fractures caused by a high-energy mechanism.[69] *Delayed union* describes fracture segments that have not united after 24 weeks or that show no radiographic evidence of callus formation for 3 consecutive months. *Nonunion* is a radiographic diagnosis, with a finding of rounded, well-corticated edges of the major fracture fragments. It is much more common in adult long bone fractures than in childhood fractures, which generally heal rapidly. Delayed vascular injuries, including pseudoaneurysm, arteriovenous fistula, and deep vein thrombosis, also may occur as a complication of tibial shaft fractures. Fat embolism also may occur acutely, especially after reamed nailing. Additional late complications include malrotation of the leg, refracture, and reflex sympathetic dystrophy.

Proximal Fibula Fractures

Anatomy and Pathophysiology

Isolated fibular fractures are relatively unimportant because the fibula is a non–weight-bearing bone. The mechanism of injury usually is a direct blow to the lateral aspect of the leg or an indirect varus stress to the knee. An important exception is the Maisonneuve fracture (Fig. 57-15). This injury involves a medial ankle disruption (deltoid ligament tear or medial malleolar fracture), with complete tearing of the syndesmotic ligament joining the tibia and fibula, and fracture of the proximal fibula. Consequently, the fibula floats free relative to the tibia, resulting in an unstable ankle mortise, for which surgical fixation is required. The possibility of this injury indicates the need for examination of the proximal fibula in all medial ankle injuries.

Clinical Features

Isolated fibular shaft fractures cause lateral leg pain that is exacerbated by walking. Local pain, swelling, and tenderness at the fracture site may be elicited, although signs and symptoms can be subtle. A thorough evaluation should be done to exclude serious associated occult neurovascular or ligamentous injuries. The common peroneal nerve courses around the neck of the fibula and may be contused or lacerated at the time of injury. The LCL of the knee may be ruptured or strained in association with the fracture, and anterior tibial artery injury with thrombosis may occur.

Diagnostic Strategies

AP and lateral radiographic views should include the knee and ankle joints.

Figure 57-15. Maisonneuve fracture, anteroposterior view. The rotatory force involved in this injury has caused fractures of the distal tibia and the proximal fibula *(arrows)*. (From Rosen P, et al: Diagnostic Radiology in Emergency Medicine. St Louis, Mosby, 1992, p 197.)

Management

Isolated fibular shaft fractures are treated symptomatically with ice, analgesia, and non–weight-bearing status. Immobilization in a long leg cast is rarely done but may provide symptomatic relief beginning 2 days after the acute injury. Weightbearing may be advanced progressively as tolerated; pain should be avoided. Patients with nondisplaced or minimally displaced fractures may have little pain and tolerate crutch walking without casting. In general, isolated fibula shaft fractures can be managed on an outpatient basis and heal without complication.

For severely displaced fibular shaft fractures or fractures with associated peroneal nerve deficit (i.e., footdrop), orthopedic consultation is indicated. Cast immobilization is not recommended in cases with concomitant nerve damage, and follow-up is scheduled at a shorter interval from injury. Elective surgical repair may be indicated if function does not return. Maisonneuve fracture results in an unstable ankle, and open reduction and internal fixation usually are required.

Proximal Tibiofibular Joint Dislocations

Anatomy and Pathophysiology

The proximal tibiofibular joint is a small synovial joint between a circular or oval facet on the head of the fibula and a similar facet on the inferior aspect of the lateral tibial condyle. The proximal tibiofibular joint is stabilized by the joint capsule and the anterior and posterior tibiofibular ligaments. Dislocation of the proximal tibiofibular joint is rare, occurring most commonly in adolescents and young adults because of its association with motor vehicle collisions and sports injuries.[70] Several types of dislocations of the joint have been described; anterolateral dislocation is the most common and usually is caused by a fall on a flexed, abducted leg. Posterior medial dislocation generally is caused by a direct blow to the flexed knee and is more often associated with peroneal nerve

www.ketabpezeshki.com 66485457-66963820

injury. Superior dislocation is associated with ankle diastasis and typically occurs simultaneously with an ankle fracture.

Clinical Features

The patient may complain that the knee feels "out of joint," or if the problem is intermittent, the knee may lock or give way periodically. Physical examination reveals tenderness and swelling over the proximal fibula and tibiofibular joint. In the absence of associated injury, findings on knee examination are otherwise normal, with full range of motion and no joint line tenderness or effusion.

Diagnostic Strategies

Plain radiography may confirm the diagnosis, although CT may be required. On the AP view, the fibular head is displaced laterally, and the interosseous space is widened. Comparison views of the uninjured knee may be necessary to appreciate these findings.

Management

Traumatic proximal tibiofibular dislocation is treated initially with closed reduction. If the patient seeks treatment within a few days of injury, reduction of an anterolateral dislocation can be accomplished in the ED by flexing the knee to 90 degrees, everting the ankle, and applying direct pressure to the head of the fibula.[70] Orthopedic referral and immobilization of the knee for a minimum of 3 to 6 weeks are necessary after reduction. If closed reduction fails, the patient may require open reduction, with repair of the torn capsule ligaments and pinning. For recurrent dislocations or injuries that do not respond to initial treatment, resection of the proximal fibula or arthrodesis may be effective.

Stress Fractures

Anatomy and Pathophysiology

The tibia is a common site of stress fracture. Usually the stress fracture occurs on the tibial shaft. Fractures typically are horizontal or oblique and uncommonly longitudinal.[71] Other sites of stress fracture include the femur, fibula, tarsals (especially navicular), and metatarsals. Stress fractures result from overuse. Stress fractures, which occur as a result of excessive repetitive force to normal bone, are distinguished from pathologic fractures, which occur as a result of normal forces acting on abnormal bone (because of osteoporosis or tumor, for example).

Clinical Features

Bone pain and tenderness without a history of direct trauma are characteristic. The most important historical information includes a recent increase in physical activity, training on hard surfaces, and inadequate footwear. The pain usually is insidious in onset and progressive but may be sudden. Pain is usually relieved with rest. The differential diagnosis for lower leg pain also includes shin splints (see later), exercise-induced compartment syndrome, contusion, muscle strains, tendinitis, periostitis, and interosseous membrane strains. The physical examination may reveal localized bone tenderness and swelling of the overlying soft tissues. Usually there is no muscle atrophy, weakness, or restriction of joint range of motion.

Diagnostic Strategies

The radiographic findings vary depending on the location of the fracture and stage of healing. Approximately one third of stress fractures are evident radiographically at the time of initial diagnosis, compared with one half after 2 to 6 weeks. The radiographic findings often are subtle and may include periosteal new bone, sclerosis, and a lucent line perpendicular to the cortex. MRI can diagnose the condition earlier and more accurately than plain films.[71]

If a stress fracture of the lower extremity is suspected and findings on initial plain radiography are unremarkable, follow-up evaluation at 10 days to 2 weeks may detect radiographic signs of fracture after a period of inactivity. Evidence of healing (periosteal reaction) in response to treatment usually is sufficient to confirm the diagnosis.

Management

Most tibial and fibula stress fractures can be treated nonoperatively. Activity should be decreased for 3 to 6 weeks to allow for healing, and serial radiographs should be obtained. In those rare instances in which walking causes pain, a cast and non–weight-bearing status may be required. Serial radiographs are used to evaluate healing. Rare cases of nonunion require surgery.

Compartment Syndrome

Compartment syndrome is caused by increased pressure within a fascial compartment, leading to necrosis of muscle and nerve, and is discussed in Chapter 49.

Soft Tissue Injuries Involving the Lower Leg

Strains

Gastrocnemius Strain. The medial head of the gastrocnemius muscle often is strained in athletics and sometimes ruptures. On physical examination, a palpable gap may be identified in the substance of the muscle, and point tenderness may be elicited in the medial and inferior borders of the muscle belly. Any attempted active or passive ankle dorsiflexion elicits pain.

Gastrocnemius strain or rupture may be confused with rupture of the plantaris tendon, which causes tenderness, swelling, and ecchymosis in the proximal calf; rupture of a Baker's cyst, which may result in the escape of fluid into the calf; thrombophlebitis; deep venous thrombosis; and Achilles tendon rupture, which typically results in a palpable gap just proximal to the calcaneus. The diagnosis is made clinically, although a soft tissue defect may be seen on plain radiographs of large ruptures. MRI can confirm the diagnosis but is rarely necessary.

A mild partial rupture of the medial head of the gastrocnemius can be treated with rest and non–weight-bearing status for several days. Treatment for more extensive incomplete ruptures involves casting for 8 weeks with the ankle plantar-flexed. For a complete tear, most orthopedists recommend surgical repair to restore normal length and tensile strength. Acute compartment syndrome can complicate gastrocnemius strain.

Plantaris Strain and Rupture. The plantaris is a small, variable muscle that originates at the lateral condyle of the femur and passes beneath the soleus to insert on the Achilles tendon. It is a feeble flexor of the knee and plantar flexor of the ankle joint with little functional significance. Rupture may occur at the myotendinous junction with or without an associated partial tear of the medial head of the gastrocnemius muscle. A strain of the more proximal plantaris muscle also may occur as an isolated injury or in conjunction with injury to the ACL of the knee. The patient may describe a sudden sharp snap in the posterior calf, followed by a duller deep ache, which may be disabling. Tenderness is

www.ketabpezeshki.com 66485457-66963820

greatest just lateral to the midline of the posterior calf. Treatment is symptomatic.

Shin Splints

Shin splints refers to anterior tibial pain occurring during or after exercise. The most common causes are a tibial stress reaction or periostitis. Tibial stress reactions are microfractures caused by stress placed on the tibia and are distinct from gross stress fractures, which predispose the affected bone to complete fracture.

The physical examination reveals localized tenderness over the tibia, usually at the junction of the middle and lower thirds. Radiographic studies are not helpful in the diagnosis of shin splints and also cannot exclude a tibial stress fracture with certainty. Treatment is symptomatic: rest, NSAIDs, ice, and supportive footwear. The patient should be referred for outpatient evaluation, where conservative therapy can be continued or further diagnostic workup can be pursued.

Foreign Bodies

Foreign bodies such as plant matter (e.g., thorns) are commonly encountered in the leg. Missed retained foreign bodies in the lower leg can be the cause of cellulitis, abscess, necrotizing fasciitis, and gangrene. Plain films are a necessary part of evaluation but will be unhelpful when the foreign body is radiolucent. Ultrasound imaging is superior for diagnosis and localization, and fluoroscopy and MRI are alternatives.[72] Surgical exploration is sometimes necessary. Extraction is difficult, and deep foreign bodies should be removed by a surgeon, often in the operating room.

KEY CONCEPTS

- Knee dislocation often causes vascular injury to the popliteal artery. Early revascularization is crucial. Traditional universal angiography has been replaced by a non-invasive algorithmic approach, which should be followed carefully to avoid missing the diagnosis.
- The most common long bone fracture is that of the tibial diaphysis, and compartment syndrome is an infrequent but serious complication.
- Toddler's fracture is a spiral fracture of the distal tibia and usually is not related to abuse. Midshaft or transverse tibial fractures, however, should trigger suspicion of abuse.
- Injuries to the cruciate and collateral ligaments may not be detectable on initial examination owing to effusion and splinting. Emergent diagnosis is not necessary, but the patient should undergo a follow-up examination by an orthopedist.
- Lipohemarthrosis is an uncommon and subtle sign of occult fracture and should be sought on radiographs of traumatized knees.

ACKNOWLEDGMENT

The author is grateful to Matthew B. Allen for his careful proofreading.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Roberts DM, Stallard TC: Emergency department evaluation and treatment of knee and leg injuries. *Emerg Med Clin North Am* 2000; 18:67.
2. Snell RS: *Clinical anatomy*. In: Snell RS, ed. *Clinical Anatomy*. Philadelphia: Lippincott, Williams & Wilkins; 2004.
3. Lassen MR, Borris LC, Nakov RL: Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. *N Engl J Med* 2002; 347:726.
4. Stannard JP, et al: Vascular injuries in knee dislocations: The role of physical examination in determining the need for arteriography. *J Bone Joint Surg Am* 2004; 86:910.
5. Lubovitz JH, Bernardini BJ, Reid JB 3rd: Current concepts review: Comprehensive physical examination for instability of the knee. *Am J Sports Med* 2003; 36:577.
6. Jackson JL, O'Malley PG, Kroenke K: Evaluation of acute knee pain in primary care. *Ann Intern Med* 2003; 139:575.
7. Hurley WL, Denegar C, Buckley WE: The relationship between grading and instrument measurements of anterior knee laxity. *J Sport Rehabil* 2008; 17:60.
8. Mustonen AO, Koskinen SK, Kiuru MJ: Acute knee trauma: Analysis of multidetector computer tomography findings and comparison with conventional radiography. *Acta Radiol* 2005; 46:866-874.
9. Stiell IG, et al: Prospective validation of a decision rule for the use of radiography in acute knee injuries. *JAMA* 1996; 275:611.
10. Stiell IG, et al: Implementation of the Ottawa Knee Rule for the use of radiography in acute knee injuries. *JAMA* 1997; 278:2075.
11. Ketelslegers E, et al: Validation of the Ottawa knee rules in an emergency teaching centre. *Eur Radiol* 2002; 12:1218-1220.
12. Seaberg DC, Jackson R: Clinical decision rule for knee radiographs. *Am J Emerg Med* 1994; 12:541.
13. Seaberg DC, Yealy DM, Lukens T, Auble T, Mathias S: Multicenter comparison of two clinical decision rules for the use of radiography in acute, high-risk knee injuries. *Ann Emerg Med* 1998; 32:8.
14. Bulloch B, et al: Validation of the Ottawa Knee Rule in children: A multicenter study. *Ann Emerg Med* 2003; 42:48.
15. Khine H, Dorfman DH, Avner JR: Applicability of Ottawa knee rule for knee injury in children. *Pediatr Emerg Care* 2001; 17:401.
16. Verma A, Su A, Golin AM, O'Marrah B, Amorosa JK: A screening method for knee trauma. *Acad Radiol* 2001; 8:392.
17. Redmond JM, Levy BA, Dajani KA, Cass JR, Cole PA: Detecting vascular injury in lower-extremity orthopedic trauma: The role of CT angiography. *Orthopedics* 2008; 31:761-767.
18. Beall DP, et al: Magnetic resonance imaging of the collateral ligaments and anatomic quadrants of the knee. *Radiol Clin North Am* 2007; 45:983.
19. Vaz CE, Camargo OP, Santana PJ, Valezi AC: Accuracy of magnetic resonance imaging in identifying traumatic intra-articular knee lesions. *Clinics (Sao Paulo)* 2005; 60:445.
20. Keese GR, Boody AR, Wongworawat MD, Jobe CM: The accuracy of the saline load test in the diagnosis of traumatic knee arthrotomies. *J Orthop Trauma* 2007; 21:442-443.
21. Wascher DC, Dvirnak PC, DeCoster TA: Knee dislocation: Initial assessment and implications for treatment. *J Orthop Trauma* 1997; 11:525.
22. Robertson A, Nutton RW, Keating JF: Dislocation of the knee. *J Bone Joint Surg Br* 2006; 88:706.
23. Frykberg ER: Popliteal vascular injury. *Surg Clin North Am* 2002; 82:67.
24. Barnes CJ, Pietrobon R, Higgins LD: Does the pulse examination in patients with traumatic knee dislocation predict a surgical arterial injury? A meta-analysis. *J Trauma* 2002; 53:1109-1114.
25. Bandyk DF: Vascular injury associated with extremity trauma. *Clin Orthop Relat Res* 1995; 318:117.
26. Niall DM, Nutton RW, Keatiing JF: Palsy of the common peroneal nerve after traumatic dislocation of the knee. *J Bone Joint Surg Br* 2005; 87:664.
27. Ríos A, Villa A, Fahandezh H, de José C, Vaquero J: Results after treatment of traumatic knee dislocations: A report of 26 cases. *J Trauma* 2003; 55:489.
28. Nicandri GT, Dunbar RP, Wahl CJ: Are evidence-based protocols which identify vascular injury associated with knee dislocation underutilized? *Knee Surg Sports Traumatol Arthrosc* 2010; 18:1005-1012.
29. Nicandri GT, Chamberlain AM, Wahl CJ. Practical management of knee dislocations: A selective angiography protocol to detect limb-threatening vascular injuries. *Clin J Sport Med* 2009; 19:125-129.
30. Peng PD, et al: CT angiography effectively evaluates extremity vascular trauma. *Am Surg* 2008; 74:103.
31. Miller-Thomas MM, West OC, Cohen AM: Diagnosing traumatic arterial injury in the extremities with CT angiography: Pearls and pitfalls. *Radiographics* 2005; 25(Suppl 1):S133.
32. Wiss DA, Watson JT, Johnson EE: *Fractures of the knee*. In: Rockwood CA Jr, Green DP, eds. *Fractures in Adults*, 4th ed. Philadelphia: Lippincott-Raven; 1996:1919.
33. Mills WJ, Tejwani N: Heterotopic ossification after knee dislocation: The predictive value of the injury severity score. *J Orthop Trauma* 2003; 17:338.
34. Mui LW, Engelsohn E, Umans H: Comparison of CT and MRI in patients with tibial plateau fracture: Can CT findings predict ligament tear or meniscus injury? *Skeletal Radiol* 2007; 36:145.
35. Papagelopoulos PJ, et al: Complications after tibia plateau fracture surgery. *Injury* 2006; 37:475.
36. Weigel DP, Marsh JL: High-energy fractures of the tibial plateau: Knee function after longer follow-up. *J Bone Joint Surg Am* 2002; 84:1541.
37. Watson JT: High-energy fractures of the tibial plateau. *Orthop Clin North Am* 1994; 25:723.
38. Pallin DJ: Images in emergency medicine: Lipohemarthrosis. *Ann Emerg Med* 2007; 50:120.
39. Aderinto J, Walmsley P, Keating JF: Fractures of the tibial spine: Epidemiology and outcome. *Knee* 2008; 15:164.
40. Schenck RC Jr: *Injuries of the knee*. In: Rockwood CA Jr, Green DP, eds. *Fractures in Adults*, 5th ed. Philadelphia: Lippincott-Raven; 2001:1843.
41. Sponseller P, Beaty JH: *Fractures and dislocations about the knee*. In: Rockwood CA Jr, Green DP, eds. *Fractures in Children*, 4th ed. Philadelphia: Lippincott-Raven; 1996:1233-1329.
42. Ogden JA: *Skeletal Injury in the Child*, 2nd ed. Philadelphia: Saunders; 1990.
43. Perron AD, Miller MD, Brady WJ: Orthopedic pitfalls in the emergency department: Pediatric growth plate injuries. *Am J Emerg Med* 2002; 20:50.
44. Bretlau T, et al: Bone bruise in the acutely injured knee. *Knee Surg Sports Traumatol Arthrosc* 2002; 10:96.
45. Kocher MS, Tucker R, Ganley TJ, Flynn JM: Management of osteochondritis dissecans of the knee: Current concepts review. *Am J Sports Med* 2006; 34:1181.
46. Lotke PA, Battish R, Nelson CL: Treatment of osteonecrosis of the knee. *Instr Course Lect* 2001; 50:483.
47. Gil HC, Levine SM, Zoga AC: MRI findings in the subchondral bone marrow: A discussion including transient osteoporosis, transient bone marrow edema syndrome, SONK, and bone marrow edema of the knee. *Semin Musculoskelet Radiol* 2006; 10:177.
48. Kellersman R, Blattert TR, Weckbach A: Bilateral patellar tendon rupture without predisposing systemic disease or steroid use: A case report and review of the literature. *Arch Orthop Trauma Surg* 2005; 125:127.
49. Maffuli N, Wong J: Rupture of the Achilles and patellar tendons. *Clin Sports Med* 2003; 22:761.
50. Scuderi GR, Scott WN, Insall JN: *Injuries of the knee*. In: Rockwood CA Jr, Green DP, Bucholz R, Heckman JD, eds. *Rockwood and Green's Fractures in Adults*, 4th ed. Philadelphia: Lippincott-Raven; 1996:2001-2126.
51. Alemparte J, et al: Patellofemoral evaluation with radiographs and computed tomography scans in 60 knees of asymptomatic subjects. *Arthroscopy* 2007; 23:170.
52. Merchant AC: Patellofemoral imaging. *Clin Orthop Relat Res* 2001; 389:15.
53. Cooper ME, Selesnick FH: Partial rupture of the distal insertion of the patellar tendon: A report of two cases in professional athletes. *Am J Sports Med* 2000; 28:402.
54. Wiss DA, Watson JT, Johnson EE: *Fractures of the knee*. In: Rockwood CA Jr, Green DP, Bucholz R, Heckman JD, eds. *Rockwood and Green's Fractures in Adults*, 4th ed. Philadelphia: Lippincott-Raven; 1996:1919-2001
55. Fredericson M, Yoon K: Physical examination and patellofemoral pain syndrome. *Am J Phys Med Rehabil* 2006; 85:234.
56. Ufberg J, McNamara R: *Management of common dislocations*. In: Roberts JR, Hedges JR, eds. *Clinical Procedures in Emergency Medicine*, 4th ed. Philadelphia: Saunders; 2004.
57. Stefancin JJ, Parker RD: First-time traumatic patellar dislocation. *Clin Orthop Relat Res* 2007; 455:93.
58. Prodromos CC, Han Y, Rogowski J, Joyce B, Shi K: A meta-analysis of the incidence of anterior cruciate ligament injury as a function of gender, sport, and knee injury-reduction regimen. *Arthroscopy* 2007; 23:1320.
59. Harner CD, Hoher J: Evaluation and treatment of posterior cruciate ligament injuries. *Am J Sports Med* 1998; 26:471.

www.ketabpezeshki.com 66485457-66963820

60. Solomon DH, Simel DL, Bates DW, Katz JN, Schaffer JL: The rational clinical examination. Does this patient have a torn meniscus or ligament of the knee? Value of the physical examination. *JAMA* 2001; 286:1610-1620.
61. Herrington L, Rivet N, Munro S: The relationship between patellar position and the length of the iliotibial band as assessed using Ober's test. *Man Ther* 2006; 11:182.
62. Ieda Y, Kotani A, Ishii Y: Bilateral plica synovialis mediopatellaris syndrome: A case report. *J Orthop Sci* 2003; 8:218.
63. Blake SM, Treble NJ: Popliteus tendon tenosynovitis. *Br J Sports Med* 2005; 39:e42.
64. Klovning J, Beadle T: Compartment syndrome secondary to spontaneous rupture of a Baker's cyst. *J La State Med Assoc* 2007; 159:43.
65. Uppal A, Lyne ED: Tibial tubercle fracture with avulsion of the patellar ligament: A case report. *Am J Orthop* 2007; 36:273.
66. Mosier SM, Sanitaki CL: Acute tibial tubercle avulsion fractures. *J Pediatr Orthop* 2004; 24:181.
67. Gholve PA, Scher DM, Khakharia S, Widmann RF, Green DW: Osgood-Schlatter syndrome. *Curr Opin Pediatr* 2007; 19:44.
68. Okike K, Bhattacharya T: Trends in the management of open fractures. *J Bone Joint Surg Am* 2006; 88:2739.
69. Mechrefe AP, Koh EY, Trafton PG, DiGiovanni CW: Tibial nonunion. *Foot Ankle Clin* 2006; 11:1.
70. Van Seymortier P, Ryckaert A, Verdonk P, Almqvist KF, Verdonk R: Traumatic proximal tibiofibular dislocation. *Am J Sports Med* 2008; 36:793.
71. Ruohola JP, Kiuru MJ, Pihlajamaki HK: Fatigue bone injuries causing anterior lower leg pain. *Clin Orthop Relat Res* 2006; 444:216.
72. Manthey DE, Storrow AB, Milbourn JM, Wagner BJ: Ultrasound versus radiography in the detection of soft-tissue foreign bodies. *Ann Emerg Med* 1996; 28:7.

www.ketabpezeshki.com 66485457-66963820

Chapter 58

Ankle and Foot

Riyad B. Abu-Laban and Nicholas G.W. Rose

To him whose feet hurt, everything hurts.
Socrates

The ankle and foot are highly evolved structures designed to support the body's weight and to facilitate locomotion over varied terrain. Findings related to ankle and foot injuries are often subtle, and diagnoses may be delayed or missed, particularly in cases of multiple trauma.

The ankle and foot are best approached clinically as a single functional unit. Although they are discussed sequentially in this chapter, mechanisms of injury overlap, and a pathologic condition in one location may accompany an associated pathologic condition in another.

ANKLE

PRINCIPLES OF DISEASE

Anatomy

The ankle joint is the articulation of the tibia and fibula with the talus. The dome of the talus fits into the "mortise" formed by the medial malleolus, the horizontal articular surface of the tibia (the plafond), and the lateral malleolus. The stability of the ankle depends on the bony and ligamentous integrity of the mortise. The calcaneus is also important to the motion and stability of the ankle.

The ankle is composed of three primary articulations: the inner surface of the medial malleolus with the medial surface of the talus, the distal tibial plafond with the talar dome, and the medial surface of the lateral malleolus with the lateral process of the talus. These three articular surfaces are contiguous, lined with cartilage, and enclosed by a single joint capsule. The distal tibia also articulates with the distal fibula just proximal to the talus, forming the distal tibiofibular joint. Collectively, these articulations are called the *talocrural joints.*

Three sets of ligaments—the syndesmotic ligaments, the lateral collateral ligaments, and the medial collateral ligaments—support the ankle joint and are essential to its stability (Figs. 58-1 and 58-2).

Tendons course through the ankle in four geographic groups. The flexor retinaculum tethers the tendons of the tibialis posterior, the flexor digitorum longus, and the flexor hallucis muscles behind the medial malleolus. The peroneal retinaculum and tendon sheath tether the peroneus longus and brevis tendons behind the lateral malleolus. The extensor retinaculum tethers the tendons of the tibialis anterior, extensor digitorum longus, extensor hallucis longus, and peroneus tertius over the anterior aspect of the ankle. Posteriorly, in the midline, lie the Achilles and plantaris tendons.

Pathophysiology

Ankle movements are complex and often involve more than one joint. It is best to consider the group of joints about the ankle as one unit, the ankle joint complex. This complex, which is made up of the talocrural joints and the talocalcaneal (subtalar) joints, allows movements along several axes of motion.[1] *Dorsiflexion* and *plantar flexion* of the ankle joint complex occur primarily at the talocrural joints, rotating about the horizontal axis that passes through the medial and lateral malleoli (Fig. 58-3; see also Fig. 58-5). Motions of the ankle joint complex in conjunction with the midtarsal joints include *inversion* and *eversion,* which are rotational movements about the oblique subtalar axis involving the subtalar joint (see Fig. 58-3A), and *abduction* (external rotation) and *adduction* (internal rotation), which are rotational movements about the longitudinal axis of the tibia (see Fig. 58-3B).

The components providing stability to the ankle are best conceptualized as a ringlike structure surrounding the talus[2] (Fig. 58-4). Disruption of one element of this ring does not, by itself, induce instability. Injury to one ring element, however, should prompt careful scrutiny for a second injury. Any disruption of two or more elements causes ankle instability and can significantly affect joint function.[2]

Clinical Features

The presence of immediate swelling and severe pain in the ankle region suggests serious ligament disruption, hemarthrosis, or fracture, and rapid progression of symptoms may represent more severe injury. Inability to bear weight immediately after an injury often implies a significant pathologic condition.[3] Patient recollection of a "pop" sound should prompt consideration of ligament, tendon, or retinacular rupture but does not necessarily increase the probability of a fracture. Finally, the inciting event causing the ankle injury should be determined and, when necessary, further investigated.

Patients with a subacute or chronic ankle problem may be unable to correlate symptom onset with a particular traumatic event. Inquiry should elicit the type and extent of physical activities and whether the ankle "gave way." In elderly patients ankle injuries or fractures may manifest as subacute problems reflecting either misdiagnosis of a serious condition as a simple sprain or neglect by the patient or caregiver.

www.ketabpezeshki.com 66485457-66963820

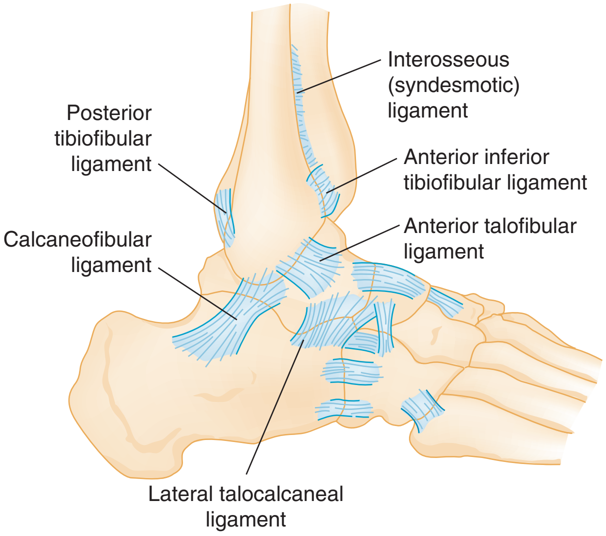


Figure 58-1. Anatomy of the lateral collateral and the syndesmotic ligaments of the ankle. (From Nicholas JA, Hershman EB [eds]: The Lower Extremity and Spine in Sports Medicine, 2nd ed. St Louis, Mosby, 1994.)

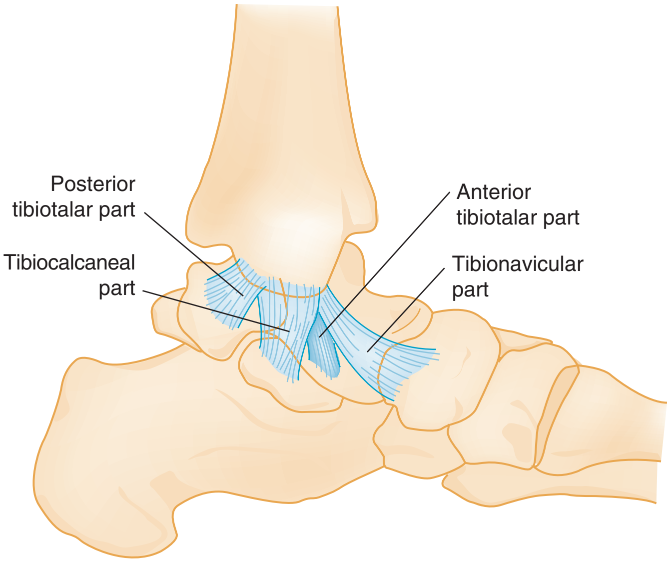


Figure 58-2. Anatomy of the medial collateral ligaments of the ankle. (Adapted from Nicholas JA, Hershman EB [eds]: The Lower Extremity and Spine in Sports Medicine, 2nd ed. St Louis, Mosby, 1994.)

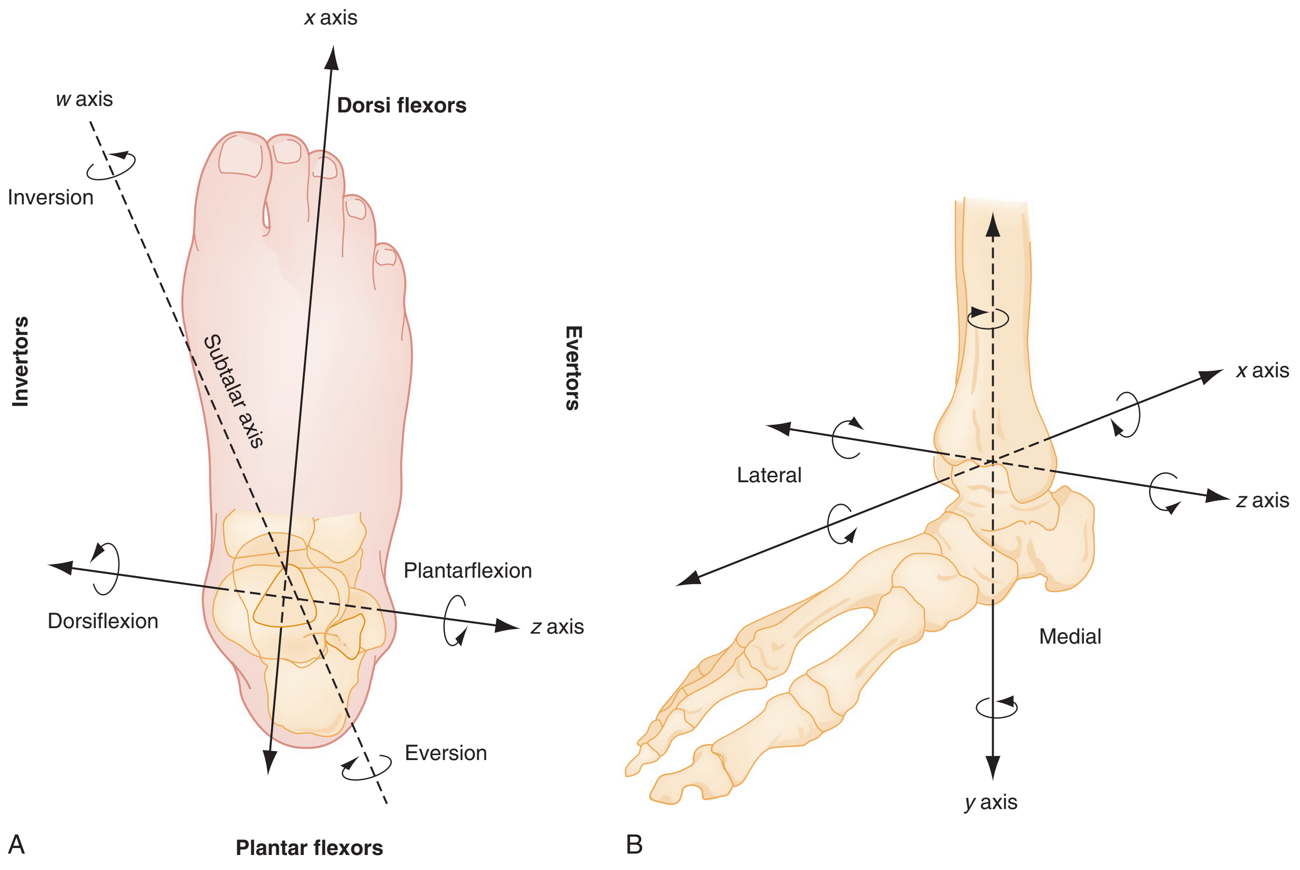


Figure 58-3. Four axes of the ankle joint complex. **A,** The horizontal axis passing through the two malleoli (*z* axis); the longitudinal axis of the foot (*x* axis); the oblique subtalar axis (*w* axis). **B,** The longitudinal axis of the tibia (*y* axis) and two additional views of the *x* and *z* axes. (**A,** From the American Academy of Orthopedic Surgeons: Atlas of Orthotics. St Louis, Mosby, 1975. **B,** Adapted from the Department of Orthopedics, Mayo Clinic and Mayo Foundation, Rochester, Minn. Reproduced in Stormont DM, Morrey BF, An KN, Cass JR: Am J Sports Med 13:295, 1985.)

www.ketabpezeshki.com 66485457-66963820

Physical Examination

The examination of the ankle starts with an assessment of deformity, ecchymosis, edema, and perfusion, followed by active and passive range of motion. Assessment of point tenderness may localize ligament, bone, or tendon injuries, particularly when the patient is seen early. Palpation should include the medial and lateral collateral ligaments, the syndesmotic ligaments, the inferior and posterior edges of the medial and lateral malleoli, the entire length of the fibula and tibia, the anterior plafond, the medial and lateral dome of the talus (palpable with the ankle in plantar flexion), the base of the fifth metatarsal, the calcaneus, the Achilles tendon, and the peroneal tendons behind the lateral malleolus. Stress testing of the ankle joint, which is discussed later, should not be performed until a fracture has been excluded. An evaluation of weight-bearing ability should proceed only if clinical suspicion of a fracture is low, the location of tenderness does not indicate the need for plain radiography, or radiographs have ruled out a fracture.[3] Specific clinical examination tests are discussed elsewhere in the appropriate sections.

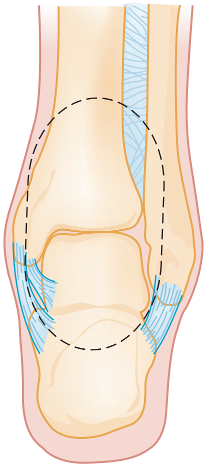


Figure 58-4. The ring structure surrounding the talus is made up of the tibial plafond, medial malleolus, deltoid ligaments, calcaneus, lateral collateral ligaments, and syndesmotic ligaments. The integrity of this ring determines the stability of the ankle. (From Simon RR, Koenigsknecht SJ: Emergency Orthopedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

DIAGNOSTIC STRATEGIES

Radiology

The anteroposterior, lateral, and mortise views make up the standard three-view radiographic series of the ankle. Although two-view ankle series have been studied, the likelihood of missing a subtle fracture is reduced with three views.[4] Subtle fractures can be easily missed on ankle radiographs,[5] and a standardized approach to radiograph interpretation can reduce the likelihood of missing low-energy ankle fractures[6] (Fig. 58-5). The anteroposterior view identifies fractures of the medial and lateral malleoli, anterior tibial tubercle, distal tibia or fibula, talar dome, body and lateral and posterior process of the talus, and calcaneus. The lateral view identifies fractures of the anterior and posterior tibial margins, talar neck, posterior talar process, calcaneus, and any anterior or posterior displacement of the talus or pathology involving the talonavicular joint. On this view, any incongruity of the articular space between the talar dome and the distal tibia suggests ankle instability, particularly if narrowing of the anterior joint space is present. The lateral view is also useful in identifying an ankle effusion, which appears as a teardrop-shaped density displacing the normal fat adjacent to the anterior or posterior margin of the joint capsule. The presence of an effusion suggests the possibility of a subtle intra-articular injury, such as an osteochondral lesion of the talar dome.[7]

The mortise view, which is taken with the ankle in 15 to 25 degrees of internal rotation, is most important for evaluating the congruity of the articular surface between the dome of the talus and the mortise. The lines formed between the articular surfaces should be parallel, the joint space should appear uniform throughout the tibiotalar and talofibular components of the joint, and the medial clear space should not exceed 4 mm[8] (Fig. 58-6).

In most cases of isolated blunt ankle trauma evaluated within 48 hours of injury, the Ottawa Ankle Rules (OAR) should be used

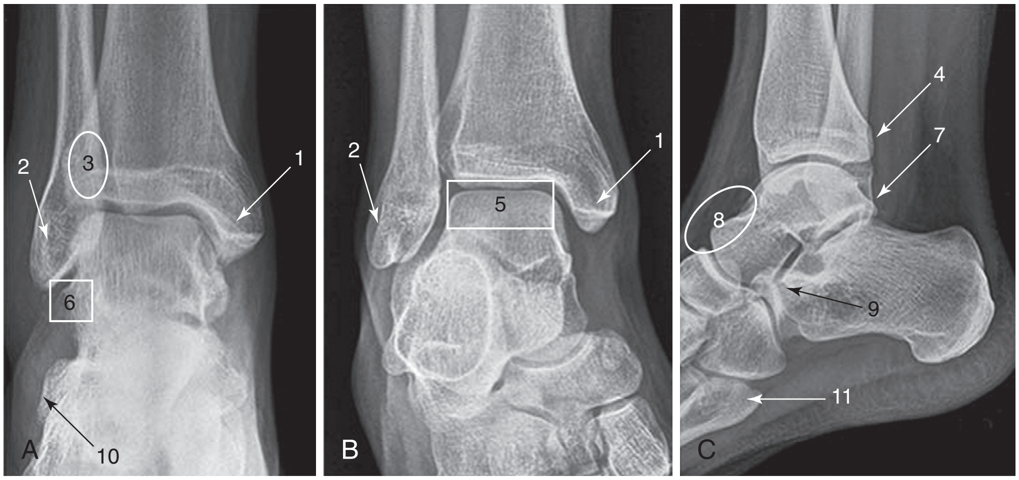


Figure 58-5. Approach to reviewing ankle radiographs. **A** to **C**, A standard radiographic series of the ankle has three views: an anteroposterior view **(A)**, an internal rotation or mortise view **(B)**, and a lateral view **(C)**. The following 11 locations should be carefully scrutinized, as they are areas where fractures frequently occur: the medial *(1)* and lateral *(2)* malleoli, anterior tibial tubercle *(3)* and posterior tibial malleolus *(4)*, talar dome *(5)*, lateral talar process *(6)*, tubercles of the posterior talus process *(7)*, dorsal to the talonavicular joint *(8)*, anterior calcaneus process *(9)*, calcaneal insertion of the extensor digitorum brevis *(10)*, and the base of the fifth metatarsal bone *(11)*. (From Yu JS, Cody ME: A template approach for detecting fractures in adults sustaining low-energy ankle trauma. Emerg Radiol 16:309, 2009.)

www.ketabpezeshki.com 66485457-66963820

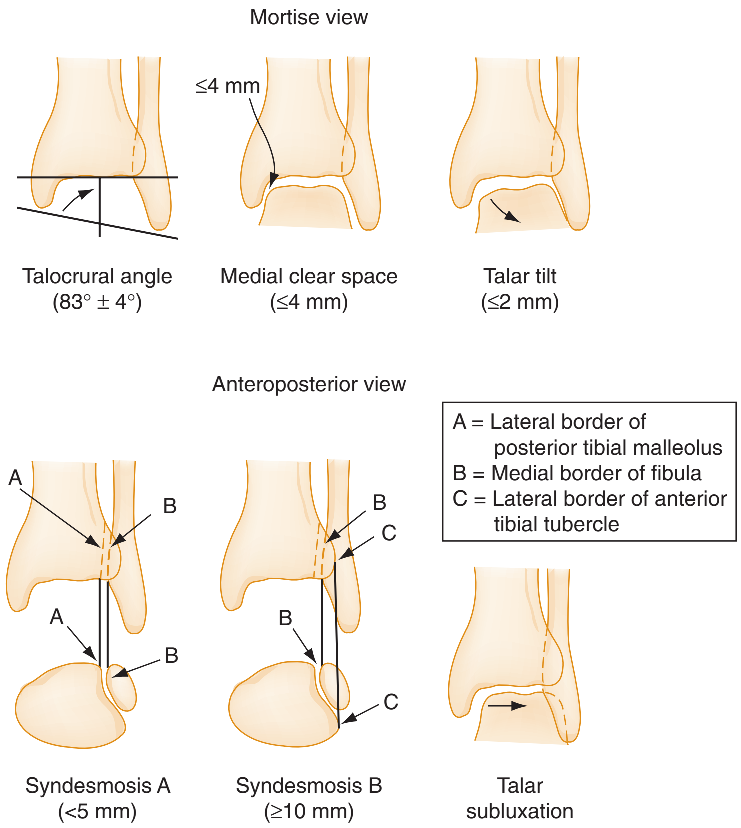


Figure 58-6. Radiologic criteria for evaluating the syndesmosis. (From Stiehl JB: Ankle fractures with diasthesis. Instr Course Lect 39[III]:79, 1990.)

to determine whether ankle or foot radiographs are necessary.[3,9] The OAR state that an *ankle radiographic series* is required if there is pain in the malleolar region with any of the following findings:

- Bone tenderness at the posterior edge of the distal 6 cm or the tip of the lateral malleolus, *or*
- Bone tenderness at the posterior edge of the distal 6 cm or the tip of the medial malleolus, *or*
- Inability to bear weight (defined as the ability to transfer weight onto each leg regardless of limping) for at least four steps both immediately after the injury and at the time of evaluation

The OAR further state that a *foot radiographic series* is required if there is pain in the midfoot region with any of the following findings:

- Bone tenderness at the navicular bone, *or*
- Bone tenderness at the base of the fifth metatarsal, *or*
- Inability to bear weight for at least four steps both immediately after the injury and at the time of evaluation

The OAR have a sensitivity approaching 100% in detecting malleolar zone ankle fractures and midfoot zone fractures.[3,9] The OAR were derived in an adult population and are not applicable in subacute or chronic injuries. The OAR appear to perform well in pediatric patients older than 5 years; however, results have varied, leading some researchers to propose alternative rules to address the unique aspects of this population.[10-18]

The decision rules for foot radiography, although applicable to blunt ankle trauma, apply only to the midfoot zone. The OAR were not designed to be general guidelines for foot radiography and certainly do not apply to the hindfoot or forefoot. Finally, the OAR are not applicable to intoxicated patients or those who are difficult to assess because of head injuries, multiple injuries, or diminished sensation related to neurologic deficits. Use of the OAR by specialized emergency and triage nurses has been found to have efficacy in application comparable to that for use by physicians.[19-21] Although the OAR are well validated, their adoption and clinical impact remains variable.[22,23]

Other Imaging Techniques

Although plain radiography is the initial imaging modality of choice for ankle injuries, it can miss subtle ankle fractures, osteochondral lesions, stress fractures, or ligamentous injuries. When unexplained symptoms persist after negative or inconclusive findings on plain radiography, other imaging modalities or orthopedic consultation may be advisable.[24]

Radionuclide imaging (bone scanning) can detect soft tissue injuries, such as distal syndesmotic disruptions, stress fractures, and osteochondral lesions.[25] Bone scan abnormalities are present once a patient is symptomatic and typically appear 1 to 2 weeks before radiographic evidence of a stress fracture. Because of its high sensitivity, a negative bone scan effectively rules out the diagnosis. Bone scan abnormalities are nonspecific, however, because infections and tumors also can lead to positive results (see further discussion on stress fracture imaging in the "Foot" section of this chapter), and bone scanning is not useful for follow-up because abnormalities can persist for up to 1 year after recovery.[25] Radionuclide imaging is virtually always ordered on an outpatient basis and has been largely supplanted by computed tomography (CT) and magnetic resonance imaging (MRI). CT scanning provides superior bone imaging and is an excellent modality to delineate abnormalities not identified or incompletely characterized by other imaging techniques.[24,25] CT can detect small fractures, subtle stress fractures, and ligamentous injuries and can facilitate surgical planning.[24,25] Newer CT image reformatting techniques can be extremely helpful, including two-dimensional multiplanar reformatting to identify small fractures, three-dimensional volume rendering to show relationships

www.ketabpezeshki.com 66485457-66963820

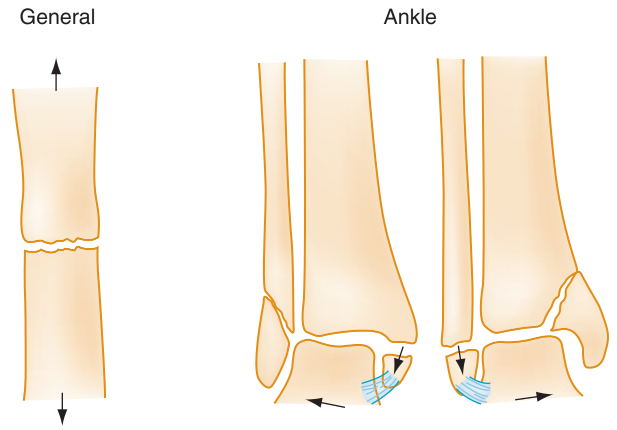


Figure 58-7. The mechanics of bone failure in tension and types of tension ankle fractures. Arrows indicate the direction of distracting forces. (From Dahners LE: The pathogenesis and treatment of bimalleolar ankle fractures. Instr Course Lect 39[III]:85, 1990.)

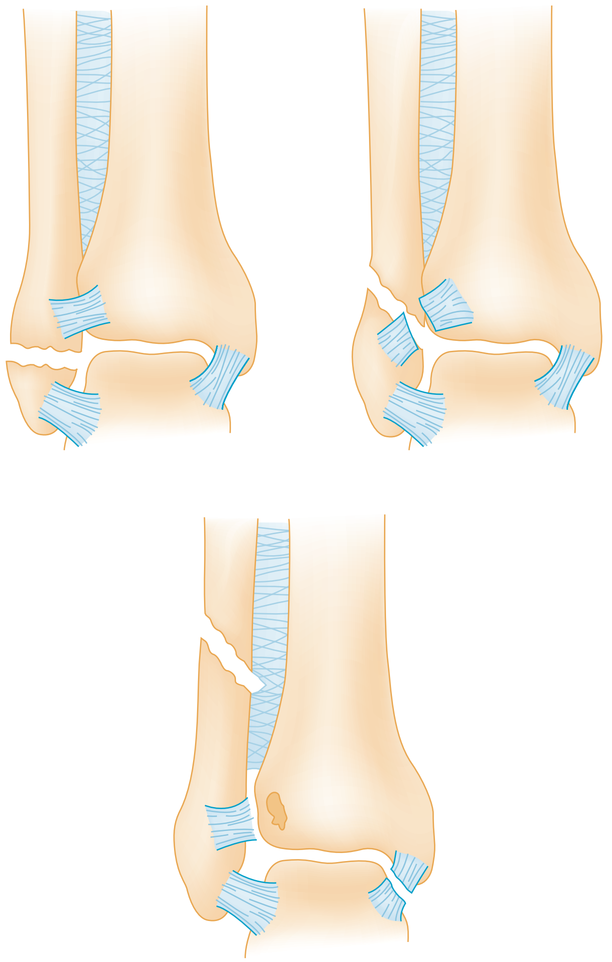


Figure 58-8. The Danis-Weber classification of ankle fractures focuses on the location of the fibular fracture in relation to the tibiotalar joint and syndesmosis. See text for explanation. (From Wilson FC: The pathogenesis and treatment of ankle fractures: Classification. Instr Course Lect 39[III]:79, 1990.)

between tendons and underlying bones, and shaded surface display to provide disarticulated views of joint surfaces and enhance diagnostic accuracy.[26,27] MRI, although not typically performed emergently, provides unprecedented clarity in depicting soft tissue structures such as ligaments and tendons and can also delineate bone marrow changes associated with stress fractures before radiographic abnormalities appear.[25] MRI can be helpful both in guiding management decisions and in following the patient's response to therapy.[28]

Additional imaging techniques such as magnetic resonance or CT arthrography can be useful in the evaluation of chronic ankle pain to detect loose bodies, ligamentous injuries, cartilaginous abnormalities, impingements, or osteochondral lesions.[29] CT/SPECT, which combines CT and radionuclide scanning with single photon emission computed tomography (SPECT), has been shown to significantly increase the diagnostic ability of imaging in osteochondral lesions, stress fractures, impingement syndromes, and osteomyelitis.[30] The decision to perform specialized imaging of this nature is typically made through orthopedic or radiologic consultation; such studies are not performed in the emergency department (ED).

SPECIFIC PATHOLOGIC CONDITIONS

Ankle Fractures

Pathophysiology

Fractures occur when a deforming force is sufficient to overcome the structural strength of a bone. A bone under tension breaks transversely along the axis of the deforming force[31] (Fig. 58-7). Alternatively, ligamentous rupture or an avulsion fracture can occur at either end of a stressed ligament or tendon.

Management

The management of ankle fractures consists of identification and classification, assessment of stability, immediate reduction of fracture-dislocations that threaten soft tissues or neurovascular status, and specific treatment and disposition.

To date, no ideal system has been developed for the classification of ankle fractures. The classic Danis-Weber (Fig. 58-8) and Lauge-Hansen classification systems are based on fracture location and mechanism of injury, respectively.[32] The Danis-Weber classification has predictive value for operative repair in isolated lateral malleolar fractures, as the location of the fibular fracture is related to the integrity of the syndesmosis, and is thus more useful to emergency physicians than the more complex Lauge-Hansen classification. Both systems have limitations, however, and neither accurately predicts management or clinical outcome in all situations. The Danis-Weber system does not adequately classify isolated medial malleolar fractures, bimalleolar, trimalleolar, or pilon fractures.[33] By contrast, the Lauge-Hansen classification was intended to characterize ligamentous injury patterns based on the radiographic appearance of ankle fractures.[34] According to a recent MRI study of 49 ankle fractures, however, this system was unable to predict patterns of ligamentous injuries in 53% of cases, and 17% of cases were unclassifiable.[35] This study also found that more than 65% of cases had a complete ligamentous disruption associated with a related malleolar fracture, calling into question the stability of the fractures. It is clear that the Lauge-Hansen system in isolation is inadequate for classifying all fractures and has particular limitations in predicting soft tissue injuries. Modifications to these two classification schemes have been proposed to better describe ankle fractures and, more important, to predict outcome; however, because of their complex nature, most modified classification schemes are relegated to research applications and trauma registries.[33-35]

www.ketabpezeshki.com 66485457-66963820

The injured ankle should be promptly immobilized, elevated, and iced to minimize swelling and further soft tissue damage. The presence of gross deformity with neurovascular compromise or skin tenting necessitates immediate intervention.[36,37] Plain radiography before reduction can be helpful but should not delay reduction in injuries with obvious vascular compromise.

Appropriate procedural sedation and analgesia techniques should be used for reduction. The fundamental principle of closed reduction is to reverse the deforming forces. For example, reduction of a fracture-dislocation caused by an adduction injury would require an abduction force. The initial application of a distracting force, sometimes combined with slightly increasing the deformity, is often helpful in achieving reduction. After reduction, neurovascular status should be reassessed, the leg should be immobilized and elevated, and postreduction radiographs should be obtained. The overarching goal in the definitive treatment of ankle fractures is to achieve anatomic reduction.

Disposition

In general, all displaced or potentially unstable ankle fractures require orthopedic consultation in the ED (Box 58-1). These injuries include all bimalleolar and trimalleolar fractures and unimalleolar fractures with contralateral ligamentous injuries (e.g., a lateral malleolar fracture with deltoid ligament disruption or a medial malleolar fracture with lateral collateral ligament disruption).[38] In addition, all intra-articular fractures, especially those with step deformity of the articular surface, require early orthopedic involvement.

Extra-articular fractures that disrupt only one ring element generally can be treated with casting for 6 to 8 weeks. Orthopedic follow-up on an outpatient basis within 1 to 2 weeks of the injury is ideal in case operative intervention is required. The presence of any abnormal measurement on the mortise view (see Fig. 58-6) suggests instability and the need for orthopedic consultation in the ED. Avulsion fractures, in which the avulsed fragment is less than 3 mm in diameter and minimally displaced, can be treated in an identical manner to an ankle sprain.

The outcome of ankle fractures depends on the extent of injuries, the number of malleoli fractured, ankle stability, and patient age.[32,33] For ankle fractures that require surgery, outcome is better in unimalleolar fractures over trimalleolar fractures, in isolated lateral malleolar fracture over isolated medial malleolar fractures, in multimalleolar fractures without medial malleolar fracture over those with malleolar fractures, and in cases with posterior fragments involving less than one third of the articular surface over larger fragments.[39]

Box 58-1 Ankle Fractures for Which Orthopedic Consultation in the Emergency Department Is Recommended

- Unimalleolar fractures
  - Displaced medial malleolar fracture
  - Medial malleolar fracture with lateral collateral ligament rupture
  - Displaced lateral malleolar fracture
  - Lateral malleolar fracture with deltoid ligament rupture
  - Lateral malleolar fracture with widened medial clear space
  - Unimalleolar fracture with syndesmotic diastasis
  - Fibula fracture at or proximal to the tibiotalar joint line
  - Displaced posterior malleolar fracture
  - Posterior malleolar fracture involving more than 25% of articular surface
- All bimalleolar fractures
- All trimalleolar fractures
- All intra-articular fractures with step deformity
- All open fractures
- All pilon fractures

Unimalleolar Fractures

Lateral Malleolar Fractures. The stability of an isolated lateral malleolar fracture depends on the location of the fracture in relation to the level of the tibiotalar joint, which defines the distal portion of the syndesmotic ligament and the stability it provides to the ankle joint. The Danis-Weber classification (see Fig. 58-8) is useful and predictive of outcome in these types of unimalleolar fractures.[33] This classification groups fractures into three groups (A, B, and C), each of which has three subgroups. Lateral malleolar fractures below the tibiotalar joint (Danis-Weber type A) rarely disrupt other bony or ligamentous structures, and in the absence of injury to the medial structures such fractures are unlikely to affect the dynamic congruity of the ankle joint.[38] The management of uncomplicated lateral malleolar fractures involves casting for 6 to 8 weeks, with no weightbearing for at least the first 3 weeks, and ongoing follow-up to ensure proper union. Concomitant tenderness over the deltoid ligament may suggest a biomechanical disruption of both malleoli, an associated fracture of the medial malleolus, or an associated fracture of the posterior malleolus and warrants orthopedic consultation in the ED, especially if the medial clear space on the mortise view is widened (see Fig. 58-6).[38] CT imaging can be useful in such situations as it may identify occult medial or posterior malleolar fractures.

Fibular fractures proximal to the tibiotalar joint line (a Danis-Weber type C injury; see Fig. 58-8) frequently, but not always, disrupt the distal tibiotalar syndesmosis and the medial structures and commonly require orthopedic consultation in the ED and operative intervention. Treatment of an isolated fracture at the level of the tibiotalar joint (a Danis-Weber type B injury; see Fig. 58-8) is controversial because 50% of these injuries are accompanied by an injury to the distal tibiofibular syndesmosis that may require operative intervention.[40] Distal tibiofibular space measurements on plain radiography have a sensitivity of only 31% and a specificity of 83%, compared with CT scan, in detecting tibiofibular syndesmosis injuries.[41] Tenderness on palpation of the syndesmotic ligament or a widening of the medial joint space on the mortise view adds further support to the need for emergency consultation.

Medial Malleolar Fractures. Medial malleolar fractures are usually the result of eversion or external rotation. These two forces exert tension on the deltoid ligament, causing an avulsion of the tip of the medial malleolus or a rupture of the deltoid ligament. Although they can occur in isolation, medial malleolar fractures are commonly associated with lateral or posterior malleolar disruption. Because of this, the identification of a medial malleolar fracture warrants a careful examination of the entire length of the fibula for tenderness, the presence of which warrants radiographic evaluation to rule out a proximal fibular fracture (Fig. 58-9).

An isolated nondisplaced medial malleolar fracture can be treated with casting for 6 to 8 weeks, with no weightbearing for at least the first 3 weeks and close orthopedic follow-up. Any displacement or concomitant disruption of the lateral components of the ankle warrants orthopedic consultation in the ED for consideration of operative management.[38]

Posterior Malleolar Fractures. Isolated fractures of the posterior malleolus are rare and imply an avulsion of the posterior tibiofibular ligament. These injuries can be associated with proximal fibular fractures and medial and lateral collateral ligament sprains. Treatment usually consists of casting for 6 weeks, provided that no associated injury or ankle instability is present.[42] Fractures

www.ketabpezeshki.com 66485457-66963820

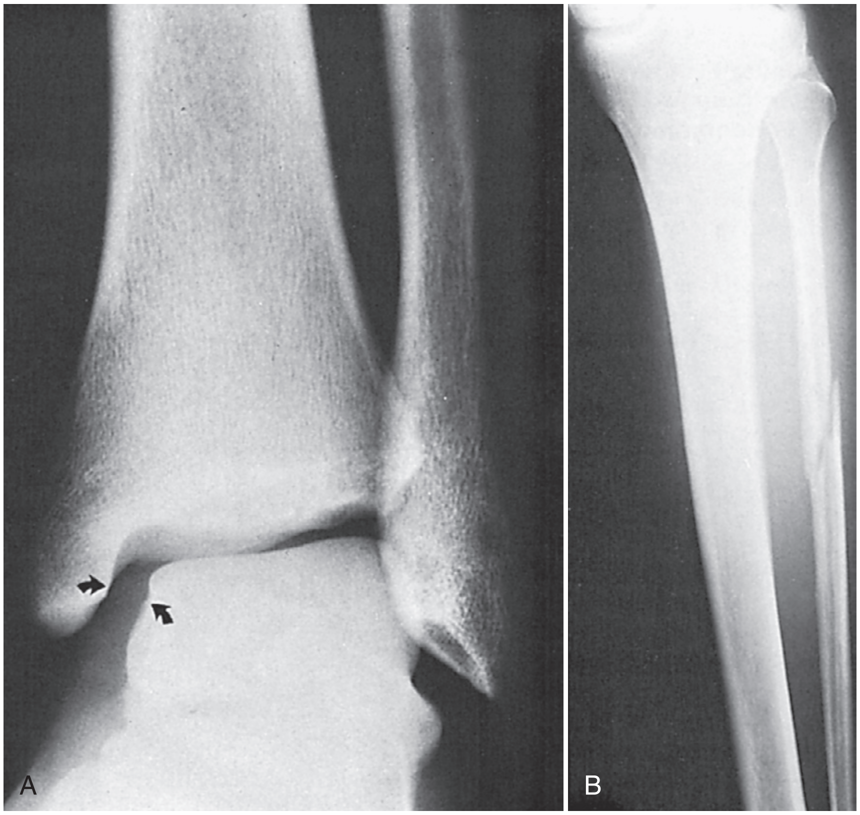


Figure 58-9. Maisonneuve fracture. **A,** Anteroposterior view shows a slight widening *(arrows)* of the ankle mortise and the medial clear space. **B,** Anteroposterior view shows an oblique fracture at the proximal shaft of the fibula. (From Nicholas JA, Hershman EB [eds]: The Lower Extremity and Spine in Sports Medicine, 2nd ed. St Louis, Mosby, 1994.)

involving more than 25% of the tibial surface usually require open reduction and internal fixation.[38]

Bimalleolar Fractures

Bimalleolar fractures involve the disruption of at least two elements of the ankle ring and are therefore unstable. These fractures result from adduction or abduction forces, the latter being more common.[31] Rotational injuries also can cause bimalleolar fractures, as well as trimalleolar fractures if the posterior malleolus is involved.

The mechanism of injury often can be deduced from the appearance of the fractures.[31] An abduction injury exerts tension on the medial malleolus, causing a horizontal fracture, and compresses the lateral malleolus, causing an oblique shear or a comminuted fracture (see Fig. 58-7). An adduction injury causes the reverse, leading to a horizontal fracture of the fibula and an oblique shear fracture of the medial malleolus. A rotational injury causes oblique or spiral fractures of the fibula or medial malleolus. Associated damage to other soft tissue structures (e.g., the syndesmosis) is common with bimalleolar fractures.

Controversy exists about whether such injuries should be treated closed or surgically.[31,43] Unstable bimalleolar fractures require surgical intervention, however, and one study found that outcomes at 1 year after surgery were worse with bimalleolar fractures than with lateral malleolar fractures with deltoid ligament disruption.[44]

Rarely, stress fractures of the medial malleolus or distal fibula can be seen, particularly in athletes and runners. Plain radiographs may be nondiagnostic, but radionuclide bone scanning, CT, or MRI—the choice of which is often influenced by local availability—can establish the diagnosis.[45] Most such injuries can be treated nonoperatively, but orthopedic consultation and follow-up are prudent.

Trimalleolar Fractures

Trimalleolar fractures involve fractures of the medial, lateral, and posterior malleoli. Closed treatment of trimalleolar fractures often leads to unsatisfactory results, so operative reduction and internal fixation is the treatment of choice.[46]

Open Fractures

Open ankle fractures usually occur from severe isolated ankle injuries or multiple trauma and require immediate orthopedic consultation. After documentation of the neurovascular status and the extent of soft tissue trauma, gross contaminants should be removed from the wound, saline-soaked sterile gauze should be applied, and the injured leg should be splinted.[36] Swabbing an open wound for bacterial culture and sensitivity testing is unnecessary. If significant deformity is present, immediate reduction before splinting is indicated.[36] Tetanus immunoprophylaxis should be administered as appropriate. Because open fractures are invariably contaminated with bacteria, patients with these injuries should receive intravenous antibiotics.[47,48] For low-energy injuries with mild to moderate contamination, a first-generation cephalosporin is usually sufficient.[36,47,48] Heavily contaminated wounds require the addition of gram-negative bacterial coverage, typically an aminoglycoside.[47,48] Adding either penicillin G or clindamycin (if penicillin allergic) as a third antibiotic is necessary for farm- or soil-related crush injuries, in which contamination with *Clostridium perfringens* can be present.[47,48] In addition to the ankle radiographs, radiographs of the foot, tibia, and fibula should be obtained.

All open fractures benefit from early surgical intervention for débridement and irrigation.[36] Therefore identification is crucial, and emergency orthopedic consultation must be sought for such injuries.

www.ketabpezeshki.com 66485457-66963820

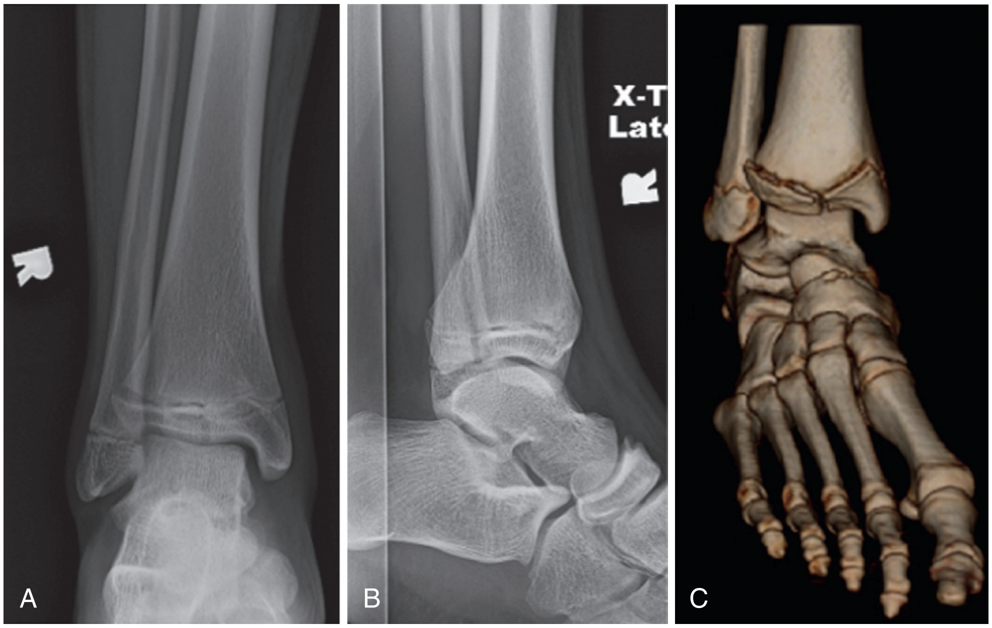


Figure 58-10. Anteroposterior **(A)** and lateral **(B)** radiographic views showing a pilon fracture with computed tomographic **(C)** three-dimensional reconstruction providing important preoperative information about joint congruity. (From Hanlon DP: Leg, ankle, and foot injuries. Emerg Med Clin North Am 28:885, 2010.)

Complications

Early operative complications of closed and open ankle fractures include pin site infection, delayed skin necrosis, skin graft rejection, and osteomyelitis. Delayed complications of both operative and nonoperative treatment include malunion, nonunion, osteopenia, traumatic arthritis, chronic instability, ossification of the interosseous membrane, avascular necrosis, and complex regional pain syndrome.[2,49]

Pilon Fractures

Pilon fractures involve the distal tibial metaphysis and usually are the result of high-energy mechanisms, such as falls from a significant height. These injuries often are comminuted and associated with significant soft tissue trauma, devastation of joint architecture, and leg shortening (Fig. 58-10). Other, higher-priority injuries can be present in such situations.

Pathophysiology

Destot first coined the term *hammer fracture* to describe the way the head of the talus drives itself into the tibial plafond and causes a pilon fracture. The primary deforming force is one of axial compression, and the position of the foot at the time of injury determines the fracture location and pattern[50] (Fig. 58-11). Secondary rotational or shear forces may cause increased comminution and fragment displacement with more extensive soft tissue injuries. One fourth of pilon fractures are open, and associated injuries include fractures of the calcaneus, tibial plateau, femoral neck, acetabulum, or lumbar vertebrae, as well as trauma to other major systems.

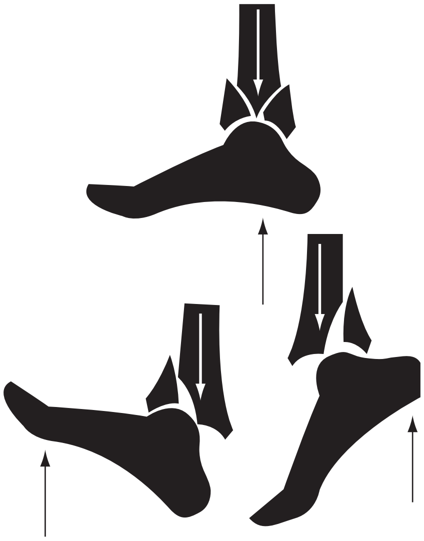


Figure 58-11. Schematic diagram of the pathophysiology of pilon fractures. The position of the foot at the time of impact determines the fracture pattern. (From Gustilo RB, et al [eds]: Fractures and Dislocations. St Louis, Mosby, 1993.)

Management

Radiographic examination should include the entire tibia and fibula, as well as the ankle. The emergency management principles for open fractures, as outlined previously, should be applied. Treatment involves restoration of the articular surface and fibular length, combined with meticulous management of soft tissue injuries.[50,51] Because surgical management is required, orthopedic consultation in the ED is necessary. Pilon fractures with low-grade soft tissue damage are managed with primary open reduction and internal fixation.[51,52] In severe pilon fractures with extensive soft tissue damage, however, results are better with a two-stage approach involving initial length restoration and external fixation followed by anatomic reduction and internal fixation after soft tissue swelling has subsided.[52-54]

Complications

Complications of pilon fractures are common, particularly in more severe cases.[51] Early complications include wound infection, skin sloughing, pin site infection, and wound dehiscence. Delayed and late complications include malunion, nonunion, leg

www.ketabpezeshki.com 66485457-66963820

shortening, post-traumatic arthritis, avascular necrosis, and protracted pain. Some patients with severe pilon fractures ultimately require arthrodesis.

Soft Tissue Injuries

Ligament Injuries

Ankle sprains are commonly seen in EDs, with a recent series estimating an annual incidence of 52.7 to 60.9 cases per 10,000 population.[55] Ankle sprains also are one of the most common injuries in young athletes, and 40% of patients experience dysfunction for up to 6 months postinjury.[56,57] The term *ankle sprain* refers to a potpourri of ligamentous and nonligamentous injuries.[58] Even when ligamentous injury is certain, the ideal treatment approach remains controversial, and significant variation in clinical practice exists.[55,59,60]

Pathophysiology. Most ankle sprains occur from extreme inversion and plantar flexion causing symptoms on the lateral aspect of the ankle. Usually the anterior talofibular ligament is injured first, followed by the calcaneofibular ligament if the deforming forces are sufficiently strong (see Fig. 58-1). Approximately two thirds of ankle sprains are isolated anterior talofibular ligament injuries, whereas 20% involve both anterior talofibular and calcaneofibular ligament injuries. In addition, the lateral talocalcaneal ligament may be stressed with an inversion injury, leading to avulsion fractures at either end of the attachment sites.[61] Isolated calcaneofibular or posterior talofibular ligament injuries are rare.

Isolated injury of the deltoid ligament occurs in less than 5% of ankle sprains. Rupture of this ligament occurs most commonly in conjunction with lateral malleolar fractures, especially when an external rotational force is involved.

Injuries of the distal tibiofibular syndesmotic ligaments are uncommon in the general population but may represent 10 to 20% of injuries in competitive athletes.[62] Dorsiflexion and external rotation forces are usually responsible for this injury, the presence of which may significantly prolong the recovery time from lateral collateral ligament sprains.[62]

Ligamentous injuries are classified into three grades based on functional and presumed pathologic findings. A *grade I* injury involves ligamentous stretching without grossly evident tearing or joint instability. A *grade II* injury involves a partial tear of the ligament with moderate joint instability, often accompanied by significant localized swelling and pain. A *grade III* injury involves a complete tear of the ligament with marked joint instability, severe edema, and ecchymosis. This classification system, although commonly used, fails to characterize ankle injuries involving two or more ligaments, and it does not consider nonligamentous injuries. Although more comprehensive classification systems have been proposed,[61] there is a strong association with increased gradation of ankle sprain and long-term risk of chronic instability, early osteoarthritis, chronic pain, and permanent disability.[63,64]

Clinical Features. Although desirable, an accurate history of ankle position and injury mechanism is often unavailable. Inversion followed by external rotation of the ankle suggests the potential for deltoid or syndesmotic injury. Forced dorsiflexion with snapping may indicate peroneal tendon displacement. Previous injuries to the same ankle or symptoms of recurrent ankle instability or pain suggest the presence of a subacute or chronic pathologic process.

On physical examination, the presence of edema, ecchymosis, and point tenderness over the medial or lateral collateral ligaments or the syndesmotic ligaments suggests a ligamentous injury. Inability to bear weight in the absence of a fracture suggests the presence of a grade II or III ankle sprain.[65] With inversion injuries, point tenderness may also be present along the distal fibula, the lateral aspect of the talus, the lateral aspect or anterior process of the calcaneus, or the base of the fifth metatarsal. Deltoid ligament tenderness necessitates palpation of the full length of the fibula to rule out a proximal fibular fracture (a type C Danis-Weber or Maisonneuve fracture; see Figs. 58-8 and 58-9) and a low threshold for imaging the entire tibia and fibula should exist. The *fibular compression test,* also known as the *squeeze test,* reveals fibular and syndesmotic injuries.[62] To perform this test, the examiner places the fingers over the fibula and the thumb over the tibia at midcalf and squeezes the two bones. Pain anywhere along the length of the fibula suggests a fibular fracture or an interosseous membrane or syndesmotic ligament disruption at that location.[62] Finally, the Achilles tendon should be assessed.

Stress testing is the application of a deforming force to assess joint motion beyond the physiologic range, the presence of which suggests ligament disruption or mechanical instability. Although rarely required, stress testing is safe to perform and can be helpful for acute and severe ankle injury in which rupture of two or more ligaments is suspected, a fracture suspected to be isolated in which the presence of an additional ligament rupture would influence management, the possibility of a concomitant syndesmotic injury, follow-up evaluation of an acute ankle injury after pain and swelling have subsided, and a chronically symptomatic ankle. With the exception of these scenarios, stress testing is not indicated because it is painful and does not alter management. The normal ranges for stress tests are controversial, so the uninjured side should be examined for comparison.

Common ankle stress tests include the anterior drawer test, the inversion stress test, and the external rotation test. The *anterior drawer test* primarily assesses the integrity of the anterior talofibular ligament. For this test to be performed, the patient is seated with the knee in 90 degrees of flexion and the ankle in a neutral position or 10 degrees of plantar flexion. The examiner then pulls on the heel with one hand and pushes the leg posteriorly with the other. Anterior displacement of the talus, the perception of a "clunk," and the induction of a sulcus anteromedially over the joint indicate partial or complete tear of the anterior talofibular ligament.

The *inversion stress test,* or talar tilt test, evaluates both the anterior talofibular ligament and the calcaneofibular ligament. It is performed by inverting the heel with the knee in 90 degrees of flexion and the ankle in neutral position. Palpation of the head of the talus laterally or a finding of increased laxity compared with the uninjured side suggests partial or complete tear of these ligaments.

The *external rotation stress test* is indicated when injury to the distal tibiofibular syndesmotic ligaments is suspected. It is performed by externally rotating the foot with the knee in 90 degrees flexion and the ankle in a neutral position. Pain at the syndesmosis or the sensation of lateral talar motion suggests partial or complete tear of the ligaments.

Diagnostic Strategies: Radiology. Standard ankle radiographic views are useful to exclude fractures and to detect instability by the measurement of joint spaces (see earlier discussion and Fig. 58-6).[8] Presence of avulsion fractures, which can be located at the bases of the malleoli, the lateral process of the talus, the lateral aspect of the calcaneus, the posterior malleolus, the lateral aspect of the distal tibia, or the base of the fifth metatarsal, constitute an important clue to the location of ligamentous injuries.

In addition to the standard mortise measurements previously discussed, two measurements on the anteroposterior radiograph further evaluate the distal tibiofibular syndesmosis (see Fig. 58-6).[8] At the distal overlap between the fibula and the tibia, the distance between the posterior edge of the lateral tibial groove and the medial fibular cortex (syndesmosis A) should not exceed 5 mm.[8] Furthermore, the amount of tibiofibular bony overlap (syndesmosis B) should be at least 10 mm.[8] Measurements outside of these values suggest a syndesmotic diastasis. Stress radiographs,

www.ketabpezeshki.com 66485457-66963820

Box 58-2 Differential Diagnosis for Presumed Ankle Sprain

Lateral collateral ligament sprain
Peroneal tendon dislocation
Osteochondral lesion of the talar dome
Fracture of the posterior process of the talus
Fracture of the lateral process of the talus
Fracture of the anterior process of the calcaneus
Midtarsal joint injury
Fracture of the base of the fifth metatarsal

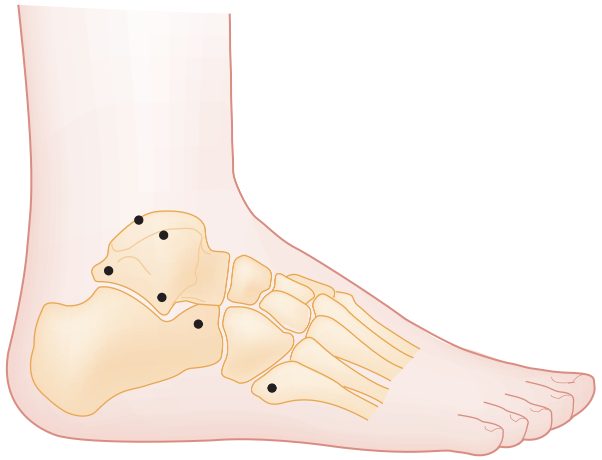


Figure 58-12. Locations of common fractures in or near the ankle that should be considered in the differential diagnosis of a presumed ankle sprain. (From Gustilo RB, et al [eds]: Fractures and Dislocations. St Louis, Mosby, 1993.)

accomplished by taking radiographs during stress testing of the ankle, generally do not influence the emergency management of ankle sprains and are not recommended.[66]

Many injuries can masquerade as ankle sprains.[58] Box 58-2 lists conditions to be considered in the differential diagnosis; Figure 58-12 shows locations of common fractures in or near the ankle that can be misdiagnosed as an ankle sprain.

Management. Most ligament sprains, regardless of severity, heal well and result in a satisfactory outcome. To date, compelling evidence for a significant difference in outcomes between surgical and functional (nonsurgical) treatment is lacking. Limited data suggest that recovery times may be longer and complications more frequent with surgical treatment.[67] Most patients with acute sprains of the ankle should start with functional treatment.[68] For the minority who fail to respond, delayed operative repair of ruptured ligaments, sometimes years after the injury, has been shown to yield results equivalent to those with primary repair.[68,69]

Functional treatment, which is defined as a form of therapy in which the ankle is not fully immobilized, allowing either complete or partial joint function, starts in the ED with RICE therapy (rest, ice, compression, and elevation); however, significant variability exists in how this combination is applied, and the optimal methods remain unclear.[60,61,70] The evidence to date suggests that lace-up ankle support is more effective in short-term edema reduction than semirigid ankle support, elastic bandaging, and taping. Elastic bandaging causes fewer complications than taping but appears to correlate with slower return to work and sports.[60] One study suggests that compared with elastic bandaging, ankle bracing with a lace-up brace such as the Air-Stirrup Ankle Brace (Aircast, DJO Inc., Vista, Calif.) leads to improved functioning at both 10 days and 1 month.[71]

For grade I or II injuries, short-term protection with a tensor bandage, taping, a laced-up support, or a commercial walking boot or brace, with the optional use of crutches for a few days, is appropriate.[68,70] For patients with first-time ankle sprains, treatment with a lace-up stirrup brace combined with elastic wrapping results in an earlier return to function compared with use of a brace alone, elastic wrap alone, or a walking cast.[72] For severe grade II or grade III injuries, there is currently equipoise regarding the merit of immobilization compared with functional rehabilitation, with little high-quality evidence to guide therapy.[73,74] A recent study supports a 10-day period of immobilization with a below-knee cast or Aircast ankle brace to speed recovery from ankle sprains, with immobilization leading to reduced symptoms and faster recovery compared with tubular compression bandages.[75] However, a weakness in this study was the lack of a control group incorporating an active ankle physiotherapy program, known to be important for improved recovery. An accelerated functional rehabilitation program carried out over the first week of injury has also recently been shown to improve function in grade I and II ankle sprains in the short term.[76]

Because there is little evidence for a more favorable outcome with complete immobilization over functional treatment incorporating a removable brace, the use of a lace-up support or air cast that permits some ankle motion is generally preferable.[68,74,77] Such patients should also use crutches to avoid weightbearing until they can stand and walk a few steps on the injured ankle without pain. How long crutches will be required varies significantly, ranging from a few days to 2 or 3 weeks. Follow-up care with the patient's primary physician within the first 2 weeks is appropriate for minor sprains, whereas orthopedic or sports medicine referral on an outpatient basis is prudent for severe sprains.

Analgesics are often necessary for pain management in ankle injuries, and studies suggest that nonsteroidal anti-inflammatory agents, acetaminophen, or oral opioids for severe cases are efficacious.[78-80] Topical diclofenac gel also has been shown to have efficacy in pain reduction and allowing early mobilization.[67,81,82]

After the acute management phase, the next two phases of functional treatment involve appropriate early rehabilitation and occur outside the ED.[83] Phase two, which begins after swelling has subsided and the patient is able to bear weight easily, involves strengthening the peroneal and dorsiflexor muscles by isometric, concentric, and eccentric exercises. The final phase begins when full range of motion has been reestablished and the patient can exercise painlessly. This starts with exercises to rebuild motor coordination and proprioception, recondition the muscles, and increase endurance. The patient uses an ankle tilt board or disk to develop coordination and performs increasingly demanding functional activities (e.g., brisk walking, running, and figure-of-eight running to hopping, jumping, and cutting) to build up the muscle groups.[83,84] With severe sprains the patient may benefit from the use of air casts, braces, or taping during the latter two phases of functional treatment and in the initial period of return to sports.[83] The entire treatment program usually lasts 4 to 6 weeks, depending on the injury's severity.[61,70,85]

Disposition. Rarely, orthopedic consultation in the ED is indicated for an acute ligament sprain. Primary surgical repair of acute ligament rupture is controversial, and possible indications include sprains with displaced osteochondral lesions, complete tears of both the anterior talofibular and calcaneofibular ligaments in a young athlete, a ligament sprain associated with a fracture causing instability (e.g., a deltoid ligament rupture with a lateral malleolar fracture), and an acute severe sprain in a patient with a history of recurrent and severe sprains.[61] Failure of nonoperative treatment also constitutes an indication for surgical repair; however, an orthopedic referral on an outpatient basis is adequate ED management.[69]

Small avulsion fractures of the fibula with minimal or no displacement can be treated in the same manner as an ankle sprain. If the avulsed fragment is larger than 3 mm or significantly

www.ketabpezeshki.com 66485457-66963820

displaced, splinting and referral for orthopedic follow-up on an outpatient basis are justified.

Despite appropriate treatment, chronic problems develop in 10 to 30% of patients with ankle sprains.[70] These include functional instability, mechanical instability, chronic pain, stiffness, and recurrent swelling and occur more often in grade III ankle sprains.

Functional instability refers to the patient's subjective sensation that the ankle gives way during activity. Although this may be a minor nuisance for some people, it can be devastating and debilitating for persons whose activities demand a high degree of ankle stability. *Mechanical instability* results from ligamentous laxity, which allows ankle joint movements beyond the physiologic range. In contrast to functional instability, mechanical instability can often be demonstrated clinically by the anterior drawer or talar tilt test and stress radiographs.[61]

Soft tissue abnormalities that cause chronic pain include synovial impingement, peroneal tendon subluxation or dislocation, intra-articular loose bodies, anterior tibiofibular syndesmotic ligament injuries, and degenerative arthritis. Bone-related causes of chronic pain include osteochondral lesions, fractures of the anterior process of the calcaneus, fractures of the lateral process of the talus, and anterior and posterior impingement.[58,86]

Patients with any of these chronic conditions should be referred for orthopedic follow-up care because they may require further imaging or arthroscopy for diagnosis or definitive treatment.

Tendon Injuries

Achilles Tendon Rupture. Achilles tendon rupture is most common in middle-aged men, and its causes are multifactorial. This condition is easily misdiagnosed, leading to a delay in therapy, a worse prognosis, and increased morbidity, including chronic weakness and loss of function. In the great majority of cases, a complete transection of the tendon is present; however, partial tears of the Achilles tendon can occur and may be more prone to misdiagnosis.

Achilles tendon rupture results from direct trauma or indirectly transmitted forces, including sudden unexpected dorsiflexion, forced dorsiflexion of a plantar-flexed foot, and strong push-off of the foot with simultaneous knee extension and calf contraction (as in a runner accelerating from the starting position). Factors predisposing to Achilles tendon rupture include preexisting disease such as rheumatoid arthritis, systemic lupus erythematosus, gout, hyperparathyroidism, or chronic renal failure, steroid use or injection, fluoroquinolone antibiotic therapy, and previous Achilles tendon rupture.[87]

The diagnosis of Achilles tendon rupture is primarily clinical. Patients usually describe a sudden onset of pain at the back of the ankle associated with an audible "pop" or "snap." Although the pain can resolve rapidly, weakness in plantar flexion persists. On examination, a visible and palpable tendon defect may be noted 2 to 6 cm proximal to the calcaneal insertion in acute presentations but will be less apparent in delayed presentations because of hematoma or edema. Even in cases of complete Achilles tendon rupture, weak plantar flexion may still be possible because of the actions of the tibialis posterior, toe flexors, and peroneal muscles. This retained ability for plantar flexion often leads to the misdiagnosis of complete ruptures as ankle strains or partial tears in as many as 25% of cases.[88] The classic maneuver to assess the integrity of the Achilles tendon is the Thompson test.[89] This is performed with the patient prone and the knee flexed at 90 degrees or the feet hanging over the end of the stretcher. Alternatively, the patient kneels on a chair with both knees flexed at 90 degrees and the feet hanging over the edge. Squeezing the calf muscles in these two positions should cause passive plantar flexion of the foot. Absence of this motion, or a markedly weakened response compared with the uninjured side, suggests complete rupture. Another recently described diagnostic test, the reverse Silfverskiöld test, compares dorsiflexion of the injured ankle with that in the uninjured ankle while the patient is in the supine position. Achilles tendon rupture results in a notably increased degree of dorsiflexion compared with the uninjured side.[90]

Lateral radiographic views of the ankle may suggest rupture by showing opacification of the fatty tissue–filled space anterior to the Achilles tendon (Kager's triangle) or an irregular contour and thickening of the tendon.[88] Ultrasonography or MRI can demonstrate partial or complete tendon ruptures, but these studies are indicated only in cases in which diagnostic uncertainty exists.[88]

A lack of consensus exists regarding the choice between operative and nonoperative management in the treatment of Achilles tendon rupture.[91-93] Surgical repair is routinely performed in active individuals owing to its lower incidence of rerupture. However, surgery carries higher rates of other complications, such as superficial or deep wound infections, in comparison with nonoperative management.[91,94] In both types of management, early mobilization improves functional recovery without increasing rerupture rates.[91,93] Minimally invasive surgery combined with early rehabilitation with postoperative functional bracing may further improve outcome.[95,96] Achilles tendon rerupture after initial nonoperative treatment usually necessitates surgical repair, with substandard results compared with primary repair.[97] ED orthopedic referral of patients with Achilles tendon rupture is necessary to determine the appropriate management.

Peroneal Tendon Dislocation or Tear. The peroneal muscles are the primary evertors and pronators of the foot and also participate in plantar flexion. The peroneus longus and brevis tendons use the posterior peroneal sulcus (the fibular groove), located behind and underneath the lateral malleolus, as a pulley for their midfoot insertions. The peroneus brevis tendon inserts onto the tuberosity of the fifth metatarsal, and the peroneus longus tendon courses beneath the cuboid to insert onto the medial cuneiform and base of the first metatarsal. The superior peroneal retinaculum (Fig. 58-13), a fibrous structure running from the distal fibula to the posterolateral aspect of the calcaneus, maintains the peroneal tendons against the fibular groove.

Anterior subluxation or dislocation of the peroneal tendons occurs as a result of a tear of the superior peroneal retinaculum attachment from the fibula.[98,99] This infrequent injury is commonly misdiagnosed as an ankle sprain and can occur in isolation or concomitant with other sprains or fractures. The mechanism of injury usually is forced dorsiflexion with reflex contraction of the peroneal muscles, resulting in avulsion of the retinaculum and anterior displacement of the peroneal tendons.[98]

Patients with a peroneal tendon dislocation complain of sudden pain and a snapping sensation over the posterolateral ankle associated with weakness of eversion. Tenderness and swelling over the lateral retromalleolar area (a location not typically involved in ankle sprains) are characteristic. When accurate examination is not precluded by swelling, the dislocated tendons also may be palpable near the inferior tip of the lateral malleolus. Inability to actively evert the foot when it is held in dorsiflexion or frank subluxation of the tendons with this maneuver confirms the diagnosis. Findings on plain radiography are often normal; however, 15 to 50% of patients will be found to have an associated avulsion fracture of the lateral ridge of the distal fibula. An MRI study or ultrasound can be helpful in confirming the diagnosis. All patients with a suspected or confirmed peroneal tendon dislocation should be referred for orthopedic follow-up because these injuries require surgical repair.[99,100] Spontaneous healing is rare in untreated cases, and chronic ankle instability and pain are common sequelae. Peroneal tendons also can tear longitudinally; such injuries manifest either acutely or subacutely with recurrent pain and swelling during activities.[100,101]

www.ketabpezeshki.com 66485457-66963820

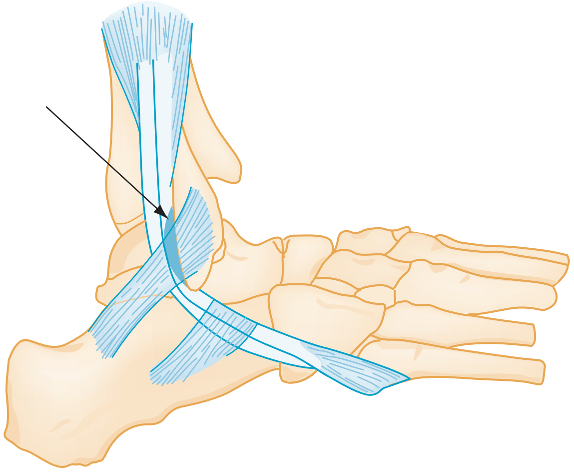


Figure 58-13. The locations of the superior *(arrow)* and inferior peroneal retinaculum in relation to the fibula and the peroneal tendons. (From Arrowsmith SR, et al: Traumatic dislocations of the peroneal tendons. Am J Sports Med 11:142, 1983.)

Tibialis Posterior Tendon Rupture. The tibialis posterior is primarily responsible for plantar flexion and inversion along the subtalar joint. Its tendon uses the posteroinferior surface of the medial malleolus as a pulley and inserts onto the navicular, the medial cuneiforms, and the bases of the second through the fifth metatarsals. The peroneus brevis opposes the action of the tibialis posterior. With rupture of the tibialis posterior tendon, the peroneus brevis becomes unopposed and the medial longitudinal arch loses its muscular support, leading to valgus deformity of the hindfoot and a unilateral flatfoot.[102]

The mechanism of traumatic tibialis posterior rupture involves forced eversion.[102] In addition to a unilateral flatfoot, pain and swelling on the medial aspect of the ankle are seen. Tenderness is present over the navicular, and the patient cannot perform a toe raise on the affected side. In addition, the patient with a tibialis posterior tendon rupture is unable to invert the foot when it is in plantar flexion and eversion. With a unilateral flatfoot, an observer standing behind the patient can see "more toes" on the lateral aspect of the affected side—a classic sign.[102] Plain radiography can exclude other bone abnormalities. Ultrasonography and MRI are useful imaging modalities to diagnose this condition.[102] Orthopedic consultation is indicated for tibialis posterior tendon ruptures, because surgical repair often is necessary.

Other Tendon Injuries. The tibialis anterior is the primary dorsiflexor of the foot. Its tendon courses under the superior extensor retinaculum and inserts onto the navicular, the medial cuneiform, and the base of the first metatarsal. Tenosynovitis of the tibialis anterior tendon is associated with overuse and characterized by swelling, tenderness, and crepitus along the tendon. Treatment involves RICE therapy, analgesia, and close follow-up. Rupture of the tibialis anterior is rare and often is misdiagnosed as lumbosacral radiculopathy or peroneal nerve palsy because of the footdrop it produces. This condition requires orthopedic consultation in the ED because surgical repair is usually necessary.

The flexor hallucis longus is responsible for flexion of the great toe and participates in plantar flexion of the foot. Its tendon courses behind the medial malleolus through a fibro-osseous canal and inserts onto the distal phalanx of the great toe. Flexor hallucis longus tendinitis, also called *dancer's tendinitis,* most often occurs at the fibro-osseous canal.[103] On examination, tenderness and edema posterior to the medial malleolus are noted, and passive extension of the first metatarsophalangeal (MTP) joint causes significant pain when the foot is in neutral position. Initial treatment involves rest, nonsteroidal anti-inflammatory drugs, and a short course of immobilization. Orthopedic follow-up on an outpatient basis should be arranged to ensure proper resolution. Rarely, surgical intervention may be necessary.[103]

Ankle Dislocations

Ankle dislocations are described according to the direction of displacement of the talus and foot in relation to the tibia. Thus dislocation may be upward, posterior, medial, lateral, posteromedial, or anterior. Medial dislocation is the most common. Most dislocations involve associated ankle fractures; rarely, however, dislocations can occur without fracture. The mechanism in all dislocations begins with axial loading of a plantar-flexed foot, which forces the talus either anteriorly or posteriorly from the ankle mortise. The eventual position of the dislocation depends on the position of the foot at the time of injury and the direction of the displacing force. Ankle dislocations can be closed or open and most commonly result from significant falls, motor vehicle collisions (MVCs), or high-speed sports.[37] The neurovascular supply to the foot usually is intact but may be compromised in open dislocations.[104]

ED management involves the assessment of neurovascular status and tendon function, followed by rapid reduction. Radiographs are helpful but should not delay reduction in cases when vascular compromise or skin tenting is present.[37] After appropriate procedural sedation and analgesia, the patient is placed supine and the knee is flexed to 90 degrees. Distraction of the foot, followed by a gentle force to reverse the direction of the dislocation, usually accomplishes the reduction.[105] Reassessment of the neurovascular status, splint immobilization, ankle elevation, and postreduction radiography should follow. Open dislocations require the same management as previously discussed for open fractures. The prognosis with an ankle dislocation is usually good, although open fractures are associated with an increased incidence of complications.[104,105]

FOOT

PRINCIPLES OF DISEASE

Anatomy

The foot is composed of 28 bones and 57 articulations (Fig. 58-14). It can be divided into three anatomic and functional regions: the hindfoot, which contains the talus and calcaneus; the midfoot, which contains the navicular, cuboid, and cuneiforms; and the forefoot, which contains the metatarsals, phalanges, and sesamoids. The midtarsal joints (Chopart's joint) join the hindfoot and midfoot, and the tarsometatarsal joints (Lisfranc's joint) join the midfoot and forefoot. The inferior aspect of the talus has three articulations with the calcaneus that are collectively known as the *subtalar joint.*

The bones of the foot interlock in a manner similar to the blocks and keystones of a bridge, forming a complex system of arches and beams tethered by ligaments and intrinsic muscles. Extrinsic muscles originating in the lower leg are responsible for most of the foot's movements, as well as for maintenance of the arch and beam structure. The course and insertion of these extrinsic muscles are important in their actions and in their association with specific avulsions and injuries. The arterial supply to the foot is from the anterior and posterior tibial arteries and the peroneal artery, a proximal branch of the posterior tibial artery. Motor and sensory innervation comes from branches of the deep and superficial peroneal, posterior tibial, saphenous, and sural nerves.

The foot is capable of numerous weight-bearing and non–weight-bearing motions (see Fig. 58-3), which vary at each articulation. Inversion and eversion of the hindfoot occur primarily

www.ketabpezeshki.com 66485457-66963820

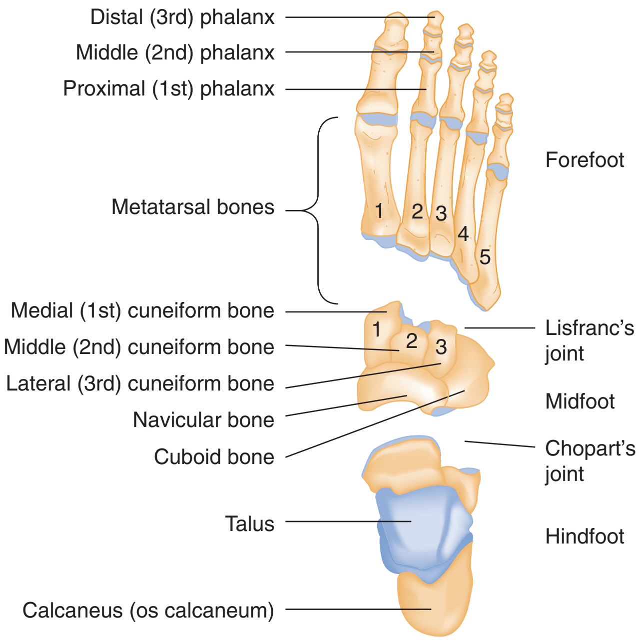


Figure 58-14. Bones and joints of the foot. (From Rockwood CA, et al [eds]: Rockwood and Green's Fractures in Adults, 3rd ed. New York, JB Lippincott, 1991.)

through the subtalar joint, adduction and abduction of the forefoot through the midtarsal joints, and flexion and extension through the MTP and interphalangeal (IP) joints. The relative importance of specific bones in supporting the body's weight varies with changes from the static to the mobile state. The biomechanics of walking and running are extremely complex, and significant forces are imparted to the foot's structures during these precisely coordinated activities.[106]

Clinical Features

An accurate history is essential in the setting of foot trauma because many mechanisms are associated with specific injury patterns. Mechanisms can be broadly divided into direct and indirect (torsional) forces. Falls and axial loads, twisting injuries, dropped objects, overuse injuries, crush injuries, burns, and penetrating wounds each suggest different potential pathologic conditions. Patient complaints may involve any combination of pain, swelling, deformity, reduced function, or altered sensation. The location of pain, along with a description of its quality, duration, and precipitants, focuses the differential diagnosis. The combination of increasing pain with decreasing sensation is particularly compelling because this may indicate neurovascular compromise requiring immediate intervention. Along with general information obtained when the history is taken, underlying pertinent medical conditions, medications, and previous foot problems should be identified.

The structures of the foot are uniquely accessible to palpation and assessment. A directed examination, specific for the patient's complaint, is most useful in the ED.[107]

If the patient is ambulatory, observation of the gait provides information on the degree of disability and pain and the potential for serious injury. Formal examination begins with observation of the foot in its position of rest, normally one of slight plantar flexion and inversion. Swelling, deformity, ecchymosis, open wounds, color, and temperature should be noted. The use of ecchymosis to localize injuries can be misleading because of pooling of blood in dependent areas after tracking through tissue planes. All patients should have a neurovascular examination with assessment of the dorsalis pedis and posterior tibial pulses, sensation, and motor function. Precise localization of pain or crepitus, when not precluded by swelling, is extremely valuable and facilitates appropriate use of further diagnostic tools. An awareness of anatomic landmarks, which some research suggests may be suboptimal among clinicians,[108] is important in this process. The entire foot should be gently palpated over both the dorsal and the plantar surfaces, methodically progressing from the heel to the toes. Particular attention should be paid to areas in which injuries commonly occur, such as the base of the fifth metatarsal.

In some situations, an evaluation of range of motion is indicated. This begins with an assessment of active motion with the foot in a dependent position. Next, if active motion is well tolerated, passive motion is assessed, beginning with the subtalar joint in the hindfoot and moving distally to the midtarsal and forefoot joints. Subtalar motion is evaluated by holding the lower leg with one hand and the heel with the other. Then, with the foot in a neutral position, the heel is inverted and everted. Normally, there should be at least 25 degrees of mobility in each direction. Midtarsal motion is evaluated by stabilizing the heel with one hand while the other hand grasps the forefoot at the bases of the metatarsals. The forefoot can then be pronated, supinated, abducted, and adducted. Normally there should be at least 20 degrees of adduction and 10 degrees of abduction.

Forefoot motion is evaluated by flexing and extending the MTP and IP joints individually. The first MTP joint has a particularly wide passive range of motion, with 45 degrees of flexion and 70 to 90 degrees of extension. Throughout the physical examination, findings can be compared with those of the opposite foot.

Diagnostic Strategies: Radiology

Plain radiography of the foot may be indicated by history, physical examination, or both. Standard three-view radiographs of the foot consist of anteroposterior, lateral, and 45-degree internal oblique projections.[109] The lateral projection gives the best imaging of the hindfoot and soft tissues, whereas the anteroposterior and oblique projections give the best imaging of the midfoot and forefoot. The numerous overlapping bones of the foot demand this complete radiographic series in all patients for whom radiographic examination is indicated.[110] Injuries to the hindfoot also warrant the addition of standard ankle projections and, when indicated, calcaneus views.

Foot radiographs can be difficult to interpret.[111] Moreover, foot fractures are often minimally displaced or nondisplaced, increasing the challenge of radiographic diagnosis. Several additional views improve the imaging of specific areas of the foot. Coned views, weight-bearing radiographs, or a 45-degree external oblique projection can be useful, particularly for detection of midfoot and forefoot pathology. The most commonly obtained atypical view is the Harris (axial) view for visualizing the calcaneus and subtalar joints. Special magnification radiographs or stress radiographs also may be useful in selected cases.

Interpretation of plain radiographs can be complicated by the numerous accessory centers of ossification and the presence of sesamoid bones (unipartite and multipartite) that exist as normal variants in up to 30% of the population (Fig. 58-15). The most commonly seen accessory bones are the os trigonum, os tibiale externum (also called an *accessory navicular bone*), os peroneum, and os vesalianum.[112] These can be differentiated from fractures by their smooth corticated surfaces. Comparison radiographs of the opposite foot may be helpful, although such variants are not inevitably bilateral. Accessory bones themselves can also fracture or cause pain syndromes.[113]

Because of the limitations of plain radiography, other imaging techniques have gained importance for specific foot injuries.

www.ketabpezeshki.com 66485457-66963820

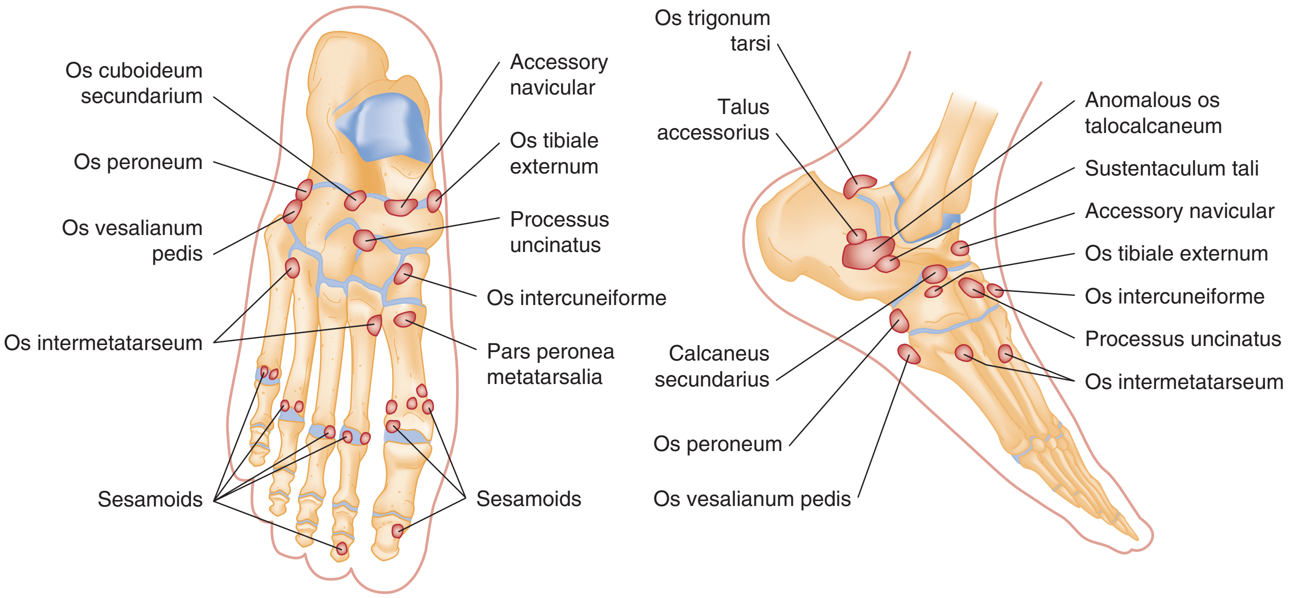


Figure 58-15. Accessory ossicles of the foot. (From Berquist TH [ed]: Radiology of the Foot and Ankle. New York, Raven Press, 1989.)

Radionuclide imaging (bone scanning) can be useful for evaluating unexplained foot pain or pain in athletic injuries.[114] In the setting of acute foot trauma, this modality often can demonstrate subtle fractures not visible with plain radiography. Historically, bone scanning has been the standard modality for the diagnosis of stress fractures; however, MRI has comparable sensitivity and better specificity and has emerged as the imaging modality of choice for this diagnosis.[25,115]

The CT scan can be valuable when complex articulations and overlapping bones make standard radiographs difficult to interpret, particularly in the midfoot and hindfoot.[116,117] As a result of the wide availability and superiority of CT scanning, plain film tomography is now virtually obsolete. CT is an excellent modality for imaging complex anatomy, including the subtalar joint, the calcaneus, and the tarsometatarsal (Lisfranc) joint complex. Three-dimensional CT images provide unprecedented clarity and detail.[27]

MRI has been used to investigate many of the same fractures and dislocations imaged by CT, and the two modalities can be used in a complementary manner.[24,28,118,119] As in the ankle, the most significant role of MRI is in the delineation of soft tissue conditions, such as athletic injuries and tendon ruptures, where it has become the imaging modality of choice. In some conditions involving the ankle joint, magnetic resonance arthrography on an outpatient basis can be useful.[120]

SPECIFIC PATHOLOGIC CONDITIONS

This section covers the major fractures and dislocations seen in the foot, progressing anatomically from the hindfoot through to the forefoot. This order corresponds with the sequence of physical examination in patients with foot trauma. Any of these fractures or dislocations may be open, necessitating appropriate wound management.

Hindfoot Injuries

The hindfoot is commonly involved in foot injuries and is a difficult area to image. Fractures or dislocations in this region can masquerade as ankle sprains and, if not considered in the differential diagnosis, can be missed.

Talar Fractures

Principles of Disease: Anatomy. The word *talus* is related to the Latin *taxillus,* meaning "a small die or cube," and dates back to the time of the Roman Empire, when soldiers made dice out of the ankle bones of horses. An appreciation of the unique anatomy of the talus is crucial to an understanding of the pathophysiology and treatment of talar fractures and dislocations. The talus is the second largest tarsal bone and has seven articulations making up 60% of its surface. It is divided into three regions: the head, which articulates with the navicular and calcaneus; the body, which articulates with the tibia, fibula, and calcaneus; and the neck, which joins the head and body and is the only portion of the talus that is predominantly extra-articular. The talus is the only bone in the lower extremity with no muscular attachments and is held in position by the malleoli and ligamentous attachments. The anterior width of the talus is greater than the posterior, causing it to be less stable and more prone to dislocation when the foot is plantar-flexed.

The blood supply to the talus is from a vascular ring formed by branches of the anterior and posterior tibial arteries and the perforating branch of the peroneal artery. Vessels enter the talus from three main sites, any or all of which can be disrupted by fractures or dislocations. Because of the tenuous nature of these vessels and the inconsistency of collateral circulation, the risk of avascular necrosis is significant with many talar fractures.

Pathophysiology. Talar fractures are the second most common tarsal fracture after fractures of the calcaneus. They are best grouped into minor and major fractures, with minor fractures being the more common.[121] Stress fractures of the talus also can occur. Minor talar fractures include avulsion fractures of the superior neck and head, and the lateral, medial, and posterior aspects of the body.[122] These fractures often involve the same mechanism as that for ankle sprains (see Fig. 58-12 and Box 58-2): a combination of plantar flexion or dorsiflexion and an inversion force. Lateral process fractures, previously uncommon, have been described with snowboarding and can be occult on plain radiographs.[123] Osteochondral lesions of the talar dome also fall into the minor fracture category.

Major talar fractures usually are produced by significant forces and occur in the head, neck, or body. Talar head fractures are uncommon, making up 5 to 10% of all talar fractures. Their

www.ketabpezeshki.com 66485457-66963820

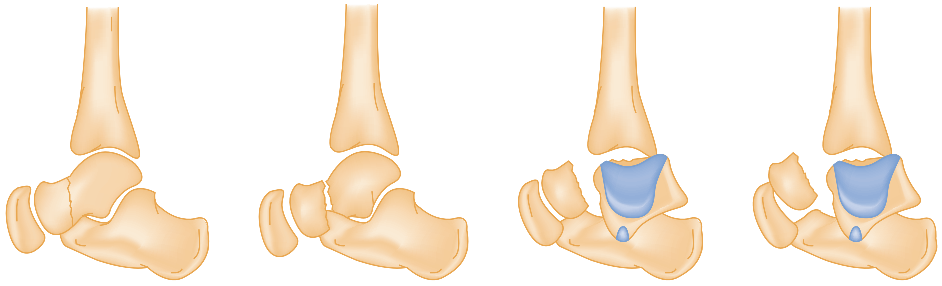


Figure 58-16. **A, B,** and **C,** Hawkins's type 1, 2, and 3 fractures, respectively. **D,** Canale and Kelly's type 4 fracture of the talar neck. Purple shading indicates the articular surface of the talar dome. (From Gustilo RB, et al [eds]: Fractures and Dislocations. St Louis, Mosby, 1993.)

mechanism is a compressive force applied on a plantar-flexed foot and transmitted up through the talonavicular joint. Comminution is common, and associated navicular fractures can occur, further disrupting the talonavicular articulation.

Talar neck fractures account for 50% of major talar injuries. Their mechanism usually is an extreme dorsiflexion force, as generated in falls or MVCs. Associated fractures are common; the most common is an oblique or vertical fracture of the medial malleolus, which is seen in up to one fourth of cases. Other associated injuries include calcaneal fractures and vertebral compression fractures.

Hawkins classified talar neck fractures into three categories (Fig. 58-16): Type 1 fractures are nondisplaced; type 2 fractures show subtalar subluxation; and type 3 fractures, 50% of which are open, involve a dislocation of the talar body from the ankle and subtalar joint. A fourth type that has been added to this classification involves the additional distraction of the talonavicular joint. This classification is important descriptively and because the type of fracture influences both treatment and outcome. Long-term complications, including avascular necrosis and arthritis, are common with talar neck fractures and more likely with increasing displacement.[124]

Talar body fractures include many of the minor talar fractures previously listed.[125] Major talar body fractures are uncommon and usually result from falls with axial compression of the talus between the tibial plafond and the calcaneus.

Clinical Features. Talar fractures range from obvious open fractures to subtle fractures requiring special imaging techniques to diagnose. Typically, a history of a twisting injury, fall, or high-energy impact can be elicited. Dorsal swelling and tenderness over the talus are characteristic findings. Although ankle motion may be preserved, inversion and eversion of the hindfoot often are painful.

Diagnostic Strategies: Radiology. With minor talar fractures, radiographs can be misinterpreted as normal in appearance. Even when supplemental views are obtained, CT or MRI may be required for visualization. Standard foot and ankle radiographic views usually demonstrate major talar fractures (Figs. 58-17 and 58-18), with the anterior and oblique projections showing talar alignment within the mortise and the lateral projection showing the talar neck and alignment of the posterior aspect of the subtalar joint. Normal variants, such as an os trigonum or os supratalare (see Fig. 58-15), are occasionally encountered and should be differentiated from fractures. Specialized imaging by CT or MRI is often required for complete assessment of talar fractures.

Management. Major talar fractures require precise reduction because more weight per unit area is borne by the superior surface of the talus than by any other bone. Most talar fractures involve multiple articular surfaces, and adequate repair often necessitates open reduction and internal fixation. Many minor talar fractures heal with casting, and the initial treatment should be with a non–weight-bearing below-knee cast or posterior plaster slab. Fragments larger than 5 mm in diameter may require excision. Other minor fractures, such as displaced lateral process fractures, require operative fixation because of their articular involvement.

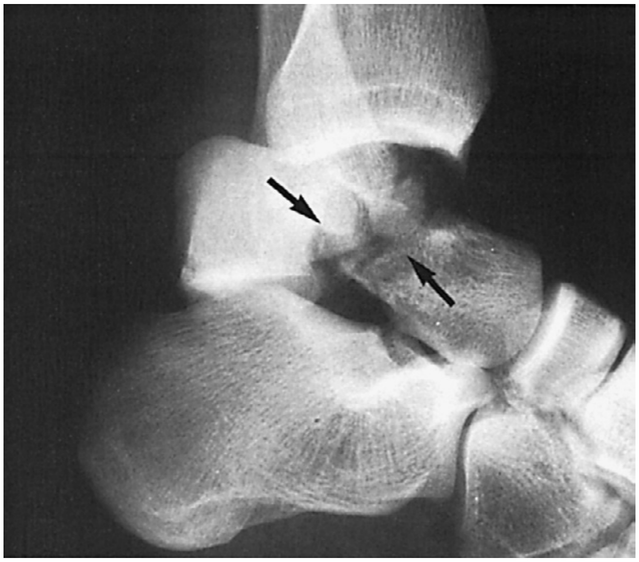


Figure 58-17. Comminuted fracture of the talar body *(arrows).* (From Rosen P, et al [eds]: Diagnostic Radiology in Emergency Medicine. St Louis, Mosby, 1992.)

The treatment of major talar fractures is controversial. Any significantly displaced fracture, particularly if associated with neurovascular or cutaneous compromise, requires an early attempt at closed reduction in the ED. Even if nonoperative reduction is impossible, as is common in type 3 and type 4 neck fractures with an intact medial malleolus, alignment often can be improved. With neurovascular or cutaneous compromise, reduction should not be delayed by waiting for radiography or consultation. After appropriate procedural sedation and analgesia, reduction is performed by grasping the hindfoot and midfoot and applying longitudinal traction with plantar flexion. This is followed by realignment of the foot as reduction is achieved. Reevaluation of the neurovascular status, posterior slab immobilization, and post-reduction radiographs should then follow.

Displaced talar head fractures or those involving more than 50% of the articular surface usually require open reduction and internal fixation, followed by non–weight-bearing casting. Smaller fragments may require excision. Type 1 fractures of the talar neck usually are treated with non–weight-bearing casting for 8 to 12 weeks. Most type 2 and all type 3 and type 4 fractures require open reduction and internal fixation. The management of talar body fractures varies with anatomic location.

www.ketabpezeshki.com 66485457-66963820

Figure 58-18. Fracture of the talar neck *(arrow)*. (From Rosen P, et al [eds]: Diagnostic Radiology in Emergency Medicine. St Louis, Mosby, 1992.)

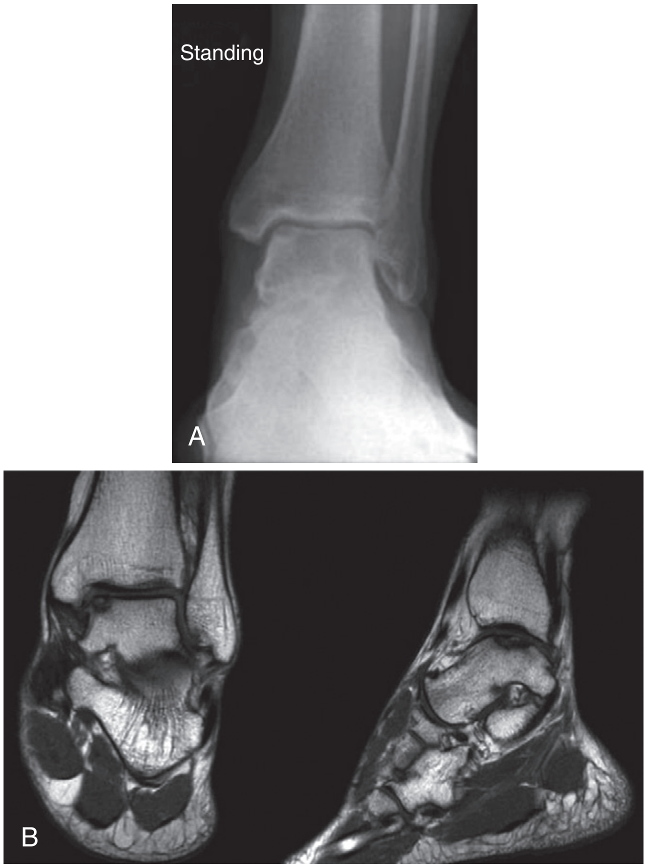


Figure 58-19. **A**, Anteroposterior view of an ankle showing an osteochondral fracture over the medial dome of the talus. **B**, Magnetic resonance imaging of the same lesion, showing improved sensitivity and detail from this modality. (From Frost A, Roach R: Osteochondral injuries of the foot and ankle. Sports Med Arthrosc Rev 17:187, 2009.)

Disposition. All patients with talar fractures require orthopedic consultation in the ED or referral for early orthopedic follow-up on an outpatient basis. Most minor talar fractures are suitable for outpatient follow-up and heal well, although some result in post-traumatic arthritis. Major talar fractures have a high incidence of complications, the most significant of which is avascular necrosis.[126] Outcome depends on the degree of anatomic reduction attained and preservation of the vascular supply. The risk of avascular necrosis increases with delay to reduction and with increasing talar displacement, ranging from 10% for type 1 neck fractures to 70% or more for type 3 neck fractures. Major fractures of the talar body are also prone to avascular necrosis, the risk of which doubles if an associated dislocation is present. Other potential complications include skin infection, skin necrosis, post-traumatic arthritis, malunion, delayed union, nonunion, and predisposition to peroneal tendon dislocation. The incidence of each complication varies with the type of fracture and the aggressiveness of ED and operative management.

Osteochondral Lesions

Osteochondral fractures of the talar dome account for 1% of talar fractures and are usually diagnosed late in the clinical course after ankle trauma.[127] The broader term "osteochondral lesion" is preferable, as it describes injuries of any origin involving the articular surface and/or subchondral region of the talus or tibial plafond and can thus involve cartilage, subchondral bone, or both.[128] These injuries are now thought to be more common than previously appreciated.[128-130] Many synonyms for this entity, including *transchondral fracture* and *dome fracture of the talus,* exist. Mechanisms identical to those causing ankle sprains are the most common cause; however, a significant number of these injuries cannot be ascribed to an acute traumatic event.

An osteochondral lesion should be considered in any patient with ligamentous ankle injury accompanied by gross edema and an effusion on plain radiographs.[7] The diagnosis is often missed initially and not made until the patient returns with chronic ankle pain.[131] Physical findings usually are nonspecific, although localized tenderness over the posteromedial aspect of the talus and increasing pain with exertion, weightbearing, or passive plantar flexion may be noted. Standard-view radiographs are commonly normal in appearance or show subtle and easily overlooked abnormalities, although specialized views may be helpful to assess the subchondral surfaces.[128] Bone scanning has been advocated as a nonspecific screening modality[129]; however, its role is becoming increasingly historic as CT or MRI studies are often required for identification and classification (Fig. 58-19). MRI is emerging as the imaging modality of choice for osteochondral lesions, owing to its ability to detect bone marrow edema and cartilage, and MRI classification schemes exist.[128-131]

When an osteochondral lesion is diagnosed or suspected, outpatient orthopedic referral is advised. The natural history of osteochondral lesions is poorly defined and variable[132]; however, chronic ankle discomfort and osteoarthritis are potential sequelae. Osteochondritis dissecans, a subacute or chronic defect, may develop in the talar dome after inadequate treatment of an osteochondral lesion. In general, however, with appropriate care, either by cast immobilization for up to 6 weeks or operative management, the prognosis is good, particularly if treatment begins within 12 months of symptom onset. The benefit of operative management, often done arthroscopically, varies with the type of lesion and its anatomic location.[133] The previous discussion underscores the necessity for orthopedic evaluation when a patient has persistent unexplained ankle pain after a previous "sprain."

www.ketabpezeshki.com 66485457-66963820

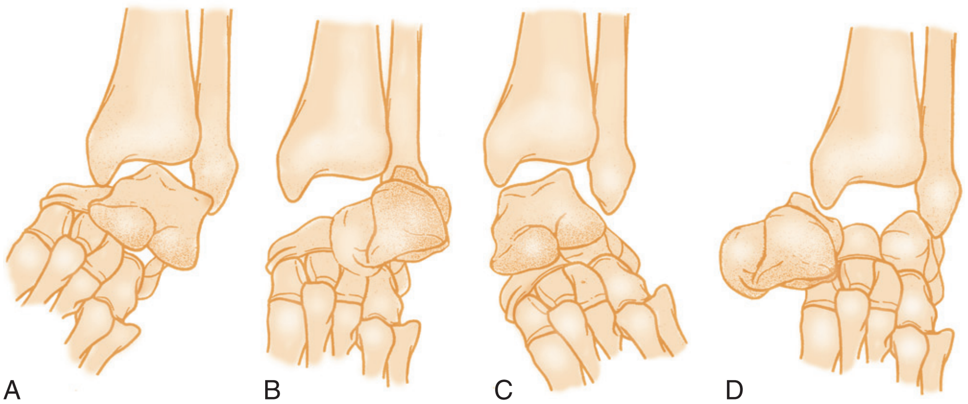


Figure 58-20. The forces that produce a subtalar dislocation can, when more extreme, produce a total talar dislocation. **A,** Medical subtalar dislocation. **B,** Total lateral dislocation of the talus from more extreme inversion forces. **C,** Lateral subtalar dislocation. **D,** Total medial dislocation of the talus from more extreme eversion forces. (Adapted from Sanders DW: Talus fractures. In Bucholz RW, Court-Brown CM, Heckman JD, Tornetta P [eds]: Rockwood and Green's Fractures in Adults, 7th ed. Philadelphia, Lippincott, Williams & Wilkins, 2010, pp 2022-2064.)

Subtalar Dislocations

Principles of Disease: Pathophysiology. Subtalar dislocation, also called *peritalar dislocation,* is the simultaneous disruption of both the talocalcaneal and talonavicular joints without disruption of the tibiotalar joint (Fig. 58-20). This occurs when the talonavicular and talocalcaneal ligaments rupture while the stronger calcaneonavicular ligament remains intact. Subtalar dislocations are rare and are classified by the direction the foot takes in relation to the talus.[134] Anterior and posterior dislocations occasionally occur; however, most subtalar dislocations are either medial or lateral, with medial dislocations accounting for a majority of cases. Dislocation of the calcaneus is an exceptionally rare event that is distinct from subtalar dislocation and involves disruption of the talocalcaneal and calcaneocuboid articulations.

Subtalar dislocations are caused by severe torsional forces such as those generated in MVCs or falls. Medial dislocations result from inversion and plantar flexion, whereas lateral dislocations arise from the combination of eversion and plantar flexion. Ten percent of subtalar dislocations are open, and associated fractures are present in one half of the cases, particularly those with lateral dislocations.

Clinical Features. Obvious deformity typically is present, often with tension of the skin on the side opposite the direction of dislocation. Neurovascular status should be carefully assessed, although it is rarely compromised. Swelling can mask the extent of the injury, thus diagnosis can be delayed or missed if only ankle radiographs are obtained.

Diagnostic Strategies: Radiology. Although standard foot radiographic views are diagnostic, properly positioning the patient for these may be difficult. Inadequate films can delay diagnosis and treatment. The single most helpful radiograph is an anteroposterior view of the foot, which will demonstrate the talonavicular dislocation.

Management. Subtalar dislocations require expeditious reduction.[135] More than 80% of closed subtalar dislocations can be treated with closed reduction, either with procedural sedation and analgesia in the ED or with general anesthesia. Closed reduction is performed by flexing the knee and applying longitudinal traction to the foot with initial accentuation, followed by reversal of the deformity (with use of eversion for medial dislocations and inversion for lateral dislocations). Sometimes direct pressure over the head of the talus aids in reduction. Closed reduction may be impossible because of buttonholing of the talus through the extensor retinaculum, entrapment in the peroneal tendons, or associated fractures. After reduction, immobilization in a below-knee cast for 4 to 6 weeks is indicated.

Disposition. Urgent ED orthopedic consultation is indicated for subtalar dislocations. Although serious complications are uncommon in cases of closed subtalar dislocation, most patients have long-term limitation of subtalar motion, a sequela that can affect gait. Avascular necrosis is uncommon.

Total Talar Dislocation

Total talar dislocation is an extremely rare and devastating injury requiring orthopedic consultation in the ED. In these injuries, which are the end result of the same forces that produce subtalar dislocation, the entire talus is distracted from all of its articulations (see Fig. 58-20). Most are open, and infection and avascular necrosis are common complications.[136]

Calcaneal Fractures

Principles of Disease: Anatomy. The calcaneus is the largest bone in the foot and the most commonly fractured tarsal bone.[137] It articulates with the talus superiorly (forming the subtalar joint) and with the cuboid anterolaterally.

Pathophysiology. Falls with direct axial compression cause most calcaneal fractures. Because of this high-energy mechanism, associated injuries are common: 7% of calcaneal fractures are bilateral, 25% are associated with other lower extremity injuries, and 10% are associated with spinal injuries, typically vertebral compression fractures.

Numerous classification schemes have been developed for calcaneal fractures. Perhaps the most intuitive is simple categorization of the fracture as either extra-articular or intra-articular. Extra-articular fractures usually involve the addition of a rotatory mechanism and include fractures of the sustentaculum tali and the calcaneal tuberosity and oblique fractures of the calcaneal body. Avulsion fractures of the anterior process by the bifurcate ligament (which joins the calcaneus, navicular, and cuboid) also are included in this category. Isolated calcaneal tuberosity fractures are rare but may require more expeditious treatment when displaced owing to compromise of the skin overlying the Achilles tendon.[138] Up to 75% of calcaneal fractures are intra-articular, ranging in severity from nondisplaced single fractures to severely crushed, comminuted fractures. Because of the cancellous nature of the calcaneus, fractures are frequently comminuted. Calcaneal stress fractures may also occur.

www.ketabpezeshki.com 66485457-66963820

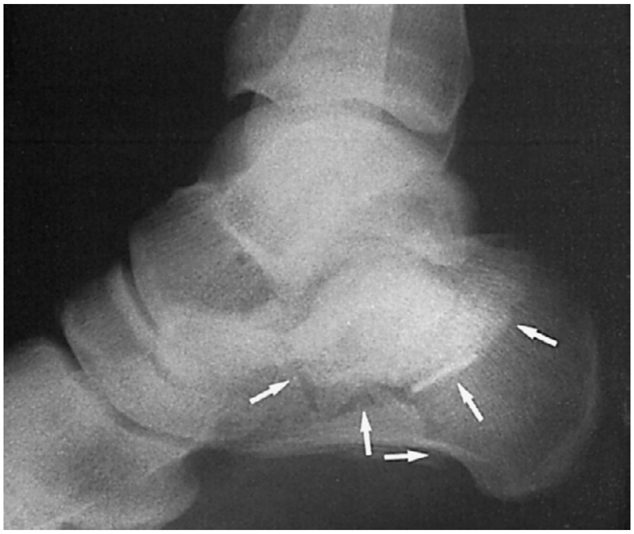


Figure 58-21. Comminuted body fracture of the calcaneus with subtalar involvement *(arrows)*. (From Rosen P, et al [eds]: Diagnostic Radiology in Emergency Medicine. St Louis, Mosby, 1992.)

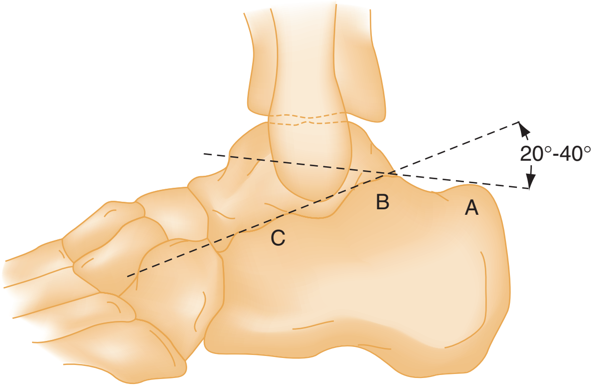


Figure 58-22. Boehler's angle is obtained by measuring the angle formed by two lines, one between the posterior tuberosity *(A)* and the apex of the posterior facet *(B)* and the other between the apex of the posterior facet *(B)* and the apex of the anterior process *(C)*. A value less than 20 degrees suggests a calcaneal compression fracture. (From Rosen P, et al [eds]: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1992.)

Clinical Features. The typical history is one of a fall resulting in a direct impact on the heel or heels. Physical examination reveals pain, swelling, and tenderness over the affected heel, and weightbearing on the hindfoot is usually impossible. In cases of significant fracture, the heel may be deformed when viewed from behind, appearing short, wide, and tilted. Ecchymoses may extend over the entire sole, a finding not seen in isolated malleolar fractures. The presence of compartment syndrome or associated injuries such as vertebral compression fractures should be considered.

Diagnostic Strategies: Radiology. Standard radiographic views of the foot and ankle should be obtained. The anteroposterior view of the foot shows the calcaneocuboid joint and the anterosuperior calcaneus, whereas the lateral view shows the posterior facet and can demonstrate compression of the calcaneal body (Fig. 58-21). In addition, a Harris (axial) view, when not precluded by pain, should be obtained to image the calcaneal tuberosity, subtalar joint, and sustentaculum tali. Anterior process fractures require differentiation from a calcaneus secundarius accessory ossification center (see Fig. 58-15).[139]

Two assessments are critical to the management of calcaneal fractures: whether the fracture involves the subtalar joint, and the degree of depression of the posterior facet.[140] Compression fractures are not always obvious, and measurement of Boehler's angle (Fig. 58-22) can be helpful. Because Boehler's angle may be normal even in the presence of severely comminuted calcaneal fractures, it has been considered more useful prognostically than diagnostically, although recent findings raise questions regarding the prognostic utility of this measurement as well.[141] Boehler's angle is measured on the lateral view as the angle between two lines, one between the posterior tuberosity and the apex of the posterior facet and the other between the apex of the posterior facet and the apex of the anterior process. Although several values for this measurement have been cited, an angle of 20 to 40 degrees defines a normal range with the best diagnostic performance.[142] An angle of less than 20 degrees suggests a compression fracture. Comparison measurement of the uninjured side may be helpful in questionable cases; however, the degree of variability between feet in the same individual is poorly defined, and advanced imaging is preferable in such situations.

Imaging of the calcaneus can be difficult because of the complex three-dimensional nature of its articulations. Plain radiography can underestimate injury severity, and the CT scan has revolutionized the assessment of calcaneal fractures, with good correlation of findings with outcome.[140,143] MRI is also an excellent modality for imaging the hindfoot and has a role in assessment of selected calcaneal fractures.

Management. The management of intra-articular or displaced calcaneal fractures is controversial, with many operative and nonoperative approaches described.[140] Minimally invasive surgical approaches and new technologies are changing the surgical approach to these injuries.[144] A recently published 15-year follow-up of a randomized trial comparing operative and nonoperative management of displaced intra-articular calcaneal fractures found no differences in clinical outcomes between the treatment groups.[141] The treatment of nondisplaced extra-articular fractures usually involves casting for 6 to 8 weeks.

Disposition. Intra-articular or displaced calcaneal fractures require orthopedic consultation in the ED. Outpatient orthopedic follow-up care can be arranged for more innocuous injuries, provided that this approach is consistent with local practice and no associated injuries that warrant hospitalization are present. In considering outpatient follow-up, it is important to bear in mind that plain radiographs often significantly underestimate the extent and severity of calcaneal fractures. Minor extra-articular fractures usually heal uneventfully; however, with significant calcaneal fractures, complications, including compartment syndrome, are frequent. In both conservatively and surgically treated patients, the incidence of long-term pain, loss of joint mobility, and functional disability approaches 50%.[145]

Midtarsal Joint Injuries

The midtarsal joint (Chopart's joint) is composed of the talonavicular and calcaneocuboid joints. Injury in this area, although rare, can occur with any ankle, hindfoot, or midfoot trauma. Midtarsal joint injuries usually result from forced dorsiflexion and often are associated with other significant fractures. Sprains, fracture-subluxations and fracture-dislocations, and an isolated "swivel dislocation" (a variant of a subtalar dislocation) all can occur at the midtarsal joint. Pain, swelling, inability to bear weight, and tenderness over the midtarsal joint are usual findings. Although standard radiographs often are abnormal in appearance, the diagnosis frequently is overlooked or delayed, with symptoms ascribed to an ankle sprain (see Fig. 58-12 and Box 58-2). The possibility of a midtarsal joint injury should be considered with any isolated midfoot fracture,[146] particularly those of the navicular tuberosity. MRI can be helpful in the evaluation of midfoot tendon

www.ketabpezeshki.com 66485457-66963820

and ligamentous injuries.[147] Undisplaced injuries may heal with casting, but operative fixation is often required and management can be difficult.[148] Complications are common and include persistent pain, arthritis, and long-term disability.

Midfoot Injuries

The midfoot is an inherently stable region of the foot and is not commonly injured. Fractures and relationships of the midfoot tarsals often are difficult to visualize on standard radiographic views because of underpenetration and the oblique orientation of the bones and joints. A compounding factor is that pain associated with midfoot injuries often is ill-defined and poorly localized. Delay in diagnosis is frequent with midfoot injuries. Although isolated fractures of the midfoot tarsals occur, associated injuries, including significant sprains, subluxations, and spontaneously reduced dislocations, are often present.

Navicular Fractures

Principles of Disease: Anatomy. The navicular has a curved shape—hence the derivation of its name from the Latin word *navis,* meaning "ship." Because of the navicular's extensive articular surface, its blood supply can enter only through a small waist of cortex, and the middle third is relatively avascular. As a result, the navicular is at particular risk for avascular necrosis after fractures, analogous to its counterpart in the wrist, the scaphoid bone.[149]

Pathophysiology. Navicular fractures, although relatively rare, are the most common midfoot fracture and are classified into dorsal avulsion fractures, tuberosity fractures, and body fractures. *Dorsal avulsion* fractures account for one half of navicular fractures and usually occur when an eversion stress causes bony avulsion from either the talonavicular capsule or the deltoid ligament. These fractures usually do not involve a significant amount of articular surface. *Tuberosity* fractures also occur from eversion forces, leading to an avulsion at the insertion of the posterior tibial tendon. A tuberosity fracture may be the only clue to the presence of a midtarsal joint injury. *Body* fractures are uncommon and result from an axial loading mechanism. They often are comminuted, intra-articular, and associated with other midtarsal pathologic conditions. Stress fractures of the navicular can also occur.

Clinical Features. Navicular fractures cause localized tenderness over the dorsal and medial aspects of the midfoot. The navicular tuberosity may be tender and is located by first identifying the sustentaculum tali, a shelf of bone on the medial aspect of the ankle approximately 2.5 cm below the tip of the medial malleolus. The tuberosity is then easily palpable just anterior to this landmark. In the case of tuberosity fractures, pain may be exacerbated by passive eversion or active inversion of the foot.

Diagnostic Strategies: Radiology. Standard foot radiographs usually demonstrate navicular fractures; however, CT or MRI may be required. Care is taken not to confuse the commonly occurring os tibiale externum, also called an *accessory navicular bone,* with an acute fracture (see Fig. 58-15).

Management. Dorsal avulsion and tuberosity fractures not involving a significant amount of articular surface are usually treated with a walking cast for 4 to 6 weeks. Body fractures and displaced fractures involving more than 20% of the articular surface often require operative fixation.

Disposition. Most navicular fractures are suitable for outpatient orthopedic follow-up; however, significant fractures, particularly if intra-articular, warrant orthopedic consultation in the ED. Navicular tuberosity fractures can be complicated by nonunion. Avascular necrosis and arthritis, particularly in body or other intra-articular fractures, are potential late sequelae.

Cuboid Fractures

Isolated cuboid fractures are uncommon and usually result from lateral subluxation of the midtarsal joint in Lisfranc's injury. Cuboid fracture has been termed a *nutcracker fracture* because the cuboid is crushed between the bases of the fourth and fifth metatarsals and the anterior calcaneus.[150] These fractures are also associated with fractures of the posterior malleolus.

The cuboid is best evaluated by the oblique view of a standard foot radiographic series because this demonstrates both the calcaneocuboid and the cuboid-metatarsal relationship. The possibility of Lisfranc's injury should be considered with any cuboid fracture. Treatment of isolated injuries ranges from casting for minor nondisplaced fractures to operative fixation.[151] Extra-articular cuboid fractures can lead to serious disability from dysfunction of the peroneus longus tendon at the level of the peroneal groove. All cuboid fractures warrant orthopedic assessment.

Cuneiform Fractures

Fractures of the cuneiforms are extremely uncommon and usually result from direct trauma. As with cuboid fractures, the patient should be assessed carefully for the presence of Lisfranc's injury. Treatment usually is by casting; however, displaced fractures require orthopedic assessment.

Dislocations of the Navicular, Cuboid, and Cuneiforms

Isolated dislocations of each of the midfoot bones have been described. These are uncommon injuries that often require open reduction. Orthopedic consultation in the ED is required for any of these injuries.

Lisfranc (Tarsometatarsal) Fractures and Dislocations

Principles of Disease: Anatomy. Collectively, the tarsometatarsal joints (see Fig. 58-14) are commonly called *Lisfranc's joint.* Any injury to this area, whether sprain, dislocation, or fracture-dislocation, is termed a *Lisfranc injury.* Knowledge of the anatomy of the Lisfranc joint complex is central to an understanding of these injuries.

Lisfranc's joint is composed of the articulations of the bases of the first three metatarsals with their respective cuneiforms and the fourth and fifth metatarsals with the cuboid. In concert, the tarsometatarsal joints act to allow supination and pronation of the forefoot. The intrinsic stability of Lisfranc's joint is provided by the bone architecture and associated ligaments. When viewed end on, the metatarsals have a trapezoidal shape and combine to form a transverse arch with the second metatarsal acting as the "keystone." The second metatarsal is essential for the stability of the entire complex and is further buttressed by its snug articulation in a recess created by the three cuneiforms. Strong transverse intermetatarsal ligaments join the bases of the second through fifth metatarsals, and Lisfranc's ligament joins the medial cuneiform with the second metatarsal base. Lisfranc's joint is further supported by dorsal and plantar ligaments, the plantar fascia, and the insertions of the tibialis anterior and peroneus longus tendons at the first metatarsal base.

Pathophysiology. Lisfranc injuries are uncommon, in part because tremendous energy is often required to disrupt this complex. Such injuries arise from three mechanisms: rotational forces, whereby the body twists around a fixed forefoot; axial loads, whereby the weight of the body drives the hindfoot into the bases of the metatarsals; and crush injuries. Because of the mechanisms involved, associated injuries, such as MTP joint

www.ketabpezeshki.com 66485457-66963820

dislocations, can occur. Most Lisfranc injuries are incurred in MVCs. Sports involving fixation of the forefoot (e.g., equestrian activities and windsurfing) also are associated with these injuries. Of note, one third of Lisfranc ligamentous injuries arise from seemingly trivial mechanisms such as stumbles or falls. Most Lisfranc injuries are closed.

Numerous classifications for displaced Lisfranc injuries exist, none of which aids in determining appropriate treatment or outcome.[152] The most intuitive classification categorizes the direction of the dislocation in the horizontal plane (Fig. 58-23).[153-155] In *homolateral* injuries, all five metatarsals are displaced in the same direction. In *isolated* injuries, one or more metatarsals are displaced away from the others. In *divergent* injuries, the metatarsals are splayed outward in both the medial and the lateral directions. These injuries usually occur between the first and second metatarsals because of their lack of an intermetatarsal connection. A component of dorsal displacement also is commonly present in displaced Lisfranc injuries, whereas plantar displacement is uncommon because of the joint's bone architecture and the strength of the plantar ligaments and fascia.

Because of ligamentous attachments, Lisfranc injuries almost invariably involve associated metatarsal fractures, usually of the second metatarsal base. Fractures of the cuboid, cuneiforms, and navicular also are common, occurring in more than one third of cases. Lisfranc injuries may be complicated by vascular injury because a critical branch of the dorsalis pedis artery dives between the first and second metatarsals to form the plantar arch. Trauma to this vessel can cause significant hemorrhage and, uncommonly, vascular compromise.

Clinical Features. Most Lisfranc injuries are clinically obvious; however, findings may be subtle, and the true extent of the pathologic condition can easily be missed or misdiagnosed.[156] Apparently trivial fractures, if viewed in isolation, fail to reflect the serious soft tissue disruption that can be present. Some estimate that the diagnosis is missed on initial ED presentation in up to 20% of cases.[157-159]

The clinical presentation varies with the extent of injury and displacement. Severe pain in the midfoot and inability to bear weight, particularly on the toes, are usual features. Paresthesias are occasionally present, and examination usually reveals edema and ecchymosis. In severe injuries, obvious deformity with forefoot abduction, equinus (a plantar-flexed position of the forefoot), and prominence of the medial tarsal area can be present. In addition, anteroposterior shortening and transverse broadening may be found. The dorsalis pedis pulse can be absent, or evidence of vascular compromise of the forefoot may be present. Typically, tenderness along the affected tarsometatarsal joints and pain with passive abduction and pronation of the forefoot are present, sometimes with pathologic mobility.

Diagnostic Strategies: Radiology. Standard radiographic views of the foot usually are sufficient to diagnose injuries to the Lisfranc complex, although findings may be subtle (Fig. 58-24). The anteroposterior view identifies fractures and alignment, with the oblique view greatly aiding this assessment by eliminating overlap at the metatarsal bases. The lateral view shows the soft tissues and identifies any dorsal or plantar displacement. Weight-bearing (stress) radiographs may be helpful in uncertain cases,[157] and, although poorly studied, it has been suggested that up to 10% of Lisfranc injuries are undetectable without stress views.[160] In situations in which pain precludes weightbearing, regional anesthesia may facilitate obtaining weight-bearing radiographs. Comparison views are extremely helpful, and a 30-degree oblique view, in addition to the standard 45-degree oblique view, also may be of value. As is the case elsewhere in the hindfoot and midfoot, CT scanning has revolutionized the diagnosis and evaluation of Lisfranc injuries.[161] Because of its ability to image ligamentous structures, MRI may be useful to predict Lisfranc joint complex instability.[162]

An appreciation of normal radiographic anatomy is essential to assess Lisfranc injuries. Radiographs should be methodically examined, with assessment of alignment, bones, and soft tissues. The first four metatarsals should each line up with the respective tarsal articulation along the medial edge on anteroposterior and oblique radiographic views. The most consistent relationship is the alignment of the medial edge of the base of the second metatarsal with the medial edge of the middle cuneiform. Dorsal

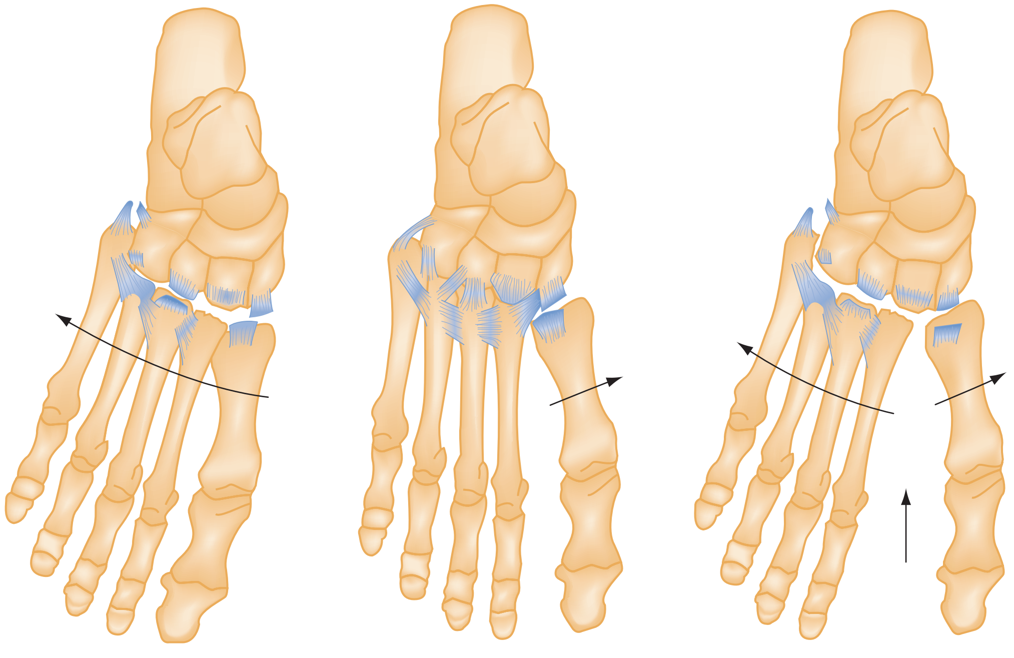


Figure 58-23. Classification of Lisfranc injuries. The ligamentous anatomy of the Lisfranc complex also is depicted. (From Hardcastle PH, et al: Injuries to the tarsometatarsal joint: Incidence, classification and treatment. J Bone Joint Surg Br 64:349, 1982.)

www.ketabpezeshki.com 66485457-66963820

Figure 58-24. **A,** Anteroposterior radiograph showing a Lisfranc injury with fractures of the bases of the second through fourth metatarsals, including a fragment suspicious for an avulsion from the Lisfranc ligament at the second metatarsal base. **B,** Lateral radiograph showing a step-off at the tarsometatarsal joints *(arrow).* **C,** Computed tomography scan of the same patient showing increased detail, including lateral displacement of the first metatarsal relative to the first cuneiform *(arrow).* (From Gupta RT, et al: Lisfranc injury: Imaging findings for this important but often-missed diagnosis. Curr Probl Diagn Radiol 37:115, 2008.)

www.ketabpezeshki.com 66485457-66963820

alignment of the tarsals with their respective metatarsals should be assessed on the lateral view.

Findings suggestive of a Lisfranc injury include widening between the first and second or second and third metatarsal bases and any fracture around Lisfranc's joint. Fracture of the second metatarsal base (called a *fleck sign*), cuboid fractures, and cuneiform fractures are particularly common. A fracture of the second metatarsal base is virtually pathognomonic for occult tarsometatarsal joint disruption.

If a suspicious fracture is present and alignment appears normal, a spontaneously reduced dislocation may be present. In addition, plain radiographs may be normal in appearance in the setting of a typical history and tenderness over the tarsometatarsal joints, suggesting a sprain of the Lisfranc complex that may or may not be unstable. In either case, stress radiographs may be diagnostic.

Management. Lisfranc injuries usually are treated with closed reduction and internal fixation with percutaneous Kirschner wires. This is followed by non–weight-bearing casting for 12 weeks and wearing of an orthotic for 1 year. Treatment of a sprain of the Lisfranc complex usually involves immobilization for 6 weeks in a below-knee walking cast.

Disposition. Any obvious or suspected Lisfranc injury requires orthopedic consultation in the ED. Patients suspected of having a sprain of the Lisfranc complex require casting and orthopedic assessment on an outpatient basis, because operative fixation can be required. The incidence of complications with a Lisfranc injury depends on the timing of diagnosis and the degree of anatomic reduction achieved. Aggressive surgical management clearly improves outcome.

Delayed treatment or missed diagnosis of Lisfranc injuries can result in significant complications.[163] Degenerative arthritis is a common complication. Other potential complications include compartment syndrome, residual pain, unequal metatarsal pressure, loss of the metatarsal arch, and complex regional pain syndrome. Unstable sprains of the Lisfranc complex can result in biomechanical problems if untreated, and delayed presentations pose management challenges and often result in complications.[164]

Forefoot Injuries

Traumatic forefoot conditions are commonly underdiagnosed and often consist of more than one fracture or dislocation occurring simultaneously. As occurs elsewhere in the foot, forefoot trauma may lead to prolonged disability and dysfunction.

Metatarsal Fractures

Metatarsal fractures are common and account for one third of foot fractures. The best approach is first to classify the injury anatomically as occurring in the shaft, the head and neck, or the base. Management is then dictated by the metatarsal involved, the specific location and type of fracture, and the nature of any associated injuries.[165,166]

Metatarsal Shaft Fractures

Principles of Disease: Pathophysiology. Metatarsal shaft fractures arise from either direct trauma (e.g., a crush injury from a heavy object) or indirect trauma (e.g., a twisting force applied to a fixed forefoot). Because of the nature of the mechanism of injury, associated phalangeal fractures often occur. Direct trauma may be highly disruptive, resulting in multiple metatarsal fractures and severe complications. The third metatarsal is the most commonly fractured, and metatarsal shaft stress fractures are common.

Biomechanics are an important consideration in the approach to metatarsal shaft fractures. During stance, weight is distributed equally between the heel and forefoot, where it is spread across the metatarsals, with the first metatarsal carrying twice its share of the load. Great toe metatarsal fractures, although uncommon, require more aggressive management because of this load-bearing function. Alignment of fractured metatarsals is important because dorsal or plantar displacement can lead to pain or functional disability by altering the transverse arch and load distribution. Dorsal angulation commonly occurs at the site of metatarsal fractures from the action of intrinsic muscles and toe flexors. Medial or lateral displacement, although less critical, can lead to the development of painful bony prominences or neuromas.

Clinical Features. Metatarsal shaft fractures cause weight-bearing difficulty and tenderness, which usually is maximal on the plantar surface and can be difficult to localize if swelling is significant. Axial compression of the involved toe often is painful, and ecchymosis usually appears within 12 hours of injury. Rotational alignment should be assessed by evaluating the position and plane of the involved digit.

Diagnostic Strategies: Radiology. Standard radiographs are sufficient to diagnose most metatarsal shaft fractures; however, radiographs usually are exposed for visualization of the talar bones, and the forefoot may be overpenetrated. Adjustment of penetration or coned views may be required for visualization of subtle fractures. Displacement and angulation, in both the sagittal and mediolateral planes, should be assessed.

Management. Most undisplaced metatarsal shaft fractures of the second through fifth metatarsals are treated with a below-knee walking cast for 2 to 4 weeks. Early casted ambulation may be beneficial to healing and may reduce the incidence of complex regional pain syndrome. Although some practitioners recommend a non–weight-bearing cast for 4 to 6 weeks for these fractures, others suggest that a metatarsal pad, stiff shoes, and crutches, if needed, are sufficient. These various approaches attest to the fact that most nondisplaced metatarsal shaft fractures heal well regardless of the treatment.

The great toe metatarsal requires more aggressive management because of its biomechanical role and the stresses imposed on it during gait. Nondisplaced first metatarsal fractures should be treated with casting for 4 to 6 weeks.[167] For at least the first 3 weeks of this immobilization, if not the entire period, the patient should not bear weight.

Reduction should be considered in any metatarsal shaft fracture with more than 3 mm of displacement or 10 degrees of angulation. Closed reduction, with toe traps and countertraction at the ankle, is often successful. Non–weight-bearing casting for 4 to 6 weeks should follow. The indications for open reduction are controversial but generally include the presence of compartment syndrome, unstable fractures, open fractures, fractures that have failed closed reduction, and multiple fractures. These are treated with fixation with either Kirschner wires or plates.[167] In particular, displaced first and fifth metatarsal shaft fractures are commonly treated operatively. Major forefoot trauma, with crushing and multiple open metatarsal fractures, requires an aggressive approach with staged operative management.

Disposition. Most undisplaced metatarsal shaft fractures are suitable for management without orthopedic referral. Orthopedic consultation in the ED should be obtained for patients with multiple or displaced fractures. Complications are rare in nondisplaced or minimally displaced metatarsal shaft fractures. Complex regional pain syndrome can occur and may be related to the unnecessary use of non–weight-bearing casting. Inadequate reduction, particularly in the sagittal plane, can lead to biomechanical problems and formation of painful callosities or metatarsalgia. Malunion in the mediolateral plane, particularly if involving the first or fifth metatarsal, can lead to development of pressure points, neuromas, or biomechanical problems. Delayed union, nonunion, compartment syndrome, and soft tissue complications occur uncommonly.

www.ketabpezeshki.com 66485457-66963820

Metatarsal Head and Neck Fractures

Metatarsal head and neck fractures, although similar in their pathophysiology and assessment to shaft fractures, commonly are multiple and often result from direct trauma. Nondisplaced fractures may be treated with a walking cast for 4 to 6 weeks. Often these fractures are displaced, with the distal fragment pulled in a plantar and lateral direction by the flexor tendons, a finding best appreciated on oblique and lateral radiographic views. Precise realignment of neck and head fractures is important to maintain the transverse arch. Although reduction may be successful with toe traps, instability is common, and operative fixation is required more commonly than with shaft fractures. Most of these fractures warrant orthopedic consultation in the ED, particularly if they are displaced or intra-articular. Complications are similar to those seen with shaft fractures.

Metatarsal Base Fractures

Principles of Disease: Pathophysiology. Isolated fractures of the first through fourth metatarsal bases are uncommon. Most are nondisplaced transverse fractures within 1 cm of the tarsometatarsal articulation and arise as a result of direct trauma. An indirect mechanism is more suggestive of the presence of an occult Lisfranc injury. The most commonly encountered metatarsal base fractures occur at the fifth metatarsal.

Fifth Metatarsal. *Jones fracture* is a term often erroneously applied to any fracture of the fifth metatarsal base. The eponym is in reference to Sir Robert Jones, a physician who in 1902 described a fracture he sustained while dancing and a series of similar injuries. In reality, two distinct acute fractures can occur in the region of the fifth metatarsal base, and debate continues regarding which one Jones actually described.[168] More important than the terminology, these two fractures differ dramatically in their mechanism, treatment, and prognosis.[169]

The more common, and benign, fracture at the fifth metatarsal base is of the tuberosity. Also called the *styloid,* the tuberosity is the bulge of the fifth metatarsal that is easily palpated over the lateral edge of the foot. It is fractured by a sudden inversion of a plantar-flexed foot. For decades, this fracture was thought to be caused by an avulsion at the insertion of the peroneus brevis tendon; however, it is now known that the plantar aponeurosis is responsible for the location and nature of this fracture.[170]

Tuberosity fractures range from tiny flecks to lesions involving the entire tuberosity and usually are extra-articular, although they may extend into the cubometatarsal joint. Often these injuries masquerade as ankle sprains (see Fig. 58-12 and Box 58-2), making the fifth metatarsal base an important area to palpate in any twisting injury.

The more serious acute fracture at the base of the fifth metatarsal is a transverse fracture occurring at least 15 mm distal to the proximal end of the bone.[169] This diaphyseal fracture probably is a true Jones fracture and involves the fourth and fifth intermetatarsal articulations but not the cubometatarsal articulation. Diaphyseal fractures result from a complex combination of forces generated when a load is applied to the lateral forefoot in the absence of inversion.[169] Typically these occur in running and jumping sports. Further subclassification schemes of proximal diaphyseal fractures exist and can be helpful in determining management.[152] Fifth metatarsal diaphyseal stress fractures can also occur and should be considered when a seemingly acute injury is preceded by a prodrome of pain in the region over weeks to months.[152,166]

Clinical Features. The assessment of metatarsal base fractures is similar to that described for fractures of the metatarsal shaft. Pain often is diffuse and difficult to localize in these injuries, with the exception of the easily palpable fifth metatarsal tuberosity. Passive inversion also may be painful with a fifth metatarsal base fracture.

Diagnostic Strategies: Radiology. Standard radiographic views easily demonstrate most metatarsal base fractures. Radiographs should be carefully assessed for fracture angulation, displacement, and articular extension. If the fracture is intra-articular, an estimation of the percentage of articular surface involved is essential in determining management. In difficult cases, CT studies may be helpful.

With fractures of the first through fourth metatarsal bases, it is important to search for other radiologic clues to a Lisfranc injury. A fracture of the second metatarsal base is virtually pathognomonic for occult tarsometatarsal joint disruption. In assessment for a fifth metatarsal base fracture, differentiation between the tuberosity and diaphysis is essential (Fig. 58-25). Care should be taken not to misinterpret an os vesalianum or os peroneum for a fifth metatarsal base fracture (see Fig. 58-15). Standard ankle radiographs also demonstrate the fifth metatarsal base, and this area should be routinely scrutinized.

Management. Nondisplaced extra-articular fractures of the first through fourth metatarsal bases usually are managed with a below-knee cast. Displaced fractures should be reduced and often require fixation. Intra-articular fractures, especially those of the first metatarsal, often lead to complications. Operative fixation may be required, even in nondisplaced intra-articular first metatarsal base fractures, if more than 25% of the articular surface is involved.

The management of fifth metatarsal base fractures depends on the type of fracture. Extra-articular tuberosity fractures, regardless of their size or degree of displacement, heal well and are managed symptomatically with a walking cast for 2 to 3 weeks, compression wrap, or stiff shoes.[168] Intra-articular tuberosity fractures involving more than 30% of the articular surface, or with more than 2 mm of displacement, may require fixation.[168] Nondisplaced intra-articular fractures usually are treated initially with non–weight-bearing casting for 6 to 8 weeks, followed by radiographic reassessment.[168] Immobilization for up to 6 months may be required for complete healing, and immediate fixation may be advisable in athletes.[169] Displaced fifth metatarsal diaphyseal fractures usually are managed operatively,[171] and prolonged treatment may be necessary particularly for diaphyseal stress fractures.

Disposition. Because they are rare and treatment varies, most first through fourth metatarsal base fractures require orthopedic assessment. Nondisplaced extra-articular fractures of the first through fourth metatarsal bases are suitable for orthopedic follow-up on an outpatient basis. Orthopedic consultation in the ED should be obtained in any other first through fourth metatarsal base fracture or if Lisfranc's injury is suspected. Significant or displaced intra-articular fifth metatarsal tuberosity fractures or diaphyseal fractures warrant orthopedic evaluation in the ED.

Intra-articular metatarsal base fractures involving the first through fourth metatarsals can lead to post-traumatic arthritis requiring arthrodesis. Complications are rare in cases of fifth metatarsal tuberosity fractures, although fibrous nonunion of the fracture fragment can occur. Fifth metatarsal diaphyseal fractures are often complicated by delayed union, nonunion, or fracture recurrence, owing to poor healing subsequent to disruption of the metatarsal vascular supply. These complications occur in more than 50% of patients treated conservatively and often require aggressive surgical therapy and have prolonged healing times.

Phalangeal Fractures

Principles of Disease: Pathophysiology. Phalangeal fractures are the most common forefoot fracture. They usually arise from direct trauma, often the result of dropped heavy objects or stubbing the toe. Less commonly, indirect mechanisms involving twisting of the forefoot can lead to phalangeal fractures. Proximal phalanges are more commonly fractured than middle or distal phalanges, and

www.ketabpezeshki.com 66485457-66963820

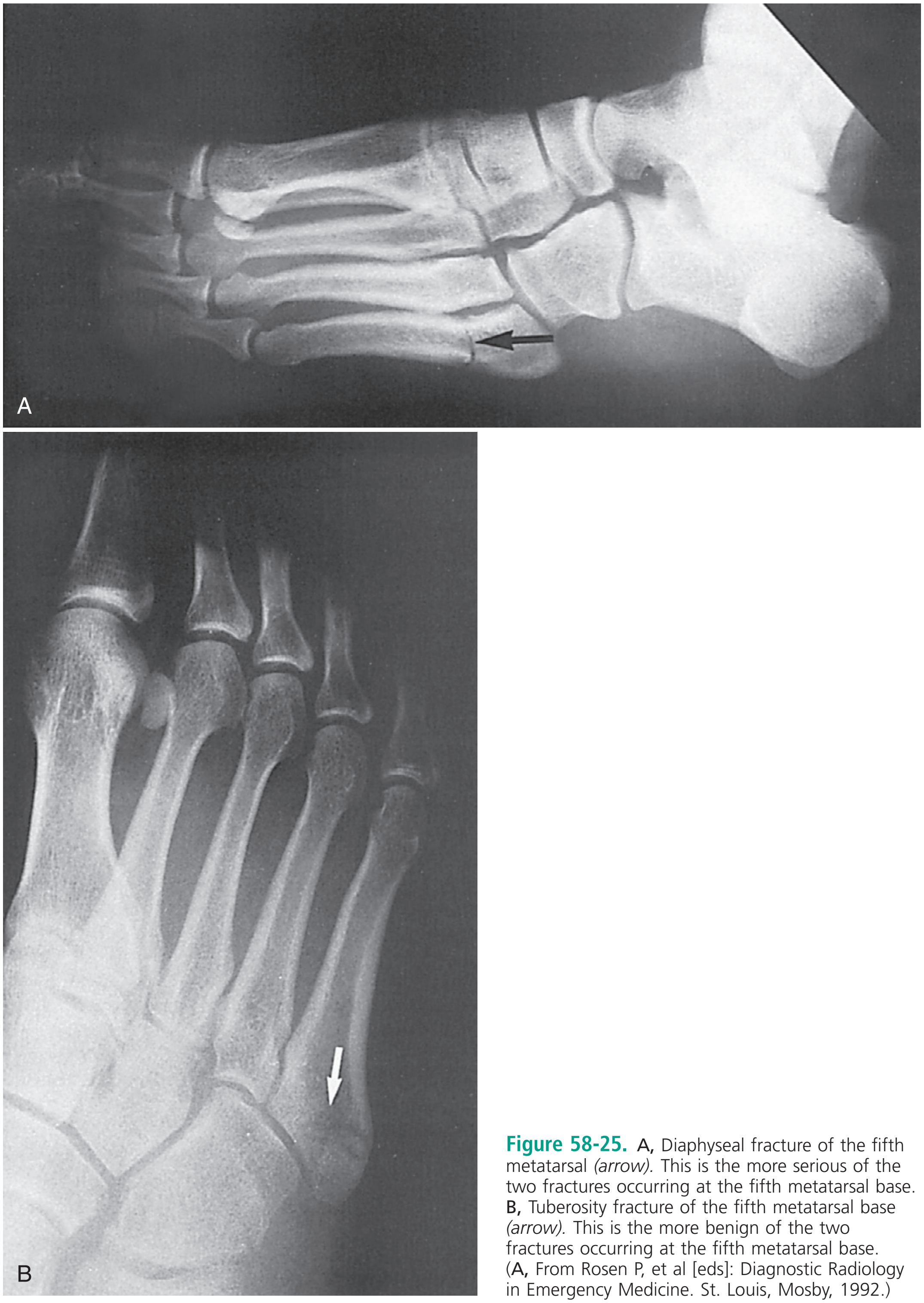


Figure 58-25. **A,** Diaphyseal fracture of the fifth metatarsal *(arrow).* This is the more serious of the two fractures occurring at the fifth metatarsal base. **B,** Tuberosity fracture of the fifth metatarsal base *(arrow).* This is the more benign of the two fractures occurring at the fifth metatarsal base. (**A,** From Rosen P, et al [eds]: Diagnostic Radiology in Emergency Medicine. St. Louis, Mosby, 1992.)

the proximal phalanx of the fifth toe is most commonly injured. Fractures of the hallux often are displaced, whereas fractures of the lesser phalanges are often comminuted but less commonly displaced.

Clinical Features. Although phalangeal fractures generally are considered minor injuries, they can lead to disabling sequelae and merit careful assessment.[172] The patient with a phalangeal fracture has acute pain and swelling of the affected toe, often with difficulty ambulating or wearing shoes. Examination may reveal tenderness, crepitus, and reduced range of motion. A subungual hematoma often is present if the distal phalanx is involved, and open fractures are common.

Diagnostic Strategies: Radiology. Standard radiographic views usually are sufficient to demonstrate phalangeal fractures, with the lateral view being most sensitive. Often the uninjured toes must be positioned out of the way for adequate radiographs to be obtained, and magnification radiographs occasionally are required. Angulation and joint involvement should be assessed.

Management. Most phalangeal fractures are easily managed and heal well. Large and symptomatic subungual hematomas

www.ketabpezeshki.com 66485457-66963820

should be evacuated, and, on rare occasions, nail bed repair may be required. Nondisplaced lesser phalangeal fractures should be stabilized by "buddy-taping"—splinting the injured toe to an adjacent, ideally longer, toe with adhesive tape. Placement of gauze between the splinted toes is advisable to prevent skin maceration. Phalangeal fractures often remain painful for 2 to 3 weeks until stabilized by callus.

If significant displacement or angulation is present, reduction should be performed with manual traction or toe traps after digital block anesthesia. Moderate persistent angulation or displacement is acceptable if the clinical appearance of the toe remains satisfactory. Rarely, operative fixation of lesser phalangeal fractures is indicated, particularly in cases with severe rotatory deformity or in open fractures requiring débridement.

Nondisplaced phalangeal fractures involving the hallux are treated by buddy-taping, with a walking cast worn for 2 to 3 weeks if the toe is painful. Alternatives to standard casting techniques, such as the slipper cast, have also been described for phalangeal fractures.[173] Displaced phalangeal fractures of the hallux require reduction. If the reduction is inadequate or unstable, operative fixation may be indicated. Unless completely nondisplaced, most intra-articular fractures involving the hallux are treated with operative fixation, although this is an area of controversy.

Disposition. Most phalangeal fractures do not require orthopedic evaluation; however, if displacement persists or causes cosmetic or functional concern, consultation is advised. Orthopedic consultation in the ED is advised for poorly reduced or intra-articular hallux fractures.

Complications of phalangeal fractures are uncommon. With intra-articular phalangeal fractures, particularly those involving the hallux, arthritis may be a late sequela, or fragments may require operative removal. Symptomatic angular malunion and osseous deformity can occur with phalangeal fractures, and exostectomy is sometimes required.

Sesamoid Fractures

The sesamoids are two flat oval bones found within the tendon of the flexor hallucis brevis, under the head of the first metatarsal. Their name comes from the Greek word *sesamoeides*, meaning "resembling a sesame seed." Ten percent of the population has sesamoid bones under the fifth metatarsal head, and uncommonly, sesamoids are found under the second, third, or fourth metatarsal (see Fig. 58-15). Sesamoid fractures are uncommon and usually are caused by direct trauma from falls. Hyperextension of the great toe can indirectly lead to a sesamoid fracture.[174] Sesamoid fractures also can be found in association with MTP joint dislocations. The medial sesamoid of the great toe is more commonly fractured than the lateral, and a suspected fracture should be differentiated from a bipartite sesamoid, which occurs in up to one third of the population and also is more common on the medial aspect. Stress fractures of the sesamoids also occur. Sesamoid fractures generally require a below-knee walking cast for 3 to 4 weeks. Most heal without complications and do not require orthopedic consultation.

Metatarsophalangeal Dislocations

Principles of Disease: Pathophysiology. Dislocations of the MTP joint are uncommon injuries because of the protection footwear provides and the inherent stability of MTP and IP joints. MTP joint dislocations can occur in any joint and in any direction. First MTP joint dislocations require large forces and usually result from MVCs. These injuries often are open and typically involve dorsal dislocations of the distal component caused by hyperextension of the MTP joint. Associated sesamoid fractures may be present. Complex dislocations, in which the sesamoids or local tendons prevent closed reduction, can occur. Second through fifth MTP dislocations usually are medial or lateral displacements that occur when the toe strikes or hooks an object. The most common is a lateral dislocation of the fifth MTP joint.

Clinical Features. Dislocations of the MTP joint cause pain, swelling, and difficulty bearing weight on the ball of the foot. First MTP joint dislocations usually are obvious on clinical examination because the toe is angled upward with dorsal and proximal displacement of the proximal phalanx. This deformity leads to a striking prominence of the metatarsal head over the plantar surface. Skin tenting or a dimple may be present. Rarely the sesamoids are palpable dorsal to the metatarsal, indicating a complex dislocation. Dislocations of the lesser toes often are more subtle in presentation, and comparison with the uninjured foot may be helpful. Neurovascular compromise is rare.

Diagnostic Strategies: Radiology. Dislocations of the MTP joint are well visualized on standard radiographic views of the foot. In first MTP joint dislocations, a double density often is present, caused by superimposition of the base of the proximal phalanx over the metatarsal head. Radiographs should be scrutinized for signs suggesting complex dislocation, such as the sesamoids lying between the two articular surfaces or dorsal to the metatarsal head.

Management. Most MTP joint dislocations, particularly of the lesser toes, are easily reduced with longitudinal traction. Appropriate analgesia or local anesthesia should be administered before reduction is attempted. Dorsal dislocations of the first MTP joint can be more challenging and may require initial accentuation of the deformity in addition to longitudinal traction for reduction. Joint stability should be assessed and repeat radiographs obtained after reduction of an MTP joint dislocation. After reduction, a walking cast with a toe plate is worn for 3 weeks, followed by physiotherapy to ensure adequate range of motion. Alternatively, buddy-taping and an aluminum splint can be used for immobilization.

Disposition. Most MTP joint dislocations can be managed without orthopedic consultation. If crepitus or obvious instability is present or postreduction radiographs show joint incongruity or an intra-articular fracture, orthopedic consultation should be obtained for possible fixation. First MTP joint dislocations that are open, show radiographic evidence of complexity, or do not easily reduce require orthopedic consultation in the ED, because open reduction may be required. Very rarely, MTP joint dislocations of the lesser toes require open reduction.

Complications are uncommon after MTP dislocations. Arthritis and reduced range of motion, particularly of the hallux, may occur. Dislocations for which the diagnosis is delayed for more than 3 weeks often are not amenable to closed reduction and may require metatarsal head excision.

Interphalangeal Joint Dislocations

IP joint dislocations are much less common than MTP joint dislocations and are sometimes overlooked. Most IP joint dislocations occur in the great toe and are a result of axial loading. IP joint dislocations usually involve dorsal displacement of the distal component and are easily managed without orthopedic consultation. Reduction is performed with longitudinal traction after digital block anesthesia is achieved. Initial accentuation of the deformity may be necessary if reduction is unsuccessful with simple traction. If the dislocation involves the great toe, a walking cast with a toe plate for 3 weeks is indicated after reduction. Lesser toes require only buddy-taping. As with the MTP joint, complex dislocations involving the first IP joint can occur, and orthopedic consultation in the ED for open reduction may be necessary. Very rarely, lesser toe IP joint dislocations are irreducible with closed methods and will require open reduction.

www.ketabpezeshki.com 66485457-66963820

Foot Pain

Perspective. Foot pain, particularly in the absence of obvious trauma, poses a diagnostic and therapeutic challenge. Plain radiographs commonly are normal in appearance, so the history and physical examination assume increased importance. Although a definitive diagnosis often is difficult to obtain in the ED, a structured approach aids in appropriate patient management and disposition. Most causes of foot pain are minor and self-limited, but the possibility of serious pathologic conditions (e.g., infection, arthritis, tumor) should be considered. Although orthopedic consultation in the ED is rarely required, orthopedic or sports medicine follow-up on an outpatient basis is indicated for selected cases.

Foot pain can be classified as acute, acute on chronic, or chronic and is best approached anatomically by localizing symptoms to the hindfoot, midfoot, or forefoot. Three conditions warrant specific mention.

Complex regional pain syndrome is a condition involving pain in the presence of trophic changes and vasomotor instability from inappropriate sympathetic nervous system activity and was previously termed "reflex sympathetic dystrophy." Complex regional pain syndrome occurs months after trauma, which may be major, as in a Lisfranc injury, or relatively innocuous. It has many synonyms, including *causalgia* and *Sudeck's atrophy,* and produces pain of a diffuse burning, aching, or searing nature, together with evidence of vasomotor instability. Complex regional pain syndrome should be considered in the differential diagnosis for foot pain after trauma.

Another important consideration in patients with previous penetrating trauma is a retained foreign body. Foreign bodies can be a source of chronic drainage or chronic pain. The inciting trauma may have occurred years previously, and a history of the event may be difficult to extract, or such an event may be unknown to the patient.

Finally, stress fractures are an important consideration in the differential diagnosis for foot pain, particularly in athletes.

Hindfoot Pain. Hindfoot pain is a common complaint that usually is the result of overuse rather than acute trauma.[175] Bone pain in the hindfoot necessitates consideration of talar or calcaneal stress fractures. A calcaneal stress fracture may be suspected when pain is elicited on squeezing the calcaneus mediolaterally. Another cause of bone pain is impingement by an os trigonum (see Fig. 58-15) or prominent lateral posterior talar process. The os trigonum syndrome involves pain during plantar flexion of the foot and is particularly common in ballet dancers. A bone scan may be required for diagnosis, and treatment is surgical.

Most patients with hindfoot pain describe subcalcaneal heel pain, a complaint with an extensive differential diagnosis.[176] The literature on this topic is conflicting and fraught with inconsistent terminology. The most common causes of subcalcaneal pain are plantar fasciitis, subcalcaneal bursitis, acute rupture of the plantar fascia, and nerve compression.

The plantar fascia is a tough layer of the sole that is functionally significant during foot strike and the early stance phase of walking. Plantar fasciitis, an overuse injury of insidious onset, usually begins with pain on first weightbearing in the morning or after prolonged sitting.[177] This progresses to persistent pain during gait. Pain and tenderness are localized to the medial aspect of the heel. Plantar fasciitis is particularly common in cavus feet, although the nature of this association is unclear.[178] Plain radiography is not diagnostic but shows a calcaneal spur in 50% of patients with plantar fasciitis. This is a stress-related ossification with a 16% incidence in asymptomatic persons and is not considered the primary cause of pain in plantar fasciitis. Rarely, fascial ossification (an os subcalcis) may be seen.

Plantar fasciitis is distinct from subcalcaneal bursitis, a condition with an identical presentation in which the pain is localized to the bursa directly below the calcaneus. Differentiating these two conditions can be difficult and usually is academic, because initial treatment is identical: a combination of avoiding precipitating conditions, rest, padding, orthotics, nonsteroidal anti-inflammatory drugs, and occasionally steroid injections. Extracorporeal shock wave therapy can be beneficial in refractory cases.[179] Very rarely, surgical release of the plantar fascia is required, a therapy that can be beneficial in either condition.

Plantar fascial rupture is a tear of the origin of the plantar fascia at the calcaneus. This injury usually occurs during the push-off phase of gait. Swelling may be noted, and typically pain is elicited by passive dorsiflexion of the hallux. Treatment is nonsurgical, often with a period of cast immobilization for symptomatic relief.

Compression of either the abductor digiti quinti nerve or the posterior tibial nerve (the so-called "tarsal tunnel syndrome") can cause subcalcaneal heel pain.[180] Diagnosis of these conditions is difficult and is sometimes facilitated by assessing the impact of selective nerve block with local anesthesia. Initial treatment of these conditions is similar to that for plantar fasciitis, although local steroid injections or surgical release may be required. Other nerve entrapments also can occur in the hindfoot area.

Many tendons course through the hindfoot, particularly the anteromedial aspect, and tendinitis can occur. Other tendon pathologic conditions (e.g., ruptures, dislocations, retinacular injuries) should be considered because they can result in significant functional disability.

Midfoot Pain. Isolated midfoot pain is less common than forefoot or hindfoot pain. Stress fractures are uncommon in the midfoot and most commonly involve the navicular. Other causes of midfoot pain include symptomatic accessory bones, particularly the accessory navicular, os tibiale externum, and os peroneum (see Fig. 58-15). An os tibiale externum is present in up to 14% of the normal population and is asymptomatic in most cases. This accessory bone can produce debilitating pain on the medial aspect of the midfoot. A bone scan facilitates diagnosis, and surgical excision may be necessary. An os peroneum is one of several conditions that can cause lateral plantar pain in the midfoot region. Localization of tenderness is aided by resisted plantar flexion, and treatment ranges from immobilization to surgical excision.

Forefoot Pain. The forefoot is the site for a myriad of painful problems. Bunions, painful bursae, blisters, corns, calluses, hammertoes, and ingrown toenails all are diagnostically obvious but can pose therapeutic challenges. Many are the result of poor footwear or a biomechanical problem with the foot and respond to appropriate padding, avoidance of precipitants, and occasionally surgical intervention.

Metatarsalgia is an often used, although loosely defined, term referring to pain in the region of the metatarsal heads.[181] This is a common presenting complaint with many potential causes. Metatarsal stress fractures are extremely common and should be considered in the differential diagnosis for any unexplained forefoot pain. Flexor or extensor tendinitis also can produce metatarsal area pain and is suggested when plain radiographs show areas of tendinous calcification. Arthritis, sesamoiditis, or a sesamoid stress fracture should be considered when pain occurs in the area of the hallux. "Turf toe" is MTP joint inflammation of the hallux resulting from repeated hyperextension stress.[117] It usually responds to symptomatic measures but can be a significant and debilitating injury in some athletes, such as football players.

An important cause of unilateral metatarsalgia is a perineural fibrosis of the intermetatarsal plantar digital nerve, more commonly known as *Morton's neuroma.*[181] This neuropathy of unknown cause was first described in 1876 and usually involves the second-third or third-fourth intermetatarsal space, causing lancinating pain with weightbearing. The pain may be associated with paresthesias and can radiate into the toes. In addition,

www.ketabpezeshki.com 66485457-66963820

"afterburn" pain can persist during rest. The pain of Morton's neuroma is reproduced when structures of the affected interspace are pinched or when the metatarsal heads are compressed together. Hence, pain may occur intermittently with tight-fitting footwear (e.g., rock-climbing shoes, ski boots). Crepitus or a nodule may be palpable. Initial treatment usually involves a metatarsal pad and the use of shoes with a widened toe box. Surgical excision or neurolysis may be required if conservative management is unsuccessful.[182]

Freiberg's disease is an osteochondrosis of the metatarsal head, usually involving the second metatarsal, and is another cause of pain in this area. *Ingrown toenails* are a common affliction that can occur in any toe, most commonly the hallux. Often the abnormality is perpetuated by short nail trimming, which affords the opportunity for a spicule of nail to grow under the nail fold.[183] Allowing the nail to grow out and providing local care usually will lead to resolution of the condition. Antibiotics are indicated if infection is present. Chronic or recurring ingrowth necessitates partial or complete excision of the nail and germinal ablation.[183]

SPECIAL CONSIDERATIONS

Stress Fractures

Principles of Disease: Pathophysiology

Stress fractures can occur anywhere in the appendicular skeleton but are particularly common in the lower extremity. Athletic activities, particularly running, account for most stress fractures. Predisposing factors include training errors, poor footwear, a previous period of inactivity, change in running surface, and the "female athlete triad" of disordered eating, menstrual disturbances, and low bone mineral density.[184] Anatomic variations may play a role, with cavus feet being more prone to stress fractures than flat feet.

Pedal stress fractures may occur anywhere but are most common in the second or third metatarsal shaft. It is not generally appreciated that calcaneal stress fractures occur almost as often as metatarsal stress fractures. Midfoot stress fractures are uncommon and usually occur in the navicular. The type of sport or activity is related to the location of stress fractures, with navicular stress fractures most often seen in basketball, metatarsal shaft stress fractures in running, and fifth metatarsal diaphyseal stress fractures in football.

Clinical Features

Although the history is variable, most stress fractures produce localized pain of insidious onset, usually with aching over a period of weeks.[185] The pain may be anywhere in the hindfoot, midfoot, or forefoot but is most common along a metatarsal. Initially symptoms occur after athletic activities, but later they limit such activities. Often a predisposing factor, such as a training regimen change, is present. A menstrual history should be obtained in female patients because amenorrhea, often a result of training, can predispose to stress fractures.[185-187]

Physical examination may reveal swelling, point tenderness, or percussion tenderness. In most patients, however, these findings are absent, and the diagnosis is suspected by history alone.

Diagnostic Strategies: Radiology

Initial plain radiographs are commonly normal because bone reaction in stress fractures depends on the length of time from symptom onset. Radiographic abnormalities in the metaphyses can take up to 4 weeks to develop, and those in the diaphyses can take 6 weeks.[25] Although plain radiographs have low sensitivity for stress fractures, their specificity is high. The three important findings are periosteal new bone, endosteal thickening, or a radiolucent line. Radiographic findings vary with location: Metatarsal fractures usually show callus or periosteal reaction, whereas navicular fractures show a lucent line, and calcaneal fractures show curvilinear sclerosis.

The diagnosis of a stress fracture is easily missed because only 50% of patients develop plain radiographic abnormalities. Until recently, radionuclide bone scanning was the imaging modality of choice for stress fractures. Bone scans are nonspecific but extremely sensitive for stress fractures, usually showing abnormal uptake within 24 hours of injury. Rarely, a bone scan may be falsely negative if pain occurs before the onset of a demonstrable pathologic condition. MRI scanning has been found to be equally sensitive and more specific and has emerged as the imaging modality of choice for the outpatient evaluation of this condition.[25,115]

Management

Athletic stress fractures are overuse injuries and necessitate an evaluation of training habits, equipment, and techniques. Most pedal stress fractures resolve in 4 to 6 weeks simply with limitation of impact activities and do not require immobilization unless symptoms are severe. Two locations, however, are unique and deserve specific discussion.

Navicular stress fractures are uncommon and often delayed in diagnosis. Healing is hampered by the relative avascularity of the middle third of the bone, and initial treatment is with non–weight-bearing casting for 6 to 8 weeks. Stress fractures of the fifth metatarsal base are also problematic. Fifth metatarsal diaphyseal stress fractures (also called *chronic Jones fractures*) are usually initially treated with non–weight-bearing status and casting. As with acute diaphyseal fractures, delayed healing is common, and casting for up to 20 weeks may be required.[168]

Disposition

Any patient diagnosed with or suspected of having a stress fracture should undergo orthopedic or sports medicine follow-up on an outpatient basis. Delayed union or nonunion can occur with stress fractures, particularly those of the navicular or fifth metatarsal base. Bone grafting or hardware fixation may be required. Most other pedal stress fractures heal without complications.

Contusions and Sprains

Contusions of the foot, usually from dropped objects, are a common injury. Sprains can occur in the foot, particularly with athletic injuries. The calcaneocuboid and intermetatarsal ligaments are common sites of injury. Localizing such injuries is difficult, and these are often diagnoses of exclusion made after appropriate clinical and radiographic assessment. Both contusions and sprains usually respond rapidly to symptomatic therapy. Sprains of the Lisfranc joint complex are unique and require orthopedic consultation in the ED.

Tendon Injuries

Acute tendon ruptures in the foot, apart from the Achilles and posterior tibial tendons, are rare. Although isolated ruptures of the flexor hallucis longus and anterior tibial tendons have been described, most tendon transections are the result of lacerations. These typically arise from one of two mechanisms: penetrating wounds to the sole of the foot or major trauma from such sources as dropped objects, lawn mowers, or MVCs. Plantar penetrating trauma usually results in flexor tendon injuries, whereas most major mechanisms involve extensor tendons.

www.ketabpezeshki.com 66485457-66963820

Orthopedic or plastic surgery consultation in the ED is indicated for any patient known or suspected to have a tendon injury in the foot. It is clear that flexor and extensor hallucis longus tendons should be repaired primarily; however, the need to repair other tendons is controversial. In general, an attempt should be made to repair any tendon transection, because apparently minor injuries can lead to complications such as claw deformity. Tendon injuries associated with innocuous lacerations are easily missed if not carefully sought. Splinting for 2 to 6 weeks is required after tendon repair.

Crush Injuries, Amputations, and Major Vascular Injuries

Rapid assessment, stabilization, and immediate consultation are priorities in the ED management of a major crush injury, amputation, or vascular injury of the foot. The injured limb is handled gently and can be irrigated with sterile saline solution to remove debris. Use of other irrigating solutions, exploration, or débridement, even if done carefully, is contraindicated.[188] Antibiotics should be administered, as with any open fracture. Compartment syndrome should be considered in crush injuries. Many factors enter into surgical decision-making for patients with such injuries,[189] and objective measures, such as the "mangled extremity score," have been developed to predict the need for amputation.[190] Local crush injuries often heal better than diffuse crush injuries.[188] A surgical goal is preservation of as much length as possible to maintain a longitudinal arch, and care plans are typically individualized.[191] In the presence of a major vascular injury, the likelihood of permanent disability is high.

Compartment Syndrome

Principles of Disease: Pathophysiology

Compartment syndrome is defined as an increase in pressure within a confined osseofascial space that impedes neurovascular function, resulting in tissue damage.[188] Compartment syndrome in the foot, as elsewhere in the body, constitutes a medical emergency. Classically, four foot compartments—medial, central, lateral, and interosseous—are described, although studies using dye injection have suggested that there may be as many as nine foot compartments.[188]

Pedal compartment syndrome is most commonly caused by significant crush injuries, fractures, or dislocations. Other causes include bleeding disorders, burns, electrical injury, postischemic swelling after arterial injury or thrombosis, drug or alcohol overdose, excessive exercise, and venous obstruction.[37] Pedal compartment syndrome after an ankle sprain has also been reported.[192] Damage is related to the duration and magnitude of compartment pressure rise and the arteriovenous gradient. Compartment syndrome can develop anywhere from 2 hours to 6 days after an insult, although the peak incidence is at 15 to 30 hours.

Clinical Features

Compartment syndrome typically causes pain out of proportion to that expected for the injury. The pain is not decreased by immobilization and can be described as a feeling of tautness within the foot.[193] In the case of calcaneal fractures, the pain often is a relentless burning involving the entire foot. Physical examination may reveal tense swelling and sensory deficits. Pain is exacerbated by any movement (active or passive) that stretches the muscles of the involved compartment. Passive dorsiflexion of the toes often is painful. Peripheral pulses and capillary refill usually are normal in compartment syndrome and thus offer no reassurance when present. Presence of an open wound does not guarantee that all compartments are decompressed.

Diagnostic Strategies: Special Procedures

The only way to diagnose a compartment syndrome is to measure intracompartmental pressure. The decision to perform this maneuver relies on appropriate clinical suspicion. Techniques of pressure measurement are well described, with a pressure greater than 30 mm Hg generally considered diagnostic.[193,194] Compartment syndrome can occur at lower pressures in hypotensive patients. More details on the pathophysiology and diagnosis of this condition can be found in Chapter 49. The needle localization and distinguishing of foot compartments is challenging because of their small size. For this reason and because of its importance in surgical decision-making, measurement of pedal compartment pressures usually should be left to an orthopedic surgeon.

Management

Early identification and prevention of further tissue damage are important considerations in any patient with a mechanism consistent with the development of compartment syndrome. Circumferential bandages and casts should be avoided during early management. In diagnosed or suspected cases of compartment syndrome, the limb should be positioned at the level of the heart. Limb elevation beyond this point is contraindicated because it would decrease arterial flow, thereby narrowing the arterial-venous pressure gradient.

Disposition

If compartment syndrome is suspected, immediate orthopedic consultation is indicated because the only treatment is decompressive fasciotomy.

ACKNOWLEDGMENT

The authors gratefully acknowledge the authorship and contributions of Dr. Kendall Ho on four previous editions of this chapter.

KEY CONCEPTS

- Ankle dislocations with obvious vascular compromise should be reduced promptly, before radiographs are obtained.
- The entire fibula should be examined if an isolated medial malleolar fracture is present, to rule out a proximal fibular (Danis-Weber type C or Maisonneuve) fracture.
- Before diagnosis of an ankle sprain, other injuries that may mimic an ankle sprain should be considered.
- Patients with Achilles tendon rupture are still capable of weak plantar flexion. The Thompson test should be performed if an Achilles tendon rupture is suspected.
- The presence of accessory ossicles may explain unexpected radiologic "lesions" in the foot.
- The possibility of a Lisfranc injury should be considered with any fracture or dislocation in the tarsometatarsal region, particularly fractures of the second metatarsal base.
- The tuberosity should be carefully differentiated from the diaphysis in all fifth metatarsal base fractures.
- The possibility of a stress fracture should be considered in patients with long-standing foot pain, particularly if symptoms are in the metatarsal region.
- Compartment syndrome of the foot can occur, with potentially devastating results if it is not diagnosed early.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Grimston SK, Nigg BM, Hanley DA, Engsberg JR: Differences in ankle joint complex range of motion as a function of age. *Foot Ankle* 1993; 14:215.
2. Simon RR, Sherman SC, Koenigsknecht SJ, eds. *Emergency Orthopedics: The Extremities*, 5th ed. New York: McGraw-Hill; 2007.
3. Stiell IG, et al: Implementation of the Ottawa Ankle Rules. *JAMA* 1994; 271:827.
4. Davidovitch RI, Egol KA: *Ankle fractures*. In: Bucholz RW, Court-Brown CM, Heckman JD Tornetta P, eds. *Rockwood and Green's Fractures in Adults*, 7th ed. Philadelphia: Wolters Kluwer Health/ Lippincott, Williams & Wilkins; 2010:1973.
5. Brandser EA, et al: Missed fractures on emergency room ankle radiographs: An analysis of 433 patients. *Emerg Radiol* 1997; Sept/ Oct:295.
6. Yu JS, Cody ME: A template approach for detecting fractures in adults sustaining low-energy ankle trauma. *Emerg Radiol* 2009; 16:309.
7. Ho K, Connell DG, Janzen DL, Grunfeld A, Clark TW: Using tomography to diagnose occult ankle fractures. *Ann Emerg Med* 1996; 27:600.
8. Stiehl JB: Ankle fractures with diastasis. *Instr Course Lect* 1990; 39:95.
9. Bachmann LM, Kolb E, Koller MT, Steurer J, ter Riet G: Accuracy of Ottawa Ankle Rules to exclude fractures of the ankle and mid foot: Systematic review. *BMJ* 2003; 326:1.
10. Plint AC, et al: Validation of the Ottawa Ankle Rules in children with ankle injuries. *Acad Emerg Med* 1999; 6:1005.
11. Libetta C, Burke D, Brennan P, Yassa J: Validation of the Ottawa Ankle Rules in children. *Pediatr Emerg Care* 1999; 19:73.
12. Boutis K, et al: Sensitivity of a clinical examination to predict need for radiography in children with ankle injuries: A prospective study. *Lancet* 2001; 358:2118.
13. Yuen MC, Saunders F: Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. The Ottawa Ankle Rules in children. *Emerg Med J* 2001; 18:466.
14. Karpas A, Hennes H, Walsh-Kelly CM: Utilization of the Ottawa Ankle Rules by nurses in a pediatric emergency department. *Acad Emerg Med* 2002; 9:130.
15. Clark KD, Tanner S: Evaluation of the Ottawa Ankle Rules in children. *Pediatr Emerg Care* 2003; 19:73.
16. Dayan PS, et al: Derivation of clinical prediction rules to identify children with fractures after twisting injures of the ankle. *Acad Emerg Med* 2004; 11:736.
17. Gravel J, Hedrei P, Grimard G, Gouin S: Prospective validation and head-to-head comparison of 3 ankle rules in a pediatric population. *Ann Emerg Med* 2009; 54:534.
18. Dowling S, et al: Accuracy of Ottawa Ankle Rules to exclude fractures of the ankle and midfoot: A meta-analysis. *Acad Emerg Med* 2009; 16: 277.
19. Fiesseler F, Szucs P, Kec R, Richman PB: Can nurses appropriately interpret the Ottawa Ankle Rule? *Am J Emerg Med* 2004; 22:145.
20. Derksen RJ, et al: Can nurses appropriately interpret the Ottawa Ankle Rule? [letter] *Am J Emerg Med* 2004; 23:201.
21. Derksen RJ, et al: Specialized emergency nurses treating ankle and foot injuries: A randomized controlled trial. *Am J Emerg Med* 2007; 25:144.
22. Holroyd BR, Wilson D, Rowe BH, Mayes DC, Noseworthy T: Uptake of validated clinical practice guidelines: Experience with implementing the Ottawa Ankle Rules. *Am J Emerg Med* 2004; 22:149.
23. Brehaut JC, Stiell IG, Visentin L, Graham ID: Clinical decision rules "in the real world": How a widely disseminated rule is used in everyday practice. *Acad Emerg Med* 2005; 12:948.
24. Bencardino JT, Rosenberg ZS: MR imaging and CT in the assessment of osseous abnormalities of the ankle and foot. *Magn Reson Imaging Clin N Am* 2001; 9:567.
25. Muthukumar T, Butt SH, Cassar-Pullicino VN: Stress fractures and related disorders in foot and ankle: Plain films, scintigraphy, CT and MR imaging. *Semin Musculoskelet Radiol* 2005; 9:210.
26. Choplin RH, Buckwalter KA, Rydberg J, Farber JM: CT with 3D rendering of the tendons of the foot and ankle: Technique, normal anatomy, and disease. *Radiographics* 2004; 24:343.
27. Johnson PT, Fayad LM, Fishman EK: Sixteen-slice CT with volumetric analysis of foot fractures. *Emerg Radiol* 2006; 12:171.
28. Leffler S, Disler DG: MR imaging of tendon, ligament, and osseous abnormalities of the ankle and hindfoot. *Radiol Clin North Am* 2002; 40:1147.
29. Buckwalter KA: CT arthrography. *Clin Sports Med* 2006; 25:899.
30. Scharf S: SPECT/CT Imaging in general orthopedic practice. *Semin Nucl Med* 2009; 39:293.
31. Dahners LE: The pathogenesis and treatment of bimalleolar ankle fractures. *Instr Course Lect* 1990; 39:85.
32. Michelson JD, Magid D, McHale K: Clinical utility of a stability-based ankle fracture classification system. *J Orthop Trauma* 2007; 21:307.
33. Kennedy JG, et al: An evaluation of the Weber classification of ankle fractures. *Injury* 1998; 29:577.
34. Shariff SS, Nathwani DK: Lauge-Hansen classification—a literature review. *Injury* 2006; 37:888.
35. Gardner MJ, Demetrakopoulos D, Briggs SM, Helfet DL, Lorich DG: The ability of the Lauge-Hansen classification to predict ligament injury and mechanism in ankle fractures: An MRI study. *J Orthop Trauma* 2006; 20:267.
36. Stiehl JB: Open fractures of the ankle joint. *Instr Course Lect* 1990; 39:113.
37. Newton EJ, Love J: Emergency department management of selected orthopedic injuries. *Emerg Med Clin North Am* 2007; 25:763.
38. Michelson JD: Fractures about the ankle. *J Bone Joint Surg Am* 1995; 77:142.
39. Broos PL, Bisschop AP: Operative treatment of ankle fractures in adults: Correlation between types of fracture and final results. *Injury* 1991; 22:403,
40. Martin AG: Weber B ankle fracture: An unnecessary fracture clinic burden. *Injury* 2004; 35:805.
41. Gardner MJ, Demetrakopoulos D, Briggs SM, Helfet DL, Lorich DG: Malreduction of the tibiofibular syndesmosis in ankle fractures. *Foot Ankle Int* 2006; 27:788.
42. Donken CC, Goorden AJ, Verhofstad MH, Edwards MJ, van Laarhoven CJ: The outcome at 20 years of conservatively treated "isolated" posterior malleolar fractures of the ankle: A case series. *J Bone Joint Surg Br* 2011; 93:1621.
43. Wei SY, Okereke E, Winiarsky R, Lotke PA: Nonoperatively treated displaced bimalleolar and trimalleolar fractures: A 20-year follow-up. *Foot Ankle Int* 1999; 20:404.
44. Tejwani NC, et al: Are outcomes of bimalleolar fractures poorer than those of lateral malleolar fractures with medial ligamentous injury? *J Bone Joint Surg Am* 2007; 89:1438.
45. Sherbondy PS, Sebastianelli WJ: Stress fractures of the medial malleolus and distal fibula. *Clin Sports Med* 2006; 25:129.
46. Grantham SA: Trimalleolar ankle fractures and open ankle fractures. *Instr Course Lect* 1990; 39:105.
47. Gosselin RA, Roberts I, Gillespie WJ: Antibiotics for preventing infection in open limb fractures. *Cochrane Database Syst Rev* 2004; 1:CD003764.
48. Nanchahal J, et al: *Standards for the Management of Open Fractures of the Lower Limb*. (Produced by BAPRAS). London: Royal Society of Medicine Press; 2010:8-9.
49. Hoiness P, Stromsoe K: Early complications of surgically managed ankle fractures related to the AO classification: A review of 118 ankle fractures treated with open reduction and internal fixation. *Arch Orthop Trauma Surg* 1999; 119:276.
50. Crist BD, Khazzam M, Murtha YM, Della Rocca GJ: Pilon fractures: Advances in surgical management. *J Am Acad Orthop Surg* 2011; 19:1610.
51. Harris AM, Patterson BM, Sontich JK, Vallier HA: Results and outcomes after operative treatment of high energy tibial plafond fractures. *Foot Ankle Int* 2006; 27:256.
52. Kilian O, Bündner MS, Horas U, Heiss C, Schnettler R: [Long-term results in the surgical treatment of pilon tibial fractures. A retrospective study.] *Chirurg* 2002; 73:65.
53. Sirkin M, Sanders R, DiPasquale T, Herscovici D Jr: A staged protocol for soft tissue management in the treatment of complex pilon fractures. *J Orthop Trauma* 2004; 18(8 Suppl):S32.
54. Blauth M, Bastian L, Krettek C, Knop C, Evans S: Surgical options for the treatment of severe tibial pilon fractures: A study of three techniques. *J Orthop Trauma* 2001; 15:153.
55. Bridgman SA, et al: Population based epidemiology of ankle sprains attending accident and emergency units in the West Midlands of England, and a survey of UK practice for severe ankle sprains. *Emerg Med J* 2003; 20:508.
56. Fernandez WG, Yard EE, Comstock RD: Epidemiology of lower extremity injuries among U.S. high school athletes. *Acad Emerg Med* 2007; 14:641.
57. McKay GD, Goldie PA, Payne WR, Oakes BW: Ankle injuries in basketball: Injury rate and risk factors. *Br J Sports Med* 2001; 35:103.
58. Fallat L, Grimm DJ, Saracco JA: Sprained ankle syndrome: Prevalence and analysis of 639 acute injuries. *J Foot Ankle Surg* 1998; 37:280.

www.ketabpezeshki.com 66485457-66963820

59. Cooke MW, Lamb SE, Marsh J, Dale J: A survey of current consultant practice of treatment of severe ankle sprains in emergency departments in the United Kingdom. *Emerg Med J* 2003; 20:505.
60. Kerkhoffs GM, et al: Different functional treatment strategies for acute lateral ankle ligament injuries in adults. *Cochrane Database Syst Rev* 2002; 3:CD002938.
61. Malliaropoulos N, Papacostas E, Papalada A, Maffulli N: Acute lateral ankle sprains in track and field athletes: An expanded classification. *Foot Ankle Clin* 2006; 11:497.
62. Williams GN, Jones MH, Amandola A: Syndesmotic ankle sprains in athletes. *Am J Sports Med* 2007; 35:1197.
63. Anandacoomarasamy A, Barnsley L: Long term outcomes of inversion ankle injuries. *Br J Sports Med* 2005; 39:e14.
64. Valderrabano V, Hintermann B, Horisberger M, Fung TS: Ligamentous posttraumatic ankle osteoarthritis. *Am J Sports Med* 2006; 34:612.
65. van Dijk CN, Lim LS, Bossuyt PM, Marti RK: Physical examination is sufficient for the diagnosis of sprained ankles. *J Bone Joint Surg Br* 1996; 78:958.
66. Frost SC, Amendola A: Is stress radiography necessary in the diagnosis of acute or chronic ankle instability? *Clin J Sport Med* 1999; 9:40.
67. Kerkhoffs GM, Handoll HH, de Bie R, Rowe BH, Struijs PA: Surgical versus conservative treatment for acute injuries of the lateral ligament complex of the ankle in adults. *Cochrane Database Syst Rev* 2007; 2:CD000380.
68. Kerkhoffs GM, et al: Functional treatments for acute ruptures of the lateral ankle ligament: A systematic review. *Acta Orthop Scand* 2003; 74:69.
69. Janis LR, Kittleson RS, Cox DG: Chronic lateral ankle instability: Assessment of subjective outcomes following delayed primary repair and a new secondary construction. *J Foot Ankle Surg* 1998; 37:369.
70. Wedmore IS, Charette J: Emergency department evaluation and treatment of ankle and foot injuries. *Emerg Med Clin North Am* 2000; 18:85.
71. Boyce SH, Quigley MA, Campbell S: Management of ankle sprains: A randomized controlled trial of the treatment of inversion injuries using an elastic support bandage or an Aircast ankle brace. *Br J Sport Med* 2005; 39:91.
72. Beynnon BD, Renström PA, Haugh L, Uh BS, Barker H: A prospective, randomized clinical investigation of the treatment of first-time ankle sprains. *Am J Sports Med* 2006; 34:1401.
73. Kerkhoffs GM, et al: Immobilisation and functional treatment for acute lateral ankle ligament injuries in adults. *Cochrane Database Syst Rev* 2002; 3:CD003762.
74. Struijs PA, Kerkhoffs GM: Ankle sprain. *Clin Evid (Online)* 2010; 5:1115.
75. Lamb SE, et al: Mechanical supports for acute, severe ankle sprain: A pragmatic, multicentre, randomised controlled trial. *Lancet* 2009; 373:575.
76. Bleakly CM, et al: Effect of accelerated rehabilitation on function after ankle sprain: Randomised controlled trial. *BMJ* 2010; 340:c1964.
77. Kerkhoffs GM, et al: Immobilisation for acute ankle sprain: A systematic review. *Arch Orthop Trauma Surg* 2001; 121:462.
78. Nadarajah A, Abrahan L, Lau FL, Hwang LJ, Fakir-Bolte C: Efficacy and tolerability of celecoxib compared with diclofenac slow release in the treatment of acute ankle sprain in an Asian population. *Singapore Med J* 2006; 47:534.
79. Cukiernik VA, et al: Naproxen versus acetaminophen for therapy of soft tissue injuries to the ankle in children. *Ann Pharmacother* 2007; 41:1368.
80. Hewitt DJ, et al: Tramadol/acetaminophen or hydrocodone/acetaminophen for the treatment of ankle sprain: A randomized, placebo-controlled trial. *Ann Emerg Med* 2007; 49:468.
81. Mahler P, et al: Double-blind, randomized, controlled study on the efficacy and safety of novel diclofenac epolamine gel formulated with lecithin for the treatment of sprains, strains and contusions. *Drugs Exp Clin Res* 2003; 29:45.
82. Predel HG, et al: Diclofenac patch for topical treatment of acute impact injuries: A randomised, double blind, placebo controlled, multicentre study. *Br J Sports Med* 2004; 38:318.
83. Arnold BL, Docherty CL: Bracing and rehabilitation—what's new. *Clin Sports Med* 2004; 23:83.
84. Rotem-Lehrer N, Laufer Y: Effect of focus of attention on transfer of a postural control task following an ankle sprain. *J Orthop Sports Phys Ther* 2007; 37:564.
85. Karlsson J, Eriksson BI, Swärd L: Early functional treatment for acute ligament injuries of the ankle joint. *Scand J Med Sci Sports* 1996; 6:341.
86. Mansour R, Jibri Z, Kamath S, Mukherjee K, Ostlere S: Persistent ankle pain following a sprain: Review of imaging. *Emerg Radiol* 2011; 18:211.
87. Parmar C, Meda KP: Achilles tendon rupture associated with combination therapy of levofloxacin and steroid in four patients and a review of the literature. *Foot Ankle Int* 2007; 28:1287.
88. Ufberg J, Harrigan RA, Cruz T, Perron AD: Orthopedic pitfalls in the ED: Achilles tendon rupture. *Am J Emerg Med* 2004; 22:596.
89. Thompson TC, Doherty JH: Spontaneous rupture of tendon of Achilles: A new clinical diagnostic test. *J Trauma* 1962; 2:126.
90. Mayich DJ, Younger A, Krause F: The reverse Silfverskiöld test in Achilles tendon rupture. *CJEM* 2009; 11:242.
91. Khan RJ, Carey Smith RL: Surgical interventions for treating acute Achilles tendon ruptures. *Cochrane Database Syst Rev* 2010; 9:CD0003674.
92. Wong J, Barrass V, Maffulli N: Quantitative review of operative and nonoperative management of Achilles tendon ruptures. *Am J Sports Med* 2002; 30:565.
93. Baer GS, Keene JS: *Tendon injuries of the foot and ankle.* In: DeLee JC, Drez D, Miller MD, eds. *DeLee and Drez's Orthopedic Sports Medicine: Principles and Practice*, 3rd ed. Philadelphia: Elsevier; 2009.
94. Strauss EJ, Ishak C, Jazrawi L, Sherman O, Rosen J: Operative treatment of acute Achilles tendon ruptures: An institutional review of clinical outcomes. *Injury* 2007; 38:832.
95. Khan RJ, et al: Treatment of acute Achilles tendon ruptures. A meta-analysis of randomized, controlled trials. *J Bone Joint Surg Am* 2005; 87:2202.
96. Lansdaal JR, et al: The results of 163 Achilles tendon ruptures treated by a minimally invasive surgical technique and functional aftertreatment. *Injury* 2007; 38:839.
97. Scott WN, Inglis AE, Sculco TP: Surgical treatment of reruptures of the tendoachilles following nonsurgical treatment. *Clin Orthop Relat Res* 1979; 140:175.
98. Selmani E, Gjata V, Gjika E: Current concepts review: Peroneal tendon disorders. *Foot Ankle Int* 2006; 27:221.
99. Ogawa BK, Thordarson DB: Current concepts review: Peroneal tendon subluxation and dislocation. *Foot Ankle Int* 2007; 28:1034.
100. Slater HK: Acute peroneal tendon tears. *Foot Ankle Int* 2007; 12:659.
101. Major NM, Helms CA, Fritz RC, Speer KP: The MR imaging appearance of longitudinal split tears of the peroneal brevis tendon. *Foot Ankle Int* 2000; 21:514.
102. Foster AP, Thompson NW, Crone MD, Charlwood AP: Rupture of the tibialis posterior tendon: An important differential in the assessment of ankle injuries. *Emerg Med J* 2005; 22:915.
103. Michelson J, Dunn L: Tenosynovitis of the flexor hallucis longus: A clinical study of the spectrum of presentation and treatment. *Foot Ankle Int* 2005; 26:291.
104. Rivera F, Bertone C, De Martino M, Pietrobono D, Ghisellini F: Pure dislocation of the ankle: Three case reports and literature review. *Clin Sports Med* 2006; 16:269.
105. Wroble RR, Nepola JV, Malvitz TA: Ankle dislocation without fracture. *Foot Ankle Int* 1988; 9:64.
106. Ounpuu S: The biomechanics of walking and running. *Clin Sports Med* 1994; 13:843.
107. Young CC, Niedfeldt MW, Morris GA, Eerkes KJ: Clinical examination of the foot and ankle. *Prim Care* 2005; 32:105.
108. Roche A, Hunter L, Pocock N, Brown D: Physical examination of the foot and ankle by orthopaedic and accident and emergency clinicians. *Injury* 2009; 40:136.
109. Koulouris G, Morrison WB: Foot and ankle disorders: Radiographic signs. *Semin Roentgenol* 2005; 40:358.
110. De Smet AA, Doherty MP, Norris MA, Hollister MC, Smith DL: Are oblique views needed for trauma radiography of the distal extremities? *AJR Am J Roentgenol* 1999; 172:1561.
111. Gratton MC, Salomone JA, Watson WA: Clinically significant radiograph misinterpretations at an emergency medicine residency program. *Ann Emerg Med* 1990; 19:497.
112. Mellado JM, et al: Accessory ossicles and sesamoid bones of the ankle and foot: Imaging findings, clinical significance, and differential diagnosis. *Eur Radiol* 2003; 13(Suppl 4):L164.
113. Miller TT: Painful accessory bones of the foot. *Semin Musculoskelet Radiol* 2002; 6:153.
114. Lewis P: Scintigraphy in the foot and ankle. *Foot Ankle Clin* 2000; 5:1.
115. Teague DC: *Stress fractures.* In: Bucholz RW, Court-Brown CM, Heckman JD Tornetta P, eds. *Rockwood and Green's Fractures in Adults*, 7th ed. Philadelphia: Wolters Kluwer Health/Lippincott, Williams & Wilkins; 2010:518-530.
116. Watura R, Cobby M, Taylor J: Multislice CT in imaging trauma of the spine, pelvis, and complex foot injuries. *Br J Radiol* 2004; 77:S46.
117. Umans HR: Imaging sports medicine injuries of the foot and toes. *Clin Sports Med* 2006; 25:763.

www.ketabpezeshki.com 66485457-66963820

118. Zoga AC, Schweitzer ME: Imaging sports injuries of the foot and ankle. *Magn Reson Imaging Clin N Am* 2003; 11:295.
119. Kavanagh EC, Zoga AC: MRI of trauma to the foot and ankle. *Semin Musculoskelet Radiol* 2006; 10:308.
120. Cerezal L, Abascal F, García-Valtuille R, Canga A: Ankle MR arthrography: How, why and when. *Radiol Clin North Am* 2005; 43:693.
121. Anmad J, Raikin SM: Current concepts review: Talar fractures. *Foot Ankle Int* 2006; 27:475.
122. Berkowitz MJ, Kim DH: Process and tubercle fractures of the hindfoot. *J Am Acad Orthop Surg* 2005; 13:492.
123. Chan GM, Yoshida D: Fracture of the lateral process of the talus associated with snowboarding. *Ann Emerg Med* 2003; 41:854.
124. Vallier HA, Nork SE, Barei DP, Benirschke SK, Sangeorzan BJ: Talar neck fractures: Results and outcomes. *J Bone Joint Surg Am* 2004; 86:1616.
125. Abrahams TG, Gallup L, Avery FL: Nondisplaced shearing-type talar body fractures. *Ann Emerg Med* 1994; 23:891.
126. Horst F, Gilbert BJ, Nunley JA: Avascular necrosis of the talus: Current treatment options. *Foot Ankle Clin* 2004; 9:757.
127. Schachter AK, Chen AL, Reddy PD, Tejwani NC: Osteochondral lesions of the talus. *J Am Acad Orthop Surg* 2005; 13:152.
128. O'Loughlin PF, Heyworth BE, Kennedy JG: Current concepts in the diagnosis and treatment of osteochondral lesions of the ankle. *Am J Sports Med* 2010; 38:392.
129. Frost A, Roach R: Osteochondral injuries of the foot and ankle. *Sports Med Arthrosc* 2009; 17:187.
130. Naran KN, Zoga AC: Osteochondral lesions about the ankle. *Radiol Clin North Am* 2008; 46:995.
131. Stroud CC, Marks RM: Imaging of osteochondral lesions of the talus. *Foot Ankle Clin* 2000; 5:119.
132. van Dijk CN, Reilingh ML, Zengerink M, van Bergen CJ: The natural history of osteochondral lesions in the ankle. *Instr Course Lect* 2010; 59:375.
133. Kelberine F, Frank A: Arthroscopic treatment of osteochondral lesions of the talar dome: A retrospective study of 48 cases. *Arthroscopy* 1999; 15:77.
134. Bibbo C, Anderson RB, Davis WH: Injury characteristics and the clinical outcome of subtalar dislocations: A clinical and radiographic analysis of 25 cases. *Foot Ankle Int* 2003; 24:158.
135. de Palma L, Santucci A, Marinelli M, Borgogno E, Catalani A: Clinical outcome of closed isolated subtalar dislocations. *Arch Orthop Trauma Surg* 2008; 128:593.
136. Wagner R, Blattert TR, Weckbach A: Talar dislocations. *Injury* 2004; 35(Suppl 2):SB36.
137. Daftary A, Haims AH, Baumgaertner MR: Fractures of the calcaneus: A review with emphasis on CT. *Radiographics* 2005; 25:1215.
138. Hess M, Booth B, Laughlin RT: Calcaneal avulsion fractures: Complications from delayed treatment. *Am J Emerg Med* 2008; 26:254e1.
139. Hodge JC: Anterior process fracture or calcaneus secundarius: A case report. *J Emerg Med* 1999; 17:305.
140. Maskill JD, Bohay DR, Anderson JG: Calcaneus fractures: A review article. *Foot Ankle Clin* 2005; 10:463.
141. Ibrahim T, et al: Displaced intra-articular calcaneal fractures: 15-year follow-up of a randomised controlled trial of conservative versus operative treatment. *Injury* 2007; 38:848.
142. Knight JR, Gross EA, Bradley GH, Bay C, LoVecchio F: Boehler's angle and the critical angle of Gissane are of limited use in diagnosing calcaneus fracture in the ED. *Am J Emerg Med* 2006; 24:423.
143. Brian PL, Mahraj RP: Imaging of the calcaneus. *Foot Ankle Clin* 2005; 10:443.
144. Swanson SA, Clare MP, Sanders RW: Management of intra-articular fractures of the calcaneus. *Foot Ankle Clin* 2008; 13:659.
145. Germann CA, Perron AD, Miller MD, Powell SM, Brady WJ: Orthopedic pitfalls in the ED: Calcaneal fractures. *Am J Emerg Med* 2004; 22:607.
146. Pinney SJ, Sangeorzan BJ: Fractures of the tarsal bones. *Orthop Clin North Am* 2001; 32:21.
147. Mengiardi B, Pfirrmann CW, Zanetti M: MR imaging of tendons and ligaments of the midfoot. *Semin Musculoskelet Radiol* 2005; 9:187.
148. Swords MP, Schramski M, Switzer K, Nemec S: Chopart fractures and dislocations. *Foot Ankle Clin* 2008; 13:679.
149. DiGiovanni CW: Fractures of the navicular. *Foot Ankle Clin* 2004; 9:25.
150. Ceroni D, De Rosa V, De Coulon G, Kaelin A: Cuboid nutcracker fracture due to horseback riding in children: Case series and review of the literature. *J Pediatr Orthop* 2007; 27:557.
151. Mihalich RM, Early JS: Management of cuboid crush injuries. *Foot Ankle Clin* 2006; 11:121.
152. Reid JJ, Early JS: *Fractures and dislocations of the midfoot and forefoot*. In: Bucholz RW, Court-Brown CM, Heckman JD Tornetta P, eds. *Rockwood and Green's Fractures in Adults*, 7th ed. Philadelphia: Wolters Kluwer Health/Lippincott, Williams & Wilkins; 2010:2110-2174.
153. Chiodo CP, Myerson MS: Developments and advances in the diagnosis and treatment of injuries to the tarsometatarsal joint. *Orthop Clin North Am* 2001; 32:11.
154. Desmond EA, Chou LB: Current concepts review: Lisfranc injuries. *Foot Ankle Int* 2006; 27:653.
155. Hunt SA, Ropiak C, Tejwani NC: Lisfranc joint injuries: Diagnosis and treatment. *Am J Orthop* 2006; 35:376.
156. Saab M: Lisfranc fracture-dislocation: An easily overlooked injury in the emergency department. *Eur J Emerg Med* 2005; 12:143.
157. Perron AD, Brady WJ, Keats TE: Orthopedic pitfalls in the ED: Lisfranc fracture-dislocation. *Am J Emerg Med* 2001; 19:71.
158. Sherief TI, Mucci B, Greiss M: Lifranc injury: How frequently does it get missed? And how can we improve? *Injury* 2007; 38:856.
159. Germann CA, Perron AD: Risk management and avoiding legal pitfalls in the emergency treatment of high-risk orthopedic injuries. *Emerg Med Clin North Am* 2010; 28:969.
160. Arntz CT, Veith RG, Hansen ST: Fractures and fracture-dislocations of the tarsometatarsal joint. *J Bone Joint Sur Am* 1988; 70:173.
161. Gupta RT, Wadhwa RP, Learch TJ, Herwick SM: Lisfranc injury: Imaging findings for this important but often-missed diagnosis. *Curr Probl Diagn Radiol* 2008; 37:115.
162. Raikin SM: Prediction of midfoot instability in the subtle Lisfranc injury. Comparison of magnetic resonance imaging with intraoperative findings. *J Bone Joint Surg Am* 2009; 91:892.
163. Philbin T, Rosenberg G, Sferra JJ: Complications of missed or untreated Lisfranc injuries. *Foot Ankle Clin* 2003; 8:61.
164. Aronow MS: Treatment of the missed Lisfranc injury. *Foot Ankle Clin* 2006; 11:127.
165. Hatch RL, Alsobrok JA, Clugston JR: Diagnosis and management of metatarsal fractures. *Am Fam Physician* 2007; 76:817.
166. Fetzer GB, Wright RW: Metatarsal shaft fractures and fractures of the proximal fifth metatarsal. *Clin Sports Med* 2006; 25:139.
167. Rammelt S, Heineck J, Zwipp H: Metatarsal fractures. *Injury* 2004; 35(Suppl 2):SB77-SB86.
168. Vorlat P, Achtergael W, Haentjens P: Predictors of outcome of non-displaced fractures of the base of the fifth metatarsal. *Int Orthop* 2007; 31:5.
169. Chuckpaiwong B, Queen RM, Easley ME, Nunley JA: Distinguishing Jones and proximal diaphyseal fractures of the fifth metatarsal. *Clin Orthop Relat Res* 2008; 466:1966.
170. Richli WR, Rosenthal DI: Avulsion fracture of the fifth metatarsal: Experimental study of pathomechanics, *AJR Am J Roentgenol* 1984; 143:889.
171. Mologne TS, Lundeen JM, Clapper MF, O'Brien TJ: Early screw fixation versus casting in the treatment of acute Jones fractures. *Am J Sports Med* 2005; 33:970.
172. Schnaue-Constantouris EM, Birrer RB, Grisafi PJ, Dellacorte MP: Digital foot trauma: Emergency diagnosis and treatment. *J Emerg Med* 2001; 22:163.
173. Smith GD, Hart RG, Wolff TW: Slipper cast management of emergency foot problems. *Am J Emerg Med* 2004; 23:343.
174. Vilke GM: Great toe pain. *J Emerg Med* 2003; 24:59.
175. Lutter LD: Hindfoot problems. *Instr Course Lect* 1993; 42:195.
176. Karr SD: Subcalcaneal heel pain. *Orthop Clin North Am* 1994; 25:161.
177. Cullen NP, Singh D: Plantar fasciitis: A review. *Br J Hosp Med* 2006; 67:72.
178. Wearing SC, Smeathers JE, Urry SR, Hennig EM, Hills AP: The pathomechanics of plantar fasciitis. *Sports Med* 2006; 36:585.
179. Rompe JD, Furia J, Weil L, Maffulli N: Shock wave therapy for chronic plantar fasciopathy. *Br Med Bull* 2007; 183:81-82.
180. Kinoshita M, Okuda R, Yasuda T, Abe Mi: Tarsal tunnel syndrome in athletes. *Am J Sports Med* 2006; 34:1307.
181. Wu KK: Morton neuroma and metatarsalgia. *Curr Opin Rheumatol* 2000; 12:131.
182. Thompson CE, Gibson JN, Martin D: Interventions for the treatment of Morton's neuroma. *Cochrane Database Syst Rev* 2004; 3:CD003118.
183. Bos AM, van Tilburg MW, van Sorge AA, Klinkenbijl JH: Randomized trial of surgical technique and local antibiotics for ingrowing toenail. *Br J Surg* 2007; 94:292.
184. Harrast MA, Colonno D: Stress fractures in runners. *Clin Sports Med* 2010; 29:399.
185. Zeni AI, Street CC, Dempsey RL, Staton M: Stress injury to bone among women athletes. *Phys Med Rehabil Clin N Am* 2000; 11:929.

www.ketabpezeshki.com 66485457-66963820

186. Gehrmann RM, Renard RL: Current concepts review: Stress fractures of the foot. *Foot Ankle Int* 2006; 27:750.
187. Feingold D, Hame SL: Female athlete triad and stress fractures. *Orthop Clin North Am* 2006; 37:575.
188. McGee DL, Dalsey WC: The mangled extremity: Compartment syndrome and amputations. *Emerg Med Clin North Am* 1992; 10:783.
189. Oakes R, Urban A, Levy PD: The mangled extremity. *J Emerg Med* 2008; 35:437.
190. Cannada L: The mangled extremity: Limb salvage vs. amputation. *Curr Surg* 2005; 62:563.
191. Tarkin IS, Sop A, Pape HC: High-energy foot and ankle trauma: Principles for formulating an individualized care plan. *Foot Ankle Clin* 2008; 13:705.
192. Maurel B, Brilhault J, Martinez R, Lermusiaux P: Compartment syndrome with food ischemia after inversion injury of the ankle. *J Vasc Surg* 2007; 46:369.
193. Fulkerson E, Razi A, Tejwani N: Review: Acute compartment syndrome of the foot. *Foot Ankle Int* 2003; 24:180.
194. Richter J, Schulze W, Klaas A, Clasbrummel B, Muhr G: Compartment syndrome of the foot: An experimental approach to pressure measurement and release. *Arch Orthop Trauma Surg* 2008; 128:199.

www.ketabpezeshki.com 66485457-66963820

Section Four

SOFT TISSUE INJURIES

Chapter 59

Wound Management Principles

Barry C. Simon and H. Gene Hern, Jr.

PERSPECTIVE

The goals of emergency wound treatment are to restore function, repair tissue integrity with strength and optimal cosmetic appearance, and minimize risk of infection. Risk of infection depends on the location, mechanism, host, and care. The risk for a clean facial wound produced by incision is less than 1%, whereas a dirty crush injury to the lower extremity may have more than a 20% risk. Wound infection generally results in delayed healing, decreased strength, and a poor cosmetic result. These facts highlight the need for high-quality wound care. Understanding the biology of wound healing and the technical aspects of wound treatment facilitates emergency management of these patients.

Emergency physicians must also be aware of the medicolegal risk associated with soft tissue injuries. Including injuries to the hand, wound-related complaints are the fourth most common cause of malpractice claims against emergency physicians. Missed foreign body, wound infection, and missed tendon or nerve injury are the most common complications leading to these claims.

PRINCIPLES OF DISEASE

Anatomy of Skin and Fascia

An understanding of skin anatomy leads to better appreciation of wound closure concepts and techniques. The skin is a complex organ that protects the body against bacterial invasion and ensures thermoregulation. The skin also helps to regulate water content and register sensory stimuli.

The skin and fascia vary in thickness from 1 to 4 mm, depending on the part of the body. The epidermis, the outermost layer, is several cell layers thick. The most important parts of the epidermis are the stratum germinativum (basal layer), where new cells originate, and the stratum corneum, the outermost cell layer that gives the skin its cosmetic appearance. The layer of skin directly beneath the epidermis is the dermis. The much thicker dermis is primarily composed of connective tissue. The dermis is the key layer for the ultimate healing of skin wounds. Optimal healing and minimal scar formation depend on the removal of debris and devitalized tissue from the dermis. The dermis also functions to anchor sutures placed percutaneously or subcutaneously.[1]

The superficial fascia lies directly beneath the dermis and encloses the subcutaneous fat. This space must be irrigated and débrided to decrease the risk of infection. The deep fascia lies beneath the fat and is a strong, off-white sheath that covers and protects the underlying muscles and helps prevent superficial infection from spreading to deeper tissues. The deep fascia must be closed to maintain its protective and functional roles.

Wound Biology

Normal wound healing is a well-choreographed sequence of biologic events. It is described as an orderly process, but it actually represents multiple phenomena that seem to occur simultaneously. These events include coagulation, inflammation, collagen metabolism, wound contraction, and epithelialization.[1,2] Maintaining the balance of these events is crucial for normal healing. Delaying any of the stages may result in a weak closure and dehiscence. Prolonging segments of the process may affect the ultimate scar appearance.

Soon after tissue integrity is altered, the process of coagulation begins. Platelet release factors initiate and enhance a response from inflammatory cells. Capillary permeability increases to allow white blood cells to migrate into the wound. Neutrophils and monocytes act as scavengers to rid the wound of debris and bacteria. Monocytes transform into macrophages, which seem to have a major role in subsequent healing phenomena. In addition to providing wound defense, macrophages release chemotactic substances, calling on other monocytes to stimulate fibroblast replication and trigger neovascularization.[1]

Collagen is the principal structural protein of most tissues of the body. Normal tissue repair depends on collagen synthesis, deposition, and cross-linking. Fibroblasts synthesize and deposit collagen compounds 48 hours after injury. Immature collagen is highly disorganized because it has a gel-like consistency.

After a series of enzymatic processes, characteristic fibrils are produced. Subsequent intermolecular cross-links are responsible for a major portion of the strength of the collagen fibril. The entire process depends on tissue lactate and ascorbic acid and is directly related to tissue arterial carbon dioxide partial pressure. In the absence of vitamin C, prolyl and lysyl hydroxylase do not activate, and oxygen is not transferred to proline or lysine. Underhydroxylated collagen is produced, and characteristic collagen fibers are unable to form. Wound healing is poor, and capillaries are fragile. Without oxygen to hydroxylate proline and lysine, a local condition resembling scurvy tends to occur.

Under normal conditions, collagen synthesis peaks by day 7, coincident with rapid increases in tensile strength. The healing wound has the greatest mass at 3 weeks but remodels itself during the next 6 to 12 months. However, the wound achieves less than 15 to 20% of its ultimate strength by 3 weeks and only 60% by 4 months.[3]

Wound contraction is the movement of whole-thickness skin toward the center of the skin defect. Immediately after injury, the wound edges retract and increase the size of the defect. Normal skin tension along the lines of minimal tension produces this retraction (Figs. 59-1 and 59-2). Wounds perpendicular to these lines are under greater tension and result in a larger scar.[1,4]

www.ketabpezeshki.com 66485457-66963820

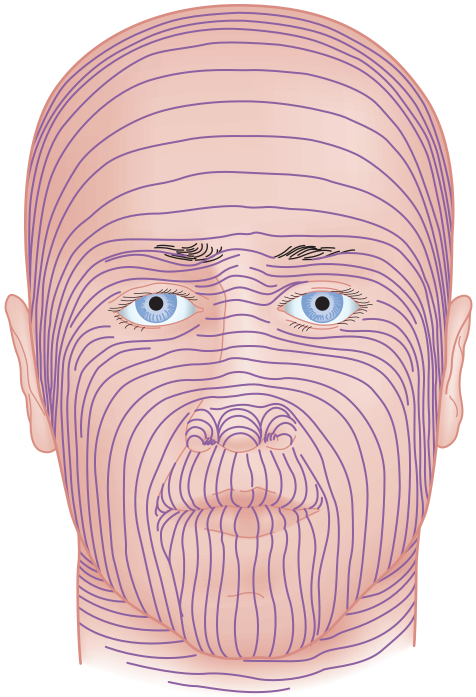


Figure 59-1. Skin tension lines of the face. Incisions or lacerations parallel to these lines are less likely to create widened scars than those that are perpendicular to these lines. (Adapted from Simon R, Brenner B: Procedures and Techniques in Emergency Medicine. Baltimore, Williams & Wilkins, 1982; as published in Trott A: Wounds and Lacerations: Emergency Care and Closure, 2nd ed. St. Louis, Mosby, 1997.)

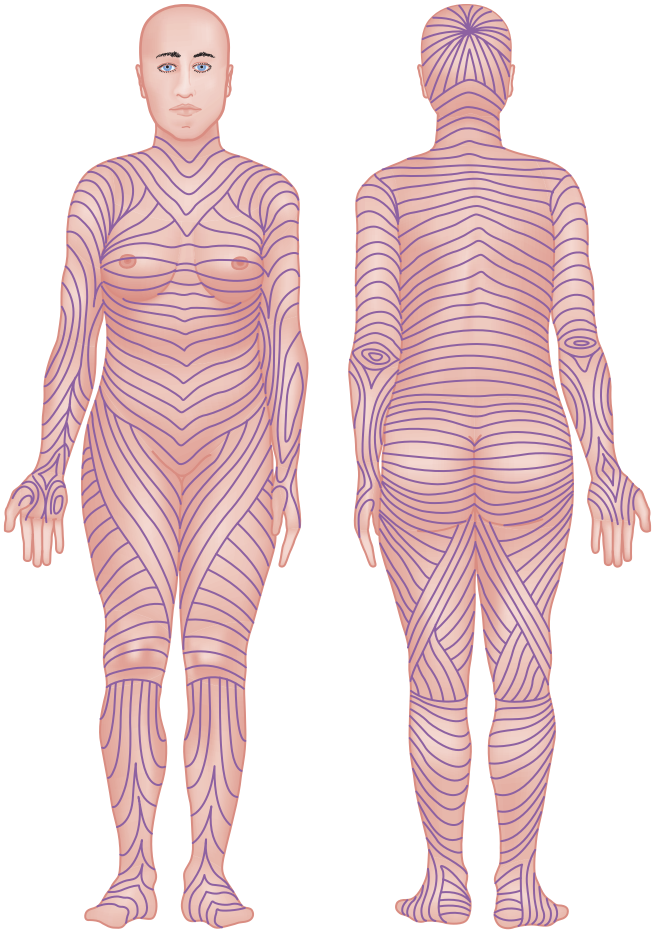


Figure 59-2. Skin tension lines of the body surface. (Adapted from Simon R, Brenner B: Procedures and Techniques in Emergency Medicine. Baltimore: Williams & Wilkins, 1982; as published in Trott A: Wounds and Lacerations: Emergency Care and Closure, 2nd ed. St. Louis, Mosby, 1997.)

During the next 3 or 4 days, the wound size shrinks as its edges move toward the center. This phenomenon is independent of epithelialization, and the presence of collagen is not necessary for it to occur. This process is considered beneficial to healing and should not be confused with contracture that results from scar shortening.[1,3]

Contracture becomes more apparent when the normal healing process is prolonged. The effect is a disfiguring hypertrophic scar. Optimizing the duration of the inflammatory phase and minimizing wound tension help to produce a more "appealing" scar.

Epithelialization is a mechanism in the healing process whereby epithelial cells migrate across the wound. Mitosis appears at the wound edge near the basal cell layer within hours of injury. Eschar or other debris impedes this process. When a wound is properly cleansed and débrided and kept moist and protected, epithelialization proceeds at a maximum rate.[3]

In a surgically repaired laceration, epithelialization bridges the defect by 48 hours. The new tissue proceeds to thicken and grow downward, beginning to resemble the layered structural characteristics of uninjured epidermis within 5 days. Simultaneously, keratin formation loosens the overlying scab.

Biomechanical Properties of Skin

Various forces (lines of tension) exist as a result of skin elasticity from collagen fibers. These static forces may vary more than fivefold with the respective area of body skin surface, but the static tension of a given area of skin remains constant. These static forces are shown clinically by the gaping of wounds after incision. The magnitude of static skin tension is directly related to ultimate scar width.[1,4]

Uneven, jagged wounds have greater surface area than do linear lacerations. The skin tension is distributed over a greater area and is less per unit length of tissue. Meticulous reapproximation of the jagged edges results in a more appealing scar. Sharp débridement, converting a jagged wound to a linear laceration, is often unwise because it may cause too much tissue loss and produce a wider, more visible scar.[4]

Skin forces produced by muscular contraction and movements of flexion and extension influence healing and scar size. These dynamic forces are greatest where skin elasticity is necessary for function. Lacerations parallel to skin folds, lines of expression, and joints do not impair function or produce unattractive scars. Wounds that traverse the skin lines heal with conspicuous scars and may impair function.[4] Knowledge of these lines and forces is necessary for optimal wound repair. In addition, the patient should be educated about wound healing and scarring potential.

CLINICAL FEATURES AND DIAGNOSTIC STRATEGIES

History

A detailed history should be obtained as part of routine wound evaluation. Serious complications can result when basic information is not obtained. If the patient has significant peripheral vascular disease, is immunocompromised, or has a high risk of a retained foreign body, wound care decisions may be changed. Essential historical information includes medical history, mechanism and setting of injury, and tetanus status.

www.ketabpezeshki.com 66485457-66963820

Box 59-1 Risk Factors for Wound Infection

1. Injury more than 8-12 hours old (varies depending on the following factors)
2. Location: leg and thigh, then arms, then feet, then chest, then back, then face, then scalp
3. Contamination with devitalized tissue, foreign matter, saliva, or stool
4. Blunt (crush) mechanism
5. Presence of subcutaneous sutures
6. Type of repair: risk greatest with sutures > staples > tape
7. Anesthesia with epinephrine
8. High-velocity missile injuries

Risk Factors

Risk factors for wound morbidity include prolonged time since injury; crush mechanism; deep wounds; age of the patient; high-velocity missiles; and contamination with saliva, feces, soil, or other foreign matter (Box 59-1).[1,4,5] Three hours after acute trauma, bacteria proliferate to a level that may result in infection. Standard wound care guidelines for the routine wound recommend closure within 8 to 12 hours of injury. Yet all risk factors must be considered before specific timeline guidelines are adopted, and flexibility is required. Lacerations produced by fine cutting forces resist infection better than crush injuries. Reduction of blood flow to wound edges in the latter may increase the infective concentration of bacteria by 100-fold.[4] High-velocity missile injuries produce damage remote from the missile tract. The extent of injury may not be apparent for several days. Clean, finely cut lacerations on the face may be safely closed in some patients 24 or more hours after injury, whereas blunt lacerations to the leg or thigh may be treated with delayed primary closure as early as 4 to 6 hours after injury. For sutured wounds, location appears to have the strongest association with infection. Lacerations repaired on the leg and thigh may have an infection rate greater than 20%, those on the torso and other extremities greater than 10%, and those on the face and scalp less than 4%.[5]

Wounds contaminated by foreign matter are at high risk of infection, despite adequate therapeutic intervention. Saliva and feces are composed of a concentration of bacteria (approximately 10^{11} per gram wet weight) that greatly exceeds the numbers needed to produce infection ($\geq 10^6$ bacteria per gram tissue).[4]

The presence of any foreign matter in the wound decreases resistance to infection. Soil fractions, which include organic components and inorganic clay particles, damage host defenses with adverse interactions between charged soil particles and white blood cells. The presence of these soil fractions greatly increases the infective potential of bacteria.[4]

Optimal physical assessment of wounds requires patience, diligence, and an organized approach. Wound closure decisions are individualized for each laceration. Sharp, clean lacerations of the face may be safe to close up to 24 hours after the time of injury, whereas highly contaminated blunt injuries to the feet should never be closed primarily. When the distal neurovascular evaluation is completed, the examination may proceed. All of these risk factors have to do with the injury, but there are three additional areas of concern: (1) immunocompetence of the host, (2) physical characteristics of the host (e.g., peripheral vascular disease), and (3) structural defects that invite bacterial seeding (e.g., damaged or prosthetic heart valves).

Physical Examination

Physical examination errors are minimized with optimal visualization and anesthesia. When the injury occurs on an extremity, use of a sphygmomanometer may help to ensure a bloodless field. The blood pressure cuff is placed proximal to the injury, and the extremity is elevated above the heart for at least 1 minute. Exsanguinating the extremity may be hastened by wrapping the limb tightly with an Ace bandage, beginning distally and ending at the base of the cuff. The sphygmomanometer is inflated to a pressure greater than the systolic pressure of the patient. Although this process causes the patient significant discomfort after 1 minute, the cuff can safely remain inflated for 2 hours. A peripheral nerve block or Bier block should be used if inflation longer than several minutes is contemplated.

A thorough examination of the wound requires that the tissues be adequately anesthetized. Subcutaneous tissues quickly reapproximate after injury, giving the appearance of a shallow wound. In addition, significant subcutaneous swelling lends to this appearance and renders examination of the laceration more difficult, as in wounds of the scalp and face. Careful probing and examination are needed to avoid missing damage to structures deep to the skin and subcutaneous tissue. This warning is more crucial for wounds on the distal aspects of upper and lower extremities. Finger lacerations are rarely gaping, but crucial structures (e.g., tendons, nerves, and vessels) are often damaged. The examiner must pry the wound margins apart, ensure a blood-free field, and examine the tissues as the digit or extremity is placed through range of motion. The injured section of tendon may have been in a different state of tension and in a more proximal or distal location at the time of injury. Wounds that cannot be explored adequately and wounds with probable trauma to underlying tissues or with foreign matter require additional studies. It may be appropriate to extend the laceration to enable improved visualization of wound depth and extent.

Sterile gloves may not be a necessary part of wound closure. Although data are limited, one study found that the use of sterile gloves makes no difference with respect to the incidence of infection.[6] However, clean nonsterile gloves should be worn to offer some protection for both the patient and the provider.

Foreign Body Assessment

No single method can guarantee the identification and removal of all foreign matter from wounds. The key is to document all efforts and to explain to the patient the possibility of a foreign body. Physical examination with wound exploration will discover about 78% of foreign bodies; plain radiography will detect glass foreign bodies in about 75% of cases, metal in 99%, and wood in 7%.[7] Good follow-up can protect the patient as well as the health care provider.

Attempts to visualize foreign matter by standard radiography are not as helpful as might be expected. The radiodensity of an object depends on the relative density of the matter and the adjacent tissue. Pieces of glass greater than 1 mm thick are visible when appropriate views are ordered.[8] Many organic substances, such as wood, are not visible on plain films, but specifically requested soft tissue views may increase the yield. A radiolucent shadow may be seen on close inspection because the foreign substance displaces tissue in its path. Xerograms are better than plain radiography but still miss some plastics and organic matter. A computed tomography (CT) scan is excellent for identifying all foreign substances but is expensive and results in significant exposure to radiation. Ultrasonography is a good technique, but the small size of many foreign bodies and pockets of air, edema, pus, and some calcifications may produce confusing echoes, limiting its clinical usefulness.[9,10] When simpler, standard methods fail to locate a foreign body that is likely or definitely present, ultrasonography or a CT scan should be considered.

www.ketabpezeshki.com 66485457-66963820

MANAGEMENT

Anesthesia

After an appropriate neurovascular examination is documented, the involved tissue should be anesthetized. Careful physical examination and thorough cleansing, irrigation, and débridement require that the patient be free of pain. Regional anesthesia may be preferable for wounds innervated by one superficial nerve. Injections at the wound site produce swelling and further distortion of landmarks. With a regional block, more than one laceration may be repaired in the same nerve distribution without additional anesthesia. Lacerations on the face, hands, fingers, feet, and toes and in the mouth are often well suited for regional anesthesia.

Anesthetic Agents

Lidocaine (Xylocaine) is the most common agent used for local and regional anesthesia.[11] It is safe and fast acting. Onset of action for direct infiltration occurs within seconds, and effects last 20 to 60 minutes. When lidocaine is administered as a regional nerve block, onset occurs in 4 to 6 minutes and the effects generally last 75 minutes, although the block may remain effective for 120 minutes. A 1% lidocaine solution contains 10 mg/mL. It is safe to use 3 to 5 mg/kg, not exceeding 300 mg at a single injection. More volume can be added safely every 30 minutes. When epinephrine is added, the resulting vasoconstriction prolongs the effect for 2 to 6 hours, and the safe dose is increased to 5 to 7 mg/kg. However, the addition of epinephrine has been shown to delay healing and lower resistance to infection. Lidocaine with epinephrine should be avoided in wounds with higher risks of infection and when tissue viability is of concern.[12] Traditional teaching has been to avoid epinephrine in the fingers and toes because of the risk of vasoconstriction in small arterioles. However, recent literature suggests that with careful screening epinephrine can be safely used in digital blocks. Digital artery vasospasm, accidentally induced by local injection of epinephrine, can be reversed successfully with a local injection of 0.5 to 2 mg of subcutaneous phentolamine or application of topical nitroglycerin.[13]

Bupivacaine (Marcaine) provides anesthesia that is equal to that of lidocaine. Onset of action is slightly slower than that of lidocaine, but the duration of anesthesia is four to eight times longer.[14] These benefits suggest that bupivacaine is the preferred local anesthetic agent for the care of most wounds. In adults the maximal reported safe dose is approximately 2.5 mg/kg without epinephrine and 3.5 mg/kg with epinephrine.[1] The dose can be repeated every 3 hours, not exceeding a total of more than 400 mg in a 24-hour period. The maximal intraoral dose is 90 mg.

Local injection of lidocaine should be done with a 27-gauge needle; the slower the injection, the less pain produced.[1] The rate of injection through a 30-gauge needle is far too slow, and the thin needle is difficult to control. A 25-gauge needle is acceptable, but the more rapid injection can result in greater patient discomfort. The needle should be introduced through the cut margin to minimize the pain of the injection. Concerns of spreading bacteria into the adjacent uninvolved tissue and increasing the frequency and severity of wound infections are unfounded. The pain of injecting lidocaine can be ameliorated with the addition of bicarbonate to buffer the solution.[15] The shelf life of the lidocaine-bicarbonate mixture decreases, but it remains effective for 1 week at room temperature and for 2 weeks if refrigerated. Adding sodium bicarbonate in a 1 : 10 volume ratio to lidocaine (1 mL bicarbonate and 10 mL lidocaine) decreases the pain of injection without compromising the quality of anesthesia. A much smaller dose of bicarbonate is added to bupivacaine because the alkalinization results in precipitation. A 1 : 100 volume ratio (0.1 mL of bicarbonate and 10 mL of bupivacaine) has been found to be effective.[16] Warming the anesthetic solution is also an effective means of decreasing the pain of injection.[17]

Topical anesthesia may be an effective painless alternative. Studies show that a combination of tetracaine, adrenaline (epinephrine), and cocaine (TAC) (0.5% tetracaine, 1 : 2000 adrenaline, and 11.8% cocaine) can function effectively on skin lacerations. The solution is administered by soaking a cotton ball with 5 mL of the combined drugs (25 mg of tetracaine, 25 mg of adrenaline, and 590 mg of cocaine) and applying it to the wound for 10 to 20 minutes. TAC is similar to infiltrative lidocaine in all respects, including risk of complications. It is more effective on the face and scalp than on extremities.[18] Data suggest that half-strength TAC solution is effective and may reduce the potential for toxicity.[19] The tetracaine component may be superfluous and can be eliminated without compromising the quality of anesthesia.[20] With use of a topical combination, time to repair is reduced, patient acceptance improves, and landmarks are left undisturbed. Although experimental studies show that TAC increases the infection rate in contaminated wounds, this is not the case with routine wound care.[12] The proven benefits and enhanced patient compliance, especially in pediatric patients, make TAC an excellent medication to use alone or in conjunction with another local anesthetic. The potential toxicity from TAC has been documented by (1) measurable plasma cocaine levels[21] and (2) a case report of a child's death from exposure to TAC.[22] The child's wound was on the upper lip between the vermilion border and the nares. The solution apparently dripped onto the nasal and oral mucosa, increasing the systemic absorption of the drugs. Until further studies are done, TAC should be avoided in the repair of highly contaminated wounds and in lacerations near mucous membranes. In children, a half-strength solution can be used to reduce potential toxicity.

The potential serious adverse effects of TAC have led to the increasing use of other topically applied anesthetic combinations. A mixture of lidocaine (1-4%), epinephrine (1 : 1000 to 1 : 2000), and tetracaine (0.5-2%) has been used successfully in place of TAC. This mixture avoids the untoward side effects of cocaine.[23] EMLA (eutectic mixture of local anesthetics) is a cream used to produce anesthesia of wounds. Although the onset of anesthesia is longer than for the other mixtures (1 hour vs. approximately 30 minutes), one study showed that the need for supplemental local anesthesia was reduced.[24] Because the time to onset is greatly delayed with EMLA, its usefulness may vary with emergency department patient volume.

A newer technique that uses topical anesthesia in a progressively layered approach appears to be safe and effective.[25] Although time to anesthesia was significantly longer (a mean of 29 minutes compared with 5 minutes), efficacy was equivalent. Patient satisfaction was much greater with the layered topical approach, and the elimination of the risk of a hollow-bore needle puncture is a major benefit.

Allergy

Allergy to local anesthetics is uncommon. Two distinct groups of "caine" anesthetics exist. The esters include procaine, tetracaine, and benzocaine. The second group, including lidocaine and bupivacaine, belong to the amide family. Allergy to the esters is uncommon. True allergy to agents in the amide family is rare. Good history taking is the best way to document a true allergic reaction.[26] Many patients labeled as allergic have experienced uncomfortable drug effects or autonomic responses to the pain and the overall setting.

The subject of allergy is complicated further because multidose vials contain the preservative methylparaben, an ester related structurally to anesthetics in the ester family. Apparent allergic

www.ketabpezeshki.com 66485457-66963820

reaction to lidocaine or bupivacaine may be a reaction to the methylparaben. Cardiac lidocaine does not contain preservatives, is a standard drug in the emergency department, and can be used for wound anesthesia when there is concern about potential allergic reactions.

When allergy to a local anesthetic is known or strongly suspected, alternatives are available. No cross-reactivity occurs between the amide and ester families, so an agent from a different group may be chosen. Single-dose vials of lidocaine or cardiac lidocaine are not mixed with methylparaben and may be used.[27] A test dose of 0.1 mL may be administered intradermally before proceeding. The patient should be observed for 30 minutes, and as with any allergy testing, the emergency physician should be prepared to treat all complications. Aqueous diphenhydramine (1%) has also been shown to provide effective local anesthesia.[28]

Skin Preparation

Disinfection of the skin (not the wound itself) may be accomplished with several different agents. The ideal agent is fast acting, has a broad spectrum of antimicrobial activity, and has a long shelf life. Povidone-iodine (Betadine) and chlorhexidine (Hibiclens) have all three characteristics. Although excellent as skin disinfectants, both products are toxic to wound defenses and may increase the incidence of wound infection. Povidone-iodine is effective against gram-positive and gram-negative bacteria, fungi, and viruses. Chlorhexidine is less effective against gram-negative bacteria, and its efficacy against viruses is unknown. Care must be taken to avoid spilling these substances into the wound. Exposure of the eye to these agents can be disastrous. Chlorhexidine has been shown experimentally and in case reports to produce serious permanent corneal opacification.[29]

Body, facial, and head hair is usually removed to clean and examine the wound, although this is not necessary to diminish the risk of wound infection. Removal of the hair makes it easier for the patient to keep the area clean and ultimately facilitates accurate suture placement and removal. Exceptions are parts of the body where hairlines provide important landmarks for the accurate reapproximation of tissue margins, most notably the eyebrow. Reports of inconsistent or absent eyebrow hair regrowth suggest that eyebrow hair should not be shaved.

Surgical studies show that hair removal with a razor is three to nine times more likely to result in a wound infection than is clipping the hair. It seems that the razor damages the infundibulum of the hair follicle.[30] The wounded follicle provides access for bacterial invasion and ultimately infection. For wounds considered to be at high risk of infection, clipping may be done with electronic shears or scissors because close shaving is not necessary. Another option is to apply a petroleum-based product to the hair adjacent to the wound margins, allowing the provider to keep the hair away from the surgical field.

Wound Preparation

Débridement

Débridement is the removal of foreign matter and devitalized tissue from the wound. With respect to ultimate wound healing and risk of infection, débridement is the most important consideration in wound care.[31] The presence of any devitalized tissue in the wound delays healing and significantly increases the risk of infection. However, the benefits of débridement have to be weighed against the consequences of producing a larger tissue defect. The resultant closure is exposed to higher tension and may result in a wider scar. Skin edges that are clearly devitalized are débrided before wound closure. On the trunk, where there is little concern for specialized tissue, wide excision and débridement are feasible. On the face and hands, where all tissue must be saved if possible, the process is more difficult. Meticulous sharp excision of small fragments of nonviable tissue should be performed only by experienced physicians. When the viability of large areas of skin or muscle is a significant concern, the wound should be prepared for delayed primary closure.

Wound Cleansing

An ideal wound cleanser has broad antimicrobial activity with a rapid onset. It is nontoxic to the tissue and does not reduce tissue resistance to infection, delay healing, or decrease the tensile strength of the healing wound. Many antiseptic solutions have been used clinically and studied in great detail (Table 59-1). Much debate exists regarding which agent comes closest to possessing these qualities. Povidone-iodine in various concentrations, saline, and, more recently, tap water have received the most attention.[32-34]

Evidence suggests that a 0.9% normal saline solution or tap water are effective irrigants when used with high-pressure syringe irrigation.[35,36] Saline is the traditional wound-irrigating fluid of choice. However, tap water has consistently produced equivalent rates of infection and cosmetic outcomes. Tap-water irrigation allows a large volume of irrigation rapidly and inexpensively and is especially suited to upper extremity and scalp injuries.

Free iodine, although possessing broad, rapid antimicrobial activity, is too toxic to tissue and its defenses to have therapeutic value in the open wound. An iodophor is a complex of iodine with a carrier to increase its solubility and decrease the availability of free iodine. The most widely used iodophor is povidone-iodine, in which the carrier molecule is povidone (formerly polyvinylpyrrolidone). It is generally available in a 10% solution, which is 1% free iodine. The clinical benefit of this complex is a solution that maintains broad antimicrobial activity and eliminates most local and systemic toxicity. It is well documented that even a 5% povidone-iodine solution is toxic to polymorphonuclear neutrophil leukocyte activity and may increase the infection rate. A 1% solution is safe and effective with little or no toxicity.[29,34] Detergent-containing cleansers, such as povidone-iodine scrub, may be excellent for skin preparation but are toxic to tissue defenses and should never be allowed to contaminate open wounds.

Although many different irrigation solutions may be beneficial, it seems that the key to cleansing is high-pressure irrigation rather than the type of solution used. Tap-water irrigation soon may become the preferred method of irrigation because it is safe, is effective, requires no preparation, and is less expensive.

Irrigation

The quality of mechanical cleansing is one of the most important determinants of wound prognosis. The most effective form of wound cleansing is high-pressure irrigation. Irrigating with pressures greater than 7 pounds per square inch (psi) significantly decreases the number of bacteria and the incidence of infection.[37,38] Although several commercial devices are available, attaching an 18-gauge needle to a 35-mL syringe yields a force of 7 or 8 psi. High pressures of 50 to 70 psi may be obtained with a commercial water pick. These pressures may cause some tissue damage, but the beneficial effect of ridding the wound of bacteria and debris outweighs this risk. Simply soaking the wound in an antiseptic solution is not beneficial and may be harmful. Scrubbing the wound with a sponge with large-pore cells inflicts tissue trauma and impairs the ability to resist infection. Tissue damage can be decreased by use of a sponge with a fine size of pore cell. Adding a surfactant further minimizes the mechanical trauma inflicted by the sponge. Flooding the wound under low pressure via a bulb syringe or gravity alone does not reduce the incidence of infection, regardless of the agent used.

www.ketabpezeshki.com 66485457-66963820

Table 59-1 Antiseptic Solutions

AGENTS	ANTIMICROBIAL ACTIVITY	MECHANISMS OF ACTION	TISSUE TOXICITY	INDICATIONS AND CONTRAINDICATIONS
Povidone-iodine solution (iodine complexes) (Betadine)	Available as a 10% solution with polyvinylpyrrolidone (povidone) containing 1% free iodine with broad rapid-onset antimicrobial activity	Potent germicide in low concentrations	Decreases PMN migration and life span at concentration >1% May cause systemic toxicity at higher concentrations; questionable toxicity at 1% concentration	Probably a safe and effective wound cleanser at a 1% concentration 10% solution is effective to prepare skin around the wound
Povidone-iodine surgical scrub	Same as the solution	Same	Toxic to open wounds	Best as a hand cleanser; never use in open wounds
Nonionic detergents Pluronic F-68 Shur-Clens	Ethylene oxide is 80% of their molecular weight No antimicrobial activity	Wound cleansers	No toxicity to open wounds, eyes, or intravenous solutions	Appear to be effective, safe wound cleansers
Hydrogen peroxide	3% solution in water has brief germicidal activity	Oxidizing agent that denatures protein	Toxic to open wounds	Should not be used on wounds after initial cleaning; may be used to clean intact skin
Hexachlorophene (polychlorinated bisphenol) (pHisoHex)	Bacteriostatic (2-5%) Greater activity against gram-positive organisms	Interruption of bacterial electron transport and disruption of membrane-bound enzymes	Little skin toxicity; the scrub form is damaging to open wounds	Never use scrub solution in open wounds Very good preoperative hand preparation
Alcohols	Low-potency antimicrobial most effective as a 70% ethyl and 70% isopropyl alcohol solution	Denatures protein	Kills irreversibly and functions as a fixative	No role in routine care
Phenols	Bacteriostatic >0.2% Bactericidal >1% Fungicidal 1.3%	Denatures protein	Extensive tissue necrosis and systemic toxicity	Never use >2% aqueous phenol or >4% phenol plus glycerol

PMN, polymorphonuclear neutrophil leukocyte.

At least one study has shown little benefit to any irrigation in facial and scalp lacerations. This study prospectively compared outcomes of almost 2000 immunocompetent patients. Infection rates and cosmetic outcomes were similar in the irrigation and the nonirrigation groups.[39]

Wound Closure

Decision-Making

The first determination required is whether the wound should be treated open or closed. Each wound, patient, and clinical circumstance must be handled individually. Certain lacerations, such as a fine linear laceration to the face, can be closed primarily 24 hours or more after injury. Other injuries may necessitate open management, regardless of the extent of delay.[40] A small study from Europe failed to show a difference in infection risk for wounds sutured more than 6 hours after injury.[40a] A large stellate laceration to the foot produced by blunt force and contaminated with dirt and grease should not be closed primarily; in addition, human and animal bites to the hand should not be closed primarily. Physician judgment is often the best method for deciding when it is safe to close a wound. In one study in which hand wounds were described as dirty, 22% became infected. When the injury was documented to be clean, the incidence of infection was 7.1%.[39]

Three wound closure options are available. The wound may be (1) closed primarily in traditional fashion, (2) closed in 4 or 5 days (delayed primary closure), or (3) left open and allowed to heal on its own. Delayed primary closure is a safe alternative to traditional primary closure.[2,40] Overall healing time is not affected, and the risk of infection is greatly decreased if proper technique is used. When a wound is slated for delayed primary closure, it is prepared, débrided, and irrigated in the same manner as for immediate closure. The wound should be packed to prevent it from closing on its own. If the wound is on an extremity, the injury should be splinted and dressed, and appropriate wound care instructions should be given. The patient should return for a wound check and packing change in 24 hours and should be instructed to follow up in another 72 hours for definitive repair, with wound closure undertaken 96 to 120 hours after injury. No studies offer guidelines for prophylactic antibiotic use when delayed primary closure is the treatment option. Extrapolation from other wound studies strongly suggests that antibiotics offer no benefit.

Individuals who do not seek medical care after an injury select the option of leaving a wound open to heal on its own. Most patients who visit an emergency department with a laceration undergo some form of wound closure. Yet one study that examined unsutured hand lacerations less than 2 cm long followed patients for 3 months and found that there was no significant difference in cosmetic appearance, and there was no difference in time to resumption of activities of daily living.[41,42]

Closing a wound loosely is occasionally discussed as an option in the treatment of contaminated wounds. This choice should rarely be considered. The loosely closed wound approximates the tissue margins enough to allow the wound to seal itself completely within 48 hours. The infection risk when this method is used is the same as when the wound is closed traditionally.

Wound Tension

The goal of wound closure is optimal anatomic and functional reapproximation of tissue with minimal risk of complication. Consideration must be given to the wound's size, shape, location,

www.ketabpezeshki.com 66485457-66963820

depth, and degree of tension. Wounds with high static and dynamic tension that require meticulous closure cannot be closed with tape or staples. Delicate approximation of wound edges under tension can be accomplished only with suture.

Several techniques may be used to reduce wound tension. Deep sutures may be placed in subcutaneous tissue to help bring the wound margins closer together. In this manner, forces on the skin are reduced, and potential dead space can be closed. Care should be taken to avoid suturing adipose tissue because it may become necrotic, increasing the likelihood of infection. The number of dermal sutures depends on the characteristics of the wound. In general, the number should be kept to a minimum because suture material acts as foreign matter in the wound and can increase the risk of infection. Subcutaneous sutures should never be placed in the hand or foot because of the major structures that reside near the surface. Another method of ameliorating static tension from cut edges of the wound is to undermine at the lacerated margin. Undermining helps free the dermis from its deeper attachments, allowing the skin edges to be approximated with less force. Care must be taken to preserve the blood supply to the wound margins and not increase dead space in the process.

Suture Technique

Careful surgical technique is important to optimize the ultimate repair. If possible, pickups, hemostats, or forceps should not be used, especially on wound margins. Blind clamping in a wound can damage a nerve, artery, or tendon. Wound margins should be everted and the sutures tied just tightly enough to allow the edges to approximate lightly. The edges can be everted by ensuring that the needle enters and exits perpendicular to the skin. Wounds with opposing margins of different thickness can be difficult to close. If this difference is not considered and corrected, the ultimate scar has uneven margins that cast a shadow on the skin and is unsightly. In closing these wounds, the needle should be pulled through the cut margin of one side before entering the opposite edge. This method gives the emergency physician the best opportunity to take an equivalent amount of tissue on both sides of the wound. Viable edges of a jagged wound must be meticulously reapproximated. Because of the greater surface area and the ultimate contraction of the wound, preserving the jagged edges results in a more "natural" scar.

Most lacerations are closed with running or interrupted percutaneous suture. The running technique is appropriate for linear lacerations under minimal tension when there is a low risk of infection. This technique is more rapid, requires less suture material, and yields equivalent cosmetic results. Curvilinear or jagged wounds are best closed with interrupted sutures to distribute tension properly. Because tensile strength of interrupted sutures may be superior, wound edges subjected to higher levels of tension should be closed with interrupted sutures.[43-45]

Basic and Advanced Techniques

Simple Sutures. Wound closure with simple interrupted sutures is the most common method of laceration repair in emergency departments. The placement of simple sutures yields excellent cosmesis and a low infection rate.

Procedure. The needle is placed to one side of the laceration margin and enters the skin at approximately 90 degrees. To pass the needle through the tissue, the clinician supinates his or her wrist and guides the needle deep but parallel to the skin surface. Wrist supination is extended as the needle exits the skin on the opposite side perpendicular to the surface. Proper technique produces wound edges that are slightly everted and are lightly touching. The art of the process takes into consideration swelling while being careful not to secure the suture too tightly because necrosis of the wound margin tissue can seriously compromise healing.

Intradermal (Buried) Sutures. Placing cutaneous sutures in wounds under tension can lead to ischemia of the wound margin and an unsightly scar. Proper placement of buried intradermal sutures helps to approximate dermal margins and reduce wound edge tension. Buried sutures should not be used in contaminated wounds because they increase the risk of wound infection. Sutures through adipose tissue also increase infection and do not relieve skin tension.

Procedure. Placement of buried sutures differs from traditional suturing because of the need to bury the knot deep to the skin. Failure to do this can interfere with dermal healing and can leave a small lump under the surface of the skin. The needle is introduced deep in the wound in the subcutaneous tissue and emerges from the dermis below the skin surface. The needle is reintroduced in the dermis on the opposite wound margin and emerges from the subcutaneous tissue at the same level on the opposite side. The knot is secured and remains buried deep below the skin surface.

Scalp Laceration Repair. In contrast to small lacerations elsewhere on the body, most scalp lacerations require repair because of the propensity to bleed profusely. The dense connective tissue beneath the skin tends to hold vessels open and delay hemostasis. Frontal scalp lacerations in young men should be considered to be a cosmetically significant wound. Although the scalp laceration currently may be well hidden by hair, most men experience some balding. Care must be taken to explore the laceration thoroughly to look for a defect in the galea, an injury that requires repair with deep sutures. Staples may be ideal for the skin closure of simple linear scalp lacerations. Hair is less of a problem in placing staples, staples can be placed more quickly than traditional suture, and staples are easier to see and can be removed 1 to 3 days earlier than traditional sutures (Fig. 59-3). Staples may produce artifact on CT scans, but useful information may still be obtained if CT is necessary. Staples may move during magnetic resonance imaging and should not be placed if this imaging modality is being considered. Lightweight stapling devices are available. Most devices come preloaded with five or more staples and are easy to use. Hair apposition may also be an option for the closure of many scalp wounds. The technique involves grabbing a bundle of hair on both sides of the wound and then twisting the hair bundles with a hemostat. A small dab of cyanoacrylate glue is applied to the twisted hair to prevent unraveling. Patient satisfaction is high with this approach.[46]

Traditional sutures are used to repair most scalp lacerations, usually with standard nylon suture. Absorbable chromic gut can be used in children and in adults who may not return for suture removal.

Procedure. Anesthesia with epinephrine is recommended to help control bleeding. Hair removal is necessary only if the hair makes closure difficult. A defect in the galea is closed with 3-0 or 4-0 absorbable suture. Failure to repair the galea can lead to a cosmetic deformity related to frontalis muscle function. Linear superficial scalp lacerations that do not require deep sutures can be closed with staples or with monofilament nylon sutures applied with a simple interrupted or running technique. Jagged or macerated lacerations may require some débridement and horizontal mattress sutures. When one chooses to staple a scalp laceration, the adjacent skin margins are pinched together with forceps to evert wound margins. The "mouth" of the stapler is placed gently on the skin surface, taking care not to indent the skin. The handle of the stapler is squeezed carefully to eject the staple into the tissue. Ideally, the staple closely approximates the wound margins without indenting the surface of the skin. For release of the staple, the wrist is pulled back to disengage itself from the last staple.

www.ketabpezeshki.com 66485457-66963820

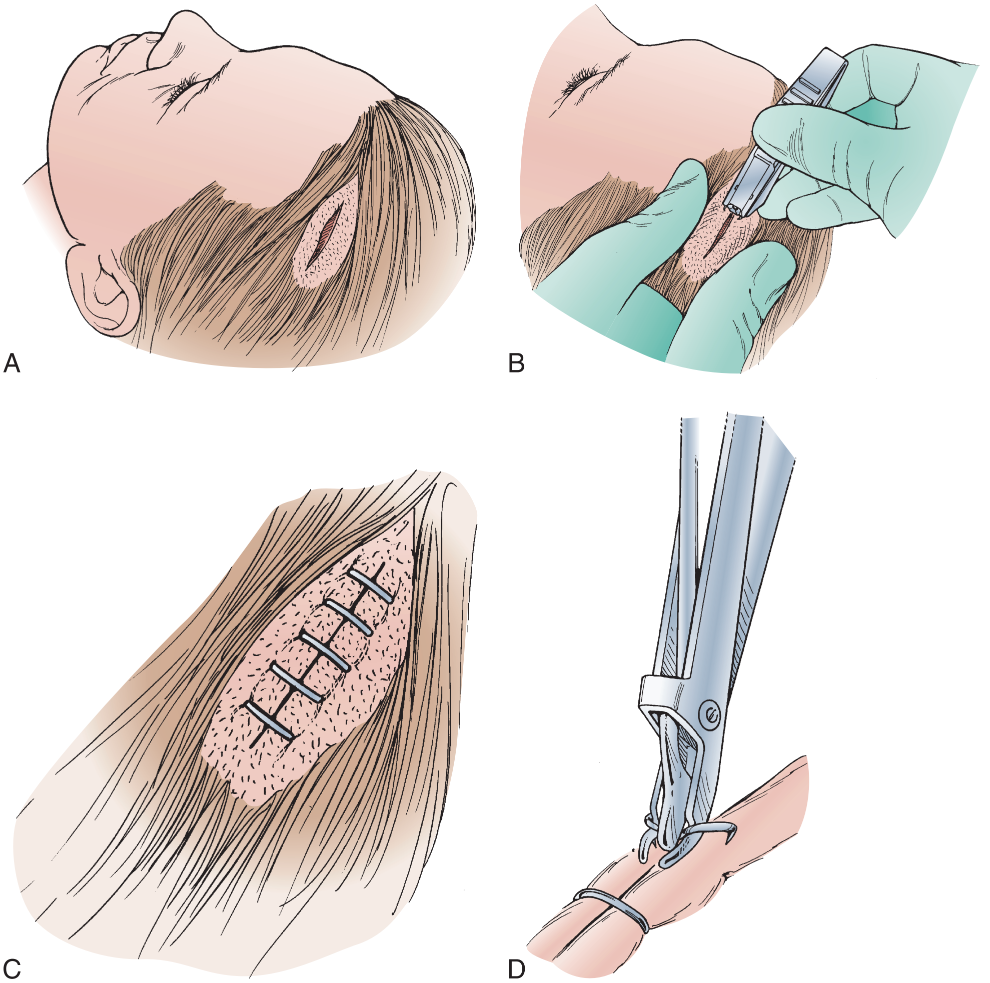


Figure 59-3. Scalp laceration repair. (Adapted from Simon BC: Skin and subcutaneous tissue. In Rosen P, et al [eds]: Atlas of Emergency Procedures. St. Louis, Mosby, 2001.)

Vigorously bleeding scalp lacerations often need temporizing measures to control bleeding while the patient is being evaluated and resuscitated. An anesthetic agent with epinephrine should be used and may be helpful to control some bleeding. Blindly clamping in an attempt to control bleeding is unwise and not likely to be successful. Raney scalp clips can be rapidly applied to the wound margins to quickly gain control of the bleeding. An applicator is used to apply and remove the clips so that they can be replaced with sutures once the patient has been stabilized. The clips are plastic and will not interfere with CT or magnetic resonance imaging.[43]

Staple removal is simple, especially if the patient has kept the wound clean and free of dried secretions. The dual prongs on the disposable staple remover slide under the staple crossbar. As the handle is squeezed and the horizontal aspect of the staple is depressed, the sharp edges are eased out of the tissue for removal.

Skin Tears. Most commonly seen in the elderly and chronically ill, skin tears can be a treatment dilemma for emergency physicians. These tears are a result of shearing forces that separate the epidermis from the underlying dermal layer of the skin. Often the result of minor trauma, these injuries may be minor tears or as large gaping wounds with extensive loss of tissue. Approximating the wound margins by aligning thin fragile tissue can be very difficult. Studies have confirmed that the use of Steri-Strips and or topical skin adhesives (cyanoacrylate-based derivatives; see later) is currently the preferred option. Either material may be used alone; however, when tension exists, placing the Steri-Strips first, then the adhesive, may be the optimal approach. Care must be taken in deciding what type of dressing to use. Transparent films can cause fluid to collect and delay healing. Adhesives are difficult to remove and can cause additional tearing. If the wound must be covered, then hydrogel sheets, hydrocolloid dressings, or both are recommended.[47]

Vertical Mattress Sutures. Vertical mattress sutures improve wound edge eversion. They are also used for the closure of gaping wounds and deep lacerations that may need more than simple sutures to close potential dead space. Areas of lax skin tension, generally where maximal skin mobility is needed such as over joint surfaces, may need assistance to ensure eversion of the wound margins. Vertical mattress sutures may be ideal to accomplish both tasks.

Procedure. A vertical mattress suture is a combination of deep and superficial components. The needle is introduced at a 90-degree angle approximately 1 cm from the wound margin. The needle courses through the depth of the wound and emerges on the opposite side, 1 cm from the laceration margin at a 90-degree angle. The needle is reintroduced 1 or 2 mm from the epidermal edge for final approximation of the wound.

Horizontal Mattress Sutures. Horizontal mattress sutures are useful to help disperse excess skin tension and to evert wound edges. The scalp, which has minimal skin mobility, is one area where gaping lacerations may benefit from this tension-reduction method. Horizontal mattress sutures may also be beneficial in

www.ketabpezeshki.com 66485457-66963820

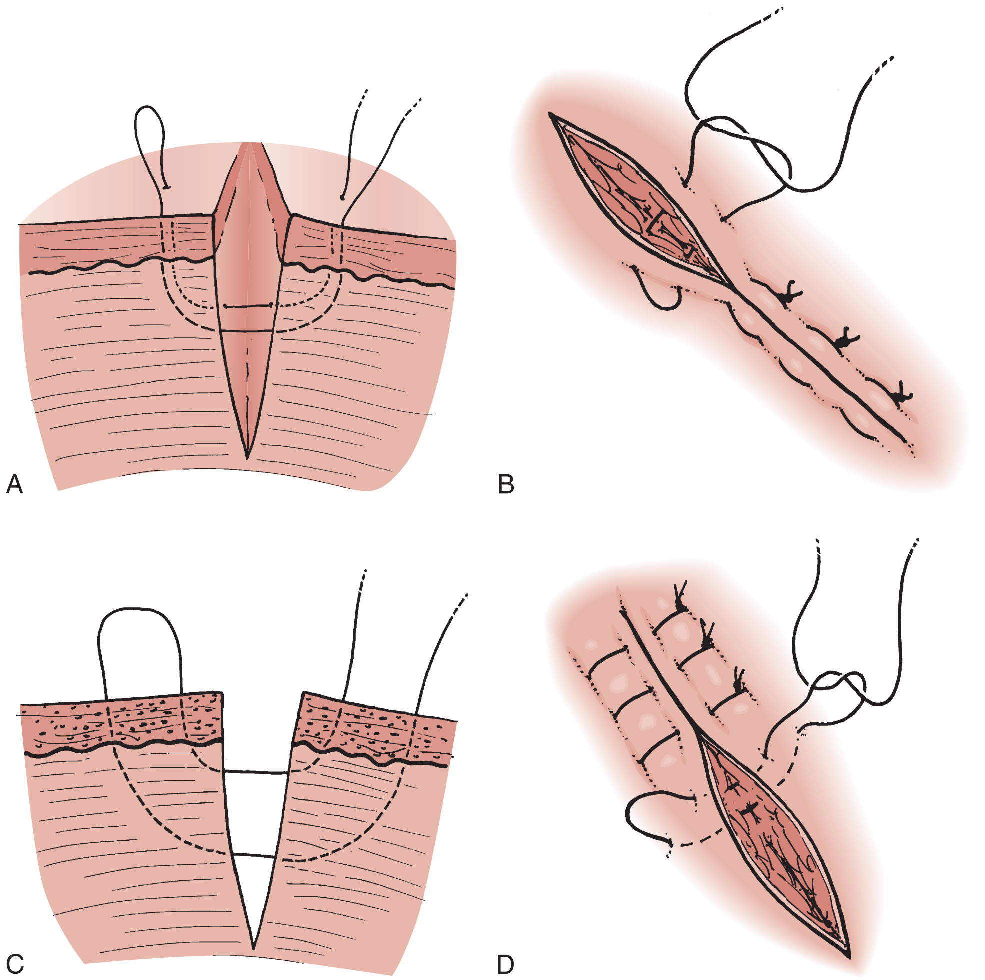


Figure 59-4. Mattress suture. (Adapted from Simon BC: Skin and subcutaneous tissue. In Rosen P, et al [eds]: Atlas of Emergency Procedures. St. Louis, Mosby, 2001.)

thin, fragile skin of elderly people and for lacerations that have lost tissue from the injury or débridement.

Procedure. The initial step is to pass the needle as for a simple interrupted stitch (Fig. 59-4). On exiting the skin, however, the needle is reintroduced approximately 0.5 cm adjacent to the exit point. This second "bite" reemerges 0.5 cm adjacent to the initial insertion point and is tied. Unlike with vertical mattress sutures, each bite is always the same distance from the wound margin.

Dog-Ear Deformity Repair. Some redundant tissue may result on one side of the repair as the closure nears completion, especially in the closure of curvilinear lacerations. This redundant tissue generally can be avoided by placing the initial suture in the middle of a curvilinear wound. If the clinician has limited experience, excision and undermining of tissue are likely to result in complications and should not be attempted.

Procedure. The laceration repair begins in a traditional manner and continues to approximately the final 1 cm of the wound (Fig. 59-5). A short incision (approximately 1 cm) is made from the end of the laceration at a 45-degree angle. The angle is cut toward the side of the redundant, bunched tissue. In most cases the subcutaneous tissue from the start of the dog-ear defect to the newly created end of the wound must be gently undermined to mobilize the skin. The next step, the final step before suturing, is the most important. The work that has just been completed leaves a small triangular piece of excess tissue. The redundant piece is gently lifted with the tissue forceps and excised in a line parallel to the incision made above. The wound can now be closed with simple interrupted suture technique. Poor technique can result in a more unsightly repair. If too much tissue is undermined, the edge of the skin can lose its blood supply and necrose.

Corner Stitch (Half-Buried Horizontal Mattress Sutures). Jagged and triangular wounds create corners that can be difficult to repair. The clinician must avoid placing the suture directly in the tip of the flap. This practice may "stretch" the tissue and further compromise blood flow to the wound margin. The corner stitch allows optimal tissue approximation with minimal tension.

Procedure. The needle is introduced percutaneously through the nonflap side of the wound a few millimeters from the corner of the wound (Fig. 59-6). The needle is passed horizontally through the dermis of the flap. The final step is to pass the needle into the dermis of the nonflap aspect of the wound a few millimeters from the opposite side of the corner. The suture is led out through the epidermis and tied. This technique can also be used to encompass multiple flaps either individually or simultaneously if the tips are adjacent to one another. The most difficult but important aspect of the corner stitch is to take bites of equal depth with each pass of the needle. Failure to take equal bites of tissue results in a wound with opposing sides that do not lie flat; this leads to a more obvious scar. When the corner has been repaired, the remaining two sides of the wound may be closed with simple interrupted or running suture technique.

V-Y Wound Closure. The V-Y closure is indicated for the repair of V-shaped wounds with tissue loss or with nonviable margins

www.ketabpezeshki.com 66485457-66963820

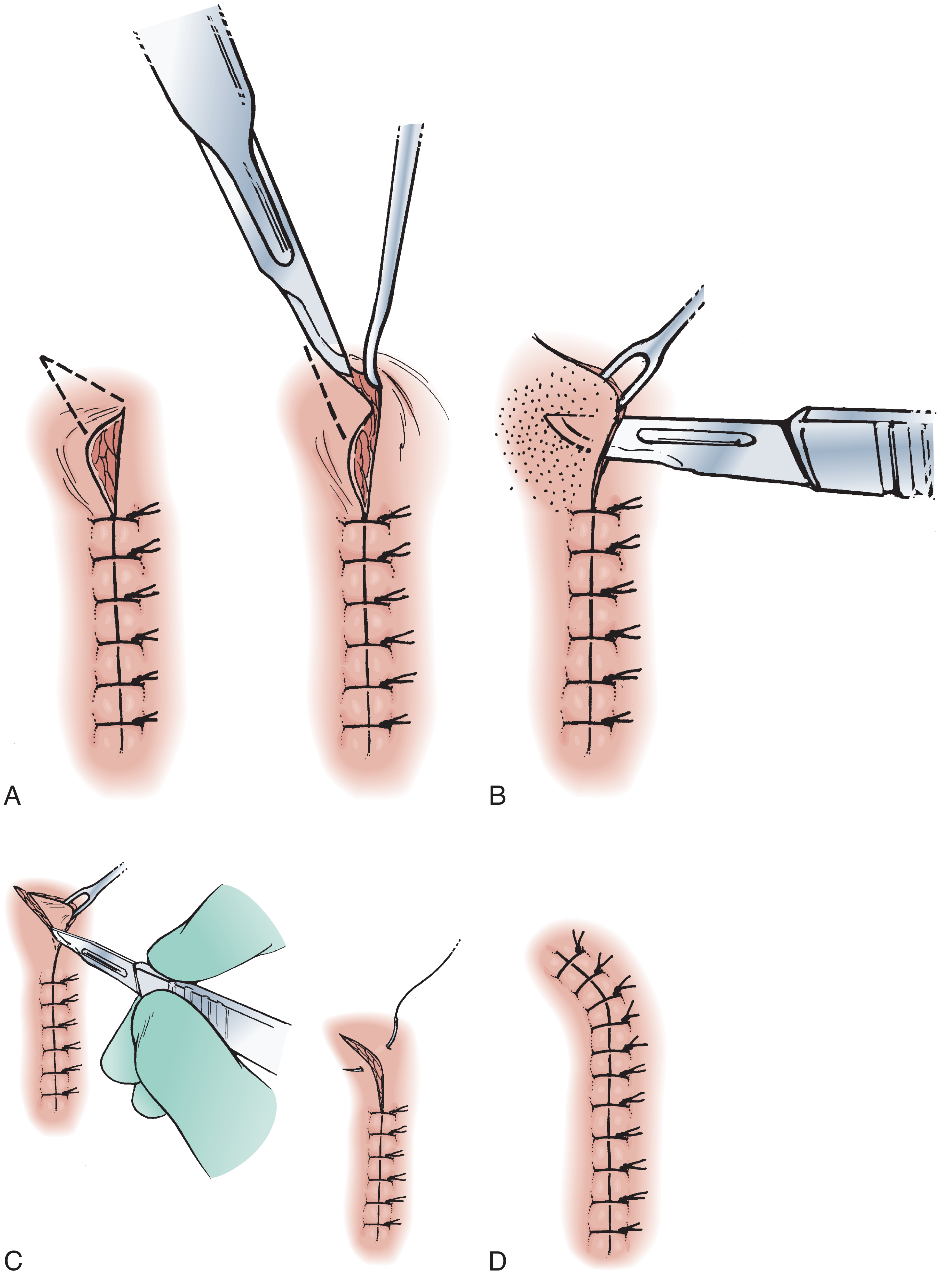


Figure 59-5. Dog-ear repair. (Adapted from Simon BC: Skin and subcutaneous tissue. In Rosen P, et al [eds]: Atlas of Emergency Procedures. St. Louis, Mosby, 2001.)

that must be trimmed. The tissue loss is such that the adjacent mobile tissue is not sufficient to close the remaining defect.

Procedure. Nonviable tissue is trimmed with fine iris scissors (Fig. 59-7). The long V-shaped portion of the wound is sutured with simple interrupted percutaneous stitches. This first step brings the tip of the flap closer to the newly created corner of the wound. A corner stitch is used to secure the tip of the flap. The remaining limbs of the Y can be repaired with simple interrupted stitches. Some degree of undermining is likely to be needed to mobilize tissue to close the defect. Débridement of too much tissue can make the final repair more difficult and can distort adjacent anatomy.

Materials

In the Middle Ages and earlier, materials used to close wounds included flax, hemp, fascia, hair, linen strips, pigs' bristles, reeds, grasses, and even the mouth parts of the pincher ant. In the early 1900s, natural organic protein products, including silk, cotton, and catgut, were the only available substances. Polyester (Dacron) and nylon were the first synthetic materials, available in the 1940s. Since then, a host of other synthetic materials have become available.

Suture.[48] The ideal suture is inert to metabolism, is resistant to infection, has great tensile strength, does not tear tissue, is easy to work with and tie, and is available in convenient colors with a variety of cutting and noncutting needles (Table 59-2). A common classification of suture material relies on relative *absorbability.* In general, the materials that maintain their tensile strength for more than 60 days after implantation have been defined as *nonabsorbable.* Materials that undergo rapid degradation in tissue and lose their strength in less than 60 days are considered *absorbable.* A second classification considers the source and nature of the material. *Biologic* substances, which include catgut, collagen, silk, linen,

www.ketabpezeshki.com 66485457-66963820

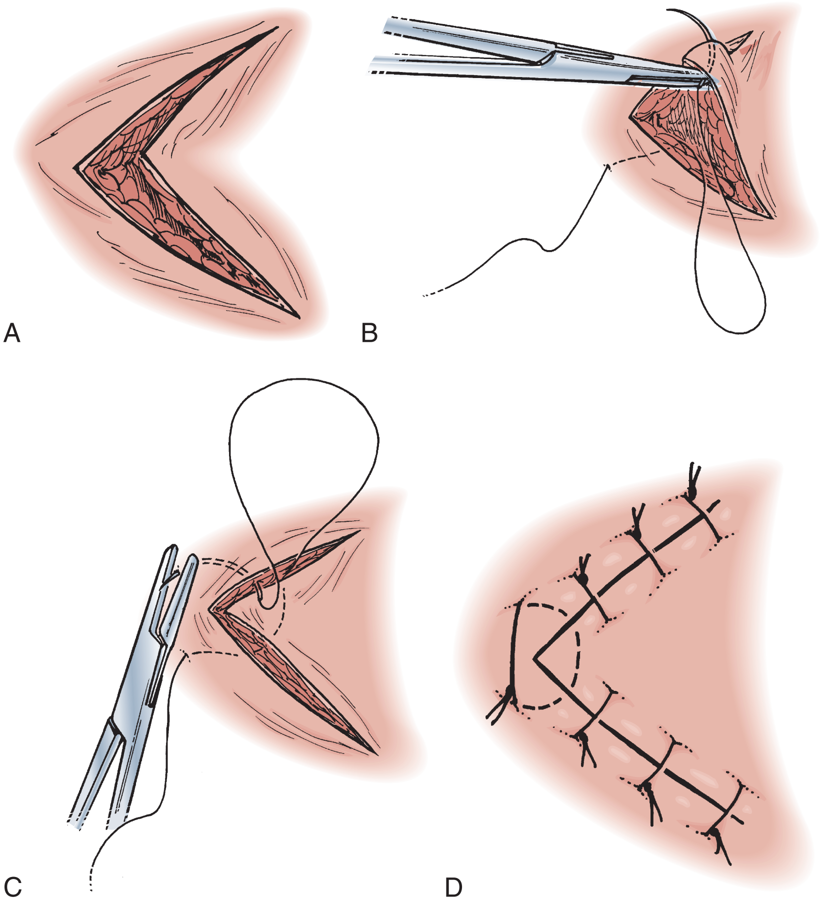


Figure 59-6. Corner stitch (half-buried horizontal mattress). (Adapted from Simon BC: Skin and subcutaneous tissue. In Rosen P, et al [eds]: Atlas of Emergency Procedures. St. Louis, Mosby, 2001.)

and cotton, generally produce the greatest tissue reaction and have the lowest relative tensile strength but have good knot security. These characteristics are in contrast to *synthetic* materials, such as polyester (Dacron), polyamide (nylon), polypropylene (Prolene), polyglycolide and polylactide polymers (Dexon and Vicryl), polydioxanone (PDS), and steel, which usually have less tissue reactivity, greater strength, and less knot security.

Knotting properties and handling characteristics tend to vary inversely. Knot security is of particular importance in maintaining wound closure and the patient's confidence in the physician. Sutures with smooth or slippery surfaces produce little friction and glide effortlessly through tissue and are easy to tie. Smoother materials are more difficult to handle and more likely to untie spontaneously. Certain monofilament synthetic materials tend to return or spring back to their original shape. To overcome this suture memory, the first part of the tie should be a "double throw" pulled tightly enough to approximate the tissue, with care taken not to strangulate the margins. The second throw locks the tension of the first part into position. A third throw is used for added security. If this is done properly, additional knotting is not needed after the third throw.

The presence of any suture material in a wound increases the likelihood of infection. Subcutaneous sutures bear the greatest risk. The degree of risk depends on characteristics of the substances used. Braided multifilament materials, such as the polyesters, polyamides, polyglycolides, and silk, yield the highest infection rates, whereas monofilament synthetic substances have the lowest risk of infection. There are several nonabsorbable monofilament synthetic sutures and one absorbable monofilament (PDS). The degree of infectivity of PDS compares well with the low rates of infectivity of similar materials.

Consideration of patient comfort in suture selection is important. Although silk is highly reactive, it ties well, is easy to handle, and is comfortable for the patient. It is an excellent choice for use in and around the lips, where comfort is a major concern. PDS is a comfortable absorbable suture and can be left in intraoral mucosa to be absorbed, with apparently low risks of infection, or it can be removed in 5 to 7 days. Staples or metallic sutures are excellent when strength is needed, but they may be uncomfortable for the patient. Nylon and polypropylene, which are the most common sutures used on skin, produce little tissue reaction and offer good tensile strength. They tend to be stiff, produce discomfort near the lips, have poor knot security, and may be difficult to work with. A braided, coated polyester nonabsorbable material, such as Ethibond, is easier to work with and has better knot stability. Although Ethibond is more expensive than nylon, its characteristics and added patient comfort suggest that it may be preferable. Absorbable suture materials, such as polyglycolide and polylactide polymers (Dexon and Vicryl), have been used strictly for subcutaneous and mucosal closures. Their highly reactive nature allows them to be broken down and absorbed over weeks. Chromic catgut, another absorbable material, has been shown to be safe and effective for the closure of scalp wounds in children.[49]

Needles. Surgical needles are available in a variety of sizes and shapes with myriad other characteristics. Cutting needles may be reverse cutting, conventional cutting, taper cut, or precision point. Most emergency wounds may be closed with a conventional cutting needle. In addition to its sharp point, it has two opposing cutting edges, with a third on the inside curve. Precision point needles are similarly shaped but are honed 24 extra times and maintain their added sharpness longer. These needles are used for

www.ketabpezeshki.com 66485457-66963820

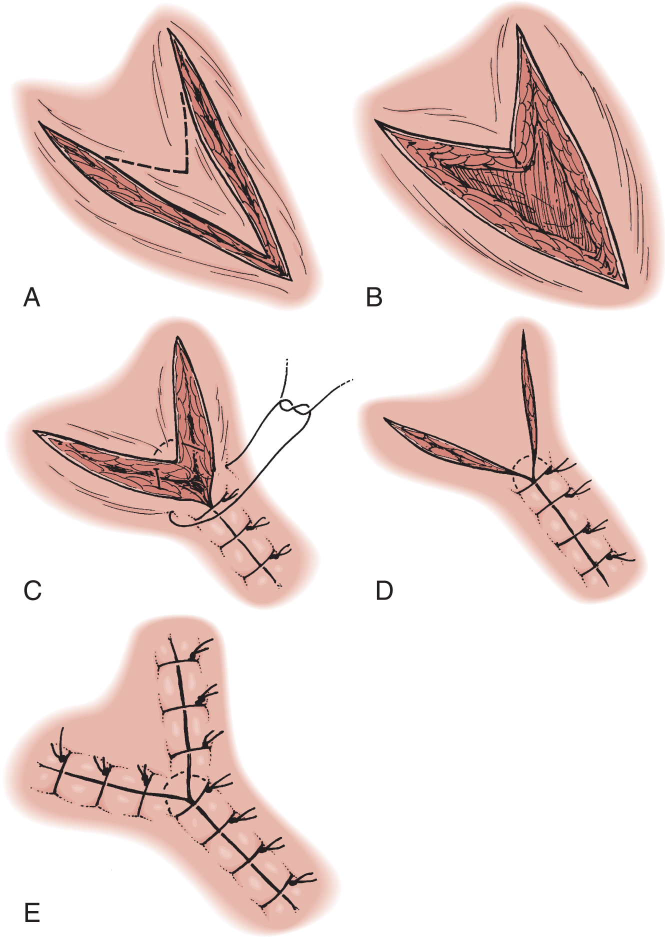


Figure 59-7. V-Y closure. (Adapted from Simon BC: Skin and subcutaneous tissue. In Rosen P, et al [eds]: Atlas of Emergency Procedures. St. Louis, Mosby, 2001.)

delicate plastic or cosmetic surgery. Noncutting needles are reserved for organ repair and subcutaneous suturing. Cutting needles may also be used to repair subcutaneous tissue. Needle nomenclature is confusing and varies by manufacturer.

Tape. Tape closure may be superior to closure with sutures and staples if applied in the appropriate circumstances. In general, the laceration should be linear and subjected to weak static and dynamic forces. Tape is not considered for wounds requiring meticulous tissue approximation. Compared with other closure materials, tape is associated with lower risk of infection, less expense, and less physician time. In addition, a painful injection of local anesthetic is not needed.

The ideal wound closure tape allows water and gas exchange and possesses elasticity, strength, and optimal adhesiveness. For adhesive properties to be maximized, tincture of benzoin should be painted on the skin adjacent to the wound. Care must be taken to avoid introducing benzoin compound in the wound. A nonwoven, microporous tape, which is not reinforced, has been found to best meet these requirements.[50,51]

Staples. Staples offer several advantages over sutures. Monofilament stainless steel staples offer less risk of infection than even the least reactive suture.[52] The time necessary to accomplish closure may be significantly lessened. Acceptable wounds must be linear and subjected to weak skin forces. Wounds requiring accurate approximation of tissue are not candidates for staple closure. Staples are also uncomfortable while in situ and on removal. Stapled wounds gain tensile strength sooner, and the staples can be removed 1 to 3 days earlier than sutures. After removal, the staples should be replaced with wound closure tape for continued reinforcement.

Various stapling devices are available. The device must allow good visual access and flexible positioning for difficult angles. A precocking mechanism is necessary to allow the physician to hold the staple securely during its placement. The angle of staple delivery is important. One brand releases the staple perpendicular to the wound with its crossbar flush with the skin; this can result in cross-hatching on the skin or tissue strangulation if placed too deeply. The device needs an ejector spring for smooth staple release and must be able to be handled without producing fatigue.

Tissue Adhesives. European and Canadian physicians have used tissue adhesives (butyl 2-cyanoacrylates) for many years. In 1998, octyl-2-cyanoacrylates were approved for use in the United States. Tissue adhesives offer many advantages over traditional sutures. The emergency physician can apply the adhesive quickly and easily with a minimum of patient discomfort. In addition, suture removal in 7 to 10 days is unnecessary because the adhesive sloughs off the skin in approximately the same amount of time. Evidence indicates that adhesives not only provide their own dressing but also have antibacterial properties and may decrease the rate of wound infections.[53] Closing wounds with adhesives is less expensive than traditional suturing and carries no risk of needle-stick injuries.[54]

Tissue adhesives achieved cosmetic results similar to those of traditional sutures in randomized trials.[55,56] Tissue adhesive may be applied in high-tension areas, but only if used in conjunction with subcutaneous or subcuticular sutures. If used alone, tissue adhesives are not recommended for lacerations longer than 4 cm or in areas of higher tension or frequent repetitive movements, such as joints or hands.[55]

Other disadvantages of tissue adhesives include the inability to use antibacterial or other petroleum-based products on the wound; the recommendation not to swim, to limit forces that may prematurely remove the adhesive; and the greater risk of dehiscence. The tensile strength of tissue adhesives is significantly less than that of sutures. Despite these disadvantages, tissue adhesives represent a tremendous advance in the management of routine uncomplicated lacerations in nontension areas. Patients routinely prefer tissue adhesives over traditional sutures.[56]

Application of tissue adhesive begins with routine skin and wound preparation. The area must be dried and adequate hemostasis achieved before application of the adhesive. The wound margins are approximated as meticulously as possible, and care should be taken to prevent adhesive from getting between the wound margins. Applying tape (Steri-Strips) before application will facilitate wound margin approximation and make it easier to apply. Adhesive between the wound margins delays healing and increases the likelihood of wound dehiscence. The adhesive is applied to the entire length of the wound sufficient to cover 5 to 10 mm of skin adjacent to the margins. Three layers of adhesive are applied. A period of 30 to 45 seconds is allowed for the first layer to polymerize, and then the subsequent two layers are applied, with approximately 10 seconds allowed between applications. Special care is taken to ensure that the adhesive does not run off and disturb adjacent tissues. Having the patient lie on the affected side will help prevent contamination of the eye near the wound and the opposing eye. Newer, high-viscosity formulations are now available that help limit this risk. Wounds may get wet but should not be immersed in water and should be blotted dry and not vigorously rubbed. An additional dressing may be desired by the patient but is not necessary.[56,57]

Antibiotic Prophylaxis

Routine antibiotic prophylaxis for simple wounds has no scientific basis. A meta-analysis compared the rates of infection in patients

www.ketabpezeshki.com 66485457-66963820

Table 59-2 Suture Materials for Wound Closure

TYPE	DESCRIPTION	SECURITY	STRENGTH	REACTION	WORKABILITY	INFECTION	COMMENT
Nonabsorbables							
Silk		++++	+	++++	++++	++	Suitable around mouth, nose, or nipples, but too reactive and weak to be used universally
Mersilene	Braided synthetic	++++	++	+++	++++		Good tensile strength; some prefer for fascia repairs
Nylon	Monofilament	++	+++	++	++	+++	Good strength; decreased infection rate; knots tend to skip, especially the first "throw"
Polypropylene (Prolene)	Monofilament	+	++++	+	+	++++	Good resistance on infection; often difficult to work with; requires an extra throw
Ethibond	Braided coated polyester	+++	++++	++½	+++	+++	
Stainless steel wire	Monofilament	++++	++++	+	+	+	Difficult to use; painful to patient; some prefer for tendons
Absorbables							
Gut (plain)	From sheep intima	+	++	+++		+	Loses strength rapidly and is quickly absorbed; rarely used today
Chromic (gut)	Plain gut treated with chromic salts	++	++	+++		+	Similar to plain gut; can be used to close intraoral lacerations
Dexon	Braided copolymer of glycolic acid	++++	++++	+		++++	Braiding may cause it to "hang up" when knots are being tied
Vicryl	Braided polymer of lactide and glycolide	+++	++++	+		+++	Low reactivity with good strength; suitable for subcutaneous healing; good in mucous membranes
Polydioxanone	Monofilament	++++	++++	+	Excellent	Unavailable	First available monofilament synthetic absorbable sutures; appears to be excellent

From Swanson NA, Tromovitch TA: Suture materials, 1980s: Properties, uses and abuses. Int J Dermatol 21:373, 1982.

with simple nonbite wounds receiving antibiotics with those in control groups. Of 1734 patients enrolled in the seven studies, patients treated with antibiotics had a slightly greater incidence of infection. The authors concluded that prophylactic antibiotics had no role in simple nonbite lacerations.[58] Routine antibiotic use also has complications: Increasing resistance to antibiotics, gastrointestinal side effects, and allergic reactions are common and may result in significant morbidity and unnecessary cost.

Although irrigation and débridement are the most important means of preventing wound infections, antibiotic prophylaxis is recommended in some circumstances. Prophylaxis must be tailored to each patient. Some recommendations are supported by scientific data, whereas others have few data to support their use and are based on custom.

Contamination, Crush, and Host Factors

Antibiotic prophylaxis is often provided for patients with wounds with gross contamination, patients with severe crush injuries, and immunocompromised patients. Some authors recommend not closing these wounds and instead using delayed primary closure. If circumstances require wound closure despite the infection risk, many emergency physicians recommend prophylaxis despite scarce data.[59]

Some authors believe that a patient with significant crush injury requires antibiotics. Crush injuries are high-risk wounds because they produce more devitalized tissue.[60] A definitive answer may not be forthcoming because it would be difficult to complete a well-controlled prospective, blinded study.

Patients with certain risk factors have increased wound infection rates. A prospective study of more than 23,000 surgical wounds showed an increased rate of wound infection in patients with diabetes, obesity, malnutrition, chronic renal failure, advanced age, and chronic steroid use.[59] Because of higher rates of infection, some authors suggest the use of antibiotics in these patients, again based on individual circumstances.[60] No controlled studies of antibiotic prophylaxis in these patients exist, however. Finally, some authors advocate prophylaxis for other host factors, such as prosthetic joints or risk for endocarditis.[61,62] Little evidence exists to support either recommendation.

Open Fractures, Joint Wounds, and Gunshot Wounds

Wounds that involve joints or open fractures necessitate use of prophylactic antibiotics. Prospective randomized controlled studies have documented decreased infection rates in patients receiving antibiotics compared with placebo. Indeed, the time to antibiotic administration in these wounds was found to be the most important factor in decreasing wound infection rates.[63] Open fractures without evidence of significant soft tissue damage (avulsions and crushed or devitalized tissue) necessitate use of antibiotics for 24 hours. Open comminuted fractures or fractures with significant tissue damage necessitate 72 hours of antibiotics.[64] For gunshot wounds, which are classified as a type of open fracture, the recommendations vary with the type of missile wound. Low-velocity missile wounds not treated with antibiotics showed no increased infection rate in a randomized controlled trial of 67 patients with fractures treated with a closed technique.[65]

www.ketabpezeshki.com 66485457-66963820

High-velocity wounds with fracture, on the other hand, are associated with an increased risk of infection, and antibiotic therapy should be initiated early and maintained for 48 to 72 hours.[66] In addition, patients with shotgun wounds with fracture should receive prophylaxis as well. Appropriate antibiotic therapy would be a cephalosporin with or without an aminoglycoside plus penicillin (to cover *Clostridia* species).[67] Use of cefazolin (Ancef) 1 g q8h and clindamycin 600 mg intravenously (IV) q8h may be considered. For the severely contaminated wounds, tobramycin 1 mg/kg q8h is added.

Bites and Puncture Wounds

Antibiotics are indicated for through-and-through intraoral lacerations, cat bites, some dog bites, some human bites, and some puncture injuries to the foot.

Cat Bites. Prophylaxis is required for patients with cat bites. These bites tend to be deep puncture wounds that are difficult to irrigate adequately. These wounds also tend to become infected at a much higher rate than other types of bites. Cat bites have been reported to cause infections in 10 to 40% of all wounds. In one study, 12.9% of patients had signs of infection when they visited the emergency department, and 15.9% eventually developed infection. Other authors report that 80% of these bites become infected, although obvious selection bias limits this interpretation. Antibiotics seem to decrease the incidence of infection.[68]

The organisms found in cat bites include *Staphylococcus* species, *Streptococcus* species, and, most often, *Pasteurella multocida. P. multocida* is usually found in infected cat bite wounds and is present in the normal oral flora of 70% of all cats. *P. multocida* is sensitive to penicillin, but the infection is often polymicrobial. *P. multocida* is resistant to dicloxacillin, cephalexin, and clindamycin, and there are many erythromycin-resistant strains. Amoxicillin with clavulanate (875 mg bid for 7 days) is the current recommendation for antibiotic prophylaxis for cat bites.

Dog Bites. Antibiotic prophylaxis for dog bites is more controversial. The infection rate has been reported as 6 to 16% for patients not receiving antibiotics. Dog bites tend to involve more crush injuries with tearing and avulsions rather than puncture wounds. As such, dog bites are usually more amenable to irrigation and débridement. Seven of eight randomized trials of dog bite wounds showed no benefit with antibiotics. However, pooled data for meta-analysis did show a small but statistically significant benefit from antibiotics.[69] It may be logical to limit the use of antibiotics to high-risk wounds, such as hand injuries, deep puncture wounds, and wounds in older or immunocompromised patients.

Hand Bites. In addition to the previous bite wound recommendations, antibiotic prophylaxis of injuries to the metacarpophalangeal joints is advised. These wounds are assumed to be human bites until proved otherwise. Also known as "fight bites," these wounds have a high incidence of infection. Patients without signs of infection may be managed as outpatients. Close inspection after anesthesia has been applied is necessary to thoroughly evaluate the area for tendon involvement and/or penetration of the joint. If the joint is involved, aggressive irrigation is required. In some institutions, all these patients are taken to the operating room for a thorough washout. Patients with early signs of infection are admitted for intravenous antibiotics and aggressive débridement and irrigation. The choice of antibiotics reflects the predominant organisms of hand bite infections. *Streptococcus* and *Staphylococcus* species are common, but *Eikenella corrodens* and *Bacteroides* species are also typical pathogens. Because *Eikenella* is often resistant to clindamycin, first-generation cephalosporins, and erythromycin, patients with early infection are treated with amoxicillin with clavulanate. Patients with later infection are treated with intravenous extended-spectrum antibiotics (e.g., ampicillin with sulbactam).

Intraoral Lacerations. Lacerations of the oral mucosa involve bacteria-rich oral secretions and may become infected slightly more often (6-12%) than other wounds. Rates of infection for through-and-through lacerations may be twice the rates for simple mucosal lacerations. Although few data suggest a clear indication for prophylactic antibiotics, one study showed that patients benefit from antibiotics if they are compliant with their regimen. Another study looked at all the literature (four studies) on antibiotics in intraoral lacerations and found the studies do not conclusively show a benefit to giving antibiotics in these types of wounds.[69a] It may be reasonable to limit antibiotic use to high-risk patients with through-and-through wounds. Penicillin 500 mg bid for 5 days is an appropriate choice of antibiotic.

Puncture Wounds of the Foot. Puncture wounds of the foot are seen frequently in the emergency department. These wounds are often caused by common nails, although other objects (e.g., glass, metal, and wood) must be considered. Despite their simple appearance, these wounds may produce significant morbidity. The infection rate for puncture wounds has been reported to be 15%.[70,71] Most wounds occur on the plantar surface, from the neck of the metatarsal to the toes. Simple cellulitis accounts for half of these infections. More significant infections include septic arthritis, abscesses, and osteomyelitis. *Pseudomonas* organisms cause 90% of osteomyelitis cases from puncture wounds. No data suggest a benefit from prophylactic antibiotics, but given the high risk of infection and serious complications, their use may be considered in select puncture wounds. Consideration of *Pseudomonas* organisms when the puncture went through a rubber-soled shoe is essential. Patients with puncture wounds to the foot require early follow-up. Ciprofloxacin is the drug of choice to treat outpatients with suspected wound infection when *Pseudomonas* is of concern. Cephalexin (Keflex) or dicloxacillin is adequate for staphylococcal and streptococcal coverage unless methicillin-resistant *Staphylococcus aureus* (MRSA) is likely. In cases suspicious for MRSA, sulfamethoxazole-trimethoprim or doxycycline is recommended.

Drains, Dressings, and Immobilization

Drains

Drains probably have no role in emergency department wound care. In general, drains are placed when a collection of fluid exists or may develop. The presence of a drain reduces the wound's resistance to infection, regardless of the materials used in its construction, and the use of drains should be avoided.[72] In wounds likely to collect fluid (e.g., around the elbow or knee), it is preferable to place the extremity at rest with a plaster splint or perform delayed primary closure.

Dressings

Various dressing materials are available. The microenvironment created by a dressing affects the biology of healing. The optimal wound climate must not interfere with the activity of fibroblasts and macrophages. The production of granulation tissue and migration of epithelial cells across the wound must be optimized.

Several factors should be considered in choosing the appropriate dressing. Dressings that prevent evaporation of water and keep tissues moist are helpful. A drying wound produces a thick, hardened scab that impedes the process of epithelialization. Excess fluid can lead to maceration of tissue and may be a potential culture medium for bacterial proliferation. Gaseous permeability is essential because epithelialization is accelerated greatly in the

www.ketabpezeshki.com 66485457-66963820

presence of oxygen. The wound-covering product should be impermeable to bacteria and other particulate matter that can contaminate the wound. It is important not to traumatize newly established tissue during dressing changes. The optimal dressing should have a nonadherent surface, be permeable to gases, and have a capacity to absorb some fluid but not allow desiccation. The outer barrier of the product should be impermeable to bacteria but permeable to water vapor. These products include films, hydrocolloids, foams, and hydrogels. The choice of dressing for emergency department wounds is primarily based on the amount of drainage that is expected.[73-75]

Film dressings are thin membranes that are transparent, adhesive, and waterproof but are not absorptive. They are best reserved for wounds with low levels of drainage. Film dressings may be left in place for up to 7 days as long as they do not leak or separate from the wound bed. For wounds with a moderate amount of drainage, moderately absorptive hydrocolloid dressings may be indicated. These dressings are thicker than films, semiocclusive, waterproof, and very comfortable for the patient. Like films, they can be left on for up to 7 days. Foam dressings are more absorptive and made of a soft cushion spongelike material. Some may require a secondary dressing for adhesion and need to be removed every 3 days. Hydrogel dressings are moisture-donating water-based gels that are available in sheets attached to a semipermeable film. These dressings do not absorb fluids, so they must be used on relatively dry wounds. Patients often find these dressings to be the most comfortable, but they need to be changed every 1 to 3 days. The least expensive and simplest method of dressing a straightforward, uncomplicated laceration is to use Vaseline-impregnated gauze or gauze on top of a thick layer of antibiotic ointment. These should be changed daily to prevent desiccation.

Immobilization

Wounds in proximity to joints must be immobilized as part of routine care. Splinting the injured body part places the injury at rest and hastens healing. Failure to splint appropriately exposes the healing tissue to the dynamic forces of muscular contractions, ultimately slowing the healing process and increasing scar size. In addition, immobilization decreases lymphatic flow and minimizes spread of microflora from the wound.

DISPOSITION

Wound Care Instructions

It is difficult for patients to identify and recognize the signs of infection (Box 59-2).[76] Discharge instructions must be clear, understandable, and reasonably comprehensive. Instructions should include daily care, observation for signs of infection, suture removal dates, and a follow-up source. It should be recommended to the patient that injured extremities be elevated during the first 24 to 48 post-traumatic hours and explained that elevation lessens edema, hastens healing, and mollifies pain. The wound should be protected as described previously or cleaned daily to remove crust formations. It is safe for patients to bathe and get the wound wet 24 hours after injury.[77] Daily swabbing with half-strength hydrogen peroxide rids the wound of debris and any blood clot that forms between the sutured edges. Hydrogen peroxide should not be used after separation of the scab because it is toxic to the epithelium and may produce bullae.

Wound infection is difficult for the untrained observer to distinguish from the inflammatory response of injury and subsequent healing. Patient education in this regard should be cautious and straightforward (e.g., return or seek follow-up for redness, swelling, increased pain, fever, pus, or red lines progressing up an extremity). An injury classified as high risk must be reexamined 48 hours after the trauma, regardless of its appearance.

Box 59-2 Wound Care Instructions

A. Elevate the injured extremity above the level of the heart. Wear a sling when appropriate.
B. Cleanse daily in a gentle manner to remove debris and crusting that develops. Use dilute hydrogen peroxide.
C. Immobilization should be maintained at least until suture removal.
D. Signs of infection
   1. Redness
   2. Increasing pain
   3. Swelling
   4. Fever
   5. Red streaks progressing up an extremity
E. Wound check
   1. As needed to check signs of infection
   2. Routine at 48 hours for high-risk wounds
F. Suture removal (*Note:* Suture may be removed earlier if Steri-Strips reinforce the wound.)
   1. Face: 3-5 days (always replace with Steri-Strips)
   2. Scalp: 7-10 days
   3. Trunk: 7-10 days
   4. Arms and legs: 10-14 days
   5. Joints: 14 days

Suture removal times vary, but generally they are approximately 4 days for the face and 7 to 14 days for other body parts (see Box 59-2). Considerations include cosmetics, dynamic forces in proximity to the injury, static skin tension, blood supply, and anticipated healing rates.

Tetanus Immunization

The reported incidence of tetanus in the United States in 2005 was 0.011 per 100,000 population (27 cases reported).[78] Most tetanus patients in the United States are older than 50 years. Immunization status needs to be considered in all patients with wounds, regardless of severity. Forty percent of all cases of tetanus occur in individuals who have either minor wounds or no recollection of injury. These numbers raise serious questions regarding the validity of separating immunization recommendations according to clean and tetanus-prone wounds. Studies show that many people are inadequately immunized, especially patients older than 70 years, immigrants, and people with no education beyond grade school.[79] Also, patient immunization histories are often unreliable. Given the inability to predict which wounds are at high risk, all wounds are approached with suspicion.

The usual incubation period for tetanus is 7 to 21 days (range, 3-56 days). Immunization is given as soon as possible but can be given days or weeks after the injury. The dose of tetanus toxoid (T) or diphtheria, pertussis, and tetanus toxoids (DTaP) is 0.5 mL intramuscularly, regardless of the patient's age. Inadequately immunized patients need a dose of DTaP and tetanus immune globulin (TIG). The TIG dose is 250 IU for all ages 7 years or older and 4 IU/kg IM up to 250 IU for ages younger than 7 years (Table 59-3). A single injection of TIG provides protective levels of passive antibodies for at least 4 weeks. The immune globulin and toxoid may be given during the same visit but should be administered with a different syringe at separate sites. The literature suggests that emergency physicians need to be more diligent administering TIG, because it is often not provided when indicated.[80]

www.ketabpezeshki.com 66485457-66963820

Table 59-3 Tetanus Prophylaxis for All Patients with All Wounds*

IMMUNIZATION HISTORY	DTAP (0.5 mL)	TIG (250 IU)
Fully immunized, <10 yr since booster	No	No
Fully immunized, >10 yr since booster	Yes	No
Incomplete series (<3 injections)	Yes[†]	Yes

DTaP, diphtheria, pertussis, tetanus toxoids; *TIG,* tetanus immune globulin. All injections are intramuscular.

*Consider more frequent immunization for elderly patients. DTaP recommended for ages 11-64 yr (diphtheria and tetanus [DT] vaccine to be used in those older than 64 years).

[†]Refer these patients to complete their series; DTaP in 6 weeks and 12 months.

Box 59-3 Summary of Wound Care

A. Stabilize patient
B. History (include tetanus immunization and allergies)
C. Physical examination
   1. Neurovascular examination
   2. Anesthesia: bupivacaine 0.5% without epinephrine, regional or local
   3. Bloodless field: tourniquet or sphygmomanometer for extremities
   4. Sterile examination of anatomic structures, skin, nerves, tendons, blood vessels, bones, muscles, fascia, other (ducts, cartilage)
   5. Consultation if indicated
D. X-ray films to detect injury to bone or the presence of foreign bodies (xeroradiograph or ultrasound)
E. Wound preparation
   1. Cut—do not shave—surrounding hair
   2. Prepare surrounding skin with povidone-iodine (Betadine) solution
   3. Sharp débridement of foreign matter and devitalized tissue
   4. High-pressure irrigation with saline, 1% Betadine, an antibiotic solution, or a nonionic solution
F. Wound closure
   1. Tape, staples, or suture
   2. Do not use subcutaneous sutures unless the wound is under high tension
G. Antibiotics
   1. Apply topical antibiotics
   2. No systemic antibiotics unless wound is very high risk
H. Dress and immobilize: Consider a transparent gas-permeable dressing
I. Wound care instructions (see Box 59-2)
   1. Signs of infection
   2. Elevation
   3. Wound check if necessary
   4. Suture removal as soon as possible

Because studies suggest that 10 to 40% of the U.S. population is inadequately immunized against diphtheria, diphtheria vaccination is recommended along with tetanus toxoid.[81] Immunity to pertussis wanes approximately 5 to 10 years after vaccination. Since the 1980s, the number of reported pertussis cases has steadily increased, especially among adolescents and adults. In 2005, 25,616 cases of pertussis were reported in the United States. In 2005 a tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed (Tdap) product formulated for use in adults and adolescents was licensed in the United States for people aged 11 to 64 years. When possible, it is recommended that this triple combined formulation be used in the emergency department. Although all four injections (T, diphtheria and tetanus toxoids [DT], TIG, and DTaP) are considered safe and effective in pregnancy, because of limited experience during pregnancy the recommendation is to use DT. However, DTaP is recommended immediately postpartum, including for breast-feeding women.[82]

SUMMARY

Box 59-3 summarizes the principles of wound care management.

KEY CONCEPTS

- Risk factors for wound infection include prolonged time since injury; crush mechanism; deep penetrating wounds; high-velocity missiles; and contamination with saliva, feces, soil, or other foreign matter.
- The most effective intervention to decrease infection is thorough cleansing, with use of saline irrigation at approximately 8 psi. Attaching an 18-gauge needle to a 35-mL syringe creates an irrigant force of 7 or 8 psi, which decreases bacterial counts.
- Soaking wounds in povidone-iodine (Betadine) is more toxic than beneficial to healthy tissue.
- Antibiotics are indicated for through-and-through intraoral lacerations, cat bites, some dog bites, some human bites, puncture injuries to the foot in high-risk individuals, open fractures, and wounds involving exposed tendons or joints.
- High-risk wounds should not be sutured primarily but may be repaired in 4 or 5 days (i.e., delayed primary closure).
- Tetanus immunization should be provided soon after injury but can be given days or weeks later. The usual incubation period for tetanus is 7 to 21 days (range, 3-56 days).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Trott AT: *Wounds and Lacerations: Emergency Care and Closure*, 2nd ed. St Louis: Mosby; 1997.
2. Jackson DS, Rovee DT: Current concepts in wound healing: Research and theory. *J Enterostomal Ther* 1988; 15:133.
3. Hunt TK: The physiology of wound healing. *Ann Emerg Med* 1988; 17:1265.
4. Edlich RF, Rodeheaver GT, Morgan RF, Berman DE, Thacker JG: Principles of emergency wound management. *Ann Emerg Med* 1988; 17:1284.
5. Lammers RL, Hudson DL, Seaman ME: Prediction of traumatic wound infection with a neural network-derived decision model. *Am J Emerg Med* 2003; 21:1.
6. Perelman VS, et al: Sterile versus nonsterile gloves for repair of uncomplicated lacerations in the emergency department: A randomized controlled trial. *Ann Emerg Med* 2004; 43:362.
7. Levine MR, Gorman SM, Young CF, Courtney DM: Clinical characteristics and management of wound foreign bodies in the ED. *Am J Emerg Med* 2008; 26:8.
8. Orlinsky M, Bright AA: The utility of x-rays in all glass caused wounds. *Am J Emerg Med* 2006; 24:233.
9. Hill R, Conron R, Greissinger P, Heller M: Ultrasound for the detection of foreign bodies in human tissue. *Ann Emerg Med* 1997; 29:353.
10. Manthey DE, Storrow AB, Milbourn JM, Wagner BJ: Ultrasound versus radiography in the detection of soft-tissue foreign bodies. *Ann Emerg Med* 1996; 28:7.
11. Fariss BL: Anesthetic properties and toxicity of bupivacaine and lidocaine for infiltration anesthesia. *J Emerg Med* 1987; 5:375.
12. Barker W, Rodeheaver GT, Edgerton MT, Edlich RF: Damage to tissue defenses by a topical anesthetic agent. *Ann Emerg Med* 1982; 11:307.
13. Krunic AL, Wang LC, Soltani K, Weitzul S, Taylor RS: Digital anesthesia with epinephrine: An old myth revisited. *J Am Acad Dermatol* 2004; 51:755.
14. Winthrop Pharmaceuticals: *Marcaine package insert*. New York: Winthrop Pharmaceuticals; 1998.
15. Parham SM, Pasieka JL: Effect of pH modification by bicarbonate on pain after subcutaneous lidocaine injection. *Can J Surg* 1996; 39:31.
16. Coventry DM: Alkalinization of bupivacaine for sciatic nerve blockade. *Anaesthesia* 1989; 44:467.
17. Brogan GX Jr, et al: Comparison of plain, warmed, and buffered lidocaine for anesthesia of traumatic wounds. *Ann Emerg Med* 1995; 26:121.
18. Hegenbarth MA, et al: Comparison of topical tetracaine, adrenaline, and cocaine anesthesia with lidocaine infiltration for repair of lacerations in children. *Ann Emerg Med* 1990; 19:63.
19. Bonadio WA, Wagner V: Half-strength TAC topical anesthetic. For selected dermal lacerations. *Clin Pediatr (Phila)* 1988; 27:495.
20. Blackburn PA, Butler KH, Hughes MJ, Clark MR, Riker RL: Comparison of tetracaine-adrenaline-cocaine (TAC) with topical lidocaine-epinephrine (TLE): Efficacy and cost. *Am J Emerg Med* 1995; 13:315.
21. Terndrup TE: Plasma cocaine and tetracaine levels following application of topical anesthesia in children. *Ann Emerg Med* 1992; 21:162.
22. Dailey RH: Fatality secondary to misuse of TAC solution. *Ann Emerg Med* 1988; 17:159.
23. Ernst AA, Marvez-Valls E, Nick TG, Weiss SJ: LAT (lidocaine-adrenaline-tetracaine) versus TAC (tetracaine-adrenaline-cocaine) for topical anesthesia in face and scalp lacerations. *Am J Emerg Med* 1995; 13:151.
24. Zempsky WT, Karasic RB: EMLA versus TAC for topical anesthesia of extremity wounds in children. *Ann Emerg Med* 1997; 30:163.
25. Gaufberg SV, Walta MJ, Workman TP: Expanding the use of topical anesthesia in wound management: Sequential layered application of topical lidocaine with epinephrine. *Am J Emerg Med* 2007; 25:379.
26. Incaudo G, et al: Administration of local anesthetics to patients with a history of prior adverse reaction. *J Allergy Clin Immunol* 1978; 61:339.
27. Swanson JG: Assessment of allergy to local anesthetic. *Ann Emerg Med* 1983; 12:316.
28. Pollack CV, Swindle GM: Use of diphenhydramine for local anesthesia in "caine"-sensitive patients. *J Emerg Med* 1989; 7:611.
29. Viljanto J: Disinfection of surgical wounds without inhibition of normal wound healing. *Arch Surg* 1980; 115:253.
30. Alexander JW, Fischer JE, Boyajian M, Palmquist J, Morris MJ: The influence of hair-removal methods on wound infections. *Arch Surg* 1983; 118:347.
31. Dimick AR: Delayed wound closure: Indications and techniques. *Ann Emerg Med* 1988; 17:1303.
32. Fernandez R, Griffiths R: Water for wound cleansing. *Cochrane Database Syst Rev* 2012 Feb 15; 2:CD003861.
33. Valente JH, Forti RJ, Freundlich LF, Zandieh SO, Crain EF: Wound irrigation in children: Saline solution or tap water? *Ann Emerg Med* 2003; 41:609.
34. Oberg MS: Povidone-iodine solutions in traumatic wound preparation. *Am J Emerg Med* 1987; 5:553.
35. Moscati RM, Mayrose J, Reardon RF, Janicke DM, Jehle DV: A multicenter comparison of tap water versus sterile saline for wound irrigation. *Acad Emerg Med* 2007; 14:404.
36. Welsh AP: A comparison of wound irrigation solutions used in the emergency department. *Ann Emerg Med* 1990; 19:704.
37. Brown LL, Shelton HT, Bornside GH, Cohn I Jr: Evaluation of wound irrigation by pulsatile jet and conventional methods. *Ann Surg* 1978; 187:170.
38. Rogness H: High-pressure wound irrigation. *J Enterostomal Ther* 1985; 12:27.
39. Hollander JE, et al: Irrigation in facial and scalp lacerations: Does it alter outcome? *Ann Emerg Med* 1998; 31:73.
40. Tobin GR: An improved method of delayed primary closure: An aggressive management approach to unfavorable wounds. *Surg Clin North Am* 1984; 64:659.

40a. van den Baar MT, van der Palen J, Vroon MI, Bertelink P, Hendrix R: Is time to closure a factor in the occurrence of infection in traumatic wounds? A prospective cohort study in a Dutch level 1 trauma centre. *Emerg Med J* 2010; 27:540.

41. Berk WA, Osbourne DD, Taylor DD: Evaluation of the "golden period" for wound repair: 204 cases from a Third World emergency department. *Ann Emerg Med* 1988; 17:496.
42. Shepard GH: Wounds treated by the healing of delayed primary closure: A clinical study. *Mil Med* 1981; 146:473.
43. Lammers L, Trott AT: *Methods of wound closure*. In: Roberts JR, Hedges JR, eds. *Clinical Procedures in Emergency Medicine*, 4th ed. Philadelphia: Saunders; 2004.
44. Quinn J: Suturing versus conservative management of lacerations of the hand: Randomized controlled trial. *Br Med J* 2002; 325:299.
45. McLean NR, Fyfe AH, Flint EF, Irvine BH, Calvert MH: Comparison of skin closure using continuous and interrupted nylon sutures. *Br J Surg* 1980; 67:633.
46. Karaduman S, Yürüktümen A, Güryay SM, Bengi F, Fowler JR Jr: Modified hair apposition technique as the primary closure method for scalp lacerations. *Am J Emerg Med* 2009; 27:1050-1055.
47. Xu X, Lau K, Taira BR, Singer AJ: The current management of skin tears. *Am J Emerg Med* 2009; 27:729.
48. Hochberg J, Meyer KM, Marion MD: Suture choice and other methods of skin closure. *Surg Clin North Am* 2009; 89:627.
49. Start NJ: The use of chromic catgut in the primary closure of scalp wounds in children. *Arch Emerg Med* 1989; 6:216.
50. Rodeheaver GT, Halverson MJ, Edlich RF: Mechanical performance of wound closure tapes. *Ann Emerg Med* 1983; 12:203.
51. Rodeheaver GT: Performance of new wound closure tapes. *J Emerg Med* 1987; 5:451.
52. Ritchie AJ, Rocke LG: Staples versus sutures in the closure of scalp wounds: A prospective double-blind randomized trial. *Injury* 1989; 20:217.
53. Quinn JV, Osmond MH, Yurack JA, Moir PJ: *N*-2-butylcyanoacrylate: Risk of bacterial contamination with an appraisal of its antimicrobial effects. *J Emerg Med* 1995; 13:581.
54. Osmond MH, Klassen TP, Quinn JV: Economic comparison of a tissue adhesive and suturing in the repair of pediatric facial lacerations. *J Pediatr* 1995; 126:892.
55. Lo S, Aslam N: A review of tissue glue used in facial lacerations: Potential problems in wound selection in accident and emergency. *Eur J Emerg Med* 2004; 11:277.
56. Quinn J, et al: A randomized trial comparing octylcyanoacrylate tissue adhesive and sutures in the management of lacerations. *JAMA* 1997; 277:1527.
57. Singer AJ, Quinn JV, Hollander JE: The cyanoacrylate topical skin adhesives. *Am J Emerg Med* 2008; 26:490.
58. Cummings P, Del Beccaro MA: Antibiotics to prevent infection of simple wounds: A meta-analysis of randomized studies. *Am J Emerg Med* 1995; 13:396.
59. Cardany CR, Rodeheaver G, Thacker J, Edgerton MT, Edlich RF: The crush injury: A high risk wound. *JACEP* 1976; 5:965.
60. Singer AJ, Hollander JE, Quinn JV: Evaluation and management of traumatic lacerations. *N Engl J Med* 1997; 337:1142.
61. Patzakis MJ, Harvey JP Jr, Ivler D: The role of antibiotics in the management of open fractures. *J Bone Joint Surg Am* 1974; 56:532.

www.ketabpezeshki.com 66485457-66963820

62. Kaplan EL: Prevention of bacterial endocarditis. *Circulation* 1977; 56:139A.
63. Patzakis MJ, Wilkins J: Factors influencing infection rate in open fracture wounds. *Clin Orthop Relat Res* 1989; 243:36.
64. Hoff WS, Bonadies JA, Cachecho R, Dorlac WC: East Practice Management Guidelines Work Group: update to practice management guidelines for prophylactic antibiotic use in open fractures. *J Trauma* 2011; 70:751-754.
65. Dickey RL, Barnes BC, Kearns RJ, Tullos HS: Efficacy of antibiotics in low-velocity gunshot fractures. *J Orthop Trauma* 1989; 3:6.
66. Hennessy MJ, Banks HH, Leach RB, Quigley TB: Extremity gunshot wound and gunshot fracture in civilian practice. *Clin Orthop Relat Res* 1976; 114:296.
67. Simpson BM, Wilson RH, Grant RE: Antibiotic therapy in gunshot wound injuries. *Clin Orthop Relat Res* 2003; 408:82.
68. Elenbaas RM, McNabney WK, Robinson WA: Evaluation of prophylactic oxacillin in cat bite wounds. *Ann Emerg Med* 1984; 13:155.
69. Cummings P: Antibiotics to prevent infection in patients with dog bite wounds: A meta-analysis of randomized trials. *Ann Emerg Med* 1994; 23:535-540.
69a. Mark DG, Granquist EJ: Are prophylactic oral antibiotics indicated for the treatment of intraoral wounds? *Ann Emerg Med* 2008; 52:368-372.
70. Resnick CD, Fallat LM: Puncture wounds: Therapeutic considerations and a new classification. *J Foot Surg* 1990; 29:147.
71. Inaba AS, Zukin DD, Perro M: An update of the evaluation and management of plantar puncture wounds and *Pseudomonas* osteomyelitis. *Pediatr Emerg Care* 1992; 8:38.
72. Magee C, et al: Potentiation of wound infection by surgical drains. *Am J Surg* 1976; 131:547.
73. Fonder MA, Mamelak AJ, Lazarus GS, Chanmugam A: Occlusive wound dressings in emergency medicine and acute care. *Emerg Med Clin North Am* 2007; 25:235.
74. Hutchinson JJ, Lawrence JC: Wound infection under occlusive dressings. *J Hosp Infect* 1991; 17:83.
75. Madden MR: Comparison of an occlusive and a semi-occlusive dressing and the effect of the wound exudate upon keratinocyte proliferation. *J Trauma* 1989; 29:924.
76. Seaman M, Lammers R: Inability of patients to self-diagnose wound infections. *J Emerg Med* 1991; 9:215.
77. Noe JM: Can stitches get wet? *Plast Reconstr Surg* 1988; 81:82.
78. McNabb SJ, et al: Summary of notifiable diseases in the United States, 2005. *MMWR Morb Mortal Wkly Rep* 2007; 54:1-92.
79. Stair TO: Tetanus immunity in emergency department patients. *Am J Emerg Med* 1989; 7:563.
80. Talan DA: Tetanus immunity and physician compliance with tetanus prophylaxis among emergency department patients presenting with wounds. *Ann Emerg Med* 2004; 43:304-314.
81. Kretsinger K, et al: Preventing tetanus, diphtheria, and pertussis among adults: Use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine. *MMWR Recomm Rep* 2006; 55(RR17):1-37.
82. Briggs GG, Freeman RK, Yaffe SJ: Drugs in Pregnancy and Lactation. Baltimore: Williams & Wilkins; 1986.

www.ketabpezeshki.com 66485457-66963820

Chapter 60

Foreign Bodies

Stephen H. Thomas and Jeffrey M. Goodloe

PERSPECTIVE

History

When people ingest or insert foreign bodies, a brief history may be sufficient to establish the diagnosis, guide initial management decisions, and predict the process required for definitive removal. Sometimes, however, diagnosis and management of a foreign body might require a meticulous history and insightful care. Those at higher risk of having a foreign body include neurologically impaired patients, edentulous individuals, patients with certain psychiatric diagnoses, incarcerated individuals, and individuals at the extremes of age. In these same groups, definitive history is often elusive, and the clinician should use situational clues. Even when patients are fully cooperative, the diagnosis of foreign body ingestion or insertion can be difficult, especially when the expression of the foreign body is delayed. Although foreign body cases are usually not diagnostic dilemmas, the emergency physician should keep in mind the unusual possibility of "foreign body mimics" (e.g., angioedema manifesting as esophageal foreign body sensation).[1]

PHYSICAL EXAMINATION

Depending on the location of the foreign body, the physical examination can provide direct or indirect evidence of the object or its complications. Specifics are described in the following sections, but there is a recurring theme: meticulous examination frequently aids in establishing a diagnosis as well as suggesting a successful extraction method.

DIAGNOSTIC IMAGING

Plain radiography, classically the primary technique used for foreign body detection, is often the test of first choice. In appropriate circumstances, plain films can aid in determination of the location, size, and number of foreign objects. Even when objects are not visualized, radiographs may show secondary changes (e.g., pulmonary air trapping) providing clues to foreign body presence. To assist in the localization, two views—anteroposterior and lateral—are usually necessary. Objects such as metal or gravel, which are denser than the tissue in which they are embedded, usually are easy to visualize on plain radiographs. Organic material, which has a density similar to that of human tissue, may not be seen on plain films.

PRINCIPLES OF DISEASE

Although foreign body removal is not always feasible or desirable, extraction is indicated in most cases. A discussion with the patient, or appropriate surrogates, outlining the need and anticipated course for foreign body removal is recommended.

When the foreign body represents an immediate threat to the patient, as is the case with an airway foreign body, the need for urgent extraction is obvious. Trauma-related foreign bodies, such as knives and bullets, pose important management decisions (see other trauma chapters in this text). Even in cases in which no immediate life threat exists, some foreign bodies should be removed because of the threat of injury from the nature or constituents of the foreign body. For instance, cocaine can kill a body packer,[2] an impacted button battery can cause fatal electrochemical tissue damage,[3] and an insect can damage otic structures.[4]

In the absence of immediate life threat or constituent-related foreign body danger, additional complications can occur. In cases in which there is luminal obstruction, the foreign body may become lodged and may exert pressure on adjacent tissue, risking necrosis and perforation. The object also may serve as a nidus for infection that is recurrent or refractory to treatment until the foreign body is removed. Such patients often seek medical attention for secondary symptoms. Specific recommendations for foreign body removal are presented in the following sections outlining foreign body management by anatomic location.

EYE

Clinical Features

Although wooden and metallic fragments are found most frequently, ophthalmic foreign objects vary widely. The diagnosis usually is self-evident. However, extraocular and intraocular foreign bodies may be subtle in presentation, with mild symptoms and uncharacteristic histories involving seemingly trivial trauma, such as brushing against a bush or falling. In some cases, foreign bodies are identified in intoxicated patients with abnormal ocular examination findings and no known history of trauma (Fig. 60-1). Early diagnosis, appropriate care, and follow-up minimize the risks of delayed sequelae, such as endophthalmitis (which may occur within 48 hours after foreign body introduction) or sight-threatening siderosis bulbi.[5,6] Controversy regarding foreign body removal and its timing does not diminish the importance of making the initial diagnosis.

www.ketabpezeshki.com 66485457-66963820

Figure 60-1. Computed tomography scan shows right intraocular foreign body (BB pellet) in intoxicated patient without known trauma history.

History

Most patients report a foreign body sensation (often on blinking) and cannot see the foreign body. If the object is corneal, the patient may be able to see something in the visual field or may see the foreign body when looking in the mirror. The patient also may complain of frequent or constant lacrimation and conjunctival reddening. Foreign bodies that create corneal injury and are no longer present may account for symptoms identical to those noted in the presence of a foreign body. In addition, patients may have symptoms in the absence of any history of known foreign body. In these cases the occupational and social history, including pets and hobbies, may shed light on the diagnosis. Another important component of the history is whether radial keratotomy has been performed. This procedure is associated with potential for foreign body entrapment in the corneal incisions, which can gape as long as 6 or more years postprocedure.[7]

Physical Examination

The initial survey includes standard elements of the emergency department (ED) eye examination. Early visual acuity is an important predictor of final visual outcome in cases of intraocular foreign body.[8] During slit-lamp examination, the emergency physician may detect a corneal foreign body by the shadow it casts on the iris. The slit lamp can facilitate identification of rust rings, and fluorescein can aid in detecting abraded corneal epithelium. The inner aspects of both lids must be examined. The lower lid is often successfully exposed with gentle manual retraction outward and downward as the patient looks upward. The upper lid is usually exposed through eversion by instructing the patient to look downward while upward traction on the eyelashes is applied; an applicator stick is placed, to act as a fulcrum, on the proximal edge of the tarsal plate. After location and removal of one foreign body, complete examination should seek presence of other ocular objects.

Diagnostic Strategies

The foreign body may have penetrated the anterior eye structures and entered the globe (see Fig. 60-1). If the history and mechanism of injury are compatible with ocular penetration by radiopaque material, or if a small wound of the globe is noted, anteroposterior and lateral radiography of the orbit is a reasonable initial step. However, the multiple advantages of computed tomography (CT) render this technique the preferred first choice when intraocular penetration is strongly suspected.[9] As compared with plain radiographs, CT delivers less radiation to the lens. Multiplanar reconstruction minimizes streak artifacts, affording better localization of intraorbital objects. When globe penetration is strongly suspected, staining with fluorescein is best avoided owing to obscuration of the physical examination. When perforation is judged unlikely and fluorescein is administered, identification of rivulets of fluorescein tracking from the puncture (i.e., positive Seidel test result) is helpful in identifying the fact that intraocular penetration has occurred. In one case series of 288 patients, Luo and Gardiner reported a near-zero incidence of intraocular foreign body in patients with corneal metal foreign bodies after low-velocity (nonexplosive) exposures.[10]

Ultrasound is a useful adjunct to CT scanning in patients with foreign bodies that are difficult to localize.[11] When CT will be delayed, or if ionizing radiation is a concern, two ultrasound techniques can be useful in searching for foreign bodies. B-scan ultrasound, available in many EDs, has occasionally been reported successful in detecting foreign bodies missed on ophthalmologic examination.[6,12] For patients in whom a foreign body is suspected despite negative ED workup and imaging, the more advanced technique of ultrasound biomicroscopy, available in ophthalmologic specialty centers, is helpful. The sensitivity of this modality is sufficient that it detects foreign bodies not visible by direct or indirect ophthalmologic examination, traditional B-scan ultrasound, or CT.[13] Given the lack of reported case series and justifiable concerns about eye damage from mobilization of ferromagnetic foreign objects, use of magnetic resonance imaging (MRI) for ophthalmologic foreign body imaging remains controversial.[5]

In some cases, orbital trauma is associated with central nervous system injury. When the workup indicates a potential for injury or foreign body involving the brain, imaging of the intracranial compartment is recommended.

Management

In nearly all cases, therapy is removal of the foreign body. If the object is located on the bulbar or palpebral conjunctiva (*not* the cornea), it often can be removed easily by sweeping the site with a moist cotton-tipped applicator. Usually, other instruments are required (Fig. 60-2). Occasionally, if the foreign body is large, it may be extracted with forceps. For small corneal foreign bodies, after application of topical ocular anesthesia, it is often necessary to use an eye spud or small-gauge needle to move gently underneath one end of the object and pick it out; magnification is usually helpful. If the attempts at foreign body removal are unsuccessful or if the foreign body is deeply embedded, preventing removal, the patient should be referred for object removal within 24 to 48 hours. Although there is a paucity of evidence addressing the oxidation rate of metallic corneal foreign bodies, prudence dictates early "rust ring" to minimize growth of metallic oxides. Overly vigorous attempts at removal may cause anterior chamber perforation. It is prudent for the emergency physician to avoid significant corneal procedures in patients who have had a laser-assisted in situ keratomileusis (LASIK) procedure for nearsightedness.

After the removal of a corneal foreign body that leaves no rust ring, treatment is essentially the same as for corneal abrasion. In

www.ketabpezeshki.com 66485457-66963820

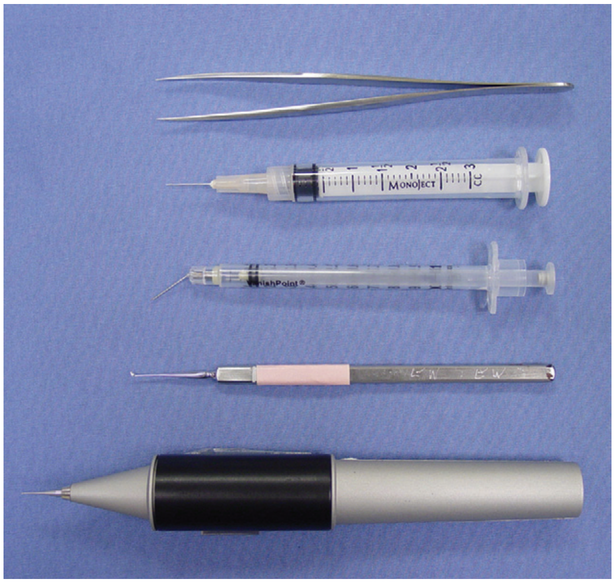


Figure 60-2. Instruments for removal of an ocular foreign object: forceps, needle (straight or bent) mounted on a syringe "handle," angled eye spud, and rotating straight-tip eye spud.

cases in which foreign bodies may have elicited an allergic response, topical steroids have been used. Therapy of patients with a rust ring is controversial. ED management should be dictated either by standing protocol (designed in collaboration with ophthalmologists), or by ED consultation with ophthalmology. Otherwise, it is prudent to recommend evaluation by an ophthalmologist within 24 to 48 hours to consider removal of retained rust.

EAR

Clinical Features

Foreign bodies of the ear are likely to prove problematic for the emergency physician. The difficulty has little to do with diagnosis. Rather, the problem is the need to remove objects from a sensitive anatomic area, in an often uncooperative patient population.

History

Adolescent and adult patients usually state something is in the ear. If the foreign body is an insect, the patient may feel motion or hear buzzing, although less specific complaints may include itching, discharge, or otalgia. Similar secondary symptoms may be present when noninsect foreign bodies are lodged in the ear canal. This type of presentation is especially common in children, who may fear telling of foreign object insertion into the ear; the problem is ignored until secondary problems, such as odor or drainage from infection, prompt an ED visit.

In patients with ear complaints with recent travel or camping history or poor living conditions, geographic information may suggest insects inhabiting the external ear canal; in most cases, the cockroach is the culprit.[14]

Patients with foreign bodies in the ear may have secondary symptoms related to pathology in adjacent structures. Malocclusion may be the chief complaint if the foreign body erodes to the temporomandibular joint.[15] Similar erosion has caused otic foreign bodies to manifest as eustachian tube dysfunction, parapharyngeal abscess, or mastoiditis with progression to fatal brain abscess and meningitis.[16] Such events are exceedingly rare.

The emergency physician should ask patients about prior attempts at foreign body removal, because these efforts may

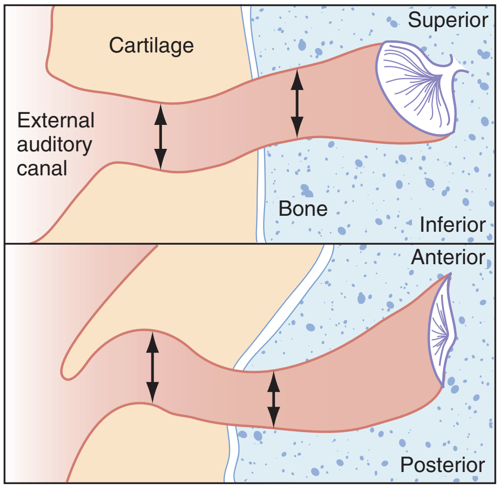


Figure 60-3. Horizontal and vertical cross sections of external ear canal showing points of anatomic narrowing.

have caused problems. Poorly executed attempts at foreign body removal may injure the ear canal, perforate the tympanic membrane, or merely push the foreign body deeper into the canal. Irrigation may cause enlargement of the foreign object, especially if it is vegetable matter.

Physical Examination

The external auditory canal is cylindrical with an elliptic cross section (Fig. 60-3). A thin layer of sensitive epithelium covers an outermost cartilaginous portion and an inner bony segment. There are two anatomic points of narrowing (and foreign object lodging) within the canal: (1) near the inner end of the cartilaginous portion of the canal and (2) at the point of bony narrowing called the *isthmus*.

The first factor crucial to successful examination is adequate lighting that can be directed by the emergency physician. This may be a strong light source and a head mirror, a headlamp, an operating otoscope, or an operating microscope. A large-size speculum is essential to obtain an adequate field of view and to enable four-quadrant injection of local ear canal anesthesia when necessary for foreign body removal. As with any examination involving the external auditory canal, the emergency physician should grasp the pinna of the ear and retract it in a posterosuperior direction to straighten the canal and afford a more complete view.

Inspection of the tympanic membrane is important because it may have been ruptured by the foreign object or by prior removal attempts. If so, medical documentation should indicate that this rupture was present before attempts at foreign object removal. As in other body locations (especially the nose), the risk of multiple foreign objects is such that if one foreign object is identified, the emergency physician should search for additional material.[17]

Diagnostic Strategies

Diagnostic imaging rarely plays a role in the ED workup of suspected otic foreign bodies. The primary indication is to identify complications from foreign body presence. CT or MRI may be performed to characterize infectious or erosive sequelae of ear canal foreign objects.

Management

In most cases, foreign body removal attempts may be instituted in the ED. Presence of a foreign body for more than a day or in a very young patient (younger than 4 years) does not constitute an

www.ketabpezeshki.com 66485457-66963820

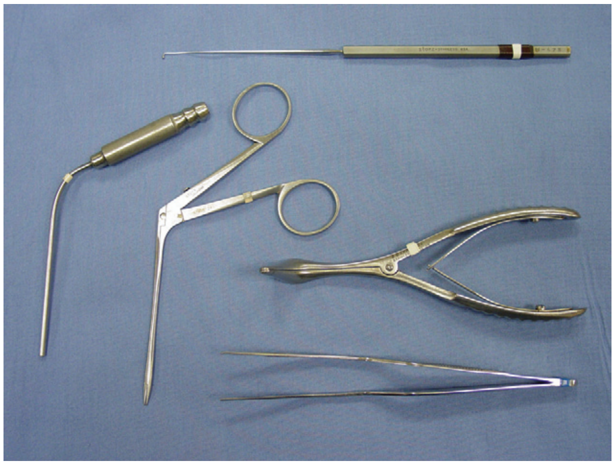


Figure 60-4. Instruments that may be useful for removal of a foreign body from ear canal or nares: right-angle probe, suction catheter, alligator forceps, nasal speculum, and bayonet forceps.

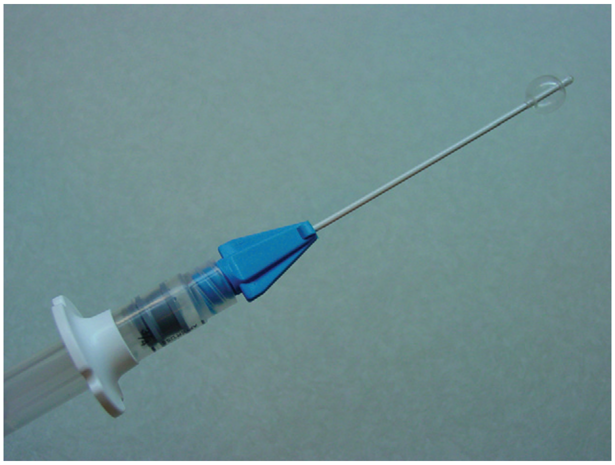


Figure 60-5. Balloon-tipped catheter that can be used for removal of otic or nasal foreign bodies.

independent risk factor for foreign body removal failure or complication; the emergency physician may thus proceed with removal efforts if not otherwise contraindicated.[18] The patient should be informed about the extreme sensitivity of the auditory passage and the likely discomfort and potential for minor bleeding. Sedation may be important to minimize patient discomfort and reduce risks of iatrogenic trauma. Lidocaine instillation may aid in topical anesthesia; liquid 1% or 2% solution is preferred to gel preparations, which impair visualization needed for removal. Less often, foreign body removal requires local anesthesia of the external ear canal. The anesthesia instillation procedure, which may cause patient discomfort and iatrogenic injury, is performed by injecting all four quadrants of the canal with lidocaine via a tuberculin syringe inserted through an otic speculum. In cases of a refractory foreign body and an uncooperative patient, definitive management should be performed with procedural sedation or even general anesthesia. Although the evidence is not universally consistent, available data suggest that approximately 95% of aural foreign bodies can be removed without the need for general anesthesia.[19]

When the ear canal is inhabited by an insect, it is important to kill or immobilize the creature to facilitate its removal. Immobilization reduces the chance of patient discomfort or ear damage caused by an insect attempting to evade forceps introduced into the ear canal. Patient comfort may also be optimized by minimization of shining light into an ear canal inhabited by light-avoiding insects (such as cockroaches). Different immobilizing agents have different reported success rates. Efficacious formulations include lidocaine as a 10% spray or less concentrated liquid, 2% lidocaine gel, mineral oil with 2% or 4% lidocaine, and alcohol.[4] One study suggests that microscope immersion oil is more efficacious than lidocaine preparations.[20]

Several extrication methods may prove effective, and various instruments may be useful (Fig. 60-4). Small objects often can be removed by the application of suction with a small plastic catheter. With soft or irregularly shaped objects, it is often possible to grasp the foreign body with forceps (alligator forceps may be best) and remove it either in one piece or in fragments. If the object cannot be grasped, it may be possible to remove it by passing a blunt-tipped right-angle hook beyond the foreign body and gently coaxing it out. Alternatively, a balloon-tipped catheter can be passed distal to the object, with subsequent attempts to withdraw the (inflated) balloon and extract the object. Any balloon-tipped catheter design may be used, as long as its caliber is small enough (about 18 gauge or smaller) to allow comfortable introduction into the ear canal; a typical commercial device is shown in Figure 60-5.

Indirect methods for foreign body removal also have been used with some success. The irrigation technique takes advantage of the elliptic shape of the external ear canal. A stream of room-temperature water or saline should be directed at the (nonvegetable) foreign body's periphery via a 20-mL syringe and a 14- or 16-gauge catheter (this setup is safe in terms of pressure on the tympanic membrane).[21] The hope with irrigation is that the jet of water will be directed past the object, against the tympanic membrane, and finally against the posterior aspect of the foreign body, driving it out of the canal. There are no significant complications with use of the technique, and it is well tolerated by children and adults. This modality should not be used if there is a known history or clinical suspicion of tympanic membrane perforation.

Removal of objects from the middle ear with cyanoacrylate adhesive-tipped swabs has been recommended in the past. This technique carries the risk, however, of contaminating the ear canal with a substance that is difficult to remove and has been associated with tympanic membrane rupture.[22] Insufficient evidence exists to condone or condemn this technique.

If these methods are unsuccessful or if the patient, especially a child, is uncooperative or in undue distress even with procedural sedation, the emergency physician should cease removal efforts and refer the patient to an otolaryngologist; timing is dependent on the acuity of the presentation. Rates of operative intervention vary in published series. Studies' case mix differences are probably responsible for the varying rates (from 5-33%) of reported need for surgical removal of otic foreign bodies.[18,19]

Inappropriately prolonged efforts at foreign object removal can result in wasted time, unnecessary patient discomfort, and high potential for complications as previously noted. Patient apprehension, untoward foreign body movement, or damage to the ear canal (including induction of edema) may prompt surgical intervention that would have been otherwise unnecessary.[23]

Otic foreign bodies are associated with many sequelae, but these are usually not serious. The most commonly occurring complications in pediatric series are external ear canal bleeding (approximately 16%), otitis externa (6%), and tympanic membrane perforation (2%).[19] One large series suggests that otitis externa is significantly more likely in adults than in children, perhaps because of relative delays in seeking medical attention.[24]

After removal of the foreign body, the canal examination is repeated to ensure the lack of retained material and to evaluate otic anatomy. In cases in which the tympanic membrane is

www.ketabpezeshki.com 66485457-66963820

ruptured and the middle ear is at risk for infection, appropriate oral antibiotics are recommended. Common practice is to prescribe topical antimicrobial therapy to decrease the risk of external otitis; the meatus may be packed with an ear wick or ribbon gauze impregnated with a broad-spectrum antibiotic.[4] Follow-up evaluation within 2 to 3 days is recommended for cases in which there was tympanic membrane rupture or in which foreign body removal was traumatic (to assess for external otitis).

NOSE

Clinical Features

The nose is perhaps the most common site for the insertion of foreign bodies by children. Perhaps because most people are right-handed, most nasal foreign bodies are right-sided.[25] Compared with patients with ear canal foreign bodies, children with nasal foreign bodies tend to be younger (most commonly younger than 5 years).[17]

Nasal foreign bodies are less problematic than foreign bodies in other locations. ED removal is nearly always successful, and, with proper technique (e.g., care to avoid aspiration), serious sequelae are rare.[25] Available data suggest that the overall risk that nasal foreign bodies will enter the bronchial tree is less than 0.06%.[26] The infrequently encountered cases of intranasal magnets or alkaline button batteries, which may cause electrical or chemical burns and tissue necrosis, are exceptions to this rule of minimal risk.[27]

History

Although most patients seek medical attention within 24 hours, patients with nasal (versus otic) foreign bodies are more likely to have secondary symptoms and delays of 1 week.[28] In fact, nasal foreign bodies may be asymptomatic, identified as incidental findings on imaging obtained for other purposes.

Patients seen in the ED with nasal foreign bodies usually have one of two histories. With the first type of presentation, the patient admits to or was seen placing an intranasal object. This is the most common history. Other patients have a constellation of signs and symptoms: purulent, unilateral, malodorous nasal discharge or even persistent epistaxis. These patients often are misdiagnosed and treated with antibiotics for supposed sinusitis. Unresolving sinusitis despite appropriate antibiotic therapy is an alert to the possibility of a nasal foreign body.[28]

Foreign objects placed intranasally may purposefully or inadvertently end up in the sinuses. These foreign bodies require more invasive intervention, and psychiatric evaluation of the patient may be indicated when self-injury is suspected. When the history suggests a foreign body but none is identified on nares examination, the emergency physician should consider imaging the sinuses.

Physical Examination

As with foreign bodies of the ear canal, preparing the patient (and the parents) for examination and subsequent removal attempts is an important component of the care plan. Because of risks of iatrogenic movement of the foreign body further posteriorly, children may need to be restrained to permit the examination. Physical examination sometimes can be delayed until after insufflation of the nares is attempted. The nasal mucosa is normally quite sensitive, and this sensitivity is increased by any infection or irritation. Examination is facilitated by provision of topical anesthesia and vasoconstriction to the nasal mucosa. Examination should include both nares, with adequate lighting and visualization with a nasal speculum. The emergency physician should note the presence of the foreign body and any secondary tissue damage. Necrosis of the nasal mucosa and septum may accompany button battery impaction.[29] During the examination the emergency physician should take care not to dislodge or drive the foreign body posteriorly into the nasopharynx and risk aspiration. In some circumstances, it may be prudent to place patients in the lateral decubitus position, perhaps with additional Trendelenburg's positioning, to help prevent aspiration of objects that are pushed into the posterior pharynx.

Diagnostic Strategies

Diagnostic imaging does not usually play a major role, although some have advocated for low-threshold use of plain radiography when button-battery foreign bodies are suspected.[30] When intrasinus foreign bodies are suspected, CT can be helpful. Rarely, CT or MRI may be indicated to visualize suspected foreign bodies or their complications. The potential risk of MRI for detection of foreign bodies may become more relevant with increasing frequency of foreign bodies related to magnetic jewelry (i.e., nose rings and studs).[31]

Management

The emergency physician can remove most nasal foreign bodies. Although the avoidance of iatrogenic injury is paramount, the structures local to an intranasal foreign body are not as sensitive or easily damaged as structures in other body cavities (e.g., the ear canal) that may harbor foreign objects. As a result, the need for subspecialty consultation and operating room removal is rare.[17,28]

Occasionally, positive pressure applied to the patient's mouth achieves rapid foreign body dislodgment while obviating the need for restraint, sedation, and other requirements attendant to more invasive removal techniques. This technique is a quick and safe primary intervention. The underlying principle is that a short burst of air blown into the mouth of a child, with finger occlusion of the nonobstructed naris, may force the foreign object out of the nose. Pretreatment with vasoconstrictive spray may improve chances of success.[32] The insufflation, preferably applied as a "kiss" from a parent, can also be provided by a manual ventilation bag. The insufflation technique is quite useful, particularly in preschoolers who are likely to be uncooperative with other removal modalities. Many children can be instructed to take a deep breath and blow hard through their nose, as a parent closes the unaffected naris. An otherwise troublesome removal can be accomplished quickly and easily.[33] Recent data suggest that the "kissing" technique's success rate of nearly 50% was associated with additional advantages of decreased use of resources (e.g., time, anesthetics).[34]

When positive-pressure insufflation is not warranted or is unsuccessful, instruments and removal techniques may be required (see Figs. 60-4 and 60-5). Regardless of the method, the patient (usually a child) may benefit from some combination of restraint, sedation, and pretreatment with vasoconstrictive agents (e.g., nebulized racemic epinephrine) and anesthetic (e.g., benzocaine spray).[32] Adequate illumination is essential. Necessary instruments include a blunt-tipped right-angle probe, suction catheter, and alligator forceps. The forceps are used when the foreign body is to be directly grasped, and the right-angle probe is used in an attempt to reach behind the foreign object and displace it forward. Other useful instruments include Fogarty (vascular) and Foley catheters; "specialized" balloon-tipped catheters also are available in many EDs (see Fig. 60-5).[17] Magnets may be useful when the intranasal foreign body is part of magnetic jewelry.[31] Suction is primarily necessary for removing purulent secretions and any blood that may obscure the field. In some cases, suction can be used to withdraw foreign bodies directly. Suction may be useful with hard-to-grasp objects or small soft objects not tightly lodged in place.

www.ketabpezeshki.com 66485457-66963820

Cyanoacrylate-tipped swabs may be useful in certain circumstances. As noted previously with respect to otic foreign bodies, there is insufficient evidence to draw definitive conclusions about this approach.

AIRWAY

Clinical Features

Although improved diagnostic and therapeutic techniques have markedly reduced fatality rates from foreign body inhalation, airway tract foreign objects still cause significant mortality and anoxic brain damage. One large-city series of ambulance-transported airway foreign body patients reports a 3.3% mortality (an average of one patient per month) in the prehospital phase alone.[35]

Alternatively, airway foreign objects can have a presentation that is less dramatic than acute respiratory distress and can go undiagnosed for years. Delay in presentation and correct diagnosis is, perhaps surprisingly, common. Only half of patients in one pediatric series of lower respiratory tract foreign body were seen within 1 day of aspiration; an additional 20% were seen during the first week, and another 20% were seen after a delay of more than 1 week.[36] Another pediatric study identified a doubling of complication rates in patients who came to the hospital more than 48 hours postaspiration.[37] Patients with uncharacteristic presentations may have unusual foreign body introduction mechanisms, such as ingestion or penetrating trauma.[38] Patients with altered mental status from a variety of causes are at risk for occult aspiration, which may be difficult to diagnose. Even in large-series reports of aspiration, specific and reliable indicators of airway foreign body presence are elusive.[39]

The most common airway foreign bodies in one series were ingestible agents, primarily meats and medications.[35] Airway foreign body series also identify pins, needles, jewelry, thermometers, pencils, and metal and plastic toys. The primary reason to characterize the type of airway foreign object is to determine the likelihood of radiopacity. Most airway foreign bodies are not visible with plain films.[40] In one 8-year pediatric series of foreign body aspiration, the most commonly identified objects were nuts (59%) or other vegetable material (23%) not likely to be visualized on plain films. In another classic paper describing childhood asphyxiation with foreign bodies, nearly half of fatal choking cases were a result of food aspiration, with hot dogs (17%), candy (10%), nuts (9%), and grapes (8%) most prominent.[41] In another report, more than 90% of pediatric aspiration cases were of organic classification (usually nuts).[42]

Airway foreign bodies are seen more commonly in pediatric patients.[43] In one case series covering two decades, 75% of patients were younger than 9 years.[42] Peak incidence of aspiration is in the second year of life, with a brisk decline after age 3.[43] Mastication difficulty secondary to premature molar teeth contributes to pediatric food aspiration.[36] Also, the fact that children explore their environment with their hands and mouth translates into aspiration of nonfood objects. In adults, the peak aspiration incidence is in the elderly.[35] Some evidence suggests that adults are more likely than children to have nonfood items aspirated into the airway.[44]

Children and adults also differ with respect to anatomic location of aspirated foreign bodies. This is crucial because foreign body location plays a major role in determining associated morbidity or mortality risk. In adults, 75% of foreign bodies lodge in the proximal airways (larynx, trachea, main bronchi). In children, fewer than half of foreign objects are located proximally, with bronchial tree locations the most common.[42]

Foreign bodies can be located as proximally as the oropharynx, with retained intraoral bodies having been found in the medial pterygoid space.[45] The foreign object can be slightly distal, causing airway obstruction at the laryngeal or subglottic level. Foreign body impaction at this level often is caused by inappropriately executed attempts to finger sweep an oropharyngeal foreign body.[44] Subglottic foreign bodies are difficult to identify and may be associated with diagnostic delay in most cases.[46] The emergency physician needs to be able to glean historical clues to differentiate epiglottitis, asthma, and laryngotracheobronchitis from subglottic foreign body.

Airway foreign bodies usually pass beyond the laryngeal inlet[44] and may cause drastic obstruction. Unfortunately, tracheal foreign bodies have a surprisingly high incidence of lack of symptoms or worrisome clinical findings. Foreign bodies passing beyond the trachea are less likely to cause acute hypoxic crisis but can cause substantial respiratory embarrassment and can be difficult to remove. In adults, bronchial foreign bodies are found more often in the right bronchial tree. In one large series, 69% of bronchial foreign bodies were right sided.[42] The preferential passage of foreign bodies to the right side of the bronchial tree is usually reported to be less common for children than for adults. Some series report roughly equal left-right distribution of lower airway foreign bodies.[36] The explanation may be that whereas the carina is positioned right of the midtrachea in a third of children (and in 40% of infants), the proximal right bronchus is both wider and more steeply angled than the left.[47] Foreign objects can be bilateral, with 3.6% of patients in one series having foreign bodies in the right and left main bronchi.[42]

History

Clinical presentation can range from chronic nonspecific respiratory complaints to acute airway obstruction.[48] In most aspiration cases, foreign body presence is suspected after a thorough history. In the most dramatic cases, patients have a history of what is commonly termed the "cafe coronary." The patient attempts to swallow a food bolus (usually meat) larger than the esophagus can accept. The bolus lodges in the hypopharynx or trachea. Often there is confusion over whether the patient is having a myocardial infarction or has an obstructing foreign body, but the conscious cardiac patient is able to speak. Patients with airway foreign bodies may have noisy breathing, inspiratory stridor, vomiting, and possibly slight hemoptysis.[35]

Some patients may give a history similar to cafe coronary, with resolution of major symptoms. These symptoms, known as the *penetration syndrome,* occur in half of patients aspirating and include a choking sensation accompanied by respiratory distress with coughing, wheezing, and dyspnea.[42] Symptom resolution may result from the patient spontaneously clearing the foreign body by coughing. In some cases, coughing does not eject the foreign body completely, but rather impacts it in the subglottic region.[44] The emergency physician should maintain concern for retained airway foreign object in cases in which the patient history is one of perceived foreign body followed by cough with incomplete (or even complete) post-tussive symptom resolution.

In a 20-year series of adult and pediatric patients with suspected foreign body aspiration, sudden onset of choking and intractable cough were present in half, with eventual foreign body identification.[42] In addition to coughing and choking, stridor is a frequent component of an acute aspiration episode in patients of all ages.[44] Symptom distribution is similar in adult and pediatric patients,[42] but choking and wheezing appear more prominently in the pediatric literature. In one series of 87 pediatric patients with suspected foreign body, 96% had a history of a choking crisis.[49] Wheezing is common, having been reported in up to 75% of patients aged 8 to 66 months with airway foreign bodies.[36,43]

Most patients aspirating objects have persistent symptoms (e.g., cough, wheezing, dyspnea) after manifesting penetration

www.ketabpezeshki.com 66485457-66963820

syndrome, but 20% have no ongoing symptoms.[42] Many patients have a history of alarming symptoms followed by few ongoing complaints; the emergency physician should not dismiss aspirated foreign body from consideration in such patients. With sudden onset of dyspnea and odynophagia, an impacted subglottic object may be present. If the object is known to be sharp and thin, the emergency physician should suspect embedding between the vocal cords or in the subglottic region, with resultant partial obstruction.[44]

Other components of the history may provide clues to airway foreign body presence and location. Even when the history cannot be obtained directly or does not suggest aspirated foreign object, the emergency physician can infer foreign body presence in certain patients. Trauma patients in the ED with injured and loose teeth may have aspirated in the field or during emergency laryngoscopy for oral intubation.[42] The incidence of airway aspiration of avulsed teeth or prosthetic dental appliances is low (0.5% of 1411 facial trauma patients), but both the initial trauma and subsequent airway management pose risks for airway embarrassment owing to lodged dental matter.[50] Besides the intubated or obtunded patient with only indirect historical evidence of aspiration, conscious and alert patients may not give a direct history of aspiration owing to lack of dramatic airway symptoms or remoteness of the aspiration event and secondary problems (e.g., pneumonia). In some cases, such as penetrating trauma or blast injuries, the patient may be unaware of the potential for aspiration and not attribute symptoms to this entity.[40] Patients aspirating needles may have minimal or no symptoms, with chronic hemoptysis or odynophagia the only manifestation of these or similar foreign bodies.[42]

There is conflicting evidence regarding the role of neurologic disease in aspiration. Patients with deficits may be unaware or unable to report problems such as denture displacement; this inability has been associated with disastrous results in the case of airway obstruction from dental hardware.[51] Neurologic impairment may result in atypical or absent histories in cases of foreign body aspiration.[40] Reports of adult[42] and pediatric[49] series have identified little role, however, for neurologic impairment in foreign body aspiration. An atypical history is a concern in neurologically impaired patients, but the problem of foreign body aspiration with atypical history is uncommon in this patient population.

The child with respiratory difficulty after eating can represent a diagnostic dilemma. Children with stridor or other respiratory symptoms may have esophageal bolus impaction. The pediatric trachea is soft, especially posteriorly, and may be compressed by a large esophageal body pressing anteriorly on the trachea. In addition, the trachea itself may be displaced anteriorly and kinked, causing a partial obstruction. Fever and localized infection may indicate bony aspiration (e.g., into the piriform fossa) that may occur when bone-containing foods are fed to very young children.[52] Unfortunately, missed esophageal foreign bodies in children can result in long-term, yet mistaken, treatment for asthma (owing to wheezing and stridor from fistula formation).[53]

Other components of the history can help diagnose and characterize foreign bodies in patients with aspiration of nonfood objects. These items may be aspirated by children who are exploring their environment, by psychiatric patients, or by individuals who normally "store" small items in their mouths. The latter group includes repairmen, construction workers, seamstresses, and others who keep nails, pins, and other paraphernalia in their mouths for quick access.

Regardless of the nature of the foreign body, the presentation of patients with a retained airway foreign object may include only infectious complications. A foreign object may cause retropharyngeal abscess. A patient with atypical or recurrent pneumonia may have pulmonary infection secondary to persistence of a foreign object serving as a nidus of infection. In some cases the respiratory infection associated with retained pulmonary foreign body is silent but seeds distant organs with organisms, raising suspicion of an airway foreign body.

Patients may visit the ED with diagnoses of diseases thought to be infectious but actually have foreign bodies in the airway. A careful history should be obtained in the setting of suspected croup or epiglottitis because a foreign body in the trachea or larynx may have a clinical presentation similar to that of these infectious entities.

Physical Examination

Physical findings depend on degree of airway obstruction and duration of the object's presence in the respiratory system. Small objects causing no obstruction may produce no findings or may manifest as infectious complications. In many cases, however, the physical assessment is helpful in diagnosis and characterization of airway foreign bodies.

Cyanosis is present in 10% of patients, and coughing, audible wheezing, or overt respiratory distress occurs in 25 to 37% of patients with aspirated objects.[42,43] Unilateral diminution of breath sounds, when present, is a useful identifier of aspirated foreign body.[48] Patients may be stridorous or hoarse with upper airway foreign objects, and sternal retractions may be noted in patients with intratracheal foreign bodies.[35] More than half of children in one series had initial oxygen saturation values of 95% or lower.[42] Patients with secondary infection may have fever.

Oropharyngeal examination may reveal a foreign body posteriorly or "donor sites" of fractured teeth. The examination should include a search for fractured or missing dental prostheses, which sometimes can be lodged in pharyngeal areas for days and can account for sudden deterioration in status when the airway becomes occluded, as can occur after coughing.[51] Oropharyngeal examination frequently can be augmented by indirect or direct laryngoscopy or nasopharyngoscopy, but these procedures should be performed only if the emergency physician judges that procedural stress does not pose undue risk of airway compromise. Furthermore, laryngoscopy or nasopharyngoscopy should be undertaken only if definitive airway management equipment and expertise are readily available. The advantage of these modalities is that they allow excellent visualization of the proximal airway, which is important diagnostically and therapeutically. Indirect laryngoscopy can prove useful in detection of radiolucent structures.

Assessment of the neck may reveal accessory muscle use. Tracheal palpation may reveal a thud, indicating movement of a mobile foreign body against the tracheal wall. Abnormal inspiratory sounds may be heard on tracheal auscultation.[44] Coughing may result from local irritation caused by bronchial foreign bodies. Localized or apparently generalized wheezing is frequently auscultated in patients with lower respiratory tract foreign bodies.[43] The emergency physician should keep in mind the dictum that "all that wheezes is not asthma." If a mainstem bronchus is completely obstructed, breath sounds are absent on the involved side. Occasionally a foreign body acts as a one-way valve, allowing air into the lung during inspiration but permitting none to exit during expiration. The involved lung becomes hyperexpanded, which may be detected as hyper-resonance to percussion.

Diagnostic Strategies

In the stable patient, plain radiography of the neck and chest remains the mainstay of airway foreign body imaging.[40] Air trapping may be visible when inspiratory and expiratory films are compared.[43] Other potentially useful imaging techniques are

www.ketabpezeshki.com 66485457-66963820

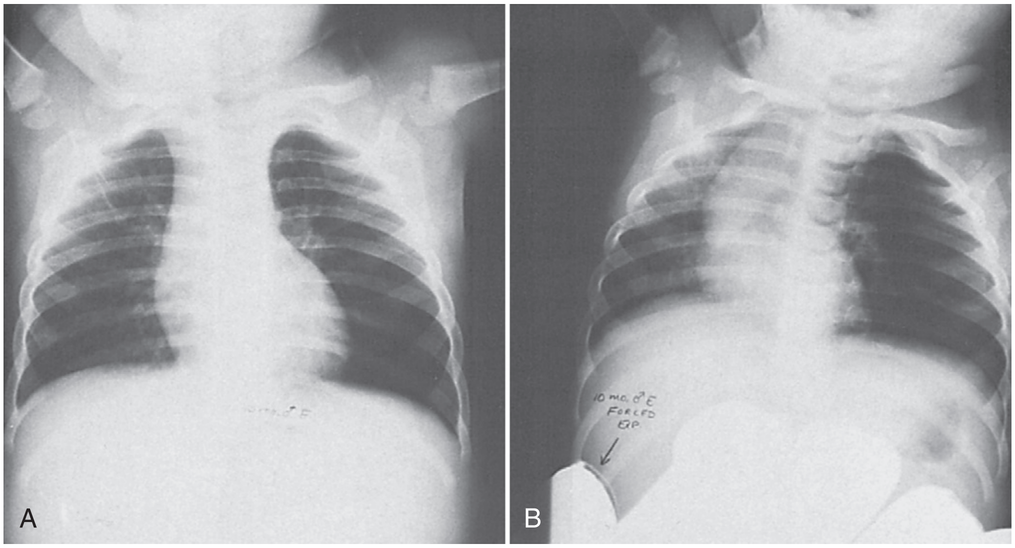


Figure 60-6. **A,** "Normal" inspiratory chest film in child with left mainstem bronchus foreign body. **B,** Forced expiratory view shows expanded lung on the left with shift of mediastinum to uninvolved right side.

fluoroscopy, CT, and MRI, although bronchoscopy and microlaryngoscopy (with an operating microscope) remain the ultimate diagnostic modalities.[43]

A normal radiograph cannot rule out an aspirated foreign body in a patient with a suggestive history. Studies of series of patients who underwent endoscopy for suspected foreign body aspiration demonstrate the mediocre sensitivity and specificity of plain x-ray films.[42,48,49] X-ray findings are indirect in most cases; radiopaque foreign bodies were found uncommonly (less than a fourth of patients in one series).[54] This series included foreign bodies in the upper airway (at the level of the trachea); plain radiographs in these patients were frequently negative.[49] If doubt exists as to the radiopacity of the suspected foreign body, and if the patient has brought a piece of the object, it may be tested for radiodensity by placing it over the shoulder during taking of the radiographs. Specific findings on plain radiography are categorized as direct (i.e., identification of the foreign body itself) or indirect (e.g., hyperinflation). Direct foreign body identification is relatively uncommon.[44] When subglottic foreign body impaction is suspected, plain soft tissue radiographs of the neck are the best initial step, provided that they are performed under the close supervision of a physician trained in provision of airway management. In some of these patients, plain radiography may definitively show an intratracheal foreign body and can provide a rapid diagnosis.[44]

Indirect or secondary signs, such as narrowing of the subglottic space from an embedded foreign object, are an important aid in foreign body radiography.[44] Air trapping and atelectasis are the most common early clues to airway foreign body presence, with bronchiectasis and bronchial stenosis developing later.[40] In air trapping, a comparison of inspiratory and expiratory films shows a flat, fixed diaphragm on the involved side, and the heart and mediastinum shift to the uninvolved side during expiration (Fig. 60-6). In one pediatric series, air trapping was found in 90% of patients with lower airway foreign bodies, but it appears that the indirect signs of airway foreign body are easily missed on initial x-ray readings.[36] The small caliber of the airways may explain the relatively higher frequency of air trapping in children compared with adult patients.[42] If obstruction becomes complete, the involved lung becomes atelectatic; patients with persistent atelectasis should have foreign objects considered as the explanation. An additional indirect radiographic sign of more proximal foreign bodies is prevertebral swelling or soft tissue emphysema seen on neck films.[40]

When a foreign body is seen on the chest radiograph but its exact location (airway or esophagus) is in doubt, the anteroposterior orientation of the object may help (Fig. 60-7). Esophageal foreign bodies usually are oriented in the coronal plane, and airway objects are oriented in the sagittal plane (Fig. 60-8). X-ray films also can provide useful information by showing whether the object is within or outside of the tracheal air column (Fig. 60-9).

Fluoroscopy was used historically, but has been largely supplanted by advances in bronchoscopy. Fluoroscopy has identified air trapping, but one case series reported a relatively low 77% sensitivity for foreign body presence using air trapping.[36,40] CT, especially helical, is useful in evaluating patients with suspected airway foreign bodies when plain films are negative. Even when an aspirated object is radiolucent, and often when the object cannot be identified by standard thoracic CT, helical CT has visualized the foreign body when it is of greater density than surrounding tissues. Helical CT can obviate the need for diagnostic flexible bronchoscopy, allowing direct progression to therapeutic rigid bronchoscopy for foreign object retrieval. CT also can be useful in delineating specific anatomic changes caused by foreign bodies. MRI may be useful in cases of aspiration of nuts, especially in children. The high fat content of the nut translates to relatively easy visualization on MRI.[40]

Management

Management of an airway tract foreign body is removal, which generally leads to rapid recovery of the patient.[42] The emergency physician can accomplish removal in some patients. When the foreign object is distal to the oropharynx, however, subspecialty consultation is the safest and most expeditious means for foreign body removal. In rare cases, even oropharyngeal foreign bodies (such as small needles) may necessitate subspecialist consultation and operative removal.[55] As a general rule, early bronchoscopy in any patient with a suspected foreign body is key to reducing morbidity and mortality, and the role of endoscopic management remains important given limitations of other diagnostic methods.[43,48] Recent pediatric data suggest that performance of bronchoscopy within 24 hours of initial ED

www.ketabpezeshki.com 66485457-66963820

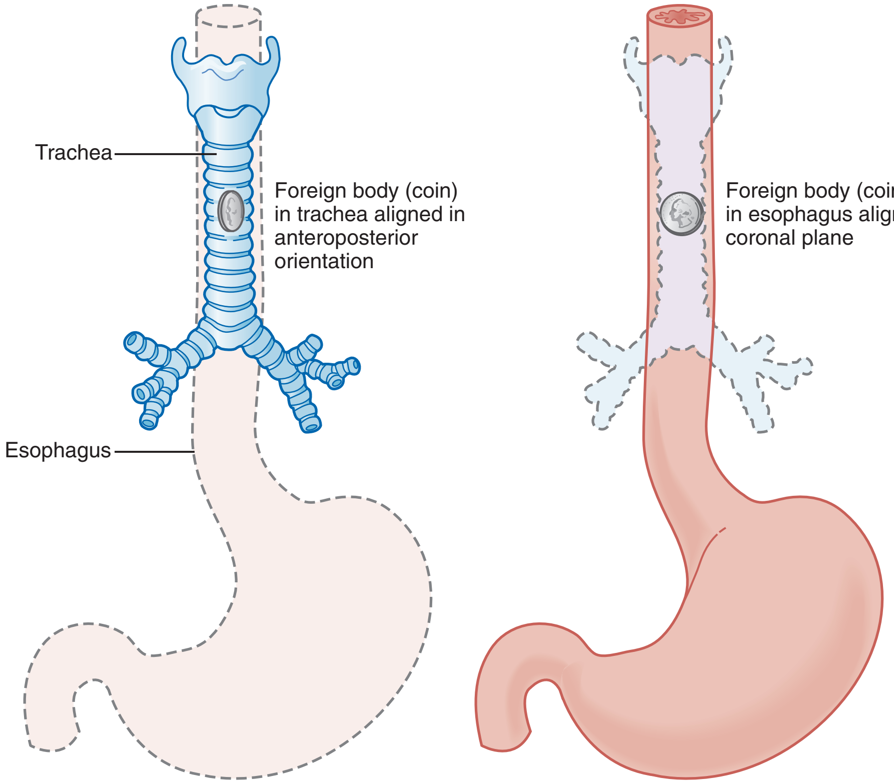


Figure 60-7. Coronal orientation of esophageal foreign object *(left)* and sagittal orientation of tracheal foreign object *(right)*.

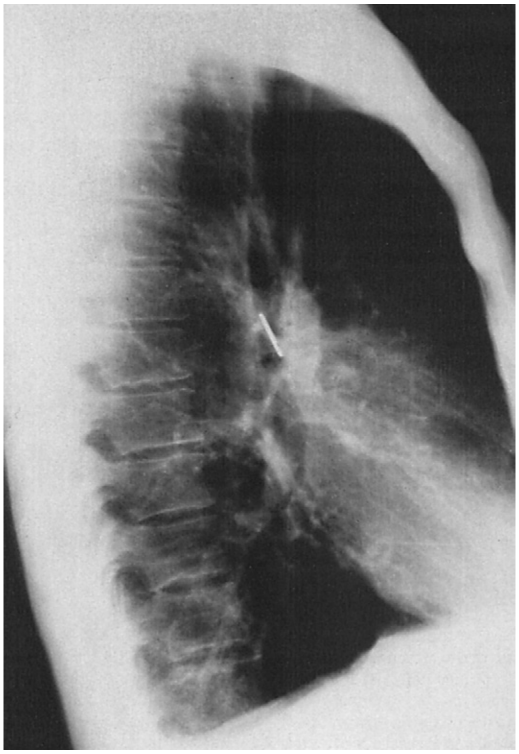


Figure 60-8. Lateral x-ray study of chest shows aspirated coin in tracheal air column.

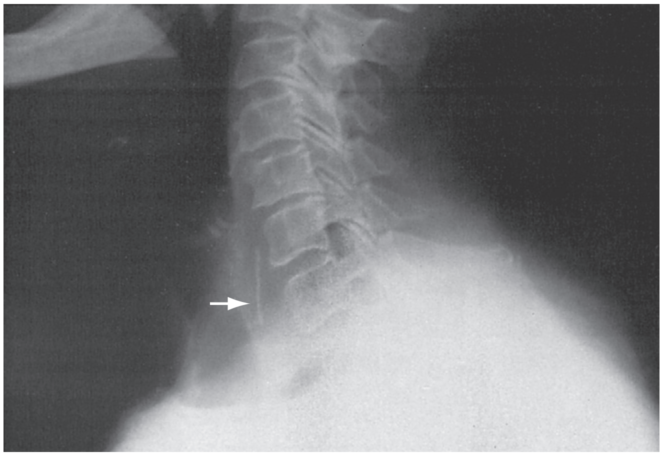


Figure 60-9. Lateral x-ray study of neck shows foreign body (chicken bone) in esophageal soft tissue shadow *(arrow)*.

presentation (as compared with later bronchoscopy) reduces complications by half.[37]

The emergency physician may need to act definitively in a patient with critical airway obstruction and impending or actual respiratory arrest. The emergency physician has three options: (1) attempt to extract the foreign body with maneuvers, (2) perform laryngoscopy with attempts at removal under direct visualization, or (3) control the patient's airway.

Some maneuvers to remove foreign bodies acutely are accomplished without direct visualization. These attempts may be directed at the proximal or distal respiratory tract. Proximal foreign body removal without direct visualization is attempted with the finger sweep, but this technique is losing favor in pediatric and adult patients. In infants, the larynx is higher, at the level of the fourth cervical vertebra; by age 4 years, it is at the C5-6 level. Blind finger sweeping has resulted in conversion of partial to complete airway obstruction when objects are displaced into the subglottic space. Finger sweeping also is less preferable in adults; abdominal thrusts and back blows are safer and at least as efficacious.[44] These procedures produce increased intraluminal

www.ketabpezeshki.com 66485457-66963820

pressure in the trachea and force objects out into the pharynx, from which they are easily removed.[56]

The optimal management of a choking infant is controversial with regard to whether back blows, chest thrusts, or abdominal thrusts should be the initial intervention. Data are limited, but the American Heart Association, National Academy of Sciences, American Academy of Pediatrics, and American Thoracic Society recommend up to five back blows with the patient in a head-down position, followed by chest thrusts. Intubation or needle cricothyroidotomy may be performed if consistent with the setting.

If indirect efforts fail to remove foreign bodies from patients in extremis, direct laryngoscopic visualization during intubation may reveal a proximal foreign object that can be removed with Magill forceps.[35] If a foreign body is not visualized on laryngoscopy, the emergency physician may choose to intubate the patient. Intubation may force the foreign body distally, especially if the endotracheal tube tip is passed beyond the carina. Placement of the endotracheal tube into the right mainstem bronchus may displace the foreign body into the right bronchus, allowing oxygenation and ventilation through the left-sided pulmonary tree when the endotracheal tube is withdrawn back to normal position proximal to the carina. In cases in which intubation fails because of positioning of the foreign object, surgical cricothyrotomy (needle cricothyrotomy in young children) is indicated. Cricothyrotomy may bypass proximal obstruction and provide sufficient oxygenation to bridge the time gap to definitive care by surgical subspecialists.

Patients who do not require immediate intubation or cricothyrotomy for complete airway obstruction may require airway management for other indications. These patients may have poor oxygenation or may require assisted ventilations during transport to surgery. In either case, if airway obstruction is not too proximal or too complete, the emergency physician should consider placement of a laryngeal mask airway. The laryngeal mask airway offers easy airway access, excellent visualization, and safe respiratory management during bronchoscopic procedures. The laryngeal mask airway allows use of larger bronchoscopes than those used in intubated children. Especially in pediatric patients requiring bronchoscopy, the laryngeal mask airway may be an appropriate airway.[42]

In noncritical situations, the only airway foreign objects generally amenable to emergency physician removal are those in the oropharynx, which are best removed by forceps under direct laryngoscopic visualization performed after administration of topical anesthesia. Care should be taken when foreign objects appear to be impaled in the oropharynx because postremoval hemorrhage can occur. Also, special care should be taken to prevent posterior displacement of oropharyngeal foreign objects or dropping of incompletely grasped foreign bodies into the airway. These complications are risked in patients who are uncooperative; in these patients, consultation for removal in the operating room is the best course. Removal of a laryngeal foreign object, even with general anesthesia, can be dangerous. Risks include hemorrhage, laryngeal trauma, and airway obstruction from the mobilized foreign object; subspecialty consultation also is indicated for laryngeal foreign body removal.[44]

The management decisions for endoscopic evaluation and treatment depend on the clinical presentation. An emerging standard is initial use of rigid bronchoscopy when there is time-critical airway obstruction, with flexible instrumentation used for diagnostic purposes in less acute patients.[43] The emergency physician may have requisite expertise to perform flexible bronchoscopy in occasional low-risk cases, but consultants may have broader experience, as well as facility with potentially useful adjuncts such as cinefluoroscopy.[57] In patients for whom overall clinical suspicion for the presence of a foreign body is reduced, fiberoptic bronchoscopy may be indicated, but rigid bronchoscopy is the optimal first step when clinical suspicion is high.[36] Foreign body removal usually is achieved with rigid bronchoscopy with the patient under general anesthesia, but in unusual circumstances flexible bronchoscopy with local anesthesia may suffice for foreign body location and removal.[42]

Even after foreign body removal, sequelae may occur. Airway fish bones, even after removal, can cause deep tissue infection, such as cervical spondylodiskitis.[58] A patient with an airway foreign body should be observed for development of sequelae, with postdischarge follow-up within a few days for reassessment. In pediatric patients, education should focus on preventive efforts to reduce the likelihood of a repeat aspiration episode.

GASTROINTESTINAL TRACT

Clinical Features

Foreign bodies in the gastrointestinal tract can be seen in all age groups, although most cases occur in pediatric patients.[59] There is no requirement for predisposing anatomic or pathologic conditions. Series have noted, however, that in addition to younger persons, those at highest risk include edentulous, incarcerated, and psychiatric patients.[60,61] Higher risk is also present in cases in which chemical and/or electrical mucosal injury is likely (e.g., button battery or magnet ingestions).[62,63]

Perforation occurs in approximately 3% of cases and most frequently involves the esophagus or the ileocecal region.[64] Because ingested objects are expected to pass spontaneously in the vast majority of patients with normal anatomy, initial management is usually expectant, with radiographic and stool follow-up to confirm passage.[64] Direct foreign body removal through surgical intervention is usually unnecessary, although some centers pursue early operative intervention for impacted esophageal objects including coins.[65] In pediatric series, endoscopy—including esophagoscopy, laryngoscopy, and anoscopy—tends to be successful in removing the foreign body in nearly all cases.[65,66] Endoscopic removal of esophageal foreign bodies also allows for simultaneous performance of mucosal biopsy, which may be useful in pediatric patients brought to the ED with esophageal food impactions (the majority of these children will have correctable abnormalities identified on biopsy).[67] Early endoscopy should usually be undertaken in cases of potential toxicity (e.g., button battery ingestion), altered anatomy (e.g., prior abdominal surgery), or sharp foreign bodies.

Pharynx and Esophagus

Foreign bodies lodged in the pharynx and esophagus are usually a sharp object (e.g., fishbone) that is impaled in the wall of the pharynx, hypopharynx, or esophagus or a larger bolus, usually a coin or food, that cannot pass beyond the anatomic points of esophageal constriction. Pediatric series analyzing both witnessed and unwitnessed esophageal foreign body ingestion report that coins are the most common culprit, making up over half of ingested foreign bodies in typical series.[65,68] Esophageal constriction locations, where foreign objects tend to lodge, are (1) the proximal esophagus at the level of the cricopharyngeal muscle and thoracic inlet or, radiographically, the clavicular level; (2) the midesophagus at the level of the aortic arch and carina; and (3) the distal esophagus just proximal to the esophagogastric junction or, radiographically, a level two to four vertebral bodies cephalad to the gastric bubble. Foreign bodies may lodge at any level of the esophagus (or remainder of the gastrointestinal tract) with abnormal anatomy. The complication rate for esophageal foreign body ingestion is estimated at less than 2%, but the sequelae can be severe. Complications become more likely with increasing impaction time and include esophageal erosion or perforation, tracheal

www.ketabpezeshki.com 66485457-66963820

compression, mediastinitis, esophagus-to-airway or esophagus-to-vascular fistulae, spondylodiskitis, extraluminal migration, abscess development, and formation of strictures or false esophageal diverticula.[65,69-71]

History

A useful history is usually available from the patient or caregivers. Children are particularly likely to have esophageal foreign bodies. The object most often encountered is a coin.[65,68] Other common objects are food, toys, bones, batteries, wood, and glass.[72] In situations in which the history is unclear, the emergency physician should consider an ingested foreign body in the differential diagnosis of atypical chest pain.[73]

Esophageal rupture is a particular risk from the button (disk) battery.[3] These batteries cause pathologic changes through pressure, electrical current, leakage of corrosives, or heavy metal poisoning.[59] Batteries containing potassium can produce liquefaction necrosis, and those containing mercury can cause mercury poisoning.[74] The identification of button batteries has both prognostic and therapeutic ramifications; esophageal button battery impaction is an indication for prompt endoscopic intervention.[59] Although not as likely as button batteries or sharp foreign bodies to cause esophageal rupture, practically any ingested foreign body (e.g., meat) can cause rupture if patients vomit repeatedly after impaction.[75]

An ingested object in place for longer than 24 hours is more likely to cause mucosal erosion. Management plans for ingested bodies are different when the objects have been in the gastrointestinal tract for a long duration.[72] Children usually are brought to the ED within 6 hours of foreign object ingestion. The most frequent presenting symptoms are dysphagia, drooling, retching, and vomiting. Pain, usually odynophagia, may be the major complaint. Anorexia, wheezing, or chest or neck pain also may be present. Patients may complain that they can feel the object in the throat or chest and are unable to pass it any farther. The victim often is able to localize the foreign body accurately, particularly in the upper esophagus, and should be asked to indicate the level of obstruction. Drooling is consistent with high-grade obstruction. Patients rarely have complaints of shortness of breath or air hunger, though when present, a large foreign body in the esophagus impinging anteriorly, compressing the trachea, should be suspected. Infants and children may experience coughing, choking, and significant respiratory compromise from foreign bodies lodged in the upper esophagus.[65]

Patients may manifest late sequelae. Foreign bodies serving as a nidus for infection result in complaints (e.g., fever) consistent with the infectious process.[65] Signs of mediastinitis indicate esophageal perforation. Perforation of the esophagus with erosion into the vasculature or pulmonary tree can result in presentations ranging from hemoptysis to pulmonary abscess to life-threatening hemorrhage.[76,77]

The history should include any known esophageal anatomic abnormality or prior instrumentation. A patient with a history of esophageal stenting should be considered to have stent migration when the history is dysphagia. Migration typically occurs within the first week of placement but has been reported up to 1 year after initial placement.[78]

Physical Examination

Examination begins with a careful inspection of the pharynx and hypopharynx. This search may reveal the foreign body or identify an oropharyngeal mucosal scratch that can cause foreign body symptoms even in the absence of an impacted object. Oropharyngeal examination also may provide indirect clues; for example, a missing dental plate on examination should lead the emergency physician to suspect this item as a possible gastrointestinal tract foreign object. The base of the tongue, vallecula, supraglottic area, epiglottis, and piriform sinus should be examined. Topical anesthesia facilitates the examination. If adequate visualization is not obtained with the indirect laryngoscopy mirror, fiberoptic nasopharyngoscopy or direct laryngoscopy may be performed.

Subcutaneous emphysema found by neck palpation indicates probable esophageal perforation. Drooling and inability to handle secretions are secondary indicators of esophageal impaction; wheezing can occur if there is airway compression.[65]

Diagnostic Strategies

Given the limitations of clinical presentation and examination in excluding a foreign body, radiography is routine and contributes to diagnosis and management in about half of cases.[79] The initial step is generally a posteroanterior (PA) and lateral chest radiograph and lateral cervical spine x-ray study using soft tissue technique. The primary utility of plain radiography lies in detection of radiopaque objects, although some series report that retrospective review of lateral neck x-ray films identifies indirect signs (e.g., soft tissue swelling) in most patients with proximal aerodigestive tract foreign body.[79] Overall, the sensitivity of plain radiography for detection of esophageal foreign bodies is relatively poor[80]; however, there are case reports of plain radiography identifying metal foreign objects missed on direct (including endoscopic) examination.[81] In patients who are transferred to the ED from an outlying hospital, repeat radiography may be useful to assess whether the foreign object has passed into the stomach in the interval since prior films (see Fig. 60-10).[72]

Esophageal foreign objects usually align themselves in the coronal plane and are posterior to the tracheal air column on lateral view. Coins in the esophagus lie in the coronal position in virtually all cases because the opening into the esophagus is much wider in this orientation.[72] Certain common foreign bodies are not radiopaque; for example, fish and chicken bones are frequently ingested, are difficult to visualize directly or radiographically, and often scratch the esophageal mucosa. Plain films of the neck and chest have a sensitivity of roughly 25% for impacted fish bones.[82] Although some studies suggest that technique variation improves fish bone detection, plain x-ray examination remains insufficiently sensitive as a means to rule out these foreign bodies.[83] Studies suggest that plain films are false-negative in at least 30 to 55% of cases and false-positive in about a fourth of cases.[82]

When plain films fail to visualize foreign bodies and suspicion remains high, one option is contrast esophagography, which can be useful with radiopaque and sometimes with radiolucent foreign bodies.[72,84] If perforation is not a concern, barium may be used as the contrast medium because it provides higher-quality images. If an esophageal leak is suspected, water-soluble contrast solution should be used; a barium follow-up study may be considered if the initial contrast study is equivocal or suspicion remains high. When initial contrast films are not definitive, patients may be asked to swallow a contrast-soaked cotton ball, which may localize the foreign body by lodging proximal to the object. Contrast studies, even performed with barium, have limitations when the suspected object is an impacted bone.[80] In one series using barium-soaked cotton balls, false-positive and false-negative rates were 27% and 40%, respectively.[85] Barium swallow yields better results but risks aspiration and coats the object and esophagus, reducing effectiveness of subsequent endoscopy.

CT scans with coronal and sagittal reconstructions are useful in identifying foreign bodies or more completely characterizing objects seen on plain films.[86] CT has been recommended as the primary diagnostic modality because it can give information about foreign body size, type, location, and orientation with respect to other anatomic structures.[60,86] In one study,

www.ketabpezeshki.com 66485457-66963820

non–contrast-enhanced CT interpreted by resident physicians detected all impacted bony foreign bodies found by esophagoscopy; the one false-positive result was caused by esophageal calcification, and no false-negative results occurred. Overall, CT use reduced the incidence of negative esophagoscopies. This study portends a potentially important role for CT in imaging of impacted bony foreign objects.[72] CT also can assist with identification of complications. Also, CT may be used in patients with positive plain films and negative esophagoscopy to search for objects that have migrated from the intraluminal to extraluminal space.[60]

A relatively inexpensive and noninvasive modality reported to be useful in detection and characterization of metal foreign bodies is the hand-held metal detector. Use of a commercial hand-held metal detector (Super Scanner; Garrett Security Systems, Garland, Tex.) has been studied in large series of adult and pediatric patients with suspected esophageal metallic foreign bodies. Early data reported no complications, with positive and negative predictive values approximating 90 to 100%.[87] More recent series confirm high positive predictive value but find much lower negative predictive value.[88] The hand-held metal detector does appear to easily detect aluminum foreign bodies missed by radiography. Its use avoids time, radiation, and costs associated with radiography. Especially when results are positive and indicate a foreign body below the diaphragm, metal detector use may obviate the need for radiography in patients with suspected coin ingestion.[88]

Management

Pharyngeal foreign bodies visualized by direct or indirect laryngoscopy usually can be removed with forceps or a clamp. The emergency physician should guard against the possibility of inducing trauma or airway obstruction during extraction attempts.

Management of esophageal foreign bodies depends on many factors. With an esophageal food bolus or coin, the emergency physician may be able to provide complete management. With sharp objects, displaced esophageal stents, or impacted button batteries, more invasive management is necessary.[72] Management strategy depends on the nature of the foreign body, the length of time the object has been lodged, and the expertise and experience of the clinicians managing the case.[72] In addition, the patient's age and prior medical and surgical history may be relevant.[66] The overall success rate for nonsurgical removal of objects from the esophagus is greater than 95%.[85]

The first basic strategy for esophageal foreign body management is applicable only if the object is known to be an impacted food bolus. In these cases, pharmacologic maneuvers may be tried to move the bolus into the stomach. Glucagon (0.5 to 2 mg) given intravenously has been used to relieve distal food obstructions. The drug acts by lowering the smooth muscle tone at the lower esophageal sphincter without inhibiting normal esophageal peristalsis. This mechanism is theoretic, and a critical assessment of the relevant evidence concluded that data supporting glucagon use for esophageal impaction were unconvincing. Benzodiazepines appear to have contributed to glucagon's success as documented in at least one report.[89] Although it remains reasonable to try glucagon, the drug should be given slowly; if glucagon is given too rapidly there is theoretic risk that vomiting could cause rupture of an obstructed esophagus. Other pharmacologic agents have been used with mixed success. Gas-forming agents have been used, and although supporting evidence is sparse, some investigators suggest that administration of these agents alone or in combination with glucagon be the procedure attempted first. Patients who report chest pain at presentation should not be given gas-forming agents because these patients may have esophageal perforation. Two other agents used for distal food bolus impaction, which are probably not as useful as glucagon, are nitroglycerin and nifedipine. Both of these agents have a relaxing action on the lower esophageal sphincter and are safe and roughly equally (if only marginally) effective maneuvers for therapy of impacted food bolus. A last approach, enzymatic degradation of an impacted meat bolus by use of the proteolytic enzyme papain, has fallen into disfavor because of risks of esophageal perforation.

The preferred strategy for esophageal foreign body removal is endoscopy. Flexible endoscopy does not require general anesthesia, can be performed in a sedated (nonintubated) patient, and may be diagnostic and therapeutic in the case of foreign bodies such as coins.[66] The high overall success of endoscopy has prompted some experts to recommend that patients with symptoms starting within 48 hours of ED presentation be taken directly to endoscopy if no suspected complication is evident.[72]

Another removal strategy, best suited for smooth, nonimpacted, and blunt objects, uses a contrast-filled balloon catheter and fluoroscopy. A Foley catheter is introduced into the esophagus, and the balloon is passed beyond the foreign body, inflated with radiographic contrast material, and withdrawn under fluoroscopic monitoring; the object is extracted with the catheter. To minimize risk of foreign body aspiration, this procedure should be performed with the patient in a steep, head-down position in lateral decubitus; the procedure is contraindicated in patients with airway compromise, complete esophageal obstruction, or an inability to cooperate.

The final strategy for active foreign body removal, bougienage, involves pushing the foreign object into the stomach. Strict criteria determine eligibility for this procedure, which generally is not performed by the emergency physician. Compared with endoscopy, bougienage appears to be at least as safe, and much more time- and cost-efficient.[90] Although patients' eligibility for bougienage may be limited by factors such as presentation delay, when performed, the procedure appears to be successful in up to 95% of attempts.[90]

The fifth approach, expectant management hoping for spontaneous foreign object passage into the stomach, is often successful. This approach is best suited for patients seen within 24 hours of ingestion who have a radiographically identified "safe" object (e.g., small coin) in the distal esophagus.[72] The button battery is associated with specific expectant management issues. If a disk battery has been ingested, its location must be ascertained, with immediate removal performed if it has lodged in the esophagus. If the button battery has passed distal to the esophagus, the patient can be observed, with follow-up radiography to confirm spontaneous passage through the gastrointestinal tract.[91]

After the removal of an esophageal foreign body, regardless of the method used, a follow-up esophagogram is frequently necessary to evaluate esophageal anatomy and patency. Referral for evaluation of dysphagia and obstruction should be made.

Stomach and Bowel

Foreign bodies that reach the stomach (Fig. 60-10) rarely cause major difficulties, although problems such as perforation and infection (e.g., after occult fish bone ingestion) may occur.[92] Although significant sequelae are more likely after ingestion of sharp foreign bodies, clinical problems may occur even with ingestion of blunt objects. Observation and expectant management are usually appropriate[91] because ingested foreign bodies reaching the stomach usually are propelled by peristalsis through the length of the gastrointestinal tract, with expulsion in a few days. Objects may pass beyond the esophagus and still become impacted, however, most often at the gastric outlet or the ileocecal valve, although complications can arise at any point throughout the intestinal portion of the gastrointestinal tract.[93,94] If the foreign body is a bezoar, a mass of undigestible food or nonfood material, there may be a palpable mass on abdominal examination. Otherwise, the physical examination is relatively unhelpful, only

www.ketabpezeshki.com 66485457-66963820

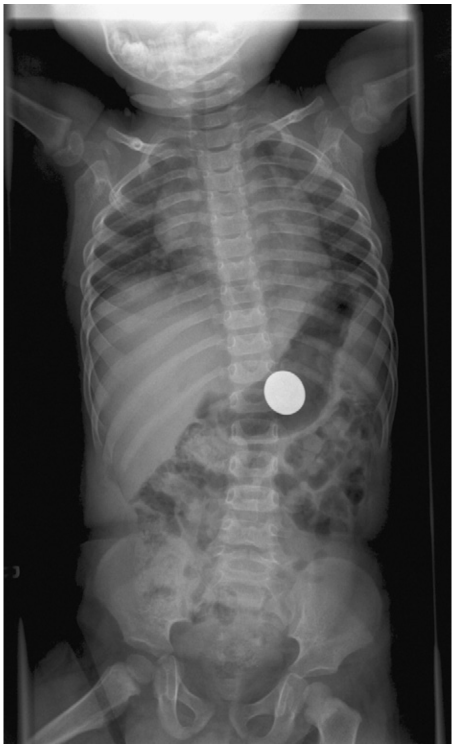


Figure 60-10. Radiograph of a child after ingestion of a coin, located in the stomach.

Figure 60-11. Radiograph of a patient after body packing. Note the appearance of previously prepared drug packages.

rarely revealing indirect evidence of foreign body presence or complications.

History

Signs and symptoms of intraluminal objects range from none to vague abdominal pain to obstruction or perforation-associated peritonitis.[94] Most patients have a specific history of ingested items, however, or the circumstances indicate the likelihood and character of an intestinal foreign object. Occasionally, emergency physicians encounter patients with psychiatric or secondary-gain reasons for foreign body ingestion.

Hiding of illicit drugs is an important motivation for foreign body ingestion. Rupture of these drug-containing packages, especially when cocaine is involved, can result in rapid and lethal consequences. Less often, packages can cause bowel obstruction. Even when obstruction is not present, vomiting may be reported. *Body packing*, which entails systematic gastrointestinal tract placement of previously prepared drug packages (Fig. 60-11), should be clinically differentiated from *body stuffing*, which denotes hurried ingestion of hastily prepared packages in the face of imminent police presence. Body stuffers are more likely to experience toxicity because of the poor packaging of drugs and are less likely to have positive plain radiography findings.[95] Drugs most often seen with body packing or body stuffing are cocaine and heroin, with amphetamines and cannabinoids seen less frequently.

Another important component of the history is medical implants in the gastrointestinal tract. Dental implants can migrate and cause complications in the distal gastrointestinal tract.[96] Expandable esophageal stents migrate in some patients, and biliary stents have also been become malpositioned with resulting complications.[97]

Patients with gastrointestinal tract foreign bodies should be asked about history possibly related to bezoar presence. A habit of chewing hairs can result in trichobezoars, which infrequently extend from the stomach into the small intestine as a “tail” (Rapunzel syndrome). Phytobezoars (composed of vegetable matter) and lactobezoars (from milk curds) also have caused complications, usually in the stomach.[98] Infants with lactobezoars from undigested formula may have a history of prematurity and often are receiving formulas that have a high casein-to-whey ratio. Other bezoars may be composed of infectious material (e.g., fungal bezoars) or inorganic substances (e.g., lithobezoars).[99]

Other specific intestinal foreign bodies, previously mentioned in the discussion of esophageal impaction, are important in the distal gastrointestinal tract. Button batteries can rupture in the intestines, and fish bones have penetrated through the gastric mucosa. Ingested toothpicks can lodge in the bowel wall, causing gastrointestinal complications and erosions or compression of nearby structures.[86]

Diagnostic Strategies

The initial imaging modality is plain radiography, which is often diagnostic (see Figs. 60-10, 60-12, and 60-13). Even when suspicion is low, radiography can identify foreign bodies as the explanation for symptoms.[101] Two-view plain radiography has proved useful for situations ranging from coin ingestion to body packing (see Figs. 60-10 and 60-11). Plain radiography is positive in approximately 90% of body packers but is nearly always negative in body stuffers and is usually negative in patients who have ingested crack vials.[95] Plain radiography usually identifies drug packets, but false-negative results do occur, and follow-up contrast radiography or CT is recommended.[102] Ultrasound has been reported useful in drug-packet cases in which plain radiography is nondiagnostic, but this modality is most helpful when results are positive (i.e., negative results are insufficient to rule out ingested packets).[103]

Contrast-enhanced upper gastrointestinal radiography has intermediate success in patients with suspected body stuffing or body packing. Contrast administration also has proved useful in outlining bezoars. CT can identify foreign bodies in the stomach

www.ketabpezeshki.com 66485457-66963820

Figure 60-12. Radiograph of a child after ingestion of a fishing lure without hooks.

Figure 60-13. Radiograph of a child after ingestion of a nail (which ultimately passed after observation).

and intestines and can help diagnose package ingestions in body stuffers. In these patients, contrast-enhanced CT outlines the bag containing the illicit drug; contrast administration also can help by identifying air trapped in the package. Some data suggest that with the advent of multidetector CT, contrast may be unnecessary to diagnose drug-containing packets; these results are preliminary and based on imaging of phantoms rather than actual patients.[104] Even contrast-enhanced CT has been found to occasionally produce false-negative results in detection of drug packages.[98] CT also has proved useful in determining whether complications of foreign body perforation are present.[83]

Management

The general rule for the management of gastric or intestinal foreign bodies is observation, although some centers favor early endoscopy and report this approach to be nearly universally successful.[68] Management decisions are based in part on the nature of the ingested object. Blunt objects can be expected to pass easily through the bowel, with expulsion verifiable by stool collection and examination. If there is particular concern, serial radiographs may be obtained after 5 to 7 days.[59] Sharp objects may be recovered by means of fiberoptic gastroscopy, although they traverse the gastrointestinal tract without incident in 90% of cases.[66] Early removal generally is required for objects wider than 2 cm because they do not pass the pylorus or longer than 5 to 6 cm because they do not clear the duodenal sweep.[59] Overall, surgery is required in less than 1% of intestinal foreign body cases, but there will be cases (e.g., bowel obstruction) in which clinical circumstances prompt early operative intervention.[93,94] When chosen, observation should be continued until (1) the object is found in the patient's stool; (2) the object causes bowel obstruction or perforation, necessitating immediate surgical intervention; or (3) the object shows no evidence of progression through the gastrointestinal tract on two radiographic examinations performed 24 hours apart, indicating impaction and need for active removal. In some cases the identity of the foreign body dictates management. In a body packer or body stuffer, regardless of external (i.e., law enforcement) pressures, the emergency physician should perform only interventions justified medically as reasonable steps to prevent injury from the ingested object or substance. If urgent drug package retrieval is unnecessary, the patient should be admitted for close observation for package passage or signs of toxicity. Monitoring of drug levels can be helpful. Usually the package passes through the gastrointestinal tract spontaneously. This passage can be facilitated with polyethylene glycol solution, laxatives, or both.

Immediate removal of drug-containing packages should be considered if the patient develops intestinal obstruction or drug intoxication. Classic teaching, citing risks of package rupture and drug toxicity, contends that endoscopic removal of cocaine-containing packages is never indicated.[105]

Button batteries represent another foreign body type with specific management implications. Intact batteries ingested into the stomach can be observed without the immediate removal necessary in cases of esophageal impaction. Repeat radiographs should be taken the next day to ensure movement of the battery into the intestinal tract, with films every 3 to 4 days thereafter to confirm continued distal movement. As with illicit drug–containing packages, administration of polyethylene glycol solution may speed distal movement. If the foreign body has not been passed after the first few clear-liquid stools, repeat radiography may identify the battery in the rectum, where it may be digitally evacuated.[91] Surgery is indicated for failure of the battery to progress, for radiographic signs of battery rupture, or for development of symptoms such as abdominal pain.[72] Endoscopy is increasingly reported to be useful for gastric button batteries, with success in 14 of 16 cases in one series (the other two batteries were endoscopically moved into the intestine and then passed spontaneously).[68] Available evidence is insufficient to confirm the usefulness of adjuvant medical therapy (e.g., steroids, antireflux agents, prophylactic antibiotics) in cases of button battery ingestion.[106]

Management of bezoars depends on type and location. Dietary therapy, endoscopic removal, and enzymatic dissolution frequently are used.[94] For some bezoars, specific therapy exists.

www.ketabpezeshki.com 66485457-66963820

Infants with lactobezoars should be changed to elemental diets and observed because most cases resolve without surgery.

Rectum

Most anorectal foreign bodies result from retrograde introduction, typically as a result of sexual practices that patients might be reluctant to discuss. The history may also be difficult as a result of mental disorders, found in over a third of patients with rectal foreign bodies in one 8-year series.[107] Prompt diagnosis is crucial because delay in definitive treatment is strongly associated with complications.

Patients with anorectal foreign bodies are often hesitant to give accurate histories. Studies have found that many patients with self-introduced anorectal foreign bodies do not initially admit to insertion, but rather report anal pain or simply constipation (which is in fact the most common complaint).[107] Other complaints include rectal pain, bleeding, or inability to void when large objects impinge on the urethra. History also may be lacking in body packers, who may have toxicity symptoms; fatal cardiovascular collapse can occur with ruptured cocaine packages.

It is possible for ingested food or objects to lodge in the rectum after passing through the proximal gastrointestinal tract. Rectal foreign masses of fish bones have been noted in many patients, all of whom strenuously denied transanal insertion, and in one series (characterized by a high proportion of mental patients) oral ingestion accounted for nearly half of the rectal foreign bodies.[107] If a patient admits to transanal foreign body placement, the emergency physician might gain more accurate information about size, shape, and physical characteristics to plan imaging and extraction. The duration for which the object has been in the anorectum has implications for mucosal failure and rupture.

Physical Examination

Patients with anorectal perforation may have findings of peritonitis or abdominal tenderness. On digital rectal examination, the foreign body might be directly palpated; this is the method of diagnosis in a large number of cases. In the absence of direct foreign body palpation, digital rectal examination may reveal findings (e.g., bloody discharge, loose sphincter tone) that raise suspicion for anorectal foreign body.

When the digital rectal examination findings are negative or when better visualization is required, anoscopy is the next step. Although the anoscope's diameter limits the size of foreign bodies that may be extracted through the instrument, anoscopy affords an improved view of the positioning of the object and information regarding its nature. Similarly, rigid sigmoidoscopy may be performed, with special care taken to minimize pressure on possibly ischemic anorectal mucosa. In many patients, especially patients in whom multiple examinations or removal attempts have been made, sedation and analgesia may be required to enable invasive examination techniques. When there is any doubt about the integrity of the anorectal mucosa, invasive examination is best done in the operating room with use of general anesthesia.

Diagnostic Strategies

The foreign body may be detected on a plain abdominal radiograph (Fig. 60-14). Plain films were diagnostic in nearly half of patients in one series and are recommended as the initial imaging technique. An important secondary finding is free intra-abdominal air secondary to anorectal perforation. If the object is not visualized on plain films, a contrast study can be performed, with care taken to minimize hydrostatic pressures on potentially compromised mucosa. Water-soluble contrast should be used if perforation is suspected. Specialized imaging, such as CT, is not usually part of the imaging workup but may be indicated if complications are suspected.

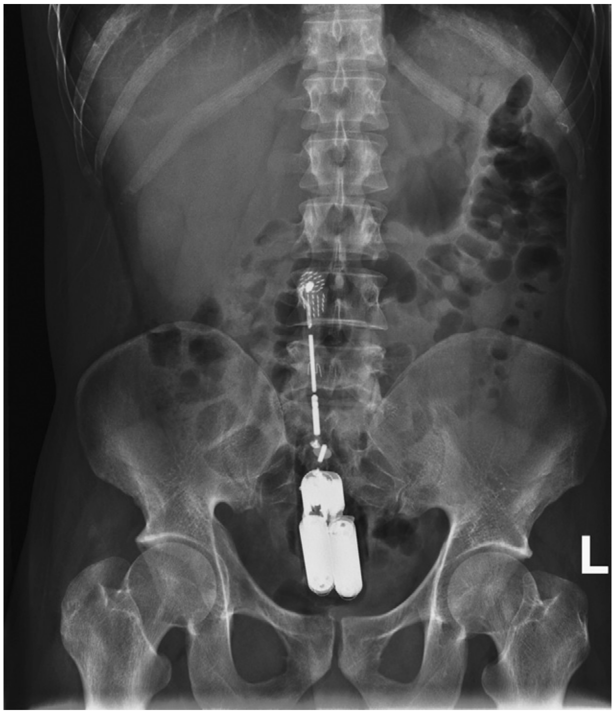


Figure 60-14. Radiograph of a patient who inserted an electronic toothbrush into the rectum. The toothbrush was removed during proctoscopy.

Management

Using patience and judicious sedation and analgesia, the emergency physician often can remove rectal foreign bodies. Surgical intervention may be necessary on occasion, and in fact has been required in the majority of patients in some series.[108] Depending on the nature of the foreign body and the presence of damage or perforation of the rectal wall, transanal removal (with or without sedation and local anesthesia) is successful in roughly half of patients, with the remainder requiring general anesthesia.[107] Some advocate early triage of patients for operating room removal if ED foreign body extraction carries undue risk of anal sphincter injury.[109] The emergency physician should not attempt to retrieve objects that pose a high risk for rectal injury because of sharp edges or the likelihood of dangerous breakage (e.g., light bulbs).

Initial efforts at foreign body removal in the ED should begin with the examiner's digit. Small rectal objects occasionally can be hooked by the finger and withdrawn; this is the initial technique in patients who do not have signs of peritoneal irritation from bowel wall perforation. The digits should be lubricated with lidocaine jelly, and abdominal pressure may be applied in an attempt to mobilize foreign objects distally.

When digital extraction fails, the emergency physician should attempt to use an anoscope or small vaginal speculum to visualize the foreign body. Ring forceps are placed through the visualizing apparatus to grasp and remove the object. Sometimes the mucosa may become tightly adherent to the distal end of the foreign body, creating a vacuum that prevents object withdrawal. Passage of a Foley catheter beyond the foreign object (sometimes through a rigid sigmoidoscope) with proximal air inflation usually breaks the vacuum and permits retrieval.[110] Passage of the catheter, followed by air inflation and balloon filling, may allow object removal with gentle catheter traction.

www.ketabpezeshki.com 66485457-66963820

Figure 60-15. Vacuum device used to remove a difficult-to-grasp rectal foreign body.

Figure 60-16. Radiograph of a patient who inserted an aerosol can into the rectum.

When the emergency physician possesses the appropriate expertise and equipment, or if consultants are available, the next step may be removal with a vacuum device, well suited for some foreign bodies (Figs. 60-15 and 60-16), or forceps; sigmoidoscopy may be a necessary adjunct to such an approach. As with other removal means, the physician should be careful to minimize risk of anorectal perforation. Removal of occult anorectal foreign objects after administration of an enema for symptomatic relief of anal pain was successful in 10% of patients in one series. Experts caution against possible perforation, however, when enemas or cathartics are administered to patients with known rectal foreign bodies, especially foreign bodies with sharp edges.

An assessment of injury to the rectum is indicated after removal of the foreign object. When foreign body retrieval has been simple and the patient does not show increased pain, tenderness, or rectal bleeding, further evaluation for rectal trauma is likely unnecessary. If any of these is present, postremoval sigmoidoscopy may identify small abrasions requiring close follow-up, but in general, hospitalization is necessary only if a rectal laceration or perforation is found. Appropriate antibiotics are indicated in all cases of suspected bowel wall perforation and peritonitis. Long-term follow-up has identified few or no sequelae in patients with rectal foreign bodies.[107]

GENITOURINARY TRACT

The literature describes a wide variety of genitourinary tract foreign objects, ranging from easily extracted tampons and condoms to penile rings removed only with great difficulty.[111,112]

History

An accurate history may not be readily obtained because most foreign bodies are placed by the patients themselves. Reports have validated the occasional value of a history, however, as a means to diagnose some genitourinary objects such as those associated with genital body piercing (in patients or sexual partners).[113] In children who fear parental disapproval of foreign object placement, secondary signs are the usual presentation. They are brought to medical attention when parents note foul-smelling, purulent discharge or bleeding from the urethra, the vagina, or both.[114] Another common presentation in infants is penile constriction caused by inadvertent wrapping of hairs around the shaft, usually just proximal to the corona.[115]

In older children, rubber bands or string may be placed around the genitalia. In adolescents and adults, metal objects are placed for autoerotic stimulation. Constricting bands may be placed proximal to the scrotum or more often on the penile shaft. These patients frequently have presentations delayed by 12 hours or more. The swelling that renders these constricting bands so difficult to remove also hinders the physical examination, emphasizing the need for an accurate history.[115]

Occasionally, an object (e.g., tampon) is forgotten until it causes purulent discharge. Secondary symptoms also can bring foreign bodies to physicians' attention in rare cases of genitourinary tract perforation by foreign bodies from the genitourinary tract or from adjacent-site erosion.[116] Migration of an intrauterine device into the bladder has occurred, with associated cystolithiasis. In another unusual case, a sewing pin caused perforation through the appendix and into the bladder.

Genitourinary tract foreign bodies may be infectious. The term *bezoar,* traditionally considered to delineate indigestible material in the gastrointestinal tract, also has been used to describe foreign collections in the bladder. One common urinary tract bezoar is the *Candida* bezoar, seen in immunosuppressed patients or in patients with diabetes mellitus, neurogenic bladder, antibiotic use, or an indwelling urinary catheter.[117]

Physical Examination

Patients of all ages require a careful gentle examination because they are often anxious about the anatomic region being examined. In a pediatric patient, a nasal speculum may be used to help visualize a vaginal foreign body. Thorough vaginal examination is indicated in patients with symptoms of vaginitis, with the search directed for infectious agents and foreign bodies. A vaginal foreign body may be palpated during digital rectal examination.

In children and adults, the presence of blood or discharge at the urethral meatus or vagina should be noted. Patients with intraurethral foreign objects also may have perineal induration and a high incidence of associated infection, which may progress to sepsis syndrome.[111] In males with penile shaft swelling, the emergency physician should perform careful inspection for constricting objects. In an infant with penile swelling, a coronal constricting hair should be sought.[115]

In patients with penile rings, especially most who seek care after some hours' delay, examination may reveal a swollen penis with

www.ketabpezeshki.com 66485457-66963820

mottling, duskiness, and excoriation. The interruption of venous and lymphatic outflow results in increasing penile enlargement with risks of tissue damage. Damage is especially likely if the patient previously has tried removal of the constriction.[115] Urethrocutaneous fistulae, relatively common in infants and children, should be sought in any patient with a constricting band.

Examination may reveal only indirect evidence of other genitourinary objects as well. Multiple abscesses in an enlarged scrotum have been reported in a patient with acute infection from embedded metallic objects placed (by the patient) decades before ED presentation.[113] Any genitourinary examination abnormalities should prompt the emergency physician to question the patient about possible foreign bodies.

Diagnostic Strategies

Often, no imaging is necessary if the foreign body's contours and extent are evident on examination. Plain films may be used when urethral or bladder radiopaque foreign bodies are suspected. Plain radiography also has proved useful in unusual cases of embedded metallic objects not palpable because of pain.[113] Urethrocystography may be useful in identifying and locating genitourinary tract foreign objects and has been an aid to surgical planning for these patients.[111] Intravenous urography may reveal a filling defect in the case of a bladder foreign body, or it can reveal delayed renal excretion as a general finding suggesting foreign object–related renal function impairment. Ultrasound is useful to investigate for hydronephrosis. Acoustic shadowing may not be seen, depending on the nature of the foreign body; *Candida* bezoars lack acoustic shadowing. These bezoars and other genitourinary tract objects are generally identifiable on CT.[117]

Management

Vaginal foreign bodies usually are removed easily. If the object has been present for some time, there may be associated bacterial or fungal infection. This should be treated with appropriate antimicrobials (e.g., metronidazole 500 mg twice daily for a week for bacterial infection, fluconazole 150 mg in a single oral dose for candidal vaginitis). In males or females, foreign bodies located just inside the urethral meatus usually can be grasped with a clamp and removed. The overriding goal is to avoid causing further damage to the already traumatized urethra. After failure of one or two attempts at removal by the emergency physician, the best course is early consultation. Objects located in the proximal urethra or bladder usually require cystoscopy for extrication. One exception is the *Candida* bezoar, which generally is treated with antifungal agents.[117] Penile urethral foreign bodies may be associated with urinary retention and secondary infection; early endoscopic intervention is necessary for these patients.[112]

Constricting penile foreign bodies are removed as early as possible because progressive swelling makes removal more difficult. Sedation and analgesia may be necessary. Also, care should be taken when removing constricting objects with instruments such as ring cutters; penile shaft lacerations may result from the tautness of the thin underlying skin. Hair and string foreign bodies are removed relatively easily with forceps and scissors or scalpel. Wrapping the penis with string and mobilizing the ring distally (as is done for digital foreign bodies) have been successful.[115] Other approaches have been used to remove penile constricting bands: A cast saw, the vibrating blade of which reduces risk of skin damage, may be useful for removal of some objects, such as acrylic rings. After penile ring removal and confirmation of ability to void, patients usually can be discharged with close follow-up.[115] Consultation should be obtained for patients with penile trauma.

SOFT TISSUES

Soft tissue foreign bodies present unique diagnostic and management dilemmas. Foreign bodies may be present not only in patients with known wounds, but also in patients with secondary symptoms who are unaware or uncertain of foreign body entry.

History

All patients with wounds should be considered for soft tissue foreign body contamination, and evaluation of soft tissue injury should include foreign objects. In straightforward cases, patients have symptoms such as pain or foreign body sensation and may specifically report a foreign body. Meticulous examination and use of diagnostic aids as needed are in order for the patient certain of a foreign body not readily seen by the emergency physician. Particularly for radiolucent objects, such as wood splinters, the history and patient sensation are used as a guide to exploration. In more difficult cases, patients have symptoms related to complications. Soft tissue infections, especially if recurrent, should suggest a foreign body serving as a nidus. A careful history in patients with soft tissue complaints should include a search for antecedent trauma, no matter how remote, that may have resulted in foreign body entry.

Physical Examination

The diagnosis is frequently obvious on visual inspection or standard wound evaluation. For smaller objects, use of loupe magnification may be a significant aid in foreign body identification and removal.[118] In addition to location of the foreign body, the examination should address injuries collateral to the object's presence. Distal neurovascular function should be tested.

Diagnostic Strategies

Anteroposterior and lateral radiographs of the involved area of the body are valuable. Plain radiography has been shown to be more than 98% sensitive when the foreign body is metal or other radiopaque material, such as gravel.[119] If silver nitrate sticks were used to achieve hemostasis before imaging, the deposited metal can be expected to appear on plain radiography.[119]

One common foreign body is glass, which has shown radiopacity.[119] In one cadaver study, nonleaded glass was visualized with 90% sensitivity and a false-positive rate of 10%; glass color and location were unimportant, but a volume of less than 15 mm^3 was associated with risk of failed visualization.[120] Other items are not easily seen on plain radiographs, which are insensitive for detection of vegetable material (e.g., wood) or plastic objects.[119] Xeroradiography, recommended in the past, has fallen out of favor. This technique has no advantage over plain films and has been discarded in favor of other modalities (e.g., CT) when plain films are negative and suspicion remains.[119] In EDs in which digital radiography and image manipulation are available, the use of "soft tissue" exposures is not necessary. For EDs in which hard-copy x-ray films are used, specification for "soft tissue" exposure should be indicated when films are requested.

Fluoroscopy has received attention as a diagnostic and therapeutic tool. In an ex vivo beef model, emergency physician–operated fluoroscopy had 100% sensitivity for gravel, metal, and glass; sensitivity was 90% for graphite and 0% for plastic and wood.[121] One advantage of fluoroscopy is that it can guide removal and later confirm absence of foreign objects.

When plain radiographs are negative and suspicion for a foreign body remains, ultrasound or CT is the next step.[122] Ultrasound is readily available in many EDs and has been the subject of intensive but ultimately unconvincing study. Initial studies by radiologists,

www.ketabpezeshki.com 66485457-66963820

interpreting scans done in an animal model, found low detection rates for gravel (40%), metal (45%), glass (50%), cactus spine (30%), wood (50%), and plastic (40%); overall, false-negative and false-positive rates were 50% and 30%.[123] Another study, which used credentialed sonographers and radiologist interpretations in a chicken breast model, found some utility for ultrasound in the ED. The investigators concluded that a 7.5-MHz probe was better at shallow depths and that a 5-MHz probe should be used for deeper searching.[124] The study found that wood had the best acoustic shadow, followed by plastic; other materials investigated (paper clip, glass, needle) had lesser shadowing and were more difficult to detect. Ultrasound results were more disappointing in a subsequent analysis of the modality's use in 900 examinations: overall sensitivity (52.6%) and specificity (47.2%) were disappointing, and interobserver reliability was poor.[125] Overall, given the availability of ultrasound in the ED and the case reports of its clear occasional utility in foreign body localization and removal, it is reasonable to employ this technique with the understanding that a positive test result is much more useful than a negative one.[126,127]

In addition to characterizing objects seen on plain films, CT is useful for items (e.g., plastic, wood) missed on plain radiographs.[119] CT also is valuable in localizing small or deep objects and delineating anatomic locations, with newer-generation CT and its on-screen image manipulation capabilities resulting in higher detection rates for wood and plastic than hard-copy CT films.[128] CT also is useful for identifying foreign body sequelae (e.g., abscess).

MRI can assist in identifying foreign body complications. Soft tissue objects can induce a chronic inflammatory reaction and lytic or blastic osseous changes that allow MRI to locate foreign bodies.[129] In other cases, MRI is less optimal. Gravel, found easily with most modalities, causes MRI streaking because of ferromagnetic material. MRI also has identified foreign objects of wood and plastic; however, CT is usually adequate for detection of these types of foreign bodies.[119]

Management

The most important determinant of successful foreign body removal is knowledge of the object's precise location. Standard radiopaque markers can aid in wound localization. For small objects, needles placed in the soft tissues can help pinpoint the location of foreign objects seen on radiographs. Fluoroscopy may allow simultaneous visualization and removal. When objects are not radiopaque, judicious probing of wounds with fine-gauge needles or forceps may allow tactile detection of the foreign body.

For removal of a foreign body, it may be necessary to extend the original wound or, if it is located away from the entrance site, to make a separate incision. The emergency physician can perform limited wound extension or make separate incisions in regions where adequate analgesia and a bloodless field can be achieved. Retrieval of foreign bodies, especially those linear in shape, is best achieved if the orientation of the foreign body is understood. In that case, the proximal end of the foreign body is grasped, and the health care provider should extract the foreign body gently following the plane of orientation. This allows easier removal and helps avoid breaking the object into multiple foreign bodies.

When objects are deeply embedded, it may be better to leave them in place than to create large surgical wounds to effect removal. Depending on foreign body location, operative intervention may be necessary for safe foreign body extraction.[130]

After foreign body removal, the emergency physician should consider tetanus prophylaxis and antibiotic coverage when warranted by clinical circumstances. Patients with contaminated hand wounds and wooden splinters may be candidates for prophylaxis. Patients with suspected vascular or neurologic injuries require early evaluation, possibly but not always in the ED, by appropriate subspecialists. Some soft tissue foreign bodies are not suspected or detected and can lead to infectious sequelae. Careful discharge instructions and timely follow-up are crucial in these patients.

KEY CONCEPTS

- If the history and mechanism of injury are compatible with ocular penetration or if a small puncture wound of the globe is noted, anteroposterior and lateral radiographs of the orbit are an appropriate initial step when the foreign body is thought to be radiopaque. CT and ultrasound are complementary diagnostic studies.
- Most airway foreign bodies are seen in pediatric patients and may not be visible on plain films. A normal radiograph does not rule out an aspirated foreign body.
- Esophageal foreign bodies (e.g., coins) usually are oriented in the coronal plane, and airway objects usually are oriented in the sagittal plane.
- The patient with critical airway obstruction and impending or actual respiratory arrest requires one of three options: (1) forced expulsion of the foreign body; (2) direct laryngoscopy with attempted manual removal; or (3) cricothyroidotomy, other transtracheal ventilation, or intubation, while pushing the foreign body distally.
- Esophageal foreign bodies typically are found at one of the three constriction locations: (1) proximal esophagus at the level of the cricopharyngeal muscle and thoracic inlet—radiographically, the clavicular level; (2) midesophagus at the level of the aortic arch and carina; and (3) distal esophagus just proximal to the esophageal-gastric junction—radiographically, a level two to four vertebral bodies cephalad to the gastric bubble.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Jordan MT, Cohen D: Esophageal foreign body sensation: A rare presentation of angioedema. *J Emerg Med* 2010; 39:174-177.
2. Heinemann A, Miyaishi S, Iwersen S, Schmoldt A, Puschel K: Body-packing as cause of unexpected sudden death. *Forensic Sci Int* 1998; 92:1-10.
3. Samad L, Ali M, Ramzi H: Button battery ingestion: Hazards of esophageal impaction. *J Pediatr Surg* 1999; 34:1527-1531.
4. Bhargava D, Victor R: Carabid beetle invasion of the ear in Oman. *Wilderness Environ Med* 1999; 10:157-160.
5. Coday MP, Colby K: Nailing down the diagnosis: Imaging intraocular foreign bodies. *Arch Ophthalmol* 1999; 117:548.
6. O'Duffy D, Salmon JF: Siderosis bulbi resulting from an intralenticular foreign body. *Am J Ophthalmol* 1999; 127:218-219.
7. Soong K: Foreign body entrapment in radial keratotomy incisions. *Arch Ophthalmol* 1999; e837.
8. Chiquet C, Zech JC, Denis P, Adeleine P, Trepsat C: Intraocular foreign bodies. Factors influencing final visual outcome. *Acta Ophthalmol Scand* 1999; 77:321-325.
9. Lakits A, et al: Helical and conventional CT in the imaging of metallic foreign bodies in the orbit. *Acta Ophthalmol Scand* 2000; 78:79-83.
10. Luo Z, Gardiner M: The incidence of intraocular foreign bodies and other intraocular findings in patients with corneal metal foreign bodies. *Ophthalmology* 2010; 117:2218-2221.
11. Barash D, et al: Ultrasound biomicroscopic detection of anterior ocular segment foreign body after trauma. *Am J Ophthalmol* 1998; 126:197-202.
12. Khoury JM, O'Day DM: Retained intraocular metallic foreign body masquerading as a ciliary body melanoma with extrascleral extension. *Arch Ophthalmol* 1999; 117:410-411.
13. Deramo VA, et al: Ultrasound biomicroscopy as a tool for detecting and localizing occult foreign bodies after ocular trauma. *Ophthalmology* 1999; 106:301-305.
14. Indudharan R, Ahamad M, Ho TM, Salim R, Htun YN: Human otoacariasis. *Ann Trop Med Parasitol* 1999; 93:163-167.
15. Tang C, Levine R, Shankar L: The mysterious case of persistent malocclusion. *Ann Plast Surg* 1998; 41:420-421.
16. Jones RL, Chavda SV, Pahor AL: Parapharyngeal abscess secondary to an external auditory meatus foreign body. *J Laryngol Otol* 1997; 111:1086-1087.
17. Francois M, Hamrioui R, Narcy P: Nasal foreign bodies in children. *Eur Arch Otorhinolaryngol* 1998; 255:132-134.
18. Marin JR, Trainor JL: Foreign body removal from the external auditory canal in a pediatric emergency department. *Pediatr Emerg Care* 2006; 22:630-634.
19. Ologe FE, Dunmade AD, Afolabi OA: Aural foreign bodies in children. *Indian J Pediatr* 2007; 74:755-758.
20. Leffler S, Cheney P, Tandberg D: Chemical immobilization and killing of intra-aural roaches: An in vitro comparative study. *Ann Emerg Med* 1993; 22:1795-1798.
21. Kumar S, Kumar M, Lesser T, Banhegyi G: Foreign bodies in the ear: A simple technique for removal analysed in vitro. *Emerg Med J* 2005; 22:266-268.
22. Abadir WF, Nakhla V, Chong P: Removal of superglue from the external ear using acetone: Case report and literature review. *J Laryngol Otol* 1995; 109:1219-1221.
23. Dubois M, Francois M, Hamrioui R: [Foreign bodies in the ear; report of 40 cases]. *Arch Pediatr* 1998; 5:970-973.
24. Ryan C, Ghosh A, Wilson-Boyd B, Smit D, O'Leary S: Presentation and management of aural foreign bodies in two Australian emergency departments. *Emerg Med Australas* 2006; 18:372-378.
25. Okoye BC, Onotai LO: Foreign bodies in the nose. *Niger J Med* 2006; 15:301-304.
26. Qureshi AA, Lowe DA, McKiernan DC: The origin of bronchial foreign bodies: A retrospective study and literature review. *Eur Arch Otorhinolaryngol* 2009; 266:1645-1648.
27. Kiger JR, Brenkert TE, Losek JD: Nasal foreign body removal in children. *Pediatr Emerg Care* 2008; 24:785-792.
28. Balbani AP, et al: Ear and nose foreign body removal in children. *Int J Pediatr Otorhinolaryngol* 1998; 46:37-42.
29. Kim KK, Kim JR, Kim JY: Button battery impaction in nasal cavity. *J Korean Med Sci* 1999; 14:210-212.
30. Glynn F, Amin M, Kinsella J: Nasal foreign bodies in children: Should they have a plain radiograph in the accident and emergency? *Pediatr Emerg Care* 2008; 24:217-218.
31. Yeh B, Roberson JR: Nasal magnetic foreign body: A sticky topic. *J Emerg Med* 2012; 43:319-321:
32. Douglas AR: Use of nebulized adrenaline to aid expulsion of intra-nasal foreign bodies in children. *J Laryngol Otol* 1996; 110:559-560.
33. Purohit N, Ray S, Wilson T, Chawla OP: The 'parent's kiss': An effective way to remove paediatric nasal foreign bodies. *Ann R Coll Surg Engl* 2008; 90:420-422.
34. Taylor C, Acheson J, Coats TJ: Nasal foreign bodies in children: Kissing it better. *Emerg Med J* 2010; 27:712-713.
35. Soroudi A, et al: Adult foreign body airway obstruction in the prehospital setting. *Prehosp Emerg Care* 2007; 11:25-29.
36. Bodart E, de Bilderling G, Tuerlinckx D, Gillet JB: Foreign body aspiration in childhood: Management algorithm. *Eur J Emerg Med* 1999; 6:21-25.
37. Shlizerman L, Mazzawi S, Rakover Y, Ashkenazi D: Foreign body aspiration in children: The effects of delayed diagnosis. *Am J Otolaryngol* 2010; 31:320-324.
38. Sokouti M, Montazeri V: Delayed massive hemoptysis 20 years after lung stabbing: An unusual presentation. *Eur J Cardiothorac Surg* 2007; 32:679-681.
39. Higuchi O, Adachi Y, Ichimaru T, Asai M, Kawasaki K: Foreign body aspiration in children: A nationwide survey in Japan. *Int J Pediatr Otorhinolaryngol* 2009; 73:659-661.
40. Kavanagh PV, Mason AC, Muller NL: Thoracic foreign bodies in adults. *Clin Radiol* 1999; 54:353-360.
41. Harris CS, Baker SP, Smith GA, Harris RM: Childhood asphyxiation by food. A national analysis and overview. *JAMA* 1984; 251:2231-2235.
42. Baharloo F, Veyckemans F, Francis C, Biettlot MP, Rodenstein DO: Tracheobronchial foreign bodies: Presentation and management in children and adults. *Chest* 1999; 115:1357-1362.
43. Righini CA, et al: What is the diagnostic value of flexible bronchoscopy in the initial investigation of children with suspected foreign body aspiration? *Int J Pediatr Otorhinolaryngol* 2007; 71:1383-1390.
44. Sharma HS, Sharma S: Management of laryngeal foreign bodies in children. *J Accid Emerg Med* 1999; 16:150-153.
45. Ferretti C, Kruger L, Tsakiris P: Foreign body in the medial pterygoid space. *S Afr J Surg* 1999; 37:53-54.
46. Halvorson DJ, Merritt RM, Mann C, Porubsky ES: Management of subglottic foreign bodies. *Ann Otol Rhinol Laryngol* 1996; 105:541-544.
47. Tahir N, Ramsden WH, Stringer MD: Tracheobronchial anatomy and the distribution of inhaled foreign bodies in children. *Eur J Pediatr* 2009; 168:289-295.
48. Tomaske M, Gerber AC, Stocker S, Weiss M: Tracheobronchial foreign body aspiration in children—diagnostic value of symptoms and signs. *Swiss Med Wkly* 2006; 136:533-538.
49. Metrangelo S, Monetti C, Meneghini L, Zadra N, Giusti F: Eight years' experience with foreign-body aspiration in children: What is really important for a timely diagnosis? *J Pediatr Surg* 1999; 34:1229-1231.
50. Casap N, Alterman M, Lieberman S, Zeltser R: Enigma of missing teeth in maxillofacial trauma. *J Oral Maxillofac Surg* 2011; 69:1421-1429.
51. Baigel GD: An unfortunate cause of death. *Anaesthesia* 1999; 54:917-918.
52. Hon KL, Chu WC, Sung JK: Retropharyngeal abscess in a young child due to ingestion of eel vertebrae. *Pediatr Emerg Care* 2010; 26:439-441.
53. Ahn D, Heo SJ, Park JH, Sohn JH: Tracheoesophageal fistula with tracheal stenosis resulting from retained esophageal foreign body. *Auris Nasus Larynx* 2011; 38:753-756.
54. Sersar SI, et al: Inhaled foreign bodies: Presentation, management and value of history and plain chest radiography in delayed presentation. *Otolaryngol Head Neck Surg* 2006;134:92-99.
55. Unadkat SN, Talwar R, Tolley N: The eye in the neck: Removal of a sewing needle from the posterior pharyngeal wall. *Case Report Med* 2010; 2010:608343.
56. Heimlich HJ: A life-saving maneuver to prevent food-choking. *JAMA* 1975; 234:398-401.
57. Hockstein NG, Jacobs IN: Flexible bronchoscopic removal of a distal bronchial foreign body with cinefluoroscopic guidance. *Ann Otol Rhinol Laryngol* 2004; 113:863-865.
58. van Ooij A, Manni JJ, Beuls EA, Walenkamp GH: Cervical spondylodiscitis after removal of a fishbone. A case report. *Spine (Phila Pa 1976)* 1999; 24:574-577.
59. Silverberg M, Tillotson R: Case report: Esophageal foreign body mistaken for impacted button battery. *Pediatr Emerg Care* 2006; 22:262-265.
60. Chee LW, Sethi DS: Diagnostic and therapeutic approach to migrating foreign bodies. *Ann Otol Rhinol Laryngol* 1999; 108:177-180.
61. Tander B, Baskin D, Mutlu G, Sever N, Bulut M: An unusual foreign body in the bowel lumen causing obstruction in a neonate. *J Pediatr Surg* 1999; 34:1289-1290.

www.ketabpezeshki.com 66485457-66963820

62. Lee BK, Ryu HH, Moon JM, Jeung KW: Bowel perforations induced by multiple magnet ingestion. *Emerg Med Australas* 2010; 22:189-191.
63. Wong HH, Phillips BA: Opposites attract: A case of magnet ingestion. *CJEM* 2009; 11:493-495.
64. Goodfellow PB, Nockolds CL, Johnson AG: Foreign body perforation of lymphoma. *J R Soc Med* 1998; 91:545.
65. Louie JP, Alpern ER, Windreich RM: Witnessed and unwitnessed esophageal foreign bodies in children. *Pediatr Emerg Care* 2005; 21:582-585.
66. Kim JK, et al: Management of foreign bodies in the gastrointestinal tract: An analysis of 104 cases in children. *Endoscopy* 1999; 31:302-304.
67. Hurtado CW, Furuta GT, Kramer RE: Etiology of esophageal food impactions in children. *J Pediatr Gastroenterol Nutr* 2011; 52:43-46.
68. Lin CH, et al: Endoscopic removal of foreign bodies in children. *Kaohsiung J Med Sci* 2007; 23:447-452.
69. Huiping Y, Jian Z, Shixi L: Esophageal foreign body as a cause of upper gastrointestinal hemorrhage: Case report and review of the literature. *Eur Arch Otorhinolaryngol* 2007; 265:247-249.
70. Tan A, et al: Neck pain and stiffness in a toddler with history of button battery ingestion. *J Emerg Med* 2011; 41:157-160.
71. Chen CY, Peng JP: Esophageal fish bone migration induced thyroid abscess: Case report and review of the literature. *Am J Otolaryngol* 2011; 32:253-255.
72. McGahren ED: Esophageal foreign bodies. *Pediatr Rev* 1999; 20:129-133.
73. Koyuncu N, Yilmaz S, Soysal S: An unusual cause of chest pain: Foreign body in the oesophagus. *Emerg Med J* 2007; 24:e1.
74. Kulig K, Rumack CM, Rumack BH, Duffy JP: Disk battery ingestion. Elevated urine mercury levels and enema removal of battery fragments. *JAMA* 1983; 249:2502-2504.
75. Koide H, Nishikawa K, Goto F: [Anesthetic management of a patient with post-emetic rupture of the esophagus induced by a foreign body]. *Masui* 2007; 56:421-424.
76. Dahiya M, Denton JS: Esophagoaortic perforation by foreign body (coin) causing sudden death in a 3-year-old child. *Am J Forensic Med Pathol* 1999; 20:184-188.
77. Pons J, Demoux R, Campan P, Constant T, Le Treut YP: [A fatal aorto-esophageal fistula due a foreign body: a foreseeable accident?] *Presse Med* 1999; 28:781-783.
78. May A, Gossner L, Feess G, Bauer R, Ell C: Extraction of migrated self-expanding esophageal metal stents. *Gastrointest Endosc* 1999; 49:524-526.
79. Karnwal A, Ho EC, Hall A, Molony N: Lateral soft tissue neck x-rays: Are they useful in management of upper aero-digestive tract foreign bodies? *J Laryngol Otol* 2008; 122:845-847.
80. Eliashar R, Dano I, Dangoor E, Braverman I, Sichel JY: Computed tomography diagnosis of esophageal bone impaction: A prospective study. *Ann Otol Rhinol Laryngol* 1999; 108:708-710.
81. Lowinger DS, Makarie L, Cole I, Szasz JJ: Retrieval of an extraluminal swallowed sharp foreign body. *Aust N Z J Surg* 1999; 69:399-402.
82. Evans RM, Ahuja A, Rhys Williams S, Van Hasselt CA: The lateral neck radiograph in suspected impacted fish bones—does it have a role? *Clin Radiol* 1992; 46:121-123.
83. Horii K, et al: Successful treatment of a hepatic abscess that formed secondary to fish bone penetration by percutaneous transhepatic removal of the foreign body: Report of a case. *Surg Today* 1999; 29:922-926.
84. Kavanagh BP, Slutsky AS: Ventilator-induced lung injury: More studies, more questions. *Crit Care Med* 1999; 27:1669-1671.
85. Derowe A, Ophir D: Negative findings of esophagoscopy for suspected foreign bodies. *Am J Otolaryngol* 1994; 15:41-45.
86. Nigri GR, et al: Duodenal perforation and right hydronephrosis due to toothpick ingestion. *J Emerg Med* 2008; 34:55-57.
87. Ramlakhan SL, Burke DP, Gilchrist J: Things that go beep: Experience with an ED guideline for use of a handheld metal detector in the management of ingested non-hazardous metallic foreign bodies. *Emerg Med J* 2006; 23:456-460.
88. Saz EU, Arikan C, Ozgenc F, Duyu M, Ozananar Y: The utility of handheld metal detector in confirming metallic foreign body ingestion in the pediatric emergency department. *Turk J Gastroenterol* 2010; 21:135-139.
89. Arora S, Galich P: Myth: Glucagon is an effective first-line therapy for esophageal foreign body impaction. *CJEM* 2009; 11:169-171.
90. Arms JL, et al: Safety and efficacy of a protocol using bougienage or endoscopy for the management of coins acutely lodged in the esophagus: A large case series. *Ann Emerg Med* 2008; 51:367-372.
91. Namasivayam S: Button battery ingestion: A solution to a management dilemma. *Pediatr Surg Int* 1999; 15:383-384.
92. Chen CK, Su YJ, Lai YC, Cheng HK, Chang WH: Fish bone-related intra-abdominal abscess in an elderly patient. *Int J Infect Dis* 2010; 14:e171-e172.
93. Tai AW, Sodickson A: Foreign body ingestion of blister pill pack causing small bowel obstruction. *Emerg Radiol* 2007; 14:105-108.
94. Samdani T, et al: An apricot story: View through a keyhole. *World J Emerg Surg* 2007; 2:20.
95. June R, Aks SE, Keys N, Wahl M: Medical outcome of cocaine bodystuffers. *J Emerg Med* 2000; 18:221-224.
96. Ghori A, Dorricott NJ, Sanders DS: A lethal ectopic denture: An unusual case of sigmoid perforation due to unnoticed swallowed dental plate. *J R Coll Surg Edinb* 1999; 44:203-204.
97. Manouras A, et al: Vertical rotation and impaction to the choledochal duct of a migrated biliary self-expanding metal stent. *Surg Laparosc Endosc Percutan Tech* 2007; 17:416-417.
98. Gayer G, et al: Bezoars in the stomach and small bowel—CT appearance. *Clin Radiol* 1999; 54:228-232.
99. Rathi P, Rathi V: Colonic lithobezoar. *Indian J Gastroenterol* 1999; 18:89.
100. Reference deleted in proofs.
101. Pan CC, Wang CP, Huang JJ, Chen WK, Yang HR: Intestinal perforation after the incidental ingestion of a fishhook. *J Emerg Med* 2010; 38:e45-e48.
102. Gherardi R, Marc B, Alberti X, Baud F, Diamant-Berger O: A cocaine body packer with normal abdominal plain radiograms. Value of drug detection in urine and contrast study of the bowel. *Am J Forensic Med Pathol* 1990; 11:154-157.
103. Chung CH, Fung WT: Detection of gastric drug packet by ultrasound scanning. *Eur J Emerg Med* 2006; 13:302-303.
104. Schmidt S, et al: Detection of ingested cocaine-filled packets—diagnostic value of unenhanced CT. *Eur J Radiol* 2008; 67:133-138.
105. McCarron MM, Wood JD: The cocaine 'body packer' syndrome. Diagnosis and treatment. *JAMA* 1983; 250:1417-1420.
106. Marom T, Goldfarb A, Russo E, Roth Y: Battery ingestion in children. *Int J Pediatr Otorhinolaryngol* 2010; 74:849-854.
107. Rodriguez-Hermosa JI, et al: Management of foreign bodies in the rectum. *Colorectal Dis* 2007; 9:543-548.
108. Clarke DL, Buccimazza I, Anderson FA, Thomson SR: Colorectal foreign bodies. *Colorectal Dis* 2005; 7:98-103.
109. Jung EJ, Ryu CG, Kim G, Hwang DY: Impaction of a foreign body in the rectum by improper use of a (electronic) massager: A case report. *J Korean Soc Coloproctol* 2010; 26:298-301.
110. Humes D, Lobo DN: Removal of a rectal foreign body by using a Foley catheter passed through a rigid sigmoidoscope. *Gastrointest Endosc* 2005; i62:610.
111. Johnin K, Kushima M, Koizumi S, Okada Y: Percutaneous transvesical retrieval of foreign bodies penetrating the urethra. *J Urol* 1999; 161:915-916.
112. Brison D, Lamba S, Jafary A, Bhalla R, Baker SR: Case report: Urinary retention secondary to a foreign body in the male urethra. *Emerg Radiol* 2006; 13:143-145.
113. Rammos L, Kapralos V, Gerzelis I, Zagilas D, Karidis G: [Multiple recurrent scrotal abscesses and metallic foreign bodies]. *Prog Urol* 1999; 9:541-543.
114. Someshwar J, Lutfi R, Nield LS: The missing "Bratz" doll: A case of vaginal foreign body. *Pediatr Emerg Care* 2007; 23:897-898.
115. Schuster G, Stockmal P: Genital incarceration with metal rings: Their safe removal. *Tech Urol* 1999; 5:116-118.
116. Kobayashi K, et al: [A case of urethrovaginal fistula caused by a foreign body in the vagina]. *Hinyokika Kiyo* 2010; 56:389-391.
117. el Fakir Y, Kabbaj N, Dafiri R, Imani F: [Imaging of urinary *Candida* bezoars]. *Prog Urol* 1999; 9:513-517.
118. Hart RG, Hall J: The value of loupe magnification: An underused tool in emergency medicine. *Am J Emerg Med* 2007; 25:704-707.
119. Madan SI, Heilpern KL: Silver nitrate as a radiopaque foreign body. *J Emerg Med* 1999; 17:1045.
120. Flom LL, Ellis GL: Radiologic evaluation of foreign bodies. *Emerg Med Clin North Am* 1992; 10:163-177.
121. Cohen DM, Garcia CT, Dietrich AM, Hickey RW Jr: Miniature C-arm imaging: An in vitro study of detecting foreign bodies in the emergency department. *Pediatr Emerg Care* 1997; 13:247-249.
122. Blankstein A, et al: Localization, detection and guided removal of soft tissue in the hands using sonography. *Arch Orthop Trauma Surg* 2000; 120:514-517.
123. Russell RC, Williamson DA, Sullivan JW, Suchy H, Suliman O: Detection of foreign bodies in the hand. *J Hand Surg Am* 1991; 16:2-11.

www.ketabpezeshki.com 66485457-66963820

124. Ginsburg MJ, Ellis GL, Flom LL: Detection of soft-tissue foreign bodies by plain radiography, xerography, computed tomography, and ultrasonography. *Ann Emerg Med* 1990; 19:701-703.
125. Crystal CS, et al: Bedside ultrasound for the detection of soft tissue foreign bodies: A cadaveric study. *J Emerg Med* 2009; 36:377-380.
126. McArthur T, Abell BA, Levsky ME: A procedure for soft tissue foreign body removal under real-time ultrasound guidance. *Mil Med* 2007; 172:858-859.
127. Pigott DC, Buckingham RB, Eller RL, Cox AJ 3rd: Foreign body in the tongue: A novel use for emergency department ultrasonography. *Ann Emerg Med* 2005; 45:677-679.
128. Kantarci M, Ogul H, Karasen RM: Detection of a giant wooden foreign body with multidetector computed tomography and multiplanar reconstruction imaging. *Am J Emerg Med* 2007; 25:211-213.
129. Uzumcu J: Medical application of the Dremel Multipro rotary tool. *Acad Emerg Med* 2000; 7:308.
130. von Riedenauer WB, Baker MK, Brewer RJ: Video-assisted thorascopic removal of migratory acupuncture needle causing pneumothorax. *Chest* 2007; 131:899-901.

www.ketabpezeshki.com 66485457-66963820

Chapter 61

Mammalian Bites

Hugh H. West and Ellen J. Weber

ANIMAL BITES

PERSPECTIVE

Epidemiology

Reliable statistics on animal bites are hard to come by, as many bites are not reported. The Centers for Disease Control and Prevention (CDC) in the United States currently estimates that 4.5 million dog bites occur per year, affecting nearly 1.5% of the population, but only 20% (885,000) of victims seek medical attention.[1] Emergency department (ED) visits for dog bites decreased 14% between 2001 and 2008, but hospital admissions for dog bite–related injuries increased 86% from 1993 to 2008, with 9% of patients requiring some type of surgical repair.[2]

Fatalities from dog bites increased 92% from 1992 to 2010 to a rate of 30.2 deaths per year (Fig. 61-1).[3-5] The majority of fatalities occur in children younger than 10 years, with children younger than 4 years at greatest risk of death; those older than 50 years also have a higher fatality rate.[6] The breeds most frequently responsible for fatalities include pit bull (59%), Rottweiler (14%), American Bulldog and Siberian Husky (5% each), and German Shepherd Dog (3%), followed by 14 other breeds with one or two fatalities each year.[1,7] The majority of fatalities involved an unrestrained dog on the owner's property (59%).[8]

The incidence of bites from species other than dogs is harder to ascertain. Some government reports combine statistics on mammalian bites with those on bites from reptiles and insects or marine envenomations. Geographic differences in incidence add to the challenge. The cat bite generally appears as the second most common animal bite injury in the United States,[9,10] accounting for 5 to 15% of domestic animal bites.[9] Most cat bites occur in or near the home, and the perpetrators are pets rather than strays (more than 80%). Whereas victims of dog bite injuries are more often male,[1,11,12] females are twice as likely as males to be victims of cat bites, with a peak age incidence in the third decade.[9] Rodent bites are probably the third most common animal bite, representing up to 7% of the total in the United States. Bites from other species combined (monkeys, ferrets, raccoons, foxes, livestock, bats, minks, and other wild animals) total less than 2% of all bites.[13,14]

Epidemiology changes with locale. In India, for example, dog bites (92%) are followed by monkey bites (3.2%), cat bites (1.8%), and fox bites (0.4%) in terms of frequency.[14]

PRINCIPLES OF DISEASE

Bites can cause damage to skin, muscle, blood vessels, nerves, tendons and tendon sheaths, joints and joint spaces, and bony structures. Some bites involve major trauma and fatalities.[15] The head and neck are areas of particular vulnerability in children younger than 4 years.[16] Less serious, but far more frequently, bite injuries involve contusions, abrasions, lacerations, avulsions, or puncture wounds. Secondary considerations in all of these animal bite wounds involve contamination with oral flora from the biting animal and local infection. The potential for tetanus or rabies exposure must also be considered. Tetanus is discussed in Chapter 59, and rabies is covered in Chapter 131.

Dog Bites

Dog bite force can exceed 310 pounds, although most bites use much less force.[17,18] Total bite force generated increases as the size of the animal skull increases.[17] Dog bites may cause relatively superficial tearing, or crush injuries that damage skin, subcutaneous tissues, and occasionally muscle and far less commonly tendons, bones, or joints. The wounds may be contusions or ecchymoses without a break in the skin but more commonly are abrasions, lacerations, avulsions, or large gaping crush wounds. A study of more than 2000 dog bites found that most injuries were superficial and most of the patients were treated with simple medication, dressing, or suturing.[19]

Face, scalp, and neck wounds occur most commonly in young children.[6,19] In children up to 2 years old, there are case reports of dog bites that have perforated the skull, resulting in open depressed fractures, brain laceration, intracranial abscess, and meningitis.[20] The trauma associated with dog bite injuries has led to residual post-traumatic stress disorder (PTSD) in children. In victims older than 15 years, more than 80% of dog bite injuries are on the extremities,[16] with the lower extremities more frequently involved.[6,19] In adults, dog bites rarely result in fracture, vascular injury, or tendon and nerve damage, but there have been cases of tendon lacerations and purulent tenosynovitis.[21] Bites from police dogs that are trained to hold their grasp until given the release command have a much higher risk of causing damage to deeper structures, in particular vascular injury; tendon and nerve injury, as well as fracture and infection, are all more common in bites from police dogs than from civilian dogs.[22]

The incidence of infection from dog bites has historically been quoted as 5 to 15%,[16,23] similar to the overall infection rate of 7% in nonbite lacerations. More recent work suggests a nonbite laceration infection rate of 3 to 4%,[24] and a recent controlled study of dog bite lacerations showed a baseline infection rate of 2% in the control arm.[25] The type of wound appears to influence infection rates, with avulsions at 3%, lacerations at 6%, and puncture wounds the highest at 7%.[26] In one study of infected bite wounds, 60% were punctures, 10% lacerations, and 30% a combination of the two.[27] Location on the body also affects risk; dog bites on the

www.ketabpezeshki.com 66485457-66963820

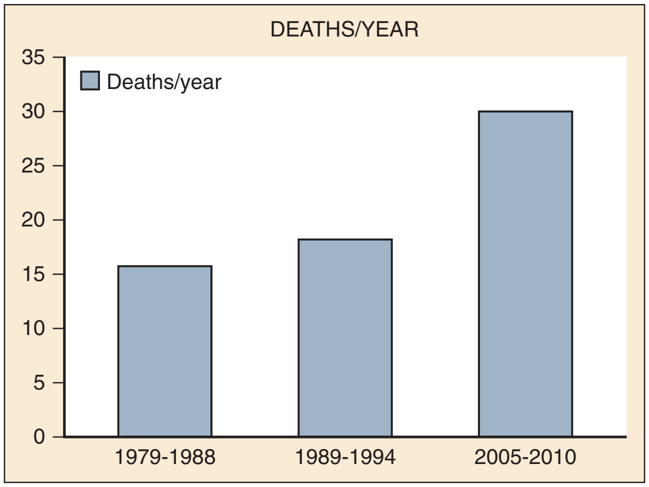


Figure 61-1. Fatal dog bites in the United States; 90% increase (40% corrected for population growth).

hand have a higher rate of infection, and bites of the face have a lower risk than bites elsewhere.[23,26]

Bacteriology

More than 100 different organisms have been isolated from infected dog bites. Most infected wounds are polymicrobial, with an average of five isolates per wound, including both aerobic and anaerobic species.[16,27] No single organism was responsible for more than 30% of infections.[28,29] *Staphylococcus aureus,* alpha-hemolytic and beta-hemolytic streptococci, *Klebsiella, Bacillus subtilis, Pseudomonas,* Enterobacteriaceae, and *Capnocytophaga canimorsus* are among the frequently isolated aerobic organisms.[27,30] Anaerobic organisms isolated from infections include *Bacteroides, Fusobacterium, Peptostreptococcus, Porphyromonas,* and *Prevotella* species.[16] Although much attention has been focused on *Pasteurella multocida,* its role in causing infections in dog bites may be overestimated.[29,31] *P. multocida* is found in the oral flora of 77% of cats but only 13% of dogs.[32] *Pasteurella* species are isolated in 25 to 50% of infected dog bite wounds, although one study of infected dog bites found no *Pasteurella.*[27,33] The *Pasteurella* species that have been isolated from dogs, such as *Pasteurella stomatis, Pasteurella canis,* and *Pasteurella dagmatis,* are less virulent varieties.[27,32] When *P. multocida* is isolated from infected dog bites, it is frequently found in mixed culture with other organisms; with infected cat bites, however, *P. multocida* is often the sole pathogen.[33]

Capnocytophaga canimorsus

C. canimorsus is a fastidious gram-negative rod that can cause overwhelming sepsis. It is part of the normal oral flora of both dogs and cats. More than 100 cases have been documented since the organism's discovery in 1976.[34,35] About 90% of cases are attributed to contact with a dog, primarily bites or scratches, but for approximately one quarter of infections, only dog contact (without a bite) is documented. A few infections have resulted from contact with cats. About 10% of cases appear unrelated to animal exposure. The disease tends to strike patients with alcoholic liver disease, functional or surgical asplenia, or lung disease or those taking corticosteroids. However, in 40% of victims, no underlying illness is identified.[34,36]

The illness usually begins within 3 days of exposure (range 1-10 days). Early manifestations include fever, chills, myalgias, and vomiting.[37] The clinical picture on presentation is often that of sepsis, with hypotension, renal insufficiency, and disseminated intravascular coagulation (DIC). Purpura, particularly on the face, and petechiae are frequent findings and may progress to symmetrical peripheral gangrene.[38] Cutaneous gangrene at the site of the bite strongly suggests *C. canimorsus.*[39] Waterhouse-Friderichsen syndrome (adrenal hemorrhage) may occur, as well as metastatic infection, with endocarditis, meningitis, or peritonitis. The mortality rate is 30%, with 70% of deaths occurring in immunocompromised patients.[37,39]

C. canimorsus grows slowly and requires special media and growth conditions. In cases of sepsis without an obvious source when contact with a dog or cat has occurred, *C. canimorsus* should be considered, and the laboratory should be notified to prevent cultures from being misidentified or discarded prematurely.[37] Although cultures may take up to 14 days, the organism can sometimes be identified in the patient's blood smear at the time of presentation, or in blood culture media before macroscopic growth.[39,40] Polymerase chain reaction (PCR) has recently proven valuable in *C. canimorsus* identification.[41,42]

Cat Bites

Cat bite injuries contrast sharply with dog bites in their propensity for infection and injury to deeper structures. The typical cat bite is a puncture wound, but abrasions, lacerations, and avulsions may also occur. Cats have long, slender, pointed teeth that can penetrate tendons, joints, and bone, inoculating bacteria deep into these tissues. The majority of these bites involve the hand and upper extremity.[9,23] The puncture wound itself often can be difficult to explore, irrigate, or débride. Cat bites are also more likely than dog bites to become infected.[23,43] The incidence of infection in untreated cat bites is reported to be as high as 67%, although this probably represents an overestimate as many patients seek treatment only after infection has developed.[26,44] One prospective ED study of patients with cat bites found an infection rate of 16%, and most infections were present when the patient first sought care.[9] In addition to generally recognized patient risk factors for infection, predictive factors for cat bite infection also include wound type, depth of penetration, and delay in seeking care.

Bacteriology

A bacteriologic analysis of infected cat bites found a median of five bacterial isolates per culture (range, 1-16), with mixed aerobic and anaerobic bacteria in 63%. Aerobic isolates alone grew in 32% of infected cat bites, and there were no infections caused solely by anaerobes. The most common pathogens were *P. multocida* and *Pasteurella septica,* found in 75%, but streptococci, staphylococci, *Moraxella,* and *Bacteroides* were also isolated among the aerobic pathogens. Anaerobes included *Bacteroides, Fusobacterium, Porphyromonas,* and *Prevotella.* Only 4% of the cat bite isolates included *S. aureus,* and no *Streptococcus pyogenes* isolates were detected, suggesting the wounds were more heavily contaminated with oral flora of the biting animal rather than the skin flora of the victim.[27]

Pasteurella multocida

An important factor contributing to the risk of infection after cat bites is the presence of *P. multocida,* a highly virulent, facultatively anaerobic, gram-negative rod found in the oral cavity or nasopharynx of 70 to 90% of healthy cats.[32] Wound infections and abscesses caused by *P. multocida* have occurred after cat scratches as well as cat bites and less often after dog bites or open wounds that have been licked by dogs.[31] *P. multocida* infections have also been reported after the bite of an opossum, rat, lion, rabbit, pig, wolf, monkey, and cougar.[45-47]

www.ketabpezeshki.com 66485457-66963820

P. multocida wound infections often have an earlier onset than typical skin organisms, causing a rapidly progressive cellulitis apparent within 6 hours and easily identifiable within 24 hours.[27] Presenting features include erythema, warmth, swelling, and tenderness, and often purulent drainage, lymphangitis, and adenopathy. In addition to cellulitis, *P. multocida* can cause abscess, tenosynovitis, joint infections, and osteomyelitis at the site and may seed arthritic joints and prosthetic valves, causing septic arthritis, endocarditis, and osteomyelitis at distant sites. Meningitis and pericarditis caused by *P. multocida* after a bite have also been reported.[48,49]

In vitro, *P. multocida* is sensitive to penicillin, ampicillin, tetracycline, fluoroquinolones, amoxicillin-clavulanate, second- and third-generation cephalosporins, and trimethoprim-sulfamethoxazole (TMP-SMX).[50,51] For prophylaxis, *Pasteurella* species are considered susceptible to all of the agents previously listed, plus doxycycline, clarithromycin, and azithromycin.[16,51] The organism is resistant to vancomycin, clindamycin, and oral first-generation cephalosporins and shows borderline susceptibility to aminoglycosides.[52] Semisynthetic penicillins, such as dicloxacillin, have only minimal activity against *P. multocida* in vitro, and erythromycin is also a relatively poor choice.[50,51]

Other Mammals

Primates

In the United States, monkey bites appear most commonly in university centers in laboratory workers who have sustained work-related injuries. Primate bites are said to have a high wound infection rate. The infecting organisms have not been well described, with the exceptions of one wound infection caused by *Eikenella corrodens* and a case of osteomyelitis caused by *P. multocida.*[47,53]

The major concern with monkey bites is B virus exposure. Only one of the 35 herpesviruses identified in nonhuman primates, cercopithecine herpesvirus 1, or B virus, causes disease in humans. Other terms for this virus include *herpesvirus simiae, herpesvirus B,* and *monkey B virus.* The virus has serologic cross-reactivity with herpes simplex virus (HSV) type 1 and type 2, which cause herpetic lesions in humans.[54] Monkeys of the genus *Macaca* (macaques) can carry B virus throughout their lives, and B virus disease in monkeys resembles that of human herpes viruses. Asymptomatic infected monkeys harbor the virus in their conjunctiva, buccal mucosa, and genital areas[55] and may shed virus but are more likely to do so when ill, under stress, immunocompromised, or breeding.

More than 40 cases of B virus infection in humans have been reported, all in laboratory workers bitten or scratched by monkeys or sustaining local injury from animal cages. Many exposures were considered trivial at the time of injury.[55,56] B virus can enter the victim host cells within 5 minutes, making immediate wound care at the scene (soap and water scrub) the most important step in prevention of transmission.[16] The incubation period may range from 2 days to 5 weeks, but most human cases manifest within 5 to 21 days, with initial symptoms of paresthesias at the site of the bite, soon followed by a vesicular rash and, if untreated, by encephalitis and coma. The case fatality rate is approximately 70%.[55] Treatment with intravenous acyclovir is most successful if begun when local vesicles first appear,[56] but even after central nervous system symptoms develop, aggressive treatment may allow survival.[55]

Rodents

Rodent bites cause small puncture wounds with a low risk of local wound infection. These bites are frequently seen in laboratory workers, in children in lower socioeconomic areas who are bitten while sleeping, and occasionally in pet owners.[57] A number of diseases may be transmitted by rodent bites or scratches, including rat-bite fever, leptospirosis, tularemia, sporotrichosis, murine typhus, and plague, although nonbite contacts are the more common routes of transmission of systemic disease to humans. Rat-bite fever, caused by *Streptobacillus moniliformis* or *Spirillum minus,* is rare. It usually manifests 1 to 3 days after the bite with abrupt onset of fever, chills, myalgias, and headache, followed by a rash. Abscesses form in many tissues, including brain, myocardium, and soft tissues. Involvement of joints occurs in 50% of patients, resulting in an asymmetrical migrating polyarthritis.[58,59] Penicillin is the antibiotic of choice, and the organisms also have sensitivity to erythromycin, cephalosporins, tetracycline, carbapenems, aztreonam, clindamycin, and vancomycin. There is intermediate sensitivity to aminoglycosides, fluoroquinolones, and chloramphenicol, with resistance to TMP-SMX, polymyxin B, and nalidixic acid.[58] Routine prophylaxis is unnecessary, as there is a low rate of wound infection.[16]

Ferrets

The European ferret *(Mustela putorius furo)* is the third most popular pet in the United States, with an estimated 5 to 7 million pet ferrets in 4 to 5 million households. The ferret is descended from the polecat, a member of the weasel, mink, and wolverine family. Hunters previously bred ferrets to hunt rats and rabbits. They are extremely ferocious and tenacious with their prey. Although domesticated for more than 2000 years, the ferret appears to retain its instinctive propensity for attacking suckling animals and an attraction to the neck of its victim. Ferrets are known to attack infants and young children suddenly and without provocation, even in the presence of an adult. They usually attack the face and neck and often have to be pried off the victim. Extensive cosmetic repair after such attacks has been required.[60,61]

Domestic Herbivores

The bites of horses may result in severe soft tissue contusions and abrasions, often involve the limbs, and may lead to soft tissue infections with *Staphylococcus, Pasteurella, Yersinia, Actinobacillus, Burkholderia,* and *Rhodococcus* species.[62] Some 1800 patients per year visit EDs with horse bite injuries, and on rare occasions, these bites result in systemic infection.[63] *Streptococcus equi* subsp. *zooepidemicus* is one of the group C streptococcal species that are common pathogens and is associated with the equine respiratory infection known as *strangles* but may also be carried by healthy animals.[64] It has been reported to cause meningitis in humans.

Cattle do not have upper incisors, so they virtually never bite. Pig bites, on the other hand, are often deep and may appear deceptively small on the surface.[65] They require careful exploration and débridement. Pathogens include *Pasteurella aerogenes, P. multocida, Escherichia coli, Bacteroides, Proteus,* and alpha- and beta-hemolytic streptococci.[45,65] Despite antibiotics and appropriate wound care, pig bites have a high risk of infection. Most domestic herbivores carry *P. multocida.* Bacterial isolates from these animals are often resistant to common antibiotics, which has been attributed to the practice of adding antibiotics to their feed.

Camels are well known for biting their handlers, reportedly in sudden vengeance for offenses committed previously. Unlike most other herbivores, the camel has canine teeth and can cause deep wounds, fractures, and amputations, most involving the handler's upper limbs. These wounds are reported to have a very high rate of infection.[66,67]

www.ketabpezeshki.com 66485457-66963820

Wild Animals

Human encounters with large wild animals, such as wolves, coyotes, large cats, elephants, or bears, may result in massive trauma and death, from some combination of biting, goring, or trampling. Attacks by such animals may cause blunt or penetrating trauma, with major arterial blood loss, airway damage, intracranial penetration, broken ribs and vertebrae, pneumothoraces, and intraperitoneal bleeding.[20,68] Hyenas are known for their tremendously strong jaws and for their attacks on humans in Africa. Hyenas target the face and can deglove a face or decapitate a human. Bites of bears usually result in multiple punctures, with crushing and tearing of soft tissues, and underlying fractures of facial bones and those of the upper extremity. Big cats tend to attack the nape of the neck; their teeth may enter the pharynx, esophagus, and intervertebral space. A common killing mechanism is to shake the victim by the neck.[68] The organisms involved in wild animal bites include staphylococci, streptococci, and anaerobes, similar to bites from domestic animals.[16]

Infection Risk Factors

As with nonbite lacerations, the location, type of wound, time to treatment and patient factors contribute to the risk of wound infection.[69,70] Dog bites in patients who delay care by as little as 6 hours have an increased risk of becoming infected.[43,70] Certain patient comorbidities increase bite wound infection risk. Asplenia, cirrhosis, lung disease, and steroid use all increase the risk of *Capnocytophaga* infections. The risk of *Pasteurella* infections is increased in patients with alcoholism, rheumatoid arthritis, or diabetes mellitus, those taking steroids, and those who have residual lymphedema after radiotherapy[70] (Table 61-1).

Table 61-1 Risk Factors for Bite Wound Infection

FACTOR	HIGH RISK	LOW RISK
Species	Cat Human Primate Pig, camel	Dog (excluding hand) Rodent
Location of wound	Hand Over joint or superficial tendon (CFI) Through-and-through oral Below the knee	Face Scalp Mucosa
Wound type	Puncture Extensive tissue damage Contaminated or devitalized tissue Old (delayed presentation) or sutured	Large Superficial Clean Recent
High-risk patients	Immunosuppressed, HIV positive Transplant patient, steroid dependent Diabetes, cancer chemotherapy Prosthetic valve patients Peripheral vascular disease Elderly, alcoholic, cirrhosis Social and compliance problems	

CFI, closed-fist injury; *HIV,* human immunodeficiency virus.

MANAGEMENT

Bite injuries, particularly those from monkeys with potential exposure to herpesvirus simiae (B virus), should be immediately cleansed with soap and water at the scene.[16,54] Washing the wound with soap and water, ideally with the use of a fine-pore sponge to minimize additional tissue trauma, also substantially decreases the risk of rabies infection if done within 3 hours.[71] Key elements of the history include the circumstances of the bite, type of animal, animal immunization status against rabies, animal behavior, and whether the animal is available for observation. Specifically ask about comorbidities with risk of poor wound healing (e.g., diabetes, peripheral vascular disease); use of immunosuppressive medications or steroids; history of splenectomy; chronic alcoholism, particularly with malnutrition; and parenteral recreational drug use. Assess the tetanus status, medication allergies, and primary care provider availability.[72] Potential language, cultural, or economic barriers to compliance are additional considerations.[14] Active bleeding is controlled with direct pressure. If necessary, a temporary 3-0 nylon suture on a large needle may be used. Intractable bleeding on an extremity may be controlled with a proximal blood pressure cuff inflated above the systolic pressure for up to 20 minutes.

The general principles of wound management apply to these patients (see Chapter 59). Radiographs are usually not necessary but may be considered when there is the possibility of bony injury or foreign body. Infants and children up to 2 years old who sustain substantial bite wounds to the scalp may require computed tomography (CT) imaging.[20] In most situations, exploration with local anesthesia or procedural sedation will be critical. The importance of adequate visualization of the depths of the wound cannot be overstated, as this may be the sole opportunity to detect a foreign body or a deep structure injury that could otherwise be missed and manifest later with increased morbidity. In the absence of deep structure injury, wound irrigation followed by conservative débridement is recommended. There is no evidence that extension of the wound to promote irrigation diminishes the chance of infection.

Much controversy and few data surround the question of suturing animal bites. Sound practice dictates that when a wound is at high risk for infection, it should not be sutured unless there is evidence of its safety or other compelling reasons. One study of 145 sutured bite wounds (dog, cat, and human) found a rate of infection of approximately 6%. The use of antibiotics was not standardized.[73] This infection rate may be acceptable in lacerations for which cosmesis is a primary concern. To date, only dog bites have had controlled studies to address the issue of primary closure.[43] The infection rate in 169 wounds was the same for sutured bites as for those left to heal by secondary intention (7.7%). Dog bites on the hand had a higher infection rate (12%), but there was no significant difference between sutured and unsutured wounds. Other studies have demonstrated an equivalent infection rate for sutured dog bites and unsutured wounds.[29,74] On the face, sutured dog bite wounds have a very low infection rate, even when punctures are sutured and no prophylactic antibiotics used.[75]

The following guidelines are suggested, even though data are limited (Table 61-2). Bite wounds of the face and scalp from any species that are less than 6 hours old may be irrigated and sutured. It is probably safe to suture most other uncomplicated dog bites. Lower extremity and hand wounds are at higher risk for infection and should rarely be sutured. Cat bites and primate bites should not be sutured in locations other than the face and scalp. Puncture wounds, contaminated wounds, wounds more than 12 hours old, or wounds infected at presentation should not be sutured. Patients at risk for infection or poor wound healing are best treated conservatively without suturing. See Chapter 59 for a discussion of

www.ketabpezeshki.com 66485457-66963820

Table 61-2 Recommendations for Bite Wound Closure and Prophylactic Antibiotic Consideration

SPECIES	SUTURING	PROPHYLACTIC ANTIBIOTICS
Dog	All (except hands)	High-risk wounds only* (all hand wounds)
Cat	Face only	All
Human	Face (as needed)	Hand, especially CFI
Monkey	No	Yes
Pig, camel	Face (as needed)	Yes
Rodent	Yes (rarely needed)	No
Hand bites	No	Yes
Other locations	Yes	High-risk wounds only*
Mucosa	Yes (as needed)	No
Oral through-and-through bite	Yes (as needed)	Yes

CFI, closed-fist injury.
*High-risk wounds: hand wounds, deep structure involvement (tendon, joint, bone), delayed presentation (>12 hours), contaminated wounds with foreign bodies or devitalized tissue, deep puncture wounds, high-risk patients (see Table 61-1).

Table 61-3 Suggested Regimens for Prophylactic Antibiotics in Bite Wounds

TYPE OF INJURY	ANTIBIOTIC	PENICILLIN ALLERGIC
1. Bite wounds to hand		
A. Human (including CFI*)	Augmentin 500 mg PO q12h × 5d Ceftin 250-500 mg PO bid × 5d	Moxifloxacin 400 mg q24h × 5d TMP-SMX 160 mg PO bid × 5d
B. Other (e.g., dog, cat)	Augmentin	Moxifloxacin
	Ceftin	Clindamycin 300 mg PO q6h × 5d
2. Cat bite wounds	Augmentin Ceftin	Moxifloxacin TMP-SMX
3. High-risk patients (Table 61-1)[†]		
A. Dog (*Capnocytophaga canimorsus* concern)	Augmentin	Clindamycin
	Dicloxacillin 250 mg PO q6h × 5d	Moxifloxacin
B. Cat (*Pasteurella multocida* concern)	Augmentin	Moxifloxacin
	Ceftin	TMP-SMX
C. Other	Augmentin Ceftin	Moxifloxacin Clindamycin
4. Other bite wounds[†]	Keflex 250-500 mg PO q6h × 5d Dicloxacillin	Erythromycin TMP-SMX

**CFI,* clenched fist injury; *PO,* orally; *TMP-SMX,* trimethoprim-sulfamethoxazole.
[†]Methicillin-resistant *Staphylococcus aureus* (MRSA) coverage is not currently thought to be necessary and thus is not recommended.
Most regimens are 3 to 5 days.
Antibiotic prophylaxis in high-risk patients has no proven efficacy but is relatively common practice. Although acknowledging the lack of scientific support in the literature for improved outcomes, to offer prophylaxis and discuss this option with the patient seems reasonable and prudent.
In the category of "other bite wounds," there are no data to demonstrate an effect of antibiotic prophylaxis. We would consider this practice optional, to be weighed against considerations of antibiotic overuse and emerging resistance. There should be no mandate or standard of care issues here.
If one decides on antibiotic prophylaxis, we would suggest use of simpler, cheaper, and narrow-spectrum antibiotics, as these have historically been used in the various studies, and there is no evidence to support broader-spectrum coverage at increased expense.

wound healing with delayed primary closure. No current evidence shows that topical adhesive closure as opposed to sutures changes the rate of infection.

Prophylactic Antibiotics

A Cochrane review including eight randomized controlled trials[26] concluded that prophylactic antibiotics did not reduce the overall rate of infection after bites by cats or dogs. The type of wound (laceration or puncture) did not have any relationship to the effectiveness of the prophylactic antibiotic. There was evidence from one trial that the use of antibiotic prophylaxis after bites of the hand was associated with a statistically significant reduction in the rate of infection, but the authors also concluded that additional confirmatory research was required.[26]

Dog Bites

In general, prophylactic antibiotics are not indicated for routine dog bite wounds, except those of the hand.[26,76,77] The most recent randomized controlled trial to address this showed a control infection rate of 4.3% (2 of 46 patients, confidence interval [CI] 0-7%) with a prophylactic antibiotic infection rate of zero (0 of 48 patients). The difference was not statistically significant.[25] A reasonable approach, therefore, would be to give prophylactic antibiotics to high-risk patients and to those with dog bite wounds of the hand or other high risk wounds (see Table 61-1).

Data to support one prophylactic regimen over another do not exist, either in terms of antibiotic choice or in terms of duration. A variety of antibiotics have been used for prophylaxis in studies, including penicillin, dicloxacillin, co-trimoxazole, cephalexin, Ceclor, Kefzol, and erythromycin.[26] A recent review recommended amoxicillin-clavulanate or a combination of penicillin plus cephalexin, and moxifloxacin or combination therapy with ciprofloxacin and clindamycin for penicillin-allergic patients, although many of these regimens have not been tested in randomized studies and, given the bacteriology, it is not clear that an antibiotic covering *Pasteurella* species is essential in prophylaxis.[16] The most recently studied approach has been the use of amoxicillin-clavulanate (Augmentin) for 3 days[25] (Table 61-3).

Coverage for *P. multocida* is recommended in established wound infections; amoxicillin-clavulanate and the second- and third-generation cephalosporins are all excellent first-line agents. Alternative regimens and those for penicillin-allergic patients can be used. The dosage and duration of treatment are individualized to the patient, the site of the infection, and the clinical severity of the presentation. Most patients do not require hospital admission. The incidence of methicillin-resistant *S. aureus* (MRSA) in dog bite wound infections has not been studied, and coverage for MRSA in prophylaxis or infections is currently not recommended. Oral colonization of the animal mouth by MRSA is unlikely, and therefore MRSA coverage would not be expected to add anything unless the patient had risk factors for MRSA (e.g., previous MRSA infections, or close contact with a known MRSA reservoir).[16]

Capnocytophaga canimorsus

There are no studies on the prevention of *C. canimorsus* infection, but it is probably prudent to give prophylactic antibiotics to immunocompromised patients (including diabetics) after a dog or cat bite.[34,39] In vitro, *C. canimorsus* is susceptible to penicillin G, ampicillin, carbenicillin, cephalothin, ceftizoxime, clindamycin,

www.ketabpezeshki.com 66485457-66963820

erythromycin, tetracycline, fluoroquinolones, vancomycin, and chloramphenicol, although one clinical case of resistance to penicillin, erythromycin, and clindamycin has occurred.[78] *C. canimorsus* displays variable susceptibility to TMP-SMX and appears to be resistant to all aminoglycosides. For prophylaxis, amoxicillin-clavulanate or penicillin is recommended. For treatment of established infections, use of a parenteral second- or third-generation cephalosporin, amoxicillin-sulbactam, or clindamycin plus a fluoroquinolone (in adults) is acceptable. *C. canimorsus* continues to appear in sepsis of obscure cause, and a history of exposure to dog bites should be actively pursued in these situations.[37,79]

Cat Bites

There is only one published randomized controlled study of prophylactic antibiotics in cat bites; though small, it demonstrated reduced infection.[44] A Cochrane review concluded there was no evidence that antibiotic prophylaxis was effective for cat bites, although the authors also concluded that animal bites on the hands (where most cat bites occur) benefit from prophylaxis.[26] We therefore recommend prophylaxis including coverage for *P. multocida* as well as *S. aureus* and *Streptococcus* species. MRSA coverage is not indicated because it is not an oral pathogen for the cat.[16] *Pasteurella* is usually sensitive to penicillin, although some β-lactamase–producing strains have been recovered. *Pasteurella* is also usually sensitive to ampicillin, ticarcillin, amoxicillin-clavulanate, tetracyclines, second- and third-generation cephalosporins, fluoroquinolones, and TMP-SMX. *P. multocida* may be resistant to semisynthetic penicillins (dicloxacillin, methicillin) as well as erythromycin, clindamycin, first-generation cephalosporins, and aminoglycosides.[51]

For prophylaxis, amoxicillin-clavulanate or a second-generation cephalosporin such as cefuroxime is recommended. For penicillin-allergic patients, moxifloxacin or clindamycin plus ciprofloxacin will cover the likely pathogens. Extended-spectrum fluoroquinolones cover *P. multocida* and have good staphylococcal and streptococcal coverage. Azithromycin may be effective for penicillin-allergic patients but has less activity against anaerobes.[16,80,81]

For very high-risk bites, such as cat bites on the hand, intravenous antibiotic prophylaxis in the ED should be considered. Although there are no experimental data to support this strategy, intravenous treatment achieves detectable levels in the wound much sooner than the oral or intramuscular route.

Other Animal Bites

Although there are no studies to support the practice, antimicrobial prophylaxis for bites from other mammals is often provided.[16] We recommend antibiotic prophylaxis with coverage against *Pasteurella* for pig bites or camel bites, for high-risk patients, and for bites on the hand. Rodent bites and those from most other species have a lower risk of wound infection, so prophylaxis is not indicated. The anecdotal data available on wild animal bites suggest that the organisms involved are similar to those in domestic animals, including staphylococci, streptococci, and anaerobes.[16] There are no studies regarding the use of antibiotic prophylaxis in these injuries.[82]

Prophylactic Antiviral Agents

Monkey Bites

Immediate management at the scene, including cleaning the wound with soap and water for at least 15 minutes, is paramount. Mechanical cleansing of the area is more important than the type of solution used. Mucosal surfaces should be rinsed with running water for 15 minutes. Immediate irrigation is thought to inactivate and wash out virus that may be present in the wound. In the ED, management includes a determination of the health status of the monkey and the historical details of the exposure; however, most reported human infections with B virus were transmitted by asymptomatic animals. Regardless of prior irrigation, repeat wound cleansing should be performed. Cultures of the bite are generally not recommended before irrigation, and they are often negative afterward.

Although human cases of infection are extremely rare given the thousands of potential exposures each year, the mortality rate for B virus infection in the absence of antiviral therapy is over 70%. Treatment with antiviral medication may decrease the death rate; rapid diagnosis and therapy are essential in controlling central nervous system spread of the virus.[54] Prophylaxis with antiviral therapy is individualized based on the risks of the exposure (Box 61-1). The dialogue with the patient regarding antiviral prophylaxis should be documented. If prophylaxis is undertaken, the recommended therapy is valacyclovir (1 g orally [PO] q8h × 14 days) or acyclovir (800 mg PO 5 times daily × 14 days). Prophylaxis can be started up to 5 days after the exposure.[55] Patients should be told about the early symptoms of B virus infection and to immediately seek care if any develop. Patients should also be advised to avoid exchange of bodily fluids, including saliva, or handling of an open wound or vesicles, as one case of human-to-human transmission has occurred.[54]

Monkey bites are also considered to be at high risk for bacterial wound infection; prophylactic antibiotics covering *S. aureus*, anaerobic cocci, and *Bacteroides* are recommended for full-thickness bites, particularly those on the hand.[53] Good choices include amoxicillin-clavulanate or moxifloxacin.

Other Prophylaxis

Rabies and tetanus prophylaxis should be considered for all bite wounds.

DISPOSITION

Patients with any of the following should be considered for hospital admission: delayed presentation (>24 hours), established infection at the time of presentation, deep structure violation, high-risk patient or high-risk wound categories, and social support or compliance issues (Table 61-1). Those with cosmetic issues requiring surgical repair such as large facial wounds also may require admission.

HUMAN BITES

PERSPECTIVE

Epidemiology

The majority of human bite wounds (60-75%) involve the hand or upper extremity. Although the overall infection rate for human bite wounds has been estimated at 10%,[83,84] human bites of the hand, especially the fight bite or closed-fist injury (CFI), are associated with a higher incidence of infectious complications. Simple human bites elsewhere on the body are probably no more significant than nonbite wounds. The reported rate of infection in human bites of the hand is 25 to 50%,[85] but the majority of these infections already exist when the patient first seeks care.[83,86] The high infection rate results from a number of factors: the relative lack of vascular supply to structures in the hand, the position of the hand at the time of injury, the mechanism and force of injury, the bacteriology of the human mouth, and a delay in seeking care.

www.ketabpezeshki.com 66485457-66963820

Box 61-1 Prophylaxis for Monkey B Virus Exposure

Prophylaxis Recommended

Skin exposure (with loss of skin integrity) or mucosal exposure to a high-risk source: macaque that is ill, immunocompromised, known to be shedding virus or has visible lesions compatible with B virus
Inadequately cleaned skin or mucosal exposure
Laceration of head, neck, or torso
Deep puncture wound
Needle-stick associated with tissue or fluid from the nervous system, lesions suspicious for B virus, eyelids, or mucosa
Puncture or laceration after exposure to objects (1) contaminated with fluid from monkey oral or genital lesions or with nervous system tissues or (2) known to contain B virus
Postcleaning culture-positive B virus

Prophylaxis Considered

Mucosal splash that has been adequately cleaned
Laceration (with loss of skin integrity) that has been adequately cleaned
Needle-stick involving blood from an ill or immunocompromised macaque
Puncture or laceration occurring after exposure to either objects contaminated with body fluid (other than from a lesion) or potentially infected cell culture

Prophylaxis Not Recommended

Skin exposure in which the skin remains intact
Exposure associated with nonmacaque species of nonhuman primates

Adapted from Cohen JI, et al: Recommendations for prevention of and therapy for exposure to B virus (cercopithecine herpesvirus 1). Clin Infect Dis 35:1191, 2002.

In a study of 50 patients with infected human bites, 56% of the injuries were CFIs; the rest were "occlusional" injuries, most on the hand.[83,87] The infections may progress to purulent tenosynovitis, septic arthritis, and osteomyelitis.

PRINCIPLES OF DISEASE

Fight Bites (Clenched Fist Injury)

A CFI results when the patient strikes another person in the mouth with a closed fist during an altercation. The patient's reticence to discuss the event may preclude an accurate history. This historical ambiguity combined with patient compliance issues may make management of these injuries even more challenging.[83,84] The CFI manifests as a minor laceration of the dorsum of the hand, most commonly over the middle finger metacarpophalangeal joint (third MCP joint), but other MCP joints are frequently involved.[88] The small laceration may involve deep structure injury to the extensor tendon sheath, the tendon itself, bones, or joint spaces. Joint penetration occurs in up to 62% of these wounds, and up to 58% involve injury to bone.[89] "Chondral divot fractures" result from a tooth striking the articular surface of the joint and chipping off fragments of articular cartilage. The incidence of these fractures varies from 6 to 30% in retrospective studies, and up to 58% in one prospective study, with an incidence of tendon damage as high as 34%.[88] The presence of an extensor tendon laceration is highly predictive of joint penetration, and patients with deep structure involvement have significantly increased morbidity from the CFI. Infection of the joint space (pyogenic arthritis, septic joint) may be aggressive and rapidly destructive to the joint tissues.[83] Deep space infection of the hand leading to amputation has also been reported.[16] These wounds may contain foreign bodies. Associated bony injuries include the *boxer's fracture* (distal ring or small finger metacarpal fractures), and occlusive bite injuries may cause traumatic amputation of the digit.

Other Human Bites

Human bites in locations other than the hand treated with proper local wound care have a rate of infection similar to that of ordinary lacerations. Human bites of the face have about a 2.5% infection rate. In children, approximately 70% of human bites are abrasions, which generally do not become infected. The reported infection rate of human bites in children is 9% to 12%, similar to the 10% infection rate of all human bite wounds quoted earlier, although the data in children come from older studies. Most of these infections are noted at the time of the initial visit, usually in patients who have delayed care for more than 12 to 18 hours.[90,91] Lacerations from the victim's own teeth, usually a result from a fall or a seizure, are considered bites. Wounds that involve only the mucosa or tongue have a low infection rate, from 0 to 12%, but mucocutaneous (through-and-through) lacerations have an infection rate as high as 30% in the absence of prophylactic antibiotics, so the latter warrant prophylaxis. Organisms cultured from these infected wounds include *Streptococcus, S. aureus, Staphylococcus epidermidis, Bacteroides, Corynebacterium, Neisseria,* and *Haemophilus haemolyticus.*[92]

Human Bite Bacteriology

The oral flora of the human mouth includes a high concentration of pathogenic organisms. Human saliva contains up to 50 different species of bacteria.[83] Not surprisingly, bite wounds have numerous bacteria of multiple species, and the bacterial count increases dramatically several hours after the injury.[16] Cultures of uninfected bite wounds, however, do not predict which patients will become infected, or which pathogen will be responsible.[16] Information on the bacteriology of infected human bites comes almost exclusively from hand bites, with the majority of these being CFIs. Infected wounds are polymicrobial. *Streptococcus anginosus* is the most common pathogen, found in 52% of infections, followed by *S. aureus* and *E. corrodens*, each in 30%.[16] Earlier studies found a predominance of *Staphylococcus* and *Streptococcus* species, followed by *Corynebacterium* species and *Eikenella.*[83,88]

Oral anaerobes are also often present in these wounds[16] and account for more than half of the isolates.[83] Anaerobes and gram-negative rods are more frequently isolated from infected human bites on the hand than other types of hand infections, including those from animal bites, and the presence of anaerobes in a mixed infection may be associated with a worse outcome. The gram-negative organisms isolated include *E. corrodens*, diphtheroids (*Corynebacterium* species), *Haemophilus,* and coliforms.[88]

E. corrodens is a facultatively anaerobic gram-negative rod harbored in human dental plaque and found in 6 to 30% of CFI infections.[16,88,93] It acts synergistically with aerobic organisms, most frequently streptococci, and was historically thought to account for greater morbidity in these wounds.[94] More recent information confirms this synergistic activity but indicates that infections involving *E. corrodens* are no more serious than other infections.[88] *E. corrodens* is usually susceptible in vitro to penicillin, ampicillin, second- and third-generation cephalosporins, carbenicillin, tetracycline, and fluoroquinolones.[80,81] Resistance to penicillin has been reported.[95] *E. corrodens* is resistant to methicillin, aminoglycosides, clindamycin, vancomycin, and metronidazole.[52] Susceptibility to first-generation cephalosporins and erythromycin is limited.[81,95]

Transmission of Disease

Human bites have resulted in transmission of hepatitis B, hepatitis C, tetanus, syphilis, tuberculosis, and herpes.[83,96,97] Herpetic

www.ketabpezeshki.com 66485457-66963820

whitlow, infection of the distal phalanx from HSV, is an occupational hazard of nurses, physicians, dentists, and oral hygienists. Although human immunodeficiency virus (HIV) is secreted at some time in the saliva of up to 44% of infected patients, the CDC does not consider human bites to carry a risk of transmission unless there is exposure to blood.[59,98] HIV is not often present in patient's saliva, and when it is, the titer of virus is very low.[97] Cases in which HIV has convincingly been transmitted through a bite involved significant amounts of blood mixed with the saliva.[99,100] Nevertheless, when a significant bite has occurred, and particularly if the biter is known to be HIV positive, it is reasonable to consult with infection control experts locally or at the CDC.

MANAGEMENT

History

As with animal bites, information regarding immunosuppression and significant comorbidity with risk for poor wound healing should be elicited. Infections are more common in the very young and the elderly.[16] The practitioner should consider tetanus status, medication allergies, social situation, availability of follow-up, and patient reliability. Likewise, the issues of language, cultural, social, or economic barriers to appropriate management and compliance may also play a part in management decisions.

Wound Evaluation and Management

The approach to the human bite depends on the location and the mechanism of injury. Any laceration in the vicinity of the MCP joint is considered a CFI. Full-thickness bites on the hand are considered high risk. Radiographs looking for tooth fragments or other foreign bodies, air in the joint space, or bony injuries are appropriate.[83,86] A "skyline" view may be required to demonstrate vertical articular fractures of the metacarpals.[101]

Assess the wound for infection and neurovascular status with particular attention to extensor tendon function in CFI injuries. Examinations that demonstrate injuries to the deeper structures generally prompt consultation with a hand surgeon. Although there are no controlled studies on suturing human bites, the infection rate and complications of human bites on the hand suggest that they should not be sutured; instead, the wound is covered with a dry sterile dressing and the hand is splinted. Human bite injuries elsewhere on the body can be treated as typical lacerations, with irrigation, aggressive débridement, and consideration of suturing if anatomy permits and cosmetic considerations are important.[102] Tetanus can be transmitted by human bites.[72,103]

Prophylactic Antibiotics

Antibiotic prophylaxis is recommended for full-thickness human bites of the hand (see Tables 61-2 and 61-3). The only randomized, placebo-controlled study of patients hospitalized with uninfected human bites on the hand found no infections in patients who received antibiotics, whereas those who received placebo had a 47% infection rate.[85] Although good results have been achieved historically in selected situations without prophylactic antibiotics when patients were treated early and received appropriate wound cleansing, this is probably not optimum wound management today.[83,86] A Cochrane review concluded prophylactic antibiotics were associated with a statistically significant reduction in the rate of infection after bites by humans, although this was based on the single study mentioned earlier.[26,85]

Irrigation of mucosal or tongue lacerations may be difficult. Suturing is advisable only for deeper and larger wounds. Through-and-through lacerations, from a tooth puncture of the skin of the lower lip, may require a layered closure. Although the one randomized study on prophylactic antibiotics in these lacerations did not find the infection rate to be lowered significantly, a trend toward reduction in infection in the treated group was seen; therefore prophylactic antibiotics may be considered for through-and-through lacerations.[92]

Prophylactic antibiotics are recommended for high-risk human bite wounds elsewhere on the body, including contaminated wounds, deep punctures, wounds with late presentation, and wounds in patients with underlying comorbidity. Antibiotic prophylaxis should cover gram-positive organisms and *E. corrodens* (see Table 61-3). Prophylaxis for MRSA is not currently recommended, as colonization of the human mouth with MRSA is unlikely.[16] When prophylaxis is undertaken, particularly in high-risk situations, we recommend giving the first dose parenterally in the ED.

Prophylactic Antiviral Agents

Victims of bites from persons potentially infected with HIV or hepatitis are managed with exceptionally rapid, vigorous, and thorough wound cleansing with soap and water, to remove saliva, followed by irrigation with virucidal agents such as 1% povidone-iodine. A baseline HIV blood test and hepatitis antibody testing should be performed at the time of injury and prophylaxis considered for hepatitis B or HIV if the victim was bitten by someone with these viruses.[16] An excellent resource to help sort out the specifics of a given situation 24 hours a day is the CDC's postexposure prophylaxis hotline (1-888-448-4911) or the website of the University of California San Francisco/San Francisco General Hospital–based National HIV/AIDS Clinicians' Consultation Center (www.nccc.ucsf.edu).

Infection

Infected human bites of the hand require aerobic and anaerobic cultures. The patient should be treated with intravenous antibiotics covering gram-positive organisms, *E. corrodens,* and anaerobes. Anaerobes isolated from human bite wounds produce β-lactamase and are often resistant to penicillin.

DISPOSITION

Patients with Infection

Delay in presentation and the presence of infection on initial evaluation are both strongly correlated with subsequent morbidity.[83,86] All patients with infected human bites of the hand should be hospitalized for parenteral antibiotics (Box 61-2). Localized infections of human bites elsewhere on the body in immunocompetent patients without significant comorbidity can usually be treated without hospitalization if appropriate follow-up can be arranged.

Box 61-2 Indications for Hospital Admission for Human Bites of the Hand

- Established infection at the time of presentation
- Deep structure violation (tendon or sheath, joint, bone)
- High-risk wound (foreign body, contaminated, devitalized tissue)
- High-risk patient (see Table 61-1)
- Wound more than 24 hours old (delayed presentation)
- Likely social support or compliance issues

www.ketabpezeshki.com 66485457-66963820

Patients without Infection

Reliable, otherwise healthy patients who are seen within 24 hours of the injury and who have no injury to the deeper structures may be treated on an outpatient basis with close follow-up, preferably within 2 days.[83,86] Prophylactic antibiotics as discussed earlier are recommended for human bites of the hand and those at high risk elsewhere on the body (contaminated wounds, later presentation). Suggested regimens include amoxicillin-clavulanate (Augmentin, 500 mg PO q12h) or a second- or third-generation cephalosporin such as cefuroxime (Ceftin, 500 mg PO bid × 5 days). Discharge instructions include immobilization, elevation, and frequent dressing changes initially, along with wound care instructions regarding symptoms that should precipitate an early return for reevaluation.

Patients at higher risk, such as those with deep structure involvement or delayed presentation, require prophylactic parenteral antibiotics in the ED and close evaluation. Consultation with a hand surgeon is usually wise, and hospitalization is generally prudent. In one series, 63% of patients with fight bites either left against medical advice or failed to follow up, and it is reasonable to admit patients who might predictably fall into this category even without associated injuries.[88] Although many human bites are a consequence of mutual aggression, the patient may be a victim or perpetrator in child, spousal, or elder abuse.[104] All states require reporting of suspected child abuse; laws vary for spousal or elder abuse. In all cases, details of the incident should be documented and the wound(s) described in the record. Counseling or referral should be offered when appropriate.

KEY CONCEPTS

- Prophylactic antibiotics are recommended for dog bites of the hand and for high-risk patients. They are not indicated for routine dog bite wounds.
- Patients at high risk should receive prophylactic antibiotics for *C. canimorsus* after a dog bite.
- Cat bites and scratches have a high rate of infection, and prophylactic antibiotics are recommended for cat bites of the hand and for cat bites in high-risk patients.
- Prophylactic antibiotics are recommended for human bites of the hand as well as for high-risk patients. They are also recommended for high-risk wounds, including deep punctures and contaminated wounds.
- Ordinary human bite wounds, such as those exchanged among children (superficial, partial thickness, minimal tissue trauma), do not represent a high risk for infection or complication and do not require prophylaxis.
- Wounds at high risk for infection should generally not be sutured.
- All bites are considered tetanus-prone wounds.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Centers for Disease Control and Prevention (CDC): *Dog Bite Prevention* 2011; CDC. Available at www.cdc.gov/. Accessed May 1, 2011. HomeandRecreationalSafety/Dog-Bites/biteprevention.html.
2. Holmquist L, Elixhauser A: *Emergency Department Visits and Inpatient Stays Involving Dog Bites, 2008*. Statistical Brief #101. Rockville, Md: Healthcare Cost and Utilization Project (HCUP) Statistical Briefs; 2006-2010. Available at http://www.hcup-us.ahrq.gov/reports/statbriefs/sb101.pdf. Accessed December 14, 2012.
3. Sacks JJ, Sattin RW, Bonzo SE: Dog bite–related fatalities from 1979 through 1988. *JAMA* 1989; 262:1489-1492.
4. Sacks JJ, Lockwood R, Hornreich J, Sattin RW: Fatal dog attacks, 1989-1994. *Pediatrics* 1996; 97(6 Pt 1):891-895.
5. DogsBite.org: *Dog Bite Fatalities*, 2011. Available at www.dogsbite.org/bite-statistics-fatalities.htm. Accessed May 1, 2011.
6. Schalamon J, et al: Analysis of dog bites in children who are younger than 17 years. *Pediatrics* 2006; 117:374-379.
7. DogsBite.org: *Report: U.S. Dog Bite Fatalities January 2006 to December 2008*, April 20, 2009. Available at www.dogsbite.org/reports/dogsbite-report-us-dog-bite-fatalities-2006-2008.pdf. Accessed May 1, 2011.
8. Sacks JJ, Kresnow JM, Houston B: Dog bites: How big a problem? *Inj Prev* 1996; 2:52-54.
9. Kwo S, Agarwal JP, Meletiou S: Current treatment of cat bites to the hand and wrist. *J Hand Surg Am* 2011; 36:152-153.
10. Mitnovetski S, Kimble F: Cat bites of the hand. *ANZ J Surg* 2004; 74:859-862.
11. Centers for Disease Control and Prevention (CDC): Nonfatal dog bite–related injuries treated in hospital emergency departments—United States, 2001. *MMWR Morb Mortal Wkly Rep* 2003; 52:605-610.
12. Bhanganada K, Wilde H, Sakolsataydorn P, Oosombat P: Dog-bite injuries at a Bangkok teaching hospital. *Acta Trop* 1993; 55:249-255.
13. Aghababian R, Conte J: Mammalian bite wounds. *Ann Emerg Med* 1980; 9:79-83.
14. Ichhpujani R: Epidemiology of animal bites and rabies cases in India: A multicentric study. *J Commun Dis* 2008; 40:27-36.
15. Avis SP: Dog pack attack: Hunting humans. *Am J Forensic Med Pathol* 1999; 20:243-246.
16. Moran GJ, Talan DA, Abrahamian FM: Antimicrobial prophylaxis for wounds and procedures in the emergency department. *Infect Dis Clin North Am* 2008; 22:117-143.
17. Polsky RH: *Dog Bite Force*, April 11, 2011. Available at www.dogexpert.com/IndexAbstracts/AnimBehEpiLiterature/Articles/Bite%20force.html. Accessed May 1, 2011.
18. Lindner DL: Measurements of bite force in dogs: A pilot study. *J Vet Dent* 1995; 12:49-52.
19. Dwyer JP, Douglas TS, van As AB: Dog bite injuries in children—a review of data from a South African paediatric trauma unit. *S Afr Med J* 2007; 97:597-600.
20. Steinbok P, Flodmark O, Scheifele DW: Animal bites causing central nervous system injury to children. *Pediatr Neurosci* 1986; 12:96-100.
21. Philipsen TE, Molderez C, Gys T: Cat and dog bites. What to do? Guidelines for the treatment of cat and dog bites in humans. *Acta Chir Belg* 2006; 106:692-695.
22. Hutson HR, et al: Law enforcement K-9 dog bites: Injuries, complications, and trends. *Ann Emerg Med* 1997; 29:637-642.
23. Matter HC, Sentinella A: The epidemiology of bite and scratch injuries by vertebrate animals in Switzerland. *Eur J Epidemiol* 1998; 14:483-490.
24. Moscati RM, Mayrose J, Reardon RF, Janicke DM, Jehle DV: A multicenter comparison of tap water versus sterile saline for wound irrigation. *Acad Emerg Med* 2007; 14:404-409.
25. Quinn JV, McDermott D, Rossi J, Stein J, Kramer N: Randomized controlled trial of prophylactic antibiotics for dog bites with refined cost model. *West J Emerg Med* 2010; 11:435-441.
26. Medeiros, I, Saconato H: Antibiotic prophylaxis for mammalian bites. *Cochrane Database Syst Rev* 2001; 2:CD001738.
27. Talan DA, Citron DM, Abrahamian FM, Moran GJ, Goldstein EJ: Bacteriologic analysis of infected dog and cat bites. Emergency Medicine Animal Bite Infection Study Group. *N Engl J Med* 1999; 340:85-92 [see comments].
28. Ordog G: The bacteriology of dog bite wounds on initial presentation. *Ann Emerg Med* 1986; 15:1324-1329.
29. Callaham M: Prophylactic antibiotics in common dog bite wounds: A controlled study. *Ann Emerg Med* 1980; 9:410-414.
30. Goldstein EJ: Bite wounds and infection. *Clin Infect Dis* 1992; 14:633-638.
31. Holst E, Rollof J, Nielsen JP: Characterization and distribution of *Pasteurella* species recovered from infected humans. *J Clin Microbiol* 1992; 30:2984-2987.
32. Ganiere JP, Escande F, Andre G, Larrat M: Characterization of *Pasteurella* from gingival scrapings of dogs and cats. *Comp Immunol Microbiol Infect Dis* 1993; 16:77-85.
33. Feder HM Jr, Shanley JD, Barbera JA: Review of 59 patients hospitalized with animal bites. *Pediatr Infect Dis J* 1987; 6:24-28.
34. Lion C, Escande F, Burdin JC: *Capnocytophaga canimorsus* infections in human: Review of the literature and cases report. *Eur J Epidemiol* 1996; 12:521-533.
35. Valtonen M, et al: *Capnocytophaga canimorsus* septicemia: Fifth report of a cat-associated infection and five other cases. *Eur J Clin Microbiol Infect Dis* 1995; 14:520-523.
36. Chadha V, Warady BA: *Capnocytophaga canimorsus* peritonitis in a pediatric peritoneal dialysis patient. *Pediatr Nephrol* 1999; 13:646-648.
37. Sacks R, Kerr K: A 42-year-old woman with septic shock: An unexpected source. *J Emerg Med* 2012; 42:275-278.
38. Findling JG, Pohlmann G, Rose H: Fulminant gram-negative bacillemia (DF-2) following a dog bite in an asplenic woman. *Am J Med* 1980; 68:154-156.
39. Kullberg BJ, Westendorp RG, van't Wout J, Meinders AE: Purpura fulminans and symmetrical peripheral gangrene caused by *Capnocytophaga canimorsus* (formerly DF-2) septicemia—a complication of dog bite. *Medicine (Baltimore)* 1991; 70:287-292.
40. Deprés-Brummer P, Buijs J, van Engelenburg K, Oosten H: *Capnocytophaga canimorsus* sepsis presenting as an acute abdomen in an asplenic patient. *Neth J Med* 2001; 59:213-217.
41. van Dam AP, Jansz A: *Capnocytophaga canimorsus* infections in The Netherlands: A nationwide survey. *Clin Microbiol Infect* 2011; 17:312-315.
42. Cleuziou C, et al: "Beware man's best friend." *Spine (Phila Pa 1976)* 2010; 35:E1520-E1521.
43. Maimaris C, Quinton D: Dog-bite lacerations: A controlled trial of primary wound closure. *Arch Emerg Med* 1988; 15:156-161.
44. Elenbaa R, McNabney W, Robinson W: Evaluation of prophylactic oxacillin in cat bite wounds. *Ann Emerg Med* 1984; 13:155-157.
45. Ejlertsen T, Gahrn-Hansen B, Søgaard P, Heltberg O, Frederiksen W: *Pasteurella aerogenes* isolated from ulcers or wounds in humans with occupational exposure to pigs: A report of 7 Danish cases. *Scand J Infect Dis* 1996; 28:567-570.
46. Kizer KW: *Pasteurella multocida* infection from a cougar bite. A review of cougar attacks. *West J Med* 1989; 150:87-90.
47. Tan C, Ti T, Lee E: *Pasteurella multocida* osteomyelitis of the cervical spine in a patient on chronic hemodialysis. *Singapore Med J* 1990; 31:400-402.
48. Layton CT: *Pasteurella multocida* meningitis and septic arthritis secondary to a cat bite. *J Emerg Med* 1999; 17:445-448.
49. Al-Allaf AK, Harvey TC, Cunnington AR: Pericardial tamponade caused by *Pasteurella multocida* infection after a cat bite. *Postgrad Med J* 2001; 77:199-200.
50. Goldstein EJ, Citron DM, Hunt Gerardo S, Hudspeth M, Merriam CV: Comparative in vitro activities of DU-6859a, levofloxacin, ofloxacin, sparfloxacin, and ciprofloxacin against 387 aerobic and anaerobic bite wound isolates. *Antimicrob Agents Chemother* 1997; 41:1193-1195.
51. Kristinsson G: *Pasteurella multocida* infections. *Pediatr Rev* 2007; 28:472-473.
52. Goldstein E, Citron D, Vagvolgy A: Susceptibility of bite wound bacteria to seven oral antimicrobial agents, including RU-985, a new erythromycin: Considerations in choosing empiric therapy. *Antimicrob Agents Chemother* 1986; 29:556-559.
53. Janda DH, Ringler DH, Hilliard JK, Hankin RC, Hankin FM: Nonhuman primate bites. *J Orthop Res* 1990; 8:146-150.
54. Huff JL, Barry PA: B-virus (cercopithecine herpesvirus 1) infection in humans and macaques: Potential for zoonotic disease. *Emerg Infect Dis* 2003; 9:246-250.
55. Cohen JI, Davenport DS, Stewart JA: Recommendations for prevention of and therapy for exposure to B virus (cercopithecine herpesvirus 1). *Clin Infect Dis* 2002; 35:1191-1203.
56. Holmes GP, et al: B virus (Herpesvirus simiae) infection in humans: Epidemiologic investigation of a cluster. *Ann Intern Med* 1990; 112:833-839.
57. Hudsmith L, Weston V, Szram J, Allison S: Clinical picture, Rat bite fever. *Lancet Infect Dis* 2001; 1:91.
58. Elliott SP: Rat bite fever and *Streptobacillus moniliformis*. *Clin Microbiol Rev* 2007; 20:13-22.

www.ketabpezeshki.com 66485457-66963820

59. Vyrostek SB, Annest SL, Ryan GW: Surveillance for fatal and nonfatal injuries—United States, 2001. *MMWR Surveill Summ* 2004; 53:1-57.
60. Applegate JA, Walhout MF: Childhood risks from the ferret. *J Emerg Med* 1998; 16:425-427.
61. Paisley J, Lauer B: Severe facial injuries to infants due to unprovoked attacks by pet ferrets. *JAMA* 1988; 259:2005-2006.
62. Langley R, Morris T: That horse bit me: Zoonotic infections of equines to consider after exposure through the bite or the oral/nasal secretions. *J Agromedicine* 2009; 14:370-381.
63. Thomas KE, Annest JL, Gilchrist J, Bixby-Hammett DM: Non-fatal horse related injuries treated in emergency departments in the United States, 2001-2003. *Br J Sports Med* 2006; 40:619-626.
64. Brouwer MC, Kasanmoentalib ES, Opstelten FW, van der Ende A, van de Beek D: A horse bite to remember. *Lancet* 2010; 376:1194.
65. Van Demark RES, Van Demark REJ: Swine bites of the hand. *J Hand Surg Am* 1991; 16:136-138.
66. al Boukai A, Hawass NE, Patel PJ, Kolawole TM: Camel bites: Report of severe osteolysis as late bone complications. *Postgrad Med J* 1989; 65:900-904.
67. Ogunbodede EO, Arotiba JT: Camel bite injuries of the orofacial region: Report of a case. *J Oral Maxillofac Surg* 1997; 55:1174-1176.
68. Wiens M, Harrison P: Big cat attack: A case study. *J Trauma* 1996; 40:829-831.
69. Singer AJ, Hollander JE, Quinn JV: Evaluation and management of traumatic lacerations. *N Engl J Med* 1997; 337:1142-1148.
70. Morgan M, Palmer J: Dog bites. *BMJ* 2007; 334:413-417.
71. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR: Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. *Am J Infect Control* 1999; 27:97-132.
72. Diphtheria, tetanus and pertussis: Recommendations for vaccine use and other preventive measures: Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR Recomm Rep* 1991; 40:1-28.
73. Chen E, Homiq S, Shepherd SM, Hollander JE: Primary closure of mammalian bites. *Acad Emerg Med* 2000; 7:157-161.
74. Dire D, Hogan D, Riggs M: A prospective evaluation of risk factors for infections from dog-bite wounds. *Acad Emerg Med* 1994; 1:258-266.
75. Guy R, Zook E: Successful treatment of acute head and neck dog bite wounds without antibiotics. *Ann Plast Surg* 1986; 17:45-48.
76. Cummings P: Antibiotics to prevent infections in patients with dog bite wounds: A meta-analysis of randomized trials. *Ann Emerg Med* 1994; 23:535-540.
77. Callaham M: Prophylactic antibiotics in dog bite wounds: Nipping at the heels of progress. *Ann Emerg Med* 1994; 23:577-579.
78. Job L, Horman JT, Grigor JK, Israel E: Dysgonic fermenter-2: A clinico-epidemiologic review. *J Emerg Med* 1989; 7:185-192.
79. O'Rourke GA, Rothwell R: *Capnocytophaga canimorsus*—a cause of septicaemia following a dog bite: A case review. *Aust Crit Care* 2011; 24:93-99.
80. Goldstein EJ, Citron DM, Hudspeth M, Hunt Gerardo S, Merriam CV: In vitro activity of Bay 12-8039, a new 8-methoxyquinolone, compared to the activities of 11 other oral antimicrobial agents against 390 aerobic and anaerobic bacteria isolated from human and animal bite wound skin and soft tissue infections in humans. *Antimicrob Agents Chemother* 1997; 41:1552-1557.
81. Goldstein EJ, Citron DM, Hunt Gerardo S, Hudspeth M, Merriam CV: Activities of HMR 3004 (RU 64004) and HMR 3647 (RU 66647) compared to those of erythromycin, azithromycin, clarithromycin, roxithromycin, and eight other antimicrobial agents against unusual aerobic and anaerobic human and animal bite pathogens isolated from skin and soft tissue infections in humans. *Antimicrob Agents Chemother* 1998; 42:1127-1132.
82. Freer L: North American wild mammalian injuries. *Emerg Med Clin North Am* 2004; 22:445-473.
83. Perron AD, Miller MD, Brady WJ: Orthopedic pitfalls in the ED: Fight bite. *Am J Emerg Med* 2002; 20:114-117.
84. Rosen T, Conrad N: Genital ulcer caused by human bite to the penis. *Sex Transm Dis* 1999; 26:527-530.
85. Zubowicz VN, Gravier M: Management of early human bites of the hand: A prospective randomized study. *Plast Reconstr Surg* 1991; 88:111-114.
86. Dreyfuss U, Singer M: Human bites of the hand: A study of one hundred six patients. *J Hand Surg* 1985; 10:884-889.
87. Talan DA, et al: Clinical presentation and bacteriologic analysis of infected human bites in patients presenting to emergency departments. *Clin Infect Dis* 2003; 37:1481-1489.
88. Tonta K, Kimble FW: Human bites of the hand: The Tasmanian experience. *ANZ J Surg* 2001; 71:467-471.
89. Dellinger EP, Wertz MJ, Miller S, Coyle MB: Hand infections. Bacteriology and treatment: A prospective study. *Arch Surg* 1988; 123:745-750.
90. Baker MD, Moore SE: Human bites in children. A six-year experience. *Am J Dis Child* 1987; 141:1285-1290.
91. Schweich P, Fleisher G: Human bites in children. *Pediatr Emerg Care* 1985; 1:51-53.
92. Steele MT, Sainsbury CR, Robinson WA, Salomone JA 3rd, Elenbaas RM: Prophylactic penicillin for intraoral wounds. *Ann Emerg Med* 1989; 18:847-852.
93. Goldstein E, Citron D, Wield B: Bacteriology of human and animal bite wounds. *J Clin Microbiol* 1978; 8:667-672.
94. Phair IC, Quinton DN: Clenched fist human bite injuries. *J Hand Surg Br* 1989; 14:86-87.
95. Goldstein E, Nesbit C, Citron D: Comparative in vitro activities of azithromycin, Bay y 3118, levofloxacin, sparfloxacin, and 11 other oral antimicrobial agents against 194 aerobic and anaerobic bite wound isolates. *Antimicrob Agents Chemother* 1995; 39:1097-1100.
96. Morgan MG, Mardel SN: Clenched fist actinomycosis in a penicillin-allergic female [letter]. *J Infect* 1993; 26:222-223.
97. Richman KM, Rickman LS: The potential for transmission of human immunodeficiency virus through human bites. *J Acquir Immune Defic Syndr* 1993; 6:402-406.
98. Smith DK, et al: Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: Recommendations from the U.S. Department of Health and Human Services. *MMWR Recomm Rep* 2005; 54:1-20.
99. Pretty IA, Anderson GS, Sweet DJ: Human bites and the risk of human immunodeficiency virus transmission. *Am J Forensic Med Pathol* 1999; 20:232-239.
100. Vidmar L, Poljak M, Tomazic J, Seme K, Klavs I: Transmission of HIV-1 by human bite [letter]. *Lancet* 1996; 347:1762.
101. Eyres KS, Allen TR: Skyline view of the metacarpal head in the assessment of human fight-bite injuries. *J Hand Surg Br* 1993; 18:43-44.
102. Donkor P, Bankas DO: A study of primary closure of human bite injuries to the face. *J Oral Maxillofac Surg* 1997; 55:479-481.
103. Agrawal K, Ramachandrudu T, Hamide A, Dutta T: Tetanus caused by human bite of the finger. *Ann Plast Surg* 1995; 34:201-202.
104. Fischer H, Hammel PW, Dragovic LJ: Images in clinical medicine. Human bites versus dog bites. *N Engl J Med* 2003; 349:e11.

www.ketabpezeshki.com 66485457-66963820

Chapter 62

Venomous Animal Injuries

Edward J. Otten

PERSPECTIVE

Epidemiology

Venomous animals account for considerable morbidity and mortality worldwide. Snakes alone are estimated to inflict 2.5 million venomous bites annually, with approximately 125,000 deaths. The actual numbers may be much larger. Southeast Asia, India, Brazil, and areas of Africa lead the world in snakebite mortality.[1] It is impossible to estimate the worldwide morbidity and mortality resulting from other venomous animals such as bees, wasps, ants, and spiders.

Approximately 45,000 snakebites occur annually in the United States; 7000 to 8000 are inflicted by venomous snakes, and 5 to 10 result in death. Insects are responsible for 52% of deaths, snakes for 30%, and spiders for 13%. Specifically, bees are responsible for the most fatalities, followed by rattlesnakes, wasps, and spiders. Historically, most of the recorded deaths from spider bites were caused by the black widow, although the brown recluse spider has been implicated in an increasing number of deaths.

The American Association of Poison Control Centers began collecting data in 1983 on deaths caused by venomous animals. Their 25-year experience shows a significant number of exposures by bite or sting but relatively few deaths (Table 62-1).[2] Although these data include most of the United States, there is no requirement that hospitals, emergency departments, coroners, or public health agencies report deaths or exposures to regional drug and poison information centers. This decline in deaths may be caused by an actual decrease in mortality or may be a result of inadequate reporting. Meaningful morbidity data, such as the number of amputations, hospitalizations, and disabilities, do not exist. The number of exposures and deaths from exotic snakes seems to be increasing, possibly because of interest in collecting so-called "hot" or venomous varieties such as cobras, mambas, and vipers. The morbidity from marine animal injuries is increasing in proportion to the number of people exposed to the ocean and the number of private collectors, but the mortality has not increased dramatically. An increase in outdoor recreational activities, such as camping, scuba diving, and wilderness trekking, puts more people in proximity to venomous animals and increases the risk of envenomation. Most exposures occur from April to October, when animals are most active and potential victims are outdoors and involved in activities that might increase their risk for envenomation. Of course, many spider bites and exotic animal envenomations that occur indoors can take place at any time. Most deaths seem to occur in very young, elderly, or inappropriately treated patients.

Venom Delivery

Animals that have developed specific venom glands and venom delivery systems can be found in every class, including birds.[3] The toxin and toxic apparatus vary from class to class. For example, the rattlesnake has modified salivary glands and maxillary teeth and uses this system primarily to obtain food. The bee has a modified ovipositor that is used mainly for defense. Poisonous and venomous animals are not the same and should be differentiated. Animals can be considered *poisonous* because of various toxins distributed in their tissues. For example, certain shellfish, toads, and barracuda have been known to cause death after ingestion. However, only animals with specific glands for producing venom connected to an apparatus for delivering that venom to another animal can be considered *venomous.*

VENOMOUS REPTILES

Snakes

Of the 3000 species of snakes, approximately 10 to 15% are venomous. Of the 14 families of snakes, four contain venomous species. Snakes are distributed throughout most of the earth's surface, including fresh and salt water. The major exceptions are the Arctic and Antarctic zones, New Zealand, Malagasy, and many small islands. Most snakebites occur in tropical and subtropical climates, especially in agricultural settings where the inhabitants go barefoot. Sea snakes are found only in the Pacific and Indian Oceans. Snakes are poikilotherms, which accounts for their distribution and activity. Their inability to raise their body temperature above ambient levels restricts their activity to a fairly narrow temperature range, approximately 25 to 35° C. All snakes are carnivorous, and their venom apparatus evolved for the purpose of obtaining food.

Epidemiology

The incidence of reported venomous snakebites in the United States is greatest in the South. States having the highest death rates are North Carolina, Arkansas, Texas, and Georgia. Of all snakebites, 97% occur on the extremities, with two thirds on the upper extremities and one third on the lower extremities. This reversal of historical distribution may reflect bites being provoked rather than accidental. Bites that occur accidentally are considered "legitimate," whereas bites that occur during attempts to handle or disturb a snake are considered "illegitimate." Men are bitten nine times more frequently than women.[4]

www.ketabpezeshki.com 66485457-66963820

Table 62-1 Venomous Animal Injuries and Deaths, 1983-2009

ANIMAL	ENVENOMATIONS	DEATHS
Coelenterates	16,019	1
Fish	26,960	0
Ants	49,793	0
Bees, wasps, hornets	351,204	23
Caterpillars, centipedes	49,237	0
Other arthropods	265,557	3
Copperheads	14,580	1
Rattlesnakes	21,122	28
Water moccasins	2,467	0
Coral snakes	1,337	0
Exotic snakes	2,196	3
Nonvenomous snakes	37,001	0
Unknown snakes	41,758	4
Black widow spiders	58,304	0
Brown recluse spiders	42,544	7
Other or unknown spiders	261,769	1
Scorpions	260,288	4

Data compiled from Watson WA, Litovitz TL, et al: American Association of Poison Control Centers data. Am J Emerg Med 2:1984–2005; Lai et al: Clin Toxicol 44, 2006; and Bronstein et al: Clin Toxicol 45, 2007, Clin Toxicol 46, 2008, Clin Toxicol 47, 2009, Clin Toxicol 48, 2010.

Imported venomous snakes have recently been an increasing problem throughout the United States. In the past, only zoos, research centers, and herpetologists kept exotic venomous snakes. Today, however, hundreds of people are raising deadly venomous snakes without the necessary precautions, such as specialized cages, safe handling techniques, and rapid access to specific antivenin. They place not only themselves, but also their families and the general public, in danger.

Classification and Characteristics

The four venomous families of snakes are the Colubridae, Elapidae, Viperidae, and Atractaspididae. The Colubridae, although representing 70% of all species of snakes, have very few venomous members dangerous to humans; these include the boomslang and bird snake. They are rear-fanged snakes, and although many possess venom, they generally do not envenomate humans. The Elapidae are more common and include the cobras, kraits, mambas, and coral snakes. The Hydrophiidae are sea snakes and a subfamily of the Elapidae. The Viperidae, or true vipers, are represented by Russell's viper, the puff adder, the Gaboon viper, the saw-scaled viper, and the European viper. The Crotalidae, or pit vipers, are sometimes considered a separate family and sometimes a subfamily (Crotalinae) of the Viperidae. Among the pit vipers are the most common American venomous snakes, such as rattlesnakes, water moccasins, copperheads, the bushmaster, and the fer-de-lance. Several species of Asian pit vipers are responsible for bites in Okinawa and bites by imported snakes in the United States. The Atractaspididae are the mole vipers, which have side-positioned fangs; they rarely envenomate humans and are found only in Africa and the Middle East.

Pit vipers, the most prevalent venomous snakes in the United States, are native to every state except Maine, Alaska, and Hawaii. They are classified into three main groups: true rattlesnakes (genus *Crotalus*), copperheads and water moccasins (genus *Agkistrodon*), and pygmy or Massasauga rattlesnakes (genus *Sistrurus*). Pit vipers account for 98% of all venomous snakebites in the United States.[5]

The Colubridae and Hydrophiidae have few venomous encounters with humans and are responsible for even fewer injuries. Some colubrid species found in the United States that were previously thought to be harmless may indeed be venomous. Examples are the lyre snake, the hognose snake, and the wandering garter snake. No deaths have been reported, but the problem has generated much interest among herpetologists and toxicologists. The yellow-bellied sea snake (*Pelamis platurus;* subfamily Hydrophiidae) has been found off the coast of southern California and western Mexico, but bites by this snake are rare.

The other major group of venomous snakes in the United States is the coral snakes. The eastern coral snake *(Micrurus fulvius)* is found in North Carolina, South Carolina, Florida, Louisiana, Mississippi, Georgia, and Texas. There are two subspecies that have similar clinical presentations and will be discussed together. The western or Sonoran *(Micruroides euryxanthus)* coral snake is native to Arizona and New Mexico. Although both species are generally quite shy unless handled, the eastern coral snake is considered deadly. There are no records of fatalities caused by the western species.

Coral snakes can be readily identified by their color pattern. At first glance, they resemble one of several varieties of king snake found in the southern United States. The coral snake can be differentiated from the king snake by two characteristics: The nose of the coral snake is black, and the red and yellow bands are adjacent on the coral snake but separated by a black band on the king snake. The popular rhyme is as follows:

Red next to yellow, kill a fellow.
Red next to black, venom lack.

This rhyme can be used only in the United States; Brazilian coral snakes have red next to black bands, and some coral snakes have no red bands.

Identification

There are two key principles for identifying venomous snakes: Only experts should handle live snakes, and even dead snakes can envenomate careless handlers.[6] It is not difficult to differentiate between pit vipers and harmless snakes found in the United States (Fig. 62-1). Pit vipers, as their name implies, have a characteristic pit midway between the eye and the nostril on both sides of the head. This pit is a heat-sensitive organ that enables the snake to locate warm-blooded prey. Pit vipers may be identified through other methods, but this characteristic is 100% consistent. The triangular shape of the head, the presence of an elliptical pupil, the tail structure, and the presence of fangs are useful characteristics but are inconsistent. The arrangement of subcaudal plates may be used for Crotalinae if the head has been damaged or is unavailable. An individual specimen may not fit the classic description, depending on the age of the snake, the time of the year, and the condition of the tail and mouthparts. Neither color nor skin pattern is a reliable method of identifying pit vipers (Fig. 62-2).

Size is not an important factor in identifying various reptiles. Venomous snakes range in length from several inches to several feet. Although a 6-foot eastern diamondback rattlesnake is much more dangerous than a 10-inch copperhead, all venomous snakes are able to envenomate from birth and should be treated as though they are dangerous.

Exotic snakes that are *not* pit vipers are not as easily identified. If possible, they should be safely transported to an expert for positive identification. Local zoos, herpetology groups, and colleges often have individuals who can identify unknown snakes.

www.ketabpezeshki.com 66485457-66963820

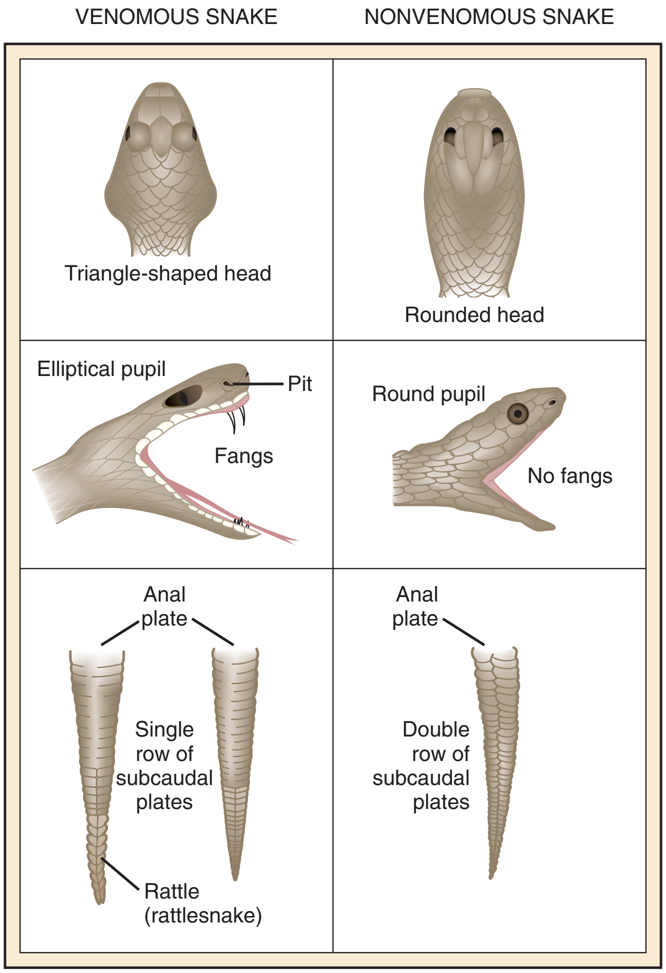


Figure 62-1. Identification of venomous and nonvenomous North American snakes.

Figure 62-2. Western diamondback rattlesnake *(Crotalus atrox).*

Other Reptiles

Only two venomous lizards are found in the world, both in the southwestern United States and Mexico. They are the Gila monster *(Heloderma suspectum)* and the Mexican beaded lizard *(Heloderma horridum)*. Fortunately, both these lizards are nonaggressive and rarely encountered. Bites usually result from handling the animals in captivity.[7] The Gila monster and the Mexican beaded lizard are easily identifiable. Both have thick bodies, beaded scales, and either white and black or pink and black coloration.

Principles of Disease

Toxins

The two main factors influencing the pathophysiology of any venomous animal injury are the toxic properties of the venom and the victim's response to these toxins. In the past, snake venoms were classified as either neurotoxic or hematotoxic, depending on the observed response of the victim to the various venoms. Modern toxicologic investigation has shown that this classification is inadequate because most snake venoms studied contain compounds that have many toxic properties. It is true, however, that the venom of a particular species of snake may cause a clinical response that is predominantly neurotoxic or hematotoxic.

The toxic components of snake venom can be classified into four broad categories: enzymes, polypeptides, glycoproteins, and low-molecular-weight compounds. They can also be classified as protein and nonprotein compounds. Proteins, which account for most of the toxic manifestations, make up 90 to 95% of venom. Symptoms can generally be classified as local or systemic. Local effects are usually caused by enzymatic action on the various cellular and noncellular structures in the victim's tissues. These enzymes can cause coagulation, anticoagulation, cell lysis, hemorrhage, hemolysis, and the destruction of nucleic acid, mitochondria, and other organelles.

Polypeptides are structurally smaller and more rapidly absorbed than proteins and may account for the venom's effects on presynaptic and postsynaptic membranes and other organ systems.

Phospholipase A can inhibit electron transfer at the level of cytochrome c and render mitochondrial-bound enzymes soluble. It can hydrolyze phospholipids in nerve axons, break down acetylcholine vesicles at the myoneural junction, cause myonecrosis, and induce lysis of red cell membranes. This single enzyme has been identified in all venoms of Hydrophiidae, Elapidae, Viperidae, and Crotalinae thus far investigated.

Elapidae and Hydrophiidae venoms have predominantly systemic effects, whereas Colubridae, Viperidae, and Crotalinae venoms have mainly local effects. There are many exceptions to this general division. For example, the venom of the Mojave rattlesnake *(Crotalus scutulatus)* may show minimal local effects and significant systemic effects, whereas the venom of the cobra *(Naja naja)* may cause extensive local tissue destruction.[8]

Venom Delivery

The mechanism for delivering venom is fairly standard among snakes. It consists of two venom glands, hollow or grooved fangs, and ducts connecting the glands to the fangs. The glands, which evolved from salivary glands, are located on each side of the head above the maxillae and behind the eyes. Each gland has an individual muscle and a separate nerve supply that allow the snake to vary the amount of venom injected. The venom duct leads from the anterior portion of the gland along the maxilla to the fangs. Pit vipers have fangs that are large anterior maxillary teeth. These teeth are hollow and rotate outward from a resting position to a striking position. The coral snake has fixed, hollow maxillary teeth that are much smaller than those of pit vipers. The fangs in most snakes are shed and replaced regularly, and it is not unusual to see a snake with double fangs on one or both sides of its mouth.[9]

The snake can control the amount of venom injected. In biting a human, a prey much too large to swallow, the snake may inject little or no venom (a "dry" bite), especially if injured or surprised.

www.ketabpezeshki.com 66485457-66963820

However, the snake may inject more than 90% of the contents of the gland for the same reasons.

Clinical Features

The signs and symptoms of a venomous snakebite vary considerably and depend on many factors. From 30 to 50% of venomous snakebites result in little or no envenomation. A person with impaired cardiovascular, renal, or pulmonary function is less able to cope with even a moderately severe envenomation. Because of these multiple variables, the individual clinical response is the only way to judge the severity of a venomous snakebite. Factors that influence the effects of a snakebite are the age, health, and size of the snake; the relative toxicity of the venom; the condition of the fangs; whether the snake has recently fed or is injured; the size, age, and medical problems of the victim; and the anatomic location of the bite.

Local envenomation, if left untreated, can cause serious systemic problems (e.g., disseminated intravascular coagulation, pulmonary edema, and shock) as the toxic products are absorbed. The victim's autopharmacologic response to the envenomation must also be taken into account. An immunoglobulin E (IgE)–mediated anaphylactic-type reaction may develop in victims of a previous snakebite when reexposed to the venom. Many venoms contain enzymes that trigger the release of bradykinin, histamine, and serotonin from the patient's cells, which may cause fatal anaphylactoid reactions. A wave of effects ranging from minimal pain to multisystem failure and death can occur over a period of several days.

Pit Vipers

The most consistent symptom associated with pit viper bites is immediate burning pain in the area of the bite, whereas pain may be minimal with bites of Elapidae and other exotic snakes. With pit vipers, the severity of pain is probably related to the amount of venom injected or the degree of swelling. Edema surrounding the bite that gradually spreads proximally is a common finding. This edema is usually subcutaneous, begins early, and may involve the entire extremity. Compartment syndrome has been described; however, it is unusual even with severe edema. It has been reported more frequently in models involving intracompartmental venom injection.[10-12] Most fangs do not penetrate into the fascial compartments, although muscle destruction may result from direct toxicity. Mortality is less frequent with distal bites to the toe and finger and is greatly increased with intravenous bites. An intravenous bite from any venomous snake is likely to be fatal. Petechiae, ecchymosis, and serous or hemorrhagic bullae are other local signs. Necrosis of skin and subcutaneous tissue is noted later and may result from inadequate doses of antivenin. Many systemic symptoms, such as weakness, nausea, fever, vomiting, sweating, numbness and tingling around the mouth, metallic taste in the mouth, muscle fasciculations, and hypotension, often occur after pit viper envenomation.

Death from pit viper bites is associated with disruption of the coagulation mechanism and increased capillary membrane permeability. Ultimately, these two processes lead to massive pulmonary edema, shock, and death. Heart and kidney damage occur secondary to these mechanisms. Specific toxins in certain species may act directly on specific organs, such as the heart or skeletal muscle. An allergic type of reaction may add to this process through release of histamine and bradykinin.[13]

Coral Snakes

Signs and symptoms can vary considerably with bites of coral snakes, Mojave rattlesnakes, and many exotic snakes, especially cobras and Australian elapids. Little pain and swelling may occur. Many of these species' venoms contain compounds that block neuromuscular transmission at acetylcholine receptor sites and have direct inhibitory effects on cardiac and skeletal muscle. Ptosis is common and often the first outward sign of envenomation. Other signs and symptoms include vertigo, paresthesias, fasciculations, slurred speech, drowsiness, dysphagia, restlessness, increased salivation, nausea, and proximal muscle weakness. The usual cause of death is respiratory failure.[14]

Gila Monster

Gila monster bites are generally associated with pain, edema, and weakness. Hypotension is common with severe bites. Envenomation involves secretion of the venom from glands along the lower jaws. The venom is introduced into the victim through grooved teeth and a chewing mechanism. There are no reported deaths from Gila monster bites.

Infection

Although snakebite envenomation has been stressed here, any bite or puncture wound carries a risk for bacterial contamination. Gram-negative organisms predominate when snake venom and mouthparts are cultured. Although several studies have shown that prophylactic antibiotics are not indicated for snakebite, tetanus, osteomyelitis, cellulitis, or gas gangrene may occur in cases of snakebite with or without envenomation. This is especially true when a large amount of local tissue destruction has occurred, treatment has been delayed, or inappropriate first aid was attempted.

Management

Out-of-Hospital Care

All snakebites are considered an emergency, and any victim should be medically evaluated. The initial 6- to 8-hour period after a snakebite is critical. During this time, medical therapy can help prevent the morbidity associated with severe envenomation. Effective out-of-hospital care can be important.[16]

Out-of-hospital care is relatively simple if guided by four basic concepts. First, the estimated time until arrival at a medical facility, as well as the skill of the on-scene assistants, must be considered when first aid is instituted. Separate the victim from the snake if possible to prevent further bites. A stick, pole, or other object longer than the snake can be used to move the snake away from the victim or, if necessary, to kill the snake by striking it behind the head. Rapid transportation to a medical facility is the best first aid for a snakebite. Any constricting jewelry or clothing should be removed from an extremity to prevent a tourniquet effect proximal to the swelling.

Second, spread of the venom should be slowed if possible; several methods are known. The patient's excitement and physical activity, movement of the bitten area, alcohol consumption, and greater depth of the bite may increase the spread of venom. Except for the last factor, these issues can be addressed by calming the victim, immobilizing the bitten area with a sling or splint, and not giving anything by mouth. A method of first aid for venomous snakebites that was developed in Australia—the *immobilization and compression technique* (also called the *Commonwealth Serum Laboratory technique*)—slows uptake of Elapidae venom and mock venom in humans. The bitten extremity is either wrapped in an elastic bandage or placed in an air splint. In another technique from Australia called the *Monash method,* a thick pad and bandage are placed over the bite wound and extremity. Both these techniques have similar postulated mechanisms of action: The

www.ketabpezeshki.com 66485457-66963820

lymphatic vessels and superficial veins are collapsed, and the proximal spread of venom is slowed.[17] Although this method is successful as first-aid therapy for Elapidae bites, its use for pit vipers has not been demonstrated. If less than 30 minutes has elapsed since the bite, a constricting band applied tightly enough to impede superficial venous and lymph flow, but not arterial blood flow, may be used. The band is applied loosely enough to admit a finger between the band and the skin after application. It is used with caution to prevent the development of a tourniquet effect under swollen tissue, which may cause more destruction than the snakebite.[18] Incision of bite wounds has no proven efficacy and poses potential danger to underlying structures and therefore is not recommended. The use of ice is not helpful in slowing the spread of venom, but an ice bag wrapped in a towel and applied to the bite area helps relieve pain. Ice water immersion and packing of the extremity in ice are dangerous and only contribute to tissue destruction. The use of suction devices has not been shown to be beneficial.[19]

Third, when feasible, the snake should be identified or brought to the treating facility with the victim, though this should not delay transport of the patient to definitive medical care. Identification of the snake must be done safely—usually only by someone expert in handling snakes. A photo may be useful in identifying the snake if a close-up of the head and tail are included. Dead snakes can be placed in a hard container, such as a bucket or ice chest. Care should be taken to not touch the head of the snake because envenomation can occur even after death.

Fourth, additional medical interventions, if available, should be initiated, including cardiac monitoring, intravenous fluids, and analgesics.

Emergency Department Care

Many snakes do not envenomate the victim when they bite, which has provided false support for the historical use of whiskey, clam juice, or split chickens in the treatment of snakebite. The only proven therapy is antivenin. Emergency department care of a snakebite focuses on supportive care and rapid treatment with the appropriate antivenin. Rapid decision-making is required to determine the optimal type, amount, and route of administration of the antivenin. By the time the emergency physician examines a snakebite victim, the venom may have already caused much damage, both locally and systemically. In this case, the emergency physician must be prepared to support the victim's cardiovascular and respiratory systems.

Patient History. Specific historical information includes time elapsed since the bite, the number of bites, whether first aid was administered and what type, location of the bite, and symptoms (e.g., pain, numbness, nausea, tingling around the mouth, metallic taste in the mouth, muscle cramps, dyspnea, and dizziness). A brief medical history includes the last tetanus immunization, medications, and cardiovascular, hematologic, renal, and respiratory problems. An allergy history with emphasis on symptoms after exposure to horse or sheep products, previous injection of horse or sheep serum, and a history of asthma, hay fever, urticaria, or allergy to wool, papain, chymopapain, papaya. or pineapple should be obtained if antivenin treatment is being considered.

Patient Examination. The bite area is examined for signs of fang marks or scratches and local envenomation (e.g., edema, petechiae, ecchymosis, and bullae). The area distal to the bite is checked for pulses. A general physical examination is performed, with emphasis on the cardiorespiratory system and the neurologic examination, especially if a Mojave rattlesnake, coral snake, or exotic snake is suspected. If the bite involves an extremity, the circumference of the extremity at the site of the bite and approximately 5 inches proximal to the bite should be measured and

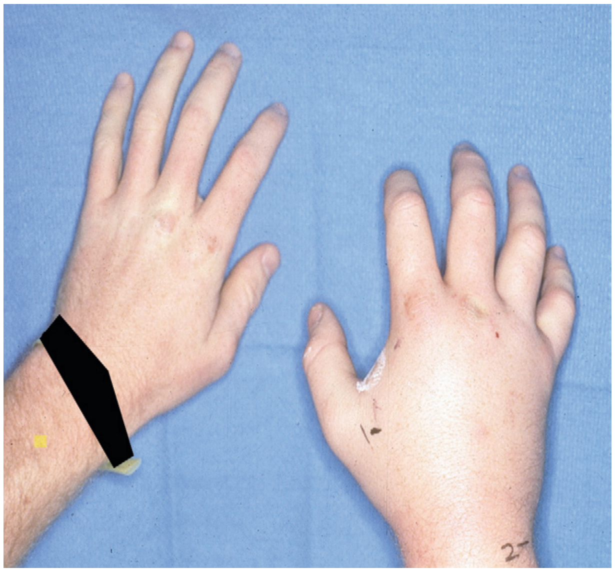


Figure 62-3. Northern copperhead *(Agkistrodon contortrix mokasen)* bite on right hand with normal left hand for comparison.

recorded. These data aid in objectively estimating both spread of the venom and the effect of antivenin (Fig. 62-3).

Initial Medical Care. If the bite occurred less than 30 minutes before arrival in the emergency department, first-aid measures can be instituted, including a constricting band until antivenin, can be obtained. Snakebite victims with clinical evidence of envenomation should have an intravenous line with normal saline placed in an unaffected extremity. An electrocardiogram, complete blood count, urinalysis, protime, and levels of fibrinogen, fibrin split products, electrolytes, blood urea nitrogen, and creatinine are recommended; blood should be typed and crossmatched for 4 units of packed red blood cells.

The patient's vital signs are monitored closely. Snakebite victims may be hypotensive because of third-space losses and hemorrhage. In an edematous extremity, the distal pulse may have to be examined with a Doppler instrument. If a compartment syndrome is suspected, insert a pressure monitor and obtain surgical consultation. If signs and symptoms of compartment syndrome are present, pressure greater than 30 mm Hg may necessitate fasciotomy, although there is evidence that administration of antivenin may lower compartment pressures.[12,13]

Once stabilization is initiated, the severity of the bite must be determined and a decision made regarding whether to administer antivenin. The more distal the bite on the extremity, the less toxicity associated with the bite.[20] Intravenous bites may be rapidly fatal. Bites occurring on the trunk, neck, and face have increased risk because of rapid transit of the venom.

Antivenin. The emergency physician must determine the type of antivenin to administer, how much, and over what period. If the bite is from a pit viper, the problem is not too difficult. Bites from copperheads usually cause a moderate amount of edema but generally do not require antivenin, although it may be indicated in selected cases.[21] Envenomation may be classified according to severity into five grades, from grade 0 (no sign of envenomation) to grade IV (very severe envenomation). The amount of antivenin to be given is correlated with the grade of envenomation:

- *Grade 0 (minimal).* There is no evidence of envenomation, but snakebite is suspected. A fang wound may be present. Pain is minimal, with less than 1 inch of surrounding edema and erythema. No systemic manifestations are present during the first 12 hours after the bite. No laboratory changes occur.

www.ketabpezeshki.com 66485457-66963820

- *Grade I (minimal).* There is minimal envenomation, and snakebite is suspected. A fang wound is usually present. Pain is moderate or throbbing and localized to the fang wound, surrounded by 1 to 5 inches of edema and erythema. No evidence of systemic involvement is present after 12 hours of observation. No laboratory changes occur.
- *Grade II (moderate).* There is moderate envenomation, more severe and widely distributed pain, edema spreading toward the trunk, and petechiae and ecchymoses limited to the area of edema. Nausea, vomiting, and a mild elevation in temperature are usually present.
- *Grade III (severe).* The envenomation is severe. The case may initially resemble a grade I or II envenomation, but the course is rapidly progressive. Within 12 hours, edema spreads up the extremity and may involve part of the trunk. Petechiae and ecchymoses may be generalized. Systemic manifestations may include tachycardia and hypotension. Laboratory abnormalities may include an elevated white blood cell count, creatine phosphokinase, prothrombin time, and partial thromboplastin time, as well as elevated fibrin degradation products and D-dimer. Decreased platelets and fibrinogen are common. Hematuria, myoglobinuria, increased bleeding time, and renal or hepatic abnormalities may also occur.
- *Grade IV (very severe).* The envenomation is very severe and is seen most frequently after the bite of a large rattlesnake. It is characterized by sudden pain, rapidly progressive swelling that may reach and involve the trunk within a few hours, ecchymoses, bleb formation, and necrosis. Systemic manifestations, often commencing within 15 minutes of the bite, usually include weakness, nausea, vomiting, vertigo, and numbness or tingling of the lips or face. Muscle fasciculations, painful muscular cramping, pallor, sweating, cold and clammy skin, rapid and weak pulse, incontinence, convulsions, and coma may also be observed. An intravenous bite may result in cardiopulmonary arrest soon after the bite.

Dart and colleagues have advocated slightly different grading systems and higher doses of antivenin: Grades 0 and I correspond to *minimal* envenomation, grade II represents *moderate* envenomation, and grades III and IV correspond to *severe* envenomation.[22,23] Either system can be used interchangeably.

Onset of symptoms after a pit viper bite may be delayed and may involve a variety of neurologic symptoms, including weakness, ptosis, stupor, bulbar paralysis, and other cranial nerve dysfunction, as well as nausea, abdominal pain, and headache.

Administration of Antivenin. Any victim of a venomous snakebite with moderate or severe envenomation is a candidate for antivenin. The choice of antivenin depends on the species of snake, and the antivenin may be horse serum- or sheep-derived Fab fragments. Wyeth Laboratories, producer of the polyvalent horse serum–derived antivenin for Western Hemisphere pit vipers, no longer manufactures that antivenin. Many zoos and hospitals still maintain vials of this antivenin until it can be replaced with the ovine-derived Fab antivenin (FabAV). This antivenin is derived from four species of U.S. pit vipers and has not been clinically studied with regard to bites from Mexican, Central American, or South American pit vipers.[23,24] There is a reported case of a patient bitten by a South American rattlesnake who was successfully treated with FabAV.[25]

Most antivenin for exotic snakes and the eastern coral snake is derived from horse serum. A recent polyvalent Fab(2) antivenin derived form horse serum and produced in Mexico has been shown to be effective against both North and South American crotalid species.[26] Skin testing was commonly performed before administration of horse serum–derived antivenin, but it is not medically indicated because of the inaccuracy of the test.

Table 62-2 Antivenin Dosage for Pit Viper Envenomation*

	FabAV†	FabAV
ENVENOMATION	INITIAL DOSE TOTAL	MAINTENANCE DOSE
Moderate	4-6 vials	2 vials
Severe	8-12 vials	2-4 vials
Very severe	12-18 vials	4-10 vials

FabAV, Fab antivenin.
*Dosage based on initial findings and clinical response to antivenin. (See also Fig. 62-4.)
†If this dose elicits a clinical response, it is recommended that an additional two vials be given at 6, 12, and 18 hours. The patient's coagulation studies should be followed to determine additional amounts.

Moreover, testing with normal horse serum may precipitate an allergic reaction, and even a positive test result may not preclude treatment if a patient has sustained severe envenomation. The incidence of allergic reactions with Fab antivenins has been much less than previously seen with whole IgG. The incidence of allergic reactions was 17% for early reactions and 12% for late reactions in postmarketing analysis. This was thought to be a result of incomplete purification of one lot contaminated by Fc fragments. Most of these reactions were minor and did not require stopping the infusion of the antivenin. The true incidence is unknown.[27-30]

Dosage and Precautions. Current treatment of pit viper envenomation in the United States is to use a FabAV polyvalent antivenin rather than the horse serum product.[31] This is designed to limit the allergic reactions associated with horse serum antivenin by use of antigen-binding fragments (Fabs) of sheep (ovine) immunized against four species of venomous snake found in the United States. CroFab has been shown to be as effective as the Wyeth antivenin, with fewer allergic reactions. Because of more rapid clearance of smaller Fab fragments by the kidney, however, a repeat-dose regimen must be used to prevent the recurrence of coagulopathy. The duration of action of the venom may be longer than the therapeutic effect of the antivenin. Initial studies have shown promise for a new affinity-purified, mixed monospecific ovine Fab antivenin that has been tested with favorable results in humans after minimal to moderate crotalid envenomation.[23] Its efficacy in pit vipers from South America or Asia has not been proved. Purification of antivenin by separation of active fractions may lead to safer administration of horse serum–derived antivenin. An algorithm has been developed that can aid in decision-making after a crotalid bite (Table 62-2 and Fig. 62-4).[31] In the next decade, snakebite management will probably change radically throughout the world. Phytotherapy (botanical therapy) and other nonantivenin drug therapies for snakebite have shown promise in experimental animal studies, and some centers have successfully treated snakebite with medical support only. Hyperbaric oxygen therapy has also been used as an adjunct to antivenin in the treatment of venomous snakebite; however, there is insufficient evidence to recommend its use.[32]

The following are general guidelines to maximize patient care when antivenin is used:

1. Because anaphylaxis may occur whenever antivenin is administered, appropriate therapeutic agents (e.g., oxygen supply, airway support, epinephrine, and other pressors) must be ready for immediate use. Any patient requiring antivenin should have two intravenous lines inserted. If an allergic reaction occurs, the line with the antivenin can be clamped and the other line used for resuscitation. Administration of 0.3 mg of 1 : 1000 epinephrine subcutaneously before administration of antivenin may

www.ketabpezeshki.com 66485457-66963820

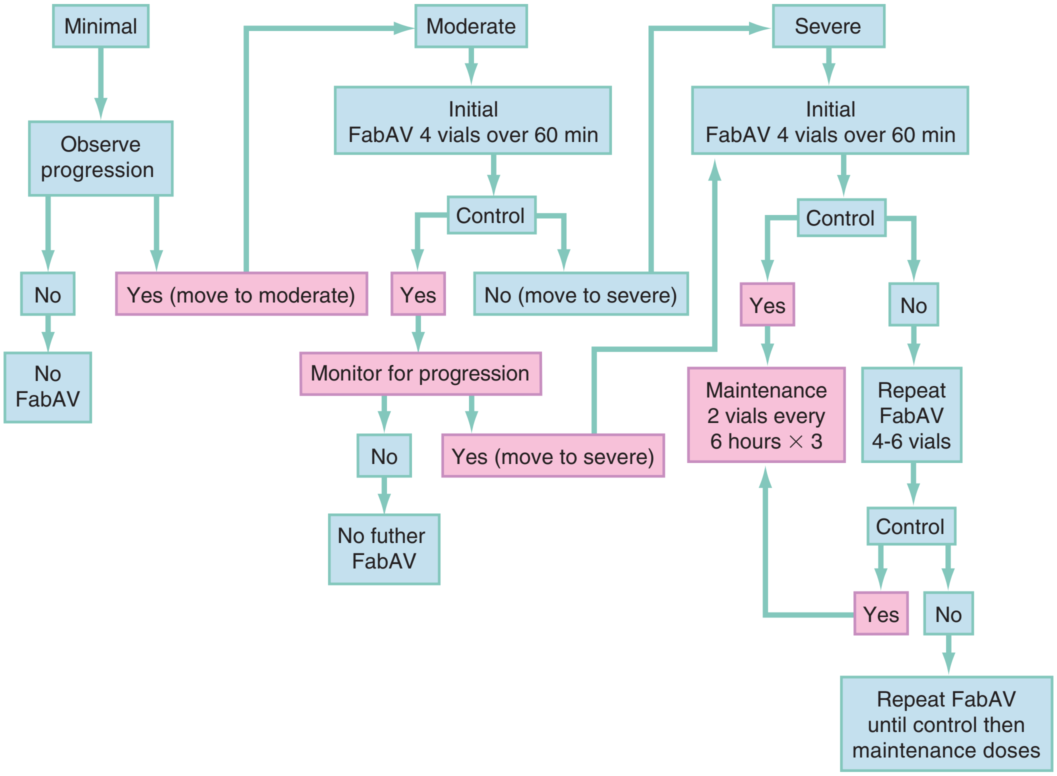


Figure 62-4. Algorithm for use of FabAV (antivenin).

prevent allergic reactions to horse serum–derived antivenin and, if not contraindicated, should be used.[33] If an allergic reaction occurs, then the epinephrine can be given intramuscularly as needed.

2. The initial dose of antivenin is prepared. The smaller the body of the patient, the larger the relative initial dose that may be required. A bitten child usually receives more venom in proportion to body weight and thus requires more antivenin to neutralize it. Because children seem to have less resistance and less body fluid with which to dilute the venom, they may require twice the adult dose of antivenin. The total fluid requirements of children are lower, however, so the antivenin is given in a more concentrated solution. All antivenin is administered intravenously.
3. Pregnancy is not a contraindication to antivenin therapy.
4. Administration of antivenin at or around the site of the bite is not recommended.
5. The need for subsequent doses is based on the patient's clinical response. The patient is monitored closely after the initial dose, and local and systemic symptoms, as well as laboratory findings, are determinants of the need for further antivenin. Additional injections of one to five vials of antivenin are administered every 1 or 2 hours if symptoms progress. Most pharmacies do not stock large amounts of antivenin, and the pharmacy should be notified to obtain additional antivenin for treating a severe bite.
6. Even with a history or signs of allergy, patients with severe envenomation are treated with a dilute form of antivenin and epinephrine to maximize antivenin administration but minimize allergic symptoms.

Coral and Exotic Snakes. It is recommended that all victims of bites by the eastern coral snake *(Micrurus fulvius)* be given antivenin even before any symptoms develop. Unfortunately, this antivenin is no longer manufactured by Wyeth, and existing stocks are slowly being depleted. The toxicity of this venom has a rapid onset, and once symptoms develop, it may be too late to reverse the effects with antivenin. The recommended dose is three to five vials in 300 to 500 mL of normal saline. Antivenin is given based on the clinical response. If no antivenin is available, management is based on meticulous supportive care emphasizing the respiratory and neurologic status. No antivenin exists for the venom of the Arizona (Sonoran) coral snake, which fortunately is less dangerous. Treatment of this type of snakebite is supportive.

The problems with bites of exotic snakes are threefold: Positive identification of the specimen is sometimes difficult, even for experts; specific antivenin is not always readily available; and even if the antivenin is available, the instructions for reconstitution and dosage may not be written in English. Many zoos maintain a supply of antivenin for their venomous snakes, and this may be the best source of antivenin for an exotic species. Some collectors keep appropriate antivenin on hand for the species that they collect. The Antivenin Index at the Arizona Poison Center (602-626-6016) can assist in identifying sources of exotic antivenin or in obtaining more pit viper antivenin. As with coral snakes, many patients do not show any early signs after envenomation by exotic snakes. The antivenin should be administered before neurologic symptoms develop.

Wound Care. The snakebite wound is cleaned and examined for foreign bodies, such as retained fangs or teeth, the area is immobilized, and analgesia is addressed. Elevation at or above heart level may relieve some of the pain. Some authors have previously advised excision of the bitten area, but such management is no longer recommended. As with any puncture wound, one should ensure that tetanus immunization is up-to-date. Broad-spectrum antibiotics have not been shown to be useful in uncomplicated snakebites. If signs of secondary infection develop, ampicillin-clavulanate is recommended.[15]

Patients admitted to the hospital require serial determinations of platelets, fibrinogen, prothrombin time, and urinalysis every 4 hours to check for myoglobin and hemoglobin. Blood products,

www.ketabpezeshki.com 66485457-66963820

including packed red blood cells, fresh frozen plasma, and other coagulation factors, are administered as needed. Usually, it is best to wait until antivenin therapy has been started, or the use of the blood products may be futile. Awake patients who have no nausea or abdominal pain can be given oral fluids. Local wound care includes daily cleansing with soap and water and the application of a sterile dressing to open wounds.

Surgical consultation is recommended for débridement or skin grafting. Débridement should probably not be performed earlier than 3 days after the bite, until the coagulopathy has resolved. Surgical exploration of the bite wound is not necessary and may be harmful. Skin grafts are occasionally necessary after bites by pit vipers that produce large necrotic areas. Fasciotomy is not usually indicated unless compartment pressures are elevated above 30 mm Hg and signs of compartment syndrome are present. Physical therapy is often needed and should begin soon after the acute phase of the envenomation is complete.

Serum Sickness. In most patients who receive more than 10 vials of horse serum–derived antivenin and in approximately 15% of those who receive FabAV, serum sickness develops up to a week later. The administration of diphenhydramine plus cimetidine, and in severe cases a tapering dose of steroids, can be used to treat this problem. Serum sickness is the only indication for the use of steroids with snakebite.[34]

Other Envenomation. Gila monster and Mexican beaded lizard bites are treated similarly to pit viper bites with regard to first aid. No definitive medical treatment exists. Antivenin is currently not available. Local wound care, tetanus prophylaxis, the use of antibiotics and analgesics, and supportive care are the extent of emergency department treatment available for this type of envenomation.

Envenomation by the yellow-bellied sea snake causes severe muscle necrosis with the release of large amounts of myoglobin and neurologic symptoms. Although a polyvalent antivenin is available from Australia, maintenance of adequate urine output, alkalinization of urine, and general supportive care are usually sufficient.

Disposition

If no envenomation is evident after clinical examination and the snake was either nonvenomous or a pit viper, the victim can be observed for 6 to 8 hours. With some snakebites, however, toxicity may be delayed by up to 8 hours. If no sign of envenomation is seen after 8 hours, the patient may be discharged. These patients require tetanus immunization when indicated, wound care instructions, and referral for follow-up within 24 to 48 hours. They require instructions on the types of delayed symptoms that may occur and when to return to the emergency department.

If only local pain and minimal edema have occurred, the patient is closely watched for 12 hours in the emergency department. If the pain and swelling decrease and no systemic symptoms or laboratory abnormalities develop, the patient may be treated with the same precautions as a patient with no signs of envenomation. Any patient with moderate or severe envenomation should be admitted to an intensive care unit for monitoring during antivenin therapy. Depending on the severity of the bite, blood products, vasopressors, and invasive monitoring may be necessary.

Any patient bitten by a coral snake, a Mojave rattlesnake, or an exotic snake is at risk for severe neurologic sequelae that may not become evident for many hours. As a result, these patients require hospital admission, preferably to an intensive care unit where they can be monitored closely. Arrangements should be made to have a ventilator, invasive monitoring, and dialysis equipment available if necessary. Appropriate antivenin should be obtained and treatment initiated at the earliest onset of symptoms. Some experienced clinicians may wait until symptoms develop before administering antivenin. All patients receiving antivenin require close monitoring for recurrence of coagulopathy, which may occur several days after initial envenomation.[35]

VENOMOUS ARTHROPODS

Arthropods are animals with segmented bodies and jointed appendages. This phylum (Arthropoda) contains approximately 80% of all known animals. The living members of this phylum are categorized into 12 classes. Two classes, the Insecta and the Arachnida, are of particular interest because numerous venomous species have evolved that are harmful to humans. Many species have developed venom glands and an apparatus for delivering the venom to obtain food. Others have developed venom delivery systems used solely for defense; most of these species are found in the orders Hymenoptera and Lepidoptera.

Arthropods account for a higher percentage of deaths from envenomation than do snakes. They are found inside dwellings, as well as in deserts, forests, and lakes. Although most arthropods are more active during the warmer months, many are active throughout the winter. Arthropods are also active 24 hours a day, and many can fly, thus increasing their range. This high level of contact results in millions of cases of envenomation annually. Most fatalities result from an autopharmacologic response by the victim rather than the toxicity of the venom. An individual stung by a bee may have a small amount of pain and local swelling or, in severe cases, an anaphylactic reaction and death.

Arthropods use three main methods of delivering venom: stinging, biting, and secreting venom through pores or hairs. Some arthropods combine two systems, one for offense and the other for defense. In general, venom systems found on the oral pole of an animal are used for offensive purposes or food acquisition, whereas systems found on the caudal pole are used for defense. Humans are not considered prey for any venomous arthropod, and therefore bites from them are defensive, accidental, or reflexive. Many venomous arthropods are omitted from this discussion because of their infrequent contact with humans or the relative impotence of their venom.[36]

Hymenoptera

Hymenoptera is a familiar order of arthropods that is composed of the families of bees, wasps, hornets, yellow jackets, and ants. Many of these species are social insects, and their defense response is related to protection of the group rather than the individual organism. Although most members of this order are stinging insects, several species of ant can bite and sting simultaneously.

Bees and wasps have similar mechanisms of delivering venom. Female insects of this type have modified ovipositors that protrude from the abdomen and act as hypodermic needles to administer the venom. The barbed stinging apparatus of the bee is quite prominent. The stinging action pulls the stinger from the bee, thereby eviscerating the insect and killing it.

The wasp, which has an unbarbed stinger, may inflict many stings without damaging itself or its stinging apparatus. The venom is produced in one or two tubular glands that empty into a venom reservoir. The venom reservoir has a duct that connects to the stinger. The venom is composed of several classes of substances varying in composition among different species. Proteins, as in snake venom, make up most of the venom by dry weight. Peptides, amino acids, carbohydrates, lipids, and other low-molecular-weight substances are also found. The most common enzymes are phospholipase A and hyaluronidase. Peptides are common in some species and constitute up to 50% of the dry weight. Most of the toxicity of the venom results from substances of low molecular weight (e.g., bradykinin, acetylcholine, dopamine, histamine, and serotonin). Many other antigenic

www.ketabpezeshki.com 66485457-66963820

substances have been identified in bee and wasp venom, and they account for the induction of hypersensitivity and anaphylaxis in humans.[37,38]

Clinical Features

The signs and symptoms of bee and wasp stings vary, depending on the degree, type, and location of envenomation, as well as the characteristics of the victim. Bee and wasp venom can cause serious injury other than allergic types of reactions, depending on the number of stings, the species of insect, the size and previous health of the victim, and the anatomic area stung. For example, a stinger in the tongue or throat may quickly compromise the airway. Honeybee venom causes a much greater release of histamine per gram than does other hymenoptera venom and thus is more dangerous. Certain species of honeybee release a pheromone, isoamyl acetate, when the ovipositor is pulled from the abdomen after stinging a victim. This pheromone attracts other bees to the victim and thus incites multiple stings.

There is little antigenic overlap among species, which may explain the variability in reaction to stings reported by victims. Victims who are allergic to honeybees and who mistakenly identify a yellow jacket as a honeybee may not have a systemic reaction and thus may think that they are no longer allergic to honeybees.[39]

The most consistent finding is immediate pain at the site of the sting, followed by local swelling, redness, and itching. A sensitive victim may experience swelling, urticaria, coughing, wheezing, coma, and respiratory arrest. Some large and especially venomous hornets have been known to cause muscle necrosis and renal damage. Most serious reactions to bee stings occur in the first 30 minutes; however, the local effects of a sting may persist for 2 or 3 days. Delayed hypersensitivity may occur 7 to 10 days after the sting.[40-42]

"Killer Bees." Health officials have been concerned about a particularly aggressive species of bee imported from Africa to Brazil in 1956 that has been known to attack humans and cattle with fatal results. This bee has managed to compete with native species and is gradually replacing some of these species while still retaining its aggressive behavior. Envenomation from these aggressive arthropods is most dangerous to very young or elderly patients and those with concomitant medical conditions.[43] Killer bees have colonized northern Mexico and have moved into the southern United States, including California, Arizona, and Texas, where the mean high temperature is at least 60° F. This type of bee is not more toxic, only more aggressive.

Fire Ants. Another unwelcome import to the United States is the fire ant. This insect is a member of the family Formicidae and is another of the Hymenoptera that is harmful to humans. Several species of fire ant are known, some native to North America and some imported. The species responsible for 95% of clinical cases, *Solenopsis invicta,* was imported from Brazil to Alabama in the 1930s. This ant is now found in nine southern states and is replacing many native species and inhabiting new niches. The only limiting factor keeping the fire ant from progressive migration seems to be cold winters. This ant is small and light reddish brown to dark brown. Its venom is unique to the animal kingdom in that it is 99% alkaloid. The remaining 1% is quite immunogenic and can sensitize an individual to the venom. Properties of this venom include hemolysis, depolarization of membranes, activation of the alternative complement pathway, and general tissue destruction. The sting is produced when the ant bites the victim with its jaws and, while holding tight, pivots around and stings the victim with its ovipositor. The sting usually produces a sterile pustule within 24 hours. Other symptoms include local burning, redness, and itching. With multiple stings and in sensitive individuals, urticaria, angioedema, dyspnea, nausea, vomiting, wheezing, dizziness, and respiratory arrest may occur. Approximately 10% of victims have some degree of hypersensitivity reaction.[44]

Management

Home Care. First aid for Hymenoptera envenomation depends on the degree of reaction to the sting. For simple stings an ice bag wrapped in a towel and applied to the sting area usually relieves the pain and swelling. In the event of an anaphylactic reaction, basic life support is administered until further medical help arrives. Many people allergic to Hymenoptera envenomation carry an emergency insect sting kit containing a tourniquet, epinephrine in a 1 : 1000 dilution, and an antihistamine. These kits are readily available, and both the patient and the patient's family should be instructed in the treatment of a severe allergic reaction.

Emergency Department Care. No specific antivenin exists for Hymenoptera stings. Treatment consists of local wound care and general supportive measures. A history of any previous allergic reactions to bee stings, hay fever, asthma, or drug reactions is obtained. The circumstances surrounding the sting and the number and location of stings are noted. In patients with a single sting and only a local reaction, the sting area is inspected for evidence of a venom apparatus, which, if present, can be removed by scraping the edge of a scalpel blade parallel to the skin and lifting the apparatus away from the skin without squeezing the venom sac. An ice bag wrapped in a towel may then be applied and the patient given an oral antihistamine (e.g., 50 mg of diphenhydramine). The patient is monitored, and if no further reaction is observed, he or she may be discharged with instructions to return to the emergency department if wheezing, dyspnea, hives, dizziness, or dysphagia occurs.

Adults in whom a severe urticarial reaction, dyspnea, or hypotension develops are treated with 0.3 mL of epinephrine in a 1 : 1000 dilution intramuscularly, 50 mg of diphenhydramine intravenously, and 50 mg of ranitidine intravenously. Although no evidence exists, it is recommended that patients with severe hypertension or cerebrovascular disease or those taking monoamine oxidase inhibitors be given epinephrine cautiously because of the potential for adverse reactions. Patients who are taking beta-blockers may not respond to epinephrine and should be given glucagon 1 to 2 mg intravenously. Based on their body weight, children are treated with 0.01 mL of a 1 : 1000 dilution of epinephrine per kilogram intramuscularly and 1 mg of diphenhydramine per kilogram intravenously.[40] These patients must be watched closely for signs of respiratory problems and treated accordingly. After 1 hour, these individuals should be totally free of symptoms (except for some itching around the sting site). A biphasic allergic reaction can occur in up to 20% of patients. Any patient requiring epinephrine should be watched for at least 6 hours and may require 23-hour observation. There is a possibility of recurrence of the reaction up to 72 hours, and patients should be warned of this in their discharge instructions. Patients with allergic reactions to a single sting should be given an emergency insect sting kit and instructed in its use and referred to an allergist for desensitization.

A general rule is urticaria plus involvement of any other organ system constitutes anaphylaxis.[40] Epinephrine is the treatment of anaphylaxis or anaphylactoid reaction and is given if these types of reactions are suspected. Patients who are wheezing after an insect sting are demonstrating a systemic reaction; they require intravenous access, inhaled beta$_2$-agonist therapy, intravenous steroids, and H_1 and H_2 blockers. Patients who have life-threatening reactions (hypotension, respiratory arrest, and cardiac arrest) may be given 0.1 mg of epinephrine in at least a 1 : 10,000 dilution, very slowly intravenously. The intramuscular route is preferred for all but the most extreme reactions.

www.ketabpezeshki.com 66485457-66963820

Treatment of allergic reactions to fire ant stings is the same. The skin lesions should be kept clean with soap and water. Ice bags may be applied initially to relieve burning and pain. Prophylactic antibiotics are not needed.

Of patients who have a systemic reaction to an insect sting, 60% can have a future allergic reaction if they have a positive skin test result. These patients should be desensitized to any specific venom to which they are allergic. Purified insect venom is currently available for most Hymenoptera, including fire ants.[45] Patients seen in the emergency department with systemic reactions to stings should be referred for skin testing and desensitization. These patients should be given emergency insect sting kits with instructions for use and should avoid activities that place them in proximity to Hymenoptera species.

Spiders and Scorpions

The class Arachnida contains the largest number of venomous species known, with approximately 34,000 species of venomous spiders and 1400 species of venomous scorpions. Virtually all known species are venomous, but most are not harmful to humans. Only approximately 50 species of arachnids in the United States cause human illness because most species do not have fangs or stingers sufficiently long to penetrate human skin. Humans fear spiders and scorpions, for good reason in certain cases. Ticks, which also belong to this class, are less feared but probably cause more morbidity because of transmission of infectious diseases, such as Rocky Mountain spotted fever and Lyme disease. Some spider bites are never diagnosed because of lack of significant symptoms and the fact that they occur while the victim is sleeping. Many nonspider bites are incorrectly diagnosed as spider bites, and unfortunately there is no gold standard for making the diagnosis.

Black Widow Spider

The black widow spider, *Latrodectus mactans,* may be the most recognized venomous spider in the world. Several other closely related species of *Latrodectus,* or widow spiders, are found throughout the United States, including *Latrodectus hesperus,* which is common in Arizona and other western states. The diagnosis and treatment of the bites of all species are the same.

The black widow is found throughout the United States (except Alaska) and in southern Canada. The female is approximately twice as large as the male, and although both are venomous, only the female is able to envenomate humans. The black widow is glossy black, occasionally with red stripes, and has a bright red marking on the abdomen. This marking may have an hourglass shape or may appear only as two spots. Abdominal markings may vary, and related *Latrodectus* species may be similar in appearance and toxicity. The combined length of the black widow's head and abdomen is approximately ½ inch, and the spider is approximately 1½ inches long, including the legs. It is found in protected places, such as under rocks, in woodpiles, and in outhouses and stables. The female is not aggressive except when guarding her eggs.

The venom apparatus of the black widow is a modified first appendage of the head known as the *chelicera.* The spider is able to control the amount of venom injected into its prey. The venom of the black widow is complex and contains both protein and nonprotein compounds.

Spiders normally use the venom to paralyze their prey and also to liquefy the tissues of the prey for digestion. The venom probably evolved from digestive glands analogous to the salivary glands in snakes. The ingredient most toxic to humans is thought to be a neurotoxin. This toxin destabilizes neuronal membranes by opening ionic channels, causing depletion of acetylcholine from presynaptic nerve terminals and increasing the frequency of spontaneous miniature endplate potentials at neuromuscular junctions.

Clinical Features. The classic symptomatology of the black widow bite is initially a pinprick sensation that may be followed by minimal local swelling and redness. If the area is examined closely, two small fang marks may be noticed. Sometimes the bite is not felt, especially if the victim is working when the bite occurs. From 15 minutes to 1 hour later, dull crampy pain develops in the area of the bite and gradually spreads to include the entire body. Usually, the pain is concentrated in the chest after upper extremity bites or in the abdomen after lower extremity bites. The abdomen may become boardlike, and the patient may complain of severe crampy pain. The abdominal manifestation may mimic pancreatitis, a peptic ulcer, or acute appendicitis, except that abdominal tenderness is usually minimal. Pregnant women may go into premature labor and precipitous delivery. Associated symptoms include dizziness, restlessness, ptosis, nausea, vomiting, headache, pruritus, dyspnea, conjunctivitis, facial swelling, sweating, weakness, difficulty speaking, anxiety, and cramping pain in all muscle groups. The patient is usually hypertensive, and cerebrospinal fluid pressure is sometimes elevated. There may be electrocardiographic changes similar to those produced by digitalis.[46]

In adults, the signs and symptoms begin to abate after several hours and usually disappear in 2 or 3 days. A small child bitten by a black widow spider, however, may not survive.[47] As with snake envenomation, the volume of distribution of black widow venom is much smaller in children than in adults. A dose that may cause only a few hours of pain in an adult may lead to complete cardiac decompensation and respiratory arrest in a child. Adult patients with preexisting hypertension, cerebrovascular disease, or cardiovascular disease are also at greater risk for complications. Symptoms usually persist for 8 to 12 hours and then subside, although in severe cases muscle cramps may continue for several days.

Management. First aid for a black widow spider bite consists of applying an ice pack to the bite area for relief of pain and transporting the victim to a hospital where supportive, symptomatic, and definitive treatment can be administered. The rescuer should obtain the specimen if possible because many dangerous spiders resemble harmless species and vice versa. The patient is monitored en route to the hospital, and basic life support is initiated if necessary. Bites in the neck or mouth area may cause airway compromise through muscle spasm. Emergency department care consists of obtaining a history of the circumstances surrounding the bite, a description of the appearance of the spider, any significant past medical history, current medications, and allergies to insect bites, horses, or horse serum.

The wound site is inspected for fang marks and cleansed with soap and water. As with any puncture wound, the patient's tetanus immunization status is assessed. The patient is observed for approximately 6 hours. If symptoms do not develop and the spider was not positively identified as a black widow, the patient may be discharged with instructions to return to the emergency department if any symptoms develop.

All patients with symptoms of moderate envenomation, pregnant women, children, and those with preexisting cardiovascular disease or hypertension require intravenous access, a complete blood count, electrolytes, blood urea nitrogen, creatinine, coagulation studies, urinalysis, and an electrocardiogram.

Symptomatic treatment involves controlling the muscle cramps responsible for most of the discomfort associated with the bite. Diazepam or other benzodiazepines given intravenously are useful for relieving muscle spasms. There is one preliminary report in the literature supporting the benefit of dantrolene sodium both orally and intravenously to provide muscle relaxation for *Latrodectus* envenomation.[48] Parenteral analgesics may be necessary to control pain; these drugs may affect an already compromised respiratory condition, and therefore their use must

www.ketabpezeshki.com 66485457-66963820

be closely monitored. Patients with moderate symptoms are admitted to the hospital and monitored until symptoms subside; usually 1 day is sufficient. Fetal monitoring is initiated for pregnant women, and patients with severe symptoms are admitted to the intensive care unit for cardiovascular monitoring.

Latrodectus Antivenin. In general, pediatric patients, pregnant women, and the elderly may need to be given *Latrodectus* antivenin (Lyovac), which is derived from horse serum. Clinical judgment is used to adjust for the age and category of patients needing antivenin. Candidates for antivenin include patients with severe envenomation manifesting as seizures, respiratory failure, or uncontrolled hypertension; pregnant women; and patients not responding to other therapy. The dose of the antivenin is one vial diluted in 50 mL of normal saline and administered intravenously over a period of 15 minutes. Precautions for allergic reactions should be taken before antivenin is administered. A dose of subcutaneous 1:1000 epinephrine may prevent allergic reactions when given before horse serum antivenin. This antivenin is also useful with other species of the *Latrodectus* genus.[46]

Brown Recluse Spider

Several deaths were attributed to the brown recluse spider, *Loxosceles reclusa,* in the 1950s, primarily in the south-central United States, thus drawing the attention of the medical community. Many species of *Loxosceles* are venomous to humans, and at least five are found in the United States. These spiders are approximately 1 inch long, including leg span, and range in color from tan to dark brown. The most distinguishing mark is a violin-shaped darker area found on the cephalothorax. Close examination may reveal that the brown recluse has three pairs of eyes rather than the usual four.

These spiders, as their name implies, are not aggressive and are usually found under rocks, in woodpiles, and occasionally in attics and closets. Their range is concentrated in the south-central United States, especially Missouri, Kansas, Arkansas, Louisiana, eastern Texas, and Oklahoma. However, they have been reported in several large cities outside this range.

The venom apparatus is similar to that of most spiders, including the black widow. The composition of brown recluse venom has not been completely determined, but sphingomyelinase D is a primary component. The local tissue destructive effects are thought to be primarily caused by hemolytic enzymes and a levarterenol-like substance that induces severe vasoconstriction. The systemic symptoms seem to be an allergic phenomenon and vary according to the individual's immune response to the venom.[49]

Clinical Features. The symptoms of a brown recluse spider bite are both local and systemic. Initially they are similar to those caused by bites of many other spiders and other conditions, including pyoderma gangrenosum, furuncles, viral and fungal infections, and foreign body reactions. The victim may notice some burning pain in the area of the bite. Some victims do not notice the initial bite at all. Pain usually develops within 3 or 4 hours, and a white area of vasoconstriction begins to surround the bite. A bleb then forms in the center of this area, and an erythematous ring arises on the periphery. The lesion at this stage resembles a bull's-eye. The bleb darkens, necroses over the next several hours to days, and continues to spread slowly and gravitationally, with involvement of skin and subcutaneous fat. The most common mimic of *Loxosceles* or other necrotic spider bite is a methicillin-resistant *Staphylococcus aureus* (MRSA) skin infection.[50,51]

Systemic symptoms include fever, chills, rash, petechiae, nausea, vomiting, malaise, and weakness. Hemolysis, thrombocytopenia, shock, jaundice, renal failure, hemorrhage, and pulmonary edema are the usual signs of severe envenomation. Fatalities are more common in children, most often the result of severe intravascular hemolysis.[51]

Management. First aid for a brown recluse spider bite is simple. The specimen is secured if possible and the victim transported to a medical facility. Because the lesion develops over a period of days, there may not be any local treatment of the lesion that is effective. The emergency department evaluation involves a history of the circumstances surrounding the bite; the time elapsed since the bite; past history of allergic reactions, medications, or medical problems; and an assessment for systemic toxicity, If a specimen is available, identification may be facilitated by recruiting the help of a local entomologist. If signs of systemic toxicity develop, an intravenous line is placed in an unaffected extremity and a complete blood count, metabolic and coagulation profile, and urinalysis are performed. Vital signs and urine output are closely monitored. Patients with delayed presentation with a necrotic lesion require standard wound management and cultures for MRSA. Excision of the lesion has not been shown to aid healing and may be detrimental. Lesions have been known to cause extensive scarring, infection, and necrosis. Bites that are in fatty areas, such as the thigh or buttocks, may cause more extensive necrosis.

Dapsone, 50 to 200 mg/day, has been shown to be helpful in preventing local effects of the venom.[51] If used within 48 hours, it may limit the size of the lesion that develops. However, dapsone may cause methemoglobinemia and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency. Hyperbaric oxygen has been shown to decrease lesion size in animal models.[52,53] Analgesics and antibiotics should be used as indicated during the course of the disease, although infection is not common. All patients with signs of systemic envenomation require hospital admission for monitoring; dialysis may be necessary if acute renal failure develops, and surgical consultation should be obtained for evaluation of the wound.

The Instituto Butantan in Sao Paulo, Brazil, and Instituto Bioclon, Mexico, both produce an antivenin for *Loxosceles* bites, but they are not available in the United States.

Other Spiders

Several other spiders can cause envenomation but are uncommon in the United States. Some of these spiders are large and can be quite aggressive. Most are imported either intentionally or as stowaways on cargo ships. Tarantulas, wandering spiders, funnel-web spiders, pallid spiders, and crab spiders are a few of the imported venomous spiders. Many of these species can cause envenomation similar to that of the brown recluse spider, and some produce neurotoxins.

Antivenin is produced for some of these groups (e.g., Brazilian *Phoneutria* and Australian *Atrax* species) but is usually available only in the country in which the species is generally found.[54] Emergency care therefore involves symptomatic and supportive treatment. An outbreak of bites by a species of *Tegenaria,* known as the *hobo* or *aggressive house spider,* has been reported. This species was imported from Europe to the Pacific Northwest. This spider is a small brown spider with a herringbone pattern on its abdomen. The lesions are similar to those caused by the brown recluse spider, but systemic symptoms include headache and weakness. Treatment is largely supportive.

Tarantulas are popular pets in the United States, and most native species are relatively nontoxic. Tarantulas are unusual in that the abdominal hairs can be thrown by the spider and embedded in human skin and the eye. These hairs can cause allergic reactions and severe conjunctivitis and must generally be removed under a slit lamp or by an ophthalmologist. A recent import from Thailand, the cobalt blue tarantula, *Haplopelma lividum,* is a very aggressive spider with toxic venom.[55]

www.ketabpezeshki.com 66485457-66963820

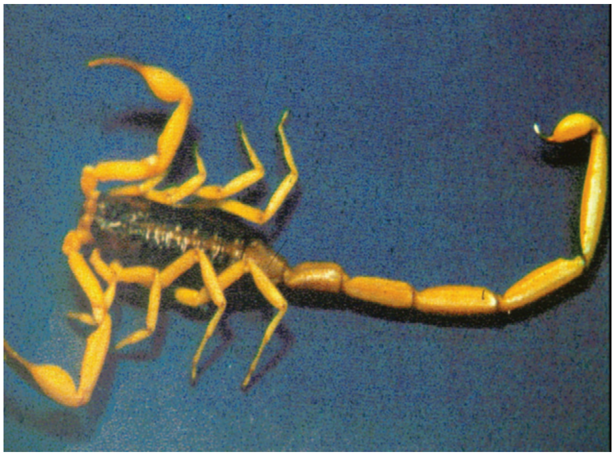


Figure 62-5. Arizona bark scorpion (*Centruroides sculpturatus,* formerly *Centruroides exilicauda*).

Scorpions

Scorpions are arachnids that resemble crustaceans and are among the oldest terrestrial animals. Scorpions are found throughout the world, and several species are located in the southwestern United States. Only one species, *Centruroides sculpturatus* (formerly *Centruroides exilicauda*), which is found in Arizona, is particularly dangerous. Scorpions are nocturnal predatory animals that usually spend the day under rocks, logs, or floors and in crevices. *C. sculpturatus,* or the bark scorpion, is found on or near trees (Fig. 62-5).

The scorpion has a tail-like structure that is actually the last six segments of its abdomen. The last segment, or the telson, contains the two venom glands and stinger. The toxicity of scorpion venom varies greatly from species to species. In general, the less dangerous species produce more local reactions, and the more dangerous species cause more systemic reactions. Several proteins have been identified in their venom; some cause hemolysis, local tissue destruction, and hemorrhage. The venom of *C. sculpturatus* is predominantly a neurotoxin that causes or enhances repetitive firing of axons by activation of sodium channels.

Clinical Features. Envenomation causes severe and immediate pain at the sting site. Local edema and erythema may or may not be present, depending on the species. After envenomation by *C. sculpturatus,* the victim may have heightened sensitivity to touch in the area of the sting along with local numbness and weakness. The diagnosis is often made by tapping on the site of the sting and causing an increase in pain at the site. Systemic symptoms may then develop, including anxiety, restlessness, muscle spasms, nausea, vomiting, excessive salivation, sweating, itching of the nose and throat, hyperthermia, blurred vision, myoclonus, hypertension, hemiplegia, syncope, cardiac dysrhythmias, and respiratory arrest. Various systemic complications may occur, depending on the species of scorpion. *Tityus trinitatis* scorpion stings cause pancreatitis to develop in 80% of victims. A wave of symptoms sometimes occurs over a 24-hour period, or respiratory failure may develop in the first 30 minutes. As with most envenomations, children are at a greater risk for severe reactions. A grading system has been developed to guide management of bark scorpion stings.[56,57]

Management. First aid for a scorpion sting consists of applying an ice bag to the area of the sting and transporting the victim to the hospital. A history of the circumstances surrounding the sting, any previous medical problems, and a description of the scorpion if no specimen is present should be obtained. It is relatively difficult for a layperson to differentiate the various scorpions. A serum Western blot test has been developed that can differentiate various scorpion venoms and thus help with diagnosis of *Centruroides* species, but it is not commercially available.[57] Anascorp (*Centruroides* [scorpion] immune F[ab]2 equine injection) is horse serum derived and has been shown to be effective and safe in both blinded and open studies of 1534 patients. It was effective in children if given within 4 hours of the sting.[58] Epinephrine 1:1000 can be given before Anascorp to prevent allergic reactions, although the incidence should be less than with whole immunoglobulin. Narcotic analgesics and barbiturates have been reported to increase the toxic effects of the venom and should be avoided.[56,57]

Approved antivenin is recommended in all cases of severe envenomation. Victims should be observed for 24 hours, and children should be admitted to the hospital for monitoring. Intravenous diazepam or another benzodiazepine may be used for myoclonus and muscle spasms. Phenobarbital, previously used in large doses in children, may be more dangerous than efficacious and may have contributed to deaths in the past. Atropine may be administered to control hypersalivation and bradycardia. Nitroprusside and prazosin have been used to control hypertension. Ventilatory assistance may be necessary, especially in children.

Other Arthropods

Ticks are vectors of human disease, and certain pregnant female ticks also secrete a toxin that causes a progressive ascending paralysis in humans and animals. The precise mechanism and structure of the toxin are unknown. The two species responsible in the United States are *Dermacentor andersoni* (wood tick) and *Dermacentor variabilis* (dog tick). The bite of the tick is usually painless, but the victim later has difficulty walking, weakness, flaccid paralysis, slurred speech, and visual disturbances.[59] The victim is usually a child, often with a history of recent outdoor activity. Treatment is removal of the offending tick before the paralysis has progressed too far. Any patient with ascending paralysis should be closely examined for the presence of a tick, especially on the head and back.

Several species of beetle, millipede, and caterpillar secrete irritating substances that cause severe burning pain, numbness, pustular contact dermatitis, edema, nausea, vomiting, and headache. Oropharyngeal exposure can cause mucosal edema and irritation.[60] No deaths have been reported. Treatment consists of washing the area thoroughly with soap and water and removing any spines or hairs present. Spines can be removed with adhesive tape or by applying white glue or facial peel. Locally applied ice bags and a paste of baking soda and water may be of benefit. Analgesics should be used as needed, and supportive therapy may be necessary for severe envenomation.[61]

Centipedes can inflict bites that cause erythema and edema. Treatment is usually local soaks and the use of analgesics. Conenose bugs, or "kissing bugs," may cause severe local and systemic allergic reactions. Treatment with antihistamines and supportive care, depending on the degree of reaction, are all that is necessary. Many other arthropods can cause local skin reactions and severe allergic reactions, depending on the individual's sensitivity. Patients are treated symptomatically with local steroid creams, antihistamines, and other symptomatic supportive measures.

VENOMOUS MARINE ANIMALS

Epidemiology

Almost 2000 species of animals found in the ocean are either venomous or poisonous to humans, and many can produce severe illness or fatalities. An estimated 40,000 to 50,000 marine envenomations occur annually. In recent years the number of injuries caused by these animals has increased dramatically because of the greater number of scuba divers, snorkelers, surfers, and others

www.ketabpezeshki.com 66485457-66963820

engaging in water sports. These animals are not usually aggressive, and many are completely immobile. Most of the venomous marine animals injure humans with defensive or food-procuring devices. Most venomous marine animals in the United States are found along the California, Gulf of Mexico, and southern Atlantic coasts. These animals range in complexity from sponges to bony fishes and contain some of the most complex and toxic venoms known.

Venom Delivery

In general, venomous marine animals are divided into three main classes according to the mechanism of venom delivery: bites, nematocysts, and stings.

Bites

Biting animals include several species of cephalopods, most often octopi. Although popular media portray a giant deadly creature that squeezes its victims to death, the most dangerous octopi are seldom larger than 20 cm. Several fatalities have been reported after a bite by the blue-ringed octopus, *Hapalochlaena maculosa*. Most victims are bitten on the upper extremity as they disturb this normally nonaggressive creature. The octopus has a pair of modified salivary glands that secrete venom into the wound produced by the animal's beak. The venom contains a potent vasodilator and an inhibitor of neuromuscular transmission similar to tetrodotoxin.[62] No known antivenin exists, and treatment is largely supportive, with respiratory support being the most important lifesaving intervention.[63]

Nematocysts

The second type of venom mechanism is the nematocyst found in coelenterates *(Cnidaria)*. This group of animals includes the Portuguese man-of-war, true jellyfish, fire corals, stinging hydroids, sea wasps, sea nettle, and anemones. Most of these organisms are sessile, but some are free floating. Because of their large numbers, this group accounts for the greatest number of envenomations by marine animals.

Many different types of nematocysts are known, but the basic mechanism is a "spring-loaded" venom gland that can, on mechanical or chemical stimulation, suddenly evert and discharge a structure that penetrates the prey and delivers the venom through a connecting tube. These nematocysts, found on the animal's tentacles, can number in the hundreds of thousands. Tentacles can be up to 100 feet long in some giant species. Nematocysts can still function even if the animal is dead or if the tentacles are separated from the animal's body. These stinging cells can remain active for weeks after an animal becomes beached. Often, not all nematocysts fire on initial contact but may discharge later during attempted rescue and treatment. Certain marine species have evolved methods of using ingested nematocysts for their own defense.

Toxicity. Nematocyst venom contains various peptides, phospholipase A, proteolytic enzymes, hemolytic enzymes, quaternary ammonium compounds, serotonin, and other toxic compounds. The venom of the coelenterates is antigenic, and allergic reactions are often seen. The severity of the envenomation is related to several factors. First, the severity of the injury is directly proportional to the number of nematocysts discharged. Second, the toxicity varies from species to species. It is unlikely that the victim or the treating physician will be able to identify the species from the appearance of the wound. Symptoms may range from simple isolated stinging to respiratory paralysis, cardiovascular collapse, and death. Therefore the diagnosis must be made according to the clinical findings. Third, the victim's autopharmacologic response to the venom may turn a relatively minor envenomation into a fatal anaphylactic reaction. Any clinician who regularly treats this type of injury should become acquainted with the common species in the particular area.

Although lethal and potentially lethal jellyfish exist worldwide, the extremely toxic specimens are found off the coast of Australia and in other Indo-Pacific waters. Probably the most notable and most toxic coelenterate is the box jellyfish *(Chironex fleckeri)*, also known as the "sea wasp." More dangerous than the famed great white shark, this small animal causes several deaths along the Australian coast annually.[64] Cardiac arrest may occur within minutes, and early aggressive resuscitation offers the best chance of recovery. Intravenous verapamil and box jellyfish antivenin are advocated for use in treatment.[65,66]

Another north Australian jellyfish, *Carukia barnesi*, also produces a devastating envenomation known as *Irukandji syndrome*. This causes major catecholamine release, hypertensive crisis, and passive death.[67]

The Portuguese man-of-war *(Physalia physalis)* is found along the southern U.S. coastline. This organism is not a true jellyfish but a hydroid colony. Envenomation is usually limited to local pain and paresthesias, but it may progress systemically to nausea, headache, chills, and even cardiopulmonary collapse. This organism has also been responsible for several deaths.[68]

Most other envenomations are minimal, and the danger is either drowning after being stung or an allergic reaction to the venom. The symptoms resulting from coelenterate envenomation usually consist of a severe burning sensation accompanied by raised erythematous lesions where nematocysts have discharged into the skin. The symptoms may progress, depending on the species and the number of nematocysts, to include nausea, vomiting, chest pain, muscle cramps, dyspnea, diarrhea, cough, convulsions, angioedema, and respiratory arrest. The initial pain and redness may last from a few hours to 2 or 3 days, depending on the therapy.

A related type of envenomation is caused by various species of coral, particularly fire coral *(Millepora)*. These injuries combine nematocyst envenomation with wound contamination. Animal protein and calcareous material left behind in these wounds cause infection and chronic inflammation.

Stings

Some marine animals cause a "sting" that is produced by a specialized apparatus that punctures the victim's skin and then introduces venom. Common examples of this type of animal are sea urchins, cone shells, bristle worms, sea snakes, crown-of-thorns starfish, stingrays, scorpion fish, weever fish, catfish, stonefish, rabbit fish, and zebra fish. Sea urchins, cone shells *(Conus californicus)*, catfish, scorpion fish, and stingrays account for most of the venomous marine animal injuries in the United States.

Sea Urchins. Sea urchins belong to the Echinodermata phylum along with starfish and sea cucumbers. These animals produce injury and envenomation mostly through toxin-coated spines. These spines often break off and introduce calcareous material and debris into the wound, thereby potentiating severe infection. Symptoms most often include severe local burning, pain, and discoloration, but they may progress systemically in some patients. The degree of envenomation is usually related to the number of spines involved and the species of animal encountered.

Cone Shells. Cone shells are much more toxic than sea urchins, and some species have been responsible for fatalities in the Indo-Pacific region. The venom apparatus is a tubular gland that connects to several teeth at the end of a retractable proboscis. All envenomations reported have occurred in persons handling the shells. The venom contains several proteins, protein-carbohydrate complexes, and 3-indolyl derivatives that act mainly on skeletal muscle and cause variably spastic and flaccid

www.ketabpezeshki.com 66485457-66963820

paralysis.[69] Symptoms may or may not include pain, depending on the species. Severe envenomation may cause diplopia, slurred speech, numbness, weakness, paralysis, and respiratory arrest. Onset and regression of symptoms may vary from minutes to days. No antivenin is available for cone shell envenomation. Airway control and supportive care are the mainstays of therapy for severe envenomations.

Stingray. The stingray is a member of the shark family. It is a broad, flat fish with a long, whiplike tail that may have one or more stingers with barbed ends. Stingrays vary in size from a few inches to several feet, and the stingers are proportional to the size of the fish. The stinger is encased in an integumentary sheath and contains venom glands. Stingrays bury themselves in the sand of shallow water, where they can be easily stepped on inadvertently. The sheath and stinger are often broken or left in the wound. The victim experiences an immediate, intense pain in the area of the wound, which may spread to the entire extremity. Systemic symptoms include salivation, nausea, vomiting, diarrhea, syncope, muscle cramps, fasciculations, dyspnea, cardiac dysrhythmias, and convulsions. The exact composition of the venom is unknown. Enzymes, proteins, serotonin, and a cholinergic substance have been identified, but the exact toxin responsible for most of the severe symptoms is yet to be isolated. The presence of foreign material may also impair healing and cause infection.

Bony Fishes. Bony fishes inflict their wounds through spines located on their fins. The spines and venom glands are encased in a sheath, and grooves along the spines act as channels for the venom. These fish injuries are typically encountered when the fish are stepped on in shallow water or handled by fishermen. The venom is made up of several classes of proteins, most of which are heat labile. The family Scorpaenidae includes three groups of species categorized by venom apparatus: zebra fish, scorpion fish, and stonefish. Zebra fish include the popular aquarium resident, the lionfish. Scorpion fish produce intense pain that can spread to the entire affected extremity within minutes.[70] Stonefish envenomation may cause serious and even life-threatening systemic illness, but manifestations such as cardiac and respiratory symptoms can be prevented by early administration of the appropriate antivenin.[71] Saltwater and freshwater catfish produce envenomation through contact with dorsal and pectoral spines.[72]

Management

Much of the venom from marine animals can be neutralized at the scene, and most fatalities can be prevented. The most important step is to remove the victim from the water. Drownings after minimal envenomation may account for more fatalities than the end effects of severe envenomation. The patient should be questioned about the circumstances of the bite, allergies, and systemic symptoms. If a severe allergic reaction has occurred, the victim is treated for this emergency before the wound is addressed. The type of wound care largely varies according to the type of venom apparatus involved. All marine stings from either bony fish or stingrays are treated with immersion in hot (110° F) water for 30 to 90 minutes. This therapy usually improves pain within minutes, but supplemental analgesics may be needed. As with all wounds encountered in the emergency department, appropriate cleansing, débridement, and tetanus prophylaxis are paramount. Prophylactic antibiotics, such as ciprofloxacin, are recommended when residual foreign body is suspected. Specific antivenins are available for some species, such as the box jellyfish and stonefish.

Bite injuries are treated with basic life-support measures and general wound care consisting of cleansing, débridement, and irrigation. Systemic signs and symptoms are treated as appropriate, with aggressive attention paid to the cardiac and respiratory systems.

Nematocysts

Nematocyst injuries are treated by first removing the nematocysts without allowing them to discharge. Tentacles are removed with a gloved hand or forceps. The remaining nematocysts are fixed by pouring vinegar (dilute acetic acid) over the wound area. For *Physalia* (man-of-war) stings, hot water may be useful or hot vinegar may be even better.[73] Baking soda and alcohol have also been shown to be effective, and deactivation of nematocysts may be species specific. Fresh water is not used, because it may stimulate continued nematocyst discharge.[74] Other methods include scraping off residual material with the use of a shaving cream or baking soda slurry. The affected area is then débrided and cleansed. Hot water immersion may relieve pain. Most lifeguard stations in areas where coelenterate stings are common have the necessary materials for this regimen. Supportive pharmacologic therapy (e.g., analgesics, antihistamines, and steroid creams) is indicated for all but the most trivial envenomation. Delayed cutaneous reactions may persist despite optimal therapy.[7]

Fish

Puncture injuries are treated by removing the spine or sting if possible. An x-ray film of the involved area is obtained because many spines and sheaths are radiopaque. Sea urchin spines usually break off in the wound; they are so fragile that removing them is difficult without the proper instruments. The stinger of the stingray should be removed with forceps, although these stingers with their sheaths have been known to penetrate body cavities and require surgery for removal. Although not usually present in the wound, the fish spines of bony fish should be removed with forceps. In all cases the wound should be copiously irrigated. Most venoms injected through puncture wounds are heat labile. Significant analgesia can be achieved by submersion of the wound in hot (110° F) water for 30 to 90 minutes or until symptoms improve.

Patients envenomated by unknown or unfamiliar organisms should be observed for systemic signs and symptoms. Careful discharge instructions are provided to the patient, warning him or her to return for increasing pain, numbness, difficulty breathing, and signs of infection.

KEY CONCEPTS

- Snake venom causes neurotoxicity and hematotoxicity, but one usually predominates, depending on the species of snake.
- The amount of crotalid antivenin given depends on the grade of envenomation, from 0 (minimal or no sign of envenomation) to IV (severe envenomation).
- Pit vipers have a characteristic pit found midway between the eye and the nostril on both sides of the head.
- Arthropods account for more deaths from envenomation than snakes, usually as a result of allergic reactions.
- Nematocyst (jellyfish) stings should be immediately neutralized with vinegar or hot water, and fish stings with hot water.
- Spider bites may be difficult to diagnose without identification of the offending spider.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. White J: Bites and stings from venomous animals: A global overview. *Ther Drug Monit* 2000; 22:65.
2. Litovitz TL, et al: 1998 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 1999; 17:435.
3. Dumbacher JP, Beehler BM, Spande TF, Garraffo HM, Daly JW: Homobatrachotoxin in the genus *Pitohui*: Chemical defense in birds? *Science* 1992; 258:799.
4. Morandi N, Williams J: Snakebite injuries: Contributing factors and intentionality of exposure. *Wilderness Environ Med* 1997; 8:152.
5. Gold BS, Wingert WA: Snake venom poisoning in the United States: A review of therapeutic practice. *South Med J* 1994; 87:579.
6. Suchard JR, LoVecchio F: Envenomations by rattlesnakes thought to be dead [letter]. *N Engl J Med* 1999; 340:1930.
7. Strimple PD, Tomassoni AJ, Otten EJ, Bahner D: Report on envenomation by a Gila monster *(Heloderma suspectum)* with a discussion of venom apparatus, clinical findings, and treatment. *Wilderness Environ Med* 1997; 8:111.
8. Minton SA: Bites by non-native venomous snakes in the United States. *Wilderness Environ Med* 1996; 4:297.
9. Russell FE: Snake venom poisoning. *Vet Hum Toxicol* 1991; 33:584.
10. Gold BS, Dart RC, Barish RA: Bites of venomous snakes. *N Engl J Med* 2002; 347:347.
11. Anz AW, et al: Management of venomous snakebite to the extremities. *J Am Acad Orthop Surg* 2010; 18:749.
12. Tanen DA, Danish DC, Clark RF: Crotalidae polyvalent immune Fab antivenom limits the decrease in perfusion pressure of the anterior leg compartment in a porcine crotaline envenomation model. *Ann Emerg Med* 2002; 41:384.
13. Gold BS, Barish RA, Dart RC, Silverman RP, Bochicchio GV: Resolution of compartment syndrome after rattlesnake envenomation utilizing non-invasive measures. *J Emerg Med* 2003; 24:285.
14. Kitchens CS, Van Mierop LH: Envenomation by the Eastern coral snake *(Micrurus fulvius fulvius):* A study of 39 victims. *JAMA* 1987; 258:1615.
15. Clark RE, Seiden BS, Furbee B: The incidence of wound infection following crotalid envenomation. *J Emerg Med* 1993; 11:583.
16. Hall EL: Role of surgical intervention in the management of crotaline snake envenomation. *Ann Emerg Med* 2001; 37:175.
17. Anker RL, Straffon WG, Loiselle DS, Anker KM: Snakebite. Comparison of three methods designed to delay uptake of 'mock venom'. *Aust Fam Physician* 1983; 12:365.
18. Burgess JL, Dart RC, Egen NB, Mayersohn M: Effects of constriction bands on rattlesnake venom absorption: A pharmacokinetic study. *Ann Emerg Med* 1992; 1:1086.
19. Alberts M, Shalit M, LoGalbo F: Suction for venomous snakebite: A study of "mock venom" extraction in a human model. *Ann Emerg Med* 2004; 43:181.
20. Moss ST, et al: Association of rattlesnake bite location with severity of clinical manifestations. *Ann Emerg Med* 1997; 30:58.
21. Lavonas EJ, et al: Initial experience with Crotalidae polyvalent immune Fab (ovine) antivenom in the treatment of copperhead snakebite. *Ann Emerg Med* 2004; 43:200.
22. Dart RC, et al: A randomized multicenter trial of Crotalinae polyvalent immune Fab (ovine) antivenom for the treatment of crotaline snakebite in the United States. *Arch Intern Med* 2001; 161:2030.
23. Dart RC, et al: Affinity-purified, mixed monospecific crotalid antivenom ovine Fab for the treatment of crotalid venom poisoning. *Ann Emerg Med* 1997; 30:33.
24. Dart RC, McNally J: Efficacy, safety and use of snake antivenoms in the United States. *Ann Emerg Med* 2001; 37:181.
25. Lynch MJ, Ritter SC, Cannon RD: Successful treatment of South American rattlesnake *(Crotalus durissus terrificus)* envenomation with Crotalidae polyvalent immune Fab (CroFab). *J Med Toxicol* 2011; 7:44.
26. Sánchez EE, et al: The efficacy of two antivenoms against the venom of North American snakes. *Toxicon* 2003; 41:357.
27. Keating GM: Crotalidae polyvalent immune Fab: In patients with North American crotaline envenomation. *BioDrugs* 2011; 25:69.
28. Clark RF, McKinney PE, Chase PB, Waletr FG: Immediate and delayed allergic reactions to Crotalidae polyvalent immune Fab (ovine) antivenom. *Ann Emerg Med* 2002; 39:671.
29. Ruha AM, et al: Initial postmarketing experience with Crotalidae polyvalent immune Fab for treatment of rattlesnake envenomation. *Ann Emerg Med* 2002; 39:609.
30. Cannon R, Ruha, AM, Kashani J: Acute hypersensitivity reactions associated with administration of Crotalidae polyvalent immune Fab antivenom. *Ann Emerg Med* 2008; 51:407.
31. Weant KA, Johnson PN, Bowers RC, Armitstead JA: Evidence-based, multidisciplinary approach to the development of a Crotalidae polyvalent antivenin (CroFab) protocol at a university hospital. *Ann Pharmacother* 2010; 44:447.
32. McGarth T, Hamilton R: Hyperbaric oxygen in the treatment of venomous snakebite. *Undersea Hyperb Med* 2010; 37:393.
33. Premawardhena AP, de Silva CE, Fonseka MM, Gunatilake SB, de Silva HJ: Low dose subcutaneous adrenaline to prevent acute adverse reactions to antivenom serum in people bitten by snakes: Randomised, placebo controlled trial. *Br Med J* 1999; 318:1041.
34. Heard K, O'Malley GF, Dart RC: Antivenom therapy in the Americas. *Drugs* 1999; 58:5.
35. Ruha AM, Curry SC, Albrecht C, Riley B: Late hematologic toxicity following treatment of rattlesnake envenomation with Crotalidae polyvalent immune Fab antivenom. *Toxicon* 2011; 57:53.
36. Binder LS: Acute arthropod envenomation: Incidence, clinical features and management. *Med Toxicol Adverse Drug Exp* 1989; 4:163.
37. Reisman RE: Insect stings. *N Engl J Med* 1994; 331:523.
38. Incorvaia C, Pucci S, Pastorello EA: Clinical aspects of Hymenoptera venom allergy. *Allergy* 1999; 54:50.
39. Cohen SG, Bianchine PJ: Hymenoptera, hypersensitivity, and history: A prologue to current-day concepts and practices in the diagnosis, treatment, and prevention of insect sting allergy. *Ann Allergy Asthma Immunol* 1995; 74:198.
40. Lee JK, Vadas P: Anaphylaxis: Mechanisms and management. *Clin Exp Allergy* 2011; 41:923.
41. Demain JG, Minaei AA, Tracy JM: Anaphylaxis and insect allergy. *Curr Opin Allergy Clin Immunol* 2010; 10:318.
42. Müller UR: Insect venoms. *Chem Immunol Allergy* 2010; 5:141.
43. Winston ML: The Africanized "killer" bee: Biology and public health. *Q J Med* 1994; 87:263.
44. Freeman TM: Hymenoptera hypersensitivity in an imported fire ant endemic area. *Ann Allergy Asthma Immunol* 1997; 78:369.
45. Stafford CT: Hypersensitivity to fire ant venom. *Ann Allergy Asthma Immunol* 1996; 77:87.
46. Clark RF, Wethern-Kestner S, Vance MV, Gerkin R: Clinical presentation and treatment of black widow spider envenomation: A review of 163 cases. *Ann Emerg Med* 1992; 21:782.
47. Woestman R, Perkin R, Van Stralen D: The black widow: Is she deadly to children? *Pediatr Emerg Care* 1996; 12:360.
48. Ryan PJ: Preliminary report: Experience with the use of dantrolene sodium in the treatment of bites by the black widow spider *Latrodectus hesperus*. *J Toxicol Clin Toxicol* 1983; 21:487.
49. Vetter RS, Isbister GK: Medical aspects of spider bites. *Annu Rev Entomol* 2008; 53:409.
50. Vetter RS, Cushing PE, Crawford RL, Royce LA: Diagnoses of brown recluse spider bites (loxoscelism) greatly outnumber actual verifications of the spider in four western American states. *Toxicon* 2003; 42:413.
51. Swanson D, Vetter R: Bites of brown recluse spiders and suspected necrotic arachnidism. *N Engl J Med* 2005; 52:700.
52. Hobbs GD, Anderson AR, Greene TJ, Yealy DM: Comparison of hyperbaric oxygen and dapsone therapy for *Loxosceles* envenomation. *Acad Emerg Med* 1996; 3:758.
53. Maynor ML, Moon RE, Klitzman B, Fracica PJ, Canada A: Brown recluse spider envenomation: A prospective trial of hyperbaric oxygen therapy. *Acad Emerg Med* 1997; 4:184.
54. Miller MK, Whyte IM, White J, Keir PM: Clinical features and management of *Hadronyche* envenomation in man. *Toxicon* 2000; 38:409.
55. Chase P, et al: Serum levels and urine detection of *Centruroides sculpturatus* venom in significantly envenomated patients. *Clin Toxicol* 2009; 47:24.
56. Bond GR: Antivenin administration for *Centruroides* scorpion sting: Risks and benefits. *Ann Emerg Med* 1992; 21:788.
57. Boyer LV, et al: Antivenom for critically ill children with neurotoxicity from scorpion stings. *N Engl J Med* 2009; 360:2090.
58. Gateau T, Bloom M, Clark R: Response to specific *Centruroides sculpturatus* antivenom in 151 cases of scorpion stings. *J Toxicol Clin Toxicol* 1994; 32:165.
59. Diaz JH: A 60 meta-analysis of tick paralysis in the United States. *J Med Toxicol* 2010; 6:15.
60. Lee D, Pitetti RD, Casselbrant ML: Oropharyngeal manifestations of lepidopterism. *Arch Otolaryngol Head Neck Surg* 1999; 125:50.
61. Hossler EW: Caterpillars and moths. *Dermatol Ther* 2009; 22:353.
62. Flachsenberger WA: Respiratory failure and lethal hypotension due to blue-ringed octopus and tetrodotoxin envenomation observed and counteracted in animal models. *J Toxicol Clin Toxicol* 1986; 24:485.

www.ketabpezeshki.com 66485457-66963820

63. Williamson JA: The blue-ringed octopus bite and envenomation syndrome. *Clin Dermatol* 1987; 5:127.
64. Fenner PJ, Williamson JA: Worldwide deaths and severe envenomation from jellyfish stings. *Med J Aust* 1996; 165:658.
65. Currie BJ: Marine antivenoms. *J Toxicol Clin Toxicol* 2003; 41:301.
66. Burnett JW, Calton GJ: Response of the box-jellyfish *(Chironex fleckeri)* cardiotoxin to intravenous administration of verapamil. *Med J Aust* 1983; 2:192.
67. Fenner P, Carney I. The Irukandji syndrome: A devastating syndrome caused by a north Australian jellyfish. *Aust Fam Physician* 1999; 28:1131.
68. Kaufman MB: Portuguese man-of-war envenomation. *Pediatr Emerg Care* 1992; 8:27.
69. Gray WR, Olivera BM, Cruz LJ: Peptide toxins from venomous *Conus* snails. *Annu Rev Biochem* 1988; 57:665.
70. Kizer KW, McKinney HE, Auerbach PS: Scorpaenidae envenomation: A five-year poison center experience. *JAMA* 1985; 253:807.
71. Lehmann DF, Hardy JC: Stonefish envenomation [letter]. *N Engl J Med* 1993; 329: 510.
72. Blomkalns AL, Otten EJ: Catfish spine envenomation: A case report and literature review. *Wilderness Environ Med* 1999; 10:242.
73. Nomura JT, et al: A randomized paired comparison trial of cutaneous treatments for acute jellyfish *(Carybdea alata)* stings. *Am J Emerg Med* 2002; 20:624.
74. Burnett JW, Rubinstein H, Calton GJ: First aid for jellyfish envenomation. *South Med J* 1983; 76:870.

www.ketabpezeshki.com 66485457-66963820

Chapter 63

Thermal Burns

Adam J. Singer, Breena R. Taira, and Christopher C. Lee

PERSPECTIVE

Background

Burns are relatively common injuries caused by direct or indirect contact with heat, electrical current, radiation, or chemical agents. The common denominator in all burns is protein denaturation and cell death. With thermal burns, the degree of injury is dependent on the temperature, the duration of the exposure, and the intrinsic structure of the burned tissue that determines its heat conductivity.[1-3] Temperatures below 44° C are generally tolerated for prolonged periods without causing burns. As the temperature rises, there is an exponential decrease in the time to produce injury, because the proportion of unfolded protein molecules increases dramatically at supraphysiologic temperatures.[4] At temperatures above 60° C, most tissue proteins are denatured. The proteins most predisposed to thermal denaturation are the lipid bilayer and membrane-bound adenosine triphosphatases. Thermal alteration of the plasma membrane is likely to be the most significant cause of the tissue necrosis.[4] Cell death occurs by one of two mechanisms.[5] Necrosis (or oncosis) is a passive process characterized by cellular swelling, depletion of intracellular energy stores, and massive release of inflammatory mediators. In contrast, apoptosis is a highly programmed, active process characterized by shrinkage and condensation of cell contents, DNA fragmentation, and budding without cellular swelling and a minimal inflammatory response. Both necrosis and apoptosis play a role in burn injury progression, although their relative role may vary.[6,7] The underlying mechanisms leading to cellular necrosis and apoptosis are discussed further in the section on pathophysiology.

The young and elderly have thinner skin and are more prone to deep burns than are nonelderly adults. Because blood flow dissipates heat, the blood supply of the skin may also affect the susceptibility to injury. Epidermal appendages within the dermis (e.g., sebaceous glands and hair follicles) also dissipate heat and reduce the degree of injury.

Epidemiology

According to the American Burn Association (ABA), 450,000 burn injuries are treated in medical facilities each year.[8] This includes 3500 deaths, which occur mostly in residential fires. Of the 45,000 burn admissions each year, more than 55% are admissions to specialized burn centers. The majority of burns occur from fire or flame (44%), scalds (33%), contact with hot objects (9%), electricity (4%), or chemical agents (3%). More than one third of admissions (38%) exceed 10% total body surface area (TBSA), and 10% exceed 30% TBSA. Most admissions include severe burns of such vital body areas as the face, hands, and feet. The overall survival rate from burns in the years 1995 to 2005 was 94.4%.[9]

The National Center for Health Statistics indicates a decrease in the number of burn visits from 1996 to 2000, possibly because of improved fire prevention strategies, with no further changes in trends from 2000 to 2005.[9] Half of burn patients in the emergency department (ED) are age 19 to 44 years. The most commonly affected body areas are the upper extremities (41%), lower extremities (26%), and head and neck (17%). Most of the burns are partial-thickness injuries, and less than 5% are full thickness.

PRINCIPLES OF DISEASE

Pathophysiology of Burns

Unlike mechanical injuries, in which the amount of tissue damage is determined at the time of injury, burns are dynamic injuries that often progress in depth and size over the first few days after injury. Traditionally the burn injury has been divided into three concentric zones.[10] At the center of the burn is a zone of irreversible coagulative necrosis that is formed immediately. Surrounding this central core is a zone of ischemia in which there is a reduction in the dermal microcirculation, putting this area at risk for subsequent necrosis if the perfusion is not improved. The zone of ischemia is the focus of intense research, directed toward reversing or preventing the conversion from ischemia to necrosis. The third and outermost zone of injury is the zone of hyperemia, characterized by an immediate and transient increase in perfusion. The ability of the skin to regenerate itself without scar formation is highly dependent on the level of injury.[11] Regeneration of the damaged epidermis occurs from two primary sources. The basal layer of cells from the uninjured adjacent epidermis can give rise to reepithelialization of the burn; however, this is limited to 1 cm from the wound edges. With large burns the major source of regenerative epidermal cells comes from the dermal skin appendages: hair follicles and sebaceous glands. More damage to the epidermal appendages increases the likelihood of scar formation.

Although the exact mechanisms that drive burn injury progression are unknown, several processes are thought to play a role.[12,13] The inflammatory response results in the release of a large number of toxic cytokines, mediators, and free oxygen and nitrogen radicals that contribute to further injury.[14-16] Occlusion of the dermal microcirculation with a combination of red blood cells, neutrophils, and microthrombi results in reduced perfusion and tissue ischemia that is exacerbated by a large amount of tissue edema.[17] Cytokines, such as tumor necrosis factor alpha, result in cellular apoptosis and further inflammation; free oxygen and nitrogen

www.ketabpezeshki.com 66485457-66963820

radicals damage vital proteins, lipids, and DNA. Cellular membranes are especially vulnerable to oxidative stress caused by lipid peroxidation.[18] The importance of these mechanisms is demonstrated by the ability of several inhibitors of inflammation and oxidative stress to reduce burn injury progression both in animals and humans.[19-22] Unfortunately, none of these agents have demonstrated clinical utility.

A predisposition to infection, metabolic derangements, and other factors also predispose partial-thickness burns to progress to deeper burns.[13] Lack of adequate fluid resuscitation and hypoperfusion contribute to the deepening of the burn wound. Impaired ability to combat infection is common in patients with large burns and appears to be cytokine mediated. In particular, interleukin-12 (IL-12) has been shown to depress immune function.[23] Abnormal complement activity also predisposes to infection in large burns.

Pathophysiology of Inhalation Injury

Exposure to heat can cause significant injury and rapidly developing edema to the upper airways in up to one third of burn patients with inhalation injury.[24] However, owing to effective heat dissipation, direct thermal injury is generally not seen below the vocal cords.[25] Other components of smoke, such as products of incomplete combustion (e.g., carbon monoxide [CO], cyanide, the aldehydes and oxides of sulfur and nitrogen), and particulate matter often result in significant ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch and pulmonary edema.[26-28] (See Chapter 159.)

The upper and lower airway pathology is secondary to airway edema and de-epithelialization of the injured tracheobronchial mucosa, with progressive shedding of the necrotic lining of the airway and the formation of pseudomembranous casts that partially or completely obstruct the airway. These casts consist of necrotic epithelium, mucus, cellular debris, fibrinous exudate, polymorphonuclear leukocytes, and clumps of bacteria. Damage to the mucociliary function of the endobronchial mucosa reduces the ability to eliminate excess mucus and secretions. In addition, the pulmonary parenchyma becomes infiltrated with leukocytes that release inflammatory mediators and reactive oxygen species that further contribute to bronchospasm, tissue inflammation, and destruction. In particular, the local formation of nitric oxide (NO) results in vasodilatation and reversal of hypoxic pulmonary vasoconstriction, further aggravating $\dot{V}/\dot{Q}$ mismatch.[28] NO combines with superoxide (O_2^-), which is released by neutrophils to form peroxynitrite ($ONOO^-$). This reactive molecule then damages DNA and activates poly(adenosine diphosphate [ADP] ribose) polymerase, which is an enzyme that repairs damaged DNA while depleting the cell of large amounts of adenosine triphosphate (ATP), leading to necrosis.[27-29]

The increase in extravascular water content and pulmonary lymph flow causes a marked decrease in the compliance of the lungs. Inhalation injury also results in deactivation of pulmonary surfactant, leading to areas of microatelectasis causing further ventilation perfusion mismatch and pulmonary shunting, and results in progressive hypoxemia and ultimately the clinical syndrome of acute respiratory distress syndrome.[29,30] Ventilator-induced barotrauma further contributes to tissue injury and the release of toxic mediators.

CLINICAL FEATURES

Classification and Diagnosis of Burns

Burns are classified by mechanism of injury, depth, extent, and associated injuries and comorbidities. Determination of the depth of injury is crucial, as healing potential and appropriate treatments are contingent on the depth of injury (Table 63-1). The current burn classification system was first described by the French barber surgeon Ambroise Paré several hundred years ago. First-degree burns are limited to the epidermis and characterized by erythema and pain. They generally heal within several days to a week. Second-degree, or partial-thickness, burns extend through the epidermis and into the dermis. They may be divided into superficial and deep partial-thickness injuries. Superficial second-degree burns are limited to the superficial (papillary) dermis. The skin is erythematous and forms blisters, and the surface can be moist (Fig. 63-1). The wound blanches on pressure and is painful. Deep second-degree burns extend through the epidermis into the deep (reticular) dermis. They appear white with some erythematous areas with less blanching and moisture than the superficial second-degree burns (Fig. 63-2). The distinction between superficial and deep second-degree burns is important because deep second-degree burns do not heal within 2 to 3 weeks and often result in severe scarring and contractures, especially in children. Deep second-degree burns that do not heal within 21 days require

Figure 63-1. Superficial second-degree burn.

Table 63-1 Burn Depth Classification

	APPEARANCE	SURFACE	SENSATION	TIME TO HEALING
First degree	Pink or red	Dry	Painful	Days
Superficial second degree	Pink, clear blisters	Moist	Painful	14-21 days
Deep second degree	Pink, hemorrhagic blisters, red	Moist	Painful	Weeks, or may progress to third-degree burn and require graft
Third degree	White, brown	Dry, leathery	Insensate	Requires excision
Fourth degree	Brown, charred	Dry	Insensate	Requires excision

www.ketabpezeshki.com 66485457-66963820

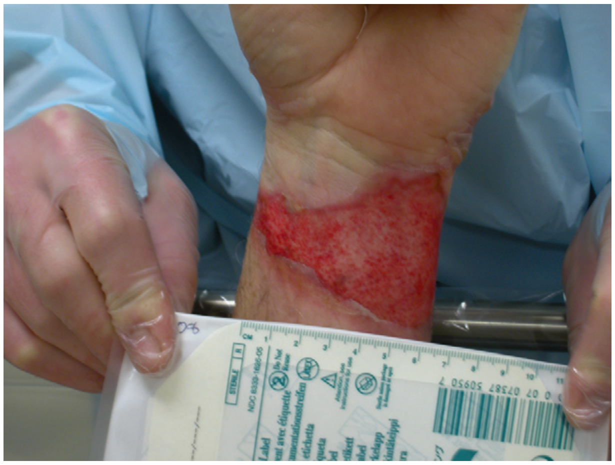
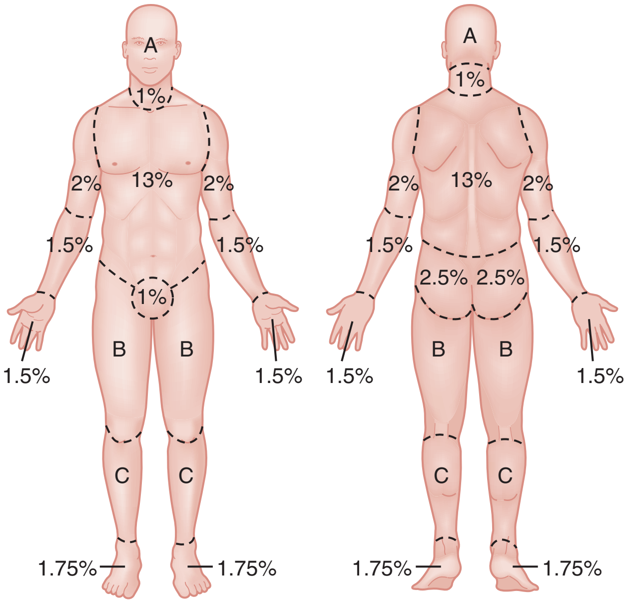


Figure 63-2. Deep second-degree burn.

Figure 63-3. Third-degree burn.



Relative percentages of areas affected by growth

Age	Half of head (A)	Half of one thigh (B)	Half of one leg (C)
Infant	9.5	2.75	2.5
1 yr	8.5	3.25	2.5
5 yr	6.5	4	2.75
10 yr	5.5	4.25	3
15 yr	4.5	4.25	3.25
Adult	3.5	4.75	3.5

Figure 63-4. Lund-Browder chart.

excision and skin grafting to minimize scarring. Deep second-degree burns may also progress to third-degree burns over the course of several days after injury. Third-degree burns extend through the entire dermis and are referred to as "full-thickness" burns. Their appearance is stiff and white or tan. They are dry or may have a charred appearance (Fig. 63-3). They do not blanch and, because of destruction of the nerves, are not painful. Finally, fourth-degree burns extend through the skin and subcutaneous fat into the underlying muscle and bone. Fourth-degree burns are stiff and charred and have visibly thrombosed vessels. Most burns are not uniform in depth and have areas of varying depth of injury.

Injection of radioactive isotopes and vital dyes, thermography, photometry, nuclear imaging, and ultrasound have been used to help determine burn depth and predict the potential of burns to heal.[31] Currently the most promising tool is laser Doppler imaging; however, even this tool has little predictive value in the early stages in the ED. As a result, clinical evaluation in the ED is required to estimate burn depth. The accuracy of non–burn specialists in predicting burn depth is approximately 50%,[32] and even among burn specialists the accuracy is only 75%.[33] This emphasizes the need for close follow-up and serial assessments to distinguish between deep and superficial burns, as the injury is dynamic and often continues to evolve after initial presentation.

The extent or surface area of the injury must be evaluated. Estimation of the percentage of TBSA burned is often inaccurate on initial inspection, and clinical rules and charts are used for more precise estimation of the percentage of TBSA.[34-36] Careful estimation is critical because the volume of fluid administered is based on this evaluation and an overestimation of the extent of injury can lead to overzealous fluid administration.[37,38] In addition, the criteria for referral to a burn unit are dependent on the surface area of the burn. Only second-degree and deeper burns should be used to calculate the percentage of TBSA affected. A useful clinical rule for smaller burns or scattered areas of burn is that the area of a patient's palm and fingers is approximately 1% TBSA.[39] For larger burns, the "rule of nines" is useful. This rule states that the allocation of percentage of TBSA in an adult patient can be estimated as follows: 18% for the front and 18% for the back of the trunk, 18% for each lower extremity, 9% for the head and 9% for each upper extremity, and 1% for the perineal area. A Lund-Browder chart is useful for estimating the extent of burns in children (Fig. 63-4).[40] The rule of nines should not be used for children as their head is larger and, in proportion, their extremities are smaller than those of adults.

Finally, burns are classified by severity into minor, moderate, and severe based on the TBSA burned, the percentage of full-thickness injury, and the involvement of specific areas such as the face, hands, feet, or perineum (Table 63-2). In addition, the presence of inhalation injury, high-voltage electrical burns, associated major trauma such as fractures, extremes of age, and comorbid conditions is considered.

MANAGEMENT

Prehospital Management

A major priority in burn victims is to stop the burning process and to protect the patient from additional injury. If clothing is

www.ketabpezeshki.com 66485457-66963820

Table 63-2 Classification of Burn Severity

	MILD	MODERATE	SEVERE
Children	<5% TBSA	5-10% TBSA	>10% TBSA
Adult	<10% TBSA	10-20% TBSA	>20% TBSA
Elderly	<5% TBSA	5-10% TBSA	>10% TBSA
All	<2% full thickness	2-5% full thickness, high voltage, inhalation, circumferential, comorbid disease	>5% full thickness, high voltage, significant burn to face, eyes, ears, genitalia, or joints, significant associated trauma
Disposition	Outpatient	Admission	Burn unit

TBSA, total body surface area.

burning, extinguish the flames with water or smother the flames with a blanket and gently remove the involved clothing. After the burning process has been stopped, the priorities are adequacy of airway and ventilation and assessment of the cardiac status and peripheral perfusion. If the patient has a compromised airway, orotracheal intubation should be performed. If there is a suspected inhalation injury or CO or cyanide intoxication, the patient should be placed on 100% oxygen delivered by a non-rebreather mask. If the patient is alert and oriented and the areas of unburned skin are warm and dry, the patient is adequately perfusing his or her vital organs. With the possibility of a traumatic injury, spinal precautions are warranted. Prehospital intravenous fluid is beneficial in patients with extensive burns (greater than 20% TBSA) if intravenous access can be established expeditiously. Whenever possible, the intravenous fluid should be initiated through unburned skin. Lactated Ringer's (LR) solution is the preferred fluid because it may reduce the risk of hyperchloremic acidosis associated with use of normal saline. The amount of LR solution required for the first hour can be rapidly estimated with the Parkland formula by multiplying the estimated TBSA of the second- and third-degree (and fourth-degree) burn by body weight in kilograms and dividing by 4. Morphine sulfate should be administered intravenously (IV) during transport via frequent 2- to 4-mg intravenous boluses to manage pain.

Burns should be covered with a clean dressing. Cooling with tap water or a commercially available cooling blanket helps reduce pain.[41,42] Care should be taken to minimize hypothermia, especially when ambient temperature is low. Topical antimicrobial agents and greasy ointment should not be used during prehospital care because they offer few benefits during transport, must be removed when the patient arrives at the hospital, and may obscure accurate determination of burn depth.

Emergency Department Management of Burns

Severely burned patients are among the most critically injured patients seen in the ED. Burn injuries are extremely painful and dramatic, and there is a tendency to focus on the burn wounds. However, all burn patients should be approached in a systematic manner, with focus on airway, breathing, and circulation (the ABCs) first. Some burn patients have associated traumatic injuries or comorbidities that must be identified and addressed.

Airway Management

Management of the upper airway in burn patients may be extremely challenging. After exposure to superheated steam and toxic fumes, rapid and progressive upper airway edema may develop within minutes. If there is doubt regarding upper airway compromise, fiberoptic laryngoscopy should be performed. Endotracheal intubation guided by fiberoptic laryngoscopy or bronchoscopy is a useful technique, and if attempts at intubation are unsuccessful, surgical cricothyrotomy or needle cricothyrotomy may be necessary. After placement of an endotracheal tube, several devices are available to help secure it.[43] With circumferential neck burns, the stiff burn eschar may compress the airway as well as the major neck vessels and require laterally placed escharotomies on either side of the neck, with extreme care taken to avoid damage to blood vessels and other underlying vital structures.

General Measures for Moderate to Severe Burns

All patients with moderate to severe burns and those with suspected inhalation injury should receive supplemental humidified oxygen to maintain an oxygen saturation greater than 92%. With severe burns, intravenous access should be obtained in peripheral veins, preferably in an uninjured limb. If peripheral access cannot be obtained, central venous access will be required. Patients with severe burns require a catheter to monitor urine output and evaluation for rhabdomyolysis and myoglobinuria. A nasogastric tube should be placed to prevent gastric distention that would compromise ventilation. Patients should also undergo continuous cardiac and oxygen saturation monitoring, as well as frequent assessment of the arterial blood pressure. The pulse oximeter probe should be placed on an uninjured limb or ear whenever possible.

Recognizing Inhalation Injury

Smoke inhalation injury affects 5 to 35% of hospitalized burn patients. With improvements in fluid resuscitation, inhalation injury has become one of the two major causes of mortality in burn patients, and the presence of inhalation injury more than doubles the mortality rate in adults.[44,45]

Traditionally, inhalation injury was diagnosed based on clinical findings such as facial burns, singed nasal vibrissae, carbonaceous sputum, and a history of injury within a closed space. However, these findings are neither highly sensitive nor highly specific.[46] Similarly, wheezing, crepitations, hypoxemia, and abnormalities on the initial chest radiograph may or may not be present in the ED, except in the most severely injured.

The diagnosis of inhalation injury in the ED is best made by direct visualization of the airways with fiberoptic laryngoscopy before intubation and bronchoscopy after intubation.[47] Findings of inhalation injury include the presence of soot, charring, and mucosal inflammation, edema, or necrosis. Bronchoscopy can identify injury to the airway, but diagnosis of injury to the parenchyma of the lung is best made with xenon ventilation scanning, which demonstrates areas of decreased alveolar gas washout secondary to small airway obstruction. Xenon scanning is rarely used in the ED.

CO levels should be measured in serum via CO-oximetry. Noninvasive devices that measure CO levels are now available in some

www.ketabpezeshki.com 66485457-66963820

Table 63-3 Indications for Endotracheal Intubation and Mechanical Ventilation in Burn Patients

Upper airway obstruction
Inability to handle secretions
Hypoxemia despite 100% O_2
Patient obtundation
Muscle fatigue suggested by a high or low respiratory rate
Hypoventilation ($Pco_2 > 50$ mm Hg and a pH < 7.2)

O_2, oxygen; *P*co_2, partial pressure of carbon dioxide.

Table 63-4 Recommended Initial Ventilator Settings

Tidal volume	6-8 mL/kg
Respiratory rate	8-12 in adults 12-45 in children
Plateau pressures	<35 cm H_2O
I/E ratio	1:1 to 1:3
Flow rates	40-100 L/min
PEEP	8 cm H_2O

I/E, inspiratory-expiratory; *PEEP,* positive end-expiratory pressure.

ambulances and hospitals; these devices expedite recognition of CO poisoning. Cyanide, a frequent combustion product of plastics, should be suspected in patients injured in a closed-space fire who have elevated CO and lactate levels. (See Chapter 159.)

Management of Inhalation Injury

Deciding when mechanical ventilation is required is critical. In addition to securement of the upper airway, there are several other indications for endotracheal intubation and mechanical ventilation (Table 63-3). Alveolar lavage may be required to help remove thick secretions and improve pulmonary toilette. This has been simplified by smaller and more flexible bronchoscopes.[46]

There are many modes of mechanical ventilation, each having its own advantages and disadvantages. In the ED most patients who are intubated will require heavy sedation with or without paralysis, and therefore the assist control mode, in which the ventilator cycles automatically at a preselected rate, is most appropriate. Rapid sequence induction is the preferred method unless airway obstruction is suspected, in which case awake intubation with sedation may be necessary. The goals of mechanical ventilation should include achieving an acceptable oxygen saturation (>92%) and limiting the plateau airway pressures to 35 cm H_2O or less to reduce the incidence of barotrauma.[48] This may require allowing the partial pressure of carbon dioxide (Pco_2) levels to rise to 35 to 55 mm Hg (permissive hypercapnia) as long as the pH remains greater than 7.25. A recent randomized trial found that low tidal volumes (6 mL/kg of predicted weight) reduced mortality.[49] Starting tidal volumes should therefore be set at 6 to 8 mL/kg of predicted body weight. Larger tidal volumes may be required if oxygenation is not adequate. Positive end-expiratory pressure may also help oxygenation. For hyperoxic lung injury to be minimized, oxygen concentrations should be titrated to the lowest concentrations that maintain adequate oxygenation. A sample of initial ventilator settings is presented in Table 63-4. High-frequency percussive ventilation that administers high-frequency, time-cycled, pressure-limited subtidal volumes may reduce the incidence of barotrauma.[50] Continuous positive airway pressure (CPAP) and BL-PAP may be considered in alert and cooperative patients who are difficult to oxygenate.[51] However, endotracheal intubation should not be delayed in patients who fail to rapidly improve with noninvasive ventilation. Airway pressure release ventilation that uses CPAP applied at a high level with intermittent releases of airway pressure has also been used to help promote alveolar recruitment while reducing the risk of barotrauma.[52]

Bronchodilators should be used in patients with wheezing, and they may also improve mucociliary function. Frequent airway suctioning and chest physiotherapy are also helpful at removing secretions. Aerosolized *N*-acetylcysteine with or without aerosolized heparin also helps break down thick mucous secretions.[53,54] An example of a treatment protocol for patients with inhalation injury may include 5000 to 10,000 units of heparin and 3 mL of normal saline nebulized every 4 hours, alternating with 3 to 5 mL of aerosolized 20% *N*-acetylcysteine.[46]

Circulation and Fluid Resuscitation

Before World War II, many burn patients died of hypovolemic shock and renal failure. The first formal fluid resuscitation protocol was developed during treatment of burn victims after the Coconut Grove nightclub fire in Boston in 1942.[55] Since then, many fluid resuscitation regimens have been described; however, the Parkland formula described by Baxter remains the most popular.[56]

Burn injury results in the activation of the complement system and the release of a large number of inflammatory mediators, such as histamine, prostaglandins, and leukotrienes. These mediators increase the permeability of the local and systemic vasculature, resulting in the extravasation of intravascular fluids and proteins into the interstitial space, contributing to vascular fluid depletion and soft tissue edema.[57] The leakage of plasma proteins during the first 3 to 5 hours reduces the intravascular oncotic pressure and increases the interstitial oncotic pressure, which leads to an increase in edema formation.[58] With large burns, half of the fluid requirements are a result of extravasation into unburned areas.[59]

Patients with small burns (less than 20% TBSA in adults and less than 10-15% TBSA in children) can be successfully treated with oral fluids only.[60] With larger burns, intravenous fluid resuscitation is required to restore intravascular volume and prevent the development of hypovolemic shock. One of the oldest controversies in the management of burn patients is the role of colloids for the resuscitation of burn patients. Because capillary leakage of proteins lasts at least 12 to 24 hours after injury, the consensus is that colloids should not be used during the initial fluid resuscitation unless the burn is very deep.[61] A recent systematic review of 23 trials that included 7754 patients concluded that there is no evidence that resuscitation with colloids reduces the risk of death compared with crystalloids in patients with trauma or burns or after surgery.[62] Recent ABA practice guidelines for burn shock resuscitation consider the addition of colloid-containing fluid after the first 12 to 24 hours to reduce overall fluid requirements.[60]

In 1968, Baxter reported that resuscitation of dogs with 50% TBSA burns with a volume of LR solution equal to 24 to 32% of their body weight corrected physiologic and metabolic derangements within 24 hours.[63] The results were optimal when half of the volume was administered within the first 8 hours after injury. This method of fluid resuscitation was then evaluated in 11 patients with burns covering 30 to 85% TBSA, demonstrating that the required fluid volume of LR was 3.5 to 4.5 mL/kg/%TBSA (excluding first-degree burns). These findings led to the Parkland formula, which called for a volume of 4 mL/kg/%TBSA of LR to be given over the first 24 hours, with half of the volume given over the first 8 hours.[64] Later studies demonstrated that most adults and children were successfully resuscitated with 24-hour fluid volumes of 3.7 to 4.3 mL/kg/%TBSA.[65] Other fluid resuscitation formulas have also been described (Table 63-5). Based on studies at the U.S. Army Institute of Surgical Research, the "rule of ten"

www.ketabpezeshki.com 66485457-66963820

has recently been suggested for estimating the initial fluid requirements, with hourly adjustments based on clinical response.[66] With this rule the estimated burn size (percent of TBSA) is multiplied by 10 to derive the initial fluid rate in milliliters per hour. For every 10 kg above 80 kg, 100 mL is added to this rate. This rule tends to overestimate fluid requirements in those weighing less than 40 kg and to underestimate fluid requirements in patients weighing more than 140 kg. The burn resuscitation index (BRI) is another simple method for calculating fluid resuscitation in burn victims.[67] The burn size score (BSS) is first determined based on the rule of nines, in which each nine is replaced with the number 1. The head and arms are each assigned 1 point, and the legs, anterior torso, and posterior torso are assigned 2 points, for a total of 11 points for the entire body. If an area is burned more than 50%, it is assigned the full point value. An area burned less than 50% is assigned half the point value. All points are added, and then the result is rounded up to determine the BSS. Once the BSS has been obtained, the initial fluid resuscitation rate is found by cross-referencing the BSS with the patient's weight (Table 63-6). Use of this index significantly increases the accuracy of calculated fluid requirements of burn victims, especially by emergency medicine residents.[67]

All fluid resuscitation formulas should be used only as general guides, and adjustments must be to maintain adequate tissue and organ perfusion. Burn patients should be resuscitated with only as much fluid as is necessary to maintain organ perfusion. Organ perfusion can be estimated by heart rate, blood pressure, level of consciousness, capillary refill, and a urine output of 0.5 to 1.0 mL/kg/hr in adults or 1.0 to 1.5 mL/kg/hr in children.[60] Certain patient groups may require additional fluid, including patients with inhalation injury, those with electrical burns, and those in whom resuscitation is delayed. Patients with inhalation injury require 35 to 65% more fluid than patients with similar-sized burns without inhalation injury.[68]

A study of transferred burn patients found that smaller burns tended to be overestimated with over-resuscitation, whereas larger burns tended to be underestimated with under-resuscitation.[69] This further emphasizes the need for careful monitoring of the volume of urine output and clinical signs of tissue turgor and adequate resuscitation.

Table 63-5 Burn Resuscitation Formulas

FORMULA	FIRST 24 HOURS	NEXT 24 HOURS
Parkland	LR 4 mL/kg/% burn ½ within first 8 hr	Colloids in amount of 20-60% of plasma volume; glucose in water added to maintain urine output 0.5-1.0 mL/kg/hr in adults and 1 mL/kg/hr in children
Modified Parkland	LR(mL) = 4 × kg × % burn in adults	Colloid infusion of 5% albumin at the amount (0.3-1.0)/16 mL/kg/%burn/hr
Evans	Crystalloids in the amount of 1 mL/kg/% burn, plus colloids at 1 mL/kg/% burn, plus 2000 mL glucose in water	Crystalloids at 0.5 mL/kg/% burn, colloids at 0.5 mL/kg/% burn, and the same amount of glucose in water as first 24 hr
Brooke	LR 1.5 mL/kg/% burn, plus colloids at 0.5 mL/kg/% burn, plus 2000 mL glucose in water	LR 0.5 mL/kg/% burn, colloids at 0.25 mL/kg/% burn, and the same amount of glucose in water as first 24 hr
Modified Brooke	LR 2 mL/kg/% burn in adults and 3 mL/kg/% burn in children	Colloids 0.3-0.5 mL/kg/% burn, glucose in water to maintain urine output
Monafo	Solution containing 250 mEq Na, 150 mEq lactate, 100 mEq Cl; amount adjusted to urine output	Solution titrated with 1/3 NS according to urine output
Galveston	LR at 5000 mL/m² TBSA burned plus 2000 mL/m² TBSA, ½ within 8 hr	3750 mL/m² TBSA burned plus 1500 mL/m² TBSA
Rule of ten	LR at 10 mL/%burn/hr For every 10 kg above 80 kg, 100 mL is added to this hourly rate	Not applicable

Cl, chloride; *LR,* Ringer's lactate; *TBSA,* total body surface area; *NA,* sodium; *NS,* normal saline.

Table 63-6 Burn Resuscitation Index

	Weight (kg)											
TOTAL BSS	40	50	60	70	80	90	100	110	120	130	140	150
1	90	113	135	158	180	203	225	248	270	293	315	338
2	180	225	270	315	360	405	450	495	540	585	630	675
3	270	338	405	473	540	608	675	743	810	878	945	1013
4	360	450	540	630	720	810	900	990	1080	1170	1260	1350
5	450	563	675	788	900	1013	1125	1238	1350	1463	1575	1688
6	540	675	810	945	1080	1215	1350	1485	1620	1755	1890	2025
7	630	768	945	1103	1260	1418	1575	1733	1890	2048	2205	2363
8	720	900	1080	1260	1440	1620	1800	1980	2160	2340	2520	2700
9	810	1013	1215	1418	1620	1823	2025	2228	2430	2633	2835	3038
10	900	1125	1350	1575	1800	2025	2250	2475	2700	2925	3150	3375
11	990	1238	1485	1733	1980	2228	2475	2723	2970	3218	3465	3713

Adapted from Kahn SA, Schoemann M, Lentz CW: Burn resuscitation index: a simple method for calculating fluid resuscitation in the burn patient. J Burn Care Res 31:616, 2010.
BSS, burn size score.
The burn size score is determined by assigning a point value of 1 for each 9% total body surface area used in the traditional Lund-Browder chart. All points are added up and cross-referenced with the patient's weight to determine the initial hourly fluid rate.

www.ketabpezeshki.com 66485457-66963820

There have been rising concerns that overly aggressive fluid resuscitation, often termed "fluid creep," may have adverse outcomes.[61] In a study of 72 patients, increased fluid volumes were associated with pneumonia, sepsis, adult respiratory distress syndrome, multiorgan failure, and death.[70] Patients who receive more fluid than needed are at risk for the abdominal compartment syndrome, which may lead to acute renal failure. Factors associated with fluid creep include a lack of careful, frequent observations by clinicians, increasing use of opioids (termed "opioid creep," in which high doses of opioids are used, leading to a drop in blood pressure and the need for further fluid boluses), and the emergence of goal-directed resuscitation. Although clinicians are often eager to increase fluid administration in patients with poor urine output and unstable vital signs, they are less likely to reduce fluids in patients with adequate or increased urine output.[71] Goal-directed therapy is aimed at achieving supranormal levels of cardiac output and oxygen delivery and consumption and normal acid-base status. In contrast, restoration of normal physiologic and metabolic conditions in severely burned patients generally requires at least 24 to 48 hours to occur, and "pushing" these parameters prematurely may be detrimental.[61] Excessive initial resuscitation should be avoided, and fluid infusions should be frequently adjusted downward to avoid overhydration and subsequent cardiac failure, especially in the elderly.

Children have a larger TBSA relative to weight when compared with adults and therefore have larger fluid requirements. Fluid resuscitation in children is often calculated based on body surface area instead of weight. The Galveston formula is used to calculate resuscitation needs as follows: LR 5000 mL/m^2 TBSA burned + 2000 mL/m^2 TBSA over the first 24 hours, with half of the volume given over the first 8 hours. The body surface area can be estimated with the Mosteller formula: $([\text{Height (cm)} \times \text{Weight (kg)}]/3600)^{1/2}$. Infants should also receive 5% glucose in their maintenance fluids because they lack adequate carbohydrate reserves.

Local Burn Wound Care

All burns are contaminated and require thorough cleansing with soap and water under a running faucet or with gauze. Obvious debris or necrotic tissue should be gently removed. Care of the burn wound generally requires administration of an oral or intravenous analgesic agent. Patients may need a tetanus toxoid booster (diphtheria and tetanus [DT] or acellular pertussis-diphtheria-tetanus [aPDT] toxoid 0.5 mL intramuscularly) if more than 5 years have elapsed since their last booster. In patients who did not receive primary immunization, tetanus immune globulin should be administered.

Cooling of the Burn

The benefits of cooling the burn surface have been recognized for many years. There is controversy regarding the best cooling agent and the optimal timing, duration, and temperature of cooling. Classic studies suggest that the optimal cooling temperature is in the range of 10 to 25°C,[72] but cooling of large burns with ice water can result in hypothermia and increased mortality. Venter and colleagues found that ice water (1-8°C) resulted in more necrosis than no cooling at all, and cooling with tap water at 12 to 18°C resulted in the least necrosis and fastest healing.[42] The beneficial effects of cooling are still present when treatment is initiated up to 30 minutes after injury. External cooling with tap water is associated with a reduction in pain and may reduce the progression of tissue necrosis and limit the requirement for skin grafting.[73,74] If the patient is made comfortable by the cooling, it should be continued until the pain is reduced. Ice and ice water should be avoided because they may lead to increased tissue injury and hypothermia.[42]

Management of Burn Blisters

The management of burn blisters is a controversial topic. Some suggest that the fluid confined by the necrotic skin can lead to a closed-space infection, whereas others have argued that the intact blister creates a moist wound environment that is beneficial to wound healing. In vitro studies show both positive and negative effects of the burn blister fluid. Small clinical studies show that intact blisters heal faster and are less likely to become infected.[75,76] However, in these studies the débrided burns were not treated with any of the advanced dressings currently available, limiting the conclusions. With blisters that have already ruptured, any necrotic epidermis should be gently removed while adherent epidermis is left intact. With large or tense blisters, the unruptured blister may be aspirated with a sterile needle.

Burn Dressings

The purposes of a burn dressing are to protect the wound, to reduce pain, to absorb wound exudate, and to reduce evaporative heat loss.[77] The routine use of systemic antibiotics is not supported in the literature.[78] Local care for first-degree burns is not required other than optional topical anesthetics, aloe vera, or topical nonsteroidal anti-inflammatory drugs (NSAIDs).[79,80] There are two general methods of treating second-degree burns: (1) the open method, which consists of topical antimicrobials with or without standard dressings, and (2) the closed method, which uses synthetic or biologic occlusive dressings.

The open method is most appropriate for contaminated, large burns with large amounts of exudate. Topical antimicrobials should be used until the burn is completely reepithelialized to prevent bacterial colonization of the wound. The burn is reepithelialized when there is a pearly opalescent coating and it is dry to the touch. Antimicrobials used for burns include bacitracin, neomycin, mupirocin, silver sulfadiazine, iodophors, and mafenide.[81] Choice of the specific topical antimicrobial should be based on physician and patient preferences. After the antimicrobial is applied, a nonadherent dressing can be used to cover the wound. With this method the dressings should be removed daily and the burns cleansed with water and soap followed by reapplication of the antimicrobial agent and dressing. Traditionally, silver sulfadiazine and mafenide were the mainstays of treatment. However, they may be associated with rare adverse reactions such as reversible bone marrow suppression and metabolic acidosis, respectively. Silver sulfadiazine should not be used in patients with sulfa allergy. The use of silver sulfadiazine is no longer recommended because there is evidence that it delays healing of partial thickness burns and in vitro is toxic to keratinocytes and fibroblasts.[82,83]

The second method of managing partial-thickness burns is with occlusive dressings. Occlusive dressings support a moist wound-healing environment that is optimal for healing.[84] Because these dressings do not need to be changed daily, they also reduce costs and the pain associated with frequent dressing changes that are required when topical antimicrobial agents are used.[85] Occlusive dressings are most appropriate for superficial second-degree burns with little to moderate exudate. Several major types of materials are used for occlusive dressings, including foams, transparent films, hydrocolloids, alginates, hydrogels, and composites (Table 63-7). The development of products containing nanocrystalline silver has renewed interest in silver-based products because silver has potent antimicrobial properties against both gram-negative and gram-positive organisms as well as fungi such as *Candida*. Nanocrystalline silver is less rapidly deactivated than the ionic form of silver and thus does not require frequent dressing changes and reapplication. Many of these dressing can be left in place for at least 1 week or until they become saturated or malodorous.

www.ketabpezeshki.com 66485457-66963820

Table 63-7 Burn Dressings

CATEGORY	EXAMPLES	ADVANTAGES	DISADVANTAGES
Nonocclusive, Absorptive			
Gauze, nonadherent	Telfa (Kendall, Mansfield, Mass.)	Nonadherent, inexpensive	Requires daily dressing changes
Occlusive			
Foams	Mepilex (Mölnlycke Health Care AB, Göteborg, Sweden); Curafoam (Kendall, Dublin, Ireland); Allevyn foam (Smith & Nephew, London, United Kingdom)	Absorbs exudate, conforms to body site, prevents surrounding maceration	Opaque, may dehydrate wounds with minimal exudate
Hydrocolloid	DuoDERM (ConvaTec, Skillman, NJ); Tegasorb (3M, St. Paul, Minn.)	Absorbs exudates, protective cushioning of wound	Opaque, no antimicrobial properties
Alginate	SeaSorb (Coloplast, Humlebaek, Denmark); Algiderm (Bard, Murray Hill, NJ); Melgisorb (Mölnlycke Health Care AB, Göteborg, Sweden)	Absorptive	Frequent dressing changes
Nanocrystalline silver	Acticoat (Smith & Nephew, Largo, Fla.); Aquacel Ag (ConvaTec, Skillman, NJ)	Antimicrobial, creates a moist environment, less frequent dressing changes	Need to keep dressing moist
Hydrogel	Curagel (Kendall, Mansfield, Mass.); Flexigel (Smith & Nephew, Largo, Fla.); Nu-Gel (Johnson & Johnson, Arlington, Tex.)	Rehydrates dry wounds	Nonabsorptive
Transparent films	Tegaderm (3M, St. Paul, Minn.); OpSite (Smith & Nephew, Largo, Fla.)	Transparent, inexpensive	Nonabsorptive

Nanocrystalline silver has been incorporated into many new sustained delivery dressings, such as Aquacel Ag (ConvaTec, Skillman, NJ) and Acticoat (Smith & Nephew, Hull, United Kingdom). Compared with silver sulfadiazine, these dressings have been shown to reduce pain, speed healing, and reduce costs because few dressing changes are required.[86-88] A silicone-coated polyurethane foam that releases silver (Mepilex Ag, Mölnlycke, Goteborg, Sweden) has recently been introduced to the market and is especially attractive as a burn dressing because the silicone base adheres to the wound bed while the foam absorbs exudate and prevents tissue maceration. The silicone base also allows easy, nontraumatic removal of the dressing after approximately 1 week. In addition, unlike some of the other silver-based dressings, this dressing does not have to be kept wet. In a recent randomized controlled trial, partial-thickness burns treated with this dressing healed faster and with fewer dressing changes than with silver sulfadiazine.[89]

Absorptive hydrocolloids (such as DuoDERM [ConvaTec, Skillman, NJ]) have also been shown to be effective and less painful than traditional silver sulfadiazine.[90] Biosynthetic composite dressings such as Biobrane (UDL Laboratories, Sugar Land, Tex.) and Apligraf (Organogenesis, Canton, Mass.) are generally limited to use by burn specialists. A recent systematic review by the Cochrane group concluded that evidence from small trials, many with methodological limitations, suggests that superficial and partial-thickness burns may be managed with hydrocolloids, silicon nylon, topical antimicrobial agents (containing silver), polyurethane film, and biosynthetic dressings. There was no evidence to support the use of silver sulfadiazine.[91]

Most patients with minor burns can be treated in the ED and discharged home. If the burn is limited in size and has a blister, the patient should be reexamined within 48 hours by a primary care physician or an emergency practitioner. However, if the burn is extensive or involves the face or the hands, or appears to be dry and deep, the patient should be referred to a surgeon experienced in the care of burns or a burn center that same day. Burns over the extremities should be loosely dressed to avoid tissue compression and elevated to enhance lymphatic drainage and reduce swelling.

For patients with superficial partial-thickness burns who go home, the discharge instructions should describe washing of the wound with mild soap and tap water, application of the prescribed topical agent, and use of a dressing (the patient should receive a prescription for additional dressings and topical agents). If a synthetic occlusive dressing is applied, it should not be removed by the patient unless it is saturated or malodorous, at which time the patient will need to be seen by a physician. The patient should be instructed to immediately return to the ED or his or her physician if fever, swelling, or increased pain occurs in or around the burn injury.

If a patient with a third-degree burn will be transferred to a burn center, it is best to simply cover the wound with a clean dressing. Silver sulfadiazine should not be applied, as this has the potential to change the appearance of the wound before evaluation by a burn specialist.

Escharotomy

Releasing the constriction of a burn eschar with a scalpel or cautery at the bedside is called *escharotomy*. Although infrequently needed, escharotomy can be a limb-saving or lifesaving procedure.[92] The dead skin hardens and forms an eschar that appears as a hard covering. Patients with a large eschar require careful monitoring, especially those with circumferential burns or extensive burns to the chest or neck, because there is danger of the development of edema beneath the eschar, which leads to constriction and eventual interruption of arterial inflow. In the chest, the increased pressure impairs respiration. Pain, loss of sensation, and delayed capillary refill may be early signs of reduced perfusion. Traditionally, decreased Doppler signals in the extremity have been used as an indication for escharotomy, but one study suggests that a pulse oximetry value of less than 90% with or without Doppler signals in the involved extremity is an indication for escharotomy of the involved extremity.[93] An increase in peak airway pressure or difficulty with ventilation may be a sign that escharotomy of the chest is required. Circumferential burns of the neck that compromise the airway or the large vessels require escharotomy of the neck with care to avoid the airway and vessels themselves.

The procedure is performed by making a longitudinal incision down to the fat in the constricting eschar (Fig. 63-5). Care should

www.ketabpezeshki.com 66485457-66963820

Figure 63-5. Performing an escharotomy on the lateral lower extremity.

be taken to avoid underlying vessels and nerves. One study of patients transferred to burn centers found that escharotomy incisions were frequently not made deep enough to relieve the obstruction of flow.[93] It is important to check that an adequate incision has been made by reassessing Doppler signals and pulse oximetry in the extremities and ensuring that the peak airway pressures are decreased after the procedure. Escharotomies may need to be extended into healthy tissue on either side of the eschar to allow adequate decompression. Use of cautery to perform escharotomy is preferred by some to minimize bleeding.

Pain Management

Burns are among the most painful injuries[94]; however, many patients do not receive analgesia while in the ED.[95] In addition to being inhumane, inadequate pain management may contribute to an exaggerated inflammatory and stress response, increased pain from a "wind-up" phenomenon (in which the pain receptors are hypersensitized), long-term chronic pain and dysesthesias, and post-traumatic stress disorder.[96-98] The release of second messenger proteins such as protein kinase C-epsilon and neurotrophins such as nerve growth factor may mediate acute-burn hyperalgesia and priming, resulting in a predilection toward the development of chronic hyperalgesia.[99] Inadequate analgesia may be a result of the distraction of the often dramatic burn wound or other associated injuries, or concern that potent analgesics may impair ventilation. Pain management should be of primary concern for all burn patients.

There are three phases of burn recovery, each with a characteristic and different type of pain, and each requiring specific assessment tools and management strategies. These three phases include the emergent or resuscitative phase, the healing phase, and the rehabilitative phase.[100] This chapter focuses on the emergent phase of pain management.

During the emergent phase of management, patients may experience three major types of pain. *Background pain* describes the underlying pain that results directly from the injury. The amount of background pain is highly variable and also depends on the patient's anxiety. This pain is usually described as a continuous sensation of burning or throbbing that exists even when the patient is immobile. Background pain may be substantially reduced simply by covering the burn with a moist cool dressing.[101] *Breakthrough pain* occurs when the patient experiences a sudden increase in the pain intensity, usually as the analgesic level decreases with time. Shortening the analgesic dosage interval usually addresses this type of pain. *Procedural pain* refers to the pain

Table 63-8 Burn Prevention Recommendations

Flame burn prevention	Check that smoke detectors are functional Create an escape plan for the home, and practice with the family Safety device around fireplace Matches, lighters in secure place away from children
Scald prevention	Use splash guards on stove Lower hot water heater maximum temperature to 49-54°C Use thermometer for bath water

experienced when the burn wound is manipulated or débrided. This pain is generally very severe but transient in nature. Addition of an anxiolytic medication to parenteral opioids and use of music are helpful during this phase of management.[102]

Pharmacologic Therapies

Morphine sulfate and acetaminophen are the most commonly used analgesics in burn patients.[103] Minor pain from burns may be managed with oral acetaminophen (1 g in adults or 15 mg/kg in children) every 4 to 6 hours or an NSAID such as ibuprofen (400-800 mg in adults or 10 mg/kg in children) every 6 to 8 hours. The pain of minor burns may also be treated with a topical NSAID or aloe vera.[79,80]

Moderate to severe burn pain is managed with parenteral opioids (such as morphine sulfate 0.05-0.1 mg/kg) titrated to effect. The intravenous route is recommended owing to its rapid and reliable effects and consistent absorption. Because of its short half-life, fentanyl 0.5 to 1.0 µg/kg may be used for managing breakthrough and procedural pain. Intranasal fentanyl at a dose of 1.4 µg/kg may be as effective as oral morphine in both children and adults.[104] Intravenous infusion of lidocaine (1 mg/kg followed by 40 µg/kg/min infusion) has also been shown to reduce the pain in burn patients.[105]

Benzodiazepines have been useful adjuncts to pain therapy in burns. Care must be exercised in administering opioids and benzodiazepines together, as they may act synergistically to induce hypoventilation and hypotension. Lorazepam (1 mg IV or orally) and midazolam (1 mg IV or intranasally) are both widely used in burn patients.[106,107]

Other drugs (including gabapentin, stimulants, beta-blockers, low-dose ketamine, and antidepressants) are useful in managing chronic pain and burn pain in the burn unit; however, there is no evidence to support their use in the ED.[108-110]

Burn Prevention

The ED visit offers a unique "teachable moment" for physicians to educate patients and their families about preventing burns in the future. Prevention programs and safety legislation have made substantial contributions to decrease the incidence and severity of burn injury, especially for parents and school-age children. Areas in which burn prevention programs have been implemented have had a significant decrease in admissions for burn injury.[111]

In addition, several initiatives are targeting vulnerable segments of the population for prevention efforts.[112,113] Mothers with less than a high school education who are younger than 20 years and have more than two children are at a much higher risk for a fatal fire event.[114] Every visit to the ED provides an opportunity for education. Although prevention initiatives are reaching increasing numbers of people, there is still the need for further education of the public and in particular those subsegments of the population at high risk for burn injury. Specific preventive recommendations are listed in Table 63-8.

www.ketabpezeshki.com 66485457-66963820

DISPOSITION

Most patients will have small and superficial burns and can be discharged with close follow-up with a burn specialist or a primary care physician who has experience managing burns (see Table 63-2). When available, telemedicine and telephone consultation have also been shown to be helpful in decision-making and follow-up of burn patients, especially in questionable cases.[116] Patients with large burns (>20% TBSA), deep burns, burns over sensitive areas (such as the face, perineum, or hands), or burns that require escharotomy should be admitted, preferably to a burn unit. Patients with inhalation injury or other significant injuries or illnesses should also be admitted. Patients with inadequate social support and in whom abuse or neglect is suspected should also be considered for admission.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Bláha J: Physiology and pathology of skin after burns and derangement of gene expression. *Acta Chir Plast* 2006; 48:127-132.
2. Moritz AR, Henriques FC Jr: Studies of thermal injury. II. The relative importance of time and surface temperatures in the causation of cutaneous burns. *Am J Pathol* 1947; 23:695.
3. Singer AJ, Berruti L, Thode HC Jr, McClain SA: Standardized burn model using a multiparametric histologic analysis of burn depth. *Acad Emerg Med* 2000; 7:1-6.
4. Despa F, Orgill DP, Neuwalder J, Lee RC: The relative thermal stability of tissue macromolecules and cellular structure in burn injury. *Burns* 2006; 31:568.
5. Hotchkiss RS, Strasser A, McDunn JE, Swanson PE: Cell death. *N Engl J Med* 2009; 361:1570-1583.
6. Gravante G, et al: Apoptotic death in deep partial thickness burns vs. normal skin of burned patients. *J Surg Res* 2007; 141:141-145.
7. Singer AJ, McClain SA, Taira BR, Guerriero JL, Zong W: Apoptosis and necrosis in the ischemic zone adjacent to third degree burns. *Acad Emerg Med* 2008; 15:549-554.
8. American Burn Association: *Burn Incidence and Treatment in the United States: 2011 Fact Sheet*. Available at www.ameriburn.org/resources_factsheet.php?PHPSESSID=fbf3c262c153c58e4c9123ef12b39682. Accessed December 21, 2012.
9. Singer AJ, Lee CC, Thode HC Jr: Epidemiology of burns in the ED, 1996-2004. *Ann Emerg Med* 2007; 14:S65.
10. Jackson D: The diagnosis of the depth of burning. *Br J Surg* 1953; 40:588.
11. Dunkin CS, et al: Scarring occurs at a critical depth of skin injury: Precise measurement in a graduated dermal scratch in human volunteers. *Plast Reconstr Surg* 2007; 119:1722.
12. Shupp JW, et al: A review of the local pathophysiologic bases of burn wound progression. *J Burn Care Res* 2010; 31:839-873.
13. Singh V, Devgan L, Bhat S, Milner SM: The pathogenesis of burn wound conversion. *Ann Plast Surg* 2007; 59:109.
14. Singer AJ, Clark RA: Cutaneous wound healing. *N Engl J Med* 1999; 341:738.
15. Parihar A, Parihar MS, Milner S, Bhat S: Oxidative stress and anti-oxidative mobilization in burn injury. *Burns* 2008; 34:6.
16. Jaskille AD, Jeng JC, Sokolich JC, Lunsford P, Jordan MH: Repetitive ischemia-reperfusion injury: A plausible mechanism for documented clinical burn-depth progression after thermal injury. *J Burn Care Res* 2007; 28:13.
17. Demling RH: The burn edema process: Current concepts. *J Burn Care Rehabil* 2005; 26:207.
18. Horton JW: Free radicals and lipid peroxidation mediated injury in burn trauma: The role of antioxidant therapy. *Toxicology* 2003; 189:75.
19. Singer AJ, McClain SA, Hacht G, Batchkina G, Simon M: Semapimod reduces the depth of injury resulting in enhanced re-epithelialization of partial-thickness burns in swine. *J Burn Care Res* 2006; 27:40.
20. Taira BR, et al: Rosiglitazone, a PPAR-gamma ligand, reduces burn progression in rats. *J Burn Care Res* 2009; 30:499.
21. Giles N, Rea S, Beer T, Wood FM, Fear MW: A peptide inhibitor of c-Jun promotes wound healing in a mouse full-thickness burn model. *Wound Repair Regen* 2008; 16:58.
22. Mileski WJ, et al: Clinical effects of inhibiting leukocyte adhesion with monoclonal antibody to intercellular adhesion molecule-1 (enlimomab) in treatment of partial-thickness burn injury. *Trauma* 2003; 54:950.
23. O'Sullivan ST, et al: Major injury leads to predominance of the T helper-2 lymphocyte phenotype and diminished interleukin-12 production associated with decreased resistance to infection. *Ann Surg* 1995; 222:482, discussion 490.
24. Haponik EF, et al: Acute upper airway injury in burn patients: Serial changes of flow-volume curves and nasopharyngoscopy. *Am Rev Respir Dis* 1987; 135:360.
25. Moritz AR, Henriques FC Jr, McLean R: The effects of inhaled heat on the air passages of lungs: An experimental investigation. *Am J Pathol* 1945; 21:311.
26. Prien T, Traber DL: Toxic compounds and inhalation injury—a review. *Burns Incl Therm Inj* 1988; 14:451.
27. Maybauer MO, Rehberg S, Traber DL, Herndon DN, Maybauer DM: [Pathophysiology of acute ling injury in severe burn and inhalation injury]. *Anaesthesist* 2009; 58:805.
28. Enkhbaatar P, Traber DL: Pathophysiology of acute lung injury in combined burn and smoke inhalation injury. *Clin Sci* 2004; 107:137.
29. Murakami K, Traber DL: Pathophysiological basis of smoke inhalation injury. *News Physiol Sci* 2003; 18:125.
30. Nieman GF, Clark WR Jr, Wax SD, Webb SR: The effect of smoke inhalation on pulmonary surfactant. *Ann Surg* 1980; 191:171.
31. Jaskille AD, Shupp JW, Jordan MH, Jeng JC: Critical review of burn depth assessment techniques: Part I. Historical review. *J Burn Care Res* 2010; 30:937.
32. Jaskille AD, Ramella-Roman JC, Shupp JW, Jordan MH, Jeng JC: Critical review of burn depth assessment techniques: Part II. Review of laser Doppler technology. *J Burn Care Res* 2010; 31:151.
33. Hlava P, Moserova J, Konigova R: Validity of clinical assessment of the depth of a thermal injury. *Acta Chir Plast* 1983; 25:202.
34. Hammond JS, Ward CG: Transfers from emergency room to burn center: Errors in burn size estimate. *J Trauma* 1987; 27:1161.
35. Berkebile BL, Goldfarb IW, Slater H: Comparison of burn size estimates between prehospital reports and burn center evaluations. *J Burn Care Rehabil* 1986; 7:411.
36. Perry RJ, Moore CA, Morgan BD, Plummer DL: Determining the approximate area of a burn: An inconsistency investigated and re-evaluated. *BMJ* 1996; 312:1338.
37. Gomez R, Cancio LC: Management of burn wounds in the emergency department. *Emerg Med Clin North Am* 2007; 25:135.
38. Collis N, Smith G, Fenton OM: Accuracy of burn size estimation and subsequent fluid resuscitation prior to arrival at the Yorkshire Regional Burns Unit: A three-year retrospective study. *Burns* 1999; 25:345.
39. Sheridan RL, et al: Planimetry study of the percent of body surface represented by the hand and palm: Sizing irregular burns is more accurately done with the palm. *J Burn Care Rehabil* 1995; 16:605.
40. Lund C, Browder N: The estimate of areas of burn. *Surg Gynecol Obstet* 1944; 79:352.
41. Singer AJ, Freidman B, Modi P, Soroff HH: The effect of a commercially available burn-cooling blanket on core body temperatures in volunteers. *Acad Emerg Med* 2006; 13:686.
42. Venter TH, Karpelowsky JS, Rode H: Cooling of the burn wound: The ideal temperature of the coolant. *Burns* 2007; 33:917.
43. Helvig B, Mlcak R, Nichols RJ Jr: Anchoring endotracheal tubes on patients with facial burns: Review from Shriner's Burns Institute, Galveston, Texas. *J Burn Care Rehabil* 1987; 8:236.
44. Barrow RE, Spies M, Barrow LN, Herndon DN: Influence of demographics and inhalation injury on burn mortality in children. *Burns* 2004; 30:72.
45. Colohan SM: Predicting prognosis in thermal burns with associated inhalation injury: A systematic review of prognostic factors in adult burn victims. *J Burn Care Res* 2010; 31:529.
46. Mlcak RP, Suman OE, Herndon DN: Respiratory management of inhalation injury. *Burns* 2007; 33:2.
47. Carr JA, Phillips BD, Bowling WM: The utility of bronchoscopy after inhalation injury complicated by pneumonia in burn patients: Results from the National Burn Repository. *J Burn Care Res* 2009; 30:967.
48. Slutsky AS: Mechanical ventilation: American College of Chest Physicians' Consensus Conference. *Chest* 1993; 104:1833.
49. Oba Y, Salzman GA: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury. *N Engl J Med* 2000; 343:813.
50. Allan PF, Osborn EC, Chung KK, Wanek SM: High-frequency percussive ventilation revisited. *J Burn Care Res* 2010; 31:510.
51. Endorf FW, Dries DJ: Noninvasive ventilation in the burned patient. *J Burn Care Res* 2010; 31:217.
52. Dries DJ, Marini JJ: Airway pressure release ventilation. *J Burn Care Res* 2009; 30:929.
53. Toon MH, Maybauer MO, Greenwood JE, Maybauer DM, Fraser JF: Management of acute smoke inhalation injury. *Crit Care Resusc* 2010; 12:53.
54. Miller AC, Rivero A, Ziad S, Smith DJ, Elamin EM: Influence of nebulized unfractionated heparin and *N*-acetylcysteine in acute lung injury after smoke inhalation injury. *J Burn Care Res* 2009; 30:249.
55. Saffle JR: The 1942 fire at Boston's Cocoanut Grove nightclub. *Am J Surg* 1993; 166:581.
56. Baxter CR: Fluid volume and electrolyte changes of the early postburn period. *Clin Plast Surg* 1974; 1:693.
57. Arturson G: Forty years in burns research: The postburn inflammatory response. *Burns* 2000; 26:599.
58. Pitt RM, Parker JC, Jurkovich GJ, Taylor AE, Curreri PW: Analysis of altered capillary pressure and permeability after thermal injury. *J Surg Res* 1987; 42:693.
59. Demling RH, Mazess RB, Witt RM, Wolberg WH: The study of burn wound edema using dichromatic absorptiometry. *J Trauma* 1978; 18:124.

www.ketabpezeshki.com 66485457-66963820

60. Pham TN, Cancio LC, Gibran NS; American Burn Association: American Burn Association Practice Guidelines burn shock resuscitation. *J Burn Care Res* 2008; 29:257.
61. Saffle JI: The phenomenon of "fluid creep" in acute burn resuscitation. *J Burn Care Res* 2007; 28:382.
62. Perel P, Roberts I: Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev* 2007; 4:CD000567.
63. Baxter CR, Shires T: Physiological response to crystalloid resuscitation of severe burns. *Ann N Y Acad Sci* 1968; 150:874.
64. Baxter C: Fluid resuscitation, burn percentage, and physiologic age. *J Trauma* 1979; 19(11 Suppl):864.
65. Baxter CR: Problems and complications of burn shock resuscitation. *Surg Clin North Am* 1978; 58:1313.
66. Chung KK, et al: Simple derivation of the initial fluid rate for the resuscitation of severely burned adult combat casualties: In silico validation of the rule of 10. *J Trauma* 2010; 69(Suppl 1):S49.
67. Kahn SA, Schoemann M, Lentz CW: Burn resuscitation index: A simple method for calculating fluid resuscitation in the burn patient. *J Burn Care Res* 2010; 31:616.
68. Dai NT, et al: The comparison of early fluid therapy in extensive flame burns between inhalation and noninhalation injuries. *Burns* 1998; 24:671.
69. Freiburg C, Igneri P, Sartorelli K, Rogers F: Effects of differences in percent total body surface area estimation on fluid resuscitation of transferred burn patients. *J Burn Care Res* 2007; 28:42.
70. Klein MB, et al: The association between fluid administration and outcome following major burn: A multicenter study. *Ann Surg* 2007; 245:622.
71. Cancio LC, et al: Predicting increased fluid requirements during the resuscitation of thermally injured patients. *J Trauma* 2004; 56:404, discussion 413.
72. Ofeigsson OJ: First-aid treatment of scalds and burns by water cooling. *Postgrad Med* 1961; 30:330.
73. Ofeigsson OJ: Water cooling: First-aid treatment for scalds and burns. *Surgery* 1965; 57:391.
74. Jandera V, Hudson DA, de Wet PM, Innes PM, Rode H: Cooling the burn wound: Evaluation of different modalities. *Burns* 2000; 26:265.
75. Swain AH, Azadian BS, Wakeley CJ, Shakespeare PG: Management of blisters in minor burns. *BMJ* 1987; 295:181.
76. Gimbel NS, Kapetansky DI, Weissman F, Pinkus HK: A study of epithelization in blistered burns. *AMA Arch Surg* 1957; 74:800.
77. Fan K, Tang J, Escandon J, Kirsner RS: State of the art topical wound-healing products. *Plast Reconstr Surg* 2011; 127(Suppl):44S.
78. Ugburo AO, Atoyebi OA, Oyeneyin JO, Sowemimo GO: An evaluation of the role of systemic antibiotic prophylaxis in the control of burn wound infection at the Lagos University Teaching Hospital. *Burns* 2004; 30:43.
79. Magnette JL, et al: Diclofenac systemic exposure is not increased when topical diclofenac is applied to ultraviolet-induced erythema. *Eur J Clin Pharmacol* 2004; 60:591.
80. Maenthaisong R, Chaiyakunapruk N, Niruntraporn S, Kongkaew C: The efficacy of aloe vera used for burn wound healing: A systematic review. *Burns* 2007; 33:713.
81. Palmieri TL, Greenhalgh DG: Topical treatment of pediatric patients with burns: A practical guide. *Am J Clin Dermatol* 2002; 3:529.
82. Hussain S, Ferguson C: Best evidence topic report: Silver sulphadiazine cream in burns. *Emerg Med J* 2006; 23:929.
83. Atiyeh BS, Costagliola M, Hayek SN, Dibo SA: Effect of silver on burn wound infection control and healing: Review of the literature. *Burns* 2007; 33:139.
84. Singer AJ, Dagum AB: Current management of acute cutaneous wounds. *N Engl J Med* 2008; 359:1037.
85. Eaglstein WH: Experiences with biosynthetic dressings. *J Am Acad Dermatol* 1985; 12(2 Pt 2):434.
86. Cuttle L, et al: A retrospective cohort study of Acticoat versus Silvazine in a paediatric population. *Burns* 2007; 33:701.
87. Caruso DM, et al: Randomized clinical study of Hydrofiber dressing with silver or silver sulfadiazine in the management of partial-thickness burns. *J Burn Care Res* 2006; 27:298.
88. Paddock HN, et al: A silver impregnated antimicrobial dressing reduces hospital length of stay for pediatric patients with burns. *J Burn Care Res* 2007; 28:409.
89. Silverstein P, et al: An open, parallel, randomized, comparative, multicenter study to evaluate the cost-effectiveness, performance, tolerance, and safety of a silver-containing soft silicone foam dressing (intervention) vs silver sulfadiazine cream. *J Burn Care Res* 2011; 32:617-626.
90. Martin FT, O'Sullivan JB, Regan PJ, McCann J, Kelly JL: Hydrocolloid dressing in pediatric burns may decrease operative intervention rates. *J Pediatr Surg* 2010; 45:600.
91. Wasiak J, Cleland H, Campbell F: Dressings for superficial and partial thickness burns. *Cochrane Database Syst Rev* 2008; 4:CD002106.
92. Piccolo NS, et al: Escharotomies, fasciotomies and carpal tunnel release in burn patients—review of the literature and presentation of an algorithm for surgical decision making. *Handchir Mikrochir Plast Chir* 2007; 39:161.
93. Brown RL, Greenhalgh DG, Kagan RJ, Warden GD: The adequacy of limb escharotomies-fasciotomies after referral to a major burn center. *J Trauma* 1994; 37:916.
94. Summer GJ, Puntillo KA, Miaskowski C, Green PG, Levine JD: Burn injury pain: The continuing challenge. *J Pain* 2007; 8:533.
95. Singer AJ, Thode HC Jr: National analgesia prescribing patterns in emergency department patients with burns. *J Burn Care Rehabil* 2002; 23:361.
96. Kawasaki Y, et al: Ionotropic and metabotropic receptors, protein kinase A, protein kinase C, and Src contribute to C-fiber-induced ERK activation and cAMP response element-binding protein phosphorylation in dorsal horn neurons, leading to central sensitization. *J Neurosci* 2004; 24:8310.
97. Ikeda H, et al: Synaptic amplifier of inflammatory pain in the spinal dorsal horn. *Science* 2006; 312:1659.
98. Van Loey NE, Maas CJ, Faber AW, Taal LA: Predictors of chronic posttraumatic stress symptoms following burn injury: Results of a longitudinal study. *J Trauma Stress* 2003; 16:361.
99. Summer GJ, et al: TrkA and PKC-epsilon in thermal burn-induced mechanical hyperalgesia in the rat. *J Pain* 2006; 7:884.
100. Ratcliff SL, et al: The effectiveness of a pain and anxiety protocol to treat the acute pediatric burn patient. *Burns* 2006; 32:554.
101. Nguyen NL, Gun RT, Sparnon AL, Ryan P: The importance of immediate cooling: A case series of childhood burns in Vietnam. *Burns* 2002; 28:173.
102. Tan X, Yowler CJ, Super DM, Fratianne RB: The efficacy of music therapy for decreasing pain, anxiety, and muscle tension levels during burn dressing changes: A prospective randomized crossover trial. *J Burn Care Res* 2010; 31:590.
103. Martin-Herz SP, et al: Pediatric pain control practices of North American Burn Centers. *J Burn Care Rehabil* 2003; 24:26.
104. Finn J, et al: A randomised crossover trial of patient controlled intranasal fentanyl and oral morphine for procedural wound care in adult patients with burns. *Burns* 2004; 30:262.
105. Jonsson A, Cassuto J, Hanson B: Inhibition of burn pain by intravenous lignocaine infusion. *Lancet* 1991; 338:151.
106. Cassuto J, Tarnow P: Potent inhibition of burn pain without use of opiates. *Burns* 2003; 29:163.
107. Patterson DR, Ptacek JT, Carrougher GJ, Sharar SR: Lorazepam as an adjunct to opioid analgesics in the treatment of burn pain. *Pain* 1997; 72:367.
108. Rice TL, Kyff JV: Intranasal administration of midazolam to a severely burned child. *Burns* 1990; 16:307.
109. Cuignet O, Pirson J, Soudon O, Zizi M: Effects of gabapentin on morphine consumption and pain in severely burned patients. *Burns* 2007; 33:81.
110. Pereira CT, Jeschke MG, Herndon DN: Beta-blockade in burns. *Novartis Found Symp* 2007; 280:238, discussion 248.
111. Richardson P, Mustard L: The management of pain in the burns unit. *Burns* 2009; 35:921.
112. Peleg K, Goldman S, Sikron F: Burn prevention programs for children: Do they reduce burn-related hospitalizations? *Burns* 2005; 31:347.
113. Ytterstad B, Smith GS, Coggan CA: Harstad injury prevention study: Prevention of burns in young children by community-based intervention. *Inj Prev* 1998; 4:176.
114. Taira BR, et al: Predictors of sustaining burn injury: does the use of common prevention strategies matter? *J Burn Care Res* 2011; 32:20-25.
115. Scholer SJ, Hickson GB, Mitchel EF Jr, Ray WA: Predictors of mortality from fires in young children. *Pediatrics* 1998; 101:E12.
116. Turk E, et al: Use of telemedicine and telephone consultation in decision making and follow-up of burn patients: Initial experience from two burn units. *Burns* 2011; 37:415.

www.ketabpezeshki.com 66485457-66963820

Chapter 64

Chemical Injuries

Michael D. Levine and Richard Zane

PERSPECTIVE

During the past century, there has been a dramatic increase in the number of chemicals produced. Worldwide, there are more than 5 million known chemicals, with an additional 10,000 to 20,000 new chemicals developed each year. Furthermore, an estimated 500,000 unique shipments of hazardous materials occur daily throughout the United States, resulting in thousands of exposures to hazardous materials annually.[1] These chemicals, which include acids, alkalis, and other highly reactive substances, not only are found throughout industry but also are ingredients in many household products. Exposure to these substances can result in injuries to many organs, including the eyes, skin, and lungs.

Despite myriad potential exposures to chemicals each day, the number of actual exposures is relatively low, largely because of sound industry practices and state and federal regulations. The Superfund Amendments and Reauthorization Act contains extensive provisions for emergency planning.

A hazardous material *(hazmat)* is defined as any substance, including gases, solids, or liquids, that has the potential to cause harm to people or the environment. The Hazardous Substances Emergency Events Surveillance (HSEES) system collects information on chemical exposures from 14 states. According to the 2007-2008 HSEES report, more than 15,000 chemical events occurred in the United States during this 2-year span. The manufacturing sector accounted for nearly half of all chemical exposures in the United States. Transportation, communication, and other public utilities accounted for nearly one third of all exposures. Employees working with the chemicals were the most likely to be injured, followed by the general public.[1] Both the current and the past HSEES reports can be found online at www.atsdr.cdc.gov/HS/HSEES/annual2008.html.

The most commonly released hazardous substances are volatile organic compounds, herbicides, acids, and ammonia. Various household products, such as cement, drain cleaners, and gasoline, are also potentially quite hazardous, and exposure can result in severe disability or death.

PATHOPHYSIOLOGY

Most chemical agents cause skin damage by producing a chemical reaction rather than a hyperthermic injury. Certain chemicals can generate significant heat production via an exothermic reaction. Nonetheless, the majority of dermal injuries result from direct damage to the skin rather than from a hyperthermic injury. The type of chemical reaction produced depends on the properties of the individual agent. In general, however, the degree of damage is directly correlated with the toxic agent's concentration and duration of exposure. Several other factors also contribute to the degree of injury—for example, areas of the body where the skin is particularly thin are more at risk than areas of the body where the skin is thicker. Skin that is particularly thin or broken can contribute to more severe injury.

When acidic compounds interact with skin, protein denaturation and coagulative necrosis ensue. This coagulative necrosis produces an eschar, which limits the depth to which the acid can penetrate. Despite this eschar formation, acidic burns can, nonetheless, produce profound burns. Various acids produce eschars with characteristic colors. For example, nitric acid burns result in a yellow eschar, whereas sulfuric acid burns result in a black or brown eschar. Hydrochloric acid and phenol burns produce a white to gray-brown eschar.

Unlike the coagulative necrosis produced from most acids, alkalis produce saponification and liquefactive necrosis of body fat. Because there is no eschar to limit penetration, alkali burns tend to penetrate deeper into the tissues, which results in significant tissue damage.

COMMUNITY PREPAREDNESS AND HAZMAT RESPONSE

Hazardous materials are found in residential, urban (e.g., manufacturing), and rural (e.g., agricultural) settings. Furthermore, because these substances are often transported on highways and railroads, a hazmat exposure could potentially occur in virtually any community. First responders, paramedics, and members of the hazmat response team must work together to identify toxic chemicals and assess hazardous environments. Placards, shipping papers, United Nations chemical identification numbers, and markings on shipping containers help identify the offending agent. In some cases, chemical analysis may be required to assist in the identification of the agent. The Chemical Transportation Emergency Center (CHEMTREC) in Arlington, Virginia, maintains a 24-hour telephone hotline (1-800-424-9300) to assist in the rapid identification and management of chemical agents. In addition, regional poison control centers (1-800-222-1222) provide specific health information regarding individual chemicals.

Contingency Plan

The contingency plan for hazmat management is divided into two parts: initiation of the site plan and evacuation. Initiation of the site plan begins after the specific offending agent has been identified and the surrounding environment has been assessed. Only after the substance has been identified can the risks to the public and the environment accurately be identified. First responders should be trained to recognize the potential for a hazmat incident and should establish a perimeter. The hazmat

www.ketabpezeshki.com 66485457-66963820

technicians are specifically trained in the use of personal protective equipment (PPE), establishing entry into a hazmat scene, victim rescue, and determining the type and extent of a hazmat emergency. A central command post should be used to coordinate the activities of the hazmat team with those of the emergency medical services personnel, firefighters, police officers, and other relevant personnel.

Coping with Hazmat Incidents

In dealing with a hazmat incident, two distinct processes occur simultaneously. First, the scene is secured, which involves containing the substance, extinguishing fires, and controlling other environmental hazards. The second process involves treatment, which begins with decontamination. The exact decontamination depends on the specific agent and route of exposure. In general, all decontamination should be performed before arrival in the emergency department. Individuals who are not exposed to the hazardous material are kept away from the scene to prevent subsequent exposure.

At the outset of any contamination event, the offending agent may not be known. Therefore first responders and those having direct contact with ill patients must wear appropriate PPE. Once the first responder is dressed appropriately, decontamination begins by removing the patient's contaminated clothes. Dry (anhydrous) chemicals can be brushed off the patient's skin, followed by copious irrigation with water delivered under low pressure. Ideally, the contaminated water will be contained on the scene for appropriate disposal. Liquid chemicals can be copiously irrigated directly. If decontamination was indicated and not performed on the scene, the patient should be decontaminated before entering the ED. The primary and secondary survey can occur simultaneously with decontamination.

Although the exact requirements for PPE among hospital personnel are somewhat controversial, at a minimum, all personnel involved with decontamination should wear chemical-resistant clothing with a hood, boots, eyewear, at least two layers of gloves, and some form of respiratory protection.

MANAGEMENT

The initial management of the chemically burned patient involves removing the individual from the hostile environment. All clothing is promptly removed and placed in plastic bags, if not already done. Dry chemical agents, such as lye, should be brushed away before hydrotherapy is instituted. The priority of decontamination is to progress from cleansing of contaminated wounds to eyes, mucous membranes, skin, and hair.

Chemical burns continue to destroy tissue until the causative agent is inactivated or removed. Therefore the more quickly the agent is removed from the skin, the less severe the injury. Prompt treatment results in a return of the skin pH to normal or near-normal conditions.

Hydrotherapy

Hydrotherapy involves the application of large amounts of water or saline to the affected skin. Gentle irrigation of a large volume of water under low pressure for a prolonged time dilutes the toxic agent and washes it out of the skin. High-pressure irrigation should not be used because it is possible to drive the chemical deeper into the skin. Furthermore, the use of high-pressure irrigation can result in splattering of the chemical into the eyes of the patient or rescuer.

Elemental metals (e.g., sodium) may produce profound exothermic reactions when combined with water. To minimize the exothermic reaction from such compounds, mineral oil is applied to the skin first, if it is immediately available. However, hydrotherapy should not be delayed while waiting for mineral oil. In addition, some have argued that phenol (carbolic acid) should not be irrigated with water owing to concern for enhanced skin penetration after exposure to water. However, the use of a substance that has both hydrophobic and hydrophilic properties (i.e., polyethylene glycol [PEG]) has not been proven to exhibit clear benefit over water alone; therefore hydrotherapy should not be delayed while waiting for PEG.[2] If PEG solution is used for decontamination, the molecular weight of the preferred solution should be 200 to 400 daltons, which is different from the molecular weight of the PEG solution used for colonoscopy preparations.

After exposure to strong alkalis, prolonged hydrotherapy is especially important to limit the severity of the injury. In experimental animal models, the pH of chemically burned skin does not approach a normal concentration unless continuous irrigation has been maintained for more than 1 hour, and the pH often does not return to normal for 12 hours despite hydrotherapy. In contrast, with hydrochloric acid skin burns, the pH usually returns to normal within 2 hours after initiation of hydrotherapy.[3] The mechanism by which sodium hydroxide (NaOH) maintains an alkaline pH despite treatment is related to the byproducts of its chemical reaction to skin. Alkalis combine with proteins or fats in tissues to form soluble protein complexes or soaps. These complexes permit passage of hydroxyl ions deep into the tissue, limiting their contact with the water diluent on the skin surface. On the other hand, acids do not form complexes, and their free hydrogen ions are easily neutralized.

Water is the agent of choice for decontaminating dermal burns from either acidic or alkali substances. The deleterious effects of attempting to neutralize acid and alkali burns were first noted in experimental models in 1927. In nearly every instance, animals with either acid or alkali burns that underwent initial irrigation with water survived longer than animals treated with chemical neutralizers. The striking difference between the results of these two treatment methods is attributed to the additional trauma of the heat generated by the neutralization reaction superimposed on the existing burn. Although the same effect may occur when certain chemicals come in contact with water, large volumes of water tend to limit the exothermic reaction.

However, scientists are beginning to question the belief that neutralization of an alkaline burn of the skin with acid does indeed increase tissue damage because of the exothermic nature of acid-base reactions.[4] Using an animal model with 5% topical acetic acid (i.e., household vinegar), researchers demonstrated that the application of acetic acid to alkaline burns resulted in rapid neutralization of the tissue and reduction of the tissue injury in comparison with water irrigation alone. However, these data are preliminary and limited, and therefore irrigation with water alone is acceptable.

Ocular Injury

Chemical burns to the eye require emergent management. Alkali burns are more common than acidic burns, and unilateral involvement is more common than bilateral involvement.[5] Common causes include inadvertent handling of chemicals with resultant splash injury, exploding batteries, airbag deployment, and intentional assaults. Alkali burns can initially appear trivial, but because of an interaction with lipids in the corneal epithelial cells, a coagulative necrosis results, and deep penetration through the corneal stroma can ensue. The injury can occur rapidly; for example, anhydrous ammonia can penetrate into the anterior chamber in less than 1 minute, resulting in complete blindness.

Similar to cutaneous burns, ocular burns are classified into four grades, with grade IV being the most severe. Grade I and II burns are associated with hyperemia, conjunctival ecchymosis, and

www.ketabpezeshki.com 66485457-66963820

defects in the corneal epithelium. Grade III and IV burns are associated with deeper penetration and therefore are associated with mydriasis, a gray discoloration of the iris, and early cataract formation.

Grade II burns are differentiated from grade I burns by the hazy appearance of the cornea in the former. Blood vessel thrombosis in the anterior chamber occurs in both grade III and grade IV burns, and as a result, limbus ischemia occurs. The degree of ischemia differentiates grade III from grade IV burns: ischemia occurs in less than half of the limbus in grade III, whereas ischemia occurs in more than half of the limbus in grade IV. In addition, grade IV burns are associated with necrosis of the bulbar and tarsal conjunctiva and significant limbal ischemia.[5,6]

Treatment

When a chemical injury to the eye is suspected, copious irrigation is started immediately. At the scene, it is recommended that the victim submerge the eyes in running tap water and continuously open and close the eyes with the head turned such that the affected eye is lower than the unaffected eye to minimize any contamination into the unaffected eye. In the emergency department, tap water irrigation can be continued during preparation for a more definitive irrigation system. The repeated application of topical anesthetics such as proparacaine can decrease pain and facilitate irrigation. Hydrotherapy can also be accomplished by connecting intravenous tubing to a bag containing normal saline or lactated Ringer's solution. The initial therapy consists of continual irrigation of the eye with 2 L of normal saline during the first 30 minutes. A Morgan lens can be used for irrigation, although there is a theoretic risk of trapping the chemical between the conjunctiva and the Morgan lens, thereby increasing the burn. If a Morgan lens is used, we recommend replacing the lens between saline applications. After 2 L has been infused, litmus paper is inserted into the conjunctiva to determine the pH; irrigation is continued until the pH is at a near-physiologic level (pH of 7.4). Alkali burns are likely to require more irrigation than acidic burns. For very severe acid or alkali burns, prolonged irrigation may be needed regardless of a normal ocular pH. It is important to also evert the upper eyelid and visually inspect the area for any lodged particulate matter, which may be hidden. A slit-lamp examination with fluorescence staining should be performed to assess for any corneal abrasion. Although of undetermined benefit, ocular antibiotics can be considered after decontamination if a corneal abrasion is present.

Some experimental settings have found benefit from the application of *N*-acetylcysteine or cysteine to eyes subjected to chemical injury.[7] These collagenase inhibitors are thought to prevent loss of the corneal stroma by limiting the amount of collagenase released from the injured tissue. In one retrospective study, the application of steroids, ascorbate, citrate, and antibiotics resulted in improved outcomes in grade III, but not grade IV, burns compared with steroids and antibiotics alone.[6] It is hypothesized that the citrate suppresses neutrophils and inhibits collagenase, thereby reducing the inflammatory response. Ascorbate has been hypothesized to promote new collagen deposition. Topical antibiotics (e.g., sulfacetamide, gentamicin, and ciprofloxacin) are recommended for any corneal injury, but this practice is not supported by strong evidence. Mobility of the eye should be encouraged to minimize the formation of adhesions (symblepharon). With the exception of the antibiotics, there are insufficient data at this time to recommend use of any of the pharmaceutical agents mentioned in this paragraph as part of routine practice.

Immediate ophthalmologic consultation and close follow-up are indicated for all significant exposures. Patients with grade I and II injuries can often be managed as outpatients, but patients with higher-grade injuries should be admitted to the hospital. All but the mildest burns should be treated with a long-acting cycloplegic, a mydriatic. After discussion with an ophthalmologist, a carbonic anhydrase inhibitor may be used for 2 weeks (or until the pain disappears). These medications decrease the potential for pupillary constriction, increased intraocular pressure, and early glaucoma. Procedures such as amniotic membrane patching, anterior chamber paracentesis, and corneal transplant have been used for chemical injuries to the eye, and these are undertaken by the ophthalmologic consultant.

Hydrofluoric Acid

Hydrofluoric acid (HF) is an acidic aqueous solution made from the element fluorine. It is commonly used in the petroleum industry to manufacture high-octane gasoline. It is also commonly used in the production of microelectronics and for etching glass, removing rust, and cleaning cement and bricks. Absorption of HF can occur after exposure to the lung, skin, and eyes. In an 11-year review of all HF deaths reported to the Occupational Safety and Health Administration, four deaths resulted strictly from dermal exposure, and five deaths resulted from both inhalational and dermal exposure. Several of these deaths were associated with inadequate medical therapy, and all of the cases were associated with unsafe workplace practices.[8] HF solutions with a concentration exceeding 50% will produce near immediate pain, whereas burns from more dilute concentrations can be delayed for hours.

HF is unique in its mechanism of action. Despite being an acid, it is capable of causing a liquefactive necrosis, similar to alkalis. However, the free fluoride ion is actually responsible for most of the damage associated with HF exposure. The free fluoride ion scavenges cations, such as calcium and magnesium, thereby resulting in systemic hypocalcemia and hypomagnesemia. In addition, free fluoride ions can inhibit sodium, potassium–ATPase (Na^+,K^+-ATPase) and the Krebs cycle. The combination of cellular destruction and inhibition of Na^+,K^+-ATPase can also result in hyperkalemia, a preterminal finding. As a result of the numerous electrolyte disturbances, QT prolongation, hypotension, and ventricular arrhythmias can occur. The severity of injury depends on the concentration of the substance and the duration of exposure.

Inhalational Exposure

Inhalation of HF is rare, and it almost always occurs in the industrial setting. Patient outcomes vary considerably depending on the concentration and duration of exposure to HF. Inhalation and skin exposure to 70% HF can result in pulmonary edema and death within 2 hours. However, delayed pneumonitis and adult respiratory distress syndrome can also occur, and once symptoms occur, they can be present for months. Pneumonitis can be severe and require ventilatory support.

Gastrointestinal Exposure

Gastrointestinal exposure is rare; it can produce symptoms ranging from nausea, vomiting, and abdominal pain to life-threatening fluoride toxicity.

Ocular Exposure

Despite the fact that HF is an acid, exposure of the eye to HF can result in a severe burn with penetration and necrosis of the structures throughout the anterior chamber. As with other ocular injuries, immediate and copious irrigation of the eye is indicated. Systemic absorption is possible.

www.ketabpezeshki.com 66485457-66963820

Dermal Exposure

Dermal exposure is perhaps the most common route of injury. Relatively dilute solutions of HF (0.6-12%) are available to the general public in the form of rust removal and aluminum cleaning products. During handling of containers in which HF is stored, contamination of inadequately protected fingers and hands often results in a chemical burn injury. The HF skin burn has a distinct characteristic: the exposure causes progressive tissue destruction. Intense pain can occur quickly or be delayed for several hours, but it can persist for days if untreated. The skin at the site of contact develops a tough coagulated appearance. Eschar formation can occur.[7] If untreated, the burn can progress to an indurated, whitish appearance with vesicle formation. In the digits, HF has a predilection for subungual tissue. Severe untreated burns can progress to full-thickness burns and can even result in loss of digits.

Initial Therapy

The initial treatment of HF skin exposure is immediate irrigation with copious amounts of water for at least 15 to 30 minutes. Most exposures to dilute solutions of HF respond favorably to immediate irrigation. Severe pain or any pain that persists after irrigation denotes a more severe burn that requires detoxification of the fluoride ion. Detoxification is accomplished when an insoluble calcium salt is formed.

All blisters are removed because necrotic tissue may harbor fluoride ions; the fluoride ions can then be detoxified through topical treatment, local infiltrative therapy, or intra-arterial infusion of calcium. Calcium gluconate (2.5%) gel is the preferred topical agent.[9,10] This gel is often not available in hospital pharmacies, but it can be made by mixing 3.5 g of calcium gluconate powder in 150 mL of a water-soluble lubricant (e.g., glycerin-hydroxyethyl cellulose lubricant [K-Y Jelly]). The gel is secured by an occlusive cover (e.g., powder-free latex glove). Because the skin is impermeable to calcium, topical treatment is effective only for mild, superficial burns.

Infiltration Therapy

Subcutaneous. Infiltrative therapy is necessary for treatment of deep, painful HF burns. Calcium gluconate is the agent of choice and can be administered by either direct infiltration or intra-arterial injection. A common technique involves injecting 0.5 mL/cm^2 of 10% calcium gluconate subcutaneously through a 27- or 30-gauge needle. The use of an equal volume mixture of 5% calcium gluconate and 0.9% normal saline has been shown to reduce irritation of tissues and decrease subsequent scarring. Patients treated in this manner should be hospitalized for observation and toxicologic consultation.

Despite its wide acceptance, the infiltration technique has disadvantages, especially in treating digits. A regional nerve block is recommended because the injections may be very painful. Removal of the nail to expose the nail bed is required if subungual tissue is involved. Vascular compromise can occur if excessive fluid is injected into the skin exposure sites, and unbound calcium ions have a direct toxic effect on tissue. Because of these disadvantages with subcutaneous infiltration, intra-arterial infusion of calcium is now recommended in most instances.

Intravenous and Intra-arterial. Patients with pain refractory to local or subcutaneous calcium administration may benefit from regional anesthesia, either in the form of an intravenous infusion (e.g., Bier block), or intra-arterial. Various dilute solutions of calcium have been used, but perhaps the most commonly used solution is a mixture of 10 mL of solution of 10% calcium gluconate in 40 to 50 mL of normal saline infused over 4 hours.[11] If more than 6 hours has elapsed since the time of HF exposure, tissue necrosis cannot be prevented, even though pain relief can be achieved up to 24 hours after exposure.

The intra-arterial infusion technique has potential disadvantages. Arterial spasm or thrombosis may result in significant skin loss. The intra-arterial procedure is more costly because it requires hospitalization for the use of the infusion pump and the monitoring of serum calcium concentrations if repeated infusions are used.

Systemic Toxicity

HF binds calcium and magnesium ions with strong affinity. Systemic manifestations of fluoride toxicity are at least partly related to hypocalcemia and include abdominal pain, muscle fasciculations, nausea, seizures, ventricular dysrhythmias, and cardiovascular collapse. Consequently, patients with significant HF exposure require hospitalization to monitor for cardiac dysrhythmias for 24 to 48 hours. Hypocalcemia can occur after significant exposure to HF and is corrected with the intravenous administration of a 10% calcium gluconate infusion. Calcium chloride can be used, but its administration requires central access. In addition, fluoride ion accumulation has cardiac and neurotoxic effects. Burns as small as 2.5% of the total body surface area have proven fatal in concentrated HF exposure.

Formic Acid

Formic acid is a caustic organic acid used in industry and agriculture. It causes cutaneous injury by inducing a coagulative necrosis. Systemic toxicity occurs after absorption and is manifested by acidosis, hemolysis, and hemoglobinuria. Hemolysis is the result of the direct effect of formic acid on the red blood cells.

Copious wound lavage should be instituted immediately. Acidosis (pH < 7.30) should be treated with sodium bicarbonate. Mannitol may be used to expand plasma volume and promote osmotic diuresis in patients with hemolysis. Exchange transfusion and hemodialysis may be needed in patients with severe formic acid poisoning.

Anhydrous Ammonia

Anhydrous ammonia is a colorless, pungent gas used extensively as a fertilizer in the agricultural setting. It can also be used in the manufacture of explosives, petroleum, plastics, and synthetic fibers. In addition, the “dry cook” or the “Nazi” method of methamphetamine production uses anhydrous ammonia as an amphetamine precursor.[12] As a result of the use of this new method, there has been an increasing number of anhydrous ammonia burns associated with illicit methamphetamine production. In one study the incidence of anhydrous ammonia exposure from methamphetamine production was three times greater than that from agricultural production.[13]

The sudden release of liquid ammonia can cause injury through two distinct mechanisms. First, anhydrous ammonia has an extremely low temperature (−33° C) and freezes any tissue it touches. Second, the ammonia vapors readily dissolve in the moisture in skin, eyes, oropharynx, and lungs to form hydroxyl ions that cause chemical burns by liquefaction necrosis, which can result in full-tissue skin loss. The severity of injury is directly related to the concentration and duration of ammonia exposure. In general, acute exposure to anhydrous ammonia produces the greatest injury to the proximal airway rather than the distal airway.

Treatment consists of prompt irrigation of the eyes and skin with water and management of inhalation injury. If necessary, the airway should be secured through standard intubation methods with a large-diameter tube to prevent distal airway obstruction

www.ketabpezeshki.com 66485457-66963820

from sloughing of mucosa. After intubation, lower airway injury is managed with positive end-expiratory pressure ventilation.

Cement

Cement is a solid material composed of salicylates and calcium aluminates. When dry cement is combined with water, hydrolysis occurs, resulting in a solution of basic lime hydrate. This solution has a pH of 10 to 12. As hydrolysis continues, however, the pH can increase up to 14, which is comparable to the pH of sodium or potassium hydroxide or lye.

There are three types of cement burns. The most common burn is a chemically abrasive form, and heat-related or blast-induced burns can also occur. Heat-related and blast-induced burns are more common in the industrial setting and are associated with severe burns, often involving the respiratory tract.

The treatment of a cement burn attempts to eliminate the toxic component via copious irrigation after all clothes have been removed. Early excision and grafting are often necessary.[14]

Phenol and Derivatives

Phenols are used industrially as starting materials for many organic polymers and plastics. They are widely used in the agricultural, cosmetic, and medical fields. Because of their antiseptic properties, they are also used in many commercial germicidal solutions. A number of phenol derivatives (e.g., hexylresorcinol and resorcinol) are more bactericidal than phenol.

Phenol (carbolic acid) is an aromatic acidic alcohol. Both phenol and its derivatives are highly reactive, corrosive poisons that damage cells by inducing cell wall disruption, protein denaturation, and coagulative necrosis. Their characteristic odor usually signals their presence. After penetrating the dermis, phenol produces necrosis of the papillary dermis. This necrotic tissue may temporarily delay its absorption. Therefore when skin comes in contact with phenol, treatment is instituted immediately. The exposed area is irrigated with large volumes of water delivered under low pressure. Because dilute phenol solutions are more rapidly absorbed through skin than concentrated solutions, gentle swabbing of the skin surface with sponges soaked in water should be avoided. Any hair, including a beard or mustache, that has come in contact with a phenol is removed as soon as possible because the phenol can become trapped in hair.

In animal studies, it was found that exposure to as little as 0.625 mg of phenol per kilogram could be lethal.[2] Systemic toxicity of phenol primarily affects the central nervous system (CNS) and cardiovascular system. In the CNS, toxicity can manifest as stimulation, lethargy, seizures, or coma. Conduction disturbances can be either tachycardic or bradycardic in nature. Marked hypotension may occur as a result of central vasomotor depression, in addition to a direct toxic effect on the myocardial cells and small blood vessels. Hypothermia and metabolic acidosis can also occur.

Dilute solutions of phenol are used by plastic surgeons for chemical face peels. Phenols are usually mixed with water, soap, and croton oil. This solution can produce a partial-thickness burn of a predictable depth in a controlled manner. Phenols have been a standard for many years and are now being used for skin resurfacing to remove wrinkles, irregular pigmentation, and actinic keratosis. The concentration is kept sufficiently low to reduce the occurrence of systemic complications. It is interesting to note that higher concentrations of phenol result in a shallower burn depth because of increased coagulation of the keratin, thereby preventing deeper penetration. Histologic studies have demonstrated that 100% concentrations of phenol produce 35 to 50% less penetration than a 50% solution.

The physician performing phenol chemical peels should be concerned about the possibility of rapid phenol absorption. Even in a controlled setting, ventricular dysrhythmias occur as a result of the phenol application.[15]

Polyethylene Glycol Therapy

Experimental studies indicate that water alone is effective in reducing the severity of burns and preventing death in animals with skin exposed to phenol and its derivatives. The most effective treatment is undiluted PEG of molecular weight 200 to 400 or isopropanol (isopropyl alcohol).[16] Adequate supplies of either PEG or isopropanol should be stocked in hospitals located near areas of phenol use and can often be found in the chemical section of hospital pharmacies. A quick wipe of the skin with PEG solutions reduces mortality and burn severity in experimental animals. These solutions can be used for phenol burns of the face because they are not irritating to the eyes. Decontamination with water should be performed until a PEG solution is obtained. Large amounts of water must be used, however, because small amounts are detrimental, enhancing dermal absorption of phenol. Removal of phenol should be undertaken in a well-ventilated room so that hospital personnel are not exposed to high concentrations of phenol fumes.

Treatment of Systemic Toxicity

The treatment of systemic symptoms is primarily supportive. Respiratory depression may require ventilatory support. Hypotension is initially treated with crystalloid fluids; if fluids are inadequate, vasopressors should be used. Metabolic acidosis can be treated with sodium bicarbonate until the pH is near 7.40. The alkalinization can also help prevent hemoglobin precipitation in the nephron as a result of hemolysis. Benzodiazepines may be required to treat seizures caused by CNS stimulation.

Phosphorus

Phosphorus is a nonmetallic element that exists in three forms: elemental phosphorus, white phosphorus, and red phosphorus. White phosphorus, which is also referred to as *yellow phosphorus*, is widely used in munitions manufacturing, in fireworks, as an ingredient in methamphetamine production, and in fertilizers. Historically, it has also been widely used as a rodenticide. The autoignition temperature (the temperature at which spontaneous combustion can occur) is 30° C (86° F). When white phosphorus comes in contact with air at temperatures above the autoignition point, the phosphorus spontaneously oxidizes, forming phosphorus pentoxide. Phosphorus pentoxide can combine with small amounts of moisture in the air, forming phosphoric acid. In wounds, oxidation of phosphorus pentoxide will continue until it is removed through débridement, neutralized, or consumed.

Tissue injury from white phosphorus appears to have both thermal and chemical causes. The corrosive action of the phosphoric acid results in an exothermic reaction, thereby liberating heat and causing a thermal burn. The hygroscopic action of the phosphorus pentoxide, however, is also responsible for causing a chemical burn. Ultimately, a profound thermal injury can occur, which frequently results in a partial-thickness or full-thickness burn.

Metabolic derangements can also occur after white phosphorus exposure, including hypocalcemia and hyperphosphatemia. Conduction system disturbances, including bradycardia, QT prolongation, and ST and T wave abnormalities, can occur and are at least partially explained by electrolyte derangements. These electrocardiogram changes may explain the sudden early death that occasionally occurs in patients with relatively minor white phosphorus burns.

www.ketabpezeshki.com 66485457-66963820

After oral ingestion of white phosphorus, three stages of toxicity are described, although only rarely do all three stages occur. The first stage is characterized by gastrointestinal tract irritation, including vomiting, abdominal pain, diarrhea, and gastrointestinal bleeding. The stool is occasionally described as being luminescent or "smoking." Hypovolemic shock can result. As many as one third of patients who ingest significant quantities of white phosphorus will die during this stage. The first stage can last 8 to 24 hours. The second stage, which lasts 1 to 3 days, is a latent phase in which symptoms appear to improve. However, the third stage is characterized by multisystem organ failure, including hepatic failure, renal failure, and CNS depression. Renal failure is usually present at days 1 to 4, whereas jaundice typically manifests at days 3 to 5.

The out-of-hospital management involves the immediate removal of contaminated clothing, followed by submersion of the injured skin in cool water. Warm or hot water is avoided because white phosphorus becomes liquid at 44° C (111° F). Phosphorus particles are removed from the victim's skin and submerged in water. The burned skin is covered with towels soaked in cool water during transport to the emergency department.

Red phosphorus can cause some gastrointestinal illness if consumed orally but is much better tolerated than white phosphorus that has been ingested.

After the patient arrives at the emergency department, the burned skin is washed copiously with normal saline. In the past, some advocated use of a suspension of 5% sodium bicarbonate, 3% copper sulfate, and 1% hydroxyethyl cellulose. Other, similar solutions containing copper sulfate have also been described. The use of 0.9% normal saline solution, however, has demonstrated better effects than copper-containing solutions.[17] Although there are some conflicting recommendations in the literature,[18] given that saline is probably at least as efficacious as copper sulfate solutions and has less associated toxicity, saline irrigation is the preferred irrigating solution.

Phosphorus particles can be identified with either ultraviolet light or copper-containing solutions. When a Wood's lamp is used, the phosphorus will fluoresce under an ultraviolet light. Unlike copper-containing solutions, the use of a Wood's lamp is not associated with any adverse or detrimental effects. The use of the copper-containing solutions causes the phosphorus particles to become coated with black cupric phosphide. These black particles are more easily identified and thus more easily removed. Copper sulfate also decreases the rate of oxidation of the phosphorus particles, thus limiting their damage to the underlying tissue. However, because the blackened particles can still cause tissue damage, they should be removed. If a copper solution is used, after 30 minutes of exposure to the burned skin the copper-containing solution must be thoroughly washed from the skin, thereby limiting the development of systemic copper toxicity.

After copious irrigation, decontamination, and treatment of associated electrolyte disturbances, definitive management of the skin burns is accomplished as with any other burn wound. Serum calcium and phosphate levels should be monitored for 24 to 48 hours.

Nitrates and Nitrites

Both nitrates (NO_3^-) and nitrites (NO_2^-) are abundant in modern society. Both sodium nitrate and sodium nitrite are used in food preservatives. Nitrites also have many medicinal uses secondary to their vasodilatory properties. Nitrates are commonly used in electroplating, engraving, and metal casting. Nitrates are also commonly used as fertilizing agents. Exposure to either nitrates or nitrites has been associated with methemoglobinemia.[19]

Reduced hemoglobin contains four heme groups, each with a ferrous (Fe^{2+}) ion. Methemoglobinemia results when the ferrous ion becomes oxidized to the ferric (Fe^{3+}) state. At physiologic levels, there is usually 1 or 2% methemoglobinemia in circulation at any given time. Cyanosis from methemoglobin occurs when methemoglobin concentrations exceeded 1.5 g/dL. Methemoglobin toxicity exists along a spectrum. Many patients with low levels are asymptomatic. When methemoglobin concentrations in nonanemic individuals exceed 20%, headache, anxiety, dyspnea, and tachycardia can occur. Confusion, lethargy, and acidosis typically occur with methemoglobin levels approaching 40 to 50%. Coma, seizures, hypotension, dysrhythmias, and death occur when levels exceed 70%.[20] Patients can develop symptoms at lower methemoglobin percentages in the setting of anemia. However, in the setting of profound anemia, cyanosis may not be apparent. The diagnosis of methemoglobinemia should be sought in any cyanotic patient whose pulse oximetry displays a saturation of 85 to 88% that is unresponsive to oxygen (O_2) therapy and whose arterial blood appears chocolate brown in color. Asymptomatic patients are treated simply by removing the offending agent. For symptomatic patients without glucose-6-phosphate dehydrogenase (G6PD) deficiency, 2 mL of 1% methylene blue per kilogram is administered over 3 to 5 minutes. Symptoms typically improve within 20 minutes. Severe cases may need repeated doses of methylene blue, and very severe cases may require exchange transfusion. Candidates for exchange transfusion include patients with G6PD deficiency with significant toxicity from methemoglobinemia and patients who fail to respond to methylene blue.

Hydrocarbons

Hydrocarbons are a heterogeneous group of organic compounds that are derived from carbon and hydrogen molecules. They have become an integral part of modern society and are found in fuels, solvents, paints, paint and spot removers, dry cleaning solutions, lamp oil, rubber cement, and lubricants.

Hydrocarbons are classified as aromatic, in which the carbon moieties are arranged in a ring, or aliphatic, in which the carbon moieties are arranged in a linear or branched chain. Halogenated hydrocarbons are a subgroup of aromatic hydrocarbons in which one of the hydrogen molecules is substituted with a halogen.

The toxicity from hydrocarbons can affect many different organs, but the lungs are the most commonly affected. The toxicity of hydrocarbons is directly related to their volatility and inversely related to the viscosity and surface tension. The primary toxicity from hydrocarbons occurs from aspiration. Thus substances with high volatility, low viscosity, and low surface tension are most likely to be aspirated.

Systemic toxicity from dermal exposure to a hydrocarbon is relatively rare. Significant dermal exposures can occasionally cause local tissue irritation. Treatment involves removal of the patient from the source and removal of any contaminated clothing. Copious irrigation with warm water should be performed, and burns managed as are other burns.

Chronic dermal exposure can result in a perioral or perinasal dermatitis with pyoderma. This so-called "huffer's rash" is primarily seen with recreational abuse.[21] The hydrocarbon inhalant can dry the skin, thereby causing microscopic cracks and allowing bacteria to enter, causing a bacterial superinfection.

Significant toxicity from inhaled (nonaspiration) exposure to hydrocarbons is also unlikely to produce serious effects. Some patients may develop mild headache, dizziness, nausea, or wheezing. These symptoms resolve after removal of the patient from the source of exposure.

Ingestion of hydrocarbons can result in aspiration and systemic toxicity. After ingestion of hydrocarbons, it is recommended that patients be monitored for 6 hours. Many clinicians advocate obtaining a chest radiograph 6 hours after ingestion, although no randomized study has demonstrated this approach to be superior

www.ketabpezeshki.com 66485457-66963820

to simply observing for clinical manifestations of aspiration (e.g., coughing, gagging, vomiting, wheezing, tachypnea, or hypoxia). There is no role for gastric decontamination. A patient can be discharged home after a 6-hour observation period, assuming no symptoms develop during the observation period and a chest radiograph (if obtained) is negative. All other patients warrant admission to observe for progression of symptoms and treatment of hydrocarbon-induced pneumonitis. Beta-agonists should be administered for bronchospasm, and supplemental oxygen administered as needed. Endotracheal intubation is occasionally required for severe hypoxia. Neither corticosteroids nor empirical antibiotic administration is indicated. Antibiotics may be warranted, however, if a superimposed bacterial infection develops, which will typically occur several days after the pneumonitis develops.

Tar

Burns from hot tar present a treatment challenge. When hot, liquefied tar comes in contact with skin, heat is transferred, and thermal injury results. The tar cools and solidifies on the skin, making removal difficult. There are two types of hot tar: coal tar pitches and petroleum-derived asphalts. Both products are heated to maintain a liquid form. Roofing tar needs to be heated to temperatures of at least 232° C in order to achieve desirable viscosities. Deeper burn injuries are associated with burns from roofing asphalt.

When hot tar touches skin, it rapidly cools, solidifies, and becomes enmeshed in the hair. It is important to facilitate this cooling process by adding cold water to the tar at the scene of the accident. Cooling tar with cold water limits the amount of tissue damage and prevents the spread. The tar is continually washed with water until it has cooled and hardened. After cooling, the skin is dried with towels to prevent systemic hypothermia.

Adherent tar should not be removed at the scene of the accident. In the emergency department, definitive care of tar burn injury involves early removal of tar because it occludes injured skin and encourages bacterial growth. Tar adheres to skin because it is enmeshed in the hair, not because of a direct bond between epidermis and tar.

Solvents used to remove tar ideally should have a close structural affinity to tar. Both petroleum-based aromatic hydrocarbon solvents and surface-active agents, such as polyoxyethylene sorbitan (Tween 80) and polysorbate (De-Solv-it), have been used to facilitate tar removal. The last two agents are more water soluble and may remove tar more easily than the petroleum-based products. Use of these surface-active agents is an effective, safe, and inexpensive means of removing tar from skin. Sunflower oil, NISA baby oil, mayonnaise, and butter have also been used to remove adherent tar from skin, requiring 30 to 90 minutes for complete removal. Sunflower oil has proved effective and safe in removing tar without causing further skin damage.

Asphalts are susceptible to both aromatic (e.g., naphthalene) and aliphatic (e.g., hexade) hydrocarbon solvents, whereas coal tars are susceptible only to aromatic hydrocarbons. Broad-spectrum antibiotic ointments can be used both to help with removal and to help prevent infection. If used, they should be removed and a new coating applied every hour until all the tar has been removed. This process typically takes 12 to 48 hours. Commonly used antibiotic ointments include bacitracin (400 µg/g), polymyxin B (5000 U/kg), and neomycin (5 mg/g). Antibiotic ointment can be used to remove tar layered over the cornea and conjunctiva.

Elemental Metals

The elemental metals, such as lithium, sodium, and potassium, are harmless unless they come in contact with water. When this happens, a violent exothermic reaction occurs that produces heat, hydrogen gas, and hydroxide. The evolved heat is sufficient to ignite the hydrogen gas, which results in further heat production and thermal burns. The formation of the hydroxide compound may also result in significant chemical injury to tissue. The reaction occurs more rapidly with elemental potassium than with sodium. These deleterious effects of potassium have been attributed to trace amounts of potassium superoxide released on exposure to room air. Water lavage is therefore contraindicated in these circumstances.

Miscellaneous Gases

Chlorine and phosgene ($COCl_2$) were both used during World War I as part of chemical warfare. However, today, exposure to chlorine most commonly results from accidental industrial exposure. Phosgene is still used in the production of polyurethanes.

Chlorine is a heavy greenish-yellow gas or liquid with a characteristic odor. The combination of bleach (sodium hypochlorite) with an acid produces chlorine gas, and the combination of bleach and ammonia produces chloramine gas.[22] Both chlorine and chloramine gas produce similar toxicities. The clinical effects observed after chlorine or chloramine exposure are directly related to the time and concentration of the gas. Mild exposure may simply cause mucosal membrane irritation, whereas more severe exposure will induce edema of both the upper airway and the lung parenchyma. With large doses, this edema results in cellular exudates, pulmonary congestion, hemorrhage, and ultimately acute lung injury or acute respiratory distress syndrome.[23] In addition, increased secretions, coughing, dyspnea, wheezing, and chest tightness can be observed. Because these gases are primarily reactive only at a local level, absorbed systemic effects are not commonly observed.

In contrast to chlorine or chloramine, phosgene is much less water soluble. As a result, injury to the lower airways is common, resulting in more severe noncardiogenic pulmonary edema.[24]

The first step in treating an exposure to chlorine, chloramine, or phosgene gas is removal of the individual from the environment. After significant exposure to these agents, the patient's cardiopulmonary status should be assessed. Endotracheal intubation may be required. Bronchospasm is treated with beta-agonists such as albuterol. Irritation of the eyes is managed with copious irrigation with water or saline, followed by an assessment for corneal abrasions if persistent eye irritation is noted. Nebulized 4% sodium bicarbonate can be used for treatment of chlorine or chloramine gas exposure.[25] The role of systemic corticosteroids, if any, has not been established.

Nitrogen oxides include nitrogen dioxide (NO_2), nitric oxide (NO), and nitrous oxide (N_2O). Nitrogen dioxide toxicity can occur from the burning of nitrocellulose, from use of Zamboni machines in poorly ventilated areas, and from silo filler's disease, in which the gas accumulates within a silo of decomposing grain. Nitrogen dioxide fumes can often be easily recognized because of their reddish-brown color. The nitrogen oxides can cause respiratory tract irritation. Toxicity varies somewhat depending on the oxide, but severe toxicity can result in delayed pulmonary edema, hypotension, hemoptysis, and methemoglobinemia.

Zinc or aluminum phosphide pellets are often used as rodenticides. When the phosphide pellets come in contact with water, phosphine (PH_3) gas is formed. In addition, phosphine gas can also be formed during the production of methamphetamine from red phosphorus. Inhalation of phosphine gas produces near instantaneous symptoms. Toxicity occurs via several mechanisms, including free radical formation, inhibition of cytochrome coxidase, and increased lipid peroxidation. Both pulmonary toxicity and gastrointestinal toxicity result after exposure to phosphine gas. Common pulmonary symptoms include cough, chest tightness, and dyspnea, followed later by pulmonary edema

www.ketabpezeshki.com 66485457-66963820

and acute lung injury. Vomiting, diarrhea, and abdominal pain are also commonly encountered. Coma, seizures, hypotension, renal failure, and various dysrhythmias are common.[26] Treatment is largely supportive. Trimetazidine, an antiarrhythmic, has been reported in the treatment of phosphine-induced dysrhythmias but is not currently available in the United States.[27]

Phosgene, phosphene, nitrogen dioxide, nickel carbonyl, diborane, and zinc smoke bombs can cause delayed-onset pulmonary edema. Therefore patients exposed to these chemicals are best admitted for observation, even if asymptomatic early on. In addition, chlorine gas, chloramine gas, cadmium, and polymer fume fever can cause delayed pulmonary edema. However, unlike the former group of gases, with which patients can be asymptomatic for hours and then develop pulmonary edema, delayed pulmonary edema is unlikely with chlorine, chloramine, cadmium, and polymer fume fever in the absence of earlier pulmonary symptoms, and asymptomatic individuals who have been exposed to these chemicals therefore do not require prolonged observation.

CHEMICAL TERRORISM

After the terrorist attack on September 11, 2001, the public has become increasingly aware of chemical terrorism. Despite being banned by the 1925 Geneva Convention, chemical weapons have been used in both the military and the civilian arenas for many years, including the decades preceding the September 11 attack. In the 1980s, chemical weapons were employed against Iraqi civilians. In 1995, Aum Shinrikyo, a Japanese cult, released VX nerve gas in the Tokyo subway, causing 12 deaths and more than 5000 casualties.[28]

As terrorist organizations continue to use unconventional weapons such as chemical and biologic agents, the civilian medical community needs to better understand their characteristics and pathophysiology.

Response

The U.S. government recognizes the emerging threat of terrorism and the potential for terrorist organizations to use nonconventional weapons. Appropriate casualty triage remains a critical component of dealing with unconventional weapons. Triage should be performed by specially trained emergency medical personnel who are familiar with these agents and with the use of PPE. The emergency department could be quickly overwhelmed with masses of noncritically injured survivors. Ideally, triage would be conducted both at the scene of the attack and again at a second point before emergency department arrival. The greatest challenge for emergency departments in caring for these individuals is the sudden increase in patients requiring treatment.[29]

Chemical Agents

Chemical agents are classified as (1) nerve agents, (2) vesicants, (3) choking agents, or (4) cyanide and related toxins (Table 64-1). The first nerve agent documented was tabun, which was synthesized by German chemist Gerhard Schrader in 1937. Schrader developed tabun (military symbol: GA) while researching new insecticides. The following year, sarin (GB) was created. Other popular nerve agents include soman (GD) and VX. Although nerve agents were stockpiled for use during both World Wars, the first documented use in a war was in the 1980s during the Iran-Iraq War. The largest use of nerve agents by terrorists was by the Aum Shinrikyo cult of Japan, which produced both VX and sarin.

Vesicants, also known as *blistering agents,* are a class of drugs that produce blisters at the site of contact. Despite their discovery in the 1800s, their introduction to warfare did not occur until the 20th century. Since World War I, however, sulfur mustard (also known as *mustard gas, mustard,* or *CAS No. 505-60-2*) has remained a constant threat in modern warfare. Other vesicants include lewisite (dichloro-2-chlorovinylarsine), which is an organic arsenical, and phosgene (dichloroformoxime), which is a halogenated oxime. Although phosgene is often considered a vesicant, it technically is not, as the urticarial lesions that develop after contact are not fluid-filled.

Choking agents have been used in both military and civilian settings. Although there are many different agents and uses, the collective term *choking agent* refers to a chemical that can potentially induce pulmonary edema. Phosgene and chlorine are two agents that were used in World War I. Although chlorine is no longer used as a warfare agent, it is still used widely in the industrial setting. Zinc-containing smoke is another choking agent that is used in conventional warfare. Other agents are used for riot control. These agents were discussed earlier in the section on miscellaneous gases.

Cyanide agents, such as hydrogen cyanide or sodium azide, are cellular toxins. Cyanide was discovered in the 18th century by the Swedish chemist Carl Wilhelm Scheele. Today, hydrogen cyanide is one of the most toxic chemicals known, with potential deadly consequences if used by a terrorist organization.

Table 64-1 Common Gases That Can Be Encountered as Weapons of Mass Destruction

CLASS	EXAMPLE*	TREATMENT
Nerve agents	Tabun (GA) Sarin (GB) Soman (GD) Cyclosarin (GF) VX	Atropine and pralidoxime
Vesicants	Mustard agents Mustard, sulfur mustard (H) Distilled mustard, sulfur mustard (HD) Nitrogen mustard (HN1, HN2, HN3) Organic arsenical agents (e.g., lewisite; L) Halogenated oxime agents (e.g., phosgene oxime; CX)	Hydrotherapy Moist dressing on blisters Supportive care
Choking agents	Phosgene (CG) Chlorine (CL) Military smoke (HC) Chloropicrin (PS)	Supportive care
Cyanide agents	Hydrogen cyanide	Cyanide kit Amyl nitrite Sodium nitrite Sodium thiosulfate Hydroxocobalamin

*Chemical or common name (military chemical symbol).

Nerve Agents

The nerve agents are classified as either “G” agents or “V” agents. The nerve agents are all derived from phosphoric acid and are volatile liquids at room temperature. As such, they must be aerosolized or evaporated in order to be used as an inhalational weapon. Because the vapors are heavier than air, they tend to remain close to the ground and will travel downwind and downhill.

The nerve agents work by affecting acetylcholine (ACh). ACh receptors are found on the postsynaptic receptor of cholinergic synapses. These receptors can be either nicotinic or muscarinic. Activation of the nicotinic receptors results in depolarization of the postsynaptic neuron or skeletal muscle cell, whereas

www.ketabpezeshki.com 66485457-66963820

muscarinic activation affects exocrine glands and smooth muscle, primarily in the CNS. Under normal conditions, the enzyme acetylcholinesterase hydrolyzes ACh in the synapse, thereby inactivating ACh. The primary mechanism of action of the nerve agents is to prevent acetylcholinesterase from hydrolyzing ACh. As a result, excess ACh accumulates in the synapse. The effects at the muscarinic receptors include excess secretions and smooth muscle contractions. The mnemonics *DUMBELS* (diarrhea, urination, miosis, bronchoconstriction or bronchorrhea, emesis, lacrimation, and salivation) and *SLUDGE* (salivation, lacrimation, urination, defecation, and gastrointestinal emesis) are often used to describe these effects. The nicotinic manifestations include muscle fasciculations and weakness. The primary clinical toxic effects are respiratory, however, and treatment should be aimed at correcting these effects.

Victims of dermal exposure are undressed and thoroughly decontaminated with large-volume, low-pressure irrigation with water. After decontamination, the initial treatment is aimed at maintaining an airway and restoring adequate oxygenation and ventilation. If rapid sequence intubation is desired for airway management, the paralytic succinylcholine is used with caution because its duration of action will be significantly prolonged, as its normal degradation will be inhibited by the nerve agent. Atropine is a direct-acting antagonist of the muscarinic receptor. Because atropine does not bind to the nicotinic receptors, all nicotinic effects, including weakness or paralysis, will not be reversed. The initial recommended dose is 2 mg of atropine for adults, although much larger doses will likely be required. The endpoint for stopping atropine administration is not improvement in heart rate but, rather, drying of bronchial secretions. Pralidoxime is also administered to patients with suspected or known ingestion with significant symptoms. The traditional dose of pralidoxime is 30 mg/kg (2 g maximum) intravenously over 30 minutes, followed by a maintenance infusion of 8 to 10 mg/kg/hr (650 mg maximum). Pawar and colleagues examined a high-dose strategy of pralidoxime for organophosphate poisoning. In their study, all patients received 2 g of pralidoxime intravenously as a loading dose. Patients were then randomized to receive either 1 g (over 1 hour) every 4 hours for a total of 48 hours or a continual infusion of 1 g/hr for 48 hours. The continual infusion strategy resulted in lower morbidity and mortality compared with the intermittent bolus group.[30] Lastly, benzodiazepines are recommended to prevent and to treat seizure activity. Exact dosage and treatment strategies are not well defined.

For pediatric patients, if accurate weight-based dosage cannot be achieved, children younger than 1 year can receive 0.5 mg atropine, whereas children older than 1 year can receive the standard adult dose of 2 mg atropine as a starting dose.[31]

Vesicants

At temperatures below 14° C, mustard exists in the solid form. Once in the liquid or gaseous form, mustard gas can be recognized by its unique garlic or fishlike odor. Mustard vapor is also much heavier than air and, as a result, tends to remain close to the ground. When stored as an oil-based liquid, it can be readily aerosolized and attached to a bomb or shell. Because vaporization occurs slowly, the risk of injury is much greater in cool environments and closed spaces. Several minutes of exposure can result in skin and eye injury, and exposure for more than 30 minutes can lead to respiratory injury and death.

Mustard gas can enter the body after inhalational, dermal, or oral exposures. After entering the body, it functions as an alkylating agent. The altered molecules then interact with proteins and nucleic acids, forming covalent bonds. Mustard is the only vesicant that does not cause immediate pain. Several hours after exposure, manifestations of exposure occur. After exposure to aerosolized mustard gas, cutaneous manifestations appear after a latent period of up to 24 hours.[32] Initial dermal symptoms include burning, itching, and erythema, followed by hyperpigmentation, vesicle formation, and, later, bullae. Electrolyte depletion and secondary bacterial infection can occur if the affected body surface area is large. In addition, inhaled mustard gas can lead to vomiting and diarrhea. Myelosuppression can occur within 3 to 5 days of exposure, resulting in leukopenia and thrombocytopenia. Direct mucosal damage in the respiratory tract can occur, resulting in bronchiolar damage and hemorrhage. The systemic manifestations can occur with any route of exposure.

Treatment consists first and foremost of removing the patient from the environment and decontaminating the vesicant. Water can be used for decontamination if that is all that is available, but it might not be the preferred agent.[33] Currently, the U.S. military recommends using an alkaline hypochlorite solution (pH 10 or 11) as the decontamination method of choice[33]; a 0.5% hypochlorite solution (diluted household bleach [1:9] is another alternative. However, these solutions should not be used on open abdominal or chest wounds. No specific antidote exists. British antilewisite (BAL; 2,3-dimercapto-1-propanol; dimercaprol) was originally developed as an antidote for lewisite. Although BAL is currently available as a chelator for several heavy-metal poisonings, it should be used cautiously, if at all, for mustard poisonings.

Cyanide

Cyanide salts and hydrocyanic acid are commonly used for metal cleaning, precious metal extraction, photographic processes, electroplating, laboratory assays, and jewelry cleaning. In addition, cyanide gas is often liberated from the combustion of plastic-containing compounds. Iatrogenic cyanide toxicity can result from exposure to cyanogens, including plant or herbal cyanogenic glycosides, nitriles, and nitroprusside. There is concern that cyanide can be used by terrorists as a weapon.

Cyanide is a cellular toxin. It binds to both Fe^{3+} and cobalt. By binding and inactivating the enzyme cytochrome oxidase, which is part of cytochrome a3 on the electron transport chain, cyanide inhibits oxidative phosphorylation. This inhibition results in profound cellular hypoxia and death.

After ingestion of cyanide, patients experience sudden cardiovascular collapse coma and profound metabolic acidosis. A characteristic odor of bitter almonds is frequently discussed but only rarely clinically noted.

Although cyanide levels are confirmatory, they are rarely immediately available and are fraught with difficulty. However, most patients with significant cyanide exposure will have a profound lactic acidosis. In addition, because the cellular utilization of O_2 is blocked, venous blood is highly oxygenated. Therefore an elevated mixed venous O_2 saturation, or an elevated peripheral venous partial pressure of oxygen (PO_2) may be observed.[34] Cyanide toxicity commonly results in shortening of the QT interval, with subsequent "T-on-R" phenomena.[35] The pulse oximeter reading may be near normal in cyanide toxicity, despite significant cellular hypoxia.

A diagnosis of cyanide poisoning requires careful consideration. The initial treatment focuses on maintaining airway, breathing, and circulation (the ABCs). Standard antiarrhythmic medications are appropriate for the treatment of cyanide-induced arrhythmias. Vasopressors may be required.

First responders need to wear PPE when rescuing a patient unresponsive after cyanide gas exposure. Patients with cyanide salts on their skin must have the salts brushed off, followed by topical irrigation; decontamination from other routes of exposure is rarely indicated. Currently, two specific types of antidotes can be used to treat known or suspected cyanide intoxication. One

www.ketabpezeshki.com 66485457-66963820

method of treatment involves the administration of amyl nitrite, sodium nitrite, and sodium thiosulfate. With this combination of medications, amyl nitrite pearls are broken open, and the patient is allowed to breathe a pearl for 30 seconds of each minute. A new pearl is needed every 3 or 4 minutes. Once intravenous access has been established, 300 mg of sodium nitrite (one 10-mL ampule of 3% solution for adults and 0.12-0.33 mL/kg for children) can be administered. Because sodium nitrite is a potent vasodilator, hypotension can ensue. Therefore the sodium nitrite is administered over a minimum of 5 minutes. After sodium nitrite administration, sodium thiosulfate is administered at a dose of 12.5 g (one 50-mL ampule of a 25% solution for adults and 1.65 mL/kg for children). The function of the nitrites is to induce methemoglobinemia. Thiosulfate enhances transulfuration of hydrogen cyanide to thiocyanate, which is renally excreted. If coexisting carbon monoxide toxicity is suspected, as can occur with smoke inhalation, nitrites should be avoided.

In December 2006, the Food and Drug Administration approved hydroxocobalamin (Cyanokit) for treatment of cyanide intoxication. Hydroxocobalamin binds to cyanide to form cyanocobalamin, which subsequently undergoes renal excretion. Hydroxocobalamin appears to be safe for use in both the hospital and the out-of-hospital settings, although there may be a reddish discoloration of the skin.[36] Its use is also associated with alteration in laboratory measurements of magnesium, iron, aspartate aminotransferase, total bilirubin, and creatinine.[37] In treating a patient for known or suspected cyanide toxicity, nitrites and sodium thiosulfate, hydroxocobalamin, or both can be used.

ACKNOWLEDGMENTS

The authors acknowledge the contributions of Richard F. Edlich, Marcus L. Martin, and William L. Long III, who wrote the chapter on chemical injuries for a previous edition.

KEY CONCEPTS

- For chemical injury, the degree of skin destruction is determined mainly by the properties of the toxic agent, its concentration, and the duration of its contact.
- Chemical injuries are commonly encountered after exposures to acids and alkalis.
- Hazmats are substances that can cause physical injury and can damage the environment if improperly handled.
- In dealing with hazmat incidents, two distinct goals must be achieved: (1) The hazmat must be contained, fire and explosions should eventually be extinguished, and the site must eventually be cleaned, and (2) people exposed to the hazmat must be treated.
- Alkali burns tend to penetrate deeper than acidic burns; as a result, alkali burns tend to be associated with greater morbidity.
- HF burns can be associated with significant hypocalcemia.
- Exposure to various toxic gases can occur from routine industrial settings, and knowledge of these agents is necessary for proper treatment by the emergency physician.
- Unconventional chemical weapons may be categorized into four major classifications: nerve agents, vesicants, choking agents, and cyanide agents.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Horton DK, Berkowitz Z, Kaye WE: Surveillance of hazardous materials events in 17 states, 1993-2001: A report from the Hazardous Substances Emergency Events Surveillance (HSEES) system. *Am J Ind Med* 2004; 45:539-548.
2. Lin TM, Lee SS, Lai CS, Lin SD: Phenol burn. *Burns* 2006; 32:517-521.
3. Wedler V, Guggenheim M, Moron M, Künzj W, Meyer VE: Extensive hydrofluoric acid injuries: A serious problem. *J Trauma* 2005; 58:852-857.
4. Andrews K, Mowlavi A, Milner SM: The treatment of alkaline burns of the skin by neutralization. *Plast Reconstr Surg* 2003; 111:1918-1921.
5. Kuckelkorn R, Schrage N, Keller G, Redbrake C: Emergency treatment of chemical and thermal eye burns. *Acta Ophthalmol Scand* 2002; 80:4-10.
6. Brodovsky SC, et al: Management of alkali burns: An 11-year retrospective review. *Ophthalmology* 2000; 107:1829-1835.
7. Sekundo W, Augustin AJ, Strempel I: Topical allopurinol or corticosteroids and acetylcysteine in the early treatment of experimental corneal alkali burns: A pilot study. *Eur J Ophthalmol* 2002; 12:366-372.
8. Blodgett DW, Suruda AJ, Crouch BI: Fatal unintentional occupational poisonings by hydrofluoric acid in the U.S. *Am J Ind Med* 2001; 40:215-220.
9. Roblin I, Urban M, Flicoteau D, Martin C, Pradeau D: Topical treatment of experimental hydrofluoric acid skin burns by 2.5% calcium gluconate. *J Burn Care Res* 2006; 6:889-894.
10. Höjer J, Personne M, Hultén P, Ludwigs U: Topical treatments for hydrofluoric acid burns: A blind controlled experimental study. *J Toxicol Clin Toxicol* 2002; 40:881-886.
11. Graudins A, Burns MJ, Aaron CK: Regional intravenous infusion of calcium gluconate for hydrofluoric acid burns of the upper extremity. *Ann Emerg Med* 1997; 30:604-607.
12. Lee JH, Farley CL, Brodrick CD, Blomquist PH: Anhydrous ammonia eye injuries associated with illicit methamphetamine production. *Ann Emerg Med* 2003; 4:157.
13. Bloom GR, Suhail F, Hopkins-Price P, Sood A: Acute anhydrous ammonia injury from accidents during illicit methamphetamine production. *Burns* 2008; 34:713-718.
14. Poupon M, Caye N, Duteille F, Pannier M: Cement burns: Retrospective study of 18 cases and review of the literature. *Burns* 2005; 31:910-914.
15. Landau M: Cardiac complications in deep chemical peels. *Dermatol Surg* 2007; 33:190-193.
16. Monteiro-Riviere NA, Inman AO, Jackson H, Dunn B, Dimond S: Efficacy of topical phenol decontamination strategies on severity of acute phenol chemical burns and dermal absorption: In vitro and in vivo studies in pig skin. *Toxicol Ind Health* 2001; 17:95-104.
17. Eldad A, et al: Phosphorus burns: Evaluation of various modalities for primary treatment. *J Burn Care Rehabil* 1995; 16:49-55.
18. Chou TD, et al: The management of white phosphorus burns. *Burns* 2001; 27:492-497.
19. Centers for Disease Control and Prevention (CDC): Methemoglobinemia following unintentional ingestion of sodium nitrite—New York, 2002. *MMWR Morb Mortal Wkly Rep* 2002; 51:639.
20. Wright RO, Lewander WJ, Woolf AD: Methemoglobinemia: Etiology, pharmacology, and clinical management. *Ann Emerg Med* 1999; 34:646-656.
21. Williams JF, Storck M: American Academy of Pediatrics Committee on Substance Abuse; American Academy of Pediatrics Committee on Native American Child Health: Inhalant abuse. *Pediatrics* 2007; 119:1009-1017.
22. White CW, Martin JG: Chlorine gas inhalation: Human clinical evidence and toxicity and experience in animal models. *Proc Am Thorac Soc* 2010; 7:257-263.
23. Evans RB: Chlorine: State of the art. *Lung* 2005; 183:151-167.
24. Borak J, Diller EF: Phosgene exposure: Mechanisms of injury and treatment strategies. *J Occup Environ Med* 2001; 43:110-119.
25. Aslan S, et al: The effect of nebulized $NaHCO_3$ treatment on "RADS" due to chlorine gas inhalation. *Inhal Toxicol* 2006; 18:895-900.
26. Rodenberg HD, Chang CC, Watson WA: Zinc phosphide ingestion: A case report and review. *Vet Hum Toxicol* 1989; 31:559-562.
27. Dueñas A, Pérez-Castrillon JL, Cobos MA, Herreros V: Treatment of the cardiovascular manifestations of phosphine poisoning with trimetazidine, a new antiischemic drug. *Am J Emerg Med* 1999; 17:219-220.
28. Lillibridge SR, Sidell FR: *A Report on the Casualties from the Tokyo Subway Incident by the U.S. Medical Team*. Atlanta, Ga: Centers for Disease Control and Prevention; 1995.
29. Macintyre AG, et al: Weapons of mass destruction events with contaminated casualties: Effective planning for health care facilities. *JAMA* 2000; 283:242-249.
30. Pawar KS, et al: Continuous pralidoxime infusion versus repeated bolus injection to treat organophosphorous pesticide poisoning: A randomized controlled trial. *Lancet* 2006; 368:2136-2141.
31. Baker MD: Antidotes for nerve agent poisoning: Should we differentiate children from adults? *Curr Opin Pediatr* 2007; 19:211-215.
32. Saladi RN, Smith E, Persaud AN: Mustard: A potential agent of chemical warfare and terrorism. *Clin Exp Dermatol* 2006; 31:1-5.
33. U.S. Army Center for Health Promotion and Preventative Medicine (USACHPPM): *Chemical*. In: *Medical NBC Battlebook, Technical Guide 244*. Aberdeen Proving Ground, Md: USACHPPM; 2000.
34. Baud FJ: Cyanide: Critical issues in diagnosis and treatment. *Hum Exp Toxicol* 2007; 26:191-201.
35. Wexler J, Whittenberger JL, Dumke PR: The effect of cyanide on the electrocardiogram of man. *Am Heart J* 1947; 34: 163-173.
36. Borron SW, Baud FJ, Barriot P, Imbert M, Bismuth C: Prospective study of hydroxocobalamin for cyanide poisoning in smoke inhalation. *Ann Emerg Med* 2007; 49:794-801.
37. Curry SC, Connor DA, Rashke RA: Effect of the cyanide antidote hydroxocobalamin on commonly ordered serum chemistry studies. *Ann Emerg Med* 1994; 24:65-67.

www.ketabpezeshki.com 66485457-66963820

Section Five

VIOLENCE AND ABUSE

CHAPTER 65

FORENSIC EMERGENCY MEDICINE

William S. Smock

PERSPECTIVE

Clinical forensic medicine is the application of forensic medical knowledge and techniques to live patients in a clinical setting. European, Australian, and British physicians—known as *police surgeons, forensic physicians, forensic medical examiners,* or *forensic medical officers*[1,2]—have a long history of performing clinical forensic examinations,[3] including evaluations of prisoners and victims of physical and sexual assault.[4,5]

All patients who are victims of physical or sexual assault, abuse, or trauma have forensic needs. When treating injuries without consideration of their forensic significance, physicians may misinterpret wounds, fail to recognize victims of abuse or domestic violence, and inadequately describe the physical appearance of the wounds. During the provision of patient care, evidence that can be of critical significance to criminal or civil proceedings can be lost, discarded, or inadvertently washed away,[6-20] despite requirements by The Joint Commission (TJC) to "preserve evidentiary materials and support future legal actions."[21]

Emergency medicine programs have identified and described the need for forensic training in their residency curricula.[9,10,14,22] In 1991 the Department of Emergency Medicine at the University of Louisville School of Medicine collaborated with the Kentucky Medical Examiner's Office and established the first clinical forensic medicine training and consultative program in the United States.[9,13,19,20] In 2006, the American College of Emergency Physicians established the Forensic Medicine Section to provide emergency physicians with additional forensic resources and training.[23] In 2010 the Louisville Police Department created a full-time clinical forensic medicine consultation service to provide forensic evaluations for living victims of crimes, staffed by a forensic emergency physician and three part-time forensic nurse examiners.

Forensic examinations are conducted with the consent of the patient, legal guardian, or court, or by implied consent. The evaluation includes a history and physical examination, photographs, and anatomic diagrams.[22] Evidentiary material, including clothing, hair, blood, saliva, bullets, bomb fragments, and the like, are collected when indicated or when ordered by the court.[24] If a patient has been admitted from the emergency department (ED) to surgery, an evaluation is done in the operating suite in conjunction with the trauma surgeons.[25]

In 2006 the British Royal College of Physicians established the Faculty of Forensic and Legal Medicine (FFLM) as the authoritative body on clinical forensic medicine in the United Kingdom.[26] The FFLM has created training and certification programs and board-type certification examinations after 2 years of forensic practice for British physicians.[26]

Evaluations of gunshot and stab wounds, physical or sexual abuse, domestic violence, and motor vehicle–related trauma should be adequately documented for possible use in future legal proceedings. Documentation should include digital photographs as well as a narrative and diagrams.[7-13,17-22,25] However, in one trauma center, 70% of cases had improper or inadequate documentation, and 38% of cases had potential evidence improperly secured, incorrectly documented, or inadvertently discarded.[8] When physical injuries are misinterpreted and these misinterpretations become the medical record or when valuable evidence is lost or destroyed in the process of providing patient care, there are consequences for the legal proceedings that may follow.[3,6-20,26-30] These acts of omission or commission may deny patients their deserved redress in the justice system. To protect the interests of patients, EDs should implement protocols for wound documentation and evidence collection.[11,12]

FORENSIC ASPECTS OF GUNSHOT WOUNDS

Firearms continue to be the second leading cause of injury-related deaths in the United States—30,913 firearm-related deaths in 2009—after motor vehicle trauma.[31] Emergency physicians treat more than 115,000 victims of gunshot wounds, principally from handguns, each year.[32] The direct and indirect costs associated with gunshot wounds total $36 billion annually.[33]

Errors of Interpretation and Terminology

The emergency physician is in the ideal position to evaluate and document the state of a gunshot wound because he or she sees and explores it before it is disturbed, distorted, or destroyed by surgical intervention.[6-14,27,30] Documentation of gunshot wounds should include the anatomic location of the wound as well as its, size, shape, and distinguishing characteristics, and digital photographs of the wound should be taken. Wounds should be described according to the standard anatomic position with the arms to the sides and palms up.

Clinicians should not describe wounds as "entrance" or "exit" but should document, using appropriate forensic terminology, a detailed description of the wound, including its appearance, characteristics, and location without attempting to interpret the wound type or bullet caliber.[27,34-39] Exit wounds are not always larger than entrance wounds, and wound size does not consistently correspond to bullet caliber.[18,27,36-42]

The size of any wound (entrance or exit) is determined by five factors: the size, shape, configuration or angle, and velocity of the projectile at the instant of impact with tissue and the physical

www.ketabpezeshki.com 66485457-66963820

characteristics of the impacted tissue itself. If the projectile is slowed and its shape unchanged on exiting the skin, the exit wound may be the same size as or smaller than the corresponding entrance wound.[34,41,42] If the projectile increases its surface area by fragmenting or changing its configuration while maintaining a substantial velocity, the exit wound may be significantly larger than the entrance wound.[34,36-42] If the bullet strikes bone, fragments may extrude from the exit wound and contribute to the size and shape of the wound. Tissue elasticity also affects the wound size so that entrance or exit wounds may be smaller, equal to, or larger than the projectile that caused them.[40-42] Wounds on the palm or sole may appear as slits and can be easily mistaken for stab wounds.[34,41,42]

Inappropriate terminology should be avoided.[8,37,41,42] One example of inappropriate terminology is the use of the obsolete term *powder burns,* rather than *soot,* to describe the carbonaceous material associated with close-range wounds.[34,35,41,42] Powder burns are literally the thermal injuries associated with flaming black powder used in muzzle loaders, antique weapons, and blank cartridges. These injuries do not occur with the smokeless powder used in modern ammunition.

It is unnecessary to comment in the medical record on the manner of a gunshot victim's death. The determination of whether a death is accidental, suicidal, or homicidal is the responsibility of the coroner or medical examiner and occurs only after a detailed investigation of the scene and circumstances of the incident. The patient's position at the time of injury can be determined only after an examination of the scene and collection of all forensic evidence.

A treating physician may be requested to render factual testimony, expert testimony, or both in a criminal case. Expert forensic testimony rendered without an appropriate forensic examination or adequate forensic training may mislead participants in the criminal justice system (e.g., "the exit wound is always larger than the entrance wound"). Opinions related to entrance versus exit wounds or the range of fire can affect the determination of innocence or guilt.* The perennial speculation about entrance and exit wounds in the assassination of President Kennedy is one example of the significance of a forensic evaluation.[29,30,44]

Forensic Aspects of Handguns

The Weapon

Handguns are the most common firearm available. There are four categories of handguns: (1) the single-shot weapon (usually a target pistol), (2) the derringer (a small, concealable weapon, usually with two barrels), (3) the revolver (a weapon with a rotating cylinder that advances with the pull of the trigger), and (4) the semiautomatic pistol (which fires with each pull of the trigger). The semiautomatic handgun is the most popular because its magazine, or *clip,* can hold up to 17 cartridges, whereas revolvers hold five or six cartridges.

Handgun Ammunition

The cartridge, or round, is composed of the primer, the cartridge case, the powder, and the bullet (Fig. 65-1). The bullet is the projectile that is propelled out of the muzzle.

The primer is a small explosive charge in the base of the cartridge that ignites the gunpowder. The primer may contain lead, barium, or antimony. These materials may be deposited on the hands of the shooter, on the victim of a close-range assault, or on objects within a room in which the weapon was discharged.[41]

*References 27, 29, 30, 37, 41, 43.

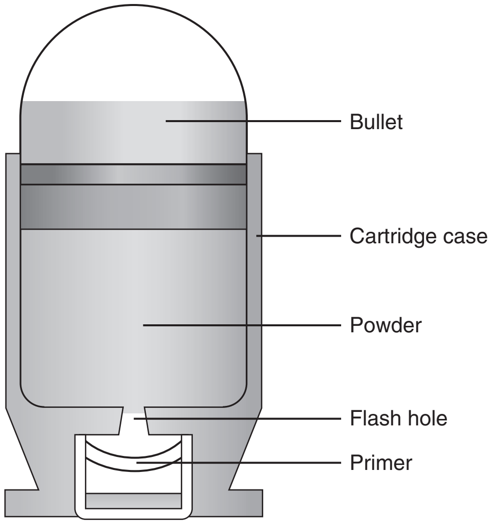


Figure 65-1. A cartridge consists of several distinct components: bullet, cartridge case, gunpowder, flash hole, and primer.

The cartridge case is typically made of brass, although other materials may be used. The function of the cartridge case is to slightly expand, sealing the chamber against the escaping gases and propelling the bullet down the barrel.[41] On detonation, a cartridge case is imprinted with unique microscopic marks that are valuable evidence and should be preserved for law enforcement.

The gunpowder found in all commercial cartridges except blanks is smokeless powder made with a single base (nitrocellulose) or a double base (nitrocellulose and nitroglycerine).[41] When a weapon is discharged, not all of the gunpowder is consumed. A percentage of the unburned or partially burned gunpowder will travel out of the end of the muzzle for a short distance (<48 inches). The distance depends on the physical characteristics and shape of the powder and the weapon's barrel length.

Blank cartridges, muzzleloaders, and other antiques or replicas may use black powder. Black powder (a combination of potassium nitrate, charcoal, and sulfur) does not burn as efficiently as the smokeless powder and results in a large flame and white smoke. It is black powder that produces *powder burns* by igniting clothing.

The bullet is the projectile that is propelled down the gun barrel at velocities ranging from 700 to 1600 ft/s. The higher velocities are achieved by the inclusion of supplemental gunpowder in the cartridge case (a *magnum load,* hence a *.357 magnum*). The diameter of the bullet's base is called its *caliber.* Bullet caliber is described in hundredths of an inch or in millimeters. Handgun bullets range from .22 caliber or 5.56 mm to .45 caliber or 11.3 mm. A bullet's weight is measured in grains, with 7000 grains/lb.

The most common bullet types are the round nose, the full metal jacket, the hollow point, the wadcutter, and the semiwadcutter. Bullets generally are a solid core of lead or steel. If a *jacket* covers the bullet core, the jacket's metal is usually copper or aluminum. If the jacket covers only a portion of the core, the bullet is said to be *semijacketed.* If the core is completely covered, it is said to have a *full metal jacket.* Some bullets have a hole in the tip and are called *hollow points.* The hole causes the bullet to expand on contact, which significantly increases the damage to tissue.

Handgun Wound Ballistics

Wound ballistics is the study of the effects of penetrating projectiles on the body.[39,45-50] Tissue disruption (wound severity) is directly related to the amount of kinetic energy ($KE = \frac{1}{2}mv^2$) transferred to it, not to the total amount of kinetic energy

www.ketabpezeshki.com 66485457-66963820

Table 65-1 Range of Fire

RANGE	INCHES (BARREL TO SKIN)	PHYSICAL PROPERTIES
Contact	0	Soot, seared skin, triangular tears
Close	0-6	Soot, abrasion collar (abrasion collar may be obscured by soot)
Intermediate	<48	Tattooing, abrasion collar
Distant or indeterminate	Any distance	Abrasion collar (intermediate objects will prevent soot and gunpowder from contacting the skin)

possessed by the bullet.[39,41,45] Bullets fired from rifles generally have a higher velocity (1500 to 4000 ft/s) than do those fired from handguns (700 to 1600 ft/s). Rifle bullets have more kinetic energy and therefore a theoretically higher wounding potential, but wound severity is the result of multiple variables, the most important of which are bullet type (weight, deforming type, fragmenting type), bullet velocity, and the characteristics, location, and nature of the impacted tissue itself (tissue over bone or tissue over organs).[39,41,46-50]

The principal mechanism for tissue damage by bullets is crushing. A bullet traveling through tissue generates two cavities, one permanent and the other temporary. The temporary cavity, a result of tissue stretching, lasts 5 to 10 msec from its generation until its collapse and leaves behind the permanently crushed tissue and the permanent cavity.[39,41,45] The size of the permanent cavity varies with the size, shape, and configuration of the bullet. A hollow-point bullet that mushrooms can increase its diameter 2.5 times on impact and will increase the area of tissue crush 6.25 times compared with a nondeformed bullet.[41]

Forensic Evaluation of Handgun Wounds

Entrance Wounds

Range of fire is the distance from the muzzle to the victim and can be divided into four general categories: contact, near-contact or close range, intermediate or medium range, and indeterminate or distant range (Table 65-1). The size of the entrance wound does not correlate with the caliber of the bullet[41] because the entrance wounds over elastic tissue will contract around the tissue defect and have a diameter much less than the caliber of the bullet.[34,41]

Contact Wounds. There are three subcategories of contact wounds: (1) tight contact, in which the muzzle is pushed hard against the skin; (2) loose contact, in which the muzzle is incompletely or loosely held against the skin; and 3) contact through clothing.

In a tight contact wound, all material—the bullet, gases, soot, the incompletely burned pieces of gunpowder, and metal fragments—is driven into the wound. These wounds can vary from a small hole with seared blackened edges from the discharge of hot gases and an actual flame to a gaping stellate wound (Fig. 65-2). Large wounds occur when the wound is inflicted over thin, inelastic or bony tissue, and the injected hot gases cause the skin to expand until it stretches and tears. These tears will have a triangular shape, with the base of the triangle overlying the entrance wound. Tears are generally associated with .32 caliber or greater, or magnum loads. Large stellate contact wounds are easily misinterpreted as exit wounds if the determination is based solely on their size (see Fig. 65-2B).[34,41]

Stellate tears are not pathognomonic for contact wounds, however. Tangential wounds, ricochet or tumbling bullets, and some exit wounds may also be stellate. These wounds' appearance differs from a tight contact wound's by the absence of soot and powder within the wound and a lack of seared wound margins.[34,41,42]

In some tight contact wounds, expanding skin is forced back against the muzzle of the gun, leaving a characteristic muzzle abrasion or muzzle contusion (Fig. 65-3).[34,41,42] Patterns such as these should be documented before wound débridement or surgery because they are helpful in determining the type of weapon used (revolver vs. semiautomatic).[25,41]

When a gun's muzzle or barrel is in loose contact with or is angled to the skin, the soot and gunpowder residues are present both within and surrounding the wound. The angle between the muzzle and the skin determines the soot pattern. A tangential, loose, or near-contact wound produces an elongated searing and soot deposit surrounding the wound.

Discharge of a weapon in contact with clothing results in the gases and soot being deposited between the garment and the skin. This results in a diffuse pattern of soot surrounding a wound with seared margins (see Fig. 65-2C).

Close-Range Wounds. Close range is the maximum range at which soot is deposited on the wound or clothing. The muzzle-to-target distance is usually less than 6 inches but may be as much as 12 inches.[40-42] Beyond 6 inches, most of the soot usually falls away and does not reach the skin or clothing. The concentration of the soot varies inversely with the muzzle-to-target distance and is influenced by the type of gunpowder and ammunition used, the length of the weapon's barrel, and the caliber and type of weapon itself (Fig. 65-4).

A precise range of fire (e.g., 2 inches vs. 5 inches) cannot be determined from examination of the wound alone. A forensic firearms examiner can attempt to reproduce the patient's soot pattern on a target by test-firing the offending weapon at different ranges using ammunition similar to the ammunition that caused the wound (Fig. 65-5). The validation of this test and the determination of a range of fire depend on the accuracy and detail in the physician's report regarding the size of the soot pattern. Because soot can be removed with débridement or wound cleansing, its presence and configuration around the wound should be noted and photographed before débridement unless the patient's clinical condition precludes this attention to detail.[25]

Intermediate-Range Wounds. *Tattooing,* or *stippling,* is pathognomonic for an intermediate-range gunshot wound. Tattooing appears as punctate abrasions and is caused by contact with partially burned and wholly unburned pieces of gunpowder (Fig. 65-6). Tattooing or stippling cannot be wiped away. Tattooing rarely occurs on the palms of hands or soles of feet because of the thickness of the epithelium.[41]

Tattooing may occur as close as 1 cm to and as far away as 1.3 m from the weapon but is generally found at distances of 60 cm or less.[40-42,51] The density of the tattooing and the associated pattern depend on the length of the barrel, the muzzle-to-skin distance, the type of gunpowder, the presence of intermediate objects, and the caliber and type of ammunition. Clothing, hair, or other barriers may prevent tattooing from occurring. The presence of partially or entirely unburned pieces of gunpowder and gunpowder residues on clothing or skin aids in determining the range of fire. On rare occasion, pieces of gunpowder can penetrate thin clothing and leave punctate abrasions (Fig. 65-7).

Long-Range Wounds. The distant or long-range wound is inflicted from far enough away that only the bullet makes contact with the skin. There is no tattooing or soot. As the bullet penetrates the skin, the skin is indented, resulting in the creation of an *abrasion collar,* also called an *abrasion margin, abrasion rim,* or *abrasion ring* (Fig. 65-8).[41,42] This collar is an abraded area of tissue that surrounds an entry wound as the result of friction between

www.ketabpezeshki.com 66485457-66963820

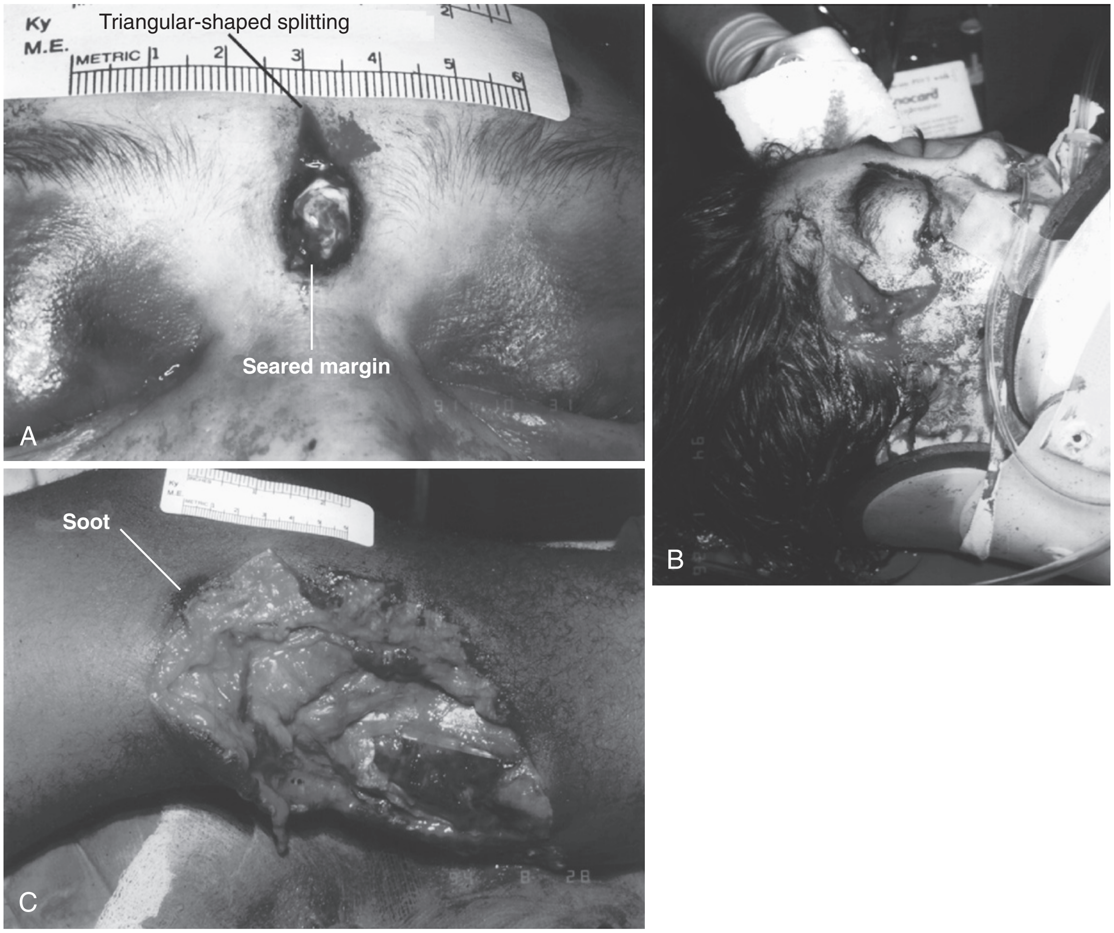


Figure 65-2. A, Tight-contact entrance wound from a .38-caliber revolver. The wound margins are seared from the discharge of hot gases and an actual flame from the end of the barrel. The triangular tear is the result of tissue expansion from the discharge of gases into the tissue. **B,** Tight-contact entrance wound with large stellate tears from a .380 semiautomatic pistol. The large triangular tears are the result of rapid expansion of gases under the skin. **C,** Tangential-contact wound from a 9-mm pistol on the medial aspect of the left calf. The presence of soot at the superior aspect indicates a close range of fire. The patient initially reported that he was shot from a distance of 3 or 4 feet and later admitted that he had accidentally shot himself while withdrawing his pistol from his boot. Large wounds as seen in B and C may be misinterpreted as exit wounds because of their size.

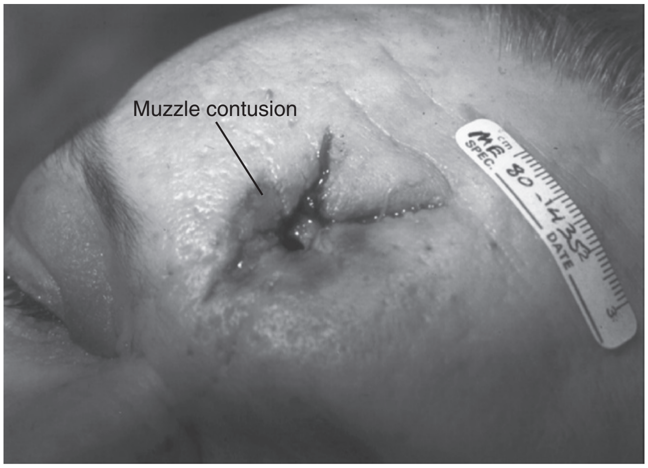


Figure 65-3. A muzzle contusion is a contusion caused by skin expansion against the barrel of the weapon. Muzzle contusions are associated with contact wounds.

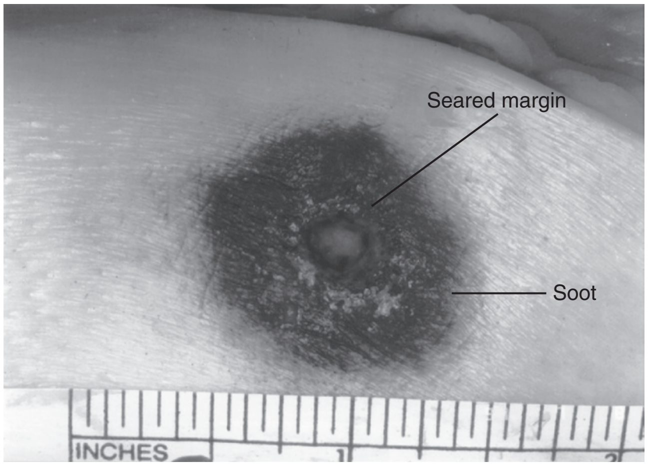


Figure 65-4. Close-range wound with soot deposition. Soot is associated with a range of fire of 6 inches or less.

www.ketabpezeshki.com 66485457-66963820

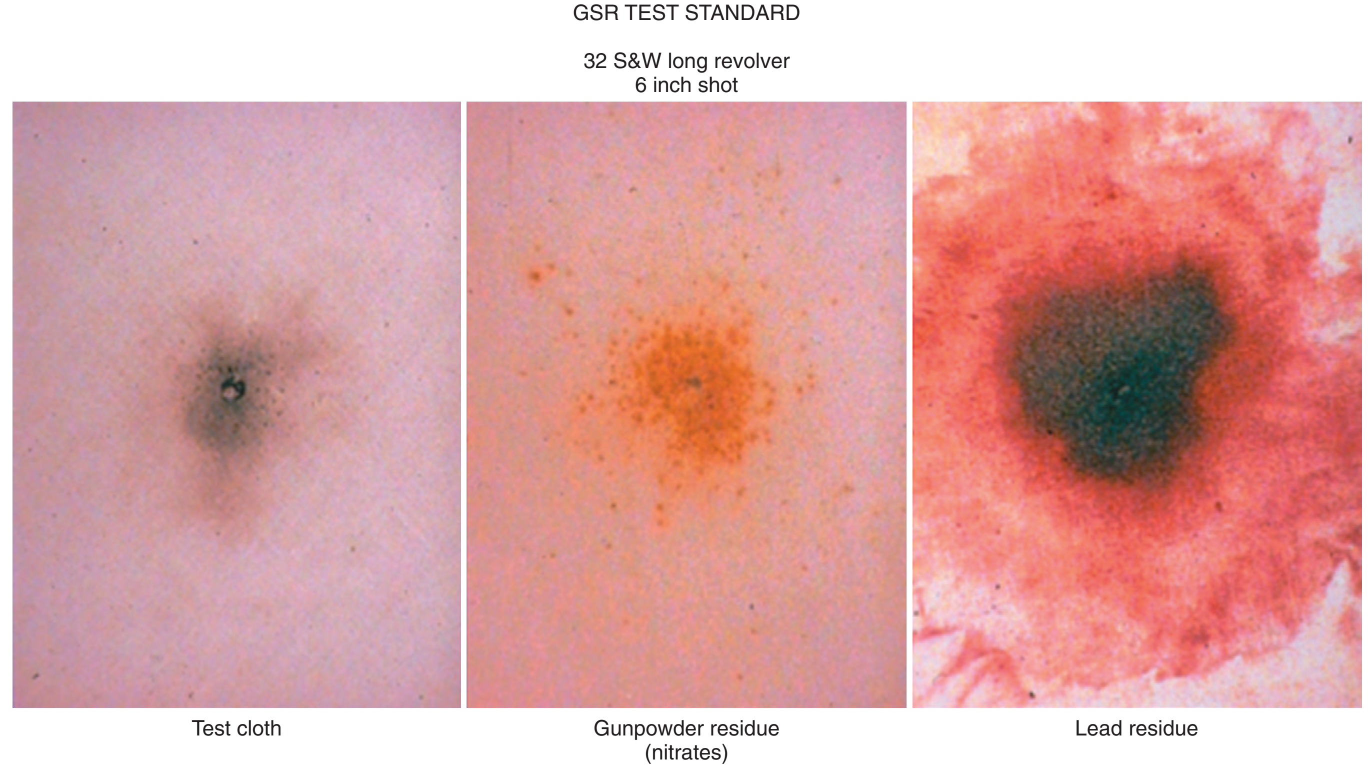


Figure 65-5. Gunshot residue testing conducted at 6 inches with a .32-caliber revolver. The testing searches for the presence of soot (burning of gunpowder), nitrites (unburned gunpowder), and vaporized lead residue. These tests determine the range of fire from the barrel to the clothing.

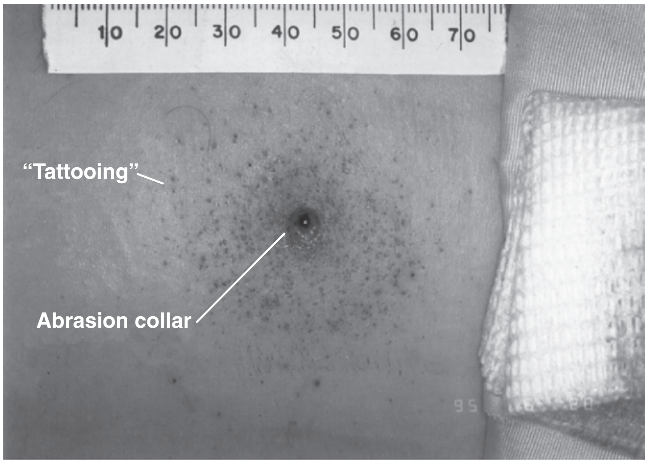


Figure 65-6. Tattooing results from contact with pieces of unburned gunpowder. These punctate abrasions are associated with an intermediate range of fire, generally less than 36 inches. The density of these abrasions depends on the length of the gun's barrel, the distance from the muzzle to the skin, the type of gunpowder used, and the presence of any intervening objects.

Figure 65-7. Gunpowder can penetrate thin clothing and deposit tattooing on the skin. A 3-year-old was shot with a .45-caliber round at close range, and pieces of gunpowder passed through the T-shirt.

the bullet and the epithelium. The width of the abrasion collar varies with the angle of impact. Most entrance wounds will have an abrasion collar. Entrance wounds on the palms and soles are exceptions. These usually appear slitlike.[41]

The abrasion collar is not the result of thermal changes associated with a hot projectile. The abrasion collar of a contact or close-range wound may be undetectable because hot gases and a flame have seared the tissue. When an abrasion collar is the only visible superficial clinical finding present, *indeterminate range* describes the range of fire. A wound inflicted from 10 feet will appear the same as a wound inflicted from 100 feet. An exact range cannot be determined with a distant wound.

Determining the range of fire may be complicated when clothing prevents the deposition of soot and powder on the skin. Without the overlying clothing or without information regarding the crime scene, the wound may appear to be from a distant range of fire. In reality, the range may have been close or intermediate. Conversely, a projectile discharged from a distant range of fire may

www.ketabpezeshki.com 66485457-66963820

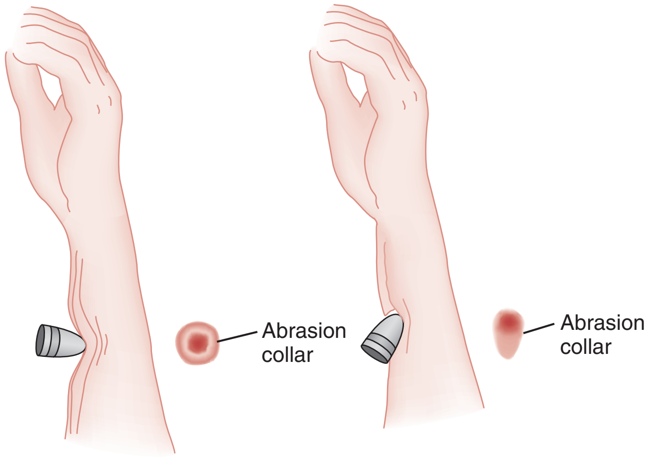


Figure 65-8. An abrasion collar is the abraded area surrounding the entrance wound created by the bullet when it indents and passes through the epithelium. The collar or rim is the result of friction between the bullet and the epithelium. The width of the abrasion collar will vary with the angle of impact.

mimic an intermediate range if it strikes an object, such as glass, that fragments. As with unburned gunpowder, when the glass fragments strike the skin, they may also cause punctate abrasions, resulting in pseudotattooing (Fig. 65-9).[41,52]

Atypical Entrance Wounds. Atypical entrance wounds occur when a bullet encounters an intermediate object, such as a window, wall, or door, before striking the victim. The intermediate object may change the bullet's size, shape, or path. Such changes can result in entrance wounds with large stellate configurations that mimic close-range or contact wounds (Fig. 65-10).[53,54] Ricochet bullets may also cause atypical entrance wounds.

Graze wounds are atypical wounds from tangential contact with a passing bullet. Directionality of the bullet may be determined from a close examination of the wound.[41,55,56] The bullet produces a trough with the formation of skin tags on the lateral wound margins that point toward the weapon and away from the direction in which the bullet was traveling (Fig. 65-11).[55]

Exit Wounds

Exit wounds are the result of a bullet pushing and stretching the skin from the inside out. The skin edges generally are everted with sharp but irregular margins.

The size of the exit wound is determined by the energy transferred from the bullet to underlying tissue and by the bullet's size and configuration as it exits the skin (Fig. 65-12).[41,42] When a bullet enters the skin, its configuration may change from its usual nose-first attitude owing to tumbling and yaw. A bullet that exits the skin sideways, or one that has increased its surface area by mushrooming or transferring its energy to underlying bone, will have an exit wound larger than its entrance wound.[34,41]

Atypical Exit Wounds. A shored-exit wound is a wound that has an associated false abrasion collar. If the skin is pressed against or supported by a firm object or surface at the moment the bullet exits, the skin can be compressed between the exiting bullet and the supporting surface (Fig. 65-13).[41,42,57] Examples of supporting structures include belts, floors, walls, doors, chairs, and mattresses.

Rarely, soot may also be present at an atypical exit wound site.[58] If a contact entrance wound is located close to its associated exit wound, soot can be propelled through the short wound track and appear faintly on the exit wound surface (Fig. 65-14).

Figure 65-9. "Pseudotattooing" or punctate abrasions from glass fragments, not unburned gunpowder, on the medial aspect of the thigh associated with a gunshot wound. The leg was showered with glass fragments after the round penetrated the windowpane.

Forensic Evaluation of Centerfire Rifle Wounds. Projectiles discharged from centerfire rifles have the potential to inflict massive tissue damage (Fig. 65-15). A bullet's wounding potential is based on the kinetic energy it possesses. Centerfire bullets, .223 to .308 caliber, are similar in diameter to handgun ammunition, but based on the formula for kinetic energy ($KE = \frac{1}{2}mv^2$), their wounding potential is greatly enhanced by the higher velocity of the round.[41] Injuries result from the transference of energy from the projectile to tissue, organs, and bony structures. With medium-velocity rounds (2000-3000 ft/s) and high-velocity rounds (>3000 ft/s), a temporary cavity is formed along the wound tract, which may be 11 or 12 times the diameter of the bullet. High velocity rounds can also cause tissue damage away from the physical tract taken by the projectile.[45] Because of the amount of energy possessed and transferred to underlying tissue, exit wounds associated with centerfire rifles, in contrast to those associated with handguns, are generally larger than their corresponding entrance wounds (see Fig. 65-15).[41,42]

Entrance wounds associated with high-velocity, centerfire projectiles do not significantly differ from those of handguns. Entrance wounds will generally exhibit abrasion collars or microtears on the skin surface (Fig. 65-16). Wounds will also have associated soot deposition and tattooing, but because of a number of variables, such as muzzle length, amount of power in a given cartridge, muzzle configuration, and type of gunpowder, the range of fire in

www.ketabpezeshki.com 66485457-66963820

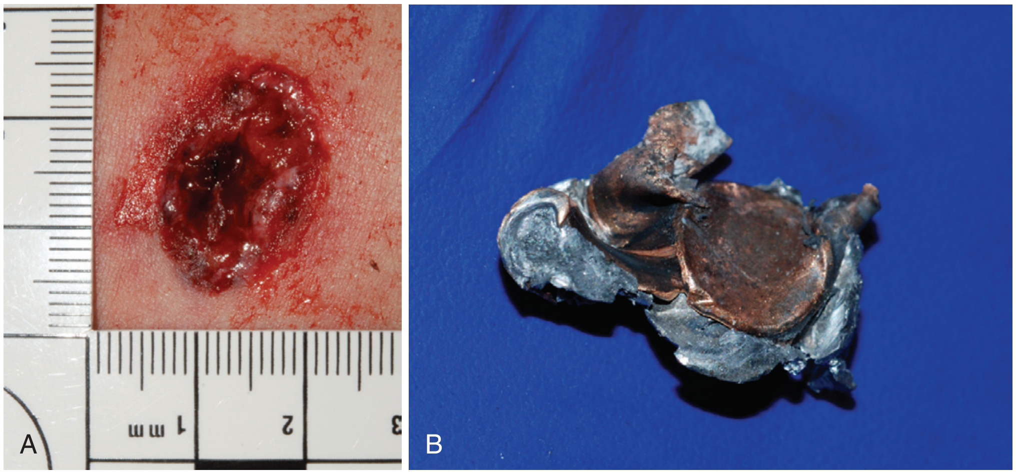


Figure 65-10. **A,** An atypical entrance wound from impact with a .40 caliber bullet. **B,** The projectile was deformed as it penetrated a windshield.

Figure 65-11. Graze wounds occur from tangential contact with a projectile. The directionality of the bullet in some cases can be determined from an examination of the skin tags on the lateral margins of the wound.

rifle wounds is not as clearly defined as in handgun wounds. The determination of an exact range of fire for rifles and shotguns is best established through controlled testing performed by a firearms examiner at a crime laboratory.

High-velocity bullets with jackets and lead cores generally break up into hundreds of fragments, called a "lead snowstorm," on entering tissue, resulting in significant tissue damage (Fig. 65-17).[41] If the tissue they penetrate is deep, the bullet fragments may fail to exit and remain embedded. It is therefore possible to sustain an injury from a high-velocity round and not exhibit an exit wound. High-velocity rounds with steel cores will almost uniformly exit intact.

Forensic Evaluation of Shotgun Wounds. Shotguns, have the barrel length of rifles, but can discharge pellets or single slugs down a smoothbore barrel. The caliber of a shotgun is defined by the term *gauge.* Historically, the gauge of a gun referred to "the number of lead balls of the given bore diameter that make up a pound"—for example, 12 lead balls to make 1 lb.[41] A shotgun cartridge may contain only a single slug or may contain hundreds of pellets (Fig. 65-18A). Pellets range in diameter from 0.05 inch (#12 birdshot) to 0.36 inch ("000" buckshot). A shotgun cartridge is made of several components that will be of forensic value and should be collected in the ED (Fig. 65-18B).

Shotgun slugs are single projectiles that may weigh 200 times more than handgun ammunition—for example, a 12-gauge slug weighs 547 grams, and a .22 long rifle bullet weighs 2.6 grams (see Fig. 65-18B). The massive damage caused by slugs may obliterate the abrasion collar usually associated with entrance wounds. Shotgun slugs will almost uniformly exit the body with large exit wounds. The velocities of shotgun slugs are in the range of 1500 to 1800 ft/s.

Microscopic Examination of Wounds

The débrided epithelial margins of wounds should be submitted to the pathology department for a histologic examination. The microscopic presence of soot, gunpowder, and thermal damaged will help determine if the wound is an entrance or exit wound and the range of fire.[58-60]

Evidence

A victim's clothing may yield information about a bullet's range of fire and help distinguish entrance from exit wounds.* Clothing fibers will deform in the direction of the passing projectile.[41,56] Gunpowder residues and soot will deposit on clothing as they do on skin. Residue may be invisible to the naked eye, but nitrites and vaporized lead can be visualized with standard forensic staining techniques. Some bullets, as they make initial contact with clothing, leave a lead or lubricant residue that is termed *bullet wipe.* Articles of clothing removed from a wounded patient need to be placed in separate paper bags to avoid cross-contamination of evidence.[11,17]

A gunshot residue (GSR) test may determine whether a victim or suspect has been in proximity to a weapon that has been discharged.[41,61-70] The GSR test checks for the presence of invisible residues from the primer: barium nitrate, antimony sulfide, and lead peroxide. The presence of residue can be checked by

*References 7, 11, 12, 22, 24, 41, 61.

www.ketabpezeshki.com 66485457-66963820

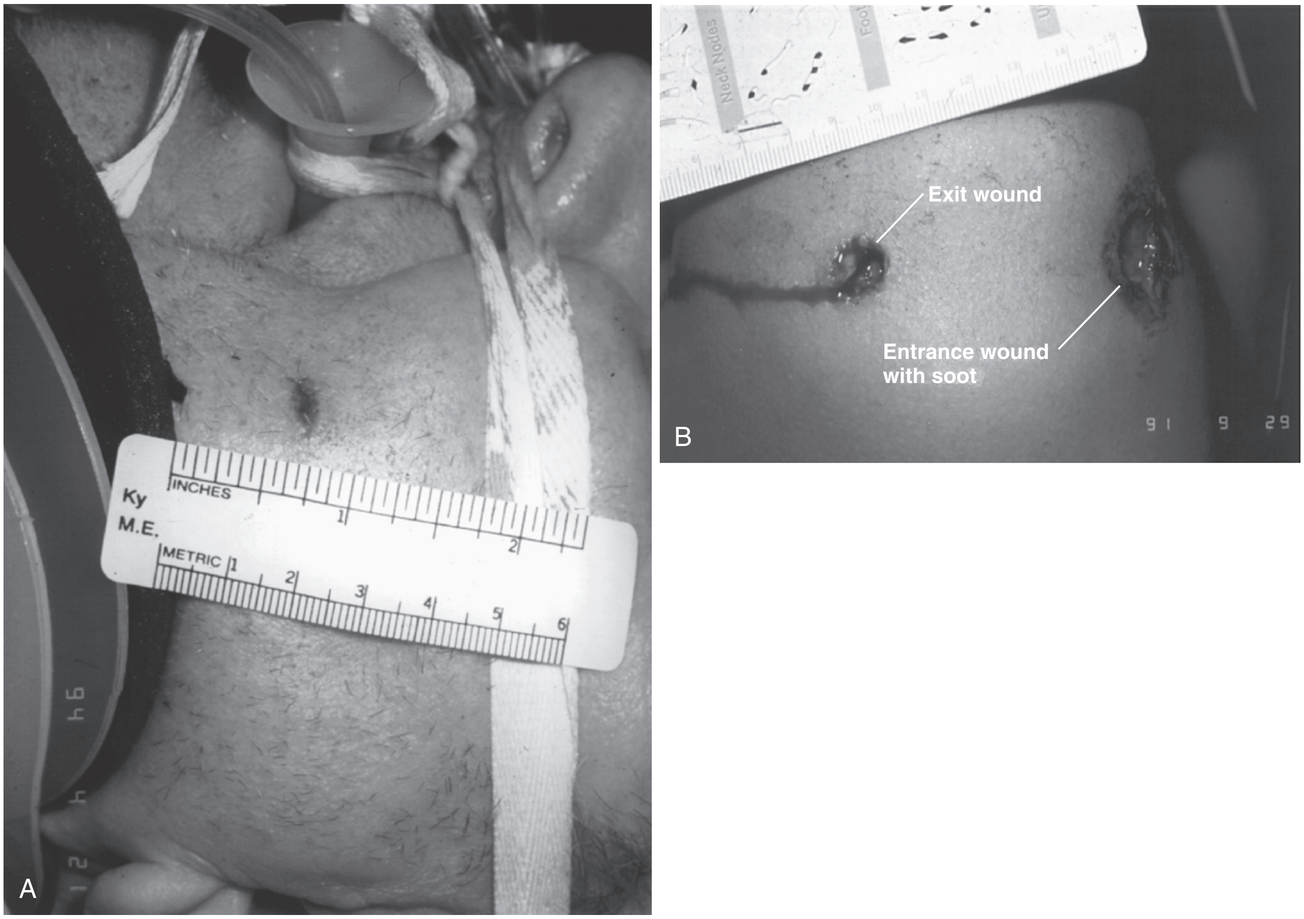


Figure 65-12. A, Slitlike exit wound from a .22-caliber bullet. B, Perforating gunshot wound to the left deltoid area with soot deposition around the larger entrance wound. No soot is present around the smaller exit wound. Exit wounds are *not* consistently larger than their corresponding entrance wounds.

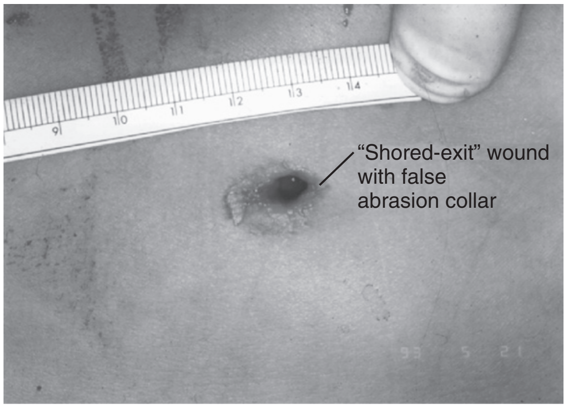


Figure 65-13. Shored-exit wound with a false abrasion collar. This type of wound occurs when the skin in the region of the exiting bullet is in contact with a supporting structure (e.g., a wall, floor, or mattress). The skin is slapped against the supporting structure, which results in a false abrasion collar.

Figure 65-14. Soot can be associated with an exit wound. The patient sustained a contact wound to the posterior aspect of the ear and the soot was forced thorough the tissue and deposited anterior to the ear.

www.ketabpezeshki.com 66485457-66963820

Figure 65-15. This patient sustained a high-velocity gunshot wound to the forehead. High-velocity rifle rounds, due to their kinetic energy, can cause massive damage when the energy is transferred to underlying tissue.

Figure 65-16. **A,** An exit wound from a high-velocity rifle round. Exit wounds from high-velocity rounds are generally larger than their corresponding entrance wounds. The large size is a result of energy transfer from the projectile to underlying tissue with the expelling of tissue, principally bone. **B,** An entrance wound from a high-velocity rifle round. Entrance wounds of high-velocity projectiles will also display an abrasion collar.

(1) swabbing the palms and the dorsum of the hands with a 5% nitric acid solution and then analyzing the swabbed contents with atomic absorption spectrophotometry or (2) placing tape or an adhesive disk on the hands and then removing it for examination under a scanning electron microscope.

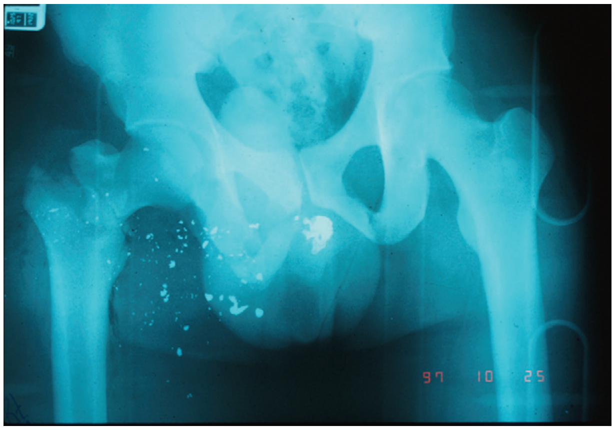


Figure 65-17. A "lead snowstorm" from a high-velocity rifle round. High-velocity projectiles have a tendency to fragment into hundreds of tiny particles on contact with bone. This fragmentation contributes to the massive tissue damage associated with these projectiles.

The specificity and sensitivity of the GSR test are unclear.[41,61,69,70] Residue will deposit on the hands of the individual who fired the weapon in only 50% of cases.[41] Residue may spread throughout a crime scene, and secondary contact with the weapon or furniture on which residue was deposited will result in a false-positive test result. The transference of residue from police officers to suspects has also been reported.[70] The sensitivity of the test decreases with time, and law enforcement agents may not have access to a patient during the "golden hour."[41] Actions that decrease sensitivity include washing the skin with alcohol or betadine, placing tape on the skin, rubbing the hands against clothing, and placing plastic bags over the patient's hands, which precipitates moisture on the skin. If a GSR test is to be performed or if soot is noted on the patient's hand, paper bags should be placed over the hands early in the treatment.

The bullet, the bullet jacket, and the cartridge case are invaluable for identifying or excluding a suspect weapon.[40,41] When a weapon is discharged, the discharge imprints multiple microscopic marks on the side of a bullet and on the bottom or side of the cartridge case.[40,41] The markings result from the bullet's contact with the tool marks or "rifling" in the gun's barrel. These marks are unique to each barrel and are reproducible. These marks are the gun's "fingerprint," so to speak. Cartridge case marks are from contact with the firing pin, the breech lock, the magazine of semiautomatic weapons, and extractor and ejector mechanisms. These microscopic "fingerprints" can be obliterated by removing a bullet with hemostats or pickups.[11,17,41] Bullets should be handled with gloves, and the tips of surgical instruments should be covered with gauze (Figs. 65-19 and 65-20) or plastic tips—"suture booties"—to ensure the preservation of these microscopic marks. It is not necessary to place initials or other markings on the bullet if adequate notes are made in the patient's medical record regarding the chain of custody.[11,17]

Radiographs also help locate retained projectiles and may be of evidentiary value in determining the number of projectiles and the direction of fire.[39-41,71]

FORENSIC ASPECTS OF PHYSICAL ASSAULT

Identifying Assault Victims

Studies estimate that up to 22 to 33% of patients in urban EDs are victims of domestic violence, yet very few are recognized as such.[28,72-85] In a study of victims of domestic violence, 43% of

www.ketabpezeshki.com 66485457-66963820

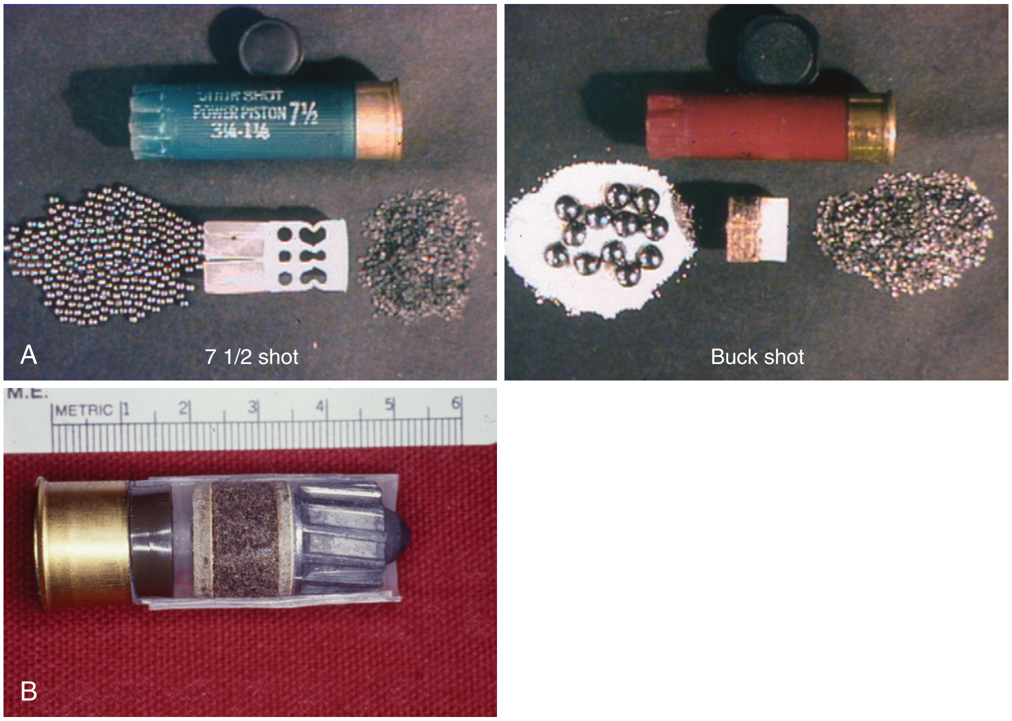


Figure 65-18. **A,** Shotgun cartridges may contain eight to hundreds of pellets. **B,** A single shotgun slug and components of the cartridge.

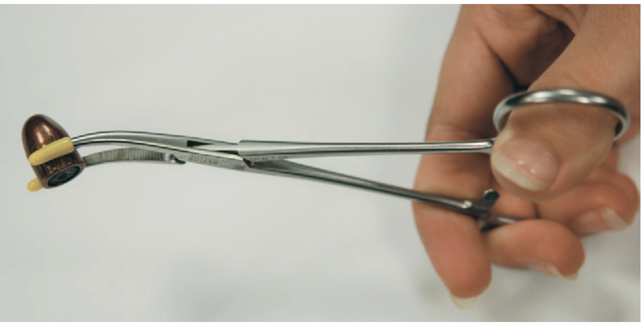


Figure 65-19. To determine whether a projectile was discharged from a specific weapon, firearms examiners use microscopic marks on the surface of the bullet.

patients with acute trauma came to the ED six or more times before they were identified as victims of abuse; nearly half of these patients came to the ED at least 12 times.[84] Victims admitted to the trauma service also go unrecognized.[85]

Every weapon leaves a mark, design, or pattern stamped or imprinted on or just below the epithelium. The epithelial imprints of these weapons, called *pattern injuries*, are consistently reproducible.[19,25,35,86] These injuries are classified into three major categories according to their source: blunt force, sharp force, and thermal.

Accurate documentation of the anatomic location of the injuries makes it easier to determine the implement, tool, or weapon responsible for producing each wound.

Blunt Force Pattern Injuries

The most common blunt force injury is the contusion, along with abrasions and lacerations. A weapon with a unique shape or configuration may stamp a mirror image of itself on the skin (Box 65-1).[19,35,86]

Pattern Contusions. A blow from a linear object leaves a contusion that is characterized by a set of parallel lines separated by an

Figure 65-20. Hemostats should be covered with gauze or plastic tips when bullets are being removed. Metal-to-metal contact destroys the microscopic marks that are used to identify the weapon from which the bullet was discharged.

area of central clearing (Fig. 65-21).[19,35,86] The blood underlying the striking object is forcibly displaced to the sides, which accounts for the pattern's appearance (Fig. 65-22).

Circular or linear contusions suggest abuse or battery. Circular contusions 1.0 to 1.5 cm in diameter are consistent with fingertip

www.ketabpezeshki.com 66485457-66963820

Box 65-1 Commonly Inflicted Pattern Injuries

Slap marks with digits delineated
Looped or flat contusions from belts or cords
Circular contusions from fingertip pressure
Parallel contusions with central clearing from linear objects
Contusions from shoe heels and soles
Semicircular contusions and abrasions from bite marks

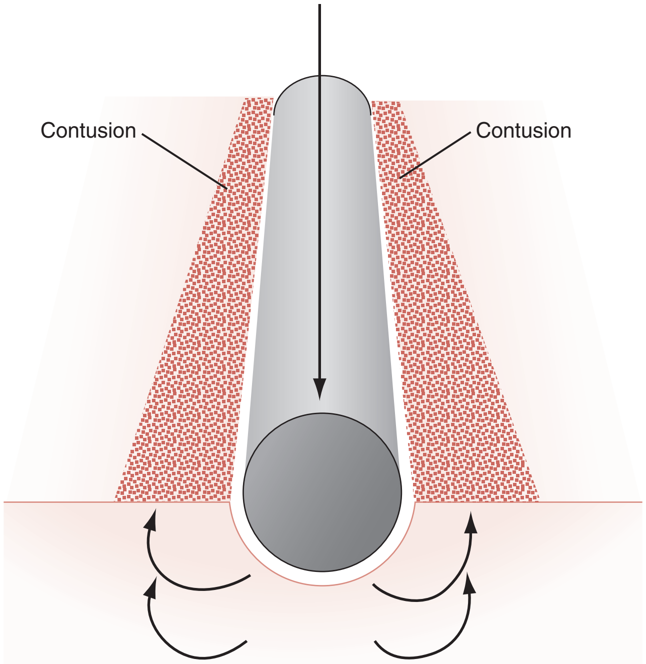


Figure 65-21. A direct blow from a linear object results in a pattern contusion with central clearing surrounded by parallel linear contusions. The blood directly beneath the impacting object is displaced laterally and accounts for the distinctive contusion.

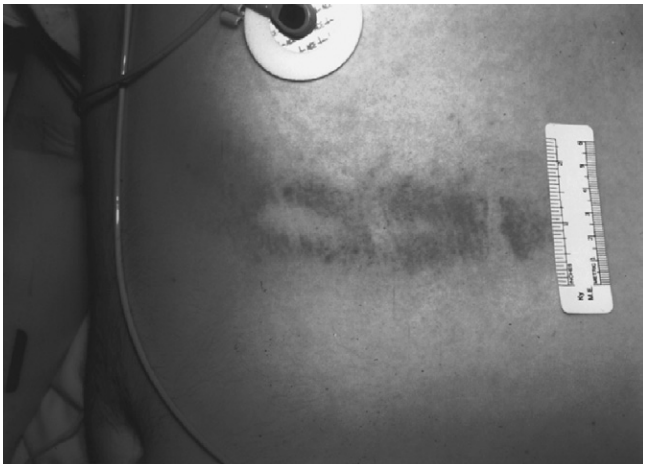


Figure 65-22. Pattern contusion with parallel lines and central clearing from contact with a baseball bat.

pressure and grab marks (Fig. 65-23). One commonly overlooked anatomic location for fingertip pressure contusions is the medial aspect of the upper arm.[35,86] The sole of a shoe from a kick or stomp may also leave a pattern contusion that can assist in identifying the assailant (Fig. 65-24).

Figure 65-23. Circular contusions documented on the medial aspect of the upper arm. These injuries resulted from fingertip pressure applied during an assault.

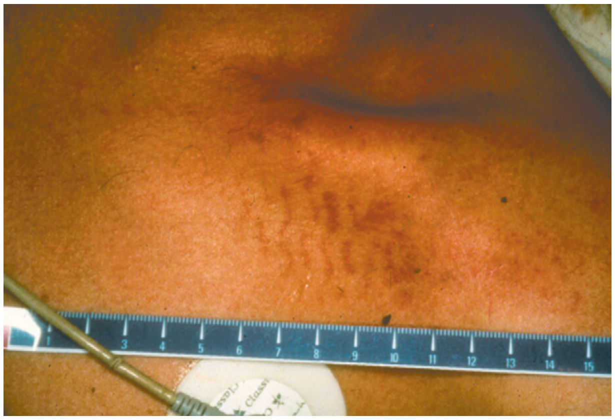


Figure 65-24. A pattern contusion on the patient's upper chest from the sole of a tennis shoe after a kick. This type of pattern injury can assist in the identification of a suspect and provide a physical connection between the victim and the attacker.

Some injuries allegedly occur during police custody. Specific pattern contusions can include parallel contusions from a flashlight or nightstick. Handcuff or shackle marks are narrow parallel contusions or abrasions on the wrists or ankles. Handcuff and shackle marks are generally more prominent on the lateral aspects of the extremity.[42]

The history should be recorded and injuries documented with diagrams and photographs, when possible. The incident is best reviewed by an internal affairs unit of the investigating law enforcement agency and not by the emergency physician. Conclusions regarding the alleged perpetrator and the mechanism of injury should generally be avoided.

www.ketabpezeshki.com 66485457-66963820

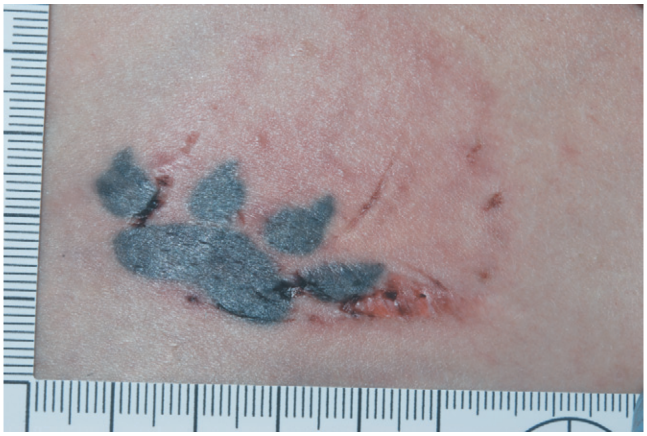


Figure 65-25. Bite marks may display characteristic arches or appear as a pattern abrasion. A bite mark can be used to identify the assailant if the injury is correctly documented by a forensic photographer or forensic odontologist.

Figure 65-26. A laceration is the result of blunt trauma and characteristically displays tissue bridges and crushed wound margins.

A bite mark may appear as a pattern contusion, an abrasion, or a combination of both (Fig. 65-25). Bite marks vary greatly in the quality of their identifiable features, depending on the location of the bite and the motion of the teeth relative to the skin. Some bite marks may not be readily identifiable as such and may appear as nonspecific contusions, abrasions, or contused abrasions.

When an acute bite mark is identified, care should be taken not to wash away potential evidence. The skin surface should be swabbed with a sterile cotton-tipped applicator moistened with sterile saline. DNA from buccal cells may also be deposited over an acute bite mark.[11,17]

When available, a forensic odontologist can evaluate a bite wound with accuracy. The use of alternative light sources, such as ultraviolet or infrared, may reveal a pattern contusion within or under the epithelium that is not visible to the naked eye.[87] These light sources are routinely used by the forensic odontologist on bite marks that are faint, old, or difficult to identify.

The emergency physician may be asked to render an opinion regarding the age of a contusion. The development of a contusion is based on a number of variables: the amount of blunt force applied to the skin, the vascularity of the tissue, the oxygenation of the extravasated hemoglobin, the depth of the hematoma, skin tone, and the amount of blood that escapes into the surrounding tissue.[88-90] As a result, no reproducible standard for the dating of a contusion is possible based on its color.[88-90] New techniques based on reflectance spectrophotometry are currently being tested.[91] A tissue biopsy examining the hemosiderin breakdown may be the only scientifically accepted method to determine the approximate age of a contusion.[92]

Pattern Abrasions and Lacerations. A *pattern abrasion* is a rubbing or scraping away of the superficial layers of the epidermis, which is not important for treatment but may be invaluable from a forensic and injury reconstruction perspective.[86]

A *laceration* is defined as a tear in the skin produced by blunt trauma and should not be confused with an incised wound produced when a sharp-edged implement (e.g., knife, scalpel, or piece of glass) is drawn across the skin.[19,35] A laceration has characteristically abraded or crushed skin edges and unique "tissue bridges" (Fig. 65-26).

Sharp Force Pattern Injuries

An *incised wound* is longer than it is deep, and the *stab wound* is defined as a puncture wound that is deeper than it is wide. The wound margins of sharp force injuries are clean and lack the abraded edges and tissue bridges of injuries resulting from blunt forces.

Forensic information can be gathered during the examination of a stab wound. Some of the characteristics of a knife blade, single edged or double edged, can be determined from visual inspection (Fig. 65-27A and B).[19,86] Additional blade characteristics, such as serrated versus sharp, can be seen if the blade was drawn across the skin during its insertion or withdrawal (see Fig. 65-27C). Serrated blades do not always leave characteristic marks.[19,86]

Patients with self-inflicted wounds frequently visit the ED claiming an accident, self-defense, or assault. When the patient history, the injuries, and the forensic evidence are not consistent, the forensically informed emergency physician is in a unique position to extrapolate the truth. With an understanding of how to identify the patterns of self-inflicted knife wounds, the physician can provide appropriate referrals, conserve resources, and assist law enforcement in the investigation of an alleged crime.

When a patient claims to have been assaulted and the victim of a crime, his or her injuries become physical evidence. It is important for the treating physician, who may be called as an expert witness, to recognize patterns of self-inflicted injury to distinguish self-inflicted wounds from those sustained during an assault (Fig. 65-28 and Box 65-2).

Thermal Pattern Injuries

A thermal pattern injury is a common form of abuse or battery. The history should include the position of the patient relative to the thermal source. This information will help determine whether the injury was intentional or accidental.[86]

A sharp or clear line of demarcation between burned and unburned tissue characterizes immersion or dipping burns. In contrast, splash burns are characterized by an irregular or undulating line or by isolated areas of thermal injury, usually round or oval in shape, caused by droplets of hot liquid.

The severity of thermal or scald injury depends on the length of contact time and the temperature. Water causes full-thickness damage in 1 second at 158° F (70° C) and in 600 seconds at 120° F (48.9° C) (Fig. 65-29).[93] Law enforcement routinely measures the household's or institution's water temperature in any investigation involving a scald injury.

www.ketabpezeshki.com 66485457-66963820

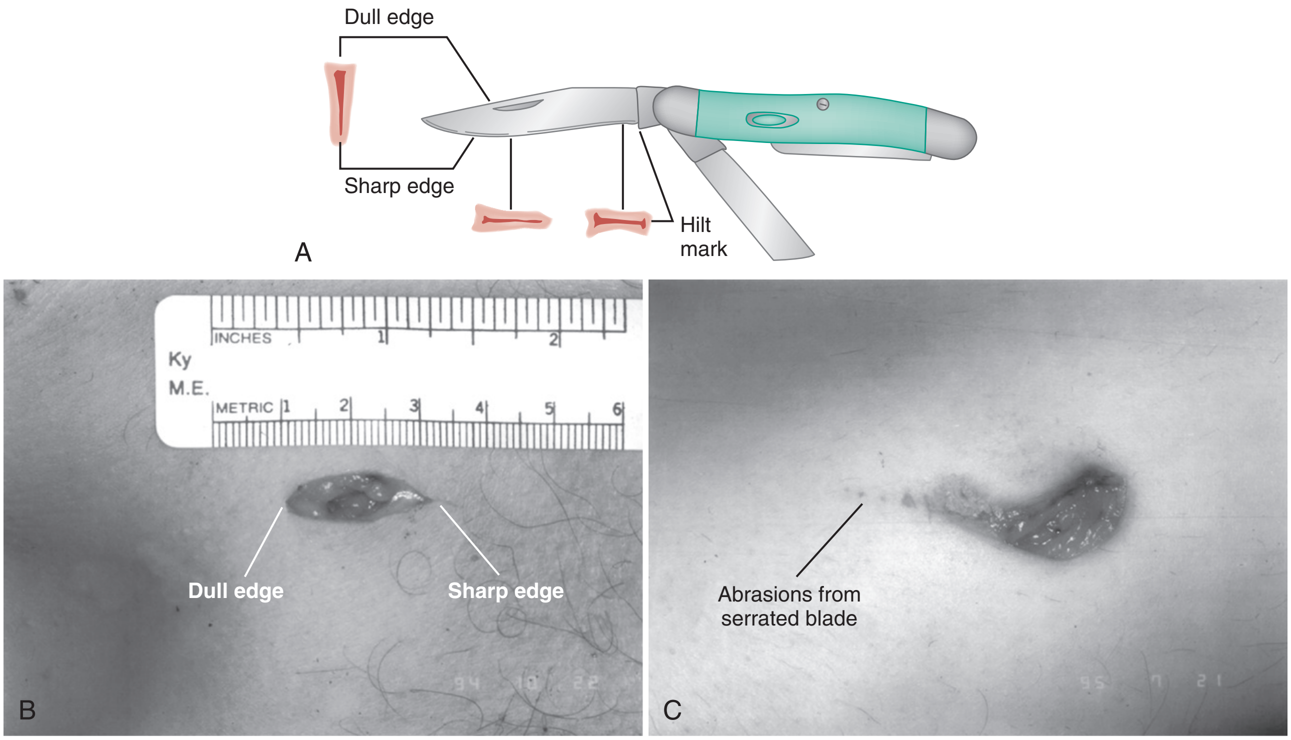


Figure 65-27. **A,** A single-edged knife blade will cause a wound to be formed with a sharp edge and a dull edge. If the blade penetrates to its hilt, a "hilt mark" may be seen overlying the sharp edge. **B,** Single-edged stab wound. **C,** Single-edged stab wound made by a serrated blade. Abrasions from the blade's serrated edges are seen on the left margin of the wound.

Figure 65-28. The presence of multiple, parallel superficial incised wounds, sometimes termed "hesitation marks," are indicators of self-inflicted wounds.

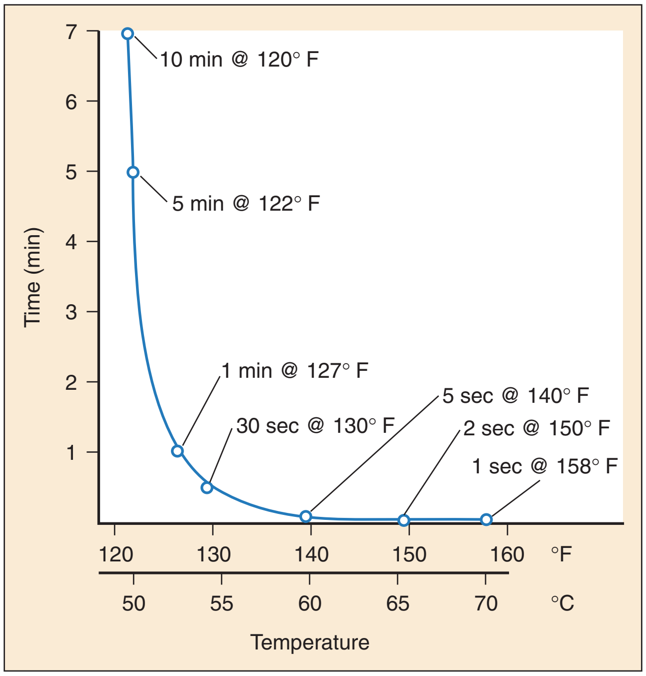


Figure 65-29. Relationship between water temperature and the duration of contact required to produce a full-thickness thermal injury. (Adapted from Katcher ML: Scald burns from hot tap water. JAMA 246:1219, 1981.)

Box 65-2 Characteristics of Self-inflicted Knife Wounds

- Multiple superficial incisions located on the anterior trunk, arms, and face
- Multiple superficial stab wounds located on the anterior trunk, arms and face
- Parallel incisions, in close proximity to each other, on the nondominant side of the body
- Sparing of sensitive body areas
- Linear or curved incisions toward the hand inflicting the wound
- Intact clothing covering the wound
- Evidence of prior wounds in repeat offenders

www.ketabpezeshki.com 66485457-66963820

FORENSIC ASPECTS OF MOTOR VEHICLE TRAUMA

Law enforcement officials investigating an incident involving serious or fatal injuries from a motor vehicle or pedestrian collision may benefit from information regarding injury patterns and the collection of trace evidence from the victim. This information can help determine whether an occupant was a driver or passenger. It may help to identify a suspect vehicle involved in a hit-and-run pedestrian collision or a pedestrian's position (standing or lying) when struck in the roadway.[42]

Determination of a vehicle occupant's role may be simple (e.g., if the driver is pinned behind the steering wheel) or complex (e.g., if the vehicle's occupants are ejected). Many impaired drivers claim to be passengers. Short-lived evidence or pattern injuries that might be destroyed or altered in the delivery of patient care should optimally be preserved and photographed.[94,95]

An opinion on an occupant's position should be avoided because an occupants' role is difficult to determine based solely on the statements and physical findings in the ED.[94,95] Such an opinion is best rendered by someone who has examined the scene, the vehicle, other occupants, and trace evidence; has reviewed postmortem examinations; and has had the collision reconstructed to determine vehicle dynamics (Box 65-3).[94-96]

Pattern Injuries

Matching pattern injuries with components within a vehicle often reveals an occupant's position during a portion of the vehicle's collision sequence.[94-96] Common pattern contusions, abrasions, and lacerations are seen from steering wheels, air bags, air bag module covers, window cranks, radio knobs, door latches, dashboard components, and front and side window glass.[94-98] An occupant's movement and subsequent contact with a vehicle's components are dictated by the forces applied to the vehicle through its interaction with the environment. Vehicle occupants, restrained or unrestrained, will initially move toward the primary area of impact.[94] Movement within the vehicle is called *occupant kinematics.* Occupant movement toward the primary area of impact is described as a motion parallel and opposite to the principal direction of the force (PDOF) developed by the impacting object.[94,95] The PDOF will predict the direction in which a particular occupant will move and therefore what component within the vehicle may be struck.

A deploying air bag may induce a pattern abrasion to the face, cornea, forearms, or other exposed tissue. Pattern lacerations, specific fracture patterns, and amputations are seen when the deploying air bag module cover impacts the hand or forearm (Fig. 65-30).[97,98] The correlation of these injuries and the transfer of DNA from the driver or passenger to the deployed air bag are helpful in assessing an occupant's role as driver or passenger.[97,98]

Laminated glass (windshields) and tempered glass (side and rear windows) produce pattern injuries. The windshield has two layers of glass laminated together with a thin layer of clear plastic sandwiched between. Laminated glass breaks into shards on impact and causes linear incised wounds. Tempered or safety glass is a single layer of glass that breaks into small cubes when fractured, imparting a "dicing" pattern to the skin (Fig. 65-31).[42,94,95]

Trace Evidence

Clothing, shoes, and biologic standards (hair, tissue, and blood) may determine an occupant's role.[95-99] The soles of leather shoes may reveal the imprint of the gas or brake pedal (Fig. 65-32). Preservation of clothing permits the comparison of clothing fibers with those fibers transferred to vehicle components during the collision.[95-99] Imprints of fabric may also be transferred to

Box 65-3 Evidence Collection—Driver versus Passenger

Victim

Examine for Pattern Injuries
Steering wheel contusion
Radio knob contusion
Window crank contusion
Striated incised facial wounds
"Dicing" wounds

Examine Clothing for Transferred Material**†
Glass (front and side windows)
Fibers
Pedal imprint on shoe
Dashboard components

Collect Biologic Standards†
Hair
Blood

Collect Clothing Standards†
Damage

Vehicle

Examine for Pattern Damage
Steering wheel
Radio, knobs, dashboard
Window crank, side door
Windshield (laminated glass)
Side and rear window (tempered glass)

Collect Standards
Glass
Carpets and seats
Gas and brake pedals
Broken dashboard components

Examine for Transferred Material of Pedestrian
Hair on windshield and components
Blood on windshield and components

Examine for Transferred Material on Car Occupants
Fabric fibers
Imprinted fabric pattern

*Each article of clothing should be collected in a separate paper bag. This avoids cross-contamination, and wet material will dry. Do not collect evidence in plastic bags because moisture will condense within the bag and may degrade biologic material.
†Each article should be marked with the patient's name, item collected, date and time collected, location of collection, name of the collector, and name of law enforcement official to whom the evidence was given. This information will preserve the "chain of custody."

Figure 65-30. A traumatic partial amputation of the hand resulted from contact with a deploying air bag module cover.

www.ketabpezeshki.com 66485457-66963820

Figure 65-31. Sliding skin contact with the tempered glass found in a side or rear window creates dicing lacerations.

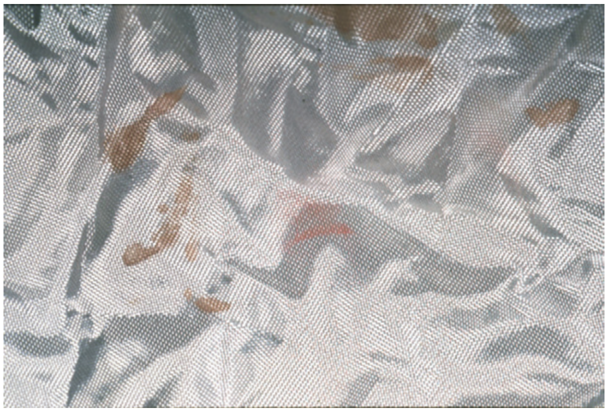


Figure 65-33. Occupant contact with the air bag often results in the transfer of trace evidence. The presence of blood, tissue, hair, and makeup will assist in the determination of the seating arrangement of a particular occupant.

Figure 65-32. Imprint of a brake pedal on a leather-soled shoe. This information will assist in determining the occupant's role and whether the patient's foot was on the brake or accelerator pedal at the moment of impact.

components within the vehicle, including the steering wheel. Contact with the windshield often transfers hair and tissue to the glass. Glass collected from within a patient's wound can be matched with a particular window within the vehicle. Airbags can be an excellent source of trace evidence. Examples of transferred evidence include skin, blood, makeup, and hair (Fig. 65-33).[97,98]

Evaluation of Pedestrian Collisions

Pattern Injuries

Approximately 59,000 people were killed or seriously injured in pedestrian collisions in 2009[100]; 87% are struck by a vehicle's front bumper or grill area.[100] When struck by the front of a vehicle, a standing adult will sustain "bumper injuries," which include open and closed fractures of the tibia and fibula, soft tissue damage, and pattern injuries from vehicle components and hardware.[42]

The height of bumper injuries, measured from the heel and including the height of the patient's shoe, can be correlated with the height of the vehicle's bumper to determine whether the vehicle was braking at the moment of impact. Application of the brake results in the dipping of a vehicle's front end. The presence or absence of braking may help determine the driver's intent. The presence of bumper injuries at one height on one leg and at another height on the other may indicate that the pedestrian was walking or running at the moment of impact, with one leg elevated. Examination of the soles may show lateral striations when a patient has been dragged.

A victim who is struck from behind may have pattern contusions on the calf or thigh (Fig. 65-34), whereas pattern contusions from a grill on the anterior aspect of the thigh indicate the pedestrian was standing and facing the vehicle. Pedestrians struck by a glancing portion of a vehicle may also display a pattern injury (Fig. 65-35). Victims who are run over may display a tire tread pattern (Fig. 65-36). Tire marks and the absence of bumper injuries suggest that the patient was supine or prone in the roadway before he or she was run over (Box 65-4).

Law Enforcement Exemptions to the Health Insurance Portability and Accountability Act

Title 45 Part 164 of the Health Insurance Portability and Accountability Act (HIPAA) of 1996 permits hospitals to disclose, without patient consent, to investigating law enforcement agencies specific information regarding a victim or suspect. Section 45 CFR 164.512 permits the release of protected health information, without a court order, "in response to a law enforcement official's request for such information for the purpose of identifying or locating a suspect, fugitive, material witness, or missing person."[101] A hospital or physician may disclose the information listed in Box 65-5 only to an investigating law enforcement officer.

www.ketabpezeshki.com 66485457-66963820

Figure 65-34. **A,** A pattern imprint contusion on the posterior aspect of a pedestrian's right thigh was the result of contact with the vehicle's grill. The location of the contusion provides information about the configuration of the patient at the moment that the car struck him. The patient was struck from the rear. **B,** The grill of the striking vehicle.

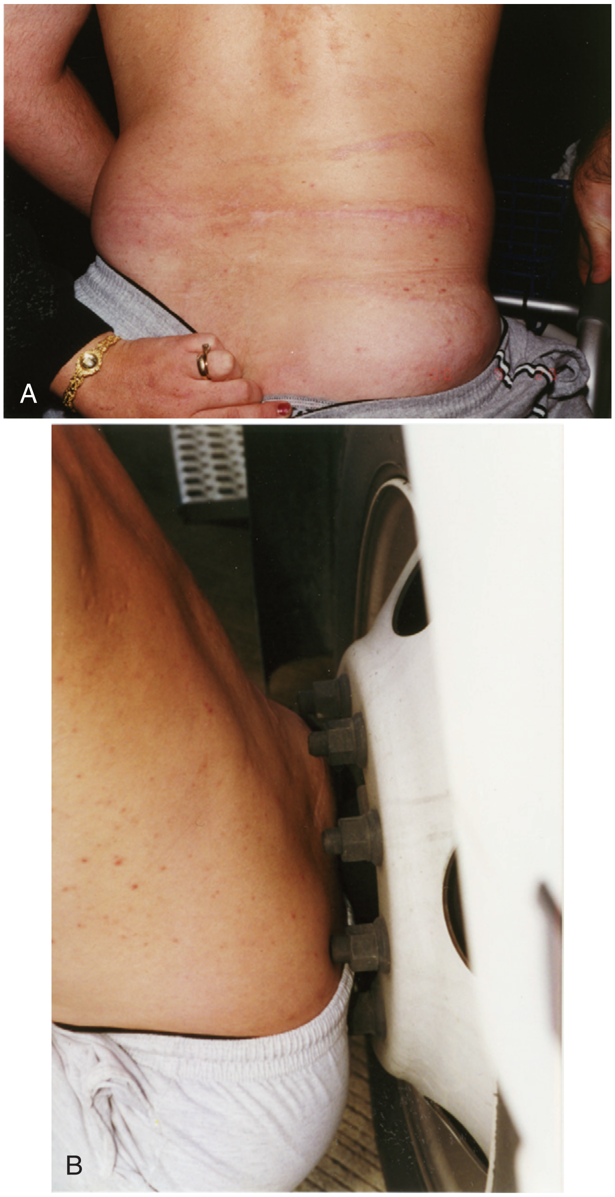


Figure 65-35. **A,** Three horizontally oriented wounds were noted on the back of a pedestrian struck by a semi–tractor trailer on a highway while changing a flat tire. **B,** The pattern injury was matched to the lug nuts of the front right wheel.

www.ketabpezeshki.com 66485457-66963820

Box 65-4 Evidence Collection—Pedestrian Collisions

Victim

Examine for Pattern Injuries

Height of bumper injuries
- Contusion
- Fracture
- Head and neck injuries
- Crush injuries

Examine Clothing for Transferred Material*†

Paint
Glass (windshield, headlight)
Oil or grease

Collect Biologic Standards†

Hair
Blood or tissue

Collect Clothing Standards†

Damage or tears

Vehicle

Examine for Pattern Damage

Bumper height and damage
Specific components
Windshield damage
Wheels and undercarriage

Collect Standards

Paint
Glass
Oil or grease

Examine for Transferred Material of Pedestrian

Hair
Blood or tissue

Examine for Transferred Material on Vehicle

Fabric fibers
Imprinted fabric pattern

*Each article of clothing should be collected in a separate paper bag. This avoids cross-contamination, and wet material will dry. Do not collect evidence in plastic bags because moisture will condense within the bag and may degrade biologic material.
†Each article should be marked with the patient's name, item collected, date and time collected, location of collection, name of the collector, and name of law enforcement official to whom the evidence was given. This information will preserve the "chain of custody."

Figure 65-36. Tire tread imprints on the skin indicate this victim of a hit and run collision was on the ground when he was hit.

Box 65-5 Law Enforcement Exemptions to the Health Insurance Portability and Accountability Act (HIPAA): 45 CFR 164.152

- Name and address
- Date and place of birth
- Social security number
- ABO blood type and Rh factor
- Type of injury
- Date and time of treatment
- Date and time of death, if applicable
- A description of distinguishing physical characteristics, including height, weight, gender, race, hair and eye color, presence or absence of facial hair (beard or moustache), scars, and tattoos

KEY CONCEPTS

- Knowledge of wound mechanics and production, as well as wound appearance, can provide practicing emergency physicians with important clues regarding the forensic interpretations of injuries.
- Wounds and injuries should be diagrammed and photographed.
- The medical record should accurately document objective findings associated with a patient's wounds. Physicians should not speculate about their mechanism or the cause.
- Any evidence collected during the course of treatment must be documented in the medical record, including to whom the evidence was given, for the chain of custody to be preserved.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Doney IV: Police surgeons of the United Kingdom. *Am J Forensic Med Pathol* 1984; 5:185.
2. McLay WDS: *Clinical Forensic Medicine*. London: Pinter; 1990.
3. Eckert W: The development of forensic medicine in the United Kingdom from the 18th century. *Am J Forensic Med Pathol* 1992; 13:124.
4. Payne-James JJ, Dean PJ: Assault and injury in clinical forensic medical practice. *Med Sci Law* 1994; 34:202.
5. Beran RG: The teaching of legal medicine in Australasia. *J Forensic Leg Med* 2007; 14:284-288.
6. Goldsmith MF: U.S. forensic pathologists on a new case: Examination of living patients. *JAMA* 1986; 256:1685.
7. Smialek JE: Forensic medicine in the emergency department. *Emerg Med Clin North Am* 1983; 1:1685.
8. Carmona R, Prince K: Trauma and forensic medicine. *J Trauma* 1989; 29:1222.
9. Ryan MT: Clinical forensic medicine. *Ann Emerg Med* 2000; 36:271.
10. Wiler JL, Bailey H, Madsen TE: The need for emergency medicine resident training in forensic medicine. *Ann Emerg Med* 2007; 50:733.
11. Eisert PJ, et al: Development of forensic evidence collection guidelines for the emergency department. *Crit Care Nurs Q* 2010; 33:190.
12. Sharma BR: Clinical forensic medicine—management of crime victims from trauma to trial. *J Clin Forensic Med* 2003; 10:267.
13. Smock WS, Nichols GR, Fuller PM: Development and implementation of the first clinical forensic medicine training program. *J Forensic Sci* 1993; 38:835.
14. Smock WS: Development of a clinical forensic medicine curriculum for emergency physicians in the USA. *J Clin Forensic Med* 1994; 1:27.
15. Smock WS, Ross CS, Hamilton FN: Clinical forensic medicine: How ED physicians can help with the sleuthing. *Emerg Legal Brief* 1994; 5:1.
16. Eckert WG, et al: Clinical forensic medicine. *Am J Forensic Med Pathol* 1986; 7:182.
17. Wick JM: Don't destroy the evidence! *AORN J* 2000; 72:807.
18. Godley DR, Smith TK: Some medicolegal aspects of gunshot wounds. *J Trauma* 1977; 17:866.
19. Smock WS: *Forensic aspects of motor vehicle trauma*. In: Olhaker JS, Jackson MC, Smock WS, eds. *Forensic Emergency Medicine*, 2nd ed. Philadelphia: Lippincott, Williams & Wilkins; 2006:72-84.
20. Busuttil A, Smock WS: *Training in clinical forensic medicine in Kentucky. Police Surg* 1990; 14:26.
21. The Joint Commission: *Hospital Accreditation Standards* 2009, PC.3.10. Oakbrook Terrace, Ill: The Joint Commission; 2009.
22. Berger N, Jones J, Smock WS: *Clinical forensic medicine*. In: *The Medical Student Survival Guide*. Dallas: Emergency Medicine Resident's Association; 2007:166-168.
23. New forensic medicine section being formed. EM Today, June 26, 2006. Available at www.acep.org. Accessed March 13, 2008.
24. Wade C, ed. *FBI Forensic Sciences Handbook*. Quantico, Va: Federal Bureau of Investigation; 2003.
25. Smock WS: *Forensic photography*. In: Stack LB, Storrow AB, Morris A, Patton DR, eds. *Handbook of Medical Photography*. Philadelphia: Hanley & Belfus; 2001:397-408.
26. Stark MM, Norfolk GA: Training in clinical forensic medicine in the UK—perceptions of current regulatory standards. *J Forensic Leg Med* 2011; 18:264.
27. Collins KA, Lantz PE: Interpretation of fatal, multiple, and exiting gunshot wounds by trauma specialists. *J Forensic Sci* 1994; 39:94.
28. McLeer SV, Anwar RA, Herman S, Maquiling K: Education is not enough: A systems failure in protecting battered women. *Ann Emerg Med* 1989; 18:651.
29. Breo DL: JFK's death: The plain truth from the MDs who did the autopsy. *JAMA* 1992; 267:2794.
30. Randall T: Clinicians' forensic interpretations of fatal gunshot wounds often miss the mark. *JAMA* 1993; 269:2058.
31. Centers for Disease Control and Prevention (CDC): Deaths: Preliminary data for 2009. *Natl Vital Stat Rep* 2011; Vol. 59, No. 4. Available at http://www.cdc.gov/nchs/data/nvsr/nvsr59/nvsr59_04.pdf.
32. Centers for Disease Control and Prevention (CDC): Surveillance for fatal and nonfatal firearm-related injuries—United States, 1993-1998. *MMWR CDC Surveill Summ* 2001; 50:1.
33. Corso PS, Mercy JA, Simon TR, Finkelstein EA, Miller TR: Medical costs and productivity losses due to interpersonal and self-directed violence in the United States. *Am J Prev Med* 2007; 32:474.
34. Dana SE, DiMaio VJM: *Gunshot trauma*. In: Payne-James J, Busuttil A, Smock W, eds. *Forensic Medicine: Clinical and Pathological Aspects*. London: Greenwich Medical Media; 2003:149-168.
35. Smock WS: *Forensic medicine: Pattern injuries of domestic violence, assault and abuse*. In: Knoop KH, Stack LB, Storrow AB, eds. *Atlas of Emergency Medicine*, 2nd ed. New York: McGraw-Hill; 2002:565-576.
36. Marlowe AL, Smock WS: The forensic evaluation of gunshot wounds by prehospital personnel. *Proc Am Acad Forensic Sci* 1996; 2:149.
37. Fackler ML, Riddic KL: Clinicians' inadequate descriptions of gunshot wounds obstruct justice: Clinical journals refuse to expose the problem. *Proc Am Acad Forensic Sci* 1996; 2:150.
38. DiMaio VJM, Spitz WU: Variations in wounding due to unusual firearms and recently available ammunition. *J Forensic Sci* 1972; 17:377.
39. Fackler ML: Wound ballistics: A review of common misconceptions. *JAMA* 1988; 259:2730.
40. Fatteh A: *Medicolegal Investigation of Gunshot Wounds*. Philadelphia: Lippincott; 1976.
41. DiMaio VJM: *Gunshot Wounds*, 2nd ed. Boca Raton, Fla: CRC Press; 1999.
42. Spitz WU: *Medicolegal Investigation of Death*, 4th ed. Springfield, Ill: Charles C Thomas; 2006.
43. Apfelbaum JD, Shockley LW, Wahe JW, Moore EE: Entrance and exit gunshot wounds: Incorrect terms for the emergency department? *J Emerg Med* 1998; 16:741.
44. Breo DL: JFK's death: Part II—Dallas MDs recall their memories. *JAMA* 1992; 267:2791.
45. Sellier KG, Kneubuehl BP: *Wound Ballistics and the Scientific Background*. Amsterdam: Elsevier; 1994.
46. Le Garde LA: *Gunshot Injuries*, 2nd rev ed. Mt Ida, Ark: Lancer Militaria; 1991.
47. Lindsey D: The idolatry of velocity, or lies, damn lies, and ballistics. *J Trauma* 1980; 20:1068.
48. Lindsey D: Review of *Management of Gunshot Wounds* by Ordog. *Am J Emerg Med* 1989; 7:117.
49. Fackler ML: Review of *Management of Gunshot Wounds* by Ordog. *Ann Emerg Med* 1988; 17:1004.
50. Barach EM, Tomlanovich MC: Civilian gunshot wounds: determinants of injury. *J Trauma* 1988; 28:1610.
51. Mason JK: *The Pathology of Trauma*, 2nd ed. London: Hodder & Stoughton; 1993.
52. Dixon DS: Tempered plate glass as an intermediate target and its effects on gunshot wound characteristics. *J Forensic Sci* 1982; 27:205.
53. Stahl CJ, et al: The effect of glass as an intermediate target on bullets: Experimental studies and report of a case. *J Forensic Sci* 1979; 24:6.
54. Donoghue ER, Kalelkar MB, Richmond JM, Teas SS: Atypical gunshot wounds of entrance: An empirical study. *J Forensic Sci* 1984; 29:379.
55. Dixon DS: Determination of direction of fire from graze gunshot wounds. *J Forensic Sci* 1980; 25:272.
56. Dixon DS: Determination of direction of fire from graze gunshot wounds of internal organs. *J Forensic Sci* 1984; 29:331.
57. Dixon DS: Characteristics of shored exit wounds. *J Forensic Sci* 1981; 26:691.
58. Adelson L: A microscopic study of dermal gunshot wounds. *Am J Clin Pathol* 1961; 35:393.
59. Murphy GK: The study of gunshot wounds in surgical pathology. *Am J Forensic Med Pathol* 1980; 1:123.
60. Torre C, Varetto L, Ricchiardi P: New observations on cutaneous firearm wounds. *Am J Forensic Med Pathol* 1986; 7:186.
61. Lee HC, Palmbach T, Miller MT: *Henry Lee's Crime Scene Handbook*. San Diego: Academic Press; 2001.
62. Molina DK, Martinez M, Garcia J, DiMaio VJ: Gunshot residue testing in suicides. Part I: Analysis by scanning electron microscopy with energy-dispersive x-ray. *Am J Forensic Med Pathol* 2007; 28:187.
63. Molina DK, Martinez M, Garcia J, DiMaio VJ: Gunshot residue testing in suicides. Part II: Analysis by inductive coupled plasma-atomic emission spectrometry. *Am J Forensic Med Pathol* 2007; 28:191.
64. Adeyl O, Duval JV, Dupre ME, Andrew TA: Role of chemical tests and scene investigation in determination of range of fire. *Am J Forensic Med Pathol* 2005; 26:166.
65. Santos A, Magalhaes T, Vieira DN, Almeida AA: Firing distance estimation through the analysis of the gunshot residue deposit pattern around the bullet entrance hole by inductively coupled plasma-mass spectrometry: An experimental study. *Am J Forensic Med Pathol* 2007; 28:24.
66. Tillman J: Automated gunshot residue particle search and characterization. *J Forensic Sci* 1987; 32:62.
67. Kee TG, Beck C: Casework assessment of an automated scanning electron microscope/microanalysis system for the detection of firearms discharge particles. *J Forensic Sci Soc* 1987; 27:321.

www.ketabpezeshki.com 66485457-66963820

68. Zeichner A, Levin N: Casework experience of GSR detection in Israel, on samples from hands, hair, and clothing using an autosearch SEM/EDX system. *J Forensic Sci* 1995; 40:1082.
69. Zoja R, Lazzaro A, Battistine A, Gentile G: Detection of gunshot residues on cadaveric skin using sodium rhodizonate and a counterstain. *Biotech Histochem* 2006; 81:151.
70. Gialamas DM, et al: Officers, their weapons and their hands: An empirical study of GSR on the hands of non-shooting police officers. *J Forensic Sci* 1995; 40:1086.
71. Dixon DS: *Gunshot wounds: Forensic implications in a surgical practice*. In: Ordog GJ, ed. *Management of Gunshot Wounds*. New York: Elsevier; 1988.
72. Kothari C, Rhodes KV: Missed opportunities: Emergency department visits by police-identified victims of intimate partner violence. *Ann Emerg Med* 2006; 47:190.
73. Tilden VP: Response of the health care delivery system to battered women. *Issues Ment Health Nurs* 1989; 10:309.
74. Randall T: Domestic violence intervention calls for more than treating injuries. *JAMA* 1990; 254:939.
75. McLeer SV, Anwar RA: The role of the emergency physician in the prevention of domestic violence. *Ann Emerg Med* 1987; 16:1155.
76. Morrison LJ: The battering syndrome: A poor record of detection in the emergency department. *J Emerg Med* 1988; 6:521.
77. Tilden VP, Shepherd P: Increasing the rate of identification of battered women in an emergency department: Use of a nursing protocol. *Res Nurs Health* 1987; 10:209.
78. Goldberg W, Carey AL: Domestic violence victims in the emergency setting. *Top Emerg Med* 1982; 3:65.
79. Delahunta EA: Hidden trauma: The most missed diagnosis of domestic violence. *Am J Emerg Med* 1995; 13:74.
80. Grunfeld AF, Ritmiller S, Mackay K, Cowan L, Hotch D: Detecting domestic violence against women in the emergency department: A nursing triage model. *J Emerg Nurs* 1994; 20:271.
81. Isaac NE, Sanches RL: Emergency department response to battered women in Massachusetts. *Ann Emerg Med* 1994; 23:85.
82. Abbott J, Johnson R, Koziol-McLain J, Lowenstein SR: Domestic violence against women: Incidence and prevalence in an emergency department population. *JAMA* 1995; 273:1763.
83. Gremillion DH, Evins G: Why don't doctors identify and refer victims of domestic violence? *N C Med J* 1994; 55:428.
84. Davis JW, Parks SN, Kaups KL, Bennink LD, Bilello JF: Victims of domestic violence on the trauma service: Unrecognized and underreported. *J Trauma* 2003; 54:352.
85. Chambliss LR, Bay RC, Jones RF: Domestic violence: An educational imperative? *Am J Obstet Gynecol* 1995; 172:1035.
86. Smock WS: *Recognition of pattern injuries in domestic violence victims*. In: Siegel JA, Saukko PJ, Knupfer GC, eds. *Encyclopedia of Forensic Sciences*. San Diego: Academic Press; 2000:384-390.
87. Patno K, C Jenny: Who slapped that child? *Child Maltreat* 2008; 13:298.
88. Maguire S, Mann MK, Sibert J, Kemp A: Can you age bruises accurately in children? A systemic review. *Arch Dis Child* 2005; 90:187.
89. Bariciak ED, Plint AC, Gaboury I, Bennett S: Dating of bruises in children: An assessment of physician accuracy. *Pediatrics* 2003; 112:804.
90. Dimitrova T, Georgieva L, Pattichis C, Neofytou M: Qualitative visual image analysis of bruise age determination: A survey. *Conf Proc IEEE Eng Med Biol Sci* 2006; 1:4840.
91. Hughes VK, NE Langious: Use of reflectance spectrophotometry and colorimetry in a general linear model for the determination of the age of bruises. *Forensic Sci Med Pathol* 2010; 6:275.
92. Vanezis P: Interpreting bruises at necropsy. *J Clin Pathol* 2001; 54:348.
93. Katcher ML: Scald burns from hot tap water. *JAMA* 1981; 246:1219.
94. Smock WS, Nichols GR 2nd, Fuller PM, Weakley-Jones B: The forensic pathologist and the determination of driver versus passenger in motor vehicle collisions. *Am J Forensic Med Pathol* 1989; 10:105.
95. Smock WS: *Driver versus passenger in motor vehicle collisions*. In: Siegel JA, Saukko PJ, Knupfer GC, eds. *Encyclopedia of Forensic Sciences*. San Diego: Academic Press; 2000:24-32.
96. Blackbourne BD: *Injury-vehicle correlations in the investigation of motor vehicle accidents*. In: Wecht CH, ed. *Legal Medicine Annual 1980*. New York: Appleton-Century-Crofts; 1980:1-19.
97. Smock WS, Nichols GR: Airbag module cover injuries. *J Trauma* 1995; 38:489.
98. Smock WS: Airbag related injuries and deaths. In Siegel JA, Saukko PJ, Knupfer GC, eds. *Encyclopedia of Forensic Sciences*. San Diego: Academic Press; 2000:1-8.
99. Laing DK, et al: A fiber data collection for forensic scientists: Collection and examination methods. *J Forensic Sci* 1987; 32:364.
100. National Highway Traffic Safety Administration: *Traffic Safety Facts 2009*. Washington, DC: Department of Transportation; 2010.
101. Department of Health and Human Services: Health Insurance Portability and Accountability Act of 1996 (HIPPA), Title 45, Part 164, Subpart E, § 164.512. Available at http://edocket.access.gpo.gov/cfr_2002/octqtr/45cfr164.512.htm. Accessed January 25, 2013.

www.ketabpezeshki.com 66485457-66963820

Chapter 66

Child Maltreatment

Carol D. Berkowitz and Sara T. Stewart

PERSPECTIVE

Background

Child maltreatment is an all-encompassing term that includes all forms of child abuse: physical abuse, sexual abuse, emotional abuse, child neglect (physical, emotional, educational), and factitious disease by proxy (also known as *Munchausen syndrome by proxy* and most recently termed *medical child abuse*).[1,2] Although the recognition of these conditions by the medical community has occurred at different times, the pivotal report describing child physical abuse, published in 1962, was the article "The Battered Child Syndrome" by Kempe and colleagues.[3] The article noted the presence of a complex of physical findings, including fractures, cutaneous bruises, and internal injuries. Since that time, multiple articles and books have described the spectrum of the disorders. During the 1980s, much of the literature focused on child sexual abuse, including the refinement of understanding of normal anogenital anatomy of prepubescent children.[4] *Child sexual abuse* is defined as the involvement of children and adolescents in sexual activity to which they cannot give consent based on their developmental level, involving an age disparity between the victim and the perpetrator, and for the sexual gratification of the older individual. Child sexual abuse may involve physical contact between the child and the adult or the involvement of the child in other activities, such as photography or the production of pornographic material.

The role of the emergency physician in caring for an abused child is multifold. Most important, the physician should recognize which presenting complaints are attributable to child abuse and should initiate medical management of diagnosed medical conditions, some of which may be life-threatening. Differentiating between inflicted injuries, noninflicted injuries, and other medical conditions is paramount to the correct diagnosis and the proper management of the case. In addition, the clinician has the primary responsibility for reporting the suspicion of child abuse to the appropriate authorities, which usually include child protective services and law enforcement.

Epidemiology

Just under 1 million cases of suspected child abuse and neglect are reported annually in the United States. Table 66-1 summarizes the data by category of abuse or neglect as noted by the 2009 Child Maltreatment report from the U.S. Department of Health and Human Services.[5] Although child abuse occurs across the spectrum of race, ethnicity, and socioeconomic class, certain factors are associated with an increased prevalence of abuse, including poverty, social isolation, parental alcohol and substance abuse, parental mental illness, and domestic violence.[6,7]

PRINCIPLES OF DISEASE

Child Physical Abuse

Child physical abuse refers to the infliction of injury on any part of a child's body. Injuries manifest in myriad forms, including cutaneous bruises, burns, skeletal fractures, internal hemorrhage, organ perforation, and brain injury.

Bruises may appear as petechiae or ecchymoses. They occur at the point of impact between the striking object, such as the hand, and the child's body. Often they mirror the form of the inflicting object and may appear as a hand print, a belt outline, or a mark resembling another object (Fig. 66-1). These bruises are referred to as *patterned injuries.* When the blow occurs at high velocity, the bruising may resemble the outline of the object as the soft tissue in the center of the impacted field moves laterally (negative image). When the thrust of the strike is slower, the central portion of the skin also may be discolored (positive image). The extent of an injury is influenced by many factors, including the force of blow and the area struck. Frequently, the struck area initially is only erythematous, swollen, or tender, and 24 hours may elapse before bleeding into the skin and subsequent discoloration are noted. The degree of discoloration and the rapidity of resolution of the discoloration are influenced by the location of the injury; large fat pads or muscle masses, such as the buttocks, can hold larger volumes of blood, and resolution takes longer. In general, extravasated blood goes through a predictable color change pattern as it resolves, progressing from purple to green to yellow and eventually to brown. However, the color of a bruise should not be used as a tool to estimate the age of a bruise.[8,9] Accidentally incurred bruises tend to occur over bony prominences, such as the shin and forehead. In addition, nonambulatory children (<1 year old) do not readily sustain accidental cutaneous injuries ("those who don't cruise, don't bruise").[8] Bites also produce a patterned injury. The distance between the maxillary canine teeth helps establish whether the perpetrator was a child (<2.5 cm), which is often alleged, or an adult (>3 cm) (Fig. 66-2).[10]

Burns may be inflicted through contact with a dry hot object or through immersion in hot water. One common type of inflicted burn occurs secondary to contact with a cigarette. Inadvertent contact with a lit cigarette tends to create less severe or linear burns; however, inflicted cigarette burns are usually circular, measuring 8 to 10 mm (Fig. 66-3). Initially they have a blistered appearance but then become ulcerated and crust over. Burn injuries also may assume a patterned appearance resembling the

www.ketabpezeshki.com 66485457-66963820

Table 66-1 Overview of Incidence of Child Abuse

TYPE	NUMBER OF CASES
Physical abuse	123,599
Sexual abuse	65,964
Psychological maltreatment	52,532
General neglect	543,035
Medical neglect	16,837
Other or unknown	68,415
Total	**870,382**

Data from U.S. Department of Health and Human Services, Administration on Children, Youth and Families: *Child Maltreatment 2009.* Washington, DC: U.S. Government Printing Office; 2010. Available at http://www.acf.hhs.gov/programs/cb/stats_research/index.htm#can. Accessed January 11, 2013.

Figure 66-1. Electrical cord bruising on a child's back. (Courtesy Marianne Gausche-Hill, MD.)

Figure 66-2. Bite mark with more than 3 cm between maxillary canines, characteristic of an adult human bite. (Courtesy Carol Berkowitz, MD.)

Figure 66-3. Cigarette burns on the soles of the feet of a child. (Courtesy EMSC Slide Set, National EMSC Resource Alliance.)

Figure 66-4. Immersion burn. (Courtesy EMSC Slide Set, National EMSC Resource Alliance.)

configuration of the hot object, such as a heating grid or an iron. Immersion burns occur when a child or infant is placed in hot water. Such burns often involve the anogenital area and may represent punishment for toilet training accidents, or they involve hands or feet (glove-stocking distribution) that have been dunked in hot water. Immersion burns are usually second-degree burns (Fig. 66-4). The extent of the burn is influenced by the temperature of the water, the body site exposed (the skin is thinner in certain areas, such as the anogenital region), the age of the individual (younger children and elderly adults have thinner skin), and the duration of the contact between the hot object and the skin (Table 66-2).[11] Burns caused by contact with viscous liquids, such as grease, oils, or syrups, may be more severe because such liquids are more adherent to the skin surface. Chemical burns may occur through contact with corrosive products, including industrial-strength cleaning agents.

Patients with burns of the hands and feet or anogenital region require specialty care; for many emergency medical service systems, once the patient's condition has been stabilized in the emergency department, he or she will be transported to a burn center. Escharotomy may be required in selected cases when the burns are circumferential and severe.

Accidental burns can occur in children and usually involve scald injuries, which happen when children spill hot liquids, such as coffee, on their clothes and skin. Spill burns have a characteristic drip appearance, with more extensive and severe injury proximal to the point of contact and less extensive and milder injury more

www.ketabpezeshki.com 66485457-66963820

Table 66-2 Time-Temperature Relationships in Scald Burns

TEMPERATURE	TIME TO PRODUCE SERIOUS BURNS
120° F	More than 5 min
125° F	1½ to 2 min
130° F	About 30 s
135° F	About 10 s
140° F	Less than 5 s
145° F	Less than 3 s
150° F	About 1½ s
155° F	About 1 s
160° F+	Instantaneously

Table courtesy Shiners Burn Institute.

Figure 66-5. Splash burn to chest and abdomen on a child, typically caused by from pulling a pan from a stove and dripping hot contents onto the chest. (Courtesy Sara T. Stewart, MD, MPH.)

distally (Fig. 66-5). Disposable diapers are very absorbent of heat as well as of liquids. Scald burns in the anogenital area that are attributed to hot beverages falling into a child's diaper should be scrutinized carefully, and if there is any concern of abuse, a report should be made by anyone who is considered a mandated reporter such as a paramedic, nurse, physician, or social worker.[12,13] The report is made to child protective services or law enforcement. Many jurisdictions have a "child abuse hotline" to facilitate such reporting.

Skeletal injuries may involve any of the bones in the body. Although approximately 42% of boys and 27% of girls have sustained a fracture before the age of 16 years, certain fractures are highly suspicious of an inflicted injury (Table 66-3).[14,15] In particular, metaphyseal fractures, rib fractures, and certain types of skull fractures should raise concern about inflicted trauma (Fig. 66-6). Metaphyseal fractures (i.e., classic metaphyseal lesions) occur because of yanking or pulling on an extremity. On radiographs they may appear as metaphyseal chips or what is referred to as a *bucket-handle injury* of the metaphysis of the long bone. They are characterized by the absence of callus as they heal (Fig. 66-7). They usually are noted in children younger than 2 years. Long bone fractures involving the lower extremities are equally concerning in

Table 66-3 Suspicious Fractures

- Long bone fracture in a preambulatory infant
- Metaphyseal fractures (classic metaphyseal lesions)
- Rib fractures
- Scapula fractures
- Spinous process fractures
- Skull
  - Multiple
  - Wide (>3 cm)
  - Growing
  - Involving more than one cranial bone
  - Occipital

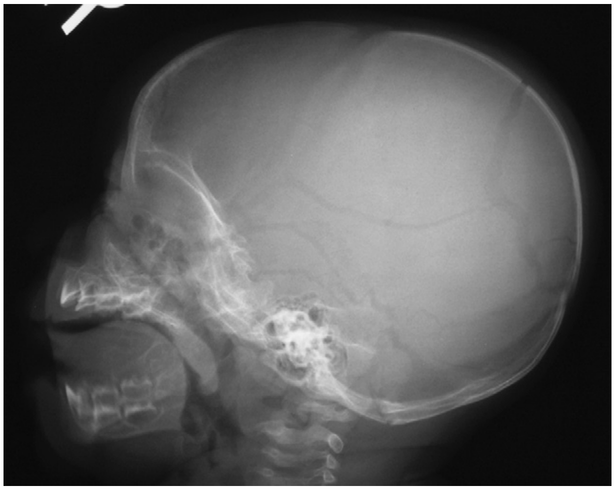


Figure 66-6. Complex skull fracture associated with child maltreatment. (Courtesy Sara T. Stewart, MD, MPH.)

Figure 66-7. Metaphyseal fracture, "bucket handle type," associated with child physical abuse. (Courtesy Sara T. Stewart, MD, MPH.)

www.ketabpezeshki.com 66485457-66963820

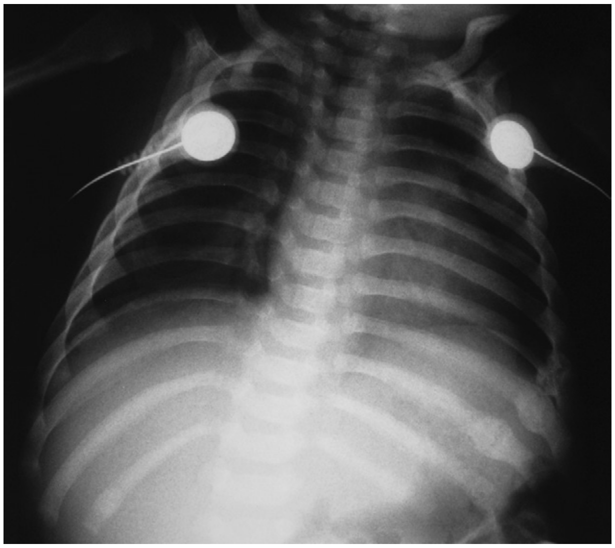


Figure 66-8. Posterior rib fractures caused by compression of the ribs from child physical abuse. (Courtesy Sara T. Stewart, MD, MPH.)

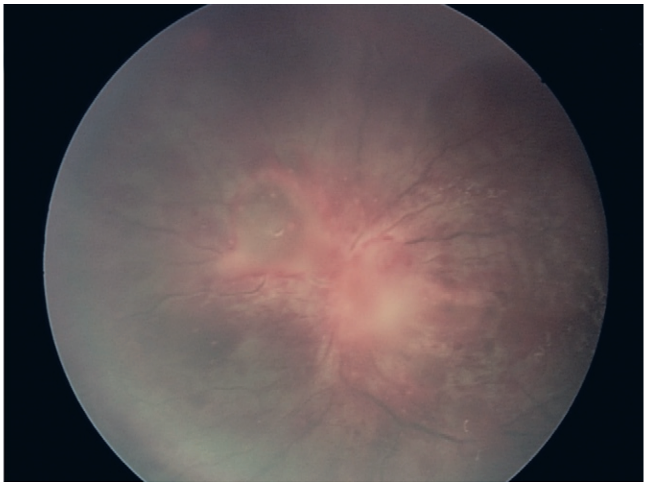


Figure 66-9. Retinal hemorrhages in an infant with shaken infant syndrome. (Courtesy Carol Berkowitz, MD.)

preambulatory children. Once children are ambulatory, accidental injuries such as toddler factures (nondisplaced spiral fractures of the distal tibia) are not uncommon. Rib fractures, particularly posterior rib fractures in an otherwise healthy infant, are virtually pathognomonic for inflicted injury[16] (Fig. 66-8). The rib cage, because of its archlike structure, must be subjected to a good deal of force for disruption to be caused. Rib fractures are extremely uncommon as a consequence of cardiopulmonary resuscitation (CPR) and are not reported across the age spectrum. In addition, there is no evidence that chest encirclement for CPR is more likely than two-finger sternal compression to cause rib fractures.[17] The presence of multiple skull fractures or skull fractures in the occipital region is unusual in cases of accidental trauma and should raise concern for inflicted trauma. Fractures that are diastatic (>3 mm in width) or grow in size are less specific as markers for nonaccidental trauma; however, they are usually associated with mechanisms of injury that involve greater traumatic forces.

Head injuries, including those associated with the classically described "shaken baby syndrome," account for most child abuse–related fatalities. The syndrome includes evidence of head trauma in association with retinal hemorrhages and skeletal injuries and occurs generally in infants younger than 1 year but may be seen in children up to 3 years old. Often, there is no evidence of an impact injury to the head, such as a scalp hematoma or skull fracture.[18,19] If impact occurs, it may be against a soft or compressible surface, such as the mattress of the crib. Such an impact results in a rapid deceleration of the head, and the brain experiences a coup-contrecoup injury by moving back and forth within the confines of the skull. Some infants have been subjected to multiple episodes of shaking.[20] Shaking of an infant or young child subjects the brain to rotational acceleration, which is capable of generating greater force and speed than linear acceleration, which is the type of acceleration that occurs with a fall. It has been postulated that severe repeated shaking of an infant or young child can lead to disruption of the neuronal cells, with or without the presence of either subarachnoid or subdural hemorrhage. Hemorrhage is a marker for the event but may be of limited clinical significance, and death, when it occurs, may not be related to bleeding, brain compression, or brain displacement. Injury to the brain cells is referred to as *traumatic axonal injury.* This injury results in disruption of the cell membrane and subsequent cerebral edema. Cerebral edema impedes the cerebral circulation, which results in further hypoxic damage to the brain. At autopsy, special staining techniques allow for the recognition of axonal injury, which may be diffuse (diffuse axonal injury).[21,22]

Retinal hemorrhages are another common associated finding and are reported to be present in about 85% of cases of shaken baby syndrome. Approximately two thirds of these children have retinal hemorrhages that are multilayered, are too numerous to count, and extend to the periphery of the retina (Fig. 66-9). The pathophysiology of retinal hemorrhages is uncertain. Current evidence points to vitreoretinal traction as a significant factor in causing retinal hemorrhage as an infant's head undergoes forceful rotational movement in which centrifugal forces are generated. It is unclear what role other factors, such as increased intracranial pressure and hypoxia, may have on the development of these hemorrhages as well. Hemorrhages may involve the vitreous in front of the retina, and retinal hemorrhages are categorized as preretinal, intraretinal, or subretinal. More superficial intraretinal hemorrhages that spread between nerve fibers may be described as flame or splinter hemorrhages, and deeper intraretinal hemorrhages may be described as "dot" or "blot" hemorrhages. Clinically, the hemorrhages may be localized or may extend to the ora serrata (the retinal edge). Extensive retinal hemorrhages have been shown to not result from typical resuscitation efforts but can occur from severe accidental mechanisms associated with rotational head movement, such as rollover motor vehicle collision or crush injuries to the chest with massive increase in intrathoracic venous pressure (Purtscher's syndrome).[23]

Abdominal trauma accounts for about 10% of injuries in abused children and carries a sixfold higher mortality rate than abdominal trauma caused by accidental means.[24] Trauma is often blunt and includes blows and kicks to the abdomen. Frequently, there is no external evidence of the injury because the force has been transmitted to the intra-abdominal structures. Injuries that include hematomas or lacerations can occur to the liver or less commonly to the spleen. In addition, children may develop duodenal hematomas, an injury that leads to symptoms of upper intestinal obstruction. Perforations of the intestine or other hollow viscera can follow a blow to the abdomen, with subsequent progression to secondary peritonitis. Pancreatitis is also a sequela of inflicted abdominal trauma, which is said to be the most common mechanism of non–medication-associated pancreatitis in children. Pancreatic pseudocyst may develop as a complication of such trauma.[25]

www.ketabpezeshki.com 66485457-66963820

Child Sexual Abuse

Physical findings present when a child or adolescent has been sexually abused depend on the nature of the abuse, the time since the abuse, and whether the abuse was repetitive or isolated. Acute injuries include disruptions (tears) of the hymen, petechiae, hematomas, or tears of other genital structures. The prepubescent hymen is significantly more fragile and more easily traumatized than the postpubertal hymen, which thickens and becomes redundant under the influence of estrogen. Physical changes in the anogenital area also may be noted when there has been prior or recurrent sexual abuse. Changes include loss of hymenal tissue and the appearance of U-shaped disruptions in the hymenal contour. Anal findings include the presence of scars and changes in anal tone and the anal contour.[26] Evidence of recent trauma also may be visible in the anal area. Acutely, there may be lacerations that appear as perianal fissures, which are characteristically wider distal to the anus. There may be post-traumatic dilation, or alternatively, anal spasm may occur in response to submucosal injury. In abused boys the penis rarely has a noticeable injury.

CLINICAL FEATURES

Signs and Symptoms

Child Physical Abuse

Children who have been physically abused may have complaints related to the abuse, or injuries may be noted during the course of an evaluation for an unrelated medical condition. Infants with head injuries may have nonspecific signs that go unrecognized as being related to inflicted head trauma. These signs may include apnea, altered mental status, an apparent life-threatening event, vomiting, or a seizure. Clinicians should remain alert that these signs may be related to intracranial bleeding or elevated intracranial pressure.[27] A careful physical examination should include an attempt to visualize the eyegrounds to determine if there is any evidence of retinal hemorrhages. Bruises on a young infant's face are suspicious for head injury (Fig. 66-10).

Refusal to use an extremity or to bear weight may be an indication of a fracture. Similarly, swelling of an extremity may be a sign of a skeletal injury. Children with older, healing fractures may have none of these symptoms, however.

Figure 66-10. Bruises on a child's face suggest occult head injury. (Courtesy Carol Berkowitz, MD.)

Children with abdominal injuries may have abdominal pain, vomiting, abdominal distention, or shock. In cases of inflicted trauma, the history may be unrevealing or may be inconsistent with the medical findings. It is common for a parent to state that he or she is uncertain how a child sustained the injury or that the child was well at bedtime and awoke in the morning refusing to walk or had severe abdominal pain. Caregivers should be queried about how they think the injury was sustained. In cases of inflicted head trauma, the scenario often includes a young infant left in the care of a male friend or partner of the mother who has gone to work or to run errands. The male companion asserts that the infant was fine, sleeping in the crib when he went to take a shower or make some coffee, and when he returned to check on the infant, the infant was not breathing or was seizing. Often the mother is called before the individual calls 911, or the infant is scooped up by the individual and carried to a hospital. The part of the history that is omitted is that the infant was crying and the companion shook the infant and thrust him or her back into the crib. The infant sustained acute traumatic axonal injury and stopped crying. The infant was then left unattended, seemingly asleep. As bleeding and cerebral edema develop, other symptoms intervene. Sometimes a family member fallaciously relates a history of a fall, usually from a height (<25 inches from the ground) to a floor that is often carpeted. Or the family member may relate that a young sibling hit or jumped on the infant. Such events are not consistent with severe intracranial injuries.[28] Histories of falls also are related in children with severe inflicted abdominal trauma. Although falls may lead to bruises of the abdominal wall and rarely damage to solid organs, they are unlikely to cause intestinal injury, such as duodenal hematomas or intestinal perforations.[29] Other mechanisms of abdominal injury include those related to seat belt restraints or an impact with handlebars. The latter is associated with pancreatic trauma. In addition to the history of the current event, past medical, developmental, and social histories are important. In children with acute injuries consistent with physical abuse, there is the possibility that the findings or their severity may be related to an underlying medical condition. A careful medical history may help exclude such conditions or bring these disorders into consideration. A history of epistaxis and bleeding gums in a child with bruises suggests an underlying coagulopathy. A family history of fractures raises the possibility of a bone disorder, such as osteogenesis imperfecta. Documenting a developmental history is important in attempting to assess the likelihood that children's injuries were related to their own activity. It is crucial to be suspicious of injuries in young infants who have limited motor skills. A caregiver may allege that a 3-week-old infant sustained a head injury when he or she fell after having been placed in the center of the bed, but a 3-week-old infant is developmentally unable to scoot or roll from the center to the edge of the bed. The developmental history should document major motor milestones, such as age of rolling over, sitting unsupported, crawling, and walking.

A social history also is important. It may be helpful for a social worker to assist with a comprehensive social interview, but the clinician can obtain basic information, such as family financial resources (e.g., are the parents working?), where the family lives, what the family's support system is (is there extended family around?), whether there has been domestic violence within the family unit, whether there is substance abuse, and whether the family has ever been reported to child protective services.

A comprehensive physical examination should be conducted. Growth parameters should be obtained and plotted to determine if there is evidence of growth impairment or failure to thrive. It is helpful to have a diagram or outline of the body to allow for precise documentation of the size and location of bruises. In addition to the routine examination, there should be a thorough inspection of the infant to detect areas of swelling or tenderness

www.ketabpezeshki.com 66485457-66963820

as might occur with fractures. The abdomen should be palpated carefully for tenderness or masses. A thorough neurologic examination should be performed, and a careful ophthalmologic examination should be carried out. It is frequently difficult to visualize the fundi of young infants without the benefit of pupil dilation and an indirect ophthalmoscope. Specialized retinal cameras allow for documentation of the findings; often ophthalmologic consultation for assessment of the fundi is requested.

Child Sexual Abuse

Children who have been sexually abused may have a history of an abusive event (e.g., "my Uncle Joey touched me"), anogenital injuries, or other related anogenital physical findings, such as a vaginal discharge. Some children have stress-related symptoms, such as recurrent headaches or abdominal pain. Concerns about sexual abuse may be raised by divorcing parents when child custody is in dispute. Other patients, particularly older children and adolescents, may be brought to the emergency department by investigative agencies for a physical examination because of a disclosure about recent or prior abuse, even in the absence of any physical or medical complaints.

The medical evaluation should include a history of the events surrounding the alleged molestation. If the child is verbal and willing to disclose to the clinician, this information should be obtained and recorded in the medical record in the patient's own words as much as possible. The report with the disclosure is admissible as evidence. In other cases, the history may be related by other individuals, such as parents, social workers, or law enforcement officers, who are accompanying the patient. The history should include who did what, when, where, and how often. To facilitate communication and understand what the child is discussing, inquiries regarding the terms the child uses for different parts of the body can be helpful.

Past medical history also should be noted, including previous anogenital injuries, surgeries, or symptoms such as the presence of vaginal discharges or recurrent urinary tract infections. Stool patterns should be noted and, if constipation is reported, whether any anal medications (suppositories or enemas) are used. In postpubertal girls, a menstrual history, including age of menarche and type of sanitary protection, as well as a sexual history, should be recorded.

The physical examination should include a full head-to-toe assessment to determine if there are acute nongenital injuries (e.g., grip marks or oral injuries) or dermatologic conditions, such as lichen planus, which may explain changes in the anogenital area. The anogenital examination should note the level of pubertal development; whether the child is prepubertal or at a more advanced stage of sexual maturity should be recorded. Prepubertal children should be examined with use of a multimethod approach.[30] Initially, children should be evaluated in the supine position. The labia majora and surrounding tissues should be assessed for evidence of injuries or other abnormalities. Separation or traction should be applied to the labia to visualize the structures covered by the labia majora. In prepubertal children the labia majora are large and full and cover the underlying area. The labia minora are small and delicate and do not fully encircle the vaginal orifice. The clitoris and urethra should be examined. The hymen should be inspected visually for evidence of disruptions and irregularities. The hymen should be precisely described—the phrase "hymen intact" is not sufficiently descriptive for the purposes of a forensic medical assessment. An appropriate description would be "hymen pink, annular, with smooth thin edge and no disruptions." The hymenal diameter is difficult to measure reliably, and an enlarged hymenal orifice without other changes in the hymen is not thought to have forensic significance. Girls also should be examined in the prone knee-chest position; however, young prepubertal girls may have difficulty holding this position. The hymen often relaxes more fully in the knee-chest position, allowing for a more thorough assessment. Speculum examinations are neither indicated nor appropriate for a prepubertal child. If intravaginal trauma is suspected on the basis of vaginal hemorrhage, examination of the child in the operating room with anesthesia is mandatory. Postpubertal adolescents should be examined on a traditional pelvic examination table with stirrups. In cases of acute sexual assault, a full evidentiary assessment, including the collection of forensic material, is indicated.

DIAGNOSTIC STRATEGIES

Child Physical Abuse

Diagnostic studies should be done to determine the extent of the injuries, detect occult injuries, and exclude medical conditions that may account for the findings. If there is evidence of hemorrhage, such as cutaneous bruises or intramuscular hematomas, coagulation studies are indicated. As a baseline, these studies would include a platelet count, prothrombin time, and partial thromboplastin time. It would be appropriate also to obtain a complete blood count to rule out a blood dyscrasia, such as leukemia in a child with multiple ecchymoses. Occasionally, rarer coagulation deficiencies may cause bruising; the detection of such disorders requires more specific diagnostic studies. In a child with suspected burn injuries, skin cultures are appropriate to rule out infections with *Staphylococcus aureus,* such as occur with bullous impetigo.

In general, children younger than age 2 to 3 years with suspected inflicted injuries should be evaluated with a skeletal series, sometimes referred to as a *trauma X* or *trauma series.* A trauma series includes radiography of the skull, long bones, ribs, and vertebrae. The presence of multiple fractures, particularly ones in different stages of healing, is the hallmark of the battered child syndrome. Acutely, some fractures, such as rib injuries, may not be readily visible. For cases with a high index of concern for skeletal injury, repeating the skeletal survey 2 weeks later may show evidence of callus formation and make a fracture more readily appreciated. Alternatively, a radionuclide bone scan can detect subtle injuries and should be performed if there is concern for a skeletal injury but the skeletal survey is negative.

Urinalysis, liver function studies, and serum amylase and lipase levels should be considered in children with symptoms of abdominal injury, such as vomiting, abdominal pain, or guarding, though the sensitivity of such studies is limited.[31] Plain x-ray films are rarely helpful but should be considered if clinical findings suggest perforation or obstruction. Computed tomography scan of the abdomen is a more precise way of delineating any abdominal injury. Computed tomography scan of the head is indicated when symptoms are consistent with head trauma or in an infant with facial bruising. Computed tomography scans may reveal extra-axial hemorrhage or findings consistent with cerebral edema. If the child is sufficiently stable, magnetic resonance imaging is helpful in determining the age of the hemorrhages and in assessing whether there has been prior intracranial hemorrhage. Magnetic resonance imaging also eliminates ionizing radiation exposure related to computed tomography scans of the head.

In recent years, certain metabolic disorders have been described that also may be associated with intracranial hemorrhage. In particular, glutaric aciduria type I may be mistaken for inflicted head trauma.[32] Urinalysis for organic and amino acids would detect this condition.

A careful ophthalmologic examination is crucial. The examination is best done by a pediatric ophthalmologist. Photographic

www.ketabpezeshki.com 66485457-66963820

recording of the retinal findings is an important part of the diagnostic workup. Photographing cutaneous injuries is also important and frequently can be carried out by a police criminalist, whose equipment includes color bars for accurate documentation of the coloration of the bruising.

Child Sexual Abuse

Child sexual abuse assessments are best done with equipment that allows for magnification of the genital tissue. An otoscope or hand-held magnifier is usually available in an emergency department. Centers that evaluate sexually abused children often use colposcopes with photographic or video capability or both to allow for recording of the physical findings. Magnification allows for the detection of microtrauma or small changes in the hymen that may not be readily apparent to the naked eye. Toluidine blue is a stain that is used to increase the ease with which minor injuries are detected. The dye is selectively taken up by endothelial cells exposed by the trauma. The collection of forensic specimens for the detection of sperm or for the retrieval of DNA of the alleged perpetrator is indicated in cases of acute sexual assault.

Evaluating a child or adolescent for the presence of a sexually transmitted infection (STI) depends on many factors, including disease prevalence in the community, patient symptoms, and the nature of the abuse. In cases of acute assault, the recommendation is often to treat the adolescent patient prophylactically against gonorrhea, chlamydia, and trichomoniasis. The prepubertal child, however, is at lower risk of acquiring an STI from abuse or assault, and prepubertal girls are at lower risk of developing ascending pelvic infection from an STI. As a result, if the prepubertal child is available for follow-up visits, prophylaxis for gonorrhea, chlamydia, and trichomoniasis may be deferred. The decision to offer prophylaxis against human immunodeficiency virus is often based on disease prevalence and other risk factors and should be made in conjunction with an infectious disease consultant (Table 66-4).[33]

Part of the assessment of a sexually abused child may include a detailed interview. Forensic interviews are carried out by an individual with expertise in interviewing children, such as a social worker or clinical psychologist. Although the preliminary interview may be carried out in an emergency department, a more in-depth interview often takes place in a diagnostic center where it may be videotaped or observed (through a one-way mirror) by other individuals, such as law enforcement officers or criminal prosecutors. This approach minimizes the number of times a child or adolescent needs to be questioned about the alleged abusive events.

Table 66-4 Sexually Transmitted Infection Prophylaxis or Treatment after Sexual Abuse/Assault

DISEASE	TREATMENT
Child, or Weight below 45 kg	
Gonorrhea	Ceftriaxone 125 mg IM (one dose) Cefixime 8 mg/kg (one dose; maximum dose 400 mg)
Chlamydia	Erythromycin base 50 mg/kg/day divided qid × 14 days
Trichomoniasis	Metronidazole 15 mg/kg/day PO divided tid × 7 days
Syphilis	Benzathine penicillin 50,000 units/kg IM (one dose; maximum dose 2.4 million units)
HSV infection (first clinical episode)	Acyclovir 80 mg/kg/day divided tid × 7-10 days
Hepatitis B*	HBIG 0.06 mL/kg IM, vaccine series
HIV infection	Contact local infectious disease specialist
Adolescent, or Weight above 45 kg	
Gonorrhea	Ceftriaxone 250 mg IM (one dose) or cefixime 400 mg PO (one dose)
Chlamydia	Older than 8 years: azithromycin 1 g PO (one dose), or doxycycline 100 mg PO bid × 7 days
Bacterial vaginosis	Metronidazole 500 mg PO bid × 7 days, or metronidazole gel 0.75% 5 g intravaginally daily × 5 days, or clindamycin cream 2% 5 g intravaginally qhs × 7 days
Trichomoniasis	Metronidazole 2 g PO (one dose)
Syphilis	Benzathine penicillin 2.4 million units IM (one dose)
HSV (first clinical episode)	Acyclovir 400 mg PO tid × 7-10 days, or valacyclovir 1 g PO bid × 7-10 days
Hepatitis B*	HBIG 0.06 mL/kg IM, vaccine series
HIV	Contact local infectious disease specialist

Adapted from Workowski KA, Berman SM: Sexually transmitted diseases treatment guidelines, 2010. MMWR 59:1, 2010; and 2009 Red Book: Report of the Committee on Infectious Diseases, 28th ed. Elk Grove, Ill, American Academy of Pediatrics, 2009.
HBIG, hepatitis B immunoglobulin; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *IM,* intramuscularly; *PO,* orally.
*Unimmunized child and perpetrator with acute hepatitis B infection.

DIFFERENTIAL CONSIDERATIONS

Child Physical Abuse

The major differential diagnosis when considering child abuse is unintentional injury. Differentiating between inflicted and noninflicted injuries requires the consideration of multiple factors, including the developmental stage of the child, the extent of the injuries, whether the injuries appear to have occurred over a period of time, whether there were witnesses to the alleged event, whether medical care was sought in a timely manner, and whether the injuries could have been sustained in the stated manner. It is important for the evaluating clinician to have an understanding of normal child development, particularly the acquisition of motor skills. Children who are ambulatory, particularly toddlers and young school-age children, are prone to bruises over bony prominences, such as the shins and forehead. Noninflicted bruises are usually unilateral, occurring on the side where a fall or collision with a solid object has occurred. Bruises in protected areas, such as the neck, medial thighs, and posterior auricular areas, must be explained by the mechanism of injury and are unusual in noninflicted trauma.

Areas of congenital dermal melanocytosis (formerly called *mongolian spots*) are bluish discolorations that are seen normally over the buttocks and lower spine in children with darker complexions (Fig. 66-11). These spots can appear on other parts of the body, such as the face and upper arm. They are usually present from birth but may not appear until the infant is several weeks old. When seen in a typical location, they are readily recognized, but when located elsewhere on the body, they may be mistaken for bruises. Bruises resolve over time; however, these spots remain unchanged (do not go through purple-green-yellow-brown transformation) because they are undistributed melanocytes.

Phytophotodermatitis also may be mistaken for bruises or burns. This condition is the result of a phototoxic reaction that develops on sun-exposed areas of the body that have been in contact with certain fruits or juices such as lime or lemon juice. The lesion initially appears as erythema and blistering and evolves to a brown discoloration, which may take the shape of the dripped

www.ketabpezeshki.com 66485457-66963820

Figure 66-11. Dermal melanocytosis in an infant. (Courtesy EMSC Slide Set, National EMSC Resource Alliance.)

Figure 66-12. Phytodermatitis on the thigh of a young girl. (Courtesy Sara T. Stewart, MD, MPH.)

juice or the object with which the juice came in contact (Fig. 66-12). For instance, if a mother is making lemonade, has the lemon juice on her hand, and holds her child, a brown discoloration in the form of a handprint may appear if the child is in the sun. These lesions fade over time, and with a careful history and physician familiarity with the condition, the correct diagnosis can be made.

Burns also may occur unintentionally. Unintentional burns are usually secondary to spills and may take the form of drip marks down a child's chest. Bullous impetigo can be mistaken for second-degree burns because of its blister-like appearance. Culturing the lesion reveals the presence of *S. aureus* in the case of bullous impetigo. Certain dermatologic conditions, such as epidermolysis bullosa, also may cause bullous lesions that may resemble second-degree burns. The history and generalized appearance of these lesions help establish the correct diagnosis.

Fractures may occur unintentionally. In young infants, fractures may be a result of birth-related injuries. The most common fractures sustained during birth are clavicular and humeral fractures. These fractures may not be appreciated immediately after birth but become apparent when callus formation is noted. Ambulatory children may sustain fractures related to falls. A toddler's fracture, also referred to as a *CAST fracture* (*c*hildhood *a*ccidental *s*piral *t*ibial fracture), occurs when there is a twisting injury to the tibia as the child falls on it.[34] Often, this fall was not witnessed or was not noted by the caretaker as being significant trauma, so the child may have no reported history of trauma. Typically, the fracture is a nondisplaced distal fracture of the tibia that is detected when a child demonstrates a limp. Sometimes the fracture may not be apparent on the initial radiograph, but delayed radiographs (1-2 weeks after injury) may show callous formation or a bone scan may show the presence of increased bony uptake in the area of the fracture.

Fractures occur with increased frequency and with lower amounts of force in certain conditions. Premature infants may experience osteopenia of prematurity (sometimes referred to as *rickets of prematurity*), the radiographic appearance of which can be mistaken for a metaphyseal fracture.[35] In addition, osteopenic bones may fracture more easily. More advanced cases of osteopenia can be noted on a plain film of the bones. Osteogenesis imperfecta is a condition in which the bone is more brittle and easily disrupted.[36] There are multiple types of osteogenesis imperfecta, each with a different gene frequency. The overall incidence of osteogenesis imperfecta is 1 in 20,000. In general, osteogenesis imperfecta is associated with other clinical findings, such as blue sclerae and brown discoloration of the teeth (dentinogenesis imperfecta). Rarely, bone fragility may be present in isolation. Scurvy, congenital syphilis, and congenital rubella are associated with bony changes that may be misinterpreted as evidence of prior bony injury.

Cerebral edema may occur with infection, such as encephalitis and meningitis, or after a hypoxic event. The history and the presence of associated medical findings help with the differentiation of these conditions.

Child Sexual Abuse

Numerous medical conditions may be misdiagnosed as child sexual abuse. Accidental trauma, most commonly straddle injuries, may occur after a fall onto the perineum. Such falls occur with climbing on monkey bars, riding on boys' bicycles, or exiting from a swimming pool. Straddle injuries usually involve the more external structures, including the labia minora, labia majora, and periurethral area. The hymen remains uninjured. Lichen sclerosus et atrophicus is a dermatologic condition of unclear cause that affects prepubertal girls and boys and postmenopausal women. The hymen is unaffected, but the adjacent skin becomes atrophic and may sustain blood blisters or petechiae (Fig. 66-13A). Characteristically, the skin in the perianal and perihymenal areas becomes hypopigmented and surrounds these orifices with a pale figure-of-eight configuration (Fig. 66-13B).

Urethral prolapse characteristically affects African American girls aged 5 and 8 years. The mucosal lining of the urethra slides forward and protrudes from the urethral orifice, appearing as an erythematous, edematous mass (Fig. 66-14). Symptoms include pain and bleeding. Management may involve sitz baths, antibiotic ointment, or referral to a urologist for ligation. Vaginal discharge may occur secondary to conditions other than STIs. *Shigella,* group A beta-hemolytic streptococci, *Candida,* pinworm infestation, and vaginal foreign bodies can cause a vaginal discharge.

Penile swelling may occur with balanoposthitis, priapism (often secondary to sickle cell disease), paraphimosis, or an infestation with chiggers. Fissures and tags in the perianal area may result from trauma but also may be associated with constipation and inflammatory bowel disease. Group A beta-hemolytic streptococci can cause painful inflammation with erythema in the perianal area (Fig. 66-15). Affected children may be febrile and experience pain with defecation. Hemorrhoids are rare in children and are associated with conditions that lead to an elevation of intra-abdominal venous pressure, as occurs with cirrhosis of the liver.

www.ketabpezeshki.com 66485457-66963820

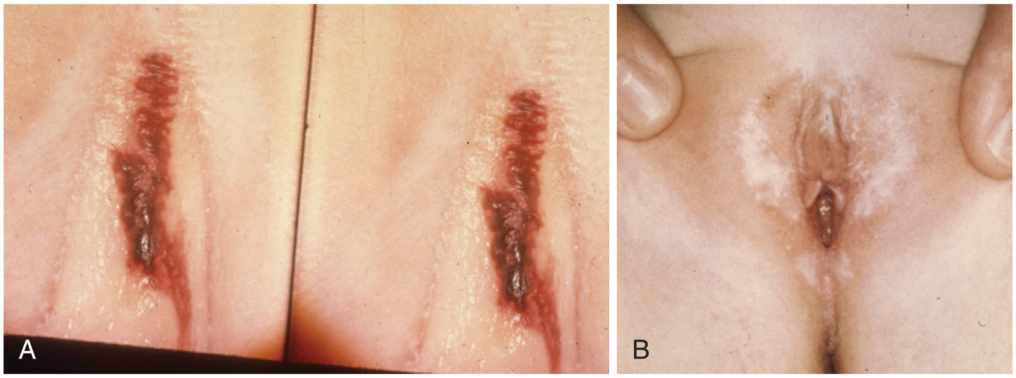


Figure 66-13 Lichen sclerosus et atrophicus. **A,** Microtrauma resulting in bruising that can be mistaken for abuse. **B,** Figure-of-eight hypopigmentation. (Courtesy Carol Berkowitz, MD.)

MANAGEMENT

The focus of management is to attend to serious or life-threatening injuries, such as significant head or abdominal trauma, and stabilize the patient. Physical problems requiring medical intervention, such as fractures, lacerations, burns, or STIs, should be managed appropriately. Key to the ultimate management of the abused child is the precise recording of the pertinent history, particularly any disclosure made by the child, and careful documentation of the physical findings. Most states require the completion of a specific child abuse reporting form as a means of notifying the authorities about the suspected case of child abuse. In addition, many jurisdictions require immediate telephonic notification to initiate an investigation of the circumstances surrounding the abuse.

Figure 66-14. Urethral prolapse. (Courtesy Carol Berkowitz, MD.)

DISPOSITION

Admission to the hospital may be warranted because of the patient's injuries, to complete the medical evaluation, and to protect the child while the evaluation is occurring. Many hospitals have suspected child abuse and neglect (SCAN) teams. These teams can offer expert consultation either in the emergency department or after the child has been admitted. SCAN teams usually have unique expertise in assessing the genital findings in prepubertal girls.

Issues may arise with the family regarding "allowing" the child to be admitted to the hospital once the concerns of the emergency physician are related to the family. If there is concern for staff or patient safety, a strong security presence is advised during both disclosure of the intent to file a report of possible child abuse and when the decision is made to admit the child to the hospital. If security is not available to provide support to the emergency physician and there is concern for personal safety, the addition of other hospital personnel should be solicited.

The outcome for an abused child varies with the nature, extent, and duration of the abuse. Some children die as a result of their inflicted injuries. Others have irreversible brain damage and may spend the remainder of their lives confined to wheelchairs or be blind or otherwise disabled. For other children, intervention and therapy for themselves and their offending parents may help reverse the adverse psychological effects of the abuse. The emergency physician has a key role in the early detection of the problem. The entire medical team, along with social services, law enforcement, and the judicial system, is responsible for implementing a treatment plan that prevents recidivism.

Figure 66-15. Perianal strep infection in an infant. (Courtesy Carol Berkowitz, MD.)

www.ketabpezeshki.com 66485457-66963820

KEY CONCEPTS

- The emergency physician is mandated to report suspicion of child physical or sexual abuse.
- The actual oral and/or written report can be generated by the physician, the social worker, or a member of the hospital's child abuse team with whom the physician has consulted. In infants and young children with any injury, the emergency physician should consider child physical abuse as a diagnosis and especially with certain injuries, such as unusual bruising; scapula, rib, or metaphyseal fractures; patterned bruises or burns; and injuries in preambulatory infants.
- Children who have been sexually abused may have vague presenting complaints, such as poor sleep pattern or recurrent abdominal pain, or may have vaginal bleeding or discharge.
- Numerous conditions mimic child abuse and should be considered in the differential diagnosis, such as dermal melanocytosis (formerly called *mongolian spots*), lichen sclerosus, impetigo, or urethral prolapse.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Goldman J, Salus MK, Wolcott D, Kennedy KY: *A Coordinated Response to Child Abuse and Neglect: The Foundation for Practice. Child Abuse and Neglect User Manual Series*. Washington, DC: U.S. Government Printing Office; 2003. Available at www.childwelfare.gov/pubs/usermanuals/foundation/foundationc.cfm. Accessed January 11, 2013.
2. Roesler TA, Jenny C: *Medical Child Abuse: Beyond Munchausen Syndrome by Proxy*. Elk Grove Village, Ill: American Academy of Pediatrics; 2008.
3. Kempe CH, Silverman FN, Steele BF, Droegemueller W, Silver HK: The battered child syndrome. *JAMA* 1962; 181:17.
4. Woodling BA, Kossoris PD: Sexual misuse: Rape, molestation and incest. *Pediatr Clin North Am* 1981; 28:481.
5. U.S. Department of Health and Human Services, Administration on Children, Youth and Families: *Child Maltreatment 2009*. Washington, DC: U.S. Government Printing Office; 2010. Available at http://www.acf.hhs.gov/programs/cb/stats_research/index.htm#can. Accessed January 11, 2013.
6. Wulczyn F: Epidemiological perspectives on maltreatment prevention. *Future Child* 2009; 19:39.
7. Dubowitz H, Bennett S: Physical abuse and neglect of children. *Lancet* 2007; 369:1891.
8. Maguire S, Mann MK, Sibert J, Kemp A: Can you age bruises accurately in children? A systematic review. *Arch Dis Child* 2005; 90:187.
9. Jenny C, Reece RM: *Cutaneous manifestations of child abuse*. In: Reece RM, Christian CW, eds: *Child Abuse: Medical Diagnosis and Management*, 3rd ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009:19-51.
10. Kellogg N: American Academy of Pediatrics Committee on Child Abuse and Neglect: Oral and dental aspects of child abuse and neglect. *Pediatrics* 2005; 116:1565.
11. Swerdlin A, Berkowitz C, Craft N: Cutaneous signs of child abuse. *J Am Acad Dermatol* 2007; 57:371.
12. Kos L, Shwayder T: Cutaneous manifestations of child abuse. *Pediatr Dermatol* 2006; 23:311.
13. Maguire S, Moynihan S, Mann M, Potokar T, Kemp AM: A systematic review of the features that indicate intentional scalds in children. *Burns* 2008; 34:1072.
14. Thompson S: *Fractures, sprains, and dislocations*. In: Osborn LM, DeWitt TG, First LR, Zenel JA, eds: *Pediatrics*. Philadelphia: Elsevier Mosby; 2005.
15. Kemp AM, et al: Patterns of skeletal fractures in child abuse: Systematic review. *BMJ* 2008; 337:a1518.
16. Bulloch B, et al: Cause and clinical characteristics of rib fractures in infants. *Pediatrics* 2000; 105:e48.
17. Maguire S, et al: Does cardiopulmonary resuscitation cause rib fractures in children? A systematic review. *Child Abuse Negl* 2006; 30:739.
18. Hymel KP, Makoroff KL, Laskey AL, Conaway MR, Blackman JA: Mechanisms, clinical presentations, injuries, and outcomes from inflicted versus noninflicted head trauma during infancy: Results of a prospective, multicentered, comparative study. *Pediatrics* 2007; 119:922.
19. Chiesa A, Duhaime AC: Abusive head trauma. *Pediatr Clin North Am* 2009; 56:317.
20. Adamsbaum C, Grabar S, Mejean N, Rey-Salmon C: Abusive head trauma: Judicial admissions highlight violent and repetitive shaking. *Pediatrics* 2010; 126:546-555.
21. Gerber P, Coffman K: Nonaccidental head trauma in infants. *Childs Nerv Syst* 2007; 23:499.
22. Case ME: Inflicted traumatic brain injury in infants and young children. *Brain Pathol* 2008; 18:571.
23. Levin A: Retinal hemorrhage in abuse head trauma. *Pediatrics* 2010; 126:961
24. Pariset JM, Feldman KW, Paris C: The pace and symptoms of blunt abdominal trauma to children. *Clin Pediatr* 2010; 49:24
25. Trokel M, DiScala C, Terrin NC, Sege RD: Patient and injury characteristics in abusive abdominal injuries. *Pediatr Emerg Care* 2006; 22:700.
26. Finkel MA: *Sexual abuse: The medical examination*. In: Giardino AP, Alexander R, eds: *Child Maltreatment*, 3rd ed. St Louis: GW Medical Publishing; 2005:253-288.
27. Jenny C, Hymel KP, Ritzen A, Reinert SE, Hay TC: Analysis of missed cases of abusive head trauma. *JAMA* 1999; 281:621.
28. Chadwick DL, et al: Annual risk of death resulting from short falls among young children: Less than 1 in 1 million. *Pediatrics* 2008; 121:1213-1224.
29. Barnes PM, et al: Abdominal injury due to child abuse. *Lancet* 2005; 366:234.
30. Adams JA, et al: Guidelines for medical care of children who may have been sexually abused. *J Pediatr Adolesc Gynecol* 2007; 20:163.
31. Eppich WJ, Zonfrillo MR: Emergency department evaluation and management of blunt abdominal trauma. *Curr Opin Pediatr* 2007; 19:265.
32. Hartley LM, Khwaja OS, Verity CM: Glutaric aciduria type 1 and nonaccidental head injury. *Pediatrics* 2001; 107:174.
33. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC): Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep* 2010; 59:1.
34. Halsey MF, et al: Toddler's fracture: Presumptive diagnosis and treatment. *J Pediatr Orthop* 2001; 21:152.
35. Mitchell SM, et al: High frequencies of elevated alkaline phosphatase activity and rickets exist in extremely low birth weight infants despite current nutritional support. *BMC Pediatr* 2009; 29:9.
36. Byers PH, Krakow D, Nunes ME, Pepin M: Genetic evaluation of suspected osteogenesis imperfecta. *Genet Med* 2006; 8:383.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 67

SEXUAL ASSAULT

Laura Slaughter

PERSPECTIVE

Background

Sexual violence is a significant problem in the United States. The Centers for Disease Control and Prevention have defined it as sexual activity in which consent is not obtained or not freely given. It pertains to a wide variety of sexual conduct and may entail, but does not require, penetration, completion, or, in certain cases, physical contact (e.g., voyeurism).[1] Referred to in statute as *sexual assault,* it is explicated more precisely by state and local governments. Emergency physicians should be aware of local, state, and federal laws because emergency physicians may be mandated reporters and involved in the evaluation, treatment, evidence collection, and documentation of sexual assault.

Major advances in the evaluation and management of sexual assault victims (SAVs) have occurred over the past 30 years. The formation of community-based multidisciplinary teams that first took hold in California is probably the most important. The development of a sexual assault response team (SART) with representatives from the district attorney's office, law enforcement officials, crime laboratory personnel, medical personnel, including both physicians and nurses, social service agents, and victim advocates came together as a group. These major players have sought to solve the logistic, medical, psychological, legal, and social problems incurred by SAVs. The commitment and mutual cooperation of the SART led to the development of standardized protocols for the care and treatment of SAVs. These protocols specify the procedures for interviewing and examining the SAV and collecting, preserving, and storing evidentiary materials, and include the evidence kit and forms for documentation. Many jurisdictions have adopted this standardized system, and in 2004 the first national protocol was released by the U.S. Department of Justice.[2] With a protocol in place, the necessity of having trained forensic examiners (FEs), irrespective of academic credentials, is evident.[3,4] Currently, this role subsumes that of the sexual assault nurse examiner (SANE); the ubiquitous, mostly hospital-based SANE programs have contributed substantially to our knowledge and understanding of sexual assault and have improved the care of the victims.[5,6] In addition, because of the use of special technologies, including colposcopy, digital photography and videography, and the alternate light source (ALS), the establishment of designated examination centers for sexual violence is increasingly prevalent.[7] Much information about the characteristics, physical examination findings, and correlates of injury in SAVs is now available. This information facilitates the management of the SAV, improves the experience of the victim, and ultimately assists in the identification of the perpetrator.

Although these changes began as a grassroots movement, a victim-centered, multidisciplinary team approach, including trained FEs, was codified by the federal government in the 1994 Violence Against Women Act (VAWA) and its subsequent iterations in 2000 and 2005. Forensic compliance issues for all states receiving grant monies from this bill began in 2009. Programs must now offer forensic examinations for all SAVs irrespective of whether they report or cooperate with law enforcement and with no out-of-pocket expenses to the SAV. This poses special problems for medical professionals practicing in states in which they are mandated reporters. As many as 18.5% of SAVs who delayed law enforcement involvement, changed their minds[8]; this raises multiple issues concerning evidence storage, as well as maintenance and chain of custody. Moreover, victim notification about the destruction of forensic evidence presents challenges in an anonymous system. Currently, health care facilities have no nationally regulated mandates, accreditation process, or quality assurance to address these specific problems. Allowing SAVs time to consider their options[9-11] and providing them with high-quality health care[12,13] have been shown to increase their cooperation with police investigations. (See Figure 67-1 for a sample of a form for special consent without law enforcement participation; also refer to www.ccfmtc.tv/pdfs/forms/CALEMA-924i.pdf for abbreviated examination form and protocol.)

Epidemiology

Based on national emergency department (ED) data, sexual assaults represented 10% of all assault-related injury visits to the ED by female patients in 2006. In 2007, for female individuals of all ages and for boys aged 1 to 9 years, sexual assault was the third leading cause of nonfatal violence-related injury.[14] It is important to note that the cost of sexual violence to the health care system is high because it may include not only the initial visit for the crime but also subsequent visits for other health-related issues.[7]

Women remain the predominate victims (94%), although male victims tend to be victimized at an earlier age.[15] Historically, sexual assault has been a largely unreported crime, with only about a third of SAVs coming forward. The major reasons for not reporting include not wanting the assailant to go to jail, having a prior relationship with the assailant, and feeling that the police would blame the victim or be insensitive. Some have sited fear of reprisal, including death, media attention, and shame, for their reluctance.[16] The closer the relationship between the victim and offender, the less likely the SAV has been to report the crime[17]; the relationship between SAV and perpetrator is often absent in the medical record, yet it is critical for safety planning.[18,19] A

www.ketabpezeshki.com 66485457-66963820

INFORMED CONSENT FOR RESTRICTED SART EXAM

I am requesting a Restricted SART Exam, which means that I want a medical forensic exam to be conducted by a SART nurse, but I have not yet decided if I want to talk with law enforcement.

I have read and understand the following:

1. I will not be billed for this exam, regardless of whether or not I talk with law enforcement.
2. There are many benefits of talking with law enforcement as soon as possible:

   a) Law enforcement has an opportunity to document and collect evidence that will perish and not be available later. This can include evidence from the crime scene(s) and suspect(s).

   b) By conducting interviews as soon as possible – with the suspect(s), witness(es), and anyone else with information – these individuals are more likely to be located and cooperate with law enforcement, and they are more likely to remember important information.

   c) I may be eligible to apply for funds through California Victim Compensation program, to be reimbursed for any out-of-pocket expenses related to this crime.

3. I realize that law enforcement can still conduct an investigation, even if I do not choose to talk with an officer. However, they generally do not pursue such an investigation, except in certain circumstances (for example, in cases with a serial stranger rapist, when the sexual assault is committed by an intimate partner, or when the victim is severely injured).
4. I can decide at any time that I am ready to talk with law enforcement. I understand an investigation becomes more difficult as time goes by, but not necessarily impossible. Other types of evidence may still be available, and people may still be able to provide information in interviews.
5. I understand that I will not be eligible for funds through California Victim Compensation program if I do not participate in a law enforcement investigation.
6. I understand that SART will arrange for the evidence that is collected today will be stored for **5 years** from the date of this exam:

   a) If I decide to talk with law enforcement within the next 5 years, it is my responsibility to call the SART office at (805)781-4878 and inform them of this decision.

   b) On the ____________ day of ____________ in __________, all evidence collected during my medical forensic exam may be ***destroyed without any further notification to me***.

7. I realize that law enforcement may contact me if the same suspect is identified in any future report.

My signature below indicates my understanding of the information above. This document will serve as my authorization for SART to destroy any evidence collected from this medical forensic exam 5 years from the date of the exam – if the SART office has not been contacted to turn the evidence over to law enforcement.

______________________ **Patient's Name (please print)**	______________________ **Nurse's Name (please print)**
______________________ **Patient's Signature**	______________________ **Nurse's Signature**

Today's Date: ____________________

Figure 67-1. Sample form: Consent for restricted forensic examination without law enforcement involvement.

substantial number of SAVs report at or after 72 hours, and they are typically adolescents. There is a high positive correlation between reporting to the police and receiving medical treatment[20]; early intervention is key to diminishing adverse psychological and physical outcomes for the SAV.[17,21]

Sexual assault is an extremely common crime, with estimates of 1 in 6 females and 1 in 33 males being assaulted during their lifetime.[15] The mean age of a female victim is approximately 20 years. She is most often single. Adolescents account for less than half of all victims seen, yet the incidence of sexual assault peaks in the age group of 16 to 19 years.[22] For nearly 40% of victims, sexual assault is the first sexual experience.[23] Eighty percent of the time, a person known to the victim perpetrates the assault.[15] Former and current boyfriends are equally common as perpetrators, lending support to the position that leaving a violent partner does not always end the violence.[19] The younger the victim, the more likely the perpetrator is to be a relative. The location of the sexual assault varies with the victim and the type of perpetrator. In general, adults are usually assaulted in their own home, whereas adolescents are more likely to be assaulted in the assailant's residence.[24] Stranger assaults are less common for both males and females[15]; they are more likely to involve adults, occur outdoors, and include the use of a weapon and have a greater likelihood of injury.[25-27] Alcohol and drug use are common accompaniments to sexual assault.[28] Other vulnerable populations include the mentally or physically disabled, the homeless, elderly individuals, sex trade workers, and those previously incarcerated.[29,30] Higher rates of sexual assault also occur during college, military service, war, and natural disaster.[31]

Most assaults involve penile-vaginal penetration,[32] and penile penetration is significantly associated with genital injury in females.[33] Typically, digital-vaginal penetration is the second most common sexual act reported. Oral-genital contact occurs in less than 30%, with anal assault slightly less common.[23,34-36] The use of a foreign object is unusual (10%) and associated with increased trauma.[32,37] Anal assault is associated with increased

www.ketabpezeshki.com 66485457-66963820

violence,[23,25,38,39] offender preference for anal sex,[40] and offender problems with sexual dysfunction.[41,42]

Injury is not an inevitable consequence of sexual assault.[4,43,44] Adolescent SAVs have been shown to sustain more anogenital injuries than their adult counterparts.[26,32,45] Nongenital trauma occurs in 40 to 81% of SAVs, and its presence is associated with anogenital injury.[39,45] For nongenital trauma, the extremities are the most commonly injured, followed by the head and neck.[46] Serious injury involving hospitalization occurs in about 5%,[7] and death associated with sexual assault is estimated at 1% or less, although this latter figure is probably a gross underestimate.[38,47,48] Psychological distress and interpersonal difficulties are the major sequelae after sexual assault. These problems are exacerbated in SAVs with known attackers who delay reporting.[21,49]

DISTINGUISHING PRINCIPLES OF DISEASE

Emergency Department Preparation

A standardized approach to the management of the SAV is important. This should include, if at all possible, the development of a multidisciplinary team that works together under a protocol. That protocol should address every detail, from the handling of the SAV's first call to dispatch to the referral for psychological support. The SAV should be taken out of the medical triage system that typifies the ED, not only to provide privacy and security for the SAV but also to prevent the deterioration of evidence. This approach ensures a consistent process of evaluation, treatment, and collection of evidence. The medical team should receive forensic training on interviewing and examination techniques; collecting, preserving, and storing evidence; and chain of custody issues. The team should be trained to use the examination form and be thoroughly familiar with the sexual assault kit (rape kit) provided by the state or local crime laboratory. Advocates, whether provided through law enforcement or by a separate entity, need to receive training from the SART about examination procedures and staff roles so they can best advise and counsel the SAV. A SART program cannot be successful unless advocates feel that the SAV will be treated with respect and receive the best treatment available. Because the SART examiner is often the first person on the medical team to greet the victim, a kind, calm, knowledgeable, and professional demeanor is of the utmost importance.

The ED should also be prepared for the unusual victim with significant or life-threatening injuries. In this instance the emergency physician needs to delegate the forensic responsibility to another forensically trained staff member whose sole purpose is to collect the evidence and, if required, follow the SAV to surgery. In cases in which there is substantial injury, following the patient from intake allows the examiner to understand better and document the nature and extent of the trauma and continue the forensic process with little further distress to the patient.[50]

Obtaining the History and Consent

Numerous consents should be obtained from the SAV, depending on state and local laws (Box 67-1). The FE should be knowledgeable about all statutes governing consent, including whether minors need parental consent. In some states, even if parental consent is not required, the FE may still be required to contact the parents and document the success or failure of this attempt. Most SAVs are concerned about access to the SART record and photographs, particularly when the SART examination facility is within the hospital setting. Keeping these records separate from the primary hospital chart system helps protect the privacy of the victim and has a precedent in the similar handling of psychiatric records. Surveys of SAVs have identified that they desire information about sexually transmitted diseases (STDs), pregnancy, emergency contraception, follow-up care, and physical and psychological health effects of sexual assault.[51] Connecting the SAV to outside resources is critically important to care.[52,53]

Providing written information on these topics to the patient and getting his or her signature in confirmation documents the patient's receipt of follow-up recommendations. Before the history taking is begun, the SAV's immediate privacy and personal needs should be addressed. Box 67-2 outlines some of the issues that may make the interview more comfortable for the patient and ensure receipt of reliable historical information from the patient. The group taking the history may include a law enforcement officer, patient advocate, medical assistant, and FE. A detailed history is important. California was the first state to mandate a uniform examination protocol and specific training for examiners (Fig. 67-2).[54]

Box 67-1 Consent Issues in Sexual Assault Cases

Consents should specify that the sexual assault victim's signature acknowledges the following:

- That hospitals and health care professionals are mandated reporters and that an anonymous Jane Doe report can be made
- Receipt of information about victim compensation funds
- Specific understanding of the examination and evidence collection procedures
- Specific understanding of the use of photography in documenting physical and genital injuries
- That information collected will be sent to law enforcement and is obtainable by defense counsel
- That data without patient identity can be collected for valid educational and scientific interest
- That consent may be withdrawn at any time
- That there is no charge for the examination whether reported to law enforcement or not

Box 67-2 Preliminary Issues and Strategies in Preparing for Taking the History from a Sexual Assault Victim (SAV)

Provide quiet, confidential, safe environment.
Briefly review the interview and examination process in private with the SAV.
Explain the sensitive, personal, embarrassing nature of questions and the right to be interviewed without family or friends.
Show concern for the SAV's immediate comfort (e.g., if thirsty, take oral swabs first so SAV may drink).
Provide advocacy.
Try to conduct the interview the same way.
Leave difficult questions until the end; some may need to be repeated during appropriate parts of the physical examination.
Explain why you are asking the question and the possible responses.
Explain that all questions will be asked.

History of Type of Sexual Assault

Questions about sexual acts need to be explicit and phrased in terms understandable to the SAV. Unless specifically asked, many victims will not disclose that injuries are a result of the assault.[19] Language used by the SAV to describe sexual acts should be documented in the medical record. It is important for the FE to ascertain whether the victim voiced her lack of consent and whether that terminated the behavior. The victim's own words should be

Text continued on p. 862

www.ketabpezeshki.com 66485457-66963820

FORENSIC MEDICAL REPORT: ACUTE (<72 HOURS)
ADULT/ADOLESCENT SEXUAL ASSAULT EXAMINATION

STATE OF CALIFORNIA
California Emergency Management Agency

CalEMA 2-923

Confidential Document — **Patient Identification**

A. GENERAL INFORMATION (print or type) — **Name of Medical Facility:**

1. Name of patient				Patient ID number			
2. Address	City		County	State	Telephone (W) (H)		
3. Age	DOB	Gender M F	Ethnicity	Arrival Date	Arrival Time	Discharge Date	Discharge Time

B. REPORTING AND AUTHORIZATION — **Jurisdiction (☐city ☐county ☐other):**

1. Telephone report made to law enforcement agency — Name of Officer | Agency | ID Number | Telephone | Reported by: Name | Date | Time

2. Responding Officer | Agency | ID Number | Telephone

3. I request a forensic medical examination for suspected sexual assault at public expense.

Law enforcement officer | ID number | Agency

Telephone | Date | Time | Case Number

Telephone Authorization
Agency:
Authorizing party:
ID number:
Date/time:

C. PATIENT INFORMATION

- I understand that hospitals and health care professionals are required by Penal Code Sections 11160-11161 to report to law enforcement authorities cases in which medical care is sought when injuries have been inflicted upon any person in violation of any state penal law. The report must state the name of the injured person, current whereabouts, and the type and extent of injuries. ________ (Initial)
- I have been informed that victims of crime are eligible to submit crime victim compensation claims to the State Victims of Crime (VOC) Restitution Fund for out-of-pocket medical expenses, psychological counseling, loss of wages, and job retraining and rehabilitation. ________ (Initial)

D. PATIENT CONSENT

Minors: Family Code Section 6927 permits minors (12 to 17 years of age) to consent to medical examination, treatment, and evidence collection for sexual assault without parental consent. See instructions for parental notification requirements for minors.

- I understand that a forensic medical examination for evidence of sexual assault at public expense can, with my consent, be conducted by a health care professional to discover and preserve evidence of the assault. If conducted, the report of the examination and any evidence obtained will be released to law enforcement authorities. I understand that the examination may include the collection of reference specimens at the time of the examination or at a later date. I understand that I may withdraw consent at any time for any portion of the examination. ________ (Initial)
- I understand that collection of evidence may include photographing injuries and that these photographs may include the genital area. ________ (Initial)
- I hereby consent to a forensic medical examination for evidence of sexual assault. ________ (Initial)
- I understand that data without patient identity may be collected from this report for health and forensic purposes and provided to health authorities and other qualified persons with a valid educational or scientific interest for demographic and/or epidemiological studies. ________ (Initial)

Signature ________________________ ☐ Patient ☐ Parent ☐ Guardian

DISTRIBUTION OF CalEMA 2-923

☐ Original - Law Enforcement ☐ Copy within evidence kit - Crime Lab ☐ Copy - Child Protective Services (if patient is a minor) ☐ Copy - Medical Facility Records

CalEMA 2-923 (Rev 7/02) 1

E. PATIENT HISTORY

1. Name of person providing history: | Relationship to patient: | Date | Time

2. Pertinent medical history:
- Last menstrual period
- Any recent (60 days) anal-genital injuries, surgeries, diagnostic procedures, or medical treatment that may affect the interpretation of current physical findings? ☐ No ☐ Yes
  If yes, describe:
- Any other pertinent medical condition(s) that may affect the interpretation of current physical findings? ☐ No ☐ Yes
  If yes, describe:
- Any pre-existing physical injuries? ☐ No ☐ Yes
  If yes, describe:

3. Pertinent pre- and post-assault related history: (No / Yes / Unsure)
- Other intercourse within past 5 days? ☐ ☐
  If yes,
  anal (within past 5 days)? When ______ ☐ ☐
  vaginal (within past 5 days)? When ______ ☐ ☐
  oral (within past 24 hours)? When ______ ☐ ☐
  If yes, did ejaculation occur? ☐ ☐ ☐
  If yes, where? ________________
  If yes, was a condom used? ☐ ☐ ☐
- Any voluntary alcohol use within 12 hours prior to assault? ☐ ☐*
- Any voluntary drug use within 96 hours prior to assault ? ☐ ☐*
- Any voluntary drug or alcohol use between the time of the assault and the forensic exam? ☐ ☐*

* If yes, collection of toxicology samples is recommended according to local policy. ☐ Blood ☐ Urine

4. Post-assault hygiene/activity: ☐ Not applicable if over 72 hours (No / Yes)
Urinated ☐ ☐
Defecated ☐ ☐
Genital or body wipes ☐ ☐
If yes, describe: ________________
Douched ☐ ☐
If yes, with what ________________
Removed/inserted tampon☐ diaphragm☐ ☐ ☐
Oral gargle/rinse ☐ ☐
Bath/shower/wash ☐ ☐
Brushed teeth ☐ ☐
Ate or drank ☐ ☐
Changed clothing ☐ ☐
If yes, describe: ________________

5. Assault-related history: (No / Yes)
Loss of memory? If yes, describe: ☐ ☐*
Lapse of consciousness? If yes, describe: ☐ ☐*

*If yes, collection of toxicology samples is recommended according to local policy. ☐Blood ☐Urine

Vomited? If yes, describe: ☐ ☐
Non-genital injury, pain and/or bleeding? If yes, describe: ☐ ☐
Anal-genital injury, pain, and/or bleeding? If yes, describe: ☐ ☐

CalEMA 2-923 (Rev 7/02) 2

Patient Identification

F. ASSAULT HISTORY

1. Date of assault(s): | Time of assault(s):

2. Pertinent physical surroundings of assault(s):

3. Alleged assailant(s) name(s)	Age	Gender	Ethnicity	Relationship to patient: Known	Unknown
#1.		M F			
#2.		M F			
#3.		M F			
#4.		M F			

4. Methods employed by assailant(s): (No / Yes / If yes, describe:)
Weapons ☐ ☐
Threatened? ☐ ☐
Injuries inflicted? ☐ ☐
Type(s) of weapons? ☐ ☐
Physical blows ☐ ☐
Grabbing/holding/pinching ☐ ☐
Physical restraints ☐ ☐
Choking/strangulation ☐ ☐
Burns (thermal and/or chemical) ☐ ☐
Threat(s) of harm ☐ ☐
Target(s) of threat(s) ☐ ☐
Other methods ☐ ☐

Involuntary ingestion of alcohol/drugs ☐No ☐Yes ☐ Unsure
If yes, ☐ Alcohol ☐ Drugs
If yes, ☐ Forced ☐ Coerced ☐ Suspected
If yes, toxicology samples collected: ☐ Blood ☐ Urine ☐None

5. Injuries inflicted upon the assailant(s) during assault? ☐No ☐Yes
If yes, describe injuries, possible locations on the body, and how they were inflicted.

Figure 67-2. Forensic Medical Report: Acute (<72 hours) Adult/Adolescent Sexual Assault CalEMA 2-923 from the State of California Emergency Management Agency. This form is available at http://www.calema.ca.gov/PublicSafetyandVictimServices/Documents/Forms%202011/Medical%20forms/Acute%20Adult%202-923.pdf. Accessed January 20, 2013.

www.ketabpezeshki.com 66485457-66963820

G. ACTS DESCRIBED BY PATIENT

- Any penetration of the genital or anal opening, however slight, constitutes the act.
- Oral copulation requires only contact
- If more than one assailant, identify by number.

Patient Identification

	No	Yes	Attempted	Unsure	
1. Penetration of vagina by:					Describe:
Penis	☐	☐	☐	☐	
Finger	☐	☐	☐	☐	
Object If yes, describe the object:	☐	☐	☐	☐	
2. Penetration of anus by:					Describe:
Penis	☐	☐	☐	☐	
Finger	☐	☐	☐	☐	
Object If yes, describe the object:	☐	☐	☐	☐	
3. Oral copulation of genitals:					Describe:
Of patient by assailant	☐	☐	☐	☐	
Of assailant by patient	☐	☐	☐	☐	
4. Oral copulation of anus:					Describe:
Of patient by assailant	☐	☐	☐	☐	
Of assailant by patient	☐	☐	☐	☐	
5. Non-genital act(s):					Describe:
Licking	☐	☐	☐	☐	
Kissing	☐	☐	☐	☐	
Suction injury	☐	☐	☐	☐	
Biting	☐	☐	☐	☐	
6. Other act(s):	☐	☐	☐	☐	Describe:
7. Did ejaculation occur?	☐	☐		☐	Describe:

If yes, note location(s):
- ☐ Mouth
- ☐ Vagina
- ☐ Anus/Rectum
- ☐ Body surface
- ☐ On clothing
- ☐ On bedding
- ☐ Other

8. Contraceptive or lubricant products:	No	Yes	Unsure	Describe Type/Brand, if known:
Foam used?	☐	☐	☐	
Jelly used?	☐	☐	☐	
Lubricant used?	☐	☐	☐	
Condom used?	☐	☐	☐	

CalEMA 2-923 (Rev 7/02) 3

H. GENERAL PHYSICAL EXAMINATION

Record all findings using diagrams, legend, and a consecutive numbering system.

1. Blood Pressure	Pulse	Resp	Temp	2. Exam Started Date	Time	Exam Completed Date	Time

3. Describe general physical appearance

4. Describe general demeanor

Patient Identification

5. Describe condition of clothing upon arrival.

6. Collect outer and underclothing if indicated. ☐ Not indicated
7. Conduct a physical examination. ☐ Findings ☐ No Findings
8. Collect dried and moist secretions, stains, and foreign materials from the body. Scan the entire body with a Wood's Lamp.
☐ Findings ☐ No Findings
9. Collect fingernail scrapings or cuttings according to local policy.

Diagram A

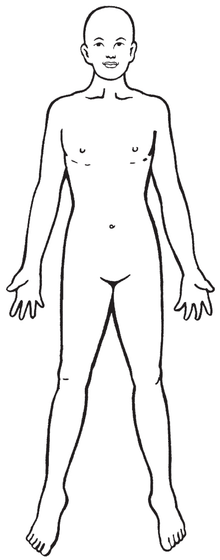
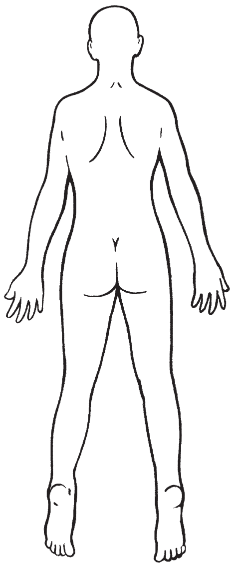


Diagram B



LEGEND: Types of Findings

AB Abrasion	**DF** Deformity	**FB** Foreign Body	**MS** Moist Secretion	**PE** Petechiae	**TB** Toluidine Blue ⊕
BI Bite	**DS** Dry Secretion	**IN** Induration	**OF** Other Foreign Materials (describe)	**PS** Potential Saliva	**TE** Tenderness
BU Burn	**EC** Ecchymosis (bruise)	**IW** Incised Wound		**SHX** Sample Per History	**V/S** Vegetation/Soil
CS Control Swab	**ER** Erythema (redness)	**LA** Laceration	**OI** Other Injury (describe)	**SI** Suction Injury	**WL** Wood's Lamp ⊕
DE Debris	**F/H** Fiber/Hair			**SW** Swelling	

Locator #	Type	Description	Locator #	Type	Description

RECORD ALL CLOTHING AND SPECIMENS COLLECTED ON PAGE 8

CalEMA 2-923 (Rev 7/02) 4

Figure 67-2, cont'd See opposite page for the legend.

Continued

www.ketabpezeshki.com 66485457-66963820

I. HEAD, NECK, AND ORAL EXAMINATION

Record all findings using diagrams, legend, and a consecutive numbering system.

1. Examine the face, head, hair, scalp, and neck for injury and foreign materials ☐ Findings ☐ No Findings
2. Collect dried and moist secretions, stains, and foreign materials from the face, head, hair, scalp, and neck.
   ☐ Findings ☐ No Findings
3. Examine the oral cavity for injury and foreign materials (if indicated by assault history). Collect foreign materials.
   Exam done: ☐ Not applicable ☐ Yes ☐ Findings ☐ No Findings
4. Collect 2 swabs from the oral cavity up to 12 hours post assault and prepare one dry mount slide from one of the swabs.
5. Collect head hair reference samples according to local policy.

Patient Identification

Diagram C

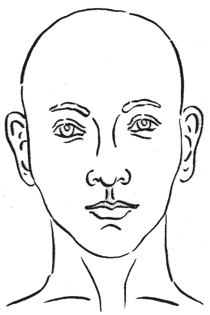


Diagram D

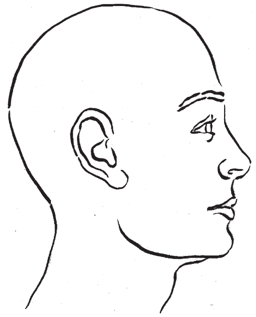


Diagram E

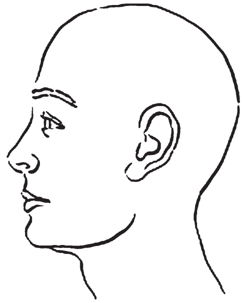
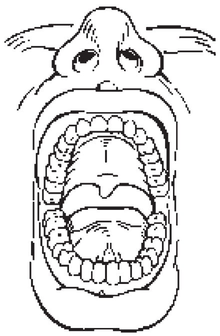


Diagram F



LEGEND: Types of Findings

AB	Abrasion	DF	Deformity	FB	Foreign Body	MS	Moist Secretion	PE	Petechiae	TB	Toluidine Blue ⊕
BI	Bite	DS	Dry Secretion	IN	Induration	OF	Other Foreign Materials (describe)	PS	Potential Saliva	TE	Tenderness
BU	Burn	EC	Ecchymosis (bruise)	IW	Incised Wound	OI	Other Injury (describe)	SHX	Sample Per History	V/S	Vegetation/Soil
CS	Control Swab	ER	Erythema (redness)	LA	Laceration			SI	Suction Injury	WL	Wood's Lamp ⊕
DE	Debris	F/H	Fiber/Hair					SW	Swelling		

Locator #	Type	Description	Locator #	Type	Description

RECORD ALL SPECIMENS COLLECTED ON PAGE 8

CalEMA 2-923 (Rev 7/02) 5

J. GENITAL EXAMINATION - FEMALES

Record all findings using diagrams, legend, and a consecutive numbering system.

1. Examine the inner thighs, external genitalia, and perineal area. Check the box(es) if there are assault related findings:
   ☐ No Findings

   ☐ Inner thighs ☐ Periurethral tissue/urethral meatus
   ☐ Perineum ☐ Perihymenal tissue (vestibule)
   ☐ Labia majora ☐ Hymen
   ☐ Labia minora ☐ Fossa navicularis
   ☐ Clitoris/surrounding area ☐ Posterior fourchette
2. Collect dried and moist secretions, stains, and foreign materials. Scan the area with a Wood's Lamp. ☐ Findings ☐ No Findings
3. Collect pubic hair combing or brushing.
4. Collect pubic hair reference samples according to local policy.
5. Examine the vagina and cervix. Check the box(es) if there are assault related findings.
   ☐ No Findings ☐ Vagina ☐ Cervix
6. Collect 4 swabs from the vaginal pool. Prepare one wet mount slide and one dry mount slide.
7. Collect 2 cervical swabs (if over 48 hours post assault).
8. Examine the buttocks, anus, and rectum (if indicated by history).
   Exam done: ☐ Yes ☐ Not applicable
   Check the box(es) if there are assault related findings:
   ☐ No Findings

   ☐ Buttocks ☐ Anal verge/folds/rugae
   ☐ Perianal skin ☐ Rectum
9. Collect dried and moist secretions, stains, and foreign materials.
   ☐ Findings ☐ No Findings
10. Collect 2 anal and/or rectal swabs and prepare one dry mount slide.
11. Conduct an anoscopic exam if rectal injury is suspected or if there is any sign of rectal bleeding.
    Rectal bleeding ☐ No ☐ Yes
    If yes, describe:________
12. Exam position used:
    ☐ Supine ☐ Other Describe:

LEGEND: Types of Findings

AB	Abrasion	EC	Ecchymosis (bruise)	MS	Moist Secretion	SI	Suction Injury
BI	Bite	ER	Erythema (redness)	OF	Other Foreign Materials (describe)	SW	Swelling
BU	Burn	F/H	Fiber/Hair			TB	ToluidineBlue⊕
CS	Control Swab	FB	Foreign Body	OI	Other Injury (describe)	TE	Tenderness
DE	Debris	IN	Induration	PE	Petechiae	V/S	Vegetation/Soil
DF	Deformity	IW	Incised Wound	PS	Potential Saliva	WL	Wood's Lamp⊕
DS	Dry Secretion	LA	Laceration	SHX	Sample Per History		

Locator #	Type	Description

Patient Identification

Diagram G

Diagram H

Diagram I

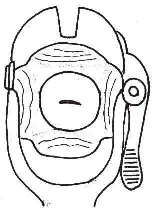
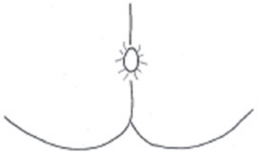


Diagram J



RECORD ALL SPECIMENS COLLECTED ON PAGE 8

CalEMA 2-923 (Rev 7/02) 6

Figure 67-2, cont'd Forensic Medical Report: Acute (<72 hours) Adult/Adolescent Sexual Assault CalEMA 2-923 from the State of California Emergency Management Agency. This form is available at http://www.calema.ca.gov/PublicSafetyandVictimServices/Documents/Forms%202011/Medical%20forms/Acute%20Adult%202-923.pdf. Accessed January 20, 2013.

www.ketabpezeshki.com 66485457-66963820

K. GENITAL EXAMINATION – MALES

Record all findings using diagrams, legend, and a consecutive numbering system.

1. **Examine the inner thighs, external genitalia, and perineal area. Check the box(es) if there are assault related findings:**
   ☐ No Findings
   ☐ Inner thighs ☐ Glans penis ☐ Scrotum
   ☐ Perineum ☐ Penile shaft ☐ Testes
   ☐ Foreskin ☐ Urethral meatus
2. **Circumcised:** ☐ No ☐ Yes
3. **Collect dried and moist secretions, stains, and foreign materials. Scan the area with a Wood's Lamp.** ☐ Findings ☐ No Findings
4. **Collect pubic hair combing or brushing.**
5. **Collect pubic hair reference samples according to local policy.**
6. **Collect 2 penile swabs, if indicated by assault history.** ☐ N/A
7. **Collect 2 scrotal swabs, if indicated by assault history.** ☐ N/A
8. **Examine the buttocks, anus, and rectum (if indicated by history) Exam done:** ☐ **Yes** ☐ **Not applicable**
   Check the box(es) if there are assault related findings:
   ☐ No Findings
   ☐ Buttocks ☐ Anal verge/folds/rugae
   ☐ Perianal skin ☐ Rectum
9. **Collect dried and moist secretions, stains, and foreign materials.**
   ☐ Findings ☐ No Findings
10. **Collect 2 anal and/or rectal swabs and prepare one dry mount slide.**
11. **Conduct an anoscopic exam if rectal injury is suspected or if there is any sign of rectal bleeding.**
    Rectal bleeding: ☐ No ☐ Yes
    If yes, describe: ____
12. **Exam position used:**
    ☐ Supine ☐ Other Describe:

LEGEND: Types of Findings

AB Abrasion	**EC** Ecchymosis (bruise)	**MS** Moist Secretion	**SI** Suction Injury
BI Bite	**ER** Erythema (redness)	**OF** Other Foreign Materials (describe)	**SW** Swelling
BU Burn	**F/H** Fiber/Hair		**TB** ToluidineBlue⊕
CS Control Swab	**FB** Foreign Body	**OI** Other Injury (describe)	**TE** Tenderness
DE Debris	**IN** Induration	**PE** Petechiae	**V/S** Vegetation/Soil
DF Deformity	**IW** Incised Wound	**PS** Potential Saliva	**WL** Wood's Lamp⊕
DS Dry Secretion	**LA** Laceration	**SHX** Sample Per History	

Locator #	Type	Description

Patient Identification

Diagram K

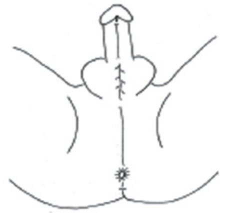


Diagram L

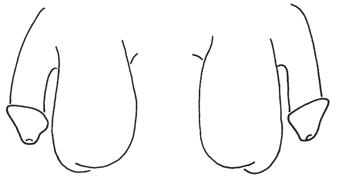


Diagram M

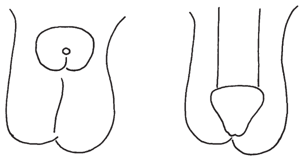
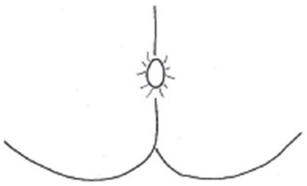


Diagram N



RECORD ALL SPECIMENS COLLECTED ON PAGE 8

CalEMA 2-923 (Rev 7/02) 7

L. EVIDENCE COLLECTED AND SUBMITTED TO CRIME LAB

1. Clothing placed in evidence kit	Other clothing placed in bags

2. Foreign materials collected

	No	Yes	Collected by:
Swabs/suspected blood	☐	☐	
Dried secretions	☐	☐	
Fiber/loose hairs	☐	☐	
Vegetation	☐	☐	
Soil/debris	☐	☐	
Swabs/suspected semen	☐	☐	
Swabs/suspected saliva	☐	☐	
Swabs/Wood's Lamp⊕ area(s)	☐	☐	
Control swabs	☐	☐	
Fingernail scrapings/cuttings	☐	☐	
Matted hair cuttings	☐	☐	
Pubic hair combings/brushings	☐	☐	
Intravaginal foreign body	☐	☐	
If yes, describe:			
Other types	☐	☐	
If yes, describe:			

3. Oral/genital/anal/rectal samples

	# Swabs	# Slides	Time collected	Collected by:
Oral				
Vaginal				
Cervical				
Anal				
Rectal				
Penile				
Scrotal				

Aspirate/washings (optional) ☐ No ☐ Yes

4. Vaginal wet mount slide

	No	Yes	Time	Examiner:
Slide prepared				
Motile sperm observed				
Non-motile sperm observed				

M. TOXICOLOGY SAMPLES

	No	Yes	Time	Collected by:
Blood alcohol/toxicology (gray top tube)				
Urine toxicology				

N. REFERENCE SAMPLES

	No	Yes	Collected by:
Blood (lavender top tube)			
Blood (yellow top tube)			
Blood Card (optional)			
Buccal swabs (optional)			
Saliva swabs			
Head hair			
Pubic hair			

O. PHOTO DOCUMENTATION METHODS

	No	Yes	Colposcope/ 35mm	Macrolens/ 35mm	Colposcope/ Videocamera	Other Optics
Body	☐	☐	☐	☐	☐	☐ ____
Genitals	☐	☐	☐	☐	☐	☐ ____

Photographed by:

CalEMA 2-923 (Rev 7/02) 8

Patient Identification

P. RECORD EXAM METHODS

	No	Yes		No	Yes
Direct visualization only	☐	☐	Toluidine Blue Dye	☐	☐
Colposcopy	☐	☐	Anoscopic exam	☐	☐
Other magnifier	☐	☐	Anal speculum exam	☐	☐
Other	☐	☐			

If yes, describe: ____

Q. RECORD EXAM FINDINGS

☐ Physical Findings ☐ **No Physical Findings**

R. RECORD ASSESSMENT OF FINDINGS

☐ Exam consistent with history
☐ Exam inconsistent with history

S. SUMMARIZE FINDINGS

T. PRINT NAMES OF PERSONNEL INVOLVED

History taken by:	Telephone:
Exam performed by:	
Specimens labeled and sealed by:	
Assisted by: ☐ N/A	
Signature of examiner	License No.

U. EVIDENCE DISTRIBUTION	GIVEN TO:
Clothing (item(s) not placed in evidence kit)	
Evidence Kit	
Reference blood samples	
Toxicology samples	

V. SIGNATURE OF OFFICER RECEIVING EVIDENCE

Signature: ____
Print name and ID #: ____
Agency: ____
Date: Phone:

Figure 67-2, cont'd See opposite page for the legend.

www.ketabpezeshki.com 66485457-66963820

Table 67-1 Useful Information Not Routinely Found on the Sexual Assault Forms

Positions used during the assault	Affects the location of injury
Positions used during the examination	Helps to orient pictures
Sexual dysfunction in the suspect	Associated with increased violence and anal attack
Repeated thrusting by suspect	May explain loss of seminal product
Victim assistance with insertion of penis	May explain lack of genital injury
Did penis remain in vagina after ejaculation?	May explain loss of seminal product
How do you know ejaculation occurred?	Helps determine where semen may be found
Prior sexual experience	Lack of sexual experience associated with increased hymenal trauma
Gravity and parity	May be a factor in genital injury
History of prior victimization	At increased risk for post-traumatic stress disorder; need triage for counseling
Mental health history, sex trade worker, previous incarceration, homeless, history of substance abuse	Increased severity of attack, worsening mental health problems, increased risk of revictimization, worsening drug use
Past medical history	May explain physical or laboratory findings
Sexual arousal and response	Need to assuage guilt, understand prevalence; may alter physical findings

used as often as possible and recorded in quotation marks to preserve the integrity of the interview; if the police record the interview, it may not be transcribed until weeks or months later. The experienced FE also gathers information about the sequence and type of sexual acts that occurred during an assault, including not only kissing, fondling, use of foreign objects, and digital manipulation, but also fetishism, voyeurism, or exhibitionism on the part of the suspect. Table 67-1 lists additional information, which may be useful for the investigation.

Use of Recording Devices by Suspect or Bystanders

The ubiquitous nature of recording devices means that an important, early question to ask of the victim is whether such devices were used by the suspect or bystanders; this may provide evidence of the assault.[55]

Drug and Alcohol Use

Inquiry about drug and alcohol usage is important and necessary.[56-58] Like driving under the influence, a sexual assault may be the first indicator that the victim has a drug or alcohol problem.[59] Recent data indicate that drug and alcohol abuse by the victim is associated with a concurrent increased risk of an additional assault in the next 2 years; assaulted drug users are at risk for an escalation of drug abuse after the assault[60] and self-blame.[61] These victims need prompt referral for counseling and drug rehabilitation programs, a service frequently overlooked by forensic teams.[62] Furthermore, the use of drugs and alcohol are relevant to issues of consent, credibility, and corroboration.[63,64] In the past, studies have not found a correlation between substance use and injury,[65] but recent studies indicate an increase in nongenital[26,43] and anogenital.[33] trauma. The FE should order drug screening if the victim reports loss of consciousness or forced ingestion, appears confused, is amnesic, or has other changes in physical or vital signs that are suspicious for drug use.[55] National drug screening data from SAVs show that the prevalence of drug use is higher among SAVs than the general population.[66,67] Moreover, drugs are frequently used in combination. The two most popular combinations are alcohol and marijuana, followed by alcohol and benzodiazepines.[68] Routine surveillance for drugs and alcohol is recommended because self-reporting is inaccurate[69] and drug-facilitated sexual assault appears to be increasing worldwide.[70,71] Screening should include blood, urine, and, with newer technology, samples of head hair.[72] Special policies and procedures need to be developed for SAVs who are incapacitated or are otherwise incapable of giving consent.[73,74] One should not forget to inquire whether the suspect used drugs or alcohol. Perpetrators who use drugs and alcohol are less likely to use condoms, and on apprehension, drug testing will be needed to confirm this information and should be routine.

History of Child Abuse

A history of childhood abuse increases the risk of repeat assault. Researchers now believe that identification of this vulnerable group is a prerequisite for prevention. The sexual assault examination may be the one time during which the question of prior abuse is raised; a positive answer provides additional justification for referral for psychological services.[29]

Mental Illness

About a quarter of the victims requiring sexual assault evaluation will have mental health problems. A history of mental illness has been shown to increase the severity of the sexual and physical attack. Moreover, the sexual assault often results in an exacerbation of the mental illness and a higher rate of post-traumatic stress disorder.[75] Similar vulnerabilities accrue to sex trade workers and to women with a history of previous incarceration, current or past substance abuse, or homelessness.[29]

Prior Sexual Experience

Knowledge about the victim's prior sexual experience is pertinent. New information has emerged that women without sexual experience are more likely to sustain genital trauma and specifically more likely to have hymenal tearing.[76] Because hymenal and vaginal tears are usually associated with the dramatic presentation of bleeding, it is incumbent on the examiner to ascertain the source of hemorrhage. The lack of visible genital injury in the female who has not had prior sexual experience does not exclude the possibility of intercourse.

SAVs are reluctant to report that they assisted the suspect in any way. Some suspects ask the victim to assist with insertion of the penis. If the SAV does this, she does so in order to avoid harming herself; this may explain the lack of the typical entry injury seen in most victims. Positioning may be another factor in the location of injury; anterior injury is more common when rear entry or female superior positions are used.

Methods of Controlling the Victim

Much can be gleaned about the suspect from a careful interview of the SAV. Areas of interest for the examiner include the methods of approach and control of the SAV, the offender's reaction to resistance by the victim, and the occurrence of sexual dysfunction in the suspect. Although the approach to the victim is usually easy to obtain, understanding how the suspect controlled the victim

www.ketabpezeshki.com 66485457-66963820

may not be immediately clear, as the mere presence of the suspect may be perceived by the victim as a threat to life and may result in control of the victim's actions. Most protocols inquire about verbal threats and weapons, but getting the exact context of these (verbatim if possible) and determining whether the threats were carried out are important. Few assaults are silent; one should inquire about demands, reassurance, compliments, questions, concern, or apologies by the perpetrator. Similarly, if a weapon was used, notation should be made regarding whether the victim saw the weapon or whether it remained a verbal threat only. Was it a weapon of choice (brought with the suspect) or one of opportunity? Did the suspect relinquish it at any time or use it? The examiner should inquire into the amount and timing of the force used by the assailant along with the use of any derogatory or profane language. The examiner should inquire about strangulation; SAVs typically do not volunteer this information. Strangulation tends to occur late in abusive relationships and has been associated with a higher risk for major morbidity and mortality.[77,78] The FE should take special care to ask questions in a manner that does not imply that the victim should have done something to protect herself or to prevent the occurrence of the sexual assault. In some cases, resistance may provoke an alternative demand, compromise, negotiation, and threat of force or use of force. If force is threatened, the examiner should be clear about whether it was used and understand how much and how long it was applied. If a change of demeanor occurred, the FE should know what caused it and what was the change.[79]

Sexual Dysfunction in Offenders

Nearly 34% of convicted rapists have a sexual dysfunction, and this information is obtainable from the SAV. Sexual dysfunction includes impotence, premature ejaculation, retarded ejaculation, or conditioned ejaculation (Box 67-3). This knowledge improves the examiner's ability to understand and collect the evidence. A premature ejaculator may have left semen on clothing or in the environment rather than intravaginally. Retarded ejaculation is associated with multiple sex acts, including anal intercourse, and a more violent attack, involving both genital and nongenital trauma.[39,80] Serial rapists have been identified based on language and demand for a specific order of sexual acts from several SAVs. In addition, the SAV can be asked about any unique lesions or pathology of the perpetrator's genitalia or other identifying characteristics.[81]

Use of Foreign Object

Penetration with a foreign object is associated with greater violence and an increased prevalence of genital and nongenital trauma, stranger assault, and multiple assailants.[33,37] The FE should understand that the definition of a foreign object on the forensic medical form is not the same as the legal definition. The legal definition of foreign object is any substance, instrument, or device, including any body part other than a sexual organ.[82]

Box 67-3 Definitions of Sexual Dysfunction Commonly Seen in Perpetrators of Sexual Assault

Erectile insufficiency: formally impotence; difficulty obtaining or maintaining an erection
Premature ejaculation: ejaculation that occurs immediately before or immediately after penetration
Retarded ejaculation: difficulty in ejaculating or failure to ejaculate
Conditioned ejaculation: able to ejaculate only after certain conditions (e.g., particular sex acts) have been met

Methods Used by the Offender to Avoid Detection

The FE should inquire about the methods used to avoid detection and facilitate escape, such as wearing masks or gloves, blindfolding the victim, or disabling the phone. An experienced assailant may also attempt to destroy evidence, such as forcing the victim to shower. Lastly, the FE should ask about missing items. Valuables or personal items retained as souvenirs have evidentiary value. The FE should ask the victim if the assailant is known to him or her; even if the assailant is unknown, the victim may have a wealth of information about characteristics and behavior of the assailant.[41]

A complete history, which is temporally related, is crucial. The preprinted checklists provided by the state or local government are a good start, but unfortunately they do not elicit a specific narrative recall of events by the SAV. In every case, a dictated narrative summary is strongly recommended.

PERFORMING THE PHYSICAL EXAMINATION AND EVIDENCE COLLECTION

The physical examination should be meticulous and include the collection of trace evidence and reference standards (see Fig. 67-2). There is a positive association between SAV injury and the filing of charges, successful prosecution, and sentencing.[5,83] In general, the sequence of observation, photography in situ, collection of evidence, and written documentation should be followed (Box 67-4). All items should be *dry* and placed in *paper* containers (plastic is not used because it inhibits drying and degrades biologic evidence) that are labeled (Box 67-5) and sealed. Each container should be sealed securely with tape, and the examiner should initial or sign across the tape and onto the container or bag. For the integrity of the evidence to be preserved, the SAV should not be left alone in the room with it, and the FE should wear powder-free gloves to prevent contamination of the evidence. If the evidence is stored, a locked unit should be available. Methods for preserving the chain of custody, a fundamental principle in the

Box 67-4 Documentation of Findings of Sexual Assault Examination

Findings or evidence to be documented includes the following:
- Preexisting injuries
- Acute injuries
- Tenderness or induration
- Foreign material
- Positive areas under Wood's lamp or alternate light source
- Secretions and stains
- Potential saliva or semen (per history)
- Swab collection sites (evidence and controls)
- Indicate any site where moist swab collection occurred

Box 67-5 Information to Document on Standard Evidentiary Label

On each item in the rape kit:
- Full name of patient
- Medical record or case identification number
- Date of collection
- Time of collection
- Brief description of item with sampling site
- Initials of the examiner

www.ketabpezeshki.com 66485457-66963820

Box 67-6 Chain of Custody

Record of signatures, dates, and times that:
- Documents handling, transfer, and storage of evidence from the time of collection
- Provides sequential accountability of everyone who handled the evidence
- Documents the location of the evidence at all times
- Ensures there has been no tampering, alteration, or loss of evidence before trial

For all transfers of evidence, documentation should include:
- Signature of person transferring custody
- Signature of person receiving custody
- Date of transfer
- Time of transfer

Documentation is written on sealed and packaged kit

Box 67-7 Wood's Lamp and Alternate Light Source

Wood's Lamp

Screening tool for detection of stains, secretions, and injuries
Long-wave ultraviolet light (310-400 nm)
Dried semen will usually fluoresces bright green-yellow or white
Moist semen fluoresces poorly or not at all
Other body fluids and substances may be seen
Room should be dark to use

Alternate Light Source (ALS)

High-intensity, tunable light source
Uses four narrow bands: 450, 485, 525, and 570 m
Two wide bands: white light, all wavelengths below 530 nm
Colored goggles used to block the reflected light and pass only the fluorescent light
Because of absorptive differences between normal and damaged tissues, can detect injuries not seen with the naked eye
More accurate for certain body fluids and substances than Wood's lamp

criminal justice system, should be understood by all personnel (Box 67-6). A complete examination and historically relevant evidence collection should be performed, irrespective of the time between assault and examination. One investigator documents the retrieval of salivary DNA from a bite mark on a body even after the body had been submerged in water for more than 5 hours.[84] The FE should not second-guess what the laboratory may or may not recover based on rigid time frames. If there is a history of loss of consciousness or significant memory impairment, then all specimens should be collected.

Examination of the Skin

The FE needs to describe the SAV's demeanor and general appearance. The examiner should be especially careful to use specific terms and note responsiveness and ability to cooperate and give a history. All clothing worn during the assault should be inspected, collected, and photographed. A Wood's lamp or ALS should be used to detect dried secretions and to document the findings (Box 67-7).

The SAV should undress on the large square of paper from the rape kit after removing shoes. Another sheet of paper should be placed underneath this square to prevent contamination from the floor. The square paper is used to catch trace evidence and should be folded carefully and placed into evidence.

When the SAV is undressed, the FE uses the Wood's lamp or ALS over the body and documents positive fluorescence. Dried

Box 67-8 Double-Swab Technique for the Recovery of Saliva from Human Skin

First swab: completely wet with sterile distilled water.
  Roll over the surface of the skin using moderate pressure and circular motions.
  Rotate swab on long axis to ensure maximal contact.
  Air dry completely (30 minutes or longer).
Second swab: used dry.
  Apply with the same action as above to pick up all the moisture left behind.
  Allow to dry completely (30 minutes or longer).
Label each and submit with other evidence.

Box 67-9 Collection of Bite-Mark Evidence

Take an orienting photograph before swabbing.
Then be certain to take close-up photographs, and use a scale.
If the bite mark is on a rounded surface, more than one photograph will be needed to avoid distortion.
Notify law enforcement immediately, so that they can contact a forensic odontologist, who may take additional photographs and collect impressions.
Serial photographs are recommended at 24-hour intervals for up to 5 days.
Use the double-swab technique to obtain saliva sample.

secretions should be removed with a cotton swab moistened with sterile, distilled water. If one side of the swab is flattened and only that side is used to collect the specimen, the material is effectively concentrated. Conversely, wet secretions should be taken in the same manner with a dry swab. Swabs should be taken from areas of contact indicated by the SAV, even if there is no fluorescence or crusting seen. A double-swab technique is used to collect saliva from skin (Box 67-8).[85] Bite marks need special attention (Box 67-9).[86] Control swabs should be taken in areas adjacent to the material removed and labeled as such. All swabs should be dried in a stream of cool air at least 60 minutes before packaging. Swab-drying machines are available with locks to facilitate this process. To prevent contamination, only one person's evidence should be in the dryer at a time, and the drying chamber should be cleaned after each use with a solution of 10% household bleach. The location of all foreign material should be documented on the body diagrams and packaged in the standard fashion. Fingernail clippings or scrapings should be collected according to local custom and only if there is historical relevancy. All preexisting injuries and acute trauma need to be documented in the report.

Diagrams of the body should be large enough to allow documentation to remain clear. If need be, copies of the state and local diagrams should be available in full-page format to accomplish this. The documentation process in some states is artistic, which means the FE draws the injury on the diagram. California has switched to a purely descriptive approach for uniformity and clarity (see Fig. 67-2).

Head, Neck, and Oral Cavity

In examining the head, neck, and oral cavity, special attention should be given to the integrity of the frenula, buccal surfaces, gums, and soft palate. The SAV should not be allowed to eat or drink before this examination. If the SAV gives a history of oral copulation with ejaculation, then the upper and lower lips should be wiped with two moistened swabs. Next, the examiner should swab from the gum to the tonsillar fossae, the upper first and second molars, behind the incisors, and in the fold of the cheek.

www.ketabpezeshki.com 66485457-66963820

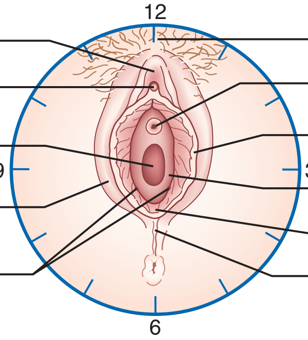


Figure 67-3. Typical genital injury among 3, 6, and 9 o'clock positions.

If more than one swab is used to swab these areas, each should be labeled appropriately. Last, with a 16-inch piece of unwaxed floss, with two knots tied about 2 to 3 inches apart in the center of the floss, the SAV should floss her teeth, using only the section between the knots. While flossing, the patient should lean over a clean 8 × 10-inch piece of paper to catch any debris. The paper and floss are dried and bundled together. If the SAV is unable to use the floss, the examiner, wearing gloves and goggles, can perform this procedure.[87]

Hair matted with secretions or debris should be cut out and packaged. Additional hair might also be needed for drug analysis depending on the laboratory.[72] Signs of manual or ligature strangulation may include neck injuries with petechiae of the skin and conjunctiva. Reference samples for head hair and saliva should be taken according to local custom, including buccal swabs made for DNA analysis. Reference standards are used to determine whether the evidence specimens are of victim origin or are foreign. In addition, they may help identify or eliminate potential suspects.

Anogenital Examination

The anogenital examination should begin with gross visualization of the inner thighs, external genitalia, and perineal area and anus, followed by Wood's lamp or ALS visualization of the area to identify secretions. All trauma, secretions, and foreign material should be noted and appropriately handled. Gross visualization yields positive findings in 20 to 30% of cases (range 5-65%).[4,6,34,42,76] Genital trauma associated with sexual assault is considered to be a mounting injury because it occurs at the point of first contact of penis to vagina. This area, the posterior fourchette (soft tissue) or the perineal body (the juncture of the tendons of the superficial transverse perineal and the bulbocavernosus muscles), is inherently weak, and continued pressure will result in tearing.[24,88] The position of restraint, male straddling female, will also effectively prevent the victim from accommodating the erect penis. The angle of the erect penis is not the same as the angle the vagina makes with the vestibule (approximately 45 degrees). Moreover, the vagina is considered a potential space. The lateral walls are more rigid than the anterior and posterior walls so that in its normal state, the anterior wall is collapsed onto the posterior wall; hence the need for a speculum to lift the anterior wall during the gynecologic examination.[89] During voluntary intercourse, the changes that occur with sexual stimulation, the human sexual response, remove these normal anatomic barriers, and the female voluntarily tilts her pelvis.[90,91] Sexual arousal and orgasm are now understood to be a reflex of the autonomic nervous system requiring an intact sacral arc.[92,93] It is hypothesized that this response can be either facilitated or inhibited by cerebral input. It can occur in both males and females even when it is not wanted or the victim is unconscious. In women, vaginal wetness can occur subconsciously and is thought to be a protective mechanism. Some perpetrators have taunted victims about its occurrence, further increasing the shame and guilt of the victim. The FE should inquire and reassure the SAV that this reaction is neither abnormal nor evidence of consent. Approximately 4% of SAVs experience this phenomenon, although this is probably a gross underestimate as a result of embarrassment[94,95] and lack of inquiry. The FE should not conflate sexual response, consent, and injury; genital injury is not an ineluctable consequence of sexual assault. Currently, there is still no finding or group of findings that can differentiate consensual from nonconsensual sex, and more research is underway.[96,97]

Box 67-10 Correlates of Genital Injury Found at Time of Sexual Assault Examination

Decreases Findings
Increased time from assault to examination
History of menstrual bleeding at the time of assault

Increases Findings
Nongenital injury is associated with genital trauma
Penile penetration
Sexual inexperience and hymenal tearing
Postmenopausal
History of anal contact
History of stranger assault
History of sexual dysfunction in the perpetrator
Use of foreign object
Sexual assault victim (SAV) use of alcohol
SAV college graduate

Typically, genital injury is located posteriorly among the 3, 6, and 9 o'clock positions (Fig. 67-3), with the posterior fourchette being the most common site of injury.[23,32,34,39] Findings are the sequelae of blunt force trauma that produces tears, ecchymosis, abrasions, redness, and swelling. The last two may be difficult to recognize without a follow-up examination, and some investigators have suggested that redness or swelling not be reported if a second examination is not performed.[23] Hymenal trauma is not the most common site of injury, as myth would have it. Hymenal trauma is more common in adolescents and those without sexual experience.[23,76] Genital injury has consistent topologic features, now well documented in the literature; this pattern is consistent with an entry injury, occurring with insertion or attempts at insertion of the penis into the vagina.

Many factors affect the prevalence of genital injury, and the FE should be familiar with them (Box 67-10). Colposcopic magnification should be used to photographically document these areas and to better identify the type of trauma seen. Colposcopy has been the preferred and best method for determining genital injury.[98,99] Currently, many centers are using digital photography

www.ketabpezeshki.com 66485457-66963820

Table 67-2 Environmental Factors Associated with Intravaginal Epithelial Changes Seen with Visual Inspection, Colposcopy, or Acetic Acid Application

FACTOR	FINDINGS
Smoking	Edema, erythema, petechiae, abrasion
Tampon use at the time of examination	Erythema, petechiae, abrasion
Speculum manipulation	Laceration
Consenting intercourse	Erythema, petechiae, abrasion, ecchymosis
Herpetic infection	Microulcerations

Table 67-3 Maximum Reported Time Intervals for Sperm Recovery

BODY CAVITY	MOTILE SPERM	NONMOTILE SPERM
Vagina	6-28 hr	14 hr-10 days
Cervix	3-7 days	7.5-19 days
Mouth	—	2-31 hr
Rectum	—	4-113 hr
Anus	—	2-44 hr

and videography with excellent results and less cost. Certain environmental factors have been identified with colposcopically recognized genital changes; this is particularly true with intravaginal findings (Table 67-2).[100] Frequently, trace evidence is seen only with the colposcope. We use adhesive note paper (Post-it notes) to capture such tiny particles while visualized under the scope. The Post-it is then folded and inserted into an envelope. Examiners should check with their local crime laboratory to see if this method is acceptable. Pubic hair brushings are collected by placing a sheet of paper under the patient's buttocks and brushing the pubic hair downward. The paper and brush should be bundled together and packaged. A pubic hair standard may be obtained according to local forensic procedures.

A warm speculum moistened with water should then be inserted into the vagina. Inspection of the vagina and cervix should be performed first grossly, then with colposcopic photography. If the SAV reports bleeding, the source needs to be determined. Bleeding is commonly associated with hymenal, vaginal, or combined tears. In contrast, menstrual bleeding at the time of an assault has been shown to decrease physical findings.[101] Swabs from the vagina and cervix should be obtained, air-dried for 60 minutes, and packaged. Cervical specimens augment those from the vaginal pool because the cervix acts as a reservoir and provides evidence of seminal products for longer periods of time (Table 67-3).[102] The examiner should inspect the cervix carefully for injury, including patterns. Injury, seen in about 10% of cases, is related to penile, digital, or foreign object penetration, but ectropion, cervicitis, or hyperplasia can be confused with trauma and make the cervix more vulnerable to injury; a follow-up examination is necessary to prevent misdiagnosis.[103] To check for motile sperm, the FE should inspect a wet mount slide. This method is useful because it gives a time frame for the assault, and sufficient numbers of sperm (60-100) allow for DNA identification of a suspect. Semen is found about 50% of the time. The FE should communicate this information to the investigator as soon as possible. The wet mount slide is then dried and prepared for deposit into the rape kit. Aside from time and site of deposition,[104-106] female and male factors influence the ability to find semen (Table 67-4). Not all cases result in the deposition of semen. Fluorescence in situ hybridization (FISH) is a sensitive and specific commercially available probe for detection of the Y chromosome in epithelial cells up to 7 days after penetration, ejaculation, or saliva deposition.[107] Typically, a bimanual examination is not performed.

Table 67-4 Factors Influencing Loss of Sperm and Seminal Fluid

FEMALE FACTORS	MALE FACTORS
Prior trauma to birth canal	Condom use
Lost on withdrawal of penis	Vasectomy
Vaginal hygiene (e.g., douching, wiping)	Azoospermia
Repeated penile thrusting	Drug and alcohol abuse
Penis remains in the vagina after coitus	Sexual dysfunction
Change of posture	Failure to ejaculate

A rectal examination is performed if indicated by the history. Because SAVs are reluctant to report this type of activity, however, the FE should always inspect the anus for signs of injury and reinquire about anal contact. Asking the patient to bring her knees up to her chest allows this examination to be done easily and quickly. If trauma is seen or the history suggests anal penetration, rectal bleeding, or use of a foreign object in the assault, a rectal examination, including anoscopy, should be performed. For contamination with vaginal secretions to be avoided, the perianal region is swabbed thoroughly with a moistened swab or 2 × 2-inch gauze, which is dried, labeled, and included in the rape kit. This procedure should be done after all vaginal samples, external secretions, and foreign material have been collected. A warm, water-moistened anoscope is used to perform the procedure. The examiner observes grossly and colposcopically, after which photographs are taken. Swabs are collected under direct visualization beyond the tip of the scope. The source of any bleeding needs to be determined.

Special Staining Techniques

The use of special staining and lubrication techniques should be reserved until all photography has been completed and all specimens have been collected. On areas that are painful, 2% lidocaine gel can be used to obtain better visualization and pictures. Toluidine blue dye is a nuclear stain that has been shown to enhance gross visualization of external genital (vulvar) injuries (Fig. 67-4). Toluidine blue dye has some spermicidal activity[108] but was shown in one small study not to influence DNA analysis.[109] Stain results depend on the presence or absence of a nucleated cell population at the exposed surface. Positive stain results can be seen with trauma, cancer, and areas of inflammation with a nucleated cellular infiltrate. Acutely, with tissue swelling and transudation, the dye may lift off quickly. Twenty-three categories of benign disease, along with columnar epithelium, and mucus will take up this stain. Toluidine blue dye is nonspecific; it does not replace a clear photograph of the injury and should be used only to enhance trauma seen with the colposcope or as an adjunct for gross visualization. It should not be used to date injuries or on the deceased because postmortem artifact can take up the dye. Diffuse staining or patchy uptake should not be reported.[110] Uptake should not be reported when no findings are seen with colposcopy.[99]

Photographic Documentation

Photographic documentation has become the standard of care. It eliminates the problem of hyperbole and understatement in the

www.ketabpezeshki.com 66485457-66963820

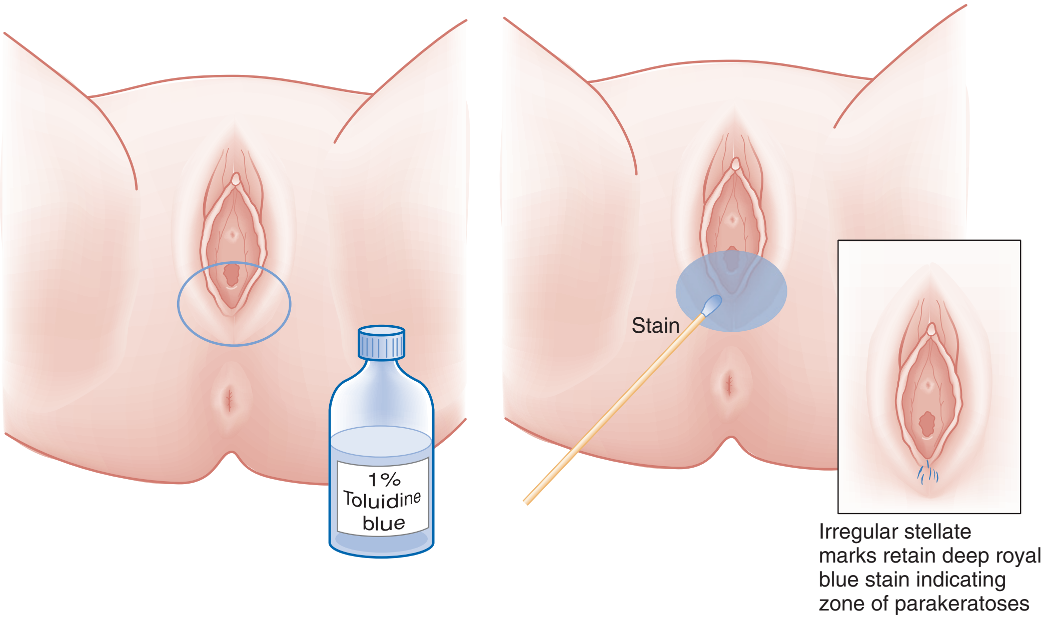


Figure 67-4. Application of toluidine blue dye with example of results.

FE's description and allows the court to see a visual representation of findings on examination. It is important to note that photographic documentation makes each case available for diagnosis, research, peer review, and consultation, alleviating the need for repeated examinations by defense experts.[111,112] The entire examination should be photographically documented if at all possible, not just the positive findings. All photographs should be correctly labeled to show patient identification, date, time, and examiner. Frequently this information can be combined with a color guide and ruler. Jurors usually want to know how pictures are identified. The FE should develop a standard photographic technique, making certain that the plane of the film is parallel with the injury to minimize distortion. Photographs of skin are enhanced if the background is blue or green because the automatic lens adjusts according to the lightest part of the photograph. The examiner should take photographs of lesions first without magnification, then take closer views as needed. The full extent of the injury needs to be captured. Use of magnification usually necessitates more than one shot. The examiner should take many photographs because he or she has this opportunity only once (Box 67-11 outlines tips for performing photographic documentation in sexual assault cases). Photographs are also a concern for SAVs. Most SAVs worry about where the photographs are kept and whether their name will appear on the photographs. Keeping the SART record separate from the medical record is reassuring. Some groups go a step further and separate the photographs from the written reports.

SEXUALLY TRANSMITTED DISEASES AND PREGNANCY

The risk of acquiring an STD after a sexual assault is small but will vary by region and number of assailants (Table 67-5). Testing for STDs is expensive, requires a reassessment of the patient, which is often difficult, and has no forensic value. Most protocols no longer require or pay for this type of assessment. In addition, many SAVs have preexisting STDs. Most providers prefer preventive therapy (Box 67-12), and it offers the SAV the psychological benefit of immediate protection from infection. For updated information and alternative therapies for patients who are pregnant or have specific allergies, the physician can consult www.cdc.gov and

Box 67-11 Tips in Photographic Documentation of Sexual Assault Findings

Lens
Best all around for photographing bodily injury: macro lens with focal length 100 to 105 mm.

Documentation
Do not photograph more than one victim per roll.
Begin each roll with facial shot and identification number.

Technique
Background
Avoid clutter.
Avoid reflective or bright background.
Use blue or green surgical towels for extremity shots.

Positioning
The plane of the film should be parallel to the plane of the finding.
For textured findings (e.g., swelling, indentation), take additional shots at a variety of tangential or oblique angles.

Anatomic Context and Scale
Every finding should appear in at least three photographs, including a regional shot that orients the viewer to the finding's general location.
Close-ups should zoom in on the finding with the camera orientation the same as for the regional shot.
At least one close-up shot should include a scale for color, size, and victim's ID number on it.
Review your photographs to make certain you captured all findings and all areas of the anogenital anatomy.

Table 67-5 Risk of Sexually Transmitted Disease after Sexual Assault

Gonorrhea	6-18%
Chlamydia	4-17%
Syphilis	0.5-3%
HIV infection	<1%

HIV, human immunodeficiency virus.

www.ketabpezeshki.com 66485457-66963820

Box 67-12 Centers for Disease Control and Prevention Prophylaxis for Sexually Transmitted Disease in Adult Sexual Assault Victims

Ceftriaxone 250 mg intramuscularly in a single dose or cefixime 400 mg orally, single dose
PLUS
Metronidazole 2 g orally in a single dose
PLUS
Azithromycin 1 g orally in a single dose
OR
Doxycycline 100 mg orally twice a day for 7 days

From Centers for Disease Control and Prevention: Sexually Transmitted Diseases (STDs). Available at www.cdc.gov/std/treatment/2010/sexual-assault.htm. Accessed January 20, 2013.

Box 67-13 Hepatitis B Infection Prophylaxis for Sexual Assault Victims (SAVs)

Serologic testing is not required.
Give vaccination if SAV is unimmunized or uncertain.
Follow-up doses should be given at 1 to 2 months and 4 to 6 months (total of three doses).

Table 67-6 Factors Influencing the Probability of Human Immunodeficiency Virus (HIV) Transmission

SAV FACTORS: SUSCEPTIBILITY	ASSAILANT FACTORS: INFECTIOUSNESS
Type of sexual contact*—anal > vaginal	Presence of foreskin*
Presence of STDs*	Late stage of infection*
Presence of genital lesions*	Primary HIV infection*
Presence of genital or anal trauma*	Viral load in the genital tract*
Exposure to ejaculate on mucous membranes*	Presence of STDs or genital lesions*
Cervical ectopy*	Antiretroviral therapy†
Contraceptive method	Multiple offenders*
Barrier†	Offenders with history of incarceration, homosexuality, or bisexuality*
Intrauterine device‡	
Nonoxynol 9†	
Pills§	
Menstruation*	
Currently pregnant‡	

SAV, sexual assault victim; *STD,* sexually transmitted disease.
*Increased probability.
†Decreased probability.
‡Unknown effect.
§Evidence to support both increased and decreased probability.

search for “std treatment.” FEs should also consult their state health departments for possible drug and dosage changes necessitated by local susceptibilities of these organisms. The efficacy of these regimens in preventing gonorrhea, trichomoniasis, bacterial vaginosis (BV), and *Chlamydia trachomatis* genitourinary infections after sexual assault has not been evaluated. If vaginal discharge, malodor, or itching is present, the wet mount slide should also be examined for BV and candidiasis. The FE should counsel patients about the possible toxicity of any regimen; gastrointestinal problems are especially common, and the FE should consider antiemetic medication, particularly if emergency contraception is also prescribed. All patients should be advised to abstain from alcohol for 24 hours after metronidazole use and from sexual intercourse until the treatment is completed.[113]

Hepatitis B

Hepatitis B vaccination, without hepatitis B immune globulin, is recommended for SAVs who are unimmunized (Box 67-13). Risk factors for hepatitis B virus include multiple sexual partners (more than one sex partner in a 6-month period), a recent history of an STD, men who have sex with men, correctional facility inmates, and intravenous drug users. Currently, testing to determine antibody levels in immunocompetent persons is not necessary because most fully vaccinated persons have long-lasting protection, and relatively high rates of protection are achieved after each vaccine dose. The FE should give the vaccination even if the completion of the series is not assured.[113] In some protocols, this cost may not be covered.

Human Immunodeficiency Virus

Although human immunodeficiency virus (HIV) exposure is of great concern to SAVs, the risk of seroconversion is low. The risk of HIV transmission from an HIV-positive male is 0.1 to 2% for consensual vaginal intercourse and 0.5 to 3% for receptive rectal intercourse, with transmission rates from oral sex substantially lower. The FE needs to be familiar with the local epidemiology of HIV and acquired immunodeficiency syndrome; state guidelines for postexposure prophylaxis for SAVs, if any; the nature of the assault; and any HIV risk behaviors exhibited by the assailant, such as high-risk sexual practices or injection drug or crack cocaine use. Specific circumstances affecting the SAV and assailant, if known, can increase the probability of transmission (Table 67-6). The rate of HIV transmission in sexual assault is likely to be higher than in consensual intercourse because of the possible presence of genital trauma. The effectiveness of postexposure prophylaxis is based solely on the treatment results of health care workers who have had occupational exposure, and these data have been extrapolated to SAVs. The Centers for Disease Control and Prevention recommends that therapy be considered in cases in which the risk for HIV is likely high and that all such cases be referred for consultation with an HIV specialist. Costs may not be covered under local protocols, and postexposure prophylaxis needs to be provided in the context of a comprehensive counseling, treatment, and follow-up program. To maximize the likelihood of success, therapy should be initiated as soon as possible or up to 72 hours after the assault, so expeditious referral is prudent.[113]

Assistance with postexposure prophylaxis decisions can be obtained 24 hours a day, 7 days a week by calling the National Clinicians’ Post-Exposure Prophylaxis Hotline (PEPLine) at 888-448-4911.

Follow-up Testing

For SAVs who do not want postexposure prophylaxis, repeat HIV testing is recommended at 6 weeks and 3 and 6 months. If a suspect is apprehended, HIV testing can be done with his consent or a blood sample held and tested at a later date after a court order has been obtained on the victim’s behalf. Some states permit testing of the suspect at the victim’s request in cases of sexual assault. Under many protocols, serologic testing is not required and the cost for this testing is not covered.

Pregnancy Prophylaxis

There is a 2 to 4% risk of pregnancy from random unprotected intercourse; this figure reaches nearly 50% in women 19 to 26 years old, who are at their most fertile period, when combined with midcycle exposure. The immediate use of an emergency contraceptive (EC) can reduce the risk of pregnancy to 1 to 2%. Its effectiveness depends on the regimen used and the time interval between exposure and treatment (Table 67-7). Data show that an EC should be offered up to 5 days after unprotected sex. There

www.ketabpezeshki.com 66485457-66963820

Table 67-7 Types of Emergency Contraception

CLASS	DOSE	BRANDS	COMMENTS
Combined oral	100 U ethinyl estradiol + 0.5 mg levonorgestrel twice 12 hr apart	Ovral*	Decreases risk of pregnancy to 2% 50% nausea 20% emesis Requires antiemetic 1 hr before dose Effective up to 5 days
Progestin only, FDA approved OTC	1.5 mg levonorgestrel 0.75 mg levonorgestrel twice 12 hr apart	Plan B One-Step Next Choice	Decreases risk of pregnancy to 1% 22% nausea 8% emesis If emesis within 2 hr, repeat dose; if severe, can be given vaginally If emesis within 1 hr, repeat Effective up to 5 days
Copper T IUD		ParaGard T 380A	Decreases risk to 0.1-0.2% Avoid if patient has untreated cervical infection caused by *Neisseria gonorrhoeae* or chlamydia Provides long-term contraception Effective up to 5 days Requires office visit for insertion
Antiprogestins	30 mg ulipristal	Ella	Decreases risk to 1% If emesis within 3 hr, repeat dose Effective up to 5 days Requires prescription

FDA, U.S. Food and Drug Administration; *IUD,* intrauterine device; *OTC,* over the counter.
*Other hormonal contraceptives that are useful to make up this combination can be found at www.not-2-late.com.

are no absolute contraindications to the use of hormonal EC, even for women who have contraindications to the long-term use of combination hormonal contraception. In those who have active migraine headaches with neurologic symptoms or a history of stroke, pulmonary embolus, or deep vein thrombosis, progestin-only EC or the insertion of an intrauterine device (IUD) should be considered first. The IUD offers the advantage of up to 10 years (depending on the device) of effective contraception. Evidence suggests that there is not an increase in ectopic pregnancy with EC use. Although there are no studies large enough to quantify the teratogenicity of hormonal ECs, no increase in birth defects has been detected in infants exposed in utero to daily oral contraceptive use. Pregnancy testing is not necessary before hormonal EC.[114,115]

As of June 2011, 17 states and the District of Columbia require hospital EDs to provide EC-related services to SAVs, and 12 states plus the District of Columbia require hospitals to dispense EC on request. Despite legal efforts and practice recommendations from the American College of Emergency Physicians (ACEP),[116] the American Medical Association (AMA),[117] the American Academy of Pediatrics (AAP),[118] and the American College of Obstetrics and Gynecology (ACOG),[119] EC remains underused, and patients are not informed about its availability.[120,121]

DEBRIEFING

Regardless of any physical injury, psychological distress is typically present after sexual assault, and the FE needs to acknowledge that from the beginning of the examination. Establishing a quiet and calm place for the examination and evidence collection reassures the SAV and gives back to her a sense of control and safety. At the termination of the examination, the FE should spend time reviewing the physical and genital injuries and address modes of therapy as appropriate. The examiner should discuss any pending laboratory data and how results will be communicated (by phone, written, or both) with the SAV. The method of communication should be acceptable to the SAV. The examiner should review all medication and vaccinations (e.g., tetanus), discuss side effects,

Box 67-14 Common Somatic and Emotional Reactions after Assault

- Increased muscle tension, chronic pain (pelvis, back)
- Fibromyalgia
- Headaches
- Genitourinary disturbances, sexual dysfunction
- Fear, guilt
- Fatigue
- Gastrointestinal disturbances, Irritable bowel syndrome
- Eating disorders
- Anger, self-blame
- Fears and phobic reactions
- Depression
- Anxiety
- Nightmares, sleep disorders
- Post-traumatic stress disorder
- Alcohol and drug abuse
- Poor overall health status

and provide contact phone numbers in case of problems or questions. The examiner should review the common psychological problems (Box 67-14) and reinforce the need for counseling. The advocate who has been present during the examination can be a personal contact already established with the SAV. Nonetheless, contact numbers for rape crisis services, local crisis intervention, social services, drug and alcohol services, HIV services, and emergency psychiatric services should be reviewed in detail, and all referrals should be discussed before departure (Box 67-15). Compensation for victims of crime should be discussed and appropriate referrals made.

A forensic follow-up examination of all patients should be scheduled. This examination is particularly important for SAVs with genital injury. It documents the healing of injury and differentiates findings that can be confused with trauma, such as hypervascularity, telangiectasis, and cherry red spots.[39,103,111] Its utility extends to nonspecific injuries such as swelling or redness, which are difficult to detect and create frequent interobserver

www.ketabpezeshki.com 66485457-66963820

Box 67-15 Rape, Abuse, Incest National Network (RAINN)

Provides 24-hour counseling and support
Trained volunteers
Anonymous
Via phone: 1-800-656-HOPE
Online hotline: www.rainn.org/get-help/national-sexual-assault-hotline

disagreements.[23] This examination also gives the FE an opportunity to review any problems, encourage counseling if it has not already begun, and connect the SAV to outside resources. One should do drug and alcohol counseling when appropriate. All of these plans should be in written format. For the SAV's needs to be met and for adverse medical or psychological outcomes to be prevented, follow-up is critical.[21,30,52,53]

ELDERLY VICTIMS

Two percent to 6% of all SAVs are older than 50 years. The risk of being sexually assaulted or physically assaulted is further increased for homeless women in this age group.[29,122] Older women are less likely to report sex crimes because of self-blame and humiliation. The asexual stereotype attributed to them by family, caretakers, and other professionals often prevents detection.[123] Whereas most elderly SAVs are seen within 72 hours, delayed reporting also occurs. This is especially true when the perpetrator is a caregiver.[124-126] In 2005, A Perfect Cause, advocates for disability and elder rights, documented that 795 registered sex offenders were living in long-term care facilities and five were employees.[127] Elder SAVs present unique challenges to the FE. The history should be expanded to include medical problems, medications, surgical procedures, history of dementia, and neurologic problems. Obtaining the history may be difficult. Some patients may be in a disorganized state without a diagnosis of dementia. Others may have hearing impairment, cognitive disabilities, or psychiatric disturbances; these conditions, considered important vulnerabilities, often require special interviewing skills, and the examiner may need to obtain the history from other reliable sources.[128] Positioning should be thoughtfully performed with regard to limitation of motion for both natural and artificial joints and the need to prevent cardiovascular problems that attend anxiety and stress in this frail population. Skin changes related to aging, infection, and trauma can be difficult to discern, and a follow-up examination, including photographic documentation, will help to resolve these important issues.[129] Bruising not may be seen initially.[130]

Usually, the SAV lives alone and the assault occurs at her home; the assailant is almost always a stranger. Among those abused in facilities, the suspect is most often an employee or a resident. Sexual dysfunction, substance use, and a history of prior sexual assault or other criminal behavior are commonly seen in these perpetrators; robbery is often involved, and female assailants are not infrequent. The most common type of assault is penile-vaginal contact, and genital injury is more frequent and severe than in younger SAVs, necessitating hospitalization and even surgery. The localized pattern and type of physical injuries are similar to those seen in younger victims.[131] Physical restraint is common and usually in excess of what is required for control.[132] The aftermath of assault is particularly devastating for this age group. Older adults have high morbidity and mortality rates, even when they have sustained relatively minor injury; this may be attributed to concurrent medical conditions, decreased physiologic reserve, or adverse reactions to and between medications. Psychologically, post-traumatic stress with subsequent illness is more frequent and severe and leads to diminished functional capacity; this is devastating to this population, in which resources and support are limited.

Sexual abuse is the most under-reported form of elder abuse. A meaningful program addressing elderly SAVs should involve education and participation of adult protective services, in-home health care or nursing home providers, and other agencies representing the elderly or disabled, along with SART. Policies and procedures addressing elderly patients unable to give consent should be in place and in accordance with state laws.[133]

MALE VICTIMS

Male sexual assault is vastly under-reported. Overall, male rape accounts for 8% of all noninstitutional U.S. rapes.[134] Certain special populations appear to be at increased risk for sexual assault: gay and bisexual men, veterans, prison inmates, and men from physical and mental health treatment facilities.[135] Most victims seen come from institutional settings, with very few indeed from the nonincarcerated population. Factors that act as barriers to reporting this crime include societal beliefs that a man can defend himself and fear that his sexual orientation is suspect. The need to maintain emotional control makes disclosure very stressful. Men need to be accorded the same sensitivity and support as their female counterparts, yet most mental health centers neither have the male staff or volunteers nor offer full services for male SAVs.[136] This is particularly troubling because depression and suicidal ideation are significantly associated with male sexual assault.[134]

Except for their anatomic differences, the procedures for the history, physical examination, evidence collection, and medical treatment are the same. Certainly, because of the typical location of injuries, some researchers have emphasized the increased risk of exposure to HIV, hepatitis B, and hepatitis C.[137] Some notable differences in the assault characteristics from those seen in female victims include a predilection for anal and oral sexual contact, with subsequent injury seen in 50 to 67%, more common use of the prone position during the assault, a higher incidence of nongenital trauma (80% in one study), use of a weapon, assault by a stranger or multiple assailants, and a history of abduction. Injuries to the penis and scrotum occur less often and may be the result of a nonsexually related injury (e.g., kicks).[138] In one study the use of colposcopy, in addition to anoscopy, allowed the discovery of increased physical examination findings in men. As with female SAVs, colposcopy is recommended because of its additional utility for photodocumentation and collection of trace evidence.[139]

A different picture emerges from survey data taken from the community setting. Male SAVs reported no physical injury, penetration, weapon use, or substance use. The vast majority did not report to police or seek medical or mental health assistance. It is important to note that of those who did seek care, most did not reveal the actual reason for the visit.[136,140]

MALE SUSPECT EXAMINATION

The importance of the male suspect examination should not be overlooked. The SAV and suspect are the two pieces of the forensic puzzle in a sexual assault. If they are evaluated and treated in the same location, it is critical that they not come in contact with each other. Expectations about this examination should be tempered by the FE's knowledge of the suspect's rights and the time elapsed between the assault and the examination. Presumed innocent, the suspect should be handled with the same courtesy and respect as any other patient.

If the FE is the same for both SAV and suspect, the examination is facilitated by the examiner's knowledge of the SAV's history. If a different examiner is used, he or she should know the history as

www.ketabpezeshki.com 66485457-66963820

given by the victim, and this usually can be obtained from law enforcement. The history obtained from the officer is *not* the history that is recorded on the suspect evaluation form. The history on the examination form should come from the suspect, but he has the right to remain silent regarding the events surrounding the assault. If, after understanding his rights, he chooses to give information about the events under inquiry, the examiner should have him sign the consent and record his statements on the suspect form. Most suspects will voluntarily give this information. For suspects in custody, the consent is not necessary because state law provides for the collection of perishable evidence. The FE should be knowledgeable about local laws, and a protocol should be developed to handle suspects who resist the collection of evidence. The interview and examination, for security reasons, are performed with law enforcement present at all times. The FE needs to record suspect statements verbatim, using quotation marks, irrespective of audio and video recording, just as is done with the SAV. Medical information about preexisting conditions and hygiene is focused on factors that could influence interpretation of current findings. If there is a history indicating the possible transfer of biologic material between the SAV and suspect, appropriate specimens should be collected irrespective of hygiene or timing.

The physical examination follows the same format as the SAV examination. Injury to the suspect occurs less often than to the SAV; however, swabs of the penis, including the glans, shaft, base (but excluding the urethral meatus), scrotum, and sulcus of the foreskin, if present, are taken. In contrast to the SAV examination, identifying features, such as tattoos and scars, should be noted and documented photographically. Reference samples, including blood, saliva, and hair, should be taken in accordance with local protocol. Typically, STD cultures and serology are performed, although they may not be required or paid for under current state protocols, and information about pending results and treatment is given as indicated.

KEY CONCEPTS

- The role of the FE is to provide a thorough examination as the basis for a report.
- Physical examination findings should be accurately, reliably, and clearly documented.
- The SAV should be offered emergency contraception and prophylaxis for sexually transmitted infection, including hepatitis B and, in select cases, HIV.
- Specific referral for alcohol and substance abuse is critical.
- A follow-up examination should be performed to review and confirm the nature of physical findings, inquire about new symptoms, and encourage the SAV to connect to community services.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Basile, KC, Saltzman, LE: *Sexual violence surveillance: uniform definitions and recommended data elements*. Atlanta: National Center for Injury Prevention and Control, Centers for Disease Control and Prevention; 2002. Available at http://www.cdc.gov/violenceprevention/pub/sv_surveillance.html. Accessed January 26, 2013.
2. Office on Violence Against Women: A national protocol for sexual assault medical forensic examinations; 2004. Available at http://www.ovw.usdoj.gov/publications.html. Accessed January 26, 2013.
3. Green W, Panacek E: Sexual assault forensic examinations in evolution. *J Emerg Med* 2003; 25:97-99.
4. Stene L, Ormstad K, Schei B: Implementation of medical examination and forensic analyses in the investigation of sexual assaults against adult women: A retrospective study of police files and medical journals. *Forensic Sci Int* 2010; 199:79-84.
5. Campbell R, Patterson D, Lichty L: The effectiveness of sexual assault nurse examiner (SANE) programs. *Trauma Violence Abuse* 2005; 6:313-329.
6. Gilles C, Van Loo C, Rozenberg S: Audit on the management of complainants of sexual assault at an emergency department. *Eur J Obstet Gynecol Reprod Biol* 2010; 151:185-189.
7. Saltzman L, et al: National estimates of sexual violence treated in the emergency departments. *Ann Emerg Med* 2007; 49:210-217.
8. Ledray L, Kraft J: Evidentiary examination without a police report: Should it be done? Are delayed reporters and nonreporters unique? *J Emerg Nursing* 2001; 27:396-400.
9. Garcia S, Henderson M: Blind reporting of sexual violence. *FBI Law Enforc Bull* 1999; 68:13-16.
10. Boyko EJ, et al: *U.S. Department of Defense. Military services sexual assault report CY 2006*. In: Response DoDSAPa. Washington, DC: U.S. Department of Defense; 2010.
11. Price B: Receiving a forensic medical exam without participating in the criminal justice process: What will it mean? *J Forensic Nurs* 2010; 6:74-87.
12. Campbell P, Greeson M, Patterson D: Defining the boundaries: How sexual assault nurse examiners (SANEs) balance patient care and law enforcement collaboration. *J Forensic Nurs* 2011; 7:17-26.
13. Campbell P, et al: *A Systems Change Analysis of SANE Programs: Identifying Mediating Mechanism of Criminal Justice System Impact*. Washington, DC: National Institute of Justice; 2009.
14. Centers for Disease Control and Prevention (CDC): *Injury Prevention and Control: Data and Statistics (WISQARS)*. Atlanta, Ga: CDC; 2011. Available at www.cdc.gov/injury/wisqars/index.html. Accessed December 10, 2011.
15. Tjaden P, Thhoennes N: *Extent, Nature, and Consequences of Rape Victimization: Findings from the National Violence Against Women Survey*. National Institute of Justice Special Report. Washington, DC: U.S. Department of Justice; 2006. Available at www.ncjrs.gov/pdffiles1/nij/210346.pdf. Accessed December 11, 2011.
16. Jones J, Alexander C, Wynn B, Rossmani L, Dunnuck C: Why women don't report sexual assault to the police: The influence of psychosocial variables and traumatic injury. *J Emerg Med* 2009; 36:417-424.
17. McCall-Hosenfeld JL, Freund KM, Liebschutx JM: Factors associated with sexual assault and time to presentation. *Prev Med* 2009; 48:593-595.
18. Campbell J: Lethality assessment approaches: Reflections on their use and ways forward. *Violence Against Women* 2005; 11:1206-1213.
19. Biroscak B, Smith P, Roznowski H, Tucker J, Carlson G: Intimate partner violence against women: Findings from one state's ED surveillance system. *J Emerg Nurs* 2006; 32:12-16.
20. Rennison C: Rape and sexual assault: Reporting to the police and medical attention, 1992-2000. *Bureau of Justice Statistics Selected Findings*. Washington, DC: U.S. Department of Justice; 2002.
21. Anderson T, Guajardo J, Luthra R, Edwards K: Effects of clinician assisted emotional disclosure for sexual assault survivors: A pilot study. *J Interpers Violence* 2010; 25:1113-1131.
22. Poirier M: Care of the female adolescent rape victim. *Pediatr Emerg Care* 2002; 18:53.
23. Adams J, Girardin B, Faugno D: Adolescent sexual assault: Documentation of acute injuries using photo-colposcopy. *J Pediatr Adolesc Gynecol* 2001; 14:175-180.
24. Jones J, Rossman L, Hartman M, Alexander C: Anogenital injuries in adolescents after consensual sexual intercourse. *Acad Emerg Med* 2003; 10:1378-1383.
25. Stermac L, Du Mont J, Kalemba V: Comparison of sexual assaults by strangers and known assailants in an urban population of women. *CMAJ* 1995; 153:1089-1094.
26. Sugar NF, Fine DN, Eckert LO: Physical injury after sexual assault: Findings of a large case series. *Am J Obstet Gynecol* 2004; 190:71-76.
27. Jones J: Comparison of sexual assaults by strangers versus known assailants in a community-based population. *Am J Emerg Med* 2004; 22:454-459.
28. Ullman SE, Najdowski CJ: Understanding alcohol-related sexual assaults: Characteristics and consequences. *Violence Vict* 2010; 25:29-44.
29. Hudson A, et al: Correlates of adult assault among homeless women. *J Health Care Poor Underserved* 2010; 21:1250-1262.
30. Boykins A, et al: Minority women victims of recent sexual violence: Disparities in recent incident history. *J Womens Health (Larchmt)* 2010; 19:453-461.
31. Marsh M, Purdin S, Navani S: Addressing sexual violence in humanitarian emergences. *Glob Public Health* 2006; 1:133-146.
32. Jones J, Rossman L, Wynn B, Dunnuck C, Schwartz N: Comparative analysis of adult versus adolescent sexual assault: Epidemiology and patterns of anogenital injury. *Acad Emerg Med* 2003; 10:872-877.
33. Drocton P, Sachs C, Chu L, Wheeler M: Validation set correlates of anogenital injury after sexual assault. *Acad Emerg Med* 2008; 15:231-238.
34. Riggs N, Hourym D, Long G: Analysis of 1, 076 cases of sexual assault. *Ann Emerg Med* 2000; 34:358-362.
35. Eckert LO, Sugar N, Fine D: Factors impacting injury documentation after sexual assault: Role of the examiner experience and gender. *Am J Obstet Gynecol* 2004; 190:1739-1746.
36. Grossin C, et al: Analysis of 418 cases of sexual assault. *Forensic Sci Int* 2003; 131:125-130.
37. Sturgiss EA, Tyson A, Parekh V: Characteristics of sexual assaults in which adult victims report penetration by a foreign object. *J Forensic Leg Med* 2010; 17:140-142.
38. Henry T: Characteristics of sex related homicides in Alaska. *J Forensic Nurs* 2010; 6:57-65.
39. Slaughter L, Brown C, Shackleford S, Peck R: Patterns of genital injury in victims of sexual assault. *Am J Obstet Gynecol* 1997; 176:609-616.
40. Hazelwood R, Warren J: The criminal behavior of the serial rapist. *FBI Law Enforc Bull* 1990; 59:11-16.
41. Hazelwood R: The behavior-oriented interview of rape victims: The key to profiling. *FBI Law Enforc* 1983; 52:8-15.
42. Magid D: Changes in sexual assault over time: A prospective comparison of 1974-1991. *Ann Emerg Med* 1992; 21:608.
43. Read K: Population-based study of police-reported sexual assault in Baltimore, Maryland. *Am J Emerg Med* 2005; 23:273-278.
44. Maguire W, Goodall E, Moore T: Injury in adult female sexual assault complainants and related factors. *Eur J Obstet Gynecol Reprod Biol* 2009; 142:149-153.
45. Palmer C, McNulty A, D'Este C, Donovan B: Genital injuries in women reporting sexual assault. *Sex Health* 2004; 1:55-59.
46. Sheridan D, Nash K: Acute injury patterns of intimate partner violence victims. *Trauma Violence Abuse* 2007; 8:281-289.
47. Choon H, Myers WC, Heide KM: An empirical analysis of 30 years of U.S. juvenile and adult sexual homicide offender data: Race and age differences in the victim-offender relationship. *J Forensic Sci* 2010; 55:1282-1290.
48. Spehr A, Hill A, Habermann N, Briken P, Berner W: Sexual murderers with adult or child victims: Are they different? *Sex Abuse* 2010; 22:290-314.
49. Millar G, Stermac L, Addison M: Immediate and delayed treatment seeking among adult sexual assault victims. *Women Health* 2002; 35:53-64.
50. Gibbon C: Sexual assault and rape. *Curr Obstet Gynaecol* 2004; 14:356-362.
51. Campbell R, Bybee D: Emergency medical services for rape victims: Detecting the cracks in service delivery. *Womens Health* 1997; 3:75-101.
52. Ellison SR, Subramanian S, Underwood R: The general approach and management of the sexual assault patient. *Mo Med* 2008; 105:435-440.
53. McGregor MJ, du Mont J, White D, Coombes M: Examination for sexual assault: Evaluating the literature for indicators of women centered care. *Health Care Women Int* 2009; 30:22-40.
54. California Emergency Management Agency: *Forensic Medical Report: Acute (<72 hours) Adult/Adolescent Sexual Assault Examination*. Sacramento, Calif: California Emergency Management Agency; 2001.
55. Slaughter L, Henry T: Rape: When the exam is normal. *J Pediatr Adolesc Gynecol* 2009; 22:7-10.
56. Ullman S: A critical review of field studies on the link of alcohol and adult sexual assault in women. *Aggress Violent Behav* 2003; 8:471-486.

www.ketabpezeshki.com 66485457-66963820

57. Scott H, Beaman R: Demographic and situational factors affecting injury, resistance, completion, and charges brought in sexual assault cases: What is best for arrest? *Violence Vict* 2004; 19:479-494.
58. Testa M, Vanzile-Tamsen C, Livingston J: The role of victim and perpetrator intoxication on sexual assault outcomes. *J Stud Alcohol* 2004; 65:320-329.
59. O'Connor PG, Schottenfeld RS: Patients with alcohol problems. *N Engl J Med* 1998; 338:592-600.
60. Kilpatrick DG, Acinero R, Resnick HS, Saunders BE, Best CL: A 2-year longitudinal analysis of the relationships between violent assault and substance use in women. *J Consult Clin Psychol* 1997; 65:834-847.
61. Littleton H, Grills-Taquechel A, Axson D: Impaired and incapacitated rape victims: Assault characteristics and postassault experiences. *Violence Vict* 2009; 24:439-457.
62. Cole J, Logan T: Sexual assault response teams' responses to alcohol using victims. *J Forensic Nurs* 2008; 4:174-181.
63. Hammock GS, Richardson DR: Perceptions of rape: The influence of closeness of relationship, intoxication and sex of participant. *Violence Vict* 1997; 12:237-246.
64. Scully D, Marolla J: Convicted rapists' vocabulary of motive: Excuses and justifications. *Soc Probl* 1984; 31:530-544.
65. Sachs C, Chu L: Predictors of genitorectal injury in female victims of sexual assault. *Acad Emerg Med* 2002; 9:1146-1151.
66. Johnston L: Contributions of drug epidemiology to the field of drug abuse prevention. *Subst Use Misuse* 1997; 32:1637-1642.
67. Johnston LD, O'Malley PM, Bachman JG: *National Survey Results on Drug Use: College Students and Young Adults from the Monitoring the Future Study, 1975-92*. Washington, DC: National Institute on Drug Abuse; 1993.
68. Slaughter L: Involvement of drugs in sexual assault. *J Reprod Med* 2000; 45:425-430.
69. Juhascik M, et al: An estimate of the proportion of drug-facilitation of sexual assault in four U.S. localities. *J Forensic Sci* 2007; 52:1396-1400.
70. Du Mont J, Macdonald S, Rotbard N, Asllani E, Bainbridge D: Factors associated with suspected drug facilitated sexual assault. *CMAJ* 2009; 180:513-519.
71. Du Mont J, et al: Drug facilitated sexual assault in Ontario, Canada: Toxicological and DNA findings. *J Forensic Leg Med* 2010; 17:333-338.
72. Parkin MC, Brailsford AD: Retrospective drug detection in cases of drug facilitated sexual assault: Challenges and perspectives for the forensic toxicologist. *Bioanalysis* 2009; 1:1001-1013.
73. Carr M, Moettus A: Developing a policy for sexual assault examinations on incapacitated patients and patients unable to consent. *J Law Med Ethics* 2010; 38:647-653.
74. Pierce-Weeks J, Campbell P: The challenges forensic nurses face when their patient is comatose: Addressing the needs of our most vulnerable patient population. *J Forensic Nurs* 2008; 4:104-110.
75. Eckert LO, Sugar N, Fine D: Characteristics of sexual assault in women with a major psychiatric diagnosis. *Am J Obstet Gynecol* 2002; 186:1284-1291.
76. White C, McLean I: Adolescent complainants of sexual assault; injury patterns in virgin and non-virgin groups. *J Clin Forensic Med* 2006; 13:172-180.
77. Funk M, Schuppel J: Strangulation injuries. *Wis Med J* 2003; 102:41-45.
78. Wilbur L, et al: Survey results of women who have been strangled while in an abusive relationship. *J Emerg Med* 2001; 21:297-302.
79. Prodan M: *Special Topics in Sexual Assault Investigations: Victim and Offender Relationship*. Irvine, Calif; 2009.
80. Jones JS, Rossman L, Wynn B, Ostovar H: Assailants sexual dysfunction during rape: Prevalence and relationship to genital trauma in female victims. *J Emerg Med* 2008; 38:529-535.
81. Reznic M, Nachman R, Hiss J: Penile lesions-reinforcing the case against suspects of sexual assault. *J Clin Forensic Med* 2004; 11:78-81.
82. State of California. California Penal Code. Section 222, Sacramento, CA.
83. Gray-Eurom K, Seaberg D, Wears R: The prosecution of sexual assault cases: Correlation with forensic evidence. *Ann Emerg Med* 2002; 39:39-46.
84. Sweet D, Shutler G: Analysis of salivary DNA evidence from a bite mark on a body submerged in water. *J Forensic Sci* 1999; 44:1069.
85. Sweet D, Lorente M, Lorente J, Valenzula A, Villanueva E: An improved method to recover saliva from human skin: The double swab technique. *J Forensic Sci* 1997; 42:320-322.
86. Crowley S: *The Medical Legal Examination*. Stamford, Conn: Appleton & Lange; 1999.
87. Henry T: Lip swabs, floss effective for collecting DNA evidence. *On the Edge* 2003; 9:7.
88. Giest R: Sexually related trauma. *Emerg Med Clin North Am* 1988; 6:439.
89. Kaufman R, Faro S: *Benign Diseases of the Vulva and Vagina*. Chicago: Year Book Medical Publishers; 1994.
90. Masters W, Johnson V: *Human Sexual Response*. Boston: Little, Brown and Company; 1966.
91. Levin R: The ins and outs of vaginal lubrication. *Sex Relatsh Ther* 2003; 18:509-513.
92. Sipski M: Sexual response in women with spinal cord injury: Neurologic pathways and recommendations for the use of electrical stimulation. *J Spinal Cord Med* 2001; 24:155-158.
93. Sipski M, Arenas A: Female sexual function after spinal cord injury. *Prog Brain Res* 2006; 152:441-447.
94. Suschinsky KD, Lalumière ML: Prepared for anything? An investigation of female genital arousal in response to rape cues. *Psychol Sci* 2011; 22:159-165.
95. Levin R, Van Berlo W: Sexual arousal and orgasm in subjects who experience forced or non-consensual sexual stimulation. *J Clin Forensic Med* 2004; 11:82-88.
96. McLean I, Roberts SA, White C, Paul S: Female genital injuries resulting from consensual and non-consensual vaginal intercourse. *Forensic Sci Int* 2011; 204:27-33.
97. Zink T, et al: Comparison of methods for identifying ano-genital injury after consensual intercourse. *J Emerg Med* 2008; 39:113-118.
98. Mancino P, Parlavecchio E, Melluso J, Monti M, Russo P: Introducing colposcopy and vulvovaginoscopy as routine examinations for victims of sexual assault. *Clin Exp Obstet Gynecol* 2003; 30:40.
99. Slaughter L, Brown C: Colposcopy to establish physical findings in rape victims. *Am J Obstet Gynecol* 1992; 166:83-86.
100. Fraser I, et al: Variations in vaginal epithelial surface appearance determined by colposcopic inspection in healthy, sexually active women. *Hum Reprod* 1999; 14:1974-1978.
101. Stevens J, Rossman L, Jones J, Wynn B: Effect of menstrual bleeding on the detection of anogenital injuries in sexual assault victims. *Ann Emerg Med* 2007; 50:S134.
102. Morgan J: Comparison of cervical os versus vaginal evidentiary findings during sexual assault exam. *J Emerg Nurs* 2008; 34:102-105.
103. Keller P, Lechner M: Injuries to the cervix in sexual assault victims. *J Forensic Nurs* 2010; 6:196-202.
104. Allard J: The collection of data from findings in cases of sexual assault and the significance of spermatozoa on vaginal, anal, and oral swabs. *Sci Justice* 1997; 37:99.
105. Collins KA, Bennett AT: Persistence of spermatozoa and prostatic acid phosphatase in specimens form deceased individuals during varied postmortem intervals. *Am J Forensic Med Pathol* 2001; 22:228-232.
106. Young KL, Jones JG, Worthington T, Simpson P, Casey PH: Forensic laboratory evidence in sexually abused children and adolescents. *Arch Pediatr Adolesc Med* 2006; 160:585-588.
107. Stefanidou M, Alevisopoulos G, Spiliopoulou C: Fundamental issues in forensic semen detection. *West Indian Med J* 2010; 59:280-283.
108. Lauber A, Souma M: Use of toluidine blue for documentation of traumatic intercourse. *Obstet Gynecol* 1982; 60:644-648.
109. Hochmeister M, et al: Effects of toluidine blue and destaining reagents used in sexual assault examinations on the ability to obtain DNA profiles from postcoital vaginal swabs. *J Forensic Sci* 1997; 42:316-319.
110. McCauley J, Guzinski G, Welch R, Gorman R, Osmens F: Toluidine blue in the corroboration of rape in the adult victim. *Am J Emerg Med* 1987; 5:105-108.
111. Heger A: Evaluation of sexual assault in the emergency department. *Top Emerg Med* 1999; 21:46-57.
112. Brennan P: The medical and ethical aspects of photography in the sexual assault examination: Why does it offend? *J Clin Forensic Med* 2006; 13:194-202.
113. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC): Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep* 2010; 59:1-109.
114. Grimes D, Raymond E: Emergency contraception. *Ann Intern Med* 2002; 137:180-189.
115. Langston A: Emergency contraception: Update and review. *Semin Reprod Med* 2010; 28:95-102.
116. American College of Emergency Physicians (ACEP): *Policy Statement: Emergency Contraception for Women at Risk of Unintended and Preventable Pregnancy*. Irving, Texas: ACEP; 2010. Available at www.acep.org/content.aspx?id=29200. Accessed January 26, 2013.
117. American Medical Association: Access to emergency contraception. Policy of the House of Delegates. H-75-985; 2011.
118. Kaplan DW, et al: American Academy of Pediatrics. Care of the adolescent sexual assault victim. *Pediatrics* 2001; 107:1476-1479.

www.ketabpezeshki.com 66485457-66963820

119. American College of Obstetrics and Gynecology: Emergency contraception. *Practice Bulletin* 2010; 112.
120. Cremer M, Masch R: Emergency contraception: Past, present and future. *Minerva Ginecol* 2010; 62:361-371.
121. Espey E, et al: Compliance with mandated emergency contraception in New Mexico emergency departments. *J Womens Health (Larchmt)* 2009; 18:619-623.
122. Dietz T, Wright J: Age and gender differences and predictors of victimization of the older homeless. *J Elder Abuse Negl* 2005; 17:37-60.
123. Poulos CA, Sheridan D: Genital injuries in postmenopausal women after sexual assault. *J Elder Abuse Negl* 2008; 24:323-335.
124. Burgess A, Brown K, Ledray L: Sexual abuse of older adults. *Am J Nurs* 2005; 105:66-71.
125. Hanrahan N, Burgess A, Gerolamo A: Core data elements tracking elder sexual abuse. *Clin Geriatr Med* 2005; 21:413-427.
126. Chihowski K, Hughes S: Clinical issues in responding to alleged elder sexual abuse. *J Elder Abuse Negl* 2008; 20:377-400.
127. Cooper G, King M: Interviewing the incarcerated offender convicted of sexually assaulting the elderly. *J Forensic Nurs* 2006; 2:130-133.
128. Burgess A, Hanrahan N, Baker T: Forensic markers in elder female sexual abuse cases. *Clin Geriatr Med* 2005; 21:399-412.
129. Collins K, Presnell S: Elder homicide: A 20-year study. *Am J Forensic Med Pathol* 2006; 27:183-187.
130. Templeton D: Sexual assault of a postmenopausal woman. *J Clin Forensic Med* 2005; 12:98-100.
131. Jones JS, Rossman L, Diegel R, Van Order P, Wynn B: Sexual assault in postmenopausal women: Epidemiology and patterns of genital injury. *Am J Emerg Med* 2009; 27:922-929.
132. Del Bove G, Stermac L, Bainbridge D: Comparisons of sexual assault among older and younger women. *J Elder Abuse Negl* 2005; 17:1-18.
133. Martin S, Housley C, Raup G: Determining competency in sexually assaulted patient: A decision algorithm. *J Forensic Leg Med* 2010; 17:275-279.
134. Masho SW, Anderson L: Sexual assault in men: A population-based study of Virginia. *Violence Vict* 2009; 24:98-110.
135. Peterson Z, Voller EK, Polusny M, Maureen M: Prevalence and consequences of adult sexual assault of men: Review of empirical findings and state of the literature. *Clin Psychol Rev* 2011; 31:1-24.
136. Monk-Turner E, Light D: Male sexual assault and rape: Who seeks counseling? *Sex Abuse* 2010; 22:255-265.
137. Pesola G, Westfal R, Kuffner C: Emergency department characteristics of male sexual assault. *Acad Emerg Med* 1999; 6:792-798.
138. Lipscomb GH, Muram D, Speck PM, Mercer BM: Male victims of sexual assault. *JAMA* 1992; 267:3064.
139. Ernst AA, Green E, Ferguson MT, Weiss SJ, Green WM: The utility of anoscopy and colposcopy in the evaluation of male sexual assault victims. *Ann Emerg Med* 2000; 36:432.
140. Light D, Monk-Turner E: Circumstances surrounding male sexual assault and rape. *J Interpers Violence* 2009; 24:1849-1858.

www.ketabpezeshki.com 66485457-66963820

Chapter 68

Intimate Partner Violence

Deirdre Anglin and Connie Mitchell

PERSPECTIVE

Background

Emergency medical specialists, by nature and by necessity, focus their problem-solving skills on the presenting health complaint or bodily symptom that motivated the patient to seek relief at that particular moment. In the case of intimate partner violence (IPV), such focus may lead to blinding tunnel vision and a missed opportunity to lift the veil of shame and empower a victim to consider options to reduce future harm and restore emotional and physical well-being. IPV is a shame-based disease not readily disclosed or discussed with the health provider, let alone anyone else. Most physicians consider partner violence in the differential diagnosis of a physically injured woman; however, patients with an acute IPV injury represent the "tip of the iceberg." Emergency physicians probably treat many more victims of IPV without realizing it because the patients seek treatment for other problems that are complications of prior physical, sexual, or emotional abuse or for conditions that may be comorbid with IPV. The portion of the IPV iceberg lying undetected beneath the water line may be the most dangerous. The intent of this chapter is to educate emergency medicine specialists about the health problem of IPV so that they can move beyond the obvious and improve IPV identification, facilitate earlier intervention, and reduce morbidity and mortality for victims and children living in an IPV home.

Epidemiology

Definition and Types of Intimate Partner Violence

In 2002 the World Health Organization (WHO) declared that "violence is a leading, world-wide public health problem" and then added that violence is not an intrinsic part of the human condition and is preventable. Gro Harlem Brutland, the Director General of WHO, wrote, "to many people, staying out of harm's way is a matter of locking doors and windows and avoiding dangerous places. To others, escape is not possible. The threat of violence is behind those doors—well hidden from public view."[1] The WHO report distinguishes three general categories of violence—individual, interpersonal, and collective—and then further divides interpersonal violence into familial or stranger violence. IPV is a form of interpersonal, familial violence (Fig. 68-1).

IPV has been defined by the Centers for Disease Control and Prevention (CDC) as the threat or infliction of physical or sexual violence by a current or former adolescent or adult intimate partner or spouse. This violence is often accompanied by psychological abuse.[2] The physical, sexual, and psychological forms of IPV occur as a pattern of assaultive and coercive behaviors. Physical violence includes aggressive behaviors, such as pushing, hitting, slapping, punching, kicking, biting, burning, strangulation, using objects and weapons, and controlling access to physical needs, such as health care, medications, food, or shelter. Sexual abuse includes behaviors such as forced sex, coerced sex with a partner or other persons, and violence in association with sexual assault and rape, as well as prevention of or interference with the use of birth control and refusal to use condoms to prevent the transmission of sexually transmitted infections and human immunodeficiency virus (HIV). Psychological abuse includes words and behaviors meant to intimidate, degrade, humiliate, or isolate the victim from family and friends. Psychological abuse may also manifest as behaviors to arouse fear in the victim, such as violence or threats of violence against family members, stalking, attacks against pets, and destruction of property; controlling access to food, shelter, clothing, transportation, and money; and controlling employment and social or professional activities.

In the past, IPV has been referred to by a number of different terms. These include *domestic violence, spouse abuse, wife abuse, battering, battered woman,* and *wife beating.* However, the use of the term *intimate partner violence* is recommended, as it is a more inclusive term and applies equally to adolescents and adults, females and males, opposite- and same-sex intimate partners, married and unmarried individuals, and current and former intimate partners.[2] State penal codes may use slightly different definitions of IPV from those of the CDC, especially as it pertains to the nature of the relationship between the two individuals or the forms of abuse that have transpired. The term *domestic violence* is generally used by the criminal justice system when referring to partner violence, whereas *intimate partner violence* is the preferred term of the CDC; of note, the International Classification of Diseases (ICD) includes IPV as a form of adult maltreatment.

Prevalence

There are numerous population-based and health care–based studies that report prevalence rates of IPV victimization. Because of the different types of IPV (i.e., physical, sexual, psychological and emotional), the pattern of the violence (i.e., first episode, ongoing, intermittent, previous experience), and the population being surveyed, the reported IPV victimization prevalence rates vary widely. The prevalence of IPV victimization is often expressed as either a 1-year prevalence (the proportion of the population experiencing IPV in the previous year) or as a lifetime prevalence (the proportion of the population that have ever experienced IPV). To fully understand the meaning of reported IPV prevalence rates or to be able to compare IPV prevalence rates between

www.ketabpezeshki.com 66485457-66963820

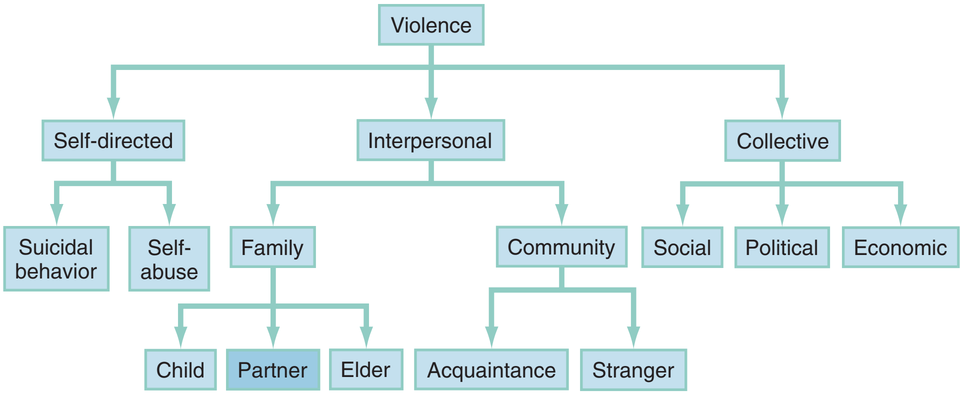


Figure 68-1. World Health Organization categories of violence.

studies, one should look at the population being studied, the types of abuse being measured, and the period of time being studied. The variation in research methodology among studies makes IPV surveillance challenging. In an attempt to improve IPV surveillance, the CDC published recommended uniform definitions and data elements for IPV research.[2]

The National Crime Victimization Survey (NCVS) and the National Intimate Partner and Sexual Violence Survey (NISVS) are two large population-based surveys. In the NCVS in 2010, a randomized telephone survey of 41,000 households and approximately 73,300 males and females 12 years and older, 22% of violent crime against women was IPV compared with 5% against men,[3] and about 80% of IPV victims were women.[4] In the NISVS in 2010, a random telephone survey of 7421 men and 9086 women 18 years and older, 35.6% of women and 28.5% of men reported having been physically or sexually assaulted and/or stalked by an intimate partner during their lifetime; 5.9% of women and 5.0% of men reported having been physically or sexually assaulted and/or stalked by an intimate partner within the previous year.[5] According to one survey, women in same-sex relationships reported lower rates of IPV (11%) than women in opposite-sex relationships (20%). On the other hand, men in same-sex relationships reported increased rates of IPV (23%) compared with men with female partners (8%).[6] According to Behavioral Risk Factor Surveillance System (BRFSS) data from 2005, 23.6% of women reported a lifetime history of IPV and 11.5% of men reported IPV.[7] The rates are about the same in rural and urban populations.[8] Domestic violence also occurs in older women.[9] The National Women's Health Initiative reported that 11% of women aged 50 to 79 years disclosed that they had experienced physical or psychological abuse over the previous year.[10]

The prevalence rates of IPV among emergency department (ED) patients are greater than those in population-based studies. Although numerous IPV prevalence studies have been conducted in the ED, they are difficult to compare owing to differing methodologies. The majority of ED-based studies have examined IPV prevalence rates among women. In general, ED-based studies report the incidence of acute abuse, 1-year, and lifetime prevalence rates. Based on several ED-based surveys, 1 to 7% of all adolescent and adult females who came to the ED for any reason did so as a result of an acute episode of physical abuse.[11] Moreover, 14 to 22% of all female patients in the ED disclosed that they had experienced IPV in the previous year.[12,13] From the Michigan Intimate Partner Violence Surveillance System, all female assault victims were identified based on International Classification of Diseases, Ninth Revision (ICD-9) diagnostic and E codes. Of 3111 assault victims, 2926 were victims of physical or sexual violence, and 38.8% (95% confidence interval [CI], 37.1-40.6) of these cases were attributed to IPV.[14] The lifetime prevalence of IPV among female ED patients may be as high as 54%.[15] Few studies have investigated the prevalence rate of IPV among male ED patients, and those that did failed to differentiate whether the relationship was homosexual or heterosexual IPV, did not specify whether injuries were sustained in the course of partner retaliation, defense, or retribution, and did not differentiate the force used and nature of injuries sustained.[16] The chief concern in comparing male and female victimization is that the dynamics and consequences of the abuse may be very different.

Homicide is one of the top five leading causes of death for females aged 1 to 34 years.[17] According to the National Violent Death Reporting System report on 2007 data, 64.4% of intimate partner–related homicides involved female victims, whereas 13.7% of non–intimate partner–related homicides involved female victims. The highest percentage of victims and suspects (26.1 and 23.5%, respectively) were persons aged 35 to 44 years, 37.8% of whom were married at the time of death.[18] Women are killed by current or former intimate partners almost nine times more often than by strangers.[19] IPV fatalities do not usually occur as a freak event in an otherwise happy family. IPV is a precursor to the homicide in 65 to 75% of cases.[20] Of even greater concern for health professionals is that almost half of IPV homicide victims saw a health care provider (HCP) within the year before their death.[21,22] The incidence of homicide attributed to IPV has continuously decreased since the mid-1970s, a phenomenon that is attributed to societal shifts to more openly address family violence and to improvements in criminal justice, social service, and health system responses to both victims and perpetrators.

The annual economic cost to society in the United States is estimated at more than $8 billion dollars for direct medical and mental health services as well as lost productivity.[23] Studies have found that female patients with documented IPV have higher health care system utilization and costs than those without IPV.[24,25] Furthermore, higher health care system utilization and costs were seen in children whose mothers had experienced IPV, even if the abuse had ceased before the children's birth.[26]

Risks for Victimization

A few individual factors have been identified that appear to place persons at risk for IPV victimization: female gender, younger age,[27] exposure to violence in family of origin,[28,29] presence of a physical or mental disability,[30] and use of alcohol. Abbott found that among women patients who abused alcohol, 71% also experienced IPV.[15] Alcohol use plays a role in both victimization and perpetration of violence, probably because of its disinhibitory effects. In Caetano's study, 30 to 40% of men and 27 to 34% of women arrested for IPV perpetration were drinking at the time of the event.[31] If men were drinking at the time of the physical assault, their female

www.ketabpezeshki.com 66485457-66963820

partners were at 3.6 (95% CI 2.2-5.9) times greater risk of sustaining a serious physical injury.[32]

Other factors appear to contribute to the risk for IPV because either they contribute to relationship stress or they heighten victim vulnerabilities. IPV appears to occur at increased rates in relationships with lower socioeconomic status in which the abuser is unemployed or at a lower level of academic achievement.[32-34] Homeless women, in general, have higher cumulative rates of violence over the life span than women with stable housing,[35] and fleeing IPV homes has been noted to be one of the causes of homelessness in women. Immigrant women are another vulnerable population, as they may be reluctant to disclose IPV, fearing deportation of themselves and/or their spouse. Immigrant women may be further isolated from services owing to language barriers, lack of social support, or lack of economic independence.[36] In one study of 1861 New York femicides, the strongest predictors of intimate partner femicide victimization were foreign country of birth and young age.[37]

Two presentations should provoke consideration of IPV as an underlying or comorbid condition. One presentation is the woman with injuries to the head, face, or neck.[38] Muelleman and other researchers found maxillofacial injuries to be the most common injury type among battered women.[39,40] Another presentation that prompts consideration of IPV is the female patient who has attempted suicide. Abbott found that among female patients with a lifetime history of a suicide attempt, 81% also had a history of IPV.[15] More than 90% of women hospitalized after a suicide attempt report current severe IPV.[41,42] Women seen at one ED in England as a consequence of IPV assault (N = 294) were compared with a matched control (N = 558) to determine risk of future self-harm. IPV victims had a relative risk of 3.6 (95% CI, 2.1-6.5) of returning to the ED because of future episodes of self-harm.[43]

Risks for Perpetration

Most of the research on persons who abuse their intimate partner is done on men who have committed violence of sufficient severity to have been arrested. Although batterers are a heterogeneous group, there are three typologies commonly described: (1) the borderline or dysphoric individual, (2) the antisocial or generally violent individual, and (3) the "family only, no psychopathology" batterer.[44] The men in the borderline or dysphoric group are often described as both charming and moody with "Dr. Jekyll–Mr. Hyde" personality changes from one extreme (complacent) to another (rageful). High rates of alcohol and drug use appear in this group, as well as increased contacts with police for violent or disorderly conduct offenses, and increased concerns about rejection or abandonment. The antisocial or generally violent batterer is described as "self-centered, self-absorbed, and lacking in empathy."[44] Intimate partners are viewed as objects or possessions that serve the perpetrator's needs. Although he may appear confident and exciting, he also manipulates and imposes his values on others. Antisocial batterers usually commit both physical and sexual violence that is more severe than with the other two types, as well as committing more violence outside the family. The third typology is composed of men described as the "guy next door," not violent outside the home but usually with evidence of passive dependency or obsessive-compulsive personality style. They are rigid, rule bound, and conventional. Any deviation from "the rules" can cause internalized resentments that occasionally erupt in aggressive outbursts of hostility and violence.[44] Other factors associated with IPV perpetration include younger age, lower socioeconomic status, exposure to violence in the family of origin,[45] alcohol abuse, history of traumatic brain injury (TBI) (anger flares and poorer impulse control), and highly or abnormally spouse-specific dependency.[46,47]

Risks to Children Living in Intimate Partner Violence Homes

Children who live in IPV homes often witness the violence and suffer physically and emotionally,[48,49] and the health impact can be acute or can lead to long-term health risks. The risk of exposure begins in the prenatal period. Pregnant women who are abused are more likely to smoke, consume alcohol, and use illicit drugs than nonabused pregnant women.[50,51] Pregnant women who experience IPV physical abuse experience miscarriage,[52] premature rupture of membranes, preterm labor,[53] and placental abruption at higher rates than pregnant women who have abdominal trauma from other causes.[54-56]

Long-term health risks associated with child exposure to adult IPV have been elucidated through the Adverse Childhood Experiences (ACE) Study based on data collected from 17,337 adult health maintenance organization members. Each person was assessed for exposure to adverse childhood experiences (verbal, physical, or sexual child abuse as well as family dysfunction caused by an incarcerated, mentally ill, or substance-abusing family member; IPV; or absence of a parent because of death or divorce or separation). Adverse childhood experiences have been linked to a range of adverse outcomes in adulthood, including substance abuse, depression, cardiovascular disease, diabetes, cancer, and premature mortality.[57-59] Adverse childhood experience exposure has also been linked to risk of perpetration and victimization of adolescent dating partner violence.[60,61] Trauma-related adverse childhood experiences have demonstrated a "dose-response" relationship to 18 selected health outcomes.[57]

Children in IPV homes are at increased risk for direct physical abuse by the IPV abuser and less often by the IPV victim.[62-64] Some state child welfare data have demonstrated that IPV appears to be associated with the most severe and fatal cases of child abuse.[65] Children of IPV mothers have been found to be twice as likely to be re-reported to Child Protective Services than children of non-IPV mothers.[66]

Of great interest is the neurobiologic impact of exposure to violence at a young age. Chronic stress can cause the emotional, more primitive parts of the developing infant or toddler brain to become overly active or reactive to the environment and may affect myelination and synaptogenesis, thus resulting in problems with learning, memory, and behavior.[67] Infants exposed to severe IPV in the home environment have demonstrated severe posttraumatic symptoms, as have their mothers.[68]

Because various forms of violence and abuse are inter-related, when an adult victim is identified, an assessment of the well-being of the children is also indicated. Alternatively, when child neglect or abuse is suspected, there is a good chance that IPV is also occurring and should be considered in the child or parental interview. Intervention programs should be prepared to address the health and safety needs of both child and adult victims that may co-occur in one family. Clinicians should interview older children alone and younger children in the presence of a guardian. If in the course of interviewing a pediatric patient IPV is disclosed, the child's medical records can be sealed by court order to prevent access by an abusive guardian parent if the physician can document sufficient concern for the health and safety of the child.

Special Considerations for Adolescents in Abusive Relationships

In a nationally representative sample of 7500 adolescents, 12% reported an experience of physical violence in an opposite sex relationship in the previous 18 months. If the question included sexual, physical, or psychological abuse, the rate rose to 32%.[69] Miller and colleagues found that 40% of adolescents who sought care at adolescent health clinics disclosed IPV—32% with

www.ketabpezeshki.com 66485457-66963820

disclosed physical abuse and 21% sexual abuse.[70] In a 2009 survey conducted by the CDC, 9.8% of male and female high school students reported an episode of dating violence (being hit, slapped, or physically hurt) in the preceding year.[71] Higher rates are found in rural populations and when youth from lower socioeconomic groups were surveyed.[72,73] Surveys show that boys and girls both report acts of physical aggression; however, girls report experiencing more serious acts, such as strangulation or use of a weapon in the physical assault or rape.[74,75] Girls are more likely to be worried or scared of relationship violence, and boys minimize the psychological impact of the aggression; however, this may be more of an enculturated response than a true reflection of boys' level of anxiety.[76] Complicating understanding regarding prevalence of relationship violence in teens is the fact that in some states it is reported as child abuse and in others as IPV. Pregnant teens seem to be a high-risk population for prior exposure to violence. In one study of 724 pregnant adolescents, 12% had been assaulted by the man who had impregnated them, and of those who had experienced relationship violence, 40% also reported having experienced violence by a family member or other relative.[77,78]

Adolescents are more likely to endorse stereotyped gender roles (dominant or aggressive males and submissive or supportive females) and are more likely to interpret jealousy, violence, or controlling behaviors as signs of love or devotion.[79] Adolescents are also less likely to disclose abuse to parents, from whom they are trying to individuate and separate, and less likely to disclose abuse to peers for fear of being considered odd or rejected by the peer group.[80] Homosexual teens have the additional anxiety of being "outed" should they disclose the abuse.[81]

Health professionals should routinely spend time alone with adolescents in the course of the history taking or physical examination to explore health issues such as reproductive and relationship health and prior exposures to violence, threats of violence, or bullying. The health professional should be familiar with the rights of minors regarding confidentiality, as well as state laws regarding mandatory reporting of relationship violence and sexual assault. Many states have enacted legal exemptions that allow minors as young as 12 years to seek a domestic violence protective order.

ETIOLOGY

Intimate Partner Violence Social Ecology Model

There are multiple theoretic explanations for the cause of IPV; these can best be organized with the Social Ecology Model, which nests individual, family, community, and cultural factors.[82]

The "individual" layer includes the biologic, ontogenic, or experiential makeup of a person, such as childhood exposure to IPV as well as certain personality psychopathologies.[44,82] A small number of studies have shown a relationship between mild traumatic brain injuries and increased anger and aggression, poor impulse control, and decreasing marital satisfaction.[44]

The second nested layer is the "family" or the relationship itself, with its own style of communication, decision-making, and conflict resolution, also referred to as the "microsystem." Male dominance and male control of financial decision-making in a family have been predictors of societies that have high rates of violence against women.[82] Not surprisingly, couples with high levels of conflict also have a greater risk of physical violence, and this risk increases when there is an asymmetrical power structure within the relationship.[82]

The third nested layer is "community" or "exosystem" and refers to the neighborhood, institutions, local services, and social structures that surround the family. Although IPV occurs across all socioeconomic strata, it appears to be more common in families with low income and in unemployed men. It is likely that income level is not the critical variable, but rather the stress of poverty, crowding, or hopelessness that actually contributes to increased violence. Lack of social support for women and delinquent peer associations for men have both been associated with victimization and perpetration, respectively.[82]

Finally, the individual, family, and community all function within a society or culture with rules, laws, taboos, attitudes, and biases—also referred to as the "macrosystem." The predominant cultural theory regarding the cause of IPV is Feminist Theory, which states that violence against women results from gender inequity, both ideologic (belief, norms, values) and structural (access to and positions within social institutions).[83] The more unequal women are to men, the more likely men are to be violent to women.[84,85]

Forms of Intimate Partner Violence

Some IPV researchers have suggested that there may be two distinct forms of IPV: intimate terrorism and situational couple violence.[86,87] The two forms are differentiated based on the use of power to control. Intimate terrorism is defined as "the attempt to dominate one's partner and to exert general control over the relationship," whereas situational couple violence is "violence that is not connected to a general pattern of control."[88] Situational couple violence is usually less injurious or severe, and more likely to be engaged in by either member of the couple. Intimate terrorism is characterized as more injurious, more frequent, and almost exclusively perpetrated by men against women.

In one study a five-item index to measure controlling behavior was created: (1) partner tries to limit your contact with family or friends,[89] (2) partner insists on knowing who you are with and where you are at all times, (3) partner becomes jealous and does not want you to talk to other people, (4) partner prevents you from knowing about or having access to family income even if you ask, and (5) partner controls most or all of your daily activities (α = .72). The study found that controlling behaviors are present in 69% of physically violent relationships but present in only 11% of non–physically abusive controls.

CLINICAL ASSESSMENT

Medical History

Patients who are currently experiencing or have previously experienced IPV may visit the ED for a wide range of health care issues. IPV patients may seek care after an acute physical or sexual assault or for the chronic sequelae related to a previous injury. They may seek treatment of an acute medical condition or care for a chronic illness exacerbated by IPV. In addition, IPV patients may require mental health care and may have conditions related to alcohol and substance abuse. IPV patients' presentations may be obvious, such as a geometrically patterned physical injury, or subtle, such as headaches resulting from repetitive blunt head trauma. Therefore it is important that the HCP be aware of the broad possibility of IPV presentations as well as the comorbid conditions that are associated with IPV (Fig. 68-2).

When HCPs are eliciting a history from a patient with injuries, they should attempt to determine the mechanism of injury. If the patient attributes the injuries to interpersonal violence, the identity of the other person, as well as that person's relationship to the patient, should be ascertained and documented. Not only is noting the nature of the relationship important for accuracy of diagnostic coding, but the intervention for a victim who lives with the assailant will be very different from the intervention for a victim of a stranger assault. If the injury is a result of IPV, the patient may be reluctant to divulge the information. Additional historical clues

www.ketabpezeshki.com 66485457-66963820

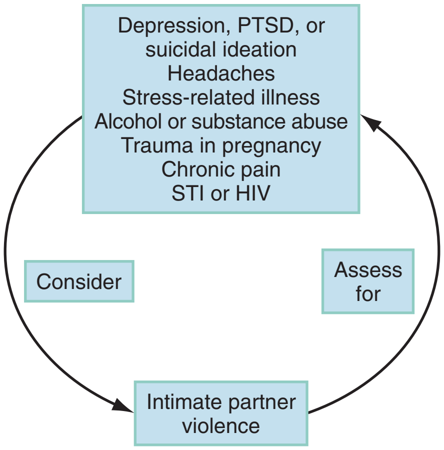


Figure 68-2. Intimate partner violence and associated comorbid conditions. *HIV,* human immunodeficiency virus; *PTSD,* post-traumatic stress disorder; *STI,* sexually transmitted infection.

that an injury may be a result of IPV are a vague or changing history, a history that is inconsistent with the injuries, a statement by the patient that he or she is "accident prone," and a past history of injuries.[90]

Many IPV patients seek care for chronic conditions that are a result of previous injuries or are comorbid medical conditions of the abuse. From results of a survey of 3568 English-speaking women that used BRFSS and Women's Experience with Battering (WEB) questions, the health status of abused and nonabused women were compared. Abused women were consistently and significantly at increased risk of psychosocial disorders (substance abuse, depression, anxiety, tobacco use), musculoskeletal disorders (degenerative joint disease, low back pain, joint trauma, cervical pain, acute sprains), reproductive complaints (menstrual disorders, vulvovaginitis, sexually transmitted infections), and others (confusion, headaches, urinary tract infections, abdominal pain, chest pain, respiratory infections, reflux disease, and lacerations).[7,91] Other common medical presentations of IPV patients include cardiorespiratory illnesses (palpitations, chest pain, asthma exacerbations, shortness of breath), gastrointestinal disorders (functional bowel disease), and general constitutional complaints (weakness, fatigue, dizziness, chronic pain). Additional analyses of the 2005-2007 BRFSS data revealed that same-sex and opposite-sex IPV victims experienced similar poor health outcomes.[92,93] When IPV victims experienced both physical and sexual IPV, they had even lower health outcome scores and more depression than those with physical abuse only.[94]

If the patient exhibits comorbid conditions common to IPV, the HCP should consider the possibility of IPV. Likewise, in the reverse, if the patient has experienced IPV, he or she should be questioned about the presence of any comorbid conditions that may warrant intervention (see Fig. 68-2). Other findings in the medical history that may be suggestive of IPV include a delay in seeking medical care or noncompliance with medications and/or medical appointments, which may be a result of the abuser controlling the patient's access to care. Frequent visits to the ED and alcohol and substance abuse are also highly associated with IPV.

Physical Examination

IPV patients may come to the ED with acute injuries, or injuries may be an incidental finding discovered during the physical examination for medical complaints. When examining an injured patient, the HCP should look for clues that the injury may be intentional in nature, such as a central location (e.g., trunk, breasts), bilateral injuries (both arms or both legs), defensive injuries (e.g., ecchymoses on the back of the hand because of protecting the face), and patterned injuries (having the markings of an object such as the sole of a shoe or a burn with the imprint of an iron). Common locations for IPV injuries are the head, face, mouth, and neck. Types of injuries may include facial contusions, lacerations, fractures, traumatic alopecia, concussion, skull fractures, intracranial hemorrhages, and strangulation. Extremity injuries with "grab" marks (fingertip contusions) to the upper arms are suggestive of IPV. In one study, 2% of women with acute fractures related their injury to IPV, and one third of injured women revealed IPV exposure at some previous time.[95]

HCPs should assess injuries for location, size, swelling, tenderness, coloration, evidence of healing, and the presence of a pattern. In noting the color of each ecchymosis, the HCP should be careful not to make a determination as to the age of each one, as this may vary depending on the force used, the vascularity of the tissue injured, the age and health status of the victim, and the use of medications or alcohol, which can alter coagulation profiles.

Mental Health Assessment

The HCP should assess any patient known or suspected to have been exposed to IPV for associated mental health conditions. IPV victims frequently experience depression, suicidal ideation, homicidal ideation, post-traumatic stress disorder (PTSD), insomnia, eating disorders, and alcohol and substance abuse. In a meta-analysis of mental health disorders among women who had experienced IPV, the weighted mean prevalence was 50% for depression, 61% for PTSD, and 20% for suicidality: higher prevalence rates were seen in women with more severe abuse or who were in shelters or court programs.[96] These rates are all significantly higher than those in individuals who have not experienced IPV. IPV patients should also be questioned about alcohol and substance abuse, a common coping mechanism or form of pain control for IPV patients.

Other Intimate Partner Violence Injuries

Strangulation, mild TBI, and intimate partner sexual abuse are three forms of injury that occur frequently in IPV and have been under-recognized by HCPs.

Strangulation

Intentional strangulation occurs as a result of the perpetrator applying compression using a body part (one or two hands, forearm, or knee) or a ligature (a necklace or piece of clothing worn by the IPV victim). In asking patients if their partner attempted to strangle them, the lay term "choked" may be more appropriate to use because people often associate strangulation with a rope or object, whereas the word "choking" is associated with neck compression by the hands. Patients may complain of a hoarse voice, pain or difficulty swallowing, neck pain, difficulty breathing, loss of consciousness, incontinence, or confusion, or they may have no symptoms. On examination they may have a hoarse or muffled voice, difficulty swallowing, neck tenderness, respiratory difficulties, stridor, laryngeal fracture, facial petechiae, subconjunctival hemorrhages, ecchymoses or ligature marks on the neck, or altered mental status. They may also have normal examination findings that do not show any specific signs of strangulation.[97,98]

Mild Traumatic Brain Injury

According to one study, 71% of women experiencing IPV have incurred TBI from a physical assault, and 51% incurred multiple

www.ketabpezeshki.com 66485457-66963820

episodes of TBI from repetitive assaults.[99] Women appear to be at greater risk for postconcussive syndrome than men.[100] IPV patients may also sustain TBI from "shaken adult syndrome," resulting in diffuse axonal injury. Like shaken babies, these patients may have retinal hemorrhages, subdural hematomas, and ecchymoses of the upper arms and chest.[101] IPV patients frequently report difficulty concentrating, memory problems, headaches, depression and anxiety, and confusion, as well as problems with judgment, problem-solving, and decision-making. In these cases, TBI can be missed, and patients may be labeled as having borderline personalities, post-traumatic stress, or depression. The sequelae of TBI, which is frequently undiagnosed and underrecognized, include neurocognitive deficits and long-term disability. It has been postulated that perhaps TBI interferes more with a patient's ability to make safer choices than has been previously recognized. The IPV patient with mild TBI should be referred for a comprehensive neurocognitive assessment.[102]

Intimate Partner Sexual Abuse

Approximately 8 to 14% of women are sexually abused during their lifetimes by an intimate partner.[34] Whereas societal biases result in intimate partner sexual abuse being considered less severe and the victim being disbelieved or blamed more often than in stranger sexual assault, the sequelae of intimate partner sexual abuse are at least as serious as those of stranger sexual assault. In addition, victims of intimate partner sexual abuse have been found to be more likely to sustain more serious nongenital injuries than victims of stranger assault.[103] When questioning IPV patients about intimate partner sexual abuse and rape, the HCP should ask whether they have ever been forced by their partner to do sexual activities they did not want to do, rather than asking if they have been raped or sexually assaulted. Many IPV patients do not consider that they have been raped or sexually assaulted if their partner, husband, or boyfriend was the perpetrator. Many IPV patients also do not recognize that sexual activity under coercion or threat is a form of sexual assault. In one study, 19% of women reported pregnancy coercion (coercion to become pregnant) and 15% reported birth control sabotage (partner interference with birth control), both of which were associated with unintended pregnancy.[104]

DIAGNOSTIC STRATEGIES

The ability of a clinician to identify and diagnose IPV in the ED largely relies on the interaction between the clinician and patient, and the rapport the patient has with the clinician. In addition, because IPV is a shame-based health care problem, the more comfortable the environment and the clinician-patient interaction, the more likely the clinician will be able to have a conversation about IPV with a patient.

Milieu Considerations

Privacy and safety are issues for all patients, but they are particularly critical for IPV patients when the consequences of a breach of either could result in further injury or death. Specific provider behaviors that foster disclosure by IPV patients have been identified and are reviewed in the following sections. In addition, there are institutional barriers, professional and personal HCP barriers, and patient barriers that should be addressed and minimized to support the disclosure of IPV.

Provide Privacy

One key behavior that promotes privacy is having a patient-only interview policy for at least part, if not all, of the interview, as patients who have experienced IPV may choose not to disclose their abusive relationship in the presence of their family, children, or friends, owing to shame and embarrassment. Research has shown that women experiencing IPV prefer to talk to their physicians alone about the abuse.[105] If a partner is reluctant or refusing to leave, the HCP may need to be creative in finding an opportunity to talk to the patient alone, such as when a patient is in the radiology department. In addition, if an interpreter is needed, only trained and authorized hospital employees or a nationally based telephone interpreter service should be used. A hospital employee should not be used as an interpreter if the employee knows the patient. If a patient is asked to complete a written or computer-based questionnaire before being assessed by the HCP, he or she should be provided with a private, safe location in which to do this. Before questioning a patient about activities that must be reported to law enforcement, such as IPV-related injuries in some states, the HCP should inform the patient about the limits of confidentiality (see the later section on ethical considerations).

Ensure Safety

The first step to ensuring patient safety in the ED is to determine the current location of the abusive partner. An abusive partner may be in the waiting room or may unexpectedly show up at the ED. In either case, the department should have a security protocol to protect patients when the threat level is high or if the batterer suddenly appears on the premises. Both IPV and sexual assault patients may feel that a room with a door is protective of both their safety and their confidentiality.

Provider Behaviors That Foster Disclosure

Numerous qualitative studies, primarily consisting of focus groups and surveys of women who are survivors of IPV, have been conducted to identify HCP behaviors that foster disclosure of IPV by patients. Women reported that they were more likely to disclose IPV to HCPs who listened attentively, conveyed compassion and concern, were nonjudgmental, and respected the woman's right to autonomy in decision-making.[106,107] In addition, IPV-related educational materials such as posters and patient brochures in the clinical setting made patients feel that the health care setting was a safe environment in which to discuss IPV with their HCP. Some women reported feeling more comfortable talking with a female HCP.[108] However, a study by Gerlach in 2007 demonstrated that the gender of the HCP did not appear to be a barrier to disclosure.[109]

HCPs' responses to surveys indicate that they are reluctant to ask patients about IPV for several reasons, including a lack of training about IPV, belief that there are no effective IPV interventions, time constraints, a perception that IPV patients are frustrating to deal with and do not follow HCPs' advice, concerns about mandated reporting to law enforcement in some states, and a reluctance to go to court if required. In addition, HCPs' personal experiences with IPV, their biases about victims and batterers, and their belief that IPV is not a health care problem are all barriers that may limit an HCP's ability to diagnose IPV in the ED.[110]

Overcoming Barriers to Care

HCPs frequently state that one barrier to care of IPV patients is that they do not have adequate time to spend assessing the patient, given the complex nature of IPV. Having other trained personnel or a multidisciplinary response team to assist with assessment, referrals, and reporting can lessen this problem. Through service agreements with community-based domestic violence organizations, trained peer counselors can provide beside, telephone, or video crisis response. Another barrier to care is the stigma of the

www.ketabpezeshki.com 66485457-66963820

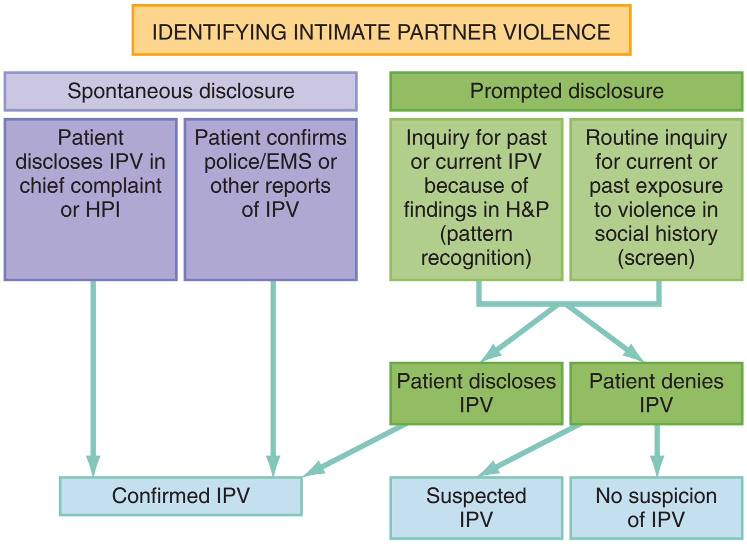


Figure 68-3. Identifying intimate partner violence algorithm. *EMS,* emergency medical services; *H&P,* history and physical examination; *HPI,* history of present illness; *IPV,* intimate partner violence.

condition. IPV patients are often embarrassed and ashamed about their situation, so IPV awareness posters and information cards in the ED and waiting room bathrooms can help them to feel safer talking about IPV. Likewise, HCPs may feel awkward about raising the issue, so appropriate education and training are important.

Identification through Disclosure and/or Pattern Recognition

IPV is identified through disclosure or suspected based on pattern recognition. Disclosure is either spontaneous or prompted and yields a confirmed diagnosis (Fig. 68-3). A patient may spontaneously disclose IPV in the chief complaint or during the history of the presenting illness. While being triaged, a patient might state in response to a question as to why she came to the ED, "I was punched in the nose by my husband." This is an example of spontaneous disclosure of IPV. Similarly, a patient being evaluated for decreased hearing might respond to a question about when the symptoms began, saying, "Ever since my partner slapped me across my ear." A prompted disclosure of IPV occurs when the patient reveals or affirms IPV when asked by the HCP. The HCP may ask about past or present IPV in the process of routine inquiry, such as in the social history, or may consider IPV in the differential diagnosis of the presenting problem based on pattern recognition. For example, for a patient with multiple ED visits for minor trauma with a history of depression and suicide attempt, the HCP might ask, "With your history of depression, previous suicide attempt, and multiple episodes of injury, I was wondering if your home situation was stressful or unsafe, perhaps because of a partner who threatens or hurts you; is this true for you?" A patient who has a pattern of signs and symptoms suggestive of IPV should be asked about current or past threats or violent injury, which may lead to a prompted disclosure of IPV by the patient.

Is There an Effective Screen for Intimate Partner Violence Identification?

Because of the high prevalence rates of IPV in health care settings and the varied presentations of patients to the health care setting, numerous professional medical organizations,[111] regulatory bodies, and advocacy organizations have recommended that patients be assessed to identify those who are experiencing IPV.[112] In a recent report from the Institute of Medicine, IPV screening and counseling were recommended as essential preventive services and are now included as part of health care reform under the Patient Protection and Affordable Care Act.[113] The term *screening* is used in the IPV literature to refer to a process of asking about past or current exposure to violent or abusive behavior regardless of whether the patient is symptomatic or not. In IPV, there is no gold standard test for diagnosis, and, contrary to other health care screens, a screen for IPV relies on volition or the patient's willingness to be truthful, which in turn depends on the degree of trust or safety the patient feels at the time of the screen. In 2013, the U.S. Preventive Services Task Force (USPSTF) reported on its evaluation of the evidence regarding screening for family violence and IPV in the health care setting. The report stated that there was adequate evidence that available screening instruments can identify current and past abuse or increased risk for abuse, and several instruments were both highly sensitive and specific. The USPSTF recommended that asymptomatic women of childbearing age be screened for IPV and that women who screen positive be provided or referred to intervention services. This recommendation was given a "B" grade, meaning there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.[114] The USPSTF found adequate evidence that effective interventions can reduce harm and adequate evidence that the risk for harm from screening or interventions is no greater than small. Houry did not find any adverse effects from questioning patients about IPV.[115] In another study of 36 women interviewed after ED screening and intervention, 97% perceived screening as nonthreatening and safe. The women did not perceive any increased risk of physical harm and believed that routine assessment for IPV was essential to "stopping it from happening."[116]

Failure to consider IPV may lead to misdiagnosis, inappropriate evaluations, excessive costs, and increased morbidity and mortality. In a retrospective chart review of 1884 women with a diagnosis of IPV, 50% had one or more visits to the ED before the diagnosis was made, and 72% had at least one visit because of injury; a third of the prior injuries were to the head, face, and neck.[117] Rhodes and colleagues confirmed the lack of identification of IPV patients in the ED. From 993 police reports of IPV with female victims, 785 (79%) had at least one ED visit over a 4-year study period. The ED records failed to document any history of IPV in 73% of the records, and, of note, 78% of the visits were for medically related complaints.[118]

Routine inquiry about IPV may be conducted with a person-to-person interview or written or computerized questionnaires,

www.ketabpezeshki.com 66485457-66963820

Box 68-1 Abuse Assessment Screen

Have you ever been emotionally or physically abused by your partner or someone important to you?
Within the last year, have you been hit, slapped, kicked, or otherwise physically hurt by someone? If yes, by whom?
Within the last year has anyone forced you to have sexual activities? If yes, who?
Are you afraid of your partner or anyone mentioned above?

Box 68-2 Partner Violence Screen

Have you been hit, kicked, punched or otherwise hurt by someone within the past year? If yes, by whom?
Do you feel safe in your current relationship?
Is there a partner from a previous relationship who is making you feel unsafe now?

and several studies have questioned women as well as IPV patients and found support for this practice.[107,119-122] Routine inquiry may also be preventive, by increasing the patient's awareness of the impact of IPV on health, decreasing the violence if referrals and interventions are provided, or lessening the impact of sequelae of violence.[119,123] The inquiry may consist of a few questions about IPV or may be part of a larger health risk assessment.

When conducting a person-to-person interview, framing statements can be helpful. These statements help to normalize the questions about IPV and make them seem routine and not prejudicial (e.g., "Because of the impact of violence on women's health, I ask all my female patients these questions"). Inclusive terms such as *partner* are preferred. In addition, the HCP should include appropriate use of both direct and indirect questions (e.g., "Were you hit or hurt?" [direct] or "Is there anything else you would like to tell me?" [indirect]). Rhodes and colleagues found that when the HCP asked at least one additional related question, patients were more likely to disclose abuse.[123] If an additional question was asked about calls to the police to respond to a fight at home, then approximately a third more cases of IPV were identified.[124] Brief instruments for use in asking about IPV are preferred by some HCPs, as they find standard questions easier to ask and remember. The Abuse Assessment Screen (AAS) (Box 68-1) and Partner Violence Screen (PVS) (Box 68-2) are brief instruments for clinical use.[125,126] The AAS has been validated in a variety of clinical settings, in multiethnic populations, and in Spanish. The PVS was developed and validated in the ED.

An extensive list of IPV assessment tools is provided in compendiums published by the CDC.[127,128] Ultimately, whether the routine inquiry is verbal, written, or computerized, the HCP will need to have an individualized conversation with the IPV patient, being sensitive to the presenting medical problems, race and ethnicity, language barriers, cultural beliefs, gender, and sexual orientation. A successful encounter with an IPV patient or a suspected IPV patient is one in which the patient is treated with compassion, feels safe, and is provided with information, resources, and referrals regardless of whether or not she discloses IPV.

Although several questionnaires have been validated for use in identifying IPV, most have been validated for use only with female patients and with select populations and clinical situations. One study attempted to validate two common tools used in women—the HITS (hurt, insult, threaten, scream) tool and the PVS—and found them to be inaccurate for use in men, so further study is needed about screening men for experiences of violence.[129] Furthermore, HCPs will be able to identify IPV with a questionnaire only if the patient chooses to disclose IPV at that particular time.

MANAGEMENT

Although patients may disclose IPV, they may be unwilling to pursue any suggestions for addressing the IPV. The reasons are myriad, but in general the first and foremost factor is fear. Victims may fear for their own safety; fear for the well-being of their children, fear because they lack any means for economic independence, fear they will be deported if their spouse is arrested for a crime; fear they will be abandoned by family, friends, church, or community; and fear that the unknown could be worse than the known risks they are willing to endure. The cost of disclosure or the cost of making a change may simply exceed the possible benefits. Patients may negotiate their options or reject any options presented to them. Patients sometimes make choices that physicians believe may increase their risk for a poorer outcome, but the physician's role is to provide recommendations for care, fully discuss the potential benefits and risks, document the discussion, and verify the patient's capacity for noncoerced decision-making. Although a patient may not make the decisions the provider would prefer, a respectful interaction that leaves the door open for reconsideration or a return visit may be more powerful than appreciated at first glance. Revictimizing an IPV patient through abusive use of professional power or disparaging remarks may be more harmful than realized.

EDs need to plan for IPV patients because their care is multifaceted, often requiring social services, law enforcement, mental health services, and occasionally child welfare services. Preplanning for a routine response or a crisis response should the threat of violence escalate not only is important for patient care, but also may increase the willingness of health care staff to address IPV in their patients. Hospital policy may need to allow for short-term admissions to provide for a safe haven in the rare case that emergency shelter services are not available and the patient has no other recourse.

Initial Assessment of Intimate Partner Violence

Once IPV has been identified, the following questions need to be asked by the IPV response team:

- What are the nature, scope, and consequences of the abuse in terms of its impact on physical and mental health?
- What is the level of danger and risk of a lethal outcome?
- What strategies have been tried, and what are possible sources of support or major barriers that need to be addressed today to assist patient safety?
- If there are children, is the parent becoming concerned for the children's safety and well-being?
- How does the patient view his or her current situation and desire for change?

The assessment then directs the intervention (Table 68-1).

In addition to understanding the nature and scope of the abuse experienced by the patient, the consequences need to be determined. These may be physical, such as chronic symptoms of TBI, or the patient may be experiencing mental health sequelae, such as PTSD, depression, or suicidal ideation. Houry has developed a brief mental health assessment tool for IPV patients that can be helpful in determining which patients have more severe mental health symptoms and therefore need more immediate referral to a mental health specialist.[130]

Assessing for risk of a lethal outcome has been extensively researched. Twenty risk factors have been validated as highly associated with an IPV homicide. Campbell and colleagues, in a multicity, retrospective, case-controlled study that used police files, surrogate interviews, and survivor interviews, compared case histories involving fatal and nearly fatal violence with the case histories of women who had been physically abused but without a

www.ketabpezeshki.com 66485457-66963820

Table 68-1 Five Components of Intimate Partner Violence (IPV) Assessment

ASSESSMENT ISSUE	TOPIC TO EXPLORE OR CONSIDER	IMPLICATIONS FOR INTERVENTION
Nature, scope, and consequences of abuse	Types of abusive behaviors: physical, sexual, emotional, financial Continued problems from prior injuries? Possibility of pregnancy or sexually transmitted infection from coerced or forced sex? Is the victim being physically or psychologically stalked?	Directs the physical and forensic examination and any additional imaging or laboratory assessment or any needs for referral to appropriate care.
Danger assessment	Threats of homicide or suicide, battering during pregnancy, access to a firearm, previous strangulation, and others	Patient may be unaware of the danger. If patient is at risk for fatal outcome, obtain additional consultation and explore with the patient the possibility of contacting police, obtaining an emergency protective order, or seeking emergency placement in a shelter or other safe haven.
Strategies and barriers to greater safety	Are there family members or friends to confide in or a place to go in an emergency? Are there any cultural or religious barriers to consider? Does the patient have a source of income, any money, health insurance, and so on, if she or he decided to separate? Does he or she understand his or her legal rights?	Many IPV community agencies provide individual and peer counseling, legal advice, and job training to help the victim gain confidence, and support to make changes to become safer and healthier.
Safety of children	Are any of the children showing signs of distress, such as behavior change at home, deterioration in school performance, depression, or acting out behavior? Are they harshly punished or verbally berated, or is there any possibility of sexual abuse?	A judgment should be made as to whether children are endangered or also being victimized, and if so, child protective services should be notified.
Process of change	How does the patient perceive the relationship? Is there a sense that the relationship may not be healthy or safe? Is the patient considering options? Has the patient tried to make a change or separate? Does the patient want immediate assistance for self and children?	Victim intervention can be tailored to the victim according to his or her stage in the change process as determined in the assessment. It is possible to use the brief negotiated interview to effect movement from one stage to another.

life-threatening assault and developed a danger assessment tool with demonstrated predictive validity.[131] Variables that significantly differentiated fatal and nearly fatal cases from controls became the elements of the danger assessment. Some of these elements include stalking and harassment of the victim, estrangement (physical or legal separation), perpetrator access to a gun or prior threats with a gun, history of forced sex, and physical abuse during pregnancy. A shorter instrument of just five questions has since been developed using stepwise logistic regression analysis; the questions are as follows:

- Has the physical violence increased in frequency or severity over the past 6 months?
- Has he ever used a weapon or threatened you with a weapon?
- Do you believe he is capable of killing you?
- Have you ever been beaten by him while you were pregnant?
- Is he violently and constantly jealous of you?

A positive answer to any three questions has a sensitivity of 83% (95% CI, 70.6-91.4%) and specificity of 56% (95% CI, 50.8-61.8%).[132]

Assessing risk factors for a possible fatal outcome is good medical care and may be protective. In one study, 54% of women killed and 45% of victims of attempted homicide did not accurately perceive their risk of being killed by their partner.[20] However, Cattaneo found that women were more likely to be right than wrong in their assessment of risk for revictimization. Women seeking help for IPV (N = 246) rated the likelihood of reabuse in the coming year, and 18 months later they were reinterviewed. True positives, women who accurately predicted violence, were more likely to be experiencing stalking behaviors; false negatives, women who inaccurately predicted violence, were more likely to be in a relationship where substance abuse was a factor.[133] In addition, as perceived danger increases, the physical and mental health consequences for the patient also worsen, as demonstrated in a follow-up study of 216 of 548 patients who disclosed IPV victimization and completed both a health assessment and a danger assessment.[134]

Clinical Intervention

Clinical intervention for IPV in the ED is just like intervention for any other potentially life-threatening disease. System readiness coupled with practitioner skill is believed to lead to improved outcomes.

System Readiness

System readiness should address procedures to promote patient privacy and safety within a multidisciplinary team approach. At a bare minimum, system readiness in the ED involves ongoing professional education, establishment of quality improvement measures to monitor benchmarks of care, protocols for intervention, patient education, and established means for safe follow-up. An acutely injured victim may merit a "code black and blue" with bedside response of appropriate medical and surgical personnel, social services, IPV experts, site security, and community law enforcement. Emergency medical services personnel should also be trained to observe, document, and report on events at the scene that raise suspicion for IPV.

EDs can take advantage of a tool developed by the Agency for Healthcare Research and Quality (AHRQ) to assess whether processes are in place to respond to IPV.[135] The tool addresses (1) hospital policies and procedures, (2) the physical environment, (3) the cultural environment, (4) provider education, (5) screening and safety assessment, (6) documentation, (7) intervention services, (8) evaluation and quality improvement measures, and (9) collaborative agreements. Inter-rater reliability was very high (Cronbach's α ranging from .97 to .99 in the experienced coders and .96 to .99 in the inexperienced coders). The instrument can be used for assessment and to set benchmarks for quality improvement.

Three models of system intervention have been identified, and they may be blended in various ways: Advocacy Partnering, Forensic Medicine, and a Specialty Care Model.[136] The Advocacy

www.ketabpezeshki.com 66485457-66963820

Partnering Model is based on negotiated agreements between health clinics or hospitals and community IPV service providers. Trained peer counselors respond to provide bedside or telephone consultation, speaking directly with patients and providers to conduct a needs assessment and plan for initial intervention or, in some places, for ongoing case management and more chronic care. The Forensic Medicine Model relies on nurses or physicians who have received advanced training in the documentation, storage, and retrieval of physical evidence; forensic photography; presentation of evidence in the courtroom; and expert interpretation of findings. Bedside IPV peer counselors also assist the patient just as they do for victims of sexual assault. In the Specialty Care Model, patients can be referred to clinical experts or centers that specialize in trauma recovery. In pediatrics, child abuse is now a recognized subspecialty given the scope of both knowledge and skills required for the care of abused children. Some departments (e.g., behavioral health) or individuals have established IPV care as an area of expertise, and once the patient is medically stabilized, referral for bedside or delayed consultation is made just as for any other ED problem.

Intervention in the Emergency Department

IPV is a socially stigmatized issue and, as such, requires concerted effort on the part of the clinician to establish trust and convey empathy. An empathic and nonjudgmental assessment and respectful discussion of options with a trusted HCP are postulated to have potential therapeutic benefits in and of themselves. The assessment guides decision-making regarding the needs for immediate or delayed intervention. The HCP will encounter five levels of patients, based on IPV exposure and risk. Each level has guidelines for varying intervention strategies and critical elements for documentation (Table 68-2).

Most IPV intervention for victims centers around theoretic constructs of the Health Belief Model, Social Cognitive Theory, and self-efficacy. The Health Belief Model's core assumption is that a person will take a health-related action if the individual believes that a negative health condition can be avoided (perceived susceptibility), has a positive expectation about taking the recommended action (perceived benefit), and believes that he or she can successfully take the recommended action (self-efficacy).[137] Both perceived susceptibility and self-efficacy have been demonstrated to be strong predictors of behavioral change. Social Cognitive Theory has a strong emphasis on cognition and posits that cognitions change over time. According to this theory, people develop perceptions about their own abilities and characteristics that guide their behavior by determining what they try to achieve. One's perceived self-efficacy for a given behavior dramatically affects one's self-motivation for performing that behavior. These are the theoretic constructs that underlie interventions for IPV victims.

Some victims are receptive to provider recommendations or referrals, and some may not be, depending on their readiness for change. The stages of change—precontemplation, contemplation, preparation, action, and maintenance—are well described. Women who normalize physical violence or emotional abuse as expected behavior are in a precontemplation phase and may only be ready to consider the negative health consequences, moving them to a contemplation stage; however they are unlikely to consider separation from the abuser, as that would be a three-step advancement to action in the stages of change. Asher reported that women who screened positive for IPV in ED visits (N = 101) populated each stage of change, but most were in the early stages of precontemplation and contemplation.[138]

Safety planning is a harm reduction intervention in that the patient may be returning to a dangerous situation, but certain behavior changes may contribute to a less negative outcome.

Table 68-2 Intervention Strategies Based on Intimate Partner Violence (IPV) Exposure and Risk Level

PATIENT TYPE BASED ON ASSESSMENT	INITIAL INTERVENTION STEPS	CRITICAL DOCUMENTATION FOR THE ENCOUNTER
I. No history of IPV or suspicion of abuse	Provide basic message that IPV is a health problem	"No history of IPV; no suspicion of IPV"
II. Prior history of IPV but no current exposure	Assess for sequelae of prior abuse; provide educational message that patient is at risk of future IPV relationship	Add history of IPV to problem list (can be coded as a V-code); describe medical and mental heath impact and any referrals made
III. Recent or current abuse but no injuries and no elements on danger assessment	Assess for sequelae of abuse; provide referrals to IPV resources	Add IPV to problem list; describe health sequelae from abuse; note referral for urgent follow-up provided to patient
IV. Recent or current abuse with injuries or positive findings on danger assessment	Crisis bedside consultation by social services or IPV advocate; discuss possibility of an order for protection; notify police if required by law	Add IPV to problem list; describe health sequelae; summarize follow-up plan as outlined by social services or IPV advocate; complete mandatory reports; describe injury findings using narration, diagrams, and photographs
V. Suspicion of current abuse but patient denies IPV	Provide basic message that IPV is health problem; request bedside consultation by social services or IPV advocate; provide referrals to IPV resources	Document IPV as a suspected health problem; note that bedside consultation was done and resources were provided; if injured, describe injury findings using narration, diagrams, and photographs

Needle exchange programs are examples of a harm reduction effort to prevent additional illness in intravenous drug users. Strategies for avoiding further harm may be both protective and empowering. Planning for safety during a violent outburst (getting to a room with a lockable door and exterior window) or for immediate escape (placing a suitcase in the safekeeping of a trusted other with clothes, documents, and extra cash) are examples of harm reduction safety planning that can be developed with the patient by the clinician or the bedside IPV peer counselor.[139]

In the past 20 years, community IPV agencies or victim advocacy organizations have been developed in every state to provide services for IPV victims and their children. The federal Violence Against Women Act (VAWA) provides considerable funding to support these service providers. Although most of the time patients are referred to such agencies for follow-up, more and more agencies now respond to health care requests with bedside, telephone, or telemedicine consultation. Information about what agencies are available in a specific community is easily available through the National Domestic Violence Hotline at 1-800-799-SAFE (7233) or (TTY) 1-800-787-3224. Sullivan examined the effect of community-based advocacy services after a shelter stay and found that at 2-year follow-up, IPV victims who had received the advocacy intervention experienced less physical abuse, had an increased quality of life, and accessed more community IPV

www.ketabpezeshki.com 66485457-66963820

resources than the control group. Of note, 25% of the intervention group, compared with 10% of the control group, had experienced no further violence after the intervention.[140]

Bedside consultation was implemented in EDs in Kansas City, Missouri, and analysis showed that patients who had not called the police for the index event and received bedside counseling with a victim advocate were more likely than those who were only given a handout with resources, to call the police for a subsequent event (39% vs. 18% [95% CI, 1-40%]), seek emergency shelter (28% vs. 11% [95% CI, 6-27%]), or obtain counseling (15% vs. 1% [95% CI, 7-21%).[141] In a study by McFarlane, telephone follow-up calls for harm reduction counseling resulted in the increased adoption of safety behaviors that remained even 2 years after counseling ended.[142] In one study that involved follow-up of 157 of 350 patients who had received a brief ED intervention, 96% of the patients perceived that their safety had improved postintervention. However, without a control group, it is not possible to attribute the improvement to the intervention.[143] One randomized, controlled trial of a brief ED screening, education, and referral intervention in New Zealand found no difference in short-term recurrence of violence between treatment and control groups.[144]

Interventions and Referrals for Perpetrators

Interventions for IPV perpetrators have not been shown to be as effective as hoped. The problem is that a "one-size-fits-all" approach appears to be inadequate for the known typologies of violent offenders. The current treatment modalities are organized according to etiologic theories[145]: (1) cognitive-behavioral treatment focuses on deficient thought patterns such as rigid beliefs and limited problem-solving; (2) psychodynamic treatment addresses unresolved physical and emotional trauma; and (3) feminist models focus on educational efforts to increase awareness of oppressive, sexist attitudes and foster nonoppressive, egalitarian behaviors. Conjoint treatment for couples remains controversial, and the primary objections center around safety concerns for victims. Right now, patients who disclose histories of interpersonal violence, with partners, acquaintances, or strangers, should all be referred to social services for further evaluation and appropriate referral. Once a perpetrator has been arrested, the criminal justice system does not generally conduct comprehensive assessments, so offenders do not have as many treatment options. Unfortunately, that usually means that recidivism for offenders is quite high.

Cultural Issues

Both the patient and the provider operate within a culture, and each culture has its own strengths and barriers that are important to recognize. With regard to IPV, a few special considerations are worth mentioning:

- Language interpreters should be professionals and non–family members, with some training and background in the dynamics of IPV. There are some languages that do not readily translate the phrases or the concepts related to family violence.
- Immigrant victims fear deportation for themselves should they disclose IPV and in most cases fear deportation for their partners. There are protections within VAWA that allow a victim to remain in this country even if his or her legal spouse and/or sponsor is deported.
- Some victims of color may be reluctant to contact law enforcement because of apprehension regarding racism. Although the desire to be safe and free from violence is real, the fear of unfair treatment for the partner is also real.
- Lower rates of disclosure have been documented in Latina women. Gender role ideologies, traditional beliefs about marriage, familism, and taboos against talking about sex are some of the reasons suggested for lower rates of disclosure in this cultural group.[146]

Although not distinct cultural groups, IPV patients from rural areas (fewer resources, less privacy), the disabled (few shelter programs with full access, need and expense for sign language interpreters), and gay and lesbian IPV victims (few shelter services for gay men, "outing" or disclosing a person's sexual orientation as a coercive threat) face barriers that health professionals should appreciate. Socioeconomic status may also be a barrier to intervention. The lack of independent financial resources or educational or vocational training limits options for change at all socioeconomic levels.

Interface with the Criminal Justice System

IPV is considered to be a public safety issue. As such, domestic violence is a crime in all 50 states, as is spousal rape. Criminal justice remedies can be helpful for some patients. Mandatory arrest policies provide a "cooling off" period that gives patients time to implement safety plans or seek safer shelter. Orders of protection may be useful in helping victims to feel safer, although at least one study among African Americans reported heightened fear of retaliation when protective orders were obtained.[147] Protective orders can be written such that they allow for immediate search and seizure of firearms, and protective orders link into databases that restrict firearm purchase by perpetrators. Finally, crime victims' restitution programs can help patients buy and install home security systems, change residences, or pay for uncompensated medical or mental health care for victims and/or their children.

In most states, HCPs negotiate with patients to determine how and when to contact law enforcement. However, in some states, HCPs are required by law to report any patients who have sustained injury with a weapon, and a few states require reports to law enforcement, regardless of patient consent, for any patient who has injuries that appear to be intentionally inflicted. The most restrictive reporting mandates have been implemented because the IPV victim is perceived as a "vulnerable person," just as in child and elder abuse, and proponents advocate that victims be assisted with the full resources of the health and safety systems. Unfortunately, there is neither sufficient evidence *for* nor sufficient evidence *against* laws mandating reporting by health professionals to law enforcement in the case of IPV. There are survey data that reveal physician anxiety about proceeding without patient consent,[148] and there are mixed results from victims themselves, with some seeing the law as helpful and others seeing it as potentially harmful.[149] A qualitative study based on interviews with women found victims to be generally supportive of mandatory reporting to law enforcement and did not perceive that the law placed them or their children at higher risk.[150]

Ethical Considerations

Confidentiality

Despite the increase in public awareness, IPV is a shame-based disease, and bias, both professional and institutional, still remains. Breaches of confidentiality could put the victim at heightened risk. Some of the questions to be addressed with regard to confidentiality are as follows:

- What if the principal insured party is the abusive partner? What procedures are in place between the provider and the third-party insurer to protect the confidentially and safety of IPV victims?

www.ketabpezeshki.com 66485457-66963820

- Are there any routine follow-up processes in place, such as patient satisfaction surveys, that might inadvertently result in contact with a patient and alert the abusive partner about a health care visit?
- What if a minor discloses IPV occurring in the home and the abusive parent seeks access to the medical record?
- If IPV is noted on the medical record, could this be grounds for health or home insurance companies to cancel insurance?
- What if the patient discloses IPV as the cause of injuries and now the provider, by law, must notify law enforcement of possible criminal behavior?

All of these have been addressed in various ways, some at the institutional level, some through collaborative agreements, and some through state legislation. Regardless, the potential for breach of confidentiality should be recognized, and limits to confidentiality, including any reporting mandates, should be communicated to patients during ED registration or as soon as possible.

There are some protections for IPV patients within the Health Information and Portability and Accountability Act (HIPAA). Under HIPAA, physicians may not generally share confidential health information without the written approval of patients unless mandated by state law. However, physicians may disclose protected health information to government authorities or social services if abusive behavior is suspected to have occurred. Likewise, unless mandated by law, a physician has discretion to withhold information when he or she believes the notification will place the patient at "serious risk of harm." HIPAA also allows patients to specifically request nonrelease of protected health information to specific persons or agencies, and patients can request that they be notified of any release that does occur. IPV patients can request their names be withheld from any registry system when hospitalized, or hospitals can routinely admit IPV patients as a "Jane Doe" to ensure both safety and confidentiality. These are HIPAA protections that an IPV response team should know and routinely discuss and facilitate with IPV patients.

If a patient discloses violent or abusive behavior, the physician operates under obligation of confidentiality and cannot disclose to police unless required by law. The duty of a citizen to report criminal behavior is a communal value and appears to clash with the duty regarding maintain patient confidentiality. However, this duty regarding confidentiality is also a communal value, and unless it is overridden by legal mandates, the HCP cannot report criminal behavior but can warn intended victims if there is a perceived threat to their safety (Tarasoff v. Regents of University of California [1976] 17 Cal. 3d 425).[151,152]

Informed Consent and Autonomy

Reporting, when required by law, is permissible by HIPAA and does not require patient consent, although addressing any concerns to safeguard the patient is an obligation of the health provider or the institution that receives the report. For example, California mandates physicians and surgeons to report patients with injuries suspected to be assault related to law enforcement. However, the reporting physician can request immediate bedside response rather than a delayed home response, and the report can indicate safe strategies for contact that the patient has identified.

IPV patients are not always free to act of their own will in health care decision-making. Coercive decision-making is not autonomous decision-making. Fear may be so profound that decision-making is impaired, thus jeopardizing informed consent. In a Montana malpractice suit, the ED physician and hospital were sued for failure to accurately diagnose and failure to provide for patient safety when an IPV patient was discharged to home only to sustain devastating physical injury by her abusive partner.[153] According to the plaintiff's attorney, the ED physician testified in deposition that IPV was discussed and safety issues addressed; however, the patient testified that she was at the hospital under duress and her decision-making capacity was diminished by the coercive threats of her boyfriend to inflict further harm should she disclose the IPV (C. Mitchell, personal communication with D. Buxbaum, September 27, 2002). Although this case was settled before court judgment, the coercive nature of extreme fear and its impact on informed consent and clinical decision-making are challenges for both clinicians and ethicists.

Documentation

Medical Record

Because violence and abuse are both health and criminal justice problems, there is increased likelihood that the medical record may be introduced or referred to in criminal or civil proceedings. In addition, many states have evidence rules that allow the introduction of prior evidence of physical abuse (e.g., the medical record) to demonstrate a pattern of behavior even if the actual criminal charges or civil litigation is pursued many years later.

Table 68-3 lists the key elements in the history of the presenting illness, physical examination, and discharge instructions that should be addressed and documented.

Table 68-3 Key Elements in Medical Record Documentation for Intimate Partner Violence (IPV) Cases

KEY ELEMENTS IN THE HISTORY	KEY ELEMENTS IN THE PHYSICAL EXAMINATION	KEY ELEMENTS IN THE DISCHARGE PLAN
A verbatim or near-verbatim statement by the patient regarding cause of injuries The relationship of the assailant to the victim The current whereabouts of the assailant (immediate safety check) Detailed account of how current assaultive injury occurred Symptoms of current and past abuse-related injuries Poststrangulation: patient description of voice change, if any IPV assessment as outlined in Table 68-1 by physician or consultant	Brief description of state of mind or demeanor of patient Mental status examination, including brief cognitive assessment for mild traumatic brain injury Poststrangulation: results of direct or indirect laryngoscopy Narrative description of new injuries Narrative description of sequelae of old injuries, such as chronic pain, decreased range of motion, or hearing loss Diagrammatic and/or photographic documentation of injuries (digital photography is acceptable for medical or forensic use)	Care instructions for medical or traumatic complaints Arrangements for follow-up for medical and IPV intervention Safety planning: Where can the patient go now that is safe? What to do if safety is placed at further risk? How to access victim advocate? How to apply for Victims of Crime restitution? If law enforcement is notified, badge name and number of officer contacted

www.ketabpezeshki.com 66485457-66963820

Diagnostic Coding

Intimate partner violence is the preferred term for health surveillance and research as defined by the CDC. *Domestic violence* is commonly used by the general public to refer to IPV but is specifically used by criminal justice to refer to physical abuse by a current or former intimate partner. *Adult Maltreatment* is the coding term used in the ICD (995.8_). The last digit varies for different types of adult maltreatment: physical abuse (995.81), emotional/psychological abuse (995.82); sexual abuse (995.83), neglect (995.84), and other abuse or multiple forms of abuse (995.85). E codes add more specific information as to the cause or means of injury.

In the 10th revision of the ICD, a prefix can be given for Adult Maltreatment to designate suspected (T4) or confirmed (T7) IPV. The reason for this is that practitioners have been hesitant to document suspicions of abuse owing to the desire to protect patient confidentiality and safety; however, failure to document adult maltreatment has impeded continuity of care and public health surveillance. In the past, victims often received a psychological diagnosis that not only failed to recognize the primary cause but also failed to recognize the relational aspect of IPV and appeared to be victim blaming, further stigmatizing patients. Documenting suspicions of abusive behavior in the differential diagnosis is important because confirmation of shame-based health issues may take time and repeat discussions are not usually within the purview of the ED physician. In addition, medical records of prior episodes of IPV can be requested and used to establish a pattern of abusive behaviors in criminal cases many years later.

Forensic Documentation

The medical record becomes a forensic record when it becomes part of a legal process. The word *forensic* means "pertaining to the law." A medical record is likely to be more focused and less detailed than a formal forensic examination. Sexual assault and child abuse patients have, for many years, benefited from the additional service and care of medical forensic teams that can coordinate with law enforcement and then follow meticulous protocols to collect and document detailed findings. Other members of the team can provide interventions for medical and mental health needs and establish care for longer-term needs. These programs have served as models for IPV forensic care. California has developed clinical guidelines, a forensic protocol, and a form for the forensic medical examination of victims, which is available online (www.ccfmtc.org/forensic.asp). Many law enforcement agencies now contract with forensic medical examiners to conduct the forensic examination, collect physical evidence, and present courtroom testimony. Forensic examinations are done only with the full consent of patients, which differs from some state laws regarding reporting. Forensic examinations are usually time-consuming and detailed and are done under contract or reimbursed through Victims of Crime funding. In contrast, mandatory reporting to law enforcement or public health departments usually only captures critical elements either for public health surveillance or to alert public safety departments of a possible violent crime.

Participation in Public Health Intimate Partner Violence Activities

ED HCPs play a critical role in surveillance of IPV both through accurate diagnosis and documentation of patients who have experienced IPV. In addition, emergency physicians serve as valuable members of fatality review teams that examine the events leading up to a domestic violence fatality and attempt to identify either missed opportunities for prevention or strategies for an improved response to family violence. Given the multidisciplinary nature of IPV, community coordinating councils examine the system response components and work to improve interagency relationships. Other opportunities to improve health policy exist within organizations, such as the Injury Control Committee of the American College of Emergency Physicians, the National Health Collaborative on Violence and Abuse, the Family Violence Prevention Forum within the American Public Health Association, and many others.

KEY CONCEPTS

- IPV is pervasive and difficult to diagnose; it affects children, adolescents, adults, and elders.
- Identification of IPV is through a process of disclosure by the patient and pattern recognition by the clinician.
- Many conditions are comorbid with IPV. Some conditions are highly associated with IPV, and when identified should prompt the HCP to consider IPV. When a patient discloses IPV, the HCP, in turn, should assess for comorbid conditions.
- A coordinated multidisciplinary team response that involves use of existing services (e.g., community advocacy agencies, forensic teams) facilitates patient access to multiple resources that are often needed to promote the safety of victims and children.
- When IPV is recognized, it should be documented in the medical record with the ICD code for Adult Maltreatment.
- The medical record is likely to become a forensic record, and therefore the HCP should carefully document all interventions, referrals, and mandatory reports.
- The goal of the HCP should be to provide a caring, compassionate environment in which the patient feels safe to talk about IPV now or in the future. Patient disclosure of IPV is not necessary for a successful encounter with a patient.
- All patients, whether they disclose IPV or the HCP suspects they are experiencing IPV, should be provided with written information and appropriate resources for IPV.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. *World Report on Violence and Health*. Geneva: World Health Organization; 2002.
2. Saltzman LE, Fanslow JL, McMahon MJ, Shelley GA: *Intimate Partner Violence Surveillance: Uniform Definitions and Recommended Data Elements*. Atlanta, Ga: Department of Health and Human Services; Centers for Disease Prevention and Control; National Center for Injury Prevention and Control; 1999.
3. Truman JL: *Criminal Victimization, 2010*. Washington, DC: Bureau of Justice Statistics, Office of Justice Programs, U.S. Department of Justice; 2011. Available at http://bjs.ojp.usdoj.gov/content/pub/pdf/cv10.pdf. Accessed January 30, 2013.
4. Catalano S: *Intimate Partner Violence, 1993-2010*. Washington, DC: Bureau of Justice Statistics, Office of Justice Programs, U.S. Department of Justice; 2012. Available at http://bjs.ojp.usdoj.gov/content/pub/pdf/ipv9310.pdf. Accessed on January 30, 2013.
5. Black MC, et al: *The National Intimate Partner and Sexual Violence Survey (NISVS): 2010 Summary Report*. Atlanta, GA: National Center for Injury Prevention and Control, Centers for Disease Control and Prevention; 2011. Available at http://www.cdc.gov/ViolencePrevention/NISVS. Accessed on January 30, 2013.
6. Tjaden P, Thoennes N, Allison CJ: Comparing violence over the life span in samples of same-sex and opposite sex cohabitants. *Violence Vict* 1999; 14:413-425.
7. Black MC, Breiding MJ: Adverse health conditions and health risk behaviors associated with intimate partner violence—United States, 2005 (Reprinted from *MMWR,* 2008; 57:113-117). *JAMA* 2008; 300:646-647.
8. Breiding MJ, Ziembroski JS, Black MC: Prevalence of rural intimate partner violence in 16 U.S. states, 2005. *J Rural Health* 2009; 25:240-246.
9. Koin D: *Intimate partner violence in the elderly*. In: Mitchell C, Anglin D, eds. *Intimate Partner Violence: A Heath-Based Perspective*. New York: Oxford University; 2009.
10. Mouton CP, et al: Prevalence and 3-year incidence of abuse among postmenopausal women. *Am J Public Health* 2004; 94:605-612.
11. Anglin D, Sachs C: Preventive care in the emergency department: Screening for domestic violence in the emergency department. *Acad Emerg Med* 2003; 10:1118-1127.
12. Dearwater SR, et al: Prevalence of intimate partner abuse in women treated at community hospital emergency departments. *JAMA* 1998; 280:433-438.
13. McFarlane J, Greenberg L, Weltge A, Watson M: Identification of abuse in the emergency departments: Effectiveness of a two-question screening tool. *J Emerg Nurs* 1995; 21:391-394.
14. Biroscak BJ, Smith PK, Roznowski H, Tucker J, Carlson G: Intimate partner violence against women: Findings from one state's ED surveillance system. *J Emerg Nurs* 2006; 32:12-16.
15. Abbott J, Johnson R, Koziol-McLain J, Lowenstein SR: Domestic violence against women: Incidence and prevalence in an emergency department population. *JAMA* 1995; 273:1763-1767.
16. Mechem CC, Shofer FS, Reinhard SS, Hornig S, Datner E: History of domestic violence among male patients presenting to an urban emergency department. *Acad Emerg Med* 1999; 6:786-791.
17. *10 Leading Causes of Death, United States, 2010, All Races, Females*. Atlanta, Ga: National Center for Injury Prevention and Control, Centers for Disease Control and Prevention; 2010. Available at http://www.cdc.gov/injury/wisqars/leading_causes_death.html.Accessed January 30, 2013.
18. Karch D, Dahlberg L, Patel N: Surveillance for violent deaths—National Violence Death Reporting System, 16 States, 2007. *MMWR Surveill Summ* 2010; 59:1-50.
19. *Homicide Trends in the United States*. Washington, DC: Bureau of Justice Statistics; 2004.
20. Campbell JC, Glass N, Sharps PW, Laughon K, Bloom T: Intimate partner homicide: Review and implications of research and policy. *Trauma Violence Abuse* 2007; 8:246-269.
21. Wadman M, Muelleman R: Domestic violence homicides: ED use before victimization. *Am J Emerg Med* 1999; 17:689-691.
22. Sharps P, Koziol-McLain J: Health care providers' missed opportunities for preventing femicide. *Prev Med* 2001; 33:373-380.
23. Max W, Rice DP, Finkelstein E, Bardwell RA, Leadbetter S: The economic toll of intimate partner violence against women in the United States. *Violence Vict* 2004; 19:259-272.
24. Ulrich YC, et al: Medical care utilization patterns in women with diagnosed domestic violence. *Am J Prev Med* 2003; 24:9-15.
25. Rivara F, Fishman P, Bonomi A: Healthcare utilization and costs for women with a history of intimate partner violence. *Am J Prev Med* 2007; 32:89-96.
26. Rivara F, Fishman P, Bonomi A: Intimate partner violence and health care costs and utilization for children living in the home. *Pediatrics* 2007; 120:1270-1277.
27. McCauley J, et al: The "battering syndrome": Prevalence and clinical characteristics of domestic violence in primary care internal medicine practices. *Ann Intern Med* 1995; 123:737-746.
28. Coker AL, Smith PH, Bethea L, King MR, McKeown RE: Physical health consequences of physical and psychological intimate partner violence. *Arch Fam Med* 2000; 9:451-457.
29. Whitfield CL, Anda RF, Dube SR, Felitti VJ: Violent childhood experiences and the risk of intimate partner violence in adults. *J Interpers Violence* 2003; 18:166-185.
30. Nosek MA, Howland CA, Hughes RB: The investigation of abuse and women with disabilities. *Violence Against Women* 2001; 7:477-499.
31. Caetano R, Cunradi C, Clark C, Schafer J: Intimate partner violence and drinking patterns among white, black, and Hispanic couples in the U.S. *J Subst Abuse* 2000; 11:123-138.
32. Kyriacou DN, et al: Risk factors for injury to women from domestic violence. *N Engl J Med* 1999; 341:1892-1898.
33. Honeycutt T, Marshall L, Weston R: Toward ethnically specific models of employment, public assistance, and victimization. *Violence Against Women* 2001; 7:126-140.
34. Coker A, Sanderson M, Fadden M, Pirisi L: Frequency and correlates of intimate partner violence by type: Physical, sexual and psychological battering. *Am J Public Health* 2000; 90:553-559.
35. Bassuk EL, et al: The characteristics and needs of sheltered homeless and low-income housed mothers. *JAMA* 1996; 276:640-646.
36. Menjivar C, Salcido O: Immigrant women and domestic violence: Common experiences in different countries. *Gend Soc* 2002; 16:898-920.
37. Frye V, et al: The role of neighborhood environment and risk of intimate partner femicide in a large urban area. *Am J Public Health* 2008; 98:1473-1479.
38. Ochs H, Neuenschwander M, Dodson T: Are head, neck and facial injuries markers for domestic violence? *J Am Dent Assoc* 1995; 127:757-761.
39. Muelleman R, Lenaghan P, Pakiese R: Battered women: Injury locations and types. *Ann Emerg Med* 1996; 28:486-492.
40. Le BT, Dierks EJ, Ueeck BA, Homer LD, Potter BF: Maxillofacial injuries associated with domestic violence. *J Oral Maxillofac Surg* 2001; 59:1277-1283.
41. Davis KE, Coker AL, Sanderson M: Physical and mental health effects of being stalked for men and women. *Violence Vict* 2002; 17:429-443.
42. Seedat S, Stein M, Forde D: Association between physical partner violence, posttraumatic stress, childhood trauma, and suicide attempts in a community sample of women *Violence Vict* 2005; 20:87-98.
43. Boyle A, Jones P, Lloyd S: The association between domestic violence and self harm in emergency medicine patients. *Emerg Med J* 2006; 23:604-607.
44. Hamberger L: *Risk factors for intimate partner violence perpetration: Typologies and characteristics of batterers*. In: Mitchell C, Anglin D, eds. *Intimate Partner Violence: A Health-Based Perspective*. New York: Oxford University Press; 2009.
45. Ernst AA, et al: Adult intimate partner violence perpetrators are significantly more likely to have witnessed intimate partner violence as a child than nonperpetrators. *Am J Emerg Med* 2009; 27:641-650.
46. Mauricio AM, Gormley B: Male perpetration of physical violence against female partners: The interaction of dominance needs and attachment insecurity. *J Interpers Violence* 2001; 16:1066-1081.
47. Brookoff D, O'Brien KK, Cook CS, Thompson TD, Williams C: Characteristics of participants in domestic violence: Assessment at the scene of domestic assault. *JAMA* 1997; 277:1369-1373.
48. Hutchison IW, Hirschel JD: The effects of children's presence on woman abuse. *Violence Vict* 2001; 16:3-17.
49. Ernst A, Weiss S, Enright-Smith S: Child witnesses and victims in homes with adult intimate partner violence. *Acad Emerg Med* 2006; 13:696-699.
50. Curry MA, Doyle BA, Gilhooley J: Abuse among pregnant adolescents: Differences by developmental age. *MCN Am J Matern Child Nurs* 1998; 23:144-150.
51. Grimstad H, Backe B, Jacobsen G, Schei B: Abuse history and health risk behaviors in pregnancy. *Acta Obstet Gynecol Scand* 1998; 77:893-897.
52. Morland LA, Leskin GA, Block CR, Campbell JC, Friedman MJ: Intimate partner violence and miscarriage: Examination of the role

www.ketabpezeshki.com 66485457-66963820

of physical and psychological abuse and posttraumatic stress disorder. *J Interpers Violence* 2008; 23:652-669.
53. Neggers Y, Goldenberg R, Cliver S, Hauth J: Effects of domestic violence on preterm birth and low birth weight. *Acta Obstet Gynecol Scand* 2004; 83:455-460.
54. Leone JM, et al: Effects of intimate partner violence on pregnancy trauma and placental abruption. *J Womens Health (Larchmt)* 2010; 19:1501-1509.
55. Coker A, Sanderson M, Dong B: Partner violence during pregnancy and risk of adverse pregnancy outcomes. *Paediatr Perinat Epidemiol* 2004; 18:260-269.
56. Janssen PA, et al: Intimate partner violence and adverse pregnancy outcomes: A population-based study. *Am J Obstet Gynecol* 2003; 188:1341-1347.
57. Anda RF, et al: The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. *Eur Arch Psychiatry Clin Neurosci* 2006; 256:174-186.
58. Felitti VJ, et al: Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med* 1998; 14:245-258.
59. Brown DW, et al: Adverse childhood experiences and the risk of premature mortality. *Am J Prev M* 2009; 37:389-396.
60. Miller E, et al: Adverse childhood experiences and risk of physical violence in adolescent dating relationships. *J Epidemiol Community Health* 2011;65:1006-1013.
61. Duke N, Pettingell S, McMorris B, Borowski I: Adolescent violence perpetration: Associations with multiple types of adverse childhood experiences. *Pediatrics* 2010; 125:e778-e786.
62. Tajima E: The relative importance of wife abuse as a risk factor for violence against children. *Child Abuse Negl* 2000; 24:1383-1398.
63. Edleson JL: The overlap between child maltreatment and woman battering. *Violence Against Women* 1999; 5:134-154.
64. Kerker BD, Horwitz SM, Leventhal JM, Plichta S, Leaf PJ: Identification of violence in the home, pediatric and parental reports. *Arch Pediatr Adolesc Med* 2000; 154:457-462.
65. Spears L: *Building Bridges between Domestic Violence Organizations and Child Protective Services*. National Resource Center on Domestic Violence; 2000. Available at http://www.vawnet.org/Assoc_Files_VAWnet/BCS7_cps.pdf. Accessed January 30, 2013.
66. Casanueva C, Martin SL, Runyan DK: Repeated reports for child maltreatment among intimate partner violence victims: Findings from the National Survey of Child and Adolescent Well-Being. *Child Abuse Negl* 2009; 33:84-93.
67. Kuelbs C: *The impact of intimate partner violence on children*. In: Mitchell C, Anglin D, eds. *Intimate Partner Violence: A Health-Based Perspective*. New York, NY: Oxford University Press; 2009.
68. Bogat GA, DeJonghe E, Levendosky AA, Davidson WS, von Eye A: Trauma symptoms among infants exposed to intimate partner violence. *Child Abuse Negl* 2006; 30:109-125.
69. Halpern CT, Oslak SG, Young ML, Martin SL, Kupper LL: Partner violence among adolescents in opposite-sex romantic relationships: Findings from the National Longitudinal Study of Adolescent Health. *Am J Public Health* 2001; 91:1679-1685.
70. Miller E, et al: Intimate partner violence and health care-seeking patterns among female users of urban adolescent clinics. *Matern Child Health J* 2010; 14:910-917.
71. Eaton DK, et al: Youth Risk Behavior Surveillance—United States, 2009. *MMWR Surveill Summ* 2010; 59:1-142.
72. Ackard DM, Neumark-Sztainer D, Hannan P: Dating violence among a nationally representative sample of adolescent girls and boys: Associations with behavioral and mental health. *J Gend Specif Med* 2003; 6:39-48.
73. Spencer GA, Bryant SA: Dating violence: A comparison of rural, suburban, and urban teens. *J Adolesc Health* 2000; 27:302-305.
74. Gray H, Foshee V: Adolescent dating violence: Differences between one-sided and mutually violent profiles. *J Interpers Violence* 1997; 12:126-141.
75. Molidor C, Tolman R, Kober J: Gender and contextual factors in adolescent dating violence. *Prev Res* 2000; 7:1-4.
76. Sheehan K, Kim L, Gavin J: Urban children's perceptions of violence. *Arch Pediatr Adolesc Med* 2004; 158:74-77.
77. Wiemann CM, Agurcia CA, Berenson AB, Volk RJ, Rickert VI: Pregnant adolescents: Experiences and behaviors associated with physical assault by an intimate partner *Maternal Child Health J* 2000; 4:93-101.
78. Miller E, et al: Adolescent intimate partner violence and contraceptive nonuse among adolescent females utilizing teen clinics. *J Adolesc Health* 2008; 42:S8.
79. Foshee V: Gender differences in adolescent dating abuse prevalence, types and injuries. *Health Educ Res* 1998; 11:275-286.
80. Rosewater A: *Promoting Prevention Targeting Teens: An Emerging Agenda to Reduce Domestic Violence*. San Francisco: Family Violence Prevention Fund; 2002.
81. Freedner N, Freed L, Yang L, Austin S: Dating violence among gay, lesbian, and bisexual adolescents: Results from a community survey *J Adolesc Health* 2002; 31:469-474.
82. Heise LL: Violence against women: An integrated, ecological framework. *Violence Against Women* 1998; 4:262-290.
83. Bograd M: Family systems approaches to wife battering: A feminist critique. *Am J Orthopsychiatry* 1984; 54:558-568.
84. Yodanis CL: Gender inequality, violence against women, and fear: A cross-national test of the feminist theory of violence against women. *J Interpers Violence* 2004; 19:655-675.
85. Dutton D, Starzomski A: Personality predictors of the Minnesota power and control wheel. *J Interpers Violence* 1997; 12:70-82.
86. Johnson MP: Patriarchal terrorism and common couple violence: Two forms of violence against women. *J Marriage Fam* 1995; 57:283-297.
87. Johnson MP, Ferraro K: Research on domestic violence in the 1990s: Making distinctions. *J Marriage Fam* 2000; 62:948-963.
88. Johnson MP, Leone J: The differential effects on intimate terrorism and situational couple issues. *J Fam Issues* 2005; 26:322-349.
89. Frye V, Manganello J, Campbell JC, Walton-Moss B, Wilt S: The distribution of and factors associated with intimate terrorism and situational couple violence among a population-based sample of urban women in the United States. *J Interpers Violence* 2006; 21: 1286-1313.
90. Anglin D: *Diagnosis through disclosure and pattern recognition*. In: Mitchell C, Anglin D, eds. *Intimate Partner Violence: A Health-Based Perspective*. New York: Oxford University Press; 2009:87-103.
91. Bonomi AE, et al: Medical and psychosocial diagnoses in women with a history of intimate partner violence. *Arch Intern Med* 2009; 169:1692-1697.
92. Blosnich JR, Bossarte RM: Comparisons of intimate partner violence among partners in same-sex and opposite-sex relationships in the United States. *Am J Public Health* 2009; 99:2182-2184.
93. Roche M, Moracco KE, Dixon KS, Stern EA, Bowling JM: Correlates of intimate partner violence among female patients at a North Carolina emergency department. *N C Med J* 2007; 68:89-94.
94. Bonomi AE, Anderson ML, Rivara FP, Thompson RS: Health outcomes in women with physical and sexual intimate partner violence exposure. *J Womens Health* 2007; 16:987-997.
95. Bhandari M, et al: The prevalence of intimate partner violence across orthopaedic fracture clinics in Ontario. *J Bone Joint Surg Am* 2011; 93:132-141.
96. Warshaw C, Brashler P, Gil J: *Mental health consequences of intimate partner violence*. In: Mitchell C, Anglin D, eds. *Intimate Partner Violence: A Health-Based Perspective*. New York, NY: Oxford University Press; 2009:147-171.
97. Strack GB, McClane GE, Hawley D: A review of 300 attempted strangulation cases. Part I: Criminal legal Issues. *J Emerg Med* 2001; 21:303-309.
98. Taliaferro E, Hawley D, McClane G, Strack G: *Strangulation in intimate partner violence*. In: Mitchell C, Anglin D, eds. *Intimate Partner Violence: A Health-Based Perspective*. New York: Oxford University Press; 2009:217-235.
99. Valera EM, Berenbaum H: Brain injury in battered women. *J Consult Clin Psychol* 2003; 71:797-804.
100. Bazarian J, McClung J: Mild traumatic brain injury in the United States 1998-2000. *Brain Injury* 2005; 19:85-91.
101. Corrigan JD, Wolfe M, Mysiw WJ, Jackson RD, Bogner JA: Early identification of mild traumatic brain injury in female victims of domestic violence. *Am J Obstet Gynecol* 2003; 188:S71-S76.
102. Wilson S: *Traumatic brain injury and intimate partner violence*. In: Mitchell C, Anglin D, eds. *Intimate Partner Violence: A Health-Based Perspective*. New York: Oxford University Press; 2009:183-199.
103. Logan TK, Cole J, Capillo A: Differential characteristics of intimate partner, acquaintance and stranger rape survivors examined by a sexual assault nurse examiner (SANE). *J Interpers Violence* 2007; 22:1066-1076.
104. Miller E, et al: Pregnancy coercion, intimate partner violence and unintended pregnancy. *Contraception* 2010; 81:316-322.

www.ketabpezeshki.com 66485457-66963820

105. Thackeray J, Stelzner S, Downs SM, Miller C: Screening for intimate partner violence: The impact of screener and screening environment on victim comfort. *J Interpers Violence* 2007; 22:659-670.
106. Bacchus L, Stelzner S, Downs SM, Miller C: Experiences of seeking help from health professionals in a sample of women who experienced domestic violence. *Health Soc Care Community* 2003; 11:10-18.
107. Rodriguez MA, Bauer HM, Flores-Ortiz Y, Szkupinski-Quiroga S: Factors affecting patient-physician communication for abused Latina and Asian immigrant women. *J Fam Pract* 1998; 47:309-311.
108. Feder GS, Hutson M, Ramsay J, Taket AR: Women exposed to intimate partner violence: Expectations and experiences when they encounter health care professionals: A meta-analysis of qualitative studies. *Arch Intern Med* 2006; 166:22-37.
109. Gerlach LB, et al: Does sex matter? Effect of screener sex in intimate partner violence screening. *Am J Emerg Med* 2007; 25:1047-1050.
110. Mezey G, Bacchus L, Haworth A, Bewley S: Midwives' perceptions and experiences of routine enquiry for domestic violence. *BJOG* 2003; 110:744-752.
111. American College of Emergency Physicians (ACEP): Domestic Family Violence Policy Statement 2007. Available at www.acep.org/Clinical—Practice-Management/Domestic-Family-Violence. Accessed January 30, 2013.
112. Family Violence Prevention Fund: *National Consensus Guidelines on Identifying and Responding to Domestic Violence Victimization in Health Care Settings*. San Francisco: The Family Violence Prevention Fund; 2002.
113. Institute of Medicine (IOM): *Clinical Preventive Services for Women: Closing the Gaps*. Washington, DC: National Academies Press; 2011.
114. Moyer VA, U.S. Preventive Services Task Force: *Screening for intimate partner violence and abuse of elderly and vulnerable adults*. A U.S. Preventive Services Task Force recommendation statement. Annals of Internal Medicine. Available at http://www.annals.org. Accessed on January 30, 2013.
115. Houry D, et al: Does screening in the emergency department hurt or help victims of intimate partner violence? *Ann Emerg Med* 2008; 51:433-442.
116. Koziol-McLain J, Giddings L, Rameka M, Fyfe E: Intimate partner violence screening and brief intervention: Experiences of women in two New Zealand health care settings. *J Midwifery Womens Health* 2008; 53:504-510.
117. Choo EK, Nicholaidis C, Lowe RA: Emergency department visits prior to the diagnosis of intimate partner violence. *Ann Emerg Med* 2008; 52:S62-S63.
118. Rhodes KV, et al: Intimate partner violence identification and response: Time for a change in strategy. *J Gen Intern Med* 2011; 26:894-899.
119. Rhodes KV, Lauderdale DS, He T, Howes DS, Levinson W: "Between me and the computer": Increased detection of intimate partner violence using a computer questionnaire. *Ann Emerg Med* 2002; 40:476-484.
120. MacMillan HL, et al: Approaches to screening for intimate partner violence in health care settings: A randomized trial. *JAMA* 2006;296:530-536.
121. Lutz K: Abuse experiences, perceptions, and associated decisions during the childbearing cycle. *West J Nurs Res* 2005; 27:802-824.
122. Lutenbacher M, Cohen A, Mitzel J: Do we really help? Perspectives of abused women. *Public Health Nurs* 2003; 20:56-64.
123. Rhodes KV, et al: "You're not a victim of domestic violence, are you?" Provider patient communication about domestic violence. *Ann Intern Med* 2007; 147:620-627.
124. Dichter ME, Rhodes KV: Reports of police calls for service as a risk indicator for intimate partner violence. *Acad Emerg Med* 2009; 16:83-86.
125. Soeken K, McFarlane J, Parker B, Lominack M: *The Abuse Assessment Screen: A clinical instrument to measure frequency, severity and perpetration of abuse against women*. In: Campbell J, ed. *Empowering Survivors of Abuse: Health Care for Battered Women and Their Children*. Thousand Oaks, Calif: Sage; 1998.
126. Feldhaus KM, et al: Accuracy of 3 brief screening questions for detecting partner violence in the emergency department. *JAMA* 1997; 277:1357-1361.
127. Basile K, Hertz M, Back S: *Intimate Partner Violence and Sexual Violence Victimization Assessment Instruments for Use in Healthcare Settings*. Version 1. Atlanta, Ga: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2007.
128. Thompson M, Basile K, Hertz M, Sitterle D: *Measuring Intimate Partner Violence Victimization and Perpetration: A Compendium of Assessment Tools*. Atlanta, Ga: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, Division of Violence Prevention; 2006.
129. Mills TJ, Avegno JL, Haydel MJ: Male victims of partner violence: Prevalence and accuracy of screening tools. *J Emerg Med* 2006; 31:447-452.
130. Houry D, Kemball RS, Click LA, Kaslow NJ: Development of a brief mental health screen for intimate partner violence victims in the emergency department. *Acad Emerg Med* 2007; 14:202-209.
131. Campbell JC, Webster DW, Glass N: The danger assessment: Validation of a lethality risk assessment instrument for intimate partner femicide. *J Interpers Violence* 2009; 24:653-674.
132. Snider C, Webster D, O'Sullivan CS, Campbell J: Intimate partner violence: Development of a brief risk assessment for the emergency department. *Acad Emerg Med* 2009; 16:1208-1216.
133. Cattaneo LB, Bell ME, Goodman LA, Dutton MA: Intimate partner violence victims' accuracy in assessing their risk of re-abuse. *J Fam Violence* 2007; 22:429-440.
134. Straus H, et al: Intimate partner violence and functional health status: Associations with severity, danger, and self-advocacy behaviors. *J Womens Health (Larchmt)* 2009; 18:625-631.
135. Coben J: *Evaluating Domestic Violence Programs*. Rockville, Md: Agency for Healthcare Research and Quality; 2002. Available at www.ahrq.gov/research/domesticviol/. Accessed June 29, 2011.
136. Mitchell C, Anglin D: Healthcare based models for IPV intervention: An analysis of intervention strategies. Paper presented at National Conference on Health Care and Domestic Violence, Atlanta, Ga, 2002.
137. Glanz K, Rimer B, Lewis F: *Health Behavior and Health Education: Theory, Research and Practice*. San Francisco, Calif: Wiley and Sons; 2002.
138. Asher L, Muelleman R, Maloney A, Schmid K: Assessing stage of change in female victims of intimate partner violence in an emergency department patient population. *Ann Emerg Med* 2008; 52:63S.
139. Larkin G, Parks J: *Acute intervention for intimate partner violence in the medical setting*. In: Mitchell C, Anglin D, eds. *Intimate Partner Violence: A Health-Based Perspective*. New York: Oxford University Press; 2009:307-317.
140. Sullivan CM, Bybee DI: Reducing violence using community-based advocacy for women with abusive partners. *J Consult Clin Psychol* 1999; 67:43-53.
141. Muelleman R, Feighny K: Effects of an emergency department-based advocacy program for battered women on community resource utilization. *Ann Emerg Med* 1999; 33:62-66.
142. McFarlane J, et al: Increasing the safety-promoting behaviors of abused women. *Am J Nurs* 2004; 104:40-50.
143. Kendall J, et al: Impact of emergency department intimate partner violence intervention. *J Interpers Violence* 2009; 24:280-306.
144. Koziol-McLain J, et al: A randomized controlled trial of a brief emergency department intimate partner violence screening intervention. *Ann Emerg Med* 2010; 56:413-423.
145. Hamberger L, Lohr J, Parker L, Witte T: *Treatment approaches for men who batter their partners*. In: Mitchell C, Anglin D, eds. *Intimate Partner Violence: A Health-Based Perspective*. New York: Oxford University Press; 2009.
146. Ahrens CE, Rios-Mandel LC, Isas L, del Carmen Lopez M: Talking about interpersonal violence: Cultural influences on Latinas' identification and disclosure of sexual assault and intimate partner violence. *Psychol Trauma* 2010; 2:284-295.
147. Carlson M, Harris S, Holden G: Protective orders and domestic violence: Risk factors for re-abuse. *J Fam Violence* 1999; 14:205-226.
148. Rodriguez MA, Bauer HM, McLoughlin E, Grumbach K: Screening and intervention for intimate partner abuse, practices and attitudes of primary care physicians. *JAMA* 1999; 282:468-474.
149. Rodriguez MA, McLoughlin E, Nah G, Campbell JC: Mandatory reporting of domestic violence injuries to the police: What do emergency department patients think? *JAMA* 2001; 286:580-583.
150. Antle B, Barbee A, Yankeelov P, Bledsoe L: A qualitative evaluation of the effects of mandatory reporting of domestic violence on victims and their children. *J Fam Soc Work* 2010; 13:56-73.
151. Bloom J, Rogers J: The duty to protect others from your patients—Tarasoff spreads to the northwest. *West J Med* 1988; 148:231-234.
152. Oppenheimer K, Swanson G: Duty to warn: When should confidentiality be breached? *J Fam Pract* 1990; 30:179-184.
153. Brown-Cranstoun J: Kringen v. Boslough and Saint Vincent Hospital: A new trend for healthcare professionals who treat victims of domestic violence? *J Health Law* 2000; 33:629-655.

www.ketabpezeshki.com 66485457-66963820

Chapter 69

Elder Abuse and Neglect

Deirdre Anglin and Diana C. Homeier

PERSPECTIVE

Background

Currently, 13% of the population in the United States is estimated to be 65 years of age or older.[1] The elderly segment of the population is expected to increase to 16% of the population by 2020 and 20% of the population by 2050.[2] Furthermore, the "oldest" old (85 years and older) will make up an increasing proportion of the population. At this time, older patients make about 15% of emergency department visits. This number is expected to increase to 25% by the year 2030, with 5% being older than 85 years.[3] As the aging population continues to increase, it is anticipated that the number of cases of elder abuse will also rise. Because older adults will make up a larger portion of emergency department visits in the future, emergency physicians need to have a greater knowledge of the risk factors and signs of abuse and neglect and consider them more frequently in the differential diagnosis.[4]

With aging, there is an increase in vulnerabilities, such as physical and cognitive decline, expended financial resources, and uncertain medical insurance. As the U.S. population ages, there is a greater need to recognize and respond to signs of elder abuse and neglect. The World Health Organization has recognized that abuse and neglect of elders are global health problems.[5] Elderly individuals may be isolated from society as a result of physical illness, disability, mental illness (e.g., dementia), and age. Visits to physicians by elderly persons may provide their only contact outside the family. Elderly persons frequently visit the emergency department for medical care. Therefore emergency physicians have the opportunity to diagnose suspected elder abuse and initiate further evaluation by elder abuse teams and Adult Protective Services.[6] However, one survey suggests that emergency physicians may lack awareness and adequate training about elder abuse. In this survey of 705 emergency physicians, 79% reported they had treated a case of elder abuse in the previous year, but only 50% said they had reported the abuse. Of respondents, 28% believed elder abuse is rare, and 84% rarely ask their patients directly about elder abuse. Only 31% of emergency physicians responded that they are aware of a written protocol for elder abuse in the emergency departments where they practice, and just 38% said they are familiar with their state laws pertaining to elder abuse. In addition, only 40% responded that they are aware of types of community services available for victims of elder abuse, and only 25% could recall receiving education about elder abuse during their residencies.[7] It is hoped that through education and increased awareness, these numbers will increase markedly, as the emergency department often serves as the first step in the detection of an abusive or neglectful situation.

Epidemiology

It has been estimated that 2 million elders are neglected or abused annually in the United States.[8] The National Elder Abuse Incidence Study found that 449,924 Americans older than age 60 years had experienced some form of mistreatment in the previous year.[9] In this study the median age of victims of elder abuse was 78 years, and two thirds of victims were women. Of identified elder abuse victims, 66% were white, 19% black, and 10% Hispanic. More than two thirds of perpetrators of elder abuse were family members, primarily spouses and grown children, and the overwhelming majority of victims lived with the perpetrators. A total of 77% of victims were unable or only somewhat able to care for themselves; 60% of victims were either very confused or occasionally confused. In addition, 37% of elder abuse victims were moderately depressed, and 6% were severely depressed. The more recent National Elder Maltreatment Study interviewed 5777 adults older than age 60 years (average age 71.5 years) and found a 1-year prevalence of 4.6% for emotional abuse, 1.6% for physical abuse, 0.6% for sexual abuse, 5.1% for potential neglect, and 5.2% for financial abuse.[10] This study also found that very little of the abuse was reported to authorities.

A systematic review of studies measuring the prevalence of elder abuse published in 2008 found that 6% of older people living in the community reported significant abuse within the previous month.[11] When looking more specifically at vulnerable older people, the review found that one fourth of those who were dependent on others for care reported significant psychological abuse, and one fifth reported neglect. One third of family caregivers reported perpetrating abuse, and of professional caregivers in long-term care, 16% admitted to perpetrating psychological abuse, and 10% admitted to perpetrating physical abuse. In this review, very few cases were reported to Adult Protective Services. Studies have shown that as few as 1 in 14 cases of elder abuse is actually reported.[12]

DEFINITIONS AND TYPES OF ELDER ABUSE

Some of the difficulty in establishing the true incidence and prevalence of elder abuse stems from the lack of uniformity of definitions of elder abuse, both among researchers and in legislation. Definitions vary from state to state and often lack objective criteria for reliably establishing a medical diagnosis. Elder abuse is a form of family violence, along with child abuse and intimate partner violence. There are three main categories of elder abuse: domestic elder abuse, institutional elder abuse, and self-neglect or self-abuse.

www.ketabpezeshki.com 66485457-66963820

Domestic elder abuse includes any form of elder abuse inflicted in the elder's home or the caregiver's home by a family member or a caregiver. *Institutional abuse* includes any form of elder abuse that occurs in a residential facility for elderly persons, usually inflicted by individuals who are hired to provide care. *Self-neglect* or *self-abuse* is the result of the behavior of an elderly person and threatens the well-being of that individual. Self-neglect usually involves the refusal or failure of elderly individuals to provide themselves with basic necessities, such as food, water, shelter, medications if indicated, and appropriate personal hygiene. In 45% of cases of self-neglect, elders 80 years of age or older are involved.[13] Self-neglect does not include mentally competent elderly individuals who understand the consequences of their decisions.

In addition to the three main categories, elder abuse can be grouped into six types: physical abuse, sexual abuse, emotional or psychological abuse, neglect, abandonment, and financial or material exploitation.[13] In a study of substantiated cases of elder abuse, 58% involved neglect, 11% physical abuse, 15% exploitation, 15% emotional abuse, and 1% sexual abuse.[14] Victims of elder abuse are often subjected to multiple types of elder abuse.

Physical abuse is defined as the intentional use of physical force that may result in bodily injury, physical pain, or impairment. Physical abuse is the most readily detected type of elder abuse. It includes any type of force inflicted on an elder that may cause harm, including slapping, hitting, kicking, pushing, pulling hair, and burning. Physical abuse may also include overmedication or undermedication, the use of physical restraints, or force-feeding. In addition, it may involve the use of household objects as weapons, as well as the use of firearms and knives.

Sexual abuse is defined as any type of sexual contact with an elderly person that is nonconsensual. It may include sexual assault, sexual coercion, verbal and physical sexual advances, and indecent exposure. Sexual abuse also occurs if an elderly individual is incapacitated and therefore incapable of giving informed consent.

Emotional or *psychological abuse* is defined as intentional infliction of suffering, pain, and distress through verbal or nonverbal means. Emotional abuse may include insulting or demeaning comments, name calling, threats of deprivation, isolation, and humiliation. Emotional abuse may accompany physical abuse or other forms of abuse.

Neglect is defined as the failure or refusal of caregivers to fulfill any of their duties or obligations to an elderly individual, which has resulted or is likely to result in serious harm to the elderly individual. Neglect may be either unintentional or intentional. However, intent is often very difficult to prove. Unintentional neglect may result from the inability of the caregiver to carry out responsibilities because of physical or mental inability or a lack of knowledge of how to care properly for the elderly individual. Neglect may consist of withholding of food, water, clothing, shelter, medications, medical equipment (e.g., walker, cane, glasses, hearing aids, dentures), or medical appointments.

Abandonment is defined as the desertion of an elderly person by the caregiver, custodian, or an individual who is responsible for providing care. As many emergency physicians are aware, elderly patients may be abandoned in the emergency department. One survey reported that a median of 24 elderly patients were abandoned annually per emergency department, with 46% living alone and no longer being able to look after themselves and 41% being left in the emergency department by family members or a caregiver.[15] Abandonment may be considered a form of neglect.

Financial or *material exploitation* is defined as the illegal or improper use of an elderly person's money, property, or assets. Financial exploitation includes denying an elderly person his or her home; stealing money or belongings; and coercing an elderly individual into signing contracts, changing a will, or assigning durable power of attorney to someone against his or her wishes. It may also include coercing an elderly individual to take out a loan or sign a legally binding document when he or she does not possess the mental capacity to do so.[16]

In this chapter the term *abuse* is used to encompass any of the types of abuse described in the previous paragraphs.

ETIOLOGY OF AND RISK FACTORS FOR ELDER ABUSE

There are several theories regarding the cause of elder abuse.[17] More recent focus has been directed toward the abusing relative or caregiver. The social learning or transgenerational violence theory proposes that children who grow up in an abusive household may go on to be abusive to their own children and perhaps parents. Another theory, the stressed caregiver theory, proposes that as a caregiver becomes increasingly stressed (from caregiving or other causes), elder abuse is more likely to occur. Some researchers theorize that it is the psychopathology of the abuser that leads to elder abuse. Proponents of the isolation theory contend that as elderly individuals become more socially isolated as a result of illness, disability, and age, they are at increased risk for abuse. Those who adhere to the dependency theory believe that increasing frailty is the underlying cause of elder abuse, whereas others contend that frailty only prevents many elders from protecting or defending themselves and that the true cause lies with the abuser. It is now recognized that no single theory can account for all situations of abuse or neglect. An integrated theoretic model may best describe all potential factors involved, and each circumstance may involve some components to a greater degree than others.

Numerous risk factors for elder abuse have been proposed. These factors may be divided into four main categories: caregiver risk factors for abusing, elder risk factors for being abused, environmental risk factors, and institutional abuse risk factors (Box 69-1).[18,19] The National Elder Maltreatment Study evaluated correlates for each type of abuse and found that the most consistent correlates across abuse types were low social support and previous traumatic event exposure. Emergency providers should be aware of these risk factors and alert to the possibility of abuse among all elderly patients.

CLINICAL FEATURES

In addition to the risk factors stated previously, other findings suggestive of elder abuse are abandonment of the patient in the emergency department by the caregiver, frequent visits to the emergency department, lack of compliance with medical appointments and medications, and the use of numerous physicians and emergency departments for care rather than one primary care physician ("doctor hopping").

Elderly patients are four times more likely to be brought to the emergency department by ambulance than nonelderly patients.[20] When elders are brought to the emergency department by ambulance, the emergency medical technicians or paramedics may be invaluable in identifying at-risk elders on the basis of their assessment of the home situation and the family dynamics at the home. The emergency provider should question prehospital care personnel about the cleanliness and upkeep of the home; the availability of electricity, heat, water, and sanitation; infestation by rodents or vermin; and the safety of the interior of the home for the older patient.

The American Medical Association (AMA) has recommended that all health care providers routinely ask their older patients about abuse, even in the absence of signs of abuse.[21] Patients should be questioned in as private a setting as possible, after the family or caregiver has left the room. If the patient has dementia or is unable to answer questions for other reasons, individuals who have knowledge about the patient, other than the caregiver, should be questioned, such as other family members, visiting home nurses

www.ketabpezeshki.com 66485457-66963820

Box 69-1 Potential Risk Factors for Elder Abuse

Caregiver Risk Factors
Alcohol or drug abuse
Mental illness
Financial stress
Stress resulting from caring for the elder (e.g., a lack of resources)
Outside factors resulting in stress (e.g., unemployment)
Financial dependence on the elder
Unrealistic expectations regarding caregiver responsibilities
Lack of caregiving skills
Long duration of time as a caregiver

Elder Risk Factors
Physical or functional impairment
Financial dependence on the caregiver
Cognitive impairment or dementia
Social isolation
Low social support
History of family violence
Previous traumatic event exposure
Aggressive behavior
Female
Advanced age
Incontinence
Frequent falls

Environmental and Family Factors
Shared living situation
Overcrowded living conditions
Lack of family and community support
Socially isolated

Risk Factors for Institutional Abuse
Poor working conditions
Inadequate training, experience, and supervision of caregivers
Low wages
Low staff-to-patient ratio

Box 69-2 Questions for Use in Asking Patients about Elder Abuse

General
Do you feel safe where you live?
Are you afraid of anyone where you live?
Who assists you if you need help?
Who makes your meals?
Who helps you take your medications?
Who manages your checkbook?
Do you have frequent arguments with your family or caregiver?
What happens when you argue?

Physical Abuse
Have you been hit, slapped, or kicked?
Have you ever been locked in a room?
Have you ever been tied down?
Have you ever been forced to eat?

Sexual Abuse
Has anyone ever touched you sexually without your consent?

Psychological or Emotional Abuse
Do you feel alone?
Are you yelled at where you live?
Has your family or caregiver ever threatened to punish you or have you put in an institution?

Neglect
Are you left alone often at home?
Do you need to use hearing aids, glasses, dentures, or a walker or a cane? Are they readily accessible to you?
Does your family or caregiver ever fail to help you when you need help?

Financial or Material Abuse
Has anyone ever taken anything from you without asking?
Have you been forced to sign a will, power of attorney, or any documents that you did not understand?
Does your family or caregiver rely on you for housing or financial support?

and assistants, therapists, primary care physician, or neighbors. If a translator is needed, someone other than a family member or the caregiver should be used. To broach the subject of elder abuse, the interviewer begins by asking about the patient's care in general and then focuses on abuse and specific types of abuse (Box 69-2). Factors that have been shown to have a significant association with suspected elder abuse include a brittle support system, feelings of loneliness, expression of conflict with family or friends, alcohol abuse, short-term memory problems, and psychiatric illness.[22] One study determined that emergency department nurses can be trained to routinely ask older patients about neglect and appropriately refer them for care.[23] There are now several instruments available to assist medical personnel in inquiring about and identifying abuse and neglect. These tools involve direct questioning of the elder, recognition of possible physical signs, or identification of risk factors. No single test has been found to be optimal, but the use of multiple approaches may be most helpful in recognizing abuse victims. If elder abuse is identified, the provider should question the patient further about the duration and frequency of the abuse, the nature of the abuse, and whether there has been intervention or assistance in the past because of the abuse.

There is increasing evidence that elder abuse is associated with adverse health outcomes, including increased dementia, depression,[24] and premature death,[25] thus making a thorough, well-documented medical history and physical examination critical. It is best to elicit the history from the patient and caregiver separately. Potential historical indicators of abuse are listed in Box 69-3. As part of the medical history, the patient and caregiver should be asked about routine medications; the discovery of caregivers who are unfamiliar with daily medications and other necessary medical care of the elderly patient (e.g., dressing changes) raises the suspicion of elder neglect. If injuries are noted, the emergency provider should question the patient about how the injuries occurred, including directed questions regarding whether anyone has hit, punched, or kicked the patient. If the injuries occurred as a result of interpersonal violence, the relationship between the patient and abuser should be ascertained. Before

Box 69-3 Indicators from the Medical History of Possible Ongoing Elder Abuse

Implausible history of injury mechanism
Inconsistent history of injury mechanism between the patient and caregiver
Delay between onset of medical illness or injury and seeking of medical attention
Unexplained injuries
Elderly patient referred to as "accident prone"
Past history of frequent injuries
Noncompliance with medications, appointments, or physician directions
Caregiver not able to give details of the patient's medical history or routine medications
Caregiver answers the questions regarding the patient
Patient or caregiver reluctant to answer questions
Strained patient-caregiver interaction
Poor living conditions according to paramedics or others

www.ketabpezeshki.com 66485457-66963820

Box 69-4 Signs of Physical Abuse, Sexual Abuse, and Neglect That May Be Noticed on the Physical Examination

Physical Abuse
Contusions
Contusions on bilateral upper arms (grab marks)
Abrasions
Burns (e.g., from cigarettes, irons, immersion)
Sprains
Patterned injuries (e.g., marks consistent with the shape of a belt, fingers, electrical cord)
Traumatic alopecia
Bite marks
Restraint marks (e.g., involving wrists, ankles, and torso)
Fractures
Multiple injuries in various stages of healing
Blunt head trauma
Intra-abdominal injuries (e.g., liver, spleen)
Gag marks
Ocular injuries (e.g., hyphema, retinal detachment)

Physical Signs of Sexual Abuse
Evidence of genital, rectal, or oral trauma (e.g., contusions, lacerations, erythema)
Evidence of sexually transmitted disease

Physical Signs of Neglect
Dehydration
Evidence that the patient has been lying in urine and stool
Malnutrition
Clothing inappropriate for the climate; dirty or severely worn
Poor body hygiene
Untreated injuries and medical problems
Poor oral hygiene
Skin breakdown (e.g., decubitus ulcers, pressure sores)
Elongated toenails

questioning patients, providers should inform them that providers are mandated to report abuse when it is disclosed. However, even in the absence of disclosure, most states mandate reporting elder abuse if it is reasonably suspected. Because elders may be afraid to disclose abuse, it is important that providers reassure their patients that the goal is to provide a safer living environment and not primarily to punish the caregiver. When a patient expresses fear about mandatory reporting, the provider should note this information in the report to Adult Protective Services so that the risk to the patient can be minimized.

When performing a physical examination of an elderly patient, the emergency provider should look for signs of physical abuse, sexual abuse, and neglect (Box 69-4). Clinical skill and judgment are required because illnesses resembling abuse occur frequently in older patients (e.g., easy bruising, fractures resulting from osteoporosis or osteopenia, dehydration). Elder abuse is included in the differential diagnosis of numerous conditions that occur frequently in the geriatric population. Elderly patients with multiple clinical findings consistent with elder abuse have a higher likelihood of being victims than do patients with isolated findings. In addition, injuries and medical conditions for which no underlying cause can be determined are more likely to be a result of abuse.

During the physical examination, the clinician should make note of the general appearance (e.g., cleanliness, hygiene, and dress) and behavior (e.g., agitated, fearful, withdrawn) of the patient. The skin should be examined for unexplained bruises, particularly of the head, face, torso, back, bilateral upper arms, inner aspect of the arms, or inner aspect of the thighs (Figs. 69-1 and 69-2). In addition, bruising on the neck, ears, genitalia, buttocks, or soles of the feet is suspicious in an elder.[26] In one study

Figure 69-1. A 70-year-old man was brought from his caregiver's home to the emergency department by police after his daughter found him severely bruised. He had multiple contusions at varying stages of healing on his chest and arms, as well as a linear patterned injury across his left anterior chest. The central and bilateral locations of the contusions, varying colors, and linear pattern of the bruise on the left side of his chest are highly suggestive of physical abuse. (Courtesy Dr. D.C. Homeier.)

Figure 69-2. A 69-year-old woman with severe dementia who resided in a skilled nursing facility was brought to the emergency department after her daughter noticed that the patient had bruises on her bilateral inner thighs. When the daughter inquired about the bruises she was told by the facility staff that the patient had fallen. These bruises are in a location that raises suspicion for sexual abuse. The emergency department health care provider consulted the hospital's Adult Protection Team, which contacted local law enforcement; the Long-Term Care Ombudsman was also notified for further investigation. The hospital's Sexual Assault Response Team was consulted and conducted a sexual assault forensic examination for evidence collection. (Courtesy Dr. D. C. Homeier).

of bruises in 67 elderly individuals who had been reported to Adult Protective Services because of suspected physical elder abuse, bruises that an expert panel determined were a result of elder physical abuse were often large (>5 cm) and found on the face, lateral right arm, or posterior torso.[27] Another study followed unintentionally acquired bruises in elders for up to 6 weeks; it was found that the color of bruises was not a reliable indicator of the age of the bruises.[26] Attention should also be paid to the state of care of decubitus ulcers, if present (Fig. 69-3). Head and facial injuries, including broken teeth, lacerations, or the absence of hair, may reflect abuse. If the genitourinary examination reveals

www.ketabpezeshki.com 66485457-66963820

Figure 69-3. A 72-year-old woman was brought to the emergency department by paramedics for "not eating for 5 days" according to her family. The paramedics noted she was covered in urine and feces. The following signs were of concern for neglect: elongated toenails **(A)**, pressure sores **(B)**, poor hygiene, and a delay in seeking medical care. (Courtesy Dr. D.C. Homeier.)

evidence of trauma or vaginal bleeding and if sexual abuse is suspected, a complete sexual assault examination, including collection of evidence by a forensic examiner, is indicated as in other cases of sexual assault. The extremities should be examined for evidence of contractures that may indicate confinement for long periods, wrist and ankle lesions from restraints (Fig. 69-4), and the general condition of the toenails and feet (see Fig. 69-3).

Dehydration and malnutrition are the most frequent physical findings of neglect. The physical examination includes a careful evaluation of both neurologic and psychiatric function. The recent development of focal neurologic deficits may be a result of blunt head trauma or stroke. Evaluation of gait may direct the assessment toward an acute neurologic process or an orthopedic injury. Long-standing focal neurologic deficits, such as hemiparesis from a cerebrovascular accident, suggest increased needs for care of the elder. The elderly patient's mental status should be assessed. Dementia may be assessed with the Mini-Mental State Examination; delirium may be assessed with the Confusion Assessment Method (CAM) score; and depression may be assessed with one of a variety of bedside depression scores. A standardized assessment form that combines the neurologic and psychiatric mental status evaluation can greatly facilitate efficiency in a busy

Figure 69-4. A 65-year-old developmentally delayed but ambulatory woman was brought to the emergency department by her family on account of "unruly behavior." Examination of her left heel revealed a pressure ulcer, and her left ankle revealed an erythematous rash in a circumferential pattern. This may represent the use of a restraint, resulting in the pressure ulcer. (Courtesy Dr. D.C. Homeier.)

emergency department. Subtle changes in the elder's mental status may indicate depression or early dementia or may be the only signs of ongoing abuse.

An elderly patient who is being emotionally or psychologically abused may display deterioration in mental health and show signs of post-traumatic stress disorder. The patient may demonstrate fear, anxiety, or infantile behavior in the presence of the caregiver and may also exhibit poor self-esteem. On questioning, the elderly patient may admit to ambivalent feelings toward the family member who is the caregiver and may express feelings of mistrust related to the caregiver. The caregiver may also be emotionally abusive in the presence of the emergency health care provider. Elderly patients who are being physically abused, sexually abused, or neglected may also demonstrate findings similar to those of emotionally abused elderly patients.

DIAGNOSTIC STRATEGIES

When elder abuse is suspected, the provider should order laboratory investigations and imaging studies as indicated by the history and physical examination. There is a low threshold for ordering imaging studies in elderly patients owing to the increased frequency of osteopenia and osteoporosis and the tendency of some elders to minimize pain. Metabolic laboratory tests may be helpful in determining electrolyte, nutritional, or endocrine abnormalities. Toxicologic studies may be helpful to document compliance with medications, overmedicating or undermedicating by the caregiver, and, in severe cases of elder abuse, evidence of poisoning.

DOCUMENTATION

Accurate and thorough documentation of the history and physical examination findings in cases of suspected elder abuse is essential. The emergency provider should document the history of any suspected types of abuse, as well as the mechanism of injury, in the patient's own words, if possible. This documentation should include details of the pertinent social history (e.g., caregiver's identity, living arrangements, functional status). In addition, the documentation should include a description of injuries of any type (e.g., fractures, lacerations, and contusions) and their number, size, location, color, and stage of healing. When possible, the provider should obtain photographs of the injuries before rendering treatment. In addition to photographs, the provider should document the locations and types of injuries on a body map or diagram. In California, a statewide form has been developed for the purpose of documenting a forensic examination in cases of elder abuse,

www.ketabpezeshki.com 66485457-66963820

although as of 2013 its use was not mandated.[28] The health care provider should document whether the mechanism of each injury, as provided by the patient, seems appropriate and compatible with the history. The results of laboratory investigations and imaging studies should also be recorded. Careful documentation of follow-up plans, referrals, and interventions should be made. If a report is made to Adult Protective Services, the provider should record the name of the individual contacted and the case number. In addition, if law enforcement is contacted, the provider should document the name and badge number of the officer taking the report. In cases of suspected elder abuse that result in legal action, thorough documentation may be critical in determining the outcome and the ultimate care of the patient.

CAREGIVER INTERVIEW

Part of the assessment of a suspected victim of elder abuse involves separately interviewing the patient and the caregiver or suspected abuser. The interview should be conducted in a nonthreatening and nonjudgmental manner in a way that addresses the needs of both the caregiver and the elder. The goal is not to punish the caregiver but rather to stop the abuse. Accusations are likely only to curtail the amount of information the caregiver provides. Conducting separate interviews may reveal discrepant histories between the caregiver and the patient. Initially, questioning is directed at the reason for the visit to the emergency department; subsequently questions are directed at the patient's medical conditions and the daily care requirements, including routine medications and assistance with activities of daily living. Caring for an individual with chronic illness who frequently requires assistance with basic activities of daily living is a difficult and tiring task. Therefore verbal expressions of sympathy, explicit recognition of the challenges, and demonstrations of support can be beneficial for the caregiver and also promote information sharing. Statements such as "Caring for your mother must be a difficult task. Do you ever feel anger or resentment toward her?" may actually allow the family member or caregiver to express valid frustrations. Questions should also explore whether any recent stresses have occurred in the household, whether the caregiver feels that the patient is a financial burden, and whether any respite services or other home help services have been made available.

INTERVENTIONS AND REFERRALS

When elder abuse is suspected or identified, provision for immediate care needs, situational assessment, long-term care planning, and steps to prevent future abuse are all required. Emergency department interventions in elder abuse differ from those in child abuse primarily because the physician is required to respect the wishes of the mentally competent elderly adult. The older adult should be able to live in the least restrictive environment possible, and institutionalization is not necessarily a solution to ending the abuse. For many elders, the prospect of being institutionalized is frightening, and they may choose instead to remain living in an abusive situation. In addition, providing home care assistance, respite care, and other in-home resources and support to the caregiver and elderly patient may be more cost-effective than institutionalization. Therefore one of the goals of management of elder abuse is to keep the family unit together, when possible, rather than have the elder removed from the home.

If there is immediate danger, the patient should be prevented from having any contact with the suspected abuser, which may involve being removed from the home. Hospitalization may be required because of injuries and ongoing medical problems. However, in the absence of an acute medical illness, medical insurance companies and third-party payers may not cover the cost of hospitalization, and a safe-house placement may be required.[29] Proper use of the diagnosis and diagnostic codes can ensure that appropriate care: Adult Maltreatment (unspecified) (ICD-9: 995.8; ICD-10: suspected T76.91, confirmed T74.91).[30,31]

If the patient refuses intervention, the emergency provider must determine whether the patient is capable of making his or her own decisions. In some instances a psychiatric consultation for the determination of capacity may be required. If the elderly patient is found not to have the capacity to make decisions, Adult Protective Services need to be notified to arrange court-ordered guardianship. The wishes of a competent elderly patient must be respected even if the patient desires to return to an abusive situation.

In suspected cases of elder abuse that pose a less imminent threat, interventions are individualized. If the patient wants to return home and may be safely discharged from the emergency department, a follow-up plan must be established and documented. This is best accomplished by a multidisciplinary team consisting of the patient's primary care physician, nurses, social workers, and occupational therapists, or a geriatrics assessment team.[32] Another approach includes Adult Protective Services caseworkers as members of the geriatric team.[33] The follow-up assessment consists of an evaluation of the patient's functional, cognitive, and medical status. Social and financial resources and the frequency, severity, and intent of the abuse should also be assessed. At least one home visit is recommended as part of the assessment.

The needs of the caregiver are an important component of the care plan. Support services, such as in-home services, respite care, psychological counseling, employment referrals, and alcohol and drug abuse rehabilitation program referrals, should be provided as needed. For the short term, the emergency health care provider may assist the caregiver by arranging increased involvement from other family members or friends, close follow-up with the patient's primary care physician, a social services consultation, home nursing assistance, and the involvement of Adult Protective Services. Other referrals and resources that may be beneficial for both the elderly patient and the caregiver include senior centers, medical transportation services, Medicare referral, Meals On Wheels, senior housing, Social Security benefits, religious communities, home health, adult day care, hospice care, and victim assistance. Addressing behavioral issues in the elderly may also be very helpful to an overwhelmed caregiver. Ultimately, if the caregiver has severe personal problems that cannot be resolved, the only solution may be separation of the elder from the caregiver. If the elderly patient is competent and does not wish to accept interventions, he or she should nonetheless be educated about elder abuse and given referral materials. Some cases of elder abuse are actually intimate partner violence committed by the elder's spouse.[34] In these cases, consultation with intimate partner violence advocacy services is recommended.

Education of elderly victims about elder abuse and the likelihood that it will increase in frequency and severity over time is important. The AMA and the American College of Emergency Physicians endorse the need for all emergency departments to have protocols for the management of suspected cases of elder abuse to facilitate management and ensure appropriate care.[21,35] The Joint Commission has standards for emergency departments that include having criteria for the detection and management of elder abuse among patients.[36] Some emergency departments also have access to in-house elder abuse response teams that can be mobilized to assist the emergency physician with the management of these complex cases.

REPORTING REQUIREMENTS

In all 50 states and the District of Columbia, laws have now been enacted that pertain to the reporting and investigation of elder

www.ketabpezeshki.com 66485457-66963820

abuse. However, the definitions of elder abuse and requirements of the laws vary from state to state.[37] In most states, physicians are mandated to file a report if they know or reasonably suspect that elder abuse has occurred, and in several additional states physicians are mandated to report only if the suspected victim resides in a nursing home.[38] Many of the states with mandatory reporting requirements grant immunity to physicians who report suspected elder abuse. Most state laws also have a penalty for failure to report. These penalties usually consist of a fine, a jail sentence, or both. In most states, Adult Protective Services is designated as the agency responsible for receiving and investigating all reports of suspected elder abuse. The laws vary widely concerning the age at which "elder" is defined, with most states defining it as 60 years or older. In addition, the laws vary in their definitions of the circumstances of the abuse, the types of abuse, the reporting and investigation of the abuse, and specifics regarding domestic and institutional abuse. Additional criminal laws regarding assault and battery, theft, fraud, rape, and murder may also pertain to elder abuse. Laws concerning guardianship and conservatorship, durable powers of attorney, intimate partner violence, and family violence may also be related to elder abuse. Emergency providers should become familiar with state laws pertaining to elder abuse and their duty to report in the state in which they practice.

There are several issues regarding the mandatory reporting laws for elder abuse. Some physicians are concerned that reporting elder abuse constitutes a breach of confidentiality with their patients. Others are concerned that mandatory reporting may deter elders from seeking medical care. The AMA has stated that health care providers should inform their patients if they have a legal obligation to report elder abuse and the medical necessity to intervene in cases of elder abuse. The AMA also emphasizes that the goal is to end the abuse by facilitating access to resources for the patient and his or her family.[21] There is a great need for standardization of legislation and increased funding to provide adequate service delivery to elder abuse victims and their families.

Elder abuse is often under-recognized and under-reported by emergency physicians. Reasons include a lack of awareness of the prevalence of elder abuse, ageism (discrimination against the elderly), lack of knowledge of the appropriate management of suspected elder abuse, lack of an emergency department protocol for suspected elder abuse, lack of time to conduct a time-consuming evaluation of the suspected abuse, the emergency physician's concern about litigation, the emergency physician's concern about having to take time away from his or her practice to testify in court, and the ethical issue of not wanting to breach physician-patient confidentiality. A systematic review of studies investigating health professionals' knowledge, detection, and reporting of abuse, published in 2009, found that professionals consistently underestimated the prevalence of elder abuse; 33.7% of health care professionals had detected a case of elder abuse in the previous year, and only half of those cases were reported.[39] Elderly patients may also contribute to the difficulty in identifying elder abuse, willingly or unwillingly, because of isolation resulting from illness or age; inability to report abuse; reluctance to disclose the elder abuse owing to embarrassment or guilt; fear of retaliation by the abuser; wanting to protect the abuser, who is often a spouse or a child; fear of the consequences of the discovery of the abuse; fear of institutionalization; cultural or ethnic beliefs and backgrounds; and feeling that they are a burden to their families.

INSTITUTIONAL ABUSE

Approximately 5% of all elderly individuals reside in institutions such as nursing homes, board and care homes, and other assisted-living facilities. With the growing elderly population, this percentage is estimated to increase significantly in the future. In 1976, the Older Americans Act established the Long-Term Care Ombudsman Program to monitor nursing homes and board and care facilities, as well as to investigate cases of suspected elder abuse. This program is present in all 50 states. In 1987 the Nursing Home Reform Act included the right to be free from physical, sexual, and emotional abuse as well as isolation. Elderly residents of institutions may be subjected to abuse by other patients, visitors, and staff. A random survey of staff in long-term care institutions in one state revealed that 10% of nurses' aides reported having committed at least one act of physical violence in the previous year, and 40% at least one act of psychological abuse.[40] Risk factors for institutional abuse are shown in Box 69-1.[41,42] A study examining ombudsman data from six states found that a higher percentage of complaints lodged on behalf of minority patients were verified, but a lower percentage were fully resolved.[43] When patients from long-term care facilities seek medical care, emergency providers should be alert to signs of possible abuse. When abuse is identified, these cases should be reported to the state long-term care ombudsman for further investigation.

ABUSE OF PERSONS WITH DISABILITIES

In most states the laws protecting elders from abuse also protect persons with disabilities, often referred to as *dependent adults, vulnerable adults,* or *disabled adults.* Included are persons aged 18 years or older who have developmental, mental, or physical disabilities. Little is known about abuse and neglect of persons with disabilities; however, adults with disabilities are reported to be at higher risk for abuse than persons without disabilities. In particular, persons with developmental disabilities are at high risk for abuse. Based on the National Crime Victimization Survey of 2008, the best conservative estimate is that people with developmental disabilities are two to three times as likely to be victims of violent crime (or abuse) than people without disabilities; the most pronounced are robbery (3.2 times higher) and sexual assault (1.9 times higher).[44] Emergency providers should have a heightened awareness of the greater likelihood of abuse when managing patients with disabilities and understand the mandatory reporting laws and resources available to disabled victims in their state.

FUTURE DIRECTIONS

Residency training should include education in identifying and managing elder abuse and the reporting requirements for elder abuse. Emergency providers should also educate their patients and the community about the problem of elder abuse and the resources available in the community to assist elders and their caregivers. They should advocate for increased availability and funding of in-home services for elders. Furthermore, they should engage in research on elder abuse to increase the understanding of risk factors for elder abuse, gain knowledge about cultural factors, develop validated questions for the detection of elder abuse, determine effective management protocols, evaluate effective preventive interventions, and examine forensic markers of elder abuse.[45]

www.ketabpezeshki.com 66485457-66963820

KEY CONCEPTS

- Providers should be alert to the possibility of elder abuse and routinely ask all elderly patients about abuse, even in the absence of signs and symptoms of abuse.
- Providers should assess the needs of the caregiver and offer support.
- Providers should hospitalize elderly patients who are in immediate danger, or implement a care plan that prevents them from having any contact with the suspected abuser, which may involve being removed from the home. If the patient is not in imminent danger, assistance may be provided to the caregiver. Preserve the family unit whenever possible.
- The wishes of a competent elderly patient are required to be respected, even if the patient is not willing to accept interventions.
- In most states, emergency physicians are mandated to report cases of known or suspected elder abuse to Adult Protective Services.
- Providers should use the diagnostic term "Adult Maltreatment" in cases of suspected or confirmed elder abuse or neglect. The use of this ICD diagnosis may facilitate hospitalization, if necessary, and will improve the accuracy of clinical prevalence data.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Resident Population by Sex and Age: 1980 to 2009. In: *Statistical Abstract of the United States: 2011*. Washington, DC: Population Division, U.S. Census Bureau; 2011. Available at www.census.gov/compendia/statab/2011/tables/11s0007.pdf. Accessed July 11, 2011.
2. Resident Population Projections by Sex and Age: 2010 to 2050. In: *Statistical Abstract of the United States: 2011*. Washington, DC: Population Division, U.S. Census Bureau; 2011. Available at www.census.gov/compendia/statab/2011/tables/11s0008.pdf. Accessed July 11, 2011.
3. Rokos E, Wilber S: The effect of future demographic changes on emergency medicine. *Ann Emerg Med* 2006; 48:65.
4. Samaras N, Chevalley T, Samaras D, Gold G: Older patient in the emergency department: A review. *Ann Emerg Med* 2010; 56:261-269.
5. *World Report on Violence and Health*. Geneva: World Health Organization (WHO); 2002.
6. Lachs M, et al: ED use by older victims of family violence. *Ann Emerg Med* 1997; 30:448-454.
7. Jones J, Veenstra T, Seamon J, Krohmer J: Elder mistreatment: National survey of emergency physicians. *Ann Emerg Med* 1997; 30:473-479.
8. Bonnie RJ, Wallace RB, eds. Panel to Review Risk and Prevalence of Elder Abuse and Neglect, National Research Council: *Elder Mistreatment: Abuse, Neglect, and Exploitation in an Aging America*. Washington, DC: The National Academies Press; 2003.
9. National Center on Elder Abuse: *The National Elder Abuse Incidence Study: Final Report*. Washington, DC: U.S. Department of Health and Human Services; 1998.
10. Acierno R, et al: Prevalence and correlates of emotional, physical, sexual, and financial abuse and potential neglect in the United States: The National Elder Mistreatment Study. *Am J Public Health* 2010; 100:292-297.
11. Cooper C, Selwood A, Livingston G: The prevalence of elder abuse and neglect: A systematic review. *Age Aging* 2008; 37:151-160.
12. Pillemer K, Finkelhor D: The prevalence of elder abuse: A random sample survey. *Gerontologist* 1998; 28:51.
13. Tatara T: *Types of Elder Abuse in Domestic Settings*. Washington, DC: National Center on Elder Abuse (NCEA); 1999.
14. Teaster P: *A 2004 Survey of State Adult Protective Services: Abuse of Adults 60 Years of Age and Older*. Washington, DC: National Center on Elder Abuse (NCEA); 2006.
15. American College of Emergency Physicians (ACEP): Elderly abandonment survey: The abandonment of the elderly in the emergency department. *Frontlines* Fall, 1992.
16. Price T, King P, Dillard R, Bulot J: Elder financial exploitation: Implications for future policy and research in elder mistreatment. *West J Emerg Med* 2011; 12:354-356.
17. Jones J, Holstege C, Holstege H: Elder abuse and neglect: Understanding the causes and potential risk factors. *Ann Emerg Med* 1997; 15:579-583.
18. Friedman L, Avila S, Tanouye K, Joseph K: A case-control study of severe physical abuse of older adults. *J Am Geriatr Soc* 2010; 59:417-422.
19. Krienert JL, Walsh JA, Turner M: Elderly in America: A descriptive study of elder abuse examining National Incident-Based Reporting System (NIBRS) data, 2000-2005. *J Elder Abuse Negl* 2009; 21:325-345.
20. Strange G, Chen E, Sanders A: Use of emergency departments by elderly patients: Projections from a multicenter data base. *Ann Emerg Med* 1992; 21:819.
21. American Medical Association (AMA): *Diagnostic and Treatment Guidelines on Elder Abuse and Neglect*. Chicago, Ill: AMA; 1992.
22. Shugarman L, Fries B, Wolf R, Morris J: Identifying older people at risk of abuse during routine screening practices. *J Am Geriatr Soc* 2003; 51:24-31.
23. Fulmer T, Paveza G, Abraham I, Fairchild S: Elder neglect assessment in the emergency department. *J Emerg Nurs* 2000; 26:436-443.
24. Dyer C, Pavlik V, Murphy K, Hyman D: The high prevalence of depression and dementia in elder abuse or neglect. *J Am Geriatr Soc* 2000; 48:205-208.
25. Dong X, et al: Elder self-neglect and abuse and mortality risk in a community-dwelling population. *JAMA* 2009; 302:517-526.
26. Mosqueda L, Burnight K, Liao S: The life cycle of bruises in older adults. *J Am Geriatr Soc* 2005; 53:1339-1343.
27. Wiglesworth A, et al: Bruising as a marker of physical elder abuse. *J Am Geriatr Soc* 2009; 57:1191-1196.
28. *Forensic Medical Report: Elder and Dependent Adult Abuse and Neglect Examination*, CalEMA 2-602. Sacramento, Calif: California Emergency Management Agency; 2004.
29. Lachs M, Williams C, O'Brien S, Hurst L, Horwitz R: Older adults: An 11-year longitudinal study of adult protective service use. *Arch Intern Med* 1996;156:449-453.
30. Rudman W: *Coding and Documentation of Domestic Violence*. San Francisco: Futures Without Violence; 2000.
31. National Center for Health Statistics, Centers for Disease Control and Prevention (CDC): *International Classification of Diseases, Tenth Revision*. Atlanta: CDC; 2011.
32. Twomey MS, et al: The successes and challenges of seven multidisciplinary teams. *J Elder Abuse Negl* 2010; 22:291-305.
33. Schneider D, Mosqueda L, Falk E, Huba G: Elder abuse forensic centers. *J Elder Abuse Negl* 2010; 22:255-274.
34. Desmarais SL, Reeves KA: Gray, black, and blue: The state of research and intervention for intimate partner abuse among elders. *Behav Sci Law* 2007; 25:377-391.
35. American College of Emergency Physicians (ACEP): *Domestic Family Violence*. Irving, TX: ACEP, 2007. Available at http://www.acep.org/Clinical—Practice-Management/Domestic-Family-Violence. Accessed February 28, 2013.
36. Futures Without Violence: *Comply with the Joint Commission Standard PC.01.02.09 on Victims of Abuse*. Available at www.futureswithoutviolence.org/section/our_work/health/_health_material/_jcaho. Accessed July 28, 2011.
37. Jogerst G, Daly J, Brinig M, Dawson J, Schmuch G, Ingram J: Domestic elder abuse and the law. *Am J Public Health* 2003; 93:2131-2136.
38. American Bar Association Commission on Law and Aging: *Analysis of State Adult Protective Laws*. Chicago: American Bar Association; 2007.
39. Cooper C, Selwood A, Livingston G: Knowledge, detection, and reporting of abuse by health and social care professionals: A systematic review. *Am J Geriatr Psychiatry* 2009; 17:826-838.
40. Pillemer K, Moore D: Abuse of patients in nursing homes: Findings from a survey of staff. *Gerontologist* 1989; 29:314-320.
41. Post L, et al: Elder abuse in long-term care: Types, patterns, and risk factors. *Res Aging* 2010; 32:323-348.
42. Schiamberg LB, et al: Elder abuse in nursing homes: An ecological perspective. *J Elder Abuse Negl* 2011; 23:190-211.
43. Huber R, Borders K, Netting F, Nelson H: Data from long-term care ombudsman programs in six states: The implications of collecting resident demographics. *Gerontologist* 2001; 41:61-68.
44. Harrell E, Rand M: *Crime Against People with Disabilities, 2008*. Washington, DC: Bureau of Justice Statistics, Office of Justice Programs, U.S. Department of Justice; 2010.
45. Pillemer K, et al: Practitioners' views on elder mistreatment research priorities: Recommendations from a research-to-practice consensus conference. *J Elder Abuse Neglect* 2011; 23:115-126.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 70

ORAL MEDICINE

James T. Amsterdam

PERSPECTIVE AND PRINCIPLES OF DISEASE

Anatomy

The stomatognathic system comprises the musculoskeletal unit of the mandible, maxilla, and muscles of mastication; the dental unit (teeth); the attachment apparatus that anchors teeth; and other soft tissues of the oral cavity.

Musculoskeletal Unit

The mandible is formed by two rami that divide into a horizontal and an ascending portion. The horizontal portion forms the body of the mandible. The ascending ramus divides into the coronoid process anteriorly and the condylar process posteriorly. The temporomandibular articulation is unique because it consists of a bilateral joint, or diarthrosis, between the mandibular fossa and articular eminence of the mandible's temporal bone and condyle (Fig. 70-1). An intervening layer of fibrous connective tissue separates the articulating surfaces. A fibrous capsule also surrounds the temporomandibular joint (TMJ) and is reinforced by capsular ligaments that help limit mandibular range of motion. Functionally, when the mandible opens, the condyles move inferiorly and anteriorly down the eminence; during closure, the mandible moves posteriorly along the eminence and superiorly into the fossa.

The muscles of mastication are divided into the mandibular elevators (the supramandibular group) and depressors (the inframandibular group). The elevators, or *masseteric sling,* consist of the masseters, medial pterygoids, and temporalis. The posterosuperior movement of the condyle during mandibular closure is the result of bilateral, simultaneous movement of this group. The muscles involved in the opening or depression of the mandible include the lateral pterygoid, digastric, geniohyoid, and mylohyoid. Bilateral activity of these muscles results in opening; unilateral contraction causes the mandible to deviate to the opposite side. At rest the mandible assumes a position in which the mandibular and maxillary teeth are separated by a few millimeters of space. During functional activity, mandibular closure occurs as the action of the elevators predominates.

Teeth

The *pulp* is the tooth's center and serves as its neurovascular supply. The primary purpose of the pulp is to provide sensation and to produce dentin, a microtubular structure that hydrates and cushions the tooth during mastication. The part of the tooth normally visible in the oral cavity is the *coronal portion* covered with enamel, the hardest substance in the body. The part that is not normally visible and anchors the tooth is called the *root.* The root is covered with cementum, which is much softer than enamel and not designed for exposure in the oral cavity (Fig. 70-2).

The normal primary, or deciduous, dentition consists of 10 mandibular and 10 maxillary teeth. The primary dentition is important for mastication, cosmesis, and growth and development and functions as a physiologic space maintainer. Starting at the midline and moving posteriorly in any quadrant, the normal dentition consists of a central incisor, lateral incisor, canine, and two primary molars. The lower central incisor is the first tooth to erupt, at approximately 6 months of age; all primary teeth should be present by 3 years of age. If not, further investigation for developmental or endocrine abnormalities is warranted. The permanent dentition begins to erupt at approximately 5 to 6 years of age with the appearance of the first molar. Normally, the permanent dentition consists of 32 teeth: the central incisor, lateral incisor, canine, two premolars, and three molars. The third molars are the last to erupt, appearing at approximately 16 to 18 years of age, and are commonly called "wisdom teeth." The primary molars are replaced by the permanent premolars. There are many numbering systems for teeth, but none are universal. Perhaps the most common system for the permanent dentition consists of numbering the teeth from 1 to 32, starting with the upper right third molar (1) and moving to the upper left third molar (16), to the lower left third molar (17), and to the lower right third molar (32). The starting point for this numbering system can be recalled by the mnemonic "upright." Because there may be congenital absence of teeth or additional, supernumerary teeth, it is perhaps best for practitioners to describe anatomically which tooth is involved—for example, the upper left second premolar or the lower right second molar (Fig. 70-3).

Specific terminology is used to describe aspects of dentition. The *labial* or *buccal surface* faces outside the oral cavity; the *oral, palatal,* or *lingual surface* faces the tongue; the *medial surface* is toward the midline; and the *distal surface* is toward the ramus of the mandible. The *interproximal surface* refers to the contacting area of adjacent teeth, and the *occlusal surface* refers to the biting area. Finally, *apical* is in the direction of the root, whereas *coronal* is toward the crown of the tooth.

Periodontium

The periodontium consists of the gingival unit and the attachment apparatus. The gingiva is covered with keratinized, stratified, squamous epithelium and invests the tooth and alveolar bone. Apical to the gingiva is the alveolar mucosa, which is covered by nonkeratinized epithelium and is more subject to trauma. In healthy individuals the gingiva is attached firmly to the tooth by connective tissue fibers inserting into the cementum, extending coronally

www.ketabpezeshki.com 66485457-66963820

from the alveolar bone to the cementoenamel junction. A 2- to 3-mm cuff of tissue, the gingival sulcus, is bordered by the enamel surface of the tooth, the gingival epithelium, and the junctional epithelium at its base (see Fig. 70-2). In a disease state, such as in the presence of the loss of alveolar bone, this cuff increases in depth and is called a "pocket."

The *attachment apparatus* refers to the cementum on the tooth, the periodontal ligament, and the alveolar bone. The periodontal ligament is a fibrous structure that surrounds the root of the tooth. It is the key structure that anchors the tooth because it serves as a double periosteum that lays down cementum on the tooth on one side and alveolar bone on its other side.

Fascial Planes of the Head and Neck

The fascial planes of the head and neck are defined as potential spaces filled with loose areolar tissue that separates the layers of fascia of the head and neck. The deep cervical fascia is most important in a discussion of the extension of oral infection to the head and neck (Fig. 70-4). The deep cervical fascia consists of the superficial and investing layer, the pretracheal layer, the prevertebral layer, and the carotid sheath. The superficial and investing layer surrounds the entire neck; it splits as it attaches to the inferior border of the internal pterygoid muscles at the mandible's ascending ramus. This split forms the masticator space. This space communicates superiorly above the level of the zygomatic arch with the superficial and deep temporal pouches.

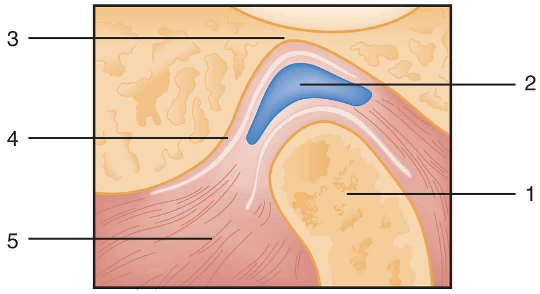


Figure 70-1. Temporomandibular joint structures in sagittal section: *1,* condyle; *2,* disk; *3,* mandibular (temporal) fossa; *4,* eminence; *5,* lateral pterygoid. (Redrawn and adapted from Weisgold AS, et al: Dental medicine. In Kaye D, Rose LF [eds]: Fundamentals of Internal Medicine, St Louis, Mosby; 1983.)

Other spaces of importance in the neck to which dental infection may spread include the *lateral pharyngeal* or *parapharyngeal space,* which is lateral to the pharynx and medial to the masticator space; the *retropharyngeal space,* which is between the deep cervical and prevertebral fascia; and the *prevertebral space,* which is posterior to the retropharyngeal space. The pharyngomaxillary space extends from the base of the skull to the hyoid bone and is especially important because it communicates with all deep spaces. The mandible itself is divided further by the *mylohyoid muscle,* which separates the superior sublingual and inferior submaxillary spaces.

Pathophysiology

Nontraumatic Dental Emergencies

Two pathophysiologic processes affect the dental health of most of the population: (1) dental caries and (2) periodontal disease. Variables related to both disease states include the oral environment, consisting of the teeth and attachment apparatus; the presence of local factors such as bacterial plaque, oral microflora, and substrate; and host states, including immunocompromising diseases and nutritional status. Factors such as water fluoridation, fluoride supplements, and plaque control techniques (e.g., flossing, brushing, orthodontic and dental surgical procedures) have significantly decreased the prevalence of dental caries and periodontal disease. However, the emergency department (ED) is the frequent source of care for dental emergencies, with toothache related to dental caries being the most common complaint. This occurs because of both lack of after-hours access for dental complaints and socioeconomic factors (self-pay and Medicaid). A recent study from Kansas City shows an increased volume from 2001 to 2006 from 13.1% up to 19%.[1]

Dental caries is a multifactorial disease involving a susceptible host, cariogenic oral flora, and a substrate. Caries results from the decalcification of enamel by the production of acids from bacteria. In the presence of saliva and a carbohydrate, cariogenic oral flora

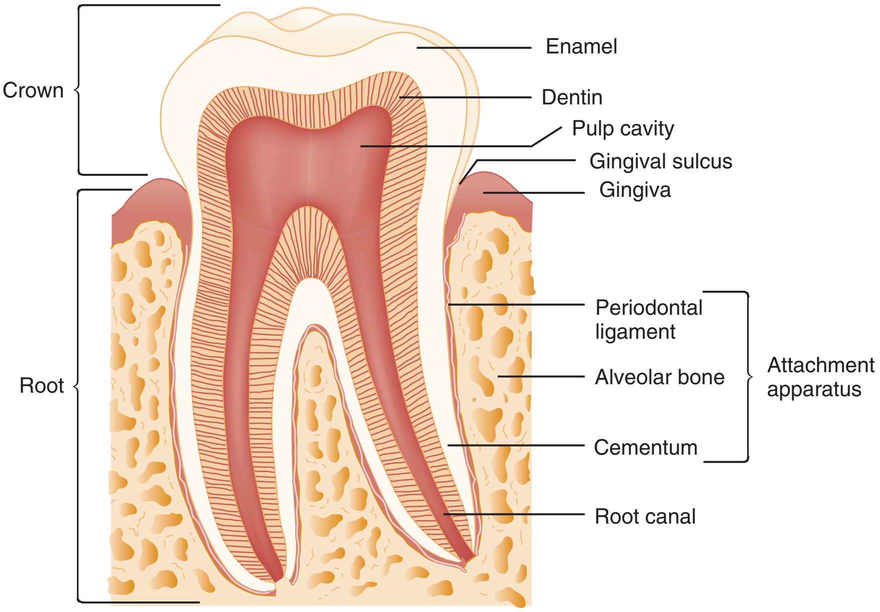


Figure 70-2. The dental anatomic unit and attachment apparatus.

www.ketabpezeshki.com 66485457-66963820

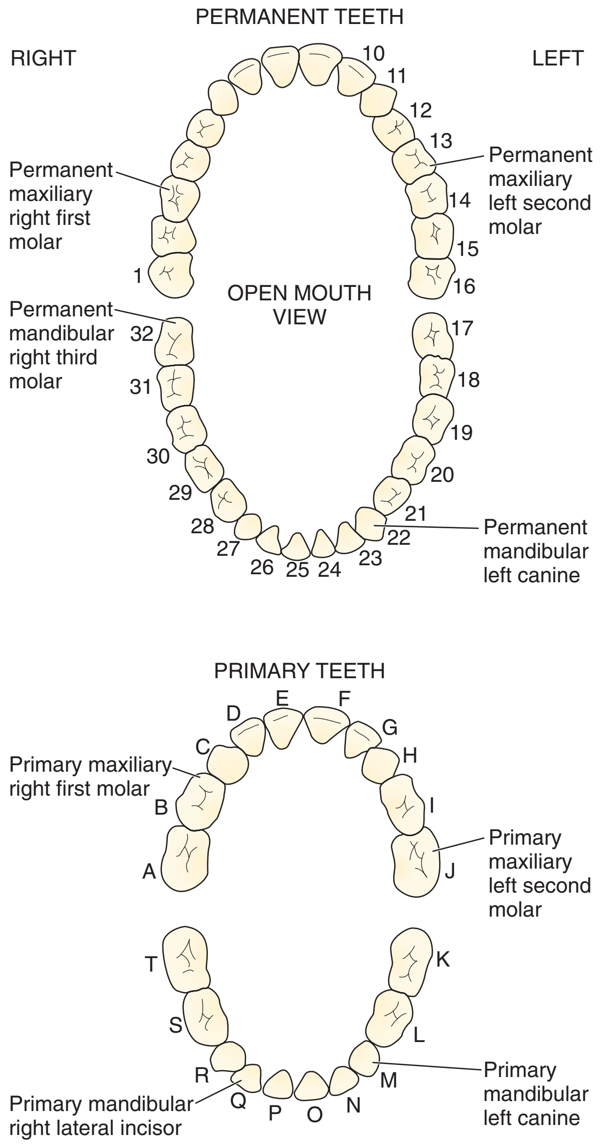


Figure 70-3. Identification of teeth, adult and child. Conventional numbering starts with the upper right third molar 1 to the upper left third molar 16; lower left third molar 17 to the lower right third molar 32. For the primary dentition, A to J and K to T. (From Roberts J, Hedges J: Clinical Procedures in Emergency Medicine. Philadelphia, Elsevier, 2010, Fig. 65-2, p 1219.)

are able to develop a matrix called *dental bacterial plaque.* The bacteria metabolize the carbohydrate to form acids that decalcify the enamel. After the carious process has invaded the enamel, the microporous dentin is able to transmit saliva, byproducts of the bacteria, and the bacteria themselves to the pulp. The pulp initially reacts with a hyperemic response, which continues to an inflammatory state, progressing to total degeneration and necrosis.

Pus leaks from the apex of the root and forms an abscess; this is termed a *periapical abscess.* Periapical abscesses are confined within the alveolar bone (Fig. 70-5). The abscess may break through the cortical plate of either the mandible or the maxilla and spread subperiosteally. Subperiosteal extensions are generally well confined anatomically by muscle attachments; however, if the muscle attachments are violated, either during a surgical procedure or by the natural extension of an infective process, the bacteria can gain access to the fascial planes of the head and neck. Infection extending to the submaxillary, sublingual, and submental spaces with elevation of the tongue is called *Ludwig's angina.* Ludwig's angina is one of the most serious mandibular infections because of its potential for airway obstruction.

Space infections also may involve the face. The canine space is bounded by the orbicularis oris, the levator labii superioris, and the buccinator; abscessed anterior maxillary teeth commonly involve this space. Infection can extend to the periorbital area. The most serious complication of such space infections is cavernous sinus thrombosis resulting from contamination of the (valveless) facial venous system. The buccal space is superficial to the buccinator and limited by the anterior border of the masseter; maxillary molar infection commonly spreads to this space. The mental space is located at the anterior table of the mandible and often is infected by abscessed lower anterior teeth.

CLINICAL FEATURES

Examination of the Oral Cavity

The examiner should wear eye protection, a mask, and gloves in compliance with universal precautions when examining the oral cavity. Ideally the patient should be placed in a dental or ear, nose, and throat chair or on a cart at a 45-degree angle. Because pediatric patients are unlikely to cooperate with the examination, the following technique is used by some experienced practitioners. The child sits in the parent's lap, or the child is first placed in the parent's lap facing the parent. The examiner then sits in front of the parent. While the parent gently restrains the child's arms and legs, the emergency physician can lean the child backward and lock the child's head between the physician's legs.[2]

An overhead examination light, headlight, or flashlight can be used for illumination. Other ancillary aids include a tongue depressor, 2 × 2-inch gauze, and possibly a dental mirror. Fogging of the mirror may be prevented by warming it under hot water or moistening it with the patient's saliva.

Examination of the oral cavity should be systematic, beginning with the soft tissues and including the tongue. The base of the tongue is examined for lesions, and Wharton's duct is milked. Stensen's duct, opposite the maxillary molars, should be examined on each side. The teeth should be examined next. Percussing a tooth with a tongue blade or the handle of a mirror is a good way to elicit tenderness.

Radiographic evaluation of teeth is best accomplished with dental (periapical) films. These films are generally not available in the ED, however. A panoramic radiograph is a useful alternative (see Fig. 70-5).

Diagnostic Imaging

Radiographic evaluation of teeth is ideally accomplished using dental (periapical) films, but these films are generally not available in the ED. More commonly, the panoramic radiograph is a useful alternative if imaging is felt to be required (see Fig. 70-5). The diagnosis and treatment of a dental abscess, for example, can be determined on the basis of clinical examination alone. A recent study compared the use of ED bedside ultrasound with the use of a panoramic radiograph. The sensitivity and specificity of the ultrasound were 92% and 100%, respectively. The advantage of the ultrasound is the lack of ionizing radiation; in addition, it assists in the determination of the presence of pus for incision and drainage.[3] Computed tomography (CT) is used primarily when there is concern for deep space abscesses.

Dental Caries

Dental caries is the most common cause of pain of odontogenic origin. The patient may give a variable history of a sudden or gradual onset of a sharp to dull, throbbing pain. In most cases

www.ketabpezeshki.com 66485457-66963820

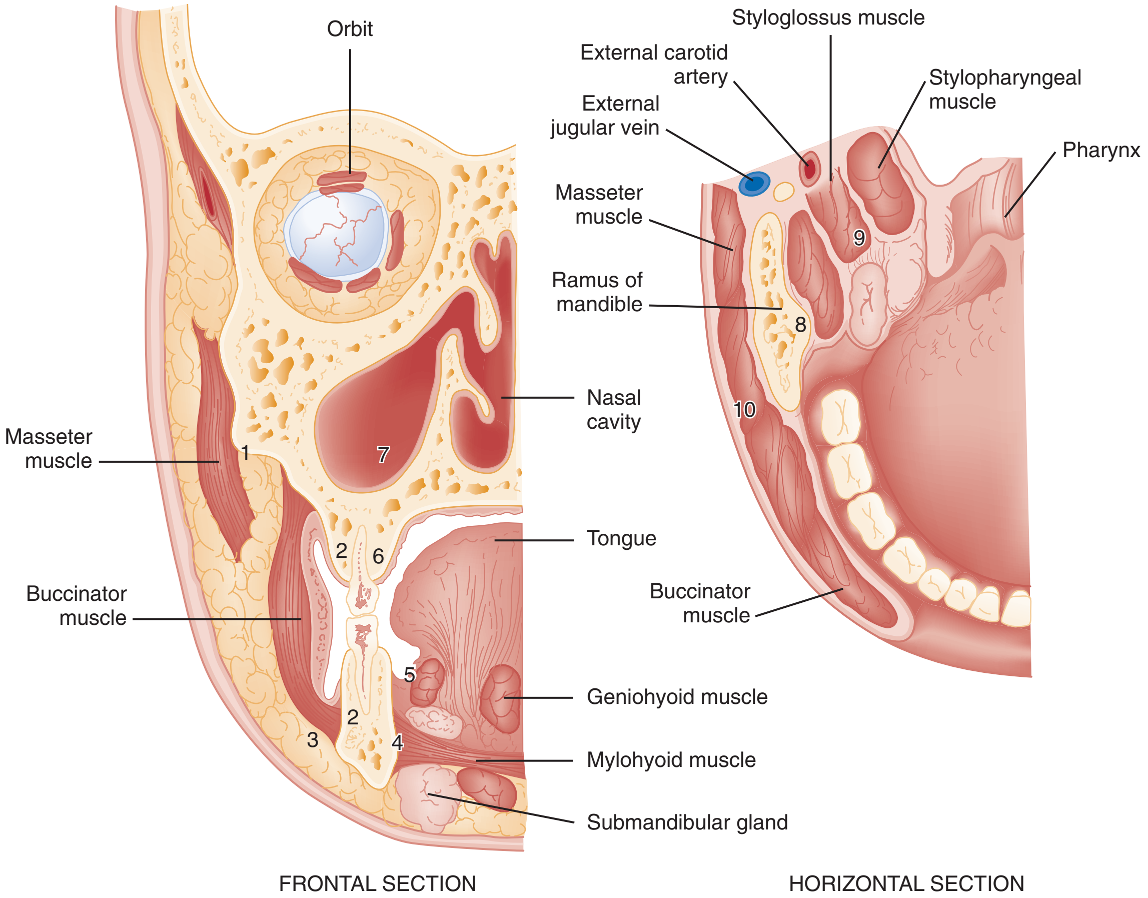


Figure 70-4. Natural progression of dental infection. The pathways by which such infections may travel are *1,* postzygomatic (from canine fossa in cuspid and bicuspid region; pterygomaxillary fossa communicates from rear); *2,* vestibular; *3,* facial; *4,* submandibular; *5,* sublingual; *6,* palatal; *7,* antral; *8,* pterygomandibular; *9,* parapharyngeal; and *10,* masseteric. (Adapated from Rose LF, Hendler BH, Amsterdam JT: Temporomandibular disorders and odontic infections. Consultant 22:125, 1982.)

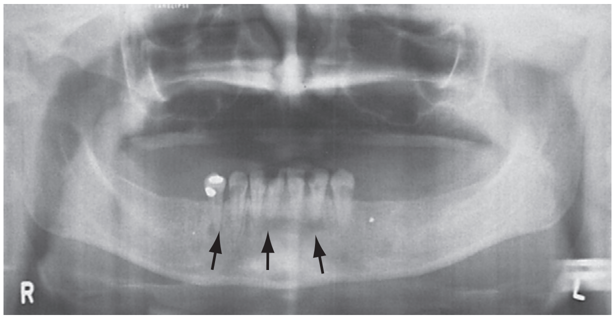


Figure 70-5. Periapical abscesses *(arrows)* as seen on panorex film.

the patient can indicate the specific tooth involved, but at times the pain may be generalized. Early pulpitis is sensitive to changes in temperature and aggravated by lying down; more advanced pulpitis is worsened by any stimulus, including air. Pain may be referred to the ear, temple, eye, neck, and rarely the opposite jaw.

Physical examination may reveal a grossly decayed tooth; however, if the carious process is between teeth (interproximal) or did not result in destruction of the outer table of enamel, the offending tooth may not be obvious. Localization of the involved tooth may be accomplished by percussing the teeth with a tongue blade or by having the patient bite on a tongue blade. Exquisite pain to percussion suggests an underlying periapical abscess, especially if the tooth is not sensitive to hot or cold (pulpal demise).

Treatment

Palliative management is indicated for most odontalgia. Systemic analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or synthetic opioid agents, are indicated. In a meta-analysis of 11 studies comparing flurbiprofen, 65 to 70% of patients experienced 50% pain relief compared with 25 to 30% with placebo; this was similar to findings with comparable NSAIDs, and patients had similar need for rescue pain control at 6 hours.[4] Although NSAIDs should be sufficient for most pain resulting from carious teeth, a therapeutic dental block may offer immediate relief. Synthetic opioids also are useful and are indicated in some cases but are generally not recommended in chronically carious teeth without an acute process.[5] A limited quantity of analgesics should be dispensed, which encourages follow-up with a general dentist.

Simple Dental Abscess

Patients with dental pain should be examined carefully for swelling caused by abscessed teeth. A periapical abscess or a localized swelling of the gingiva adjacent to the apex of the tooth (called a *parulis*) may cause pain from distention of the tissues. More commonly, fluctuant abscesses are a result of either periodontal

www.ketabpezeshki.com 66485457-66963820

abscesses or subperiosteal abscesses from a periapical abscess that has eroded through the bony cortex.

Treatment

Dental abscesses are treated with a conservative incision and drainage (involving blunt dissection with a mosquito hemostat). The gingiva and tooth are anesthetized by apical nerve block or block of the major nerve supplying the area (e.g., superior alveolar, inferior alveolar) as long as this can be accomplished without the needle passing through inflamed or infected tissue, or the gingiva is anesthetized superficially with 2% lidocaine with 1:100,000 epinephrine. A stab incision is made toward the alveolar bone and extended through the periosteum; blunt dissection is carried out with a mosquito hemostat. Unlike with other abscess drainage, it is unnecessary to open the abscess from end to end—such a large incision exposes too much alveolar bone. The simple stab incision is sufficient. The cavity is irrigated, and, assuming there is sufficient space, a Penrose or iodoform drain is placed and secured with a No. 4-0 suture.

Standard practice for years included starting the patient on phenoxymethylpenicillin (penicillin V) 250 mg four times daily or doxycycline 100 mg bid for 10 days and warm saline rinses and referring him or her to an oral maxillofacial surgeon or general dentist. Drains are removed in 24 to 48 hours, and antibiotics are continued for 7 to 10 days.[5] However, recent reviews have questioned the need for routine prescribing of antibiotics if sufficient drainage of pus has been achieved.[6,7]

Spread of Infection to the Head and Neck

Figure 70-6. Extensive spread of infection of odontogenic origin involving masseteric, sublingual, submental, and submandibular spaces with extension to mediastinum. **A,** Preoperative. **B,** Postoperative. Note drainage from mediastinum. (From Guernsey LH: Practical problem solving in oral surgery. In Cohen DW [ed]: Continuing Dental Education, vol 2, suppl 10. Philadelphia, University of Pennsylvania School of Dental Medicine, 1979.)

The presence of cellulitis or swelling in the contiguous spaces of the head and neck indicates the spread of a localized infection. In the early stages of such an infection, the upper half of the face is generally involved, with extension of infection from maxillary teeth; cellulitis from mandibular teeth generally involves extension to the lower half of the face and the neck (Fig. 70-6). More advanced infections may extend into any of the fascial planes of the head and neck down to the mediastinum. In the nondebilitated host, untreated dental infections tend to localize and drain spontaneously and extraorally. In the presence of a compromised host or aggressive microorganisms, spread into the fascial planes is more common, with a potential for greater morbidity and mortality. General indications for admission include suggested spread of infection to fascial planes, high fever, toxic appearance, trismus, and an immunocompromised host.

The potential sequelae of sepsis and airway obstruction must be appreciated. CT of the head and neck can be useful if the diagnosis is in doubt. Airway management should be undertaken when indicated, particularly if signs or symptoms of impending airway obstruction are present or developing (altered voice, drooling, stridor). The intubation should be approached as a difficult airway, as outlined in Chapter 1. An ear, nose, and throat specialist or oral maxillofacial surgeon should be consulted for ongoing management, including determination of the site of the initial focus so that pus can be evacuated.

Fever is common as with any infection. Any irritation of the internal pterygoid or masseter muscles results in trismus. Trismus is the inability to open the mouth because of involuntary muscle spasm. Trismus limits visualization of the pharynx and may make diagnosis of lateral or retropharyngeal space involvement difficult. Trismus is muscular in origin, not a result of impaired or augmented neuromuscular transmission, and so is often minimally improved or not improved at all after administration of a neuromuscular blocking agent (e.g., succinylcholine) for intubation, especially if the trismus is caused by localized swelling (vs. pain and spasm). Intubation in all patients with trismus is presumed to be difficult. Preparations should be made to perform a fiberoptic intubation or to establish a surgical airway.[8] Difficulty swallowing or handling secretions suggests the possibility of retropharyngeal or parapharyngeal infection. Respiratory distress may be apparent, or the airway may occlude rapidly after a period of minimal signs of impending obstruction.

Spread of mandibular dental infection frequently results in a cellulitis called *Ludwig's angina,* a bilateral, boardlike swelling involving the submandibular, submental, and sublingual spaces with elevation of the tongue. The most serious immediate sequela is airway obstruction. A characteristic brawny induration is present; there is no fluctuance for incision and drainage. Hemolytic *Streptococcus* is most commonly responsible for the infection, although a mixed staphylococcal-streptococcal flora is common, and both may lead to an overgrowth of anaerobic gas-producing organisms, including *Bacteroides fragilis.* Treatment consists of antibiotics and airway management. Although oral intubation can

www.ketabpezeshki.com 66485457-66963820

be attempted, an "awake" technique is recommended (see Chapter 1) because inability to displace the tongue into the submandibular space with a laryngoscope may make oral intubation impossible; fiberoptic nasopharyngoscopy is an option progressing to cricothyrotomy. In a study of 10 cases of Ludwig's angina requiring surgical decompression, after inhalational anesthesia, the vocal cords were visualized in 9 of the 10 patients. One patient required tracheostomy.

High-dose antibiotic therapy, such as 24 million U of intravenous penicillin daily divided every 4 hours plus metronidazole 1 g intravenously (IV), followed by 500 mg IV q6h, is necessary to achieve good tissue penetration and to cover anaerobes (most commonly *B. fragilis* infections). Clindamycin 900 mg q6h also is effective for a penicillin-allergic patient. If antibiotic therapy is not helpful, surgery is performed to eliminate causative factors, to explore for pockets of pus, and/or to place drains. A CT scan can help to compartmentalize infection and guide the surgical approach.

Figure 70-7. Acute necrotizing ulcerative gingivitis involving lower anterior teeth.

Periodontal Disease

Periodontal disease represents a continuum of pathology. Early periodontal disease is manifested by inflammation of the gingiva, termed *gingivitis*. Gingivitis is generally the result of an inflammatory response to an irritant, such as dental bacterial plaque and calculus. With extension of inflammation, alveolar bone is ultimately lost, a condition termed *periodontitis*. A physiologic space from the crest of the alveolar bone to the base of the junctional epithelium is maintained for the insertion of gingival fibers into cementum. In response to a loss of alveolar bone, the gingiva migrates down the root of the tooth, a condition termed *gingival resorption*. This is often accompanied by formation of gingival pockets. Advanced periodontitis results from a continuation of this process and causes marked mobility of the teeth and eventual loss as the attachment apparatus is destroyed.

Space infections of the head and neck occasionally result from periodontal disease. The combination of periodontal lesions and resultant pulpal pathology can create periapical abscesses with the same sequelae as those caused by dental caries alone.

Gingivitis and periodontitis in themselves rarely cause a patient to come to the ED, unless there is sudden alarm at seeing blood on a toothbrush or the realization that certain teeth are loose. Occasionally, a patient reports sensitive teeth. The patient can be advised to improve home care and see a dentist as soon as possible.

Treatment

More commonly, a patient experiences pain from a periodontal abscess or swelling of the gingiva when food or pus becomes trapped in a "pocket." In the dental office a periodontal abscess is treated with curettage to establish drainage. (ED management is covered earlier in the discussion of simple dental abscess.) Use of doxycycline 100 mg bid in patients older than 8 years is preferable because it provides better coverage for the gram-negative and anaerobic organisms found in the gingival pocket. The patient should be referred to the general dentist or periodontist for further treatment.

Acute Necrotizing Ulcerative Gingivitis

In contrast to gingivitis, in which the gingiva becomes inflamed in response to an irritant such as bacterial plaque but is not invaded by bacteria, acute necrotizing ulcerative gingivitis (ANUG) is a periodontal lesion in which bacteria actually invade non-necrotic tissue. ANUG lesions commonly are accompanied by systemic manifestations of fever, malaise, and regional lymphadenopathy. ANUG is characterized by painful edematous interdental papillae. The normally pointed interdental papillae are blunted and ulcerated. A gray pseudomembrane covers the tissue and leaves a bleeding surface when removed. The lesions can involve any part of the gingiva but are more common in the anterior incisor and posterior molar regions. The patient develops pain, a metallic taste, and foul breath (Fig. 70-7).

Gingival crevices in ANUG show a predominance of fusobacteria and spirochetes. Electron microscopy reveals a layering pattern showing fusobacteria in superficial layers with spirochetes invading in deeper layers. Other necrotizing ulcerative oral diseases, such as Vincent's angina (extension of ANUG to the fauces and tonsils), cancrum oris (extension of ANUG to the lips and buccal mucosa, eroding through the teeth), and some pulmonary abscesses, also are caused by fusospirochetes. Because ANUG results from an overgrowth of bacteria normally present in the gingival crevice, immunologic factors probably contribute to the disease. ANUG has been associated with immunocompromised hosts, fatigue, local trauma, emotional stress, and smoking.

Treatment

ANUG treatment consists of prescribing warm saline rinses; systemic analgesics so that the patient can improve oral hygiene; and systemic antibiotics, such as penicillin or tetracycline. Topical local anesthetics, such as viscous lidocaine, may provide some relief. Antibiotics (penicillin VK 250 mg four times a day or doxycycline 100 mg bid for 10 days) provide dramatic relief within 24 hours, as do dilute (3%) hydrogen peroxide rinses. Although the patient feels better, he or she should be advised to see a general dentist or periodontist for follow-up (this should be documented on the chart). The soft tissue and alveolar bone destruction from ANUG predisposes the patient to further periodontal disease; corrective procedures are necessary to create an environment conducive to maintaining periodontal health.

Oral Pain

Although dental caries is the most common source of oral pain, the following disease entities also may cause oral or facial pain.

Root Canal Pain

Endodontic or root canal therapy involves opening the pulp chamber of the tooth, removing pulp tissue from the chamber and the root portion of the tooth to the apex, irrigating and effectively sterilizing the canal, and sealing the pulp chamber to prevent

www.ketabpezeshki.com 66485457-66963820

ingress of saliva and contamination. After surgery the patient may experience exquisite pain caused by irritation beyond the apex of the tooth from instrumentation or from the buildup of gas from the irrigation solutions. Swelling may cause the tooth to be elevated slightly out of the socket so that premature contact during chewing causes extreme pain. These patients may have no relief with either systemic analgesics or anesthetic nerve blocks, presumably because of the sensation of intense pressure.[9] Treatment may consist of opening the canal to allow the gas or fluid to escape and of occlusal adjustment to take the tooth out of contact; the patient's general dentist or endodontist may have to be contacted.

Cracked Tooth and Split Root Syndromes

Patients with cracked teeth or a split root may report having a toothache. Pain occurs primarily with chewing or forced closure. The patient may have had an extensive dental restoration or previous endodontic therapy or may have a history of having received an upward blow to the jaw. In the ED the diagnosis is made from the history and from having the patient bite on a piece of wood. In the dental office the diagnosis is made by removing a restoration and inspecting the cavity floor. Management is similar to that for carious teeth, including symptomatic pain medication and referral back to the dentist to consider possible causes.

Maxillary Sinusitis

Dental pain often is referred to the area of the sinuses; similarly, congested or inflamed sinuses in the proximity of the apices of the maxillary teeth may cause apparent odontogenic pain. The patient may report throbbing pain unrelated to changes in temperature. On examination, there is no apparent dental cause. There may be tenderness over the maxillary sinuses or periorbital regions. Nasal discharge may be present. The panorex film can screen for dental and sinus pathology, although a CT scan would show sinus pathology more clearly.[10]

Atypical Odontalgia

Atypical odontalgia describes dental pain for which there is no dental cause. The patient may have a history of multiple dental procedures with no relief. The pain is chronic and occurs spontaneously. Percussion may elicit pain, and there may be thermal sensitivity as if a vital tooth were present. If paroxysmal pain of neuropathic origin is excluded, atypical odontalgia can be entertained. The patient should be referred to the dentist for evaluation of more occult reasons for dental pain, for example, "cracked-tooth" syndrome.

Postextraction Pain

Pain after an extraction (i.e., immediate periosteitis) is common for approximately 24 hours. Systemic analgesics are usually adequate for pain control. NSAIDs (e.g., ibuprofen 600 mg q6h) are effective analgesics and are commonly prescribed.[11]

A much more painful condition, acute alveolar osteitis or dry socket, may occur approximately 3 to 4 days after an extraction. The patient has a pain-free interval followed by sudden onset of excruciating pain associated with a foul odor. The pathophysiology involves premature loss of the healing blood clot from the socket, with a localized infection and inflammation of the of the bone.[12]

Treatment of a dry socket consists of an anesthetic nerve block, gentle irrigation of the socket, and packing of the socket with iodoform gauze saturated with a medicated dental paste, such as Sed-A-Dent, or barely dampened with eugenol (oil of cloves). The packing affords almost immediate relief, although it is recognized to delay natural wound healing.[12] Patients with a dry socket require daily follow-up for pack changes until sufficient natural wound healing has occurred. Most dentists include oral antibiotic (e.g., penicillin, clindamycin, or doxycycline) coverage, analgesics, and NSAIDs with this regimen until the condition resolves. However, there is no evidence to support this as a routine practice, and the use of antibiotics postoperatively after third molar tooth extraction is controversial.

Paroxysmal Pain of Neuropathic Origin

Paroxysmal pain of neuropathic origin is most commonly caused by tic douloureux, or trigeminal neuralgia. The diagnosis is made principally on the basis of history. The patient reports paroxysmal episodes of an excruciating, lancinating pain, also described as recurrent bursts of an electric shock. The pain follows the anatomic distribution of the involved division of the fifth cranial nerve. On physical examination the pain sometimes can be elicited by tapping specific areas of the face (the so-called "trigger zones") in the region of the distribution of the nerve involved. Medical management for tic douloureux consists of carbamazepine, starting at 100 mg bid, although some patients may be afforded no relief.[13] In a study of 61 patients, a positive response to carbamazepine in the presence of a distinct trigger zone was a strong indicator of trigeminal neuralgia.[14]

When medical management fails and the patient is in significant distress, he or she may be a candidate for neurosurgical procedures that ablate the nerve. Close follow-up is required if treatment for tic douloureux is initiated in the ED. Patients taking carbamazepine require adjustment of the dosage to achieve therapeutic effect and require monitoring for toxicity. Patients in whom the diagnosis is considered need additional evaluation to exclude the presence of multiple sclerosis, cerebellopontine angle tumor, acoustic neuroma, or nasopharyngeal carcinoma. Patients with this condition commonly require a full dental, otolaryngologic, and neurologic evaluation to investigate correctable causes.

Other causes of orofacial pain of the paroxysmal type include headaches (see Chapter 16). Vascular headaches, such as migraine and cluster headaches, may have facial pain as their principal manifestation. Rheumatologic disorders, such as giant cell arteritis and polymyalgia rheumatica in the elderly, can result in facial pain. Dull pain in the lower jaw is not always of dental origin. Myocardial ischemia may cause isolated jaw pain.

Temporomandibular Myofascial Pain Dysfunction Syndrome

The TMJ is a bilateral joint subject to almost continuous use. It is extremely sensitive to proprioceptive stimuli and can react to interferences in occlusion of only fractions of a millimeter. TMJ syndrome results from anatomic disharmony (see Fig. 70-1) and occlusal disturbances. The condition is aggravated by trauma, clenching of the teeth, or bruxism. Patients report pain in the region of the TMJ, usually unilateral. The pain is dull, worsens during the course of a day, and, in extreme cases, may result in trismus with palpable masseter and internal pterygoid spasm.[15]

TMJ radiographs are not helpful. Treatment consists of the external application of heat for 15 minutes four to six times per day, soft diet, analgesics including NSAIDs, and a muscle relaxant, such as diazepam 2 to 10 mg up to four times per day.[16] Patients should be referred to a dentist specializing in TMJ disorders, such as a periodontist or a periodontal prosthodontist. Insufficient evidence exists for or against the current treatment at this stage, which consists of continued physiotherapy, bite appliances that put the musculature at rest, and occlusal adjustment.[17,18] Although

www.ketabpezeshki.com 66485457-66963820

certain anatomic abnormalities are amenable to surgical correction, most oral maxillofacial surgeons consider surgery only for the most intractable cases.[19]

Pericoronitis

Pain from the eruption of the third molar teeth (i.e., wisdom teeth) in an adult is common. Trapped food and plaque cause the gingiva surrounding crowded, malerupted, or impacted third molar teeth to become inflamed and swollen. This condition is called *pericoronitis* and is extremely painful because of repeated trauma from the opposing third molar biting on tender tissues and from distention of retromolar tissue on opening of the mandible. Pericoronitis is treated locally with warm saline irrigation, with or without hydrogen peroxide rinses. The microbiology of pericoronitis is similar to that of other dentoalveolar infection and periodontitis. Antibiotics that are effective against viridans streptococci and oral anaerobes are prescribed.[20] Common options include penicillin VK 250 mg four times per day, doxycycline 100 mg bid for 10 days, or metronidazole for its anaerobic coverage. If fluctuant pus is present, incision and drainage should be performed, with care taken not to track the infection posteriorly or to dissect deeply into distorted tissues, possibly encountering the internal carotid artery. Definitive treatment involves removal of the opposing third molar tooth for immediate relief and removal of the involved third molar tooth after the infection is resolved. These patients should be referred to an oral maxillofacial surgeon.

Aphthous Stomatitis

Patients may report recurrent small oral mucosal ulcers. The ulcers are approximately 2 to 3 mm in size with a white center. The lesions tend to be tender but rarely become infected. Multiple ulcers that have coalesced can create an impressively large lesion. One third of the population may be affected by this condition, which is believed to be related to stress, nutrition, oral trauma, and hormonal causes. The condition is self-limiting, and treatment is symptomatic. There are numerous over-the-counter preparations that help with symptoms (hydrogen peroxide rinse; topical dental preparations such as benzocaine and an emollient gel; 50 : 50 mixture of diphenhydramine [Benadryl]; and Kaopectate or Maalox).[21] Prescription regimens, such as steroid-antibiotic ointment (Kenalog in Orabase) or sucralfate are also useful. A topical sulfuric acid phenolic, Debacterol, available only by prescription, is applied to the ulcer and appears to seal the ulcer and promote rapid healing. Ulcers that may appear similar to aphthous ulcers are those on the soft palate associated with hand-foot-and-mouth disease or lesions on the gingivae and tongue from herpetic stomatitis.[22]

Oral Manifestations of Systemic Disease

Although the oral manifestations of many systemic diseases are nonspecific, several diseases have distinct oral presentations. In certain instances, recognition of the oral signs aids in the specific diagnosis. In other disease states, the oral condition is a contributing factor to the overall pathophysiology.

Diabetes Mellitus

Oral manifestations of diabetes mellitus are associated primarily with periodontal lesions. Diabetic patients seem to be more susceptible to periodontitis. Acute gingival abscess and sessile or pedunculated gingival proliferations have been described as being caused by or intimately associated with diabetes. As with other systemic manifestations of diabetes, the degree of control of diabetes seems to correlate with its effects on the periodontium. Uncontrolled diabetes generally results in greater periodontal disease. Control of diabetes helps decrease periodontal severity, although irreversible damage, such as bone loss, may result.

Although the severity of periodontal disease in diabetic patients is a function of the response to local factors, such as plaque and calculus, there is also evidence to support the role of vascular changes and alterations in the role of polymorphonuclear leukocytes, monocytes, oral microflora, the patient's immune response, and genetic variables. Patients with diabetes who have advanced retinal changes also have been found to have more periodontal manifestations.

Maintenance of a healthy periodontium is important in a diabetic patient. Just as the degree of diabetic control affects the periodontium, so too does periodontal disease affect the degree of control. Patients with brittle diabetes or those subject to repeated episodes of ketoacidosis might be thrown out of control from a simple periodontal abscess. The presence of advanced periodontal disease in a young patient, especially in the absence of local factors, should lead one to exclude the diagnosis of diabetes. A sudden change from a healthy periodontium to a diseased state suggests a similar diagnosis in an adult. Human immunodeficiency virus (HIV) infection also should be ruled out.

Collagen Vascular Diseases

Systemic lupus erythematosus is the most common collagen vascular disease to have oral manifestations. Patients commonly have large ulcerated intraoral lesions with necrotic borders. The lesions are usually secondarily infected and painful (Fig. 70-8).

Scleroderma usually is recognized by the characteristic facies. The periodontal ligament may appear thickened on dental radiographs. Characteristic microscopic changes can be seen on gingival biopsy specimens. Rare entities, such as the midline lethal granuloma or Wegener's granulomatosis, manifest with large intraoral ulcerative lesions, usually involving the hard palate.

Granulomatous Diseases

Oral manifestations of granulomatous diseases are fairly rare today but are still seen. Tuberculosis may give rise to lesions of the tongue or tonsillar area. These lesions are confused most commonly with syphilitic ulcerations or infections caused by actinomycosis. A more common and benign entity is pyogenic granuloma, which is a proliferation of highly vascular connective tissue in response to an irritant. The lesions range from sessile to pedunculated and have a warty texture. Pyogenic granulomas in the oral

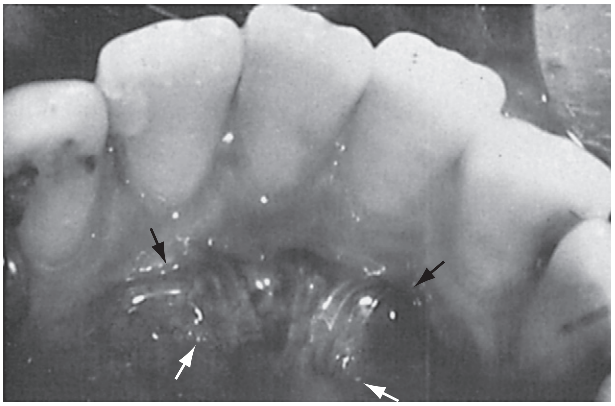


Figure 70-8. Lesion *(arrows)* secondary to systemic lupus erythematosus involving the floor of mouth.

www.ketabpezeshki.com 66485457-66963820

cavity are usually gingival in origin. They are especially common in pregnancy and are called *pregnancy tumors.* Pregnancy tumors generally resolve 2 to 3 months after delivery; tumors that do not resolve require surgical excision.

Blood Dyscrasias

The gingiva may be massively infiltrated by leukemic cells in acute leukemic states, especially acute granulocytic leukemia. The gingiva is edematous and bluish red and may cover the teeth. These gingivae are compromised and may allow for the ingress of bacteria, leading to sepsis. Chronic leukemic states have no specific gingival lesions, and leukemic states in remission are associated with normal gingiva. In addition to sepsis, gingival hemorrhage is a serious sequela. Gingival sequelae are more severe with underlying periodontal disease; during remissions, it is imperative to maintain good periodontal health. Acute hemorrhage is controlled with the application of gauze pressure and hemostatic agents, such as topical thrombin, absorbable gelatin powder, and oxidized regenerated cellulose.

Thrombocytopenic purpura commonly causes oral manifestations. Spontaneous gingival bleeding from minor trauma is characteristic. Acute hemorrhage is managed in a fashion similar to that discussed for acute leukemia. Less serious persistent oozing responds to treatment of the underlying state.

Drug-Induced Gingival Hyperplasias

Some degree of gingival hyperplasia is present in 40% of patients undergoing long-term phenytoin therapy. Younger patients seem to be affected more often than older patients. The degree of gingival hyperplasia does not seem to be related to dosage. The disease ranges from slight enlargements of the interdental papillae to massive enlargement of the gingiva, which covers the crowns of the teeth and may move the teeth. The risk of gingival hyperplasia has been shown to be two times higher in users of calcium channel blockers.[23] The hyperplastic tissue is subject to infection. The presence of local irritants seems to make the hyperplasia worse. Treatment of the condition includes removal of local irritants and surgical excision of the hyperplastic tissue; therefore referral to a periodontist is appropriate. If the causative agent is not discontinued, hyperplasia is likely to recur, although less severely if good oral hygiene is maintained.

TRAUMATIC DENTAL EMERGENCIES

Fractures of Teeth

The anterior teeth are commonly injured from falls or direct blows to the teeth. Forceful blows to the mandible directed superiorly may result in fractures of the premolars and molars caused by a wedgelike effect of the cusps of the mandibular teeth in the central fossae of the maxillary teeth. Many children have an anterior overbite, which makes this part of the dentition more prone to injury. Blunt trauma to the dentition may result in damage to the neurovascular supply to the tooth, bleeding within the tooth, fractures of the root or crown, loosening of the tooth, or actual expulsion of the tooth from its socket. A long-term sequela of blunt trauma or reimplantation of teeth is resorption of the root.[24] Fractures of the anterior teeth are managed based on the type of fracture, its relation to the pulp of the tooth, and the patient's age. Table 70-1 describes the classification of trauma to the teeth.

The simplest and most common dental fracture involves only the enamel portion of the tooth, leaving a chalky-white appearance. These injuries are usually minor unless a sharp portion of the tooth causes soft tissue trauma, in which case the sharp edge

Table 70-1 Classification of Tooth Fractures

Tooth Injuries	
Crown Fractures	
Enamel infraction	A crack or craze line in the enamel.
Uncomplicated crown fracture	Fracture of enamel and dentin only.
Complicated crown fracture	Fracture involving enamel and dentin with pulp exposure.
Root Fractures	
Crown-root fracture	Fracture through the crown and extending into the root (oblique or transverse).
Intra-alveolar root fracture	Fracture of the root within the alveolar bone (diagnosed with a periapical radiograph; tooth may be mobile on clinical examination.
Luxation Injuries	
Consussion	Blunt trauma to the tooth, but it does not change position.
Subluxation	Slight mobility but no significant displacement from the socket.
Intrusion	The tooth is displaced apically into the alveolus.
Extrusion	Tooth is displaced out of the socket but is still attached by periodontal ligament fibers to the alveolar bone.
Avulsion	The tooth has been completely dislodged out of the socket and has no attachment to the alveolar bone.

Adapted from Fuks AB, Camp J: Crown fractures: A practical approach for the clinician. Chapter 3 in Berman LH, Cohen S, Blanco L: A Clinical Guide to Dental Traumatology. St Louis, Mosby, 2007:4-5.

may be smoothed with an emery board. The patient or parents usually are concerned about the cosmetic deformity, but they can be reassured that the tooth can be restored to its natural appearance with the use of enamel-bonding plastic materials. Referral to the dentist is necessary but not urgent.

Fractures involving the dentin have an ivory-yellow appearance. The pulp continually lays down dentin throughout the life of the tooth in response to normal and noxious stimuli. In a child, the pulp is relatively large in size, and there is less dentin; the inverse is true in the adult. Because dentin is a microtubular tissue capable of allowing bacteria to percolate into the pulp chamber, fractures involving dentin are more serious in children and adolescents, as there is little dentin to protect the pulp after it is exposed to the oral cavity.

In younger patients the management of dentin fractures involves the immediate placement of a dressing of calcium hydroxide paste over the exposed dentin covered with dry foil, a metal band, or, more commonly, an enamel-bonded plastic. Early intervention may prevent contamination of the pulp and avoid the need for subsequent root canal treatment. A pediatric or general dentist should be notified as soon as possible. Exposed dentin may be exquisitely sensitive, so the patient should avoid extremes in temperature. In an adult, who has a greater thickness of dentin compared with pulpal tissue, there is less need for urgent referral to a dentist. A dressing can be placed on the tooth for comfort. Referral should be made to a dentist for the next working day.

Fractures of teeth resulting in pulp exposure are the most serious class of fractures of anterior teeth because the pulp chamber is immediately contaminated. Care should be taken to

www.ketabpezeshki.com 66485457-66963820

differentiate dentin exposure from the pulp. The tooth is wiped clean with a piece of gauze and examined for a pink blush or a drop of blood, indicating a pulpal exposure. There may be excruciating pain from exposure of the nerve, or the shock of the trauma may have disrupted the neurovascular supply at the apex of the tooth, eliminating most sensitivity. This injury is often accompanied by serious fractures of the tooth, possibly involving the entire crown or root.

Pulp exposures are true dental emergencies. In the primary dentition, exposure of the pulp can be treated by performing a pulpotomy, in which the pulp in the chamber is removed, the remaining tissue is mummified with formocresol and covered with a layer of calcium hydroxide, and the tooth is restored. In most cases, if there has been minimal contamination, the primary tooth lasts its natural lifetime. In an adult, the pulpotomy is not a successful procedure, and all pulpal tissue from the crown and root must be completely removed by means of a root canal, endodontic, treatment. Although management of pulp exposures is more urgent in a child, endodontic (root canal) therapy is less complicated and more successful in an adult if there is also a minimum of contamination; in the case of a pulpal exposure from a dental fracture, a general dentist, pedodontist, or endodontist should be notified immediately if possible, or the patient should be instructed to follow up the next working day. If no dentist is available, a piece of moist cotton can be placed over the exposed pulp and covered with a piece of dry foil or sealed with a temporary root canal sealant (e.g., Cavit). Although some authors have advocated removal of the exposed pulpal tissue by the emergency physician with a dental endodontic instrument called a *barbed broach,* this procedure is not recommended because this instrument breaks easily, even in the hands of a skilled endodontist. In cases of extreme pain, a dental anesthetic nerve block might be helpful.

Subluxed and Avulsed Teeth

Teeth that are loosened in their sockets as a result of a force are said to be *subluxed.* There may or may not be associated fractures. The diagnosis of subluxation can be made by gently tapping a tooth with two tongue blades. Any perceptible mobility is evidence of subluxation. A ring of blood may surround the gingival crevice. Minimally mobile teeth respond well to a soft diet for several days. Markedly mobile teeth require stabilization as soon as possible for 10 to 14 days. Teeth can be stabilized (generally by a dentist) by means of Erich arch bars, wire ligation, enamel bonding plastics, or a combination of modalities. Most of these techniques require an oral maxillofacial surgeon, hospital dentist, or pedodontist. They should be performed as soon as possible.

As a temporizing measure, the patient can bite gently on a piece of gauze, or the teeth can be stabilized for 24 to 48 hours with the application of a periodontal pack (e.g., Coe-Pak). A resin and catalyst paste are mixed together in equal quantities to a firm consistency and molded over the anterior and posterior aspects of the involved tooth and two or three adjacent teeth on each side. The patient is asked to close the mouth while the mixture hardens (Fig. 70-9). The patient is advised to avoid hot liquids, which would soften the pack; eat a liquid to soft diet; and see a dentist as soon as possible.

Avulsed teeth are completely torn from the socket and are a true dental emergency. If teeth are unaccounted for, the possibility of aspiration or entrapment in soft tissues should be considered. Management of recovered avulsed teeth depends on the age of the patient and the length of time for which the tooth has been absent from the oral cavity.[25] Avulsed primary teeth in a pediatric patient age 6 months to 6 years are not replaced in the socket. Reimplanted primary teeth ankylose or fuse to the bone, so although the dentofacial complex grows downward and forward, the reimplantation site does not. There also may be interference with the eruption of the permanent tooth. Cosmetic deformity results in either case.[26] Such patients should be referred to a pedodontist for consideration of a space maintainer or cosmetic appliance.

Avulsed permanent teeth require prompt intervention. When a tooth has been avulsed from its socket, the periodontal ligament fibers are torn; fragments remain attached both to the cementum on the root of the tooth and to the alveolar bone in the socket. Ideally, the best environment for an avulsed tooth is its socket, and it has been known since the mid-1960s that an avulsed tooth can be successfully replanted if it is returned to its socket within 30 minutes of the avulsion. A 1% chance of successful reimplantation is lost for every minute that the tooth is outside of its socket; however, there is often difficulty with immediate reimplantation. On-site personnel (parents, teachers, trainers, paramedics) may be unfamiliar or uncomfortable with tooth reimplantation. The tooth may be soiled, or the patient may be uncooperative. Occasionally, other, more serious life threats may preclude immediate reimplantation. Because of these factors, investigations were undertaken to find the ideal medium for transport and storage of an avulsed tooth.

The worst situation is to allow the tooth to be transported in a dry medium. Storage in plain water is not much better. Although saliva is a reasonable storage medium, milk is preferable because of its osmolarity and essential ion concentration of Ca^{2+} and Mg^{2+}.[27] The best storage and transport medium is Hank's solution, a balanced pH cell culture medium. This solution is commercially available as the Save-a-Tooth system (3M). Hank's solution can maintain the viability of the cells for 12 to 24 hours or more.[27] If the tooth has been avulsed for more than 30 minutes or has been allowed to dry, placement of the tooth in Hank's solution helps restore the periodontal ligament cells. With the Save-a-Tooth system, the tooth is simply dropped into the basket and the lid replaced. For removal, the lid is removed, the basket is lifted out of the solution, and the tooth is retrieved by tipping the basket over onto the padded lid.

If a call is received about an avulsed tooth, it first should be determined whether the tooth is permanent. If it is, the caller should be instructed to rinse the tooth off in saline or water and reimplant it immediately into the socket. If this cannot be performed for technical or emotional reasons, the patient should be instructed to place the tooth under his or her tongue or in the buccal pouch so that it is bathed in saliva. If the patient is too young, the tooth can be placed in the parent's mouth. If this is unacceptable to the parent or if there is concern about aspiration or swallowing of the tooth, it should be transported in a cup of milk. If milk is unavailable, saline should be used. Ideally, the tooth should be transported in Hank's solution.

When the patient arrives in the ED, the tooth should be reimplanted at the earliest opportunity. If this cannot be done, the tooth can be placed in Hank's solution or a Save-a-Tooth system (especially if avulsion occurred more than 30 minutes previously or if the patient has other life threats that are being managed). A recent study demonstrated that simple oral rehydration solution is as effective as Hanks solution for this purpose and may be more readily available in an ED.[28] If Hank's solution or oral rehydration solution is not available, the tooth is rinsed with saline, the socket is suctioned if necessary, and the tooth is immediately implanted. Local anesthesia may be necessary. The tooth should be manipulated only by the crown, if possible, so that the remaining periodontal ligament fibers are not damaged. Stabilization must be performed immediately, or the tooth will exfoliate. Stabilization is performed as described for markedly subluxated teeth (see Fig. 70-9). Other methods of stabilization with use of light-cured bonding resins are possible and, in a recent study, have been shown to be very satisfactory for the emergency physician if he or she has been trained to use them.[29] The status of tetanus immunization should be checked, and the patient should be treated according to the standard for a non–tetanus-prone wound (i.e.,

www.ketabpezeshki.com 66485457-66963820

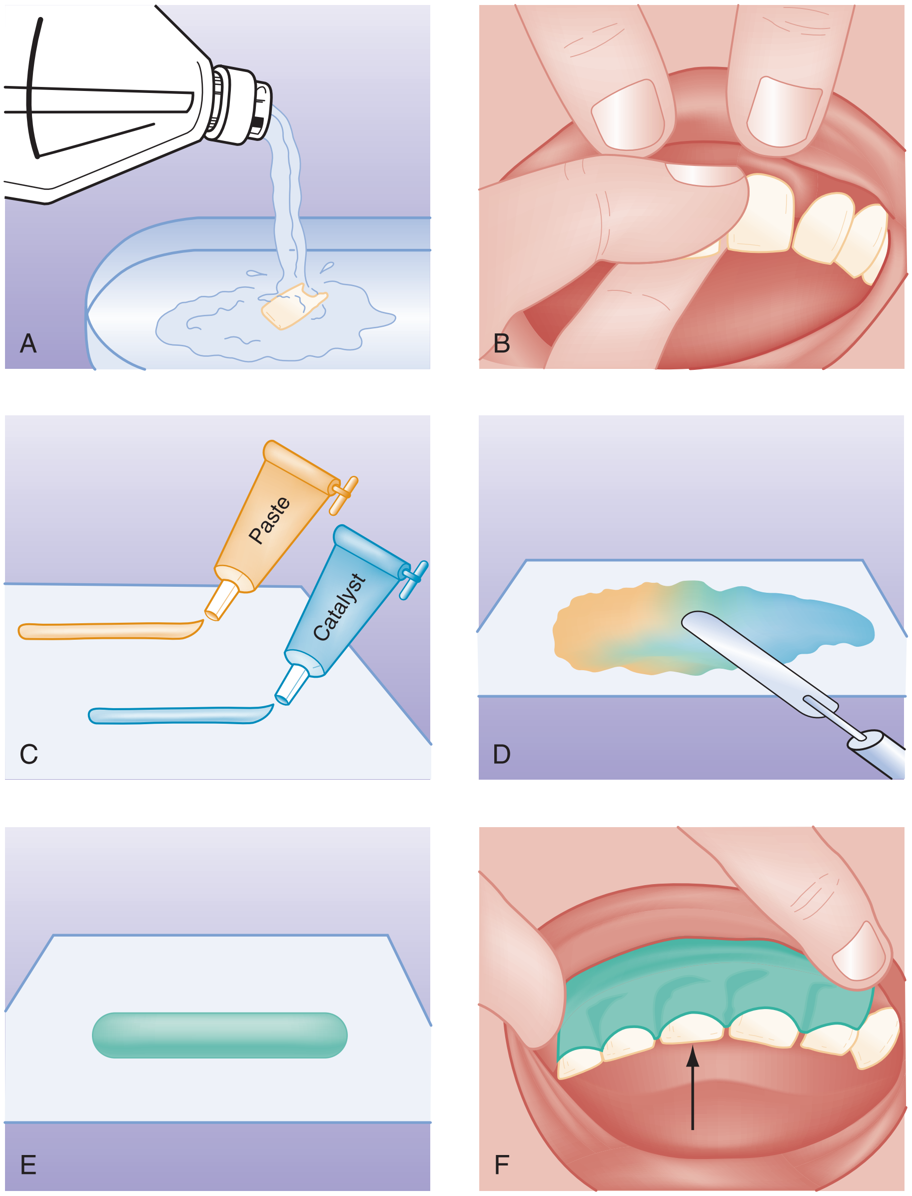


Figure 70-9. Reimplantation and stabilization of an avulsed tooth. **A,** Tooth is rinsed. **B,** Tooth is placed back into socket. **C** and **D,** Periodontal pack is mixed. **E,** Splint material is ready for application. **F,** Packing is molded over reimplanted tooth and two adjacent teeth to either side.

10-year immunization update). Although there is inconclusive evidence to support the practice, dentists typically place patients on phenoxymethylpenicillin (penicillin VK) 250 mg four times a day or doxycycline 100 mg bid in an effort to increase the likelihood of periodontal ligament healing.[30]

The patient is placed on a liquid diet for several days and advanced to a soft diet for 1 week. Stabilization is maintained for approximately 2 weeks, and the tooth is gradually brought into function to prevent ankylosis. Teeth that have been avulsed for longer than 30 minutes invariably require endodontic therapy owing to loss of pulp viability.[26,31] Although there may be concern about the anatomic orientation of the tooth or more confusion about which socket to use when several teeth are avulsed, each tooth should be placed into a socket with the best fit so that the tooth remains in a good physiologic environment. The dentist can make any necessary readjustments before final stabilization.

Alveolar Bone Fractures

Dental fractures and subluxated or avulsed teeth may be associated with fractures of the alveolus. Alveolar fractures may be apparent clinically from exposed pieces of bone or diagnosed radiographically. In massive facial trauma, care should be taken to conserve as much of the alveolar bone as possible, unless there is a great danger of aspiration. Indiscriminate loss of alveolar bone results in tremendous cosmetic deformity that is difficult to restore with prosthetic devices or leaves no foundation for a dental implant, thus necessitating autologous bone grafting procedures.[32]

An alveolar fracture requires 6 weeks of stabilization for adequate healing; if there is an associated subluxed or avulsed tooth, stabilization is maintained at the expense of possible ankylosis of the tooth. The loss of alveolar bone ultimately results in more cosmetic deformity for the patient. A permanently ankylosed tooth can remain functional for some time, and although it may be difficult for an oral and maxillofacial surgeon to remove, it can be reconstructed more easily than supporting alveolar bone. The dental materials, including local anesthesia supplies and the Save-a-Tooth system, are conveniently assembled in a commercial package called The Dental Box (Dental Box Co., Pittsburgh, Penn.).

Soft Tissue Injuries

Dentoalveolar trauma is commonly associated with soft tissue injuries of the lips, intraoral mucosa, and tongue. Wounds should

www.ketabpezeshki.com 66485457-66963820

be examined for debris and tooth fragments. As with any surgical wound, débridement and irrigation should be performed. Final closure of soft tissue injuries should await the initial management of fractured teeth or the procedures necessary for stabilizing teeth because manipulation of the soft tissues is required. Carefully placed sutures may be torn and have to be replaced in already compromised tissue if soft tissue closures are performed first.

Gaping intraoral lacerations tend to become ulcerated, secondarily infected, and painful. Fibrotic healing results in a cumbersome scar that is subject to repeated trauma during chewing. A well-prepared mucosal wound is closed with No. 4-0 absorbable suture. Chromic gut has the advantage of dissolving more rapidly in the oral cavity; some physicians prefer polyglactin 910 (Vicryl) owing to its softer nature for both handling and patient comfort.[33] Gingival and tongue lacerations are best closed with an absorbable polyglactin or nonabsorbable suture or black silk (4-0 or 5-0) because these materials are less irritating to the touch. Absorbable suture is preferred for children. Large tongue lacerations, especially if the border is involved, should be well approximated or a cleft will form during healing, necessitating a revision. Anesthesia can be achieved by either direct local injection or lingual block. Small (<1 cm) lacerations are best left alone, especially in children. Even larger tongue lacerations can be left alone in children if there is no chance of a resulting cleft deformity.[34] The management of through-and-through lacerations involving skin and oral mucosa is controversial. With proper preparation, mucosa can be closed as described previously. Subcutaneous sutures (absorbable) are placed to close the subcutaneous tissues from the outside, removing tension from the skin. Skin is closed with No. 6-0 or No. 7-0 synthetic nonabsorbable sutures that are removed in 3 to 4 days, depending on the amount of muscle tension on the wound. Intraoral silk closures are removed in approximately 7 days. There has been no well-designed prospective randomized trial to evaluate the benefit of prophylactic antibiotics after intraoral laceration repair. Some studies show, at best, a potential trend in benefit for through-and-through lacerations. Simple lacerations do not seem to benefit, and wounds that are over 24 hours old become universally infected. Therefore at this time the use of prophylactic antibiotic coverage is based on clinical judgment.[35] Typically, if antibiotics are prescribed for prophylaxis, choices would include penicillin 250 mg four times a day or doxycycline 100 mg bid for 10 days. The patient is advised to maintain oral hygiene, use saline rinses six times a day, place a triple-antibiotic ointment over the skin closure, and watch carefully for infection. These patients should be seen in 48 to 72 hours to check for infection. Normal postoperative soft tissue swelling should not be mistaken for an infected wound.

Temporomandibular Joint Dislocation

The mandibular condyles may dislocate from trauma, but more often, dislocation follows extreme opening of the mandible such as occurs after a yawn or laughter. TMJ dislocation occurs when the condyle travels anteriorly along the eminence and becomes locked in the anterosuperior aspect of the eminence. The masseter, internal pterygoid, and temporalis go into spasm attempting to close the mandible; trismus results, and the condyle cannot return to the temporal fossa. Mandibular dislocation is painful and frightening for the patient. Patients prone to mandibular dislocation include individuals with anatomic disharmonies between the fossa and articular eminence, weakness of the capsule and the temporomandibular ligaments, or torn ligaments. Dystonic reaction to drugs may result in mandibular dislocation. Patients who have had one episode of mandibular dislocation are predisposed to further dislocations. If a unilateral dislocation has occurred, the jaw deviates to the opposite side. More commonly, a symmetrical dislocation occurs. In cases of traumatic dislocation, a panorex or

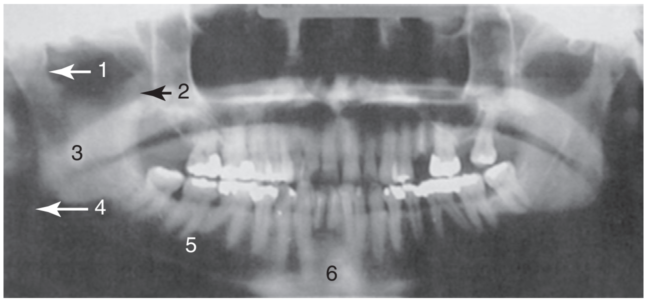


Figure 70-10. Panoramic view. *1,* Condylar process; *2,* coronoid process; *3,* ramus; *4,* angle of the mandible; *5,* body of the mandible; *6,* symphysis. (From Druelinger L, Guenther M, Marchand GE: Radiographic evaluation of the facial complex. Emerg Med Clin North Am 18:393-410, 2000.)

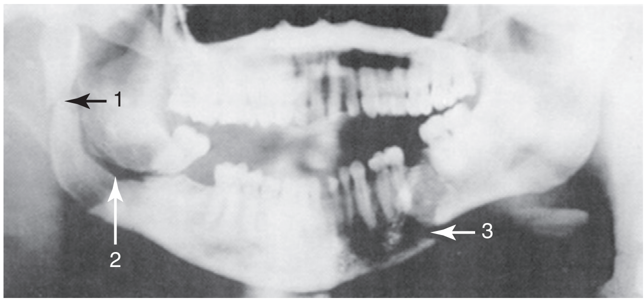


Figure 70-11. Panoramic view demonstrates a comminuted fracture of the mandible. *1,* Fracture of the condylar process; *2,* fracture of the ramus extending to the angle of the mandible; *3,* fracture through the body of the mandible. (From Druelinger L, Guenther M, Marchand GE: Radiographic evaluation of the facial complex. Emerg Med Clin North Am 18:393-410, 2000.)

CT scan of the facial bones should be taken to exclude the possibility of a fracture (Figs. 70-10 and 70-11).

Reduction of a dislocated mandible is straightforward, although often difficult because the strength of the masseter contraction must be overcome. The patient requires procedural analgesia and sedation as for any other dislocation. Either facing the patient or from behind, the emergency physician grasps the mandible with both hands; the thumbs rest on the ridge of the mandible intraorally, posterior to the molars, and the fingers wrap around the outside of the jaw. It is best to have the patient sitting up, with a firm surface behind the head, so that posterior and inferior pressure can be exerted without accompanying movement of the patient's entire head. Some physicians prefer to place the thumbs on the occlusal surfaces of the teeth; in this case the thumbs are wrapped with gauze to protect them when reduction is accomplished because the masseter muscles can contract with tremendous force. Firm, progressive, downward pressure is applied on the mandible to free the condyles from the anterior aspect of the eminence; the mandible is guided caudally, then posteriorly and superiorly back into the temporal fossae (Fig. 70-12). If this maneuver is unsuccessful, both hands can be used on the affected side of the mandible, with reported success.[36] The patient is advised to avoid extreme opening of the mandible such as occurs during laughing and yawning, to begin a soft diet for 1 week, and to apply warm compresses in the TMJ area. NSAIDs and muscle relaxants may be helpful. Patients with chronic dislocation may be helped initially with the application of a Barton bandage (elastic fabricated bandage that wraps around the top of the head and mandible). Intermaxillary fixation with wire and elastics may be necessary. Patients who have difficulty reducing the dislocation by

www.ketabpezeshki.com 66485457-66963820

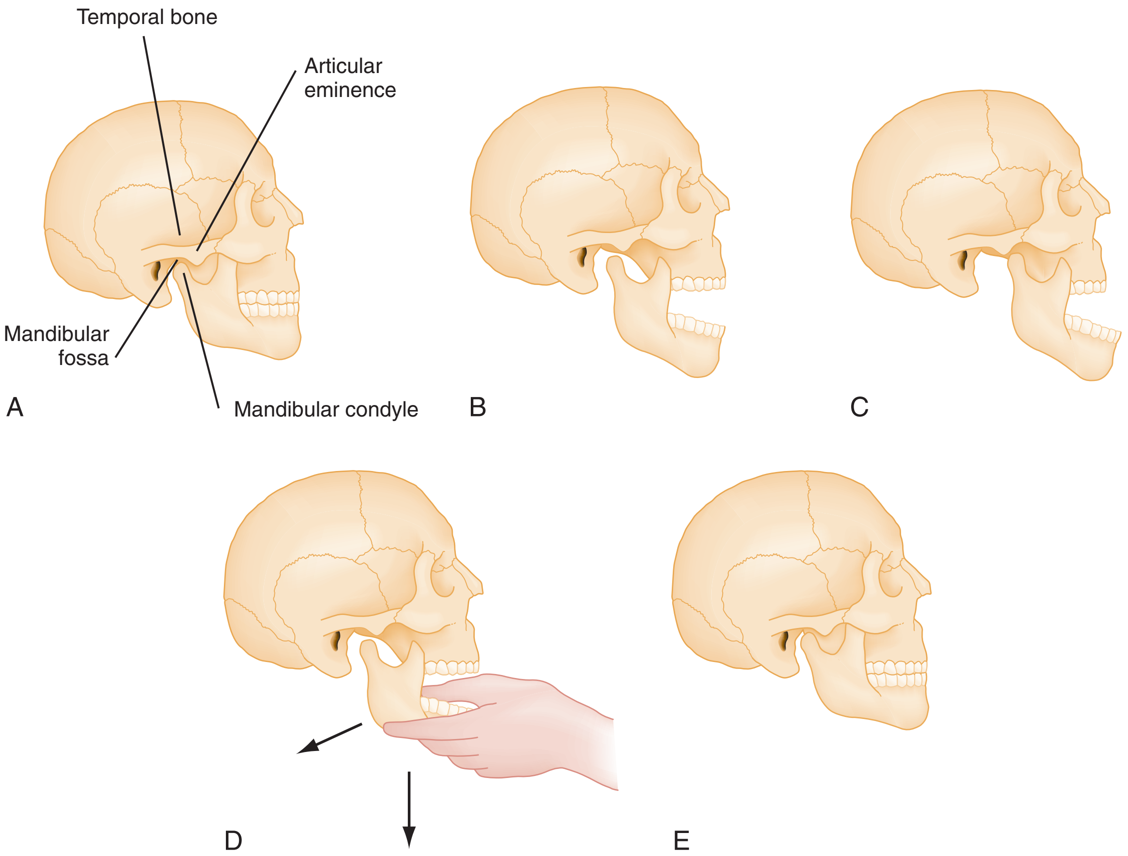


Figure 70-12. Reduction of temporomandibular joint dislocation. The temporomandibular joint is illustrated in normal and dislocated positions. **A,** Closed position, with the mandibular condyle resting in the mandibular fossa behind the articular eminence. **B,** In maximally open position the mandibular condyle is just under and slightly behind the articular eminence. **C,** In dislocated position the mandibular condyle moves forward and upward slightly above the articular eminence; muscle spasm then occurs. **D,** For reduction of dislocation, the thumbs are placed intraorally and lateral to the lower molars, and pressure is applied to the lower molar ridge area near the jaw angle in a downward and backward direction. **E,** When the mandibular condyle has cleared the articular eminence, muscle contraction returns the jaw to a normal closed position. (Adapted from Rose LF, Hendler BH, Amsterdam JT: Temporomandibular disorders and odontic infections. Consultant 22:125, 1982.)

themselves or who experience frequent recurrences may require surgical revision of the eminence for relief.

Hemorrhage

Oral hemorrhage is a common complication of dental scalings, periodontal surgery, and dental extractions. Hemorrhage is controlled easily with local measures postoperatively. Patients may have sustained or recurrent hemorrhage after these procedures, however, and visit the ED. History should be obtained for recent dental procedures, drugs with antiplatelet activity such as aspirin or clopidogrel, underlying coagulopathy, or a history of spontaneous bleeding. Spontaneous gingival hemorrhage without an inciting factor warrants a screen for coagulopathy and a complete blood count and differential. Diseases that result in spontaneous gingival hemorrhage are discussed in the section on oral manifestations of systemic disease. Management of coagulopathies caused by factor deficiencies requires factor replacement, and other coagulopathies require appropriate management based on the cause (e.g., warfarin reversal or platelets for platelet-inhibiting agents).

Bleeding after extraction is the most common cause of oral hemorrhage. History of cigarette smoking, excessive spitting, or use of straws is helpful information because each behavior creates negative pressure in the oral cavity, which dislodges blood clots from the socket. Excessive clots should be removed from the oral cavity. The patient should be allowed to bite on gauze for 20 minutes. If bleeding has not stopped, the extraction site should be infiltrated with 2% lidocaine with 1 : 100,000 epinephrine so that the tissue blanches. Gauze pressure should be repeated for another 20 minutes. If bleeding continues, the socket should be packed with an absorbable gelatin sponge or oxidized regenerated cellulose and secured with a No. 4-0 silk suture. Gauze pressure is applied again. Failure to respond to these measures warrants an evaluation for an underlying coagulopathy. Patients who have had multiple extractions without adequate bone recontouring and soft tissue closure may require revision of the surgical site to achieve hemostasis.

Patients who have bleeding after periodontal surgery usually respond to local measures and continued application of gauze pressure. Patients who are bleeding excessively after a deep scaling may be helped by injection of local anesthetic with epinephrine or the placement of a periodontal pack. Patients who recently have undergone periodontal surgery involving gingival flaps may have dislodged the periodontal packs that were placed to ensure proper tissue alignment and wound healing. The periodontist should be informed if possible so that the pack can be replaced as soon as possible to ensure appropriate healing.

Crown and Bridge

On occasion, a patient may have a loose artificial crown or a bridge that may have come loose from the underlying tooth. The crown or the bridge can be recemented in the ED. First, the inside of the crown is inspected for any residual cement. The tooth surface

www.ketabpezeshki.com 66485457-66963820

needs to be relatively free of cement. An attempt is made to insert the crown or bridge, and the patient is asked to bite. If the patient says the occlusion feels like it always has (not high), the crown or bridge can be cemented with any commercial dental cement. The crown surfaces are covered with some Vaseline so the cement does not stick; care is taken not to get Vaseline inside the crowns. Usually, dental cements will come as a powder and a liquid, which need to be mixed together to a thick, pudding-like consistency. The crown(s) are filled with the cement and immediately placed over the teeth. The patient is asked to bite and hold until the cement hardens. Any residual cement around the gingival border is flicked off with a dental explorer. The patient should be referred to the dentist the next working day to have the crown checked, the subgingival space checked for any residual cement, or, often, the crown recemented.

KEY CONCEPTS

- The most common nontraumatic dental emergencies are pain from dental caries, periodontal abscesses, and spread of infection of dental origin.
- The most important concern of dental infection is any compromise of the airway.
- Fractures of teeth are managed differently depending on which structures are involved—enamel, dentin, or pulp exposure.
- Avulsed teeth are reimplanted as quickly as possible and are best preserved in Hank's solution.
- Soft tissue injuries, such as lip lacerations, when involved with dental injuries should be managed after the teeth have been stabilized.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Hong I, et al: Secular trends in hospital emergency department visits for dental care in Kansas City, Missouri, 2001-2006. *Public Health Rep* 2011; 126:210-219.
2. Peretz G, Gluck GM: The use of restraint in the treatment of paediatric dental patients: Old and new insights. *Int J Paediatr Dent* 2002; 12:392-397.
3. Adhikari S, Blaivas M, Lander L: Comparison of bedside ultrasound and panorex radiography in the diagnosis of a dental abscess in the ED. *Am J Emerg Med* 2011; 29:790-795.
4. Sultan A, McQuay HJ, Moore RA, Derry S: Single dose oral flurbiprofen for acute postoperative pain in adults. *Cochrane Database Syst Rev* 2009; 3:CD007358.
5. Rodriguez DS, Sarlani E: Decision making for the patient who presents with acute dental pain. *AACN Clin Issues* 2005; 16:359-372.
6. Ellison SJ: The role of phenoxymethylpenicillin, amoxicillin, metronidazole, and clindamycin in the management of acute dentoalveolar abscesses—a review. *Br Dent J* 2009; 206:357-362.
7. Pantlin L: Is there a role for antibiotics in periodontal treatment? *Dent Update* 2008; 35:493-496.
8. Howaldt HP, Kessler P: Fiberoptic intubation as a safe method for the treatment of odontogenic abscesses. *Dtsch Zahnarztl Z* 1992; 47:46-47.
9. Klasser DG, Kugelmann AM, Villines D, Johnson BR: The prevalence of persistent pain after nonsurgical root canal treatment. *Quintessence Int* 2011; 42:259-269.
10. Hansen JG, Lund E: The association between paranasal computerized tomography scans and symptoms and signs in a general practice population with acute maxillary sinusitis. *APMIS* 2011; 1119:44-48.
11. Barden J, Edwards JE, McQuay HJ, Wiffen PJ, Moore RA: Relative efficacy of oral analgesics after third molar extraction. *Br Dent J* 2004; 197:407-411.
12. Kolokythas A, Olech E, Miloro M: Alveolar osteitis: A comprehensive review of concepts and controversies. *Int J Dent* 2010; 2010:249073. Epub Jun 24, 2010.
13. Jorns TP, Zakrewska JM: Evidence-based approach to the medical management of trigeminal neuralgia. *Br J Neurosurg* 2007; 21:253-261.
14. Sato J, et al: Diagnostic significance of carbamazepine and trigger zones in trigeminal neuralgia. *Oral Surg Oral Med Oral Pathol Oral Radiol Oral Endod* 2004; 97:544.
15. Reneker J, Paz J, Petrosino C, Cook CE: Diagnostic accuracy of clinical tests and signs of temporomandibular joint disorders: A systematic review of the literature. *J Orthop Sports Phys Ther* 2011; 41:408-416.
16. Martins-Júnior RL, Palma AJ, Marquardt EJ, Gondin TM, Kerber Fde C: Temporomandibular disorders: A report of 124 patients. *J Contemp Dent Pract* 2010; 11:071-078.
17. Al-Ani MZ, Davies SJ, Gray RJM, Sloan P, Glenny AM: Stabilisation splint therapy for temporomandibular pain dysfunction syndrome. *Cochrane Database Syst Rev* 2004; 1:CD002778.
18. Koh H, Robinson PG: Occlusal adjustment for treating and preventing temporomandibular joint disorders. *Cochrane Database Syst Rev* 2003; 1:CD003812.
19. Fricton JR, et al: Critical appraisal of methods used in randomized controlled trials of treatments for temporomandibular disorders. *J Orofac Pain* 2010; 24:139-151.
20. Kuriyama T, et al: Bacteriologic features of antimicrobial susceptibility in isolates from orofacial odontogenic infections. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000; 90:600-608.
21. Burgess JA, van der Ven PF, Martin M, Sherman J, Haley J: Review of over-the-counter treatments for aphthous ulceration and results from use of a dissolving oral patch containing glycyrrhiza complex herbal extract. *J Contemp Dent Pract* 2008; 9:88-98.
22. Chattopadhyay A, Shetty KV: Recurrent aphthous stomatitis. *Otolaryngol Clin North Am* 2011; 44:79-88.
23. Kaur G, et al: Association between calcium channel blockers and gingival hyperplasia. *J Clin Periodontol* 2010; 37:625-630.
24. Miller SA, Miller G: Use of evidence-based decision making in private practice for emergency treatment of dental trauma: EB case report. *J Evid Based Dent Pract* 2010; 10:135-146.
25. Söder PO, Otteskog P, Andreasen JO, Modéer T: Effect of drying on viability of periodontal membrane. *Scand J Dent Res* 1977; 85:164.
26. Hecova H, Tzigkounakis V, Merglova V, Netolicky J: A retrospective study of 889 injured permanent teeth. *Dent Traumatol* 2010; 26:466-475.
27. Sigalas E, Regan JD, Kramer PR, Witherspoon DE, Opperman LA: Survival of human periodontal ligament cells in media proposed for transport of avulsed teeth. *Dent Traumatol* 2004; 20:21-28.
28. Mousavi B, et al: Standard oral rehydration solution as a new storage medium for avulsed teeth. *Int Dent J* 2010; 60:379-382.
29. McIntosh MS, et al: Stabilization and treatment of dental avulsions and fractures by emergency physicians using just-in-time training. *Ann Emerg Med* 2009; 54:585-592.
30. Evans D: Prescribing systemic antibiotics when replanting avulsed teeth. *Evid Based Dent* 2009; 10:103.
31. Krasner P: Endodontic treatment of reimplanted avulsed teeth. *Dent Today* 2004; 23:104-107.
32. Rabelo GD, de Paula PM, Rocha FS, Jordão Silva C, Zanetta-Barbosa D: Retrospective study of bone grafting procedures before implant placement. *Implant Dent* 2010; 19:342-350.
33. Armstrong BD: Lacerations of the mouth. *Emerg Clin North Am* 2000; 18:471-480, vi.
34. Lamell CW, Fraone G, Casamassiomo PS, Wilson S: Presenting characteristics and treatment outcomes for tongue lacerations in children. *Pediatr Dent* 1999; 21:34-38.
35. Mark DG, Granquist EJ: Are prophylactic oral antibiotics indicated for the treatment of intraoral wounds? *Ann Emerg Med* 2008; 52:368-372.
36. Cheng D: Unified hands technique for mandibular dislocation. *J Emerg Med* 2010; 38:366-367.

www.ketabpezeshki.com 66485457-66963820

Chapter 71

Ophthalmology

Rahul Sharma and Douglas D. Brunette

PERSPECTIVE

Background and Epidemiology

Two percent of emergency department (ED) patients have eye complaints, including primary ophthalmologic pathology, infectious problems, and traumatic injuries. Eye injuries account for 3.5% of all occupational injuries in the United States, and about 2000 U.S. workers injure their eyes each day.[1] The majority of eye complaints can be treated without ophthalmologic consultation, but a few require the involvement of a specialist as well as immediate action. Some specific problems, such as central retinal artery occlusion and caustic exposure, require emergent therapy, even as assessment proceeds. Eye emergencies can be categorized into three main categories, including the red eye, the painful eye, and visual loss. Figures 71-1 and 71-2 are provided as brief reviews of normal ocular anatomy and funduscopic appearance.

OCULAR TRAUMA

Perspective

Approximately 3% of all visits to the ED are a result of eye trauma.[2] A systematic evaluation of the periorbital and orbital structures aids in the evaluation of patients with ocular trauma. Many extraocular structures are found in close proximity, and concomitant, nonocular injury is common.

Nonpenetrating Trauma

Orbit and Lid

Clinical Features and Management

Contusion. Blunt injury to the orbits and surrounding tissues results in ecchymosis, swelling, and an often dramatic appearance. Related significant injury should be considered. Basilar skull fractures may occur with bilateral ecchymosis (raccoon eyes). Underlying globe injury may be present, and complete examination may be impeded by swelling. The emergency physician should attempt to visualize and examine all structures underlying the eyelids and obtain an accurate determination of visual acuity. This should be done soon after the patient arrives, before further swelling occurs. Examining the structures underlying severely swollen eyelids is difficult. A Desmarres retractor may help avoid global pressure. An orbital computed tomography (CT) scan is indicated if examination of the underlying structures is not possible owing to severe swelling.

Treatment of isolated soft tissue injury to the eyelids and surrounding area is symptomatic. Head elevation and intermittent cold compresses started in the ED and continued for up to 48 hours may decrease the pain and swelling. Complete resolution takes 2 to 3 weeks. Patients are instructed to seek follow-up care for any increase in pain or swelling, decreased vision, double vision, or significant flashing lights or floaters.

Orbital Wall Fractures. An orbital wall fracture is suspected when a patient has soft tissue swelling and trauma to the globe. When blunt force causes an acute rise in intraorbital pressure, the thin walls of the orbit frequently fracture. Prolapse of orbital soft tissues into the maxillary sinus may result because the orbital floor is generally the weakest point. Entrapment of the inferior rectus and inferior oblique ocular muscles, orbital fat, and connective tissues results in enophthalmos, ptosis, diplopia, anesthesia of the ipsilateral cheek and upper lip, and limitation of upward gaze. Subcutaneous orbital emphysema may be palpable. Associated globe injuries occur in 10 to 25% of patients with orbital floor fractures.[3] Plain radiographic examination of the face can help but is imperfect. A CT scan of the orbits with axial and coronal views is preferred (Fig. 71-3A). Plain x-ray films have limited utility given the lower sensitivity to delineate soft tissue structures and extent of bony deformity. On x-ray film, the teardrop sign, a bulge extending from the orbit into the maxillary sinus, and an air-fluid level in the maxillary sinus are indirect signs of orbital floor injury. The use of bedside ultrasound has also been shown to be useful in the identification of orbital wall fractures.[4] If the fracture involves an infected sinus, treatment consists of nasal decongestants such as pseudoephedrine 30 mg every 6 hours, broad-spectrum oral antibiotics such as amoxicillin clavulanate 875 mg bid for 10 days, and ice packs to the orbit for 48 hours. Some ophthalmologists use steroids to reduce swelling. Surgical repair is performed only for persistent diplopia or to address cosmetic concerns and generally not until swelling subsides in 7 to 10 days. Patients can usually be discharged to be reevaluated by an ophthalmologist in 1 to 2 weeks.

Medial orbital wall fractures, through the lamina papyracea of the ethmoid bone, involve entry into the ethmoid sinus. Clinical features include orbital emphysema and epistaxis. Diplopia from medial rectus impingement can occur. The finding of orbital emphysema prompts a search for associated injury. Rarely is orbital emphysema significant enough to compress the optic nerve and result in acute visual loss. In most cases, orbital emphysema is a benign finding that resolves with time. Prophylactic antibiotics are not needed unless the fracture involves an infected sinus.[5]

Patients with orbital floor and medial orbital wall fractures are instructed to avoid blowing their noses and performing the Valsalva maneuver to limit the extent of emphysema. Patients with orbital fractures can safely be discharged home if there is no globe rupture or visual impairment; close follow-up with an ophthalmologist is recommended, and patients are given strict discharge

www.ketabpezeshki.com 66485457-66963820

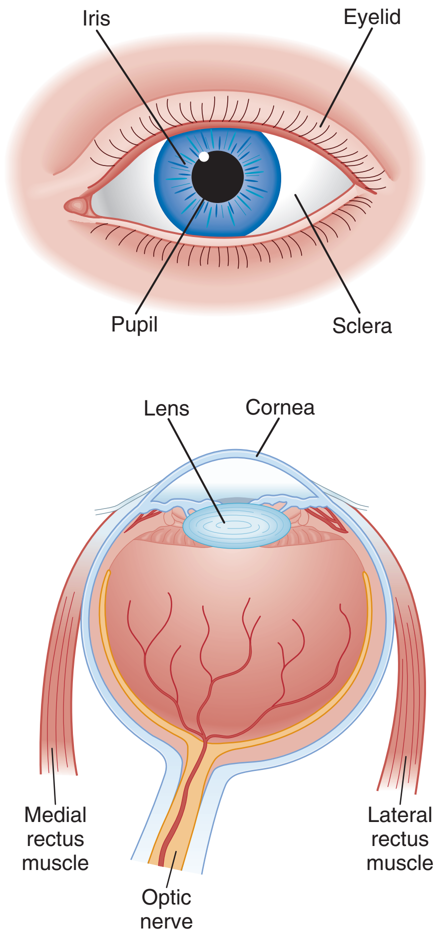


Figure 71-1. Normal eye anatomy.

Figure 71-2. Normal fundus. (Image courtesy www.tedmontgomery.com.)

instructions to return for any significant changes such as increased pain or changes in vision.

Retrobulbar Hemorrhage. Orbital hemorrhage in the potential space surrounding the globe may occur after blunt trauma and injury to the orbital vessels. Significant hemorrhage results in an acute rise in intraorbital pressure that is transmitted to the globe and optic nerve. This may result in occlusion of the central retinal artery and optic nerve ischemia. Clinical findings include proptosis, limitation of ocular movement, visual loss, and increased intraocular pressure. An orbital CT scan demonstrates a hematoma; however, treatment should not be delayed by waiting for imaging to be performed.

When a retrobulbar hematoma compromises retinal circulation, immediate ophthalmologic consultation for decompression is warranted. Treatment of increased intraocular pressure includes a carbonic anhydrase inhibitor, a topical beta-blocker, and 1 to 2 g of intravenous mannitol per kilogram. A lateral canthotomy can be performed in the ED as a temporizing measure before definitive decompression[6] (see Fig. 71-3B and C).

Cornea and Conjunctiva

Clinical Features and Management

Chemical Burns. Exposure of the eye to chemicals is a true ocular emergency. Exposure to strong alkaline chemicals, found in drain cleaners, in chemical detergents, in industrial solvents, and as lime in plaster and concrete, produces a liquefactive necrosis that penetrates and dissolves tissues until the alkaline agent is removed. Acid burns tend to be less devastating than alkali burns because acidic exposure causes coagulation necrosis and the precipitation of tissue proteins limits the depth of the injury.

Treatment should begin at the scene with immediate irrigation with copious amounts of water continued for at least 30 minutes before transport. Any particulate matter should be removed from the fornices with a cotton swab. On hospital arrival, irrigation should continue. There is evidence that buffered eye wash solutions might be significantly better for irrigation of ocular caustic injuries than standard intravenous solutions. There are human case series reports demonstrating that an amphoteric, hypertonic chelating solution, Diphoterine (Prevor, Valmondois, France), provides faster correction of pH as well as improved outcomes.[7,8] Cederroth Eye Wash (Cederroth Industrial Products, Upplands Vasby, Sweden) is a borate-based buffering solution that has demonstrated faster pH correction in exposed eyes in an animal model.[9]

Use of irrigation devices, such as a Morgan Lens (MorTan, Missoula, Mont.), can assist in delivering continuous irrigation to the affected eye. Topical anesthetics and manual lid retraction may be needed for proper irrigation. Irrigation is needed until the pH of the tear film is neutral as tested with nitrazine paper dipped into the inferior conjunctival fornix. If the pH tested immediately after irrigation is still alkaline, irrigation is reinstituted and the pH checked again after 10 minutes and periodically thereafter. Treatment after irrigation consists of a cycloplegic (phenylephrine is avoided), topical antibiotics such as 0.5% erythromycin eye ointment applied every 4 to 6 hours to the affected eye, and pain management. Intraocular pressure should also be measured because high intraocular spikes in pressures can be seen immediately after an alkali burn.[10]

Ophthalmologic consultation is indicated in all significant chemical exposures. Identification of the substance and its pH value is important. In general, alkaline substances with a pH less than 12 and acidic substances with a pH greater than 2 do not cause significant injury, although high concentration and prolonged contact time can alter this general rule (Fig. 71-4).

Severity of injury is judged by the degree of corneal cloudiness and scleral whitening. Long-term complications include perforation, scarring, and neovascularization of the cornea; adhesions of the lids to the globe (symblepharon); glaucoma; cataracts; and retinal damage.

Miscellaneous Irritants, Solvents, Detergents, and Glues. Unknown exposures are best treated as though they were from an alkali or acid substance, prompting immediate irrigation. Detergents generally cause conjunctival irritation only. More irritating substances may denude the corneal epithelium and cause anterior chamber inflammation. After copious irrigation, these injuries are treated as corneal abrasions.

www.ketabpezeshki.com 66485457-66963820

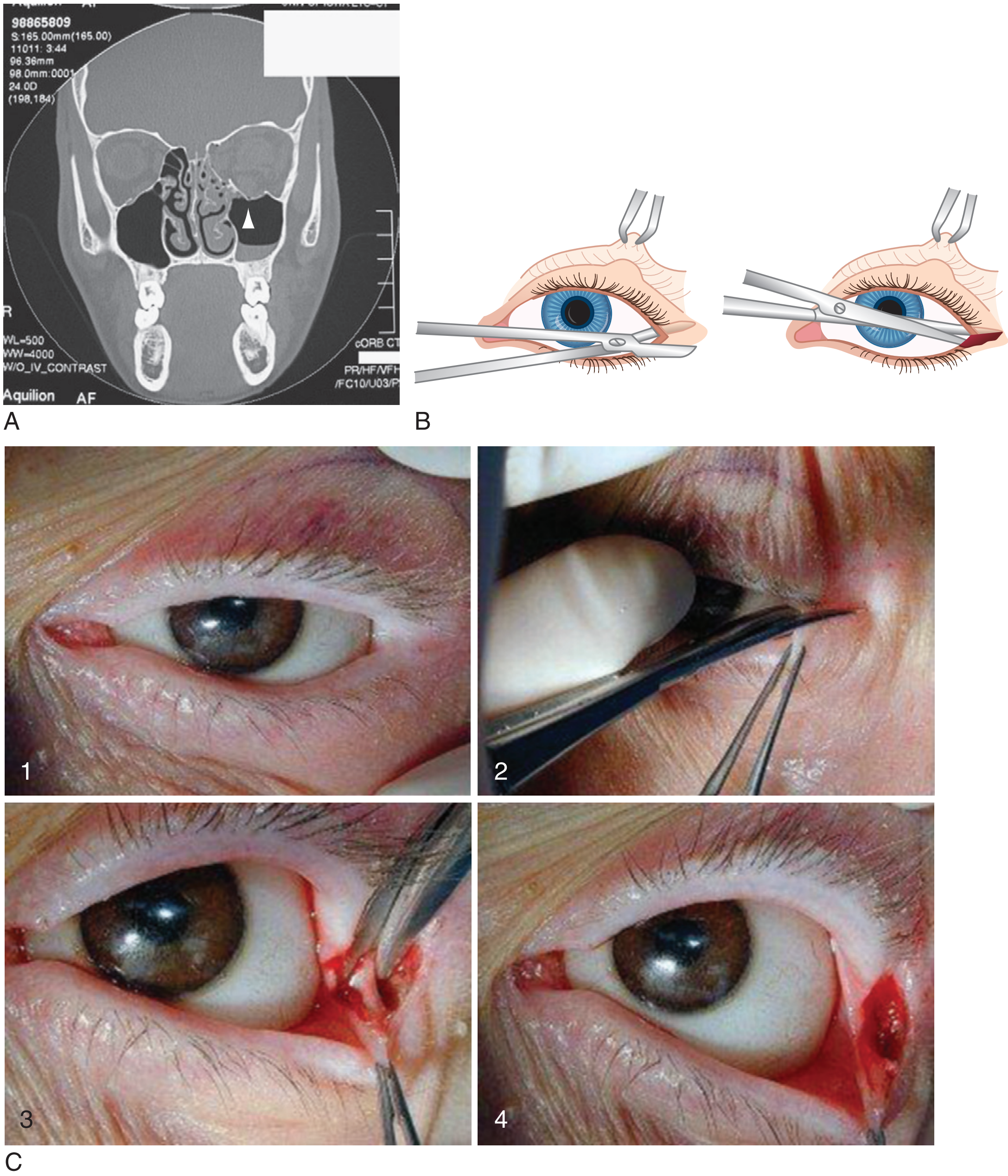


Figure 71-3. **A,** Facial computed tomography scan showing left inferior orbital fracture with blood in maxillary sinus. **B,** Lateral canthotomy. **C,** *(1)* Preoperative view of orbit. *(2)* Incision for lateral canthotomy. *(3)* Identification and incision of inferior canthal tendon, completing cantholysis. *(4)* View after lateral canthotomy and inferior cantholysis, creating maximal immediate decompression by allowing eyeball and orbital contents to move anteriorly. (**A,** Courtesy University of Iowa Department of Ophthalmology, http://webeye.ophth.uiowa.edu/eyeforum/Images/floorfx_08232004.jpg. **C,** From Ramakrishnan VR, Palmer JN: Prevention and management of orbital hematoma. Otolaryngol Clin North Am 43:789-800, 2010.)

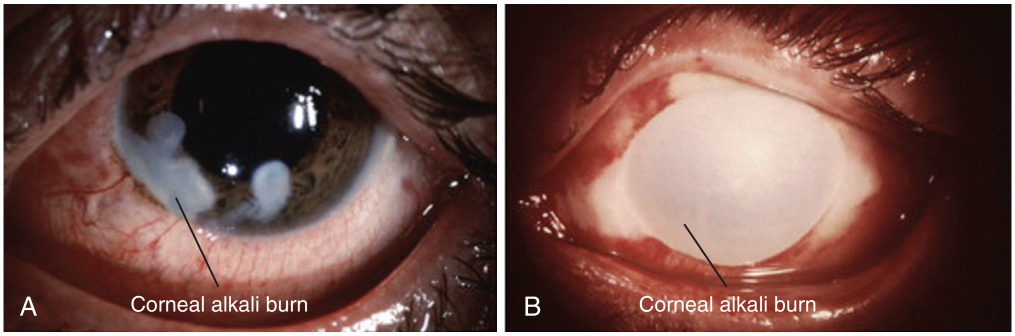


Figure 71-4. **A,** Alkali burn demonstrating corneal burns and conjunctival injection on the day of the accident. **B,** Complete corneal tissue destruction 7 days after alkali burn. (From Kaiser PK, Friedman NJ, Pineda R II: The Massachusetts Eye and Ear Infirmary Illustrated Manual of Ophthalmology, 2nd ed. Philadelphia, WB Saunders, 2004.)

www.ketabpezeshki.com 66485457-66963820

Aerosol eye exposures are common, and intraocular foreign bodies may result from the propellant. Exposure to the compounds found in personal defense devices (e.g., Mace) is treated in the same manner as other chemical injuries.

Super Glue (cyanoacrylate adhesive) exposure is also common. Cyanoacrylate adhesive is used in many industrial and domestic settings but is considered to have relatively little toxicity.[11] These glues harden rapidly, and typically the eyelids are sealed shut. Misdirected lashes and the hardened glue may act as foreign bodies and cause corneal defects. Gentle traction on the eyelids and separation of glued eyelashes may open the eyelids. If the eyelids are sealed shut in a normal anatomic position and cannot be opened with gentle traction, the eye may be left alone, allowing time for the glue to dissolve by physiologic mechanisms over several days. If the eyelids are inverted and sealed shut, surgical intervention may be needed. Attempts to dissolve the glue with other substances should be avoided. Ophthalmic consultation and arrangements for follow-up are recommended for Super Glue exposures.

Thermal Burns. Thermal burns affect the eyelids more than the globe because of reflex blinking and Bell's phenomenon. Superficial eyelid burns can be treated by copious irrigation, application of a cold compress to decrease the thermal injury, and topical antibiotic ophthalmic ointment. Second- or third-degree eyelid burns require ophthalmic consultation. Hot liquid splashes and cigarette ashes to the cornea usually result in a superficial corneal epithelial injury and are treated as corneal abrasions. Molten metals and other hot objects may result in globe perforation. The severity of the burn is related to the duration of exposure as well as the nature of the causative agent.

Radiation Burns (Ultraviolet Keratitis). Ultraviolet light from sun lamps, tanning booths, high-altitude environments, snow or water reflection, or a welder's arc results in direct corneal epithelial damage. After a latent period of 6 to 10 hours, patients develop a foreign body sensation, tearing, intense pain, photophobia, and blepharospasm. Topical ophthalmic anesthetics facilitate physical examination. Examination reveals decreased visual acuity, injected conjunctiva, and diffuse punctate corneal lesions, often with a discrete lower border defining the cornea protected by the inferior lid. Treatment consists of a short-acting cycloplegic and a topical broad-spectrum antibiotic ointment, although evidence for the latter is scant. Oral opioids are commonly needed. Patients should also not routinely be prescribed traditional topical anesthetics because use has been shown to inhibit the migration of corneal epithelial cells, resulting in severe corneal scarring and keratopathy.[12] One recent study demonstrated that dilute proparacaine 0.05% can be used as an analgesic for acute corneal injuries; however, this study enrolled a small number of patients and was not powered for safety outcomes.[13] Patients should be counseled on the adverse effects of ultraviolet radiation, and education provided regarding the use of various protective devices. Ophthalmologic follow-up in 24 hours is recommended if symptoms have not resolved.

Biologic Exposures. Exposure of the eye to any human blood or body fluid (e.g., semen, urine, saliva) may result in infection with a blood-borne pathogen. The risk of infection through mucous membrane exposure (e.g., conjunctiva) is less than that via a needle-stick and is dependent on the volume and concentration (e.g., viral load) of the body fluid. Copious irrigation of the affected eye is begun immediately after the exposure; the immunization status of the patient and, if known, the source patient should be determined. Postexposure prophylaxis should be discussed with the patient and arrangements made for follow-up with occupational health or the patient's primary care provider.

Mechanical Corneal Abrasions. Patients with a corneal abrasion may complain of a foreign body sensation, pain, photophobia, and decrease in visual acuity. The degree of relief afforded by topical anesthesia can differentiate corneal injury from other causes of acute eye pain.[14] Physical examination reveals injected conjunctiva, decreased visual acuity if the defect is large or lies in the visual axis, and demonstration of the epithelial defect with slit-lamp examination and fluorescein (Fig. 71-5). Aqueous humor leaking from the anterior chamber during fluorescein examination (Seidel's test) suggests a corneal perforation. Multiple vertical abrasions suggest a foreign body, and a thorough examination of the area under the eyelid should be performed. Treatment consists of cycloplegia and topical antibiotics. There is evidence that treatment with topical nonsteroidal anti-inflammatory medications, ketorolac 0.5% four times daily, or diclofenac 0.1% four times daily reduces the pain associated with corneal abrasions, and therefore these medications are adjuvant therapy for patients with traumatic corneal abrasions.[15] Patients with contact lenses should be treated with topical antibiotics with pseudomonal coverage such as tobramycin 0.5% solution 1 or 2 drops every 4 hours to the affected eye.[16] Eye patching, especially with injuries involving vegetable matter or contact lens use, is avoided. A 2006 Cochrane review concluded that use of an eye patch does not improve healing rates and does not reduce pain for simple corneal abrasions and is not recommended for routine use.[17] Patients with corneal abrasions should not wear their contact lenses. Oral pain medications may be needed. There are no known cases of clinical tetanus developing from a simple corneal abrasion[18]; however, updating a patient's tetanus immunization status is part of emergency care and should be considered in any tetanus-prone injury such as corneal perforation or injuries containing dirt and organic matter.

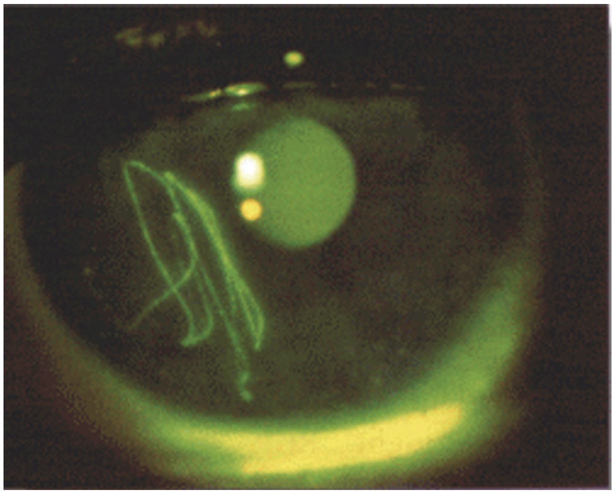


Figure 71-5. Corneal abrasion demonstrated by slit-lamp examination. (Image courtesy http:/www.perret-optic.ch/optometrie/symptomes_diagnostiques/symptomes/opto_symfor_gb.htm#abrasion.)

Most corneal abrasions heal within 3 to 5 days, and patients should have follow-up in 24 hours if their symptoms have not resolved.

Corneal Foreign Bodies. Patients with corneal foreign bodies experience pain, foreign body sensation, injected conjunctiva, tearing, and blepharospasm. Administration of a topical ophthalmic anesthetic facilitates physical examination. Diagnosis may be facilitated by use of a slit lamp (Fig. 71-6). After a topical anesthetic is applied, the initial attempt at removing corneal foreign bodies is made with a stream of sterile saline solution. Alternatively, a moistened cotton-tipped applicator can be used to gently roll over the foreign body and lift it off the corneal surface. If this fails, an attempt can be made to remove the foreign body through use of a 25-gauge needle with a 1- to 3-mL syringe as a handle

www.ketabpezeshki.com 66485457-66963820

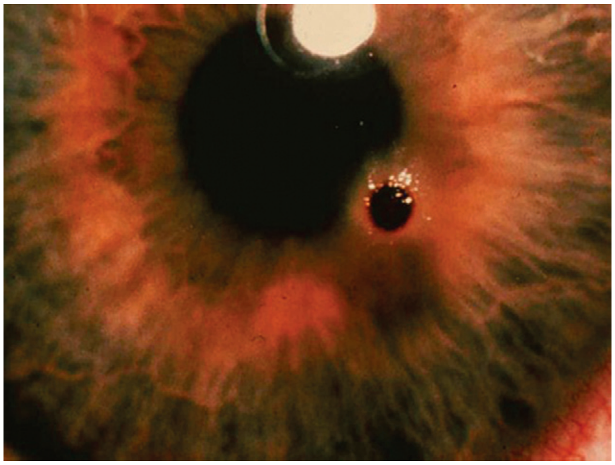


Figure 71-6. Corneal foreign body seen on slit-lamp examination. (Image courtesy www.tedmontgomery.com.)

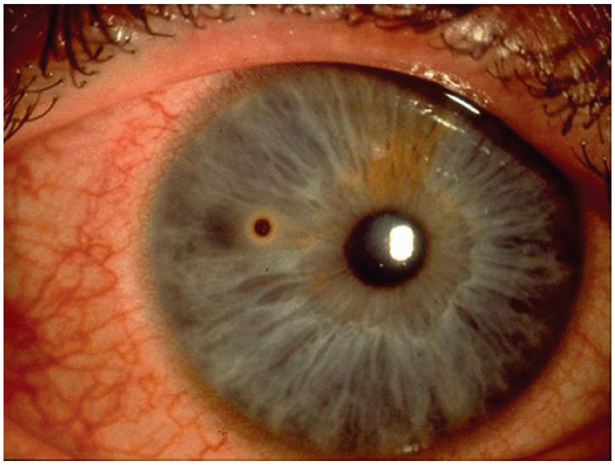


Figure 71-7. Corneal rust ring after removal of iron-containing foreign body demonstrated by slit-lamp examination. (Image courtesy www.tedmontgomery.com.)

and magnification, generally the slit lamp. The patient should be totally cooperative, with his or her head firmly stabilized within the slit lamp. Alternatively, a short plastic 20-gauge catheter can be placed on a syringe, and with slit-lamp visualization the foreign body can sometimes be irrigated out of the cornea.

Iron-containing corneal foreign bodies leave a residual rust ring (Fig. 71-7). Removal of the rust ring is best left to the ophthalmologist or for a return visit to the ED in 24 hours, because the affected cornea gradually softens and the rust migrates toward the corneal surface, making removal easier.

Ophthalmologic consultation for corneal foreign bodies is recommended if a large area of the visual axis is involved, the object is deeply embedded within the cornea, the risk of perforation is increased for any reason, or there are multiple foreign bodies.

Treatment after foreign body removal is similar to that for corneal abrasion, with ophthalmologic or ED follow-up within 24 hours for patients who require rust ring removal or who remain symptomatic.

Use of high-speed drills, saws, grinders, and pounding objects and involvement in explosions are risk factors for perforation. Any concern for ocular perforation warrants immediate ophthalmologic consultation. If there is no evidence of ocular penetration on a thorough ophthalmic examination, then imaging is not required.

Figure 71-8. Subconjunctival hemorrhage. (Image courtesy www.tedmontgomery.com.)

If there is any evidence or concern for ocular penetration and a metallic foreign body is visualized, plain-film radiographs can be used to ensure that multiple intraocular foreign bodies are not present. CT scan is used if there is suspected ocular penetration but an intraocular foreign body is not visualized on plain-film radiographs or if there are multiple intraocular foreign bodies. If a nonopaque foreign body is suspected after CT imaging, the clinician may consider ultrasound or magnetic resonance imaging (MRI).[19]

Conjunctival Foreign Body. Conjunctival foreign bodies can be removed under topical anesthesia with a cotton-tipped applicator or fine forceps. Topical phenylephrine can be used to reduce the conjunctival bleeding.

Subconjunctival Hemorrhage. Rupture of small subconjunctival blood vessels is common and occurs as a result of trauma or the Valsalva maneuver or often without an identified cause. Pain, diminished visual acuity, or photophobia suggests a more serious pathologic condition. Subconjunctival hemorrhage is flat, bright red, smooth, limited to the bulbar conjunctiva, and sharply demarcated at the limbus (Fig. 71-8). If there is a history of blunt or penetrating trauma, a thorough examination is indicated to exclude an underlying scleral penetration. Subconjunctival hemorrhage should be distinguished from bloody chemosis, which is indicative of more serious globe pathology. Bilateral or recurrent subconjunctival hemorrhage may require workup for bleeding diathesis. Treatment consists of local cold compresses for 24 hours, with resolution in 2 to 3 weeks.

Anterior Chamber and Iris

Clinical Features and Management

Traumatic Hyphema. Disruption of blood vessels in the iris or ciliary body results in a hyphema, blood in the clear aqueous humor in the anterior chamber. If the patient is sitting, the blood often layers and forms a meniscus with the aqueous humor. Hyphemas range from minimal blood seen only with the slit lamp to the "eight ball" or a total hyphema with blood that has clotted (Fig. 71-9). Patients report pain, photophobia, and decreased visual acuity. Intraocular pressure is elevated in approximately 27% of patients acutely but is usually mild and is self-limited. Pressures greater than 35 mm Hg with durations greater than 5 to 14 days are more likely to be associated with optic atrophy.[20] Hyphemas are usually not associated with an afferent pupillary defect (or Marcus Gunn pupil). An afferent pupillary defect occurs when the abnormal eye paradoxically dilates rather than constricts

www.ketabpezeshki.com 66485457-66963820

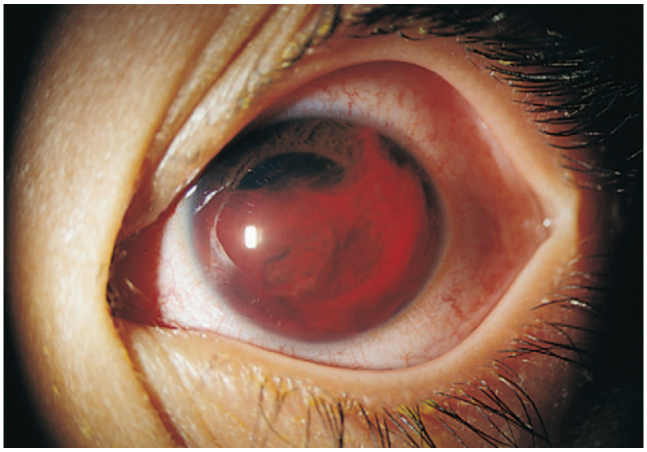


Figure 71-9. Hyphema in the anterior chamber. (Courtesy Steve Chalfin, MD, University of Texas Health Science Center, San Antonio, Texas.)

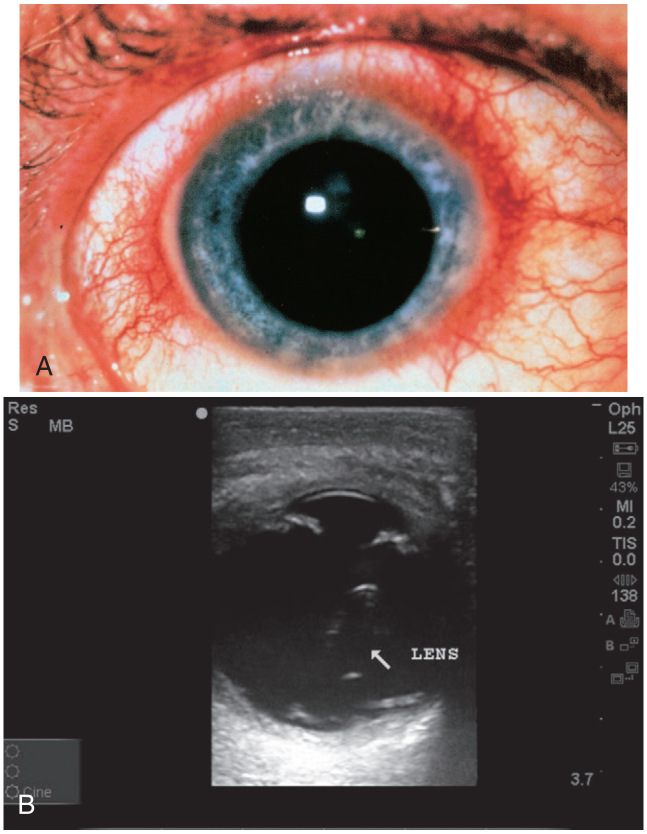


Figure 71-10. **A,** Ciliary flush. Note that conjunctival injection is most prominent immediately around the limbus. **B,** Ocular ultrasound showing lens dislocation. (**A** and **B,** image courtesy Douglas Brunette, MD.)

when light is directed to that eye during the swinging flashlight test. If the hyphema is large enough to result in increased intraocular pressure, an afferent pupillary defect may be seen.

Management of hyphema is individualized for a given patient. Selected low-grade hyphemas in reliable patients may be managed on an outpatient basis. Patients with hyphemas greater than 50%, decreased vision, increased intraocular pressure, and sickle cell disease are candidates for admission. Interventions such as elevating the bed 30 to 45 degrees, bed rest, and eye protection with an eye shield have been recommended in the past for the management of hyphema. However, a recent Cochrane review showed that the beneficial effect of these interventions is still unclear and evidence is inconclusive owing to the small number of studies and participants.[21] Analgesics are appropriate, but the patient should avoid taking aspirin and other platelet inhibitors. Antiemetics and sedatives should be used cautiously. Increased intraocular pressure occurs as a result of aqueous flow blockage from the blood present. In patients without sickle cell disease, initial treatment is a topical beta-blocker; a topical alpha-agonist or topical carbonic anhydrase inhibitor is added if needed. Oral acetazolamide 20 mg/kg/day in four divided doses or 1.5 g/kg of intravenous mannitol every 8 hours may also be used.

There is limited evidence regarding the benefit of cycloplegics and steroids; thus their use varies depending on the specific clinical situation and is best left to the ophthalmologist. Antifibrinolytics, such as aminocaproic acid, also may be considered in the treatment of traumatic hyphema. Both systemic and topical aminocaproic acid reduce the rate of recurrent bleeding but do not affect final visual acuity.[21] Failure of medical therapy to control high intraocular pressure, failure of a large clot to resolve, and corneal blood staining are indications for surgical intervention.

The major complication of hyphema is rebleeding, which occurs after 2 to 5 days when the initial clot retracts and loosens. The reported incidence of rebleeding is 6% to 33%.[22,23] Rebleeding is more common in those with visual acuities of 20/200, initial hyphema covering more than one third of the anterior chamber, medical attention delayed more than 1 day after injury, and elevated intraocular pressure at the initial examination. Other complications include corneal blood staining, acute or chronic glaucoma, and anterior or posterior synechia formation.

Patients with hemoglobinopathies (e.g., sickle cell disease, sickle cell trait, thalassemia) are at increased risk for hyphema complications, as even small amounts of blood in the anterior chamber can result in increased intraocular pressure. Red blood cells in the anterior chamber sickle in the relatively acidic and hypoxic environment, which leads to decreased aqueous humor outflow and a rapid rise in intraocular pressure. Increased intraocular pressure in a sickle cell patient with a hyphema is treated with topical timolol; other treatments, including topical brimonidine or apraclonidine, topical dorzolamide, mannitol, glycerin, methazolamide, and topical epinephrine, are coordinated with ophthalmology.

Traumatic hyphema may result in anterior chamber angle recession, which is a separation between the longitudinal and circular fibers of the ciliary body muscle. Blunt injury to the ciliary body may cause posterior displacement of the iris and surrounding tissues, deepening the anterior chamber, widening the anterior chamber angle, and causing potential damage to the trabecular meshwork that drains the aqueous humor. Some reports have shown a 70 to 100% incidence of angle recession after a traumatic hyphema. Severe damage can cause acute glaucoma.

Traumatic Iridocyclitis (Uveitis). Blunt injury of the globe may contuse and inflame the iris and ciliary body, resulting in ciliary spasm. Patients report photophobia and deep, aching eye pain. Examination reveals perilimbal conjunctival injection (ciliary flush), cells (white or red blood cells) and flare (protein content) in the anterior chamber, and a small, poorly dilating pupil (Fig. 71-10A). Patients may also experience direct photophobia when the light is directed to the affected eye and consensual photophobia when light is directed to the uninvolved eye.

Treatment consists of paralyzing the iris and ciliary body with a long-acting cycloplegic agent, such as homatropine hydrobromide 5%, given four times daily for 7 to 10 days. Prednisolone acetate 1% may be given to help relieve the inflammation

www.ketabpezeshki.com 66485457-66963820

if there is no improvement after 5 to 7 days but should be avoided in patients with a corneal epithelial defect. Resolution occurs within 1 week.

Traumatic Mydriasis and Miosis. Blunt injury may result in either pupillary dilation or constriction and may persist for days. For significant head trauma and altered mental status, a cranial nerve palsy should be ruled out before pupillary mydriasis is ascribed to local contusion.

Permanent pupillary mydriasis may result from small radial tears in the pupillary sphincter muscle. The pupil margin may look irregular or scalloped. No specific ED treatment is warranted.

Iridodialysis. Traumatic iridodialysis is a tearing of the iris root from the ciliary body, leading to the formation of a "secondary pupil." This injury is often the cause of a hyphema. If no associated hyphema is present, no specific ED treatment is needed. Large tears can lead to monocular diplopia and may require surgical correction. Immediate ophthalmologic consultation is warranted when iridodialysis has caused a hyphema or a decrease in visual acuity.

Scleral and Lens Injuries

Clinical Features and Management

Cataract. If the lens capsule is disrupted by either blunt or penetrating trauma, the relatively dehydrated stroma absorbs fluid, swells, and becomes cloudy. Acute glaucoma may develop from blockage of the aqueous humor flow through the pupil, necessitating surgical intervention. Bilateral cataract formation may also develop after electrical injury or lightning injury. In less severe injury, cataract formation may occur over weeks to months. Definitive treatment of cataract is lens replacement.

Lens Subluxation and Dislocation. Complete disruption of the lens zonule fibers by blunt trauma may result in anterior or posterior dislocation of the lens (see Fig. 71-10B). Incomplete disruption of the lens zonule fibers results in subluxation of the lens. Lens dislocation may occur with minor trauma in patients with Marfan syndrome, homocystinuria, tertiary syphilis, and other predisposing conditions. Patients report monocular diplopia or visual distortion with subluxation and marked visual blurring with dislocation. Examination reveals decreased visual acuity. The edge of a subluxated lens can be seen when the pupil is dilated. Iridodonesis is a trembling or shimmering of the iris after rapid eye movements and is a helpful sign of lens dislocation. Secondary glaucoma can also result after traumatic lens dislocation. The dislocated lens can cause pupillary block by preventing the flow of aqueous humor from the posterior chamber through the pupil into the anterior chamber, resulting in increased intraocular pressure.[24] Treatment ranges from observation to surgical removal and is dictated by the location of the dislocated lens and associated eye injury. Immediate ophthalmologic consultation is warranted.

Scleral (Globe) Rupture. Penetrating or blunt trauma to the eye can result in scleral rupture. Significant blunt force can result in globe compression with resultant globe rupture. Ruptures are most common at the insertions of the intraocular muscles or at the limbus, where the sclera is thinnest. The diagnosis of scleral rupture is obvious when intraocular contents are visualized; however, occult global rupture can be difficult to diagnose. Patients report eye pain and decreased vision. Examination may reveal a bloody chemosis or severe subconjunctival hemorrhage overlying the scleral rupture site. When the rupture occurs at the limbus, an irregularly shaped (teardrop) pupil may also be seen. Uveal prolapse through the scleral wound, appearing as a brownish black discoloration, can also be seen (Fig. 71-11A). Blunt globe injuries associated with an afferent pupillary defect, retinal detachment, poor initial visual acuity, or absence of a red reflex carry a poor prognosis with a higher rate of subsequent enucleation.[25] Although

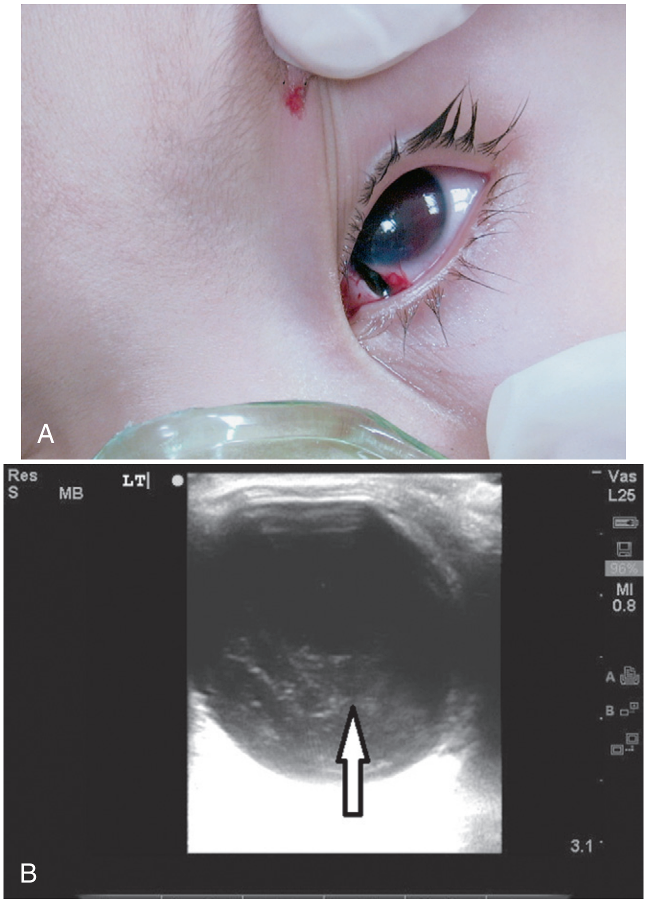


Figure 71-11. **A,** Scleral laceration with penetrating globe injury. Note care being taken not to increase intraocular pressure with examiner's fingers. **B,** Ocular ultrasound showing vitreous hemorrhage *(white arrow).* (Image courtesy Douglas Brunette, MD.)

a lower-than-normal intraocular pressure is a good indication of rupture, tonometry should not be performed in patients with suspected globe rupture. Any maneuvers that increase intraocular pressure need to be avoided. CT scan is increasingly being used to evaluate ocular trauma and possible globe rupture. However, CT has limited sensitivity and specificity (75% and 93%, respectively) in diagnosing open globe injuries. CT scan should be used as a complement to clinical findings (e.g., globe contour and volume loss) in diagnosing globe rupture.[26]

Treatment in the ED for a known globe rupture includes avoidance of further examination or manipulation and the placement of a protective metal eye shield to prevent accidental pressure on the globe. Keep the patient on nothing-by-mouth (NPO) status pending evaluation by ophthalmology and use antiemetics as needed. Broad-spectrum intravenous antibiotics should be instituted to cover the common organisms (*Bacillus* species, *Staphylococcus aureus, Pseudomonas* species, gram-negative organisms, and anaerobes) that cause post-traumatic endophthalmitis—for example, a third-generation cephalosporin (ceftazidime 2 g intravenously [IV] q8-12h), an aminoglycoside (gentamycin 3-6 mg/kg/day IV divided q8-12h), and vancomycin (2 g/day IV divided q12h).

Theoretic classic teaching states that the use of succinylcholine is contraindicated in the presence of a penetrating ocular injury because of the rise in intraocular pressure and potential for ocular extrusion, but a search of the literature does not identify a single case report. One study reported on the use of succinylcholine after pretreatment with nondepolarizing agents in 100 patients with

www.ketabpezeshki.com 66485457-66963820

penetrating eye injury; no adverse events were found.[27] Given the need for rapid airway management in a patient with penetrating ocular injury, rapid sequence intubation with succinylcholine and an induction agent is appropriate. Succinylcholine may be preceded by pretreatment with a defasciculating dose of a nondepolarizing neuromuscular blocking agent (e.g., 0.01 mg/kg of vecuronium or pancuronium), but there is no evidence that this improves outcome. Ophthalmologic consultation is required for all patients with suspected or proven globe rupture.

Posterior Segment Injuries

Clinical Features and Management

Vitreous Hemorrhage. Bleeding into the vitreous may occur from injuries to the retina and uveal tract and their associated vascular structures. Causes include diabetic retinopathy, posterior vitreous detachment, retinal vein occlusion, and trauma such as shaken baby syndrome in infants. Patients note decreased visual acuity and floaters. Floaters, described by the patient as dark dots or strands moving in the visual field in the direction of the preceding eye movement, are caused by vitreous blood. There is a diminished red reflex and an inability to visualize the fundus clearly with the direct ophthalmoscope (see Fig. 71-11B). Ocular ultrasound has shown to be an effective diagnostic tool in patients with vitreous hemorrhage and can help identify the cause.[28] Treatment of vitreous hemorrhage includes elevating the head of the bed to allow settling of the blood and avoiding platelet-inhibiting drugs and the Valsalva maneuver. If the patient is receiving warfarin, the international normalized ratio (INR) should be checked. Ophthalmologic consultation is warranted for acute traumatic vitreous hemorrhage, and a vitrectomy is generally performed when the vitreous hemorrhage is associated with a retinal detachment.

Retinal Injuries. Blunt injury to the retina may result in hemorrhage, a tear or detachment, or commotio retinae. Hemorrhage can occur in the preretinal (subhyaloid), superficial retinal, or deep (subretinal) spaces. Preretinal hemorrhage appears as boat shaped, superficial retinal hemorrhage as flame shaped, and deep retinal hemorrhage as rounded and grape-purple in color.

Tears and detachments from blunt trauma are common. Trauma is responsible for approximately 10% of all retinal detachments in the general population.[2] Symptoms include floaters from bleeding, flashing lights from stimulation of retinal neurons, and visual field cuts or decreased visual acuity. Retinal tears or detachments do not cause pain. Examination may reveal the hazy gray membrane of the retina billowing forward (Fig. 71-12A), but many tears are peripherally located and not seen via direct ophthalmoscopy. Bedside ocular ultrasound can be a useful and rapid test in the detection of retinal detachment (Fig. 71-12B).[29] Visual acuity may be normal unless the macula is involved. Indirect ophthalmoscopy is warranted if historical clues to the presence of retinal tears are present.

The sooner treatment is initiated, the greater the chance of visual preservation and recovery. After detachment, retinal ischemia ensues owing to loss of the choroid's blood supply. Patients with suspected or confirmed retinal breaks or detachments require emergent ophthalmologic consultation. Treatment includes photocoagulation or operative repair; prognosis depends on the condition of the macula.

Commotio retinae, also known as *Berlin's edema,* occurs after ocular trauma. A study showed that it was present in approximately 6% of patients who had surgically treated orbital blowout fractures.[30] Patients may have decreased visual acuity or may be asymptomatic. Examination reveals a cloudy whitening of the involved area that subsides in a few weeks with no specific treatment. Serial follow-up is necessary to ensure that retinal tear or detachment has not occurred.

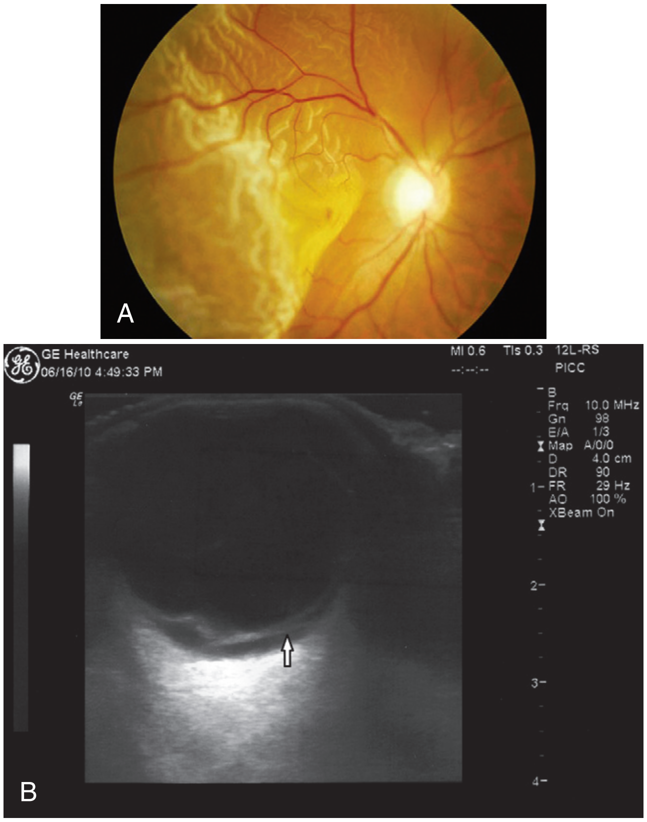


Figure 71-12. A, Retinal detachment. Note large portion of retina billowing forward. B, Bedside emergency department ultrasound showing retinal detachment *(white arrow).* (A, Image courtesy www.tedmontgomery.com. B, Image courtesy Nicholas Connors, MD and Sophia Lin, MD, New York Presbyterian-Weill Cornell Medical Center.)

Optic Nerve Injury. Significant blunt force to the orbital contents may avulse, transect, compress, or contuse the optic nerve. Fractures may extend into the orbital canal and cause optic nerve damage. Patients note visual field cuts or decreased visual acuity. Examination reveals an afferent pupillary defect, assorted visual field cuts, a decrease in visual acuity, or total blindness. The optic disk is normal initially, but pallor eventually develops. An orbital CT scan can help define the location and extent of injury. Management of traumatic optic neuropathy with steroids has been controversial. A 2011 Cochrane review looking at the use of steroids for traumatic optic neuropathy concluded that there is a high rate of spontaneous visual recovery in traumatic optic nerve damage and that steroids do not provide any additional benefit over observation.[31] Surgical decompression may be considered when decreasing visual acuity is occurring from a known orbital canal fracture. However, this procedure should be considered on a case-by-case basis and the decision left to the ophthalmologist because there does not appear to be any clear evidence that surgical decompression of the optic nerve provides any additional benefit.[32]

Penetrating Trauma

Lacerations of the Eyelids

Clinical Features and Management. Any laceration involving the eyelids prompts a search for penetrating globe injury and, if indicated, a thorough search for a foreign body. The use of soft eye pads is avoided to prevent increases in intraocular pressure.

www.ketabpezeshki.com 66485457-66963820

Figure 71-13. Canalicular laceration. This patient experienced a laceration of the upper canaliculus. (From Zitelli BJ, Davis HW [eds]: Atlas of Pediatric Physical Diagnosis, 5th ed. St Louis, Mosby, 2002.)

Figure 71-14. Corneal laceration with prolapse of the iris. The pupil is irregular and teardrop shaped, pointing toward the laceration. (From Roberts JR, Hedges JR [eds]: Clinical Procedures in Emergency Medicine, 5th ed. Philadelphia, Saunders, 2010.)

Emergency physicians can manage simple horizontal or oblique partial-thickness lid lacerations. Simple superficial lid lacerations not involving the lid margin and that are parallel to the relaxed skin tension lines may be stabilized with Steri-Strips. Otherwise, these lacerations can be closed primarily with 6-0 or 7-0 nylon interrupted sutures, which are then removed in 3 to 5 days.

The following fall into the category of complex lid lacerations, and affected patients are often best referred to a plastic surgeon or ophthalmologist:

1. Lacerations involving the lid margins.
2. Lacerations involving the canalicular system (suspected in any laceration involving the medial eyelid area) (Fig. 71-13).
3. Lacerations involving the levator or canthal tendons.
4. Laceration through the orbital septum. Orbital fat protrudes through septal lacerations into the wound. Because eyelids have no subcutaneous fat, the appearance of fat in a lid laceration confirms this diagnosis. These wounds are associated with a high incidence of globe penetration and intraorbital foreign bodies.
5. Lacerations with tissue loss.

Conjunctival Lacerations

Clinical Features and Management. Lacerations of the bulbar conjunctiva commonly involve intraocular foreign bodies or underlying scleral perforation. Slit-lamp examination can distinguish superficial from deeper lacerations. Small, superficial lacerations require no suturing and heal quickly. Topical prophylactic ophthalmic antibiotics are advisable. Larger (>1 cm) and deeper lacerations may require repair by an ophthalmologist.

Corneal and Scleral Lacerations

Clinical Features and Management

Corneal Lacerations. Signs of corneal perforation (full-thickness corneal lacerations) include loss of anterior chamber depth, teardrop-shaped pupil caused by iris prolapse through the corneal laceration, and blood in the anterior chamber (Fig. 71-14). Small corneal lacerations can be difficult to diagnose. If aqueous humor is leaking from the corneal wound, it appears as streaming fluorescent dye surrounded by an orange pool of solution on slit-lamp examination (Seidel's test). Full-thickness corneal lacerations are managed as described for blunt traumatic globe rupture.

Superficial partial-thickness corneal lacerations without a widened wound are treated with a cycloplegic, a topical antibiotic, and a pressure patch. Repairs of partial-thickness corneal lacerations requiring suture closure are performed in the operating room.

Scleral Lacerations. Penetrating scleral lacerations occur with the signs and symptoms of blunt globe rupture. Globe perforation may be unrecognized in the absence of significant physical examination findings.

Orbital and Intraocular Foreign Bodies

Clinical Features and Management. Penetrating orbital and intraocular injuries are approached with concern for an intracranial injury. If there is any evidence of ocular penetration, plain radiographs and CT scan can help in diagnosing the presence of an intraocular foreign body. Treatment of intraocular foreign bodies is dictated by clinical circumstances and is left to the ophthalmologist. Patients with acute intraocular foreign bodies should be hospitalized, have nothing by mouth, have a protective shield placed, and be given systemic antibiotics, such as ceftazidime 2 g IV q8-12h, and topical antibiotics, such as erythromycin 0.5% ointment applied every 4 to 6 hours. Generally speaking, acute intraocular foreign bodies are surgically removed; removal can be facilitated by intraoperative fluoroscopy.[33] Plastic, glass, and many metals are relatively inert, and their removal may cause more damage than their permanent presence. Organic foreign bodies are more important to remove because of their propensity for causing infection. Siderous oxidation of ocular tissues is a late complication of iron-containing intraocular foreign bodies and can lead to visual loss. Chalcosis, a sterile inflammatory reaction to copper-containing compounds, may occur, necessitating removal of the offending object.

Complications of Ocular Trauma

Clinical Features and Management

Post-traumatic Corneal Ulcers. Any defect in the corneal epithelium may become infected with bacteria or fungi. Ulcerations are surrounded by a cloudy white or gray-appearing cornea (Fig. 71-15). A reactive sterile hypopyon (pus or puslike fluid) may be present in the anterior chamber. Emergent ophthalmologic

www.ketabpezeshki.com 66485457-66963820

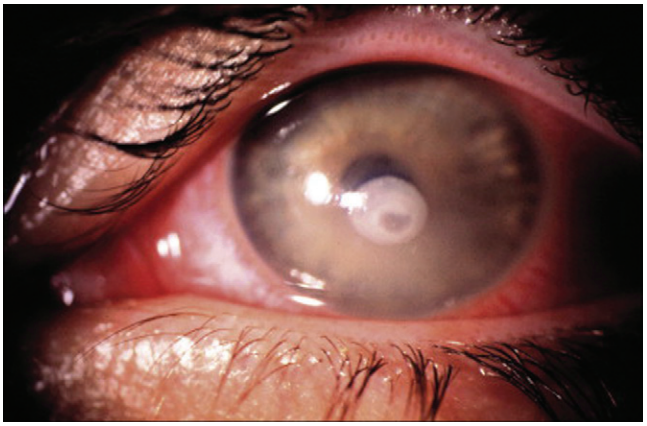


Figure 71-15. This corneal ulcer caused by *Pseudomonas aeruginosa* occurred in a young man who wore decorative contact lenses without professional supervision. (From Yanoff M, Duker JS [eds]: Ophthalmology, 3rd ed. Philadelphia, Mosby, 2008.)

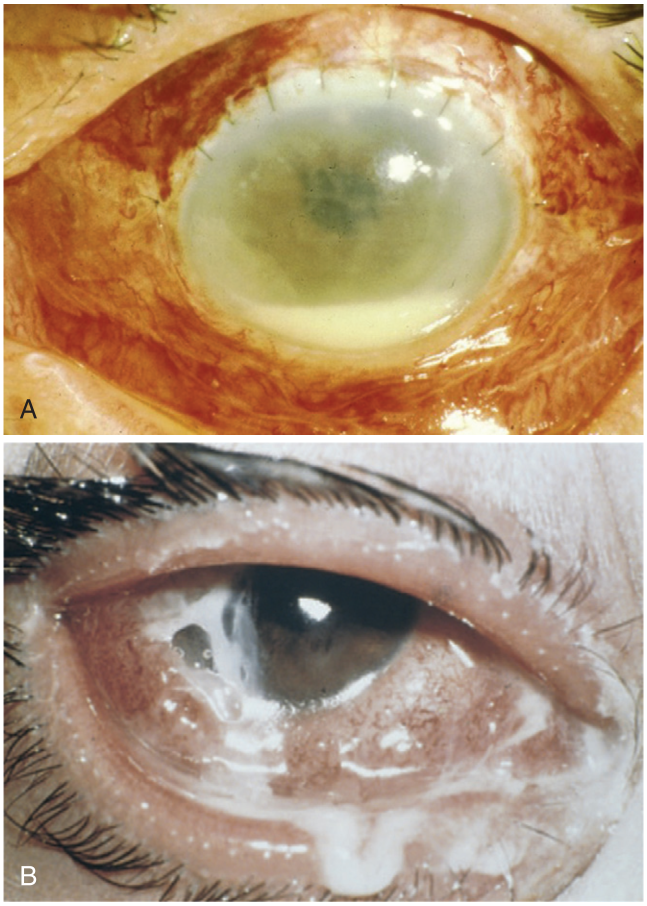


Figure 71-16. **A,** Eye with endophthalmitis, illustrating a hypopyon (pus in the anterior chamber). **B,** Purulent discharge and conjunctival hyperemia suggest bacterial conjunctivitis. (**A,** Courtesy Donald J. D'Amico. **B,** From Goldman L, Schaefer AI [eds]: Goldman's Cecil Medicine, 24th ed. Philadelphia, Saunders, 2012.)

consultation is needed. Treatment includes cycloplegia, topical antibiotics, and often admission to the hospital. Corneal perforation is a complication.

Endophthalmitis. Endophthalmitis is an infection involving the deep structures of the eye, namely the anterior, posterior, and vitreous chambers. Patients report pain and visual loss. Examination reveals decreased visual acuity, chemosis, and hyperemia of the conjunctiva, and the infected chambers are hazy or opaque (Fig. 71-16A). Endophthalmitis is a complication of blunt globe rupture, penetrating eye injury, foreign bodies, and ocular surgery. Prompt diagnosis and early treatment with intraocular and systemic antibiotics, such as ceftazidime 2 g IV q8-12h and vancomycin 1 g IV q12h, are important in the successful management of post-traumatic endophthalmitis. Intraocular gentamicin sulfate and clindamycin have been shown to be effective in the prevention of endophthalmitis after penetrating eye injuries.[34] Common pathogens are *Staphylococcus, Streptococcus,* and *Bacillus.*

Sympathetic Ophthalmia. Sympathetic ophthalmia is an inflammation that occurs in the uninjured eye weeks to months after the initial insult to the injured eye, usually after trauma or ocular surgery. It is thought to be an autoimmune response to the normally sequestered uveal tissues of the injured eye becoming exposed with injury. Sympathetic ophthalmia affects approximately 0.03 per 100,000 persons per year.[35] Patients have pain, photophobia, and decreased visual acuity. Treatment includes steroids and other immunosuppressive agents. Enucleation of the blind injured eye can reduce symptoms even after the sympathetic ophthalmia has developed.

DISEASE OF THE CONJUNCTIVA

Clinical Features and Management

Conjunctivitis

Conjunctivitis is the most common cause of red eye. Patients report pinkeye, redness, a foreign body sensation, lid swelling, drainage, and eye crusting in the morning. Photophobia and visual loss are notably absent. Conjunctivitis is an inflammation of the bulbar and palpebral conjunctiva caused by various viral, bacterial, mechanical, allergic, and toxic agents. When the cornea is also involved, the condition is known as *keratoconjunctivitis.* A viral cause is by far the most common, and in most cases, antibiotics are not indicated. *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus* organisms, *Moraxella catarrhalis,* and *Neisseria gonorrhoeae* are the most common bacterial pathogens. Less common bacterial causes are *Klebsiella* and *Pseudomonas.* There has also been an increased prevalence of methicillin-resistant *S. aureus* conjunctivitis over the last decade.[36]

Treatment of acute bacterial conjunctivitis includes warm compresses and topical ophthalmic antibiotics. Although bacterial conjunctivitis is frequently self-limiting, use of topical antibiotics has shown significantly improved rates of clinical and microbiologic remission.[37]

In uncomplicated acute bacterial conjunctivitis, topical trimethoprim/polymyxin is a good initial selection. Other agents commonly used include sodium sulfacetamide, ciprofloxacin, ofloxacin, gatifloxacin, and erythromycin. However, there is recent evidence that shows increasing resistance of gram-positive organisms to ciprofloxacin.[37] Neomycin ophthalmic solutions should be avoided because of the high incidence of hypersensitivity reactions. Ophthalmic ointments provide a soothing effect and have prolonged contact with the ocular surface, and ophthalmic drops do not interfere with vision. Medications should be continued for 7 days. Corticosteroids and eye patching should be avoided.

Cultures are indicated when symptoms are severe or when prior treatment has been inadequate or unsuccessful. Complications of acute bacterial conjunctivitis include corneal ulcer formation, keratitis, and corneal perforation. Patients with complicated bacterial conjunctivitis require referral to an ophthalmologist.

Acute bacterial infection caused by *N. gonorrhoeae* is uncommon but important because of its significant complications. Infection results from direct contact with infected individuals: the

www.ketabpezeshki.com 66485457-66963820

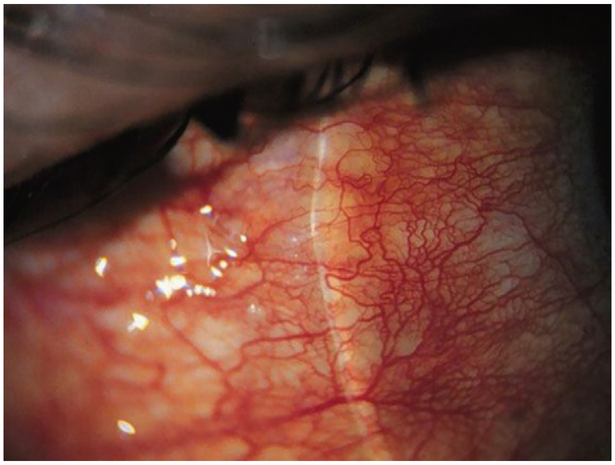


Figure 71-17. Conjunctival injection resulting from viral conjunctivitis. (Image courtesy www.tedmontgomery.com.)

infection is sudden in onset and progresses rapidly. Signs and symptoms are markedly increased, including pain and a copious purulent discharge (see Fig. 71-16B). Gram's stain may reveal the diagnosis, although cultures are more sensitive. Treatment is more aggressive than with other causes of bacterial conjunctivitis. Hospital admission for intravenous antibiotics such as ceftriaxone 1 g IV, saline irrigation, and topical ophthalmic antibiotics is warranted in moderate and severe cases and for any patient with corneal involvement. Outpatient management may be used in selected mild cases with ceftriaxone 1 g intramuscularly as a single dose, topical erythromycin ointment, and saline solution irrigation of the conjunctiva. A substantial proportion of patients have concomitant *Chlamydia trachomatis* infection, which is treated with oral doxycycline, tetracycline, or erythromycin or a single dose of 1 g of azithromycin.

Viral Conjunctivitis. Viral infection is by far the most common cause of conjunctivitis, with adenovirus being the most prevalent. Viral conjunctivitis generally produces more redness, itching, and eye irritation than bacterial disease. There is initially a watery discharge, which often becomes purulent appearing. Viral causes also are associated with preauricular lymphadenopathy and longer duration of symptoms than bacterial causes (Fig. 71-17). It commonly occurs in the setting of concurrent or earlier symptoms of viral illness (e.g., fever, upper respiratory infection [URI] symptoms, myalgias, malaise). The patient usually reports initial eye irritation in one eye that spread to the other eye a few days later.

Viral conjunctivitis is very contagious as long as symptoms persist, up to 12 days after onset, and appropriate preventive measures, such as frequent handwashing, are important to contain the spread of infection. Treatment consists of artificial tears, if needed, and cool compresses. A vasoconstrictor and antihistamine combination can be used if itching is severe. It may be difficult to differentiate between viral and bacterial conjunctivitis, although some clues in the history and physical examination (such as presence of recent viral infection, preauricular lymphadenopathy, and duration of symptoms) may point to one direction.

Topical antibiotics are indicated only when a primary bacterial infection or bacterial superinfection is suspected. Viral conjunctivitis and many cases of bacterial conjunctivitis will resolve spontaneously, so the majority of patients require only supportive, symptomatic care—often simply reassurance. We recommend that patients with a presumptive diagnosis of viral conjunctivitis not be prescribed antibiotics unless their symptoms have persisted without improvement for 72 hours after evaluation (see Chapter 22). Because the diagnosis of viral conjunctivitis can be made clinically, viral culture and laboratory investigation are not necessary.

Ophthalmia Neonatorum. Conjunctivitis that occurs within the first month of life is termed *ophthalmia neonatorum* and has several causes, including bacterial, viral, and chemical. A bacterial cause should be investigated with Gram's stain and cultures within the first 2 weeks of life. *N. gonorrhoeae* and *Chlamydia* are both transmitted from mother to infant through the birth canal.

Infection with *N. gonorrhoeae* manifests within 2 to 4 days after birth. The infant should be carefully examined for evidence of systemic gonococcal infection. Hospitalization and blood and cerebrospinal fluid examination may be indicated. Nonsystemically infected neonates can be effectively treated with a single dose of ceftriaxone 25 to 50 mg/kg up to a total dose of 125 mg intramuscularly, topical polymyxin B–bacitracin ointment, and saline washes. These patients also require coverage for ocular chlamydial infection, which is the most common cause of neonatal conjunctivitis in the United States. Neonates usually develop symptoms 5 to 14 days after delivery. Dual therapy with topical erythromycin ointment and oral erythromycin syrup 50 mg/kg/day in four divided doses for 14 days is recommended.

Chemical conjunctivitis from antibiotic ointment administration immediately after delivery occurs within 1 to 2 days of birth but should not be the diagnosis if the infant has significant symptoms, the time course is inappropriate, or other historical and physical examination parameters are not classic. In such cases a bacterial cause is assumed.

In neonates with no information from stains or cultures and in whom an organism is not known or suspected, topical erythromycin ointment and oral erythromycin are used.

Miscellaneous Conjunctivitis. Allergic conjunctivitis is common and is associated with type 1 hypersensitivity reaction medicated by immunoglobulin E (IgE) and mast cell activation. Allergens include drugs, cosmetics, and environmental agents. Eye itching is generally more pronounced in patients with allergic conjunctivitis and tends to be bilateral. Mild to moderate injection with glassy chemosis and watery discharge can also be seen. Artificial tears, cool compresses, combination topical ocular decongestants, topical vasoconstrictor-antihistamine combinations, and topical nonsteroidal agents may be used for treatment. In addition, systemic medications such as loratadine can be helpful. Other types of conjunctivitis include toxic conjunctivitis from topical ocular medications (aminoglycosides, antivirals, and preservatives), molluscum contagiosum, and chronic conjunctivitis.

DISEASE OF THE CORNEA

Differential Considerations

Clinical Features and Management

Pterygium and Pinguecula. A pterygium is a wedge-shaped area of conjunctival fibrovascular tissue that usually grows from the nasal side of the sclera and extends onto the cornea. Pterygium is associated with increased exposure to ultraviolet light, especially in subtropical and tropical climates. Patients usually have eye irritation as well as visual changes if a significant portion of the cornea is involved. A pinguecula is white or yellow, flat to slightly raised tissue on the conjunctiva, immediately next to but not on the cornea. Pinguecula can also be associated with ultraviolet light exposure or dryness. Patients can be asymptomatic or may have irritation and redness. Treatment of pterygium and pinguecula includes protection from wind, dust, sunlight, and artificial tears. An inflamed pinguecula can be treated with a short course of a topical nonsteroidal agent. Nonemergent referral to an ophthalmologist is recommended. Surgical removal is possible in selected cases.

www.ketabpezeshki.com 66485457-66963820

Superficial Punctate Keratitis. Superficial punctate keratitis consists of superficial, multiple, pinpoint corneal epithelial defects. Patients experience pain, photophobia, redness, and a foreign body sensation. Superficial punctate keratitis is a nonspecific finding that is seen in many conditions. The most common precipitating conditions are ultraviolet burns (welders or users of sun lamps), conjunctivitis, topical eye drug toxicity (neomycin, gentamicin, and drugs with preservatives, including artificial tears), contact lens disorders, dry eye and exposure keratopathy, blepharitis, mild chemical injury, and minor trauma. Specific treatment is aimed at the underlying offending cause. Nonspecific treatment for symptomatic non–contact lens–associated superficial punctate keratitis includes nonpreserved artificial tears, topical antibiotics such as trimethoprim/polymyxin drops, and cycloplegia. Patients with a significant contact lens–associated superficial punctate keratitis should be advised to stop wearing their contact lenses and should be treated with a topical fluoroquinolone or tobramycin drops during the day, ointment at night, and ophthalmologic follow-up the next day.

Corneal Ulcers and Infiltrate from Infection. Corneal infiltrates arise as a focal white opacity without an epithelial defect. Corneal ulcers have an overlying corneal epithelial defect that stains with fluorescein in addition to the corneal infiltrate. Patients experience pain, redness, photophobia, and decreased vision. The most common cause is bacterial, but fungal and herpes simplex infections are also possible. Corneal culturing is recommended before treatment is initiated.

Herpes Simplex. Herpes simplex may be either primary or reactivation of preexisting disease. Symptoms include foreign body sensation, tearing, photophobia, clear discharge, and decreased visual acuity. Physical examination reveals a red eye and may or may not include the classic herpetic vesicles located on the lids or conjunctiva. Corneal involvement is seen on slit-lamp examination and may appear as a superficial punctate keratitis, ulcer, or the classic dendritic lesions (Fig. 71-18). Treatment for epithelial keratitis consists of topical antiviral agents, such as trifluridine 1% every 2 hours for 14 to 21 days.[39] Up to 97% of patients heal within 2 weeks following treatment with trifluridine therapy. Topical prophylactic antibiotics, such as 0.5% erythromycin ophthalmic ointment applied every 3 to 4 hours, and a cycloplegic, such as 1% cyclopentolate (1 or 2 drops, which last up to 24 hours), are also used. Topical steroids are contraindicated in corneal epithelial disease but have proved to be beneficial in stromal disease.[39] Emergent ophthalmologic consultation is advised for all patients with suspected herpes simplex infections with corneal involvement.

Figure 71-18. Herpes simplex keratitis infection. Note typical dendritic pattern on cornea. (Image courtesy www.tedmontgomery.com.)

Herpes Zoster. Herpes zoster keratoconjunctivitis occurs as a result of activation of the virus along the ophthalmic division of the trigeminal nerve. The rash follows dermatomal patterns, involves the forehead and upper eyelid, and produces significant pain. Involvement of the nasociliary branch of the trigeminal nerve, which manifests with zoster lesions on the tip of the nose (Hutchinson's sign), is associated with a 76% risk of ocular involvement versus a 34% risk if the nerve is not involved. Ophthalmic herpes zoster accounts for approximately 10 to 20% of all zoster cases and necessitates emergent ophthalmologic consultation. If not treated and recognized immediately, herpes zoster of the eye may result in acute necrotizing retinitis and vision loss. Treatment is complex and depends on the type, location, and degree of ocular involvement. Antiviral agents (acyclovir, valacyclovir, or famciclovir), topical steroid agents, and topical antibiotics are used. The use of topical antibiotics is mostly for the prevention of secondary bacterial infection. Early treatment with antiviral therapy within 72 hours of the onset of the rash has been shown to reduce acute pain and ocular complications.[40] Clinical trials have also shown that topical ganciclovir 0.15% ophthalmic gel is safe and effective in the treatment of herpetic epithelial disease.[41] Patients should also be prescribed adequate analgesia for pain control, cool compresses, and lubrication drops for comfort. Some patients may require admission for intravenous antiviral therapy, whereas many can be treated as outpatients with close ophthalmologic follow-up. In a recent study, orally administered valacyclovir resulted in substantial vitreous penetration of this antiviral agent and was as effective as intravenous acyclovir treatment.[42]

Contact Lens Complications. The common complications of contact lens use involving the cornea include mechanical damage such as abrasions, corneal neovascularization, infections producing corneal ulcers, hypersensitivity or toxicity reactions to preservatives in solutions, and contact lens deposits. Contact lens wear can produce hypoxia because the barrier of the contact lens reduces the available oxygen for the corneal surface. In most cases, if patients experience discomfort and remove the contact lens for 2 to 3 days, there is complete resolution of the symptoms. However, long-term contact lens use produces chronic hypoxia, resulting in thinning of the corneal epithelium and increasing the chance of bacterial infection. There has been an increased prevalence of ocular infections in the adolescent population owing to increased contact lens use, with coagulase-negative *Staphylococcus* being the most common pathogen. *Pseudomonas* is also an important pathogen in contact lens–acquired infections.

The newer topical fluoroquinolones (e.g., gatifloxacin and moxifloxacin) cover both staphylococcal species and *Pseudomonas* and should be applied six to eight times daily to the affected eye.[43] If no significant signs or symptoms exist that indicate corneal infection, the patient is advised to discontinue contact lens use and follow up with an ophthalmologist. When corneal infection is present or suspected, immediate ophthalmologic consultation is indicated.

DISORDERS OF THE LIDS AND OCULAR SOFT TISSUES

Differential Considerations

Clinical Features and Management

Hordeolum and Chalazion. Hordeola and chalazia are localized, nodular, inflammatory processes of the eyelids. Hordeola, also known as *styes,* are acute inflammations of the glands of Zeis or hair follicles caused most commonly by *Staphylococcus* species. A hordeolum typically begins as a diffuse swelling, discomfort, and erythema of the lid margin and is not obvious until it coalesces

www.ketabpezeshki.com 66485457-66963820

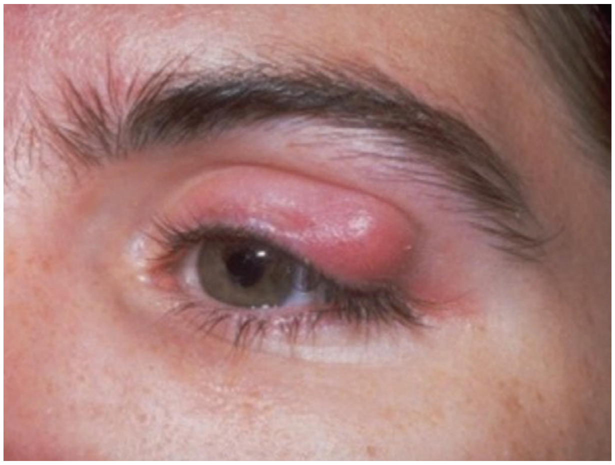


Figure 71-19. Chalazion of the upper eyelid. (Image courtesy www.tedmontgomery.com.)

Figure 71-20. Dacryocystitis.

into a discrete nodule. Even when symptoms and signs are diffuse, though, localized tenderness at the culprit gland almost always is present. A chalazion is the result of an obstructed meibomian gland that results in swelling within the lid surface with the lid margin being normal. Symptoms and signs include pain, swelling, and redness (Fig. 71-19). Spontaneous rupture may occur, and most resolve spontaneously. Warm compresses applied for 15 minutes four to six times each day often are recommended, but there have been no studies proving the value of this approach. Topical antibiotics (erythromycin) rarely are indicated, and only if there is a significant blepharitis that persists after coalescence of the lesion into a clear hordeolum. Incision and drainage are indicated for chalazia unresponsive to conservative therapy but require referral to an ophthalmologist.

Dacryocystitis. Dacryocystitis is an acute infection of the lacrimal sac from nasolacrimal duct obstruction. The most common causative organism is *S. aureus*. Symptoms and signs include pain, tenderness, swelling, and erythema over the lacrimal sac (Fig. 71-20). Pressure over the sac may express purulent material from the puncta. Treatment includes topical ocular and oral antistaphylococcal antibiotics and warm compresses. Gentle massage of the area during warm compress application may help decompress purulent material and relieve symptoms. Systemically ill patients should be hospitalized.

Blepharitis. Patients have thickened, mattered, red eyelid margins with pronounced blood vessels. They report burning, itching, tearing, foreign body sensation, and morning crusting of the eyelids. Treatment includes rubbing the eyelid margins with a mild shampoo on a cotton-tipped applicator or cloth twice per day, warm compresses, and artificial tears. Severe blepharitis can also be treated with topical antibiotic ointment applied at night.

Preseptal Cellulitis. Patients have lid erythema and warmth, tenderness, and swelling and may have a low-grade fever. Preseptal cellulitis is more common in younger children, with sinusitis being the most common cause. It may also occur after minor skin trauma, such as an insect bite, or may spread from a focus of impetigo. Evaluation focuses on identifying associated findings that may indicate a more dangerous postseptal (orbital) cellulitis: these findings include proptosis, restriction of extraocular movements, pain with eye movement, chemosis, and patient toxicity. If any of these findings are present, orbital cellulitis or abscess is suspected, and the patient is managed more aggressively with CT scan of the brain and orbits and hospitalization. Orbital cellulitis can result in meningitis and cavernous sinus thrombosis if it is not recognized or is left untreated. Preseptal cellulitis is characterized by a continuum of disease, and treatment is tailored to the degree of the patient's toxicity. Mild disease can be treated on an outpatient basis with oral antibiotics, but hospitalization with IV antibiotics may be needed for moderate to severe disease and for younger children. The choice of antibiotic should cover *Streptococcus* and *Staphylococcus* species because these are the most common pathogens. The species *Streptococcus anginosus* has been recently shown to be an emerging pathogen in cases of pediatric orbital cellulitis.[44] The mainstay of treatment for orbital skin infections is β-lactam antibiotics.[45] Amoxicillin-clavulanate 875 mg orally (PO) two times daily for 10 to 14 days is an excellent choice for adult outpatient management, whereas an intravenous second- or third-generation cephalosporin, such as cefuroxime or ceftriaxone, is recommended for inpatient treatment. Children are treated as outpatients with amoxicillin-clavulanate 20 to 40 mg/kg PO divided into three doses for 10 to 14 days, and an intravenous second- or third-generation cephalosporin for inpatient treatment. Routine empirical antibiotic coverage for methicillin-resistant *S. aureus* is not recommended owing to emerging resistance patterns and adverse effects of additional antibiotics; each patient should be looked at on a case-by-case basis based on community prevalence and in consultation with an infectious disease specialist. Patients with orbital cellulitis that is not improving with initial treatment or is secondary to trauma or surgery and those who appear toxic should have empirical coverage with vancomycin or clindamycin. If the patient is admitted and shows improvement with intravenous antibiotics within 48 to 72 hours, a trial of oral antibiotics as outpatient therapy can be considered with close follow-up.

GLAUCOMA

Clinical Features and Management

Aqueous humor is produced by the ciliary processes. In addition to providing structural support to the eye, aqueous humor delivers oxygen and nutrients to the avascular lens and cornea and removes their waste products. This fluid passes from the posterior chamber to the anterior chamber through the pupillary aperture. The aqueous humor is transported into the trabecular meshwork located at the anterior chamber angle formed by the junction of the root of the iris and the peripheral cornea. The trabecular meshwork serves as a one-way valve and filter for the aqueous humor into the canal of Schlemm, which in turn drains into episcleral veins. Intraocular pressure is determined by the rate of aqueous humor production relative to its outflow and removal. Normal intraocular pressure is 10 to 20 mm Hg.

www.ketabpezeshki.com 66485457-66963820

Glaucoma is an optic neuropathy caused by increased intraocular pressure. Irreparable optic nerve damage can result. The simplest classification is to divide the glaucomas into primary or secondary and open angle or closed angle. Secondary glaucoma is associated with another ocular or nonocular event, whereas primary glaucoma is not. Closed-angle glaucoma is caused when the anterior chamber angle is narrowed, reducing the outflow and removal of aqueous humor, whereas open-angle glaucoma occurs with a normal anterior chamber angle.

Patients vary in their susceptibility to a given level of intraocular pressure. Some may develop significant optic nerve findings despite a relatively low intraocular pressure (low-tension glaucoma), whereas others may have scant optic nerve changes despite relatively high intraocular pressure (ocular hypertension).

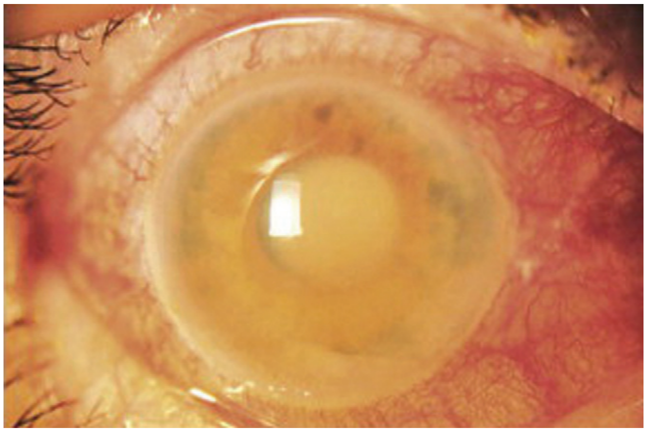


Figure 71-21. Acute narrow angle glaucoma. (From Yanoff M, Duker JS [eds]: Ophthalmology, 3rd ed. Philadelphia, Mosby, 2008.)

Primary Open-Angle Glaucoma

Primary open-angle glaucoma is the most common form of glaucoma and is a leading cause of blindness in the United States. There is increased resistance to aqueous humor outflow through the trabecular meshwork. Primary open-angle glaucoma is generally insidious, slowly progressive, chronic, bilateral, and painless. Advanced disease occurs before symptoms. Symptoms begin as visual field loss at the periphery that progresses centrally. Signs include an optic cup to optic nerve ratio of greater than 0.6. Other findings include vertically oval, deep, and pale optic cups, with nasal displacement of blood vessels.

The three treatment options are medications, argon laser trabeculoplasty, and guarded filtration surgery. Initial treatment is generally with one or more topical agents. Beta-blockers, selective alpha$_2$-receptor agonists, carbonic anhydrase inhibitors, prostaglandin agonists, miotics, and sympathomimetics are all used (see later).[46]

Topical ocular medications are absorbed and may produce significant systemic side effects. Topical beta-blockers have produced asthma, heart block, congestive heart failure, hypoglycemia, and depression. Adrenergics have produced hypertension and cardiac dysrhythmias, whereas carbonic anhydrase inhibitors have produced renal calculi and hypokalemia. Complications may arise as a result of drug interaction. Prolonged apnea, for example, has resulted when succinylcholine has been given to a patient receiving topical ophthalmologic acetylcholinesterase inhibitors.

Secondary Open-Angle Glaucoma

Secondary open-angle glaucoma has a number of causes, including lens-induced, inflammatory, exfoliative, pigmentary, steroid-induced, and traumatic causes, angle recession, and ocular tumor. Treatment is directed to the offending mechanism and includes the methods used for primary open-angle glaucoma.

Primary Angle Closure Glaucoma

Primary angle closure glaucoma occurs in patients who have anatomically small and shallow anterior chambers. The peak incidence occurs at ages 55 to 70. This anatomic variation results in the iris being nearly in contact with the lens, resulting in resistance to aqueous humor flow from the posterior to anterior chamber. This is called *pupillary block.*

Attacks of primary angle closure glaucoma are precipitated by pupillary dilation. Dimly lit rooms, emotional upset, and various anticholinergic and sympathomimetic medications are common precipitating events. The dilation of the pupil increases the degree of pupillary block, leading to an accumulation of aqueous humor in the posterior chamber. The iris bulges forward, obliterating the angle between the cornea and iris, obstructing the trabecular meshwork, decreasing outflow, and leading to a rapid rise in intraocular pressure.

A second, less common mechanism of acute angle closure glaucoma, produced without pupillary block, is caused by a flat or plateau iris. This leads to a narrow-angle recess. Dilation of the pupil causes the iris to fold and bunch over the angle, blocking aqueous humor outflow into the trabecular meshwork.

Symptoms are abrupt in onset and include severe eye pain, blurred vision, headache, nausea, vomiting, and occasionally abdominal pain. Patients see a halo around lights. Signs include conjunctival injection and a cloudy (steamy) cornea with a mid-positioned to dilated pupil that is sluggish or fixed (Fig. 71-21). The affected globe may be tender and firm compared with the unaffected side. Visual acuity may be significantly decreased, and intraocular pressures are markedly elevated.

Treatment is begun promptly with the goal of reducing intraocular pressure and preserving vision. If visual acuity is markedly reduced (hand movements or less), a combination of all topical glaucoma medications with intravenous osmotics and acetazolamide is recommended. Intraocular pressures below 50 mm Hg without significant visual acuity change can be managed without the intravenous medications. Topically administered timolol 0.5% decreases intraocular pressure within 30 to 60 minutes. Pilocarpine, a miotic agent, 1 to 2% is topically administered, 1 drop every 15 minutes for two doses, and 1 drop may be placed prophylactically in the unaffected eye. A topical alpha$_2$-agonist (apraclonidine 1.0%) for one dose and topical steroid (prednisolone acetate 1% every 15 minutes for four doses) should be given. In the setting of a severe attack, acetazolamide, a carbonic anhydrase inhibitor, is given in an intravenous dose of 250 to 500 mg, and mannitol 1.5 g/kg over 45 minutes. Sedatives and antiemetics may be administered as needed. Emergent ophthalmologic consultation is warranted.

The definitive therapy for primary angle closure glaucoma is surgical.

Secondary Angle Closure Glaucoma

Pupillary block may develop from a swollen or dislocated lens or posterior synechiae (adhesions between the iris and lens). Secondary angle closure glaucoma, without pupillary block, can be caused by intraocular tumors or by central retinal vein occlusion or may develop postoperatively. Treatment is directed at the offending cause.

www.ketabpezeshki.com 66485457-66963820

ACUTE VISUAL LOSS

Differential Considerations

Acute visual loss, usually in only one eye, occurs over a period ranging from a few seconds to a day or two. The vision is generally reduced to 20/200 or worse. Patients need to be quickly evaluated to determine whether a treatable cause exists. The differential diagnosis of acute visual loss not related to trauma includes vascular occlusion, retinal detachment, vitreous hemorrhage, macular disorders, neuro-ophthalmologic disease, and hysteria. Most of these patients need ophthalmic or neurologic referral for a complete workup.

Patients may report acute visual loss when they may have neither an acute process nor a visual loss caused by the eye itself. For example, a patient with a visual field cut secondary to a neuro-ophthalmologic lesion may have an acute visual loss when the patient discovers the field cut. A patient with a hemianopsia usually has normal visual acuity even though both eyes are affected. An accurate history of how the patient discovered the visual loss, as well as the timing of that loss, is vital.

Clinical Features and Management

Central Retinal Artery Occlusion. Acute visual loss as a result of vascular occlusion of the central retinal artery is typically painless. The ophthalmic artery is the first intracranial branch of the internal carotid artery, and the central retinal artery is the first intraorbital branch of the ophthalmic artery. Central retinal artery occlusion causes an ischemic stroke of the retina. It occurs most commonly in those aged 50 to 70 years, and 45% have carotid artery disease. Risk factors include hypertension, cardiac disease, diabetes, collagen vascular disease, vasculitis, cardiac valvular abnormality, and sickle cell disease. Patients with increased orbital pressure are also at risk, including patients with acute glaucoma, retrobulbar hemorrhage, and endocrine exophthalmos. Patients report a severe loss of vision that develops over seconds. Examination reveals a markedly reduced visual acuity with a prominent afferent pupillary defect. On funduscopic examination, the retina is edematous with a pale gray-white appearance, and the fovea appears as a cherry-red spot (Fig. 71-22).

Central retinal artery occlusion is a true ocular emergency and requires immediate management directed at dislodging the embolus, dilating the artery to promote forward blood flow, and reducing intraocular pressure to allow an increase in perfusion gradient. A number of interventions have been recommended, though there is little evidence to support the benefit of any. Immediate initiation of digital global massage in the ED is recommended and performed by applying direct digital pressure through closed eyelids. The pressure can be applied for 10 to 15 seconds and followed by a sudden release. Increased carbon dioxide pressure (P_{CO_2}) leads to retinal artery vasodilation and increased retinal blood flow and is accomplished by inhaling a 95% oxygen–5% carbon dioxide mixture (carbogen). Intraocular pressure may be reduced by instilling timolol maleate 0.5% topically. Acetazolamide, 500 mg IV or PO, lowers intraocular pressure and increases retinal blood flow. Emergent ophthalmologic consultation is indicated, as anterior chamber paracentesis may be attempted to facilitate the lowering of the intraocular pressure. One study, however, failed to find any therapeutic benefit for patients who received anterior chamber paracentesis and inhaled carbogen.[47] Another study found lack of efficacy of current standard treatment, including anterior chamber paracentesis, globe massage, and intraocular pressure–lowering agents, in acute central retinal artery occlusion.[48]

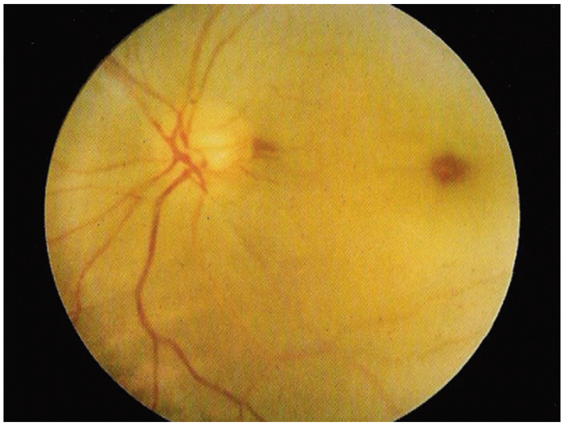


Figure 71-22. Central retinal artery occlusion. Note cherry-red spot (fovea).

Central retinal artery occlusion is an ischemic stroke and may be amenable to the use of thrombolytic agents as in other ischemic conditions, such as myocardial infarction and central nervous system stroke. A complete medical evaluation is necessary because central retinal artery occlusion is usually an embolic event. Thrombolytic agents have been studied, but no clear guidelines for their use exist. One study showed improvement of visual acuity in 10 of 12 patients who were given intravenous tissue plasma activator for central retinal or ophthalmic artery occlusion. However, all of these patients had residual visual field defects.[49] Another study demonstrated that use of a low-dose thrombolytic improved visual acuity by three or more lines in 32% of patients treated.[50]

Use of a local intra-arterial thrombolytic demonstrated improved visual acuity compared with standard therapy in one study.[51] In a review of eight original studies in which 158 patients treated with an intra-arterial thrombolytic were represented, visual improvement occurred on average in 93% of patients, with 13% achieving 20/20 or better, 25% achieving 20/40 or better, and 41% achieving 20/200 or better. Complications occurred in 4.5% of cases.[52] However, a prospective randomized multicenter clinical trial showed no benefit of intra-arterial thrombolytic therapy.[53] Intra-arterial thrombolytic therapy may produce superior visual outcomes compared with conventional treatments for central retinal artery occlusion when instituted in certain situations. A 2011 study demonstrated that the effective therapeutic time window of opportunity for intra-arterial thrombolytic therapy is likely less than 6 hours.[54] Conflicting evidence precludes the ability to make a recommendation on the use of thrombolytics in the treatment of central retinal artery occlusion, and management is tailored to the individual patient and the setting in which care is provided.

Central Retinal Vein Occlusion. A painless loss of vision, central retinal vein occlusion leads to edema, hemorrhage, and vascular leakage. The wide spectrum of clinical appearances depends on the degree of venous obstruction present. Loss of vision ranges from minimal to recognition of hand motion only. There are two types of central retinal vein occlusion, ischemic and nonischemic. The nonischemic type involves mild fundus changes and does not include an afferent pupillary defect. These patients tend to have less severe visual loss, with two thirds of the patients having 20/40 or better visual acuity without therapy.[55] Patients with ischemic central retinal vein occlusion have a marked decrease in visual acuity and often an afferent pupillary defect. Appearance can vary but classically includes dilated and tortuous veins, retinal hemorrhages, and disk edema. Hemorrhages can cover the entire fundus, giving a "blood and thunder" appearance (Fig. 71-23A). Branch retinal vein occlusions occur just distal to an arteriovenous crossing, and hemorrhages occur distal to the site of occlusion. The differential diagnosis of central retinal vein occlusion includes

www.ketabpezeshki.com 66485457-66963820

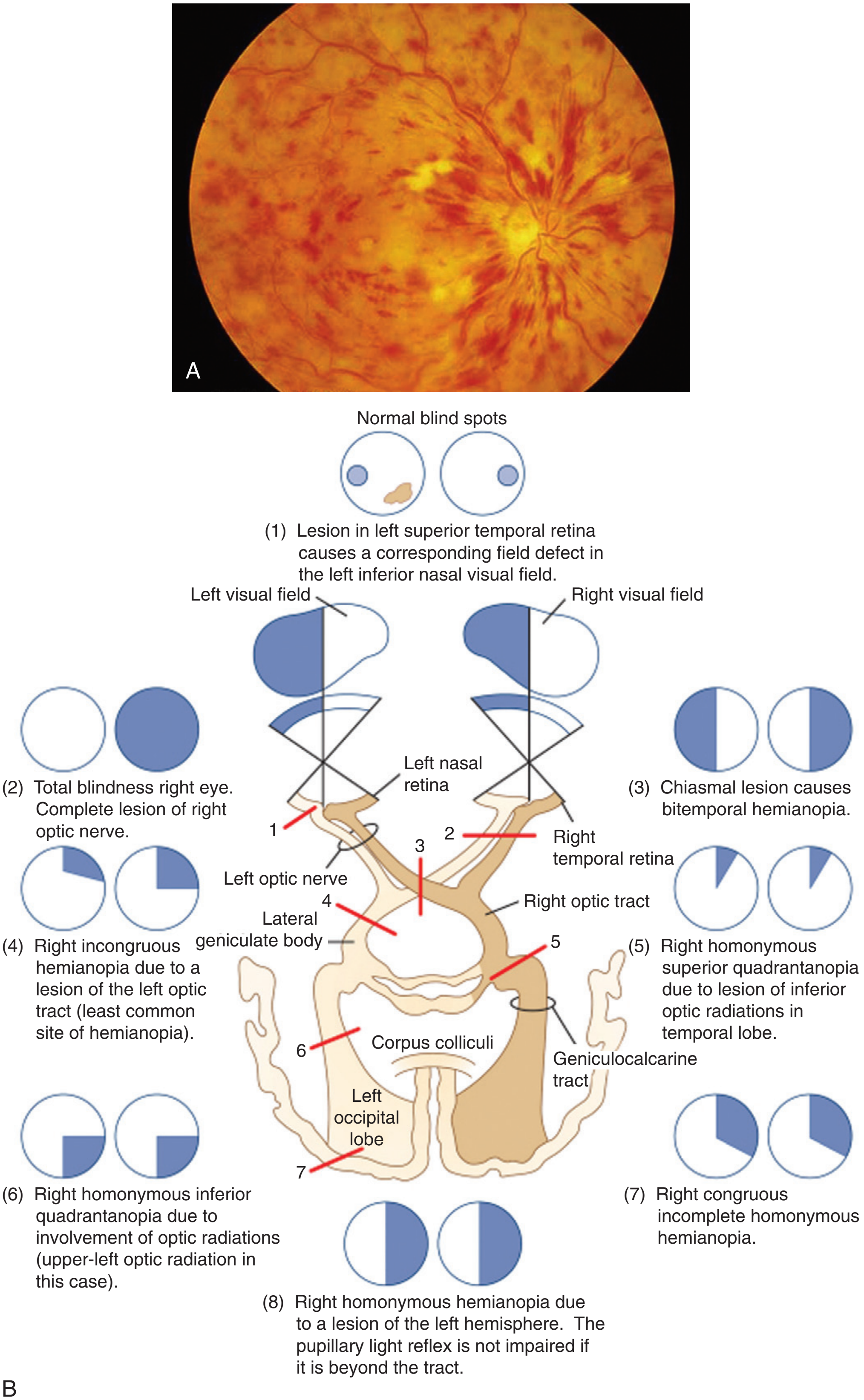


Figure 71-23. **A,** Central retinal vein occlusion. Note "blood and thunder" appearance. **B,** Topographic diagnosis of visual field defects. (**A,** Image courtesy www.tedmontgomery.com and **B,** from Bradley WG, Duroff RB, Fenichel GM, Jankovic J: Neurology in Clinical Practice, 5th ed. Oxford, Butterworth-Heinemann, 2007.)

www.ketabpezeshki.com 66485457-66963820

hypertension, diabetes mellitus, hyperviscosity syndromes, and papilledema. All of these are bilateral processes, whereas central retinal vein occlusion is generally unilateral. Neovascular glaucoma and macular edema are the major complications of ischemic central retinal vein occlusion.

Treatment of central retinal vein occlusion includes lowering of intraocular pressure, topical steroids, cyclocryotherapy, and photocoagulation. Recent studies of patients with central retinal vein occlusion who developed macular edema treated with intraocular antivascular growth factor demonstrated benefit.[56,57] Intravitreal injection of steroids also shows promise in the management of macular edema associated with central retinal vein occlusion.[58] The use of antithrombotic therapy, in particular the use of low-molecular-weight heparin, has also shown recent promise.[59] Underlying medical disease should be managed as well. The prognosis depends on the degree of obstruction and resultant complications.

Retinal Breaks and Detachment. The retina has two layers—the inner neuronal retina layer and the outer retinal pigment epithelial layer—which can be separated by fluid accumulation. A retinal break is a tear in the retinal membranes and may or may not lead to retinal detachment. Retinal detachments occur by three mechanisms: rhegmatogenous, exudative, and tractional. Rhegmatogenous retinal detachment occurs as a result of a tear or hole in the neuronal layer, causing fluid from the vitreous cavity to leak between and separate the two retinal layers. Rhegmatogenous retinal detachment, the most common type of retinal detachment, generally occurs in patients older than 45 years, is more common in men than in women, and is associated with degenerative myopia. Retinal detachment is fairly uncommon, affecting about 1 in 300 people over the course of their lifetime, and the history of a rhegmatogenous retinal detachment is a risk factor for disease in the other eye.[60] Trauma may be associated with rhegmatogenous detachment by causing tears in the retina or by causing a disinsertion of the retina from its attachment at the ora serrata anteriorly. Traumatic retinal detachment can occur at any age. There is greater risk with severe myopia.

Exudative retinal detachment occurs as a result of fluid or blood leakage from vessels within the retina. Conditions leading to exudative retinal detachment include hypertension, toxemia of pregnancy, central retinal venous occlusion, glomerulonephritis, papilledema, vasculitis, and choroidal tumor.

Traction retinal detachment is a consequence of fibrous band formation in the vitreous and contraction of these bands. These fibrous bands result from the organization of inflammatory exudates or blood from prior vitreous hemorrhage.

Typically, patients note flashes of light related to the traction on the retina, floaters related to vitreal blood or pigmented debris, and visual loss. The visual loss is commonly described as a filmy, cloudy, or curtain-like appearance. Pain is absent. Visual acuity can be minimally changed to severely decreased. Visual field cuts relate to the location of the retinal detachment, and an afferent pupillary defect occurs if the detachment is large enough. When the detachment is visualized by ophthalmoscopy, the retina appears out of focus at the site of the detachment. In large retinal detachments with large fluid accumulation, the bullous detachment, with retinal folds, can easily be seen (see Fig. 71-12A). Retinal detachment cannot be ruled out by direct funduscopy. Indirect ophthalmoscopy is needed to visualize the more anterior portions of the retina. Bedside ED ultrasonography can be a useful tool in confirming the presence of a retinal detachment[61] (see Fig. 71-12B).

The timing of repair of acute rhegmatogenous and tractional retinal detachment is important. Patients in whom the macula is not detached on presentation should undergo prompt surgery, with the goal of preventing macular detachment. The duration of macular detachment, measured from the reported time of the loss of central visual acuity, is inversely related to final visual acuity. One recent study showed that there was a significant decrease in final visual acuity if the macula was not reattached within 6 days.[62] Treatment of exudative detachment is aimed at the underlying cause or use of laser photocoagulation. Any patient suspected of having a retinal break or detachment requires immediate ophthalmologic consultation.

Posterior Vitreous Detachment. Posterior vitreous detachment is a common occurrence in patients older than 60 years. With aging, the vitreous gel pulls away from the retina, which can lead to symptoms similar to those of retinal break, vitreous hemorrhage, and retinal detachment. No specific treatment is indicated for posterior vitreous detachment unless it is accompanied by a retinal break, vitreous hemorrhage, or retinal detachment. Patients with a new posterior vitreous detachment require a prompt evaluation by an ophthalmologist to rule out these complications, which are amenable to surgery.

Vitreous Hemorrhage. Vitreous hemorrhage results from bleeding into the preretinal space or into the vitreous cavity. The most common causes are diabetic retinopathy and retinal tears. Additional causes include neovascularization associated with branch vein occlusion, sickle cell disease, retinal detachment, posterior vitreous detachment, trauma, age-related macular degeneration (AMD), retinal artery microaneurysms, trauma, and intraocular tumor. Symptoms begin with floaters or "cobwebs" in the vision and may progress over a few hours to severe visual loss without pain. Direct ophthalmoscopy reveals a reddish haze in mild cases to a black reflex in severe cases. Details of the fundus are usually difficult to visualize. Vitreous hemorrhage by itself does not cause an afferent pupillary defect, which, if present, indicates a retinal detachment behind the vitreous hemorrhage. The hemorrhage may be evenly distributed throughout the vitreous or focal. Long-standing preretinal hemorrhage can become a white mass that may be misdiagnosed as a tumor, exudate, or infection. Initial therapy consists of bed rest with elevation of the head of the bed and avoidance of anticoagulative medications. Definitive therapy is targeted at the underlying cause. Vascular retinopathy is managed with laser photocoagulation or cryotherapy, and retinal tears and detachments are repaired. If the cause of the hemorrhage is unknown, prompt diagnostic workup is indicated to look for surgically correctable lesions. Ultrasonography can be used to determine whether a retinal detachment is present and may also determine the cause. Vitrectomy is indicated in certain patients.

Macular Disorders. Many disease processes cause acute changes in the macula leading to acute visual loss. The role of the emergency physician is to recognize the maculopathy and refer the patient to an ophthalmologist. Keys to the diagnosis of macular dysfunction include loss of central vision with preservation of peripheral vision, complaints of central visual distortion, and anatomic changes in the retina.

Degenerative maculopathies occur as a result of trauma, radiation exposure, inflammatory or infectious disease, vascular disease, toxins, or hereditary disease, or they may be idiopathic in nature.

The most common form is AMD after the age of 65 years. It is a leading reason for legal blindness in the United States. Patients have either a gradual or rapid onset of visual loss. Funduscopy reveals scattered drusen. Drusen are small, sharply defined yellow-white masses. Some patients with AMD and drusen develop a choroidal (subretinal) neovascular membrane, which appears as a grayish-green membrane beneath the retina. If this membrane is left untreated, hemorrhage, transudation, scar formation, or exudative detachment of the retina can result. If a large hemorrhage occurs from the neovascular membrane, it can cause severe central visual loss and may break through the retina into the vitreous, causing peripheral visual loss. The use of intraocular antivascular endothelial growth factor medications has significantly changed the management of wet AMD.[63] Laser photocoagulation is another treatment for choroidal neovascular membrane formation.

www.ketabpezeshki.com 66485457-66963820

Inflammatory processes involving the retina may also cause visual loss, especially if the macula is involved. Bacterial, viral, and protozoal agents have been shown to cause maculopathy. The presenting symptoms and signs vary according to the disease process and severity. Inflammatory debris from exudative processes may fill the vitreous, leading to a cloudy appearance. Infections within the eye are often associated with severe pain, redness, and periocular edema. If the retina and choroid are obliterated, the lesions appear white. Patients suspected of having an inflammatory maculopathy need emergent consultation and thorough medical evaluation.

Neuro-ophthalmologic Visual Loss. Visual loss not readily explained by an abnormality on physical examination is called *neuro-ophthalmologic visual loss.* In these patients, a cause distal to the retina is sought. Patients can be divided into those who report decreased vision and have reduced visual acuity and those who report visual loss but have normal visual acuity. It is important to conduct careful visual field testing in the latter group.

Neuro-ophthalmologic visual loss is further divided into prechiasmal, chiasmal, and postchiasmal anatomic areas (see Fig. 71-23B).

Prechiasmal Visual Loss. Patients with prechiasmal disease have decreased visual acuity or visual field loss in the eye on the affected side. Prechiasmal disease may be a unilateral or bilateral process and results from dysfunction of the optic nerve. The swinging flashlight test reveals an afferent pupillary defect on the side involved unless the process is bilateral. In such cases, the relative degree of afferent defect determines the results. Visual field testing demonstrates a field defect that does not respect the vertical meridian and is often localized to the center of the visual field. Causes of prechiasmal visual loss include optic neuritis, ischemic optic neuritis, compressive optic neuritis, and toxic and metabolic optic neuritis.

Optic Neuritis

Optic neuritis is an acute monocular loss of vision caused by focal demyelination of the optic nerve. The patients' ages range from 15 to 45 years. Symptoms include a progressive loss of vision over several hours or days and ocular pain with eye movement. Visual acuity can range from minimal loss to no light perception. An afferent pupillary defect is usually present, and direct ophthalmoscopic examination reveals a normal or swollen disk (Fig. 71-24). The natural history of optic neuritis is for visual acuity to reach its poorest within 1 week and then slowly improve over the next several weeks. Approximately 30% of patients with acute optic neuritis develop multiple sclerosis within 5 years.[64] Approximately 30% of patients with optic neuritis have a recurrence within 10 years of initial presentation. In an initial study of patients with acute optic neuritis, treatment with a 3-day course of intravenous methylprednisolone reduced the rate of development of multiple sclerosis over a 2-year period; unfortunately, 5-year follow-up of the same cohort of patients revealed no significant differences between treatment groups in the development of multiple sclerosis.[65] Use of oral steroids for hastening optic neuritis is controversial. A randomized and controlled study of high-dose oral methylprednisolone in acute optic neuritis showed improved recovery from optic neuritis at 1 and 3 weeks but no effect at 8 weeks or on subsequent attack frequency.[66] Long-term visual outcome is no different from that with observation alone.

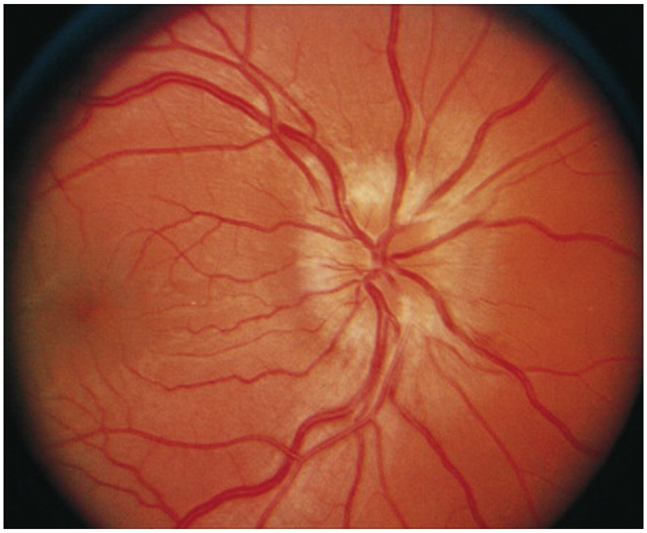


Figure 71-24. Optic disk swelling (papillitis) associated with acute optic neuritis. (From Yanoff M, Duker JS [eds]: Ophthalmology, 3rd ed. Philadelphia, Mosby, 2008.)

Ischemic Optic Neuropathy

Ischemic optic neuropathy is the most common optic neuropathy and one of the most common causes of visual loss past middle age. Ischemic optic neuropathy can be giant cell arteritis or idiopathic. Temporal arteritis (giant cell arteritis) is characterized by weight loss, malaise, jaw pain, headache, scalp tenderness, polymyalgia rheumatica, low-grade fever, and severe painless visual loss. It is extremely rare in people younger than 50 years, but the incidence rises with each subsequent decade. A significant proportion of patients sustain visual loss, which can be sudden, severe, and bilateral. Occasionally, visual loss is preceded by episodes of amaurosis fugax. In one series of patients, visual loss was unilateral in 46%, sequential in 37%, and simultaneously bilateral in 17%.[67] Signs include a large afferent pupillary defect, visual loss, and a visual field defect that may respect the horizontal meridian. The optic disk shows pallor and swelling. The diagnosis can be aided by an elevated erythrocyte sedimentation rate (ESR), but the condition can occur with normal sedimentation rates.[68] A guide to the upper limit of normal ESR is age/2 for men and (age + 10)/2 for women. The diagnosis is confirmed by temporal artery biopsy, although biopsy results have been normal early in the disease. Treatment for temporal arteritis should be instituted when typical signs and symptoms, particularly visual loss, exist. The standard treatment is high-dose corticosteroids, which are started as soon as the diagnosis is suspected and not delayed pending biopsy results.[69] Biopsy should be performed within 1 week of diagnosis. Patients treated with oral prednisone are less likely to have visual improvement and more likely to develop fellow eye involvement than those receiving high-dose intravenous methylprednisolone. Patients with visual loss have a 34% chance of improvement with intravenous methylprednisolone.

Nonarteritic Ischemic Optic Neuropathy

Nonarteritic ischemic optic neuropathy (NION) is much more common than temporal arteritis. These patients lack the classic symptoms of temporal arteritis and do not have an elevated ESR. Most of these patients have systemic vascular disease, diabetes, or hypertension, and they tend to be younger. They have painless visual loss, afferent pupillary defects, disk swelling, and visual field defects that respect the horizontal meridian. The visual loss is less severe than with temporal arteritis, and improvement occurs in one third of patients. Steroids have been advocated but have not been shown to be of benefit.[70] If there is doubt about whether a particular patient has temporal arteritis or another form of arteritic ischemic optic neuropathy, he or she should be treated with steroids pending artery biopsy.

Compressive Optic Neuropathy

Compressive optic neuropathy occurs at any age and can be caused by tumor, aneurysm, sphenoid sinusitis or mucocele, blunt

www.ketabpezeshki.com 66485457-66963820

trauma, or thyroid disorders. Although defined as a prechiasmal disorder, compression can occasionally occur far enough posteriorly to affect the optic chiasm. Patients with compressive optic neuropathy have visual loss that continues to progress beyond 7 days. Compressive optic neuropathies require neuroradiographic evaluation and rapid medical and surgical intervention. Optic neuritis can be difficult to distinguish from a compressive optic neuropathy, but compressive syndromes tend to involve other cranial nerves. If the signs and symptoms do not closely fit optic neuritis or ischemic optic neuropathy, a compressive lesion is presumed to exist until proved otherwise.

Toxic and Metabolic Optic Neuropathy

Numerous toxic and metabolic neuropathies exist. Common toxic causes include barbiturates, chloramphenicol, emetine, ethambutol, ethylene glycol, isoniazid, heavy metals, and methanol. Causes of metabolic optic neuropathies include thiamine deficiency and pernicious anemia. These processes are bilateral, progressive, and symmetrical. Visual loss can be severe, and visual field testing reveals central defects. Treatment is aimed at the underlying toxin or metabolite involved.

Chiasmal Visual Loss. Chiasmal disease is the second category of neuro-ophthalmologic visual loss, most commonly caused by chiasmal compression from pituitary tumors, craniopharyngioma, or meningioma. Visual loss is gradual and progressive. Although formal visual field testing is necessary to stage the condition, the diagnosis can usually be made by confrontation visual field testing. The classic defect is a bitemporal hemianopsia; however, tumors often compress the optic chiasm and optic nerves asymmetrically, resulting in combined central and temporal defects. When a visual field defect respects the vertical meridian from a neuro-ophthalmologic visual loss, the lesion is out of the globe and must be either chiasmal or postchiasmal (see Fig. 71-23B).

Postchiasmal Visual Loss. Postchiasmal disease represents the third category of neuro-ophthalmologic visual loss. The most common causes are infarction, tumor, arteriovenous malformation, and migraine disorders. Patients report difficulty in performing a certain task, such as reading. Lesions can be located from the immediate postchiasmal optic tract to the occipital cortex. The classic visual field defect is homonymous hemianopsia, a visual field loss on the same side of both eyes (see Fig. 71-23B). Patients with such lesions have a focal neurologic deficit and need neurologic consultation. Cortical blindness is a special cause of neuro-ophthalmologic visual loss that is most commonly caused by bilateral occipital infarction. Cortical blindness is often mistaken for functional blindness because patients have both normal funduscopic examination findings and intact pupillary reflexes. Anton's syndrome is characterized by bilateral blindness, normal pupillary reflexes, bilateral occipital lesions, and, interestingly, denial of blindness. It is this denial of blindness that may be incorrectly assumed to be evidence for a functional process.

Functional Visual Loss. Patients with functional visual loss fall into two categories: hysterical conversion reactions and malingering. Patients with hysterical conversion reactions have a nondeliberate, imagined visual loss. The patient has a flatter affect than one would expect under the circumstances of acute visual loss. The patient might appear completely unaffected emotionally by the acute visual loss. The malingerer, on the other hand, is a patient who is well aware that no visual loss exists, yet deliberately feigns visual loss for secondary gain. This patient is typically overemotional concerning the visual loss.

Examination of a patient with a suspected functional visual loss should be conducted in the same manner as every other ophthalmologic examination, with particular attention to possible neuro-ophthalmologic deficits. Normal pupillary reflexes and the absence of an afferent pupillary defect, together with normal funduscopic examination findings, point toward functional visual loss. Multiple tests can ascertain whether a visual loss is organic or functional. Patients with feigned visual loss are hesitant to try to oppose the index fingers of each hand and often write their names in a disorderly fashion, whereas genuinely blind patients can sign their names without difficulty. One effective test involves placing a large mirror directly in front of the patient's face and asking the patient to look straight ahead. The mirror is then tilted slightly back and forth. Most patients follow the reflection of their eyes in the mirror as it changes position, proving feigned visual loss. Another test commonly used is the optokinetic nystagmus (OKN) drum. The drum should be turned in front of the patient's open eyes. If the patient is properly seeing, the eyes will automatically follow the stripes of the drum. Some difficult cases require more sophisticated tests. Definitive treatment of functional visual loss should include a collaborative effort by the emergency physician, ophthalmology, and psychiatry. If the diagnosis of feigned visual loss cannot be definitively made, consultation is required to rule out neuro-ophthalmologic visual loss.

ANISOCORIA

Clinical Features

Anisocoria in a patient with head trauma or decreased level of consciousness requires immediate and aggressive evaluation and intervention because it may result from increased intracranial pressure. If a patient is awake and alert, has no signs of trauma, and has anisocoria of unknown cause, less urgency exists. The first step is to determine which pupil is abnormal. If one pupil constricts poorly to a light stimulus, it is likely to be the abnormal one. Anisocoria that is greater in darkness suggests that the abnormal pupil is the smaller pupil, whereas anisocoria that is greater in light suggests that the abnormal pupil is the larger pupil. If anisocoria exists in a patient with a normal afferent visual system, either an innervational or a structural defect in the iris sphincter exists. Most structural defects in the iris can be diagnosed by slit-lamp examination. If both pupils react well to light and no iris abnormalities are seen with slit-lamp examination, the next step is to determine whether the anisocoria increases in light or darkness. Adie's tonic pupil, pharmacologic blockade, and third-nerve palsy are associated with anisocoria that increases in light, whereas benign anisocoria and Horner's syndrome are associated with anisocoria that increases in darkness. Comparing pupillary size in a brightly and dimly lit room is the easiest method to evaluate the effect of lighting on anisocoria.

Adie's Tonic Pupil

With Adie's tonic pupil, patients have blurred near vision but normal distant vision. Adie's syndrome is seen in young women 70% of the time and has associated symmetrically reduced deep tendon reflexes. Examination reveals poor accommodation with a very slow constriction to near testing. The pupil redilates slowly when the vision is again made distant. Slit-lamp examination reveals sector palsies of the iris. The diagnosis is confirmed when a weak cholinergic agent (pilocarpine 0.1%) causes an intense pupillary constriction as a result of cholinergic supersensitivity in the affected pupil compared with the normal pupil. These patients need to be referred to an ophthalmologist on a nonemergent basis for cholinergic agent therapy.

Pharmacologic Mydriasis

Pharmacologic mydriasis can be caused by deliberate or inadvertent local administration of both sympathomimetic and parasympatholytic agents. Phenylephrine and cocaine are two sympathomimetic substances commonly used as a nasal

www.ketabpezeshki.com 66485457-66963820

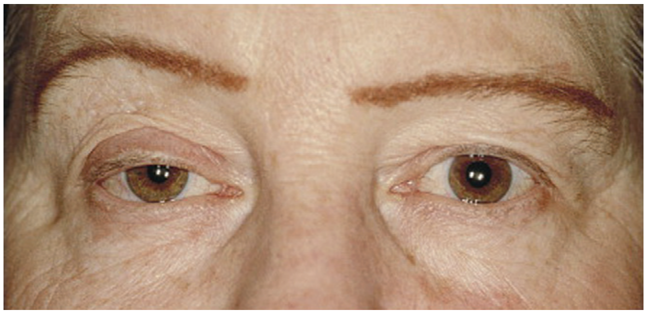


Figure 71-25. Horner's syndrome with ipsilateral right upper eyelid ptosis and pupillary miosis. (From Yanoff M, Duker JS [eds]: Ophthalmology, 3rd ed. Philadelphia, Mosby, 2008.)

premedicant for nasotracheal intubation; careless administration may lead to anisocoria. Parasympatholytic agents, such as atropine and scopolamine, have been implicated in the development of anisocoria. The transdermal scopolamine patches placed for the prevention of motion sickness can cause anisocoria. Pilocarpine 1.0% can be used in special circumstances to help differentiate a third-nerve palsy from pharmacologically mediated mydriasis. The administration of pilocarpine 1.0% rapidly constricts the pupil that is dilated secondary to a third-nerve palsy but does not produce miosis in a pupil dilated from anticholinergic agents.

Third-Nerve Palsy

Patients with anisocoria that increases in light, without evidence of Adie's tonic pupil or pharmacologic medication, are suspected of having a third-nerve palsy. They almost always have other signs of third-nerve involvement, including ptosis and extraocular muscle dysfunction. Patients report diplopia, and the involved eye is turned down and out. Patients may have ptosis and extraocular dysfunction with or without pupil dilation. Emergent neuroimaging and specialty consultation are indicated for any patient who has a new-onset third-nerve lesion involving the pupil.

Horner's Syndrome

Horner's syndrome consists of ptosis, miosis, and facial anhidrosis resulting from an interruption of sympathetic innervation (Fig. 71-25). The dilation lag, a classic finding, results from Horner's pupil requiring up to 15 seconds to dilate fully. The anisocoria is greater at 3 to 5 seconds of darkness than at 15 seconds of darkness, although the anisocoria is still more pronounced than in light. Topical ophthalmologic cocaine 10% can be used to aid the diagnosis. Horner's pupil dilates less than a normal pupil in reaction to topical cocaine. Central nervous system strokes and tumors, lung carcinomas, thyroid adenomas, Pancoast tumors, headache syndrome, carotid dissection, herpes zoster, otitis media, and trauma to brachial plexus during delivery are all causes of Horner's syndrome. In addition, inadvertent administration of anesthetic into the carotid sheath during a dental block can also cause temporary Horner's syndrome. Hydroxyamphetamine 1% administered 24 hours after the cocaine test can be used to determine the level of sympathetic interruption and dictate the type of workup indicated. In general, patients with new-onset Horner's syndrome should receive a thorough and immediate workup to determine the cause.

Physiologic Anisocoria

Twenty percent of the population may have anisocoria of greater than 0.4 mm at any given examination. This anisocoria may be transient or prolonged and may alternate pupils. Although the anisocoria increases in darkness, there is no dilation lag as seen with Horner's syndrome. No associated features, such as loss in vision and diplopia, are seen, and no further treatment is required.

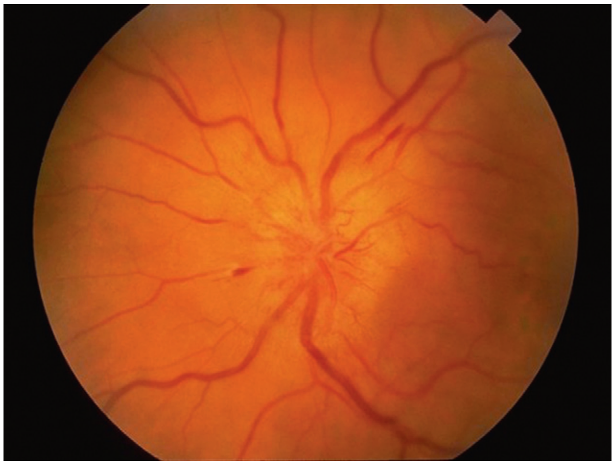


Figure 71-26. Papilledema. Note the blurred disk margins.

ABNORMAL OPTIC DISK

Clinical Features and Differential Considerations

An important acquired cause of an abnormal optic disk is papilledema. *Papilledema* refers to the changes in the optic disk from increased intracranial pressure. The subarachnoid space of the brain is continuous with the optic nerve sheath. Any increase in the cerebrospinal fluid pressure can be transmitted to the optic nerve, resulting in swelling of the optic nerve head. Causes include intracranial tumor, pseudotumor cerebri, intracranial hematomas from trauma, subarachnoid hemorrhage, brain abscess, and meningitis or encephalitis. Swelling of the optic disk and blurring of the disk margins, hyperemia, and loss of physiologic cupping are present (Fig. 71-26). There may be obliteration of spontaneous venous pulsations. Flame-shaped hemorrhages and yellow exudates appear near the disk margins as the edema progresses. Patients may have significant headaches or be completely asymptomatic. Visual acuity is not affected until the papilledema is long-standing. Brief obscurations of vision, enlargement of the physiologic blind spot, and inferior nasal visual field loss are common. Papilledema is a bilateral process but may be asymmetrical. A patient with newly diagnosed papilledema should receive immediate neuroradiographic evaluation.

Many conditions may mimic papilledema, including central retinal vein occlusion, papillitis, hypertensive retinopathy, ischemic optic neuropathy, optic disk vasculitis, and diabetic papillitis with retinopathy.

NYSTAGMUS

Clinical Features and Differential Considerations

Clinically significant nystagmus is an oscillation of the eyes that occurs within 30 degrees of the midline. Pendular nystagmus is of equal velocity in both directions. With jerk nystagmus, the velocity is faster in one direction. The pathologic component is the slow movement, but the nystagmus is named according to the direction of the fast component. Nystagmus can also be divided into

www.ketabpezeshki.com 66485457-66963820

monocular or binocular, conjugate (both eyes moving in the same direction) or disconjugate (eyes moving in opposite directions), and primary gaze position or gaze position nystagmus. Important questions include the presence of tinnitus, nausea, vomiting, oscillopsia, and vertigo.

Congenital nystagmus is noted at birth or within the perinatal period and is usually horizontal, conjugate, bilateral, symmetrical, and pendular. On lateral gaze, this nystagmus may become jerky in nature but remains horizontal despite upward or downward gaze. Congenital nystagmus is damped by convergence, increased with fixation, accentuated by covering one eye, and abolished with sleep. These patients do not have oscillopsia, nor do they have other neurologic complaints. Almost all of these patients have recognized their nystagmus previously, and the diagnosis is generally straightforward.

There are many causes of acquired nystagmus. General categories of disease that result in nystagmus include toxic exposure, defective retinal impulses, diseases of the labyrinths or of the vestibular nuclei, and lesions of the brainstem or cerebellum controlling ocular posture. The workup includes drug and toxic screening and neuroradiologic testing with a CT or MRI scan.

DISORDERS OF EXTRAOCULAR MOVEMENT

Clinical Features and Differential Considerations

Patients report diplopia produced or exacerbated by certain eye movements. A knowledge of the anatomy of the extraocular muscles is useful (Fig. 71-27). The first step is to determine whether the diplopia is monocular or binocular. Binocular diplopia disappears with either eye covered. Monocular diplopia is less concerning, caused most commonly by refractive errors, a dislocated lens, iridodialysis, or feigned disease.

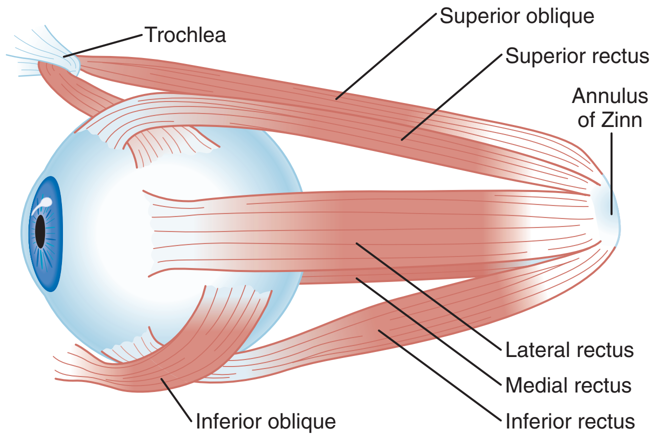


Figure 71-27. Extraocular muscles. (Image courtesy www.tedmontgomery.com.)

Binocular diplopia from misalignment of the eyes has a multitude of causes. Local mechanical defects, such as hematoma, orbital floor fractures, or abscess and palsy of cranial nerve III, IV, or VI, can lead to motility problems. Thyroid disease, progressive ophthalmoplegia, extraocular muscle fibrosis syndrome, multiple sclerosis, and myasthenia gravis can all lead to newly acquired extraocular movement dysfunction.

The most common cause is cranial nerve palsy. Patients with brainstem disease often have involvement of other cranial nerves, disturbances in level of consciousness, and sensorimotor loss. Isolated third-nerve lesions produce a palsy in which the patient develops ptosis, an inability to turn the eye inward or upward, and pupillary mydriasis. The causes of third-nerve palsy are varied and require aggressive and immediate neurologic and radiologic examination.

Isolated fourth-nerve palsy is an easily missed disorder. Patients note double vision, which is made worse in downgaze, or gaze away from the paretic side. These patients typically have a head tilt to the opposite shoulder to compensate for the vertical extorsion and have weakness in downward gaze. Trauma and vascular disease account for most cases of isolated fourth-nerve palsy, but aneurysm, intracranial tumor, and myasthenia gravis have been implicated.

Sixth cranial nerve palsies are the most commonly reported ocular motor palsies. Patients with sixth cranial nerve palsies have an esotropia that is worsened by lateral gaze and often turn their heads laterally toward the paretic side to compensate. Sixth-nerve palsy is caused by a variety of diseases, including Wernicke-Korsakoff syndrome, aneurysm, vascular disease (diabetes, hypertension, atherosclerosis), trauma, neoplasm, multiple sclerosis, meningitis, thyroid eye disease, and increased intracranial pressure. Workup consists of careful neurologic and radiologic examination.

MANAGEMENT

Ophthalmic Drugs

General Considerations

Most ocular medications are administered as drops, which have the advantage of concentrating drug delivery to the anterior segment of the eye and reducing unwanted systemic side effects. Eye drops have the additional advantages of rapid absorption, brief effect, and minimal interference with the visual media.

Drug Classification

Ophthalmologic medications can be classified into several categories, including anesthetics, antibiotics, antivirals, corticosteroids, and others. The emergency physician should be familiar with some common agents that are part of these categories and should be familiar with indications of each type of medication (Table 71-1).

www.ketabpezeshki.com 66485457-66963820

Table 71-1 Ophthalmologic Medications

MEDICATION	MECHANISM OF ACTION	INDICATIONS	COMMENT
Topical Anesthetics			
Proparacaine, tetracaine	Block transmission of sensory nerves	Facilitate ocular examination Foreign body removal Irrigation Tonometry Contact lens removal	Inhibits wound healing Should never be prescribed as pain medication
Topical Antibiotics			
Trimethoprim/polymyxin Fluoroquinolones Macrolides Aminoglycosides Sulfacetamide	Various	Bacterial infection	Ointments increase contact time with anterior eye segment
Topical Antiviral Agents			
Trifluridine Ganciclovir	Various	Viral infection	Consult ophthalmologist before prescribing
Cycloplegics and Mydriatics			
Tropicamide Cyclopentolate Phenylephrines Homatropine	Cycloplegics are muscarinic blockers and paralyze ciliary muscle; mydriatics stimulate adrenergic receptors; all cycloplegics result in mydriasis, but mydriatics are not all cycloplegic	Cycloplegics are useful in relieving pain and photophobia from ciliary spasm, which may occur in corneal abrasion, ocular trauma, and iridocyclitis	Contraindicated in lens implant, narrow-angle glaucoma, globe perforation; effects of homatropine lasts for 2 days
Acute Glaucoma—Topical Ophthalmics			
Beta-blockers (timolol) Carbonic anhydrase inhibitors (brinzolamide) Miotics (pilocarpine) Alpha$_2$-agonist (apraclonidine) Dorzolamide 2%–timolol 0.5%	Various, including decrease in aqueous humor production, promotion of drainage of aqueous humor, decrease in intraocular pressure	Acute narrow-angle glaucoma episode	Topical timolol should be first topical medication given, followed by topical pilocarpine and topical apraclonidine Topical medications are systemically absorbed
Acute Glaucoma—Systemic Medications			
Isosorbide Mannitol Acetazolamide Glycerol			Systemic acute glaucoma medications can result in or exacerbate dehydration

KEY CONCEPTS

- Surgical repair is performed only for persistent diplopia or cosmetic concerns and is generally not performed until swelling subsides in 7 to 10 days. CT scan is the imaging choice.
- When a retrobulbar hematoma compromises retinal circulation, immediate treatment of increased intraocular pressure includes a carbonic anhydrase inhibitor, a topical beta-blocker, and intravenous mannitol. A lateral canthotomy should be done in the ED as a temporizing measure before definitive decompression.
- Data suggest that eye patching confers no benefit in healing small, uncomplicated corneal abrasions.
- Treatment of globe rupture includes avoidance of further examination or manipulation and placement of a protective metal eye shield to prevent accidental pressure on the globe. Broad-spectrum intravenous antibiotics are administered, and antiemetics are given if nausea is present.
- Retinal tears or detachments do not cause pain. Examination may reveal the hazy gray membrane of the retina billowing forward, but many tears are peripherally located and not seen with direct ophthalmoscopy. Visual acuity may be normal unless the macula is involved. Indirect ophthalmoscopy is warranted if historical clues to the presence of retinal tears are present. Bedside ocular ultrasound may be diagnostic.
- In uncomplicated acute bacterial conjunctivitis, neomycin ophthalmic solutions are avoided because of their high incidence of hypersensitivity reactions. Corticosteroids and eye patching are also avoided.
- Attacks of primary angle closure glaucoma produce symptoms that are abrupt in onset and include severe eye pain, blurred vision, headache, nausea, vomiting, and occasionally abdominal pain. Signs include conjunctival injection and a cloudy (steamy) cornea with a midpositioned to dilated pupil that is sluggish or fixed. Intraocular pressures are markedly elevated.
- Topical anesthetics should not be prescribed for painful eye disorders as prolonged use may result in corneal scarring.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Xiang H, Stallones L, Chen G, Smith G: Work-related eye injuries treated in hospital emergency departments in the U.S. *Am J Ind Med* 2005; 48:57-62.
2. Bord SP, Linden J: Trauma to the globe and orbit. *Emerg Med Clin North Am* 2008; 26:97-123.
3. O'Hare TH: Blowout fractures: A review. *J Emerg Med* 1991; 9:253-263.
4. McIlrath ST, Blaivas M, Lyon M: Diagnosis of periorbital gas on ocular ultrasound after facial trauma. *Am J Emerg Med* 2005; 23:517-520.
5. Joseph JM, Glavas PL: Orbital fractures: A review. *Clin Ophthalmol* 2011; 5:95-100.
6. Ramakrishnan VR, Palmer JN: Prevention and management of orbital hematoma. *Otolaryngol Clin North Am* 2010; 43:789-800.
7. Nehles J, Hall AH, Blomet J, Mathieu L: Diphoterine for emergent decontamination of skin/eye chemical splashes: 24 cases. *Cutan Ocul Toxicol* 2006; 25:249-258.
8. Merle H, et al: Ocular burns in Martinique (French West Indies): Evaluation of the use of an amphoteric solution as the rinsing product. *Burns* 2005; 31:205-211.
9. Rihawi S, Frentz M, Reim M, Schrage NF: Rinsing with isotonic saline solution for eye burns should be avoided. *Burns* 2008; 34:1027-1032.
10. Dohlman CH, Cade F, Pfister R: Chemical burns to the eye: Paradigm shifts in treatment. *Cornea* 2011; 30:613-614.
11. Spector J, Fernandez WG: Chemical, thermal, and biological ocular exposures. *Emerg Med Clin North Am* 2008; 26:125-136.
12. Yagci A, et al: Topical anesthetic abuse keratopathy: A commonly overlooked health care problem. *Cornea* 2011; 30:571-575.
13. Ball IM, Seabrook J, Desai N, Allen L, Anderson S: Dilute proparacaine for the management of acute corneal injuries in the emergency department. *CJEM* 2010; 12:389-394.
14. Sklar DP, Lauth JE, Johnson DR: Topical anesthesia of the eye as a diagnostic test. *Ann Emerg Med* 1989; 18:1209-1211.
15. Calder LA, Balasubramanian S, Fergusson D: Topical nonsteroidal anti-inflammatory drugs for corneal abrasions: Meta-analysis of randomized trials. *Acad Emerg Med* 2005; 12:467-473.
16. Stern GA: *Pseudomonas* keratitis and contact lens wear: The lens/eye is at fault. *Cornea* 1990; 9(Suppl 1):S36-S40.
17. Turner A, Rabiu M: Patching for corneal abrasion. *Cochrane Database Syst Rev* 2006; 19:CD004764.
18. Mukherjee P, Sivarkumar A: Tetanus prophylaxis in superficial corneal abrasions. *Emerg Med J* 2003; 20:62-64.
19. Saeed A, Cassidy L, Malone DE, Beatty S: Plain x-ray and computed tomography of the orbit in cases and suspected cases of intraocular foreign body. *Eye (Lond)* 2008; 22:1373-1377.
20. Tingey DP, Shingleton BJ: *Glaucoma associated with ocular trauma*. In: Yanoff M, Duker JS, eds. *Ophthalmology*, 3rd ed. Philadelphia: Mosby; 2008:1187-1192.
21. Gharaibeh A, Savage HI, Scherer RW, Goldberg MF, Lindsley K: Medical interventions for traumatic hyphema. *Cochrane Database Syst Rev* 2011; 19:CD005431.
22. Fong LP: Secondary hemorrhage in traumatic hyphema: Predictive factors for selective prophylaxis. *Ophthalmology* 1994; 101:1583-1588.
23. Rahmani B, Jahadi H, Rajaeefard A: An analysis of risk for secondary hemorrhage in traumatic hyphema. *Ophthalmology* 1999; 106:380-385.
24. Netland K, Martinez J, LaCour O 3rd, Netland P: Traumatic anterior lens dislocation: A case report. *J Emerg Med* 1999; 17:637-639.
25. Rahman I, Maino A, Devadason D, Leatherbarrow B: Open globe injuries: Factors predictive of poor outcome. *Eye (Lond)* 2006; 20:1336-1341.
26. Joseph DP, Pieramici DJ, Beauchamp N: Computed tomography in the diagnosis and prognosis of open-globe injuries. *Ophthalmology* 2000; 107;1899-1906.
27. Libonati MM, Leahy JJ, Ellison N: The use of succinylcholine in open eye surgery. *Anesthesiology* 1985; 62:637-640.
28. Rabinowitz R, Yagev R, Shoham A, Lifshitz T: Comparison between clinical and ultrasound findings in patients with vitreous hemorrhage. *Eye (Lond)* 2004; 18:253-256.
29. Yoonessi R, Hussain A, Jang TB: Bedside ocular ultrasound for the detection of retinal detachment in the emergency department. *Acad Emerg Med* 2010; 17:913-917.
30. Chi MJ, Ku M, Sh K, Baek S: An analysis of 733 surgically treated blowout fractures. *Ophthalmologica* 2010; 224:167-175.
31. Yu-Wai-Man P, Griffiths PG: Steroids for traumatic optic neuropathy. *Cochrane Database Syst Rev* 2011; 1:CD006032.
32. Yu-Wai-Man P, Griffiths PG: Surgery for traumatic optic neuropathy. *Cochrane Database Syst Rev* 2005; 4:CD005024.
33. Cho RI: Intraoperative fluoroscopy-guided removal of orbital foreign bodies. *Ophthal Plast Reconstr Surg* 2009; 25:215-218.
34. Soheilian M: Prophylaxis of acute posttraumatic bacterial endophthalmitis: A multicenter randomized clinical trial of intraocular antibiotic injection, report 2. *Arch Ophthalmol* 2007; 125:460-465.
35. Sen HN, Nussenblatt RB: Sympathetic ophthalmia: What have we learned. *Am J Ophthalmol* 2009; 148:632-633.
36. Cavuoto K, Zutshi D, Karp CL, Miller D, Feuer W: Update on bacterial conjunctivitis in Florida. *Ophthalmology* 2008; 115:51-56.
37. Sheikh A, Hurwitz B: Antibiotics versus placebo for acute bacterial conjunctivitis. *Cochrane Database Syst Rev* 2006; 2:CD001211.
38. Reference deleted in proofs.
39. Barequet IS, O'Brien TP: Ocular infections: Update on therapy. Therapy of herpes simplex viral keratitis. *Ophthalmol Clin North Am* 1999; 12:63-69.
40. Liesegang TJ: Herpes zoster virus infection. *Curr Opin Ophthalmol* 2004; 15:531-536.
41. Tabbara KF, Al Balushi N: Topical ganciclovir in the treatment of acute herpetic keratitis. *Clin Ophthalmol* 2010; 19:905-912.
42. Huynh TH, Johnson MW, Comer GM, Fish DN: Vitreous penetration of orally administered valacyclovir. *Am J Ophthalmol* 2008; 145:682-686.
43. Wong VW, Lai TY, Chi SC, Lam DS: Pediatric ocular surface infections: A 5-year review of demographics, clinical features, risk factors, microbiological results, and treatment. *Cornea* 2011; 30:995-1002.
44. Seltz LB, Smith J, Durairaj VD, Enzenauer R, Todd J: Microbiology and antibiotic management of orbital cellulitis. *Pediatrics* 2011; 127:e566-e572.
45. Takle LM, Bernardino RC: A rapidly emerging ocular adnexal villain. *Rev Ophthalmol* 2007; 14:115-120.
46. Ou Y, Goldberg I, Migdal C, Lee PP: A critical appraisal and comparison of the quality and recommendations of glaucoma clinical practice guidelines. *Ophthalmology* 2011; 118:1017-1023.
47. Atebara N, Brown GC, Cater J: Efficacy of anterior chamber paracentesis and carbogen in treating nonarteritic central retinal artery occlusion. *Ophthalmology* 1995; 102:2029-2038.
48. Rudkin AK, Lee AW, Aldrich E, Miller NR, Chen CS: Clinical characteristics and outcome of current standard management of central retinal artery occlusion. *Clin Experiment Ophthalmol* 2010; 38:496-501.
49. Rumelt S, Brown GC: Update on treatment of retinal arterial occlusions. *Curr Opin Ophthalmol* 2003; 14:139-141.
50. Hattenbach LO, Kuhli-Hattenbach C, Scharrer I, Baatz H: Intravenous thrombolysis with low-dose recombinant tissue plasminogen activator in central retinal artery occlusion. *Am J Ophthalmol* 2008; 146:700-706.
51. Aldrich EM, et al: Local intraarterial fibrinolysis administered in aliquots for the treatment of central retinal artery occlusion: The Johns Hopkins Hospital experience. *Stroke* 2008; 39:1746-1750.
52. Noble J, Weizblit N, Baerlocher MO, Eng KT: Intra-arterial thrombolysis for central retinal artery occlusion: A systematic review. *Br J Ophthalmol* 2008; 92:588-593.
53. Schumacher M, et al: Central retinal artery occlusion: Local intra-arterial fibrinolysis versus conservative treatment, a multicenter randomized trial. *Ophthalmology* 2010; 117:1367-1375.
54. Chen CS, et al: Efficacy of intravenous tissue-type plasminogen activator in central retinal artery occlusion: Report from a randomized, controlled trial. *Stroke* 2011; 42:2229-2234.
55. Hayreh SS, Podhajsky PA, Zimmerman MB: Natural history of visual outcome in central retinal vein occlusion. *Ophthalmology* 2011; 118:119-133.
56. Braithwaite T, Nanji AA, Greenberg PB: Anti-vascular endothelial growth factor for macular edema secondary to central retinal vein occlusion. *Cochrane Database Syst Rev* 2010; 10:CD007325.
57. Brown DM, et al: Ranibizumab for macular edema following central retinal vein occlusion: Six-month primary end point results of a phase III study. *Ophthalmology* 2010; 117:1124-1133.
58. Tao Y, Hou J, Jiang YR, Li XX, Jonas JB: Intravitreal bevacizumab vs triamcinolone acetonide for macular oedema due to central retinal vein occlusion. *Eye (Lond)* 2010; 24:810-815.
59. Squizzato A, Manfredi E, Bozzato S, Dentali F, Ageno W: Antithrombotic and fibrinolytic drugs for retinal vein occlusion: A systematic review and a call for action. *Thromb Haemost* 2010; 103:271-276.
60. Mitry D, et al: The fellow eye in retinal detachment: Findings from the Scottish Retinal Detachment Study. *Br J Ophthalmol* 2012; 96:110-113.
61. Lewin MR, Williams S, Ahuja Y: Ultrasonographic diagnosis of retinal detachment in the emergency department. *Ann Emerg Med* 2005; 45:97-98.
62. Diederen RM, et al: Scleral buckling surgery after macula-off retinal detachment: Worse visual outcome after more than 6 days. *Ophthalmology* 2007; 114:705-709.

www.ketabpezeshki.com 66485457-66963820

63. French DD, Margo CE: Age related macular degeneration, anti-vascular endothelial growth factor agents, and short term mortality. *Retina* 2011; 31:1036-1042.
64. The 5-year risk of MS after optic neuritis: Experience of the optic neuritis treatment trial. Optic Neuritis Study Group. *Neurology* 1997; 49:1404-1413.
65. Beck RW, et al: The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis. *N Engl J Med* 1993; 329:1764-1769.
66. Sellebjerg F, Nielsen H, Frederikson J, Olesen J: A randomized, controlled trial of oral high-dose methylprednisolone in acute optic neuritis. *Neurology* 1999; 52:1479-1484.
67. Liu GT, Glaser J, Shatz N, Smith J: Visual morbidity in giant cell arteritis: Clinical characteristics and prognosis for vision. *Ophthalmology* 1994; 101:1779-1785.
68. Wong RL: Temporal arteritis without an elevated erythrocyte sedimentation rate: Case report and review of the literature. *Am J Med* 1986; 80:959-964.
69. Borg FA, Dasgupta B: Treatment and outcomes of large vessel arteritis. *Best Pract Res Clin Rheumatol* 2009; 23:325-337.
70. Mathews MK: Nonarteritic anterior ischemic optic neuropathy. *Curr Opin Ophthalmol* 2005; 16:341-345.

www.ketabpezeshki.com 66485457-66963820

Chapter 72

Otolaryngology

James A. Pfaff and Gregory P. Moore

OTITIS MEDIA

Perspective

Background

Otitis media (OM) is the most common diagnosis made by U.S. physicians for children younger than 15 years. In 2002, 16.7 million visits were made to physician offices across the country for OM, with an estimated 2.65 million visits made to emergency departments (EDs), making it the sixth most common ED discharge diagnosis.[1] More than 80% of children will have at least one episode of acute otitis media (AOM) during their lifetime, and by age 3, up to 40% will have had at least three episodes. The financial repercussions are enormous; one estimate is that $5 billion per year is spent on the evaluation, treatment, and socioeconomic effects of OM.[2] The most frequent outpatient use of antimicrobials in the United States is for OM, with the number of prescriptions having increased from 12 million in 1980 to more than 23.6 million in 1992.

Epidemiology

Male gender, daycare attendance, parental smoking, pacifier use, and a family history of middle ear disease have been implicated as risk factors. Children with anatomic abnormalities, such as cleft palate and Down syndrome, have a higher rate of OM, probably because of eustachian tube abnormalities. Some immunocompromised patients, including patients with human immunodeficiency virus (HIV) infection, may have recurrent OM as an initial symptom of their underlying disease. OM and upper respiratory infections occur primarily in the winter. Breast-feeding seems to be protective.

Definitions

Otitis media is broadly defined as inflammation of the inner ear and is a continuum of disease. *Acute otitis media* is defined as the signs and symptoms of an acute infection, with evidence of effusion; this has also been called *acute suppurative* or *purulent otitis media*. *Otitis media with effusion* (OME) includes effusion without signs or symptoms of an acute infection; additional descriptive terms include *serous, mucoid, nonsuppurative,* or *secretory otitis media*. *Chronic otitis media* or *chronic suppurative otitis media* refers to chronic discharge from the ear through perforation of an intact membrane. *Recurrent otitis media* is defined by three or more episodes over 6 months or four episodes in 1 year.

Principles of Disease

Pathophysiology

Eustachian tube dysfunction is the central theme of most theories of AOM pathogenesis. The eustachian tube, between the middle ear cavity and the nasopharynx, ventilates the middle ear to equilibrate pressure, allows for middle ear drainage, and provides protection from nasopharyngeal secretions. In children, it measures approximately 18 mm and is almost horizontal. As individuals age, the eustachian tube widens, doubles in length, becomes more vertically oriented, and stiffens (which may explain the decreased incidence of AOM in adults). Normally the tube is collapsed, but it opens during yawning, chewing, and swallowing.

The eustachian tube may become either mechanically or functionally obstructed, decreasing middle ear ventilation. Examples of mechanical obstruction include inflammations from an upper respiratory infection, hypertrophied adenoids, and a cleft palate. Functional obstruction from persistent tubal collapse occurs primarily in young children, who have less fibrocartilage support of the medial eustachian tube than older children or adults. It has been postulated that this dysfunction results in negative middle ear cavity pressure, causing a transudate of fluid that combines with the reflux of nasopharyngeal secretions and bacteria.

Etiology

The most common causes of bacterial infection in children are *Streptococcus pneumoniae, Haemophilus influenzae* (primarily nontypeable), and *Moraxella (Branhamella) catarrhalis. Streptococcus pyogenes, Staphylococcus aureus,* and gram-negative bacteria are much less common.[3] The widespread use of the pneumococcal 7-valent conjugate vaccine (Prevnar) has changed the frequency of these common organisms, with *H. influenzae* increasing in frequency,[4] particularly in persistent AOM and treatment failures.[5] As the advent of reverse transcriptase polymerase chain reaction technology and other techniques for viral identification has improved, the number of viral agents identified in the middle ear has increased. In a study of 79 patients with tympanostomy tubes with OM, bacteria were found in 92% of the patients, viruses in 70%, and both viruses and bacteria in 66%.[6] Respiratory syncytial virus is the most common virus, but parainfluenza virus, influenza virus, rhinovirus, and adenovirus have also been found in the middle ear aspirates of children. Some authors believe that viral infection is the cause of the inflammatory reaction in most cases and antibiotics are not necessary.[7] Viruses have contributed to poor treatment outcome by increasing middle ear inflammation, decreasing

www.ketabpezeshki.com 66485457-66963820

neutrophil function, and decreasing antibiotic penetration into the middle ear.[8] The clinical implications of this are that antibiotic treatment may not be predictable, and a failed course of antibiotic treatment may not be promptly blamed on antibiotic-resistant bacteria, leading to continuous changes in antibiotic regimens.[8]

In young children, it was formerly believed that gram-negative organisms and *S. aureus* were the causative organisms. Although these bacteria may be the causes in intubated patients or patients in the neonatal intensive care unit, healthy newborns tend to be infected by the same pathogens as healthy older children. Bullous myringitis produces bullae on the tympanic membrane (TM) and may be present in up to 5% of cases of OM in children younger than 2 years.[9] Although bullous myringitis was previously thought to be caused by *Mycoplasma pneumoniae,* culture of middle ear aspirates in this condition generally grows the usual organisms that cause AOM, and *M. pneumoniae* is uncommon.[10]

More than 70% of children with purulent conjunctivitis may have OM, a symptom complex described as the otitis-conjunctivitis syndrome, which is predominantly caused by *H. influenza.*[11] Other, less likely organisms that can cause AOM include *Mycobacterium tuberculosis* (primarily in children) and *Chlamydia trachomatis* (most commonly seen in children younger than 6 months with pneumonia).

Up to 10% of the general pediatric population may be at risk for developing four or more episodes of OM in the first year of life; these children are generally said to be *otitis-prone.*[12] They may have subtle immunologic abnormalities or a greater baseline colonization of virus and bacteria than the general population.

Clinical Features

OM may manifest with a multitude of symptoms, such as cough, upper respiratory tract symptoms, poor appetite, diarrhea, vomiting, fever, and pulling at ears and ear pain, all of which are nonspecific. Of all these symptoms, pain seems to be the most useful for making the diagnosis of AOM. In one systematic review, ear pain had a positive likelihood ratio (3-7.3) but was present in only 50 to 60% of children with AOM.[13] Fever may be present, but in one large series, a temperature of 38.3° C or greater was present in only 26% of the episodes, with only 4% of cases involving a fever of 40° C or greater.

The auricle and external canal should be inspected for signs of erythema, discharge, or tenderness. If the canal is occluded with cerumen, curettage may be successful; if not, the placement of 3% hydrogen peroxide or emulsifying drops, followed by gentle irrigation, may cleanse the canal. A bulging TM increases the likelihood of AOM, whereas a retracted TM is seen in chronic OME. The color may be red, pink, yellow, or a normal pearly gray or translucent. The presence of erythema in itself does not indicate infection because crying or fever may cause hyperemia; however, a TM that is distinctly red (defined as *hemorrhagic,* strongly or moderately red) suggests AOM.[13]

Landmarks that should be visible include the pars flaccida, the malleolus, and the light reflex below the umbo. The TM may have air-fluid levels, there may be bubbles behind the TM, or the TM may be completely opacified, all of which indicate middle ear effusion. Pneumatic otoscopy is particularly helpful in diagnosing AOM. The lack of mobility is one of the most sensitive indicators of middle ear effusion. In fact, mobility in response to insufflation should raise serious doubt as to the diagnosis of AOM. A TM that is cloudy, bulging, and distinctly immobile indicates AOM. In OME the TM often is retracted, with the malleolus being particularly prominent. The landmarks all may be obscured in the presence of significant fluid. A comparison examination of the other ear may help in confirming suspected infection.

In neonates, the TM appears thickened and opaque normally in the first few weeks of life, and the TM is in a highly oblique position. With tympanostomy tubes, in the absence of infection the TM may have decreased mobility, altered landmarks, opacity, or dullness. If the tube is patent, erythema and discharge may indicate infection. If not, erythema, bulging of the TM, and immobility indicate AOM.

Complications

Before the use of antibiotics there was a 20% incidence of complications from AOM, with mastoiditis and otic meningitis being relatively common. Complications are either intratemporal or intracranial, occurring in both adults and children. The development of either complication of OM occurs by one of three mechanisms: (1) direct extension of infection through bone weakened by osteomyelitis or cholesteatoma; (2) retrograde spread of infection by thrombophlebitis; or (3) extension of infection along preformed pathways, such as the round or oval windows or through dehiscences that are the result of congenital malformations. The use of antibiotics has led to a reduction of all complications to less than 1%.

Intratemporal. TM perforation occurs most commonly at the pars tensa and usually resolves spontaneously. It may persist for a longer period, resulting in a chronic perforation, chronic OM, or both. *Chronic otitis media* refers to inflammation of the middle ear that persists for 6 weeks or longer accompanied by discharge through perforation of an intact membrane.[14] Cholesteatoma is an accumulation of keratin-producing squamous epithelium in the middle ear and may result in erosion of bone within the middle ear cavity. It is seen most often in OME, in which retraction of the TM is a common problem, and its presence may alter the courses of some treatment therapies.

The facial nerve courses through the middle ear, and facial paralysis is a known complication in OM. The exact mechanism is unknown, but the paralysis may be a result of infection, surrounding osteitis, facial nerve swelling, demyelination of the facial nerve from bacterial toxins, or facial nerve ischemia.

Intracranial. Meningitis is the most common intracranial complication of AOM, resulting from hematogenous spread and direct invasion. Brain abscesses are most commonly caused by chronic otitis and are the second most common intracranial complication.[15] Extradural abscesses, subdural empyema, and lateral venous sinus thrombosis have all been identified as complications of OM.

Diagnostic Strategies

Pneumatic otoscopy to confirm immobility of the TM is an important part of diagnosis in all cases (see earlier discussion). Tympanocentesis is aspiration of the middle ear effusion to identify causative organisms and is rarely indicated in the ED. Indications include patients with AOM who are seriously ill or appear toxic, are unresponsive to therapy, are younger than 4 weeks old, are immunocompromised, are receiving antimicrobials, or have suppurative complications.

Differential Considerations

OM usually does not cause a significant fever, so other causes should be investigated in a febrile, ill-appearing infant. In addition to OM, other causes of otalgia include OME, trauma, foreign bodies, and complications of OM, such as mastoiditis and referred pain from the teeth, sinuses, throat, or temporomandibular joint.

Management

Physicians in the Netherlands in the early 1990s suggested that OM was a self-limited disease and recommended observation as an initial treatment option, followed by the use of antibiotics if

www.ketabpezeshki.com 66485457-66963820

the patient's condition did not improve within 72 hours. With these practice recommendations, the concern for rising rates of antibacterial resistance, and the growing costs of antibacterial preparations in the United States, the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians developed guidelines for the diagnosis and management of AOM to assist physicians in clinical decision-making. The guidelines recommend an age-stratified approach that incorporates age with a combination of diagnostic certainty and illness severity.[16] The introduction of the guidelines was not without controversy, with some authorities voicing concerns that the clinical trials used in decision-making lacked stringent diagnostic criteria, did not include very young children, or used antimicrobial drugs that had limited efficacy or were given in suboptimal doses. The components of these guideline include diagnosis, the management of pain, observation, and antibiotic recommendations.

Making the diagnosis of AOM can be challenging but critical. One study suggested that physicians were uncertain of their diagnosis of AOM as much as 40% of the time.[17] This lack of confidence may contribute to the unnecessary use of antibiotics. Making a diagnosis of AOM requires three findings: (1) history of acute onset, (2) signs of middle ear effusion (including TM immobility), and (3) signs or symptoms of middle ear inflammation.

AOM can cause substantial pain, which should be appropriately addressed. Acetaminophen and ibuprofen are safe over-the-counter medicines that are first-line analgesics. The use of narcotic analgesia has not been well studied. Benzocaine-antipyrine, a local anesthetic, may be helpful in some patients with an intact TM and has been shown to be more effective than placebo.[18]

There is evidence that children younger than 2 years, those with bilateral OM, or those with otorrhea gain the greatest benefit from antibiotic treatment,[19] but because more than 80% of cases of AOM resolve spontaneously, the use of observation versus antibiotics has been advocated. This approach of "watchful waiting" for 48 hours has resulted in lower rates of antibiotic-resistant bacteria.[20] The observation option has been restricted to children older than 6 months. In children older than 6 months to 2 years, treatment recommendations are based on the certainty of the diagnosis and severity of illness, with observation as an option if the diagnosis is uncertain. In children older than 2 years, treatment is necessary only in patients with severe illness, defined as severe otalgia or temperature higher than 39° C. Unless severe illness is present, children older than 2 years should be clinically observed. Table 72-1 summarizes the AAP recommendations.

Observation recommendations are also based on the reliability of the caregivers and ability for close follow-up. If there is concern about the ability to get follow-up, parents can be given a prescription to be filled if the patient's condition does not improve within 48 hours, a so-called "safety net prescription."[21] Several studies in the ED have shown success with use of this approach.[22,23] An analysis from the National Ambulatory Medical Care Survey revealed that management without antibiotics has not increased since the guidelines were published, although children who did not receive antibiotics were more likely to have mild infections.[24]

The decision to treat is balanced against the medication's adverse effects, which may include allergic reactions, gastric upset, accelerated bacterial resistance, and unfavorable changes in the bacterial flora. Several large systematic reviews revealed that antibiotics are modestly more effective than no treatment but that 4 to 10% of children experienced adverse effects from the treatment itself.[25,26] Two recent randomized controlled trials comparing amoxicillin-clavulanate versus placebo in a total of 610 patients reported modestly improved time to resolution of symptoms and otoscopic findings but with more side effects, diarrhea being the most common.[27,28] Although some authorities believe that these studies settled the treatment controversy, the studies were far from conclusive, and observation as recommended by the previously published guidelines remains an acceptable treatment.

Table 72-1 Clinical Practice Guidelines: Diagnosis and Management of Acute Otitis Media

1. To diagnose acute otitis media, the clinician should confirm a history of acute onset *and* identify signs of middle ear effusion (bulging of the TM, limited or absent mobility of the TM, air-fluid level behind the TM, otorrhea) *and* signs or symptoms of middle ear inflammation as indicated by either distinct erythema of the TM or distinct otalgia.
2. The management of AOM should include an assessment of pain. If pain is present, the clinician should recommend treatment to reduce pain.

3A. Observation without use of antibacterial agents in a child with uncomplicated AOM is an option for selected children based on diagnostic certainty, age, illness severity, and assurance of follow-up.

3B. If a decision is made to treat with an antibacterial agent, the clinician should prescribe amoxicillin for most children. When amoxicillin is used, the dose should be 80-90 mg/kg/day.

4. If the patient fails to respond to the initial management option within 48-72 hr, the clinician must reassess the patient to confirm AOM and exclude other causes of illness. If AOM is confirmed in the patient initially managed with observation, the clinician should begin antibacterial therapy. If the patient was initially managed with an antibacterial agent(s), the clinician should change the antibacterial agent(s).
5. Clinicians should encourage the prevention of AOM through reduction of risk factors.

AGE	CERTAIN DIAGNOSIS	UNCERTAIN DIAGNOSIS
<6 mo	Antibacterial therapy	Antibacterial therapy
6 mo-2 yr	Antibacterial therapy	Antibacterial therapy; Observation option if nonsevere illness
>2 yr	Antibacterial therapy	Observation option if severe illness; observation option if nonsevere illness

From American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media: Diagnosis and management of acute otitis media. Pediatrics 113:1451, 2004.
AOM, acute otitis media; *TM,* tympanic membrane.
Type I sensitivity—urticaria or anaphylaxis.
Note: Nonsevere illness is mild otalgia and fever <39° C in the previous 24 hours. Severe illness is moderate to severe otalgia or fever >39° C. A certain diagnosis meets all three criteria: (1) rapid onset, (2) signs of middle ear effusion, and (3) signs and symptoms of middle ear inflammation.

Amoxicillin's cost, efficacy, safety profile, and palatability continue to make it a good first-line agent, and the guidelines recommend it as the first-line agent in the non–penicillin-allergic patient.[16] It can be given twice a day at a dose of 45 mg/kg. This higher concentration is preferred because it is effective against susceptible and intermediately resistant strains of *S. pneumoniae* and because 15 to 20% of children have poor gastrointestinal absorption of amoxicillin.[29] In patients who are allergic to penicillin, the guidelines distinguish between those with type I sensitivity (urticaria or anaphylaxis) and those with non–type I sensitivity, but second- and third-generation cephalosporins have little cross-reactivity. Options for treatment of patients with non–type I reactions include cefdinir (14 mg/kg/day in one or two doses), cefpodoxime (10 mg/kg once a day), cefuroxime (30 mg/kg/day in two divided doses), and intramuscular ceftriaxone (50 mg/kg/day) as a single injection.[16,29] Treatment of patients with type I reactions can include macrolides such as azithromycin (10 mg/kg for one day, then 5 mg/kg for an additional 5 days), clarithromycin (7.5 mg/kg twice a day for 10 days), and clindamycin (7.5 mg four times a day). Patients with severe otalgia or a temperature greater than 39° C should be given amoxicillin-clavulanate

www.ketabpezeshki.com 66485457-66963820

Table 72-2 Treatment Guidelines for Otitis Media

	At Diagnosis for Patients Being Treated Initially with Antibacterial Agents		*Clinically Defined Treatment Failure at 48-72 hours after Initial Management with Observation Option*		*Clinically Defined Treatment Failure at 48-72 Hours after Initial Management with Antibacterial Agents*	
TEMPERATURE ABOVE 39° C OR SEVERE OTALGIA OR BOTH	**RECOMMENDED**	**ALTERNATIVE FOR PENICILLIN ALLERGY**	**RECOMMENDED**	**ALTERNATIVE FOR PENICILLIN ALLERGY**	**RECOMMENDED**	**ALTERNATIVE FOR PENICILLIN ALLERGY**
No	Amoxicillin (80-90 mg/kg/day)	Non–type I: cefdinir, cefuroxime, cefpodoxime Type I*: azithromycin, clarithromycin Ceftriaxone—1 or 3 days	Amoxicillin (80-90 mg/kg/day)	Non–type I: cefdinir, cefuroxime, cefpodoxime Type I*: azithromycin, clarithromycin Ceftriaxone—1 or 3 days	Amoxicillin-clavulanate (amoxicillin 90 mg/kg/day with clavulanate 6.4 mg/kg/day)	Non–type I: ceftriaxone—3 days Type I*: clindamycin
Yes	Amoxicillin-clavulanate (amoxicillin 90 mg/kg/day with clavulanate 6.4 mg/kg/day)		Amoxicillin-clavulanate (amoxicillin 90 mg/kg/day with clavulanate 6.4 mg/kg/day)		Ceftriaxone—3 days	Tympanocentesis—clindamycin

From American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media: Diagnosis and management of acute otitis media. Pediatrics 113:1451, 2004.
*Type I sensitivity—urticaria or anaphylaxis.

(80-90 mg of the amoxicillin component per kilogram per day) or intramuscular ceftriaxone for 1 to 3 days.

Patients should be reevaluated in 3 days if the treatment fails. Treatment failure is defined by lack of clinical improvement in signs and symptoms such as ear pain, fever, and TM findings of redness, bulging, or otorrhea. In these cases, treatment includes agents effective against the β-lactamase–producing organisms *H. influenzae* and *M. catarrhalis.* Recommended agents include amoxicillin-clavulanate (80-90 mg of the amoxicillin component per kilogram per day) and intramuscular ceftriaxone and clindamycin for 3 days.[16] Table 72-2 is a synopsis of the treatment guidelines.

Recurrent AOM is encountered in roughly 20% of children before age 1 year; 20 to 30% occur within a month after successful completion of therapy.[30] These episodes are usually a result of a new pathogen. Patients with AOM in whom treatment with a conventional β-lactam antibiotic has failed and β-lactam–allergic patients with AOM in whom macrolide therapy has failed may benefit from the use of fluoroquinolones, though the lack of liquid suspension and lack of approval in children may limit this treatment option.[31]

Response to antibiotics is only one of a number of factors that affect clinical outcome. Other factors include impairment of eustachian tube function, coinfection with nonbacterial pathogens, and host immune response. Local practice patterns and antimicrobial sensitivities may also play a role in the types of treatment given. Treatment historically involved a 10-day course. Numerous studies have compared traditional treatment courses with shorter therapy, which is most appropriate for uncomplicated AOM. Patients with TM perforations and patients at high risk for treatment failure or those with chronic or recurrent OM probably are more appropriately treated with a longer course. Shorter courses also are not appropriate for children younger than 2 years. The antibiotic treatment of AOM in adults is the same as in children. There is no indication for the use of antihistamines, decongestants, steroids, or tympanostomy tubes for an acute episode of AOM.

After a 10-day treatment with antibiotics, 50% of children may exhibit OME, but 90% of cases resolve within 3 months. However, about 30 to 40% of children have recurrent OME, and 5 to 10% of cases last 12 months or longer. The treatment of OME is controversial, but OME may interfere with hearing and subsequent development of speech and language. OME is, by definition, asymptomatic, and the effusion may be sterile or contain infectious agents, but there is little benefit derived by antibiotics, and they should not be used.[32,33] Antihistamines, decongestants, steroids, or surgical procedures are not beneficial in patients with OME.[33] Myringotomy and tympanostomy tubes may be beneficial in children who have had OME for more than 4 months with persistent hearing loss, those with a hearing loss greater than 40 dB, children with structural damage to the TM or middle ear, and children with persistent OM who are at risk for speech, language, or hearing problems.[33] Tonsillectomy is not beneficial, but adenoidectomy may be helpful in older children who have a specific indication such as nasal obstruction or chronic adenoiditis.

Tympanostomy tubes have also been used in recurrent AOM unresponsive to prophylactic antibiotics, complications of AOM, and complications of eustachian tube dysfunction, including TM retraction with hearing loss, ossicular erosions, and retraction pocket formation.

Tympanostomy tube insertion is one of the most common operative procedures among children the United States, and emergency physicians will frequently encounter patients with these tubes. There is no consensus for the most appropriate treatment in a patient with an acutely draining ear. A meta-analysis concluded that there was little high-quality evidence available to identify the most effective treatment.[34] The organisms involved are the same ones that cause AOM acutely, particularly in children younger than 2 years, but *Pseudomonas aeruginosa, S. aureus, and Staphylococcus epidermidis* are also implicated.[35] In the acute setting, topical antibiotic administration with 5 oxfloxin drops to the affected ear twice a day or 4 drops of ciprofloxacin-dexamethasone twice a day is an effective treatment.[36] Systemic treatment (usually with amoxicillin-clavulanate 45 mg/kg twice a day) should be reserved for patients showing signs of complicated or invasive infections or signs of systemic disease.

www.ketabpezeshki.com 66485457-66963820

Disposition

Children normally are seen in 10 to 14 days for follow-up. This follow-up appointment may not be necessary in children older than 2 years in whom symptoms have resolved and who have no recurrent risk factors. Patients with complications need ear, nose, and throat (ENT) referral. Adults who have persistent OME need ENT referral to rule out nasopharyngeal carcinoma.

OTITIS EXTERNA

Principles of Disease

External otitis is an inflammation of the external auditory canal. There is a lifetime incidence of 10%, and it accounts for 7.5 million annual ototopical prescriptions in the United States.[37] The external auditory canal is lined with squamous epithelial cells and cerumen glands that provide a protective lipid layer. This protective layer may be disrupted by high humidity, increased temperature, maceration of the skin after prolonged exposure to moisture, and local trauma (e.g., cotton swabs or the use of hearing aids), resulting in the introduction of bacteria. Otitis externa (OE) is a bacterial disease most commonly caused by *P. aeruginosa* and *S. aureus* but can also be polymicrobial.[38] Occurring most often in the summer and in tropical climates, it is also known as *swimmer's ear* or *tropical ear.*

Clinical Features

The diagnosis is made clinically. The external auditory canal may be initially pruritic and may become erythematous and increasingly swollen. Symptoms include otalgia and ear fullness, as well as possible hearing loss or jaw pain. Physical findings include erythema or edema of the canal and reproduction of the discomfort with pulling on the auricle or tragus. There may be associated lymphadenitis, TM erythema, or local cellulitis. The disease may progress to a chronic form with itching, eczema, and flaking of the epithelium, which may be from bacterial, fungal, or dermatologic conditions. In children, it is usually secondary to chronic OM.

Differential Considerations

It may be difficult to distinguish OE from OM with drainage from a ruptured TM, particularly in children. The TM may be erythematous in both conditions, and the edema may preclude diagnosis. The discharge may be from OE or a perforated TM, and in equivocal cases, it is prudent to treat for both conditions.

Otomycosis or fungal infection can occur as a primary or secondary infection and accounts for 10% of cases of OE.[4] Itching is the prominent symptom, often with minimal pain or otorrhea. Aspergillosis is the cause in most cases. Otomycosis appears most often in individuals in tropical climates, in patients with diabetes, in immunocompromised patients, and in patients on immunosuppressive therapy. Treatment involves cleansing and the use of acidifying and antifungal eardrops, such as acetic acid or a topical antifungal such as clotrimazole.

Furunculosis is a small, erythematous, and well-circumscribed infection of the cartilaginous portions of the external canal, usually caused by *S. aureus.* There is usually no drainage, and treatment involves incision, drainage, and oral antibiotics that are effective for cellulitis based on local sensitivities. Cellulitis of the auricle and canal may cause erythema, induration, and other systemic signs. Treatment is with antibiotics directed at the offending organisms.

Herpes zoster oticus, also known as the *Ramsay Hunt syndrome,* is a viral manifestation of disease affecting the auricle, with resulting facial paralysis that may involve multiple cranial nerves. It initially causes pain, with erythema, swelling, with vesicles developing approximately 3 to 7 days later. Treatment consists of analgesia and antivirals (acyclovir 800 mg five times a day, famciclovir 500 mg or valacyclovir 1000 mg three times a day), but there is little evidence supporting its efficacy.[39]

Management

Treating OE involves both cleaning the canal and treating the infection. The external canal may be cleaned with a small cotton swab or combination of gentle suctioning and irrigation, depending on the amount of obstructing exudates and whether there is an intact TM. Cleansing solutions include tap water, sterile saline, 2% acetic acid, and Burow's solution.

Topical antibiotics are highly effective for OE treatment, with clinical cure rates of 65 to 80% within 10 days.[40,41] A combination of polymyxin B, neomycin, and hydrocortisone (such as Cortisporin) can be given at a dose of 3 or 4 drops to the affected ear four times a day, though occasionally patients may react to the neomycin. Ofloxacin (5 drops) or ciprofloxacin with hydrocortisone 3 drops given twice a day may result in improved patient compliance. The addition of steroid drops may decrease inflammation and the formation of granulation tissue in the canal.[40,42]

Having the patient lie down for 5 minutes after the solution has been placed may obviate the need for packing. Commercially available wicks made of compressed cotton or hydroxycellulose are useful to facilitate medication delivery. They are most effective in patients with a severely occluded canal but can be used in patients with moderate disease. The wick is placed 10 to 12 mm into the canal, moistened with antibiotic drops, and left in place for 2 to 3 days. If wicks are used, patients should be referred to an ENT specialist or a physician with experience in their use. There is no evidence that systemic antibiotics alone or in combination with topical preparations improve treatment outcome compared with topical antibiotics alone,[40,43] but systemic medication, such as ciprofloxacin (500 mg twice a day), may be indicated in immunocompromised patients with diabetes or HIV infection or in infections involving the skin and periauricular areas. OE can be extremely painful, and severe symptoms may require opiate analgesia. Topical anesthesia, such as benzocaine with or without antipyrine, may also be used for pain relief.

NECROTIZING (MALIGNANT) EXTERNAL OTITIS

Previously known as *malignant otitis externa* because of its associated high mortality rate, necrotizing external otitis is an extremely aggressive form of OE. Patients affected include elderly patients with diabetes, patients with acquired immunodeficiency syndrome (AIDS), and, rarely, immunocompromised children. *Pseudomonas* is the predominant pathogen, but *S. aureus, S. epidermidis, Proteus mirabilis, Klebsiella, Aspergillus,* and *Salmonella* all have been described. The infection begins in the external canal and progresses through the periauricular tissue and cartilaginous bony junction of the external auditory meatus. It then spreads into the adjacent tissues along clefts in the floor of the meatus known as the *fissures of Santorini.* It may spread to the base of the skull at the temporal bone, with a resultant skull-base *osteomyelitis,* another term often used to describe this entity. The facial nerve is the first cranial nerve affected, but additional nerves may be involved. The pathogenesis is uncertain but may be related to vascular insufficiency or immune dysfunction.

Patients may have persistent otorrhea unresponsive to topical medications, otalgia, headache, and periauricular pain and swelling. The diagnosis should be considered in patients at risk who have a prolonged course of OE. The clinical finding characteristic for the disease is granulation tissue in the floor of the ear canal at

www.ketabpezeshki.com 66485457-66963820

the bony cartilaginous junction. Cranial nerve VII is most often involved; involvement manifests with facial paralysis, which occurs when the stylomastoid foramen is involved. Further extension can result in involvement of the glossopharyngeal, vagal, spinal accessory, hypoglossal, trigeminal, and abducens nerves.[44] Cranial nerve involvement does not affect mortality rates.[45] Additional complications include meningitis, brain abscess, and thrombosis of the sigmoid sinus.

There is no single diagnostic criterion for necrotizing external otitis. The diagnosis is made from a range of clinical, laboratory, and radiographic findings. Bone scanning (technetium 99m) is sensitive but is often positive in patients with OE. Gallium scans are more specific, but computed tomography (CT) and magnetic resonance imaging (MRI) are better for detecting infratemporal spread of the disease, bony erosions, and abscess formation. The bioavailability of oral ciprofloxacin and its penetration to bone have made it the ideal treatment for necrotizing external otitis, eliminating the need for hospitalization in all but the most recalcitrant cases. Treatment may be required for 6 to 8 weeks. Although extensive surgical treatment was previously required, its use is now limited to diagnostic confirmation or débridement of granulation tissue.[46] Hyperbaric oxygen has been used as an adjunct treatment for advanced disease with significant skull base or intracranial involvement, recurrent cases, and infections secondary to antibiotic treatment, but there is little evidence of its effectiveness.[47]

MASTOIDITIS

Mastoiditis is the most frequent complication of OM. The incidence of acute and chronic mastoiditis has decreased significantly since the advent of antibiotics, though debate exists regarding whether there has been an increase in the disease. Although it is still associated primarily with AOM, many patients have not had an episode of OM. Mastoiditis also has been described as a complication of leukemia, mononucleosis, sarcoma of the temporal bone, and Kawasaki disease.

Pathophysiology

Acute mastoiditis is a natural extension of middle ear infections because the mastoid air cells are generally inflamed during an episode of AOM. The aditus ad antrum is a narrow connection between the middle ear and mastoid air cells. If this connection becomes blocked, a closed space is formed, with the potential for abscess development and bone destruction. The infection may spread from the mastoid air cells by venous channels, resulting in inflammation of the overlying periosteum. Progression results in the destruction of the mastoid bone trabeculae and coalescence of the cells, resulting in acute mastoid osteitis or coalescent mastoiditis. The resulting pus may track through many routes: (1) through the aditus ad antrum with resultant spontaneous resolution; (2) lateral to the surface of the mastoid process, resulting in a subperiosteal abscess; (3) anteriorly, forming an abscess below the pinna or behind the sternocleidomastoid muscle of the neck, resulting in an abscess (often called a *Bezold abscess*); (4) medial to the petrous air cells of the temporal bone, resulting in a rare condition known as *petrositis*; and (5) posterior to the occipital bone, resulting in osteomyelitis of the calvaria or a Citelli abscess.

Chronic mastoiditis is generally a complication of chronic OM. There may be extensive invasion of granulation tissue from the middle ear into the mastoid air cells. Another entity, latent or "masked" mastoiditis, also has been described. It is indolent in nature, with minimal signs and symptoms, little or no fever, and a history of otalgia. The TM may be intact or perforated. Suspicion should be raised by the presence of intracranial complications without an apparent source. Patients at risk include newborns and immunosuppressed patients (those who have undergone recent chemotherapy or steroid administration; diabetic or geriatric patients).

Etiology

S. pneumoniae is the most common organism found in mastoiditis. The introduction of the pneumococcal conjugate vaccine has resulted in an increase of a particularly virulent strain, serotype 19A.[48] Other organisms include group A streptococci, *S. aureus, H. influenzae, and P. aeruginosa.*[49] Chronic mastoiditis also often has mixed cultures, with *P. aeruginosa* being the predominant organism.

Diagnostic Findings

Clinical findings in acute mastoiditis include fever, headache, otalgia, and erythema.[50] Pain is universally present. There are no specific diagnostic criteria, but the most common physical findings are postauricular erythema and tenderness, protrusion of the auricle, and an abnormal TM. The TM is similar to that in AOM (erythema, bulging, and decreased mobility) but may be normal in 10% of cases. Suspicion should be heightened if symptoms of AOM have lasted longer than 2 weeks. In chronic mastoiditis, symptoms include persistent drainage through the perforated TM, redness, edema, and retroauricular sensitivity.

Ancillary Testing

CT scans can identify the evidence of bony erosions, whereas MRI may be more useful in cases of possible intracranial complications.

Management

Antibiotics are the initial treatment of choice, with most cases responding without the need for surgical drainage.[51,52] Choices include a third-generation cephalosporin such as ceftriaxone or cefotaxime (50 mg/kg/day), clindamycin in the penicillin-allergic patient, and the addition of an antipseudomonal agent if *P. aeruginosa* infection is suspected. If indicated, surgical procedures may range from myringotomy and tympanostomy tube placement (for drainage and identification of the offending organism) to mastoidectomy and drainage for more extensive disease progression.

SUDDEN HEARING LOSS

Sudden sensorineural hearing loss (SSNHL), defined as the idiopathic loss of hearing of 30 dB over at least three test frequencies occurring over a period of less than 3 days, is considered an otolaryngologic emergency.[53] Any age group can be affected, but the peak incidence occurs in the fifth or sixth decade of life with an equal distribution between the sexes. The overall incidence ranges from 5 to 20 per 100,000 people per year. Severity ranges from difficulty with conversation to complete hearing loss.

A recent systematic literature review found the causes of SSNHL to be idiopathic causes (71%), infectious disease (12.8%), otologic disease (4.7%), trauma (2.4%), vascular or hematologic causes (2.8%), neoplastic causes (2.3%), and other causes (2.2%).[54] A delay in diagnosis is common because the patient may report ear fullness that is often attributed to cerumen impaction or congestion from upper respiratory infections. Tinnitus is a common finding. The likelihood of recovery is related to the severity of the hearing loss, age of the patient, and associated vestibular symptoms.[55] A history should include the time of onset, a history of trauma or recent illnesses, medications, and the presence of both otologic and neurologic symptoms.

www.ketabpezeshki.com 66485457-66963820

Physical examination includes a thorough inspection of the external canal and TM integrity. Weber's test for hearing and Rinne's test may help in distinguishing conductive versus sensorineural deficits. A comprehensive neurologic examination including cranial nerve and cerebellar testing may localize brainstem involvement. An MRI with gadolinium of the brain is the study of choice but is most appropriately performed in consultation with an otolaryngologist. A tapered dose of oral steroids is the most common treatment, though their efficacy is unproven.[56] Additional treatments have included intratympanic steroids, hyperbaric oxygen, antiviral therapy, vasoactive and hemodilution therapies, dextran, and magnesium, all with mixed results.[57-59]

EPISTAXIS

Epidemiology

Epistaxis is a common otolaryngologic problem, with 15 per 10,000 people requiring physician care annually and 1.6 per 10,000 requiring admission to the hospital.[60] It is estimated that 60% of the population experiences epistaxis during their lifetime, but only 6% of cases involve presentation to an ED. Epistaxis is more common in males than in females, and most cases occur in children younger than 10 years. The incidence decreases with age, though some studies have found a bimodal distribution of patients younger than 25 years and those older than 50 years. Epistaxis is more common in colder seasons and in northern climates because of decreased humidity and subsequent drying of the nasal mucosa.

Nasal bleeding is a frightening condition for patients but is seldom life-threatening. A solid understanding of physiology and treatment allows for prompt and efficient management of the disorder. Anterior epistaxis accounts for 90% of all nosebleeds and usually involves Kiesselbach's plexus on the anteroinferior nasal septum. Epistaxis is unilateral and can be controlled with anterior packing. Posterior epistaxis accounts for 10% of nosebleeds and usually arises from a posterior branch of the sphenopalatine artery; therefore it cannot be controlled with a well-placed anterior pack. Posterior bleeding is rare in children.

Principles of Disease

Anatomy

Three arteries with anastomoses among them supply the nasal area. The sphenopalatine artery supplies the turbinates and meatus laterally and the posterior and inferior septum medially. The anterior and posterior ethmoidal arteries from the ophthalmic branch of the internal carotid artery supply the superior mucosa medially and laterally. The superior labial branch of the facial artery provides circulation to the anterior mucosal septum and anterior lateral mucosa (Fig. 72-1).

Etiology

There are many reasons for epistaxis, but the most common are upper respiratory infection with concomitant mucosal congestion and vasodilation and trauma, either accidental or iatrogenic (e.g., nose picking) (Box 72-1). Recurrent unilateral epistaxis should raise the consideration of a neoplastic process.

Diagnostic Strategies

Patients initially should have their hemodynamic status evaluated, with resuscitation and laboratory studies performed as needed based on the possible causes (Box 72-2). Patients often are anxious and hypertensive. Elevated blood pressure is usually a result of stress and anxiety and resolves with treatment. Hypertension has

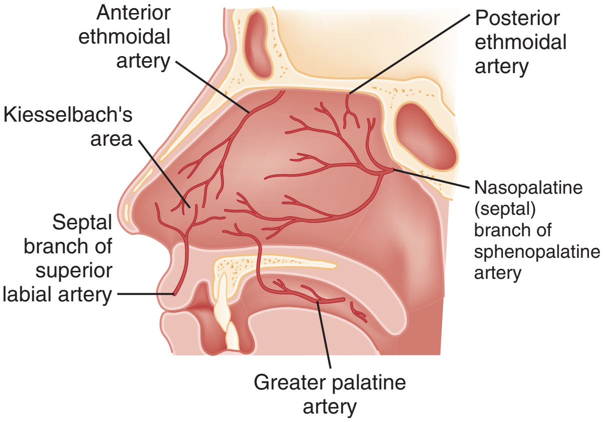


Figure 72-1. Arterial supply to medial wall of nose.

Box 72-1 Differential Diagnosis of Neck Masses

Inflammatory
Adenitis
- Bacterial (*Streptococcus, Staphylococcus*)
- Viral (HIV, EBV, HSV)
- Fungal (coccidioidomycosis)
- Parasitic (toxoplasmosis)

Cat-scratch disease
Tularemia
Local cutaneous infections
Sialoadenitis (parotid and submaxillary glands)
Thyroiditis
Mycobacterium avium-intracellulare
Mycobacterium tuberculosis

Congenital or Developmental
Brachial cleft cyst
Thyroglossal duct cyst
Dermoid cyst
Cystic hydromas
Torticollis
Thymic masses
Teratomas
Ranula
Lymphangioma
Laryngocele

Neoplastic
Benign
Mesenchymal tumors (lipoma, fibroma, neural tumor)
Salivary gland masses
Vascular abnormalities (hemangiomas, AVM, lymphangiomas, aneurysm)

Malignant
Primary tumors
Sarcoma
Salivary gland tumor
Thyroid or parathyroid tumors
Lymphoma

Metastasis
From primary head and neck tumors
From infraclavicular primary tumors (e.g., lung or esophageal cancer)

AVM, arteriovenous malformation; *EBV,* Epstein-Barr virus; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus.

www.ketabpezeshki.com 66485457-66963820

Box 72-2 Etiology of Epistaxis

Local Causes
Nasal or facial trauma
Upper respiratory tract infections
Nose picking
Allergies
Low home humidity
Nasal polyps
Foreign body in the nose
Environmental irritants
Nasopharyngeal mucormycosis
Traumatic internal carotid artery aneurysm
Chlamydial rhinitis neonatorum
Surgery (postoperative epistaxis)

Idiopathic Epistaxis
Habitual
Familial

Systemic Causes
Atherosclerosis of nasal blood vessels
Hypertension (controversial)
Anticoagulant therapy
Pregnancy
Abrupt changes in barometric pressure
Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease)
Blood dyscrasias (e.g., hemophilia, leukemia, lymphoma, polycythemia vera, anemias, idiopathic thrombocytopenic purpura, granulocytosis, inherited platelet disorders, acquired platelet disorders [i.e., aspirin use])
Hepatic disease
Rupture of internal carotid artery aneurysm
Diabetes mellitus
Alcoholism
Vitamin K deficiency
Folic acid deficiency
Chronic nephritis
Chemotherapy
Blood transfusion reactions
Migraine headache
Drug use (drug-induced thrombocytopenia)

From Wurman LH, et al: The management of epistaxis. Am J Otolaryngol 13:193, 1992.

never been shown to cause epistaxis, although it can worsen the bleeding when present. Sedation with benzodiazepines or narcotics may help these patients.

The key to successful management is identifying the site of nasal bleeding and whether it is anterior or posterior. If the nose is actively bleeding, the patient should clear clots by blowing the nose then apply bilateral pressure on the nasal septum by compressing the cartilaginous part of the nose for 10 to 15 minutes. This simple maneuver also educates the patient on how to self-manage further episodes. It is important to optimize the examination and to prepare by assembling all of the equipment needed, including an illumination source, suction, vasoconstriction medications, and packing materials. The patient must have the floor of the nose parallel to the floor. If the head is tilted, only the anterior and upper aspect of the nares can be visualized. The nasal speculum should be opened in an upper-lower direction rather than side to side in the nares. Anterior clots and obstructions may give the appearance of posterior epistaxis if the blood runs posteriorly. Persistent bleeding should be controlled with pledgets soaked in cocaine, lidocaine-epinephrine, or phenylephrine (Neo-Synephrine) to promote vasoconstriction and anesthesia. One ED study found that 65% of epistaxis patients had bleeding resolve with simple administration of oxymetazoline spray.[60]

Management

Anterior Epistaxis

After having identified the site of bleeding in anterior epistaxis, the clinician has several treatment options. Application of silver nitrate chemically cauterizes the area, though it often is unsuccessful if there is active bleeding. With 4 to 5 seconds of application, nitric acid is formed and coagulates tissue. Cauterization should never be maintained longer than 15 seconds because septal damage may occur. The area should be cauterized peripherally to centrally and superiorly to inferiorly to avoid blood, which renders the sticks ineffectual. Bilateral application of silver nitrate to the septum is not advised because it may deprive the septum of a blood supply and theoretically could lead to necrosis. Cautery should not be performed in the presence of coagulopathy. An alternative treatment is the application of topical agents, such as absorbable gelatin sponge (Gelfoam, Pfizer, New York, N.Y.) and absorbable knitted fabric (Surgicel, Johnson & Johnson, New Brunswick, N.J.), with light packing. If bleeding persists, anterior tamponade with a commercially available nasal tampon or balloon or a formal anterior nasal pack may be necessary. Occasionally, for uncontrolled bleeding despite the presence of a tampon, a second tampon can be inserted adjacent to the first. These work by three mechanisms. Direct pressure is applied, resultant mucosal irritation from the foreign body decreases bleeding, and surrounding clot formation adds further pressure. A study of 42 patients found no difference in efficacy or discomfort when the Merocel sponge was compared with the Rapid Rhino; however, patients experienced greater subjective discomfort from the latter on insertion and removal.[61] When placed, anterior packs should be left in place for about 48 to 72 hours. Discomfort caused by anterior packs may require sedatives and opioid pain medication. Bilateral packs usually are required to obtain adequate compression when the patient has significant septal deviation. Use of anterior packs in epistaxis that is refractory to pressure and vasoconstrictors has been found to stop bleeding in 60 to 80% of cases.[60]

It is customary to place patients who have undergone packing on antibiotics to prevent sinusitis from obstruction; there is no proof, however, that this is effective. Toxic shock syndrome has also been reported in patients with nasal packing.[62] Patients should be instructed on proper nose compression techniques and, after packing has been removed, to keep mucosa moist with antibiotic ointment. Patients are counseled to avoid closed-mouth sneezing, nose picking, coughing, nose blowing, and aspirin.

Posterior Epistaxis

Posterior epistaxis is suggested when posterior bleeding occurs with a properly placed anterior nasal pack. A posterior pack is therefore necessary, with either a commercially available device or basic Foley catheter. A standard Foley catheter may be inserted into the nasopharynx, partially inflated, and then pulled anteriorly, creating pressure posteriorly. A small amount of fluid can be added to the balloon, but caution should be exercised to avoid pressure necrosis. It is recommended that plain water rather than saline be used because saline can crystallize and cause problems with balloon deflation later.[63] Vaseline gauze should be packed around the catheter anteriorly. Commercially available balloons, such as the Nasostat and Epistat, are more comfortable than the posterior pack. The packs are left in for 2 to 5 days to minimize rebleeding and to avoid tissue necrosis associated with prolonged placement.[64] Antibiotics, such as cephalexin (500 mg four times daily) and amoxicillin-clavulanate (875 mg twice a day), are recommended while the packing is in place, but there is not sufficient evidence to prove effectiveness of this approach.[64a] If packing does not provide successful control, ENT

www.ketabpezeshki.com 66485457-66963820

consultation is necessary. Definitive care may require internal maxillary artery ligation or embolization with Gelfoam or posterior endoscopic cautery.

Patients with posterior nasal packs are generally admitted to the hospital and may require sedation and supplemental oxygen. The partial pressure of oxygen (Po_2) may decrease 10 mm Hg, and partial pressure of carbon dioxide (Pco_2) may increase 10 mm Hg after posterior packing. This is thought to be secondary to a postulated nasopulmonary reflex. Dysrhythmias, bradycardia, myocardial infarction, stroke, apnea, and aspiration also have been reported after posterior nasal packing.[64]

Newer Agents in Epistaxis

Several promising new agents have been developed and offer variety and choice in the treatment of epistaxis. At this point, few comparison studies or clinical trials have been conducted, and the provider should use these agents according to personal experience and preference.

QuikClot (Z-Medica, Wallingford, Conn.) hemostatic agent is a molecular sieve, sifting molecules by size. When QuikClot comes into contact with blood in and around a wound, it rapidly absorbs the smaller water molecules from the blood. The larger platelet and clotting factor molecules remain in the wound in a highly concentrated form. This promotes extremely rapid natural clotting. The particles provide key surface chemistry, rapidly enhancing the coagulation process. QuikClot is available over the counter and is being actively marketed to the public, including police, fire, sports, and military personnel. The third generation of product is directed for use by health care professionals and is composed of rayon-polyester gauze that is impregnated with kaolin, an aluminosilicate. No clinical trials have been completed, though several are underway. This preparation does not have the thermal release caused by an exothermic reaction that characterized the first generation of product, making it better tolerated by the patient; therefore it is now more reasonable and safe to use this agent to control epistaxis.

The Thrombin-JMI Epistaxis Kit (King Pharmaceuticals, Bristol, Tenn.) is a topical thrombin that was released in 2007. It clots the fibrinogen directly and is indicated in oozing bleeding from capillaries and small venules. It requires mixing of the thrombin powder with the saline diluent before use. After the agent has been drawn up in a 5-mL syringe, a special nasal drug delivery device is attached. The contoured tip is inserted into the naris, and the solution is sprayed as a fine mist across the nasal mucosa. Approximately half should be used initially, and the remainder used after 3 to 5 minutes if bleeding persists.

FloSeal Hemostatic Matrix (Baxter, Deerfield, Ill.) is a combination of human thrombin (from pooled plasma), calcium chloride, and a gelatin matrix, which are mixed together and placed at a bleeding site. The manufacturer claims that bleeding, whether it is oozing or pulsatile, ceases within 2 minutes. Bleeding must be active for this method to be effective. Injection into blood vessels or open lacerations is contraindicated. After application the volume swells approximately 20%, and excess volume other than the induced clot should be gently irrigated away. Preparation of the material requires mixing of the materials and then passage of the liquid back and forth between two connected syringes 20 times. The material may not be used for at least 30 seconds. After mixing, it is active for 2 hours. Clinical trials have shown that FloSeal is able to stop 97% of epistaxis within 2 minutes.[65,66] One trial found it stopped 80% of bleeding refractory to other treatments and prevented the need for surgical treatment. FloSeal offers the advantages of conforming to the three-dimensional structure of any given patient anatomy and being better tolerated than packing. It avoids the inconvenience and cost of a follow-up visit, as it begins to break down within 3 to 5 days.

SIALOLITHIASIS

Stones of the salivary glands occur in 1% of the population.[67] They are found most commonly in people aged 30 to 50 years. They are found in the sublingual gland about 6% of the time and in the parotid gland 2%. The most common gland affected is the submandibular (submaxillary) gland, accounting for 80 to 95% of cases. Although these stones are less common in children, a study of 210 stones found that 14% occurred in children younger than 18 years.[68] Pediatric stones were more likely to be distal in the duct and smaller.

The stones occur when calcification occurs around an organic nidus. The patient has pain and swelling of the gland. Differential diagnosis includes infections, inflammation, and granulomatous and neoplastic processes. The most common viral pathogen is mumps. *Staphylococcus, Streptococcus viridans, S. pneumoniae,* and *H. influenzae* predominate in bacterial infections. Stones may be confirmed by palpation or purulent discharge from the glandular duct with massage. CT provides more accurate sizing and location within the duct; however, ultrasonography is rapidly becoming the diagnostic modality of choice because it avoids radiation and may reveal diagnoses other than stones.

Many providers routinely prescribe antibiotics (covering penicillinase-resistant organisms); however, there is no evidence to support this practice unless infection is suspected because of increasing pain, fever, or purulent ductal drainage. Treatment consists of moist heat, massage, sialagogues (lemon or other tart candies to promote glandular secretions), and sialolithotomy, if necessary, with probes or endoscopy. Lithotripsy is also used and works better for parotid than for submandibular stones. One study of 323 submandibular and 132 parotid stones found lithotripsy to be successful in 39.4%, basket retrieval in 74.7%, and intraoral surgical removal in 95.8% of patients in which these treatments were attempted.[69] Procedures are chosen based on stone size and location. Stones smaller than 2 mm are usually managed nonsurgically. For recalcitrant cases, the entire gland may require removal, but this may lead to chronic decreased function and morbidity. Follow-up within 24 hours should be arranged for patients with stones that are not removed in the ED and in 4 to 5 days if the removal is successful in the ED.

NECK MASSES

Perspective

Neck masses are a relatively common clinical finding with a multitude of causes. The differential diagnosis can generally be broken down into three categories: inflammatory, congenital, or neoplastic. Children and young adults are more likely to have benign disorders, such as inflammatory or congenital abnormalities, including thyroglossal or brachial cleft cysts. Adult neck masses are more likely to be neoplastic. In general, 80% of nonthyroid neck masses in adults are neoplastic, of which 80% are malignant. In children, however, more than 80% of neck masses are benign. This is often referred to as *the rule of 80* or the *80% rule.* Risk factors that may predispose patients to ENT malignancies include alcohol and tobacco use, viruses such as herpesvirus, sunlight exposure, genetics, diet, exposure to dust, and inhalation exposures.

Principles of Disease

Identifying the location of the parotid and submandibular glands, thyroid cartilage, thyroid gland, and lymph nodes can help distinguish normal structure from other types of masses (Fig. 72-2). The neck is divided into cervical triangles with the sternocleidomastoid muscle as the common boundary. The anterior portion is

www.ketabpezeshki.com 66485457-66963820

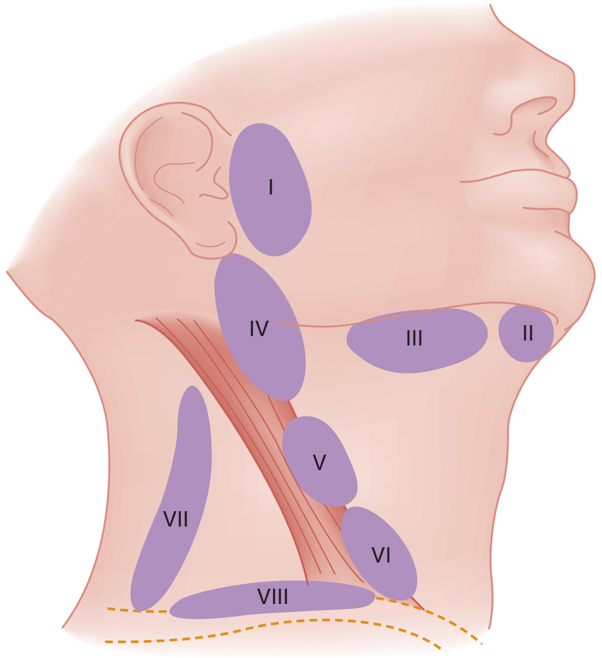


Figure 72-2. Major lymph node groups in the head and neck: *I,* parotid nodes; *II,* submental nodes; *III,* submandibular nodes; *IV,* jugulodigastric nodes (superior jugular nodes); *V,* midjugular nodes; *VI,* lower jugular nodes; *VII,* spinal accessory nodes; *VIII,* subclavian nodes. Groups VI and VII are often termed "scalene nodes." (Redrawn and adapted from Moloy PJ: How to [and how not to] manage the patient with lump in the neck. In American Academy of Otolaryngology–Head and Neck Surgery Foundation: Common Problems of the Head and Neck Region. Philadelphia, WB Saunders, 1995:134.)

bordered by the midline of the neck, the inferior aspect of the mandible superiorly, and the anterior border of the neck posteriorly. Lesions of the skin, scalp, oral cavity, oropharynx, hypopharynx, larynx, and tongue may manifest here.[70] The posterior triangle is bordered by the sternocleidomastoid anteriorly, posteriorly by the trapezius muscle, and inferiorly by the clavicle. Lesions in this area may include those from the nasopharynx and metastatic lesions from the lung and the gastrointestinal and genitourinary tracts.[70]

Clinical Features

Important associated symptoms include dysphagia, odynophagia, otalgia, stridor, speech disorders, and globus phenomena. Dysphagia is difficulty swallowing and may be caused by physical obstruction or neurologic disorders. Odynophagia is pain on swallowing and can be caused by many entities, such as tonsillitis or carcinoma of the pharynx. In an adult, a sore throat that lasts for several weeks should raise the suspicion of a neoplastic process. Otalgia is pain felt in the ear that may be referred from the larynx, pharynx, and cranial nerves V, IX, and X. Referred ear pain is considered an ominous sign in adults and should be presumed to be cancer until proved otherwise.[71] Unilateral OME in older adults should be considered nasopharyngeal carcinoma until proved otherwise. Stridor, specifically inspiratory stridor, is diagnostic of upper airway obstruction. It localizes a lesion to above or at the level of the larynx and when present in adults with a neck mass increases the possibility of carcinoma. Speech disorders, particularly "hot potato" speech, are suggestive of space-occupying lesions above the oropharynx, a classic example being peritonsillar abscess. The globus symptom is a lump in the throat. It has occurred in almost everyone at one time or another, is localized to the pharynx, and is often a functional complaint. Hoarseness, the final symptom, is a fairly common complaint, with myriad causes ranging from viral pharyngitis to laryngeal cancer. Also, similar to the term *dizziness, hoarseness* has many descriptions, including breathiness, muffling, harshness, scratchiness, or unnatural deepening of the voice. Hoarseness lasting longer than 2 weeks needs investigating. Additional history about the location of the mass, rate of growth, presence of pain, and constitutional symptoms, such as fever, night sweats, and weight loss, will also be helpful.

Physical Examination

The head and neck examination may identify masses, lesions, mucosal ulcerations or discolorations, and cranial nerve abnormalities. The mass itself should be palpated for location, size, and consistency. Lymph nodes are generally smaller than 1 to 1.5 cm, so any nodes larger than 1.5 cm should be considered abnormal. Lymph nodes are also mobile, soft, and fleshy. Decreased mobility and firmness are warning signs of malignancy.

Diagnostic Strategies

The diagnostic strategy is tailored to results of the history and physical examination. Hoarseness for longer than 2 weeks should be investigated, generally with a fiberoptic examination. Serologic and skin tests may be helpful in certain instances but are best performed by the referring specialist. Chest radiography may identify lung carcinoma as the source of metastasis. CT of the neck is the initial study of choice in most patients, but additional modalities include ultrasound and MRI.

Differential Considerations

Box 72-1 lists common possibilities for the differential diagnosis of neck masses.

Management and Disposition

Most masses in children are inflammatory; it is a reasonable strategy, therefore, to start the patient on antibiotics with a 2-week follow-up. If inflammation is considered in adults, a similar strategy can be used. Adults generally need ENT referral if the mass does not resolve in 2 weeks, the mass is enlarging, the mass is fixed, cervical lymph nodes are matted, or masses are noted in the parotid or thyroid gland.

KEY CONCEPTS

- Most cases of AOM resolve spontaneously. Children older than age 2 years may be observed for 3 days to determine whether antibiotics are required. When indicated, amoxicillin is the initial choice for treatment of AOM at a dose of 80 to 90 mg/kg/day.
- Necrotizing OE should be considered in immunocompromised patients who have persistent otitis externa.
- Patients with epistaxis with posterior nasal packing should be admitted to the hospital. Antibiotic therapy typically is prescribed.
- All neck masses that do not respond to antibiotics or persist for more than 2 weeks or hoarseness lasting for more than 2 weeks needs ENT referral.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Johnson NC, Holger JS: Pediatric acute otitis media: The case for delayed antibiotic treatment. *J Emerg Med* 2007; 32:279.
2. McCracken GH Jr: Diagnosis and management of acute otitis media in the urgent care setting. *Ann Emerg Med* 2002; 39:413.
3. Hoberman A, Paradise JL: Acute otitis media: Diagnosis and management in the year 2000. *Pediatr Ann* 2000; 29:609.
4. Benninger MS: Acute bacterial rhinosinusitis and otitis media: Changes in pathogenicity following widespread use of pneumococcal conjugate vaccine. *Otolaryngol Head Neck Surg* 2008; 138:274.
5. Casey JR, Pichichero ME: Changes in frequency and pathogens causing acute otitis media in 1995-2003. *Pediatr Infect Dis J* 2004; 23:824.
6. Ruohola A, et al: Microbiology of acute otitis media in children with tympanostomy tubes: Prevalences of bacteria and viruses. *Clin Infect Dis* 2006; 43:1417.
7. Heikkinen T: Role of viruses in the pathogenesis of acute otitis media. *Pediatr Infect Dis J* 2000; 9:S17.
8. Chonmaitree T: Acute otitis media is not a pure bacterial disease. *Clin Infect Dis* 2006; 43:1423.
9. McCormick DP, et al: Bullous myringitis: A case-control study. *Pediatrics* 2003; 112:982.
10. Kotikoske MJ, Kleemola M, Plamu AA: No evidence of mycoplasma in acute myringitis. *Pediatr Infect Dis J* 2004; 23:426.
11. Bingen D, Cohen R, Jourenkova J, Gehanno P: Epidemiologic study of conjunctivitis-otitis syndrome. *Pediatr Infect Dis J* 2005; 24:731.
12. Faden H: The microbiologic and immunologic basis for recurrent otitis media in children. *Eur J Pediatr* 2001; 60:407.
13. Rothman R, Owens T, Simel D: Does this child have acute otitis media? *JAMA* 2003; 90:1633.
14. Verhoeff M, van der Veen EL, Rovers MM, Sanders EA, Schilder AG: Chronic suppurative otitis media: A review. *Int J Pediatr Otorhinolaryngol* 2006; 70:1.
15. Sennaroglu L, Sozeri B: Otogenic brain abscess: A review of 41 cases. *Otolaryngol Head Neck Surg* 2000; 123:751.
16. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media: Diagnosis and management of acute otitis media. *Pediatrics* 2004; 113:1451.
17. Rosenfeld RM: Diagnostic certainty for acute otitis media. *Int J Pediatr Otorhinolaryngol* 2002; 64:89-95.
18. Hoberman A, Paradise JL, Reynolds EA, Urkin J: Efficacy of Auralgan for treating ear pain in children with acute otitis media. *Arch Pediatr Adolesc Med* 1997; 151:675.
19. Rovers MM, et al: Antibiotics for acute otitis media: A meta-analysis with individual patient data. *Lancet* 2006; 368:1429
20. McCormick DP, et al: Nonsevere acute otitis media: Clinical trial comparing outcomes of watchful waiting versus immediate antibiotic treatment. *Pediatrics* 2005; 115:1455.
21. Siegel RM, et al: Treatment of otitis media with observation and a safety net antibiotic prescription. *Pediatrics* 2003; 112:527.
22 Spiro DM, et al: Wait and see prescription for the treatment of acute otitis media: A randomized controlled trial. *JAMA* 2006; 296:1235.
23. Fischer T, Singer AJ, Chale S: Observation option for acute otitis media in the emergency department. *Pediatr Emer Care* 2009; 25:575-578.
24. Coco A, Vernacchio L, Horst M, Anderson A: Management of acute otitis media after publication of the 2004 AAP and AAFP clinical practice guideline. *Pediatrics* 2010; 125:214.
25. Coker TR, et al: Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: A systematic review. *JAMA* 2010; 304:2161.
26. Glasziou PP, Del Mar CB, Sanders SL, Hayem M: Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev* 2004; 1:CD000219.
27. Hoberman A, et al: Treatment of acute otitis media in children under 2 years of age. *N Engl J Med* 2011; 363:114.
28. Tähtinen PA, et al: A placebo controlled trial of antimicrobial treatment for acute otitis media. *N Engl J Med* 2011; 364:116.
29. Block SL: Searching for the holy grail of acute otitis media. *Arch Dis Child* 2006; 91:959.
30. Pelton SI, Leibovitz E: Recent advances in otitis media. *Pediatr Infect Dis J* 2009; 28:S133-137.
31. Sabharwal V, Marchant CD: Fluoroquinolone use in children. *Pediatr Infect Dis J* 2006; 25:257-258.
32. Koopman L, et al: Antibiotic therapy to prevent the development of asymptomatic middle ear effusion in children with acute otitis media: A meta-analysis of individual patient data. *Arch Otolaryngol Head Neck Surg* 2008; 134:128.
33. American Academy of Family Physicians, American Academy of Otolaryngology–Head and Neck Surgery, American Academy of Pediatrics Subcommittee on Otitis Media with Effusion: Otitis media with effusion. *Pediatrics* 2004; 113:1412.
34. Vaile L, Williamson T, Waddell A, Gaylor GJ: Interventions for ear discharge associated with grommets (ventilation tubes). *Cochrane Database Syst Rev* 2006; 2:CD001933.
35. Ruohola, Roland PS, Parry DA, Strohman DW: Microbiology of acute otitis media with tympanostomy tubes. *Otolaryngol Head Neck Surg* 2005; 133:585.
36. Schmelzle J, Birtwhilstle RV, Tan AK: Acute otitis media in children with tympanostomy tubes. *Can Fam Physician* 2008; 54:1123.
37. Rosenfeld RM, et al: Clinical practice guideline: Acute otitis externa. *Otolaryngol Head Neck Surg* 2006; 134:S4
38. Roland PS, Stroman DW: The microbiology of acute otitis externa. *Laryngoscope* 2002; 112:1166.
39. Uscategui T, Dorée C, Chamberlain IJ, Burton MJ: Antiviral therapy for Ramsay Hunt syndrome in adults. *Cochrane Database Syst Rev* 2008; 8:CD006851.
40. Rosenfeld, RM, Singer M, Wasserman JM, Stinnett SS: Systematic review of topical antimicrobial therapy for acute otitis externa. *Otolaryngol Head Neck Surg* 2006; 134:S24-S48.
41. Kaushik V, Malik T, Saeed SR: Interventions for acute otitis externa. *Cochrane Datatbase Syst Rev* 2010; 1:CD004740.
42. Van Balen FAM, Smit, WM, Zuithoff NP: Clinical efficacy of three common treatments in acute otitis externa in primary care: Randomized controlled trial. *BMJ* 2003; 327:1-5.
43. Hannley MT, Denneny JC 3rd, Holzer SS: Use of ototopical antibiotics in treating 3 common ear diseases. *Otolaryngol Head Neck Surg* 2000; 122:934.
44. Grandis JR, Branstetter BF, Yu VL: The changing face of malignant (necrotizing) otitis: Clinical, radiological and anatomic correlations. *Lancet Infect Dis* 2006; 4:34.
45. Mani N, Sudhoff H, Rajagopal S, Moffat D, Axon PR: Cranial nerve involvement in malignant external otitis: Implications for clinical outcome. *Laryngoscope* 2007; 117:907.
46. Sreepada GS, Kwarler JA: Skull base osteomyelitis secondary to malignant otitis externa. *Curr Opin Otolaryngol Head Neck Surg* 2003; 11:316.
47. Phillips JS, Jones SE: Hyperbaric oxygen as an adjuvant treatment for malignant otitis externa. *Cochrane Database Syst Rev* 2005; 2:CD004617.
48. Ongkasuwan J, Valdez TA, Hulten KG, Mason EO Jr, Kaplan SL: Pneumococcal mastoiditis in children and the emergence of multidrug resistant serotype 19A isolates. *Pediatrics* 2008; 122:34-39.
49. Harrison WL, Shargorodsky J, Gopen Q: Clinical strategies for the management of acute mastoiditis in the pediatric population. *Clin Pediatr* 2010; 49:110-115.
50. van den Aardweg MT, Rovers MM, de Ru JA, Albers FW, Schilder AG: A systematic review of diagnostic criteria for acute mastoiditis in children. *Otol Neurotol* 2008; 29:751-757.
51. Zanetti D, Nassif N: Indication for surgery in acute mastoiditis and their complications in children. *Int J Pediatr Otorhinolaryngol* 2006; 70:1175.
52. Taylor MF, Berkowitz RG: Indications for mastoidectomy in acute mastoiditis in children. *Ann Otol Rhinol Laryngol* 2004; 113:69.
53. Conlin AE, Parnes LS: Treatment of sudden sensorineural hearing loss, I: A systemic review. *Arch Otolaryngol Head Neck Surg* 2007; 133:573.
54. Chau JK, Lin JR, Atashband S, Irvine RA, Westerberg BD: Systematic review of the evidence for the etiology of adult sudden sensorineural hearing loss. *Laryngoscope* 2010; 120:1011.
55. Rauch SD: Idiopathic sudden sensorineural hearing loss. *N Engl J Med* 2008; 359:833-840.
56. Wei BPC, Mubiru S, O'Leary S: Steroids for idiopathic sudden sensorineural hearing loss. *Cochrane Database Syst Rev* 2006; 1:CD003998.
57. Bennett MH, Kertesz T, Yeung P: Hyperbaric oxygen for idiopathic sudden sensorineural hearing loss and tinnitus. *Cochrane Database Syst Rev* 2007; 1:CD004739.
58. Horn CE, Himel HN, Selesnick SH: Hyperbaric oxygen therapy of sudden sensorineural hearing loss: A prospective trial of patients failing steroid and antiviral treatment. *Otol Neurotol* 2005; 26:882.
59. Doyle KJ, et al: Intratympanic steroid treatment: A review. *Otol Neurotol* 2004; 25:1034.
60. Schlosser RJ: Epistaxis. *N Engl J Med* 2009; 360:784.
61. Moumoulidis I, Draper MR, Patel H, Jani P, Price T: A prospective randomized controlled trial comparing Merocel and Rapid Rhino nasal tampons in the treatment of epistaxis. *Eur Arch Otorhinolaryngol* 2006; 268:719.
62. Frazee TA, Hauser MS: Nonsurgical treatment of epistaxis. *J Oral Maxillofac Surg* 2000; 58:419.

www.ketabpezeshki.com 66485457-66963820

63. Cruise A: Warning—when using a Foley catheter for post-nasal space packing fill the balloon with water rather than saline: Letter to the editor. *Clin Otolaryngol* 2006; 31:344.
64. Viducich RA, Blanda MP, Gerson LW: Posterior epistaxis: Clinical features and acute complications. *Ann Emerg Med* 1995; 25:592.
64a. Pepper C, Lo S, Toma A: Prospective study of the risk of not using prophylactic antibiotics in nasal packing for epistaxis. *J Laryngol Otol* 2012; 126:257-259.
65. Côté D, Barber B, Diamond C, Wright E: FloSeal hemostatic matrix in persistent epistaxis: Prospective clinical trail. *J Otolaryngol Head Neck Surg* 2010; 39:304-308.
66. Mathiasen R, Cruz R: Prospective, randomized controlled clinical trial of a novel matrix hemostatic sealant in patients with acute anterior epistaxis. *Laryngoscope* 2005; 115:899.
67. Andretta M, Tregnaghi A, Prosenikliev V, Staffieri A: Current opinions in sialolithiasis diagnosis and treatment. *Acta Otorhinolaryngol Ital* 2005; 25:145.
68. Chung MK, et al: Pediatric sialolithiasis: What is different from adult sialolithiasis? *Int J Pediatr Otorhinolaryngol* 2007; 71:787.
69. McGurk M, Esdudier MP, Brown JE: Modern management of salivary calculi. *Br J Surg* 2005; 92:107.
70. Rosenberg TL, Brown JJ, Jefferson GD: Evaluating the adult patient with a neck mass. *Med Clin North Am* 2010; 94:1017-1029.
71. Moloy PJ: How to (and how not to) manage the patient with lump in the neck. In American Academy of Otolaryngology–Head and Neck Surgery Foundation: Common Problems of the Head and Neck Region. Philadelphia: WB Saunders; 1995:134.

www.ketabpezeshki.com 66485457-66963820

Chapter 73

Asthma

Richard M. Nowak and Glenn F. Tokarski

PERSPECTIVE

The word *asthma* is derived from the Greek ασυμα, signifying panting, and was used initially as a synonym for "breathlessness." In 1698, Floyer published *A Treatise of the Asthma,* in which he attempted to differentiate asthma more clearly from other pulmonary disorders. Subsequent definitions of asthma highlight concepts of airway hyper-responsiveness, bronchospasm, and reversible airway obstruction but fail to encompass the many facets of this complex disease.

The National Heart, Lung, and Blood Institute summarizes our current understanding of asthma as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role … this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing … episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyper-responsiveness to a variety of stimuli. Reversibility … may be incomplete in some patients."[1] Asthma is thus a chronic inflammatory disease, and control of symptoms ultimately depends on ameliorating the inflammatory reaction that produces alterations in airway function and structure. Irreversible structural airway changes occurring in response to chronic airway inflammation may influence emergency department (ED) asthma therapies.

EPIDEMIOLOGY

In 2008, it was estimated that 38.1 million Americans had been diagnosed with asthma by a health professional within their lifetime.[2] The prevalence of asthma (defined as individuals who have been diagnosed and currently have asthma) in 2009 was 24.6 million (17.5 million adults and 7.1 million children), and the asthma attack prevalence (the number of persons who had had at least one asthma attack in the previous year) was 12.8 million, representing 52% of persons who had asthma.[2,3] Asthma is more prevalent in children than adults, in females than males, and in blacks than whites or Hispanics (Fig. 73-1).[4] Puerto Ricans have a current asthma prevalence 100% higher than non-Hispanic whites and 50% higher than non-Hispanic blacks. Females have a 33% higher prevalence than males (this pattern is reversed in children). Asthma is more prevalent in the impoverished and in those residing in nonmetropolitan locales. The northeastern states have the highest asthma prevalence (Fig. 73-2).[3,5]

Asthma was responsible for more than 1.75 million ED visits and 456,000 hospitalizations in the United States in 2007 (Fig. 73-3).[3] Females were 1.08 times more likely to require hospitalization and had a death rate 1.29 times greater than males. African Americans had an ED visit rate 3.32 times higher, a hospitalization rate 2.22 times higher, and a death rate 1.93 times higher than whites. Children (ages 0-17) accounted for more than 640,000 ED visits and had a hospitalization rate 1.23 times higher than adults. Decreases in hospitalization rates have been noted in those older than 45 years from the late 1980s into the early 2000s.[6] Between 1995 and 2006, hospital discharges for asthma decreased by 13%. The only age group that did not experience a decrease in hospital discharge rates was patients older than 65 years.[2] The estimated financial burden of asthma totaled $20.7 billion in the United States in 2010, with approximately 75% attributable to direct costs (hospital care and physician services).[2] Prescription drugs represented the highest single direct cost at $5.9 billion. Less than 20% of asthma patients account for 80% of the direct costs.[7] Indirect costs attributable to asthma are reflected by decreased productivity. In 2008, asthma accounted for an estimated 14.2 million lost work days and 14.4 million lost school days. In those not currently employed, 22 million days of housework or other activities were missed.[3,8] Asthma ranks within the top 10 prevalent conditions causing limitation of activity.

The United States has one of the lowest rates of asthma mortality in the world.[9] A downward trend in asthma-related deaths has occurred since 2003, when 4055 deaths from asthma were reported[10]; 3447 deaths from asthma occurred in 2007, and 3395 in 2008.[11] Despite these positive indicators, asthma mortality is 44% higher in females than in males and three times higher in blacks than in whites.[2] Asthma death rates are higher in Puerto Rico than in the U.S. general population.[12] Deaths from asthma are rare in children.[3]

Developed nations have higher rates of asthma, which suggests that urbanization and westernization are correlated with increased asthma prevalence. It is interesting to note that migrants who move from an area of low asthma prevalence to an area of high asthma prevalence assume an increased asthma prevalence, suggesting that environmental factors play a role. Urban areas in the United States (New York City, Los Angeles, and Chicago) have high mortality rates associated with asthma, indicating that poverty and lack of access to medical care may also be major determinants of asthma complications.

Factors that contribute to asthma morbidity and mortality include inadequate patient and physician assessment of an acute episode resulting in undertreatment; overuse of prescribed or over-the-counter medications leading to delays in seeking treatment; failure of physicians to consider previous ED visits, hospitalizations, or life-threatening episodes of asthma; and failure to initiate corticosteroid therapy early in the course of an exacerbation. Socioeconomic factors, environmental influences, and overreliance on emergency facilities for all asthma care are also contributing factors. Initiatives to educate physicians and patients

www.ketabpezeshki.com 66485457-66963820

about asthma pathophysiology, monitoring, and therapy (e.g., National Asthma Education and Prevention Program [NAEPP], Global Initiative for Asthma [GINA], and Healthy People 2010) may be in part responsible for the moderation of asthma morbidity and mortality rates.

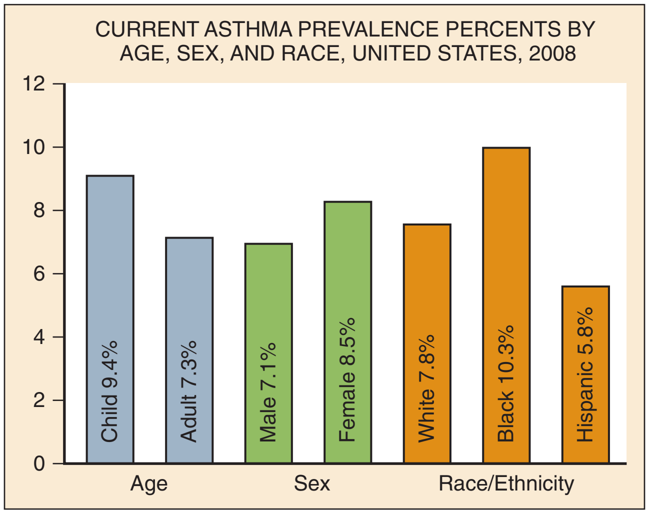


Figure 73-1. Asthma prevalence percentages by age, sex, and race, United States, 2008. (Adapted from National Health Interview Survey, National Center for Health Statistics, Centers for Disease Control and Prevention. www.cdc.gov/asthma/asthmadata.htm.)

PRINCIPLES OF DISEASE

Pathophysiology

A variety of airway alterations occur in asthma, but airway inflammation is the final common pathway limiting airflow. Allergens and nonallergic stimuli (e.g., exercise; aspirin-induced and menstrual-related asthma) induce bronchoconstriction via release of mediators and metabolic products from inflammatory cells. Compared with healthy individuals, patients with asthma show bronchial hyper-reactivity (hyper-responsiveness) in response to bronchoconstricting stimuli (e.g., methacholine). Edema, inflammation, mucous production, and airway smooth muscle hypertrophy contribute to bronchoconstriction and hyper-reactivity and further airway obstruction and airflow limitation. Permanent structural airway changes *(airway remodeling)* may contribute to increased airway obstruction and hyper-responsiveness and decrease the response to therapy. The interaction of these features determines the clinical manifestations and severity of asthma and significantly influences the response to therapy.

Evidence that inflammation is a component of asthma physiology was initially derived from autopsy findings in patients with fatal asthma. The airways revealed infiltration by neutrophils, eosinophils, and mast cells and the presence of subbasement membrane thickening, loss of epithelial cell integrity, goblet cell hyperplasia, and mucous plugs. Antemortem bronchial biopsy findings in patients with even mild degrees of asthma also demonstrate inflammatory changes in the central and peripheral airways that correlate with disease severity.[13] Inflammatory and

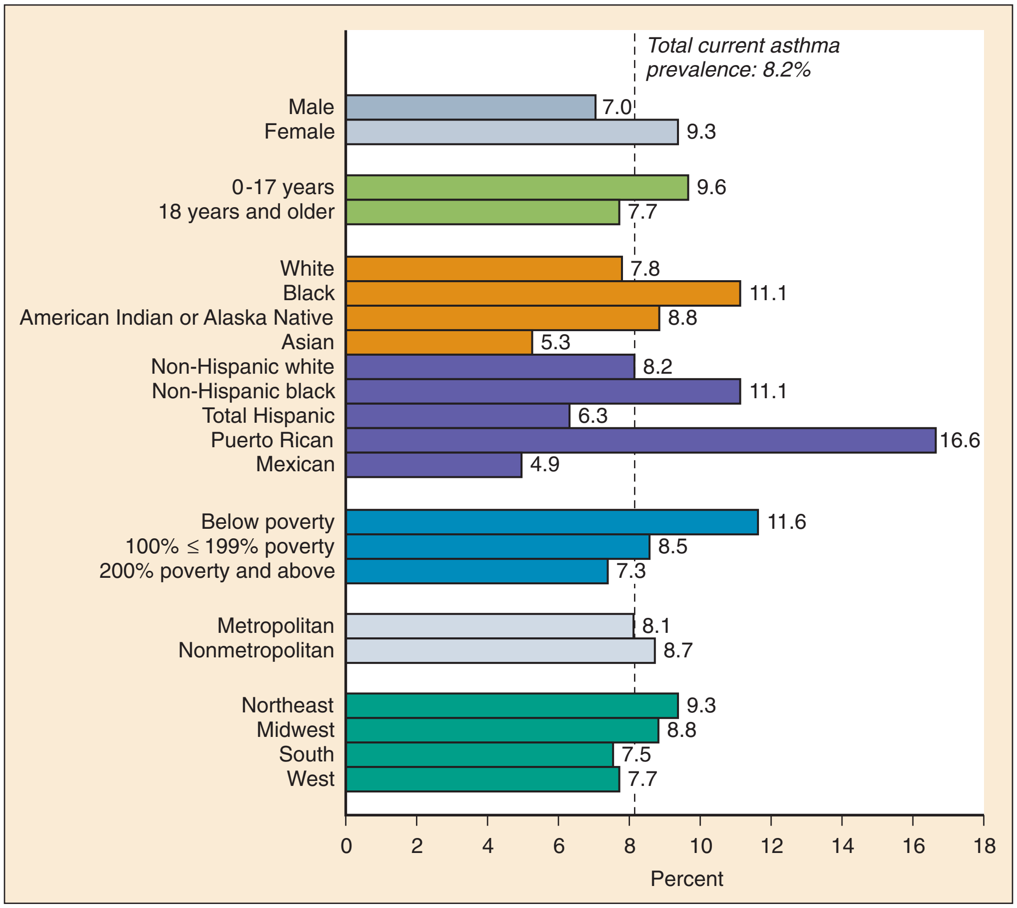


Figure 73-2. Prevalence of asthma by selected characteristics, United States, 2009. *Note:* Estimates (except age-group–specific estimates) are age-adjusted to the year 2000 U.S. standard population. (Adapted from Akinbami LJ, Moorman JE, Liu X: Asthma prevalence, health care use, and mortality: United States 2005-2009. National health statistics reports: no 32. Hyattsville, Md, National Center for Health Statistics, 2011.)

www.ketabpezeshki.com 66485457-66963820

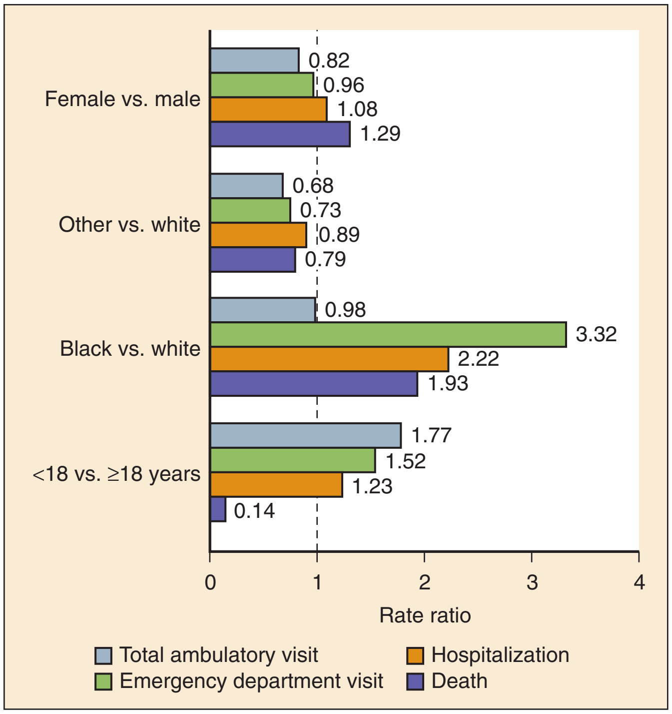


Figure 73-3. Relative burden of asthma health care use and mortality: United States, annual average 2005-2007. *Note:* A rate ratio of 1.0 *(dashed line)* indicates equal rates between the groups being compared. (Adapted from Akinbami LJ, Moorman JE, Liu X: Asthma prevalence, health care use, and mortality: United States 2005-2009. National health statistics reports: no 32. Hyattsville, Md, National Center for Health Statistics, 2011.)

chemotactic cytokines produced by both resident airway and recruited inflammatory cells are identified in bronchoalveolar lavage washings and pulmonary secretions.

Asthma has been divided into allergic and nonallergic types based on the presence or absence of immunoglobulin E (IgE) antibodies to common environmental antigens (pollen, dander, mites) and microbiologic antigens (bacteria, viruses). Immunologic responses suggest an acquired cause of asthma, whereas the absence of an immunologic response suggests an innate cause. Exposure to microbes and allergens (or lack of) during childbirth, infancy, and childhood may influence expression of the asthma phenotype later in life (the *hygiene hypothesis*).[14-16] Trigger factors precipitating acute asthma exacerbations are typically environmental or viruses, but a specific inciting agent may not be identifiable. Regardless of an allergic or nonallergic basis, both forms of asthma are characterized by infiltration of the airways by T-helper cells that release cytokines such as interleukin (IL)-4, IL-5, and IL-13, stimulating basophil, eosinophil, mast cell, and leukocyte migration to the airways. Release of inflammatory cell mediators results in bronchospasm, mucous production, airway edema, and amplification of the inflammatory response.

Mast cells are found in airway mucosa and submucosa, and increased numbers are identified in and around airway smooth muscle and airway mucous glands. Mast cell activation occurs via cross-linking of antigen and surface-bound IgE. Nonimmunologic activation by cytokines, complement, proteases, and local hyperosmolality also occurs.[17] Mast cells release histamine, prostaglandin D_2 (PGD_2), and leukotriene C_4 (LTC_4), leading to bronchospasm, mucous production, and airway edema and causing acute symptoms (the early asthmatic response). Cytokines produced by mast cells result in airway smooth muscle hyperresponsiveness, eosinophil recruitment, and IgE synthesis. Mast cells release proteases that damage airway epithelium and contribute to airway remodeling. Tumor necrosis factor alpha (TNF-α) is a potent bronchoconstrictor produced by mast cells. In chronic asthma there is evidence of persistent mast cell activation resulting in continuous mediator release, cytokine production, and amplification of airway inflammation.[18] The presence of mast cells in airway smooth muscle contributes to propagation of the inflammatory response, persistent bronchoconstriction, and over time, airway smooth muscle hypertrophy that plays a role in airway remodeling.[19,20]

Eosinophils are major effector cells in asthma, and their presence is evidence of the allergic nature of this disease. Increased numbers of eosinophils are found in the airways of most but not all asthmatics.[21] Eosinophils contain granules that release inflammatory mediators, including major basic protein, eosinophil cationic protein, and eosinophil peroxidase. Major basic protein is a potent bronchoconstrictor. Eosinophil cationic protein increases airway mucous production and causes histamine release from mast cells. Leukotrienes (LTs) produced by eosinophils are bronchoconstrictors and promote the secretion of thick viscid mucus, leading to airway plugging, LTs also enhance airway vascular permeability, leading to airway edema. Platelet-activating factor, superoxides, and free radicals produced by eosinophils also cause bronchospasm and bronchial tissue injury. Eosinophilic mediators damage and cause desquamation of the airway epithelium, expose nerve endings, provide submucosal access for inflammatory cells and mediators, and negate epithelial cell regulation of the inflammatory process.

Although eosinophils appear to be important in airway allergic and inflammatory processes, eosinophilia is not universal in asthmatics. Confounding the role of the eosinophil are studies with anti–IL-5 that significantly reduced sputum and blood eosinophilia but did not significantly affect asthma control.[22,23] Clinically, eosinophils are important biomarkers in predicting response to corticosteroid therapy. Steroid-naïve asthmatics with sputum eosinophilia have a good response to inhaled corticosteroid (ICS) therapy, whereas those without sputum eosinophilia do not.[24-26] Suppressing sputum eosinophilia with oral or inhaled steroids reduces the number of acute exacerbations in patients with severe asthma.[17,27]

Mediator and cytokine release from mast cells, eosinophils, and other airway inflammatory cells (macrophages, lymphocytes, basophils, neutrophils) contributes to prolonged bronchial smooth muscle spasm, edema, and mucous production (the late asthmatic response). Ongoing synthesis and release of cytokines, prostaglandins (PGs), and LTs (Fig. 73-4) are responsible for propagation and intensification of airway inflammation and disruption of the airway epithelial border.[28] Airway epithelial cells are more than a passive barrier and are recognized to produce proinflammatory mediators. Tight junctions between airway epithelial cells are altered in asthma, which may allow access of allergens, microbes, and viruses into the airway submucosa. Inflammatory cells, mediators, and airway viruses can directly damage the epithelial barrier and stimulate airway epithelial cells to produce inflammatory mediators. Abnormal repair processes may further airway inflammation and obstruction and contribute to airway remodeling.[29,30] Nitric oxide (NO) produced by airway epithelial cells in the large and small airways and alveoli is a reflection of ongoing airway inflammation. Measurements of fractional exhaled nitric oxide (FENO) may prove useful for monitoring the response to asthma therapy.[31]

Airway remodeling refers to the persistent structural changes in airways seen in patients with asthma and is caused by the presence of repetitive or chronic airway inflammation. Microscopic remodeling features include epithelial thickening, subepithelial fibrosis, mucous gland metaplasia, increases in airway smooth muscle, angiogenesis, and loss of cartilage integrity.[32] Airway remodeling

www.ketabpezeshki.com 66485457-66963820

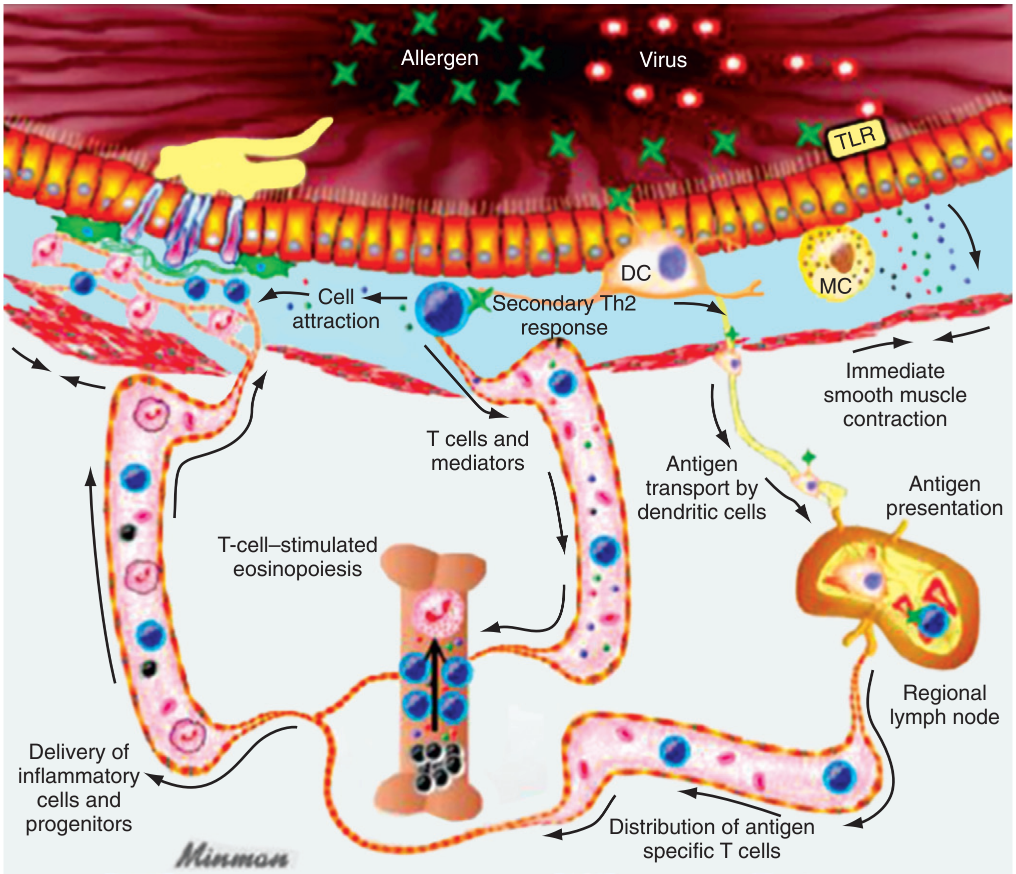


Figure 73-4. The physiologic mechanism of asthma. *DC,* dendritic cell; *MC,* mast cell; *Th,* T-helper; *TLR,* toll-like receptor. (From Murphy DM, O'Byrne PM: Recent advances in the pathophysiology of asthma. Chest 137:1417, 2010.)

occurs very early in asthma (childhood) and may precede clinical symptoms.[14,33] Remodeling features are prominent in patients with severe asthma.[34] Basement membrane thickening may be protective by preventing inflammatory cells and proteins from entering the airway submucosa through a damaged epithelium; simultaneously, this process may be counterproductive by reducing the elasticity of the small airways. Airway remodeling may explain the resistance to therapy observed in patients with prolonged asthma histories and the decline in pulmonary function noted with age. Airway remodeling induced by chronic inflammation may lead to the development of chronic irreversible airflow limitation and increased asthma mortality.

The clinical implications of the immune and inflammatory nature of the early and late asthmatic responses are crucial because therapy may be directed differently toward each phase. Mast cell stabilizers (e.g., beta-agonists) are more effective in the early asthmatic response but are of less use later in the course of an exacerbation. Anti-inflammatory therapy (e.g., corticosteroids, LT antagonists) is more effective in the late asthmatic response. Interference with or inhibition of cytokine activities, suppression of chronic inflammation, and modulation of airway remodeling are potential therapeutic targets.

Miscellaneous Situations

Aspirin-exacerbated respiratory disease (AERD) was first described more than 100 years ago. Clinically, AERD includes the tetrad of nasal polyps, eosinophilic sinusitis, asthma, and sensitivity to cyclooxygenase (COX)-1 inhibitor drugs (e.g., aspirin).The prevalence of AERD is 21% in adults with asthma and 5% in children with asthma.[35] Ethnic and familial associations are rare, and it occurs more frequently in females.[36] Nonsteroidal anti-inflammatory drugs (NSAIDs) also precipitate AERD. AERD is a common precipitant of life-threatening asthma; one survey notes that 25% of asthmatics who require mechanical ventilation have AERD.[37]

Clinically, most patients with AERD develop symptoms in the third decade (average age of onset is 34 years), frequently after a viral respiratory illness. A previous history of asthma or allergic rhinitis may be noted, but many patients have no prior respiratory disease. Chronic rhinitis, nasal polyps, and anosmia develop and are often followed by chronic pansinusitis. Bronchial asthma and sensitivity to aspirin (acetylsalicylic acid [ASA]) then results. After ingestion of aspirin or a nonsteroidal drug, acute asthma symptoms occur within 3 hours, usually accompanied by profuse rhinorrhea, conjunctival injection, periorbital edema, and occasionally a scarlet flushing of the head and neck.[38]

The pathogenesis of AERD is detailed in Figure 73-5. ASA inhibits COX,[39] of which two isoforms have been identified. COX-1 produces PGs that are involved in normal physiologic maintenance of renal function, gastric mucosal integrity and hemostasis, and inflammatory states. COX-2 is not expressed in normal physiologic circumstances but produces PGs only in response to inflammatory stimuli. COX is necessary for the production of PGE_2 in mast cells and eosinophils. PGE_2 has a stabilizing effect on these cells via blockade of the enzyme 5-lipoxygenase and the subsequent production of proinflammatory LTs (LTC_4, LTD_4, and LTE_4). AERD occurs as a result of ASA inhibition of COX and a decrease in the production of PGE_2. The end results are an increase in production of LTs, some of which are potent bronchoconstrictors, and inflammatory mediator release from mast cells and eosinophils. Most patients with AERD

www.ketabpezeshki.com 66485457-66963820

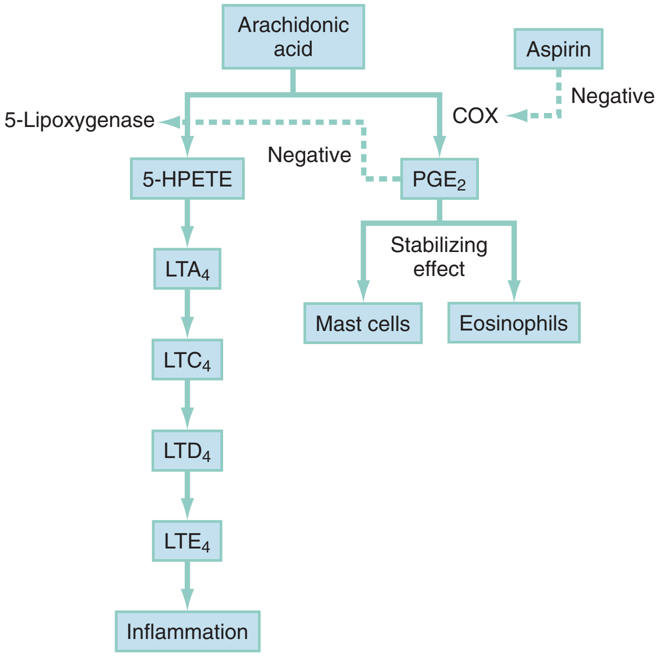


Figure 73-5. Mechanism of aspirin-exacerbated respiratory disease. Inhibition of cyclooxygenase *(COX)* decreases production of prostaglandin E_2 *(PGE_2)*. PGE_2 has an inhibitory effect on leukotriene *(LT)* synthesis. *5-HPETE,* 5-hydroperoxyeicosatetraenoic acid.

benefit from anti-LT treatment. These agents block synthesis of LTs (e.g., zileuton) or block specific LT receptors (e.g., zafirlukast, montelukast). Desensitization with slowly increased doses of oral aspirin may be used when aspirin avoidance is not possible (e.g., in patients with cardiovascular disease).[39]

COX-2 inhibitors have the advantage of inhibiting inflammation without renal, gastrointestinal, or hematologic side effects. AERD is not reported after administration of COX-2 inhibitors. These agents provide a potentially safe alternative for treatment of inflammatory conditions in patients with AERD.[39,40]

Acetaminophen is a poor COX inhibitor. Most patients with AERD can tolerate up to 500 mg of acetaminophen safely, but 28 to 34% experience mild respiratory reactions when administered 1000 to 1500 mg. Reactions to acetaminophen tend to be milder than those to NSAIDs.[39]

Exercise-induced asthma (EIA) has been recognized since the first Olympic Games. It occurs in 5 to 20% of the general population, 30 to 70% of elite winter and summer endurance athletes, and up to 90% of patients with persistent asthma.[41] Atopy is strongly associated with EIA, and up to 40% of patients with allergic rhinitis have EIA. EIA may be another reflection of chronic airway inflammation. Clinically, EIA is usually preceded by 3 to 8 minutes of exercise. Peak symptoms usually occur 8 to 15 minutes after exercise is complete and then begin to remit spontaneously; recovery occurs within 60 minutes.

The cause of EIA remains unclear. In the "osmotic" hypothesis, airway cooling leads to mucosal drying and increased surface osmolality that causes mast cell degranulation and release of inflammatory mediators. The "thermal" hypothesis suggests that airway cooling during exercise followed by rapid rewarming after exercise causes airway vascular congestion and increased permeability, resulting in airway edema and obstruction. Another exercise-specific factor is autonomic deregulation associated with prolonged high-intensity physical training. The predominantly parasympathetic drive of athletes (evidenced by low heart rates) may also increase bronchomotor tone and increase the risk of EIA.[41]

Prophylaxis for EIA with warm-up and a short-acting inhaled beta-agonist is the therapy of choice. Pretreatment with cromolyn, LT antagonists (montelukast), and inhaled parasympatholytics is also effective.[42,43] Breathing through the nose may allow warming and humidification of cool dry air during exercise. Long-acting beta-agonists are usually effective, but tachyphylaxis and loss of efficacy may occur if these agents are used regularly.[44]

Menstruation-associated asthma affects up to 40% of asthmatic women yet receives little emphasis in asthma treatment guidelines.[1] The ratio of female-to-male asthma prevalence increases dramatically after puberty, and health care for asthma increases in the perimenstrual phase. Perimenstrual reductions in peak expiratory flow rates (PEFRs) of 35 to 80% are reported. Fluctuations in estrogen and progesterone levels are postulated as causal factors.[45,46] Estradiol inhibits eosinophil degranulation and suppresses LT activity; estrogen withdrawal in the luteal phase may enhance these actions. Progesterone may also have bronchodilator and anti-inflammatory activity, and the rapid decline in progesterone levels before menstruation may contribute to increased bronchospasm. Beneficial therapies for perimenstrual asthma include LT antagonists, long-acting beta-agonists, and oral contraceptives.[46,47]

Psychological factors may precipitate bronchospasm. Panic disorder, generalized anxiety disorder, and mood disorders are more common in asthmatics than the general population. An association between asthma, anxiety, and depression is noted. The mechanisms of bronchospasm associated with chronic stress may be related to the cholinergic nervous system or the hypothalamus-pituitary-adrenal axis, resulting in decreased cortisol secretion.[48,49] Compliance may be adversely affected by psychological factors. Relaxation as a therapy for asthma has inconsistent effects; hypnosis may be beneficial.[50]

Genetics and Asthma

It is likely that asthma is not a single disease but a syndrome with various phenotypes. The natural history of asthma is highly variable. Most asthma begins in childhood and resolves with age. Remissions of variable duration may occur, whereas others experience progressive severe disease. Many aspects of asthma (e.g., atopy susceptibility, IgE levels, degree of bronchial hyperreactivity, asthma severity) have identifiable genetic associations. Family history of both atopy and asthma are associated with lower rates of remission. Environmental influences (e.g., allergens, pollutants, tobacco, and occupational exposures) are associated with asthma, and the interaction of genetic variability and environmental factors may allow prediction of future disease risk, expression, and severity.[51,52]

Pathology

The pathology of the asthmatic airway reflects the inflammatory process described earlier. Mucous gland hyperplasia and viscous mucous plugs in the smaller airways are present. Airway secretions reveal increased numbers of inflammatory cells. Airway epithelial damage and remodeling are evident. In contrast to patients with mild to moderate asthma, patients with acute severe asthma have extensive mucous hyperplasia, subepithelial thickening, and infiltration of inflammatory cells (particularly eosinophils).[53]

Necropsies of patients with status asthmaticus reveal grossly inflated lungs that may fail to collapse on opening of the pleural cavities. Histologic examination reveals luminal plugs consisting of inflammatory cells, desquamated epithelial cells, and mucus. Marked thickening of the airway basement membrane, submucosal inflammatory cells, increased deposition of connective tissue, mucous gland hyperplasia, and hypertrophy of airway smooth muscle are also observed. Reports of slow-onset asthma fatalities

www.ketabpezeshki.com 66485457-66963820

reveal greater bronchial eosinophilia and basement membrane thickening when compared with rapid-onset fatal asthma.[54,55] Reports of rapid-onset fatal asthma describe less mucus in the airway lumens, suggesting that terminal events may be dominated by bronchoconstriction without excessive luminal plugging; however, an alternative view is that "dry airways" are more reflective of postmortem tissue processing.[55]

CLINICAL FEATURES

National and International Guidelines for the Diagnosis and Management of Asthma

In response to the increasing prevalence of asthma, many countries publish guidelines. Some of these, including NAEPP (National Institutes of Health [NIH]) Expert Panel Report 3 (EPR-3), devote specific portions to the management of acute exacerbations of asthma.[1] A task force of physicians representing the American Academy of Asthma, Allergy and Immunology, the American Academy of Emergency Medicine, and the American Thoracic Society (ATS) have summarized the aspects of the EPR-3 that are relevant for the ED and have developed evidence-based recommendations for acute care gaps in the NIH national guidelines. These include (1) use of noninvasive ventilation, (2) use of intubation and mechanical ventilation, (3) appropriate discharge medications, and (4) techniques for ensuring proper follow-up after an ED visit. These additional acute care recommendations were simultaneously published in 2009 in supplemental issues of *Journal of Allergy and Clinical Immunology* (volume 124, issue 2), *Journal of Emergency Medicine* (volume 37, issue 2), and *Proceedings of the American Thoracic Society* (volume 6, issue 4). The EPR-3 and task force recommendations are graded from levels A through D based on the strength of the scientific evidence.

ED concordance with the EPR-3 treatment recommendations is reported as moderate, with significant regional variations in quality of care.[56] In addition, ED overcrowding is associated with longer lengths of stay for acute asthma exacerbations.[57]

Symptoms

Most patients with acute asthma have a constellation of symptoms, including cough, dyspnea, and wheezing. Cough often begins early in the attack, may be the sole manifestation of the disease in cough-variant asthma and elder patients, can be associated with sputum production, and is probably the result of subepithelial vagal stimulation. Nocturnal worsening is common, with most patients reporting cough or wheeze at least once per week. Nighttime mortality is higher than in the general population.

Although increased airway resistance, diminished flow rates, and increased bronchial hyperactivity are contributing factors, asthmatic patients who come to the ED with nocturnal asthma attacks have disease severity similar to that of other asthmatics. Up to 40% of asthmatic women experience premenstrual worsening of symptoms, which peak 2 to 3 days before menses and are associated with more severe disease; ED visits increase during the preovulatory and perimenstrual intervals.[58]

There are interindividual differences in the dyspnea perceived by asthmatic subjects for the same level of airway narrowing. This difference results in poor correlation of symptoms with airway obstruction as determined by pulmonary function testing (PFT), both chronically and on presentation to the ED. Patients with a blunted perception of dyspnea (the "poor perceivers") have more ED visits, hospitalizations, and near-fatal and fatal asthma attacks.[59]

Wheezing reflects air movement velocity and turbulence, and its intensity varies according to the radius of the bronchi. With severe airway obstruction, it decreases or vanishes because air movement velocity is insufficient to produce sound.

Many asthmatics report symptoms of gastroesophageal reflux that may cause airway narrowing through a vagally mediated pathway or microaspiration. Proton pump inhibitor therapy decreases asthma symptoms in these patients. Approximately 80% of patients with asthma have symptoms of rhinitis. Approximately 5 to 15% of patients with perennial rhinitis have asthma, and control of sinonasal inflammation can lead to asthma improvement. Overweight (body mass index [BMI] of 25 kg/m^2 or higher) asthmatics have poorer asthma control, higher admission rates, and a greater risk of complications, possibly secondary to a difference in the perception of dyspnea or in response to asthma controller agents.[60,61] In addition, obese patients have different bronchial and systemic inflammatory characteristics and a specific pattern of pulmonary function changes, suggesting a different asthma phenotype.[62]

One third of patients who come to the ED with acute asthma are current cigarette smokers, and these patients have poorer asthma control and greater acute care needs than lifelong nonsmokers or former smokers.[63,64] African Americans with acute asthma have lower flow rates and more potentially life-threatening episodes than whites, but they respond equally well to albuterol.[65] There are no racial disparities in inpatient asthma care when comparing whites, blacks, and Hispanics.[66]

Lastly, as asthma can appear at any age, including the ninth decade, wheezing and dyspnea may be misascribed by both patients and physicians to heart failure, bronchitis, chronic obstructive pulmonary disease (COPD), occupational lung disease, or poor exercise capacity.

Historical Components

Slow-onset asthma with progressive deterioration over a period of at least 6 hours (usually days) occurs in over 80% of cases. This type has a female predominance, is triggered by upper respiratory tract infections, and has an airflow inflammation mechanism that results in a slower response to treatment. Sudden-onset asthma with rapid deterioration in less than 6 hours occurs in less than 20% of cases. This type has a male predominance, is triggered by respiratory allergens, exercise, and psychosocial stress, and has a bronchospastic cause resulting in more severe airway obstruction with a faster response to therapy.[67]

Risk factors for death from asthma are important to determine and are listed in Box 73-1.[1,68-71] In urban areas, heroin and cocaine abuse are commonly associated with life-threatening asthma requiring noninvasive positive-pressure ventilation (NIPPV) or intubation in the ED.[70,71]

The brief history pertinent to the current exacerbation should include onset and possible triggers, severity of symptoms especially as compared with previous exacerbations, and other comorbidities (especially those that may be worsened by systemic corticosteroids such as diabetes, peptic ulcer, hypertension, and psychosis). In addition, all current asthma medications should be noted, including times and amounts recently used, and any potential asthma exacerbators such as aspirin or NSAIDs, beta-blockers (including topical agents used for glaucoma), and angiotensin-converting enzyme inhibitors. Cardioselective and nonselective beta-blocker use increases hospitalizations and ED visits.[72]

Physical Assessment

Patients with mild acute asthma usually speak in sentences, those moderate asthma in phrases, and those with severe asthma in words. Although alterations in mentation indicate severe asthma, restlessness and agitation do not reliably indicate hypoxia or hypercapnia. Patients who sit upright have severe airway

www.ketabpezeshki.com 66485457-66963820

Box 73-1 Risk Factors for Death from Asthma

Asthma History
Previous severe exacerbation (intubation or ICU admission for asthma)
Two or more hospitalizations for asthma in the past year
Three or more ED visits for asthma in the past year
Hospitalization or an ED visit for asthma in the past month
Use of more than two MDI short-acting beta$_2$-agonist canisters per month
Current use of or recent withdrawal from systemic corticosteroids
Difficulty perceiving asthma symptoms or severity of exacerbations

Social History
Low socioeconomic status or inner-city residence
Serious psychosocial problems
Illicit drug use, especially inhaled cocaine and heroin

Comorbidities
Cardiovascular disease
Other chronic lung disease
Chronic psychiatric disease

ED, emergency department; *ICU,* intensive care unit; *MDI,* metered-dose inhaler.

obstruction; cyanosis is uncommon because of the left shift of the oxyhemoglobin dissociation curve produced by respiratory alkalosis. Diaphoresis can be seen secondary to the work of breathing, but if profound may be preterminal.

Tachypnea and tachycardia are associated with severe obstruction, but a lower rate does not rule out severe asthma. The respiratory rate correlates poorly with PFT and indicates severe obstruction if it is higher than 40 breaths/min.

A pulsus paradoxus or inspiratory fall in systolic blood pressure greater than 10 mm Hg usually signifies severe disease, but its absence does not exclude severe disease. Its use predates bedside pulmonary function tests, which are more accurate and reliable. When pulsus paradoxus is present, it may disappear with minimal improvement in airflow through larger airways. Similarly, use of accessory muscles of respiration (sternocleidomastoid and scalenus muscles) is not prognostic.

Wheezing does not designate the presence, severity, or duration of asthma. It correlates poorly with the degree of functional derangement and may be absent when maximal effort produces minimal airflow. Physical examination may help to identify such complications of asthma as pneumonia, pneumothorax, or pneumomediastinum.

DIAGNOSTIC STRATEGIES

Pulmonary Function Studies

The severity of airflow obstruction cannot be accurately assessed from symptoms and physical examination alone.[73] Physicians initially tend to underestimate the degree of airway obstruction in acute asthma. Therefore routine PFT should be part of ED assessment and monitoring. The forced expiratory volume in 1 second from maximal inspiration (FEV_1) or the PEFR in liters per second, starting with fully inflated lungs and sustained for at least 10 msec, may be used. Both measurements require the patient's cooperation for maximal effort and are effort dependent. Whenever possible, the best of three consecutive values should be recorded. Any patient not able to perform a pulmonary function study should be considered to have severe airway obstruction.

Although FEV_1 can be adequately measured in most acutely ill asthmatics to meet modified ATS performance goals,[73] most assessments in the ED use single-patient-use portable peak flow meters because PEFR is easier to measure. The identical device should be used to assess then reassess an individual patient, and different portable meters should not be used interchangeably. Lastly, the FEV_1 and PEFR measurements are not interchangeable in assessing acute airway obstruction, which is not addressed in all management guidelines. Although absolute PFT measurements can be used, percentage of predicted performance (% predicted) values are preferable to account for age (now to age 85), sex, and height.

Arterial Blood Gas Analysis

Equilibration of oxyhemoglobin saturation occurs within 3 to 4 minutes of initiation or alteration of supplemental oxygen during an acute asthma attack. Stimulated hyperventilation leads to a modest fall in the partial pressure of carbon dioxide in arterial blood ($Paco_2$). As airway obstruction increases, the $Paco_2$ normalizes (PFT values 15-25% predicted) and then increases (PFT values <15% predicted) with worsening hypoxemia. Because neither pretreatment nor post-treatment arterial blood gases (ABGs) correlate with PFTs or predict clinical outcome, ABG determination is rarely clinically useful in acute asthma exacerbations unless oxygen saturation cannot be obtained reliably via pulse oximetry.

ABG sampling should be limited to a subset of patients with predicted PFT values of less than 30%, whose clinical course is perplexing, and for whom capnography is not available. Occasionally, despite improvement in PFT values with bronchodilator therapy, some patients have a transient fall in the partial pressure of oxygen in arterial blood (Pao_2) secondary to pulmonary vasodilatation and worsening ventilation-perfusion mismatch.[74] The assessment of ventilation may be simplified because there is a high concordance between end-tidal partial pressure of CO_2 (Pco_2) measured by capnography and the $Paco_2$ obtained with ABG measurements.[75] Also, capnographic waveform analysis can indicate improvements in airway diameter in acute asthma and has the advantages of being effort independent and providing continuous monitoring.[76]

Other Blood Testing

Laboratory studies rarely are helpful in evaluating the patient with an acute asthma attack. Leukocytosis is common with acute asthma exacerbation but is not of discriminatory value in detecting acute superimposed pulmonary infection. Corticosteroids and catecholamines demarginate polymorphonuclear leukocytes after 1 to 2 hours, and patients on chronic steroid therapy may have normal or significantly elevated white blood cell (WBC) counts.

Serum electrolytes are not primarily altered unless the patient is taking corticosteroids or diuretics or has cardiovascular disease and is receiving aggressive beta$_2$-agonist therapy. Frequent albuterol treatments can cause transient hypokalemia, hypomagnesemia, and hypophosphatemia, but this is rarely of clinical significance. The rare asthmatics undergoing chronic theophylline therapy should be assessed for possible toxicity. In the older asthmatic with cardiovascular comorbidities, measurement of the B-type natriuretic peptide (BNP) level may reveal unrecognized congestive heart failure.

Radiology Studies

A chest radiograph is of little value in most acute asthma exacerbations and should be restricted to patients with a complicating cardiopulmonary process, such as pneumonia, pneumothorax, pneumomediastinum, or congestive heart failure. Also, patients who do not respond to optimal therapy and require hospital

www.ketabpezeshki.com 66485457-66963820

admission have a higher likelihood of radiographically identifiable, unsuspected, clinically significant pulmonary complications of asthma (15% of cases).

Electrocardiogram and Cardiac Monitoring

The electrocardiogram (ECG) is selectively helpful in assessing patients with chest pain or a history of significant cardiovascular disease, in whom the asthma attack may be a physiologic stress test. In patients with severe asthma, the ECG may show a right ventricular strain pattern that reverses with improvement in airflow. Older patients, especially those with coexistent heart disease or with severe exacerbation, could require continuous cardiac monitoring to detect dysrhythmias. All patients with severe hypoxemia, and those for whom intubation is contemplated, should receive continuous cardiac monitoring.

Future Monitoring Strategies

Noninvasive monitoring of bronchial inflammation may customize the ED assessment of acute asthma. This may include measurement of biologic biomarkers, such as cytokine profiles in the blood, evaluation of LTE_4 in the urine, and the monitoring of exhaled pentane, hydrogen peroxide, NO, or carbon monoxide levels. Of these measurements, exhaled NO, a marker of airway inflammation, shows the most promise, as studies show that FENO can be measured in the ED with good reproducibility, and levels measured after 6 hours of care are associated with better asthma control after discharge.[77,78]

Assessment Summary

The severity of airflow obstruction cannot be accurately judged by patients' symptoms, physical examination findings, and laboratory test results. Serial measurements of airflow obstruction (FEV_1 or PEFR) are key components of disease assessment and response to therapy (Table 73-1).

Table 73-1 Objective Findings in Asthma Assessment

FACTOR	SEVERE ASTHMA (FEV_1 <1.0 L)
Pulse rate (beats/min)	≥120 but may be less with equally severe asthma
Respiratory rate (breaths/min)	≥40 but most are >20, therefore nondiscriminating
Pulsus paradoxus (mm Hg)	≥10 but may be absent with equally severe asthma in 50% of cases
Pulse rate ≥120, respiratory rate ≥20, pulsus paradoxus ≥10	If all three abnormal, 90% with severe asthma, but only 40% with FEV_1 <1.0 L have all three abnormal
Use of accessory muscles of respiration	If present, may indicate severe asthma; if absent, may have equally severe asthma in 50% of cases
ABG analysis (mm Hg)	Pao_2 ≤60 or $Paco_2$ ≥42 indicates severe asthma; all other values difficult to interpret unless PEFR or FEV_1 known
Pulmonary function studies	PEFR and FEV_1 measure directly the degree of airflow obstruction; most useful in assessing severity and guiding treatment decisions

ABG, arterial blood gas; *FEV_1*, forced expiratory volume in 1 second; *$Paco_2$*, partial pressure of carbon dioxide in arterial blood; *Pao_2*, partial pressure of oxygen in arterial blood; *PEFR*, peak expiratory flow rate.

DIFFERENTIAL CONSIDERATIONS

See Box 73-2. Of note, vocal cord dysfunction may mimic or coexist with asthma and is gaining recognition as a common cause of respiratory symptoms often misdiagnosed as steroid-refractory asthma.[79]

MANAGEMENT OF ACUTE EXACERBATIONS

Home and First-Responder Strategies

Subacute lack of asthma control (more than four outpatient visits or more than five short-acting $beta_2$-agonist prescriptions per year) is associated with increased risk of acute asthma exacerbation.[80] Thus patients should be provided a plan to monitor their symptoms, signs, and PEFR to recognize early deterioration in the event of an exacerbation. Early therapy can prevent progression to severe attacks. Home management includes increased use of inhaled $beta_2$-agonists, early administration of systemic corticosteroids (not simply doubling the dose of current ICSs), and specific instructions regarding emergency care.[1] Emergency medical service providers should provide albuterol inhalation therapy by protocol, and basic emergency medical technicians can be authorized to administer the patient's own inhaler.[81,82] Further studies are needed to determine whether paramedics should be trained to administer continuous positive airway pressure ventilation in asthmatics with severe respiratory failure to decrease tracheal intubation and mortality rates.[83]

Management of Acute Asthma in the Emergency Department

The rapidity of reversal of the acute airflow obstruction is directly predictive of the outcome. Effective bronchodilation often results in a decreased need for hospitalization with significant cost

Box 73-2 The Differential Diagnosis of Asthma

- Cardiac conditions
  - Valvular heart disease
  - Congestive heart failure
- COPD exacerbation
  - Pulmonary infection
  - Pneumonia
  - Allergic bronchopulmonary aspergillosis
  - Löffler's syndrome
  - Chronic eosinophilic pneumonia
- Upper airway obstruction
  - Laryngeal edema
  - Laryngeal neoplasm
  - Foreign body
  - Vocal cord dysfunction
- Endobronchial disease
  - Neoplasm
  - Foreign body
  - Bronchial stenosis
- Pulmonary embolus
- Carcinoid tumor
- Allergic or anaphylactic reaction
- Miscellaneous conditions
  - GERD
  - Noncardiogenic pulmonary edema
  - Addison's disease
  - Invasive worm infection

COPD, chronic obstructive pulmonary disease; *GERD*, gastroesophageal reflux disease.

www.ketabpezeshki.com 66485457-66963820

Table 73-2 Initial Severity Assessments and Therapies in the Emergency Department

	MILD TO MODERATE	SEVERE
FEV_1 or PEFR (% predicted/personal best)	≥40%	Unable or <40%
Oxygen therapy	Maintain Sao_2 ≥90%	Maintain Sao_2 ≥90%
Nebulized albuterol solution		
Levalbuterol (optimal)	1.25 mg q20min for up to three doses	1.25 mg q20min for three doses Continuous for 1 hr if severe
Racemic albuterol	2.5 mg q20min for up to three doses	5.0 mg q20min for three doses Continuous for 1 hr if severe
Albuterol MDI with VHC		
Levalbuterol (45 µg/puff) (optimal)	6-12 puffs q20min for up to three doses WS	Same for three doses (if able to do), WS
Racemic albuterol (90 µg/puff)	6-12 puffs q20min for up to three doses WS	Same for three doses (if able to do), WS
Ipratropium therapy		
Nebulized solution	If previous response (same dose as for severe)	0.5 mg q20min for three doses (may mix with albuterol solution)
MDI (18 µg/puff) with VHC	If previous response (same dose as for severe)	8 puffs q20min for three doses
Systemic corticosteroids		
Oral (preferred)	40-80 mg of prednisone or prednisolone per day if no immediate response to albuterol	40-80 mg of prednisone or prednisolone per day
Intravenous (unable to take orally or absorb)	40-80 mg of methylprednisolone per day	40-80 mg of methylprednisolone per day
Intravenous magnesium sulfate	Not indicated	2-3 g over 20 min (or at rates of up to 1 g/min) if FEV_1 ≤ 25% predicted

FEV_1, forced expiratory volume in 1 second; *MDI,* metered-dose inhaler; *PEFR,* peak expiratory flow rate; *Sao_2*, oxygen saturation in arterial blood: *VHC,* valved holding chamber; *WS,* with supervision.

savings. As outlined in Table 73-2, the severity of attack as measured by PFTs determines the aggressiveness of the therapy.

Oxygen Administration

All patients should receive supplemental oxygen titrated to maintain arterial oxygen saturation above 90% (above 95% in pregnant women and those with coexistent heart disease) rather than at predetermined concentrations or flow rates. Continuous oxygen saturation monitoring is essential during the acute phase. Humidification of the inspired air-oxygen mixture is not essential, although studies suggest that active airway rehydration should be revisited.[84]

Adrenergic Medication

Controversies in Use. Epidemiologic studies report an association between death and near death from asthma and the use of inhaled beta$_2$-agonists. The use of more than one canister per month doubles the risk for each additional monthly canister used.[85] This relationship does not imply causality but may be a marker for severe disease, particularly if anti-inflammatory treatment is underused. Guidelines for chronic use of inhaled beta$_2$-agonists, however, recommend limited daily use in a rescue-only mode.[1]

One form of albuterol is a racemic mixture of equal amounts of *R* and *S* isomers. Data from animal and human studies suggest that the *S* isomer, which contributes no bronchodilator activity, is proinflammatory, is spasmogenic, and induces bronchial hyperreactivity. This possibly explains the adverse effects of increased morbidity and mortality rates associated with regular or excessive use of this drug.[86]

Short-Acting Inhaled Beta$_2$-Agonist Choice and Administration Schedule

Racemic albuterol has remained the main beta$_2$-agonist used in the ED for more than 30 years. It is more beta$_2$-selective, is longer acting, and has fewer side effects than other previously available drugs such as metaproterenol or isoetharine.

Table 73-3 Response after 1 Hour of Initial Treatment

	MODERATE EXACERBATION	SEVERE EXACERBATION
FEV_1 or PEFR (% predicted)	40-69%	<40%
Oxygen therapy	Unnecessary	Maintain Sao_2 ≥90%
Albuterol therapy		
Levalbuterol (optimal)	Reassess as may need less than with racemic dosing	Reassess as may need less than with racemic dosing
Racemic albuterol	q1-3h, admit decision in <4 hr	q1h or continuous
Ipratropium therapy	Unnecessary	q1h or continuous
Corticosteroids	Every 6-8 hr	Every 6-8 hr

FEV_1, forced expiratory volume in 1 second; *PEFR,* peak expiratory flow rate; *Sao_2*, oxygen saturation in arterial blood.

Levalbuterol, the *R* isomer of racemic albuterol, is available as a preservative-free nebulizer solution (unit doses of 0.31, 0.63, or 1.25 mg) and in a metered-dose inhaler (MDI) for prevention and treatment of bronchospasm. In chronic asthma, levalbuterol provides a better therapeutic index than the standard dose of racemic albuterol, further fueling the debate on the potential adverse effects of the *S* isomer of beta-agonists.[87] Clinical studies in acute disease report that levalbuterol on a milligram-for-milligram basis is a better bronchodilator than similar amounts of *R*-albuterol delivered with the *S* isomer in the racemic mixture.[88-90] The amount and frequency of delivery of levalbuterol and racemic albuterol depend on the initial severity and response to therapy, as shown in Tables 73-2 and 73-3. Patients with more severe obstruction with a poor response to initial therapy should receive

www.ketabpezeshki.com 66485457-66963820

higher dosage schedules and possible continuous administration.[91] When patients are stable but require admission to the hospital, it may be possible to administer nebulized levalbuterol at 1.25 mg every 8 hours as opposed to racemic albuterol at 2.5 mg every 4 to 6 hours.[92]

The PFT response to the initial bronchodilator therapy over the initial 15 to 60 minutes is a better predictor of the need for hospitalization than is the severity of an exacerbation. A PEFR variation over baseline of more than 50 L/min and a rate that exceeds 40% of predicted measured at 15 to 60 minutes suggest a good outcome.[93] Pharmacogenetic studies suggest that variations in the beta$_2$-adrenergic receptor gene may have important effects on modulating bronchodilator response.[94]

Nebulizer versus Metered-Dose Inhaler and Valved Holding Chamber. An MDI plus a valved holding chamber ("spacer") provides similar bronchodilation and side effects, even in severe asthma, when compared with wet nebulization (see Table 73-2).[95] This therapy requires more supervision because some patients have difficulty firing the canister before inhalation, breathing slowly, and holding their breath for 5 seconds, which may explain the infrequent use of canisters in the ED.[96,97] The MDI with a spacer, however, uses less treatment time and may be more economical.[98,99]

Intravenous Use of Adrenergic Agonists. Most international asthma guidelines, with the exception of those in the United States, recommend the use of intravenous beta-agonists for severe nonresponsive acute asthma. Intravenous albuterol (not available in the United States) is given as a loading dose of 4 µg/kg for 2 to 5 minutes followed by an infusion of 0.1 to 0.2 µg/kg/min, with close monitoring.[100]

Evidence to support the use of intravenous beta-agonists in ED patients with severe acute asthma is lacking; the potential risks are warranted only when inhaled therapy is not feasible.[1,90] Epinephrine is used cautiously in patients older than 40 years or those with suspected cardiovascular disease, because it might provoke myocardial ischemia. Intravenous epinephrine titrated to effect (average 1.5 µg/min with a range of 0.5-13.3 µg/min) is associated with a low rate of major (3.6% of cases) and moderate or minor adverse events.[101]

Subcutaneous Adrenergic Agents. Subcutaneous use of adrenergic agents does not have an advantage over aerosol delivery. It may be considered in patients who cannot adequately inhale albuterol or who experience severe bronchospasm.

Epinephrine, a mainstay for almost 100 years, has both alpha and beta effects. It can produce tachycardia, hypertension, dysrhythmias, and vasoconstriction, especially in older asthmatics with heart disease. Given the potential for increased side effects, it can be given subcutaneously (1:1000 solution 0.2 to 0.5 mL every 20 to 30 minutes as needed for three doses).

Terbutaline is a longer-acting beta$_2$-agonist with bronchodilating properties equivalent to those of epinephrine in acute asthma. It can cause skeletal muscle tremor and tachycardia. A 0.25-mg dose can be given subcutaneously every 20 minutes for three doses.

Long-Acting Beta$_2$-Agonists (LABAs) and Acute Disease. Salmeterol is a long-acting (12 hours) beta$_2$-agonist that is an effective additional medication for management of symptoms that are not adequately controlled by regular and adequate doses of effective controller medications such as inhaled steroids. It has an onset of action of 20 minutes and thus is not a rescue medication. Regular use of this drug without concomitant use of inhaled steroids results in greater hospitalizations and asthma-related deaths, resulting in a black box warning on the package insert.[102]

Racemic formoterol dry powder and both racemic and single-isomer formoterol solution for nebulization are also long-acting beta-agonists that have an onset of action within minutes (similar to albuterol) and maximal effect within 2 hours. These drugs could evolve as acute rescue medications with extended length of action (12 hours) and similar safety profiles.[103,104] The controversies regarding the safety of regular use of short-acting beta-agonists extend to the long-acting classes. The U.S. Food and Drug Administration (FDA) has changed the labeling for LABAs to contraindicate their chronic use in patients of all ages without concomitant use of an asthma controller medication such as an ICS.[105]

Corticosteroids

Corticosteroids inhibit recruitment of inflammatory cells and release of proinflammatory mediators and cytokines. Corticosteroids activate cytoplasmic glucocorticoid receptors to regulate the transcription of certain target genes, resulting in the synthesis of new proteins.

Despite decades of corticosteroid use, controversy persists regarding the types and quantities required to induce a rapid remission, the time needed for drug action, the route of administration, the existence of dose-response effects, and the determination of which patient populations respond to this therapy.[106]

Systemic Corticosteroids in the Emergency Department. Corticosteroids are indicated for all patients with moderate to severe attacks or those experiencing an incomplete response to initial beta-agonist therapy. In addition, early systemic corticosteroids should be considered for patients who are taking oral corticosteroids or ICSs, have relapsed after a recent exacerbation, or have prolonged symptoms. Steroid effects begin within hours (not minutes) in acute asthma and peak at about 24 hours. Use of systemic steroids speeds the resolution of airflow obstruction, reduces the rate of relapse, and may decrease admissions in severe but not in mild to moderate attacks.[1,106] The PEFR may improve within 2 hours of steroid therapy in those not responding to initial albuterol inhalation.[107]

Many studies clearly demonstrate that oral corticosteroids are as beneficial as intravenous corticosteroids in the ED. The initial oral dose is usually 60 mg of prednisone. If intravenous methylprednisolone is used, the dose is 40 to 80 mg/day in one or two divided doses until the switch to oral therapy or until PEFR reaches 70% of predicted or personal best.

Continuing therapy with oral prednisone or prednisolone is given in an adult dose of 40 to 80 mg/day, usually as a single dose. No study demonstrates the superiority of intravenous corticosteroids over oral preparations. Oral steroid therapy is preferred unless the patient is very ill, is unable to swallow or is vomiting, or is thought to have impaired gastrointestinal transit or absorption.

Side effects of short-term (hours or days) steroid use include reversible increases in glucose (important in diabetics) and decreases in potassium, fluid retention with weight gain, mood alterations including rare psychosis, hypertension, peptic ulcers, aseptic necrosis of the femur, and rare allergic reactions.

Inhaled Corticosteroids in the Emergency Department. Use of ICSs, either alone or in addition to systemic steroids, to treat acute asthma has the potential benefits of reducing systemic side effects, directly delivering medication to the airway, and reducing airway reactivity and edema more effectively. Patients treated with ICSs are less likely to be admitted whether they received systemic steroids or not, and no increased cough or bronchospasm is seen with the use of ICSs.[108,109] Patients treated with these agents have early improvement in outcomes (<3 hours) because of the topical effects. High doses of ICSs given over hours may be necessary.[110] Evidence suggests that treating both systemically and via airway with corticosteroids in acute disease is more effective than either treatment method alone.[111]

Corticosteroids and Discharged Patients. Discharged patients who receive systemic corticosteroids in the ED should continue oral outpatient "burst" therapy to control disease and prevent

www.ketabpezeshki.com 66485457-66963820

relapse. Any need for additional steroids should be determined at follow-up. An acceptable regimen is 40 to 60 mg of prednisone (or equivalent) in single daily dose for a total of 5 to 10 days. Dose tapering to prevent asthma rebound or out of concern for adrenal suppression is unnecessary unless the patient was already receiving systemic steroids or unless a prolonged course of therapy (more than 2 weeks) is deemed necessary. An alternative approach, if compliance or inability to obtain oral corticosteroids is an issue, is to give an equally efficacious single depot dose of dexamethasone 10 mg, triamcinolone diacetate 40 mg, or methylprednisolone 160 mg before ED discharge.[112,113]

Patients with acute exacerbations of asthma may be taking insufficient amounts of chronic controller medications based on their symptoms and excessive use of beta$_2$-agonists.[1] If the patient is not taking oral corticosteroids or ICSs, the addition of inhaled high-dose budesonide (400 μg, two puffs twice per day) to the patient's regular asthma medications on discharge improves symptoms and decreases relapse by approximately 50% in the ensuing 3 weeks.[114] Thus patients with a history compatible with persistent asthma but not taking any ICS should be given a prescription (1- to 2-month supply). Suggested regimens include budesonide dry powder inhaler (DPI) 1200 μg, flunisolide MDI 2000 μg, fluticasone DPI 500 μg, mometasone DPI 400 μg, or triamcinolone MDI 1500 μg in daily divided doses (twice per day) in addition to prednisone.[115] Patients already on ICS therapy should continue. Patients should use a spacer device if using an MDI and rinse the mouth after steroid inhalation to decrease the side effects of dysphonia and oral or esophageal candidiasis.

Corticosteroid-Resistant Asthma. Chronic asthma is considered a steroid-responsive disease. A small proportion of asthmatics do not respond to high doses of oral and inhaled glucocorticoids, which complicates management. The mechanism of this steroid resistance may be related to abnormalities in the glucocorticoid receptor number or binding properties or may suggest an alternative diagnosis such as vocal cord dysfunction. These patients are usually receiving alternative therapies, such as cyclosporine, methotrexate, troleandomycin, hydroxychloroquine, azathioprine, gold, intravenous immune globulin, or (in the patient with severe allergic asthma) omalizumab.

Anticholinergic Agents

The atropine-containing botanicals *Datura stramonium* (stinkweed or thorn apple) and *Atropa belladonna* (deadly nightshade) were smoked centuries ago in India for treatment of asthma. In the 19th century, smoking leaves of the *Datura* species was common in England, and by the middle of the last century Salter's treatise on asthma listed *D. stramonium* as one of asthma's truly effective remedies. Atropine-containing cigarettes or powders smoked in pipes were available into the 20th century.

The anticholinergic drugs available for inhalation therapy include atropine sulfate, atropine methylnitrate, glycopyrrolate, and ipratropium bromide. They are all bronchodilators that override the smooth muscle constrictor and secretory consequences of the parasympathetic nervous system, blocking reflex bronchoconstriction and reversing acute airway obstruction. Ipratropium bromide (Atrovent), a quaternary derivative of atropine, is preferable to atropine or glycopyrrolate.

The maximum effect with inhaled ipratropium is in 30 to 120 minutes, with the effect lasting up to 6 hours. Its bronchodilating potency is lower and onset of action slower than those of the beta$_2$-agonists; hence it should not be used alone for therapy of acute attacks. Trials assessing the role of this agent in combination therapy with beta$_2$-agonists for acute disease have found that ipratropium provides a modest improvement in PFT results and a reduction in hospitalization.[116,117] These benefits are higher in patients with more severe disease. Treatment recommendations (see Table 73-2) include adding ipratropium (0.5 mg) with the first three albuterol treatments in severe acute asthma (PEFR/FEV$_1$ <40% predicted). The equivalent MDI dose is approximately eight puffs (18 μg/puff) every 20 minutes three times. Data suggest that less ipratropium might be needed in patients treated with levalbuterol nebulizations. Ipratropium can be given to anyone, both acutely and at discharge, who has improved with its past use. Ipratropium may be more effective in patients older than 40 years, should be used in reversing bronchospasm secondary to beta-blocking agents, and might help those in whom psychological factors contribute to their disease.

Inhaled tiotropium bromide is a long-acting (>24 hours) anticholinergic agent (FDA approved for treatment of COPD) that improves symptoms and lung function when added to an inhaled glucocorticoid with inadequately controlled asthma.[118] The role of tiotropium in acute disease therapy is undetermined.

Magnesium Sulfate

Magnesium relaxes bronchial smooth muscle and dilates asthmatic airways in vitro. Mechanisms include calcium channel–blocking properties, inhibition of cholinergic neuromuscular transmission, stabilization of mast cells and T lymphocytes, and stimulation of NO and prostacyclin. Intracellular magnesium levels are lower in acute asthma,[119] and the level correlates with airway reactivity in chronic disease.

There is evidence that intravenous magnesium therapy for severe attacks might obviate the need for intubation. Magnesium adjunctive administration in severe asthma attacks (FEV$_1$ <25% predicted) improves airflow obstruction and decreases the need for hospital admission.[120-122] The optimal dose and rates of infusion are unclear, but it is reasonable to administer 2 to 3 g of intravenous magnesium sulfate over 20 minutes or at rates of up to 1 g/min to patients with severe refractory asthma while continuing aggressive inhalation therapy. Intravenous magnesium therapy is widely used in patients with acute severe asthma and life-threatening exacerbations.[123]

Side effects of magnesium infusion are dose related and include warmth, flushing, sweating, nausea and emesis, muscle weakness and loss of deep tendon reflexes, hypotension, and respiratory depression. Inhalation magnesium in acute asthma may also have a role as an isotonic vehicle for nebulized bronchodilator therapy in improving the PFT response,[124,125] or it may be nebulized alone for bronchodilation.[126] Magnesium nebulizations remain investigational.

Methylxanthines

The naturally occurring methylxanthines caffeine and theobromine (in coffee, tea, and cacao) have been used by asthmatics for hundreds of years to treat wheezing. Theophylline was the main oral methylxanthine used to treat asthma, and a small subset of ambulatory asthma patients may benefit from the chronic administration of theophylline. The NAEPP EPR-3 does not recommend the use of methylxanthines for treatment of acute disease in the ED or in the hospital because of their lack of demonstrated efficacy and increases in adverse events.[1]

Leukotriene Modifiers

The cysteinyl LTs (LTC$_4$, LTD$_4$, and LTE$_4$) are highly potent mediators of inflammation that play a large role in the pathogenesis of asthma. Zafirlukast (20 mg twice a day) and montelukast (10 mg daily) are rapid-acting, safe, oral asthma controller drugs that are potent and highly selective antagonists of type 1 cysteinyl LT receptors.

www.ketabpezeshki.com 66485457-66963820

Asthmatics generally produce elevated levels of LTs, and in acute attacks the levels in the urine can be markedly increased. The addition of either 7 or 14 mg of intravenous montelukast (not available in the United States) to standard therapy for acute asthma causes a 15% non–beta$_2$-mediated increase in FEV_1 over placebo.[127] The onset of action is as early as 10 minutes and persists throughout the 2 hours after admission.[128] Oral zafirlukast, when given as adjunctive therapy (20 or 160 mg) for acute asthma in the ED, improves PFT results and dyspnea but does not decrease admission rates.[129] Oral montelukast (10 mg) given during acute asthma in the ED results in significantly increased PEFR the morning after admission when compared with standard treatment.[130] The rapid onset and sustained non–beta-mediated bronchodilating effects of these medications may help manage acute disease.

Other and Future Therapies

In patients without dehydration or hypovolemia, vigorous administration of fluids does not clear airway secretions. Mucolytics may worsen cough or airflow obstruction, and chest physical therapy is not beneficial. Sedatives are contraindicated in acute disease because of their respiratory depression.

Bacterial, chlamydial, and mycoplasmal respiratory tract infections infrequently contribute to acute asthma. Antibiotics should generally be reserved for patients with fever, purulent sputum, pneumonia, or evidence of bacterial sinusitis, to prevent inappropriate ED prescription of antibiotics for acute asthma.[131]

Neurokinin antagonists, inhaled loop diuretics (furosemide in acute attacks), and lidocaine may inhibit neurogenic inflammation, and heparin may have a role in the inhibition of mast cell products. Infused BNP can cause significant bronchodilation.[132] Specific cytokine antagonists, agonists, inhibitors of T-cell function, selective inducible NO synthetase inhibitors, and possibly gene-directed therapies may become novel treatments. There are currently biologic therapies available for the management of chronic asthma. Omalizumab, a recombinant humanized monoclonal anti-IgE antibody, is indicated for the treatment of severe allergic asthma.[133] Lastly, the use of rescue therapy with an inhaled combination of a rapid-onset beta-agonist and a corticosteroid might provide both bronchodilation and self-titrated anti-inflammatory therapy.[134]

Pregnancy and Acute Asthma

Asthma complicates 3.7 to 8.4% of pregnancies, and hospitalizations for acute exacerbations are reported in 9 to 11% of pregnant women.[135] The effect of pregnancy on asthma is unpredictable. Asthma exacerbation rates and hospitalizations are directly proportional to the severity of asthma control (according to NAEPP guidelines),[1] and pregnant patients with severe asthma have an exacerbation rate of 51.9% and a hospitalization rate of 26.9%.[136] Knowledge of a pregnant patient's baseline asthma severity is thus important to predict the risk of severe exacerbation. Obesity and female fetal sex are also associated with an increased risk of exacerbation.[137] Maternal and neonatal outcome are excellent in patients with mild or moderate asthma; severe asthma during pregnancy is associated with gestational diabetes and delivery before 37 weeks.[135,138]

The hyperventilation of pregnancy is compensated for by a metabolic acidosis. Typical pregnant patients have ABGs with a pH of 7.40 to 7.45, Po_2 of 106 to 110, and Pco_2 of 28 to 32 mm Hg; therefore when ABG values in a pregnant patient are interpreted, a normal Pco_2 actually represents hypercarbia. Maternal hypoxemia quickly results in fetal hypoxemia. PEFR remains unchanged during pregnancy, and monitoring in the ED is strongly recommended. The smallest amount of medication needed to maintain the pregnant asthmatic in the mild severity range is recommended. ICSs are not associated with adverse perinatal outcomes and are recommended for all pregnant patients with asthma (budesonide is preferred). Inhaled beta-agonists, ipratropium, oral or intravenous corticosteroids, magnesium sulfate ($MgSO_4$), cromolyn, theophylline, and LT antagonists are safe during pregnancy.[139] Acute exacerbations should be treated in the ED as in any nonpregnant patient. Oxygen saturation should be maintained at 95% or above. Intensive care unit (ICU) admission and mechanical ventilation are recommended as in any other patient, with the caveat that a Pco_2 of 40 to 45 represents early respiratory failure in the pregnant patient. Refractory status asthmaticus may be improved by delivery. Fetal monitoring is recommended for third-trimester ED patients with moderate or severe asthma exacerbations. There are no contraindications to any asthma medication in the breast-feeding patient.

Severe, Near-Fatal, and Fatal Asthma

The ATS has developed a consensus definition for identifying severe and refractory asthma that is unresponsive to conventional therapies (Fig. 73-6).[140] This condition is termed *severe asthma;* patients with these symptoms represent only about 10% of all asthmatics yet account for 30% of asthma-related health care costs. For the definition to be met, medical conditions that mimic asthma must be excluded, exacerbating factors (e.g., allergens) identified and treated, and patients compliant.

Cellular features of severe asthma include persistent eosinophilic inflammation unresponsive to high-dose corticosteroids plus the presence of neutrophilic inflammation in the distal airways. TNF-α, an inflammatory cytokine produced by mast cells, is present in increased concentration in bronchoalveolar lavage fluid with severe asthma. The potential role of TNF-α antagonists such as etanercept and infliximab, and anti–TNF-α antibodies such as golimumab, is unclear.[141-143] Studies in which monoclonal antibodies have been used against IL-5, IL-4, and IL-13 show promise, but large definitive trials are lacking.[144,145]

Clinical features of severe asthma include a lesser prevalence of atopy, a history of aspirin sensitivity, and a higher incidence of sinusitis and use of nasal corticosteroids (suggesting involvement of the upper as well as the lower respiratory tract). Exacerbations are also associated with menses.[146] Other clinical features that

Major characteristics
- Treatment with continuous or near-continuous (≥50% of year) oral corticosteroids
- Requirement for treatment with high-dose intravenous corticosteroids

Minor characteristics
- Requirement for additional daily treatment with a controller medication (e.g., long-acting beta-agonist, theophylline, or leukotriene antagonist)
- Asthma symptoms requiring short-acting beta-agonist use on a daily or near-daily basis
- Persistent airway obstruction (FEV_1 < 80% predicted, diurnal peak expiratory flow variability > 20%)
- One or more urgent care visits for asthma per year
- Three or more oral steroid bursts per year
- Prompt deterioration with ≤25% reduction in oral or intravenous corticosteroid dose
- Near-fatal asthma event in the past

Figure 73-6. American Thoracic Society workshop consensus for definition of severe or refractory asthma (requires one or both major and two minor criteria and that other conditions have been excluded, exacerbating factors have been treated, and patient is generally compliant).

www.ketabpezeshki.com 66485457-66963820

distinguish severe asthma are being identified to focus therapy in this small but important group of asthmatics.[147]

Status asthmaticus refers to severe bronchospasm that does not respond to aggressive therapies within 30 to 60 minutes. *Near-fatal asthma* is identified by respiratory arrest or evidence of respiratory failure ($Paco_2$ above 50 mm Hg).

Two types of near-fatal asthma are recognized. Slow-onset near-fatal asthma typically reflects a gradual deterioration of asthma symptoms over several days, usually superimposed on chronic poorly controlled asthma. Slow-onset fatal asthma is associated with a greater frequency of health care usage.[55] Deaths associated with the slow-onset mechanism are preventable in many cases because of the gradual progression of symptoms. Rapid-onset near-fatal asthma is characterized by symptom onset and progression to life-threatening status in 3 hours or less. Clinically, rapid-onset near-fatal asthma is characterized by greater hypercapnia than occurs in the slow-onset type. It is interesting to note that the hypercapnia in rapid-onset near-fatal asthma is more responsive to therapy than that in the slow-onset type, and these patients require shorter durations of mechanical ventilation.

Risk factors for death from asthma have been identified (see Box 73-1). Other risk factors linked to near-fatal and fatal asthma include a decreased use of corticosteroids,[148] hospital admission for asthma treatment within the previous 12 months, low socioeconomic status (related to increased allergen exposure and less access to health care), environmental exposures (air pollution, cigarette smoking), and psychosocial problems. Patients with an episode of near-fatal asthma are also likely to depend on EDs for asthma crisis management. Patients with fatal asthma commonly tend to be African American, live in inner-city areas, and are 15 to 34 years of age. Most deaths occur outside or on the way to the hospital, at night, and within 24 hours of the onset of symptoms.

Clinical Approach to the Critically Ill Asthmatic

The critically ill asthmatic appears agitated (hypoxemic), assumes an upright position, and appears to be in severe respiratory distress. Tachypnea, diaphoresis, and accessory muscle use are evident. Speech is fragmented into single or short bursts of syllables or words. Absence of wheezing indicates severe expiratory obstruction and minimal air movement. Peak expiratory testing is difficult for the patient to perform but when possible indicates severe expiratory obstruction. Alterations in consciousness and bradypnea indicate hypercarbia and impending respiratory arrest.

No laboratory markers identify patients with near-fatal asthma. In critically ill patients, elevated lactic acid levels may be produced by fatigued respiratory muscles or changes in glycolysis induced by beta-agonist administration. Persistent elevations of arterial lactate levels are often associated with a poor prognosis. An elevated lactic acid level is not predictive of respiratory failure in critically ill asthmatics, and blood lactate levels are not generally prognostic.

Noninvasive Strategies. Attempts to abort the episode include continuously nebulized beta and anticholinergic agents (see Table 73-2). If parenteral adrenergic therapy is desired, terbutaline is preferred because of its $beta_2$ selectivity. Intravenous magnesium sulfate or beta-agonists (where available) may be of benefit. Oral prednisone 60 mg or intravenous methylprednisolone 125 mg should be administered. Helium is an inert gas with one eighth the density of nitrogen. When 60 to 80% helium is blended with 20 to 40% oxygen, the resulting gas mixture (heliox) has a threefold reduction in density compared with air. Heliox reduces the resistance associated with gas flow through airways with nonlaminar flow and reduces respiratory muscle work; it also increases the diffusion of carbon dioxide and may improve alveolar ventilation.[149] Although heliox is not intrinsically therapeutic, it may decrease the work of breathing long enough to abort intubation by carrying bronchodilators to the distal airways and allowing anti-inflammatory agents time to achieve their effects. The results when heliox is used to drive nebulized beta-agonist therapies in both children and adults are mixed.[150-152] No data indicate that heliox reduces the need for intubation or hospital admission, length of hospital stay, or mortality rates.[152-154] Heliox is administered by nonrebreather mask and may be an adjunctive strategy to mechanical ventilation in selected asthmatics. Close monitoring of oxygen saturation and continuous capnography are advisable. Considerations for heliox include cases of severe airflow obstruction (PEFR <30% predicted and a rapid onset of symptoms within 24 hours), a history of labile asthma or previous intubation, and inability to be adequately mechanically ventilated.[149]

Noninvasive positive-pressure ventilation may benefit carefully selected patients (see Chapter 2). Continuous positive airway pressure improves oxygenation and reduces respiratory muscle fatigue by increasing functional residual capacity and lung compliance and supplying some of the inflating pressure required during inspiration. Biphasic positive airway pressure (BPAP) provides continuous positive airway pressure but delivers higher pressure during inspiration than expiration. BPAP allows speech and reduces the need for sedation. Nebulized bronchodilators can be delivered through the BPAP circuitry. BPAP is well tolerated by children with status asthmaticus and may decrease the need for intubation and mechanical ventilation.[155] BPAP may also decrease the need for intubation and ICU care in adults with status asthmaticus.[156,157]

BPAP is not a substitute for endotracheal intubation and mechanical ventilation. Recommendations for BPAP are conditional—a trial of BPAP before intubation and mechanical ventilation should be considered in select patients.[158] Patient considerations for BPAP include alert mental status and intact airway reflexes. Providers should be familiar with BPAP use in other medical conditions (e.g., COPD, congestive heart failure), and ICU admission is mandatory. Intermittent ABG monitoring after institution of this therapy identifies nonresponders. Ketamine is an intravenous dissociative anesthetic with potent bronchodilator effects. Case reports suggest benefit when used in acute asthma as a temporizing measure during preparation for intubation, but no randomized trials have been conducted. Adverse effects include increased airway secretions and emergence reactions. At present, ketamine is not recommended for therapy of acute asthma in the nonintubated patient.

Intubation and Ventilator Strategy. Endotracheal intubation is required in 2% of all asthma exacerbations and 10 to 30% requiring ICU admission.[159,160] Indications for intubation in the asthmatic patient include coma, altered consciousness, cardiac or respiratory arrest, paradoxical breathing pattern, refractory hypoxemia, and failure of NIPPV. Some authors recommend threshold levels for intubation based on ABG results, but there is no evidence that ABG results provide better guidance regarding need for intubation than does overall clinical assessment.[161]

Orotracheal rapid sequence intubation with induction agents and muscle paralysis is preferred (see Chapter 1). Ketamine (1-2 mg/kg) is the preferred agent for induction in rapid sequence intubation of the asthmatic patient. Succinylcholine (1.5 mg/kg) or a competitive neuromuscular blocking agent, such as rocuronium (1 mg/kg), can be used for intubation paralysis. Pretreatment with intravenous lidocaine to mitigate exacerbation of bronchospasm induced by upper airway instrumentation and endotracheal tube insertion is controversial, with studies showing conflicting results.[162] It is unlikely that lidocaine adds benefit when full doses of inhaled beta-agonists have been given. After intubation, additional ketamine may be given as a small number of intermittent boluses of 0.5 to 1.0 mg/kg, and a benzodiazepine should be administered to keep the patient sedated and to prevent

www.ketabpezeshki.com 66485457-66963820

a ketamine emergence reaction. Alternatively, propofol (1.5-2 mg/kg) offers rapid-onset deep sedation and also possesses bronchodilating properties. Continued deep sedation with propofol or an equivalent agent (e.g., long-acting benzodiazepine) usually avoids the need for muscle paralysis. After intubation, an opioid that does not release histamine, such as fentanyl, can improve the patient's comfort.

A ventilator strategy providing adequate oxygenation and ventilation while minimizing high airway pressure, barotrauma, and systemic hypotension must be instituted. The technique of permissive hypercapnia (also known as *controlled hypoventilation*) is common (see Chapter 2). Oxygenation is maintained by use of a high fraction of inspired oxygen (FIO_2); hypercarbia and respiratory acidosis (pH maintained at 7.15-7.2 with sodium bicarbonate) are tolerated. Airway pressure is kept low by providing low tidal volumes (6-8 mL/kg), thus preventing excessive increases of intrinsic positive end-expiratory pressure ("auto-PEEP"), stacking of ventilations, and barotrauma. Low ventilation rates (below 10 breaths/min) and high inspiratory flow rates (above 60 L/min) provide prolonged time for expiration. Adjunctive therapies (in-line beta-agonists and anticholinergics, intravenous corticosteroids, intravenous ketamine, and possibly intravenous magnesium) to decrease airway pressure and airway obstruction are delivered simultaneously.

Continuous capnography is advisable. Moderate levels of hypercapnia are well tolerated and have few deleterious effects. Elevated CO_2 levels have vasodilatory effects on cerebral vessels. Cerebral blood flow reaches its maximum at a $PaCO_2$ level of 120 mm Hg, which may increase intracranial pressure. Although there is no consensus on what constitutes a safe level of hypercapnia, $PaCO_2$ levels above 100 mm Hg should be avoided.[160] Hypercapnia can decrease cardiac contractility and produce cardiovascular collapse; thus permissive hypercapnia should be supplemented by generous repletion of intravascular volume through intravenous fluid administration.

Neuromuscular blockade, once widely used for ventilation of asthmatic patients to rest fatigued airway muscles, is now used only in cases in which deep sedation with adequate analgesia fails to provide sufficient patient relaxation for successful mechanical ventilation (see Chapter 1). Myopathy attributed to the prolonged use of competitive neuromuscular blocking agents occurs in about 30% of asthmatic patients with neuromuscular blockade.[159] Although hazards of mechanical ventilation (nosocomial infection, barotrauma) may occur, the treatment of critically ill asthmatics with mechanical ventilation is associated with low mortality and few complications. Complications of mechanical ventilation in the asthmatic patient include hypoxemia, hypotension, and barotrauma. Hypotension is almost uniformly secondary to increased intrathoracic pressure with a subsequent decrease in venous return and cardiac output. Slowing the rate of mechanical ventilation or removing the patient from the ventilator for a short time (20-30 seconds) allows more time for expiration, thereby decreasing intrathoracic pressure. Volume depletion and medication effects (e.g., narcotic agents used for sedation) are other potential explanations for hypotension. Pneumothorax should be considered whenever sudden deterioration occurs or when hypotension is accompanied by a significant rise in peak inspiratory ventilator pressures.

Treatment of the Refractory Critically Ill Asthmatic. If the intensively treated, intubated critically ill asthmatic continues to have elevated airway pressures, persistent hypoxemia, and continued bronchospasm, general anesthesia should be considered. Isoflurane, a bronchodilator, has lower arrhythmogenic and hypotensive properties than halothane.[163]

External lateral chest compression may be of assistance when patients cannot exhale. Chest compression is delivered by bilateral squeezing of the lower chest walls immediately after end inspiration occurs. Compression delivered too early (i.e., during inspiration) may increase airway pressure and result in barotrauma.

Unrecognized barotrauma may cause cardiac arrest. Rapid bedside ultrasound may identify occult pneumothorax and reveal nonpalpable cardiac contractions. Empirical bilateral tube thoracostomy should be performed if unexplained cardiac arrest occurs, especially in the context of dramatic increases in peak inspiratory pressure. Intravenous epinephrine is a logical agent in the setting of cardiopulmonary arrest because it has inotropic, chronotropic, and bronchodilatory properties.[164] Isoproterenol, a pure beta-agonist, may increase heart rate and provide bronchodilation but decreases coronary perfusion pressure. Cardiopulmonary bypass and extracorporeal lung assist are also used in the treatment of near-fatal asthma.

DISPOSITION

Prediction of Relapse

Asthmatic patients discharged from the ED have rates of relapse that vary from 11% over 3 days to 45% at 8 weeks. In a multicenter study, the relapse rate was 17% in the 2 weeks after ED discharge. The risk for relapse increases in those with numerous asthma-related ED visits within the previous year, with more outpatient medications, and with longer duration of symptoms before the ED visit.[165] Other studies find similar out-of-control indices predicting relapse but have also included insufficient improvement in PFTs with hospital-based treatment for an attack.[166]

Inpatient versus Observation or Clinical Decision Unit

Patients requiring extended care who are without life-threatening exacerbations, pregnancy, or complications of asthma can generally be treated in a clinical decision unit (CDU) or observation unit with 8-week outcomes equal to those of patients admitted and with significant cost savings.[167] The ability to predict discharge from the CDU can be assessed by the ED PEFR response to the third $beta_2$-agonist treatment (PEFR >40% predicted is often associated with successful CDU discharge).[165] In addition, patients prefer CDU treatment of acute attacks over routine inpatient care.[168]

Table 73-4 summarizes disposition guidelines.

Table 73-4 Emergency Department Disposition Decision-Making Guidelines

	GOOD RESPONSE	INCOMPLETE RESPONSE	POOR RESPONSE
FEV_1 or PEFR (% predicted/ personal best)	≥70%	≥40% but <69%	<40%
Disposition site			
Home	Yes	Individualized decision (see text)	No, continue therapy
Clinical decision unit	No	Yes, if available	Yes, if available and appropriate
Hospital ward	No	Yes, if no CDU	Yes, if appropriate and available
Critical care unit	No	No	Yes, if with respiratory insufficiency or failure

CDU, clinical decision unit; *FEV_1,* forced expiratory volume in 1 second; *PEFR,* peak expiratory flow rate.

www.ketabpezeshki.com 66485457-66963820

Box 73-3 Instructions for Metered-Dose Inhaler (MDI) Use

1. Remove cap from the MDI container.
2. Assemble the MDI and hold it upright.
3. Shake the canister.
4. Place the mouthpiece loosely between the teeth (or hold it 3-4 cm in front of the open mouth).
5. Exhale fully (to functional residual capacity).
6. Actuate the inhaler at the beginning of a slow and full inhalation (as if sipping hot soup) lasting 5 or 6 seconds.
7. Hold breath for at least 10 seconds.
8. Wait 1 minute before reuse.

Planning Discharge from the Emergency Department

An asthma exacerbation does not end on ED discharge; airway inflammation and peripheral obstruction may take hours to days to resolve. Patients are likely to need continued beta$_2$-agonist rescue therapy, and they should demonstrate the correct use of their inhalers (Box 73-3). If the patient is having difficulty coordinating the canister activation with inhalation, a breath-activated inhaler or spacer device can be prescribed or the need for a home nebulizer discussed. A patient using a portable, preloaded, multidose DPI must be able to inhale from the mouthpiece in a rapid and forceful inhalation to total lung capacity.

Patients receiving systemic corticosteroids in the ED should continue these orally for 5 to 10 days. Asthma patients treated in the ED are more likely to have moderate to severe disease; not receive controller therapy; and be younger, poorer, and less educated. They have reduced asthma management skills and are more likely to miss school or work. If the patient was not using controller medications before the acute ED visit and has characteristics of persistent asthma (symptoms or rescue therapy more than twice per week, interference with sleep more than twice per month, activity limitation caused by asthma or exacerbations requiring oral corticosteroids more than once in the past year), moderate-dose inhaled steroids or a combination inhaled steroid and long-acting beta-agonist should be started.[169,170] A less preferred option is to prescribe an LT modifier (e.g., zafirlukast 20 mg twice a day or montelukast 10 mg daily) to decrease relapse and improve asthma control.[169]

Patients should contact their physician for asthma-related problems within the following 3 to 5 days and should make a follow-up medical appointment (ideally done while the patient is still in the ED) within 1 to 4 weeks. Interventions that include free medications, transportation vouchers, and appointment assistance significantly increase the likelihood that discharged asthma patients will obtain primary care follow-up. These assistances, however, may not affect long-term outcomes.[169]

Patients that follow up and are managed by asthma specialists have fewer symptoms, less beta-agonist use, improved quality of life, and reduced ED visits and hospitalizations than those managed by generalists. Patients with severe persistent asthma or prior severe exacerbations should be referred from the ED to an asthma specialist.[169]

The asthma patient can be provided written education about discharge medications, medication adjustment if the condition is not improving (such action plans are not often created and when done are often inadequate),[171] and a peak flow meter for daily measurements, especially for those who have difficulty perceiving airflow obstruction or who have symptoms of worsening asthma. At a minimum, focused education should address the need for follow-up and for understanding the difference between controller and rescue medications and their use.[169] Lastly, smoking asthmatics have more respiratory symptoms, lower lung function, and more parenchymal abnormalities noted on chest computed tomography, so the need for smoking cessation should be discussed.[172]

KEY CONCEPTS

- Inhaled and systemic steroid medications are effective in controlling airway inflammation and have important roles in management of asthma exacerbations.
- Single-isomer albuterol (levalbuterol), the result of improving isomer technology, is a better bronchodilator in acute asthma than the traditional racemic form.
- Severe and refractory asthma exacerbations require rapid identification. Treatment must be aggressive and may use strategies not used in mild to moderate exacerbations.
- A normal P_{CO_2} in a pregnant patient represents hypercarbia.
- ED management of acute asthma is expanding (up to 24 hours) as more noncritically ill asthmatics are treated in the clinical decision units.
- Integration of discharged patients with acute asthma into chronic management strategies to prevent relapse requires that asthma patients' physicians be familiar with controlling medications such as ICSs and LT modifiers.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. National Asthma Education and Prevention Program Expert Panel: *Report 3: Guidelines for the Diagnosis and Management of Asthma*. NIH Publication No. 08-5846. Washington, DC: U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung and Blood Institute; 2007.
2. American Lung Association Epidemiology and Statistics Unit Research and Program Services Division: *Trends in Asthma Morbidity and Mortality*, February 2010. Available at www.lungusa.org/finding-cures/our-research/trend-reports/asthma-trend-report.pdf. Accessed March 2011.
3. Akinbami LJ, Moorman JE, Liu X: Asthma prevalence, health care use, and mortality: United States, 2005-2009. *Natl Health Stat Report* 2011; 32:1-14
4. Centers for Disease Control and Prevention: *Asthma Data and Surveillance*. Available at www.cdc.gov/asthma/asthmadata.htm. Accessed April 2011.
5. Moorman JE, Zahran H, Truman BI, Molla MT, Centers for Disease Control and Prevention (CDC): Current asthma prevalence—United States, 2006-2008. *MMWR Surveill Summ* 2011; 60(Suppl):84.
6. National Institutes of Health, National Heart, Lung, and Blood Institute: *Morbidity and Mortality: 2007 Chart Book on Cardiovascular, Lung, and Blood Diseases*. Available at www.nhlbi.nih.gov/resources/docs/07-chtbk.pdf. Accessed March, 2011.
7. Weiss KB, Sullivan SD: The health economics of asthma and rhinitis. I. Assessing the economic impact. *J Allergy Clin Immunol* 2001; 107:3.
8. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion: *Healthy Youth! Health Topics: Asthma*. August 14, 2009. Available at http://www.nhlbi.nih.gov/guidelines/asthma/index.htm. Accessed April 2011.
9. National Institutes of Health, National Heart, Lung, and Blood Institute: *Morbidity and Mortality: 2009 Chart Book on Cardiovascular, Lung, and Blood Diseases*. Available at www.nhlbi.nih.gov/resources/docs/2009_ChartBook.pdf. Accessed April 2011.
10. National Center for Health Statistics: *Asthma Prevalence, Health Care Use and Mortality: United States, 2003-05*. Available at http://www.cdc.gov/nchs/data/hestat/asthma03-05/asthma03-05.htm. Accessed April, 2011.
11. Miniño AM, Xu J, Kochanek KD: Deaths: Preliminary data for 2008. *Natl Vital Stat Rep* 2010; 59:1.
12. Bartolomei-Díaz JA, Amill-Rosario A, Claudio L, Hernández W: Asthma mortality in Puerto Rico: 1980-2007. *J Asthma* 2011; 48:202.
13. Hamid QA, Minshall EM: Molecular pathology of allergic disease. 1. Lower airway disease. *J Allergy Clin Immunol* 2000; 105:20.
14. Murphy DM, O'Byrne PM: Recent advances in the pathophysiology of asthma. *Chest* 2010; 137:1417.
15. Von Hertzen L, Haahtela T: Disconnection of man and the soil: Reason for the asthma and atopy epidemic? *J Allergy Clin Immunol* 2006; 117:334.
16. Roduit C, et al: Asthma at 8 years of age in children born by caesarean section. *Thorax* 2009; 64:107.
17. Bradding P: Asthma: Eosinophil disease, mast cell disease or both? *Allergy Asthma Clin Immunol* 2008; 4:84.
18. Bradding P, Walls AF, Holgate ST: The role of the mast cell in the pathophysiology of asthma. *J Allergy Clin Immunol* 2006; 117:277.
19. Brightling CE, et al: Mast cell infiltration of airway smooth muscle in asthma. *N Engl J Med* 2002; 346:199.
20. Black J: The role of mast cells in the pathophysiology of asthma. *N Engl J Med* 2002; 346:1742.
21. Williams TJ: The eosinophil enigma. *J Clin Invest* 2004; 113:507.
22. Leckie MJ, et al: Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000; 356:2144.
23. O'Byrne PM: Cytokines or their antagonists for the treatment of asthma. *Chest* 2006; 130:244.
24. Green RH, et al: Asthma exacerbations and sputum eosinophil counts: A randomised controlled trial. *Lancet* 2002; 360:1715.
25. Green RH, et al: Analysis of induced sputum in adults with asthma: Identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. *Thorax* 2002; 57:875.
26. Berry M, et al: Pathological features and inhaled corticosteroid response of eosinophilic and non-eosinophilic asthma. *Thorax* 2007; 62:1043.
27. Barnes PJ: How corticosteroids control inflammation. *Br J Pharmacol* 2006; 148:245.
28. Fireman P: Understanding asthma pathophysiology. *Allergy Asthma Proc* 2003; 24:79.
29. Holgate ST, Roberts G, Arshad HS, Howarth PH, Davies DE: The role of the airway epithelium and its interaction with environmental factors in asthma pathogenesis. *Proc Am Thorac Soc* 2009; 6:655.
30. Holgate ST: Epithelium dysfunction in asthma. *J Allergy Clin Immunol* 2007; 120:1233.
31. Barnes PJ, et al: Exhaled nitric oxide in pulmonary diseases: A comprehensive review. *Chest* 2010; 138:682.
32. Bergeron C, Al-Ramli W, Hamid Q: Remodeling in asthma. *Proc Am Thorac Soc* 2009; 6:301.
33. Barbato A, et al: Epithelial damage and angiogenesis in the airways of children with asthma. *Am J Respir Crit Care Med* 2006; 174:975.
34. Cohen L, et al: Epithelial cell proliferation contributes to airway remodeling in severe asthma. *Am J Respir Crit Care Med* 2007; 176:138.
35. Jenkins C, Costello J, Hodge L: Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. *BMJ* 2004; 328:434.
36. Lee RU, Stevenson DD: Aspirin-exacerbated respiratory disease: Evaluation and management. *Allergy Asthma Immunol Res* 2011; 3:3.
37. Marquette CH, et al: Long-term prognosis for near fatal asthma: A 6 year follow-up study of 145 asthmatic patients who underwent mechanical ventilation for near-fatal attack of asthma. *Am Rev Respir Dis* 1992; 146:76.
38. Jawien J: A new insight into aspirin-induced asthma. *Eur J Clin Invest* 2002; 32:134.
39. Stevenson DL, Szczeklik A: Clinical and pathologic perspectives on aspirin sensitivity and asthma. *J Allergy Clin Immunol* 2006; 118:773.
40. Knowles SR, Drucker AM, Weber EA, Shear NH: Management options for patients with aspirin and nonsteroidal anti-inflammatory drug sensitivity. *Ann Pharmacother* 2007; 41:1191.
41. Weiler JM, et al: American Academy of Allergy, Asthma and Immunology Work Group report: Exercise-induced asthma. *J Allergy Clin Immunol* 2007; 119:1349.
42. Hallstrand TS, Henderson WR: An update on the role of leukotrienes in asthma. *Curr Opin Allergy Clin Immunol* 2010; 10:60.
43. Grzelewski T, Stelmach I: Exercise-induced bronchoconstriction in asthmatic children: A comparative systematic review of the available treatment options. *Drugs* 2009; 69:1533.
44. Anderson SD: Single-dose agents in the prevention of exercise-induced asthma: A descriptive review. *Treat Respir Med* 2004; 3:365.
45. Vrieze A, Postma DS, Kerstjens HA: Perimenstrual asthma: A syndrome without known cause or cure. *J Allergy Clin Immunol* 2003; 112:271.
46. Dratva J, et al: Perimenstrual increase in bronchial hyperreactivity in premenopausal women: Results from the population-based SAPALDIA 2 cohort. *J Allergy Clin Immunol* 2010; 125:823.
47. Redmond AM, James AW, Nolan SH, Self TH: Premenstrual asthma: Emphasis on drug therapy options. *J Asthma* 2004; 41:687.
48. Ritz T, et al: Airway response to emotional stimuli in asthma: The role of the cholinergic pathway. *J Appl Physiol* 2010; 108:1542.
49. Di Marco F, Santus P, Centanni S: Anxiety and depression in asthma. *Curr Opin Pulm Med* 2011; 17:39.
50. Anbar RD: Hypnosis in pediatrics: Applications at a pediatric pulmonary center. *BMC Pediatr* 2002; 2:11.
51. Postma DS, Koppelman GH: Genetics of asthma: Where are we and where do we go? *Proc Am Thorac Soc* 2009; 6:283.
52. Holloway JW, Arshad SH, Holgate ST: Using genetics to predict the natural history of asthma? *J Allergy Clin Immunol* 2010; 126:200.
53. Hamid Q: Gross pathology and histopathology of asthma. *J Allergy Clin Immunol* 2003; 111:431.
54. Chen FH, et al: Airway remodeling: A comparison between fatal and nonfatal asthma. *J Asthma* 2004; 41:631.
55. Hyzy RC, et al: Slow-onset asthma deaths have more eosinophils and health care utilization than rapid-onset deaths. *Respir Med* 2008; 102:1819.
56. Tsai CL, et al: Quality of care for acute asthma in 63 U.S. emergency departments. *J Allergy Clin Immunol* 2009; 123:3549.
57. Pines JM, Prabhu A, Hilton JA, Hollander JE, Datner EM: The effect of emergency department crowding on length of stay and medication treatment times in discharged patients with acute asthma. *Acad Emerg Med* 2010; 17:834.
58. Zimmerman JL, Woodruff PG, Clark S, Camargo CA: Relation between phase of menstrual cycle and emergency department visits for acute asthma. *Am J Respir Crit Care Med* 2000; 162:512.
59. Magadle R, Berar-Yanny N, Weiner P: The risk of hospitalization and near-fatal and fatal asthma in relation to the perception of dyspnea. *Chest* 2002; 121:329.
60. Rodrigo GJ, Plaza V: Body mass index and response to emergency department treatment in adults with severe asthma exacerbations. *Chest* 2007; 132:1513.

www.ketabpezeshki.com 66485457-66963820

61. Peters-Golden M, et al: Influence of body mass index on the response to asthma controller agents. *Eur Respir J* 2006; 27:495.
62. Lessard A, Turcotte H, Cornier Y: Obesity and asthma: A specific phenotype? *Chest* 2008; 134:317.
63. Patel SN, et al: Multicenter study of cigarette smoking among patients presenting to the emergency department with acute asthma. *Chest* 2009; 103:121.
64. Boulet LP, FitzGerald JM, McIvor RA, Zimmerman S, Chapman KR: Influence of current or former smoking on asthma management and control. *Can Respir J* 2008; 15:275.
65. El-Ekiaby A, et al: Impact of race on the severity of acute episodes of asthma and adrenergic responsiveness. *Am J Respir Crit Care Med* 2006; 174:508.
66. Chandra D, Clark S, Camargo CA: Race/ethnicity differences in the inpatient management of acute asthma in the United States. *Chest* 2009; 135:1527.
67. Rodrigo GJ, Rodrigo C, Hall JB: Acute asthma in adults. *Chest* 2004; 125:1081.
68. Levine M, Iliescu ME, Margellos-Anast H, Estarziau M, Ansell DA: The effects of cocaine and heroin use on intubation rates and hospital utilization in patients with acute asthma exacerbations. *Chest* 2005; 128:1951.
69. Krantz AJ, et al: Heroin insufflation as a trigger for patients with life-threatening asthma. *Chest* 2003; 123:510.
70. Corbridge T, Cygan J, Greenberger P: Substance abuse and acute asthma. *Intensive Care Med* 2000; 26:347.
71. Elia D, Marinou A, Chetta A: Life-threatening asthma after heroin inhalation. A case report and a review of the literature. *Acta Biomed* 2010; 81:63.
72. Brooks TW, et al: Rates of hospitalizations and emergency department visits in patients with asthma and chronic obstructive pulmonary disease taking beta-blockers. *Pharmacotherapy* 2007; 27:684.
73. Silverman RA, Flaster E, Enright PL, Simonson SG: FEV_1 performance among patients with acute asthma: Results from a multicenter clinical trial. *Chest* 2007; 131:164.
74. Nowak RM, Tomlanovich MC, Sarkar DD: Arterial blood gases and pulmonary function testing in acute bronchial asthma: Predicting patient outcomes. *JAMA* 1983; 249:2043.
75. Corbo J, Bijur P, Lahn M, Gallagher EJ: Concordance between capnography and arterial blood gas measurements of carbon dioxide in acute asthma. *Ann Emerg Med* 2005; 46:323.
76. Nik Hisamuddin NA, et al: Correlations between capnographic waveforms and peak flow meter measurements in emergency department management of asthma. *Int J Emerg Med* 2009; 2:83.
77. Baptist AP, Sengupta R, Pranathiageswaran S, Wang Y, Ager J: Evaluation of exhaled nitric oxide measurements in the emergency department for patients with acute asthma. *Ann Allergy Asthma Immunol* 2008; 100:415.
78. Delclaux C, et al: Offline exhaled nitric oxide in emergency department and subsequent acute asthma control. *J Asthma* 2008; 45:867.
79. Stephenson JJ, Quimbo RA, Gutierrez B: Subacute lack of asthma control as a predictor of subsequent acute asthma exacerbation in a managed care population. *Am J Manag Care* 2010; 16:108.
80. Kenn K, Balkissoon R: Vocal cord dysfunction: What do we know? *Eur Respir J* 2011; 37:194.
81. Camargo CA Jr: A model protocol for emergency medical services management of asthma exacerbations. *Prehosp Emerg Care* 2006; 10:418.
82. Richmond NJ, Silverman R, Kusick M, Matallana L, Winokur J: Out-of-hospital administration of albuterol for asthma by basic life support providers. *Acad Emerg Med* 2005; 12:396.
83. Thompson J, Petrie DA, Ackroyd-Stolarz S, Bardua DJ: Out-of hospital continuous positive airway pressure ventilation versus usual care in acute respiratory failure: A randomized controlled trial. *Ann Emerg Med* 2008; 52:232.
84. Moloney E, O'Sullivan S, Hogan T, Poulter LW, Burke CM: Airway dehydration: A therapeutic target in asthma? *Chest* 2002; 121:1806.
85. Spitzer WO, et al: The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992; 326:501.
86. Nowak RM: Single-isomer levalbuterol: A review of the acute data. *Curr Allergy Asthma Rep* 2003; 3:172.
87. Jenne JW: The debate on *S*-enantiomers of beta-agonists: Tempest in a teapot or gathering storm? *J Allergy Clin Immunol* 1998; 102:893.
88. Nowak RM, et al: Levalbuterol compared with racemic albuterol in the treatment of acute asthma: Results of a pilot study. *Am J Emerg Med* 2004; 22:29.
89. Nowak R, et al: A comparison of levalbuterol with racemic albuterol in the treatment of acute severe asthma exacerbations in adults. *Am J Emerg Med* 2006; 24:259.
90. Carl CC, Myers TR, Kirchner HL, Kercsmar CM: Comparison of racemic albuterol and levalbuterol for treatment of acute asthma. *J Pediatr* 2003; 143:731.
91. Peters SG: Continuous bronchodilator therapy. *Chest* 2007; 131:286.
92. Truitt T, Witko J, Halpern M: Levalbuterol compared to racemic albuterol: Efficacy and outcomes in patients hospitalized with COPD or asthma. *Chest* 2003; 123:128.
93. Rodrigo GJ: Predicting response to therapy in acute asthma. *Curr Opin Pulm Med* 2009; 15:35.
94. Carroll CL, Stoltz P, Schramm CM, Zucker AR: Beta2-adrenergic receptor polymorphisms affect response to treatment in children with severe asthma exacerbations. *Chest* 2009; 135:1186.
95. Newman KB, Milne S, Hamilton C, Hall K: A comparison of albuterol administered by metered-dose inhaler and spacer with albuterol by nebulizer in adults presenting to an urban emergency department with acute asthma. *Chest* 2002; 121:1036.
96. Osmond MH, et al: Barriers to metered-dose inhaler/spacer use in Canadian pediatrics emergency department: A national survey. *Acad Emerg Med* 2007; 14:1106.
97. Hurley KF, et al: Perceptual reasons for resistance to change in the emergency department use of holding chambers for children with asthma. *Ann Emerg Med* 2008; 51:70.
98. Mason N, Roberts N, Yard N, Partridge MR: Nebulisers or spacers for the administration of bronchodilators to those with asthma attending emergency departments? *Respir Med* 2008; 102:993.
99. Dhuper S, et al: Efficacy and cost comparisons of bronchodilatator administration between metered dose inhalers with disposable spacers and nebulizers for acute asthma in an inner-city adult population. *J Emerg Med* 2008; 40:247.
100. Travers AH, Rowe BH, Barker S, Jones A, Camargo CA Jr: The effectiveness of IV beta-agonists in treating patients with acute asthma in the emergency department: A meta-analysis. *Chest* 2002; 122:1200.
101. Putland M, Kerr D, Kelly AM: Adverse events associated with the use of intravenous epinephrine in emergency department patients presenting with severe asthma. *Ann Emerg Med* 2006; 47:559.
102. Liao MM, Ginde AA, Clark S, Camargo CA Jr: Salmeterol use and risk of hospitalization among emergency department patients with acute asthma. *Ann Allergy Asthma Immunol* 2010; 104:478.
103. Rodrigo GJ, Neffen H, Colodenco FD, Castro-Rodriguez JA: Formoterol for acute asthma in the emergency department: A systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2010; 104:247.
104. Najafizadeh K, et al: A randomised, double-blind, placebo-controlled study to evaluate the role of formoterol in the management of acute asthma. *Emerg Med J* 2007; 24:317.
105. Chowdhury BA, Dal Pan G: The FDA and safe use of long-acting beta-agonists in the treatment of asthma. *N Engl J Med* 2010; 362:1169.
106. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW: Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane Database Syst Rev* 2000; 2:CD002178.
107. Lin RY, et al: Rapid improvement of peak flow in asthmatic patients treated with parenteral methylprednisolone in the emergency department: A randomized controlled study. *Ann Emerg Med* 1999; 33:487.
108. Edmonds ML, Camargo CA, Pollack CV, Rowe BH: Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. *Cochrane Database Syst Rev* 2003; 3:CD002308.
109. Edmonds ML, Camargo CA Jr, Pollack CV Jr, Rowe BH: The effectiveness of inhaled corticosteroids in the emergency department treatment of acute asthma: A meta-analysis. *Ann Emerg Med* 2002; 40:145.
110. Rodrigo GJ: Comparison of inhaled fluticasone with intravenous hydrocortisone in the treatment of adult acute asthma. *Am J Respir Crit Care Med* 2005; 172:1231.
111. Rowe BH, Vethanayagam D: The role of inhaled corticosteroids in the management of acute asthma. *Eur Respir J* 2007; 30:1035.
112. Schuckman H, et al: Comparison of intramuscular triamcinolone and oral prednisone in the outpatient treatment of acute asthma: A randomized controlled trial. *Ann Emerg Med* 1998; 31:333.
113. Lahn M, Bijur P, Gallagher EJ: Randomized clinical trial of intramuscular vs oral methylprednisolone in the treatment of asthma exacerbations following discharge from an emergency department. *Chest* 2004; 126:362.
114. Rowe BH, et al: Inhaled budesonide in addition to oral corticosteroids to prevent asthma relapse following discharge from the emergency department: A randomized controlled trial. *JAMA* 1999; 281:2119.

www.ketabpezeshki.com 66485457-66963820

115. Krishnan JA, Nowak R, Davis SQ, Schatz M: Anti-inflammatory treatment after discharge home from the emergency department in adults with acute asthma. *Proc Am Thoracic Soc* 2009; 6:380.
116. Rodrigo G, Rodrigo C, Burschtin O: A meta-analysis of the effects of ipratropium bromide in adults with acute asthma. *Am J Med* 1999; 107:363.
117. Rodrigo GJ, Rodrigo C: The role of anticholinergics in acute asthma treatment: An evidence-based evaluation. *Chest* 2002; 121:1977.
118. Peters SP, et al: Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010; 363:1715.
119. Zervas E, et al: Reduced intracellular Mg concentrations in patients with acute asthma. *Chest* 2003; 123:113.
120. Silverman RA, et al: IV magnesium sulfate in the treatment of acute severe asthma: A multicenter randomized controlled trial. *Chest* 2002; 122:489.
121. Alter HJ, Koepsell TD, Hilty WM: Intravenous magnesium sulfate as an effective adjunct in acute bronchospasm: A meta-analysis. *Acad Emerg Med* 1999; 6:521.
122. Cheuk DK, Chau TC, Lee SL: A meta-analysis on intravenous magnesium sulfate for treating acute asthma. *Arch Dis Child* 2005; 90:74.
123. Jones LA, Goodacre S: Magnesium sulphate in the treatment of acute asthma: Evaluation of current practice in adult emergency departments. *Emerg Med J* 2009; 26:783.
124. Nannini LJ Jr, Pendino JC, Corna RA, Mannarino S, Quispe R: Magnesium sulfate as a vehicle for nebulized salbutamol in acute asthma. *Am J Med* 2000; 108:193.
125. Mahajan P, Haritos D, Rosenberg N, Thomas R: Comparison of nebulized magnesium sulfate plus albuterol to nebulized albuterol plus saline in children with acute exacerbations of mild to moderate asthma. *J Emerg Med* 2004; 27:21.
126. Blitz M, et al: Aerosolized magnesium sulfate for acute asthma: A systematic review. *Chest* 2005; 128:337.
127. Camargo CA Jr, Smithline HA, Malice MP, Green SA, Reiss TF: A randomized controlled trial of intravenous montelukast in acute asthma. *Am J Respir Crit Care Med* 2003; 167:528.
128. Camargo CA Jr, et al: A randomized placebo-controlled study of intravenous montelukast for the treatment of acute asthma. *J Allergy Clin Immunol* 2010; 125:374.
129. Silverman RA, et al: Zafirlukast treatment for acute asthma: Evaluation in a randomized, double-blind multicenter trial. *Chest* 2004; 126:1480.
130. Ramsay CF, Pearson D, Mildenhall S, Wilson AM: Oral montelukast in acute asthma exacerbations: A randomised, double-blind, placebo-controlled trial. *Thorax* 2011; 66:7.
131. Vanderweil SG, et al: Inappropriate use of antibiotics for acute asthma in United States emergency departments. *Acad Emerg Med* 2008; 15:736.
132. Akerman MJ, et al: Bronchodilator effect of infused B-type natriuretic peptide in asthma. *Chest* 2006; 130:66.
133. Rodrigo GJ, Neffen H, Castro-Rodriquez JA: Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma. *Chest* 2011; 139:28.
134. Papi A, Caramori G, Adcock IM, Barnes PJ: Rescue treatment in asthma: More than as-needed bronchodilation. *Chest* 2009; 135:1628.
135. Hardy-Fairbanks AJ, Baker ER: Asthma in pregnancy: Pathophysiology, diagnosis and management. *Obstet Gynecol Clin North Am* 2010; 37:159.
136. Schatz M, et al: Asthma morbidity during pregnancy can be predicted by severity classification. *J Allergy Clin Immunol* 2003; 112:283.
137. Tamási L, et al: Asthma in pregnancy—immunological changes and clinical management. *Respir Med* 2011; 105:159.
138. Enriquez R, et al: Effect of maternal asthma and asthma control on pregnancy and perinatal outcomes. *J Allergy Clin Immunol* 2007; 120:625.
139. Schatz M, et al: The relationship of asthma medication use to perinatal outcomes. *J Allergy Clin Immunol* 2004; 113:1040.
140. Holgate ST, et al: Understanding the pathophysiology of severe asthma to generate new therapeutic opportunities. *J Allergy Clin Immunol* 2006; 117:496.
141. Howarth PH, et al: Tumour necrosis factor (TNFalpha) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax* 2005; 60:1012.
142. Erin EM, et al: The effects of a monoclonal antibody directed against tumor necrosis factor–alpha in asthma. *Am J Respir Crit Care Med* 2006; 174:753.
143. Wenzel SE, et al: A randomized double-blind placebo-controlled study of tumor necrosis factor–alpha blockade in severe persistent asthma. *Am J Respir Crit Care Med* 2009; 179:549.
144. Clienti S, Morjaria JB, Basile E, Polosa R: Monoclonal antibodies for the treatment of severe asthma. *Curr Allergy Asthma Rep* 2011; 11:253.
145. Corren J: Cytokine inhibition in severe asthma: Current knowledge and future directions. *Curr Opin Pulm Med* 2011; 17:29.
146. Wenzel SE, Busse WW: Severe asthma: Lessons for the severe asthma research program. *J Allergy Clin Immunol* 2007; 119:14.
147. Wenzel S, Szefler SJ: Managing severe asthma. *J Allergy Clin Immunol* 2006; 117:508.
148. Romagnoli M, et al: Near fatal asthma phenotype in the ENFUMOSA cohort. *Clin Exp Allergy* 2007; 37:552.
149. Kass JE: Heliox redux. *Chest* 2003; 123:673.
150. Lee DL, Hsu CW, Lee H, Chang HW, Huang YC: Beneficial effects of albuterol therapy driven by heliox versus by oxygen in severe asthma exacerbation. *Acad Emerg Med* 2005; 12:820.
151. Brandão DC, et al: Heliox and posture optimize action of nebulization with bronchodilators for asthma attacks. Randomized trial. *Respir Med* 2011; 56:947-952. DOI:10.4187/respcare.00963.
152. Bigham MT, et al: Helium/oxygen-driven albuterol nebulization in the management of children with status asthmaticus: A randomized placebo-controlled trial. *Pediatr Crit Care Med* 2010; 11:356.
153. Rodrigo G, Pollack C, Rodrigo C, Rowe BH: Heliox for nonintubated acute asthma patients. *Cochrane Database Syst Rev* 2006; 4: CD002884.
154. Hurford WE, Cheifetz IM: Respiratory controversies in the critical care setting: Should heliox be used for mechanically ventilated patients? *Respir Care* 2007; 52:582.
155. Beers SL, Abramo TJ, Bracken A, Wiebe RA: Bilevel positive airway pressure in the treatment of status asthmaticus in pediatrics. *Am J Emerg Med* 2007; 25:6.
156. Fernández MM, Villagrá A, Blanch L, Fernández R: Non-invasive mechanical ventilation in status asthmaticus. *Intensive Care Med* 2001; 27:486.
157. Soroksky A, Stav D, Shpirer I: A pilot prospective, randomized placebo-controlled trial of bilevel positive airway pressure in acute asthma attack. *Chest* 2003; 123:1018.
158. Nowak R, Corbridge T, Brenner B: Noninvasive ventilation. *J Emerg Med* 2009; 37(Suppl 2):S18.
159. Phipps P, Garrard CS: The pulmonary physician in critical care. 12: Acute severe asthma in the intensive care unit. *Thorax* 2003; 58:81.
160. Mutlu GM, Factor P, Schwartz DE, Sznajder JI: Severe status asthmaticus: Management with permissive hypercapnia and inhalation anesthesia. *Crit Care Med* 2002; 30:477.
161. Brenner B, Corbridge T, Kazzi A: Intubation and mechanical ventilation of the asthmatic patient in respiratory failure. *J Emerg Med* 2009; 37(Suppl 2):S23.
162. Maslow AD, et al: Inhaled albuterol, but not intravenous lidocaine, protects against intubation-induced bronchoconstriction in asthma. *Anesthesiology* 2000; 93:1198.
163. Tobias JD: Inhalational anesthesia: Basic pharmacology, end organ effects, and applications in the treatment of status asthmaticus. *J Intensive Care Med* 2009; 24:361.
164. Smith D, et al: Intravenous epinephrine in life-threatening asthma. *Ann Emerg Med* 2003; 41:706.
165. McCarren M, et al: Prediction of relapse within eight weeks after an acute asthma exacerbation in adults. *J Clin Epidemiol* 1998; 51:107.
166. McDermott MF, et al: A comparison between emergency diagnostic and treatment unit and inpatient care in the management of acute asthma. *Arch Intern Med* 1997; 157:2055.
167. McCarren M, Zalenski RJ, McDermott M, Kaur K: Predicting recovery from acute asthma in an emergency diagnostic and treatment unit. *Acad Emerg Med* 2000; 7:28.
168. Rydman RJ, Roberts RR, Albrecht GL, Zalenski RJ, McDermott M: Patient satisfaction with an emergency department asthma observation unit. *Acad Emerg Med* 1999; 6:178.
169. Schatz M, Rachelefsky G, Krishnan JA: Follow-up after acute asthma episodes: What improves future outcomes? *Proc Am Thorac Soc* 2009; 6:386.
170. Rowe BH, et al: Adding long-acting beta-agonists to inhaled corticosteroids after discharge from the emergency department for acute asthma: A randomized controlled trial. *Acad Emerg Med* 2007; 14:833.
171. Camargo CA Jr, et al: A prospective multicenter study of written action plans among emergency department patients with acute asthma. *J Asthma* 2008; 45:532.
172. Boulet LP, et al: Smoking and asthma: Clinical and radiologic features, lung function, and airway inflammation. *Chest* 2006; 129:661.

www.ketabpezeshki.com 66485457-66963820

Chapter 74

Chronic Obstructive Pulmonary Disease

Stuart P. Swadron and Phillip F. Gruber

PERSPECTIVE

Chronic obstructive pulmonary disease (COPD) is one of the most common causes of death worldwide. Although prevalence estimates vary by measurement methods and by population studied, there is general agreement that COPD is underdiagnosed and under-reported. Regardless of the success of smoking cessation programs, smoking behavior in the past several decades and the delay of the appearance of symptoms in an aging population virtually guarantee an increase in prevalence, especially in developed nations. In addition, it is becoming increasingly clear that other risk factors besides cigarette smoking contribute significantly to the worldwide burden of COPD.[1]

It is estimated that COPD will be the fifth leading cause of lost disability-adjusted life years worldwide by 2030.[2] The financial burden of COPD is enormous, accounting for billions of dollars every year for treatment and lost productivity. The majority of these costs are related to hospitalization for acute exacerbations.[3] Despite its enormous effects, COPD has received relatively less attention from basic medical researchers and clinicians than other diseases. Large multinational collaborations, such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD), sponsored jointly by the National Heart, Lung, and Blood Institute and the World Health Organization, have reinvigorated the scientific and medical communities frustrated by the unrelenting progressive nature of COPD and its poor response to existing therapies.

The definition of COPD is imprecise and incorporates advances in our understanding of its underlying mechanisms and natural history. In their consensus statement, the GOLD collaborators define COPD as "a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible." They also state that "the airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases."[4] This definition reflects new data underscoring the systemic nature of the disease, as well as a deliberate optimism with respect to new prevention and treatment strategies. It specifically avoids mention of chronic bronchitis and emphysema, two entities that have been traditionally included in the definition of COPD. Chronic bronchitis, defined as the presence of cough and sputum production for at least 3 months in each of 2 consecutive years, can occur without airflow limitation. Emphysema, the destruction of alveoli, is a pathologic term, not one that pertains to clinical diagnosis. Unlike with many earlier definitions of COPD, the GOLD collaborators also specifically exclude asthma, which is reversible airflow limitation. Whether reversible airflow limitation is considered to be part of COPD itself or caused by coexisting asthma is of limited significance to the emergency physician, who will continue to make every attempt to identify and reverse airflow limitation.

As many as 50% of all acute COPD exacerbations are not reported to physicians. In addition, not all reported exacerbations necessitate hospitalization.[5] Nonetheless, in 2007 almost 2% of all hospital admissions in the United States were directly attributed to COPD, and it was considered a contributory factor in another 9%. In patients older than 65 years, the percentage of all hospitalizations related to COPD approaches 20%.[6] As the severity of the underlying disease progresses, so does the frequency of exacerbations.[7] Moreover, in a subset of patients, incomplete recovery from acute exacerbations may reflect a contribution of exacerbations to the pathophysiology of relentless disease progression.

PRINCIPLES OF DISEASE

Pathophysiology

In the past several decades the discovery that chronic airway inflammation plays a central role in the pathophysiology of asthma has led to an important change in its management, specifically, the liberal use of corticosteroids for treating moderate to severe disease. Airway inflammation is also at the center of the pathophysiology of COPD, but the inflammatory process of COPD differs from that of asthma. In COPD, neutrophils, CD8+ lymphocytes, and macrophages predominate in bronchial washings, whereas in asthma the cellular response is characterized by the presence of eosinophils.[8] The inflammatory mediators differ in COPD, and several mediators, such as tumor necrosis factor, leukotriene B4, and interleukin-8, are linked to the destruction of parenchyma. These differences in the nature of the inflammatory response in COPD may account for its relatively poor response to current anti-inflammatory treatment compared with asthma.

Pathologically, the abnormalities in COPD are found throughout the lungs. Although certain changes may be more or less prominent in a given patient, most patients have at least some component of the two main pathologic entities: chronic obstructive bronchitis and emphysema. Evidence of airway inflammation is found from the trachea down to the smallest peripheral airways, which become progressively scarred and narrowed. An increase in both the number and size of mucus-secreting goblet cells results in the formation of mucous plugs, which further contributes to airflow obstruction. Damage to the endothelium impairs the mucociliary response that clears bacteria and mucus. The lung parenchyma is progressively destroyed over time, usually in a pattern of centrilobular emphysema. This consists of a destruction of alveoli, loss of lung elasticity, and the closure of small airways, which rely on the radial support of surrounding connective tissues to maintain their patency during expiration.

www.ketabpezeshki.com 66485457-66963820

The combination of airway obstruction and obliteration of the pulmonary vascular bed results in a failure of gas exchange. Thus arterial blood gases (ABGs) may reveal both hypoxemia and hypercapnia. As the overall size of the pulmonary vascular bed decreases with time, chronic hypoxia induces a thickening of the vessel walls. Both of these factors contribute to the development of pulmonary hypertension, polycythemia and, eventually, right-sided heart failure (cor pulmonale).

The pathophysiology of COPD reflects the apparent imbalance between proteases and antiproteases that favors the destruction of connective tissue in the lungs. In one small subset of COPD patients with congenital α_1-antitrypsin deficiency, a lack of α_1-antitrypsin, an enzyme that inhibits neutrophil elastase, leads to the pathology of severe panacinar emphysema. In the majority of patients, however, the specific genetic factors are less well elucidated. Oxidative stress, the imbalance of oxidant to antioxidant activity in favor of oxidants, is another important facet of the pathophysiology of COPD. External oxidants are found in cigarette smoke, whereas the products of the inflammatory process result in intrinsic oxidants. Not only may oxidants cause direct parenchymal damage, but oxidative stress indirectly fuels further inflammation and protease activity.

Cigarette smoking, the most significant risk factor for the development of COPD, exerts its effects at multiple points in the inflammatory cascade of COPD, negatively affecting both the protease to antiprotease and oxidant to antioxidant balances. Although smoking cessation slows the progression of the disease, it does not end the chronic inflammatory process within the airways, indicating that mechanisms independent of smoking are involved.[9] Moreover, although a majority of COPD patients have a significant smoking history, only a minority of smokers ever develop airflow limitation. This suggests the importance of other factors, both environmental and genetic.[1] Other identified causative factors include heavy occupational exposure to dusts and air pollution from indoor cooking, particularly in the developing world.[10-12] Long-term passive exposure to tobacco smoke and urban air pollution also appear to be contributory.[13,14] Although there is an association between early childhood lower respiratory tract infections and later development of COPD, a causal relationship is less certain.

Compensatory physiologic responses in COPD vary according to the balance of underlying pathologic derangements seen in individual patients. In a minority of patients, ventilatory drive is increased to maintain a near normal partial pressure of oxygen (Po_2), preventing any cyanosis. The resultant tachypnea may also cause a slightly low partial pressure of carbon dioxide (Pco_2). In patients with relatively normal blood gases, pulmonary hypertension and cor pulmonale may not occur until very late in the course of the disease.

Although the precise mechanisms are ill-defined, the pathologic processes of COPD extend beyond the cardiac and pulmonary systems. The effects of circulating inflammatory mediators, oxidative stress, and protease-antiprotease imbalance may be responsible for the weight loss, muscular wasting, metabolic derangements, and depression often seen in the later stages of disease. These features of COPD are partly responsible for the influence of COPD as a comorbid illness, even when the presenting complaint is nonpulmonary. COPD influences a variety of management decisions in the emergency department (ED), ranging from the choice of agents for procedural sedation and rapid sequence intubation to the appropriate disposition of patients with nonpulmonary diagnoses.

Staging the Severity of Disease

Most classifications of disease severity are based on quantitative measurements of airflow limitation, such as the forced expiratory volume in 1 second (FEV_1) and FEV_1/forced vital capacity (FVC) ratio. These indices are measured after any *reversible* airflow limitation is addressed by treatment with bronchodilator medications. The GOLD collaborators define four stages, beginning with a mild stage (stage I), when spirometry is abnormal but symptoms may not yet be apparent, and ending in very severe COPD (stage IV), when FEV_1 is less than 30% of predicted (Table 74-1). Frequent exacerbations are usually seen when the FEV_1 falls below 50% predicted (stages III and IV).[4,15,16]

Table 74-1 The GOLD Classification of Severity of Chronic Obstructive Pulmonary Disease (COPD)

STAGE	CHARACTERISTICS
I: Mild COPD	$FEV_1/FVC < 70\%$ $FEV_1 \geq 80\%$ of predicted Symptoms may or may not be present
II: Moderate COPD	$FEV_1/FVC < 70\%$ $50\% \leq FEV_1 < 80\%$ predicted Usually symptomatic with SOB on exertion or acute exacerbations or both
III: Severe COPD	$FEV_1/FVC < 70\%$ $30\% \leq FEV_1 < 50\%$ predicted Increasingly symptomatic with frequent exacerbations and deleterious effects on quality of life
IV: Very severe COPD	$FEV_1/FVC < 70\%$ $FEV_1 < 30\%$ of predicted or $FEV_1 < 50\%$ with chronic respiratory failure ($Pao_2 <$ 60 mm Hg ± $Paco_2 >$ 50 mm Hg) May or may not have clinical signs of right-sided heart failure

Adapted from Rabe K, Hurd S, Anzueto A, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 176:532, 2007.

FEV_1, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *$Paco_2$*, arterial partial pressure of carbon dioxide; *Pao_2*, arterial partial pressure of oxygen; *SOB*, shortness of breath.

Acute Exacerbations

Unlike asthma exacerbations, COPD exacerbations are not necessarily associated with major reductions in peak flow and FEV_1 measurements. As with COPD itself, the definition of an acute exacerbation is imprecise and relies on clinical parameters that are often subjective. The definition adopted by the GOLD collaborators is "an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant change in regular medication in a patient with underlying COPD."

As with asthma, viral infection appears to be a frequent inciting agent in COPD exacerbations. Commonly implicated viruses include rhinovirus, respiratory syncytial virus, coronavirus, and influenza virus.[17-19] Exacerbations associated with a viral cause are longer and more severe than those without an apparent inciting agent.[18,20]

Controversy remains regarding the role of bacterial pathogens in acute exacerbations of COPD, because the evidence for the role of bacteria in the pathogenesis remains indirect. Almost half of all exacerbations are associated with negative cultures for the typical respiratory pathogens, such as *Haemophilus influenzae, Streptococcus pneumoniae, Moraxella (Branhamella) catarrhalis,* and *Pseudomonas aeruginosa.* In addition, these organisms are recovered from the tracheobronchial tree of patients in their chronic, steady state,

www.ketabpezeshki.com 66485457-66963820

suggesting that bacteria may play a more important role in the pathogenesis of chronic COPD than in acute exacerbations.[21] Although molecular typing shows that recent colonization with new serotypes of the common pathogens is associated with an exacerbation, there is a possibility that this relationship is not causal. Experimental evidence of specific immunologic responses to bacteria in exacerbations suggests, however, that they do play a significant role.[22,23]

Environmental factors, such as air pollution, are also implicated in COPD exacerbations. Indirect evidence for this relationship is largely derived from hospitalization rates for exacerbations during periods of increased air pollution.[24] Finally, in as many as one third of all COPD exacerbations, no specific cause can be identified.

In addition to having acute exacerbations, patients with COPD may experience worsening symptoms because of comorbid conditions, such as pneumonia, congestive heart failure (CHF), pneumothorax, pulmonary embolism (PE), lobar atelectasis, pleural effusion, or dysrhythmias. All of these are associated with COPD and may mimic or coexist with an acute exacerbation.

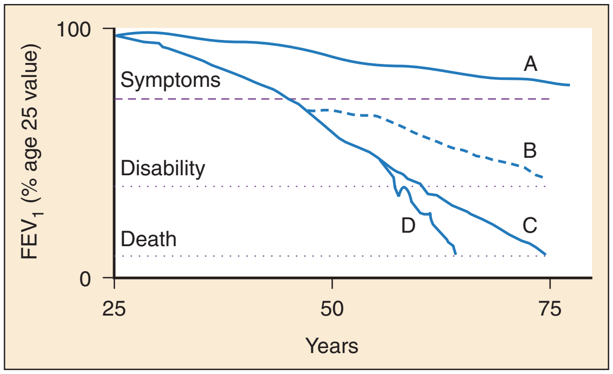


Figure 74-1. The progression of chronic obstructive pulmonary disease (COPD) over time. Natural history of COPD as measured by forced expiratory volume in 1 second (FEV_1) as a percentage of the baseline value at age 25. Normal nonsmoking individuals **(A)** have a progressive loss of FEV_1 but never become symptomatic with airway obstruction. Patients with COPD who quit smoking **(B)** experience an FEV_1 decline that parallels a nonsmoking, age-matched person. Patients with progressive COPD **(C)** can develop a loss of FEV_1 that may eventually produce symptoms, disability, and death. Some COPD patients **(D)** have steep declines in lung function during discrete clinical episodes. (From Heffner JE: Chronic obstructive pulmonary disease on an exponential curve of progress. Respir Care 47:586, 2002.)

CLINICAL FEATURES

Symptoms and Natural History

COPD patients have a long premorbid course during which decreases in air flow indices can be measured in the absence of symptoms. Intermittent cough or shortness of breath on exertion may be easily misattributed to poor physical conditioning. Moreover, patients may remain asymptomatic for many years by gradually limiting their activities in proportion to their pulmonary reserve. After several years, a daily productive cough frequently develops, and periods of dyspnea, the cardinal symptom of airflow limitation, increase. The clinical progression of COPD is slow and insidious, with gradual decreases in airflow punctuated by increasingly frequent and debilitating exacerbations. Eventually the patient becomes truly incapacitated by dyspnea on minimal or no exertion. Profound muscle wasting and weight loss and the emergence of cor pulmonale or chronic ventilatory failure are characteristic of end-stage disease. Figure 74-1 depicts the progression of COPD over time.

Physical Examination

The division of patients with COPD into two phenotypes, the "blue bloater" (for the patient with chronic obstructive bronchitis) and the "pink puffer" (for the patient with emphysema), is outdated because many patients with COPD do not conform to these descriptions. Nonetheless, these classic images do highlight some of the important clinical features that may be encountered in the patient with COPD and have implications for management. Most patients have some combination of chronic obstructive bronchitis and emphysema and appear with a mixture of the syndromes described later. The precise identification of which process is predominant is less important than the evaluation of each patient and formulation of a specific treatment plan based on the individual clinical findings. In particular, the degree of chronic hypoxemia and dependence on home oxygen therapy, the presence of cor pulmonale, and evidence of comorbid illness, such as ischemic heart disease, should be determined.

In patients in whom chronic obstructive bronchitis predominates, the findings are those of chronic respiratory failure and cor pulmonale. Little air hunger or anxiety is present, and the combination of polycythemia and hypoxemia creates a plethoric, cyanotic appearance. Cough, as the clinical hallmark of bronchitis, is prominent and, when vigorous, causes expectoration. If acute ventilatory failure is present, the patient's consciousness is clouded. This often is described as "irritable somnolence," and asterixis may be present. Chronic ventilatory failure and cor pulmonale account for the prominent peripheral edema and chronic jugular venous distention. If there is relatively little emphysema, the thoracic anteroposterior diameter is normal, and the diaphragm is not abnormally low. The presence of severe bronchopulmonary secretions is evidenced by scattered rhonchi and rales, especially at both lung bases posterolaterally. These patients often have chronic carbon dioxide (CO_2) retention, requiring close monitoring of oxygen therapy because of their relative dependency on hypoxemic drive for ventilation.

When emphysema predominates, the patient is often thin, anxious, alert and oriented, dyspneic, and tachypneic and uses accessory muscles of breathing. The patient often self-administers positive end-expiratory pressure (PEEP) by using a pursed lip exhalation pattern to increase intraluminal bronchial pressure and provide internal support for bronchial walls that have lost their external support. Such patients usually assume a sedentary existence, chronically hunched forward. Gross lung overinflation occurs, with a low immobile diaphragm and an increased anteroposterior diameter of the thorax. Percussion of the chest reveals hyper-resonance, and auscultation demonstrates diminished breath sounds with faint end-expiratory rhonchi. Despite air hunger caused by the extensive lung parenchyma destruction, the patient maintains adequate oxygen saturation and often has near-normal ABG levels. The heart is small and hypodynamic, and the blood pressure is usually low.

Cardiac examination in a patient with suspected COPD is crucial in the diagnosis of cor pulmonale and coexisting left ventricular failure. A subxiphoid or retrosternal heave suggests chronic right ventricular hypertrophy (RVH), an S_4 suggests decreased left ventricular compliance, an S_3 indicates left ventricular failure, and a holosystolic blowing murmur of tricuspid insufficiency is secondary to right ventricular and tricuspid ring dilation. Accentuation of the pulmonic component of the secondary sound reflects pulmonary hypertension. Chronic visceral congestion causes hepatomegaly, hepatojugular reflux, and sometimes prominent abnormalities of liver function.

www.ketabpezeshki.com 66485457-66963820

DIAGNOSTIC STRATEGIES

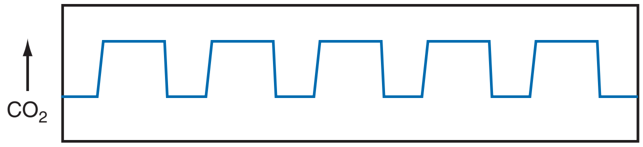
Pulse Oximetry, Arterial Blood Gas Analysis, and Waveform Capnography

Pulse oximetry is part of the evaluation and monitoring of every patient with a COPD exacerbation. Comparison with prior values, both in crisis and in baseline state, helps to interpret measurements obtained during an acute exacerbation. The change in pulse oximetry from baseline or in response to emergency therapy is generally more important than absolute levels.

The stages of COPD severity correlate with arterial gas tensions. Abnormal ventilation-perfusion relationships of COPD produce only modest decrements in arterial partial pressure of oxygen ($Pa{O_2}$) in its early stages (80-100 mm Hg). Later in the course of the disease, hypoxemia below 60 mm Hg stimulates respiratory centers, producing hyperventilation ($P{CO_2}$ over 35) and acute respiratory alkalosis. As pulmonary dysfunction progresses, the work of hyperventilation becomes cost-ineffective—that is, more CO_2 is produced by the effort than is cleared by the increased ventilation. Eventually, alveolar hypoventilation impairs gas exchange, leading to CO_2 retention and acute respiratory acidosis. With renal compensation through bicarbonate retention, the pH normalizes. Finally, when acute ventilatory failure is superimposed at this stage of the disease, an elevated $P{CO_2}$, lowered pH, and elevated bicarbonate are found.

ABG values, once a mainstay of ED evaluation of COPD patients, are of limited value in management of acute COPD episodes. Status and response to therapy often are monitored noninvasively by capnography and pulse oximetry. The presence of respiratory failure unresponsive to therapy (defined as $Pa{O_2}$ <40 mm Hg, $Pa{CO_2}$ >60 mm Hg, and pH <7.25 mm Hg) warrants consideration of admission to an intensive care unit, but clinical evaluation is much more important than any particular blood gas values.[4] When baseline blood gas levels are not available, the usefulness of ABGs is even more limited, and interpretation should be based on the degree of acidemia present, which likely represents the extent of acute CO_2 retention. ABGs should not be used to determine whether a patient requires intubation or noninvasive ventilatory support (NIVS). These decisions should rather be guided by the overall state of the patient, progression of fatigue, comorbid illness, and response to therapy. Patients with very poor blood gas values may do well without intubation or NIVS, but others with mildly disturbed values may require urgent airway intervention. Thus measurement of ABGs should not be performed routinely in the ED and should be undertaken only in response to specific circumstances, such as irregular or apparently unreliable pulse oximetry values or when a single baseline correlation with end-tidal carbon dioxide ($ET{CO_2}$) is desired.

Waveform capnography represents the continuous quantitative measurement of exhaled CO_2. It has emerged as a potential diagnostic and monitoring tool in patients with acute respiratory distress. The appearance of the waveform may assist the clinician in differentiating acute exacerbation of COPD from other causes of acute dyspnea, such as CHF. In patients with obstructed airways, the plateau phase of the waveform typically steepens in proportion to the severity of the obstruction, as depicted in Figure 74-2. Unfortunately, in patients with COPD, the actual end-tidal $P{CO_2}$ measurements obtained from capnography do not correlate well with arterial $P{CO_2}$ measurements, especially in more severe disease. Nonetheless, the patterns and trends from capnography may be helpful in guiding management and assessing response to therapy.[25]



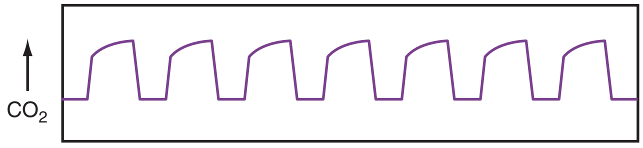


Figure 74-2. Capnography tracing in bronchospasm and obstruction. The upslope at the beginning of the expiratory phase is blunted because of expiratory airflow limitation.

Chest Radiography

In patients who are known to have COPD, the primary role of the chest radiograph is to determine whether there is an acute, treatable cause for clinical deterioration, especially pneumothorax or parenchymal consolidation (atelectasis secondary to mucous plugging, pneumonia, or obstruction by tumor). Otherwise, the chest radiograph is of limited use and may exhibit a range of chronic changes, depending on disease severity and the relative degree of the various pathologic processes. Findings may include hyperinflated lung fields, decreased vascular markings, and a small cardiac silhouette or, in contrast, normal inflation with increased vascular markings and an enlarged heart.[26,27] In cor pulmonale, impingement on the retrosternal airspace by the enlarged right ventricle can be seen on the lateral film.

Bullae may also be present and may mimic or mask a pneumothorax. In addition, chest radiography may reveal important coexistent pathology, including CHF, effusions, and tumors. Routine chest radiography, although challenged, is appropriate in patients with acute exacerbations of COPD.

Forced Expiratory Volume and Peak Expiratory Flow Rate

Pulmonary function tests (PFTs) are more useful in asthma, in which there is a significant reversible component of airway obstruction. In addition, the patient in acute respiratory distress is often unable to cooperate, making testing unreliable. Thus PFTs add little to decision-making in cases of acute COPD exacerbation.

Sputum Examination

During acute exacerbations of bronchitis, sputum may be thicker and grossly purulent, but neither Gram's stain nor culture of sputum is of value in acute COPD exacerbation.

Electrocardiogram and Cardiac Monitoring

The classic descriptions of P pulmonale (peaked P waves in leads II, III, and aVF), low QRS voltage, clockwise rotation, and poor R wave progression in the precordial leads are interesting correlates of COPD but are both insensitive and nonspecific. The presence of electrocardiogram (ECG) criteria for RVH suggests established cor pulmonale. These findings, however, can be easily obscured on the ECG by other processes, and the absence of criteria for RVH cannot be relied on to rule out cor pulmonale.[28]

In severely ill patients or those with concomitant chest pain, continuous ECG monitoring may be helpful, at least for the initial

www.ketabpezeshki.com 66485457-66963820

phase of the patient's evaluation and treatment. ECG monitoring can detect dysrhythmias associated with COPD exacerbations and changes of rate and rhythm in response to therapy. The most common dysrhythmias associated with COPD are atrial tachydysrhythmias, such as atrial fibrillation and multifocal atrial tachycardia. Although atrial fibrillation may require treatment with rate control or conversion, multifocal atrial tachycardia often resolves with the treatment of the COPD exacerbation itself.[29]

Blood Tests

Routine hematologic evaluation adds little to the treatment of the patient with COPD and acute exacerbation. A complete blood count may reveal polycythemia associated with chronic hypoxia. An elevated white blood cell (WBC) count is nonspecific and should not be interpreted as indicative of coexistent infection; nor should a normal-range WBC count support a contention that infection is not present. Elevations in WBCs in COPD are more often related to the hyperadrenergic state of acute dyspnea.

The measurement of B-type natriuretic peptide (BNP) may be useful as a diagnostic adjunct in patients with acute dyspnea. BNP is a naturally occurring peptide that is released by the ventricles in response to volume expansion and stretch. It plays a central role in the neurohormonal response to "unload" the ventricles in CHF through natriuresis, diuresis, vasodilation, and suppression of the renin-angiotensin system. BNP values above 500 pg/mL are suggestive of decompensated heart failure, and levels below 100 pg/mL are very suggestive of the absence of CHF.[30]

Despite the sensitivity of BNP in detecting the physiologic presence of heart failure, its utility as a routine test in the assessment of dyspneic patient is debated. Some data indicate that routine use reduces evaluation times, total costs, and diagnostic accuracy.[31-33] Data on the clinical usefulness of BNP, however, are derived from studies that include patients with clear clinical features of either pulmonary or cardiac disease, casting doubt on its usefulness in the subset of patients who present a true diagnostic dilemma.[34,35] BNP measurements may be helpful in revealing patients with unsuspected CHF, but caution should be exercised to prevent over-reliance on this test (see the discussion of differential considerations).

DIFFERENTIAL CONSIDERATIONS

The differential diagnosis of the acutely dyspneic and hypoxic patient is broad. The condition that is most commonly mistaken for COPD is cardiogenic pulmonary edema, which may manifest with dyspnea and wheezing ("cardiac asthma"). Other serious cardiac causes include myocardial ischemia and pericardial effusion. Important pulmonary diagnoses include pneumothorax, PE, pneumonia, asthma, acute respiratory distress syndrome, bronchiectasis, pulmonary fibrosis, pleural effusions, and tuberculosis. In addition, metabolic acidosis and shock may manifest as dyspnea and ventilatory failure.

In most cases, differentiation of COPD exacerbation from acute CHF can be made on clinical grounds. Nonetheless, a significant percentage of patients who come to the ED with acute dyspnea and an established diagnosis of COPD are ultimately diagnosed with acute CHF despite having no prior history of heart failure. The addition of a BNP assay to the ED evaluation of such patients identifies some in whom a new diagnosis of CHF is not suspected.[33]

Because BNP can be elevated in association with right ventricular stretch, incautious interpretation of an elevated BNP may lead the clinician to favor the diagnosis of acute left-sided CHF and overlook cor pulmonale and PE, both critical considerations in the patient with COPD.[36] Moreover, acute CHF and COPD often coexist, and even severe elevations in BNP do not obviate the identification and treatment of acute pulmonary pathology. Thus, although BNP measurement may be helpful in the evaluation of the acutely dyspneic patient, it cannot be interpreted in isolation and must not supplant clinical judgment.

Acute pneumothorax can occur with COPD. This diagnosis should be actively pursued in patients with worsening respiratory status, especially when its onset is abrupt. In older patients with COPD, chest pain is often absent. A small pneumothorax cannot be excluded by physical examination and can be very difficult to detect on inspiratory chest films, especially in patients with bullous emphysema. Bedside ultrasound is a useful modality for diagnosing pneumothorax in the ED, particularly in major trauma, and may have a future role in diagnosing pulmonary edema.[37,38] In assessing for pneumothorax, however, the presence of COPD may result in false-positive results, and data in this setting are limited.[39] Ultimately, it is appropriate to perform chest computed tomography (CT) when clinical suggestion of a pneumothorax remains high and results of plain films and ultrasound are nondiagnostic.

Patients with COPD are often sedentary and consequently at increased risk for venous thromboembolic disease.[40] The patient with cor pulmonale is at even higher risk because of increased blood viscosity, high peripheral venous pressure, and venous stasis. PE should be considered when an acute exacerbation is more severe than prior episodes, particularly if deterioration occurs quickly with no other apparent cause.[41] Unfortunately, because there is significant overlap in their patterns of presentation, differentiating PE from a COPD exacerbation can be extremely difficult. Prophylactic measures to prevent venous thromboembolic disease are important considerations in the inpatient management of an acute exacerbation of COPD.

A negative screening with a sufficiently sensitive D-dimer assay (enzyme-linked immunosorbent assay [ELISA] or whole-blood agglutination) excludes venous thromboembolic disease in all but high pretest likelihood situations.[42,43] Pretest probability can be assessed via any one of several structured, validated scoring systems. If either the D-dimer is elevated or the pretest probability for PE is high, CT pulmonary angiography should be performed.[44] This requires multislice CT capability and may include indirect CT venography to evaluate the lower extremities for deep vein thrombosis or lower limb duplex ultrasonography.[45-48] A more detailed discussion of the diagnostic evaluation and treatment of PE can be found in Chapter 88.

Lobar atelectasis occurs as a result of mucous plugging of bronchi and can be lethal. Similar to pneumothorax and PE, it may manifest abruptly. The chest film may show linear horizontal streaking or small flarelike shadows; more often, it is normal. Hypoxemic reactive airway patients with a protracted course unresponsive to bronchodilators should be presumed to have either PE or atelectasis. If PE is excluded, such patients often require endotracheal intubation and aggressive interventional pulmonary toilet.

Pneumonia is a common, devastating complication of COPD that leads to mortality in many patients. Its clinical appearance is more muted than the classically described lobar pneumonia of young adults. Classic symptoms of cough, fever, and toxicity are seen less often than the more nonspecific and subtle symptoms of malaise, weakness, decreased activity, and anorexia. Leukocytosis may or may not be present, and its presence should not be taken as indicative of infection because of its low specificity. Radiographic infiltrates may be subtle or absent, especially in patients whose lung parenchyma has been distorted or obliterated by emphysema, and correlation with previous radiographic studies may be necessary.

Rib fractures occur in patients with COPD secondary to trauma, but in patients receiving steroid therapy, they can be caused by vigorous cough alone. When rib fractures are identified, secondary

www.ketabpezeshki.com 66485457-66963820

Box 74-1 Causes of Acute Decompensation in the Patient with Chronic Obstructive Pulmonary Disease

Acute Exacerbations

Infectious

1. Viral
   Rhinovirus, respiratory syncytial virus, coronavirus, influenza virus
2. Bacterial
   Haemophilus influenzae, Streptococcus pneumoniae, Moraxella (Branhamella) catarrhalis, Pseudomonas aeruginosa
3. Atypical bacteria
   Chlamydia pneumoniae, Legionella

Air Pollution

1. Nitrogen dioxide
2. Ozone
3. Particulates, dust

Other Critical Events

1. Pneumothorax
2. Pulmonary embolism
3. Lobar atelectasis
4. Congestive heart failure
5. Pneumonia
6. Pulmonary compression (e.g., obesity, ascites, gastric distention, pleural effusion)
7. Trauma (e.g., rib fractures, pulmonary contusion)
8. Neuromuscular and metabolic disorders
9. Unrelated treatable chronic pulmonary disease (bronchiectasis, tuberculosis, sarcoidosis)
10. Noncompliance with prescribed treatment regimens
11. Iatrogenic
    a. Inadequate therapy
    b. Inappropriate therapy (e.g., deleterious drugs)

pulmonary contusion and pneumothorax also are considered. An intercostal nerve block may relieve enough discomfort to restore baseline pulmonary function.

Electrolyte disturbances, such as hypokalemia, hypomagnesemia, hypocalcemia, or hypophosphatemia, may impair the contractility of muscles.

There are other treatable chronic, nonobstructive pulmonary diseases. For example, bronchiectasis is an often overlooked cause of purulent expectoration. It may accompany and contribute to COPD exacerbations. Although its pathologic characteristic is dilation, not constriction, of airways, the secretions that accompany it may result in an obstructive component. Active tuberculosis is considered in patients with infiltrates (not only apical), a chronic wasting course, and risk factors for active disease, such as human immunodeficiency virus (HIV) disease and homelessness. Sarcoidosis, which can manifest with chronic cough and constitutional symptoms, usually causes a dry cough and may be suggested on the basis of the chest film appearance.

Finally, there are some iatrogenic causes of acute decompensation in COPD. Many agents, such as beta-blockers and cholinergic agents, may directly or indirectly produce bronchospasm. A second group of potentially deleterious drugs is sedatives. It is important not to confuse hypoxic agitation with anxiety because patients with chronic respiratory failure are abnormally sensitive to the respiratory depressant effect of sedatives, and even small doses may significantly worsen hypoventilation.

Box 74-1 summarizes the causes of acute decompensation in the patient with COPD.

MANAGEMENT

Until recently, the only modalities found to alter the progression of COPD and reduce mortality rates were smoking cessation and, for those with severe disease, chronic oxygen therapy.[49,50] Outpatient therapy with long-acting bronchodilators and inhaled steroids may slow the progression of COPD[51] and reduce exacerbation frequency,[52] although the effects are modest. Vaccines are another important aspect of ongoing outpatient care. Although only influenza vaccines reduce mortality,[53] both influenza and pneumococcal vaccinations are recommended for COPD patients.[4] An overview of the emergency assessment and management of COPD exacerbations is provided in Table 74-2.

Table 74-2 General Therapeutic Guidelines for Chronic Obstructive Pulmonary Disease Exacerbations

LIFE-THREATENING	MODERATE OR SEVERE	MILD
Address ABCs	Oxygen to maintain O_2 saturation near 90%	Oxygen to maintain O_2 saturation near 90%
Bag-valve ventilation, preoxygenation	Nebulized beta-agonist, anticholinergic	MDI or nebulized beta-agonist, anticholinergic
Intubation with or without rapid sequence technique	Noninvasive ventilation if severe	Consider oral or intravenous corticosteroid
In-line beta-agonist, anticholinergic	Intravenous corticosteroid	Consider oral antibiotic on discharge
Intravenous corticosteroid	Intravenous antibiotic	
Intravenous antibiotic		

ABC, airway, breathing, and circulation; *MDI,* metered dose inhaler.
It is important to consider an inciting or aggravating factor and provide specific therapy as discussed in text.

Oxygenation and Ventilation

All COPD patients in acute respiratory distress need continuous ECG and pulse oximetry monitoring. Patients who are hypoxemic should receive controlled oxygen therapy, with a goal of oxygen saturation as measured by pulse oximetry (Spo_2) of 88 to 92% or Pao_2 above 60 mm Hg.[54] The method of administration should be tailored to the clinical circumstances: nasal cannulae are well tolerated but are less useful for patients who are markedly tachypneic or mouth-breathing. Venturi masks are excellent for delivering a more reliable, high-flow, and adjustable concentration of supplemental oxygen but may be difficult for a distressed patient to tolerate.

Some patients with moderate to severe COPD and other chronic pulmonary diseases will respond to high-flow supplemental oxygen by developing hypercapnic respiratory failure. The mechanism for this response is debated but may be a result of several factors, including the suppression of hypoxic respiratory drive in patients accustomed to hypercapnia and the release of hypoxic vasoconstriction in poorly oxygenated areas of the lung, worsening ventilation-perfusion mismatch.[55,56] Data from a prospective, randomized clinical trial clearly support setting a specific target of 88 to 92% and avoiding uncontrolled high-flow oxygen in dyspneic COPD patients, including in the prehospital environment.[57]

The patient in terminal ventilatory failure is cyanotic, speechless, lethargic, usually and confused and has gasping, ineffective respirations. Such patients require immediate endotracheal intubation and mechanical ventilation. Because these patients have exhausted all pulmonary reserve, rapid sequence intubation should be performed with the goal of rapid paralysis and unconsciousness (see Chapter 1). For induction and paralysis, a

www.ketabpezeshki.com 66485457-66963820

combination of a hemodynamically stable sedative-hypnotic such as etomidate and a rapidly acting paralytic such as succinylcholine is an appropriate regimen.

Initial ventilator settings should include a fraction of inspired oxygen (FIO_2) of 100%, tidal volume in the 6- to 8-mL/kg range, and respiratory rate of 8 to 10 breaths/min in an assist-control mode with an inspiratory flow rate of 80 to 100 L/min. Sedation and analgesia are indicated to facilitate ventilation. Neuromuscular blockade is not routinely required and should be avoided when possible (see Chapter 1). Increased air trapping and resultant high intra-alveolar pressures induce intrinsic positive end-expiratory pressure (iPEEP) that can cause barotrauma. In addition, increased intrathoracic pressure decreases cardiac filling and output; therefore peak flow pressures and systemic blood pressures must be carefully monitored. If continuous capnography is not available, ABGs should be drawn after 15 to 20 minutes to ensure that ventilation is appropriate. In some settings, placement of an arterial line is helpful for monitoring blood pressure and ABG tensions. After intubation, permissive hypercapnia is essential to the ventilatory treatment of these patients, and subsequent normalization of pH and PCO_2 should be gradual over many hours. Low volume and rate settings will result in hypercapnia and respiratory acidosis, but this approach helps prevent associated barotrauma often seen in treating these patients. Moreover, hyperventilation alkalosis must be scrupulously avoided, particularly because patients may have preexisting chronic metabolic alkalosis. This alkalosis can result in seizures and dysrhythmias, especially with coexisting hypokalemia.

NIVS is an accepted alternative to invasive ventilation in many patients with ventilatory failure (see Chapter 2). NIVS can be highly effective in avoiding intubation, increasing pH, reducing PCO_2 and dyspnea in the first 4 hours of treatment, and reducing mortality rates.[58,59] If the patient fails NIVS and requires intubation, NIVS, at the least, optimizes preoxygenation for the intubation. Patients likely to benefit from NIVS are those with moderate to severe ventilatory failure and elevated PCO_2, but without marked hypoxemia.[60] NIVS cannot substitute for invasive ventilation in patients who are hemodynamically unstable or in whom respiratory arrest appears inevitable. On the opposite end of the spectrum, it remains unclear whether NIVS should be instituted in patients with mild to moderate exacerbations. Although the Cochrane systematic review stresses early NIVS therapy to prevent the development of worsening acidosis and need for intubation, there is insufficient evidence to recommend the routine use of NIVS in mild exacerbations.[59,61] Table 74-3 outlines inclusion and exclusion criteria for the use of NIVS.

NIVS can be delivered by either nasal or full-face mask. It is not uncommon for patients to experience claustrophobia and panic with either type of mask. Coaching and reassurance may help some of these patients tolerate NIVS long enough to feel some relief of their dyspnea and anxiety. Moreover, some patients who do not tolerate nasal masks will tolerate full-face masks, and vice versa. Repeated and prolonged attempts at NIVS, however, in a patient who is panicked and in obvious respiratory failure should not delay definitive airway intervention if necessary.

Modes of ventilation include continuous positive airway pressure (CPAP) and biphasic positive airway pressure (BPAP). Patients with COPD and respiratory distress have significant iPEEP, and this acts as an inspiratory threshold for the patient and increases the work of breathing. Both modes of NIVS help to counteract this iPEEP and thereby decrease the work of breathing. Nasal CPAP is a simple technique, and 5 to 10 cm H_2O pressure is required. When bilevel positive airway pressure (BL-PAP, often referred to as "BiPAP") ventilation, is used, expiratory positive airway pressures are typically set at 2.5 to 5 cm H_2O, whereas inspiratory pressures range from 7.5 to 15 cm H_2O.

Table 74-3 Suggested Selection and Exclusion Criteria for the Use of Noninvasive Ventilatory Support

SELECTION CRITERIA (ONE OR MORE MAY BE PRESENT)	EXCLUSION CRITERIA (ANY MAY BE PRESENT)
Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion	Respiratory arrest
Respiratory rate 25 breaths/min	Cardiovascular instability
Moderate to severe acidosis (pH < 7.35) and hypercapnia ($PaCO_2$ > 45 mm Hg)	Uncooperative patient (agitated or severely somnolent)
	Upper airway obstruction
	High aspiration risk
	Recent facial or gastroesophageal surgery
	Craniofacial trauma, fixed nasopharyngeal abnormalities
	Nonfitting mask

Adapted from Rabe K, Hurd S, Anzueto A, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 176:532, 2007; and Soto F, Varkey B: Evidence-based approach to acute exacerbations of COPD. Curr Opin Pulm Med 9:117, 2003.
$PaCO_2$, arterial partial pressure of carbon dioxide.

Box 74-2 Proposed Indications for Mechanical Ventilation

Respiratory arrest
Worsening level of consciousness despite maximal therapy*
Cardiovascular instability (shock, heart failure)*
NIPPV failure or exclusion criteria (see Table 74-3)
Severe dyspnea with use of accessory muscles and paradoxical abdominal motion*
Severe tachypnea*
Life-threatening hypoxia
Severe acidosis and hypercapnia*
Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotraumas, massive pleural effusion)*

Adapted from Rabe K, Hurd S, Anzueto A, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 176:532, 2007.
NIPPV, nasal intermittent positive-pressure ventilation.
*For several of these parameters, criteria are deliberately imprecise; clinical decisions must be individualized in each case.

If the patient experiences relief of dyspnea, has stronger respirations, and becomes more alert, intubation may be averted, but the patient must be diligently observed for deterioration. Increasing respiratory rate, lethargy, exhaustion, speechlessness, paradoxical abdominal breathing movements, and falling oxygen saturation despite therapy necessitate invasive ventilation.

The most important factor in the decision to intubate is the patient's clinical status, not ABG measurements. Even in the face of a significant rise in PCO_2 with oxygen administration, intubation may be unnecessary if the patient's clinical status has stabilized. Similarly, improving ABG values should not overrule the clinical impression of deterioration. Temporary improvement may be followed by exhaustion and respiratory failure. Box 74-2 outlines indications for invasive mechanical ventilation. Several of these criteria, adapted from the GOLD collaborators, are subject to interpretation, underscoring the critical role of clinical judgment in airway management decisions.

General Drug Therapy

Bronchodilators

Although bronchospasm is not the primary inciting event in acute COPD exacerbation, both beta-agonists and anticholinergic

www.ketabpezeshki.com 66485457-66963820

agents are considered first-line agents. The choice of agent for treating a given patient may depend on the respective side effect profiles of these two classes of drugs.[62,63]

Although many choices are available, inhaled albuterol, which is short acting with selective beta$_2$-receptor action, is the beta-agonist of choice. The nebulization dose of albuterol is 2.5 to 5.0 mg (0.5-1.0 mL of 0.5% solution). Most patients tolerate two to three rapid successive doses of oxygen-nebulized beta-agonist with little difficulty. Therapy must occasionally be titrated if the side effects of tremor, tachycardia, or ventricular ectopy are significant.

Anticholinergic agents block muscarinic receptors and prevent smooth muscle contraction while decreasing the release of secretions from submucosal glands. Inhaled anticholinergic agents are as effective as beta$_2$-agonists in COPD and can be used alone or in conjunction with beta$_2$-agonists as first-line therapy in acute exacerbations.[64] Although evidence regarding the efficacy of their coadministration is controversial, for moderate to severe exacerbations in the ED, these drugs should be given together for their possible synergistic effects.[4] Anticholinergics can be administered by nebulization or metered dose inhaler (MDI) and are also effective for intubated patients. Ipratropium bromide, a quaternary ammonium compound, has been extensively studied in COPD. It has few systemic effects, yet has powerful bronchodilating properties. The nebulization dose is 0.5 mg, which may be repeated every half hour for a total of three doses and subsequently every 4 hours.

Long-acting bronchodilator agents, such as salmeterol (beta$_2$-agonist) and tiotropium (anticholinergic), are added to treatment recommendations for chronic stable COPD.[4] Although these agents may reduce the frequency of COPD exacerbations, no role for their use in ED management of acute exacerbation has been defined.

The COPD patient with a mild to moderate exacerbation may be able to self-administer bronchodilator agents through use of an MDI with a spacer device, which is equally effective as nebulized treatment. Studies also demonstrate the efficacy and cost benefit of MDI therapy over nebulization in acutely hospitalized patients. Because of the smaller dose delivered with single MDI puffs, MDI protocols often involve multiple puffs at each administration interval. This mode of therapy should be considered only for stable, cooperative emergency patients. The intubated patient should receive bronchodilator therapy via in-line nebulization.

Methylxanthines, principally aminophylline, were once commonly used in COPD exacerbations. Evidence is not supportive of their use, however, because they do not improve outcomes, even when combined with beta-agonists and anticholinergic agents. Recommendations that include methylxanthines as a second-line therapy when other modalities have failed are tempered by concerns about toxicity, which may outweigh the positive effects of these agents.[65] If a rare patient is encountered who is taking methylxanthines on a chronic, ambulatory basis, additional methylxanthines should not be used in the course of treatment in the ED.

Corticosteroids

The anti-inflammatory effects of steroids provide a strong rationale for their use in acutely ill patients with COPD. Although steroids may not alter the immediate ED course, evidence points to a modest decrease in the relapse rate of acute exacerbations and improvement of dyspnea.[66-68] For severe exacerbations necessitating admission, intravenous methylprednisolone or oral prednisone (1-2 mg/kg) is given early in treatment and continued daily.[69] Oral prednisone (40 mg once daily) is appropriate for discharged patients. Recommended doses of corticosteroids vary widely in the published studies. Consensus guidelines emphasize use of doses on the lower end of the accepted range to minimize common adverse effects, such as hyperglycemia, myopathy, and immunosuppression.[4,70]

Antibiotics

In contrast to asthma exacerbation and acute bronchitis in the setting of normal lung function, in which antibiotics are of no benefit, some COPD patients with an acute exacerbation appear to benefit from antibiotic therapy.[71-73] The GOLD collaborators recommend administering antibiotics to patients with an increase in sputum purulence and either increased dyspnea or increased sputum volume, as well as to any patients requiring invasive or noninvasive ventilation (see later discussion of pneumonia).[4] Furthermore, some patients may have clinical pneumonia without radiographic evidence, which may also warrant antibiotic therapy. Because the potential benefits of antibiotics outweigh their adverse effects in most patients with acute exacerbations, these agents should be considered in patients in the ED.

Most of the randomized, controlled trials suggesting a treatment benefit with antibiotics were conducted before the emergence of widespread resistance. Amoxicillin, tetracycline, and trimethoprim-sulfamethoxazole were the most common antibiotics used in these studies. Although antibiotics with broader-spectrum coverage, such as the fluoroquinolones and third-generation cephalosporins, are commonly prescribed, the evidence for the superiority of these newer agents is indirect. The GOLD collaborators recommend use of antibiotics that reflect local patterns of antibiotic sensitivity to *S. pneumoniae, H. influenzae,* and *M. catarrhalis.*[4] Studies suggest that short (3- to 5-day) courses of antibiotics, such as respiratory fluoroquinolones or macrolides, may be as effective as more traditional, longer (7- to 14-day) courses of β-lactams and tetracyclines.[74-76]

Other Therapeutic Agents

Mucokinetic Medications and Mucus Clearance Strategies

Mucus production and cough are cardinal symptoms of COPD. Unfortunately, little evidence exists that mucokinetic agents are successful, and they are not recommended. Nebulized saline, oral expectorants, and chest physiotherapy fail to demonstrate benefit.

Respiratory Stimulants

Several respiratory stimulants have been studied in patients with COPD, including opioid antagonists, progesterone, acetazolamide, doxapram, and almitrine. Doxapram appears to be the most effective of these agents. Although doxapram can effect small, temporary improvements in blood gas exchange in the first hours of treatment, it is less effective than other techniques, such as NIVS.[77] Respiratory stimulants are therefore not recommended for routine use in the ED.

Heliox

Helium-oxygen mixtures decrease the work of breathing and improve airflow by virtue of their low density. Such mixtures, however, fail to demonstrate a benefit in either ventilated or nonventilated patients with COPD exacerbations.[78,79]

Other Anti-inflammatory Therapy

Preliminary evidence points to the possibility that other therapeutic strategies may reduce exacerbation frequency via immunomodulatory effects, such as long-term macrolide administration,[80-82] or the use of roflumilast.[83,84] As of yet, however, there does not

www.ketabpezeshki.com 66485457-66963820

Box 74-3 General Guidelines for Admission of the Patient with Chronic Obstructive Pulmonary Disease

Significant worsening of symptoms from baseline
Inadequate response of symptoms to emergency department management
Significant comorbid condition (e.g., pneumonia, heart failure)
Worsening hypoxia or hypercarbia (from baseline)
Inability to cope at home or insufficient home resources

Adapted from Rabe K, Hurd S, Anzueto A, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 176:532, 2007.

appear to be any role for roflumilast in the management of acute exacerbations.

DISPOSITION

Significant deterioration from baseline is the general guideline for admission of patients with COPD. Important factors in the decision include the presence of coexisting conditions, failed outpatient management for the current exacerbation, and lack of improvement while in the ED.[85,86] The GOLD collaborators propose guidelines for admission, and these are adapted in Box 74-3. If the decision is made to discharge the patient, attention should also be directed to the patient's vaccination status, proper technique of inhaler use, evaluation of outpatient support systems, appropriate referrals and, perhaps most important, smoking cessation.[4,72]

KEY CONCEPTS

- BNP can be elevated as a result of right ventricular stretch. The clinician should look beyond left-sided CHF and consider cor pulmonale or pulmonary embolus.
- Beta-agonists, anticholinergics, and corticosteroids are the mainstay of drug therapy for acute COPD exacerbation.
- Noninvasive ventilatory support (NIVS) is an important therapeutic option in the COPD patient with respiratory failure. It has significant advantages over traditional mechanical ventilation and should be considered when significant dyspnea, acidosis, hypercapnia, and elevated respiratory rate are present.
- Acute complications are common aggravating factors and need consideration during evaluation. These include pneumonia, pneumothorax, and pulmonary embolism.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Eisner MD, et al: An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010; 182:693-718.
2. Mathers C, Boerma T, Ma Fate D: *The Global Burden of Disease: 2004 Update*. Geneva: World Health Organization; 2008.
3. Wilson L, Devine E, So K: Direct medical costs of chronic obstructive pulmonary disease: Chronic bronchitis and emphysema. *Respir Med* 2000; 94:204-213.
4. Global Strategy for the Diagnosis, Management and Prevention of COPD: *Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2010*. Available at www.goldcopd.org.
5. Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA: Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161:1608-1613.
6. Centers for Disease Control and Prevention, National Center for Health Statistics: *Health Data Interactive*. Available at www.cdc.gov/nchs/hdi.htm. Accessed May 27, 2011.
7. Hoogendoorn M, Feenstra TL, Hoogenveen RT, Al M, Mölken MR: Association between lung function and exacerbation frequency in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2010; 5:435-444.
8. Barnes PJ: Immunology of asthma and chronic obstructive pulmonary disease. *Nat Rev Immunol* 2008; 8:183-192.
9. Barnes PJ: Chronic obstructive pulmonary disease. *N Engl J Med* 2000; 343:269-280.
10. Balmes J, et al: American Thoracic Society Statement: Occupational contribution to the burden of airway disease. *Am J Respir Crit Care Med* 2003; 167:787-797.
11. Sezer H, Akkurt I, Guler N, Marakoglu K, Berk S: A case-control study on the effect of exposure to different substances on the development of COPD. *Ann Epidemiol* 2006; 16:59-62.
12. Orozco-Levi M, et al: Wood smoke exposure and risk of chronic obstructive pulmonary disease. *Eur Respir J* 2006; 27:542-546.
13. Andersen ZJ, et al: Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: A cohort study. *Am J Respir Crit Care Med* 2011; 183:455-461.
14. Eisner MD, et al: Lifetime environmental tobacco smoke exposure and the risk of chronic obstructive pulmonary disease. *Environ Health* 2005; 4:7.
15. Hurst JR, et al: Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; 363:1128-1138.
16. Celli BR, et al: The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350:1005-1012.
17. Kherad O, et al: Upper-respiratory viral infection, biomarkers, and COPD exacerbations. *Chest* 2010; 138:896-904.
18. Seemungal TA, Harper-Owen R, Bhowmik A, Jeffries DJ, Wedzicha JA: Detection of rhinovirus in induced sputum at exacerbation of chronic obstructive pulmonary disease. *Eur Respir J* 2000; 16:677-683.
19. Greenberg SB, Allen M, Wilson J, Atmar RL: Respiratory viral infections in adults with and without chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 162:167-173.
20. Steer J, Gibson GJ, Bourke SC: Predicting outcomes following hospitalization for acute exacerbations of COPD. *QJM* 2010; 103:817-829.
21. Sethi S, Evans N, Grant BJ, Murphy TF: New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 2002; 347:465-471.
22. Sethi S, Wrona C, Grant BJ, Murphy TF: Strain-specific immune response to *Haemophilus influenzae* in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 169:448-453.
23. White AJ, et al: Resolution of bronchial inflammation is related to bacterial eradication following treatment of exacerbations of chronic bronchitis. *Thorax* 2003; 58:680-685.
24. Anderson HR, et al: Air pollution and daily admissions for chronic obstructive pulmonary disease in 6 European cities: Results from the APHEA project. *Eur Respir J* 1997; 10:1064-1071.
25. Lujan M, et al: Capnometry in spontaneously breathing patients: The influence of chronic obstructive pulmonary disease and expiration maneuvers. *Med Sci Monit* 2008; 14:CR485-CR492.
26. Washko GR: Diagnostic imaging in COPD. *Semin Respir Crit Care Med* 2010; 31:276-285.
27. Takasugi J, Godwin J: Radiology of chronic obstructive pulmonary disease. *Radiol Clin North Am* 1998; 36:29-55.
28. Harrigan R, Jones K: ABC of clinical electrocardiography. Conditions affecting the right side of the heart. *BMJ* 2002; 324:1201-1204.
29. McCord J, Borzak S: Multifocal atrial tachycardia. *Chest* 1998; 113:203-209.
30. Abroug F, et al: Association of left-heart dysfunction with severe exacerbation of chronic obstructive pulmonary disease: diagnostic performance of cardiac biomarkers. *Am J Respir Crit Care Med* 2006; 174:990-996.
31. Mueller C, et al: Use of B-type natriuretic peptide in the management of acute dyspnea in patients with pulmonary disease. *Am Heart J* 2006; 151:471-477.
32. Steg PG, et al: B-type natriuretic peptide and echocardiographic determination of ejection fraction in the diagnosis of congestive heart failure in patients with acute dyspnea. *Chest* 2005; 128:21-29.
33. McCullough PA, et al: Uncovering heart failure in patients with a history of pulmonary disease: Rationale for the early use of B-type natriuretic peptide in the emergency department. *Acad Emerg Med* 2003; 10:198-204.
34. Hohl C, Mitelman B, Wyer P, Lang E: Should emergency physicians use B-type natriuretic peptide testing in patients with unexplained dyspnea? *CJEM* 2003; 5:162-165.
35. Hohl C: Should natriuretic peptide testing be incorporated into emergency medicine practice? *CJEM* 2006; 8:259-261.
36. Collins SP, Ronan-Bentle S, Storrow AB: Diagnostic and prognostic usefulness of natriuretic peptides in emergency department patients with dyspnea. *Ann Emerg Med* 2003; 41:532-545.
37. Volpicelli G, Cardinale L, Garofalo G, Veltri A: Usefulness of lung ultrasound in the bedside distinction between pulmonary edema and exacerbation of COPD. *Emerg Radiol* 2008; 15:145-151.
38. Lichtenstein DA, Mezière GA: Relevance of lung ultrasound in the diagnosis of acute respiratory failure: The BLUE protocol. *Chest* 2008; 134:117-125.
39. Slater A, Goodwin M, Anderson K, Gleeson F: COPD can mimic the appearance of pneumothorax on thoracic ultrasound. *Chest* 2006; 129:545-550.
40. Ambrosetti M, Ageno W, Spanevello A, Salerno M, Pedretti RF: Prevalence and prevention of venous thromboembolism in patients with acute exacerbations of COPD. *Thromb Res* 2003; 112:203-207.
41. Erelel M, Cuhadaroglu C, Ece T, Arseven O: The frequency of deep venous thrombosis and pulmonary embolus in acute exacerbation of chronic obstructive pulmonary disease. *Respir Med* 2002; 96:515-518.
42. Gunen H, Gulbas G, In E, Yetkin O, Hacievliyagil SS: Venous thromboemboli and exacerbations of COPD. *Eur Respir J* 2010; 35:1243-1248.
43. Frost SD, Brotman DJ, Michota FA: Rational use of D-dimer measurement to exclude acute venous thromboembolic disease. *Mayo Clin Proc* 2003; 78:1385-1391.
44. van Belle A, et al: Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA* 2006; 295:172-179.
45. Kavanagh EC, O'Hare A, Hargaden G, Murray JG: Risk of pulmonary embolism after negative MDCT pulmonary angiography findings. *AJR Am J Roentgenol* 2004; 182:499-504.
46. Remy-Jardin M, et al: CT angiography of pulmonary embolism in patients with underlying respiratory disease: Impact of multislice CT on image quality and negative predictive value. *Eur Radiol* 2002; 12:1971-1978.
47. Cham MD, et al: Deep venous thrombosis: Detection by using indirect CT venography. The Pulmonary Angiography–Indirect CT Venography Cooperative Group. *Radiology* 2000; 216:744-751.
48. Ghaye B, Szapiro D, Willems V, Dondelinger RF: Combined CT venography of the lower limbs and spiral CT angiography of pulmonary arteries in acute pulmonary embolism: Preliminary results of a prospective study. *JBR-BTR* 2000; 83:271-278.
49. Stoller JK, et al: Oxygen therapy for patients with COPD: Current evidence and the Long-term Oxygen Treatment Trial. *Chest* 2010; 138:179-187.
50. Anthonisen NR, et al: Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA* 1994; 272:1497-1505.
51. Celli BR, et al: Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: Results from the TORCH study. *Am J Respir Crit Care Med* 2008; 178:332-338.
52. Niewoehner DE, et al: Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: A randomized trial. *Ann Intern Med* 2005; 143:317-326.

www.ketabpezeshki.com 66485457-66963820

53. Schembri S, Morant S, Winter JH, MacDonald TM: Influenza but not pneumococcal vaccination protects against all-cause mortality in patients with COPD. *Thorax* 2009; 64:567-572.
54. O'Driscoll BR, Howard LS, Davison AG; British Thoracic Society: BTS guideline for emergency oxygen use in adult patients. *Thorax* 2008; 63(Suppl 6):vi1-68.
55. Dick C, Liu Z, Sassoon C, Berry R, Mahutte C: O_2-induced change in ventilation and ventilatory drive in COPD. *Am J Respir Crit Care Med* 1997; 155:609-614.
56. Robinson T, Freiberg D, Regnis J, Young I: The role of hypoventilation and ventilation-perfusion redistribution in oxygen-induced hypercapnia during acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161:1524-1529.
57. Austin MA, Wills KE, Blizzard L, Walters EH, Wood-Baker R: Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: Randomised controlled trial. *BMJ* 2010; 341:c5462.
58. Berkius J, Sundh J, Nilholm L, Fredrikson M, Walther SM: Long-term survival according to ventilation mode in acute respiratory failure secondary to chronic obstructive pulmonary disease: A multicenter, inception cohort study. *J Crit Care* 2010; 25:539.e13-18.
59. Ram F, Picot J, Lightowler J, Wedzicha J: Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2004; 1:CD004104.
60. Crummy F, Buchan C, Miller B, Toghill J, Naughton M: The use of noninvasive mechanical ventilation in COPD with severe hypercapnic acidosis. *Respir Med* 2007; 101:53-61.
61. Keenan S, Sinuff T, Cook D, Hill N: Which patients with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation? A systematic review of the literature. *Ann Intern Med* 2003; 138:861-870.
62. McCrory DC, Brown CD: Inhaled short-acting beta2-agonists versus ipratropium for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2001; 2:CD002984.
63. McCrory DC, Brown CD: Anti-cholinergic bronchodilators versus beta2-sympathomimetic agents for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2002; 4:CD003900.
64. Campbell S: For COPD a combination of ipratropium bromide and albuterol sulfate is more effective than albuterol base. *Arch Intern Med* 1999; 159:156-160.
65. Barr R, Rowe B, Camargo C: Methylxanthines for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2003; 2:CD002168.
66. Walters JA, Gibson PG, Wood-Baker R, Hannay M, Walters EH: Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2009; 1:CD001288.
67. Niewoehner D, et al: Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *N Engl J Med* 1999; 340:1941-1947.
68. Aaron SD, et al: Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *N Engl J Med* 2003; 348:2618-2625.
69. Lindenauer PK, et al: Association of corticosteroid dose and route of administration with risk of treatment failure in acute exacerbation of chronic obstructive pulmonary disease. *JAMA* 2010; 303: 2359-2367.
70. Quon BS, Gan WQ, Sin DD: Contemporary management of acute exacerbations of COPD: A systematic review and metaanalysis. *Chest* 2008; 133:756-766.
71. Daniels JM, et al: Antibiotics in addition to systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010; 181:150-157.
72. Celli B, MacNee W: Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23:932-946.
73. Rothberg MB, et al: Antibiotic therapy and treatment failure in patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease. *JAMA* 2010; 303:2035-2042.
74. Anzueto A, Miravitlles M: Short-course fluoroquinolone therapy in exacerbations of chronic bronchitis and COPD. *Respir Med* 2010; 104:1396-1403.
75. El Moussaoui R, et al: Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: A meta-analysis of double-blind studies. *Thorax* 2008; 63:415-422.
76. Grossman RF, Ambrusz ME, Fisher AC, Khashab MM, Kahn JB: Levofloxacin 750 mg QD for five days versus amoxicillin/clavulanate 875 mg/125 mg BID for ten days for treatment of acute bacterial exacerbation of chronic bronchitis: A post hoc analysis of data from severely ill patients. *Clin Ther* 2006; 28:1175-1180.
77. Greenstone M, Lasserson TJ: Doxapram for ventilatory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2003; 1:CD000223.
78. Maggiore SM, et al: A multicenter, randomized trial of noninvasive ventilation with helium-oxygen mixture in exacerbations of chronic obstructive lung disease. *Crit Care Med* 2010; 38:145-151.
79. Rodrigo G, Pollack C, Rodrigo C, Rowe B: Heliox for treatment of exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2002; 2:CD003571.
80. He ZY, et al: Effect of 6 months of erythromycin treatment on inflammatory cells in induced sputum and exacerbations in chronic obstructive pulmonary disease. *Respiration* 2010; 80:445-452.
81. Seemungal TA, et al: Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med* 2008; 178:1139-1147.
82. Albert RK, et al: Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011; 365:689-698.
83. Rabe KF: Roflumilast for the treatment of chronic obstructive pulmonary disease. *Expert Rev Respir Med* 2010; 4:543-555.
84. Calverley PM, et al: Roflumilast in symptomatic chronic obstructive pulmonary disease: Two randomised clinical trials. *Lancet* 2009; 374:685-694.
85. Roche N, Rabbat A, Zureik M, Huchon G: Chronic obstructive pulmonary disease exacerbations in emergency departments: Predictors of outcome. *Curr Opin Pulm Med* 2010; 16:112-117.

www.ketabpezeshki.com 66485457-66963820

Chapter 75

Upper Respiratory Tract Infections

Frantz R. Melio and Laurel R. Berge

PHARYNGITIS (TONSILLOPHARYNGITIS)

Perspective and Principles of Disease

Tonsillopharyngitis (from this point on referred to as *pharyngitis*) is an inflammatory syndrome of the oropharynx. Transmission is mainly through contact with respiratory secretions but can also occur through food and fomite contact. Although most cases of pharyngitis are uncomplicated and self-limited, the associated swelling may threaten airway patency or preclude ingestion of adequate liquids, leading to clinically significant dehydration. Furthermore, a few infectious causes of pharyngitis can also affect other organs, such as the spleen, brain, heart, kidneys, lung, and liver.

Etiology

Viruses are responsible for most cases of pharyngitis in both children and adults. Group A beta-hemolytic *Streptococcus* (GABHS) is the most common bacterial cause of pharyngitis in children, with a peak incidence of 30%. As in adults, non–group A streptococci, *Mycoplasma pneumoniae,* and *Chlamydia pneumoniae* infections are on the rise in pediatric populations.[1-4] In adults, sexually transmitted diseases should be considered, as well.[1-8] Whereas immunization has led to a decline in diphtheria as a cause of pharyngitis, it can result in serious complications and needs to remain in any differential diagnosis.

Mixed aerobic and anaerobic bacteria often cause chronic or recurrent pharyngitis, especially those that produce β-lactamase. Epstein-Barr virus (EBV) and *Actinomyces* are also implicated in chronic or recurrent pharyngitis. Rare causes of bacterial pharyngitis include *Francisella tularensis, Yersinia pestis,* and *Yersinia enterocolitica.*[1,2,5]

Clinical Features

The most common symptom is pharyngeal pain that is aggravated by swallowing and may radiate to the ears. Examination usually reveals fever, pharyngeal erythema, pharyngeal or tonsillar exudate, and tonsillar enlargement (Fig. 75-1). The infection tends to localize to lymphatic tissue and produces suppuration and swelling of the tonsils, along with tender cervical adenopathy. Occlusion of the eustachian tubes may result in secondary otitis media. Clinical differentiation of the causative organisms is virtually impossible.[1,2,5-7]

Viral pharyngitis usually occurs in conjunction with cough, rhinorrhea, myalgia, headache, stomatitis, conjunctivitis, exanthem, and odynophagia. Low-grade fever and pharyngeal exudates may be present. Cervical lymphadenopathy is generally absent.[1,2] Mild pharyngeal edema and erythema associated with a "scratchy" throat are present in 50% of patients with the common cold. Systemic viral infections, including measles, cytomegalovirus (CMV), rubella, and human immunodeficiency virus (HIV), may initially manifest as mild pharyngitis.[1,2,5] HIV and CMV pharyngitis may be clinically indistinguishable from infectious mononucleosis.[1,2]

Influenza occurs in epidemics and is associated with high fever, myalgia, and headache. Although 50 to 80% of patients with influenza experience pharyngeal discomfort, pharyngeal exudate and cervical lymphadenopathy are rare. Adenovirus may cause severe exudative pharyngitis with cervical adenitis similar to that in streptococcal pharyngitis. Thirty percent to 50% of cases of adenoviral pharyngitis are associated with a follicular, usually unilateral, conjunctivitis, and preauricular lymphadenopathy. Coxsackieviruses are the most frequent causes of hand-foot-and-mouth disease and herpangina.[1,2]

Pharyngitis is a common manifestation of infectious mononucleosis (caused by EBV) in young adults.[1,2,5] Symptoms develop after an incubation period of 4 to 7 weeks. Fever and a tonsillar exudate or a membrane (that is cheesy or creamy white) is often present. Cervical as well as generalized lymphadenopathy (90-100%) and splenomegaly (50%) are usually noted, and palatal petechiae may be present. Hepatomegaly is present in 10 to 15% of cases. Periorbital edema and rash are rare findings. In up to 90% of patients with mononucleosis who are given ampicillin or amoxicillin, a diffuse macular rash develops that may be misdiagnosed as an allergic reaction.[1,2]

Patients with early (days to weeks) HIV infection can develop an acute retroviral syndrome. This is manifested by fever, sore throat, generalized nontender lymphadenopathy, a diffuse maculopapular rash, arthralgias, mucocutaneous ulcerations, and, commonly, diarrhea. Nonexudative pharyngitis is present in 50 to 70% of patients. Oral thrush and ulcers may be present. Acute HIV infection can be differentiated from infectious mononucleosis by a more acute presentation, the absence of tonsillar hypertrophy or exudates, the frequent occurrence of rash, and the presence of oral ulcerations.[1]

Herpes simplex infections, which typically affect young adults, also cause pharyngitis and are signaled by the presence of painful vesicles with erythematous bases. Ulcers may be present on the pharynx, lips, tongue, gums, and buccal mucosa. Pharyngeal erythema and exudate, fever, and tender lymphadenopathy are common for 1 to 2 weeks. In an immunocompromised host, large painful ulcers may be present. Herpes pharyngitis can be caused by primary infection or reactivation. Concomitant bacterial superinfection may occur.[1,2]

www.ketabpezeshki.com 66485457-66963820

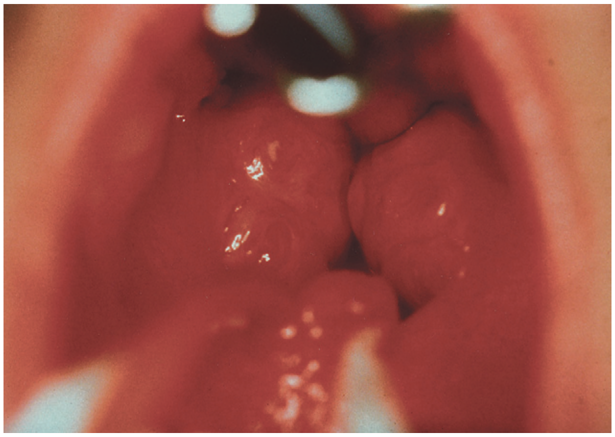


Figure 75-1. Bilateral tonsillopharyngitis.

GABHS pharyngitis is primarily a disease of children 5 to 15 years old and, in temperate climates, occurs in winter and early spring.[1,2] It is responsible for less than 15% of cases of pharyngitis in patients older than 15 years and is rare in patients younger than 3 years. In epidemics, the incidence may double.[1,2] GABHS pharyngitis is associated with sudden-onset sore throat, temperature over 38.3° C (101° F), tonsillar erythema and exudates, palatal and uvular petechiae, uvular edema and erythema, and tender anterior cervical lymphadenopathy. Headache, nausea, vomiting, and abdominal pain may be present, especially in children. Cough, rhinorrhea, coryza, and other viral symptoms are usually absent. GABHS pharyngitis associated with a fine sandpaper erythematous rash that subsequently desquamates is termed *scarlet fever.* These findings, however, cannot be used to reliably diagnose or exclude streptococcal pharyngitis. Patients with recent exposure to others at risk for GABHS pharyngitis or in whom it has been diagnosed are more likely to become infected.[1,2,5-7] Non-GABHS species can cause pharyngitis indistinguishable from GABHS.[1]

Diphtheria is a potentially lethal cause of pharyngitis that is uncommon where adequate vaccinations are administered. U.S. serologic surveys indicate that a large percentage of adults and adolescents lack immunity to diphtheria toxin.[1] After a 2- to 4-day incubation period, patients develop malaise, sore throat, fever, and dysphagia. Examination early in the disease process may reveal pharyngeal erythema and isolated spots of gray or white exudate that later coalesce to form a pseudomembrane. This gray-green pseudomembrane is usually well demarcated and covers the nares, tonsils, soft palate, pharyngeal mucosa, and occasionally the uvula. The membrane may extend to involve the larynx and tracheobronchial tree, leading to hoarseness, cough, stridor, and airway obstruction. Painful cervical lymphadenopathy may be found. Severe inflammation and edema can produce dysphonia and a characteristic "bull neck" appearance. Some strains of *Corynebacterium diphtheriae* produce a systemic toxin that may cause myocarditis, polyneuritis (at first autonomic and then peripheral), vascular collapse, diffuse focal organ necrosis, and death. Asymptomatic carriers may transmit the disease.[1,2] *Corynebacterium ulcerans* is an animal pathogen passed on by consumption of raw milk that can produce infection indistinguishable from that caused by *C. diphtheriae.*

Arcanobacterium haemolyticum typically affects the 10- to 30-year-old age group and can be indistinguishable from streptococcal pharyngitis. Most patients have an associated rash that may be scarlatiniform, urticarial, or erythema multiforme (occasionally, skin manifestations may be the only complaint). Patients report a moderately severe sore throat and are usually nontoxic and afebrile. *A. haemolyticum* may cause a membranous pharyngitis that strongly mimics diphtheria; it is also associated with chronic tonsillitis.[1,2,5]

Anaerobic pharyngitis, or Vincent's angina, is characterized by superficial ulceration and necrosis that often results in the formation of a pseudomembrane. Foul-smelling breath, odynophagia, submandibular lymphadenopathy, and exudate are often present. Patients typically have poor oral hygiene.[5]

Gonococcal pharyngitis is a sexually transmitted disease that may occur independently of genital infection. Those at highest risk are persons who practice receptive oral sex, especially men who have sex with men (in whom the incidence is reported to be as high as 15%). Its severity is variable, and it may result in an exudative or nonexudative pharyngitis. These differing manifestations occur after a lack of symptoms during the latent period of infection. Asymptomatic carriers are described, as is chronic and recurrent pharyngitis. Gonococcal pharyngitis is an important source of gonococcemia.[1,2,5] Syphilitic pharyngitis is a manifestation of primary or late (tertiary) syphilis and manifests with painless mucosal lesions. *Chlamydia trachomatis* pharyngitis is a sexually transmitted disease that manifests similarly to gonococcal pharyngitis and is associated with orogenital sex. Urogenital culturing is necessary, along with treatment of sexual contacts. Patients are usually asymptomatic or may have only mild symptoms.[1,2]

Tuberculous pharyngitis usually occurs in patients with advanced disease. Symptoms and signs include hoarseness and dysphagia with pharyngeal ulcerations. Candidal pharyngitis is usually found in immunocompromised adults. Patients have dysphagia, odynophagia, and adherent white plaques with focal bleeding points.

M. pneumoniae infection usually causes a mild pharyngitis. *Mycoplasma* infection occurs in epidemics and in crowded conditions and can be responsible for approximately 10% of cases of adult pharyngitis. Pharyngeal and tonsillar exudates, cervical lymphadenopathy, and hoarseness are common. Lower respiratory tract infection may also be present.[1,2,5]

C. pneumoniae pharyngitis resembles *M. pneumoniae* pharyngitis. It also occurs in epidemics or crowded conditions. Severe pharyngitis with laryngitis is suggestive of *C. pneumoniae* infection. Swelling and pain in the deep cervical lymph nodes may be prominent. Lower respiratory tract and concomitant sinusitis occur. The hallmarks of chlamydial pharyngitis are recurrence and persistence.[2,5]

Diagnostic Strategies

Monospot test results may be negative in up to 10% of patients with infectious mononucleosis, especially in the early stages of the illness. Immunoglobulin M (IgM) antibodies to EBV capsid antigen develop in 100% of cases. EBV nuclear antigens develop within 3 to 6 weeks and are useful if an initially negative test result becomes positive at a later date. Peripheral blood smears demonstrate atypical mononuclear cells in 75% of patients, with the peak incidence occurring in the second to third week of illness.[1,2] Herpes pharyngitis may be diagnosed by culture, cytopathologic tests on scrapings of lesions, and serologic tests. Enzyme-linked immunosorbent assay testing for HIV can be falsely negative during the first 3 to 4 weeks of illness. During this period of time, quantitative assays for plasma RNA should be performed.[1]

Diagnosis of GABHS infection is important to prevent complications, particularly rheumatic fever. Even the most experienced practitioner has difficulty clinically diagnosing streptococcal pharyngitis.[1,2,5-7] Several authors have proposed scoring systems based on clinical findings,[2,5-7] but the only valid method of determining acute GABHS infection is by use of acute and convalescent antistreptolysin O titers, which is not practical in the emergency department (ED). A single throat culture has a sensitivity of 90 to 95% in detecting *Streptococcus pyogenes* in the pharynx. Variables

www.ketabpezeshki.com 66485457-66963820

that affect the accuracy of throat cultures include collection and culturing technique, as well as the recent use of antibiotics.[1,5-7]

Rapid diagnostic tests for GABHS detect streptococcal antigens. Rapid streptococcal tests (RSTs) have a reported specificity and sensitivity of up to 95%. Sensitivity and specificity in actual practice are lower than in controlled trials.[1] Patients with positive cultures or RSTs may actually be carriers who may not need treatment and are at low risk for transmission and complications. The use of RSTs in patients without clinical findings consistent with GABHS increases false-positive results. A positive RST result seems to reliably indicate the presence of *S. pyogenes* in the pharynx. In contrast, RST results are often negative in the setting of pharyngitis with a low bacterial count (these patients are still at risk for complications, including rheumatic fever). It is recommended that a negative RST result in a child be followed by a confirmatory culture.[1,5-7]

Diagnosis and treatment of GABHS in adults is controversial and the subject of two expert panel recommendations.[5-7] Use of clinical criteria in conjunction with RSTs improves the accuracy of RSTs, adults with negative RST results do not require confirmatory cultures (because of the lower incidence of GABHS infection and the extremely low risk for complications), and neither testing nor antibiotic treatment should be used in patients who are clinically at low risk for GABHS infection. Both panels agree that the most useful clinical criteria for determining GABHS pharyngitis are the Centor criteria (Box 75-1).[5-7]

The position of the Infectious Diseases Society of America is that a positive throat culture or RST result, in addition to clinical symptoms and signs, is needed to confirm the diagnosis of GABHS pharyngitis. The society stresses that clinical criteria alone are appropriate to determine which patients do not need testing but are insufficient, without bacterial confirmation, to diagnose GABHS pharyngitis.[1]

We recommend that any patient with none or only one Centor criterion not be tested or treated; patients with all four criteria should be treated without testing. Patients with two or three criteria should undergo RSTs and should be treated only if they have positive results (Box 75-2).[6,7]

These recommendations apply only to immunocompetent patients with no underlying comorbid conditions or a history of rheumatic fever. They do not apply in settings of outbreaks of GABHS infection or rheumatic fever, nor are they appropriate in situations in which the endemic rate of rheumatic fever is higher than that in the United States. It is important to consider local epidemics and be prepared to revise the approach to treatment if evidence of GABHS infection or complications exists.[5-7] Non–group A streptococcal pharyngitis should also be treated, because

Box 75-1 Centor Criteria for Determining Group A Beta-Hemolytic Streptococcal Pharyngitis

- Tonsillar exudates
- Tender anterior lymphadenopathy or lymphadenitis
- Absence of cough
- History of fever

Box 75-2 Centor Criteria Scoring for Determining Testing and Treatment for Group A Beta-Hemolytic Streptococcal Pharyngitis

Centor Score	Testing and Treatment
0-1	None
2-3	Treatment based on results of rapid streptococcal test results
4	Treat without testing

the same suppurative complications occur as with group A streptococcal pharyngitis. Pharyngitis caused by other treatable organisms should also be considered and is associated with serious complications.[1,2,6] Confirmation of diphtheria requires culturing on the proper media and immunologic testing (polymerase chain reaction). Toxigenicity testing should also be performed.[1,2] The diagnosis of *A. haemolyticum* infection should be considered if rash, including erythema multiforme, accompanies pharyngitis. The diagnosis of Vincent's angina is based on clinical findings and Gram's stain. In cases of possible gonococcal infection, a sample should be plated on Thayer-Martin agar. Tuberculous pharyngitis is diagnosed by acid-fast staining. Syphilitic pharyngitis is diagnosed with darkfield microscopy, direct immunofluorescence, and serologic testing. Candidal pharyngitis is diagnosed by noting yeast on potassium hydroxide preparations of throat swabs or Sabouraud's agar.[2] The diagnosis of mycoplasmal pharyngitis can be confirmed serologically or by culture. Rapid antigen tests for *Mycoplasma* are available. Chlamydial pharyngitis can be diagnosed by serologic testing, by culture, or by antigen detection tests. Studies of patients with chronic pharyngitis find that surface cultures do not correlate well with the causal pathogens, which are often concealed within the tonsillar crypts.

Differential Diagnosis Considerations

The differential diagnosis of adult pharyngitis includes deep space infections, tumors, foreign bodies, pemphigus, Stevens-Johnson syndrome, drug reactions, allergic reactions, uvulitis, angioneuropathic edema, chemical and thermal burns, esophagitis, gastroesophageal reflux disease, cricoarytenoid arthritis, thyroiditis, and epiglottitis.[7]

Management

Patients with pharyngitis should be treated symptomatically with topical anesthetic rinses or lozenges and with acetaminophen or ibuprofen. Oral hydration and saltwater gargles are helpful. Most cases of pharyngitis are self-limited and follow a benign course.[1,5-7] Antibiotics are overused in the treatment of pharyngitis and are not indicated in the vast majority of cases of pharyngitis diagnosed in the United States.

Treatment of infectious mononucleosis is supportive (see Chapter 130). Patients should avoid contact sports for 6 to 8 weeks to minimize the small risk of splenic rupture. Corticosteroids are indicated for patients with tonsillar hypertrophy that threatens airway patency, severe thrombocytopenia, or hemolytic anemia.[1,2] Acyclovir, valacyclovir, or famciclovir is indicated in immunocompromised patients with herpetic pharyngitis and may be beneficial in the treatment of acute herpetic pharyngitis.[1,7] The use of antiretrovirals is indicated in acute HIV infection.[1]

GABHS pharyngitis in children and adolescents should be treated adequately (within 9 days) to prevent rheumatic fever. The incidence of rheumatic fever parallels that of GABHS and has markedly diminished with the use of antibiotics. Patients with mild cases of GABHS pharyngitis may develop rheumatic fever. Rheumatic fever complicates 0.3% of cases of GABHS pharyngitis, but in epidemics the incidence increases to 3%. More troubling is an increase in sporadic outbreaks of rheumatic fever.[5-7] The incidence and course of poststreptococcal glomerulonephritis caused by nephritogenic strains are unaffected by antibiotic therapy.[1,5-7] Antibiotic therapy is extremely effective in eradicating GABHS and its other complications. Untreated, GABHS pharyngitis is a self-limited illness that lasts 3 to 4 days. Early antibiotic treatment of streptococcal pharyngitis leads to a 13% earlier resolution of symptoms and shortens the course of illness by about 1 day. Antibiotic therapy also decreases transmission, and patients are no longer infectious after 24 hours of antibiotic treatment.[1,5-8]

www.ketabpezeshki.com 66485457-66963820

The antibiotic regimen of choice for adults with GABHS pharyngitis is either a single intramuscular injection of 1.2 million units of benzathine penicillin or a 10-day course of penicillin V, 500 mg orally twice a day. Less frequent administration is less effective in preventing rheumatic fever.[1,5-7] Intramuscular penicillin may be more effective than oral penicillin and ensures compliance, but allergic reactions are more severe as a result of procaine allergy, and treatment is more expensive. Penicillin failure usually reflects noncompliance, reinfection, or the presence of β-lactamase–producing organisms. Erythromycin or azithromycin is recommended for patients who are allergic to penicillin. A 1-g total daily dose of erythromycin is given for 10 days, but administration intervals of two, three, and four times a day are equally effective in preventing rheumatic fever. A 5-day course of azithromycin is recommended.[1,5-7] Use of cephalosporins or clindamycin is also acceptable for penicillin-allergic patients. Once-daily amoxicillin therapy may be effective in children.[1,9] Oral cephalosporins or clindamycin should be reserved for patients not responding to penicillin or unable to tolerate either penicillin or erythromycin.[1,5,8,9]

Patients whose symptoms return within a few weeks of treatment may have been noncompliant with oral therapy or may have acquired a new infection (at times from asymptomatic close contacts). Evaluation and treatment should be similar to that of the first episode, with consideration given to treatment with intramuscular penicillin. Further recurrences require more extensive evaluation. Pharyngeal cultures should be obtained and consideration given to evaluating and treating close contacts for GABHS infection.[5]

Although many studies focus on GABHS pharyngitis, proper treatment of nonstreptococcal pharyngitis can also prevent serious complications. Because clinical judgment is insufficient and rapid diagnostic tests are not always accurate and diagnose only GABHS, this disease process is often treated empirically. The choice of antibiotic for the empirical treatment of adult bacterial pharyngitis is not fully elucidated. It is unclear how effective antibiotics are in uncomplicated cases of non-GABHS pharyngitis in adults. Antibiotics may modestly shorten the course of the disease process, but they are also associated with increased recurrence, increased bacterial drug resistance, decreased immune response, and patient expectations for antibiotics with subsequent episodes of pharyngitis.[1,5-8]

Successful treatment of diphtheria is inversely related to the duration of disease. When diphtheria is strongly suspected on the basis of clinical findings, treatment is begun empirically. Airway collapse may occur suddenly and without warning. The mainstay of therapy is antitoxin (a horse serum product), which should be administered immediately on clinical suggestion of diphtheria. The dose of antitoxin varies widely and depends on the site of infection and the duration of symptoms. Antibiotics have little effect on the resolution of systemic toxicity, but they are useful in eradicating *C. diphtheriae* infection and preventing transmission. Infected patients should remain in strict isolation to prevent transmission. The antibiotic of choice is penicillin G for 5 days, followed by penicillin VK for 5 days, or erythromycin 500 mg four times a day for 10 days. A small percentage of patients require an additional 10-day course of erythromycin for persistent infection. Rifampin 600 mg/day for 10 days is also effective in eradicating the carrier state of *C. diphtheriae* and treating erythromycin-resistant diphtheria. Diphtheria toxoid should be administered during convalescence and to unvaccinated close contacts.[1,2,10]

A. haemolyticum may be resistant to penicillin. Erythromycin 250 mg orally four times a day for 10 days is the treatment of choice.[1,2] Vincent's angina is treated with penicillin or clindamycin and rinses with an oral oxidizing agent (hydrogen peroxide).[10] Gonococcal pharyngitis is often more difficult to eradicate than genital infections. Treatment is similar to that for gonococcal urethritis and consists of ceftriaxone (125 mg intramuscularly) with concomitant treatment of chlamydial infection with a single oral dose of 1 g of azithromycin or a course of doxycycline 100 mg orally twice a day for 7 days.[2,10] Oral fluoroquinolones are no longer recommended owing to the high prevalence of gonococcal resistance. Tuberculous pharyngitis is seen with disseminated disease. Patients should be isolated and treated with a multidrug regimen. Pharyngitis caused by primary syphilis is treated with 2.4 million units of benzathine penicillin (long acting), with 14 days of tetracycline or doxycycline used as an alternative. Candidal pharyngitis is treated with systemic fluconazole or itraconazole. Alternative therapy includes nystatin (suspension or tablets) or oral clotrimazole for 14 days. Chronic suppression therapy with ketoconazole, clotrimazole, or fluconazole is usually required for HIV pharyngitis.[10]

M. pneumoniae is treated with erythromycin, tetracycline, or doxycycline for 7 to 14 days.[2,10] Chlamydial pharyngitis is treated with doxycycline, trimethoprim-sulfamethoxazole, or a macrolide antibiotic. *C. pneumoniae* pharyngitis should be treated for 7 to 10 days to prevent treatment failure and recurrence. *C. trachomatis* pharyngitis may require prolonged or repeated courses of antibiotics.[2,10]

Treatment of recurrent or chronic tonsillitis should include β-lactamase–resistant antibiotics active against aerobic and anaerobic organisms. Choices include oral cephalosporins, amoxicillin-clavulanic acid, penicillin with rifampin or metronidazole, and clindamycin.[2]

Steroids given in conjunction with oral antibiotics in adults with acute pharyngitis may significantly shorten the duration of symptoms and provide a greater degree of pain relief without increasing complications. Oral (40-60 mg of prednisone per day for 1-5 days) or intramuscular (a single dose of 10 mg of dexamethasone) administration is equally effective.[11,12]

Disposition

Although most cases of pharyngitis follow a benign course, life-threatening complications can rarely occur. Airway compromise from tonsillar enlargement, local and distant spread of infection, deep neck abscesses, necrotizing fasciitis, sleep apnea, bacteremia, sepsis, and death have been reported but are very rare, given the prevalence of these diseases.[1,5]

Infectious mononucleosis may lead to hepatic dysfunction, splenic injury, neurologic disorders, pneumonitis, pericarditis, and hematologic disorders, including thrombocytopenia and hemolytic anemia.[1,2] Complications of GABHS pharyngitis are both suppurative and nonsuppurative. Suppurative complications include peritonsillar abscess, deep space abscesses, suppurative cervical lymphadenitis, otitis media, sinusitis, mastoiditis, bacteremia, sepsis, osteomyelitis, empyema, meningitis, and soft tissue infections. Nonsuppurative complications include scarlet fever, rheumatic fever, poststreptococcal glomerulonephritis, nonrheumatic perimyocarditis, erythema nodosum, and streptococcal toxic shock syndrome. In contrast to rheumatic fever, other complications of GABHS pharyngitis are increasing in incidence and severity. A chronic carrier state of streptococcal infection exists and can persist for several months despite treatment. Affected patients are asymptomatic, at low risk for rheumatic fever, and not considered highly contagious. Non–group A streptococcal pharyngitis may be complicated by the same suppurative complications as group A infections. Scarlet fever and acute glomerulonephritis, but not rheumatic fever, are linked to group C and G pharyngitis.[1,2,5-7]

LINGUAL TONSILLITIS

Lingual tonsillitis is a rarely diagnosed cause of pharyngitis that predominantly occurs in patients who have had palatine

www.ketabpezeshki.com 66485457-66963820

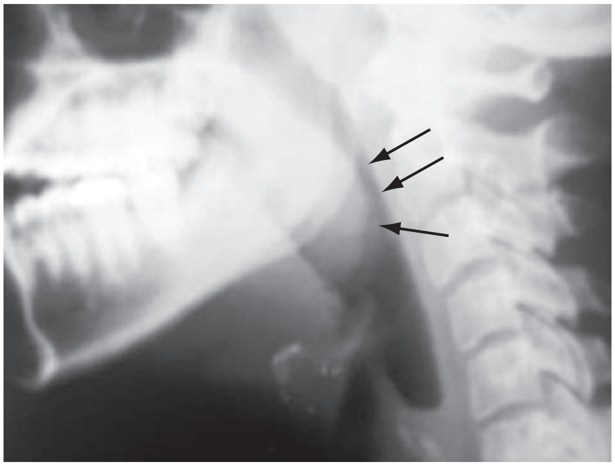


Figure 75-2. Lingual tonsillitis. Notice the scalloped appearance of the lingual tonsil on the anterior surface of the vallecula *(arrows)* with a normal epiglottis and aryepiglottic fold.

tonsils removed. The lingual tonsils are most commonly (size and location are highly variable) located symmetrically on either side of the midline just below the inferior pole of the palatine tonsils and anterior to the vallecula at the base of the tongue. This lymphoid tissue may enlarge after puberty, repeated infection, and tonsillectomy.[13] Patients with lingual tonsillitis have a sore throat that worsens with movement of the tongue (including tongue depression) and phonation. The patient may have a classic "hot potato" voice (the muffled voice one has when eating very hot food) and report feeling a swelling in the throat. Dysphagia, fever, respiratory distress, and stridor may be present. Chronic or recurrent lingual tonsillitis may also cause a chronic cough or sleep apnea. Physical findings often include a normal-appearing pharynx with mild hyperemia. Direct or indirect laryngoscopy reveals an edematous lingual tonsil covered with a purulent exudate. Lateral soft tissue neck films aid in the diagnosis. These films demonstrate a normal-appearing epiglottis and arytenoepiglottic folds, with a scalloped appearance on the anterior surface of the vallecula caused by an enlarged lingual tonsil (Fig. 75-2).[13]

Management includes maintenance of airway patency, antibiotics, and supportive therapy. Rarely, acute lingual tonsillitis may be a life-threatening condition. Airway management includes warmed humidified oxygen, hydration, and corticosteroids. Nebulized epinephrine can relieve the acute respiratory distress and stridor. Antibiotics of choice are similar to those used for the treatment of pharyngitis.[13]

LARYNGITIS

Laryngitis is manifested as hoarseness and aphonia. It is usually caused by viral upper respiratory tract infections. In up to 10% of cases, bacterial infections (including streptococcal infection and diphtheria) may be responsible. Rare causative entities are tuberculosis, syphilis, leprosy, actinomycosis, and fungi. Noninfectious causes include tumors, caustic or thermal injuries, trauma, and esophageal reflux disease.[14,15] Laryngitis generally is a benign viral illness with peak symptoms lasting 3 to 4 days. "Voice rest" often is recommended, but there is no evidence that this is of any benefit in terms of duration or severity of symptoms. Antibiotics are not indicated unless signs of bacterial infection are present.[16] Steroids may hasten resolution of symptoms.[17]

ADULT EPIGLOTTITIS

Perspective

Adult epiglottitis can lead to rapid, unpredictable airway obstruction. The incidence of pediatric epiglottitis has diminished since the introduction of *Haemophilus influenzae* vaccine. At the same time, there has been an apparent increase in adult epiglottitis, possibly because of increased recognition.[1,6,18,19]

Principles of Disease

Adult epiglottitis is a localized cellulitis involving the supraglottic structures, including the base of the tongue, vallecula, aryepiglottic folds, arytenoid soft tissues, lingual tonsils, and epiglottis. Inflammation does not extend to the infraglottic regions. Some adults have a normal epiglottis in the setting of severe supraglottic involvement. The term *supraglottitis* is a more accurate description of this disease process. Adults with epiglottic involvement are prone to epiglottic abscesses.[18,19]

Adult epiglottitis can be caused by many viral, bacterial, or, rarely, fungal pathogens, but the most commonly isolated bacterial pathogen is *H. influenzae* type b.[20] Although it is isolated from only a minority of affected patients, *H. influenzae* infection is associated with a more aggressive disease course. The predominant organisms isolated from epiglottic abscesses are *Streptococcus* and *Staphylococcus* species. Adult epiglottitis may also result from thermal injury.[1,18,19]

Clinical Features

Adult epiglottitis has no age or seasonal prevalence. Males and smokers are more commonly affected. Adults with epiglottitis typically experience a prodrome resembling that of a benign upper respiratory tract infection. The duration of the prodrome is usually 1 to 2 days but may be as long as 7 days or as short as several hours. Patients who have a rapid onset of the disease as well as those with comorbid conditions (especially diabetes) are more likely to require airway intervention.[1,18,19]

Patients typically have dysphagia, odynophagia, and a sore throat. Pain may be severe, and suspicion of epiglottitis is raised when the patient reports severe symptoms of pharyngitis and has obvious odynophagia or dysphagia but examination of the oral pharynx and tonsils shows only minimal or no signs of inflammation or exudate. Ear pain may also be a manifestation of adult epiglottitis. Dysphonia and a muffled voice are common, whereas hoarseness is unusual. Fever is absent in up to 50% of cases and may develop only in the later stages of the disease. Tachycardia disproportionate to fever correlates with severe disease. Tenderness to palpation of the anterior aspect of the neck in the region of the hyoid and when the larynx is moved side to side is a suggestive finding in epiglottitis.[21]

Concomitant uvulitis, pharyngitis, tonsillitis, Ludwig's angina, peritonsillar abscess, and parotitis can occur. Symptoms and signs of imminent airway obstruction may not appear until immediately before complete obstruction occurs. Patients who are unable to swallow their own saliva and are spitting into a cup or drooling should be considered to have impending airway compromise. Patients who assume a classic sniffing position are at imminent risk for rapid airway obstruction. These patients should not be laid flat, and immediate preparations made to rapidly secure the airway (see Chapter 1).[1,18,19]

Diagnostic Strategies

Although severe cases of adult epiglottitis are easily recognized, a large number of less severe cases are initially misdiagnosed.[6]

www.ketabpezeshki.com 66485457-66963820

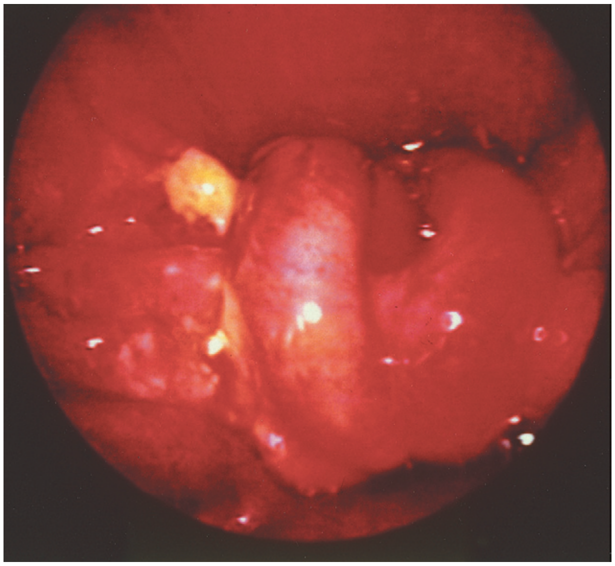


Figure 75-3. Epiglottitis.

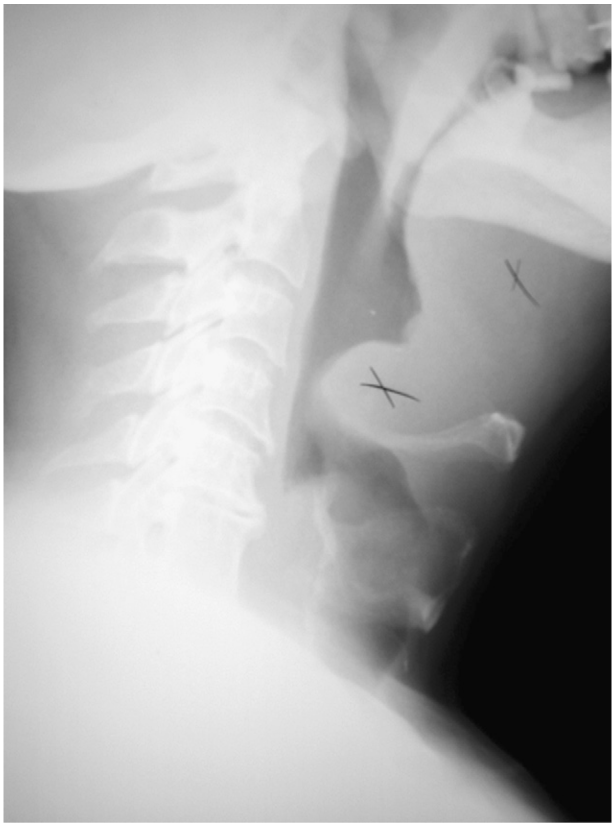


Figure 75-4. Radiograph of epiglottitis.

When epiglottitis is suspected, visualization of the epiglottis is indicated. Although indirect laryngoscopy can be used to assess the epiglottis, it provides a much more limited examination of the upper airway structures than is accomplished via flexible or rigid laryngoscopy, either with a conventional laryngoscope or a videolaryngoscope. Depending on the perceived urgency of the airway examination, preparations should include a drying agent, preferably glycopyrrolate 0.2 mg intravenously (IV), topical anesthesia, such as 4% lidocaine by atomizer (after the glycopyrrolate has reduced secretions), and light sedation (such as midazolam in 1-mg increments, often with small doses [50-µg increments] of fentanyl). Necessary equipment to provide bag-mask ventilation, intubation, or cricothyrotomy must be immediately available. Laryngospasm and complete obstruction can occur during instrumentation of the inflamed airway. Flexible laryngoscopy is the preferred approach as it provides direct, minimally invasive examination of the upper airway and because intubation, if necessary, can be completed over the scope if this was planned in advance. Laryngoscopy reveals a swollen epiglottis and surrounding structures (Fig. 75-3). The epiglottis may appear "cherry red" but is often pale and edematous. In patients with respiratory distress, drooling, aphonia, or stridor, the patient is maintained in his or her chosen position to preserve remaining airway patency. Airway examination is undertaken as soon as equipment has been obtained and requires a "double setup" with the ability to proceed immediately to cricothyrotomy.[1,19]

The primary diagnostic technique for adult epiglottitis is laryngoscopy, as described previously. Although lateral cervical soft tissue radiographic films have a sensitivity of up to 90% when compared with the gold standard of laryngoscopy, radiographs are not a substitute for visualization of the upper airway structures by flexible or rigid laryngoscopy. Patients with severe pain, altered voice, complaints of dyspnea, or inability to swallow secretions should undergo prompt upper airway examination and should not be sent to radiology for x-ray examination. Radiologic findings, when present, include obliteration of the vallecula, swelling of the arytenoids and aryepiglottic folds, edema of the prevertebral and retropharyngeal soft tissues, and "ballooning" of the hypopharynx and mesopharynx. The edematous epiglottis appears enlarged and thumb shaped (Fig. 75-4). An epiglottic width greater than 8 mm or an aryepiglottic fold width greater than 7 mm is suggestive of epiglottitis. Adults with possible epiglottitis and normal soft tissue radiographic films should undergo laryngoscopy, because normal soft tissue plain films do not exclude the presence of adult epiglottitis. Similarly, patients determined to have epiglottitis by radiograph also require upper airway examination by laryngoscopy to determine the extent of airway compromise and the need for intubation.

Differential Diagnosis Considerations

Adult epiglottitis is often misdiagnosed as pharyngitis. Other entities to be considered include mononucleosis, deep space abscesses, lingual tonsillitis, diphtheria, pertussis, and croup. Noninfectious considerations include angioedema, allergic reactions, foreign body aspiration, laryngospasm, tumors, toxic inhalation or aspiration, and laryngeal trauma.

Management

Most adults with epiglottitis do not require intubation, but all patients with epiglottitis should be treated with extreme care because of the possibility of unpredictable sudden airway obstruction. Endotracheal intubation should be performed under direct visualization. Awake flexible endoscopic intubation is the optimal method, but awake orotracheal intubation by direct laryngoscopy or videolaryngoscopy also can be done.[1,19] Blind nasotracheal intubation can lead to airway obstruction and is contraindicated in the setting of epiglottitis.

Antibiotics should be initiated against *H. influenzae* and other likely bacterial pathogens. First-line agents pending culture and sensitivity results are cefotaxime and ceftriaxone. Alternative antibiotics include ampicillin-sulbactam and trimethoprim-sulfamethoxazole.[1,10,11] The role of steroids is unresolved, but racemic epinephrine is used only as a temporizing measure while preparations are made to secure the airway, because short-term use can produce improvement, only to be followed by a "rebound"

www.ketabpezeshki.com 66485457-66963820

effect in which the symptoms and signs revert to their pretreatment level of severity or become even worse.[20]

Disposition

If upper airway endoscopy shows mild or moderate disease with preservation of a widely patent airway, and the patient's symptoms have developed gradually over a long period of time (i.e., 24 hours), treatment with intravenous antibiotics, parenteral opioid analgesia, and humidified oxygen in a monitored inpatient unit (often the intensive care unit [ICU]) or an ED observation unit is appropriate, providing the patient is without dyspnea and is handling his or her secretions. Laryngoscopy is repeated in 6 to 12 hours to ensure that the patient's condition is improving and to determine readiness for discharge. Even with only moderate laryngoscopic findings, in patients with a rapidly progressive course, such as those whose symptoms have increased greatly in severity over 4 to 6 hours, preventative intubation is indicated, as progression of swelling and airway compromise can occur rapidly and with little warning. Intubation also is undertaken despite only moderate findings on laryngoscopy for patients who are immunocompromised or diabetic or who have an epiglottic abscess.[1,18,19] For patients admitted to the hospital, consultation with an otolaryngologist should be arranged.

Extraepiglottic infections are less likely to occur in adults than children. Meningitis, retropharyngeal abscess, pneumothorax, empyema, pneumonia, sepsis, acute respiratory distress syndrome, necrotizing fasciitis, mediastinitis, and pulmonary edema all have been reported, but the vast majority of patients have isolated epiglottitis.

DEEP SPACE INFECTIONS OF THE LOWER PART OF THE FACE AND NECK

Patients with deep space infections of the head and neck (Fig. 75-5) can decompensate rapidly. The incidences and complications of deep space infections have decreased dramatically because of improved dental hygiene and antibiotics.[22]

The submandibular space comprises two spaces: the sublingual and submaxillary spaces. The submandibular space is involved in Ludwig's angina.[23] Five potential communicating spaces in the neck are clinically relevant. The parapharyngeal space contains the carotid artery, the jugular vein, the cervical sympathetic chain, and cranial nerves IX through XII. The retropharyngeal space lies in the midline (medial to the parapharyngeal space) and extends from the base of the skull to the superior mediastinum (at about the level of T2). Retropharyngeal abscesses tend to occur lateral to the midline. Posterior to the retropharyngeal space lies the "danger" space, which extends from the base of the skull to the diaphragm. The prevertebral space extends from the base of the skull to the coccyx. Danger space and prevertebral abscesses are located in the midline. Infections in the retropharyngeal, danger, and prevertebral spaces easily access the mediastinum. There is little anatomic resistance to spread of infection within the fascial planes and spaces, which allows rapid spread of infection and life-threatening complications.[22,24]

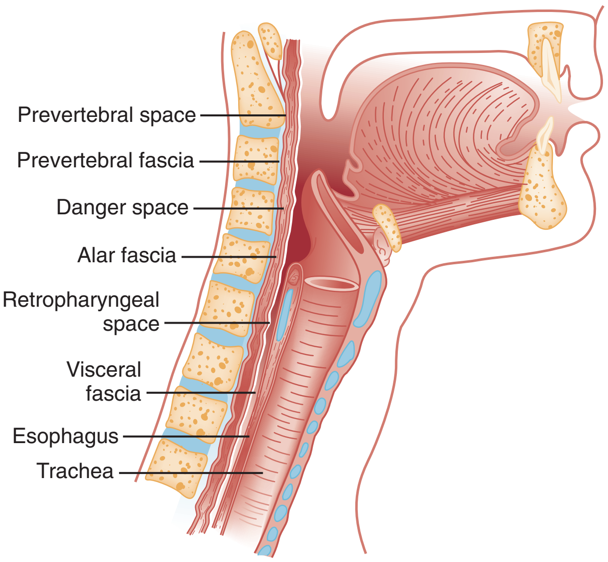


Figure 75-5. Lateral view of the neck showing the relationship of fascia to the prevertebral, "danger," retropharyngeal, and submandibular space.

The primary pathologic process of deep space infection is regional cellulitis. The fasciae may confine infections within their boundaries, thereby leading to abscess formation. Infections are most commonly caused by polymicrobial mixed aerobic-anaerobic oral bacteria. The most frequently isolated organisms are streptococci, staphylococci, and *Bacteroides* species. β-Lactamase–producing organisms are isolated in up to two thirds of cases. Other organisms include *H. influenzae, Pseudomonas aeruginosa, Klebsiella* species, and *Candida albicans.*[22,23,25]

Ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) can help distinguish cellulitis from abscess formation and guide therapy. Patients with cellulitis usually respond well to high-dose antibiotic therapy. Patients with small abscesses can be successfully treated with high-dose intravenous antibiotics or needle aspiration. The presence of a larger abscess, however, usually requires surgical incision and drainage. With the exception of patients with uncomplicated peritonsillar abscesses, patients with deep space abscess usually require admission and intravenous antibiotics, and consultation with otolaryngologists for possible surgical intervention is usually necessary.[26]

Airway distortion and trismus may complicate intubation attempts. Neuromuscular blockade is generally ill-advised, unless as part of a double setup with the ability to proceed directly to cricothyrotomy, because both intubation and bag-mask ventilation may be difficult or impossible. Neuromuscular blockade may not resolve trismus, so use of a neuromuscular blocking agent must be part of a double setup intubation. Awake, flexible endoscopy intubation techniques are preferable.[22,23,27] Blind nasotracheal intubation is contraindicated.[23,27] Should it be necessary to secure an airway surgically, cricothyroidotomy is the procedure of choice, except in some cases of Ludwig's angina, in which anatomic distortion may necessitate tracheostomy.

PERITONSILLITIS (PERITONSILLAR CELLULITIS AND PERITONSILLAR ABSCESS)

Perspective

Peritonsillar cellulitis and abscess should be regarded as the clinical continuum of peritonsillitis. Peritonsillar abscess, also termed *quinsy,* is the most common deep infection of the head and neck in adults.

Principles of Disease

Peritonsillitis may occur as a result of acute tonsillitis. Infection in either Weber's glands or the tonsillar crypts invades the peritonsillar tissues and thereby leads to cellulitis and abscess formation. Fibrous fascial septae divide the peritonsillar space into compartments and direct the infection anteriorly and superiorly.[1,22]

www.ketabpezeshki.com 66485457-66963820

Dental infections, chronic tonsillitis, infectious mononucleosis, smoking, chronic lymphocytic leukemia, and tonsilloliths are predisposing factors. Peritonsillar abscess occurs in patients who have undergone complete tonsillectomy and is seen in all age groups. Peritonsillitis recurs in up to 50% of patients, with the incidence of recurrent peritonsillar abscess approximately 10%. The highest incidence of recurrence is seen in patients younger than 40 years and in those with a history of chronic tonsillitis.

Most peritonsillar abscesses are polymicrobial. β-Lactamase–producing organisms are isolated more commonly in patients who have received prior antibiotics.[1,22]

Clinical Features

There is often a delay of 2 to 5 days between abscess formation and local and systemic symptoms. Symptoms and signs include odynophagia, dysphagia, drooling, trismus, and referred otalgia. Patients may have a characteristic muffled, hot potato voice and rancid breath. Systemic manifestations include fever, malaise, and dehydration. Patients may relate a history of recurrent tonsillitis.

The examination of the pharynx can be limited by trismus. Physical findings of peritonsillitis include inflamed and erythematous oral mucosa, purulent tonsillar exudates that obscure the tonsil, and tender cervical lymphadenopathy. Peritonsillar cellulitis mimics peritonsillar abscess. Peritonsillar abscess is characterized by a greater frequency of drooling, trismus, and dysphagia, whereas peritonsillar cellulitis is more commonly bilateral. The distinguishing feature of peritonsillar abscess is inferior medial displacement of the infected tonsil (at times involving the soft palate), with contralateral deviation of the uvula (Fig. 75-6). The abscess is generally unilateral and located in the superior pole of the tonsil. Bilateral peritonsillar abscesses occur occasionally.[1,22]

Diagnostic Strategies

Aspiration of pus establishes the diagnosis of peritonsillar abscess. Because patients with peritonsillar abscess have a 20% incidence of mononucleosis, laboratory testing for mononucleosis should be considered when systemic symptoms or findings of mononucleosis are present (see Chapter 130.)

Radiographs are of no value when clinical examination identifies peritonsillar abscess. Although contrast-enhanced CT and ultrasonography (both intraoral and transcutaneous) aid in differentiating peritonsillar abscess from cellulitis, especially when patients are unable to cooperate with needle aspiration, these rarely, if ever, are required. Ultrasound, if available, may be useful in guiding needle aspiration.[22,26,28]

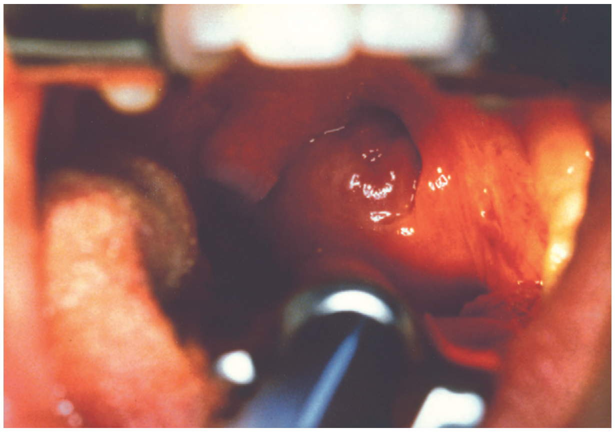


Figure 75-6. Peritonsillar abscess with uvular displacement to the right.

Differential Diagnosis Considerations

The differential diagnosis of peritonsillitis includes hypertrophic tonsillitis, infectious mononucleosis, tubercular granuloma, diphtheria, other deep space infections of the neck, cervical adenitis, congenital or traumatic internal carotid artery aneurysms, foreign bodies, and neoplasms.

Management

Needle aspiration is indicated when abscess is present or suspected. Antibiotics alone may suffice with peritonsillar cellulitis. Regimens include high-dose penicillin plus metronidazole, cefoxitin, ampicillin-sulbactam, and clindamycin. Alternative antimicrobial agents include a carbapenem, high-dose penicillin and rifampin, ticarcillin-clavulanate, or piperacillin-tazobactam.[1,10,22] The use of steroids may also be beneficial.[29]

Drainage of an abscess is usually curative. Needle aspiration of abscesses by both emergency physicians and otolaryngologists is diagnostic (although false-negative aspirations occur in approximately 10% of cases, and another 10% may require repeated aspirations) and therapeutic. This immediately relieves symptoms and is more cost-effective, less painful, and easier to perform than incision and drainage.[1,22,28,29] Intraoral ultrasound-guided needle aspiration is a useful adjunct in the presence of trismus.[28,29]

Disposition

Hospital admission rarely is indicated but is considered for patients who have significant comorbidity, appear toxic, or are unable to tolerate oral fluids or whose pain is not managed by oral analgesics. Most patients can be observed for 4 to 6 hours after aspiration in the ED observation unit or the ED, receiving antibiotics, intravenous hydration, and analgesia. The most dangerous immediate complication of peritonsillitis is pharyngeal obstruction with upper airway compromise. Other complications include sepsis, abscess rupture and pulmonary aspiration leading to pneumonia, empyema, and pulmonary abscess formation. Infection can spread contiguously to the parapharyngeal and retropharyngeal spaces. Ludwig's angina, mediastinal involvement (including mediastinitis, pneumonia, empyema, and pericarditis), myocarditis, carotid artery erosion, jugular vein thrombophlebitis, septic embolization, abscess formation, Lemierre's syndrome (see discussion in parapharyngeal abscess section), and cervicothoracic necrotizing fasciitis can complicate peritonsillitis. Intracranial extension of peritonsillitis may result in meningitis, cavernous sinus thrombosis, and cerebral abscess.[22]

LUDWIG'S ANGINA

Perspective and Principles of Disease

Ludwig's angina is a potentially fulminant disease process that can lead to death within hours.[23,25,30] This is a progressive cellulitis of the connective tissues of the floor of the mouth and neck that begins in the submandibular space. Dental disease is the most common cause of Ludwig's angina. An infected or recently extracted lower molar is noted in most affected patients.[23,25,30] Other causes of Ludwig's angina include a fractured mandible, a foreign body or laceration in the floor of the mouth, tongue piercing, traumatic intubation and bronchoscopy, secondary infections of an oral malignancy, osteomyelitis, otitis media, submandibular sialadenitis, a peritonsillar abscess, a furuncle, an infected thyroglossal cyst, and sepsis.[23,25]

www.ketabpezeshki.com 66485457-66963820

Clinical Features

Infection of the sublingual and submaxillary spaces leads to edema and soft tissue displacement, which may result in airway obstruction. The most common presentation in patients with Ludwig's angina includes dysphagia, odynophagia, neck swelling, and neck pain. Other symptoms and signs include dysphonia, a hot potato voice, dysarthria, drooling, tongue swelling, pain in the floor of the mouth, restricted neck movement, and sore throat. Patients should be questioned regarding recent dental extraction and disease. Rapid development of crepitus and unilateral pharyngitis in patients with recent dental extractions should suggest the diagnosis of Ludwig's angina.[23,25,30]

The most common physical findings in Ludwig's angina are bilateral submandibular swelling and elevation or protrusion of the tongue. Other findings include elevation of the floor of the mouth, posterior displacement of the tongue, and a "woody" consistency of the floor of the mouth. The combination of tense edema and brawny induration of the neck above the hyoid may be present and is described as a "bull neck." Marked tenderness to palpation of the neck and subcutaneous emphysema may be noted. Usually trismus and fever are present, but there is no palpable fluctuance or cervical lymphadenopathy. Tenderness to percussion may be elicited over the involved teeth.[23,25,30]

Diagnostic Strategies

The diagnosis is made clinically. Soft tissue plain films of the neck may confirm the diagnosis by identifying swelling of the affected area and airway narrowing and gas collections but in general are not of value. CT and MRI can identify deep space neck infections and airway compromise. Ultrasonography is also useful in diagnosing abscesses and edema in the setting of Ludwig's angina.[23,25,30]

Differential Diagnosis Considerations

The differential diagnosis includes deep cervical node suppuration, peritonsillar and other deep neck space abscess, parotid and submandibular gland abscess, oral carcinoma, angioedema, submandibular hematoma, and laryngeal diphtheria.

Management

Sudden asphyxiation is the most common cause of death in patients with Ludwig's angina.[25] Stridor, tachypnea, dyspnea, inability to handle secretions, and agitation all suggest impending airway compromise. Flexible endoscopically guided oral or nasal intubation under sedation with topical anesthesia is the preferred method of airway control. Direct laryngoscopy can be particularly difficult because of inability to retract the tongue into the submandibular space, and posterior and cephalad displacement of the tongue by the infection.[25] There is no literature reporting the use of video laryngoscopes in this condition. Cricothyrotomy may be difficult and opens tissue planes that increase the risk of spreading infection into the mediastinum but is the procedure of choice if flexible endoscopic intubation cannot be accomplished.[27]

Emergent high-dose intravenous antibiotic regimens are used as for peritonsillar abscess.[10,25,30] The value of corticosteroids in the setting of Ludwig's angina is unclear. With the exception of dental extractions, surgery is reserved for patients who do not respond to medical therapy and those with crepitus and purulent collections.[23,25,30]

Disposition

The mortality rate associated with Ludwig's angina is less than 10% with early aggressive antibiotic therapy and adequate protection of the airway. Infection can easily spread into other deep spaces of the neck and into the thoracic cavity and cause empyema, mediastinitis, mediastinal abscess, and pericarditis. Aspiration may lead to pneumonia and the formation of lung abscesses. Other complications include internal jugular vein thrombosis, carotid artery infection and erosion, bacteremia and sepsis, pneumoperitoneum, subphrenic abscess, cervicothoracic necrotizing fasciitis, and spontaneous pneumothorax.[23,25,30]

RETROPHARYNGEAL ABSCESS

Perspective and Principles of Disease

Retropharyngeal swelling reflects expansion of the retropharyngeal, danger, or prevertebral space. This discussion refers to infections in these spaces collectively as *retropharyngeal abscesses.*

Retropharyngeal abscess is an uncommon condition that previously was a disease of childhood, with 96% of cases occurring in patients younger than 6 years. Adults are now increasingly affected.[10,26,31] In adult patients, cellulitis develops in the retropharyngeal area.[26] Once the retropharyngeal space is involved, the infection spreads rapidly and an abscess may form. Nasopharyngitis, otitis media, parotitis, tonsillitis, peritonsillar abscess, dental infections and procedures, upper airway instrumentation, endoscopy, lateral pharyngeal space infection, and Ludwig's angina are all implicated in the development of retropharyngeal abscess. Other causes include blunt and penetrating trauma (usually from foreign bodies, commonly fish bones), ingestion of caustic substances, vertebral fractures, and hematologic spread from distant infection.[22,31] Vertebral osteomyelitis and diskitis may lead to infection of the prevertebral space. Danger space infections are caused by extension of infection from either the retropharyngeal or prevertebral space. Underlying systemic disorders (e.g., diabetes and depressed immune system) may predispose individuals to retropharyngeal infections.[22,31]

Retropharyngeal abscesses are most commonly polymicrobial, with a mixture of aerobes and anaerobes. β-Lactamase–producing organisms are present in two thirds of the cases. Tuberculosis is rarely reported in the United States as a cause of retropharyngeal abscess. *Staphylococcus* is the most common cause of pyogenic vertebral osteomyelitis, leading to the formation of retropharyngeal abscess. Disseminated coccidioidomycosis may also cause retropharyngeal abscess.[22,26,31,32]

Clinical Features

Patients typically have a sore throat, dysphagia, odynophagia, drooling, a muffled voice, neck stiffness, neck pain, and fever. Dysphonia is usually present and is described as a duck "quack" *(cri du canard).* Patients may report feeling a lump in the throat. Patients with a retropharyngeal abscess may appear quite ill and generally prefer to hold their necks extended and remain in the supine position. This position keeps the swollen posterior pharynx from compressing the upper airway. Forcing the patient to sit may lead to increased dyspnea.[22,30]

Physical examination may reveal tender cervical lymphadenopathy and cervical musculature, neck swelling, torticollis, and a high fever. Trismus may be present and make visualization of the pharynx difficult. With retropharyngeal cellulitis, diffuse edema and erythema of the posterior pharynx are present.[22,30] Once an abscess has developed, palpation of the pharynx may demonstrate a unilateral mass if the retropharyngeal space is affected and a midline mass if the abscess is in the prevertebral or danger space. Palpation of a fluctuant mass is unreliable and carries a risk of inadvertent rupture. Tenderness on moving the larynx and trachea side to side (tracheal "rock" sign) is commonly present. A retropharyngeal abscess may also cause pain in the back of the neck or

www.ketabpezeshki.com 66485457-66963820

shoulder that is precipitated by swallowing. Cold abscesses (caused by tuberculosis) are characterized by insidious onset, chronicity, constitutional symptoms, and a lower fever. Symptoms disproportionate to the findings should prompt further evaluation.[32]

Diagnostic Strategies

Diagnosis rests on the clinical findings and particularly on lateral cervical radiographs, CT, and MRI. The anteroposterior (AP) diameter of the soft tissue along the anterior bodies of C1-4 should be less than 40% of the AP diameter of the vertebral body just behind it; an increase in this tissue thickness suggests infection or abscess. Soft tissue swelling may be diffuse in the case of cellulitis or more focal if an abscess cavity is present. A pathologic process is suggested if the retropharyngeal space on lateral neck films (measured from the anteroinferior aspect of the second vertebral body to the posterior pharyngeal wall) is wider than 7 mm in both children and adults or the retrotracheal space (measured from the anteroinferior aspect of the sixth vertebral body to the posterior pharyngeal wall) is more than 14 mm in children and 22 mm in adults. True lateral films with the neck fully extended during deep inspiration are the most reliable. Other radiographic findings include reversal of the normal lordosis of the cervical spine, air-fluid levels in the abscess cavity, foreign bodies, and vertebral body destruction.

Plain films may not be sufficiently sensitive to diagnose retropharyngeal abscess. CT or MRI should be performed when doubt persists after plain x-ray examination. These studies not only aid in the diagnosis and differentiation between cellulitis and abscess but also determine the extent of the disease process and the presence of complications (Fig. 75-7).[24,26,32] Ultrasonography is useful for differentiating retropharyngeal cellulitis from retropharyngeal abscess.

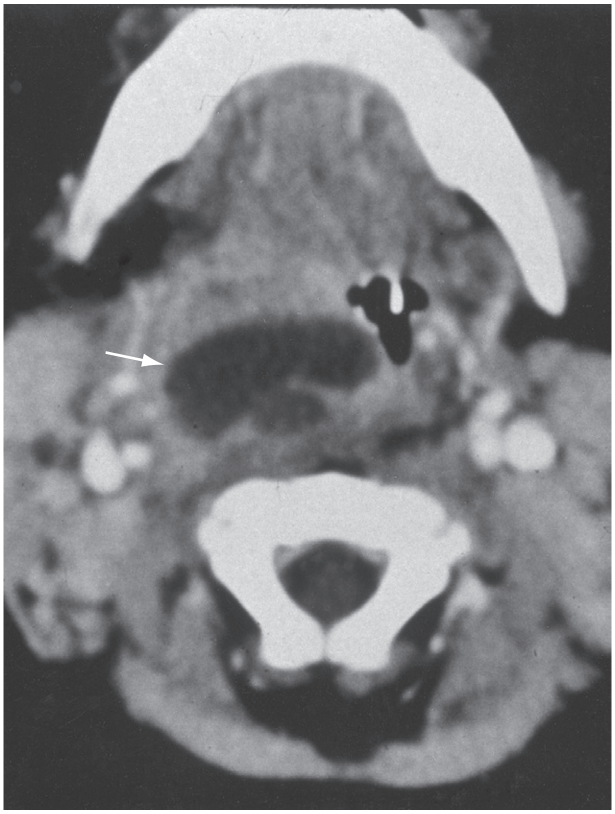


Figure 75-7. Computed tomographic scan demonstrating a right-sided retropharyngeal abscess *(arrow).*

Differential Diagnosis Considerations

The differential diagnosis includes retropharyngeal tumors, foreign bodies, inflammation, hematoma, aneurysms, hemorrhage, lymphadenopathy, and edema. Other considerations include tendinitis of the longus colli muscle and retropharyngeal thyroid tissue.[24]

Management

Patients with retropharyngeal cellulitis are best treated with high-dose intravenous antibiotics. Appropriate regimens are similar to those used for peritonsillar abscess. Tuberculosis and fungal infections also are considered. Resolution of retropharyngeal cellulitis is possible without surgical intervention.[10,22,26,30,32]

In general, retropharyngeal abscesses are treated with antibiotics, in conjunction with operative incision and drainage by an otolaryngologist. In selected cases, retropharyngeal abscesses can be treated successfully with antibiotics alone or in combination with needle aspiration. Tuberculous (cold) abscesses should be drained only extraorally, unless the patient is in acute respiratory distress. Ear, nose, and throat (ENT) and infectious disease consultation is advised when TB is suspected as the causative agent.[26,30,32]

Neck immobilization may be necessary in patients with vertebral body destruction caused by osteomyelitis or atlantoaxial separation. These patients need neurosurgical or orthopedic evaluation and may require fixation.

Disposition

Airway compromise can be caused by anterior displacement of the pharyngeal tissues. Pulmonary complications include abscess rupture with aspiration and subsequent pneumonia, empyema, and asphyxiation. Extension of the infection along tissue planes and through other deep spaces may lead to mediastinitis and mediastinal abscess formation, pericarditis, pleuritis, and empyema. In addition, abscesses may track into the back of the neck and into the axillae. Vascular complications occur from the extension of the retropharyngeal abscess into the lateral pharyngeal space. Atraumatic atlantoaxial separation is caused by damage to the transverse ligament of the atlas from the abscess. These patients may have neurologic symptoms and a widened predental space on plain films, CT scans, or MRI images. Acute transverse myelitis and epidural abscesses also occur, and both can result in quadriplegia. Other complications include internal carotid pseudoaneurysm, erosion into the esophagus and auditory canal, necrotizing fasciitis of the neck, acute respiratory distress syndrome, sepsis, and death.[22,32]

PARAPHARYNGEAL ABSCESS

Perspective

The parapharyngeal space, also known as the *lateral pharyngeal* and *pharyngomaxillary space,* is divided into two compartments by the styloid process. The anterior compartment contains connective tissue, muscle, and lymph nodes. The carotid sheath (which contains the carotid artery, the internal jugular vein, the vagus nerve, cranial nerves IX through XII, and the cervical sympathetic chain) runs in the posterior compartment.[22]

Principles of Disease

Parapharyngeal abscesses are most often polymicrobial infections. Odontogenic and pharyngotonsillar infections are the most common causes of parapharyngeal space abscesses.

www.ketabpezeshki.com 66485457-66963820

Parapharyngeal space infections can also arise by contiguous spread from other surrounding deep neck space infections. Other causes include parotitis, sinusitis, spread from infected neck tumors, infected branchial cleft cysts, suppuration of local lymphadenitis, iatrogenic introduction of organisms during a mandibular nerve block or anesthesia for tonsillectomy, nasal intubation, dental extraction, chronic otitis with cholesteatoma, and mastoiditis.[22]

Clinical Findings

Pain and swelling of the neck are the most common complaints. Odynophagia is present in most patients. A history of an antecedent sore throat may be elicited in some patients. Torticollis caused by irritation of the sternocleidomastoid muscle is also reported.[22]

The classic physical findings of infection involving the anterior compartment of the parapharyngeal space are medial tonsillar displacement and posterolateral pharyngeal wall bulging. Other findings include fever, trismus (caused by irritation of the muscles of mastication), edema, and swelling at the angle of the jaw. An erythematous, tender, nonfluctuant swelling at the angle of the mandible is a consistent finding in patients with an anterior parapharyngeal abscess.[22]

Involvement of the posterior space is associated with many of these same signs. If the anterior compartment is spared, however, little or no trismus occurs. Instead, posterior displacement of the tonsillar pillar and retropharyngeal swelling may be present.[22]

Diagnostic Strategies and Differential Diagnosis Considerations

The diagnosis of parapharyngeal abscess is suggested by the presence of a severe sore throat with the characteristic physical findings. Jugular vein thrombophlebitis that complicates parapharyngeal space infection may be suggested by positive blood cultures. Ultrasonography, CT, and MRI are more useful than lateral radiographs in diagnosing parapharyngeal abscess and its complications. Angiography, Doppler flow studies, and magnetic resonance angiography may also be helpful in evaluating vascular complications.[22,26,33]

The differential diagnosis includes infections in other deep spaces of the neck, tumors and metastatic lymph nodes, thyroiditis, branchial cleft cyst, and carotid artery aneurysms.

Management

Treatment includes high-dose intravenous antibiotics and consultation with an otolaryngologist for surgical drainage. Appropriate antibiotic regimens are those used for peritonsillar abscess. Intravenous antibiotics alone will cure parapharyngeal space infections in patients without abscess.[10,22,26,33,34] Successful resolution of parapharyngeal abscesses with intravenous antibiotics and needle aspiration has been reported.[26,33]

Disposition

Complications of a parapharyngeal abscess include airway obstruction and abscess rupture with subsequent aspiration, pneumonia, and empyema. Infection can spread to surrounding spaces and into the mediastinum and pericardium. Such spread may lead to mediastinitis, mediastinal abscess, pericarditis, myocardial abscess, and empyema. Other complications include osteomyelitis of the mandible, cervicothoracic necrotizing fasciitis, parotid abscess, cavernous sinus thrombosis, and meningitis.[22]

Posterior parapharyngeal space infections are particularly dangerous. These infections may affect the cervical sympathetic chain, carotid artery, or internal jugular vein. Ipsilateral Horner's syndrome and neuropathies of cranial nerves IX through XII may occur. Carotid artery erosion may lead to hemorrhage and the formation of aneurysms. Oral, nasal, and aural warning bleeding is common with carotid artery erosion, with aural bleeding being particularly ominous. Any unexplained bleeding associated with parapharyngeal or other deep neck space infection should be investigated thoroughly. Persistent peritonsillar swelling, despite resolution of the parapharyngeal abscess or a tender unilateral pulsatile mass, may indicate an arterial aneurysm. Aspiration or incision of a carotid artery aneurysm thought to be a parapharyngeal abscess may have disastrous complications.[22]

Involvement of the internal jugular vein may lead to septic thrombosis and Lemierre's syndrome.[1,35] This entity, also called *postanginal septicemia,* affects primarily young healthy patients and is easily confused with right-sided endocarditis or aspiration pneumonia. The manifestation is one of a pharyngitis that initially improves but is then followed by severe sepsis. It is thought that the pharyngeal infection spreads to the parapharyngeal space and causes septic thrombophlebitis of the jugular vein. Patients usually appear ill and are febrile. Metastatic infections involve primarily the lung and are manifested by bilateral nodular infiltrates, pleural effusion, and pneumothorax. Septic arthritis, osteomyelitis, soft tissue cellulitis and abscesses, meningitis, and a vesiculopustular rash are also reported as a result of septic embolization. Leukocytosis and elevated bilirubin and liver function test values, with and without hepatomegaly and jaundice, are often present. Albuminuria, hematuria, and elevations in serum creatinine and blood urea nitrogen are reported. Septic shock rarely develops, although acute respiratory distress syndrome, transient coagulopathies, and hypotension commonly occur. The most frequent cause of this entity is *Fusobacterium* (primarily *Fusobacterium necrophorum*), although *Staphylococcus aureus* is the most common pathogen in intravenous drug users. Treatment consists of parenteral antibiotics (high-dose penicillin or clindamycin) and incision and drainage of abscesses. Jugular vein ligation and resection are necessary in patients with uncontrolled sepsis and respiratory failure caused by repeated septic pulmonary emboli. The value of anticoagulation is unknown.[1,35]

RHINOSINUSITIS

Perspective and Principles of Disease

As sinusitis usually involves the nasal cavity, the term *rhinosinusitis* is preferred. These terms will be used interchangeably in this section.[36,37]

The paranasal sinuses (frontal, maxillary, ethmoid, and sphenoid) are named for the facial bones with which they are associated. Pneumatization may involve other bones but represents extension from the main sinus. The maxillary, anterior ethmoid, and frontal sinuses drain into the medial meatus, located between the inferior and middle nasal turbinates. This area is named the *ostiomeatal complex* and is the focal point of sinus disease. The posterior ethmoid sinus drains into the superior meatus and the sphenoid sinus just above the superior turbinate.[36,37]

A healthy sinus is sterile, depends on a patent ostium with free air exchange, and is reliant on appropriate mucus drainage. Many different processes can result in ostial obstruction and rhinosinusitis, but the most common are viral upper respiratory tract infections and allergic rhinitis. Ciliary abnormality or immobility also inhibits drainage, resulting in sinusitis. Bacteria are introduced into the sinus by coughing and vigorous nose blowing, leading to increased inflammation and bacterial overgrowth. Other factors predisposing to rhinosinusitis include immunocompromised status, nasal septal deviation and other structural abnormalities, nasal polyps, tumors, trauma and fractures, rhinitis medicamentosa, rhinitis secondary to toxic mucosal exposure, barotrauma,

www.ketabpezeshki.com 66485457-66963820

foreign bodies, nasal cocaine abuse, and instrumentation (including nasogastric and nasotracheal intubation).[36,37]

Sinusitis can be classified into acute viral, acute bacterial, chronic, and recurrent acute variations. Approximately 90% of patients with colds have an element of the acute viral form. Acute viral sinusitis may lead to the development of the acute bacterial variety. *Streptococcus pneumoniae*, nontypable *H. influenzae*, and *M. catarrhalis* are the primary pathogens responsible for acute bacterial and recurrent acute sinusitis. *P. aeruginosa* is associated with sinusitis in the setting of HIV infection and cystic fibrosis. Anaerobic bacteria, streptococcal species, and *S. aureus* are more prominent causes of chronic sinusitis. Fungi also have a role in chronic sinusitis. *Rhizopus, Aspergillus, Candida, Histoplasma, Blastomyces, Coccidioides,* and *Cryptococcus* species, as well as other fungi, may cause sinusitis, primarily in immunocompromised hosts. It is important to distinguish infectious from allergic sinusitis. Allergic sinusitis is associated with sneezing, itchy eyes, allergen exposure, and previous episodes.[36-39]

Clinical Features

Frontal sinusitis can cause severe headache localized to the forehead and orbit. Sphenoid sinusitis may cause vague headaches and focal pain almost anywhere in the head. Maxillary sinusitis may be seen with pain over the zygoma, in the canine or bicuspid teeth, or periorbitally. Ethmoid sinusitis can cause medial canthal pain and periorbital or temporal headaches.[36,37,40]

The cardinal findings of acute rhinosinusitis are mucopurulent nasal discharge, nasal obstruction or congestion, and facial pain, fullness, or pressure lasting less than 4 weeks. Other symptoms and signs include postnasal drip (which may lead to coughing), pressure over the involved sinus, malaise, hyposmia, anosmia, fever, maxillary dental pain, and ear fullness or pressure. Acute sinusitis typically progresses over a period of 7 to 10 days and resolves spontaneously. During the first 3 to 5 days of illness, it may be difficult to differentiate acute viral from acute bacterial sinusitis, and antibiotics are not indicated in this phase, as most cases are viral and will resolve without treatment. When symptoms persist beyond 10 days, bacterial sinusitis is more likely, and treatment is indicated. Bacterial origin also is suggested by "double sickening," which refers to patients who improve initially, only to have worsening sinus congestion and discomfort.[36,37,40]

Chronic sinusitis is slow in onset, prolonged in duration (greater than 12 weeks), and recurrent in frequency. Symptoms can be nonspecific but are generally similar to those of acute disease. Symptoms of chronic disease may also include chronic cough, fetid breath, laryngitis, bronchitis, and worsening asthma. Recurrent acute sinusitis is diagnosed when four or more episodes of acute bacterial infection, without its symptoms or signs between episodes, occur per year. The presentation and treatment of recurrent acute disease is similar to that for acute bacterial sinusitis.[36,37,40] Invasive fungal sinusitis (mucormycosis) is an aggressive opportunistic rhinocerebral infection that affects immunocompromised hosts. Mucormycosis *(Rhizopus)* is generally associated with fever, localized nasal pain, and cloudy rhinorrhea. On examination, the affected tissue (usually the turbinates) appears gray, friable, anesthetic, and nonbleeding because of infarction caused by mucormycotic angioinvasion. In advanced cases the affected tissues are necrotic and black, and the infection spreads beyond the sinus.[38,39]

Diagnostic Strategies

Physical examination is best performed after the application of a topical decongestant. Mucosal erythema and edema are usually present. Purulent discharge from the nasal meatus may be observed if the sinus ostia are not completely obstructed. In the setting of acute sinusitis, nasal and nasopharyngeal cultures do not differentiate between acute viral and acute bacterial infections. Culture and biopsy are indicated in suggested chronic, recurrent acute, and fungal sinusitis.[36,37]

For suspected acute sinusitis, routine radiographic examination is not recommended and should be limited to diagnosis of chronic or recurrent acute sinusitis, cases of questionable diagnoses, patients with unresponsive disease, or investigation of complications. Axial and coronal CT is the imaging modality of choice. CT findings suggestive of sinusitis include air-fluid levels, sinus opacification, sinus wall displacement, and mucosal thickening. CT is sensitive, though not specific. Incidental sinus mucosal thickening is seen in 40% of asymptomatic patients, and abnormal CT findings can also be noted in just half of patients with seasonal allergies. CT with intravenous contrast or MRI may be required to evaluate complications of rhinosinusitis and are helpful in determining alternative diagnoses. Sinus endoscopy is another option.[36,37]

Differential Diagnosis Considerations

Rhinitis can be differentiated from sinusitis by the increased response of nasal obstruction to treatment, clear nasal discharge, and absence of pain. Rhinitis does not lead to ostial obstruction, and thus patients do not complain of facial pain. Malignancy, tension headache, vascular headache, foreign body, dental disease, brain abscess, epidural abscess, meningitis, and subdural empyema may also manifest in a manner similar to sinusitis.

Management

Most cases of acute sinusitis are self-limited and resolve spontaneously; therefore management should focus on symptomatic treatment and patient education. The goal of symptomatic treatment should be to reduce patient discomfort and includes appropriate pain management and local decongestant therapy. When allergic symptoms are prominent or the patient has a history of allergic rhinosinusitis, antihistamines, such as loratadine 10 mg daily, are helpful, but antihistamines otherwise are of no value. Sinus self-irrigation with a Neti pot or powered commercial irrigator can be helpful for patients with chronic low-grade symptoms or frequently recurring acute episodes.

Decongestant therapy, available in topical and systemic preparations, can be used to reduce tissue edema, facilitate drainage, and maintain patency of the sinus ostia.[31,36] Topical agents provide more relief than systemic decongestants. Longer-acting agents, such as 0.05% oxymetazoline hydrochloride, which is available in generic forms, are easy to use and highly effective. Topical agents should be used for up to 5 days, as extended use results in rebound vasodilation and nasal obstruction, a condition termed *rhinitis medicamentosa.* Systemic oral adrenergic agonists (e.g., phenylpropanolamine or pseudoephedrine) reduce nasal blood flow and congestion. These medications have no advantage over topical agents and have significant systemic effect, so they should not be used unless the patient is not willing to use topical decongestants. They should not be used in patients with poorly controlled hypertension or patients who are taking tricyclic antidepressants, monoamine oxidase inhibitors, or nonselective beta-adrenergic blockers.[36,37] Topical, but not systemic, steroids are indicated for chronic and allergic sinusitis. Systemic steroids may be indicated in allergic and chronic sinusitis with nasal polyps.[36,38,41]

Saline nasal irrigation is beneficial for treatment of acute bacterial, recurrent acute, and chronic sinusitis and even may be efficacious for the prevention of sinusitis. Hypertonic saline preparations have superior anti-inflammatory properties and may be more effective than normal saline.[36,37]

The choice of antibiotics should consider β-lactamase production and multidrug-resistant pneumococci. High-dose

www.ketabpezeshki.com 66485457-66963820

amoxicillin, 1 g three times a day administered for 7 to 10 days, is still the first-line agent, but benefits are limited, and treatment failures occur in areas with a high percentage of β-lactamase–producing bacteria.[10,36,37] High-dose amoxicillin should be considered for patients who have a child in daycare in the household. Penicillin-allergic patients may be treated with trimethoprim-sulfamethoxazole or a macrolide antibiotic. A 3-day course of trimethoprim-sulfamethoxazole or azithromycin and decongestants may be as effective as the standard 10-day antibiotic course.[36,37]

Failure of symptoms to resolve after 7 days of therapy, or antibiotic usage in the previous 4 to 6 weeks, necessitates a change to a broader-spectrum antibiotic, reassessment of the patient to confirm the diagnosis of acute bacterial sinusitis, and referral to an otolaryngologist. Appropriate management includes a 10- to 14-day course of high-dose amoxicillin-clavulanate, cefuroxime axetil, other second- or third-generation cephalosporins, clindamycin alone or in combination with ciprofloxacin, sulfamethoxazole, azithromycin, clarithromycin, or one of the respiratory fluoroquinolones (levofloxacin, moxifloxacin, gemifloxacin). Metronidazole may be added to any of these regimens to increase activity against anaerobic organisms. Treatment of life-threatening complications requires consultation and high-dose intravenous antibiotics, including cefuroxime, ceftriaxone, one of the respiratory fluoroquinolones, or ampicillin-sulbactam.[10,36,37,42] Patients with chronic sinusitis should be referred to an otolaryngologist. Antibiotics for chronic sinusitis should be effective against anaerobic and β-lactamase–producing bacteria. Antifungals may be beneficial in the treatment of chronic sinusitis.[38,39]

Complications

Frontal or sphenoid sinusitis with air-fluid levels may necessitate hospitalization. A previously healthy, nontoxic patient with good home support can be treated as an outpatient but should return immediately for any symptoms or signs of complications, including severe headache, neurologic changes, or visual changes. Patients who appear toxic, who are immunocompromised, or who have poor home resources require hospital admission and intravenous antibiotics.

Infectious processes of the sinuses can spread to the orbit or central nervous system and can be fulminant. Sinusitis may extend to involve the bones and soft tissues of the face and orbit. Facial and periorbital cellulitis, periorbital abscess, optic neuritis, blindness, and orbital abscess may develop. Patients with orbital complications may have marked swelling, proptosis, decreased ocular motility, and decreased visual acuity. Sinusitis may also lead to intracranial complications. Meningitis, cavernous sinus thrombosis, epidural or subdural empyema, and brain abscess occur. Intracranial involvement may result in headache, decreased sensorium, or focal neurologic deficits and has a rapidly progressive course. Acute fulminant fungal sinusitis requires intravenous antifungal therapy and aggressive surgical débridement.[36,37,39] Complications of mucormycosis are directly related to delay in diagnosis and treatment. This opportunistic fungal infection rapidly progresses to involve the central nervous system and is associated with high morbidity and mortality rates. Sinusitis is associated with an increased incidence of bronchitis and asthma.

KEY CONCEPTS

- A severe sore throat with surprisingly minimal findings on examination of the oropharynx suggests serious soft tissue infection, such as epiglottitis or retropharyngeal abscess.
- Deep space cellulitis is difficult to differentiate from deep space abscess and may require needle aspiration after CT or MRI.
- Patients with upper airway infections should be kept in a position of comfort. Patients with epiglottitis prefer the classic sniffing position, whereas those with a retropharyngeal abscess prefer to lie supine.
- Posterior parapharyngeal abscess may involve the cervical sympathetic chain, carotid artery, or internal jugular vein.
- Posterior to the retropharyngeal space lies the danger space, which extends from the base of the skull to the superior mediastinum at about the level of T2.
- Resolving pharyngitis followed by severe sepsis, right-sided endocarditis, or aspiration pneumonia should suggest septic thrombosis of the internal jugular vein and Lemierre's syndrome.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Alcaide ML, Bisno AL: Pharyngitis and epiglottitis. *Infect Dis Clin North Am* 2007; 21:449.
2. Bisno AL: Acute pharyngitis. *N Engl J Med* 2001; 344:205.
3. Esposito S, et al: Acute tonsillopharyngitis associated with atypical bacterial infection in children: Natural history and impact of macrolide therapy. *Clin Infect Dis* 2006; 43:206.
4. Tiemstra J, Miranda RL: Role of non–group A streptococci in acute pharyngitis. *J Am Board Fam Med* 2009; 22:663.
5. Bisno AL, et al: Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. *Clin Infect Dis* 2002; 35:113.
6. Snow V, et al: Principles of appropriate antibiotic use for acute pharyngitis in adults. *Ann Intern Med* 2001; 134:506.
7. Cooper RJ, et al: Principles of appropriate antibiotic use for acute pharyngitis in adults: Background. *Ann Intern Med* 2001; 134:509.
8. Del Mar CB, Glasziou PP, Spinks AB: Antibiotics for sore throat. *Cochrane Database Syst Rev* 2006; 4:CD000023.
9. Casey JR, Pichichero ME: The evidence base for cephalosporin superiority over penicillin in streptococcal pharyngitis. *Diagn Microbiol Infect Dis* 2007; 57(Suppl 3):39S.
10. Gilbert DN, Moellering RC, Eliopoulos GM, Chambers HF, Saag MS, eds: *The Sanford Guide to Antimicrobial Therapy*, 40th ed. Sperryville, Va: Antimicrobial Therapy Inc; 2010.
11. Marvez-Valls EG, Stuckey A, Ernst AA: A randomized clinical trial of oral versus intramuscular delivery of steroids in acute exudative pharyngitis. *Acad Emerg Med* 2002; 9:9.
12. Bulloch B, Kabani A, Tenenbein M: Oral dexamethasone for the treatment of pain in children with acute pharyngitis: A randomized, double-blind, placebo-controlled trial. *Ann Emerg Med* 2003; 41:601.
13. Allen DM, Hall KN, Barkman HW: Lingual tonsillitis: An uncommon cause of airway compromise responsive to epinephrine [letter]. *Am J Emerg Med* 1991; 9:622.
14. Napierkowski J, Wong RK: Extraesophageal manifestations of GERD. *Am J Med Sci* 2003; 326:285.
15. Joniau S, et al: Reflux and laryngitis: A systematic review. *Otolaryngol Head Neck Surg* 2007; 136:686.
16. Reveiz L, Cardona AF, Ospina EG: Antibiotics for acute laryngitis in adults. *Cochrane Database Syst Rev* 2007; 2:CD004783.
17. Colton RH, Casper JK, eds: *Understanding Voice Problems. A Physiological Perspective for Diagnosis and Treatment*, 2nd ed. Baltimore: Williams & Wilkins; 1996.
18. Berger G, et al: The rising incidence of adult acute epiglottitis and epiglottic abscess. *Am J Otolaryngol* 2003; 24:374.
19. Chang YL, Lo SH, Wang PC, Shu YH: Adult acute epiglottitis: Experiences in Taiwanese setting. *Otolaryngol Head Neck Surg* 2005; 132:689.
20. Sack JL, Brock CD: Identifying acute epiglottitis in adults. High degree of awareness, close monitoring are key. *Postgrad Med* 2002; 112:81.
21. Ehara, H: Tenderness over the hyoid bone can indicate epiglottitis in adults. *J Am Board Fam Med* 2006; 19:517.
22. Brook I: Microbiology and management of peritonsillar, retropharyngeal and parapharyngeal abscesses. *J Oral Maxillofac Surg* 2004; 62:1545.
23. Bansal A, Miskoff J, Lis RJ: Otolaryngologic critical care. *Crit Care Clin* 2003; 19:55.
24. Chong VF, Fan YF: Radiology of the retropharyngeal space. *Clin Radiol* 2000; 55:740.
25. Barakate MS, Jensen MJ, Hemli JM, Graham AR: Ludwig's angina: Report of a case and review of management issues. *Ann Otol Rhinol Laryngol* 2001; 110:453.
26. McClay JE, Murray AD, Booth T: Intravenous antibiotic therapy for deep neck abscesses defined by computed tomography. *Arch Otolaryngol Head Neck Surg* 2003; 129:1207.
27. Ovassapian A, Tuncbilek M, Weitzel EK, Joshi CW: Airway management in adult patients with deep neck infections: A case series and review of the literature. *Anesth Analg* 2005; 100:585.
28. Blaivas M, Theodoro D, Duggal S: Ultrasound-guided drainage of peritonsillar abscess by the emergency physician. *Am J Emerg Med* 2003; 21:155.
29. Johnson RF, Stewart MG: The contemporary approach to diagnosis and management of peritonsillar abscess. *Curr Opin Otolaryngol Head Neck Surg* 2005; 13:157.
30. Srirompotong S, Art-Smart T: Ludwig's angina: A clinical review. *Eur Arch Otorhinolaryngol* 2003; 260:401.
31. Craig FW, Schunk JE: Retropharyngeal abscess in children: Clinical presentation, utility of imaging, and current management. *Pediatrics* 2003; 111:1394.
32. Kamath MP, Bhojwani KM, Kamath SU, Mahabala C, Agarwal S: Tuberculous retropharyngeal abscess. *Ear Nose Throat J* 2007; 86:236.
33. Oh JH, Kim Y, Kim CH: Parapharyngeal abscess: Comprehensive management protocol. *ORL J Otorhinolaryngol Relat Spec* 2006; 69:37.
34. Sichel JY, Dano I, Hocwald E, Biron A, Eliashar R: Nonsurgical management of parapharyngeal space infections: A prospective study. *Laryngoscope* 2002; 112:906.
35. Wang D, et al: Lemierre's syndrome with septic shock caused by *Fusobacterium necrophorum*. *Anaesth Intensive Care* 2007; 35:796.
36. Rosenfeld RM, et al: Clinical practice guideline: Adult sinusitis. *Otolaryngol Head Neck Surg* 2007; 137(Suppl 3):S1.
37. Brook I: Acute and chronic bacterial sinusitis. *Infect Dis Clin North Am* 2007; 21:427.
38. Ponikau JU, Sherris DA, Kita H, Kern EB: Intranasal antifungal treatment in 51 patients with chronic rhinosinusitis. *J Allergy Clin Immunol* 2002; 110:862.
39. Thrasher RD, Kingdom TT: Fungal infections of the head and neck: An update. *Otolaryngol Clin North Am* 2003; 36:577.
40. Young J, et al: Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data. *Lancet* 2008; 371:908.
41. Landsberg R, et al: Systemic corticosteroids for allergic fungal rhinosinusitis and chronic rhinosinusitis with nasal polyposis: A comparative study. *Otolaryngol Head Neck Surg* 2007; 136:252.
42. Snow V, et al: Principles of appropriate antibiotic use for acute sinusitis in adults. *Ann Intern Med* 2001; 134:495.

www.ketabpezeshki.com 66485457-66963820

Chapter 76

Pneumonia

Gregory J. Moran and David A. Talan

PERSPECTIVE

Pneumonia is the seventh leading cause of death and the leading cause of death from infectious disease in the United States.[1] The annual incidence of community-acquired pneumonia (CAP) in the United States ranges from 2 to 4 million, resulting in approximately 500,000 hospital admissions. Most cases of CAP are managed in the outpatient setting and the mortality is low (approximately 1%), but pneumonia necessitating hospitalization is associated with a higher mortality rate (approximately 15%). Pneumonia remains challenging because of an expanding spectrum of pathogens, changing antibiotic resistance patterns, the continued introduction of newer antimicrobial agents, and increasing emphasis on cost-effectiveness and outpatient management.

The epidemiology of CAP is changing. As the percentage of the population older than 65 years continues to increase, the incidence of pneumonia is expected to increase. An increasing number of patients are taking immunosuppressive drugs related to treatment of malignancy, transplantation, or autoimmune disease, resulting in more cases of pneumonia from other opportunistic pathogens. Antibiotic resistance is more common among *Streptococcus pneumoniae* and other pathogens. In addition, the threat exists of respiratory infections caused by biologic terrorism or newly recognized pathogens that have the potential to spread quickly through international travel.

The ability to identify a specific cause of pneumonia during emergency department (ED) evaluation is limited. Even after a thorough inpatient evaluation, a specific pathogen is never identified in many patients with pneumonia. When pneumonia is diagnosed, the priorities in the ED are to initiate appropriate empirical antibiotic therapy based on the most likely pathogens, provide respiratory support, assess disease severity, and recognize the need for hospitalization and intensive care.

PRINCIPLES OF DISEASE

Despite the constant presence of potential pathogens in the respiratory tract, the lungs are remarkably resistant to infection. The alveolar surface of the lungs covers an area of approximately 140 m^2. Approximately 10,000 L of air passes through the respiratory tract each day, and typical ambient air can contain hundreds to thousands of microorganisms per cubic meter. Although the cough and laryngeal reflexes prevent most large particulate matter from entering the lower respiratory tract, aspiration of oropharyngeal contents may be a common occurrence during normal sleep. Despite these hazards, healthy lungs are usually a virtually sterile environment.

The development of clinical pneumonia requires a defect in host defenses, the presence of a particularly virulent organism, or the introduction of a large inoculum of organisms. If the challenge of invading organisms overwhelms host defenses, then microbial proliferation leads to inflammation, an immune response, and clinical pneumonia. If host defenses are weak, then a minimal challenge may lead to the development of pneumonia.

Causative Agents

The challenge with pneumonia is identifying the causative agent rather than making the diagnosis in general. Empirical therapy should be chosen with activity against the spectrum of likely pathogens based on the overall clinical picture.

Difficulty in determining the specific cause of pneumonia exists even with advanced microbiologic and serologic testing that is not generally available during an ED evaluation. In CAP, a microbial cause cannot be determined in approximately half of cases, even after thorough investigation. Among hospitalized adults in whom a pathogen can be identified, organisms such as *S. pneumoniae* and *Haemophilus influenzae,* referred to as "typical" pathogens, account for approximately half of cases. *Legionella, Mycoplasma,* and *Chlamydophila* (previously known as *Chlamydia*) species, referred to as "atypical" pathogens, are also common.[2] Testing for common viral agents reveals a viral cause in approximately 18% of cases, with influenza and parainfluenza viruses being the most common.[3]

Among adults requiring intensive care unit (ICU) admission, *S. pneumoniae* is the most common pathogen, with even higher prevalence among fatal cases. *Legionella* species, *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]), and aerobic gram-negative bacilli also appear to be relatively more common among adults with severe CAP.[4] Atypical organisms, such as *Mycoplasma* species or viruses, account for a relatively higher proportion of pneumonia in patients who have milder illness that is amenable to outpatient therapy.[5] Atypical organisms occur with significant frequency, however, in patients with severe illness requiring hospitalization, particularly because of *Legionella* infection. Coinfection, such as with *Chlamydophila pneumoniae* and *S. pneumoniae,* is also well recognized.

S. pneumoniae is a gram-positive coccus that is the most common cause of CAP in adults requiring hospitalization. It colonizes the nasopharynx in 40% of healthy adults. Although this organism can cause pneumonia in healthy people, patients with a history of diabetes, cardiovascular disease, alcoholism, sickle cell disease, splenectomy, and malignancy or other immunosuppressive illness are at increased risk. A vaccine containing the 23

www.ketabpezeshki.com 66485457-66963820

capsular polysaccharides of pneumococcal types most commonly associated with pneumonia reduces the likelihood of serious pneumococcal infection. It is recommended for people at increased risk because of underlying illness or age older than 65 years.[6] Many ED patients have not received pneumococcal vaccine, and vaccinating eligible patients in this setting seems to be feasible and effective.[7] A 13-valent protein-conjugate pneumococcal vaccine effectively reduces invasive pneumococcal disease and pneumonia in infants and young children.[8]

H. influenzae, the second most frequently isolated organism in CAP among adults, is a pleomorphic gram-negative rod. It is a common pathogen in adults with chronic obstructive pulmonary disease (COPD), alcoholism, malnutrition, malignancy, or diabetes.

S. aureus may be emerging as a more common cause of CAP and has been found more frequently than *H. influenzae* in some recent series. Community-associated strains of methicillin-resistant *S. aureus* (CA-MRSA) are uncommon in CAP but are more likely to cause severe disease.[9] This is often associated with influenza. Staphylococcal pneumonias are often necrotizing, with cavitation and pneumatocele formation. Intravenous drug users may develop hematogenous spread of *S. aureus* that involves both lungs with multiple small infiltrates or abscesses (e.g., tricuspid endocarditis resulting in septic pulmonary emboli).

Klebsiella pneumoniae is a gram-negative rod that rarely causes disease in a normal host and accounts for a small percentage of cases of CAP. It may cause severe pneumonia in debilitated patients with alcoholism, diabetes, or other chronic illness. There is a high incidence of antibiotic resistance because the organism is often hospital acquired.

Mycoplasma pneumoniae is one of the most common causes of CAP in previously healthy patients younger than age 40 years. Another important organism in CAP is *C. pneumoniae,* an intracellular parasite that is transmitted between humans by respiratory secretions or aerosols. Seroprevalence studies indicate that virtually everyone is infected with *C. pneumoniae* at some time and that reinfection is common, particularly in older adults. It accounts for at least 8% of cases, although this is an underestimate owing to difficulty in diagnosing infection with this organism.

At least 30 species of *Legionella* have been isolated since the 1976 convention-related outbreak in Philadelphia, from which the organism derives its name. At least 19 are known human pathogens. *Legionella* is an intracellular organism that lives in aquatic environments. There is no person-to-person transmission. Although it is implicated in point outbreaks related to cooling towers and similar aquatic sources, the organism also lives in ordinary tap water and is underdiagnosed as a cause of CAP. *Legionella* prevalence seems to vary greatly by region.

Lower respiratory infections caused by anaerobic organisms generally result from the aspiration of oropharyngeal contents with large amounts of bacteria. These infections are typically polymicrobial, including *Peptostreptococcus, Bacteroides, Fusobacterium,* and *Prevotella* species. Presentation is often subacute or chronic and may be difficult to distinguish clinically from other causes of pneumonia. Clinical factors that suggest an anaerobic infection include risk factors for aspiration, such as central nervous system depression or swallowing dysfunction, severe periodontal disease, fetid sputum, and the presence of a pulmonary abscess or empyema.

Viral pneumonias are common in infants and young children and are recognized as an important cause of pneumonia in adults. Respiratory syncytial virus and parainfluenza viruses are the most common causes of pneumonia in infants and small children, occurring mostly during autumn and winter. Influenza viruses are the most common cause of viral pneumonia in adults. Winter influenza outbreaks, usually of influenza type A, may cause 40,000 deaths annually in the United States. More than 90% occur in people age 65 years or older.[10] Metapneumovirus is a paramyxovirus that seems to be an important cause of viral pneumonia in children and adults.

Fungal infections caused by organisms such as *Histoplasma capsulatum, Blastomyces dermatitidis,* and *Coccidioides immitis* commonly manifest as pulmonary disease. These organisms are present in the soil in various geographic areas of the United States: *H. capsulatum* in the Mississippi and Ohio River valleys, *C. immitis* in desert areas of the Southwest, and *B. dermatitidis* in a poorly defined area extending beyond that of *H. capsulatum.* These infections should be considered in people in appropriate geographic areas, especially in those who are near activities that disturb the soil, such as construction or dirt bike riding, and in patients who do not respond to antibacterial antibiotics. Clinical presentation varies from an acute or chronic pneumonia to asymptomatic granulomas and hilar adenopathy.

Pneumocystis pneumonia (PCP) occurs in immunocompromised hosts, principally people with acquired immunodeficiency syndrome (AIDS) or malignancy. *Pneumocystis jiroveci* (previously known as *Pneumocystis carinii*) is one of the most common infections leading to a diagnosis of HIV infection and AIDS. Patients with pulmonary complaints should be questioned about HIV risk factors, and clinicians should search for signs of HIV-related immunosuppression, such as weight loss, lymphadenopathy, and oral thrush. PCP typically manifests subacutely with fatigue, exertional dyspnea, nonproductive cough, pleuritic chest pain, and fever.

Mycobacterium tuberculosis is a slow-growing bacterium transmitted between people by droplet nuclei produced from coughing and sneezing. *M. tuberculosis* survives within macrophages as a facultative intracellular parasite and may remain dormant in the body for many years. Active tuberculosis (TB) develops within 2 years of infection in approximately 5% of patients, and another 5% develop reactivation disease at some later time. Reactivation is more likely to occur in people with impaired cell-mediated immunity, such as patients with diabetes, renal failure, immunosuppressive therapy, malnutrition, or AIDS. Approximately one third of the world's population is infected with *M. tuberculosis.* Approximately 8 million new cases of active disease develop annually, resulting in 3 million deaths worldwide. An estimated 10 to 15 million people in the United States (3-5% of the population) are infected with TB. Multidrug-resistant strains of *M. tuberculosis* are found in increasing numbers, especially among immigrants from Southeast Asia and AIDS patients.

CLINICAL FEATURES

ED evaluation should focus on establishing the diagnosis of pneumonia and determining the presence of epidemiologic and clinical features that would influence decisions regarding hospitalization and antibiotics. Key history includes character of symptoms, setting in which the pneumonia is acquired, geographic or animal exposures, and host factors that predispose to certain types of infections and are associated with outcome.

Pneumonia generally manifests as a cough productive of purulent sputum, shortness of breath, and fever. In most healthy older children and adults, the diagnosis can be reasonably excluded on the basis of history and physical examination, with suspected cases confirmed by chest radiography. The absence of any abnormalities in vital signs or chest auscultation substantially reduces the likelihood of pneumonia as demonstrated by radiography. No single isolated clinical finding, however, is highly reliable in establishing or excluding a diagnosis of pneumonia.[11]

Elder or debilitated patients with pneumonia often have nonspecific complaints, such as acute confusion or a deterioration of baseline function, without classic symptoms. Elder patients

www.ketabpezeshki.com 66485457-66963820

are more likely to have advanced illness at the time of presentation and may have sepsis in the absence of a previous syndrome suggestive of pneumonia. Rarely, patients with lower lobe pneumonia have abdominal or back pain as a presenting symptom. The diagnosis may be more difficult in infants and small children who are unable to give an adequate history. Pneumonia may manifest in infants as a fever associated with irritability, tachypnea, tachycardia, intercostal retractions, nasal flaring, or grunting. Cough may be minimal or absent.

Pneumonia can be divided based on clinical patterns into typical pneumonia caused by pyogenic bacteria, such as *S. pneumoniae* or *H. influenzae,* and atypical pneumonia caused by organisms such as *Mycoplasma* and *Chlamydophila* species. This division is artificial, and a clear differentiation between these two types of pneumonia on clinical grounds alone is impossible. Certain clinical factors are often said to be suggestive of atypical organisms. Factors studied prospectively and found *not* to help differentiate atypical pneumonias from those with pyogenic bacterial causes include gradual onset, viral prodrome, absence of rigors, nonproductive cough, lower degree of fever, absence of pleurisy or consolidation, normal leukocyte count, and an ill-defined infiltrate on a chest radiograph. Although it is impossible to determine with a high degree of certainty the specific cause of pneumonia without results of microbiologic or serologic tests, certain clinical factors suggest that a specific pathogen should be considered.

Patients with pneumococcal pneumonia usually appear acutely ill, and the classic presentation is the abrupt onset of a single shaking chill, followed by fever, cough productive of rust-colored sputum, and pleuritic chest pain. Patients with a history of asplenia, sickle cell disease, AIDS, multiple myeloma, or agammaglobulinemia are at increased risk of pneumococcal bacteremia and sepsis with high mortality rates. Adults with chronic lung disease who develop pneumonia caused by *H. influenzae* typically demonstrate an insidious worsening of baseline cough and sputum production, and bacteremia is rare. *K. pneumoniae* may cause severe pneumonia in elderly or debilitated patients. Sputum is often described as “currant jelly” because of the necrotizing, hemorrhagic nature of the infection. Abscess formation, empyema, and bacteremia are common with this organism, and mortality is high.

Atypical pneumonia is caused by organisms such as *M. pneumoniae, C. pneumoniae,* viruses, *Legionella* species, or rickettsiae such as *Coxiella burnetii.* Mycoplasmal infection usually begins as a flulike illness with headache, malaise, fever, and nonproductive cough. Skin lesions, including maculopapular, vesicular, urticarial, or erythema multiforme–type rashes, are common, especially in younger patients. Although bullous myringitis is described as a classic finding, it is not specific for mycoplasmal infection and is present in only a few cases. Patients generally do not have a toxic appearance, and most can be treated as outpatients. Although mucopurulent sputum generally indicates the presence of pyogenic bacterial pneumonia or bronchitis, it may also be present with mycoplasmal or viral pneumonia. Viral pneumonia in adults is often preceded by symptoms of upper respiratory infection, such as rhinitis or sore throat. Most *C. pneumoniae* infections in young adults cause a minor, self-limited upper respiratory illness that is subacute in onset. This organism is also associated with bronchitis, wheezing, sinusitis, and pharyngitis. Development of radiographically evident pneumonia is more common in the elderly. Some patients with *Legionella* infection have a mild, self-limited atypical pneumonia presentation. Older patients, smokers, and those with chronic disease or immunosuppression are more prone to develop the more acute and severe systemic illness of legionnaires’ disease. Gastrointestinal symptoms, such as diarrhea and abdominal cramping, confusion, and muscle aches are sometimes prominent.

In addition to age, the presence of underlying illness, and presenting symptoms, the setting of acquisition of pneumonia may provide clues to likely causes. CAP that occurs in otherwise healthy individuals is likely to be caused by viruses, *Mycoplasma* species, or *S. pneumoniae. S. aureus,* including MRSA, can cause severe pneumonia associated with influenza. Recently hospitalized and long-term care patients may develop pneumonia from agents that are uncommon in CAP, such as Enterobacteriaceae, *Pseudomonas aeruginosa,* and *S. aureus.* Healthy patients in an institutional setting, such as a dormitory or military barracks, are likely to have pneumonia caused by *Mycoplasma* species or viruses.

Patients with underlying lung disease, especially COPD, constitute an important group likely to develop pneumonia. The lower respiratory tract of these patients is commonly colonized with organisms such as *S. pneumoniae, H. influenzae,* and *Moraxella catarrhalis.* Cystic fibrosis patients are prone to pneumonia caused by *P. aeruginosa* or *S. aureus.* Defective mucociliary clearance in both of these groups makes them highly susceptible to repeated episodes of pneumonia.

Patients with immunosuppression as a result of hematologic malignancy, patients receiving chemotherapy for malignancy, and transplant recipients are prone to pulmonary infections with a wide variety of organisms. In addition to the usual pathogens, these patients may develop pneumonia secondary to viruses such as cytomegalovirus (CMV), varicella, or herpes simplex virus. They are also more likely to develop pneumonia caused by aerobic gram-negative bacilli, *Aspergillus* and geographic fungi, and *P. jiroveci.*

Although the use of highly active antiretroviral therapy (HAART) has decreased the incidence of opportunistic infections among HIV-infected patients, individuals who are not under regular care often come to the ED. In addition to *P. jiroveci*, there is also an increased incidence *M. tuberculosis* and common bacterial pathogens such as *S. pneumoniae.* Other less common causes of pneumonia in HIV-infected patients include *Mycobacterium avium* complex, CMV, aerobic gram-negative bacilli, *Cryptococcus neoformans,* and *Rhodococcus equi.* PCP usually has a subacute presentation characterized by nonproductive cough, exertional dyspnea, and weight loss. Tachypnea and tachycardia are usually present. Hypoxemia, hypocapnia, and an increased arterial-alveolar oxygenation gradient are usually present.

The potential for opportunistic pulmonary infection can be predicted by a recent absolute CD4 lymphocyte count less than $200/mm^3$. This count is often known by patients with recognized HIV infection or may be surmised by a peripheral total lymphocyte count less than $1000/mm^3$. In patients who do not know their HIV status, the presence of findings such as weight loss, hairy leukoplakia, and oral candidiasis strongly suggests immunosuppression.

Patients in nursing homes or other extended-care facilities are at increased risk for infection with resistant organisms such as *P. aeruginosa, K. pneumoniae* (including strains producing extended-spectrum β-lactamases), *Acinetobacter* species, and hospital-associated strains of MRSA. Other risk factors for infection with multidrug-resistant pathogens include (1) hospitalization for 2 or more days in an acute care facility within 90 days of infection; (2) attendance at a hemodialysis clinic; and (3) intravenous antibiotic therapy, chemotherapy, or wound care within 30 days of infection. Any patient with pneumonia in whom any one of these historical features is present, including patients from a nursing home or long-term care facility, is designated as having health care–associated pneumonia (HCAP). HCAP is associated with a greater likelihood of resistant pathogens such as *Pseudomonas* and MRSA, and mortality is higher than that for CAP.[12]

www.ketabpezeshki.com 66485457-66963820

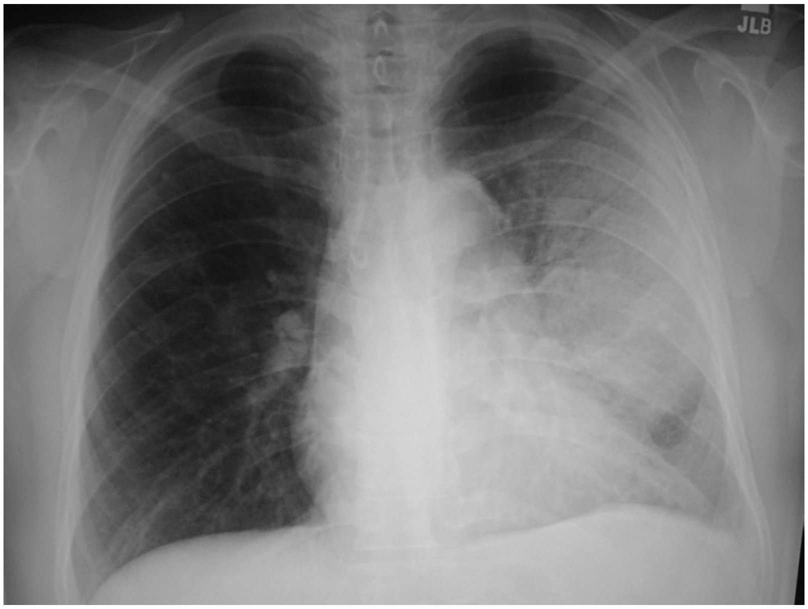


Figure 76-1. Posteroanterior chest radiograph reveals a left upper lobe pneumonia. A variety of organisms can produce this pattern, most commonly *Streptococcus pneumoniae*, *Haemophilus influenzae*, or gram-negative bacilli, but also *Chlamydophila pneumoniae, Mycoplasma,* or *Legionella* species.

DIAGNOSTIC STRATEGIES

Although many chest radiographs are obtained unnecessarily for patients with upper respiratory tract infections or bronchitis, it is difficult to identify a set of specific criteria to direct test ordering that is better than the clinical judgment of an experienced physician. A routine chest radiograph for all patients with cough is not necessary. Clinical judgment is more sensitive than suggestive findings (e.g., fever, tachycardia, oxygen desaturation, and an abnormal lung examination). Patients with serious underlying disease, severe sepsis, or shock and those in whom hospitalization is considered should undergo chest radiography. Computed tomography (CT) of the chest is more sensitive than plain radiography for detecting the presence of pulmonary consolidation, although the natural history of CT-positive, plain radiograph–negative pneumonia is not clear.[13] Young, healthy adults with a presumptive diagnosis of pneumonia who will be treated as outpatients may have a chest radiograph deferred unless there is a suspicion of immunocompromise or other unusual features of disease. A chest radiograph should be obtained subsequently if there is a poor initial response to treatment. Routine performance of chest radiography for patients with exacerbation of chronic bronchitis or COPD is of low yield and may be limited to patients with other signs of infection or congestive heart failure. Studies of infants with fever show that a routine chest radiograph is of low yield in the absence of other symptoms or signs of lower respiratory tract infection (e.g., abnormal auscultation or elevated respiratory rate).[14]

Although the causative agent cannot be determined solely by the results of chest radiography, certain radiographic patterns may suggest the possibility of specific pathogens. In pyogenic bacterial pneumonias, radiographs usually show an area of segmental or subsegmental infiltration and air bronchograms (Fig. 76-1). Lobar consolidation is present in a few cases of bacterial pneumonia, often caused by pneumococci or *Klebsiella.* A dense lobar infiltrate with a bulging fissure appearance on a chest radiograph is often described with pneumonia caused by *Klebsiella,* but this finding is nonspecific, and most cases manifest as a subtler bronchopneumonia. Pneumonia resulting from spread of infection along the intralobular airway results in fluffy or patchy infiltrates in the involved areas of the lung. A wide variety of bacteria and agents such as *Chlamydophila* species, *Mycoplasma* species, *Legionella* species, viruses, and fungi may cause this pattern.

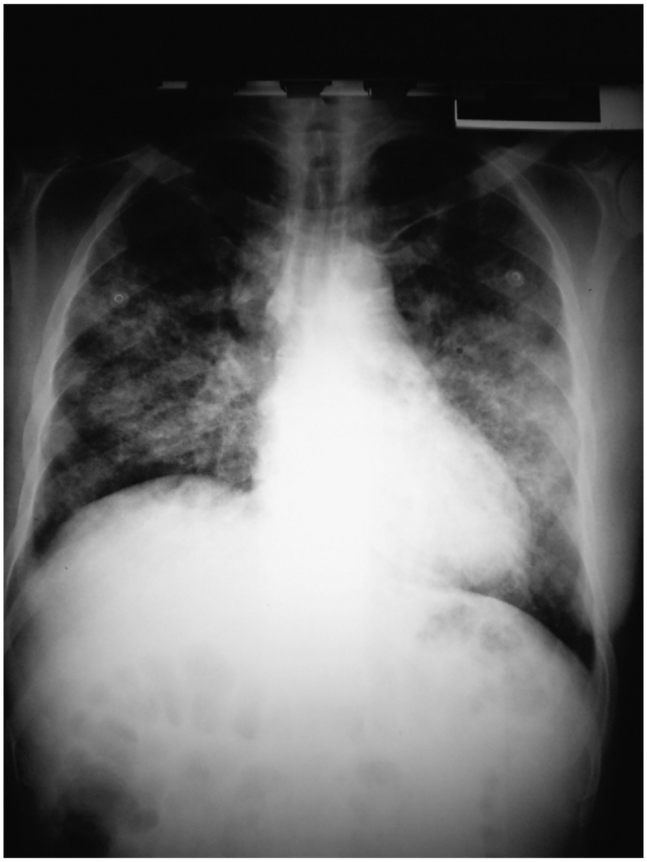


Figure 76-2. Posteroanterior chest radiograph reveals patchy interstitial infiltrates. Viruses and *Mycoplasma* are the most likely causes in an otherwise healthy patient, but many bacterial organisms may also produce this pattern.

An interstitial pattern on a chest radiograph (Fig. 76-2) typically is caused by *Mycoplasma* species, viruses, or *P. jiroveci.* The classic radiographic findings in PCP are bilateral interstitial infiltrates that begin in the perihilar region (Fig. 76-3). Radiographic manifestations of PCP can vary considerably, including normal appearance and lobar infiltrates, pleural effusions, hilar

www.ketabpezeshki.com 66485457-66963820

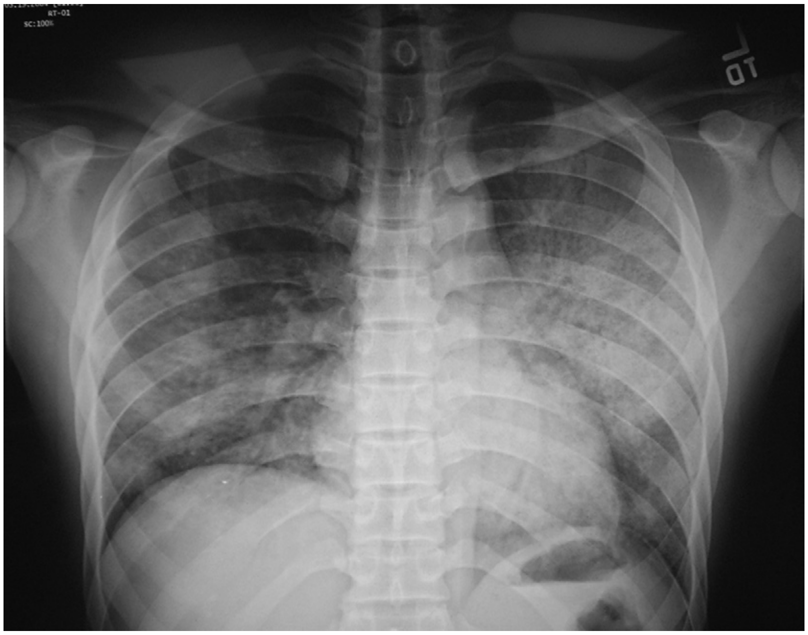


Figure 76-3. Posteroanterior chest radiograph of a human immunodeficiency virus (HIV)–infected patient reveals interstitial disease mixed with patchy alveolar infiltrates. *Pneumocystis jiroveci* is the most common cause, but bacterial pathogens and tuberculosis also are considered.

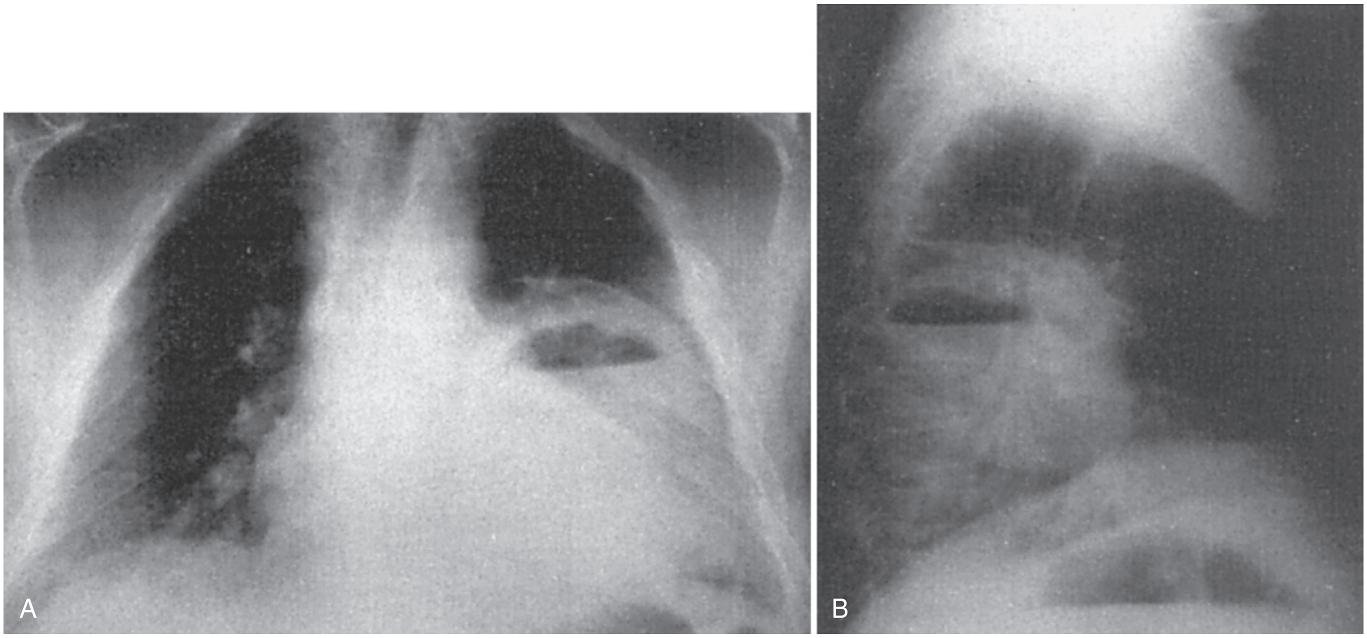


Figure 76-4. Posteroanterior **(A)** and lateral **(B)** chest radiographs reveal a lung abscess in the left lower lobe with a distinct air-fluid level.

adenopathy, parenchymal nodules, and cavitary disease. Tiny nodules disseminated throughout both lungs represent a miliary pattern typical of granulomatous pneumonias, such as TB or fungal disease. The location of infiltrates may also give a clue to the cause. Aspiration pneumonia occurs in dependent areas of the lung, most commonly the superior segments of the lower lobes or posterior segments of the upper lobes. Infiltrates from pneumonias produced by hematogenous spread (e.g., *S. aureus*) tend to be multiple and peripheral. Apical infiltrates suggest TB.

The presence of additional radiographic features in association with infiltrates may suggest a specific cause. An infiltrate associated with hilar or mediastinal adenopathy suggests the presence of TB or fungal disease or may indicate pneumonia associated with a neoplasm. Bacteria most likely associated with cavitation (Fig. 76-4) are anaerobes, aerobic gram-negative bacilli, and *S. aureus*. Cavitation also may be present in fungal disease or TB and with noninfectious processes (e.g., malignancy and pulmonary vascular disease). Pneumatoceles or spontaneous pneumothorax may be seen in AIDS patients with PCP. Pleural effusions occur with a wide variety of organisms, including many types of pyogenic bacterial pneumonias, *Chlamydophila* species, *Legionella* species, and TB. Anaerobic infections associated with an effusion are especially prone to development of empyema. The diagnosis and aspiration of pleural effusions can be aided by use of ED bedside ultrasonography.

Radiographic findings are nonspecific for predicting a particular infectious cause. *Mycoplasma* pneumonia may manifest as a dense infiltrate, or pneumococcal pneumonia may manifest as a diffuse interstitial infiltrate. Immunocompromised patients are particularly prone to having atypical radiographic appearances.

www.ketabpezeshki.com 66485457-66963820

Rarely, patients with a clinical picture strongly suggestive of pneumonia have a normal chest radiograph, and some are found to have an infiltrate within the next 24 to 48 hours. The absence of findings on a chest radiograph should not preclude the use of antimicrobial therapy in appropriate patients with a clinical diagnosis of pneumonia.[15] Laboratory studies also are nonspecific for identifying the cause of pneumonia. Although the finding of a white blood cell (WBC) count greater than 15,000/mm^3 increases the probability of the patient having a pyogenic bacterial cause rather than a viral or atypical cause, the predictive value of this finding depends on the stage of the illness and likely prevalences of various causes. This is neither sensitive nor specific enough to aid decisions regarding therapy in an individual patient. A WBC count may be helpful if it yields evidence of immunosuppression, such as neutropenia, or if it reveals lymphopenia that may indicate immunosuppression from AIDS. Basic metabolic panels may help identify patients with renal or hepatic dysfunction or metabolic acidosis associated with sepsis. These findings predict a complicated course and influence decisions regarding disposition, choice of antimicrobial agents, and dosages. Serum lactate dehydrogenase is significantly elevated in AIDS patients with PCP compared with patients with non-PCP pneumonia. Inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein are not helpful in clinical decision-making regarding pneumonia. Procalcitonin level has been suggested as a means to assess likelihood of bacterial cause, response to antimicrobial therapy, and prognosis in pneumonia. Its utility in the ED to assess need for hospitalization or ICU admission compared with other risk-stratification systems (see later) has not been validated.[16]

Assessment of respiratory function with pulse oximetry is important in evaluation of patients with pneumonia because clinical assessment of oxygenation can be inaccurate. Pulse oximetry should be performed in any patient suspected to have pneumonia, and pneumonia should be considered in patients with a low oxygen saturation.

Sputum Gram's stain rarely results in a change in therapy or outcome. Correlation between identification of pneumococcus on Gram's stain and sputum culture results is poor, even when commonly used criteria for an adequate sputum specimen (fewer than five squamous epithelial cells and more than 25 WBCs per high-power field) are applied. Gram's stains are even less likely to show gram-negative pathogens, such as *H. influenzae,* and should not be relied on to rule out a gram-negative cause. Empirical antimicrobial agents are usually highly clinically effective if chosen based on clinical information without sputum analysis. Guidelines for management of CAP from the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) support limiting sputum Gram's stain and culture to those patients with more severe disease or risk factors for unusual pathogens.[1] Confirmation of the diagnosis of PCP requires sputum induction and staining and, in some cases, further invasive procedures, such as bronchoscopy with bronchoalveolar lavage or biopsy.

Routine blood cultures are of essentially no value in nonimmunocompromised adults with pneumonia, in whom there is a very low prevalence of bacteremia, and management is rarely changed based on the results.[17,18] Follow-up of false-positive blood cultures is costly and labor-intensive and may lead to unnecessary use of antibiotics such as vancomycin or linezolid when contaminant growth is initially reported as gram-positive cocci. Blood cultures should be obtained from immunocompromised patients, those with severe sepsis or shock, or those with risk factors for endovascular infection (e.g., prosthetic valves, intravenous drug use, or cavitary infiltrates).[1] When culture specimens are drawn, they should be obtained before the initiation of antibiotics (although antibiotics should not be delayed for this reason).

Patients with a pleural effusion greater than 5 cm on lateral upright posterior-anterior chest radiograph should undergo diagnostic thoracentesis,[1] with fluid sent for cell count, differential, pH (pH below 7.2 predicts the need for a thoracostomy tube), Gram's stain, and culture. For most patients, thoracentesis can be safely deferred until after hospital admission. Patients in significant respiratory distress, however, or with evidence of tension and mediastinal shift require emergent diagnostic and therapeutic thoracentesis.

Serologic tests are available for the diagnosis of many organisms, including *C. pneumoniae, Legionella* species, and fungi. The use of serologic tests to determine the cause of pneumonia may be helpful retrospectively, but they usually require acute and convalescent serum titers and are of little use in the ED. Urine antigen tests for *S. pneumoniae* and *Legionella* are available, and in some facilities results can be obtained within the time frame of an ED evaluation. It is not clear, however, that a positive result should prompt a change in empirical treatment.[1] Rapid diagnostic tests for viral antigens are available for several viruses, including respiratory syncytial virus (RSV) and influenza. These tests may be useful for infection control decisions in hospitalized patients, and they may provide an indication for influenza therapy and family prophylaxis. Some commercially available rapid influenza tests are insensitive for certain strains, notably the 2009 pandemic H1N1 strain. Rapid testing for respiratory viruses (i.e., RSV, influenza A including the H1 subtype, influenza B, metapneumovirus, adenovirus, and entero-rhinovirus) with use of technology such as the polymerase chain reaction may become increasingly available to emergency physicians to determine the specific cause of pneumonia.

DIFFERENTIAL DIAGNOSIS CONSIDERATIONS

Differentiation between upper and lower respiratory tract infections may be difficult. A chest radiograph helps differentiate between upper respiratory tract infection or bronchitis and pneumonia, but it is probably unnecessary for all patients with cough and sputum production unless other factors are present that suggest the possibility of pneumonia or obscure its clinical diagnosis (e.g., toxic appearance, extremes of age, underlying illness, and abnormal chest examination).

Many noninfectious conditions may result in inflammatory lung processes, including exposure to mineral dusts (e.g., silicosis), chemical fumes (e.g., chlorine and ammonia), toxic drugs (e.g., bleomycin), radiation, thermal injury, or oxygen toxicity. Immunologic diseases (e.g., sarcoidosis, Goodpasture's syndrome, and collagen vascular disease) or hypersensitivity to environmental agents (e.g., farmer's lung disease) may also result in pneumonia. Tumors may be confused with pneumonia radiographically or may appear initially as a postobstructive infection or adenopathy with peripheral infiltrates. Lymphangitic spread of lung malignancy may resemble interstitial pneumonia.

Aspiration

It is important to distinguish between the acute aspiration of gastric contents or other liquids and bacterial pneumonia that may develop later as a complication of aspiration. Aspiration of liquids into the lung disrupts surfactant and causes an inflammatory response that may lead to hypoxia and respiratory failure. Aspiration of acidic gastric contents is particularly damaging to lungs and is common in patients who are unconscious from intoxication or anesthesia or who have neurologic deficits. Patients may initially have coughing or shortness of breath or may appear well initially and then develop respiratory dysfunction during the next several hours.

Acute aspiration of acidic fluid into the lungs may produce fever, leukocytosis, purulent sputum, and radiographic infiltrates

www.ketabpezeshki.com 66485457-66963820

that mimic bacterial pneumonia. Although many such patients go on to develop bacterial pneumonia, prophylactic administration of antibiotics is controversial.[19] Antibiotics should be initiated if the patient develops signs of bacterial pneumonia, including new fever, expanding infiltrate appearing more than 36 hours after aspiration, or unexplained deterioration. Systemic corticosteroids for acute aspiration are of no benefit.

MANAGEMENT

The possibility of communicable disease should suggest early isolation.[20] Patients with a history of TB exposure or suggestive symptoms (e.g., persistent cough, weight loss, night sweats, and hemoptysis) or who belong to a group at high risk for TB (e.g., homeless, intravenous drug user, alcoholic, HIV risk, and immigrant from high-risk area) should be given a mask and placed in respiratory isolation before evaluation, including chest radiography.[21] Because AIDS patients with pulmonary TB cannot be distinguished reliably from AIDS patients with other pulmonary infections at presentation, TB should be considered in all HIV-infected patients with respiratory complaints, and respiratory isolation should be initiated. EDs that frequently care for patients at risk for TB should consider triage protocols to identify these individuals rapidly before patients, visitors, or staff are unnecessarily exposed. Suspected infection with organisms transmitted by respiratory droplet (e.g., influenza) should prompt infection control precautions such as a mask being placed on the patient.

Antimicrobials should be administered in the ED for patients who are being admitted to the hospital. Timely administration of antimicrobials is associated with improved outcomes for hospitalized pneumonia patients,[22] although confounding factors limit a full understanding of this relationship. A rush to treatment without a diagnosis of pneumonia, however, can result in inappropriate antibiotic use. Although the Centers for Medicare and Medicaid Services have used specific time cutoffs for blood culture and antibiotic administration as a quality measure, the evidence that antibiotic delay on the order of hours is significantly deleterious is weak, and the IDSA/ATS guidelines for management of pneumonia do not recommend use of a specific time threshold. Any presumed benefit of early antibiotic administration should be weighed against the risk of inappropriate use for cases in which the diagnosis is unclear. The antibiotics selected should cover the likely causes based on clinical, laboratory, radiologic, and epidemiologic information. The regimen should also be as selective as possible to avoid drug toxicity, emergence of resistance to broad-spectrum agents, and excessive cost.

The prevalence of drug-resistant *S. pneumoniae* (DRSP) is increasing. In most areas of the United States, high-level penicillin resistance occurs in approximately 15 to 20% of outpatient pneumococcal sputum isolates. DRSP that is resistant to penicillin is usually resistant to other β-lactams, macrolides, tetracyclines, and trimethoprim-sulfamethoxazole (TMP-SMX). Extended-spectrum or "respiratory" fluoroquinolones, such as levofloxacin and moxifloxacin, are active against DRSP and other typical and atypical bacterial pathogens. Because oral bioavailability of fluoroquinolones is high, oral therapy provides serum and tissue levels essentially equivalent to parenteral therapy. It is not clear, however, the extent to which in vitro resistance is related to adverse clinical outcome. Most cephalosporins and macrolides achieve adequate levels in serum and tissues to successfully treat *S. pneumoniae* respiratory tract infections, even if the laboratory reports that the organism is resistant.

CA-MRSA is the most common pathogen isolated in community-acquired skin and soft tissue infections. It causes severe, rapidly progressing pneumonia with sepsis, often in children or healthy young adults with influenza.[23] CA-MRSA remains an uncommon cause of CAP in the United States,[9] but empirical coverage of MRSA should be strongly considered for patients with severe pneumonia associated with sepsis,[24] especially those with a presumed influenza infection, contact with someone infected with MRSA, or radiographic evidence of necrotizing pneumonia. Antimicrobials with consistent in vitro activity against CA-MRSA isolates include vancomycin, TMP-SMX, daptomycin, tigecycline, linezolid, and ceftaroline. Although vancomycin is used most often for documented MRSA infections, vancomycin may be losing efficacy in light of increasing minimum inhibitory concentrations. Daptomycin is inactivated by pulmonary surfactant and consequently is not indicated for pneumonia.

Appropriate agents for outpatient treatment of adults with CAP include macrolides, doxycycline, and fluoroquinolones with enhanced activity against *S. pneumoniae* (Table 76-1).[1] In patients properly identified as being at low risk for complications with careful outpatient follow-up, use of a macrolide such as azithromycin 500 mg orally (PO) once, followed by 250 mg PO daily for 4 days, is preferred. Doxycycline is an alternative choice that has activity against some uncommon causes of pneumonia such as MRSA, but it has more side effects. For patients at higher risk of DRSP owing to recent antibiotic use or comorbidities such as chronic heart, lung, liver, or renal disease, a respiratory fluoroquinolone should be considered. For patients who have received a fluoroquinolone within the previous few months, a combination of a macrolide plus a β-lactam agent (e.g., high-dose amoxicillin [1 g three times daily], amoxicillin-clavulanate [2 g PO twice daily], or cefpodoxime) is appropriate. For school-age children and adolescents, amoxicillin is an appropriate first-line agent, and azithromycin can be used for those with findings suggestive of *Mycoplasma* pneumonia.[25]

For patients whose illness is severe enough to necessitate hospital admission and parenteral antibiotics, a combination of a

Table 76-1 Community-Acquired Pneumonia in Older Children and Adults: Outpatient Treatment

CLINICAL SETTING	ANTIBIOTIC REGIMEN*	COMMENTS
Previously healthy, no antimicrobials in last 3 mo	Doxycycline 100 mg PO bid	Preferred for adolescent or young adult when likelihood of *Mycoplasma* is high; variable activity vs. *Streptococcus pneumoniae.*
	Azithromycin 500 mg once, followed by 250 mg daily for 4 days	Treats common typical bacterial and atypical pathogens. Clarithromycin can be substituted.
Comorbidities, or antimicrobials in last 3 mo	Levofloxacin 750 mg PO daily for 5 days	Can substitute moxifloxacin 400 mg daily for 7-14 days. Treats common typical and atypical bacterial pathogens; active vs. DRSP. Use fluoroquinolone if recently received β-lactam or macrolide.
	Cefpodoxime 200 mg PO bid + azithromycin 500 mg PO daily	Use if fluoroquinolones recently received. Can substitute cefdinir, cefprozil, or amoxicillin-clavulanate for cefpodoxime. Variable activity against DRSP.

DRSP, drug-resistant *S. pneumoniae*; *PO,* orally.
*Doses are for 70-kg adult with normal renal and hepatic function.

www.ketabpezeshki.com 66485457-66963820

Table 76-2 Community-Acquired Pneumonia in Older Children and Adults: Inpatient Antimicrobial Treatment

CLINICAL SETTING	ANTIBIOTIC REGIMEN*	COMMENTS
Community-acquired, nonimmunocompromised	Ceftriaxone 1 g q24h + azithromycin 500 mg q24h IV or PO Respiratory fluoroquinolone (levofloxacin 750 mg IV q24h or moxifloxacin 400 mg IV q24h)	Can substitute cefotaxime, ceftaroline, ampicillin-sulbactam, or ertapenem for ceftriaxone. Treats most common bacterial and atypical pathogens. Active vs. DRSP.
Severe pneumonia (ICU)	Ceftriaxone 1 g IV q24h + levofloxacin 750 mg IV q24h + vancomycin 1 g IV q12h	Can substitute cefotaxime, cefepime, ceftaroline, ertapenem, or β-lactam or β-lactamase inhibitor for ceftriaxone. Can substitute moxifloxacin for levofloxacin. Can substitute linezolid for vancomycin.
Health care–associated pneumonia or severe pneumonia with neutropenia, bronchiectasis (risk for *Pseudomonas*)	Cefepime 2g IV q12h + ciprofloxacin 500 mg IV q12h + vancomycin 1 g IV q12h	Can substitute other antipseudomonal β-lactam, such as piperacillin-tazobactam, imipenem, meropenem, or doripenem, for cefepime. Can substitute aminoglycoside plus macrolide for ciprofloxacin.
Presumed PCP	TMP-SMX 240/1200 mg IV q6h	Add ceftriaxone to TMP-SMX if severe, until PCP confirmed. Alternatives for sulfa allergy include clindamycin + primaquine.

DRSP, drug-resistant *S. pneumoniae*; *ICU,* intensive care unit; *IV,* intravenously; *PCP, Pneumocystis* pneumonia; *PO,* orally; *TMP-SMX,* trimethoprim-sulfamethoxazole.
*Doses are for a 70-kg adult with normal renal and hepatic function.

β-lactam agent, such as ceftriaxone 1 g intravenously (IV) q24h (or ceftaroline, cefotaxime, ampicillin-sulbactam, or ertapenem), plus a macrolide (e.g., intravenous or oral azithromycin 500 mg daily) is the preferred regimen. Alternatively, an extended-spectrum fluoroquinolone (levofloxacin or moxifloxacin) can be given as monotherapy, but this regimen may be more likely to promote antimicrobial resistance. Fluoroquinolones have some activity against TB and should be avoided in patients for whom TB is a possible cause, owing to risk of obscuring the correct diagnosis and selection of resistant TB. These regimens treat the most common bacterial pathogens, such as *S. pneumoniae*, and *H. influenzae*, and atypical pathogens, such as *Mycoplasma, Chlamydophila,* and *Legionella* species A regimen with activity against atypical pathogens is recommended by IDSA/ATS guidelines, but studies do not clearly demonstrate better outcomes in hospitalized patients compared with regimens without atypical activity.[26] Intravenous azithromycin alone may be an option for patients with milder illness who are unlikely to be bacteremic; it does not achieve significant serum levels and lacks significant activity against many aerobic gram-negative bacilli and DRSP. If anaerobic organisms are suspected (e.g., aspiration), clindamycin or metronidazole could be added to the regimen, or the regimen could include an antibiotic with anaerobic activity, such as ertapenem, ampicillin-sulbactam, piperacillin-tazobactam, tigecycline, or moxifloxacin (Table 76-2).

Seriously ill patients with severe sepsis or septic shock require aggressive fluid resuscitation and may benefit from more intensive management with vasopressors, transfusion, and inotropic agents as part of early goal-directed therapy.[27] Severely ill and compromised patients are at relatively greater risk of infection with *S. pneumoniae,* aerobic gram-negative bacilli, *S. aureus* (including MRSA), and, in some areas, *Legionella* species. For pneumonia patients admitted to an ICU, adequate activity against DRSP may be more important. Outcomes with severe pneumonia may be better with combination therapy.[28] A third-generation cephalosporin or β-lactam or β-lactamase inhibitor can be combined with a macrolide or fluoroquinolone, and addition of vancomycin or linezolid should be considered for MRSA activity. Addition of an aminoglycoside could be considered if septic shock is present.

Patients with recent hospitalization, neutropenia, or underlying bronchiectasis are at increased risk of infection with *P. aeruginosa.* Empirical therapy should include two agents with extended gram-negative activity, including *P. aeruginosa.* Empirical regimens include cefepime, imipenem, meropenem, doripenem, or piperacillin-tazobactam, plus either ciprofloxacin (high dose) or an aminoglycoside and a macrolide. For life-threatening pneumonia in populations at risk for MRSA, and for patients recently exposed to fluoroquinolones who may have fluoroquinolone-resistant *S. pneumoniae,* vancomycin or linezolid may be considered. The regimen should also cover atypical pathogens and gram-negative bacilli.

Because HCAP is associated with higher mortality and a greater likelihood of unusual pathogens, the use of broader-spectrum empirical therapy is appropriate, usually with a combination of antimicrobials to increase the chance that at least one antibiotic will be active against the causative pathogen. Appropriate combinations include an antipseudomonal β-lactam agent, such as piperacillin-tazobactam, cefepime, imipenem, or meropenem, with either an aminoglycoside or a fluoroquinolone and vancomycin or linezolid for MRSA.[29]

For patients with AIDS, it is important to treat *P. jiroveci* and bacterial pathogens such as *S. pneumoniae.* TMP-SMX is the treatment of choice; the usual regimen is 15 mg/kg of TMP and 75 mg/kg of SMX daily in four divided doses, to be continued for 21 days, in addition to a regimen to cover CAP organisms.[30] For most adult patients a regimen of three ampules (80 mg of TMP and 400 mg of SMX per ampule) every 6 hours is appropriate. For patients allergic to sulfa, options include clindamycin 600 mg IV every 8 hours plus primaquine 30 mg PO daily. The addition of corticosteroids (prednisone 40 mg PO twice daily) reduces mortality and clinical deterioration in patients with partial arterial oxygen tension (Pao_2) less than 70 mm Hg or alveolar-arterial gradient greater than 35 mm Hg. *Mycoplasma, Legionella,* and *Chlamydophila* species are uncommon causes of severe pneumonia in AIDS patients, so empirical therapy with erythromycin or doxycycline is not routinely recommended.

Moderately ill patients for whom hospitalization might be considered can be treated with an initial parenteral dose of a long-acting antibiotic, such as ceftriaxone, and observed (e.g., 12-24 hours) while supportive care, such as hydration, antipyretics, and bronchodilators, is administered, before discharge on an oral regimen. Patients at higher risk for deterioration (e.g., comorbidities, borderline hypoxia) may be brought back to the ED for follow-up in 24 hours and receive a second parenteral or observed oral dose of antibiotics. An extended-spectrum fluoroquinolone (oral or parenteral) is another option that may be

www.ketabpezeshki.com 66485457-66963820

advantageous because of additional activity against atypical pathogens and DRSP.

CAP guidelines recommend a 7- to 10-day duration of antimicrobial treatment and further indicate that antibiotic discontinuation can be considered in a patient who is afebrile for 48 to 72 hours. Levofloxacin 750 mg daily and azithromycin are approved as a 5-day course for CAP.

Patients with influenza may benefit from antiviral treatment as described in Chapter 130.

DISPOSITION

There is tremendous variability in physician admission decisions for pneumonia.[31] The more common tendency is overestimation of disease severity, leading to hospitalization of patients at low risk for death or serious complications. The decision to hospitalize a patient with pneumonia does not necessarily mean that a prolonged inpatient stay is required. Observation for 12 to 24 hours in the ED observation unit or hospital may allow the early discharge of certain moderate-risk patients. Inpatient treatment of pneumonia is 15 to 20 times more expensive per patient than outpatient treatment, and most patients are more comfortable in a home environment.

Although no firm guidelines exist regarding hospital admission, scoring systems may assist with hospitalization decisions. One commonly used system is based on the Pneumonia Patient Outcomes Research Team study, a prospectively validated predictive rule for mortality among immunocompetent adults with CAP.[32] This model (also known as the Pneumonia Severity Index [PSI]) suggests a two-step approach to assess risk. Patients in the lowest risk class who are recommended for outpatient management are those younger than 50 years, without significant comorbid conditions (neoplasm, congestive heart failure, cerebrovascular disease, renal disease, liver disease, or HIV), and without the following findings on physical examination: altered mental status, pulse 125 beats/min or greater, respiratory rate 30 breaths/min or greater, systolic blood pressure less than 90 mm Hg, or temperature less than 35° C or 40° C or greater. Patients who do not fit the lowest risk category are classified into categories based on a scoring system that accounts for age, comorbid illness, physical examination findings, and laboratory abnormalities (Table 76-3). Hospitalization is recommended for patients with a score greater than 91, and brief admission or observation may be considered for patients with a score of 71 to 90. Although this method of assessing the likelihood of successful outpatient management is helpful, it can be cumbersome, is not modeled to predict acute life-threatening events, does not take into account dynamic evaluation over time, and has many important exceptions (e.g., an otherwise low-risk patient with severe hypoxia would be discharged by strict interpretation of this rule). Clinical judgment should supersede a strict interpretation of this scoring system. A study in which physicians were educated, however, and provided the patient's risk score revealed a significantly lower overall admission rate, cost savings, and similar quality-of-life scores compared with those for patients conventionally managed by their physicians.[33] Additional discharge criteria include improving and stable vital signs over a several-hour observation period, ability to take oral medications, an ambulatory pulse oximetry greater than 90%, home support, and access to follow-up.

A simpler tool is the CURB-65 rule.[34] This rule uses only five simple criteria to determine patients at lower risk for adverse events: *c*onfusion, *u*remia (blood urea nitrogen >20 mg/dL), *r*espiratory rate greater than 30, *b*lood pressure less than 90 systolic or less than 60 diastolic, and age *65* years or greater. The risk of 30-day mortality increases with a greater number of these factors present: 0.7% with zero factors, 9.2% with two factors, and 57% with five factors. Patients with zero or one feature can receive outpatient care, those with two should be admitted, and ICU care should be considered for those with three or more. No randomized trials of hospital admission strategies directly compare the PSI with the CURB-65 score. In a comparison of scores in the same population of CAP patients, the PSI yields a slightly higher percentage of patients in the low-risk category, with a similar low mortality rate.[35]

The decision to admit a patient to the ICU is straightforward when patients are intubated or require vasopressors. It is more difficult to identify patients who do not require these interventions initially but may be at greater risk for deterioration and require a level of monitoring that may be beyond that available on the typical hospital ward. Objective criteria using the PSI (class V) and CURB-65 have been proposed but are not prospectively validated for the ICU admission decision.[36] When similar criteria were retrospectively studied in a cohort of CAP patients, they did not perform better than actual physician decisions.[37] IDSA/ATS guidelines include criteria for defining severe CAP (Box 76-1), but these have not been validated.[1] An ICU risk-stratification score is abbreviated SMART COP; intensive respiratory or vasodepressor support is predicted by low systolic blood pressure (2 points), multilobar chest radiography involvement (1 point), low albumin level (1 point), high respiratory rate (1 point), tachycardia (1 point), confusion (1 point), poor oxygenation (2 points), and low arterial pH (2 points). A SMART-COP score above 3 points identified 92% of patients who received intensive respiratory or vasodepressor support, including 84% of patients who did not need immediate admission to the ICU.[38] The decision to admit a patient to the hospital largely reflects the potential for acute deterioration, and some rate of floor to ICU transfer is inevitable.

Most patients with CAP do not need respiratory isolation. Patients who could pose a threat of transmission to other patients (e.g., influenza, varicella, TB, and plague) should be isolated. Neutropenic patients generally are placed in reverse isolation.

Table 76-3 Scoring System for Pneumonia Mortality Prediction

PATIENT CHARACTERISTICS	POINTS
Demographic factor	
Age	
Male	No. years of age
Female	No. years of age − 10
Nursing home resident	10
Comorbid illness	
Neoplastic disease	30
Liver disease	20
Congestive heart failure	10
Cerebrovascular disease	10
Renal disease	10
Physical examination finding	
Altered mental status	20
Respiratory rate >30	20
Systolic blood pressure <90 mm Hg	20
Temperature <35°C or >40°C	15
Pulse >125 beats/min	10
Laboratory or radiographic finding	
Arterial pH <7.35	30
Blood urea nitrogen >30mg/dL	20
Sodium <130 mEq/L	20
Glucose >250 mg/dL	10
Hematocrit <30%	10
Arterial Po_2 <60 mm Hg	10
Pleural effusion	10

Adapted from Mandell LA, et al: Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 37:1405, 2003.

www.ketabpezeshki.com 66485457-66963820

Box 76-1 Criteria for Severe Community-Acquired Pneumonia

Minor Criteria*

Respiratory rate >30 breaths/min†
Pa_{O_2}/F_{IO_2} ratio <250†
Multilobar infiltrates
Confusion, disorientation
Uremia (BUN level >20 mg/dL)
Leukopenia‡ (WBC count <4000 cells/mm^3)
Thrombocytopenia (platelet count <100,000 cells/mm^3)
Hypothermia (core temperature <36° C)
Hypotension requiring aggressive fluid resuscitation

Major Criteria

Invasive mechanical ventilation
Septic shock with the need for vasopressors

Adapted from Mandell LA, et al: Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 44:S27, 2007.
BUN, blood urea nitrogen; *Pa_{O_2}/F_{IO_2}*, arterial oxygen pressure/fraction of inspired oxygen; *WBC,* white blood cell.
*Other criteria to consider include hypoglycemia (in patients who do not have diabetes), acute alcoholism or alcoholic withdrawal, hyponatremia, unexplained metabolic acidosis or elevated lactate level, cirrhosis, and asplenia.
†A need for noninvasive ventilation can substitute for a respiratory rate higher than 30 breaths/min or a PaO2/FIO2 ratio below 250.
‡As a result of infection alone.

HIV-infected patients with pneumonia should be isolated until TB status can be evaluated via sputum acid-fast bacilli smears; this is particularly true for patients with other risk factors for TB. The chest radiograph cannot exclude TB in AIDS patients because it often does not have the typical appearance of TB. Isolation should be strongly considered for others at high risk for TB, such as inner-city homeless people and intravenous drug users.

KEY CONCEPTS

- Empirical antimicrobial therapy should be started in the ED for patients admitted with pneumonia.
- Empirical therapy should treat the most likely pathogens, including *S. pneumoniae, H. influenzae, M. pneumoniae,* and *C. pneumoniae,* and should be consistent with current national treatment guidelines, such as those from the IDSA.
- HIV or other immunosuppressive conditions should be considered in all patients in whom pneumonia is suspected.
- The disposition of patients with pneumonia is dictated by the patient's underlying medical conditions, the severity of illness and likelihood of clinical deterioration, and the feasibility of home care and outpatient follow-up.
- *Mycoplasma* pneumonia may manifest as a dense infiltrate, and pneumococcal pneumonia may manifest as a diffuse interstitial infiltrate.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Mandell LA, et al: Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44:S27.
2. Johansson N, Kalin M, Tiveljung-Lindell A, Giske CG, Hedlund J: Etiology of community-acquired pneumonia: Increased microbiological yield with new diagnostic methods. *Clin Infect Dis* 2010; 50:202.
3. de Roux A, et al: Viral community-acquired pneumonia in nonimmunocompromised adults. *Chest* 2004; 125:1343.
4. Rello J, et al: Microbiological testing and outcome of patients with severe community-acquired pneumonia. *Chest* 2003; 123:174.
5. Marrie TJ, Poulin-Costello M, Beecroft MD, Herman-Gnjidic Z: Etiology of community-acquired pneumonia treated in an ambulatory setting. *Respir Med* 2005; 99:60.
6. Centers for Disease Control and Prevention (CDC): *Adult Immunization Schedule*. Available at www.cdc.gov/vaccines/schedules/hcp/adult.html.
7. Rudis MI, et al: Pneumococcal vaccination in the emergency department: An assessment of need. *Ann Emerg Med* 2004; 44:386.
8. Centers for Disease Control and Prevention (CDC): *Birth-18 Years & "Catch-up" Immunization Schedules*. Available at www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html.
9. Moran GJ, et al: Prevalence of methicillin-resistant *Staphylococcus aureus* as an etiology of community-acquired pneumonia. *Clin Infect Dis* 2012; 54:1126.
10. Centers for Disease Control and Prevention (CDC): *Season Influenza Information for Health Professionals*. Available at www.cdc.gov/flu/professionals/index.htm.
11. Metlay JP, Kapoor WN, Fine MJ: Does this patient have community-acquired pneumonia? *JAMA* 1997; 278:1440.
12. Kollef MH, et al: Epidemiology and outcomes of health-care-associated pneumonia: Results from a large U.S. database of culture-positive pneumonia. *Chest* 2005; 128:3854.
13. Lähde S, Jartti A, Broas M, Koivisto M, Syrjälä H: HRCT findings in the lungs of primary care patients with lower respiratory tract infection. *Acta Radiol* 2002; 43:159-163.
14. Frederick RC: The clinical diagnosis of infantile pneumonia. *Ann Emerg Med* 2006; 48:627.
15. Basi SK, Marrie TJ, Huang JQ, Majumdar SR: Patients admitted to hospital with suspected pneumonia and normal chest radiographs: Epidemiology, microbiology, and outcomes. *Am J Med* 2004; 117:305-311.
16. Huang DT, et al: Risk prediction with procalcitonin and clinical rules in community-acquired pneumonia. *Ann Emerg Med* 2008; 52:48-58.
17. Kennedy M, et al: Do emergency department blood cultures change practice in patients with pneumonia? *Ann Emerg Med* 2005; 46:393.
18. Moran GJ, Abrahamian FM: Blood cultures for pneumonia: Can we hit the target without a shotgun? *Ann Emerg Med* 2005; 46:407.
19. Raghavendran K, Nemzek J, Napolitano LM, Knight PR: Aspiration-induced lung injury. *Crit Care Med* 2011; 39:818-826.
20. Rothman RE, et al: Respiratory hygiene in the emergency department. *Ann Emerg Med* 2006; 48:570.
21. Jensen PA, Lambert LA, Iademarco MF, Ridzon R: Centers for Disease Control and Prevention (CDC): Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR Recomm Rep* 2005; 54(RR-17):1.
22. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG: Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. *Arch Intern Med* 2004; 164:637.
23. Moran GJ, Talan DA: MRSA community-acquired pneumonia: Should we be worried? *Ann Emerg Med* 2009; 53:366-368.
24. Liu C, et al: Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis* 2011; 52:e181.
25. Bradley JS, et al: Executive summary: The management of community-acquired pneumonia in infants and children older than 3 months of age: Clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2011; 53:617-630.
26. Shefet D, Robenshtock E, Paul M, Leibovici L: Empiric antibiotic coverage of atypical pathogens for community acquired pneumonia in hospitalized adults. *Cochrane Database Syst Rev* 2005; 2:CD004418.
27. Nguyen HB, et al: Severe sepsis and septic shock: Review of the literature and emergency department management guidelines. *Ann Emerg Med* 2006; 48:28.
28. Martin-Loeches I, et al: Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. *Intensive Care Med* 2010; 36:612.
29. American Thoracic Society, Infectious Disease Society of America: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171:388.
30. Thomas CF, Limper AH: Pneumocystis pneumonia. *N Engl J Med* 2004; 350:2487.
31. Dean NC, et al: Hospital admission decision for patients with community-acquired pneumonia: Variability among physicians in an emergency department. *Ann Emerg Med* 2012; 59:35.
32. Fine MJ, et al: A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; 336:243.
33. Marrie TJ, et al: A controlled trial of a critical pathway for treatment of community-acquired pneumonia. *JAMA* 2000; 283:749.
34. Lim WS, et al: Defining community acquired pneumonia severity on presentation to hospital: An international derivation and validation study. *Thorax* 2003; 58:377.
35. Aujesky D, et al: Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia. *Am J Med* 2005; 118:384.
36. Moran GJ, Talan DA, Abrahamian FM: Diagnosis and management of pneumonia in the emergency department. *Infect Dis Clin North Am* 2008; 22:53.
37. Angus DC, et al: Severe community-acquired pneumonia: Use of intensive care services and evaluation of American and British Thoracic Society Diagnostic criteria. *Am J Respir Crit Care Med* 2002; 166:717.
38. Charles PG, et al: SMART-COP: A tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. *Clin Infect Dis* 2008; 47:375-384.

www.ketabpezeshki.com 66485457-66963820

Chapter 77

Pleural Disease

Joshua M. Kosowsky and Heidi H. Kimberly

Pleural disease is commonly encountered in the emergency department (ED). Presentations range in severity from asymptomatic pleural effusion to tension pneumothorax. This chapter reviews the two most common nontraumatic pleural problems: spontaneous pneumothorax and pleural inflammation with effusion. Pleural space problems associated with trauma are discussed in Chapter 45, and the approach to a patient with pleuritic chest pain in Chapter 26.

SPONTANEOUS PNEUMOTHORAX

Perspective

Under normal conditions, the visceral and parietal pleurae lie in close apposition, with only a potential space between them. *Pneumothorax* is defined as the presence of free air in the intrapleural space. A *spontaneous pneumothorax* occurs in the absence of any external precipitating factor, either traumatic or iatrogenic. *Primary spontaneous pneumothorax* occurs in individuals without clinically apparent lung disease. *Secondary spontaneous pneumothorax* arises in the context of an underlying pulmonary disease process.

The incidence of primary spontaneous pneumothorax is approximately 15 cases per 100,000 population per year among men and 5 cases per 100,000 population per year among women.[1,2] Primary spontaneous pneumothorax typically occurs in healthy young men of taller than average height. Factors associated with primary spontaneous pneumothorax include cigarette smoking and changes in ambient atmospheric pressure. Familial patterns suggest an inherited propensity in some cases of primary spontaneous pneumothorax. Mitral valve prolapse and Marfan syndrome are associated with spontaneous pneumothorax in the absence of clinically apparent lung disease.

Approximately one third of spontaneous pneumothoraces occur in the context of underlying pulmonary disease (Box 77-1). The incidence of secondary spontaneous pneumothorax is three times higher in men. The most common condition associated with secondary spontaneous pneumothorax is chronic obstructive pulmonary disease (COPD), which accounts for nearly 70% of cases. Patients with severe COPD (e.g., with forced expiratory volume in 1 second below 1 L) are at highest risk. The incidence of spontaneous pneumothorax among patients hospitalized for emphysema is 0.8% and for asthma 0.3%.

Spontaneous pneumothorax occurs in approximately 2% of patients with acquired immunodeficiency syndrome, almost always in the setting of *Pneumocystis jiroveci* (previously known as *Pneumocystis carinii*) pneumonia.

Malignancy is another common cause of secondary spontaneous pneumothorax. The occurrence of spontaneous pneumothorax in a patient with known malignancy should suggest lung metastases. In developing countries, tuberculosis and lung abscess remain leading causes of secondary spontaneous pneumothorax.

Catamenial pneumothorax is a rare condition in which recurrent spontaneous pneumothorax occurs in association with menses (typically within 72 hours of onset). Although it is termed *thoracic endometriosis syndrome* and often responds to ovulation-suppressing medications, the exact cause of catamenial pneumothorax is uncertain.

Spontaneous pneumothorax is rare in childhood. The principles of diagnosis, imaging, treatment, and surgical management for pediatric primary spontaneous pneumothorax are similar to those for adult pneumothorax.[1]

Pathophysiologic Principles

Normally, intrapleural pressure is negative (less than atmospheric), fluctuating from −10 mm Hg to −12 mm Hg during inspiration to approximately −4 mm Hg during expiration. Intrabronchial and intra-alveolar pressures are negative during inspiration (−1 to −3 mm Hg) and positive during expiration (+1 to +3 mm Hg). The alveolar walls and visceral pleura form a barrier that separates the intrapleural and intra-alveolar spaces and maintains the pressure gradient. If a defect occurs in this barrier, air enters the pleural space until either the pressures equalize or the communication seals.

With the loss of negative intrapleural pressure in one hemithorax, the ipsilateral lung collapses. A large pneumothorax results in restrictive ventilation impairment, with reduced vital capacity, functional residual capacity, and total lung capacity. Shunting of blood through nonventilated lung tissue may result in acute hypoxemia, although over time this effect is mitigated by compensatory vasoconstriction in the collapsed lung.

In tension pneumothorax, the alveolar-pleural defect acts as a one-way valve, allowing air to pass into the pleural space during inspiration and trapping it there during expiration (Fig. 77-1). This trapping leads to progressive accumulation of intrapleural air and increasingly positive intrapleural pressure, causing compression of the contralateral lung with asphyxia and worsening hypoxia. Intrapleural pressure exceeding 15 to 20 mm Hg impairs venous return to the heart. If the situation is allowed to progress, cardiovascular collapse and death ensue.

In primary spontaneous pneumothorax, disruption of the alveolar-pleural barrier occurs when a subpleural bulla (or bleb), typically located at the lung apex, ruptures into the pleural space. Subpleural bullae are found in almost all patients who undergo

www.ketabpezeshki.com 66485457-66963820

Box 77-1 Causes of Secondary Spontaneous Pneumothorax

Airway Disease
Chronic obstructive pulmonary disease
Asthma
Cystic fibrosis

Infections
Necrotizing bacterial pneumonia, lung abscess
Pneumocystis jiroveci pneumonia
Tuberculosis

Interstitial Lung Disease
Sarcoidosis
Idiopathic pulmonary fibrosis
Lymphangiomyomatosis
Tuberous sclerosis
Pneumoconioses

Neoplasms
Primary lung cancers
Pulmonary or pleural metastases

Miscellaneous
Connective tissue diseases
Pulmonary infarction
Endometriosis, catamenial pneumothorax

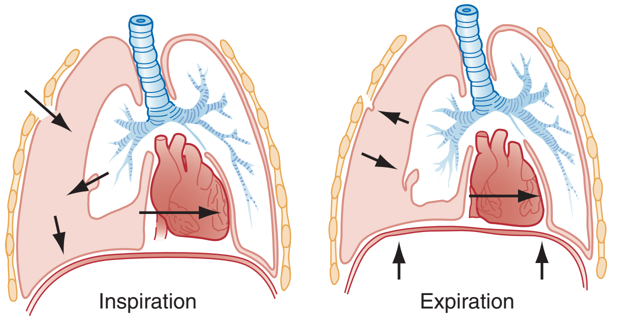


Figure 77-1. Tension pneumothorax with total collapse of the right lung and shift of mediastinal structures to the left. Air is forced into the pleural space during inspiration and cannot escape during expiration.

surgical treatment for primary spontaneous pneumothorax and are identified on computed tomography (CT) of the chest in 90% of cases. The cause of these bullae may be related to degradation of elastic fibers within the lung and an imbalance in the protease-antiprotease and oxidant-antioxidant systems.[2]

In the case of secondary spontaneous pneumothorax, the underlying lung disease weakens the alveolar-pleural barrier. In patients with *P. jiroveci* pneumonia, the cytotoxic effects of repeated episodes of inflammation lead to bullous and cystic changes. In patients with COPD, chronic exposure to cigarette smoke results in the development of large, thin-walled bullae that are at an increased risk for rupture. Other factors, including increased intrabronchial and intra-alveolar pressures generated by bronchospasm and coughing, also play a role.

Clinical Features

Symptoms of primary spontaneous pneumothorax typically begin suddenly while the individual is at rest. Ipsilateral chest pain and dyspnea are the most common symptoms. At the outset, the pain is typically "pleuritic" in nature (i.e., often described as sharp and made worse with deep inspiration), but it often evolves over time into a dull, steady ache. Although patients frequently describe shortness of breath, extreme dyspnea is uncommon in the absence of underlying lung disease or tension pneumothorax. Cough is present in a few individuals. Occasionally, patients are asymptomatic or have only nonspecific complaints. Patients may wait several days before they seek medical attention, and a significant number delay presentation for 1 week or more. Without treatment, symptoms often resolve spontaneously within 24 to 72 hours, although the pneumothorax is still present.

Physical findings tend to correlate with the degree of symptoms. A mild sinus tachycardia is the most common physical finding. With a large pneumothorax, decreased or absent breath sounds with hyper-resonance to percussion may be present. Other classic signs include unilateral enlargement of the hemithorax, decreased excursion with respirations, absent tactile fremitus, and inferior displacement of the liver or spleen. Absence of any or all of these findings does not exclude pneumothorax, however, and a chest radiograph should be obtained when pneumothorax is suspected.

With tension pneumothorax, signs of asphyxia and decreased cardiac output develop. Tachycardia (often >120 beats/min) and hypoxia are common. Hypotension is a late and ominous finding. Distention of the jugular veins is common but may be difficult to detect. Displacement of the trachea to the contralateral side is classically described but is an uncommon finding, usually occurring only in the immediately preterminal phase of the pneumothorax, if at all. Its absence should not be considered evidence that a tension phenomenon is not present.

In patients with significant underlying lung disease, pneumothorax manifests differently. Because of poor pulmonary reserve, dyspnea is nearly universal, even when the pneumothorax is small, and symptoms tend not to resolve on their own. Physical findings, such as hyperexpansion and distant breath sounds, often overlap considerably with the underlying lung disease, making the clinical diagnosis difficult. For this reason the diagnosis of pneumothorax should be considered whenever a patient with COPD experiences an exacerbation of dyspnea.

Although suggested by the patient's history and physical examination, the diagnosis of pneumothorax is generally made with the chest radiograph. The classic radiographic appearance is that of a thin, visceral pleural line lying parallel to the chest wall, separated by a radiolucent band devoid of lung markings. The average width of this band can be used to estimate the size of the pneumothorax with a fair degree of accuracy (Fig. 77-2). In general, however, it is more reasonable simply to characterize the pneumothorax as small, moderate, large, or total. The estimated size of the pneumothorax and the patient's clinical status can be useful in guiding management decisions.

Tension pneumothorax is a clinical diagnosis, and delay in treatment to obtain radiographic confirmation is inadvisable. When the diagnosis of tension pneumothorax is not apparent clinically and a chest radiograph is obtained, the classic appearance is one of complete lung collapse with gross distention of the thoracic cavity on the affected side and shift of mediastinal structures across the midline (Fig. 77-3A). In patients with underlying pulmonary disease, however, pleural adhesions and lack of lung elasticity may mask the fact that a pneumothorax is under significant positive pressure.

When pneumothorax is suspected but not seen on a standard chest radiograph, an expiratory film may be obtained. Theoretically, the volumes of the lungs and the chest cavity are reduced during expiration so that the relative size of the pneumothorax is enhanced. Although expiratory films are occasionally helpful in identifying a small apical pneumothorax, their routine use does not improve diagnostic yield. In critically ill patients for whom only a supine chest radiograph can be obtained, the finding of a "deep sulcus" (i.e., a deep lateral costophrenic angle) can suggest the presence of pneumothorax on that side (see Fig. 77-3A).

www.ketabpezeshki.com 66485457-66963820

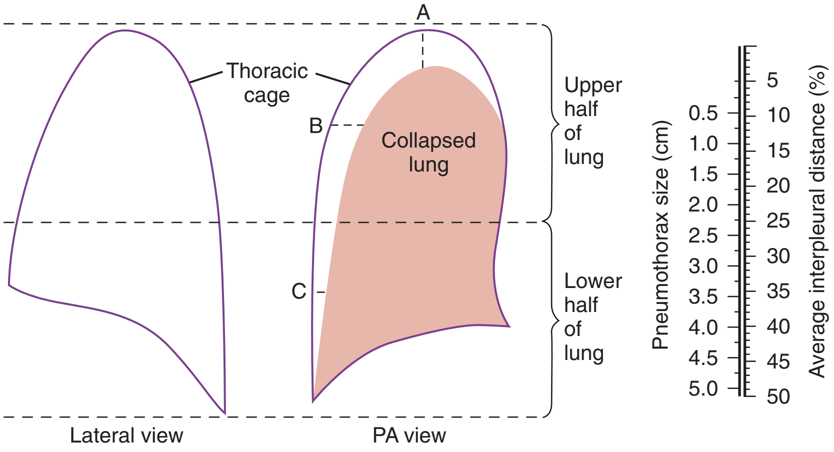


Figure 77-2. Determining the size of a pneumothorax. Calculation of average interpleural distance to predict pneumothorax size. *PA,* posteroanterior.

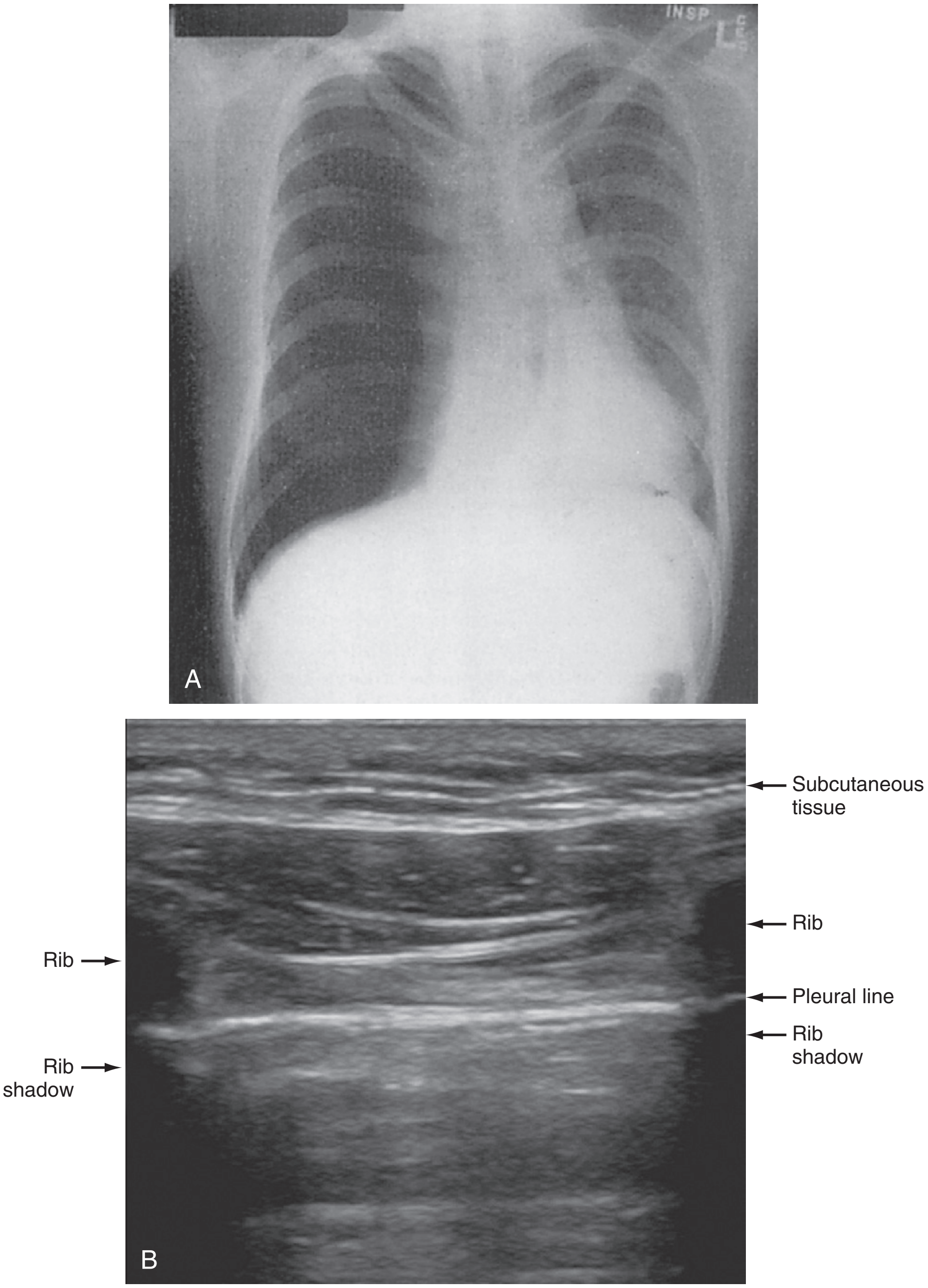


Figure 77-3. A, Radiograph of tension pneumothorax with mediastinal shift to left. B, Ultrasound demonstrating location of pleural line. Lung sliding is dynamic and visualized in real time as shimmering or sliding of the pleural line.

www.ketabpezeshki.com 66485457-66963820

Special care should be taken in viewing the chest radiographs of patients with underlying lung disease. In patients with COPD, the relative paucity of lung markings makes pneumothorax more difficult to detect. At the same time, giant bullae may simulate the radiographic appearance of pneumothorax. A clue to differentiating a pneumothorax from a giant bulla is that the former tends to run parallel to the chest wall, whereas the latter tends to have a more concave appearance. When the diagnosis is unclear, CT can differentiate between the two entities.

Chest CT is considered the gold standard for the diagnosis of pneumothorax; however, it requires that patients be stable enough for transport. Although portable chest radiography is convenient and commonly used, it has poor overall sensitivity.[3] Point-of-care thoracic ultrasound is a rapid and accurate diagnostic aid performed and interpreted by the clinician at the bedside.[4,5] Bedside thoracic ultrasound is more sensitive than a supine chest radiograph for the diagnosis of pneumothorax and avoids ionizing radiation.[6,7] In addition to routine use for the diagnosis of both traumatic and spontaneous pneumothorax, thoracic ultrasound can be used to evaluate for postprocedural pneumothorax and for the diagnosis of occult pneumothorax in critically ill patients.[8,9] In normal lung the closely opposed visceral and parietal pleura create the appearance of shimmering or sliding of the pleural interface during respiration. Assessment for pneumothorax is optimally performed with a high-frequency linear probe to most accurately visualize the lung sliding at the pleural line (see Fig. 77-3B). In supine patients, air rises; scanning a few interspaces on the anterior chest wall along the midclavicular line can effectively evaluate the most likely areas for pneumothorax. Extending the examination to the lateral chest wall can help identify the "lung point" or boundary between normal lung and pneumothorax and is highly specific for the detection of pneumothorax.[10] Visualization of lung sliding at the pleural line effectively rules out pneumothorax in the area being scanned. A small pneumothorax may not be detected with ultrasound, and false-positive results can occur in patients with blebs, pleural scarring, or severe acute respiratory distress syndrome (ARDS) or in single-lung intubation.

The differential diagnosis of pneumothorax includes numerous conditions associated with chest pain and dyspnea. Among the most important is pulmonary embolism, which may manifest in similar fashion with unilateral pleuritic chest pain. Most pleural-based processes (pneumonia, embolism, tumor) have characteristic radiographic findings. Rarely, pneumothorax may mimic an acute myocardial infarction with electrocardiographic changes simulating an acute injury pattern.

Spontaneous pneumomediastinum is a closely related clinical entity, diagnosed by the presence of subcutaneous emphysema and the finding of mediastinal air on chest radiography. In contrast to spontaneous pneumothorax, spontaneous pneumomediastinum typically occurs during exertion, particularly after a strenuous Valsalva maneuver. Most cases of spontaneous pneumomediastinum occur in the absence of known underlying disease and have a benign course. Secondary causes of pneumomediastinum (e.g., Boerhaave's syndrome) are more serious, and treatment is aimed at the underlying disorder.

Spontaneous hemopneumothorax is a rare but potentially serious condition that occurs when collapse of the lung is associated with rupture of a vessel in a parietopleural adhesion. The clinical presentation is similar to that of spontaneous pneumothorax but may be accompanied by symptoms and signs of hemorrhagic shock. Treatment entails large-caliber tube thoracostomy to evacuate the pleural space, reexpand the lung, and tamponade bleeding.

Pneumothorax has a readily available, highly reliable confirmatory diagnostic test (i.e., chest radiography). Absence of a pneumothorax on chest radiography should prompt a search for an alternative diagnosis.

Management

Whether in the field or in the ED, if the clinical circumstances suggest tension pneumothorax, treatment should be initiated without awaiting further cardiovascular compromise or definitive diagnosis by chest radiography. As soon as tension pneumothorax is suspected, the pleural space should be decompressed. This decompression may be accomplished by insertion of an intravenous catheter or by immediate tube thoracostomy, depending on the availability of equipment and the expertise of the providers. The diagnosis is confirmed by the hiss of air escaping under positive pressure as the needle or chest tube enters the pleural space. Needle decompression is only a temporizing procedure, and definitive management requires prompt tube thoracostomy. In morbidly obese patients, the needle and catheter may be of insufficient length to reach the pleural space, and a longer needle may be required.

The management of spontaneous pneumothorax has two goals: (1) to evacuate air from the pleural space, and (2) to prevent recurrence. Pursuit of the latter goal extends beyond the realm of the ED but may influence the initial approach to management. Therapeutic options for treatment of pneumothorax range from simple observation or aspiration with a catheter to video-assisted thoracoscopic surgery or thoracotomy. Decisions should be individualized and consider several factors, including size of the pneumothorax, severity of signs, presence of underlying pulmonary disease, other comorbidities, history of previous pneumothoraces, patient reliability, degree and persistence of the air leak, and available follow-up monitoring.

For otherwise healthy, young patients with a small primary spontaneous pneumothorax (i.e., <20% of the hemithorax), and minimal symptoms, observation alone may be appropriate. The intrinsic reabsorption rate ranges from 1 to 2% per day, a rate that is accelerated by a factor of 4 with the administration of 100% oxygen. By lowering the alveolar partial pressure of nitrogen, supplemental oxygen increases the rate at which air diffuses across the pleural-alveolar barrier. Admission to the hospital generally is not required for a patient with a small pneumothorax and no hemodynamic disturbance or hypoxia. Although there are no evidence-based guidelines, we recommend observing these patients in the ED for a 4- to 6-hour period. This observation period also can occur in an ED-based observation unit. A repeat chest radiograph obtained before discharge confirms that there is no interval worsening in the size of the pneumothorax. Discharged patients should be able to return to an ED if they worsen and should undergo telephone or in-person follow-up with a primary care provider in 24 to 48 hours. Air travel and underwater diving must be avoided until the pneumothorax has completely resolved. Patients who are not able to follow up with a primary care physician in the desired interval are advised to return to the ED for follow-up evaluation.

For primary spontaneous pneumothoraces that are larger in size (i.e., ≥20% of the hemithorax), aspiration with an intravenous catheter may be attempted. If 6 hours after aspiration the chest radiograph shows no reaccumulation of the pneumothorax, the catheter is removed and the patient can be discharged home, with the same caveats that apply to patients managed with observation alone.

Although there is no universal agreement on the optimal treatment of patients with a first episode of primary spontaneous pneumothorax, data suggest that aspiration may be equally effective as chest tube drainage and clearly causes much less patient discomfort.[11] Advantages of simple aspiration include low morbidity, lack of invasiveness, and overall cost savings, with reported rates of successful outcome ranging from 45 to 71%.[12] Success is less likely when the patient is older than 50 years or the volume of air aspirated exceeds 2.5 L, suggesting a continuing air leak. If

www.ketabpezeshki.com 66485457-66963820

aspiration fails to reexpand the lung fully, the catheter can be attached to a water-seal device or to a one-way Heimlich valve and managed like a small-caliber chest tube.

Most recurrent spontaneous pneumothoraces should be managed with tube thoracostomy because less invasive approaches (i.e., observation or simple aspiration) are associated with significantly lower success rates.[13] Similarly, patients who have respiratory distress, have tension physiology, or are likely to require mechanical ventilation should undergo tube thoracostomy to reexpand the lung definitively. Also, if there is significant pleural fluid (hemothorax or hydrothorax), tube thoracostomy is required. Finally, tube thoracostomy may be considered in uncomplicated cases of primary spontaneous pneumothorax either as a first-line intervention or after a less invasive approach (i.e., observation or simple aspiration) fails.

For most primary spontaneous pneumothoraces, placement of a small-caliber (7-14F) tube is generally sufficient because air leakage tends to be minimal. Small-caliber tubes are easy to insert, are well tolerated by patients, and leave only a small scar after removal. Complications associated with small-caliber tubes include kinking, malposition, inadvertent removal, occlusion by pleural fluid or clotted blood, and large persistent air leaks. For secondary spontaneous pneumothorax, a standard size (20-28F) thoracostomy tube is recommended. When there is detectable pleural fluid or an anticipated need for mechanical ventilation, a larger tube size (≥28F) is required.

After insertion, the tube is attached to a water-seal device and left in place until the lung has reexpanded fully and the air leak has ceased. A Heimlich valve, which consists of a one-way flutter valve covered in transparent plastic, can be used in place of a water-seal device and allows unhindered ambulation. Specific complications associated with the use of a Heimlich valve include accidental disconnection and occlusion by fluid.

Routine application of suction neither increases the rate at which the lung reexpands nor improves patient outcome and is no longer recommended. The use of suction (with a pressure of 20 cm H_2O) is reserved for situations in which the lung fails to reexpand after drainage through a water-seal device or Heimlich valve for 24 to 48 hours.

In most cases, chest tube management requires hospital admission, although outpatient management of spontaneous pneumothorax with a small-caliber tube and Heimlich device also is reasonable in a stable, responsible patient with good follow-up availability. Common complications of chest tube placement include incorrect placement, pleural infection, and prolonged pain. Reexpansion pulmonary edema and reexpansion hypotension are rare occurrences after rapid evacuation of large pneumothoraces.

Outcome

Most spontaneous pneumothoraces resolve within 7 days of tube thoracostomy. Air leaks that persist for longer than 2 days are less likely to resolve on their own. If an air leak persists beyond 4 to 7 days, tube thoracostomy is considered to have failed, and surgical intervention generally is recommended.

Failure of tube thoracostomy is more common with secondary spontaneous pneumothoraces because these tend to be associated with larger and more persistent air leaks. In the setting of COPD, healing of the alveolar-pleural barrier may be impaired by chronic inflammatory changes and loss of vascularity in pulmonary tissue. The success rate also decreases substantially with recurrent episodes of pneumothorax, declining from 91% for treatment of a first pneumothorax to 52% for treatment of a first recurrence and to 15% for treatment of a second recurrence.[14]

Recurrences of spontaneous pneumothorax are common. The risk of recurrence after a primary spontaneous pneumothorax is approximately one in three, with studies reporting rates of 16 to 50%.[15] Younger age, lower weight-to-height ratio, and a history of smoking are associated with an increased rate of recurrence. Recurrence rates after a secondary spontaneous pneumothorax are slightly higher (39-47%).[2]

Recurrences may be life-threatening for patients with serious underlying lung disease, and intervention is advocated to prevent recurrence as part of the initial approach to secondary spontaneous pneumothorax. In contrast, for patients with primary spontaneous pneumothorax, interventions typically are not considered until after a second ipsilateral pneumothorax. Preventive treatment also is recommended for patients who plan to continue activities such as flying or diving that increase the risk of serious complications if a pneumothorax recurs. CT can be used in primary spontaneous pneumothorax to detect emphysematous changes, predict the likelihood of recurrence, and guide intervention decisions.

A variety of operative and nonoperative interventions prevent recurrences. One strategy promotes adherence of parietal and visceral pleura, which obliterates the pleural space. Pleurodesis can be accomplished by mechanical pleural abrasion or by instillation of sclerosing agents. Another strategy involves resection of apical bullae or other lesions at risk for causing recurrences. Often the two strategies are combined. Minimally invasive procedures, such as video-assisted thoracoscopic surgery, allow for resection of bullae and pleurodesis. Patients with extensive bullae may require thoracotomy for wider visualization of lesions. Success rates are generally good, ranging from 86 to 100%.

PLEURAL INFLAMMATION AND EFFUSION

Perspective

Under normal circumstances, a thin layer of fluid lies between the visceral and the parietal pleurae. Pleural effusion implies the presence of an abnormally large amount of fluid in the pleural space. Pleural effusions are relatively common. The most common cause of pleural effusions in Western countries is congestive heart failure, followed by malignancy, bacterial pneumonia, and pulmonary embolism. In other countries, tuberculosis is the leading cause of pleural effusions. Other conditions commonly associated with pleural effusions include viral infections of the lung parenchyma or pleura, uremia, myxedema, cirrhosis, nephrotic syndrome, ovarian hyperstimulation syndrome, collagen vascular diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis), and intra-abdominal processes (e.g., acute pancreatitis, subphrenic abscess, ascites). Esophageal perforation is a rare but uniquely morbid cause of a pleural effusion.

Pleuritis (also referred to as *pleurisy*) is a nonspecific term denoting inflammation of the pleura. Pleuritis can occur with or without significant exudation of fluid into the pleural space. Pleuritis is a common presentation for a range of disease processes, from self-limited viral syndromes to more serious acute conditions, such as pneumonia and pulmonary embolism, to chronic illnesses, such as systemic lupus erythematosus and other connective tissue diseases.

A pleural effusion associated with bacterial pneumonia, bronchiectasis, or lung abscess is called a *parapneumonic effusion.* The term *complicated parapneumonic effusion* refers to parapneumonic effusions that require tube thoracostomy for their resolution. The diagnosis of empyema (or pus in the pleural space) requires the presence of bacteria on Gram staining of the pleural fluid.

Fluid anatomically confined and not freely flowing in the pleural space is termed a *loculated effusion.* Loculated effusions occur when there are adhesions between the visceral and the parietal pleurae. Hemothorax and chylothorax (i.e., from rupture of

www.ketabpezeshki.com 66485457-66963820

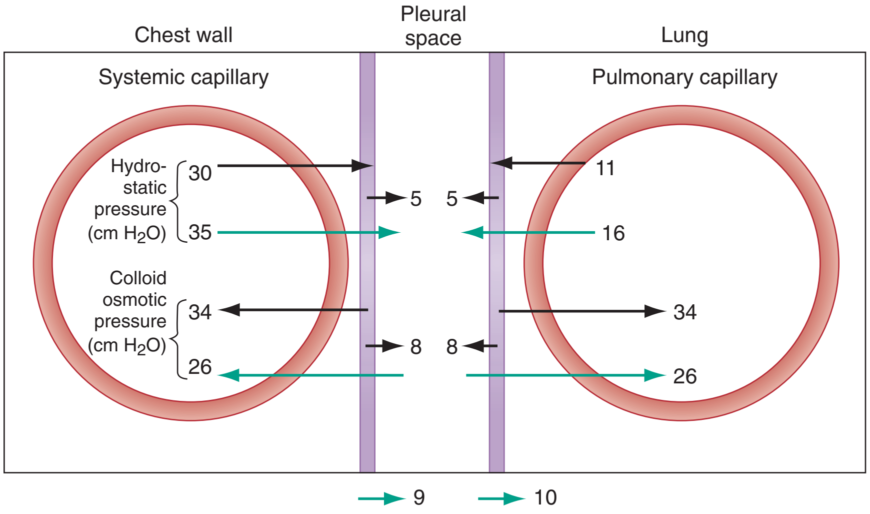


Figure 77-4. Diagram representing pressures involved in formation and absorption of pleural fluid. (Adapted from Fraser RG, et al: Diagnosis of Diseases of the Chest, 3rd ed. Philadelphia, WB Saunders, 1988.)

the thoracic duct) are special instances of pleural effusion that are approached separately.

Pathophysiologic Principles

Pleural fluid is produced from systemic capillaries at the parietal pleural surface and absorbed into pulmonary capillaries at the visceral pleural surface. Lymphatics also play an important role in removing pleural fluid. Movement of fluid across the pleural surfaces is governed by Starling's law. Under normal circumstances, the direction of pleural fluid flow is largely governed by the difference in hydrostatic pressure between the systemic and the pulmonary circulations (Fig. 77-4). Pleural fluid exists in a dynamic equilibrium in which influx equals efflux, with approximately 1 L of fluid traversing the pleural space in 24 hours. Under normal conditions, the amount of fluid that remains in the pleural space is small (~0.1-0.2 mL/kg body weight) and clinically or radiographically undetectable. Pleural effusion develops whenever influx of fluid into the pleural space exceeds efflux. Numerous disorders can lead to formation of a pleural effusion. Pleural effusions classically are divided into two groups—*transudates* and *exudates*—according to the composition of the pleural fluid (Box 77-2).

Transudates are essentially ultrafiltrates of plasma, containing very little protein. A *transudative effusion* develops when there is an increase in the hydrostatic pressure or decrease in the oncotic pressure within pleural microvessels. The primary cause of increased hydrostatic pressure is congestive heart failure, which is responsible for about 90% of transudative effusions. In hepatic cirrhosis and nephrotic syndrome, increased hydrostatic pressure is combined with loss of plasma oncotic pressure because of significant decreases in serum albumin. Patients with severe malnutrition may develop transudative effusions resulting from severe isolated hypoalbuminemia.

Exudates contain relatively high amounts of protein, reflecting an abnormality of the pleura itself. An *exudative effusion* is the result of increased membrane permeability or defective lymphatic drainage. Any pulmonary or pleural process associated with inflammation can result in an exudative effusion. In the absence of clinically apparent effusion, pleuritic symptoms may still be present. Pleurisy without pleural effusion is typical of most viral pleuritis, for example. The most common form of an exudative effusion is a parapneumonic effusion, in which infection of the adjacent lung elicits an intense inflammatory response in pleura, disrupting normal membrane permeability. Malignant effusions are the second most common form of exudative effusion and often reflect alterations in pleural permeability and problems with lymphatic drainage. Exudative effusions also may arise in response to inflammatory abdominal processes, such as pancreatitis or subphrenic abscess, presumably owing to altered permeability of the diaphragm itself. Exudative effusions may be reabsorbed or organize into fibrous tissue, resulting in pleural adhesions.

Box 77-2 Causes of Pleural Effusion

Transudates
Congestive heart failure
Cirrhosis with ascites
Nephrotic syndrome
Hypoalbuminemia
Myxedema
Peritoneal dialysis
Glomerulonephritis
Superior vena cava obstruction
Pulmonary embolism

Exudates
Infections
Bacterial pneumonia
Bronchiectasis
Lung abscess
Tuberculosis
Viral illness

Neoplasms
Primary lung cancer
Mesothelioma
Pulmonary or pleural metastases
Lymphoma

Connective Tissue Disease
Rheumatoid arthritis
Systemic lupus erythematosus

Abdominal or Gastrointestinal Disorders
Pancreatitis
Subphrenic abscess
Esophageal rupture
Abdominal surgery

Miscellaneous Conditions
Pulmonary infarction
Uremia
Drug reactions
Postpartum
Chylothorax

www.ketabpezeshki.com 66485457-66963820

Some pleural effusions can manifest as either transudates or exudates or may have characteristics of both. In the case of pulmonary embolism, the pathogenesis of pleural effusion is often multifactorial, reflecting increased pulmonary vascular pressure (a transudative process) and ischemia and breakdown of the pleural membrane (an exudative process).

Massive effusions (>1.5-2 L) are most commonly associated with malignancy but also can arise in the setting of congestive heart failure, cirrhosis, and other conditions. Massive effusions may restrict respiratory movement, compress the lungs, and result in intrapulmonary shunting. In extremely rare cases, tension hydrothorax can develop, with mediastinal shift and circulatory embarrassment.

Clinical Features

Symptoms associated with pleural effusion are most often caused by the underlying disease process and not the effusion itself. Small pleural effusions often are entirely asymptomatic. A new or enlarging pleural effusion may be heralded by localized pain or pain referred to the shoulder. Viral pleuritis and pulmonary infarction commonly are associated with pleuritic chest pain. When the volume of pleural fluid reaches 500 mL, dyspnea on exertion or at rest may occur as a result of compromised pulmonary function.

The patient's history often helps to establish the diagnosis for pleural effusion or pleural inflammation. A history of congestive heart failure, liver disease, uremia, or malignancy can direct subsequent evaluation. The pain of viral pleuritis usually is preceded by several days of a typical viral prodrome, with low-grade fever, sore throat, and other upper respiratory or constitutional symptoms. In the absence of such prodromal symptoms, an alternate cause for pleuritis such as pulmonary embolism should be considered.

Physical findings depend on the size of the effusion but are often either dominated or obscured by the underlying disease process. Classic physical signs of pleural effusion include diminished breath sounds, dullness to percussion, decreased tactile fremitus, and occasionally a localized pleural friction rub. The simple technique of auscultatory percussion (i.e., percussing the chest while listening for a dullness with the stethoscope) may be even more sensitive and specific for the physical diagnosis of pleural effusion. Egophony and enhanced breath sounds can often be appreciated at the superior border of the effusion because of underlying atelectatic lung tissue. In the setting of pleuritis, a pleural friction rub may be appreciated. With massive effusions, signs of mediastinal shift may be present.

Chest radiography confirms the clinical suspicion of pleural effusion and occasionally reveals a pleural effusion as an incidental finding. The classic radiographic appearance of a pleural effusion is blunting of the costophrenic angle on the upright chest radiograph. On a frontal (anteroposterior or posteroanterior) projection, a volume of 250 to 500 mL of pleural fluid is required before radiographic demonstration is possible. A lesser amount of fluid may be visible in the posterior costophrenic gutter on a lateral projection. With larger effusions, the hemidiaphragm is obscured, and an upwardly concave meniscus may be seen because pleural fluid has a tendency to layer higher laterally than centrally. Pleural fluid can extend up a major fissure and appear as a homogeneous density in the lower two thirds of the lung field. Massive pleural effusion can appear as a totally opacified hemithorax.

In the recumbent patient, free pleural fluid gravitates superiorly, laterally, and posteriorly and may not be clearly discernible on a supine radiograph. If the effusion is large enough, diffuse haziness or partial opacification of a hemithorax may be seen. Other findings on the supine radiograph may include apical capping, obliteration of the hemidiaphragm, and a widened minor fissure. The radiographic appearance of pleural effusions can be confusing. Subpulmonic effusions (fluid collections between the lung base and the diaphragm) can be difficult to diagnose, often simulating an elevated hemidiaphragm. Clues to the presence of a subpulmonic effusion include shifting of the apparent dome of the diaphragm toward the lateral chest wall and, when located on the left side, an increase in the distance between the gastric bubble and aerated lung. Loculated fluid in a fissure may assume a fusiform appearance and can simulate a mass (Fig. 77-5A and B). Such "fluid pseudotumors" are common in patients with congestive heart failure.

Other imaging techniques, such as ultrasound and CT, may be helpful in localizing and quantifying effusions and characterizing underlying lung processes. Bedside thoracic ultrasound is particularly helpful because it is more sensitive than chest radiography and can be used to guide thoracentesis in real time.[16,17] It decreases the risk of complications during thoracentesis, even in mechanically ventilated patients.[18] Sonographically, pleural effusions are typically visualized as hypoechoic fluid located above the diaphragm and can be visualized with a curvilinear probe in the midaxillary line (Fig. 77-5C). Not all pleural fluid is hypoechoic, however, and both hemothorax and pyothorax can appear heterogeneous. Ultrasound guidance for thoracentesis is best performed with the patient sitting upright using either a curved or linear probe. The largest fluid pocket is visualized, and a measurement is taken to estimate the depth the needle will need to be advanced. The procedure can be static, with the ultrasound used to mark the location for drainage, or dynamic, in which the procedure is performed with real-time visualization of the needle. Often, compressed lung or pleural adhesions can be visualized within the effusion, and careful observation of these findings as well as the location of the diaphragm, liver, or spleen can aid in the correct localization for thoracentesis or tube thoracostomy.

Pulmonary embolism easily can be overlooked in the workup of a pleural effusion. A patient with an otherwise unexplained pleural effusion in a setting of predisposing conditions or signs and symptoms of pulmonary embolism should be evaluated as described in Chapter 88.[19] Pleural effusion resulting from pulmonary embolism typically is small, occupying less than one third of the hemithorax, but dyspnea often is disproportionately severe for the size of effusion present.

An unexplained pleural effusion requires further investigation, but not necessarily on an emergency basis. Unless there is suspicion of an immediately life-threatening condition such as empyema or hemothorax, pleural fluid evaluation may be deferred to an inpatient or outpatient setting. The primary goal of pleural fluid analysis is to distinguish between transudative and exudative effusions. Transudative effusion usually is found in patients with known underlying disorders (e.g., congestive heart failure, nephrotic syndrome), whereas the presence of an exudate requires a detailed diagnostic evaluation. Although numerous alternative measurements have been proposed, Light's criteria remain a widely accepted means of differentiating transudates and exudates (Box 77-3).[20]

In the presence of an exudative effusion, additional pleural fluid analyses further classify the effusion. A pleural fluid pH of less than 7.3 is associated with parapneumonic effusions, malignancies, rheumatoid effusions, tuberculosis, and systemic acidosis. A pH of less than 7.0 strongly suggests empyema (or esophageal rupture). A pleural fluid pH of less than 7.0 and glucose less than 50 mg/dL are reasonable indications for tube thoracostomy.

Normal pleural fluid contains less than 1000 white blood cells/mm^3; exudative pleural fluid may contain over 10,000 white blood cells/mm^3. Although the absolute cell count has limited diagnostic value, a predominance of neutrophils suggests an acute process, such as pneumonia, pulmonary embolus, or acute tuberculous pleuritis. A predominance of monocytes or lymphocytes suggests a more chronic process, such as malignancy or established tuberculosis. Pleural fluid from any patient with an undiagnosed

www.ketabpezeshki.com 66485457-66963820

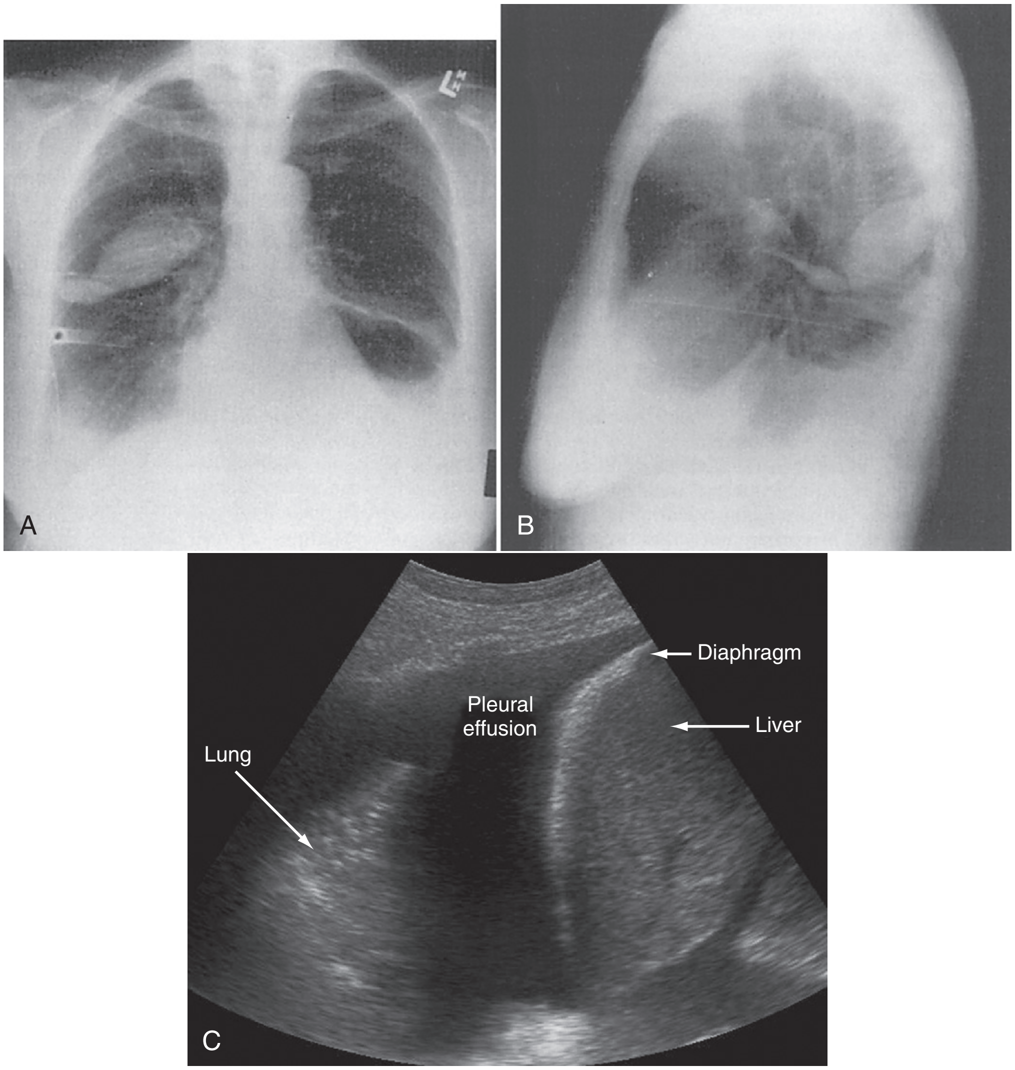


Figure 77-5. **A** and **B**, Radiographs of pleural effusion along major and minor fissures. **C**, Ultrasound image of the right upper quadrant demonstrating the typical hypoechoic appearance of a pleural effusion.

Box 77-3 Light's Criteria for Differentiating Transudates from Exudates

Pleural fluid is considered an exudate if one or more of the following conditions are met:

1. Pleural fluid protein level: serum protein level exceeds 0.5
2. Pleural fluid lactate dehydrogenase (LDH) level: serum LDH level exceeds 0.6
3. Pleural fluid LDH level exceeds ⅔ × (upper limit of normal for serum LDH level)

From Light RW, et al: Pleural effusions: The diagnostic separation of transudates and exudates. Ann Intern Med 77:507, 1972.

exudative pleural effusion should undergo Gram staining and culture for bacteria (aerobic and anaerobic), mycobacteria, and fungi.

In the absence of a traumatic tap, bloody fluid suggests trauma, neoplasm, or pulmonary infarction. If the hematocrit of the pleural fluid is more than 50% that of the peripheral blood, the effusion is, by definition, a hemothorax. Atraumatic hemothorax is relatively rare but can occur with spontaneous rupture of a tumor or blood vessel (e.g., ruptured aortic aneurysm).

If the diagnosis of a malignant pleural effusion is being considered, pleural fluid should be submitted for cytologic examination. Contrary to popular perception, the sensitivity for diagnosis of pleural malignancy does not depend on the volume of pleural fluid extracted during thoracentesis.[21] Cytologic analysis provides the diagnosis of cancer in a majority of malignant effusions.

Management

In patients with large effusions, urgent therapeutic thoracentesis may stabilize respiratory or circulatory status. The presence of empyema necessitates insertion of a chest tube to drain the pleural space adequately and prevent the development of loculations. If an effusion is already loculated, streptokinase or urokinase can be injected by a thoracic surgeon, pulmonologist, or interventional radiologist into the pleural space in an attempt to dissolve adhesions and allow fluid to drain freely. Hemothorax requires tube thoracostomy to evacuate the pleural space, quantify bleeding, and allow apposition of the two pleural surfaces to tamponade hemorrhage. If bleeding exceeds 200 mL/hr, thoracotomy should be considered.

In most other cases, the decision to proceed with therapeutic thoracentesis in the ED can be individualized. For example,

www.ketabpezeshki.com 66485457-66963820

therapeutic thoracentesis may be considered in patients with known, recurrent malignant effusion, in whom symptomatic relief may permit discharge. Thoracentesis under ultrasound guidance decreases complications and should be used when possible.

Pain relief is an important consideration in the management of patients with significant pleuritic pain. Nonsteroidal anti-inflammatory drugs are relatively successful in treating pleural pain. Opioid analgesia is safe and effective, but care should be exercised in debilitated patients or patients with severe lung disease because of potential respiratory depression.

Relative contraindications to thoracentesis include coagulopathy and other bleeding disorders. Thoracentesis may be safe with a prolonged prothrombin time in the absence of active bleeding.[22] Pleural adhesions, suggested by a prior history of empyema, represent a relative contraindication to thoracentesis because of the high risk of pneumothorax associated with blind needle insertion.

After thoracentesis has been completed, a chest radiograph should be obtained to evaluate for an iatrogenic pneumothorax. Other potential complications of thoracentesis include hemothorax, lung laceration, shearing of the catheter tip, and infection. Transient hypoxia caused by ventilation-perfusion mismatch often occurs, whereas unilateral, postexpansion pulmonary edema is rare except when large volumes (>1500 mL) are drained in one session. Hypotension also can occur after removal of a large volume of fluid, particularly in patients who are already intravascularly volume depleted.

Outcome

Some pleural effusions reflect little clinical significance. For example, small pleural effusions are common after abdominal surgery and in the postpartum state and resolve spontaneously within a few days. Viral pleuritis, with or without effusion, is generally self-limited and resolves without specific treatment.

For patients with congestive heart failure, pleural effusions generally respond well to diuretic therapy. If a significant effusion persists despite several days of aggressive diuresis, a diagnostic thoracentesis should be considered.

Pleural effusions associated with malignancy are a significant cause of morbidity in patients with advanced cancer. The presence of a malignant effusion indicates disseminated disease, and most of the malignancies that cause pleural effusions—mainly lung or breast carcinoma and lymphoma—are not curable at this stage. Therapeutic thoracentesis can relieve dyspnea in the short term, but malignant effusions tend to be recurrent, often rapidly so. Management strategies include chemical or mechanical pleurodesis to obliterate the pleural space or placement of a pleuroperitoneal shunt to provide continual drainage. Control of pleural effusions can improve quality of life in these patients.

Parapneumonic effusions contribute significantly to the morbidity and mortality of pneumonia. Therefore the presence of a parapneumonic effusion may influence the decision to hospitalize a patient with community-acquired pneumonia.[23] Empyema can develop in 5 to 10% of patients with a parapneumonic effusion, but in most cases, it responds well to parenteral antibiotics and pleural drainage. Early surgical drainage results in shorter hospital stays and may be more cost-effective than conservative management.[24] In nearly 20% of pleural effusions, no definitive diagnosis can be established even after extensive investigation. A sizable percentage of these effusions may be caused by viral infections, and most resolve spontaneously without sequelae.

KEY CONCEPTS

- Point of care thoracic ultrasound can be used to rule out pneumothorax with greater sensitivity than a portable supine chest x-ray examination. Chest CT is the gold standard for diagnosis of pneumothorax.
- For healthy, young patients with a small (<20%) primary spontaneous pneumothorax, observation alone (with administration of 100% oxygen) is an appropriate treatment option; for larger symptomatic pneumothoraces, simple aspiration with an intravenous catheter is often successful.
- In most cases of secondary spontaneous pneumothorax, tube thoracostomy should be considered because less invasive approaches are associated with lower rates of success.
- Routine application of suction after tube thoracostomy is no longer recommended and does not accelerate lung reexpansion.
- The most common cause of pleural effusions in Western countries is congestive heart failure, followed by malignancy and bacterial pneumonia; however, the diagnosis of pulmonary embolism should not be overlooked in a patient with pleural effusion of unknown cause.
- Therapeutic thoracentesis is indicated for the relief of acute respiratory or cardiovascular compromise and should be performed under ultrasound guidance if possible.
- The clearest indication for diagnostic thoracentesis in the ED is to diagnose immediately life-threatening conditions, such as empyema or esophageal rupture in a toxic patient; in most other cases, diagnostic thoracentesis to distinguish between transudative and exudative processes can be deferred.
- On a frontal (anteroposterior or posteroanterior) projection, a volume of 250 to 500 mL of pleural fluid is required before radiographic demonstration is possible. A smaller amount of fluid may be visible in the posterior costophrenic gutter on a lateral projection. Subpulmonic effusions (fluid collections between the lung base and the diaphragm) can be difficult to diagnose, often simulating an elevated hemidiaphragm.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Shaw KS, Prasil P, Nguyen LT, Laberge JM: Pediatric spontaneous pneumothorax. *Semin Pediatr Surg* 2003; 12:55.
2. Sahn SA, Heffner JE: Spontaneous pneumothorax. *N Engl J Med* 2000; 342:868.
3. Ball CG, et al: Factors related to the failure of radiographic recognition of occult posttraumatic pneumothoraces. *Am J Surg* 2005; 189:541-546.
4. Lichtenstein D: *Pneumothorax*. In: Lichtenstein D, ed. *Whole Body Ultrasound in the Critically Ill*. New York: Springer; 2010:163-179.
5. Moore CL, Copel JA: Point-of-care ultrasonography. *N Engl J Med* 2011; 364:749-757.
6. Kirkpatrick AW, et al: Hand-held thoracic sonography for detecting post-traumatic pneumothoraces: The Extended Focused Assessment with Sonography for Trauma (EFAST). *J Trauma* 2004; 57:288-295.
7. Wilkerson RG, Stone MB: Sensitivity of bedside ultrasound and supine anteroposterior chest radiographs for the identification of pneumothorax after blunt trauma. *Acad Emerg Med* 2010; 17:11-17.
8. Vezzani A, et al: Ultrasound localization of central vein catheter and detection of postprocedural pneumothorax: An alternative to chest radiography. *Crit Care Med* 2009; 38:533-538.
9. Lichtenstein DA, et al: Ultrasound diagnosis of occult pneumothorax. *Crit Care Med* 2005; 33:1231-1238.
10. Lichtenstein D, Mezière G, Biderman P, Gepner A: The "lung point": An ultrasound sign specific to pneumothorax. *Intensive Care Med* 2000; 26:1434-1440.
11. Noppen M, Alexander P, Driesen P, Slabbynck H, Verstraeten A: Manual aspiration versus chest tube drainage in first episodes of primary spontaneous pneumothorax: A multicenter, prospective, randomized pilot study. *Am J Respir Crit Care Med* 2002; 165:1240.
12. Packham S, Jaiswal P: Spontaneous pneumothorax: Use of aspiration and outcomes of management by respiratory and general physicians. *Postgrad Med J* 2003; 79:345.
13. Soulsby T: British Thoracic Society guidelines for the management of spontaneous pneumothorax: Do we comply with them and do they work? *J Accid Emerg Med* 1998; 15:317.
14. Jain SK, Al-Kattan KM, Hamdy MG: Spontaneous pneumothorax: Determinants of surgical intervention. *J Cardiovasc Surg* 1998; 39:107.
15. Schramel FM, Postmus PE, Vanderschueren RG: Current aspects of spontaneous pneumothorax. *Eur Respir J* 1997; 10:1372.
16. Gordon CE, Feller-Kopman D, Balk EM, Smetana GW: Pneumothorax following thoracentesis: A systematic review and meta-analysis. *Arch Intern Med* 2010; 170:332-339.
17. Lichtenstein D: *Pleural effusion*. In: Lichtenstein D, ed. *Whole Body Ultrasound in the Critically Ill*. New York: Springer; 2010:129-138.
18. Mayo PH, Goltz HR, Tafreshi M, Doelken P: Safety of ultrasound-guided thoracentesis in patients receiving mechanical ventilation. *Chest* 2004; 125:1059-1062.
19. Light RW: Pleural effusion due to pulmonary emboli. *Curr Opin Pulm Med* 2001; 7:198.
20. Light RW, Macgregor MI, Luchsinger PC, Ball WC Jr: Pleural effusions: The diagnostic separation of transudates and exudates. *Ann Intern Med* 1972; 77:507.
21. Sallach SM, Sallach JA, Vasquez E, Schultz L, Kvale P: Volume of pleural fluid required for diagnosis of pleural malignancy. *Chest* 2002; 122:1913.
22. McVay PA, Toy PT: Lack of increased bleeding after paracentesis and thoracentesis in patients with mild coagulation abnormalities. *Transfusion* 1991; 31:164.
23. Fine MJ, et al: A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; 336:243.
24. Lim TK: Management of parapneumonic pleural effusion. *Curr Opin Pulm Med* 2001; 7:193.

www.ketabpezeshki.com 66485457-66963820

Section Three

CARDIAC SYSTEM

Chapter 78

Acute Coronary Syndrome

Michael C. Kurz, Amal Mattu, and William J. Brady

Acute coronary syndrome (ACS) refers to the constellation of clinical diseases occurring as a result of acute myocardial ischemia. ACS includes a spectrum of clinical presentations ranging from unstable angina (UA) to non–ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI). ACS and in particular acute myocardial infarction (AMI) remain the leading causes of death in much of the developed world.

HISTORICAL PERSPECTIVE

Several advances in the mid-20th century drastically changed the approach to acute coronary care. The development of external defibrillators and cardiac pacemakers as well as new pharmacologic agents provided physicians with effective approaches for treating life-threatening dysrhythmias. The introduction of selective coronary arteriography by Sones in 1959 revolutionized the management of patients with coronary artery disease (CAD). In 1960, Kouwenhoven inaugurated the era of cardiopulmonary resuscitation (CPR).

These developments led to the recognition that the time between onset of symptoms and the initiation of therapy is critical. Day organized a cardiac arrest team in 1960 and established the first coronary care unit 2 years later, reducing AMI mortality by half. In the 1980s, DeWood performed coronary angiography early in the course of AMI and demonstrated coronary occlusion in the infarct-related artery. The early experience of Rentrop with the intracoronary administration of streptokinase in AMI ushered in the era of thrombolysis, now termed *fibrinolytic therapy*.

Recognition that the majority of sudden deaths from ischemic heart disease occur outside the hospital led to numerous advances for preadmission ACS care. In 1969, advanced prehospital cardiac care was initiated in Belfast with Pantridge's mobile cardiac care units. In 1970, Nagel reported the benefits of preadmission telemetry for field providers of advanced cardiac life support in patients experiencing dysrhythmias or sudden cardiac death. In the 1980s portable 12-lead electrocardiograms (ECGs) were introduced into the emergency medical services (EMS) environment. Although the ECG is the cornerstone of the diagnostic evaluation of ACS, diagnostic tools such as echocardiography, stress testing, nuclear imaging, and computed tomography (CT) play increasingly important roles, particularly when the diagnosis is not straightforward.

Fibrinolytic therapy and interventional, catheter-based techniques revolutionized the treatment of patients with STEMI during the 1980s. Combination therapies with antiplatelet, antithrombotic, and fibrinolytic agents continue to be studied for STEMI patients. Interventional success is improving with the use of newer stenting devices and various platelet and coagulation system inhibitors. STEMI systems of care address the management of STEMI from a systems-based perspective, starting with EMS in the prehospital setting, through the emergency department (ED) to the cardiac catheterization laboratory, and to the coronary care unit. This systems-based approach stresses a number of factors crucial in the management of STEMI, including the time-sensitivity of treatment, the multidisciplinary composition of the management team, and the multistep nature of the overall process. In addition to further development of the STEMI systems of care approach, current efforts focus on the establishment of regional cardiac centers and the expansion of interventional capabilities to smaller hospitals. Furthermore, appropriate methods of evaluation of potential ACS patients without obvious STEMI or other diagnostic findings continue to mature. The observation unit–based "rule-out myocardial infarction (MI)" strategy has been shortened in total time, rendered more efficient in process, and made safer with respect to medical management and detection of ACS events. Although this strategy of chest pain evaluation is more efficient than previous approaches, further improvements in reducing the missed MI in the ED are under development.

EPIDEMIOLOGY

Ischemic heart disease and CAD continue to be the leading causes of death among adults in many developed countries. Ischemic heart disease accounts for nearly 1 million deaths in the United States annually, of which approximately 160,000 occur in persons 65 years of age or younger. More than half of all deaths from cardiovascular disease occur in women, and CAD remains a major cause of morbidity and mortality in women beyond their middle to late fifties. The incidence of cardiovascular disease is expected to continue to increase owing to lifestyle and behavioral changes that promote heart disease.[1]

A significant reduction in age-adjusted mortality from CAD has occurred in the United States over the past four decades.[2,3] In large part, the decline has been accompanied by diminished mortality from AMI. This decrease is a result of a reduction in the incidence of AMI by 25% and a sharp drop in the case-fatality rate. Reduction in cigarette smoking, management of lipids, and improved management of hypertension and diabetes mellitus undoubtedly play a role, along with significant advances in medical treatment.

In 2005, 5.8 million patients were evaluated for chest pain or related complaints in EDs in the United States, constituting 5% of all ED visits. In 2004, 4.1 million visits to the ED had a primary diagnosis of cardiovascular disease, and over 1.5 million patients were hospitalized for a primary or secondary diagnosis of ACS.[4-7] In addition, approximately 2% of patients with ACS are discharged

www.ketabpezeshki.com 66485457-66963820

from the ED. In the United States, approximately 900,000 persons every year experience an AMI, of whom 20% die before reaching the hospital, and 30% die within 30 days.[8,9] The majority of fatalities from CAD occur outside the hospital, usually from an ACS-related dysrhythmia within 2 hours of onset of symptoms. For many patients who experience a nonfatal AMI, their lives are limited by an impaired functional status, anginal symptoms, and a diminished quality of life. The economic cost of ACS is estimated to be $100 to $120 billion annually.[10]

SPECTRUM OF DISEASE

Coronary heart disease includes the spectrum from asymptomatic CAD and stable angina to UA, AMI, and sudden cardiac death. ACS includes the "acute" subtypes of coronary heart disease, including UA, AMI, and sudden cardiac death.

Stable Angina

Stable angina pectoris is transient, episodic chest discomfort resulting from myocardial ischemia. This discomfort is typically predictable and reproducible, with the frequency of attacks constant over time. Physical or psychological stress (physical exertion, emotional stress, anemia, dysrhythmias, or environmental exposures) may provoke an attack of angina that resolves spontaneously over a constant, predictable period of time with rest or nitroglycerin (NTG).

The Canadian Cardiovascular Society classification for angina is defined as follows: class I, no angina with ordinary physical activity; class II, slight limitation of normal activity as angina occurs with walking, climbing stairs, or emotional stress; class III, severe limitation of ordinary physical activity as angina occurs on walking one or two blocks on a level surface or climbing one flight of stairs in normal conditions; and class IV, inability to perform any physical activity without discomfort as anginal symptoms occur at rest.

Unstable Angina

Unstable angina is broadly defined as angina occurring with minimal exertion or at rest, new-onset angina, or a worsening change in a previously stable anginal syndrome in terms of frequency or duration of attacks, resistance to previously effective medications, or provocation with decreasing levels of exertion or stress. *Rest angina* is defined as angina occurring at rest, lasting longer than 20 minutes, and occurring within 1 week of presentation. New-onset angina is angina of at least class II severity with onset within the previous 2 months. Increasing or progressive angina is diagnosed when a previously known angina becomes more frequent, longer in duration, or increased by one class within the previous 2 months of at least class III severity. Symptoms that last longer than 20 minutes despite cessation of activity are consistent with angina at rest and reflect UA.

UA is often referred to as *preinfarction angina, accelerating* or *crescendo angina, intermediate coronary syndrome,* and *preocclusive syndrome,* underscoring its difference from stable angina. UA should be considered a possible harbinger of AMI and hence should be treated aggressively. A patient with a diagnosis of angina in the ED should be presumed to have UA until a thorough clinical evaluation reliably determines otherwise.

UA can also be defined from a pathophysiologic perspective. Plaque rupture accompanied by thrombus formation and vasospasm illustrate the intracoronary events of UA. This is frequently characterized by an electrocardiographic abnormality, including T wave and ST segment changes.

Variant angina—also known as *Prinzmetal's angina*—is caused by coronary artery vasospasm at rest with minimal fixed coronary artery lesions; it may be relieved by exercise or NTG. The ECG reveals ST segment elevation that is impossible to discern from AMI electrocardiographically and, at times, clinically.

Acute Myocardial Infarction

Acute myocardial infarction is defined as myocardial cell death and necrosis of the myocardium. The four-decade-old World Health Organization (WHO) definition for AMI has been replaced by clinical criteria developed jointly by the European Society for Cardiology and American College of Cardiology (ACC) that focus on defining infarction as any evidence of myocardial necrosis. This definition for an acute, evolving, or recent MI requires a typical rise and fall of a cardiac biochemical marker, currently troponin, with clinical symptoms, ECG changes, or coronary artery abnormalities based on interventional evaluation.[11] The actual definition,[11] referred to as the "Universal Definition of Myocardial Infarction," includes the following; either one of these criteria satisfies the diagnosis for an *acute, evolving, or recent MI:*

1. Typical rise and gradual fall or more rapid rise and fall of biochemical markers of myocardial necrosis with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following clinical parameters:
   - Ischemic symptoms
   - ECG changes indicative of ischemia (T wave changes or ST segment elevation or depression)
   - Development of pathologic Q waves on the ECG
   - Imaging evidence of presumably new findings, such as a loss of viable myocardium or a regional wall motion abnormality
2. Pathologic findings of an AMI

Furthermore, regarding an *established MI,* any one of the following criteria satisfies this diagnosis[11]:

- Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time since the infarct developed.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a nonischemic cause.
- Pathologic findings of a healed or healing MI.

Considering the myriad clinical situations in which MI is encountered, the five primary "types" of infarction are described by the following categorization:

- Type 1—Spontaneous MI related to ischemia resulting from a primary coronary event, such as plaque erosion rupture, erosion, fissuring, or dissection with accompanying thrombus formation and vasospasm. Type 1 infarctions represent the "true" ACS event.
- Type 2—MI secondary to ischemia caused by either increased oxygen demand or decreased supply, as seen in coronary artery spasm, coronary embolism, severe anemia, compromising arrhythmias, or significant systemic hypotension.
- Type 3—Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST segment elevation or new left bundle branch block (LBBB) pattern. Fresh coronary thrombus is noted via either angiography or autopsy; death occurs before appropriate sampling of the blood to detect the abnormal cardiac biomarker.
- Type 4—MI associated with coronary instrumentation, such as occurring after percutaneous coronary intervention (PCI). For PCIs in patients with normal baseline troponin values,

www.ketabpezeshki.com 66485457-66963820

elevations of cardiac biomarkers above the 99th percentile URL are indicative of periprocedural myocardial necrosis. By convention, increases of biomarkers greater than 3 times the 99th percentile URL are designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is similarly recognized.

- Type 5—MI associated with coronary artery bypass grafting (CABG). For CABG in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of periprocedural myocardial necrosis. By convention, increases of biomarkers greater than five times the 99th percentile URL plus any of the following are designated as defining CABG-related MI:
  - New pathologic Q waves or new LLLB
  - Angiographically documented new graft or native coronary artery occlusion
  - Imaging evidence of new loss of viable myocardium

This categorization is more than a simple semantic description of AMI. Diagnostic and management issues clearly are different depending on the subtype of MI encountered. For instance, the type 1 event should be approached with attention to platelet, coagulation system, and vasospasm considerations, whereas the type 2 infarction should have attention paid to the frequent primary, inciting pathophysiologic situations that are actually causing the AMI.

AMI is further classified by findings on the ECG at presentation, as either STEMI or NSTEMI. Previous descriptors, such as *transmural* and *nontransmural,* as well as *Q wave* and *non–Q wave MI*, fail to adequately describe the coronary event and its related pathophysiology, electrocardiographic presentation, and pathologic outcome. The differentiation between STEMI and NSTEMI has important implications in terms of management, outcome, and prognosis for patients with AMI. In fact, the ACC and the American Heart Association (AHA) have separate clinical guidelines for the management of patients with UA/NSTEMI and those patients with STEMI.[6,7,12]

PATHOPHYSIOLOGY

The underlying pathophysiology of ACS is myocardial ischemia as a result of inadequate perfusion to meet myocardial oxygen demand. Myocardial oxygen consumption is determined by heart rate, afterload, contractility, and wall tension. Inadequate perfusion most commonly results from coronary arterial vessel stenosis as a result of atherosclerotic CAD. Usually the reduction of coronary blood flow does not cause ischemic symptoms at rest until the vessel stenosis exceeds 95%. Myocardial ischemia, however, may occur with exercise and increased myocardial oxygen consumption with as little as 60% vessel stenosis.[13]

CAD is characterized by thickening and obstruction of the coronary vessel arterial lumen by atherosclerotic plaques. Although atherosclerosis is usually diffuse and multifocal, individual plaques vary greatly in composition. Fibrous plaques are considered stable but can produce anginal symptoms with exercise and increased myocardial oxygen consumption because of the reduction in coronary artery blood flow through the fixed, stenotic lesions. Vulnerable or unstable fibrolipid plaques consist of a lipid-rich core separated from the arterial lumen by a fibromuscular cap. These lesions are likely to rupture, resulting in a cascade of inflammatory events, thrombus formation, and platelet aggregation that can cause acute obstruction of the arterial lumen and myocardial necrosis.[14]

Thrombus formation is considered an integral factor in ACS, including all subtypes ranging from UA to NSTEMI and STEMI. These syndromes are initiated by endothelial damage and atherosclerotic plaque disruption, which leads to platelet activation and thrombus formation. Platelets play a major role in the thrombotic response to rupture of coronary artery plaque and subsequent ACS. Platelet-rich thrombi are also more resistant to fibrinolysis than fibrin- and erythrocyte-rich thrombi. The resulting thrombus can occlude the vessel lumen, leading to myocardial ischemia, hypoxia, acidosis, and eventually infarction. The consequences of the occlusion depend on the extent of the thrombotic process, the characteristics of the preexisting plaque, the extent of the vessel obstruction, and the availability of collateral circulation.

In the setting of UA, acute stenosis of the vessel is noted; complete obstruction, however, is encountered in only 20% of cases. In these cases, it is likely that extensive collateral vessel circulation prevents total cessation of blood flow, averting frank infarction.[13] With AMI, the occlusive fibrin-rich thrombus is fixed and persistent, resulting in myonecrosis of the cardiac tissue supplied by the affected artery. Angiographic studies demonstrate that the preceding coronary plaque lesion is often less than 50% stenotic, indicating that the most important factors in the infarction are the acute events of plaque rupture, platelet activation, and thrombus formation rather than the severity of the underlying coronary artery stenosis.

Another important aspect of ACS is vasospasm. After significant coronary vessel occlusion, local mediators and vasoactive substances are released, inducing vasospasm, which further compromises blood flow. Central and sympathetic nervous system input increases within minutes of the occlusion, resulting in vasomotor hyperreactivity and coronary vasospasm. Sympathetic stimulation by endogenous hormones, such as epinephrine and serotonin may also result in increased platelet aggregation and neutrophil-mediated vasoconstriction. Approximately 10% of MIs occur as a result of coronary artery spasm and subsequent thrombus formation without significant underlying CAD. This mechanism may be more prevalent during UA and other coronary syndromes that do not result in infarction.

Further myocardial injury occurs at the cellular level as inflammatory, thrombotic, and other debris from the occlusive plaque lesion is released and embolizes into the distal vessel. Such embolization can result in obstruction at the microvasculature, leading to hypoperfusion and ischemia of the distal myocardial tissue, even after reopening of the more proximal, initial, obstructing lesion. In particular, the introduction of calcium, oxygen, and cellular elements into ischemic myocardium can lead to irreversible myocardial damage that causes reperfusion injury, prolonged ventricular dysfunction (known as *myocardial stunning*), or reperfusion dysrhythmias. Neutrophils probably play an important role in reperfusion injury, occluding capillary lumens, decreasing blood flow, accelerating the inflammatory response, and resulting in the production of chemoattractants, proteolytic enzymes, and reactive oxygen species.

CLINICAL FEATURES

Clinical features associated with ACS vary based on the patient type, including gender, comorbid conditions, and age considerations. Women, patients with diabetes mellitus, and the elderly, among other populations, can exhibit differing presentations of ACS. Women demonstrate less remarkable, if not subtle, ACS presentations. Diabetic patients frequently exhibit nontraditional symptoms of AMI, such as dyspnea. The elderly commonly note only weakness, confusion, or other nonclassic symptoms as the primary manifestation of ACS. The detection of AMI, ACS, and symptomatic obstructive coronary lesions are all part of the focus on ED management. The primary focus of the diagnostic effort changes significantly at different phases of the ED evaluation. Early, usually within the initial 15 minutes of presentation, the principal task is the identification of STEMI. Once STEMI has been excluded (and the patient remains clinically stable), the

www.ketabpezeshki.com 66485457-66963820

evaluation over the next several hours then focuses on the detection of ACS, including UA and NSTEMI. If excluded (and again, in a stable patient), the identification of symptomatic coronary obstructive lesions is the evaluation's goal; this last task can be accomplished during the initial ED presentation or later at follow-up.

Preadmission Evaluation

Appropriate pharmacotherapy for persistent anginal chest pain in the preadmission setting includes sublingual NTG, oral aspirin (acetylsalicylic acid [ASA]) that is preferably chewed, and intravenous morphine sulfate; the acronym *MONA* summarizes preadmission pharmacotherapeutic interventions (*m*orphine, *o*xygen, *n*itroglycerin, and *a*spirin). Establishment of the diagnosis of ACS in this setting is difficult, however, as chest pain is a poor predictor of the diagnosis and adjunctive tools are limited.[15] Preadmission 12-lead ECG offers high specificity (99%) and positive predictive value (93%) for AMI in patients with atraumatic chest pain while increasing the paramedic scene time by an average of only 3 minutes. This approach offers many advantages, including (1) earlier detection of STEMI, (2) ability to base the destination on the availability of PCI, and (3) more rapid reperfusion therapy.[7] Preadmission 12-lead ECG would be necessary in the limited populations in whom preadmission fibrinolytic therapy might be applicable, such as those with prolonged out-of-hospital times (90-120 minutes).

Emergency Department Evaluation

The History

The character of the chest discomfort as well as the onset, location, radiation, duration, prior presence, and any exacerbating or alleviating factors should be sought. Associated symptoms, especially of a cardiac, pulmonary, gastrointestinal, and neurologic nature, should be elicited. Results from any prior cardiac testing should be obtained.

Traditionally, a history of risk factors for CAD is sought; these include male gender, age, tobacco smoking, hypertension, diabetes mellitus, hyperlipidemia, family history, artificial or early menopause, and chronic cocaine abuse. Approximately 80% of a population of more than 122,000 patients with known CAD had at least one of the four conventional risk factors (diabetes mellitus, cigarette smoking, hypertension, or hyperlipidemia).[16] Cardiac risk factor burden has little impact on the ED diagnosis of ACS; however, in patients older than 40 years, ACS is 22 times more likely if four of the five major risk factors (diabetes mellitus, smoking, hypertension, hyperlipidemia, and family history) are present (compared with none).[17] Nevertheless, Bayesian analysis indicates that risk factors are a populational phenomenon and do not increase or decrease the likelihood of any condition in any one patient. Thus the presence of an individual risk factor or a collection of risk factors is far less important in diagnosing acute cardiac ischemia in the ED than the history of presenting illness, prior diagnosis of ischemic cardiac disease in the patient, the presence of ST segment or T wave changes, or cardiac marker abnormalities.[18]

Risk assessment tools, such as the PURSUIT (Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) risk model, the GRACE (Global Registry of Acute Coronary Events) risk model, and the TIMI (Thrombolysis in Myocardial Infarction) risk score, can be used to determine risk of death and ischemia in NSTEMI and STEMI. The TIMI risk score assigns a point each for seven factors based on history, cardiac markers, and the ECG. It can be accessed at www.timi.org.[6] Although these tools may aid in decision-making and in risk stratification for patients to properly determine their disposition (telemetry bed vs. intensive care unit), none of them are designed to identify patients who may safely be discharged home.

There are several nontraditional risk factors for coronary disease. Antiphospholipid syndrome, rheumatoid arthritis, human immunodeficiency virus (HIV),[19] and particularly systemic lupus erythematosus (SLE) are associated with a higher risk of cardiovascular disease.[20] Women with SLE who are 35 to 44 years of age are over more than 50 times more likely to have an MI than a similar age- and gender-matched Framingham population.[21]

The Classic History

The term *angina* refers to "tightening," not pain. *Classic angina pectoris* may not be pain at all but rather a "discomfort," with a "squeezing," "pressure," "tightness," "fullness," "heaviness," or "burning" sensation. Classically, it is substernal or precordial in location and may radiate to the neck, jaw, shoulders, or arms. If the discomfort does extend down the arm, it classically involves the ulnar aspect. Discomfort in the left chest and radiation to left-sided structures is typical, but location and radiation to both sides or to only the right side may be consistent with angina. Radiation of the discomfort to the right arm or shoulder, or to both arms or shoulders, exceeds radiation to the left arm or shoulder in terms of likelihood of the chest pain being caused by ACS, although all exceed a positive likelihood ratio of 2.[22,23]

Furthermore, classic features of angina pectoris include exacerbation with exertion, a heavy meal, stress, or cold, and alleviation with rest. The onset of pain at rest in no way excludes the diagnosis of angina. Anginal discomfort characteristically lasts from 2 to 5 minutes up to 20 minutes, and it is rare for it to last only a few seconds or to endure for hours or incessantly, "all day" (Table 78-1).

Symptoms characteristically associated with angina pectoris, or other entities of ACS, include dyspnea, nausea, vomiting, diaphoresis, weakness, dizziness, excessive fatigue, or anxiety (Table 78-2). If these symptoms arise, either alone or in combination, as a presenting pattern of known ischemic coronary disease, they are termed *anginal equivalent symptoms.* Recognition that coronary ischemia may arise with an anginal equivalent rather than a classic symptom is the key to understanding the atypical presentation of ACS. Complaints of "gas," "indigestion," or "heartburn" in the absence of a known history of gastroesophageal reflux disease, or if the heartburn is different from the patient's usual gastroesophageal reflux, or reproducible pain on abdominal palpation should raise suspicion of ACS. Gastroesophageal reflux disease is a common misdiagnosis in cases of missed ACS.

Table 78-1 Clinical Characteristics of Classic Anginal Chest Discomfort

CHARACTERISTIC	MORE LIKELY TO BE ANGINA	LESS LIKELY TO BE ANGINA
Type of pain	Dull, pressure	Sharp, stabbing
Duration	2-5 min, often 15-20 min	Seconds or hours
Onset	Gradual	Rapid
Location	Substernal	Lateral chest wall, back
Reproducible	With exertion	With inspiration
Associated symptoms	Present	Absent
Palpation of chest wall	Not painful	Painful, exactly reproduces pain complaint

Adapted from Zink BJ: Angina and unstable angina. In Gibler WB, Aufderheide TP (eds): Emergency Cardiac Care. St. Louis, Mosby, 1994.

www.ketabpezeshki.com 66485457-66963820

Table 78-2 Symptoms of Acute Myocardial Infarction: Typical and Atypical

SYMPTOM	BAYER ET AL*†	TINKER‡	URETSKY ET AL§	PATHY‖
Typical				
Chest pain	515	51	75	75
Atypical				
Dyspnea	118	19	14	77
Syncope	72	4	1	27
Confusion	46	1		51
Stroke	32	6		26
Fatigue	36	2	4	10
Nausea or emesis	28		1	10
Sudden death	31			31
Giddiness	18	3		22
Diaphoresis	18			2
Arterial embolus	3			19
Palpitation	4			14
Renal failure				11
Pulmonary embolus				8
Restlessness				4
Abdominal pain			5	
Arm pain only			1	
Cough			1	
Silent				
No symptoms				
Total	777*	87¶	102**	387¶

Adapted from Scott PA, Gibler WB, Dronen SC: Acute myocardial infarction presenting as flank pain and tenderness: Report of a case. Am J Emerg Med 9:547, 1991.
*Patients able to report multiple symptoms; therefore total exceeds 777.
†Bayer AJ, et al: Changing presentation of myocardial infarction with increasing age. J Am Geriatr Soc 34:263, 1986.
‡Tinker GM: Clinical presentation of myocardial infarction in the elderly. Age Ageing 10:237-240, 1981.
§Uretsky BF, Farquhar DS, Berezin AF, et al: Symptomatic myocardial infarction without chest pain: Prevalence and clinical course. Am J Cardiol 40:498-503, 1977.
‖Pathy MS: Clinical presentation of myocardial infarction in the elderly. Br Heart J 29:190-198, 1967.
¶Patients classified by principal symptom, although all patients with complaint of chest or epigastric discomfort were placed in typical group.
**Same as ¶, except patients with epigastric complaints were placed in atypical group.

Table 78-3 Key Entities in the Differential Diagnosis of Chest Pain

Acute myocardial infarction	Unstable angina
Stable angina	Prinzmetal's angina
Pericarditis	Myocardial or pulmonary contusion
Pneumonia	Pulmonary embolism
Pneumothorax	Pulmonary hypertension
Pleurisy	Aortic dissection
Boerhaave's syndrome	Gastroesophageal reflux
Peptic ulcer disease	Gastritis or esophagitis
Esophageal spasm	Mallory-Weiss syndrome
Cholecystitis or biliary colic	Pancreatitis
Herpes zoster	Musculoskeletal pain

The Atypical History

A description of typical symptoms (crushing, retrosternal chest pain or pressure) is often lacking in ACS; this may be a result of atypical features of the pain (e.g., character, location, duration, exacerbating and alleviating factors) or the presence of anginal equivalent symptoms (e.g., dyspnea, nausea, vomiting, diaphoresis, indigestion, syncope). Patients with an ultimate diagnosis of AMI or UA can have pain that is pleuritic, positional, or reproduced by palpation. Some patients describe their pain as burning or indigestion, sharp, or stabbing (see Table 78-2).[23,24]

In a large study of nearly 435,000 patients ultimately diagnosed with AMI, one third did not have chest pain on presentation.[25] Multiple studies have identified risk factors for atypical presentation of ACS: diabetes mellitus, older age, female gender, nonwhite ethnicity, dementia, no prior history of MI or hypercholesterolemia, no family history of coronary disease, and previous history of congestive heart failure (CHF) or stroke.[25-27] In patients with AMI or UA, atypical presenting complaints include dyspnea, nausea, diaphoresis, syncope, or pain in the arms, epigastrium, shoulder, or neck.

Atypical features of ACS are present with increasing frequency in sequentially older populations. Before age 85, chest pain is found in the majority of patients with acute MI, although dyspnea, stroke, weakness, and altered mental status are notably present. In those older than 85 years, however, atypical symptoms are more common than chest pain, with 60 to 70% of patients older than 85 having an anginal equivalent complaint, especially dyspnea.[27] Coincident ACS is more likely to occur in the elderly; patients with another acute condition (e.g., trauma, infection) should be scrutinized for concurrent ACS.[28]

Patients with diabetes mellitus are at heightened risk for ACS as well as an atypical presentation, such as dyspnea, nausea or vomiting, confusion, or fatigue. Medically unrecognized AMI can occur in 40% of patients with diabetes mellitus compared with 25% of a nondiabetic population, and myocardial scar unaccompanied by antemortem diagnosis of MI is three times more likely in diabetics.[29]

As with age and diabetes, female gender is an important risk factor for MI without chest pain. In some series, less than 60% of women reported chest discomfort at the time of their MI, with others reporting dyspnea, indigestion, or vague symptoms, such as weakness, unusual fatigue, cold sweats, sleep disturbance, anxiety, or dizziness.[30]

Finally, nonwhite racial and ethnic populations may have atypical symptoms in ACS.[25] Compelling data demonstrate a disparity in treatment approach related to race in patients with acute manifestations of coronary heart disease.[31] Whether this is related to the atypical nature of presenting symptoms in different racial groups is not clear. Although certain features of the chest pain history serve to increase or decrease the likelihood of ACS, none of them is strong enough to endorse discharge of the patient based on the history alone.[24]

Physical Examination

The physical examination focuses on the cardiac, pulmonary, abdominal, and neurologic examinations, looking for signs of complications of ACS as well as alternative diagnoses for chest pain and the anginal equivalent syndromes (Table 78-3). Altered mental status, diaphoresis, and signs of CHF are all ominous findings in patients with symptoms consistent with ACS. Historical studies using untrained physicians identified chest wall tenderness

www.ketabpezeshki.com 66485457-66963820

or "reproducible" chest wall tenderness in up to 15% of patients ultimately diagnosed with AMI, but these data are highly suspect. The real incidence of truly reproducible chest wall tenderness (i.e., when the patient reliably identifies to the examiner that the pain produced on palpation is identical to the pain causing the patient's presentation) in ACS is probably very small. It is suggested that patients with chest pain that is fully *p*leuritic, *p*ositional, or reproducible by *p*alpation (the three *P*s) are at low risk (yet not no risk) for ACS.[22]

Outcomes in Atypical Presentations

Not surprisingly, atypical presentation of patients with ACS is associated with a delay in diagnosis and poorer outcomes. In the Second National Registry of Myocardial Infarction (NRMI-2) study, patients with MI without chest pain were significantly more likely to die in the hospital (23 vs. 9% for patients with chest pain) and were more likely to experience stroke, hypotension, or heart failure that required intervention, possibly reflecting the older age and greater comorbidity in this group.[25] Patients with atypical symptomatology seek medical care later and are less likely to receive standard therapies, such as aspirin, beta-adrenergic blockers, heparin, fibrinolysis, and emergent reperfusion therapy.[25] Patients 65 years of age or younger with NSTEMI have a 1% chance of dying during their hospitalization, but this risk is increased to 10% for patients ages 85 years and older.[28]

Missed Diagnosis of Acute Coronary Syndrome

Approximately 2% to 4% of patients with acute MI in the ED are discharged without diagnosis.[32] Missed ACS is the misdiagnosis that accounts for the largest amount of payment by emergency physicians in medical malpractice claims. Atypical presenting symptoms are an obvious causative consideration. Patients with undiagnosed ACS discharged from the ED are younger, more likely to be women or nonwhite, more likely to have atypical complaints, and less likely to have ECG evidence of acute ischemia.[32,33] Among all patients with cardiac ischemia, women younger than 55 years seem to be at highest risk for inappropriate discharge. With respect to ECG findings, 53% of patients with missed AMI and 62% of patients with missed UA have normal or nondiagnostic ECGs. Finally, the risk-adjusted mortality ratio for all patients with acute cardiac ischemia is 1.9 times higher among nonhospitalized patients.[32] Factors associated with misdiagnosis of ACS in medical malpractice closed claims analysis include physicians with less experience who document histories less clearly, admit fewer patients, and misinterpret the ECG.

Early Complications of Acute Myocardial Infarction

Bradydysrhythmia and *atrioventricular (AV) conduction block* occur in 25 to 30% of patients with AMI; sinus bradycardia is most commonly seen.[34-36] Symptomatic bradydysrhythmias in the first few hours after inferior AMI tend to be atropine responsive; conduction abnormalities that appear beyond 24 hours of MI tend not to respond to atropine.[37] Patients with AV block in the setting of anterior AMI tend to respond poorly to therapy and have a poor prognosis.

Tachydysrhythmias are quite common in the setting of AMI and may be atrial in origin (e.g., sinus tachycardia and atrial fibrillation) or ventricular (e.g., ventricular tachycardia and fibrillation). Not all require treatment, such as a compensatory sinus tachycardia in patients with AMI complicated by CHF. Primary ventricular fibrillation occurs in an estimated 4 to 5% of patients with AMI, with 60% of those cases occurring in the first 4 hours and 80% within 12 hours.

Cardiogenic shock is hypotension with end-organ hypoperfusion resulting from decreased cardiac output that is unresponsive to restoration of adequate preload. Patients at risk include those with large infarcts, prior MI, low ejection fraction on presentation (<35%), older age, and diabetes mellitus. Although some differential diagnoses can usually be reasonably excluded (e.g., sepsis, anaphylaxis, adrenal crisis, and hypovolemic or hemorrhagic states), other causes of shock with similar presentations should be considered, such as aortic dissection, pulmonary embolism (PE), pericardial tamponade, and ventricular free wall rupture accompanying acute MI. Adjunctive diagnostic measures include bedside echocardiography and invasive hemodynamic monitoring, with the latter demonstrating systemic hypotension, low cardiac output, elevated filling pressures, and increased systemic vascular resistance. Therapeutic measures include vasopressor and inotropic support, intra-aortic balloon counterpulsation, and early revascularization; fibrinolytic therapy does not decrease mortality in cardiogenic shock.

Left ventricular free wall rupture is uncommon. Approximately one third of cases occur in the first 24 hours, and the remainder occur 3 to 5 days after transmural MI. Clinically, free wall rupture may occur with sudden death, pulseless electrical activity, or precipitous deterioration in the presence of AMI. Subacute presentations include agitation, chest discomfort, and repetitive vomiting. Signs of pericardial effusion on the ECG or echocardiogram are suggestive of the diagnosis in the setting of acute or recent MI. Free wall rupture is almost universally fatal, although prompt diagnosis followed by emergent surgical intervention may rarely be lifesaving; pericardiocentesis is indicated as an immediate temporizing intervention.

Rupture of the interventricular septum may also occur; it may arise similarly to cardiogenic shock and free wall rupture of the ventricle. The clue to this diagnosis on physical examination is the development of a new, harsh, loud holosystolic murmur heard best at the left lower sternal border. The diagnosis can be confirmed by echocardiography with color flow Doppler imaging. The presentation of acute, catastrophic deterioration with a new, harsh systolic murmur should prompt immediate cardiac surgery consultation for repair of a septal defect or ruptured papillary muscle of the mitral valve. Medical therapy including vasopressor and inotropic support, as well as intra-aortic balloon counterpulsation, is an important bridge to the definitive surgical treatments of valve repair or replacement.

Pericarditis, when associated with AMI, can occur early or in a delayed fashion; the former is termed *infarct pericarditis,* and the latter is known as *post-MI syndrome* or *Dressler's syndrome. Infarct pericarditis* is associated with transmural insult and thus principally involves the pinnacle of the infarct zone near the epicardium. Although the characteristic ST segment changes may be obscured by ST segment abnormalities related to the infarction itself, if they are evident, they are logically quite localized. Infarct pericarditis is a common cause of new chest pain in the first week after MI. This pain is characteristically pleuritic and worse in the supine position. Embolic complications are more common in patients with infarct pericarditis; linked to this is the higher rate of ventricular aneurysm development in this population.

Dressler's syndrome, unlike infarct pericarditis, does not require transmural involvement. It is a relatively uncommon, late complication occurring from 1 week to several months after the MI. Clinical features include fever, malaise, pleuropericardial pain, and at times the presence of a rub on cardiac auscultation. Laboratory findings are highly nonspecific and include an elevated erythrocyte sedimentation rate and leukocyte count. The ECG may show ST segment–T wave findings of pericarditis, although as with infarct pericarditis, these changes may be overshadowed by the evolving changes of the recent MI. PR segment depression is a telltale clue. Pericardial or pleural effusions may be evident

www.ketabpezeshki.com 66485457-66963820

and can be serous or bloody. Echocardiography assesses pericardial fluid and risk of tamponade. The pericardial reaction is believed to be immune mediated, and treatment includes anti-inflammatory agents.

Stroke may also complicate AMI, most commonly ischemic or thromboembolic. The major predisposing mechanisms with a recent MI are embolization from left ventricular mural thrombus with decreased ejection fraction, embolization from the left atrial appendage with atrial fibrillation, and hypercoagulability with concomitant carotid arterial disease. The rate of stroke is higher in the setting of MI (0.9% tapering to 0.1% at day 28 after MI) than in control subjects (0.014%).[38]

Hemorrhagic stroke is an obvious concern in the patient undergoing fibrinolytic therapy. The rate of hemorrhagic stroke with varying fibrinolytic agents is less than 1%, although the rate climbs in older patients. PCI lowers the overall risk of stroke compared with fibrinolytic therapy. Analysis of only fibrinolytic-eligible patients from the NRMI-2 database yields more than 24,000 patients treated with alteplase and more than 4000 who received primary angioplasty. The difference in stroke rate is highly significant (1.6% in the fibrinolytic group vs. 0.7% in the angioplasty group). Considering hemorrhagic strokes, the difference is again dramatic (1.0% in the fibrinolytic group vs. 0.1% in the angioplasty group).[39]

Hyperglycemia in the setting of AMI may be viewed as a complication, as well as a complicating disease process in AMI. Hyperglycemia is present in up to one half of all patients with STEMI, yet only one fifth to one fourth of those patients are recognized diabetics. Elevated glucose at the time of admission has independent negative implications for mortality rates in AMI patients. Although fasting blood sugar the day after presentation is a better predictor, an admission blood glucose level higher than 200 mg/dL is linked to similar mortality rates among diabetics and nondiabetics. There is a 4% mortality increase for nondiabetic patients for every 18-mg/dL elevation in blood glucose level. Hyperglycemia seems to induce a complex set of unfavorable cellular and biochemical circumstances, including negative effects on coronary flow and microvascular perfusion, as well as adverse effects on platelet function, fibrinolysis, and coagulation. Intravenous insulin therapy for glucose normalization is linked to improved outcomes in patients with STEMI as well as those in the medical intensive care unit. ACC/AHA guidelines acknowledge that tight control of blood glucose during and after STEMI decreases acute and 1-year mortality rates.[40]

Adverse events of ACS therapy should also be considered as potential complications, including hemorrhage associated with medications and resulting from invasive procedures. The various antiplatelet, anticoagulant, and fibrinolytic therapies (as noted earlier) are all associated with hemorrhage as a major complicating issue. In fact, within a single class of medications, many of these agents are so similar in efficacy that superiority is determined by the rate of occurrence of adverse effects. Aggressive supportive care coupled with "antidote" therapy is the most appropriate approach to patients with hemorrhagic complication from medications. Protamine can be helpful in the reversal of the heparins. Fresh frozen plasma (FFP) and platelet infusions are of value in certain anticoagulant and antiplatelet scenarios. The low-molecular-weight heparins (LMWHs) cannot be reversed. Fibrinolytic agents also cannot be reversed; rather, therapy including FFP and packed red blood cell (PRBC) transfusions is most appropriate. These various antidotal agents should be considered only with life-threatening hemorrhage. The clinician at the bedside, who can evaluate the risks and benefits of these treatments in the setting of a complicated ACS event, is in the best position to determine management strategies.

Procedural complications include arterial injury with hemorrhage related to percutaneous interventions; the most typical is a pseudoaneurysm of the femoral artery with hemorrhage into the thigh compartment or retroperitoneal area. The diagnosis is made based on a high degree of clinical suspicion in a patient with recent femoral artery cannulization. Physical examination findings, including extensive bruising in the thigh and bruits over the femoral artery, are suggestive; ultrasonography or CT of the thigh or retroperitoneal area can confirm the diagnosis.

DIAGNOSTIC INVESTIGATIONS

Electrocardiography

In the patient with chest discomfort or other symptoms suggestive of ACS, the 12-lead ECG helps establish the diagnosis and determines candidacy for therapy and risk assessment. In the setting of STEMI, the ECG provides crucial data regarding the diagnosis—anatomically arrayed ST segment elevation of at least 1 to 2 mV in at least two leads. Furthermore, the ECG provides pivotal information regarding therapeutic intervention—ST segment elevation establishes candidacy for emergent reperfusion therapy, either fibrinolysis or PCI. Regarding risk assessment, a number of ECG findings, such as ST segment deviation, LBBB, left ventricular hypertrophy (LVH), and QT interval prolongation, indicate an increased cardiovascular hazard.

Other 12-lead ECG determinations include cardiac rhythm, evolution of the ACS event, response to therapy, and clinical information suggesting an alternative diagnosis. Of course, rhythm determination is quite important, particularly if a compromising dysrhythmia is present. Lastly, an alternative diagnosis, such as PE or acute myopericarditis, can be suggested by the ECG.

In ACS, morphologic changes may occur in the T wave, the ST segment, the QRS complex, and even the PR segment (e.g., ST segment depression in atrial infarction or infarct-related pericarditis). Various rhythm disturbances also occur. Notably, the ECG may be normal or nonspecifically abnormal in the presence of ACS, including AMI. The ECG is limited by individual variations in coronary anatomy and preexisting coronary disease (e.g., previous MI, collateral circulation, coronary bypass surgery) and because it does not view the posterior, lateral, and apical left ventricular walls well.[37] In context, a single ECG is neither 100% sensitive nor 100% specific for AMI and reflects a single point in time.

Over-reliance on a normal or nonspecifically abnormal ECG in a sensation-free patient with anginal chest pain should be avoided. Patients with an initial nondiagnostic ECG who later develop AMI during that hospitalization are often sensation free or minimally uncomfortable on presentation. These patients frequently lack a past history of ischemic heart disease. Furthermore, the total elapsed time from chest pain onset in patients with normal ECGs does not assist in ruling out the possibility of AMI in patients with chest pain with a single ECG. Although the negative predictive value is quite high, it is not 100%, even up to 12 hours after the onset of the patient's chest symptoms.[41] The patient's history of the event—and the physician's interpretation of the history—is the most important diagnostic study.

Electrocardiographic Abnormalities in Acute Coronary Syndromes

The earliest electrocardiographic finding in AMI is the *hyperacute T wave,* which maintains its vector but becomes tall and peaked within minutes of the interruption of blood flow. It is usually broad based and slightly asymmetrical. The hyperacute T wave progresses to ST segment elevation in classic MI. This hyperacuity may not be appreciated on the initial ECG. The differential diagnosis of the tall T wave includes hyperacute T waves of ischemia, hyperkalemia, benign early repolarization (BER), LVH, LBBB, and pericarditis (Fig. 78-1).

www.ketabpezeshki.com 66485457-66963820

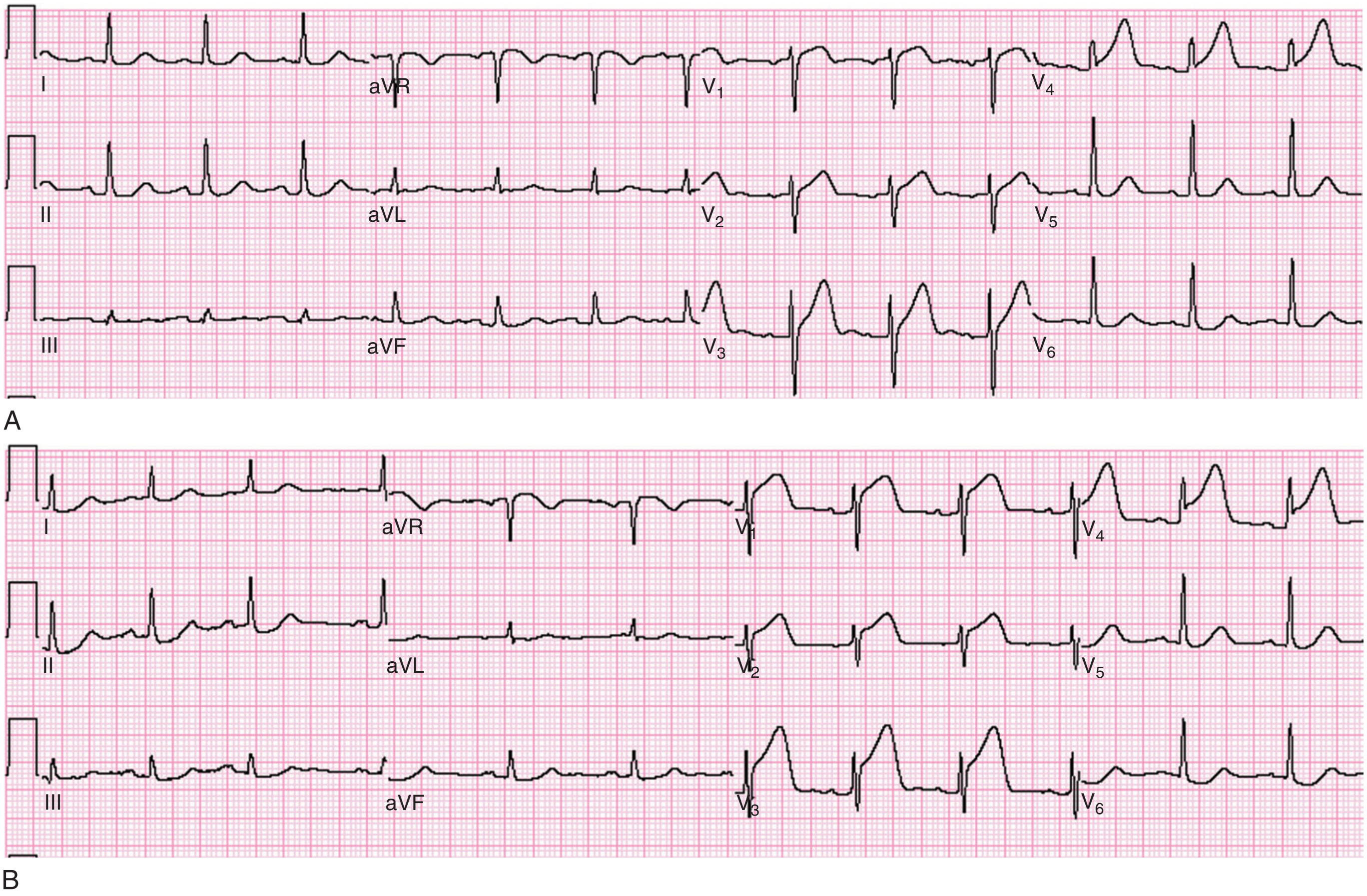


Figure 78-1. Hyperacute T wave of acute myocardial infarction. **A,** Note the broad, tall T waves in leads V_3 and V_4 in this patient with chest pain and diaphoresis. These are the hyperacute T waves of early ST segment elevation myocardial infarction. The ST segment is just beginning to rise in leads V_3 and V_4; leads V_1 and V_2 are also suspicious. **B,** This tracing is from the same patient, roughly 30 minutes after the electrocardiogram in **A.** Note the prominent ST segment elevation in leads V_1 to V_4.

Table 78-4 Differential Diagnosis of ST Segment Elevation on the Electrocardiogram

Acute myocardial infarction	Acute pericarditis
Left ventricular hypertrophy	Left ventricular aneurysm
Ventricular paced rhythm	Benign early repolarization
Normal variant	Osborn wave of hypothermia
Hyperkalemia	Brugada's syndrome
Pulmonary embolism	Acute cerebral hemorrhage
Prinzmetal's angina	Postelectrical cardioversion

As the AMI progresses, *ST segment elevation* may become evident. Morphologic variations of ST segment elevation can be seen from the J (or junction) point at the end of the QRS complex to the apex of the T wave. This upsloping portion of the ST segment usually progresses as it elevates from flat to convex, domed or "tombstoned"; if flat, it is characteristically horizontal or oblique. At times the ST segment may be concave or scooped in its elevation with AMI.[42] This morphology may progress to a convex shape or may stay the same throughout the infarction. The concave morphology, if noted in all elevated ST segments, is atypical for AMI and more commonly seen with other ST segment elevation syndromes (Table 78-4 and Fig. 78-2).[43,44]

ST segment elevation is measured in millimeters; one block on the ECG tracing is equivalent to 1 mm in height. The baseline is usually considered to be the TP segment, although some clinicians advocate use of the terminal point of the PR segment. In general, the most definable, constant baseline evident on the ECG should be used.

ST segment elevation, both benign and pathologic, is common (see Table 78-4). Most normal ECGs, especially those of men, may have some degree of ST segment elevation—indeed, upward of 90%. This elevation is seen in the precordial leads and is usually 1 mm or more in men and 1 mm or less in women. The ST segment elevation is concave and is more prominent as the corresponding S wave becomes deeper. Because of the common occurrence of this finding, it is not a normal variant but rather a normal finding.[44-47] A helpful point in differentiating normal ST segment elevation from the pathologic ST segment elevation of AMI is that the latter is a *dynamic* phenomenon; ECGs recorded sequentially over time with waxing and waning symptoms should demonstrate some fluctuation in the degree of ST segment deviation in the presence of ACS.

ST segment depression generally represents subendocardial or noninfarction ischemia. Ischemic ST segment depression is typically horizontal or downsloping; an upsloping contour may be seen but is less frequently associated with ischemia. Subendocardial ischemic ST segment depression may be diffuse, spanning anterior and inferior leads. The differential diagnosis of ST segment depression includes myocardial ischemia or infarction, repolarization abnormality of ventricular hypertrophy (the "strain" pattern), bundle branch block, ventricular paced rhythm (VPR), digoxin effect, hyperkalemia, hypokalemia, PE,

www.ketabpezeshki.com 66485457-66963820

intracranial hemorrhage, myocarditis, rate-related ST segment depression, postcardioversion of tachydysrhythmias, and pneumothorax (Fig. 78-3).

ST segment depression in ACS (1) may be seen in non–ST segment elevation AMI, (2) may precede ST segment elevation in ST segment elevation AMI, (3) may reflect a "mirror image" of ST segment elevation from posterior MI when found in the right-sided precordial leads (i.e., ST segment depression in V_1 to V_3 in posterior MI), and (4) may represent reciprocal ST segment depression seen with ST segment elevation AMI. With *reciprocal ST segment depression*, such changes are seen in leads on the "opposite" side of the heart from simultaneous ST segment elevation. For example, the ST segment depression seen in leads V_1 to V_3 with a posterior MI is actually a reciprocal finding resulting from the ST segment elevation that would be recorded in posterior leads V_8 and V_9. Inferior MI with ST segment elevation more frequently manifests reciprocal ST segment depression than does the anterior counterpart. The reciprocal ST segment depression in inferior MI is best seen in lead aVL, which is 150 degrees removed from lead III when the positive poles of these leads in the frontal plane are considered. Anterior ST segment elevation AMI may feature reciprocal ST segment depression in at least one of the inferior leads (II, III, or aVF). Reciprocal changes in the setting of STEMI increase the specificity and positive predictive value of the ECG in AMI.[45,46]

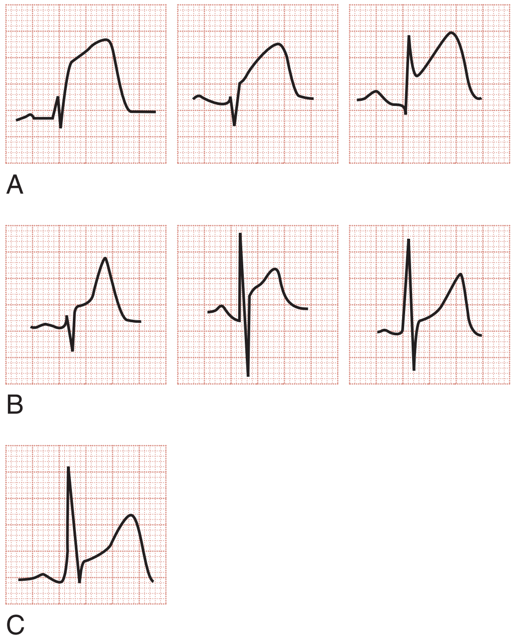


Figure 78-2. Analysis of ST segment–T wave morphology in acute myocardial infarction (AMI), benign early repolarization (BER), and acute pericarditis. An analysis of the ST segment–T wave morphology (from the beginning at the J point to the end at the apex of the T wave) may be particularly helpful in distinguishing among the various causes of ST segment elevation (STE) and identifying the AMI case. **A,** The initial upsloping portion of the ST segment is usually either flat (horizontally or obliquely) or convex in the patient with AMI. This morphologic observation, however, should be used only as a guideline; it is not infallible. **B,** Non-AMI causes of STE are seen here with concavity of the ST segment–T wave (left BER, middle pericarditis, right BER). **C,** Patients with STE related to AMI may demonstrate concavity of this portion of the waveform.

Ischemic ST segment depression is typically horizontal or downsloping; an upsloping contour may be seen but is less frequently associated with ischemia. Subendocardial ischemic ST segment depression may be diffuse, spanning anterior and inferior leads. The differential diagnosis of ST segment depression includes myocardial ischemia or infarction, repolarization abnormality of ventricular hypertrophy (the "strain" pattern), bundle branch block, VPR, digoxin effect, hyperkalemia, hypokalemia, PE, intracranial hemorrhage, myocarditis, rate-related ST segment depression, postcardioversion of tachydysrhythmias, and pneumothorax (see Fig. 78-3).

T wave inversions, although frequently nonspecific, should suggest possible myocardial ischemia. Normally the T wave is upright in the left-sided leads I, II, and V_3 to V_6 and inverted in the right-sided lead aVR. T wave vectors are variable in leads III, aVL, and aVF. They are usually normally inverted in V_1 and are occasionally normally inverted in lead V_2. The T wave inversions of ACS are classically narrow and symmetrically inverted. The preceding ST segment is typically isoelectric and may be bowed slightly upward or concave. Associated ST segment depression may occur. T wave inversions are best evaluated in comparison with the most recent prior ECG, given the multitude of normal variations (Fig. 78-4).

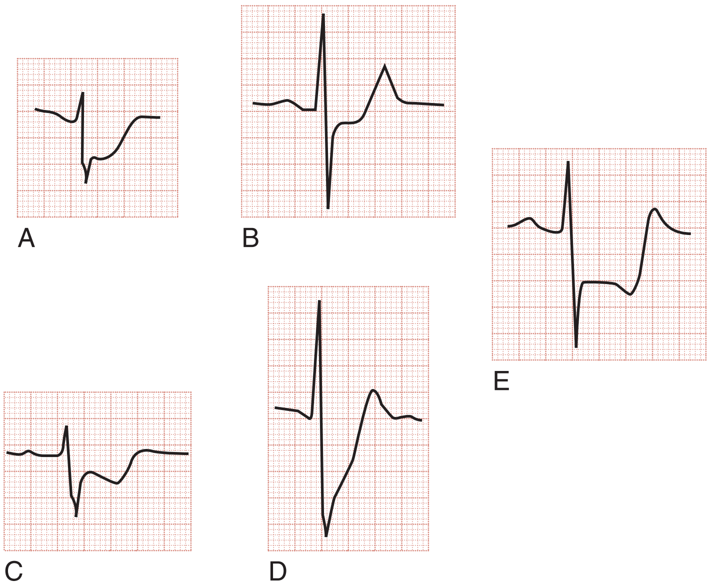


Figure 78-3. ST segment depression (STD) in acute coronary syndrome. **A,** Horizontal STD unstable angina pectoris (USAP). **B,** Horizontal STD (non–ST segment elevation [STE] acute myocardial infarction). **C,** Downsloping STD (USAP). **D,** Upsloping STD (USAP). **E,** Horizontal STD as seen in lead III in a patient with anterior wall acute myocardial infarction, an example of reciprocal STD, also known as *reciprocal change.*

www.ketabpezeshki.com 66485457-66963820

A notable subgroup of ischemic T wave inversions is associated with *Wellens syndrome*, which classically manifests with either deep symmetrical T wave inversions (type I) or biphasic T wave changes (type II) in the anterior precordial leads. The presence of biphasic T waves is suggestive of ischemic heart disease. Other electrocardiographic features include isoelectric or minimally elevated (<1 mm) ST segments and no precordial Q waves. This finding may manifest in the anginal or pain-free state and may or may not be accompanied by cardiac marker elevations, which is indicative of a lesion of the left anterior descending artery.

Although T wave inversion is sought as a harbinger of ACS, it can also occur as an evolutionary change after MI. In MI without culprit artery reperfusion, as the ST segments return to baseline the T waves may invert, although not particularly deeply. In hearts that are reperfused, T wave inversion may follow ST segment elevation, in either a biphasic or a deeply inverted morphology, an appearance much like the T wave changes of Wellens syndrome.[48,49]

The clinician must also consider *pseudonormalization* of the T wave as a potential electrocardiographic indicator of ACS. Pseudonormalization occurs when, during an acute episode of chest discomfort or anginal equivalent, an apparently normal-appearing T wave on the ECG replaces the "normally" inverted T wave that existed prior to the development of symptoms. The T wave assumes a normal appearance and may indicate ACS at this presentation.

The differential diagnosis of T wave inversion is broad and includes ACS, ventricular hypertrophy, bundle branch block, VPR, myocarditis, pericarditis, PE, pneumothorax, Wolff-Parkinson-White syndrome, cerebrovascular accident, hypokalemia, gastrointestinal disorders, hyperventilation, persistent juvenile T wave pattern, and normal variants.

Q waves are generally representative of irreversible myocardial necrosis but are rarely the sole manifestation of AMI. Pathologic Q waves may emerge within the first hour of infarction but most commonly develop 8 to 12 hours into the infarction. It follows that ST segment elevation with concomitant Q waves does not preclude consideration of emergent reperfusion therapy. Q waves may persist after MI as enduring markers of previous infarction on the ECG; in some cases, however, Q waves disappear with time regardless of whether the infarcted territory was reperfused.

Anatomic Location of Acute Myocardial Infarction

The regional distribution of an AMI can be derived from noting the pattern of the various morphologic changes that are described (Table 78-5). *Anterior infarctions* are primarily evidenced by changes in the precordial leads V_1 to V_4 (Fig. 78-5). Septal involvement is reflected by changes in V_1 and V_2. Extension to the lateral wall (i.e., anterolateral MI) is evident if the pathologic changes extend beyond leads V_1 to V_4 to include leads V_5, V_6, I, and aVL. In anterior ST segment elevation AMI, reciprocal ST segment depression may occur in leads III and aVF. The anterior wall is served by the left anterior descending artery. The first diagonal branch of the left anterior descending artery is likely to be involved when the ST segment elevation extends to leads I and aVL. Isolated occlusion of the diagonal branch of the left anterior descending artery displays similar findings, but of smaller amplitude, to those seen with left anterior descending artery occlusion (ST segment elevation in leads V_2 and V_3, and possibly leads V_1 and V_4, or both, along with ST segment depression in lead II and either III, aVF, or both).[50]

Lateral infarctions are frequently seen in concert with anterior infarction (anterolateral), inferior infarctions (inferolateral), or inferior infarctions with posterior extension (inferoposterolateral). This is because the lateral wall of the heart is variably served by the left anterior descending, right coronary, and left circumflex coronary arteries. Thus lateral involvement is manifested by changes in some or all of the lateral leads I, aVL, V_5, and V_6. So-called "high lateral infarctions" are restricted to leads I and aVL (Fig. 78-6) and are suggestive of occlusion of the left circumflex coronary artery; ST segment elevation in these leads may be accompanied by reciprocal ST segment depression in leads III, aVF, and V_1. Based on cardiac magnetic resonance imaging localization of some of these lesions, new Q waves appearing in leads I and aVL (but not V_6) indicate a "mid-anterior wall MI," previously referred to as a "high lateral MI."[6]

Inferior infarctions are characterized by morphologic changes in limb leads II, III, and aVF. The inferior wall of the heart and the

Table 78-5 Regional ST Segment Changes in Acute Myocardial Infarction

LOCATION	LEADS	ST SEGMENT
Anterior wall MI	V_1 through V_4	Elevation
Lateral wall MI	I, aVL, V_5, and V_6	Elevation
Inferior wall MI	II, III, and aVF	Elevation
Right ventricular wall MI	V_4R	Elevation
Posterior wall MI	V_8 and V_9 V_1 through V_3	Elevation Depression

Adapted from Aufderheide TP, Brady WJ: Electrocardiography in the patient with myocardial ischemia or infarction. In Gibler WB, Aufderheide TP (eds): Emergency Cardiac Care. St. Louis, Mosby, 1994.
MI, myocardial infarction.

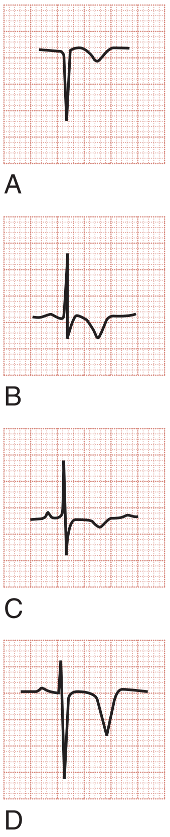


Figure 78-4. T wave inversions of acute coronary syndrome (ACS). **A** and **B,** T wave inversions in patients with ACS. **C,** T wave inversion in a patient with non–-ST segment elevation (STE) acute myocardial infarction. **D,** Deeply inverted T waves in a patient with proximal left anterior descending artery stenosis, Wellens syndrome.

www.ketabpezeshki.com 66485457-66963820

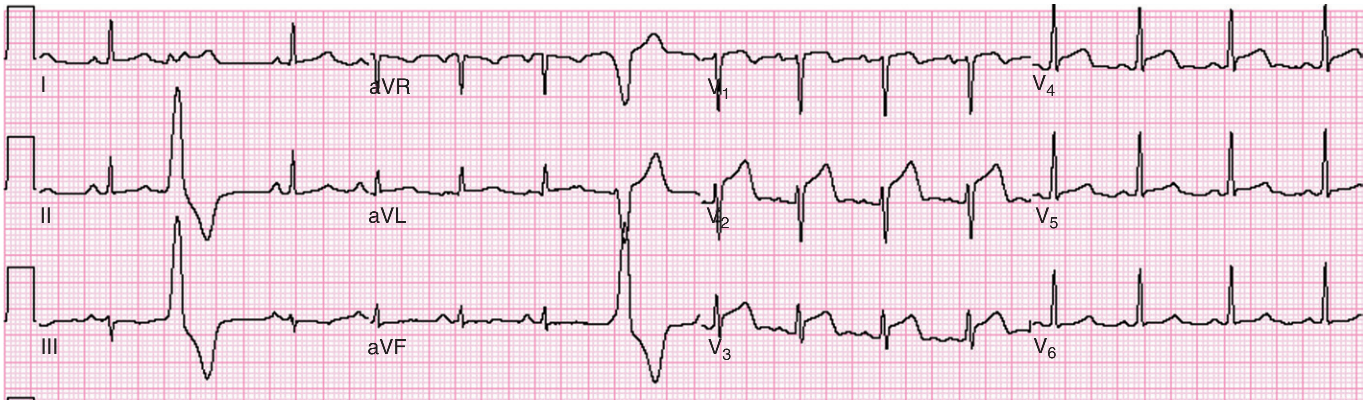


Figure 78-5. Anterior wall acute myocardial infarction (AMI). ST segment elevation is evident in leads V_1 to V_4. The morphology seems obliquely straight. Emergency cardiac catheterization revealed a 90% stenotic lesion in the left anterior descending artery; the patient did well after placement of a coronary stent but showed serum marker evidence of AMI.

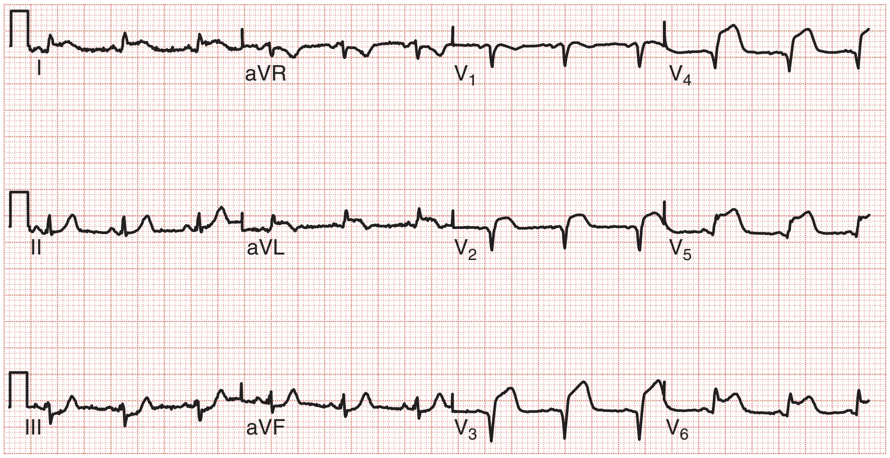


Figure 78-6. Anterolateral acute myocardial infarction. ST segment elevation is seen in leads I, aVL, V_5, and V_6. A proximal left anterior descending artery lesion with thrombus was noted at emergent percutaneous coronary intervention.

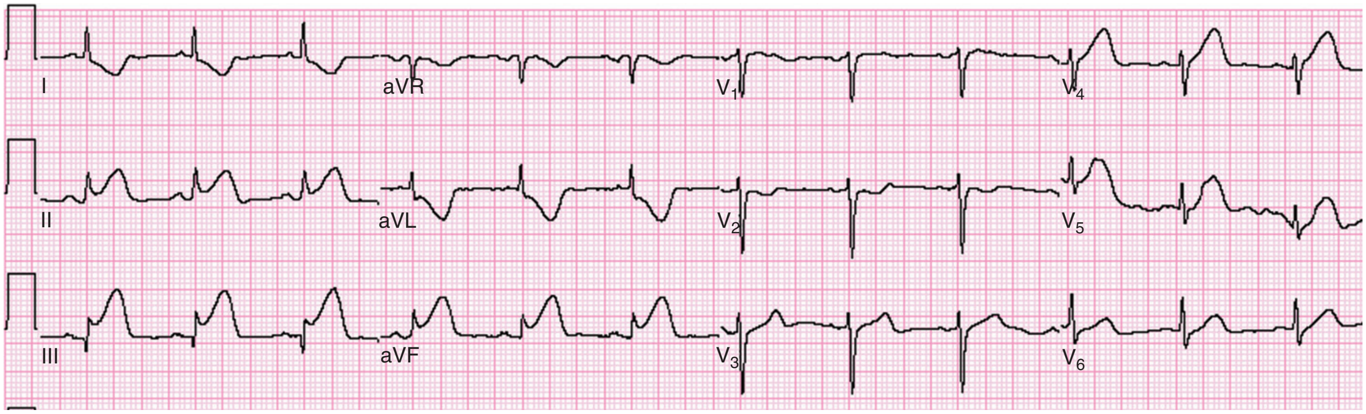


Figure 78-7. Inferior acute myocardial infarction with reciprocal changes. Marked ST segment elevation is seen inferiorly (leads II, III, and aVF). Classic reciprocal ST segment depression is evident in leads I and aVL.

AV node are served by the right coronary artery in roughly 90% of cases (right dominant); in the remainder, the left circumflex artery serves that function (left dominant). An inferior ST segment elevation AMI is present if two or more contiguous inferior leads (III, aVF, II) are involved; reciprocal ST segment depression is frequently seen in lead aVL, lead I, or both (Fig. 78-7) and perhaps in the anterior precordial leads: V_1 less than V_2 and V_3. ST segment depression in leads V_1 to V_3 in the presence of inferior MI can be caused by reciprocal change, posterior extension, or simultaneous anterior ischemia during inferior infarction. ST segment elevation inferiorly that is greater in lead III than in lead II, accompanied by ST segment depression in lead aVL, I, or both, is 90% sensitive and 71% specific for right coronary artery occlusion.[37] ST segment elevation in lead V_1 in the presence of an ST segment elevation inferior MI (with elevation greater in lead III than in lead II) suggests concomitant right ventricular infarction. Coexistent reciprocal change with inferior STEMI is associated with larger infarct size and increased mortality. Occlusion of the left circumflex

www.ketabpezeshki.com 66485457-66963820

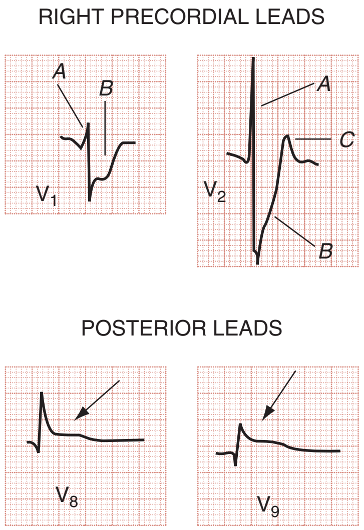


Figure 78-8. Isolated posterior wall acute myocardial infarction (PMI); complexes from right precordial leads and posterior leads. The right precordial leads V_1 and V_2 reveal typical findings of PMI with prominent R wave *(A),* ST segment depression (STD) *(B),* and upright T wave *(C).* The posterior leads V_8 and V_9 in the same case demonstrate ST segment elevation (STE) *(arrows),* confirming isolated PMI.

artery may be occult on the 12-lead ECG. If it is responsible for inferior ST segment elevation, the ST segment elevation in lead III would not be expected to exceed that seen in lead II, and lead aVL may display an isoelectric or elevated ST segment.[37]

Posterior infarctions are estimated to contribute to 15 to 20% of all AMIs and are usually seen along with inferior or inferolateral infarctions. Posterior infarctions occur in isolation in about 4% of AMI cases (demonstrating elevated ST segments only in accessory leads V_7 through V_9).[6] The culprit lesion may be in the right coronary artery, its posterior descending branch, or the left circumflex artery. In that the 12-lead ECG features no electrodes placed directly over the posterior wall of the heart, one has only the reciprocal ST segment changes in the right precordial leads (V_1 to V_3) with which to infer acute STEMI of the posterior wall. Findings include (1) horizontal ST segment depression; (2) a tall, upright T wave; (3) a tall, wide R wave; and (4) an R wave amplitude/S wave amplitude ratio greater than 1 (Fig. 78-8). The combination of horizontal ST segment depression with an upright T wave increases the diagnostic accuracy of the 12-lead ECG for posterior MI. In that the tall R wave in the right precordial leads is actually the mirror image of a posterior Q wave, its emergence may be delayed in posterior infarction. Additional leads (posterior leads V_8 and V_9) increase the sensitivity for detection of acute posterior MI. Patients with inferior MI who have either ST segment depression in leads V_1 to V_3 or ST segment elevation in the posterior leads V_8 and V_9 generally have larger infarction zones, lower resultant ejection fractions, and higher cardiovascular morbidity and mortality than patients with isolated inferior MI.[39] Cardiac magnetic resonance imaging suggests that these “posterior” infarctions producing tall R waves in leads V_1 and V_2 are actually lateral left ventricular wall MIs.[6] A consensus document suggests reclassifying posterior infarctions as inferobasal infarctions.[11]

Right ventricular infarctions rarely occur in isolation and are usually associated with inferior or inferoposterior MI, although only about one third of inferior infarctions have associated infarction of the right ventricle. At times, an anterior MI involves some (but less than half) of the right ventricular wall. It follows that occlusion in any of the major coronary arteries may lead to right ventricular infarction, although the right coronary is most commonly involved. Clinically, right ventricular infarction features include elevated jugular venous pressure and hypotension in the setting of inferior wall MI. These findings, however, are also suggestive of pericardial tamponade. Nitrate-induced hypotension is also suggestive of right ventricular infarction, and of tamponade. Initial therapy for both would include volume loading and avoidance of vasodilators or other agents that may lower the blood pressure.

ST segment elevation in lead V_1 in the setting of inferior MI (i.e., ST segment elevation in leads II, III, and aVF rather than in the setting of concomitant ST segment elevation in all anterior precordial leads) is suggestive of right ventricular infarction; this is not surprising in that lead V_1 is the most rightward of the precordial leads. These changes occasionally extend into lead V_2 with right ventricular infarction. ST segment elevation is usually greater in lead III than in lead II when right ventricular infarction coexists with inferior AMI.[51] This logically follows in that (in the frontal plane) the positive vector of lead III is more rightward than that of lead II. Application of “right-sided” precordial leads is the best means to diagnose right ventricular infarction with the ECG. These leads, as a mirror image of the left precordial leads, demonstrate ST segment elevation with right ventricular infarction in leads V_3R to V_6R, with V_4R having the highest sensitivity. ECG changes in the right-sided precordial leads with right ventricular infarction may be subtle owing to the smaller muscle mass of the right ventricle and the resulting diminution in QRS size (Fig. 78-9). Patients with inferior MI with concomitant right ventricular infarction have larger infarcts and experience more in-hospital complications and higher mortality rates.[52]

Left Main Coronary Artery Occlusion. In a patient with symptoms of ACS, ST segment elevation in lead aVR should prompt consideration of occlusion of the left main coronary artery. Pooled data demonstrate that ST segment elevation in lead aVR (>0.5 mV) is approximately 78% sensitive and 83% specific for left main coronary artery disease; alternatively, this finding in lead aVR may represent multivessel disease, acute proximal left anterior descending occlusion, or (less commonly) left circumflex or right coronary occlusion.[53] If ST segment elevation occurs in both lead aVR and lead V_1, greater elevation in the former lead favors left main disease, whereas if it is greater in the latter lead, occlusion in the left anterior descending artery is more likely.[54]

Electrocardiographic Differential Diagnosis of ST Segment Elevation

ST segment elevation on the ECG in the context of a presentation compatible with ACS is considered to represent acute myocardial ischemia until proved otherwise. Several other conditions, particularly LBBB and LVH, also feature ST segment elevation that mimics infarction (see Table 78-4).[47] Caution is required when interpreting ST segment elevation as to the decision to administer systemic fibrinolytic therapy.[55]

Benign early repolarization is a normal electrocardiographic variant that does not imply, or exclude, ACS or CAD. BER includes the following electrocardiographic characteristics: (1) ST segment elevation; (2) upward concavity of the initial portion of the ST segment; (3) notching of the terminal portion of the QRS complex at the J point (i.e., junction of the QRS complex with the ST segment); (4) symmetrical, concordant T waves of large amplitude; (5) diffuse ST segment elevation on the ECG; and (6) relative temporal stability over the short term, although these changes may regress with old age. J point elevation is usually less than 3.5 mm, and the concave ST segment is usually elevated less than 2 mm (although it may be elevated as much as 5 mm in some cases) in the precordial leads and 0.5 mm in the limb leads. Maximal ST segment elevation in BER is typically seen in leads V_2 to V_5. Isolated BER in the limb leads is quite rare and should prompt

www.ketabpezeshki.com 66485457-66963820

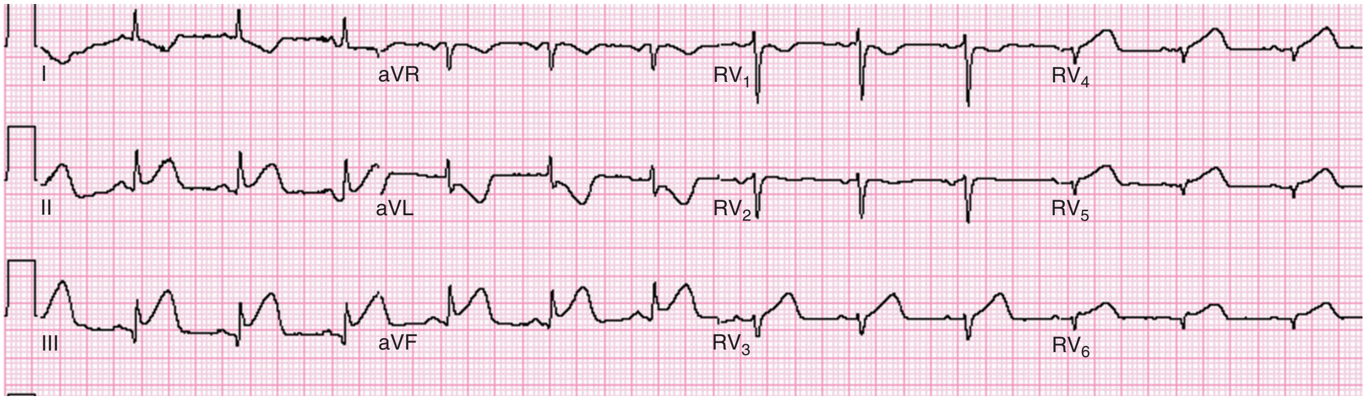


Figure 78-9. Right ventricular infarction demonstrated with right-sided precordial leads (RV_1 to RV_6). This tracing is taken from the same patient as in Figure 78-7. The ST segment elevation of inferior acute myocardial infarction is still present, as is the reciprocal ST segment depression in leads I and aVL. The precordial leads are right-sided chest leads, as might be inferred from the relatively low voltage. ST segment elevation is noted in leads RV_3 to RV_6 (V_3R to V_6R), consistent with right ventricular infarction.

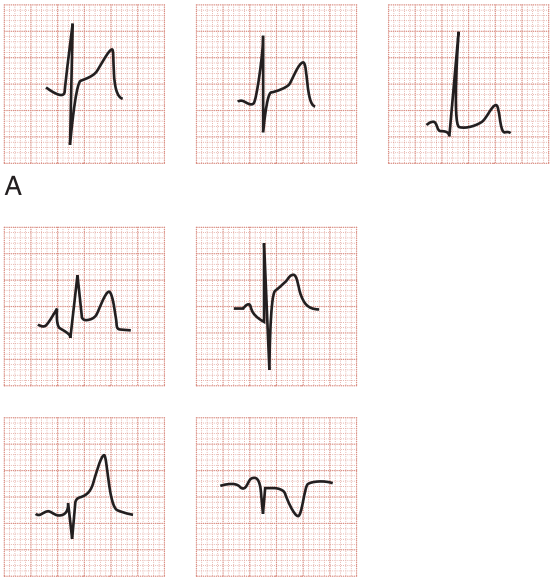


Figure 78-10. Noninfarctional ST segment elevation (STE). **A,** Benign early repolarization (BER) with concave STE. **B,** Acute pericarditis with concave STE and PR segment depression *(upper two examples)*; concave STE without PR segment abnormalities *(lower left example)*; and "reciprocal" STD and PR segment elevation in lead aVR *(lower right example)*.

reconsideration of AMI (Figs. 78-10A and 78-11). Reportedly, 31% of predominantly white individuals younger than 60 years who are resuscitated after idiopathic ventricular fibrillation have early repolarization changes in the inferolateral leads, as opposed to only 5% in a well-matched cohort of patients without syncope or heart disease. Whereas significant malignant dysrhythmias may occur in patients with this electrocardiographic finding, there are many who do well over a lifetime.[56]

Pericarditis, in the acute phase, features diffuse ST segment elevation as well. In pericarditis the ST segments are concave with an initial upsloping contour and are usually less than 5 mm in height. Occasionally the initial contour is obliquely flat, but convex or domed ST segment morphology is suggestive of AMI. The ST segment elevation is usually seen in all leads with the exception of aVR (where it is depressed); V_1 is variable. Focal pericardial inflammation manifests as a more accentuated change in the leads reflecting the affected region. PR segment depression is an insensitive yet specific associated electrocardiographic finding in pericarditis, which is typically best seen in the inferior leads and in lead V_6; correspondingly, PR segment elevation may be evident in lead aVR (Fig. 78-12; see Fig. 78-10B). In that ST segment changes are encountered in such patients, the most appropriate term applied is myopericarditis, rather than pericarditis. Recall that the pericardium is electrically silent; thus, electrocardiographic changes result from epicardial irritation and ST segment elevation—hence the term *myopericarditis.*

Left ventricular aneurysm (LVA), wherein a focal area of myocardium paradoxically bulges outward during systole, has characteristic electrocardiographic changes that can be difficult to differentiate from those of AMI. Considerable overlap exists between populations of patients with potential for AMI and LVA, and the electrocardiographic changes of LVA tend to be regional rather than diffuse.[56] Anatomically, LVA is most commonly found anteriorly, and changes are most often seen in leads V_1 to V_6 as well as leads I and aVL. ST segment elevation may be of any morphology (e.g., convex or concave), and Q waves may be present (Fig. 78-13). The calculation of the ratio of the amplitude of the T wave to the QRS complex may help distinguish acute anterior MI from LVA. If the ratio of the amplitude of the T wave to the QRS complex exceeds 0.36 in any single lead, the ECG probably reflects acute MI. If the ratio is less than 0.36 in all leads, however, the findings are probably a result of ventricular aneurysm.[57]

Left bundle branch block is a confounding pattern that reduces the ECG's ability to detect ACS. A new, or presumably new, LBBB is strongly suggestive of ACS when noted in the appropriate clinical presentation. Preexisting LBBB, however, shares many similarities to various electrocardiographic findings of ACS. In the right precordial leads (leads V_1 to V_3), ST segment elevation and tall, vaulted, upright T waves mimic those seen in acute anterior MI. The QS pattern of LBBB in these leads resembles the Q waves seen in infarction. Depressed ST segments with T wave inversions are seen in some or all of the lateral leads (leads V_5, V_6, I, and aVL) in LBBB; both of these resemble ischemic changes seen in ACS. Yet these findings in LBBB are merely expressions of the "rule of appropriate discordance." The ST segment and T wave vectors are expectedly discordant, or opposite in direction, to the major vector of the QRS complex in those leads. Because LBBB is a frequent finding on the ECG of a patient at risk for CAD, the normal findings in LBBB (Fig. 78-14) and the presentation of ST segment AMI in a patient with LBBB must be distinguished.

Sgarbossa used the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO-I) trial database to

www.ketabpezeshki.com 66485457-66963820

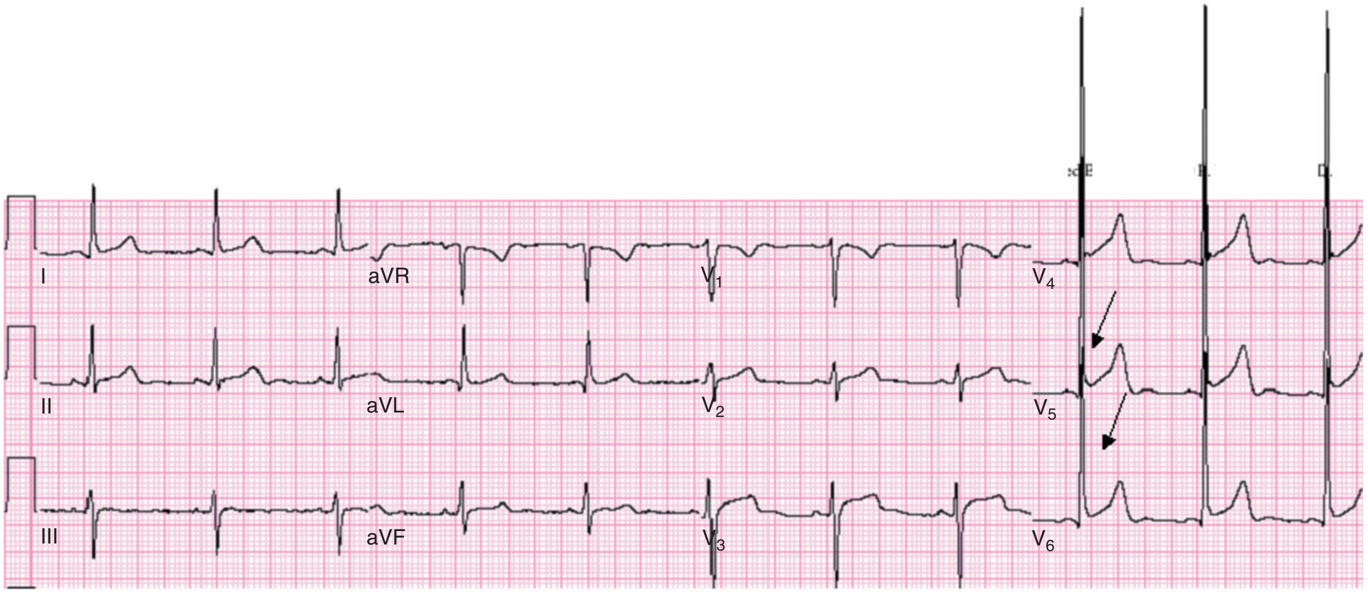


Figure 78-11. Benign early repolarization. Note the upwardly concave ST segment elevation, best seen in leads V_4 to V_6. The T waves are relatively large in the same leads. Subtle notching is also seen at the J point in leads V_4 and V_5. Prior electrocardiograms of this patient were unchanged.

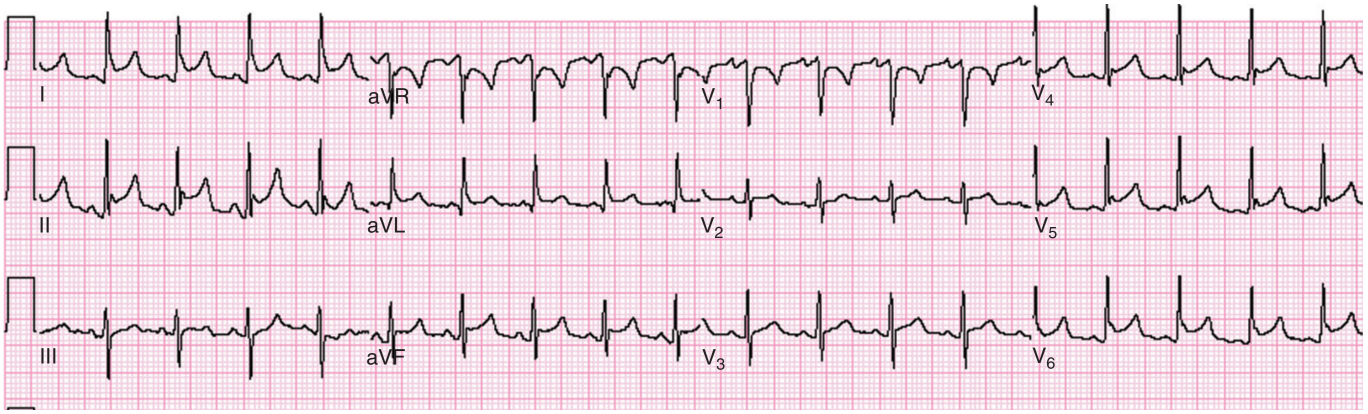


Figure 78-12. Pericarditis. This tracing demonstrates several classic signs of pericarditis: (1) sinus tachycardia; (2) diffuse, concave upward ST segment elevation; (3) PR segment depression, best seen in lead II; and (4) PR segment elevation in lead aVR.

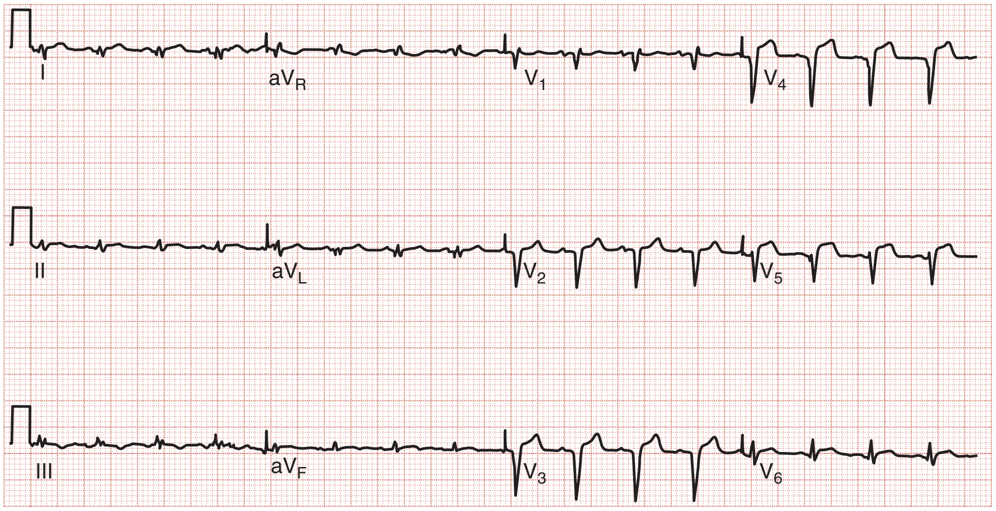


Figure 78-13. Left ventricular aneurysm: representative example of 12-lead electrocardiogram from patient with anterior left ventricular aneurysm. Note well-developed, completed Q waves in leads V_2 through V_5 and absence of reciprocal changes in contralateral leads. (Adapted from Aufderheide TP, Brady WJ: Electrocardiography in the patient with myocardial ischemia or infarction. In Gibler WB, Aufderheide TP [eds]: Emergency Cardiac Care. St. Louis, Mosby, 1994, p 196-216.)

www.ketabpezeshki.com 66485457-66963820

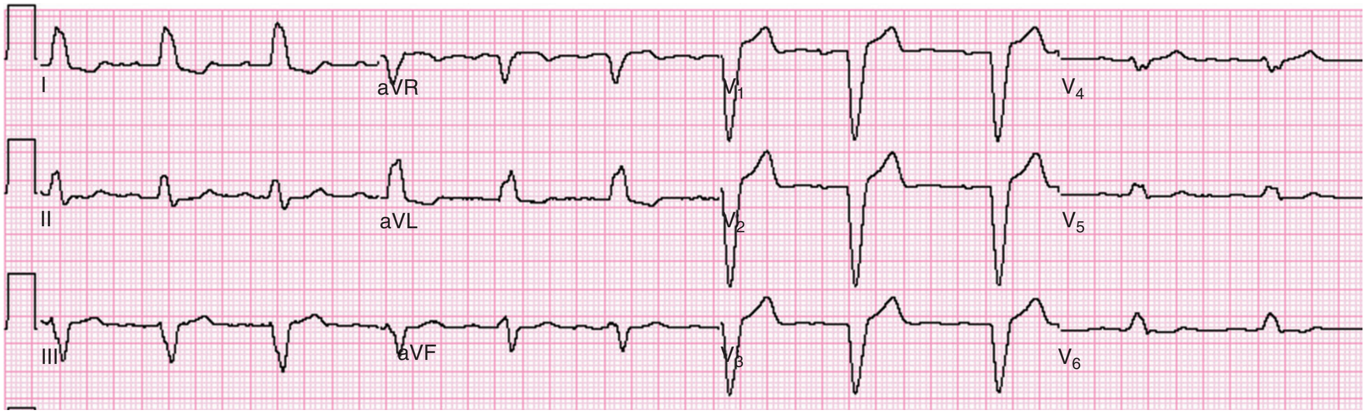


Figure 78-14. Left bundle branch block (LBBB) (normal). This tracing demonstrates the classic findings of LBBB: (1) QRS complex width greater than 0.12 second; (2) absence of Q wave in lead V_6; (3) broad monophasic R wave in leads V_5, V_6, I, and aVL; (4) discordant ST segment–T wave changes in leads V_1 to V_3 (simulating acute myocardial infarction), I, and aVL. A first-degree atrioventricular block is also apparent.

obtain a population of patients with LBBB and enzymatic evidence of AMI.[58] Three independent electrocardiographic predictors of MI in the presence of LBBB were identified: (1) ST segment elevation of at least 1 mm that is concordant with the QRS complex; (2) ST segment depression of at least 1 mm in lead V_1, V_2, or V_3; and (3) ST segment elevation of at least 5 mm that is discordant with the QRS complex. These findings were assigned weighted scores of 5, 3, and 2, respectively. For accuracy in diagnosis, a specificity of 90% requires a score of at least 3. Thus if an ECG features only discordant ST segment elevation of 5 mm or more but neither of the other two criteria, further testing is recommended before one can conclude that the ECG is indicative of AMI (Fig. 78-15).[58] Subsequent literature yields mixed reviews of the Sgarbossa criteria for diagnosis of AMI in the presence of LBBB.[58,59] Ultimately the approach to the patient with LBBB and possible MI remains complicated; diagnostic adjuncts to the history and physical examination (e.g., serial ECGs, comparison with prior ECGs, echocardiography, serum cardiac marker measurement) should be liberally used when the ECG does not show obvious evidence of AMI as noted by the Sgarbossa criteria.[58] A new LBBB, together with a clinical impression of AMI, remains an indication for fibrinolytic therapy or PCI.

Ventricular paced rhythms can mimic and mask the manifestations of AMI. VPRs originating in the right ventricular apex create a wide QRS complex, with a pseudo-LBBB pattern. As with LBBB, the right precordial leads in VPR typically feature predominantly negative QRS complexes with discordant ST segments and T waves that are elevated and tall or vaulted, respectively. Unlike LBBB, however, VPR originating in the right ventricular apex often yields a predominantly negative QRS complex in leads V_5 and V_6 as well (which is oriented leftward and slightly downward, whereas the impulse generated from the pacemaker wire is oriented superiorly). Furthermore, small vertical pacemaker spikes immediately preceding the QRS complex should be a clue to VPR, although these deflections are at times hard to detect on the 12-lead ECG.

Limited data exist to guide the clinician in interpretation of the 12-lead ECG in this setting. As with the LBBB scenario, the VPR pattern represents a significant confounding variable in the evaluation of the patient with chest pain suspected of having ACS. Sgarbossa and associates advanced criteria for detection of AMI in the presence of VPR that are similar to those for LBBB.[58,60] These, too, are derived from the GUSTO-I database, but from a smaller group of patients. The criteria are essentially the same as the LBBB criteria: (1) ST segment elevation of at least 5 mm that is discordant with the QRS complex; (2) ST segment elevation of at least 1 mm that is concordant with the QRS complex; and (3) ST segment depression of at least 1 mm in lead V_1, V_2, or V_3 (Fig. 78-16).[60]

Left ventricular hypertrophy may mimic or obscure ACS on the ECG. LVH may feature prominent left-sided forces, manifesting as large rS or QS complexes in the right precordial leads—yet these changes seldom extend beyond V1 and V2 in the case of LVH. Consistent with the rule of appropriate discordance, the leads demonstrating such a pattern feature discordant ST segment elevation and tall, vaulted T waves, paralleling the changes of AMI. The initial portion of the elevated ST segment in LVH is generally concave, as opposed to the obliquely straight or convex pattern that usually (but not always) is seen with ST segment elevation in AMI. In LVH, the left precordial leads (and at times leads I and aVL) may show evidence of repolarization abnormality (or strain pattern), with ST segment depression and asymmetrically inverted T waves. The presence of this strain pattern in the left precordial leads is reassuring when ST segment elevation and tall T waves in the right precordial leads are being attributed to LVH rather than to AMI because one is essentially the mirror image of the other. The changes in LVH should be static over time (Fig. 78-17).

Takotsubo cardiomyopathy is referred to as *left apical ballooning* or "broken heart" syndrome. Takotsubo cardiomyopathy features ST segment elevation (or deep T wave inversions) without evidence of obstructive CAD. Positive serum markers for cardiac ischemia may be present, as well as hemodynamic compromise. It occurs principally in postmenopausal women and characteristically is triggered by intense emotional stress. Ballooning of the left ventricular apex is seen on ventriculography or echocardiography. Prognosis is excellent, typically with recovery of normal wall motion within a month or less.[6,60]

Non–ST Segment Elevation Myocardial Infarction

Non–ST segment elevation myocardial infarction supplants *non–Q wave MI,* previously termed *subendocardial infarction.* Precise terminology is difficult because Q waves may disappear with time and the criteria for "significant" Q waves vary. Moreover, transient ST segment elevation may simply be missed on ECG. Nonetheless, it is useful to describe the entity wherein there is serum marker evidence of MI in the appropriate clinical scenario but no captured ST segment elevation.

Pathophysiologically, total occlusion of the diseased artery may not have occurred, or the infarct zone may have been partially spared by collateral circulation or therapeutic intervention. ECG manifestations of NSTEMI include ST segment depression and T wave inversion, which may be deep and symmetrical. Absence of

www.ketabpezeshki.com 66485457-66963820

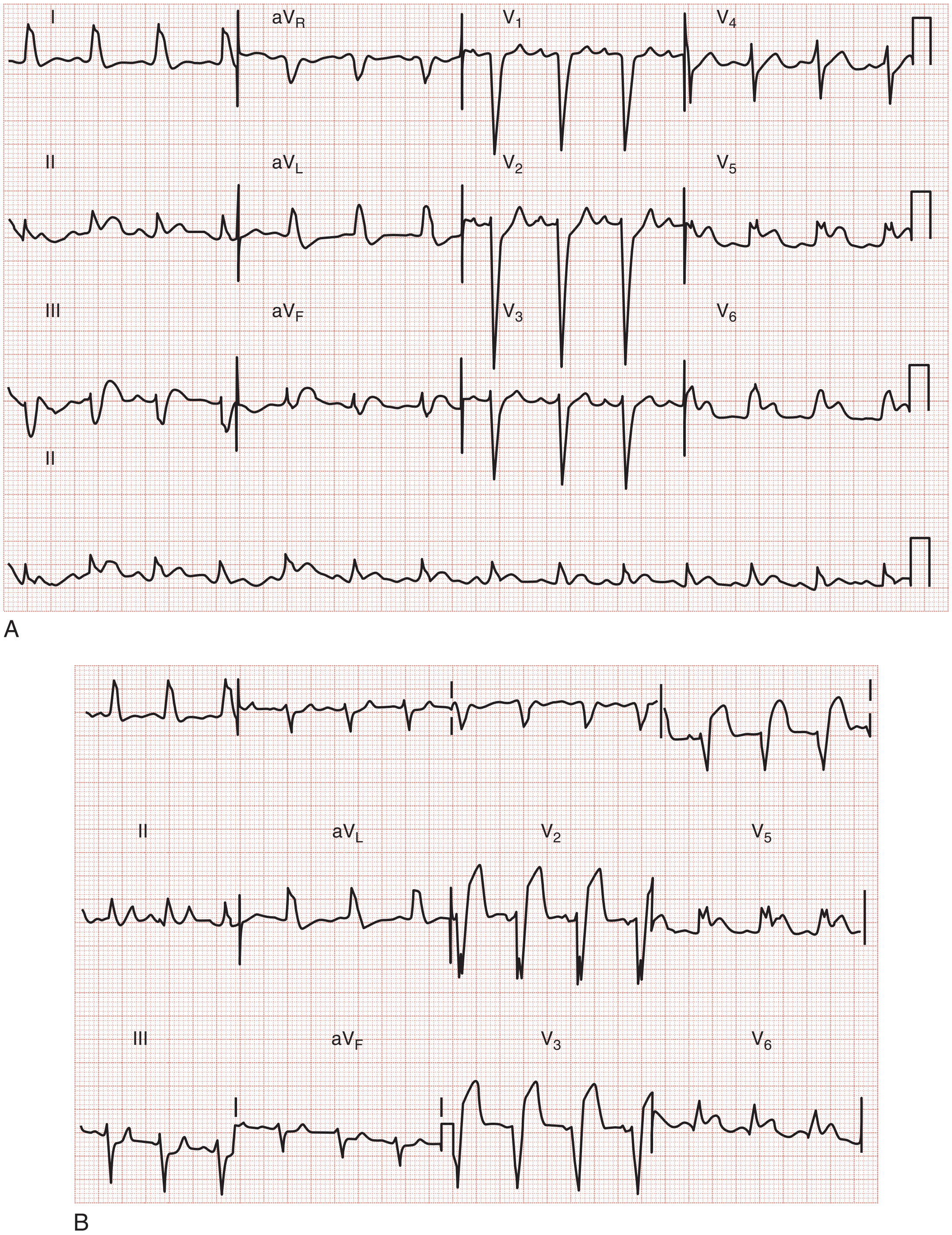
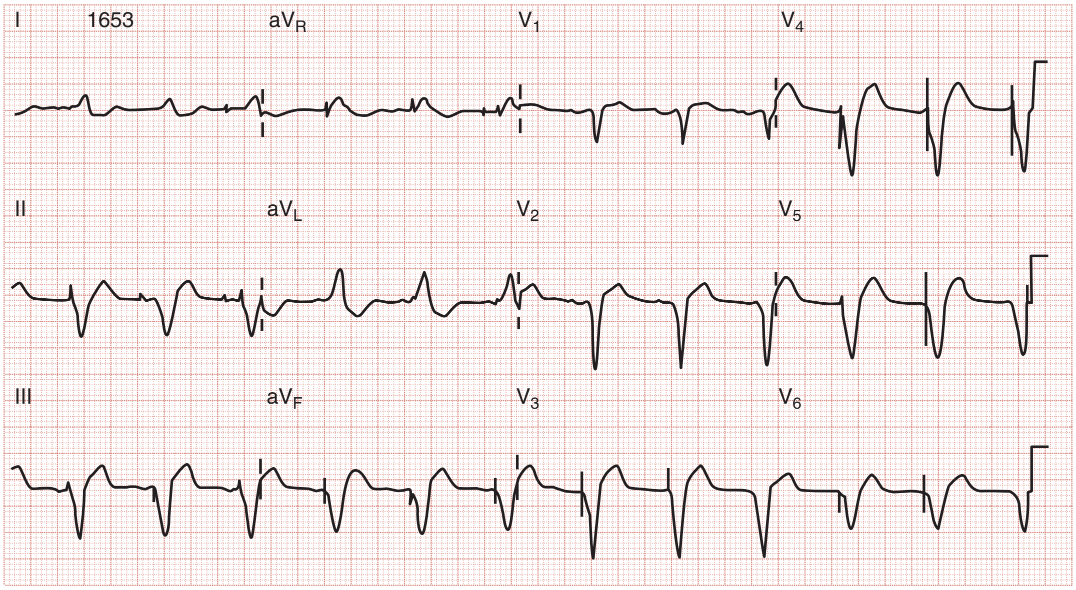
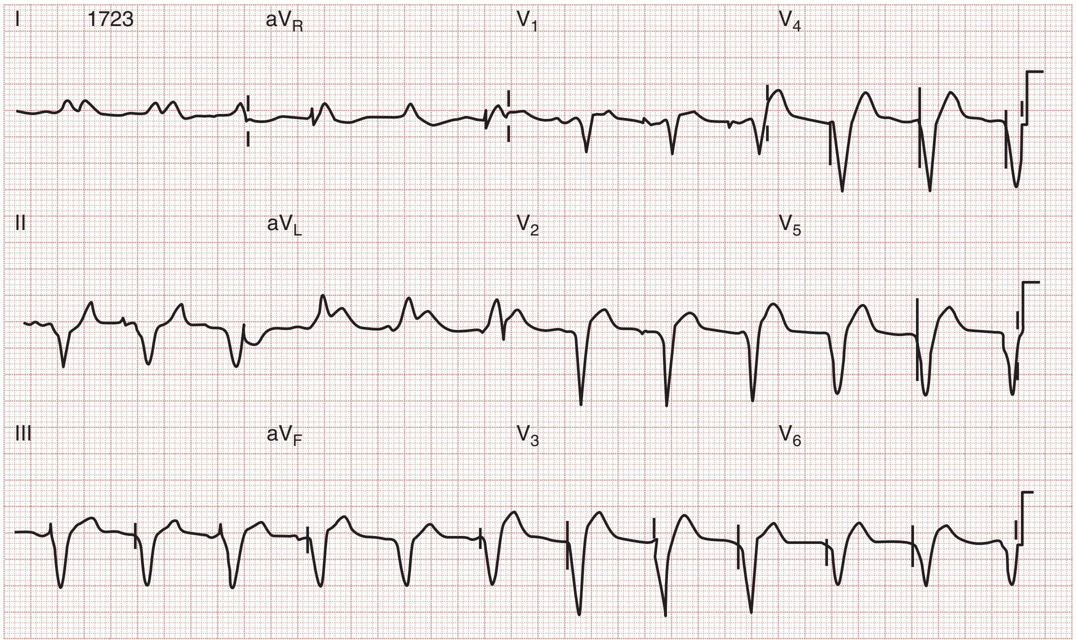


Figure 78-15. Acute myocardial infarction (AMI) in left bundle branch block (LBBB). **A,** Using the Sgarbossa criteria,[58] there is strong evidence of AMI because of the concordant ST segment elevation greater than 1 mm in leads II, V_5, and V_6; also suggestive is the ST segment depression seen in V_2. **B,** Again, applying the Sgarbossa criteria to this tracing with underlying LBBB, AMI is strongly suggested.[58] There is concordant ST segment elevation in leads V_5 and V_6 that appears to exceed 1 mm; furthermore, there is excessively discordant ST segment elevation in leads V_2 and V_3, probably greater than 5 mm.

www.ketabpezeshki.com 66485457-66963820



A



B

Figure 78-16. Permanent right ventricular paced pattern with acute myocardial infarction (AMI); ventricular paced rhythm. **A,** Appropriate ST segment–T wave findings in the patient with a paced rhythm. **B,** Serial electrocardiogram from the patient in **A,** revealing evolution of changes worrisome for AMI, including concordant ST segment elevation in leads I and aVL consistent with lateral wall AMI.

www.ketabpezeshki.com 66485457-66963820

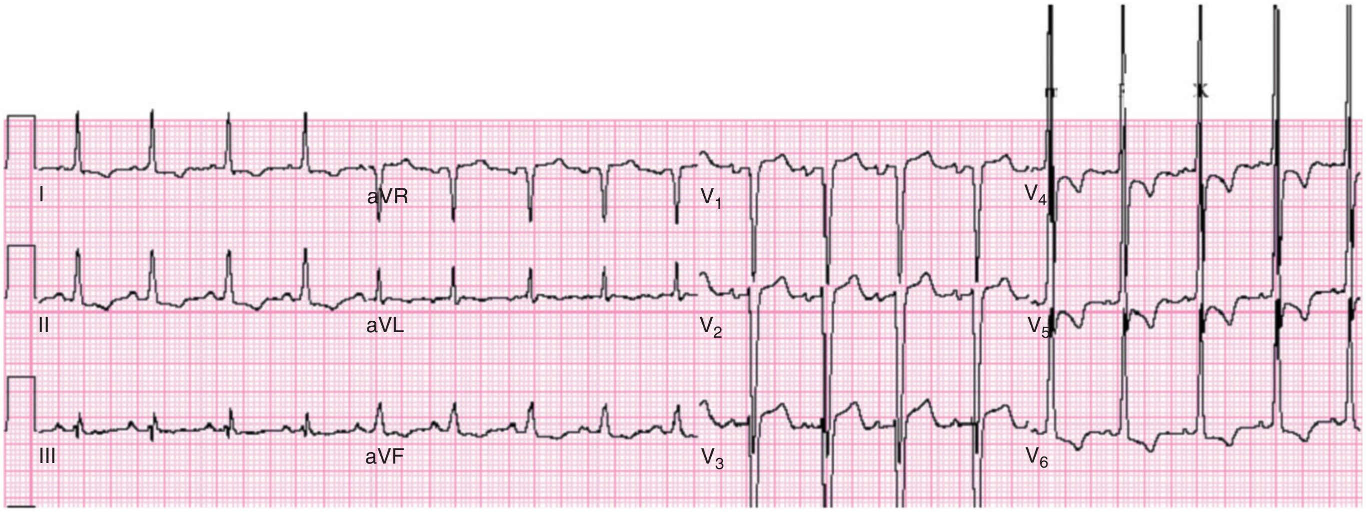


Figure 78-17. Left ventricular hypertrophy (LVH) with repolarization abnormality. This tracing demonstrates classic repolarization abnormality, with ST segment depression in the left-sided precordial leads following large-amplitude R waves. The T waves in these leads are asymmetrically inverted. The right precordial leads (V_1 and V_2) show a mirror image of the changes seen in V_3 to V_6, with slight ST segment elevation (contour initially concave) and asymmetric tall T waves. See Figure 78-20B for evidence of evolving acute myocardial infarction in a patient with LVH and repolarization abnormality.

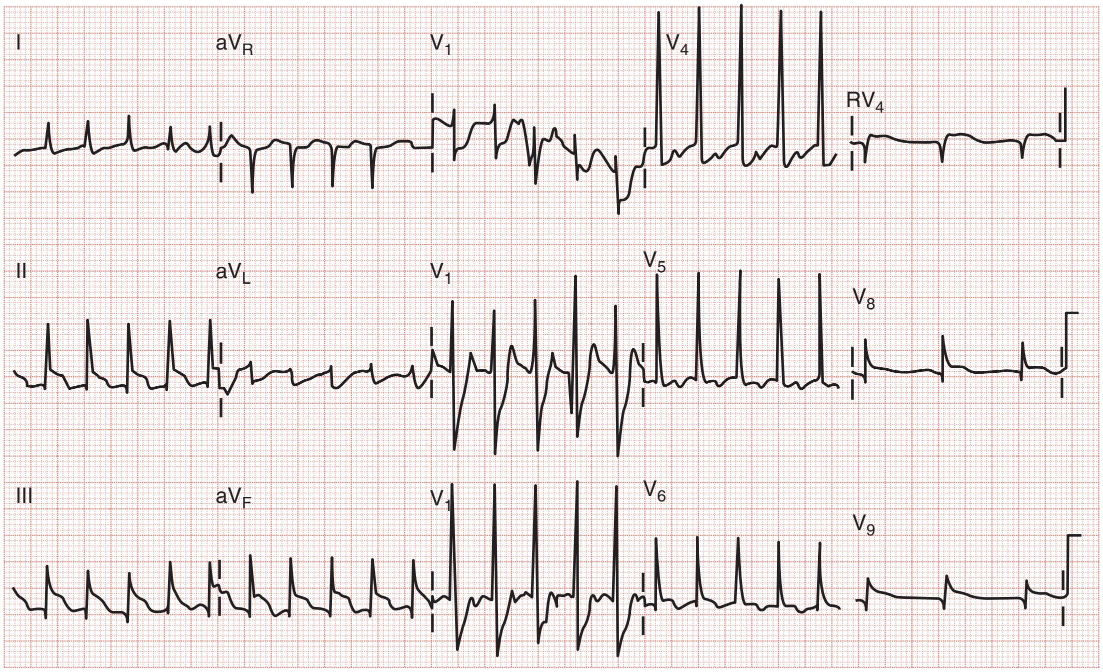


Figure 78-18. Fifteen-lead electrocardiogram (ECG) with inferior, lateral, posterior, and right ventricular acute myocardial infarction (AMI). The standard 12-lead ECG reveals the typical ST segment elevation (STE) in the inferior and lateral leads as well as ST segment depression (STD) with prominent R wave in the right precordial leads. Posterior AMI is indicated by both the right precordial STD with prominent R wave and the STE in posterior leads V_8 and V_9. Note that the degree of STE is less pronounced than that seen in the inferior leads because of a relatively longer distance from the posterior epicardium to surface leads. The right ventricular infarction is noted in this case, using the simplified approach with only RV_4, which demonstrates STE of relatively small magnitude.

STEMI, however, does not necessarily translate to better outcomes. A study analyzing more than 250,000 AMI patients from the NRMI-2, NRMI-3, and NRMI-4 databases determined that patients with ST segment depression on the initial ECG have an in-hospital mortality rate of 15.8%—similar to that of patients with ST segment elevation or LBBB (15.5%).[61] ST segment depression may herald true posterior infarction on the 12-lead ECG. Acute posterior (inferobasal) MI is one entity wherein emergent fibrinolysis or PCI is indicated in the absence of ST segment elevation on the 12-lead ECG.

Electrocardiographic Adjuncts in the Diagnosis of Acute Coronary Syndrome

Additional lead ECGs can increase sensitivity for AMI by evaluating regions of the heart prone to electrical silence on the 12-lead tracing. Most commonly, additional lead ECGs use posterior (leads V_8 and V_9) and right ventricular (V_4R) electrodes, thus constituting the 15-lead ECG (Fig. 78-18). Posterior leads V_8 and V_9 are placed under the tip of the left scapula and at the left paraspinal area, at the same level as leads V_4 to V_6. Morphologic

www.ketabpezeshki.com 66485457-66963820

changes in the posterior leads may be subtle, principally because of the increased distance between these electrodes and the posterior wall of the heart (Fig. 78-19).

Electrocardiographic imaging of the right ventricle is enhanced with the use of the right-sided chest leads V_1R to V_6R (also termed RV_1 to RV_6). These are placed in mirror image fashion across the right precordium. Of the right precordial leads, V_4R has the highest sensitivity for right ventricular infarction and is the lead of choice to include in the 15-lead tracing. Morphologically, less pronounced changes can be expected in the right-sided chest leads because of the relatively thinner wall of the right ventricle.

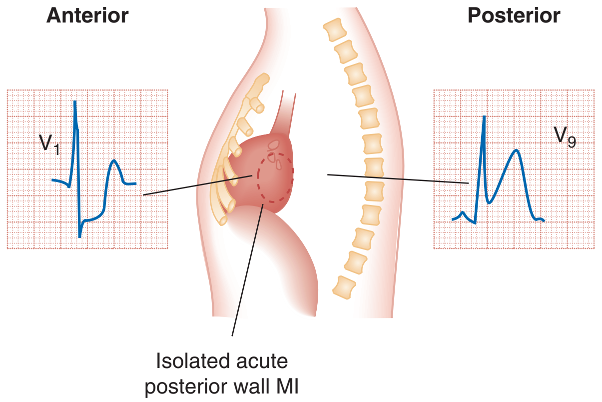


Figure 78-19. Schematic of thorax depicting single anterior and posterior complexes in posterior wall acute myocardial infarction (AMI). The standard electrocardiographic precordial (anterior) leads image the posterior wall of the left ventricle from the anterior perspective of the thorax. Acute infarction of this region manifests electrocardiographic changes that are frequently the reverse of the typical abnormalities of AMI. In this schematic example, lead V_1 reveals ST segment depression with an upright T wave and prominent R wave. Use of the posterior lead V_9 demonstrates ST segment elevation, consistent with AMI.

Use of the 15-lead ECG may improve diagnostic precision but does not appear to affect the rate of AMI diagnosis, use of reperfusion therapy, disposition, or outcome in patients with chest pain evaluated for ACS.[62] In the subset of ED patients identified as candidates for admission to the cardiac care unit (i.e., high-risk patients), the 15-lead ECG increased the sensitivity of ACS detection by 12%.[63] Possible applications for additional lead ECGs include the following: (1) ST segment changes (depression or elevation) in leads V_1 to V_3, either in an isolated lead or in more than one; (2) equivocal ST segment elevation in the inferior (II, III, aVF) or lateral (I, aVL) limb leads or both; (3) all inferior STEMI; and (4) hypotension in the setting of ACS. Additional lead applications can be used, including the 18- and 24-lead ECG; electrocardiographic body mapping with use of multiple ECG leads, such as the 80-lead ECG, can also be used. In general, the clinician is able to image larger segments of the heart with more electrocardiographic leads in use. It is suggested that these additional lead ECGs, including body mapping, can increase the rate of STEMI diagnosis and thus the number of patients who are candidates for emergent reperfusion therapy.

Serial ECGs and ST segment trend monitoring overcome the limitations of the snapshot 12-lead ECG. The use of increased electrocardiographic surveillance demonstrates diagnostic benefit in patients with recurrent or continuous chest pain, particularly in patients with an initially normal nondiagnostic or possible ST segment mimicking syndrome (e.g., ST segment elevation potentially resulting from BER) ECG. Examination of ST segment trends (measured every 20 seconds for at least the first hour) and automated serial ECGs (at least every 20 minutes) in ED patients with chest pain can significantly increase the sensitivity and specificity for detection of AMI (16%) and ACS compared with the initial ECG (Fig. 78-20).[64] In more than 600 patients admitted with nondiagnostic initial ECGs and symptoms consistent with ACS, 12 hours of continuous 12-lead ECG monitoring in a coronary care unit setting revealed that only serum cardiac marker

Figure 78-20. Serial electrocardiography. **A,** Representative example of lead III in a patient with chest pain and an initially nondiagnostic electrocardiogram depicting the evolution of ST segment elevation (STE) acute myocardial infarction (AMI). **B,** Representative example of lead V_2 in a patient with the left ventricular hypertrophy pattern. Serial sampling of this patient with ongoing chest pain and a confounding electrocardiographic pattern reveals the progression to STE AMI. **C,** Representative example of lead V_3 in a patient with left bundle branch block and evolving AMI. **D,** Representative examples of lead III in a patient with chest pain and noninfarctional STE; note the lack of change (degree of elevation as well as morphology of elevation) over time in this patient with benign early repolarization.

www.ketabpezeshki.com 66485457-66963820

elevation and presence of ST segment episodes (defined as ST segment elevation or depression more than 1 mm different from baseline that endured for at least 1 minute) predict cardiac death or MI.[65]

Measuring QT dispersion may facilitate risk stratification, assessment of therapeutic success, and monitoring of ongoing pharmacotherapy. QT dispersion is the calculated difference between the longest and shortest QT intervals on a 12-lead ECG. Ischemic myocardium has a prolonged repolarization time, and the QT interval measures time from ventricular depolarization to repolarization. Increased variability in measured QT intervals translates to greater QT dispersion, which reflects underlying regional ischemia. Comparing ACS or AMI patients with those found to be free of such disease reveals a difference between populations in QT dispersion values.

Body surface mapping increases the amount of electrocardiographic data for processing and decision-making. Whereas serial ECGs and ST segment trend monitoring increase the period of time over which data are collected on a 12-lead ECG, body surface mapping increases the number of electrodes used to gather data and increases the vantage points from which the heart is evaluated. Various devices use 40 to 120 leads. With an 80-electrode device, 64 chest and 16 back electrodes are applied in a vestlike fashion with self-adhering strips. Recording from all electrodes simultaneously, the body surface map enters ST segment elevation and depression data into a computer, which transforms the data into a color-coded torso image. With red representing ST segment elevation, blue signifying ST segment depression, and green reflecting normal, the degree of disease is also expressed in terms of color intensity.[66-68] Body surface mapping may increase sensitivity for MI, especially in areas that are relatively electrically silent on the 12-lead ECG (e.g., posterior and lateral walls of the left ventricle and the right ventricle) and in patients with underlying LBBB.[66-68] In the Optimal Cardiovascular Diagnostic Evaluation Enabling Faster Treatment of Myocardial Infarction (OCCULT MI) trial, the 80-lead ECG provided an incremental 27.5% increase in STEMI detection as compared with the 12-lead ECG. Patients with 80-lead ECG-only STEMI had adverse outcomes similar to those encountered in the 12-lead STEMI patients, yet these individuals were treated much less aggressively.[69]

Limitations of Electrocardiography in Acute Coronary Syndrome

The sensitivity and specificity of a single ECG for AMI are approximately 60% and 90%, respectively. Serial ECGs in the setting of continued or recurrent pain increase the diagnostic utility.[70] The initial ECG is nondiagnostic in approximately half of the patients in the ED who are ultimately diagnosed with AMI. Moreover, nondiagnostic and even normal ECGs do not exclude the diagnosis for AMI because around 20% of patients ultimately diagnosed with AMI have nondiagnostic ECGs earlier in their course. As time elapses from symptom onset to ECG recording, the ability of the ECG to exclude AMI does not markedly increase.[41] Thus a single normal or nondiagnostic ECG does not ensure absence of ACS, even if the ECG was recorded well after the onset of symptoms. In patients being evaluated for ACS, only serial electrocardiography, combined with serial cardiac marker determinations, can exclude AMI, and even then UA without actual myocardial necrosis may be present.

Chest Radiography

The chest radiograph provides information concerning the application of therapies (e.g., an evaluation of mediastinal width in the consideration of fibrinolytic agent use and the determination of pulmonary congestion in the consideration of acute parenteral beta-adrenergic blocking therapy). Furthermore, the presence of CHF on the chest radiograph increases risk in AMI patients who may benefit from an aggressive therapeutic approach.

There is radiographic evidence of pulmonary congestion in approximately one third of AMI patients. AMI patients who develop CHF have increased mortality, as reported by the Killip classification. The chronicity of the CHF syndrome may also be suggested by the heart size. Patients with AMI complicated by pulmonary edema who have a normal heart size most often have no past history of CHF. In fact, AMI is the most frequent cause of pulmonary edema with a normal cardiac size. In other instances, patients with AMI and cardiomegaly with or without pulmonary edema frequently have a preexisting history of CHF, anterior wall infarct, and multiple-vessel CAD (Fig. 78-21).

Serum Markers

Biochemical markers play a pivotal role in the diagnosis, risk stratification, and guidance of treatment. The European Society of Cardiology and the ACC define the criteria for AMI diagnosis on biochemical grounds because specific markers, particularly the troponins, indicate irreversible cell damage.[11] In the past, detection of AMI by characteristic enzyme elevations over 48 to 72 hours was sufficient to establish the diagnosis of AMI because there was essentially no specific therapy to reverse or prevent the developing myocardial necrosis. The evolution of fibrinolytic therapy and acute mechanical intervention has created significant pressure to identify patients with AMI rapidly.

For patients with a nondiagnostic ECG, early elevation of serum markers of myocardial necrosis confirms a presumptive diagnosis of NSTEMI. Caution is advised, however, when a single serum marker is not elevated. This single test is too insensitive to be used to support a decision that the patient can be discharged or to determine that no acute coronary event has occurred. The patient's history remains the most vital portion of the diagnostic evaluation of potential ACS. Serial testing substantially improves the sensitivity of these tests (Table 78-6 and Fig. 78-22).[71]

Troponins

Because of their superior sensitivity and specificity compared with other biochemical markers, cardiac troponins are the best markers for myocardial cell injury. Two myocardium-specific proteins, myocardial troponin I (TnI) and troponin T (TnT), precede the release of creatine kinase (CK-MB) into the serum. The cardiac troponins are genetically distinct from troponin forms found in other muscle tissue, rendering them highly cardiac specific. Monoclonal antibodies have little cross-reactivity with troponins from skeletal muscle. TnI and TnT are very similar in their diagnostic and prognostic utility as well as their serum kinetics and rates of rise and fall associated with myocardial ischemia, infarction, and ACS.

The biokinetics of troponin release relate to the location of the protein within the cell. Normally, small quantities of troponins are free in the cytosol, and the majority is entwined in the muscle fiber. After injury a biphasic rise in serum troponins corresponds to early release of the free cytoplasmic proteins, followed by a slower and greatly prolonged rise with breakdown of the actual muscle fiber. The slow destruction of the myocardial cell contractile proteins provides a sustained release of the troponins for 5 to 7 days. Serum troponin concentrations begin to rise measurably in the serum at about the same time as CK-MB elevations become detectable, as early as 3 hours after onset, but troponin levels remain elevated for 7 days or more.

The cardiac-specific troponins, determined serially, are highly sensitive for the early detection of myocardial injury. A positive test result is associated with significant risk, and serial negative

www.ketabpezeshki.com 66485457-66963820

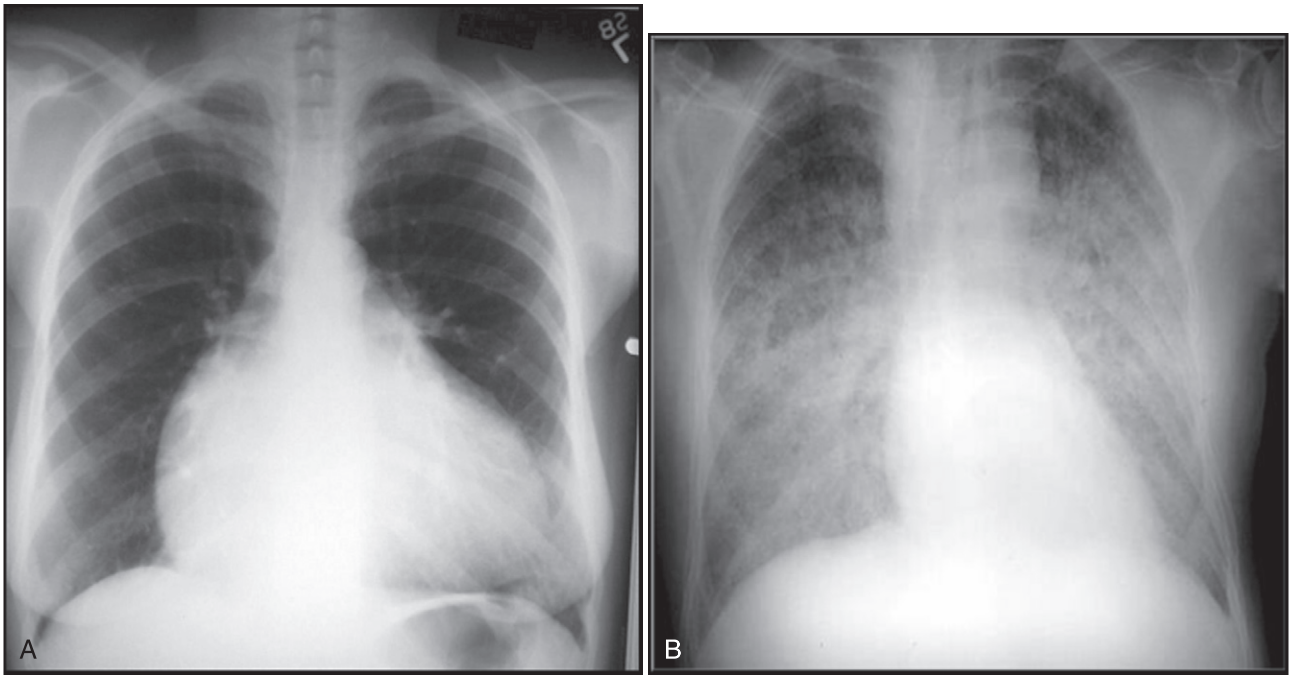


Figure 78-21. Chest radiographs in patients with acute coronary syndrome. **A,** Cardiomegaly. **B,** Borderline cardiomegaly with pulmonary edema.

Table 78-6 Summary of Test Performance Studies of Diagnostic Technologies for Acute Coronary Syndrome in the Emergency Department

TECHNOLOGY	DISEASE STUDIED	NO. OF STUDIES (SUBJECTS)	PREVALENCE RANGE OF STUDIES, %	DISEASE SENSITIVITY,* % (95% CI)	DISEASE SPECIFICITY,* % (95% CI)
Creatine kinase (single)	AMI	12 (3195)	7-41	37 (31-44)	87 (80-91)
Creatine kinase (serial)	AMI	2 (786)	26-43	69-99	68-84
CK-MB (presentation)	ACS AMI	1 (1042) 19 (6425)	20 6-42	23 42 (36-48)	96 97 (95-98)
CK-MB (serial)	ACS AMI	1 (1042) 14 (11,625)	20 1-43	31 79 (71-86)	95 96 (95-97)
Myoglobin (presentation)	AMI	18 (4172)	6-62	49 (43-55)	91 (87-94)
Myoglobin (serial)	AMI	10 (1277)	11-41	89 (80-94)	87 (80-92)
Troponin I (presentation)	AMI	4 (1149)	6-39	39 (10-78)	93 (88-97)
Troponin I (serial)	AMI	2 (1393)	6-9	90-100	83-96
Troponin T (presentation)	AMI	6 (1348)	6-78	39 (26-53)	93 (90-96)
Troponin T (serial)	AMI	3 (904)	5-78	93 (85-97)	85 (76-91)
CK-MB and myoglobin combination (presentation)	AMI	3 (2283)	9-28	83 (51-96)	82 (68-90)
CK-MB and myoglobin combination (serial)	AMI	2 (291)	11-20	100	75-91
Exercise stress ECG	ACS	2 (312)	6-10	70-100	82-93
Rest echocardiography	ACS AMI	2 (228) 3 (397)	3-30 3-30	70 (43-88) 93 (81-91)	87 (72-94) 66 (43-83)
Stress echocardiography	AMI	1 (139)	4	90	89
Sestamibi (rest)	ACS AMI	3 (702) 3 (702)	9-17 92 (78-98)	81 (74-87) 67 (52-79)	73 (56-85)

Adapted from Pope JH, Selker HP: Diagnosis of acute cardiac ischemia. Emerg Med Clin North Am 21:217, 2003.
ACS, acute coronary syndrome; *AMI,* acute myocardial infarction; *CI,* confidence interval; *CK-MB,* creatine phosphokinase MB fraction; *ECG,* electrocardiogram.
*Point estimate from a single study or a range of reported values; meta-analysis not performed.

www.ketabpezeshki.com 66485457-66963820

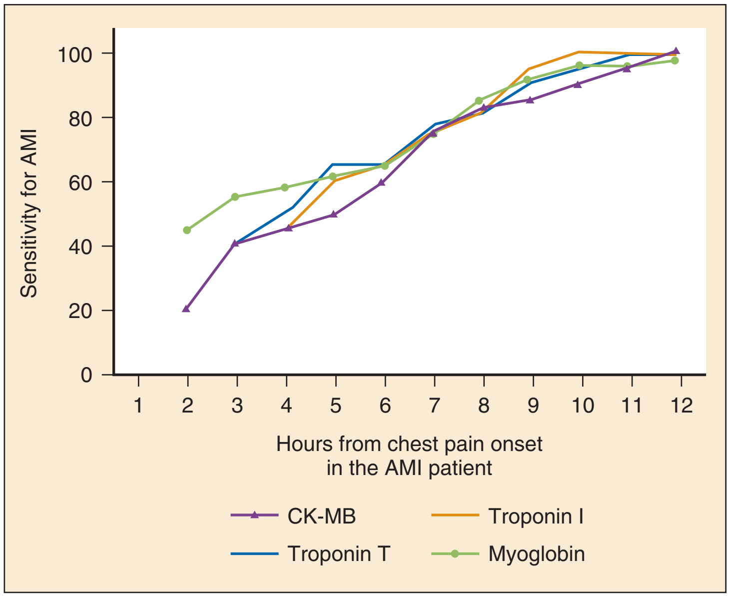


Figure 78-22. Serum marker sensitivity relative to the time of onset of chest pain in the patient with acute myocardial infarction. Data obtained from the medical literature. *AMI,* acute myocardial infarction; *CK-MB,* creatine phosphokinase MB fraction.

results predict low risk. A single troponin measurement on presentation, however, has limited utility in excluding AMI and no ability to detect UA without infarction because cell injury is required and because of the time delay in the rise in levels (which may not be detected until 10 hours after symptom onset in some AMI patients).[71] Serial measurements, particularly when performed at least 6 hours after symptom onset, markedly improve the sensitivity of the cardiac troponins for AMI, and the pattern of rise may assist in determining the acuity of the event. The sensitivity of TnT approaches 50% within 3 to 4 hours of the event. The test result is positive in about 75% of patients at 6 hours after onset of symptoms; at 12 hours, the test is almost 100% sensitive. More recent "highly sensitive troponin assays" produce positive results after AMI reliably within several hours. The newer assays, however, seem to have more false-positive results and are still limited in sensitivity because they do not detect UA.[72]

Because cardiac troponins are not found in the serum of healthy individuals, an abnormally elevated level is defined as that exceeding the 99th percentile in a healthy population. Sensitivity to detect abnormal low troponin levels, however, varies among the multiplicity of existing assays, particularly with respect to TnI. Physicians therefore must be familiar with the sensitivity and limitations of the particular assay used at their institution and the cutoff concentrations for clinical decisions.

Data indicate that even very low levels of troponin elevations are associated with significant adverse clinical prognosis.[73] In a number of studies, up to 33% of patients diagnosed with UA with normal CK-MB levels had elevated troponin levels, indicating the markers' improved sensitivity for myocardial cell injury.[74] The fact that the risk of these patients for cardiac events and mortality is similar to that of the patients diagnosed with AMI by traditional WHO criteria led to the redefinition of AMI on the basis of biochemical markers. On the basis of data from the TIMI-IIIB study, there is almost a linear correlation between increasing troponin levels and risk of cardiac events and mortality, even in patients with a nondiagnostic ECG and normal CK-MB levels.[74,75] In a review of more than 7000 NSTEMI patients, troponin levels identified patients at low mortality risk. Small elevations of troponin may be used as an objective measure of "preinfarcts" that characterize UA and are associated with increased risk of infarction in the near term. Marked elevations in troponin consistent with AMI represent further progression along the continuum of ACS toward "traditional" AMI.

Cardiac troponins may also guide ACS treatment. Data from the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction (TACTICS–TIMI 18) trial suggest that patients with elevated troponin who are treated with an early invasive interventional strategy within 48 hours have a marked improvement in recurrent ischemia, infarction, and mortality, both in the short term and at 6 months. These studies include patients without major ECG criteria for immediate interventional reperfusion strategies.[61] The use of glycoprotein IIb/IIIa inhibitors (GPIs) in patients with elevated troponins may prevent early complications in patients with ACS. It is likely that the improved sensitivity of troponin has captured a high-risk ACS population not previously diagnosed or treated. It is important to note that elevated troponin levels identify patients with UA or NSTEMI who stand to gain the greatest benefit from an early invasive strategy with coronary angiography and revascularization.[73,76]

Elevated troponin levels occur in a variety of cardiac and noncardiac conditions unrelated to the typical ACS and AMI pathophysiology. Cardiac conditions that can result in significant increased troponin levels in patients without evidence of ACS include myocarditis, pericarditis, CHF, LVH, and nonpenetrating cardiac trauma. Although the presence of elevated troponin levels in these conditions might be considered false-positive results, data support the contention that the source of these levels is underlying noninfarction myocyte injury that occurs with these conditions. Moreover, elevated troponin levels in many of these non-ACS cardiac conditions have prognostic significance.[77]

Troponin elevations can also be seen in noncardiac conditions, including PE, sepsis, and renal insufficiency. Troponin elevation may result from right ventricular dysfunction and myocyte injury in the case of submassive and massive PE and is a significant predictor of adverse outcome. Similar elevated troponin levels are reported in patients with sepsis and critically ill patients with multiple organ system failure.[77]

Elevated troponin levels are commonly seen in asymptomatic patients with end-stage renal disease. This finding may relate to the high prevalence of cardiac disease in this population rather than any reduced renal clearance, and may still represent evidence of subclinical myocardial damage.[78] The TnT isoform is associated

www.ketabpezeshki.com 66485457-66963820

with elevated levels in renal failure more often than TnI, particularly in patients undergoing hemodialysis. Elevated troponin levels in the setting of renal failure are associated with increased risk of death and major cardiac and vascular morbidity and should not be ascribed to chronic renal failure unless old records are present to corroborate that the elevated troponin level is actually the patient's normal baseline level.[78]

Creatinine Phosphokinase

Creatinine phosphokinase (CK) is found in large quantities not only in cardiac muscle but also in skeletal muscle, brain, kidney, lung, and the gastrointestinal tract. Myocardial cells are by far the most abundant potential sources of CK-MB; thus the appearance of CK-MB in the serum is highly suggestive of MI. The CK-MB fraction remains the best alternative to the troponins as a cardiac marker.[79] In the setting of AMI, CK-MB is released and is detectable in the serum as early as 3 hours after onset of the necrosis. CK-MB characteristically peaks at 20 to 24 hours and becomes normal within 2 to 3 days after injury. Elevated CK-MB values identify a patient at considerable risk for a poor outcome but do not correlate well with infarct size. Unfortunately, skeletal muscle does contain small amounts of CK-MB, particularly the pelvic musculature. Abnormal CK-MB elevations may be seen in patients with trauma, muscular dystrophies, myositis, and rhabdomyolysis and after extremely vigorous exercise.

The sensitivity of a single CK-MB determination in diagnosing AMI is dependent on the elapsed time from chest pain onset. Values obtained within 3 hours of onset are poor diagnostic tools, with a sensitivity of only 25 to 50%. CK-MB determinations obtained beyond this 3-hour time period have increasing sensitivities for the diagnosis of AMI, ranging from 40% to nearly 100%, particularly when obtained 12 to 16 hours after onset.[70] As a result, the use of single determinations of CK-MB is of little value in excluding ACS. Serial sampling, even over relatively short time periods (12 hours), increases sensitivity considerably, particularly when considered with serial electrocardiography and repeated assessments of the patient. Diagnostic utility is also improved by requiring that the CK-MB value not only be elevated but also be at least 5% of the total CK value. False-positive elevations can occur with noncoronary conditions, such as pericarditis, myocarditis, skeletal muscle disease, rhabdomyolysis, trauma, and exercise. In presentations in which dual biomarkers are obtained, the presence of nominal elevations in the CK-MB with simultaneous normal serum troponin value is of less clinical concern.

Myoglobin

Myoglobin, a small protein (17,000 daltons) found in muscle tissue, is rapidly released into the circulation after cellular injury. In cases of myocardial injury, myoglobin rises in the initial 1 to 2 hours, peaks at 5 to 7 hours, and returns to baseline by 24 hours. Because of its rapid rise, myoglobin is attractive as an early indicator of myocardial injury. Myocardial myoglobin, however, is not currently distinguishable immunologically from skeletal muscle myoglobin. Thus myoglobin is elevated in any clinical situation involving the skeletal muscle, such as trauma, exercise, and significant systemic illness. In addition, myoglobin increases are seen in patients with renal failure because of reduced clearance.

The sensitivity of an initial myoglobin at presentation for AMI varies from as low as 21% to as high as 100%.[70] Serial testing at 2 to 4 hours after presentation significantly improves the assay's diagnostic power. A doubling of the level as soon as 1 to 2 hours after the initial measurement greatly increases the sensitivity for the diagnosis of AMI, but this approach is very nonspecific. The value of myoglobin may be in its excellent negative predictive power for AMI and its early rise kinetics compared with other markers. Although some evidence suggests that a normal myoglobin value 2 hours after presentation may be used safely to rule out active AMI but not ACS, myoglobin has largely fallen out of favor.

Other Cardiac Markers

Troponin, CK, and myoglobin are all measures of myonecrosis. Biochemical assays for potential new cardiac markers for necrosis are being developed in the hope of finding ones with improved sensitivity, risk determination capability, and prognostic power. One such new cardiac-specific myonecrosis marker is heart-type fatty acid-binding protein. Other potential markers with usefulness in ACS include those that may detect ischemia before actual necrosis, and plaque instability or inflammation.

Episodes of ischemia can result in biochemical changes before actual irreversible cell necrosis. Ischemic-modified albumin (so-called "cardiac albumin") is a potentially useful ACS biomarker that reportedly detects early myocardial ischemia rather than the later myocyte necrosis, and may have even earlier elevation than myoglobin. Other potential ischemia markers include unbound free fatty acids and whole blood choline levels. Markers of hemodynamic status, including the natriuretic peptides, may also be useful in ACS. These markers, such as B-type natriuretic peptide (BNP) and NT-proBNP, are released from cardiac myocytes in response to increases in ventricular wall stress. BNP is most commonly used as a marker for CHF but is a useful adjunct to the standard cardiac markers and has good predictive power for recurrent ACS events and cardiac-related deaths, as well as CHF exacerbations, in patients with AMI.[80,81] Moreover, the natriuretic peptides are excellent predictors of both short- and long-term mortality in patients with UA, NSTEMI, and STEMI.[80,81]

Given the underlying pathophysiology of ACS, a variety of biochemical markers for inflammation and plaque instability may prove useful in evaluating risk of a cardiac event. Chief among these are the inflammatory markers C-reactive protein (CRP) and high-sensitivity CRP (hsCRP), which have long-term prognostic value for cardiac events in healthy individuals as well as potential short-term prognostic value when combined with other markers for ACS. Other inflammatory markers include interleukin-6 and tumor necrosis factor alpha. Elevated plasma levels of myeloperoxidase, an abundant leukocyte enzyme found in vulnerable coronary plaques that have ruptured, predict short-term risk of adverse cardiac events even with negative cardiac troponin and no evidence of myocardial necrosis.[82]

Multiple Marker Strategies

Diagnostic, risk stratification, and prognostic accuracy might be enhanced by the use of multiple markers for AMI and ACS.[83] The combination of CK-MB and myoglobin measurement has a sensitivity of 62 to 100% and specificity of 72 to 89% for AMI on presentation. Serial measurements of these markers significantly improve the performance of this combined marker approach. McCord reported on the usefulness of a multimarker strategy involving the early but non–cardiac-specific marker myoglobin with the more specific and prognostic marker TnI. In 817 patients evaluated for ACS in the ED, the combined marker approach had a sensitivity of 96.9% and negative predictive value of 99.6% for AMI when applied at presentation and at 90 minutes.[84] Similarly, a three-marker approach (CK-MB, TnI, and myoglobin) in an accelerated critical pathway was reported to have 100% sensitivity and 100% negative predictive power for AMI in 1285 patients assessed for ACS.[85] In a large series of ED chest pain patients with an initial nondiagnostic ECG, a 2-hour delta CK-MB combined with a 2-hour delta TnI had a sensitivity of 93% and specificity of

www.ketabpezeshki.com 66485457-66963820

94% for AMI.[86] Other multimarker strategies include combining measurement of a conventional marker for myocardial necrosis (troponin) with a marker for inflammation (CRP) and a hemodynamic marker (BNP). Many of these multimarker strategies, however, have low specificity. As a result, a positive multimarker test result requires confirmation with later-appearing, more definitive cardiac biomarkers.[6] Thus the multimarker approach does not offer substantial benefit over the individual biomarker determinations and is therefore not recommended.

Echocardiography

Two-dimensional echocardiography detects regional wall motion abnormality associated with ACS. Impaired myocardial contractility can range from hypokinesis to akinesis. Impaired myocardial relaxation during diastole results in decreased ventricular distensibility. After AMI, paradoxical wall motion and decreased ejection fraction observed during systole indicates the subsequent loss of muscle tone from necrosis.

Particularly in individuals with nondiagnostic ECGs, the presence of regional systolic wall motion abnormalities in a patient without known CAD is a moderately accurate indicator of acute myocardial ischemia or infarction, with a positive predictive accuracy of about 50%.[6] The age of wall motion abnormalities, however, often cannot be determined without prior echocardiograms.

The absence of segmental abnormalities (presence of either normal wall motion or diffuse abnormalities) has a significant high negative predictive value, as high as 98% for cases of suspected MI.[6] Moreover, segmental wall motion abnormalities can be seen not only in the zone of acute infarction but also in regions of ischemic stunning. Resting echocardiography provides an assessment of global and regional function, an important predictor of complications and mortality in patients with ACS. Data from the ACC/AHA task force indicate that patients with mild and localized as opposed to extensive wall motion abnormalities, have a low risk of ACS complications.[6] In addition, echocardiography can help evaluate other causes of clinical presentations mimicking ACS, including valvular heart disease, aortic dissection, pericarditis, mitral valve prolapse, and pulmonary embolus. Finally, echocardiography is an important tool to assess for various complications of AMI, including acute mitral regurgitation, pericardial effusion, ventricular septal and free wall rupture, and intracardiac thrombus formation.

Technical limitations restrict the use of echocardiography in the ED. These limitations include the quality of the study and the expertise of the reader interpreting the study at the patient's bedside. Injury involving more than 20% of the myocardial wall is required before segmental wall motion abnormalities can be detected echocardiographically.[11] In addition, the inability of the two-dimensional echocardiogram to distinguish among ischemia, AMI, or old infarction and the potential absence of wall motion abnormality in nontransmural infarctions can further limit the usefulness of two-dimensional echocardiography.

Stress echocardiography, as opposed to resting echocardiography, can detect CAD as well as assess cardiac function early after an AMI. This can be performed with graded increases in cardiac workload, either by standardized exercise or pharmacologic adrenergic stimulating agents such as dobutamine. In addition, vasodilating agents, such as dipyridamole and adenosine, induce heterogeneous myocardial perfusion and reveal functional myocardial ischemia in susceptible patients. Stress echocardiography is superior to conventional treadmill testing for CAD in women. Graded dobutamine stress echocardiography assesses myocardial viability and ventricular function within the first few days after an AMI. Clinical studies of patients with nondiagnostic ECGs, negative markers, and negative rest echocardiography suggest a role for emergency pharmacologic stress echocardiography as a provocative test after a period of observation with at least two marker and ECG assessments in a chest pain or ED observation unit.[87]

Myocardial contrast echocardiography (MCE) uses microbubble ultrasonic contrast agents to assess microvascular perfusion and regional function with echocardiography. MCE evaluation of perfusion and regional function allows accurate risk stratification of ED patients with chest pain and nondiagnostic ECGs even before serum markers are available.[88] Smaller studies report low rates of adverse cardiac events in chest pain patients with normal MCE findings after a nondiagnostic ECG and negative serum markers.[89] The clinical value of MCE in the ED, like that of resting and stress echocardiography, remains uncertain.

Myocardial Scintigraphy

Radionuclide tracer injection and scintigraphy, such as with single-photon emission computed tomography (SPECT), allows real-time assessment of myocardial perfusion and function. Technetium-99 sestamibi has a slow redistribution to ischemic myocardium. This property allows immediate injection and imaging, which detects altered distribution consistent with some form of ischemic heart disease, followed by subsequent scanning, which provides more definitive data regarding the particular subtype of ACS. In patients with a normal initial study, the likelihood of ACS is extremely low. In patients with an initial study revealing abnormal distribution (i.e., reduced uptake) of the tracer, some form of ischemic heart disease is likely. Subsequent imaging then reveals one of two patterns: normal redistribution (normal uptake) or continued reduced uptake. The redistribution pattern is consistent with active coronary ischemia, and the continued reduced uptake is found in patients with MI, either remote or recent. Myocardial scintigraphy has promising positive and negative predictive values for cardiac events, with high sensitivity and a good specificity for CAD.[90,91]

Immediate myocardial scintigraphy is useful in detecting ACS and risk of cardiac events in patients in the ED with atypical chest pain, nondiagnostic ECGs, and low to moderate risk of AMI. Multiple studies find a relatively high incidence of cardiac events, presence of AMI, and need for revascularization in patients with a positive nuclear scan. The probability of a cardiac event is tenfold higher in patients with abnormal scans than in patients with a normal scan. The incidence of cardiac events with a normal scan is lower than 1% for the 30-day period after the index study.[92] Myocardial scintigraphy can reduce the number of patients admitted from the ED with chest pain who are ultimately determined not to have ACS without reducing appropriate admissions for patients with ACS.[93]

Myocardial scintigraphy studies are difficult to perform early after the patient's presentation to the ED. Radioisotopes and the personnel to administer them may not be immediately available, and physician interpretation experience is quite variable. Studies of ED perfusion imaging are resting studies, rather than more provocative stress (exercise or pharmacologically induced) perfusion studies.

Computed Tomography

CT imaging is a noninvasive imaging modality to assess for ACS. Electron beam computed tomography (EBCT) was introduced nearly two decades ago to screen for coronary calcium as a marker of underlying atherosclerotic heart disease and risk of ACS.[94] Whereas calcium scoring systems exist to assess cardiovascular disease risk, few studies have examined the role of EBCT in the assessment of patients with acute chest pain.[95] The few studies that have examined EBCT have demonstrated good sensitivity and

www.ketabpezeshki.com 66485457-66963820

excellent negative predictive value for subsequent cardiac events but have design limitations.

Technical advances in imaging include multidetector computed tomography (MDCT) with multislice 16-, 64-, and 256-slice CT scanning, as well as ECG-gated MDCT. These may revolutionize noninvasive cardiovascular imaging in the setting of ACS. These enhancements allow imaging of the beating heart with minimal motion artifact and accurate resolution to the level of the coronary vessels. Improvements in image reconstruction and reformatting software not only allow direct visualization of the coronary arteries, or CT angiography (CTA), but also can provide functional information on perfusion, wall motion, and left ventricular ejection fraction.

The use of MDCT in the ED focuses on two potential protocols: a coronary CTA by MDCT and a more global "triple rule-out" thoracic or chest MDCT. Noninvasive coronary CTA by MDCT performs well when compared with standard invasive coronary angiography.[96,97] Cardiac CT provides excellent detection of calcified and noncalcified coronary artery plaque and stenosis, indicative of atherosclerosis and risk of ACS.[94] CTA may be less useful, however, in a patient with preexisting CAD and extensive coronary calcifications or in those who have undergone prior interventions and have resulting imaging artifacts from coronary stents.[97]

The *triple rule-out* or *global assessment protocol* refers to the use of CT to assess for three life-threatening causes of chest pain, including PE and aortic dissection as well as ACS. The scanning protocol is a compromise between coronary CTA and PE or aortic dissection with larger field-of-view requirements and alterations in contrast delivery. A high-resolution, fast MDCT (64-slice or higher) is necessary so that adequate contrast enhancement, imaging, and visualization of the pulmonary vessels, coronary arteries, and aorta can all be obtained.

The literature regarding the use of cardiac CT in patients with acute chest pain is limited. A study of 69 ED patients with chest pain and nondiagnostic ECGs noted that an ECG-gated 16-slice MDCT had a 96% negative predictive value when compared with the final diagnosis of CAD. Three patients were diagnosed by CT with other causes for their chest pain, including pneumonia and PE.[98] A study of 64-slice MDCT coronary angiography in 92 ED patients at low risk for ACS reported a sensitivity of 86% and specificity of 92%, which are comparable with values for stress nuclear imaging.[99] Another report on use of 64-slice MDCT in 103 patients admitted to the hospital for ACS with nondiagnostic ECGs and negative cardiac markers notes a 100% negative predictive power for CTA.[100] The greatest benefit of MDCT appears to lie within its powerful negative predictive value, but this occurs at the expense of some false-positive findings that result in further testing, cost, and radiation exposure.[101]

The clinical indications for and utility of coronary CTA in the ED, as well as global assessment triple rule-out MDCT protocols, require further investigation. Impediments include the limited availability of high-end MDCT technology; the unknown economic and workflow impact of increased MDCT use; the lack of guidelines for the use of dedicated coronary CTA or the more global assessment, the triple rule-out MDCT, for acute chest pain; and radiation exposure.

Graded Exercise Testing

Exercise stress testing for ED patients is feasible. In more than 1000 patients with low-risk chest pain (5% incidence of CAD) who underwent exercise testing after negative serial markers and 9 hours of ECG monitoring in the ED,[102] stress testing had a negative predictive value of 98.7% for the diagnosis of ACS or cardiac event within 30 days. An abbreviated ED-based "rule out MI" protocol followed by mandatory stress testing appears to be an effective diagnostic method for the detection of symptomatic CAD in low- to moderate-risk patients.

ACC/AHA guidelines on exercise testing state that such testing can be performed when patients are free of active ischemic or heart failure symptoms for a minimum of 8 to 12 hours.[103] Immediate stress testing without the rule-out MI evaluation, however, may be safe and cost-effective in patients with chest pain felt possibly to be of cardiac origin but with low suspicion of ACS. For determination of the safety and value of immediate exercise testing in the ED, 1000 low-risk patients underwent immediate exercise testing with no adverse effects.[104] Negative exercise test results were found in 640 patients (64%), all of whom were discharged home from the ED. The rate of CAD diagnosis or cardiac event within 30 days was 29% for the positive stress group, 13% for the nondiagnostic group, and 0.3% for the negative stress group. In total, 30-day follow-up was achieved in 888 (89%) patients and revealed no mortality in any of the three groups.

Graded exercise testing in the ED at most institutions is not available continuously. The mortality rate is extremely low (1 in 2500), but absolute contraindications include recent AMI (within 2 days), high-risk UA, uncontrolled cardiac dysrhythmias causing symptoms or hemodynamic compromise, symptomatic severe aortic stenosis, uncontrolled symptomatic heart failure, acute pulmonary embolus or infarction, acute myocarditis or pericarditis, and acute aortic dissection.[103]

Patients with a high pretest probability of CAD have a significant rate of false-negative results, and patients with a low pretest probability have a significant rate of false-positive stress test results. The specificity of the test is decreased in the presence of underlying electrocardiographic abnormalities secondary to medications, electrolyte abnormalities, LVH, or artifact. A false-positive test outcome may result from aortic stenosis or insufficiency, hypertrophic cardiomyopathy, hypertension, arteriovenous fistula, anemia, hemoglobinopathies, low cardiac output states, chronic obstructive pulmonary disease, digitalis toxic states, LVH, hyperventilation, mitral valve prolapse, and bundle branch blocks. An increase in the rate of false-positive test results in women tends to decrease the usefulness of graded exercise testing in this population.

EMERGENCY DEPARTMENT–BASED CHEST PAIN CENTERS

Specialized units for the lower-risk population are used in 30% of the EDs in the United States The goal of the chest pain center (CPC) is to provide an integrated approach to patients with chest pain or potential ACS that includes rapid triage, early identification, and treatment of low-risk ACS patients. Guidelines and critical pathways play an essential role in the CPC process. Staff, resources, and space are often dedicated for a CPC, but the unit can be part of an ED observation unit or a "virtual" unit located near or within the ED.

A CPC protocol should rapidly direct patients with possible ACS into a high-level treatment area where an ECG and clinical examination can be performed within the first 10 minutes. Patients with STEMI who require immediate reperfusion therapy or with UA who need further intervention can be identified quickly. This goal can be combined with an efficient ED evaluation of patients with low to moderate risk of ACS. The greatest medical benefit from the CPC is the early identification of patients with AMI and UA; the most significant financial impact is the reduction of low-yield hospital admissions.

The National Heart Attack Alert Program (NHAAP) of the National Heart, Lung, and Blood Institute (NHLBI) challenges clinicians to provide care for ED patients with clear symptoms and

www.ketabpezeshki.com 66485457-66963820

signs of AMI within 30 minutes of arrival. The NHAAP recommends (1) a specific area of the ED equipped for assessing and monitoring patients potentially having ischemia, including standing orders for initial diagnostic and therapeutic actions; (2) a standing protocol with inclusion and exclusion criteria for reperfusion therapies, including language authorizing the physician to administer fibrinolytic therapy or to mobilize the catheterization laboratory for prespecified cases; (3) a clear demarcation of responsibilities for all members of the reperfusion team; and (4) policies and procedures for the treatment and possible transfer of patients with ST segment elevation AMI who are ineligible for fibrinolytic therapy.

These recommendations highlight the advantages of a target "door-to-drug" time of less than 30 minutes or a door-to-balloon time of less than 90 minutes (where percutaneous procedures are available) for patients with typical and uncomplicated presentations of AMI with ST segment elevation. For example, the CPC can have assigned nursing personnel who rapidly evaluate the patient with chest pain with a 12-lead ECG, as well as screening vital signs and cardiac monitoring, and deliver the ECG directly to a clinician capable of making a decision about activation of the catheterization laboratory or administration of fibrinolytic therapy.

The CPC may also be used as an observation and evaluation unit where patients with chest pain and low to intermediate clinical likelihood of ACS can be monitored with electrocardiography, ST segment trending, serial 12-lead ECGs, and sequential serum markers. In addition, many CPCs now use further ACS evaluation with stress testing, echocardiography, or myocardial scintigraphy before disposition.[105] Significant cost savings occur, with typical charges and actual costs ranging from 20 to 50% of the costs for the usual inpatient approach.

The Chest Pain Evaluation in the Emergency Room (CHEER) investigators in a prospective, randomized trial compared a CPC with the traditional hospital admission to rule out MI.[106] Over a 16-month period, patients with chest pain at intermediate ACS risk on the basis of history, examination findings, and ECG were randomly assigned to either CPC or hospital admission. CPC patients underwent serial serum marker and ECG determinations over a minimum of 6 hours. If investigations were negative and the course uncomplicated, patients were evaluated with an exercise stress test, nuclear stress test, or stress echocardiography. If the results of this evaluation were positive, the patient was admitted; if negative, the patient was discharged with cardiology follow-up within 72 hours. In the CPC group, all events occurred in patients with a positive stress test result; no cardiac events occurred in the negative stress test group after ED discharge. Admissions were reduced by 45.8%.

A chest pain–accelerated diagnostic protocol approach to low-to intermediate-risk patients can be feasible, safe, and effective. In a study of comprehensive diagnostic 9-hour evaluation (Heart ER Program) for 1010 patients with possible ACS, patients underwent serial testing with the following: CK-MB at presentation, 3, 6, and 9 hours; continuous 12-lead ECGs; and serial ST segment trend monitoring. Two-dimensional echocardiography and graded exercise testing were performed in the ED after the 9-hour evaluation.

Approximately 80% of patients with chest pain can be safely evaluated in the ED with ultimate discharge to home. The resources required for a successful CPC-based operation in which patients undergo rapid exclusion of ACS through serial testing, continuous monitoring, and immediate provocative stress testing are considerable. Although studies suggest that CPCs decrease the number of admissions, they may increase the number of patients seen in the ED for chest pain, and physicians may overuse the CPC accelerated diagnostic protocol approach in patients whom they would otherwise have discharged.[107]

MANAGEMENT OF ACUTE CORONARY SYNDROME

The pathophysiology of an acute coronary event includes (1) endothelial damage through plaque disruption, irregular luminal lesions, and shear injury; (2) platelet aggregation; (3) thrombus formation causing partial or total lumen occlusion; (4) coronary artery vasospasm; and (5) reperfusion injury caused by oxygen free radicals, calcium, and neutrophils. In patients with noninfarction ACS, spontaneous fibrinolysis of the thrombus occurs rapidly, minimizing ischemic insult; persistence of the occlusive thrombus, however, results in MI.

Relationship of Time to Treatment with Outcome

The beneficial effect of reperfusion is a function of the length of ischemic time. In the late 1970s, with the "wavefront phenomenon" of ischemic cell death, it was hypothesized that myocardial necrosis progresses from the subendocardium to the epicardium after coronary occlusion (Fig. 78-23).

Early patency resulting in myocardial salvage is the key benefit of emergent revascularization therapy using either fibrinolysis or primary angioplasty. Timely treatment within the first hours after symptom onset may result in substantial, if not complete, myocardial salvage. Delivered later, from 2 to 12 hours after AMI onset,

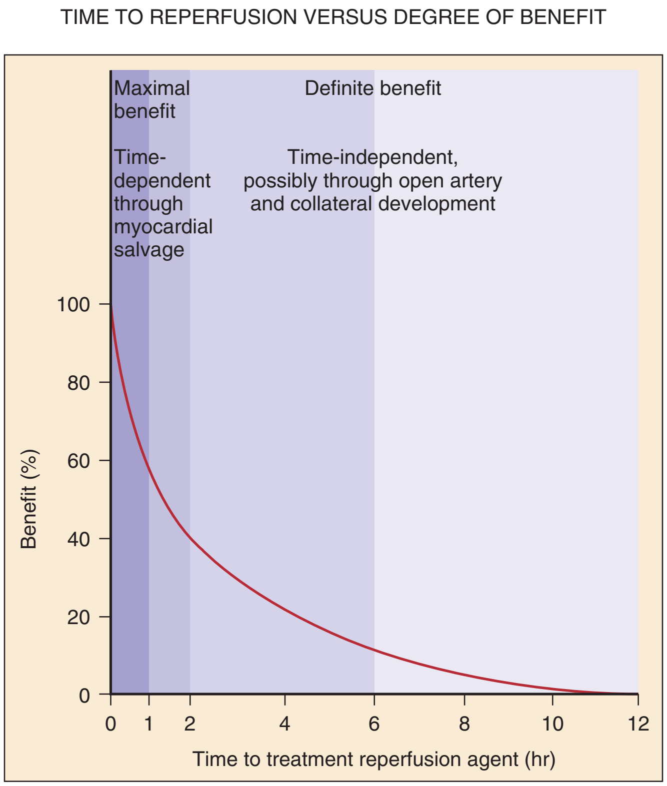


Figure 78-23. Relationship between time to reperfusion and benefit in ST segment elevation acute myocardial infarction. This figure depicts combined human and animal data and represents the time-dependent benefit anticipated, depending on the length of the interval between coronary artery occlusion and reperfusion. (Adapted from Tiefenbrunn AJ, Sobel BE: Timing of coronary recanalization. Paradigms, paradoxes, and pertinence. Circulation 85:2311, 1992; Reproduced from U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute [NIH Publication No. 93-3278], September 1993, p 8. Copyright ©1992 American Heart Association.)

www.ketabpezeshki.com 66485457-66963820

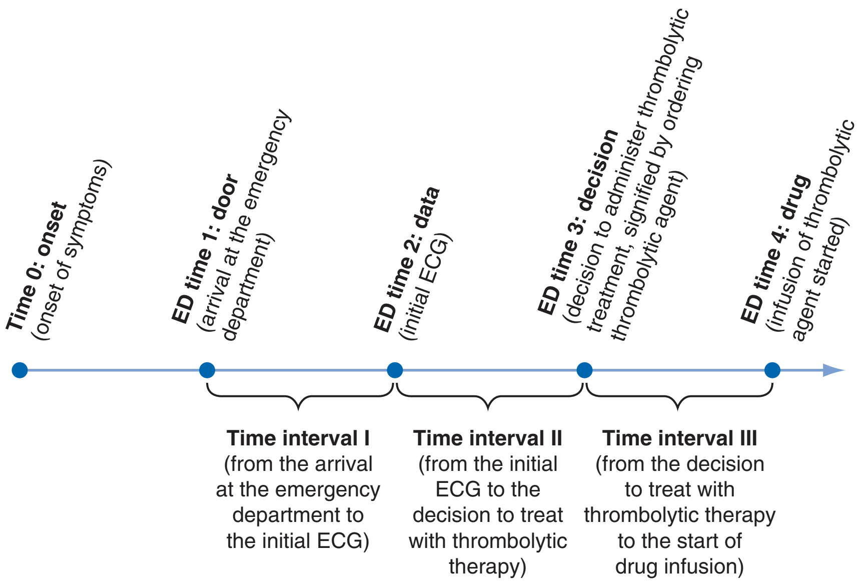


Figure 78-24. The four Ds of emergency department (ED)–based diagnosis and management of the patient with acute myocardial infarction (AMI). Shown are the process time points and intervals through which the patient with AMI passes until treatment in the emergency department. *ECG*, electrocardiogram. (From U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute [NIH Publication No. 93-3278], September 1993, p 10.)

treatment may result in a more modest, but significant benefit. The opening of the occluded artery causes less adverse ventricular modeling, reduces occurrence of ventricular aneurysm, increases blood flow to myocardium, and improves electrophysiologic stability. In the angiographic substudy of GUSTO, preserved left ventricular function and mortality at both the 24-hour and the 30-day endpoints were related to angiographic patency at 90 minutes.[108] The relationship between rapid revascularization and mortality was demonstrated by De Luca, with each additional 30 minutes of delay to PCI compounding relative mortality risk by 7.5% at 1 year even when adjusted for baseline characteristics.[109]

Substantial delays often occur between symptom onset and hospital-based initiation of reperfusion therapy.[110] In 1991 the NHLBI launched the NHAAP to promote the rapid identification and treatment of AMI. The factors responsible for delay in the care of AMI patients are grouped by the NHAAP into three phases: patient-bystander, preadmission, and hospital. Patient-bystander factors are those that prevent immediate medical care through the EMS system. Median delays range from 2 to 6.5 hours; in fact, 26 to 44% of AMI patients delay more than 4 hours before seeking medical care. In all major studies evaluating patients' delay, the median time of arrival at the hospital is delayed well beyond the critical first hour during the time period in which half of AMI deaths occur.

Preadmission delay factors occur from the time the patient decides to seek medical attention until the patient arrives at the ED. It is not uncommon for patients to call their primary care physician, which may delay definitive care significantly. For less than half of patients with suspected AMI, the EMS system is the point of first medical contact.[111] Many transport themselves or wait for someone other than EMS personnel to take them to the hospital. Further complicating preadmission issues include wide variations in the availability of EMS systems and their integration into systems of care that seek to minimize delays to treatment.

Further delays can occur between the time a patient arrives at the hospital and the initiation of acute revascularization therapy. Overall, the average time to fibrinolysis ranges from 45 to 90 minutes. The GUSTO trial demonstrates a median time from hospital arrival to treatment with fibrinolytic therapy of 70 minutes.[108] The AHA recommends that all patients with STEMI receive fibrinolytic therapy within 30 minutes of arrival or undergo primary PCI (i.e., device across culprit artery) no later than 90 minutes after arrival.[7]

STEMI patients who receive hospital-based reperfusion therapies (fibrinolytic agent or PCI) progress through a sequence of steps that can define process time points (Fig. 78-24). Within each interval, various impediments to timely care can occur. Reducing delay times is applicable to all time points in the ED by addressing the four *D*s: *d*oor (events before arrival at the ED), *d*ata (obtaining the ECG), *d*ecision (arriving at the AMI diagnosis and deciding on therapy), and *d*rug (administering the fibrinolytic agent or passing the angioplasty catheter across the culprit lesion for PCI candidates).

Preadmission care providers may alert the ED to the impending arrival of a patient with a suspected AMI. A field 12-lead ECG may assist in diagnosis and decrease the reperfusion time by initiating the hospital-based sequence of necessary events to occur in parallel as opposed to serially. Self-transported patients with possible ACS should be evaluated by the triage nurse immediately and an ECG acquired within 10 minutes of arrival. Development of hospital-based protocols and system response plans for identifying and rapidly treating patients reduces the amount of time to treatment. When using fibrinolysis in uncomplicated cases, the emergency physician should activate the hospital-based system for reperfusion. Checklists of inclusion and exclusion criteria for fibrinolytic therapy should be available, and those fibrinolytic agents should be stored and administered in the ED. In a system in which fibrinolysis is the sole reperfusion therapy, the decision to administer that therapy rests solely with the emergency physician. Nonconsultative communications with family physicians, internists, or cardiologists before administration of the agent may result in unnecessary delays. Only in complicated situations should consultative discussions be required before administration of therapy.

If the hospital offers primary PCI, many hospitals activate "STEMI alert" responses with an ST segment elevation AMI patient. Analogous to the "trauma alert," the cardiologist and catheterization laboratory personnel are immediately mobilized. Emergency physician activation of the catheterization laboratory demonstrates very high rates of accurate STEMI diagnosis with very low rates of false activation (i.e., the STEMI mimicker) while markedly reducing the time to definitive therapy.[112] Interhospital transfer of STEMI patients for PCI when they are also candidates for fibrinolysis should be discouraged if definitive therapy (i.e., catheter placement across the culprit lesion) is likely to be delayed beyond 90 minutes, except in cases of hemodynamic

www.ketabpezeshki.com 66485457-66963820

shock as discussed later or in patients in whom fibrinolysis is contraindicated.

Pharmacologic Intervention

Nitroglycerin

Nitrates decrease myocardial preload and, to a lesser extent, afterload. Nitrates increase venous capacitance and induce venous pooling, which decreases preload and myocardial oxygen demand. Direct vasodilation of coronary arteries may increase collateral blood flow to ischemic myocardium. Most studies of intravenous NTG in the setting of AMI are from the prefibrinolytic era. Although a meta-analysis of multiple small trials noted a 35% mortality reduction with intravenous NTG,[113] no contemporary evidence supports the routine use of any form of nitrate therapy in patients with AMI.[114]

Patients with possible ACS and a systolic blood pressure greater than 90 mm Hg should receive a sublingual NTG tablet (0.4 mg or 400 μg) on presentation. If symptoms and pain are not fully relieved with three sublingual tablets, intravenous NTG should be considered. With bradycardia, hypotension, inferior wall AMI, and right ventricular infarction, a sudden decrease in preload associated with NTG can result in profound hypotension. An initial infusion rate of 10 μg/min is titrated to pain symptoms. The clinician should increase the infusion at regular intervals, allowing a 10% reduction in the mean arterial pressure if the patient is normotensive and a 20 to 30% reduction if hypertensive. Sublingual bolus therapy, the use of additional sublingual NTG in the setting of intravenous NTG infusions, more rapidly increases the serum level of the medication with delivery of 400-μg boluses. Maximal benefit is probably achieved at 200 μg/min, although certain patients may receive additional benefit at higher infusion rates.

Morphine

Morphine is a potent opioid analgesic with weak sympathetic blockade, systemic histamine release, and anxiolysis. If a patient with possible ACS is unresponsive to NTG or has recurrent symptoms despite maximal anti-ischemic therapy, administration of morphine sulfate is reasonable. The relief of pain and anxiety decreases oxygen consumption and myocardial work. Some vasodilatory effects are also noted with preload reduction. Standard doses of morphine sulfate are 2 to 5 mg delivered intravenously, repeated every 5 to 30 minutes as necessary. In addition to allergic reactions, the most significant adverse effect of morphine sulfate administration is hypotension, which is managed with intravenous crystalloid in bolus fashion.[115]

Beta-Adrenergic Blockers

Historically, beta-adrenergic blocking agents have been effective in ameliorating catecholamine-induced tachycardia, including ventricular fibrillation, increased contractility, and heightened myocardial oxygen demand. Although beta-blockade decreases mortality for patients with AMI, these observations occurred when adjunctive therapies were few and beta-adrenergic blockade was essentially monotherapy in AMI. Contemporary management strategies include highly effective reperfusion therapies coupled with potent anticoagulant and antiplatelet agents.

Two large reports suggest that the intravenous use of beta-adrenergic blockade should be reconsidered. The GUSTO-1 trial involved fibrinolytic agents for STEMI followed by early intravenous atenolol. The use of the early intravenous beta-adrenergic blocking agents in this study was associated with higher rates of death, heart failure, shock, recurrent ischemia, and pacemaker use than when patients received early oral administration. These increases occurred despite exclusion of patients with obvious contraindications, including preexisting hypotension, bradycardia, or heart failure.[116] The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) evaluated approximately 46,000 patients with suspected STEMI, comparing early intravenous beta-adrenergic blocking agent use followed by continued oral therapy versus placebo. There was no significant difference between the two groups in terms of mortality. The group receiving beta-adrenergic blocking agents did demonstrate a minimal reduction of reinfarction (2.0 vs. 2.5%) and ventricular fibrillation (2.5 vs. 3.0%) at the expense of a significantly higher rate of cardiogenic shock (5.0 vs. 3.9%). This was more common in patients who were elderly or who had a systolic blood pressure below 120 mm Hg, a heart rate above 110 beats/min, or mild, acute heart failure. Patients receiving the beta-adrenergic blocking agents also had increased rates of development of heart failure requiring treatment, persistent hypotension, and bradycardia.[117]

The early *intravenous* use of beta-adrenergic blocking agents, when coupled with contemporary therapy, does not appear to offer significant benefit and is associated with an increased rate of adverse events.[118] Oral administration to patients without contraindication during the first day of management is an appropriate approach to the ACS patient. Empirical therapy in the ED, however, should be reconsidered and reserved for only those patients who have adverse effects from significantly elevated blood pressure despite application of NTG, or significant tachydysrhythmia.

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitor agents benefit patients with CHF. ACE inhibitors may also reduce morbidity and mortality after AMI. In particular, patients treated with ACE inhibitors experience a reduction in cardiovascular mortality, decreased rates of significant CHF, and fewer recurrent AMIs. These benefits increase when ACE inhibitors are used in conjunction with other agents, such as aspirin and fibrinolytics. The mechanism of action regarding a reduction in recurrent AMI is unknown but may involve a reduction in plaque rupture related to decreased intracoronary shear force or neurohumoral influences.

Captopril, enalapril, lisinopril, or ramipril may be used in this setting. The ultimate doses should be maximized after careful titration with these potent agents to avoid hypotension. Therapy should be initiated within the first 24 hours, although ED administration is usually not indicated. In patients with asymptomatic left ventricular dysfunction, therapy should continue for a minimum of 2 to 4 months. In patients with symptomatic CHF, ACE inhibitors should be administered indefinitely. Contraindications to ACE inhibitor therapy include hypotension, volume depletion, and borderline perfusion. Renal function must be monitored closely. The angiotensin receptor blockers also inhibit the renin-angiotensin system, so these drugs are possible alternatives to ACE inhibitors in patients post-MI with or without heart failure.

HMG–Coenzyme A Reductase Inhibitors (Statins)

A number of investigations have demonstrated a reduction in inflammation and reinfarction, angina, and lethal arrhythmia with the administration of statin drugs in the first few days after an ACS event.[119] Initiation of this therapy should occur within the first 24 hours or should continue if patients are already undergoing statin therapy, as discontinuation during hospitalization is associated with an increase in near-term mortality and adverse events.[120] Administration of statin therapy before elective or urgent PCI for ACS is reasonable to decrease the incidence of periprocedure AMI; however, there are no specific risk or safety data regarding its use in this setting.[121]

www.ketabpezeshki.com 66485457-66963820

Calcium Channel Blockade

As with beta-blockade, the primary benefit of calcium channel blockers appears to be with symptom resolution. Unfortunately, these agents may be accompanied by a significant vasodilatory effect resulting in hypotension and potentiation of the coronary ischemic process. Like beta-blocking agents, calcium channel blockers have a substantial negative inotropic effect. AV nodal blockade is also a significant side effect that may be exacerbated in patients previously treated with beta-blockers or with ischemia-related conduction disturbance. Unless specifically used for rate control of supraventricular dysrhythmia in a patient who cannot tolerate beta-blockade, calcium channel blocker agents are not recommended for ACS.

Antiplatelet Therapy

In non-AMI ACS patients, dramatic reductions in the progression to acute infarction are noted with appropriate antiplatelet therapy. The administration of antiplatelet therapy, particularly aspirin, is indicated in the ED for most ACS patients, because in AMI, antiplatelet therapy reduces mortality from 25 to 50%.

Aspirin. Aspirin, the prototypical antiplatelet agent, is the most cost-effective treatment. It irreversibly acetylates platelet cyclooxygenase, thereby removing all activity for the life span of the platelet (8-10 days). Thus aspirin stops the production of proaggregatory thromboxane A2 and is an indirect antithrombotic agent. Aspirin also has important nonplatelet effects because it inactivates cyclooxygenase in the vascular endothelium, thereby diminishing formation of antiaggregatory prostacyclin.

The Second International Study of Infarct Survival (ISIS-2) trial provides the strongest evidence that aspirin independently reduces the mortality of patients with AMI without fibrinolytic therapy (overall 23% reduction) and is synergistic when used with fibrinolytic therapy (42% reduction in mortality).[122] The usual dose is 324 mg of non–enteric-coated aspirin, chewed and swallowed. Administration of aspirin in the ED is strongly recommended immediately on identification of any patient with suspected ACS, either AMI or UA. It should be administered to all such patients unless significant allergy, hemorrhage, or other issue, such as a potential aortic dissection, contraindicates its use.

Glycoprotein IIb/IIIa Receptor Inhibitors. The GPIs are potent antiplatelet agents and include abciximab, eptifibatide, and tirofiban. GPIs, however, demonstrate clinical usefulness in only a subset of ACS patients—those undergoing PCI as a reperfusion strategy. Therefore the primary indication regarding GPI administration is planned mechanical coronary intervention.

Numerous trials demonstrate the effectiveness of these agents in the subset of ACS patients who are managed with PCI with or without an intracoronary stent, consistently showing reduced mortality, need for subsequent revascularization, and recurrent ischemia, although at the cost of an increase in hemorrhagic complications.[123-128] A meta-analysis of GPI use in ACS patients concluded that patients who undergo PCI benefit markedly from GPI administration.[129] In ACS patients who are managed medically without mechanical revascularization, consistent benefit with GPI therapy is not found with use of either direct outcome measures or secondary markers of successful reperfusion, and hemorrhagic complications are increased.[130,131] The Integrilin to Manage Platelet Aggregation to Combat Thrombus in Acute Myocardial Infarction (IMPACT-AMI) investigators reported the results in AMI patients receiving fibrinolytic agents and varying doses of eptifibatide (i.e., nonmechanical means of reperfusion)[132]; they noted similar rates of death, recurrent MI, and the need for revascularization procedures but observed an increase in TIMI grade 3 flow at 90 minutes. Furthermore, using troponin values as an estimate of infarct size, investigators did not demonstrate benefit in eptifibatide-treated patients with non–ST elevation ACS presentations.[133]

GPI therapy, in the invasively managed patient, continues to offer improved outcome.[134,135] In one large series, patients who received GPIs experienced lower in-hospital mortality (3 vs. 6.2%), which was noted in all STEMI risk groups managed.[134] Subsequent analysis of the subgroup of patients receiving stents during PCI noted both a lower mortality rate (10.9 vs. 14.3%) and a lower reinfarction rate (2.3 vs. 5.5%) in the treatment group; also, the composite endpoint (death and reinfarction) occurred much less frequently in the treatment group, with a relative risk reduction of 37%. In a large meta-analysis of similar construction, major bleeding was not significantly different.[135]

The benefits of GPI therapy were established largely before contemporary invasive strategies, raising questions about the timing (i.e., upstream initiation in the ED) when combined with other antiplatelet therapies. Although small preliminary studies showed promise for upstream GPI administration,[123,124] larger trials do not support their routine use in the ED.[136,137] Evidence supports a highly selective strategy for use of GPI that balances ACS risk in the treatment of a patient with dual-agent platelet inhibition and planned PCI versus the potential bleeding risk. The glycoprotein IIb/IIIa receptor inhibitors consistently demonstrate benefit in ACS patients treated with urgent mechanical revascularization; in other groups of ACS patients, such as medically managed patients, patients receiving a combination fibrinolytic agent, or transferred patients, an invariable positive effect has not been established.

PSY_{12} Receptor Inhibitor Agents. The thienopyridines—ticlopidine, clopidogrel, and prasugrel—are more potent platelet inhibitors than aspirin. They inhibit the transformation of the PSY_{12} receptor into its high-affinity ligand-binding state, irreversibly inhibiting platelet aggregation for the duration of the life of the platelet. Ticlopidine has nonlinear kinetics and, with repeated administration, reaches a maximal effect after 8 to 11 days of use. Clopidogrel, a ticlopidine analogue, and prasugrel have the advantage of a rapid onset of action.

Clopidogrel and prasugrel are the preferred agents in this class because of their more rapid onset of action and improved safety profile. Prasugrel incurs a higher bleeding risk than clopidogrel, however, in patients older than 75 years, those who weigh more than 60 kg, those who have had a previous transient ischemic attack (TIA) or stroke, and those at high risk for bleeding. Ticlopidine is associated with a risk of neutropenia and agranulocytosis; furthermore, it demonstrates a much slower onset of platelet inhibition. With clopidogrel, maximal platelet inhibition occurs after 3 to 5 days of clopidogrel therapy with 75 mg daily; an earlier onset of platelet inhibition is seen when a higher loading dose is used (300 to 600 mg). For instance, there is clear benefit to clopidogrel administration (300-mg loading dose) at least 6 hours before PCI in patients with STEMI; higher doses (e.g., 600 mg) demonstrate a trend toward improvement at slightly earlier time periods (i.e., 3 to 4 hours).

Ticagrelor, a nucleoside analogue, also acts as a PSY_{12} receptor inhibitor, however, via a different mechanism not requiring hepatic activation. It is rapidly absorbed reaching peak serum concentration at 2.5 hours. Clinical data from the PLATO trial of 18,624 ACS patients demonstrated that those given ticagrelor were less likely to die from cardiovascular causes, but these improved outcomes are tempered by higher rates of nonprocedure related bleeding, including more frequent fatal intercranial hemmorrage when compared with clopidogrel adminstration.[138]

In accordance with the 2013 AHA Guidelines for STEMI management, patients should receive a loading dose of clopidogrel, prasugrel, or ticagrelor in addition to standard ACS care (ASA, anticoagulants, and reperfusion therapy) assuming there are no contraindications to its use, prior to PCI.[139] For patients with

www.ketabpezeshki.com 66485457-66963820

moderate-to high-risk NSTEMI, the administration of a PSY_{12} receptor inhibitor should be deferred "downstream" to the attending cardiologist as the best revascularization strategy is determined.[140]

Another indication is the patient with a high-risk ACS presentation who is truly allergic to ASA (ACC/AHA class I indication)[6]; this high-risk presentation would be characterized by objective clinical abnormality, including a significantly abnormal serum marker or 12-lead ECG. Considerations include the ultimate treatment strategy chosen (i.e., medical vs. invasive) and the time to angiography if an invasive plan is selected. ACS patients managed medically (i.e., noninvasively) or invasively with coronary angiography deferred to a later time are the most appropriate potential candidates for clopidogrel.[141-144] In the patient selected for invasive management, the time to the procedure is a primary issue in considering clopidogrel; patients undergoing early angiography (within 6 hours) are less likely to derive significant benefit, whereas deferred catheterization likely will gain advantage.

In the patient with UA or NSTEMI, clinical benefit is confirmed in UA patients when treated with clopidogrel in a noninvasive strategy scenario, with an increase in major hemorrhage.[141] As noted, invasively managed patients receiving the drug with less time to procedure performance do not benefit from such treatment. The NSTEMI patient demonstrates improved outcome with clopidogrel therapy when a conservative treatment scenario is initially followed.[143] Of note, a large portion of these patients will undergo PCI within the first 24 hours after admission; yet this "delayed" PCI allows for benefit to occur from clopidogrel administered earlier in the course of management.

The STEMI patient who is managed medically (i.e., with a fibrinolytic agent) will also benefit from clopidogrel use. Clopidogrel therapy in conjunction with fibrinolysis, followed by deferred cardiac catheterization occurring at least 2 days after AMI—clearly beyond the 6-hour window—decreases the rates of death, recurrent ACS, and urgent coronary revascularization. This improvement occurs without a significant increase in hemorrhage.[144]

The potential need for urgent CABG should also be strongly considered. The higher-risk ACS patient will more likely benefit from PSY_{12} receptor inhibitor therapy; however, that same patient is also more likely to need urgent CABG. It is not possible, however, to reliably identify ACS patients requiring urgent CABG. Of the 60,000 patients in the CRUSADE registry, 14% underwent CABG, a reasonably frequent rate of surgical intervention[145]; most centers, however, report a 2 to 5% incidence of coronary surgery. Mehta, in a review of ED ACS patients, was unable to demonstrate a single or combination of clinical features apparent in the ED that reliably identify patients not requiring CABG.[146] It is interesting to note that an analysis of the Clopidogrel in Unstable angina to prevent Recent ischemic Events (CURE) database suggests that although these CABG patients had a greater incidence of bleeding perioperatively, outcomes were not statistically different in clopidogrel versus placebo groups in this surgical subset.[143] It is likely that as the cardiovascular surgeon gains more experience with PSY_{12} receptor inhibitor administration, this concern will cause less anxiety, as concerns regarding ASA and heparin in years past.

The ACC and AHA suggest—in the form of a class I recommendation—that clopidogrel or ticagrelor should be withheld for at least 24 hours before urgent on-pump CABG if possible.[140] If CABG is performed within 5 days of clopidogrel use, patients have an increased incidence of operative and postoperative hemorrhage, increased need for transfusions, increased need for reoperation for hemostasis, and increased postoperative mortality. Nevertheless, the recommendation suggests that early PSY_{12} receptor inhibitor therapy be considered in patients who likely will not require CABG.[6] In that it does not appear possible for the emergency physician to reliably predict which patients will require urgent CABG, collaborative multidisciplinary pathways should be developed, with emergency medicine physicians, cardiologists, and cardiovascular surgeons providing input.

Antithrombins

As with antiplatelet therapies in ACS patients, significant reductions in the progression to acute, recurrent, or extensive infarction and death are noted in individuals treated with aggressive antithrombin therapy. The antithrombins include unfractionated heparin (UFH), low-molecular-weight (fractionated) heparin (LMWH), and the direct thrombin inhibitors (hirudin and bivalirudin). Antithrombotic therapy is indicated in ACS patients with recurrent anginal pain, AMI (NSTEMI and STEMI), a positive serum marker, and a dynamic 12-lead ECG.

Heparins. The term *heparin* refers not to a single structure but rather to a family of mucopolysaccharide chains of varying lengths and composition—hence, unfractionated—with pronounced antithrombotic properties. At standard doses, UFH binds to antithrombin III, forming a complex that is able to inactivate factor II (thrombin) and activated factor X. This prevents the conversion of fibrinogen to fibrin, thus preventing clot formation. Heparin by itself has no anticoagulant property. This indirect effect on thrombin inhibits clot propagation; it prevents heparin, however, from having any effect on bound thrombin in a thrombus. UFH also assists in the inactivation of factors XIa and IXa through antithrombin and interacts with platelets.

UFH has a profound synergistic effect with aspirin in preventing death, AMI, and refractory angina in ACS patients, particularly those with AMI and, to a lesser extent, high-risk UA. UFH should be administered early in patients with the following ACS features: recurrent or persistent chest pain, AMI, positive serum marker, and dynamic ECG. In patients undergoing PCI, bleeding and mortality were higher in TIMI 14 in patients receiving an 80-unit/kg bolus and 18-unit/kg infusion compared with patients with a lower bolus amount and infusion rate. Therefore the weight-adjusted regimen recommended is an initial bolus of 60 units/kg (maximum 4000 units) and an initial infusion of 12 units/kg/hr with an activated partial thromboplastin time goal of 1.5 to 2.5 times the control value.

LMWHs constitute approximately one third of the molecular weight of heparin and are less heterogeneous in size. The LMWHs inhibit the coagulation system in a fashion similar to that of UFH. Approximately one third of the heparin molecules bind to both antithrombin III and thrombin. The remaining molecules bind only to factor Xa. The variable efficacy found among the LMWHs is attributed to different ratios of antifactor Xa to antifactor IIa. High-ratio preparations have a clear advantage over standard heparin; enoxaparin has the highest ratio of available LMWHs. LMWH was designed on the basis of the hypothesis that inhibition of earlier steps in the blood coagulation system would be associated with a more potent antithrombotic effect than inhibition of subsequent steps. This results from the amplification process inherent in the coagulation cascade—that is, a single factor Xa molecule can lead to the generation of multiple thrombin molecules.

Potential advantages of LMWH over UFH include easier administration, greater bioavailability, more consistent therapeutic response among patients, and longer serum half-life producing a more manageable administration schedule, albeit at a higher cost. The combination of aspirin, beta-blocker, and LMWH (dalteparin) significantly decreases the rate of nonfatal AMI or death at 1 week of therapy, with a less pronounced effect at 40 to 150 days, but with an increase in minor bleeding episodes.[147] Studies comparing outcomes between LMWH and UFH

www.ketabpezeshki.com 66485457-66963820

show mixed results; some show better outcomes with LMWH, but others do not.[148,149] In summary, the LMWH enoxaparin demonstrates some degree of benefit compared with UFH in patients at higher risk for non–ST-segment elevation-ACS who are treated conservatively without immediate PCI (i.e., beyond 24 hours).[150] For STEMI patients managed aggressively with rapid PCI, UHF is the preferred over enoxaparin.[140]

Enoxaparin is administered in a twice-daily regimen subcutaneously at a dose of 1 mg/kg for all ACS patients. If patients have renal dysfunction with an estimated glomerular filtration rate of less than 30 mL/min, the dose should be reduced to 1 mg/kg in a single daily administration. Few safety data are available for enoxaparin in ACS patients with renal insufficiency, and UFH may be preferable.

Contraindications to heparin therapy include known allergy, active ongoing hemorrhage, and predisposition to such hemorrhage. Furthermore, patients who have their heparin therapy changed (UFH to LMWH and vice versa) during the active treatment phase of their ACS care experience higher rates of bleeding.

The vast majority of patients with AMI require therapy with heparin, whether it is fractionated or unfractionated. Non-AMI ACS, however, is an entirely different issue because UA is a heterogeneous condition. For example, the stable patient with a classic description of new-onset angina, who is sensation free with a negative serum marker and a normal ECG, is still correctly diagnosed with UA.[151] In contrast, an individual with ongoing pain, either intermittent or constant, with a dynamic ECG clearly is experiencing an active, unstable coronary event. The latter patient, who is at higher risk, can benefit from heparin therapy more than the former. Heparin therapy, however, can be a major contributor to morbidity and mortality among hospitalized patients. Major bleeding develops in 1 of every 90 patients treated, and heparin-induced thrombocytopenia in 1 of 34 patients. LMWH is as effective as UFH in patients with non–ST-segment elevation ACS and does not greatly increase the bleeding risk while decreasing the risk of thrombocytopenia.[152]

Other Antithrombins (Hirudin, Bivalirudin, and Fondaparinux). The direct thrombin inhibitors hirudin and bivalirudin (formerly known as *Hirulog*) are potent antithrombin anticoagulants providing significant theoretical advantages compared with heparin. Hirudin is a peptide derived from the leech salivary gland but is also synthesized as recombinant hirudin. It binds directly with high affinity to thrombin and can inactivate thrombin already bound to fibrin (clot-bound thrombin) more effectively than UFH. Hirudin does not require endogenous cofactors, such as antithrombin III, for its activity. Also, unlike heparin, hirudin can inhibit thrombin-induced platelet aggregation. Hirudin demonstrates little significant benefit over other anticoagulants in ACS, with a possibly increased rate of hemorrhage; thus it offers little value in the ACS patient.

Bivalirudin is a bifunctional 20–amino acid peptide designed on the basis of the structure of hirudin. It has properties similar to those of hirudin but also interacts with the catalytic site of thrombin. Bivalirudin, however, is more effective than heparin in reducing death or reinfarction in patients with ACS, particularly those patients undergoing very early PCI.[153]

Bivalirudin, compared with heparin, produces similar rates of ischemia and major bleeding at 1 month. Bivalirudin when used with clopidogrel is comparable to the combination of heparin and GPI before coronary angiography or PCI. When used alone, it is inferior to the combination of heparin and GPI.[154] Bivalirudin should be considered an acceptable alternative anticoagulant agent compared with the UFH in the STEMI patient undergoing PCI.[140]

Fondaparinux is a synthetic oligosaccharide with a structure similar to the heparins. It is the first widely used selective factor Xa inhibitor. With the increased emphasis on the reduction of hemorrhagic complications in ACS care, this drug may be considered as a reasonable alternative to UFH; however, the increased risk of catheter-associated thrombi during PCI prevents its use without additional UFH administration.[155]

In the large Optimal Antiplatelet Strategy for Interventions (OASIS) trial, fondaparinux was found to be similar to enoxaparin in the short-term reduction of ischemic events, yet substantially reduced major bleeding and improved long-term outcome.[156] The OASIS-6 investigators reviewed the use of fondaparinux in 5436 STEMI patients managed medically with streptokinase. Fondaparinux significantly reduced hemorrhage and the primary study outcome (death or MI) as well as the individual occurrence of these endpoints at 30 days.[157]

Reperfusion Therapies

Rapidly reestablishing perfusion in the infarct-related coronary artery with the use of fibrinolytic therapy or PCI increases the opportunity for myocardial salvage. Pharmacologic and mechanical methods of reperfusion are both effective under specific clinical conditions. The importance of early coronary artery patency was affirmed by the GUSTO investigators in their angiographic substudy. They demonstrated that 90-minute patency predicts improved rates of survival and preserves left ventricular function.

Fibrinolytic therapy unequivocally improves survival in patients with STEMI and is an ACC/AHA class I recommendation.[6] Although fibrinolysis has widespread availability and a proven ability to improve coronary flow, limit infarct size, and improve survival in AMI patients, many individuals with acute infarction are not suitable candidates. Patients with absolute contraindications to fibrinolytic therapy, certain relative contraindications, cardiogenic shock, and UA may not be eligible. The temporal constraints and other limitations of fibrinolytic therapy suggest that *rapidly* performed PCI is often the treatment of choice in the STEMI patient. To provide the most significant benefit, PCI must be performed as soon as possible after the initial presentation. In other settings and situations, PCI that is delayed is inferior to rapidly administered fibrinolysis.

Fibrinolytic Therapy

Fibrinolytic Agent Selection. Three megatrials compared tissue-type plasminogen activator (t-PA) with streptokinase. The Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI-2) trial and the closely related International Study compared a 100-mg infusion of t-PA over 3 hours with streptokinase with or without heparin.[158,159] The GISSI-2 study was the first large-scale mortality trial directly comparing t-PA and streptokinase in AMI. The investigators found no difference in mortality between the two treatment groups. More strokes occurred with t-PA than with streptokinase (1.3 vs. 1%) in the International Study, yet the frequency of confirmed hemorrhagic stroke was similar for both agents. Similar results were found in the ISIS-3 trial,[160] the next fibrinolytic megatrial, which compared t-PA, streptokinase, and anisoylated plasminogen-streptokinase activator complex in approximately 40,000 patients. In contrast to standard practice, the inclusion criteria allowed entry up to 24 hours after symptom onset and did not require diagnostic electrocardiographic change. All patients received adjunctive aspirin therapy, and approximately half of the patients were given delayed, unmonitored subcutaneous heparin. A significant difference in both 35-day mortality and intracranial hemorrhage was not found. The results of the ISIS-3 study proved controversial because of the unmonitored, delayed subcutaneous heparin protocol,[160] particularly with studies now proving improved infarct artery patency with use of early therapeutic intravenous doses of heparin.

www.ketabpezeshki.com 66485457-66963820

Fibrinolytic practice remains highly affected by the results of the GUSTO-I trial. The hypothesis of the GUSTO-I trial was that early and sustained infarct vessel patency is associated with better survival rates in patients with AMI. More than 41,000 patients were randomly assigned to four different fibrinolytic strategies: accelerated t-PA given over 90 minutes plus intravenous heparin, a combination of streptokinase plus a reduced dose of t-PA along with intravenous heparin, and two control groups (streptokinase plus subcutaneous heparin and streptokinase plus intravenous heparin). Unlike in previous trials, t-PA was given in a more aggressive, front-loaded 90-minute infusion (referred to as *accelerated t-PA*). In addition to a primary endpoint of 30-day mortality, the GUSTO investigators explored coronary artery patency and degree of normalization of flow in the angiographic substudy. This portion of the larger trial was designed to determine the relationship between early coronary artery patency and outcome. In this trial, accelerated t-PA, administered with intravenous heparin, reduced 30-day mortality significantly by 15% compared with streptokinase with either form of heparin or the combination of t-PA and streptokinase with intravenous heparin. The benefit out to 1-year follow-up was highly consistent across virtually all subgroups, including elderly patients, AMI location, and time since symptom onset. The angiographic substudy demonstrated a strong relationship between TIMI flow and outcome. Patients with strong forward flow (i.e., TIMI grade 3 flow) at 90 minutes had significantly lower mortality rates than patients with little to no flow. The mechanism for this benefit was found to be earlier, more complete infarct vessel patency with accelerated t-PA; this early t-PA patency advantage over other agents was lost by 180 minutes after symptom onset. As would be expected, the patients with the higher risk derived the most substantial benefit with accelerated t-PA compared with streptokinase in this large study. Patients who received accelerated t-PA did experience more hemorrhagic strokes than those who received streptokinase, but the combined endpoint of death and disabling stroke still favored the accelerated t-PA regimen.

Another important fibrinolytic investigation is GUSTO-III.[161] This study compared accelerated t-PA with r-PA; r-PA is a mutant form of t-PA that can be administered in a fixed double-bolus dose with no adjustment required for weight, which simplifies administration. In this very large trial, r-PA was found to be equivalent to accelerated t-PA, and the results were nearly identical for the two drugs. The one exception was the patient with presentation more than 4 hours after onset of symptoms—a significant number of patients in many institutions. In this group, accelerated t-PA may be superior to r-PA because of its greater fibrin specificity.[161]

The Assessment of the Safety and Efficacy of a New Thrombolytic Agent (ASSENT-2) trial investigated the use of TNK, another mutant of wild-type t-PA. TNK has several potential benefits: (1) its longer half-life allows it to be administered as a single bolus; (2) it is 14 times more fibrin specific than t-PA and even more so than r-PA; and (3) it is 80 times more resistant to plasminogen activator inhibitor type 1 than t-PA. The ASSENT-2 trial randomly assigned approximately 17,000 patients with AMI to single-bolus TNK (30-50 mg on the basis of body weight) or accelerated t-PA (100 mg total infusion).[162] The investigators found no differences in mortality or intracranial hemorrhage.[162] In a subgroup analysis, however, significantly lower 30-day mortality was noted among patients with presentation more than 4 hours after onset of symptoms in those treated with TNK. Furthermore, fewer nonintracranial major bleeding episodes were encountered in the TNK group. On the basis of these results, it is concluded that TNK is equally or minimally more effective, particularly in late presenters. Concerning adverse reactions, TNK also appears modestly safer than accelerated t-PA. Lastly, because of its single-bolus administration, TNK is markedly easier to use in preadmission environments and the ED. At the present time it appears that TNK is marginally more effective, minimally safer, and easier to administer than t-PA and thus is recommended; furthermore, cost differences are minimal and likely will not affect medical decision-making in the ED.

Eligibility Criteria for Fibrinolytic Agent Therapy

The 12-Lead Electrocardiogram. Combined with the patient's history and physical examination, the 12-lead ECG is the key determinant of eligibility for fibrinolysis. The electrocardiographic findings include two basic issues: (1) ST segment elevation of 1 mm or more in two or more anatomically contiguous *standard limb* leads or elevation of 2 mm or more in two or more contiguous *precordial* leads, and (2) new or presumed new LBBB. No evidence of benefit from fibrinolytic therapy is found in patients with ischemic chest pain who lack either appropriate ST segment elevation or the development of a new LBBB.[7]

Patients with new LBBB and AMI are at an increased risk for a poor outcome and need rapid reperfusion therapy. The new development of LBBB in the setting of AMI suggests proximal occlusion of the left anterior descending artery and places a significant portion of the left ventricle in ischemic jeopardy. Unfortunately, patients with LBBB receive fibrinolytic agents less often than those with the more electrocardiographically alarming STEMI.

Patients with AMI in anterior, inferior, or lateral anatomic locations benefit from fibrinolytic therapy. The relatively favorable prognosis associated with inferior infarction without fibrinolytic therapy requires larger sample sizes to detect a significant survival benefit. The ISIS-2 trial demonstrated a statistically significant mortality benefit for fibrinolytic therapy in patients with inferior AMI.[122] Patients with inferior AMI with coexisting right ventricular infarction, as detected by additional lead ECGs, are likely to benefit because of the large amount of jeopardized myocardium. Acute, isolated posterior wall MI, diagnosed by posterior leads, may be another electrocardiographic indication for fibrinolysis. Although unproven in large fibrinolytic agent trials, patients with isolated posterior AMI may be considered for reperfusion therapy.

Fibrinolytic therapy should not be used routinely in patients with only ST segment depression on the 12-lead ECG, and the mortality rate may actually be increased. The TIMI-III trial demonstrated a significant difference in outcome in fibrinolytic-treated patients with only ST segment depression—7.4% incidence of death compared with 4.9% in the placebo group.[163] These findings are further supported in the Fibrinolytic Therapy Trialists' (FTT) meta-analysis, which demonstrated that the mortality rate among patients with ST segment depression who received fibrinolytic therapy was 15.2% compared with 13.8% among control subjects.[164]

Patient's Age. Past trials do not provide evidence to support withholding fibrinolytic therapy or choosing one particular agent over another on the basis of the patient's age. In fact, the FTT Collaborative Group concludes that "clearly, age alone should no longer be considered a contraindication to fibrinolytic therapy."[164] Patients older than 75 years do have a higher incidence of hemorrhagic stroke than younger patients.

Time from Symptom Onset. The generally accepted therapeutic time window for administration of a fibrinolytic agent after the onset of ST segment elevation AMI is 12 hours. Patients treated within the first 6 hours of AMI have the best outcome. Later administrations, from 6 to 12 hours after AMI onset, also confer benefit, although of a lesser magnitude. The Late Assessment of Fibrinolytic Efficiency (LATE) trial, which compared fibrinolytic therapy with placebo, found a significant 26% decrease in 35-day mortality in patients treated with t-PA, heparin, and aspirin 6 to 12 hours after the onset of symptoms.[165] There was no significant decrease in mortality among patients treated 12 to 24 hours after symptom onset.

www.ketabpezeshki.com 66485457-66963820

These studies clearly establish benefit from 0 to 12 hours in patients who are otherwise appropriate candidates for fibrinolytic therapy. Treatment beyond that time is not supported by the literature. The single exception may be a patient with a "stuttering" nature of chest pain 12 to 24 hours after symptom onset, which emphasizes the importance of an adequate history.

Blood Pressure Extremes. Patients with a history of chronic hypertension should not be excluded from fibrinolytic therapy if their blood pressure is under control at the time of presentation or can be lowered to acceptable levels with standard therapy for ischemic chest pain. The admission blood pressure is also an important indicator of risk of intracerebral hemorrhage. The FTT meta-analysis demonstrates that the risk of cerebral hemorrhage increases with systolic blood pressure higher than 150 mm Hg on admission and further increases when systolic blood pressure is 175 mm Hg or higher.[164] Despite an increased mortality rate during days 0 and 1, the FTT meta-analysis demonstrated an overall long-term benefit of 15 lives saved per 1000 for patients with systolic blood pressures higher than 150 mm Hg and 11 lives saved per 1000 for patients with systolic blood pressures of 175 mm Hg or higher.[164] Although the FTT meta-analysis appears to indicate an acceptable risk-benefit ratio for patients with substantially increased systolic blood pressure, a persistently elevated blood pressure higher than 200/120 mm Hg is generally considered to be an absolute contraindication to fibrinolytic therapy.

The benefit of fibrinolytic therapy in patients with hypotension is unclear. The GISSI-1 and GISSI-2 trials showed no apparent reduction in mortality rate with fibrinolytic therapy among patients classified as Killip class III or IV.[158] The FTT meta-analysis, however, demonstrated that patients with an initial systolic blood pressure below 100 mm Hg who were not treated with fibrinolytic therapy had a very high risk of death (35.1%), and those who were treated with fibrinolytic therapy had the largest absolute benefit (60 lives saved per 1000 patients).[164] Although cardiogenic shock and CHF are not contraindications to fibrinolysis, PCI is the preferred method of reperfusion if it can be accomplished on site.

Retinopathy. Active diabetic hemorrhagic retinopathy is a strong relative contraindication to fibrinolytic therapy because of the potential for permanent blindness caused by intraocular bleeding. There is no reason, however, to withhold the use of a fibrinolytic agent in a diabetic patient with evidence of simple background retinopathy. Patients with diabetes mellitus who sustain an AMI have an almost doubled incidence of mortality.

Cardiopulmonary Resuscitation. CPR is not a contraindication to fibrinolytic therapy unless CPR is prolonged—more than 10 minutes—or extensive chest trauma from manual compression is evident. Although the in-hospital mortality rate is higher in AMI patients who experience cardiac arrest and then receive fibrinolytic agents in the ED, no difference is found in the rates of bleeding complications. Specifically, hemothorax and cardiac tamponade were not diagnosed in those cardiac arrest patients receiving CPR and fibrinolytics who survived to admission. Even CPR prolonged beyond 10 minutes does not appear to be associated with higher rates of complication.[166]

Previous Stroke or Transient Ischemic Attack. A history of previous stroke or TIA is a major risk factor for hemorrhagic stroke after treatment with fibrinolytic therapy. A history of previous ischemic stroke should remain a strong relative contraindication to fibrinolytic therapy, and previous hemorrhagic stroke an absolute contraindication.

Previous Myocardial Infarction or Past Coronary Artery Bypass Graft. In the setting of AMI, a previous MI should not preclude consideration for treatment with fibrinolytic agents. Without treatment there is a potential for greater loss of function in the newly infarcting region of the myocardium. Although the GISSI-1 trial showed no treatment benefits for patients with previous MIs, the ISIS-2 trial demonstrated a 26% relative mortality rate reduction.[122] The FTT meta-analysis further demonstrates that patients with a history of past MI who receive fibrinolytic therapy for recurrent acute infarction have a mortality rate of 12.5% compared with 14.1% among control patients.[164]

Many studies report successful fibrinolysis in AMI patients with a prior CABG. Complete thrombotic occlusion of the bypass graft is the cause of AMI in approximately 75% of cases as opposed to native vessel occlusion. Because of the large mass of thrombus and absent flow in the graft, conventional fibrinolytic therapy may be inadequate to restore flow. These patients should be preferentially considered for direct angioplasty if immediately available or combined fibrinolysis and rescue angioplasty.

Recent Surgery or Trauma. Recent surgery or trauma is considered a relative contraindication to fibrinolytic therapy. The term *recent* is subject to variable interpretation in fibrinolytic trials. In the GISSI-1 trial,[167] patients were excluded if they had had surgery or trauma within the previous 10 days. In the Anglo-Scandinavian Study of Early Thrombolysis (ASSET) trial, patients were excluded for surgery or trauma within the previous 6 weeks.[168] Other fibrinolytic therapy trials do not define "recent surgery or trauma." We recommend avoidance of systemic fibrinolytic therapy and use of an alternative intervention in patients with AMI within 10 days of surgery or significant trauma.

Menstruation. Because natural estrogen is partially cardioprotective, there is little experience with fibrinolysis among premenopausal women. Gynecologists indicate that any excessive vaginal bleeding that may occur after receipt of fibrinolytic therapy should be readily controllable by vaginal packing and therefore can be considered as a compressible site of bleeding.

Contraindications. A list of absolute and relative contraindications is shown in Box 78-1.

Box 78-1 Fibrinolysis in Acute Myocardial Infarction: Absolute and Relative Contraindications

- Recent (within 10 days) major surgery (e.g., coronary artery bypass graft, obstetric delivery, organ biopsy, previous puncture of noncompressible vessels)
- Cerebrovascular disease
- Recent gastrointestinal or genitourinary bleeding (within 10 days)
- Recent trauma (within 10 days)
- Hypertension: systolic BP 180 mm Hg or diastolic BP 110 mm Hg
- High likelihood of left heart thrombus (e.g., mitral stenosis with atrial fibrillation)
- Acute pericarditis
- Subacute bacterial endocarditis
- Hemostatic defects, including those secondary to severe hepatic or renal disease
- Significant liver dysfunction
- Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic condition
- Septic thrombophlebitis or occluded AV cannula at seriously infected site
- Advanced age (older than 75 years)
- Patients currently receiving oral anticoagulants (e.g., warfarin sodium)
- Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location

Adapted from Physicians' Desk Reference, 50th ed. Montvale, NJ, Medical Economics, 1996.
AV, atrioventricular; *BP,* blood pressure.

www.ketabpezeshki.com 66485457-66963820

Percutaneous Coronary Intervention

Although fibrinolysis has widespread availability and a proven ability to improve coronary flow, limit infarct size, and improve survival in AMI patients, many individuals with acute infarction are not suitable candidates. Patients with absolute contraindications to fibrinolytic therapy, certain relative contraindications, cardiogenic shock, and UA may be ineligible to receive fibrinolytic therapy. The requirement of administering prompt reperfusion therapy to these patients, as well as the other limitations of fibrinolytic therapy, have led many clinicians to advocate for PCI. PCI has many theoretic advantages over fibrinolysis, including an increased number of eligible patients, a lower risk of intracranial bleeding, a significantly higher initial reperfusion rate, an earlier definition of coronary anatomy with rapid triage to surgical intervention, and risk stratification allowing safe, early hospital discharge. Potential disadvantages include lack of operator expertise and numerous catheterization laboratory logistical issues, including limited geographic availability and delay to therapy application.

Several trials of varying sizes comparing primary PCI with fibrinolysis have been reported. Interventions in the early trials were performed before the widespread adoption of coronary stents with GPI. Despite a clear and consistent benefit of PCI in restoring patency of the infarct-related artery, differences in mortality in the individual trials were difficult to evaluate because of the smaller sample sizes. The Primary Angioplasty in Myocardial Infarction (PAMI) trial enrolled 395 patients randomly assigned to undergo PCI or to receive t-PA.[169] Compared with standard-dose t-PA, PCI reduced the combined occurrence of nonfatal reinfarction or death, was associated with a lower rate of intracranial hemorrhage, and resulted in a similar left ventricular function. The results of the Netherlands trial indicate that primary angioplasty is associated with a higher rate of patency of the infarct-related artery, a less severe residual stenotic lesion, better left ventricular function, and less recurrent myocardial ischemia and infarction than in patients receiving streptokinase.[170]

In a substudy of the GUSTO-IIb trial,[171] the investigators randomly assigned 1138 patients with AMI to either PCI or accelerated t-PA. The composite 30-day endpoint included death, nonfatal reinfarction, and nonfatal disabling stroke. Of the patients assigned to PCI therapy, 83% were candidates for such treatment and underwent angioplasty 1.9 hours after ED arrival for a total elapsed time from chest pain onset to therapy of 3.8 hours. Ninety-eight percent of the patients assigned to fibrinolytic therapy received t-PA 1.2 hours after hospital arrival. The composite endpoint was encountered significantly less often in the PCI group (9.6%) than in the t-PA group (13.7%) at 30 days. When the individual components of the composite endpoint at 30 days were considered separately, death, infarction, and stroke occurred at statistically similar rates for both treatment groups. A meta-analysis reviewed 10 major studies comparing fibrinolysis with primary PCI in more than 2600 patients. The 30-day mortality and stroke occurrence were significantly lower in the PCI group.[172]

The second Danish Acute Myocardial Infarction (DANAMI-2) trial comprehensively investigated the PCI strategy.[173] Investigators randomly assigned AMI patients to receive either PCI or accelerated treatment with alteplase (t-PA). Patients arrived at hospitals without invasive capabilities (totaling 24) or with angioplasty capability (totaling 5). Stents and GPI were available and were used at the discretion of the treating physicians. For angioplasty-managed patients at noninvasive centers, transfer to PCI-capable institutions had to occur within a 3-hour time period. Significant differences were observed in a composite endpoint of death, reinfarction, or disabling stroke at 30 days between the groups, with rates of 8.5% in the PCI group versus 14.2% in the fibrinolytic group. Transfer for PCI occurred within 2 hours in 96% of patients. These additional studies support the findings of the DANAMI-2 trial.[169-172]

The Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) investigators compared angioplasty and PCI using coronary stents in STEMI patients undergoing urgent reperfusion therapy; abciximab was added to portions of both treatment groups. At 6 months, the primary endpoint (a composite of death, recurrent infarction, stroke, and urgent revascularization) had occurred in 20% of patients after angioplasty, 17% after PCI with abciximab, 12% after stenting, and 10% after stenting with abciximab.[174]

The longer-term results with PCI, however, are less clear. Much of the literature comparing the acute reperfusion therapies in AMI does not include the use of coronary stenting during PCI or contemporary dual-agent platelet therapy. The GUSTO-IIb study showed no overall mortality advantage of PCI at 6 months.[171] The issue of long-term outcome in PCI-managed STEMI patients is further complicated by drug-eluting stents (DESs). Early studies used bare metal stents (BMSs), which, in the setting of an acute thrombotic event such as STEMI, raised concern regarding stent thrombosis with obstruction and recurrent AMI.

In comparing BMS and DES with both angiographic and clinical outcome variables in STEMI patients treated with PCI using intracoronary stenting, event-free survival at 12 months was significantly higher in the DES group, with 74% in BMS patients and 86% in DES patients. Furthermore, the target-vessel–failure-free (i.e., correctly functioning culprit artery stent) survival was also significantly greater in the DES patients compared with the BMS group. The rates of death, MI, and stent thrombosis, however, were not significantly different between the groups. Also, a higher rate of stent malposition was noted in the DES group, despite a lower rate of event occurrence in this contingent.[175]

A meta-analysis of seven randomized trials compared the effects of DES and BMS in 2357 AMI patients. This study reported that DES significantly reduces the need for revascularization without changes in death or MI out to 1-year follow-up; no increased risk of thrombosis was found in the DES group.[176] Another group extended the follow-up period of patients managed with coronary stenting. This patient group, undergoing PCI with stenting in an elective setting, extended the period of observation out to 2 years. These investigators found that target vessel revascularization was needed less often in the DES group, yet the rates of AMI and death were similar.[177]

Thus PCI with stenting appears to be superior to standard angioplasty. The addition of DES to the equation has produced less favorable results, however, with similar rates of MI and death coupled with a lower rate of revascularization in the DES patients to several years postintervention.

Rescue Percutaneous Coronary Intervention. Historically, rescue PCI has been considered advantageous in patients whose infarct-related arteries fail to reperfuse after fibrinolytic therapy.[178] These patients are profoundly ill, with a markedly worse outcome. Some centers routinely catheterize patients after fibrinolytic therapy to determine whether successful reperfusion has occurred and to perform angioplasty if feasible. Other centers catheterize patients after fibrinolytic therapy only if there is clinical evidence that the infarct-related artery fails to open, as suggested by continued chest pain or persistent ST segment elevation.[179-182]

The Middlesbrough Early Revascularization to Limit INfarction (MERLIN) trial compared outcomes after rescue PCI with a conservative management strategy in STEMI patients in whom fibrinolysis failed. Rescue PCI was not associated with improved survival at 1 month; furthermore, increased rates of stroke and transfusion were noted in this group. At 1- and 3-year intervals, the lack of survivor benefit persisted.[179-181] In a meta-analysis of STEMI patients who did not achieve satisfactory reperfusion after fibrinolysis, rescue PCI was not associated with mortality

www.ketabpezeshki.com 66485457-66963820

reductions. In this very ill group, however, the incidence of heart failure and recurrent infarction was reduced. Repeat fibrinolysis was not associated with significant improvements in mortality or recurrent infarction.[182] Although the decision to offer rescue PCI in the patient in whom fibrinolytic therapy has failed remains controversial, evidence favors rescue PCI and does not support the use of repeat fibrinolysis.

Facilitated Percutaneous Coronary Intervention. *Facilitated percutaneous coronary intervention* refers to combination therapy involving fibrinolysis coupled with emergent PCI. This concept originally was developed to maximize therapy in STEMI patients who would be transferred urgently for PCI; the patient would receive the additive benefit of medical therapy (a fibrinolytic agent) before transfer, optimizing the culprit artery for the benefit of mechanical therapy before arrival at the PCI-capable institution. Unfortunately, outcomes from this facilitated approach are less optimal than either fibrinolysis or standard PCI alone. The ASSENT-4 PCI investigators considered this approach with tenecteplase in a facilitated PCI protocol for STEMI patients. The tenecteplase group had a higher rate of the primary endpoint (death, acute CHF, or shock) within 90 days as well as increased occurrences of stroke, ischemic cardiac complications, and need for repeat revascularization.[183] A larger meta-analysis of 17 trials compared facilitated PCI with standard PCI in the STEMI patient. Patients undergoing facilitated PCI experienced higher rates of poor outcome and complication than patients in the standard PCI group. The facilitated PCI group fared less well, with a higher rate of nonfatal recurrent infarction, urgent need for revascularization, major bleeding, and stroke.[184] The Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial, though stopped early, clearly supported this conclusion.[185] In light of these results, the continued use of a facilitated PCI approach is unclear outside of a scientific investigation.[186]

Choice of Reperfusion Therapy

The principal choices for reperfusion therapy in the STEMI patient include fibrinolysis and PCI, although numerous recommendations exist. Regardless of the strategy selected, "the systems goal should be a first medical contact–to-[therapy] time within 90 minutes."[7] The following recommendations should be considered by the emergency physician and other involved clinicians in determining the most appropriate reperfusion therapy for the STEMI patient. A fibrin-specific fibrinolytic agent is the preferred strategy in the patient without contraindication to such therapy who is seen early in the time course of the infarction (i.e., within 3 hours). In this fibrinolytic-preferred strategy, PCI either is not available (i.e., a noninvasive center) or is delayed (transfer or other logistical problems). The system goal for fibrinolytic therapy is to deliver the drug within 30 minutes of patient presentation.[7]

PCI is the preferred reperfusion strategy in the STEMI patient who can arrive in the catheterization laboratory with placement of the catheter adjacent to the culprit artery lesion within 90 minutes of initial hospital arrival.[7] High-risk STEMI patients, "late presenters" (i.e., more than 3 hours since the onset of STEMI symptoms), and individuals with contraindication to fibrinolysis are also candidates for PCI. When the diagnosis of STEMI is in doubt, PCI is the most appropriate diagnostic and therapeutic strategy.

If applied early and without delay, PCI provides improved outcome over fibrinolysis in the STEMI patient. It should be initiated within 90 minutes of arrival at the initial hospital ED.[7] As noted in the DANAMI-2 study,[173] PCI initiated within 3 hours of initial hospital arrival is also superior to fibrinolysis. Because many hospital systems do not have the capability of meeting the time goal for primary PCI, fibrinolytic therapy is preferred because of the critical importance of time to treatment from onset of symptoms of STEMI in reducing morbidity and mortality.[7]

If the time required to mobilize staff and arrange for PCI is prolonged or if delays in transfer are anticipated, fibrinolysis is preferred. Prior agreement between the ED and the cardiovascular physicians at institutions with invasive capability must be obtained so that PCI consideration does not introduce further delays in fibrinolytic drug administration. Consensus clinical pathways limit additional delays in the administration of fibrinolytic agents in patients who are considered for PCI in AMI.[187]

An elegant analysis of the "PCI versus fibrinolysis" consideration in the STEMI patient asks: How long should the practitioner wait for PCI in a patient who is fibrinolytic eligible? Considerations include the important time-to-therapy question and also factors such as the time from onset to presentation, patient age, and infarct location. Time recommendations are also provided with respect to patient age, infarct duration, and MI anatomic location. The maximal elapsed times one should wait for PCI (the actual time to balloon inflation), at which point the survival benefit of the invasive strategy is lost and the patient should receive a fibrinolytic agent, are discussed here.[188]

In a complex analysis of 192,509 patients in a national STEMI registry,[188] acceptable PCI "waiting times" range broadly from approximately 40 to 180 minutes. For instance, the relatively younger patient who is experiencing an anterior STEMI and is seen within 2 hours of symptom onset should be in the catheterization laboratory with the catheter across the lesion within 40 minutes or should receive a fibrinolytic agent. Conversely, the older patient with an inferior or lateral STEMI who is seen more than 2 hours after symptom onset could wait up to 179 minutes (almost 3 hours) before any PCI survival benefit is lost. Patient presentations with the "maximal allowable" time to catheter placement across the lesion are as follows:

- Within 2 hours of symptom onset—94 min
- Beyond 2 hours of symptom onset—190 min
- Younger than 65 years—71 min
- Older than 65 years—155 min
- Anterior STEMI—115 min
- Nonanterior STEMI—112 min

Further analysis combined commonly encountered clinical variables in typical STEMI presentations:

- Patient presentation within 2 hours of symptom onset and:
  - Anterior STEMI with age younger than 65 years—40 min
  - Anterior STEMI with age older than 65 years—107 min
  - Nonanterior STEMI with age younger than 65 years—58 min
  - Nonanterior STEMI with age older than 65 years—168 min
- Patient presentation beyond 2 hours of symptom onset and:
  - Anterior STEMI with age younger than 65 years—43 min
  - Anterior STEMI with age older than 65 years—148 min
  - Nonanterior STEMI with age younger than 65 years—103 min
  - Nonanterior STEMI with age older than 65 years—179 min

Symptom duration as well as patient age and infarct location affects reperfusion therapy decisions. Patients who are not able to rapidly reach the PCI suite should receive fibrinolysis. This analysis does not represent the standard for treatment comparisons.[188]

Delays to reperfusion therapy have negative consequences, as noted in a subset of patients in the GRACE database. The investigators examined the outcome impact of treatment delays on STEMI patients receiving reperfusion therapy. This study involved 3959 patients from 106 hospitals in 14 countries with presentation within 6 hours of chest pain onset who underwent either PCI (55%) or fibrinolysis (45%). Delays in reperfusion were associated with increased mortality for both treatment strategies and were more pronounced in those patients receiving fibrinolysis.[189]

www.ketabpezeshki.com 66485457-66963820

A cooperative effort among all providers and units can reduce markedly the door-to-therapy time in STEMI patients.[190] A "STEMI alert" system, analogous to the "trauma alert" approach, mobilizes hospital-based resources, optimizing the approach to the AMI patient. This system, whether activated by data gathered in the ED or in the field, has the potential to offer time-sensitive therapies in a rapid fashion. In fact, emergency physician activation of the catheterization laboratory demonstrates very high rates of accurate STEMI diagnosis while markedly reducing the time to definitive therapy with very low rates of inappropriate activation (i.e., the STEMI mimicker).[112,191,192] The ACC and AHA recognize the numerous challenges and potential difficulties in achieving these reperfusion therapy time goals.[7]

Reperfusion Therapy in Cardiogenic Shock

Patients with AMI with cardiogenic shock, which occurs in up to 10% of cases, demand special consideration because of a mortality rate approaching 80%. Fibrinolysis is not effective in these patients owing to a significantly lower coronary perfusion pressure. In shock, the occlusive thrombus is not exposed to the fibrinolytic agent, resulting in clinical failure of the drug. In large fibrinolytic trials such as GISSI-1 and ISIS-2,[163,168] AMI patients in cardiogenic shock do not benefit from fibrinolysis. Conversely, primary PCI has been investigated in more than 600 patients in several small studies. A cumulative analysis revealed a significantly lower mortality rate (45%) compared with placebo or historical controls.[193] The SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK? (SHOCK) trial compared the outcomes of AMI patients in cardiogenic shock.[194] Patients were randomly assigned to emergency revascularization (PCI or emergent CABG) or initial medical stabilization, including fibrinolysis. The primary endpoint was mortality from all causes at 30 days; 6-month survival was the secondary endpoint. Overall mortality at 30 days did not differ significantly between the revascularization and medical therapy groups. Six-month mortality was lower in the revascularization group than in the medical therapy group. The investigators conclude that in AMI patients with cardiogenic shock, emergency revascularization does not significantly reduce overall mortality at 30 days. After 6 months, however, there is a significant survival benefit. Thus, emergency revascularization with PCI or CABG is preferred in patients with STEMI complicated by cardiogenic shock irrespective of the delay to treatment (i.e., more than 120 minutes first medical contact to PCI time usually measured for transferring these patients). Fibrinolytic therapy should be given to eligible patients who are otherwise unsuitable candidates for PCI or CABG.[140]

Resuscitated Cardiac Arrest with ST Segment Elevation Myocardial Infarction

The management of the STEMI patient resuscitated from cardiac arrest includes: (1) rapid revascularization with PCI, (2) strict hemodynamic monitoring, (3) serum glucose control, (4) oxygen and volume-limiting ventilation, and (5) immediate application of therapeutic hypothermia for those patients whose cardiac arrest was caused by ventricular fibrillation or pulseless ventricular tachycardia.[195] A clinical presentation of coma after cardiac arrest should not be considered a contraindication to reperfusion therapy, as such findings are commonly present. In a series of 186 patients who underwent immediate PCI after successful resuscitation for cardiac arrest complicating STEMI, PCI was successful in almost 90%, restoring adequate coronary perfusion. It is interesting to note that 54% survived beyond 6 months, with a large proportion having intact neurologic function.[196] A second investigation reviewed 135 patients with resuscitated cardiac arrest complicated by STEMI. Among those patients who were conscious at the time of PCI, invasive therapy restored coronary perfusion in 96% of cases, and all of these patients survived without neurologic deficit. The outcome in the comatose patient subgroup was less favorable, with approximately a 50% survival rate and good neurologic outcome.[197]

Therapeutic hypothermia, when combined with PCI, in resuscitated cardiac arrest STEMI patients demonstrates an impressive rate of survival with good neurologic outcome. In a series of 40 such patients, therapeutic hypothermia coupled with PCI demonstrated a significantly improved rate of survival.[198]

It is reasonable to include PCI as part of a standard postresuscitation care program, including therapeutic hypothermia, as almost 50% of cardiac arrest survivors have an acute occlusion or culprit lesion amenable to intervention.[199] Furthermore, PCI need not preclude or delay the initiation of therapeutic hypothermia, as many methods may be used concurrently in the catheterization laboratory.

Another study compared reperfusion strategies in cardiac arrest survivors who experienced STEMI in the immediate postresuscitation period. Regardless of the reperfusion method, approximately 65% of patients survived to 6 months, with 53% demonstrating good neurologic function. The rate of an adverse event, such as significant hemorrhage in patients who received more than 10 minutes of CPR, was similar in those patients who did and did not receive a fibrinolytic agent.[166]

Transfer of a Patient with Acute Coronary Syndrome

There are several indications for the transfer of a patient with ACS to a facility with PCI capability. These include rapid access to PCI (catheter across the lesion within 90 minutes of arrival to the initial hospital), persistent hemodynamic instability or ventricular dysrhythmias, and postinfarction or postreperfusion ischemia. Hospital transfer for PCI is also suggested for patients with fibrinolytic contraindications who may benefit from PCI or CABG.

The urgent transfer of a fibrinolytic-eligible STEMI patient to another institution for PCI is not recommended until fibrinolytic therapy has been initiated if a delay in PCI application is anticipated.[174] In fact, the ACC/AHA guidelines note that in hospitals without PCI capability, immediate transfer for primary PCI is a treatment option when it can be accomplished within 120 minutes of first medical contact.[140] If delays in PCI performance are anticipated and the patient is an acceptable candidate for fibrinolysis, the fibrinolytic should be started before or during transport to the receiving hospital.

Many institutions are not PCI capable. Thus the decision for the emergency physician involves not only the relatively simple "lytic versus PCI" issue but also the potential need for urgent transfer to a larger center. The PRimary Angioplasty in patients transferred from General community hospitals to specialized percutaneous coronary angioplasty (PTCA) Units with or without Emergency thrombolysis (PRAGUE) investigators explored the potential benefit of PCI over fibrinolysis and the all-important impact of transfer of the STEMI patient in a noninterventional hospital over a multiyear follow-up study. At the end of the 5-year period, the cumulative incidence of composite endpoint (death from any cause, recurrent infarction, stroke, and/or revascularization) was 53% in fibrinolytic patients compared with 40% in the PCI group. The investigators concluded that the early benefit from a transfer-related invasive strategy was sustained over the 5-year follow-up period. The benefit was largely a result of a lower event rate in the first 30 days after presentation.[200]

The potential need to transfer the STEMI patient over long distances can also affect reperfusion therapy decisions. In a study of patients in rural hospitals in central Illinois, a standard treatment protocol initiated by the emergency physician included rapid

www.ketabpezeshki.com 66485457-66963820

hospital transfer for PCI. Fibrinolysis was used at the discretion of the treating emergency physician when either unanticipated delays occurred or the physician felt such therapy was necessary. In this study, the median initial hospital arrival to transfer initiation time was 46 minutes; a large portion of this delay was a to the transport vehicle. The transferring and accepting hospitals' arrival to catheter median placement times were 29 minutes and 35 minutes, respectively. Overall, the initial hospital arrival to catheter placement time was 117 minutes. No transfer-related complications occurred. Sixty percent of STEMI patients received some form of reperfusion therapy in this rural system within 120 minutes.[201] This prolonged transport issue was also explored in an established treatment system involving 30 hospitals ranging up to 210 miles from the PCI center. Over a 2.5-year period, 1345 consecutive STEMI patients were managed, including 1048 patients transferred from non-PCI hospitals.[202] These two investigations suggest that rapid transfer for PCI in the STEMI patient can occur in the rural setting with acceptable time to therapy.

Potential Pharmacologic Management Approach

The patient with stable chest pain with a normal to minimally abnormal ECG and a negative serum marker is best managed initially with NTG sublingually or topically in combination with aspirin. Resolution of the discomfort with continued stability probably does not warrant further ED pharmacologic management. Continued or recurrent pain in the ED may be treated with parenteral morphine sulfate. Continued pain may ultimately require intravenous NTG and heparinization with UFH or LMWH, with additional antiplatelet therapy with either a thienopyridine or GPI. The patient with "stable" UA (i.e., new-onset or altered pattern but now symptom free and lacking abnormal serum markers and ECG) does not require heparin or other more aggressive platelet inhibition therapy in most cases.

The ACS patient with an abnormal ECG, particularly ST segment and T wave abnormalities, or elevated serum markers may warrant numerous therapies, including ASA, heparin, and other antiplatelet agents. NTG may be administered by the topical or intravenous route. The patient with recurrent angina may also benefit from such an approach. Heparin therapy is generally indicated in this instance.

The AMI patient without ST segment elevation requires aspirin, NTG, heparin, and morphine sulfate. Depending on hospital protocols and the type of ACS, a thienopyridine can be administered in the ED or in the coronary care area. The patient with ST segment elevation AMI is treated with the preceding medications and is considered for urgent revascularization, achieved by fibrinolytic agents, PCI, or, in the rare case, CABG.

KEY CONCEPTS

- Anginal equivalent symptoms that are not characteristically associated with ACS vary widely and often distract from the diagnosis. The patient's age, diabetes status, ethnicity, and gender are considered with an atypical history.
- Limitations of the 12-lead ECG in ACS include initial nondiagnostic findings, evolving fluctuations with ongoing symptoms, anatomic myocardial "blind spots," and confounding or obscuring patterns, such as LBBB.
- Patients with proximal left anterior descending artery stenosis (Wellens syndrome) may have deeply inverted or biphasic T waves in the anterior precordial leads.
- ST segment elevation in lead aVR over 0.5 mV suggests left main coronary artery disease.
- Functional testing strategies for ACS include graded exercise testing, echocardiography, myocardial scintigraphy, and coronary CT. Graded exercise testing with or without nuclear scintigraphy can be used in the patient with low to moderate likelihood of CAD who is able to exercise. Myocardial scintigraphy with pharmacologic stress can be used in the debilitated or older patient (i.e., unable to exercise). Echocardiography with pharmacologic stress is appropriate for the woman older than 45 years, the patient with diabetes mellitus, and patients with other forms of organic heart disease (valvular dysfunction and low cardiac output states). The use of coronary CT is most appropriate in the younger patient, yet its widespread application cannot be advised.
- Fibrinolysis is not effective in patients with AMI in cardiogenic shock.
- Advancements in other noninvasive imaging modalities to assess ACS include coronary CTA and triple rule-out MDCT protocols; their role in the ED remains undefined.
- Unless used for rate control of supraventricular dysrhythmia in a patient who cannot tolerate beta-blockade, calcium channel blockade is not recommended for ACS.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Mackay J, Mensah G, eds. *The Atlas of Heart Disease and Stroke*. Geneva: World Health Organization; 2004.
2. Hunink MG, et al: The recent decline in mortality from coronary heart disease, 1980-1990: The effect of secular trends in risk factors and treatment. *JAMA* 1997; 227:535.
3. McCaig LF, Burt CW: National Hospital Ambulatory Medical Care Survey: 2001 emergency department summary. *Adv Data* 2003; 335:1.
4. Nawar EW, Niska RW, Xu J: National hospital ambulatory medical care survey: 2005 emergency department summary. *Adv Data* 2007; 386:1.
5. Rosamond W, et al: Heart disease and stroke statistics—2007 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2007; 115:e69.
6. Anderson JL, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2007; 50:e1.
7. Antman EM, et al: 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction. *Circulation* 2008; 117:296.
8. Ryan TJ, Melduni RM: Highlights of latest American College of Cardiology and American Heart Association Guidelines for Management of Patients with Acute Myocardial Infarction. *Cardiol Rev* 2002; 10:35.
9. Spertus JA, et al: Challenges and opportunities in quantifying the quality of care for acute myocardial infarction. *J Am Coll Cardiol* 2003; 41:1653.
10. Weinstein MD, Stason WB: Cost-effectiveness of interventions to prevent or treat coronary heart disease. *Annu Rev Public Health* 1985; 6:41.
11. Thygesen K, et al: Universal definition of myocardial infarction. *Circulation* 2007; 116:2634.
12. Antman EM, et al: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *J Am Coll Cardiol* 2004; 44:E1.
13. Diop D, Aghababian RV: Definition, classification, and pathophysiology of acute coronary ischemic syndromes. *Emerg Med Clin North Am* 2001; 19:259.
14. Badimon L, Badimon JJ, Vilahur G, Segalés E, Llorente V: Pathogenesis of the acute coronary syndromes and therapeutic implications. *Pathophysiol Haemost Thromb* 2002; 32:225.
15. Hargarten KM, et al: Limitations of prehospital predictors of acute myocardial infarction and unstable angina. *Ann Emerg Med* 1987; 16:1325.
16. Khot UN, et al: Prevalence of conventional risk factors in patients with coronary heart disease. *JAMA* 2003; 290:898.
17. Han JH, et al: The role of cardiac risk factor burden in diagnosing acute coronary syndromes in the emergency department setting. *Ann Emerg Med* 2007; 49:145.
18. Body R, McDowell G, Carley S, Mackway-Jones K: Do risk factors for chronic coronary heart disease help diagnose acute myocardial infarction in the emergency department? *Resuscitation* 2008; 79:41-45.
19. Currier JS, et al: Coronary heart disease in HIV-infected individuals. *J Acquir Immune Defic Syndr* 2003; 33:506-512.
20. Shoenfeld Y, et al: Accelerated atherosclerosis in autoimmune rheumatic diseases. *Circulation* 2005; 112:3337.
21. Mattu A, Petrini J, Swencki S, Chaudhari C, Brady WJ: Premature atherosclerosis and acute coronary syndrome in systemic lupus erythematosus. *Am J Emerg Med* 2005; 23:696-703.
22. Swap CJ, Nagurney JT: Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. *JAMA* 2005; 294:2623.
23. Body R, et al: The value of symptoms and signs in the emergent diagnosis of acute coronary syndromes. *Resuscitation* 2010; 81:281-286.
24. Tierney WM, et al: Physicians' estimates of the probability of myocardial infarction in emergency room patients with chest pain. *Med Decis Making* 1986; 6:12.
25. Canto JG, et al: Prevalence, clinical characteristics, and mortality among patients with myocardial infarction without chest pain. *JAMA* 2000; 283:3223.
26. Canto JG, et al: Atypical presentations among Medicare beneficiaries with unstable angina pectoris. *Am J Cardiol* 2002; 90:248.
27. Grossman SA, et al: Predictors of delay in presentation to the ED in patients with suspected acute coronary syndromes. *Am J Emerg Med* 2003; 21:425.
28. Alexander KP, et al: Acute coronary care in the elderly. Part I: Non-ST segment elevation acute coronary syndromes. *Circulation* 2007; 115:2549.
29. Jacoby RM, Nesto RW: Acute myocardial infarction in the diabetic patient: Pathophysiology, clinical course, and prognosis. *J Am Coll Cardiol* 1992; 20:736.
30. McSweeney JC, et al: Women's early warning symptoms of acute myocardial infarction. *Circulation* 2003; 108:2619.
31. Venkat A, et al: The impact of race on the acute management of chest pain. *Acad Emerg Med* 2002; 10:1199.
32. Pope JH, et al: Missed diagnosis of acute cardiac ischemia in the emergency department. *N Engl J Med* 2000; 342:1163.
33. McCarthy BD, Beshansky JR, D'Agostino RB, Selker HP: Missed diagnoses of acute myocardial infarction in the emergency department: Results from a multicenter study. *Ann Emerg Med* 1993; 22:579.
34. Brady WJ, Perron A: Acute cardiovascular complications in ED patients with AMI. *Ann Emerg Med* 2000; 36:S33.
35. Brady WJ, Swart G, DeBehnke DJ, Ma OJ, Aufderheide TP: The efficacy of atropine in the treatment of hemodynamically unstable bradycardia and atrioventricular block: Prehospital and emergency department considerations. *Resuscitation* 1999; 41:47.
36. Swart G, Brady WJ Jr, DeBehnke DJ, Ma OJ, Aufderheide TP: Acute myocardial infarction complicated by hemodynamically unstable bradyarrhythmia: Prehospital and emergency department treatment with atropine. *Am J Emerg Med* 1999; 17:647.
37. Zimetbaum PJ, Josephson ME: Use of the electrocardiogram in acute myocardial infarction. *N Engl J Med* 2003; 348:933.
38. Mooe T, Eriksson P, Stegmayr B: Ischemic stroke after acute myocardial infarction: A population-based study. *Stroke* 1997; 28:762.
39. Tiefenbrunn AJ, Chandra NC, French WJ, Gore JM, Rogers WJ: Clinical experience with primary percutaneous transluminal coronary angioplasty compared with alteplase (recombinant tissue-type plasminogen activator) in patients with acute myocardial infarction: A report from the Second National Registry of Myocardial Infarction (NRMI-2). *J Am Coll Cardiol* 1998; 31:1240.
40. Zarich W, Nesto RW: Implications and treatment of acute hyperglycemia in the setting of acute myocardial infarction. *Circulation* 2007; 115:e436.
41. Singer AJ, et al: Effect of duration from symptom onset on the negative predictive value of a normal ECG for exclusion of acute myocardial infarction. *Ann Emerg Med* 1997; 29:575.
42. Smith SW: Upwardly concave ST segment morphology is common in acute left anterior descending coronary artery occlusion. *Acad Emerg Med* 2003; 10:516.
43. Brady WJ, et al: Electrocardiographic ST segment elevation: The diagnosis of AMI by morphologic analysis of the ST segment. *Acad Emerg Med* 2001; 8:961.
44. Wang K, Asinger RW, Marriott HJ: ST-segment elevation in conditions other than acute myocardial infarction. *N Engl J Med* 2003; 349:2128.
45. Otto LA, Aufderheide TP: Evaluation of ST segment elevation criteria for the prehospital electrocardiographic diagnosis of acute myocardial infarction. *Ann Emerg Med* 1994; 23:17.
46. Brady WJ, et al: Reciprocal ST segment depression: Impact on the electrocardiographic diagnosis of ST segment elevation acute myocardial infarction. *Am J Emerg Med* 2002; 20:35.
47. Brady WJ, et al: Electrocardiographic ST segment elevation in emergency department chest pain center patients: Etiology responsible for the ST segment abnormality. *Am J Emerg Med* 2001; 9:25.
48. Doevendans PA, et al: Electrocardiographic diagnosis of reperfusion during thrombolytic therapy in acute myocardial infarction. *Am J Cardiol* 1995; 75:1206-1210.
49. Wehrens XH, Doevendans PA, Ophuis TJ, Wellens H: A comparison of electrocardiographic changes during reperfusion of acute myocardial infarction by thrombolysis or percutaneous transluminal coronary angioplasty. *Am Heart J* 2000; 139:430.
50. Szymanski FM, et al: Electrocardiographic features and prognosis in acute diagonal or marginal branch occlusion. *Am J Emerg Med* 2007; 25:170.
51. Saw J, Davies C, Fung A, Spinelli JJ, Jue J: Value of ST elevation in lead III greater than lead II in inferior wall acute myocardial infarction for predicting in-hospital mortality and diagnosing right ventricular infarction. *Am J Cardiol* 2001; 87:4481.
52. Zehmer U, et al: Effects of fibrinolytic therapy in acute myocardial infarction with or without right ventricular involvement. *J Am Coll Cardiol* 1998; 2:876.

www.ketabpezeshki.com 66485457-66963820

53. Rostoff P, et al: Electrocardiographic prediction of acute left main coronary artery occlusion. *Am J Emerg Med* 2007; 25:852.
54. Yamaji H, et al: Prediction of acute left main coronary artery obstruction by 12-lead electrocardiography. ST segment elevation in lead aVR with less ST segment elevation in lead V_1. *J Am Coll Cardiol* 2001; 38:1348.
55. Sharkey SW, Berger CR, Brunette DD, Henry TD: Impact of the electrocardiogram on the delivery of thrombolytic therapy for acute myocardial infarction. *Am J Cardiol* 1994; 73:550-553.
56. Haissaguerre M, et al: Sudden cardiac arrest associated with early repolarization. *N Engl J Med* 2008; 358:2016-2023.
57. Smith S, Nolan M: Ratio of T amplitude to QRS amplitude best distinguishes acute anterior MI from anterior left ventricular aneurysm. *Acad Emerg Med* 2003; 10:516.
58. Sgarbossa EB, et al: Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle-branch block: GUSTO-1 (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) Investigators. *N Engl J Med* 1996; 334:481.
59. Edhouse JA, Sakr M, Angus J, Morris FP: Suspected myocardial infarction and left bundle branch block: Electrocardiographic indicators of acute ischaemia. *J Accid Emerg Med* 1999; 16:331.
60. Sgarbossa EB, Pinski SL, Gates KB, Wagner GS: Early electrocardiographic diagnosis of acute myocardial infarction in the presence of ventricular paced rhythm: GUSTO-1 Investigators. *Am J Cardiol* 1996; 77:423.
61. Pitta SR, et al: ST segment depression on the initial electrocardiogram in acute myocardial infarction: Prognostic significance and its effect on short-term mortality: A report from the National Registry of Myocardial Infarction (NRMI-2, 3, 4). *Am J Cardiol* 2005; 95:843.
62. Brady WJ, et al: A comparison of the 12-lead ECG to the 15-lead ECG in emergency department chest pain patients: Impact on diagnosis, therapy, and disposition. *Am J Emerg Med* 2000; 18:239.
63. Zalenski RJ, Cooke D, Rydman R, Sloan EP, Murphy DG: Assessing the diagnostic value of an ECG containing leads V4R, V8, and V9: The 15-lead ECG. *Ann Emerg Med* 1993; 22:786.
64. Fesmire FM, Percy RF, Bardoner JB, Wharton DR, Calhoun FB: Usefulness of automated serial 12-lead ECG monitoring during the initial emergency department evaluation of patients with chest pain. *Ann Emerg Med* 1998; 31:3.
65. Jernberg T, Lindahl B, Wallentin L: ST-segment monitoring with continuous 12-lead ECG improves early risk stratification in patients with chest pain and ECG nondiagnostic of acute myocardial infarction. *J Am Coll Cardiol* 1999; 34:1413.
66. Ornato J: *Electrocardiographic body surface mapping*. In: Chan TC, et al, eds. *The ECG in Emergency Medicine and Acute Care*. Philadelphia: Elsevier; 2004.
67. Ornato JP, et al: 80-lead body map detects acute ST-elevation myocardial infarction missed by standard 12-lead electrocardiography. *J Am Coll Cardiol* 2002; 39:L332A.
68. Self WH, et al: Body surface mapping in the emergency department evaluation of the chest pain patient: Use of the 80-lead ECG system. *Am J Emerg Med* 2006; 24:87.
69. Hoekstra JW, et al: Acute detection of ST-elevation myocardial infarction missed on standard 12-lead ECG with a novel 80-lead real-time digital body surface map: Primary results from the multicenter OCCULT MI trial. *Ann Emerg Med* 2009; 54:779.
70. Menown IB, Mackenzie G, Adgey AA: Optimizing the initial 12-lead electrocardiographic diagnosis of acute myocardial infarction. *Eur Heart J* 2000; 21:275.
71. Balk EM, Ioannidis JP, Salem D, Chew PW, Lau J: Accuracy of biomarkers to diagnose acute cardiac ischemia in the emergency department. *Ann Emerg Med* 2001; 37:478.
72. Reichlin T, et al: Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* 2009; 361:858.
73. Kontos MC, et al: Implication of different cardiac troponin I levels for clinical outcomes and prognosis of acute chest pain patients. *J Am Coll Cardiol* 2004; 43:958.
74. Ohman EM, et al: Cardiac troponin T levels for risk stratification in acute myocardial ischemia. *N Engl J Med* 1996; 335:1333.
75. James S, et al: Troponin T levels and risk for 30-day outcomes in patients with acute coronary syndrome: Prospective verification in the GUSTO-IV trial. *Am J Med* 2003; 115:178.
76. Fromm RE: Cardiac troponins in the intensive care unit: Common causes of increased levels and interpretation. *Crit Care Med* 2007; 35:584.
77. Agewall S, Giannitsis E, Jernberg T, Katus H: Troponin elevation in coronary vs. non-coronary disease. *Eur Heart J* 2011; 32:404-411.
78. Khan NA, Hemmelgarn BR, Tonelli M, Thompson CR, Levin A: Prognostic value of troponin T and I among asymptomatic patients with end-stage renal disease: A meta-analysis. *Circulation* 2005; 112:3088.
79. Fesmire FM, Christenson RH, Fody EP, Feintuch TA: Delta creatine kinase-MB outperforms myoglobin at two hours during the emergency department identification and exclusion of troponin positive non-ST segment elevation acute coronary syndromes. *Ann Emerg Med* 2004; 44:12.
80. Bassan R, et al: B-type natriuretic peptide: A novel early blood marker of acute myocardial infarction in patients with chest pain and no ST-segment elevation. *Eur Heart J* 2005; 26:234.
81. Galvani M, et al: *N*-terminal pro-brain natriuretic peptide on admission has prognostic value across the whole spectrum of acute coronary syndromes. *Circulation* 2004; 110:128.
82. Brennan ML, et al: Prognostic value of myeloperoxidase in patients with chest pain. *N Engl J Med* 2003; 349:1595.
83. Morrow DA, Braunwald E: Future of biomarkers in acute coronary syndromes: Moving toward a multimarker strategy. *Circulation* 2002; 108:250.
84. McCord J, et al: Ninety-minute exclusion of acute myocardial infarction by use of quantitative point-of-care testing of myoglobin and troponin I. *Circulation* 2001; 104:1483.
85. Ng SM, et al: Ninety-minute accelerated critical pathway for chest pain evaluation. *Am J Cardiol* 2001; 88:403.
86. Fesmire FM, et al: The Erlanger chest pain evaluation protocol: A one-year experience with serial 12-lead ECG monitoring, two-hour delta serum marker measurements, and selective nuclear stress testing to identify and exclude acute coronary syndromes. *Ann Emerg Med* 2002; 40:584.
87. Bedetti G, et al: Stress echo in chest pain unit: The SPEED trial. *Int J Cardiol* 2005; 102:41.
88. Tong KL, et al: Myocardial contrast echocardiography versus thrombolysis in myocardial infarction score in patients presenting to the emergency department with chest pain and a nondiagnostic electrocardiogram. *J Am Coll Cardiol* 2005; 46:920.
89. Jeetley P, Burden L, Greaves K, Senior R: Prognostic value of myocardial contrast echocardiography in patients presenting to hospital with acute chest pain and negative troponin. *Am J Cardiol* 2007; 99:1369.
90. Hilton TC, et al: Technetium-99m sestamibi myocardial perfusion imaging in the emergency room evaluation of chest pain. *J Am Coll Cardiol* 1994; 23:1016.
91. Kontos MC, Jesse RL, Schmidt KL, Ornato JP, Tatum JL: Value of acute rest sestamibi perfusion imaging for evaluation of patients admitted to the emergency department with chest pain. *J Am Coll Cardiol* 1997; 30:976.
92. Kontos MC, Wackers FJ: Acute rest myocardial perfusion imaging for chest pain. *J Nucl Cardiol* 2004; 11:470.
93. Udelson JE, Beshansky JR, Ballin DS: Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia: A randomized controlled trial. *JAMA* 2002; 288:2693.
94. Budoff MJ, et al: Assessment of coronary artery disease by cardiac computed tomography: A scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation* 2006; 114:1761.
95. Stillman AE, et al: Use of multidetector computed tomography for the assessment of acute chest pain: A consensus statement of the North American Society of Cardiac Imaging and the European Society of Cardiac Radiology. *Eur Radiol* 2007; 17:2196.
96. Hoffman MH, et al: Noninvasive coronary angiography with multislice computed tomography. *JAMA* 2005; 293:2471.
97. Gallagher MJ, Raff GL: Use of multislice CT for the evaluation of emergency room patients with chest pain: The so-called "triple rule-out". *Catheter Cardiovasc Interv* 2008; 71:92.
98. White CS, et al: Chest pain evaluation in the emergency department: Can MDCT provide a comprehensive evaluation? *AJR Am J Roentgenol* 2005; 185:533.
99. Gallagher MJ, et al: The diagnostic accuracy of 64-slice computed tomography coronary angiography compared with stress nuclear imaging in emergency department low-risk chest pain patients. *Ann Emerg Med* 2007; 49:125.
100. Hoffman U, et al: Coronary multidetector computed tomography in the assessment of patients with acute chest pain. *Circulation* 2006; 114:2251.

www.ketabpezeshki.com 66485457-66963820

101. Newman DH: Computed tomographic angiography for low risk chest pain: Seeking passage. *Ann Emerg Med* 2009; 53:305.
102. Gibler WB, et al: A rapid diagnostic and treatment center for patients with chest pain in the emergency department. *Ann Emerg Med* 1995; 25:1.
103. Gibbons RJ, et al: ACC/AHA 2002 guideline update for exercise testing: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *J Am Coll Cardiol* 2002; 40:1531-1540.
104. Amsterdam EA, Kirk JD, Diercks DB, Lewis WR, Turnipseed SD: Immediate exercise testing to evaluate low-risk patients presenting to the emergency department with chest pain. *J Am Coll Cardiol* 2002; 40:251.
105. Amsterdam EA, Kirk JD, Diercks DB, Lewis WR, Turnipseed SD: Exercise testing in chest pain units: Rationale, implementation, and results. *Cardiol Clin* 2005; 23:503.
106. Farkouh ME, et al: A clinical trial of a chest-pain observation unit for patients with unstable angina: Chest Pain Evaluation in the Emergency Room (CHEER) Investigators. *N Engl J Med* 1998; 339:1882.
107. Goodacre S, et al: Effectiveness and safety of chest pain assessment to prevent emergency admissions: ESCAPE cluster randomized trial. *BMJ* 2007; 335:659.
108. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. The GUSTO Angiographic Investigators. *N Engl J Med* 1993; 329:1615.
109. De Luca G, Suryapranata H, Ottervanger JP, Antman EM: Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction. *Circulation* 2004; 109:1223-1225.
110. Weaver WD, et al: Prehospital-initiated vs. hospital-initiated thrombolytic therapy. The Myocardial Infarction Triage and Intervention Trial. *JAMA* 1993; 270:1211.
111. O'Connor RE, et al: Part 10: Acute Coronary Syndromes: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122:S787-S817.
112. Kurz MC, Babcock C, Sinha S, Tupesis JP, Allegretti J: The impact of emergency physician–initiated primary percutaneous coronary intervention on mean door-to-balloon time in patients with ST-segment–elevation myocardial infarction. *Ann Emerg Med* 2007; 50:527-534.
113. Yusuf S, Collins R, MacMahon S, Peto R: Effect of intravenous nitrates on mortality in acute myocardial infarction: An overview of the randomised trials. *Lancet* 1988; 1:1088.
114. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. *Lancet* 1995; 345:669-685.
115. Meine TJ, et al: Association of intravenous morphine use and outcomes in acute coronary syndromes: Results from the CRUSADE Quality Improvement Initiative. *Am Heart J* 2005; 149:1043.
116. Pfisterer M, et al: Atenolol use and clinical outcomes after thrombolysis for acute myocardial infarction: The GUSTO-I experience: Global utilization of streptokinase and TPA (alteplase) for occluded coronary arteries. *J Am Coll Cardiol* 1998; 32:634.
117. Chen ZM, et al: Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: Randomized placebo-controlled trial. *Lancet* 2005; 366:1622.
118. Bates ER: Role of intravenous beta-blockers in the treatment of ST-elevation myocardial infarction. *Circulation* 2007; 115:2904.
119. Kinlay S, et al: High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study. *Circulation* 2003; 108:1560-1566.
120. Heeschen C, et al: Withdrawal of statins increases event rates in patients with acute coronary syndromes. *Circulation* 2002; 105:1446-1452.
121. Patti G, et al: Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: Results of the ARMYDA-ACS randomized trial. *J Am Coll Cardiol* 2007; 49:1272-1278.
122. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988; 2:349.
123. Bellandi F, Maioli M, Leoncini M, Toso A, Dabizzi RP: Early abciximab administration in acute myocardial infarction treated with primary coronary intervention. *Int J Cardiol* 2006; 108:36.
124. Rakowski T, et al: Early abciximab administration before primary percutaneous coronary intervention improves infarct-related artery patency and left ventricular function in high-risk patients with anterior wall myocardial infarction: A randomized study. *Am Heart J* 2007; 153:360.
125. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty: The EPIC Investigation. *N Engl J Med* 1994; 330:956.
126. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. The EPILOG investigators. *N Engl J Med* 1997; 336:1689.
127. van den Merkhof LF, et al: Abciximab in the treatment of acute myocardial infarction eligible for primary percutaneous transluminal coronary angioplasty. Results of the Glycoprotein Receptor Antagonist Patency Evaluation (GRAPE) pilot study. *J Am Coll Cardiol* 1999; 33:1528.
128. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT II. Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis–II. *Lancet* 1997; 349:1422.
129. Boersma E, et al: Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: A meta-analysis of all major randomised clinical trials. *Lancet* 2002; 359:189.
130. Simoons ML, GUSTO IV-ACS Investigators: Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: The GUSTO IV-ACS randomised trial. *Lancet* 2001; 357:1915.
131. Zhao XQ, Theroux P, Snapinn SM, Sax FL: Intracoronary thrombus and platelet glycoprotein IIb/IIIa receptor blockade with tirofiban in unstable angina or non–Q-wave myocardial infarction: Angiographic results from the PRISM-PLUS trial (Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms): PRISM-PLUS Investigators. *Circulation* 1999; 100:1609.
132. Ohman EM, et al: Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with Integrilin in acute myocardial infarction: Results of a randomized, placebo-controlled, dose-ranging trial: IMPACT-AMI Investigators. *Circulation* 1997; 95:846.
133. Roe MT, et al: A randomized, placebo-controlled trial of early eptifibatide for non–ST-segment elevation acute coronary syndromes. *Am Heart J* 2003; 146:993.
134. Srinivas VS, et al: Effectiveness of glycoprotein IIb/IIIa inhibitor use during primary coronary angioplasty: Results of propensity analysis using the New York State Percutaneous Coronary Intervention Reporting System. *Am J Cardiol* 2007; 99:482.
135. Montalescot G, et al: Abciximab in primary coronary stenting of ST-elevation myocardial infarction: A European meta-analysis on individual patients' data with long-term follow-up. *Eur Heart J* 2007; 28:443.
136. Stone GW, et al: Antithrombotic strategies in patients with acute coronary syndromes undergoing early invasive management: One-year results from the ACUITY trial. *JAMA* 2007; 298:2497-2506.
137. Giugliano RP, et al: Early versus delayed, provisional eptifibatide in acute coronary syndromes. *N Engl J Med* 2009; 360:2176-2190.
138. Wallentin L, et al: Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; 361:1045-1057.
139. O'Gara PT, et al: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013; 127:529-555.
140. Wright RS, et al: 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011: 123:2022-2060.
141. Yusuf S, et al: Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; 345:494 [erratum, *N Engl J Med* 2001; 345:1506, 1716].
142. Bromberg-Marin G, et al: Effectiveness and safety of glycoprotein IIb/IIIa inhibitors and clopidogrel alone and in combination in non–ST-segment elevation myocardial infarction (from the National Registry of Myocardial Infarction–4). *Am J Cardiol* 2006; 98:1125.
143. Fox KA, et al: Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for

www.ketabpezeshki.com 66485457-66963820

non–ST-elevation acute coronary syndrome: The Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial. *Circulation* 2004; 110:1202.
144. Sabatine MS, et al: Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; 352:1179.
145. Hoekstra JW, et al: Improving care of patients with non–ST-elevation acute coronary syndromes in the emergency department: The CRUSADE initiative. *Acad Emerg Med* 2002; 9:1146.
146. Mehta RH, et al: Challenges in predicting the need for coronary artery bypass grafting at presentation in patients with non–ST-segment elevation acute coronary syndromes. *Am J Cardiol* 2006; 98:624.
147. Low-molecular-weight heparin during instability in coronary artery disease: Fragmin during Instability in Coronary Artery Disease (FRISC) Study Group. *Lancet* 1996; 347:561.
148. Cohen M, et al: A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease: Efficacy and safety of subcutaneous enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med* 1997; 337:447.
149. Klein W, et al: Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease: Fragmin in Unstable Coronary Artery Disease Study (FRIC). *Circulation* 1997; 96:61.
150. Petersen JL, et al: Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non–ST-segment elevation acute coronary syndromes: A systematic overview. *JAMA* 2004; 292:89.
151. Brewster GS, Herbert ME: Medical myth: Heparin should be administered to every patient admitted to the hospital with possible unstable angina. *West J Med* 2000; 173:138.
152. Ferguson JJ, et al: Enoxaparin vs. unfractionated heparin in high-risk patients with non–ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: Primary results of the SYNERGY randomized trial. *JAMA* 2004; 292:45.
153. Sinnaeve PR, et al: Direct thrombin inhibitors in acute coronary syndromes: Effect in patients undergoing early percutaneous coronary intervention. *Eur Heart J* 2005; 26:2396.
154. Stone GW, et al: Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; 355:2203.
155. Yusuf S, et al: Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 2006; 295:1519-1530.
156. The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators: Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006; 354:1464.
157. Peters RJ, et al: The role of fondaparinux as an adjunct to thrombolytic therapy in acute myocardial infarction: A subgroup analysis of the OASIS-6 trial. *Eur Heart J* 2008; 29:324.
158. GISSI-2: A factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction: Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. *Lancet* 1990; 336:65.
159. In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with or without heparin. The International Study Group. *Lancet* 1990; 336:71.
160. ISIS-3: A randomised comparison of streptokinase vs. tissue plasminogen activator vs. anistreplase and or aspirin plus heparin vs. aspirin alone among 41,299 cases of suspected acute myocardial infarction. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. *Lancet* 1992; 339:753.
161. A comparison of reteplase with alteplase for acute myocardial infarction: The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. *N Engl J Med* 1997; 337:1118.
162. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: The ASSENT-2 double-blind randomised trial. *Lancet* 1999; 354:716.
163. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. *Circulation* 1994; 89:1545.
164. Indications for fibrinolytic therapy in suspected acute myocardial infarction: Collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients: Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet* 1994; 343:311.
165. Late Assessment of Thrombolytic Efficacy (LATE) study with alteplase 6-24 hours after onset of acute myocardial infarction. *Lancet* 1993; 342:759.
166. Richling N, et al: Thrombolytic therapy vs. primary percutaneous intervention after ventricular fibrillation cardiac arrest due to acute ST-segment elevation myocardial infarction and its effect on outcome. *Am J Emerg Med* 2007; 25:545.
167. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). *Lancet* 1986; 1:397.
168. Wilcox RG, et al: Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction: Anglo-Scandinavian Study of Early Thrombolysis (ASSET). *Lancet* 1988; 2:525.
169. Grines CL, et al: A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction: The Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med* 1993; 328:673.
170. Zijlstra F, et al: A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med* 1993; 328:680.
171. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction: The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. *N Engl J Med* 1997; 336:1621.
172. Weaver WD, et al: Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: A quantitative review. *JAMA* 1997; 278:2093.
173. Andersen HR, et al: A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med* 2003; 349:733.
174. Stone GW, et al: Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 2002; 346:957.
175. van der Hoeven BL, et al: Sirolimus-eluting stents versus bare-metal stents in patients with ST-segment elevation myocardial infarction: 9-month angiographic and intravascular ultrasound results and 12-month clinical outcome results from the MISSION! Intervention Study. *J Am Coll Cardiol* 2008; 51:618.
176. Pasceri V, et al: Meta-analysis of clinical trials on use of drug-eluting stents for treatment of acute myocardial infarction. *Am Heart J* 2007; 153:749.
177. Marzocchi A, et al: Long-term safety and efficacy of drug-eluting stents: Two-year results of the REAL (REgistro AngiopLastiche dell'Emilia Romagna) multicenter registry. *Circulation* 2007; 115:3181.
178. Califf RM, et al: Evaluation of combination thrombolytic therapy and timing of cardiac catheterization in acute myocardial infarction: Results of thrombolysis and angioplasty in myocardial infarction phase 5 randomized trial. *Circulation* 1991; 83:1543.
179. Sutton AG, et al: A randomized trial of rescue angioplasty versus a conservative approach for failed fibrinolysis in ST-segment elevation myocardial infarction: The Middlesbrough Early Revascularization to Limit INfarction (MERLIN) trial. *J Am Coll Cardiol* 2004; 44:287.
180. Sutton AG, et al: One-year results of the Middlesbrough Early Revascularisation to Limit INfarction (MERLIN) trial. *Heart* 2005; 91:13305.
181. Kunadian B, et al: Early invasive versus conservative treatment in patients with failed fibrinolysis—no late survival benefit: The final analysis of the Middlesbrough Early Revascularisation to Limit INfarction (MERLIN) randomized trial. *Am Heart J* 2007; 153:763.
182. Wijeysundera HC, et al: Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: A meta-analysis of randomized trials. *J Am Coll Cardiol* 2007; 49:422.
183. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) Investigators: Primary vs. tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): Randomised trial. *Lancet* 2006; 367:569.
184. Keeley EC, Boura JA, Grines CL: Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: Quantitative review of randomised trials. *Lancet* 2006; 367:579.
185. Leopold JA: Does thrombolytic therapy facilitate or foil primary PCI? *N Engl J Med* 2008; 358:2277-2279.
186. Boden WB, Faxon DP: Facilitated percutaneous coronary intervention. *J Am Coll Cardiol* 2006; 48:1120-1128.

www.ketabpezeshki.com 66485457-66963820

187. Brady WJ, Esterowitz D, Syverud SA: Consideration for primary angioplasty: Impact on the door-to-drug time in AMI patients ultimately treated with thrombolytic agent. *Am J Emerg Med* 2001; 19:15.
188. Pinto DS, et al: Hospital delays in reperfusion for ST-elevation myocardial infarction: Implications when selecting a reperfusion strategy. *Circulation* 2006; 114:2019.
189. Nallamothu B, et al: Relationship of treatment delays and mortality in patients undergoing fibrinolysis and primary percutaneous coronary intervention: The Global Registry of Acute Coronary Events. *Heart* 2007; 93:1552.
190. Camp-Rogers T, Kurz MC, Brady WJ: Hospital-based strategies contributing to percutaneous coronary intervention time reduction in the patient with ST-segment elevation myocardial infarction: A review of the "system-of-care" approach. *Am J Emerg Med* 2012; 30:491.
191. Kraft PL, Newman S, Hanson D, Anderson W, Bastani A: Emergency physician discretion to activate the cardiac catheterization team decreases door-to-balloon time for acute ST-elevation myocardial infarction. *Ann Emerg Med* 2007; 50:520.
192. Singer AJ, et al: Emergency department activation of an interventional cardiology team reduces door-to-balloon times in ST-segment elevation myocardial infarction. *Ann Emerg Med* 2007; 50:538.
193. Goldberg RJ, et al: Cardiogenic shock after acute myocardial infarction: Incidence and mortality from a community-wide perspective, 1975 to 1988. *N Engl J Med* 1991; 325:1117.
194. Hochman JS, et al: Early revascularization in acute myocardial infarction complicated by cardiogenic shock. *N Engl J Med* 1999; 341:625.
195. Sunde K, et al: Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation* 2007; 73:29-39.
196. Garot P, et al: Six-month outcome of emergency percutaneous coronary intervention in resuscitated patients after cardiac arrest complicating ST-elevation myocardial infarction. *Circulation* 2007; 115:1354.
197. Gorjup V, Radsel P, Kocjancic ST, Erzen D, Noc M: Acute ST-elevation myocardial infarction after successful cardiopulmonary resuscitation. *Resuscitation* 2007; 72:379.
198. Knafelj R, Radsel P, Ploj T, Noc M: Primary percutaneous coronary intervention and mild induced hypothermia in comatose survivors of ventricular fibrillation with ST-elevation acute myocardial infarction. *Resuscitation* 2007; 74:227.
199. Spaulding CM, et al: Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. *N Engl J Med* 1997; 336:1629-1633.
200. Widimsky P, et al: Long-term outcomes of patients with acute myocardial infarction presenting to hospitals without catheterization laboratory and randomized to immediate thrombolysis or interhospital transport for primary percutaneous coronary intervention: Five years' follow-up of the PRAGUE-2 Trial. *Eur Heart J* 2007; 28:679.
201. Aguirre FV, et al: Rural interhospital transfer of ST-elevation myocardial infarction patients for percutaneous coronary revascularization: The Stat Heart Program. *Circulation* 2008; 117:1145.
202. Henry TD, et al: A regional system to provide timely access to percutaneous coronary intervention for ST-elevation myocardial infarction. *Circulation* 2007; 116:721.

www.ketabpezeshki.com 66485457-66963820

Chapter 79

Dysrhythmias

Donald M. Yealy and Joshua M. Kosowsky

The term *dysrhythmia* denotes any abnormality in cardiac rhythm. In this chapter, we review dysrhythmias outside the context of cardiac arrest specific toxidromes. We then review the physiology of normal and abnormal cardiac impulse formation and conduction. Finally, we discuss the diagnostic tools for evaluating the patient with a known or suspected dysrhythmia, including the history, physical examination, and surface electrocardiogram (ECG). For each rhythm disturbance, we identify the treatment options for prehospital and emergency department (ED) management.

CARDIAC CELLULAR ELECTROPHYSIOLOGY

The function of individual cells in the conductive and contractile tissues of the heart depends on an intact resting membrane potential. Na^+, K^+, and Ca^{2+} ions create the membrane potential and regulate conduction and contractility. The membrane potential is the result of a differential concentration of Na^+ and K^+ on either side of the cell membrane, measuring approximately −90 mV in normal resting, nonpacemaker cells. This electrical gradient exists mainly because of the Na^+-K^+ exchange pump and the natural concentration-dependent flow of K^+ out of the cell. Adenosine triphosphate (ATP) fuels Na^+ transport out to the extracellular fluid, with Mg^{2+} used as a cofactor (Fig. 79-1). This process creates an osmotic gradient, allowing Ca^{2+} to be passively exchanged for Na^{2+} and promoting conduction as well as myofibril contraction. The resting membrane potential is generated from the flow of K^+ down a concentration gradient toward the extracellular fluid. The cell membrane is far more permeable to potassium than sodium ions, resulting in a net loss of intracellular positive charge.

In normal nonpacemaker cells, the application of an electrical stimulus causes the membrane potential to become less negative, termed *depolarization.* When the membrane potential reaches −70 mV, specialized Na^{2+} channels open, causing a rapid influx of positive charge into the cell. This "fast" channel activity further decreases the membrane potential and is augmented at 30 to 40 mV by a second "slow" channel that allows Ca^{2+} influx. When these channels close, resting potential is restored by the sodium-potassium pump, an event known as *repolarization* (Fig. 79-2).

In nonpacemaker cells, additional depolarization from a second electrical stimulus is not possible when the membrane potential is more positive than −60 mV. This period is termed the *effective refractory period* (Fig. 79-3). At a membrane potential of −60 to −70 mV, a strong impulse can cause a response that is likely to be propagated, although abnormally; this response represents the *relative refractory period.* At a membrane potential of −70 mV or less, virtually all fast channels are ready for activity if properly stimulated (see Fig. 79-3).

Pacemaker cells differ from non–impulse-generating cells in two ways: their resting membrane potential is less negative, and they can spontaneously depolarize via slow Na^+ influx . Pacemaker cells exist normally within the sinoatrial (SA) and atrioventricular (AV) nodes and can also be found on the atrial surfaces of the AV valves and within the His-Purkinje system. Nonpacemaker cells may undergo spontaneous depolarization under pathologic conditions, especially during ischemia.

Afterdepolarizations are fluctuations in membrane potential that occur as the resting potential is restored. These fluctuations may precipitate another depolarization, either just before full resting potential is reached (early afterdepolarizations) or after full resting potential is reached (delayed afterdepolarizations). Early afterdepolarizations are associated with high resting membrane potentials and are more likely with slower heart rates. Delayed afterdepolarizations can arise from ischemia, catecholamine excess, or electrolyte disturbances (especially K^+, Mg^{2+}, and Ca^{2+}) and are enhanced by faster heart rates.

ANATOMY AND CONDUCTION

The SA node is an area of specialized impulse-generating tissue located at the junction of the right atrium and the superior vena cava. Its blood supply is from the right coronary artery (RCA) in 55% of patients and the left circumflex artery (LCA) in 45%. The normal SA node produces spontaneous depolarizations at a faster rate than other pacemakers and functions as the dominant pacemaker. The SA node maintains a rate of 60 to 90 beats/min in most adults. Hypothermia and vagal stimulation slow the sinus rate, whereas hyperthermia and sympathetic stimulation increase the rate. In the setting of low or absent parasympathetic tone—for example, with certain drugs or after heart transplantation—the resting sinus rate tends to be faster.

In the absence of normal SA node activity, other myocardial tissues may assume the role of pacemaker. The AV node has an intrinsic impulse-generating rate of 45 to 60 beats/min. Infranodal pacemakers, found within the His bundle, the Purkinje system, and the bundle branches, maintain intrinsic rates ranging from 30 to 45 beats/min. Other atrial and ventricular tissues may assume pacemaker-like activity under conditions of ischemia or metabolic derangement. Rates of ectopic pacemaker activity vary widely depending on the underlying pathology.

Figure 79-4 correlates the surface ECG tracings with tissue electrical events. Impulses generated from within the SA node itself, imperceptible on the surface ECG, are propagated through the

www.ketabpezeshki.com 66485457-66963820

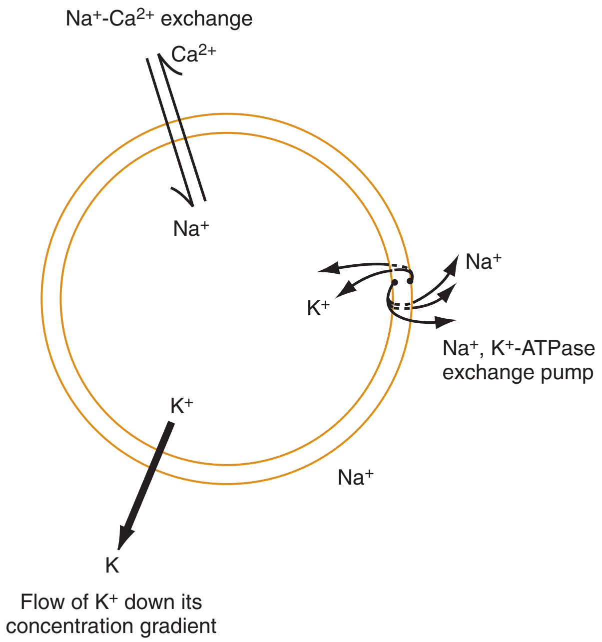


Figure 79-1. Flow of various ions across the myocardial cell membrane. Na^{+}-K^{+} pump exchanges three Na^{+} ions for each two K^{2+} ions, generating a net negative flow of 10 mV. The flow of K down the concentration gradient *(dark arrow)* generates another 80 mV of current. The Na^{+}-Ca^{2+} exchange adds little to the resting potential. *ATPase,* adenosine triphosphatase. (From Marriott HJL, Conover MB: Advanced Concepts in Dysrhythmias, 2nd ed. St Louis, Mosby, 1989.)

atrial tissue to the AV node. Atrial depolarization is characterized by the P wave on the surface ECG.

The AV node is an area of specialized tissue between the atria and the ventricles of the heart, located in the posterior-inferior region of the interatrial septum. Its blood supply is from a branch of the RCA in 90% of patients (right dominant) and from the LCA in the remaining 10% (left dominant). Transmission of impulses within the AV node is slower than in parts of the conducting system (Table 79-1) because of a dependence on slow-channel ion influx for membrane depolarization. In some patients, pathologic “accessory pathways” connect atrial and ventricular tissues. These accessory pathways do not share the normal conduction delay of the AV node and may allow for rapid ventricular rates. *Preexcitation* refers to the early depolarization of ventricular myocardium when accessory paths are used instead of the normal conduction system.

On the surface ECG, the PR interval (normally 0.10 to 0.20 second) represents the time it takes for conduction of a sinus impulse through the atria and AV node and into the ventricles. Impulses originating in lower atrial tissues are associated with a shortened PR interval, as are impulses conducted to the ventricles via accessory pathways outside the AV node. PR prolongation is usually a result of nodal or supranodal conduction system disease.

After passing through the AV node, impulses propagate down the His bundle to the three main bundle branch fascicles: the right bundle branch (RBB), the left anterior-superior bundle (LASB), and the left posterior-inferior bundle (LPIB). The RBB and LASB are typically supplied by the left anterior descending (LAD) artery, whereas the LPIB may be supplied by either the RCA or the LCA. After conduction down the three main bundle branches, impulses are delivered to the Purkinje fibers, which propagate impulses to myocardial tissues in a swift and orderly fashion, allowing for coordinated ventricular contraction. If an impulse arrives prematurely, it may be conducted aberrantly (if bundles are relatively refractory), or it may be blocked (if the bundles are completely refractory).

On the surface ECG, the QRS complex represents ventricular depolarization, and the normal QRS interval is 0.09 seconds or less, with a duration of 0.12 seconds or greater being clearly abnormal. The T wave corresponds to ventricular repolarization and varies in duration depending, among other things, on the length of the cardiac cycle. The total time of ventricular depolarization and repolarization is represented by the QT interval. Shorter cycle lengths (i.e., shorter R-R intervals) result in a shorter repolarization time. Conversely, longer cardiac cycles are associated with longer repolarization times.

MECHANISMS OF DYSRHYTHMIA FORMATION

There are three electrophysiologic mechanisms: enhanced automaticity, triggered activity, and reentry. *Enhanced automaticity* includes spontaneous depolarization of nonpacemaker cells or a lower threshold for depolarization in normal pacemaker cells (Fig. 79-5). Both types of enhanced automaticity can occur in the setting of ischemia, electrolyte disturbances, or drugs. Examples of enhanced automaticity include idioventricular rhythms in the setting of acute myocardial infarction, and atrial tachycardias or junctional tachycardias (JTs) seen with digitalis toxicity.

Triggered activity occurs as the result of early or delayed afterdepolarizations. The classic dysrhythmia associated with early afterdepolarization is torsades de pointes. Triggered dysrhythmias caused by delayed afterdepolarizations are frequently found in the setting of intracellular Ca^{2+} overload as occurs with digitalis toxicity or with reperfusion therapy for acute myocardial infarction. Many ectopic atrial, junctional, and ventricular rhythms fall into this category and are amenable to treatment with medications that slow the heart rate or interfere with calcium entry into the cell.

Reentry dysrhythmias occur as a consequence of abnormal conduction (Fig. 79-6). For a reentry mechanism, two alternate pathways for conduction must be present and one path must have a longer refractory period. The unequal responsiveness of the limbs creates a functional unidirectional block such that when the impulse exits one limb, it may then reenter the other in retrograde fashion. The cycle is then repeated, creating a self-sustaining or “circus movement” tachycardia that can appear orderly or disorderly (i.e., fibrillatory).

Reentry mechanisms are responsible for most narrow-complex tachycardias and many ventricular tachycardias (VTs). Treatment is predicated on altering conduction in one or both limbs of the reentry circuit.

CLASSIFICATION OF ANTIDYSRHYTHMIC DRUGS

Medications used to treat dysrhythmias are classified into four major categories on the basis of their electrophysiologic effects (Box 79-1). Other agents fall outside this classification system and are discussed separately.

Class I agents exert their major effects on the fast Na^{+} channels, resulting in membrane stabilization. The subclasses IA, IB, and IC are distinguished on the basis of differential effects on depolarization, repolarization, and conduction. Class II agents are the beta-adrenergic antagonists, which depress SA node automaticity and slow AV node conduction. Beta-blockers can also suppress conduction in ischemic myocardial tissue. Class III agents prolong repolarization and refractory period duration, predominantly via

www.ketabpezeshki.com 66485457-66963820

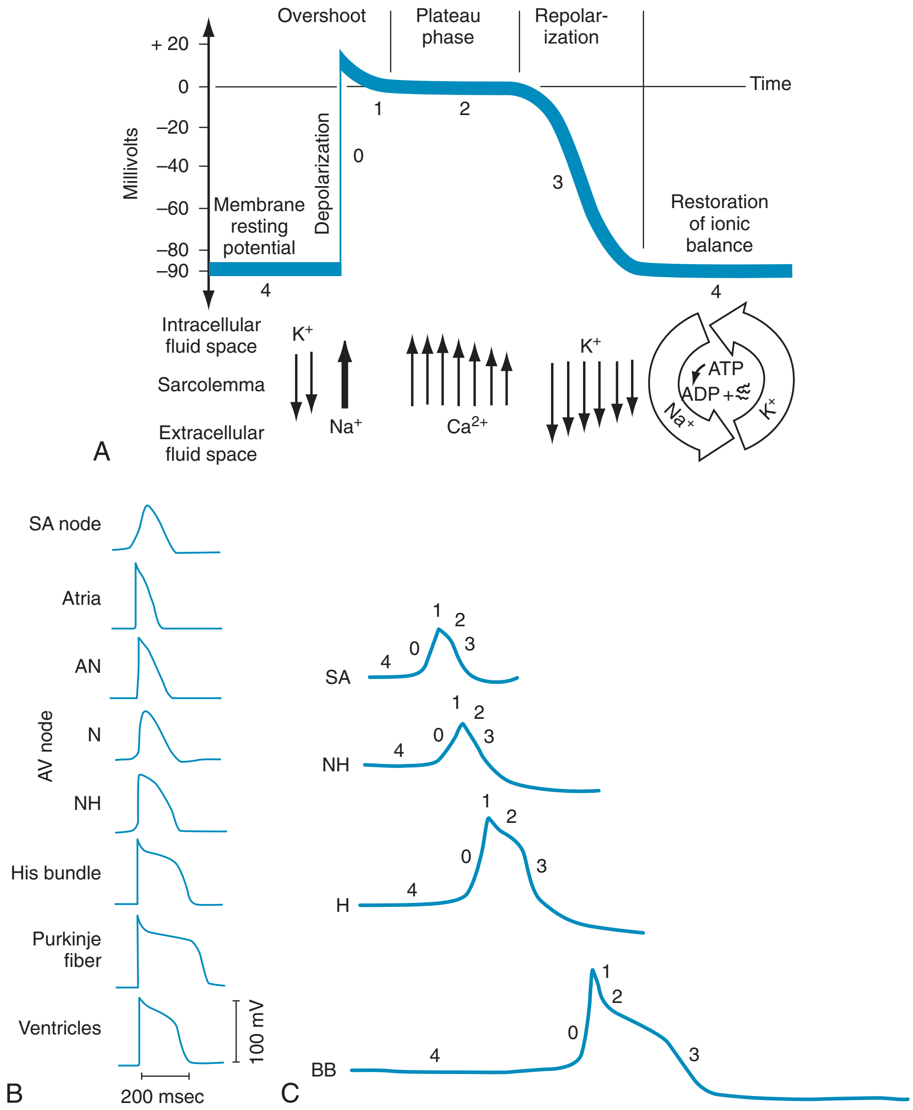


Figure 79-2. **A,** Action potential of a myocardial cell and its relation to ion flow. **B,** Action potentials of various myocardial tissues. **C,** Action potentials of various pacemaker cells. Note that phase 4 becomes flatter as location becomes more distal. *AN,* atria-nodal; *AV,* atrioventricular; *BB,* bundle branch fascicles; *H,* His bundle; *N,* nodal; *NH,* nodal-His; *SA,* sinoatrial. (**A** and **B,** From Calcium in Cardiac Metabolism. Whippany, NJ, Knoll Pharmaceutical Co., 1980. **C,** From Conover M: Understanding Electrocardiography, 5th ed. St Louis, Mosby, 1988.)

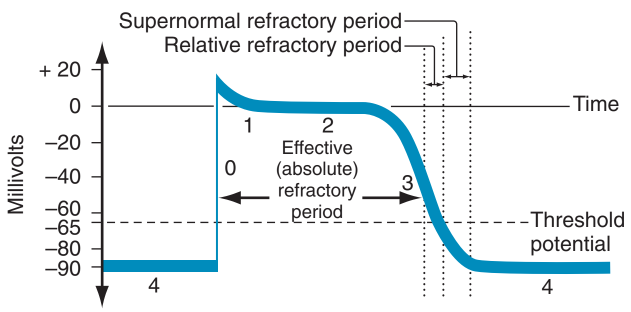


Figure 79-3. Action potential showing various refractory periods. (From Calcium in Cardiac Metabolism. Whippany, NJ, Knoll Pharmaceutical Co., 1980.)

their effects on K^+ channels. Class IV agents are the Ca^{2+} channel blockers, which slow conduction through the AV node and suppress other calcium-dependent dysrhythmias. Other agents important in the emergency treatment of dysrhythmias include magnesium sulfate, digitalis, and adenosine.

All antidysrhythmics can cause "prodysrhythmic effects." This occurs most often in patients with existing structural heart disease and in patients receiving new or higher doses of antidysrhythmic agents. The class I and III agents are associated with prodysrhythmic effects in up to 15% of patients.[1,2]

Class IA Agents

Class IA agents slow conduction through the atria, AV node, and His-Purkinje system and suppress conduction via accessory pathways. Class IA agents also exhibit anticholinergic and mild negative inotropic effects, with procainamide having the least effect on contractility. Procainamide is the most commonly used class IA agent in the emergency treatment of ventricular and supraventricular dysrhythmias. Intravenous procainamide is administered at a rate of 20 to 30 mg/min in stable patients until the dysrhythmia is terminated, hypotension occurs, or the QRS complex widens (to 50% of the pretreatment width), or up to a total dose of 18 to 20 mg/kg (12 mg/kg if congestive heart failure is present). The peripheral vasodilatory effects cause the hypotension, and the risk of prodysrhythmia is approximately 5%.

www.ketabpezeshki.com 66485457-66963820

Table 79-1 Conduction Velocities in Various Heart Tissues

TISSUE	VELOCITY (M/S)
Atrium	1000
Atrioventricular node	200
His-Purkinje system	4000
Ventricles	400

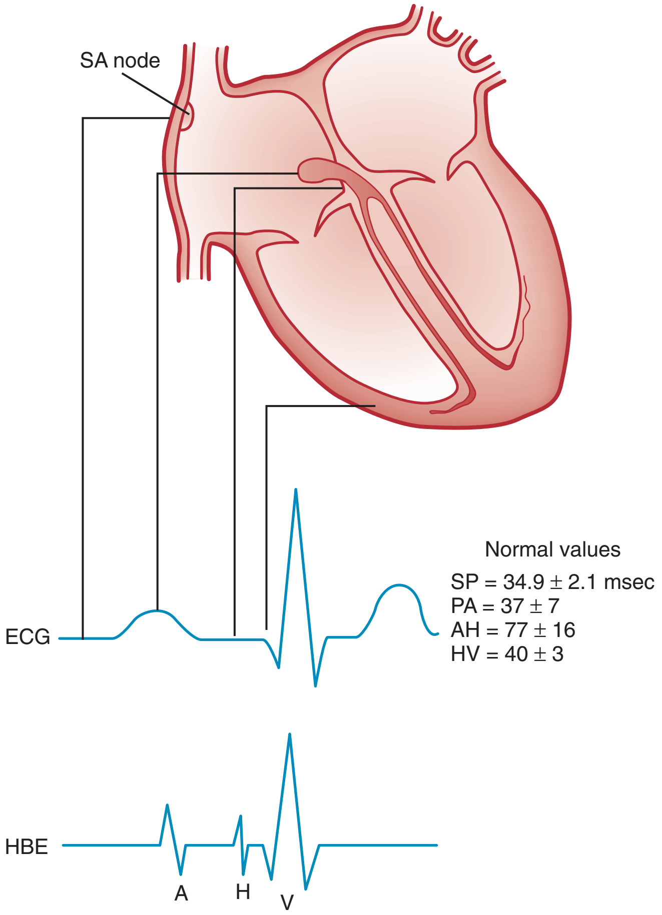


Figure 79-4. Electrical events in the heart related to surface electrocardiogram *(ECG)* and His bundle electrogram *(HBE)*. Approximate relationship of sinus node discharge is also related to surface ECG. *AH,* atrioventricular nodal conduction time; *HV,* His-Purkinje conduction; *PA,* intra-atrial conduction time; *SA,* sinoatrial; *SP,* SA conduction time. (From Marriott HJL, Conover MB: Advanced Concepts in Dysrhythmias, 2nd ed. St Louis, Mosby, 1989.)

Class IB Agents

Class IB agents slow conduction and depolarization less than other class I agents, and they shorten repolarization rather than prolonging it. Class IB agents have little effect on accessory pathway conduction. Lidocaine is the sole class IB agent used in emergency rhythm management. Lidocaine is useful for suppressing dysrhythmias from enhanced automaticity such as VT. Lidocaine also suppresses SA and AV node function and is associated with asystole in the setting of myocardial ischemia.

Class IC Agents

The class IC agents profoundly slow depolarization and conduction and have pronounced antidysrhythmic properties.[1,2] Up to 15% of patients treated with class IC agents experience new or increased ventricular dysrhythmias. Class IC agents are approved only for oral use in the United States.

Flecainide

Flecainide is used in the treatment of supraventricular tachycardias (SVTs) and certain forms of VT outside the setting of acute ischemia. Initiation of oral therapy requires continuous ECG monitoring. Flecainide has high oral bioavailability, but its half-life is variable, and the therapeutic index (in terms of QRS and QT prolongation) is narrow. Long-term use of flecainide in those with a previous myocardial infarction is associated with an increased risk of fatal dysrhythmia.

Propafenone

Propafenone shares properties with both class IA and IC agents, with intermediary effects on sodium channels. It also possesses some beta-adrenergic and calcium channel–blocking properties.

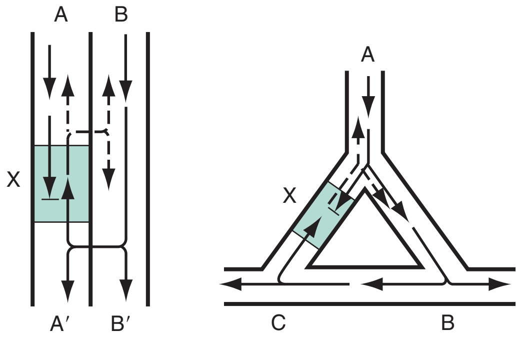


Figure 79-6. Mechanism of reentry.

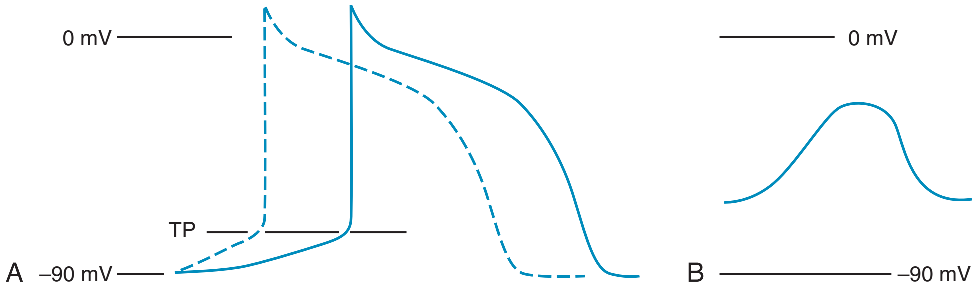


Figure 79-5. A, Enhanced normal automaticity *(dashed line)*. B, Abnormal automaticity. *TP,* threshold point. (From Marriott HJL, Conover MB: Advanced Concepts in Dysrhythmias, 2nd ed. St Louis, Mosby, 1989.)

www.ketabpezeshki.com 66485457-66963820

Box 79-1 Classification of Antidysrhythmic Drugs

Class I
Sodium (fast) channel blockers. Slow depolarization with varying effects on repolarization. These "membrane-stabilizing" drugs have prominent antiectopic effects.

Class IA
Moderate slowing of depolarization and conduction. Prolong repolarization and action potential duration.
Procainamide
Quinidine
Disopyramide

Class IB
Minimally slow depolarization and conduction. Shorten repolarization and action potential duration.
Lidocaine
Phenytoin
Tocainide
Mexiletine

Class IC
Markedly slow depolarization and conduction. Prolong repolarization and action potential duration.
Flecainide
Encainide
Lorcainide
Propafenone (shares properties with class IA agents)
Vernakalant (atrial specific, investigational)

Class II
Beta-adrenergic blockers
Propranolol
Esmolol
Metoprolol
Atenolol

Class III
Antifibrillatory agents. Prolong action potential duration and refractory period duration with antifibrillatory properties.
Bretylium (historical significance)
Amiodarone
Dofetilide
Ibutilide*
Sotalol†
Dronedarone
Azimilide

Class IV
Calcium (slow) channel blockers
Verapamil
Diltiazem

Miscellaneous
Digitalis
Magnesium sulfate
Adenosine

*Shares activity with class I agents.
†Shares activity with class II agents.

Propafenone is used for the oral treatment of atrial fibrillation and ventricular dysrhythmias. Compared with flecainide, propafenone has a lower observed prodysrhythmic rate at therapeutic doses.

Class II Agents

Class II agents suppress SA node automaticity and slow conduction through the AV node. Because of their effect on AV node conduction, class II agents are well suited to control the ventricular rate in patients with atrial fibrillation and flutter. Beta-blockers can terminate AV nodal reentrant tachycardias (AVNRTs). In the setting of acute myocardial ischemia, beta-blockers play a role in preventing ventricular dysrhythmias.

Side effects of beta-blockers include bronchospasm, bradycardia, hypotension, and heart failure. All beta-blockers are active at both beta$_1$ and beta$_2$ receptors (Table 79-2) to varying degrees. Those with more prominent beta$_1$ effects are said to be *cardioselective.* Relative contraindications to the use of beta-blockers include asthma or chronic obstructive lung disease, advanced congestive heart failure, and third-trimester pregnancy. Beta-blockers should not be used in patients with preexisting bradycardia or heart block beyond first-degree. Intravenous beta-blockers should be used cautiously in conjunction with calcium channel blockers because of the risk of additive side effects. Acute side effects of beta-blockers include bronchospasm, heart failure, excessive bradycardia, and hypotension.

Table 79-2 Cardiac and Respiratory Beta-Adrenergic Receptors and Responses to Pharmacologic Manipulation

RESPONSE TO RECEPTORS	LOCATION	STIMULATION	ANTAGONISM
Beta$_1$	Heart	Increased heart rate and ectopy	Decreased heart rate and ectopy
		Increased contractility	Decreased contractility
Beta$_2$	Airway (smooth muscle)	Decreased tone (relaxation)	Increased tone (contraction)
	Peripheral vasculature	Decreased tone (relaxation)	Increased tone (contraction)

Esmolol

Esmolol is a beta$_1$-selective agent attractive in the emergency setting because of its rapid onset of action and short elimination half-life (minutes). An intravenous bolus of 500 µg of esmolol per kilogram followed by a continuous infusion starting at 50 µg/kg/min is a common starting approach, with titration to need and effect.

Metoprolol

Metoprolol is available in oral and intravenous preparations. Although not approved for dysrhythmia treatment in the United States, metoprolol (5-10 mg intravenously [IV] every 10-15 minutes titrated to response) will slow atrial and nodal fast rhythms and is often used for these purposes.

Class III Agents

All class III agents prolong the refractory period by blocking K^+ channels, and they have variable effects on the QT interval.[1-4] In general, class III agents are alternatives to the class I agents for the treatment of many ventricular and atrial dysrhythmias.

Bretylium

Bretylium was once the most commonly used class III agent, but its hemodynamic side effects were unfavorable, and it is no longer available in the United States.

Amiodarone

Amiodarone is approved for the treatment of both ventricular and supraventricular dysrhythmias. In addition to features in common

www.ketabpezeshki.com 66485457-66963820

Box 79-2 Adverse Effects of Amiodarone

Acute Effects
Hypotension
Slowing of heart rate
Decreased contractility

Long-Term Effects
Common
Corneal deposits
Photosensitivity
Gastrointestinal intolerance

Less Common
Hyperthyroidism
Heart failure
Pulmonary toxicity, fibrosis
Hypothyroidism
Bradycardia
Prodysrhythmic effect

Drug Interactions
Increase Levels
Phenytoin
Procainamide
Warfarin
Digoxin
Flecainide

with all class III agents, amiodarone has numerous other effects, including actions that are similar to those of class IA, class II, and class IV agents.

The serum half-life of amiodarone is 25 hours after a single intravenous dose and up to 50 days during long-term oral use. Because of the unusual pharmacokinetics, oral regimens vary widely. The acute side effects of amiodarone are primarily limited to hypotension, bradycardia, and heart failure (Box 79-2). There is an additive risk of bradycardia and hypotension when amiodarone is used in conjunction with calcium channel or beta-adrenergic blockers. Rates of prodysrhythmia are relatively low (1-3%). Long-term amiodarone use, however, is associated with significant extracardiac side effects, including irreversible lung and thyroid disease. Amiodarone alters the pharmacokinetics of numerous other drugs, including digoxin and warfarin.

Ibutilide

Ibutilide has a unique mechanism of action characterized by induction of a slow inward Na^{2+} current, thereby prolonging the refractory period. Intravenous ibutilide is approved for cardioversion of atrial fibrillation and atrial flutter.[5] Ibutilide is associated with QT interval prolongation, and polymorphic VT is more common than with amiodarone although still relatively rare (0.9-2.5%).

Sotalol

Sotalol is beta-adrenergic receptor blocker with type III antidysrhythmic properties via inhibition of K^+ channels. It is used orally for suppression of supraventricular and ventricular dysrhythmias. The incidence of QT prolongation and risk of polymorphic VT require that initiation of sotalol therapy occur in a monitoring setting.

Dofetilide

Dofetilide is a pure class III agent that blocks K^+ efflux, increasing the refractory period. It is approved for chemical cardioversion and maintenance of sinus rhythm in patients with atrial fibrillation or flutter,[6] but because of its prodysrhythmic effects, it has limited usefulness.

Dronedarone

Structurally related to amiodarone, dronedarone displays class III properties plus those of other antidysrhythmic classes. The incidence of polymorphic VT associated with dronedarone is very low. Dronedarone is approved for oral use to maintain sinus rhythm in patients with atrial fibrillation or flutter but is contraindicated in patients with severe or recent heart failure decompensation.[7] Long-term effects and the ideal populations for the use of this drug remain unclear.[8]

Class IV Agents

Class IV agents block the slow Ca^{2+} channels, slowing conduction within the AV node and suppressing the SA node to a lesser degree. Like beta-blockers, their primary use is in patients with SVTs. Of the two commonly used class IV agents, diltiazem is more frequently used for ventricular rate control in patients with atrial fibrillation or flutter.

All class IV agents are associated with peripheral vasodilation. Verapamil has the least effect on peripheral vascular tone, and diltiazem has an effect between that of verapamil and purely peripherally acting calcium channel blockers, such as nifedipine. In the acute setting, intravenous calcium salts (1 g slow intravenous delivery) can attenuate peripheral vasodilatory effects. Class IV drugs should not be used in patients with second- or third-degree AV block and should be used with close monitoring in those with first-degree block.

Diltiazem

Intravenous diltiazem 0.25 to 0.35 mg/kg over 2 minutes controls the ventricular response rate in 90% of patients with atrial fibrillation and atrial flutter and is associated with minimal hypotension. If the intravenous bolus is successful, a continuous infusion (5-15 mg/hr initially, titrated to need) or an oral dose (60-90 mg initially) will help sustain the response.

Verapamil

Verapamil terminates or controls the ventricular response rate in 80 to 90% of tachycardic rhythms.

Intravenous verapamil is given at a dose of 0.1 mg/kg over 1 to 2 minutes; for the average healthy adult, this translates to a dose of 5 to 10 mg. In elderly patients or those with preexisting borderline hypotension (systolic blood pressure of 90-110 mm Hg), a smaller dose (0.05 mg/kg, or 2.5-mg increments) is preferred.

Miscellaneous Agents

Digoxin

Digitalis compounds have a variety of effects on myocardial cells. Digoxin inhibits the ATP-dependent Na^+-K^+ exchange pump, increasing intracellular Na^+ concentrations and decreasing intracellular K^+ concentrations. The resultant increase in intracellular Ca^{2+} concentration accounts for the positive inotropic effects of digitalis. Digoxin can behave as an excitant, a depressant, or both. Excitant effects of digoxin have to do with enhanced automaticity and triggered activity, particularly at high therapeutic or toxic doses. At the same time, digoxin slows AV node conduction at therapeutic doses via lengthening of the refractory period.

www.ketabpezeshki.com 66485457-66963820

Box 79-3 Adverse Effects of Digitalis

Common Effects

Gastrointestinal intolerance (nausea, vomiting, abdominal pain, diarrhea, anorexia)
Fatigue
Drowsiness
Visual color disturbances
Headache
Depression
Apathy

Less Common Effects

Psychosis
Cardiac symptoms
Heart block
Increased ectopy
Combined block and ectopy (multifocal atrial tachycardia with block or complete atrioventricular block with accelerated junctional rhythm, usually in overdose setting)
Ventricular tachycardia

Digoxin (0.25-0.5 mg IV) can control the ventricular rate in patients with SVTs, including atrial fibrillation and atrial flutter. Because of its delayed onset of action and narrow therapeutic window, however, digitalis is not a first-line agent for emergency therapy. It is not true that digoxin promotes conversion to a sinus rhythm any more than other rate-controlling agents.[9]

Side effects of digoxin are listed in Box 79-3 and are aggravated by hypokalemia, hypercalcemia, hypomagnesemia, increased catecholamines, and acid-base disturbances. Digoxin overdose therapy is covered elsewhere.

Magnesium

Magnesium can aid control of many tachydysrhythmias. Magnesium (1-2 g IV) plays a central role in terminating torsades de pointes and as an aid in VT therapy. Aside from these indications, magnesium is considered at best an adjunctive, second- or third-line agent in other settings.

Adenosine

Adenosine is a naturally occurring purine nucleoside used for the termination of narrow-complex tachydysrhythmias. Administered as an intravenous bolus, adenosine causes an abrupt slowing of AV conduction in both anterograde and retrograde pathways. Adenosine usually has an onset of action of 5 to 20 seconds and a duration of effect of 30 to 40 seconds. Except in rare cases of catecholamine-induced ventricular dysrhythmias, adenosine has little or no effect on infranodal conduction. For this reason, adenosine is often used as a diagnostic agent in patients with wide-complex tachydysrhythmias when the cause is unclear.[10-12] An initial dose of 6 mg as a rapid bolus for adults weighing 50 kg or greater is recommended, with flush through a large peripheral vein. If no response is seen within 1 to 2 minutes, the second dose is doubled (12 mg) and administered. If no effect is seen after a final 12-mg dose, the rhythm should be reassessed and another agent used. Pediatric doses are 0.05 mg/kg initially with doubling at similar intervals up to a total dose of 0.25 mg/kg. Side effects coincide with the onset of clinical effects and occur in up to a third of patients but are usually minor. These include flushing, dyspnea, chest pressure, nausea, headache, dizziness, transient bradycardia or heart block, and hypotension (seen rarely, from the vasodilatory properties). These side effects usually resolve rapidly without treatment, although many patients are intensely uncomfortable for a short period. Asystole can occur but is usually transient though unsettling to those observing.

Because of its short duration of action, adenosine is not an effective rate control agent for atrial fibrillation or flutter, although it can help unmask these rhythms when not apparent on the initial surface ECG. Similarly, some narrow-complex tachydysrhythmias that terminate with adenosine will recur later given the short duration of action.

APPROACH TO DYSRHYTHMIA RECOGNITION AND MANAGEMENT

Dysrhythmias are classified according to their electrophysiologic origin, ECG appearance, and underlying ventricular rate. Although overlap exists, the following categorization is useful:

- Bradycardias
- Extrasystoles
- Narrow-complex (QRS less than 0.12 second) tachycardias (regular and irregular)
- Wide-complex (QRS 0.12 second or greater) tachycardias (regular and irregular)

Classically, the approach to any specific dysrhythmias is defined on the basis of the clinical stability. *Unstable patients* demonstrate evidence of severe or multiple end-organ features of hypoperfusion, such as altered sensorium, respiratory distress, hypotension, syncope, or chest pain suggestive of myocardial ischemia. *Stable patients* may be asymptomatic or have mild symptoms, such as light-headedness, dyspnea on exertion, palpitations, or mild anxiety. In practice, clinical stability is a continuum; in the absence of profound altered sensorium or hypotension, a clear line distinguishing stable and unstable patients is often not present.

It is important to consider whether a dysrhythmia is the cause or an effect of a clinical presentation; for example, rapid atrial fibrillation may be causing hypotension or resulting from profound volume depletion. Failure to consider the clinical situation can lead to an inappropriate focus on diagnosing and treating the rhythm to the detriment of the patient. With recognition of this need to incorporate the overall clinical picture, treatment of those with a dysrhythmia and clear instability is empirical and assumes the rhythm is the cause, whereas stable patients can be approached in a more systematic and thoughtful manner to identify the cause and choose the most appropriate therapy.

Initial Assessment of Stable Patients

The approach to the patient with a stable dysrhythmia begins with gathering evidence from the history, physical examination, 12-lead ECG, and a rhythm strip. The nature of any symptoms, including the timing, velocity of onset (gradual vs. abrupt), and duration, is important. For the patient with "palpitations," questions about the rate and regularity of the heartbeat are often asked, but having the patient tap out the rhythm with a finger can often be more valuable. Inquiring about precipitating events and associated symptoms such as dizziness, chest pain, dyspnea, or syncope is critical to understanding the context of any dysrhythmia. The past history—of rhythm disturbances or a prior history of ischemic or structural heart disease—and a thorough medication history are essential. For example, a new and symptomatic wide-complex tachycardia in a patient with known ischemic heart disease is much more often VT than a supraventricular event. Occasionally the family history can be helpful, particularly if there are first-degree relatives with a history of dysrhythmia, unexplained syncope, or sudden death—all of which suggest an inherited disorder such as an accessory pathway or Brugada's syndrome.

Aside from palpating the pulse and listening to the heart sounds, the physical examination should focus on detecting subtle

www.ketabpezeshki.com 66485457-66963820

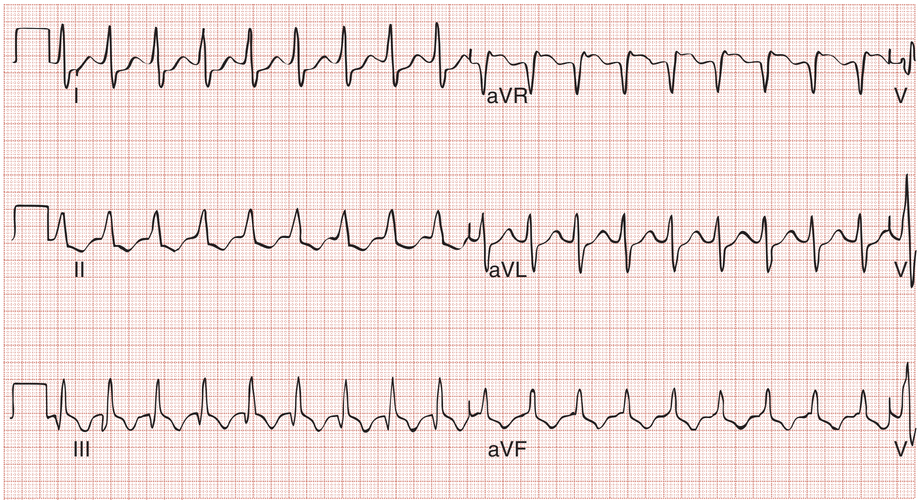


Figure 79-7. Note the P waves before the QRS complexes in lead aVF.

Box 79-4 Basic Electrocardiographic Observations during Dysrhythmia Analysis

1. Ventricular rate: Fast (>100 complexes/min), slow (<60 complexes/min), or normal (60-100 complexes/min).
2. Rhythm: Regular, completely irregular (irregularly irregular or chaotic), regular with occasional irregularity, or grouped impulses. Calipers and long strips are recommended to detect subtle irregularity.
3. QRS width: Prolonged (>0.12 s), borderline (0.09-0.12 s), or normal. If determined without electrocardiogram being physically present (e.g., prehospital radio medical command), it is helpful to ask for QRS duration in number of small boxes from printed rhythm strip (each box equals 0.04 s) to ensure accuracy.
4. P wave presence and relationship to QRS complexes: This may require mapping of P waves with calipers to detect those falling within QRS complex or T wave.
5. Rhythm changes: Examine these areas closely for clues.
6. Multiple leads, especially chest leads or esophageal lead if difficulties with P wave visualization are experienced.
7. Comparison with previous tracings (if available) is often valuable.

evidence of end-organ hypoperfusion or clues to an underlying cause of the dysrhythmia (e.g., heart failure). Palpating the pulse for several minutes while asking the patient to report any symptoms can be helpful in detecting pauses, extrasystoles, or brief runs of tachycardia. This technique can be enhanced by observing the patient's rhythm on a continuous cardiac monitor.

The 12-lead ECG is essential for evaluation of any patient with a suspected dysrhythmia. Use of a single ECG lead is often adequate for diagnosis, but multiple leads are often required to detect such things as the presence or absence of P waves (often best seen in inferior leads or V_{1-2}; Fig. 79-7), the relationship between P waves and QRS complexes, prolongation of the QRS and QT interval, and evidence of ischemia or prior myocardial infarction (Box 79-4). For certain conditions, such as Brugada's syndrome, the 12-lead ECG together with a history of syncope is diagnostic.

In some cases, it may be useful to record a 12-lead rhythm strip to better define a particular dysrhythmia. Normally, a paper speed of 25 mm/s is used; when the speed is increased to 50 or 100 mm/s, the relationship of P waves to the QRS complexes is more easily observed. Because the most useful information about paroxysmal dysrhythmias is often at the onset or termination of the rhythm, these areas of tracings should be inspected carefully and saved for future reference.

The use of maneuvers that alter autonomic tone can help expose certain dysrhythmias and terminate others. Vagal maneuvers, such as carotid sinus massage and the Valsalva maneuver, transiently slow AV conduction, which may help terminate or uncover a supraventricular rhythm disturbance. For example, AVNRTs may terminate abruptly with vagal maneuvers, whereas the ventricular response to atrial fibrillation or atrial flutter may slow temporarily and VTs rarely show any change. Auscultation of the neck for bruits should be performed before carotid sinus massage is attempted, particularly in elderly patients. Vagal maneuvers are frequently unsuccessful in terminating a dysrhythmia but are safe to perform and will rarely result in clinical deterioration. Vagal maneuver failure may occur because of poor technique, including the patient being upright instead of the preferred supine position or the carotid artery being massaged instead of the carotid body.

Pseudodysrhythmias

Loose leads, muscle contraction, shivering, tremors, and other patient movement can produce artifactual findings on a monitor, rhythm strip, or 12-lead ECG (Fig. 79-8). Such *pseudodysrhythmias* can mimic and are often mistaken for serious dysrhythmias, including ventricular fibrillation, illustrating the need to avoid making decisions on the basis of ECG tracings without incorporating the clinical context.

SPECIFIC DYSRHYTHMIAS

Sinus Bradycardia, Sinoatrial and Atrioventricular Block

Bradycardia is defined as a ventricular rate of less than 60 beats/min, although in practice rates above 50 beats/min are not usually a concern. Bradycardia may occur because of depression of the sinus node discharge or because of a conduction system block; when the ventricular rate falls, a subsidiary pacemaker elsewhere in the atrium, AV junction, or ventricle may assume the dominant role, resulting in an *escape* rhythm.

Sinus Bradycardia

Sinus bradycardia is characterized by a P wave with normal morphology and a fixed P-P interval that is equal to the R-R interval,

www.ketabpezeshki.com 66485457-66963820

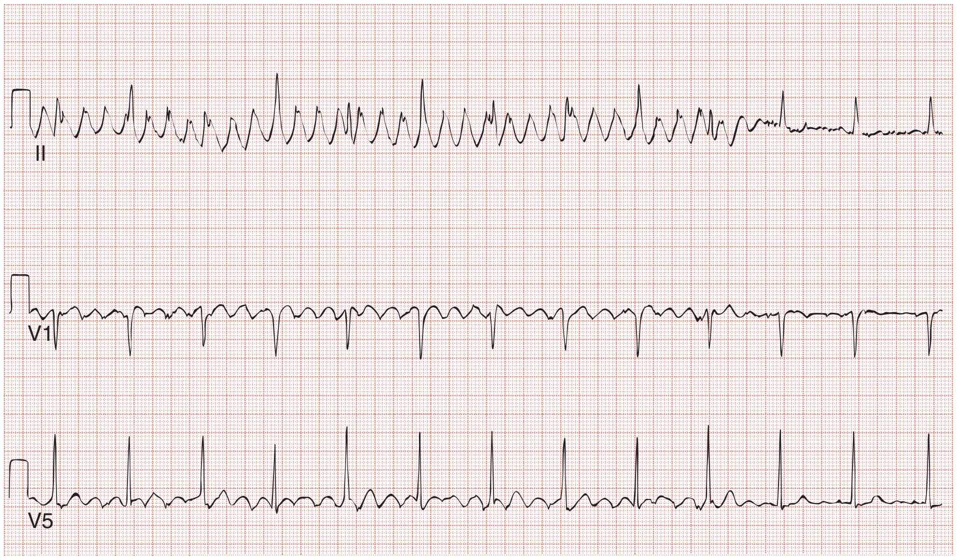


Figure 79-8. Pseudodysrhythmia. In this case, atrial flutter waves appear to be present but are recognized as an artifact when the patient and the right side of the electrocardiogram are examined.

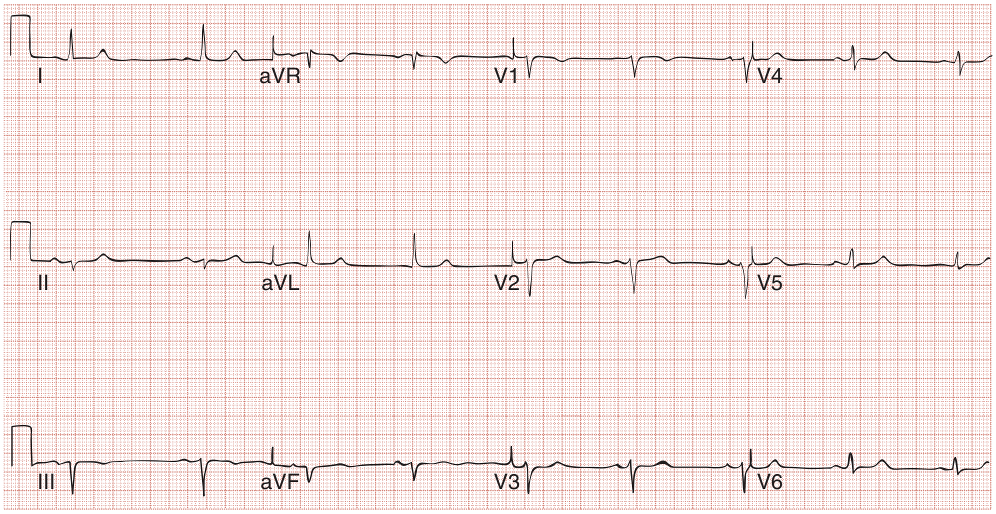


Figure 79-9. Sinus bradycardia.

with a ventricular rate below 60 beats/min (Fig. 79-9). This pattern may be found in healthy adults, particularly among well-conditioned athletes. It can also be seen in virtually any condition associated with vagal stimulation, ranging from a simple fainting event to hemoperitoneum from a ruptured ectopic pregnancy. Sinus bradycardia is described in the early stages of an acute inferior wall myocardial infarction as a consequence of parasympathetic stimulation. Other pathologic causes of sinus bradycardia include hypothermia, hypoxia, drug effects (especially of beta-blockers and calcium channel blockers), and sick sinus syndrome (SSS; see later). In cases of profound sinus bradycardia (i.e., rates below 40-50), it is not uncommon for a junctional escape rhythm to emerge.

Sinus bradycardia usually requires no specific treatment unless symptomatic. If needed, first-line treatment for symptomatic sinus bradycardia is atropine at an initial dose of 0.5 mg, repeated as needed every 3 to 5 minutes to a total dose of 3 mg. Occasionally, a second-line agent such as dopamine or epinephrine infusion may be required. In the acute setting, transcutaneous pacing for sinus bradycardia is rarely indicated.

Sinus Dysrhythmia

Sinus dysrhythmia is similar to sinus bradycardia and is managed in the same manner; it is diagnosed when a variable P-P interval is seen (Fig. 79-10). It is considered a normal variant and is seen frequently in children and young adults.

Sinus Arrest and Sinoatrial Exit Block

Aside from sinus bradycardia and sinus dysrhythmia, disturbances in sinus rhythm are characterized by an absence of atrial depolarization, diagnosed by missing P waves on the ECG (Fig. 79-11). A lack of atrial depolarization can occur because of either failure of the sinus node to generate an impulse (sinus arrest) or failure of impulse conduction out of the SA node (SA exit block). When incomplete block (i.e., one or more missing P waves) exists, a compensatory pause equal to the P-P interval implies the presence of SA exit block, whereas a shorter pause more likely represents sinus arrest. Also, with SA exit block, it is not uncommon to see dropped P waves in regularly occurring patterns, representing 2 : 1,

www.ketabpezeshki.com 66485457-66963820

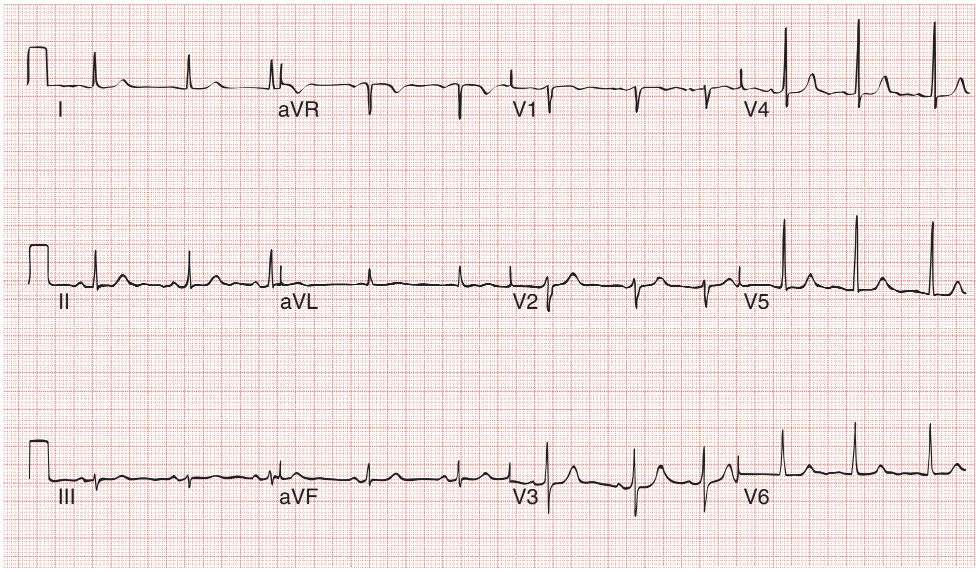


Figure 79-10. Sinus dysrhythmia (note slight irregularity).

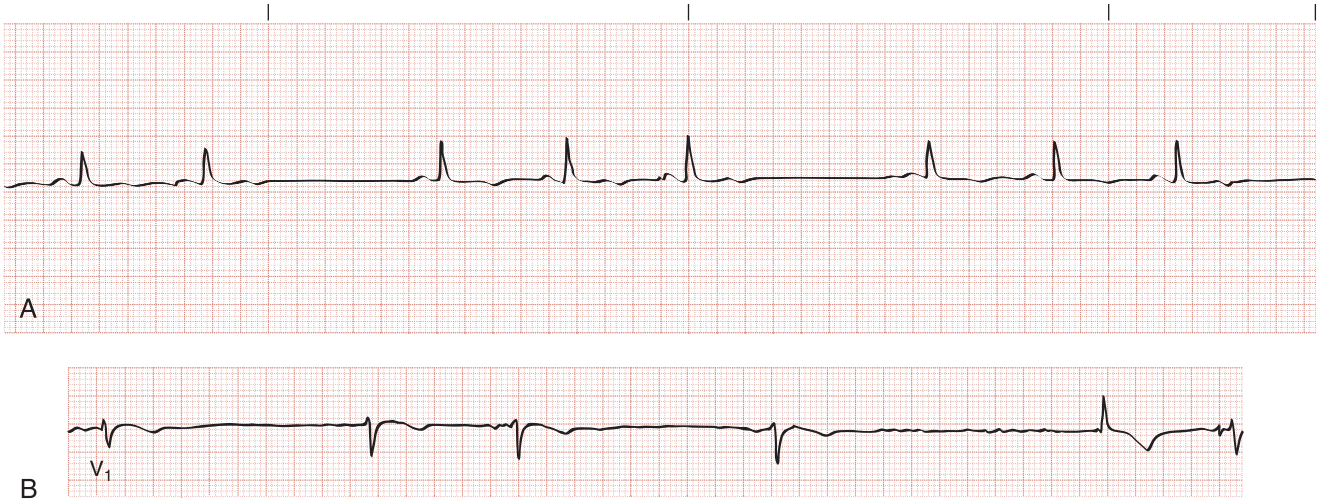


Figure 79-11. **A,** Incomplete sinus block. **B,** Complete sinus block (sinus arrest) with ventricular escape rhythm.

3:1, or 4:1 block. Both sinus arrest and SA exit block are often manifestations of intrinsic SA node disease or looming SSS, but they can also be seen under conditions of increased vagal tone, both benign and pathologic. When the patient is symptomatic, the approach to treatment is similar to that for sinus bradycardia.

Sick Sinus Syndrome

Sick sinus syndrome refers to a group of dysrhythmias from disease of the sinus node and its surrounding tissues, including sinus bradycardia, sinus arrest, and SA exit block. A variant of SSS known as *bradycardia-tachycardia syndrome* is characterized by one or more of these bradydysrhythmias alternating with a tachydysrhythmia, typically atrial fibrillation. SSS is most common in elderly adults, a result of fibrotic degeneration of the cardiac conduction system. It is also associated with cardiomyopathies, connective tissue diseases, and certain drugs. In the acute setting, SSS is suspected when an elderly patient has syncope and the ECG demonstrates sinus impulse abnormalities. Long-term management often requires permanent pacemaker placement for symptomatic bradycardia, in addition to any conventional therapy for atrial fibrillation.

Atrioventricular Block

AV block results from impaired conduction through the atria, AV node, or proximal His-Purkinje system. First- and second-degree AV blocks represent an incomplete conduction disturbance, whereas third-degree block indicates a complete interruption.

First-Degree Atrioventricular Block. First-degree AV block is characterized by prolonged conduction of atrial impulses without the loss of any single impulse. This can occur at the level of the atria, the AV node (most common), or the His-Purkinje system. On the ECG, first-degree AV block is defined by a prolonged PR interval (>0.20 second), typically with a narrow QRS complex (Fig. 79-12). First-degree AV block is a normal variant in up to 2% of healthy young adults but is also seen in pathologic conditions associated with depression of AV node conduction. First-degree AV block requires no specific treatment, but nodal depressing agents should be given with caution in this setting.

Second-Degree Atrioventricular Block. Second-degree AV block is characterized by one or more (but not all) sinus impulses failing to reach the ventricles. The *conduction ratio* is defined as the ratio of the number of P waves to the number of QRS complexes over a period of time (e.g., 3:2, 2:1). A 2:1 conduction ratio does not

www.ketabpezeshki.com 66485457-66963820

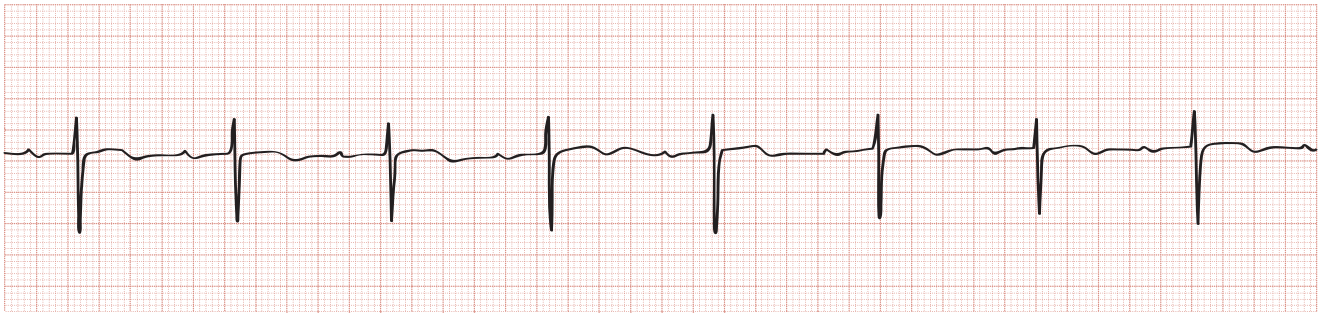


Figure 79-12. First-degree atrioventricular block.

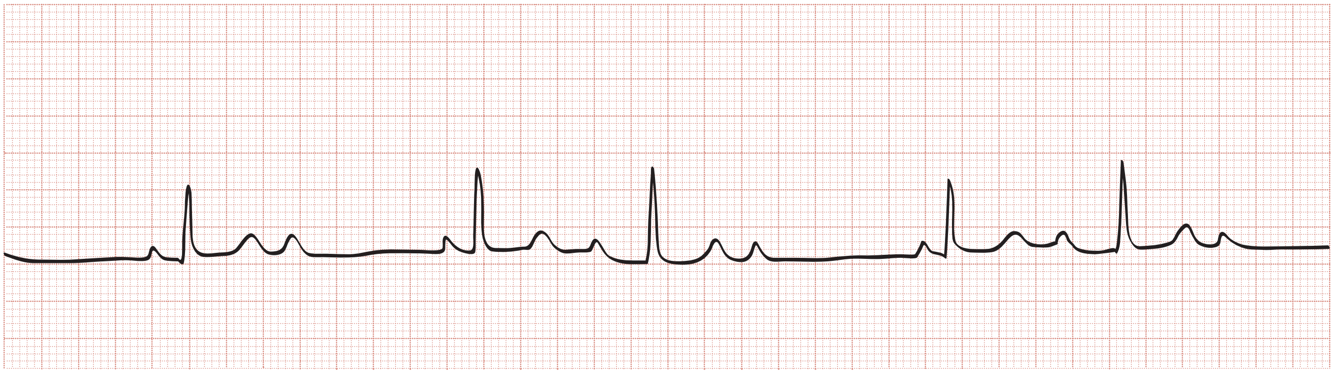


Figure 79-13. Second-degree atrioventricular block, type I (Wenckebach). Note the prolongation of the PR interval between the second and third beats, followed by a nonconducted atrial impulse.

always mean worse conduction system disease than a 4:2 ratio, and not all 2:1 conduction is pathologic. For example, an atrial impulse rate of 300 complexes per minute (common in atrial flutter) presented to the AV node usually results in conduction of half the impulses, producing a ventricular rate of 150 beats/min. This conduction ratio does not represent AV dysfunction or important block because the AV node is responding normally and preventing excessive ventricular stimulation. Conversely, a sinus rhythm at a rate of 70 P waves per minute with a 2:1 ratio (a ventricular rate of 35 beats/min) represents profound AV block and dysfunction. The term *high-grade second-degree block* is best applied to conduction disturbances that prevent physiologic ventricular response rates and not solely to higher conduction ratios. Second-degree AV block can be further classified into two types on the basis of the underlying pathophysiology and ECG appearance (Table 79-3).

Type I Second-Degree Atrioventricular Block. Type I second-degree AV block, also called Wenckebach or Mobitz I AV block, is associated with a conduction disturbance within the AV node. The surface ECG is characterized by a progressive lengthening of the PR interval until an impulse is not conducted ("dropped beat"). The progressive lengthening of the PR interval gives the appearance of successive P waves retreating into the preceding QRS complexes (Fig. 79-13). By definition, the longest R-R interval (i.e., following the dropped beat) is less than twice the length of the shortest. On a rhythm strip, type I second-degree AV block gives the appearance of "grouped beating," especially pairs or trios (i.e., 3:2 or 4:3 block), but occasionally in larger multiples. Grouped beating is not unique to type I second-degree AV block; it occurs in a variety of other conditions (Box 79-5), including SA exit block, type II second-degree AV block, and extrasystoles with or without block.

Type I second-degree AV block occurs in acute and chronic conditions associated with increased vagal tone and usually requires no treatment. In well-conditioned adults, type I second-degree AV block may be a normal variant. In the setting of an acute inferior myocardial infarction, this type of AV block is generally transient and is associated with a good outcome.

Type II Second-Degree Atrioventricular Block. Type II second-degree AV block, or Mobitz II block, represents a conduction block just below the level of the AV node and is never a

Table 79-3 Features of Type I and Type II Second-Degree Atrioventricular Block

FEATURE	TYPE I	TYPE II
Clinical	Usually acute Inferior myocardial infarction Rheumatic fever Digitalis or beta-blockers	Often chronic Anteroseptal Lenègre's disease Lev disease Cardiomyopathy
Anatomic	Usually AV node	Infranodal
Electrophysiology	Increased relative refractory period Decremental conduction	No relative refractory period All-or-none conduction
ECG features	RP/PR reciprocity Prolonged PR interval QRS duration normal	PR interval stable PR interval usually normal QRS duration prolonged
Response to atropine and exercise	Improves	Worsens
Response to carotid massage	Worsens	Improves*

AV, atrioventricular; *ECG,* electrocardiogram.
*Primarily refers to conduction ratio.

www.ketabpezeshki.com 66485457-66963820

normal variant. On the surface ECG, conduction of atrial impulses is sporadic and typically periodic, but the PR interval does not widen (Fig. 79-14). The QRS complex is intrinsically narrow, but concomitant infranodal conduction disturbances (i.e., bundle branch blocks) are not uncommon with type II second-degree AV block.

Type II second-degree AV block can occur at conduction ratios similar to those seen with type I second-degree block but can also occur at higher conduction ratios (e.g., 3 : 1, 4 : 1, or higher). When the conduction ratio is 2 : 1, it may be impossible to distinguish type I from type II second-degree AV block on the basis of the surface ECG because there is no progression of PR intervals. In general, the presence of a prolonged PR interval makes type I block more likely, whereas the presence of wide QRS complexes makes type II block more likely. A rhythm strip demonstrating periods of block with higher or lower conduction ratios can be useful in distinguishing between type I and type II AV block.

Type II second-degree AV block generally carries a worse prognosis than type I second-degree AV block. In acute myocardial infarction, type II AV block is associated with anterior wall ischemia and often progresses to complete AV block. The presence of any form of new type II second-degree AV block, even if asymptomatic, requires prolonged observation or admission for monitoring and preparation for temporary pacing. For patients with signs of hypoperfusion at rest, immediate temporary pacing—either transcutaneous or transvenous—is the treatment of choice. Atropine typically has no effect on conduction disturbances below the AV node and is a temporizing measure during preparation for pacing when required.

Third-Degree Atrioventricular Block. Third-degree AV block (also known as *complete AV block* or *complete heart block*) is characterized by absent conduction of all atrial impulses (Fig. 79-15) accompanied by a slow escape rhythm. The width and frequency of QRS complexes depends on the site of the escape-rhythm pacemaker. Pacemakers above the His bundle are associated with a

BOX 79-5 Causes of Grouped Impulses

- Wenckebach mechanism (usually at atrioventricular node, but can occur elsewhere)
- Atrial tachycardia or flutter with alternating conduction
- Frequent extrasystoles
- Nonconducted atrial trigeminy
- Concealed or interpolated extrasystoles

Mobitz type II second-degree AV block

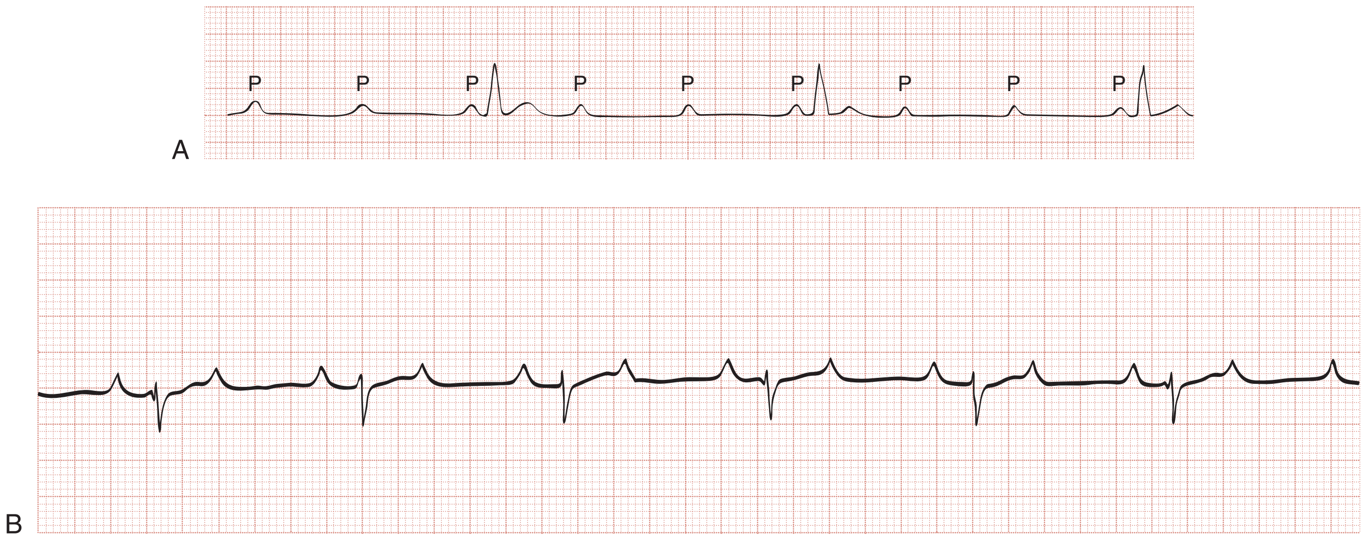


Figure 79-14. **A,** Second-degree atrioventricular (AV) block, type II. In this example, 3 : 1 conduction is shown. **B,** Second-degree AV block with 2 : 1 conduction. From the rhythm strip alone, it is difficult to categorize this as type I or II block. (**A,** From Goldberger AL, Goldberger E: Clinical Electrocardiography, 2nd ed. St Louis, Mosby, 1981.)

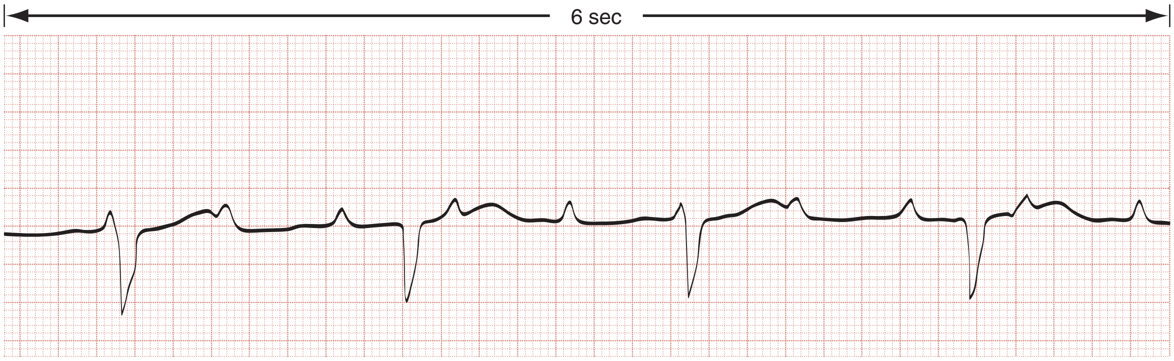


Figure 79-15. Complete (third-degree) atrioventricular block. Note that there is no constant relationship of P waves to QRS complexes even though some are noted in close proximity.

www.ketabpezeshki.com 66485457-66963820

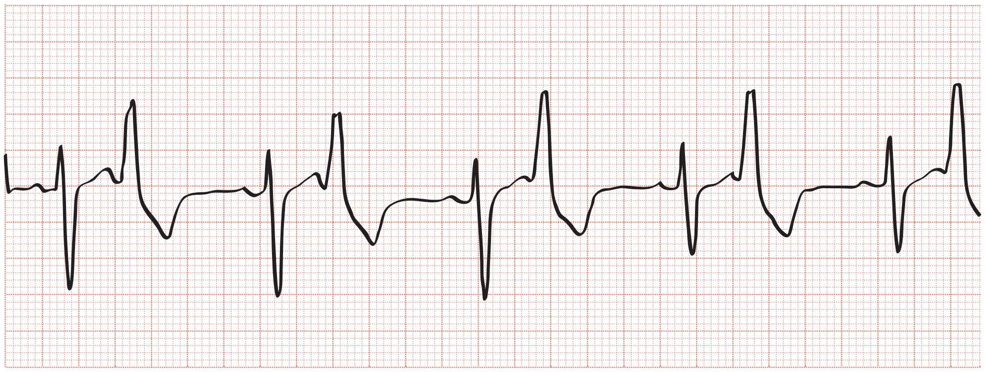


Figure 79-16. Ventricular bigeminy.

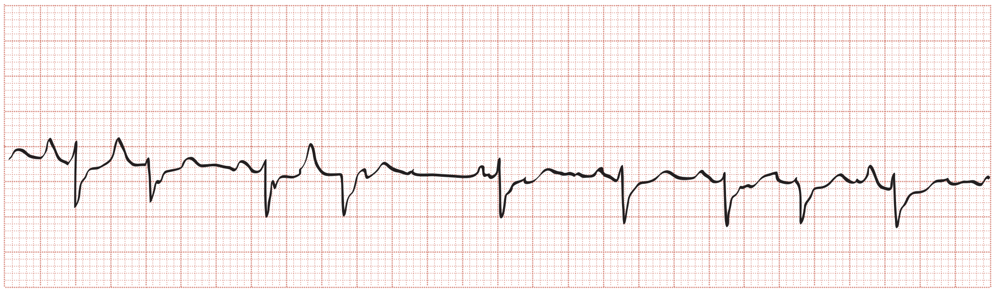


Figure 79-17. Premature atrial contractions.

narrow-complex QRS at a rate of 45 to 60 beats/min, whereas pacemakers at or below the His bundle produce a wide-complex QRS at a rate of 30 to 45 beats/min.

The hallmark of complete heart block is AV dissociation (i.e., no electrocardiographic relationship between atrial and ventricular activity), with an R-R interval that is longer than the P-P interval. Conversely, the presence of AV dissociation with an R-R interval that is *shorter than* the P-P interval (e.g., as occurs with accelerated junctional rhythms and VTs) does *not* imply third-degree heart block. When the atrial rate and the escape rates are similar (or *isorhythmic*), AV dissociation is difficult to appreciate unless a long rhythm strip is examined and the P waves and QRS complexes are closely tracked. One particular challenge in diagnosing AV dissociation occurs when atrial fibrillation is accompanied by complete heart block; the fibrillatory waves, which may not be apparent, are followed by a slow and regular ventricular response (so-called *regularized atrial fibrillation*). This specific dysrhythmia is classically associated with digitalis toxicity.

Third-degree AV block can be congenital, but newly symptomatic third-degree block is commonly acquired, either because of senescent degeneration of the electrical conduction system or as a result of acute ischemia, drug therapy, or other pathologic conditions (e.g., Lyme disease).

In the field or ED, the approach to third-degree heart block depends on the cause and symptoms. Patients with newly acquired or symptomatic third-degree AV block should be admitted to the hospital. For patients with third-degree heart block who are markedly symptomatic (i.e., signs of hypoperfusion at rest), temporary transvenous or transcutaneous pacing is best until either a reversible cause is addressed (e.g., ST elevation myocardial infarction, beta-blocker overdose) or a permanent pacemaker is placed. Atropine is usually ineffective.

Extrasystoles

An extrasystole is an electrical impulse originating from an ectopic atrial or ventricular focus. Depending on the site of origin and the timing of the impulse, there may not be an associated mechanical contraction. The terms "premature atrial contraction" and "premature ventricular contraction" are misleading but widespread and used here for ease. The extrasystole and its preceding impulse are referred to as a *couplet,* and the *coupling interval* refers to the period between these two beats. *Bigeminy* (Fig. 79-16) occurs when there is an extrasystole after every native beat, so that every other impulse is extrasystolic; *trigeminy* (every third beat) and *quadrigeminy* (every fourth beat) are similar. Most extrasystoles are the result of enhanced automaticity, whether in the atria, AV node, His-Purkinje system, or ventricles.

Premature Atrial Contractions

Premature atrial contractions (PACs; Fig. 79-17) are common and usually have little clinical significance. On occasion, a PAC can be the precipitant of a more important dysrhythmia, such as atrial fibrillation, atrial flutter, or SVT. PACs can be distinguished on the ECG by the presence of an abnormal P wave early within a cardiac cycle, although sometimes the P wave may be difficult to detect if it is buried within the preceding T wave.

Most PACs will depolarize the sinus node, resetting its refractory period. Because of this, the P-P interval between two sinus beats surrounding a PAC will be less than twice the intrinsic P-P cycle length (see Fig. 79-17). If a PAC reaches the AV node or the infranodal conducting system during its absolute refractory period, there will be no ventricular depolarization. A nonconducted (or *blocked*) PAC typically results in a *noncompensatory pause* (i.e., R-R interval less than twice the intrinsic R-R cycle; Fig. 79-18) because the sinus node is reset. Blocked PACs are among the most common causes of pauses seen on an ECG but can be easily overlooked if one is not careful to inspect for ectopic P waves.

If a PAC reaches the infranodal conducting system during its relative refractory period, the QRS complex may appear wide or *aberrant,* typically with a right bundle branch block (RBBB) pattern. Because the refractory period depends on the previous cycle length, an early-arriving PAC that follows a long cardiac cycle

www.ketabpezeshki.com 66485457-66963820

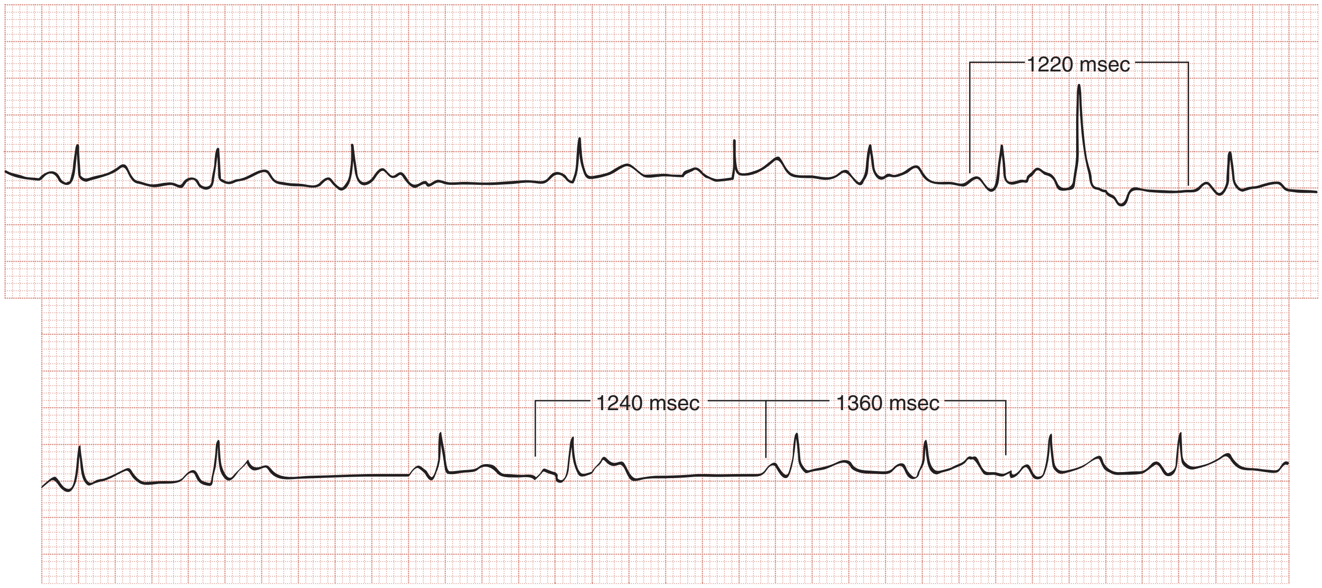


Figure 79-18. Premature atrial contractions (PACs) with noncompensatory pauses and one aberrantly conducted impulse *(upper strip)*. Note that both conducted and nonconducted PACs reset the sinus node, with the latter creating a pause.

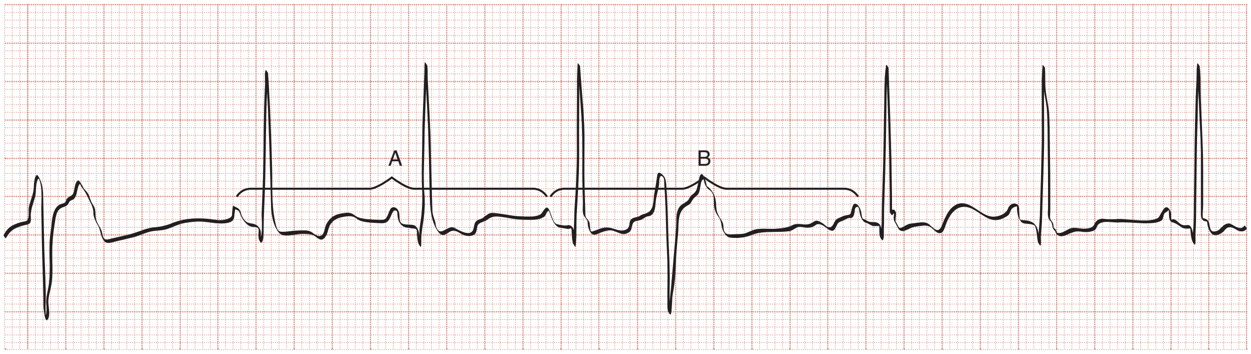


Figure 79-19. Premature ventricular contractions with compensatory pause. Note that a sinus P wave can be seen in the T wave of the extrasystolic beat. Also note the secondary T wave changes in beats 1 and 4 (T wave is opposite the main deflection of the QRS complex).

is more likely to be aberrantly conducted. PACs are benign and require no specific treatment, but they may signify an underlying condition associated with myocardial irritability, such as catecholamine excess, ischemia, heart failure, hyperthyroidism, or a metabolic abnormality.

Premature Ventricular Contractions

Premature ventricular contractions (PVCs) occur in wide a variety of pathologic and nonpathologic states. Occasional PVCs are commonly seen in healthy adults, more so under conditions associated with catecholamine excess, such as pain, anxiety, and use of stimulants (e.g., caffeine, nicotine, cocaine, amphetamines). Pathologic conditions associated with frequent PVCs include myocardial infarction, electrolyte disturbances, and medication toxicity. Although usually not requiring any intervention, frequent PVCs may occasionally herald the onset of VT—for example, in the setting of ST elevation myocardial infarction or in patients with a prolonged QT interval.

A PVC appears as a wide–QRS complex extrasystole without a preceding P wave (Fig. 79-19). Most PVCs capture the AV node, making it refractory to the next arriving atrial impulse. Because retrograde conduction of a PVC rarely extends far enough to capture and reset the SA node, however, atrial impulses continue to arrive at the AV node at the intrinsic sinus rate. As a result, the R-R interval surrounding a PVC ends up being equal to twice the intrinsic R-R interval length (see Fig. 79-19), a phenomenon known as a *compensatory pause.* Rarely, a PVC will capture the SA node, resulting in a *noncompensatory pause,* or will fail to capture the AV node, leaving the underlying rhythm completely unaffected (a so-called *interpolated PVC;* Fig. 79-20).

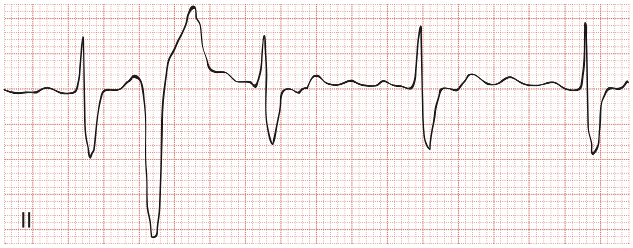


Figure 79-20. Interpolated premature ventricular contraction.

The morphology of a PVC depends on the origin of the impulse, with a left bundle branch block (LBBB) appearance resulting from an extrasystolic focus in the right ventricle and vice versa. Multiform (or "multifocal") PVCs come from more than one source

www.ketabpezeshki.com 66485457-66963820

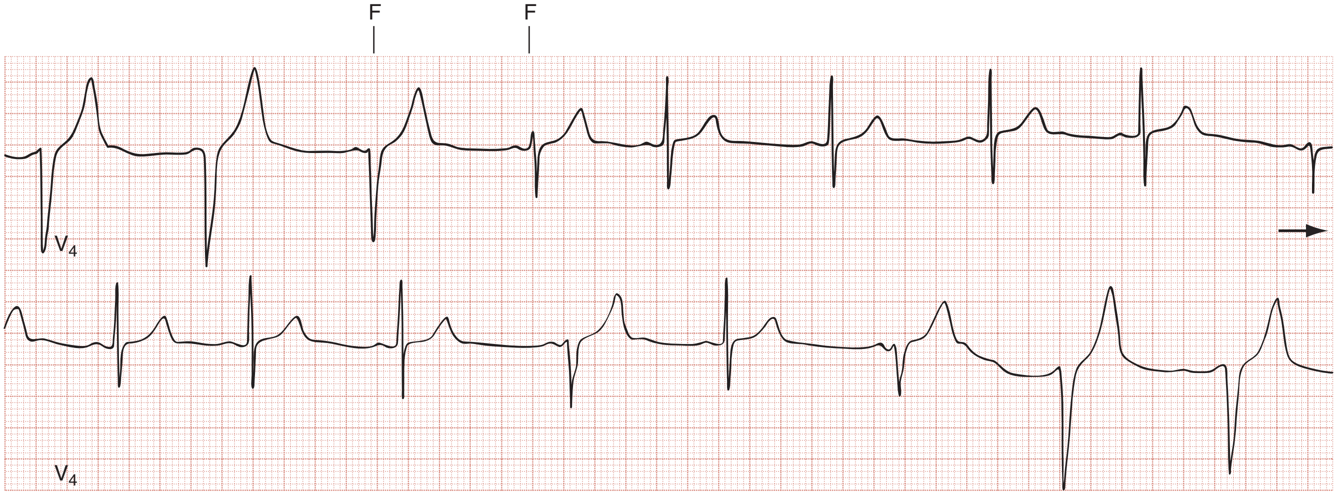


Figure 79-21. Sinus rhythm with premature ventricular contraction (PVC) and run of accelerated idioventricular rhythm. Note fusion beats *(F)* displaying hybrid appearance of both morphologies.

Table 79-4 Features to Distinguish Premature Atrial Contractions with Abnormal Conduction from Premature Ventricular Contractions

PREMATURE ATRIAL CONTRACTIONS	PREMATURE VENTRICULAR CONTRACTIONS
No compensatory pause	Fully compensatory pause (unless interpolated)
Preceding P wave (different from sinus P wave; occasionally buried in T wave)	No preceding P waves (although retrograde atrial conduction can cause inverted P wave after QRS)
Usually classic right bundle branch block pattern (especially if long-short cycle sequence appears) identical to sinus QRS	Left bundle branch block, right bundle branch block, or hybrid pattern
QRS axis normal or near normal	Frequently bizarre QRS axis
QRS rarely >0.14 s	QRS often >0.14 s

Box 79-6 Causes of Premature Ventricular Contractions and Ventricular Tachycardia

Acute or previous myocardial infarction or ischemia
Hypokalemia
Hypoxemia
Ischemic heart disease
Valvular disease
Catecholamine excess*
Other drug intoxications (especially cyclic antidepressants)
Idiopathic causes†
Digitalis toxicity
Hypomagnesemia
Hypercapnia
Class I antidysrhythmic agents
Ethanol
Myocardial contusion
Cardiomyopathy
Acidosis
Alkalosis
Methylxanthine toxicity

*Relative increase in sympathetic tone from drugs (direct or indirect) or conditions that augment catecholamine release or decrease parasympathetic tone.
†Isolated premature ventricular contractions (PVCs) can occur in up to 50% of young subjects without obvious cardiac or noncardiac disease; however, multiform and repetitive PVCs and ventricular tachycardia are rarely seen in this population.

and have variable morphologies. When a PVC occurs at or around the time that a supraventricular impulse is set to depolarize the ventricle, the result is a *fusion QRS complex* (Fig. 79-21). Table 79-4 notes common features of PACs and PVCs.

Therapy for PVCs is directed toward correcting any precipitating condition, be it a catecholamine excess, a drug effect, an electrolyte imbalance, or cardiac ischemia (Box 79-6). When occurring in isolation, symptomatic PVCs can be treated with low-dose beta-blocker therapy, but this is rarely an emergency need. Although lidocaine will suppress PVCs, it is not recommended in the absence of VT owing to limited clinical benefit and the risk of asystole.

Narrow-Complex Tachycardia

Narrow-complex tachycardias are defined by a QRS complex duration of 0.12 second or less on surface ECG with a ventricular rate of greater than 100 beats/min. The term *supraventricular tachycardia* is a confusing one because it is sometimes used in reference specifically to AV reentry tachycardia, but in other contexts it can denote any tachycardia originating at or above the AV node.

ECG features that help in distinguishing between different narrow-complex tachycardias include the appearance of P waves and the regularity or irregularity of the R-R interval. For example, a narrow-complex tachycardia with absent P waves and an irregular R-R interval is almost certainly atrial fibrillation. With rapid tachycardias, however, evidence of atrial depolarization is often obscured by ventricular repolarization; for example, with a regular, narrow-complex tachycardia at a rate of 150 beats/min, it can be difficult to distinguish sinus tachycardia from atrial flutter or a JT. Vagal maneuvers or adenosine can be used to transiently slow AV nodal conduction and expose evidence of atrial depolarization and aid diagnosis. Alternatively, the patient may convert to sinus rhythm, in which case AVNRT is both diagnosed and treated.

Sinus Tachycardia

Sinus tachycardia is characterized electrocardiographically by a regular, narrow-complex tachycardia with normal P waves preceding each QRS complex (Fig. 79-22). In adults, sinus tachycardia rarely exceeds a rate of 170 beats/min, but in infants and young children, it is not unusual to see rates above 200 to 225 beats/min.

www.ketabpezeshki.com 66485457-66963820

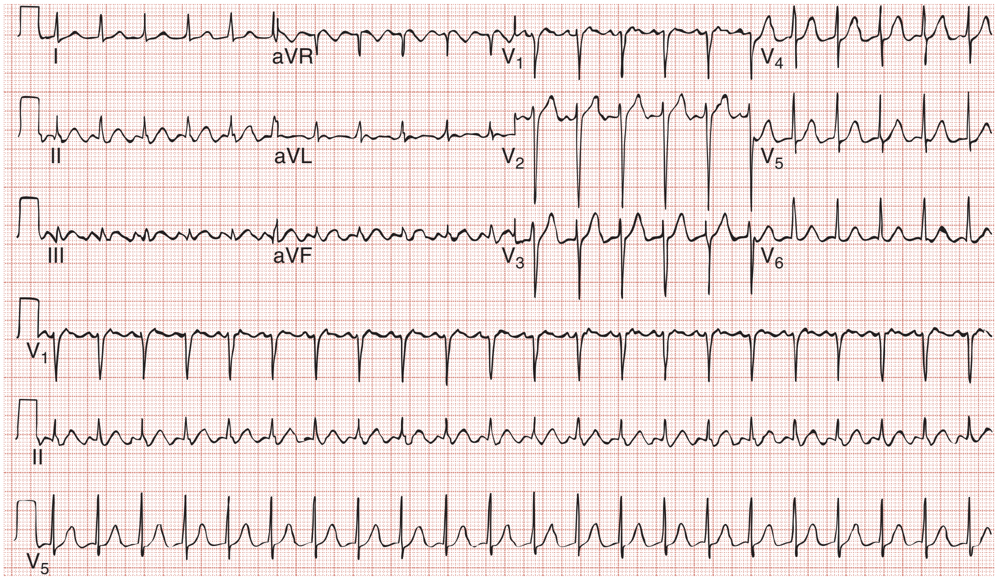


Figure 79-22. Sinus tachycardia.

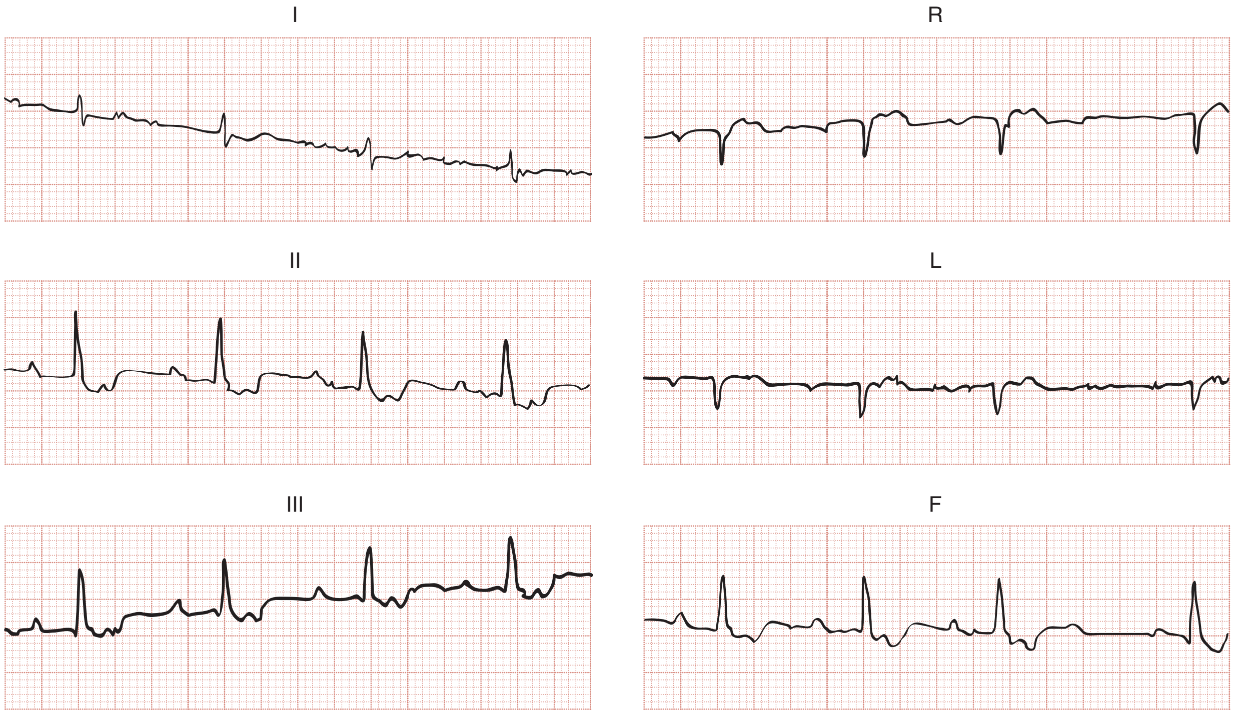


Figure 79-23. Atrial tachycardia (with 2 : 1 conduction) in a patient with digitalis toxicity. (From Marriott HJL, Conover MB: Advanced Concepts in Dysrhythmias, 2nd ed. St Louis, Mosby, 1989.)

As opposed to other forms of narrow-complex tachycardia, sinus tachycardia tends to speed up or slow down in a graded and continuous manner over time.

Sinus tachycardia is often a response to physiologic stress, intended to compensate for a relative lack of perfusion or oxygen delivery by increasing cardiac output. Usually the effect is salutary, as seen with hypovolemia, anemia, or hypoxemia; therefore efforts to slow the heart rate without addressing the underlying pathophysiology are likely to make things worse. At other times, sinus tachycardia is a counterproductive response, as in acute decompensated heart failure or aortic stenosis, in which a decrease in filling time further compromises cardiac output. Even in these settings, therapy should be first aimed at the underlying problem rather than the tachycardia.

Sinus tachycardia can be seen in any context associated with sympathetic excess, whether endogenous (e.g., pain, anxiety, fever, hyperthyroidism) or exogenous (stimulants and other drugs). The approach to the patient with sinus tachycardia centers on identifying and addressing the cause(s); rarely is specific rhythm therapy indicated.

Atrial Tachycardia

Atrial tachycardia (AT) is an atrial rhythm occurring at a rate of more than 100 beats/min arising from a non–sinus node site (or sites) within the left or right atrium. The hallmark of AT is the presence morphologically *abnormal* P waves on the surface ECG (Fig. 79-23). If the site of origin is close to the sinus node,

www.ketabpezeshki.com 66485457-66963820

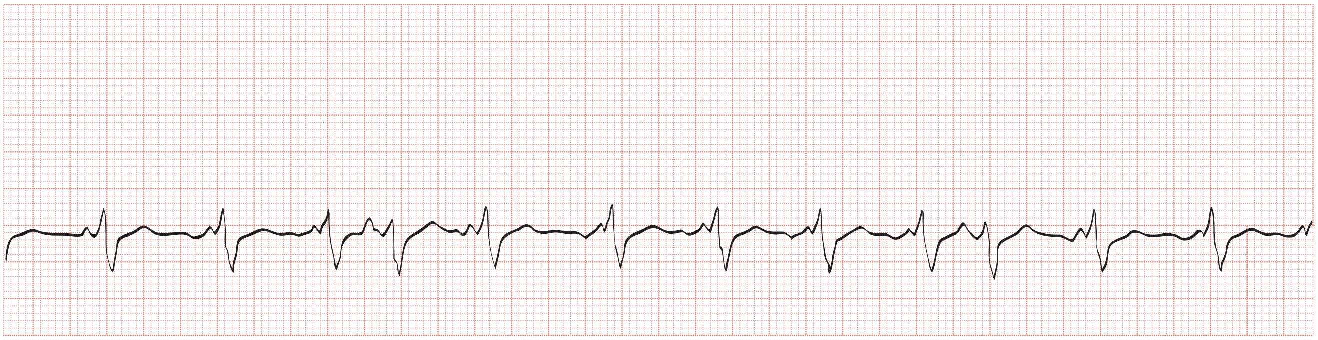


Figure 79-24. Multifocal atrial tachycardia. Note that although the rhythm is irregular, at least three distinct P wave morphologies are present.

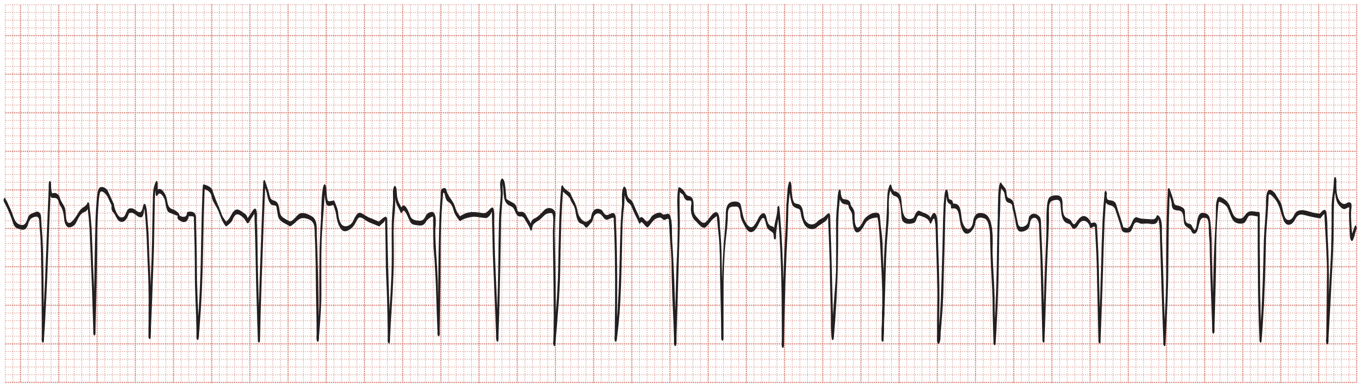


Figure 79-25. Atrial fibrillation with rapid ventricular response. Note that the irregularity could be easily overlooked.

atrial depolarization waves may look like a normal P wave. Depending on the atrial rate, the AV conduction ratio may be 1 : 1, 2 : 1 or higher.

AT is commonly seen in children and young adults with structural heart disease, often precipitated by the occurrence of a PAC. The rhythm is usually transient and does not require specific therapy. Other forms of focal AT can occur in patients with structural heart disease but are also found in settings such as hypoxemia, metabolic disturbances, and drug toxicity. In patients taking digitalis, for example, toxicity should be suspected if AT is seen, particularly in the presence of 2 : 1 or higher grade AV block.

Multifocal atrial tachycardia (MAT) is a form of AT with three or more distinct P wave morphologies, and varying PR and P-P intervals from the multiple ectopic atrial foci (Fig. 79-24). MAT is associated with pulmonary disease (chronic obstructive pulmonary disease [COPD] in particular) in up to 60% of cases, but it can also be seen in the presence of primary cardiac pathology. On the surface ECG, MAT can be mistaken for course atrial fibrillation because of the nonuniform atrial activity and irregular R-R intervals.

The approach to patients with AT is based on identifying and treating any precipitating factors, such as hypoxia or hypoxemia, electrolyte abnormalities, and drug toxicity. In patients with suspected hypomagnesemia, supplemental magnesium (2 g IV over 5 minutes) is an option. Vagal maneuvers and adenosine are unlikely to be effective in AT or MAT, though these may help unmask the atrial activity. Pharmacologic therapy to slow AV conduction (with a beta-blocker or calcium channel blocker) may be appropriate for the hemodynamically stable patient. Because AT and MAT are often precipitated by underlying illnesses, the effect of cardioversion is limited and the likelihood of recurrence is high.

Box 79-7 Causes of Completely Irregular (Chaotic) Rhythms

- Atrial fibrillation
- Atrial tachycardia or flutter with varying conduction
- Multifocal atrial tachycardia
- Multiple extrasystoles
- Wandering pacemaker (usually atrial)
- Parasystole

Atrial Fibrillation

Atrial fibrillation is usually identified by electrical chaos; it starts from chaotic depolarization of atrial tissues caused by multiple microreentry circuits, generating 300 to 600 atrial impulses per minute. This chaotic activity reduces cardiac output from a loss of coordinated atrial contractions and from a rapid ventricular rate, both of which may limit the diastolic filling and stroke volume of the ventricles. Patients with atrial fibrillation are at risk for developing left atrial thrombi, especially in the left atrial appendage, and consequent embolic events.

Atrial fibrillation may be paroxysmal, persistent, or permanent, and long-term approaches to management depend on many factors, including chronicity, symptomatology, underlying heart disease, and other comorbidities.

Electrocardiographically, the hallmark of atrial fibrillation is a "irregularly irregular" QRS pattern (Fig. 79-25). Although atrial fibrillation is not the sole cause of an irregular ventricular rhythm, it is by far the most common (Box 79-7). Atrial fibrillatory waves appear "coarse" or "fine" on the basis of their amplitude and are often best appreciated in the inferior leads or lead V_1.

www.ketabpezeshki.com 66485457-66963820

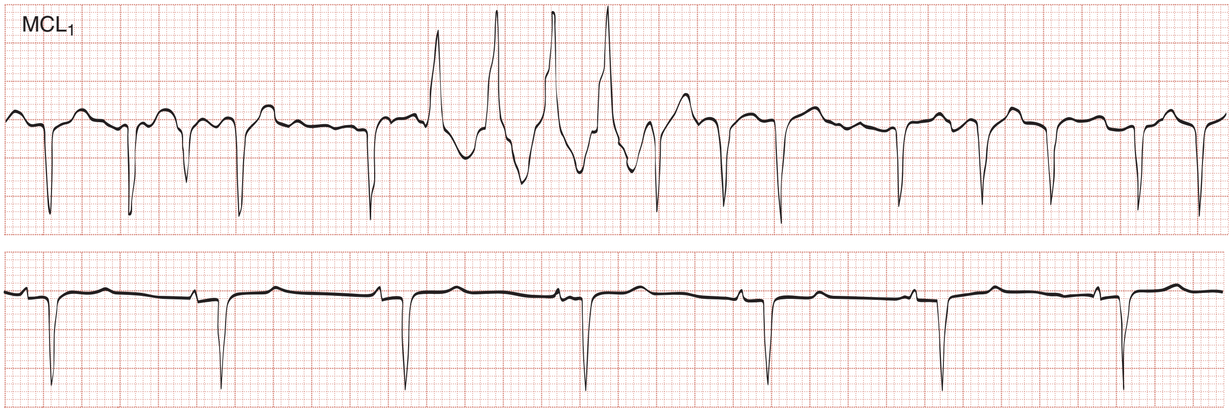


Figure 79-26. Atrial fibrillation with classic Ashman phenomenon series of beats. Note long-short cycle before aberrantly conducted impulses that are sustained for four beats. (From Marriott HJL, Conover MB: Advanced Concepts in Dysrhythmias, 2nd ed. St Louis, Mosby, 1989.)

Typically, the ventricular rate in atrial fibrillation is limited by the refractory period of the AV node, with response rates rarely exceeding 150 to 170 beats/min and often slower, particularly in the presence of nodal blocking agents. Atrial fibrillation in an adult with a ventricular rate exceeding 200 beats/min strongly suggests the presence of an accessory conduction pathway and has important implications for management (see later). Frequently, this rapid atrial fibrillation with an accessory path will have a wide QRS complex; if the irregularity of ventricular depolarization is not sought, it is easy to mistake this for VT. When a wide QRS complex is seen at rates below 200 beats/min but with ventricular chaos, an existing or acquired bundle branch block is likely present.

The *Ashman phenomenon* refers to aberrant ventricular conduction of an early-arriving atrial impulse following a relatively long R-R interval, as a result of a partially refractory His bundle. Such aberrantly conducted impulses are often seen in atrial fibrillation but can occur in any irregular rhythm in which long-short cycle sequences occur, and they typically assume an RBB block pattern (Fig. 79-26). Ashman beats can be mistaken for PVCs or paroxysmal VT.

Atrial fibrillation is most commonly associated with underlying heart disease or hypertension (Box 79-8), but it can also occur in isolation (so-called *lone atrial fibrillation*) or as a manifestation of hyperthyroidism. As many as one third of patients with congestive heart failure also have atrial fibrillation.

Box 79-8 Causes of Atrial Fibrillation

- Hypertensive heart disease
- Cardiomyopathy
- Ischemic heart disease
- Valvular disease (especially mitral)
- Congestive heart failure
- Pericarditis
- Hyperthyroidism
- Sick sinus syndrome
- Myocardial contusion
- Acute ethanol intoxication (holiday heart syndrome)
- Idiopathic
- Cardiac surgery
- Catecholamine excess
- Pulmonary embolism
- Accessory pathway (Wolff-Parkinson-White) syndrome

The presentation of patients with atrial fibrillation is variable. For example, patients without underlying cardiopulmonary disease may tolerate atrial fibrillation with ventricular rates of 150 to 170 at rest and complain only of palpitations or exercise intolerance. On the other hand, a patient with left ventricular dysfunction and new or worsened rate control may experience dyspnea at rest even with a modest rate increase. In a patient with preexisting atrial fibrillation and a new rapid ventricular rate, it is key to seek evidence that the rapid rate is a response to some other hemodynamic stress, such as decompensated heart failure, sepsis or hypovolemic shock, massive pulmonary embolism, or cardiac tamponade. Failure to recognize and take into account the underlying cause of instability may result in counterproductive attempts at rate control or cardioversion.

For stable patients with new or recurrent rapid atrial fibrillation, administration of a nodal blocking agent with a goal of achieving a target ventricular rate of 120 beats/min or less is a first step.[13] Intravenous calcium channel blockers (diltiazem and verapamil) or beta-blockers (metoprolol) offer the advantage of being easily titrated and can be followed by an oral agent before discharge. Nodal agents should *not* be used for rate control in the setting of accessory pathway conduction because AV conduction (with retrograde conduction into the accessory pathway) may be the only thing preventing the ventricular rate from accelerating even further and degenerating into ventricular fibrillation. The debate as to whether asymptomatic patients with persistent atrial fibrillation benefit additionally from rhythm control, either via cardioversion or by other means (e.g., ablation), is ongoing without a definitive answer. In choosing rate control for the long term, the ideal target rate is debated, with some advocating less than 80 beats/min at rest instead of the common goal of 110 beats/min or less; no clear evidence of either target being superior exists yet.

For stable patients with new-onset or newly recurrent atrial fibrillation—defined as having a duration of 72 hours or less—ED cardioversion is an option. If atrial fibrillation has been present longer or for an uncertain interval in the absence of ongoing anticoagulation, however, cardioversion is not recommended to avoid the risk (1-4% at 30 days) of systemic embolization. The choice of electrical versus pharmacologic cardioversion is dependent on institutional factors and patient preference, although published success rates are higher (80% or greater) with electrical conversion.[13,14] Among patients with new or recurrent atrial fibrillation of less than 48 to 72 hours' duration, up to 50% will convert spontaneously to sinus rhythm within 24 hours. Prehospital cardioversion is not recommended.

Various agents are available for pharmacologic cardioversion of patients with stable atrial fibrillation in the ED, including the class IA, IC, and III antidysrhythmics (Box 79-9). In practice,

www.ketabpezeshki.com 66485457-66963820

Box 79-9 Pharmacologic Approach to Atrial Fibrillation and Flutter Conversion

Intravenous procainamide 30-50 mg/min up to a total dose of 18 to 20 mg/kg (12 mg/kg in patients with congestive heart failure) or until conversion or side effects occur
or
Amiodarone 3 to 5 mg/kg intravenously (IV) over 15 to 20 minutes
or
Ibutilide 0.015 to 0.02 mg/kg IV over 10 to 15 minutes (conversion usually occurs within 20 minutes if successful)
or
Oral propafenone 600 mg (contraindicated in setting of structural heart disease or ischemia)
or
Oral flecainide 300 mg (contraindicated in setting of structural heart disease or ischemia)
If needed:
A calcium channel blocker can be given before the type IA agent (if no contraindications are present) to lower the ventricular response rate to below 120 beats/min and to attenuate further tachycardia from the vagolytic effects of these agents.

intravenous procainamide, amiodarone, and ibutilide are the agents most commonly used in ED setting. Although differences in success rates exist among agents, the overall response is 40 to 65% for drug-based ED cardioversion. The class IC antidysrhythmics are contraindicated in patients with structural or ischemic heart disease. For atrial fibrillation with accessory pathway conduction, procainamide is recommended because it has no effect on AV conduction.

For patients for whom electrical cardioversion is selected, adequate procedural sedation should be used. An initial attempt with 100 J (biphasic preferred) is usually adequate for cardioversion of atrial fibrillation, but occasionally a second attempt at 100 to 200 J is required.

Many patients with atrial fibrillation, whether frequent paroxysmal or permanent, benefit from long-term anticoagulation as prophylaxis against stroke. Although long-term anticoagulation typically falls beyond the scope of the ED, it is important that any patient for whom anticoagulation may be appropriate be referred for timely follow-up to address this issue.

Atrial fibrillation alone is not an indication for hospital admission. Observation or admission should be considered for symptomatic patients with atrial fibrillation that is complicated by significant underlying cardiopulmonary disease, in those in whom duration is unknown and follow-up uncertain, in those in whom cardioversion fails or the rhythm returns, and in all patients with concomitant new noncardiac illnesses.

Atrial Flutter

Atrial flutter is defined by atrial depolarization occurring at a regular rate of 250 to 350 beats/min (300 beats/min is classic) caused by an atrial reentry mechanism (Fig. 79-27). So-called *flutter waves* are distinguished by their broad, sawtooth appearance on the surface ECG. The ventricular rate in atrial flutter is often rapid, but in the absence of a bypass tract (in which 1:1 conduction is possible), the conduction ratio is limited by the refractory period of the AV node. With 2:1 conduction, the ventricular rate is approximately 150 beats/min, often making flutter waves themselves difficult to appreciate and allowing the rhythm to be mistaken for sinus tachycardia. Often the conduction ratio will change from beat to beat, called *atrial flutter with variable conduction,* with a resultant irregular ventricular rate; this is hard to distinguish from atrial fibrillation.

Atrial flutter can be associated with structural heart disease, particularly valvular heart disease and cardiomyopathies. The acute management of atrial flutter is similar to that of atrial fibrillation with a few special considerations. Because AV conduction occurs at fixed ratios in atrial flutter, the administration of beta-blocker or calcium channel blocker therapy can result in an abrupt rate change, making it more challenging to titrate therapy to a desired target rate. Atrial flutter is more sensitive to DC cardioversion (up to 90% conversion rate) than atrial fibrillation, and usually requires lower energy (20-50 J) for conversion to sinus rhythm.[15] Conversely, atrial flutter is more resistant to chemical cardioversion (less than 50%) than new-onset nonvalvular atrial fibrillation.

Atrioventricular Nodal Reentrant Tachycardia

Also known by the less precise term *paroxysmal supraventricular tachycardia* (PSVT), AVNRT is characterized by a regular narrow-complex rhythm and a ventricular rate of 160 beats/min or greater (Fig. 79-28). It is the most common nonsinus tachydysrhythmia in young adults. As its name suggests, AVNRT occurs as the result of a reentry circuit within the AV node, with normal conduction (narrow QRS) down the bundles of His, and with retrograde conduction (inverted P waves typically buried within the QRS) up into the atria (Fig. 79-29).

The onset of AVNRT is typically abrupt and frequently arises in the context of strenuous exercise or emotional stress. Termination is also abrupt, either spontaneously or following vagal maneuvers that patients are taught or just adopt instinctively. Most patients with AVNRT are symptomatic, but hemodynamic instability is unusual in the absence of underlying cardiopulmonary disease.

If vagal maneuvers fail to restore sinus rhythm, first-line field or ED therapy for AVNRT is adenosine (6 mg rapid large-bore intravenous bolus followed by a flush; repeat with 12 mg if no effect on rate). This approach is successful in 85 to 90% of cases. In refractory cases, diltiazem, esmolol, or metoprolol may be used. Rarely, synchronized cardioversion (at 100-200 J, synchronized and biphasic preferred) is required to terminate AVNRT that is refractory to pharmacologic therapy or in a patient with hemodynamic instability.

Most patients can be discharged once AVNRT has been terminated with adenosine or vagal maneuvers. Patients with frequent recurrences are candidates for prophylaxis (typically with a beta-blocker or calcium channel blocker) or ablation therapy.

Junctional Tachycardia

In contrast to the bursts seen in AVNRT, JTs (also known as *nonparoxysmal* or *sustained junctional tachycardia*) show sustained ventricular rates but rarely exceed 130 beats/min. JTs are commonly associated with structural heart disease, metabolic disturbances, or drug toxicity. Treatment is aimed at addressing underlying conditions, although a cautious trial of nodal blockade is not unreasonable.

Preexcitation and Accessory Pathway Syndromes

Preexcitation refers to depolarization of the ventricular myocardium by circumvention of the AV node via an accessory pathway or bypass tract linking the atria to the ventricles. Accessory pathways lend themselves to reentry tachycardias and very rapid ventricular rates. Wolff-Parkinson-White (WPW) syndrome is the classic accessory pathway syndrome, characterized by paroxysmal tachycardia and the following three resting ECG features (Fig. 79-30):

www.ketabpezeshki.com 66485457-66963820

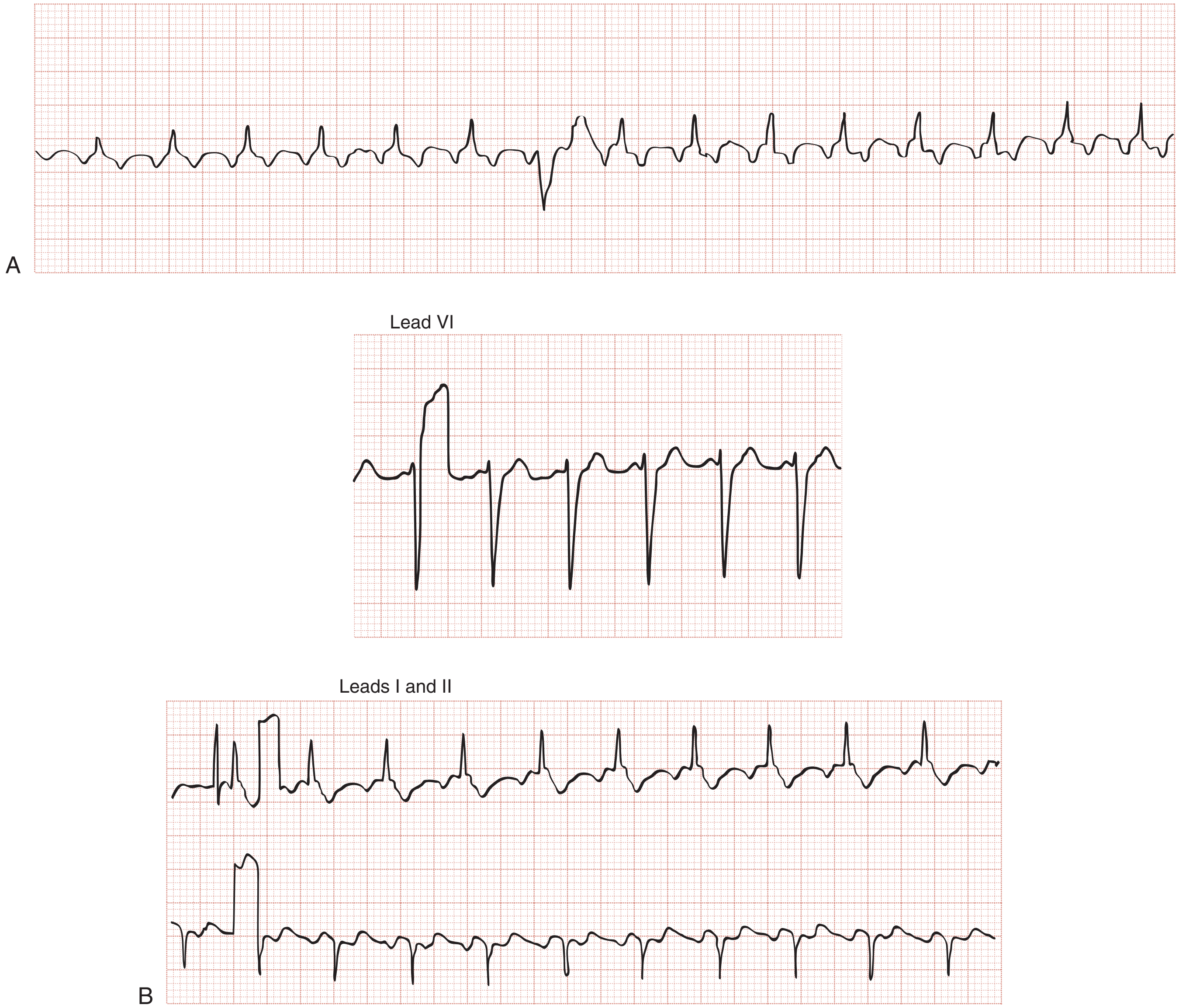


Figure 79-27. **A,** Atrial flutter with 2 : 1 conduction and isolated premature ventricular contraction. **B,** Atrial flutter with 2 : 1 conduction. Lead II helps identify characteristic flutter waves.

Continued

www.ketabpezeshki.com 66485457-66963820

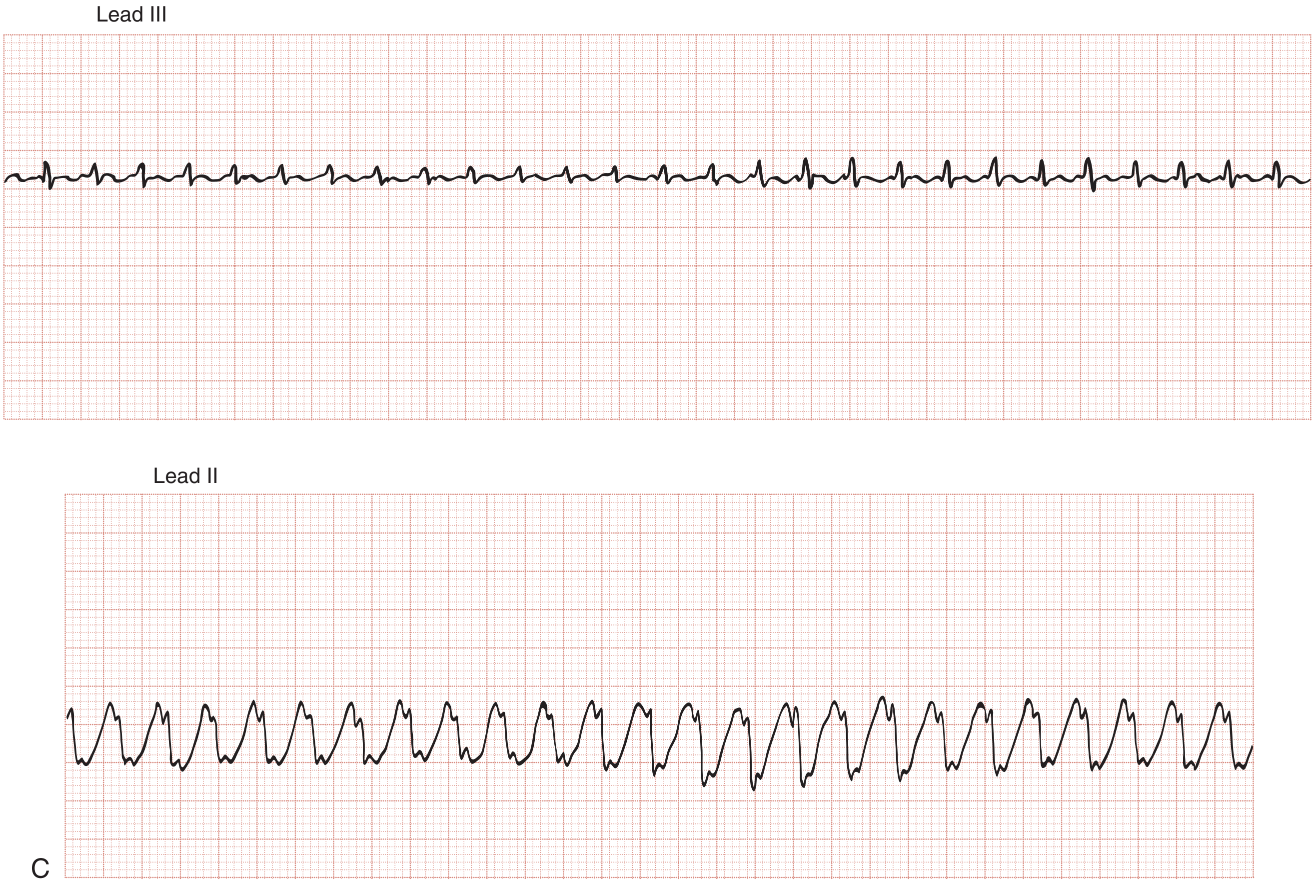


Figure 79-27, cont'd. C, Atrial flutter with 1 : 1 conduction. This is rare and can be mistaken for ventricular tachycardia (lead II).

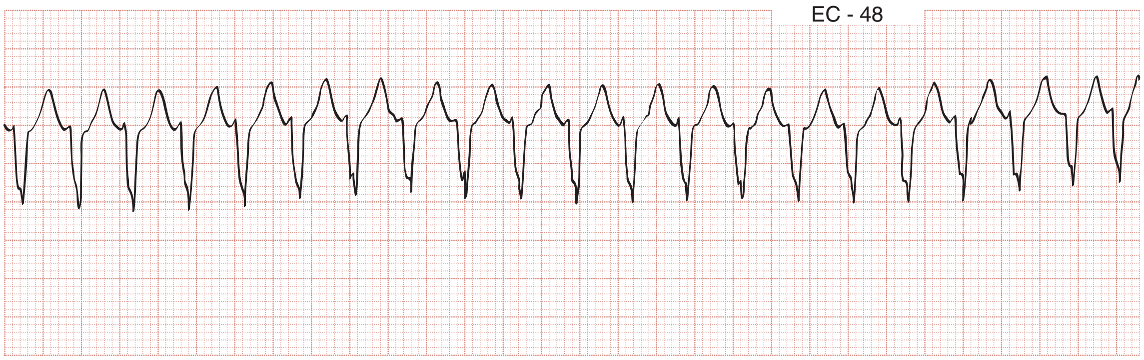


Figure 79-28. Paroxysmal supraventricular tachycardia. Note the narrow, regular QRS complexes.

www.ketabpezeshki.com 66485457-66963820

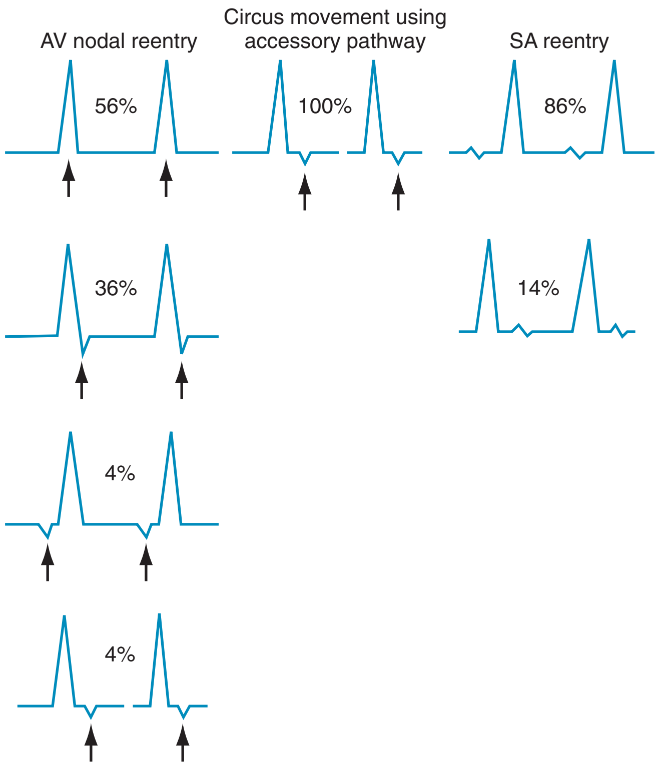


Figure 79-29. Location of P waves in common causes of regular narrow-complex tachycardia. *AV,* atrioventricular; *SA,* sinoatrial. (From Marriott HJL, Conover MB: Advanced Concepts in Dysrhythmias, 2nd ed. St Louis, Mosby, 1989.)

- A short PR interval (<0.12 second)
- QRS duration greater than 0.10 second
- A slurred upstroke to the QRS complex, referred to as a *delta wave*

Patients with WPW and other preexcitation syndromes often have one or more of the classic features missing on the surface ECG. Also, some patients with WPW-like patterns on their resting ECG never develop symptomatic tachycardia.

Together with the AV node, an accessory pathway can form a reentry circuit to produce and sustain a tachycardia (Fig. 79-31). When the AV node is being used for anterograde conduction to the ventricles and the accessory path is used for retrograde conduction, it is called an *orthodromic AV-reentrant tachycardia*; the QRS complex will be narrow and the ventricular rate is constrained. Conversely, when the accessory pathway is being used as the anterograde limb and the AV node as the retrograde limb of the reentry circuit, it is called an *antidromic AV-reentrant tachycardia* with a wide QRS complex. The ventricular rate can be normal or rapid and more than 200 beats/min. Fortunately, in patients with WPW and most other preexcitation syndromes, orthodromic tachycardia is much more common than antidromic tachycardia. WPW syndrome is associated with a variety of conditions, although the majority of patients have no underlying structural heart disease (Box 79-10).

Orthodromic AV-reentrant tachycardia is the most common presenting dysrhythmia in WPW (70-80%), but atrial fibrillation can be seen in up to 30% of patients. Orthodromic AV-reentrant tachycardia is indistinguishable clinically from AVNRT unless the presence of an accessory pathway is known and is treated in the same way, with vagal maneuvers and adenosine as first-line therapy, followed by calcium channel blockers and beta-blockers as second-line agents.

In contrast, antidromic AV-reentrant tachycardia often causes a very rapid rate (200 beats/min or greater) and a wide-complex QRS. In this situation, **AV nodal blocking agents are contraindicated** because it is the presence of anterograde AV conduction that provides a brake on even more rapid retrograde conduction. Unopposed retrograde conduction through the AV node can result in ventricular fibrillation.[16] Likewise, with a very rapid *irregular* tachycardia (i.e., atrial fibrillation with a ventricular rate exceeding 200) accompanied by a wide-complex QRS, the likelihood of accessory pathway conduction should be considered and nodal blocking agents again withheld. Procainamide is recommended any time an accessory pathway with wide QRS complexes or very rapid rates exists, with amiodarone as a secondary choice despite theoretic concerns about its nodal blocking properties. Electrical cardioversion (100-200 J) is indicated for ventricular rates greater than 250 beats/min, clinical deterioration, or failure of pharmacologic therapy.

The Lown-Ganong-Levine syndrome is an uncommon accessory pathway syndrome associated with paroxysmal narrow-complex tachycardia, a short PR interval, and a normal QRS complex without a delta wave. The treatment parallels that for the WPW syndrome.

Wide-Complex Tachycardias

Wide-complex tachycardia refers to any tachydysrhythmia accompanied by a QRS duration of 0.12 second or more. Wide-complex tachycardias can derive from the ventricles themselves (i.e., VT) or can result from a tachycardia originating at or above the AV node accompanied by aberrant AV conduction, caused by either an accessory pathway or a preexisting or rate-related conduction delay, such as a bundle-branch block. The presence of AV dissociation or fusion beats on the 12-lead ECG clearly points to VT; all else being equal, older age and a prior history of myocardial infarction make VT much more likely than a supraventricular tachycardia with aberrancy. On the other hand, an irregular tachycardia with a wide QRS approximating a bundle-branch morphology is most likely atrial fibrillation with aberrant conduction. For stable patients, there are decision tools that can be used to distinguish VT with relatively good accuracy (Table 79-5 and Fig. 79-32).[17-21]

In practice, it can be difficult to make the distinction between VT versus SVT and abnormal conduction when confronted with a patient displaying a wide-complex tachycardia. Many of the decision rules rely on an ability to discern subtleties of the QRS morphology, and none has perfect discriminatory power. As a general rule, because failure to treat VT appropriately can be associated with dire consequences, any new wide-complex tachycardia should be presumed initially to be VT. Hemodynamic stability does not help to exclude VT.

The Brugada ECG criteria search for four pieces of evidence of VT from among those listed previously; as soon as one is found,[18,20,21] the diagnosis of VT is made. The rhythm needs to be regular for these to be used (chaos suggests atrial fibrillation with altered conduction). The sequential criteria are as follows (see Figs. 79-32 and 79-33):

1. Absence of any RS complexes in the chest leads
2. RS duration (measured from beginning of R to deepest part of S wave) greater than 100 msec
3. AV dissociation (often present but overlooked; may be best appreciated in inferior limb leads and $V_{1\text{-}2}$; Fig. 79-34)
4. Specific VT morphologic criteria (see Fig. 79-33)

Only when none of the Brugada criteria are present is a supraventricular cause diagnosed. Although the original investigators found excellent sensitivity (98.7%) and specificity (96.5%) in detecting VT, follow-up investigations have not duplicated this level of accuracy in ED patients (sensitivity 92-94%). Often, physicians either cannot complete the assessment or cannot agree on the findings. In patients receiving class I agents, the Brugada criteria are less reliable.

www.ketabpezeshki.com 66485457-66963820

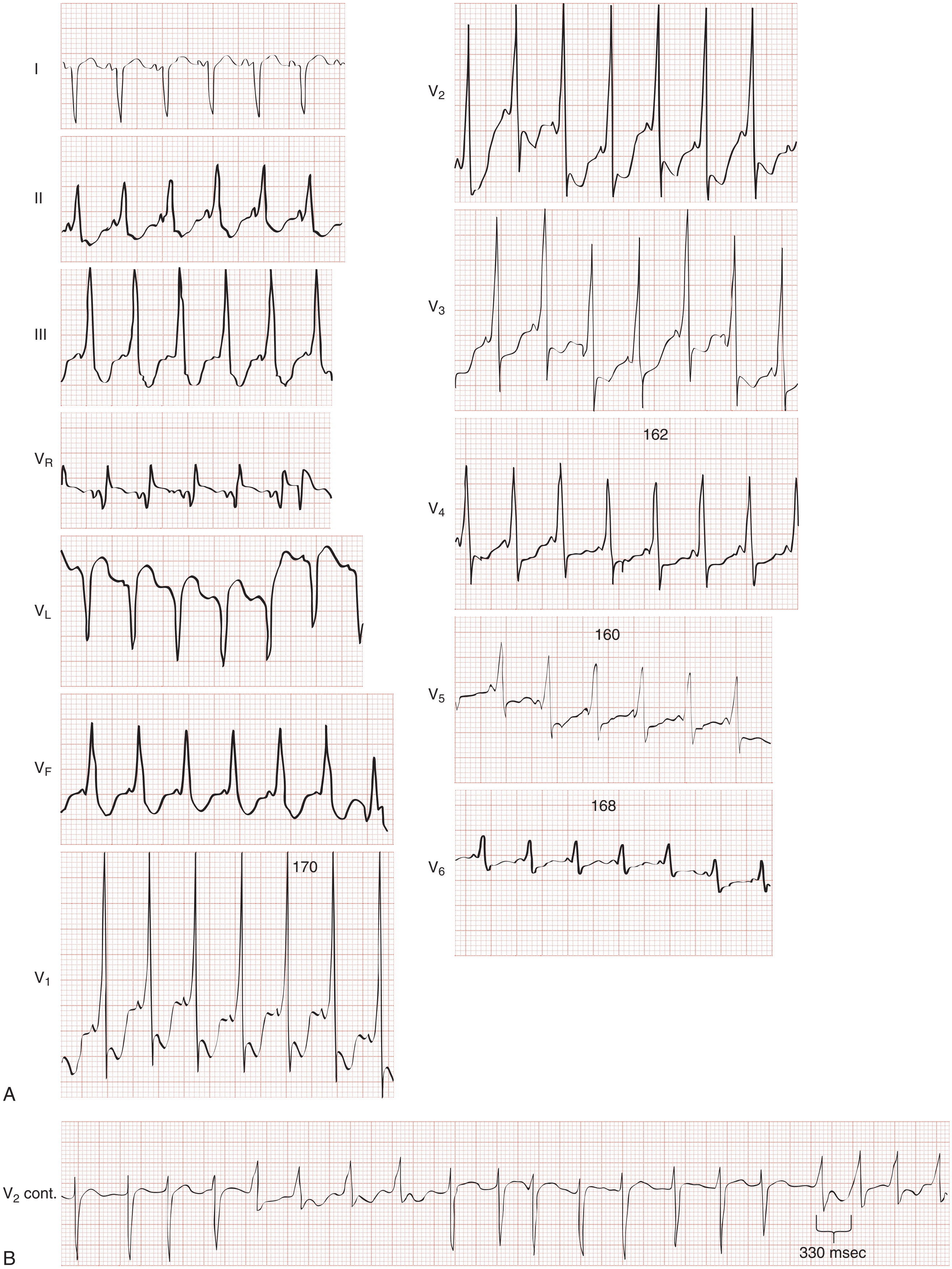


Figure 79-30. **A,** Wolff-Parkinson-White (WPW) syndrome. **B,** WPW syndrome with atrial fibrillation. Note short refractory period (330 msec). (**A,** From Watanabe Y, Dreifus LS: Cardiac Dysrhythmias. New York, Grune & Stratton, 1977.)

www.ketabpezeshki.com 66485457-66963820

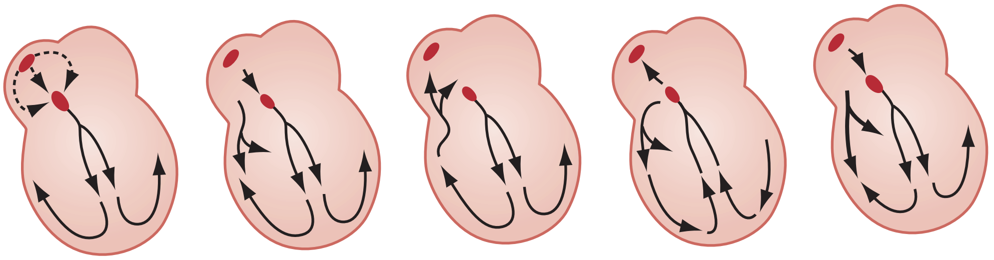


Figure 79-31. Wolff-Parkinson-White *(WPW)* paths and associated rhythms. *AV,* atrioventricular. (**A,** From Watanabe Y, Dreifus LS: Cardiac Dysrhythmias. New York, Grune & Stratton, 1977.)

Box 79-10 Diseases Associated with Wolff-Parkinson-White Syndrome

Idiopathic*
Cardiomyopathy (especially hypertrophic)
Transposition of great vessels
Endocardial fibroelastosis
Mitral valve prolapse
Tricuspid atresia
Ebstein's disease

*Most common.

The Griffith criteria use a three-step approach to identify aberrancy,[19,20] first through classic RBBB or LBBB morphologies in V_1 and V_6 to identify SVT, then seeking AV dissociation in the remainder to identify VT (see Figs. 79-32 and 79-34). This approach has a reported sensitivity of 92%, although specificity may be less than seen with the Brugada approach (though head-to-head in-practice comparative data do not exist).

Unstable patients with a wide-complex tachycardia should be treated with cardioversion (100 J, synchronized and biphasic if possible). For stable patients in whom pharmacologic treatment is sought, procainamide or amiodarone are attractive choices because they can effectively convert both ventricular and supraventricular dysrhythmias. A diagnostic and therapeutic trial of adenosine is reasonable if no irregularity is noted and if the ventricular rate is less than 250 beats/min; this is done based on the facts that most SVTs will either slow or terminate with this intervention and that any ill effects of adenosine will be fleeting. Other pharmacologic therapies for stable VT are discussed later. If pharmacologic treatment fails, synchronized cardioversion is an option.

Ventricular Tachycardia

VT originates within or below the His bundle. *Nonsustained* VT refers to short episodes (<30 seconds) that revert spontaneously, whereas *sustained* VT refers to more prolonged episodes. Reentry mechanisms are the most common cause of VT, although automatic and triggered mechanisms also occur. Most patients with VT have underlying heart disease.

Monomorphic ventricular tachycardia is the most common form of VT and is characterized by morphologically consistent QRS complexes, usually in a regular pattern and at a rate of 150 to 200 beats/min (Fig. 79-35). *Polymorphic ventricular tachycardia* is seen with varying QRS morphologies and suggests more severe underlying disease (Figs. 79-36 and 79-37). VT is prevalent in patients with both ischemic and nonischemic cardiomyopathy.

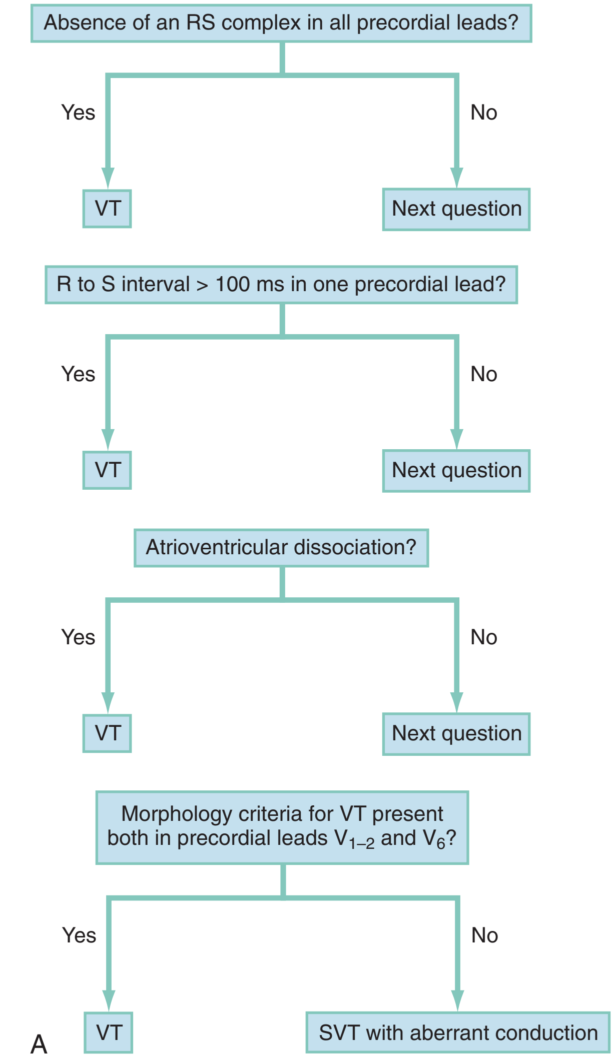
Table 79-5 Features Helpful in Distinguishing Ventricular Tachycardia from Supraventricular Tachycardia (SVT) with Abnormal Conduction

	VENTRICULAR TACHYCARDIA	SVT PLUS ABERRANCY
Clinical features	Age 50 or older	Age 35 or younger
	History of myocardial infarction, congestive heart failure, CABG, or ASHD	None
	Previous history of ventricular tachycardia	Previous history of SVT
Physical examination	Cannon A waves	Absent
	Variation in arterial pulse	Absence of variability
	Variable first heart sound	Absence of variability
Electrocardiogram	Fusion beats	None
	AV dissociation	Preceding P waves with QRS complexes
	QRS >0.14 s	QRS usually <0.14 s
	Extreme LAD artery (30 degrees)	Axis normal or near normal
	No response to vagal maneuvers	Slow or terminate with vagal maneuvers
Specific QRS patterns	V_1: R, qR, or RS	V_1: rSR′
	V_6: S, rS, or qR	V_6: qRs
	Identical to previous ventricular tachycardia tracing*	Identical to previous SVT tracing*
	Concordance of positivity or negativity†	

ASHD, arteriosclerotic heart disease; *AV,* atrioventricular; *CABG,* coronary artery bypass graft; *LAD,* left anterior descending; *SVT,* supraventricular tachycardia.
*If proven by electrophysiologic studies or by a preponderance of evidence.
†Main deflection of QRS complex either positive or negative in every precordial lead.

For stable patients with VT, amiodarone (3-5 mg/kg IV over minutes) or lidocaine (1.0-1.5 mg/kg IV bolus, up to 3 mg/kg maximum and followed by an infusion) are first-line choices in the field or ED, with successful termination of up to 90%. Procainamide (30-50 mg/min IV up to a total of 18 mg/kg or until VT is terminated) is a second-line agent. Unstable patients or those with VT refractory to drug therapy should undergo

www.ketabpezeshki.com 66485457-66963820



	BBB pattern
Right	
V_1	rSR′ pattern with R′ > rRS (RS) pattern with R > S; Q wave
V_6	<40 msec and <2 mm (0.2 mV) were allowed
Left	
V_1	rS or QS pattern with time to 5 wave nadir <70 ms
V_6	R wave with no Q wave

BBB = bundle branch block.

If no classic BBB pattern as noted above that would define SVT with aberrancy, search for AV dissociation; if present, VT is diagnosed and if absent, SVT diagnosed by default.

B

Figure 79-32. **A,** Brugada four-step approach for differentiating ventricular tachycardia *(VT)* and wide-QRS supraventricular tachycardia *(SVT)*. Only when the response to all four questions is negative is a supraventricular rhythm with abnormal conduction diagnosed. As soon as a single "yes" answer is noted, VT is diagnosed. **B,** Griffith approach, in which aberrant conduction is sought in leads V_1 and V_6 (right bundle branch block [RBBB] or left bundle branch block [LBBB] classic appearances), followed by a search for atrioventricular (AV) dissociation. If classic RBBB and LBBB patterns are absent, or if the remainder of leads have no AV dissociation, VT is diagnosed. (**A,** From Brugada P, et al: A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex. Circulation 83:1649, 1991. **A,** Redrawn from Griffith MJ, et al: Ventricular tachycardia as default diagnosis in broad complex tachycardia. Lancet 343:386, 1994.)

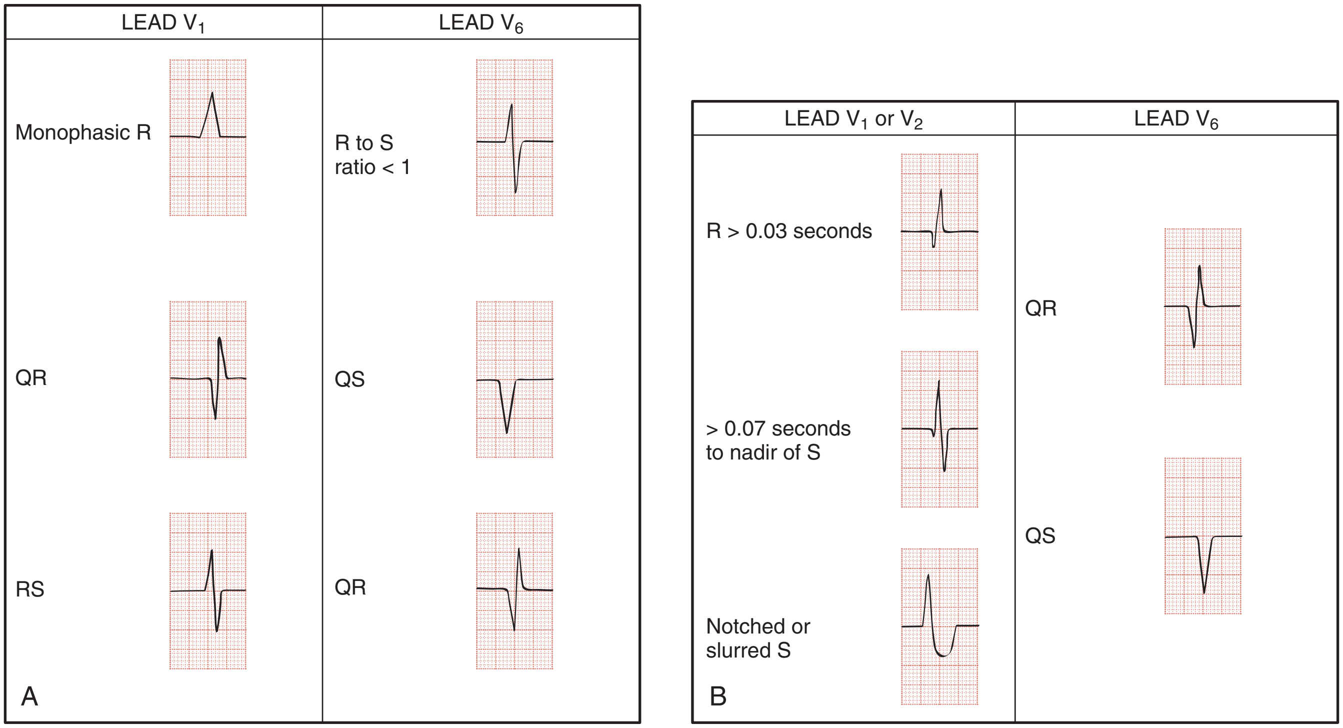


Figure 79-33. The morphology associated with the fourth criterion in the Brugada system: **A,** in patients with a right bundle branch–appearing complex; **B,** in patients with a left bundle branch–appearing complex.

www.ketabpezeshki.com 66485457-66963820

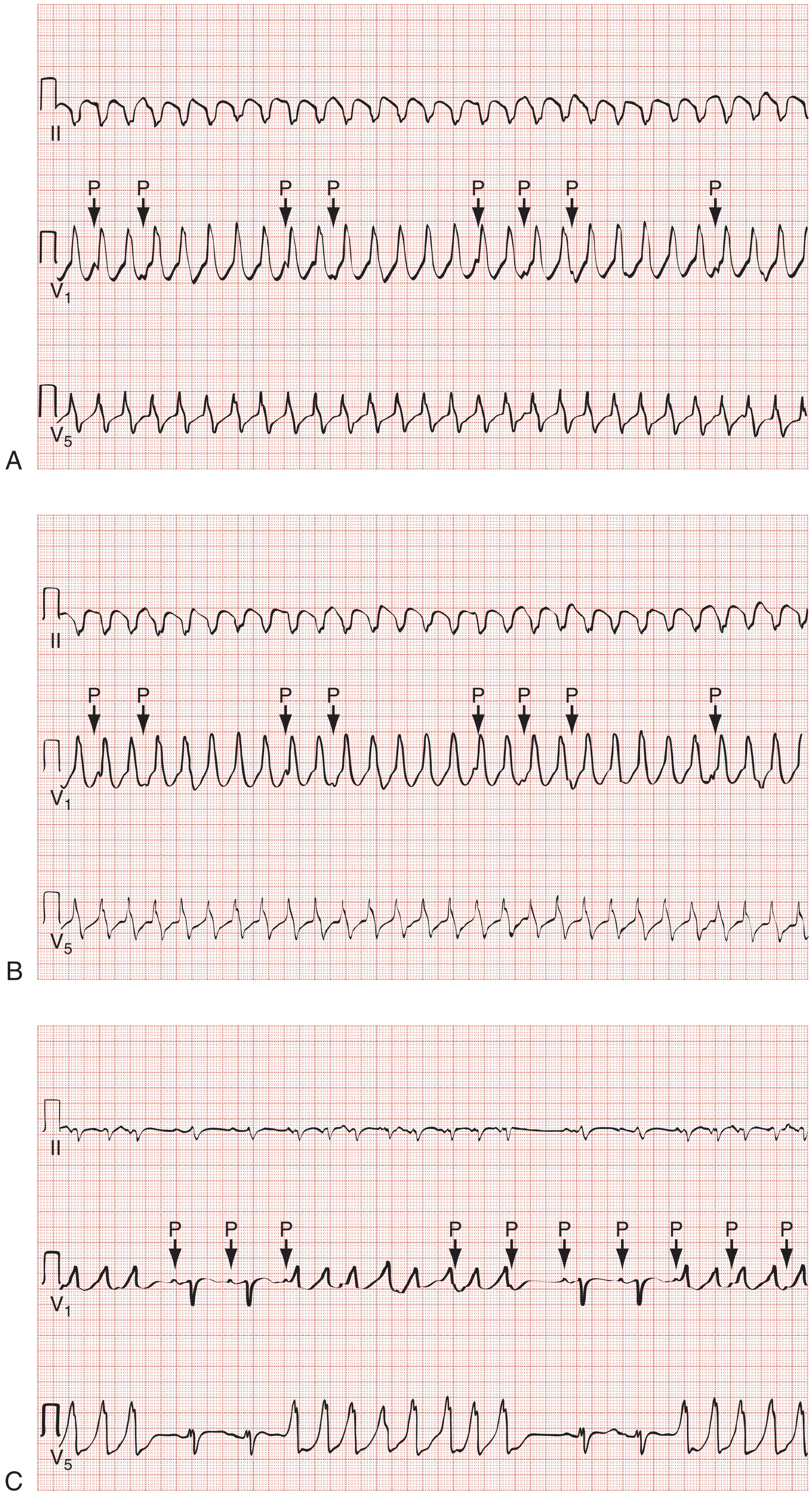


Figure 79-34. **A** and **B,** Ventricular tachycardia. Note atrioventricular dissociation. **C,** Intermittent, nonsustained ventricular tachycardia. Atrioventricular dissociation is evident. (Courtesy Edward Curtis, MD.)

www.ketabpezeshki.com 66485457-66963820

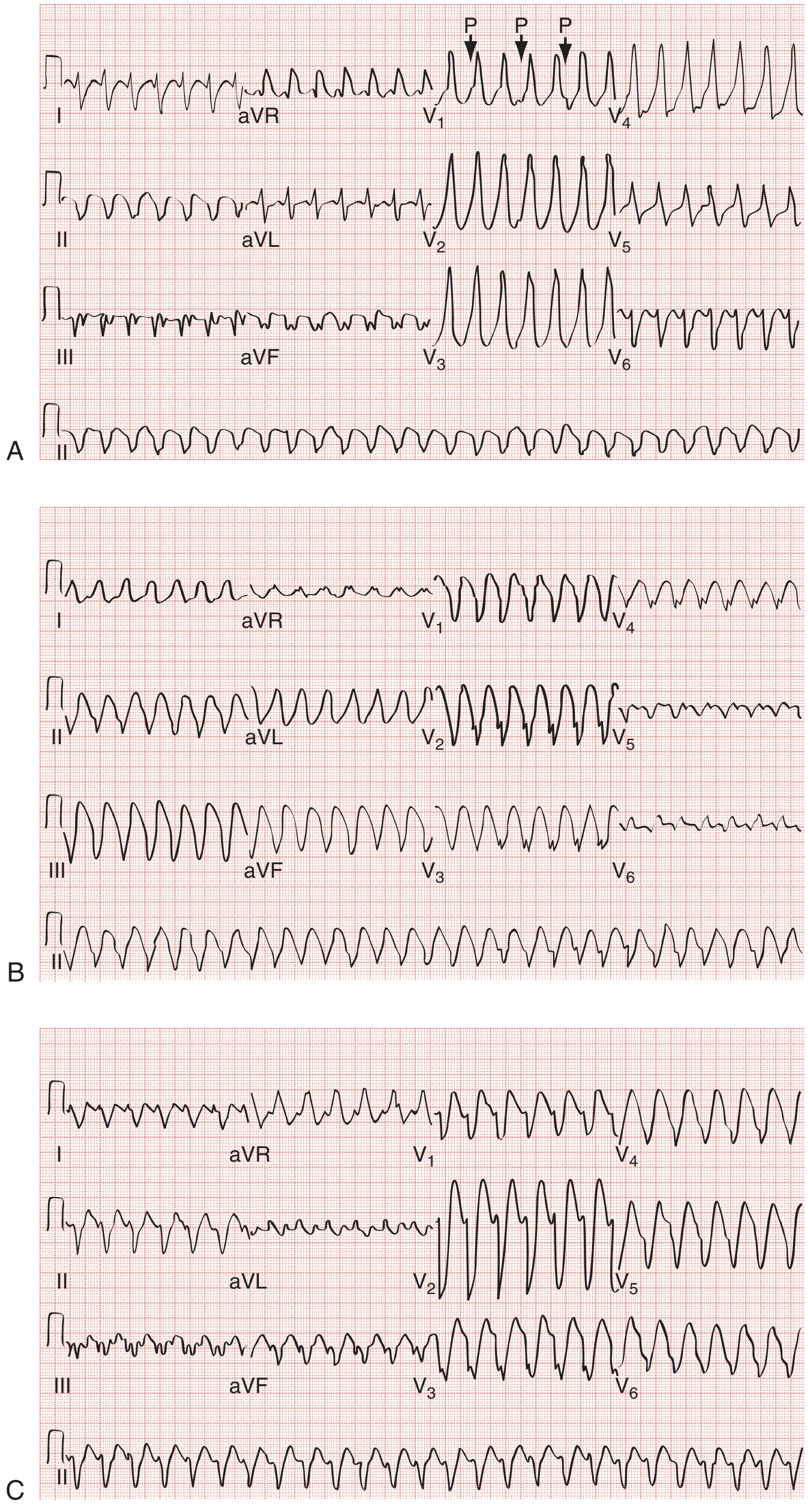


Figure 79-35. Ventricular tachycardia. **A,** RS complexes are present in chest leads, but RS duration is greater than 100 msec. Although the Brugada criteria indicate that no further analysis is necessary, atrioventricular dissociation is also evident, and QRS morphology in lead V_6 is consistent with ventricular tachycardia. **B,** Some RS complexes are present, RS duration is not greater than 100 msec, and atrioventricular dissociation is difficult to appreciate; morphologic criteria for ventricular tachycardia are fulfilled because S is notched in V_1 and QR is present in V_6. **C,** Diagnosis is based on morphologic criteria because S is notched in V_1 and V_2 and QS is present in V_6. (Courtesy Edward Curtis, MD.)

www.ketabpezeshki.com 66485457-66963820

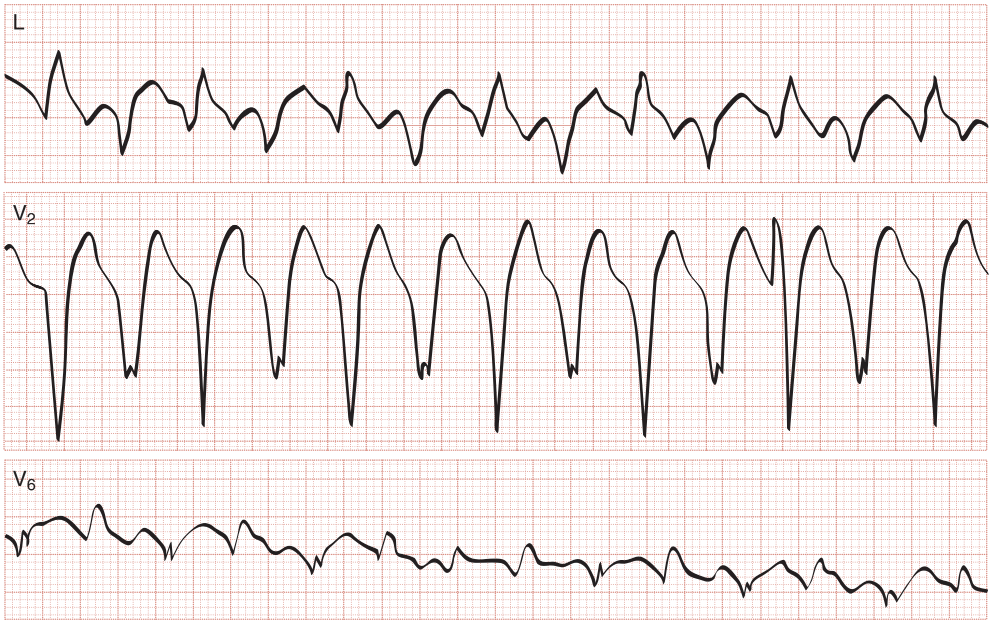


Figure 79-36. Bidirectional ventricular tachycardia in a patient with digitalis toxicity. (From Marriott HJL, Conover MB: Advanced Concepts in Dysrhythmias, 2nd ed. St Louis, Mosby, 1989.)

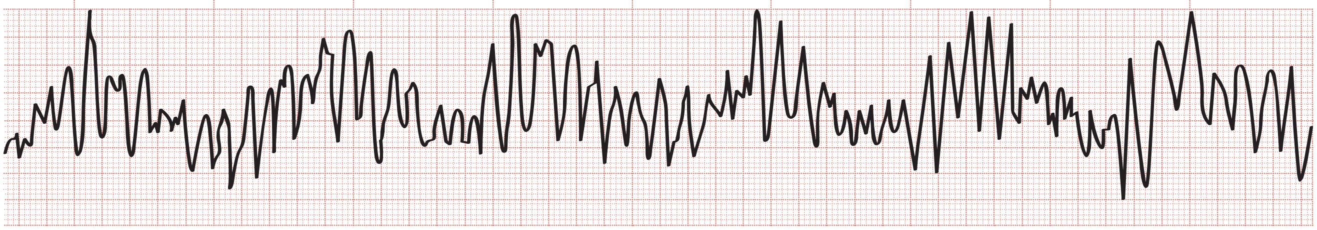


Figure 79-37. Torsades de pointes with classic spiraling of QRS complexes around baseline.

synchronized cardioversion with 100 J (biphasic preferred), with escalating doses (up to 200 J biphasic or 360 J monophasic) as needed.

All patients with new or symptomatic VT should be admitted, the exception being those who have implanted defibrillators that are functioning appropriately (see Chapter 80).

Torsades de Pointes

Torsades de pointes is literally translated as "twisting of the points" and is a paroxysmal form of polymorphic VT that meets the following clinical criteria (see Fig. 79-37):

1. Ventricular rate greater than 200 beats/min
2. Undulating QRS axis, with the polarity of the complexes appearing to shift about the baseline
3. Paroxysms of less than 90 seconds

Torsades de pointes occurs in the setting of a prolonged QT interval, a reflection of abnormal ventricular repolarization. A prolonged QT interval can be congenital or acquired. Women are at a greater risk for torsades de pointes. Acquired torsades de pointes is much more common than congenital and is termed "pause dependent," triggered by a slow heart rate.

Acquired QT prolongation is often multifactorial (Box 79-11). Common triggers include electrolyte disturbances (hypokalemia and hypomagnesemia) and many different drugs (notably class IA and IC agents but also many others; see Box 79-11), especially when used in combination. Treatment of torsades de pointes in

Box 79-11 Classification and Causes of Prolonged QT Syndromes That Produce Torsades de Pointes

Pause Dependent (Acquired)

Drug induced: Class IA and IC antidysrhythmics; many phenothiazines and butyrophenones (notably haloperidol and droperidol), cyclic antidepressants, antibiotics (especially macrolides), organophosphates, antihistamines, antifungals, antiseizure and antiemetic agents
Electrolyte abnormalities: hypokalemia, hypomagnesemia, hypocalcemia (rarely)
Diet related: starvation, low protein
Severe bradycardia or atrioventricular block
Hypothyroidism
Contrast injection
Cerebrovascular accident (especially intraparenchymal)
Myocardial ischemia

Adrenergic Dependent (Tachycardia Prompted)

Congenital

Jervell and Lange-Nielsen syndrome (deafness, autosomal recessive)
Romano-Ward syndrome (normal hearing, autosomal dominant)
Sporadic (normal hearing, no familial tendency)
Mitral valve prolapse

Acquired (Rare)

Cerebrovascular disease (especially subarachnoid hemorrhage)
Autonomic surgery: radical neck dissection, carotid endarterectomy, truncal vagotomy

www.ketabpezeshki.com 66485457-66963820

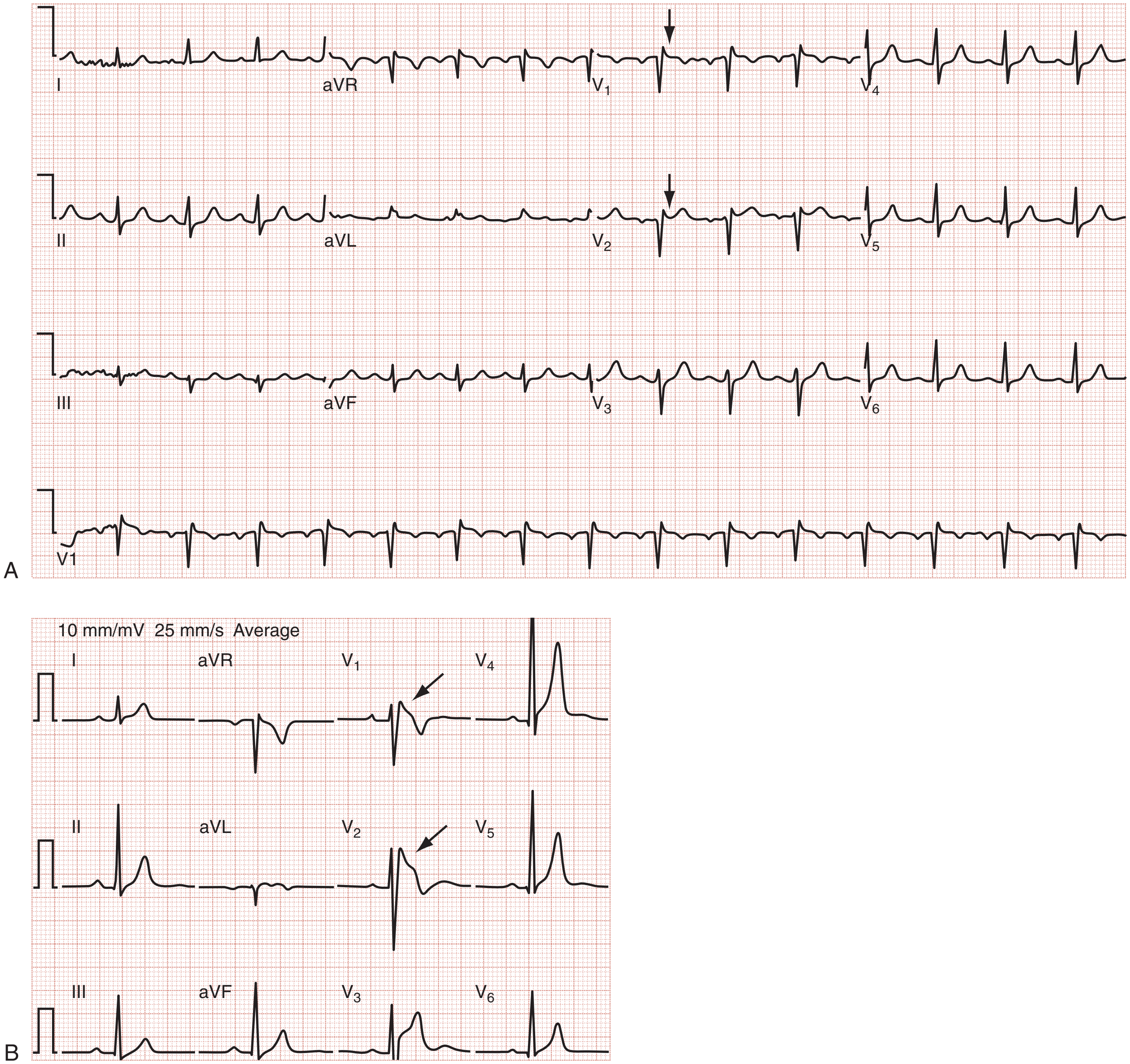


Figure 79-38. Brugada's syndrome, with ST elevation in $V_{1\text{-}2}$. The ST elevation is coved (*upper,* **A**) or "saddle back" (*lower,* **B**) and may be transient.

stable patients involves correcting any underlying metabolic or electrolyte abnormalities and increasing the heart rate to shorten ventricular repolarization. For obvious reasons, classes IA and IC antidysrhythmics are contraindicated. Intravenous magnesium sulfate should be given empirically and is effective in treating torsades de pointes even in the absence of hypomagnesemia.

A baseline ventricular rate of 100 to 120 is usually enough to prevent acquired torsades de pointes and can be achieved by overdrive pacing (i.e., external pacing at a rate greater than the patient's intrinsic rate) or via beta-adrenergic infusion. Unstable patients with sustained torsades de pointes should be electrically cardioverted as with any VT, although synchronization will not be possible.

Congenital torsades de pointes is much rarer, is triggered adrenergically or by tachycardia, and is seen in children and young adults. Patients often have syncope during exertion and a prolonged QT interval on the ECG. In contrast to acquired torsades de pointes, it is treated with agents to slow the heart rate, usually a beta-blocker.

Brugada's Syndrome

Brugada's syndrome is also associated with ventricular dysrhythmias and syncope or sudden cardiac death in the absence of structural heart disease.[22] Brugada's syndrome results from an inherited disorder of sodium channels and is most commonly present in males during young adulthood. The Brugada syndrome ECG pattern is characterized by a downward coved or humped (saddleback) ST segment elevation in leads V_1 to V_3 (Fig. 79-38), sometimes simulating an RBBB appearance. The ST segment findings may be transient or elicited only with pharmacologic stimulation.

www.ketabpezeshki.com 66485457-66963820

Any patient with unexplained syncope and a Brugada-pattern ECG requires admission for consideration of an implanted defibrillator. For patients in whom a Brugada-pattern ECG is noted incidentally, there is no consensus on treatment, but referral to a cardiologist is advisable.

KEY CONCEPTS

- Electrical therapy is used for any unstable patient in whom the rhythm is the cause of symptoms—pacing if the heart rate is slow, countershock with sedation if fast.
- A regular, new-onset, symptomatic wide-complex tachycardia should be assumed to be VT until proven otherwise.
- Type II second-degree AV block is never a normal variant and implies a conduction block below the AV node. When the conduction ratio is 2 : 1, type II block should be assumed until proven otherwise.
- The possibility of an accessory pathway should be considered in any tachycardia exceeding a rate of 200 to 250, regardless of the QRS complex morphology, and nodal blocking agents should not be used without careful consideration.
- One should look closely for irregularity in tachycardia over 200 beats/min; this and underlying atrial fibrillation can be missed if R-R intervals at fast rates are not carefully tracked.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Roden DM: Drug-induced prolongation of the QT interval. *N Engl J Med* 2004; 350:1013.
2. Nygaard TW, Sellers TD, Cook TS, DiMarco JP: Adverse reactions to antiarrhythmic drugs during therapy for ventricular arrhythmias. *JAMA* 1986; 256:55.
3. Schrickel JW, et al: Pro-arrhythmic effects of amiodarone and concomitant rate-control medication. *Europace* 2006; 8:403-407.
4. Goldschlager N, et al: A practical guide for clinicians who treat patients with amiodarone. *Heart Rhythm* 2007; 4:1250-1259.
5. Naccarelli GV, Lee KS, Gibson JK, VanderLugt J: Electrophysiology and pharmacology of ibutilide. *Am J Cardiol* 1996; 78:12-16.
6. Banchs JE, et al: Efficacy and safety of dofetilide in patients with atrial fibrillation and atrial flutter. *J Interv Card Electrophysiol* 2008; 23:111-115.
7. Singh BN, et al: Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007; 357:987-999.
8. Hohnloser SH, et al: Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009; 360:668-678.
9. Falk RH, Knowlton AA, Bernard SA, Gotlieb NE, Battinelli NJ: Digoxin for converting recent-onset atrial fibrillation to sinus rhythm: A randomized double-blinded trial. *Ann Intern Med* 1987; 106:503-508.
10. Tan HL, Spekhorst HHM, Peters RJG, Wilde AAM: Adenosine induced ventricular dysrhythmias in the emergency room. *Pacing Clin Electrophysiol* 2011; 24:450-455.
11. Sharma AD, Klein GJ, Yee R: Intravenous adenosine triphosphate during wide QRS complex tachycardia: Safety, therapeutic efficacy, and diagnostic utility. *Am J Med* 1990; 88:337.
12. Marill KA, et al: Adenosine for wide-complex tachycardia: Efficacy and safety. *Crit Care Med* 2009; 37:2512-2518.
13. Stiell IG, Macle L, CCS Atrial Fibrillation Guidelines Committee: Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Management of recent-onset atrial fibrillation and flutter in the emergency department. *Can J Cardiol* 2011; 27:38-46.
14. Burton JH, et al: Electrical cardioversion of emergency department patients with atrial fibrillation. *Ann Emerg Med* 2004; 44:20-30.
15. Scheuermeyer FX, Grafstein E, Heilbron B, Innes G: Emergency department management and 1-year outcomes of patients with atrial flutter. *Ann Emerg Med* 2011; 57:564-571.
16. Montoya PT, et al: Ventricular fibrillation in the Wolff-Parkinson-White syndrome. *Eur Heart J* 1991; 12:144-150.
17. Wellens HJ, Bar FW, Lie KI: The value of the electrocardiogram in the differential diagnosis of a tachycardia with a widened QRS complex. *Am J Med* 1977; 64:27-33.
18. Brugada P, Brugada J, Mont L, Smeets J, Andries EW: A new approach to the differential diagnosis of a regular tachycardia with a wide QRS complex. *Circulation* 1991; 83:1649-1659.
19. Griffith MJ, Garratt CJ, Mounsey P, Camm AJ: Ventricular tachycardia as default diagnosis in broad complex tachycardia. *Lancet* 1994; 343:386-388.
20. Lau EW, Ng GA: Comparison of the performance of three diagnostic algorithms for regular broad complex tachycardia in practical application. *Pacing Clin Electrophysiol* 2002; 25:822-827.
21. Herbert ME, Votey SR, Morgan MT, Cameron P, Dziukas L: Failure to agree on the electrocardiographic diagnosis of ventricular tachycardia. *Ann Emerg Med* 1996; 27:35-38.
22. Wilde AA, et al: Proposed diagnostic criteria for the Brugada syndrome: Consensus report. *Circulation* 2002; 106:2514-2519.

www.ketabpezeshki.com 66485457-66963820

Chapter 80

Implantable Cardiac Devices

James T. Niemann and Benjamin Squire

PERSPECTIVE

Electrical cardiac pacing for the management of bradyarrhythmias was first described in 1952, and permanent transvenous pacing devices were introduced into clinical practice in the early 1960s.[1] The first devices for endocardial defibrillation were implanted in surviving victims of sudden cardiac death in 1980.[2] Implanted electrical devices for the management of cardiac dysrhythmias have changed rapidly over the years, with both increasing complexity and miniaturization. Survey data from 2002 indicated that approximately 612 new pacemakers per million population were implanted in the United States.[3] Indications for the use of permanent pacemakers in the management of congenital and acquired heart disease include cardiac resynchronization therapy for heart failure.[4-6]

A number of large clinical trials comparing implantable cardioverter-defibrillators (ICDs) with antiarrhythmic drugs for the prevention of sudden cardiac death resulting from ventricular dysrhythmias have indicated that ICDs significantly improve survival.[7,8] Such studies have led to a dramatic increase in ICD implantations, and it is estimated that there are more than 125,000 new ICD implants annually in the United States.[9] The widespread use of these devices ensures that the emergency physician frequently encounters such patients, often with symptoms that may be related to malfunction of the pacemaker or ICD.

INDICATIONS FOR PERMANENT PACEMAKERS AND ANTIARRHYTHMIA DEVICES

Guidelines for the implantation of these devices have been developed by a joint task force of the American Heart Association (AHA) and the American College of Cardiology (ACC) and are periodically updated.[10] With use of an evidence-based approach, recommendations are categorized as class I, II, or III. Class I includes conditions for which there is general agreement that a device should be implanted. A class II recommendation includes conditions for which these devices are frequently used but for which there is disagreement about their need or benefit. Class III is reserved for conditions for which there is general agreement that a device is not needed.

In the case of pacemaker therapy, additional factors are considered when selecting the mode of pacing and include, but are not limited to, overall health, lifestyle, and occupation of the patient. Class I indications for a permanent pacemaker or ICD are listed in Boxes 80-1 and 80-2. In general, pacing is recommended for patients with symptomatic heart block, symptomatic sinus bradycardia, and atrial fibrillation with a symptomatic bradycardia (low ventricular response rate) in the absence of medications that affect atrioventricular (AV) conduction. Controversial indications include pacing in patients with syncope, heart block, or fatigue in the presence of some conduction disease or bradycardia. The likelihood of a patient's improvement after pacing can be assumed only if the symptoms can be closely correlated with inadequate rate.

Pacemaker Terminology

A letter code, initially established in 1974 and revised as technology advances, standardizes nomenclature for pacemakers.[11] Table 80-1 includes an explanation of the five-letter code scheme and the standard abbreviations in each category. The first three code letters are used most commonly. Using this table, one should be able to understand the features of any pacing mode. For example, a VDD pacemaker is capable of pacing only the ventricle, sensing both atrial and ventricular intrinsic depolarization, and responding by dual inhibition of both atrial and ventricular pacing if intrinsic ventricular depolarization occurs; a paced ventricular beat is triggered in response to a sensed intrinsic atrial depolarization. The codes of a permanent pacemaker that are used most frequently and the indications, advantages, and disadvantages of each are listed in Table 80-2. Detailed algorithms for matching a patient with a pacemaker exist.[10] The majority of permanent pacemakers are dual chamber and often rate adaptive.[12]

Pacemaker Components

All pacemaker systems have three basic components: the pulse generator, which houses the power source (battery); the electronic circuitry; and the lead system, which connects the pulse generator to the endocardium.

Nearly all implanted pacemakers are lithium powered. Lithium-powered pulse generators function normally for 4 to 10 or more years, depending on the pacemaker features, such as single versus dual chamber, pacing threshold, and rate adaptiveness. This long "battery life" and the fact that the output voltage of the lithium-iodine cell decreases gradually rather than abruptly, as occurred with the early mercury-zinc cell, make sudden pulse generator failure an unlikely cause of pacemaker malfunction.

Permanent pacemakers have endocardial leads that are positioned in contact with the endocardium of the right ventricle and, in the case of a dual-chamber device, the right atrium, with a subclavian or cephalic vein approach used for insertion. Occasionally, an epicardial lead may be implanted during open-heart surgery performed for another indication, such as prosthetic valve insertion or correction of a congenital cardiac defect. Pacemaker leads, like power sources, continue to undergo major technical

www.ketabpezeshki.com 66485457-66963820

improvements.[1] Innovations include resilient plastic insulation surrounding the electrodes that reduces the chance of complete lead disruption or breakage (resulting in failure to pace or sense) and the chance of partial fracture (resulting in a "make or break" contact with intermittent failure to sense or pace). Despite these advances, problems with the electrical circuitry remain the most common cause of pacemaker malfunction.[13] A lead capable of active fixation is more commonly used in patients with cardiomyopathies and right ventricular dilation complicated by tricuspid regurgitation.

Pacemaker leads may be either bipolar or unipolar in configuration. A bipolar endocardial lead has both the negative (distal) and the positive (proximal) electrodes, separated by approximately 1 cm, within the heart. A unipolar lead has the negative electrode in contact with the endocardial surface, and the positive pole is the metallic casing of the pulse generator. Each lead system has potential advantages and disadvantages.[1] The unipolar configuration is not compatible with ICD systems and is prone to oversensing of myopotentials and electromagnetic interference but is of smaller diameter and less susceptible to fracture. The bipolar configuration is compatible with ICD systems but is larger and more prone to lead fractures. Oversensing, however, is rarely a problem. The selection of lead configuration usually depends on the experience and preference of the operator.

Box 80-1 Class I Indications for Permanent Pacing in Adults

1. Third-degree and advanced second-degree AV block at any anatomic level associated with any of the following:
   - Symptomatic bradycardia (including heart failure) or ventricular dysrhythmia presumed to be a result of AV block
   - Symptomatic bradycardia secondary to drugs required for dysrhythmia management or other medical condition
   - Documented periods of asystole lasting more than 3 seconds or an escape rate of less than 40 beats/min or an escape rhythm originating below the AV node in an awake, asymptomatic patient in sinus rhythm
   - Awake, asymptomatic patients with atrial fibrillation and bradycardia a documented pause of 5 seconds or longer
   - After catheter ablation of the AV node
   - Postoperative AV block that is not expected to resolve
   - Neuromuscular disease with AV block (e.g., the muscular dystrophies)
2. Symptomatic bradycardia resulting from second-degree AV block regardless of type or site of block
3. Asymptomatic, persistent third-degree AV block with awake ventricular rate over 40 beats/min with cardiomegaly or left ventricular dysfunction or if block is below AV node
4. Chronic bifascicular or trifascicular block with intermittent third-degree AV block or type II second-degree AV block
5. Second or third-degree AV block with exercise in the absence of myocardial ischemia

AV, atrioventricular.

Box 80-2 Class I Indications for Implantable Cardioverter-Defibrillator Therapy

1. Cardiac arrest resulting from VF or VT not caused by a transient or reversible event
2. Spontaneous sustained VT
3. Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiologic study when drug therapy is ineffective, not tolerated, or not preferred
4. Nonsustained VT with coronary artery disease, prior myocardial infarction, left ventricular dysfunction, and inducible VF or sustained VT at electrophysiologic study that is not suppressible by a class I antiarrhythmic drug

VF, ventricular fibrillation; *VT,* ventricular tachycardia.

Table 80-1 Five-Letter Pacemaker Code

Letter 1	*Letter 2*	*Letter 3*	*Letter 4*	*Letter 5*
CHAMBER PACED	CHAMBER SENSED	SENSING RESPONSE	PROGRAMMABILITY	ANTITACHYCARDIA FUNCTIONS
A = atrium	A = atrium	T = triggered*	P = simple	P = pacing
V = ventricle	V = ventricle	I = inhibited	M = multiprogrammable	S = shock
D = dual	D = dual	D = dual (A and V inhibited)	R = rate adaptive	D = dual (shock pace)
O = none	O = none	O = none	C = communicating O = none	

*In the triggered response mode, the pacemaker discharges or fires when it recognizes an intrinsic depolarization. As a result, pacemaker spikes occur during inscription of the QRS complex. Because this mode results in high energy consumption and a shortened battery life and because the sensing response can be misinterpreted as pacemaker malfunction, this sensing mode is not used with modern pacemakers.

Table 80-2 Common Permanent Pacemakers

CODE	INDICATION	ADVANTAGES	DISADVANTAGES
VVI	Intermittent backup pacing; inactive patient	Simplicity; low cost	Fixed rate; risk of pacemaker syndrome
VVIR	Atrial fibrillation	Rate responsive	Requires advanced programming
DDD	Complete heart block	Atrial tracking restores normal physiology	No rate responsiveness; requires two leads and advanced programming
DDDR	Sinus node dysfunction; for rate responsiveness atrioventricular block and need	Universal pacer; all options available by programming	Complexity, cost, programming, and follow-up evaluation

www.ketabpezeshki.com 66485457-66963820

The Standard Electrocardiogram during Normal Cardiac Pacing

The modern pacemaker has two basic functions: to stimulate the heart electrically and to sense intrinsic cardiac electrical activity. Additional functions are available and are noted in the pacemaker code system (see Table 80-1, letters 4 and 5). The pacemaker delivers an electrical stimulus to either the atrium or the ventricle if it does not recognize (sense) any intrinsic electrical activity from that chamber after a selected time interval. This interval is usually programmed at the time of implantation and can be changed noninvasively at a later time, if necessary, with use of a programming and "interrogating" device provided by the pacemaker manufacturer. If the pacemaker recognizes or senses an intrinsic atrial depolarization (P wave) or ventricular depolarization (QRS complex), it inhibits or resets its output to prevent competition with the underlying intrinsic rhythm. The stimulus intensity and sensing threshold (amplitude of electrical activity that is detected as being intrinsic) are typically set at the time of implantation but can also be reprogrammed later.

The two basic functions of a pacemaker can be easily recognized and confirmed on a standard 12-lead electrocardiogram (ECG) or rhythm strip. The normal function of a single-chamber VVI pacemaker is most easily recognized (Fig. 80-1). After a programmed interval is surpassed during which intrinsic ventricular activity does not occur, a pacer "spike" or stimulus artifact appears. The pacer spike is a narrow deflection that is usually less than 5 mm in amplitude with a bipolar lead configuration and usually 20 mm or more in amplitude with a unipolar lead. A wide QRS complex appears immediately after the stimulus artifact. Depolarization begins in the right ventricular apex, and the spread of excitation does not follow normal conduction pathways. Characteristically, a left bundle branch block conduction pattern is seen. A right bundle branch pattern is abnormal and suggests lead displacement. In VVI pacing the paced QRS complexes are independent of intrinsic atrial depolarization if present (AV dissociation).

The recognition of normal dual-chamber pacing is more complex owing to the interactive sensing and pacing of the right atrium and ventricle (Fig. 80-2).[14] Pacing intervals are preprogrammed, may be changed noninvasively at a later time, and are generally specific to the patient's needs. Pacing rates and delay intervals typically vary from patient to patient. Dual-chamber devices are typically used in patients with nonfibrillating atria

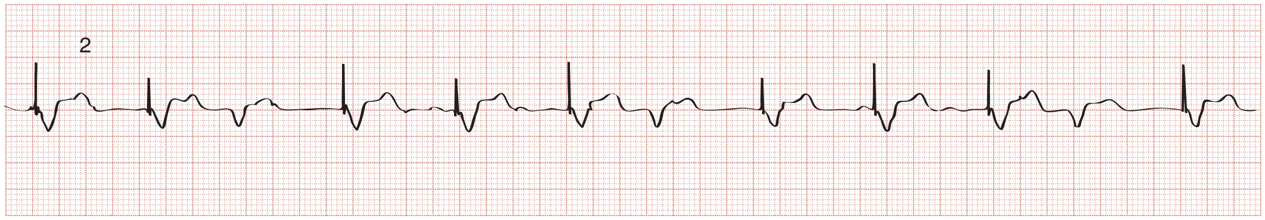


Figure 80-1. Normal VVI pacemaker (rhythm strip). This rhythm strip was recorded in a patient with a VVI pacemaker implanted for the treatment of symptomatic complete heart block. The pacing rate is approximately 75 beats/min (determined by measuring the time between consecutive pacemaker spikes). Each pacemaker spike is followed by a paced QRS complex. The third QRS from the left has a slightly different morphology than the paced QRS complexes. It is an intrinsic QRS complex that is sensed by the pacemaker, and a paced beat does not occur again until the programmed rate of the pacemaker is exceeded. The time interval between the spontaneous QRS and the next paced beat is approximately the same as the interval between consecutive pacemaker spikes. This sequence is subsequently repeated twice on this strip.

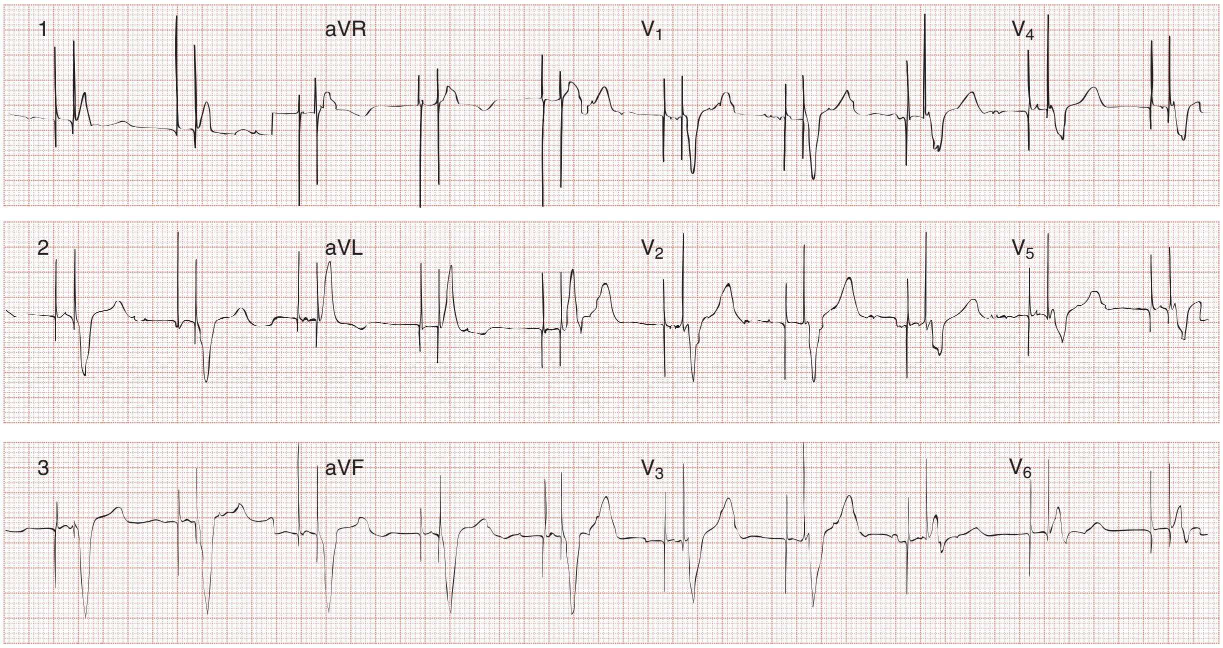


Figure 80-2. Normal DDD pacemaker (12-lead electrocardiogram). Each QRS complex is preceded by two pacemaker spikes. The first spike results in atrial depolarization, and the second produces a wide QRS complex. The QRS complex is conducted with a left bundle branch morphology, which is expected with endocardial pacing at the right ventricular apex.

www.ketabpezeshki.com 66485457-66963820

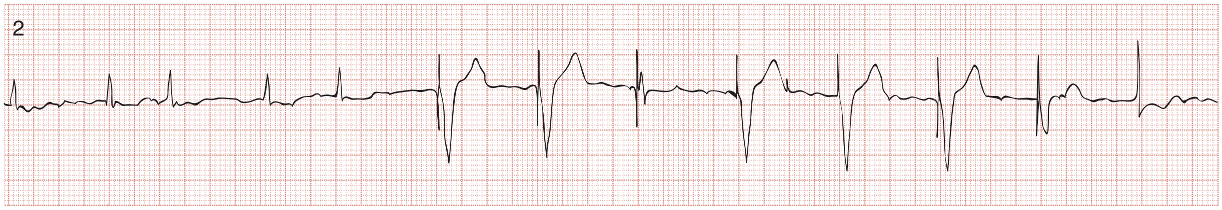


Figure 80-3. VVI pacemaker with fusion beats (pseudomalfunction). This VVI pacemaker was implanted in a patient with atrial fibrillation and intermittent symptomatic complete heart block. In the lead II rhythm strip, the first five QRS complexes are normal in morphology and irregular, as would be expected in atrial fibrillation. The next two QRS complexes are wide and preceded by a pacemaker spike. This represents normal sensing and pacing. The eighth QRS complex is narrow but preceded by a pacemaker spike. The spikes occur at a fixed and regular interval. In this instance, spontaneous ventricular depolarization had begun at approximately the time the pacemaker discharged. The 12th QRS complex in the sequence represents a fusion beat. Within the QRS complex of the 13th beat, a pacemaker spike is visible. Again, this represents nearly simultaneous conduction of a supraventricular beat and pacemaker electrical discharge. At first glance, this may appear to be failure to sense; however, the pacemaker is functioning normally and competing with the underlying rhythm.

coupled with intact AV conduction. A normal-appearing QRS complex may follow an intrinsic "P" wave as a result of normal sinoatrial node discharge if the intrinsic atrial depolarization is conducted to the ventricles. The intrinsic p wave and QRS complex inhibit the atrial and ventricular circuitry. A normal QRS complex follows a paced p wave if the paced atrial beat is conducted through the AV node and the programmed AV delay period is not exceeded. If it is not conducted to the ventricles (AV delay period exceeded), the pacemaker stimulates the ventricle, resulting in a paced p wave and a wide, paced QRS complex with left bundle branch block configuration.

Recognition of the interactivity of the paced chambers is important. A paced p wave may be mistaken for failure to sense or pace, and malfunction may be diagnosed when it is not present (pseudomalfunction). In addition, if the programmed rate of the pacemaker approximates the patient's intrinsic heart rate, fusion of paced and native beats may occur and represents another common type of pseudomalfunction (Fig. 80-3).

Complications of Implantation

Infection

Pacemaker implantation is a surgical procedure and, like all surgery, carries a risk of infection; the presence of a foreign body enhances this risk. The incidence of infection is small—approximately 2% for wound and subcutaneous pacemaker "pocket" infection and approximately 1% for bacteremia with sepsis. The presence of a foreign body complicates management, and few cases of bacteremia that develop after implantation can be managed with antibiotics alone. In most instances, reimplantation and replacement of the lead system are necessary.[15]

Pain and local inflammation at the site of the pacemaker are the first manifestations of a wound infection, cellulitis, or pocket infection. Approximately 20 to 25% of patients with a local infection have positive blood cultures. Bacteremia may occur in the absence of a focal infection and may arise with the typical manifestations of the systemic inflammatory response syndrome or sepsis. A hematoma of the pacemaker pocket may mimic a wound or pocket infection. Needle aspiration of the pocket should be done only under fluoroscopy because the needle may cut the insulation surrounding the pulse generator or the portion of the pacemaker lead that lies within the pacemaker pocket.

When a local infection or bacteremia is suspected, blood cultures should be obtained and intravenous antibiotic therapy initiated. *Staphylococcus aureus* and *Staphylococcus epidermidis* are isolated in approximately 60 to 70% of cases. Empirical antibiotic therapy should include vancomycin pending culture and sensitivity data. If blood cultures are positive, the pulse generator and pacemaker lead are usually removed, temporary transvenous pacing is performed, and intravenous antibiotic therapy is continued for 4 to 6 weeks. The permanent pacemaker and lead are subsequently reimplanted.[15]

Thrombophlebitis

The incidence of venous obstruction associated with permanent transvenous pacemakers ranges from 30 to 50%, with approximately one third of patients having complete venous occlusion.[16] Thrombosis of varying degrees can involve the axillary, subclavian, and innominate veins or the superior vena cava (SVC). The site of insertion does not appear to affect the incidence of this complication. Chronic thrombosis of the veins of the upper arm is common and usually asymptomatic owing to extensive venous collateral circulation.

Because of extensive collateralization, only approximately 0.5 to 3.5% of patients develop symptoms usually indicative of acute thrombosis. These patients typically have edema, pain, and venous engorgement of the arm ipsilateral to the site of lead insertion. Although rare, SVC syndrome resulting from pacemaker lead-induced thrombosis occurs. The symptoms and signs of lead-induced SVC syndrome are identical to those described in patients with SVC syndrome and malignancy. Whether pulmonary embolism is associated with pacemaker therapy and thrombosis is controversial.

Although symptoms might suggest thrombosis, definitive diagnosis of acute thrombosis usually requires duplex sonography of the jugular venous system or contrast-enhanced computed tomography. The symptoms typically respond to intravenous heparin therapy followed by long-term warfarin administration. Directed thrombolytic therapy is most effective if used early in management (within 7-10 days).

The "Pacemaker Syndrome"

After pacemaker implantation, a patient may develop new complaints or report a worsening of the symptoms that prompted evaluation and eventual pacemaker therapy. Such complaints often include syncope or near-syncope, orthostatic dizziness, fatigue, exercise intolerance, weakness, lethargy, chest fullness or pain, cough, uncomfortable pulsations in the neck or abdomen, right upper quadrant pain, and other nonspecific symptoms.

These symptoms are termed the *pacemaker syndrome.*[17] The cause of this syndrome is the loss of AV synchrony and the presence of ventriculoatrial conduction, and it is most commonly encountered in the setting of VVI pacing. It is also described with the DDI mode. With VVI pacing, the ventricle is electrically stimulated and depolarized, resulting in ventricular systole. If sinus

www.ketabpezeshki.com 66485457-66963820

node function is intact, the atria can be depolarized by a sinus impulse and contract when the tricuspid and mitral valves are closed. This contractile asynchrony results in an increase in jugular and pulmonary venous pressures and may produce symptoms of congestive heart failure.

Atrial distention can result in reflex vasodepressor effects mediated by the central nervous system. Elevated levels of B-type natriuretic peptide and diuresis are considered markers for the syndrome in its more severe form. If the contribution of atrial contraction to late diastolic ventricular filling is important in maintaining an adequate cardiac output, basal and orthostatic hypotension may occur. DDI pacing in a patient with AV block may result in this syndrome if the sinus node discharge rate exceeds the programmed rate of the pacemaker.

Approximately 20% of patients report symptoms suggesting the pacemaker syndrome after pacemaker insertion. In most instances, symptoms are mild and patients adapt to them. In approximately one third of these patients, symptoms are severe. Treatment usually requires replacing a VVI pacemaker with a dual-chamber pacemaker or lowering the pacing rate of the VVI unit. If symptoms occur in a patient paced in the DDI mode, optimizing the timing of atrial and ventricular pacing is usually required. Patients appear to prefer dual-chamber pacing to the VVI modality.[18] Persistence or worsening of symptoms of congestive heart failure may also be caused by the altered ventricular activation sequence inherent with stimulation of the right ventricle.[19] Biventricular pacing may be required in selected patients.

Although the pacemaker syndrome may be suspected in the ED in the patient with suggestive symptoms soon after pacemaker implantation, consultation with a cardiologist for interrogation of the pacemaker is recommended. The same symptoms may be observed in patients with true pacemaker malfunction, which may necessitate pacemaker reprogramming or replacement of the pulse generator or pacemaker lead.

Pacemaker Malfunction

The term *pacemaker malfunction* refers specifically to problems with the circuitry or power source of the pulse generator, the pacemaker lead (most commonly displacement or fracture), or the interface between the pacing electrode and the myocardium (pacing or sensing threshold). In addition, environmental factors, such as extracardiac or extracorporeal electrical signals, may interfere with normal pacemaker function.[20,21] With use of the standard ECG, pacemaker malfunction can be separated into three broad categories: (1) failure to capture (no pacemaker spikes or spikes not followed by an atrial or ventricular complex), (2) inappropriate sensing (oversensing or undersensing spikes occur prematurely or do not occur even though the programmed interval is exceeded), or (3) inappropriate pacemaker rate. Symptomatic pacemaker malfunction after implantation occurs in less than 5% of patients and is rarely immediately life-threatening. Malfunction is most commonly a result of inappropriate sensing, followed by failure to capture.[17] Typical presentations and causes of pacemaker malfunction are listed in Box 80-3.

In the context of suspected pacemaker malfunction, knowledge of the pacing modalities (see Table 80-1) and what is normal for a given pacing modality are critical when the ECG is reviewed. Fortunately, patients are provided with important identifying information, usually in the form of a wallet card, after pacemaker implantation. The most important information is provided in the five-letter code. If this information is not available, a standard posteroanterior and a lateral chest radiograph can provide critical information. A single lead in the apex of the right ventricle indicates a VVI pacemaker. With VVI pacing, only one stimulus artifact or spike is seen with each stimulated ventricular depolarization (see Fig. 80-1). If sinus node activity is present, the paced QRS complex is dissociated from the intrinsic P waves. If separate leads are identified in the right atrium and right ventricle, the pacing modality is most often DDD or DVI, and paced p waves and QRS complexes (two spikes for each QRS complex) are seen (see Fig. 80-2). Although DDD and DVI units are capable of pacing both the right atrium and the right ventricle, only one spike may be seen (Fig. 80-4). Failure to identify two spikes with a DDD or DVI unit can represent normal pacemaker function.

A magnet placed externally over the pulse generator is frequently used in the assessment of pacemaker function. Magnet application causes closure of a reed switch within the pacemaker circuitry, converting the pacemaker to an asynchronous or fixed-rate pacing mode, and the pacemaker is no longer inhibited by the patient's intrinsic electrical activity. The technique is most commonly used when the patient's intrinsic heart rate exceeds the pacemaker's set rate and pacemaker function is inhibited. Magnet application then allows pacing to occur, despite the patient's native cardiac activity, and pacing rate and the presence of capture can be determined. Magnets are made by each manufacturer, but any cardiac pacemaker magnet will typically activate the reed switch within any of the devices.

Box 80-3 Causes of Pacemaker Malfunction

Failure to Capture
- Lead disconnection, break, or displacement
- Exit block
- Battery depletion

Undersensing
- Lead displacement
- Inadequate endocardial lead contact
- Low-voltage intracardiac P waves and QRS complexes
- Lead fracture

Oversensing
- Sensing extracardiac signals: myopotentials
- T wave sensing

Inappropriate Rate
- Battery depletion
- Ventriculoatrial conduction with pacemaker-mediated tachycardia
- 1 : 1 response to atrial dysrhythmias

Failure to Capture

Failure to capture may range from the complete absence of pacemaker spikes to spikes not followed by a stimulus-induced complex (Fig. 80-5). A complete absence of pacemaker spikes may result from battery depletion, fracture of the pacemaker lead, or disconnection of the lead from the pulse generator unit.

Current lithium-iodine batteries are not subject to sudden power failure, and they display typical end-of-life functional changes over a period of months to a year before complete depletion.[1] Usually the first sign of voltage depletion is a decrease in the programmed pacing rate. This change is gradual and should be detected during the regular follow-up evaluations that pacemaker patients receive. When voltage output falls to a critical level, stimulus strength falls below the required threshold, and failure to capture or intermittent failure to capture may be observed late in battery life. As a result, urgent or emergent battery replacement is rare.

Failure to capture, which may be complete or intermittent, is most commonly a lead problem. Lead displacement is the most common cause and is most likely to occur within the first month of pacemaker insertion. The chest radiograph may demonstrate

www.ketabpezeshki.com 66485457-66963820

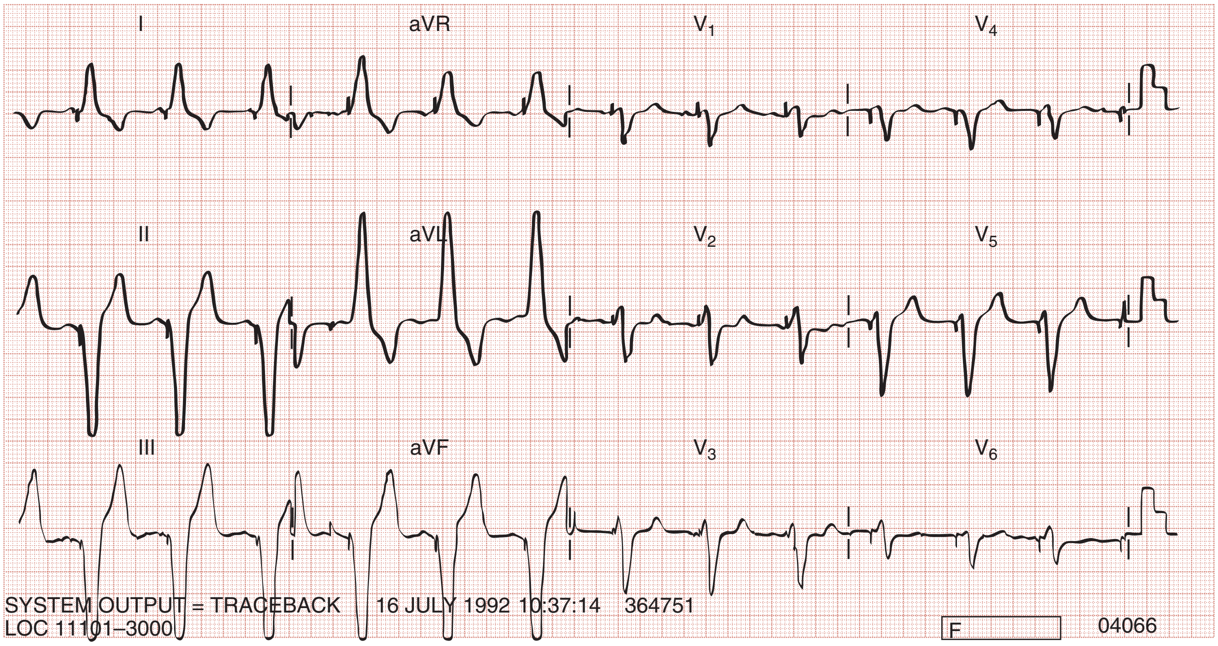


Figure 80-4. Normal DDD pacemaker (half-standard 12-lead electrocardiogram [ECG]). Three paced QRS complexes preceded by a stimulus artifact or spike are evident in leads I, II, and III. Paced QRS complexes occur after spontaneous or intrinsic P waves are sensed and atrioventricular (AV) conduction delay exceeds the pacemaker's programmed AV interval. The first QRS complex in the augmented leads, best seen in lead aVF, demonstrates both a paced P wave and a paced QRS complex. Although the pacemaker is a dual-chamber device, two spikes may not always be seen preceding every QRS complex, and the presence of only one spike, or no spikes, should not be interpreted as evidence of pacemaker malfunction. Also evident on this ECG are the different amplitudes of the pacemaker spikes from lead to lead. When a single-lead rhythm strip is recorded, the selected lead should be the one in which the pacemaker spikes are most easily identified.

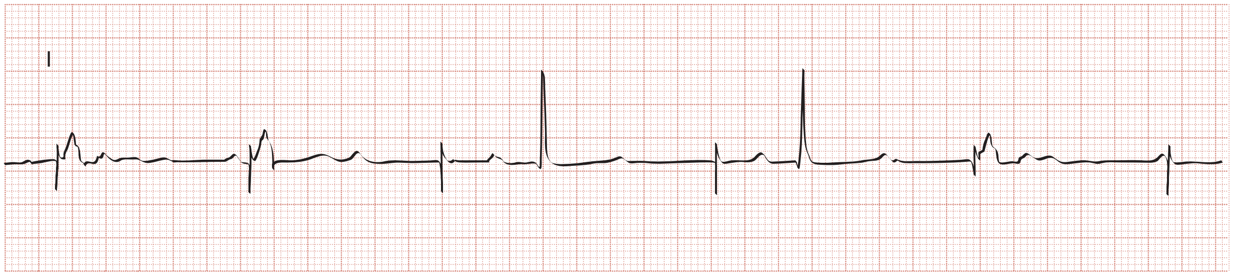


Figure 80-5. Intermittent failure to capture and slow pacing rate (lead I). This lead I rhythm strip demonstrates intermittent failure to capture of a VVI pacemaker. The first and second pacemaker spikes are followed by wide-paced QRS complexes; the third and fourth spikes are not. The pacemaker spikes occur at a rate of approximately 50/min. The device was programmed to pace at a rate of 75/min. This is a typical example of "end-of-life" pacing characteristics of a depleted battery.

the tip of the pacing catheter displaced from the right ventricular apex. The catheter tip is commonly found in the pulmonary outflow tract, where it may have intermittent contact with endocardium, resulting in intermittent failure to pace and sense. The atrial leads of dual-chamber devices are commonly displaced into the body of the right atrium, resulting in loss of contact between the pacing lead and the atrial endocardium.

Lead fracture, which is uncommon with the current polyurethane lead coating,[1] produces an insulation break, resulting in failure to capture as a result of current leakage. It can be detected as a change in pacing threshold during pacemaker interrogation. Lead fractures occur at predictable locations, usually at the site of attachment to the pulse generator or at abrupt angulations that serve as stress points. Inadequate contact of the lead with the pulse generator can mimic a lead fracture. Occasionally, when a lead fracture is complete or nearly complete, a break in the catheter or its insulation can be detected on an overpenetrated posteroanterior chest radiograph. Loss of lead-pulse generator contact can be detected on the chest radiograph with close inspection of the pulse generator.

Exit block (the failure of an adequate stimulus to depolarize the paced chamber) can also result in failure to pace. Exit block should be considered when the preprogrammed pacing stimulus output fails to result in capture in the presence of a normally functioning pulse generator and an intact lead system. This problem is most commonly a result of changes in the endocardium in contact with the pacing system. Causes include ischemia or infarction of the endocardium in contact with the electrodes; systemic hyperkalemia; and the use of class III antiarrhythmic drugs, such as amiodarone, which affect ventricular depolarization. Although other drugs alter pacemaker threshold, the effect is small and is rarely clinically important.[20] At the time of pacemaker insertion, stimulus strength, defined as the amplitude and duration of the electrical output, is always set above the minimum required to result in an artificial electrical depolarization.

Inappropriate Sensing

For a pacemaker to function in a noncompetitive mode, it must be capable of sensing the intrinsic or "native" electrical activity of

www.ketabpezeshki.com 66485457-66963820

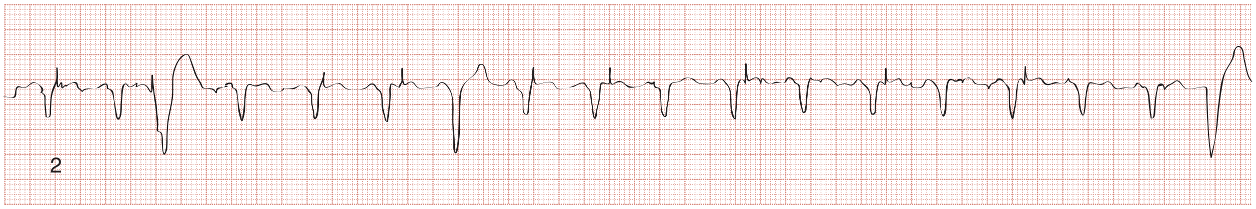


Figure 80-6. Failure to sense or undersensing (lead II). Pacemaker spikes are evident during inscription of the ST segment on this rhythm strip. These spikes do not produce QRS complexes because they occur during the ventricular refractory period of the preceding spontaneous QRS complex. The third QRS complex on the strip is a paced QRS complex. The device is capable of capture but is undersensing the spontaneous rhythm.

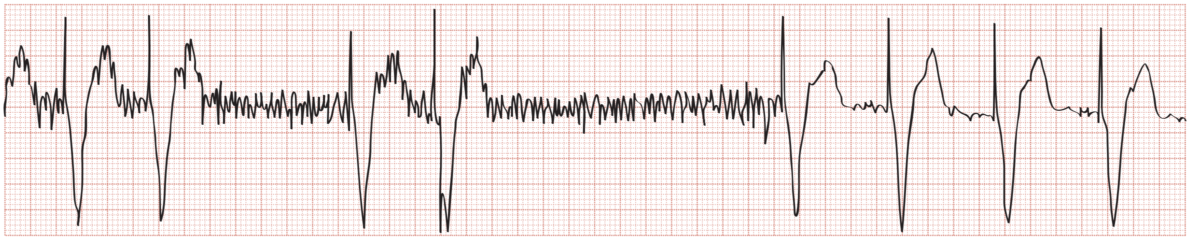


Figure 80-7. Oversensing (lead II). This VVI unipolar lead pacemaker is oversensing myopotentials produced by contraction of the pectoralis major. Myopotentials result in the undulating and irregular baseline seen in the middle of the strip. After muscular contraction ceases, normal pacing resumes (last four complexes on the strip).

the heart. The electrical activity that is sensed is determined by the pacing modality (see Table 80-1). Sensing parameters are determined at the time of pacemaker insertion on the basis of the signal size of the intracardiac ECG and can be changed or fine-tuned externally at a later time if needed.

Undersensing

Failure to sense may be complete or intermittent. It may result from a change in the sensing parameters selected at the time of insertion. This is most commonly encountered after acute right ventricular infarction or during the progressive fibrosis that accompanies many cardiomyopathies, causing intracardiac signals to decrease in amplitude. Lead displacement, fracture, and poor contact with the endocardium may also cause undersensing.

Undersensing is typically recognized electrocardiographically as the appearance of pacemaker spikes occurring earlier than the programmed rate. The spike may or may not be followed by a paced complex, depending on when it occurs during the cardiac refractory period (Fig. 80-6). Failure of a stimulus spike to produce a complex when it occurs during the atrial or ventricular refractory period should not be interpreted as failure to pace.

Oversensing

In rare instances the pacemaker may detect electrical activity that is not of cardiac origin. The result may be intermittent, irregular pacing or an apparent complete absence of pacemaker function. Myopotentials produced by the pectoralis muscle (Fig. 80-7) and extracorporeal electrical signals are frequently oversensed when a unipolar lead system is used. T waves that follow an intrinsic ventricular depolarization are the most common oversensed cardiac signals. Common medical sources of electrical interference include electrocautery, which can cause temporary pacemaker inhibition, and magnetic resonance imaging, which can alter pacemaker circuitry and result in fixed-rate or asynchronous pacing. Electromagnetic interference resulting from close proximity to a microwave oven should not cause pacemaker problems with currently implanted pacemaker units. Interference can be caused by the use of a digital cellular phone.[20,21] These devices may cause pacemaker inhibition, inappropriate ventricular tracking, or asynchronous pacing. Malfunction is most commonly seen when the phone is within 10 cm of the pulse generator and often occurs when the phone is applied to the ear ipsilateral to the site of the pacemaker pocket.

Inappropriate Pacemaker Rate

A pacing rate below the programmed rate is a typical finding in pulse generator depletion and does not occur abruptly with lithium-iodine batteries. An extreme increase in pacing rate, the so-called "runaway pacemaker," is rarely, if ever, encountered with current pacemaker technology and circuitry in which upper rate limits are set (typically 140 beats/min). An "endless loop" tachycardia may develop during dual-chamber pacing when ventriculoatrial conduction occurs, and the resulting retrograde atrial depolarization results in a stimulated or paced ventricular depolarization.[22] If atrial flutter develops during dual-chamber pacing, flutter waves may be sensed and tracked, resulting in a rapid, paced ventricular rate. In both instances, the ventricular rate does not exceed its set upper limit. Patients with such rhythms may complain only of palpitations or symptoms of hemodynamic compromise. When such rhythms are detected, magnet application usually converts the pacemaker to a fixed rate in a competitive mode and terminates the tachyarrhythmia.

Management

History

The patient should be asked for the pacemaker identification card. The information on the card explains why a pacemaker was placed and the pacing modality used.

Most patients with pacemaker malfunction have symptoms reminiscent of those that prompted pacemaker therapy: syncope, near-syncope, orthostatic dizziness, lightheadedness, dyspnea, or palpitations.

The majority of pacemaker complications and most instances of pacemaker malfunction occur within the first few weeks or months of pacemaker implantation. After wound healing,

www.ketabpezeshki.com 66485457-66963820

palpation of the pulse generator site should not elicit tenderness. A wound infection or pocket infection typically arises with localized pain. Bacteremia secondary to infection of the pacing catheter, however, may arise only with fever and without other manifestations of the systemic inflammatory response syndrome. Pain in the arm ipsilateral to the site of insertion should suggest acute thrombophlebitis.

Patients who develop the pacemaker syndrome secondary to the loss of AV synchrony may have nonspecific complaints of easy fatigability, generalized weakness, dyspnea, or an uncomfortable fluttering or "pounding" sensation in the neck or abdomen. Syncope or near-syncope may also occur, but these complaints should prompt an evaluation for true pacemaker malfunction. The pacemaker syndrome should be a diagnosis of exclusion.

Physical Examination

A pacemaker infection should be suspected in the presence of fever, even if another potential source of infection can be identified. Extremely low (<60 beats/min) or high (>100 beats/min in the resting patient) pulse rates are suggestive of altered pacing parameters (battery depletion or pacemaker-mediated tachycardias). Hypotension may be present in either instance. Cannon "A" waves on inspection of the jugular venous pulse wave indicate AV asynchrony. Auscultation of lungs may reveal bibasilar rales if congestive heart failure is present.

During pacing, the first heart sound may vary in intensity as a result of AV dissociation (VVI mode), and the second heart sound may be paradoxically split when ventricular pacing occurs (the right ventricle is activated first). A pericardial friction rub may also be heard if the tip of the pacing catheter has perforated the wall of the right ventricle. Perforation, however, usually occurs at the time of pacemaker implantation and is usually recognized at that time. Although the pacing catheter traverses the tricuspid valve, tricuspid regurgitation is rarely heard unless there is myocardial disease such as right ventricular dilation, which is common in the cardiomyopathies. Pedal edema may be present and is important if it is a new symptom or if chronic edema has recently worsened.

Chest Radiograph

A chest radiograph should be obtained to define pacing catheter tip position and to determine the number of pacing leads, unless this information is available from another source. A ventricular pacing catheter tip in the right ventricular outflow tract or an atrial catheter tip in the SVC or right ventricle is abnormal. The pulse generator site should also be examined on the radiograph.

12-Lead Electrocardiogram

A standard ECG and a long rhythm strip should be obtained in all patients. With bipolar pacing systems, the stimulus artifact may be extremely small and difficult to recognize in some leads (see Fig. 80-4). Inspection of the rhythm strip may reveal failure to sense or pace, a low pacing rate, or an abnormally rapid rhythm, suggesting a pacemaker-mediated tachycardia.

Disposition of the Emergency Department Patient with a Pacemaker

As a result of the current design of modern pacemakers and the frequent follow-up evaluation of patients with pacemakers, life-threatening emergencies resulting from pacemaker malfunction requiring immediate ED intervention are rare. Most instances of malfunction are subtle and difficult to recognize without interrogation of the pacemaker with manufacturer-specific devices by someone skilled in the technique. In all instances of suspected pacemaker malfunction, the patient's cardiologist should be consulted.

Advanced Cardiac Life Support Interventions

Electrical defibrillation at recommended shock strengths (200, 300, and 360 J) can be safely performed in the patient with a pacemaker.[17] If the sternal paddle is placed adjacent to the sternum, it is at a safe distance (>10 cm) from the pulse generator. Alternatively, defibrillation electrodes can be placed in an anteroposterior configuration. A cardiologist or technician should ensure that the pacing parameters of the unit are not altered if the resuscitation is successful. A chest radiograph should also be obtained after resuscitation to ensure that the pacing catheter was not displaced during chest compression, although this is an extremely uncommon occurrence.

Immediate return of pacing (capture) may not occur after defibrillation; this is commonly the result of global myocardial ischemia and increased pacing threshold and is not an indication of pacemaker malfunction. Temporary transcutaneous pacing may be needed if the pacemaker cannot be reprogrammed or normal pacing does not resume spontaneously. Transcutaneous pacing can also be safely used because the anterior and posterior pacing electrodes, if properly positioned, are distant from the pulse generator. Attempting temporary transvenous pacing is usually not necessary and is unlikely to be successful, especially if undertaken without fluoroscopic guidance. Chronic venous thrombosis, which is common and most often asymptomatic after pacemaker insertion, may preclude temporary catheter insertion through the neck veins. Insertion through the femoral vein is also difficult because the permanently implanted catheter may prevent entry into the right ventricle. Blind insertion may also dislodge the permanent catheter.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

The ICD was first used clinically in 1980. Technical refinements in this modality for treating ventricular dysrhythmias have progressed even more rapidly than refinements in the less complex standard pacemaker. A surge in the use of ICDs reflects improved survival with ICDs versus antiarrhythmic therapy in patients at risk for sudden death resulting from ventricular dysrhythmias. Generally accepted indications for ICD implantation are noted in Box 80-2. Many patients still require drug therapy after ICD implantation to suppress ventricular dysrhythmias, minimize the frequency of ICD shocks, improve patients' tolerance, and decrease energy use, which prolongs ICD life.

Terminology and Components

The majority of ICDs are now placed percutaneously in a manner similar to that of the standard pacemaker. A transvenous electrode system has largely replaced epicardial lead placement, which required thoracotomy. An epicardial defibrillation lead may occasionally be placed during coronary artery bypass surgery or in a few patients who cannot be defibrillated with use of existing transvenous electrode systems.

The typical modern ICD consists of components similar to those in the standard permanent pacemaker—namely, a power source, electronic circuitry, and lead system. In addition, the standard ICD has a high-voltage capacitor and complex microprocessor memory.[23] The power source is lithium chemistry based with a battery life of 5 to 10 years. The longevity is largely determined

www.ketabpezeshki.com 66485457-66963820

by the frequency of shocks. All ICDs are also ventricular pacemakers, providing pacing for bradyarrhythmias.

The right ventricular lead is used for sensing and pacing, and shocks are typically delivered between a coil in the right ventricular lead and the pulse generator. If dual-chamber pacing is required, a second lead is placed in contact with the endocardium of the right atrium. A biphasic waveform is currently the preferred waveform for internal defibrillation. The shape and characteristics of the shock waveform vary among manufacturers. The biphasic waveform is more effective at lower energies than earlier monophasic waveforms and allows a smaller capacitor to be used, thereby reducing the size and increasing the comfort of the ICD unit.

The diagnostic and treatment functions of the ICD are determined at the time of implantation. In most instances, the cardioversion and defibrillation thresholds are determined at the time of ICD insertion by inducing ventricular tachycardia (VT) and ventricular fibrillation (VF) and adjusting the shock strength at a level above the minimum required to terminate the induced rhythm. Optimally, the required shock strength for defibrillation is less than half the maximum output (approximately 30 J) of the device. VT is typically managed with use of either low-energy shocks or programmed pacing that interrupts the VT reentrant circuit. Programmed pacing is less likely to have proarrhythmic effects and requires less energy, thereby extending battery life. In the setting of VF, ICDs are capable of delivering up to five additional discharges if the first shock fails.

The patient with an ICD should have close follow-up monitoring by a cardiologist familiar with ICD programming. This allows the cardiologist to determine the frequency of ICD activation (programmed antitachycardia pacing or shocks) and to confirm the programmed functions of the device. The majority of patients with ICDs have underlying heart disease, most commonly extensive atherosclerotic coronary artery disease, which is complicated by a low ejection fraction and congestive heart failure. The patient's medications and metabolic status, such as electrolyte disorders that accompany diuretic usage, may also affect ICD function.

Complications of Implantation

Complications of ICD implantation are nearly identical in type and frequency to those of permanent pacemaker implantation. They include infection of the wound, the subcutaneous pouch fashioned for the device, and the lead system as well as acute thrombophlebitis and chronic thrombosis of the veins traversed for lead insertion. Management of these complications is similar to that for patients with permanent pacemakers.

Malfunction

Patients with ICD malfunction usually come to the ED with a limited number of specific symptoms (Box 80-4).

In contrast to patients with a permanent pacemaker, ICD patients are aware of when the ICD discharges to terminate VT or VF. The most common complaint of ICD patients is the occurrence of frequent shocks (i.e., occurring at a rate greater than they are accustomed to).[24] An increasing shock rate may be appropriate and not indicative of ICD malfunction if the patient is experiencing an increase in the frequency of VT or VF episodes. An increase in the frequency of episodes may occur in the setting of hypokalemia, hypomagnesemia, ischemia (with or without infarction) related to underlying coronary artery disease, or the proarrhythmic effect of drugs administered to decrease the frequency of ventricular tachyarrhythmias. Many ICD patients, particularly those to whom the technology is new, report that their device discharged, but subsequent device interrogation reveals that no discharge occurred.

Box 80-4 Causes of Implantable Cardioverter-Defibrillator Malfunction

Increase or abrupt change in shock frequency
- Increased frequency of VF or VT (consider ischemia, electrolyte disorder, or drug effect)
- Displacement or break in ventricular lead
- Recurrent nonsustained VT
- Sensing and shock of supraventricular tachyarrhythmias
- Oversensing of T waves
- Sensing noncardiac signals

Syncope, near-syncope, dizziness
- Recurrent VT with low shock strength (lead problem, change in defibrillation threshold)
- Hemodynamically significant supraventricular tachyarrhythmias
- Inadequate backup pacing for bradyarrhythmias (spontaneous or drug induced)

Cardiac arrest
- Assume malfunction, but probably caused by VF that failed to respond to programmed shock parameters

VF, ventricular fibrillation; *VT,* ventricular tachycardia.

An increase in the shock frequency is a manifestation of ICD sensing malfunction if (1) a supraventricular tachyarrhythmia is inappropriately sensed as VT, (2) shocks are delivered for nonsustained VT, or (3) intracardiac T waves detected by the ICD system are sensed as QRS complexes and the ICD interprets this as an increased heart rate. Temporary ICD deactivation with magnet application may be necessary if oversensing is the problem. Syncope, near-syncope, dizziness, or lightheadedness in the patient with an ICD may indicate undersensing of sustained VT or inappropriately low shock strength to terminate the rhythm. An approach to the evaluation of ICD malfunction is shown in Figure 80-8.

Advanced Cardiac Life Support Interventions

An ICD does not prevent sudden death in all patients at risk, and a patient with an ICD may arrive in cardiac arrest (2% annual incidence in patients with implanted devices). Cardiac arrest is not necessarily an indication of ICD malfunction. Appropriate repeated shocks may have been delivered but were ineffective. Alternatively, the ICD may not have sensed VF or the ventricular ectopic activity that typically precedes VF. Resuscitation efforts in the patient with an ICD should be undertaken in accordance with current recommendations. Transthoracic defibrillation can be performed in the standard manner with a monophasic or biphasic defibrillator if VF is the arrest rhythm. The sternal electrode or paddle should be placed in a parasternal location approximately 10 cm from the ICD subcutaneous pouch if the device has been implanted in the right deltopectoral area. If it has been implanted in the left deltopectoral region, this recommended safety distance is usually exceeded.

ICD discharge during manual chest compressions poses no risk to providers, although the rescuer may feel a weak shock. Although this generally is not indicated, the device can be deactivated with magnet application during resuscitation efforts. Deactivation is probably more important in the immediate postresuscitation period because recurrent ventricular dysrhythmias are common at this time after prolonged global myocardial ischemia during the arrest period, reperfusion, and the hyperadrenergic state, which is worsened by the use of intravenous epinephrine during resuscitation. ICD malfunction should be assumed, and these postresuscitation rhythms treated with standard pharmacologic agents (lidocaine and amiodarone). Although class 1

www.ketabpezeshki.com 66485457-66963820

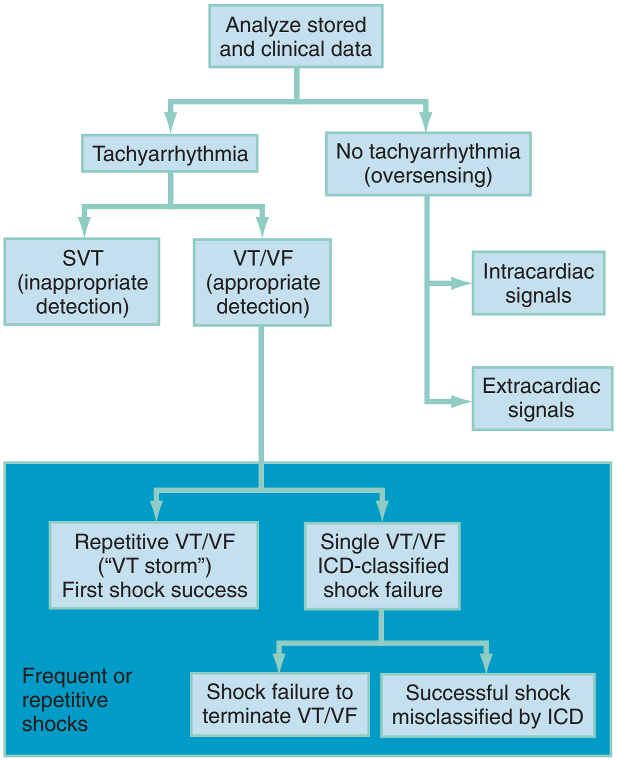


Figure 80-8. Approach to the patient with shocks. *Top,* Flow diagram for one or infrequent shocks. *Bottom,* Diagram for multiple or repetitive shocks. *ICD,* implantable cardioverter-defibrillator; *SVT,* supraventricular tachycardia; *VT/VF,* ventricular tachycardia/ventricular fibrillation. (Redrawn from Swerdlow CD, Zhang J: Implantable cardioverter defibrillator shocks: A troubleshooting guide. Rev Cardiovasc Med 2:61, 2001.)

antidysrhythmic agents may raise the defibrillation threshold of the ICD, their impact on the defibrillation threshold during transthoracic countershock is clinically inconsequential owing to the high shock strengths that are used.

Disposition of the Emergency Department Patient with an Implantable Cardioverter-Defibrillator

As a result of the difficulty in documenting or excluding ICD function or malfunction in the patient with transient symptoms, the device should be interrogated to guide further evaluation and therapy. In cases in which the patient reports a single ICD shock, an assessment for acute cardiac ischemia, worsening of chronic congestive heart failure, symptoms of new-onset heart failure, and electrolyte abnormalities should be performed. In the absence of a change in clinical status, such patients can be discharged in consultation with the managing or consulting cardiologist after timely follow-up is ensured. For patients reporting multiple shocks, interrogation is essential, because in many of these cases the defibrillator has not discharged and the patient is experiencing hiccoughs, diaphragmatic twitching, or other nonelectrical phenomena. In such cases, discharge home is the rule. When multiple defibrillator discharges are confirmed by interrogation, immediate consultation is required along with admission to a monitored setting for extended telemetric observation. If frequent ventricular ectopy is noted, intravenous amiodarone should be given.[24] ICD interrogation allows assessment of ICD function and preceding dysrhythmia episodes.[25] Reprogramming may be necessary. If a lead problem is detected, reimplantation is required. A magnet can be placed over the ICD to inactivate the defibrillator. This should be done only if the emergency physician is confident that the ICD is delivering inappropriate shocks, such as a supraventricular tachycardia.

Biventricular Pacing

Biventricular pacing, also known as *cardiac resynchronization therapy,* is a therapy for patients with left-sided heart failure and ventricular dyssynchrony. It is beneficial for patients with New York Heart Association (NYHA) class III or IV heart failure despite optimal medical therapy, a left ventricular ejection fraction of 35% or less, and sinus rhythm with QRS duration of 120 msec or greater.[26,27] Left bundle branch block causes an altered sequence of depolarization of the left ventricle such that the interventricular septum contracts before the left ventricular free wall, leading to inefficient mechanical pumping. Biventricular pacing "resynchronizes" the ventricles by simultaneously pacing the left and right ventricles, eliminating the delay in left ventricular free wall contraction and improving systolic function. Right atrial and right ventricular leads are positioned as for conventional atrial and univentricular pacing. The left ventricular lead is positioned in a left ventricular epicardial location via the coronary sinus and veins, preferably in a posterolateral or lateral location. The QRS duration of paced ventricular complexes is often but not always less than the QRS duration measured before resynchronization therapy.[28]

Biventricular pacing can usually be recognized on the standard ECG (Fig. 80-9). Two stimulus artifacts or "spikes" may be seen preceding a paced QRS complex. With biventricular pacing, a predominantly negative QRS complex is seen in lead I, in contrast to the typical upright complex seen with right ventricular pacing (see Fig. 80-2). A predominantly positive QRS complex is seen in lead V_1 with biventricular pacing.[28]

The complications and malfunctions inherent with conventional cardiac pacing are also observed with biventricular pacing. In addition, biventricular pacing has unique complications related to placement of the left ventricular pacing lead through the coronary sinus. In large clinical trials, coronary sinus dissection occurred in 0.3 to 4.0% of patients and coronary vein or coronary sinus perforation in 0.8 to 2.0% of patients. Cardiac tamponade caused by perforation of the coronary venous system is seen in less than 1% of patients. Dislodgement of the left ventricular electrode with resultant loss of pacing occurs as an early complication in approximately 10% of patients. Patients with malfunction of a biventricular pacing system frequently report palpations or acute decompensation of chronic heart failure.

Left Ventricular Assist Devices

Mechanical ventricular assistance devices have been used as a "bridge" to transplantation since the 1960s.[29] These implanted devices replace or support the pump function of the left ventricle and were originally bulky and mechanically complex owing to the pulsatile nature of the pump mechanisms. This usually resulted in extended in-hospital care while the patient awaited cardiac transplantation. Newer devices, such as the Jarvik 2000 and HeartMate II, are continuous flow pumps that are portable and powered with a comparatively smaller battery pack. Implantation is associated with fewer infectious complications and lower immediate postoperative mortality, and survival for more than 1 year is increasingly common. The greatest mortality is noted within the first 30 days after implantation and during hospitalization. Left ventricular assistance devices (LVADs) are commonly used as "destination" therapy in patients who do not qualify for cardiac transplantation.[29,30]

www.ketabpezeshki.com 66485457-66963820

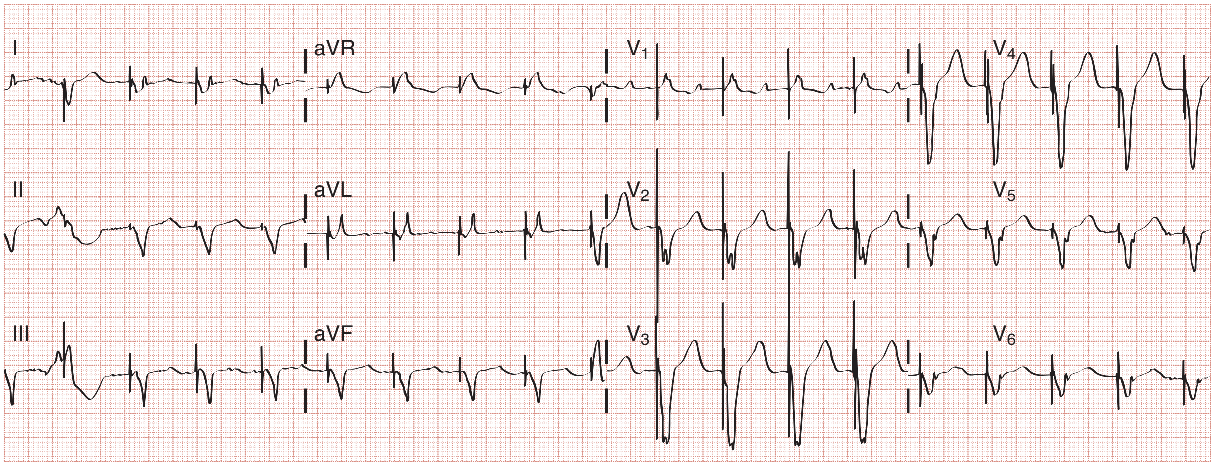


Figure 80-9. Biventricular pacemaker. This 12-lead ECG demonstrates an atrial sensed, biventricular pacemaker in a patient with cardiac synchronization therapy (CRT) and implantable cardioverter-defibrillator (ICD) system (CRT-D). The PR interval is 350 msec and represents the programmed AV delay for this patient. The paced QRS complexes have an S wave in lead I and an R wave in lead V_1 that are distinctly different from the morphology and axes seen with right ventricular apical pacing. The second beat from the left is a premature ventricular contraction (PVC). There is a pacemaker "spike" superimposed on this complex, likely representing safety pacing in CRT-D.

Table 80-3 Comparison of Common Ventricular Assist Devices

	THORATEC VAD	HEARTMATE II	HEARTMATE I OR XVE
Flow type	Pulsatile—patient will have a pulse and BP.	Axial—patient will not have a pulse or BP. Use Doppler to confirm flow.	Pulsatile—patient will have a pulse and BP.
Backup method	Hand pump	No external method	Hand pump
Battery life	Up to 3 hr	Up to 10 hr	Up to 10 hr
Defibrillation or cardioversion	No precautions	No precautions	Use hand pump during procedure
Cardiac arrest	Use hand pump	No external method	Use hand pump

BP, blood pressure.

Patients with an LVAD typically require care at cardiac transplant centers. As technology progresses, emergency physicians not based at a transplant center may encounter a patient with an LVAD. In such cases, telephone consultation with an expert at a transplant center may help avoid missteps. The more common complications with this device include infection and embolic stroke. Device failure usually results in severe heart failure. If necessary, dopamine, dobutamine, or a combination of these drugs may be given to treat congestive heart failure symptoms while the patient awaits transfer. If cardiac arrest occurs, chest compressions may dislodge the device. The hand pump should be used to provide circulation if this backup method is available and early transition to cardiopulmonary bypass should be considered (Table 80-3).

KEY CONCEPTS

- Pacemaker malfunction soon after implantation (within 6-8 weeks) is usually a result of a lead problem, such as a lead displacement, or a pacemaker programming failure, such as a pacing rate too slow for the patient's needs.
- Pacemaker malfunction arises in a limited number of ways: failure to pace, oversensing, undersensing, and pacing at an inappropriate rate (too fast or too slow).
- With lithium-iodine batteries, abrupt failure is an unlikely cause of pacemaker malfunction.
- If a patient with a pacemaker has a fever of unclear cause, pacemaker lead infection and endocarditis should be considered.
- Because paced ventricular complexes are conducted with a left bundle branch block pattern, a paced rhythm obscures the electrocardiographic diagnosis of acute myocardial infarction. A right bundle branch pattern is abnormal and suggests lead displacement.
- Magnet application does not turn off a pacemaker, it turns off the sensing or inhibition function. Fixed-rate pacing that is independent of or in competition with the underlying native rhythm will ensue. Removal of the magnet restores the inhibitory activity of the pacemaker and returns it to demand pacing mode.
- Defibrillation is safe in patients with a pacemaker or ICD. Paddles should be placed at least 10 cm from the subcutaneous implant site of the device. Alternatively, anteroposterior defibrillation with adhesive defibrillation electrodes can be performed. There are no reports of injury to rescuers from ICD discharges during manual chest compressions.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Beck H, et al: 50th anniversary of the first successful permanent pacemaker implantation in the United States: Historical review and future directions. *Am J Cardiol* 2010; 106:810.
2. Passman R, Kadish A: Sudden death prevention with implantable devices. *Circulation* 2007; 116:561.
3. Birnie D, et al: Reasons for escalating pacemaker implants. *Am J Cardiol* 2006; 98:93-97.
4. Ramani GV, Uber PA, Mehra MR: Chronic heart failure: Contemporary diagnosis and treatment. *Mayo Clin Proc* 2010; 85:180.
5. Tang AS, et al: Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010; 363:2385.
6. Al-Majed NS, McAlister FA, Bakal JA, Ezekowitz JA: Meta-analysis: Cardiac resynchronization therapy for patients with less symptomatic heart failure. *Ann Intern Med* 2011; 154:401.
7. Zipes DP, et al: ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006; 114:e385.
8. Packer DL, et al: ICDs: Evidence, guidelines, and glitches. *Heart Rhythm* 2011; 8:800.
9. Maisel WH: Safety issues involving medical devices: Implications of recent implantable cardioverter-defibrillator malfunctions. *JAMA* 2005; 294:955.
10. Epstein AE, et al: ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008; 51:e1.
11. Bernstein AD, et al: The revised NASPE/BPEG generic code for antibradycardia, adaptive-rate, and multisite pacing. *Pacing Clin Electrophysiol* 2002; 25:260.
12. Kaszala K, Huizar JF, Ellenbogen KA: Contemporary pacemakers: What the primary care physician needs to know. *Mayo Clin Proc* 2008; 83:1170.
13. Maisel WH, et al: Pacemaker and ICD generator malfunction: Analysis of Food and Drug Administration annual reports. *JAMA* 2006; 295:1901.
14. Kusumoto FM, Goldschlager N: Device therapy for cardiac arrhythmias. *JAMA* 2002; 287:1848.
15. Baddour LM, et al: Update on cardiovascular implantable electronic device infections and their management. A scientific statement from the American Heart Association. *Circulation* 2010; 121:458.
16. Kucher N: Deep-vein thrombosis of the upper extremities. *N Engl J Med* 2011; 364:861.
17. McMullan J, et al: Care of the pacemaker/implantable cardioverter defibrillator patient in the ED. *Am J Emerg Med* 2007; 25:812.
18. Dretzke J, et al: Dual chamber versus single chamber ventricular pacemakers for sick sinus syndrome and atrioventricular block. *Cochrane Database Syst Rev* 2004; 2:CD003710.
19. Tops LF, Schalij MJ, Bax JJ: The effects of right ventricular apical pacing on ventricular function and dyssynchrony. *J Am Coll Cardiol* 2009; 54:764.
20. Goldschlager N, et al: Environmental and drug effects on patients with pacemakers and implantable cardioverter/defibrillators: A practical guide to patient treatment. *Arch Intern Med* 2001; 161:649.
21. Shah PM, Ellenbogen KA: Life after pacemaker implantation: Management of common problems and environmental interactions. *Cardiol Rev* 2001; 9:193.
22. Barold SS, Leonelli F, Khan N, Cutro R, Herweg B: Pacemaker tachycardia: Is it pacemaker-mediated tachycardia or sinus tachycardia? *Pacing Clin Electrophysiol* 2007; 30:256.
23. Stevenson WG, et al: Clinical assessment and management of patients with implanted cardioverter-defibrillators presenting to nonelectrophysiologists. *Circulation* 2004; 110:3866.
24. Gehi AK, Mehta D, Gomes JA: Evaluation and management of patients after implantable cardioverter-defibrillator shock. *JAMA* 2006; 296:2839.
25. Swerdlow CD, Friedman PA: Advanced ICD troubleshooting. Part II. *Pacing Clin Electrophysiol* 2006; 29:70.
26. Jarcho JA: Biventricular pacing. *N Engl J Med* 2006; 355:288.
27. Cubbon RM, Witte KKA: Cardiac resynchronization therapy for chronic heart failure. *BMJ* 2009; 338:1064.
28. Burkhardt JD, Wilkoff BL: Interventional electrophysiology and cardiac resynchronization therapy. Delivering electrical therapies for heart failure. *Circulation* 2007; 115:2208.
29. Boilson BA, Raichlin E, Park SJ, Kushwaha SS: Device therapy and cardiac transplantation for end-stage heart failure. *Curr Probl Cardiol* 2010; 35:8.
30. Starling RC, et al: Results of the post–U.S. Food and Drug Administration–approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: A prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). *J Am Coll Cardiol* 2011; 57:1890.

www.ketabpezeshki.com 66485457-66963820

Chapter 81

Heart Failure

John F. O'Brien and Christopher L. Hunter

Heart failure (HF) is a debilitating cardiac syndrome characterized by dyspnea, poor exercise tolerance, and chronic fatigue along with high morbidity and mortality. *Heart failure* may be defined as the pathophysiologic state in which the heart is incapable of pumping a sufficient supply of blood to meet the metabolic requirements of the body or requires elevated ventricular filling pressures to accomplish this goal. The caveat about high filling pressures acknowledges that a failing heart may continue to maintain systemic perfusion via the compensatory Frank-Starling mechanism, resulting in the maintenance of normal stroke volume (SV) despite reduced ejection fraction (EF). Conversely, low filling pressure with hypoperfusion indicates a pump-priming problem distinct from cardiac disease. The American Heart Association (AHA) and American College of Cardiology (ACC) guidelines define HF related to systolic dysfunction as a left ventricular (LV) ejection fraction (LVEF) less than 40%. Diastolic dysfunction, a pathologic condition involving failure of ventricular relaxation with consequent high filling pressures, may exist in up to half of older individuals with HF.

HF is a progressive and multifaceted disease that begins long before symptoms and signs are evident. A complex neurohormonal regulatory relationship exists between the heart and multiple organ systems. Feedback loops mediated through a variety of vasoactive substances secreted by the heart, autonomic nervous system, kidneys, adrenals, lungs, and vascular endothelium are most important. Perturbations of function in any of these organs affect the others (Fig. 81-1). Accordingly, the cardiovascular system should be viewed as a dynamic one, continually adapting to optimize organ perfusion. Dysfunction of the heart or any component of the cardiopulmonary system initiates adaptive neurohormonal activation of the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS), natriuretic peptides, endothelin (ET), vasopressin, and other regulatory mechanisms. Neurohormonal activation initially compensates for circulatory system dysfunction. These mechanisms eventually lead to increased mechanical stress on the failing heart, however, causing maladaptive electrical and structural events, progressive cardiac fibrosis and apoptosis, and further impairment of systolic and diastolic function.[1] This creates a vicious cycle of increasing myocardial dysfunction causing further neurohormonal modulation, leading to a progressive downward spiral. The degree of myocardial dysfunction depends on both the amount of primary myocardial disease and other pathologic conditions, particularly in the pulmonary, renal, and peripheral vascular systems. Understanding these underlying compensatory mechanisms is leading to progressive improvement in the management of HF, with a shift from a hemodynamic to a neurohormonal model.

EPIDEMIOLOGY

HF represents the only significant cardiovascular disease that is increasing in prevalence in our society. It is a common cause of poor quality of life and premature death. About 5,800,000 individuals (approximately 2% of the population) in the United States in 2009 had HF, and almost 550,000 new cases are diagnosed annually.[2] The incidence approaches 10 per 1000 in people older than 65 years.[3] Decompensated HF is the most common reason for hospital admission in this age group and also for readmission within 60 days of discharge.[4] The ED is the main portal of entry for acute HF patients, with admission rate approximately 80%. HF results in an annual estimated health care cost of about $40 billion.[5] It is also responsible for high rates of outpatient visits, hospitalizations, and readmissions. The aging population, coupled with improvements in the medical therapy of HF, will result in increased prevalence of this disease.

HF carries approximately a 50% mortality at 5 years after symptom onset, and one third of patients with the most severe disease die within the first year after diagnosis.[5,6] Females have a survival advantage over males.[7,8] Progressive hemodynamic deterioration accounts for approximately 50% of deaths, but sudden death resulting from malignant ventricular dysrhythmias occurs in up to half.[9] Multiple medical therapies decrease the death rate by improving functional status and slowing progression of pump dysfunction.[10]

The prognosis in HF is related to a number of factors, including age, LVEF,[11,12] exercise tolerance, plasma norepinephrine and B-type natriuretic peptide (BNP) levels, cardiothoracic ratio on chest radiograph,[13] resting heart rate (HR),[14-16] electrocardiogram (ECG) evidence of left ventricular hypertrophy,[17] atrial fibrillation (AF),[18] or presence of ventricular dysrhythmias, hemoglobin A_{1c} level,[19,20] and renal function. One third to one half of patients with HF have some degree of renal insufficiency,[21] which is one of the strongest predictors of mortality in patients with HF.[22-24] HF disproportionately affects black compared with white Americans, and they have a higher mortality.[25,26]

CELLULAR MECHANISMS

The heart is composed of a mass of individual striated muscle cells (myocytes) that form a branching syncytium. Each myocyte contains an intracellular tubular system termed the *sarcoplasmic reticulum,* and numerous cross-banded strands termed *myofibrils* that traverse the length of the myocyte. Myofibrils, in turn, contain multiple subunits called *sarcomeres,* which form the basic functional unit of myocardial contraction. Sarcomeres occupy

www.ketabpezeshki.com 66485457-66963820

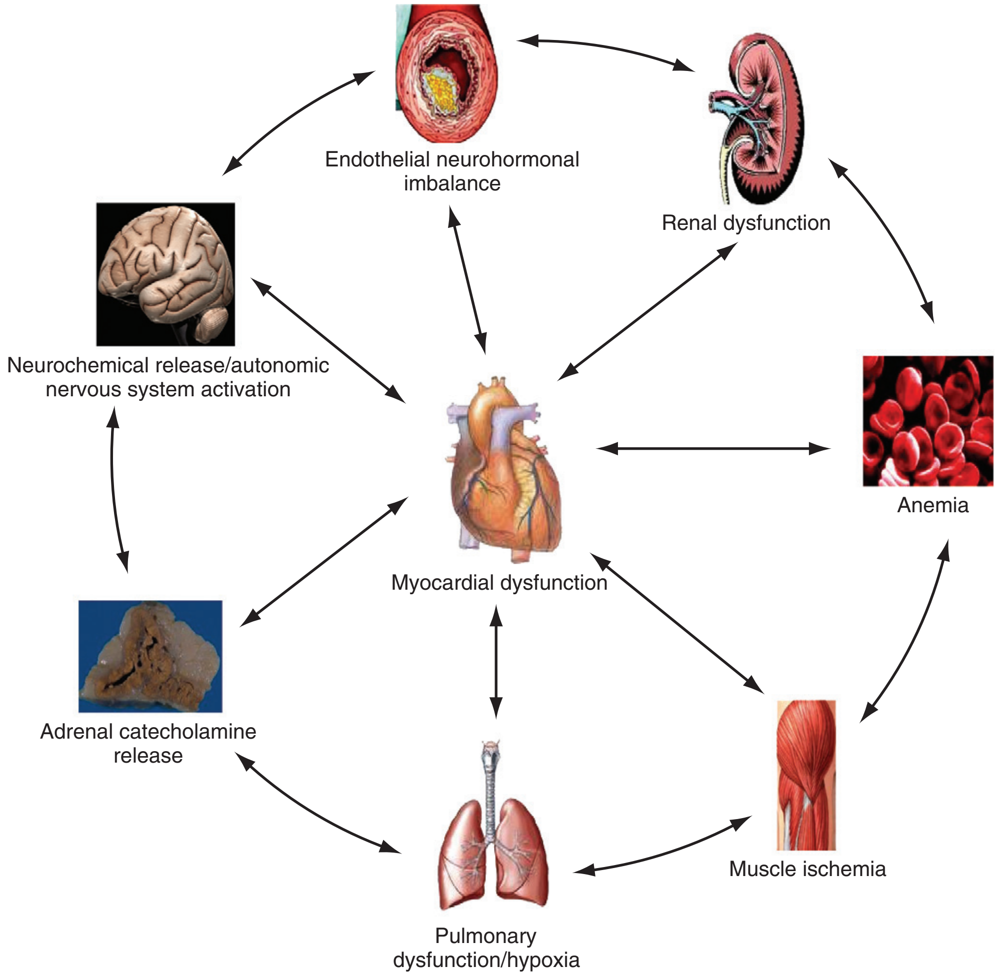


Figure 81-1. The neurohormonal model of heart failure describes a complex interdependence among many organ systems in which a functional disturbance in any component causes complex compensatory changes in the others that are eventually maladaptive. Correction of organ system dysfunction by medications and other interventions may result in correction of these perturbations.

approximately 50% of myocardial cell mass and are composed of contractile proteins actin and myosin along with regulatory proteins troponin and tropomyosin. These proteins are surrounded by invaginations of the myocardial cell membrane (sarcolemma) and sarcoplasmic reticulum.

The sarcomere ranges in length from 1.6 to 2.2 μm, depending in part on the tension exerted on the muscle before contraction (preload). Sarcomere contraction occurs when thin, double-helix actin is exposed to thick myofilament myosin. Contraction as well as relaxation is controlled by calcium ion (Ca^{2+}) release from the sarcoplasmic reticulum. When intracellular Ca^{2+} is increased, it binds to the contraction regulatory protein troponin, which causes a conformational change in tropomyosin that exposes actin to myosin. In the presence of adenosine triphosphate (ATP), linkages between actin and myosin are rapidly made and broken, causing the actin to slide along the myosin filaments. This process generates muscle tension and ultimately myocyte contraction. A decrease in intracellular Ca^{2+} by sarcoplasmic reticulum reaccumulation reconforms the troponin-tropomyosin complex in such a way that myosin and actin linkages are broken, allowing sarcomere relaxation. Intracellular ionic calcium is thus the principal mediator of the inotropic state of the heart and is mainly stored and regulated by the sarcoplasmic reticulum. Most positive inotropic agents, including digitalis and catecholamines, act by increasing availability of intracellular calcium. On the downside, increased intracellular calcium reduces diastolic relaxation.

CARDIAC PHYSIOLOGY

The normal cardiac index is 2.5 to 4.0 L/min/m^2 at rest. It is determined by contractility, preload, afterload, and HR. In normal hearts, the collective force of contraction of the cardiac chamber is the sum of forces generated by individual myocytes. Myocyte force is in turn a function of the ability of contractile proteins to generate power (inotropic state or contractility) as well as degree of sarcomere stretch at the start of contraction (preload). Stretching the sarcomere progressively toward its optimal length of 2.2 μm increases the force of contraction by allowing the maximum number of actin-myosin myofilament interactions. This forms the basis of the Frank-Starling relation, which states that within physiologic limits, force of ventricular contraction is directly related to end-diastolic length of the myofibril. Contractility may be affected by a host of factors. Multiple physiologic depressants (e.g., hypoxia, hypercarbia, acidosis, ischemia) and pharmacologic depressants (e.g., antidysrhythmic agents, calcium channel blockers, beta-blockers, alcohol) decrease myocardial contractility. Correcting physiologic myocardial depressant factors and discontinuing unnecessary medications with negative inotropic properties are important first steps in managing HF. Inotropic agents enhance contractility and may improve hemodynamics both acutely, such as with catecholamines, and chronically, as with cardiac glycosides.

Preload is the amount of force stretching the myofibril before contraction. In the intact ventricle, preload is produced by venous

www.ketabpezeshki.com 66485457-66963820

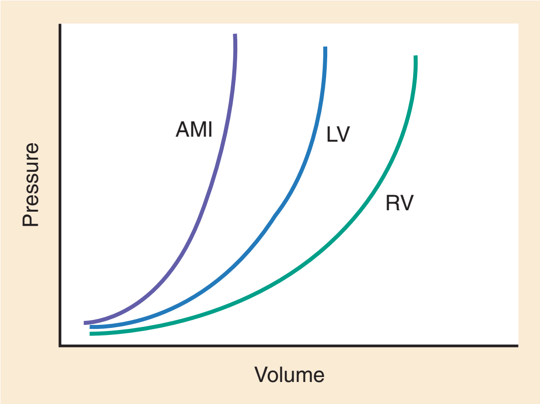


Figure 81-2. The end-diastolic pressure of the chamber is determined by the filling volume and the compliance characteristics of the chamber. The right ventricle *(RV)* is more compliant than the more muscular left ventricle *(LV)*, which becomes stiffer still under conditions of ischemia or acute myocardial infarction *(AMI)*.

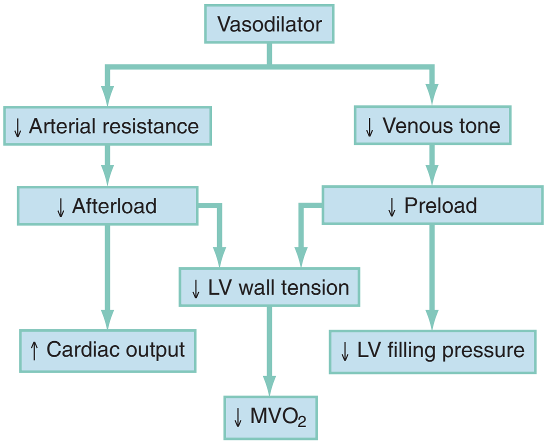


Figure 81-4. Arterial vasodilators decrease resistance to flow and result in increased carbon dioxide. Venodilators decrease venous return to the heart and relieve pulmonary congestion. Balanced agents (e.g., nitrates) do both. Decreased mural tension reduces myocardial oxygen demand (*MVO_2*) and may relieve ischemia. *LV,* left ventricular.

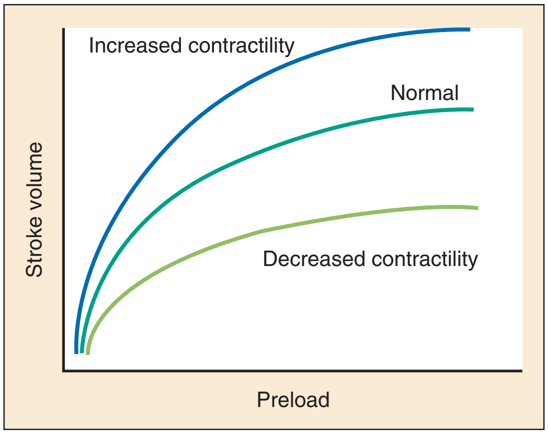


Figure 81-3. Increased preload improves stroke volume irrespective of the contractile state of the ventricle. At any level of contractility, an optimal preload is reached beyond which further increases in chamber pressure may result in increased risk of pulmonary edema, with minimal incremental increase in stroke volume.

return into the chamber, resulting in stretch of the myofibrils constituting the chamber walls. The volume filling the chamber also results in development of pressure that can be measured in either ventricle. The pressure measured within a chamber is determined by both the volume stretching the chamber wall and compliance characteristics of the muscle. For this reason, ventricular pressure is only an indirect reflection of preload. Changes in compliance may occur acutely with ischemia or chronically with hypertrophy and may substantially alter the relationship between chamber volume, pressure, and preload (Fig. 81-2).

Optimal preload is the filling pressure that stretches ventricular myofibrils maximally and leads to greatest stroke output per contraction. The actual optimal preload is unique for each patient because it is affected by LV loading conditions and compliance characteristics. For example, patients with acute myocardial infarction (AMI) tend to have a stiffer, less compliant left ventricle. In these patients, optimal LV pressure ranges are higher. Despite the inotropic state of the ventricle, optimizing preload results in the maximum stroke output for that ventricle (Fig. 81-3). Ventricles with normal compliance accommodate larger volumes before the chamber pressure rises. Accordingly, if pressure is used to estimate preload, the normal ventricle has more dramatic increases in stroke output for similar increases in filling pressure (steeper Starling curve). The risk of pulmonary edema increases when LV end-diastolic pressure rises significantly above normal ranges (6-12 mm Hg). In patients with low colloid osmotic pressures secondary to hypoalbuminemia, pulmonary edema may occur at even lower filling pressures.

Afterload, for clinical purposes, can be thought of as the pressure against which the heart must pump to eject blood. Blood pressure (BP) is determined by the product of cardiac output (CO) and systemic vascular resistance (SVR) (BP = CO × SVR). Hypertension is a major contributor to HF in about 75% of cases.[27] Patients with HF and low CO tend to maintain BP through peripheral vasoconstriction mediated mainly by endogenous catecholamines and the RAAS. Afterload represents the mural tension on myocardial cells during contraction and is determined by the total peripheral vascular resistance and the cardiac chamber size. The peripheral resistance is affected by the total cross-sectional area of the circulation, the blood viscosity, and other factors. The arterioles are the major resistance vessels in the circulation. Flow is directly proportional to the fourth power of the vessel radius (Poiseuille's law). The larger the ventricular cavity, the more mural tension and thus myocardial work is required during contraction (law of Laplace).

Failing ventricles have difficulty overcoming increases in peripheral resistance, instead dilating further, increasing end-diastolic volume to maintain SV, even with decreasing EF (preload reserve). Failing hearts are therefore extremely afterload sensitive, and modest vasodilation can dramatically increase CO, particularly in those most compromised (Fig. 81-4). Afterload reduction may be beneficial because it allows conversion of pressure work into flow work. When BP is decreased, CO increases as long as preload is maintained. Because flow work is proportionally less oxygen demanding, afterload reduction therapy has the additional benefit of decreasing myocardial oxygen demand.

HR and rhythmic contraction are important determinants of optimal CO (CO = HR × SV). As HR increases to the range of 150 to 160 beats/min in the adult, CO increases progressively. Tachycardia above this level compromises diastolic filling time and may lead to decreased CO. Coronary perfusion, which occurs only during diastole, also becomes impaired by severe tachycardia. SV is maximized when atrial contraction "primes" the ventricular pumps before they contract. Therefore any derangement of intracardiac conduction or dysrhythmia can reduce SV. Loss of atrial priming (e.g., in AF) can lead to marked deterioration in CO,

www.ketabpezeshki.com 66485457-66963820

especially in diseased, stiffer hearts that require high filling pressures to optimize preload. Synchronized contraction of myocardial tissue and chambers is now a focus of therapeutic intervention.

PRIMARY DISEASE PROCESSES RESULTING IN HEART FAILURE

HF can result from primary disease of coronary arteries, myocardium, cardiac valves, pericardium, peripheral vessels, or lungs. Frequently the cause is multifactorial. Often, determination of the causes of HF is simpler early in its course than during later stages.

Coronary Artery Disease

In developed countries, atherosclerotic coronary artery disease remains the leading cause of HF, present in almost 70% of patients in multicenter HF trials.[28] Acute coronary thrombosis leads to focal myocardial necrosis, with resultant fibrosis and scarring. This process leads to areas of dyskinesis that result in decreased EF. Aneurysmal dilation of infarcted areas with paradoxical motion during systole may disproportionately decrease EF. When approximately 40% of the LV muscle mass is acutely infarcted, cardiogenic shock ensues. Transient loss of contractile function may result from episodes of myocardial ischemia that do not cause frank necrosis, or from an ischemic zone surrounding the infarct. This "myocardial stunning" may persist for several days. Owing to improved treatment of acute coronary syndromes, the rates of secondary death and HF are decreasing.[29]

Chronic coronary insufficiency leads to a more diffuse myocardial fibrosis termed *ischemic cardiomyopathy.* Revascularization of ischemic but not infarcted myocardial tissue provides a survival benefit in patients with HF related to ischemic LV systolic dysfunction.[30] Diseases affecting the coronary microcirculation, such as vaso-occlusive sickle cell anemia and diabetes mellitus, result in similar pathology. Compensatory mechanisms may occur after large MI and progressive cardiac disease, which are collectively termed *ventricular remodeling.* They include cardiac dilation, reactive hypertrophy, progressive fibrosis, and changes in wall conformation. These may result from elevated chamber filling pressures as well as neurohumoral adaptive responses.

Cardiomyopathy and Myocarditis

Cardiomyopathies are a group of disease processes that primarily affect myocardium. Myocardial diseases resulting from coronary, valvular, and pericardial pathologies are excluded. Cardiomyopathy is categorized as primary if cause is unknown, or secondary if some cause is identified. Clinically, patients with cardiomyopathy tend to have three forms—dilated, hypertrophic, or restrictive—each associated with HF. Dilated cardiomyopathy is much more common than the other two and is the second most common cause of HF. The specific cardiomyopathies and myocarditis, which may also cause HF, are discussed in Chapter 82.

Valvular Heart Disease

Cardiac valvular disease is the third leading cause of HF, after ischemic heart disease and dilated cardiomyopathy. Most acute valvular dysfunction involves either the mitral or the aortic valve, and usually results in severe regurgitation. Acutely stenotic lesions are predominantly restricted to mechanical catastrophes of prosthetic valves. These patients may be in extremis with fulminant pulmonary edema. Valvular disease is discussed in Chapter 83.

Mitral insufficiency and aortic stenosis are most commonly associated with chronic HF. Knowledge of the precise valvular pathology may have important implications for emergent HF therapy. For example, patients with decompensated aortic stenosis should generally not receive vasodilator agents, as flow cannot increase across a fixed obstruction. These patients may become hypotensive owing to reduced preload, with resultant decreased systemic and coronary perfusion. On the other hand, patients with mitral regurgitation benefit greatly from vasodilators, which improve antegrade flow by reducing afterload.

Pericardial Diseases

Pericardial diseases may significantly affect ventricular function, decreasing CO and increasing intracardiac pressures. In particular, cardiac tamponade may cause dyspnea and hypoperfusion not easily clinically distinguished from HF. ED use of bedside ultrasound has great usefulness in rapidly identifying this problem. Pericardial diseases are fully discussed in Chapter 82.

Pulmonary Disease

Chronic obstructive pulmonary disease (COPD), which has a prevalence of 20 to 30% in HF, may obscure recognition of HF.[31] Pulmonary dysfunction reduces myocardial oxygen supply while CO must be increased because tissue is being perfused with suboptimally oxygenated blood. Hypoxia leads to pulmonary arteriolar vasoconstriction, reducing lung vascular bed area and elevating pulmonary artery pressures. Chronic increases in pulmonary arterial pressure lead to right ventricular (RV) hypertrophy and dilation. When compensatory mechanisms fail, the patient develops right-sided HF (cor pulmonale), usually with LV output preserved, at least at rest. Causes of acute cor pulmonale, such as a large pulmonary embolus, may precipitate sudden systemic hypotension and death, partly because of decreased LV priming.

Distinguishing primary pulmonary disease causing predominantly right-sided HF from LV failure with secondary right-sided dysfunction is clinically challenging. Wheezing or rhonchi may be seen in both entities. The chest radiograph may be difficult to interpret because both presentations cause interstitial changes. Hyperinflation depresses the diaphragm, which elongates the cardiac silhouette and may mask cardiomegaly. Competition for intrathoracic space reduces lung capacity in patients with chronic HF.[32] Natriuretic peptide levels are only slightly elevated in primary pulmonary disease compared with much higher levels in LV failure.[31,33,34]

COMPENSATORY MECHANISMS IN HEART FAILURE

Physiologic Mechanisms

Increase in Stroke Volume

Increased SV occurs in response to increase in preload (Frank-Starling mechanism). This compensatory mechanism is immediate and effective in improving CO in response to acute systemic demands. It is a limited response, however, because myofibril stretch to a sarcomere length beyond 2.2 μm does not further increase and may actually reduce stroke output. Also, this mechanism greatly increases myocardial oxygen demand, which may lead to dysfunction in the setting of significant coronary artery disease.

Increased Systemic Vascular Resistance

Increased SVR results in redistribution of a subnormal CO away from skin, skeletal muscles, and kidneys to maintain normal

www.ketabpezeshki.com 66485457-66963820

blood flow to the brain and heart. This elevated afterload also greatly increases myocardial work.

Development of Cardiac Hypertrophy

Development of cardiac hypertrophy is the primary chronic adaptation of the heart to compensate for pump failure. This hypertrophy occurs mainly by increasing the number of myofibrils per cell, as the heart has very limited ability to produce new cells (hyperplasia). New myofibrils arrange in series in response to an increase in chamber volume (leading to dilation over time) and in parallel when responding to higher pressure loads (leading to increased chamber wall thickness). In addition to myofibril hypertrophy, mitochondrial mass expands, leading to additional ATP provision for the expanded myofibril mass.

Initially, hypertrophy leads to improved function of each myocardial cell but at a higher energy cost. Hypertrophy is associated with myosin synthesis shifts from V_1 to V_3 isoforms, however, with related slowing of contraction, prolongation of time to peak tension, and reduced rate of relaxation.[35] With the continued influence of volume overload, myofibril mass expands more than mitochondrial mass. Relative capillary blood flow is reduced, leading to progressive myocyte death with fibrosis and increased stress on the remaining myocytes. Thus the hypertrophic response, if allowed to continue, eventually becomes maladaptive, accelerating myocyte death and reducing pump function. This process gradually occurs as a normal part of aging.[36]

Neurohormonal Modulation

Neurohormonal mechanisms maintain BP and vital organ perfusion and are activated by LV dysfunction. Regrettably, these neurohormonal mechanisms also increase the hemodynamic burden and oxygen consumption of the failing ventricle and are counterproductive on a chronic basis.

Cardiac Neurohormonal Response

Increases in myocardial wall stretch activate release of cardiac natriuretic peptides, which are structurally related proteins important in volume and sodium homeostasis. They include atrial, brain (BNP), and C-type natriuretic peptide. All are elevated in patients with LV dysfunction and HF. A variety of natriuretic peptide receptors exist on endothelial cells, vascular smooth muscle cells, and renal epithelial cells and in the myocardium. Natriuretic peptides promote water and sodium excretion, increase peripheral vasodilation, and inhibit the RAAS. In early HF they play a key role in compensation for LV dysfunction. Attenuation of renal response to natriuretic peptides occurs as HF progresses.

Central and Autonomic Nervous System Neurohormonal Response

The heart and great vessels contain sensory receptors that detect changes in perfusion. Metabolic receptors in muscles also exert inhibitory and excitatory influences on brainstem vasomotor neurons. Arginine vasopressin (antidiuretic hormone) is released from the pituitary gland in response to decreases in perfusion. Elevated vasopressin levels in HF increase volume overload while decreasing osmolality. This adversely affects hemodynamics and cardiac remodeling while potentiating effects of angiotensin II and norepinephrine.[37]

HF results in a generalized stimulation of sympathetic activity and inhibition of parasympathetic tone. Increased sympathetic outflow results in release of epinephrine and norepinephrine from the adrenal glands and norepinephrine at peripheral sympathetic nerve endings. These elevated catecholamine levels stimulate surface receptors in the heart and blood vessels, increasing cardiac contractility, HR, and vascular tone. The resulting increased vascular tone augments preload through venous contraction as well as afterload by arterial vasoconstriction. Acutely, arterial BP is improved and CO increased by catecholamines. Chronically, a decrease in the number and affinity of surface catecholamine receptors occurs in myocardial tissue, reducing responsiveness to epinephrine and norepinephrine. Elevated catecholamines adversely affect myocardial perfusion, leading to progressive apoptosis and cardiac fibrosis.

Renal Neurohormonal Response

Decreased glomerular perfusion results in reduced renal excretion of sodium. Renal arteriolar and adrenergic receptors stimulate renin release by the juxtaglomerular apparatus. Renin facilitates the conversion of angiotensinogen to angiotensin I, which is further converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II is a potent vasoconstrictor and an important stimulus for aldosterone release by the adrenal cortex. Aldosterone increases renal sodium retention and potassium excretion. Renal adaptation to hypoperfusion occurs mainly through production of vasodilatory hormones such as prostacyclin, along with prostaglandins PGI_2 and PGE_2. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) interfere with prostaglandin synthesis by inhibiting cyclooxygenase. Therefore, except for the useful antiplatelet effect of aspirin, NSAIDs optimally should be avoided in patients with chronic HF because they may contribute to acute renal insufficiency with concomitant salt and water retention.

Vascular Endothelial Neurohormonal Response

Endothelial function locally regulates vasomotor tone. A family of ETs is produced by endothelial and smooth muscle cells as well as neural, renal, pulmonary, and inflammatory cells. This occurs in response to hemodynamic stress, hypoxia, catecholamines, angiotensin II, and many inflammatory cytokines. ET-1 is the most important ET and the most potent vasoconstrictor known.[38] It exerts its main vascular effects, vasoconstriction and cell proliferation, through specific ET_A and ET_B receptors on vascular smooth muscle cells. ET_A receptor activation causes vasoconstriction, whereas ET_B receptor stimulation increases prostacyclin and nitric oxide (NO) release, causing vasodilation. ET-1 plasma levels are elevated in HF, correlate with symptoms as well as hemodynamic stress, and are associated with adverse prognosis.

NO is produced in almost all tissues and plays a critical role in the homeostasis of cardiac function.[39] NO exerts its biologic signaling through production of cyclic guanosine monophosphate (cGMP), which is broken down by cyclic nucleotide phosphodiesterases (PDEs).[40] Reduced synthesis or increased degradation of NO at the endothelial level is detrimental in HF. NO-mediated endothelial dysfunction may represent the earliest stage of target organ damage, which ultimately leads to hypertensive heart disease and HF.[41]

CLASSIFICATION OF HEART FAILURE

Many different methods of classifying HF exist, including acute versus chronic, systolic versus diastolic, right sided versus left sided, and high output versus low output. Early in HF, these may be useful clinical descriptors suggesting particular causes and treatment strategies. Late in the disease process, these distinctions blur.

www.ketabpezeshki.com 66485457-66963820

Acute versus Chronic Heart Failure

The prototypical case of acute HF involves a healthy person who develops a large myocardial infarction (MI) or acute valvular dysfunction. Chronic HF is best characterized by a disease state such as dilated cardiomyopathy, with gradual deterioration of cardiac function. In acute HF, early presentation may be a result of systolic dysfunction and hypoperfusion, often with acute pulmonary edema (APE) resulting from sudden reduction in chamber compliance. Chronic HF usually arises with symptoms related to fluid retention, with compensatory mechanisms adjusted so that normal perfusion exists, at least in the resting state. In clinical practice, approximately 80% of HF cases seen the ED involve acute decompensation of chronic heart disease.[42]

Systolic versus Diastolic Dysfunction

Systolic dysfunction refers to impairment of contractility, with stroke output reduced and forward flow compromised. Systolic dysfunction is typically caused by myocyte damage such as in MI or myocarditis. Asymptomatic LV systolic dysfunction in patients 45 years of age or older has an estimated prevalence of 6% and is much more common than symptomatic systolic HF.[43,44] Most cases of systolic dysfunction also involve some degree of diastolic dysfunction.

Diastolic dysfunction indicates a primary problem with ability of the ventricles to relax and fill normally.[45] In many cases, normal or even supernormal systolic function is preserved. Echocardiographic and nuclear imaging techniques demonstrate that 40 to 50% of patients with congestive symptoms have normal EFs and experience diastolic dysfunction,[46,47] also termed *heart failure with normal ejection fraction.*[48] The proportion of HF that is primarily diastolic increases with age, from about 45% in patients younger than 45 years to almost 60% in patients older than 85 years. Asymptomatic diastolic dysfunction is much more common than asymptomatic systolic dysfunction. Diastolic dysfunction is the predominant pathophysiology in hypertrophic and restrictive cardiomyopathies, valvular aortic stenosis, and, most important, hypertension.

Diastolic dysfunction occurs predominantly as a result of one of three mechanisms: impaired ventricular relaxation, increased ventricular wall thickness, or accumulation of myocardial interstitial collagen. Impaired lusitropic capacity of the myocardium leads to higher ventricular filling pressure, resulting in congestive symptoms. Myocardial relaxation is an active, energy-requiring process. Failure of myocytes to relax may be secondary to low intracellular energy stores. Physiologic stresses causing increased cardiac demands can precipitate lusitropic abnormalities. In chronic renal disease, mortality is higher in diastolic than systolic HF.[49] In addition, systolic contractile dyssynchrony occurs in one third of diastolic HF patients, whereas diastolic dyssynchrony is present in more than half, with therapeutic implications.[50,51]

As with the other classification schemes, most patients with HF have components of both systolic and diastolic dysfunction, with the predominant type allowing specific treatment strategies. For example, patients with predominantly diastolic dysfunction have the advantage of intact myocardial contractile function. Stiffer hearts, however, have steep pressure-volume curves. Therefore small reductions in diastolic filling volume, as may occur with aggressive vasodilator or diuretic therapy, may markedly decrease ventricular filling and compromise stroke output (see Fig. 81-3).

Right-Sided versus Left-Sided Heart Failure

The notion that one cardiac chamber can fail independently of the others is somewhat artificial. The right and left circulations are connected and, over time, output from the two sides must be equal. Furthermore, the right and left ventricles share an interventricular septum, and dysfunction in one chamber may have an immediate impact on the other. For example, acute right-sided HF from pulmonary hypertension secondary to acute respiratory failure causes bulging of the interventricular septum into the LV chamber. This so-called "septal shift" results in decreased LV preload and low CO that is volume responsive. Chronic left-sided HF leads to pulmonary hypertension with resultant right-sided HF. In addition, cardiac biochemical changes such as an abnormal catecholamine response affect all chambers.

Nonetheless, the terms have usefulness in identifying the predominant clinical presentation. Fluid accumulation "behind" the involved ventricle is responsible for many of the clinical manifestations of HF. For example, LV failure leads primarily to pulmonary congestion with symptoms mostly of dyspnea and orthopnea. Patients with right-sided HF have symptoms of systemic venous congestion, such as pedal edema and hepatomegaly.

When previously healthy patients have acute pathology, the concept of left- versus right-sided HF may be clinically useful. Patients with acute MI may have APE; yet unlike patients with chronic HF, they may not have jugular venous distention or pedal edema because central venous pressure may remain within normal limits. A chest radiograph reveals evidence of pulmonary venous congestion, interstitial edema, and, in fulminant cases, alveolar edema. Because there has not yet been time for cardiac dilation, the cardiac shadow is often of normal size.

Acute RV infarction is an important cause of hypoperfusion with jugular venous distention and absent pulmonary congestion. There is often evidence of ST segment elevation or depression in the V_1 lead, and right-sided leads may provide further evidence of RV infarction. Approximately one third of patients with acute inferior infarction have significant RV involvement, leading to inadequate pulmonary perfusion and low LV priming (decreased preload). These patients have right-sided HF with hypotension that is often symptomatic. Aggressive crystalloid resuscitation, followed by inotropic support with norepinephrine, may be required for adequate LV preload and restoration of BP.

High-Output versus Low-Output Failure

High-output failure refers to a hyperdynamic state with supranormal CO and low arteriovenous oxygen difference (decreased oxygen extraction ratio). The hyperdynamic state may result from increased preload (e.g., renal retention of salt and water, or excess mineralocorticoids), decreased SVR (e.g., arteriovenous fistulas, pregnancy, cirrhosis, severe anemia, beriberi, thyrotoxicosis, Paget's disease, or vasodilator medications), increased beta-sympathetic activity, or persistent tachycardia. A persistent hyperdynamic state results in myocardial damage over time. Early recognition of the hyperdynamic state may allow effective therapy of the underlying condition, thus avoiding development of HF. As the condition progresses, myocardial dysfunction with circulatory overload is superimposed on this background, and symptoms progress. At some point, CO becomes normal or even low, indistinguishable from classic HF.

Low-output failure is the more typical variety of HF and occurs as a result of entities such as ischemic heart disease, dilated cardiomyopathy, valvular disease, and chronic hypertension. Low CO (systolic dysfunction), high filling pressures (diastolic dysfunction), and an increased systemic oxygen extraction ratio (widened arteriovenous oxygen difference) characterize this more commonly encountered form of HF.

www.ketabpezeshki.com 66485457-66963820

CLINICAL EVALUATION OF PATIENTS WITH SUSPECTED HEART FAILURE

Precipitating Causes of Heart Failure and Exacerbating Factors

When cardiac decompensation occurs because of an acute precipitating cause, intervention can focus on the precipitating factor(s), and the prognosis is much better than when there is simply progression of intrinsic cardiac failure. Causes of acute cardiac decompensation are provided in Box 81-1.

Iatrogenic causes of HF should also be considered, especially in patients who have recently received intravenous fluids. Patients with known renal insufficiency most often experience pulmonary edema as a consequence of salt and fluid overload, as well as missed dialysis. In chronic HF, the most common cause of decompensation is inappropriate decrease in intensity of treatment, including drug therapy, dietary sodium restriction, limited physical activity, or a combination of these measures.

Sodium and Volume Excesses

Increased sodium ingestion, most often a result of dietary noncompliance, or plasma volume expansion by excessive crystalloid infusion or transfusion, may prompt cardiac decompensation. Noncompliance with renal dialysis, in particular, is a very common cause of HF in patients who come to the ED.

Systemic Hypertension

Sudden elevation of arterial pressure acutely increases afterload, which may precipitate rapid onset of HF. This is particularly common when antihypertensive therapy is abruptly discontinued. Pheochromocytoma and other states associated with high sympathetic outflow may be implicated. Cocaine and other sympathomimetic drugs of abuse frequently precipitate HF. Emotional upset can dramatically increase afterload as well as precipitate coronary vasospasm, with the extreme example being acute stress cardiomyopathy (Takotsubo syndrome; see Chapter 78).

Myocardial Infarction and Ischemia

A new ischemic event may precipitate HF by impairing contractility and decreasing LV compliance. Pulmonary edema may occur rapidly in this setting, especially when large areas of myocardium are involved. In the compromised heart, even local ischemia may precipitate HF. Occult acute coronary syndrome is common, particularly in the elderly, and should be considered in any HF exacerbation. The presence of HF on admission in patients with acute coronary syndromes is associated with increased short- and long-term rates of death and MI.[52-54]

Systemic Infection

Infection results in increased systemic metabolic demands. The sepsis syndrome is associated with a reversible form of myocardial depression, mediated by various cytokines, including interleukin (IL)-1, IL-2, and IL-6, as well as tumor necrosis factor.[55] Proinflammatory cytokines such as tumor necrosis factor alpha and IL-6 also play an important pathogenic role in chronic HF.[56]

Dysrhythmia

Both tachydysrhythmias and bradydysrhythmias can severely affect CO, especially when acute. Tachydysrhythmias compromise diastolic filling time, reduce CO, and impair coronary perfusion as well as myocardial oxygen delivery. The tachycardia also results in increased myocardial oxygen demand. These factors may precipitate ischemia, which may further impair contractility and exacerbate HF.

The prevalence of AF in patients with HF increases from less than 10% in New York Heart Association (NYHA) functional class I to approximately 50% in NYHA functional class IV.[57] Neurohormonal alterations, electrophysiologic changes, and mechanical factors create an environment in which HF predisposes to AF and AF exacerbates HF. New-onset AF or other dysrhythmias that affect coordinated atrial priming of the ventricular pump may seriously reduce preload, especially in disease states with reduced ventricular compliance. Significant bradydysrhythmias may also reduce CO simply by reducing the number of systolic ejections per minute ($CO = SV \times HR$).

Acute Hypoxia and Respiratory Problems

Both COPD exacerbations and respiratory tract infections are very important precipitating factors for HF exacerbation.[58] Pulmonary infection, which is more common in patients with pulmonary vascular congestion, may add hypoxia to the metabolic stressors of fever, tachycardia, and increased tissue perfusion requirements.

Anemia

With chronic anemia, oxygen delivery to tissues is maintained by increased CO (isovolumic hemodilution). Anemia increases in prevalence with increasing severity of HF, especially with declining renal function and increasing age. Anemia is associated with poorer survival in HF,[59-61] with greater disease severity, greater LV mass index, and higher hospitalization rates. Abrupt exacerbations of anemia increase systemic perfusion demands and, especially if coupled with reduced coronary oxygen delivery, may prompt onset or exacerbation of HF.

Pregnancy

CO is normally increased significantly during pregnancy, which may lead to decompensation with underlying valvular disease or other cardiac pathology. Peripartum cardiomyopathy is a type of dilated cardiomyopathy that may occur late in pregnancy or more commonly in the early postpartum period.

Box 81-1 Common Precipitating Causes of Acute Heart Failure

- Sodium and volume excess
- Systemic hypertension
- Myocardial infarction or ischemia
- Systemic infection
- Dysrhythmias
- Acute hypoxia or respiratory problems
- Anemia
- Pregnancy
- Thyroid disorders
- Acute myocarditis
- Acute valvular dysfunction
- Pulmonary embolus
- Excess exertion or trauma
- Pharmacologic complications

www.ketabpezeshki.com 66485457-66963820

Thyroid Disorders

HF may be a clinical manifestation in patients with previously compensated cardiac disease who develop hyperthyroidism. Hypothyroidism also adversely affects myocardial pump function. Restoration of normal thyroid function usually reverses the abnormal cardiovascular hemodynamics.[62]

Acute Myocarditis

A variety of infectious and inflammatory diseases, including viral agents and acute rheumatic fever, may precipitously impair myocardial contractility.

Acute Valvular Dysfunction

Almost all causes of acute HF resulting from cardiac valve dysfunction are secondary to aortic or mitral insufficiency. Mitral valve papillary muscle dysfunction or rupture may result from acute MI, whereas acute aortic insufficiency is more commonly precipitated by acute bacterial endocarditis or aortic dissection. Occasionally, acute valvular stenosis may occur, usually as a consequence of acute dysfunction of a prosthetic valve.

Pulmonary Embolus

The pulmonary hypertension and hypoxia that accompany pulmonary embolus may cause acute HF. Accordingly, this diagnosis should be entertained in patients who have unexplained HF and risk factors for pulmonary embolism.

Excessive Exertion or Trauma

Increased physical activity may lead to decompensation, particularly in patients with significant HF. Trauma and injury also increase demand on the heart.

Pharmacologic Complications

Beta-blocking and calcium channel blocking agents have negative inotropic effects and may precipitate overt HF with excessive administration. Many antidysrhythmic agents have similar effects. Glucocorticoids, NSAIDs, vasodilator medications, and others may result in sodium retention with substantial increases in plasma volume that may precipitate HF.[63] NSAIDs in particular interfere with prostaglandin synthesis through cyclooxygenase inhibition, thereby impairing renal homeostasis in patients with HF. They also interfere with the effects of diuretics and ACE inhibitors. Nonadherence to medication regimens for hypertension, HF, or ischemia is the most common pharmacologic cause of HF decompensation.

Evaluation of Heart Failure

The NYHA classification system is a time-honored categorization for patients with chronic HF based on degree of activity causing symptoms (Box 81-2).[64] Careful consideration of the differential diagnosis of HF is symptom based. The most common manifestation of acute HF is respiratory distress caused by pulmonary edema. Therefore the differential diagnosis includes exacerbation of COPD or asthma, pulmonary embolus, pneumonia, anaphylaxis, and other causes of acute respiratory distress. Hypoperfusion may be caused by some of these as well as by sepsis syndrome, hypovolemia, hemorrhage, cardiac tamponade, and tension pneumothorax.

Box 81-2 Classification System for Chronic Heart Failure: New York Heart Association Functional Classes

I. Asymptomatic on ordinary physical activity
II. Symptomatic on ordinary physical activity
III. Symptomatic on less than ordinary physical activity
IV. Symptomatic at rest

History

The presence and character of dyspnea, chest pain, previous heart disease, cardiac catheterization, surgery, current medications (and adherence), and possible intercurrent illness should be explored.

Paroxysmal nocturnal dyspnea results from pulmonary congestion precipitated by plasma volume expansion that occurs during recumbency as interstitial edema is reabsorbed into the circulation. Orthopnea occurs through the same mechanism, with the supine position causing rapid increases in diastolic filling pressure. Symptoms abate after the patient stands or props up the trunk and venous return decreases. Nocturia results from the same pathophysiologic process. Many historical features increase the likelihood of HF. Most predictive is a past history of HF or paroxysmal nocturnal dyspnea, and the absence of dyspnea on exertion reduces the likelihood of chronic HF.[65]

Physical Examination

Most HF patients are hypertensive, which is prognostically preferable to normal or low BP. Clammy, vasoconstricted patients with a thready pulse and delayed capillary refill may have systemic hypoperfusion despite adequate BP, which is maintained by intense vasoconstriction. Noninvasive assessment of BP in the vasoconstricted patient with low CO can be inaccurate.[66] If available, intra-arterial pressure monitoring may more accurately reflect the systemic hemodynamic state and guide the choice of inotropic or vasoconstrictor therapy in hypotensive HF patients.

Most patients with APE are diaphoretic because of intense sympathetic activation. Patients with pulmonary congestion secondary to HF develop interstitial and alveolar pulmonary edema, causing reduced pulmonary compliance and decreased functional residual capacity. Clinical findings include diffuse moist rales, which may be absent with decreased ventilation in more agonal patients. Peribronchial edema may cause wheezing or rhonchi, which can mimic bronchospastic disease ("cardiac asthma"). A positive response to bronchodilator therapy does not exclude HF. Jugular venous distention is present in approximately 50% of cases, and one third of patients have peripheral edema. An S_3 gallop may be present in up to 25% but is often difficult to hear.

These common clinical findings of chronic HF are prevalent among patients with APE because most patients have acute exacerbations superimposed on chronic underlying disease. Jugular venous distention, pedal edema, and cardiomegaly may be absent in previously healthy individuals with pulmonary edema resulting from an initial episode of acute HF. The presence of a third heart sound significantly increases the likelihood of HF, whereas absence of rales decreases the likelihood.[65] Physical examination of patients with APE resulting from acute MI may identify surgically correctable lesions such as acute mitral regurgitation or ventricular septal defect.

Diagnostic Testing in Heart Failure

An upright chest radiograph helps distinguish cardiogenic pulmonary edema from other causes of dyspnea. An enlarged cardiac silhouette is seen in 70% of cases. A normal heart size suggests acute cardiogenic pulmonary edema in a patient without prior HF,

www.ketabpezeshki.com 66485457-66963820

diastolic dysfunction, COPD, or noncardiogenic pulmonary edema. An early ECG for arrhythmia recognition and management is important, as well as for identification of acute coronary syndrome. Absence of cardiomegaly on chest radiography and a normal ECG greatly decrease the likelihood that HF is causing the presentation.[65] Obtaining a complete blood count (CBC) to evaluate for anemia and a basic metabolic panel to determine electrolyte status as well as renal function is generally useful. Cardiac biomarkers help evaluate for ongoing myocyte injury, which may be clinically silent.

In most cases, and particularly when the diagnosis of HF is unclear, natriuretic peptide levels should be obtained. Pre-proBNP is synthesized in the ventricles in response to myocyte stretch, then released and enzymatically cleaved to NH_2-terminal–proBNP (NT-proBNP) and BNP. NT-proBNP and BNP levels help identify patients with HF and may improve management of patients in the ED with dyspnea.[67-69] The "breathing not properly" BNP Multinational Study was a prospective evaluation of patients who came to the ED with acute dyspnea. BNP levels above 500 pg/mL were highly associated with HF (likelihood ratio [LR] 8.1), and levels of 100 to 500 pg/mL were generally indeterminate (LR = 1.8). A low BNP level (<100 pg/mL) indicated that HF was highly unlikely (LR = 0.13).[70,71] ED use of BNP and NT-proBNP assays aids diagnosis of HF and can reduce admission rates and length of hospitalization in acute dyspnea.[72]

Natriuretic peptide levels correlate with ventricular function, NYHA classification, and prognosis.[73-76] Results of large clinical trials confirm that BNP levels are the strongest predictor of outcome in HF compared with other neurohormones and clinical markers.[77] There is often a disconnect between the perceived severity of HF by clinicians and the degree of BNP elevation, yet BNP levels are better predictors of 90-day outcome than physician judgment.[78] High predischarge BNP and NT-proBNP levels are strong, independent predictors of death or rehospitalization after decompensated HF.[79,80]

NT-proBNP– and BNP-guided therapy reduces all-cause mortality and provides a strong measure of therapeutic response in chronic HF compared with usual care.[81-83] Mildly elevated BNP levels may also be seen in right-sided HF related to cor pulmonale or pulmonary embolism. BNP levels are only slightly elevated in patients with end-stage renal disease, and in this setting marked elevation reflects ventricular dysfunction.[84] Admission BNP and troponin levels are independent predictors of in-hospital mortality in acute decompensated HF.[85] Increased concentrations of these and other biochemical markers of myocyte injury in the absence of discrete ischemic events in HF help identify patients most likely to have adverse outcomes.[86] Plasma levels of cardiac troponins in stable HF also predict adverse outcomes.[87,88]

The ESCAPE trial demonstrates that pulmonary artery catheterization in severe symptomatic HF increases anticipated adverse effects but does not affect overall mortality or duration of hospitalization.[89] Noninvasive impedance cardiography appears to be an effective and developing technology to measure CO and other hemodynamic variables in HF and may obviate the need for a pulmonary artery catheter, although it cannot reliably measure LV filling pressures.[90,91]

Bedside ultrasound can be an important ED screening tool in HF, with attention to wall motion abnormalities, EF, and valvular function, as well as exclusion of cardiac tamponade. Echocardiography is similarly useful and can provide detailed measures of LV function and determine structural heart disease.[92,93] Multidetector computed tomography coronary angiography can distinguish ischemic from other forms of cardiomyopathy but is rarely useful in acute HF.[94] Radionuclide imaging and cardiac magnetic resonance imaging have an expanding role in evaluating chronic HF but no utility in the acute setting.

TREATMENT OF ACUTE HEART FAILURE

Of patients with HF in the ED, about 20% are experiencing their first episode of HF, and 80% have had prior hospital visits for the same condition.[42] The approach focuses on (1) determining underlying cardiac pathology, (2) identifying the acute precipitant, and (3) mitigating the acute decompensation. The immediate therapeutic goals are to improve respiratory gas exchange, maintain adequate arterial saturation, and decrease LV diastolic pressure while maintaining adequate cardiac and systemic perfusion.

The acute congestive state can be controlled by (1) reducing cardiac workload through decreased preload and afterload, (2) controlling excessive retention of salt and water, and (3) improving cardiac contractility. Patients may have a wide spectrum of symptoms and signs ranging from mild dyspnea on exertion to full-blown cardiogenic shock with hypotension and concomitant respiratory failure.

Acute Heart Failure

Pulmonary edema is classified clinically into cardiogenic and noncardiogenic forms. Most patients in the emergency setting with pulmonary edema have the acute cardiogenic variety, resulting mainly from elevated LV end-diastolic pressure, forcing a protein-sparse plasma ultrafiltrate across the pulmonary capillary membrane into the pulmonary interstitium. Large amounts of edema accumulate, leading to alveolar flooding. Volumes as large as 1 or 2 L may leave the plasma over a short time and create serious respiratory compromise. Most commonly, cardiogenic pulmonary edema occurs with acute myocardial ischemia or infarction, cardiomyopathy, valvular heart disease, or hypertensive emergencies.

Patients with acute cardiogenic pulmonary edema have substantially lower plasma volumes than control patients. These changes are reflected by initial hemoconcentration as evidenced by higher hematocrits and colloid osmotic pressures. Despite the presence of pulmonary congestion, concomitant hypotension may require fluid challenge to rapidly restore preload, CO, systemic perfusion, and BP. Thus careful volume infusion with aliquots of normal saline is appropriate initial resuscitation for the hypoperfusing patient with acute-onset cardiogenic pulmonary edema.

In contrast, noncardiogenic pulmonary edema generally results from an alteration in the permeability characteristics of the pulmonary capillary membrane. The alteration may have such diverse causes as septic shock, inhalation injuries, drugs or toxins, aspiration syndromes, fat emboli syndrome, neurogenic causes, and high altitude.

Acute Heart Failure with Adequate Perfusion

Many patients with acute HF demonstrate adequate systemic perfusion with elevated BP because of activation of various compensatory mechanisms. The ability of the left ventricle to generate normal or elevated systolic pressures indicates the presence of considerable myocardial reserve and is associated with lower mortality in both acute and chronic HF.[95] These patients should be quickly distinguished from those with pulmonary edema and evidence of hypoperfusion. Hypertensive pulmonary edema is easier to manage because afterload reduction with vasodilators is extremely effective.

Therapeutic interventions should decrease both preload and afterload. Excessive preload reduction may result in an abrupt decrease in CO, however, which could cause hypotension. This occurs more readily in patients with less compliant hearts. Fluid

www.ketabpezeshki.com 66485457-66963820

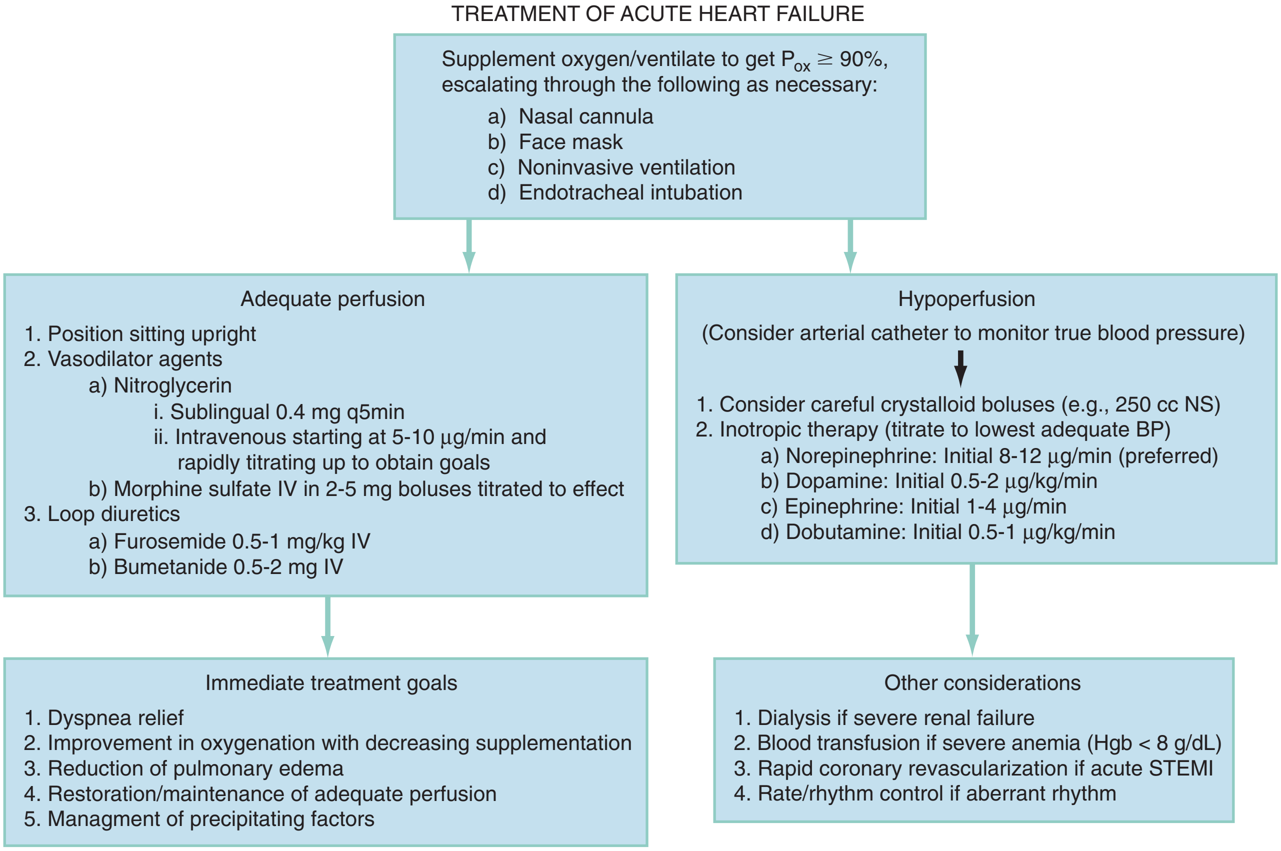


Figure 81-5. A general therapeutic strategy for acute heart failure requires thoughtful application of interventions to achieve a reasonable improvement in early clinical treatment goals. Appropriate interpretation of the perfusion with use of clinical criteria and occasionally arterial pressure monitoring is central to the strategy. *BP,* blood pressure; *Hgb,* hemoglobin; *IV,* intravenously; *NS,* normal saline; P_{ox}, pulse oximetry; *STEMI,* ST segment elevation myocardial infarction.

challenge generally restores BP. Therapy for APE with adequate perfusion should begin with upright positioning, supplemental oxygen, nitrates, morphine sulfate, and loop diuretics (Fig. 81-5). This allows prompt improvement in most of these patients.

Oxygen and Ventilation

All patients with significant pulmonary edema have hypoxemia and require high-flow oxygen by face mask if spontaneously breathing and if oxygen saturation as measured by pulse oximetry (Spo_2) is below 90%. Excessive oxygen therapy, however, may significantly increase afterload and worsen cardiac function in decompensated HF.[96] The typical acid-base disturbance of acute HF is mixed. Patients with fulminant APE may have lactic acidosis, and many also have concomitant respiratory alkalosis resulting from the tachypnea stimulated by metabolic acidosis, hypoxemia, and decreased pulmonary compliance. In more severe cases, respiratory acidosis ensues as the patient fatigues and respirations fail. The ratio of dead space to total ventilation (V_D/V_T) may be significantly increased owing to alveolar flooding. Patients with inadequate ventilation or with severe hypoxia that does not respond to supplemental oxygen require ventilatory support. Noninvasive ventilation (NIV) techniques are effective in treating severely compromised, but not agonal, APE patients (see Chapter 2.) Continuous positive airway pressure (CPAP) or biphasic positive airway pressure (BPAP) applied by an adjustable, snugly fitting face mask increases functional residual capacity, improves oxygenation, reduces work of breathing, and results in decreased LV preload and afterload by raising intrathoracic pressure (Fig. 81-6). These

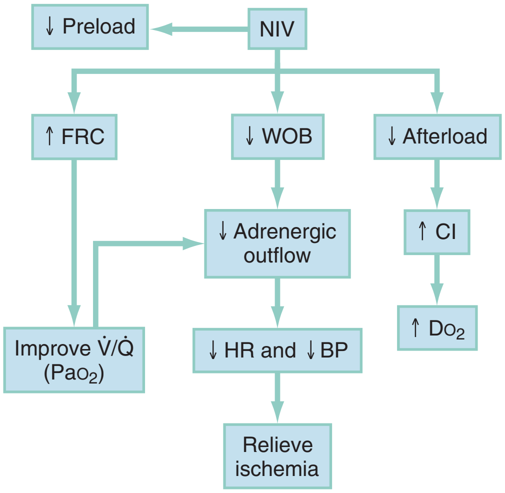


Figure 81-6. Noninvasive ventilation *(NIV)* techniques recruit collapsed alveoli and increase functional residual capacity *(FRC),* which improves oxygenation and reduces work of breathing *(WOB).* These factors tend to reduce sympathetic tone, heart rate *(HR),* and blood pressure *(BP),* relieving myocardial ischemia. NIV also acts as an afterload-reducing agent, which tends to directly improve cardiac index *(CI),* systemic oxygen delivery (Do_2), partial pressure of oxygen in arterial blood (Pao_2), and ventilation-perfusion ratio ($\dot{V}/\dot{Q}$). Preload is also reduced by NIV.

www.ketabpezeshki.com 66485457-66963820

techniques result in more rapid restoration of normal vital signs and oxygenation than supplemental oxygen alone. Even in studies using only CPAP, fewer patients will require endotracheal intubation. The addition of pressure support (BPAP) further reduces the work of breathing and more rapidly improves hypercarbia than CPAP alone. Selected patients may benefit greatly from these techniques when appropriately applied in conjunction with pharmacotherapy.[97,98] These ventilatory therapies do not increase the risk of MI in APE.[99] A large multicenter trial demonstrated that NIV provides earlier improvement in respiratory distress and related metabolic abnormalities than supplemental oxygen alone in APE but does not improve short-term mortality.[100]

Patients too ill for noninvasive ventilation are supported with bag-valve-mask assisted oxygenation in preparation for tracheal intubation. Intubation is indicated for apneic patients and those with respiratory distress, agitation, or hypoxemia not responsive to high-flow oxygen or NIV. Most spontaneously breathing patients respond rapidly to medical therapy, and the majority of alert hypercarbic patients can also be managed without mechanical ventilation.

Vasodilator Agents

Nitrates and Nitroprusside

Organic nitrates activate the enzyme guanylate cyclase, leading to accumulation of cGMP, which relaxes vascular smooth muscle by sequestering calcium in the sarcoplasmic reticulum. At lower doses, nitrates are primarily venodilators. They effectively decrease preload and are therefore very effective in the initial therapy of APE. At higher doses, intravenous nitroglycerin also causes arteriolar dilation that decreases BP and afterload. Thus pump function is improved while myocardial oxygen demand is decreased. Nitroglycerin may further reduce myocardial ischemia by its direct coronary vasodilator effect and is particularly effective when myocardial ischemia is contributing to the acute decompensation. Prolonged nitrate therapy over hours to days leads to tachyphylaxis secondary to depletion of intracellular sulfhydryl groups.

Nitroglycerin may be initiated by the sublingual route, followed by titrated intravenous administration. Intravenous nitroglycerin has rapid onset and offset of action. Hypotension from excessive preload reduction or vagally mediated idiosyncratic reactions may occur. Nitroglycerin should be avoided in patients who have taken impotence medications (PDE type 5 inhibitors) within the previous 24 hours (up to 48 hours for tadalafil), as the combination may precipitate refractory hypotension. Transcutaneous absorption may be erratic because of diaphoresis and poor skin perfusion, so ointment should not be used as a delivery mechanism until the patient's condition has stabilized. Also, transcutaneous nitroglycerin patches may ignite during defibrillation. Sodium nitroprusside works similarly to nitroglycerin, acting as a balanced vasodilator to reduce both preload and afterload. Continuous intra-arterial pressure monitoring is preferred in patients receiving this drug to avoid precipitous hypotension. Nitroprusside is useful for patients with pulmonary edema and significant systemic hypertension. In the presence of acute myocardial ischemia or infarction, however, nitroglycerin is preferable because it avoids the coronary steal syndrome, in which normal vessels dilate and divert flow from more diseased vessels. These patients are also particularly vulnerable to unintended hypotension, an event more likely to occur with nitroprusside than nitroglycerin. Patients with renal failure may experience thiocyanate toxicity from high-dose nitroprusside infusions. Cyanide toxicity, recognized clinically by the presence of agitation and lactic acidosis, may occur in individuals with a genetic predisposition. Nitroglycerin is thus preferred over nitroprusside in HF.

Morphine Sulfate

Morphine sulfate, an opioid analgesic, reduces pulmonary congestion through a central sympatholytic effect and release of vasoactive histamine, causing peripheral vasodilation and reduced preload. In addition, through reduced systemic catecholamines, morphine decreases HR, BP, cardiac contractility, and myocardial oxygen consumption. Patients with APE tend to be agitated as a result of air hunger. The calming effect of morphine is advantageous in this setting. Morphine is administered in repetitive 2- to 5-mg intravenous doses carefully titrated to effect. If oversedation results in hypoventilation, gentle stimulation usually restores ventilatory effort. In APE, mild carbon dioxide (CO_2) retention does not contraindicate morphine use because it results from acute alveolar flooding that is improved by the mechanisms just delineated. Airway support should be considered, however, before morphine use in obtunded HF patients

Nesiritide

Nesiritide, a recombinant human BNP, is a balanced vasodilator that reduces aldosterone and ET levels while increasing sodium and water excretion, without a resultant reflex tachycardia. Nesiritide, however, is not superior to nitroglycerin, nor does it provide additional benefit when added to a treatment regimen that includes intravenous nitroglycerin. Treatment of acute HF with nesiritide did not reduce return to the ED or 30-day hospitalization in one ED study.[101] Meta-analyses of studies using nesiritide in acute HF suggest the possibility of increased drug-related mortality.[102-104] Nesiritide is not indicated in the emergency department treatment of episodes of acute HF.

Loop Diuretics

Loop diuretics inhibit sodium resorption from renal filtrate, resulting in significant increases in salt and water excretion. In patients with volume overload, this diuretic action lowers plasma volume, decreasing preload and pulmonary congestion. Although the renal effects of intravenously administered loop diuretics begin within 10 minutes, symptom relief in patients with APE often occurs much faster, probably the result of diuretic-induced neurohumoral changes. Furosemide acts as a vasodilator, promoting both renal PGE_2 and natriuretic peptide secretion, and as a vasoconstrictor, stimulating renin release. Loop diuretics (furosemide or bumetanide) should be administered to patients with hypertensive APE. The half-life of furosemide in patients with APE is double that in healthy volunteers, and caution is required with frequent administration. Continuous infusion of furosemide is not superior to bolus therapy.[105]

Patients with abrupt onset of APE who do not have underlying chronic HF may have low plasma volumes at presentation, and diuresis in this group of patients may be unnecessary. Patients who fail to respond to loop diuretic administration may have severely compromised renal perfusion. In these situations, invasive hemodynamic monitoring may be beneficial. Diuretic therapy causes depletion of the important cations K^+ and Mg^{2+}, which may be significant in patients in whom these cations are already depleted by chronic diuretic therapy or other agents. High-dose diuretic therapy in APE is associated with deterioration in renal function and increased mortality.[106,107]

Other Therapies

Most patients with APE and adequate systemic perfusion respond promptly to treatment with oxygen, nitrates, morphine, and diuretics. Hemodialysis is useful in patients with renal insufficiency. Blood transfusion candidates in acute HF have worse

www.ketabpezeshki.com 66485457-66963820

clinical features but derive some benefit from RBC repletion for hemoglobin levels below 8 g/dL.[108,109] Therapies such as ET receptor antagonists,[110,111] vasopressin receptor antagonists,[112-114] beta-endorphins,[115] adenosine receptor antagonists,[116,117] and other agents have undefined therapeutic potential. Urodilatin, a synthetic renal natriuretic peptide, has effectiveness in acutely decompensated HF.[118] Levosimendan, a calcium-sensitizing drug that opens ATP-dependent potassium channels, provides prompt hemodynamic improvement in acute HF.[119] In cardiogenic shock treated with percutaneous coronary intervention (PCI), levosimendan improves cardiovascular hemodynamics compared with conventional inotropic therapy.[120] Relaxin, a vasodilating hormone produced in pregnant women, shows promise in the treatment of decompensated HF.[121] Trials with a tumor necrosis factor antagonist have failed to demonstrate benefit in HF.[122] Historical therapies (e.g., rotating tourniquets, phlebotomy, and theophylline) have no demonstrated efficacy in APE. Endotracheal intubation should be reconsidered if the patient develops severe respiratory deterioration unresponsive to NIV, significant cardiac dysrhythmias, or low CO or has ongoing chest pain.

Treatment of Acute Heart Failure in Hypotensive Patients

Patients with acute cardiogenic pulmonary edema and apparent systemic hypotension present a therapeutic dilemma. Coronary perfusion in patients depends on the pressure gradient between the aorta and LV chamber in diastole. The combination of hypotension and elevated left-sided filling pressure dramatically decreases coronary perfusion, particularly with coronary artery disease, leading to further impairment of contractility from increased ischemia. Vasopressor administration to maintain coronary perfusion pressure is necessary if this set of conditions truly exists. Vasopressors, however, can increase afterload, decrease CO, increase myocardial oxygen demand, exacerbate ischemia, and precipitate dysrhythmias. As previously discussed, an intra-arterial catheter provides more accurate and immediate BP monitoring and is helpful in guiding therapy.

If the patient is truly hypoperfusing, initial measures should aim to maintain or restore coronary perfusion pressure. In this setting, the patient is either in true cardiogenic shock (pulmonary edema, hypotension, and decreased peripheral perfusion) or is volume depleted. Patients in true cardiogenic shock have lost as much as 40% of their ventricular muscle mass. Nearly 25% of patients with acute MI and clinical evidence of systemic hypoperfusion, however, have low preload, indicating the presence of hypovolemia. Fluid challenge alone in these patients restores hemodynamic stability in half. Hypotensive patients with APE should receive a judicious fluid challenge in the form of 250-mL crystalloid boluses over 5 to 10 minutes. If respiratory status is not deteriorating, repeated aliquots may be administered. If hypovolemia is contributing to hypotension, this intervention should restore BP and systemic perfusion without need for vasopressors. If the patient has true cardiogenic shock, more intensive interventions, including vasopressor therapy, intra-aortic balloon counterpulsation, and endotracheal intubation with mechanical ventilation, may be needed. APE with systemic hypoperfusion in the setting of acute coronary syndrome represents ischemic cardiogenic shock. Emergency coronary revascularization is the treatment of choice.[123]

Inotropic or Vasopressor Therapy

Inotropic agent use in HF increases myocardial oxygen demand, cardiac arrhythmias, and mortality.[124] Intravenous inotropic agents with vasoactive properties should be reserved for hypoperfused patients with low CO despite a high LV filling pressure.[125] In patients with acute MI or ischemia and severe LV dysfunction, the use of a catecholamine may be counterproductive, as all increase myocardial cell work and thus further injure ischemic myocardium. Revascularization to reperfuse stunned or hibernating myocardium is preferable.

In hypotensive patients who are adequately volume repleted (true cardiogenic shock), norepinephrine is the pressor of choice.[126] It raises BP and coronary perfusion pressure (alpha-vasoconstrictor effect) with a modest beta effect for inotropy and the least overall increase in HR and contractility, which could further increase myocardial oxygen demand. In cardiogenic shock, norepinephrine administration is a temporizing maneuver to maintain coronary perfusion pending rescue strategies, such as angioplasty, intra-aortic balloon pumping, or cardiac surgery.

Dopamine is a naturally occurring catecholamine and a norepinephrine precursor. It has a dose-dependent effect on peripheral vascular tone and is a positive inotropic and chronotropic agent. Despite previous impressions, dopamine in HF has no clinically significant perfusion-sparing effect on the kidneys at any dose.[127,128] Epinephrine is a potent alpha- and beta-agonist that maintains BP and increases CO. In cardiac surgery patients, it combats myocardial stunning after cardiopulmonary bypass. Dobutamine is a synthetic catecholamine that is mainly a beta$_2$-receptor agonist with some beta$_1$- and alpha-agonist activity. It is an inotropic vasodilator at therapeutic doses and should be used with caution in patients with borderline hypotension because it occasionally reduces BP further. Isoproterenol is a potent beta-agonist that causes profound tachycardia and vasodilation, which would be dangerous in HF.

Amrinone and milrinone are PDE type III inhibitors that increase cyclic adenosine monophosphate (cAMP) in the myocardium and peripheral smooth muscle. These intravenous vasodilating inotropic agents increase CO and reduce LV pressures without producing significant changes in HR and BP. The positive inotropic effects of amrinone and dobutamine are additive, and concomitant use of both drugs appears to be better tolerated than high doses of dobutamine alone, with lower metabolic costs. Amrinone and milrinone may be useful on a short-term basis in patients awaiting heart transplantation. They should be used with caution in selected patients—in general in the context of invasive hemodynamic monitoring. These agents are prodysrhythmic, and long-term use of PDE type III inhibitors reduces survival in HF.[129]

Rate and Rhythm Controllers

Rate and rhythm control is occasionally necessary in HF. Compensatory tachycardia is the rule in HF, unless the patient is taking beta-blocking agents. Noncompensatory tachycardia increases myocardial oxygen consumption while reducing coronary perfusion and is a particular problem with atrial flutter or fibrillation with rapid ventricular response. As with other causes of HF, diltiazem is a more prompt and safe alternative to digoxin in normotensive patients.[130] Electrical cardioversion is indicated when a new-onset tachydysrhythmia is causing or exacerbating HF, especially with hypoperfusion or ongoing evidence of myocardial ischemia. Transcutaneous pacing may be necessary in severe bradycardia with hypotension.

Chronic Heart Failure

Chronic HF often involves a more gradual onset of symptoms, with a slow increase in dyspnea on exertion, progressive orthopnea, fatigue, and other symptoms. Patients with chronic HF often have complex multiorgan dysfunction and comorbidities for which polydrug medical regimens are used. In this clinical setting, the potential impact of any therapeutic intervention on the

www.ketabpezeshki.com 66485457-66963820

entire spectrum of disease and compensatory mechanisms should be considered. For example, adding an NSAID to the medical regimen of a patient with chronic HF may negatively affect renovascular function and precipitate increased fluid retention and pulmonary edema.[89]

U.S. guidelines approved by the AHA and ACC reflect a new classification system for chronic HF that includes four categories: patients at risk, patients with asymptomatic LV dysfunction, patients with symptomatic HF, and those with refractory HF. The number of patients with asymptomatic LV dysfunction is approximately fourfold greater than the number of patients with symptomatic HF.[131] Echocardiography is a very useful modality in screening for asymptomatic LV dysfunction in high-risk subgroups.[132]

A main goal in the management of HF is to modify long-term maladaptive responses as well as achieve short-term functional improvement.[133] Treatment should ideally be initiated in patients at risk to prevent disease progression. Atherosclerotic coronary artery disease, hypertension, diabetes mellitus, hyperlipidemia, cocaine or ethanol abuse, smoking, and obesity are significant risk factors for HF.[134] Hypertension precedes HF in 75% of patients, particularly in blacks. Control of hypertension reduces the risk of development of HF,[135] as does improvement of dyslipidemias in patients with atherosclerosis. Approximately two thirds of patients with systolic HF have significant coronary artery disease. Those with diabetes mellitus have more than a threefold increased risk of cardiac ischemic events and HF.[136] High dietary sodium is associated with impaired diastolic relaxation.[137] Appropriate lifestyle changes, including smoking cessation, weight reduction, restriction of salt and water intake, and modest exercise programs, reduce symptoms in HF and may delay progression. Excessive lipid accumulation within the myocardium is directly cardiotoxic and causes LV remodeling and dilated cardiomyopathy.[138] Substantial weight loss in patients with HF associated with obesity produces a reversal of many of the clinical manifestations and improves NYHA functional class in most patients.[139,140] Paradoxically, however, overweight and obese patients have lower cardiovascular mortality in chronic HF.[141]

The LV remodeling process is triggered by volume or pressure overload as well as loss of cardiac myocytes (e.g., MI). Therapeutic interventions in HF aim to slow remodeling. Ventricular remodeling correlates with poor clinical outcomes in HF.[142] Serial measurements of various neurohormones may serve as surrogate markers of ventricular remodeling.[143] Various antihypertensive therapies allow regression of LV hypertrophy and reduce the rate of sudden cardiac death.[144] Reverse remodeling is a concept in which progressive LV dysfunction is not simply arrested but also partially reversed.[145] Beta-blockers, ACE inhibitors, aldosterone antagonists, and angiotensin receptor blockers (ARBs) all inhibit or reverse remodeling.[146,147]

The mainstay of treatment for chronic HF and asymptomatic LV dysfunction is vasodilator therapy, which benefits pump function by reducing both afterload and preload. The most important vasodilators for chronic HF are ACE inhibitors, angiotensin II receptor antagonists, and nitrates.

Common Therapeutic Agents in Chronic Heart Failure

Angiotensin-Converting Enzyme Inhibitors. ACE inhibitors provide the most effective therapy for LV dysfunction. They increase survival in all classes of chronic HF and reduce development of HF in patients with MI and asymptomatic LV dysfunction.[148-150] ACE inhibitors are natriuretic vasodilators that block production of angiotensin II and aldosterone secretion, reducing diuretic and potassium supplement requirements. Additional ACE inhibitor effects include inhibition of bradykinin degradation and reduction of intrinsic ET-dependent vasoconstriction.[151] Unlike other vasodilators, they do not induce reflex tachycardia.

The main side effects of ACE inhibitors are hypotension, deterioration of renal function, chronic cough, and upper airway angioedema. ACE inhibitors should be initiated at low doses with careful attention to the potential for hypotension, with concomitant reduction in diuretic and potassium supplementation. Optimization of ACE inhibitor dosage appears to be neglected in many patients with HF, particularly the elderly.[152,153] In patients with chronic HF, high-dose aspirin (>325 mg/day) may impair some clinical benefits of ACE inhibitors.[154]

Angiotensin II Receptor Blockade. In HF patients intolerant of ACE inhibitors, angiotensin type I (AT_1) receptor blockers are useful.[155] In a meta-analysis of 17 trials comparing angiotensin II receptor blockers with ACE inhibitors, both ACE inhibitors and ARBs allowed reverse remodeling in HF[156] and reduced the risk of development of AF.[157] ARBs were not superior to ACE inhibitors in reducing mortality or hospitalization for HF.[158,159] The combination of an ARB and an ACE inhibitor, however, increases hyperkalemia and hypotension and worsens renal function. Because of marginal benefit and increased side effects, dual renin-angiotensin blockade with an ACE inhibitor and an ARB is no longer recommended in HF.[160] ARBs are most useful in patients intolerant of ACE inhibitors[155] and have reduced side effects of cough and bradykinin accumulation.[161,162]

Beta-Blocker and Combined Alpha-, Beta-Blocker Therapy. Despite the apparent paradox of use of agents that reduce myocardial contractility, beta-adrenergic blocking agents have significant efficacy in chronic HF. Long-term activation of the sympathetic nervous system in HF, activation of the RAAS, myocardial beta-adrenergic receptor downregulation, and direct cardiotoxicity because of elevated norepinephrine levels are associated with adverse effects. An extensive meta-analysis revealed that beta-blockers in chronic HF significantly increase EF and decrease mortality.[163-165] HR reduction with use of beta-blockers correlates with improvement in LVEF and reduced death rate in HF.[166-167] AHA/ACC guidelines recommend beta-blockers for all patients with symptomatic LV systolic dysfunction.[168]

Beta-blockers should not normally be initiated in acute HF. They are most useful in chronic HF associated with conditions having indications for beta-blocker therapy, including hypertension, angina pectoris, and significant dysrhythmias. Slow upward titration of beta-blocker therapy facilitates maximal tolerability.[169] Vasodilating beta-blockers such as carvedilol and nebivolol may have special use in chronic HF.[170,171] Carvedilol, a third-generation alpha- and beta-blocker with antioxidant properties, may be a particularly effective agent in chronic HF.[172-174] In one large study comparing metoprolol with carvedilol for HF, the number needed to treat was 15 to prevent one excess death at 5 years for carvedilol.[175] Nebivolol is a $beta_1$-receptor blocker with NO-potentiating vasodilatory effects that improves hemodynamics and prognosis in chronic HF.[170]

Diuretics. Patients with chronic HF exhibit a reduced ability to excrete a sodium and water load, with abnormal cardiac and hemodynamic adaptations to salt excess.[176] Low-dose diuretics are one of the most effective treatments to prevent recurrence of HF.[177] Loop diuretics, although commonly used, are associated with significant side effects, including hypovolemia, electrolyte disturbances (low K^+, Mg^{2+}, and Na^+), hyperuricemia, worsening renal function, and metabolic alkalosis. Torasemide may block the aldosterone cascade, unlike furosemide, and may be clinically a better loop diuretic in chronic HF.[178] The addition of thiazide diuretic therapy to loop diuretics greatly increases sodium and fluid excretion but increases side effects.[179]

In patients hospitalized for HF exacerbation, admission serum sodium is an independent predictor for increased days of hospitalization for cardiovascular causes and increased mortality

www.ketabpezeshki.com 66485457-66963820

within 60 days of discharge.[180-182] Persistent hyponatremia is an independent predictor of mortality, hospitalization for HF, and death or rehospitalization, despite clinical and hemodynamic improvements similar to those in patients without hyponatremia.[183,184]

The hypokalemia and hypomagnesemia secondary to diuretic therapy are prodysrhythmic. The use of potassium-sparing diuretics in HF is associated with a reduced risk of death. Spironolactone and eplerenone directly antagonize aldosterone. They significantly reduce mortality while improving LV function in patients with severe HF (EF below 35%) already being treated with an ACE inhibitor and a loop diuretic, with or without digoxin.[185,186] Spironolactone reverses remodeling in patients with mild to moderate chronic systolic HF.[187,188] Eplerenone, when used in addition to standard therapy, results in significant reduction in morbidity and mortality in patients after acute MI.[189-191] Aldosterone antagonists may lead to serious hyperkalemia in the presence of significant renal insufficiency or in patients taking supplemental potassium.

Nitrates. Nitrate therapy, by virtue of a direct vasodilator effect, improves exercise tolerance in chronic HF and offers potential hemodynamic improvement.[192] Isosorbide used in combination with the arteriolar dilator hydralazine prolongs survival in patients with HF, but less so than ACE inhibitors. ACE inhibitors, however, are less effective in African Americans. A fixed-dose isosorbide dinitrate–hydralazine regimen is particularly effective in chronic HF in African Americans,[193] reducing hospitalization and mortality by about 40%,[194] with these positive effects sustained over time.[195,196] The main problem with nitrate therapy appears to be rapid drug tolerance, which can be partially addressed by daily nitrate drug-free intervals.

Cardiac Glycosides. The cardiac glycosides inhibit the adenosine triphosphatase–dependent sodium-potassium pump in the cell membrane of the cardiac myocyte. This inhibition increases the availability of intracellular calcium to contractile proteins in myocardial cells, with modest positive inotropic effect. Digoxin is of benefit in patients with all degrees of chronic HF by reducing symptoms and improving quality of life and exercise tolerance.[197] Digoxin reduces the rate of hospitalization in chronic HF, and it decreases mortality when added to an ACE inhibitor and diuretic therapy.[198,199] Digoxin should be used in low doses for most persistently symptomatic HF patients whose treatment already includes ACE inhibitors, diuretics, and beta-blocker therapy when HF is caused by systolic or diastolic dysfunction.[200]

Other Considerations in Chronic Heart Failure

Electrical Therapy. Implantable cardioverter-defibrillators (ICDs) have a substantial mortality advantage over antiarrhythmics in chronic HF,[9,201] particularly in patients with previous MI and low LVEF. Prophylactic placement in appropriate patients undergoing coronary artery bypass grafting (CABG), however, has been found to be ineffective in reducing mortality in the first 6 months after surgery.[202] Although a meta-analysis of ICD therapy continues to show benefit in MI patients with low EF,[203] the economic impact is unclear.

Patients with severe HF and significant LV dyssynchrony benefit from atrioventricular sequential pacing.[204,205] RV apical pacing is often used in chronic HF but creates abnormal LV contraction, hypertrophy, and reduced pump function.[206] Cardiac resynchronization therapy (CRT) via LV or biventricular pacing attempts to coordinate the activation of the interventricular septum and left ventricle free wall in HF. LV or biventricular pacing allows more physiologic LV contraction, and both are equally effective.[207,208] CRT improves HF symptoms and exercise capacity and can reverse chronic cardiac dilation.[209-214] CRT combined with ICD use greatly reduces risk of sudden cardiac death[215-221] and other cardiac events.[222] Cardiac resynchronization in patients with AF is also effective in improving EF as well as functional outcome[223] and appears more effective than pharmacologic therapy.[224] CRT also reduces functional mitral regurgitation at rest.[225]

Intrathoracic impedance monitoring is available on some devices to continuously monitor hemodynamic status in HF.[226,227] Potential roles for telemonitoring in chronic HF are evolving.

Antidysrhythmic Therapy. From 70 to 95% of patients with cardiomyopathy and HF have frequent premature ventricular beats, and 40 to 80% develop nonsustained ventricular tachycardia,[228] with an associated increased risk of sudden death. Amiodarone and classmate dronedarone are useful in acute management of sustained ventricular tachyarrhythmias. In chronic HF, amiodarone prevents the development of AF and converts significantly more patients with AF to sinus rhythm.[229] In patients with AF and HF, however, rhythm control was not found to reduce the cardiovascular death rate compared with rate control.[230] Unfortunately, amiodarone and other antidysrhythmic agents have significant toxicities and may be prodysrhythmic, and none demonstrates decreased mortality in HF.[231,232] Dronedarone has been found to similarly increase mortality and worsen HF in patients with LV systolic dysfunction.[233] In patients with post-MI LV systolic dysfunction with or without HF, amiodarone is associated with increased early and late all-cause cardiovascular mortality.[234,235] ICD therapy is also superior to amiodarone in terms of psychological well-being and quality of life in HF.[236]

Rate control of sinus rhythm is recognized as an avenue for therapeutic intervention in HF.[237,238] In patients with LV dysfunction and stable coronary artery disease, elevated HR above 70 beats/min is associated with higher cardiovascular mortality and admission for MI or HF.[239] In particular, for every increase of 5 beats/min above 70 beats/min, there are increases in cardiovascular death, admission for HF or MI, and coronary revascularization. Ivabradine, a selective sinus node inhibitor, demonstrates reduced hospitalization and death rates in chronic HF with resting HR over 70 beats/min and EF below 35%.[240]

Calcium Channel Blockers. First-generation calcium channel blockers (verapamil, diltiazem, and nifedipine) do not improve survival in chronic HF and may precipitate clinical deterioration.[241] Second-generation dihydropyridines (nicardipine and amlodipine) have more moderate negative inotropic effects. Amlodipine reduces fatal and nonfatal cardiac events in nonischemic but not in ischemic heart disease.[242] Calcium channel blockers used to treat hypertension increase the incidence of HF compared with other regimens.[243] There is no compelling evidence for the use of calcium channel blockers in chronic HF, although they may be needed in patients intolerant of beta-blockers, ACE inhibitors, ARBs, and combined nitrates plus hydralazine.[244] Calcium channel blockers are indicated for the treatment of hypertension, angina, and dysrhythmias, but benefits may be reduced in patients with associated chronic HF.[245]

Ultrafiltration and Renal Dialysis. Ultrafiltration reduces volume overload when diuretic therapy is inadequate.[246,247] In decompensated HF, ultrafiltration may be more effective than intravenous diuretics in volume overloaded states.[248-250] Renal dialysis is important for HF treatment in end-stage renal disease. Potential complications of renal disease that may require special consideration include fluid overload, severe hyperkalemia, iatrogenic hypermagnesemia, uremic pericardial effusion, and drug toxicity (e.g., digitalis).

Coronary Artery Bypass Grafting and Angioplasty. Although there is little consensus regarding the role of revascularization in the management of ischemic cardiomyopathy, registry data suggest a benefit of CABG over PCI in HF.[251] In patients with coronary artery disease amenable to CABG and EF below 35%, CABG combined with medical therapy, compared with medical therapy alone, reduced death from cardiovascular causes but not all-cause mortality.[252] Another study shows no advantage in preventing HF,

www.ketabpezeshki.com 66485457-66963820

death, or reinfarction in stable patients with occlusion of the infarct-related artery 3 to 28 days after MI.[253] Assessing for myocardial viability in ischemic LV dysfunction does not identify a survival benefit from CABG.[254] Revascularization in non–ST elevation acute coronary syndrome and HF reduces mortality.[255]

Phosphodiesterase Inhibitors. There is no indication for long-term PDE type 3 inhibitors (amrinone or milrinone), which increase morbidity and mortality in patients with severe chronic HF.[89,256] They should be used only in hypoperfusion states unresponsive to other therapies. PDE type 5 inhibition with sildenafil, used commonly for erectile dysfunction, is safe in HF and may have other beneficial effects, including better CO and exercise capacity.[257-260] Long-term use of sildenafil in chronic HF improves exertional ventilation and aerobic efficiency.[261,262]

Statins and Polyunsaturated Fatty Acids. Statins improve endothelial function and have anti-inflammatory, antioxidative, and immunomodulatory effects that are beneficial in patients with chronic HF.[263-268] Early use of statin therapy after acute MI reduces risk of HF,[269] and use in nonischemic HF improves LVEF and NYHA classification and reduces serum levels of multiple inflammatory markers.[270-271] A statin reduces risk of HF substantially in high-risk populations and also decreases risk of major vascular effects.[272] Statin therapy is associated with lower hospitalizations, reduced inflammatory markers, improved EF, and decreased mortality among patients with severe HF.[273-275] High-dose statin therapy adds benefit to lower doses in HF.[276] Polyunsaturated fatty acids (n-3 PUFA) show improved LV systolic function and functional capacity and reduced hospitalizations in patients with dilated cardiomyopathy.[277] In patients with HF from any cause, n-3 PUFA use leads to a small decrease in mortality and admissions for cardiovascular reasons.[278]

Anemia. Anemia is present in about one-third of chronic HF patients[279] and is associated with increased mortality in both systolic and diastolic HF.[61] An aggressive approach to anemia in chronic HF using iron supplements and intermittent erythropoietin improves LV systolic function, LV remodeling, BNP levels, NYHA class,[63,280] sleep-related breathing disorders,[60] and renal function, as well as need for hospitalization.[281-283]

Sleep Apnea-Related Respiratory Support. Hypoxemia and related hemodynamic stress underlies the impact of sleep disorders in HF.[284] Obstructive sleep apnea is more prevalent in chronic HF than previously recognized, and treatment with CPAP can be therapeutic,[285-287] even improving LVEF and heart transplant–free survival.[288,289] CPAP for central sleep apnea and HF improves nocturnal oxygenation, EF, and exercise capacity but is not proven to increase survival.[290,291] BPAP is superior to CPAP in improving EF in systolic HF with obstructive sleep apnea.[292]

Exercise Programs. Cardiopulmonary exercise testing provides prognostic information in patients with HF.[293] Various exercise programs in chronic HF show benefits in terms of functional status and quality of life, and reduce rehospitalization rates.[294-297] Growth hormone and testosterone replacement in HF increase exercise capacity and quality of life.[298,299]

Left Ventriculoplasty, Ventricular Assist Devices, and Transplantation. After a promising beginning, left ventriculoplasty has largely been abandoned because of failure to demonstrate long-term efficacy in HF. A study of ventriculoplasty during coronary artery bypass surgery also failed to show functional improvement or reduced mortality in HF.[300] In contrast, LV aneurysm repair is useful in HF.[301]

Multiple implantable LV assist devices are in trials for chronic HF as a bridge to transplantation and as a surgical alternative to chronic medical management.[302-307] Heart transplantation is still the most effective therapy for end-stage HF, with 88% survival at 8 years in one study in which statins were used to prevent vasculopathy,[308] with rejection also reduced by immunosuppressive therapy.[309] The limited availability of donors (2500 heart transplants per year in the United States), however, makes alternative surgical techniques of interest in end-stage HF.[310] There is increasing evidence that stem cell therapy may offer promise in chronic HF.[311,312] Mononuclear bone marrow cell transplantation during CABG surgery in patients with ischemic HF improves cardiac function and regional perfusion.[313] Autologous stem cell transplantation leads to significant improvement in cardiac function in patients undergoing CABG for ischemic cardiomyopathy.[314-316] Myoblast transplantation in coronary surgery patients with depressed LV function, however, fails to improve EF and increases postoperative arrhythmias.[317]

Psychosocial Factors. Depression is common in patients with HF and increases cardiovascular mortality. Treatment is challenging.

Palliative care is important to manage multiple sources of distress in end-of-life issues related to end-stage HF.[318]

Admission Criteria and Predictors of Readmission in Heart Failure

In general, exacerbations of chronic HF require admission if the cause of the exacerbation cannot be readily recognized and corrected, if the disease process is unstable because of increased ischemia or new dysrhythmia, or if clinical deterioration appears likely. Many patients in the ED with acute decompensated HF are admitted because of comorbidities, inability to identify those at low risk for poor outpatient outcomes, or difficulty providing proper bedside HF education and close follow-up. In-hospital mortality for acute decompensated HF is about 4% but higher with increased age, elevated HR, hyponatremia, hypotension, LV systolic dysfunction, increased blood urea nitrogen (BUN) or creatinine, troponin, natriuretic peptides, or HF as the primary cause for admission.[319] Precipitating events, including acute coronary syndrome, concomitant pneumonia, or worsening renal function increase hospital mortality and should prompt admission. Several risk factors predict poor postdischarge outcome, including ischemic ECG changes, elevated troponins or natriuretic peptide levels, hyponatremia, elevated BUN or creatinine, and low systolic BP.[320] Worsening renal function during HF hospitalization is an independent predictor for early readmission and mortality.[321] Conversely, those with rectifiable dietary or medication noncompliance issues may occasionally be discharged with close follow-up. Observation units may have a substantial role in avoiding HF admission.

The difficulties of outpatient HF management range from compliance and understanding of the multifactorial therapeutic strategies to optimization of care after hospital discharge including diet, medications, and weight monitoring. Patients with HF are frequently readmitted for both cardiac and unrelated causes.[322] Several studies have demonstrated reduced readmission rates with individualized, comprehensive discharge planning,[323,324] structured postdischarge follow-up,[325] telemonitoring,[326,327] and directed home self-management.[328] A meta-analysis of 18 studies that used an international patient population demonstrated reduced readmission rates for those with comprehensive discharge planning and postdischarge support versus standard therapy. There is significant variability in the adherence to HF quality-of-care issues in the United States.[329] Initiation of proven therapeutic modalities at hospitalization leads to early benefits, including decreased risks of mortality and rehospitalization for HF.[330]

SUMMARY

Evaluation and management of patients with HF remains a challenge in emergency medicine. HF exacerbation remains among the most frequent conditions resulting in ED visits and hospital admissions. APE requires deliberate consideration of multiple different diagnostic entities. Recognition of common precipitating

www.ketabpezeshki.com 66485457-66963820

events allows early understanding of appropriate management issues. Most acute decompensated HF can be managed with adequate oxygenation along with vasodilator and loop diuretic therapy. Advances in the chronic medical management of HF, including the routine use of beta-blockers, ACE inhibitors or ARBs, diuretics including spironolactone, and occasionally digoxin have resulted in sustained symptomatic improvement and reduced 5-year mortality. A sound understanding of HF pathophysiology and pharmacotherapy allows rewarding results in caring for this ever-challenging diverse group of patients.

KEY CONCEPTS

- Neurohormonal mechanisms provide initial compensation for cardiac dysfunction but are ultimately deleterious in HF. Chronic therapy to negate these effects is important even in asymptomatic myocardial dysfunction.
- Recognition of precipitating causes in heart failure allows more disease-specific management.
- Biomarkers such as BNP may improve recognition of heart failure in dyspnea of questionable cause, correlate with severity, help stratify risk, and help monitor therapeutic response.
- Distinguishing primary pulmonary disease causing predominantly right-sided HF from LV failure with secondary right-sided dysfunction is clinically challenging because the physical examination findings and chest radiograph may be similar. Natriuretic peptide levels are much higher in LV failure.
- Most acute heart failure can be managed with upright positioning, supplemental oxygen, vasodilators, and loop diuretics.
- Hypoperfusing patients with acute pulmonary edema often have unreliable cuff BP readings and may benefit from invasive arterial monitoring.
- Patients with poor perfusion may require fluid challenge to rapidly restore preload, CO, systemic perfusion, and BP. Thus careful volume infusion with aliquots of normal saline is appropriate initial resuscitation for the hypoperfusing patient with acute-onset cardiogenic pulmonary edema.
- In hypoperfusing patients who are adequately volume repleted (true cardiogenic shock), norepinephrine is the pressor of choice.
- In chronic HF, routine use of beta-blockers, ACE inhibitors or ARBs, diuretics including spironolactone, and occasionally digoxin has resulted in sustained symptomatic improvement and reduced 5-year mortality.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Sharma R, Anker SD: Immune and neurohormonal pathways in chronic heart failure. *Congest Heart Fail* 2002; 8:23.
2. Lloyd-Jones D, et al: Heart disease and stroke statistics—2010 update: A report from the American Heart Association. *Circulation* 2010; 121:e46.
3. Shih H, Lee B, Lee RJ, Boyle AJ: The aging heart and post-infarction left ventricular remodeling. *J Am Coll Cardiol* 2011; 57:9.
4. Fonarow GC: Epidemiology and risk stratification in acute heart failure. *Am Heart J* 2007; 155:200.
5. Bui AL, Horwich TB, Fonarow GC: Epidemiology and risk profile of heart failure. *Nat Rev Cardiol* 2011; 8:30.
6. Goldberg RJ, Ciampa J, Lessard D, Meyer TE, Spencer FA: Long-term survival after heart failure: A contemporary population based perspective. *Arch Intern Med* 2007; 167:490.
7. Alla F, et al: Relation of sex to morbidity and mortality in patients with heart failure and reduced or preserved left ventricular ejection fraction. *Am Heart J* 2007; 153:1074.
8. Frazier CG, et al: Associations of gender and etiology with outcomes in heart failure with systolic dysfunction: A pooled analysis of 5 randomized control trials. *J Am Coll Cardiol* 2007; 49:1450.
9. Estes NA 3rd, Weinstock J, Wang PJ, Homoud MK, Link MS: Use of antiarrhythmics and implantable cardioverter-defibrillators in congestive heart failure. *Am J Cardiol* 2003; 91:45D.
10. Fang J, Mensah GA, Croft JB, Keenan NL: Heart failure-related hospitalization in the U.S., 1979 to 2004. *J Am Coll Cardiol* 2008; 52:428.
11. Solomon SD, et al: Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation* 2005; 112:3738.
12. Curtis JP, et al: The association of left ventricular ejection fraction, mortality, and cause of death in stable outpatients with heart failure. *J Am Coll Cardiol* 2003; 42:736.
13. Kearney MT, et al: Predicting sudden death in patients with mild to moderate chronic heart failure. *Heart* 2004; 90:1137.
14. Fox K, et al: Resting heart rate in cardiovascular disease. *J Am Coll Cardiol* 2007; 50:823.
15. Palatini P: Elevated heart rate: A "new" cardiovascular risk factor? *Prog Cardiovasc Dis* 2009; 52:1.
16. Orso F, Baldasseroni S, Maggioni AP: Heart rate in coronary syndromes and heart failure. *Prog Cardiovasc Dis* 2009; 52:38.
17. Hawkins NM, et al: Prevalence and prognostic implications of electrocardiographic left ventricular hypertrophy in heart failure: Evidence from the CHARM programme. *Heart* 2007; 93:59.
18. Olsson LG, et al: Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: Results from the Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006; 47:1997.
19. Gerstein HC, et al: The hemoglobin A1c level as a progressive risk factor for cardiovascular death hospitalization for heart failure, or death in patients with chronic heart failure: An analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Arch Intern Med* 2008; 168:1699.
20. Yamaji M, et al: Effect of eplerenone versus spironolactone on cortisol and hemoglobin A_1(c) levels in patients with chronic heart failure. *Am Heart J* 2010; 160:915.
21. Obialo CI: Cardiorenal consideration as a risk factor for heart failure. *Am J Cardiol* 2007; 99:21D.
22. Smith GL, et al: Renal impairment and outcomes in heart failure: Systematic review and meta-analysis. *J Am Coll Cardiol* 2006; 47:1987.
23. Hage FG, et al: The scope of coronary heart disease in patients with chronic kidney disease. *J Am Coll Cardiol* 2009; 53:2129.
24. Liang KV, Williams AW, Greene EL, Redfield MM: Acute decompensated heart failure and the cardiorenal syndrome. *Crit Care Med* 2008; 36(Suppl 1):S75.
25. Gordon HS, Nowlin PR, Maynard D, Berbaum ML, Deswal A: Mortality after hospitalization for heart failure in blacks compared to whites. *Am J Cardiol* 2010; 105:694.
26. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE: Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). *Am J Cardiol* 2008; 101:1016.
27. Davis BR, et al: Role of diuretics in the prevention of heart failure: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Circulation* 2006; 113:2201.
28. Gheorghiade M, et al: Navigating the crossroads of coronary artery disease and heart failure. *Circulation* 2006; 114:1202.
29. Fox KA, et al: Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. *JAMA* 2007; 297:1892.
30. Chatterjee K: Is detection of hibernating myocardium necessary in deciding revascularization in systolic heart failure? *Am J Cardiol* 2010; 106:236.
31. Le Jemtel TH, Padeletti M, Jelic S: Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol* 2007; 49:171.
32. Olson TP, Beck KC, Johnson JB, Johnson BD: Competition for intrathoracic space reduces lung capacity in patients with chronic heart failure: A radiographic study. *Chest* 2006; 130:164.
33. Bozkanat E, et al: The significance of elevated brain natriuretic peptide levels in chronic obstructive pulmonary disease. *J Int Med Res* 2005; 33:537.
34. Rutten FH, et al: Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: Cross sectional diagnostic study. *BMJ* 2005; 331:1379.
35. Gupta MP: Factors controlling cardiac myosin-isoform shift during hypertrophy and heart failure. *J Mol Cell Cardiol* 2007; 43:388.
36. Bernhard D, Laufer G: The aging cardiomyocyte: A mini-review. *Gerontology* 2008; 54:24.
37. Rehsia NS, Dhalla NS: Potential of endothelin-2 and vasopressin antagonists for the treatment of congestive heart failure. *Heart Fail Rev* 2010; 15:85.
38. Kawanabe Y, Nauli SM: Endothelin. *Cell Mol Life Sci* 2011; 68:195.
39. Pepine CJ: The impact of nitric oxide in cardiovascular medicine: Untapped potential utility. *Am J Med* 2009; 122:S10.
40. Francis SH, Busch JL, Corbin JD, Sibley D: cGMP-dependent protein kinases and cGMP phosphodiesterases in nitric oxide and cGMP action. *Pharmacol Rev* 2010; 62:525, 2010.
41. Lapu-Bula R, Ofili E: From hypertension to heart failure: Role of nitric oxide-mediated endothelial dysfunction and emerging insight from myocardial contrast echocardiography. *Am J Cardiol* 2007; 99:7D.
42. Mebazaa A, et al: Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes. *Crit Care Med* 2008; 36(Suppl 1):S129.
43. Wang J, Nagueh SF: Current perspectives on cardiac function in patients with diastolic heart failure. *Circulation* 2009; 119:1146.
44. Verma A, Solomon SD: Diastolic dysfunction as a link between hypertension and heart failure. *Med Clin North Am* 2009; 93:647.
45. Zile MR, Baicu CF, Bonnema DD: Diastolic heart failure: Definitions and terminology. *Prog Cardiovasc Dis* 2005; 47:307.
46. Hoit BD: Left ventricular diastolic function. *Crit Care Med* 2007; 35:S340.
47. Persson H, et al: Diastolic dysfunction in heart failure with preserved systolic function: Need for objective evidence: Results from the CHARM Echocardiographic Substudy—CHARMES. *J Am Coll Cardiol* 2007; 49:687.
48. Sanderson JE: Heart failure with a normal ejection fraction. *Heart* 2007; 93:155.
49. Ahmed A, et al: Chronic kidney disease associated mortality in diastolic versus systolic heart failure: A propensity matched study. *Am J Cardiol* 2007; 99:393.
50. Wang J, Kurrelmeyer KM, Torre-Amione G, Nagueh SF: Systolic and diastolic dyssynchrony in patients with diastolic heart failure and effect of medical therapy. *J Am Coll Cardiol* 2007; 49:88.
51. Yu CM, et al: Diastolic and systolic asynchrony in patients with diastolic heart failure: A common but ignored condition. *J Am Coll Cardiol* 2007; 49:97.
52. Segev A, et al: Prognostic significance of admission heart failure in patients with non–ST-elevation acute coronary syndromes (from the Canadian Acute Coronary Syndrome Registries). *Am J Cardiol* 2006; 98:470.
53. Roe MT, et al: Impact of congestive heart failure in patients with non–ST-segment elevation acute coronary syndromes. *Am J Cardiol* 2006; 97:1707.
54. Flaherty JD, et al: Acute heart failure syndromes in patients with coronary artery disease early assessment and treatment. *J Am Coll Cardiol* 2009; 53:254.
55. Fildes JE, Shaw SM, Yonan N, Williams S: The immune system and chronic heart failure: Is the heart in control? *J Am Coll Cardiol* 2009; 53:1013.
56. Chen D, Assad-Kottner C, Orrego C, Torre-Amione G: Cytokines and acute heart failure. *Crit Care Med* 2008; 36:S9.
57. Deedwania PC, Lardizabal JA: Atrial fibrillation in heart failure: A comprehensive review. *Am J Med* 2010; 123:198.

www.ketabpezeshki.com 66485457-66963820

58. Fonarow GC, et al: Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: Findings from OPTIMIZE-HF. *Arch Intern Med* 2008; 168:847.
59. Lindenfeld J: Prevalence of anemia and effects on mortality in patients with heart failure. *Am Heart J* 2005; 149:391.
60. Mitchell JE: Emerging role of anemia in heart failure. *Am J Cardiol* 2007; 99:15D.
61. Groenveld HF, et al: Anemia and mortality in heart failure patients: A systematic review and meta-analysis. *J Am Coll Cardiol* 2008; 52:818.
62. Klein I, Danzi S: Thyroid disease and the heart. *Circulation* 2007; 116:1725.
63. Slørdal L, Spigset O: Heart failure induced by non-cardiac drugs. *Drug Saf* 2006; 29:567.
64. Russell SD, et al: New York Heart Association functional class predicts exercise parameters in the current era. *Am Heart J* 2009; 158:S24.
65. Wang CS, FitzGerald JM, Schulzer M, Mak E, Ayas NT: Does this dyspneic patient in the emergency department have congestive heart failure? *JAMA* 2005; 294:1944.
66. Cohn JN: Blood pressure measurement in shock: Mechanisms of inaccuracy of auscultatory and palpatory methods. *JAMA* 1967; 199:118.
67. Daniels LB, Maisel AS: Natriuretic peptides. *J Am Coll Cardiol* 2007; 50:2357.
68. Rutten JH, et al: N-terminal pro-brain natriuretic peptide testing in the emergency department: Beneficial effects on hospitalization, costs, and outcome. *Am Heart J* 2008; 156:71.
69. Ray P, Delerme S, Jourdain P, Chenevier-Gobeaux C: Differential diagnosis of acute dyspnea: The value of B natriuretic peptides in the emergency department. *QJM* 2008; 101:831.
70. Maisel A: B-type natriuretic peptide measurements in diagnosing congestive heart failure in the dyspneic emergency department patient. *Rev Cardiovasc Med* 2002; 3:S10.
71. Strunk A, et al: Impact of the history of congestive heart failure on the utility of B-type natriuretic peptide in the emergency diagnosis of heart failure: Results from the Breathing Not Properly Multinational Study. *Am J Med* 2006; 119:69.
72. Lam LL, et al: Meta-analysis: Effect of B-type natriuretic peptide testing on clinical outcomes in patients with acute dyspnea in the emergency setting. *Ann Intern Med* 2010; 153:728.
73. deFilippi CR, Christenson RH, Gottdiener JS, Kop WJ, Seliger SL: Dynamic cardiovascular risk assessment in elderly people: The role of repeated N-terminal pro-B-type natriuretic peptide testing. *J Am Coll Cardiol* 2010; 55:441.
74. Januzzi JL Jr, et al: The N-terminal Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study. *Am J Cardiol* 2005; 95:948.
75. van Kimmenade RR, et al: Usefulness of intermediate amino-terminal pro-brain natriuretic peptide concentrations for diagnosis and prognosis of acute heart failure. *Am J Cardiol* 2006; 98:386.
76. Doust JA, Pietrzak E, Dobson A, Glasziou P: How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: Systematic review. *BMJ* 2005; 330:625.
77. Battaglia M, et al: Accuracy of B-type natriuretic peptide tests to exclude congestive heart failure: Systematic review of test accuracy studies. *Arch Intern Med* 2006; 166:1073.
78. Maisel A, et al: Primary results of the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT): A multicenter study of B-type natriuretic peptide levels, emergency department decision making, and outcomes in patients presenting with shortness of breath. *J Am Coll Cardiol* 2004; 44:1328.
79. Masson S, Latini R: Amino-terminal pro-B-type natriuretic peptides and prognosis in chronic heart failure. *Am J Cardiol* 2008; 101:56.
80. Logeart D, et al: Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. *J Am Coll Cardiol* 2004; 43:635.
81. Lainchbury JG, et al: N-terminal pro-B-type natriuretic peptide–guided treatment for chronic heart failure: Results from the BATTLESCARRED (NT-proBNP–Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial. *J Am Coll Cardiol* 2009; 55:53.
82. Felker GM, Hasselblad V, Hernandez AF, O'Connor CM: Biomarker-guided therapy in chronic heart failure: A meta-analysis of randomized controlled trials. *Am Heart J* 2009; 158:422.
83. Pfisterer M, et al: BNP-guided vs symptom-guided heart failure therapy: The Trial of Intensified vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF) randomized trial. *JAMA* 2009; 301:383.
84. Dhar S, et al: Natriuretic peptides and heart failure in the patient with chronic kidney disease: A review of current evidence. *Postgrad Med J* 2009; 85:299.
85. Fonarow GC, et al: Usefulness of B-type natriuretic peptic and cardiac troponin levels to predict in-hospital mortality from ADHERE. *Am J Cardiol* 2008; 101:231.
86. Sato Y, Kita T, Takatsu Y, Kimura T: Biochemical markers of myocyte injury in heart failure. *Heart* 2004; 90:1110.
87. Kociol RD, et al: Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. *J Am Coll Cardiol* 2010; 56:1071.
88. Latini R, et al: Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. *Circulation* 2007; 116:1242.
89. Binanay C, et al: Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: The ESCAPE trial. *JAMA* 2005; 294:1625.
90. Packer M, et al: Utility of impedance cardiography for the identification of short-term risk of clinical decompensation in stable patients with chronic heart failure. *J Am Coll Cardiol* 2006; 47:2245.
91. Kamath SA, et al: Correlation of impedance cardiography with invasive hemodynamic measurements in patients with advanced heart failure: The BioImpedance CardioGraphy (BIG) substudy of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) Trial. *Am Heart J* 2009; 158:217.
92. Kirkpatrick JN, Vannan MA, Narula J, Lang RM: Echocardiography in heart failure: Applications, utility, and new horizons. *J Am Coll Cardiol* 2007; 50:381.
93. Grayburn PA, et al: Echocardiographic predictors of morbidity and mortality in patients with advanced heart failure: The Beta-blocker Evaluation of Survival Trial (BEST). *J Am Coll Cardiol* 2005; 45:1064.
94. Mowatt G, et al: Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease. *Health Technol Assess* 2008; 12:iii.
95. Raphael CE, et al: Quantifying the paradoxical effect of higher systolic blood pressure on mortality in chronic heart failure. *Heart* 2009; 95:56.
96. Park JH, Balmain S, Berry C, Morton JJ, McMurray JJ: Potentially detrimental cardiovascular effects of oxygen in patients with chronic left ventricular systolic dysfunction. *Heart* 2010; 96:533.
97. Collins SP, et al: The use of noninvasive ventilation in emergency department patients with acute cardiogenic pulmonary edema: A systematic review. *Ann Emerg Med* 2006; 48:260.
98. Masip J: Noninvasive ventilation in acute cardiogenic pulmonary edema. *Curr Opin Crit Care* 2008; 14:531.
99. Ferrari G, et al: Noninvasive positive airway pressure and risk of myocardial infarction in acute cardiogenic pulmonary edema: Continuous positive airway pressure vs noninvasive positive pressure ventilation. *Chest* 2007; 132:1804.
100. Gray A, et al: Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med* 2008; 359:142.
101. Miller AH, et al: Acutely decompensated heart failure in a county emergency department: A double-blind randomized controlled comparison of nesiritide versus placebo treatment. *Ann Emerg Med* 2008; 51:571.
102. Arora RR, Venkatesh PK, Molnar J: Short- and long-term mortality with nesiritide. *Am Heart J* 2007; 152:1084.
103. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K: Short-term risk of death after treatment with nesiritide for decompensated heart failure: A pooled analysis of randomized controlled trials. *JAMA* 2005; 293:1900.
104. Sackner-Bernstein JD, Skopicki HA, Aaronson KD: Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation* 2005; 111:1487.
105. Allen LA, et al: Continuous versus bolus dosing of furosemide for patients hospitalized for heart failure. *Am J Cardiol* 2010; 105:1794.
106. Goldsmith SR, Brandimarte F, Gheorghiade M: Congestion as a therapeutic target in acute heart failure syndromes. *Prog Cardiovasc Dis* 2010; 52:33.
107. Ahmed A, et al: Heart failure, chronic diuretic use, and increase in mortality and hospitalization: An observational study using propensity score methods. *Eur Heart J* 2006; 27:1431.
108. Aronson D, et al: Impact of red blood cell transfusion on clinical outcomes in patients with acute myocardial infarction. *Am J Cardiol* 2008; 102:115.
109. Garty M, et al: Blood transfusion for acute decompensated heart failure—friend or foe? *Am Heart J* 2009; 158:653.

www.ketabpezeshki.com 66485457-66963820

110. Berger R, et al: Effects of endothelin a receptor blockade on endothelial function in patients with chronic heart failure. *Circulation* 2011; 103:981.
111. McMurray JJ, et al: Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: The VERITAS randomized controlled trials. *JAMA* 2007; 298:2009.
112. Gheorghiade M, et al: Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: The EVEREST Clinical Status Trials. *JAMA* 2007; 297:1332.
113. Udelson JE, et al: Acute hemodynamic effects of tolvaptan, a vasopressin V2 receptor blocker, in patients with symptomatic heart failure and systolic dysfunction: An international, multicenter, randomized, placebo-controlled trial. *J Am Coll Cardiol* 2008; 52:1540.
114. Goldsmith SR, Gheorghiade M: Vasopressin antagonism in heart failure. *J Am Coll Cardiol* 2005; 46:1785.
115. Cozzolino D, et al: Acute effects of beta-endorphin on cardiovascular function in patients with mild to moderate chronic heart failure. *Am Heart J* 2004; 148:E13.
116. Massie BM, et al: Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. *N Engl J Med* 2010; 363:1419.
117. Givertz MM, et al: The effects of KW-3902, an adenosine A1-receptor antagonist, on diuresis and renal function in patients with acute decompensated heart failure and renal impairment or diuretic resistance. *J Am Coll Cardiol* 2007; 50:1551.
118. Mitrovic V, et al: Effects of the renal natriuretic peptide urodilatin (ularitide) in patients with decompensated chronic heart failure: A double-blind, placebo-controlled, ascending-dose trial. *Am Heart J* 2005; 150:1239.
119. Follath F, Franco F, Cardoso JS: European experience on the practical use of levosimendan in patients with acute heart failure syndromes. *Am J Cardiol* 2005; 96:80G.
120. Russ MA, et al: Hemodynamic improvement following levosimendan treatment in patients with acute myocardial infarction and cardiogenic shock. *Crit Care Med* 2007; 35:2862.
121. Teerlink JR, et al: Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): A multicenter, randomized, placebo-controlled, parallel-group, dose-finding phase IIb study. *Lancet* 2009; 373:1429.
122. Mann DL, et al: Targeted anticytokine therapy in patients with chronic heart failure: Results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation* 2004; 109:1594.
123. Sleeper LA, et al: Functional status and quality of life after emergency revascularization for cardiogenic shock complicating acute myocardial infarction. *J Am Coll Cardiol* 2005; 46:266.
124. Petersen JW, Felker GM: Inotropes in the management of acute heart failure. *Crit Care Med* 2008; 36:S106.
125. Bayram M, De Luca L, Massie MB, Gheorghiade M: Reassessment of dobutamine, dopamine, and milrinone in the management of acute heart failure syndromes. *Am J Cardiol* 2005; 96:47G.
126. De Backer D, et al: Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010; 362:779.
127. Smit AJ: Dopamine in heart failure and critical care. *Clin Exp Hypertens* 2000; 22:269.
128. Ungar A, et al: Renal, but not systemic, hemodynamic effects of dopamine are influenced by the severity of congestive heart failure. *Crit Care Med* 2004; 32:1125.
129. Felker GM, et al: Heart failure etiology and response to milrinone in decompensated heart failure: Results from the OPTIME-CHF study. *J Am Coll Cardiol* 2003; 41:997.
130. Goldenberg IF, Lewis WR, Dias VC, Heywood JT, Pedersen WR: Intravenous diltiazem for the treatment of patients with atrial fibrillation or flutter and moderate to severe congestive heart failure. *Am J Cardiol* 1994; 74:884.
131. Frigerio M, Oliva F, Turazza FM, Bonow RO: Prevention and management of chronic heart failure in management of asymptomatic patients. *Am J Cardiol* 2003; 91:4F.
132. Colonna P, et al: The emerging role of echocardiography in the screening of patients at risk of heart failure. *Am J Cardiol* 2005; 96:42L.
133. Katz AM: Pathophysiology of heart failure: Identifying targets for pharmacotherapy. *Med Clin North Am* 2003; 87:303.
134. Katz DL: Lifestyle and dietary modification for prevention of heart failure. *Med Clin North Am* 2004; 88:1295.
135. Gradman AH, Alfayoumi F: From left ventricular hypertrophy to congestive heart failure: Management of hypertensive heart disease. *Prog Cardiovasc Dis* 2006; 48:326.
136. Avogaro A, Vigili de Kreutzenberg S, Negut C, Tiengo A, Scognamiglio R: Diabetic cardiomyopathy: A metabolic perspective. *Am J Cardiol* 2004; 93:13A.
137. Williams JS, Solomon SD, Crivaro M, Conlin PR: Dietary sodium intake modulates myocardial relaxation responsiveness to angiotensin II. *Transl Res* 2006; 148:49.
138. McGavock JM, et al: Adiposity of the heart, revisited. *Ann Intern Med* 2006; 144:517.
139. Alpert MA: Management of obesity cardiomyopathy. *Am J Med Sci* 2001; 321:237.
140. Kenchaiah S, Gaziano JM, Vasan RS: Impact of obesity on the risk of heart failure and survival after the onset of heart failure. *Med Clin North Am* 2004; 88:1273.
141. Oreopoulos A, et al: Body mass index and mortality in heart failure: A meta-analysis. *Am Heart J* 2008; 156:13.
142. Konstam MA: Reliability of ventricular remodeling as a surrogate for use in conjunction with clinical outcomes in heart failure. *Am J Cardiol* 2005; 96:867.
143. Yan RT, et al: Usefulness of temporal changes in neurohormones as markers of ventricular remodeling and prognosis in patients with left ventricular systolic dysfunction and heart failure receiving either candesartan or enalapril or both. *Am J Cardiol* 2005; 96:698.
144. Wachtel K, et al: Regression of electrocardiographic left ventricular hypertrophy during antihypertensive therapy and reduction in sudden cardiac death: The LIFE study. *Circulation* 2007; 116:700.
145. Sutton MS, Keane MG: Reverse remodeling in heart failure with cardiac resynchronisation therapy. *Heart* 2007; 93:167.
146. Frigerio M, Roubina E: Drugs for left ventricular remodeling in heart failure. *Am J Cardiol* 2005; 96:10L.
147. Ferrari R: Effects of angiotensin-converting enzyme inhibition with perindopril on left ventricular remodeling and clinical outcome: Results of the randomized Perindopril and Remodeling in Elderly with Acute Myocardial Infarction (PREAMI) study. *Arch Intern Med* 2006; 166:659.
148. Khalil ME, Basher AW, Brown EJ Jr, Alhaddad IA: A remarkable medical story: Benefits of angiotensin-converting enzyme inhibitors in cardiac patients. *J Am Coll Cardiol* 2001; 37:1757.
149. Abdulla J, et al: A meta-analysis of the effect of angiotensin-converting enzyme inhibitors on functional capacity in patients with symptomatic left ventricular systolic dysfunction. *Eur J Heart Fail* 2004; 6:927.
150. Abdulla J, Abildstrom SZ, Christensen E, Kober L, Torp-Pedersen C: Effect of angiotensin-converting enzyme inhibition on functional class in patients with left ventricular systolic dysfunction: A meta-analysis. *Eur J Heart Fail* 2006; 8:90.
151. Böhm M: Angiotensin receptor blockers versus angiotensin-converting enzyme inhibitors: Where do we stand now? *Am J Cardiol* 2007; 100:38J.
152. Rochon PA, et al: Use of angiotensin-converting enzyme inhibitor therapy and dose-related outcomes in older adults with new heart failure in the community. *J Gen Intern Med* 2004; 19:676.
153. Roffman DS: High- versus low-dose ACE inhibitor therapy in chronic heart failure. *Ann Pharmacother* 2004; 38:831.
154. Guazzi M, Brambilla R, Reina G, Tumminello G, Guazzi MD: Aspirin–angiotensin-converting enzyme inhibitor coadministration and mortality in patients with heart failure: A dose-related adverse effect of aspirin. *Arch Intern Med* 2003; 163:1574.
155. Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators, et al: Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: A randomized controlled trial. *Lancet* 2008; 372:1174.
156. Jong P, Demers C, McKelvie RS, Liu PP: Angiotensin receptor blockers in heart failure: Meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2002; 39:463.
157. Zhang Y, et al: The role of renin-angiotensin system blockade therapy in the prevention of atrial fibrillation: A meta-analysis of randomized controlled trials. *Clin Pharmacol Ther* 2010; 88:521.
158. Solomon SD, et al: Effect of candesartan on cause-specific mortality in heart failure patients: The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) program. *Circulation* 2004; 110:2180.
159. Pfeffer MA, et al: Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; 349:1893.
160. Messerli FH: The sudden demise of dual renin-angiotensin system blockade or the soft science of the surrogate end point. *J Am Coll Cardiol* 2009; 53:468.
161. Lakhdar R, Al-Mallah MH, Lanfear DE: Safety and tolerability of angiotensin-converting enzyme inhibitor versus the combination of angiotensin-converting enzyme inhibitor and angiotensin receptor

www.ketabpezeshki.com 66485457-66963820

blocker in patients with left ventricular dysfunction: A systematic review and meta-analysis of randomized controlled trials. *J Card Fail* 2008; 14:181.
162. Phillips CO, Kashani A, Ko DK: Adverse effects of combination angiotensin II receptor blockers plus angiotensin-converting enzyme inhibitors for left ventricular dysfunction: A quantitative review of data from randomized clinical trials. *Arch Intern Med* 2007; 167:1930.
163. Klapholz M: Beta-blocker use for the stages of heart failure. *Mayo Clin Proc* 2009; 84:718.
164. Foody JM, Farrell MH, Krumholz HM: Beta-blocker therapy in heart failure: Scientific review. *JAMA* 2002; 287:883.
165. Dulin BR, Haas SJ, Abraham WT, Krum H: Do elderly systolic heart failure patients benefit from beta blockers to the same extent as the non-elderly? Meta-analysis of >12,000 patients in large-scale clinical trials. *Am J Cardiol* 2005; 95:896.
166. Flannery G, Gehrig-Mills R, Billah B, Krum H: Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure receiving beta-blockers. *Am J Cardiol* 2008; 101:865.
167. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW: Meta-analysis: Beta-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med* 2009; 150:784.
168. Yilmaz MB, Laribi S, Mebazaa A: Managing beta-blockers in acute heart failure: When to start and when to stop? *Curr Heart Fail Rep* 2010; 7:110.
169. Ko DT, et al: Adverse effects of beta-blocker therapy for patients with heart failure: A quantitative overview of randomized trials. *Arch Intern Med* 2004; 164:1389.
170. Münzel T, Gori T: Nebivolol: The somewhat-different beta-adrenergic receptor blocker. *J Am Coll Cardiol* 2009; 54:1491.
171. Basile JN: One size does not fit all: The role of vasodilating beta-blockers in controlling hypertension as a means of reducing cardiovascular and stoke risk. *Am J Med* 2010; 123:S9.
172. Di Lenarda A, et al: Long-term effects of carvedilol in idiopathic dilated cardiomyopathy with persistent left ventricular dysfunction despite chronic metoprolol: The Heart-Muscle Disease Study Group. *J Am Coll Cardiol* 1999; 33:1926.
173. Remme WJ, et al: Carvedilol protects better against vascular events than metoprolol in heart failure: Results from COMET. *J Am Coll Cardiol* 2007; 49:963.
174. Torp-Pedersen C, et al: Effects of metoprolol and carvedilol on cause-specific mortality and morbidity in patients with chronic heart failure—COMET. *Am Heart J* 2005; 149:370.
175. Cleland JG, et al: A comparison of the effects of carvedilol and metoprolol on well-being, morbidity, and mortality (the "patient journey") in patients with heart failure: A report from the Carvedilol Or Metoprolol European Trial (COMET). *J Am Coll Cardiol* 2006; 47:1603.
176. Selektor Y, Weber KT: The salt-avid state of congestive heart failure revisited. *Am J Sci* 2008; 335:209.
177. Psaty BM, et al: Health outcomes associated with various antihypertensive therapies used as first-line agents: A network meta-analysis. *JAMA* 2003; 289:2534.
178. Kasama S, et al: Effects of torasemide on cardiac sympathetic nerve activity and left ventricular remodelling in patients with congestive heart failure. *Heart* 2006; 92:1434.
179. Jentzer JC, DeWald TA, Hernandez AF: Combination of loop diuretics with thiazide-type diuretics in heart failure. *J Am Coll Cardiol* 2010; 56:1527.
180. Klein L, et al: Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: Results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic heart failure (OPTIME-CHF) study. *Circulation* 2005; 111:2454.
181. Goldsmith SR: Current treatments and novel pharmacologic treatments for hyponatremia in congestive heart failure. *Am J Cardiol* 2005; 95:14B.
182. Oren RM: Hyponatremia in congestive heart failure. *Am J Cardiol* 2005; 95:2B.
183. Haley H, Ploth DW: Dyshomeostasis of serum sodium concentration in congestive heart failure. *Am J Med Sci* 2010; 340:42.
184. Gheorghiade M, et al: Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE trial. *Arch Intern Med* 2007; 167:1998.
185. Zannad F, et al: Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; 364:11.
186. Tang WH, Parameswaran AC, Maroo AP, Francis GS: Aldosterone receptor antagonists in the medical management of chronic heart failure. *Mayo Clin Proc* 2005; 80:1623.
187. Vizzardi E, et al: Effect of spironolactone on left ventricular ejection fraction and volumes in patients with class I or II heart failure. *Am J Cardiol* 2010; 106:1292.
188. Chan AK, et al: Aldosterone receptor antagonism induces reverse remodeling when added to angiotensin receptor blockade in chronic heart failure. *J Am Coll Cardiol* 2007; 50:591.
189. Pitt B, Fonarow GC, Gheorghiade M, Deedwania PC, Duprez DA: Improving outcomes in post-acute myocardial infarction heart failure: Incorporation of aldosterone blockade into combination therapy to optimize neurohormonal blockade. *Am J Cardiol* 2006; 97:26F.
190. Gheorghiade M, et al: The effects of eplerenone on length of stay and total days of heart failure hospitalization after myocardial infarction in patients with left ventricular systolic dysfunction. *Am Heart J* 2009; 158:437.
191. Pitt B, et al: Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardiol* 2005; 46:425.
192. Tingberg E, Roijer A, Thilen U, Eskilsson J, Ohlin H: Randomized, double-blind, placebo-controlled long-term study of isosorbide-5-mononitrate therapy in patients with left ventricular dysfunction after acute myocardial infarction. *Am Heart J* 2003; 145:E1.
193. Ferdinand KC: African American Heart Failure Trial: Role of endothelial dysfunction and heart failure in African Americans. *Am J Cardiol* 2007; 99:3D.
194. Taylor AL, et al: Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004; 351:2049.
195. Yancy CW, et al: Evidence for the continued safety and tolerability of fixed-dose isosorbide dinitrate/hydralazine in patients with chronic heart failure (the extension to African-American Heart Failure Trial). *Am J Cardiol* 2007; 100:684.
196. Taylor AL, et al: Early and sustained benefit on event-free survival and heart failure hospitalization from fixed-dose combination of isosorbide dinitrate/hydralazine: Consistency across subgroups in the African-American Heart Failure Trial. *Circulation* 2007; 115:1747.
197. Ahmed A: Digoxin and reduction in mortality and hospitalization in geriatric heart failure: Importance of low doses and low serum concentrations. *J Gerontol A Biol Sci Med Sci* 2007; 62:32.
198. Digitalis Investigation Group, et al: Effectiveness of digoxin in reducing one-year mortality in chronic heart failure in the Digitalis Investigation Group trial. *Am J Cardiol* 2009; 103:82.
199. Ahmed A, et al: Effects of discontinuation of digoxin versus continuation at low serum digoxin concentrations in chronic heart failure. *Am J Cardiol* 2007; 100:280.
200. Ahmed A, et al: Effects of digoxin on morbidity and mortality in diastolic heart failure: The ancillary digitalis investigation group trial. *Circulation* 2006; 114:397.
201. Yan AT, Yan RT, Liu PP: Narrative review: Pharmacotherapy for chronic heart failure: Evidence from recent clinical trials. *Ann Intern Med* 2005; 142:132.
202. Goldenberg I, et al: Time dependence of defibrillator benefit after coronary revascularization in the Multicenter Automatic Defibrillator Implantation Trial (MADIT)–II. *J Am Coll Cardiol* 2006; 47:1811.
203. Salukhe TV, Briceno NI, Ferenczi EA, Sutton R, Francis DP: Is there benefit in implanting defibrillators in patients with severe heart failure? *Heart* 2010; 96:599.
204. Ciampi Q, et al: Clinical and prognostic role of pressure-volume relationship in the identification of responders to cardiac resynchronization therapy. *Am Heart J* 2010; 160:906.
205. Spragg DD, Kass DA: Pathobiology of left ventricular dyssynchrony and resynchronization. *Prog Cardiovasc Dis* 2006; 49:26.
206. Sweeney MO, Hellkamp AS: Heart failure during cardiac pacing. *Circulation* 2006; 113:2082.
207. Boriani G, et al: A randomized double-blind comparison of biventricular versus left ventricular stimulation for cardiac resynchronization therapy: The Biventricular versus Left Univentricular Pacing with ICD Back-up in Heart Failure Patients (B-LEFT HF) trial. *Am Heart J* 2010; 159:1052.
208. Gasparini M, et al: Comparison of 1-year effects of left ventricular and biventricular pacing in patients with heart failure who have ventricular arrhythmias and left bundle-branch block: The Bi vs Left Ventricular Pacing: An International Pilot Evaluation on heart failure Patients with Ventricular Arrhythmias (BELIEVE) multicenter prospective randomized pilot study. *Am Heart J* 2006; 152:155.
209. Linde C, et al: Cardiac resynchronization therapy in asymptomatic or mildly symptomatic heart failure patients in relation to etiology:

www.ketabpezeshki.com 66485457-66963820

Results from the REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) study. *J Am Coll Cardiol* 2010; 56:1826.
210. St John Sutton M, et al: Cardiac resynchronization induces major structural and functional reverse remodeling in patients with New York Heart Association class I/II heart failure. *Circulation* 2009; 120:1858.
211. Anand IS, et al: Cardiac resynchronization therapy reduces the risk of hospitalizations in patients with advanced heart failure: Results from the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial. *Circulation* 2009; 119:969.
212. Burkhardt JD, Wilkoff BL: Interventional electrophysiology and cardiac resynchronization therapy: Delivering electrical therapies for heart failure. *Circulation* 2007; 115:2208.
213. Rao RK, et al: Reduced ventricular volumes and improved systolic function with cardiac resynchronization therapy: A randomized trial comparing simultaneous biventricular pacing, sequential biventricular pacing, and left ventricular pacing. *Circulation* 2007; 115:2136.
214. Herre J: Keys to successful cardiac resynchronization therapy. *Am Heart J* 2007; 153:18.
215. Solomon SD, et al: Effect of cardiac resynchronization therapy on reverse remodeling and relation to outcome: Multicenter automatic defibrillator implantation trial: Cardiac resynchronization therapy. *Circulation* 2010; 122:985.
216. Auricchio A, et al: Long-term survival of patients with heart failure and ventricular conduction delay treated with cardiac resynchronization therapy. *Am J Cardiol* 2007; 99:232.
217. Lindenfeld J, et al: Effects of cardiac resynchronization therapy with or without a defibrillator on survival and hospitalizations in patients with New York Heart Association class IV heart failure. *Circulation* 2007; 115:204.
218. Gasparini M, et al: Four-year efficacy of cardiac resynchronization therapy on exercise tolerance and disease progression: The importance of performing atrioventricular junction ablation in patients with atrial fibrillation. *J Am Coll Cardiol* 2006; 48:734.
219. Higgins SL, et al: Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol* 2003; 42:1454.
220. Bristow MR, et al: Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; 350:2140.
221. Young JB, et al: Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: The MIRACLE ICD trial. *JAMA* 2003; 289:2685.
222. Moss AJ, et al: Cardiac-resynchronization therapy for the prevention of heart failure events. *N Engl J Med* 2009; 361:1329.
223. Upadhyay GA, Choudhry NK, Auricchio A, Ruskin J, Singh JP: Cardiac resynchronization in patients with atrial fibrillation: A meta-analysis of prospective cohort studies. *J Am Coll Cardiol* 2008; 52:1239.
224. Khadjooi K, et al: Long-term effects of cardiac resynchronisation therapy in patients with atrial fibrillation. *Heart* 2008; 94:879.
225. Lancellotti P, et al: Effect of cardiac resynchronization therapy on functional mitral regurgitation in heart failure. *Am J Cardiol* 2004; 94:1462.
226. Andruilli J: Device monitoring of intrathoracic impedance: Clinical observations from a patient registry. *Am J Cardiol* 2007; 99:23G.
227. Wang L: Fundamentals of intrathoracic impedance monitoring in heart failure. *Am J Cardiol* 2007; 99:3G.
228. Berruezo A: Arrhythmias: Complex ventricular arrhythmias: A therapeutic nightmare. *Heart* 2010; 96:723.
229. Vassallo P, Trohman RG: Prescribing amiodarone: An evidence-based review of clinical indications. *JAMA* 2007; 298:1312.
230. Roy D, et al: Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008; 358:2667.
231. Kamath GS, Mittel S: The role of antiarrhythmic drug therapy for the prevention of sudden cardiac death. *Prog Cardiovasc Dis* 2008; 50:439.
232. Arshad A, Mandava A, Kamath G, Musat D: Sudden cardiac death and the role of medical therapy. *Prog Cardiovasc Dis* 2008; 50:420.
233. Køber L, et al: Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008; 358:2678.
234. Packer DL, et al: Impact of implantable cardioverter-defibrillator, amiodarone, and placebo on the mode of death in stable patients with heart failure: Analysis from the sudden cardiac death in heart failure trial. *Circulation* 2009; 120:2170.
235. Thomas KL, et al: Amiodarone use after acute myocardial infarction complicated by heart failure and/or left ventricular dysfunction may be associated with excess mortality. *Am Heart J* 2008; 155:87.
236. Mark DB, et al: Quality of life with defibrillator therapy or amiodarone in heart failure. *N Engl J Med* 2008; 359:999.
237. Böhm M, et al: Heart rate as a risk factor in chronic heart failure (SHIFT): The association between heart rate and outcomes in a randomized placebo-controlled trial. *Lancet* 2010; 376:886.
238. Ahmadi-Kashani M, et al: Heart rate predicts outcomes in an implantable cardioverter-defibrillator population. *Circulation* 2009; 120:2040.
239. Fox K, et al: Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): A randomised, double-blind, placebo-controlled trial. *Lancet* 2008; 372:807.
240. Swedberg K, et al: Ivabradine and outcomes in chronic heart failure (SHIFT): A randomized placebo-controlled study. *Lancet* 2010; 376:875.
241. Elkayam U, Shotan A, Mehra A, Ostrzega E: Calcium channel blockers in heart failure. *J Am Coll Cardiol* 1993; 22:139A.
242. Follath F, Cleland JG, Klein W, Murphy R: Etiology and response to drug treatment in heart failure. *J Am Coll Cardiol* 1998; 32:1167.
243. Shibata MC, León H, Chatterley T, Dorgan M, Vandermeer B: Do calcium channel blockers increase the diagnosis of heart failure in patients with hypertension? *Am J Cardiol* 2010; 106:228.
244. Aronow WS: Left ventricular diastolic heart failure with normal left ventricular systolic function in older persons. *J Lab Clin Med* 2001; 137:316.
245. De Vries RJ, van Veldhuisen DF, Dunselman PH: Efficacy and safety of calcium channel blockers in heart failure: Focus on recent trials with second-generation dihydropyridines. *Am Heart J* 2000; 139:185.
246. Agostoni P, et al: Sustained improvement in functional capacity after removal of body fluid with isolated ultrafiltration in chronic cardiac insufficiency: Failure of furosemide to provide the same result. *Am J Med* 1994; 96:191.
247. Bart BA, et al: Ultrafiltration versus usual care for hospitalized patients with heart failure: The Relief for Acutely Fluid-Overloaded Patients with Decompensated Congestive Heart Failure (RAPID-CHF) trial. *J Am Coll Cardiol* 2005; 46:2043.
248. Kazory A, Ross EA: Ultrafiltration for decompensated heart failure: Renal implications. *Heart* 2009; 95:1047.
249. Costanzo MR, et al: Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2007; 49:675.
250. Costanzo MR, Saltzberg M, O'Sullivan J, Sobotka P: Early ultrafiltration in patients with decompensated heart failure and diuretic resistance. *J Am Coll Cardiol* 2005; 46:2047.
251. Phillips HR, O'Connor CM, Rogers J: Revascularization for heart failure. *Am Heart J* 2007; 153:65.
252. Velazquez EJ, et al: Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N Engl J Med* 2011; 364:1607.
253. Hochman JS, et al: Coronary intervention for persistent occlusion after myocardial infarction. *N Engl J Med* 2006; 355:2395.
254. Bonow RO, et al: Myocardial viability and survival in ischemic left ventricular dysfunction. *N Engl J Med* 2011; 364:1617.
255. Steg PG, et al: Impact of in-hospital revascularization on survival in patients with non-ST-elevation acute coronary syndrome and congestive heart failure. *Circulation* 2008; 118:1163.
256. Chatterjee K, De Marco T: Role of nonglycosidic inotropic agents: Indications, ethics, and limitations. *Med Clin North Am* 2003; 87:391.
257. Katz SD, et al: Efficacy and safety of sildenafil citrate in men with erectile dysfunction and chronic heart failure. *Am J Cardiol* 2005; 95:36.
258. Hirata K, Adji A, Vlachopoulos C, O'Rourke MF: Effect of sildenafil on cardiac performance in patients with heart failure. *Am J Cardiol* 2005; 96:1436.
259. Patel MD, Katz SD: Phosphodiesterase 5 inhibition in chronic heart failure and pulmonary hypertension. *Am J Cardiol* 2005; 96:47M.
260. Guazzi M, Tumminello G, Di Marco F, Guazzi MD: Influences of sildenafil on lung function and hemodynamics in patients with chronic heart failure. *Clin Pharmacol Ther* 2004; 76:371.
261. Behling A, et al: Effects of 5'-phosphodiesterase four-week long inhibition with sildenafil in patients with chronic heart failure: A double-blind, placebo-controlled clinical trial. *J Card Fail* 2008; 14:189.
262. Guazzi M, Samaja M, Arena R, Vicenzi M, Guazzi MD: Long-term use of sildenafil in the therapeutic management of heart failure. *J Am Coll Cardiol* 2007; 50:2136.
263. Yamada T, et al: Long-term effect of atorvastatin on neurohumoral activation and cardiac function in patients with chronic heart failure: A prospective randomized controlled study. *Am Heart J* 2007; 153:1055.
264. Domanski M, Coady S, Fleg J, Tian X, Sachdev V: Effect of statin therapy on survival in patients with nonischemic dilated

www.ketabpezeshki.com 66485457-66963820

cardiomyopathy (from the Beta-blocker Evaluation of Survival Trial [BEST]). *Am J Cardiol* 2007; 99:1448.
265. Khush KK, et al: Effect of high-dose atorvastatin on hospitalizations for heart failure: Subgroup analysis of the Treating to New Targets (TNT) study. *Circulation* 2007; 115:576.
266. Raina A, Pickering T, Shimbo D: Statin use in heart failure: A cause for concern? *Am Heart J* 2006; 152:39.
267. Strey CH, et al: Short-term statin treatment improves endothelial function and neurohormonal imbalance in normocholesterolaemic patients with non-ischaemic heart failure. *Heart* 2006; 92:1603.
268. Shanes JG, Minadeo KN, Moret A, Groner M, Tabaie SA: Statin therapy in heart failure: Prognostic effects and potential mechanisms. *Am Heart J* 2007; 154:617.
269. Sakamoto T, et al: Effects of early statin treatment on symptomatic heart failure and ischemic events after acute myocardial infarction in Japanese. *Am J Cardiol* 2006; 97:1165.
270. Wojnicz R, et al: Usefulness of atorvastatin in patients with heart failure due to inflammatory dilated cardiomyopathy and elevated cholesterol levels. *Am J Cardiol* 2006; 97:899.
271. Sola S, Mir MQ, Lerakis S, Tandon N, Khan BV: Atorvastatin improves left ventricular systolic function and serum markers of inflammation in nonischemic heart failure. *J Am Coll Cardiol* 2006; 47:332.
272. Heart Protection Study Collaborative Group: N-terminal pro-B-type natriuretic peptide, vascular disease risk, and cholesterol reduction among 20,536 patients in the MRC/BHF heart protection study. *J Am Coll Cardiol* 2007; 49:311.
273. Lipinski MJ, et al: Meta-analysis of randomized controlled trials of statins versus placebo in patients with heart failure. *Am J Cardiol* 2009; 104:1708.
274. Horwich TB, MacLellan WR, Fonarow GC: Statin therapy is associated with improved survival in ischemic and non-ischemic heart failure. *J Am Coll Cardiol* 2004; 43:642.
275. Mozaffarian D, Nye R, Levy WC: Statin therapy is associated with lower mortality among patients with severe heart failure. *Am J Cardiol* 2004; 93:1124.
276. LaRosa JC, et al: Comparison of 80 versus 10 mg of atorvastatin on occurrence of cardiovascular events after the first event (from the Treating to New Targets [TNT] trial). *Am J Cardiol* 2010; 105:283.
277. Nodari S, et al: Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2011; 57:870.
278. Gissi-HF Investigators, et al: Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): A randomised, double-blind, placebo-controlled trial. *Lancet* 2008; 372:1223.
279. Adams KF Jr, et al: Prospective assessment of the occurrence of anemia in patients with heart failure: Results from the Study of Anemia in a Heart Failure Population (STAMINA-HFP) Registry. *Am Heart J* 2009; 157:926.
280. Zilberman M, et al: Improvement of anemia with erythropoietin and intravenous iron reduces sleep-related breathing disorders and improves daytime sleepiness in anemic patients with congestive heart failure. *Am Heart J* 2007; 154:805.
281. Parissis JT, et al: Effects of darbepoetin alpha on right and left ventricular systolic and diastolic function in anemic patients with chronic heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am Heart J* 2008; 155:751.
282. van der Meer P, Groenveld HF, Januzzi JL Jr, van Veldhuisen DJ: Erythropoietin treatment in patients with chronic heart failure: A meta-analysis. *Heart* 2009; 95:1309.
283. Palazzuoli A, et al: Erythropoietin improves anemia, exercise tolerance and renal function and reduces B-type natriuretic peptide and hospitalization in patients with heart failure and anemia. *Am Heart J* 2006; 152:1096.
284. Gottlieb JD, et al: Hypoxia, not the frequency of sleep apnea, induces acute hemodynamic stress in patients with chronic heart failure. *J Am Coll Cardiol* 2009; 54:1706.
285. Garcia-Touchard A, Somers VK, Olson LJ, Caples SM: Central sleep apnea: Implications for congestive heart failure. *Chest* 2008; 133:1495.
286. Sharma B: Sleep in congestive heart failure. *Med Clin North Am* 2010; 94:447.
287. Arzt M, et al: Nocturnal continuous positive airway pressure improves ventilatory efficiency during exercise in patients with chronic heart failure. *Chest* 2005; 127:794.
288. Noda A, et al: Beneficial effect of bilevel positive airway pressure on left ventricular function in ambulatory patients with idiopathic dilated cardiomyopathy and central sleep apnea-hypopnea: A preliminary study. *Chest* 2007; 131:1694.
289. Arzt M, et al: Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: A post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and heart failure Trial (CANPAP). *Circulation* 2007; 115:3173.
290. Naughton MT, Lorenzi-Filho G: Sleep in heart failure. *Prog Cardiovasc Dis* 2009; 51:339.
291. Bradley TD, et al: Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med* 2005; 353:2025.
292. Khayat RN, et al: Cardiac effects of continuous and bilevel positive airway pressure for patients with heart failure and obstructive sleep apnea: A pilot study. *Chest* 2008; 134:1162.
293. Chase P, et al: Prognostic usefulness of the functional aerobic reserve in patients with heart failure. *Am Heart J* 2010; 160:922.
294. Pozehl B, Duncan K, Hertzog M, Norman JF: Heart Failure Exercise And Training Camp: Effects of a multicomponent exercise training intervention in patients with heart failure. *Heart Lung* 2010; 39:S1.
295. Flynn KE, et al: Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009; 301:1451.
296. Nilsson BB, Westheim A, Risberg MA: Effects of group-based high-intensity aerobic interval training in patients with chronic heart failure. *Am J Cardiol* 2008; 102:1361.
297. Haykowsky MJ, et al: A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: The benefit depends on the type of training performed. *J Am Coll Cardiol* 2007; 49:2337.
298. Cittadini A, et al: Growth hormone deficiency in patients with chronic heart failure and beneficial effects of its correction. *J Clin Endocrinol Metab* 2009; 94:3329.
299. Naghi JJ, Philip KJ, DiLibero D, Willix R, Schwarz ER: Testosterone therapy: Treatment of metabolic disturbances in heart failure. *J Cardiovasc Pharmacol Ther* 2011; 16:14.
300. Jones RH, et al: Coronary bypass surgery with or without surgical ventricular reconstruction. *N Engl J Med* 2009; 360:1705.
301. Daneshmand MS, Milano CA: Surgical treatments for advanced heart failure. *Surg Clin North Am* 2009; 89:967.
302. Slaughter MS, et al: Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 2009; 361:2241.
303. Greenberg B, et al: Effects of continuous aortic flow augmentation in patients with exacerbation of heart failure inadequately responsive to medical therapy: Results of the Multicenter Trial of the Orqis Medical Cancion System for the Enhanced Treatment of Heart Failure Unresponsive to Medical Therapy (MOMENTUM). *Circulation* 2008; 118:1241.
304. Starling RC, et al: Sustained benefits of the CorCap Cardiac Support Device on left ventricular remodeling: Three year follow-up results from the Acorn clinical trial. *Ann Thorac Surg* 2007; 84:1236.
305. Park SJ, et al: Left ventricular assist devices as destination therapy: A new look at survival. *J Thorac Cardiovasc Surg* 2005; 129:9.
306. Miller LW, et al: Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med* 2007; 357:885.
307. Soran O, Kennard ED, Kfoury AG, Kelsey SF, IEPR Investigators: Two-year clinical outcomes after enhanced external counterpulsation (EECP) therapy in patients with refractory angina pectoris and left ventricular dysfunction (report from the International EECP Patient Registry). *Am J Cardiol* 2005; 97:17.
308. Wenke K, et al: Simvastatin initiated early after heart transplantation: 8-year prospective experience. *Circulation* 2003; 107:93.
309. Hershberger RE, et al: Daclizumab to prevent rejection after cardiac transplantation. *N Engl J Med* 2005; 352:2705.
310. Gray NA Jr, Selzman CH: Current status of the total artificial heart. *Am Heart J* 2006; 152:4.
311. Gersh BJ, Simari RD, Behfar A, Terzic CM, Terzic A: Cardiac cell repair therapy: A clinical perspective. *Mayo Clin Proc* 2009; 84:876.
312. Mazhari R, Hare JM: Advances in cell-based therapy for structural heart disease. *Prog Cardiovasc Dis* 2007; 49:387.
313. Zhao Q, Sun Y, Xia L, Chen A, Wang Z: Randomized study of mononuclear bone marrow cell transplantation in patients with coronary surgery. *Ann Thorac Surg* 2008; 86:1833.
314. Miettinen JA, et al: Determinants of functional recovery after myocardial infarction of patients treated with bone marrow-derived stem cells after thrombolytic therapy. *Heart* 2010; 96:362.
315. Dill T, et al: Intracoronary administration of bone marrow-derived progenitor cells improves left ventricular function in patients at risk for adverse remodeling after acute ST-segment elevation myocardial infarction: Results of the Reinfusion of Enriched Progenitor cells And Infarct Remodeling in Acute Myocardial Infarction study

www.ketabpezeshki.com 66485457-66963820

(REPAIR-AMI) cardiac magnetic resonance imaging substudy. *Am Heart J* 2009; 157:541.

316. Lunde K, et al: Exercise capacity and quality of life after intracoronary injection of autologous mononuclear bone marrow cells in acute myocardial infarction: Results from the Autologous Stem cell Transplantation in Acute Myocardial Infarction (ASTAMI) randomized controlled trial. *Am Heart J* 2007; 154:710.
317. Menasché P, et al: The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial: First randomized placebo-controlled study of myoblast transplantation. *Circulation* 2008; 117:1189.
318. Goodlin SJ: Palliative care in congestive heart failure. *J Am Coll Cardiol* 2009; 54:386.
319. Formiga F, et al: Predictors of in-hospital mortality present at admission among patients hospitalized because of decompensated heart failure. *Cardiology* 2007; 108:73.
320. Muzzarelli S, et al: Predictors of early readmission or death in elderly patients with heart failure. *Am Heart J* 2010; 160:308.
321. Patel UD, et al: Associations between worsening renal function and 30-day outcomes among Medicare beneficiaries hospitalized with heart failure. *Am Heart J* 2010; 160:132.
322. Krumholz HM, et al: Readmission after hospitalization for congestive heart failure among mediocre beneficiaries. *Arch Intern Med* 1997; 157:99.
323. Aguado O, et al: Long-term implications of a single home-based educational intervention in patients with heart failure. *Heart Lung* 2010; 39:S14.
324. Koelling TM, Johnson ML, Cody RJ, Aaronson KD: Discharge education improves clinical outcomes in patients with chronic heart failure. *Circulation* 2005; 111:179.
325. Phillips CO, et al: Comprehensive discharge planning with postdischarge support for older patients with congestive heart failure: A meta-analysis. *JAMA* 2004; 291:1358.
326. Chaudhry SI, et al: Telemonitoring in patients with heart failure. *N Engl J Med* 2010; 363:2301.
327. Ferrante D, et al: Long-term results after a telephone intervention in chronic heart failure: DIAL (Randomized Trial of Phone Intervention in Chronic Heart Failure) follow-up. *J Am Coll Cardiol* 2010; 56:372.
328. Powell LH, et al: Self-management counseling in patients with heart failure: The heart failure adherence and retention randomized behavioral trial. *JAMA* 2010; 304:1331.
329. Fonarow GC, et al: Adherence to heart failure quality-of-care indicators in U.S. hospitals: Analysis of the ADHERE Registry. *Arch Intern Med* 2005; 165:1455.
330. Fonarow GC, Gheorghiade M, Abraham WT: Importance of in-hospital initiation of evidence-based medical therapies for heart failure: A review. *Am Heart J* 2007; 153:2.

www.ketabpezeshki.com 66485457-66963820

Chapter 82

Pericardial and Myocardial Disease

Nicholas J. Jouriles

PERICARDIAL DISEASE (PERICARDITIS)

PERSPECTIVE

Our knowledge of pericardial function and disease has increased greatly since Hippocrates described the pericardium in 460 BC as "a smooth tunic that envelops the heart and contains a small amount of fluid resembling urine." Galen provided the first description of a pericardial effusion and performed the first pericardial resection.[1] Lancisi first described the appearance of constrictive pericarditis at autopsy in 1728. Also in the 18th century, Laennec said, "There are few diseases attended by more variable symptoms and more difficult to diagnose than [pericarditis]."[1] In 1935, Beck described the clinical presentation of cardiac tamponade, known as *Beck's triad* (hypotension, jugular venous distention, and muffled heart sounds).[2] Despite the passage of time and the modern availability of many diagnostic tools, the diagnosis and treatment of pericardial disease still present a challenge.

ETIOLOGY

Each of the disorders listed in Box 82-1 can produce acute pericarditis, with or without pericardial effusion. In addition, most of these disorders can progress to cardiac tamponade or constrictive pericarditis.

Most cases of pericarditis in developed countries are idiopathic. Even exhaustive clinical testing identifies a specific cause in less than 20% of patients, with the remainder being idiopathic despite often being putatively of viral cause.

EPIDEMIOLOGY

Acute pericarditis is a syndrome caused by inflammation of the pericardium. Although the exact incidence is unknown, autopsy series show an incidence of pericarditis of approximately 5%. The incidence of pericarditis in the emergency department (ED) is not known.

PRINCIPLES OF DISEASE

Pericardial Anatomy and Physiology

The normal pericardium envelops the heart and attaches to the great vessels. It consists of parietal and visceral layers, with a narrow potential space between them. The visceral layer or epicardium adheres to the myocardium. It is separated from the parietal layer by a potential space. Each layer is 1 or 2 mm thick and is composed of elastic fibers. The position of the heart within the chest is stabilized by the attachment of the parietal pericardium to the sternum, the diaphragm, and the vertebral column. Its blood supply comes from the internal mammary artery, and its nerve supply from the phrenic nerve.[3]

An ultrafiltrate of plasma, 15 to 35 mL of fluid, is normally contained in the pericardial space. Abnormal amounts of pericardial fluid can accumulate when the venous or lymphatic drainage of the heart is obstructed. The pericardium serves several functions: it maintains the heart's position, lubricates the heart's surface, prevents the spread of infection, prevents cardiac overdilation, augments atrial filling, and maintains the normal pressure-volume relationships of the cardiac chambers. Patients with congenital absence (or surgical removal) of the pericardium, however, show few, if any, problems.

PATHOPHYSIOLOGY

The inflammation of pericarditis is characterized by a granulocytic and lymphocytic infiltration of the pericardium. There is an increase in the number of antibodies in the pericardial fluid.

IDIOPATHIC PERICARDITIS

Clinical Features

The classic symptoms of pericarditis include chest pain, pericardial friction rub, and electrocardiogram (ECG) abnormalities. A history of fever and myalgia is common. Pericarditis chest pain usually is sharp and pleuritic and varies with position. It is typically relieved by sitting forward and is worsened by lying down, deep inspiration, or swallowing. Pericarditis pain is usually retrosternal, can radiate to the trapezius muscles, and may manifest as isolated shoulder pain. Pain can also be felt in the area of the diaphragm.

The physical examination hallmark of acute pericarditis is the pericardial friction rub. The rub may be caused by friction between inflamed or scarred visceral and parietal pericardium or may result from friction between the parietal pericardium and adjacent pleura. It may be audible anywhere over the anterior chest wall but usually is best heard at the lower left sternal border. Friction rubs are best heard via the diaphragm of the stethoscope, with the patient leaning forward in full expiration. The rub also can be accentuated by a full inspiration, followed by a breath hold, during which auscultation is performed. The rub tends to be intermittent, migratory, and difficult to hear in a loud ED.

Diagnostic Strategies

There is no single test that is diagnostic for pericarditis. The ECG is the most reliable diagnostic tool. It evolves through stages that

www.ketabpezeshki.com 66485457-66963820

Box 82-1 Etiology of Pericarditis

Infectious
- Viral
- Bacterial
- Fungal
- Parasite
- Rickettsia

Postinjury
- Trauma
- Surgery
- Myocardial infarction
- Radiation

Metabolic diseases
- Uremia
- Medications

Systemic diseases
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Sarcoidosis
- Scleroderma
- Dermatomyositis
- Amyloidosis

Tumors
Aortic dissection

occur over time. The first stage occurs in the first hours to days of illness. It includes diffuse ST segment elevation seen in leads I, II, III, aVL, aVF, and V_2 through V_6 and also reciprocal ST segment depression in aVR and V_1. Most patients with acute pericarditis have concurrent PR segment depression (Fig. 82-1). In the next stages, the ST and PR segments normalize, but the T waves flatten, and then there is deep, symmetrical T wave inversion. At the last stage, the ECG reverts to normal, although the T wave inversions may become permanent.[4]

The early ECG findings of acute pericarditis may be difficult to distinguish from acute myocardial infarction (MI), coronary artery spasm, or benign early repolarization. The differentiation of acute MI from acute pericarditis is essential. Thrombolytic therapy is contraindicated in pericarditis because its use may precipitate hemorrhagic cardiac tamponade. In contrast to the ECG in acute MI, the ST segment elevations in stage 1 acute pericarditis are concave rather than convex upward, and simultaneous T wave inversions are not seen. Subsequent tracings do not evolve through a typical MI pattern, and Q waves do not appear.

Differentiation of pericarditis from ST elevation MI is often difficult, especially if the history is atypical or the patient has a significant communication barrier, such as language. When the ECG pattern suggests ACS and the pain is not clearly pericarditic

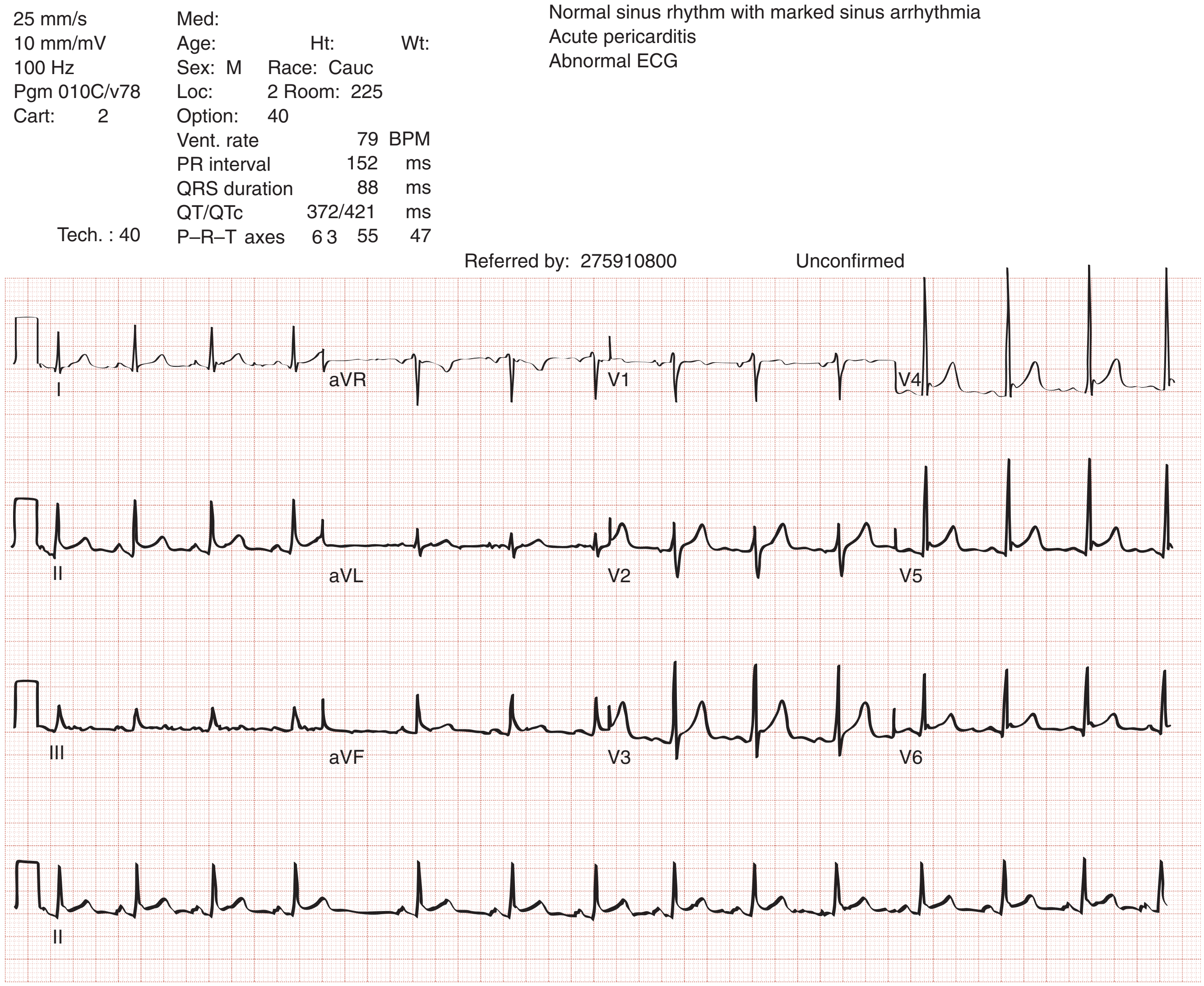


Figure 82-1. Electrocardiogram showing acute pericarditis. (Courtesy Ohio Chapter of the American College of Emergency Physicians.)

www.ketabpezeshki.com 66485457-66963820

in nature, often the best course is early diagnostic coronary angiography.

Ventricular dysrhythmias are rare in pericardial disease. Patients with pericarditis who have ventricular dysrhythmias should be presumed to have concomitant myocarditis or another cardiac disease or to have been misdiagnosed.

Echocardiography facilitates the definitive diagnosis of pericarditis with effusion, although it will be normal in patients without significant effusion, and a normal echocardiogram cannot be used to exclude pericarditis. In addition, cardiac tamponade, increased pericardial thickness, pericardial tumors and cysts, constrictive pericarditis, and the congenital absence of the pericardium can all be diagnosed by echocardiography.

Some patients with acute pericarditis have elevated cardiac markers caused by myopericarditis, myocarditis, or MI. The white blood cell count and erythrocyte sedimentation rate (ESR) may be elevated or normal and are not sensitive or specific. Other laboratory studies should be directed at determining nonidiopathic causes of pericarditis.

Management and Disposition

If a specific cause of pericarditis is found, therapy should be specific for that cause. Otherwise, therapy for acute pericarditis is symptomatic. Anti-inflammatory therapy will reduce pain, and a nonsteroidal anti-inflammatory drug (NSAID) is the treatment of first choice. Ibuprofen has the best side effect profile, but other NSAIDs should be equally effective. The patient will often report significant pain relief from the analgesic effect of the ibuprofen while in the ED, even before onset of the anti-inflammatory effect. A dose of 600 mg four times a day for 1 week is a good initial therapy. If the chosen NSAID is not effective within 1 week, a different class of NSAIDs should be tried, such as indomethacin 25 mg three times a day for 1 week. Colchicine (1.2 initially then 0.6 mg daily for up to 6 months) is effective for recurrent pericarditis, and steroid therapy (1 mg/kg daily) has shown mixed results.[5,6]

Complications

The clinical course of pericarditis is variable: 60% of patients have complete recovery within 1 week, and almost 80% have complete recovery within 3 weeks. Patients with fever, pericardial effusion, a subacute course, or failure of initial NSAID treatment have a worse prognosis. Eighteen percent of patients can have recurrent pericarditis that may require serial echocardiography to exclude effusion or tumor.[6]

UREMIC PERICARDIAL DISEASE

Perspective and Etiology

Pericarditis may occur secondary to renal failure or dialysis. It occurs more frequently in hemodialysis patients than in those receiving peritoneal dialysis. Acute renal failure is also associated with pericarditis, and the cause is unknown. The evaluation of a chronic renal disease patient with pericarditis requires a diligent search for infectious causes.

Clinical Features and Diagnostic Strategies

Patients with uremic pericarditis have chest pain, unexplained fever, and possibly a coarse friction rub. They also may have significant effusions. The ECG in uremic pericarditis is often normal because little epicardial inflammation occurs.[7] In a dialysis patient, cardiac enlargement on chest radiograph in the absence of signs of volume overload or congestive heart failure (CHF) should prompt consideration of pericardial effusion. An echocardiogram will provide the definitive answer. Pericardiocentesis may be needed to exclude infection.

Management and Disposition

Uremic pericarditis is initially treated with intensive dialysis. NSAIDs are ineffective and often are contraindicated by the patient's underlying renal impairment. Systemic steroids (prednisone 1 mg/kg daily) may require 1 or 2 weeks of therapy in the few patients who do not respond to dialysis.

Complications

Uremic pericardial effusions are among the most common causes of cardiac tamponade. Uremic pericardial effusions may be locular and difficult to fully drain with a catheter, and surgical options should be considered.

POST–MYOCARDIAL INFARCTION PERICARDITIS

Approximately 20% of patients with transmural MIs experience a different quality of chest pain 2 to 4 days after infarction. This pain may represent early post-MI pericarditis. There is frequently low-grade fever and a transient pericardial friction rub. A large pericardial effusion is unusual. Early post-MI pericarditis is generally short-lived and disappears with 1 to 3 days with aspirin therapy (325 mg/day).

The ECG changes of pericarditis usually are masked by the acute MI changes. Patients with early post-MI pericarditis have more dysrhythmias and heart failure. Pericarditis in acute MI may be an indicator of greater myocardial damage and a worse outcome.

Dressler reported a syndrome of fever, pleuritis, leukocytosis, pericardial friction rub, and chest radiograph evidence of new pericardial or pleural effusions in post-MI patients.[8] Frequent relapses and a high incidence of friction rubs led Dressler to describe this syndrome as a delayed complication of MI in contrast to the well-known syndrome of early post-MI pericarditis. The cause of late post-MI pericarditis (Dressler's syndrome) may be immunologic, but the syndrome may also occur with pulmonary embolus and after pericardiotomy. Anticoagulants should be discontinued to reduce the risk of hemorrhage. Delayed post-MI pericarditis is treated with NSAIDs such as ibuprofen 600 mg four times per day or indomethacin 25 mg three times per day.

POSTINJURY PERICARDITIS

Perspective

Postcardiac injury syndrome is defined as pericarditis after MI, cardiac surgery, or trauma. The incidence ranges from approximately 5% after MI to 30% after thoracic surgery or trauma. Pericarditis develops in 20% of patients with a penetrating cardiac injury, few of whom have cardiac tamponade. It can also occur after chest trauma that does not involve the heart or pericardium.

Principles of Disease

Injury to the pericardium in blunt trauma may range from contusion to laceration or rupture. Some degree of traumatic pericarditis is found during surgery or at autopsy in many patients sustaining severe blunt trauma of the chest.

Penetrating wounds to the heart usually cause laceration of the pericardium and the myocardium, with secondary pericarditis

www.ketabpezeshki.com 66485457-66963820

and pericardial infections. Although the exact incidence is unknown, infection, tamponade, myocarditis, and inflammatory pericarditis may occur.

An immune pathogenesis is suggested by the development of cardiac autoantibodies, although these autoantibodies are common after injury, even in patients who do not develop pericarditis. Constrictive pericarditis occurs secondary to trauma. This may be caused by pericardial blood, possibly secondary to the decreased resorptive power of damaged pericardium, with secondary fibrosis and constriction.

Clinical Features

Symptoms and signs of postcardiac injury syndrome include pericardial rub, fever, and chest pain. Although the diagnosis is usually established clinically, confirmation by echocardiography is helpful. The interval between injury and the onset of pericarditis ranges from 4 to 12 days. During hospitalization, purulent pericarditis should be considered as a possible source of febrile illness in a trauma patient with multisystem organ failure.

Management and Disposition

Most patients respond to aspirin (325 mg daily) or NSAIDs (ibuprofen 600 mg four times per day). Uncomplicated pericarditis secondary to blunt trauma usually resolves. The patient should be observed until other life-threatening disease processes have been excluded.

NEOPLASTIC PERICARDIAL DISEASE

Perspective

Malignant pericardial tumors typically manifest late, which complicates diagnosis and treatment. Malignant involvement of the pericardium is observed in 3.4% of general autopsies and 2 to 31% of cancer autopsies. The most common causes are lung cancer (30%), breast cancer (23%), lymphoma (17%) and leukemia (9%). Primary malignancies of the pericardium are rare.[9]

Principles of Disease and Pathophysiology

The pattern of cardiac involvement by a malignant tumor is determined by the heart's lymphatic drainage system.

Malignant pericardial effusions contribute directly to the patient's death in most cases commonly from cardiac tamponade. Although the underlying disease process is often advanced when tamponade develops, the patient's quality of life can usually be improved if tamponade is treated promptly.

Clinical Features

Primary cardiac neoplasms, such as angiosarcoma and teratoma, can initially cause symptoms consistent with pericarditis. The typical course is that of an acute pericarditis that resolves and subsequently recurs. Malignant pericardial disease is difficult to diagnose. Most patients are asymptomatic or have nonspecific symptoms, such as shortness of breath, cough, palpitations, ill-defined chest pain, weakness, dizziness, hiccups, or fatigue.

Diagnostic Strategies

The diagnostic workup for malignant pericardial effusion includes an echocardiogram, computed tomography (CT), or magnetic resonance imaging (MRI). When a pericardial effusion is identified, pericardial fluid cytology is recommended if the underlying malignancy is undiagnosed.

Management and Disposition

Malignant pericardial effusion treatment may include pericardiocentesis, local instillation of sclerosing or chemotherapeutic agents, systemic chemotherapy, cardiac radiation, and pericardial window. The method chosen depends on the primary tumor and the patient's expected length of survival.

The prognosis for patients with malignant pericardial disease depends on the type and extent of the underlying cancer.

RADIATION-INDUCED PERICARDITIS

Fewer than 5% of patients treated with radiation therapy develop pericarditis. The incidence has decreased with improved radiation therapy techniques. The percentage of pericardial volume irradiated and the dosage determine which patients develop pericarditis. Radiation-induced pericarditis is seen most commonly in patients with Hodgkin's lymphoma or breast cancer. Pericardial effusion and constrictive pericarditis are common, and tumor recurrence should be considered.

PERICARDIAL DISEASE RELATED TO CONNECTIVE TISSUE DISORDERS

Pericarditis occurs in approximately one third of patients with rheumatoid arthritis (RA), usually within 3 years of the initial diagnosis. Rheumatoid pericardial disease is rarely clinically significant. Occasional patients develop effusions, constrictive pericarditis, or cardiac tamponade. These patients usually have rheumatoid nodules, elevated circulating rheumatoid factor levels, and valvular heart disease. Pericardial fluid may have rheumatoid factor or a low glucose level. Corticosteroid treatment is useful. Prednisone 1 mg/kg/day is the initial treatment, with close follow-up appointment.

Pericarditis is found at autopsy in more than 50% of patients with systemic lupus erythematosus (SLE). The effusion is usually thick and fibrinous. Either cardiac tamponade or constrictive pericarditis may develop. Lupus erythematosus cells may be identified in pericardial fluid specimens. Corticosteroid therapy is indicated.

Other connective tissue diseases that may cause pericarditis include Sjögren's syndrome, giant cell arteritis, ankylosing spondylitis, Reiter's syndrome, Behçet's disease, systemic sclerosis, and polyarteritis nodosa.

MISCELLANEOUS INFECTIOUS CAUSES OF PERICARDITIS

Other causes of pericarditis include *Rickettsia conorii,* which causes Mediterranean spotted fever (treated with doxycycline), *Mycoplasma pneumoniae* (treated with a macrolide), *Nocardia asteroides* (treated with pericardiectomy and long-term use of antibiotics such as sulfisoxazole), *Chlamydia trachomatis,* Epstein-Barr virus, cytomegalovirus infection, *Haemophilus actinomycetemcomitans* (treated with chloramphenicol), and coccidioidomycosis (endemic in the southwestern United States). Viral and bacterial causes of pericarditis can coexist, such as varicella-zoster infection superinfected with *Staphylococcus aureus.* These bacterial superinfections associated with varicella are more common in children.

www.ketabpezeshki.com 66485457-66963820

PERICARDIAL EFFUSION

Etiology and Clinical Features

The most common causes of pericardial effusion are viral or idiopathic pericarditis, malignancy, uremia, trauma, and radiation therapy. Drug reactions and autoimmune diseases are less common causes.

Pericardial effusion is often asymptomatic. Patients with known associated conditions (e.g., cancer or renal failure) with cough, fever, chest pain, or dyspnea may have an effusion.

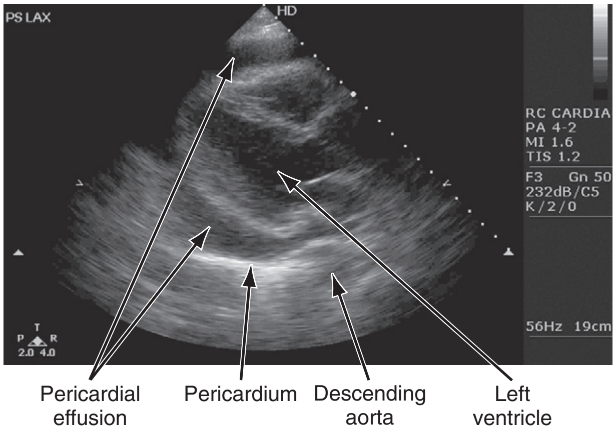
Diagnostic Strategies

Pericardial effusion may cause an enlarged cardiac silhouette on chest radiograph, usually with normal pulmonary vasculature. A minimum of 200 to 250 mL of pericardial fluid is necessary to produce cardiomegaly on a chest radiograph.

Echocardiography is the diagnostic modality of choice (Fig. 82-2). It easily differentiates pericardial fluid from cardiac chamber enlargement and provides information about myocardial wall motion.

CT may be useful in diagnosing pericardial effusion when the echocardiogram is technically unsatisfactory. MRI can also be diagnostic. Nuclear scans may be useful in detecting purulent pericardial effusions.

A



B

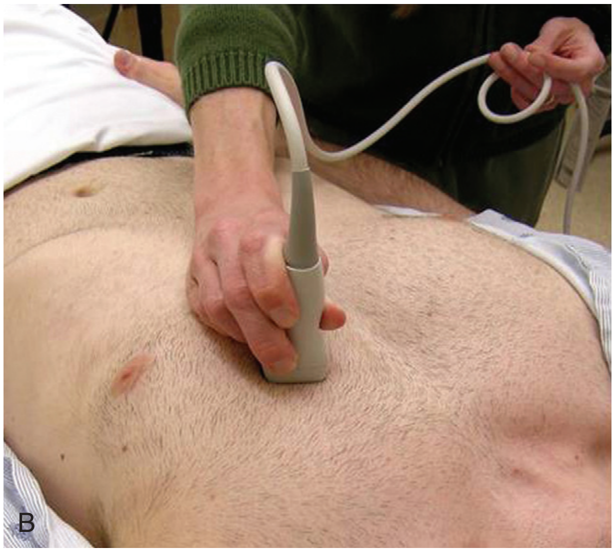


Figure 82-2. A, Bedside ultrasound showing a pericardial effusion. The effusion is best seen superior to the left ventricle at the top of the image. B, The proper technique for emergency department ultrasound of pericardial effusion. (Courtesy Jessica Resnick, MD.)

Pericardiocentesis may be performed for either diagnostic or therapeutic purposes. Elective diagnostic pericardiocentesis is indicated in cancer patients (to differentiate malignant effusion from postradiation pericarditis), for failure to respond to usual treatment, or when bacterial infection is suspected. Common complications of pericardiocentesis include induction of cardiac dysrhythmias, pneumothorax, perforation of myocardium, laceration of coronary or internal mammary arteries, and liver laceration. Echocardiographic-guided pericardiocentesis is the procedure of choice.

Pericardial fluid should be analyzed for protein, glucose, specific gravity, cell count and differential, Gram's stain, and culture. Other tests, depending on the clinical picture, include cytology, acid-fast stain, fungal smear, and connective tissue disease screening.

The gross appearance of the pericardial fluid provides a clue to the cause. Serosanguineous effusions are associated most commonly with neoplasms, tuberculosis, uremia, radiation, and idiopathic pericarditis. Grossly bloody effusions are caused by blunt or penetrating trauma, postinfarction myocardial rupture, aortic dissection, coagulopathies, and iatrogenic cardiac perforation. Purulent pericardial fluid is seen with pneumonia, empyema, and sepsis.

CARDIAC TAMPONADE

Etiology and Pathophysiology

Ten percent of all patients with cancer develop cardiac tamponade.[10] Cardiac tamponade should be suspected in patients with penetrating chest wounds. It is also common in patients with uremic pericarditis.

Cardiac tamponade is the result of compression of the myocardium by the contents of the pericardium. This compression is usually caused by fluid, but it may be caused by gas, pus, blood, or a combination of factors.

Cardiac tamponade is a physiologic continuum reflecting the amount of fluid, the rate of accumulation, and the nature of the heart. The three stages necessary for tamponade to develop are fluid filling the recesses of the parietal pericardium, fluid accumulating faster than the rate of the parietal pericardium's ability to stretch, and accumulation that exceeds the body's ability to increase blood volume to support right ventricle filling pressure. The final result is increased pericardial pressure, which causes decreased ventricle compliance and decreased flow of blood into the heart. The reduction of blood inflow into the right ventricle results in decreased stroke volume that leads to decreased cardiac output.[10] The most important factor in the development of tamponade is the rate of fluid accumulation.

The heart initially responds to tamponade by increasing heart rate to maintain cardiac output. This compensatory mechanism is maintained until late in the clinical course, followed by decompensation.

Symptoms and Signs

Cardiac tamponade symptoms are often nonspecific, but particularly include chest pain, cough, or dyspnea, any of which may be progressive and severe. The classic triad of cardiac tamponade signs described by Beck is hypotension, distended neck veins, and muffled heart sounds.[11] These signs may not be present if tamponade develops quickly.

Diagnostic Strategies

The chest radiograph shows cardiomegaly only if there is a large accumulation of fluid (250 mL). The ECG classically shows decreased voltage or electrical alternans (Fig. 82-3), but the latter

www.ketabpezeshki.com 66485457-66963820

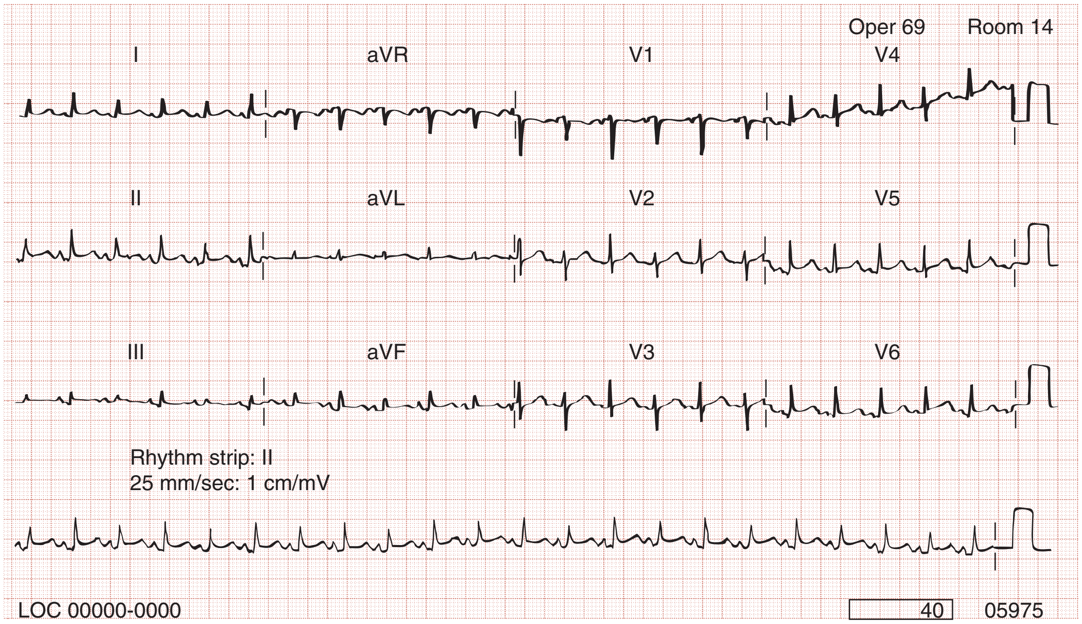


Figure 82-3. Electrocardiogram showing electrical alternans.

is rare. Echocardiography confirms the diagnosis when an effusion and paradoxical systolic wall motion are seen. Thermodilution catheters can also be diagnostic, showing equalization of right and left ventricular pressures.

Management and Prognosis

Initial treatment includes volume augmentation to the right ventricle with intravenous fluids to increase the filling pressure to overcome the pericardial constriction. Pericardiocentesis or pericardial window is the treatment of choice. Enough fluid should be withdrawn to stabilize the patient. If tamponade recurs, pericardiocentesis may be repeated, or a drainage catheter may be left in the pericardial space. A pericardiectomy ultimately may be necessary. Cardiac tamponade has a high mortality that depends on the severity and nature of the underlying disease, the time course of onset, and the rapidity of diagnosis and intervention. Traumatic cardiac tamponade is discussed in Chapter 45.

PURULENT PERICARDITIS

Epidemiology and Etiology

Purulent pericarditis is a life-threatening process that is seen most commonly in a hospitalized patient with systemic illnesses who develops sepsis. It can occur in any age group and can be caused by any type of infectious agent, with bacteria, especially *Streptococcus* and *Staphylococcus*, being the most common. *Candida* pericarditis is found after cardiac surgery or in patients with impaired host defenses or severe debilitating underlying diseases. *Histoplasma* infection of the pericardium occurs in endemic areas, including the Ohio and Mississippi River valleys.

Principles of Disease and Pathophysiology

Purulent pericarditis occurs by several mechanisms: (1) spread from an adjacent infection, such as pneumonia or empyema; (2) hematogenous spread from a distant site; (3) direct inoculation of bacteria (trauma or procedure); and (4) spread from an intracardiac source. The most common mechanism is spread from a distant site.

Clinical Features and Diagnostic Strategies

Purulent pericarditis usually manifests as a febrile illness lasting 2 or 3 days. Common presenting signs include tachycardia, dyspnea, hepatomegaly, elevated central venous pressure, chest pain, friction rub, and leukocytosis. The most common presentation is a hospitalized patient with a serious underlying disease who initially improves after treatment of the primary process but later develops fever, dyspnea, and chest pain.

The diagnosis should be suspected in any febrile patient with multisystem illness who has a pericardial effusion. Pericardiocentesis is necessary to establish the diagnosis, obtain fluid for microbiologic studies, and relieve cardiac tamponade.

Management and Disposition

Pericardiectomy is the traditional treatment of choice. Indwelling catheters, coupled with lavage, antibiotics (such as vancomycin 1 g two times per day or ampicillin-sulbactam 3 g four times a day), and fibrinolytics, may avoid the need for surgery. Intravenous antibiotics or antifungals are also needed.

The overall survival rate for purulent pericarditis is approximately 30% with antibiotic therapy alone and 50% when combined with early surgical drainage. In addition to the initial complications related to sepsis and tamponade, long-term sequelae of purulent pericarditis include the development of constrictive pericarditis.

TUBERCULOUS PERICARDITIS

Tuberculous pericarditis is estimated to occur in 1 or 2% of patients with pulmonary tuberculosis.[12] In Africa, it is the most common cause of pericarditis. In countries in which tuberculosis is not a major health problem, tuberculous pericarditis is most common in patients who are socioeconomically deprived or immunodeficient. In many patients the chest radiograph shows an enlarged cardiac silhouette without a pulmonary infiltrate. Pericardial fluid aspirates reveal acid-fast bacilli by smear or culture (which may require 4-6 weeks to become positive) in approximately 50% of cases. Diagnostic workup should include

www.ketabpezeshki.com 66485457-66963820

assessment for human immunodeficiency virus (HIV). Patients with tuberculous pericarditis should be hospitalized and observed for evidence of cardiac tamponade. Triple-drug therapy should be started in the hospital and continued for at least 9 months. Patients with chronic pericardial effusions may benefit from oral prednisone therapy. The mortality rate is approximately 15% in HIV-negative patients and 20 to 35% in HIV-positive patients.[12]

OTHER CAUSES OF PERICARDITIS

Amyloid deposition can cause either restrictive cardiomyopathy (RCM) or constrictive pericarditis. Pericarditis can occur rarely as an extraintestinal complication of inflammatory bowel disease and is independent of the clinical course of the gut disorder.

Iatrogenic pericarditis can also occur as a complication of an implantable defibrillator or an atrial lead of a permanent pacemaker. A polymicrobial bacterial pericarditis can occur after transbronchial needle aspiration or as a complication of endoscopic variceal sclerotherapy. Rarely, pericarditis can also be caused by erosion of a foreign body, such as a sewing needle or toothpick, through the esophagus into the pericardium.

Less than 1% of patients with HIV develop acute pericarditis, but 40% have asymptomatic pericardial effusion. Pericardial effusion is more frequent in patients in the more advanced stages of HIV infection. The clinical features and diagnostic evaluation of patients with HIV-related pericarditis are the same as those in patients without acquired immunodeficiency syndrome (AIDS).

PNEUMOPERICARDIUM

Perspective and Etiology

Pneumopericardium and pyopneumopericardium are rare. Pneumopericardium may be caused by diseases that can lead to formation of fistulae between the pericardial and pleural space, bronchial tree, or upper gastrointestinal tract (e.g., peptic ulcer disease, carcinoma of the esophagus or stomach, and esophageal diverticulum). It may result from bronchial carcinoma or infection with gas-producing microorganisms, or it can be idiopathic. Pyopneumopericardium may result from trauma, foreign body, ingestion of caustic substances, or invasive procedures (e.g., esophagoscopy, thoracentesis, and endotracheal intubation).

Spontaneous pneumopericardium may complicate asthma, labor, barotrauma from positive-pressure ventilation, or Valsalva maneuvers, such as might occur during weightlifting. Cocaine inhalation from positive-pressure devices can also cause pneumopericardium.

Pathophysiology

Pneumopericardium is caused most commonly by an increase in intra-alveolar pressure above atmospheric pressure, resulting in rupture of alveoli. Air dissects into the hilum and mediastinum, through the pericardial reflection on the pulmonary vessels, and into the pericardium.

Clinical Features and Diagnostic Strategies

Physical findings depend on the quantity of fluid and gas in the pericardial space. Heart sounds can be of variable intensity, change depending on body position, and have a metallic quality that may be accompanied by splashing sounds. *Hamman's sign* and *mediastinal crunch* are the terms used for a loud, crunching sound associated with pneumopericardium or pneumomediastinum. This is best heard with the patient in a left lateral recumbent position and is diagnostic for the presence of mediastinal air. The diagnosis of pneumopericardium is confirmed by chest radiograph, CT scan, or echocardiography. Tension pneumopericardium manifests with clinical findings of acute cardiac tamponade.

Management

Stable patients with uncomplicated spontaneous pneumopericardium can usually be observed. After all other life-threatening injuries and complications have been excluded, no long-term sequelae are expected. Tension pneumopericardium should be treated with emergency pericardiocentesis.

CONSTRICTIVE PERICARDITIS

Perspective and Etiology

Constrictive pericarditis may be a late consequence of acute pericarditis of virtually any cause. There is an increased incidence of constrictive pericarditis as a result of improved survival in patients with chronic renal disease. Other predisposing conditions include radiation, trauma, purulent pericarditis, actinomycosis, and post-pericardiotomy adhesions. Tuberculosis is still the leading cause of constrictive pericarditis in some countries.

Principles of Disease and Pathophysiology

Constrictive pericarditis usually results from fibrous reaction of the pericardium. The key pathophysiologic feature is impaired diastolic filling from external cardiac compression caused by the thickened pericardium. In advanced cases the visceral and parietal pericardial layers may be adherent.

Because the pericardium limits volume, ventricular filling is rapid and completed within the first third of diastole, after which left ventricular volume and pressure remain unchanged. Early ventricular filling followed by a period of unchanging pressure yields a corresponding dip and plateau pattern or square root sign on the left ventricular diastolic pressure curve, which suggests the diagnosis of constrictive pericarditis.

Clinical Features

The symptoms and signs of constrictive pericarditis are identical to those of CHF. Dyspnea, fatigue, and weight gain are the most common complaints. Hepatomegaly, marked pitting lower extremity edema, and ascites can be seen on physical examination. The characteristic auscultatory finding of constrictive pericarditis is a pericardial knock in early diastole. A friction rub may also be heard.

Diagnostic Strategies

The diagnosis is considered in a patient with right-sided heart failure symptoms. Heart size on the chest radiograph is typically small but may be increased by atrial enlargement. Pericardial calcification is suggestive when present on CT or MRI. Liver function tests are consistent with passive congestion. ECG findings include low QRS voltage, nonspecific ST-T wave abnormalities, and atrial dysrhythmias.

Doppler echocardiography may help differentiate constrictive pericarditis from RCM or cardiac tamponade.[13] Cardiac catheterization and simultaneous measurement of right ventricular and left ventricular end-diastolic pressures or endomyocardial biopsy may be necessary.

www.ketabpezeshki.com 66485457-66963820

Differential Considerations and Management

Constrictive pericarditis is often confused with CHF. The diagnosis should also be considered with signs of elevated venous pressure but no history of myocardial dysfunction. Pericardiectomy is the therapy of choice.

MYOCARDIAL DISEASES (MYOCARDITIS)

PERSPECTIVE

The term *myocarditis* was coined initially by Sobernheim in 1837. Romberg reported the association with scarlet fever and typhus in 1891, and “isolated idiopathic interstitial myocarditis” was described by Fiedler in 1899.

EPIDEMIOLOGY AND ETIOLOGY

Some degree of myocarditis is detected in almost 10% of routine autopsies but is often not recognized clinically. The overall incidence is unknown and probably underdiagnosed. The Coxsackie B virus was originally named as the causative organism, but the predominant agents in the 1990s were the adenoviruses, followed by parvovirus 19 and human herpesvirus 6 since 2000.[14] In reality, any infectious agent can cause myocarditis (Box 82-2). The etiology varies by patient age and region. Cytomegalovirus and *Toxoplasma gondii* have emerged as potential causes of myocarditis in cardiac transplant patients. Of patients who have died of AIDS, 67% have myocarditis on autopsy. Worldwide, Chagas’ disease is a leading cause of myocarditis, especially in South America. Mortality from myocarditis has not changed since before 1990. The mortality rate is approximately 20% at 1 year and 50% at 5 years.[15]

PRINCIPLES OF DISEASE AND PATHOPHYSIOLOGY

Myocarditis occurs by (1) necrosis from direct invasion of an offending infectious agent and its replication within or near myocytes, (2) destruction of cardiac tissue from infiltration of host cellular immune components or from cytotoxic effects of host immunity activated by the infectious agent, or (3) the toxic effect of exogenous or endogenous chemicals produced by a systemic pathogen. Three stages are proposed: acute (early after infection), with viral cytotoxicity and focal necrosis; subacute, in which there is an increase in humoral factors leading to autoimmune injury; and chronic, in which there is diffuse myocardial fibrosis and cardiac dysfunction that may lead to dilated cardiomyopathy (DCM). In neonates, the pathologic changes are more often related to direct viral damage, whereas adults are more often injured by immunologic damage.

Isolation of a Coxsackievirus-adenovirus receptor shows how these two types of viruses, one RNA and one DNA, may enter the heart.

Cardiac autoantibodies develop after myocarditis. There is also a higher concentration of immunoglobulin G (IgG) anti–β-myosin antibodies in patients with myocarditis and DCM than in controls. Because myocarditis is linked to the development of DCM, idiopathic DCM after myocarditis may be predominantly autoimmune in origin, resulting from either shared antigens or molecular mimicry.[16] The amino acid sequences of the Coxsackie B virus and β-myosin heavy chain protein are similar. An immune response to the former yields damage to the latter (molecular mimicry).

Box 82-2 Infectious Causes of Myocarditis

- Adenovirus
- Chagas’ disease
- Coxsackie B virus
- Chlamydia
- Cytomegalovirus
- H1N1 virus
- Hepatitis A
- Hepatitis B
- Hepatitis C
- Human herpesvirus 6
- Influenza A
- Influenza B
- Lymphocytic choriomeningitis virus
- Mononucleosis
- Mumps
- Mycoplasma
- Parainfluenza
- Parvovirus 19
- Rabies
- Rubeola
- Rubella
- Streptococcus
- *Toxoplasma gondii*
- Varicella zoster

CLINICAL FEATURES

Flulike complaints, including fever, fatigue, myalgias, vomiting, and diarrhea, are usually the first symptoms and signs of myocarditis. The most common presentation in children is dyspnea. In adults, it is dyspnea, chest pain, and dysrhythmias. Altered vital signs include fever, tachycardia, tachypnea, and, uncommonly, hypotension. Tachycardia disproportionate to the temperature or apparent toxicity may occur but is a nonspecific finding. No symptom or sign is sensitive or specific. Cardiac examination is often unremarkable. When chest pain or CHF occurs at initial presentation, there is a worse prognosis.[17]

In children, prominent physical findings include grunting respirations and intercostal retractions. Although the lungs are clear to auscultation in most patients, approximately 10 to 15% have rhonchi. This may be related to infection with respiratory syncytial virus (RSV), which can cause these symptoms with or without associated myocarditis. Infants often have a fulminant syndrome characterized by fever, cyanosis, respiratory distress, tachycardia, and cardiac failure. When children have ventricular dysrhythmias, myocarditis and idiopathic DCM are commonly seen on endomyocardial biopsy, despite findings of a structurally normal heart by noninvasive studies. Long-term prognosis in children correlates with the severity of their initial presentation.

DIAGNOSTIC STRATEGIES

Common ECG changes include sinus tachycardia, a widened QRS, and low electrical activity. There may be a prolonged corrected QT interval, atrioventricular block, or acute MI pattern abnormalities.

Cardiac troponin may be elevated although when in the course of the disease is unknown. The prognostic significance of elevation is not known, although one can assume that a higher level correlates with more myocardial damage. The white blood cell count and ESR may be elevated or normal and so are not of diagnostic value. The echocardiographic features of myocarditis, although nonspecific, include reduced left ventricular ejection fraction, global hypokinesis, and regional wall motion abnormalities. Contrast-enhanced MRI may be diagnostic. Indium-111 antimyosin antibodies bind specifically to exposed myosin in damaged myocardial cells, providing a noninvasive approach for

www.ketabpezeshki.com 66485457-66963820

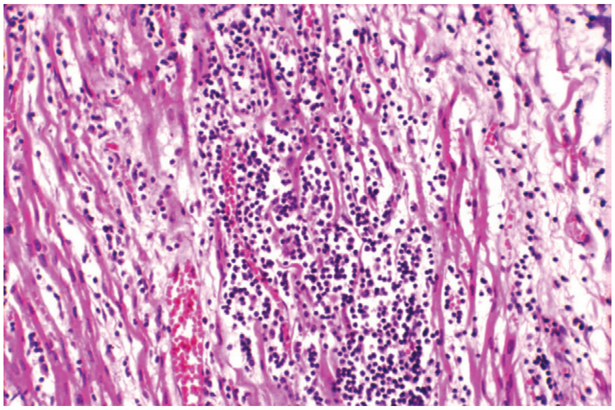


Figure 82-4. Myocardial biopsy specimen showing myocarditis. Note the lymphocytic infiltrate.

the diagnosis of myocardial necrosis. Acute and convalescent viral titers are positive in less than 40% of cases. A rise in viral titers or a high titer of viral-specific IgM may help establish a viral cause, although not in the ED.

Endocardial biopsy, the historical gold standard, has variable sensitivity and specificity owing to sampling error when the tissue taken is different from the tissue involved (Fig. 82-4). Histologic criteria for myocarditis are present in only 5 to 30% of patients with clinically suspected myocarditis and up to half of patients with DCM. Molecular genetic probes, such as polymerase chain reaction assays, are used to supplement standard histologic analysis. In addition, polymerase chain reaction analysis of tracheal aspirates of intubated patients with myocarditis shows a correlation with endocardial biopsy. Because of the limitations of biopsy, magnetic imaging may become the diagnostic test of choice and the next gold standard.

DIFFERENTIAL DIAGNOSIS

Myocarditis can masquerade as acute MI with severe chest pain, ECG changes, elevated cardiac markers, and heart failure. Patients with myocarditis are usually young and have few risk factors for coronary artery disease. ECG abnormalities may extend beyond the distribution of a single coronary artery, or there may be global, rather than segmental, wall motion abnormalities on echocardiography. In myocarditis, chest pain continues, but there are no further ischemic ECG changes. The diagnosis of myocarditis should also be considered in an otherwise healthy patient with symptoms and signs of new CHF or dysrhythmias.

If the differentiation of myocarditis from MI is unclear, catheterization may be necessary. Coronary angiography is usually normal in myocarditis, which should prompt consideration of endomyocardial biopsy.

MANAGEMENT

Treatment is supportive and aimed at preserving left ventricular function. The type of supportive care necessary is determined by the patient's clinical presentation and the stage and severity of disease. This may extend from simple limitation of activity to rhythm and CHF treatment, extracorporeal membrane oxygenation, ventricular assist devices (VADs), and eventual cardiac transplantation.

Therapy is stage specific, given the three distinct phases of the disease. In the first phase, demonstration of replicating virus suggests that early antiviral agents, such as pleconaril or ribavirin, may be effective. Unfortunately, the diagnosis is often made after the initial viral phase. Agents active at the Coxsackievirus-adenovirus receptor present an intriguing theoretic approach.[15]

Multicenter trials of immunosuppressive therapy for the subacute phases of myocarditis have shown no benefit.[15] Efforts to identify patient and treatment subsets in which immunosuppressive therapy may be beneficial are ongoing. High-dose gamma globulin therapy has been studied in a pediatric population. High-dose intravenous immunoglobulin may be associated with improved recovery of left ventricular function and better survival during the first year after presentation.

In the chronic stage, CHF symptoms predominate and standard pharmacologic treatment for CHF is indicated. In some cases the deterioration of cardiac function is reversible with the aid of a VAD. These devices have been used successfully over extended periods, including up to 70 days. Their use should be considered before transplantation.

DISPOSITION

All patients should be monitored, and those with persistent hemodynamic instability require intensive care. Paradoxically, patients with fulminant myocarditis have the best prognosis. Complications of myocarditis include ventricular dysrhythmias, left ventricular aneurysm, and cardiac failure.

The mortality rate is 20% at 1 year and 50% at 5 years, despite optimal medical management. Ejection fraction and right ventricular function 1 year after initial presentation may be the best predictors of subsequent survival. The long-term prognosis in survivors is variable.

Patients who undergo transplantation because of myocarditis heart failure have decreased 1-year survival compared with patients who undergo transplantation for other reasons. They also have higher allograft rejection rates than other recipients. The overall 5-year survival rate for children is 70%.

CHAGAS' DISEASE

Chagas' disease is one of the leading causes of myocardial disease in many countries in Latin America, particularly in Central America. Chagas' disease is caused by the protozoan *Trypanosoma cruzi* with transmission by insect vectors.[18]

Approximately 75% of seropositive patients with Chagas' disease never have symptoms. Systemic symptoms include fever, hepatic or splenic enlargement, and unilateral periorbital edema. Cardiac manifestations include angina-like chest pain, dysrhythmias, embolic episodes, heart failure, conduction abnormalities, multifocal ventricular premature contractions, and abnormal ST segment and T wave abnormalities. Ventricular tachycardia is common. Syncopal or near-syncopal episodes occur in nearly two thirds of patients.[19]

Serum parasites establish the diagnosis, as does measuring anti-IgG for *T. cruzi.* Chagas' disease should be included in the differential diagnosis for patients with new cardiac symptoms and a Latin American travel or immigration history. Echocardiography may show a left ventricular apical aneurysm or scar, which is a reliable marker of the disease.

Chagas' disease is treated with the antitrypanosomal drugs benznidazole (5 mg/kg/day divided into two daily doses for 60 days) and nifurtimox (15-20 mg/kg/day for patients younger than 10 years, 12.5-15 mg/kg/day for patients aged 10-18 years, and 8-10 mg/kg/day for patients older than 18 years, divided into four doses for 90 days). These medications are available from the Center for Disease Control and Prevention. Amiodarone may be useful to treat ventricular tachycardia. An angiotensin-converting enzyme inhibitor may be useful for CHF. Increased world attention, with elimination of the vector and improved blood donation screening, especially for platelet transfusions, is decreasing the incidence of this disease in Latin America.[20]

www.ketabpezeshki.com 66485457-66963820

TRICHINOSIS

Trichinosis is caused by ingestion of the cysts of *Trichinella spiralis* in undercooked meat. Historically, pork was the most commonly implicated meat, but *Trichinella* has been eradicated from commercial domestic pork for many decades in the United States. Trichinosis in the United States is most likely caused by wild game. Hunters, immigrants who home raise pork, and international travelers are at risk. Larvae may be deposited in the muscles, which incite an inflammatory reaction and necrosis of muscle fibers. The acute illness consists of fever, myalgias, muscle tenderness, neck stiffness, and a characteristic periorbital edema. Laboratory studies reveal an eosinophilia and often elevated creatine phosphokinase CPK or lactate dehydrogenase (LDH).

Myocardial involvement is present in approximately 20% of clinically diagnosed cases and appears in the second or third week of illness, when other symptoms are declining. Cardiac manifestations include chest pain, dyspnea, cardiomegaly, dysrhythmias, and CHF. ECG findings, such as nonspecific ST-T wave abnormalities and conduction blocks, may appear transiently, even in the absence of cardiac symptoms.

The diagnosis is usually established with serologic studies or biopsy of any symptomatic muscle group. Treatment usually involves corticosteroids (1 mg/kg/day) together with anthelminthic drugs such as albendazole (400 mg twice a day for 14 days) and mebendazole (400 mg four times per day for 14 days).[21]

DIPHTHERIA

Diphtheria presentation, diagnosis, and treatment are discussed in Chapter 129. Myocardial involvement is clinically evident in 10 to 25% of cases and is the major cause of death.[22] Early signs of myocarditis are tachycardia and faint heart sounds. Cardiac enzymes are often elevated. Prolongation of the PR interval and ST-T wave abnormalities occur early in the course of the disease. Bundle branch block or complete heart block, when they occur, precede total circulatory collapse and are associated with a poor prognosis. Treatment with oral carnitine, a cofactor in the transport of fatty acids to mitochondria, is associated with a lower incidence of mortality, heart failure, and severe conduction blocks.[22]

LYME DISEASE

Epidemiology and Clinical Features

Lyme disease is caused by infection with the spirochete *Borrelia burgdorferi* and is discussed in Chapter 141.[134] Lyme disease–related carditis occurs weeks to months after the onset of erythema migrans. Cardiac complications occur in 4 to 10% of patients. Such complications most commonly is a conduction delay, usually a reversible effect on the AV node. Pericarditis and CHF also occur.

Lyme disease–related carditis should be suspected in otherwise healthy persons with unexplained heart block and potential exposure to ticks in an endemic area. Lyme disease is diagnosed by identification of the spirochete with serologic testing. A screening ECG should be performed whenever the diagnosis of Lyme disease is suspected.

Temporary placement of a pacemaker is often required in unstable patients. Antibiotic therapy with intravenous penicillin (2 million units four times per day) or oral doxycycline (100 mg twice per day for 21 days) is effective and can reverse atrioventricular block. Erythromycin (250 mg four times per day for 21 days) should be prescribed in place of tetracycline in young children. Ceftriaxone (500 mg twice per day for 21 days) is also effective. Most patients recover completely, and a permanent pacemaker is rarely needed.

OTHER CAUSES OF MYOCARDITIS

The cardiac manifestations of AIDS are diverse and cause death in at least 6% of patients with HIV (HIV is discussed in Chapter 132). The prevalence of left ventricular dysfunction in adult AIDS patients is approximately 20%. Myocarditis is described in approximately 46% of AIDS patients undergoing postmortem examination. Cardiac involvement increases as the disease worsens. HIV treatment may also lead to cardiac toxicity. Pentamidine can cause torsades de pointes ventricular tachycardia. Zidovudine and dideoxyinosine also can lead to cardiac dysfunction.

Cardiac involvement with *Legionella pneumophila* is uncommon, although the heart may be the only affected organ. Clinical symptoms resemble pericarditis and myocarditis, including dysrhythmias and conduction blocks. After treatment with erythromycin, normal cardiac function may return.

Cardiac *Toxoplasma* infection may lead to clinically significant disease. Infection is well described in recipients of bone marrow and cardiac transplantation. Immunocompromised patients with toxoplasmic myocarditis may have bundle branch block, CHF, pericarditis, and dysrhythmias as a result of lesions in the conducting system. Untreated toxoplasmic myocarditis is fatal.

Myocarditis associated with *M. pneumoniae* may be caused by direct invasion of the myocardium, an autoimmune mechanism, or intravascular coagulation. Miliary tuberculosis, including tuberculosis myocarditis, can produce granulomas within the myocardial conduction system that can precipitate fatal dysrhythmias. Sudden death can also occur secondary to *Chlamydia pneumoniae* myocarditis. In addition, myocarditis, presumably mediated by exotoxin, is associated with *Shigella* infection. Cardiac involvement of the conduction system and the pericardium also may occur in dermatomyositis and polymyositis. Patients are usually asymptomatic, but pericarditis, myocarditis, and dysrhythmias can occur.

COCAINE CARDIOTOXICITY

Cocaine has various cardiac effects in addition to ischemia, including myocarditis and DCM. Myocarditis is a common autopsy finding in patients with cocaine abuse. The mechanism responsible for the cardiotoxic effects of cocaine is largely unknown. Theories include the following: (1) cocaine may have a direct effect on lymphocyte activity; (2) intravenous cocaine can increase natural killer cell activity in blood, which may be cytotoxic to myocardial cells; (3) there is a cocaine-related eosinophilic infiltrate that suggests a hypersensitivity reaction; and (4) catecholamine administration can induce a focal myocarditis. Cocaine has a direct, negative inotropic effect on cardiac muscle.

Patients who die with detectable cocaine levels have myocarditis and myocardial contraction bands more often than controls. The severity of contraction-band necrosis correlates with the serum and urine concentrations of cocaine. Catecholamine excess caused by cocaine use may contribute to contraction-band necrosis, which may supply the anatomic substrate for ventricular dysrhythmias.

Lastly, acute and chronic cardiotoxicity occur secondary to the use of doxorubicin. Manifestations of acute cardiotoxicity include dysrhythmias, pericarditis, myocarditis, and left ventricular dysfunction.

KAWASAKI DISEASE

Kawasaki disease, or mucocutaneous lymph node syndrome, is of unknown cause and primarily affects children. This self-limited vasculitis affects many organ systems. Twenty-five percent of all patients develop coronary artery abnormalities, usually several

www.ketabpezeshki.com 66485457-66963820

weeks after symptom onset. These are usually reversible but may lead to aneurysm formation, secondary thrombosis, or myocardial ischemia. Myocarditis and pericarditis also occur during the initial phase of the disease.

CARDIOMYOPATHIES AND SPECIFIC HEART MUSCLE DISEASE

Cardiomyopathies are a heterogeneous group of diseases associated with mechanical or electrical dysfunction.[24] They usually exhibit inappropriate ventricular hypertrophy or dilation and have a variety of causes. It is becoming increasingly evident that many of these diseases result from genetic mutations. The diseases included are listed in Box 82-3.

A variety of pathologic processes may initiate myocyte injury. When injury occurs, common pathophysiologic pathways are activated. These pathways involve neurohumoral factors, immune factors, and cytokines that cause myocyte dysfunction and subsequent remodeling. At the organ level the remodeling is hypertrophy or dilation. There is also an increase in interstitial fibrosis, which impairs ventricular filling; this leads to increased metabolic demands on the myocardium. At a cellular level, the pathophysiologic derangement may be the troponin complex, intracellular concentration of calcium, myocardial subproteins, or the sarcomere. These lesions lead to alteration in the cardiac muscle's ability to contract, which eventually leads to clinical pathology.[25] There is also change in the cardiac microvascular circulation that is an independent predictor of morbidity and mortality.[26] Although traditionally defined by organ level pathology, the classification of cardiomyopathies may evolve into a unified theory that shows all types of cardiomyopathy to be variations of a common genetic, anatomic, and humoral pathophysiologic process.

Mutations of genes for myocardial protein components lead to molecular changes in the myocardium that eventually lead to clinical disease. Mutations have been found for abnormalities in cytoskeleton force transmission, impaired force production, and cell junction regulation.[27] The exact correlation between genotype, phenotype, and clinical presentation is unknown, as is the point when molecular level changes transition from compensatory to pathologic.

DILATED CARDIOMYOPATHY

Epidemiology and Etiology

DCM is a spectrum of disorders that have in common a dilated and failing heart. The incidence of DCM is estimated to be 1 case per 2500 adults and 0.57 cases per 100,000 children. The true incidence is probably underestimated because many asymptomatic cases remain undiagnosed. DCM is estimated to affect 5.5 million adults and 500,000 children in the United States, costing $10 billion annually.[28] Many cases previously thought to be of unknown cause may be secondary to infection. Myocarditis is the most common cause of DCM in children.[28] It is now known that 30 to 40% of DCM cases have a genetic cause, with more than 35 gene mutations discovered, primarily coding for cytoskeleton or sarcomere proteins.[29]

DCM affects men more often than women, affects African Americans more often than whites, and may occur in any age group, with middle age (40-65 years old) being the most common. Risk factors include ethanol and tobacco abuse, pregnancy, hypertension, and infection.

Box 82-3 The Cardiomyopathies

- Arrhythmogenic right ventricular
- Dilated
- Hypertrophic
- Ion channel disorders
- Inflammatory
- Mitochondrial
- Peripartum
- Restrictive
- Takotsubo

Pathophysiology

There are both primary and secondary causes for DCM. Possible pathophysiologic causes include myocardial inflammation mediated by cytokines, macrophages, and natural killer cells; local inflammation caused by the release of cytokines by infiltrating lymphocytes; direct reaction of antibodies with receptors on myocardial muscle; toxins, such as ethanol, impairing myocardial biochemical processes; and loss or dysfunction of myocardial matrix proteins.[30] Myocardial damage initiates a vicious cycle of hypertrophic cell death that increases the burden of the remaining cells; this leads to signaling, more work, and cell death.[31]

Clinical Features

Symptoms of DCM have an insidious onset. Left-sided heart failure occurs as the initial manifestation in 75% of adults, with dyspnea (usually with exertion or while supine) being the major symptom. Exacerbation of heart or renal disease, dietary indiscretion, and medication noncompliance are key contributors. CHF symptoms are the most common presentation in children. Chest pain on exertion is the initial symptom in 10% of adults, and systemic or pulmonary emboli are the initial manifestation in 4%. Right-sided heart failure is a late and ominous sign.

Diagnostic Strategies

ECG findings are nonspecific and may include poor R wave progression, intraventricular conduction delay, or a left bundle branch block pattern. Holter monitoring may show frequent premature ventricular contractions and occasional ventricular tachycardia. Sudden death is uncommon. The chest radiograph reveals cardiomegaly.

Echocardiography shows left ventricular dilation, reduced systolic function, and variable wall motion abnormalities. Abnormal ventricular contractility defines DCM, and an ejection fraction less than 45% is required for diagnosis. End-diastolic and systolic volumes are increased, as are pulmonary capillary wedge pressure and central venous pressure.

Endomyocardial biopsy may also be necessary, although histologic abnormalities are nonspecific. New histochemical, immunologic, and molecular biologic techniques improve the diagnostic yield, especially for infectious causes. MRI may help diagnose cardiomyopathy. Right-side failure should have occult atrial septal defect ruled out.

As many as one third of patients may have a genetic defect as the underlining cause. Obtaining a family history and genetic counseling may be indicated.[32]

Management and Disposition

Therapy includes supportive measures, such as adequate rest, weight control, abstinence from tobacco, moderate salt and ethanol consumption, and reduced physical activity. Medical treatment includes standard measures for CHF.

Angiotensin-converting enzyme inhibitors reduce morbidity and mortality. Other afterload-reducing agents, such as isosorbide dinitrate and hydralazine, also prolong survival in patients with

www.ketabpezeshki.com 66485457-66963820

heart failure. Spironolactone and the angiotensin receptor-blocking agents also prolong survival. Implantable defibrillators improve survival and should be considered in patients with an ejection fraction less than 30% or symptoms for more than 9 months. Short-term statin therapy may help.[33] Antidysrhythmics are not usually effective.

Beta-blockers can reduce symptoms and improve left ventricular function, functional capacity, and survival. In addition, the improvement in cardiac function associated with beta-blockers is also associated with changes in expression of genes encoding for α- and β-myosin heavy chain and sarcoplasmic reticulum calcium adenosine triphosphate.

Outcome

Because medical therapy usually fails, DCM is the leading indication for cardiac transplantation in adults and children. Mortality from DCM is 18% by 1 year, 35% by 5 years, and 50% by 10 years. Patients with DCM show progressive deterioration, with 75% of patients dying within 5 years of diagnosis.

The clinical course for children is variable, with a better prognosis in young children. Most deaths occur within the first 2 years. Some children show delayed, spontaneous, and unexplained improvement.

HYPERTROPHIC CARDIOMYOPATHY

Perspective

Hypertrophic cardiomyopathy (HCM), formerly called *idiopathic hypertrophic subaortic stenosis* (IHSS), is a complex disorder with variable clinical manifestations. The prevalence is estimated to be 1 in 500 persons in the general population. It affects all races, men and women equally, and can manifest at any age.

Principles of Disease

Anatomy

HCM is a disease involving abnormalities of heart muscle at anatomic, cellular, and genetic levels. Specifically, it is a genetic disease of sarcomere proteins. The defining anatomic feature of HCM is a hypertrophied left ventricle in the absence of another cause of left ventricular hypertrophy. The thickening is usually asymmetrical and involves the septum more than the free ventricular wall. The extent of hypertrophy at any given site can vary greatly and bears significantly on the manifestation of the disease. The dimensions of the left ventricular and right ventricular cavities are small or normal. Atrial dilation is another feature.

Histologically, individual muscle cells are hypertrophied, with a disorganized, characteristic whorled pattern.[34] Sarcomere disarray is the histologic hallmark. Abnormal fibrous tissue is often found in the left ventricle, and the scarring mimics a healed MI.

Pathophysiology

HCM is an autosomal dominant disease caused by mutations in genes that encode for sarcomere contractile proteins. Ten genes encoding for cardiac sarcomere proteins and more than 200 different mutations of these genes have been identified. Half the mutations involve three genes: those for β-myosin heavy chain (which constitutes 30% of myocardial protein), myosin-binding protein C, and troponin T.

The hypertrophy in HCM may be a compensatory response to the cardiac protein abnormalities. In vitro studies show that mutant β-myosin heavy chain protein exhibits impaired contractility and disrupts formation of the normal sarcomere. The usual cardiac response to physiologic stress is hypertrophy, dilation, or a combination of both. A gene mutation may lead to mutant protein that impairs cellular structure and function owing to fibrous changes in the sarcomere. This causes compensatory tissue hypertrophy manifests as HCM.

Clinically, patients with HCM have asymmetrical left ventricular hypertrophy. They have an abnormal echocardiogram or cardiac magnetic resonance image that shows hyperdynamic ventricles. There may be an outflow obstruction, although this usually occurs with exertion. The thickness of the ventricle and degree of outflow obstruction correlate with disease severity. The pathophysiology involves impaired ventricular filling during diastole.

Genetic studies of families with HCM identify specific mutations that correlate with sudden cardiac death. In families with Arg403Gln mutation, less than half of affected family members survive past 45 years of age. Genetics alone does not account for the clinical manifestation of HCM, because patients with the same genotype differ in phenotypic expression and clinical course. This indicates that modifier genes and environmental factors are also important.

Clinical Features

Although HCM occurs at all ages, the average age at diagnosis is 30 to 40 years. Approximately 2% of cases are diagnosed in children younger than age 5 years, and 7% are diagnosed before 10 years of age. HCM gained notoriety after the press coverage of the sudden deaths of several young athletes. There is advocacy for large-scale ECG screening of young athletes, but no studies demonstrate an appropriate strategy for effective screening. The presentation of HCM varies widely, and it may be discovered by screening relatives of patients who have HCM.[34]

In many patients the initial event is sudden death, which usually occurs during exertion. Ninety percent of patients have shortness of breath. Other symptoms include chest pain, syncope, near-syncope, and palpitations.

Physical examination may reveal a loud S_4 gallop and a harsh crescendo-decrescendo midsystolic murmur. This murmur is accentuated by the Valsalva maneuver or changing from a standing to a squatting position. Such position interventions change preload and afterload, which accentuates the murmur. Other physical findings may include a bifid arterial pulse, paradoxical splitting of the second heart sound, and, rarely, a mitral leaflet septal contact sound. Many dysrhythmias are seen in HCM, including premature atrial and ventricular contractions, multifocal ventricular ectopy, and ventricular and supraventricular tachydysrhythmias. In the ED, the diagnosis should be suspected in anyone with a family history, characteristic murmur, and cardiopulmonary symptoms (i.e., chest pain, dyspnea, and dysrhythmia) not explained by other life-threatening conditions.

Diagnostic Strategies

Patients with suspected HCM should have an ECG, chest radiograph, and echocardiogram. The ECG is abnormal in approximately 90% of patients. The most common abnormalities are left ventricular hypertrophy, ST segment alterations, T wave inversion, left atrial enlargement, abnormal Q waves, and diminished or absent R waves in the lateral leads. The chest radiograph may be normal or may show left ventricular or atrial enlargement.

Echocardiography is the most important clinical diagnostic strategy. Findings include asymmetrical left ventricular hypertrophy, left ventricular outflow tract narrowing, a small left ventricular cavity, and reduced septal motion. The dynamic characteristic of HCM distinguishes it from the discrete forms of obstruction to ventricular flow. Doppler techniques help assess

www.ketabpezeshki.com 66485457-66963820

the severity of this obstruction at rest and with provocative maneuvers.

Magnetic resonance is helpful when the echocardiogram is not. Nuclear studies can be used to assess systolic and diastolic ventricular function and ventricular scarring. Electrophysiologic studies may show dysrhythmias but are not more predictive of sudden death than clinical factors. Genetic screening may be helpful to predict other family members at risk.

Differential Diagnosis

HCM mimics many disorders. In individuals who have a gradient and a loud systolic murmur, HCM may be confused with valvular diseases or a ventricular septal defect. In the absence of a murmur, symptoms may suggest mitral valve prolapse, primary pulmonary hypertension, or coronary artery disease. ECG changes, without a history of preceding MI, may also suggest HCM. Echocardiography is often helpful, but ultimately cardiac catheterization may be necessary to confirm the diagnosis.

Management

Long-term beta-blocker therapy is the mainstay of therapy, and modulates the effect of catecholamines on the outflow gradient. This prolongs diastole, increases ventricular filling, and results in symptomatic improvement (primarily dyspnea and chest pain) and exercise tolerance. Calcium channel blockers are also useful. Verapamil reduces obstruction, decreases contractility, and improves diastolic relaxation and filling. This improves exercise capacity, and the negative effects on heart rate and blood pressure decrease oxygen consumption and the incidence of angina. Verapamil is contraindicated when conduction blocks are present but should be considered when there is no response to beta-blockers. Another option is disopyramide.

Nitroglycerin, the traditional initial ED management for chest pain, is avoided in HCM-associated chest pain because it decreases ventricular volume. Amiodarone is the drug of choice for treatment of ventricular dysrhythmias in HCM. Amiodarone may also control atrial fibrillation. Automatic implantable cardioverter defibrillators are indicated for patients with sudden death or a history of a sudden death risk factor.[35] Updated American Heart Association guidelines do not recommend prophylactic antibiotics in patients with HCM.[36]

Surgical treatment is reserved for patients with large (>50 mm Hg) systolic gradients, severe symptoms, and poor quality of life who do not respond to drug therapy. The most common procedure is septal myomectomy. Dual-chamber pacing decreases outflow gradient and improves symptoms, but it does not improve outcome.

Disposition

The natural history of HCM is variable and probably reflects the many different genetic causes. The annual mortality rate is 1%.

The onset of atrial fibrillation in patients with HCM may precipitate marked hemodynamic compromise and severe CHF. Cardioversion is indicated, as is rate control and anticoagulation to prevent thromboembolism.

Risk factors for sudden death include malignant genotype, unexplained syncope, sudden death in first-degree relatives, abnormal hemodynamic response to exercise, and greater than 30-mm ventricular thickening.

Patients with HCM initially diagnosed in the ED should have strenuous physical activity specifically proscribed until they have been evaluated by a cardiologist. Patients with HCM who have angina, syncope, near-syncope, dysrhythmias, and abrupt changes in cardiopulmonary status should be hospitalized.

RESTRICTIVE CARDIOMYOPATHY

Perspective

The hallmark of RCM is a gradual and progressive limitation of ventricular filling secondary to myocardial infiltration. RCM is the least common type of cardiomyopathy, accounting for less than 5% of all cases. The most common cause is amyloidosis in the United States. Other causes include sarcoidosis, hemochromatosis, scleroderma, neoplastic cardiac infiltration, glycogen storage disorders, Fabry's disease, Gaucher's disease, and mutations related to myocardial muscle proteins.

The most common cause of RCM worldwide is tropical endomyocardial fibrosis, which is endemic to India, Africa, and Latin America. Symptoms include an initial viral-like illness followed by persistent fever, malaise, and the development of severe right-sided heart failure.[37]

Pathophysiology

Restriction of ventricular filling results in low ventricular volumes, high end-diastolic ventricular pressures, and decreased cardiac output. Systolic function is maintained. Grossly, there is atrial enlargement with small ventricles. As the disease progresses the ventricular cavities may become obliterated by fibrous tissue, scarring, or thrombus.

Clinical Features and Diagnostic Strategies

Symptoms are those of worsening diastolic dysfunction and include exercise intolerance (cardiac output cannot be increased because ventricular filling is compromised), elevated central venous pressure, peripheral edema, pulmonary edema, and S_3 and S_4 gallops. Children can demonstrate failure to thrive.

Differentiation from constrictive pericarditis requires CT, MRI, or Doppler echocardiography. Pericardial calcification favors a diagnosis of constrictive pericarditis over the diagnosis of RCM. Myocardial biopsy may be necessary.

Management and Disposition

Most of the underlying causes of RCM are untreatable. The exception is hemochromatosis. Symptomatic treatment with vasodilators and diuretics may help in all patients. Patients with RCM should be maintained in sinus rhythm, because loss of the "atrial kick" is devastating. Transplantation is a possibility in some patients with better survival than controls. RCM is relentless, with 90% of patients dying within 10 years of diagnosis. Patients with hemochromatosis are treated with phlebotomy.

PERIPARTUM CARDIOMYOPATHY

Perspective

Peripartum cardiomyopathy (PPCM) is uncommon and represents less than 1% of the cardiovascular problems associated with pregnancy. PPCM is a form of DCM with symptoms and signs of heart failure that appear initially during the last 3 months of pregnancy or the first 5 months postpartum. The diagnosis is made if there is no previous heart disease and no other cause for the heart failure.[38]

Etiology and Epidemiology

The cause of PPCM is unknown. Risk factors include myocarditis, excessive use of tocolytics, preeclampsia, advanced maternal

www.ketabpezeshki.com 66485457-66963820

age, multiparity, twins, and genetic predisposition. The incidence is estimated to be 1 case of PPCM per 13,000 to 15,000 live births.[39]

Clinical Features and Diagnostic Strategies

PPCM is clinically identical to DCM. Patients usually have symptoms of CHF but may also have chest pain, palpitations, or thromboembolism. Physical examination often reveals tachycardia, tachypnea, pulmonary rales, an enlarged heart, and an S_3 heart sound.

The ECG may show left ventricular hypertrophy or nonspecific ST-T wave changes. On echocardiography, all four chambers are enlarged with reduction in left ventricular systolic function.

Management and Disposition

Treatment of PPCM includes limitation of physical activity, beta-blockers, alteration of preload with nitrates and diuretics, increase in ventricular contractility, and afterload reduction.[40] Angiotensin-converting enzyme inhibitors are teratogenic and should be avoided, if possible, in pregnancy. Hydralazine and labetalol are effective choices.

Mortality for PPCM in the United States is approximately 2%.[39] Half of the survivors have complete or near-complete recovery of cardiac function within the first 6 months. Patients who do not recover completely show either continuous clinical deterioration or persistent left ventricular dysfunction. Subsequent pregnancies may be associated with a high risk of maternal mortality. In the ED, patients with signs of hemodynamic instability or failure to maintain oxygenation should be admitted for treatment and fetal monitoring.

TAKOTSUBO CARDIOMYOPATHY

Perspective

Takotsubo cardiomyopathy (TCM), also known as *stress cardiomyopathy, broken heart syndrome,* or *tako-tsubo cardiomyopathy,* was first reported from Japan in 1991.[41] In Japanese, *tako-tsubo* means octopus trap. The term was used because the cardiac abnormality observed in this disease resembles that of the device used to catch octopi.[42] There have been hundreds of cases reported in the medical literature since that time (Box 82-4). The pathophysiology of TCM is a sudden temporary myocardial weakening. The exact mechanism is unknown. Speculated causes include stress hormones, microvascular spasm, focal myocarditis, and cellular level muscle changes.

Box 82-4 Published Causes of Takotsubo Cardiomyopathy

Achalasia	Seizures
Addison's disease	Sepsis
Anaphylaxis	Sexual intercourse
Anesthesia	Stress testing
Asthma	Subarachnoid hemorrhage
Chemotherapy	Surgery or medical procedures
Closed head injury	Abdominal aneurysm repair
Depression	Bronchoscopy
Diarrhea	Carotid endarterectomy
Diving	Colonoscopy
Emotional stress	Esophagogastroduodenoscopy (EGD)
Foley catheter insertion	Electroconvulsive therapy
Hanging	Epidural anesthesia
Hypoglycemia	Mitral valve replacement
Inferior vena cava clot	Radiofrequency ablation
Lightning strike	Sclerotherapy
Multiple trauma	Thrombotic thrombocytic purpura
Myocardial infarction	Thyrotoxicosis
Near drowning	Transient ischemic attack
Opiate withdrawal	Tricyclic overdose
Pancreatitis	Vomiting
Pheochromocytoma	
Pneumopericardium	
Pregnancy	

Clinical Features and Diagnostic Strategies

The clinical presentation is usually chest pain, although dyspnea occurs, especially on exertion. Almost 90% of cases involve women.[43] There is uniformly a significant stressful incident that precedes the onset of symptoms. ECG is often consistent with an anterior MI. There are transient Q waves and ST elevation. Later, the ECG shows T wave inversion and a prolonged QT interval. Cardiac enzymes are elevated slightly and resolve to normal levels quickly. Coronary artery angiography shows no—or very little—disease. The diagnosis is made by left ventricular angiography or echocardiography that shows a ballooning of the apex during the acute phase of the disease. The involved area does not match a coronary artery anatomic distribution.

Management and Disposition

In the ED, TCM is not distinguishable from acute MI. Patients should be treated the same as any patient with acute MI. Treatment is supportive care. Beta-blockers and angiotensin-converting enzymes are the mainstay of therapy. Almost all patients show complete resolution of symptoms and reversal to normal of their left ventricular apex ballooning and contractile function.

ION CHANNELOPATHIES

Several uncommon dysrhythmic diseases are caused by mutations of genes for ionic channel proteins, which are cell membrane transport proteins for sodium and potassium. These include long QT syndrome, short QT syndrome, Brugada's syndrome, and catecholaminergic polymorphic ventricular tachycardia.

SPECIFIC HEART MUSCLE DISEASES

Amyloidosis

Massive amyloid deposition results in an increased cardiac weight and the diastolic dysfunction of RCM. CHF occurs in most cases of cardiac amyloidosis. Treatment involves standard CHF and antidysrhythmic therapy, although the dysrhythmias in amyloid heart disease are often refractory to treatment. The prognosis is poor, with death often resulting from progressive heart failure within 1 year of symptom onset.[44]

Sarcoidosis

Cardiac granulomas occur in approximately 25% of cases of systemic sarcoidosis. Granulomas located in the septum cause severe conduction defects, those in the papillary muscles cause

www.ketabpezeshki.com 66485457-66963820

mitral regurgitation, and those in the ventricular walls produce scarring and wall motion abnormalities. Complete heart block is the most common conduction block. Ventricular dysrhythmias are often refractory to therapy. Myocardial involvement in sarcoidosis is an indication for systemic corticosteroid therapy. Refractory cardiac failure and dysrhythmias are indications for heart transplantation.

Connective Tissue Disorders and Disease of the Myocardium

Myocarditis associated with various connective tissue diseases occurs more often than is recognized clinically. Cardiac abnormalities occur in RA, juvenile RA, mixed connective tissue disease, and primary Sjögren's syndrome. SLE is the connective tissue disease most commonly associated with cardiac abnormalities. Cardiac involvement in SLE includes pericarditis, endocarditis, and myocarditis.

Primary myocardial involvement is a major complication of diffuse scleroderma and develops as scleroderma worsens. Estimates of the frequency of myocardial involvement in scleroderma vary widely. The clinical presentation includes CHF, angina, and dysrhythmias. Pericardial disease can also occur. Although prognosis is poor, azathioprine may be a beneficial adjunct to steroid therapy.[45]

Sudden Death

Approximately 25% of sudden deaths in patients younger than age 21 years can be attributed to disease of the myocardium. Cardiac causes include myocarditis, HCM, and anomalous coronary artery circulation. In patients with sudden death attributed to cardiac causes, prodromal symptoms are reported in more than half of the patients, most commonly chest pain (25%) in patients older than age 20 years and dizziness (16%) in patients younger than age 20 years. The distribution of sudden death causes by age is as follows:

- Age younger than 20 years—myocarditis 22% and HCM 22%
- Age 20 to 29 years—myocarditis 22% and HCM 13%
- Age 30 to 39 years—myocarditis 11% and HCM 2%

Coronary artery disease becomes the leading cardiac cause (58%) in sudden death in people ages 30 to 39 years. HCM is the cardiac disease most commonly found on postmortem diagnosis of athletes with sudden death. HCM and anomalous coronary arteries are seen more often in sports-related deaths.

KEY CONCEPTS

- Pericarditis and myocarditis should be differentiated from acute MI. Thrombolytic therapy is contraindicated in pericarditis because of the potential for hemorrhagic pericarditis or tamponade.
- Cardiac tamponade is suspected on the basis of distended neck veins, hypotension, and muffled heart sounds. Diagnosis is by presumptive pericardiocentesis in severe cases or by echocardiography.
- Myocarditis should be considered in any patient with the combination of viral illness symptoms and a new presentation of cardiac disease (dysrhythmia, failure.)
- Patients with newly diagnosed hypertrophic cardiomyopathy should avoid strenuous exertion until evaluated by a cardiologist. Beta-blockers are the mainstay of therapy for HCM; nitrates are avoided.
- Many of the cardiomyopathies are now known to have genetic origins.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Spodick DH: Medical history of the pericardium. *Am J Cardiol* 1970; 26:447.
2. Beck CS: Two cardiac compression triads. *JAMA* 1935; 104:714.
3. Troughton R, Asher C, Klein A: Pericarditis. *Lancet* 2004; 363:717.
4. Lange RA, Hills D: Acute pericarditis. *N Engl J Med* 2004; 351:2195.
5. Lotrionte M, et al: International collaborative systematic review of controlled clinical trials on pharmacologic treatment for acute pericarditis and its recurrences. *Am Heart J* 2010; 160:662.
6. Imazio M, et al: Indicators of poor prognosis of acute pericarditis. *Circulation* 2007; 115:2739.
7. Gunukula S, Spodick D: Pericardial disease in renal patients. *Semin Nephrol* 2001; 21:52.
8. Dressler W: A post-myocardial infarction syndrome. *JAMA* 1956; 160:1379.
9. Retter A: Pericardial disease in the oncology patient. *Heart Dis* 2002; 4:387.
10. Spodick DH: Acute cardiac tamponade. *N Engl J Med* 2003; 349:684.
11. Roy CL, Minot MA, Brookhart MA, Choudhry NK: Does this patient with pericardial effusion have cardiac tamponade? *JAMA* 2007; 297:1810.
12. Mayosi BM, Burgess LJ, Doubell AF: Tuberculous pericarditis. *Circulation* 2005; 112:3608.
13. Goldstein J: Cardiac tamponade, constrictive pericarditis and restrictive cardiomyopathy. *Curr Probl Cardiol* 2004; 29:503.
14. Cooper L: Myocarditis. *N Engl J Med* 2009; 360:1526.
15. Magnani JV, Dec W: Myocarditis. Current trends in diagnosis and treatment. *Circulation* 2006; 113:876.
16. Cunningham MW: T cell mimicry in inflammatory heart disease. *Mol Immunol* 2004; 40:1121.
17. Marholdt H, et al: Presentation, patterns of myocardial damage, and clinical course of viral myocarditis. *Circulation* 2006; 114:1581.
18. Moncayo A, Ortiz Yanine MI: An update on Chagas disease (human American trypanosomiasis). *Ann Trop Med Parasitol* 2006; 100:663.
19. Bern C, et al: Evaluation and treatment of Chagas disease in the United States. *JAMA* 2007; 298:2171.
20. Rassi A Jr, Rassi A, Marin-Neto JA: Chagas disease. *Lancet* 2010; 375:1388.
21. Kennedy E, et al: Trichinellosis surveillance—United States, 2002-2007. *MMWR Surveill Summ* 2009; 58:SS9.
22. Vitek C: Diphtheria. *Curr Top Microbiol Immunol* 2006; 304:71, 2006.
23. Steere AC: Lyme disease. *N Engl J Med* 2001; 345:115.
24. Maron BJ, et al: Contemporary definitions and classifications of the cardiomyopathies: An American Heart Association scientific statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care Outcomes and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation* 2007; 113:1807.
25. Gomes A, Potter J: Molecular and cellular aspects of troponin cardiomyopathies. *Ann N Y Acad Sci* 2004; 1015:214.
26. Camici PG, Crea F: Coronary microvascular dysfunction. *N Engl J Med* 2007; 356:830.
27. Thiene G, Corrado D, Basso C: Cardiomyopathies: Is it time for a molecular classification? *Eur Heart J* 2004; 25:1772.
28. Towbin JA, et al: Incidence, causes and outcomes of dilated cardiomyopathy in children. *JAMA* 2006; 296:1867.
29. Jefferies J, Towbin J: Dilated cardiomyopathy. *Lancet* 2010; 375:752.
30. Maisch B, Richter A, Sandmoller A: Inflammatory dilated cardiomyopathy (DCM). *Herz* 2005; 30:535.
31. Katz A: Pathophysiology of heart failure: Identifying targets for pharmaceutical therapy. *Med Clin North Am* 2003; 87:303.
32. Howlett JG, et al: Canadian Cardiovascular Society Consensus Conference guidelines on heart failure, update 2009: Diagnosis and management of right sided heart failure, myocarditis, device therapy and recent important clinical trials. *Can J Cardiol* 2009; 25:85.
33. Dickinson MG, et al: Statin use was associated with reduced mortality in both ischemic and nonischemic cardiomyopathy and in patients with implantable defibrillators: Mortality data and mechanistic insights from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Am Heart J* 2007; 153:573.
34. Maron BJ, et al: Recommendations and considerations related to preparticipation screening for cardiovascular abnormalities in competitive athletes: 2007 update: A scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: Endorsed by the American College of Cardiology Foundation. *Circulation* 2007; 115:1643.
35. Maron BJ, Spirito P, Shen WK: Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA* 2007; 298:405.
36. Wilson W, et al: Prevention of infective endocarditis: Guidelines from the American Heart Association: A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007; 116:1736.
37. Nihoyannopoulos P, Dawson D: Restrictive cardiomyopathies. *Eur J Echocardiogr* 2009; 10:iii23.
38. Abboud J, Murad Y, Chen-Scarabelli C, Saravolatz L, Scarabelli TM: Peripartum cardiomyopathy: A comprehensive review. *Int J Cardiol* 2007; 118:295.
39. Mielniczuk LM, et al: Frequency of peripartum cardiomyopathy. *Am J Cardiol* 2006; 97:1765.
40. Sliwa K, Fett J, Elkayam U: Peripartum cardiomyopathy. *Lancet* 2006; 368:687.
41. Dote K, et al: Myocardial stunning due to simultaneous multivessel coronary spasms: A review of 5 cases. *J Cardiol* 1991; 21:203.
42. Bielecka-Dabrowa A, et al: Takotsubo cardiomyopathy—the current state of knowledge. *Int J Cardiol* 2010; 142:120.
43. Dorfman T, Iskandrian A: Takutsubo cardiomyopathty: State-of-the-art review. *J Nucl Cardiol* 2009; 16:122.
44. Shah KB, Inoue Y, Mehra MR: Amyloidosis and the heart. *Arch Int Med* 2006; 166:1805.
45. Leyngold I, Baughman K, Kasper E, Ardehali H: Comparison of survival among patients with connective tissue disease and cardiomyopathy (systemic sclerosis, systemic lupus erythematosus, and undifferentiated disease). *Am J Cardiol* 2007; 100:513.

www.ketabpezeshki.com 66485457-66963820

Chapter 83

Infective Endocarditis and Valvular Heart Disease

Joshua M. Kosowsky and Sukhjit S. Takhar

INFECTIVE ENDOCARDITIS

Perspective

The natural history of infective endocarditis (IE) has undergone considerable changes in the antibiotic era. The older classifications of acute, subacute, and chronic have become less meaningful; immunologic phenomena, such as Osler's nodes and glomerulonephritis, are rarely seen; and nosocomial infections from indwelling catheters and devices are increasing. Early diagnosis and treatment play a significant role in the clinical outcomes because IE remains a disease that causes considerable morbidity and mortality.

Principles of Disease

Estimates of the incidence of IE in the United States vary widely, in part because of changing case definitions throughout the years but also because of differences in predisposing conditions among studied populations. For example, the incidence of IE among patients admitted to hospitals in Philadelphia was estimated to be 11.6 cases per 100,000 person-years from 1988 to 1990.[1] In contrast, the incidence of endocarditis in Olmsted County, Minnesota, during the period from 1970 to 2000 was 5.0 to 7.0 cases per 100,000 person-years.[2] Others report significantly lower rates.[3] IE is increasingly a disease of the aged, with more than 50% of cases occurring in individuals older than 60 years. This reflects the pervasiveness of degenerative valve disease in the elderly and the increased prevalence of prosthetic heart valves.[4] Nosocomial endocarditis is increasingly common; the source is often infected intravascular devices, pacemakers, and hemodialysis catheters.[5]

Most patients with bacterial endocarditis have a predisposing valvular abnormality. Among elderly patients, calcific or degenerative disease of the aortic and the mitral valve is the most common predisposing factor. Rheumatic heart disease (RHD), although less prevalent than in prior decades, remains an important predisposing factor for IE among individuals from developing countries. Congenital cardiac lesions involving high pressure gradients (e.g., ventricular septal defects, pulmonary stenosis, and tetralogy of Fallot) also increase risk of IE. A history of previous endocarditis is a major risk factor for recurrence because infected valves heal with irregularities that become a nidus for future vegetations. Mitral valve prolapse (MVP) is now the most common predisposing abnormality for IE in developed countries.

The incidence of IE associated with injection drug use is estimated at 150 to 2000 per 100,000 person-years.[6] Although any valve can be affected, injection drug use is classically associated with right-sided endocarditis.

Prosthetic valve endocarditis (PVE) is a unique and potentially devastating complication of valve replacement.[7] The incidence of endocarditis in prosthetic valve recipients ranges from 0.5 to 4% per year. PVE can arise early or late after surgery, and the timing of infection reflects different portals of entry and microbiology.

The hospital mortality rate for IE ranges from 10 to 26%, varying according to the causative microorganism and presence of complications; viridans streptococci and *Streptococcus bovis* carry a mortality of as low as 4%; but the mortality is more than 50% in patients with fungal disease, Enterobacteriaceae, or *Pseudomonas aeruginosa;* and patients with severe acute heart failure have a mortality of nearly 100% without an operation.[8,9] The mortality for right-sided endocarditis in a patient with a history of injection drug use is approximately 10%.[10]

Pathophysiology

The classic lesion of endocarditis is the vegetation, originating as a sterile thrombus on which microorganisms adhere and colonize. The target is most often the cardiac valve; however, chordae tendineae, septal defects, and the endocardium can be involved. The initial thrombus may form at a site of mechanical damage induced by inflammation, degenerative changes, or abnormal turbulence. In injection drug users, contaminants such as talc can injure the previously normal valve leaflets and encourage bacterial implantation. Theoretically, the onset of bacterial endocarditis is preceded by a period of subclinical bacteremia. Dental procedures, cystoscopy, endoscopy, and other invasive procedures result in transient bacteremia, but more commonly there is no clear precipitant for community-acquired IE.

A number of microorganisms cause IE, with staphylococci and streptococci accounting for the majority of cases (Table 83-1). In a study of nearly 2800 patients with IE from 58 medical centers in 25 countries, staphylococci were the causative agents in 31% (commonly associated with injection drug use) and streptococci in 29%.[10] But a community-based study from Minnesota, where referral bias was minimized, showed that viridans group streptococci continued to be the most common culprit organism.[2]

Although many organisms cause IE, a few have such a predilection that they count as a major criterion in the modified Duke score. A blood culture positive for community-acquired enterococcus and *S. bovis* should suggest IE. In addition, the HACEK group (*Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae*), a collection of fastidious gram-negative bacilli, is commonly reported in large studies of IE. Lastly, a positive blood culture or positive antibody titer to *Coxiella burnetii* (Q fever) is also included in the modified Duke score.[11]

www.ketabpezeshki.com 66485457-66963820

Table 83-1 Epidemiology of Infective Endocarditis

MICROORGANISM	%
Staphylococcus aureus	32
Viridans group streptococci	18
Enterococci	11
Coagulase-negative staphylococci	11
Streptococcus bovis	7
Other streptococci	5
Non-HACEK gram-negative bacteria	2
Fungi	2
HACEK	2
Other organisms	3
Polymicrobial	1
Culture negative	8

HACEK group, *Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.

The microbiology of PVE relates to the time of onset: *Staphylococcus aureus* is now the most prevalent pathogen in the first 2 months after valve replacement, followed by coagulase-negative staphylococci. One year after surgery, the microbiology mirrors native valve endocarditis.[12] Among injection drug users, the most common infecting organism by far is *S. aureus,* often causing right-sided infections.[13]

Candida and *Aspergillus* species cause most cases of fungal endocarditis. Predisposing factors include indwelling intravenous catheters, immunocompromise, and injection drug use. Large fungal vegetations can embolize, and analysis of these emboli may be the only clue suggesting fungal endocarditis. *Bartonella* species are another group of fastidious organisms associated with IE in immunocompromised patients.

Clinical Features

Symptoms associated with IE are nonspecific and diverse. The most common symptoms are intermittent fever (85%) and malaise (80%). Other nonspecific symptoms (e.g., weakness, myalgias, back pain, dyspnea, chest pain, cough, headaches, and anorexia) vary widely in their incidence. Many patients seen early during the bacteremic phase of the illness do not have a cardiac murmur and are indistinguishable from the large population of patients who come to the emergency department (ED) with a febrile viral illness. During the initial assessment a careful history should be taken, with attention to any preexisting cardiac pathology or clues suggesting a recent source of bacteremia, such as intravenous drug use, indwelling intravascular catheters, or invasive procedures. In the absence of specific risk factors, the diagnosis of IE may be suspected when infectious symptoms persist or do not follow a typical course for viremia. The classic triad of fever, anemia, and heart murmur is rare.

Some patients will have complications of IE as presenting complaints. The most common and severe are congestive heart failure and neurologic events. Heart failure results from valvular destruction. A patient with strokelike symptoms and a fever should alert one to the possibility of IE. Strokes can be the result of septic emboli or ruptured mycotic aneurysms.

Almost all patients with IE have a cardiac murmur at some time during the course of their illness. A murmur, however, may be absent at presentation. For example, fewer than 35% of intravenous drug users with endocarditis have a murmur at presentation.[14] In this population, unexplained fever alone is sufficient to raise concern about possible endocarditis. A substantial minority of patients exhibit some form of vasculitic lesion, including petechiae, splinter hemorrhages, Osler's nodes, and Janeway lesions. Approximately 30% of patients have splenomegaly. Ocular findings include conjunctival or retinal hemorrhages, the latter of which may have a characteristic pale center surrounded by a red halo (Roth's spots).

Diagnostic Strategies

Laboratory findings in bacterial endocarditis are nonspecific. As with other infectious conditions, leukocytosis is insensitive (occurring in approximately 50% of patients diagnosed with IE) and nonspecific. An elevated erythrocyte sedimentation rate or C-reactive protein level may be present, but these are also nonspecific. Most patients have a mild anemia, and up to 50% have microscopic hematuria as a result of embolic lesions of the kidney. A chest radiograph may show signs of heart failure or embolic disease, and an electrocardiogram (ECG) may display conduction abnormalities if an abscess has formed in the myocardium.

Although not always practical, three blood cultures from three separate venipuncture sites are recommended for patients with a presumptive diagnosis of possible endocarditis, with the first and last cultures drawn at least 1 hour apart. Approximately 90 to 95% of blood cultures are positive unless antibiotics have already been administered.[15] If the patient appears septic, cultures may be obtained more rapidly to permit initiation of early empirical therapy. Cultures need not be timed to the presence of chills or fever because patients with IE typically have a continuous bacteremia.

An echocardiogram should be performed in all patients for whom suspicion of endocarditis is moderate to high. Although transthoracic echocardiography (TTE) is highly specific for vegetations in IE, it may be nondiagnostic in up to 20% of patients because of obesity, chronic obstructive pulmonary disease, and chest wall deformities. Overall sensitivity of TTE is at most 60%.[16] Transesophageal echocardiography (TEE), on the other hand, although more invasive and time-consuming, is far superior to TTE in its sensitivity and specificity.[17,18]

Explicit criteria for the diagnosis of IE are important because underdiagnosis can lead to serious morbidity and death, whereas overdiagnosis can result in weeks of unnecessary antimicrobial therapy. The Duke criteria are the most widely accepted, and they stratify patients with suspected bacterial endocarditis into three distinct categories: definite, possible, and rejected (Box 83-1).[18] The sensitivity and specificity of the Duke criteria are approximately 95% and 99%, respectively.[19-22]

Management

Once the diagnosis of IE is established, whether by clinical, echocardiographic, or microbiologic methods, antimicrobial therapy should be administered. Choice of antibiotics depends on the likely (or known) causative organism but is usually empirical. Guidelines for empirical antibiotic therapy in patients with suspected IE are provided in Box 83-2.[23] In the ED, however, usually without results of an echocardiogram (TTE or TEE), the diagnosis of endocarditis is not confirmed. In addition, there is increasing concern regarding community-acquired methicillin-resistant *S. aureus.* Thus a combination of 15 mg/kg of vancomycin and 2 g of ceftriaxone is a reasonable empirical antibiotic choice in someone with undifferentiated sepsis and suspected endocarditis.

Endocarditis is a heterogeneous disease. Although initial treatment is medical, early consultation with a cardiac surgeon is

www.ketabpezeshki.com 66485457-66963820

Box 83-1 Duke Criteria (Clinical) for Diagnosis of Infective Endocarditis

Definite Endocarditis
Endocarditis is considered definitely present if any one of the following combinations of clinical findings is present:
- Two major clinical criteria
- One major and any three minor clinical criteria
- Five minor clinical criteria

Possible Endocarditis
Possible endocarditis is defined as the presence of any one of the following combinations of clinical findings:
- One major and one or two minor clinical criteria
- Three minor clinical criteria

Rejected Endocarditis
The diagnosis of endocarditis is considered rejected if any of the following occurs:
- A firm alternate diagnosis is made.
- Resolution of clinical manifestations occurs after 4 days of antibiotic therapy or less.
- Clinical criteria for possible or definite infective endocarditis not met.

Major Criteria
Positive blood cultures (of typical pathogens) from at least two separate cultures
Evidence of endocardial involvement by echocardiography, such as the following:
- Endocardial vegetation
- Paravalvular abscess
- New partial dehiscence of prosthetic valve
- New valvular regurgitation

Minor Criteria
Predisposition: Predisposing heart condition or intravenous drug use
Fever: Temperature >38° C
Vascular phenomena: Arterial emboli, septic pulmonary infarcts, mycotic aneurysm, conjunctival hemorrhages, or Janeway lesions
Immunologic phenomena: Osler's nodes, Roth's spots, and rheumatoid factor
Microbiologic evidence: Single positive blood culture (except for coagulase-negative *Staphylococcus* or an organism that does not cause endocarditis)
Echocardiogram findings: Consistent with endocarditis but do not meet major criteria

Box 83-2 Initial Empirical Therapy for Bacterial Endocarditis[38]

Native Valve
Penicillin G 4 million units IV q4h + nafcillin 2 g IV q4h
Or
Vancomycin 15 mg/kg IV q12h
Plus
Gentamicin 1 mg/kg IV q8h

Native Valve (+ Injection Drug Use)
Vancomycin 15 mg/kg IV q12h

Prosthetic Valve
Vancomycin 15 mg/kg IV q12h
Plus
Gentamicin 1 mg/kg IV q8h

IV, intravenously.

Box 83-3 Surgical Therapy for Infective Endocarditis

Infective endocarditis with acute heart failure
Fungal endocarditis
Periannular extension of infection
Recurrent emboli
Large mobile vegetations
Persistent bacteremia

Box 83-4 High-Risk Conditions for Bacterial Endocarditis

Prosthetic heart valve
History of endocarditis
Unrepaired cyanotic congenital heart disease, including palliative shunts and conduits
Completely repaired congenital heart defects with prosthesis during the first 6 months after the procedure
Repaired congenital heart disease with residual defect at or adjacent to the site of the prosthetic device
Cardiac valvulopathy in a transplanted heart

advisable when mechanical complications are observed or expected (such as in patients with acute heart failure or those with infections involving prosthetic valves). See Box 83-3. Consultation with an infectious diseases specialist or a cardiologist is also useful.

Febrile patients with suspected IE require admission for definitive diagnosis and initiation of empirical therapy. An exception might be an otherwise well-appearing injection drug user with transient fever that is attributed to an injected contaminant ("cotton fever").

With appropriate antibiotic therapy, most patients with IE will defervesce within 1 week. The duration of antibiotic therapy must be sufficient to eradicate microorganisms present within the valvular vegetations. This may require 6 weeks, or more, depending on the organism and the type of vegetation. Historically, most patients with IE received the entire course of antimicrobial therapy while in the hospital. The development of home health care, however, allows selected patients with endocarditis to be treated as outpatients during much or all of their therapy. Patients selected for outpatient therapy should be hemodynamically stable, compliant, and capable of managing the technical aspects of intravenous therapy.

Prophylaxis

The American Heart Association has updated guidelines, limiting prophylaxis to conditions with the highest risk of adverse outcome from IE (Box 83-4).[24] Virtually all of the procedures that are routinely performed in the ED, including suturing of lacerations, endotracheal intubation, placement of central venous catheters, vaginal deliveries, and placement of Foley catheters (in the absence of infection), do not require prophylactic antibiotics.

RHEUMATIC FEVER

Perspective

From 1920 to 1950, acute rheumatic fever (ARF) was the leading cause of death in U.S. children and the most common cause of heart disease in individuals younger than age 40 years. During the 1960s and 1970s, the incidence of ARF in the United States and other developed countries declined dramatically because of widespread antibiotic treatment of streptococcal infections, declining

www.ketabpezeshki.com 66485457-66963820

prevalence of the more virulent strains of group A streptococci, and improved living conditions. Children 4 to 9 years of age remain at greatest risk, with an incidence of ARF of 2 to 14 cases per 100,000.[25] In many developing nations, however, ARF continues to be a leading cause of childhood mortality. RHD peaks in adults between the ages of 25 and 34 years and continues to be a leading cause of morbidity and mortality in impoverished areas.[26]

Principles of Disease

ARF is a delayed, nonsuppurative complication of streptococcal pharyngitis. Although the pathogenesis remains obscure, ARF results from an exaggerated immunologic response to group A beta-hemolytic streptococci that results in antibodies cross-reacting with tissues in the heart, joints, skin, and central nervous system. Patients with a history of ARF are predisposed to recurrent infections, and repeated infections lead to progressive heart damage.

Clinical Features

After the initial pharyngitis, there is a latency period ranging from 1 to 5 weeks (average, 18 days) before symptoms and signs of ARF appear. Up to one third of patients with documented ARF do not remember having had pharyngitis in the preceding month. Fever is present during the acute phase of rheumatic fever. It rarely lasts more than 2 weeks and has no characteristic pattern. Along with fever, manifestations of ARF may include arthritis, carditis, chorea, subcutaneous nodules, and erythema marginatum.

Migratory polyarthritis is the most common manifestation of ARF. Arthritis tends to occur early in the course of ARF and often coincides with a rising titer of streptococcal antibodies. The polyarthritis classically affects larger joints, such as the knees, ankles, elbows, and wrists, and the pain can be more severe than physical findings suggest. Analysis of the synovial fluid generally reveals a sterile inflammatory fluid.

Cardiac manifestations of ARF may be subtle and can include symptoms and signs of pericarditis, myocarditis, and endocarditis. The mitral valve is the most common valve affected in ARF, causing mitral regurgitation accompanied by a new, high-pitched, systolic murmur. Inflammation of the valvular endocardium can result in permanent deformity and impairment of one or more cardiac valves over the course of decades. Stenotic lesions of the mitral or aortic valves are unusual at presentation, but they are common late manifestations of RHD.

Chorea (Sydenham's chorea and St. Vitus' dance) is manifested by random, rapid, purposeless movements usually of the upper extremities and face. These can be associated with emotional outbursts. Chorea is relatively rare in ARF and tends to emerge after a longer latency period than some of the other manifestations. Erythema marginatum and subcutaneous nodules are found in fewer than 10% of cases of ARF. Their presence, however, should immediately suggest the diagnosis. Erythema marginatum is a nonpruritic, painless, evanescent "smoke ring" of erythema that commonly appears on the trunk and proximal extremities. Subcutaneous nodules are pea sized and nontender. They typically appear over the extensor surfaces of the wrists, elbows, knees, and occasionally the spine.

Diagnostic Strategies

In 1944, Jones formulated major and minor criteria for the diagnosis of ARF. After multiple revisions, the Jones criteria remain the diagnostic basis for this disease (Box 83-5).[27] The diagnosis of ARF requires evidence of an antecedent streptococcal infection plus at least two major, or one major and two minor, manifestations from the Jones criteria. Although throat cultures are usually negative at the time of clinical onset of ARF, antistreptolysin antibody titers remain positive for 4 to 6 weeks from the time of infection. Erythrocyte sedimentation rate and C-reactive protein levels are typically elevated, and a prolonged PR interval is common and suggestive in ARF.

Box 83-5 Jones Criteria (Revised) for the Diagnosis of Acute Rheumatic Fever

Major Manifestations
Carditis
Polyarthritis
Chorea
Erythema marginatum
Subcutaneous nodules

Minor Manifestations
Arthralgias
Fever
Increased erythrocyte sedimentation rate or C-reactive protein
Prolonged PR interval

Evidence of Preceding Streptococcal Infection
Positive throat culture for group A beta-hemolytic streptococci or positive rapid streptococcal antigen test
Elevated or rising streptococcal antibody titer, most often antistreptolysin O

Management

All patients with ARF should receive antibiotic therapy regardless of the clinical history of pharyngitis. Penicillin can be administered orally (250 mg for children and 500 mg for adults, two or three times daily for 10 days) or intramuscularly (600,000 units of benzathine penicillin in children weighing <25 kg and 1.2 million units in adults as a one-time dose).

Treatment for arthritis consists of anti-inflammatory agents, most commonly aspirin, administered until symptoms are absent and the erythrocyte sedimentation rate and C-reactive protein concentration normalize. Patients with severe carditis are often treated with corticosteroids, but their effects show conflicting results.[28] Patients with congestive heart failure should be managed accordingly. Treatment of patients with ARF involves only symptom relief and does not decrease the likelihood of progression to RHD. Primary prevention involves treating those with group A streptococcal pharyngitis within 9 days of the onset of symptoms because this greatly decreases the risk of ARF. Patients with a history of ARF should receive ongoing prophylactic antibiotics (generally penicillin) to prevent recurrences. The recommended duration of secondary prophylaxis varies depending on the presence and severity of cardiac involvement.[29]

VALVULAR HEART DISEASE

Valvular Anatomy

Of the four heart valves, three (tricuspid, pulmonic, and aortic) are composed of three cusps, whereas the mitral valve has only two cusps. Each cusp is a double layer of endocardium that is attached at its base to the fibrous skeleton of the heart. The margins of the cusps are attached to muscular projections from the ventricles (papillary muscles) via tendinous cords (chordae tendineae). Contraction of the ventricle, and consequently the papillary muscle, results in the opening or closing of the valve depending on its location.

www.ketabpezeshki.com 66485457-66963820

Mitral Stenosis

The most common cause of mitral stenosis is RHD. Symptoms of valvular dysfunction typically develop after a latency period of one to three decades. Many patients will not recall a history of ARF. Less common causes of mitral stenosis include congenital mitral stenosis and mitral annular calcification.

Pathophysiology

The normal cross-sectional area of the mitral valve orifice is 4 to 6 cm^2. Stenosis becomes clinically significant when the area falls below 2 cm^2. Impeded flow from the left atrium to the left ventricle results in left atrial hypertension, restricted cardiac output, and, ultimately, pulmonary congestion. As the disease progresses, patients may develop pulmonary hypertension and right ventricular failure.

The most common complication of mitral stenosis is atrial fibrillation, which in the absence of rate control is not well tolerated. Patients with underlying mitral stenosis will decompensate under other conditions associated with increased cardiac demand and reduced ventricular filling, such as pregnancy, anemia, infection, and hyperthyroidism.

Clinical Features

Early symptoms of mitral stenosis include reduced exercise tolerance and dyspnea on exertion. Patients with more advanced disease may have orthopnea and, if right ventricular failure is present, peripheral edema. Hemoptysis, caused by rupture of a bronchial vein, and hoarseness, caused by compression of the recurrent laryngeal nerve, are classic but rare presentations. Aside from the typical signs of heart failure, findings that suggest the presence of mitral stenosis include a loud S_1 and an opening snap in early diastole accompanied by a low-pitched, rumbling diastolic apical murmur.

Although the chest radiograph may be normal, in more advanced cases, left atrial enlargement may be suggested by straightening of the left heart border. Common ECG abnormalities in addition to atrial fibrillation include left atrial enlargement and, ultimately, right ventricular hypertrophy. Echocardiography confirms the diagnosis and assesses the severity of disease.

Management

Medical treatment for patients with mitral stenosis comprises diuresis for symptoms of vascular congestion and anticoagulation for atrial fibrillation.[30] Once symptoms have developed, however, median survival without intervention is 7 years. Several surgical options exist, ranging from balloon valvulotomy or open commissurotomy to valve reconstruction or replacement. Management of the patient with mitral stenosis in the ED centers on identification and treatment of underlying precipitants such as atrial fibrillation or anemia, diuresis, and referral for definitive intervention.

Mitral Regurgitation

Acute and chronic mitral regurgitation are two distinct disease entities. Acute mitral regurgitation is a true emergency. It can result from idiopathic rupture of chordae tendineae, papillary muscle dysfunction in the setting of acute ischemia (or rupture 2-7 days postinfarction), or, rarely, perforation of a valve leaflet in the setting of infectious endocarditis or trauma. Chronic mitral regurgitation, on the other hand, most commonly occurs either in the setting of dilated cardiomyopathy (caused by enlargement of the mitral annular ring) or in the setting of RHD. This frequently coexists with mitral stenosis. Other causes of chronic mitral regurgitation include MVP and connective tissue disorders, such as Marfan syndrome and Ehlers-Danlos syndrome.

Pathophysiology

Acute mitral regurgitation is associated with low left atrial compliance and thus sharply elevated left atrial pressure that results in acute pulmonary congestion. In contrast, chronic mitral regurgitation is characterized by high left atrial compliance and near-normal left atrial pressures with reduced forward output. Patients with chronic mitral regurgitation typically decompensate in the setting of volume overload.

Clinical Features

The characteristic presentation of acute mitral regurgitation is one of fulminant pulmonary edema. This is accompanied by a unique, harsh, midsystolic murmur that radiates to the base and not the axilla. Patients typically have no prior history of heart failure. The ECG may display signs of ischemia or infarction.

The presentation of chronic mitral regurgitation is similar to that of chronic systolic heart failure with clinical symptoms and signs of decompensated congestion. The murmur is classically described as holosystolic, heard best at the apex and radiating to the axilla. The ECG often reflects both left atrial and ventricular hypertrophy. Atrial fibrillation is common, and left atrial enlargement may be suggested by the chest radiograph. Echocardiography may demonstrate a normal or above-normal ejection fraction, but much of the diastolic flow is retrograde.

Management

When the diagnosis of acute mitral regurgitation is suspected, emergency echocardiography and cardiac catheterization will assess the degree of regurgitation and urgency for surgery. Initial stabilization should include treatment of pulmonary edema with nitrates and diuretics. In a hypotensive patient, a counterpulsation intra-aortic balloon pump may provide temporary stabilization as a bridge to surgery.

The natural history of chronic mitral regurgitation is generally a very slow progression with a 15-year survival approaching 70% with medical therapy, including diuretics and afterload-reducing agents. Once the ejection fraction falls below 60%, valve repair or replacement is advisable before the development of irreversible left ventricular dysfunction.[31]

Aortic Stenosis

The most common cause of aortic stenosis is calcific degeneration, which is prevalent in the elderly with coronary artery disease. This also occurs in younger individuals with a bicuspid aortic valve. Aortic stenosis can also occur along with mitral stenosis in RHD.

Pathophysiology

The normal aortic valve area is greater than 3 cm^2. Significant obstruction occurs when the valve area is reduced by more than 50%. Critical aortic stenosis is defined by a valve area of less than 0.8 cm^2 or a pressure gradient across the valve that exceeds 50 mm Hg. Compensatory left ventricular hypertrophy can maintain cardiac output until the stenosis becomes severe. Further progression of disease is associated with left ventricular dysfunction, left atrial enlargement, and atrial fibrillation. Individuals with severe or critical aortic stenosis are preload dependent and have very little cardiovascular reserve. Disruption of the delicate

www.ketabpezeshki.com 66485457-66963820

balance between myocardial oxygen supply and demand (e.g., ischemia, rapid atrial fibrillation, dehydration, and acute blood loss) can result in precipitous decompensation.

Clinical Features

Classic symptoms of aortic stenosis progress from angina (increased demand resulting from wall stress, and decreased supply resulting from reduction in perfusion pressure) to exertional syncope (fixed cardiac output and vasodepressor response) and congestive heart failure (diastolic and systolic dysfunction). In an older patient with chest pain, particularly if seemingly preload dependent, the possibility of aortic stenosis should be considered.[32]

The classic auscultatory finding in aortic stenosis is a crescendo-decrescendo systolic murmur heard best at the base (right second intercostal space) that radiates into the carotids and is associated with the presence of an S_4 gallop and a soft aortic component of S_2. It is important to note that as the severity of disease increases, the murmur peaks later and becomes less apparent. Carotid pulses may be delayed *(tardus)* and diminished in intensity *(parvus)*. The ECG typically reveals left ventricular hypertrophy. Echocardiography is required for assessment of the severity of stenosis and the presence of left ventricular dysfunction.

Management

The natural history of aortic stenosis is one of slow progression without symptoms for years. Once symptoms develop, survival is markedly reduced unless the valve is replaced, and medical management has a limited role. Management of decompensated aortic stenosis in the acute setting centers on judicious fluid resuscitation, blood transfusion, restoration of sinus rhythm, and avoidance of vasodilators and diuretics and inotropic agents if possible. When there is no response to medical therapy and the patient is a candidate for valve replacement, an intra-aortic balloon pump may provide a bridge to surgery.

Aortic Insufficiency

Aortic insufficiency, whether acute or chronic, may reflect valvular abnormalities caused by a congenital bicuspid valve, RHD, or infectious endocarditis. In addition, aortic root abnormalities, such as ectasia, aneurysm, or dissection, may be associated with a variety of connective tissue diseases, including Marfan syndrome.

Pathophysiology

With acute aortic insufficiency, left ventricular compliance is low and left ventricular pressure increases rapidly, leading to acute pulmonary congestion. The pressure gradient between the aorta and the left ventricle is minimal. In chronic aortic insufficiency, the left ventricle dilates, allowing the heart to maintain normal or near-normal cardiac output despite significant regurgitation. The enhanced stroke volume results in a wide pulse pressure and the associated clinical signs. Congestion is typically associated with volume overload.

Clinical Features

Patients with acute aortic insufficiency may have a history suggestive of aortic dissection or aneurysm or severe respiratory distress and even frank cardiogenic shock. Acute aortic insufficiency can cause subtle physical findings. The pulse pressure may not be widened, and the short, soft, diastolic murmur may be difficult to detect. Echocardiography, which may be required emergently, is diagnostic.

With chronic aortic insufficiency, a widened pulse pressure may be accompanied by a number of physical findings, such as a rapidly rising and falling carotid pulse (water-hammer or Corrigan's pulse), spontaneous nail bed pulsations (Quincke's sign), or a to-and-fro murmur over the femoral artery (Duroziez's sign). A high-pitched, blowing, diastolic murmur at the left sternal border is characteristic of chronic aortic insufficiency. An Austin-Flint murmur, a soft diastolic rumble caused by the regurgitant stream against the mitral valve, may also be present.

Management

Acute aortic insufficiency is typically a surgical emergency necessitating urgent valve replacement. Medical stabilization entails the cautious use of vasodilators and diuretics. Intra-aortic balloon counterpulsation is contraindicated in the presence of an incompetent aortic valve. In contrast, chronic aortic insufficiency is managed like other types of decompensated heart failure. Valve repair or replacement should be contemplated before the development of left ventricular systolic dysfunction.[33]

Mitral Valve Prolapse

MVP is defined pathophysiologically as an abnormal movement of one or both of the mitral valve leaflets across the plane of the valve during systole. Although generally a benign condition, it is infrequently associated with more serious cardiac pathology such as mitral regurgitation, endocarditis, and arrhythmias. Echocardiographic studies report a true prevalence of less than 1% in both men and women versus the previously reported 5% with a female predominance.[34]

Pathophysiology

Structurally, MVP is characterized by myxomatous proliferation of the spongiosa layer within the mitral valve that results in abnormal billowing of the leaflet during systole. MVP may be associated with other connective tissue disorders, such as Marfan syndrome and Ehlers-Danlos syndrome. Although any of the leaflets may prolapse, involvement of the posterior leaflet is more likely to be associated with mitral regurgitation and other cardiovascular complications.[35]

Clinical Features

MVP is associated with a wide variety of clinical symptoms, including chest pain, palpitations, dyspnea, lightheadedness, and fatigue. Appropriately controlled clinical studies, however, such as the Framingham Heart Study, suggest that patients with MVP and control subjects may be equally symptomatic.[36] The classic auscultatory features of MVP are a midsystolic "click" followed by a midsystolic to late systolic murmur over the mitral area. This click results from snapping of the chordae tendineae during the prolapse of the valve.

Diagnostic Strategies

The typical auscultatory findings should suggest MVP that is confirmed by echocardiography. Symptoms attributed to MVP, however, are often not explained by the degree of prolapse or mitral regurgitation. In some of these patients, autonomic or neuroendocrine dysfunction may be a cause of nonspecific symptoms.

Management

Cardioselective beta-blockers may control symptoms such as palpitations, chest pain, and anxiety. Lifestyle modifications, such as

www.ketabpezeshki.com 66485457-66963820

exercise, relaxation techniques, and avoidance of ethanol or caffeine and other stimulants is also helpful. Often, simple reassurance about the benign nature of the disease will suffice. The 2007 American Heart Association endocarditis prophylaxis guidelines no longer included consideration of MVP as one of the conditions requiring antibiotic prophylaxis.

Complications of Prosthetic Valves

Prosthetic heart valves are classified as either mechanical, constructed entirely of synthetic material, or biologic. The latter category includes whole valve transplants (porcine or human) as well as bioprosthetic valves manufactured from bovine pericardium. All prosthetic heart valves are associated with complications, ranging from structural failure and thrombosis to systemic embolization, hemolysis, and endocarditis. The diagnosis of a prosthetic valve complication can be challenging because symptoms and signs are often subtle. The overall incidence of complications is approximately 3% per year.[37]

Primary structural failure is extremely uncommon with modern mechanical valves. When it does occur, the presentation is one of acute severe regurgitation and shock, mandating emergent replacement. With biologic valves, in contrast, structural failure is less dramatic but relatively more common. At 10 years, 20 to 30% of bioprosthetic valves will exhibit evidence of structural failure, and most are replaced electively. Symptoms are characteristically insidious in onset and mimic native valve disease.

Prosthetic valve thrombosis has an incidence of approximately 2% per year, both with biologic valves and with appropriately anticoagulated mechanical valves. Symptoms are of variable duration, are generally subacute, and typically mimic congestive heart failure. The diagnosis is often initially overlooked, and untreated mortality approaches 15%. On physical examination the diagnosis is suggested by a decreased or absent valve click, a new regurgitant murmur, or a louder than expected stenotic murmur. Echocardiography may demonstrate the thrombus or restricted leaflet motion suggesting obstruction. Treatment options include fibrinolytic therapy and surgery.[38]

The incidence of systemic embolization from a prosthetic valve is approximately 1% per year. Compared with patients with aortic valve prostheses, those with mitral valve prostheses have twice the risk of systemic embolization, with an incidence roughly the same in the case of a biologic valve or mechanical valve in an appropriately anticoagulated patient. The target international normalized ratio is 3.0 to 3.5 with a mechanical mitral valve versus 2.5 to 3.0 with an aortic valve. The vast majority of diagnosed embolic events (85%) involve the central nervous system, and roughly half of these result in permanent impairment. In this context, the risk of continued anticoagulation and possible hemorrhagic conversion should be weighed against the risk of a second embolic event.

Hemolytic anemia resulting from sheer forces around a prosthetic valve is usually mild and subclinical, but it may be severe in up to 15% of patients with certain prostheses. Presenting features can be subtle and include dyspnea, fatigue, jaundice, or dark urine. Iron replacement is effective in the majority of patients, although transfusion can be required, and reoperation may be indicated if hemolysis is a result of a periprosthetic leak or other structural failure.

The incidence of PVE is highest during the initial months after surgery and is similar for both mechanical and bioprosthetic valves.[12] Early PVE (within 60 days of surgery) is presumed to be caused by a pathogen acquired perioperatively and is associated with higher morbidity and mortality, whereas late PVE is more likely related to transient bacteremia and is generally associated with a more benign course. As with other forms of endocarditis, fever is by far the most common presenting symptom, and other manifestations are quite variable. Echocardiography can identify vegetations, but a normal study does not rule out endocarditis. In the ED, the diagnosis of PVE is presumptive because the definitive diagnosis requires blood cultures or biopsy. Therefore prosthetic valve patients with no obvious extracardiac source of fever, particularly within 60 days of surgery, should be considered for inpatient admission.

KEY CONCEPTS

- Many patients seen early in the bacteremic phase of IE lack a murmur and are indistinguishable from those with viremia.
- Patients for whom suspicion of endocarditis is moderate to high require blood cultures, echocardiography, and admission for definitive diagnosis and initiation of empirical therapy.
- Prophylaxis for IE is rarely if ever indicated for procedures performed in the ED.
- Acute rheumatic fever is a delayed, nonsuppurative complication of streptococcal pharyngitis characterized by arthritis, carditis, chorea, subcutaneous nodules, and erythema marginatum.
- In a patient with severe mitral stenosis, hypovolemia and tachycardia are poorly tolerated. "Slow and full" are appropriate goals.
- In patients with critical aortic stenosis, excessive preload reduction with vasodilators and diuretics is to be avoided.
- In patients with acute aortic insufficiency, classic physical findings may be absent. Medical stabilization entails the cautious use of vasodilators and diuretics. Intra-aortic balloon counterpulsation is contraindicated.
- Complications of prosthetic heart valves range from structural failure and thrombosis to systemic embolization, hemolysis, and endocarditis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Berlin JA, et al: Incidence of infective endocarditis in the Delaware Valley, 1988-1990. *Am J Cardiol* 1995; 76:933.
2. Tleyjeh IM, et al: Temporal trends in infective endocarditis: A population-based study in Olmsted County, Minnesota. *JAMA* 2005; 293:3022.
3. Hogevik H, Olaison L, Andersson R, Lindberg J, Alestig K: Epidemiologic aspects of infective endocarditis in an urban population: A 5-year prospective study. *Medicine (Baltimore)* 1995; 74:324.
4. Watanakunakorn C, Burkert T: Infective endocarditis at a large community teaching hospital, 1980-1990: A review of 210 episodes. *Medicine (Baltimore)* 1993; 72:90.
5. Murdoch DR, et al: Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: The International Collaboration on Endocarditis—Prospective Cohort Study. *Arch Intern Med* 2009; 169:463-473.
6. Frontera JA, Gradon JD: Right-side endocarditis in injection drug users: Review of proposed mechanisms of pathogenesis. *Clin Infect Dis* 2000; 30:374.
7. Wang A, et al: Contemporary clinical profile and outcome of prosthetic valve endocarditis. *JAMA* 2007; 297:1354.
8. Mylonakis E, Calderwood SB: Infective endocarditis in adults. *N Engl J Med* 2001; 345:1318.
9. Carapetis JR, McDonald M, Wilson NJ: Acute rheumatic fever. *Lancet* 2005; 366:155.
10. Hecht SR, Berger M: Right-sided endocarditis in intravenous drug users: Prognostic features in 102 episodes. *Ann Intern Med* 1992; 117:560.
11. Durack DT, Lukes AS, Bright DK: New criteria for diagnosis of infective endocarditis: Utilization of specific echocardiographic findings: Duke Endocarditis Service. *Am J Med* 1994; 96:200.
12. Houpikian P, Raoult D: Blood culture-negative endocarditis in a reference center: etiologic diagnosis of 348 cases. *Medicine* 2005; 84:162.
13. Moss R, Munt B: Injection use and right sided endocarditis. *Heart* 2003; 89:577.
14. Delaney KA: The double challenge of endocarditis. *Emerg Med* 1990; 22:53.
15. Hoen B, et al: Infective endocarditis in patients with negative blood cultures: Analysis of 88 cases from a one year nationwide survey in France. *Clin Infect Dis* 1995; 20:501.
16. Shively BK, Gurule FT, Roldan CA, Leggett JH, Schiller NB: Diagnostic value of transesophageal compared with transthoracic echocardiography in infective endocarditis. *J Am Coll Cardiol* 1991; 18:391.
17. Daniel WG, et al: Comparison of transthoracic and transesophageal echocardiography for detection of abnormalities of prosthetic and bioprosthetic valves in the mitral and aortic positions. *Am J Cardiol* 1993; 71:210.
18. Lowry RW, Zoghbi WA, Baker WB, Wray RA, Quiñones MA: Clinical impact of transesophageal echocardiography in the diagnosis and management of infective endocarditis. *Am J Cardiol* 1994; 73:1089.
19. Heiro M, Nikoskelainen J, Hartiala JJ, Saraste MK, Kotilainen PM: Diagnosis of infective endocarditis: Sensitivity of the Duke vs. von Reyn criteria. *Arch Intern Med* 1998; 158:18.
20. Nettles RE, McCarty DE, Corey GR, Li J, Sexton DJ: An evaluation of the Duke criteria in 25 pathologically confirmed cases of prosthetic valve infective endocarditis. *Clin Infect Dis* 1997; 25:1401.
21. Hoen B, et al: The Duke criteria for diagnosing infective endocarditis are specific: Analysis of 100 patients with acute fever or fever of unknown origin. *Clin Infect Dis* 1996; 23:298.
22. Dodds GA, et al: Negative predictive value of the Duke criteria for infective endocarditis. *Am J Cardiol* 1996; 77:403.
23. Baddour LM, et al: Infective endocarditis: Diagnosis, antimicrobial therapy, and management of complications: A statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: Endorsed by the Infectious Diseases Society of America. *Circulation* 2005; 111:e394-e434.
24. Wilson W, et al: Prevention of infective endocarditis: Guidelines from the American Heart Association: A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007; 116:1736.
25. Miyake CY, Gauvreau K, Tani LY, Sundel RP, Newburger JW: Characteristics of children discharged from hospitals in the United States in 2000 with the diagnosis of acute rheumatic fever. *Pediatrics* 2007; 120:503.
26. Carapetis JR, Steer AC, Mulholland EK, Weber M: The global burden of Group A streptococcal diseases. *Lancet Infect Dis* 2005; 5:685.
27. Dajani AS, et al: Guidelines for the diagnosis of rheumatic fever: Jones criteria, updated 1992. *Circulation* 1993; 87:302.
28. Cilliers AM, Manyemba J, Saloojee H: Anti-inflammatory treatment for carditis in acute rheumatic fever. *Cochrane Database Syst Rev* 2003; 2:CD003176.
29. World Health Organization: *Rheumatic Fever and Rheumatic Heart Disease: Report of a WHO Expert Consultation (WHO Technical Report Series 923)*. Geneva: World Health Organization; 2001.
30. American College of Cardiology, et al: ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing committee to revise the 1998 guidelines for the management of patients with valvular heart disease). *J Am Coll Cardiol* 2006; 48:e1.
31. Rosenhek R, et al: Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation* 2006; 113:2238.
32. Julius BK, et al: Angina pectoris in patients with aortic stenosis and normal coronary arteries. Mechanisms and pathophysiological concepts. *Circulation* 1997; 95:892.
33. Bekeredjian R, Grayburn PA: Valvular heart disease: Aortic regurgitation. *Circulation* 2005; 112:125.
34. Flack JM, et al: Anthropometric and physiologic correlates of mitral valve prolapse in a biethnic cohort of young adults: The CARDIA study. *Am Heart J* 1999; 138:486.
35. Kim S, et al: Relation between severity of mitral regurgitation and prognosis of mitral valve prolapse: Echocardiographic follow-up study. *Am Heart J* 1996; 132:348.
36. Freed LA, et al: Prevalence and clinical outcome of mitral-valve prolapse. *N Engl J Med* 1999; 341:1.
37. Vongpatanasin W, Hillis LD, Lange RA: Prosthetic heart valves. *N Engl J Med* 1996; 335:407.
38. Alpert JS: The thrombosed prosthetic valve: Current recommendations based on evidence from the literature. *J Am Coll Cardiol* 2003; 41:659.

www.ketabpezeshki.com 66485457-66963820

Section Four

VASCULAR SYSTEM

CHAPTER 84

HYPERTENSION

Phillip D. Levy

PERSPECTIVE

Hypertension (HTN) is a ubiquitous condition affecting close to one third of Americans and approximately 1 billion people worldwide.[1,2] Although tremendous strides have been made over the past 20 years in management of chronic HTN, prevalence has been on a steady rise, and blood pressure (BP) is controlled (defined as below 140/90 mm Hg for most individuals and below 130/80 mm Hg for those with diabetes mellitus or chronic kidney disease [CKD]) in only 50% of patients.[3,4] Among those with poorly controlled HTN, over 10% have persistent BP elevations of greater than 160/100 mm Hg—a circumstance that is particularly concerning, because the independent risk of pressure-related cardiovascular mortality is known to double with each 20/10 mm Hg rise in BP above the ''ideal'' level of 115/75 mm Hg. Of note, the distribution of HTN is not uniform, and, especially in the United States, individuals of African descent have a higher disease prevalence (41.4% vs. 28.1% for Caucasians) and poorer BP control, leading to an increased risk of adverse outcome.[1,4,5] In fact, HTN is the single most important contributor to racial differences in life-years lost from cardiovascular disease, accounting for half of the excess risk within the African American community.[6]

These data have important implications for the emergency department (ED).[7] According to the National Hospital Ambulatory Medical Care Survey, nearly 3.5 million ED visits related to chronic HTN occurred in 2005 (a 75% increase from 10 years earlier); in 2006,[8] more than 40% of those treated in EDs across the United States had an initial BP that was moderately elevated (i.e., >140-159/90-99 mm Hg) or severely elevated (i.e., ≥160/100 mm Hg).[9] The vast majority of those with increased BP will be asymptomatic (from the perspective of hypertensive end-organ damage), and their BP elevation often will diminish without treatment within a few hours of arrival.[10,11] When patients are symptomatic, however, uncontrolled HTN may represent a true emergency that requires rapid intervention. Differentiating patients who warrant immediate treatment for potentially serious complications of acute HTN from those with simple BP elevations with a low likelihood of near-term adverse outcomes is thus a critical aspect of emergency medicine practice.

PRINCIPLES OF DISEASE

Definition of Hypertension and Relevant Terminology

Although BP below 120/80 mm Hg is considered normal, delineation of what constitutes HTN is evolving. For decades, 140/90 mm Hg has existed as the universally established threshold that separates HTN from prehypertension (i.e., the BP range above normal but below elevated) or normotensive state. This cutoff point was derived from studies of manual BP measurements obtained by specifically trained personnel in an office using proper technique in a nonstressful setting.[12] Automated BP measurement is more reliable than office-based manual assessment and, when obtained from a patient sitting alone in a quiet environment, yields numerical values that are equivalent to mean BP as measured by the "gold standard"—24-hour ambulatory BP monitoring (ABPM).[12-14] Newer automated office BP (AOBP) measurement devices are so much more precise that recent guidelines have suggested lowering the cutoff for establishing a diagnosis of HTN to 135/85 mm Hg (the level above which the American Heart Association considers ABPM measurements abnormal) when BP is obtained via this approach.[14,15]

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) defines BP levels of 120-139/80-89 mm Hg as pre-HTN, 140-159/90-99 mm Hg as stage I HTN, and 160/100 mm Hg or higher as stage II HTN.[3] Despite its inherent usefulness, the JNC 7 classification system lacks sufficient granularity to help emergency physicians discern, even among patients with stage II HTN, specific subgroups for whom intervention in the ED is beneficial. This is especially true for patients with substantial (i.e., ≥180/110 mm Hg) BP elevation, where the focus of care is often erroneously placed on cosmetic improvement in numbers without regard for clinical necessity.[16,17]

Prior attempts to classify patients have relied on ambiguous and overlapping terms such as "hypertensive crisis," "hypertensive urgency," and "accelerated" or "malignant" HTN, causing confusion on the part of clinicians and reliance on non–evidence-based interventions. A better approach focuses on the presence (or absence) of signs or symptoms attributable to acute target-organ injury within the context of established or newly "diagnosed" severe HTN, thus distinguishing patients with active vasculopathy from those without. Moreover, such categorization helps to identify patients in whom acutely elevated BP may be transient or reactive rather than indicative of an underlying chronic disease process. Along these lines, three distinct classes of HTN are relevant to emergency medicine practice:

1. *Hypertensive emergency:* A condition distinguished by acute target-organ dysfunction, manifesting with newly developed clinical sequelae or consequential diagnostic test abnormalities. It has been estimated that 1 to 2% of patients with HTN will experience a hypertensive emergency in their lifetime, and in the United States the frequency of hospital admission for such a diagnosis is approximately 110 per 100,000.[18]
2. *Poorly controlled chronic HTN:* A presentation in which patients with established HTN are found to have elevated

www.ketabpezeshki.com 66485457-66963820

BP without specific attributable symptoms or evidence of acute target-organ damage. Such presentations most often result from nonadherence to treatment regimens or inadequate medical management but also may reflect refractory disease. Concurrent use of seemingly innocuous medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, decongestants, appetite suppressants, over-the-counter stimulants, oral contraceptives, and tricyclic antidepressants or rebound from short-acting antihypertensives, such as clonidine, may be contributory.

3. *Elevated BP without prior history of HTN:* A relatively frequent occurrence in which routine ED vital signs identify an elevated BP. Such individuals also may visit the ED after an outpatient physical examination, community health-screening event, or automated BP measurement by the patient identifies elevated BP. Whether or not this truly represents HTN can be difficult to determine in the ED, and subsequent reexamination in an outpatient setting will usually be required. Studies have shown, however, that approximately 70% of those with high BP in the ED but no established history of HTN will have elevated BP on ABPM or at clinic follow-up.[19-21] Patients should not be diagnosed with HTN, however, until a series of properly performed BP measurements in a nonemergency ambulatory setting confirms the diagnosis.

Pathophysiology of Chronic Hypertension

Whereas BP is known to rise with increasing age, onset of HTN in the nonelderly represents a complex interplay of multiple inciting factors including neurohormonal dysregulation, vascular modulation, sodium intake, psychosocial stress, and obesity. Alterations in cardiac and renal function are also important, serving as both contributors to and consequences of ongoing BP elevation. Despite an advanced understanding of the pathophysiology of HTN, the definitive cause of elevated BP remains unknown in more than 90% of patients. These individuals are labeled as having *primary* or *essential* HTN, and the cause is considered idiopathic. In the subset of patients for whom an identifiable cause can be ascertained, the term *secondary HTN* applies (Table 84-1).

Neurohormonal Dysregulation

The sympathetic nervous system (SNS) has a pivotal role in the development of HTN.[22] Norepinephrine, the principal sympathetic neurotransmitter, is a potent stimulator of vasoconstriction. This effect is mediated through peripheral alpha$_1$-adrenergic

Table 84-1 Secondary Causes of Hypertension

CAUSE	DIAGNOSTIC TEST	CLINICAL CLUES
Endocrine		
Cushing's syndrome and other glucocorticoid excess states	History; dexamethasone suppression test	Glucose intolerance; purple striae
Hyperaldosteronism and other mineralocorticoid excess states	24-Hour urinary aldosterone level or other mineralocorticoids	Unexplained hypokalemia
Oral contraceptive use	History	
Pheochromocytoma	24-Hour urinary metanephrine and normetanephrine	Labile or paroxysmal HTN with palpitations, pallor and perspiration
Thyroid disease Parathyroid disease	Serum TSH Serum PTH	Temperature intolerance, weight loss, tachycardia Hypercalcemia
Pulmonary		
Obstructive sleep apnea	Sleep study with O_2 saturation	Obesity; narcolepsy
Renal		
Chronic pyelonephritis	History; urinalysis, urine culture	
Diabetic nephropathy and other chronic kidney disease	Estimated GFR; urine albumin/creatinine ratio	
Nephritic and nephrotic syndromes	Urinalysis	
Polycystic kidney disease	Renal ultrasound	
Renovascular conditions (renal artery stenosis)	Doppler flow study; magnetic resonance angiography	HTN onset before the age of 30 yr or after 55 yr; abdominal bruit; refractory HTN control; recurrent pulmonary edema; unexplained renal failure
Toxic or Metabolic		
Chronic alcohol abuse	History; ETOH level	
Sympathomimetic drug use	History; drug screen	
Tyramine containing foods	History	Paroxysms of HTN, especially in those taking monoamine oxidase inhibitors
Vascular		
Atherosclerosis		
Coarctation of the aorta	CT angiography	Decreased lower extremity pulses

CT, computed tomography; *ETOH,* ethyl alcohol; *GFR,* glomerular filtration rate; *HTN,* hypertension; O_2, oxygen; *PTH,* parathyroid hormone; *TSH,* thyroid-stimulating hormone.

www.ketabpezeshki.com 66485457-66963820

receptor activation in vascular smooth muscle cells and occurs predominantly in small-diameter arterioles. Although individually these vessels contribute a miniscule amount to BP, in sum they serve as the primary driver of systemic vascular resistance (SVR) and constitute the main force that amplifies afterload in HTN.[23] The SNS also stimulates beta$_1$-adrenergic receptors in the heart, leading to an increase in cardiac output (CO) through augmentation of stroke volume and heart rate, but these are considered lesser contributors to the pathologic process of high BP. Sympathoactivation exerts additional, direct effects on the kidney that promote sodium reabsorption leading to an increase in circulating blood volume and trigger renin release, which results in angiotensin II production and further vasoconstriction.[24]

Independent of SNS activity, the renin-angiotensin-aldosterone system (RAAS) is critical to BP dynamics. Renin is an enzyme produced by juxtaglomerular cells in the kidney in response to several factors, including sodium load in the distal tubule, renal perfusion status, and, as noted earlier, adrenergic stimulation. Renin cleaves angiotensin I from its plasma globulin precursor, angiotensinogen. Angiotensin I is then converted to angiotensin II by circulating and tissue-bound (especially lung) angiotensin-converting enzyme (ACE). Angiotensin II exerts systemic and renal effects by binding to angiotensin II type I (AT_1) receptors, which results in arterial vasoconstriction, sodium reabsorption, and modulation of glomerular filtration rate (GFR).[25] Through AT_1 receptor binding in the adrenal gland, angiotensin II also serves as a potent stimulator of aldosterone release, which promotes further sodium reabsorption and potassium excretion.

Vascular Modulation

Continued vascular stimulation by both the SNS and RAAS coupled with an increase in wall tension caused by HTN itself leads to ongoing remodeling throughout the arterial tree.[26,27] In large vessels such as the aorta or carotid arteries, this results in increasing intima-media thickness (IMT) with minimal luminal narrowing (unless there is unrelated plaque buildup). In contrast, small-vessel and arteriolar remodeling reduces the lumen diameter.[28] Although both forms of remodeling work to normalize wall stress associated with HTN, they reduce vasodilatory capacity and enhance the vasoconstrictor response when faced with a hypertensive stimulus.[27]

Sodium Intake

The average American has a daily sodium intake of close to 3500 mg (150 mEq)—more than double the recommended level of 1500 mg (approximately 65 mEq) put forth by the U.S. Department of Agriculture in its 2010 dietary guidelines. Randomized trials have consistently demonstrated a reduction in systolic BP with diminished daily sodium intake (up to 7 mm Hg/1200 mg or 52-mEq decrease in hypertensive individuals).[29,30] Salt sensitivity is defined by an increase in BP with intake of a high-sodium diet. It is linked to obesity but may be more directly related to defects in renal ion transport mechanisms that lead to ongoing sodium retention and potassium depletion.[31,32] Relative hypokalemia plays a critical role, and the entire effect of salt sensitivity on BP can be abolished with high-dose (approximately 4000 mg or 100 mEq per day) potassium supplementation.[5,29]

Psychosocial Stress

Life stressors, especially socioeconomic status, are known to adversely affect health and wellness.[33] There is increasing evidence that such stress is an important modulator of BP (through its effects on SNS function and the hypothalamic-pituitary axis) and a specific contributor to disparities in HTN.[34,35] Although episodic stress reactions can lead to transient sympathetic surges, sustained stimulation related to ongoing concern over life circumstances (e.g., financial security, crime and safety, racism) triggers a chronic adaptive response and is emerging as an important consideration in patients with seemingly idiopathic HTN.

Obesity

Increased body mass index (>30 kg/m^2) is a known risk factor for HTN (odds ratio 3.4; 95% confidence interval, 2.5-4.6) and explains 20 to 80% of the recent rise in HTN prevalence.[36] Elevated BP in obese individuals correlates with high circulating aldosterone and cortisol levels, which in turn may be a related to salt sensitivity. Obesity, especially truncal, is also strongly associated with diabetes and obstructive sleep apnea, both of which contribute to poor BP control.

Pathophysiology of Target-Organ Damage

Uninterrupted by treatment, continued vasoconstriction leads to a number of deleterious consequences that culminate in target-organ damage. On a macrocirculatory level, the central component of the cardiovascular system (i.e., heart and large blood vessels) is most affected. Sustained elevations in SVR cause significant augmentation of the pressure wave reflected from the periphery back to the central circulation (termed the *augmentation index*), thus driving up left ventricular (LV) afterload; the increase manifests with a rise in the central aortic pressure and change in the morphology of its waveform.[23,37] This results in increasing impedance to forward flow from the heart, which in turn requires greater contractile force to maintain aortic valve opening and the duration of ventricular ejection.[38,39] Active contraction against this resistance also increases intraventricular wall tension, which, together with ongoing stimulation from, among other things, the SNS and RAAS, triggers cardiomyocyte hypertrophy and myocardial fibrosis. Initially, this leads to an increase in LV mass, which enhances the heart's pumping against excessive afterload. When progressive, however, this process results in LV stiffening and impaired diastolic function with a reduction in LV filling and diminished flow from the left atrium to the LV. If the increase in afterload is sudden, an abrupt decrease in stroke volume occurs, precipitating backflow of fluid into the lungs and rapid onset of "flash pulmonary edema." If excess afterload is more gradual or even chronic, a subacute rise in LV end-diastolic pressure may cause increased wall tension with compression of the subendocardial microvasculature and non–coronary artery–mediated myocardial ischemia. Over time, this contributes to LV wall thinning, chamber dilation, and eventually systolic dysfunction.

On a microcirculatory level, the initial, beneficial effect of vascular remodeling gradually gives way to critical luminal narrowing and the potential for regional ischemia from occlusion or loss of vessel wall integrity with leakage or rupture. Autoregulation, the intrinsic capacity of resistance vessels to rapidly dilate or constrict in response to dynamic perfusion pressure changes, works to maintain relatively constant blood flow and is protective with moderate fluctuations. Small-vessel ischemic episodes, many of which are "silent," are the primary cause of chronic target-organ damage, including progressive white matter (i.e., multi-infarct) disease in the brain and hypertensive nephropathy. In a hypertensive emergency, however, an abrupt rise in vascular pressure overwhelms autoregulatory mechanisms, triggering endothelial injury. A subsequent drop in nitric oxide (NO)–mediated vascular smooth muscle relaxation and excess release of endothelin further increase SVR, which functionally maintains BP at severely elevated levels. Unchecked wall tension ensues, and terminal arterioles dilate and eventually rupture, leading to a proinflammatory, hypercoagulable state with fibrin deposition and diffuse ischemia.

www.ketabpezeshki.com 66485457-66963820

Rising pressure in the proximal capillary beds causes fluid leakage and tissue edema, which, combined with the process of fibrinoid necrosis, produces acute target-organ damage and possibly microangiopathic hemolytic anemia.

CLINICAL FEATURES

Although BP elevation alone does not define any particular clinical syndrome, acute target-organ damage does not occur in the absence of moderate to severe HTN (i.e., ≥180/110 mm Hg). Conversely, in the absence of symptoms, the mere presence of an excessively high BP in the ED (regardless of the level) does not herald imminent development of target-organ damage.

Hypertensive Emergency

Most hypertensive emergencies occur in patients with chronic HTN.[40] Organ systems involvement is relatively consistent and is dominated by injury to the brain, heart, or kidneys (Table 84-2). True hypertensive emergencies are defined by the target-organ acutely involved. Focal neurologic deficit or altered mentation therefore point to brain injury, whereas chest pain or shortness of breath is indicative of cardiac or vascular involvement. Although frequently accompanied by an elevated BP, symptoms such as headache, epistaxis, and dizziness are not, in and of themselves, evidentiary of end-organ injury and in isolation, do not constitute a hypertensive emergency, nor indicate the need for acute BP reduction.

Hypertensive Encephalopathy

Hypertensive encephalopathy is a true hypertensive emergency and is a manifestation of diffuse vasogenic cerebral edema. It is caused by a failure of autoregulation in the brain, with vasospasm, ischemia, increased vascular permeability, punctate hemorrhages, and interstitial edema. The patient generally has severe headache, vomiting, and altered mental status, which may progress to seizures or coma. Retinal involvement may cause blurred vision progressing to complete blindness. When present, focal neurologic deficits do not follow a singular anatomic pattern and may occur on opposite sides of the body, indicating diffuse cerebral dysfunction rather than an anatomically localized stroke syndrome or space-occupying lesions. Papilledema, although difficult to recognize, is often present, along with significant hypertensive retinopathy. Computed tomography (CT) does not show acute hemorrhage or other acute pathology. The combination of diffuse cerebral dysfunction, normal CT scan, and markedly elevated systemic BP, particularly if supported by objective findings such as papilledema or retinal hemorrhage, is sufficient to make a presumptive diagnosis of hypertensive emergency and necessitates initiation of acute antihypertensive therapy. Hypertensive encephalopathy is fully reversible with early, aggressive BP reduction (30-40% decrease). Treatment is described later.

Table 84-2 Hypertensive Emergencies by Organ System

INJURY PATTERN BY TARGET ORGAN	APPROXIMATE INCIDENCE* (%)
Brain (cumulative)	37-45
Acute ischemic stroke	6-25
Hypertensive encephalopathy	8-16
Intracerebral or subarachnoid bleed	5-23
Heart (cumulative)	27-49
Acute heart failure syndromes	14-37
Acute coronary syndromes	11-12
Kidney	
Acute renal risk	15
Acute kidney injury	8
Vascular	
Aortic dissection	1-2
Other	
Eclampsia	2
Acute hypertensive retinopathy	1

Adapted from Levy P: Hypertensive Emergencies: On the Cutting Edge. Advancing the Standard of Care: Cardiovascular and Neurovascular Emergencies. EMCREG-International Symposia Monograph, February 2011, pp 19-26. Available at www.emcreg.org.

*Range based on percentages compiled from Szczech and others,[106] Katz and others,[52] and Zampaglione and others.[111]

Acute Stroke, Heart Failure Syndromes, and Other Hypertension-Related Emergencies

Acute stroke per se is not a hypertensive emergency, although treatment of acute intracranial hemorrhage often includes BP control (see Chapter 101). Chronic HTN is the primary population-attributable risk factor for development of heart failure,[41] and more than 50% of ED patients with acute cardiac decompensation have HTN (see Chapter 81). Although the relationship between acute systemic HTN and pulmonary edema is not uniform, in up to half of cases, HTN may be the sole cause or a major contributor to the acute episode.[42,43] Acute heart failure often responds well to vasodilatory agents and a reduction in afterload. Similarly, acute BP management may play a key role in therapy of acute coronary syndrome and demand ischemia (see Chapter 78), and acute aortic dissection (see Chapter 85). Acute kidney injury in the setting of elevated BP may be a consequence of associated target-organ damage, especially acute heart failure, and particularly when such patients are on baseline diuretic or calcium channel blocker therapy. Recent or chronic NSAID or newly initiated ACE inhibitor (ACEI) therapy may also contribute, but the effect of these agents are usually transient (see Chapter 97).[44] Preeclampsia and eclampsia are discussed in Chapter 178.

Blood Pressure Elevation in the Absence of Target-Organ Dysfunction

Most patients who are found to be significantly hypertensive on intake vital sign measurement or who come to the ED because BP was found to be elevated in an outpatient setting or by self-measurement do not have an acute hypertensive emergency, and for such patients, acute reduction of BP is not indicated. These patients do not have target-organ injury and most often have poorly controlled chronic HTN, HTN in the context of nonadherence to medication regimen, or, less commonly, elevated BP without prior history of HTN. When symptoms are present, they generally are nonspecific (e.g., low-grade or recurrent headache, atypical chest pain, dyspnea, dizziness, generalized weakness, focal but anatomically uncorrelated weakness or numbness, vague visual disturbances) and, with the exception of dyspnea, appear to be unrelated to the degree of BP elevation.[45,46] Despite widespread belief among the public (and some physicians) to the contrary, existing evidence does not support a causal relationship between epistaxis and acute, severe HTN.[47,48] There is no evidence of benefit for acute BP reduction in patients with these vague symptoms and elevated BP, regardless of the level. If chronic medications have been missed, as usually is the case, these should be restarted. The patient should be observed in a quiet area of the ED and reassured; in many cases the BP spontaneously improves.[10] There are no data supporting either a threshold BP warranting treatment or a target BP to be achieved before discharge. Although well-intentioned, some misguided providers may be tempted to administer a short-acting, potent antihypertensive agent such as clonidine or hydralazine to achieve an immediate but transient (and

www.ketabpezeshki.com 66485457-66963820

clinically meaningless) reduction in BP. This practice is without rationale or evidence of benefit and, according to a recent retrospective cohort study, may be associated with an increased likelihood of subsequent ED visitation for issues related to HTN.[49]

DIAGNOSTIC STRATEGIES

The diagnostic evaluation of hypertensive emergency is guided by symptoms and signs identified on clinical examination but will often involve a number of tests. In nearly all instances, laboratory testing may be required to look for acute or worsening renal dysfunction (i.e., basic metabolic panel and urinalysis) and microangiopathic hemolytic anemia (i.e., complete blood count with manual differential and peripheral smear). Individuals with chest pain or shortness of breath may require a chest radiograph, an electrocardiogram, and cardiac biomarker (i.e., troponin and natriuretic peptide [NP]) measurement. Although echocardiography is a reasonable consideration, routine CT of the thorax is not indicated and can be reserved for patients with suspected aortic dissection. When focal neurologic deficits or altered mentation is present, nonenhanced brain imaging with CT is helpful, often with follow-up magnetic resonance imaging (MRI) (depending on CT findings, availability, and clinical circumstances).

Funduscopy can provide evidence of hypertensive target-organ damage. Findings of acute hypertensive retinopathy include focal intraretinal periarteriolar transudates (whitish ovoid lesions deep in the retina), focal retinal pigment epithelial lesions (evidence of choroidal injury), macular and optic disk edema, and cotton-wool spots (fluffy white lesions that consist of swollen, ischemic axons caused by small-vessel occlusion).[50] Hard exudates, which consist of lipid deposits located deep in the retina, are also a common but late occurrence. When identified, such funduscopic abnormalities are considered diagnostic; however, they may be absent in more than 30% of patients with a clinically evident hypertensive emergency.[51] Lesions of acute retinopathy are distinct from more chronic changes, which include arterial narrowing, "copper" or "silver" wiring of the arterioles, arteriovenous nicking, and retinal hemorrhages. The spectrum of retinal findings in HTN can be graded on a 5-point scale (Box 84-1). Despite its potential usefulness, funduscopy is infrequently and inadequately performed in the evaluation of severely elevated BP in the busy ED.[45,52]

Whether any further testing beyond funduscopy is needed to identify occult target-organ damage in those who are asymptomatic is a matter of debate. Although the JNC 7 provides recommendations on routine testing in the primary care setting, there is no specific guidance for the ED.[3] In a multicenter ED-based study of asymptomatic hypertensive patients, clinically meaningful, unanticipated abnormalities on a basic metabolic panel, urinalysis, electrocardiography, and chest x-ray examination were detected in only 6%; none of these abnormalities were definitively attributable to HTN.[53] However, in an urban setting with predominantly African American patients, there is a high prevalence of previously undetected kidney disease (16.2%); so, depending on the population,[54] evaluation of renal function by basic metabolic panel is a reasonable consideration. Although such information may not affect immediate management, there is value in knowing baseline renal function and electrolyte levels, particularly if initiation of chronic antihypertensive therapy is planned. Often used as a gross estimate of glomerular function, urinalysis is a low-yield screening test. Spot measurement of the urine albumin/creatinine (Cr) ratio is a more sensitive method to detect subclinical renal disease.[55] In some settings, it may be reasonable to consider ordering this from the ED, if adequate follow-up of test results (which often take longer than 24 hours) can be ensured. Newer markers of renal dysfunction, including cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), and kidney injury molecule–1 (KIM-1), may ultimately supplant existing laboratory tests.[56]

Unlike with renal function, there is no simple, efficient test for detecting subclinical cardiac disease in the ED, and evaluation in this setting is guided by symptoms. Although chest x-ray examination and electrocardiography are often used, they have poor sensitivity for target-organ damage (especially LV hypertrophy), and abnormalities, when identified, are unlikely to alter clinical management.[53,57] Serum NP levels (i.e., B-type NP [BNP] and N-terminal pro-BNP [NT-proBNP]) have yielded conflicting results and are not optimal screening tests.[58,59] Based on findings from a recent study in which echocardiography was used as the criterion standard, the prevalence of subclinical hypertensive heart disease appears to be substantial (approximately 75%), suggesting the need for development of a more effective screening strategy.[60] Emphasis is not on ED screening tests but on referral for further evaluation, and management is vital for all of these patients.

Box 84-1 Funduscopic Grading of Suspected Hypertensive Retinopathy

Grade 0—Normal
Grade 1—Minimal arterial narrowing
Grade 2—Obvious arterial narrowing with focal irregularities
Grade 3—Arterial narrowing with retinal hemorrhages and/or exudate
Grade 4—Grade 3 plus disk swelling

CONSIDERATION OF DIFFERENTIAL DIAGNOSES

Differential considerations are based on patient subtype. For those with a suspected hypertensive emergency, the decision point centers on the potential causal relationship between patient presentation and acutely elevated BP. Clinical entities within this broader heading, such as stroke syndromes and acute heart failure, do carry their own differentials, but a full discussion of each is beyond the scope of this chapter. Depending on the clinical scenario, ancillary testing may be needed to rule out alternatives to a hypertensive cause. For patients with poorly controlled chronic HTN, a consideration of etiology (i.e., primary vs. secondary) may be warranted. Related diagnostic workup (see Table 84-1) can usually be pursued on an outpatient basis, but for some (i.e., individuals with multiple episodes of flash pulmonary edema, symptomatic paroxysmal episodes of labile BP, or suspected poor follow-up), initiation of treatment from the ED or admission to the hospital is needed. The final factor to consider is whether or not a newly detected BP elevation is truly caused by HTN. Although diagnostic accuracy of ED BP can be enhanced by a second repeat measurement,[7,21] the ideal approach may be to average several measurements taken over a brief period of observation.[61] For those without a previous history of HTN, definitive diagnosis will require reassessment in an outpatient setting.

MANAGEMENT

Acute Blood Pressure Control

Antihypertensive Therapy

Antihypertensive therapy is indicated in treatment of acute hypertensive encephalopathy and in the presence of specific target-organ injury (see earlier discussion). The goal of acute antihypertensive therapy is to safely and effectively lower BP in a relatively rapid fashion while maintaining peripheral perfusion. Although some oral (i.e., clonidine) or sublingual (i.e., captopril, nitroglycerin) medications are capable of this, patients who truly require acute lowering of BP benefit from the predictable,

www.ketabpezeshki.com 66485457-66963820

Table 84-3 Hemodynamic Effect Profile of Common Intravenous Antihypertensive Medication

		Hemodynamic Effect		
CLASSIFICATION	AGENT(S)	CARDIAC OUTPUT	SYSTEMIC VASCULAR RESISTANCE	CENTRAL VENOUS PRESSURE
Adrenergic inhibitors				
Alpha$_1$-blockers	Phentolamine, urapidil*	↑	↓	↑
Beta$_1$-blockers	Esmolol, metoprolol	↓	↑↓	↑↓
Mixed alpha$_1$/beta-blockers	Labetalol	↓	↓	↑↓
Angiotensin-converting enzyme inhibitors	Enalaprilat	↑↓	↓	↑↓
Calcium channel blockers				
Dihydropyridine	Clevidipine, nicardipine	↑	↓	↑↓
Nondihydropyridine	Diltiazem, verapamil	↓	↓	↑↓
Direct-acting vasodilators	Hydralazine	↑	↓	↑↓
Dopamine-1 receptor agonists	Fenoldopam	↑↓	↓	↑↓
Loop diuretics	Furosemide, bumetanide, torsemide	↑↓	↓	↓
Natriuretic peptide receptor agonists	Nesiritide	↑	↓	↓
Nitric oxide donors	Sodium nitroprusside, nitroglycerin, isosorbide dinitrate	↑	↓	↓

Adapted from Levy P: Hypertensive Emergencies: On the Cutting Edge. Advancing the Standard of Care: Cardiovascular and Neurovascular Emergencies. EMCREG-International Symposia Monograph, February 2011, pp 19-26. Available at www.emcreg.org.
*Also has 5-HT$_{1A}$ agonist properties.

controlled effect of a parenteral agent, either by titrated intravenous boluses or by adjustable infusion.

Mean arterial pressure (MAP), a summary measure that represents the average arterial pressure during one cardiac cycle, is a composite of circulatory inputs. The relationship is defined by the following equation:

$$MAP = (CO \times SVR) + CVP$$

where SVR reflects vasogenic tone in the arterioles (i.e., afterload), CO reflects the pumping force of the heart, and central venous pressure (CVP) represents intravascular volume (i.e., preload) and, more roughly, hydrostatic force in the circulatory system. The hemodynamic response to a specific medication or a class of medications is a function of how they interact with this equation, and, as shown in Table 84-3, effects can differ substantially. Depending on the desired response profile, certain agents may be more appealing than others for a specific indication. With the exception of pure beta-blockers, however, all produce a decrease in SVR—an optimal characteristic in the management of hypertensive emergencies.

Existing intravenous antihypertensive agents exert their effect either directly through receptor-mediated actions (largely agonist or antagonist properties) or indirectly through a decrease in production or release of endogenous vasoconstrictors. The magnitude of BP reduction reflects the mechanism of action as well as the pharmacokinetic and pharmacodynamic activity, with some variability in the latter based on aging.[62] According to the STAT (Studying the Treatment of Acute hyperTension) registry, labetalol is the most common intravenous bolus medication used, and nitroglycerin is the infusion medication used most frequently for severe HTN in the ED.[63] Comparative trial data, however, are lacking with regard to superiority of any of the different agents. A Cochrane review of 15 randomized, controlled trials (N = 869) involving seven different drug classes (nitrates, ACEIs, diuretics, calcium channel blockers, alpha$_1$-adrenergic antagonists, direct vasodilators, and dopamine agonists) found minor differences in the degree of BP lowering with little evidence to suggest a differential effect on morbidity or mortality.[64] Two more recent prospective trials, ECLIPSE (Evaluation of CLevidipine In the Perioperative treatment of hypertension assessing Safety Events),[65] which compared clevidipine with nitroglycerin, sodium nitroprusside, and nicardipine, and CLUE (Evaluation of intravenous niCardipine and Labetalol Use in the Emergency department),[66] demonstrated more rapid attainment of the BP goal and increased time spent within a prespecified BP target range for the intravenous dihydropyridine calcium channel blockers, nicardipine and clevidipine. In ECLIPSE there was no difference in mortality rates among nicardipine, clevidipine, and nitroglycerin, but mortality was significantly higher for those treated with sodium nitroprusside versus clevidipine. There is insufficient benefit, however, to argue for the dihydropyridine calcium channel blockers over other agents for acute BP treatment in the ED. A general guide to intravenous antihypertensive therapy is provided in Table 84-4.

Blood Pressure Goals

Optimal treatment of a true hypertensive emergency is best achieved when therapy is directed toward (1) the precipitant of specific target-organ dysfunction and (2) the acute consequences of elevated BP rather than the BP itself. Based on recommendations in JNC 7, the long-standing approach to acute antihypertensive therapy has been to target a maximal reduction in MAP of 20 to 25% within the first hour and a goal BP of 160/100 mm Hg by 2 to 6 hours.[3,67] This arises from an understanding of the cerebral autoregulation curve, which under normal circumstances maintains stable blood flow within a range of pressures (MAP of 60-160 mm Hg) but resets in chronic HTN with a shift of the lower limit toward the right. This shift tends to settle at a point approximately 25% below baseline MAP, resulting in concern that an excessive BP decrease during acute treatment will actually decrease cerebral blood flow.[17] Such a consideration is consistent with adverse events following sublingual nifedipine administration in asymptomatic hypertensive pseudoemergencies.[68] As described throughout this chapter, however, asymptomatic patients differ from true hypertensive emergencies, and mechanisms for the latter are heterogeneous. Moreover, in hypertensive emergencies the presenting BP is often markedly elevated compared with baseline and well above the lower limit of the

www.ketabpezeshki.com 66485457-66963820

Table 84-4 User's Guide to Intravenous Antihypertensive Therapy

MEDICATION BY CLASS	BOLUS OR LOADING DOSE	INFUSION RATE	TIME TO ONSET	DURATION OF ACTION	COMMENTS
Adrenergic Inhibitors					
Phentolamine	5-15 mg q5min	0.2-0.5 mg/min	1-2 min	10-30 min	Avoid with coronary artery disease
Urapidil	12.5-50 mg q5min	9-30 mg/hr	1-2 min	2.5 hr	Not FDA approved
Esmolol	0.5-1 mg/kg × 1	50-300 µg/kg/min	1-2 min	20 min	
Metoprolol	5 mg q5min	None	10-30 min	5-8 hr	
Labetalol	20-80 mg q10min	1-2 mg/min	2-5 min	3-6 hr	Beta-blocker effects predominate (1:7)
ACE Inhibitor					
Enalaprilat	0.625-1.25 mg q15min	1-2 mg/hr	15-30 min	6-12 hr	May produce prolonged hypotension; avoid in pregnancy
Calcium Channel Blockers					
Clevidipine	None	2-32 µg/hr	1-2 min	1-5 min	
Nicardipine	None	5-15 mg/hr	5-15 min	4-6 hr	Avoid with aortic stenosis and liver failure (hepatic metabolism)
Diltiazem	0.25-0.35 mg/kg q15min	5-15 mg/hr	5-15 min	6 hr	Will decrease blood pressure but not often used for this indication
Verapamil	2.5-5 mg IV q15min	None	5-15 min	6 hr	
Direct-Acting Vasodilator					
Hydralazine	5-20 mg q30min	1.5-5 µg/kg/min	10-20 min	2-4 hr	Causes reflex activation of the sympathetic nervous system
Dopamine Antagonist					
Fenoldopam	None	0.1-0.3 µg/kg/min; titrate by 0.1 µg/kg	<5 min	30 min	Increases intraocular pressure; contains sodium metabisulfate—avoid in patient with sulfa allergy
Loop Diuretics					
Furosemide	40-240 mg q12hr	10-40 mg/hr	30-60 min	2-4 hr	Limited anithypertensive effect compared with other agents listed
Bumetanide	0.5-4 mg q12hr	None	30-60 min	2-4 hr	
Torsemide	10-20 mg q12hr	None	30-60 min	2-4 hr	
Natriuretic Peptide					
Nesiritide	2 µg/kg × 1	0.01 µg/kg/min	15 min	18 min	Indicated only for use in acute heart failure
Nitric Oxide Donors					May cause precipitous drop in blood pressure with right ventricular ischemia or renal artery stenosis; bolus administration controversial; risk of cyanide toxicity with nitroprusside; avoid entire class in patients taking phosphodiesterase-5 inhibitors (e.g., sildenafil)
Sodium nitroprusside	None 1-2 mg q5min	0.25-10 µg/kg/min	Immediate	1-2 min	
Nitroglycerin		5-200 µg/min	2-5 min	5-10 min	
Isosorbide dinitrate	3-4 mg q5min	1-10 mg/hr	2-5 min	5-10 min	

ACE, angiotensin-converting enzyme; *FDA,* U.S. Food and Drug Administration; *IV,* intravenously.

individual patient's autoregulation curve, providing a margin of safety with reductions down to or along the perfusion plateau (Fig. 84-1). Use of a single BP goal for all hypertensive emergencies may preclude the ability to effectively interrupt the acute pathologic process, and, as described in the following sections, the best approach is to focus on condition-specific targets. An overview of respective treatment goals and relevant caveats for differing indications can be found in Table 84-5.

Acute Coronary and Acute Heart Failure Syndromes

In acute coronary syndromes complicated by HTN, the primary goal (beyond immediate reperfusion) is a decrease in cardiac work and improved coronary artery perfusion, each of which can be dramatically affected by changes in afterload. Similarly, in patients with acute hypertensive heart failure, in which a rise in SVR, and more specifically the augmentation index, impedes forward flow and exacerbates ventricular stiffness, intervention aimed at reducing afterload can offset resistive force, enabling more effective contraction. NO donors (i.e., medications that exert their effect by providing an exogenous source of NO), such as nitroglycerin, can be highly beneficial in both circumstances, as they produce small-vessel dilation, which yields a dose-dependent decrease in overall vascular resistance, and diminish the intensity of arterial waveform reflection, thus improving systolic ejection time (and diastolic coronary artery filling).[37,69-71] Reductions in MAP exceeding 30% have been associated with more rapid symptom resolution and improved outcomes among patients with severe, acute hypertensive heart failure.[69,72]

To achieve such a profound decrease in MAP, higher doses of nitroglycerin (i.e., 1-2 mg by bolus or >250 µg/min) may be needed; and whereas sodium nitroprusside achieves a similar effect, it provides limited benefit over aggressive doses of nitroglycerin and has a number of added disadvantages, including the need for arterial line monitoring, risk of cyanide toxicity, and potential for compound photodegradation. All nitrates should be used with caution in patients who have taken a phosphodiesterase-5 (PDE5) inhibitor such as sildenafil (Viagra) or tadalafil (Cialis) within the preceding 24 to 48 hours as this can lead to a persistent hypotensive episode.[73] ACEIs, on the other hand, are well tolerated

www.ketabpezeshki.com 66485457-66963820

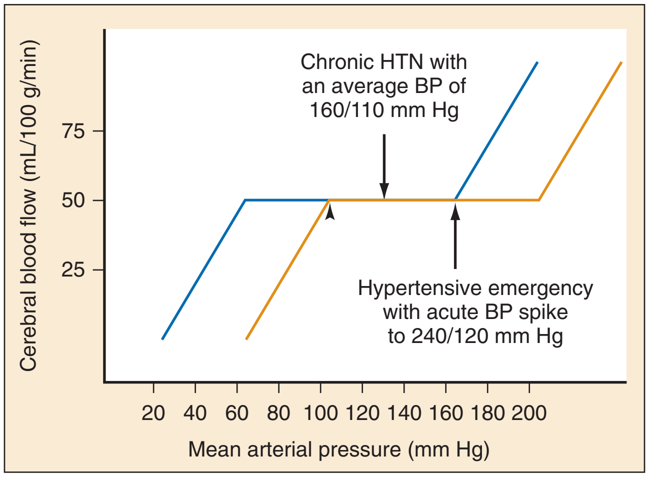


Figure 84-1. The cerebral blood pressure autoregulation curve *(blue line)* and its right-shift response to chronic hypertension *(red line).* Data shown are for a hypothetical patient with chronic hypertension and poor blood pressure control at baseline with a hypertensive emergency *(black arrows).* As indicated by the arrowhead, the lower limit of the shifted autoregulation curve in this scenario sits well beyond a 25% reduction in mean arterial pressure.

in such patients and have been associated with rapid symptom improvement in patients with hypertensive heart failure.[74,75] Enalaprilat can be administered by intravenous bolus or infusion and is the preferred ACEI in the setting of acute heart failure, but cautious dosages (0.625-1.25 mg per dose up to a maximum of 2.5 mg over 30 minutes) are recommended as the drug is long acting and can precipitate a sustained drop in BP. Given their short half-life, third- and fourth-generation intravenous dihydropyridine calcium channel blockers (i.e., nicardipine and clevidipine) are emerging as potential alternatives, though prospective trial data are lacking.[76] Labetalol and other intravenous agents with inhibitory beta-adrenergic effects, such as metoprolol, should be avoided in the early stages of treatment, as they produce a decrease in CO, and in acute coronary syndrome, patients have increased the likelihood of cardiogenic shock.[77]

As highlighted by a recent subanalysis of the STAT registry, however, the potential to excessively reduce BP is real, and adverse events may be increased when systolic BP is rapidly normalized (i.e., decreased to ≤120/80 mm Hg) in the setting of compromised cardiac function.[78] Therefore, although aggressive BP control is important, antihypertensive therapy for acute coronary or acute heart failure syndromes should be titrated to symptom resolution rather than a specific MAP with short-term tolerance of persistently elevated BP in a clinically improving patient.

Table 84-5 Indication-Specific Approach to Management of Hypertensive Emergencies

INDICATION	GOALS OF TREATMENT	OPTIMAL AGENTS	ALTERNATIVE THERAPY	CAVEATS
Acute coronary syndromes	Diminish cardiac workload and improve coronary artery perfusion	*Primary:* nitroglycerin *Secondary:* metoprolol, labetalol	Esmolol, nicardipine	Routine use of intravenous beta-blocker therapy is controversial.
Acute heart failure syndromes	Reduce impedance to forward flow and diminish cardiac workload	*Primary:* nitroglycerin, furosemide *Secondary:* enalaprilat	Clevidipine, nicardipine, sodium nitroprusside	Intubation or noninvasive ventilatory support decreases preload and may drop BP. Enalaprilat may cause sustained hypotension. Though FDA approved, use of nesiritide is controversial.
Aortic dissection	Reduce shear force and dP/dt	*Primary:* esmolol plus sodium nitroprusside *Secondary:* labetalol	Esmolol plus (clevidipine or nicardipine), diltiazem, verapamil	Avoid beta-blockers if aortic regurgitation is present.
Acute ischemic stroke*	Reduce hemorrhagic conversion and edema while avoiding regional hypoperfusion	*Primary:* nicardipine *Secondary:* labetalol	Esmolol	Acute BP reduction is indicated only with planned fibrinolytic administration or when secondary target-organ dysfunction is involved.
Acute intracerebral hemorrhage*	Reduce hematoma expansion and perihematomal edema	*Primary:* nicardipine *Secondary:* labetalol	Esmolol	BP may decrease with pain management alone. Clevidipine is currently under investigation.
Hypertensive encephalopathy*	Decrease brain edema, reduce intracranial pressure, and improve autoregulatory control	*Primary:* nicardipine *Secondary:* labetalol	Esmolol, enalaprilat	Other causes of altered mental status should be considered in the workup.
Acute kidney injury	Decrease pressure in renal parenchyma and glomerular apparatus	*Primary:* fenoldopam *Secondary:* clevidipine, nicardipine	Labetalol, sodium nitroprusside	Angiotensin-converting enzyme inhibitors and diuretics should be avoided.
Preeclampsia and eclampsia	Decrease intracranial pressure while maintaining placental perfusion	*Primary:* hydralazine *Secondary:* labetalol	Nicardipine	Intravenous magnesium (6 g initially) is administered in all cases. Emergent cesarean section is definitive treatment.
Sympathetic crisis	Reduce alpha$_1$-adrenergic receptor–mediated vasoconstriction	*Primary:* phentolamine *Secondary:* nitroglycerin	Fenoldopam, clevidipine, nicardipine, sodium nitroprusside	Benzodiazepines are first-line therapy when sympathetic crisis is caused by cocaine or amphetamines. Beta-blocker monotherapy (including labetalol) is contraindicated.

Adapted from Levy P: Hypertensive Emergencies: On the Cutting Edge. Advancing the Standard of Care: Cardiovascular and Neurovascular Emergencies. EMCREG-International Symposia Monograph, February 2011, pp 19-26. Available at www.emcreg.org.
BP, blood pressure; *dP/dt,* change in pressure/change in time; *FDA,* U.S. Food and Drug Administration.
*Nitric oxide donors and hydralazine should be avoided with these indications.

www.ketabpezeshki.com 66485457-66963820

Aortic Dissection

In contrast to the situation with other cardiovascular hypertensive emergencies, with aortic dissection, BP control to a specific target (systolic BP below 110 mm Hg) is essential, as it decreases ongoing injury and reduces the likelihood of perioperative adverse events.[79] The immediate goal is to reduce intimal shear forces by driving down the pressure that results from LV ejection with each cardiac cycle (termed *dP/dt*). This is best accomplished by decreasing heart rate and stroke volume through administration of a rapid-acting intravenous beta-blocker such as esmolol. Although a direct reduction in BP is also critical, it is important that beta-blocker therapy be initiated before vasodilation as the latter can lead to reflex tachycardia and worsening of dP/dt. Once beta-blockers have been initiated, agents such as sodium nitroprusside, nicardipine, or clevidipine can be rapidly titrated to reduce systolic BP as low as can be tolerated (and ideally to below 120 mm Hg) within 30 minutes. Because labetalol has both alpha- and beta-blocker properties, it may be an acceptable alternative, particularly if used as a continuous infusion. Diltiazem and verapamil, which are both mixed calcium channel blockers (i.e., agents with both cardiac and vascular effects), may also be used, though neither is ideal as monotherapy.

Acute Stroke Syndromes

Understanding the importance of BP control is critical in treating acute stroke syndromes. For acute ischemic stroke, the current American Heart Association/American Stroke Association (AHA/ASA) guidelines call for a BP reduction to below 185/110 mm Hg only when thrombolysis is planned. Otherwise, antihypertensive therapy is not indicated unless BP is greater than 220/120 mm Hg, and even in such cases the goal is to decrease by approximately 15 % gradually, over the first 24 hours after onset.[80] This is supported by a metaregression of BP control trials in stroke that suggests an association between (1) large falls or increases in BP and worse outcome and (2) modest reductions and a decrease in death and/or dependency.[81] In contrast, for acute intracerebral hemorrhage, the 2010 AHA/ASA guidelines state that “aggressive” reduction is warranted when systolic BP exceeds 200 mm Hg or MAP exceeds 150 mm Hg, and more modest decreases are indicated (target BP 160/90 mm Hg or MAP 110 mm Hg) when lesser elevations (systolic BP >180 mm Hg or MAP >130 mm Hg) are present.[82] These recommendations, however, are vague on specific targets and timing of antihypertensive therapy. The recent Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT; N = 404) and the Antihypertensive Treatment of Acute Cerebral Hemorrhage study (ATACH; N = 60) suggest an association between early antihypertensive therapy (within 6 hours of onset) targeting a systolic BP of 140 mm Hg and attenuation of hematoma expansion.[83-86] Despite overall demonstration of no benefit and possible harm from routine antihypertensive therapy, the Scandinavian Candesartan Acute Stroke Trial (SCAST), a study in which less than 15% of the total enrolled population had a hemorrhagic cause, also found a trend toward reduction in vascular events, but not functional outcomes, for those treated within 6 hours.[87]

Although several ongoing prospective trials, including follow-ups to INTERACT and ATACH, should help clarify residual questions surrounding BP control in acute stroke, present evidence-based recommendations can be summarized as follows: (1) administration of antihypertensive therapy in the ED for a suspected ischemic cause should be avoided, unless thrombolysis is planned; and (2) aggressive BP reduction should be initiated in the setting of acute intracranial hemorrhage, targeting a systolic BP between 160 and 180 mm Hg within the first few hours of arrival. Both labetalol and nicardipine appear to maintain adequate cerebral perfusion while producing generalized reductions in vascular resistance and have emerged as the favored therapies in the setting of acute stroke syndromes.[88-90] Nicardipine may offer some advantage over labetalol as it results in a more rapid achievement of BP goals and is associated with reduced BP variability—a potentially important determinant of patient outcome.[88,91,92] Nimodipine, an oral dihydropyridine calcium channel blocker, is specifically indicated for patients with subarachnoid hemorrhage, though its benefit appears to be more related to a reduction in intracranial arterial vasospasm than to an effect on SVR. Esmolol may also be used, though its BP effects depend more on a reduction in CO than peripheral vascular resistance. Although sodium nitroprusside is a highly effective antihypertensive option, it and other NO donors should be avoided as they can cause an increase in intracranial pressure.

Hypertensive Encephalopathy

Unlike acute stroke syndromes in which HTN may be reactive rather than causative, a direct association exists between the degree of BP elevation and neurologic symptoms in patients with hypertensive encephalopathy. Once alternative causes of altered mentation have been ruled out, therapy should be directed toward initiation of immediate, aggressive antihypertensive therapy. The goal is to return BP to a point at which autoregulation can regain control of cerebral blood flow and the process leading to cerebral edema can be reversed—a circumstance that requires MAP to be brought back down to the pressure curve plateau. To achieve this, reductions in MAP of 30 to 40% may be needed. Whereas MAP targets should be kept in mind, symptom resolution is the best gauge of therapeutic effectiveness, with treatment directed specifically toward improvement of encephalopathy.

Sodium nitroprusside is often used as primary treatment for hypertensive encephalopathy patients, but the vascular effects of this and other NO donors appear to be more substantial in the systemic (vs. cerebral) circulation, resulting in a relative increase in cerebral BP and a shunt effect to the peripheral circulation.[93] This serves to decrease cerebral blood flow and may produce a greater than anticipated reduction in cerebral perfusion, thereby increasing the risk of ischemia watershed areas of the brain. This may be worsened by the relative increase in intracranial pressure known to occur with sodium nitroprusside therapy. Similar differential circulatory effects may also occur with hydralazine (a direct-acting vasodilator that inhibits calcium release from the sarcoplasmic reticulum), and unless BP is completely refractory to other therapy, it is best to avoid use of nitroprusside or hydralazine.[90,94] In contrast, nicardipine and labetalol produce an even reduction in resistance across vascular beds and have become the agents of choice for patients with hypertensive encephalopathy.

Acute Kidney Injury

Defined by a decrease in estimated GFR (eGFR) of more than 50% or a doubling of serum Cr when either is compared with baseline,[95] acute kidney injury (AKI) represents an abrupt worsening of renal function. Though largely a manifestation of ongoing glomerular injury from chronic poor BP control, AKI in the setting of severe HTN may represent deterioration precipitated by prerenal causes, including volume depletion (often related to concurrent diuretic therapy) and extrinsic alterations in GFR (often triggered by drug-mediated afferent arteriolar vasoconstriction and ACEI-induced autoregulatory modulation) or intrinsic nephron destruction caused by acute pressure overload. Consequently, some patients require fluid administration to augment volume, whereas others need antihypertensive therapy to mitigate pressure-mediated nephrogenic damage. Laboratory testing is useful to differentiate which approach is needed. A blood urea

www.ketabpezeshki.com 66485457-66963820

nitrogen (BUN)/Cr ratio over 20 and a fractional excretion of sodium (FENa; calculated as [urine Na/serum Na ÷ urine Cr/serum Cr] × 100) below 1%—or for those on chronic diuretic therapy, a fractional excretion of urea (FEurea; calculated as [urine urea/serum urea ÷ urine Cr/serum Cr] × 100) below 35%—serve as indictors of a prerenal cause.

When antihypertensive therapy is indicated, fenoldopam, a potent dopamine 1A receptor agonist, is preferred as it leads to improved perfusion of the corticomedullary region and has been associated with a reduction in need for subsequent dialysis and rate of in-hospital death.[96] Enalaprilat should be avoided as it produces differential effects on the precapillary and postcapillary glomerular vascular bed (i.e., greater vasodilation in efferent than afferent arterioles), which increases the risk of further deterioration in eGFR. Peripheral-acting calcium channel blockers, such as clevidipine and nicardipine, have no adverse effect on glomerular autoregulation and are acceptable first-line alternatives to fenoldopam. Other agents, including labetalol and sodium nitroprusside, may also be used.

Preeclampsia and Eclampsia

Whereas delivery is the definitive treatment, BP control is a critical part of early management. Similar to hypertensive encephalopathy, preeclampsia, and to a greater degree eclampsia, represent an overwhelming of cerebral autoregulation, and rapid BP reduction is essential.[97] Because they are acute (rather than chronic) complications in a relatively healthy, young population, there is generally not a resetting of the autoregulation curve in preeclampsia or eclampsia, and adverse consequences can develop at seemingly "low" (but relatively high) pressures. The threshold for intervention, therefore, is set lower than with other hypertensive emergencies (i.e., systolic BP exceeding 160 mm Hg).

Magnesium sulfate is considered first-line therapy for all cases of preeclampsia and eclampsia. It relaxes smooth muscle (partly through calcium antagonism), which leads to some decrease in peripheral and cerebral vascular resistance; limits cerebral edema formation by protecting the blood-brain barrier; and has central anticonvulsant activity.[98] Its antihypertensive effects, however, are modest, and additional treatment is typically needed to control BP. Hydralazine and labetalol by intravenous bolus are equally effective for this purpose and have limited impact on placental blood flow.[99] Nicardipine is a reasonable alternative and may produce a more profound decrease in BP than labetalol.[100]

Sympathetic Crises

Hyperadrenergic states can result from endogenous sources of catecholamine excess (i.e., pheochromocytoma), but more commonly, they are triggered by intake of exogenous substances that interfere with norepinephrine (and to a lesser degree, epinephrine) metabolism, such as cocaine, amphetamines, and tyramine-containing foods (especially in patients on monoamine oxidase inhibitors). The net result is a cardiostimulatory and vasopressor response that manifests clinically as tachycardia and marked HTN. In patients with cocaine or amphetamine intoxication, such peripheral effects are compounded by central sympathetic activation, and the hemodynamic derangements can often be improved by administration of benzodiazepines and other sedative medications.

When BP is persistently elevated and end-organ compromise is present, antihypertensive treatment will be needed. Phentolamine, a reversible pure alpha-blocker, is considered first-line therapy, producing a reliable decrease in peripheral vasoconstriction with little adverse effect. Nitroglycerin can also be used and is specifically indicated for patients with associated chest pain and suspected coronary artery vasospasm. Other agents, including fenoldopam, clevidipine, nicardipine, and sodium nitroprusside, are acceptable alternatives. Heart rate control may also be needed (especially in patients with pheochromocytoma, in whom adrenal release of epinephrine may be particularly high), and a short-acting beta-blocker such as esmolol is ideal for this purpose when paired with a vasodilator to avoid precipitation of unopposed alpha-receptor activity, worsening HTN. Although labetalol has combined alpha- and beta-blocker properties, beta-receptor effects strongly predominate when the drug is administered in intravenous form (alpha to beta ratio of 1 : 7). Consequently, intravenous labetalol is susceptible to a similar differential response and should be used with caution in the setting of catecholamine excess.

Chronic Antihypertensive Therapy

Poorly controlled chronic HTN on a single visit or a clear trend toward persistently elevated BP over time requires referral for timely follow-up with reinforcement of goal BP recommendations and emphasis on the need for lifelong dietary and medication compliance. Initiation of oral antihypertensive therapy for new-onset HTN and reinitiation or up-titration for patients with chronic HTN is appropriate from the ED if follow-up cannot be ensured.[7] Although the JNC 7 recommends initial treatment with thiazide diuretics for virtually all patients, ACEIs or angiotensin receptor blockers are acceptable first-line alternatives and optimal as add-on agents, particularly in those with a history of diabetes or cardiac comorbidities.[3,5,25,101] Beta-blockers are relegated to a minor support role but are used in patients whose therapy with other agents has been maximized without adequate BP control.[102] Of note, most patients with stage II HTN will require multiple agents to control their BP, and there is increasing evidence that significant benefit with improved compliance and reduced side effects can be achieved with use of low-dose combination tablets (especially combined ACEIs and calcium channel blockers).[101,103,104] A listing of most currently available monotherapy and combined antihypertensive therapy agents is provided in Table 84-6.

Acute BP reduction in the ED provides absolutely no benefit to patients with chronic HTN and exposes them to unnecessary risk of potential hypoperfusion in regions where blood flow has been governed by long-standing autoregulation.[7,68] When such patients do have symptoms such as headache or chest pain and there is no suspicion of acute target-organ damage, one should consider treating the symptoms, not the BP. Anxiolytic or analgesic medication administration accompanied by resumption of chronic oral antihypertensive therapy is more rational and beneficial than initiation of short-acting antihypertensive therapy.

DISPOSITION

Asymptomatic individuals without evidence of acute target-organ dysfunction can be discharged home, but hypertensive emergency patients warrant admission, most often to an intensive care unit. In certain circumstances (e.g., atypical chest pain with elevated BP, apparent deterioration of chronic renal disease), short-term management in an observation unit may allow for time to determine whether presenting features represent a true emergency. Effective use of the observation unit, however, requires a coordinated care plan and expeditious completion of a proscribed diagnostic workup.

Outcomes associated with a given hypertensive emergency are largely a function of underlying target-organ damage. Data from STAT, however, suggest that severe HTN (at least in the subset of patients in whom intravenous antihypertensives are administered)

For online-only Table 84-6, please go to www.expertconsult.com.

www.ketabpezeshki.com 66485457-66963820

Table 84-6 Summary of Oral Agents Available for Management of Chronic Hypertension

AGENT BY CLASS	TRADE NAME(S)	USUAL DOSE RANGE, TOTAL MILLIGRAMS PER DAY, AND INTERVAL	COMMON SIDE EFFECTS AND COMMENTS
Diuretics (Common)			Short-term: increase cholesterol and glucose levels
Thiazides			
Chlorothiazide	Diuril	125-500 qd	Biochemical abnormalities: decrease potassium, sodium, and magnesium levels, increase uric acid and calcium levels
Chlorthalidone*	Hygroton	12.5-50 qd	
Hydrochlorothiazide (HCTZ)	HydroDIURIL, Microzide, Esidrix	12.5-50 qd	
Polythiazide	Renese	2-4 qd	
Indapamide*	Lozol, Mykrox Zaroxolyn	1.25-5 qd	Rare: blood dyscrasias, photosensitivity, pancreatitis, hyponatremia
Metolazone*		0.5-1 bid or tid	
		2.5-5 qd	
Loop			
Bumetanide	Bumex	0.5-4 bid or tid	
Furosemide	Lasix	40-240 bid or tid	
Torsemide	Demadex	20-100 qd or bid	
Potassium-Sparing			Hyperkalemia may occur
Amiloride hydrochloride	Midamor	5-10 qd	
Triamterene	Dyrenium	25-100 qd	
Mineralocorticoid Receptor Antagonists			
Spironolactone	Aldactone	25-100 qd	
Eplerenone	Inspra	50-100 qd or bid	
Adrenergic Inhibitors			Postural hypotension
Central Alpha-Agonists			Sedation, dry mouth, bradycardia, withdrawal hypertension
Reserpine		0.05-0.25 qd	
Clonidine hydrochloride	Catapres	0.2-1.2 bid or tid	
	Catapres-TTS	0.1-0.3 weekly	
Guanabenz acetate	Wytensin	4-8 bid	
Guanfacine hydrochloride	Tenex	0.5-2 qd	
Methyldopa	Aldomet	250-1000 bid	
Alpha$_1$-Blockers			Hepatitis and lupus-like syndrome
Doxazosin mesylate	Cardura	1-16 qd	Postural hypotension
Prazosin hydrochloride	Minipress	2-20 bid or tid	
Terazosin hydrochloride	Hytrin	1-20 qd	
Beta-Blockers			Bronchospasm, bradycardia, heart failure; may mask insulin-induced hypoglycemia
Acebutolol†‡	Sectral	200-800 qd	
Atenolol†	Tenormin	25-100 qd or bid	
Betaxolol†	Kerlone	5-20 qd	Less serious: impaired peripheral circulation, insomnia, fatigue, exercise intolerance, hypertriglyceridemia (except agents with sympathomimetic activity)
Bisoprolol fumarate†	Zebeta	2.5-10 qd	
Metoprolol tartrate†	Lopressor	50-300 bid	
Metoprolol succinate†	Toprol-XL	50-300 qd	
Nadolol	Corgard	40-320 qd	
Nebivolol hydrochloride	Bystolic	5-20 qd	
Penbutolol sulfate‡	Levatol	10-20 qd	
Pindolol‡	Visken	10-60 bid	
Propranolol hydrochloride	Inderal	40-480 bid	
Timolol maleate	Inderal LA	40-480 qd	
	Blocadren	20-60 bid	
Mixed Alpha$_1$/Beta-Blockers			Postural hypotension, bronchospasm
Carvedilol	Coreg	6.25-50 bid	
Labetalol hydrochloride	Normodyne, Trandate	200-1200 bid	
Direct Vasodilators			Headaches, fluid retention, tachycardia
Hydralazine hydrochloride	Apresoline	50-300 bid	Lupus syndrome
Minoxidil	Loniten	5-100 qd	Hirsutism
Calcium Channel Blockers (CCBs)			Conduction defects, worsening of systolic dysfunction, gingival hypertrophy
Nondihydropyridines			
Diltiazem hydrochloride	Cardizem SR, Cardizem CD,	50-300 bid	
	Dilacor XR, Tiazac	5-100 qd	
Verapamil hydrochloride	Isoptin SR, Calan SR	90-480 bid	Constipation
	Verelan, Covera-HS	120-480 qd	
Dihydropyridines			Pedal edema, flushing, headache, gingival hypertrophy
Amlodipine besylate	Norvasc	2.5-10 qd	
Felodipine	Plendil	2.5-20 qd	
Isradipine	DynaCirc	5-20 bid	
Nicardipine	DynaCirc CR	5-20 qd	
Nifedipine	Cardene SR	60-90 bid	
Nisoldipine	Procardia XL, Adalat CC	30-120 qd	
	Sular	20-60 qd	

Continued

www.ketabpezeshki.com 66485457-66963820

Table 84-6 Summary of Oral Agents Available for Management of Chronic Hypertension—cont'd

AGENT BY CLASS	TRADE NAME(S)	USUAL DOSE RANGE, TOTAL MILLIGRAMS PER DAY, AND INTERVAL	COMMON SIDE EFFECTS AND COMMENTS
Angiotensin-Converting Enzyme Inhibitors (ACEIs)			Common: cough
Benazepril hydrochloride	Lotensin	5-40 qd or bid	Rare: angioedema, hyperkalemia, rash, loss of taste, leukopenia
Captopril (G)	Capoten	25-150 bid or tid	
Enalapril maleate	Vasotec	5-40 qd or bid	
Fosinopril sodium	Monopril	10-40 qd or bid	
Lisinopril	Prinivil, Zestril	5-40 qd	
Moexipril	Univasc	7.5-15 qd or bid	
Perindopril	Aceon	4-8 qd or bid	
Quinapril hydrochloride	Accupril	5-80 qd or bid	
Ramipril	Altace	1.25-20 q or bid	
Trandolapril	Mavik	1-4 qd	
Angiotensin II Receptor Blockers (ARBs)			Angioedema (very rare), hyperkalemia
Candesartan	Atacand	8-32 qd	
Eprosartan	Tevetan	400-800 qd or bid	
Losartan potassium	Cozaar	25-100 qd or bid	
Valsartan	Diovan	80-320 qd	
Irbesartan	Avapro	150-300 qd	
Olmesartan	Benicar	20-40 qd	
Telmisartan	Micardis	20-80 qd	
Direct Renin Inhibitors			Rare angioedema, hyperkalemia (especially with ACEI use), hypotension, diarrhea, rash, renal stones
Aliskiren	Tekturna	150-300 qd	
Fixed Dose Combinations			Side effect profile of combination tablets is similar to individual components, but the overall incidence is greatly diminished
ACEI + Diuretic			
Benazepril + HCTZ	Lotensin HCT	5/6.25, 10/12.5, 20/12.5, 20/25 qd	
Captopril + HCTZ	Capozide	25/15, 25/25, 50/15, 50/25 qd	
Enalapril + HCTZ	Vaseretic	5/12.5, 10/25 qd	
Lisinopril + HCTZ	Prinzide, Zestoretic	10/12.5, 20/12.5, 20/25 qd	
Moexipril + HCTZ	Uniretic	7.5/12.5, 15/12.5, 15/25 qd	
Quinapril + HCTZ	Accuretic	10/12.5, 20/12.5 qd	
Perindopril + indapamide			
ARB + Diuretic			
Irbesartan + HCTZ	Avalide	150/12.5, 300/12.5, 300/25 qd	
Losartan + HCTZ	Hyzaar	50/12.5, 100/25 qd	
Olmesartan + HCTZ	Benicar HCT	20/12.5, 40/12.5, 40/25 qd	
Telmisartan + HCTZ	Micardis HCT	40/12.5, 80/12.5, 80/25 qd	
Valsartan + HCTZ	Diovan HCT	80/12.5, 160/12.5, 160/25 qd	
Beta-Blocker + Diuretic			
Atenolol + chlorthalidone	Tenoretic	50/25, 100/25 qd	
Bisoprolol + HCTZ	Ziac	2.5/6.25, 5/6.25, 10/6.5 qd	
Metoprolol + HCTZ	Lopressor HCT	50/25, 100/25, 100/50 qd	
Timolol + HCTZ	Timolide	10/25 qd	
CCB + ACEI			
Amlodipine + benazepril	Lotrel	2.5/10, 5/10, 5/20 qd	
Felodipine + enalapril	Lexxel	5/2.5, 5/5 qd	
Felodipine + ramipril	Triapin Mite	2.5/2.5 qd	
	Triapin	5/5 qd	
Verapamil + trandolapril	Tarka	180/2, 240/1, 240/2, 240/4 qd	
CCB + ARB			
Amlodipine + olmesartan	Azor	5/20, 5/40, 10/20, 10/40 qd	
Amlodipine + telmisartan	Exforge	5/160, 5/320, 10/160, 10/320 qd	
	Twynsta	5/40, 5/80, 10/40, 10/80 qd	
Renin Inhibitor + Other			
Aliskiren + HCTZ	Tekturna HCT	150/12.5, 150/25, 300/12.5, 300/25 qd	
Aliskiren + amlodipine	Tekamlo	150/5, 150/10, 300/5, 300/10 qd	
Aliskiren + amlodipine + HCTZ	Amturnide	150/5/12.5, 300/5/12.5, 300/5/25, 300/10/12.5, 300/10/25 qd	
Aliskiren + valsartan	Valturna	150/160, 300/320 qd	
Diuretic Combinations			
Amiloride + HCTZ	Moduretic	5/50 qd	
Triamterene + HCTZ	Dyazide, Maxzide	37.5/25, 75/50 qd	

*Technically classified as a thiazide-like diuretic.
†Beta$_1$ selective.
‡Possess intrinsic sympathomimetic activity; beta$_1$ selective with no related vasodilation.

www.ketabpezeshki.com 66485457-66963820

is a high-risk condition with in-hospital and 30-day mortality rates of 6.9% and 11%, respectively, and a 90-day readmission rate of nearly 40%.[52,105] When associated with AKI, mortality is even greater, with an odds ratio 1.05 (P = .03) per 10-mL/min eGFR decline.[106] Although risk for short-term deterioration is minimal in patients with poorly controlled HTN who lack evidence of acute target-organ injury, the long-term risk of cardiovascular disease and the likelihood of a future hypertensive emergency are relatively high.[1,7,107,108] Recidivism for uncontrolled HTN is also very common in this group, underscoring the need for more effective action on the part of ED physicians and health case systems when confronted with such patients.[105,107,109,110]

KEY CONCEPTS

- Hypertension, particularly asymptomatic elevations in blood pressure, is exceedingly common in the emergency department.
- A true hypertensive emergency is defined by the presence of acute target-organ dysfunction and is distinct from other clinical presentations.
- An organ system–based approach to evaluation and management of patients with elevated blood pressure can optimize decision-making while ensuring timely delivery of condition-specific, goal-directed treatment for those in need of immediate antihypertensive therapy.
- Acute blood pressure reduction is not indicated for patients with asymptomatic hypertension who lack evidence of acute target-organ injury; emphasis should instead be placed on patient education and coordinated outpatient follow-up.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Lloyd-Jones D, et al: Heart Disease and Stroke Statistics—2010 Update. A Report From the American Heart Association. *Circulation* 2010; 121:e1.
2. Kearney PM, et al: Global burden of hypertension: Analysis of worldwide data. *Lancet* 2005; 365:217.
3. Chobanian AV, et al: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; 42:1206.
4. Egan BM, Zhao Y, Axon RN: U.S. trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. *JAMA* 2010; 303:2043.
5. Flack JM, et al: Management of high blood pressure in Blacks: An update of the International Society on Hypertension in Blacks consensus statement. *Hypertension* 2010; 56:780.
6. Wong MD, Shapiro MF, Boscardin WJ, Ettner SL: Contribution of major diseases to disparities in mortality. *N Engl J Med* 2002; 347:1585.
7. Decker WW, et al: Clinical policy: Critical issues in the evaluation and management of adult patients with asymptomatic hypertension in the emergency department. *Ann Emerg Med* 2006; 47:237.
8. Nawar EW, Niska RW, Xu J: National Hospital Ambulatory Medical Care Survey: 2005 emergency department summary. *Adv Data* 2007; 386:1.
9. Pitts SR, Niska RW, Xu J, Burt CW: National Hospital Ambulatory Medical Care Survey: 2006 emergency department summary. *Natl Health Stat Report* 2008; 7:1.
10. Grassi D, et al: Hypertensive urgencies in the emergency department: Evaluating blood pressure response to rest and to antihypertensive drugs with different profiles. *J Clin Hypertens (Greenwich)* 2008; 10:662.
11. Pitts SR, Adams RP: Emergency department hypertension and regression to the mean. *Ann Emerg Med* 1998; 31:214.
12. Myers MG, et al: Measurement of blood pressure in the office: Recognizing the problem and proposing the solution. *Hypertension* 2010; 55:195.
13. Leenen FH, Schiffrin EL: Control rates of hypertension in North America. *Hypertension* 2010; 56:571.
14. Quinn RR, et al: The 2010 Canadian Hypertension Education Program recommendations for the management of hypertension: Part I—blood pressure measurement, diagnosis and assessment of risk. *Can J Cardiol* 2010; 26:241.
15. Pickering TG, et al: Recommendations for blood pressure measurement in humans and experimental animals: Part 1: Blood pressure measurement in humans: A statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Hypertension* 2005; 45:142.
16. Gallagher EJ: Hypertensive urgencies: Treating the mercury? *Ann Emerg Med* 2003; 41:530.
17. Shayne PH, Pitts SR: Severely increased blood pressure in the emergency department. *Ann Emerg Med* 2003; 41:513.
18. Deshmukh A, et al: Effect of Joint National Committee VII Report on Hospitalizations for Hypertensive Emergencies in the United States. *Am J Cardiol* 2011; 108:1277.
19. Backer HD, Decker L, Ackerson L: Reproducibility of increased blood pressure during an emergency department or urgent care visit. *Ann Emerg Med* 2003; 41:507.
20. Tanabe P, et al: Increased blood pressure in the emergency department: Pain, anxiety, or undiagnosed hypertension? *Ann Emerg Med* 2008; 51:221.
21. Umscheid CA, et al: Untreated hypertension and the emergency department: A chance to intervene? *Acad Emerg Med* 2008; 15:529.
22. Grassi G: Assessment of sympathetic cardiovascular drive in human hypertension: Achievements and perspectives. *Hypertension* 2009; 54:690.
23. Chirinos JA, Segers P: Noninvasive evaluation of left ventricular afterload: Part 2: Arterial pressure-flow and pressure-volume relations in humans. *Hypertension* 2010; 56:563.
24. Goldsmith SR, Sobotka PA, Bart BA: The sympathorenal axis in hypertension and heart failure. *J Card Fail* 2010; 16:369.
25. Paulis L, Unger T: Novel therapeutic targets for hypertension. *Nat Rev Cardiol* 2010; 7:431.
26. Martinez-Lemus LA, Hill MA, Meininger GA: The plastic nature of the vascular wall: A continuum of remodeling events contributing to control of arteriolar diameter and structure. *Physiology (Bethesda)* 2009; 24:45.
27. Mayet J, Hughes A: Cardiac and vascular pathophysiology in hypertension. *Heart* 2003; 89:1104.
28. Mulvany MJ, et al: Vascular remodeling. *Hypertension* 1996; 28:505.
29. Adrogue HJ, Madias NE: Sodium and potassium in the pathogenesis of hypertension. *N Engl J Med* 2007; 356:1966.
30. Sacks FM, et al: Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med* 2001; 344:3.
31. Blaustein MP, Zhang J, Chen L, Hamilton BP: How does salt retention raise blood pressure? *Am J Physiol Regul Integr Comp Physiol* 2006; 290:R514.
32. Iwamoto T: Vascular Na^+/Ca^{2+} exchanger: Implications for the pathogenesis and therapy of salt-dependent hypertension. *Am J Physiol Regul Integr Comp Physiol* 2006; 290:R536.
33. Szanton SL, Gill JM, Allen JK: Allostatic load: A mechanism of socioeconomic health disparities? *Biol Res Nurs* 2005; 7:7.
34. Logan JG, Barksdale DJ: Allostasis and allostatic load: Expanding the discourse on stress and cardiovascular disease. *J Clin Nurs* 2008; 17:201.
35. Myers HF: Ethnicity- and socio-economic status–related stresses in context: An integrative review and conceptual model. *J Behav Med* 2009; 32:9.
36. Ong KL, Cheung BM, Man YB, Lau CP, Lam KS: Prevalence, awareness, treatment, and control of hypertension among United States adults 1999-2004. *Hypertension* 2007; 49:69.
37. Munir S, et al: Peripheral augmentation index defines the relationship between central and peripheral pulse pressure. *Hypertension* 2008; 51:112.
38. Ooi H, Chung W, Biolo A: Arterial stiffness and vascular load in heart failure. *Congest Heart Fail* 2008; 14:31.
39. Subherwal S, et al: Central aortic pressure is independently associated with diastolic function. *Am Heart J* 2010; 159:1081.
40. Varon J: The diagnosis and treatment of hypertensive crises. *Postgrad Med* 2009; 121:5.
41. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK: The progression from hypertension to congestive heart failure. *JAMA* 1996; 275:1557.
42. Nieminen MS, et al: EuroHeart Failure Survey II (EHFS II): A survey on hospitalized acute heart failure patients: Description of population. *Eur Heart J* 2006; 27:2725.
43. Pang PS, Komajda M, Gheorghiade M: The current and future management of acute heart failure syndromes. *Eur Heart J* 2010; 31:784.
44. Lafrance JP, Miller DR: Selective and non-selective non-steroidal anti-inflammatory drugs and the risk of acute kidney injury. *Pharmacoepidemiol Drug Saf* 2009; 18:923.
45. Karras DJ, et al: Evaluation and treatment of patients with severely elevated blood pressure in academic emergency departments: A multicenter study. *Ann Emerg Med* 2006; 47:230.
46. Karras DJ, et al: Lack of relationship between hypertension-associated symptoms and blood pressure in hypertensive ED patients. *Am J Emerg Med* 2005; 23:106.
47. Herkner H, et al: Hypertension in patients presenting with epistaxis. *Ann Emerg Med* 2000; 35:126.
48. Theodosis P, Mouktaroudi M, Papadogiannis D, Ladas S, Papaspyrou S: Epistaxis of patients admitted in the emergency department is not indicative of underlying arterial hypertension. *Rhinology* 2009; 47:260.
49. Levy P, et al: Acute blood pressure reduction and outcomes in asymptomatic hypertension: A retrospective cohort study. *Ann Emerg Med* 2011; 58:S238.
50. Hayreh SS: Classification of hypertensive fundus changes and their order of appearance. *Ophthalmologica* 1989; 198:247.
51. Amraoui F, van Montfrans GA, van den Born BJ: Value of retinal examination in hypertensive encephalopathy. *J Hum Hypertens* 2010; 24:274.
52. Katz JN, et al: Practice patterns, outcomes, and end-organ dysfunction for patients with acute severe hypertension: The Studying the Treatment of Acute hyperTension (STAT) registry. *Am Heart J* 2009; 158:599.
53. Karras DJ, et al: Utility of routine testing for patients with asymptomatic severe blood pressure elevation in the emergency department. *Ann Emerg Med* 2008; 51:231.
54. Nishijima DK, Paladino L, Sinert R: Routine testing in patients with asymptomatic elevated blood pressure in the ED. *Am J Emerg Med* 2010; 28:235.
55. Viazzi F, et al: Microalbuminuria is a predictor of chronic renal insufficiency in patients without diabetes and with hypertension: The MAGIC study. *Clin J Am Soc Nephrol* 2010; 5:1099.

www.ketabpezeshki.com 66485457-66963820

56. Chaudhary K, et al: The emerging role of biomarkers in diabetic and hypertensive chronic kidney disease. *Curr Diab Rep* 2010; 10:37.
57. Bartha GW, Nugent CA: Routine chest roentgenograms and electrocardiograms. Usefulness in the hypertensive workup. *Arch Intern Med* 1978; 138:1211.
58. Betti I, et al: The role of N-terminal PRO-brain natriuretic peptide and echocardiography for screening asymptomatic left ventricular dysfunction in a population at high risk for heart failure. The PROBE-HF study. *J Card Fail* 2009; 15:377.
59. de Lemos JA, et al: Screening the population for left ventricular hypertrophy and left ventricular systolic dysfunction using natriuretic peptides: Results from the Dallas Heart Study. *Am Heart J* 2009; 157:746.
60. Levy P, et al: Prevalence and predictors of preclinical cardiac dysfunction in asymptomatic hypertensive patients in an urban emergency department. *Acad Emerg Med* 2009; 16:S117.
61. Baumann BM, Abate NL, Cowan RM, Boudreaux ED: Differing prevalence estimates of elevated blood pressure in ED patients using 4 methods of categorization. *Am J Emerg Med* 2008; 26:561.
62. Rhoney D, Peacock WF: Intravenous therapy for hypertensive emergencies, part 1. *Am J Health Syst Pharm* 2009; 66:1343.
63. Devlin JW, et al: Patterns of Antihypertensive Treatment in Patients with Acute Severe Hypertension from a Nonneurologic Cause: Studying the Treatment of Acute hyperTension (STAT) Registry. *Pharmacotherapy* 2010; 30:1087.
64. Perez MI, Musini VM: Pharmacological interventions for hypertensive emergencies. *Cochrane Database Syst Rev* 2008; 1:CD003653.
65. Aronson S, et al: The ECLIPSE trials: Comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients. *Anesth Analg* 2008; 107:1110.
66. Peacock WF, et al: CLUE: A randomized comparative effectiveness trial of IV nicardipine versus labetalol use in the emergency department. *Crit Care* 2011; 15:R157.
67. Grossman E, Ironi AN, Messerli FH: Comparative tolerability profile of hypertensive crisis treatments. *Drug Saf* 1998; 19:99.
68. Grossman E, Messerli FH, Grodzicki T, Kowey P: Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? *JAMA* 1996; 276:1328.
69. Levy P, et al: Treatment of severe decompensated heart failure with high-dose intravenous nitroglycerin: A feasibility and outcome analysis. *Ann Emerg Med* 2007; 50:144.
70. den Uil CA, et al: Dose-dependent benefit of nitroglycerin on microcirculation of patients with severe heart failure. *Intensive Care Med* 2009; 35:1893.
71. Soma J, Angelsen BA, Techn D, Aakhus S, Skjaerpe T: Sublingual nitroglycerin delays arterial wave reflections despite increased aortic "stiffness" in patients with hypertension: A Doppler echocardiography study. *J Am Soc Echocardiogr* 2000; 13:1100.
72. Cotter G, et al: Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. *Lancet* 1998; 351:389.
73. Kloner RA, et al: Time course of the interaction between tadalafil and nitrates. *J Am Coll Cardiol* 2003; 42:1855.
74. Hamilton RJ, Carter WA, Gallagher EJ: Rapid improvement of acute pulmonary edema with sublingual captopril. *Acad Emerg Med* 1996; 3:205.
75. Annane D, et al: Placebo-controlled, randomized, double-blind study of intravenous enalaprilat efficacy and safety in acute cardiogenic pulmonary edema. *Circulation* 1996; 94:1316.
76. Peacock FW 4th, Varon J, Ebrahimi R, Dunbar L, Pollack CV Jr: Clevidipine for severe hypertension in acute heart failure: A VELOCITY trial analysis. *Congest Heart Fail* 2010; 16:55.
77. Chen ZM, et al: Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: Randomised placebo-controlled trial. *Lancet* 2005; 366:1622.
78. Peacock F, et al: Hypertensive heart failure: Patient characteristics, treatment, and outcomes. *Am J Emerg Med* 2011; 29:855.
79. Cheung AT, Hobson RW 2nd: Hypertension in vascular surgery: Aortic dissection and carotid revascularization. *Ann Emerg Med* 2008; 51:S28.
80. Adams HP Jr, et al: Guidelines for the early management of adults with ischemic stroke: A guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Circulation* 2007; 115:e478.
81. Geeganage CM, Bath, PM: Relationship between therapeutic changes in blood pressure and outcomes in acute stroke: A metaregression. *Hypertension* 2009; 54:775.
82. Morgenstern LB, et al: Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2010; 41:2108.
83. Qureshi AI, et al: Effect of systolic blood pressure reduction on hematoma expansion, perihematomal edema, and 3-month outcome among patients with intracerebral hemorrhage: Results from the Antihypertensive Treatment of Acute Cerebral Hemorrhage study. *Arch Neurol* 2010; 67:570.
84. Arima H, et al: Lower treatment blood pressure is associated with greatest reduction in hematoma growth after acute intracerebral hemorrhage. *Hypertension* 2010; 56:852.
85. Anderson CS, et al: Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage: The Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT). *Stroke* 2010; 41:307.
86. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) investigators: Antihypertensive treatment of acute cerebral hemorrhage. *Crit Care Med* 2010; 38:637.
87. Sandset EC, et al: The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): A randomised, placebo-controlled, double-blind trial. *Lancet* 2011; 377:741.
88. Liu-Deryke X, et al: A comparison of nicardipine and labetalol for acute hypertension management following stroke. *Neurocrit Care* 2008; 9:167.
89. Narotam PK, et al: Management of hypertensive emergencies in acute brain disease: Evaluation of the treatment effects of intravenous nicardipine on cerebral oxygenation. *J Neurosurg* 2008; 109:1065.
90. Panciol AM: Hypertension management in neurologic emergencies. *Ann Emerg Med* 2008; 51:S24.
91. Stead LG, et al: Impact of acute blood pressure variability on ischemic stroke outcome. *Neurology* 2006; 66:1878.
92. Peacock WF 4th, Hilleman DE, Levy PD, Rhoney DH, Varon J: A systematic review of nicardipine vs. labetalol for the management of hypertensive crises. *Am J Emerg Med* 2012; 30:981.
93. Immink RV, et al: Cerebral hemodynamics during treatment with sodium nitroprusside versus labetalol in malignant hypertension. *Hypertension* 2008; 52:236.
94. Aiyagari V, Gorelick PB: Management of blood pressure for acute and recurrent stroke. *Stroke* 2009; 40:2251.
95. Bellomo R, et al: Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; 8:R204.
96. Landoni G, et al: Beneficial impact of fenoldopam in critically ill patients with or at risk for acute renal failure: A meta-analysis of randomized clinical trials. *Am J Kidney Dis* 2007; 49:56.
97. Euser AG, Cipolla MJ: Cerebral blood flow autoregulation and edema formation during pregnancy in anesthetized rats. *Hypertension* 2007; 49:334.
98. Euser AG, Cipolla MJ: Magnesium sulfate for the treatment of eclampsia: A brief review. *Stroke* 2009; 40:1169.
99. Vigil-De Gracia P, et al: Severe hypertension in pregnancy: Hydralazine or labetalol. A randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol* 2006; 128:157.
100. Elatrous S, et al: Short-term treatment of severe hypertension of pregnancy: Prospective comparison of nicardipine and labetalol. *Intensive Care Med* 2002; 28:1281.
101. Hackam DG, et al: The 2010 Canadian Hypertension Education Program recommendations for the management of hypertension: Part 2—therapy. *Can J Cardiol* 2010; 26:249.
102. Magid DJ, et al: Comparative effectiveness of angiotensin-converting enzyme inhibitors versus beta-blockers as second-line therapy for hypertension. *Circ Cardiovasc Qual Outcomes* 2010; 3:453.
103. Feldman RD, et al: A simplified approach to the treatment of uncomplicated hypertension: A cluster randomized, controlled trial. *Hypertension* 2009; 53:646.
104. Jamerson K, et al: Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008; 359:2417.
105. Gore JM, et al: Predictors of 90-day readmission among patients with acute severe hypertension. The cross-sectional observational Studying

www.ketabpezeshki.com 66485457-66963820

the Treatment of Acute hyperTension (STAT) study. *Am Heart J* 2010; 160:521.
106. Szczech LA, et al: Acute kidney injury and cardiovascular outcomes in acute severe hypertension. *Circulation* 2010; 121:2183.
107. Levy PD, Cline D: Asymptomatic hypertension in the emergency department: A matter of critical public health importance. *Acad Emerg Med* 2009; 16:1251.
108. Vlcek M, et al: Association between hypertensive urgencies and subsequent cardiovascular events in patients with hypertension. *J Hypertens* 2008; 26:657.
109. Baumann BM, et al: Characteristics and referral of emergency department patients with elevated blood pressure. *Acad Emerg Med* 2007; 14:779.
110. Baumann BM, et al: Provider self-report and practice: Reassessment and referral of emergency department patients with elevated blood pressure. *Am J Hypertens* 2009; 22:604.
111. Zampaglione B, Pascale C, Marchisio M, Cavallo-Perin P: Hypertensive urgencies and emergencies. Prevalence and clinical presentation. *Hypertension* 1996; 27:144.

www.ketabpezeshki.com 66485457-66963820

Chapter 85
Aortic Dissection
Felix K. Ankel

PERSPECTIVE

Aortic dissection is a longitudinal cleavage of the aortic media created by a dissecting column of blood. The term "dissecting aortic aneurysm" has been inaccurately applied to this entity since 1819, when Laënnec first used the term *aneurysme dissequant.* The term *aortic dissection* is preferred to *dissecting aortic aneurysm* because the affected aorta is only rarely aneurysmal. In 1955, DeBakey outlined the principles that remain the basis for the surgical treatment of this entity. Medical treatment of aortic dissection was first advocated in the 1960s and is indicated for certain types of dissections.[1-5] The in-hospital mortality rate for patients treated for aortic dissection is 27%.[5]

Epidemiology

Aortic dissection occurs more often in men and increases with age.[5,6] The incidence and prevalence are difficult to determine because of under-reporting of this condition. Mortality is 1 to 5 per 100,000 population per year. Hypertension is the most common risk factor associated with aortic dissection and is seen in most patients.[5-7] A history of cardiac surgery is present in 18% and a bicuspid aortic valve in 14% of all patients with aortic dissections but more often in proximal dissections.[5,7] Atherosclerosis is rarely involved at the site of dissection. Patients with aortic dissection may have a positive family history.[8]

Aortic dissection is uncommon before age 40 except in association with congenital heart disease, connective tissue disease, or inflammatory vasculitides. As many as 44% of patients with Marfan syndrome develop aortic dissection and account for about 5% of cases.[5,7,9] Women with Marfan syndrome are at particular risk during pregnancy.[10] In patients without connective tissue disease and with an aortic root size of less than 40 mm, pregnancy does not appear to be an independent risk factor.[11,12] Loeys-Dietz syndrome is an autosomal dominant genetic syndrome associated with aortic aneurysms and skeletal features similar to Marfan syndrome. The vascular disease in these patients is aggressive, and the mean age of death is 26 years.[13] Inflammatory vasculitides associated with thoracic aortic disease include Takayasu's arteritis, giant cell arteritis, and Behçet's disease.[1] Acute aortic dissection also occurs with stimulant use, exertion, cardiac surgery, or intra-aortic balloon pump insertion.[5]

Blunt trauma from a high-speed deceleration injury usually causes traumatic aortic rupture, which is an entity distinctly different from aortic dissection (see Chapter 45).

PRINCIPLES OF DISEASE

Anatomy and Physiology

With each contraction the heart swings from side to side, resulting in flexion of both the ascending aorta and the descending aorta. The descending aorta flexes just distal to the left subclavian artery, where the mobile aorta is tethered. At an average of 70 heartbeats per minute, this sequence occurs about 37 million times a year, causing repetitive stress on the aorta.

The aortic wall has three distinct layers: the intima, the media, and the adventitia. The media is composed of elastic tissue and smooth muscle. Dissection occurs through a degeneration of the media characterized by loss of smooth muscle cells and elastic tissue, accompanied by scarring, fibrosis, and hyalin-like changes. Pathologic studies show that this process is neither cystic nor necrotic; therefore the old term *cystic medial necrosis* is no longer used.

Pathophysiology

Medial degeneration, previously thought to be specific for aortic dissection, is now considered to be part of normal aging, although it is augmented by hypertension and with aortic dissection. The anatomic differences between the "normal" aorta and a dissection are quantitative rather than qualitative. Although medial degeneration was initially thought to be noninflammatory, more recent evidence suggests that inflammatory cell infiltration results from medial degeneration.[14]

The repetitive hydrodynamic forces produced by the ejection of blood into the aorta with each cardiac cycle contribute to weakening of the aortic intima and to medial degeneration. These hydrodynamic forces primarily affect the ascending aorta. Sustained hypertension intensifies these forces and results in an increase in medial degeneration. A bicuspid valve, present in 1 to 2% of the population, is the most common congenital abnormality affecting the aortic valve and proximal aorta.[15,16] A bicuspid aortic valve may disrupt laminar flow and reorient the flow of blood toward the aortic wall, producing local injury. In Marfan and Ehlers-Danlos syndromes, normal hydrodynamic forces act on an aortic media that is already weakened.

As a result of medial degeneration and repeated flexion of the aorta, hydrodynamic stress tears the aortic intima, and a column of blood gains access into the aortic media. An alternative theory suggests that these forces damage the vasa vasorum of the aorta,

www.ketabpezeshki.com 66485457-66963820

which rupture and hemorrhage into the aortic media, which may explain the absence of an intimal tear in some cases of dissection. Regardless of which of these theories is correct, the depth of penetration into the media and the distance and direction of dissection are at least partially determined by the degree of medial degeneration.

Once a dissecting hematoma is established in the media, migration of the hematoma occurs in an antegrade or retrograde fashion, or both, forming a "false lumen." The false lumen forms in the outer half of the media and propagates until it ruptures back into the "true lumen" of the aorta, resulting in a rare "spontaneous cure," or through the adventitia into the pericardial sac or pleural cavity. Because the outer wall of the aorta that contains the hematoma is thin, rupture is much more likely to occur to the outside. The most important factors favoring continued dissection of the aorta are (1) the degree of elevation of blood pressure and (2) the steepness (slope) of the pulse wave (upstroke pattern on apex cardiogram, dP/dt).

Classification

Anatomic classification is important for diagnosis and therapy. The *Stanford classification* is based on the involvement of the ascending aorta. Type A dissections involve the ascending aorta; type B dissections do not (Fig. 85-1). Dissections that involve the ascending aorta are more often lethal than those limited to the distal aorta and call for a different therapeutic approach. In the International Registry of Acute Aortic Dissection (IRAD), 62% of dissections are type A and 38% are type B.[3-5] Patients with distal dissections tend to be older, heavy smokers with chronic lung disease and more often have generalized atherosclerosis and hypertension compared with patients who have proximal aortic dissections.

Two other aortic conditions are closely related to aortic dissection: intramural hemorrhage (IMH) and penetrating aortic ulcer (PAU).[17,18] Both groups of patients have clinical symptoms and management recommendations similar to those for patients with aortic dissection. An IMH is a contained hematoma within the aortic wall and occurs in about 10% of aortic dissections.[5] Rupture of the vasa vasorum is believed to be the initial event. Penetrating atherosclerotic ulcers of the aorta occur in older hypertensive patients with evidence of coronary artery disease. Computed tomography (CT) shows a focal ulceration without dissection, most commonly in the distal descending aorta. The progression of penetrating ulcers results in progressive aortic enlargement with saccular and fusiform aneurysm formation. Patients can have both an intramural hematoma and a penetrating atherosclerotic ulcer.[19]

A dissection is *acute* if it is of less than 2 weeks' duration and *chronic* if has been present for more than 2 weeks.

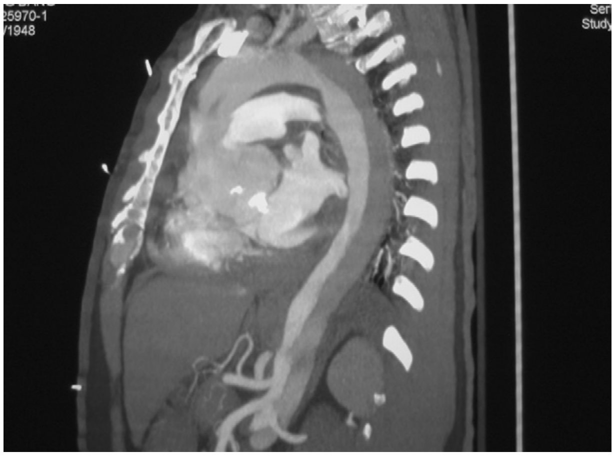


Figure 85-1. Computed tomographic reconstruction of Stanford type B or DeBakey type III dissection distal to the subclavian artery.

CLINICAL FEATURES

History

Pain is by far the most common presenting complaint, affecting more than 90% of patients.[5,7,9] Most cases of painless aortic dissection are chronic in nature.[7] The pain is usually excruciating, occurs abruptly, is most severe at onset, and is typically described as "sharp" more often than "tearing" or "ripping."[4] A family history of thoracic aortic disease may be reported.[8]

The location of the pain may help localize the dissection. Anterior chest pain is associated with the ascending aorta, neck and jaw pain with the aortic arch, pain in the interscapular area with the descending thoracic aorta, and pain in the lumbar area or abdomen with involvement below the diaphragm. Migration of the pain consistent with propagation of the dissection suggests aortic dissection but occurs in only 17% of cases.[5] The onset of aortic dissection is often accompanied by visceral pain symptoms, such as diaphoresis, nausea, vomiting, lightheadedness, and severe apprehension.

Syncope occurs early in aortic dissection in approximately 9% of cases and may be the sole presentation in some patients.[5,9] It most often heralds dissection into the pericardium, causing pericardial tamponade, but may occur from transient interruption of blood flow to the cerebral vasculature. Other causes of syncope from aortic dissection are hypovolemia, excessive vagal tone, and cardiac conduction abnormalities. Patients with aortic dissection and syncope have a higher mortality.[20] Neurologic symptoms such as focal weakness or change in mental status occur in up to 17% of cases.[5,7,9]

Physical Examination

The presentation varies greatly, depending on the patient and the location and extent of the dissection. In general, the patient appears apprehensive. Most of the patients have a history of chronic hypertension that may be exacerbated by a catecholamine release related to the acute event. Severe hypertension refractory to medical therapy may occur if the dissection involves the renal arteries with subsequent renin release. If hypotension is present, either the dissection has progressed back into the pericardium, with resulting pericardial tamponade, or hypovolemia has occurred from rupture through the adventitia. *Pseudohypotension,* a condition in which the blood pressure in the arms is low or unobtainable and the central arterial pressure is normal or high, may be present. This results from the interruption of blood flow to the subclavian arteries.

Aortic regurgitation occurs in up to 32% of patients and is more common with type A dissections.[5,7] The murmur of aortic insufficiency may have a musical, vibrating quality with variable intensity, and congestive heart failure may develop. The patient with presumed aortic dissection should be examined carefully for findings that suggest hemorrhage into the pericardium or tamponade, such as jugular venous distention, muffled heart sounds, tachycardia, and hypotension.

When the integrity of one of the branches of the aorta is compromised, the expected ischemic findings occur. Pulse deficits and discrepancies in blood pressure between limbs can be helpful if present but have a sensitivity of only around 30%.[5,7,9,21] Usually these are present in the upper extremities and result from involvement of one or both of the subclavian arteries.

www.ketabpezeshki.com 66485457-66963820

Table 85-1 Characteristics of Aortic Dissection from the International Registry of Acute Aortic Dissection[4]

	CHEST PAIN (%)	SYNCOPE (%)	AORTIC INSUFFICIENCY MURMUR (%)	PULSE DEFICIT (%)	NORMAL CXR (%)	WIDENED MEDIASTINUM ON CXR (%)	NORMAL ECG (%)	ISCHEMIA (%)	LEFT VENTRICULAR HYPERTROPHY (%)
All (N = 464)	73	9	32	15	12	62	31	15	26
Type A (n = 289)	79	13	44	19	11	63	31	17	25
Type B (n = 175)	63	4	12	9	16	56	32	13	32

CXR, chest radiographic film; *ECG,* electrocardiogram.

Obstruction of one or both common iliac or superficial femoral arteries may produce pulse deficits in the lower extremities. Arterial obstruction may occur by either of two mechanisms. An intimal flap produced by the dissection may cover the true lumen of a branch vessel, or the dissecting hematoma may compress an adjacent true lumen. Frequent reexamination may detect transient pulse deficits.

Neurologic findings are related to the site of blood flow interruption. Proximal dissections are a more frequent cause of strokes or coma. Stroke treatment with a fibrinolytic agent in the patient with aortic dissection can be fatal. Distal dissections occluding the anterior spinal artery commonly cause ischemic paraparesis or ischemic peripheral neuropathy.[7]

In up to 3% of cases, a proximal dissection can dissect into the ostium of a coronary artery, most frequently the right coronary artery, and cause an acute myocardial infarction (MI), usually inferior to posterior.[5] Failure to identify the inciting aortic dissection with incorrect administration of a fibrinolytic agent occurs in about 0.1 to 0.2% of MIs.[22] Distal extension of aortic dissections into the abdomen can cause mesenteric ischemia, renal failure, femoral pulse deficits, and lower extremity ischemia.[23]

DIAGNOSTIC STRATEGIES

Routine laboratory tests are of little value in the diagnosis of aortic dissection. The hemoglobin usually is normal or unchanged from the patient's baseline. The leukocyte count is commonly mildly elevated. Recently, there has been increasing interest in the biochemical diagnosis of acute aortic dissection, including C-reactive protein, myosin heavy chain, soluble elastin, and D-dimer levels.[24] D-dimer is the most readily available plasma marker and has the most diagnostic promise. Several authors have suggested that a negative D-dimer testing result makes a diagnosis of aortic dissection unlikely, but there is insufficient evidence to support use of a D-dimer as the sole screening test for aortic dissection, and 2010 guidelines from several major specialty societies recommend against this practice.[1,25-31] Studies using a combination of a clinical pretest probability rule and D-dimer testing are needed.[32]

Electrocardiography

The electrocardiogram (ECG) is often useful in excluding MI; however, 15% of patients with aortic dissection may have ECG abnormalities suggesting ischemia.[5] Proximal dissections that involve the right coronary artery may show an inferior wall MI, and the constellation of symptoms and signs (pain, diaphoresis, hypotension) may be difficult to distinguish from those associated with primary acute MI. The ECG typically shows left ventricular hypertrophy in 26%, reflecting long-standing hypertension. Other findings include nonspecific ST-T wave changes and prior Q wave infarction. No abnormalities are noted on the ECG in 31% of cases (Table 85-1).[5]

Table 85-2 Sensitivities and Specificities of Imaging Modalities for Diagnosing Aortic Dissection

TEST	TEE	HELICAL CT	MRI
Sensitivity (%)	98	100	98
Specificity (%)	95	98	98

From Shiga T, Wajima Z, Apfel CC, et al: Diagnostic accuracy of transesophageal echocardiography, helical computed tomography, and magnetic resonance imaging for suspected thoracic aortic dissection: Systematic review and meta-analysis. Arch Intern Med 166:1350-1356, 2006.

CT, computed tomography; *MRI,* magnetic resonance imaging; *TEE,* transesophageal echocardiography.

Chest Radiography

Routine chest radiographic studies are abnormal in 80 to 90% of patients, but the abnormalities are nonspecific and rarely diagnostic.[5,7,9,33] Mediastinal widening occurs in the majority of cases[5,7]; may occur in the ascending aorta, the aortic arch, or the descending portion of the thoracic aorta; and may be difficult to differentiate from the aortic tortuosity that is associated with chronic hypertension. A plain chest radiograph is inadequate for ruling out aortic dissection. Up to 12% of patients with aortic dissection have a normal chest radiograph (see Table 85-1).[5,9]

Other helpful radiographic signs include a double-density appearance of the aorta, suggesting true and false channels, a localized bulge along a normally smooth aortic contour, a disparity in the caliber between the descending and ascending aorta, obliteration of the aortic knob, and displacement of the trachea or nasogastric tube to the right by the dissection. Previous chest radiographs when available, are useful for comparison.

Echocardiography

Transthoracic echocardiography (TTE) is an insensitive tool for detecting aortic dissection because it does not visualize the aortic arch or much of the descending aorta, and imaging quality may not be optimal because of the patient's body habitus. While more sensitive imaging tests are being scheduled, however, TTE can provide valuable information about pericardial effusion or aortic regurgitation and can help determine whether cardiac tamponade is the cause of hypotension in a patient with aortic dissection.[34]

Transesophageal echocardiography (TEE) is highly sensitive (Table 85-2) for the diagnosis of aortic dissection.[35,36] The proximity of the esophagus to the aorta and the ability to use higher transducer frequencies help the operator to visualize the entire aorta and to detect pericardial effusion and aortic regurgitation.[35] TEE can be quickly performed at the patient's bedside with sedation or light anesthesia and requires no radiation or contrast agent injection. Visualization of the distal ascending aorta and proximal arch used to be difficult because of the interposition of the air-filled trachea and left mainstem bronchus, but

www.ketabpezeshki.com 66485457-66963820

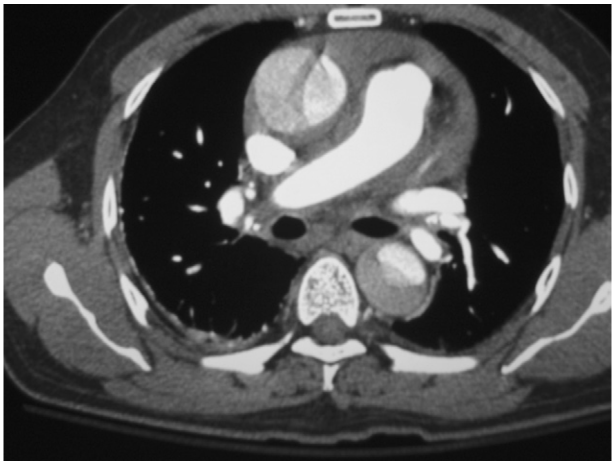


Figure 85-2. Computed tomography scan demonstrating the true lumen and false lumen.

evaluation of this "blind spot" has been aided by biplane and multiplane probes.[35]

The diagnostic accuracy of TEE depends on the experience and availability of the echocardiographer. It is the primary diagnostic method in many institutions for detecting aortic dissection and is the procedure of choice in unstable patients,[5] in whom it can be performed in the resuscitation area of the ED, or in the operating room coincident with induction of anesthesia.

Computed Tomography

CT aortography is a reliable test for diagnosing aortic dissection (see Table 85-2) and is the diagnostic test of choice in most institutions.[5] Findings suggestive of aortic dissection include dilation of the aorta, identification of an intimal flap, and the clear demonstration of both the false and true lumina (Fig. 85-2). Dynamic scanning, in which rapid scans are obtained at multiple levels immediately after a bolus injection of an intravenous contrast agent, improves the accuracy of the CT scan in the diagnosis of aortic dissection by allowing detection of differential filling rates in the true and false lumina (see Fig. 85-1). Dynamic scanning performed with helical CT improves sensitivity and specificity.[37] Sixty-four–slice multidetector computed tomography (MDCT) may soon alter the approach to chest pain in the emergency department (ED). MDCT may reliably evaluate for coronary artery disease,[38,39] pulmonary embolus, and aortic dissection as a "triple" scan.[40,41]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is an appealing option in the detection of low-grade aortic dissection in stable patients in whom the diagnosis is uncertain. Sensitivity and specificity are excellent (see Table 85-2).[42] MRI shows the site of intimal tear, type and extent of dissection, presence of aortic insufficiency, and differential flow velocities in the true and false channels and in the aortic side branches. It requires no contrast material or ionizing radiation and is noninvasive. It is particularly useful in the evaluation of chronic aortic dissection, in the follow-up of postoperative patients, and for monitoring nonoperative patients for progression of the dissection. Its availability, however, is limited, and it is difficult to perform in unstable patients.

Choice of Diagnostic Test

Although aortic dissection can be suspected on the basis of history and physical examination, diagnostic imaging is necessary for the diagnosis to be established. With a mortality rate in excess of 1% per hour after the onset of aortic dissection, a diagnostic study should be performed as soon as feasible.[6] Frequently, more than one test is required to make the diagnosis and to assess associated complications.

The clinical strategy should consider (1) the technology available at the institution, (2) the institution-specific sensitivities and specificities for the diagnostic tests, (3) the benefits of diagnosing nondissection causes of chest pain, and (4) the ease of performing each test, especially "after hours."[43] Some tests (e.g., CT, MRI, aortography) may require moving a potentially unstable patient outside the ED. In IRAD, the initial choice of diagnostic test was CT in 61%, TTE or TEE in 33%, aortography in 4%, and MRI in 2% of patients.[5] "Real-world" sensitivities of diagnostic tests in IRAD were CT 93%, TEE 88%, aortography 87%, and MRI 100%; and patients averaged 1.85 imaging studies.[44] A recent meta-analysis suggested that TEE, helical CT, and MRI are of similar diagnostic value in ruling aortic dissection in or out.[45]

Unless institutional circumstances do not permit, contrast CT aortography is recommended as the test of first choice. In patients with renal failure or contrast allergy, or for those considered too unstable to undergo CT scan, TEE is recommended. If the patient has a diagnostic (i.e., positive) TTE, the diagnosis is established, but an additional confirmatory study may or may not be required, depending on the preference of the physician who will be assuming care of the patient. A negative TTE does not exclude dissection, and further imaging is indicated in such cases.

DIFFERENTIAL CONSIDERATIONS

The differential diagnosis for the patient with symptoms suggestive of aortic dissection is extensive. Signs and symptoms associated with aortic dissection vary and depend on the extent of aortic and branch vessel involvement. Patients with the ultimate diagnosis of aortic dissection are often initially thought to have other conditions such as myocardial ischemia, congestive heart failure, or pulmonary embolus.[7] Several clinical syndromes are particularly suggestive of aortic dissection—chest pain that is of sudden onset, migratory pain, chest pain with concomitant neurologic deficits or syncope, and chest pain with pulse deficits.[46]

Although chest pain is the most common symptom of aortic dissection, it is also the most common presenting complaint of at least three other serious and more common clinical entities: acute MI, pulmonary embolus, and pericarditis. An ECG can be helpful in excluding MI, although aortic dissection and MI may coexist as a result of the dissection proceeding retrograde to the ostium of a coronary artery and causing infarction. In cases in which aortic dissection is excluded, CT may reveal other abnormalities that explain a patient's presentation (e.g., pulmonary embolus). TEE is helpful in identifying causes of chest pain other than aortic dissection (e.g., cardiac ischemia).

When the initial presentation of the aortic dissection is pain or dysfunction in an extremity resulting from disruption of the blood supply, peripheral neurologic diagnoses should be included in the differential diagnosis. An aortic dissection may involve the carotid artery and may initially mimic a primary central nervous system lesion such as a stroke. The diagnosis of aortic dissection should be considered in any patient with a new diagnosis of pericardial effusion, pericardial tamponade, or aortic insufficiency.

MANAGEMENT

Emergency Department

Early therapy for aortic dissection is critical and should be initiated while diagnostic tests are being performed.[47] Opioids should be administered in adequate doses to control pain and decrease

www.ketabpezeshki.com 66485457-66963820

sympathetic tone.[48] Patients with aortic dissections are typically hypertensive. The two goals of medical management are to (1) reduce blood pressure and (2) decrease the rate of rise of the arterial pulse (dP/dt) to diminish shearing forces. A target blood pressure of 100 to 120 mm Hg systolic and a heart rate below 60 beats/min are recommended.[1,49] Beta-adrenergic blockers are the cornerstone of aortic dissection management and are effective when used as the sole agent (in addition to opioid analgesia for pain). Because vasodilators such as sodium nitroprusside or fenoldopam reflexively increase the heart rate and may also increase the dP/dt, they necessitate concomitant use of a beta-blocker and so are a more complicated form of therapy. Initial therapy with either esmolol or labetalol, as described later, and use of opioid analgesia, such as morphine or fentanyl, for pain are recommended.

Recommended Therapy

Esmolol and labetalol are titratable short-acting beta-blockers that can be used as monotherapy for hemodynamic control in aortic dissection. Esmolol is an ultra-short-acting beta-blocker that is given as an initial bolus of 500 μg/kg, followed by an infusion of 50 to 200 μg/kg/min. Labetalol has both alpha- and beta-blocking activity and is given as an initial series of 20-mg intravenous boluses every 5 to 10 minutes, incrementally increased to 80 mg intravenously (IV) until a target heart rate of 60 has been reached or a total of 300 mg has been given. A maintenance infusion of labetalol is then given at 1 to 2 mg/min. If a patient is normotensive, a beta-blocker should still be used to lower the dP/dt and maintain a heart rate of 60. In patients with a history of chronic obstructive pulmonary disease or at risk for bronchospasm, a selective beta-blocker, such as metoprolol or atenolol, should be considered.

Alternative Agents

Sodium nitroprusside was widely used before esmolol and labetalol became available and is a reasonable agent to use but necessitates concomitant use of a beta-blocker to mitigate reflex tachycardia and requires more effort to prepare and administer. The initial infusion is 0.5 to 3 μg/kg/min, and the infusion is adjusted to reach the same hemodynamic goals described earlier.

The calcium channel blocker nifedipine is not recommended to treat aortic dissection. Nifedipine has minimal inotropic or chronotropic effects and may reflexively stimulate sympathetic activity and increase shear stress on the aortic wall. Intravenous nitroglycerin is often used initially in patients with hypertensive chest pain and possible or uncertain aortic dissection. Nitroglycerin is a less effective arterial dilator than nitroprusside and less desirable than nitroprusside for the treatment of patients with aortic dissection. Like nitroprusside, nitroglycerin should be accompanied by a beta-blocker. Some physicians prefer an infusion of fenoldopam over nitroprusside, but this has not been specifically studied in patients with aortic dissection.

Patients with hypotension secondary to aortic rupture or pericardial tamponade should be resuscitated with intravenous fluids and immediately transported to the operating room if they are to have a chance to survive. Blood pressure should be measured in all four limbs, if necessary, to ensure that the condition is not a pseudohypotension caused by an intimal flap obstructing the extremity in which the blood pressure is measured. In patients with electromechanical dissociation or marked hypotension, pericardiocentesis may raise the blood pressure pending definitive surgery.

Surgery

Type A acute aortic dissections require prompt surgical treatment. The aortic segment containing the original intimal tear is resected when possible, with graft replacement of the ascending aorta to redirect blood into the true lumen. If aortic insufficiency is present, it can be corrected through aortic valve resuspension or replacement. Patients with type A dissections have an in-hospital mortality rate of 27% when treated surgically versus an in-hospital mortality of 56% when treated medically.

Definitive treatment of type B acute aortic dissections is less clear.[50,51] These patients in general tend to be worse surgical risks. Uncomplicated distal dissections have traditionally been treated with blood pressure control, and patients have an in-hospital mortality of 10% when treated in this manner.[4] Surgery has been reserved for patients who have persistent pain, uncontrolled hypertension, occlusion of a major arterial trunk, frank aortic leaking or rupture, or development of a localized aneurysm. These patients have an in-hospital, 30-day mortality rate of 32%. A "deadly triad" of absence of chest pain, hypotension, and branch vessel involvement is an independent predictor of in-hospital death.[4]

Interventional Therapy

Interventional stent-graft and fenestration techniques are replacing surgery for complicated type B dissections in some centers, especially for patients with renal and mesenteric ischemia.[52,53] Patients treated with interventional therapy have an in-hospital mortality rate of 6.5%.[3] Interventional therapy for stable type B dissections is currently under study, and treatment decisions should rest with the primary treating physician.[54,55] In general, interventional endovascular techniques are not applicable to type A dissections.

DISPOSITION

Patients with chronic aortic dissection have already survived their period of greatest mortality risk and are usually treated by blood pressure control and close monitoring unless complications lead to surgery. Regardless of the type of definitive therapy, all patients who have sustained and survived an aortic dissection require careful long-term treatment. Major complications that may occur with time are redissection, the development of a localized aneurysm, and progressive aortic insufficiency.

KEY CONCEPTS

- Most patients with aortic dissection have chest pain, typically of sudden onset, sharp, and migratory. Chest pain associated with neurologic symptoms or syncope increases the likelihood of aortic disease.
- Physical examination findings may include pulse deficit, aortic insufficiency murmur, or neurologic findings, but often the physical examination is not diagnostic, and imaging is essential to establish or exclude the diagnosis of dissection.
- Of the confirmatory tests, CT aortography is recommended. Transesophageal echocardiography also is an excellent test and can be used when CT is not available or for patients with contrast allergy, renal insufficiency, or critical illness that precludes CT scan.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Hiratzka LF, et al: 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: Executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Circulation* 2010; 121:e266-e369.
2. Eagle KA, Isselbacher EM, DeSanctis RW, International Registry for Aortic Dissection (IRAD) Investigators: Cocaine-related aortic dissection in perspective. *Circulation* 2002; 105:1529-1530.
3. Mehta RH, et al: Predicting death in patients with acute type a aortic dissection. *Circulation* 2002; 105:200-206.
4. Suzuki T, et al: Clinical profiles and outcomes of acute type B aortic dissection in the current era: Lessons from the international registry of aortic dissection (IRAD). *Circulation* 2003; 108(Suppl 1):II312-II317.
5. Hagan PG, et al: The international registry of acute aortic dissection (IRAD): New insights into an old disease. *JAMA* 2000; 283:897-903.
6. Mészáros I et al: Epidemiology and clinicopathology of aortic dissection. *Chest* 2000; 117:1271-1278.
7. Spittell PC, et al: Clinical features and differential diagnosis of aortic dissection: Experience with 236 cases (1980 through 1990). *Mayo Clin Proc* 1993; 68:642-651.
8. Hasham SN, et al: Nonsyndromic genetic predisposition to aortic dissection: A newly recognized, diagnosable, and preventable occurrence in families. *Ann Emerg Med* 2004; 43:79-82.
9. Klompas M: Does this patient have an acute thoracic aortic dissection? *JAMA* 2002; 287:2262-2272.
10. Elkayam U, Ostrzega E, Shotan A, Mehra A: Cardiovascular problems in pregnant women with the Marfan syndrome. *Ann Intern Med* 1995; 123:117-122.
11. Nienaber CA, Eagle KA: Aortic dissection: New frontiers in diagnosis and management: Part I: From etiology to diagnostic strategies. *Circulation* 2003; 108:628-635.
12. Immer FF, et al: Aortic dissection in pregnancy: Analysis of risk factors and outcome. *Ann Thorac Surg* 2003; 76:309-314.
13. Loeys BL, et al: Aneurysm syndromes caused by mutations in the TGF-beta receptor. *N Engl J Med* 2006; 355:788-798.
14. He R, et al: Characterization of the inflammatory and apoptotic cells in the aortas of patients with ascending thoracic aortic aneurysms and dissections. *J Thorac Cardiovasc Surg* 2006; 131:671-678.
15. Braverman AC, et al: The bicuspid aortic valve. *Curr Probl Cardiol* 2005; 30:470-522.
16. Loscalzo ML, et al: Familial thoracic aortic dilation and bicommissural aortic valve: A prospective analysis of natural history and inheritance. *Am J Med Genet A* 2007; 143:1960-1967.
17. Nienaber CA, Sievers HH: Intramural hematoma in acute aortic syndrome: More than one variant of dissection? *Circulation* 2002; 106:284-285.
18. von Kodolitsch Y, et al: Intramural hematoma of the aorta: Predictors of progression to dissection and rupture. *Circulation* 2003; 107:1158-1163.
19. Ganaha F, et al: Prognosis of aortic intramural hematoma with and without penetrating atherosclerotic ulcer: A clinical and radiological analysis. *Circulation* 2002; 106:342-348.
20. Nallamothu BK, et al: Syncope in acute aortic dissection: Diagnostic, prognostic, and clinical implications. *Am J Med* 2002; 113:468-471.
21. Teece S, Hogg K: Best evidence topic report. Peripheral pulses to exclude thoracic aortic dissection. *Emerg Med J* 2004; 21:589.
22. Kamp TJ, Goldschmidt-Clermont PJ, Brinker JA, Resar JR: Myocardial infarction, aortic dissection, and thrombolytic therapy. *Am Heart J* 1994; 128(6 Pt 1):1234-1237.
23. Pacifico L, Spodick D: ILEAD—ischemia of the lower extremities due to aortic dissection: The isolated presentation. *Clin Cardiol* 1999; 22:353-356.
24. Wen D, Zhou XL, Li JJ, Hui RT: Biomarkers in aortic dissection. *Clin Chim Acta* 2011; 412:688-695.
25. Elefteriades JA, Barrett PW, Kopf GS: Litigation in nontraumatic aortic diseases—a tempest in the malpractice maelstrom. *Cardiology* 2008; 109:263-272.
26. Marill KA: Serum D-dimer is a sensitive test for the detection of acute aortic dissection: A pooled meta-analysis. *J Emerg Med* 2008; 34:367-376.
27. Shimony A, Filion KB, Mottillo S, Dourian T, Eisenberg MJ: Meta-analysis of usefulness of D-dimer to diagnose acute aortic dissection. *Am J Cardiol* 2011; 107:1227-1234.
28. Suzuki T, et al: Diagnosis of acute aortic dissection by D-dimer: The international registry of acute aortic dissection substudy on biomarkers (IRAD-bio) experience. *Circulation* 2009; 119:2702-2707.
29. Fan QK, et al: Evaluation of D-dimer in the diagnosis of suspected aortic dissection. *Clin Chem Lab Med* 2010; 48:1733-1737.
30. Hazui H, et al: Young adult patients with short dissection length and thrombosed false lumen without ulcer-like projections are liable to have false-negative results of D-dimer testing for acute aortic dissection based on a study of 113 cases. *Circ J* 2006; 70:1598-1601.
31. Ohlmann P, et al: Lower circulating Sta-Liatest D-Di levels in patients with aortic intramural hematoma compared with classical aortic dissection. *Crit Care Med* 2009; 37:899-901.
32. Carrier M, et al: VIDAS D-dimer in combination with clinical pre-test probability to rule out pulmonary embolism. A systematic review of management outcome studies. *Thromb Haemost* 2009; 101:886-892.
33. Hogg K, Teece S: Best evidence topic report. The sensitivity of a normal chest radiograph in ruling out aortic dissection. *Emerg Med J* 2004; 21:199-200.
34. Blaivas M, Sierzenski PR: Dissection of the proximal thoracic aorta: A new ultrasonographic sign in the subxiphoid view. *Am J Emerg Med* 2002; 20:344-348.
35. Keren A, et al: Accuracy of biplane and multiplane transesophageal echocardiography in diagnosis of typical acute aortic dissection and intramural hematoma. *J Am Coll Cardiol* 1996; 28:627-636.
36. Willens HJ, Kessler KM: Transesophageal echocardiography in the diagnosis of diseases of the thoracic aorta: Part 1. Aortic dissection, aortic intramural hematoma, and penetrating atherosclerotic ulcer of the aorta. *Chest* 1999; 116:1772-1779.
37. Sommer T, et al: Aortic dissection: A comparative study of diagnosis with spiral CT, multiplanar transesophageal echocardiography, and MR imaging. *Radiology* 1996; 199:347-352.
38. Gallagher MJ, et al: The diagnostic accuracy of 64-slice computed tomography coronary angiography compared with stress nuclear imaging in emergency department low-risk chest pain patients. *Ann Emerg Med* 2007; 49:125-136.
39. Goldstein JA, et al: A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. *J Am Coll Cardiol* 2007; 49:863-871.
40. Limkakeng AT, Halpern E, Takakuwa KM: Sixty-four-slice multidetector computed tomography: The future of ED cardiac care. *Am J Emerg Med* 2007; 25:450-458.
41. Gallagher MJ, Raff GL: Use of multislice CT for the evaluation of emergency room patients with chest pain: The so-called "triple rule-out." *Catheter Cardiovasc Interv* 2008; 71:92-99.
42. Laissy JP, et al: Thoracic aortic dissection: Diagnosis with transesophageal echocardiography versus MR imaging. *Radiology* 1995; 194:331-336.
43. Sarasin FP, Louis-Simonet M, Gaspoz JM, Junod AF: Detecting acute thoracic aortic dissection in the emergency department: Time constraints and choice of the optimal diagnostic test. *Ann Emerg Med* 1996; 28:278-288.
44. Moore AG, et al: Choice of computed tomography, transesophageal echocardiography, magnetic resonance imaging, and aortography in acute aortic dissection: International registry of acute aortic dissection (IRAD). *Am J Cardiol* 2002; 89:1235-1238.
45. Shiga T, Wajima Z, Apfel CC, Inoue T, Ohe Y: Diagnostic accuracy of transesophageal echocardiography, helical computed tomography, and magnetic resonance imaging for suspected thoracic aortic dissection: Systematic review and meta-analysis. *Arch Intern Med* 2006; 166:1350-1356.
46. Bushnell J, Brown J: Evidence-based emergency medicine/rational clinical examination abstract. Clinical assessment for acute thoracic aortic dissection. *Ann Emerg Med* 2005; 46:90-92.
47. Grossman E, Ironi AN, Messerli FH: Comparative tolerability profile of hypertensive crisis treatments. *Drug Saf* 1998; 19:99-122.
48. Nienaber CA, Eagle KA: Aortic dissection: New frontiers in diagnosis and management: Part II: Therapeutic management and follow-up. *Circulation* 2003; 108:772-778.
49. Ince H, Nienaber CA. Diagnosis and management of patients with aortic dissection. *Heart* 2007; 93:266-270.

www.ketabpezeshki.com 66485457-66963820

50. Elefteriades JA, et al: Management of descending aortic dissection. *Ann Thorac Surg* 1999; 67:2002-2005; discussion 2014-2019.
51. Coady MA, et al: Surgical management of descending thoracic aortic disease: Open and endovascular approaches: A scientific statement from the American Heart Association. *Circulation* 2010; 121:2780-2804.
52. Dake MD, et al: Endovascular stent-graft placement for the treatment of acute aortic dissection. *N Engl J Med* 1999; 340:1546-1552.
53. Shimono T, et al: Transluminal stent-graft placements for the treatments of acute onset and chronic aortic dissections. *Circulation* 2002; 106(12 Suppl 1):I241-I217.
54. Svensson LG, et al: Expert consensus document on the treatment of descending thoracic aortic disease using endovascular stent-grafts. *Ann Thorac Surg* 2008; 85(Suppl 1):S1-S41.
55. Nienaber CA, et al: Randomized comparison of strategies for type B aortic dissection: The INvestigation of STEnt grafts in Aortic Dissection (INSTEAD) trial. *Circulation* 2009; 120:2519-2528.

www.ketabpezeshki.com 66485457-66963820

Chapter 86

Abdominal Aortic Aneurysm

Howard A. Bessen and Cori McClure Poffenberger

PERSPECTIVE

Abdominal aortic aneurysm (AAA) is a true aneurysm, meaning a localized dilation of the aorta caused by weakening of its wall, and involving all three layers (intima, media, and adventitia) of the arterial wall (Fig. 86-1). A false aneurysm, or pseudoaneurysm, is a collection of flowing blood that communicates with the arterial lumen but is not enclosed by the normal vessel wall; it is contained only by the adventitia or surrounding soft tissue. Pseudoaneurysms can arise from a defect in the arterial wall or a leaking anastomosis after AAA repair.

AAA is distinct from aortic dissection, which sometimes is incorrectly called a "dissecting aortic aneurysm." In aortic dissection, blood enters the media of the aorta and splits (dissects) the aortic wall (see Chapter 85). Aortic aneurysm and aortic dissection are very different diseases, with different clinical presentations, complications, diagnostic methods, and treatments.

An aneurysm can develop in any segment of the aorta, but most involve the aorta below the renal arteries. The diameter of the normal adult infrarenal aorta is approximately 2 cm, and a diameter of 3 cm or more defines an AAA.[1]

Epidemiology

AAA is a disease of aging, and the prevalence of AAA is expected to increase as the population of elderly patients grows. AAA is rare before the age of 50 years but is found in 2 to 5% of men older than 50.[2,3] The average age at the time of diagnosis is 65 to 70, and men are affected much more often than women. The patient often has concomitant atherosclerotic occlusive disease of the coronary, carotid, or peripheral vessels, which may influence the clinical presentations, complications, and management.

Several risk factors for the development of an AAA have been established, but risk factors are populational, not individual characteristics. An AAA can be found in 5 to 10% of elderly men who are screened with ultrasonography[4,7] and in an even higher percentage of patients with coronary artery disease or peripheral vascular disease.[4,6-8] The presence or absence of risk factors should not strongly influence diagnostic considerations in any individual patient (Table 86-1). A family history of an AAA is a very strong risk factor; those with an affected first-degree relative have a markedly increased risk of developing an AAA.[9] Smoking is also a significant risk factor for AAA.[10] Although awareness of high-risk groups can speed the recognition of AAAs, the consideration of AAA should not be restricted to patients in these groups. Recent data suggest that women may experience delays in diagnosis and worse operative mortality after ruptured AAA,[11] and that up to half of AAAs in the United States occur in women, nonsmokers, and those younger than 65.[12]

PRINCIPLES OF DISEASE

Pathophysiology

AAAs have traditionally been attributed to atherosclerosis, but patients with advanced atherosclerosis have occlusive disease, not aneurysms. Recent data suggest that patients with AAA have biochemical abnormalities leading to the loss of elastin and collagen, the major structural components of the aortic wall.[13] The propensity to form aneurysms may have a genetic basis, but the exact mode of inheritance is uncertain. The Society for Vascular Surgery recommends labeling the typical degenerative AAA as "nonspecific," rather than "atherosclerotic," to reflect this uncertainty surrounding the etiology.

AAAs may also have specific causes, such as infection, trauma, connective tissue diseases, and arteritis. However, such aneurysms are rare compared with nonspecific, degenerative aneurysms.

Natural History

AAAs progressively enlarge, ultimately resulting in rupture of the aneurysm and fatal hemorrhage. Although other complications are possible, by far the most common and most critical is rupture.

The most important factor determining the risk of rupture is the size of the aneurysm.[14-17] The risk increases dramatically with increased aneurysm size, and most ruptured AAAs have diameters greater than 5 cm. The growth rate of the AAA, in addition to other anatomic factors, may also be important in determining the risk of rupture.[18,19] Although rupture of aneurysms smaller than 4 cm is rare,[16] no aneurysm is completely "safe."[3,20] Any aneurysm can rupture and cause the patient's emergency department (ED) presentation.

Rupture of an AAA usually occurs into the retroperitoneum, where hemorrhage may be temporarily limited by clotting and tamponade at the rupture site, but 10 to 30% involve free intraperitoneal rupture, which is often rapidly fatal.[21] Occasionally, rupture occurs into the gastrointestinal tract or the inferior vena cava.

Complications can also arise from an intact AAA. The walls of an AAA are often lined with clot and atheromatous material, which can embolize and occlude distal vessels.[22] Aortic thrombosis may occur rarely. Patients can also have complications caused by impingement on adjacent structures.

In approximately 5% of AAAs, a dense inflammatory and fibrotic reaction develops in the aneurysm wall and adjacent retroperitoneal tissue. In these "inflammatory" AAAs, the periaortic fibrosis may incorporate and obstruct adjacent structures, such as the ureters or duodenum.[23]

www.ketabpezeshki.com 66485457-66963820

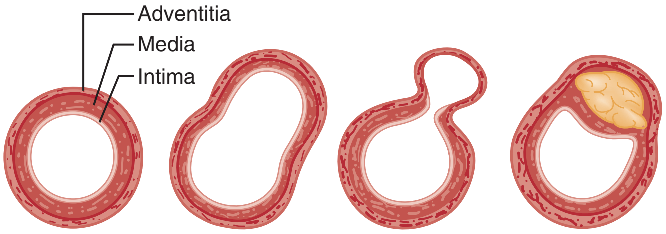


Figure 86-1. Types of aortic aneurysms. (Adapted from LaRoy LL, et al: Imaging of abdominal aortic aneurysms. AJR Am J Roentgenol 152:785, 1989.)

Table 86-1 Prevalence of Abdominal Aortic Aneurysms (AAAs) in Selected Risk Groups

GROUP	INCIDENCE (%)
Men aged 65 years or older[4,5]	5-10
Patients with coronary artery disease[7] or occlusive peripheral vascular disease[10]	10-15
Brothers of patients with AAAs[12]	20-30

The overwhelming concern in the patient with an AAA is the potential for rupture of the aneurysm. The natural history of expansion and rupture can be interrupted only by timely repair.

CLINICAL FEATURES

Unruptured Aneurysms

Because most AAAs cause no symptoms until they rupture, the prevalence of symptoms in patients with unruptured AAAs is unknown. Patients may have symptoms that lead to the aneurysm's discovery and are therefore believed to be caused by the aneurysm, although true causation cannot be determined in most cases. These symptoms can include pain in the abdomen, back, or flank; an awareness of an abdominal mass or fullness; or a sensation of abdominal pulsations.

The pain associated with stable, intact aneurysms has a gradual onset and a vague, dull quality. It is usually constant but may be described as throbbing or colicky. Acute or severe pain is an ominous symptom that suggests imminent or actual aortic rupture.

In most cases, an AAA is asymptomatic and is discovered incidentally on physical examination, on a radiologic study done for other reasons, or by an ultrasonography aneurysm screening program.[1,24] Symptoms usually do not develop until the aneurysm ruptures.

The most prominent physical finding is a pulsatile, expansile abdominal mass. The aortic bifurcation is at the level of the umbilicus, and an AAA can be palpated at or above this level. If the iliac arteries are also aneurysmal, the mass may extend below the umbilicus. The right border of an AAA may be palpable to the right of midline, whereas a normal or tortuous aorta is usually not. Most intact AAAs are nontender; tenderness suggests aneurysm expansion or rupture.

Symptomatic aneurysms are usually fairly large and are often palpable. Likewise, the patient with an aneurysm large enough to warrant elective repair often has a palpable abdominal mass.[25,26] However, an AAA may be difficult to palpate if the aneurysm is small or the patient is obese. Published reports indicate that 30 to 60% of unruptured aneurysms measuring 3.0 to 3.9 cm on ultrasonography can be detected by abdominal palpation; 50 to 70% of aneurysms measuring 4.0 to 4.9 cm and 75 to 85% of aneurysms 5 cm or larger can be palpated.[25,26] These reports are based on the examination of patients with intact, asymptomatic aneurysms, with the examination specifically directed at sizing the aorta. The sensitivity is likely much lower when the abdomen is not palpated deeply, or in hypotensive patients or those with significant abdominal guarding. There is virtually no risk of causing aneurysm rupture by abdominal palpation.[25]

Physical examination may raise suspicion regarding an AAA even when the aorta is of normal size.[25] A tortuous aorta may feel enlarged, and prominent aortic pulsations, especially in a thin patient, may simulate an aneurysm. Moreover, pulsations from a normal aorta may be transmitted to an adjacent abdominal mass. Nonetheless, clinical suspicion of AAA warrants further investigation.

An abdominal bruit is an uncommon finding in patients with AAAs. The presence of a bruit is also nonspecific, as bruits can originate in a stenotic renal, iliac, or mesenteric artery. A loud continuous bruit suggests the diagnosis of aortovenous fistula, a rare complication of AAAs.[27]

Perfusion distal to an AAA is usually well maintained, and most patients have normal femoral pulses. Diminished femoral pulses may result from iliofemoral occlusive disease or from hypotension in the patient with a ruptured aneurysm.

Thromboembolic complications can occur spontaneously or when atheromatous plaques are disrupted during invasive intravascular procedures. Large emboli can acutely occlude major vessels such as the iliac, femoral, or popliteal artery, causing acute painful lower extremity ischemia with absent distal pulses. Rarely, the aneurysm itself can thrombose, rendering both lower extremities acutely ischemic. More often, however, microemboli consisting of cholesterol crystals or clot obstruct small distal vessels, such as the digital arteries of the toes and arterioles and capillaries of the skin. These patients have livedo reticularis; one or more cool, painful, cyanotic toes; and palpable pedal pulses. This constellation of findings, often called the *blue toe syndrome*,[28] is highly suggestive of a proximal source of emboli. When an AAA is the source, the aneurysm is often too small to palpate and may be discovered only after radiologic investigation.[22,28]

Rarely, an intact AAA causes symptoms by compressing adjacent structures, with symptoms depending on the structures involved. Large, long-standing aneurysms can cause vertebral body erosion and severe back pain. Compression of the duodenum between the superior mesenteric artery and an AAA can cause duodenal obstruction, vomiting, and weight loss.[29] Obstruction of the ureters in the patient with an inflammatory aneurysm can cause symptoms suggestive of ureteral colic.[23]

Ruptured Aneurysms

Pain-Hypotension-Mass Triad

Although the classic triad of a ruptured AAA is pain, hypotension, and a pulsatile abdominal mass, many patients have only one or two components of this triad, and an occasional patient has none of the classic features.

Rupture is often the first manifestation of an AAA. Some patients, however, have a previously diagnosed AAA, and a decision not to operate electively may have been made because the aneurysm was small or the patient was considered too high risk. If such a patient has acute symptoms, the presumptive diagnosis is aneurysm rupture.

Most patients with a ruptured AAA experience pain in the abdomen, back, or flank. The pain is usually acute, severe, and constant and can radiate to the chest, thigh, inguinal area, or scrotum. If the patient's mental status is compromised by severe hypotension, the history of pain may be unobtainable.

www.ketabpezeshki.com 66485457-66963820

The mechanism of the pain associated with aneurysm rupture is poorly understood. It may be caused by expansion of the aortic wall or by stimulation of sensory nerves in the retroperitoneum. Identical pain can occur with intact but acutely expanding aneurysms, which may be impossible to differentiate clinically from ruptured aneurysms.[30,31] Acute pain in the patient with an AAA should be considered a symptom of rupture or impending rupture.

In patients with a ruptured aneurysm, the duration of symptoms before presentation varies greatly. Some patients are seen shortly after severe pain and hypotension develop. In others, rupture is initially contained in the retroperitoneum, blood loss is small, and the presentation is delayed. Rare patients with a ruptured AAA may have symptoms for several days or even weeks before seeking medical attention[32]; therefore a long duration of symptoms does not exclude the diagnosis of ruptured AAA.

Rupture of an AAA may be accompanied by nausea and vomiting, and sudden hemorrhage can cause syncope or near-syncope. Compensatory hemodynamic mechanisms may then return the blood pressure and cerebral perfusion to normal. Transient improvement in symptoms is common but will be followed by hemodynamic deterioration if diagnosis and treatment are delayed.[33]

Ruptured AAAs are often large, and most patients have palpable abdominal masses.[34] As with intact aneurysms, a ruptured AAA may not be palpable if the aneurysm is small or the patient is obese. The examination may be difficult if abdominal guarding is present or if an ileus causes significant distention. Aortic pulsations may not be prominent if the blood pressure is low. When a mass is not palpable, the diagnosis may be delayed.

Hypotension is the least consistent part of the triad, occurring in approximately half of patients, and is often a late finding.[33,34] When the initial blood loss is minor, vital signs are often normal. Patients with initially normal vital signs are more likely to be misdiagnosed[33] and may quickly and unpredictably deteriorate and become hypotensive.

Occasionally, rupture into the retroperitoneum is sealed and contained for many weeks or months.[32] When this occurs, patients develop abdominal or back pain, presumably at the time of aneurysm leakage, which subsequently diminishes or resolves completely. If the diagnosis is made, chronic rupture (organized hematoma) is found at surgery. These patients can have chronic pain and may progress to free rupture and massive hemorrhage at any time.[32]

Aortoenteric Fistula

An AAA can rupture into the gastrointestinal tract (aortoenteric fistula [AEF]) or inferior vena cava (aortocaval fistula). A primary AEF is formed when an unrepaired AAA erodes into the gastrointestinal tract,[35] usually the third or fourth portion of the duodenum. A secondary AEF, a communication between the site of previous aortic surgery and the gastrointestinal tract,[36,37] can occur as a late complication of AAA repair and should be considered as the leading diagnosis in any patient with a severe gastrointestinal bleed and a history of aortic graft placement.

Early in the formation of a primary AEF, the bowel wall is eroded from the outside by the adjacent AAA. This can lead to the leakage of intestinal contents, with local infection and sometimes abscess formation. Eventually, breakdown of the aortic wall leads to an AEF and gastrointestinal bleeding.

The patient with an AEF may have abdominal or back pain, fever and other signs of intra-abdominal infection, or gastrointestinal bleeding. Because most of these fistulae are into the duodenum, hemorrhage usually manifests as hematemesis or melena. The initial bleeding results from erosion of vessels in the bowel wall and is often minor.[37] Later, often after several days to a week or longer, massive bleeding results from rupture into the intestinal lumen.

Primary AEF, although rare, should be considered in any patient older than 50 years with unexplained gastrointestinal bleeding. If an AAA is diagnosed by history, physical examination, or any other modality, the patient should be presumed to have an AEF until proven otherwise.

Aortovenous (Aortocaval) Fistula

An aortovenous (usually aortocaval) fistula arises when periaortic inflammation causes adherence of the aorta to an adjacent vein, with pressure on the vessel walls causing the development of an arteriovenous communication. If concomitant extravasation of blood into the retroperitoneum occurs, the clinical presentation is similar to that of other patients with ruptured AAAs, often with hypovolemic shock. More commonly, however, the aneurysm ruptures into the vena cava without leaking externally, and the signs and symptoms of a large arteriovenous fistula dominate the clinical picture.[27,38]

As in other patients with AAAs, a patient with an aortovenous fistula may have abdominal or back pain. An aneurysm that becomes fistulous with the vena cava is usually large, and 80 to 90% are palpable. A continuous abdominal bruit can be auscultated in approximately 75% of patients with aortovenous fistulae, and 25% of patients have a palpable abdominal thrill.[38]

Shunting of blood from the arterial to the venous system increases venous pressure, venous volume, and venous return to the heart. Signs and symptoms of high-output congestive heart failure (dyspnea, jugular venous distention, pulmonary edema) are often present.[38] The increased venous volume and pressure can cause lower extremity edema or cyanosis, and dilated superficial veins can be seen on the legs or abdominal wall. Distention and rupture of veins in the bladder mucosa can cause gross or microscopic hematuria; rectal bleeding can occur for similar reasons. Because of shunting of arterial blood into the venous system, the lower extremities may be cool with diminished pulses.

The patient with an aortovenous fistula often has renal insufficiency caused by a decrease in renal perfusion as a result of high-output congestive heart failure and increased renal venous pressure. Such patients may exhibit hematuria, which is common when an aortovenous fistula is present but not in other patients with AAAs.[38] Computed tomography (CT; preferably CT angiography) can rule out aortovenous fistula formation.

DIAGNOSTIC STRATEGIES

Abdominal Radiography

Plain film radiography is not indicated in the evaluation of a patient for suspected AAA. A normal plain abdominal radiograph does not exclude the presence of an AAA and rarely identifies alternative pathology. Even if an aneurysm is identified on plain film because it is calcified, imaging with CT is required to identify whether the aneurysm is an incidental or culprit lesion in the patient's presentation (Fig. 86-2).

Ultrasonography

Ultrasonography is virtually 100% sensitive in detecting AAAs (Fig. 86-3), when a technically adequate study can be obtained.[1] Measurements of aortic diameter are very accurate and reproducible. Because it is relatively inexpensive and requires no contrast agents or radiation exposure, ultrasonography is used for nonemergency aneurysm diagnosis and to follow patients with known aneurysms.

www.ketabpezeshki.com 66485457-66963820

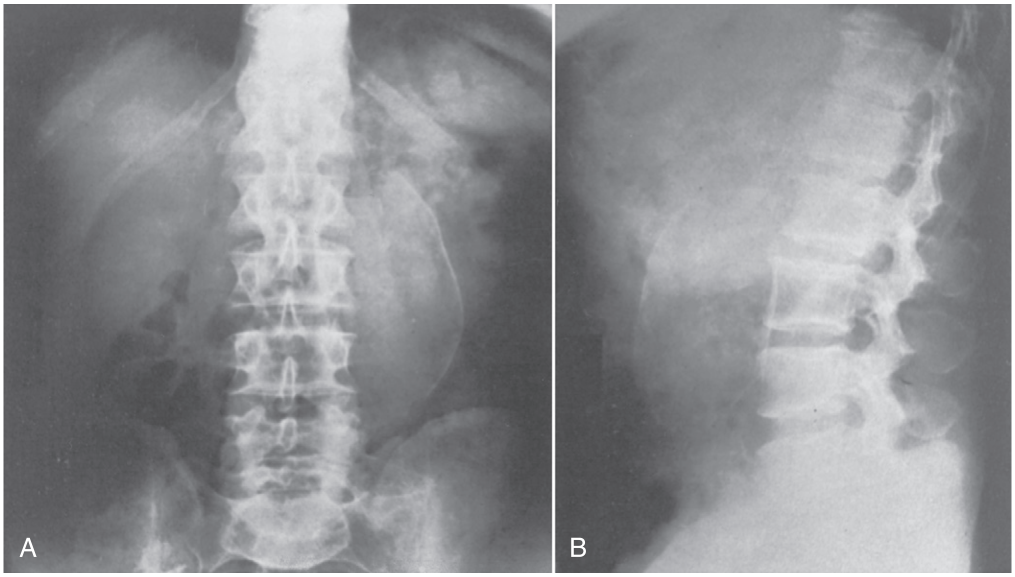


Figure 86-2. Anteroposterior **(A)** and lateral **(B)** views of large abdominal aortic aneurysms with calcification of aortic wall. (From Juergens JL, et al: Peripheral Vascular Diseases, 5th ed. Philadelphia, WB Saunders, 1980; by permission of the Mayo Foundation.)

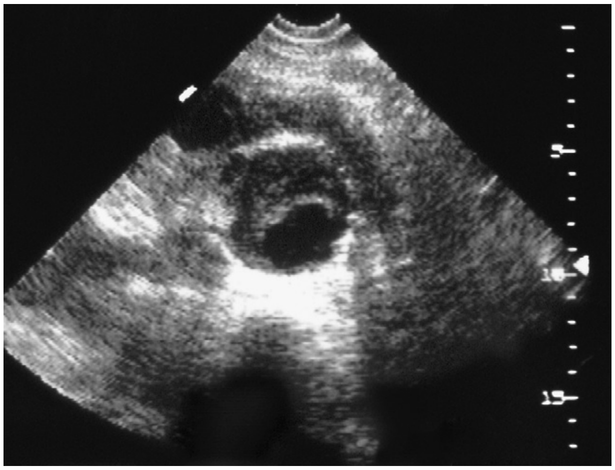


Figure 86-3. Transverse sonogram of an abdominal aortic aneurysm. The central patent lumen is surrounded by an echogenic mural thrombus. (Courtesy Richard Rensio, MD.)

Ultrasonography has distinct advantages in the emergency evaluation of a patient with a suspected ruptured AAA.[39] It can be performed very rapidly at the patient's bedside, obviating the need to take a potentially unstable patient to the radiology suite. If an aorta with a normal diameter throughout its abdominal course is visualized, the patient does not have an AAA. In addition, ultrasonography sometimes provides alternative explanations for the patient's pain by revealing other conditions, such as acute cholecystitis.

However, ultrasonography has certain limitations. It is more operator dependent than other diagnostic modalities and may be prone to technical or interpretive error.[40] Even more than with elective studies, in the emergency department the aorta may not be well visualized because of obesity or excess bowel gas.[40-42] Ultrasonography is not immediately available in some EDs, requiring the patient to wait for the arrival of a technologist. Although ultrasonography is extremely sensitive in detecting an AAA, it cannot be relied on to reveal whether an AAA has ruptured.[39]

Free intraperitoneal or retroperitoneal blood, seen in the presence of an AAA, confirms a rupture.[40] However, the sensitivity of emergency ultrasonography in detecting extraluminal blood is very low. The purpose of the study is to confirm or exclude the presence of an aneurysm; clinical information (or a CT scan) must be used to determine the likelihood of rupture. Ultrasonography with the use of contrast agents may aid in the detection of leaking blood,[43] but the clinical usefulness of this modality remains to be determined. If ultrasonography reveals an AAA in an unstable patient, aneurysm rupture is presumed, and the patient requires immediate aneurysm repair.

Computed Tomography

The abdominal CT scan is the diagnostic test of choice in the evaluation of a patient with suspected ruptured AAA and is virtually 100% accurate in determining the presence or absence of an AAA and the presence of bleeding.[40] CT also provides detailed anatomic information about the aneurysm.[44,45]

An intravenous contrast agent is desirable, but not essential, in emergency situations. With significant, prolonged hypotension or known renal disease, intravenous contrast should be avoided to prevent contrast-exacerbated nephropathy. Intravenous contrast will opacify the aortic lumen and distinguish the patent lumen from mural thrombus. It can also demonstrate periaortic fibrosis because the soft tissue surrounding an inflammatory AAA often enhances. However, intravenous contrast is not necessary to identify the aneurysm or acute hemorrhage.

CT is much more sensitive than ultrasonography in detecting retroperitoneal hemorrhage associated with aneurysm rupture. The reported sensitivity approaches 100% with the use of current-generation scanning technology, with falsely negative studies sometimes occurring with very small ruptures. Blood is seen as a retroperitoneal fluid collection adjacent to the aneurysm, often tracking into the perinephric space or along the psoas muscle (Fig. 86-4).

Although a CT scan sometimes reveals signs of impending aneurysm rupture, it cannot reliably determine whether an AAA is the cause of the patient's pain or whether rupture of the aneurysm is imminent. Another cause of pain can be diagnosed only if the CT scan shows no aneurysm or shows an intact aneurysm

www.ketabpezeshki.com 66485457-66963820

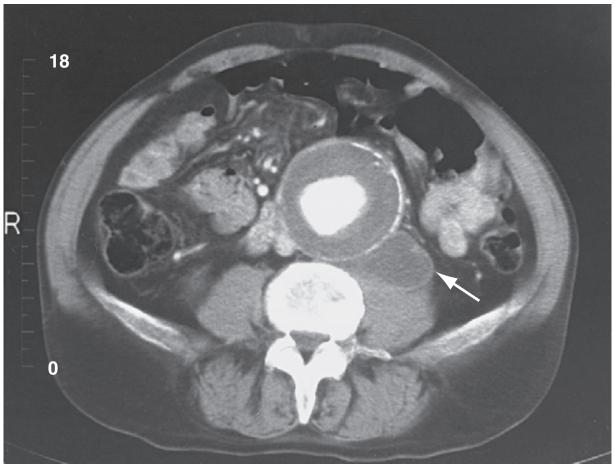


Figure 86-4. Computed tomography scan of ruptured abdominal aortic aneurysm, with calcification of the aortic wall and intraluminal thrombus. The patent lumen enhances with the administration of contrast material, but the periaortic hematoma *(arrow)* does not. (Courtesy Richard Rensio, MD.)

Box 86-1 Common Misdiagnoses in Patients with Ruptured Abdominal Aortic Aneurysms

Renal colic	Appendicitis
Acute abdomen	Perforated viscus
Pancreatitis	Bowel obstruction
Intestinal ischemia	Musculoskeletal back pain
Diverticulitis	Acute myocardial infarction
Cholecystitis	

and clearly demonstrates an alternative explanation for the patient's symptoms.

Other Diagnostic Modalities

Conventional angiography has no place in the emergency evaluation of the suspected ruptured AAA. Because contrast opacifies only the patent lumen and not mural thrombus, angiography often underestimates aneurysm size and can miss the aneurysm entirely. In addition, angiography is time-consuming and performed away from the ED. If detailed information is needed about the anatomy of the aneurysm or its relationship to nearby vessels, a CT angiogram can provide the needed information.

Magnetic resonance imaging and magnetic resonance angiography are very time-consuming, are logistically challenging, and provide no benefit over CT scan. Magnetic resonance scanning is not indicated in the evaluation of a patient with acute symptoms suspected to be related to AAA.

DIFFERENTIAL CONSIDERATIONS

Because the patient with a ruptured AAA usually has abdominal, back, or flank pain, with or without hypotension, common misdiagnoses are other disease processes that cause these symptoms (Box 86-1). The sudden onset of back pain often leads to the clinical suspicion of renal colic, with which AAA is often confused.[33] Abdominal pain and tenderness can suggest pancreatitis, intestinal ischemia, or other intra-abdominal disorders. Musculoskeletal back pain is part of the differential diagnosis but should be confirmed by detailed history and physical examination, so that pain related to AAA is not mistakenly labeled as mechanical low back pain.

Presentation with epigastric pain and hypotension may lead to a presumptive diagnosis of acute myocardial infarction. Because the patient with a ruptured AAA often has coexistent coronary artery disease, blood loss from a ruptured aneurysm may diminish coronary perfusion and cause chest pain or electrocardiographic changes consistent with cardiac ischemia. These findings do not exclude the presence of a ruptured AAA.

Ruptured AAA should be considered in middle-aged or elderly patients with any part of the classic triad. The diagnosis of ruptured AAA should also be considered in making the diagnoses listed in Box 86-1, especially when the diagnosis is not clear-cut or the patient is at risk for an AAA.

MANAGEMENT

Ruptured Aneurysms

The patient with a ruptured AAA is unstable until the aorta is cross-clamped in the operating room or stabilized with endovascular techniques. No patient with a known or suspected aortic rupture should be considered stable, regardless of the initial vital signs or initial hemoglobin level. Patients taken to the operating room soon after ED arrival have a much higher survival rate than those in whom surgical care is delayed.[46]

When the patient arrives at the ED, large-bore intravenous access should be established and blood sent for crossmatch. At least 6 units of blood should be made available initially, with notification to the blood bank of the potential need for significantly more, because patients with ruptured AAAs often have large transfusion requirements.[47] The surgical and anesthesia team should be notified immediately. Further management depends on the current hemodynamic condition and the level of diagnostic certainty.

The hemodynamically unstable patient in whom a ruptured AAA has been diagnosed or is strongly suspected should be taken to the operating room as soon as possible (in this chapter, the term "operating room" includes other locations that may be used for endovascular aneurysm repair). Diagnostic testing should be kept to a minimum. The diagnosis can often be made from the clinical presentation and abdominal examination, and bedside ultrasonography can quickly confirm or exclude the presence of an aneurysm. A CT scan is appropriate only if it can be obtained very quickly without compromising the patient's care. Time-consuming tests inappropriately delay definitive therapy and increase the risk of exsanguination. Hypotensive patients may have to be taken to the operating room based on a strong clinical presumption of the diagnosis, without definitive diagnostic imaging. Some of these patients will not have ruptured aneurysms, but they usually have other acute abdominal conditions requiring laparotomy.[48]

Attempts to resuscitate these patients fully and normalize the vital signs in the ED should be avoided. Hypotensive patients need to be taken to the operating room so that the aorta can be clamped, or occluded with a balloon, and hemorrhage stopped. Attempts to stabilize the patient in the ED are often fruitless and waste valuable time.

Fluid Resuscitation

The appropriate degree of preoperative volume resuscitation is controversial. Preoperative hypotension is the strongest predictor of mortality in the patient with a ruptured AAA.[21,49] However, correction of the hypotension before the aorta is clamped may not improve mortality and may even be harmful.

It has been argued that hypotension slows bleeding in patients with AAA and allows local clot formation and tamponade of the rupture site. Raising the intravascular volume and blood pressure before occluding the aorta may dislodge clots and cause further

www.ketabpezeshki.com 66485457-66963820

bleeding.[47,50,51] Large volumes of crystalloid solution may contribute to bleeding by causing a dilutional coagulopathy. These concerns are similar to those in trauma patients with uncontrolled hemorrhage.

However, delaying resuscitation of hypotensive patients until they reach the operating room may also have deleterious effects. The patient with a ruptured AAA often survives the surgery but dies in the early postoperative period. These deaths are caused by complications of prolonged hypotension, such as myocardial infarction, respiratory failure, and renal failure. The patient with a ruptured AAA is usually elderly, often has coexisting conditions, and tolerates hypovolemia and hypotension poorly.

No prospective studies have compared different preoperative fluid regimens in hypotensive patients with ruptured AAAs, and the optimal resuscitation strategy has not been determined. The priority in these patients is expeditious transportation to the operating room for definitive control of aortic hemorrhage. In the prehospital setting and in the ED before the surgeon and the operating room are available, the blood pressure should be raised with crystalloid or blood products to a level that maintains adequate cerebral and myocardial perfusion.[50] The goal is to prevent irreversible end-organ damage. An arbitrary blood pressure goal cannot be specified because the blood pressure necessary for vital organ perfusion varies among patients, but a reasonable target is a systolic blood pressure of 90 to 100 mm Hg.

If blood products are to be administered in large amounts, fresh frozen plasma (FFP) and packed red blood cells (PRBCs) are beneficial in patients with ruptured AAAs.[47] As with trauma patients, a PRBC:FFP ratio of less than 2:1 results in improved mortality.[47]

Rarely, patients with a ruptured AAA may be hypertensive on admission because of pain or underlying chronic hypertension. Unlike the situation with aortic dissection, no evidence exists that lowering the blood pressure is beneficial in the patient with a ruptured AAA, and these patients are at risk of developing precipitous hypotension.

Diagnostic Confirmation

If an AAA can be diagnosed with bedside testing (abdominal examination or ultrasonography), the surgeon will often proceed immediately to the operating room with a clinical diagnosis of aneurysm rupture, as a delay in surgery places the patient with a ruptured AAA at risk for sudden and unpredictable hemodynamic deterioration. If the patient remains hemodynamically stable and an AAA cannot be identified with bedside testing, or if anatomic detail is needed for endovascular repair, an abdominal CT scan can be obtained. This will confirm or exclude the presence of an aneurysm, define the aortic anatomy, and determine the patient's suitability for endovascular repair. The patient who is sent for a CT scan should be monitored closely and taken to the operating room immediately if hemodynamic deterioration occurs.

CT may provide confirmation of rupture, allowing the surgeon to avoid the complications of emergency surgery in a patient with an intact aneurysm. With emergency surgery, detailed anatomic evaluation and careful preoperative planning are often impossible, evaluation and optimization of the patient's cardiopulmonary and renal function may be precluded, and invasive hemodynamic monitoring may be unavailable. For these reasons, patients who are taken for emergency surgery and are found to have intact, symptomatic aneurysms have a higher mortality rate than patients undergoing elective aneurysm repair.[30,31,52]

Surgery and Mortality

Ruptured AAA is uniformly fatal unless treated surgically. Thus once this diagnosis has been made, repair should be attempted in almost all patients. Attempts have been made to identify patients with a very low likelihood of survival, and it has been suggested that surgery can be withheld in patients with prehospital or ED cardiac arrest. However, no variables that can be assessed in the ED, including cardiac arrest, are universally predictive of a fatal outcome.[21] Repair is indicated unless the patient's life expectancy is very short because of underlying illnesses or the patient's quality of life is so poor that repair is considered unreasonable. Hypotension is the most important factor predicting a poor outcome in patients undergoing surgery.[21,47,49,50]

Although patients with ruptured AAAs have a mortality of 30 to 40% with open repair,[11,49,51,53] recent data suggest significantly lower mortality at centers experienced with the endovascular approach, with an operative mortality rate of 20 to 25%.[51,54-57] Endovascular repair of ruptured aneurysms is becoming increasingly more common, even in unstable patients.[54,58-60] If necessary, the surgeon can stabilize the patient by placing an aortic occlusion balloon above the aneurysm after rapidly accessing the femoral artery.

Not all patients with ruptured aneurysms will have an aorta that is anatomically suitable for endovascular repair.[58,59] The method of repair will clearly be the surgeon's decision. Planning for the care of such patients should include the development of a well understood protocol that advises the ED staff about which services to mobilize and which diagnostic tests to perform for patients with ruptured AAA.[60]

Unfortunately, even with the recent improvement in treatment outcomes, operative mortality rates significantly underestimate the true lethality of ruptured AAAs. The patient with a ruptured AAA may die at home or may reach the hospital but die before surgery. When patients who do not reach the operating room are considered, the overall mortality rate may be as high as 80%.[61]

Intact, Asymptomatic Aneurysms

An incidental diagnosis of AAA may be made in the ED. The decision to repair an asymptomatic aneurysm depends on the risk of aneurysm rupture, the patient's life expectancy and likelihood of dying from other causes, and the surgical risk. The last factors are determined by the patient's age and coexisting illnesses, whereas the risk of rupture is largely a function of aneurysm size.

In two clinical trials, one of which has long-term follow-up, patients with small (<5.5 cm) aneurysms were randomized to early surgery or close follow-up.[62-64] In the latter group, aneurysms were followed with serial ultrasounds or CT scans, and surgery was performed only if symptoms developed, rapid expansion was documented, or a diameter of 5.5 cm was reached. Both studies showed equivalent survival rates in the two groups. As a result, fewer small aneurysms are now repaired electively, potentially leaving a larger group of patients who may come to the ED with complications of an AAA. It is important to note that the "watchful waiting" approach is appropriate only for asymptomatic aneurysms, and rupture of the AAA should be strongly considered in the evaluation of any symptoms in these patients.

Traditional Repair

The conventional technique for repair of AAAs is an open approach with a laparotomy. The aneurysm is opened longitudinally and repaired from within (Fig. 86-5). A graft is inserted inside the aneurysm and anastomosed to uninvolved vessels above and below. When possible, a straight graft is used between the infrarenal and distal aorta, but if the aneurysm involves the aortic bifurcation or if iliac artery aneurysmal or occlusive disease is present, a bifurcation graft is used, with the distal anastomosis to the iliac or femoral arteries. The aneurysm wall is then closed around the graft to help separate it from adjacent structures.

www.ketabpezeshki.com 66485457-66963820

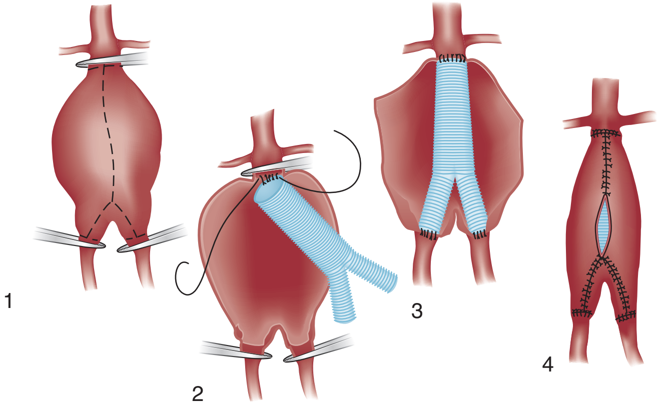


Figure 86-5. Steps in repair of an abdominal aortic aneurysm. See text for details. (From Kent KC, et al: Surgical principles for operative treatment of aortic aneurysms. In Lindsay J Jr [ed]. Diseases of the Aorta, Philadelphia, Lea & Febiger, 1994, p 287.)

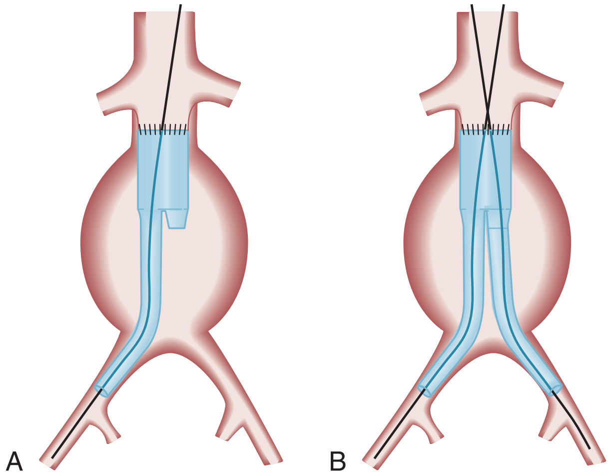


Figure 86-6. Endovascular repair of an abdominal aortic aneurysm. A, Aortic section with attached iliac limb. B, Addition of contralateral iliac limb. (From Blum U, et al: Endoluminal stent-grafts for infrarenal abdominal aortic aneurysms. N Engl J Med 336:13-20, 1997. Copyright © 1997, Massachusetts Medical Society. All rights reserved.)

Endovascular Repair

More than half of all AAA repairs are now performed without laparotomy, with use of endovascular techniques.[44,45,65,66] A stent graft (a fabric graft supported by an internal wire frame) is placed into the femoral artery percutaneously or through a groin incision and is advanced under fluoroscopic guidance to a position that spans the aneurysm (Fig. 86-6A). The contralateral iliac limb is placed to form a bifurcated graft (Fig. 86-6B). Once in position, the graft is expanded to fit tightly against the walls of the aorta. Early straight (tube) grafts are now rarely used because of a high failure rate.

Endovascular surgery avoids the morbidity of a laparotomy and may allow the repair of AAAs in some high-risk patients who would not tolerate conventional surgery. Perioperative mortality is lower than that with open repair,[65,67-69] but it is unclear whether this mortality benefit is sustained in the long-term.[69,70] Endovascular repair requires more frequent reinterventions for graft-related complications.[70] Because not all aneurysms are anatomically suitable for endovascular repair, detailed preoperative imaging and planning are required to make this determination.[44,45] In addition, patients who have had endovascular aneurysm repair remain at risk for several complications, most importantly rupture of the aneurysm.[45,70]

Survival

The operative mortality rate for elective AAA repair is approximately 1 to 2% for endovascular repair and 3 to 5% for open repair,[69,70] in contrast to the much higher operative mortality with ruptured aneurysms.[51,53,54,71,72] Patients who survive the operation have an excellent prognosis, with a long-term survival close to that of the general population. After repair of the aneurysm, long-term survival is primarily limited by associated cardiac disease.

LATE COMPLICATIONS OF REPAIR

Graft infection, AEF formation, and anastomotic aneurysm (pseudoaneurysm) formation can occur at any time from weeks to many years after the surgery.[36,73] These complications often occur together, their clinical presentations overlap, and they are diagnosed by similar means. In addition, endovascular aneurysm repair has several unique complications, the most important of which is endoleak.

Graft Infection

Graft infection can result from contamination of the graft at surgery, spread of a contiguous infection, or hematogenous seeding. Infection can disrupt the anastomosis between native artery and graft, leading to leakage of blood from the anastomosis and pseudoaneurysm formation. The infection can be localized to a portion of the graft, most often the inguinal portion of an aortofemoral graft, or can involve the entire graft.

Infection of the distal limb of an aortofemoral graft may cause local signs of infection or a palpable false aneurysm. Intra-abdominal graft infection is often subtle, with low-grade fever and vague abdominal or back pain. Abdominal tenderness or a palpable mass may be present if there is a leaking anastomosis. Collections of fluid or gas around the graft on CT provide evidence of infection, although CT scans are sometimes falsely negative.

Aortoenteric Fistula

As discussed earlier in this chapter, an AEF should be considered in any patient with gastrointestinal bleeding and a history of abdominal aortic surgery. Most of these patients, however, ultimately prove to have other, more common causes of gastrointestinal bleeding. The diagnostic approach depends on the patient's hemodynamic stability.

If the patient with a suspected AEF is unstable with massive bleeding, diagnostic testing may be dangerously time-consuming. In these patients, emergency laparotomy may be necessary to control hemorrhage and diagnose or exclude the presence of an AEF.[37] Stable patients can be evaluated with endoscopy or a CT scan. Some patients with AEF may be treated endovascularly, which may result in improved perioperative morbidity and mortality.[37]

Upper gastrointestinal endoscopy is occasionally recommended as the initial diagnostic test. Direct visualization of the fistula into the distal duodenum is sometimes possible. However, endoscopy cannot be relied on to identify an AEF, and its main value is in establishing another diagnosis. Emergency surgery can be avoided if an active bleeding site other than an AEF is clearly seen.

An abdominal CT scan can also be used to evaluate a suspected AEF.[36] Although imaging of the fistula may not be possible, graft infection is almost invariably present in patients with secondary AEFs, and the CT scan will demonstrate the associated infection. Radiographically distinguishing an AEF from intra-abdominal

www.ketabpezeshki.com 66485457-66963820

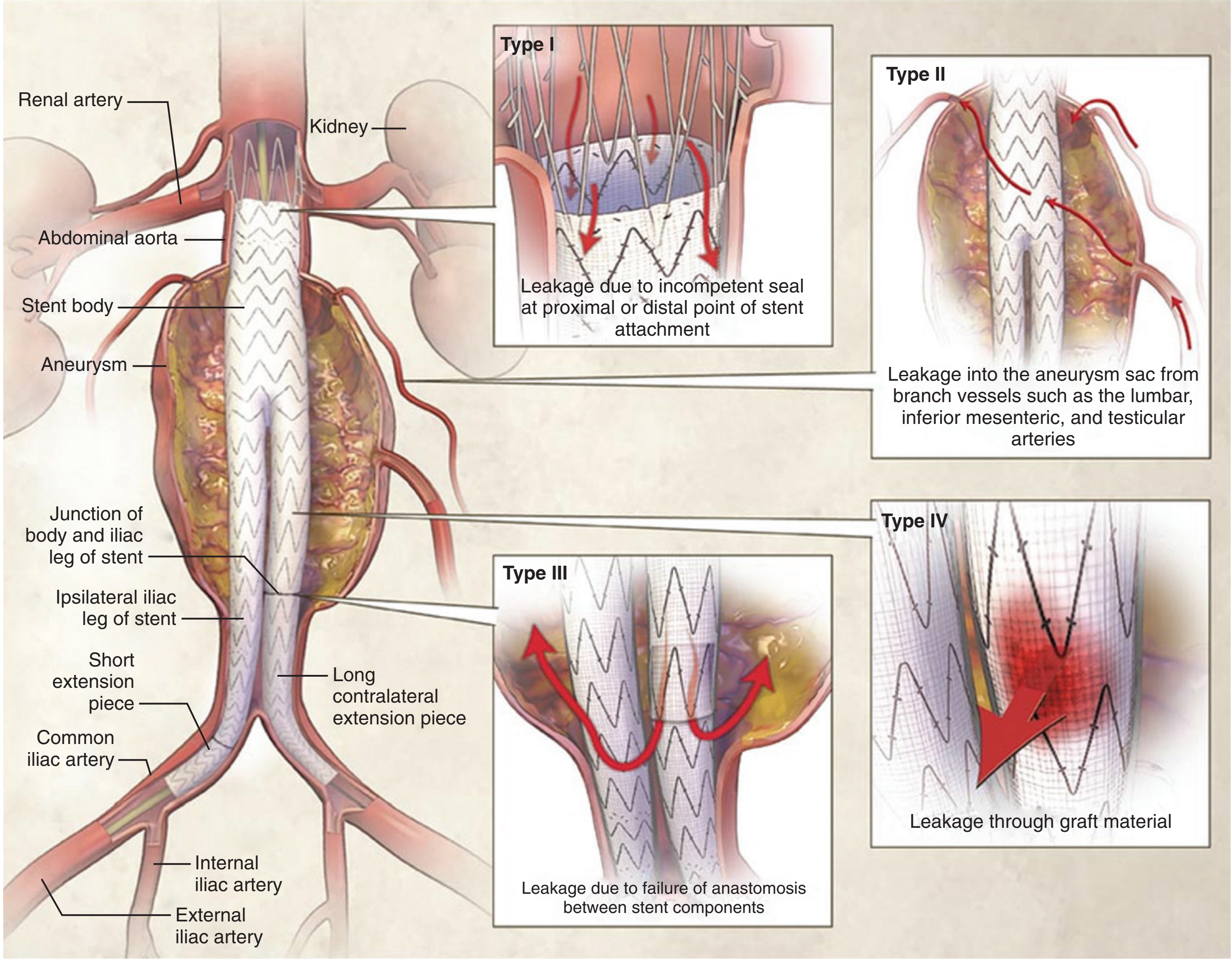


Figure 86-7. Types and causes of endoleaks. (From N Engl J Med 358:494-501, 2008. Copyright 2008, Massachusetts Medical Society. All rights reserved.)

graft infection alone may be difficult, but the distinction is not crucial, as both need surgical management.

Pseudoaneurysm (Anastomotic Aneurysm)

Pseudoaneurysms can arise at the site of a leaking anastomosis. They may be associated with graft infection or AEF formation but more often result from degeneration of the native vessel.

The patient with an anastomotic aneurysm may have pain or a pulsatile mass in the abdomen or groin. The aneurysm may give rise to distal emboli or may rupture and cause life-threatening hemorrhage. Suspected pseudoaneurysms can be evaluated with angiography, CT scan, or ultrasonography.

Complications of Endovascular Aneurysm Repair

A rapidly increasing percentage of elective AAA repairs are done with endovascular techniques, and these patients may come to the ED with postoperative complications. The most serious of these is endoleak—blood flow outside of the graft lumen but within the aneurysm sac, potentially allowing enlargement of the aneurysm. Endoleaks may be caused by separation of the proximal or distal end of the graft from the aortic wall (type I), back-bleeding into the aneurysm sac from branch vessels such as lumbar arteries (type II), leakage between the modular components of the graft (type III), or leakage through the graft fabric itself (type IV) (Fig. 86-7).[45,74] It is important to note that with persistent leakage of blood into the aneurysm sac, the patient is at risk for rupture of the aneurysm.[44,45,70,74,75]

Endoleaks may develop soon after the procedure or much later. They have been reported in as many as 20% of patients who have had endovascular aneurysm repair.[74,76] Because many endoleaks resolve spontaneously, patients are sometimes observed for months before repair of the leak with secondary endovascular procedures or surgical intervention.

Patients sometimes sustain other complications, such as graft migration, stenosis or thrombosis, and structural failure of various elements of the graft. These complications often lead to endoleak and the risk of rupture.

In the ED, CT with intravenous contrast should be used to evaluate for possible complications of endovascular repair.[77] A specific CT imaging protocol may be desired; this should be discussed with the radiologist or vascular surgeon.

Because of the many potential complications of endovascular aneurysm repair, these patients require lifelong close follow-up.

www.ketabpezeshki.com 66485457-66963820

Prompt surgical consultation should be obtained for patients with any symptoms possibly caused by device malfunction, and the potential for aneurysm rupture should always be considered.

DISPOSITION

A patient with an acutely symptomatic AAA requires hospital admission and urgent or emergency repair. A patient whose aneurysm is asymptomatic and discovered incidentally should be referred for consideration of elective repair. The patient with an AAA should be referred for an outpatient workup only if it is clear that the symptoms prompting the ED visit are unrelated to the aneurysm. Although the incidental detection of AAA is common, such patients may suffer from poor subsequent follow-up and monitoring.[24] If the patient is discharged, appropriate referral for follow-up is crucial, and instructions should be given to seek immediate medical attention if abdominal, back, or flank pain develops.

In the patient who has had an AAA repaired, unexplained fever, abdominal pain, or gastrointestinal bleeding suggests the presence of a graft-related complication and the need for inpatient evaluation.

KEY CONCEPTS

- A ruptured AAA should be considered in any patient older than 50 years with otherwise unexplained abdominal or back pain. The complete triad of pain, hypotension, and a pulsatile mass is often absent.
- In the patient with an AAA and acute symptoms, rupture is imminent or has already occurred.
- The patient with a ruptured AAA who appears to be hemodynamically stable can suddenly deteriorate at any time.
- The patient who has had endovascular repair of an AAA remains at risk for aneurysm rupture.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Lederle FA: Ultrasonographic screening for abdominal aortic aneurysms. *Ann Intern Med* 2003; 139:516-522.
2. Lederle FA, et al: The aneurysm detection and management study screening program: Validation cohort and final results. Aneurysm Detection and Management Veterans Affairs Cooperative Study Investigators. *Arch Intern Med* 2000; 160:1425-1430.
3. Ashton HA, et al: The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: A randomised controlled trial. *Lancet* 2002; 360:1531-1539.
4. Norman PE, et al: Population based randomised controlled trial on impact of screening on mortality from abdominal aortic aneurysm. *BMJ* 2004; 329:1259-1264.
5. Webster MW, et al: Ultrasound screening of first-degree relatives of patients with an abdominal aortic aneurysm. *J Vasc Surg* 1991; 13:9-14.
6. Madaric J, et al: Frequency of abdominal aortic aneurysm in patients >60 years of age with coronary artery disease. *Am J Cardiol* 2005; 96:1214-1216.
7. Lindholt JS, Sorensen J, Sogaard R, Henneberg EW: Long-term benefit and cost-effective analysis of screening for abdominal aortic aneurysms from a randomized controlled trial. *Br J Surg* 2010; 97:826-834.
8. Barba A, Estallo L, Rodríguez L, Baquer M, Vega de Céniga M: Detection of abdominal aortic aneurysm in patients with peripheral artery disease. *Eur J Vasc Endovasc Surg* 2005; 30:504-508.
9. Larsson E, Granath F, Swedenborg J, Hultgren R: A population-based case-control study of the familial risk of abdominal aortic aneurysm. *J Vasc Surg* 2009; 49:47-51.
10. Forsdahl SH, Singh K, Solberg S, Jacobsen BK: Risk factors for abdominal aortic aneurysms: A 7-year prospective study: The Tromso Study, 1994-2001. *Circulation* 2009; 119:2202-2208.
11. Mureebe L, et al: National trends in the repair of ruptured abdominal aortic aneurysms. *J Vasc Surg* 2008; 48:1101-1107.
12. Kent KC, et al: Analysis of risk factors for abdominal aortic aneurysm in a cohort of more than 3 million individuals. *J Vasc Surg* 2010; 52:539-548.
13. Diehm N, et al: Novel insight into the pathobiology of abdominal aortic aneurysm and potential future treatment concepts. *Prog Cardiovasc Dis* 2007; 50:209-217.
14. Brewster DC, Cronenwett JL, Hallett JW: Guidelines for the treatment of abdominal aortic aneurysms. Report of a subcommittee of the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery. *J Vasc Surg* 2003; 37:1106-1117.
15. Lederle FA, et al: Rupture rate of large abdominal aortic aneurysms in patients refusing or unfit for elective repair. *JAMA* 2002; 287:2968-2972.
16. Powell JT, Greenhalgh RM: Clinical practice: Small abdominal aortic aneurysms. *N Engl J Med* 2003; 348:1895-1901.
17. Krupski WC, Rutherford RB: Update on open repair of abdominal aortic aneurysms: The challenges for endovascular repair. *J Am Coll Surg* 2004; 199:946-960.
18. Thompson AR, Cooper JA, Ashton HA, Hafez H: Growth rates of small abdominal aortic aneurysms correlate with clinical events. *Br J Surg* 2010; 97:37-44.
19. Powell JT, Brown LC, Greenhalgh RM, Thompson SG: The rupture rate of large abdominal aortic aneurysms: Is this modified by anatomical suitability for endovascular repair? *Ann Surg* 2008; 247:173-179.
20. Noel AA, et al: Ruptured abdominal aortic aneurysms: The excessive mortality rate of conventional repair. *J Vasc Surg* 2001; 34:41-46.
21. Alonso-Pérez M, et al: Factors increasing the mortality rate for patients with ruptured abdominal aortic aneurysms. *Ann Vasc Surg* 2001; 15:601-607.
22. Baxter BT, et al: Distal embolization as a presenting symptom of aortic aneurysms. *Am J Surg* 1990; 160:197-201.
23. Yusuf K, et al: Inflammatory abdominal aortic aneurysm: Predictors of long-term outcome in a case-control study. *Surgery* 2007; 141:83-89.
24. van Walraven C, et al: Incidence, follow-up, and outcomes of incidental abdominal aortic aneurysms. *J Vasc Surg* 2010; 52:282-289.
25. Lederle FA, Simel DL: Does this patient have abdominal aortic aneurysm? *JAMA* 1999; 281:77-82.
26. Fink HA, et al: The accuracy of physical examination to detect abdominal aortic aneurysm. *Arch Intern Med* 2000; 160:833-836.
27. Takaseya T, et al: A case of unilateral leg edema due to abdominal aortic aneurysm with aortocaval fistula. *Ann Thoracic Cardiovasc Surg* 2007; 13:135-138.
28. Karmody AM, Powers SR, Monaco VJ, Leather RP: "Blue toe" syndrome. An indication for limb salvage surgery. *Arch Surg* 1976; 111:1263-1268.
29. Deitch JS, et al: Abdominal aortic aneurysm causing duodenal obstruction: Two case reports and review of the literature. *J Vasc Surg* 2004; 40:543-547.
30. De Martino RR, et al: Outcomes of symptomatic abdominal aortic aneurysm repair. *J Vasc Surg* 2010; 52:5-12.
31. Soisalon-Soininen S, Salo JA, Perhoniemi V, Mattila S: Emergency surgery of non-ruptured abdominal aortic aneurysm. *Ann Chir Gynaecol* 1999; 88:38-43.
32. Sterpetti AV, et al: Sealed rupture of abdominal aortic aneurysms. *J Vasc Surg* 1990; 11:430-435.
33. Gaughan M, McIntosh D, Brown A, Laws D: Emergency abdominal aortic aneurysm presenting without haemodynamic shock is associated with misdiagnosis and delay in appropriate clinical management. *Emerg Med J* 2009; 26:334-339.
34. Rose J, Civil I, Koelmeyer T, Haydock D, Adams D: Ruptured abdominal aortic aneurysms: Clinical presentation in Auckland 1993-1997. *ANZ J Surg* 2001; 71:341-344.
35. Saers SJ, Scheltinga MR: Primary aortoenteric fistula. *Br J Surg* 2005; 92:143-152.
36. Armstrong PA, et al: Improved outcomes in the recent management of secondary aortoenteric fistula. *J Vasc Surg* 2005; 42:660-666.
37. Baril DT, et al: Evolving strategies for the treatment of aortoenteric fistulas. *J Vasc Surg* 2006; 44:250-257.
38. Cinara IS, et al: Aorto-caval fistulas: A review of eighteen years experience. *Acta Chir Belg* 2005; 105:616-620.
39. Kuhn M, et al: Emergency department ultrasound scanning for abdominal aortic aneurysm: Accessible, accurate, and advantageous. *Ann Emerg Med* 2000; 36:219-223.
40. Hermsen K, Chong WK: Ultrasound evaluation of abdominal aortic and iliac aneurysms and mesenteric ischemia. *Radiol Clin North Am* 2004; 42:365-381.
41. Hoffman B, et al: Successful sonographic visualization of the abdominal aorta differs significantly among a diverse group of credentialed emergency department providers. *Emerg Med J* 2010; 28:472-476.
42. Blaivas M, Theodoro D: Frequency of incomplete abdominal aorta visualization by emergency department bedside ultrasound. *Acad Emerg Med* 2004; 11:103-105.
43. Catalano O, Lobianco R, Cusati B, Siani A: Contrast-enhanced sonography for diagnosis of ruptured abdominal aortic aneurysm. *AJR Am J Roentgenol* 2005; 184:423-427.
44. Brewster DC, et al: Long-term outcomes after endovascular abdominal aortic aneurysm repair: The first decade. *Ann Surg* 2006; 244: 426-438.
45. Eliason JL, Upchurch GR Jr: Endovascular abdominal aortic aneurysm repair. *Circulation* 2008; 117:1738-1744.
46. Hans SS, Huang RR: Results of 101 ruptured abdominal aortic aneurysm repairs from a single surgical practice. *Arch Surg* 2003; 138:898-901.
47. Mell MW, et al: Effect of early plasma transfusion on mortality in patients with ruptured abdominal aortic aneurysm. *Surgery* 2010; 148:955-962.
48. Valentine RJ, Barth MJ, Myers SI, Clagett GP: Nonvascular emergencies presenting as ruptured abdominal aortic aneurysms. *Surgery* 1993; 113:286-289.
49. Verhoeven EL, et al: Mortality of ruptured abdominal aortic aneurysm treated with open or endovascular repair. *J Vasc Surg* 2008; 48:1396-1400.
50. Roberts K, Revell M, Youssef H, Bradbury AW, Adam DJ: Hypotensive resuscitation in patients with ruptured abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* 2006; 31:339-344.
51. Veith FJ, et al: Collected world and single center experience with endovascular treatment of ruptured abdominal aortic aneurysms. *Ann Surg* 2009; 250:818-824.
52. Baxter BT, Terrin MC, Dalman RL: Medical management of small abdominal aortic aneurysms. *Circulation* 2008; 117:1883-1889.
53. Bown MJ, Sutton AJ, Bell PR, Sayers RD: A meta-analysis of 50 years of ruptured abdominal aortic aneurysm repair. *Br J Surg* 2002; 89:714-730.
54. McPhee J, Eslami MH, Arous EJ, Messina LM, Schanzer A: Endovascular treatment of ruptured abdominal aortic aneurysms in the United States (2001-2006): A significant survival benefit is independently associated with increased institutional volume. *J Vasc Surg* 2009; 49:817-826.
55. Davenport DL, et al: Thirty-day NSQIP database outcomes of open versus endoluminal repair of ruptured abdominal aortic aneurysms. *J Vasc Surg* 2010; 51:305-309.
56. Rayt HS, Sutton AJ, London NJ, Sayers RD, Bown MJ: A systematic review and meta-analysis of endovascular repair for ruptured abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* 2008; 36:536-544.

www.ketabpezeshki.com 66485457-66963820

57. Mayer D, et al: 10 years of emergency endovascular aneurysm repair for ruptured abdominal aortoiliac aneurysms: Lessons learned. *Ann Surg* 2009; 249:510-515.
58. Najjar SF, et al: Percutaneous endovascular repair of ruptured abdominal aortic aneurysms. *Arch Surg* 2007; 142:1049-1052.
59. Balm R: Endovascular repair of ruptured abdominal aortic aneurysm. *Br J Surg* 2008; 95:133-134.
60. Mehta M, et al: Establishing a protocol for endovascular treatment of ruptured abdominal aortic aneurysms: Outcomes of a prospective analysis. *J Vasc Surg* 2006; 44:1-8.
61. Adam DJ, Mohan IV, Stuart WP, Bain M, Bradbury AW: Community and hospital outcome from ruptured abdominal aortic aneurysm within the catchment area of a regional vascular surgical service. *J Vasc Surg* 1999; 30:922-928.
62. Lederle FA, et al: Immediate repair compared with surveillance of small abdominal aortic aneurysms. *N Engl J Med* 2002; 346:1437-1444.
63. United Kingdom Small Aneurysm Trial Participants: Long-term outcomes of immediate repair compared with surveillance of small abdominal aortic aneurysms. *N Engl J Med* 2002; 346:1445-1452.
64. Powell JT, et al: Final 12-year follow-up of surgery versus surveillance in the UK Small Aneurysm Trial. *Br J Surg* 2007; 94:702-708.
65. Schermerhorn ML, et al: Endovascular vs. open repair of abdominal aortic aneurysms in the Medicare population. *N Engl J Med* 2008; 358:464-774.
66. Landon BE, O'Malley AJ, Giles K, Cotterill P, Schermerhorn ML: Volume-outcome relationships and abdominal aortic aneurysm repair. *Circulation* 2010; 122:1290-1297.
67. Blankensteijn JD, et al: Two-year outcomes after conventional or endovascular repair of abdominal aortic aneurysms. *N Engl J Med* 2005; 352:2398-2405.
68. Prinssen M, et al: A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. *N Engl J Med* 2004; 351:1607-1618.
69. Lederle FA, et al: Outcomes following endovascular vs. open repair of abdominal aortic aneurysm: A randomized trial. *JAMA* 2009; 302:1535-1542.
70. United Kingdom EVAR Trial Investigators: Endovascular versus open repair of abdominal aortic aneurysm. *N Engl J Med* 2010; 362:1863-1871.
71. Heller JA, et al: Two decades of abdominal aortic aneurysm repair: Have we made any progress? *J Vasc Surg* 2000; 32:1091-1100.
72. Hoornweg LL, et al: Meta analysis on mortality of ruptured abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg* 2008; 35:558-570.
73. Hallett JW Jr, et al: Graft-related complications after abdominal aortic aneurysm repair: Reassurance from a 36-year population-based experience. *J Vasc Surg* 1997; 25:277-284.
74. Conrad MF, et al: Secondary intervention after endovascular abdominal aortic aneurysm repair. *Ann Surg* 2009; 250:383-389.
75. Leurs LJ, Buth J, Laheij RJ: Long-term results of endovascular abdominal aortic aneurysm treatment with the first generation of commercially available stent grafts. *Arch Surg* 2007; 142:33-41.
76. van Marrewijk C, et al: Significance of endoleaks after endovascular repair of abdominal aortic aneurysms: The EUROSTAR experience. *J Vasc Surg* 2002; 35:461-473.
77. Schmieder GC, Stout CL, Stokes GK, Parent FN, Panneton JM: Endoleak after endovascular aneurysm repair: Duplex ultrasound imaging is better than computed tomography at determining the need for intervention. *J Vasc Surg* 2009; 50:1012-1018.

www.ketabpezeshki.com 66485457-66963820

Chapter 87

Peripheral Arteriovascular Disease

Tom P. Aufderheide

PERSPECTIVE

Arteries are classified into three categories on the basis of their size and histologic features: (1) large or elastic arteries (the aorta and its immediate proximal, larger branches, including the innominate, subclavian, common carotid, and pulmonary arteries); (2) medium-sized or muscular arteries (located just distal to elastic arteries, including the common femoral, axillary, and carotid arteries); and (3) small arteries (usually <2 mm in diameter) that course in the substance of tissues and organs. This chapter considers diseases of medium and small arteries.

PRINCIPLES OF DISEASE

Arterial Anatomy

All arteries possess three layers: the tunica intima, tunica media, and tunica adventitia. As peripheral arteries diminish in caliber, these three layers become progressively indistinct and are no longer identifiable at the level of the arteriole (precapillary vessel containing smooth muscle).

The tunica intima has an inner lining of endothelial cells surrounded by subendothelial connective tissue. The single layer of continuous endothelium is a unique thromboresistant layer between blood and the potentially thrombogenic subendothelial tissues. The integrity of the endothelium is a fundamental requirement for maintenance of normal structure and function of the entire vessel wall. Endothelial injury can result in intraluminal thrombosis and may contribute to the initiation of atherosclerosis.

The tunica media is made up primarily of circular or spiral smooth muscle cells arranged in concentric layers. The outer limit of this layer is marked by a well-defined, external elastic membrane. The elastic content of the tunica media gives resilience to medium-sized arteries. With age, the elastic fibers deteriorate and are replaced by fibrous tissue. This loss of elasticity results in stretching and elongation and accounts for the progressive tortuosity and development of arterial aneurysms with aging. Vascular smooth muscle cells may be important in lipid accumulation in the vessel wall during atherosclerosis and participate in vasoconstriction and dilation.

The tunica adventitia is a poorly defined layer of connective tissue in which nerve fibers and small, thin-walled nutrient vessels (vasa vasorum) are dispersed. Medium-sized arteries contain more nerve fibers than larger vessels, reflecting the importance of their role in the autonomic regulation of blood flow.

The peripheral arterial vascular system can be considered as a single end-organ subject to eight basic pathophysiologic processes: (1) atherosclerosis, (2) aneurysm, (3) embolism, (4) thrombosis, (5) inflammation, (6) trauma, (7) vasospasm, and (8) arteriovenous fistula. Two of these—atherosclerosis and thrombosis—are responsible for most peripheral arterial problems.

Pathophysiology

Atherosclerosis

Atherosclerosis is a disease of large- and medium-sized muscular arteries. The basic lesion, the atheroma, or fibrofatty plaque, is a raised focal plaque within the intima; it has a lipid core (mainly cholesterol, usually complexed to proteins and cholesterol esters) covered by a fibrous cap. As the plaques increase in size and number, they progressively encroach on the lumen of the artery and the adjacent media. Atheromas compromise arterial blood flow and weaken the walls of the affected arteries.

The distribution of atherosclerotic plaques is rather constant. The abdominal aorta has more atherosclerotic disease than the thoracic aorta, and aortic lesions are much more common and prominent around the ostia of major branches. Other vessels affected by atherosclerosis are the aortoiliac, femoral, and popliteal arteries; the descending thoracic aorta; the coronary arteries; the internal carotid arteries; and the circle of Willis. Vessels of the upper extremities are usually spared.

As atherosclerosis progresses, atheromas almost always calcify, resulting in hard, brittle vessels. Ulceration of the luminal surface and rupture of the atheromatous plaques discharge debris, producing atheroemboli (cholesterol emboli). Fissured or ulcerated lesions can produce in situ thrombosis, causing acute intraluminal occlusion.

Hemorrhage into the plaque may further compromise the arterial lumen. Although atherosclerosis primarily affects the intima, in severe cases, the tunica media undergoes pressure atrophy and loss of elastic tissue, with sufficient weakening to create aneurysmal dilation.

Aneurysms

A true aneurysm is an abnormal localized dilation of the intact vessel wall. With a pseudoaneurysm the entire wall perforates or ruptures, and the extravasated blood is contained by the surrounding tissues, eventually forming a fibrous sac that communicates with the artery.

Mural and mechanical factors contribute to true aneurysm formation.[1] The major cause of aneurysms is a weakness or defect in the integrity of the arterial wall. The only aneurysms that develop in a normal arterial segment are poststenotic aneurysms, such as with coarctation. Acceleration of flow past a narrow point creates slower flow beyond the stenosis lateral to the jet stream, producing

www.ketabpezeshki.com 66485457-66963820

increased lateral pressure. Aneurysmal dilation accelerates, increasing the risk of rupture as diameter increases, as predicted by Laplace's law: tension (lateral pressure) in the wall of a hollow viscus varies directly with its radius (tension = pressure × radius).

The most common cause of aneurysms is severe atherosclerosis resulting from thinning and destruction of the tunica media. Atheromatous ulcers covered by mural thrombi are common within an aneurysm. Such mural thrombi can form emboli that lodge in distal vessels. When an entire aneurysm is filled with thrombus material, arterial occlusion results.

Aneurysms cause clinical symptoms through (1) rupture with subsequent hemorrhage, (2) impingement on adjacent structures, (3) occlusion of a vessel by either direct pressure or mural thrombus formation, (4) embolism from mural thrombus, and (5) presentation as a pulsatile mass.

Arterial Embolism

An embolus is a blood clot or other foreign body that is carried by the blood to a site distant from its point of origin. Most emboli are the result of detached thrombus formation (thromboembolism). Less common sources include debris from ruptured atherosclerotic plaques, tumor debris, or foreign bodies. Unless otherwise specified, the term embolus in this chapter is defined as thromboembolus.

Thromboembolism. Most arterial emboli (85%) originate in thrombus formation in the heart. Left ventricular thrombus formation resulting from myocardial infarction accounts for 60 to 70% of arterial emboli. Atrial thrombi associated with mitral stenosis and rheumatic heart disease account for only 5 to 10% of arterial emboli.[2] Coexisting atrial fibrillation, often without mitral stenosis, is present in 60 to 75% of patients with peripheral arterial embolic events, because atrial fibrillation itself can predispose patients to intracardiac clotting.[3]

Acute arterial emboli often cause distal tissue infarction. Clinical outcome depends mostly on the amount of collateral circulation present but also on the size of the vessel and the degree of obstruction. Patients with long-standing atherosclerosis have well-developed collateral circulation, whereas sudden occlusion of a normal artery without collateral pathways results in severe ischemia. After acute obstruction, the embolus can propagate proximally or distally, fragment and embolize further to distal vessels, or precipitate associated venous thrombosis by initiating a localized inflammatory reaction.

Because vessel diameters change most abruptly at branch points, embolic occlusion most often occurs at major arterial bifurcations. The bifurcation of the common femoral artery is the most frequent site of arterial embolism, accounting for 35 to 50% of all cases.[2] The smaller femoral and popliteal arteries are involved twice as often as the larger aortic and iliac vessels, reflecting the small size of most emboli.

Cell death from arterial ischemia can produce high concentrations of potassium, lactic acid, and myoglobin in the extremity distal to an arterial occlusion. Their sudden release after revascularization can produce life-threatening hyperkalemia, metabolic acidosis, and myoglobinuria. This myonephropathic-metabolic syndrome accounts for approximately one third of the deaths from arterial embolism after revascularization.[4]

Atheroembolism. *Atheroembolism* refers to microemboli consisting of cholesterol, calcium, and platelet aggregates dislodged from proximal complicated atherosclerotic plaques that lodge in distal end arteries. In the central nervous system, atheroemboli cause transient ischemic attacks and strokes. In the peripheral vascular system, atheroemboli characteristically cause cool, painful, and cyanotic toes, or the blue toe syndrome.[5]

Atheroemboli are caused by a proximally located arterial lesion, usually atherosclerotic plaques or aneurysms. Bilateral distal extremity involvement usually implies an aortic source, whereas unilateral atheroemboli usually arise from sites distal to the aorta. Distal lesions are most common in the femoropopliteal arteries (60%) and the aortoiliac arteries (40%). Aortic lesions (e.g., aneurysms, polytetrafluoroethylene grafts) are a less common source of microemboli.[5]

Atheroemboli are small and tend to lodge in distal arteries, such as the digital arteries, which are 100 to 200 μm in size. Single atheroembolic events seldom result in tissue loss, but atheroemboli tend to cluster. If unrecognized, repeated events ultimately result in loss of collateral circulation, progressive symptoms, and extensive tissue infarction.[5]

Infectious emboli from bacterial endocarditis can produce septic infarcts that may convert to large abscesses. Rarely, cardiac and noncardiac tumors or foreign bodies may gain access to the arterial circulation and embolize. Primary or metastatic lung neoplasms, malignant melanoma, and bullet emboli have been reported. In patients with cyanotic congenital heart disease (e.g., patent foramen ovale), venous emboli may pass directly to the arterial circulation (paradoxical emboli). Although rare, this possibility should be considered in any patient with simultaneous arterial and venous emboli, particularly if a source of the arterial embolus is not evident.

Arterial Thrombosis

Thrombosis is the in situ formation of a blood clot within the uninterrupted arterial vascular system. Complicated atherosclerotic plaques are usually responsible for the two major factors that cause in situ thrombosis: endothelial injury and alterations in normal blood flow. Less common causes include acute vasculitis and trauma. Thrombosis is rare in normal arteries.[6]

Peripheral arterial thrombi are usually occlusive, although they may be limited to one wall (mural) in larger vessels. Peripheral arterial thrombi are usually firmly attached to the damaged arterial wall and infrequently embolize. The clot may propagate proximally and distally, which intensifies ischemia.

Inflammation

Inflammatory arterial injury can be caused by drugs, irradiation, mechanical trauma, or bacterial invasion. The major cause of arteritis is noninfectious systemic necrotizing vasculitis. Most cases of infectious arteritis are caused by direct invasion of the arterial wall. Septicemia, intravenous drug abuse, or infective endocarditis is most often responsible. Certain fungal infections, particularly aspergillosis and mucormycosis, are frequently associated with vasculitis and thrombosis.

Trauma

Different types of vascular injury result in characteristic pathologic syndromes. Partial arterial lacerations continue to bleed because the intact portion of the vessel wall prevents retraction and closure of the arterial wound. This may form an expanding hematoma, causing progressive deformity, pain, and nerve compression. Complete arterial transection usually has only moderate or insignificant bleeding because of arterial spasm of the transected ends of the artery and the formation of a temporary thrombus. Delayed hemorrhage in completely transected arteries may result from relaxation of arterial spasm, eventual liquefaction of the thrombus, or displacement of the thrombus by arterial pressure. Blunt injury may produce partial or complete intimal disruption. Dissection of the distal intima can lead to progressive obstruction and thrombosis. Complete occlusion may not occur for hours or days after injury. Vasospasm can accompany injuries that are adjacent to blood vessels; spontaneous

www.ketabpezeshki.com 66485457-66963820

resolution always occurs in the absence of arterial disruption or intimal injury.

Vasospasm

Vasospastic disorders (Raynaud's disease, Raynaud's phenomenon, livedo reticularis, acrocyanosis, erythromelalgia) produce an abnormal vasomotor response in distal small arteries. The cause of these disorders is unknown but may be related to the autonomic innervation of the peripheral arterioles. The vasospastic disorders are characterized by the presence of ischemic symptoms and the absence of tissue loss. True organic changes within the arterial wall are absent. In contrast, patients with digital ulceration and gangrene always have fixed arterial occlusions in the distal extremity arteries.

Arteriovenous Fistulae

Abnormal communication between arteries and veins may result from congenital defects, rupture of an arterial aneurysm into an adjacent vein, penetrating injuries, and inflammatory necrosis associated with neoplasms or infection. Arteriovenous fistulae can occur in any region of the body. The artery proximal to the fistula becomes distended, tortuous, and aneurysmal. Similar changes occur in the venous side of the fistula. Proximal and distal veins respond to alterations in hemodynamics with intimal proliferation and fibrosis, followed by a decrease in the internal elastic lamina, resulting in distention, tortuosity, and aneurysm formation. The resultant chronic venous hypertension may cause dermatitis and ulceration of overlying skin. The size of the fistula generally increases with time.

Approximately 60% of arteriovenous fistulae are associated with a false aneurysm.[7] False aneurysm formation can occur as part of the fistulous tract or as the result of arterial or venous dilation.[7]

The increase in cardiac output that occurs when blood switches from the arterial to the venous system can result in a widened pulse pressure or high-output cardiac failure.

CLINICAL FEATURES

History

Patients with peripheral arterial disease have pain, tissue loss (ulceration or gangrene), or a change in sensation or appearance (swelling, discoloration, or temperature change). Because the primary cause of peripheral arterial disease is atherosclerosis, related conditions providing evidence of atherosclerosis are cardiac disease, myocardial infarction, cardiac dysrhythmias (e.g., atrial fibrillation), stroke, transient ischemic attacks, and renal disease. Factors that increase the likelihood of atherosclerosis are cigarette smoking, diabetes, hypercholesterolemia, and hypertension. Intravenous drug use can lead to arterial injury.

Risk factors not related to atherosclerosis include prior injuries or surgeries, major illnesses, a history of phlebitis or pulmonary embolism, the presence of autoimmune disease or arthritis, and a history of prior coagulation abnormalities.

Acute Arterial Occlusion

The patient with acute arterial occlusion usually exhibits some variant of the five *P*s: pain, pallor, pulselessness, paresthesias, and paralysis. Paresthesias and paralysis indicate limb-threatening ischemia that requires emergency surgical intervention regardless of the cause. In patients with non–limb-threatening ischemia, accurate differentiation between embolism and in situ thrombosis as the cause of acute arterial occlusion determines management.

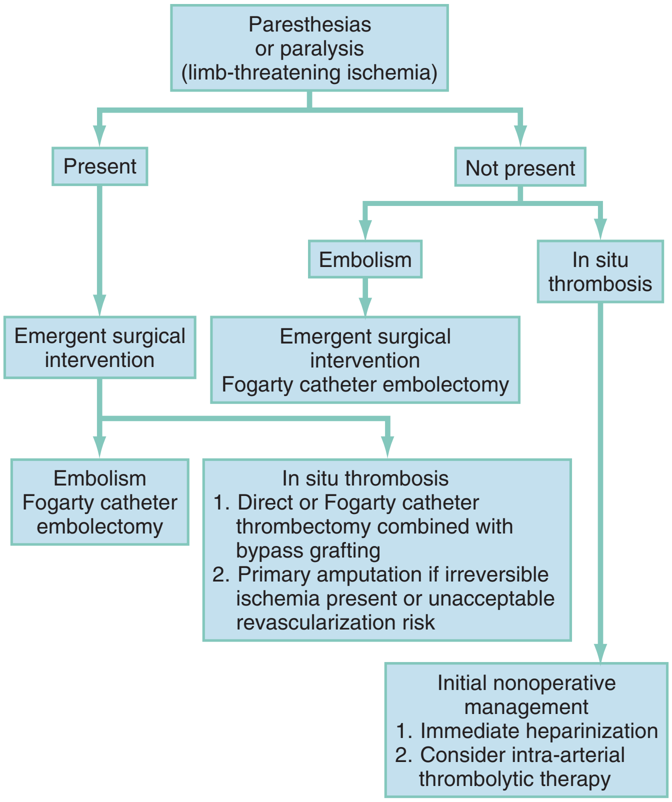


Figure 87-1. Clinical presentation and management of acute arterial occlusion.

Arterial embolism is best managed by emergency Fogarty catheter embolectomy. Non–limb-threatening ischemia from in situ thrombosis is often aggravated by emergency surgical intervention and is therefore initially best managed nonoperatively, if possible (Fig. 87-1). Because acute arterial embolism usually occurs in patients without significant peripheral atherosclerosis and without well-developed collateral circulation, it usually manifests as sudden limb-threatening ischemia. Patients describe a sensation of the leg's being "struck" by a severe shocking pain. Often the patient has to sit or fall to the ground during the sudden event.

In situ thrombosis usually occurs in patients who have long-standing significant peripheral atherosclerosis and well-developed collateral circulation and is often seen subacutely with non–limb-threatening ischemia. A history of claudication is common with in situ thrombosis and rare in patients with arterial embolism.

Chronic Arterial Insufficiency

Chronic arterial insufficiency causes two characteristic types of pain: intermittent claudication and ischemic pain at rest. The location of arterial occlusion determines the location of claudication. Calf claudication is associated with femoral and popliteal disease, typically a cramping pain, reliably reproduced by the same degree of exercise and completely relieved by rest (usually 1-5 minutes). Aortoiliac occlusive disease causes claudication in the buttocks and hips, as well as the calves. The calf pain in aortoiliac disease is generally more severe than the buttock and thigh pain, which is more often described as an aching, discomfort, or weakness. Some patients deny pain, complaining only that the thigh or hip "gives out" with exercise. Aortoiliac occlusive disease severe enough to produce bilateral claudication is almost always associated with impotence in men (Leriche's syndrome). Even in the absence of impotency, bilateral hip or thigh pain in a man should indicate the possibility of aortoiliac occlusive disease.

www.ketabpezeshki.com 66485457-66963820

Chronic arterial insufficiency may progress so that ischemic pain occurs at rest. Rest pain often begins in the feet and typically involves the foot distal to the metatarsals, awakening the patient from sleep. Ischemic rest pain is a severe, unrelenting pain aggravated by elevation and unrelieved by analgesics, but patients have prompt relief with any activity that involves a standing position. Patients often sleep with the leg dangling over the side of the bed or sleep in a chair to improve perfusion pressure to the distal tissues.

Physical Examination

A systematic assessment of the peripheral vascular system includes palpation of the pulse volume in the pairs of brachial, radial, femoral, posterior tibial, and dorsalis pedis arteries documented on a scale of 0 to 4+. Approximately 10% of the population does not have one of the dorsalis pedis pulses.[8] Carotid arteries should be gently palpated one at a time.

The lower extremities should be examined for signs of chronic and advanced ischemia. Muscular atrophy, particularly in the lower extremities, and loss of hair over the toes and feet with thickening of the toenails resulting from slowness of nail growth are common signs of arterial insufficiency. As ischemia becomes more advanced, the skin becomes shiny, scaly, and "skeletonized" from atrophy of the skin, subcutaneous tissue, and muscle.

Areas where ischemia is suspected can be tested by blanching with finger pressure; a delay in return of normal color (compared with that of the unaffected extremity) implies reduced perfusion.

Buerger's sign provides reliable evidence of severe advanced ischemia. With the patient supine, his or her legs are elevated to 45 degrees to bring the feet more than 12 inches above the right atrium, and any pallor of the feet is noted. If the color does not change, the patient dorsiflexes the feet five or six times; pallor induced by exercise also connotes inadequate arterial flow. The patient is then moved to the sitting position with the feet hanging down. Within 10 to 15 seconds, color should return, and the veins should fill. Typically in the ischemic foot the first color return is cyanotic, transitioning to red as reactive hyperemia occurs. If the veins require more than 20 seconds to become distended, advanced ischemia is present. With severely restricted arterial inflow and chronic dilation of the peripheral vascular bed, the foot turns chalk white on elevation and intensely hyperemic after 1 minute of dependency. Localized pallor or cyanosis associated with poor capillary filling is usually a prelude to ischemic gangrene or ulceration.

Doppler ultrasonography should be used in patients with questionable or absent pulses. The ankle-brachial index (ABI) is made by comparing the systolic blood pressure at the level of the ankle with the brachial systolic pressure. With the patient supine, a blood pressure cuff is applied just proximal to the malleolus, inflated above brachial systolic pressure, and then deflated slowly. Ankle systolic pressure can be accurately measured with a Doppler probe placed over the dorsalis pedis or posterior tibial artery. This pressure is normally 90% or more of the brachial systolic pressure; with mild arterial insufficiency, it is between 70 and 90%; with moderate insufficiency, between 50 and 70%; and with severe insufficiency, less than 50%.

The Allen test is helpful in assessing patency of the radial or ulnar artery distal to the wrist. The patient initially opens and closes the hand and then clenches the fist to expel as much blood from the hand as possible; the examiner then compresses the radial and ulnar arteries. When the patient opens the fist, the hand is pale. The examiner then releases pressure from the radial artery but maintains it on the ulnar artery. If the radial artery distal to the wrist is patent, the hand becomes pink rapidly; if it is occluded, the hand remains pale. The maneuver is then repeated by maintaining pressure on the radial artery while releasing the ulnar artery. A comparison can be made with the opposite hand.

Arterial Embolism

The physical examination can differentiate arterial embolism from in situ thrombosis. The sudden loss of a pulse is the hallmark of arterial embolism but may be difficult to recognize if the prior pulse status is unknown or is abnormal as the result of associated atherosclerosis. A bounding pulse may be felt initially at the location of an embolus from transmitted pulsations through the fresh clot. In general, patients with arterial embolism have few physical findings suggestive of long-standing peripheral vascular disease with normal proximal and contralateral limb pulses. Tenderness to palpation may occur at the site of an embolic occlusion.

If arterial embolism is suspected, the physical examination should be directed toward identifying its source, most commonly a left ventricular mural thrombus secondary to a prior myocardial infarction and a left atrial thrombus in a patient with mitral valve disease. Coexistent atrial fibrillation is common.

The limb distal to an embolic occlusion is initially chalk white. Because of absence of blood from the venules of the subcapillary layer, the demarcation between ischemic and nonischemic tissue is sharp. With time, cyanosis may appear, indicating desaturation of blood with continued ongoing ischemia. Paresthesia or paralysis indicates limb-threatening ischemia. The presence of sensitivity to light touch is often the best guide to viability of the tissue. Complete anesthesia demands immediate surgical intervention. Paralysis represents severe skeletal muscle and neural ischemia, which may be irreversible. Involuntary muscle contracture with woody hardness represents irreversible ischemia.

Arterial Thrombosis

Physical findings of in situ thrombosis are often accompanied by evidence of atherosclerotic occlusive disease. Proximal or contralateral limb pulses are usually diminished or absent. An embolic source, such as mitral valve disease or atrial fibrillation, is usually absent. Because of collateral circulation, demarcation of limb ischemia is less well defined in these patients (Table 87-1).

Carotid, renal, and femoral arteries may have bruits, and there may be an abdominal aortic aneurysm. If an occlusion of the

Table 87-1 Differentiation of Embolus from Thrombosis

CLINICAL FINDINGS	EMBOLUS	THROMBOSIS
Identifiable source for embolus	Usual, particularly atrial fibrillation	Less common
History of claudication	Rare	Common
Physical findings suggestive of occlusive disease	Few; proximal and contralateral limb pulses normal	Often present; proximal or contralateral limb pulses diminished or absent
Demarcation of ischemia	Sharp	Diffuse
Arteriography	Minimal atherosclerosis; sharp cutoff; few collaterals	Diffuse atherosclerosis; tapered, irregular cutoff; well-developed collaterals

From Brewster DC, Chin AK, Fogarty TJ: Vascular Surgery. Philadelphia, WB Saunders, 1990.

www.ketabpezeshki.com 66485457-66963820

upper extremity vessels is suggested, the subclavian artery should be evaluated by palpating for thrills and listening for bruits in the supraclavicular fossa.

A funduscopic examination may yield evidence of arteriosclerosis or hypertension. Hollenhorst plaques (atheromatous emboli containing cholesterol crystals in the retinal arterioles) may be detected. Roth's spots (round or oval white spots seen near the optic disk) may be present in patients with infective endocarditis.

Embolic phenomena can cause diverse end-organ damage: hemiplegia from cerebral emboli, flank pain with hematuria from renal emboli, left upper quadrant abdominal pain from splenic infarcts, and pleuritic pain with hemoptysis from pulmonary emboli. Septic pulmonary embolism from right-sided endocarditis may be confused with pneumonia.

Inflammation

Inflammatory vascular disease manifests primarily as skin involvement. Skin lesions typically appear as palpable purpura; other cutaneous manifestations of vasculitis include macules, papules, vesicles, bullae, subcutaneous nodules, ulcers, and recurrent or chronic urticaria. The skin lesions may be pruritic or even painful, with a burning or stinging sensation. Lesions are more common in dependent areas: in the lower extremities in ambulatory patients or in the sacral area in bedridden patients. Edema accompanies some lesions, and hyperpigmentation occurs in areas of recurrent or chronic lesions.

Vasospasm

Vasospastic disorders cause a sharp border between ischemic and normal tissue. Raynaud's disease is characterized by intermittent attacks of triphasic color changes: pallor, cyanosis, and then rubor.[9] The most important element is pallor, during which the digits turn chalk white. Attacks last 15 to 60 minutes, and rewarming the hands restores normal color and sensation. Color changes do not occur above the metacarpophalangeal joints and rarely involve the thumb.

Livedo reticularis is characterized by a persistent cyanotic mottling of the skin that has a typical "fishnet" appearance and may involve all parts of the extremities and trunk. Acrocyanosis, the least common vasospastic disorder, is characterized by persistent, painless, diffuse cyanosis of the fingers, hands, toes, and feet. Cyanosis usually intensifies with exposure to cold and decreases with warming. The involved parts are nearly always cold, exhibit excessive perspiration, and have normal arterial pulses.

Arteriovenous Fistulae

Arteriovenous malformations and fistulae, although rare, must be distinguished from vascular bruits or aneurysms. True aneurysms and arterial stenoses are associated with a systolic murmur. Pseudoaneurysms generally have a loud systolic and sometimes a separate faint diastolic murmur. Arteriovenous fistulae have a constant systolic and diastolic (to-and-fro) murmur heard best directly over the lesion and often associated with a palpable thrill, precisely analogous to the findings of a therapeutic dialysis arteriovenous fistula. Unless congenital, arteriovenous fistulae occur at prior operative or trauma sites. The skin overlying the lesion may be warm, but distally the temperature is often decreased. Veins peripheral to the fistula are usually distended and varicose. Large and long-standing arteriovenous fistulae produce high cardiac output and widened pulse pressure. Digital pressure on the artery leading to the fistula or the fistula itself may decrease the tachycardia (Branham's sign).

DIAGNOSTIC STRATEGIES

An accurate diagnosis of peripheral arterial occlusive disease can be achieved in most patients by careful history and physical examination supplemented by bedside testing.

Noninvasive Assessment

Doppler ultrasonography measures blood flow velocity by detecting the frequency shift of sound waves reflected from red blood cells that move toward and away from the transducer. The Doppler signal generates a normal triphasic velocity waveform. Progressive arterial narrowing alters the triphasic waveform to biphasic and finally monophasic shape. Such Doppler ultrasonographic waveform analysis can detect significant arterial occlusive disease, although it is less accurate in determining exact location.

Ultrasound is useful in detecting and evaluating atherosclerotic plaques and mural thrombi and in sizing aneurysms of the abdominal aorta and iliac, femoral, and popliteal arteries.[10] B-mode ultrasonography is noninvasive, painless, less expensive than other modalities, and universally available and is the diagnostic procedure of choice for the initial evaluation and determination of the size of peripheral artery aneurysms. Bedside ultrasound can lead to rapid diagnosis of life-threatening conditions and reduce the number of delayed or invasive diagnostic procedures.[11] B-mode duplex ultrasonography combines the image of B-mode ultrasonography and sophisticated online computer analysis of accurately sampled Doppler waveforms to allow simultaneous acquisition of both the image of a vascular structure and the characteristics of blood flow velocity within it. Duplex scanning permits noninvasive and accurate diagnosis of peripheral vascular, cerebrovascular, and venous disease.

Color imaging of blood flow combined with duplex scanning is known as *color-coded Doppler, Doppler angiography*, or *angiodynography*. The procedure of choice for most conditions, this combination allows noninvasive and accurate detection of atherosclerotic plaques and stenoses, their effect on intraluminal blood flow, and the presence of venous thrombosis.

Contrast Arteriography

Angiography is the definitive test of abnormal peripheral artery anatomy but is often inconclusive about the physiologic condition of the tissues. Adverse effects of contrast media and catheter-related complications must be weighed against the benefits of this procedure. Contrast media have a direct toxic effect on vascular endothelium; can produce renal failure, especially in diabetic patients; may cause peripheral vasodilation with hypotension; may result in seizures and stroke in patients with neurologic conditions; and can cause severe idiosyncratic and allergic reactions. Catheter-related complications, including embolization, catheter breakage, and vascular disruption, vary with operator skill and anatomic location but average 0.5%. The overall mortality rate from angiography is 0.03%.[11] Emergency angiography is usually necessary in the following circumstances: (1) acute arterial embolus or thrombosis if the clinical diagnosis is uncertain, (2) consideration of emergency vascular bypass grafting, and (3) characterization of vascular abnormality before emergency surgical correction.

Computed Tomography and Magnetic Resonance Imaging

Computed tomography angiography is the most useful test for evaluation of the abdominal aorta.[12] In the peripheral arteriovascular system, CT angiography is useful primarily for atherosclerotic, infected, and false aneurysms and for imaging the cerebral

www.ketabpezeshki.com 66485457-66963820

circulation. Magnetic resonance imaging (MRI) has the capability for angiography (magnetic resonance angiography) and has been particularly useful in delineating cerebrovascular problems (see Chapter 101); it is seeing expanded use in the evaluation of peripheral vascular disease. The ability to make axial, coronal, and sagittal sections provides accurate visualization of anatomy. MRI detects changes in the relaxation variables of tissues before obvious structural changes, uniquely differentiating blood, thrombus, fat, and fibrosis.

MANAGEMENT OPTIONS

The management of acute arterial occlusion depends on the degree and cause of ischemia. Patients with limb-threatening ischemia from embolism should undergo emergency Fogarty catheter embolectomy.[13] Patients with limb-threatening ischemia caused by in situ thrombosis require direct or Fogarty catheter thrombectomy combined with vascular bypass grafting. Thrombectomy alone often fails because of recurrent thrombosis. Patients who have a lesion that cannot be bypassed, who have evidence of irreversible ischemia, or who are too ill to tolerate revascularization are treated with primary amputation.

A patient with non–limb-threatening ischemia from embolism still is treated with Fogarty catheter embolectomy. Non–limb-threatening ischemia from in situ thrombosis is managed nonoperatively with immediate systemic heparinization and possibly with intra-arterial fibrinolytic therapy (see Fig. 87-1).

Elective surgical repair of an asymptomatic atherosclerotic peripheral arterial aneurysm is usually accomplished by excision of the aneurysm with end-to-end anastomosis or graft interposition. Infected true and false peripheral aneurysms require aneurysm resection, débridement of infected tissue, and ligation of the proximal and distal uninfected arteries. Autogenous vein bypass through uninfected tissue planes is attempted, because prosthetic grafts carry a high risk of graft infection. The surgical approach for uninfected false aneurysms is similar to that for peripheral atherosclerotic aneurysms.

Patients with thoracic outlet syndrome who have cervical ribs, arterial involvement, or significant neurologic symptoms require surgical decompression with removal of anomalous fibromuscular bands and resection of the first rib, if present. Subclavian and subclavian-axillary aneurysms can be treated with resection and end-to-end anastomosis, graft reconstruction, or surgical revision. Patients with distal embolic occlusions are treated with Fogarty catheter embolectomy. Axillary and subclavian vein thromboses are best managed with surgical thrombectomy or systemic fibrinolytic therapy. Patients with only brachial plexus involvement and minimal signs and symptoms should be followed closely with conservative treatment.

Surgical treatment of peripheral arteriovenous fistulae requires interrupting the fistula tract and restoring both arterial and venous continuity with end-to-end anastomosis or graft interposition. If the anatomic location precludes surgical intervention, percutaneous transvascular embolization with liquid tissue adhesives (e.g., isobutyl 2-cyanoacrylate) is usually successful.

Noninvasive Therapy

Acute Anticoagulation with Heparin

For acute arterial embolism, acute arterial thrombosis, and subclavian vein thrombosis, heparin is indicated at standard intravenous doses (80 units/kg by intravenous bolus, followed by a maintenance infusion of 18 units/kg/hr). Heparin quickly reduces thrombin generation and fibrin formation, minimizing clot propagation, which can intensify limb ischemia and jeopardize tissues. Relative contraindications include recent neurosurgery (especially within 2 weeks), major surgery within 48 hours, childbirth within 24 hours, a known bleeding diathesis, thrombocytopenia, a potentially hemorrhagic lesion, and active bleeding.

Fibrinolytic Therapy

Low-dose intra-arterial fibrinolytic therapy is increasingly used for acute arterial occlusion. Patients with limb-threatening ischemia are not candidates because clot lysis generally takes 6 to 72 hours. Patients with limb-threatening ischemia cannot tolerate several more hours of ischemia without tissue or limb loss. Fibrinolytic therapy is generally reserved for patients with in situ thrombosis and non–limb-threatening ischemia.

Intra-arterial fibrinolytic agents induce clot lysis in the small, distal runoff vessels, decreasing outflow resistance and enabling the native artery to remain open longer. Fibrinolysis often uncovers a critical stenosis that, untreated, may lead to another episode of thrombosis. After successful fibrinolytic therapy, most patients require secondary bypass grafting or percutaneous transluminal angioplasty. Streptokinase, urokinase, and tissue plasminogen activator have all been used successfully. Intravenous administration of a fibrinolytic agent is less effective than direct administration into the clot. Clots more than 30 days old are more organized and less likely to achieve successful lysis.

Invasive Therapy

Fogarty Catheter Thrombectomy

The Fogarty catheter is most frequently used for iliac, femoral, and popliteal embolectomy, often with only local anesthesia.[13] Aortic saddle embolus is removed by sequentially passing the Fogarty catheter through bilateral common femoral arteriotomies.

Newly formed in situ thrombosis can often be successfully removed with the Fogarty catheter. An older thrombus adheres more firmly to the damaged vessel wall, requiring direct surgical thrombectomy. The Fogarty catheter is not used in the venous system because of valves.

Peripheral Percutaneous Transluminal Angioplasty

The initial success and long-term patency achieved with angioplasty depend on the location of the lesion and the extent of atheromatous disease. Proximal larger arteries (e.g., iliac, femoropopliteal) have the best initial and long-term results. Discrete stenotic lesions (<5 cm) have better long-term patency rates than vessels that are diffusely involved or have multiple involved segments. Balloon angioplasty is the accepted treatment for isolated stenotic lesions in the renal, iliac, and superficial femoral vessels.

Transluminal angioplasty with intravascular stent is used in more distal vessels, including the popliteal and tibial circulation, in cases of more diffuse lesions, and for patients who are prohibitive surgical risks, although its value remains to be determined.[14]

Recanalization devices include the percutaneous atherectomy catheter, percutaneous angioscope, hot-tip laser, excimer laser, and high-speed rotating wire and drill.

Grafting

Vascular grafting is associated with a variety of complications that can be diagnosed in the emergency department. Autogenous vein grafts (usually a reversed greater saphenous vein) provide excellent long-term patency for small arteries. Vein grafts respond to arterial pressure with gradual intimal proliferation and medial fibrosis. They may develop atherosclerosis, which can lead to graft stenosis and thrombosis. False aneurysms can form along the suture line.

www.ketabpezeshki.com 66485457-66963820

Polytetrafluoroethylene (Teflon) prosthetic grafts are widely used in medium and large arteries that are impossible to bridge with smaller vein grafts. Prosthetic grafts have a higher rate of thrombosis than venous grafts. Distal emboli may result from poor fixation of luminal fibrin. If the prosthetic graft has not been adequately covered by viable tissue, it can erode into adjacent structures and hollow viscera. Prosthetic graft infection is a devastating complication requiring removal of the entire graft.

Vascular grafts can be used to bypass arterial occlusions and reconstruct a diseased arterial bifurcation, or can be interposed between sections of resected artery. The two most common complications of both prosthetic and vein grafts are thrombosis and development of a false aneurysm at one or more suture lines. Bypass grafting is most often used as palliative treatment for symptoms of atherosclerotic occlusive disease. Patients with localized unilateral stenosis (<3-5 cm in length) may have a comparable rate of success with percutaneous transluminal angioplasty with or without stent placement.[15]

Patients with calf claudication from superficial femoral or popliteal occlusive disease can slow progression if they stop smoking and maintain an active exercise regimen. Patients who have progression of disease, significant rest pain, or tissue loss require surgical revascularization.

Sympathectomy

Lumbar sympathectomy is no longer used for treatment of ischemia from arterial occlusion. The benefit of sympathectomy in patients with symptomatic Raynaud's phenomenon is unclear, but it remains a potential intervention to assist healing of superficial ischemic ulcers and relieve rest pain in patients with Buerger's disease.[16]

Hyperbaric Therapy

Scant objective evidence indicates that hyperbaric therapy alters the long-term course of chronic obliterative vascular disorders, presumably by accelerating formation of fine vessels. More success has been achieved with healing chronic diabetic ischemic ulcers and salvaging ischemic skin grafts and flaps.[17] Referral to a hyperbaric unit for chronic therapy should be made by the patient's primary physician or vascular surgeon and not in the emergency department.

Figure 87-2. Clinical presentation of atheromatous emboli, or blue toe syndrome. (Courtesy Gary R. Seabrook, MD.)

SPECIFIC ARTERIOVASCULAR DISEASES

DISEASES OF CHRONIC ARTERIAL INSUFFICIENCY

Arteriosclerosis Obliterans

Arteriosclerosis obliterans (atherosclerotic occlusive disease, chronic occlusive arterial disease, obliterative arteriosclerosis) is the peripheral arterial presentation of atherosclerosis. Most often, arteriosclerosis obliterans affects the lower abdominal aorta, the iliac arteries, and the arteries supplying the lower extremities. Upper extremity manifestations are rare.

Arteriosclerosis obliterans is responsible for 95% of cases of chronic occlusive arterial disease. It is most common in persons older than 50 years, but as many as 19% of cases occur in patients aged 30 to 49 years. Men are affected more often than women (5:1 to 10:1). Approximately one third of patients with arteriosclerosis obliterans have coexistent coronary artery disease. The incidence of diabetes mellitus is 20 to 30%.[18]

Risk factors for arteriosclerosis obliterans include cigarette smoking, hyperlipidemia, and hypertension. Of patients with arteriosclerosis obliterans, 70 to 90% are smokers when first examined, 75% have hyperlipidemia, and 30% have hypertension.[18]

Clinical Features and Differential Diagnosis

Acute arterial occlusion from embolism, thrombosis, or trauma is ruled out primarily by history. Atheromatous emboli from proximal ulcerated plaques or aneurysms can cause small scattered ischemic lesions in the toes, feet, or legs, causing blue toe syndrome (Fig. 87-2). The peripheral pulses are present in blue toe syndrome. Exercise-induced claudication must be distinguished from the nocturnal muscle cramps that frequently occur during rest in elderly patients. Aortoiliac occlusive disease must be differentiated from osteoarthritis of the hip, which tends to be more variable from day to day, is not relieved completely with rest, and is not reliably reproduced by the same amount of exercise. Pseudoclaudication from the cauda equina syndrome is caused by narrowing of the lumbar canal from spondylosis, disease of the intervertebral disks, or spinal cord tumor. The symptoms mimic intermittent claudication but are less closely related to exercise and rest than true claudication.

The cause of lower extremity ulcers should be carefully determined. Approximately 5% of lower extremity ulcerations are caused by arterial insufficiency.[19] These are usually located distal to the ankle, typically at the terminal portion of the digits, around the nail beds, or between the toes, caused by friction of one toe on another. Less common locations include the metatarsal heads, heel, and malleoli. Arterial insufficiency ulcers are painful but improve when the extremity is in a dependent position. They are associated with evidence of coexistent chronic arterial insufficiency (absence of hair growth on the dorsum of the feet, skin atrophy, absent pulses, and nail deformities). Ulcers are initially small, shallow, and dry. The base is gray, yellow, or black, with

www.ketabpezeshki.com 66485457-66963820

minimal or no granulation tissue. The rim of the ulcer is sharp and indolent, showing no signs of cellular proliferation or epithelialization.

Approximately 90% of lower extremity ulcers are caused by chronic venous insufficiency.[19] These typically occur proximal to or in the region of the ankle, especially near the medial malleolus. Venous stasis ulcers are only mildly painful and improve with elevation of the extremity. Evidence of long-standing chronic venous insufficiency, including edema, prominent superficial veins, and stasis dermatitis, is present. Ulcers are moderate in size, with a weeping base and extensive granulation tissue. A rapidly developing ulcer is more suggestive of venous insufficiency.

Most of the remaining lower extremity ulcers are caused by diabetic neuropathy, alone or with arterial insufficiency.[19] The location reflects sites of repeated trauma, including the toes, heels, and plantar surface of the feet, especially the metatarsal heads. Neurotrophic ulcers are typically painless. Patients may have evidence of coexistent peripheral arterial insufficiency. The ulcers are deep and penetrating, often with suppurative drainage caused by an underlying infection or chronic osteomyelitis. Neurotrophic ulcers are usually surrounded by a rim of thick callus.

Hypertensive ulcers are rare and reflect long-standing, uncontrolled hypertension. These ulcers are typically near the lateral malleolus and start as painful, reddish blue areas of infarcted skin. A hemorrhagic bleb develops then breaks down into a superficial ulcer, which can reach a size of 5 to 10 cm. The ischemic ulcer has sharply demarcated borders, little granulation tissue, and minimal drainage. The pain is the most severe of all lower extremity ulcers.

Multiple ischemic ulcerations above and below the ankle suggest vasculitis or atheromatous embolization. Ulcers with regular edges in unusual locations may be factitial or may result from subcutaneous injection of illicit drugs. Thickened, rolled, and elevated edges with a central depression containing granulation tissue are characteristic of malignant ulcers.

Management

The first step is to identify patients whose symptoms are the sole result of arteriosclerosis obliterans without coexistent thromboembolic disease. Treatment for symptomatic patients depends on whether patients have functional ischemia or limb-threatening ischemia.[20]

Limb-threatening ischemia constitutes a surgical emergency. Angiography should be arranged to identify sufficiently localized disease to permit emergency bypass grafting.[20] Patients with functional ischemia should have outpatient arrangements for noninvasive vascular testing or elective invasive contrast arteriography to determine treatment options such as bypass grafting. Ischemic ulcers or skin lesions should be cultured in the emergency department. Systemic antibiotics to cover skin organisms should be instituted if infection is present. Wet to dry dressings may help débride ulcers containing fibrin, debris, or infection. Radiographs of the underlying bones should rule out osteomyelitis. Patients with ischemic rest pain require hospitalization even if they are not surgical candidates. Bed rest, a warm environment, and maintenance of the limb in a dependent position usually relieve pain.

Buerger's Disease (Thromboangiitis Obliterans)

First described by Buerger in 1908, thromboangiitis obliterans is an idiopathic inflammatory occlusive disease primarily involving the medium-sized and small arteries of the hands and feet.[21] Patients are usually men aged 20 to 40 years who use tobacco, although recent reports indicate an increasing frequency of this disease in women. Buerger's disease affects people of all races but is more prevalent in the Middle and Far East.[22] The incidence in the United States is 20 per 100,000.[23] The exact pathogenesis of Buerger's disease is unknown, but virtually all patients are smokers.

Thromboangiitis obliterans is characterized by segmental acute and chronic inflammation in the smaller arteries of both upper and lower extremities. The initial arterial inflammatory process progresses to affect the adjacent veins and nerves, often leading to associated venous thrombosis and progressive fibrous encasement of these structures. There are painful, tender, reddened, or dark nodules over a peripheral artery with either a reduced or an absent pulse (phlebitis migrans).

Clinical Features

Clinical criteria for Buerger's disease include (1) a history of smoking, (2) onset before the age of 50, (3) infrapopliteal arterial occlusive lesions, (4) either upper limb involvement or phlebitis migrans, and (5) absence of atherosclerotic risk factors other than smoking. A characteristic symptom of Buerger's disease is foot or instep claudication caused by infrapopliteal arterial occlusion. Intense rubor of the affected extremity, particularly with dependency, is also characteristic. Foot pulses may be absent in the presence of normal femoral and popliteal pulses. Involvement of the hands is often bilateral and symmetrical, leading to the development of hand claudication or fingertip ulcers. Phlebitis migrans occurs early in the disease. Approximately 50% of patients experience Raynaud-type triphasic color response to cold. In the upper extremities, the digital arteries are usually more involved than the radial or ulnar arteries.[22]

Diagnostic Strategies

Adherence to diagnostic clinical criteria should be sufficient for emergency department diagnosis of Buerger's disease. Noninvasive vascular laboratory testing can confirm the diagnosis and determine the extent of involvement. Although rarely required, angiography demonstrates multiple segmental occlusions.

Differential Diagnosis

Arteriosclerosis obliterans is most likely in patients older than 50 years who have signs of peripheral ischemia. In young women, autoimmune diseases, such as scleroderma or systemic lupus erythematosus, should be considered.[22]

Management

Permanent complete abstinence from tobacco is the only effective treatment for Buerger's disease. If a patient does not completely stop smoking, alternating periods of quiescence are followed by exacerbations of severe arterial insufficiency. Patients who quit smoking have a benign clinical course. Despite this, many individuals who have Buerger's disease continue to smoke, incurring severe pain at rest, tissue loss, and eventually amputation.

With early symptoms without threat of tissue loss, patient education and follow-up with a vascular surgeon are sufficient. Vascular surgery treatment options are varied for patients with severe symptoms or threatened tissue loss. Intractable pain can be controlled with epidural anesthesia. Intra-arterial or intravenous prostaglandin E_1 and antithrombotic agents, including aspirin and heparin, have been used successfully.[22] Patients with large-vessel arterial occlusion may benefit from arterial reconstruction. Sympathectomy is a potential treatment in advanced cases for cutaneous ulceration or relief of rest pain.[16]

www.ketabpezeshki.com 66485457-66963820

Because patients with Buerger's disease have good healing, intensive conservative treatment is usually successful in avoiding amputation.

DISEASES OF ACUTE ARTERIAL OCCLUSION

Arterial Embolism

Despite advances in diagnosis and treatment, acute arterial embolus continues to cause substantial morbidity and mortality. Approximately 50% of acute arterial occlusions are caused by arterial embolism, and the incidence appears to be increasing. The other 50% are caused by in situ thrombosis.[2]

Differential Diagnosis

Phlegmasia cerulea dolens is a massive iliofemoral deep venous thrombosis. The initial symptom may be acute onset of a swollen and painful leg. As swelling continues, secondary arterial insufficiency with associated pallor (phlegmasia cerulea albens) may occur. In acute arterial embolism, leg swelling is usually absent, especially at the onset of pain. In addition, acute embolism produces a sharply demarcated pallor; phlegmasia cerulea dolens causes a cyanotic-appearing leg.

Aortic dissection may involve the arteries of the upper or lower extremity and may mimic acute embolus. A history of progressive severe pain, the presence of aortic insufficiency, and involvement at multiple sites suggest dissection. Acute neurologic syndromes (e.g., transverse myelitis, spinal subarachnoid hemorrhage, ruptured intervertebral disk) may produce sudden onset of unilateral or bilateral lower extremity weakness or sensory loss that mimics an acute aortic saddle occlusion.

Cold, blue extremities may result from low-output states such as hypovolemia, decreased cardiac output, dehydration, myocardial infarction, and pulmonary emboli in patients with longstanding atherosclerotic disease.

Management

Acute arterial embolism is a surgical emergency. The likelihood of limb salvage decreases after 4 to 6 hours. On the basis of clinical diagnosis alone, full doses of intravenous heparin should be administered immediately to minimize clot propagation. Patients whose history and physical examination findings clearly indicate an acute arterial embolism should undergo immediate Fogarty catheter embolectomy without prior angiography. In these patients, preoperative ultrasonography and angiography are rarely useful diagnostically and prolong the limb's ischemic status.

If the differentiation of acute embolism and in situ thrombosis is uncertain, pretreatment angiography is usually diagnostic. Patients with acute emboli generally show minimal signs of atherosclerosis, occlusion at the site of an arterial bifurcation, sharply demarcated cutoffs, and lack of flow distal to the occlusion. In patients with in situ thrombosis, arteriography shows diffuse atherosclerosis, occlusion at sites other than arterial bifurcations, a tapered irregular cutoff, and well-developed collateral vessels. Emboli tend to lodge at arterial bifurcations, whereas arterial thrombi do not (see Table 87-1).

Intra-arterial thrombolytic therapy for acute embolism remains investigational. Immediate limb-threatening ischemia precludes consideration of treatment with thrombolytic therapy in most patients. Potential risks of thrombolytic therapy in arterial embolism patients with non–limb-threatening ischemia include partial clot lysis with distal embolization or recurrent embolic events from the primary source of the initial embolus.[23]

Atheroembolism (Blue Toe Syndrome)

Atheroemboli are microemboli consisting of cholesterol, calcium, platelet aggregates, and hemorrhagic debris that break off from proximal atherosclerotic plaques or aneurysms and lodge in distal end arteries. In the central nervous system, atheroembolism causes transient ischemic attacks and strokes. In the peripheral vascular system, atheroemboli characteristically are found in the lower extremities with cool, painful cyanotic toes in the presence of palpable distal pulses (see Fig. 87-2).

Clinical Features

The typical presentation of atheroembolism is the sudden onset of a small painful (cyanotic and tender) area on the foot, typically the toe.[24] If bilateral involvement is present, the distribution is not symmetrical. Posterior tibial and dorsalis pedis pulses are present. The physical examination should be directed toward identification of a proximal source, such as an atherosclerotic aneurysm in the aorta or iliac, femoral, or popliteal artery.

Differential Diagnosis

A variety of conditions can mimic the blue toe syndrome. Acrocyanosis is painless, has a symmetrical distribution, and is located in the hands, nose, and lips. Poor peripheral perfusion from low cardiac output must also be considered. Vasculitis typically causes palpable purpuric lesions and is associated with constitutional symptoms of low-grade fever, myalgias, and weight loss. Previous frostbite may leave the extremities sensitive to cold. Local injury to the foot of the diabetic patient is easily differentiated.

Management

Treatment is directed toward identifying and removing the proximal source of atheroembolism. Angiography is the most accurate diagnostic method for determining the source of emboli. If the source is an aortic aneurysm and the patient is a surgical candidate, operative repair should be performed. Stenotic lesions in the iliac or femoral arteries can be treated with local endarterectomy, vascular bypass, or angioplasty.[14] Medical management with aspirin, dipyridamole, crystalline warfarin sodium (Coumadin), or steroids has variable results.

Arterial Thrombosis

Approximately 50% of acute arterial occlusions are caused by in situ thrombosis.[2] Acute arterial thrombosis is almost always superimposed on a complicated atherosclerotic lesion but can be caused by vasculitis or trauma. With limb-threatening ischemia, angiography can be used to evaluate the feasibility of emergency bypass grafting. In patients with non–limb-threatening ischemia, angiography may be required to distinguish acute embolism from thrombosis (see Table 87-1).

Management

Heparinization should be started when the diagnosis is made. Patients with severe limb-threatening ischemia require emergency direct or Fogarty catheter thrombectomy combined with bypass grafting. Simple thrombectomy alone often fails as a result of rethrombosis. Patients who have atherosclerotic disease not amenable to vascular bypass, who are too ill to tolerate revascularization, or who have irreversible ischemia require primary amputation. Patients with non–limb-threatening ischemia are best treated nonoperatively with heparin and low-dosage intra-arterial thrombolytic therapy.

www.ketabpezeshki.com 66485457-66963820

PERIPHERAL ARTERIAL ANEURYSMS

A true aneurysm is an abnormal localized dilation of the intact wall of any vessel caused by a combination of mural weakness and hemodynamic forces. Aneurysms enlarge at a rate determined by the cause. Those caused by atherosclerosis progress slowly over years; those caused by trauma or infection enlarge over days, weeks, or months. The primary risk of central aneurysms (abdominal aorta, iliac arteries, and visceral arteries) is rupture (see Chapter 84). Peripheral arterial aneurysms rarely rupture; instead, they are complicated by thrombosis or embolism that jeopardizes distal tissues.[25]

The cause of an aneurysm depends on its anatomic location. Lower extremity aneurysms are most often atherosclerotic in origin. Upper extremity aneurysms are usually caused by local trauma. Visceral aneurysms are from abnormal hemodynamics, atherosclerosis, or infectious causes.

Lower Extremity

Femoral and popliteal artery aneurysms almost always occur in older men with advanced atherosclerosis. Twenty-five percent of patients have distal atheroembolism or thromboembolism; an additional 15% have total occlusion from in situ thrombosis.[25]

Popliteal aneurysms are the most common peripheral aneurysms and occur bilaterally in approximately 60% of patients.[25] An abdominal aortic aneurysm occurs in almost 80% of patients with bilateral popliteal aneurysms. Most patients have claudication, thromboembolic events, atheroembolic events, or gangrene. Aneurysmal dilation can cause venous compression with associated deep venous thrombosis.

Femoral aneurysms are the second most common peripheral aneurysms and manifest similarly to popliteal aneurysms. Femoral aneurysm dilation can also compress the femoral nerve, producing anterior thigh pain or weakness.

Diagnosis of both popliteal and femoral aneurysms is by palpation of a pulsatile mass. Plain radiographs may show unilateral or bilateral calcified aneurysms. Ultrasonography and CT are diagnostic. Arteriography yields definitive diagnosis and indicates involvement of distal vessels. Patients with a lower extremity aneurysm should be evaluated for the presence of other aneurysms.

Asymptomatic patients can undergo elective surgical excision of the aneurysm and end-to-end anastomosis or graft interposition. Simultaneous repair of coexisting abdominal aorta or contralateral extremity aneurysms combined with vascular bypass is typically done. Patients with limb-threatening thromboembolic events are first treated with Fogarty catheter embolectomy.[25]

Upper Extremity

Atherosclerosis generally spares the upper extremities, so peripheral arterial aneurysms in the upper extremities are rare, making localized trauma the most common cause.

The causes of proximal subclavian artery aneurysms are thoracic outlet obstruction, trauma, and, rarely, atherosclerosis. Subclavian aneurysms from atherosclerosis represent severe disease, and 30 to 50% of patients so afflicted also have aortoiliac or other peripheral aneurysms.[26] Symptoms depend on the aneurysm's anatomic location. Patients may have chest, neck, and shoulder pain from acute expansion. Compression of the right recurrent laryngeal nerve can lead to voice change. Compression of the trachea can lead to stridor or other respiratory complaints. The chest radiograph may reveal a superior mediastinal mass, easily confused with a neoplasm.

The subclavian artery can be compressed by a complete cervical rib that articulates with the first rib, producing a poststenotic dilation in the proximal subclavian and distal axillary artery. This syndrome occurs more often in women and in the dominant upper extremity. Cervical ribs occur in 0.6% of the population.[27]

Axillary artery aneurysms are most often caused by blunt trauma from inappropriate and prolonged use of crutches. Humerus fracture and anterior shoulder dislocation are less common causes.[26]

Subclavian, subclavian-axillary, and axillary artery aneurysms share the common complications of thromboembolism and limb-threatening ischemia, neuromuscular and sensory dysfunction from brachial plexus compression, and central nervous system ischemia produced by retrograde thromboembolism in the vertebral and right carotid circulation. A systolic bruit with a palpable thrill is common.

Arteriography to confirm the diagnosis and determine involvement of distal vessels is the diagnostic procedure of choice. Surgical treatment consists of aneurysm resection, vascular grafting, and reestablishment of arterial continuity.

The rare syndrome of ulnar artery aneurysm (hypothenar hammer syndrome) is associated with occupational trauma in which the heel of the palm is used to hammer, push, or twist objects.[28] Patients are often mechanics, carpenters, and machinists.

The ulnar artery fits snugly into the bony canal at the hypothenar eminence under the hook of the hamate bone. Long-term repetitive damage to this region results in aneurysm formation.[28] The aneurysm may develop a mural thrombus that repeatedly embolizes to the superficial palmar arch or to a digital artery. Symptoms consist of paresthesias, pain, coolness, and cyanosis, most often in the little and ring fingers and occasionally in the middle and index fingers. The thumb is characteristically spared because of its radial artery blood supply. Diagnosis is easily made by finding a pulsatile or nonpulsatile tender mass in the hypothenar eminence of the dominant hand. The Allen test may demonstrate occlusion of the ulnar artery. Angiography of the distal vessels is diagnostic. Proximal angiography rules out the subclavian and axillary arteries as embolic sources. Treatment requires surgical resection of the aneurysm and reestablishment of ulnar artery continuity. Adjunctive preoperative fibrinolytic therapy may be helpful.[28]

Viscera

Splenic Artery Aneurysms

Splenic artery aneurysms account for 60% of all visceral arterial aneurysms. They are the only aneurysms that are more common in women, with a female-to-male ratio of 4 : 1.[29] The development of aneurysms in the splenic artery has been attributed to systemic arterial fibrodysplasia, portal hypertension, and increased splenic arteriovenous shunting that occurs in pregnancy.

Splenic artery aneurysms are most often asymptomatic. Symptomatic patients exhibit vague left upper quadrant or epigastric discomfort and occasional radiation of pain to the left shoulder or subscapular area. Because most splenic artery aneurysms are less than 2 cm in diameter, a pulsatile mass is not palpable. Occasionally, a systolic bruit can be heard.

Only 2% of splenic artery aneurysms result in life-threatening rupture.[29] More than 95% of ruptures occur in young women during pregnancy and can be confused with ectopic pregnancy or placental abruption.

Splenic artery aneurysms are usually an incidental discovery on the abdominal radiograph as signet ring calcifications in the left upper quadrant. Ultrasonography, CT, and MRI can distinguish aneurysms from other cystic lesions in the left upper quadrant.[29] An angiogram is usually required to confirm the diagnosis. Symptomatic splenic artery aneurysms require immediate operative

www.ketabpezeshki.com 66485457-66963820

intervention, particularly in pregnant women or in women of childbearing age. The rate of maternal mortality from rupture during pregnancy is approximately 70%. In asymptomatic patients, transcatheter embolization is an alternative to surgery.[30]

Hepatic Artery Aneurysms

Hepatic artery aneurysms represent 20% of visceral artery aneurysms. The lesions are caused by atherosclerosis, infection (most often as a complication of intravenous drug abuse), major abdominal trauma, and polyarteritis nodosa. Hepatic artery aneurysms affect men twice as often as women and usually occur after 60 years of age.

Most aneurysms remain asymptomatic, but unruptured symptomatic aneurysms generally produce symptoms consistent with cholecystitis: vague, persistent, right upper quadrant or epigastric pain radiating to the back. Large aneurysms can cause severe upper abdominal discomfort, similar to pancreatitis. Hepatic artery aneurysms may rupture into the common bile duct, peritoneum, or adjacent hollow viscera, with a mortality rate of 35%.

An abdominal bruit or palpable pulsatile mass is usually not present on physical examination. Aneurysmal calcification may be seen on a plain abdominal radiograph, but the diagnosis can be made reliably by angiography. Ultrasonography and CT can detect asymptomatic hepatic artery aneurysms.[29]

Because of the high mortality rate with aneurysmal rupture, an aggressive approach to management is warranted. Surgical resection of the aneurysm is performed in operative candidates. Transarterial catheter occlusion can be used in patients who are high surgical risks.[31]

Superior Mesenteric Artery Aneurysms

Superior mesenteric artery aneurysms are the third most common visceral aneurysms. Nearly 60% are infected aneurysms caused by nonhemolytic streptococci from left-sided bacterial endocarditis. Atherosclerosis and trauma are much less common causes. Patients are usually younger than 50 years of age; men and women are affected equally.

Patients generally have intermittent upper abdominal pain consistent with abdominal angina. Fifty percent have a pulsatile abdominal mass on physical examination. The stigmata of subacute bacterial endocarditis may be present. Plain abdominal radiographs may show a calcified aneurysm. Angiography is necessary to confirm the diagnosis.

Management of superior mesenteric artery aneurysm should address any underlying infectious process. The surgical approach is difficult and varies with the condition of the patient, the shape of the aneurysm (saccular or fusiform), and the intraoperative assessment of bowel viability.

Infected Aneurysms

Mycotic Aneurysms

The term *mycotic aneurysm* is a source of confusion because there is no association with fungal disease. Although the term has been used to describe any infected aneurysm regardless of cause, it should be reserved for infected aneurysms resulting from bacterial endocarditis, as originally described in 1885 by Osler.[32,33]

Septic emboli from infective endocarditis implant in one of two ways. First, hematogenous seeding of bacteria can occur in nonaneurysmal arteries whose vessel walls have been damaged by preexisting atherosclerosis. Second, septic emboli can become lodged in the vasa vasorum of larger vessels, causing vessel wall ischemia and infection. In smaller vessels, septic emboli tend to lodge at arterial bifurcations, arteriovenous fistulae, or sites of arterial stenosis. Mycotic aneurysms are most common in the aorta, superior mesenteric artery, and intracranial and femoral arteries.

The infecting organism in mycotic aneurysms reflects the bacteriology of infective endocarditis. Viridans streptococci are the most common organisms, although intravenous drug abusers are most often infected by *Staphylococcus aureus.* Patients who have mycotic aneurysms tend to be 30 to 50 years of age. The mortality rate is 25% (Table 87-2).[32,33]

Atherosclerotic Arteries

Currently, the most common cause of an infected aneurysm is sepsis with hematogenous spread of bacteria, such as *Salmonella, Staphylococcus,* and *Escherichia coli,* to atherosclerotic arteries. Large vessels (especially the aorta) rather than peripheral arteries are the most common site. Patients tend to be older than 50 and to have well-established atherosclerosis. Perforation often occurs before diagnosis and carries a mortality rate of 75%.[33]

Preexisting Aneurysms

The incidence of infection in patients with preexisting atherosclerotic aneurysms is estimated at 3 to 4%, and patients with

Table 87-2 Clinical Characteristics of Infected Aneurysms

	MYCOTIC ANEURYSM	INFECTION OF ATHEROSCLEROTIC ARTERIES	INFECTION OF EXISTING ANEURYSM	POST-TRAUMATIC INFECTED FALSE ANEURYSM
Cause	Endocarditis	Bacteremia	Bacteremia	Drug addiction Trauma
Age (years)	30-50	>50	>50	<30
Incidence	Rare	Most common	Unusual	Very common
Location	Aorta Visceral Intracranial Peripheral	Atherosclerotic Aortoiliac Intimal defects	Infrarenal Aorta	Femoral Carotid
Bacteriology	*Viridans streptococci* *S. aureus*	*Salmonella* Others	*Staphylococcus* Others	*Staphylococcus aureus* Polymicrobial
Mortality	25%	75%	90%	5%

From Wilson SE, Van Wagenen P, Passaro E Jr: Arterial infection. Curr Probl Surg 15:1, 1978.

www.ketabpezeshki.com 66485457-66963820

ruptured aneurysms have a higher incidence of positive bacterial culture results than those who have elective surgical treatment of an asymptomatic aneurysm. Gram-positive organisms, especially *Staphylococcus,* predominate (60%). The rate of mortality is extremely high (90%) because of aneurysm rupture.[32,33]

Post-traumatic Pseudoaneurysms

Post-traumatic infected aneurysms result from invasive hemodynamic monitoring, angiography, and intravenous drug use. The most common artery affected is the femoral because of its involvement in groin injection. *S. aureus* is isolated in 30 to 70% of cases. Because of the more peripheral location and early identification, the mortality rate is low (5%).[34]

The clinical presentation of an infected aneurysm varies with anatomic location and underlying pathophysiologic process. Patients with infected abdominal aneurysms are often misdiagnosed. Onset is usually insidious; low-grade fever may be present for several months. Common findings are fever (75%), back and abdominal pain (33%), and palpable aneurysm (53%). More peripheral aneurysms, especially infected femoral pseudoaneurysms, are characterized by a tender groin mass, some manifestation of sepsis, or bleeding.[35] Almost all are easily palpable. Although rare, fungal infections should be considered in patients who are chronically immunosuppressed, have been treated recently for disseminated fungal disease, or have diabetes mellitus.[35,36]

Positive blood cultures in a patient with a preexisting aneurysm should prompt treatment as an infected aneurysm until disproven. Bacteremia often is continuous, and blood cultures are positive in approximately 70% of cases, so negative blood cultures do not rule out this diagnosis. Angiography should be performed when an infected aneurysm is suggested.[36] Indium-111–labeled white blood cells can confirm or rule out infected aneurysms.[37]

Treatment includes both antibiotics and surgical repair. Antibiotic therapy is usually continued for at least 6 to 8 weeks, although some physicians advocate lifelong treatment after successful surgical repair.[38] The most important intervention is timely repair.[32,33] Without surgery, aneurysm rupture with exsanguinating hemorrhage is inevitable.[33]

Traumatic Aneurysms

Traumatic aneurysm refers to a pseudoaneurysm that follows perforation of the arterial wall, with formation of a perivascular hematoma. Chronic traumatic aneurysms may or may not be associated with an arteriovenous fistula. *Pseudoaneurysm* is a synonym for *false aneurysm.*

The usual presentation is a pulsatile mass found near the course of an extremity artery, with a history of trauma more than 1 month earlier.[39] The expanding aneurysm may compress associated peripheral nerves and produce neuropathy. Distal perfusion is usually well maintained, and thromboembolism is rare. A loud systolic and possibly a separate faint diastolic murmur are characteristic.

The diagnosis can be verified with conventional angiography, digital subtraction arteriography, or CT. Surgical excision of the aneurysm is indicated as soon as possible to decrease the risk of complications, including rupture, thrombosis, or neurologic dysfunction caused by continued expansion.

VASOSPASTIC DISORDERS

Vasospastic disorders are characterized by an abnormal vasomotor response in the distal small arteries. Blood flow in the peripheral circulation is controlled by local, autonomic, and humoral mechanisms.[9] The cause of the increased vasospastic response is unknown.

Raynaud's disease is the most common vasospastic disorder and occurs five times more often in women than in men. By definition, cases of Raynaud's disease have no evidence of an underlying cause. The diagnosis is correct in 95% of cases that meet these criteria: (1) episodes are precipitated by cold or emotion; (2) symptoms are bilateral; (3) gangrene is absent or is minimal and confined to the skin; (4) no disease or condition that could cause a secondary Raynaud's phenomenon is present; and (5) symptoms have been occurring for at least 2 years.[40]

The classic Raynaud's attack is triphasic: the fingers become white, then blue, and finally red. This is produced initially by complete closure of the palmar and digital arteries (and possibly arterioles), producing cessation of capillary perfusion. When a slight relaxation of arterial spasm occurs, a slight flow of blood returns into the dilated capillary bed, where it rapidly dissipates, producing cyanosis. Arterial spasm usually spontaneously resolves, arterial flow returns to baseline, but reactive hyperemia produces a red extremity. Attacks are often precipitated by cold and emotional stress. Raynaud's disease usually has a benign course. True histologic changes within the vessel wall are absent. Reassurance, education, and primary care follow-up are the only treatment necessary for true Raynaud's disease.

Raynaud's phenomenon is the term given to Raynaud's disease when there is an identifiable underlying causative disorder. Connective tissue disorders, including scleroderma, rheumatoid arthritis, and systemic lupus erythematosus, have the highest association with Raynaud's phenomenon. Treatment should be directed toward identifying the underlying disorder and minimizing threatened tissue loss if present.[40]

Benign livedo reticularis is caused by spasm of the dermal arterioles and may involve all parts of the upper and lower extremities, and the trunk. It is most common when skin is exposed to a cool environment. It is never associated with histologic vascular abnormality and quickly resolves when the exposed skin is covered or the environment is warmed. Other conditions, similar to the causes of Raynaud's phenomenon, can have secondary livedo reticularis along with other peripheral vascular disease manifestations.[40]

Acrocyanosis is the least common of the vasospastic disorders and is characterized by persistent, painless, symmetrical cyanosis of the fingers, the hands, and less often the feet. The disease is benign and not associated with either vascular abnormality or an underlying disorder. Pain, trophic skin changes, and ulceration do not occur. This disorder occurs more often in women, is intensified by exposure to cold, and decreases with warming. The diagnosis is made by the bilateral and persistent nature of the findings, localized to the hands or feet in the presence of normal arterial pulses. The involved extremities are nearly always cold, and excessive perspiration is common. Except for reassurance and protection from cold, treatment is usually unnecessary.[40]

Primary erythromelalgia is a rare syndrome of paroxysmal vasodilation with burning pain, increased skin temperature, and redness of the feet and less often the hands. However, secondary erythromelalgia can occur in patients with underlying disease processes, most often systemic lupus erythematosus, myeloproliferative disorders, hypertension, venous insufficiency, or diabetes mellitus. Erythromelalgia is as common in children as adults, but in children it is less likely to be associated with an underlying systemic illness. Attacks are not triggered by cold and usually occur in modest ambient temperatures. Skin temperature of the involved digits is high compared with the patient's core temperature. Symptoms may remain mild for years or may become disabling. Tissue loss and trophic skin changes do not occur. Although rest, elevation of the extremities, and cold compresses or immersion in ice can provide temporary relief, no consistently effective treatment has been found for the multiple, often daily episodes of pain that occur with erythromelalgia.[40]

www.ketabpezeshki.com 66485457-66963820

THORACIC OUTLET SYNDROME

Thoracic outlet syndrome involves compression of the brachial plexus, subclavian vein, or subclavian artery at the superior aperture of the thorax. Thoracic outlet syndromes were previously categorized by cause as scalenus anticus, costoclavicular, hyperabduction, cervical rib, and first thoracic rib syndromes. They are now most easily divided into three types—neurologic, venous, and arterial—depending on the predominant symptoms.

Compression of the brachial plexus causes the neurologic type of thoracic outlet syndrome and accounts for approximately 95% of all cases.[41] Symptoms begin between the ages of 20 and 50 years, with women predominating at a ratio of about 3 : 1. Compression or thrombosis of the subclavian vein constitutes the venous type of thoracic outlet syndrome and is responsible for 4% of all cases. It occurs most often in men 20 to 35 years of age. The arterial type of thoracic outlet syndrome is rare, occurring in approximately 1% of all cases, but is potentially the most serious of the three types. Men and women are equally affected in a bimodal age distribution of young adults (from cervical rib compression) and patients older than age 50 (from localized atherosclerosis caused by arterial compression). Figure 87-3 demonstrates the relationship between anatomic abnormalities and neurovascular compression.

Principles of Disease

Roos[42] has described four basic concepts of thoracic outlet syndromes: (1) patients who have a thoracic outlet syndrome develop an anatomic abnormality predisposing them to symptoms under certain conditions; (2) brachial plexus compression or irritation constitutes approximately 95% of all thoracic outlet syndrome cases and is rarely caused by compression of the subclavian artery; (3) bedside testing for thoracic outlet syndrome based on positional compression of the subclavian artery is insensitive and unreliable; and (4) in advanced or refractory cases, the causative anatomic abnormalities must be surgically corrected.

The subclavian artery courses over the first rib between the scalenus anticus muscle anteriorly and the scalenus medius muscle posteriorly, when passing under the clavicle to the axilla, where the brachial plexus lies posteriorly and laterally. Four anatomic abnormalities have been associated with thoracic outlet syndrome.

Cervical rib syndrome results from an uncommon abnormality (0.5-0.7% of all chest radiographs), which is bilateral in 70% of patients.[41] It occurs twice as often in women as men. Most cervical ribs are incomplete, attached to a fibrous band on the scalene tubercle of the first rib. The site of compression is the scalene hiatus, made up of the scalene anterior muscle anteriorly, the scalene medius posteriorly, and the cervical rib inferiorly.

Scalenus anticus syndrome results when the neurovascular bundle is compressed by various insertions of the anterior scalene muscle as it passes through the interscalene triangle. In some patients the subclavian artery passes through the body of the muscle.

Costoclavicular syndrome results when the shoulders are moved backward and downward. Causes include hypertrophy of the

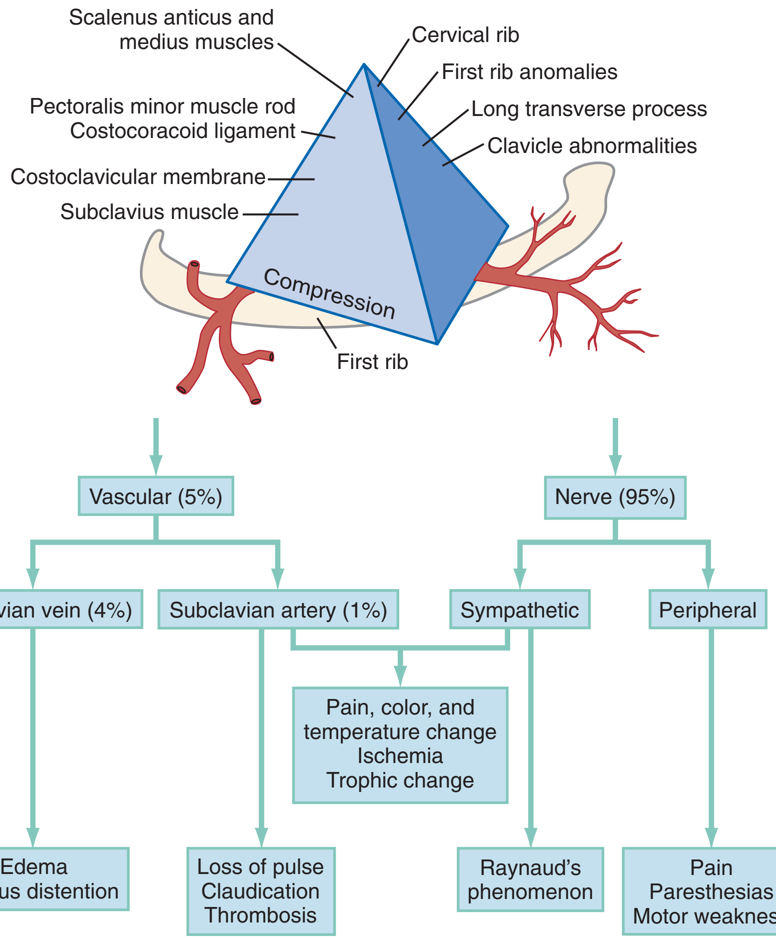


Figure 87-3. Inter-relationships of muscle, ligament, and bone abnormalities in the thoracic outlet that may compress neurovascular structures. (From Urschel HC Jr: Management of thoracic outlet syndrome. N Engl J Med 286:1140, 1972.)

www.ketabpezeshki.com 66485457-66963820

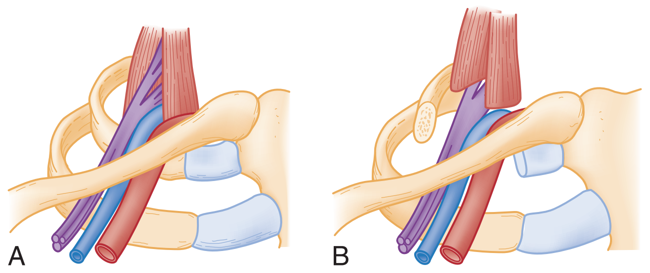


Figure 87-4. A, Thoracic outlet compression in costoclavicular space. B, Decompression of thoracic outlet by resection of first rib with disarticulation of the costochondral joint. (From Etheredge S, et al: Thoracic outlet syndrome. Am J Surg 138:175, 1979.)

subclavius muscle, abnormalities of the first rib, and past clavicular fractures.

Hyperabduction syndrome results from the neurovascular compression that occurs when the arms are placed in the hyperabducted position. The site of compression is in the retroclavicular space anterior to the first rib or at the point where the neurovascular bundle passes beneath the pectoralis minor muscle.

The neurologic and venous compression type of thoracic outlet syndrome can be associated with any underlying anatomic abnormality. Bony abnormalities (cervical rib, first thoracic rib, or clavicle) are the most common causes of the arterial type of thoracic outlet syndrome (Fig. 87-4A).

Clinical Features

Compression or irritation of the brachial plexus most often affects the lower two nerve roots, eighth cervical (C8) and first thoracic (T1), producing pain and paresthesias in the ulnar nerve distribution. The second most common anatomic pattern is involvement of the upper three nerve roots of the brachial plexus (C5, C6, and C7), with symptoms referable to the neck, ear, upper chest, upper back, and outer arm in the radial nerve distribution. Venous compression eventually progresses to intimal damage and subclavian vein thrombosis, with venous engorgement and swelling of the affected extremity. Persistent subclavian artery compression eventually results in poststenotic aneurysm formation and its sequelae.

Physical Examination

The Adson, costoclavicular, and hyperabduction maneuvers are unreliable as diagnostic tests.[42] The most reliable test in screening for thoracic outlet syndrome is the elevated arm stress test (EAST).[42] With the patient sitting, the arms are abducted 90 degrees from the thorax and the elbows flexed 90 degrees, with the shoulders braced slightly behind the frontal plane. The patient is asked to open and close the fists slowly but steadily for a full 3 minutes and to describe any symptoms that develop. Normal patients perform this test without symptoms other than mild fatigue. The patient with thoracic outlet syndrome, however, usually has early heaviness and fatigue of the involved limb, gradual onset of numbness of the hand, and progressive aching through the arm and top of the shoulder. Within the 3 minutes the patient usually drops the hand to the lap for relief of the progressive, crescendo distress that becomes intolerable. Patients with carpal tunnel syndrome may experience dysesthesias in the fingers but do not have shoulder or arm pain. Patients with cervical disk syndromes may have pain in the neck and shoulder but have no arm or hand symptoms.

The EAST evaluates all three types of thoracic outlet syndrome: neurologic, venous, and arterial. Radial pulses can be palpated by the examiner during the test. The presence of a radial pulse and a positive EAST test result are strong indications that the basis of symptoms is neurologic involvement of the brachial plexus.

The hands should be observed for changes in skin color, warmth, moisture, or muscular atrophy. Triceps muscle strength (innervated by C7) should be tested bilaterally. Muscle strength of the interosseous muscles (innervated by C8 and T1) should be tested by asking the patient to spread the fingers apart against resistance. The muscles innervated by the radial nerve are tested by having the patient hyperextend the thumb and dorsiflex the wrist against resistance. The median nerve innervates the thenar muscles, which can be tested by asking the patient to abduct the thumb away from the palm with the thumb pointing straight to the ceiling. Tinel's sign ("electric shock" to tips of fingers) is an indication of carpal tunnel compression of the median nerve and is elicited by percussing the volar aspect of the wrist. Gentle pressure with the thumb in the supraclavicular fossa over the brachial plexus may reproduce thoracic outlet symptoms after several seconds. The cervical spine and upper extremity reflexes should be assessed.

A blood pressure difference between the two arms is a reliable indication of arterial involvement. The blood pressure in the affected arm is lower. Doppler ultrasonography may be helpful in demonstrating comparatively reduced pressure over the pairs of radial, ulnar, and brachial arteries. The supraclavicular area should be auscultated bilaterally for subclavian bruits.

Ancillary Evaluation

Cervical spine radiographs with oblique views and chest radiographs are used to identify skeletal abnormalities (first rib, cervical rib, clavicle deformity), trauma, arthritis, scoliosis, Pancoast tumor, or other pulmonary disease. Electromyography, nerve conduction times, and somatosensory evoked potentials are generally unreliable and do not provide objective evidence of thoracic outlet syndrome.[42] Patients thought to have cervical disk or spinal cord disease may require cervical myelography, CT, or MRI.

Arteriography is recommended with (1) obliteration of radial pulse on the EAST, (2) blood pressure 20 mm Hg less than that of the opposite asymptomatic limb, (3) possible subclavian stenosis or aneurysm (bruit or abnormal supraclavicular pulsation), and (4) evidence of peripheral emboli in the upper extremity.[42] Venography is indicated if the patient has a history of intermittent or persistent edema of the hand or arm, peripheral unilateral cyanosis, or a prominent venous pattern over the arm, shoulder, or chest.[43]

Differential Diagnosis

The differential diagnosis of thoracic outlet syndrome includes herniated cervical disk, cervical spondylitis, spinal cord tumor, ulnar nerve compression at the elbow, carpal tunnel syndrome, orthopedic shoulder problems (sprain, rotator cuff injury, tendinitis), trauma, postural palsy, angina pectoris, and a variety of neuropathies, including those associated with multiple sclerosis, alcoholism, and diabetes.

Patients with a herniated cervical disk have more severe persistent pain radiating in a sharply demarcated dermatomal distribution (usually C4-5 or C5-6) and often have localized tenderness of the cervical spine at the affected level. Carpal tunnel syndrome is characterized by nocturnal symptoms of pain and paresthesias and an associated Tinel's sign on physical examination. Brachial plexus compression and irritation can be confused with other vascular conditions, such as Raynaud's disease, vasospastic disorders, vasculitis, or arterial ischemia. Unilateral symptoms should suggest thoracic outlet syndrome, whereas bilateral symptoms suggest a systemic process. Subclavian or axillary venous thrombosis from thoracic outlet syndrome must be differentiated from

www.ketabpezeshki.com 66485457-66963820

thrombophlebitis or mediastinal venous obstruction from a benign or malignant process (Pancoast tumor).

Management

Treatment varies depending on whether the involvement is neurologic, arterial, or venous. In patients with only brachial plexus involvement and with minimal signs and symptoms, conservative treatment with physiotherapy and shoulder girdle exercises is sufficient. Surgery is reserved for patients with intolerable pain or progressive loss of function and strength of the arm or hand. First rib and anomalous muscle or fibrous tissue resection provides consistent relief of symptoms and minimal morbidity (see Fig. 87-4B).

Patients with arterial complications of thoracic outlet syndrome (thrombosis, thromboembolism, or acute ischemia) require immediate heparinization and angiography; Fogarty catheter embolectomy, if appropriate; and emergency or urgent surgical exploration. Patients with axillary and subclavian vein thromboses require immediate heparinization and venography and are treated with surgical thrombectomy or systemic fibrinolytic therapy.[44]

Disposition

The correct diagnosis of thoracic outlet syndrome can be achieved in more than 90% of patients with a careful history, physical examination, and bedside testing alone.[42] Neurologic, orthopedic, or vascular surgery consultation is indicated according to the pathologic condition.

PERIPHERAL ARTERIOVENOUS FISTULAE

Acquired peripheral arteriovenous fistulae are most often caused by trauma (gunshot wounds, stab wounds, or surgery), with malignancy, infection, and arterial aneurysms as less common causes. Patients generally seek medical care several months after an invasive surgical procedure or penetrating injury.

Differential Diagnosis

The correct diagnosis of an arteriovenous fistula can usually be made with clinical examination alone. A constant systolic and diastolic (to-and-fro) murmur associated with a palpable thrill is characteristic. Sixty percent of arteriovenous fistulae are also associated with a coexisting false aneurysm. Patients with peripheral venous disease may have similar cutaneous manifestations (varicose veins and stasis pigmentation) but lack vascular bruits. Infection in the form of bacterial endarteritis may complicate large fistulae.

Management

Acquired peripheral arteriovenous fistulae usually increase in size with time if surgery is delayed. Vessel dilation, peripheral ischemia, and cardiac output increase.[45] Transcatheter embolization with detachable balloons and liquid acrylic tissue adhesives (e.g., isobutyl 2-cyanoacrylate) is used for surgically inaccessible fistulae.[46]

VASCULAR ABNORMALITY CAUSED BY DRUG ABUSE

Principles of Disease

The vascular complications of parenteral drug use have risen significantly in both frequency and severity since the late 1980s.[47] These intravenous or intra-arterial injuries can result in acute arterial ischemia, infected pseudoaneurysms, lymphatic obstruction, or direct neurologic injury.

Acute arterial ischemia results from direct drug effects or endogenous catecholamine release after injection. Endothelial wall damage can stimulate platelet aggregation and thrombus formation. Precipitated crystals, talc, or foreign body emboli can cause arterial occlusion. Necrotizing arteritis can produce ischemia and is especially prevalent in patients who abuse intravenous methamphetamines.

Infected pseudoaneurysms associated with arteriovenous fistulae result from a through-and-through puncture of the artery with simultaneous contamination from either skin flora or contaminated needles or drug. These fistulae are the most common vascular lesions resulting from intravenous drug abuse. Secondary infection of the vascular structure may be covered by a surrounding soft tissue infection (cellulitis or abscess). Infected aneurysms at sites distant from the injection can occur.

Intravenous drug abusers can develop unilateral hand edema or “puffy hand syndrome” because of gradual obliteration of the superficial venous vessels and chronic lymphatic obstruction. Direct injury to adjacent nerves, polyneuritis, and ischemic neuritis can result from intravenous drug abuse. Coexisting infections include cellulitis, septicemia, and bacterial endocarditis.[47]

Clinical Features

Patients may withhold information about the use of intravenous drugs, but objective evidence such as track marks may be present. Distal ischemia after intra-arterial injection most often occurs in the upper extremity after injection of the brachial or radial artery. The immediate onset of a severe, burning pain at the time of injection is a characteristic hallmark.[48] Patients have a painful, edematous upper extremity with patchy blue-purple skin discoloration. Distal pulses are generally present, but the skin temperature of the involved extremity is decreased. Because patients tend to seek attention early, the site of injection may be identifiable over the radial or brachial artery. Evidence of gangrene, pregangrenous changes, or neuromuscular deficits may accompany this syndrome.

Patients with infected pseudoaneurysms have a painful mass develop several days to weeks after injection, with resultant bleeding or “hitting pink.” The mass is usually pulsatile, and 50% have an associated bruit.[47] Infected pseudoaneurysm is part of the differential diagnosis of cutaneous abscess or cellulitis in an intravenous drug user. Infected pseudoaneurysms are most often encountered in the lower extremities (80%). All patients should be carefully evaluated for sepsis, metastatic infection, and bacterial endocarditis. A peripheral vascular examination with careful documentation of pulses should be performed. A radiograph of the affected extremity can detect subcutaneous needle fragments or foreign body. Angiography is the diagnostic procedure of choice for suggested pseudoaneurysm or distal ischemia. Ultrasonography is often unable to distinguish an aneurysm from an abscess or cellulitis.

Management

Therapeutic considerations for acute ischemia from intra-arterial injection are primarily conservative. Intra-arterial vasodilators, heparin, low-molecular-weight dextran, fibrinolytic therapy, analgesics, systemic warming to stimulate vasodilation, antibiotics, elevation of the affected limb to promote venous drainage, and physical therapy have not significantly altered the outcome or amputation rate in this patient population. Surgical treatment is reserved for delayed amputation, with the goal of preserving as much tissue as possible. Gradual resolution of

www.ketabpezeshki.com 66485457-66963820

symptoms without surgical intervention is the most common outcome.

Patients with infected pseudoaneurysms require aneurysm resection, débridement of infected tissue, and ligation of the proximal and distal uninfected arteries. Autogenous vein bypass through uninfected tissue planes may require an extensive surgical approach.[49] Intravenous nafcillin is recommended for mild infections, nafcillin and a second- or third-generation cephalosporin for major infections, and vancomycin and a second- or third-generation cephalosporin or an aminoglycoside for patients who are bacteremic or overtly septic.[47] Methicillin-resistant *S. aureus* and gram-negative rods are increasing in frequency as the causative agents in infections and vascular injury resulting from drug abuse, and vancomycin should be added if these organisms are suspected.

PROBLEMS RELATED TO LONG-TERM CENTRAL VENOUS ACCESS

Hickman-Broviac Catheter

The Hickman-Broviac double-lumen catheter is in common use, with the smaller Broviac line used for the administration of intravenous therapy and the larger Hickman line reserved for additional venous access and blood withdrawal (Fig. 87-5; see also Fig. 87-7B). This catheter is generally inserted into the cephalic, subclavian, external, or internal jugular vein, with the distal tip just above the right atrium.[50] The proximal end exits through a subcutaneous tunnel from the lower anterior chest wall. A felt cuff (Dacron) is used to anchor it in place subcutaneously. The Hickman-Broviac catheter is made of polymeric silicone rubber that is of low thrombogenic potential but extremely flexible and soft. Because of the pliability of the material, the catheter must be treated gently. Clearing an obstructed catheter with a guidewire may perforate the catheter. Forcing fluid through the catheter by positive pressure carries the risk of catheter rupture or catheter embolus. For this reason, no syringe larger than 5 mL should be used for irrigation.

Routine Care and Use

The smaller Broviac line is most often used for the infusion of total parenteral nutrition or fat emulsions. This line should be irrigated with 6 mL of normal saline solution between different infusions to prevent mixing of incompatible solutions, development of precipitation, and resultant catheter occlusion. The larger Hickman line should be used to withdraw blood. This line should be irrigated with 6 mL of heparinized saline after blood withdrawal to prevent clot formation in the catheter lumen. When a clamp is used, it should be placed over a piece of tape wrapped around the line. The clamp should have a smooth surface, because teeth or prongs could sever or abrade the line.

Routine care and frequency of catheter dressing changes vary with the preference of the treating physician.[50,51] Most patients become skilled in routine catheter maintenance and are a reliable source of information. Absolute sterile technique is essential when the catheter is manipulated.

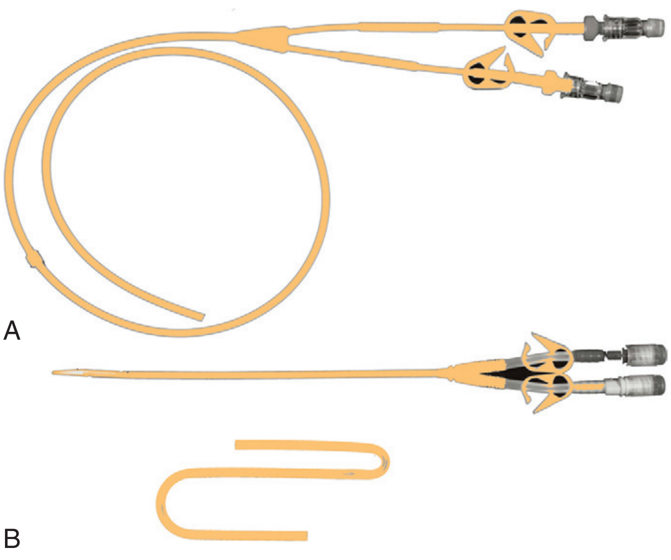


Figure 87-5. A, Double-lumen Hickman-Broviac catheter. B, Quinton-Mahurkar catheter.

Catheter Occlusion

Hickman catheters can exhibit complete or partial obstruction to flow in either line. Complete obstruction, in decreasing order of frequency, results from (1) clots within the catheter lumen, (2) precipitates within the catheter lumen, and (3) mechanical obstruction. In catheters that accept infusions at normal rates but cannot be aspirated, the causes, in decreasing order of frequency, are (1) catheter lodged against the wall of the vessel, (2) occluding fibrin sheath around the catheter tip, (3) ball valve or mural thrombus, and (4) central venous thrombosis. Patients who have intermittent complete occlusion and withdrawal occlusion have a type of mechanical obstruction called *pinch-off syndrome,* in which the catheter lumen is compromised from mechanical forces acting on it between the clavicle and the first rib. Clots within the catheter lumen, obstructing fibrin sheaths, and ball valve or mural thrombus often respond to low-dose intracatheter urokinase, whereas central venous thrombosis, precipitants in the catheter lumen, and mechanical obstruction do not respond (Box 87-1).

Precipitants within the catheter lumen most often result from flushing of the line with a heparin solution instead of saline after total parenteral nutrition. Heparin precipitates with total parenteral nutrition fluids. Clots within the catheter lumen usually result from failure to flush the line with a heparinized saline solution after blood aspiration.

A chest radiograph should be obtained in all patients with persistently occluded catheters to evaluate catheter position and integrity. The catheter tip should be positioned just above the right atrium.[50] Persistent right atrial placement can cause perforation of this thin-walled heart chamber or result in a right atrial thrombosis. Comparison with previous radiographs may be necessary to ensure lack of movement or displacement. In patients with withdrawal occlusion but appropriate catheter position and without

Box 87-1 Differential Diagnosis of Occluded Chronic Indwelling Catheters

Complete Occlusion
Clot in catheter lumen*
Precipitate in catheter lumen
Mechanical obstruction

Withdrawal Occlusion
Catheter against vessel wall
Fibrin sheath*
Ball valve or mural thrombus*
Subclavian vein thrombosis

Intermittent Complete Occlusion and Withdrawal Occlusion
Pinch-off syndrome

*Usually responds to low-dose intracatheter urokinase.

www.ketabpezeshki.com 66485457-66963820

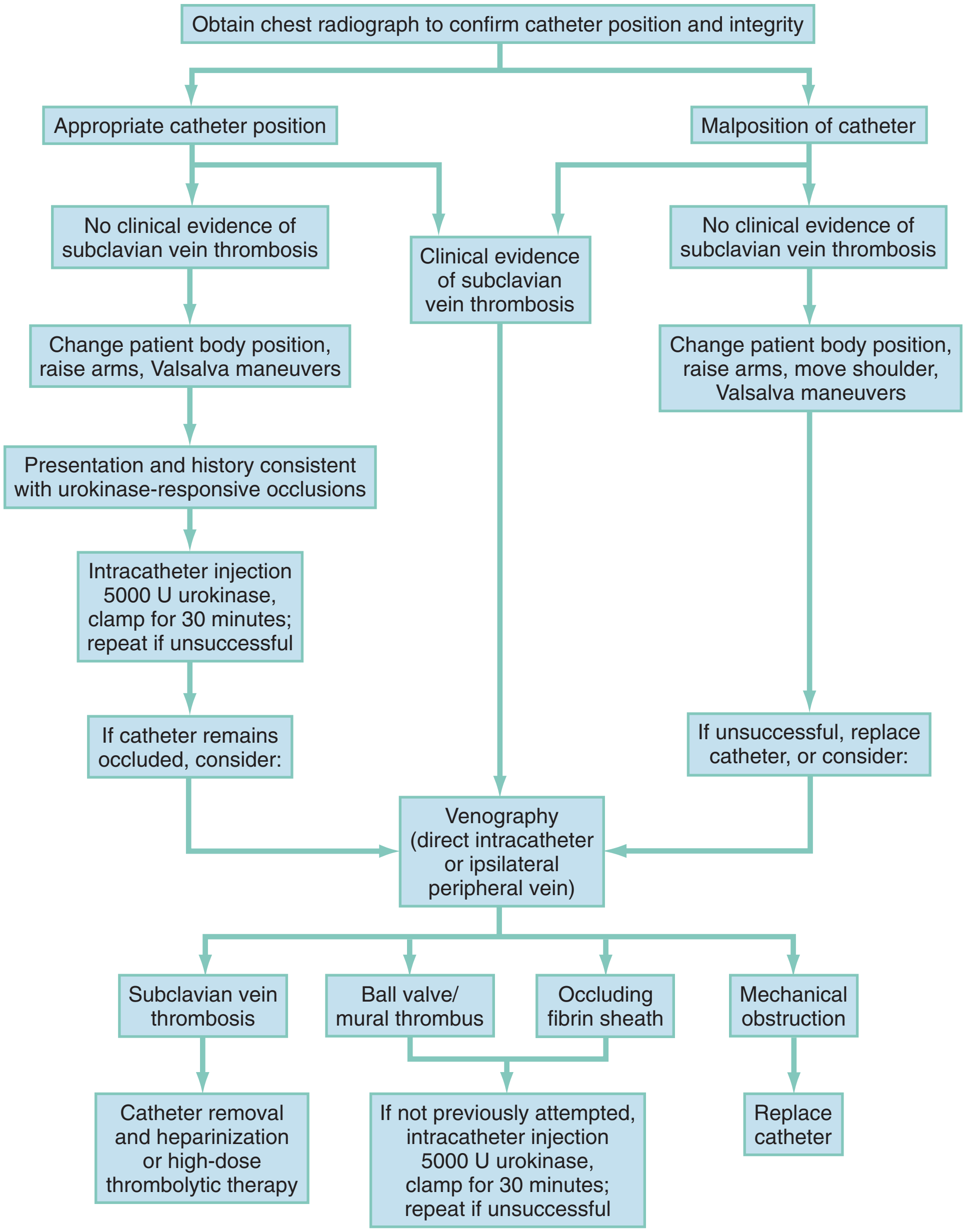


Figure 87-6. Approach to occluded indwelling catheter.

clinical evidence of subclavian vein thrombosis, the catheter may be lodged against the vessel wall. The patient's changing body position, raising the arms above the head, or performing the Valsalva maneuver may relieve withdrawal occlusion. If this is unsuccessful, some occlusions respond to low-dose intracatheter urokinase (see Box 87-1). Urokinase (5000 units) should be injected into the catheter and left for 30 minutes before aspiration is attempted. If this is also unsuccessful, a second dose of urokinase can be injected and the procedure repeated.[52] Although contraindications to fibrinolytic agents should be considered, low-dose therapy for occluded catheters appears to be well tolerated.[52,53]

In the pinch-off syndrome the catheter is intermittently obstructed during both administration and withdrawal of fluids, typically within 3 weeks after catheter placement. A chest radiograph demonstrates narrowing of the catheter lumen as it passes between the clavicle and the first rib. The catheter must be removed because of fragmentation or embolization if left in place.[54]

Because engorged collateral circulation or swelling in the affected extremity is not universally present with subclavian vein thrombosis, this diagnosis should be considered in all patients who are unresponsive to declotting attempts. Catheter removal with systemic heparinization or catheter maintenance with high-dose fibrinolytic therapy is a therapeutic option for subclavian vein thrombosis.[52,55] Mechanical occlusion is rare and requires surgical catheter replacement. Because of variations in approach, early consultation is recommended in patients who have occluded central venous catheters (Fig. 87-6).

Catheter Laceration

If an external catheter laceration or fracture occurs, the catheter should be clamped over tape distal to the laceration close to the chest wall. The catheter can be repaired as long as the damage is more than 4 cm from the chest wall. After clamping, as an interim measure, the next step is to insert a 14-gauge, 2-inch shielded intravenous catheter (Angiocath) into the catheter; remove the stylus; tape securely; and flush with heparin. The catheter can then be used while a repair kit is obtained.[56]

www.ketabpezeshki.com 66485457-66963820

Catheter-Related Infections

Catheter infections can be local or systemic. Local infections primarily involve the skin and subcutaneous tissues surrounding the exit site, with erythema, tenderness, and no clinical or laboratory evidence of sepsis. Skin organisms are primarily responsible for local infections, especially coagulase-negative staphylococci.[51] Studies show that local infections usually do not require catheter removal and resolve with antimicrobial therapy alone.[57]

The source of systemic infection in patients with Hickman-Broviac catheters may be difficult to localize, particularly in immunosuppressed patients. The most common sites of systemic infection in any patient with a central venous catheter, in decreasing order of frequency, are the urinary tract, the anorectal area, the upper respiratory tract, and the catheter.[51] The most common organisms causing catheter infection are coagulase-negative staphylococci, *S. aureus,* and *Candida albicans.* In immunocompromised patients with Hickman-Broviac catheters, gram-positive organisms now are responsible for more cases of sepsis than gram-negative bacteria. Accordingly, initial empirical therapy should include an antistaphylococcal drug in addition to the usual gram-negative coverage. A good empirical regimen is vancomycin (1 g) and gentamicin (1 mg/kg intravenously [IV]). All patients who have a possible vascular access infection should have two blood culture samples drawn. Comparison of blood culture samples drawn simultaneously through the catheter and from a peripheral blood vessel may assist in determining whether the catheter is the source of infection. Infections that do not extend through the vessel wall (pericatheter infections) can be successfully treated without catheter removal. Catheter removal is mandatory in patients with continued positive blood culture results despite therapy and in those with vascular access infections caused by *Candida* species.[57]

Catheter-related septic central venous thrombosis can progress through and around the vessel wall to cause a perivascular infection or abscess. This rare but devastating complication is associated with serious morbidity and a reported mortality rate as high as 83%. Because of the lack of specific clinical findings, the most prominent diagnostic feature is continued bacteremia after catheter removal. Diagnosis is confirmed by venography or CT.[58] Removal of the catheter, intravenous administration of antimicrobials, and anticoagulation constitute appropriate initial therapy. Surgical treatment with thrombectomy and possible abscess drainage are indicated after failure of an adequate course of antibiotics and anticoagulation. Fibrinolytic agents are an adjunct for catheter-related septic venous thrombosis, but the risk-benefit ratio has not been established.[59] In patients who require catheter removal, a quantitative culture of the number of organisms on the catheter's surface correlates well with a positive blood culture result for the same organism. This technique involves rolling the catheter on a culture medium and is probably more reliable than broth culture of catheter tips in determining whether the catheter is the source of infection.[60]

Groshong Catheter

The Groshong catheter is a single, thin-walled silicone rubber catheter designed for prolonged venous cannulation. It differs from the Hickman-Broviac catheter in insertion, design, and maintenance and can be inserted into a smaller vein through a smaller introducer sheath. The catheter can be inserted under local anesthesia without fluoroscopy, and a subcutaneous tunnel is created. A Dacron cuff stabilizes the catheter's placement in subcutaneous tissues and reduces the chance of inadvertent removal or retrograde infection.[61]

The Groshong catheter has a closed end and a vocal cord–type integral valve at the distal end (Fig. 87-7A) that minimizes back-bleeding, eliminating the need for heparin flushes or external clamping, but permits blood sampling with gentle negative pressure. Patency of the catheter is maintained with 5 mL of saline flush once a week. A 20-mL saline irrigation is necessary after any blood transfusion or if blood is observed in the catheter lumen. A 30-mL saline irrigation is performed before blood sampling after infusion of hyperalimentation solutions.

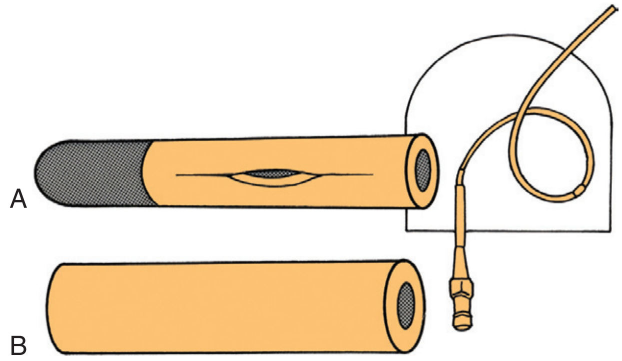


Figure 87-7. **A,** Groshong catheter with closed distal end and vocal cord-type valve. **B,** Hickman catheter with open distal end. (From Delmore JE, et al: Experience with Groshong long-term central venous catheter. Gynecol Oncol 34:216, 1989.)

A lower incidence of complete obstruction to flow from clots or precipitates within the catheter lumen, however, has not been shown.[62] Groshong catheters are otherwise subject to the same complications as Hickman-Broviac catheters.

Vascular Access for Hemodialysis

Quinton-Mahurkar Catheter

The Quinton-Mahurkar catheter provides immediate and short-term vascular access for hemodialysis. Its advantages include bedside placement and a functional life up to 18 months.[63] This single, flexible, polyurethane cannula has two separate D-shaped channels, each connected by a molded Y piece to a color-coded external port (see Fig. 87-5B). To protect against a disconnected cap, each limb of the Y piece has an attached clamp. The Quinton-Mahurkar catheter is placed by the Seldinger technique, most often in the subclavian vein and less often in the femoral vein.

The complication rate from central venous catheter hemodialysis is near 30%,[64] most commonly catheter-related infections and thrombosis.

A Quinton-Mahurkar catheter can be used to obtain blood samples. After blood withdrawal, the line should be flushed with more than 10 mL of normal saline solution, followed by 5000 units of heparin in 1 mL of saline to prevent intracatheter clot formation. The catheter can also be used for the administration of intravenous therapy. Routine care and use are otherwise similar to the care and use previously described for chronic indwelling central venous catheters.

Cimino-Brescia Fistula and Prosthetic Bridge Fistula

The subcutaneous Cimino-Brescia fistula is the preferred access for long-term hemodialysis. The fistula is created through a side-to-side and side-to-end anastomosis with use of the radial artery and the cephalic forearm vein. The high blood flow and pressure on the venous side of the fistula "arterialize" the veins in 3 to 5 weeks. The Cimino-Brescia fistula is well tolerated by patients, has a low infection rate, and has the longest functional

www.ketabpezeshki.com 66485457-66963820

use of any vascular access method. The fistula has a 90% patency rate at 12 months, which gradually decreases to approximately 75% at 4 years.

An alternative to the Cimino-Brescia fistula is the arteriovenous bridge fistula. Formed by a prosthetic conduit, this fistula connects a superficial artery (usually the radial or brachial) with a large antecubital vein. The prosthetic material is usually expanded polytetrafluoroethylene. Arteriovenous bridges can be constructed in the leg between the superficial femoral or femoral artery and the saphenous vein. Lower extremity arterial bridges have a higher blood flow rate and are less likely to thrombose but also have a higher infection rate because of their proximity to the bacteria-laden perineum.

Thrombosis

Thrombosis is the most common complication of a subcutaneous arteriovenous fistula or prosthetic graft. Circumferential bandages, tourniquets, or blood pressure cuffs are avoided in the fistula-bearing arm because restricted venous outflow may predispose to thrombosis. The fistula can be used to acquire blood or vascular access (without use of a tourniquet). Normal graft flow is verified by feeling a thrill or hearing a bruit on auscultation. A strong palpable pulse with no matching thrill suggests venous outflow obstruction or early graft thrombosis. Thrombosis of arteriovenous fistulae necessitates temporary vascular access and usually the creation of a new fistula proximal to the thrombosed shunt.

Blood Withdrawal

Ideally, an alternative peripheral venipuncture site should be sought first before a Cimino-Brescia fistula is used for blood withdrawal. When an alternative site is unavailable, however, the arteriovenous fistula is a reasonable choice. An individual skilled in venipuncture techniques should maintain absolute sterility with antiseptic skin preparation, sterile gloves, and sterile gauze. Tourniquets are contraindicated and unnecessary. Venipuncture should be performed on the well-developed venous side of the fistula. After blood acquisition, gentle pressure should be maintained for 5 minutes, with care taken not to occlude the vessel lumen. The site should then be observed for several minutes to ensure that bleeding does not occur. A prosthetic arteriovenous bridge fistula can also be used to obtain blood samples with careful perforation of the superficial wall of the prosthetic graft; otherwise, the technique is identical.

Clinically differentiating a Cimino-Brescia fistula from a prosthetic arteriovenous bridge fistula may be difficult. The prosthetic portion of an arteriovenous bridge fistula connects the arterial to the venous vessels in an H shape and is tunneled for some distance beneath the skin, giving the appearance of a single large blood vessel. The prosthetic fistula has a thrill but is not as pulsatile as a Cimino-Brescia fistula when gently palpated. If asked, most patients are knowledgeable about their fistula.

Peripheral intravenous access is best established at an alternative site. When an alternative site is unavailable and the patient requires timely intravenous access, the Cimino-Brescia fistula or bridge fistula can be used, following the guidelines for venipuncture. Careful attention to sterile technique, operator skill, and avoidance of tourniquets can provide timely venipuncture or intravenous therapy while preventing infectious or thrombotic complications. If an intravenous line is used in a fistula, it should be replaced by alternative intravenous access as soon as possible.

Infection

Infections of an arteriovenous fistula or graft are potentially life-threatening and manifest with signs of septicemia and local inflammation. Once the diagnosis of infected fistula is considered, blood cultures should be obtained and intravenous antibiotics for gram-positive skin organisms administered. Prosthetic graft infection cannot be eradicated with intravenous antibiotics alone and requires prosthetic graft removal. Infections are the second leading cause of death of patients undergoing long-term dialysis.

Steal Phenomenon

Vascular steal from the ulnar artery via the palmar arch occasionally occurs in patients with atherosclerotic disease distal to the shunt, particularly in diabetic patients. Symptoms of fingertip ischemia occur during periods of increased shunting (hemodialysis or increased activity). The steal phenomenon usually requires graft ligation with construction of a new fistula in the opposite extremity.

Venous Hypertension

Acute venous hypertension is a true surgical emergency that occurs in the first few weeks after fistula construction. The early rise in venous pressure produces marked swelling of the extremity, severe venous stasis and characteristic skin pigmentation, edema, and occasionally venous ulceration. Management of venous hypertension requires hospitalization and urgent ligation of the vein immediately distal to the fistula before a potentially exsanguinating vessel rupture.

Bleeding

Patients also are seen in the emergency department with bleeding from their fistula after dialysis. Persistent, gentle pressure, with care taken not to occlude blood flow, usually resolves this problem.

KEY CONCEPTS

- Acute arterial occlusion is a limb-threatening emergency requiring early heparinization and Fogarty catheter embolectomy. The clinical diagnosis is based on some variant of the five *P*s: pain, pallor, pulselessness, paresthesias, and paralysis. Confirmatory tests are unnecessary and increase the limb's ischemic status.
- Atheroembolism (blue toe syndrome) is associated with cool, painful cyanotic toes in the presence of palpable distal pulses. A proximal source should be localized, most often an atherosclerotic aneurysm in the aorta or the iliac, femoral, or popliteal artery.
- Popliteal aneurysms are bilateral in 60% of patients and often coexist with an abdominal aortic aneurysm.
- The classic Raynaud attack is triphasic: the fingers become white, blue, then red. Raynaud's disease has no detectable underlying cause and usually has a benign course. Raynaud's phenomenon has an underlying disorder, usually connective tissue disease.
- The only reliable clinical test for detection of thoracic outlet syndrome is the elevated arm stress test (EAST).
- The most common sites of systemic infection in patients with long-term central venous catheters are the urinary tract, the anorectal area, the upper respiratory tract, and the catheter, in that order. Local skin infection at the catheter site without systemic signs or symptoms usually responds to antibiotics and does not require catheter removal.
- Acute venous hypertension can occur in the first few weeks of an arteriovenous fistula. Hospitalization is required for ligation of the vein before a potentially exsanguinating vessel rupture occurs.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Ehsan O, Murray D, Farquharson F, Serracino-Inglott F: Endovascular repair of complex aortic aneurysms. *Ann Vasc Surg* 2011; 25:716-725.
2. Ali Kausar Rushdi Y, Hina H, Patel B, Cross FW: The incidence of peripheral arterial embolism in association with a patent foramen ovale (right-to-left shunt). *JRSM Short Rep* 2011; 2:35.
3. Hori M, et al: Efficacy and safety of dabigatran vs. warfarin in patients with atrial fibrillation—sub-analysis in Japanese population in RE-LY trial. *Circ J* 2011; 75:800-805.
4. Sezai A, et al: New treatment with human atrial natriuretic peptide for postoperative myonephropathic metabolic syndrome. *Ann Thorac Surg* 2009; 88:1333-1335.
5. Kronzon I, Saric M: Cholesterol embolization syndrome. *Circulation* 2010; 122:631-641.
6. de Donato G, et al: Hybrid procedures for acute limb ischemia. *J Cardiovasc Surg* 2010; 51:845-853.
7. Lebreton G, Uzel AP, Celerien J, Roques F, Deneuville M: Popliteal arteriovenous fistula due to a gunshot injury. *Ann Vasc Surg* 2010; 24:952.
8. Armstrong DW, Tobin C, Matangi MF: The accuracy of the physical examination for the detection of lower extremity peripheral arterial disease. *Can J Cardiol* 2010; 26:e346-e350.
9. Botzoris V, Drosos AA: Management of Raynaud's phenomenon and digital ulcers in systemic sclerosis. *Joint Bone Spine* 2011; 78:341-346.
10. Perkins AM, Liteplo A, Noble VE: Ultrasound diagnosis of type a aortic dissection. *J Emerg Med* 2010; 38:490-493.
11. Johnson CA: Endovascular management of peripheral vascular trauma. *Semin Intervent Radiol* 2010; 27:38-43.
12. Demirpolat G, Ozturk N, Parildar M, Posacioğlu H, Tamsel S: Duplex ultrasound evaluation of endoluminally treated aortic aneurysms with emphasis on diameter measurement: A comparison with computed tomography. *J Clin Ultrasound* 2011; 39:263-269.
13. Fogarty TJ, Cranley JJ, Krause RJ, Strasser ES, Hafner CD: A method of extraction of arterial emboli and thrombi. *Surg Gynecol Obstet* 1963; 116:241.
14. Mendiz OA, Fava CM, Valdivieso LR, Lev GA, Villagra LG: Angioplasty for treatment of isolated below-the-knee arterial stenosis in patients with critical limb ischemia. *Angiology* 2011; 62:359-364.
15. Abularrage CJ, et al: Long-term outcomes of diabetic patients undergoing endovascular infrainguinal interventions. *J Vasc Surg* 2010; 52:314-322.
16. Piazza G, Creager MA: Thromboangiitis obliterans. *Circulation* 2010; 121:1858-1861.
17. Löndahl M, Landin-Olsson M, Katzman P: Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer. *Diabet Med* 2011; 28:186-190.
18. Saha SP, Whayne TF Jr, Mukherjee DP: Current management of peripheral vascular disease: Where is the evidence? *Cardiovasc Hematol Agents Med Chem* 2011; 9:128-136.
19. Chiriano J, et al: Management of lower extremity wounds in patients with peripheral arterial disease: A stratified conservative approach. *Ann Vasc Surg* 2010; 24:1110-1116.
20. Weis-Müller BT, et al: Critical chronic peripheral arterial disease: Does outcome justify crural or pedal bypass surgery in patients with advanced age or with comorbidities? *Ann Vasc Surg* 2011; 25:783-795.
21. Buerger L: Thromboangiitis obliterans: A study of vascular lesions leading to presenile spontaneous gangrene. *Am J Med Sci* 1908; 136:567.
22. Malecki R, Zdrojowy K, Adamiec R: Thromboangiitis obliterans in the 21st century—a new face of disease. *Atherosclerosis* 2009; 206:328-334.
23. Razavi MK, Lee DS, Hofmann LV: Catheter-directed thrombolytic therapy for limb ischemia: Current status and controversies. *J Vasc Interv Radiol* 2004; 15(1 Pt 1):13-23.
24. Paraskevas KI, Koutsias S, Mikhailidis DP, Giannoukas AD: Cholesterol crystal embolization: A possible complication of peripheral endovascular interventions. *J Endovasc Ther* 2008; 15:614-625.
25. Koksoy C, et al: Surgical treatment of peripheral aneurysms in patients with Behçet's disease. *Eur J Vasc Endovasc Surg* 2011; 42:525-530.
26. Vierhout BP, Zeebregts CJ, van den Dungen JJ, Reijnen MM: Changing profiles of diagnostic and treatment options in subclavian artery aneurysms. *Eur J Vasc Endovasc Surg* 2010; 40:27-34.
27. Brooke BS, Freischlag JA: Contemporary management of thoracic outlet syndrome. *Curr Opin Cardiol* 2010; 25:535-540.
28. Yuen JC, Wright E, Johnson LA, Culp WC: Hypothenar hammer syndrome: An update with algorithms for diagnosis and treatment. *Ann Plast Surg* 2011; 67:429-438.
29. Sachdev-Ost U: Visceral artery aneurysms: Review of current management options. *Mt Sinai J Med* 2010; 77:296-303.
30. Roddy SP: The contemporary management of splenic artery aneurysms. *J Vasc Surg* 2011; 53:1157.
31. Dwivedi AJ, Greben C, Krishnasastry KV: Catheter embolization of an hepatic artery aneurysm: A case report. *Vasc Endovascular Surg* 2006; 40:79-83.
32. Hagendoorn J, de Vries JP, Moll FL: Primary infected, ruptured abdominal aortic aneurysms: What we learned in 10 years. *Vasc Endovascular Surg* 2010; 44:294-297.
33. Vallejo N, et al: The changing management of primary mycotic aortic aneurysms. *J Vasc Surg* 2011; 54:334-340.
34. Georgiadis GS, Lazarides MK, Polychronidis A, Simopoulos C: Surgical treatment of femoral artery infected false aneurysms in drug abusers. *ANZ J Surg* 200; 75:1005-1010.
35. Salimi J: On the management of mycotic femoral pseudoaneurysms in intravenous drug abusers. *Ann Vasc Surg* 2009; 23:824.
36. Minz M, et al: Use of autogenous internal iliac artery for bridging the external iliac artery after excision of *Aspergillus* mycotic aneurysm in renal transplant recipients. *J Vasc Surg* 2011; 53:802-804.
37. Samoukovic G, Bernier PL, Lachapelle K: Successful treatment of infected ascending aortic prosthesis by omental wrapping without graft removal. *Ann Thorac Surg* 2008; 86:287-289.
38. Dubois M, Daenens K, Houthoofd S, Peetermans WE, Fourneau I: Treatment of mycotic aneurysms with involvement of the abdominal aorta: Single-centre experience in 44 consecutive cases. *Eur J Vasc Endovasc Surg* 2010; 40:450-456.
39. Joglar F, Kabutey NK, Maree A, Farber A: The role of stent grafts in the management of traumatic tibial artery pseudoaneurysms: Case report and review of the literature. *Vasc Endovascular Surg* 2010; 44:407-409.
40. Klein-Weigel P, Opitz C, Riemekasten G: Systemic sclerosis—a systematic overview: Part 1—disease characteristics and classification, pathophysiologic concepts, and recommendations for diagnosis and surveillance. *Vasa* 2011; 40:6-19.
41. Laulan J, et al: Thoracic outlet syndrome: Definition, aetiological factors, diagnosis, management and occupational impact. *J Occup Rehabil* 2011; 21:366-373.
42. Brantigan CO, Roos DB: Diagnosing thoracic outlet syndrome. *Hand Clin* 2004; 20:27-36.
43. Thompson JF, et al: Venous thoracic outlet compression and the Paget-Schroetter syndrome: A review and recommendations for management. *Cardiovasc Intervent Radiol* 2011; 34:903-910.
44. Ferrante MA: The thoracic outlet syndromes. *Muscle Nerve* 2012; 45:780-795.
45. Sexton JA, Ricotta JJ: Endovascular approaches to arteriovenous fistula. *Adv Surg* 2011; 45:83-100.
46. Kulungowski AM, Fishman SJ: Management of combined vascular malformations. *Clin Plast Surg* 2011; 38:107-120.
47. Peirce C, et al: The management of mycotic femoral pseudoaneurysms in intravenous drug abusers. *Ann Vasc Surg* 2009; 23:345-349.
48. Vávrova M, et al: Endovascular treatment of mycotic pseudoaneurysms. *Vasa* 2010; 39:256-261.
49. Tan KK, Chen K, Chia KH, Lee CW, Nalachandran S: Surgical management of infected pseudoaneurysms in intravenous drug abusers: Single institution experience and a proposed algorithm. *World J Surg* 2009; 33:1830-1835.
50. McGee WT, Mailloux PT, Martin RT: Safe placement of central venous catheters: A measured approach. *J Intensive Care Med* 2011; 26:392-396.
51. Bowen A, Carapetis J: Advances in the diagnosis and management of central venous access device infections in children. *Adv Exp Med Biol* 2011; 697:91-106.
52. Seifert G, Riess H, Seeger K, Henze G, Borgmann A: Intraluminal instillation of urokinase and autologous plasma: A method to unblock occluded central venous ports. *BMC Cancer* 2006; 6:103.
53. Kashyap VS, Gilani R, Bena JF, Bannazadeh M, Sarac TP: Endovascular therapy for acute limb ischemia. *J Vasc Surg* 2011; 53:340-346.
54. Kim JT, Oh TY, Chang WH, Jeong YK: Clinical review and analysis of complications of totally implantable venous access devices for chemotherapy. *Med Oncol* 2012; 29:1361-1364.
55. Yilmaz KB, et al: Central venous catheter–associated thrombosis in the perioperative period: A frequent complication in cancer patients that can be detected early with Doppler examination. *Tumori* 2010; 96:690-694.
56. Perdikaris P, Petsios K, Vasilatou-Kosmidis H, Matziou V: Complications of Hickman-Broviac catheters in children with malignancies. *Pediatr Hematol Oncol* 2008; 25:375-384.
57. Weber DJ, Rutala WA: Central line–associated bloodstream infections: Prevention and management. *Infect Dis Clin North Am* 2011; 25:77-102.

www.ketabpezeshki.com 66485457-66963820

58. Ghanem G, Adachi J, Han XY, Raad I: Central venous catheter–related *Streptomyces* septic thrombosis. *Infect Control Hosp Epidemiol* 2007; 28:599.
59. Adler A, et al: Infectious complications of implantable ports and Hickman catheters in paediatric haematology-oncology patients. *J Hosp Infect* 2006; 62:358.
60. Pascual A, et al: Update on pathogenesis and diagnosis of intravascular catheter-related infections. *Enferm Infecc Microbiol Clin* 2011; 29(Suppl 4):16-21.
61. Nishinari K, Wolosker N, Bernardi CV, Yazbek G: Totally implantable ports connected to valved catheters for chemotherapy: Experience from 350 Groshong devices. *J Vasc Access* 2010; 11:17-22.
62. Ruggiero A, et al: Groshong catheter–related complications in children with cancer. *Pediatr Blood Cancer* 2010; 54:947-951.
63. Wadelek J: Haemodialysis catheters. *Anestezjol Intens Ter* 2010; 42:213-217.
64. Besarab A, Pandey R: Catheter management in hemodialysis patients: Delivering adequate flow. *Clin J Am Soc Nephrol* 2011; 6:227-234.

www.ketabpezeshki.com 66485457-66963820

Chapter 88

Pulmonary Embolism and Deep Vein Thrombosis

Jeffrey A. Kline

PERSPECTIVE

This chapter discusses the diagnosis and treatment of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), from the perspective of the emergency physician and provides a functional resource for the evaluation and treatment of VTE in the emergency department (ED).

Pathophysiology of Thrombosis

VTE forms as a result of excessive fibrin production from the action of thrombin on fibrinogen. Factors that enhance fibrinogen synthesis and promote its catalysis to fibrin include systemic inflammation, traumatic or immune-related vascular trauma, inherited thrombophilias and hemoglobinopathies, cancer, pregnancy, and sluggish blood flow. Venous injury, slow blood flow, and hypercoagulability are the cardinal inciting mechanisms for VTE, and most clinical decision rules for VTE incorporate these factors. In addition, each year of life independently increases the likelihood of imbalanced clot formation.[2]

DEEP VEIN THROMBOSIS

DVT represents a disease spectrum ranging from a minimally symptomatic isolated calf vein thrombosis to a limb-threatening iliofemoral venous obstruction. Although the true incidence is unknown in the ED population, DVT accounts for approximately 600,000 hospital admissions per year.

Anatomy

The venous anatomy of the lower extremity is divided into the deep and superficial systems. The superficial venous system consists primarily of the greater and short saphenous veins and the perforating veins. The deep venous system includes the anterior tibial, posterior tibial, and peroneal veins, collectively called the *calf veins.* The calf veins join together at the knee to form the popliteal vein, which extends proximally and becomes the femoral vein at the adductor canal. The femoral vein sometimes is called the *superficial femoral vein,* and this nomenclature contributes to confusion in interpreting radiology reports. A clot in the superficial femoral vein is indeed a DVT and should be treated as such. The femoral vein joins with the deep femoral vein to form the common femoral vein, which subsequently becomes the external iliac vein at the inguinal ligament. *Proximal DVT* refers to a clot in the popliteal vein or higher, whereas *distal clot* refers to an isolated calf vein thrombosis.

Clinical Presentation

The initial symptoms of DVT can be as subtle and nonspecific as a mild cramping sensation or sense of fullness in the calf, without objective swelling, and may be difficult to differentiate clinically from myriad other, unrelated disorders (Box 88-1). Many patients use the term *charley horse* to describe the sensation of an early DVT. It is precisely at this early stage, however, that DVT can be treated most effectively to minimize the potential morbidity and mortality associated with VTE. Because the left iliac vein is vulnerable to compression by the left iliac artery, leg DVT occurs with a slightly higher frequency in the left leg compared with the right; bilateral leg DVT is found in fewer than 10% of ED patients diagnosed with DVT. Likewise, the clinical signs of DVT vary and may include unilateral swelling, edema, erythema, and warmth of the affected extremity; tenderness to palpation along the distribution of the deep venous system; dilation of superficial collateral veins; and a palpable venous "cord." The classic Homan's sign (pain felt in the calf or posterior aspect of the knee on passive dorsiflexion of the foot while the knee is extended) is insensitive and nonspecific for DVT and has no role in clinical assessment of the patient. *Upper extremity DVT* refers to a thrombosis in the axillary vein and causes arm swelling on the same side as an indwelling catheter or recent intravenous infusion site. In the absence of a catheter, the most frequent location of arm DVT is on the dominant hand side. Patients frequently note that their rings become tight as an early sign of DVT.

Diagnosis

Diagnosis of DVT and PE starts with an estimation of the pretest probability (PTP). This estimation may be accomplished either by the clinical gestalt of an experienced practitioner or in conjunction with a clinical decision tool, such as that derived and validated by Wells and colleagues (Table 88-1). Patients with a low PTP can have DVT excluded with a normal quantitative D-dimer.

Laboratory Evaluation

The D-dimer is a protein derived from enzymatic breakdown of cross-linked fibrin, and an elevated plasma concentration indicates the presence of a clot formed somewhere in the body within the previous 72 hours. D-dimer concentration may be elevated with any condition that causes fibrin deposition, including malignancy, pregnancy, advanced age, prolonged bed rest, recent surgery, infection, inflammation, new indwelling catheters, stroke, and myocardial infarction. D-dimer concentration is proportionate to

www.ketabpezeshki.com 66485457-66963820

Box 88-1 Differential Diagnosis of Deep Vein Thrombosis

Muscle strain, hematoma
Popliteal (Baker's) cyst
Lymphedema
Cellulitis
Vasculitis
Fracture
Superficial thrombophlebitis
Chronic venous insufficiency
Proximal venous compression (e.g., tumor, gravid uterus)
Congestive heart failure (swelling usually bilateral)
Hypoalbuminemia (swelling usually bilateral)

Table 88-1 Clinical Model for Estimating the Pretest Probability of Deep Vein Thrombosis

CLINICAL FEATURE	SCORE*
Active cancer (treated within the previous 6 mo or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for ≥3 days or major surgery within 12 wk requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than on the asymptomatic side (measured 10 cm below the tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented deep vein thrombosis	1
Alternative diagnosis at least as likely as deep vein thrombosis	−2

Adapted from Wells PS, Anderson D, Bormanis J: Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet 350:1795, 1997.
*A score of <2 indicates that the probability of deep vein thrombosis is low.

the size of the clot and decreases as the clot matures, so the test is less sensitive with small or chronic clots.

The D-dimer protein can be measured in plasma with several techniques, and the differences in D-dimer assay methodology greatly affect diagnostic accuracy. All commercially available assays share the concept of antibody capture followed by detection. The U.S. Food and Drug Administration (FDA) has approved over 75 different D-dimer assays for clinical use. One way to categorize the D-dimer assay format is as quantitative or qualitative (which includes semiquantitative assays). The two most common detection methods for quantitative assays are the enzyme-linked immunosorbent assay (ELISA) and the immunoturbidimetric technique. Because of variable properties of the test capture antibody and differences in test standardization, their cutoffs for the upper limit of normal vary for different quantitative D-dimer assays. For many assays, less than 500 ng/mL (or 1000 fibrinogen equivalent units ([FEUs]) is a negative test result and carries an 88 to 97% diagnostic sensitivity for symptomatic proximal DVT and 83 to 94% sensitivity for calf DVT or asymptomatic proximal DVT. A negative quantitative D-dimer assayed by the ELISA or immunoturbidimetric technique is sensitive enough to exclude the diagnosis of DVT in patients at low or moderate risk without further evaluation.

Qualitative D-dimer assays include whole-blood assays done on single-use cartridges that resemble home pregnancy tests and semiquantitative, manual latex fixation assays that use test cards containing several wells for plasma in various folds of dilution (note that latex fixation assays have lower sensitivity than automated latex agglutination assays). Because qualitative D-dimer assays have a diagnostic sensitivity of only 78 to 93% for symptomatic proximal DVT, a negative qualitative D-dimer excludes proximal DVT only in patients deemed to have a low clinical possibility by the physician.

Radiographic Evaluation

DVT evaluation is by a combination of D-dimer testing and duplex venous ultrasonography.

Venous duplex ultrasonography, performed by a certified sonographer and interpreted by a board-certified radiologist or similarly credentialed expert, has a sensitivity and specificity of approximately 95% for proximal DVT and is the diagnostic test of choice in most centers. It is important for emergency physicians to know the technique of the examination. Most radiology departments use the three point sequence (common and superficial femoral veins and popliteal vein, excluding the calf and saphenous veins). Although management of calf vein and saphenous clots remains controversial, the diagnostic sensitivity of a single venous ultrasound for the exclusion of a clot at risk of progressing to a proximal DVT is increased significantly by including the calf and saphenous veins. A patient at low risk may have the diagnosis of DVT effectively excluded by a negative three-point venous duplex ultrasound. However, for patients at higher than low risk, a single negative three-point ultrasound is inadequate as a sole method to exclude DVT, whereas a single normal whole-leg ultrasound (including normal calf and saphenous veins) is sufficient to exclude DVT with any PTP.[1] A negative three-point ultrasound together with a negative quantitative D-dimer is sufficient to exclude DVT with any PTP. In a patient with a high PTP in whom the D-dimer is elevated (or not performed), a negative three-point ultrasound at the index visit should be followed by a repeat ultrasound in 2 to 7 days, which if negative is sufficient to exclude PE. An expertly performed and interpreted positive ultrasound is sufficient to confirm the diagnosis of DVT. Ultrasound cannot be used to rule out iliac or pelvic vein thrombosis.

Many emergency physicians use bedside ED ultrasound in their daily practice, but at present the data are conflicting as to whether emergency physician–performed ultrasound (EPPU) for lower-extremity DVT has adequate diagnostic accuracy. Follow-up with formal diagnostic duplex ultrasound seems reasonable.[2]

Indirect computed tomography (CT) venography (CTV) is not a primary imaging modality for DVT but may be performed in conjunction with CT pulmonary angiography (CTPA) of the chest during the evaluation of suggested PE. Adding CTV to CTPA provides an incremental increase in the sensitivity for VTE, identifying DVT in approximately 2% of patients in whom the CTPA is read as negative for PE but at the expense of significant additional radiation exposure to the pelvis and lower extremities.[3] Interobserver agreement among radiologists interpreting CTV appears to be less than that for the CTPA portion of the study, possibly because of poor venous opacification in many cases.[4] At this time, routine use of CTV is not necessary when CTPA is performed.[11]

Magnetic resonance imaging (MRI) can evaluate the pelvic vasculature and vena cava, which is not possible with ultrasound. MRI does not produce ionizing radiation, making it an attractive option for pregnant patients but limited by cost, availability, patient size, and tolerance to close quarters. MRI is not a primary diagnostic test for patients with suspected DVT.

www.ketabpezeshki.com 66485457-66963820

Treatment

When the diagnosis of DVT has been established, anticoagulation should be initiated, unless contraindicated, with a low-molecular-weight heparin (e.g., enoxaparin 1 mg/kg subcutaneously [SQ] every 12 hours), fondaparinux (5-10 mg SQ once daily, depending on patient weight), or unfractionated heparin (70-80 units/kg intravenous bolus followed by 17-18 units/kg/hr infusion), assuming normal renal function. The treatments work equally well and are safe in the absence of contraindications to anticoagulation. Treatment requires transition to oral anticoagulation with warfarin for at least 3 months. Hospital admission is obviated by initiation of outpatient low-molecular-weight heparin or fondaparinux therapy in the ED or ED observation unit, followed by self-administration at home (with appropriate patient teaching) or home administration by a visiting nurse. If admission is contemplated, after heparin has been given, the first dose of warfarin can be given in the ED to help reduce overall length of stay in the inpatient unit. Patients should be encouraged to ambulate after anticoagulation for DVT. Bed rest promotes DVT extension, increases the risk of embolization, and ultimately predisposes the patient to the postphlebitic syndrome. Patients who cannot be given anticoagulants or who have a recurrence of VTE despite anticoagulation therapy should be considered for vena caval intervention.

Superficial Leg Thrombophlebitis

Based on the results of a large randomized controlled trial, patients with a clot in the greater saphenous vein that extends above the knee are at risk for progression to DVT via the saphenous-femoral vein junction and may require an abbreviated course of anticoagulation.[5] The published evidence suggests that saphenous vein thrombophlebitis can adequately be treated with nonsteroidal anti-inflammatory drugs, heat, and graded compression stockings (fitted to exert 30-40 mm Hg of pressure at the ankle) followed by a mandatory repeat ultrasound in 2 to 5 days. If the clot is extending, then anticoagulation is indicated. The duration of anticoagulation treatment remains uncertain, but full-dose low molecular weight heparin or fondaparinux for 10 days followed by repeat ultrasound seems reasonable.

Isolated Calf Vein Thrombosis

The optimal management strategy for thromboses of the tibial or peroneal veins remains controversial.[7] Approximately 25% of isolated calf vein thromboses propagate proximally, prompting recommendations for treatment with anticoagulation as for proximal leg DVT.[8] However, most of these data were from hospitalized or postoperative patients with a higher risk of propagation than ambulatory patients.[9] For tibial or peroneal vein thrombosis in an otherwise healthy, ambulatory patient with no other indication for anticoagulation, I recommend antiplatelet therapy with aspirin (325 mg of enteric-coated acetylsalicylic acid per day) and close follow-up with repeat duplex ultrasound scan at 2 to 5 days to evaluate for clot propagation.

Phlegmasia Cerulea Dolens (Painful Blue Leg)

Massive iliofemoral occlusion results in swelling of the entire leg with extensive vascular congestion and associated venous ischemia, producing a painful, cyanotic extremity. There may be an associated arterial spasm resulting in phlegmasia alba dolens (painful white leg or milk leg), which may mimic an acute arterial occlusion. Prompt consultation with a vascular surgeon should be obtained because patients with phlegmasia cerulea dolens may require emergent thrombectomy. If timely consultation is not possible, early thrombolytic therapy may be a limb-salvaging procedure in the absence of contraindications. One strategy is to infuse alteplase (1 mg/min to a total dose of 50 mg) via a peripheral intravenous catheter placed distal to the thrombus.

Upper Extremity Venous Thromboses

DVTs of the upper extremity have become more common in association with increased use of indwelling venous catheters and wires for electronic cardiac devices. Upper extremity DVT can cause PE, and all patients with DVT above the elbow require definitive treatment.[10-12]

About one half of all upper extremity DVTs are associated with an indwelling catheter. Upper extremity DVT is diagnosed and excluded with venous ultrasound. The use of D-dimer testing in this population is inadequately studied.

In the absence of pain or infection, catheter-associated DVT does not automatically warrant catheter removal if the catheter serves a current, vital purpose. However, these patients should receive anticoagulation if they do not have contraindications. The duration of anticoagulation after catheter removal for DVT remains controversial, but most published guidelines recommend at least 3 months.

The rate of PE from axillary vein DVT appears to be similar to that for femoral vein DVT, although many experts believe the severity of PE tends to be less with upper extremity DVT.

Isolated upper extremity DVT, especially axillary-subclavian vein thrombosis, also can be seen in relatively young, active, otherwise healthy patients. Although standard DVT risk factors, such as hypercoagulable state or malignancy, may be present, most of these patients have no apparent predisposing condition. Some patients with arm DVT have inherited or acquired subclavian vein stenosis or extrinsic compression. It is not known whether strenuous, repetitive activity ("effort DVT") causes the DVT by exacerbating the anatomic compromise through movement of the arm or hypertrophy of adjacent muscles, or whether effort simply brings out the symptoms of an otherwise occult upper extremity DVT. Optimal treatment of isolated brachial vein thrombosis, often the result of a recent intravenous infusion ("infusion phlebitis"), also remains uncertain. No study has demonstrated clear benefit for systemic anticoagulation, but a good strategy is to use the same management plan as described for superficial thrombophlebitis of the leg.

Complications

Although the most feared complication of DVT is fatal PE, DVT damages venous valves, causing venous insufficiency. Venous insufficiency, in turn, manifests as a spectrum ranging from painless varicosities to severe postphlebitic syndrome, which can cause unremitting pain and swelling, varicose veins, skin changes, and nonhealing ulcers. Figure 88-1 shows the leg of a construction worker with a femoral DVT that produces swelling on the job, impairing his ability to work.

PULMONARY EMBOLISM

PE results from a clot that formed hours, days, or weeks earlier in the deep veins and dislodged, traveled through the venous system, and traversed the right ventricle into the pulmonary vasculature. What the patient experiences during this process varies widely, ranging from no symptom to cardiovascular collapse. No one knows exactly how many patients pass through the ED with PE because there is no reliable way of identifying missed cases. Assuming that ED populations have a risk for PE somewhere between that of hospitalized patients (who are at high risk for PE)

www.ketabpezeshki.com 66485457-66963820

Figure 88-1. Patient with moderate post-thrombophlebitic syndrome in the left leg several months after diagnosis with a common femoral deep vein thrombosis. Observe the swollen appearance and slight color change in the foot.

Box 88-2 Pulmonary Embolism Rule-Out Criteria (PERC Rule)

Low pretest probability for PE by the treating clinician's unstructured estimate, plus:
- Age less than 50
- Pulse rate less than 100 beats/min
- Oxygen saturation greater than 94%
- No hemoptysis
- No unilateral leg swelling
- No recent major surgery or trauma
- No prior pulmonary embolism or deep venous thrombosis
- No hormone use

PE, pulmonary embolism.

and outpatients (who are at lower risk), approximately 1 in every 500 to 1000 ED patients has PE. About 8% of ED patients with PE die within 30 days, even when PE is promptly diagnosed and treated.[10]

Pathophysiology of Pulmonary Vascular Occlusion

The pulmonary vascular tree normally has a low resistance to fluid flow, and young persons without cardiopulmonary disease (e.g., congestive heart failure, chronic obstructive lung disease, advanced sarcoidosis, pulmonary fibrosis, scleroderma, and primary pulmonary hypertension) can tolerate at least 30% obstruction, often with minimal symptoms or signs. Pulmonary infarction is a more dramatic exception. Although a segmental pulmonary artery constitutes only about one sixteenth of the entire pulmonary vascular circuit, a clot lodged deeply in a segmental artery can obstruct blood flow to a sufficient degree to cause tissue necrosis. The patient can feel focal, sharp, pleuritic pain and exhibit a splinting response to breathing. Over several days the infarcted segment becomes consolidated on chest radiography and exudes a pleural effusion, manifesting an intense underlying inflammatory process. Chest pain from noninfarcting PE can be highly variable and vague. About 30% of patients with definite PE have no perception of chest pain.

In contrast, if asked in a detailed and structured way, about 90% of patients with noninfarcting emboli admit to the sensation of dyspnea. The dyspnea may be constant and oppressive or may be intermittent and perceived only with exertion, possibly because of an exercise-induced increase in pulmonary vascular resistance. Rest dyspnea seems to be the clinical manifestation of distorted and irregular blood flow within the lung, referred to as *ventilation-perfusion inequality.* With each breath a patient with PE wastes ventilation because of increased alveolar dead space (alveoli that are ventilated but not perfused). A lodged clot can redistribute blood flow to areas of the lung with already high perfusion relative to ventilation and therefore cause more blue blood to pass through the lung without being fully oxygenated. This venous admixture is probably the primary cause of hypoxemia with PE and the increased alveolar-arterial oxygen difference (the A-a gradient). About 15% of patients with PE have a normal A-a gradient of oxygen (with normal defined as age in years/4 + 4), however, and the A-a gradient is abnormally high in most patients who are evaluated for PE but ultimately found to not have PE. In a multicenter registry of 348 patients with PE, 37 (10.6%) had a pulse oximetry reading of 100% at the time of arrival to the ED, while breathing room air. Despite its shortcomings as a single diagnostic step, the presence of hypoxemia (pulse oximetry <95%, breathing room air) that cannot be explained by a known disease process increases the probability of PE. Conversely, a normal oxygen saturation can be used only when considered together with multiple other clinical features and should not alone or independently be used to forego testing for PE (Box 88-2).[18,19] In addition, when PE is diagnosed, the severity of hypoxemia represents a powerful independent predictor of patient outcome.

PE also causes highly variable effects on vital signs. In the ED, about half of all patients with PE have a heart rate greater than 100 beats/min.[11] Tachycardia from PE probably results from impaired left ventricular filling, leading to a pathophysiologic process that parallels that of hemorrhagic shock. In one study, the probability of PE was not reduced in patients who normalized any vital sign while in the ED.[12] When PE obstructs more than 50% of the vasculature, it usually causes an acute increase in right ventricular pressure. In contrast to the left ventricle, the right ventricle does not show an elastic response to acutely increased afterload; it quickly dilates, showing echocardiographic hypokinesis early in the course. In about 40% of cases, the right ventricular damage persists for at least 6 months and probably longer. Arterial hypotension represents an ominous hemodynamic consequence of PE; it occurs in only about 10% of patients but signifies a fourfold increase in risk of death compared with normotensive patients.[20] In its most extreme form, PE can obstruct the right ventricular outflow entirely, either by casting the entire pulmonary vascular tree (Fig. 88-2) or by acutely occluding the main pulmonary artery. Pulseless electrical activity (PEA) is the most common electrocardiogram (ECG) result from obstructive PE. The survival rate for cardiac arrest from PE is abysmally low, even if the arrest is witnessed and heroic treatment is initiated.

Clinical Presentation

Table 88-2 presents a listing of factors that significantly increase the probability of PE in the ED population.[11] As is the case for cardiac risk factors in the evaluation of acute chest pain, variables that increase the probability of PE in epidemiologic studies are not useful for individual ED patients with signs and symptoms suggesting PE. From an epidemiologic standpoint, people who smoke are at a significantly higher risk for venous clots than are people who do not smoke. However, in the ED, smoking by a given patient does not seem to increase that person's risk for PE over that of a nonsmoker with an otherwise identical clinical presentation. It is possible that smokers are simply more likely to have other lung problems that manifest a clinical presentation similar to PE. As many as 50% of patients diagnosed with PE have no apparent

www.ketabpezeshki.com 66485457-66963820

clinical risk factors for VTE, but testing for genetic thrombophilia has no value in the ED setting.[13]

Virtually any ED visit related to weakness, shortness of breath, dizziness or syncope, pain, extremity discomfort, or nonspecific malaise or functional deterioration could represent a potential PE; however, this does not mean that every patient with one of these symptoms should be worked up for PE, and these symptoms should be considered in the context of the entire clinical picture. A patient with PE typically presents with 2 to 3 days of shortness of breath, now worsened enough to seek care. The chest pain usually is vaguely described. A few patients have focal pleuritic chest pain, but many say nonspecifically that their chest hurts with breathing, usually on the lateral aspects. Purely substernal chest pain is a rare presentation for PE and in general suggests a cardiac or other origin. The presence or absence of sudden onset of symptoms neither increases nor decreases the probability of PE.[11] When the antemortem histories of patients who die suddenly and unexpectedly from PE are reconstructed by interviewing family and examining medical records, most have complained of nagging symptoms for weeks before collapse, and 40% already had seen a physician for care.[14] PE with lung infarction can result in a clinical picture that is similar to lobar pneumonia, including focal chest pain, fever, and unilateral rales on auscultation. However, a temperature greater than 101.5° F suggests infection rather than infarction. An occasional clue to pulmonary infarction is the onset of pain and blood-red hemoptysis on the same day, whereas lobar pneumonia usually causes productive cough for a few days before rust-tinged sputum.

The physical examination can sometimes provide specific information about the presence of PE, including unilateral leg asymmetry, suggesting presence of DVT. Jugular venous distention in

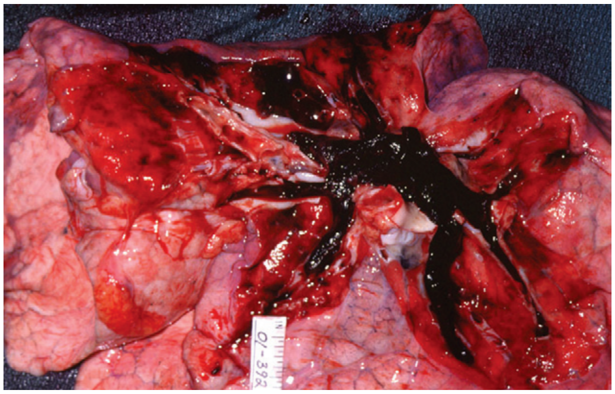


Figure 88-2. Massive pulmonary embolism on autopsy. This man died with a large clot burden that plugged the distal lobar arterial branches, eventually producing nearly complete obstruction to blood flow and subsequent cardiac arrest. This man had had vague respiratory symptoms for 2 weeks, causing him to see a physician who diagnosed bronchitis.

Table 88-2 Classic Risk Factors and Physiologic Findings for Pulmonary Embolism

FACTOR	MECHANISMS	STRENGTH OF ASSOCIATION WITH PE IN ED POPULATIONS
Inherited thrombophilia	Hypercoagulability	++
Connective tissue disease	Inflammation	Unknown
Acquired thrombophilia	Hypercoagulability	Unknown
Active cancer (under treatment)	Hypercoagulability	+
Inactive cancer (considered in remission)	Presumed hypercoagulability	Not significant
Limb or generalized immobility	Stasis	++
Prior PE or DVT	Multiple	+
Trauma within previous 4 wk requiring hospitalization	Inflammation, venous injury and stasis	+++
Surgery within previous 4 wk requiring general anesthesia	Inflammation, venous injury and stasis	++++
Smoking	Inflammation	Not significant
Estrogen	Hypercoagulability	++
Pregnancy or postpartum	Hypercoagulability	Minimal
Family history of VTE	Inherited condition	Not significant
Symptoms		
Pleuritic chest pain	Lung ischemia, muscle strain	
Substernal chest Pain	Presumed cardiac ischemia	Not significant
Dyspnea	$\dot{V}/\dot{Q}$ mismatch	+
Sudden onset of symptoms	Vascular obstruction	Not significant
Hemoptysis	Infarction	+++
Syncope	Vascular obstruction	Minimal
Signs		
Pulse rate >100 beats/min	Cardiac stress, baroreceptors	+++
Pulse oximetry reading <95%	$\dot{V}/\dot{Q}$ mismatch	+++
Unilateral leg or arm swelling	Venous obstruction	++++
Normalization of vital signs	Presumptive from treatment or Hawthorne effect	Not significant

DVT, deep vein thrombosis; *PE,* pulmonary embolism; $\dot{V}/\dot{Q}$, ventilation-perfusion ratio; *VTE,* venous thromboembolism.

www.ketabpezeshki.com 66485457-66963820

a patient with severe dyspnea and clear lung fields on auscultation suggests pure right-sided heart failure. The presence of wheezing suggests bronchospasm, which is not common in PE and makes the diagnosis less likely (but does not exclude it). Bilateral rales suggest the diagnosis of left ventricular failure, although localized rales often are heard over infarcted lung tissue. Astute clinicians may hear an accentuated pulmonic component of the second heart sound, or a right ventricular S_3 sound.

Diagnosis

Chest radiography seldom provides specific information but is useful to suggest alternative diagnoses, such as pneumonia, congestive heart failure, or pneumothorax. Unilateral basilar atelectasis on the chest radiograph increases the probability of PE. If symptoms have been present for 3 days or more, pulmonary infarction sometimes shows an apex-central, pleural-based, wedge-shaped area of infiltrate, producing the Hampton's hump finding. Unilateral lung oligemia (Westermark's sign) is a rare radiographic manifestation of a large PE.

Likewise, a 12-lead ECG provides more information about the presence of alternative diagnoses, such as pericarditis or cardiac ischemia, than the presence of PE. When PE causes ECG changes, this is usually a result of acute or subacute pulmonary hypertension. The most common effects of pulmonary hypertension on ECG are rapid heart rate, symmetrical T-wave inversion in the anterior leads (V_1-V_4), the McGinn-White S1Q3T3 pattern, and incomplete or complete right bundle branch block (Fig. 88-3); any one of these findings approximately doubles the probability of PE in a symptomatic patient.[15]

In the ED, inability to identify a cause of otherwise unexplained symptoms and signs is an important stimulus to evaluate the patient for PE. Because as many as 50% of patients diagnosed with PE have no identifiable classic risk factors for thrombosis, the decision to pursue the diagnosis of PE is based on that particular patient's presentation and should not rely on the presence or absence of population risk factors.

In some cases PE can be excluded with reasonable certainty based on data that are available at the bedside, gathered only via the medical history and physical examination. Multicenter studies of urban academic EDs have suggested that emergency physicians currently evaluate about 1 to 2% of all patients for PE.[16] Each year more than 16 million patients come to the ED with chest pain or dyspnea. Although numerous cases of PE are probably still missed, overtesting for PE can also be harmful. Specific risks include exposure to the ionizing radiation and intravenous contrast necessary for CTPA and CTV and the risk of false-positive interpretation, which may occur in as many as 10% of scans read as positive for PE.[17] The appropriate use of D-dimer testing decreases the need for imaging in all but patients at high risk.

Accordingly, there should be a rational, reproducible strategy to guide the decision-making and diagnostic processes. This strategy should begin with estimation of PTP. Methods for estimating PTP can be *implicit* (meaning the clinician's best guess) or *explicit* (meaning use of a scoring system or flow algorithm to categorize the probability).

One approach to the workup for PE is to compare the PTP with the "test threshold" for PE. The test threshold represents the point above which some type of workup should be initiated and below which the clinician can justify not starting the workup. For PE the test threshold is 1 to 2.5%.[18] Patients with a PTP less than 2.5% are more likely to be harmed than benefited by a workup and vice versa for patients with a PTP greater than 2.5%.

The question becomes how to quantify the PTP accurately.[19] Clinical judgment alone is subject to cognitive error inherent to medical diagnosis, including framing heuristic and conditions in the ED at the time (e.g., is one less likely to pursue a relatively low-likelihood diagnosis when the department is very busy), conditions of the clinician (e.g., fatigue, dysphoria, subjective feelings about the patient), and the availability of diagnostic studies (e.g., daytime vs. nighttime, weekday vs. weekend). In addition, there is variability among clinicians who may not agree that a 19-year-old with cough and pleuritic chest pain, a normal chest radiograph, and no other risk factors has less than a 2% probability of PE.

Decision rules help to deal with these problems because they are structured and more transparent. Several rules have been derived and validated for the risk stratification of patients with possible PE; however, difficulty with spontaneous recall and a preference for gestalt reasoning by clinicians may limit their use in clinical practice.[20] Fortunately, clinical reasoning appears to be comparable to at least two of the validated decision rules. In a large single-center study of 2603 ED patients evaluated for PE, the

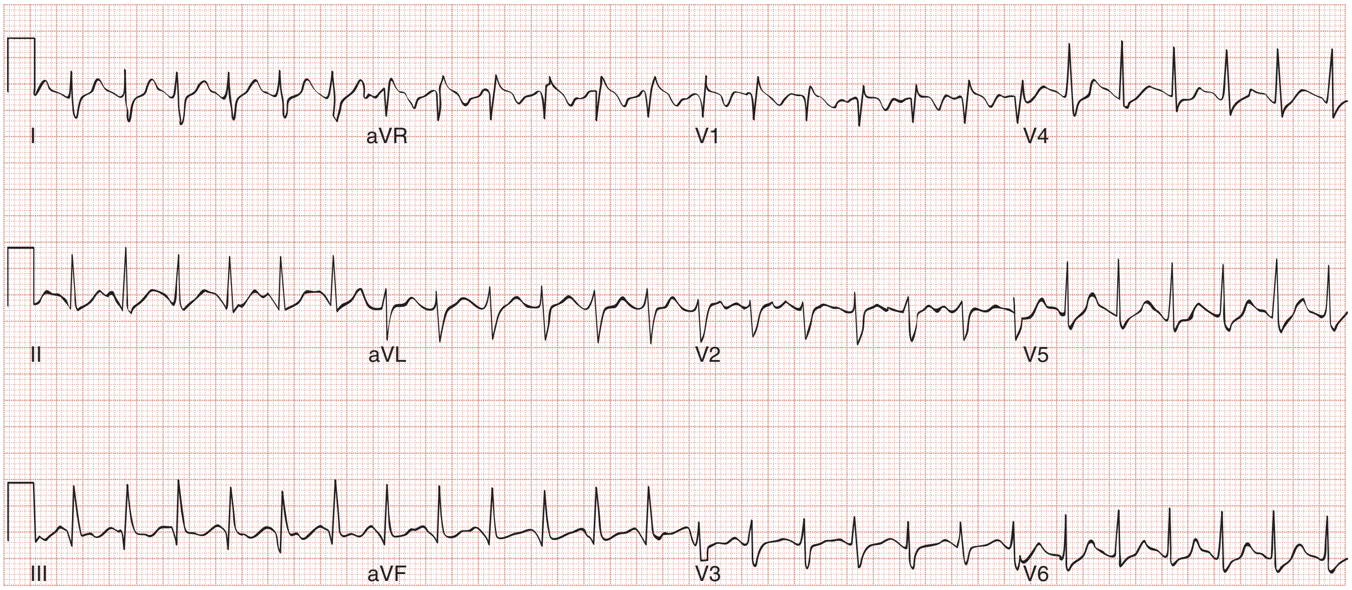


Figure 88-3. Initial electrocardiogram tracing from an 18-year-old woman on oral contraceptives in the ED with syncope. Several findings consistent with pulmonary embolism are shown, including tachycardia, the S1Q3T3 pattern, and an incomplete right bundle branch block. Computed tomography angiography revealed extensive bilateral pulmonary emboli, and echocardiography showed severe right heart dysfunction.

www.ketabpezeshki.com 66485457-66963820

treating clinician's unstructured estimate of PTP was equivalent to that provided by the Wells score and the Charlotte rule. This finding was independent of training level.[21]

Although gestalt reasoning and clinical decision rules may provide adequate stratification to guide the workup (i.e., D-dimer vs. pulmonary vascular imaging), they have not been able to reproducibly identify the "very low-risk" population whose PTP lies below the 2% test threshold. In one validation study, patients with Wells score less than 2 had a 1.3% probability of PE,[30] but this finding has not been repeated. To identify the very low-risk group in whom PE could be safely excluded at the bedside with no diagnostic testing, the PE rule-out criteria (the PERC rule) were derived and prospectively validated in 8138 patients in 13 different hospitals across the United States and in New Zealand (see Box 88-2).[16]

When the physician's unstructured clinical suspicion for PE is low *and* each of the eight elements of the rule is satisfied, the PERC rule identifies a very low-risk population among whom no patient has a PTP for PE of greater than 2%. In the large validation series, the rule excluded PE at the bedside in 20% of cases and yielded a false-negative rate of 1% (95% confidence interval [CI] 0.6-1.6%). This finding supports a rational and reproducible method for avoiding unnecessary testing in a low-risk patient with a sign or symptom partially suggestive of PE. Patients with risk factors but without any symptoms or signs of PE (e.g., no chest pain, no shortness of breath, no dyspnea on exertion, normal vital signs, and no recent syncope) do not warrant workup for PE unless there is some compelling clinical indication to the contrary.

PE also is less likely when some other disease process can explain the patient's complaints and findings (e.g., asthma causing bronchospasm proven by a low peak expiratory flow rate, or findings of wheezing and prolonged expiration on auscultation) in a patient otherwise not believed to be at high risk for PE. A tangible alternative diagnosis reduces the probability of coincident PE. The flow algorithms provided here are predicated on the following goals: (1) to identify as many ED patients as possible who have PE; (2) to avoid mislabeling (and administering anticoagulants to) patients who do not have PE; and (3) to use available resources efficiently and effectively (Fig. 88-4).

For a patient for whom suspicion is implicit or with explicit score suggesting a PTP over 40%, clinicians should skip the D-dimer, order pulmonary vascular imaging, and strongly consider initiating anticoagulation in the absence of contraindications. Because the half-life of circulating D-dimer is less than 8 hours, the sensitivity of the D-dimer may decrease if the patient's symptoms have been present for longer than 3 days. False-negative D-dimer measurements may also be seen with ongoing warfarin therapy and in the subset of patients with pulmonary infarction.

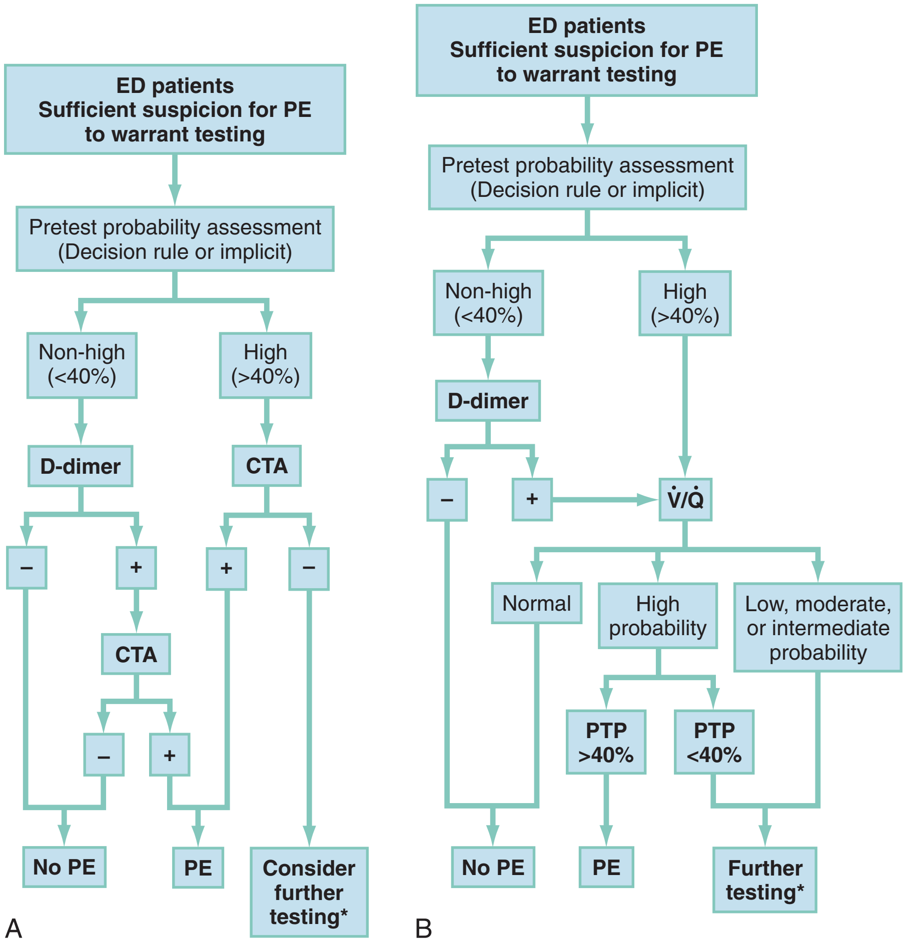


Figure 88-4. Suggested algorithms to evaluate for pulmonary embolism *(PE)* in the emergency department *(ED).* These algorithms include the use of pretest probability *(PTP),* enzyme-linked immunosorbent assay (ELISA), or immunoturbidimetric quantitative D-dimer assay, and pulmonary vascular imaging (computed tomography angiography [*CTA*]). **A,** Algorithm incorporating contrast-enhanced CTA. A negative D-dimer is an immunoturbidimetric assay or ELISA that returns a concentration less than 500 fibrinogen equivalent units (FEUs) (ng) per milliliter. **B,** Algorithm incorporating ventilation-perfusion ($\dot{V}/\dot{Q}$) scanning.
*May require patient admission. Additional testing—Option 1: "Crossover" to perform either scanning or computed tomography for algorithms A and B. Option 2: Perform lower extremity venous ultrasound, and if initial venous ultrasound is negative, repeat the lower extremity venous ultrasound in 1 week. Option 3: Perform formal pulmonary angiography.

www.ketabpezeshki.com 66485457-66963820

As was discussed in the DVT section, quantitative D-dimer assays are more reliable for the exclusion of PE than are qualitative assays.[32-35]

The post-test probability to safely exclude the diagnosis of PE must be equal to 1%, which is at least equivalent to that of a normal scan or a negative CTPA. This combination can be achieved by the combination of a PTP assessment less than 40% (i.e., a patient not at high risk) and a quantitative D-dimer concentration less than 500 ng/mL. When the PTP is high or the screening D-dimer is positive, pulmonary vascular imaging by CTPA or scanning is advised. Although CTPA is not perfect, it has multiple advantages over scanning and usually can confirm or exclude the presence of PE.

Most academic centers now use CTPA as the primary method of evaluating for PE. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II study evaluated the test characteristics of CTPA for the diagnosis of PE in a prospective, multicenter study of 824 patients imaged primarily with four-row multidetector scanners.[3] CTPA images were deemed adequate for interpretation in 773 (94%), and the sensitivity in these patients was 83% (95% CI 76-92%) with a specificity of 96% (95% CI 93-97%).

When CTPA fails to identify PE in a situation of high clinical suspicion, the clinician should review with the radiologist any issues of image acquisition quality that adversely affected diagnostic accuracy. As with any imaging study, if CTPA quality was poor and the results do not match the clinical picture, more testing should be performed.

The importance of isolated subsegmental pulmonary embolus either missed or detected by CTPA can arise because of a radiologist's statement that "subsegmental clot cannot be excluded by CTPA." More recently, increased detection of isolated subsegmental filling defects has occurred, with more thinly collimated images acquired with a higher number multidetector scanner.[17] No firm evidence yet exists to guide these circumstances. When two radiologists independently evaluate CTPA, their agreement on the presence of isolated subsegmental filling defects is poor.[17] The same lack of agreement with regard to subsegmental clots holds for formal pulmonary angiography. It is reasonable that if the patient has no evidence of DVT, no signs of cardiopulmonary stress, and no ongoing major risk for thrombosis (e.g., active malignancy), isolated subsegmental findings are the equivalent of no findings, and anticoagulation is not indicated. If a patient with negative CTPA has signs of pulmonary hypertension or hypoxemia without an apparent alternative cause, or has a known thrombophilia, further testing is advised. Subsequent testing after negative CTPA is individualized by institution in consultation with radiology. Most commonly, if venous studies were not performed as part of the CTPA, duplex ultrasonography of both lower extremities should be undertaken. Positive sonographic evidence of DVT is considered confirmation of the presence of PE. A negative sonogram does not exclude the diagnosis, however, and the procedure should be repeated in 2 to 7 days.

CTPA can provide additional information to enhance its usefulness in the ED. Although the scan can be extended to include the leg veins, this is not recommended as a routine (see earlier discussion.) CTPA often provides information about alternative processes that might explain the patient's symptoms (Box 88-3). Pneumonia is the most common alternative diagnosis found in ED patients. In about 10% of ED patients evaluated for PE, CT as a single test could (1) show absence of PE; (2) provide evidence of alternative disease, which can be used with other evidence to reduce the probability of PE to a reasonably low level to stop the workup; and (3) facilitate treatment for the alternative disease.

The scintillation scan remains a good diagnostic option for patients with contraindications to iodinated intravenous contrast. The accuracy and precision of the scan were shown in the PIOPED study, which compared the results of scanning with the most accurate criterion standard test available at the time—formal pulmonary angiography (Table 88-3).[22] This multicenter study showed that a high-probability scan can be used to diagnose PE, and a normal scan (i.e., no perfusion defect) excludes the diagnosis of PE with an acceptable degree of certainty. A moderate probability or indeterminate scan requires additional formal pulmonary angiography or a CTPA. Even in patients with a low PTP, a low-probability scan usually indicates a need for additional testing, such as either CTPA or venous duplex ultrasonography of the legs. The latter should be repeated at least once, 2 to 7 days later, if negative at the initial presentation. In patients with a chest radiograph that shows airspace disease, the specificity of scanning can be expected to decrease, and the relative diagnostic utility of CTPA can be expected to increase.

Management

Anticoagulation

Either unfractionated heparin (80 units/kg intravenous bolus, followed by 18 units/kg/hr intravenous infusion), fractionated

Box 88-3 Frequency of Nonpulmonary Embolism Diagnoses Discovered on Computed Tomography

Pneumonia (6%)*
Unsuspected pericardial effusion (1%)
Mass suggesting new carcinoma (1%)
Aortic dissection (0.5%)
Pneumothorax (0.5%)

*Percentage of all 1025 emergency department patients who underwent computed tomography to evaluate for pulmonary embolism.

Table 88-3 Prevalence of Pulmonary Embolism Stratified by Ventilation-Perfusion Scan Result and Pretest Probability Estimate

	Clinician Estimate of Pretest Probability for PE			
$\dot{V}/\dot{Q}$ RATIO SCAN RESULT	**80-100%**	**20-79%**	**0-19%**	**ALL**
High probability	28/29 (96%)	70/80 (88%)	5/9 (56%)	103/118 (87%)
Intermediate probability	27/41 (66%)	66/236 (28%)	11/68 (16%)	104/345 (30%)
Low probability	6/15 (40%)	30/191 (16%)	4/90 (4%)	40/296 (14%)
Near-normal or normal	0/5 (0%)	4/62 (6%)	1/61(2%)	5/128 (4%)
Total	61/90 (68%)	170/569 (30%)	21/228 (9%)	252/887 (28%)

Adapted from the PIOPED Investigators: Value of the ventilation/perfusion scan in acute pulmonary embolism. JAMA 263:2753, 1990.
PE, pulmonary embolism; $\dot{V}/\dot{Q}$, ventilation-perfusion ratio.

www.ketabpezeshki.com 66485457-66963820

Table 88-4 Risk-Stratification and Associated Treatment Recommendations for Acute Pulmonary Embolism (PE)

CATEGORY	CRITERIA	ACTION
Low-risk PE	SBP >90 mm Hg at all times and all of the following: Shock index <1 Sao_2 almost always > 94% Daniel score <3 Normal troponin or BNP or proBNP level PESI score <66	Begin low-molecular-weight heparin Optional admission to unmonitored regular bed Consider outpatient treatment if adequate compliance and follow-up can be ensured
Moderate-risk PE	SBP >90 mm Hg at all times and any one of the following: Shock index 1 or greater at any time Sao_2 persistently <94% Daniel score >3 Elevated troponin or BNP or proBNP level PESI score >65 and <125 Echocardiography with any degree of right ventricular hypokinesis	Begin heparin treatment Fibrinolytics in the minority of cases Admission to a telemetry bed
More severe (submassive) moderate-risk PE	Appearance of at least moderate distress AND Shock index >1 and severe right ventricular hypokinesis on echocardiography Worsening Daniel score, particularly a new incomplete right bundle branch block (RBBB) or progression of iRBBB to complete RBBB Sao_2 <90% and serum troponin level clearly elevated PESI score >124	Begin heparin treatment Fibrinolytic treatment in the majority of patients without contraindications in the ED Admission to a step-down or intensive care unit
High risk (major) PE	Any SBP <90 mm Hg or <20 mm Hg below documented baseline and appearance of distress Any persistent SBP <90 mm Hg regardless of appearance	Begin heparin treatment Fibrinolytic treatment in all patients without contraindications in the ED Admission to intensive care unit

BNP, B-type natriuretic peptide; *ED,* emergency department; *iRBBB,* incomplete right bundle branch block; *PESI,* Pulmonary Embolism Severity Index; *proBNP,* pro-B–type natriuretic peptide; *Sao_2*, arterial oxygen saturation; *SBP,* systolic blood pressure.

low-molecular-weight heparin (e.g., enoxaparin, 1 mg/kg SQ or intravenously [IV] every 12 hours), or the pentasaccharide factor Xa inhibitor fondaparinux (5-10 mg, depending on body mass) can be used for treatment of most patients with PE. Low-molecular-weight heparin is recommended over unfractionated heparin because meta-analyses clearly indicate a lower rate of major hemorrhage with low-molecular-weight heparin, a lower rate of heparin-induced thrombocytopenia, and lower rate of VTE recurrence compared with unfractionated heparin, and a similar overall economic cost. However, the anticoagulant effect of unfractionated heparin can be almost completely and rapidly reversed with protamine, whereas low-molecular-weight heparin can be neutralized only about 50% with protamine, and protamine has no effect on fondaparinux. Both forms of heparin work equally well, and both are safe in the absence of contraindications to anticoagulation. Heparin provides several immediate benefits, including the reduction in clot extension (which can occur rapidly); reduces the transient hypercoagulable effect of warfarin treatment; and over a period of days to weeks allows the natural fibrinolytic system to reduce clot size.

A large registry found that emergency physicians begin heparin in approximately 10% of patients who are diagnosed with PE, before knowing the results of pulmonary vascular imaging ("empirical heparin"). Only 15% of patients who died from PE received empirical heparin, but this fact in the absence of other published data can be used to assert that empirical heparin administration can improve outcomes from PE.[23] In consideration of its risks and benefits, empirical treatment probably confers more benefit than harm in a hemodynamically stable patient when the PTP of PE exceeds 30%, the patient has no major contraindication to anticoagulation, and the clinical circumstances predict that imaging will not be available for several hours.[24] All patients with a high PTP, no contraindication to anticoagulation, and evidence of hemodynamic instability, including recent syncope, any hypotension, hypoxemia, or clinical evidence of right-sided heart strain (criteria defined in Table 88-4 as more severe moderate PE or high-risk PE), should receive immediate empirical heparin.

Recent evidence has indicated that up to 50% of outpatients diagnosed with PE may be stable enough to be treated as outpatients.[25-27] A multicenter trial that randomized patients with low-risk PE (see Table 88-4 for definition) found equivalent outcomes for patients who were discharged from the ED compared with hospital admission.[25] It should be noted that more than 95% of patients in that study were enrolled from Europe, where the public health resources for initiation and maintenance of high-quality anticoagulation generally exceed those of the United States. In settings where good follow-up can be obtained, the patient can be taught to self-administer low-molecular-weight heparin, and the patient can access an anticoagulation clinic within 48 hours, a low-risk patient with PE can be discharged from the ED.

For a patient diagnosed with PE in the presence of a major contraindication to anticoagulation, such as a recent cerebral hemorrhage or large cerebral infarction, the appropriate consultant should be contacted for urgent placement of an inferior vena cava filter. If vena caval interruption cannot be performed within 12 hours, one option is to perform a baseline head CT scan, then start an unfractionated heparin infusion at 18 units/kg/hr (without a bolus) and admit the patient to the intensive care unit for close neurologic monitoring and frequent partial thromboplastin time determinations. The rationale for use of unfractionated heparin is that it can be reversed more reliably (by discontinuing the heparin drip and administering protamine, 1 mg/kg IV) than fractionated heparin. Case reports and series have suggested that inhaled nitric oxide might be helpful for patients with severe PE and an absolute contraindication to anticoagulation, but this treatment has not been subjected to rigorous study.

Most patients with PE look and feel better the day after starting heparin anticoagulation, and more than half go on to a nearly full

www.ketabpezeshki.com 66485457-66963820

recovery of pre-PE health status. The in-hospital mortality rate of patients diagnosed with PE who remain hemodynamically stable while in the ED has been thought to be 10%, but a recent large, multicenter United States–based registry of 1880 patients diagnosed with PE in the ED found an in-hospital mortality rate directly attributable to PE of 1.1% and an all-cause mortality rate of 5.4%.[23] Approximately 10 to 20% of patients report persistent dyspnea and exercise intolerance that permanently degrades their quality of life. Systolic hypotension (<90 mm Hg) represents a highly specific and moderately sensitive indicator of severe PE and increases the mortality rate dramatically. In the absence of hypotension, several parameters available at the bedside can help with prognosis. A heart rate that is persistently above the systolic blood pressure indicates more severe clot, as does a pulse oximetry reading less than 95%. Presence of prior congestive heart failure or advanced chronic obstructive pulmonary disease serves to magnify the severity of PE. An elevated serum troponin measurement or an elevated brain natriuretic peptide or pro-brain natriuretic peptide concentration portend a worse outcome. Echocardiography demonstrating right ventricular hypokinesis or dilation also increases the probability of death from PE. Table 88-4 summarizes the criteria that can be used to risk stratify patients with PE into four groups. Table 88-4 also shows how consideration of these criteria may help guide the decision to place the patient in an ICU versus an intermediate or regular inpatient bed, and whether to administer heparin only or consider escalated therapy.

Thrombolytic Therapy

Thrombolytic therapy in PE is controversial. Administration of alteplase to patients with PE results in more rapid symptomatic improvement than standard antithrombotic therapy alone and causes more rapid and complete normalization of right ventricular function.[28] Alteplase also increases the risk of hemorrhage, especially minor hemorrhage. It is not known with certainty how many patient lives would be saved, or definitively improved, by the addition of thrombolytic treatment to heparin therapy versus the number of patients who would experience a fatal or life-threatening bleeding event as a result of thrombolytic treatment. On balance, the benefit-risk analysis suggests that fibrinolysis is of greatest value in the subset of patients with proven, massive PE. Massive PE is defined by hypotension with a systolic blood pressure below 90 mm Hg for more than 15 minutes. In patients with preexisting hypertension, the threshold is adjusted to below 100 mm Hg or a reduction in the baseline systolic blood pressure of more than 60 mm Hg. In the absence of contraindications, patients with proven massive PE probably benefit from fibrinolysis. There is insufficient evidence to recommend initiation of empirical fibrinolysis in the absence of confirmatory pulmonary vascular imaging or the presence of otherwise unexplained shock in a patient with known DVT and high clinical suspicion for PE.

A subset of patients with submassive PE may benefit from fibrinolysis, including those with moderate-to-severe respiratory distress and hypoxia (oxygen saturation less than 95%) and those with echocardiographic evidence of right ventricular dysfunction. When echocardiography is unavailable in a timely manner, surrogate laboratory markers of right ventricular dysfunction may be useful, including an elevated troponin level or a brain natriuretic peptide level greater than 90 pg/mL (see Table 88-4).[29] Consultation with cardiology or cardiac surgery should be obtained before administration of fibrinolytic therapy for patients with PE who are not in extremis. The FDA-approved regimens for thrombolysis are shown in Table 88-5.

Tenecteplase (TNKase) is a recombinant plasminogen-activating enzyme with several pharmacologic properties that may favor its use for fibrinolysis of acute PE; it has been studied in one

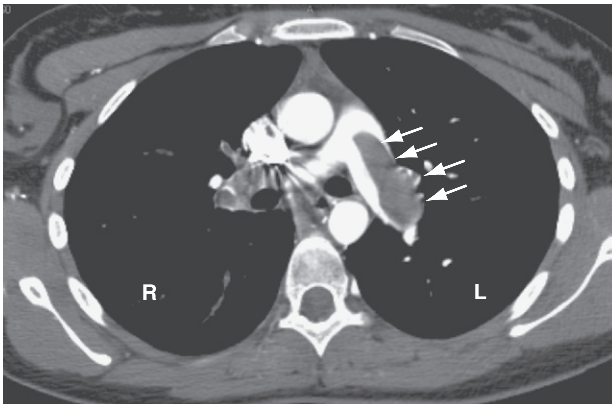


Figure 88-5. Massive pulmonary embolism on a contrast-enhanced computed tomography (CT) scan of the chest. This CT scan is at the level of the bifurcation of the main pulmonary artery. The left main branch of the pulmonary artery shows a massive filling defect *(arrows)*. The patient was a young woman who recently began taking oral contraceptives; she had come to the emergency department after passing out at work after a 1-week duration of dyspnea. The patient had cyanosis, hypoxemia, and worsened hemodynamic findings when supine but was normotensive when sitting upright. She was given anticoagulant therapy, had emergent surgical embolectomy, and survived with excellent outcome. Her DNA had factor V Leiden mutation, by polymerase chain reaction testing in both alleles.

Table 88-5 Food and Drug Administration–Approved Fibrinolytic Regimens for Acute Treatment of Pulmonary Embolism

Streptokinase	1 million units infused over 24 hr
Urokinase	1 million–unit bolus followed by 24-hr infusion at 300,000 units/hr
Alteplase	15-mg bolus followed by 2-hr infusion of 85 mg; discontinue heparin during infusion

randomized controlled trial.[30] Tenecteplase does not have FDA approval for PE treatment. Tenecteplase differs from alteplase because it has a longer half-life, resistance to plasminogen activator inhibitor–1, and increased fibrin specificity, which results in less fibrinogenolysis and less coagulopathy.

The clinical course of patients with obstructive PE can be unpredictable. Many patients with massive PE remain stable in the ED. Other patients are stable on arrival but progressively deteriorate over hours as right ventricular function declines. Three percent of ED patients without hypotension while in the ED experience cardiac arrest and die within 24 hours.[23] A patient can be stable and then hypotensive within minutes because of the highly variable effect of the clot on right ventricular outflow obstruction, especially when it is perched in the main pulmonary artery (Fig. 88-5). Additional mechanisms of rapid instability include new embolization of clot material, release of mediators of pulmonary vasospasm, sudden bradycardiac or asystolic arrhythmias, and respiratory failure. Clues to oncoming cardiopulmonary decompensation include worsening respiratory distress and worsening hypoxemia, a rising shock index (the heart rate divided by the systolic blood pressure), systolic arterial blood pressure less than 90 mm Hg, and syncope or a seizure-like convulsive episode while in the ED. A particularly ominous finding is the evolution on ECG from a narrow-complex tachycardia to an incomplete right bundle branch block to a complete right bundle branch block (Fig. 88-6) as evidence of life-threatening pulmonary hypertension and incipient cardiac arrest.

Clinical evidence of impending or actual respiratory failure indicates the need for prompt endotracheal intubation with use

www.ketabpezeshki.com 66485457-66963820

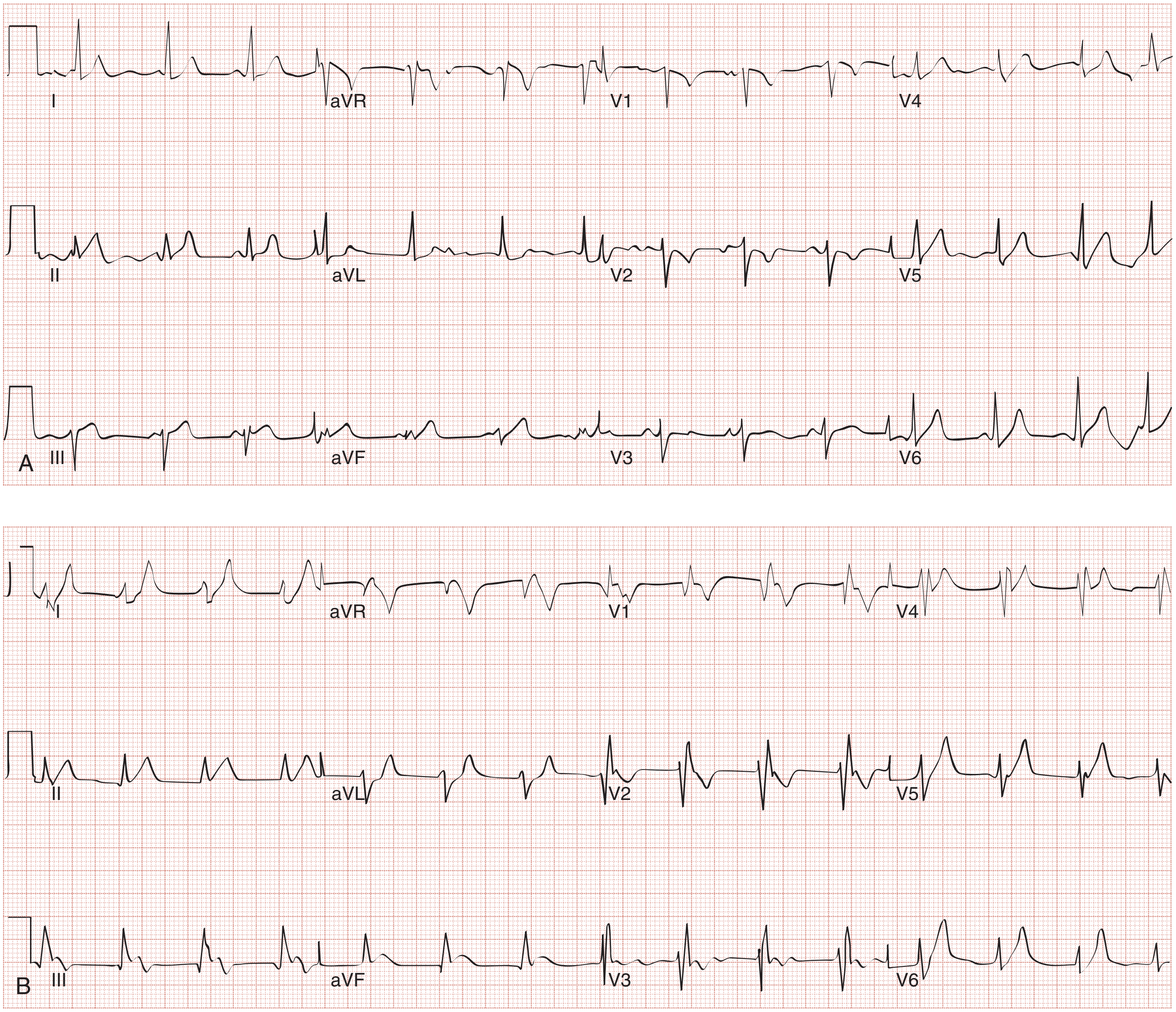


Figure 88-6. Serial electrocardiograms obtained 2 minutes apart show the progression from a narrow complex rhythm **(A)** to a right bundle branch block pattern **(B)** in a patient with massive bilateral pulmonary emboli. Shortly after the second tracing was obtained, the patient developed cardiovascular collapse refractory to vigorous resuscitation efforts.

of standard rapid sequence intubation technique, preferably with either ketamine or etomidate for induction of anesthesia with neuromuscular blockade. Other induction agents that depress cardiac function or reduce preload may precipitate severe hypotension and should be avoided or their dosage reduced. In the case of impending respiratory or cardiac arrest, fibrinolytic therapy should be strongly considered.

Surgical Embolectomy

For patients with known floating thrombi in the right side of the heart or for patients with severe refractory hypotension, surgery is the most likely intervention to save the patient's life. Surgical embolectomy requires extracorporeal cardiopulmonary bypass and an experienced cardiothoracic surgeon. Surgical embolectomy may be the best option for patients who have severe PE with a contraindication to fibrinolysis; however, extracorporeal perfusion requires intensive heparin anticoagulation, and the patient's mental status cannot be monitored during surgery—a key concern in patients with high risk of intracranial hemorrhage. Catheter-directed thrombectomy also may be lifesaving but requires that the patient be sent to the relatively uncontrolled environment of the interventional radiology suite. No data support the use of catheter intervention for treatment of PE.[31]

PE can manifest as cardiac arrest. Most patients with incipiently fatal PE have overt respiratory distress, syncope or seizure-like activity, or a high heart rate relative to the systolic blood pressure before arrest. First responders who observe a patient dying from PE most commonly observe PEA as the initial cardiac arrest rhythm (>20 depolarizations per minute without palpable pulses). The mechanism for PEA manifests from right ventricular outflow obstruction and impaired right ventricular contractility. Ultrasound performed during PEA arrest from PE usually shows weak cardiac contractions with a swollen right ventricle and small left ventricle. Some patients manifest slow agonal rhythms with fatal or near fatal PE possible owing to septal wall tension leading to ischemia or ischemic-equivalent effect on the atrioventricular node and infranodal conducting pathways.

Regardless of the initial rhythm, pulselessness from PE imparts a published mortality rate exceeding 70%. Numerous case reports

www.ketabpezeshki.com 66485457-66963820

Box 88-4 Unique Questions That Commonly Arise in the Emergency Department (ED)

1. **I cannot get imaging at night. Is it reasonable to treat the patient with heparin until morning?**

The short answer to this question is yes, if the patient has no contraindications. Many smaller hospitals routinely use this method and use a single dose of enoxaparin.

2. **How do I manage the patient who is being treated for pulmonary embolism who returns to the ED for chest pain?**

If the patient has a therapeutic international normalized ratio (1.5-2.5) and returns with symptoms only (e.g., chest pain, dyspnea) and without syncope, appears relatively comfortable, has normal vital signs, and has no new changes suggesting pulmonary hypertension on ECG (in particular, no S1Q3T3 pattern and no T wave inversion in leads V_1 through V_4), follow-up imaging is probably not needed. Other causes of chest pain (especially acute coronary syndrome) should be considered. In the absence of an identified alternative diagnosis, symptomatic care with an anti-inflammatory agent is safe and reasonable therapy for the return complaint of chest pain. Persistent dyspnea at rest raises more concerns of unresolved or recurrent thrombosis with secondary effects, including bronchospasm or, worse, pulmonary vascular hyperplasia with pulmonary hypertension. Repeat pulmonary vascular imaging may provide evidence of an unresolved or new clot. More important, a transthoracic echocardiogram can disclose evidence of persistent right ventricular dysfunction and pulmonary hypertension. Symptomatic patients with unresolved filling defects and pulmonary hypertension can progress to chronic thromboembolic pulmonary hypertension. For prevention of this decline, patients who return to the ED with persistent rest dyspnea and have unresolved filling defects and pulmonary hypertension should be admitted or referred to a program that offers the option of pulmonary thrombectomy.

3. **How can I rule out pulmonary embolism in a pregnant patient without use of ionizing radiation?**

One clinical conundrum is the fact the pregnancy is accompanied by both an increased risk of PE and a predictable elevation in D-dimer, even in the absence of PE. Given that PE is the most common nontraumatic cause of death in pregnant women, clinicians are justified in adopting a liberal "rule-out PE" approach to all pregnant women with dyspnea.

To evaluated suspected PE in pregnancy, I recommend the following sequence. First, assess the PERC rule criteria and apply a modified version of the PERC rule with a slightly elevated top limit for the pulse rate (normal up to 104 beats/min instead of 99 beats/min). If the result of this modified PERC rule is negative, then order a quantitative D-dimer. Use thresholds to define a normal D-dimer that is elevated on the basis of trimester (first trimester, 1.5×; second trimester, 2×; and third trimester, 2.5× standard threshold).[32] If the result of the modified PERC rule is positive or the D-dimer is above the adjusted threshold, then order bilateral lower extremity ultrasound; if this is positive for DVT, then treat for PE. If the bilateral ultrasound is negative, proceed to pulmonary vascular imaging.

The issue of the optimal imaging procedure in pregnancy remains controversial. A 2003 survey of radiologists indicated an almost equal split (53% in favor of CTPA, 47% in favor of $\dot{V}/\dot{Q}$ scanning) in their choice for imaging for PE in pregnancy.[33] Very few published data are available to compare outcomes after $\dot{V}/\dot{Q}$ scanning with those after CTPA scanning in pregnancy.[34-36] Facts to consider include the following:

1. No empirical data are available to accurately measure the radiation dose absorbed by the fetus in utero during imaging, as dosimeters cannot be placed on the fetal body. Thus estimates of fetal radiation dose come from models and simulations. These studies generally suggest that the radiation dose from CTPA is lower than that from $\dot{V}/\dot{Q}$ scanning, but the dose is approximately equal between CTPA and perfusion-only "$\dot{Q}$" scanning.[34,37,38]
2. Available data show that the overall rate of indeterminate studies is about 10-15% for both $\dot{V}/\dot{Q}$ and CTPA, but for the subset of pregnant patients with a plain film chest radiograph that is normal, the indeterminate rate is lower for $\dot{V}/\dot{Q}$ scanning than for CTPA scanning.[34-36]
3. CTPA may show alternative diagnoses that $\dot{V}/\dot{Q}$ scanning does not, although one study showed that most alternative diagnoses were pneumonia, which were also seen on plain film chest radiography.[34]
4. CTPA may increase the risk of breast cancer in the mother by about 1.5%, whereas $\dot{V}/\dot{Q}$ scanning is not believed to confer this risk.[39]
5. Nonionic contrast media readily cross the placenta, and the long-term risks of contrast exposure to the fetus remains unknown.
6. Tube voltage modulation and other technology can significantly reduce fetal radiation exposure with CTPA, possibly even to a greater extent than does shielding with lead or antimony-bismuth aprons.[40]
7. Fetal radiation exposure with CTPA increases with each trimester, although this effect is mitigated with 64-channel scanners, as they produce less scatter radiation than 16- or 4-channel CT scanners.[34,37,38]

Taken together, these facts suggest no clear benefit to either procedure for any trimester of pregnancy. I recommend that a plain film chest radiograph be taken first, and if this radiograph shows no air space disease, that scintillation scanning can be considered—but only the perfusion phase is performed, the radiation "dose" is halved, and the patient receives prehydration, and consideration is given to placement of a Foley catheter to accelerate removal of radiolabel in the bladder. If the chest radiograph has any evidence of airspace disease, CTPA scanning should be performed and the abdomen should be shielded. Obviously, these recommendations must be considered in the clinical context of availability of equipment and personnel and the opinion of the responsible radiologist. Scintillation perfusion scanning, if normal, excludes the diagnosis. A perfusion scan with two or more segmental perfusion defects in the presence of a normal chest radiograph establishes the diagnosis, and heparin (which does not cross the placental barrier) can be initiated. If is the perfusion scan is nondiagnostic, CTPA scanning will be required.

4. **How do I evaluate the patient with possible pulmonary embolism who is too obese to fit in a CT scanner?**

Each CT scanner has a maximum patient weight that it will accommodate. When a patient's weight exceeds the scanner limit and a larger capacity scanner is not available, I recommend duplex venous ultrasonography of the lower extremities to rule out DVT. Although often technically suboptimal in a massively obese patient, venous ultrasound occasionally provides positive evidence of DVT, ostensibly clinching the diagnosis. Another option is to anticoagulate empirically based on a moderate-to-high pretest probability and a D-dimer concentration that exceeds 1000 ng/mL. The adequate regimen for anticoagulation is uncertain, but many experts recommend subcutaneous enoxaparin, 1 mg/kg of actual body weight up to a maximum of 200 μg/kg.

CT, computed tomography; *CTPA,* CT pulmonary angiography; *DVT,* deep vein thrombosis; *ECG,* electrocardiogram; *PE,* pulmonary embolism; $\dot{V}/\dot{Q}$, ventilation-perfusion ratio.

www.ketabpezeshki.com 66485457-66963820

have suggested heroic results from bolus administration of thrombolytic therapy to patients with cardiac arrest from PE. The administration of fibrinolytic therapy does not absolutely preclude surgical intervention. Patients who have been treated with a fibrinolytic agent can undergo sternotomy or thoracotomy for embolectomy and survive without fatal hemorrhage. The decision to perform embolectomy ultimately resides with the cardiac surgeon.

Box 88-4 details questions that commonly arise regarding the diagnosis and treatment of PE in the ED.

KEY CONCEPTS

- Deep vein thrombosis often manifests as a nonspecific crampy sensation in the upper or lower extremity without obvious swelling.
- The absence of a sudden onset of symptoms is of no value in excluding PE as the cause of the patient's presentation.
- An ELISA or immunoturbidimetric D-dimer concentration below 500 ng/mL can rule out PE or DVT in all but high-risk patients. Patients with low or moderate pretest probability should not undergo imaging without a screening D-dimer test.
- A patient with a pretest probability below 2% need not be tested for PE.
- A patient with PE and a pulse oximetry reading below 95% is at increased risk for a bad outcome.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Johnson SA, et al: Risk of deep vein thrombosis following a single negative whole-leg compression ultrasound: A systematic review and meta-analysis. *JAMA* 2010; 303:438-445.
2. Kline JA, O'Malley PM, Tayal VS, Snead GR, Mitchell AM: Emergency clinician–performed compression ultrasonography for deep venous thrombosis of the lower extremity. *Ann Emerg Med* 2008; 52:437-445.
3. Stein PD, et al: Multidetector computed tomography for acute pulmonary embolism. *N Engl J Med* 2006; 354:2317-2327.
4. Burnside PR, Green E, Kline JA: Indirect computed tomography venography: A report of vascular opacification. *Emerg Radiol* 2010; 17:195-201.
5. Decousus H, et al: Fondaparinux for the treatment of superficial-vein thrombosis in the legs. *N Engl J Med* 2010; 363:1222-1232.
6. Schwarz T, et al: Therapy of isolated calf muscle vein thrombosis: A randomized, controlled study. *J Vasc Surg* 2010; 52:1246-1250.
7. Righini M: Is it worth diagnosing and treating distal deep vein thrombosis? No. *J Thromb Haemost* 2007; 5:55-59.
8. Meissner MH, Caps MT, Bergelin RO, Manzo RA, Strandness DE: Early outcome after isolated calf vein thrombosis. *J Vasc Surg* 1997; 26:749-756.
9. Righini M, et al: Clinical relevance of distal deep vein thrombosis. Review of literature data. *Thromb Haemost* 2006; 95:56-64.
10. Laporte S, et al: Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: Findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. *Circulation* 2008; 117:1711-1716.
11. Courtney DM, et al: Clinical features from the history and physical examination that predict the presence or absence of pulmonary embolism in symptomatic emergency department patients: Results of a prospective, multicenter study. *Ann Emerg Med* 2010; 55:305-315.
12. Kline JA, Corredor DM, Hogg MM, Hernandez J, Jones AE: Normalization of vital signs does not reduce the probability of acute pulmonary embolism in symptomatic emergency department patients. *Acad Emerg Med* 2012; 19:11-17.
13. Kruse L, Mitchell AM, Camargo CA Jr, Hernandez J, Kline JA: Frequency of thrombophilia-related genetic variations in patients with idiopathic pulmonary embolism in an urban emergency department. *Clin Chem* 2006; 52:1026-1032.
14. Courtney DM, Kline JA: Identification of prearrest clinical factors associated with outpatient fatal pulmonary embolism. *Acad Emerg Med* 2001; 8:1136-1142.
15. Marchick MR, et al: 12-Lead ECG findings of pulmonary hypertension occur more frequently in emergency department patients with pulmonary embolism than in patients without pulmonary embolism. *Ann Emerg Med* 2009; 55:331-335.
16. Kline JA, et al: Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J Thromb Haemost* 2008; 6:772-780.
17. Courtney DM, et al: Prospective multi-center assessment of interobserver agreement for radiologist interpretation of multidetector CT angiography for pulmonary embolism. *J Thromb Haemost* 2010; 8:533-540.
18. Lessler AL, Isserman JA, Agarwal R, Palevsky HI, Pines JM: Testing low-risk patients for suspected pulmonary embolism: A decision analysis. *Ann Emerg Med* 2010; 55:316-326.
19. Lucassen W, et al: Clinical decision rules for excluding pulmonary embolism: A meta-analysis. *Ann Intern Med* 2011; 155:448-460.
20. Runyon MS, Richman PB, Kline JA: Emergency medicine practitioner knowledge and use of decision rules for the evaluation of patients with suspected pulmonary embolism: Variations by practice setting and training level. *Acad Emerg Med* 2007; 14:53-57.
21. Runyon MS, Webb WB, Jones AE, Kline JA: Comparison of the unstructured clinician estimate of low clinical probability for pulmonary embolism to the Canadian score or the Charlotte rule. *Acad Emerg Med* 2005; 12:587-593.
22. Zagorski J, Marchick MR, Kline JA: Rapid clearance of circulating haptoglobin from plasma during acute pulmonary embolism in rats results in HMOX1 up-regulation in peripheral blood leukocytes. *J Thromb Haemost* 2010; 8:289-296.
23. Pollack CV, et al: Clinical characteristics, management, and outcomes of patients diagnosed with acute pulmonary embolism in the emergency department: Initial Report of EMPEROR (Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry). *J Am Coll Cardiol* 2011; 57:700-706.
24. Hogg KE, Brown MD, Kline JA: Estimating the pretest probability to justify the empiric administration of heparin prior to pulmonary vascular imaging for pulmonary embolism. *Thromb Res* 2006; 118:547-553.
25. Aujesky D, et al: Outpatient versus inpatient treatment for patients with acute pulmonary embolism: An international, open-label, randomised, non-inferiority trial. *Lancet* 2011; 378:41-48.
26. Erkens PM, et al: Safety of outpatient treatment in acute pulmonary embolism. *J Thromb Haemost* 2010; 8:2412-2417.
27. Baglin T: Fifty per cent of patients with pulmonary embolism can be treated as outpatients. *J Thromb Haemost* 2010; 8:2404-2405.
28. Kline JA, Steuerwald MT, Marchick MR, Hernandez-Nino J, Rose GA: Prospective evaluation of right ventricular function and functional status six months after acute submassive pulmonary embolism: Frequency of persistent or subsequent elevation in estimated pulmonary artery pressure. *Chest* 2009; 136:1202-1210.
29. Kline JA, Hernandez J, Rose G, Norton HJ, Camargo CA Jr: Surrogate markers for adverse outcomes in normotensive patients with pulmonary embolism. *Crit Care Med* 2006; 34:2773-2780.
30. Becattini C, et al: Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. *Thromb Res* 2010; 125:e82-e86.
31. Verstraete M, et al: Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism. *Circulation* 1988; 77:353-360.
32. Kline JA, Hambleton GW, Hernandez J: D-dimer concentrations in normal pregnancy: New diagnostic thresholds are needed. *Clin Chem* 2005; 51:825-829.
33. Schuster ME, et al: Pulmonary embolism in pregnant patients: A survey of practices and policies for CT pulmonary angiography. *AJR Am J Roentgenol* 2003; 181:1495-1498.
34. Shahir K, Goodman LR, Tali A, Thorsen KM, Hellman RS: Pulmonary embolism in pregnancy: CT pulmonary angiography versus perfusion scanning. *AJR Am J Roentgenol* 2010; 195:W214-W220.
35. Cahill AG, Stout MJ, Macones GA, Bhalla S: Diagnosing pulmonary embolism in pregnancy using computed-tomographic angiography or ventilation-perfusion. *Obstet Gynecol* 2009; 114:124-129.
36. Ridge CA, et al: Pulmonary embolism in pregnancy: Comparison of pulmonary CT angiography and lung scintigraphy. *AJR Am J Roentgenol* 2009; 193:1223-1227.
37. Gilet AG, Dunkin JM, Fernandez TJ, Button TM, Budorick NE: Fetal radiation dose during gestation estimated on an anthropomorphic phantom for three generations of CT scanners. *AJR Am J Roentgenol* 2011; 196:1133-1137.
38. Winer-Muram HT, et al: Pulmonary embolism in pregnant patients: Fetal radiation dose with helical CT. *Radiology* 2002; 224:487-492.
39. Parker MS, et al: Female breast radiation exposure during CT pulmonary angiography. *AJR Am J Roentgenol* 2005; 185:1228-1233.
40. Chatterson LC, Leswick DA, Fladeland DA, Hunt MM, Webster ST: Lead versus bismuth-antimony shield for fetal dose reduction at different gestational ages at CT pulmonary angiography. *Radiology* 2011; 260:560-567.

www.ketabpezeshki.com 66485457-66963820

Chapter 89

Esophagus, Stomach, and Duodenum

Jamie M. Hess and Mark J. Lowell

ESOPHAGEAL OBSTRUCTION

Perspective

Patients with ingestion of foreign objects and esophageal food boluses commonly are seen in the emergency department (ED). Although most objects pass spontaneously, approximately 10 to 20% require a nonoperative intervention, and fewer than 1% require surgical removal. Death as a result of foreign body ingestion or impaction is rare. Patients with esophageal foreign bodies can be classified into four major categories: (1) pediatric patients, (2) psychiatric patients and prisoners, (3) patients with underlying esophageal disease, and (4) edentulous adults. Pediatric patients account for more than 75% of ingestions, with the peak incidence between the ages of 18 and 48 months.[1] Coins account for the majority of pediatric ingestions, whereas most adult impactions involve pieces of food, particularly meat and bones.[2] Patients with structural abnormalities of the esophagus, such as strictures, rings, webs, diverticuli, or malignancies, are at greater risk for foreign body impaction. Edentulous adults are also at increased risk because of impaired oral sensation and have a risk of accidental ingestion of their dental prosthesis.[3]

Principles of Disease

The adult esophagus is approximately 25 to 30 cm in length. Superiorly, it begins in the hypopharynx as a transverse slit posterior to the larynx and approximately at the level of the cricoid cartilage. On either side of this cephalad slit are the piriform recesses, which are blind pouches that may occasionally harbor a foreign body. The esophagus is distensible; an adult can usually pass an object up to 20 mm in size without difficulty. Throughout its course, the esophagus has four natural areas of narrowing where the majority of foreign bodies become entrapped: at the cricopharyngeus muscle (the upper esophageal sphincter [UES]), the aortic arch, the left mainstem bronchus, and the lower esophageal sphincter (LES) at the diaphragmatic hiatus. Pediatric entrapment occurs primarily at the level of the cricopharyngeus, whereas adult entrapment occurs mainly at the UES. Large, proximal impactions can impinge on the trachea, leading to airway compromise that manifests as choking, stridor, or cough.

The esophagus comprises two main bands of muscle: an inner circular layer and an outer longitudinal layer. The resting tone of these muscles causes the inner epithelium to fold in on itself, effectively obliterating the lumen. Elastic fibers enable the esophageal lumen to expand and allow passage of a food bolus. The upper third of the esophagus, including the cricopharyngeus muscle, contains striated muscle to allow the voluntary initiation of swallowing. The middle portion of the esophagus is a mixture of skeletal and smooth muscle, and the distal third is composed only of smooth muscle.

Although it is relatively fixed at its origin, the esophagus becomes mobile as it traverses the mediastinum. Thus it can be easily displaced by adjacent structures such as an enlarged left atrium or ventricle, a goiter, or a mediastinal tumor. Displacement of the esophagus may alter its shape enough to impede the passage of a food bolus or foreign body.

Clinical Features

Patients with an esophageal obstruction have a wide range of symptoms. Most adults are able to describe the precipitating event and commonly complain of dysphagia (difficulty swallowing), odynophagia (painful swallowing), and neck or chest pain. Entrapment at the UES can generally be localized by the patient because of somatic nerve endings in the upper esophagus. In contrast, entrapment in the lower esophagus causes more visceral-type chest and epigastric discomfort.[1] The obstruction may be partial or complete. The patient with complete obstruction is unable to swallow oral secretions and may be violently retching in an attempt to regurgitate the obstructing bolus. Patients should be evaluated for the presence of stridor or signs of perforation or peritonitis.

Pediatric patients are often brought to the ED after a witnessed ingestion. A high degree of suspicion is needed to diagnose foreign body ingestion when the event was unwitnessed, because 7 to 35% of children with proven esophageal foreign body impactions are asymptomatic at the time of presentation. Symptoms that should prompt consideration of unwitnessed foreign body ingestion include fever, wheezing, stridor, rhonchi, or poor feeding.[4]

A proximal obstruction may arise as a "café coronary," characterized by sudden cyanosis and collapse caused by food (usually an unchewed piece of meat) lodging in the upper esophagus or oropharynx leading to airway obstruction. Similarly, "steakhouse syndrome" results when a large piece of food, usually improperly chewed, is swallowed and causes esophageal obstruction in the distal esophagus. The obstruction may be transient with spontaneous passage of the bolus and may be complete or partial. Intense discomfort develops shortly after swallowing a large piece of meat, and the patient is usually unable to swallow anything else. Ingestion of alcohol and absence of teeth are predisposing factors. Although obstruction may occur in a patient with a normal esophagus, preexisting structural abnormalities such as carcinoma, peptic stricture, or Schatzki's ring are identified in almost 90% of patients with an esophageal obstruction. Schatzki's ring is a fibrous, diaphragm-like stricture near the gastroesophageal junction present in up to 15% of the population.

www.ketabpezeshki.com 66485457-66963820

Aside from naturally occurring areas of anatomic narrowing, there are other pathologic causes of esophageal stenosis that may lead to symptoms of obstruction. Intrinsic causes of luminal narrowing include carcinoma and webs. An esophageal web is a thin structure composed of mucosa and submucosa most commonly found in the middle or proximal esophagus. Although webs can occur in isolation, they are also seen in the Plummer-Vinson syndrome, which is characterized by anterior webs, dysphagia, iron deficiency anemia, cheilosis, spooning of the nails, glossitis, and thin friable mucosa in the mouth, pharynx, and upper esophagus. Most patients with this syndrome are women 30 to 50 years of age. Patients usually report dysphagia that is initially intermittent and worse with solids. If untreated, it may progress and become constant. Surgical changes after a gastric bypass can also predispose a patient to esophageal obstruction.[5]

Extrinsic compression of the esophagus can occur in a variety of conditions. In the neck, thyroid enlargement from goiter or carcinoma may cause dysphagia. Symptoms may also be seen with a pharyngoesophageal or Zenker's diverticulum, a progressive outpouching of the pharyngeal mucosa as a result of increased pressure generated by failure of proper relaxation of the cricopharyngeus muscle. Noisy deglutition, dysphagia, halitosis, and a palpable compressible mass in the neck may be present. Laryngotracheal aspiration when the patient is supine results from the emptying of contents from the diverticulum.

Diagnostic Strategies

Anteroposterior (AP) and lateral radiographs of the neck, chest, and/or abdomen can be obtained based on symptoms. Flat objects in the esophagus such as coins or button batteries orient in the coronal plane and appear as a circular object on an AP projection. Button batteries can be differentiated from coins by a characteristic radiographic "double-density" appearance. Small bones or radiopaque objects may occasionally be visualized. Air in the tissues may be present if perforation has occurred. However, failure to demonstrate a foreign body on radiographs does not rule out its presence. Contrast studies with barium or Gastrografin are rarely performed in this setting because they present a significant risk for aspiration and can obscure visualization if subsequent endoscopy is necessary.[3] Computed tomography (CT) can be used in equivocal cases to identify and localize foreign bodies before endoscopy. CT is more sensitive than radiography at identifying foreign bodies including chicken or fish bones and other nonorganic objects. CT scans have the additional value of visualizing changes in the surrounding tissues associated with perforation.[6]

Hand-held metal detectors have been reported to be useful screening devices for locating metallic foreign bodies in children without exposing them to radiation. They may also be of use in finding radiolucent metallic foreign bodies such as aluminum pull tabs. They do not, however, pinpoint the location of the object.[7] Caution should be used in interpreting negative metal detector tests in obese children because esophageal coins have been missed in this scenario.[8]

Persistent or concerning symptoms in a patient without evidence of a radiographic foreign body can be further evaluated by endoscopy.

Differential Considerations

Esophageal foreign bodies should be distinguished from foreign bodies in the airway. This distinction can be especially difficult in small children. Radiographically, esophageal foreign bodies usually lie in the frontal plain and are best visualized in AP views. Tracheal foreign bodies tend to lie sagittally.

Patients with esophageal obstruction may have retrosternal pain that can appear similar to that of an acute ischemic cardiac syndrome. The presence of odynophagia suggests an underlying mucosal lesion.

Management

Both flexible and rigid endoscopy are effective in removing esophageal foreign bodies. Flexible endoscopy is recommended in most cases as the first line in managing esophageal foreign bodies because it is better tolerated by patients and can usually be completed with use of procedural sedation.[9] In contrast, rigid endoscopy requires general anesthesia, has a higher complication rate, and more commonly results in postinterventional dysphagia.

Upper Esophagus

Oropharyngeal foreign bodies can usually be removed with a Kelly clamp or Magill forceps under direct visualization. Smooth upper esophageal foreign bodies can often be removed with a Foley catheter. This procedure requires an experienced clinician, a cooperative patient, and fluoroscopic guidance. The patient is placed in a prone position, and the catheter is passed into the esophagus past the point of the foreign body impaction. The balloon is then inflated and the catheter withdrawn, pulling the foreign body with it. In a large study of children undergoing Foley balloon extraction with fluoroscopic guidance, 80% of foreign bodies were successfully removed, and an additional 8% were advanced into the stomach. Failure rates were highest with infants younger than 1 year of age. Controversy exists regarding the safety of this technique because there is no direct control of the foreign body. However, several large studies have shown complication rates to be less than 1% when patients are carefully chosen.[10-12] This technique should not be used for a foreign body that has been impacted for more than 1 week, for objects that are not smooth, for patients with radiographic evidence of esophageal perforation, or for patients with any underlying structural esophageal abnormalities. This technique has a significant economic advantage when compared with the costs of general anesthesia in an operating room for performance of rigid endoscopy.[10] Another technique is bougienage, which has been shown to be both safe and effective in coin removal.[11] In this technique, an esophageal dilator is passed through the mouth into the esophagus to advance the coin into the stomach; the dilator is then quickly removed. In a large study, this procedure took less than 5 seconds to perform and was successful in 95% of cases with no serious complications.[12] When these maneuvers fail to dislodge the esophageal foreign body, consultation with a qualified endoscopist is indicated.

Lower Esophagus

Lower esophageal obstruction is usually the result of an impacted food bolus. Anecdotally, administration of 1 mg of glucagon intravenously (IV) (up to a total of 2 mg) can cause enough relaxation of the esophageal smooth muscle to allow passage of a food bolus in the lower esophagus. However, no randomized controlled trials have shown a statistically significant benefit of using glucagon compared with placebo. In a small double-blind placebo-controlled study in children with esophageal coin impaction, glucagon was shown to be ineffective.[13] In addition to lack of demonstrated efficacy, glucagon has multiple side effects such as vomiting, which can increase the risk of aspiration or esophageal perforation.[14]

Effervescent agents are sometimes effective in accelerating the passage of an obstructing food bolus. Although the mechanism of action is unclear, it is hypothesized that the carbon dioxide released from bubbles escaping the fluid acts to disrupt the impacted food bolus and to distend the distal esophagus. There are case reports and case series in which administration of carbonated beverages

www.ketabpezeshki.com 66485457-66963820

(including soft drinks) has resulted in the passage of the obstructing food bolus in 60 to 80% of patients treated. However, there is only low-level evidence to support this practice, and the studies showing this benefit had multiple confounding factors.[15] It has been recommended that effervescent agents be avoided in cases of complete obstruction and in cases in which an obstruction has been present for over 24 hours because of the theoretic potential of inducing perforation of a possibly ischemic distal esophagus. The use of meat tenderizer (papain) to soften a food bolus is not recommended. Although intact mucosa is resistant to papain's effects, an inflamed mucosa becomes much more inflamed when exposed to this proteolytic enzyme, and esophageal digestion or perforation may occur.[16]

Endoscopy should be performed immediately for patients experiencing significant distress and for children with impaction of an alkaline button battery. Button batteries lodged in the esophagus can cause severe tissue damage in just 2 hours. Damage is primarily related to localized corrosive effects and occurs by three main mechanisms: leakage of an alkaline electrolyte, pressure necrosis, and generation of an external current that causes electrolysis of tissue fluids and generates hydroxide at the battery's negative pole. Larger batteries carry a greater risk of impaction and leakage. Delayed complications include esophageal perforation, tracheoesophageal fistula, exsanguination after development of a fistula with a major blood vessel, and esophageal strictures. In a review of over 8000 battery ingestions that were reported to the National Battery Ingestion Hotline, outcomes have significantly worsened over the past decade. This is primarily attributable to newer 20 mm–diameter lithium cell batteries that now account for 92% of fatal ingestions.[17] Batteries that pass into the stomach should be followed radiographically and clinically to ensure passage. Assistance with the management of a patient with button battery ingestion can be obtained through the National Button Battery Ingestion Hotline at 1-202-625-3333 or at www.poison.org/prevent/battery.asp.[18]

Urgent intervention is also indicated for sharp objects, coins in the proximal esophagus, and impactions that impair the handling of secretions. It is unclear whether patients with mild to moderate symptoms of esophageal obstruction from a suspected food bolus require immediate endoscopy. In such cases, some experts believe that emergent intervention is unnecessary if the patient is still able to handle secretions because the bolus often passes on its own. Others believe that the softened bolus makes endoscopic removal more difficult and predisposes to complications such as ulcers, lacerations, erosions, and perforations. In a recent retrospective review, factors associated with a risk of complications included a longer duration of impaction, bone foreign bodies, and larger-size foreign bodies.[19] Although it may be acceptable to delay endoscopy in stable patients without high-grade obstruction to allow possible spontaneous passage, a foreign body or food bolus impaction should not be allowed to remain in the esophagus for longer than 24 hours. Any object remaining in the esophagus for more than 24 hours carries a higher risk of complications, including perforation, aortoenteric fistula, tracheoesophageal fistula, or abscess. These complications may occur up to years after the ingestion. Many experts advocate follow-up endoscopic evaluation after an esophageal obstruction to rule out underlying pathologic conditions.

Stomach

Conservative outpatient management is appropriate for the vast majority of foreign bodies that have entered the stomach. However, certain foreign bodies that pass into the stomach still require endoscopic retrieval. Objects longer than 5 cm or wider than 2.5 cm in diameter (e.g., toothbrushes, spoons) rarely pass the duodenum. All sharp and pointed foreign bodies (e.g., toothpicks, bones) should be removed before they pass into the stomach because up to 35% may cause intestinal perforation. Smaller objects that pass into the stomach can be followed with stool inspections and with serial radiographs if necessary to confirm passage. Surgical removal should be considered for objects that remain in the stomach for more than 3 to 4 weeks or that remain in the same intestinal location for more than 1 week.[3]

ESOPHAGEAL PERFORATION

Perspective

Esophageal perforation is a potentially life-threatening condition that is critical to identify and treat early to minimize morbidity and mortality. Boerhaave's syndrome was first described in the early 1700s as a result of a rapid increase in intraesophageal pressure related to forceful vomiting. It can also result from any Valsalva-like maneuver, including childbirth, coughing, or heavy lifting.[20,21] Iatrogenic esophageal perforation has become increasingly common in the past two decades, with endoscopy being the most common cause. Perforation has also been reported as a complication of both nasogastric tube placement and endotracheal intubation. Other causes of perforation include foreign body ingestion, caustic substance ingestion, severe esophagitis, carcinoma, and direct injury related to blunt or penetrating trauma.

Principles of Disease

Spontaneous rupture occurs because of a rapid increase in intraluminal esophageal pressure through a patent LES. The cricopharyngeal muscle fails to relax, leading to transmural rupture of the esophagus. More than 90% of spontaneous esophageal ruptures occur in the distal esophagus. In contrast, rupture resulting from blunt trauma to the neck or thorax usually occurs in the proximal and middle third of the esophagus. Most iatrogenic injuries occur at the pharyngoesophageal junction because the wall in this area is thin and there is no serosal layer to reinforce it, and force is frequently used to pass the tube beyond the level of the cricopharyngeus. Another site of frequent iatrogenic injury is the esophagogastric junction. In this area the esophagus curves anteriorly and to the left as it enters the abdomen, and an endoscope has a greater likelihood of perforating the posterior wall. This usually occurs during therapeutic dilation for strictures or achalasia. Other factors predisposing to iatrogenic perforation include anterior cervical osteophytes, Zenker's diverticulum, esophageal strictures, and malignancy.

Perforation has been reported as a complication of most endoscopic procedures, including transesophageal echocardiography, sclerotherapy, and inflation of the gastric balloon of a Sengstaken-Blakemore tube to control bleeding esophageal varices. When a perforation occurs, saliva and gastric contents can enter the mediastinum. Rapid spread of an infectious or inflammatory response to the surrounding tissues and organs occurs because of the thinness of the esophageal wall. Changes in intrathoracic pressure during respiration draw contaminants deeper into the mediastinum. The presence of gastric enzymes and other foreign material in the mediastinum induces an intense inflammatory response that may result in enough fluid buildup to displace adjacent structures.

Clinical Features

Clinical presentations vary and can depend on the cause, location, size, degree of contamination, and site of injury. Patients with an upper esophageal perforation usually have neck or chest pain, dysphagia, respiratory distress, and fever. Odynophagia, nausea, vomiting, hoarseness, or aphonia may also result. Mackler's triad

www.ketabpezeshki.com 66485457-66963820

of subcutaneous emphysema, chest pain, and vomiting is considered pathognomonic for spontaneous esophageal rupture. However, the complete triad is seen in less than half of cases.[22] Patients with perforation of the lower esophagus may have abdominal pain, pneumothorax, hydropneumothorax, and pneumomediastinum. The pain often radiates into the back, to the left side of the chest, and to the left or both shoulders. Early physical examination findings include epigastric or generalized abdominal tenderness, often with involuntary guarding and rigidity. Up to 30% of patients develop mediastinal or cervical emphysema, which may be noted by crepitus on palpation or by the pathognomonic Hamman's sign with a "crunching" sound heard during auscultation. Patients with severe mediastinitis may be in fulminant shock.

Pain, fever, dyspnea, or crepitus after esophageal instrumentation should be considered an indication of perforation until proven otherwise. Symptoms related to iatrogenic perforation may not appear until several hours after the procedure.

Diagnostic Strategies

Radiographic studies are used to establish the diagnosis of an esophageal perforation. A chest and an upright abdominal radiograph are usually obtained first. Soft tissue lateral neck radiographs should be considered if a proximal perforation is suspected and may reveal air in the prevertebral fascial planes. Radiographic abnormalities may be detected in up to 90% of patients with esophageal perforation. Patients with upper esophageal injuries commonly have chest radiographs that show pneumomediastinum alone or a right-sided pleural effusion, whereas patients with distal esophageal perforations typically have a left-sided effusion. Other radiographic abnormalities include subcutaneous emphysema, mediastinal widening, or pulmonary infiltrates. These classic radiographic changes are often not present in the first few hours after perforation, so a normal radiograph should not be used early to exclude the possibility of esophageal perforation.[23]

Patients with possible perforation should undergo contrast radiographic studies. Controversy exists regarding the contrast agent of choice. Barium sulfate is superior in identifying small perforations; however, it may incite an inflammatory response in tissues. For this reason, some experts advocate the use of water-soluble agents (e.g., Gastrografin). However, the water-soluble agents are less dense and may not demonstrate the abnormality. In addition, pneumonitis may result if these agents are aspirated because of their hypertonicity. A prudent approach would be to attempt the study with a water-soluble agent first in patients who are not at risk for aspiration. If a clinically suggested perforation is not identified, the examination should be repeated with barium.

CT of the chest may be considered if a contrast study does not demonstrate a clinically suggested perforation. It can also be used in patients who are intubated or cannot complete an esophagram. Findings such as mediastinal air, extraluminal contrast material, or fluid collections or abscesses adjacent to the esophagus confirm a perforation. CT also allows evaluation of other adjacent areas that may suggest an alternative diagnosis.[6] Flexible esophageal endoscopy may be useful to directly visualize the perforation, especially in cases of penetrating external trauma, where this has a sensitivity of 100% and a specificity of 83%.[24] This technique is not recommended for other situations because insufflation could potentially enlarge a minimal transmural opening.[23] Laboratory studies are not usually helpful soon after a perforation, although leukocytosis may be noted.

Differential Considerations

Misdiagnosis occurs in more than half of patients with esophageal perforation or rupture because of the broad differential diagnosis of chest and abdominal pain. This includes pulmonary embolism, acute myocardial infarction, aortic dissection, perforated ulcer, pneumothorax, lung abscess, pericarditis, or pancreatitis. Esophageal perforations should be diagnosed as soon as possible because the morbidity and mortality associated with unrecognized perforations dramatically increase with time.

Management

Clinically unstable patients with esophageal perforation require rapid resuscitation and treatment. Broad-spectrum intravenous antibiotics should be initiated early. Patients should receive nothing by mouth (NPO), and a nasogastric tube should be considered to eliminate oral and gastric secretions. Early surgical consultation is warranted. A recent study compared survival of patients with esophageal perforation who were treated within 24 hours of perforation and those treated after 24 hours. This study found that aggressive treatment within the first 24 hours resulted in a 97% survival versus 89% survival in those treated after 24 hours.[25]

There is growing evidence that some iatrogenic perforations in certain patients at low risk can be managed conservatively. These include clinically stable patients with minimal symptoms or fever, those whose perforation is contained, and those who are seen long after their procedure and have demonstrated no ill effects. In a recent retrospective study, patients who had a contained leak without respiratory compromise had worse outcomes when managed operatively compared with nonoperative management. Patients should be kept NPO and treated with broad-spectrum antibiotics and parenteral nutrition. These patients require diligent observation and assessment for failure of nonoperative therapy. In addition to true "nonoperative" management with close observation and intravenous antibiotics, other "palliative interventions," including endoscopy, stent placement, drainage gastrostomy, feeding jejunostomy, and tube thoracostomy, have become more common.[26]

ESOPHAGITIS

Perspective

Esophagitis is defined as inflammation of the esophagus. The most common cause of esophagitis is gastroesophageal reflux disease (GERD). Other important causes include infectious esophagitis, pill esophagitis, and injuries from the effects of caustic ingestion, radiation, or sclerotherapy. In addition, eosinophilic esophagitis is being diagnosed with increasing frequency.

Principles of Disease

Infectious Esophagitis

Esophageal infections primarily occur in immunocompromised hosts. When they occur in healthy patients, there is usually an underlying esophageal abnormality or local area of immune compromise, as might occur with the use of inhaled steroids. Iatrogenic alterations in host defenses through the use of immunosuppressive agents, potent chemotherapeutic agents, and broad-spectrum antibiotics can predispose an individual to the development of an esophageal infection. Human immunodeficiency virus (HIV) is a significant risk factor for infectious esophagitis, but rates have decreased since the advent of highly active antiretroviral therapy (HAART). Esophageal candidiasis is one of the most common acquired immunodeficiency syndrome (AIDS)–defining illnesses, but the incidence decreased by over 90% from 1994 to 2004.[27] Patients with acute HIV seroconversion syndrome that occurs 2 to 3 weeks after primary

www.ketabpezeshki.com 66485457-66963820

exposure to HIV can develop esophageal ulcerations and severe odynophagia.[28]

In addition to iatrogenic immunosuppression, diseases that weaken immunologic defenses in otherwise normal hosts can predispose the esophagus to infections. These conditions include diabetes mellitus, alcoholism, underlying malignancy, use of corticosteroids, and advanced age. Changes that occur in the mucosal barrier of the esophagus as a result of these conditions lead to an increased susceptibility to infection. The *Candida* species (primarily *Candida albicans*) are the most common esophageal pathogens.

As empirical antifungal prophylaxis in immunosuppressive states has become more common, viral esophagitis has become more prominent. Herpes simplex virus 1 (HSV) and cytomegalovirus (CMV) are the most common viral pathogens. Human papillomavirus has been implicated as well. Bacteria, mycobacteria, other fungi, and parasitic organisms such as *Trypanosoma cruzi*, *Cryptosporidium,* and *Pneumocystis* are uncommon causes of infectious esophagitis and are usually diagnosed by culture or biopsy.

Pill Esophagitis

More than 1000 cases of pill-induced esophageal injury have been reported in the literature from nearly 100 different types of pills. The exact incidence of pill esophagitis is unknown because most cases are unrecognized and therefore unreported. The condition results when a pill or capsule fails to pass into the stomach and remains in contact with the esophageal mucosa for a prolonged period. This results in inflammation and injury of the esophageal mucosa. Pill esophagitis has been reported in all age groups. Predisposing factors include advanced age, decreased esophageal motility, and extrinsic compression. Large pills are more likely to be retained, as are those coated with gelatin. Pills can stick to a normal esophagus, especially when taken without water or by a patient in the supine position. Any area of the esophagus can be affected, although sites of natural compression may be more susceptible. Sustained-release compounds may be more damaging than standard preparations. Injury can range from minor irritation to frank ulceration, hemorrhage, and ultimately stricture formation. Some of the more common offending medications include antibiotics (especially the tetracycline family) and antivirals, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), potassium chloride, quinidine, ferrous sulfate, alendronate, and pamidronate.[29]

Eosinophilic Esophagitis

Eosinophilic esophagitis was first described in 1978 and is defined by the presence of eosinophils within the esophageal mucosa or deeper tissues. Initially thought to be a disease of children, it is being diagnosed in adults with increasing frequency. Although diagnostic guidelines vary, recent reports have suggested use of the following criteria: clinical symptoms of esophageal dysfunction, more than 15 eosinophils in one high-power field on esophageal biopsy, and lack of responsiveness to high-dose proton pump inhibitors (PPIs) or normal pH monitoring of the distal esophagus.[30] The cause is unknown, although there is an association with food allergens, especially in the younger age group.[31] More than 50% of patients have associated atopic disorders, such as asthma or eczema.[32]

Caustic and Radiation-Induced Esophagitis

Esophagitis from caustic substance ingestion occurs most commonly in children, although adults may intentionally ingest a large amount of a caustic substance in a suicide attempt. The most corrosive agents are strongly acidic with a pH less than 2 or alkaline with a pH greater than 12. The degree of injury depends on the concentration of the substance, the volume ingested, and the duration of mucosal contact. Strong acids produce coagulation necrosis, which results in eschar formation that usually limits the damage. In contrast, alkalis produce liquefaction necrosis, which continues to cause injury as long as the substance or its active breakdown products are in contact with tissue.[29]

Patients undergoing radiation treatment for underlying malignancy may develop esophagitis. The degree of injury is related to the total dose of radiation received. The mucosa becomes inflamed and friable. Agents used during sclerotherapy can also cause esophagitis.

Clinical Features

Esophagitis, regardless of cause, most commonly manifests with dysphagia or odynophagia. Chest pain is frequently present, and esophageal bleeding ranging from localized oozing as a result of inflammation to frank hemorrhage can occur. Ulceration and perforation can result in mediastinitis.

Infectious Esophagitis

Most commonly, infectious esophagitis causes severe odynophagia. Dysphagia of both solids and liquids may be present. Pain may be so severe that the patient refuses to eat or drink. Chest pain may also be present and may be described as acute in onset, constant, and not improved by antacid therapy. Heartburn and nausea may be presenting symptoms. Some immunocompromised patients may have fever or bleeding without dysphagia or odynophagia.

Pill Esophagitis

Patients with pill esophagitis have odynophagia. Most patients have no prior history of esophageal disease and experience sudden onset of pain worsened by swallowing. Dysphagia may be present. Although some patients complain that a pill has become "stuck," the history of pill ingestion can be difficult to obtain because symptoms may begin hours after the offending pill was taken. Atypical presentations include a burning type of pain suggesting GERD as the cause.

Eosinophilic Esophagitis

Patients usually have dysphagia, nausea and vomiting, food impaction, or heartburn. This diagnosis should be considered in patients who have severe GERD symptoms despite the use of acid suppression medications and in patients with chronic unexplained dysphagia or recurrent esophageal food impaction. The diagnosis is confirmed by biopsy during endoscopy.[33]

Caustic and Radiation-Induced Esophagitis

Patients with caustic injuries may have pain in the mouth, chest, or epigastrium. Dysphagia and vomiting can also occur. Drooling and airway compromise may be present because of direct tissue injury or resulting edema. Later, perforation may occur, and strictures are a common long-term complication. Radiation-induced esophagitis usually causes odynophagia and dysphagia. Strictures may ultimately develop.

Diagnostic Strategies

Endoscopy is the best method of diagnosing pill-induced, eosinophilic, and infectious esophagitis. With infectious esophagitis,

www.ketabpezeshki.com 66485457-66963820

direct visualization may reveal characteristic signs of infection, such as white plaques of *Candida* or herpetic vesicles. Definitive diagnosis can be made through brushings and biopsies. Radiographic studies are usually not helpful because the findings are nonspecific. A strong clinical suspicion is necessary to diagnose pill esophagitis. The other causes of esophagitis are usually clinically apparent.

Differential Considerations

Other causes of esophageal pain include GERD, esophageal motility disorder, foreign body, and perforation. Chest pain may also be a component, and therefore an acute coronary syndrome should be considered. Esophageal pain is more likely to be positional and related to swallowing.

Management

Infectious Esophagitis

For infectious esophagitis, therapy should be directed at the causative organism. Patients with normal immune systems and mild cases of oropharyngeal candidiasis can be treated with clotrimazole troches (10 mg dissolved in the mouth five times a day for 1 week) or nystatin (400,000-600,000 million units orally [PO] four to five times per day for 2 weeks). Patients with true esophageal candidiasis should be treated with fluconazole (400 mg as a loading dose and then 100-400 mg daily for 14 to 21 days). In patients unable to tolerate taking oral medication, fluconazole can be given IV.[34]

Herpes esophagitis is generally a self-limited process that resolves over about 7 days. Immunocompromised patients should be treated with antivirals, such as acyclovir (400 mg PO five times per day for 7-14 days or 5-10 mg/kg IV every 8 hours for 7-14 days), famciclovir (500 mg PO three times a day for 7-14 days), or valacyclovir (1 g three times a day for 7-14 days).[35] For CMV, initial treatment can begin with ganciclovir (5 mg/kg IV every 12 hours for 2-3 weeks) or foscarnet (60 mg/kg IV every 8 hours or 90 mg/kg IV every 12 hours for 2-3 weeks).

If the causative organism cannot be adequately identified or if the patient is severely debilitated, admission to the hospital may be required. Patients discharged from the ED should receive appropriate follow-up with the relevant specialist (e.g., gastroenterology, infectious disease). In addition to therapy directed at the infecting organism, treatment with antacids, topical anesthetics, or sucralfate may provide symptomatic relief.

Pill Esophagitis

If a patient with suspected pill esophagitis has persistent symptoms, endoscopy may be necessary. It also helps to determine alternative causes. No data exist supporting any specific treatment, although, intuitively, antacid medication may prevent further erosion of damaged mucosa. Symptoms may take up to 6 weeks to resolve.

The best treatment for pill esophagitis is prevention. Patients should be instructed to drink at least 4 ounces of liquid with any pill. All medications should be taken when the patient is in an upright position, and the patient should remain upright for several minutes after medication ingestion. Patients with underlying esophageal abnormalities or those who are bedridden should avoid the use of pills whenever practical.

Eosinophilic Esophagitis

These patients usually are seen after standard antireflux measures have failed or after they have developed a food impaction. The treating physician should consider the possibility of food impaction, ensure that appropriate antacid therapy is used, and refer the patient to a gastroenterologist for further treatment. Untreated eosinophilic esophagitis can lead to esophageal remodeling and stricture formation in up to 40% of adult patients. Although consensus has not yet been reached regarding an optimal treatment regimen, success has been reported with the use of topical (e.g., swallowed) corticosteroids. Recent pediatric studies have also shown efficacy with oral viscous budesonide.[36]

Caustic and Radiation-Induced Esophagitis

Management of caustic injuries includes evaluation and treatment of possible airway injury, followed by assessment of the extent of esophageal involvement. Although the use of mild diluents like water or milk to limit the extent of chemical injury has been advocated by some authorities, others warn against the possibility of inducing emesis, which reexposes the esophagus to the caustic substance. In general, it is probably best to avoid having patients ingest anything by mouth while undergoing evaluation. Likewise, gastric lavage and the administration of charcoal are not indicated. Symptomatic patients should be admitted to a monitored setting for observation, further evaluation with endoscopy, and treatment of potential complications, such as perforation. There is a high morbidity associated with caustic ingestions, with stricture formation in 26 to 55% of patients and possible later malignant transformation.[37] As a result, multiple other treatments have been tried in an effort to improve long-term outcomes. This includes the use of intravenous corticosteroids and antibiotics, although the data on these have been mixed and they are not currently recommended.[38] Asymptomatic patients who give a reliable history of a low-volume, accidental ingestion of a low concentration of an acidic or alkaline substance can be discharged after a period of observation and followed as outpatients.

Treatment of radiation esophagitis is supportive. Patients who cannot eat or drink because of radiation injury to the esophagus should be admitted for intravenous fluid therapy.

GASTROESOPHAGEAL REFLUX DISEASE

Perspective

Asymptomatic reflux of gastric contents from the stomach into the esophagus occurs in most people several times a day as a normal physiologic phenomenon. GERD occurs when reflux becomes symptomatic or causes histopathologic alterations in the upper gastrointestinal (GI) or respiratory tracts. In the United States, symptomatic reflux in the form of heartburn occurs daily in 7% of adults, weekly in 14%, and monthly in 40%.

Principles of Disease

The primary mechanism that enables reflux of gastric contents into the esophagus is inappropriate relaxation of the LES. This can occur because of general hypotension of the LES, increased intra-abdominal pressure, or transient LES relaxations. Multiple risk factors can decrease LES pressure and lead to reflux, including medications (nitrates, calcium channel blockers, anticholinergics, albuterol), fatty meals, and chocolate. Other mechanisms that may contribute to GERD include esophageal motility abnormalities, increased intragastric pressure (e.g., obesity, pregnancy), acid hypersecretion, gastric outlet obstruction, and conditions that cause delayed gastric emptying (e.g., gastroparesis, neuromuscular disease).[39]

www.ketabpezeshki.com 66485457-66963820

Box 89-1 Agents and Conditions Related to Gastroesophageal Reflux

Decreased Lower Esophageal Sphincter Pressure
Anticholinergic drugs
Benzodiazepines
Caffeine
Calcium channel blockers
Chocolate
Estrogen
Ethanol
Fatty foods
Nicotine
Nitrates
Peppermint
Pregnancy
Progesterone

Decreased Esophageal Motility
Achalasia
Diabetes mellitus
Scleroderma

Increased Gastric Emptying Time
Anticholinergic drugs
Diabetic gastroparesis
Gastric outlet obstruction

Clinical Features

Symptoms

The most common clinical manifestation of GERD is heartburn, defined as a burning sensation that begins in the subxiphoid area and radiates toward the neck. Reflux may also cause a dull discomfort, localized pressure, or severe squeezing pain across the middle of the chest. The patient may appear comfortable or may have associated diaphoresis, pallor, nausea, and vomiting, leading to the consideration of an ischemic cardiac syndrome. A detailed history is often helpful in differentiating cardiac chest pain from reflux, although the distinction may not be possible in the ED.

Other symptoms of GERD include regurgitation (the spontaneous appearance of acid or bitter material in the mouth or pharynx) and water brash (a vagally mediated hypersalivation response that may produce as much as 10 mL of saliva in 1 minute). Dysphagia and odynophagia may also be presenting complaints and may be associated with more serious complications.

Any condition or agent that decreases LES pressure, decreases esophageal motility, or prolongs gastric emptying predisposes patients to reflux (Box 89-1). Positions that place the esophagus in a position that is dependent to the stomach or increase intra-abdominal pressure tend to precipitate reflux. Stooping, bending, leaning forward, performing Valsalva-type maneuvers, and assuming a supine position are common precipitants.

GERD can manifest itself in extraesophageal locations. Reflux-induced asthma may result from either microaspiration of gastric contents into the lung or activation of a vagal reflex arc from the gut to the lung. GERD has been identified in up to 80% of asthmatic patients based on pH probe monitoring, but up to half of these patient have no reflux symptoms. However, studies have shown no benefit in treating poorly controlled asthmatic patients with proton pump inhibitors (PPIs) in the absence of GERD symptoms.[40]

If the refluxate reaches the proximal esophagus, otolaryngologic manifestations may result, even in the absence of esophageal symptoms. Reflux can cause hoarseness, chronic laryngitis, refractory sore throat, and globus sensation.[41] Refluxate that enters the oropharynx may lead to gingivitis, halitosis, or dental problems such as erosion of the lingual sides of the teeth as a result of acid exposure. Otalgia and hiccups can also result from reflux.

Complications

Repetitive exposure to acid can lead to changes in the esophageal mucosa. Continued reflux can lead to thinning of the normal stratified squamous epithelial layer. With the development of esophagitis, an inflammatory response occurs within the mucosa and submucosa with infiltration of polymorphonuclear leukocytes. The inflammatory response is the result of chemical irritation of the esophageal mucosa from reflux of gastric acid, pepsin, and bile acids. Both acid and alkaline refluxes produce the same pathologic changes. Continued exposure can lead to further endoscopically visible changes of erosion, ulceration, and scarring. Ultimately, stricture formation may result. The most severe histologic consequence of GERD is replacement of the normal stratified squamous epithelium with metaplastic columnar epithelium in a condition known as *Barrett's metaplasia*. In patients with reflux undergoing endoscopy, approximately 10 to 15% are found to have Barrett's esophagus. There is a strong correlation between the development of Barrett's metaplasia and adenocarcinoma of the esophagus.[42]

Diagnostic Strategies

GERD is a common problem, and additional diagnostic testing in the ED is rarely necessary, assuming other, more serious causes of the patient's symptoms have been excluded. Patients with dysphagia, odynophagia, or bleeding should be referred for further study. Endoscopy can be used to evaluate pathologic changes, but clinicians should realize that there is not a direct correlation between symptoms and endoscopic features.[39]

Differential Considerations

Acute cardiac ischemia should be considered as a possible cause of chest pain in adults. Radiation of pain can be a feature in both esophageal and cardiac chest pain. The pain seen with reflux may radiate into the neck, jaw, shoulders, back, arms, and abdomen. Radiation into the back is more often ascribed to the esophagus. Radiation of pain into one arm or into the neck or jaw is not helpful in distinguishing ischemic cardiac pain from esophageal pain. Radiation of pain into the abdomen is present approximately three times more often in reflux than in ischemic heart disease. Radiation into both arms is rarely seen in reflux, whereas it may be present in approximately one quarter of patients with ischemic heart disease. Precipitation of pain by exercise and relief by rest may occur in pain from reflux as well as in ischemic cardiac disease. Emotional precipitation of pain occurs in reflux, although it is also seen with coronary artery disease. The occurrence of reflux after meals is another important feature in the history. A feeling of fullness after meals occurs commonly in reflux and is helpful in differentiating it from coronary artery disease.

Relief of chest pain from reflux by antacids is a key point in the history; however, one should not place too much weight on this point as evidence against a cardiac cause. The relief is often short-lived, and pain may recur in a short time. Esophageal pain may be provoked by swallowing. The physical examination in patients with esophageal reflux is not usually helpful in diagnosis. Thus the history is by far the most valuable aid. It is important to maintain an acute awareness of the diverse presentations of ischemic heart disease and to be cautious in attributing chest pain to esophageal causes solely on the basis of historical elements. Other GI disorders such as gastritis, esophagitis, peptic ulcer disease (PUD), and biliary tract disease should be considered in the differential diagnosis.

www.ketabpezeshki.com 66485457-66963820

Management

Earlier treatment guidelines for GERD recommended lifestyle modification solely as an initial approach; however, this has been shown to have little therapeutic benefit without concomitant medical management. Lifestyle modifications to reduce GERD symptoms include avoidance of foods that can precipitate reflux (caffeine, alcohol, chocolate, fatty foods) and avoidance of acidic foods that can cause heartburn (citrus, spicy foods). In addition to these dietary changes, other behavioral modifications include weight loss, smoking cessation, elevation of the head of the bed, and avoidance of a recumbent position for several hours after eating. The only lifestyle recommendations that have evidence-based support are weight loss and head-of-bed elevation; however, others can be useful adjuncts in selected patients.[43] The pharmacologic therapy of GERD includes agents that neutralize acids, decrease acid production, act on the LES or affect motility, and protect the mucosa. The most effective treatment for GERD is reduction of acid production. Many patients initially self-medicate with antacids or over-the-counter-strength type 2 histamine receptor (H_2)–receptor antagonists or PPIs, both of which have been demonstrated to relieve and prevent symptoms. A recent Cochrane review revealed that PPIs are more effective than H_2 blockers in eliminating symptoms and healing mucosal damage.[44] However, H_2 blockers are often effective in patients with mild-to-moderate GERD. These agents do not stop the reflux but rather reduce the potency of the refluxate. Choices of H_2 blockers and PPIs are listed in Tables 89-1 and 89-2. All of these agents are generally regarded as safe and effective. PPIs should be avoided in patients with acute coronary syndrome (ACS) who are taking clopidogrel, as multiple studies have demonstrated an increased risk of reinfarction and rehospitalization.[45,46]

Prokinetic agents treat GERD by increasing LES pressure. They may also be used for patients whose symptoms suggest a superimposed motility disturbance (e.g., regurgitation, choking, abdominal distention). In addition to improving propulsive activity of the stomach and small and large intestine, the increase in esophageal peristalsis and LES tone make an effective therapy for reflux by improving the clearance of refluxate. Cisapride (Propulsid) was formerly used for this purpose but was withdrawn from the marketplace by the manufacturer because of adverse cardiac effects. Metoclopramide, a dopamine antagonist, may be used for these patients, but its efficacy has not been conclusively demonstrated and it can cause significant irreversible extrapyramidal side effects such as tardive dyskinesia.[47] Baclofen has been used in conjunction with PPI therapy with some success in selected patients.[48] Candidates for this type of therapy are probably best chosen by a gastroenterologist.

Another agent that may be of benefit in refractory cases of symptomatic esophageal reflux is sucralfate, which is a mucosal protectant that binds to inflamed tissue to create a protective barrier. It blocks the diffusion of gastric acid and pepsin across esophageal mucosa and can limit the erosive action of pepsin and bile. It has limited side effects and can be safely used in pregnant women.[49]

Although the emergency physician can initiate antireflux therapy, the patient with clinically suggested GERD who does not improve with empiric therapy or those who are at high risk for complications should be referred to a gastroenterologist for confirmation of the diagnosis and follow-up care. In these cases, further diagnostic evaluation may be necessary. Patients who are intolerant of acid suppressive medications may be candidates for surgical therapy with laparoscopic fundoplication. Less invasive endoscopic therapies include thermal ablation to narrow the esophagus at the LES, suturing to create a plication at the LES, and injection or implantation techniques to bulk up the LES.[50]

Table 89-1 Summary of Histamine Receptor Antagonists

	GERD	PUD*
Cimetidine	800 mg bid or 400 mg qid	800 mg qhs or 400 mg bid
Famotidine	20 or 40 mg bid	40 mg qhs or 20 mg bid
Nizatidine	150 mg bid	300 mg qhs or 150 mg bid
Ranitidine	150 mg bid	300 mg qhs or 150 mg bid

GERD, gastroesophageal reflux disease; *PUD,* peptic ulcer disease.
*Maintenance dose for PUD is half the qhs dose.

Table 89-2 Summary of Proton Pump Inhibitors*

	GERD	PUD OR NSAID-INDUCED ULCERS†
Esomeprazole	20 mg qd or 40 mg qd	40 mg PO qd
Lansoprazole	30 mg qd or 30 bid	30 mg PO qd
Omeprazole	20 mg qd or 20 bid	20 mg PO qd
Pantoprazole	40 mg qd or 40 bid	40 mg PO qd
Rabeprazole	20 mg qd or 20 bid	20 mg PO qd

Adapted from Wolfe MM, Sachs G: Acid suppression: Optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology 118:S9, 2000.
GERD, gastroesophageal reflux disease; *NSAID,* nonsteroidal anti-inflammatory drug; *PO,* orally; *PUD,* peptic ulcer disease.
*All doses should be administered before breakfast; second doses (when necessary) should be administered before the evening meal.
†Patients with duodenal ulcer should be treated for 4 weeks; patients with gastric ulcer should be treated for 8 weeks.

GASTRITIS

Perspective

Strictly speaking, gastritis is a histologic diagnosis denoting inflammation of the gastric mucosa. Hence the diagnosis of gastritis can be made only by endoscopy and biopsy. However, it is common practice for clinicians to use the term *gastritis* to refer to symptoms of dyspepsia. To confuse the picture further, gastroenterologists frequently use the term to refer to the endoscopic finding of an edematous, friable mucosa. However, without accompanying inflammation, this is more appropriately termed *gastropathy* rather than gastritis. Controversy exists regarding how best to classify the entities that cause gastritis or gastropathy. This section considers gastritis and gastropathy together as one entity because the distinction makes little difference in the ED setting. Regardless of the cause, up to half of the population has endoscopic evidence of gastritis or gastropathy by age 50.

Principles of Disease

The most common cause of gastritis is infection with *Helicobacter pylori.* Although most patients are asymptomatic at the time of initial exposure, acute infection with *H. pylori* can cause severe gastritis and upper GI symptoms. Suppurative gastritis (also known as *acute phlegmonous gastritis*) can result from a bacterial infection of the stomach wall, usually from gram-positive cocci or gram-negative rods. Patients usually have an underlying mucosal

www.ketabpezeshki.com 66485457-66963820

abnormality such as cancer, ulcer, or preexisting gastritis. Less common infectious causes of gastritis include mycobacterial, viral, parasitic, and fungal organisms.

Gastritis can also result from exposure to drugs. Aspirin or other NSAIDs are the most common offending agents. Inflammation occurs as a result of prostaglandin inhibition both locally and systemically and is probably a precursor to gastric ulcer formation. Other drugs implicated in causing gastritis are potassium preparations and iron supplements. Gastritis can result from both short- and long-term exposure to ethanol, although some authors feel that the long-term effects are more likely a result of *H. pylori* than the ethanol itself.

The presence of corrosive agents in the stomach can induce gastritis. Intrinsic substances such as bile or ingested substances such as acids, alkali, and corrosive agents can induce an inflammatory response and subsequent gastritis.

Any condition that causes hypovolemia or hypotension can lead to gastritis. Ulcer formation may ultimately result. This may be a major causative factor in the development of gastritis and upper GI bleeding in intensive care unit patients. Other causes of gastritis include radiation, autoimmune reactions, Crohn's disease, and sarcoidosis. These disorders can only be diagnosed by biopsy.

Clinical Features

No particular symptoms are characteristic of gastritis. Acute gastritis may cause abdominal pain, nausea, and vomiting, although most patients are asymptomatic unless ulcers or other complications develop. By definition, it is not possible to diagnose gastritis or gastropathy on the basis of clinical features alone. However, a good clinical history such as recent NSAID use or alcohol ingestion in the setting of the classic symptoms supports a presumptive clinical diagnosis of gastritis.

Acute infection with *H. pylori* may cause epigastric abdominal pain, nausea, and vomiting. Systemic signs such as fever are usually absent. Symptoms may last days to weeks. If the infection goes untreated, chronic gastritis may result. Patients with phlegmonous gastritis usually appear toxic. Patients with gastritis as a result of decreased mucosal blood flow may have symptoms of abdominal pain and upper GI bleeding in addition to those of their underlying disease. Complications of gastritis include perforation and gastric outlet obstruction.

Diagnostic Strategies

Because the presumptive diagnosis of gastritis is made empirically, no specific diagnostic tests are necessary. Ancillary tests should be ordered as clinically indicated to rule out other possible diagnoses or to assess for complications of gastritis, such as bleeding, obstruction, and perforation.

Differential Considerations

Before the diagnosis of gastritis is made, other diseases that cause nausea, vomiting, and upper abdominal pain, such as pancreatitis, biliary tract disease, and small bowel obstruction, should be excluded. The possibility of an acute coronary syndrome should also be considered, particularly in elderly patients.

Management

Therapy of presumptive gastritis should be directed toward treating the suggested underlying cause. Acid suppression may improve symptoms of dyspepsia in patients taking NSAIDs. Patients with persistent symptoms should be referred to a gastroenterologist for further diagnostic evaluation.

PEPTIC ULCER DISEASE

Perspective

Gastric and duodenal ulcers are usually grouped together as PUD because of the similarity in their pathogenesis and treatment. Approximately 500,000 people in the United States are diagnosed with PUD each year. The annual cost to the health care system is estimated to be over $10 billion.[51] PUD is now considered to have two main causes: *H. pylori* infection and NSAID use. Approximately 1% of PUD is caused by increased levels of circulating gastrin from gastrin-secreting tumors (Zollinger-Ellison syndrome). These patients have increased parietal cell mass and hypersecretion of acid leading to ulcer formation. A small minority of patients have no identifiable cause for their ulcers.

Principles of Disease

Histologically, the stomach is composed of different types of cells with varying secretory functions. Mucous cells secrete acidic mucus, parietal cells secrete hydrochloric acid and intrinsic factor, chief cells secrete pepsinogens, and enterochromaffin-like cells release substances such as histamine and gastrin. There are over 1 billion parietal cells, which can generate a hydrogen ion concentration gradient of greater than 1 million to 1 within the lumen of the stomach.

Many mechanisms exist to protect the gastric mucosa from the digestive effects of the hydrochloric acid, proteolytic enzymes, bile, and other deleterious substances to which it is exposed. Normally a gastric mucosal barrier to intraluminal gastric acid is present and prevents the back-diffusion of hydrogen ions from the gastric lumen. Sodium ions are barred from moving in the opposite direction. This ionic impermeability protects the gastric mucosa from damage in a hostile environment. Damage to the gastric mucosal barrier from any cause (Box 89-2) allows hydrogen ions and digestive enzymes to make contact with the gastric mucosa, leading to inflammation, bleeding, and potential ulceration.

The identification of *H. pylori* has dramatically shifted our notion of PUD from an acid-related to an infectious disease–mediated process. *H. pylori* is a spiral, flagellated, gram-negative rod whose natural habitat is the human stomach between the epithelial cell surface and the overlying mucus. Infection with *H. pylori* is a primary risk factor for development of PUD. It is estimated that 70 to 80% of patients with duodenal ulcer and 60 to 70% of patients with gastric ulcer are infected with *H. pylori.* It is more prevalent in lower socioeconomic groups and in developing countries. It is probably spread by the fecal-oral route, although oral-to-oral and iatrogenic transmissions have also been suggested. It is estimated that 30 to 40% of the U.S. population is infected with *H. pylori.* It is found in people of all age groups, although infection is typically acquired during childhood. Its presence is believed to cause mucosal inflammation that disrupts the normal defense mechanisms and leads to ulceration. It also

Box 89-2 Substances and Conditions That Damage the Gastric Mucosal Barrier

Bile
Cigarette smoking
Ethanol
Glucocorticoids
Helicobacter pylori
Nonsteroidal anti-inflammatory drugs
Pancreatic secretions
Shock conditions
Stress

www.ketabpezeshki.com 66485457-66963820

increases the risk of gastric carcinoma and, less often, lymphoma. Although there is a strong association between *H. pylori* and PUD, only 5 to 10% of infected patients develop ulcers.[52] It is unclear what role environmental and host factors (such as diet) play. It is now accepted that almost all non–NSAID-related ulcers are caused by *H. pylori*. Eradication of infection with *H. pylori* results in more rapid healing of ulcers, prevents relapse, and diminishes the rate of ulcer complications. It is also more cost-effective than chronic antisecretory therapy. Patients can be tested for *H. pylori* by both invasive and noninvasive methods. These include a urea breath test, serum antibody testing, stool antigen testing, and direct mucosal biopsy during endoscopy. None of these methods are currently practical to use in the ED. There are multiple treatment regimens that are more than 80% effective at eradication of *H. pylori*.[53]

The second most common cause of peptic ulcer formation is the use of NSAIDs. Up to 25% of chronic NSAID users develop ulcer disease, and 2 to 4% of patients have serious complications including perforation or bleeding. The cause of NSAID-related ulcers was traditionally linked to "ion trapping" and reduction of mucosal hydrophobicity. However, it is now believed that the primary mechanism is related to suppression of gastric prostaglandin synthesis. Prostaglandins promote mucosal integrity by maintaining mucosal blood flow, promoting mucosal mucus and bicarbonate formation, and reducing mucosal acid secretion.[54] It is believed that the inhibition of cyclooxygenase by NSAIDs leads to a diminished level of protective prostaglandins in the stomach. In addition, the antiplatelet aggregation effect of NSAIDs may increase the amount of bleeding associated with the development of NSAID-induced ulcers. NSAIDs differ in their ulcerogenic potential. Studies have shown a higher risk of upper GI bleeding with ketorolac and piroxicam.[55] The cyclooxygenase-2 specific inhibitors (celecoxib, rofecoxib, and valdecoxib) were initially felt to have a better GI safety profile than traditional NSAIDs. However, further studies refuted this belief and noted an increased risk of cardiovascular side effects, including myocardial infarction and stroke.[56] As a result, rofecoxib (Vioxx) and valdecoxib (Bextra) were withdrawn from the market. Celecoxib (Celebrex) is still available in the United States as a treatment for arthritis and familial polyposis but has a black box warning regarding both an increased incidence of GI side effects and an increased cardiovascular risk. Certain patients are at higher risk for NSAID-induced gastroduodenal toxicity. These include patients older than 60, those with a prior history of an ulcer or hemorrhage, those receiving higher doses of NSAIDS, and patients concurrently taking glucocorticoids or anticoagulants.[57] These patients should be considered for ulcer prophylaxis with a PPI or misoprostol.[58] Other drugs with ulcerogenic potential include 5-fluorouracil, mycophenolate mofetil, and the bisphosphonates.

PUD also occurs in infants and children. Infants with PUD usually demonstrate poor feeding, vomiting, or failure to thrive. Up to a quarter of children have isolated hematemesis or melena as presenting signs. Toddlers and preschool children may have abdominal pain, vomiting, and bleeding. Eighty percent of ulcers in this age group are stress ulcers associated with systemic illness such as sepsis, head trauma, burns, or sickle cell disease. Older children and adolescents usually have primary PUD, with presentations similar to those of adults.[59]

Clinical Features

Presenting Symptoms

The classic presenting symptom of PUD is epigastric pain that is described as "burning" or "gnawing." However, up to 2% of patients with endoscopically proven PUD are asymptomatic. Patients may also have atypical symptoms, including pain in other areas of the abdomen, chest, or back, and may describe the pain as vague or crampy. Associated symptoms include fullness, nausea, early satiety, and bloating. Pain usually occurs 2 to 5 hours after a meal or at night. Symptoms that awaken a patient from sleep between midnight and 3 AM is a classic indicator of ulcer disease, because in most people gastric acid output is highest at about 2 AM. Ulcer pain is usually not present on awakening in the morning because gastric acid output is at its lowest at this time. Colicky pain is rarely gastric or duodenal in origin. Well-defined periods of exacerbation and remission are usually present with duodenal ulcer and aid in the diagnosis. A constant pain lasting from weeks to months is uncommonly caused by ulcer disease. Relief of pain after eating is another feature of gastric or duodenal ulcer. The pain from a duodenal ulcer is usually worse immediately before a meal, and the complex of pain-eating-relief is typical of duodenal ulcer.

Although some patients with ulcers may vomit, alternative diagnoses such as gastric volvulus, gastric outlet obstruction, small-bowel obstruction, pancreatitis, or biliary tract disease should be considered in patients with epigastric pain and vomiting. Relief of abdominal pain with antacids is an important aspect of the history. Antacids usually afford relief of pain in both PUD and gastritis. Ninety percent of patients with PUD have pain relief with antacids, and 75% with gastritis have relief. Patients with duodenal ulcer usually experience pain relief within 5 minutes after taking an antacid.

Physical findings in patients with PUD are usually minimal. Mild epigastric tenderness may be elicited. A positive stool guaiac test may be evidence of a bleeding ulcer, but other causes of occult bleeding should also be considered.

Complications

The most serious complications of PUD include hemorrhage, perforation, penetration, and gastric outlet obstruction. Hemorrhage is the most common complication, occurring in 15 to 20% of patients. Ulceration into an artery can lead to life-threatening hemorrhage. Patients older than age 60 are at greater risk. Approximately 2 to 10% of patients experience perforation, which occurs when an ulcer erodes through the wall and leaks air and digestive contents into the peritoneal cavity. Perforation most commonly involves the anterior wall of the duodenum. Penetration is pathologically similar to perforation, except that the ulcer erodes into another organ such as the liver (usually from a gastric ulcer) or the pancreas (usually from a duodenal ulcer) instead of into the peritoneal cavity. Gastric outlet obstruction occurs in 2% of ulcer patients as a result of edema and scarring near the gastroduodenal junction. Symptoms may manifest as gastroesophageal reflux, early satiety, weight loss, abdominal pain, and vomiting.[51]

Pain patterns may be helpful in diagnosing some of the complications of PUD. Pain from a perforated duodenal ulcer is usually appreciated first in the epigastrium but becomes generalized within a short time. Vomiting is present in 50% of patients, and peritoneal findings usually result. Pneumoperitoneum commonly occurs after duodenal ulcer perforation, and the accumulated air under the diaphragm may cause referred pain to the shoulder. One or both shoulders may be involved, depending on the location of the free air.

A history of ulcer-like anterior abdominal pain that begins to radiate into the back suggests penetration of a duodenal ulcer. The pain is usually described as steady and is perceived at the level of the lower thoracic and upper lumbar vertebrae. The pain becomes refractory to treatment with antacids and food. Also, the pain may radiate to the chest, right upper quadrant, and left upper quadrant in up to 20% of patients. The sudden onset of pain, especially if unrelated to eating, suggests either ulcer perforation or gastric volvulus.

www.ketabpezeshki.com 66485457-66963820

Diagnostic Strategies

The initial diagnosis of PUD is usually made clinically. Upper endoscopy is the procedure of choice for confirming the diagnosis. Ancillary tests may be of benefit in evaluating possible complications of PUD in patients in distress. They may also be of benefit in providing indirect evidence of another disease. A complete blood count may diagnose anemia, and liver enzyme levels may help elucidate a hepatic or biliary tree cause. Electrolytes may provide indirect evidence of disease, and a lipase level should be considered to rule out pancreatitis and may provide indirect evidence of a posterior penetrating ulcer.

Abdominal and chest radiographs should be ordered if obstruction, perforation, or penetration is suggested or if a pulmonary cause is being considered, although negative radiographs do not definitively rule out these diagnoses. Electrocardiography should be performed in any patient thought to have a cardiac cause for the pain. A pregnancy test should be performed on any woman of childbearing age.

As noted earlier, several methods exist for diagnosing infection with *H. pylori,* although at this time none is of practical application in the ED.

Box 89-3 Suggested Treatment Regimens for *Helicobacter pylori*

Triple Therapy (10- to 14-day treatment regimen)
Clarithromycin 500 mg bid
Plus
Amoxicillin 1 g bid
Or
Metronidazole 500 mg bid (if penicillin allergic)
Plus
A PPI

Quadruple Therapy (10- to 14-day treatment regimen)
Bismuth subsalicylate (Pepto-Bismol) 525 mg PO qid
Plus
Metronidazole 250 mg PO qid
Plus
Tetracycline 500 mg PO qid
Plus
A PPI or ranitidine 150 mg PO bid

From Chey WD, Wong BCI: American College of Gastroenterology Guideline for Management of *Helicobacter pylori* Infection. Am J Gastroenterol 102:1808, 2007.
PO, orally; *PPI,* proton pump inhibitor.

Differential Considerations

Fifty percent of patients with symptoms of dyspepsia have no identifiable cause. These patients are classified as having functional or nonulcer dyspepsia (NUD). The most recent definition by the Rome III consensus is the presence of epigastric pain or burning, postprandial fullness, and early satiety in the absence of underlying organic disease.[60] NUD may be caused by peptic ulcers that are not yet large enough to appear endoscopically. Gastritis related to hypersecretion of gastric acid, *H. pylori* infection, bile reflux, or viral infection may cause NUD, although these cases should be identifiable endoscopically or pathologically. Maldigestion or malabsorption of carbohydrates can arise as NUD in patients with lactase deficiency or in patients who consume large quantities of nonabsorbable sugars, such as sorbitol, mannitol, and fructose. Intestinal parasites such as *Giardia intestinalis* or *Strongyloides stercoralis* may cause NUD, as can chronic pancreatitis. NUD may also be caused by gastric motility disorders, which have been reported in 25 to 60% of patients with NUD. Abnormalities in the biliary tract, such as increased resting pressure of the sphincter of Oddi, or incomplete relaxation of the sphincter on gallbladder contraction, may lead to bile duct distention and pain.

Many other disorders can produce epigastric pain that mimics the pain of an ulcer. It can be difficult to distinguish between gastritis and PUD. The discomfort associated with gastritis is often mild to moderate in severity and described as a hot, burning pain or bloating. In particular, burning pain is twice as common in gastritis as in PUD. Esophageal disorders such as GERD, esophagitis, or esophageal spasm can arise with abdominal symptoms. Mesenteric ischemia ("abdominal angina") should be considered, especially in elderly patients and those with underlying vascular disease or atrial fibrillation. Aortic dissection, other intra-abdominal processes such as biliary tract and pancreatic disease, and atypical presentation of an acute cardiac syndrome or other intrathoracic process should be considered in the differential diagnosis. Finally, abdominal pain may be the presenting symptom in psychiatric patients with somatoform disorders. These patients have an altered perception of visceral pain and have an increased sensation of pain when the stomach or small intestine is dilated.

MANAGEMENT

It is now well recognized that PUD is a result of either infection with *H. pylori* or NSAID use, so initial treatment should target the presumed underlying cause. For NSAID-related ulcers, treatment should begin with discontinuation of the offending agent and initiation of a PPI. A Cochrane review recently examined methods of preventing NSAID-associated gastroduodenal ulcers. There is evidence that misoprostol, PPIs, and double doses of H_2 blockers reduce the risk of both endoscopic gastric and duodenal NSAID-induced ulcers.[54] If NSAIDs are not being used by a patient with suggested PUD, it is currently recommended to treat for *H. pylori* infection. Dyspeptic symptoms without proven ulcer may also be an indication for treatment, but that decision may best be left to a gastroenterologist. Antacid therapy may be started with a PPI or H_2 blocker. Nonendoscopic testing for *H. pylori* is available in the form of antibody detection, urea breath test, and fecal antigen tests; however, their role in the evaluation of ED patients is not yet defined.

Some recommended regimens combine antibiotics with acid-suppressing agents for treatment of *H. pylori* infection (Box 89-3). Commercially available combination products may also be prescribed that may assist in compliance (Prevpac, which contains lansoprazole, amoxicillin, and clarithromycin; and Helidac, which contains bismuth subsalicylate, metronidazole, and tetracycline). Most gastroenterologists recommend continued therapy with antisecretory agents after the antibiotic-containing regimens.

GASTRIC VOLVULUS

Perspective

Gastric volvulus is a rare cause of severe abdominal pain that occurs when the stomach rotates on itself more than 180 degrees, creating a closed-loop obstruction. Only 400 cases have been reported in the literature, although its true incidence is unknown because some types of volvulus are intermittent and resolve spontaneously. It most commonly occurs in persons 40 to 50 years of age and is usually associated with the presence of a paraesophageal hernia. Approximately 20% of cases occur in infants younger than 1 year, often associated with a congenital diaphragmatic defect. If an acute volvulus is not identified and corrected early, it may lead to gastric ischemia, perforation, and death. The mortality rate from acute gastric volvulus has been reported to be 30 to 50%.[61]

www.ketabpezeshki.com 66485457-66963820

Principles of Disease

The stomach is fixed at only two points: the esophagocardiac junction and the pylorus. The remainder of the organ is relatively distensible and mobile and can occupy various positions within the abdomen. When a person is supine, the stomach lies entirely above the umbilicus, whereas it descends below the umbilicus in the erect position. Regardless of its position, the stomach maintains its familiar morphology because of ligamentous attachments to the surrounding organs. A primary (or subdiaphragmatic) volvulus occurs when the stabilizing ligaments are too lax or are congenitally abnormal in such a way that the stomach is able to twist on itself. Approximately one third of cases are of this type.

Secondary (or supradiaphragmatic) volvulus occurs in patients with diaphragmatic defects such as a paraesophageal hiatal hernia, an elevated diaphragm, gastric ulcer or carcinoma, diaphragmatic paralysis, extrinsic pressure on the stomach from other organs, or abdominal adhesions. The combination of one of these factors and ligamentous laxity makes a volvulus more likely.

Gastric volvulus can be classified on the basis of its axis of rotation. The most common form is organoaxial volvulus, which occurs when the stomach twists on its long axis. Less commonly, the stomach folds on its short axis from the lesser to greater curvature and is classified as a mesenteroaxial volvulus. Approximately one third of cases of gastric volvulus are of this type.

Clinical Features

Presenting Symptoms

The presenting features of a gastric volvulus vary depending on the type. Primary volvulus may arise with the sudden onset of severe abdominal pain. The upper abdomen may demonstrate marked distention. Patients with secondary volvulus may experience predominant symptoms in the chest, with pain radiating to the back and shoulders along with accompanying dyspnea. The abdominal examination may be unremarkable. Nonbilious vomiting is usually present and may be persistent and severe. The combination of severe epigastric pain and distention, vomiting followed by violent nonproductive retching, and inability to pass a nasogastric tube (Borchardt's triad) increases the likelihood of a gastric volvulus. Up to a quarter of children with acute gastric volvulus are presented with life-threatening events that necessitate resuscitation, including apnea, cyanosis, and acute respiratory distress.[62] A volvulus may be chronic if the rotation is minimal and there is no vascular compromise. Symptoms usually consist of mild intermittent upper abdominal pain. Early satiety, dyspnea, bloating, eructation, and upper abdominal fullness may be present. It is unknown how often a chronic volvulus can lead to an acute volvulus.

Complications

If not recognized, volvulus can lead to bowel ischemia and necrosis of the stomach. Untreated, this may lead to shock and death. Fortunately, the frequency of gastric infarction is low (reportedly 5 to 28% for organoaxial volvulus) because of the redundant blood supply of the stomach. Other complications include ulceration, perforation, hemorrhage, pancreatic necrosis, and omental avulsion.

Diagnostic Strategies

A plain abdominal radiograph often demonstrates a large, gas-filled loop of bowel in the abdomen or chest. A barium swallow may help visualize the abnormality, and CT can be used for confirmation in equivocal cases. There are no laboratory findings specific for volvulus, although elevations in amylase and alkaline phosphatase have been reported.[61]

Differential Considerations

The differential diagnosis of gastric volvulus includes any disease that can arise with sudden upper abdominal pain and vomiting. Perforated peptic ulcer, gastric outlet obstruction, biliary tract disease, and acute pancreatitis should be considered. Symptoms of a volvulus may suggest an acute cardiac syndrome.

Management

The goal of treatment of an acute gastric volvulus is reduction. Mortality rates increase with delayed diagnosis because of complications of ischemia. Acutely, one should attempt passage of a nasogastric tube, which may occasionally reduce the volvulus. Although somewhat controversial, patients without signs of gastric infarction may undergo an attempt at endoscopic reduction. Ultimately, treatment is a surgical emergency, with the goal of reducing the volvulus and preventing recurrence by fixing the stomach within the abdomen. Surgical repair of predisposing diaphragmatic defects is also recommended to prevent recurrence.[61]

DYSPHAGIA

Perspective

Precise motor control of the act of swallowing is necessary to ensure that food is successfully transferred from the mouth through the esophagus into the stomach. This includes the muscles of the oropharynx, the UES, the body of the esophagus, and the LES. Failure at any one of these levels results in a motility disorder, the primary symptom of which is dysphagia, which literally means "difficulty swallowing."

Principles of Disease

Normal Physiology

Swallowing is a complex phenomenon requiring both voluntary and involuntary skeletal muscle activity. Control of swallowing is coordinated by the swallowing center in the medulla. Afferent sensory input involves the trigeminal, glossopharyngeal, vagus, and spinal accessory cranial nerves; efferent motor activity travels through the trigeminal, facial, glossopharyngeal, vagus, and hypoglossal cranial nerves. The act of swallowing begins a process of both simultaneous and sequential activity in all three esophageal zones. A rapidly progressive pharyngeal contraction transfers the food bolus through a relaxed UES into the esophagus, where a moving ringlike contraction begins in the upper esophagus and propagates distally, making the transition from striated to smooth muscle, culminating with the propulsion of the bolus through a relaxed LES. Three mechanisms have been described that regulate the peristaltic wave, ensuring a smooth transition from the striated muscle in the upper esophagus to the smooth muscle of the middle and lower esophagus and coordination of UES and LES activity. These mechanisms are sequential firing of vagal afferents that begin in the brainstem, an intramural neural mechanism that responds to local stimuli, and myogenic propagation of the contraction through the myocytes themselves.

Physiologically, swallowing can be divided into oral, pharyngeal, and esophageal phases. The oral phase involves preparation of the food bolus by mastication and lubrication. The tongue then propels the bolus into the pharynx by progressive AP contractions. In the pharyngeal phase of swallowing, events are initiated by

www.ketabpezeshki.com 66485457-66963820

delivery of the food bolus to the oropharynx. Voluntary contraction of the pharyngeal muscles seals the nasopharynx by elevation of the soft palate. The oropharynx is sealed by the upward movement of the tongue against the palate. The larynx and hyoid bone are elevated to seal off the respiratory passage. The cricopharyngeus muscle, or UES, relaxes, and the bolus is swept into the esophagus by sequential peristaltic waves initiated in the upper pharynx. During the esophageal phase, the bolus is propelled toward the stomach by sequential peristaltic waves. Peristalsis can be initiated by swallowing or in response to luminal distention of the gut or changes in the pH or osmotic environment of the mucosa. The lower sphincter normally maintains a degree of tone sufficient to prevent reflux of gastric contents. When the food bolus reaches the lower sphincter, the sphincter relaxes to allow passage of the bolus and then regains its degree of resting tone.

Pathophysiology

Disturbances of the interactions between the components of the upper GI tract lead to a motility disorder. The motor disorders of the body of the esophagus are only now beginning to be understood. The major primary esophageal motility disorders are achalasia, diffuse esophageal spasm, hypercontractile esophagus ("nutcracker esophagus"), and nonspecific motor disorder. Of these, the only two that are well defined are achalasia and diffuse esophageal spasm. Controversy exists about whether the other entities are true disease states because symptoms are not always associated with manometric abnormalities and correction of the abnormalities does not always result in symptom improvement. Motor disorders may be the primary cause of other esophageal abnormalities such as GERD or esophageal diverticula.

Clinical Features

Dysphagia at any age is abnormal and requires evaluation. Dysphagia can be classified into one of two types. The first is oropharyngeal dysphagia (also known as *transfer dysphagia*), which involves difficulty transferring a food bolus from the oropharynx to the proximal esophagus. The second type, esophageal dysphagia, involves difficulty in transporting material down the esophagus. Although dysphagia has many causes, a thorough history reveals the diagnosis in most patients (Box 89-4). It is crucial to determine what types of food cause the symptoms (liquids, solids, or both) and whether the symptoms are intermittent or progressive. One should determine where the bolus sticks, whether it is associated with pain, and whether the patient has any previous gastroesophageal history (e.g., esophageal reflux). Any family history of neurologic disease should be obtained.

The examination should include a thorough evaluation of the head and neck and a detailed neurologic examination. The patient should be observed while swallowing. Difficulty in initiating the swallow, misdirection of the bolus with regurgitation or aspiration, and unusual posturing of the patient when swallowing should be noted. Many patients with neuromuscular disorders depend on gravity to swallow, and having the patient swallow in the prone position may be helpful in diagnosis.

Box 89-4 Causes of Dysphagia

Neuromuscular

Vascular
Cerebrovascular accident

Immunologic
Dermatomyositis
Multiple sclerosis
Myasthenia gravis
Polymyositis
Scleroderma

Infectious
Botulism
Diphtheria
Poliomyelitis
Rabies
Sydenham's chorea
Tetanus

Metabolic
Lead poisoning
Magnesium deficiency

Other
Alzheimer's disease
Amyotrophic lateral sclerosis
Brain tumor
Depression
Diabetic neuropathy
Familial dysautonomia
Metabolic myopathies (e.g., thyrotoxicosis)
Muscular dystrophies
Parkinson's disease

Obstructive
Aortic aneurysm
Esophageal motility disorder (e.g., achalasia, diffuse esophageal spasm, hypertensive LES, nutcracker esophagus)
Esophageal rings
Esophageal stricture
Esophageal webs
Esophagitis
Foreign bodies
Hypertrophic cervical spurs
Inflammatory lesions
Left atrial enlargement
Mediastinal mass
Neoplasm
Thyroid enlargement
Vascular anomalies (e.g., enlarged aorta, aberrant subclavian artery)
Zenker's diverticulum

Other
Alcoholism
Decreased saliva production (Sjögren's syndrome, postirradiation)
Diabetes
Functional
Gastroesophageal reflux disease
Postoperative

LES, lower esophageal sphincter.

Oropharyngeal Dysphagia

Oropharyngeal causes of dysphagia inhibit the initiation of swallowing. Patients complain that "food gets stuck" on swallowing, often pointing to the cervical region when describing their symptoms. Coughing, choking, or drooling may be associated. Neuromuscular diseases cause approximately 80% of oropharyngeal dysphagias, with most remaining causes being localized structural lesions. Most neuromuscular causes of dysphagia result in misdirection of the bolus, sticking, and the need for repeated swallowing attempts. Patients may drool and turn the head and neck to the side to facilitate swallowing. Liquids, especially of extreme temperatures, usually cause dysphagia more commonly than solids, and symptoms are more often intermittent. Progressive unremitting dysphagia is usually not caused by neuromuscular disorders of the oropharynx. Cerebrovascular accidents are probably the most common cause of neuromuscular dysphagia, especially those involving the vertebrobasilar system and posteroinferior cerebellar

www.ketabpezeshki.com 66485457-66963820

arteries and when some degree of dysarthria is present. The mechanism in such cases is pharyngeal weakness, with failure of the cricopharyngeus muscle to relax. Weakness of the tongue may occur, resulting in poor transfer of the bolus, or weakness of the buccal muscles may produce drooling and difficulty initiating the swallow.

The second most common cause of neuromuscular dysphagia is inflammatory myopathies such as polymyositis or dermatomyositis. These disorders are characterized by inflammatory and degenerative changes in striated muscle that can produce dysphagia from weakness of the palate, pharynx, and upper esophagus. Dysphagia is a presenting symptom in 21% of patients with these disorders.[63]

A cause of oropharyngeal dysphagia that deserves particular mention is myasthenia gravis. At least 40% of patients with myasthenia gravis have dysphagia, and it is the presenting symptom in up to 15% of patients. The dysphagia becomes progressively worse with repeated swallowing attempts and is temporarily reversible with edrophonium.[64]

Disorders in the pharyngeal phase of swallowing may lead to misdirection of the food bolus, pain, sticking, or multiple swallowing attempts. Tongue weakness can result in oral regurgitation. Inability to seal the nasopharynx because of obstruction or muscular weakness can cause nasal regurgitation. Inefficient laryngeal elevation from muscular weakness or a fixed larynx can result in laryngotracheal aspiration. Delayed aspiration can occur with pharyngeal weakness and with pooling of food in the piriform recesses or in a diverticulum. Inability to contract the pharyngeal muscles is often compounded by failure of the cricopharyngeus to relax. Failure of relaxation of the cricopharyngeus with or without pharyngeal weakness causes misdirection of the food bolus or necessitates repeated swallowing attempts. Inflammatory lesions of the tongue or oropharynx can result in odynophagia and even complete inability to swallow because of pain.

Congenital anomalies of the aortic arch may cause dysphagia in both children and adults. In children, respiratory symptoms are usually present and commonly predominate. In adults, an anomalous right subclavian artery is the most common vascular cause for dysphagia, often referred to as *dysphagia lusoria.* Patients often do not become symptomatic until the fourth decade of life. The most common symptoms in adults are dyspnea on exertion and dysphagia.[65] Vascular compression of the esophagus with dysphagia may also occur with aneurysms of the aortic arch and great vessels. Bronchogenic carcinoma can cause dysphagia by direct involvement of the esophagus or by compression with nodes.

Esophageal Dysphagia

Dysphagia from upper esophageal lesions is usually perceived 2 to 4 seconds after the initiation of swallowing. Dysphagia that the patient localizes to the substernal or retrosternal area may be anatomically accurate, but localization to the neck may be referred from anywhere in the esophagus.

Esophageal dysphagia can be caused by mechanical lesions or a motility disorder. Mechanical lesions include strictures, webs, rings, tumors, esophagitis, or postsurgical changes. Pressure from extrinsic lesions such as osteophytes, mediastinal masses, or aortic aneurysms can also cause dysphagia.

Patients with esophageal dysphagia who have no readily identifiable cause may have a motor disorder. The motor disorders include achalasia, diffuse esophageal spasm, nutcracker esophagus, and hypertensive LES. Achalasia is a disorder of unknown cause in which the resting pressure of the LES is markedly increased and peristalsis in the body of the esophagus is absent. The incidence increases with age, with the highest incidence in the seventh decade of life and a smaller peak incidence in patients aged 20 to 40 years.[66] Dysphagia is the most common presenting symptom and usually begins insidiously with equal frequency for solids and liquids. Patients may report that maneuvers that increase esophageal pressure (raising arms above the head, standing erect with back straight) help pass the food. Odynophagia from esophageal spasm may also be seen early in the course of achalasia. The symptoms are often worse with rapid eating and during periods of stress. The patient may also report chest pain as a symptom. As dilation occurs above the sphincter, retention of undigested food in the esophagus occurs, and the patient may be aware of gurgling while eating. Regurgitation of the undigested material can occur after a meal (prompting consideration of the diagnosis of an eating disorder) or with changes in position or vigorous exercise. The regurgitated food usually has no acid taste, although bacterial contamination may lead to fermentation of the undigested food. Laryngotracheal aspiration may occur, especially at night, and may cause nocturnal coughing. Physical examination is usually unremarkable except for weight loss. Radiographically, a dilated esophagus is seen proximal to a narrowed gastroesophageal junction that has a beaklike appearance.[67]

The second type of intrinsic motor disorder of the esophagus is diffuse esophageal spasm. Manometrically, simultaneous prolonged strong esophageal contractions are noted to be interspersed over normal peristaltic waves. If a barium swallow is performed during a spasm, findings such as a "corkscrewing," or curling, of the esophagus may be noted. Diffuse spasm may be precipitated by swallowing very hot or cold liquids. Symptoms include chest pain, dysphagia, or both.[68]

Nutcracker esophagus is the term used to describe prolonged, high-intensity peristaltic waves. Many experts feel that this represents a variant of diffuse esophageal spasm. Nonspecific motor disorders include repetitive esophageal contractions, nontransmitted esophageal contractions, or low-amplitude esophageal contractions.[69]

Diagnostic Strategies

Given the myriad causes of dysphagia, a careful history and physical examination are essential. Patients with oropharyngeal dysphagia should undergo laboratory studies and central nervous system imaging as indicated. Nasopharyngoscopy may also be performed to rule out obvious structural abnormalities. If these are nondiagnostic, patients may be referred for a swallowing study (videoesophagram). Patients with esophageal dysphagia in whom carcinoma, radiation or caustic injury, or achalasia is suggested should undergo a barium swallow. If a motor disorder is suggested, a swallowing study may prove helpful as well, but this may not detect intermittent dysfunction. In such cases, referral to a gastroenterologist for manometric examination may be required. At that time, additional provocative studies can be performed.

Differential Considerations

The differential diagnosis of lower esophageal dysphagia includes acute coronary syndromes. Substernal chest pain is the main symptom in 80 to 90% of patients with esophageal motility disorders. The chest pain can be similar to angina, described as crushing or squeezing with patterns of radiation similar to those of cardiac chest pain. Nitroglycerin may relieve the pain of spasm as well, further confusing the picture.

Symptoms that suggest an esophageal cause of chest pain are pain that is prolonged and nonexertional, pain that interrupts sleep, pain related to meals, relief with antacids, and presence of other symptoms of esophageal disease such as heartburn, dysphagia, or regurgitation. Because of considerable overlap in symptoms, the emergency physician must exclude a cardiac diagnosis before attributing chest pain to an esophageal cause.

www.ketabpezeshki.com 66485457-66963820

Management

Appropriate management of dysphagia is based on the identified or suggested cause. Most patients with no readily identifiable cause can be evaluated as outpatients; however, it is prudent to admit patients who are at high risk for aspiration. Patients in whom an esophageal motility disorder is suggested should be referred to a gastroenterologist because the diagnosis is usually made manometrically. Achalasia is the only motility disorder for which reasonably good studies support specific treatment. Surgical management is the mainstay of treatment for the majority of patients with severe achalasia. Pharmacologic therapy is directed at decreasing the tone of the LES. Nitrates and calcium channel blockers have been used with some success; however, adverse effects limit their usefulness. Other therapies used with some degree of success have included botulinum toxin injection, pneumatic dilation, and surgical intervention.[70]

Medical therapy for esophageal motility disorders is rather limited, and clinical results are usually minimal. Anticholinergic drugs such as hyoscyamine sulfate or dicyclomine have been used because they decrease the amplitude of esophageal peristalsis and LES pressure. However, these drugs may also exacerbate reflux symptoms because they cause delayed gastric emptying and decreased esophageal peristalsis. Other therapies include calcium channel blockers, which decrease both LES pressure and the amplitude of esophageal contractions. Psychotropic medications such as trazodone have been used to treat some esophageal motility disorders. Although no study has demonstrated specific beneficial manometric effects, it is believed that these medications may reduce the discomfort experienced and the patient's perception of the pain.[71]

PHARMACOLOGIC AGENTS FOR UPPER GASTROINTESTINAL DISORDERS

Antacids

By the time most patients seek treatment for upper GI complaints, they have already tried some form of antacid therapy because these agents are readily available as over-the-counter preparations. Antacids afford pain relief in most patients with PUD. Doses with low neutralizing capacity (as low as 30 mEq) promote ulcer healing. Antacids may also work by binding bile acids or inhibiting pepsin.

The choice of antacid should be individualized. The magnesium-containing antacids can produce diarrhea in up to 25% of patients. Magnesium-containing antacids can also lead to an increase in serum magnesium levels and should be avoided or used with caution in patients with impaired renal function. Aluminum-containing antacids may cause constipation, and prolonged use may lead to phosphate depletion. Calcium-containing antacids have been marketed both as acid neutralizers and as a means of calcium supplementation, especially for postmenopausal women. Calcium-containing antacids have been traditionally believed to cause the highest incidence of acid rebound, a paradoxical increase in gastrin secretion and acid production. Calcium antacids can also lead to constipation, and their excess consumption can lead to hypercalcemia, alkalosis, and renal insufficiency (the milk-alkali syndrome).

Antacids can also decrease the absorption of warfarin, digoxin, some anticonvulsants, and some antibiotics. It is recommended that antacids be administered 1 to 3 hours after meals and at bedtime. Antacids are the least expensive drugs available to treat PUD, but their use is somewhat limited by side effects and inconvenient administration schedules.

Histamine Blockers

Histamine is the primary stimulus to gastric acid secretion. It binds to the H_2 receptor located on the basolateral portion of the parietal cell to stimulate the release of hydrochloric acid. The discovery of the ability of H_2 blockers to inhibit gastric acid production was a major advance in antiulcer therapy because ulcers cannot develop in the absence of acid. These drugs are highly selective competitive inhibitors of histamine for the H_2 receptor on parietal cells and reduce both the volume of gastric juice and its hydrogen ion concentration. All of the currently available H_2 blockers are rapidly absorbed after an oral dose, with peak levels reached within 1 to 2 hours. All have half-lives of approximately 2 to 3 hours, so the effects last for about 6 hours. Most are now available over the counter in lower dosage strength. H_2 blockers are effective in treating duodenal ulcer and, to a lesser extent, gastric ulcer, although they are not as effective as the PPIs. They are widely prescribed for symptoms of dyspepsia and work well in patients with episodic heartburn. All H_2 blockers are mainly hepatically and renally metabolized with the exception of nizatidine, which is almost exclusively renally metabolized. Dosages of all these agents should be reduced in patients with renal failure.

H_2 blockers are safe and generally well tolerated. Side effects are rare, including central nervous system effects such as somnolence, dizziness, and confusion. Transient increases in liver enzyme levels may be noted. Some patients may exhibit abnormalities in cardiac conduction, as there are H_2 receptors in the heart. Cimetidine has been shown to cause gynecomastia. Dosages of the various agents are summarized in Table 89-1.

Proton Pump Inhibitors

The H^+, K^+-ATPase (proton pump) is located on the apical portion of the parietal cell and is responsible for the production of hydrogen ions in gastric acid. PPIs are the most potent inhibitors of gastric acid secretion. They work by irreversibly binding to stimulated proton pumps to block secretion of hydrogen ions. Although they have no effect on the volume of gastric juice produced, production of acid can be reduced by up to 95%. Both basal and stimulated gastric acid secretions are reduced. The antisecretory effects last up to 72 hours. PPIs should be administered before the first meal of the day, as the number of proton pumps is maximized after a fasting state. At the cellular level, additional proton pumps are continually recruited to produce more acid in response to stimulation; therefore several doses of a PPI are necessary for maximal antacid effect to be achieved. The use of these medications on an as-needed basis would not be expected to provide a good clinical response. H_2 blockers are more suitable for this purpose.[43]

PPIs are hepatically metabolized, and dosage should be modified in patients with hepatic failure. Side effects are usually minimal, and the long-term safety of these drugs has been shown in multiple studies.[72] PPIs may be used at significantly higher dosages in patients with Zollinger-Ellison syndrome. Dosages of the various agents are summarized in Table 89-2. Lansoprazole, pantoprazole, and esomeprazole are available as intravenous formulations.

Prostaglandins

Prostaglandins exert protective effects on the gastric mucosa by inhibiting acid secretion and decreasing the amount of cyclic adenosine monophosphate generated in response to histamine. Inhibition of gastric acid secretion, increased secretion of mucus

www.ketabpezeshki.com 66485457-66963820

and bicarbonate, and stimulation of mucosal blood flow have all been demonstrated. Misoprostol is an analogue of prostaglandin E_1 with a longer duration of action and greater potency than endogenous prostaglandins. It should be used only for prevention of NSAID-induced gastric ulcers in patients at high risk. The dose is 200 μg four times a day with food, but crampy abdominal pain and diarrhea may necessitate the use of a somewhat less effective dose of 100 μg four times a day. Misoprostol is an abortifacient and therefore is contraindicated in any female patient of child-bearing age who is not using contraception.

Other Agents

Sucralfate binds to epithelial cells and especially to ulcerated surfaces, providing a protective layer that inhibits further acid damage. Its mechanism of action is not completely understood, although it has been shown to enhance epithelial growth, suppress acid secretion, and inhibit growth of *H. pylori.* The usual dose is 1 g four times a day given 30 to 60 minutes before meals.

Bismuth compounds such as bismuth subsalicylate decrease pepsin activity, increase mucus secretion, and form a barrier to further acid damage in ulcer craters. They also increase prostaglandin synthesis and retard hydrogen ion diffusion through the mucosal barrier. Bismuth may also help heal ulcers through its bactericidal action on *H. pylori.* Bismuth compounds are not approved for the treatment of peptic ulcers.

KEY CONCEPTS

- Radiographic contrast studies of patients with suggested perforation of the esophagus or stomach should first be performed with water-soluble agents such as Gastrografin.
- There is a growing role for nonsurgical management of esophageal perforation for selected low-risk patients.
- GERD treatment includes lifestyle modification and therapy with an antisecretory agent, usually a PPI.
- Peptic ulcer disease results primarily from NSAID use or infection with *H. pylori.*
- Proton pump inhibitors are the most effective means of suppressing gastric acid secretion.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Digoy GP: Diagnosis and management of upper aerodigestive tract foreign bodies. *Otolaryngol Clin North Am* 2008; 41:485-496.
2. Wyllie R: Foreign bodies in the gastrointestinal tract. *Curr Opin Pediatr* 2006; 18:563-564.
3. Eisen GM, et al: Guideline for the management of ingested foreign bodies. *Gastrointest Endosc* 2002; 55:802-806.
4. Louie JP, Alpern ER, Windreich RM: Witnessed and unwitnessed esophageal foreign bodies in children. *Pediatr Emerg Care* 2005; 21:582-585.
5. Conway WC, Sugawa C, Ono H, Lucas CE: Upper GI foreign body: An adult urban emergency hospital experience. *Surg Endosc* 2007; 21:455-460.
6. Young CA, Menias CO, Bhalla S, Prasad SR: CT features of esophageal emergencies. *Radiographics* 2008; 28:1541.
7. Siddiqui M: The use of metal detectors as a tool for diagnosing ingested metal foreign bodies. *Webmedcentral Emerg Med* 2010; 1:1-9.
8. Chung S, Forte V, Campisi P: A review of pediatric foreign body ingestion and management. *Clin Pediatr Emerg Med* 2010; 11:225-230.
9. Gmeiner D, et al: Flexible versus rigid endoscopy for treatment of foreign body impaction in the esophagus. *Surg Endosc* 2007; 21:2026-2029.
10. Little DC, et al: Esophageal foreign bodies in the pediatric population: Our first 500 cases. *J Pediatr Surg* 2006; 41:914-918.
11. Dahshan AH, Kevin Donovan G: Bougienage versus endoscopy for esophageal coin removal in children. *J Clin Gastroenterol* 2007; 41:454-456.
12. Arms JL, et al: Safety and efficacy of a protocol using bougienage or endoscopy for the management of coins acutely lodged in the esophagus: A large case series. *Ann Emerg Med* 2008; 51:367-372.
13. Mehta D, Attia M, Quintana E, Cronan K: Glucagon use for esophageal coin dislodgment in children: A prospective, double-blind, placebo-controlled trial. *Acad Emerg Med* 2001; 8:200-203.
14. Arora S, Galich P: Myth: Glucagon is an effective first-line therapy for esophageal foreign body impaction. *CJEM* 2009; 11:169-171.
15. Lee J, Anderson R: Best evidence topic report. Effervescent agents for oesophageal food bolus impaction. *Emerg Med J* 2005; 22:123-124.
16. Lee J, Anderson R: Best evidence topic report. Proteolytic enzymes for oesophageal meat impaction. *Emerg Med J* 2005; 22:122-123.
17. Litovitz T, Whitaker N, Clark L, White NC, Marsolek M: Emerging battery-ingestion hazard: Clinical implications. *Pediatrics* 2010; 125:1168-1177.
18. Litovitz T, Whitaker N, Clark L: Preventing battery ingestions: An analysis of 8648 cases. *Pediatrics* 2010; 125:1178-1183.
19. Sung SH, et al: Factors predictive of risk for complications in patients with esophageal foreign bodies. *Dig Liver Dis* 2011; 43:4-7.
20. de Schipper JP, Pull ter Gunne AF, Oostvogel HJ, van Laarhoven CJ: Spontaneous rupture of the oesophagus: Boerhaave's syndrome in 2008. Literature review and treatment algorithm. *Dig Surg* 2009; 26:1-6.
21. Vial CM, Whyte RI: Boerhaave's syndrome: Diagnosis and treatment. *Surg Clin North Am* 2005; 85:515-524.
22. Wu JT, Mattox KL, Wall MJ: Esophageal perforations: New perspectives and treatment paradigms. *J Trauma* 2007; 63:1173-1184.
23. Chirica M, et al: Esophageal perforations. *J Visc Surg* 2010; 147:e117-e128.
24. Brinster CJ, et al: Evolving options in the management of esophageal perforation. *Ann Thorac Surg* 2004; 77:1475-1483.
25. Kiernan PD, Khandhar SJ, Fortes DL, Sheridan MJ, Hetrick V: Thoracic esophageal perforations. *Am Surg* 2010; 76:1355-1362.
26. Abbas G, et al: Contemporaneous management of esophageal perforation. *Surgery* 2009; 146:749-756.
27. Mocroft A, et al: Decline in esophageal candidiasis and use of antimycotics in European patients with HIV. *Am J Gastroenterol* 2005; 100:1446-1454.
28. Geagea A, Cellier C: Scope of drug-induced, infectious and allergic esophageal injury. *Curr Opin Gastroenterol* 2008; 24:496-501.
29. Pace F, Antinori S, Repici A: What is new in esophageal injury (infection, drug-induced, caustic, stricture, perforation)? *Curr Opin Gastroenterol* 2009; 25:372-379.
30. Dellon ES: Diagnosis of eosinophilic esophagitis: Current approach and future directions. *Curr Gastroenterol Rep* 2011; 13:240-246.
31. Sgouros SN, Bergele C, Mantides A: Eosinophilic esophagitis in adults: A systematic review. *Eur J Gastroenterol Hepatol* 2006; 18:211-217.
32. Liacouras CA: Eosinophilic esophagitis. *Gastroenterol Clin North Am* 2008; 37:989-998.
33. Pasha SF, et al: Patient characteristics, clinical, endoscopic, and histologic findings in adult eosinophilic esophagitis: A case series and systematic review of the medical literature. *Dis Esophagus* 2007; 20:311-319.
34. Pappas PG, et al: Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 48:503-535.
35. Lavery EA, Coyle WJ: Herpes simplex virus and the alimentary tract. *Curr Gastroenterol Rep* 2008; 10:417-423.
36. Dohil R, Newbury R, Fox L, Bastian J, Aceves S: Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. *Gastroenterology* 2010; 139:418-429.
37. Salzman M, O'Malley RN: Updates on the evaluation and management of caustic exposures. *Emerg Med Clin North Am* 2007; 25:459-476.
38. Fulton JA, Hoffman RS: Steroids in second degree caustic burns of the esophagus: A systematic pooled analysis of fifty years of human data: 1956-2006. *Clin Toxicol (Phila)* 2007; 45:402-408.
39. Kahrilas P: Gastroesophageal reflux disease. *N Engl J Med* 2008; 359:1700-1707.
40. American Lung Association Asthma Clinical Research Centers, et al: Efficacy of esomeprazole for treatment of poorly controlled asthma: A randomized controlled trial. *N Engl J Med* 2009; 360:1487.
41. Heidelbaugh JJ, Gill AS, Van Harrison R, Nostrant TT: Atypical presentations of gastroesophageal reflux disease. *Am Fam Physician* 2008; 78:483-488.
42. Sharma P: Barrett's esophagus. *N Engl J Med* 2009; 361:2548-2556.
43. Kahrilas PJ, et al: American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. *Gastroenterology* 2008; 135:1383-1391.
44. van Pinxteren B, Sigterman KE, Bonis P, Lau J, Numans ME: Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease–like symptoms and endoscopy negative reflux disease. *Cochrane Database Syst Rev* 2010; 11:CD002095.
45. Stockl KM, et al: Risk of rehospitalization for patients using clopidogrel with a proton pump inhibitor. *Arch Intern Med* 2010; 170:704-710.
46. Ho PM, et al: Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009; 301:937-944.
47. Manzotti ME, et al: Prokinetic drug utility in the treatment of gastroesophageal reflux esophagitis: A systematic review of randomized controlled trials. *Open Med* 2007; 1:171-180.
48. Beaumont H, Boeckxstaens GEE: Does the presence of a hiatal hernia affect the efficacy of the reflux inhibitor baclofen during add-on therapy? *Am J Gastroenterol* 2009; 104:1764-1771.
49. Hershcovici T, Fass R: Pharmacological management of GERD: Where does it stand now? *Trends Pharmacol Sci* 2011; 32:258-264.
50. Chen D, et al: Systematic review of endoscopic treatments for gastro-oesophageal reflux disease. *Br J Surg* 2009; 96:128-136.
51. Ramakrishnan K, Salinas RC: Peptic ulcer disease. *Am Fam Physician* 2007; 76:1005-1012.
52. Malfertheiner P, Chan FK, McColl KE: Peptic ulcer disease. *Lancet* 2009; 374:1449-1461.
53. Ables AZ, Simon I, Melton ER: Update on *Helicobacter pylori* treatment. *Am Fam Physician* 2007; 75:351-358.
54. Rostom A, et al: Prevention of NSAID-induced gastroduodenal ulcers. *Cochrane Database Syst Rev* 2002; 4:CD002296.
55. Massó González EL, Patrignani P, Tacconelli S, García Rodríguez LA: Variability among nonsteroidal antiinflammatory drugs in risk of upper gastrointestinal bleeding. *Arthritis Rheum* 2010; 62:1592-601.
56. Antman EM, et al: Use of nonsteroidal antiinflammatory drugs: An update for clinicians: A scientific statement from the American Heart Association. *Circulation* 2007; 115:1634-1642.
57. Lanza FL, Chan FKL, Quigley EM: Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol* 2009; 104:728-738.
58. Jones R, Rubin G, Berenbaum F, Scheiman J: Gastrointestinal and cardiovascular risks of nonsteroidal anti-inflammatory drugs. *Am J Med* 2008; 121:464-474.
59. Sullivan PB: Peptic ulcer disease in children. *Paediatr Child Health* 2010; 20:462-464.
60. Geeraerts B, Tack J: Functional dyspepsia: Past, present, and future. *J Gastroenterol* 2008; 43:251-255.
61. Gourgiotis S, Vougas V, Germanos S, Baratsis S: Acute gastric volvulus: Diagnosis and management over 10 years. *Dig Surg* 2006; 23:169-172.
62. Cribbs RK, Gow KW, Wulkan ML: Gastric volvulus in infants and children. *Pediatrics* 2008; 122:e752-e762.

www.ketabpezeshki.com 66485457-66963820

63. Oh TH, et al: Dysphagia in inflammatory myopathy: Clinical characteristics, treatment strategies, and outcome in 62 patients. *Mayo Clin Proc* 2007; 82:441-447.
64. Warnecke T, et al: Fiberoptic endoscopic evaluation of swallowing with simultaneous Tensilon application in diagnosis and therapy of myasthenia gravis. *J Neurol* 2008; 255:224-230.
65. Morris ME, Benjamin M, Gardner GP, Nichols WK, Faizer R: The use of the Amplatzer plug to treat dysphagia lusoria caused by an aberrant right subclavian artery. *Ann Vasc Surg* 2010; 24:416.e5-e8.
66. Francis DL, Katzka DA: Achalasia: Update on the disease and its treatment. *Gastroenterology* 2010; 139:369-374.
67. Walzer N, Hirano I: Achalasia. *Gastroenterol Clin North Am* 2008; 37:807-825.
68. Grübel C, Borovicka J, Schwizer W, Fox M, Hebbard G: Diffuse esophageal spasm. *Am J Gastroenterol* 2008; 103:450-457.
69. Agrawal A, Hila A, Tutuian R, Mainie I, Castell DO: Clinical relevance of the nutcracker esophagus: Suggested revision of criteria for diagnosis. *J Clin Gastroenterol* 2006; 40:504-509.
70. Cheatham JG, Wong RK: Current approach to the treatment of achalasia. *Curr Gastroenterol Rep* 2011; 13:219-225.
71. Lacy BE, Weiser K: Esophageal motility disorders. *J Clin Gastroenterol* 2008; 42:652-658.
72. Thomson AB: Safety of the long-term use of proton pump inhibitors. *World J Gastroenterol* 2010; 16:2323.

www.ketabpezeshki.com 66485457-66963820

Chapter 90

Disorders of the Liver and Biliary Tract

Leslie C. Oyama

HEPATIC DISORDERS

GENERAL PERSPECTIVE

The liver is one of the largest organs in the body, serving a multitude of critical functions. The average weight of the normal adult liver is 1500 g. It receives approximately 30% of the resting cardiac output by way of the portal vein and the hepatic artery.

The liver can be affected by a variety of disorders, and because of its varied synthetic and metabolic functions, liver disease may manifest with a broad range of clinical signs and symptoms. Acute and chronic diseases of the liver are common in the general population and represent a common cause for presentation to the emergency department (ED).

HEPATITIS

Perspective

Hepatitis is a generic term referring to inflammation of the liver. Hepatitis most commonly is a consequence of viral infection but can be secondary to bacterial, fungal, or parasitic infection; a result of toxic exposure; a side effect of prescribed medication; or a consequence of an immunologic disorder. Hepatitis in its generic context represents the most common variety of liver disease encountered by the emergency physician.

Viral Hepatitis

Although many viruses are associated with some degree of measurable liver inflammation, the most significant and potentially severe cases of viral hepatitis are caused by type A (infectious), type B (serum), type C (post-transfusion), and delta viruses. Although the Epstein-Barr virus, the causative agent of mononucleosis, is a common cause of hepatitis, it is more important clinically for its nonhepatic effects.

Epidemiology

The number of cases of hepatitis A declined steadily from 12.0 cases per 100,000 population in 1995 to 1.0 case per 100,000 population in 2007.[1,2] Western states have historically shown a higher incidence of hepatitis A, which in 1999 led to routine vaccinations of children from these areas. The greater decline in incidence of hepatitis A among children has resulted in a relative increase in the proportion of cases among adults.[3] The number of reported cases of hepatitis B declined by more than 80% in the interval between 1990 and 2005, again with the greatest decline occurring among children younger than 15 years.[3] The number of new cases of hepatitis C declined by approximately 80% during this period.[2] The reduced rates of hepatitis A and B most likely reflect today's broad use of effective vaccines.[4] Since the late 1980s, the incidence of acute hepatitis C has declined as a consequence of improved blood product screening. A majority of cases occur among adults, with injection drug use recognized as the most common risk factor.[3]

Hepatitis A virus (HAV), the causative agent of hepatitis A, is an RNA enteroviral picornavirus. It is spread by the fecal-oral route either directly or through contaminated water or foodstuffs. Transmission by blood is a theoretic possibility but is exceedingly rare. HAV can occur sporadically but is notorious for its association with epidemics generally linked to common-source outbreaks. HAV infection is common worldwide; serologic evidence of previous infection exists in nearly 100% of the adult population in some regions. In the United States, close to one half of all urban-dwelling adults are seropositive for antibody for HAV.[5] High rates of seropositivity in association with the relatively small number of reported episodes support the notion that many cases may be asymptomatic. Occult disease appears to be more common in children, and 70% of those infected may be asymptomatic.[5] The incidence of hepatitis A infection varies among ethnic groups. In the United States, the incidence among different geographic areas and ethnic groups has changed notably since endemic areas have been targeted for routine vaccination of children. In 2005, recommendations on immunization were expanded to include routine vaccination of children in all 50 states.[5] The declines have shifted the pattern of reported risk factors, showing an increasing proportion of cases among adults—specifically, men who have sex with men (MSM), illicit intravenous drug users (IVDUs), and non–injection drug users. The most common risk factor for hepatitis A in persons older than 15 years of age is travel outside of the United States.[1,2,5]

The typical incubation period for hepatitis A is 30 days, with a range of 15 to 45 days. Viremia is of relatively short duration and is most prominent before the onset of symptoms. Fecal shedding and maximum infectivity occur before the onset of symptomatic disease and generally have waned by the time jaundice appears (Fig. 90-1). HAV is not associated with a chronic carrier state.

Hepatitis B virus (HBV) is contained in a 42-nm structure called the *Dane particle*. Within this enveloped virion are the viral DNA, DNA polymerase, hepatitis B surface antigen (HBsAg), and hepatitis B core antigen (HBcAg). Hepatitis B e antigen (HBeAg) is an immunologically distinct antigen not incorporated into virions and instead secreted from cells into the serum of infected patients. In contrast to HAV, for which there is only a single antigenic variety, several genotypes of HBV, as defined by surface antigen, are recognized. HBV is transmitted principally by

www.ketabpezeshki.com 66485457-66963820

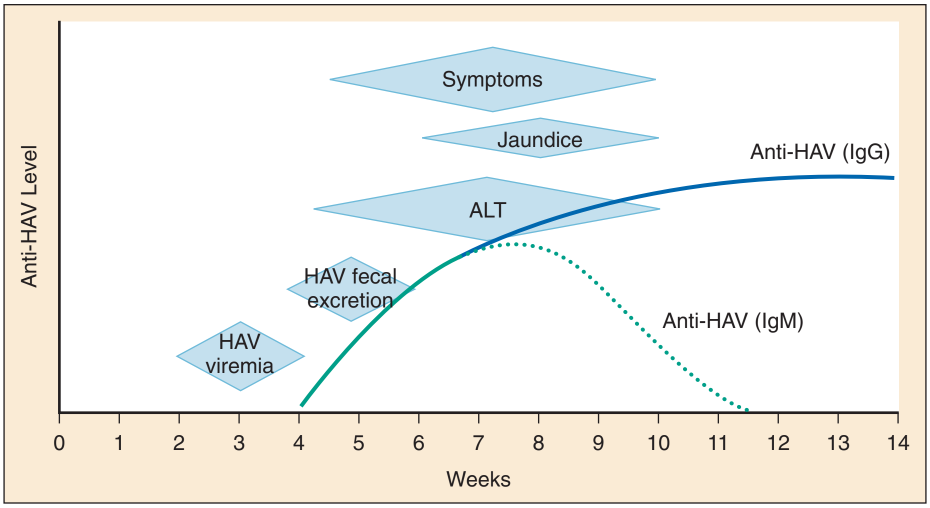


Figure 90-1. Acute hepatitis A virus *(HAV)* infection. *ALT,* alanine aminotransferase; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M.

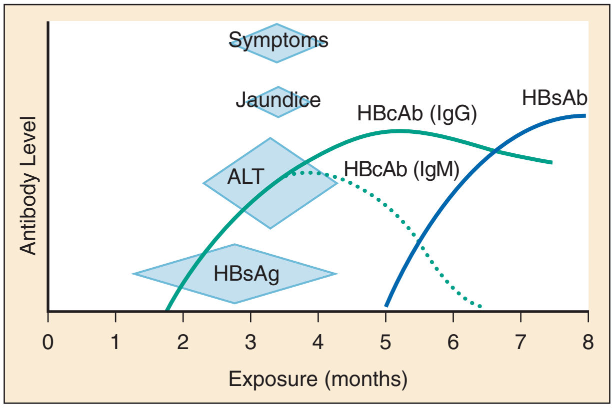


Figure 90-2. Acute hepatitis B virus infection. *Ab,* antibody; *Ag,* antigen; *ALT,* alanine aminotransferase; *HBc,* hepatitis B core; *HBs,* hepatitis B surface; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M.

parenteral exposure but also can be transmitted through intimate contact. The highest rates of infection are among IVDUs and homosexual men. Transmission by blood transfusion, previously a common source of infection, has been eliminated because of modern blood bank screening techniques.

HBsAg has been detected in a variety of bodily secretions, including saliva, semen, stool, tears, urine, and vaginal secretions. Although the presence of HBsAg is not synonymous with infectivity, HBV DNA has been identified in several of these fluids and is likely to be infectious. The typical interval between exposure and onset of clinical illness is 60 to 90 days; however, serologic markers of infection generally appear within 1 to 3 weeks (Fig. 90-2). Approximately 10% of adults and 90% of infected neonates with immature immune systems will become asymptomatic chronic carriers of HBsAg.[6] Health care workers who routinely come in contact with blood have a prevalence of HBsAg of 1 to 2%, and 15 to 30% show serologic evidence of previous infection. Among emergency physicians, seropositivity rates of 12% and 15% have been reported.[7] The likelihood of becoming chronically infected with HBV varies inversely with the age at which infection occurs. HBV transmitted from HBsAg-positive mothers to their newborns results in HBV carriage in up to 90% of infants, whereas only 6 to 10% of acutely infected adults become carriers.[6] In general, less than 5% of hepatitis B infections in healthy immunocompetent adults will progress to chronic hepatitis.[8] Chronic hepatitis is most commonly defined as the presence of HBsAg in serum for longer than 6 months, serum HBV DNA greater than 20,000 IU/mL (105 copies/mL) (lower values are often seen in HBeAg-negative chronic hepatitis B), persistent or intermittent elevation in ALT/AST levels, and a liver biopsy showing chronic hepatitis with moderate or severe necroinflammation.[9]

What was historically referred to as *non-A, non-B hepatitis* is caused by at least two distinct RNA viruses: hepatitis C virus (HCV) and hepatitis E virus. Before the advent of widespread screening of the blood supply in 1992, hepatitis C was commonly transmitted through blood transfusions and organ transplants in the United States. With the screening of donor blood for surrogate markers (aminotransferases), antibody to hepatitis C, and nucleic acid amplification testing, the hepatitis C transmission risk from blood transfusion has been reduced to approximately 1 in 2 million blood units.[10] The strongest risk factors for HCV infection are a history of intravenous drug use, having had 20 or more lifetime sex partners, and having undergone blood transfusions before 1992.[11] Among patients infected with human immunodeficiency virus (HIV), the incidence of coinfection with hepatitis C is 15 to 30%. This rate approaches 50 to 90% in those who acquired HIV through intravenous drug use.[12] Patients coinfected with HIV and HCV generally have a more aggressive course of both infections. In 40 to 57% of cases of hepatitis C, no source of infection is identified. The incubation period for hepatitis C is 30 to 90 days, with a mean of 50 days. Approximately 90% of HCV infections progress to chronic hepatitis. Long-term follow-up studies indicate that clinical liver disease develops in only 10 to 20% of those infected, during a period of approximately 20 years after transfusion.[12] In the United States, it is estimated that 4.1 million persons are infected with HCV, and 3.2 million persons have chronic hepatitis C infection.[12] Hepatitis E, which is associated with fecal-oral transmission, is encountered most often in Asia, Africa, and Russia. Hepatitis E has an incubation period of 15 to 60 days.

Hepatitis delta virus (HDV) was discovered in 1977 in liver specimens from patients with chronic HBV infection. It is a defective RNA virus that can infect only patients who are actively producing HBsAg, which is required for its viral coating. In the United States the incidence of HDV antibody is 4 to 30% of patients with chronic HBV infection.[13] As a consequence of the routine association with chronic HBV infection, it is likely that many cases of HDV infection are misdiagnosed as acute or reactivated hepatitis B. HDV infection is spread in a manner similar to that for hepatitis B, being most common among IVDUs, promiscuous homosexual men, and patients with hemophilia. Infection with HDV can occur either concomitantly with HBV (coinfection) or subsequent to earlier HBV infection (superinfection), because HDV cannot replicate in the absence of HBV. In cases of superinfection the

www.ketabpezeshki.com 66485457-66963820

presentation may range from acute self-limited disease to fulminant hepatitis or chronic infection. Severe or fulminant hepatitis is more often observed with HBV-HDV coinfection than with HBV monoinfection.[13]

Hepatitis G virus (HGV), also referred to as *hepatitis GB virus type C,* is the most recently identified virus associated with hepatitis. It is an RNA virus in the Flaviviridae family. Transmission of HGV seems to occur through blood transfusion and parenteral exposure to blood or blood products, and possibly during intimate sexual contact. The virus has been identified in patients with acute and chronic hepatitis. However, it generally is believed to be an "innocent bystander," with disease manifestations attributable to coinfection with another hepatitis virus.[14]

Principles of Disease

The pathophysiology of viral hepatitis is not completely understood. In the most common varieties of hepatitis, liver injury appears to be related to the development of the immunologic response to infection rather than to the cytopathologic effect of the virus. HDV appears to be an exception, having significant direct cytotoxic potential.

Clinical Features

The clinical presentation of viral hepatitis is highly variable. A significant number of cases, possibly a majority, are asymptomatic. The protean nature of symptoms and the common occurrence of anicteric disease can result in misdiagnosis. The most common symptoms and signs are malaise, fever, and anorexia, followed by nausea, vomiting, abdominal discomfort, and diarrhea. The first symptom leading to physician consultation typically is jaundice. A small number of patients with hepatitis B may experience a prodromal illness characterized by arthralgia or arthritis and dermatitis. The joint involvement typically is polyarticular; the small joints of the hands and the wrists are most commonly affected. Joint fluid usually is noninflammatory, but cell counts for aspirated fluid can be as high as 90,000/mm^3. The characteristic dermatitis is urticarial but may be macular, papular, or petechial.

Fulminant hepatitis is characterized by acute onset and progresses to hepatic failure and encephalopathy over a period of days. Although most often encountered with HBV and HDV coinfection, fulminant hepatitis can occur in association with all of the causative viruses. The overall incidence of fulminant hepatitis is 1 to 2% of all cases. The hallmarks of fulminant disease are altered mentation and spontaneous mucosal bleeding.

Physical findings include elevated temperature, scleral or cutaneous icterus, and abdominal tenderness. If significant vomiting has occurred, tachycardia and supine or orthostatic hypotension may be noted. Hepatomegaly may be detected and generally is characterized by a smooth, homogeneous, and tender liver surface. Even if liver enlargement is not appreciated, the patient often exhibits tenderness to percussion over the lower right ribs. Scleral icterus is generally noticeable earlier than cutaneous discoloration, particularly in people of pigmented races. Muddy sclera, commonly found among African-American patients, may obscure or confuse this finding. An alternative in this setting is examination of sublingual or subungual surfaces. Scleral icterus usually is not clinically apparent until serum bilirubin is above 2.5 mg/dL. Spider angiomata and splenomegaly, although more commonly associated with cirrhosis, may be features in acute presentations. Gray or acholic stools are distinctly uncommon.

Diagnostic Strategies

Laboratory tests are critically important in diagnosing hepatitis and determining the specific cause. The most useful tests are measurements of the hepatic aminotransferases and bilirubin. Typically, hepatitis is associated with elevations (tenfold to 100-fold) of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), with ALT generally elevated in excess of AST. Bilirubin may be moderately increased (5-10 mg/dL) and occasionally is markedly elevated (15-25 mg/dL). Hyperbilirubinemia typically emerges several days to a week or more after the onset of clinical symptoms. Both direct and indirect bilirubin levels are elevated in close to equal proportions. Alkaline phosphatase and lactate dehydrogenase may be elevated but rarely are more than two to three times normal. Prothrombin time (PT) or international normalized ratio (INR) is useful in assessing the degree of hepatic synthetic dysfunction. Elevation of the PT or INR may be the first clue to a complicated course. The white blood cell (WBC) count generally is not useful in the diagnosis because values range from low overall counts with a lymphocytic predominance to marked polymorphonuclear leukocytosis.

Although determination of the precise cause of hepatitis can rarely be achieved in the ED, this evaluation should be initiated as soon as possible. Identification of the causative agent has significant impact on prognosis and public health issues. In this regard, it is important to be able to interpret the significance of certain serologic tests (Table 90-1).

Acute hepatitis A is diagnosed by the presence of immunoglobulin M (IgM) HAV antibody, whereas previous infection is determined by detection of an immunoglobulin G (IgG) antibody.

Table 90-1 Serologic Markers in Hepatitis

SEROLOGIC MARKER	ABBREVIATION	INTERPRETATION
Antibody to HAV	Anti-HAV	A combination of IgG and IgM antibody defining infection with HAV, acute or past
IgM antibody to HAV	Anti-HAV IgM	Antibody to HAV, indicating acute infection
Hepatitis B surface antigen	HBsAg	Surface antigen associated with acute or chronic HBV infection
Hepatitis B e antigen	HBeAg	Antigen associated with active infection, acute or chronic, and indicative of high infectivity
Antibody to B surface antigen	HBsAb	Antibody indicative of acute or past infection or immunization
Antibody to B core antigen	HBcAb	A combination of IgG and IgM antibody defining infection with HBV, acute or past
IgM antibody to B core antigen	HBcAb-IgM	Antibody to B core antigen, indicating acute infection with HBV
Antibody to B e antigen	HBeAb	Antibody to e antigen, possibly representing resolving HBV infection and decreased infectivity
Antibody to HDV	Anti-HDV	Antibody defining infection with HDV; HBsAg should be present
Antibody to HCV	Anti-HCV	A new antibody that defines infection with HCV, acute or past

HAV, hepatitis A virus; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HDV,* hepatitis delta virus; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M.

www.ketabpezeshki.com 66485457-66963820

Acute hepatitis B is characterized by the presence of HBsAg and IgM antibody to HBcAg. HBsAg alone does not establish the diagnosis of acute hepatitis B because it can be either absent late in the course of acute disease or present chronically unrelated to the cause of the current episode. Anti-HBcAg antibody generally is the best indicator of previous HBV infection, whereas anti-HBsAg antibody is the best marker for immunity to HBV.

Currently, the diagnosis of hepatitis C is based on the exposure history and the elimination of other causes. The serologic assay for an antibody to this virus facilitates a definitive diagnosis, but there can be a delay between the onset of symptoms and the development of assayable antibody. Furthermore, the HCV test does not distinguish acute from chronic infection.

Diagnosing HDV infection requires an aggressive search because the disease can easily be mistaken for acute or chronic HBV infection. A serologic test for the antibody to HDV (anti-HDV) is available. The presence of this antibody in conjunction with IgM antibody to HBcAg suggests coinfection with HDV and HBV. Anti-HDV in association with IgG antibody to HBcAg supports the diagnosis of superinfection.

The temporal relationships among infection, clinical symptoms, and serologic responses for the two most common causes of viral hepatitis—HAV and HBV—are delineated in Figures 90-1 and 90-2.

Differential Considerations

The protean nature of the symptoms and signs associated with viral hepatitis makes the differential diagnosis of this disorder quite broad in scope. Beyond a variety of nonhepatic viral illnesses, all of the infectious, chemical, and immunologic causes of hepatic inflammation in addition to biliary tract disease must be considered. A viral cause often is suggested by a history of exposure and a suggestive medical history, but serologic tests are required for confirmation. Alcoholic hepatitis usually is associated with a history of chronic or excessive alcohol consumption, less marked elevation of hepatic transaminases, and AST levels elevated above those of ALT. Extrahepatic obstruction, cholecystitis, and cholelithiasis are excluded by their lack of association with significant elevation of aminotransferases; however, abdominal ultrasound imaging may be required to eliminate these other diseases.

Management

Treatment of viral hepatitis is primarily symptomatic. It often is necessary to correct fluid and electrolyte imbalances secondary to poor oral intake or excessive diarrhea or vomiting. Antiemetics may allow resumption of adequate oral intake, thereby avoiding the need for hospital admission. In the anorexic or nauseated patient, fluid intake should be encouraged, with avoidance of solids until they are palatable. Medications requiring primarily hepatic metabolism generally do not need to be discontinued nor the dosage modified unless there is significant hepatic dysfunction. Nonessential drugs with hepatotoxic potential should be avoided. Alcohol consumption should be completely discontinued until signs of liver injury have disappeared. Although various active interventions (e.g., corticosteroid administration) have been suggested, no reliable data suggest that such therapies offer clear benefit; they may even be harmful.

Complications of acute hepatitis are most commonly related to fluid or electrolyte imbalance as a result of inadequate oral intake or refractory emesis. Severe vomiting can result in upper gastrointestinal (GI) bleeding from an esophageal tear. The most severe complication of acute disease is the development of liver failure, heralded by the emergence of hepatic encephalopathy. Most patients with viral hepatitis have self-limited disease, with symptomatic and histologic resolution in 2 to 4 weeks. Chronic disease will develop in approximately 10% of patients with hepatitis B and in as many as 50 to 84% of those with hepatitis C.[15] Clinical liver disease develops in only 10 to 20% of chronically infected patients within approximately 20 years after becoming infected. Many of these patients will eventually die of cirrhosis secondary to their disease.[15]

Disposition

Hospital admission is rarely required for management of viral hepatitis and generally is reserved for the patient with significant fluid and electrolyte imbalance or refractory vomiting. Patients with less severe illness may require hospitalization for concomitant medical problems or if suitable living arrangements are not available. Altered sensorium, prolongation of the PT beyond 5 seconds, or increase in the INR above 1.5 may suggest fulminant disease or an increased likelihood of a complicated course, necessitating hospitalization for observation. The emergence of fulminant disease should lead to consideration of transfer to a facility that can offer liver transplantation.

Treatment with interferon alfa-2b has resulted in a 35 to 45% remission rate after a 4-month course of treatment in selected patients with active immune responses in the symptomatic stage 2 period of hepatitis B infection. Early treatment of acute hepatitis C infection with interferon alfa-2b alone prevents the development of chronic HCV infection in most patients.[15] Hepatitis C treatment recommendations suggest that duration of treatment with interferon and ribavirin should be based on the HCV genotype and pretreatment viral load. Polyethylene glycol added to interferon alfa (peginterferon alfa) extends the half-life and duration of the therapeutic activity of the interferon. Corresponding clinical benefits include both a higher rate of response than with conventional daily interferon monotherapy and feasibility of once-weekly administration. Referral to a hepatic disease specialist is recommended.

Anxiety about disease communicability may affect the ease of disposition. Patients with possible HAV infection should be advised to practice meticulous personal hygiene, not to share toiletries, and to ensure cleaning of utensils and kitchenware between uses. In patients with suspected HBV or HDV infection, the relatively low risk of transmission by means of intimate personal contact or parenteral exposure should be emphasized.

Viral hepatitis is a reportable disease requiring notification of the local health department. Immunoprophylaxis should be provided to the patient's family members and close personal contacts. Although the nature of prophylaxis depends on the specific viral cause, it is wise to offer gamma globulin to household contacts immediately unless they are known to have been previously immunized, pending serologic determination. Table 90-2 outlines the guidelines for immunoprophylaxis. Patients with HAV infection who process or handle food must not return to work while potentially infectious. Although infectivity is greatly diminished by the time jaundice emerges, it is best to delay return to work until after jaundice has cleared.

Special Considerations

Effective preexposure and postexposure prophylaxis for HBV has been available for more than two decades. The rates of seropositivity for HBV infection among health care workers have historically been high compared with those in the general population. Health care workers in an ED are at increased risk because of frequent contact with blood and interaction with high-risk patients. Historically, the seropositivity rate among ED nurses is 30%, and among ED physicians it is 12 to 15%.[11] The 1-year risk of infection among unimmunized emergency physicians is approximately

www.ketabpezeshki.com 66485457-66963820

Table 90-2 Postexposure Hepatitis Prophylaxis

Hepatitis A	
NATURE OF EXPOSURE	**RECOMMENDED TREATMENT**
Close personal contact	ISG 0.02 mL/kg IM
Daycare center	
Employee	ISG 0.02 mL/kg IM
Attendee	ISG 0.02 mL/kg IM
School contacts	None
Hospital contacts	None
Workplace contacts	None
Food-borne source	
Within 2 weeks of exposure	ISG 0.02 mL/kg IM
After 2 weeks of exposure	None
After common source outbreaks have begun to occur	None

Hepatitis B		*Exposed Individual*	
NATURE OF EXPOSURE	**SOURCE**	**UNVACCINATED**	**VACCINATED***
Percutaneous or mucosal	HBsAG (+)	1. HBIG ×1 2. Initiate hepatitis B vaccination series	Test exposed person for anti-HBs; if titer is adequate, no treatment If anti-HBs titer inadequate: 1. HBIG ×1 2. Hepatitis B vaccination booster
	HBsAG (−)	1. Initiate Hep B vaccination series	No treatment
	Unknown source (treat as if HBsAG [+])	1. HBIG ×1 2. Initiate Hep B vaccination series	Test exposed person for anti-HBs; if titer is adequate, no treatment If anti-HBs title inadequate: 1. HBIG ×1 2. Hepatitis B vaccination booster
Intimate sexual	HBsAG (+)	1. HBIG ×1 2. Initiate hepatitis B vaccination series	Test exposed person for anti-HBs; if titer is adequate, no treatment If anti-HBs titer inadequate: 1. HBIG ×1 2. Hepatitis B vaccination booster

Hepatitis C
Unknown benefit from prophylaxis; ISG 0.06 mL/kg IM can be considered for parenteral exposures in patients with evidence of viral hepatitis and negative results on serologic studies
Hepatitis Delta
Same as for hepatitis B

Adapted from Protection against viral hepatitis. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR Recomm Rep 39(RR-2):1, 1990 and Guidelines for the management of occupational exposures to HBV, HVC and HIV: recommendations for postexposure prophylaxis. MMWR Recomm Rep 50(RR-11):1-42, 2001.
HBIG, hepatitis B immune globulin; *HBsAg,* hepatitis B surface antigen; *IM,* intramuscularly; *ISG,* immune serum globulin.
*The HB vaccine recombinant dose comes in three formulations (pediatrics, adults, and those on hemodialysis). The adult formulation (without preservative) comes in a concentration of 10 µg/mL. The dose is 1 mL for adults. Each 1-mL dose contains 10 µg of hepatitis B surface antigen.

0.25%, with a 30-year risk approaching 7.5%. During a 30-year career, the risk of death from hepatitis B is estimated at 1 in 540.[16] Markers for hepatitis C were identified in 18% of patients in an inner-city ED; the potential associated health risk to staff is unknown.

All ED personnel involved in patient care or custodial work should be vaccinated for HBV before or soon after starting employment. The vaccine is highly effective and associated with minimal acute or delayed toxicity. A complete three-injection series of vaccine produces protective antibody in approximately 95% of persons.[17] Optimal immunologic response is obtained with deltoid injection. Hepatitis B immune globulin (HBIG) is recommended for immediate passive immunization of persons not previously immunized who have been exposed to potentially infective material. HBIG alone diminishes the risk of HBV infection by 75%.[17] Unvaccinated, exposed people should receive HBIG 0.06 mL/kg intramuscularly (IM) in addition to the HBV vaccine. Concerns related to the potential risk of HIV infection from gamma globulin preparations are unfounded. Figure 90-3 outlines an approach for managing health care workers exposed to blood or other potentially infectious secretions. A safe and effective vaccine for HAV is available; however, health care workers are not currently on the list of those recommended for routine immunization.

The risk of seroconversion after percutaneous exposure from an HCV-positive source is approximately 1.8%. Despite the theoretic risk of blood-borne HCV exposure among health care workers, the prevalence of HCV infection in this group is approximately the same as in the general population. No effective vaccine for HCV is available, and despite evidence to suggest effectiveness

www.ketabpezeshki.com 66485457-66963820

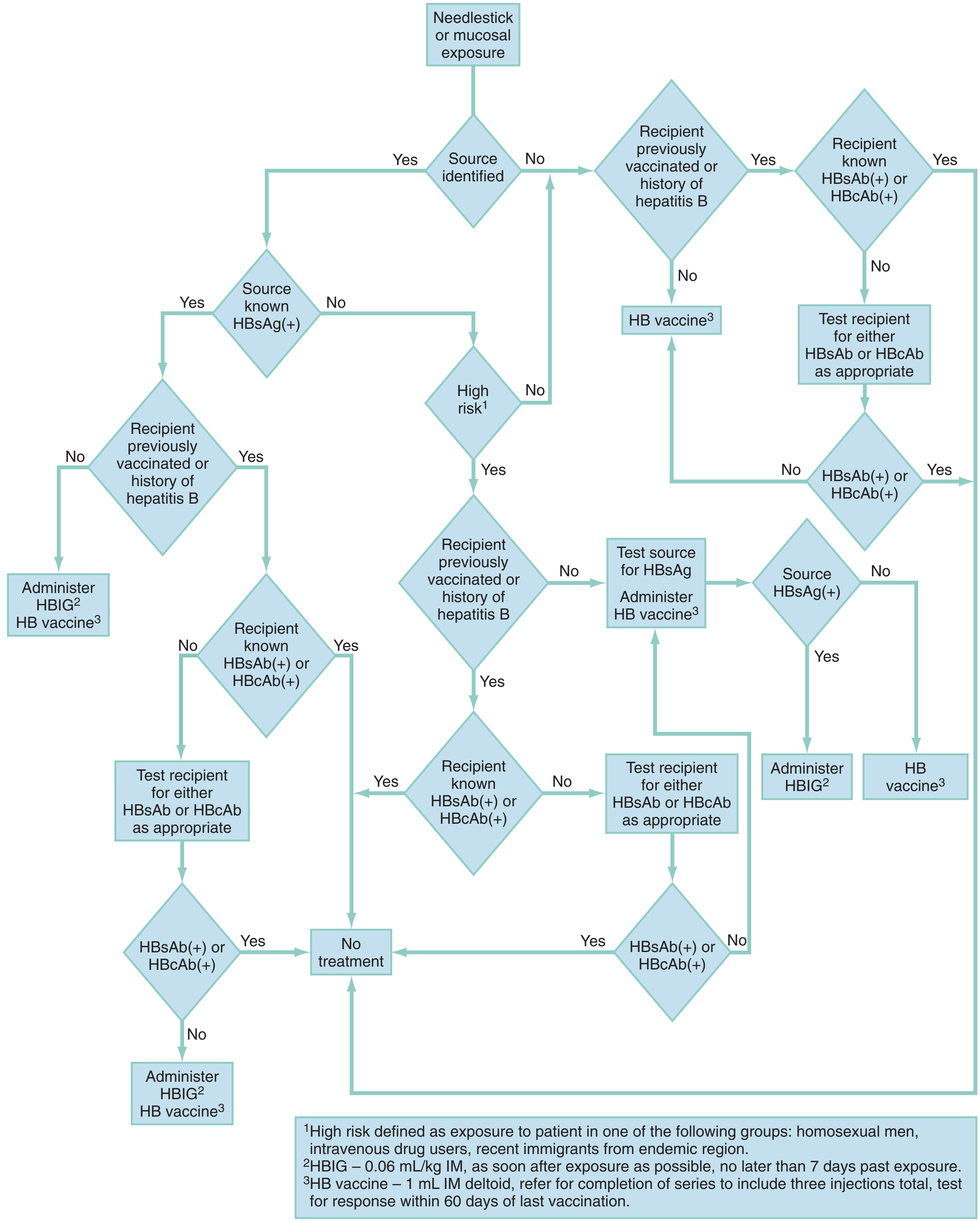


Figure 90-3. Management of health care workers exposed to blood or other infectious secretions. *HB,* hepatitis B; *HBIG,* HB immune globulin; *HBcAb,* hepatitis B core antibody; *HBsAb,* hepatitis B surface antibody; *HBsAg,* hepatitis B surface antigen; *IM,* intramuscularly.

www.ketabpezeshki.com 66485457-66963820

of interferon in acute hepatitis C, there is no accepted preexposure or postexposure prophylaxis regimen.[18] Universal precautions—the use of gloves, masks, protective eyewear, and gowns—constitute the first and best means of defense for persons who work in proximity to potentially infective bodily fluids.

KEY CONCEPTS

- Viral hepatitis is a common disorder that can be caused by several agents.
- Clinical presentation is highly variable, and many cases, particularly in children, are asymptomatic.
- The process of identifying the causative agent should be initiated in the ED because it affects both prognosis and public health interventions.
- Many of the causative agents of viral hepatitis represent a potential threat to health care workers, necessitating proper precautions in handling potentially infectious body fluids and preexposure and postexposure prophylaxis.

Alcohol-Related Liver Disease

Perspective

In the United States, an estimated 15 to 20 million people are chronic alcoholics. Alcohol and its metabolites are toxic to most organ systems and contribute to disease or death from many different causes. The liver is the most common site of injury from chronic ethanol ingestion. Alcoholic liver disease is the third leading preventable cause of death in the United States. Alcohol-associated mortality is disproportionately high among young people, resulting in approximately 30 years of life lost because of alcohol-associated death.[19]

Principles of Disease

Alcohol is largely eliminated by metabolic degradation in the liver. Approximately 2 to 15% of alcohol is excreted unchanged in the urine or expired air.[20] The precise pathogenesis of alcoholic liver disease is unknown and probably is multifactorial. Coexistent malnutrition, accumulation of toxic metabolites (e.g., acetaldehyde), excessive production of nicotinamide adenine dinucleotide (NADH), induction of microsomal enzymes as a result of the metabolism of alcohol, and alteration of immune function all may play a role.[20]

Regardless of the precise mechanism of injury, genetic heterogeneity in susceptibility to liver damage is likely. Women and possibly Native Americans appear to have an increased propensity for injury relative to white men. Although susceptibility to alcohol varies, a rough correlation is recognized between the amount of ethanol ingested and the risk of developing liver disease. The risk of liver injury increases as daily consumption exceeds 80 g of ethanol daily in men and 20 g in women. For men, this is equivalent to a six-pack of beer, four to six glasses of wine, or three to four mixed drinks daily.

The most common variety of alcohol-induced liver disease is steatosis. Fatty infiltration of the liver is most likely a consequence of altered fatty acid metabolism resulting from a diminished NAD^+/NADH ratio, which favors triglyceride production. Fatty infiltration appears to depend on the duration and amount of alcohol consumed and, in general, is reversible when the patient stops drinking. Beyond enlargement of the liver, which usually is painless, this tends to be a benign process.

Clinical Features

Alcoholic hepatitis is a potentially severe form of alcohol-induced liver disease. Most cases probably are subclinical, but the spectrum of presentation can range from nausea, vomiting, and abdominal pain to acute liver failure. Physical findings include tachycardia, fever, and supine or orthostatic hypotension. Abdominal tenderness usually can be elicited, especially in the right upper quadrant. Coexistent fatty infiltration may produce palpable hepatomegaly; cirrhosis from chronic disease may result in a small, nonpalpable liver. The characteristic physical signs of cirrhosis (gynecomastia, spider angiomata, muscle wasting, ascites, and palmar erythema) may be present. Jaundice can be noted in patients with a bilirubin level of at least 2.5 mg/dL.

Diagnostic Strategies

Laboratory tests reveal moderate elevations of AST and ALT. Values in excess of 10 times normal are unusual, even in severe cases associated with eventual liver failure. Compared with viral hepatitis, a relative predominance of AST to ALT is expected. Bilirubin is commonly elevated. The WBC count often is high, with a polymorphonuclear leukocytosis in the range of 10,000 to 20,000/mm^3. The PT and the INR provide a rough assessment of hepatic dysfunction. An acutely prolonged PT or elevated INR in a patient not suspected to have chronic cirrhotic disease suggests a complicated course. Electrolyte or acid-base disturbances may develop as a consequence of excessive vomiting or alcoholic ketoacidosis.

Differential Considerations

The differential diagnosis of alcoholic hepatitis is quite broad in scope and includes a variety of other alcohol-related GI maladies (e.g., gastritis, pancreatitis). Patients often have several ethanol-induced diseases simultaneously. Initially, all of the potential etiologic disorders must be considered; however, the clinical history and aminotransferase profile should facilitate accurate diagnosis. Mild aminotransferase elevation and marked bilirubin elevation are consistent with alcoholic hepatitis; ultrasonography will differentiate this from common duct obstruction. Serum should be sent for testing for anti-HAV IgM and hepatitis B core antibody (HBcAb) IgM, but results usually are not available to establish these diagnoses in the ED.

Management

Management of alcoholic hepatitis is principally supportive. Fluid and electrolyte imbalance must be corrected, usually requiring parenteral fluid replacement; antiemetics may mitigate the need for intravenous treatment. Alcohol may suppress gluconeogenesis, thereby causing hypoglycemia. Blood glucose should be measured and supplemented as indicated. Many alcoholics are malnourished, and if thiamine deficiency is suspected, thiamine should be given at a dose of 100 mg intravenously (IV) before glucose administration to avoid induction of acute Wernicke's encephalopathy. Ethanol-induced magnesium wasting may not be apparent on serum magnesium measurement, and replacement should be given empirically unless the patient has a contraindication such as renal failure or known hypermagnesemia. Magnesium can be given as the sulfate salt in a dose of 1 g IV or IM or as an oxide, chloride salt, or amino acid conjugate for oral replacement therapy at a daily dose of 200 to 1000 mg.

The overall nutritional status of the patient should be addressed with the administration of a high-calorie, vitamin-supplemented diet. Protein content may require restriction if evidence of cirrhosis and incipient encephalopathy exists. Coexisting gastritis

www.ketabpezeshki.com 66485457-66963820

should be treated with histamine H_2 antagonists, proton pump inhibitors, or antacids. The patient should be evaluated for GI bleeding and treated appropriately. Corticosteroids, propylthiouracil, insulin-glucagon infusions, pentoxifylline, and anti–tumor necrosis factor alpha (TNF-α) therapy have been investigated for treatment of alcoholic hepatitis and look promising in severe cases, but none of these agents have gained acceptance as part of routine management.[20,21]

Disposition

Disposition is determined by the patient's clinical state: the degree of fluid and electrolyte abnormality, the ability to retain oral intake, any coexistent illnesses or complications, and the patient's socioeconomic circumstances. Admission to the hospital generally is not required. All patients should be advised to abstain from further alcohol ingestion and should be provided referral for detoxification or alcohol dependency treatment.

KEY CONCEPTS

- The liver is one of the most common targets of alcohol toxicity.
- Alcoholic hepatitis, although generally a mild disease with minor clinical manifestations, can be a cause of fulminant hepatitis.
- Management of patients with alcoholic hepatitis should include referral for alcohol dependence treatment.

Cirrhosis

Principles of Disease

Cirrhosis is a generic term for an end stage of chronic liver disease characterized by destruction of hepatocytes and replacement of normal hepatic architecture with fibrotic tissue and regenerative nodules. *Laennec's cirrhosis* is a diffuse process that involves the entire lobule and most often is related to chronic alcohol ingestion. From 10 to 20% of chronic alcoholics develop this type of cirrhosis. Amount and duration of alcohol ingestion, heredity, and underlying nutritional status all seem to play some role in the development of this disorder. *Postnecrotic cirrhosis* usually is nonhomogeneous, characterized by regions of fibrosis and hepatocyte loss alternating with normal areas. It most often is a consequence of chronic hepatitis of various causes: infectious (viral, bacterial, fungal), drug induced, or metabolic. *Biliary cirrhosis* is much less common and is a consequence of chronic extrahepatic biliary obstruction or a primary disorder of autoimmune-mediated intrahepatic duct inflammation and scarring. Nonalcoholic fatty liver disease has become an increasingly recognized cause of *cryptogenic cirrhosis.* This still poorly understood disease, with features similar to those of Laennec's cirrhosis, is more common in obese patients and those with type 2 diabetes mellitus.[22]

Clinical Features

The clinical manifestations of cirrhosis are related to loss of hepatocytes, leading to metabolic and synthetic dysfunction, or to fibrosis and altered hepatic architecture, resulting in impaired portal vein blood flow and portal hypertension. Typically the patient with cirrhosis complains of chronic fatigue and poor appetite. With the exception of those with biliary cirrhosis, many patients with cirrhosis can be asymptomatic until some dramatic complication develops, such as GI bleeding, ascites, or hepatic encephalopathy. Patients with biliary cirrhosis generally complain of pruritus or exhibit obvious jaundice before end-stage cirrhosis or complications develop. Primary biliary cirrhosis may be associated with other immune-mediated disorders; these patients may have signs and symptoms characteristic of scleroderma or the CREST syndrome (i.e., calcinosis cutis, Raynaud's phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia).

Physical examination may reveal muscle wasting, thinning of the skin with patchy ecchymosis, spider angiomata, palmar erythema, Dupuytren's contracture, and in men, gynecomastia or testicular atrophy. Jaundice generally is absent in mild cases or in early disease. The liver may not be palpable if it is extensively scarred, but a large regenerative nodule, tumor, or fatty infiltration can result in hepatomegaly. Ascites is common, particularly in advanced disease, and may be present in association with a characteristic pattern of abdominal wall vein distention known as *caput medusae.*

Diagnostic Strategies

Laboratory tests are not specific. Aminotransferase levels are rarely more than minimally elevated. Bilirubin may be increased but usually not until cirrhosis is far advanced. Elevation of alkaline phosphatase out of proportion to other liver enzymes is suggestive of biliary cirrhosis. Coagulation studies commonly show abnormalities, and the serum albumin level is low as a result of impaired hepatic synthetic function. Mild to moderate anemia and thrombocytopenia often are present in Laennec's cirrhosis. Elevated blood urea nitrogen (BUN) or creatinine suggests dehydration or hepatorenal syndrome.

Ancillary tests are rarely of use in the ED setting. Ultrasonography is highly sensitive for the detection of ascites, but a carefully performed physical examination generally can yield equivalent results. In patients with ascites and fever or abdominal pain, paracentesis should be considered to rule out spontaneous bacterial peritonitis (SBP). Nuclear scintigraphy or computed tomography (CT) imaging may reveal a hepatic or splenic appearance characteristic of cirrhosis and portal hypertension, but in general these tests should be deferred to an elective setting.

Management

Treatment of cirrhosis in the ED is limited. Fluid and electrolyte imbalances should be corrected, and vitamin and nutritional supplements should be provided. Most patients can be discharged with referral to a general internist for further evaluation and treatment. Ascites associated with respiratory compromise or significant discomfort can be treated with paracentesis and removal of 2 L of fluid or more. Removal of very large quantities of ascitic fluid can result in body fluid and electrolyte abnormalities and hemodynamic instability. If SBP is a consideration, diagnostic paracentesis should be done.

A low-sodium diet, in conjunction with an aldosterone antagonist, may be of use in the chronic management of ascites. A low-dose regimen of a thiazide or loop diuretic may accelerate resolution of ascites and probably is safe if the patient has coexistent peripheral edema and normal renal function. Coagulopathy noted before a planned invasive procedure or in conjunction with active bleeding should be corrected with fresh frozen plasma. With uncomplicated prolongation of PT or INR, treatment with vitamin K supplementation can be given but often is ineffective. GI bleeding requires aggressive treatment. Early consultation with a gastroenterologist for endoscopy often will permit identification of a bleeding site and initiation of appropriate adjunctive treatment. An elevated creatinine level may herald the onset of hepatorenal syndrome and necessitates hospitalization of the patient for optimal fluid and electrolyte management.

www.ketabpezeshki.com 66485457-66963820

Complications of cirrhosis include GI bleeding, ascites with or without infection, encephalopathy, and hepatorenal syndrome. Although GI bleeding often is related to esophageal or gastric varices, more than one half of the cases result from some other source (e.g., gastritis or a duodenal ulcer). Ascites occurs as a consequence of portal hypertension, impaired hepatic lymph flow, hypoalbuminemia, or renal salt retention. Ascites generally causes few signs and symptoms beyond abdominal distention and discomfort. However, massive ascites can lead to respiratory compromise. SBP is an important and often subtle complication. Encephalopathy occurs as a result of impaired hepatic metabolic function and portal hypertension (see later). *Hepatorenal syndrome* is defined as renal failure occurring in the setting of cirrhosis without obvious renal pathology. The mechanism of this almost universally fatal complication is not understood. An otherwise unexplained elevation of creatinine or BUN suggests an emerging hepatorenal state.

KEY CONCEPTS

- Cirrhosis is an advanced stage of liver disease from a variety of causes.
- Patients with cirrhosis most often are seen in the ED with complications of their disease: ascites, variceal bleeding, and hepatic encephalopathy.
- Impaired hepatic synthetic and metabolic function in patients with cirrhosis may necessitate correction of coagulopathy before invasive procedures and modification of medication dosage.

Hepatic Encephalopathy

Principles of Disease

Hepatic encephalopathy is a clinical state of disordered cerebral function that may develop as a consequence of acute or chronic liver disease. The pathophysiology of hepatic coma is complex and related to the diseased liver's failure to adequately perform its normal metabolic functions. Ammonia, formed primarily in the GI tract by the action of bacteria on proteinaceous compounds, is a common marker of this process. Normally, absorbed ammonia is converted to urea in the liver. In severe hepatic disease, ammonia accumulates, crosses the blood-brain barrier, and combines sequentially with α-ketoglutarate and glutamate to form glutamine. Serum ammonia levels correlate inconsistently with the severity of encephalopathy, but there is an association of ammonia levels with cerebrospinal fluid (CSF) glutamine levels. Whether glutamine is itself toxic or simply represents a marker for disordered central nervous system (CNS) metabolism is unknown. Other agents presumed to play a role in the pathophysiology of this disorder include mercaptans, octopamine, γ-aminobutyric acid, and the aromatic amino acids, particularly tryptophan.

Clinical Features

The clinical manifestations of hepatic encephalopathy vary depending on the severity of the process, ranging from mild cognitive dysfunction, irritability, and confusion to profound coma. Asterixis, a low-amplitude, alternating flexion and extension of the wrist occurring when it is held in extension, is characteristic of mild to moderate degrees of encephalopathy. A similar finding may be elicited in the dorsiflexed foot, or similar head movements may occur with extension of the neck. Fetor hepaticus, a musty breath odor presumably from mercaptans, may be detected in severe cases.

Physical examination commonly reveals signs of cirrhosis, including spider angiomata, testicular atrophy, muscle wasting, superficial bruising, gynecomastia, and ascites.

Diagnostic Strategies

Laboratory test results may be normal or indicate fulminate liver failure or chronic cirrhosis. Serum ammonia levels generally are elevated but do not necessarily correlate with the severity of encephalopathy. Results of tests reflective of hepatic synthetic function, serum albumin and PT, generally are abnormal.

Differential Considerations

The differential considerations in patients with suspected hepatic encephalopathy include all causes of altered sensorium. The scope of the differential diagnosis can be narrowed if the patient's history includes previous episodes of hepatic encephalopathy or if the patient has severe underlying liver disease and physical signs are supportive. It may be useful to perform a full electrolyte panel, glucose level, toxicology screen, and, if conditions warrant, a head CT scan and CSF examination to rule out potentially life-threatening conditions.

Management

Aggressive management of the patient with hepatic encephalopathy may reverse the condition. As with any comatose patient, the airway is assessed first, not only to determine the need for respiratory support but also for prevention of aspiration. Affected patients generally are hemodynamically stable but have an increased incidence of GI bleeding. Hypokalemia, alkalosis, and GI bleeding contribute to increased ammonia production or absorption, and the cause must be addressed when any of these abnormalities is detected. Relatively mild degrees of hyponatremia, hypoglycemia, azotemia, or dehydration often will have a disproportionate effect on cerebral function and require immediate correction. All CNS-depressant drugs must be discontinued, and care should be taken not to prescribe even mild sedatives.

The current standard of care for patients with hepatic encephalopathy is treatment with nonabsorbable disaccharides (lactitol or lactulose). Lactulose decreases the absorption of ammonia through its osmotic cathartic effects and by altering colonic pH. This results in trapping of ammonia as ammonium in the stool.[23] The usual dose of lactulose is 30 to 60 g daily or in a quantity sufficient to result in several loose bowel movements daily. The principal adverse effect is excessive diarrhea, with resultant fluid and electrolyte imbalance. Oral aminoglycoside antibiotics (neomycin, vancomycin) as well as metronidazole have been effectively used with and without lactulose to reduce ammonia-producing enteric bacteria in patients with hepatic encephalopathy. Neomycin is a poorly absorbed aminoglycoside. It is believed to act by reducing colonic bacteria responsible for the production of ammonia. Neomycin is administered orally (PO) at an initial dose of 250 mg orally 2 to 4 times a day. Doses as high as 4000 mg/day may be administered. Ototoxicity or renal injury may occur in patients with impaired renal function. In obtunded patients, lactulose and neomycin can be administered by nasogastric tube or rectal enema. Long-term use of aminoglycosides in patients with renal impairment or injury may result in nephrotoxicity and ototoxicity. Prolonged use of metronidazole may result in nausea and peripheral neuropathy. Rifaximin is a minimally absorbed oral antimicrobial agent that concentrates in the GI tract, offering minimal systemic bioavailability and fewer detrimental side effects. It has equal or greater efficacy compared with other antibiotics in hepatitis encephalopathy and appears to have a lower bacterial

www.ketabpezeshki.com 66485457-66963820

resistance than systemic antibiotics.[23] Constant daily management requires diet modification for significant protein restriction.

Alternative therapies include *Lactobacillus acidophilus* (to increase non–urease-producing bacteria), eradication of *Helicobacter pylori* (urease-producing), zinc replacement (because metabolism of ammonia is dependent on zinc, which often is deficient in liver disease), ornithine aspartate (which converts ammonia), benzoate (which metabolizes with glycine), and the benzodiazepine antagonist flumazenil.[24-26] The molecular adsorbent recirculating system (MARS) uses albumin in a dialysis solution to bind and remove circulating toxins. This novel experimental approach to treat liver failure and hepatic encephalopathy appears to be safe and cost-effective but at present is approved in the United States only for treatment of liver failure resulting from drug overdose or poisonings.[27-29]

Disposition

Although most patients with hepatic encephalopathy will require hospitalization, those with grade I or II encephalopathy without complicating factors and a supportive home environment can be managed at home. In addition to a prescription for lactulose or rifaximin, a diet with limited amounts of protein is essential to effective ongoing management.

KEY CONCEPTS

- The differential diagnosis for hepatic encephalopathy should consider all causes of altered sensorium. The correct diagnosis may be determined by the clinical setting, but the broad scope of the differential diagnosis may necessitate additional testing, including chemistry and CSF studies, toxicology, and a head CT scan.
- Management of hepatic encephalopathy includes correction of underlying electrolyte abnormalities, strict protein restriction, and administration of lactulose and neomycin.

Spontaneous Bacterial Peritonitis

Perspective

SBP is an acute bacterial infection of ascitic fluid in patients with liver disease, without an apparent external or intra-abdominal focus of infection. The syndrome is not new, but it was not until in the late 1960s and early 1970s that this potentially fatal disorder was commonly recognized. Although the disease occurs most often in patients with cirrhosis from alcohol use, it can occur in any patient with ascites secondary to cirrhosis. Retrospective studies have identified SBP in 5 to 27% of patients hospitalized with cirrhosis and ascites.[30]

Principles of Disease

The pathophysiology of SBP remains speculative but is most likely to be related to a combination of impaired phagocytic function in the liver and portal systemic hypertension, which can cause bowel mucosal edema and transmural migration of enteric organisms. Additional contributing factors may include impaired activity of opsonins and complement in ascitic fluid. Gram-negative enteric organisms, primarily *Escherichia coli,* are the most frequently identified organisms in SBP.[30] Newer invasive treatments of cirrhosis, including variceal ligation, transjugular intrahepatic portosystemic shunt placement, and long-term antibiotic prophylaxis, have changed the type and etiology of acute bacterial infections in cirrhosis.[30] Polymicrobial and anaerobic infections have been reported but are not common.

Clinical Features

The clinical presentation can be variable, ranging from the acute onset of severe abdominal pain, fever, chills, and hemodynamic instability to the slow, insidious onset of abdominal discomfort or low-grade fever, or hepatic encephalopathy. Although by definition ascites must be present for SBP to develop, free peritoneal fluid may not always be clinically apparent. An elevated temperature is not always detected. [31]

On physical examination, palpation may elicit only mild tenderness or may reveal abdominal rigidity and guarding with rebound tenderness. One study identified a positive peritoneal fluid culture rate of 3.5% among patients who were judged to have asymptomatic ascites.[31] This observation underscores the exceptionally broad spectrum of manifestations and often very minimal physical findings with this disorder and the need to consider the diagnosis of SBP in any patient with ascites who has abdominal pain or exhibits unexplained clinical deterioration.

Diagnostic Strategies

Diagnosis is made by culture of the ascitic fluid, but treatment decisions should be made in advance of these results. An ascitic fluid granulocyte count greater than 500 cells/mm^3 correlates with positive cultures in more than 90% of cases; however, ED treatment for SBP should be initiated if the neutrophil count is greater than 250 cells/mm^3.[31,32] A positive result on urine reagent strip testing for leukocyte esterase has a high degree of correlation with a clinically significant elevation of neutrophil cell count.[33] If ascitic fluid is available for testing, a pH of less than 7.34 or a pH gradient between arterial blood and ascitic fluid of more than 0.10 also is a reliable early indicator of SBP.[32,33] Other laboratory parameters (e.g., aminotransferase, bilirubin, peripheral blood count) are commonly abnormal, but such findings are nonspecific and more often are a consequence of underlying liver disease than infection. PT and INR should be measured in advance of paracentesis, and fresh frozen plasma should be administered if significant coagulopathy is identified.

Differential Considerations

The differential diagnosis for SBP includes all entities that may lead to peritonitis and abdominal pain in patients with or without liver disease.

Management

Treatment of SBP requires intravenous antibiotics. The choice of agents is driven by the anticipated bacteriology of the process. A third-generation cephalosporin such as cefotaxime is considered to be the agent of choice, with a demonstrated cure rate of 90%.[34] An alternative is an ampicillin-sulbactam combination. Ampicillin with an aminoglycoside also is effective but is associated with an increased risk of renal toxicity.

Disposition

Any patient with ascites is at risk for the development of SBP. This risk is markedly increased in patients with ascitic fluid protein levels less than 1 g/dL.[31] Other important risk factors include serum bilirubin level greater than 3.2 mg/dL, platelet count less than 98,000/mm^3, and a previous history of SBP. Antibiotic prophylaxis for high-risk patients can reduce SBP incidence by 60 to 80% and can be cost-effective.[31] The preferred prophylaxis regimen consists of norfloxacin 400 mg daily.[35,36] The emerging problem of quinolone resistance has prompted investigation of trimethoprim-sulfamethoxazole as an alternative for prevention

www.ketabpezeshki.com 66485457-66963820

of SBP. If a high-risk patient with ascites is identified in the ED and contraindications are absent, prophylactic therapy should be initiated. Referral to a primary care physician or gastroenterology specialist is recommended. Patients with diagnosed SBP require hospitalization.

KEY CONCEPTS

- SBP should be considered in any patient with ascites with abdominal pain, fever, or unexplained clinical deterioration.
- The diagnosis is dependent on obtaining ascitic fluid for cell count and culture. An ascitic fluid granulocyte count greater than 250 cells/mm^3 is an indication for antibiotic treatment. Urine reagent strips that test for leukocyte esterase may provide a convenient means of bedside screening of ascitic fluid for SBP.
- Identification of a high-risk patient with ascites is an indication for initiation of SBP prophylaxis with a fluoroquinolone antibiotic.

Drug-Induced Liver Disease

Perspective

In addition to alcohol, various other chemical agents can induce injury to the liver. Most of these agents are commonly prescribed medicinal agents or drugs available over the counter. Although hepatic injury represents a relatively small proportion of all adverse drug reactions, it may account for up to 5% of hospital admissions for jaundice.[37] Drug-induced liver disease is one of the most common reasons for market withdrawal of drugs by the U.S. Food and Drug Administration (FDA) and is responsible for approximately 50% of the cases of fulminant liver failure in the United States.[37] For reasons not entirely clear, the incidence of liver injury related to drugs appears to increase with patient age. Notable exceptions include valproic acid and aspirin, which more often cause hepatic damage in children.

Principles of Disease

The pathogenesis of liver injury from drug exposure is variable. It may occur as a result of a direct cytotoxic effect of the primary agent or, as is more often the case, a major or minor metabolite. Alternatively, toxicity can be related to a hypersensitivity or allergic reaction. Antimetabolites (e.g., azathioprine, comfrey tea) have been associated with hepatic injury caused by veno-occlusive disease; oral contraceptives have been implicated in cases of hepatic vein thrombosis. Antiretroviral drug therapy (ARVT) is a common cause of liver toxicity defined by elevations in ALT greater than AST. Increases in ALT or AST of 3.5-fold and 5-fold are considered to represent moderate and severe hepatotoxicity, respectively.[30] Mechanisms identified as leading to liver toxicity from ARVT include metabolic host-mediated factors, hypersensitivity, mitochondrial toxicity, and immune reconstitution.[38]

Not all agents commonly associated with hepatic toxicity will cause injury in all patients. This nonuniformity may be a consequence of variations in metabolic pathways, simultaneous ingestion of other substances that may facilitate toxicity, amount and duration of drug exposure, or patient idiosyncrasy. For example, isoniazid appears to have differential toxicity depending on both the patient's age and the rate of conversion to a particular toxic metabolite, acetyl hydrazine. Acetaminophen is relatively nontoxic when taken in the usually recommended amounts but universally toxic and potentially fatal when taken in significant excess.

In general, drugs that induce liver injury cause hepatocellular necrosis or cholestasis. Although specific agents tend to cause damage characterized by a particular pattern of injury, there is considerable overlap. Cellular necrosis commonly is associated with anesthetic agents (e.g., halothane, the antimicrobials amphotericin and ketoconazole, or the antidysrhythmic amiodarone). A cholestatic picture is characteristic of liver injury from chlorpromazine, haloperidol, anabolic or oral contraceptive steroids, or erythromycin estolate.

Clinical Features

Many patients with drug-induced liver disease will be asymptomatic, with injury manifesting only with moderate elevations of aminotransferase levels. Other patients may experience painless jaundice resulting from agents associated with cholestatic pathology or as a result of acute hepatitis indistinguishable from virally induced disease.

Physical examination findings will vary depending on the nature of the underlying pathology. The liver can be enlarged and tender. A rash frequently is seen in halothane-induced hepatitis, consistent with its presumed allergic causation. Aminotransferase levels commonly are elevated, but only mildly so in cholestatic cases. Bilirubin often is elevated, most dramatically in cases associated with cholestasis. Eosinophilia is a frequent finding in cases of chlorpromazine- or halothane-induced injury.

It can be difficult to differentiate drug-induced liver injury from infectious causes or extrahepatic biliary obstruction. A careful history in conjunction with knowledge of the drugs commonly associated with hepatic toxicity should facilitate diagnosis (Table 90-3). On occasion, particularly in cases with a cholestatic presentation, abdominal ultrasound imaging and liver biopsy may be necessary.

Management

The offending agent(s) should be discontinued and appropriate supportive measures instituted, as in the treatment of acute hepatitis. For patients with cholestasis and significant pruritus, a bile acid-sequestering agent such as cholestyramine may provide relief. If an allergic mechanism is suspected, corticosteroids may be of benefit. Although drug-induced liver disease generally is a benign disorder, it can be associated with fulminant hepatic failure or the development of cirrhosis.

Disposition

Mild cases of drug-induced hepatitis can be managed effectively on an outpatient basis. Telephone consultation with a gastroenterology specialist is recommended to aid in the diagnosis and ensure reliable follow-up. In severe cases the patient should be hospitalized, and if signs of fulminant hepatitis are apparent, consideration should be given to transfer to a treatment center with the capacity to perform liver transplantation.

HEPATIC ABSCESSES

Hepatic abscesses fall into two broad categories: pyogenic and amebic. Although there may be similarities in clinical presentation, the pathophysiology and treatment differ significantly.

Pyogenic Abscess

Principles of Disease

Pyogenic hepatic abscess is uncommon, being reported in only 8 to 16 cases per 100,000 hospital admissions. The disorder increases

www.ketabpezeshki.com 66485457-66963820

Table 90-3 Common Agents Involved in Hepatic Injury

AGENT	INJURY PATTERN
Acetaminophen	Cytotoxic
Amiodarone	Cytotoxic
Amphotericin	Cytotoxic
Anabolic steroids	Cholestatic, veno-occlusive
Azathioprine	Cytotoxic, cholestatic, veno-occlusive
Carbamazepine	Cytotoxic, cholestatic
Chlorpromazine	Cholestatic
Cisplatinum	Cytotoxic
Contraceptive steroids	Cholestatic, hepatic vein thrombotic
Cyclophosphamide	Cytotoxic
Erythromycin estolate	Cholestatic
Gold salts	Cytotoxic, cholestatic
Haloperidol	Cholestatic
Isoniazid	Cytotoxic
Ketoconazole	Cytotoxic
Lovastatin	Cytotoxic
Methotrexate	Cytotoxic
Methoxyflurane	Cytotoxic
Methyldopa	Cytotoxic
Phenobarbital	Cholestatic
Phenytoin	Cytotoxic
Quinidine	Cytotoxic
Salicylate	Cytotoxic
Tetracycline	Cytotoxic, fatty infiltrative
Valproic acid	Cytotoxic
Verapamil	Cholestatic

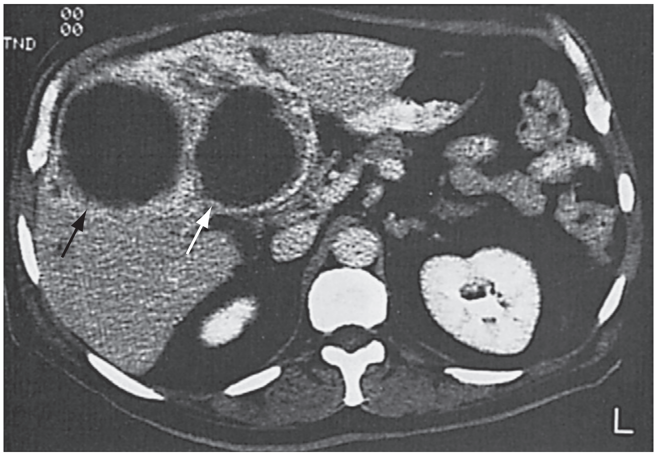


Figure 90-4. Contrast computed tomography scan of liver showing large cystic masses *(black arrow, white arrow)* with irregular, contrast-enhancing borders in a patient with pyogenic liver abscess caused by *"Streptococcus milleri."*

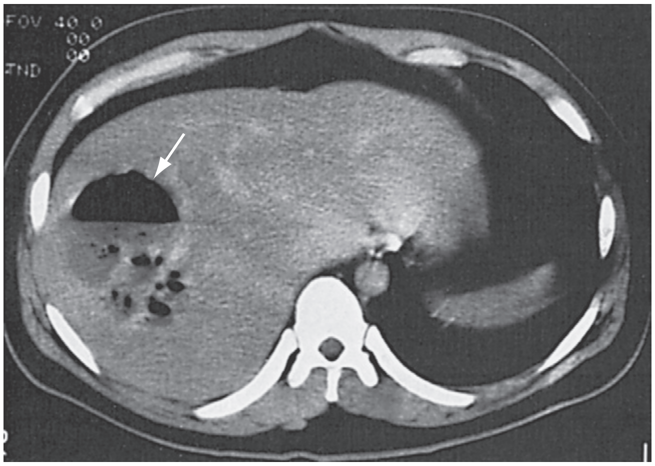


Figure 90-5. Contrast computed tomography scan of liver showing pyogenic liver abscess. Complex cystic mass with air-fluid level *(arrow)* caused by gas-producing *Klebsiella pneumoniae.*

in frequency with patient age and is distributed equally between men and women. Liver abscesses are most commonly associated with biliary tract obstruction or cholangitis but also may be related to diverticulitis, pancreatic abscess, omphalitis, appendicitis, inflammatory bowel disease, or bacteremia of any cause. In a significant number of cases, no underlying cause for liver abscess is identified.

Solitary and multiple abscesses occur with approximately equal frequency, most often in the right lobe of the liver. Patients with multiple lesions tend to be more severely ill, with less favorable outcomes. Both anaerobic and aerobic organisms are causative; *E. coli, Klebsiella, Pseudomonas,* and *Enterococcus* species; anaerobic streptococci; and various *Bacteroides* species are the microbes most commonly isolated.[39]

Clinical Features

Clinical presentation is characterized by the onset of high fever, chills, right upper quadrant pain, nausea, and vomiting. Patients generally have an acute presentation and appear quite ill, particularly if there is underlying cholangitis. A more insidious chronic presentation, although atypical, has been described. Physical findings include elevated temperature, right upper quadrant tenderness, hepatomegaly, and occasionally dullness to percussion and decreased breath sounds over the right lower chest. Jaundice may be apparent, especially if coexistent biliary tract obstruction is present.

Diagnostic Strategies

Laboratory findings include leukocytosis in 70 to 80% of cases, elevated alkaline phosphatase in up to 90%, and bilirubin in excess of 2 mg/dL in 50% of patients. Serum aminotransferase levels commonly are elevated to two to four times normal. Chest radiographs may reveal a right pleural effusion, basilar atelectasis, or an elevated right hemidiaphragm.[39]

Many imaging techniques are useful in delineating hepatic abscesses, including ultrasonography, CT scan (Figs. 90-4 and 90-5), and magnetic resonance imaging (MRI). In the ED, ultrasonography and CT scan are the most sensitive and expeditious modalities.

Differential Considerations

The differential diagnosis of pyogenic hepatic abscess includes amebic liver abscess, hepatitis, and cholangitis, as well as pancreatic and subphrenic abscess. Although clinical evaluation may not

www.ketabpezeshki.com 66485457-66963820

allow definitive diagnosis, appropriate use of imaging techniques generally does.

Management

The initial treatment of a pyogenic hepatic abscess is hemodynamic stabilization, intravenous antibiotics, and pain control. Pending definitive microbial identification, broad-spectrum antibiotic coverage should be provided. Triple antibiotic coverage is warranted and should include an aminoglycoside or third-generation cephalosporin for gram-negative coverage, metronidazole or clindamycin for anaerobes, and ampicillin for streptococcal species.

Definitive treatment requires abscess drainage. This usually is done percutaneously, with open surgical drainage reserved for complex cases associated with intraperitoneal soiling, intestinal perforation, or biliary obstruction. Complications include rupture of the abscess into the peritoneal cavity or an adjacent anatomic structure (e.g., the thoracic cavity, lung, pericardium).

Disposition

Patients with pyogenic hepatic abscess require admission to the hospital. Consultation with a general surgeon, gastroenterologist, or interventional radiologist will be necessary.

Amebic Abscess

Principles of Disease

Amebiasis is one of the most common protozoal infections worldwide. Up to 10% of the world's population and approximately 1 to 2% of the U.S. population may be infected. Transmission generally occurs by way of the fecal-oral route and usually is a consequence of ingesting contaminated water or foodstuffs. The illness is more common in homosexual men, presumably as a result of oral-anal contact during sexual activity. Although intestinal disease is by far the most common manifestation of infection, extraintestinal disease is not rare, with the liver most commonly affected. *Entamoeba histolytica* is the only ameba responsible for invasive disease, and evidently only certain varieties of *E. histolytica* are pathogenic. Pathogenic amoebae reach the liver after invasion of the intestinal mucosa and transit through the portal vein. As with a pyogenic abscess, involvement of the right liver lobe is more common.

Clinical Features

The clinical presentation generally is acute, with fever, chills, abdominal pain, nausea, and vomiting. Diarrhea is common in children but is present in less than one third of adults. Careful questioning of patients without diarrhea often yields a history of intestinal illness several weeks before. Many patients complain of cough, which can serve to direct attention away from the liver.

Chronic illness of several months' duration, although less common than the acute presentation, has been described.[40] Physical examination reveals an elevated temperature, right upper quadrant tenderness, hepatomegaly, and dullness with decreased breath sounds over the right lower chest.

Diagnostic Strategies

Laboratory parameters are not specific. Neutrophilic leukocytosis is common. Alkaline phosphatase is elevated in 75% of cases and aminotransferases in 50%. Hyperbilirubinemia is uncommon and when present is indicative of biliary obstruction. The chest radiograph may reveal a right pleural effusion, basilar atelectasis, or an elevated right hemidiaphragm. Ultrasound imaging of the liver can be diagnostic, revealing a peripherally based mass with well-circumscribed borders and a heterogeneous hypoechoic center. Nuclear scintigraphy with technetium, CT scan, and MRI are alternative imaging modalities if ultrasonography is inconclusive.

Diagnosis is supported by identification of a pathogenic protozoan in the stool. Even in cases of invasive intestinal disease, however, the yield may be low. An enzyme-linked immunosorbent assay (ELISA) or counterimmune electrophoresis generally is preferred. The indirect hemagglutination test remains positive for an extended period and is therefore not helpful in establishing the presence of acute infection.

Differential Considerations

The correct diagnosis is not often made in the ED.[40] In order of their frequency of occurrence, considerations in the differential diagnosis of an amebic liver abscess include pyogenic abscess, biliary tract disease, hepatitis, pneumonia, appendicitis, and pancreatitis. Respiratory symptoms and abnormalities on the chest radiograph may cause confusion with pulmonary illnesses. Hepatic imaging is helpful in establishing the correct diagnosis; however, differentiation from pyogenic illness may still be difficult.

Management

Management consists of supportive therapy and initiation of amebicidal therapy. Metronidazole, 750 mg PO or IV three times daily for 7 to 10 days, is the therapeutic agent of choice. Most patients will respond to this regimen. Percutaneous catheter drainage is required only in refractory or complicated cases.

The most serious complication of amebic liver disease is rupture into adjacent anatomic structures. Involvement of the lung occurs in 20 to 35% of cases of extrahepatic disease, often manifesting with signs and symptoms of massive pleural effusion or consolidative pneumonia. With rupture into a bronchus, the patient can have cough productive of an anchovy paste–like substance or necrotic debris, or frank hemoptysis. Abdominal pain with peritonitis can result from rupture into the abdominal cavity. Involvement of the pericardium occasionally is seen with lesions in the left lobe of the liver and can be catastrophic, either acutely as a consequence of pericardial tamponade or chronically from constrictive pericarditis.

Disposition

Select patients with amebic liver abscess can be managed as outpatients. This approach is best suited for persons with mild clinical disease, stable living circumstances, and adequate access to medications as well as follow-up care. In patients with more severe disease, evidence of complications, or questionable social circumstances, hospitalization is advised.

MISCELLANEOUS DISORDERS AND CONDITIONS OF THE LIVER

Chronic Hepatitis

Chronic hepatitis is defined as persistent inflammation of the liver for at least 6 months. Chronic persistent hepatitis (CPH) is characterized clinically by a lack of symptoms, persistent mild complaints, or intermittent episodes of moderate hepatitis. Despite persistent elevation of aminotransferases, CPH rarely progresses to hepatic failure or cirrhosis. Chronic active hepatitis (CAH), on the other hand, commonly progresses to cirrhosis. CAH initially

www.ketabpezeshki.com 66485457-66963820

may follow a clinical course indistinguishable from that of CPH; however, biopsy of the liver, even early in the disease, reveals diffuse inflammation, bridging necrosis, and evidence of scarring and macronodular cirrhosis.

The causes of chronic hepatitis include all of the recognized causes of acute hepatitis; however, the chronic form is rare with HAV infection. It may occur in 5 to 10% of patients with HBV infection, in 50 to 60% of those with HCV infection, and probably in an even greater percentage of patients with HDV infection.[13] The incidence of chronic disease from other causes is closely related to the reversibility of the metabolic or immunologic disorder or to the duration of exposure to the incriminated toxic substance.

Chronic hepatitis, in its precirrhotic stage, rarely causes ED presentations. It is not unusual, however, for an elevated aminotransferase level to be detected during the course of evaluation of some seemingly unrelated entity. Evaluation generally is limited to obtaining a careful history and ordering appropriate viral serologic studies (HBsAg, HBeAg, and anti-HCV assays). The active treatment of CAH goes beyond the bounds of the ED. Referral to an internist or gastroenterology specialist is advisable.

Liver Disease in Pregnancy

The two primary hepatic disorders associated with pregnancy are benign cholestasis and acute fatty liver. Cholestasis is common and appears to have a familial linkage. Onset is in the third trimester and is heralded by the development of progressive pruritus. Bilirubin may be elevated but not dramatically, so jaundice is uncommon. Laboratory tests reveal elevated alkaline phosphatase, 5′-nucleotidase, and bilirubin. Although the chief concern to the mother is discomfort from pruritus, the illness can bode poorly for the fetus, with increased incidence of prematurity, stillbirth, and fetal distress. Malabsorption of vitamin K can result in serious coagulopathy in the fetus, predisposing to spontaneous intracranial hemorrhage. Treatment is supportive and should include subcutaneous vitamin K for the mother antepartum and for the newborn after delivery. Cholestasis resolves without incident after delivery.

Acute fatty liver of pregnancy is a malignant disorder that, if unrecognized, can progress rapidly to maternal and fetal demise. The incidence is approximately 1 in 7000 live births. The illness occurs in the latter part of the third trimester and is more common in primigravidas and twin pregnancies. The initial clinical features include fatigue, anorexia, nausea, and vomiting. Abdominal pain may be present, most prominently in the midepigastrium and right upper quadrant. Physical examination may reveal mild jaundice and abdominal tenderness. The liver may not be palpable because of the enlarged uterus.

Abnormal laboratory findings include moderate elevation of aminotransferases (5 to 10 times normal) hyperbilirubinemia, hypoglycemia, and evidence of disseminated intravascular coagulation (prolonged PT and partial thromboplastin time, hypofibrinogenemia, elevated fibrin split products, and thrombocytopenia). Treatment involves aggressive fluid and electrolyte support, glucose administration, and immediate delivery. Liver disease generally resolves without permanent sequelae after delivery.

Budd-Chiari Syndrome

Budd-Chiari syndrome is a disorder of the liver caused by hepatic venous outflow obstruction located anywhere above the level of hepatic venules. It is an uncommon disorder with a prevalence of 1 in 100,00 worldwide and is more common in females. The disorder is associated with hypercoagulable states, such as factor V Leiden, protein S and C deficiency, thrombophilia, antithrombin III deficiency, myeloproliferative disorder, Behçet's disease, paroxysmal nocturnal hemoglobinuria, and oral contraceptive use.[41,42] In Asia, an association with a membranous obstruction of the inferior vena cava has been reported.[42]

Clinical presentation is variable, ranging from fulminant hepatic failure in acute high-grade obstruction to the insidious onset of jaundice and ascites in more subacute forms. Fulminant disease is clinically indistinguishable from acute hepatic necrosis from hepatocellular disease secondary to viral infection. It is important to make the distinction between these two causes of hepatic failure early because treatment options differ. Prompt intervention in patients with Budd-Chiari syndrome offers the possibility of effective relief of signs and symptoms with potentially favorable outcome.

Doppler ultrasound imaging is reported to have sensitivity of 85 to 95% for diagnosis of Budd-Chiari syndrome and emerges as the diagnostic modality of choice in the ED setting.[41]

Management of Budd-Chiari syndrome relates to the severity and acuity of disease. Previously diagnosed disease with worsening ascites can be managed with modification of diuretics and therapeutic paracentesis, followed by referral to a primary care physician or gastroenterology specialist. Newly diagnosed Budd-Chiari syndrome with acute decompensation will require immediate consultation and consideration for transjugular intrahepatic portosystemic shunt placement or percutaneous angioplasty or thrombolytic therapy. Portacaval shunting and liver transplantation are options for disease refractory to medical or other less invasive percutaneous interventions.[41,43,44]

Hepatic Cancer

Hepatocellular carcinoma is the most common primary hepatic malignancy. It is especially common in undeveloped areas of the world, particularly in regions in which chronic HBV infection is prevalent. In parts of Korea and Mongolia, the incidence of hepatocellular carcinoma approaches 48 to 98 per 100,000 population; in the United States, it is below 10 per 100,000.[45] It has been estimated that 75 to 80% of primary liver cancer is attributable to persistent viral infections with either HBV (50 to 55%) or HCV (25 to 30%).[45] Associations beyond HBV include infection with *Clonorchis* and schistosomiasis, chronic alcoholic liver disease, primary biliary cirrhosis, hemochromatosis, and several chemical agents (e.g., estrogens, androgens, the contrast agent Thorotrast, vinyl chloride, aflatoxins, tobacco). Metastases to the liver from GI, lung, breast, or other tumors are more common than primary malignancy in the United States.

The clinical presentation of hepatic carcinoma or metastases is nonspecific. Symptoms and signs may include nausea, vomiting, jaundice, and right upper quadrant abdominal pain. Physical examination may reveal evidence of recent weight loss or cachexia. Hepatocellular carcinoma is linked with cirrhosis; many of these patients have manifestations of that process on presentation. An enlarged liver, particularly in patients with a history of cirrhosis, is strongly suggestive of malignant transformation. Although results of laboratory tests (e.g., blood count, aminotransferase measurements, bilirubin assay) often are abnormal, these tests are nonspecific and generally are of little aid in diagnosis. Alpha-fetoprotein often is elevated in patients with a hepatoma but is nonspecific and of limited use in diagnosis. Ultrasound imaging, CT scan, and MRI of the liver all are effective means of identifying tumor. Liver biopsy is recommended for the definitive diagnosis of hepatoma; biopsy of an alternative site may be preferable in cases of metastatic disease.

Management in the ED is limited to supportive measures, provision of analgesic agents, and possibly nutritive supplementation. Hepatitis B and C serologic studies should be performed in cases of hepatoma to determine linkage with chronic HBV infection and to assess infection risk to family members.

www.ketabpezeshki.com 66485457-66963820

Liver Transplantation

Human orthotopic liver transplantation was pioneered in the 1960s, and approximately 5000 liver transplant procedures are now performed annually in the United States. The 5-year survival rate generally is reported to be approximately 80%, but complications are common.[46] Early complications include bleeding, acute rejection, vascular and biliary tract problems, and infection. Delayed complications include malignancy, recurrence of underlying disease, infection, chronic rejection, medication toxicity, and renal failure. Many early complications will manifest during the immediate postoperative period while the patient is in the hospital or being closely followed by the transplantation team. Delayed complications may occur a year or more after transplantation.

The clinical signs that lead the transplant recipient to seek care in the ED are related to the nature of the underlying problem. The signs of malignancy or recurrence of underlying disease will mirror those in the patient who has not undergone transplantation. Infectious complications will be relatively straightforward when common pyogenic organisms are involved; however, liver transplant recipients are at increased risk for opportunistic infections as a consequence of their immunosuppressive therapy. Presenting signs and symptoms may be subtle. Chronic rejection manifests with low-grade temperature elevation, fatigue, and jaundice. Expected laboratory abnormalities include elevated bilirubin and transaminases, prolonged PT or INR, and low serum albumin. Renal failure may not be clinically apparent until the glomerular filtration rate has declined significantly. Routine serum creatinine measurement is the best means of identifying this disorder early, when successful intervention is still possible.

The most common immunosuppressive agents used after liver transplantation include corticosteroids, cyclosporine, tacrolimus, sirolimus, mycophenolate, and azathioprine. Corticosteroid toxicity may produce glucose intolerance, osteoporosis, gastric ulceration, and muscle wasting. Cyclosporine and tacrolimus can cause renal impairment, which is the most common dose-limiting effect of these agents. Azathioprine can be hepatotoxic but is more often associated with bone marrow suppression, placing the patient at increased risk for infectious complications and bleeding diathesis.

Management of patients with complications related to their liver transplant is directed by the nature of the problem. Infections are evaluated and managed in the usual fashion, with emphasis on evaluation of the patient's underlying immune function and a search for uncommon pathogens. Accordingly, assessment may include complete blood count and measurement of glucose, BUN, creatinine, serum electrolytes, transaminases, bilirubin, and albumin, as well as coagulation studies. Hepatobiliary imaging is indicated if tumor, vascular occlusion, or biliary tract obstruction is suspected. Ultrasound studies with Doppler interrogation can be particularly useful in the ED setting. Consultation with a transplantation specialist is recommended for any patient with a problem potentially related to the organ transplant or immune-modulating medications.

BILIARY TRACT DISORDERS

GENERAL PERSPECTIVE

The biliary tract is composed of the hepatic bile canaliculi, intrahepatic and extrahepatic bile ducts, the common bile duct, and the gallbladder. Bile, required for absorption of fats and fat-soluble nutrients, is produced in the canaliculi. During the fasting state, approximately 50% of the bile produced flows directly into the duodenum; the other half is stored in the gallbladder. The gallbladder serves to acidify and concentrate the bile and can store up to 50 mL of bile for immediate availability at the time of feeding. The presence of food in the stomach, in particular fat, results in both vagal impulses and the secretion of cholecystokinin-pancreozymin, which serve as potent stimuli for gallbladder contraction. Removal of the gallbladder generally is not associated with measurable changes in intestinal fat absorption or in clinical symptomatology.

Biliary tract disorders constitute a relatively common cause of presentation to the ED. Signs and symptoms typically result from obstruction of the biliary tree. The clinical picture is variable but often includes abdominal pain, which may or may not be referred; nausea and vomiting; and jaundice.

SPECIFIC DISORDERS

Cholelithiasis

As noted, the principal cause of biliary tract disease is related to the development of gallstones. It is estimated that 20% of women and 8% of men have gallstones, resulting in approximately 500,000 operations annually.

Principles of Disease

There are two categories of gallstones. *Cholesterol stones* most commonly occur as a consequence of an elevated concentration of cholesterol in bile relative to the other principal constituents, bile acids and phospholipids. Bile acids and lecithin, the primary bile phospholipid, act in concert to solubilize cholesterol. As cholesterol levels rise or bile acids and lecithin levels decline, cholesterol has an increasing tendency to form crystals. These crystals, particularly in an incompletely emptying gallbladder, serve as a nidus for stone formation. Factors associated with an enhanced risk of cholesterol stone formation include increased age, female gender, massive obesity, rapid weight loss, cystic fibrosis, parity, drugs (e.g., clofibrate, oral contraceptive agents), and familial tendency. The hereditary nature of cholelithiasis is most dramatically demonstrated by the high concordance for stone formation in monozygotic twins and the exceedingly high incidence of cholelithiasis among Pima Indians.[47]

Two varieties of *pigmented stones* have been identified: black and brown. Black stones occur exclusively in the gallbladder and contain a high concentration of calcium bilirubinate. They are more commonly encountered in elders and have a strong association with diseases that cause intravascular hemolysis (e.g., sickle cell anemia, hereditary spherocytosis). Brown stones are associated with infection and can form in both the gallbladder and the intrahepatic and extrahepatic bile duct system. Although bacterial infections are most commonly incriminated, parasites (e.g., *Ascaris lumbricoides, Clonorchis sinensis*) have also been linked to brown stone formation. Both types of pigmented stones contain calcium bilirubinate and therefore may be visible on plain abdominal radiographs. For a stone to be radiopaque, it must contain at least 4% calcium by weight.

Clinical Features

The most common clinical manifestation of cholelithiasis is biliary colic. The pathophysiology of this process is not entirely clear, but it appears to be related to the passage of small stones from the gallbladder through the cystic duct into the common bile duct. The term *colic* is often misleading; affected patients commonly report steady pain, rather than intermittent or cramping discomfort. The pain most often is perceived in the right upper quadrant but may be localized over a wide region of the upper abdomen. Radiation of pain, if it occurs, generally is to the base of the scapula or shoulder. Associated signs and symptoms include nausea and vomiting, which may be severe enough to lead to fluid

www.ketabpezeshki.com 66485457-66963820

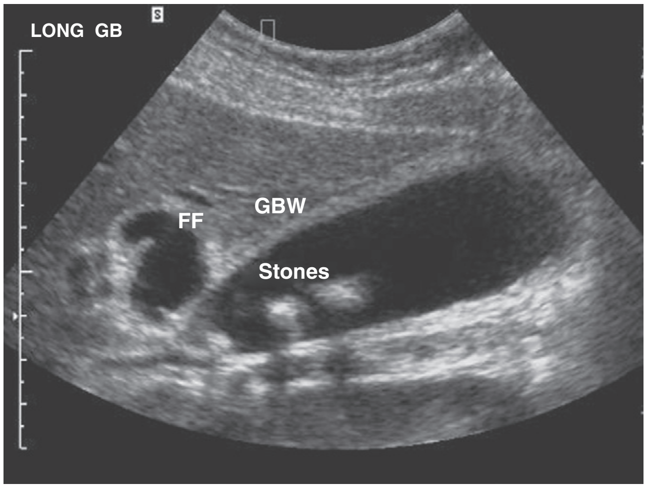


Figure 90-6. Gallbladder with gallstones *(Stones),* thickened gallbladder wall *(GBW),* and pericholecystic fluid *(FF).* Together these findings constitute the sonographic signs of cholecystitis.

and electrolyte imbalance. Patients with biliary colic commonly report similar self-limited occurrences in the past and may offer an association between symptom onset and eating. A relationship between fatty food ingestion and symptoms is as likely to occur in patients with gallstones as it is in those without. Physical examination usually reveals mild tenderness to palpation without guarding or rebound in the right upper quadrant or epigastric region.

Diagnostic Strategies

No pathognomonic clinical laboratory findings are recognized; results of commonly performed tests typically are within normal limits. Important tests to perform include ALT and AST measurements to evaluate for the presence of hepatitis, bilirubin and alkaline phosphatase determinations to look for evidence of common duct obstruction, and lipase assay to assess for the presence of pancreatitis.

The diagnosis of biliary colic is made clinically in conjunction with demonstration of stones in the gallbladder. Plain radiography has little role in the evaluation of cholelithiasis because only a minority of stones have sufficient calcium to allow visualization. Ultrasonography is the procedure of choice for investigating the gallbladder. Ultrasound imaging can be performed rapidly, is highly sensitive, and provides the added utility of permitting evaluation of surrounding structures (Fig. 90-6). Ultrasonography also can be used in the ED setting, adding further convenience to the patient and reducing turnaround times. Oral cholecystography with use of iopanoic acid is an alternative when ultrasonography either is not available or cannot be performed successfully. This technique can identify gallstones in 95% of patients with cholelithiasis in whom visualization of the gallbladder can be achieved.

Differential Considerations

Considerations in the differential diagnosis of biliary colic include cholecystitis, peptic ulcer disease of the stomach or duodenum, pancreatitis, and hepatitis. Patients with cholelithiasis may occasionally have chest pain, so cardiopulmonary syndromes must be considered as well. A compatible clinical history in conjunction with normal laboratory test values (ALT, AST, lipase, and alkaline phosphatase), gallstones on ultrasound imaging, and minimal or no tenderness in the right upper quadrant favors the diagnosis of cholelithiasis. If abnormalities are visualized, a chest radiograph or electrocardiogram may help differentiate between cardiopulmonary and biliary pathology.

Management

The initial management of biliary colic is directed at correction of fluid and electrolyte disturbances and relief of symptoms. Vomiting is managed with antiemetics and, if necessary, nasogastric suction. Pain often can be controlled with antispasmodics (e.g., glycopyrrolate), nonsteroidal antiinflammatory agents, and opiate analgesic agents as needed. With clinical evidence of volume depletion, adequate intravenous fluid replacement is indicated.

The definitive management of cholelithiasis usually involves surgical removal of the gallbladder; however, other options are available. Oral administration of bile acid (e.g., chenodeoxycholate, ursodeoxycholate) over a period of months to years can result in dissolution of small- to medium-sized stones. Extracorporeal shock wave lithotripsy may be successful in a select, technically suitable set of patients who have functioning gallbladders and ideally have a small number of stones.

The most common complication of biliary colic is fluid and electrolyte imbalance secondary to vomiting. Other adverse consequences include Mallory-Weiss tear, from uncontrolled emesis, and cholangitis, from unrecognized and persistent common bile duct obstruction.

Special Considerations

Biliary colic is an uncommon symptom in children, in whom it most often is associated with an underlying hemolytic disorder (e.g., sickle cell anemia or spherocytosis). Acute management of biliary colic is the same for children as for adults.

Cholelithiasis may be encountered in pregnant women. Diagnosis in this population is made more difficult by the common occurrence of nausea and vomiting, particularly in the first trimester, and the presence of an enlarged uterus in later pregnancy, which alters anatomic relationships and interferes with abdominal examination. Ultrasound imaging is of considerable diagnostic use in this setting. Treatment in the ED is comparable to that for the nonpregnant patient; however, definitive therapy generally is delayed until after parturition.

Cholecystitis

Perspective

Acute cholecystitis is defined as sudden inflammation of the gallbladder. The incidence ranges from 5 to 19% among patients undergoing surgery for biliary tract disorders. The risk factors for cholecystitis are similar to those for cholelithiasis: female gender, increasing age and parity, and obesity. Although gallstones play a prominent role in the pathogenesis of cholecystitis, a minority of cases are categorized as acalculous.

Principles of Disease

Obstruction of the cystic duct appears to be the critical factor in the development of gallbladder inflammation. Gallstones are identified in 95% of patients with cholecystitis and may be located in the common bile duct in many patients with acalculous cholecystitis. Causes of cystic duct obstruction unrelated to stone disease include tumor, lymphadenopathy, fibrosis, parasites, and kinking of the duct. Regardless of cause, obstruction of the cystic duct leads to filling and distention of the gallbladder. The ensuing inflammatory reaction may be related to mucosal ischemia from increased hydrostatic pressure or to the action of cytotoxic products of bile metabolism (e.g., lysophosphatidylcholine).

www.ketabpezeshki.com 66485457-66963820

Although bacteria are isolated from the bile of inflamed gallbladders in a majority of cases, the role of infection in the pathogenesis of cholecystitis is not completely understood. Coliforms (e.g., *E. coli*) represent the most common isolates, but anaerobes have been identified in as many as 40% of cases.

Clinical Features

The most common presenting symptom of cholecystitis is pain, usually in the right upper quadrant. Although the pain initially may be described as colicky, it will become constant in virtually all cases. A previous history of similar but less severe and self-limited symptoms is a valuable diagnostic clue, as is documentation of previous gallstones. Radiation of pain generally is to the tip of the scapula on the right. Nausea and vomiting are typical features, and the patient may exhibit fever.

Physical examination reveals tenderness in the right upper quadrant or epigastric region, often with guarding or rebound. Murphy's sign (tenderness and an inspiratory pause elicited by palpation of the right upper quadrant during a deep breath) is compatible with, but not specific for, gallbladder inflammation. Fever and tachycardia are commonly absent, so cholecystitis remains a diagnostic consideration in the absence of these findings in patients with abdominal pain and right upper quadrant pain and tenderness to palpation.

Diagnostic Considerations

A polymorphonuclear leukocytosis with left shift is common, but the WBC count has been reported to be in a normal range in up to 40% of patients.[48] Serum aminotransferase, bilirubin, and alkaline phosphatase may be mildly elevated but more often are within normal limits. An elevated lipase level should suggest the diagnosis of pancreatitis, either instead of or in addition to cholecystitis. Plain abdominal radiographs may reveal calcified stones, gas in the gallbladder, or an upper quadrant sentinel loop. These findings are so uncommon and nonspecific, however, that plain radiography is not recommended unless other diagnostic considerations are present.

Ultrasound imaging is the most useful test in the ED setting. Visualization of the gallbladder without identification of stones has an extremely high negative predictive value for cholecystitis, whereas the presence of stones, a thickened gallbladder wall, and pericholecystic fluid has a positive predictive value in excess of 90% (Fig. 90-7).

Nuclear scintigraphy with technetium-99m–labeled iminodiacetic acid (IDA) generally is considered the most sensitive and specific imaging test for cholecystitis. IDA administered IV is taken up by hepatocytes and secreted into the bile canaliculi. Failure to obtain an outline of the gallbladder within 1 hour of administration of IDA in the face of hepatic and common duct visualization proves cystic duct obstruction. In the appropriate clinical setting, this finding is diagnostic of cholecystitis. Conversely, visualization of the gallbladder and common duct within 1 hour of administration has a high negative predictive value. Scintigraphy with IDA loses its sensitivity as serum bilirubin rises above 5 to 8 mg; however, scintigraphy with diisopropyl IDA (diisopropyl iminodiacetic acid, or mebrofenin) allows visualization of the biliary tree in patients with total serum bilirubin in the range of 20 to 30 mg. Although not the preferred imaging modality, CT can identify cholecystitis with a reported sensitivity of 92% and a specificity of 99%. It is of particular value in cases of emphysematous and hemorrhagic cholecystitis.[49]

Differential Considerations

Diagnostic considerations in the patient suspected of having cholecystitis include hepatitis, hepatic abscess, pyelonephritis, right lower lobe pneumonia or pleurisy, pancreatitis, peptic ulcer disease of the duodenum with perforation or penetration, and appendicitis. Accurate diagnosis often requires the use of sonographic or, less commonly, scintigraphic or CT studies.

Management

Basic supportive measures provide the foundation for initial management of acute cholecystitis. Volume status should be optimized with intravenous crystalloid administration. Emesis can be managed with antiemetics and nasogastric suction. Nasogastric suctioning may have the added benefit of diminishing the stimulus for biliary secretion and excretion, thereby adding to pain relief. Narcotic analgesic agents are useful for pain control. Despite the questionable role of microbial infection in the pathogenesis of cholecystitis, antibiotics are recommended. Unless clinical evidence of sepsis exists, coverage with a single broad-spectrum antibiotic (e.g., a second- or third-generation cephalosporin) is adequate.

The most serious complication of cholecystitis is gangrene of the gallbladder, with necrosis and perforation. Localized perforation may lead to pericholecystic abscess or fistula formation, the

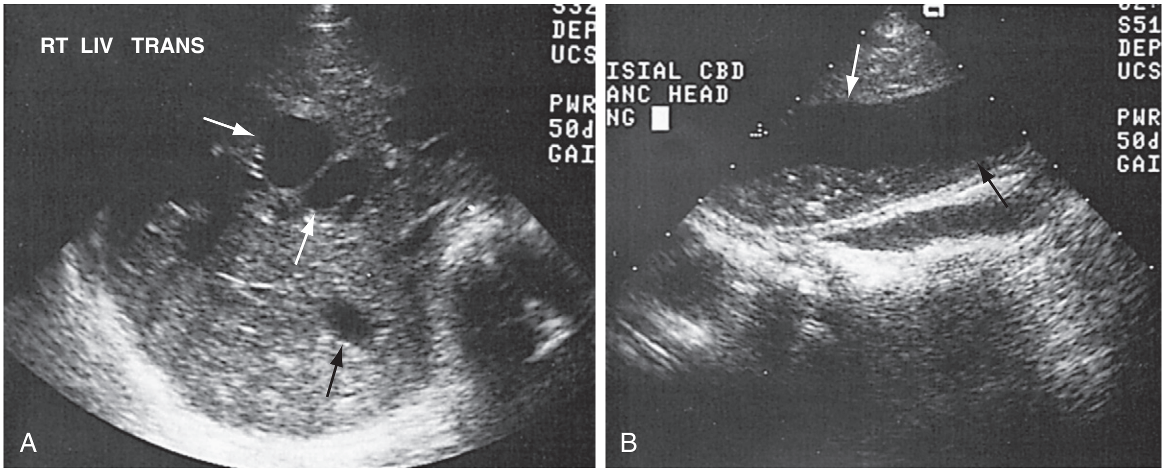


Figure 90-7. Abdominal ultrasound images from a patient with common bile duct obstruction. **A,** Multiple dilated intrahepatic ducts *(arrows)*. **B,** Significant dilated common bile duct *(arrows)*. The duct measures 2 cm in diameter.

www.ketabpezeshki.com 66485457-66963820

latter predisposing to gallstone ileus at a later date. Patients with diabetes mellitus are at increased risk for bacterial invasion of the gallbladder wall and for the development of emphysematous cholecystitis.

Disposition

Hospitalization for antibiotic therapy and pain management is required. Surgery is recommended for patients with cholecystitis; however, optimal timing for operation is not certain. Surgery usually is performed after symptoms have subsided but while the patient is still hospitalized.[50] Immediate cholecystectomy or cholecystotomy is reserved for the complicated case in which the patient has gangrene or perforation.

Special Considerations

Cholecystitis is uncommon in the pediatric age group; when it occurs, however, pediatric cholecystitis should be managed as in the adult. Cholecystitis in the pregnant woman poses challenges in both diagnosis and therapy. Initial therapy is identical to that for the nonpregnant patient, but the issue of surgical intervention requires an individualized consultation between surgeon and obstetrician.

Acalculous cholecystitis is more common in elders and most often is encountered in patients who are recovering from non–biliary tract surgery. Over the past decade, acalculous disease has been increasingly encountered as a complication of advanced acquired immunodeficiency syndrome (AIDS), usually secondary to infection with cytomegalovirus (CMV) or *Cryptosporidium.* In comparison with calculous disease, acalculous cholecystitis tends to have a more acute and malignant course, with a high mortality rate. The same techniques are used to diagnose acalculous disease as in other forms of cholecystitis but are less sensitive and specific for this entity. Sonographic findings include thickening of the gallbladder wall, pericholecystic fluid, and lack of response to cholecystokinin. Scintigraphic findings are the same as in calculous disease.

Emphysematous cholecystitis is an uncommon variant of cholecystitis, occurring in approximately 1% of cases. It is characterized by the presence of gas in the gallbladder wall, presumably consequent to the invasion of the mucosa by gas-producing organisms (e.g., *E. coli*, *Klebsiella* species, *Clostridium perfringens*). It is more common in diabetic patients, has a male predominance, and is acalculous in up to 50% of cases. Clinical presentation and physical findings are similar to those in cholecystitis. Plain radiographs or CT scans of the abdomen will reveal gas in the gallbladder wall. Because of a high incidence of gangrene and perforation, emergency cholecystectomy is recommended. Antibiotic coverage should include penicillin, an aminoglycoside, and clindamycin or an ampicillin-sulbactam combination agent. The mortality rate for emphysematous cholecystitis is approximately 15%.

KEY CONCEPTS

- The vast majority of patients with cholecystitis have gallstones; however, approximately 7 to 9% have acalculous disease. The latter group of patients tend to have more severe disease and are at increased risk for complications.
- Despite an unclear relationship between bacterial infection and pathophysiology, antibiotic therapy is recommended.
- Patients with acalculous and emphysematous cholecystitis are at increased risk for gangrene and perforation and require emergency cholecystectomy.

Cholangitis

Perspective

Acute obstructive cholangitis was first described by Charcot in 1877. Cholangitis most often is a consequence of common duct blockage by a gallstone but may be associated with malignancy or a benign stricture.

Principles of Disease

The key factors in the pathogenesis of cholangitis are obstruction, elevated intraluminal pressure, and bacterial infection. Incomplete obstruction occurs more commonly than complete blockage. Bacteria may gain access to the obstructed common duct either in a retrograde manner from the duodenum, by way of the lymphatics, or from portal vein blood. The most commonly encountered organisms are similar to those encountered in other varieties of biliary tract disease: *E. coli* and *Klebsiella, Enterococcus,* and *Bacteroides.*

Clinical Features

Patients most often experience fever, chills, nausea, vomiting, and abdominal pain. The classic triad of physical findings first described by Charcot consists of right upper quadrant pain, fever, and jaundice. Although these findings are compatible with cholangitis, they also can be seen with both cholecystitis and hepatitis. Sepsis is a common complication and may be heralded by tachycardia, tachypnea, and frank hypotension. The presence of Charcot's triad along with the clinical signs of sepsis—hypotension and altered sensorium—is referred to as Reynolds' pentad.

Diagnostic Considerations

Common laboratory abnormalities include polymorphonuclear leukocytosis, hyperbilirubinemia, elevated alkaline phosphatase, and moderately increased aminotransferases. Arterial blood gas (ABG) measurements are useful to identify base deficit as an early sign of sepsis.

Sonography can be helpful if it demonstrates common and intrahepatic ductal dilation, whereas identification of stones in the gallbladder or common duct suggests the underlying cause of obstruction (see Fig. 90-7). Although nuclear scintigraphy cannot determine the cause, it appears to be a more sensitive means to diagnose early obstruction. Several studies have demonstrated a high incidence of nonvisualization of the biliary tree with cholescintigraphy in patients with common duct obstruction when sonography failed to identify dilation.[49]

Alternative imaging techniques include CT scan, percutaneous transhepatic cholangiography (THC), and endoscopic retrograde cholangiopancreatography (ERCP). Although these techniques may be more expensive and time-consuming, the last two have the added benefit of offering potential therapeutic benefit. Endoscopic cholangioscopy can permit culture of bile, direct removal of obstructing stones, or decompression of the biliary tree by sphincterotomy or stent placement.

Differential Considerations

Although patients with cholangitis generally have a higher fever and appear more ill than those with cholecystitis, considerable variability and overlap are possible. The presence of jaundice is the clinical sign most helpful in differentiating between these two disorders. An elevated bilirubin level is characteristic of cholangitis and uncommon in cholecystitis. Ultrasonographic evidence of

www.ketabpezeshki.com 66485457-66963820

dilated common and intrahepatic ducts usually is required to distinguish cholangitis from cholecystitis.

Management

Treatment of cholangitis includes hemodynamic stabilization with crystalloid fluid and, if necessary, vasopressors. Broad-spectrum antibiotic coverage should be initiated immediately after blood culture specimens have been obtained. The choice of antibiotics should be guided by local sensitivities and must provide coverage for enteric microbes. Therapies include pieracillin/tazobactam, mezlocillin, imipenem, meropenem, ticarcillin/clavulanate, and ampicillin/sulbactam (which may be combined with metronidazole). Combination therapy includes a regimen of extended-spectrum cephalosporin, metronidazole, and ampicillin. The key to successful treatment is early biliary tract decompression. This can be achieved with THC, ERCP, or surgery.

Disposition

Patients with cholangitis will require hospitalization, preferably in a monitored setting. Prompt consultation with a service that can provide for biliary tract decompression (surgery, interventional radiology, or gastroenterology) is necessary.

KEY CONCEPTS

- Cholangitis is an emergency condition resulting from extrahepatic bile duct obstruction and bacterial infection.
- Effective management requires prompt administration of broad-spectrum antibiotics and early biliary tract decompression.
- Biliary tract decompression can be achieved surgically, transhepatically, or by ERCP.

Sclerosing Cholangitis

Sclerosing cholangitis is an idiopathic inflammatory disorder affecting the biliary tree. It is characterized by diffuse fibrosis and narrowing of the intrahepatic and extrahepatic bile ducts. It is commonly associated with inflammatory bowel disease, particularly ulcerative colitis; however, in 25% of cases it appears as an isolated disorder.

Patients usually report weight loss, lethargy, jaundice, and pruritus. Rarely, infective cholangitis may develop. Prompt diagnosis may be more difficult in these cases because of the sclerotic nature of the bile ducts and the absence of duct dilation on ultrasound imaging. Surgical exploration or ERCP often is required for diagnosis. The management of uninfected cases is primarily symptomatic. Cholestyramine, a bile acid sequestrant, may diminish pruritus.

AIDS Cholangiopathy

Manifestations of advanced HIV disease, generally associated with CD4+ counts less than 200/mm^3, may include any one of a group of disorders collectively referred to as *AIDS cholangiopathy.* These disorders include bile duct stricture, papillary stenosis, and sclerosing cholangitis. The precise pathophysiology is not completely understood but is related to infection with CMV, *Cryptosporidium,* microsporidia, or *Mycobacterium avium* complex. Clinical presentation may be similar to that in other causes of cholangitis, with fever and right upper quadrant pain. Laboratory test results include increased levels of alkaline phosphatase and minor elevation of transaminases. Bilirubin is less commonly elevated than in other disorders that cause cholangitis. Ultrasonography generally is helpful in identifying bile duct stricture, thickening, or dilation. IDA scans are useful, as they are in other causes of cholangitis. Management involves endoscopic sphincterotomy or stent placement in conjunction with treatment of the underlying infection.

Porcelain Gallbladder

The porcelain gallbladder is a dramatic radiographic finding caused by either linear or punctate calcifications within the gallbladder wall. Most patients are women, with a mean age in the 50s. Gallstones are commonly present. The gallbladder may be palpable in the right upper quadrant and is usually nontender to palpation. Patients with this disorder should be referred for cholecystectomy because of the high incidence of associated carcinoma.

Malignancy

Carcinoma of the biliary tract is uncommon. Gallbladder carcinoma is the most common malignancy of the biliary tract, accounting for 5% of all cancers found at autopsy. Gallbladder cancer is more frequent in patients with gallstones, especially if the gallstones are symptomatic and large. Other factors associated with gallbladder cancer include female gender, obesity, and high carbohydrate intake, all associated with gallstone disease. Metastatic disease to regional nodes and the liver is common at the time of initial diagnosis because of the relatively silent nature of early disease. Symptoms include chronic right upper quadrant pain and jaundice. Physical examination may reveal a palpable mass in the right upper quadrant. These tumors will occasionally perforate, and the patient may have symptoms of pericholecystic abscess. Noninvasive imaging techniques may be of some aid in identifying the tumor. Ultrasound imaging is more sensitive than CT, but even the sequential use of both tests fails to identify malignancy in 49% of cases.[51]

Carcinoma of the extrahepatic bile ducts is less frequent than gallbladder malignancy and is more common in men. Jaundice is the most frequent finding. A palpable gallbladder (Courvoisier's sign) may be present on physical examination in one third of cases. The diagnosis is suggested by the presence of dilated intrahepatic and extrahepatic bile ducts on sonography. THC and ERCP may serve to better delineate the location and extent of tumor. Scirrhous carcinomas may have a radiographic appearance similar to that of sclerosing cholangitis, and the two conditions can be effectively differentiated only with surgical biopsy. Both gallbladder and ductal carcinomas carry a similarly dismal prognosis, with 5-year survival rates. Carcinoma of Vater's ampulla is more common in elders and in males. The critical location of the ampulla results in relatively early symptomatology and thus a more prompt diagnosis. Ultrasound imaging is the most useful initial imaging technique, but GI endoscopy and ERCP generally are necessary to provide a definitive diagnosis. Early detection contributes to the more favorable prognosis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Centers for Disease Control and Prevention (CDC): Surveillance for acute viral hepatitis—United States, 2007. *MMWR Surveill Summ* 2009; 58:1-27.
2. McNabb SJ, et al: Summary of notifiable diseases—United States, 2005. *MMWR Morb Mortal Wkly Rep* 2007; 54:1.
3. Wasley A, Miller JT, Finelli L; Centers for Disease Control and Prevention (CDC): Surveillance for acute viral hepatitis—United States, 2005. *MMWR Surveill Summ* 2007; 56(SS-3):1.
4. Weinbaum C, Lyerla R, Margolis HS; Centers for Disease Control and Prevention: Prevention and control of infections with hepatitis viruses in correctional settings. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 2003; 52(RR-1):1.
5. Advisory Committee on Immunization Practices (ACIP), Fiore AE, Wasley A, Bell BP: Prevention of hepatitis A through active or passive immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2006; 55(RR-7):1.
6. Dienstag JL: Hepatitis B virus infection. *N Engl J Med* 2008; 359:1486-1500.
7. Iserson KV, Criss EA: Hepatitis B prevalence in emergency physicians. *Ann Emerg Med* 1985; 14:119.
8. Ganem D, Prince AM: Hepatitis B virus infection—natural history and clinical consequences. *N Engl J Med* 2004; 250:1118-1129.
9. Lok ASF, McMahon BJ: Chronic hepatitis B. *Hepatology*. 2007; 45:507-539.
10. Goodman JL: The safety and availability of blood and tissues—progress and challenges. *N Engl J Med* 2004; 351:819-822.
11. Armstrong GL, et al: The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006; 144:705.
12. Sulkowski MS, Thomas DL: Hepatitis C in the HIV-infected patient. *Clin Liver Dis* 2003; 7:261.

12a. Schreiber GB, Busch M, Kleinma S, Korelitz J: The risk of transfusion-transmitted viral infections. *N Engl J Med* 1996; 334:1685.

13. Yurdaydın C, Idilman R, Bozkaya H, Bozdayi AM: Natural history and treatment of chronic delta hepatitis. *J Viral Hepat* 2010; 17:749-756.
14. Wiwanitkit V: Hepatitis G virus RNA positivity among the voluntary blood donors: A summary. *Ann Hepatol* 2005; 4:43-46.
15. Jaeckel E, et al: Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med* 2001; 345:1452-1457.
16. Iserson KV, Criss EA, Wright AL: Hepatitis B and vaccination in emergency physicians. *Am J Emerg Med* 1987; 5:227.
17. Mast EE, et al: A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States. *MMWR Recomm Rep* 55:1, 2006.
18. Lauer GM, Walker BD: Hepatitis C virus infection. *N Engl J Med* 2001; 345:41.
19. Lucey MR, Mathurin P, Morgan TR: Alcoholic hepatitis. *N Engl J Med* 2009; 360:2758-2769.
20. Lieber CS: Alcoholic liver disease: New insights in pathogenesis lead to new treatments. *J Hepatol* 2000; 32:113.
21. Mathurin P, et al: Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): Individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. *J Hepatol* 2002; 36:480-487.
22. Angulo P: Nonalcoholic fatty liver disease. *N Engl J Med* 2002; 346:1221.
23. Bass NM, et al: Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* 2010; 362:1071-1081.
24. Butterworth RF: Pathophysiology of hepatic encephalopathy: A new look at ammonia. *Metab Brain Dis* 2002; 17:221.
25. Kircheis G, Wettstein M, Dahl S, Häussinger D: Clinical efficacy of L-ornithine-L-aspartate in the management of hepatic encephalopathy. *Metab Brain Dis* 2002; 17:453.
26. Kircheis G, Häussinger D: Management of hepatic encephalopathy. *J Gastroenterol Hepatol* 2002; 17:S260.
27. Hassanein TI, et al: Randomized controlled study of extracorporeal albumin dialysis for hepatic encephalopathy in advanced cirrhosis. *Hepatology* 2007; 46:1853.
28. Hassanein T, Oliver D, Stange J, Steiner C: Albumin dialysis in cirrhosis with superimposed acute liver injury: Possible impact of albumin dialysis on hospitalization costs. *Liver Int* 2003; 23:61.
29. Jalan R, et al: Extracorporeal liver support with molecular adsorbents recirculating system in patients with severe acute alcoholic hepatitis. *J Hepatol* 2003; 38:24.
30. Fernández J, et al: Bacterial infections in cirrhosis: Epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology* 2002; 35:1.
31. Evans LT, Kim WR, Poterucha JJ, Kamath PS: Spontaneous bacterial peritonitis in asymptomatic outpatients with cirrhotic ascites. *Hepatology* 2003; 37:897.
32. Wong CL, Holroyd-Leduc J, Thorpe KE, Straus SE: Does this patient have bacterial peritonitis or portal hypertension? How do I perform a paracentesis and analyze the results? *JAMA* 2008; 299:1166.
33. Castellote J, et al: Rapid diagnosis of spontaneous bacterial peritonitis by use of reagent strips. *Hepatology* 2003; 37:893.
34. Rimola A, et al: Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: A consensus document. *J Hepatol* 2000; 32:142.
35. Ginès P, Cárdenas A, Arroyo V, Rodés J: Management of cirrhosis and ascites. *N Engl J Med* 2004; 350:1646.
36. Runyon BA; AASLD Practice Guidelines Committee: Management of adult patients with ascites due to cirrhosis: An update. *Hepatology* 2009; 49:2087.
37. Lee WM: Drug-induced hepatotoxicity. *N Engl J Med* 2003; 349:474.
38. Soriano V, et al: Antiretroviral drugs and liver injury. *AIDS* 2008; 22:1.
39. Lederman ER, Crum NF: Pyogenic liver abscess with a focus on *Klebsiella pneumoniae* as a primary pathogen: An emerging disease with unique clinical characteristics. *Am J Gastroenterol* 2005; 100:322-331.
40. Hoffner RJ, Kalghbian T, Esekogwu VI, Henderson SO: Common presentations of amebic liver abscess. *Ann Emerg Med* 1999; 34:351.
41. Menon KV, Shah V, Kamath PS: The Budd-Chiari syndrome. *N Engl J Med* 2004; 350:578.
42. Aydinli M, Bayraktar Y: Budd-Chiari syndrome: Etiology, pathogenesis and diagnosis. *World J Gastroenterol* 2007; 13:2693.
43. Panagiotou I, et al: Treatment of Budd-Chiari syndrome by transjugular intrahepatic portosystemic shunt. *Hepatogastroenterology* 2007; 54:1813.
44. Amarapurkar DN, Punamiya SJ, Patel ND: Changing spectrum of Budd-Chiari syndrome in India with special reference to non-surgical treatment. *World J Gastroenterol* 2008; 14:278.
45. Bosch FX, Ribes J, Diaz M: Primary liver cancer: Worldwide incidence and trends. *Gastroenterology* 2004; 127:S5.
46. Hussain HK: Imaging of hepatic transplantation. *Clin Liver Dis* 2002; 6:247.
47. Comess LJ, Bennett PH, Burch TA: Clinical gallbladder disease in Pima Indians. *N Engl J Med* 1967; 277:894.
48. Gruber PJ, Silverman RA, Gottesfeld S, Flaster E: Presence of fever and leukocytosis in acute cholecystitis. *Ann Emerg Med* 1996; 28:273.
49. Bennett GL, Balthazar EJ: Ultrasound and CT evaluation of emergent gallbladder pathology. *Radiol Clin North Am* 2003; 41:1203.
50. Lee AY, et al: The timing of surgery for cholecystitis: A review of 202 consecutive patients at a large municipal hospital. *Am J Surg* 2008; 195:467-470.
51. Rodríguez-Fernández A, et al: Application of modern imaging methods in diagnosis of gallbladder cancer. *J Surg Oncol* 2006; 93:650-664.

www.ketabpezeshki.com 66485457-66963820

Chapter 91

Disorders of the Pancreas

Robin R. Hemphill and Sally A. Santen

BACKGROUND

The pancreas is a retroperitoneal organ extending across the posterior abdomen in the epigastrium that provides essential endocrine and exocrine functions (Fig. 91-1). In the general population, diabetes is the most common disorder of the pancreas, followed by pancreatitis. *Acute pancreatitis* is an inflammatory process of the pancreas usually associated with abdominal pain, elevated pancreatic enzymes, and variable involvement of other regional tissues or remote organ systems. Both local and systemic complications may occur. Repeated bouts of pancreatitis from any cause may eventuate in chronic pancreatitis as a result of permanent alterations in function and morphology. *Chronic pancreatitis* is an ongoing inflammation of the pancreas, which may be interrupted by spells of acute pancreatitis. Pancreatic tumors may develop from the endocrine or nonendocrine structures. These tumors may cause acute pancreatitis, which usually manifest in an indolent fashion. The most common is adenocarcinoma originating from the pancreatic ducts.

The head of the pancreas sits in the loop of the first part of the duodenum, and the tail lies against the hilum of the spleen. The main pancreatic duct (the duct of Wirsung) traverses from the tail through the body to the head of the pancreas where the common bile duct enters the second part of the duodenum through the sphincter of Oddi. Accessory ducts and anomalies are common. Anterior to the pancreas (from right to left) are the transverse colon, the lesser sac of the omentum, and the stomach. Posteriorly lie the bile duct, portal vein, splenic vein, vena cava, aorta, and superior mesenteric artery. To the left are the psoas muscle, kidney, and adrenal gland. Because of their close proximity, inflammation of the pancreas not only may injure these structures but also can mimic a variety of diseases.

The pancreas has both essential exocrine and endocrine functions. Exocrine products include amylase, lipase, trypsin, chymotrypsin, elastase, carboxypeptidase, phospholipase, and other enzymes. In addition, bicarbonate is produced in greatest quantity from this organ. The bicarbonate serves to neutralize gastric acids as well as the enzymes that break down proteins, carbohydrates, and fats. Cholecystokinin, pancreozymin, and secretin, as well as other factors, control secretion of these enzymes. The endocrine functions of the pancreas are managed by insulin, glucagon, pancreatic polypeptide, and somatostatin.

ACUTE PANCREATITIS

Perspective

The first reports of pancreatitis date to the 1700s, and the first accurate study and description were completed by Fitz in 1889.[1] He noted that performing surgery in the early stages of this disease was "extremely hazardous." Since then, the understanding of pancreatitis has evolved; however, treatment remains largely supportive rather than curative. Advances in care have decreased hospital mortality for all patients with pancreatitis, from 10 to 15% as reported 20 years ago to 4 to 7% more recently.[2,3] Most patients with pancreatitis have a mild course; however, 10 to 15% of cases will progress to severe disease, with a mortality rate in this subset of 20 to 50%. Children are at increased risk for death, with mortality rates of approximately 10%.[4] Severity also is increased in obese patients.

Pancreatitis can be classified as mild or severe, the latter category of the disease being defined by the presence of organ failure or local complications, such as necrosis, pseudocysts, or abscess.[2,5] The gravity of the impending illness may not be apparent at the initial presentation, and in all patients, disease progression and outcome are difficult to predict at onset. Death in the first week usually is from pulmonary failure, multiorgan failure, or cardiovascular collapse. Later deaths are more likely to be from infective complications. In approximately 40% of cases, fatal pancreatitis on autopsy was undiagnosed. Therefore pancreatitis should be suspected in moribund patients with multiorgan failure, particularly elders.

The incidence of acute pancreatitis in the United States ranges from 4.8 per 100,000 to 40 per 100,000, varying with age, gender, and social characteristics of the population studied.[2] The incidence appears to be increasing, although the increase may be related to both improved diagnosis and greater prevalence of risk factors. Gallstones are the most common obstructive cause of pancreatitis and occur more commonly in women than in men, with peak symptomatic incidence between the ages of 50 and 60 years. Some variations of ductal anatomy are associated with increased risk of obstruction. Many gallstones are asymptomatic; however, among people with gallstones, pancreatitis occurs with a frequency of 8 to 20 per 1000 person-years 2.

Alcoholic pancreatitis is more common in men than in women. In most (but not all) populations, this is the second leading cause of pancreatitis after obstructive causes. In children, trauma is the most common identifiable cause of acute pancreatitis.[4,6]

Principles of Disease

Pathophysiology

Many of the pathobiologic responses that occur in acute pancreatitis, such as edema, inflammation, and parenchymal cell death, are easy to conceptualize. However, knowledge about the exact molecular mechanisms that ultimately lead to these events is still evolving. Intense research to further the understanding of

www.ketabpezeshki.com 66485457-66963820

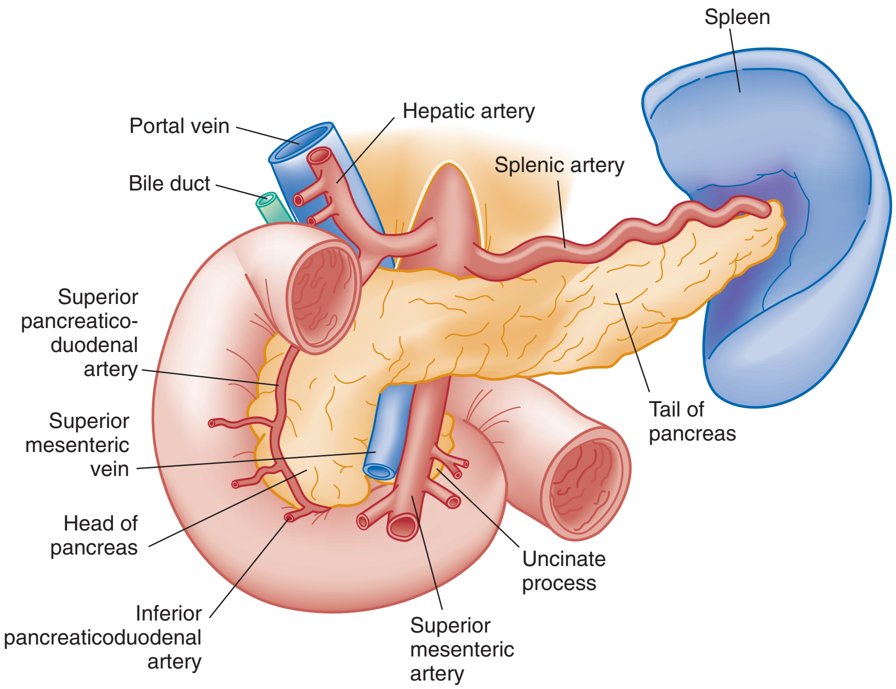


Figure 91-1. Diagrammatic representation of the pancreas, anterior view. (Redrawn from Feldman M, Friedman LS, Sleisenger MH [eds]: Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management, 7th ed. Philadelphia, Saunders, 2002.)

pancreatic intracellular digestive enzyme activation, pancreatic inflammatory response, and cell death responses, such as necrosis and apoptosis, is ongoing, with the aim of identifying new strategies for treatment.[7]

Acute pancreatitis may be divided into three pathologic phases. The first phase is the local inflammation from obstruction of the pancreatic or bile ducts, direct toxicity of the pancreatic cells, toxins, infections, trauma, or idiopathic causes. Local inflammation subsequently causes premature activation of pancreatic enzymes, such as trypsinogen and zymogen, either in the ducts or in the acinar cells.[2,8] This activation causes the release of enzymes that are intended to digest dietary proteins and fats; instead they produce cellular breakdown and pancreatic tissue autodigestion. Initially the inflammatory process is localized, creating focal pancreatic injury and edema. With increasing severity, the inflammation becomes generalized and causes necrosis of the pancreas and spreads to the surrounding fat and tissues. During this second phase of generalized injury, there may be necrosis of the pancreatic ducts as well as the vascular structures, leading to hemorrhage. Necrosis involving more than 30% of the pancreas increases both morbidity and mortality.[9,10]

Enzyme activation, inflammation, and necrosis cause a variety of complications. For example, fluid collections develop in 30 to 50% of patients with severe pancreatitis.[10] Over time, a fibrinous or granulation wall may form around this fluid collection, creating a pseudocyst. Thus, pseudocysts are not present in the initial phases of pancreatitis but instead develop over 4 to 6 weeks. Fluid collections, necrotic areas, or pseudocysts may become infected in a small number of cases, usually after several weeks. In addition, irritation of the surrounding bowel is common, creating bowel wall edema, ileus, and third-spacing of fluid. Formation of ascites is common and, together with bowel edema, can lead to significant intravascular fluid loss and hypotension.

The final stage of injury occurs with the development of multiorgan damage. Because of the release of inflammatory mediators, the initial localized inflammatory response may cause a systemic immune response syndrome (SIRS), resulting in multiple organ failure. This is a sepsis-like response, and any organ system can be involved, potentially resulting in myocardial depression, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), or renal failure.[2,11]

Etiology

Pancreatitis has several causes, but the vast majority of cases (80%) will be a result of either gallstones or alcohol, with gallstones the most common cause in most series (approximately 45% vs. 35%)[2] (Box 91-1). The exact pathomechanism of biliary pancreatitis is not clear. Either a stone within the bile duct applies transmural pressure on the pancreatic duct, or a stone in the common channel of the pancreatic duct or common bile duct causes obstruction. Obstruction or pressure on the pancreatic duct causes bile reflux or increased pressure of pancreatic secretions. Either mechanism leads to the activation of pancreatic enzymes, setting off the cascade of pancreatitis. Many cases presumed to be idiopathic probably are caused by small stones, sludge, or crystals that are too small to be detected on ultrasound examination but may be seen on endoscopic retrograde cholangiopancreatography (ERCP). This cause of pancreatitis is potentially correctable; if it is missed, recurrences are likely.

Alcohol is the cause of approximately 35% of pancreatitis cases. As with the other causes of pancreatitis, the mechanism by which alcohol is toxic to the pancreas is not well understood. Possible mechanisms include toxic effects of the ethanol metabolite acetaldehyde, ethanol-related lipid metabolism, or spasm of the sphincter of Oddi. Patients with alcoholic pancreatitis usually have 5 to 10 years of chronic alcohol use before the onset of pancreatitis.[8]

In addition to alcohol, many medications and toxins may cause pancreatitis, including didanosine, pentamidine, oral contraceptives, and selected scorpion venoms[12] (Box 91-2) Pancreatitis can be caused by hypertriglyceridemia, with levels more than 500 mg/dL being implicated. In pregnancy, both gallstones and increased triglyceride levels can cause pancreatitis.[8] When this occurs, both maternal and fetal mortality rates are high.

www.ketabpezeshki.com 66485457-66963820

Box 91-1 Etiology of Pancreatitis

Toxic
Alcohol, methanol
Drugs
Scorpion bites (in Trinidad)

Metabolic
Hypercalcemia (often from hyperparathyroidism)
Hyperlipidemia and hypertriglyceridemia (triglyceride levels >1000 mg/dL)

Obstructive
Biliary tract disease
Ampullary tumors
Pancreas divisum with obstruction of the accessory duct
Periampullary duodenal diverticula
ERCP and postpancreatography
Pancreatic neuroendocrine tumors
Pancreatic carcinoma
Sphincter of Oddi fibrosis, stricture, tumor, or hypertension

Infectious
Viral
Adenovirus
Coxsackievirus
CMV
EBV
Echovirus
Hepatitis A, B, C viruses
HIV
Varicella
Rubella

Other Infections
Aspergillus
Campylobacter
Clonorchiasis
Cryptococcus
Cryptosporidium
Dysentery
MAI
Mumps
Mycobacterium TB
Mycoplasma species
Legionella species
Leptospirosis
Salmonella typhimurium
Scarlet fever
Streptococcal food poisoning
Toxoplasma infection
Tuberculosis
Ascariasis

Other Causative Disorders and Conditions
Diabetic mellitus, DKA
Crohn's disease
Cystic fibrosis
Emboli (atherosclerotic)
Hemochromatosis
Hereditary pancreatitis
Hypothermia
Vasculitis
Lupus
Polyarteritis nodosa, malignant hypertension
Ischemia from hypoperfusion
Perforated ulcer
Postoperative
Pregnancy
Reye's syndrome
Trauma
Uremia
Idiopathic causes

CMV, cytomegalovirus; *DKA,* diabetic ketoacidosis; *EBV,* Epstein-Barr virus; *ERCP,* endoscopic retrograde cholangiopancreatography; *HIV,* human immunodeficiency virus; *MAI, Mycobacterium avium-intracellulare; TB,* tuberculosis.

Box 91-2 Drug-Induced Pancreatitis

Definite
Acetaminophen
Azathioprine
Cimetidine
Cisplatin
Corticosteroids
Didanosine
Erythromycin
Estrogens
Ethyl alcohol
Furosemide
L-Asparaginase
Mercaptopurine
Methyldopa
Metronidazole
Nitrofurantoin
Octreotide
Organophosphates
Pentamidine
Ranitidine
Tetracycline
Salicylates
Sulfonamides, trimethoprim-sulfamethoxazole, sulfasalazine
Sulindac
Valproic acid

Possible
Bumetanide
Carbamazepine
Chlorthalidone
Clonidine
Colchicine
Cyclosporine
Cytarabine
Diazoxide
Enalapril
Ergotamine
Ethacrynic acid
Indomethacin
Isoniazid
Isotretinoin
Mefenamic acid
Opiates
Phenformin
Piroxicam
Procainamide
Rifampin
Thiazides

Blunt and penetrating abdominal trauma can disrupt the ductal system and the pancreatic cells, setting off the enzyme cascade that will result in acute pancreatitis. Pancreatitis also may result from iatrogenic ductal injury in 1 to 10% of ERCP procedures.[2,8,13] Likewise, postoperative pancreatitis is well recognized and carries a higher mortality than that associated with other causative disorders.

Although both viral and bacterial disorders may precipitate pancreatitis, the two most common viral causes of pancreatitis are mumps and Coxsackievirus B infection. Pancreatitis is more common in patients with human immunodeficiency virus (HIV) infection than in the general population.[14] In addition to the common etiologic risk factors for pancreatitis, this population is at additional risk because of the risk of opportunistic infections, toxicity from HIV-specific medications, and acquired immunodeficiency syndrome (AIDS)–related cancers.[2,12] Acute pancreatitis is ultimately classified as idiopathic in approximately 10% of cases.[2] Suspected but uncertain causes may include sphincter of Oddi dysfunction and pancreas divisum, which arises from a failure of the dorsal and ventral ducts to fuse. With this entity, most of the pancreatic juice flows through the minor pancreatic duct and papilla.

The etiologies of pancreatitis in adults and children are similar, although incidence rates for specific causative disorders are different. Trauma (including child abuse), infection, and idiopathic causes account for 70% of the cases in children.[4] Hereditary pancreatitis is an autosomal dominant trait, with onset frequently

www.ketabpezeshki.com 66485457-66963820

noted during childhood. Other causes include infections and congenital anomalies.

Clinical Features

Pancreatitis should be suspected in all patients with epigastric abdominal pain, regardless of age. Once the diagnosis has been made, the underlying cause and presence of complications related to the disease should be sought.

Almost all patients with pancreatitis give a history of abdominal pain, most commonly in the midepigastric area; however, the pain also can be in the right or left upper quadrant. If significant inflammation is present, the pain may be diffuse and the patient may have difficulty localizing the discomfort. Typically, onset of symptoms is relatively rapid, increasing in severity over a few hours. The pain generally is described as constant and severe and may radiate to the midback. The degree of pain does not correlate with the severity of disease. Even though gallstones are frequently the cause of pancreatitis, the onset of pain is not usually related to eating. Nausea and vomiting often will accompany the pain. Although the discomfort may be lessened by lying on the side or sitting up, more typically little relief is obtained with position change, moving, eating, vomiting, or bowel movement. Colicky pain or pain that waxes and wanes suggests another diagnosis. Approximately 50% of patients will have a history of similar abdominal pain that may represent a previous episode of biliary colic or mild pancreatitis.[15]

On physical examination, vital signs may be stable but frequently are abnormal. Hypotension, tachycardia, and shock indicate severe disease with complications or an alternate diagnosis. Vital signs also may be influenced by pain (tachycardia, tachypnea, hypertension) or alcohol withdrawal (tachycardia, hypertension, fever). A low-grade fever is present in approximately half of patients with pancreatitis, both at presentation and for the first several days thereafter, even in the absence of infection.[9] A high fever is uncommon during the acute phase of pancreatitis; infection is usually a late complication. Ongoing evaluation should include pulse oximetry because acute hypoxia is an indicator of systemic complications and severe disease.

Patients with pancreatitis generally appear restless and in moderate distress as they search to find a position to relieve their discomfort. They may be jaundiced if an obstructing stone is present. The cardiopulmonary examination may be significant for rales or diminished breath sounds if the patient is hypoventilating from pain or if a pleural effusion (developing more commonly on the left) is present. On inspection, the abdomen may appear normal or may be notably distended. Only rarely will there be evidence of blood within the peritoneum or retroperitoneum resulting from severe hemorrhagic pancreatitis. Presence of blood within these areas is classically manifested as Cullen's sign (discoloration around the umbilicus) or Grey Turner's sign (discoloration of the flank). Auscultation of the abdomen may reveal normal, decreased, or absent bowel sounds, depending on whether the patient has a concomitant ileus. Because the pancreas is a retroperitoneal organ, palpation of the abdomen generally reveals epigastric guarding, with rebound tenderness being a less common finding. Murphy's sign may be present if the pancreatitis is secondary to a biliary source. Very rarely the physician may see evidence of subcutaneous fat necrosis: red nodules most prominent on the extremities. Other physical findings, such as the stigmata of alcoholism or xanthomas of hyperlipidemia, may help point to the cause of the pancreatitis.

Complications

The patient with acute pancreatitis will often have low grade fever, tachycardia, and leukocytosis; these findings represent three of the four criteria for SIRS. These patients may progress to fulminant sepsis or other severe illness related to the intense localized inflammation of pancreatitis.

Shock may result from volume loss. Fluid sequestration occurs in the pancreas and the bowel lumen and wall. Hemorrhage into necrotic pancreatic tissue also may occur. In addition, release of vasodilator and cardiodepressive substances may occur and worsen hypoperfusion.

Approximately 18 to 30% of patients may have pulmonary complications, including degradation of surfactant by pancreatic phospholipases; pleural effusions (more commonly noted on the left and frequently with elevated amylase levels); hypoxia from atelectasis, hypoventilation, and intrapulmonary shunting; and ARDS. ARDS, caused by the loss of surfactant as well as capillary leak caused by the inflammatory mediators, is rare but carries a 60% mortality rate.

Metabolic complications of pancreatitis include hyperglycemia and hypocalcemia. Hyperglycemia is caused by decreased insulin and increased glucagon. The mechanisms for hypocalcemia are sequestration or saponification of calcium in areas of fat necrosis; hypoalbuminemia, hypomagnesemia, or hyperglucagonemia; and inactivation of parathyroid hormone.

Coagulopathy develops from circulating proteases that affect the coagulation cascade. Acute tubular necrosis can cause acute renal failure and results from the effects of circulating inflammatory mediators or from hypotension and hypoperfusion. Ultimately, multisystem organ failure will occur if the balance of proinflammatory cytokine production overwhelms the anti-inflammatory response, which seeks to restrict the inappropriate movement of proinflammatory agents into the circulation.[15]

Late complications occur after the second week of illness and include involvement of local structures, abscess formation (1-4%), gastrointestinal bleeding from stress ulcers, splenic vein thrombosis, rupture of pancreatic pseudoaneurysms, fistula formation, splenic rupture, venous thrombosis, and right hydronephrosis. Pancreatic pseudocysts develop in 1 to 8% of patients after 4 to 6 weeks and are more common with alcoholic pancreatitis (Fig. 91-2). Long-term complications of acute pancreatitis include recurrent or chronic pancreatitis, diabetes mellitus, and digestive and malabsorption problems.

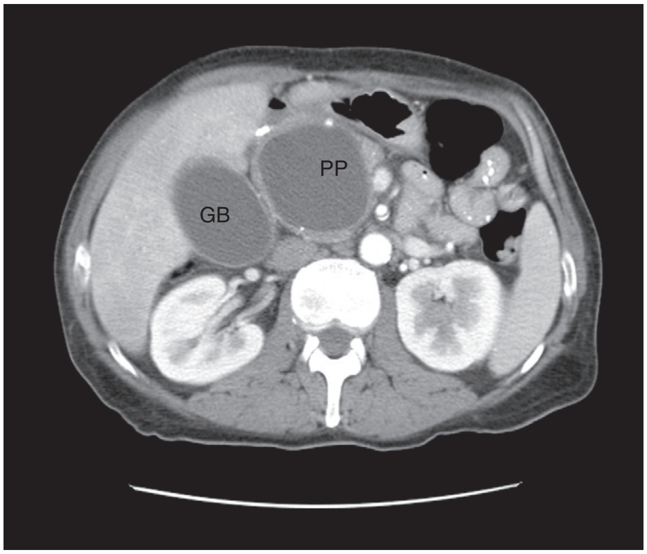


Figure 91-2. Computed tomography scan showing pancreatic pseudocyst *(PP).* In this patient the pseudocyst was so large that it compressed the common bile duct, causing obstructive jaundice. *GB,* gallbladder.

www.ketabpezeshki.com 66485457-66963820

Diagnostic Strategies

Laboratory Tests

The diagnosis of acute pancreatitis and the differentiation from other abdominal disorders depend on careful clinical assessment in conjunction with abnormalities on certain laboratory tests and supportive radiographic findings. Three enzymes are derived from pancreatic acinar cells: amylase, lipase, and the proenzyme trypsinogen. Each has been tested as a biochemical marker of acute pancreatitis.

Amylase Assay. Amylase is an enzyme that cleaves carbohydrates. It is produced primarily in the salivary glands and pancreas, although it also can be found in small amounts in the fallopian tubes, ovary, testis, muscle, intestines, and other organs. Elevations of amylase may be seen in healthy persons, patients with ectopic pregnancy, macroamylasemia, parotitis, renal failure (decreased clearance), mesenteric ischemia, bowel obstruction or infarction, perforated duodenal ulcer, acute peritonitis from other causes, and many other diseases. Pancreatic amylase can be differentiated from other sources of amylase by electrophoresis, a test that is not readily available in the emergency department (ED). Because of the other nonspecific sources of amylase, elevations of amylase lack specificity for the diagnosis of pancreatitis.[16] In acute pancreatitis, amylase rises within 6 to 24 hours, peaks in 48 hours, and normalizes in 3 to 7 days. Thus the sensitivity of amylase decreases after the first 24 to 48 hours.[16]

In addition to the uncertain source of an elevated amylase, several other limitations are recognized for its use in the diagnosis of acute pancreatitis. The application of different assays and the lack of an international standard have led to designation of various measured levels as “normal” or “elevated” across institutions. As expected, the sensitivity and specificity of amylase vary in accordance with the cutoff value selected to make the diagnosis of pancreatitis. Complicating matters is the lack of a universal modality for the diagnosis of pancreatitis; amylase assay, autopsy, computed tomography (CT), and laparoscopy all have been used. The sensitivity of amylase for the diagnosis of pancreatitis ranges widely, depending on the comparative choice of the standard test. In up to 25% of patients with pancreatitis, especially in alcoholics and patients with hypertriglyceridemia (which interferes with the assay) or chronic pancreatitis, the amylase level can be normal. Mild amylase elevations in patients with severe acute abdominal pain of unclear cause, particularly in elders, should raise suspicion for another serious abdominal pathology. Thus the amylase assay, although recognized as an imperfect standard with which to make the diagnosis of pancreatitis, is used by default in some circumstances because of its low cost and rapid availability. However, its precise value is unclear in the initial diagnosis of pancreatitis, particularly in cases with an atypical clinical presentation. Amylase levels alone, whether normal, mildly elevated, or extremely elevated, are not diagnostic for pancreatitis unless accompanied by the appropriate clinical picture.

Lipase Assay. Lipase is a pancreatic enzyme that hydrolyzes triglycerides and has been used both as an adjunctive test and an alternative test for the diagnosis of pancreatitis. Unfortunately, lipase assays are associated with many of the same pitfalls as amylase assays. In the presence of pancreatic inflammation, lipase levels increase within 4 to 8 hours and peak at 24 hours. The levels stay elevated longer than amylase levels, falling over 8 to 14 days,[8,16] thus providing greater sensitivity in patients with delayed presentations. Lipase, like amylase, is present in other tissues and tends to be elevated in similar clinical situations. Improved assays have rendered lipase more specific than amylase. Yet, there are still nonpancreatic causes of elevations of lipase, such as duodenal ulcers, bowel obstruction, and idiopathic causes.[8,16] Comparisons between amylase and lipase are limited by the lack of a true “gold standard” for the diagnosis of pancreatitis, as well as the choice of cutoff values used for the diagnosis. Despite these limitations, lipase is at least as sensitive as and probably more specific than amylase (specificity of 80 to 99%). At values five times the upper limits of normal, lipase is 60% sensitive and 100% specific. The use of twice the upper limit of normal has been recommended to decrease the possibility of missing the diagnosis of pancreatitis.[16] Expert guidelines recommend the use of lipase over amylase in the diagnosis of pancreatitis.[17,18]

The degree of elevation of amylase or lipase is not a marker of disease severity.[3] For example, compared with nonalcoholic patients, alcoholics will frequently have lower amylase levels but may have more severe disease. In a patient with prolonged abdominal pain or a history of pancreatitis, elevated biomarkers for longer than a week may suggest pseudocyst or pancreatic absess.[19] Use of the amylase-to-lipase ratio has not proved helpful in the determination of a specific cause of pancreatitis.[14]

Other Tests. Several new tests aimed at improving the diagnostic accuracy for acute pancreatitis are under development. Trypsinogen exists in two major forms, with trypsinogen-2 present in high serum concentrations in patients with acute pancreatitis. In a recent study, the sensitivity and specificity for urinary trypsinogen-2 dipstick testing were 93% and 92%, respectively. At present, however, neither this test nor any others have proved useful in standard clinical practice.[20]

Additional Laboratory Evaluation

In evaluating a patient with abdominal pain, amylase or lipase assays, along with other blood tests, are necessary to narrow the differential diagnosis, detect complications, and determine prognosis. Ranson developed a two-step list of primarily laboratory parameters, performed at hospital admission and after 48 hours, to determine the risk of death from pancreatitis[21,22] (Box 91-3). With this in mind, additional testing should consist of a complete blood count (CBC), lactate dehydrogenase (LDH) determination, and a comprehensive metabolic panel (including measurement of liver enzymes, calcium, renal function, and glucose). In patients with liver disease, coagulation studies should be performed to determine the degree of liver dysfunction. Arterial blood gas analysis should be done selectively in patients who are acidotic or

Box 91-3 Ranson’s Criteria for Pancreatitis-Associated Mortality

At Admission	Within 48 Hours of Admission
Age >55 years	Hematocrit fall >10%
WBCs >16,000/mm^3	BUN rise >5 mg/dL
Glucose >200 mg/dL	Calcium <8 mg/dL
LDH >350 IU/L	P_{O_2} <60 mm Hg
AST >250 SF units	Base deficit >4 mEq/L
	Fluid sequestration >6 L
Substitute if Gallstone Induced Admission:	**Within 48 Hours of Admission**
Age >70 years	Hematocrit fall >10%
WBCs >18,000/mm^3	BUN rise > mg/dL
Glucose >220 mg/dL	Calcium <8 mg/dL
LDH >400 IU/L	Base deficit >5 mEq/L
AST >250 SF units	Fluid sequestration >4 L

Add the total number of signs at 48 hours:

Number	Associated Mortality Rate
0-3	1%
3-4	15%
5-6	40%
>7	100%

AST, aspartate transaminase; *BUN,* blood urea nitrogen; *LDH,* lactate dehydrogenase; *SF,* Sigma-Frankel; *WBCs,* white blood cells.

www.ketabpezeshki.com 66485457-66963820

Table 91-1 Sensitivity and Specificity of Liver Enzymes for the Cause of Pancreatitis[26]

ENZYME AND LEVEL	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)
ALT >150 mmol/L	48	96	95
AST >150 mmol/L	44	95	87
Alkaline phosphatase >300 units/L	24	95	87
Bilirubin 2.8 mg/dL	38	93	89

Data from Yadav D, Agarwal N, Pitchumoni CS: A critical evaluation of laboratory tests in acute pancreatitis. Am J Gastroenterol 97:1309, 2002.

ALT, alanine aminotransferase; *AST,* aspartate transaminase; *PPV,* positive predictive value.

Box 91-4 APACHE II Clinical and Laboratory Parameters for Scoring*

Age	pH or serum HCO_3
Chronic health problems	Sodium
Temperature	Potassium
Mean arterial pressure	Creatinine
Heart rate	Hematocrit
Respiratory rate	White blood cell count
Pao_2 or A-a gradient	Glasgow Coma Scale score

A-a gradient, alveolar-arterial gradient; *APACHE II,* Acute Physiology and Chronic Health Evaluation II; *HCO_3,* bicarbonate; *Pao_2,* arterial oxygen concentration.
*Each clinical or laboratory parameter is assigned points with 0 being normal and 4 being most abnormal (high or low). Use either table or medical calculator to calculate the score. The score is then used to predict mortality.

hypoxic. This information can be used for treatment decisions and to determine prognosis based on Ranson's criteria. Magnesium should be checked in alcoholic patients and in those patients with electrolyte abnormalities. Both hypocalcemia and hyperglycemia are common in pancreatitis, with the hyperglycemia resulting from glucagon and insulin abnormalities. Calcium is best determined with use of the ionized calcium level. Serum calcium is falsely low in the presence of low albumin levels, as may be seen in patients with pancreatitis. Elevations of creatinine and blood urea nitrogen (BUN) may indicate the presence of hypovolemia or renal involvement, or both.

Elevation in liver enzymes may result from biliary-induced pancreatitis or from other diseases of the liver or biliary tract. In addition, liver enzyme levels may increase from the pressure on the common bile duct that results from the surrounding pancreatic inflammation. Mild elevations of bilirubin are common in all types of pancreatitis, as well as in many other liver disorders. For the patient diagnosed with pancreatitis, higher elevations of aspartate transaminase (AST) and LDH are related to worse prognosis according to Ranson's criteria.

When liver enzymes are elevated, the pattern of elevation may help determine the underlying cause of the pancreatitis (Table 91-1). Alanine aminotransferase (ALT) is the best single marker for a biliary cause; levels greater than three times baseline support the diagnosis of biliary pancreatitis.[16,23] The higher the elevation of ALT, the greater the specificity and predictive value for gallstones. ALT levels higher than 150 IU/L have 96% specificity, positive predictive value (PPV) of 95%, and 48% sensitivity for gallstone pancreatitis. Significant rises in AST, alkaline phosphatase, and bilirubin also are more likely to be related to biliary pancreatitis but are not as sensitive as ALT.

The CBC may be notable for an elevated white blood cell count; the hematocrit may be either high or low. Early in the disease course, the hematocrit may be elevated because of third-space volume loss. A decrease in hematocrit is a poor predictor of prognosis because it indicates intra-abdominal hemorrhage and severe pancreatitis. An electrocardiogram also should be included early in the workup to determine whether the patient's abdominal pain may be cardiac in origin.

Prognosis

At present, a variety of markers are available to aid in the detection of severe pancreatitis, including specific laboratory values that measure the systemic inflammatory response, scoring systems that tabulate the extent of inflammation or organ failure, and findings on imaging studies. The most commonly used scoring system is Ranson's criteria (see Box 91-3). In this system, the five criteria evaluated on hospital admission indicate the degree of local inflammation; the six criteria assessed at 48 hours reflect the development of systemic complications. Ranson recognized that the model did not work well for patients with gallstone pancreatitis, so he revised the criteria to reflect the improved mortality. Although Ranson's criteria have an 89% negative predictive value, the obvious drawback to use of this system in the ED is that the scoring cannot be completed until 48 hours after diagnosis. Furthermore, in patients with AIDS, Ranson's criteria may not be as accurate because of HIV-induced changes in some laboratory values (such as calcium and LDH).

Although Ranson's criteria constitute a simple and well-known scoring system, reliance on these criteria alone may result in delayed recognition of illness severity; therefore the Acute Physiology and Chronic Health Evaluation II (APACHE II) system also may be used to judge severity.[24] This system uses 12 physiologic variables, age, and chronic health status to generate a total point score (Box 91-4). Many online medical calculators are available to allow easy calculation of the APACHE score by summing the weighed values of the measured physiologic parameters. Scoring can be performed on admission and throughout the hospital stay. An APACHE score of 8 or higher indicates severe disease.[18,23] A score greater than 13 is associated with high likelihood of death. An APACHE III scoring system also has been developed and includes additional physiologic variables, but this system has not proved to be better at predicting outcomes in patients with acute pancreatitis.

C-reactive protein level above 150 mg/L at 48 hours after symptom onset are poor prognostic predictors of disease severity.[8] To account for the various factors that indicate the severity of disease in patients with acute pancreatitis, the Atlanta criteria for severity are widely accepted (Box 91-5).[25] Finally, a four-variable predictive model that uses BUN, age, LDH, and interleukin-6 has been proposed; initial analysis indicates that it is as accurate as other scoring systems.[25] This scoring system will need further validation, however. Given the limitations in the ability to accurately predict severity of illness, patients with acute pancreatitis should initially be treated as though the disease is severe.

Radiographic Studies

In pancreatitis, plain abdominal radiographs may reveal an ileus with a sentinel jejunal loop or spasm of the transverse colon and dilation of the ascending colon. Pancreatic calcifications of chronic pancreatitis or gallstones may rarely be seen. The portion of the chest seen as part of the abdominal series may show left-sided or bilateral pleural effusions, atelectasis, or ARDS. Up to 80% of radiographs obtained in patients with pancreatitis will demonstrate some abnormality.[8] Unfortunately, many of these findings are nonspecific, and plain radiography has largely been replaced by more advanced imaging.

www.ketabpezeshki.com 66485457-66963820

Box 91-5 Atlanta Criteria for Predicting Severe Acute Pancreatitis

Criteria for severe acute pancreatitis—one or more of the following:

1. Ranson score 3 or higher on admission (or during the first 48 hours)
2. APACHE II score 8 or higher at any time during course
3. Presence of organ failure
   - Shock (systolic blood pressure <90 mm Hg) *or*
   - Pulmonary insufficiency (PaO_2 60 mm Hg or less on room air) *or*
   - Renal failure (serum creatinine >2 mg/dL after fluid resuscitation)
4. Systemic complications
   - DIC (thrombocytopenia and hypofibrinogenemia and fibrin split products) *or*
   - Metabolic complications (serum calcium 7.5 mg/dL or less) *or*
5. Presence of one or more local complications (pancreatic necrosis, pancreatic abscess, pancreatic pseudocyst)

From Bradley EL 3rd: A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, Sept 11-13, 1992. Arch Surg 128:586, 1993.
APACHE II, Acute Physiology and Chronic Health Evaluation II; *DIC,* disseminated intravascular coagulation; PaO_2, arterial oxygen concentration.

Box 91-6 Differential Diagnosis for Pancreatitis

Abdominal Disorders
Perforated viscus
Peptic ulcer disease
Cholecystitis, gallbladder colic
Cholangitis
Gastroenteritis
Nephrolithiasis or pyelonephritis
Bowel obstruction
Mesenteric ischemia
Abdominal aortic aneurysm
Ectopic pregnancy

Cardiopulmonary Disorders
Myocardial infarction
Pericarditis
Pneumonia
ARDS
Pleural effusion

Systemic Disease
Sickle cell crisis

ARDS, acute respiratory distress syndrome.

CT and ultrasound imaging are complementary studies in the evaluation of pancreatitis. Magnetic resonance imaging (MRI) offers no significant advantages over CT. Ultrasonography provides more accurate images of the biliary tract than CT; however, the pancreas itself, as well as local complications, are less well visualized by ultrasound. If a biliary cause is suspected, an ultrasound study performed within the first 24 hours of admission may help determine whether gallstones or dilation of the common bile duct is present. In one study that compared the results of CT and initial ultrasonography among patients with pancreatitis, ultrasound findings resulted in a change in treatment in 55% of patients, compared with no changes after CT. CT was 39% sensitive for biliary disease, whereas ultrasonography was 83% sensitive.[26,27] In another study, ultrasound imaging was 94% sensitive for gallstones but only 19% for common duct stones and 38% for common duct dilation.[28] Because of these limitations, when gallstone pancreatitis is highly suspected, an endoscopic ultrasound study may be more accurate and can help guide the emergency use of ERCP.[23] Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive test that may be used to help determine the cause of acute pancreatitis.[26] Although ultrasound imaging is more sensitive than CT for investigating biliary causes of pancreatitis, CT may be useful in evaluating for other causes of abdominal pain, the presence of peripancreatic complications (such as hemorrhage, pseudocyst, abscess, or vascular abnormalities), and the extent of any pancreatic necrosis.[9,14,29,30] The Atlanta International Symposium recommended CT in patients with (1) an uncertain diagnosis; (2) severe clinical pancreatitis, abdominal distention, tenderness, fever with temperatures higher than 102° C, and leukocytosis; (3) a Ranson score greater than 3 or APACHE score greater than 8; (4) no improvement within 72 hours; and (5) acute deterioration.[12] If the diagnosis is clear and evidence of obstruction is lacking, CT or ultrasound imaging can be delayed until after the patient has been admitted to the hospital. The main indication for obtaining a CT in the ED is to exclude other diagnoses; if the patient is significantly ill and can tolerate the procedure, early CT may determine whether complications are already present.

CT also may be used to stage the severity and prognosis of acute pancreatitis. Older studies suggested that both oral and intravenous contrast were appropriate, but with newer CT technology, a discussion with the radiologist may help determine whether oral contrast is needed. The CT severity index is an additional grading system that uses the CT to evaluate how the pancreas looks, as well as evidence of fluid collections or gas adjacent to the pancreas.[29] Grades A (no abnormality) and B (focal or diffuse pancreatic enlargement) indicate lower levels of inflammation. Grade C shows mild peripancreatic inflammation and is associated with an increased risk of complications. Grade D (enlarged pancreas with fluid in the anterior pararenal space) and grade E (enlarged pancreas with two or more fluid collections) are associated with significant risk of infection, with mortality rates of up to 15%. Another CT-based scoring system, the extrapancreatic inflammation on CT scan score, is based on the presence of pleural effusion, ascites, and retroperitoneal fluid collection. The initial study was small but showed this system to be superior to the CT severity index in prediction of outcome.[30]

Differential Considerations

Pancreatitis should be differentiated from other abdominal processes, cardiopulmonary disorders, and systemic diseases (Box 91-6). A number of acute surgical conditions may mimic pancreatitis in presentation and also may cause elevated biomarkers. Examples are bowel perforation, peritonitis, ischemic bowel, small and large bowel obstruction, and ruptured ectopic pregnancy.

Management

The management of pancreatitis is primarily supportive; rehydration, pain and nausea control, nutritional supplementation, and monitoring for complications constitute the foundations of care. The supportive care given to the patient with acute pancreatitis has multiple objectives. Because of vomiting and fluid sequestration, most patients with pancreatitis are dehydrated. Fluids should be replaced with normal saline; several liters may be required. Vital signs and urine output should be used to judge the adequacy of volume replacement. Electrolytes should be monitored and replenished.

Abdominal pain associated with pancreatitis is severe and will generally necessitate use of narcotic analgesia. Meperidine has been used historically in pancreatitis and biliary disease. Although

www.ketabpezeshki.com 66485457-66963820

morphine may increase the tone of the sphincter of Oddi, evidence that it worsens the disease process in pancreatitis is lacking.[31] Patient-controlled analgesia may be the most effective method of pain control. Antiemetics are indicated to control nausea or vomiting.

In the past, patients with pancreatitis were allowed nothing by mouth and nasogastric suctioning was initiated out of concern that oral intake would stimulate the release of pancreatic enzymes. However, randomized clinical trials in patients with mild-to-moderate pancreatitis have shown no benefit from either fasting or use of nasogastric suctioning. Currently, nasogastric suctioning is indicated only in cases of intractable vomiting or ileus, and some enteral feeding should begin as soon as it is tolerable. Some evidence suggests that early enteral nutrition (delivered by feeding tubes placed beyond the ligament of Treitz) may improve outcomes even in severe pancreatitis[32]; however, if oral feedings are not tolerated or are inadequate, then parenteral feedings should be initiated.

A key management principle is frequent reevaluation for complications of pancreatitis. Hypotension should be corrected with large volumes of normal saline (up to 6 L). In fact, hemodynamic instability in severe pancreatitis results from similar processes seen in sepsis, and management approaches used in septic patients (early goal-directed therapy) are appropriate.[33] Invasive hemodynamic monitoring may be necessary. Respiratory support is appropriate for respiratory failure or continued shock. Hyperglycemia should be treated cautiously because it may self-correct as the pancreatitis resolves. Hypocalcemia may be the result of decreased albumin or hypomagnesemia; ionized calcium and magnesium levels should be checked before replacement therapy is initiated. If true hypocalcemia is present and the patient is experiencing symptoms, treatment is appropriate. Calcium gluconate should be used if calcium needs to be replenished. The serum potassium should be normalized before calcium replacement, however, because calcium will cause intravascular potassium shifts.

In the case of gallstone pancreatitis, gastroenterology consultation is appropriate to discuss the use of ERCP. Early operative removal of gallstones and the gallbladder has been shown to increase mortality; however, early removal of common bile duct stones by ERCP may reduce morbidity. At present, consensus is lacking regarding the optimal timing of ERCP in the presence of gallstone pancreatitis. Early endoscopic sphincterotomy (in 24-48 hours) and stone removal are recommended in the setting of cholangitis, sepsis, and severe obstructive pancreatitis.[34] In mild pancreatitis, early ERCP has not consistently been shown to decrease morbidity. In addition, there is approximately a 5% rate of pancreatitis with ERCP and papillotomy, as well as other complications associated with the procedure (bleeding and perforation). In view of the ongoing controversy, it is appropriate to involve the consultant early in the case so that a well-coordinated management plan can be created.

Theoretically, certain medications should moderate the course of pancreatitis; histamine H_2 receptor blockers decrease the release of secretin by inhibition of gastric acid, glucagon directly suppresses pancreatic exocrine secretion, and octreotide inhibits pancreatic secretion. However, these therapies have not been shown to be clinically effective. Other approaches that use inhibitors of inflammatory mediators also have failed to produce clinical improvement. For patients with severe pancreatitis, an H_2 blocker, although not helpful for the acute disease, may decrease stress-induced ulcers.

Use of antibiotics in patients with severe pancreatitis with or without evidence of necrosis of pancreatic tissue is controversial. Prophylactic antibiotics have been reported to be effective in reducing subsequent infection. These positive effects have not been consistently observed, however, and some evidence indicates that use of prophylactic antibiotics in patients with severe pancreatitis may increase the risk of fungal infection.[35] Two recent studies found no difference with respect to the development of infected pancreatic necrosis with the use of prophylactic antibiotics.[36,37] The usefulness of early antibiotic treatment remains unclear, although there appears to be a consensus to withhold antibiotics until clear evidence of infection is present.[9,18,23,32,37]

Surgical intervention or percutaneous drainage may be necessary for cases of infected pancreatic necrosis, infected pseudocyst, or unresolved pseudocyst. Surgery is preferred when percutaneous drainage is not effective or not possible (as with extensive pancreatic necrosis or deteriorating clinical status).

Disposition

The course of acute pancreatitis is unpredictable, and complications may occur hours or days after the onset of illness; therefore almost all patients with acute pancreatitis should be admitted to the hospital. Patients with evidence of severe pancreatitis should be admitted to the intensive care unit (ICU), especially if findings include agitation, confusion, rising hematocrit, pulmonary insufficiency, or cardiovascular problems such as hypotension, progressive tachycardia, or poor urine output. Specifically, patients with a score greater than 2 on Ranson's criteria on admission or other evidence of organ failure, local complications, or significant comorbid illness will also require ICU management.

In hospitals without appropriate intensive care facilities, patients with evidence of severe pancreatitis should be transferred to an appropriate treatment center. If the cause of pancreatitis is suspected or confirmed to be gallstones, discussion with a specialist (gastroenterologist or surgeon) is necessary. Pediatric patients have increased morbidity and mortality from pancreatitis and should be considered for early transfer to a pediatric specialty center.

CHRONIC PANCREATITIS

Principles of Disease

Chronic pancreatitis is an ongoing inflammatory process leading to irreversible structural damage and impairment of exocrine and endocrine pancreatic function. Normal pancreatic structure is replaced with fibrotic tissue, resulting in pancreatic ducts that are strictured in some areas and dilated in others. The incidence is approximately 4 per 100,000.[38] In 70 to 80% of people, the cause is thought to be chronic alcohol use. The risk increases with the duration and amount of alcohol consumption. The ingestion of more than 150 g of alcohol per day for an average of 5 to 15 years is associated with the development of chronic pancreatitis in 3 to 10% of chronic alcoholics.[38-41] It is possible that chronic pancreatitis also may develop in persons sensitive to small amounts of alcohol.

Three theories exist as to the mechanisms by which alcohol causes chronic pancreatitis: (1) direct cellular toxicity, (2) alcohol-induced precipitation of proteinaceous fluid in the ductules, which causes obstruction and calcification, and (3) injury caused by recurrent acute pancreatitis leading to irreversible damage and chronic inflammation.[38,41,42] Chronic pancreatitis can continue even after the cessation of alcohol use, although it is more commonly associated with alcoholic relapse. Smoking increases the risk of chronic pancreatitis in a dose-dependent fashion, with earlier onset and progression in alcohol-induced pancreatitis.

Other, less common causes of chronic pancreatitis include ductal obstruction, hereditary pancreatitis, cystic fibrosis, trauma, autoimmune, hyperparathyroidism, α_1-antitrypsin deficiency, hyperlipidemia, and tropical pancreatitis (cassava fruit is implicated).[38] Idiopathic chronic pancreatitis occurs in approximately

www.ketabpezeshki.com 66485457-66963820

10% of patients. In the 25% of cases of unknown cause, occult alcohol use may be the culprit. In children the most common causes are cystic fibrosis and hereditary pancreatitis.[38,42]

The pathophysiology of chronic pancreatitis includes chronic calcific pancreatitis, usually seen in alcoholics and characterized by patchy fibrosis, ductal injury, intraductal protein plugs, stones, and chronic inflammatory pancreatitis with diffuse fibrosis and inflammatory changes. As in acute pancreatitis, chronic inflammation can cause local injury resulting in lesions such as pseudoaneurysms, splenic vein thrombosis, pancreatic ascites, or pancreatic fistulae. Pancreatic pseudocyst formation is seen in up to 25% of patients with chronic pancreatitis. Rarely, pseudocysts can erode into vascular structures or can become infected. Narrowing of the bile duct from extrinsic pressure or strictures may lead to elevation of liver enzymes and jaundice. In approximately 5% of patients, duodenal obstruction develops secondary to inflammation around the head of the pancreas. Thus, chronic pancreatitis in an acutely ill patient may be a manifestation of the primary disease or a complication.

The most common endocrine complication is the presence of glucose intolerance in many patients with chronic pancreatitis. Over years, insulin-dependent diabetes develops in 50 to 75% of patients.[38,42] Patients with chronic pancreatitis have an increased risk for the development of pancreatic carcinoma of approximately 4%, as do patients with hereditary pancreatitis. In addition, patients with chronic disease have exocrine pancreatic insufficiency with steatorrhea and malabsorption.

Chronic pancreatitis is associated with considerable morbidity in terms of pain and complications. In addition, patients with chronic pancreatitis have an excess mortality of approximately 50% in 20 years.[39] However, the cause of death is more likely to be related to other consequences of alcoholism than to pancreatitis.

Clinical Features

Patients with chronic pancreatitis may be in near-constant and intractable chronic pain or may be experiencing complications from chronic pancreatitis or an acute flare of chronic underlying disease. These flares may be severe, and if the patient is relatively well during the interim it may be difficult to distinguish this episode from a recurrent bout of acute pancreatitis. Pain is epigastric, usually radiating to the back and associated with nausea and vomiting. Often the pain is similar to that in previous attacks of acute pancreatitis or flares of chronic pancreatitis. Use of alcohol or eating exacerbates the pain. No correlation has been found between remaining pancreatic function and the degree of pain, although a few studies have shown that the pain may diminish over years of chronic disease. Patients may experience weight loss because of malabsorption or decreased intake secondary to nausea and vomiting or to the recognition that eating may precipitate the pain.

In approximately 15% of patients with chronic pancreatic disease, signs and symptoms of pancreatic exocrine function insufficiency, including malabsorption, diarrhea, steatorrhea, and weight loss, may develop over time. Malabsorption occurs after approximately 90% of the pancreas is nonfunctional. Functional endocrine insufficiency will develop in approximately one to two thirds of patients with chronic disease. The symptoms primarily manifest as hyperglycemia; however, the development of diabetic ketoacidosis is rare. Hypoglycemia is multifactorial in origin, with causes including insufficiency of glucagon, decreased liver glucose stores, malnourishment, and hypoglycemic medications.

On physical examination, patients usually have significant discomfort. They may appear chronically ill from alcoholism, poor nutrition, and malabsorption. On abdominal examination, palpation frequently reveals tenderness without peritoneal signs. The abdomen should be carefully palpated for a mass that may represent a pseudocyst or tumor. Stigmata of chronic alcohol abuse also may be noted; however, jaundice may be from pressure on the common bile duct or from alcohol-related liver injury.

Diagnostic Strategies

The diagnosis of chronic pancreatitis frequently is made clinically rather than on the basis of laboratory testing. The serum levels of amylase and lipase initially are mildly elevated in chronic pancreatitis, but as the disease progresses, these levels normalize. As in acute pancreatitis, the degree of elevation of amylase and lipase is not prognostic. In the patient with the appropriate clinical picture of history of pancreatitis and chronic abdominal pain, normal amylase and lipase levels are consistent with a diagnosis of chronic pancreatitis.

Blood work should include a CBC and complete metabolic profile. The white blood cell count usually is normal. There may be elevations of hepatic enzymes (alkaline phosphatase, bilirubin, or transaminases) either from alcoholic hepatitis or from compression on the biliary duct from pancreatic inflammation or a mass in the head of the pancreas. Elevations in serum glucose also may be seen; hypoglycemia is less common. Decreases in albumin and calcium are common because of the chronic nature of the disease. If the diagnosis is in question, stool may be tested for fecal fat and pancreatic enzymes such as elastase, chymotrypsinogen, and trypsinogen.[34,43]

Although abdominal radiographs are not necessary, presence of pancreatic calcifications is pathognomonic. Such calcifications are seen in 30 to 50% of patients, usually related to chronic alcohol-induced pancreatitis (Fig. 91-3). Patients with calcifications have had pancreatitis for an average of several years; therefore these patients should be evaluated for long-term complications such as diabetes and malabsorption.

In patients with the clinical manifestations of chronic pancreatitis, including pain, malabsorption, and diabetes, additional corroborating data may be obtained by CT scan, MRCP, ERCP, or endoscopic ultrasound.[37,38] In the ED setting, patients with known chronic pancreatitis do not need imaging except when the underlying cause of the pain is in question or if the pain is prolonged, significantly increased, or unresponsive to treatment. CT is 90%

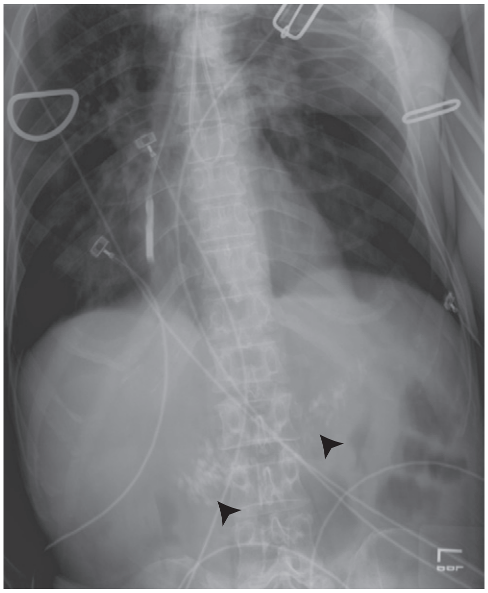


Figure 91-3. Pancreatic calcifications *(arrowheads)* throughout the pancreas as seen in chronic pancreatitis. (Incidental finding of feeding tube in main bronchus.) (Image courtesy Ronald Arildsen.)

www.ketabpezeshki.com 66485457-66963820

sensitive for chronic pancreatitis and may show dilated intrapancreatic ducts, microcalcifications, pseudocysts, or other complications. Although ultrasound imaging is useful in diagnosing the cause of acute pancreatitis, it is less useful in chronic pancreatitis (sensitivity of 75% and specificity of 80-90%). The primary ultrasound findings are pancreatic calcifications and ductal abnormalities.

Although endoscopic retrograde pancreatography (ERP) is not an ED procedure, it can be helpful in diagnosing pancreatic duct abnormalities and measuring pancreatic function. Some gastroenterologists consider the ductal abnormalities seen on ERP and endoscopic ultrasound to be pathognomonic for chronic pancreatitis. MRCP has an increased role in the evaluation of chronic pancreatitis.[34,42]

Differential Considerations

The diagnosis of chronic pancreatitis usually is straightforward in the alcoholic patient with hyperamylasemia who has chronic abdominal pain and a history of similar, previous flares of pancreatitis. The diagnosis may be more difficult when amylase and lipase levels are normal. However, the clinician should not forget that other abdominal processes, unrelated to either the pancreas or the complications of pancreatitis, are legitimate considerations in the differential diagnosis (see Box 91-6). In addition, other chronic abdominal disease such as peptic ulcers, irritable bowel, gallstones, and endometriosis may manifest with recurrent abdominal pain. Finally, narcotic-dependent patients in withdrawal may experience vomiting and abdominal pain that may be difficult to differentiate from chronic pancreatitis.

Management

The initial management of chronic pancreatitis is supportive. Depending on the patient's clinical status and electrolyte values, replenishment of fluids and electrolytes may be necessary. An "alcohol cocktail" with thiamine, multivitamins, and folate often is indicated because patients frequently are malnourished. Antiemetics should be used to manage recurrent emesis.

Management of pain is one of the most important and most difficult aspects of treatment. Laboratory values may be normal despite significant pain, and patients with chronic pain syndromes may not exhibit signs of autonomic hyperactivity when experiencing exacerbations of their underlying disease. This lack of correlation may lead to a concern that the expressed need for pain medication constitutes drug-seeking behavior. Physicians should err on the side of treatment in most patients, except those with documented abuse. Nonsteroidal analgesics and acetaminophen are the preferred drugs for control of pain but often are not adequate. Either morphine, hydromorphone, or meperidine may be used and should be titrated to effect. Tramadol (Ultram) also has been used effectively.[44,45] The use of narcotics over extended periods may be necessary. Non-narcotic modulators of pain, such as selective serotonin reuptake inhibitors, tricyclic antidepressants, or gabapentin, may be helpful for chronic pain. In the ideal medical system, the primary care physician or a pain management specialist monitors the narcotic prescription because narcotic dependence may become an issue.

The removal of inciting factors, especially alcohol, is important. Smoking also plays a role in the development of chronic pancreatitis that is independent of alcohol.[41] Patients with significant pain should have nothing by mouth, although, as in acute pancreatitis, a nasogastric tube is not indicated. The use of oral pancreatic replacement enzymes increases the amount of trypsin in the duodenum and may decrease stimulation of the pancreas, with subsequent decrease in pain. Studies of the effectiveness of pancreatic enzyme replacement on pain have yielded contradictory results.[41] These enzymes should be used in patients with malabsorption or steatorrhea. In theory, proton pump inhibitors or H_2 receptor blockers also may reduce pancreatic stimulation; however, these agents have not been shown to decrease pain or hasten recovery. Octreotide lowers cholecystokinin levels and may inhibit pancreatic secretion.[41]

Beyond ED treatment, helpful adjuncts may include endoscopic dilation, ductal stone removal, extracorporeal shock wave lithotripsy, or stenting of the pancreatic ducts. Common bile duct stenting also may be necessary, because obstruction occurs in approximately 5 to 10% of cases.[41] Surgery such as pancreatic head resection, lateral pancreaticojejunostomy, or Whipple pancreatic duodenectomy is sometimes an option when conservative treatment has failed. One recent study showed improved pain and physical health summary scores in patients randomized to undergo surgery rather than endoscopy.[46] Pancreatic pseudocysts in chronic pancreatitis are less likely to resolve spontaneously and should be drained either endoscopically under ultrasound guidance, percutaneously, or in an open procedure. Celiac plexus blocks also have been used with variable success for pain control.

Disposition

In general, patients with chronic pancreatitis are managed as outpatients and come to the ED with exacerbations or complications. Because acute pancreatitis can occur in patients with chronic pancreatitis, the same prognostic indicators for severity of acute pancreatitis should be considered. Patients with severe disease should be admitted to the ICU. Patients with dehydration, abdominal pain unresponsive to medications, or questionable diagnosis should be hospitalized for evaluation and treatment. After a careful ED evaluation, in the absence of dehydration, unstable vital signs, or uncontrolled pain, the patient may be managed on an outpatient basis with close follow-up. After hospital discharge, it is important to stress lifestyle modifications of abstinence from alcohol and tobacco, as well as intake of frequent, small, low-fat meals.

PANCREATIC CANCER

Perspective

Pancreatic cancer is a particularly lethal cancer, with a 5-year survival rate of less than 5% despite aggressive surgery and advances in chemotherapy. It is the fourth most common cause of cancer-related death in the United States. The disease is diagnosed in approximately 11 people per 100,000 per year, and the incidence has increased threefold over the past 40 years. Because early symptoms are few, a minority of patients are diagnosed at an early stage.

Principles of Disease

Little is known about the cause of pancreatic cancer. The most consistently reported risk factors are smoking, advanced age, a high-fat diet, and a positive family history. Chronic alcoholism, chronic pancreatitis, and diabetes have been shown to be risk factors in some studies.[47-50]

Ductal adenocarcinomas account for 95% of malignant pancreatic tumors. The pancreatic head is the location of origin in 70% of cases. The tumor extends locally into adjacent structures and can metastasize by hematogenous or lymphatic spread to liver, peritoneum, lungs, bones, and brain. Neuroendocrine tumors, such as gastrinomas, vasoactive intestinal peptide tumors (VIPomas), and glucagonomas make up the remaining cases.[51] These types of tumors carry a better prognosis.

www.ketabpezeshki.com 66485457-66963820

Clinical Features

The presentation of pancreatic adenocarcinoma is variable because progression of the disease is indolent. The tumor usually has been present for several months before the cancer is diagnosed; therefore, presenting complaints may include pain of long duration or one of the many complications of the disease. One of the most common presentations is weight loss, which usually is the result of anorexia rather than malabsorption. The patient may report dull, constant abdominal pain in the epigastrium that may radiate to the back. Alternatively, the patient may have painless jaundice from common bile duct obstruction, and progressive jaundice develops in approximately 75% of patients. When the mass presses on the pancreatic duct, pancreatitis can develop. An enlarged, palpable, but painless gallbladder in the presence of jaundice is most commonly associated with pancreatic cancer (termed *Courvoisier's sign*). Glucose intolerance also may develop. As the tumor enlarges, patients may exhibit evidence of bowel obstruction. Pancreatic cancer (as well as other cancers) may render patients hypercoagulable, resulting in thromboembolic presentations. Varices and gastrointestinal bleeding may be caused by compression of the portal system.

Neuroendocrine tumors of the pancreas are rare and manifest with symptoms that reflect the hormones they produce. For example, with insulinomas, the presenting manifestation may be hypoglycemia with weakness, sweating, and tremulousness. Gastrinomas are related to Zollinger-Ellison syndrome and recurrent peptic ulcers. VIPomas (also known as *Verner-Morrison syndrome*) manifest with extreme watery diarrhea, hypokalemia, and achlorhydria. Glucagonomas manifest with glucose intolerance, stomatitis, and necrolytic migratory erythema. Some tumors produce multiple hormones.[51,52] Carcinoid causes flushing, sweating, and diarrhea. Most tumors produce multiple gastrointestinal hormones but manifest as a dominant clinical syndrome as described earlier. Other, nonfunctional tumors also may be noted incidentally on CT scans as small pancreatic masses. Diagnosis is made by measurement of abnormal levels of hormones and recognition of the appropriate clinical syndrome. Depending on the type, up to 50 to 80% of pancreatic neuroendocrine tumors are malignant.[53]

Diagnostic Strategies

Evaluation of a patient in whom pancreatic cancer is suspected should focus on diagnosis and staging of the disease, assessment of resectability, and palliation of symptoms. CT is the procedure of choice, although pancreatic masses may be seen on ultrasound. MRI also may provide information. Percutaneous ultrasound-guided biopsy, endoscopic ultrasound examination and biopsy, CT-guided biopsy, and laparotomy can be used to obtain tissue specimens for diagnosis.[47] Histologic samples are needed to differentiate ductal adenocarcinoma from islet cell tumors, other metastatic cancers, and lymphoma. Serologic markers have not proved satisfactory for diagnosis or follow-up evaluation, although several oncogenes and tumor markers are under study (for example, CA19-9).

Management

Complete resection of the carcinoma is the only effective treatment. Unfortunately, few tumors (less than 20%) are diagnosed at a stage at which this may be possible.[47] This suggests that even seemingly resectable pancreatic cancer has microscopic systemic spread before operative intervention occurs. Both adjuvant and neoadjuvant therapies have been studied in an effort to improve survival. In patients with unresectable tumors, the median survival period is approximately 6 months. Palliative surgery may be performed to relieve obstruction. Biliary drainage by percutaneously placed or ERCP-placed stents also may help to relieve jaundice. Chemotherapy and radiation therapy may decrease tumor size to ease pain and prolong survival in some patients.[47,53] Treatment of neuroendocrine tumors is aimed at limiting tumor growth by both excision and reversal of hormone excess.[54]

Patients may be seen in the ED with complications of the cancer such as bowel obstruction, jaundice, or problems with pain control. In view of the grim prognosis for this disease and the significant associated pain, narcotics should not be withheld, and end-of-life issues should be addressed by the oncologist.

KEY CONCEPTS

- Most cases of acute pancreatitis are caused by gallstones (45%) and alcoholism (35%). Other causes include medications, toxins, and trauma.
- The clinical spectrum of acute pancreatitis ranges from mild (epigastric discomfort often associated with vomiting) to life-threatening (severe abdominal pain in the presence of an acute abdomen and hemodynamic instability caused by systemic complications). The mortality rate for severe pancreatitis approaches 30%.
- There is no perfect test for diagnosing acute pancreatitis. The most useful tests include serum amylase and lipase assays. Unfortunately, both tests can yield normal results in up to 25% of cases; mild elevations are not specific for acute pancreatitis and can be seen in many other acute surgical disorders that cause abdominal pain. Both tests are highly specific for pancreatitis when serum levels are elevated five times above the upper limits of normal.
- Emergent abdominal CT should be performed in patients with clinically suspected pancreatitis who appear acutely ill (to exclude peripancreatic complications such as hemorrhage, pseudocyst, or abscess) and in patients with an uncertain diagnosis (to exclude other surgical causes of acute abdominal pain).
- Because the course of acute pancreatitis is unpredictable, most patients require hospitalization for pain control, hydration, observation, and the management of complications. Patients with severe pancreatitis (i.e., those who have more than two of Ranson's criteria, an APACHE score over 7, or evidence of systemic complications) usually need ICU admission.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Leach SD, Gorelick FS, Modlin IM: Acute pancreatitis at its centenary. *Ann Surg* 1990; 212:109.
2. Lowenfesl RB, Maisonneuve E, Sullivan T: The changing character of acute pancreatitis: Epidemiology, etiology, and prognosis. *Curr Gastroenterol Rep* 2009; 11:97.
3. Bank S, Singh P, Pooran N, Stark B: Evaluation of factors that have reduced mortality from acute pancreatitis of the past 20 years. *J Clin Gastroenterol* 2002; 351:50.
4. Lowe MB, Greer JE: Pancreatitis in children and adolescents. *Curr Gastroenterol Rep* 2008; 10:128.
5. Muddana V, Whitcomb DC, Papachristou GI: Current management and novel insights in acute pancreatitis. *Expert Rev Gastroenterol Hepatol* 2009; 3:435.
6. Yadav D, Lowenfels AB: Trends in the epidemiology of the first attack of the acute pancreatitis: A systematic review. *Pancreas* 2006; 33:323.
7. Pandol SJ: Acute pancreatitis. *Curr Opin Gastroenterol* 2006; 22:481.
8. Harper SJ, Cheslyn-Curtis S: Acute pancreatitis. *Ann Clin Biochem* 2011; 48:23.
9. Mitchell RMS, Byrne MF, Baille J: Pancreatitis. *Lancet* 2003; 361:1447.
10. Bharwani N, Patel S, Prabhudesai S, Fotheringham T, Power N: Acute pancreatitis: The role of imaging in diagnosis and management. *Clin Radiol* 2011; 66:164.
11. Kingsnorth A, O'Reilly D: Acute pancreatitis. *BMJ* 2006; 332:1072.
12. Trivedi CD, Pitchumoni CS: *J Clin Gastroenterol* 2005; 39:709.
13. Freeman ML, et al: Risk factors for post-ERCP pancreatitis: A prospective, multicenter study. *Gastrointest Endosc* 2001; 54:425.
14. Kusnierz-Cabala B, Kedra B, Sierzega M: Current concepts on diagnosis and treatment of acute pancreatitis. *Adv Clin Chem* 2003; 37:473.
15. Grander J, Remick D: Acute pancreatitis: Models, markers, and mediators. *Shock* 2005; 24:45.
16. Matsull WR, Pereira SP, O'Donohue JW: Biochemical markers of acute pancreatitis. *J Clin Pathol* 2006; 59:340.
17. Yadav D, Agarwal N, Pitchumoni CS: A critical evaluation of laboratory tests in acute pancreatitis. *Am J Gastroenterol* 2002; 97:1309.
18. Working Party of the British Society of Gastroenterology; Association of Surgeons of Great Britain and Ireland; Pancreatic Society of Great Britain and Ireland; Association of Upper GI Surgeons of Great Britain and Ireland: UK guidelines for the management of acute pancreatitis. *Gut* 2005; 54(Suppl 3):iii1.
19. Schneider L, Büchler MW, Werner J: Acute pancreatitis with an emphasis on infection. *Infect Dis Clin North Am* 2010; 24:921-941.
20. Kylänpää-Bäck ML, et al: Comparison of urine trypsinogen-2 test strip with serum lipase in the diagnosis of acute pancreatitis. *Hepatogastroenterology* 2002; 49:1130.
21. Ranson JHC, Rifkind KM, Turner JW: Prognostic signs and nonoperative peritoneal lavage in acute pancreatitis. *Surg Gynecol Obstet* 1976; 143:209.
22. Ranson JH, et al: Prognostic signs and operative management in acute pancreatitis. *Surg Gynecol Obstet* 1974; 139:69.
23. Whitcomb DC: Acute pancreatitis. *N Engl J Med* 2006; 354:2142.
24. Chatzicostas C, et al: Comparison of Ranson, APACHE II and APACHE III scoring systems in acute pancreatitis. *Pancreas* 2002; 4:331.
25. Spitzer AL, et al: Applying Ockham's razor to pancreatitis prognostication: A four-variable predictive model. *Ann Surg* 2006; 243:380.
26. Reitz S, Slam K, Chambers LW: Biliary, pancreatic, and hepatic imaging for the general surgeon. *Surg Clin North Am* 2011; 91:59.
27. Harvey RT, Niller WT: Acute biliary disease: Initial CT and follow-up US vs. initial US and follow-up CT. *Radiology* 1999; 213:831.
28. Liu CL, Lo CM, Fan ST: Acute biliary pancreatitis: Diagnosis and management. *World J Surg* 1997; 21:149.
29. Balthazar EJ: Acute pancreatitis: Assessment of severity with clinical and CT evaluation. *Radiology* 2002; 223:603.
30. De Waele JJ, et al: Extrapancreatic inflammation on abdominal computed tomography as an early predictor of disease severity in acute pancreatitis: Evaluation of a new scoring system. *Pancreas* 2007; 34:185.
31. Thompson DR: Narcotic analgesic effects on the sphincter of Oddi: A review of the data and therapeutic implications in treating pancreatitis. *Am J Gastroenterol* 2001; 96:1266.
32. Kahl S, Zimmermann S, Malfertheiner P: Acute pancreatitis: Treatment strategies. *Dig Dis* 2003; 21:30.
33. Greer SE, Burchard KW: Acute pancreatitis and critical illness: A pancreatic tale of hypoperfusion and inflammation. *Chest* 2009; 136:1413.
34. Beglinger C: Diagnosis of chronic pancreatitis. *Dig Dis* 2010; 28:359.
35. Illatoro E, Bassi C, Larvin M: Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database Syst Rev* 2006; 4:CD002941.
36. Isenmann R, et al: Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: A placebo-controlled, double-blind trial. *Gastroenterology* 2004; 126:997.
37. Dellinger EP, et al: Early antibiotic for severe acute necrotizing pancreatitis: A randomized, double-blind, placebo-controlled study. *Ann Surg* 2007; 245:674-683.
38. Tellado JM: Prevention of infection following severe acute pancreatitis. *Curr Opin Crit Care* 2007; 13:416.
39. Braganza JM, Lee SH, McCloy FR, McMahon MJ: Chronic pancreatitis. *Lancet* 2011; 377:1184.
40. Uomo G, Manes G: Risk factors of chronic pancreatitis. *Dig Dis* 2007; 25:282.
41. Ahmed SA, Wray C, Rilo HL, Choe KA, Gelrud A: Chronic pancreatitis: Recent advances and ongoing challenges. *Curr Probl Surg* 2006; 43:135.
42. DiMagno MJ, DiMagno EP: Chronic pancreatitis. *Curr Opin Gastroenterol* 2010; 26:490.
43. Tattersall SJN, Apte MV, Wilson JS: A fire inside: Current concepts in chronic pancreatitis. *Intern Med J* 2008; 38:592.
44. Chauhan S, Forsmark CE: Pain management in chronic pancreatitis: A treatment algorithm. *Best Pract Res Clin Gastroenterol* 2010; 24:323.
45. Fasanella KE, et al: Pain in chronic pancreatitis and pancreatic cancer. *Gastroenterol Clin North Am* 2007; 36:335.
46. Cahen DL, et al: Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. *N Engl J Med* 2007; 356:676.
47. Yang GY, Wagner TD: Multimodality approaches for pancreatic cancer. *CA Cancer J Clin* 2005; 55:352.
48. Rocha Lima CM, Centeno B: Update on pancreatic cancer. *Curr Opin Oncol* 2002; 14:424.
49. Bornman PC, Beckingham IJ: Pancreatic tumours. *BMJ* 2001; 322:721.
50. Krejs GK: Pancreatic cancer: Epidemiology and risk factors. *Dig Dis* 2010; 28:355.
51. Eriksson G, Oberg K: Neuroendocrine tumors of the pancreas. *Br J Surg* 2000; 87:128.
52. Oberg P: Pancreatic endocrine tumors. *Semin Oncol* 2010; 39:594.
53. Hidalgo M: Pancreatic cancer. *N Engl J Med* 2010; 362:1605.
54. Castellanos EH, Cardin DB, Berlin JD: Treatment of early-stage pancreatic cancer. *Oncology* 2010; 25:182.

www.ketabpezeshki.com 66485457-66963820

Chapter 92

Disorders of the Small Intestine

Chad E. Roline and Robert F. Reardon

SMALL BOWEL OBSTRUCTION

Perspective

The signs and symptoms of small bowel obstruction (SBO), as well as the potentially life-threatening nature of the condition, have been recognized since ancient times. The Egyptian Ebers Papyrus, which is thought to date to as early as 3400 BC, contains an ominous passage detailing what some modern researchers have suggested may describe a small intestinal volvulus. It states, "if thou examinest one who suffers…with colicky pains, and whose belly is stiff through it, and has pain in his cardia…nor is there any way it can come out, then it shall rot in his belly…it grows into a twist in the bowel."[1]

Over the centuries numerous therapeutic treatments have been used to treat SBO, including the administration of metallic mercury, opium, enemas, inflation of the bowels with air, electrical stimulation, percutaneous puncture of the bowel, horseback riding, leeches, and even "suspending the patient in an upside-down position over an attendant's shoulder," as suggested by Sir Astley Cooper in 1804 to assist in the reduction of a hernia, and by Jonathan Hutchinson in 1878 to treat intussusception.[2] By the close of the 19th century, proximal intestinal decompression via gastric suctioning was found to quickly reduce the symptoms of intestinal obstruction. Although the management of SBO has remained challenging, over the last century advancements in imaging as well as operative techniques have greatly improved the prognosis for patients with this condition and have decreased the mortality rate from nearly 60% in 1900 to less than 8% today.[3,4]

Intestinal obstruction is a relatively common problem encountered in the emergency department (ED), accounting for an estimated 15% of all emergency admissions for abdominal pain.[5] This translates to over 300,000 patients per year in the United States, at an estimated yearly cost of over 1.3 billion dollars for the treatment of SBOs caused by adhesions alone.[6] Despite the high frequency with which SBO is encountered, the ideal management remains controversial.

There are several different types of SBO with a vast array of causes ranging from the common to the truly unusual. The term *mechanical obstruction* implies the presence of a physical barrier to the movement of the intestinal contents. Obstructions of this type can be further subclassified according to the cause of the obstruction relative to the intestinal wall (Box 92-1). Lesions external to the intestinal tract can cause obstruction via compression from outside the gut. This is most commonly a result of postoperative adhesions, but hernias and intraperitoneal neoplasms are other causes. Lesions intrinsic to the intestinal wall itself can cause mechanical obstruction; such lesions include primary intestinal neoplasms, localized infection (i. e., intestinal wall TB), and trauma-related conditions (i. e., a hematoma of the intestinal wall). Lesions within the intestinal lumen itself can lead to obstruction. Bezoars, ingested foreign bodies, and gallstone ileus are all examples of the cause of this type of obstruction.[7]

Another important distinction of SBO is whether the obstruction is a *simple* or *closed-loop* obstruction. A simple obstruction occurs at a single point. On the other hand, in a closed-loop type obstruction the intestine is obstructed at two locations, which creates a segment of bowel with both proximal and distal blood flow compromised. This can occur when a twist develops in the mesentery or, in the case of an internal hernia, when a loop of bowel becomes entrapped in a defect in the mesentery (Fig. 92-1). If not promptly recognized and relieved, a closed loop obstruction can quickly lead to intestinal infarction and necrosis, which, in most studies, has been shown to double the mortality rate.[8]

In contrast to a mechanical obstruction, a *neurogenic* or *functional* obstruction occurs as a result of disruption of the normal coordinated peristaltic activity of the gastrointestinal tract in the absence of a physical blockage within the intestinal lumen. This is also commonly referred to as an *adynamic ileus.* The causes of adynamic ileus are listed in Box 92-2. Most often it occurs in patients who have undergone abdominal surgery and is transient in nature. In fact, some degree of functional obstruction is considered normal after surgery and is thought to result from multiple factors, including an inflammatory response to intestinal manipulation, the effects of analgesics, and the release of hormones and several neurotransmitters.[9] In addition to surgery, a number of metabolic abnormalities and medical conditions can lead to the development of a functional SBO, including infection, medications, and metabolic abnormalities.

Finally, the term *pseudo-obstruction* refers to a poorly understood and complex syndrome in which the signs and symptoms of a mechanical obstruction, including the appearance of dilated bowel on radiography, are present in the absence of a mechanical lesion. This is thought to involve disruption of the intestinal "pacemaker activity" controlled by a specialized group of cells found in the gastrointestinal tract called the interstitial cells of Cajal (ICCs). These cells regulate the contractility of the intestinal smooth muscle and are under the influence of the enteric nervous and autonomic systems. Because of this, pathology at any one of these sites can lead to pseudo-obstruction. Pseudo-obstruction can arise from many causes, including degenerative neuropathies, autoimmune and paraneoplastic disease, and

www.ketabpezeshki.com 66485457-66963820

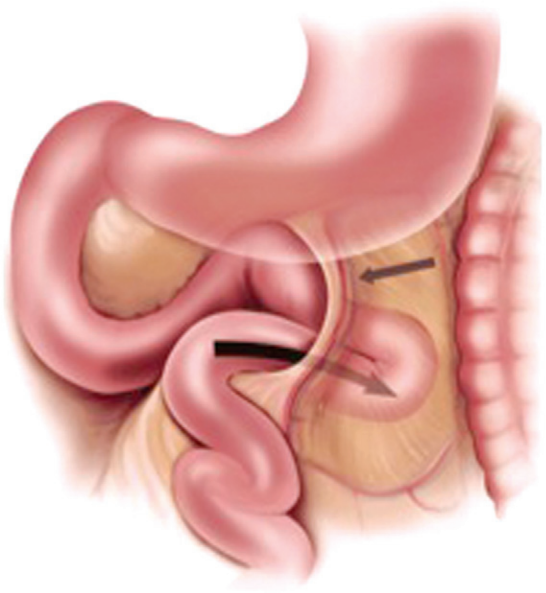


Figure 92-1. Diagram of internal hernia. Note the formation of a "closed-loop," which creates a high risk for strangulation. (From Martin LC, Merkle EM, Thompson WM: Review of internal hernias: Radiographic and clinical findings. AJR Am J Roentgenol 186:703-717, 2006. Reprinted with permission from the American Journal of Roentgenology.)

Box 92-1 Lesions Causing Small Bowel Obstruction Relative to the Intestinal Wall

External to Intestinal Wall
Postoperative adhesions
Hernias
Volvulus
Compressing masses (tumors, abscesses, hematomas)

Intrinsic to Intestinal Wall
Primary neoplasms
Inflammatory (e.g., Crohn's disease, radiation enteritis)
Infectious causes (e.g., intestinal tuberculosis)
Intussusception
Traumatic (intestinal wall hematoma)

Intraluminal
Bezoars
Foreign bodies
Gallstones
Ascaris infestation

Box 92-2 Causes of Adynamic Ileus

Metabolic disease (especially hypokalemia)
Medications (e.g., narcotics)
Infection (retroperitoneal, pelvic, intrathoracic)
Abdominal trauma
Laparotomy

hereditary conditions.[10] Unlike in adynamic ileus, the symptoms of pseudo-obstruction are often chronic and respond poorly to treatment.

Principles of Disease

Interruption of normal flow through the intestinal lumen triggers a cascade of physiologic changes that correlate with the progressive development of symptoms. In the presence of a mechanical obstruction, the bowel proximal to the blockage first becomes mildly dilated by the accumulation of partially digested food and normal intestinal secretions. These secretions are referred to as *succus entericus* and are secreted by cells lining the intestinal wall in response to mechanical stimulation. Increased intestinal dilation causes an increase in peristalsis throughout the intestines, which can trigger frequent and loose bowel movements early in the progression of the obstruction as well as episodes of nausea and vomiting. As the process continues, the bowel wall becomes edematous and the normal absorptive function of the intestinal wall decreases, leading to further accumulation of contents in the intestinal lumen proximal to the obstruction. Owing to the loss of normal intestinal motility, bacterial overgrowth begins to occur in the proximal small bowel. It is this overgrowth in a location of the intestines that is normally relatively sterile that explains the feculent nature of the emesis frequently observed in patients with SBO. As the obstruction continues, transudative fluid loss occurs into the peritoneal cavity, leading to worsening hypovolemia and dehydration. In addition, if the obstruction is proximal in location, continued bouts of emesis can lead to electrolyte abnormalities, metabolic alkalosis, and severe hypovolemia and shock.

In the presence of a closed-loop obstruction, the increase in the intraluminal pressure occurs much more rapidly because the intestinal contents cannot flow retrograde. Intestinal venous congestion and then arterial obstruction can also progress quickly to intestinal ischemia and infarction. This is referred to as a *strangulation obstruction*. If it is not promptly relieved, necrosis and intestinal perforation can occur. The resulting leakage of the intestinal contents into the peritoneum can lead to peritonitis and sepsis.

In the developed world the most common cause of SBO is postoperative adhesions, which account for approximately 60% of cases. These adhesions develop as a result of a process involving the interaction among numerous types of cells, cytokines, and coagulation factors caused by damage to peritoneal surfaces.[11,12] It has been estimated that 93 to 100% of patients who undergo transperitoneal surgery will develop postoperative adhesions.[13] Of these, up to 25% will develop SBO, with those undergoing intestinal or pelvic surgeries at greater risk.[14] Over the last several years, numerous physical bioabsorbable barriers and pharmacologic agents have been evaluated as potentially useful in decreasing the formation of postoperative adhesions.[15]

The second most common cause of SBO is tumors, which are responsible for roughly 20% of cases. This includes both malignancies, such as adenocarcinomas, carcinoid tumors, lymphomas, and sarcomas, and benign conditions, including adenomas, leiomyomas, and lipomas.[16] In addition to these primary gastrointestinal tumors, gynecologic cancers, especially ovarian cancer, are a very common cause of SBO.[17] There are also numerous case reports of metastatic disease leading to SBO, including metastatic breast, skin, and testicular cancers.[18]

Hernias are the third most common cause of SBO, found in approximately 10% of cases. Similar to their relative frequency in general, ventral and inguinal hernias are most often encountered, but femoral hernia, parastomal hernia, lateral ventral hernia (also called *spigelian hernia*), and internal hernia may also lead to SBO.

Although rare in the general population, internal hernias (Fig. 92-1) are a recognized complication of bariatric surgery, especially when a Roux-en-Y type procedure has been performed. In this group, internal hernias have been described in up to 5% of patients and usually develop at the mesocolic window.[19]

Another rare type of hernia is the obturator hernia. This hernia develops into the obturator foramen and is especially common in elderly women who have recently lost a significant amount of weight. The female pelvis is wider and the obturator canal is more

www.ketabpezeshki.com 66485457-66963820

Figure 92-2. Gallstone ileus of the small intestine at laparotomy. (Photograph courtesy J.C. Campbell, Plymouth, England. www.surgical-tutor.org.uk Accessed February 15, 2011.)

oblique in women than in men. This, in combination with a loss of preperitoneal fat in elder, often emaciated patients, predisposes to the development of an obturator hernia. Because an external mass is absent, the diagnosis can be especially challenging, which explains why it carries the highest mortality of any abdominal hernia, at nearly 70% when incarcerated.[20]

Gallstone ileus is another rare but important cause of mechanical SBO (Fig. 92-2). It is responsible for 1 to 4% of all cases of mechanical obstruction and is most frequently seen in elder patients with significant underlying medical problems.[21] The pathogenesis involves the entry of a gallstone into the intestinal tract through a biliary-enteric fistula. This results from the localized inflammation of cholecystitis, and in the majority of cases entry occurs via a cholecystoduodenal fistula, although cholecystocolonic and cholecystogastric fistulae can also be involved. After entering the intestinal lumen, the gallstone migrates distally. As a stone moves through the intestinal lumen, it often increases in size as bowel content sedimentation attaches. Eventually, the gallstone becomes lodged, most often in the ileum, which is the narrowest segment of the small bowel, and the patient then develops symptoms of obstruction.

Small bowel volvulus occurs infrequently in this country but is a potentially catastrophic cause of SBO. This condition results from the abnormal twisting of a loop of small bowel around the axis of its own mesentery. This accounts for only 3.5 to 6.2% of SBO in the Western world. However, it is much more common in Africa, India, and the Middle East, where it is responsible for up to 20% of cases of SBO.[22] Primary small bowel volvulus occurs in an otherwise normal abdominal cavity; secondary small bowel volvulus occurs when a congenital or acquired abnormality leads to the development of the volvulus, as in the case of intestinal malrotation or as a result of postoperative adhesions.[23] Although primary small bowel volvulus is poorly understood, there are several proposed factors that may predispose to its development. Diet is thought to play a role in some cases. One study found a tenfold increase in the incidence of small bowel volvulus among Muslims in Afghanistan during the festival of Ramadan.[24] During this period observers abstain from food or drink from dawn to sunset and then consume large quantities of food and liquid. The researchers proposed that eating a large amount of food bulk after prolonged fasting causes the proximal jejunum to descend into the pelvis, displacing empty small bowel loops upward and initiating malrotation. Alterations in gut motility and increased small bowel length have also been suggested as possible predisposing factors. Secondary causes of small bowel volvulus include intestinal malrotation caused by the arrest of normal rotation of the embryonic gut or as a result of postoperative adhesions. In the case of malrotation, more than 50% of affected children present for evaluation before 1 month of age with small bowel volvulus.[25] Because a small bowel volvulus is a classic closed-loop obstruction, prompt recognition and surgical treatment are imperative, as the risk of strangulation is high.

Intussusception describes the invagination or "telescoping" of a part of the small intestine into itself. This results in the development of venous and lymphatic congestion with consequent intestinal edema, which can lead to intestinal ischemia and perforation. Intussusception occurs in patients of all ages but is most frequently seen in children younger than 2 years. It is the most common cause of intestinal obstruction in infants 6 to 36 months of age.[26] In children the cause is most often idiopathic, but several studies have shown an association with adenovirus infection. It has been postulated that enteric adenovirus infection may trigger stimulation of the lymphatic tissue in the intestinal tract, which may create a "lead point" for the intestine to be "dragged" into itself by the normal peristaltic activity of the intestines.[27] In contrast to the idiopathic nature of intussusception in children, a mechanical cause is found in more than 90% of adult cases. Tumors, either benign or malignant, are discovered as the initiating cause in more than 65% of adult cases. Several reports have also described adult intussusception in association with acquired immunodeficiency syndrome (AIDS).[28] These patients are at an increased risk of lymphoma or unusual infections, such as atypical mycobacterial infections, as the cause of the development of intussusception.

Clinical Features

History

Patients with SBO commonly report crampy abdominal pain, abdominal distention, nausea, vomiting, constipation, or the inability to pass flatus. The pain is often described as periumbilical in location and typically has a crescendo-decrescendo pattern. The recurrent waves of discomfort can last from seconds to minutes. In more proximal obstruction, symptoms of nausea and vomiting can be much more severe, and the onset of symptoms is often more abrupt. Distal obstructions typically cause symptoms over a slower period of 1 to 2 days and are frequently accompanied by greater abdominal distention. It is important to remember that the colon requires up to 24 hours to empty after the formation of SBO, and the associated small bowel distention stimulates peristalsis. Because of this, flatus and the passage of stool may continue even in the presence of a complete obstruction. A thorough past surgical history should be obtained, and any history of malignancy or inflammatory bowel disease should be determined.

Physical Examination

As with all patients in the ED, the physical examination should start with a careful evaluation of the patient's hemodynamic status, degree of distress, and general condition. Thus patients requiring resuscitation can be quickly identified, and the appropriate interventions, including aggressive intravenous fluids, can be initiated early. Inspection of the patient should include a careful search for abdominal distention and hernias and should include a genital examination. Although bowel sounds in SBO are frequently described as high pitched and "tinkling" in nature, studies have shown that they are also frequently decreased or absent in SBO. One study showed that physicians listening to recordings of bowel sounds were able to correctly identify SBO in only 42% of affected patients.[29]

www.ketabpezeshki.com 66485457-66963820

The presence of peritoneal signs usually indicates late obstruction with complications, including strangulation. However, it should be noted that abdominal palpation in the setting of significant bowel dilation can give the false impression of peritonitis, because quick compression-decompression of dilated bowel may elicit a significant pain response. For this reason it may be helpful to determine the presence of pain with cough or gentle shaking of the patient's pelvis to better investigate for true peritonitis.

Complications

There are numerous serious complications associated with SBO. Persistent vomiting can lead to significant hypovolemia, metabolic alkalosis, and shock. If strangulation occurs, necrosis of the bowel can lead to perforation and leakage of contaminated bowel contents into the peritoneal space. This can cause peritonitis, intra-abdominal abscess formation, and sepsis. As one would expect, complications are more common in older patients and in those with comorbidities.[30] There are also several potential complications related to surgical intervention for SBO, including wound infection and short bowel syndrome. Unfortunately, in addition to these adverse events, the rate of recurrence of SBO is quite high. For patients treated nonoperatively the rate is 40%, and in those treated operatively, 27%.[31] For patients with SBO secondary to adhesions, the relative risk of recurrence increases with the number of prior episodes of obstruction. For those with four or more episodes of adhesional SBO, the recurrence rate is more than 80%.[32]

Diagnostic Strategies

Although laboratory tests are not helpful in diagnosing the presence of SBO, they can be very useful in assessing the degree of dehydration and metabolic disruption resulting from the obstruction. Several studies have evaluated the use of various biomarkers to identify strangulation complicating SBO. These have included lactate and creatinine phosphokinase (CPK), and some studies have evaluated the use of intestinal fatty acid binding protein (I-FABP), which is released by necrotic enterocytes, to attempt to identify strangulation.[33] Unfortunately, these may be normal until very late in the process of intestinal strangulation and have proven to be overall unreliable.

Several imaging modalities are applicable in the diagnosis and evaluation of SBO. Plain radiographic findings are estimated to be diagnostic in approximately 50 to 60% of cases of SBO, equivocal in 20 to 30%, and normal, nonspecific, or misleading in 10 to 20%. The cause of the obstruction can rarely be elicited from plain radiographs. In addition, there is occasionally a discrepancy between terms used by emergency physicians and radiologists to describe abdominal plain film results. For example, many emergency physicians use the term "nonspecific bowel gas pattern" to mean normal. However, one survey showed that 65% of radiologists use that same term to describe normal bowel gas findings, 22% use it to mean that they cannot tell if the findings are normal or abnormal, and 13% use it to indicate an abnormal study, but one in which they cannot determine if the findings represent mechanical obstruction or adynamic ileus.[34]

Abdominal plain film radiographs should include both supine and upright or decubitus studies. An upright chest radiograph may also be obtained to evaluate for subdiaphragmatic free air resulting from a bowel perforation. Characteristic plain radiographic findings of SBO include distended loops of bowel, normally greater than 3 cm in diameter, seen centrally in the radiograph (Fig. 92-3). In addition, unlike the haustra of the large intestine, which do not cross the full diameter of the bowel, the valvulae conniventes (or plicae circulares) of the small bowel cross the entire lumen of the small intestine. Noting these structures crossing the lumen of distended bowel on plain radiographs helps to differentiate SBO from large bowel obstruction. In general, the greater the number of distended loops, the more distal the obstruction. No gas should be seen in the large bowel, unless the films are obtained early in the course of the obstruction, or in the presence of a partial SBO.

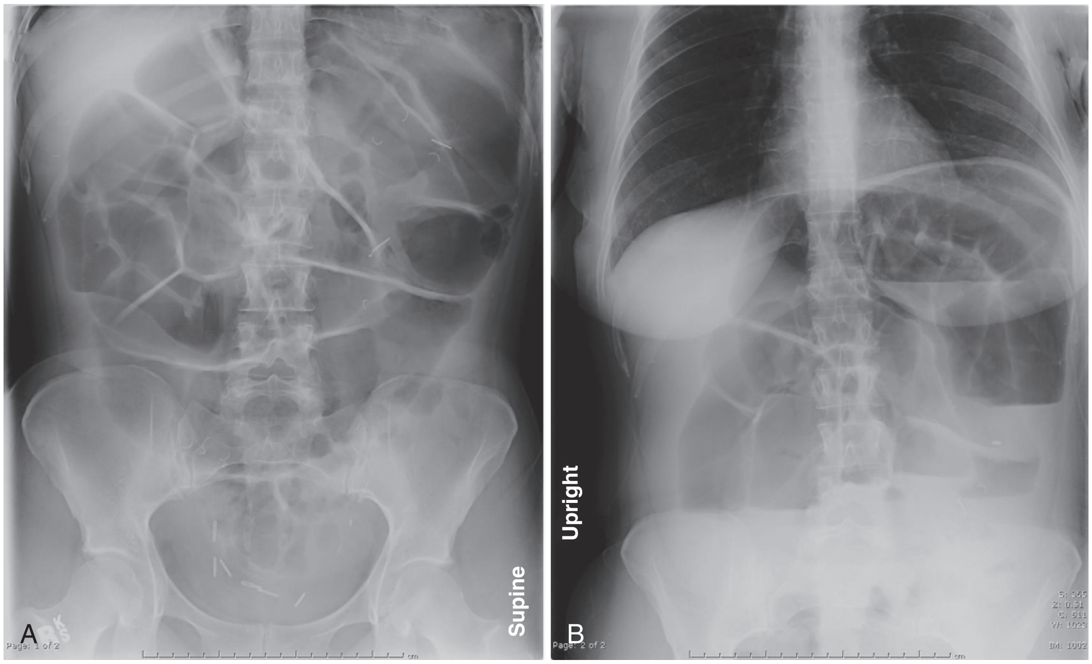


Figure 92-3. A, Supine plain film radiograph showing dilated loops of small bowel in a patient with small bowel obstruction. B, Upright abdominal plain radiograph revealing multiple air-fluid levels and small bowel dilation, consistent with a diagnosis of small bowel obstruction.

www.ketabpezeshki.com 66485457-66963820

If the obstructed small bowel contains more fluid than air, the classic radiographic findings may be absent. In this setting, a row of air bubbles seen on upright or decubitus plain films may be present. These represent small amounts of air trapped between the valvulae conniventes. The meniscal effect of the surrounding fluid gives the air an ovoid or rounded appearance, which is referred to as the "string of pearls" or "string of beds" sign and is very suggestive of SBO.[35] An adynamic ileus, on the other hand, tends to show extensive air-filled loops throughout the entire gastrointestinal system, and no small bowel dilation.

Computed tomography (CT) has become an increasingly popular imaging modality in the evaluation of SBO and has largely replaced the small bowel series, in which barium or water soluble contrast that is swallowed or introduced into the duodenum via a nasogastric tube is followed fluoroscopically. CT has been shown to detect SBO with a high degree of sensitivity and specificity. In addition, unlike plain films and the small bowel follow-through studies, CT provides more information about the cause of obstruction, such as a tumor.[36]

Finally, any discussion of the diagnostic strategies in SBO would be incomplete without addressing the challenges of identifying strangulation complicating SBO. Despite several decades of investigations into the problem, numerous studies have failed to elicit clinical indicators that reliably predict this life-threatening condition. One study that evaluated 72 preoperative clinical, laboratory, and radiologic findings at admission showed that only the CT finding of reduced intestinal wall enhancement, elevated white blood cell (WBC) count, and guarding on physical examination were independent predictors of bowel strangulation. Of these, the CT finding was by far the most specific at 96%, with a likelihood ratio of 9.3 for the presence of strangulation. The likelihood ratios for leukocytosis and guarding for the presence of strangulated bowel were much less impressive at 1.7 and 2.8, respectively.[37]

Differential Considerations

The diagnosis of SBO should be considered in any patient with abdominal pain and vomiting, especially if he or she has a history of prior abdominal surgery. It may be difficult to differentiate SBO from nonobstructive intestinal motility disorders such as adynamic ileus or intestinal pseudo-obstruction by history and physical examination alone.

The other conditions to consider in the differential diagnosis range widely from benign to potentially life-threatening. These include constipation, cholelithiasis or nephrolithiasis, ectopic pregnancy, pancreatitis, peptic ulcer disease, atypical myocardial infarction, leaking abdominal aortic aneurysm (AAA), and mesenteric ischemia. These pathologies have typical signs, symptoms, and diagnostic findings that can help differentiate them from one another and from SBO, but this may be challenging, especially early in the course of the particular disorder.

Management and Disposition

Hemodynamically unstable patients should be aggressively resuscitated with crystalloid solution via a large-bore catheter. Although use of nasogastric decompression is considered dogma by many emergency physicians and surgeons, its effect in decreasing the duration of SBO has scant support in the medical literature. In the era of modern antiemetics, if the patient's symptoms of nausea and vomiting can be controlled with medication, it may be reasonable to delay nasogastric tube insertion. However, if symptoms persist or if the patient has an altered level of consciousness that places him or her at risk for aspiration, a nasogastric tube should be promptly inserted and attached to wall suction. Studies have shown no benefit to the use of long intestinal tubes over a traditional nasogastric tube.[38] Placement of a nasogastric tube is a noxious procedure, and attempts should be made to anesthetize the patient's nasopharynx with topical anesthetic before insertion.

All patients with SBO merit admission to the hospital. One recent study found that patients with SBO admitted to a surgical service for inpatient management had a shorter length of stay, lower hospital charges, and lower mortality than those admitted to the medical service.[39] This was attributed largely to the fact that those patients in whom conservative management was failing and who needed surgical intervention were identified more quickly when being managed primarily by the surgical team. However, in the community setting, where hospitalists with internal medicine and family practice training have assumed a large role in the management of surgical patients, it may not be logistically possible to admit patients with SBO directly to a surgical service.

Bacterial translocation is thought to result from simple SBO; in one series, 59% of patients who underwent operative intervention for simple SBO had bacteria (most commonly *Escherichia coli*) cultured from mesenteric lymph nodes, compared with 4% of patients who underwent operations for other reasons. However, this has not been shown to be clinically relevant,[40] and there is no convincing evidence to recommend the empirical use of antibiotics in the nonoperative management of a simple SBO. In patients in whom surgical exploration is planned or perforation is suspected, antibiotics are recommended. The antibiotic used should provide coverage against the gram-negative and anaerobic organisms that colonize the intestinal tract (e.g., second-generation cephalosporins).

SBO in the presence of known malignancy is very common, occurring in up to 30% of patients with colon cancer and 50% of patients with ovarian cancer at some time in the course of their disease. Surgery should be the primary treatment for selected patients with malignant bowel obstruction (MBO). In patients who do not qualify for surgical intervention because of intra-abdominal carcinomatosis, massive ascites, or poor overall health status, treatment with self-expanding metal stents and the use of octreotide to rapidly reduce gastrointestinal secretions may provide significant palliative relief.[41] A collaborative approach with the patent's oncologist and consulting surgeon can provide the ideal individualized treatment for the patient in this situation.

Finally, although laparoscopic surgery was once considered inappropriate for the management of SBO, several studies have shown that laparoscopy is a safe and effective surgical method in the treatment of SBO in adults and children, particularly those with obstructions caused by adhesions.[42,43] The risk of recurrence seems to be similar to that of an open surgical approach.[44] As surgeons continue to gain experience with laparoscopy, it will likely become more commonly applied to the surgical management of SBO.

KEY CONCEPTS

- Intestinal obstruction is a very common problem encountered in the ED, accounting for up to 15% of all emergency admissions for abdominal pain.
- Postoperative adhesions are the most common cause of SBO in the United States. Other common causes include neoplasms and hernias.
- Plain radiographs can diagnose SBO in 50 to 60% of cases but usually cannot identify the cause of the obstruction. CT scanning is much better for determining the cause and is also very useful in identifying strangulation complicating SBO.

www.ketabpezeshki.com 66485457-66963820

ACUTE MESENTERIC ISCHEMIA

Perspective

In his 1926 treatise on mesenteric vascular occlusion, A.J. Cokkinis wrote, "occlusion of the mesenteric vessels is apt to be regarded as one of those conditions of which…the diagnosis is impossible, the prognosis is hopeless and the treatment almost useless."[45] Despite significant advances in the understanding of the pathophysiology of this condition since that time, the mortality rate has remained as high as 60 to 80%, and the diagnosis and treatment of this vascular catastrophe have remained difficult.[46]

Acute mesenteric ischemia (AMI) involves the acute insufficiency of the blood supply to the small bowel and may also involve the right colon. The left colon has a much higher degree of collateral blood flow and is less prone to AMI.[47] When AMI occurs, rapid intestinal injury results. This condition should be clearly differentiated from chronic mesenteric ischemia (CMI), which is often referred to as "intestinal angina" and often manifests as recurrent episodes of abdominal pain resulting from insufficient intestinal blood flow during periods of increased postprandial metabolic demand.[48] CMI does not usually require emergent therapy; however, it is possible for AMI to develop in these patients as well.

Overall AMI is a rare clinical problem, accounting for 0.1% of hospital admissions.[49] Within the diagnosis of AMI there are four specific clinical categories that make up the overwhelming majority of causes, each having distinct epidemiologic risk factors. These categories include mesenteric arterial embolus, mesenteric arterial thrombosis, nonocclusive mesenteric ischemia, and mesenteric venous thrombosis.

Principles of Disease

The mesenteric vessels arise from the primitive ventral segmental arteries. Although there is a significant amount of person-to-person variability, as embryologic development proceeds, these vessels typically regress with the exception of the 10th, 13th, and 21st segmental arteries. These become the celiac trunk, superior mesenteric artery (SMA), and inferior mesenteric artery (IMA), respectively.[50] The celiac trunk arises from the anterior aspect of the abdominal aorta and branches into the common hepatic, splenic, and left gastric arteries. These vessels supply the distal esophagus to the duodenum at the entrance of the bile duct. The SMA normally arises 1 cm below the celiac trunk and runs toward the cecum, terminating as the ileocolic artery. The SMA supplies the distal half of the duodenum to the proximal two thirds of the transverse colon. The IMA originates approximately 6 to 7 cm below the SMA and gives rise to the left colic artery, the sigmoid arteries, and the hemorrhoidal arteries. Anatomically, this vessel provides blood flow to the distal third of the transverse colon to the rectum.

The gut receives 20% of cardiac output at rest, and up to 35% after eating. Of this, up to 70% supplies the mucosa. This is because of the high metabolic demands required for the absorptive function of this intestinal layer.

Intestinal blood flow is regulated by a complex combination of intrinsic and extrinsic mechanisms to match intestinal demands with blood supply. Intrinsic factors provide the moment-to-moment control of the intestinal circulation; they function independently from neural control. This intrinsic modulation has been proposed to involve the release of local metabolites produced as a result of mucosal ischemia. These metabolites are then thought to diffuse to the local arterioles, triggering relaxation in the smooth muscle and increased blood flow, thereby allowing for efficient adjustments to the intestinal blood supply. Smooth muscle relaxation can also be brought about directly by a decrease

Figure 92-4. Gross pathologic image of intestinal ischemia and infarction. Note mucosal hyperemia and hemorrhage. (From Gore RM, et al: Imaging in intestinal ischemic disorders. Radiol Clin North Am 46;845-875, 2008.)

in the perfusion pressure in the arterioles themselves. These two mechanisms are referred to as the *metabolic* and *myogenic pathways.* Intestinal blood flow is also controlled extrinsically through neural and hormonal mechanisms. Increased sympathetic tone to the paired celiac ganglia located adjacent to the celiac trunk results in mesenteric and arteriolar vasoconstriction. Hormonal influences include the direct action of angiotensin II released as a result of decreased extracellular volume, as well as vasopressin to cause mesenteric vasoconstriction.[51]

Although these mechanisms allow for the mesenteric circulation to adapt to wide variations in the metabolic needs of the gut and systemic perfusion, in the setting of acute compromise the bowel is very quickly injured. Because of the high metabolic demands of the intestinal mucosa, within 15 minutes of absolute ischemia, structural damage to the intestinal villi can be observed histologically (Fig. 92-4). If not corrected, within 3 hours mucosal sloughing occurs. By 6 hours, transmural necrosis is complete.[52] Complicating the situation even further, reestablishment of blood flow at this point results in the systemic release of several proinflammatory cytokines and toxic oxygen radicals caused by reperfusion, which can lead to multiorgan failure and rapid death.[53]

Mesenteric Arterial Embolism

Arterial emboli are the most common cause of AMI and are responsible for approximately 50% of cases. The median age of patients with mesenteric arterial emboli is 70 years, and two thirds are women. Emboli are most often cardiac in origin and arise from left atrial or ventricular mural thrombi or valvular lesions. Risk factors for the development of such thrombi include myocardial ischemia or infarction, cardiomyopathies, ventricular aneurysms, endocarditis, and atrial dysrhythmias, specifically atrial fibrillation.[54] Compared with the estimated annual risk of stroke of 2.3%, the annual risk of AMI caused by thromboembolism secondary to atrial fibrillation is 0.14%.[55] The SMA is most frequently affected because of the large caliber of the vessel and its narrow takeoff angle from the aorta. The embolus typically lodges 3 to 10 cm distal to the origin of the SMA (Fig. 92-5). The jejunum is most often involved, as it is distant from the collateral flow provided from the celiac and inferior mesenteric arteries.

Mesenteric Arterial Thrombosis

Mesenteric arterial thrombosis results from the progression of atherosclerotic disease of the mesenteric vasculature. Risk factors for development include advanced age, hypertension, diabetes, and tobacco use. Affected patients frequently have a history

www.ketabpezeshki.com 66485457-66963820

Figure 92-5. Coronal abdominal computed tomography angiogram with large superior mesenteric artery embolism *(arrow)*. (From Gore RM, et al: Imaging in intestinal ischemic disorders. Radiol Clin North Am 46:845-875, 2008.)

suggestive of CMI of several months' or years' duration. Unlike embolic occlusions, thrombosis usually occurs in the proximal SMA at the origin of the vessel.[56]

Nonocclusive Mesenteric Ischemia

Nonocclusive mesenteric ischemia occurs as a result of mesenteric vasospasm in the absence of a physical obstruction. This vasospasm is triggered by mesenteric hypoperfusion or excessive sympathetic nervous system activity. Mesenteric hypoperfusion can result from a wide variety of conditions, including sepsis, severe dehydration, pancreatitis, or hemorrhagic shock. Excessive sympathetic activity can result from congestive heart failure, or the use of medications and drugs such as vasopressors, cocaine, or digoxin.[57] Once initiated, this vasospasm often persists even after correction of the underlying condition, and repeated episodes of ischemia and reperfusion occur. Studies suggest that this recurrent pattern of ischemia and reperfusion may result in more severe histologic injury than a single episode of prolonged ischemia.[58]

Mesenteric Venous Thrombosis

Mesenteric venous thrombosis is the least common cause of AMI, accounting for only 5 to 15% of all mesenteric ischemic events. It most frequently involves the superior mesenteric vein and its branches. In the vast majority of cases (over 75%), an underlying inherited thrombotic disorder or an inherited or acquired hypercoagulable state can be identified. The most common cause is factor V Leiden mutation, which is thought to account for 20 to 40% of cases. Other inherited prothrombotic states implicated in the development of mesenteric venous thrombosis include deficiency in antithrombin III, protein C, or protein S. Hematologic conditions predisposing to this condition include polycythemia vera and essential thrombocythemia. Oral-contraceptive use accounts for 9 to 18% of the episodes of mesenteric venous thrombosis in young women. Local intra-abdominal inflammation secondary to pancreatitis, malignancy, or inflammatory bowel disorders also increase the risk of mesenteric venous thrombosis.

Box 92-3 Factors Associated with Mesenteric Venous Thrombosis

- Hypercoagulable states
  - Polycythemia vera
  - Sickle cell disease
  - Antithrombin III deficiency
  - Protein C or S deficiency
  - Malignancy
  - Myeloproliferative disorders
  - Estrogen therapy, oral contraceptive pills
  - Pregnancy
- Inflammatory conditions
  - Pancreatitis
  - Diverticulitis
  - Appendicitis
  - Cholangitis
- Trauma
  - Operative venous injury
  - Postsplenectomy
  - Blunt or abdominal trauma
  - Miscellaneous
  - Congestive heart failure
  - Renal failure
  - Decompression sickness
  - Portal hypertension

Finally, the venous stasis caused by portal hypertension is a recognized risk factor.[59]

Box 92-3 summarizes causes of mesenteric venous thrombosis.

Unusual Causes of Mesenteric Ischemia

In addition to the conditions already described, there are numerous case reports of unusual causes of mesenteric ischemia. These include SMA dissection leading to occlusion, tumor emboli, retroperitoneal fibrosis, and various types of vasculitis, including Buerger's disease, polyarteritis nodosa, and Takayasu's arteritis. Because these conditions involve a rare cause of an already rare condition, they frequently go unrecognized until patients develop major adverse outcomes.[60]

Clinical Features

History

The history at presentation is largely dependent on the nature of the underlying cause. The traditional historical triad of AMI is the sudden onset of poorly localized abdominal pain and gastric emptying (vomiting or diarrhea) in a patient with cardiac disease. This is especially true in cases of SMA embolism or thrombosis, in which symptoms and clinical deterioration can rapidly occur. In cases of mesenteric venous thrombosis the symptoms are slower in onset and often have been present for several days by the time the patients seeks medical attention. Approximately one third of patients with acute embolic mesenteric ischemia and one half of patients with acute mesenteric venous thrombosis have a personal history of an embolic event such as a pulmonary embolism, deep vein thrombosis, or ischemic stroke.[61] Patients with nonocclusive mesenteric ischemia are often already critically ill and in the hospital, making it difficult or impossible for them to provide historical details to the treating physician.

Physical Examination

The pain is classically described as being "out of proportion" to the physical examination findings. The patient may be writhing in

www.ketabpezeshki.com 66485457-66963820

pain but have a soft abdomen without guarding, especially early in the course of the event when only the visceral structures are ischemic. As the parietal peritoneum becomes ischemic, the abdominal physical findings progress. If the ischemia progresses to infarction, peritonitis may be present. Heme-positive stools may also be noted. Hypotension, tachycardia, and tachypnea are all signs of severe ischemia and suggest a poor prognosis.

Complications

Even with prompt recognition and aggressive treatment of AMI, a complicated course is expected. Secondary reperfusion injury is common, and bowel initially identified as viable may progress to necrosis. Other complications include wound infections, sepsis, and pneumonia. Given the population in which AMI tends to occur, the physiologic stress of this disease process also places patients at high risk for myocardial infarction, renal failure, and pulmonary embolism while in the hospital.

Diagnostic Strategies

Because of the rare and potentially devastating nature of AMI, it is imperative that a high index of suspicion for this condition be maintained. The emergency physician should be especially vigilant in patients older than 50 years with the complaint of the sudden onset of abdominal pain. Despite significant advances in the understanding of the pathology of AMI, its rapid diagnosis remains challenging. Owing to the rarity of this condition, there are few clinical data comparing treatments, and most suggested treatment guidelines have been created from expert opinion.

Initial laboratory results are often nonspecific and may include leukocytosis, an elevated hematocrit secondary to hemoconcentration, and metabolic acidosis. Several serum biomarkers have been investigated as early indicators of AMI. These include lactate, D-dimer, interleukin (IL)-6, and serum ischemia-modified albumin levels.[62,63] One small study showed that an elevated plasma lactate level was 100% sensitive for AMI but only 42% specific.[64] To date, no biomarkers have been found that are sufficiently sensitive and specific to diagnose or eliminate mesenteric ischemia. In addition, several of the biomarkers currently being investigated require up to several hours for results to become available, which significantly limits their usefulness in this time-sensitive emergency.

Mesenteric angiography remains the "gold standard" in the radiographic evaluation for mesenteric ischemia, and offers the benefit that diagnosis and initial treatment can occur concurrently. However, in reality, angiographic services may not be widely available to the treating emergency physician. Plain radiographs in mesenteric ischemia are most often nonspecific. Later in the disease course, plain radiograph findings may show so-called *thumbprinting,* in which multiple, round, smooth soft tissue densities project into the intestinal lumen because of mucosal and submucosal edema and hemorrhage. More specific but very late plain radiographic findings indicating infarction include pneumatosis intestinalis and portal venous gas.

CT has largely replaced conventional angiography as the initial imaging study of choice in the evaluation of mesenteric ischemia (Fig. 92-6). Several studies have shown that with the emergence of multidetector scanners the sensitivity and specificity for mesenteric ischemia are quite high, at approximately 96% and 94%, respectively.[65,66] Although the current management guidelines for AMI created by the American Gastroenterological Association suggest frequent and rapid traditional angiographic evaluation in cases of suspected AMI, these recommendations predate numerous studies on the accuracy of CT angiography in the diagnosis of AMI.[67] Future revisions of these guidelines will likely be amended to include more use of CT angiography in the initial evaluation of these patients.

Figure 92-6. Superior mesenteric venous thrombus (identified here by arrow) in a patient with nondescript abdominal pain. Hematologic workup revealed factor V Leiden thrombophilia. (From Gore RM, et al: Imaging in intestinal ischemic disorders. Radiol Clin North Am 46:845-875, 2008.)

Duplex sonography has also been evaluated as an imaging tool in the diagnosis of AMI. It has been found to be very specific (92-100%) for the detection of occlusions, but its sensitivity is decreased (70-89%) by the limited evaluation beyond the proximal main vessel that is possible with ultrasound.[68] It is unable to provide much information about complications of AMI, including bowel infarction.

Differential Considerations

Other potentially devastating conditions to consider in the differential diagnosis of acute-onset severe abdominal pain include leaking AAA, perforated viscus, bowel obstruction, biliary disease, and atypical myocardial infarction.

Management and Disposition

Once AMI has been diagnosed, the goals of treatment are to restore mesenteric blood flow as rapidly as possible, manage underlying conditions, treat persistent mesenteric vasospasm if present, and mitigate the risk of further clot propagation. Initial interventions should focus on aggressive fluid resuscitation and hemodynamic stabilization. Because these patients are often elders with significant cardiac comorbidities, invasive monitoring may be indicated. If vasopressors are required, dobutamine, low-dose dopamine, or milrinone is advised, as these agents have been shown in human and animal studies to have less of a vasoconstrictive effect on the mesenteric vasculature than other agents.[69,70] Broad-spectrum antibiotics should be administered without delay, and a general or vascular surgeon should be immediately consulted. Further management is dependent on the cause of ischemia, and controversies exist as to the optimal management of these critically ill patients.

Regardless of the cause, if signs of intestinal infarction or perforation with peritonitis are present, prompt emergent laparotomy is warranted. Some have suggested that preoperative conventional angiography may be beneficial to attempt rapid revascularization, and recent data suggest that initial endovascular revascularization may significantly improve patient outcomes and

www.ketabpezeshki.com 66485457-66963820

dramatically alter the future treatment of AMI.[71] Numerous reports exist detailing the use of thrombolytic agents, angioplasty, embolectomy, or vascular stenting to restore mesenteric blood flow.[72-74] In addition, the phosphodiesterase inhibitor papaverine may be continuously infused directly into the compromised vessel.[75] This agent results in elevated levels of cyclic adenosine monophosphate (cAMP), which results in profound smooth muscle relaxation. Because this medication undergoes over 90% first-pass hepatic metabolism, few systemic effects are noted when the agent is infused directly into the mesenteric circulation. However, catheter migration into the aorta can cause rapid hemodynamic collapse if not quickly recognized. A "second-look" laparotomy may be indicated, as bowel that initially appears viable may become gangrenous later.[76]

Primary treatment of nonocclusive mesenteric ischemia involves aggressive interventions to reverse the underlying cause and consideration for papaverine infusion via angiographic catheter as well as intravenous heparin to prevent thrombosis in the vasospastic vessel. Papaverine infusion is often maintained for 24 hours, at which time repeated angiography may be performed to evaluate for the resolution of vasospasm. If peritoneal signs develop, laparotomy is indicated. If the underlying medical condition persists, the mortality of nonocclusive mesenteric ischemia remains high.

The treatment of mesenteric venous thrombosis is unique in that, in the absence of peritoneal findings, initial treatment with heparin infusion alone may be adequate. However, if peritoneal findings are present or develop later in the patient's hospital course, bowel necrosis is likely and prompt laparotomy. If the patient recovers, long-term anticoagulation with warfarin usually is provided to prevent recurrence. An appropriate workup for hypercoagulable conditions should be undertaken.

Acknowledgement

The contributors would like to thank Drs. Susan P. Torrey and Philip Henneman for their work in earlier editions.

KEY CONCEPTS

- Acute mesenteric ischemia is a rare vascular catastrophe with a very high mortality. It should be considered in patients older than 50 years with a history of cardiac disease who have acute abdominal pain, which may initially appear as severe pain that seems "out of proportion" to physical examination findings.
- Within the diagnosis of AMI are four distinct clinical entities with specific associated risk factors, clinical presentations, and treatments: mesenteric arterial embolism, mesenteric arterial thrombosis, nonocclusive mesenteric ischemia, and mesenteric venous thrombosis.
- Traditionally, conventional angiography has been the imaging test of choice. However, recent advancements in multidetector CT angiographic scanning have made this modality a very sensitive and specific tool for the diagnosis of AMI.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Aufderheide AC: *The Scientific Study of Mummies*. Cambridge, England: Cambridge University Press; 2003.
2. Wangensteen OH: Historical aspects of the management of acute intestinal obstruction. *Surgery* 1969; 65:363-383.
3. Miller CJ: A study of three hundred forty-three surgical cases of intestinal obstruction. *Ann Surg* 1929; 89:91-107.
4. Foster NM, McGory ML, Zingmond DS, Ko CY: Small bowel obstruction: A population-based appraisal. *J Am Coll Surg* 2006; 203:170-176.
5. Irvin TT: Abdominal pain: A surgical audit of 1190 emergency admissions. *Br J Surg* 1989; 76:1121-1125.
6. Ray MS: Abdominal adhesiolysis: Inpatient care and expenditures in the United States in 1994. *J Am Coll Surg* 1998; 186:1-9.
7. Hayanga AJ, Bass-Wilkins K, Bulkley GB: Current management of small-bowel obstruction. *Adv Surg* 2005; 39:1-33.
8. Bizer LS, Liebling RW, Delany HM, Gliedman ML: Small bowel obstruction: The role of nonoperative treatment in simple intestinal obstruction and predictive criteria for strangulation obstruction. *Surgery* 1981; 89:407-413.
9. Luckey A, Livingston E, Taché Y: Mechanisms and treatment of postoperative ileus. *Arch Surg* 2003; 138:206-214.
10. De Giorgio R, Sarnelli G, Corinaldesi R, Stanghellini V: Advances in our understanding of the pathology of chronic intestinal pseudo-obstruction. *Gut* 2004; 53:1549-1552.
11. Holmdahl L, Ivarsson ML: The role of cytokines, coagulation, and fibrinolysis in peritoneal tissue repair. *Eur J Surg* 1999; 165:1012-1019.
12. Imudia AN, Kumar S, Saed GM, Diamond MP: Pathogenesis of Intra-abdominal and pelvic adhesion development. *Semin Reprod Med* 2008; 26:289-297.
13. Menzies D, Ellis H: Intestinal obstruction from adhesions—how big is the problem? *Ann R Coll Surg Engl* 1990; 72:60-63.
14. Attard JA, MacLean AR: Adhesive small bowel obstruction: Epidemiology, biology and prevention. *Can J Surg* 2007; 50:291-300.
15. Schnüriger B, et al: Prevention of postoperative peritoneal adhesions: A review of the literature. *Am J Surg* 2011; 201:111-121.
16. Bilimoria KY, et al: Small bowel cancer in the United States: Changes in epidemiology, treatment, and survival over the last 20 years. *Ann Surg* 2009; 249:63-71.
17. Ripamonti CI, Easson AM, Gerdes H: Management of malignant bowel obstruction. *Eur J Cancer* 2008; 44:1105-1115.
18. Idelevich E, Kashtan H, Mavor E, Brenner B: Small bowel obstruction caused by secondary tumors. *Surg Oncol* 2006; 15:29-32.
19. Filip JE, Mattar SG, Bowers SP, Smith CD: Internal hernia formation after laparoscopic Roux-en-Y gastric bypass for morbid obesity. *Am Surg* 2002; 68:640-643.
20. Chang SS, Shan YS, Lin YJ, Tai YS, Lin PW: A review of obturator hernia and a proposed algorithm for its diagnosis and treatment. *World J Surg* 2005; 29:450-454.
21. Reisner RM, Cohen JR: Gallstone ileus: A review of 1001 reported cases. *Am Surg* 1994; 60:441-446.
22. Vaez-Zadeh K, Dutz W, Nowrooz-Zadeh M: Volvulus of the small intestine in adults: A study of predisposing factors. *Ann Surg* 1969; 169:265-271.
23. Frazee RC, Mucha P Jr, Farnell MB, van Heerden JA: Volvulus of the small intestine. *Ann Surg* 1988; 208:565-568.
24. Duke JH Jr, Yar MS: Primary small bowel volvulus: Cause and management. *Arch Surg* 1977; 112:685-698.
25. Ford EG, Senac MO Jr, Srikanth MS, Weitzman JJ: Malrotation of the intestine in children. *Ann Surg* 1992; 215:172-178.
26. Buettcher M, Baer G, Bonhoeffer J, Schaad UB, Heininger U: Three-year surveillance of intussusception in children in Switzerland. *Pediatrics* 2007; 120:473-480.
27. Bhisitkul DM, Todd KM, Listernick R: Adenovirus infection and childhood intussusception. *Am J Dis Child* 1992; 146:1331-1333.
28. Blazes DL, Lipscomb SJ, Schoenfeld PS, Martin GJ: Intussusception in an HIV-infected patient: A case report and review of the literature. *AIDS Read* 2001; 11:525-528.
29. Gu Y, Lim HJ, Moser MA: How useful are bowel sounds in assessing the abdomen? *Dig Surg* 2010; 27:422-426.
30. Fevang BT, et al: Complications and death after surgical treatment of small bowel obstruction: A 35-year institutional experience. *Ann Surg* 2000; 231:529-537.
31. Williams SB, Greenspon J, Young HA, Orkin BA: Small bowel obstruction: Conservative vs. surgical management. *Dis Colon Rectum* 2005; 48:1140-1146.
32. Fevang BT, et al: Long-term prognosis after operation for adhesive small bowel obstruction. *Ann Surg* 2004; 240:193-201.
33. Cronk DR, et al: Intestinal fatty acid binding protein (I-FABP) for the detection of strangulated mechanical small bowel obstruction. *Curr Surg* 2006; 63:322-325.
34. Patel NH, Lauber PR: The meaning of a nonspecific abdominal gas pattern. *Acad Radiol* 1995; 2:667-669.
35. Nevitt PC: The string of pearls sign. *Radiology* 2000; 214:157-158.
36. Maglinte DD, Balthazar EJ, Kelvin FM, Megibow AJ: The role of radiology in the diagnosis of small-bowel obstruction. *AJR Am J Roentgenol* 1997; 168:1171-1180.
37. Jancelewicz T, et al: Predicting strangulated small bowel obstruction: An old problem revisited. *J Gastrointest Surg* 2009; 13:93-99.
38. Brolin RE, Krasna MJ, Mast BA: Use of tubes and radiographs in the management of small bowel obstruction. *Ann Surg* 1987; 206:126-133.
39. Oyasiji T, Angelo S, Kyriakides TC, Helton SW: Small bowel obstruction: Outcome and cost implications of admitting service. *Am Surg* 2010; 76:687-691.
40. Deitch EA: Simple intestinal obstruction causes bacterial translocation in man. *Arch Surg* 1989; 124:699-701.
41. Ripamonti C, Mercadante S: How to use octreotide for malignant bowel obstruction. *J Support Oncol* 2004; 2:357-364.
42. Tierris I, et al: Laparoscopy for acute small bowel obstruction: Indication or contraindication? *Surg Endosc* 2011; 25:531-535.
43. Aguayo P, et al: Laparoscopic management of small bowel obstruction in children. *J Laparoendosc Adv Surg Tech A* 2011; 21:85-88.
44. Ghosheh B, Salameh JR: Laparoscopic approach to acute small bowel obstruction: Review of 1061 cases. *Surg Endosc* 2007; 21:1945-1949.
45. Cokkinis AJ: *Mesenteric Vascular Occlusion*. London: Baillière, Tindall and Cox; 1926.
46. Oldenburg WA, Lau LL, Rodenberg TJ, Edmonds HJ, Burger CD: Acute mesenteric ischemia: A clinical review. *Arch Intern Med* 2004; 164:1054-1062.
47. Fisher DF Jr, Fry WJ: Collateral mesenteric circulation. *Surg Gynecol Obstet* 1987; 164:487-492.
48. Moawad J, Gewertz BL: Chronic mesenteric ischemia. Clinical presentation and diagnosis. *Surg Clin North Am* 1997; 77:357-369.
49. Klein HM, Lensing R, Klosterhalfen B, Töns C, Günther RW: Diagnostic imaging of mesenteric infarction. *Radiology* 1995; 197:79-82.
50. Granger DN, Richardson PD, Kvietys PR, Mortillaro NA: Intestinal blood flow. *Gastroenterology* 1980; 78:837-863.
51. Rosenblum JD, Boyle CM, Schwartz LB: The mesenteric circulation. Anatomy and physiology. *Surg Clin North Am* 1997; 77:289-306.
52. Bradbury AW, Brittenden J, McBride K, Ruckley CV: Mesenteric ischaemia: A multidisciplinary approach. *Br J Surg* 1995; 82:1446-1459.
53. Gibot S, et al: Effects of the TREM-1 pathway modulation during mesenteric ischemia-reperfusion in rats. *Crit Care Med* 2008; 36:504-510.
54. McKinsey JF, Gewertz BL: Acute mesenteric ischemia. *Surg Clin North Am* 1997; 77:307-318.
55. Menke J, Lüthje L, Kastrup A, Larsen J: Thromboembolism in atrial fibrillation. *Am J Cardiol* 2010; 105:502-510.
56. Stoney RJ, Cunningham CG: Acute mesenteric ischemia. *Surgery* 1993; 114:489-490.
57. Bassiouny HS: Nonocclusive mesenteric ischemia. *Surg Clin North Am* 1997; 77:319-326.
58. Clark ET, Gewertz BL: Intermittent ischemia potentiates intestinal reperfusion injury. *J Vasc Surg* 1991; 13:601-606.
59. Kumar S, Sarr MG, Kamath PS: Mesenteric venous thrombosis. *N Engl J Med* 2001; 345:1683-1688.
60. Krupski WC, Selzman CH, Whitehill TA: Unusual causes of mesenteric ischemia. *Surg Clin North Am* 1997; 77:471-502.
61. Harward TR, Green D, Bergan JJ, Rizzo RJ, Yao JS: Mesenteric venous thrombosis. *J Vasc Surg* 1989; 9:328-333.
62. Dundar ZD, Cander B, Gul M, Karabulut KU, Girisgin S: Serum ischemia-modified albumin levels in an experimental acute mesenteric ischemia model. *Acad Emerg Med* 2010; 17:1233-1238.
63. Chiu YH, et al: D-dimer in patients with suspected acute mesenteric ischemia. *Am J Emerg Med* 2009; 27:975-979.
64. Lange H, Jäckel R: Usefulness of plasma lactate concentration in the diagnosis of acute abdominal disease. *Eur J Surg* 1994; 160:381-384.
65. Ofer A, et al: Multidetector CT angiography in the evaluation of acute mesenteric ischemia. *Eur Radiol* 2009; 19:24-30.
66. Kirkpatrick ID, Kroeker MA, Greenberg HM: Biphasic CT with mesenteric CT angiography in the evaluation of acute mesenteric ischemia: Initial experience. *Radiology* 2003; 229:91-98.

www.ketabpezeshki.com 66485457-66963820

67. Brandt LJ, Boley SJ: AGA technical review on intestinal ischemia. American Gastrointestinal Association. *Gastroenterology* 2000; 118:954-968.
68. Bowersox JC, et al: Duplex ultrasonography in the diagnosis of celiac and mesenteric artery occlusive disease. *J Vasc Surg* 1991; 14:780-788.
69. Joynt C, et al: Intestinal hemodynamic effects of milrinone in asphyxiated newborn pigs after reoxygenation with 100% oxygen: A dose-response study. *Shock* 2009; 31:292-299.
70. Woolsey CA, Coopersmith CM: Vasoactive drugs and the gut: Is there anything new? *Curr Opin Crit Care* 2006; 12:155-159.
71. Arthurs ZM, et al: A comparison of endovascular revascularization with traditional therapy for the treatment of acute mesenteric ischemia. *J Vasc Surg* 2011; 53:698-705.
72. Schoots IG, et al: Thrombolytic therapy for acute superior mesenteric artery occlusion. *J Vasc Interv Radiol* 2005; 16:317-329.
73. Wyers MC, Powell RJ, Nolan BW, Cronenwett JL: Retrograde mesenteric stenting during laparotomy for acute occlusive mesenteric ischemia. *J Vasc Surg* 2007; 45:269-275.
74. Resch TA, Acosta S, Sonesson B: Endovascular techniques in acute arterial mesenteric ischemia. *Semin Vasc Surg* 2010; 23:29-35.
75. Tabriziani H, Frishman WH, Brandt LJ: Drug therapies for mesenteric vascular disease. *Heart Dis* 2002; 4:306-314.
76. Endean ED, et al: Surgical management of thrombotic acute intestinal ischemia. *Ann Surg* 2001; 233:801-808.

www.ketabpezeshki.com 66485457-66963820

Chapter 93

Acute Appendicitis

Jeannette M. Wolfe and Philip L. Henneman

PERSPECTIVE

Epidemiology

Appendicitis is a common condition requiring emergency surgery. About 7% of people will develop appendicitis sometime during their lifetime. Most cases occur in adolescents and young adults, with the incidence in men being slightly higher than in women.[1,2]

Although the diagnosis is clinically clear in classic presentations, it still remains elusive in atypical presentations; after missed myocardial infarction and fractures, missed appendicitis represents the largest number of malpractice claims for practicing emergency physicians.[3]

Historical Perspective

The earliest evidence of appendicitis is suggested by the presence of right lower quadrant adhesions in an Egyptian mummy from the Byzantine era. In 1492, Leonardo da Vinci drew pictures of the colon and the appendix and called the structure an "orecchio," which literally means ear. Claudius Amyand removed the first appendix incidentally in 1735 during the repair of a scrotal hernia in an 11-year-old boy. The appendix had perforated, and a cutaneous fecal-draining fistula had developed.[4] The half-hour operation was done without anesthesia, and the boy fully recovered. In the early 1800s during the Lewis and Clark expedition, the only trip mortality was Charles Floyd, who was rumored to have died from a ruptured appendix.[5]

In 1880 in Europe, Lawson Tait performed the first successful planned appendectomy by removing a gangrenous appendix from a 17-year-old woman. Six years later Reginald Fitz, a pathologist, coined the term "appendicitis" when he read his classic paper at the first meeting of the Association of American Physicians. Fitz correctly described many of the pathophysiologic changes associated with appendicitis and advocated early surgery. Three years later, Charles McBurney described a point "determined by the pressure of one finger" between "one and a half and two inches from the anterior spinous process" which, when palpated, was associated with the greatest discomfort in patients with acute appendicitis (McBurney's point). The general acceptance that appendicitis is a surgical disease did not occur until several decades later. Early surgical intervention became popular in the early 1900s around the time that King Edward VII perforated his appendix and was operated on days before his coronation.[6]

PRINCIPLES OF DISEASE: PATHOPHYSIOLOGY

The appendix is a hollow, muscular, closed-ended tube arising from the posterior medial surface of the cecum, about 3 cm below the ileocecal valve. Its average length is approximately 10 cm, and its normal capacity is 0.1 to 0.3 mL. The role of the appendix in human physiology is unclear, but some recent studies on biofilms suggest that the appendix may act as a repository for commensal bacteria that inoculate the large bowel and protect it from pathogens.[7] Innervation of the appendix is derived from sympathetic and vagus nerves from the superior mesenteric plexus. Afferent fibers that conduct visceral pain from the appendix accompany the sympathetic nerves and enter the spinal cord at the level of the 10th thoracic segment. This causes referred pain to the umbilical area.

The majority of patients develop appendicitis because of an acute obstruction of the appendiceal lumen. This is often from an appendicolith, but obstruction can also be caused by a calculi, a tumor, a parasite, or enlarged lymph nodes. Of historical note, one of the more common causes of acute appendicitis from foreign objects in the early 19th century was ingested lead shells buried in quail meat.[8] A recent case study describes lumen obstruction from a swallowed tongue stud.[9]

After acute obstruction, intraluminal pressures rise and mucosal secretions are unable to drain. The resulting distention stimulates visceral afferent pathways and is perceived as a dull, poorly localized pain. Abdominal cramping may occur as a result of hyperperistalsis. Next, ulceration and ischemia develop as the intraluminal pressure exceeds the venous pressure, and bacteria and polymorphonuclear cells begin to invade the appendiceal wall. The appendix may appear grossly normal at this time with evidence of pathology apparent only on microscopic examination. With time, the appendix becomes swollen and begins to irritate surrounding structures, including the peritoneal wall. The pain then becomes more localized to the right lower quadrant. If swelling does not abate, hypoxia leads to necrosis and perforation through the appendiceal serosal layer. This can lead to abscess formation or diffuse peritonitis. The time required for the appendix to perforate is highly variable and controversial; some experts believe that unless a virulent organism or genetic predisposition exists, many cases will spontaneously resolve. In most cases, perforation occurs within 24 to 36 hours. Elders may be more prone to earlier perforation owing to anatomic changes in the appendix associated with aging, such as a narrowed

www.ketabpezeshki.com 66485457-66963820

appendiceal lumen, thinner mucosal lining, decreased lymphoid tissue, and atherosclerosis.[10]

No direct cause of obstruction is noted in approximately one third of cases; it is surmised that in these cases inflammation is caused by viral, bacterial, or parasitic infection with subsequent mucosal ulceration or lymphoid hyperplasia.[2]

CLINICAL FEATURES

History

Appendicitis is classically described as starting with the vague onset of dull periumbilical pain and continuing with the development of anorexia, nausea, and vomiting. The pain then migrates to the right lower quadrant, and a low-grade fever may develop. In most instances the patient has not previously experienced similar pain.[2] Unfortunately, the presentation may be highly variable. If the appendix is retrocecal or retroiliac, the pain may be blunted by the presence of overlying bowel. If the appendix is elongated, the pain may be referred to the flank, pelvis, or right upper quadrant. Other, less typical symptoms seen with appendicitis are increased urinary frequency and the desire to defecate.[2]

Physical Examination

The most common finding on physical examination is localized abdominal tenderness, usually in the right lower quadrant. Tenderness is often noted over McBurney's point, an area approximately 2 cm from the anterior superior iliac spine on an imaginary line drawn from that anatomic landmark to the umbilicus. However, because only 35% of patients have the base of their appendix within 5 cm of this point, the pain of appendicitis can be localized in other areas of the abdomen.[11]

Other physical examination findings include guarding and rigidity. Guarding is usually voluntary, and the patient can often be persuaded to relax. Rigidity is involuntary and implies more significant underlying pathology.[2] Both of these findings reflect the tensing of the abdominal wall musculature to protect the underlying bowel.

Rovsing sign is present when palpation of the left lower quadrant causes pain referred to the right lower quadrant. *Psoas sign,* indicative of a retrocecal appendix, is the increase in pain when the psoas muscle is stretched by extending the right leg at the hip while the patient lies on the left side. *Obturator sign,* indicative of a pelvic appendix, is the elicitation of pain in a supine patient as the right hip is flexed and externally rotated.

Rebound tenderness, indicative of peritoneal inflammation, is a late finding in patients with appendicitis and usually occurs only after the appendix is significantly inflamed or ruptured. Rebound tenderness can be elicited by gradually pressing over the area of tenderness for 5 to 10 seconds and then quickly withdrawing the hand to just above the skin level. A positive response occurs when the patient reports increased pain as the hand is removed. Patients with rebound tenderness are very uncomfortable with this maneuver, and it should not be repeated unnecessarily.[11] Evidence of peritoneal irritation can also be elicited by abdominal wall percussion or by having the patient cough, resulting in pain referred to the right lower quadrant.

Isolated rectal tenderness may rarely be the only site of localized pain in patients with a low-lying or retrocecal appendix. In general, however, rectal tenderness has a very limited diagnostic value, especially if concurrent right lower quadrant pain and tenderness are present.[12,13] Although a single rectal examination may provide other important information, such as the discovery of a rectal mass or occult blood, multiple examinations are not justified.

Although any of the aforementioned signs may be present in patients with acute appendicitis, a review of 10 studies that evaluated 13 signs and symptoms of adult appendicitis identified certain findings that have a high positive likelihood ratio of identifying patients with appendicitis. These were migration of pain from the periumbilical area to the right lower quadrant, right lower quadrant tenderness, and abdominal wall rigidity.[2] Conversely, the presence of pain for more than 48 hours, a history of previous episodes of similar pain, the lack of migration and right lower quadrant pain, and the lack of worsening pain with movement or cough make appendicitis less likely.[2,13] A similar review of children with appendicitis concluded that fever and rebound tenderness are the most common findings.[14]

Vital signs are often normal, particularly early in the course. A low-grade fever is present in 15% of all patients with appendicitis, and in 40% of patients if perforation has occurred.[15]

Special Considerations

Children

Young children with acute appendicitis usually are diagnosed after perforation has occurred. This may be because many common childhood illnesses are associated with nausea, anorexia, and vomiting, and young children may have difficulty communicating their discomfort.[16] Anatomically, children have a thinner appendiceal wall and a less developed omentum, which may predispose them to perforation and diffuse peritonitis.

Women

The diagnosis of acute appendicitis in women of childbearing age is especially challenging. Before the advent of imaging, as many as 45% of women with symptoms suggestive of appendicitis had a normal appendix at surgery, and as many as one third of women with true appendicitis were initially misdiagnosed. Gynecologic disease can easily masquerade as appendicitis owing to the proximity of the right ovary, the fallopian tube, and the uterus to the appendix.[17,18] Findings that may be more suggestive of abdominal pain of gynecologic origin are included in Table 93-1. Of note, although cervical motion tenderness is more common in patients with pelvic inflammatory disease, up to a quarter of women with appendicitis may also exhibit it.[19] Because obtaining an accurate diagnosis of appendicitis is especially challenging in women, ancillary imaging should strongly be considered.

Pregnant Women

Pregnant women have an overall risk of developing appendicitis similar to the general population.[20] Of the three trimesters, appendicitis appears to occur slightly more often in the second trimester

Table 93-1 Abdominal Pain in Women

More suggestive of appendicitis	Migration of pain and tenderness localized to the right lower quadrant, anorexia, normal or minimally abnormal pelvic examination findings (i.e., isolated right adnexal tenderness)
More suggestive of pelvic inflammatory disease	Several days of symptoms, history of pelvic inflammatory disease, hunger, diffuse lower abdominal pain, bilateral adnexal tenderness, cervical motion tenderness, vaginal discharge

www.ketabpezeshki.com 66485457-66963820

for unknown reasons. The diagnosis of appendicitis during pregnancy can be difficult, as early symptoms of appendicitis such as nausea and vomiting occur frequently in a normal pregnancy. Laboratory values are even less helpful, as leukocytosis is common during pregnancy. The accuracy of the physical examination may also be compromised, as enlargement of the uterus may alter the location of the appendix to the right flank or right upper quadrant. However, one study of pregnant patients with appendicitis found that most women still had presenting symptoms of right lower quadrant pain and tenderness, even when it occurred late in pregnancy.[21]

Although maternal death from appendicitis is extremely rare, fetal abortion occurs in about 5 to 15% of simple appendicitis cases and up to 37% of complicated cases.[22] Because the morbidity is high, extra caution should be taken with pregnant women with abdominal pain.

Elder Patients

Elders are three times more likely to have a perforated appendix at surgery compared with the general population. There appear to be multiple causes for this, including anatomic age-related changes of the appendix, delay in seeking medical care, atypical presentations, and minimally elevated laboratory values.[9]

Complications

The complication rate after the removal of a normal appendix or an acutely inflamed appendix is roughly 3% and increases approximately three to four times if perforation occurs.[14] The most common complication is infection. Localized wound infection occurs in about 2 to 7%, and deep intra-abdominal abscess occurs in 0.8 to 2%, with the higher percentages representing cases in which perforation has occurred.[23]

Other complications include a prolonged ileus, small bowel obstruction, pneumonia, and urinary retention and infection. In young women, perforation may cause obstruction of the fallopian tubes, leading to infertility, though recent studies suggest this is not as prevalent as once believed.[24,25] Pregnant patients with appendicitis have an increased risk of premature labor (15-45%) and fetal death.

The mortality of uncomplicated appendicitis in otherwise healthy individuals is less than 0.1% but increases to about 3 to 4% with perforation in patients with comorbidities or advanced age. Although reported perforation rates vary significantly from study to study, the overall average is 20 to 30%. This increases greatly at the extremes of age. Elders have perforation rates as high as 60%, and children younger than 3 years can have perforation rates as high as 80 to 90%.[9,15]

The identification of factors that may increase a patient's risk for perforation is evolving. The traditional belief has been that the natural course of appendicitis is inflammation that, if surgery is delayed, ultimately progresses to necrosis and perforation. Many experts now feel that in most patients the natural course of appendicitis is spontaneous resolution without perforation.[26] This view is supported by general autopsy reports from the presurgical era, in which up to one third of corpses had evidence of periappendiceal scarring, and by studies that report successful resolution of early appendicitis with nonoperative management.[27] It is hypothesized that a subset of the population is genetically predisposed to perforation owing to an early aggressive and exaggerated inflammatory response.[28] The evidence for this is the relatively consistent population perforation rate even with the advent of increased imaging and earlier diagnoses. Most cases of perforation occur before medical evaluation, and hospital delays in operative management rarely appear to increase perforation rates.[29]

DIAGNOSTIC STRATEGIES

Laboratory Testing

Leucocyte Count and C-Reactive Protein

Approximately 80 to 90% of patients with acute appendicitis have a white blood cell (WBC) count above 10,000/mm^3. Unfortunately, the WBC count is nonspecific and often elevated with other causes of abdominal pain.

C-reactive protein (CRP) is an acute-phase reactant synthesized by hepatocytes in response to an acute injury or inflammation. It has a slower rate of rise than the WBC count and a shorter half-life. A meta-analysis suggests that the overall sensitivity of CRP is approximately 62% and specificity 66%, thereby limiting its usefulness as a stand-alone diagnostic tool in patients with appendicitis.[30] Several studies, however, have examined the diagnostic utility of combining the CRP and WBC count. Although most patients with complicated (perforated) appendicitis will have elevations of either or both laboratory values, most authorities have concentrated on the negative predictive value of a normal WBC count and CRP in ruling out appendicitis. Two meta-analyses assessing use of the combined values in adults found that patients with a WBC count below 10,000/mm^3 and a CRP below 6 to 12 mg/L were unlikely to have appendicitis (negative likelihood ratio of 0.09), whereas those with a WBC count above 10,000/mm^3 and a CRP above 8 mg/L were likely to have appendicitis (positive likelihood ratio of 23.32).[31,32] Unfortunately, this test combination appears less helpful in pediatric patients, with one study showing that 7% of patients with acute uncomplicated appendicitis have a normal WBC count and CRP.[32]

In infection, CRP doubles every 8 hours and peaks at 36 to 50 hours; there is therefore growing interest in tracking a repeat CRP in patients with examination findings equivocal for appendicitis. A recent pediatric study showed that children with appendicitis had a 6-hour CRP increase of at least 4.8 mg/L.[33]

Urinalysis

A urinalysis is helpful in differentiating urinary tract disease from acute appendicitis. Mild sterile pyuria may be seen if the inflamed appendix lies in proximity to the ureter. Significant pyuria (>20 WBCs per high-power field [hpf]) or hematuria (>30 red blood cells [RBCs]/hpf) is highly suggestive of urinary tract pathology.

Pregnancy Test

A urine pregnancy test should be performed for all women of childbearing age with abdominal pain, as a positive test result expands the differential diagnosis.

Diagnostic Scores

Several scoring systems have been developed that assign numerical values to different aspects of the history, physical examination, and laboratory test results in patients with right lower quadrant pain in an attempt to assist risk stratification in clinical decision-making. The modified Alvarado score uses a 9-point scoring system as follows: migratory right lower quadrant pain, 1 point; anorexia, 1 point; nausea or vomiting, 1 point; temperature above 37.5° C, 1 point; right lower quadrant tenderness, 2 points; rebound tenderness, 1 point; and leukocytosis, 2 points. A score below 4 is considered low risk, 4 to 6 represents moderate risk, and more than 6 represents high risk. Unfortunately, these scoring systems have yielded inconsistent results when used by themselves to determine the need for operative intervention and were particularly inaccurate when applied to female patients and patients at

www.ketabpezeshki.com 66485457-66963820

the extremes of age.[2,34] Recent renewed interest in these scales has occurred, however, to determine if they can be used to stratify a patient's need for advanced imaging. Whereas a low modified Alvarado score (<4) does not reliably exclude acute appendicitis, high scores (>6) may identify patients who would benefit from surgical consultation without imaging studies.[35,36]

Imaging Studies

Plain Radiographs

Plain radiographs are not useful in diagnosing appendicitis owing to very low sensitivity and specificity. They are not recommended in the evaluation of appendicitis unless there is a significant concern for bowel obstruction, free air, or pneumonia.[37]

Barium Enemas

Barium enemas have a sensitivity of about 80 to 90% for detection of appendicitis, and the diagnosis is essentially ruled out if the entire appendix is filled with contrast.[35] Unfortunately, a normal appendiceal lumen is often not visualized with this technique. Barium enemas are most helpful when other colon pathology is high in the differential diagnosis.

Nuclear Medicine Scans

The use of nuclear imaging with tagged WBCs has been well studied as a diagnostic tool for acute appendicitis.[36,38] The reported sensitivities of nuclear scans depend on the tag used and range from 88 to 98%. The overall usefulness of these scans is limited owing to poor specificity; any process causing inflammatory changes in the lower abdomen can lead to a false-positive scan.

Ultrasonography

Graded compression ultrasound (US) has been prospectively shown to improve the clinical accuracy of the diagnosis of acute appendicitis.[39] The reported sensitivity and specificity of US for acute appendicitis in most studies are 75 to 90% and 85 to 95%, respectively.[40] There have been some recent advances in US techniques. One group reports an astonishing 98% visualization rate (compared with the often cited 2-45%) with the addition of simple repositioning maneuvers.[41] Similarly, small studies using contrast-enhanced Doppler or harmonic waves (which allow for better resolution) show promise of higher sensitivities with lower radiation exposure.[42-44]

US is considered positive for appendicitis if the appendix is noncompressible and has a diameter of more than 6 to 7 mm. US is inexpensive, requires no exposure to radiation or dye, adds no extra time for contrast filling, and has had long-standing success in diagnosis of pelvic pathology in women. It also allows the ultrasonographer to correlate the patient's pain with the direct visualization of underlying abdominal contents. The major disadvantage of US is that the visualization of the appendix (normal or abnormal) is operator dependent, and can be especially difficult if the patient is obese, has strictures from previous surgeries, or has a retrocecal appendix. A diagnostic US also becomes more difficult after the appendix has perforated, and patients with significant right lower quadrant pain may not tolerate the graded compression.

A positive US study for appendicitis has a positive predictive value of about 90%. A negative study, however, is not helpful unless the appendix is clearly visualized or alternative pathology is identified. For this reason, it is appropriate to follow a negative US study with either in-hospital observation or a computed tomography (CT) scan if the patient's symptoms have not improved.

Computed Tomography

Abdominal pelvic CT scanning has been prospectively studied and shown to improve the clinical accuracy of the diagnosis of appendicitis.[45,46] CT findings suggestive of appendicitis include an enlarged appendix (diameter greater than 6 mm), pericecal inflammation, the presence of an appendicolith (Fig. 93-1), or a periappendiceal phlegmon or abscess (Fig. 93-2). The sensitivity

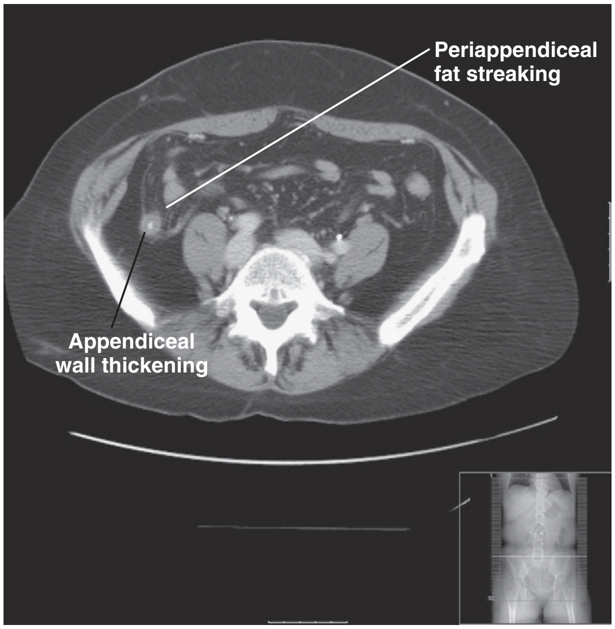


Figure 93-1. Oral contrast computed tomography scan showing evidence of acute appendicitis with periappendiceal fat streaking. (Courtesy Jefferson Radiology.)

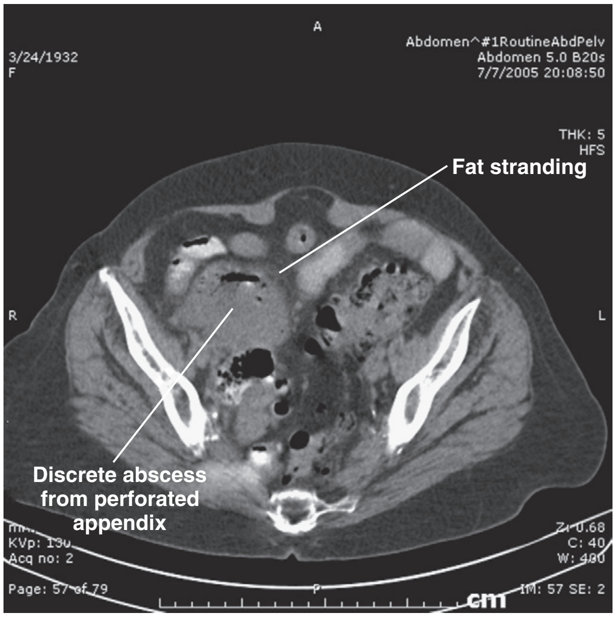


Figure 93-2. Oral contrast computed tomography scan showing discrete abscess from appendiceal perforation, with periappendiceal fat streaking. (Courtesy Jefferson Radiology.)

www.ketabpezeshki.com 66485457-66963820

(87-100%) and specificity (89-98%) of CT scan varies by study and technique and by how authors categorize inconclusive scans in their statistical analyses. There are several different protocols used in scanning patients with right lower quadrant pain, including any one or a combination of oral contrast, rectal contrast, intravenous contrast, no contrast, low-dose radiation, and a 15-cm focused scan.

CT scanning has some advantages over US in the diagnostic evaluation of appendicitis. The appendix can usually be visualized, the technique is standardized, and alternative pathology often is identified. An added benefit is that the CT signs are relatively straightforward in most patients with appendicitis. This is an important consideration because the initial interpretation of the CT scan usually dictates patient disposition, and in academic teaching centers the scans may be interpreted by junior radiology residents after hours.[47]

The biggest disadvantages of CT scanning are the radiation exposure and the expense. The amount of radiation exposure on a routine full abdominal and pelvic CT study can vary dramatically depending on scanning parameters but is usually cited as being around 10 millisieverts (mSv), which is the same radiation dose as 500 chest radiographs. This amount is theoretically carcinogenic, and it has been proposed, based on World War II atomic bomb data, that the radiation from a single abdominal CT scan could cause a fatal cancer in 1 of every 2000 adults or 500 children scanned.[48] One study estimates that of the 70 million patients who underwent CT scanning in 2007, over 27,000 patients (14,000 from abdominal pelvic CT) will ultimately develop a radiation-induced cancer.[49]

There are techniques that can be used to decrease radiation exposure in the evaluation of appendicitis. A limited focused scan through the right lower quadrant will decrease exposure but must be weighed against the possibility of missing an unusually placed appendix or alternative pathology. There have also been a few recent studies examining the use of low-dose CT scans in the diagnosis of appendicitis.[50,51] Seo studied the utility of a noncontrast low-dose scan that uses a new software technology called *sliding slab ray-sum* to rule out appendicitis. The researchers estimated that a low-dose scan (approximately 4 mSv) would have a sensitivity of 95% for appendicitis and have a less than 10% required rescan rate.[52] A small study in 2009 obtained similar results.[53] Further research is needed to clarify several questions, such as the accuracy of the identification of a noninflamed appendix, the ability to distinguish between simple and complicated appendicitis, the sensitivity of diagnosing alternative pathology, and optimal scanning parameters.

Currently the most commonly used protocol to scan patients with right lower quadrant pain is with oral and intravenous contrast. Enteric contrast (either oral or rectal) is advocated by many radiologists because they feel it helps better delineate right lower quadrant anatomy by cecal contrast opacification. Oral contrast abdominal pelvic CT generally requires a 60- to 90-minute delay after contrast administration for distal small bowel opacification (though even then contrast may not be visualized in the cecum 20-30% of the time) and may be poorly tolerated in patients with nausea or an ileus. One study addressed poor oral transit time by adding polyethylene glycol to the oral contrast, which allowed good cecal opacification in 1 hour.[49]

Rectal contrast appears to be very sensitive for detecting acute appendicitis, with rates as high as 98%.[54] It confers a number of theoretic advantages over oral contrast: It may be better tolerated in nauseated patients; there is no delay in scanning because of contrast transit time; and there is more consistent cecal opacification.[55,56] These benefits must be weighed against patient and technician preference, as many find these scans invasive and messy.

Intravenous contrast is used at many institutions, as it will enhance an inflamed appendiceal wall and may aid in delineating alternative pathology. In one study, patients received oral contrast, followed by a focused 15-cm right lower quadrant scan, followed by a scan of the entire abdomen with intravenous contrast. CT sensitivities increased from 83 to 93% with the addition of the intravenous contrast scan.[57]

Several studies have given convincing arguments in favor of the use of an intravenous-contrasted scan without enteric contrast. Kharbanda looked at historical data comparing a protocol that included both rectal and IV contrast with a new IV contrast only protocol and found similar sensitivities (92 and 93%, respectively).[58] Likewise, Kaiser reported sensitivities of 97% with intravenous contrast alone in children for appendicitis.[59] The downside of intravenous contrast is the potential for adverse reactions, such as anaphylactoid reactions, skin extravasation, and renal injury, and its slightly increased cost.

Recently there has been increased interest in the use of CT scans that bypass the need for both enteric and intravenous contrast. The argument is that CT technology is advancing with multidetector helical scanners and that an enlarged inflamed appendix with surrounding periappendiceal fat streaking should be visualized on most noncontrast scans. These scans avoid the potential complications of enteric and intravenous contrast and decrease emergency department (ED) length of stay. A meta-analysis of seven studies showed an overall sensitivity and specificity of 93% and 96%, respectively, for the diagnosis of appendicitis with noncontrast scans.[60] However, the study that contributed the most data to the analysis had a large number of patients with equivocal scans and a 23% rescan rate.[61] It is not clear that such a high rescan rate is justifiable in lieu of the additional radiation exposure. At this time, the sensitivities for these noncontrast scans appear to be institution-specific. Several studies have found that noncontrast scans have sensitivities for appendicitis that range from 60 to 83%.[62-65]

The results of all these studies raise more questions than provide definitive answers regarding the ideal CT protocol to detect appendicitis. However, three salient points seem to consistently emerge. First, young or slender patients are less likely to have significant intra-abdominal fat, and the use of additional contrast (intravenous or enteric) may help delineate their anatomy. Second, intravenous contrast may be useful in identifying other causes of pain, which may be especially helpful in older patients with broader differential diagnoses. Third, the use of intravenous or oral contrast may be less important in establishing the diagnosis than the interpreting radiologist's preference, experience, and access to clinical information. Hof showed that the difference in the inter-reader sensitivities of a noncontrast scan for appendicitis depends on the experience level of the radiologist, with sensitivities ranging from 81 to 95%.[66] Kaiser compared real-time CT interpretations with blinded retrospective interpretations and found the latter to be associated with decreased sensitivities for appendicitis (90% vs. 97%).[67] Keyzer found that perfect agreement regarding what was consistently identified as the appendix occurred only 71% of the time on noncontrast and intravenous scans interpreted by three different readers, and that scan reproducibility appeared to be more related to the presence of intra-abdominal fat and the skills of the individual radiologist than to the use of intravenous contrast.[68]

Finally, CT is not 100% accurate. Overall, approximately 5 to 10% of CT scans are considered inconclusive for appendicitis, and this number varies significantly among hospitals. Care should be taken not to label all inconclusive CT scans as "negative," because up to 30% of these patients ultimately have histologic confirmation of appendicitis.[62] The appendix is not visualized in 10 to 15% of inconclusive examinations. When this happens in patients with adequate cecal fat, secondary findings of appendicitis such as free fluid or fat stranding may suggest the diagnosis. Levine retrospectively reviewed 24 patients with histologically proven

www.ketabpezeshki.com 66485457-66963820

appendicitis who had "missed" CT scans and found 96% had a paucity of fat and 50% had a lack of cecal contrast opacification.[63] When the appendix is not seen in an otherwise normal CT scan in a patient with adequate abdominal fat, the risk of acute appendicitis appears to be extremely low, with one study showing it to be less than 2%.[64,65]

These studies underscore the importance of sharing accurate clinical information with radiologists and considering their experience and comfort level when institutional scanning protocols are being developed. Because accuracy rates vary among radiologists, institutions should consider periodic review of their own experiences. The Washington state surgical study, the SCOAP Collaborative, showed that CT accuracy rates and negative appendectomy rates vary significantly across hospitals and recommended that local data be used in quality improvement and education interventions.[69]

In general, even patients with a true "negative" scan should be explicitly told to be reevaluated if their symptoms progress or do not resolve in the following 24 to 36 hours. This is particularly true in patients evaluated within the first few hours of symptoms, as early appendicitis may be missed on CT scan.[70]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is an emerging tool used in the evaluation of suspected appendicitis, with reported sensitivities similar to those of CT. Access to MRI is currently limited in most EDs, and its use is often confined to pregnant patients with an indeterminate US as an alternative to CT.[70-74] As MRI becomes more available and concerns about nephrotoxicity from intravenous contrast and cancer-related deaths from ionizing radiation continue, MRI is likely to become increasingly popular and may eventually replace CT scanning in the evaluation of select patients with possible appendicitis.[75]

Laparoscopy

Laparoscopy can be performed for diagnosis or definitive treatment. Historically, its greatest advantage was in the differentiation of appendicitis from gynecologic disease in young female patients. Enteric contrast CT scan can now usually visualize the appendix, and the use of diagnostic laparoscopy with its anesthetic risks has therefore decreased significantly.

In-Hospital Observation

Despite the increased tendency to pursue diagnostic imaging in patients with right lower quadrant abdominal pain, studies suggest that most cases of appendicitis can be accurately diagnosed by performing serial physical examinations.[76,77] A review of studies that have used active inpatient observation in patients with an equivocal diagnosis of appendicitis found a negative appendectomy rate of roughly 6% without an increase in perforation rates.[59] Alternatives to inpatient observation that are used but have not been well studied include use of an ED observation unit and discharge with short-term follow-up for reevaluation.

DIFFERENTIAL DIAGNOSIS

An elongated appendix can irritate almost any abdominal structure, so the differential diagnosis of appendicitis includes essentially any pathology that can cause abdominal pain. The more common diseases that can mimic appendicitis are listed in Table 93-2. Of note, the diagnosis of gastroenteritis should be made with caution and only in patients with vomiting and diarrhea.

Table 93-2 Differential Diagnosis for Appendicitis

ALL PATIENTS	WOMEN	CHILDREN
Nonspecific abdominal pain	Ovarian cyst	Henoch-Schönlein purpura
Gastroenteritis	Ovarian torsion	Testicular torsion
Ascending diverticulitis	Pelvic inflammatory disease	Epiploic appendagitis
Gallbladder disease	Ectopic pregnancy	Mesenteric adenitis or ileocolitis
Inflammatory bowel disease		Meckel's diverticulum
Renal colic		

MANAGEMENT

In recent years there has been renewed debate as to whether acute appendicitis is truly a surgical emergency. The traditional view that untreated early appendicitis inevitably progresses to a necrotic and perforated appendix has been questioned. As stated previously, some experts believe that patients with complicated appendicitis have either a genetic predisposition to an exaggerated inflammatory response or possible infection with a more virulent pathologic organism, leading to early aggressive disease.[28] In general, this group of patients arrive for medical care with already-advanced disease. Along this reasoning, the remaining subset of patients usually have acute uncomplicated appendicitis and often will get better with medical management, including antibiotics and intravenous fluid alone. A meta-analysis of three studies that looked at nonoperative versus operative management of acute appendicitis showed that although the majority of patients recover without surgery, 42% require surgery, either during their initial hospitalization or during readmission.[78] Currently, a nonsurgical approach is probably best reserved only for patients who are poor operative candidates.

A strategy to manage patients with possible appendicitis is depicted in Figure 93-3. Patients should be kept on nothing-by-mouth (NPO) status and undergo a complete physical examination, including a pelvic examination, with consideration of a rectal examination if there is concern for an atypically placed appendix or strong alternative diagnosis. Dehydrated patients should receive intravenous crystalloid fluids, and parenteral antiemetics should be given to patients who are nauseated or vomiting. All patients should be offered pain medicine. Multiple studies show that giving opiate pain medicine to adults or children with signs of appendicitis does not mask important physical findings or impair surgical decision-making.[79,80] A recently published meta-analysis examining the relationship of opiate administration and changing abdominal findings concluded that, although the existing literature was not definitive, changes in physical signs appear to be minor and do not alter patient management.[81] The practice of withholding analgesia from patients with abdominal pain pending surgical consultation is not supported by the medical literature. In rare instances in which local surgical preference or institutional policy requires this approach, delays in obtaining consultations should be minimized.

A urine dipstick or urinalysis is suggested for all patients, along with a WBC count and, in women of childbearing age, a pregnancy test.

Controversy exists regarding when and how to best use advanced imaging techniques. Some authors have shown that CT scanning significantly decreases the rate of negative laparotomies, even in patients for whom the clinical suspicion of appendicitis is high.[82-84] Others feel that diagnostic imaging is overused and has not improved patient care.[85,86] Considering both these views, diagnostic imaging appears to be most helpful in a select group of patients, with the initial history, physical examination, and laboratory tests used to stratify patients by risk.

www.ketabpezeshki.com 66485457-66963820

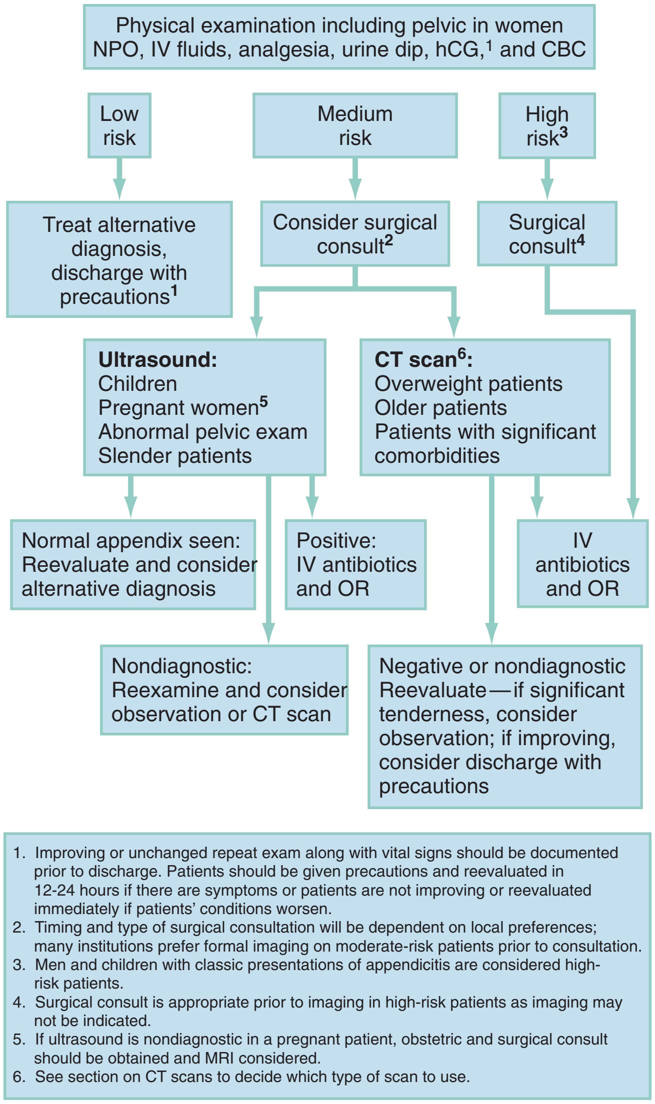


Figure 93-3. Suggested emergency department management of patients with possible appendicitis. *CBC,* complete blood count; *CT,* computed tomography; *HCG,* human chorionic gonadotropin; *IV,* intravenous; *MRI,* magnetic resonance imaging; *NPO,* nil per os ("nothing per mouth"); *OR,* operating room.

Low-Risk Patients

Patients may be considered low risk if they have minimal physical findings and a strong alternative diagnosis or if they have had previous multiple episodes of similar pain. Excessive imaging in patients who are at low risk for appendicitis will result in increased false-positive studies, as these patients have a low prevalence of disease. In these patients, the best course of action is education concerning worsening signs of appendicitis and arrangement of close follow-up. They should be instructed to be reevaluated immediately if their symptoms acutely worsen, or in 12 to 24 hours if their condition has not improved.

Equivocal-Risk Patients

"Equivocal" patients include most women (especially those of childbearing age), and men and children with atypical signs of appendicitis. Patients with equivocal signs of appendicitis should be considered for diagnostic testing or active observation. Surgical input by phone or formal consultation may be appropriate before imaging, depending on local surgical preference.

Historically, it has been very difficult to accurately diagnose women with appendicitis, and negative laparotomy rates of 40 to 45% were common. Fortunately, imaging can dramatically decrease these rates and should be strongly considered. US is the reasonable initial test if there is increased suspicion for gynecologic pathology, if the patient is slender, or if the institution has excellent experience in diagnosing appendicitis with US. Having patients drink oral contrast while waiting for their US examination allows them to be fully prepared for CT if the US is nondiagnostic.

US is also the first-line test to exclude other obstetric diagnoses in pregnant patients. If the US is equivocal, MRI should be considered if it is readily available. Although CT is less preferable, its use may still be justified after appropriate surgical and gynecologic consultation to avoid the risks of potentially unnecessary anesthesia and surgery.

Children with a suspicious presentation for appendicitis but who lack classic findings and have no clear alternative diagnosis may also be considered "equivocal." US is usually considered the initial imaging study in children because it does not expose them to radiation. This should be a significant consideration, as children are particularly vulnerable to the risks of radiation owing to their increased cell division and their longer life expectancy.[52,55]

Researchers at Packard Children's Hospital at Stanford published their experience using a graded approach of US with selected follow-up CT for children with equivocal workups for appendicitis.[87] They found that the US findings were definitively positive or negative in about 30% of patients. In patients with an equivocal US who went on to undergo CT, about 20% had appendicitis. It is interesting to note that only 52% of children with equivocal US findings went on to undergo CT. This was a retrospective study with limited follow-up, but the authors did not detect large missed appendicitis rates. Although they did not quantify the specific reasons that led to patient discharge without CT, their study opens the door for further research in this area. Improving physical examination findings after an equivocal US is reassuring, but this may be a circumstance in which repeating the CRP determination may be useful.[35] If the US is nondiagnostic and the child's clinical status has not improved, conservative management with a follow-up CT scan or admission for observation is encouraged.[54]

Men with an equivocal presentation for appendicitis should be considered candidates for US (if they are slender) or CT.

High-Risk Patients

Men and children with classic presentations of appendicitis are at high risk for appendicitis and receive little benefit from further imaging. Men with classic signs of appendicitis have the disease more than 90% of the time.[89,90] A review of CT imaging for appendicitis at one institution showed that imaging dramatically decreased the number of negative appendectomies in women (from 43 to 7%) but had no significant effect in men.[91] Another study showed that 65% of men were able to go to the operating room without a scan, with only a 4% negative appendectomy rate.[92] Surgical consultation before imaging is therefore encouraged in these high-risk groups.

Emergency physicians should advocate institutional polices that prevent unnecessary radiation in these high-risk groups. The exception may be clinically toxic high-risk patients for whom there is a concern for perforation of the appendix. Patients with walled-off abscesses may be initially managed nonoperatively, and therefore a CT scan may direct their clinical course.

Once the decision to operate has been made, prophylactic antibiotics should be given to cover gram-negative and anaerobic organisms, as this has been proven to decrease both superficial

www.ketabpezeshki.com 66485457-66963820

and deep postoperative wound infections. Intravenous second-generation cephalosporins, such as cefotetan or cefoxitin, provide good coverage. If there is a high suspicion of perforation, the traditional treatment has been broad-spectrum triple antibiotics. However, new studies suggest that monotherapy with a second-generation cephalosporin or meropenem or piperacillin and tazobactam is effective with easier administration. Alternatively a once-a-day combination of ceftriaxone and metronidazole is also sufficient.[93,94]

The timing of surgical intervention has recently been challenged, with several studies suggesting that complication rates are not adversely affected if surgery is delayed until daylight hours.[95,96] If this practice is to be considered, it needs to be balanced against the condition of the individual patient, the potential for disrupting the morning operating room schedule, and increase in the overall length of hospital stay.

The appendix can be surgically removed either through the traditional open technique or through laparoscopy. A Cochrane review of 45 randomized studies favors laparoscopic removal.[97] The authors conclude that laparoscopic appendix removal results in less frequent wound infections, less postoperative pain on day 1, shorter lengths of hospital stay, shorter time to return to normal activity, and decreased overall costs. Laparoscopy may be most helpful in female patients, as it allows inspection for pelvic pathology that may masquerade as acute appendicitis.

Some institutions have developed extensive operative and postoperative guidelines for the care of appendicitis patients.[98,99] Use of these guidelines has decreased postoperative complications and costs and appears to be most helpful in the subgroup of patients with perforation.

For patients with evidence of perforation and abscess formation, many surgeons prefer to nonoperatively drain the abscess and treat the patient with intravenous antibiotics initially, followed by appendectomy 6 weeks later.[100] Recently, it was even suggested that the appendix may not have to be removed after successful abscess resolution.[101]

DISPOSITION

If the suspicion for appendicitis is low, the patient may be sent home after appropriate counseling and arrangement of follow-up. Discharged patients should be encouraged to start on a liquid diet and advance to solids when their symptoms improve. Patients with abdominal pain of unclear cause who require significant doses of opiates to control their pain should be considered for admission.[102]

If follow-up cannot be arranged, if there are concerns regarding patient or family reliability, or if a significant language or transportation barrier exists, admission for continued observation should be considered.

KEY CONCEPTS

- Classic appendicitis is a clinical diagnosis.
- Patients with a low risk of appendicitis may be sent home with close follow-up and education about progressive symptoms.
- Patients with equivocal findings of appendicitis should undergo advanced diagnostic imaging or in-hospital serial examinations.
- Men and children with classic signs and symptoms of appendicitis should undergo prompt surgical evaluation, as imaging may be unnecessary.
- Ultrasound is an appropriate initial test in children, pregnant patients, women suspected to have pelvic pathology, and slender adults.
- Helical CT with enteric contrast is considered the initial test in all males with equivocal signs of appendicitis and in obese females in whom gynecologic disease is not suspected.
- Pain medicine should be offered to all patients with suspected appendicitis.
- Antibiotics should be given preoperatively.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Körner H, et al: Incidence of acute nonperforated and perforated appendicitis: Age-specific and sex-specific analysis. *World J Surg* 1997; 21:313-317.
2. Wagner JM, McKinney WP, Carpenter JL: Does this patient have appendicitis? *JAMA* 1996; 276:1589-1594.
3. Brown TW, McCarthy ML, Kelen GD, Levy F: An epidemiologic study of closed emergency department malpractice claims in a national database of physician malpractice insurers. *Acad Emerg Med* 2010; 17:553-560.
4. Seal A: Appendicitis: A historical review. *Can J Surg* 1981; 24:427-433.
5. Vastag B: *Medicine on the Lewis and Clark Trail: Exhibit explores expedition's medical adventures.* JAMA 2003; 289;1227-1230.
6. Smith S: Appendicitis, appendectomy and the surgeon. *Bull Hist Med* 1996; 70:414-441.
7. Randal Bollinger R, Barbas AS, Bush EL, Lin SS, Parker W: Biofilms in the large bowel suggest an apparent function of the human vermiform appendix. *J Theor Biol* 2007; 249:826-831.
8. Klingler PJ, Smith SL, Abendstein BJ, Brenner E, Hinder RA: Management of ingested foreign bodies within the appendix: A case report with review of the literature. *Am J Gastroenterol* 1997; 92:2295-2297.
9. Hadi HI, Quah HM, Maw A: A missing tongue stud: An unusual appendicular foreign body. *Int Surg* 2006; 91:87-89.
10. Watters JM, Blakslee JM, March RJ, Redmond ML: The influence of age on the severity of peritonitis. *Can J Surg* 1996; 39:142-146.
11. Ramsden WH, Mannion RA, Simpkins KC, deDombal FT: Is the appendix where you think it is—and if not does it matter? *Clin Radiol* 1993; 47:100-103.
12. Andersson RE, et al: Diagnostic value of disease history, clinical presentation, and inflammatory parameters of appendicitis. *World J Surg* 1999; 23:133-140.
13. Dixon JM, Elton RA, Rainey JB, Macleod DA: Rectal examination in patients with pain in the right lower quadrant of the abdomen. *BMJ* 1991; 302:386-389.
14. Bundy DG, et al: Does this child have appendicitis? *JAMA* 2007; 298:438-451.
15. Hale DA, Molloy M, Pearl RH, Schutt DC, Jaques DP: Appendectomy: A contemporary appraisal. *Ann Surg* 1997; 225:252-226.
16. McLario D, Rothrock S: Understanding the varied presentation and management of children with acute abdominal disorders. *Pediatr Emerg Med Rep* 1997 Nov.
17. Webster DP, Schneider CN, Cheche S, Daar AA, Miller G: Differentiating acute appendicitis from pelvic inflammatory disease in women of childbearing age. *Am J Emerg Med* 1993; 11:569-572.
18. Morishita K, Gushimiyagi M, Hashiguchi M, Stein GH, Tokuda Y: Clinical prediction rule to distinguish pelvic inflammatory disease from acute appendicitis in women of childbearing age. *Am J Emerg Med* 2007; 25:152-157.
19. Bongard F, Landers DV, Lewis F: Differential diagnosis of appendicitis and pelvic inflammatory disease. *Am J Surg* 1985; 150:90-96.
20. Al-Mulhim AA: Acute appendicitis in pregnancy. A review of 52 cases. *Int Surg* 1996; 81:295-297.
21. Mourad J, Elliott JP, Erickson L, Lisboa L: Appendicitis in pregnancy: New information that contradicts long-held clinical beliefs. *Am J Obstet Gynecol* 2000; 182:1027-1029.
22. McGory ML, et al: Negative appendectomy in pregnant women is associated with substantial risk of fetal loss. *J Am Coll Surg* 2007; 205:534-540.
23. Chung RS, Rowland DY, Li P, Diaz J: A meta-analysis of randomized controlled trials of laparoscopic versus conventional appendectomy. *Am J Surg* 1999; 177:250-256.
24. Urbach D, Cohen M: Is the perforation of the appendix a risk factor for tubal infertility and ectopic pregnancy? An appraisal of the evidence. *Can J Surg* 1999; 42:101-108.
25. Andersson R, Lambe M, Berstrom R: Fertility patterns after appendicetomy: A historical cohort study. *BMJ* 1999; 318:963-967.
26. Andersson R: Resolution and predominance of prehospital perforations imply that a correct diagnosis is more important than an early diagnosis. *World J Surg* 2007; 31:86-92.
27. Styrud J, et al: Appendectomy versus antibiotic treatment in acute appendicitis. A prospective multicenter randomized controlled trial. *World J Surg* 2006; 30:1033-1037.
28. Livingston EH, Woodward WA, Sarosi GA, Haley RW: Disconnect between incidence of nonperforated and perforated appendicitis. Implications for pathophysiology and management. *Ann Surg* 2007; 245:886-892.
29. Abou-Nukta F, et al: Effects of delaying appendectomy for acute appendicitis for 12 to 24 hours. *Arch Surg* 2006; 141:504-506.
30. Hallan S, Asberg A: The accuracy of C-reactive protein in diagnosing acute appendicitis—a meta-analysis. *Scand J Clin Lab Invest* 1997; 57:373-380.
31. Andersson RE: Meta-analysis of the clinical and laboratory diagnosis of appendicitis. *Br J Surg* 2004; 91:28-37.
32. Grönroos JM: Do normal leucocyte count and C-reactive protein value exclude acute appendicitis in children? *Acta Paediatr* 2001; 90:649-651.
33. Wu H, Fu Y: Application with repeated serum biomarkers in pediatric appendicitis in clinical surgery. *Pediatr Surg Int* 2010; 26:161-166.
34. Malik AA, Wani NA: Continuing diagnostic challenge of acute appendicitis: Evaluation through modified Alvarado score. *Aust N Z J Surg* 1998; 68:504-505.
35. Rao PM, Boland GW: Imaging of acute right lower abdominal quadrant pain. *Clin Radiol* 1998; 53:639-649. (Comment in *Clin Radiol* 1999; 54:271.)
36. Pouget-Baudry Y, et al: The use of the Alvarado score in the management of right lower quadrant abdominal pain in the adult. *J Visceral Surg* 2010; 147:e40-e44.
37. Rao PM, Rhea JT, Rao JA, Conn AK: Plain abdominal radiography in clinically suspected appendicitis: Diagnostic yield, resource use and comparison with CT. *Am J Emerg Med* 1999; 17:325-328.
38. Lin WY, et al: 99Tcm-HMPAO–labelled white blood cell scans to detect acute appendicitis in older patients with an atypical clinical presentation. *Nucl Med Commun* 1997; 18:75-78.
39. Weston AR, Jackson TJ, Blamey S: Diagnosis of appendicitis in adults by ultrasonography or computed tomography: A systematic review and meta-analysis. *Int J Technol Assess Health Care* 2005; 21:368-379.
40. Terasawa T, Blackmore CC, Bent S, Kohlwes RJ: Systematic review: Computed tomography and ultrasonography to detect acute appendicitis in adults and adolescents. *Ann Intern Med* 2004; 141:537-546.
41. Lee JH, et al: Operator-dependent techniques for graded compression sonography to detect the appendix and diagnose acute appendicitis. *AJR Am J Roentgenol* 2005; 184:91-97.
42. Rice HE, et al: Does early ultrasonography affect management of pediatric appendicitis? A prospective analysis. *J Pediatr Surg* 1999; 34:754-759.
43. Rompel O, Huelsse B, Bodenschatz K, Reutter G, Darge K: Harmonic US imaging of appendicitis in children. *Pediatr Radiol* 2006; 36:1257-6124.
44. Incesu L, Yazicioglu AK, Selcuk MB, Ozen N: Contrast enhanced power Doppler US in the diagnosis of acute appendicitis. *Eur J Radiol* 2004; 50:201-209.
45. Peck J, Peck A, Peck C, Peck J: The clinical role of noncontrast helical computed tomography in the diagnosis of acute appendicitis. *Am J Surg* 2000; 180:133-136.
46. Balthazar EJ, Rofsky NM, Zucker R: Appendicitis: The impact of computed tomography imaging on negative appendectomy and perforation rates. *Am J Gastroenterol* 1998; 93:768-771.
47. Albano MC, et al: Resident interpretation of emergency CT scans in the evaluation of acute appendicitis. *Acad Radiol* 2001; 8:915-918.
48. Brenner D, Elliston C, Hall E, Berdon W: Estimated risks of radiation induced fatal cancer from pediatric CT. *AJR Am J Roentgenol* 2001; 176:289-296.
49. Berrington de González A, et al: Projected cancer risks from computed tomographic scans performed in the United States in 2007. *Arch Intern Med* 2009; 169:2071-2077.
50. Keyzer C, et al: MDCT for suspected acute appendicitis in adults: Impact of oral and IV contrast media at standard-dose and simulated low-dose techniques. *AJR Am J Roentgenol* 2009; 193:446-454.
51. Kim K, et al: Low-dose abdominal CT for evaluating suspected appendicitis. *N Engl J Med* 2012; 366:1596-1605.
52. Seo H, et al: Diagnosis of acute appendicitis with sliding slab ray-sum interpretation of low-dose unenhanced CT and standard-dose IV contrast-enhanced CT scans. *AJR Am J Roentgenol* 2009; 193:96-105.
53. Platon A, et al: Evaluation of a low-dose CT protocol with oral contrast for assessment of acute appendicitis. *Eur Radiol* 2009; 19:446-454.
54. Garcia Peña BM, et al: Ultrasonography and limited computed tomography in the diagnosis and management of appendicitis in children. *JAMA* 1999; 282:1041-1046.
55. Acosta R, Crain EF, Goldman HS: CT can reduce hospitalization for observation in children with suspected appendicitis. *Pediatr Radiol* 2005; 35:495-500.
56. Berg ER, et al: Length of stay by route of contrast administration for diagnosis of appendicitis by computed-tomography scan. *Acad Emerg Med* 2006; 13:1040-1045.

www.ketabpezeshki.com 66485457-66963820

57. Jacobs JE, et al: Acute appendicitis: Comparison of helical CT diagnosis focused technique with oral contrast material versus nonfocused technique with oral and intravenous contrast material. *Radiology* 2001; 220:683-690.
58. Kharbanda AB, Taylor GA, Bachur RG: Suspected appendicitis in children: Rectal and intravenous contrast–enhanced versus intravenous contrast–enhanced CT. *Radiology* 2007; 243:520-526.
59. Kaiser S, Frenckner B, Jorulf HK: Suspected appendicitis in children: US and CT—a prospective randomized study. *Radiology* 2002; 223:633-638.
60. Hlibczuk V, Dattaro JA, Jin Z, Falzon L, Brown MD: Diagnostic accuracy of noncontrast computed tomography for appendicitis in adults: A systematic review. *Ann Emerg Med* 2010; 55:51-59.
61. Tamburrini S, Brunetti A, Brown M, Sirlin C, Casola G: Acute appendicitis: Diagnostic value of nonenhanced CT with selective use of contrast in routine clinical settings. *Eur Radiol* 2007; 17:2055-2061.
62. Daly CP, et al: Incidence of acute appendicitis in patients with equivocal CT findings. *AJR Am J Roentgenol* 2005; 184:1813-1820.
63. Levine CD, Aizenstein O, Lehavi O, Blachar A: Why we miss the diagnosis of appendicitis on abdominal CT: Evaluation of imaging features of appendicitis incorrectly diagnosed on CT. *AJR Am J Roentgenol* 2005; 184:855-859.
64. Ganguli S, Raptopoulos V, Komlos F, Siewert B, Kruskal JB: Right lower quadrant pain: Value of the nonvisualized appendix in patients at multidetector CT. *Radiology* 2006; 241:175-180.
65. Nikolaidis P, Hwang CM, Miller FH, Papanicolaou N: The nonvisualized appendix: Incidence of acute appendicitis when secondary inflammatory changes are absent. *AJR Am J Roentgenol* 2004; 183:889-892.
66. in't Hof KH, et al: Interobserver variability in CT scan interpretation for suspected acute appendicitis. *Emerg Med J* 2009; 26:92-94.
67. Kaiser S, Finnbogason T, Jorulf HK, Söderman E, Frenckner B: Suspected appendicitis in children: Diagnosis with contrast-enhanced versus nonenhanced helical CT. *Radiology* 2004; 231:427-433.
68. Keyzer C, et al: Normal appendix in adults: Reproducibility of detection with unenhanced and contrast-enhanced MDCT. *AJR Am J Roentgenol* 2008; 191:507-514.
69. SCOAP Collaborative, et al: Negative appendectomy and imaging accuracy in the Washington State Surgical Care and Outcomes Assessment Program. *Ann Surg* 2008; 248:557-563.
70. Mori Y, Yamasaki M, Furukawa A, Takahashi M, Murata K: Enhanced CT in the diagnosis of acute appendicitis to evaluate the severity of disease: Comparison of CT findings and histological diagnosis. *Radiat Med* 2001; 19:197-202.
71. Pedrosa I, et al: MR imaging evaluation of acute appendicitis in pregnancy. *Radiology* 2006; 238:891-899.
72. Oto A, et al: Right lower quadrant pain and suspected appendicitis in pregnant women: Evaluation with MR imaging—initial experience. *Radiology* 2005; 234:445-451.
73. Hörmann M, et al: MR imaging in children with nonperforated acute appendicitis: Value of unenhanced MR imaging in sonographically selected cases. *AJR Am J Roentgenol* 1998; 171:467-470.
74. Pedrosa I, Zeikus EA, Levine D, Rofsky NM: MR imaging of acute right lower quadrant pain in pregnant and nonpregnant patients. *Radiographics* 2007; 27:721-753.
75. Leeuwenburgh MM, et al: Optimizing imaging in suspected appendicitis (OPTIMAP Study): A multicenter diagnostic accuracy study of MRI in patients with suspected acute appendicitis. Study Protocol. *BMC Emerg Med* 2010; 10:19.
76. Jones PF: Suspected acute appendicitis: Trends in management over 30 years. *Br J Surg* 2001; 88:1570-1577.
77. Rennie AT, Tytherleigh MG, Theodoroupolou K, Farouk R: A prospective audit of 300 consecutive young women with an acute presentation of right iliac fossa pain. *Ann R Coll Surg Engl* 2006; 88:140-143.
78. Varadhan KK, Humes DJ, Neal KR, Lobo DN: Antibiotic therapy versus appendectomy for acute appendicitis: A meta-analysis. *World J Surg* 2010; 34:199-209.
79. Bailey B, Bergeron S, Gravel J, Bussières JF, Bensoussan A: Efficacy and impact of intravenous morphine before surgical consultation in children with right lower quadrant pain suggestive of appendicitis: A randomized controlled trial. *Ann Emerg Med* 2007; 50:371-378.
80. Green R, Bulloch B, Kabani A, Hancock BJ, Tenenbein M: Early analgesia for children with acute abdominal pain. *Pediatrics* 2005; 116:978-983.
81. Ranji SR, Goldman LE, Simel DL, Shojania KG: Do opiates affect the clinical evaluation of patients with acute abdominal pain? *JAMA* 2006; 296:1764-1774.
82. Rhea JT, Rao PM, Novelline RA, McCabe CJ: A focused appendiceal CT technique to reduce the cost of caring for patients with clinically suspected appendicitis. *AJR Am J Roentgenol* 1997; 169:113-118.
83. Rao PM, Rhea JT, Novelline RA, Mostafavi AA, McCabe CJ: Effect of computed tomography of the appendix on treatment of patients and use of hospital resources. *N Engl J Med* 1998; 338:141-146.
84. Rao PM, Rhea JT, Rattner DW, Venus LG, Novelline RA: Introduction of appendiceal CT: Impact on negative appendectomy and appendiceal perforation rates. *Ann Surg* 1999; 229:344-349.
85. Morris KT, et al: The rational use of computed tomography scans in the diagnosis of appendicitis. *Am J Surg* 2002; 183:547-550.
86. Reich JD, Brogdon B, Ray WE, Eckert J, Gorell H: Use of CT scan in the diagnosis of pediatric acute appendicitis. *Pediatr Emerg Care* 2000; 16:241-243.
87. Ramarajan, N, et al: An interdisciplinary initiative to reduce radiation exposure: Evaluation of appendicitis in a pediatric emergency department with clinical assessment supported by a staged ultrasound and computed tomography pathway. *Acad Emerg Med* 2009; 16:1258-1265.
88. Reference deleted in proofs.
89. Wilson EB, Cole JC, Nipper ML, Cooney DR, Smith RW: Computed tomography in the diagnosis of appendicitis: When are they indicated? *Arch Surg* 2001; 136:670-675.
90. Flum D, Morris A, Koepsell T, Dellinger E: Has misdiagnosis of appendicitis decreased over time? A population-based analysis. *JAMA* 2001; 286:1748-1753.
91. Coursey CA, et al: Making the diagnosis of acute appendicitis: Do more preoperative CT scans mean fewer negative appendectomies? A 10-year study. *Radiology* 2010; 254:460-468.
92. Antevil JL, et al: Computed tomography–based clinical diagnostic pathway for acute appendicitis: Prospective validation. *J Am Coll Surg* 2006; 203:849-856.
93. Goldin AB, Sawin RS, Garrison MM, Zerr DM, Christakis DA: Aminoglycoside-based triple-antibiotic therapy versus monotherapy in children with ruptured appendicitis. *Pediatrics* 2007; 119:905-911.
94. Faser JD, et al: A complete course of intravenous antibiotics vs. a combination of intravenous and oral antibiotics for perforated appendicitis in children: A prospective, randomized trial. *J Pediatr Surg* 2010; 45:1198-1202.
95. Ingraham AM, et al: Effect of delay to operation on outcomes in adults with acute appendicitis. *Arch Surg* 2010; 145:886-892.
96. Yardeni D, et al: Delayed vs. immediate surgery in acute appendicitis: Do we need to operate during the night? *J Pediatr Surg* 2005; 39:464-469.
97. Sauerland S, Lefering R, Neugebaur E: Laparoscopic versus open surgery for suspected appendicitis. *Cochrane Database Syst Rev* 2002; 1:CD001546.
98. Helmer KS, et al: Standardized patient care guidelines reduce infectious morbidity in appendectomy patients. *Am J Surg* 2002; 183:608-613.
99. Katkhouda N, et al: Intraabdominal abscess rate after laparoscopic appendectomy. *Am J Surg* 2000; 180:456-461.
100. Yamini D, Vargas H, Bongard F, Klein S, Stamos MJ: Perforated appendicitis: Is it truly a surgical urgency? *Am Surg* 1998; 64:970-975.
101. Ein SH, Shandling B: Is interval appendectomy necessary after rupture of an appendiceal mass? *J Pediatr Surg* 1996; 31:849-850.
102. Rusnak R, Borer J, Fastow J: Misdiagnosis of acute appendicitis: Common features discovered in cases after litigation. *Am J Emerg Med* 1994; 12:397-402.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 94

GASTROENTERITIS

Sandy A. Craig

BACKGROUND

Gastroenteritis is defined as an inflammation of the stomach or intestines resulting in some combination of nausea, vomiting, and diarrhea. Although most affected patients will prove to have an infectious cause for their symptoms, the clinician also should consider noninfectious causes of vomiting and diarrhea, which are considered in detail in Chapters 29 and 31, respectively. Infectious gastroenteritis is associated with dozens of causative pathogens. Most of these organisms cause benign and self-limited illness, but in a few cases the morbidity may be significant, necessitating prompt diagnosis and treatment. Diagnostic testing should be targeted to those patients who have clinically significant illness or suspected reportable disease. It is neither feasible nor necessary to identify the specific pathogen during the emergency department (ED) evaluation. Instead, the clinician should classify the gastroenteritis as acute or chronic and invasive or noninvasive, based on readily available clinical information. This classification narrows the differential diagnosis considerably and is a valuable guide to further testing.

Acute gastroenteritis lasts less than 2 weeks. The vast majority of ED patients have acute gastroenteritis, and viral and bacterial pathogens should be the primary considerations in the differential diagnosis. *Chronic gastroenteritis* persists longer than 2 weeks. In such cases, parasitic pathogens and noninfectious causes should be considered in the differential diagnosis.

Invasive gastroenteritis is a clinical diagnosis made in the presence of signs or symptoms of intestinal mucosal invasion, such as fever, gross or occult blood in the stool, tenesmus, or abdominal pain. When invasive disease is suspected, further diagnostic testing is indicated. Patients with *noninvasive gastroenteritis* do not exhibit fever, produce bloody stools, or experience significant abdominal pain. Noninvasive gastroenteritis suggests the presence of a viral pathogen or toxin-producing bacteria. This illness typically is brief and self-limited, and diagnostic testing is not likely to be of benefit.

ACUTE INVASIVE BACTERIAL ENTERITIS

Potential pathogens in acute invasive bacterial enteritis are summarized in Table 94-1.

Campylobacter Enteritis

Epidemiology

Campylobacter is the most common documented cause of bacterial enteritis in developed countries. In a Swedish study of 100,000 persons, *Campylobacter* was isolated in 56% of cases of enteritis. Worldwide, *Campylobacter* accounts for up to 14% of cases of acute infectious diarrhea.[1] In the United States, the Foodborne Diseases Active Surveillance Network (FoodNet) estimated the 2009 incidence to be 13 cases per 100,000 population.[2] Most cases occur in children younger than 5 years or in male patients aged 20 to 29 years, but people of all ages are affected. The disease is more common during the summer months. *Campylobacter* species are a common cause of "backpacker's diarrhea," along with *Giardia,* both of which are frequently acquired by drinking from wilderness water sources.

Pathophysiology

Campylobacter organisms are small, spiral-shaped gram-negative bacteria. The most common species isolated are *Campylobacter jejuni* (94%), *Campylobacter coli* (1%), and *Campylobacter fetus*.[1] *Campylobacter* species produce disease primarily by direct invasion of the colonic epithelium and may induce inflammatory changes that are endoscopically indistinguishable from inflammatory bowel disease.

Most infections are acquired by handling raw poultry or eating raw or undercooked poultry meat. The primary reservoirs for *Campylobacter* organisms are chickens, with more than one half of U.S. flocks silently infected and approximately one half of the chicken in U.S. supermarkets contaminated.[2] Other causes include consumption of tainted beef, pork, raw milk, or untreated water and contact with infected pets (particularly cats and puppies) and farm animals.[2]

Clinical Presentation

The incubation period for *Campylobacter* enteritis is approximately 2 to 5 days. Disease onset usually is rapid, with signs and symptoms of fever, cramping abdominal pain, and diarrhea. Constitutional symptoms of anorexia, malaise, myalgias, and headache are the rule, and some patients experience backache, arthralgias, and vomiting. The clinical picture can mimic that in acute appendicitis. Onset of diarrhea often lags 24 to 48 hours after the onset of fever and abdominal pain. Typically the stools are loose and bile-colored but then become watery, grossly bloody, or melanotic approximately 40% of the time. Either gross or occult blood is found in the stool of 60 to 90% of patients with *Campylobacter* gastroenteritis. At the height of the illness, patients usually pass 8 to 10 stools or more per day.[3]

Most patients are well within a week or less; however, diarrhea can persist for weeks. Relapses are common, although generally milder than the original episode. Fatalities are rare; the Centers

www.ketabpezeshki.com 66485457-66963820

Table 94-1 Epidemiologic Aspects of Invasive Bacterial Enteritis

PATHOGEN	SOURCES AND RISK FACTORS OR GROUPS	INCUBATION PERIOD (I); DURATION (D)	UNTREATED FEATURES
Campylobacter	Contaminated food or water, wilderness waters (backpacker's diarrhea), chickens, animals	I: 2-5 days D: 5-14 days	May cause bloody diarrhea May mimic acute appendicitis or inflammatory bowel disease; recurrence common
Salmonella	Grade A shell eggs, poultry, unpasteurized milk, domestic pets	I: 8-24 hr D: 2-5 days	Family and cafeteria-type food poisoning outbreaks common; increased incidence in patients with cancer or immunodeficiency
Shigella	Person-to-person, confined populations, poor hygiene, water-borne	I: 24-48 hr D: 4-7 days	Toxigenic watery diarrhea, followed by invasive picture; may produce severe dysentery
Yersinia	Food, water milk; person-to-person, dogs, cats, pigs	I: 12-48 hr D: 5-14 days	Appendicitis, terminal ileitis-like syndrome; postinfection polyarthritis; long duration of fecal excretion of the organism
Vibrio parahaemolyticus	Raw or inadequately cooked seafood, especially shrimp	I: 8-24 hr D: 1-2 days	High attack rates, summer months; self-limited
Shiga toxin–producing *Escherichia coli* (STEC)	Raw ground beef, raw milk, meats, person-to-person, water-borne, travel	I: 3-8 days D: 5-10 days	Bloody diarrhea, hemorrhagic colitis; hemolytic uremic syndrome or thrombotic thrombocytopenic purpura
Plesiomonas	Uncooked shellfish, travel	I: 1-2 days D: 5-20 days	Severe abdominal cramps and vomiting with dehydration
Bacillus anthracis	Infected herbivores, undercooked meat, bioterrorism	I: 1-6 days D: weeks	Oral ulcers, neck swelling, lymphadenopathy, fever, gastrointestinal hemorrhage, possible ascites

for Disease Control and Prevention (CDC) estimates 124 fatal cases in the United States each year.[2]

Diagnostic Strategies

Because the clinical presentation is similar to that with other invasive bacterial pathogens, the diagnosis of campylobacteriosis cannot be made on the basis of clinical presentation alone. Identification of the pathogen will require stool culture or real-time polymerase chain reaction (PCR); specimens should be obtained from patients with acute enteritis associated with fever, abdominal pain, occult blood, or hematochezia. In borderline cases, stool methylene blue stain for fecal leukocytes is readily available and may help identify those patients who are likely to harbor an invasive pathogen. One study of outpatients with acute diarrhea found that the presence of fecal leukocytes (more than five white blood cells per high-power field) was associated with a likelihood ratio (LR) of 5.0 for the presence of an invasive pathogen (95% confidence interval [CI], 2.9 to 8.6).[4] Blood culture results are rarely positive, so these studies are not routinely indicated. Sigmoidoscopy reveals a nonspecific inflammatory colitis, and *Campylobacter* infection should be considered before a new diagnosis of inflammatory bowel disease is made.

Differential Considerations

The differential diagnosis for suspected campylobacteriosis includes all infections with organisms that produce invasive diarrhea or fecal leukocytes, particularly salmonellosis, shigellosis, yersiniosis, and Shiga toxin–producing *Escherichia coli* (STEC) infection.

Management

Empirical antibiotic therapy is not recommended for otherwise healthy patients with acute invasive diarrhea. (Travel-related diarrhea is an exception; see later). Initial treatment of invasive diarrhea should focus on rehydration, and the decision to initiate antibiotic therapy should be deferred pending identification of a specific organism via stool studies. Treatment with antibiotics is not needed for patients who demonstrate clinical improvement by the time results become available. For those who are not improving, antibiotic therapy shortens the duration of campylobacteriosis by approximately 1.3 days.[5] Erythromycin 500 mg twice a day for 5 days is the recommended first-line therapeutic regimen. Azithromycin 500 mg daily for 3 days is acceptable as well. Ciprofloxacin 500 mg twice a day can be used and was previously the treatment of choice, but alarming resistance to the fluoroquinolones has emerged, thought to be mainly a result of antibiotic use in the poultry industry, which was halted by the U.S. Food and Drug Administration (FDA) in 2005. Roughly 20% of *Campylobacter* strains are now resistant in the United States, and resistance of more than 80% has been documented in Thailand. *Campylobacter* organisms generally also are resistant to trimethoprim-sulfamethoxazole (TMP-SMX). Suggested antibiotic regimens for treatment of diarrhea are listed in Table 94-2. Relapses can occur, but the likelihood is decreased with appropriate antibiotic treatment.[3] Because *Campylobacter* infection causes an invasive enteritis, antimotility agents are not recommended unless treatment with antibiotics also is given.

Complications of *Campylobacter* infection are rare. Cholecystitis, pancreatitis, and massive gastrointestinal bleeding all have been documented, as have meningitis, endocarditis, and osteomyelitis. In addition, a definite association has been made with Guillain-Barré syndrome. Guillain-Barré syndrome associated with *Campylobacter* infection tends to be more severe than Guillain-Barré syndrome from other triggers and can occur even with asymptomatic infections. Luckily, the incidence is estimated at less than 1 per 1000 cases.[2]

Salmonellosis

Epidemiology

Salmonella is the most common cause of documented bacterial enteritis in the United States, with approximately 40,000

www.ketabpezeshki.com 66485457-66963820

Table 94-2 Antibiotic Therapy for Diarrhea in Immunocompetent Adults

PATHOGEN	ANTIBIOTIC*†	DOSE
Campylobacter	1. Erythromycin 2. Azithromycin	500 mg PO bid × 5 days 500 mg PO qd × 3 days
Salmonella	1. Ciprofloxacin 2. Azithromycin	500 mg PO bid × 7 days 1 g PO once, then 500 mg qd × next 6 days
Shigella	1. Ciprofloxacin 2. TMP-SMX	500 mg PO bid × 3 days 160 mg/800 mg PO bid × 3 days
Yersinia	1. TMP-SMX 2. Ciprofloxacin	160 mg/800 mg PO bid × 3 days 500 mg PO bid × 3 days
Vibrio parahaemolyticus	Not recommended	
Vibrio cholerae	1. Ciprofloxacin 2. Doxycycline 3. TMP-SMX	1 g PO once + intravenous fluids 300 mg PO once + intravenous fluids 160 mg/800 mg PO bid × 3 days + intravenous fluids
Shiga toxin–producing *Escherichia coli*	None recommended	
Enterotoxigenic *E. coli*	*Mild symptoms*: ciprofloxacin 1. Ciprofloxacin 2. TMP-SMX	750 mg PO × 1 dose 500 mg PO bid × 3 days 160 mg/80 mg PO bid × 3 days
Plesiomonas shigelloides	1. TMP-SMX 2. Ciprofloxacin	160 mg/80 g PO bid × 3 days 500 mg PO bid × 3 days
Clostridium difficile		
Diarrhea	1. Metronidazole 2. Vancomycin	250 mg PO qid × 10-14 days 125 mg PO qid × 10-14 days
Colitis	1. Metronidazole *or* vancomycin 2. Metronidazole	500 mg PO qid × 10-14 days 500 mg IV qid × 10-14 days
Aeromonas	1. TMP-SMX 2. Ciprofloxacin	160 mg/800 mg PO bid × 3 days 500 mg PO qid × 3 days
Bacillus anthracis	1. Ciprofloxacin 2. Doxycycline	400 mg IV q12h 100 mg IV q12h
Giardia lamblia	1. Metronidazole 2. Furazolidone	250 mg PO tid × 5 days 100 mg PO qid × 7-10 days
Entamoeba histolytica (confirmed by PCR assay or other test to be distinct from *Entamoeba dispar*)	1. Paromomycin 2. Iodoquinol 3. Diloxanide furoate *Severe symptoms*: start treatment with metronidazole	500 mg PO tid × 7 days 650 mg PO tid × 20 days 500 mg PO tid × 10 days 750 mg PO tid × 10 days followed by above
Cryptosporidium	1. Paromomycin 2. Nitazoxanide	500-750 mg PO qid × 14-21 days 1 g bid × 14 days
Cystoisospora belli	1. TMP-SMX	160 mg/800 mg PO bid × 10 days,
Cyclospora cayetanensis	1. TMP-SMX	160 mg/800 mg PO bid × 7 days
Strongyloides stercoralis	1. Ivermectin 2. Thiabendazole	200 μg/kg/PO day × 1-2 days 50 mg/kg/day in two doses × 2 days (max 3 g/day)
Enterobius vermicularis	1. Mebendazole *or* pyrantel pamoate 2. Albendazole	100 mg PO once, repeated after 2 wk 11 mg/kg PO once (max 1 g), repeated after 2 wk 400 mg PO once, repeated after 2 wk

PCR, polymerase chain reaction; *PO,* orally; *TMP-SMX,* trimethoprim-sulfamethoxazole.
*Another quinolone agent, norfloxacin, can be substituted for ciprofloxacin in the treatment of diarrheas. The equivalent dosage is 400 mg bid.
†Listed drugs are numbered in order of preference: 1 indicates the drug of first choice; 2 and 3 indicate alternative drugs.

documented cases reported to the CDC per year and an estimated 15 cases per 100,000 population.[6] U.S. surveillance systems found a 12% decrease in documented *Salmonella* infections in 2005 compared with 1995. Enteritis caused by this organism affects people of all age groups but particularly children, with those younger than 5 years accounting for 20% of cases.[7]

Almost all *Salmonella* infections are acquired from ingestion of contaminated food or drink. Direct person-to-person transmission can occur, but most human infections are related to the vast reservoir of salmonellae in lower-order animals. Poultry products and beef constitute the most common sources of *Salmonella.* Unpasteurized milk, eggs, fish, and domestic pets are other sources. Outbreaks also have been associated with consumption of fruits, vegetables, baked goods, rattlesnake meat, and medicinal preparations. Approximately 10% of household dogs and cats excrete salmonellae, and pet reptiles, such as turtles, snakes, and iguanas, have been responsible for outbreaks of salmonellosis.[7]

Cooking contaminated foods decreases the possibility of infection but does not eliminate it. Salmonellae can survive cooking deep inside certain foods, where temperatures may not reach the

www.ketabpezeshki.com 66485457-66963820

lethal range. Very large outbreaks of *Salmonella* infection have been traced to contaminated, unbroken, grade A eggs.[7] Although the organism is present in the uncracked egg, thorough cooking usually eradicates or reduces the inoculum to clinically insignificant levels.

Common raw egg–based sources of *Salmonella* infections include homemade hollandaise sauce, eggnog, Caesar salad dressing, ice cream, mayonnaise, tiramisu, cookie dough (often consumed unbaked), frosting, and French toast mix.[7] *Salmonella enterica* subsp. *enterica* serovar Enteritidis (i.e., "*S.* Enteritidis") is the species universally associated with egg-related infections. Patients convalescing from *Salmonella*-related enterocolitis and persons with asymptomatic infection may continue to excrete *Salmonella* organisms for weeks or months, thus serving as ongoing sources of infection.[7]

Pathophysiology

Approximately 2000 *Salmonella* serotypes are known to cause human illness. Based on 2010 U.S. surveillance figures, the most common isolates are the *S. enterica* serovars Typhimurium, Enteritidis, and Newport, which together account for approximately half of culture confirmed serotypes.[7] Different *Salmonella* serotypes show marked variations in invasive potential and are associated with particular presentations: *S. enterica* serovar Typhi with enteric fever (typhoid fever), *S. enterica* serovar Choleraesuis with septicemia, *S. enterica* serovar Typhimurium with acute gastroenteritis, and *S. enterica* serovar Enteritidis infections from grade A shell eggs.[7]

Relatively large numbers of salmonellae must be ingested for illness to be produced. However, a carrier state can be induced, with ingestion of 10 to 100 times fewer bacteria needed to induce the carrier state relative to the number needed to induce illness. In infants and adults with certain underlying diseases, a much smaller inoculum may produce illness. Decreased gastric acidity or an alteration of intestinal flora resulting from the administration of antibiotics can impressively reduce the size of the required inoculum.

Rates of invasive infection and disease severity are increased in infants, elders, and people with hemoglobinopathies such as sickle cell anemia, malignant neoplasms, or acquired immunodeficiency syndrome (AIDS).[7] The CDC estimates that more than 400 fatal cases occur each year.[7]

Clinical Presentation

Family outbreaks and sporadic cases are more common than large epidemics. Ingested salmonellae penetrate the intestinal mucosal cells and lodge in the lamina propria. After an incubation period of 8 to 48 hours, the typical patient with *Salmonella* gastroenteritis develops fever, colicky abdominal pain, and loose, watery stools, occasionally containing mucus and blood. Nausea and vomiting are common but rarely are severe or protracted. Mild to moderate diffuse abdominal tenderness can be elicited in most patients, but severe tenderness and even rebound tenderness may occasionally be noted. Symptoms usually abate within 2 to 5 days, and recovery typically is uneventful. Sustained or intermittent bacteremia may occur, especially in those with sickle cell anemia, malignancy, or AIDS. Focal infections are identified in 10% of those with *Salmonella* bacteremia.[8]

Diagnostic Strategies

The diagnosis of salmonellosis cannot be made on the basis of clinical presentation alone; performance of stool cultures or real-time PCR assay is needed for confirmation. Stool methylene blue staining for fecal leukocytes may help identify patients who are likely to harbor an invasive pathogen. Blood culture results occasionally are positive, and samples should be obtained from severely ill or immunocompromised patients. The possibility of an underlying disease or immunodeficiency state should be considered in every patient with a severe *Salmonella* infection.

Differential Considerations

Family or communal outbreaks can suggest *Staphylococcus*-related food poisoning, but staphylococcal enteritis has a shorter incubation period, is not associated with fever, and produces the typical toxigenic, noninvasive, diarrheal picture. Vomiting is also much more prominent in cases of staphylococcal food poisoning than in most cases of *Salmonella* infection. The differential diagnosis for salmonellosis includes all organisms that produce invasive diarrhea or fecal leukocytes, particularly campylobacteriosis, shigellosis, yersiniosis, and STEC infection.

Management

Empirical antibiotic therapy is not recommended for otherwise healthy patients with suspected *Salmonella* enteritis. Antibiotic therapy does not shorten the duration of the disease and may prolong the duration of the carrier state. Although its effectiveness is unproven, antibiotic therapy is recommended for patients with severe colitis and for infants younger than 3 months, adults older than 50 years, and individuals at risk for severe disease including the immunocompromised, those with sickle cell disease, and those with prosthetic grafts. Persons who represent a public health risk also should be treated in an attempt to eradicate the carrier state and prevent spread of the organism.[3,7] The choice of antibiotic should be based on sensitivities of the isolate. Any of the following antibiotic regimens typically is effective for outpatient management of *Salmonella* gastroenteritis: ciprofloxacin 500 mg twice a day for 5 to 7 days, norfloxacin 400 mg twice a day for 5 to 7 days, or azithromycin 1 g by mouth and then 500 mg a day for the next 6 days.[3] TMP-SMX also can be used if the organism is susceptible. Ciprofloxacin is effective in the treatment of chronic *S.* Typhi carriers. However, treatment with fluoroquinolones can actually prolong shedding of non-Typhi organisms. Patients requiring hospitalization are best treated with intravenous ceftriaxone until results of sensitivity studies become available.[3]

Follow-up with the patient's primary care physician should be arranged. Food handlers and health care personnel should not be allowed to work until the carrier state has been eradicated. Repeated stool studies and further decisions regarding job or school situations will be required. Personal hygiene should be emphasized, because untreated patients may continue to shed infective organisms in the stool for weeks or even months. As with other invasive pathogens, the use of antimotility drugs alone is contraindicated. These drugs prolong fever and diarrhea, increase the incidence of bacteremia, and promote development of a carrier state in patients with *Salmonella* enteritis. However, administration of loperamide is safe when it is given concomitantly with an appropriate antibiotic.

Prevention of salmonellosis depends on adequate cooking and minimizing the time that foods are allowed to stand at room temperature to reduce the chance of bacterial growth to an infectious inoculum. Careful personal hygiene, including handwashing, also is important. *Salmonella* infection is a nationally notifiable disease (Box 94-1).

Although most patients recover fully without long-term sequelae, up to 30% (primarily adults) will experience transient reactive arthritis. Reiter's syndrome, consisting of reactive arthritis, conjunctivitis, and urethritis, is a well-known complication and occurs in approximately 2% of patients.[8]

www.ketabpezeshki.com 66485457-66963820

Box 94-1 Notifiable Food-borne Diseases and Related Conditions*

Bacterial
Botulism
Brucellosis
Cholera
Shiga toxin–producing *Escherichia coli* (STEC)
Hemolytic uremic syndrome, postdiarrheal
Salmonellosis
Shigellosis
Typhoid fever
Vibriosis (with noncholera *Vibrio* species)

Viral
Hepatitis A

Parasitic
Cryptosporidiosis
Cyclosporiasis
Trichinosis

From Centers for Disease Control and Prevention: Nationally Notifiable Infectious Diseases—United States. 2011. Available at www.cdc.gov/osels/ph_surveillance/nndss/phs/infdis2011.htm. Accessed April 23, 2011.
*In the United States, additional reporting requirements may be mandated by state and territorial laws and regulations. Details on specific state reporting requirements are available from the Council of State and Territorial Epidemiologists (www.cste.org) and the Centers for Disease Control and Prevention (www.cdc.gov).

Shigellosis

Epidemiology

Shigellosis, or bacillary dysentery, is worldwide in distribution and particularly common in countries lacking effective sanitation. In the United States, approximately 14,000 laboratory-confirmed cases occur annually, representing an estimated rate of 44 cases per 100,000 population.[6,9] The CDC estimates that there are actually approximately 450,000 cases each year.[10] *Shigella sonnei* is responsible for approximately 75% of the infections occurring in the United States. *Shigella flexneri* causes most of the remaining cases, with *Shigella boydii* and *Shigella dysenteriae* responsible for less than 4% of cases.[11]

Shigella infections are common in confined populations, such as those in mental or penal institutions, in nursing homes or daycare centers, or on Native American Indian reservations. Children younger than 5 years account for 30% of cases. An increased incidence has been documented among men who have sex with men and in the AIDS population.[9] Spread is by the fecal-oral route, and humans are the only natural hosts. Shigellae can be found in large numbers around the base of toilets used by infected persons, and the organism readily passes through toilet tissue onto the fingers. Shigellae can be recovered in cultures of samples taken as long as 3 hours after contamination. In the last few years, a number of large outbreaks have been associated with recreational water venues such as swimming pools, water parks, fountains, hot tubs, and spas.[10]

Pathophysiology

Unlike *Salmonella*, which requires a very large inoculum to produce disease, as few as 50 to 100 *Shigella* bacilli can cause infection. No other enteric pathogen is so efficient at producing overt disease in humans. Infection generally is superficial, localized to the epithelial lining of the colonic mucosa; therefore bowel perforation or invasion into the bloodstream is extremely rare. Bleeding occurs from superficial ulcerations of the mucosa.

Clinical presentation varies among *Shigella* species. *S. sonnei* typically causes high-volume, watery diarrhea with relatively few systemic signs. Infection with *S. flexneri, S. dysenteriae,* or *S. boydii* typically causes low-volume bloody diarrhea and more severe systemic symptoms.[11]

Clinical Presentation

The usual incubation period is 24 to 48 hours, and the clinical manifestations vary considerably, often appearing in a bimodal fashion. Mild, watery diarrhea with few if any constitutional symptoms or asymptomatic infection occurs in a significant proportion of infected persons. It is estimated that fever occurs in 58% to 100%, abdominal pain in 75% to 100%, tenesmus in 55% to 96%, bloody stool in 46% to 73%, and nausea or vomiting in 63% to 100%.[3]

When true dysentery develops, it ordinarily is preceded by a recognizable period of watery diarrhea lasting a few hours to a few days. Patients with dysentery have grossly bloody diarrhea, tenesmus, and significant constitutional symptoms and signs, such as fever, nausea, vomiting, headache, and myalgias. If symptoms are severe enough, profound dehydration and even circulatory collapse can occur. Children younger than 2 years may have associated neurologic manifestations, most commonly seizures, although lethargy or frank coma develops in a small percentage of patients. *S. dysenteriae* type 1 infection, rarely diagnosed in developed countries, is associated with the hemolytic uremic syndrome (HUS).

Generally, shigellosis is a self-limited disease. Patients become afebrile in 3 to 4 days, and the abdominal cramping and diarrhea resolve within 1 week. A significant number of untreated patients continue to shed organisms in the stool for 2 or more weeks, and approximately 10% of patients will have a relapse unless the infection is treated with antibiotics.

Diagnostic Strategies

As with other invasive pathogens, most cases of shigellosis remain undiagnosed. Patients with mild, watery diarrhea and few if any constitutional symptoms can be sent home with conservative management and no investigative procedures. However, shigellosis should be considered in every patient with an acute febrile illness associated with diarrhea, especially patients who appear ill or who have dysenteric stools.

Fecal white blood cells are present, usually in large numbers, in 85 to 95% of the cases, regardless of the gross appearance of the stool.[3] Thus, finding leukocytes in watery stools can help identify shigellosis even in the absence of classic dysenteric stools. Occult blood usually is present in the stools of infected patients. Blood leukocytosis is common, and a significant leftward shift in the differential count is almost always seen. Results of blood cultures for *Shigella* are rarely positive. Sigmoidoscopic examination reveals diffuse mucosal inflammation, often with multiple ulcerations.

A definitive diagnosis of shigellosis is made with stool culture or real-time PCR. Stool culture results are positive in more than 90% of cases when samples are obtained during the first 3 days of illness; however, results are positive in only approximately 75% if samples are obtained more than 1 week after the onset of diarrhea.[11,12]

Differential Considerations

Considerations in the differential diagnosis include salmonellosis, *Campylobacter* enteritis, yersiniosis, STEC infection, amebic dysentery, and ulcerative colitis.

Management

Treatment primarily involves the correction of fluid and electrolyte abnormalities. If *S. sonnei* or *S. flexneri* is cultured from the

www.ketabpezeshki.com 66485457-66963820

stool, the decision to administer antibiotics is based on the patient's clinical condition and the feasibility of sanitary control. Asymptomatic or recovering patients do not need to be treated with antibiotics unless treatment is necessary for public health measures. Patients whose condition is not improving and those who are immunocompromised should be treated. Antibiotics shorten the clinical course and eradicate the pathogen from the stool, often within 48 hours.[11,12] Whenever *S. dysenteriae* is isolated, the patient should be treated to prevent outbreaks of dysentery, even if the patient is asymptomatic when the culture result returns from the laboratory.

In the United States, more than 80% of *Shigella* organisms are resistant to ampicillin, and 47% are resistant to TMP-SMX.[7,11] Significant resistance has not yet been found to the quinolone agents ciprofloxacin and norfloxacin, and one of these should be considered the drug of choice unless sensitivity studies demonstrate that the organism is sensitive to either ampicillin or TMP-SMX. Treatment is required for only 3 days in immunocompetent patients but should be extended to 7 to 10 days in the immunocompromised.[3]

Antimotility agents may prolong the fever, diarrhea, and excretion of *Shigella* in the stools and are contraindicated in patients with invasive shigellosis. However, they may be safe when used simultaneously with antibiotics. Follow-up stool cultures should be done for patients treated for *S. dysenteriae* infection to ensure eradication of the organism. Follow-up cultures, however, are not necessary after treatment for *S. sonnei* or *S. flexneri* infection, provided that the patient's condition improves clinically. Shigellosis is a nationally notifiable disease.

Complications are rare and include bacteremia, Reiter's syndrome (after *S. flexneri* infection), HUS (after *S. dysenteriae* infection), toxic megacolon, colonic perforation, seizures, and toxic encephalopathy.[11]

Yersinia enterocolitica Gastroenteritis

Epidemiology

Y. enterocolitica, a gram-negative facultatively anaerobic bacterium, is a member of the family Enterobacteriaceae. *Y. enterocolitica* is a relatively infrequent cause of enteritis in the United States, with FoodNet surveillance systems documenting approximately one case of culture-verified yersiniosis per 100,000 population.[13] *Y. enterocolitica* infections are the third most common notifiable bacterial zoonoses throughout Scandinavia and Europe behind campylobacteriosis and salmonellosis. Between 2002 and 2008 the annual number of confirmed cases of yersiniosis fell from 9.2 to 5.3 cases per 100,000 population Germany.[14] Yersiniosis is more prevalent in children and is fairly evenly distributed throughout the calendar year.

Pathophysiology

After oral ingestion, the bacterium invades the intestinal epithelium and localizes to lymphoid tissue of the intestinal mucosa, particularly Peyer's patches. It then invades the regional mesenteric lymph nodes. Invasive enteritis is the clinical presentation in approximately two thirds of patients. Pseudoappendicitis and mesenteric adenitis account for the remainder of presentations. Infection originates from contaminated food or drink. The consumption of contaminated milk or contaminated raw pork has accounted for sporadic cases and several large outbreaks. Fecal-oral transmission to humans from a variety of animals, particularly dogs, cats, and pigs, and direct person-to-person spread probably occur, but communicability appears to be low.[13]

Clinical Presentation

The clinical picture with *Yersinia* enterocolitis often resembles that with infection by other invasive intestinal organisms: fever (68%); colicky abdominal pain (65%); watery, greenish, and sometimes bloody (26%) diarrhea; and constitutional symptoms of anorexia, vomiting (39%), and malaise.[3] However, in cases of *Y. enterocolitica* gastroenteritis, the abdominal pain and diarrhea usually persist for 10 to 14 days or longer.

In a substantial number of patients with yersiniosis, particularly adolescents and young adults, an ileocecitis may develop. In these cases, lower abdominal pain with little or no diarrhea is the predominant symptom, and the clinical presentation may perfectly mimic that of acute appendicitis. Historically, large outbreaks have been traced to contaminated milk, largely because in the relevant series, physicians noticed an extraordinary rise in the number of negative appendectomies. With modern food processing techniques, almost all cases are now reported as isolated events.[13,14]

Postinfection manifestations, such as erythema nodosum or a persistent polyarthritis, occur in 2 to 5% of patients, mainly adults. Other presentations include sacroiliitis, ankylosing spondylitis, Reiter's syndrome, exudative pharyngitis, pneumonia, empyema, and lung abscess. *Y. enterocolitica* septicemia is rare but is known to occur, most often in patients with diabetes mellitus, severe anemia, hemochromatosis, cirrhosis, or malignancy.[15]

Diagnostic Strategies

Approximately 70% of patients with *Y. enterocolitica* infection have signs and symptoms of invasive enteritis. The diagnosis of yersiniosis cannot be made on the basis of clinical presentation; a positive stool culture or real-time PCR is required. Methylene blue staining of stool for fecal leukocytes yields a positive result in approximately 48% of cases of yersiniosis.[3] Most laboratories do not routinely include *Y. enterocolitica* in the standard stool testing; *Yersinia* identification can be done by special request if clinically indicated (e.g., by history of *Yersinia* exposure, prolonged invasive enteritis despite a negative result on standard stool culture, or right lower quadrant pain with a normal appendix on imaging studies).

Stool cultures require special techniques and a long time for growth. Patients with *Yersinia* enterocolitis often continue to shed organisms in the stools well into convalescence, long after the diarrhea subsides. The mean duration of fecal shedding is approximately 6 weeks.

Differential Considerations

The diagnosis should be suspected in a patient with prolonged abdominal pain and diarrhea after what appears to be a common, usually self-limited gastroenteritis syndrome, or in a patient with symptoms similar to those of appendicitis or mesenteric adenitis. *Y. enterocolitica* infection also should be considered in the differential diagnosis of regional enteritis, which it can closely mimic.

Management

Generally, *Y. enterocolitica* infection is self-limited at the diarrheal stage and resolves without treatment. As with other invasive gastrointestinal pathogens, antiperistaltic drugs are not recommended unless the patient is simultaneously treated with antibiotics.

Treatment with antibiotics has not been proved to be essential or efficacious in the management of uncomplicated *Yersinia* enterocolitis or in the pseudoappendicitis syndrome. However, because *Yersinia* organisms take a long time to grow on culture, in most studies the duration of illness before antibiotics were started was 1 to 2 weeks. *Yersinia* organisms usually are susceptible to

www.ketabpezeshki.com 66485457-66963820

TMP-SMX, which is the agent of choice when antibiotic therapy is indicated.[3] Drug treatment does decrease the fecal shedding of the organism. Doxycycline in combination with an aminoglycoside is an alternative regimen, as is single-agent therapy with a quinolone.[3] In immunocompetent adults, a 3-day course is sufficient; the course is extended to 7 to 10 days if the patient is immunocompromised. Treatment should be considered in patients who are still significantly ill at the time stool results return, particularly if the patients are immunocompromised or have a significant underlying medical illness, or in cases in which the fecal shedding could represent a public health hazard. In patients who interact with potentially susceptible persons, appropriate steps should be taken to ensure that they do not spread their infection.

Vibrio parahaemolyticus Gastroenteritis

Epidemiology

V. parahaemolyticus is a halophilic (salt-requiring) gram-negative bacillus found naturally in warm marine environments such as the coastal seawaters of Japan, the United States, and other temperate-zone nations. In Japan, *V. parahaemolyticus* is the most common cause of bacterial enteritis, being responsible for approximately 70% of cases. The typical source is raw fish. In the United States, *V. parahaemolyticus* disease is much less common, though it has increased approximately 85% over the past 10 years to approximately 215 documented cases annually, or 0.35 per 100,000 population. The CDC estimates that approximately 4500 cases, 30 hospitalizations, and 1 or 2 deaths occur each year. Cases in the United States typically are related to consumption of raw or undercooked shellfish, especially oysters (49%), although clams (38%), shrimp, lobsters, mussels, cockles, crabs, and scallops all have been implicated. Many cases occur as outbreaks on cruise ships or in persons who have patronized a common restaurant or seafood market. *V. parahaemolyticus* enteritis is much more common in the summer months, with 70% of cases occurring in the months of May to October, when warm seawater temperatures favor replication of the organism.[16] At such times, 100% of oysters in local beds have been shown to harbor the organism. Attack rates from a common-source exposure are fairly high, but little evidence is available for human-to-human spread among family members of infected patients.[16]

Pathophysiology

The mechanism by which *V. parahaemolyticus* causes human enteritis is incompletely understood but seems to be related to production of two thermostable direct hemolysin (TDH) virulence factors. Serotypes that produce one or both virulence factors attach to the colonic epithelium and induce a secretory diarrhea as well as local cell lysis. An infectious dose of *V. parahaemolyticus* is thought to be 100,000 colony-forming units (CFUs) or more. Still, transmission has occurred from oyster beds in which the colony count was less than 200 CFUs per gram of oyster meat.[17]

Although enteritis is the most common clinical presentation, accounting for 60 to 80% of cases, *V. parahaemolyticus* infections also manifest as wound infections (34%) and septicemia (5%).[6,18,20] Serious wound infections and septicemia occur primarily in persons with underlying liver disease, alcoholism, or diabetes mellitus.[15,17]

Clinical Presentation

Signs and symptoms usually appear 8 to 12 hours after the ingestion of contaminated food, but the incubation period can range from 4 to 48 hours. The predominant manifestation is acute diarrhea, but the volume of fluid lost generally is not large. Moderately severe abdominal cramps occur in 88%, nausea in 52%, vomiting in 39%, and fever in 33%. Vomiting generally is not prominent. The illness is almost invariably self-limited and seldom lasts longer than 24 to 48 hours.[17]

V. parahaemolyticus infection should be suspected when a common-source outbreak of acute diarrheal disease occurs in persons exposed to fresh or frozen seafood. It also should be considered when fecal white blood cells are present in cases of acute invasive diarrhea linked to food poisoning.

Diagnostic Strategies

As with other types of acute invasive enteritis, the diagnosis of *V. parahaemolyticus* cannot be made on the basis of clinical presentation alone. The diagnosis is made by stool culture or real-time PCR. Although blood agar and other nonselective media support the growth of this species, isolation from the stool usually requires the use of a selective medium containing thiosulfate, citrate, bile salts, and sucrose (TCBS agar). This selective culture procedure is not part of the standard stool culture in most U.S. hospitals but can be obtained by special request in cases of outbreaks related to consumption of raw or undercooked shellfish, especially in coastal areas of the United States.[16,17]

Management

Because the disease is self-limited, most patients require no therapy. Although data on efficacy of antibiotic therapy are lacking, patients who still have diarrhea when culture results become available may benefit from treatment with tetracycline, fluoroquinolones, or ceftriaxone or another antibiotic as guided by susceptibility testing.[15,17] An occasional patient may require fluid replacement. Antimotility agents are not indicated.

Because *V. parahaemolyticus* is widely present in coastal waters, the only effective preventive measures are adequate cooking, refrigeration, and hygienic practice in the preparation of seafood for human consumption.

Enterohemorrhagic (Shiga Toxin–Producing) *Escherichia coli* Gastroenteritis

Epidemiology

Enterohemorrhagic *E. coli* was first recognized as a human pathogen in 1982 after two outbreaks of hemorrhagic colitis were traced to undercooked ground beef contaminated with *E. coli* serotype O157 : H7 and distributed at a fast food restaurant chain. It is now recognized that *E. coli* O157 : H7 is one of more than 30 serotypes of *E. coli* known to produce *Shigella*-like toxins and that these STEC serotypes as a group constitute a major cause of hemorrhagic colitis, HUS, and thrombotic thrombocytopenic purpura (TTP) in humans.[15] The CDC estimates 110,000 cases and 3200 hospitalizations per year in the United States and reports a 41% decrease in the incidence from 1998 to 2009, probably a result of improvements in food safety protocols.[18-20] STEC infections have been documented in more than 30 countries on six continents. Children younger than 10 years are at greatest risk for serious STEC infection. Approximately 15% of children with STEC diarrhea develop HUS.[20]

Inadequately cooked hamburger has caused many large outbreaks.[15,18] STEC, present in the intestines of healthy cattle, contaminates the meat during slaughter, and the grinding process then transfers the organisms from the surface of the meat to the interior. The infectious dose is low, approximately 100 bacteria. U.S. Department of Agriculture food safety regulations now require that hamburger be cooked to an internal temperature of 70° C (160° F) to effectively kill *E. coli* organisms. Outbreaks also

www.ketabpezeshki.com 66485457-66963820

have occurred from consumption of venison, salami, pepperoni, cured mutton sausage, cheese curds, apple cider, raw milk, uncooked cookie dough, and fruits and vegetables; from contamination of municipal water supplies; from animal contact in petting zoos; and from person-to-person spread in daycare centers.[8,20] Food handlers with STEC-related diarrhea have contaminated meals, causing institutional outbreaks. STEC enteritis is more common in the summer months.

Pathophysiology

Ingested STEC multiply in competition with normal bacterial enteric flora, adhere to the intestinal epithelial cells, and elaborate Shiga toxin. Toxins bind to absorptive enterocytes on the luminal surface of the small and large intestine, enter the cell, and irreversibly inhibit protein synthesis, resulting in death of enterocytes. Shiga toxins can then enter the bloodstream via damaged intestinal epithelium and cause death of vascular endothelial cells by the same mechanism. Endothelial cell lysis is accompanied by platelet activation and aggregation, cytokine secretion, vascular constriction contributing to fibrin deposition, and clot formation within the capillary lumen. Microangiopathy propagates distally as the toxins are carried to the kidneys, causing the clinical syndrome of hematuria and renal failure (HUS).[20] The development of HUS is associated primarily with serotypes that produce Shiga toxin 2. The CDC estimates that 90% of U.S. cases of HUS are caused by *E. coli* O157:H7.

Clinical Presentation

After an incubation period of 3 to 4 days, patients initially produce watery diarrhea that becomes bloody hours to days later. Approximately 90% of patients report bloody stools.[20] The amount of blood varies, but stools passed may appear to consist wholly of blood, and the infection may masquerade as gastrointestinal bleeding from noninfectious causes. The bloody diarrhea typically is accompanied by severe abdominal cramps, pain, and often vomiting. Fever is a feature in fewer than one third of cases and, if present, usually is low grade.[8] This helps differentiate STEC infection from infection with other invasive organisms. Fecal leukocytes are found in approximately 50% of cases, but in small numbers, in contrast with the sheets of white blood cells seen in *Shigella* dysentery.[3] Endoscopic, histologic, and radiographic studies demonstrate only nonspecific changes consistent with an inflammatory hemorrhagic colitis and do not accurately distinguish STEC infection from other causes of colitis.[20]

Uncomplicated infection resolves spontaneously over 7 to 10 days. A carrier state may last another 1 to 2 weeks, but it also resolves spontaneously.

Complications

STEC colitis has been associated with two serious complications: HUS and TTP. These clinically similar disorders share the following features: microangiopathic hemolytic anemia, thrombocytopenia, fever, neurologic deficits, and renal dysfunction. In TTP, neurologic findings predominate, and renal dysfunction is unusual. The opposite is seen with HUS, which is more common in children, especially those younger than 4 years, occurring in approximately 15% of cases.[8,18,20] Of these, approximately 5% are fatal.[18] Approximately 22 to 40% of elders in nursing home outbreaks acquire HUS, and 50 to 80% of these patients die. TTP is seen in 2 to 3% of cases, most often in immunosuppressed patients. HUS and TTP typically appear 5 to 20 days after the onset of infection, and the diarrhea can be totally resolved and forgotten by the time a diagnosis is established. Death from STEC colitis alone or from one of the complications occurs primarily among elders.[15]

Diagnostic Strategies

The CDC recommends that all stools submitted for routine testing from patients with acute community-acquired diarrhea (regardless of age, season, or presence or absence of blood in the stool) be simultaneously cultured for *E. coli* O157:H7 and tested with an assay that detects Shiga toxins to detect non-O157 STEC.[21] Culture-based diagnosis requires specific stool culture techniques. In addition to the routine battery of media, specimens should be plated onto sorbitol-MacConkey (SMAC) medium. The O157:H7 strains of *E. coli* are sorbitol negative at 18 to 24 hours of growth on this medium and can be rapidly identified with various serologic tests, such as latex agglutination or fluorescent antibody testing. A commercial Shiga toxin enzyme immunoassay (EIA) was introduced in 1995 to assist clinical laboratories in identifying non-O157 Shiga toxin–producing strains of *E. coli.* The CDC now recommends that all stools submitted for culture also be tested for STEC-associated verotoxin with use of commercially available immunoassays, and that non-O157 STEC be sent to the CDC for typing.

Differential Considerations

Hemorrhagic *E. coli* infections may be misdiagnosed as ischemic colitis, inflammatory bowel disease, intussusception, or another infectious colitis. The examining physician should test for STEC when considering a diagnosis of one of these entities.

Management

Antibiotic therapy does not shorten the clinical course or eradicate the organism. Moreover, treatment with antibiotics to which the organism is resistant may increase the risk for HUS by eliminating competing bowel flora. However, the degree to which antibiotic treatment truly increases the risk for HUS remains controversial.[3,8,18] Retrospective studies in adults suggest an association between antibiotic use and the development of HUS but may have been biased by preferential use of antibiotics in the more serious cases. Because antibiotic treatment is of no clinical benefit and may increase the risk of HUS, it is not recommended for patients with known infection with *E. coli* O157:H7.

Empirical antibiotic treatment for bloody diarrhea should be approached with caution. Empirical treatment is not recommended in children because of the increased incidence of HUS. In adults, empirical treatment is recommended only for those with a temperature above 38.5° C, because the presence of significant fever suggests a pathogen other than *E. coli* O157:H7.

Aeromonas Gastroenteritis

Epidemiology

Aeromonas organisms are gram-negative, facultatively anaerobic, rod-shaped bacteria of the family Aeromonadaceae. *Aeromonas* species are ubiquitous worldwide in fresh and brackish water and also contaminate the food and water supply.[15,22] *Aeromonas* organisms grow at a range of temperatures but are isolated with increased frequency in summer months. *Aeromonas* infection is not a reportable condition in the United States or most other countries worldwide. No figures are available on the incidence of *Aeromonas* gastroenteritis in the United States. An association with human enteritis is difficult to confirm for several reasons. No major clonally related outbreaks have been linked to *Aeromonas* species, and the organism often is found in the feces of asymptomatic persons. In addition, a number of "suspected" *Aeromonas* outbreaks related to seafood (prawns, oysters, shrimp, and sashimi) and fish have been associated with incubation periods of less than 24 hours,

www.ketabpezeshki.com 66485457-66963820

which is not characteristic of *Aeromonas*. Despite many attempts, *Aeromonas* has failed to fulfill Henle-Koch requirements for a human pathogen—that the pathogen be fully isolated from the body, grown in pure culture, and capable of inducing disease when reintroduced to the human body.[22] Still, several small outbreaks have been documented in travelers and by case-control studies; it is thought that certain serotypes do cause gastroenteritis in humans.[22,23] Drinking untreated water, usually from private wells or springs, is thought to cause most cases of diarrhea from *Aeromonas* bacteria.[22] Although bivalves such as oysters and mussels concentrate *Aeromonas* in their meats during the filter-feeding process, *Aeromonas* infection has not been definitively associated with consumption of shellfish. *Aeromonas hydrophila* causes wound infection; septicemia occurs in persons of advanced age or with underlying gastrointestinal disease such as colon cancer, cirrhosis, or hepatobiliary or inflammatory bowel disease or history of recent hospitalization or antibiotic treatment. In some published series, *Aeromonas* infection causes 2 to 10% of all cases of diarrhea in children.[22,23]

Pathophysiology

The exact mechanism by which *Aeromonas* species produce diarrhea has not yet been explained. Both enterotoxins and cytopathic toxins may be produced, and the organisms may have some invasive characteristics.

Clinical Presentation

Aeromonas enteritis is thought to have five distinct clinical presentations. By far the most common, occurring in approximately 75 to 89% of cases, is as a secretory (watery) diarrheal syndrome. A more severe form can be accompanied by bloody stools, similar to infection with the invasive pathogens mentioned earlier. *Aeromonas* infection also manifests as traveler's diarrhea or, rarely, a cholera-like syndrome with loss of 10 or more L of diarrheal fluid per day. Subacute and chronic enteritis syndromes have also been described, with symptoms lasting from months to years.[22] Stool should be examined for the presence of *Aeromonas* infection before a diagnosis of inflammatory bowel disease is established.

Diagnostic Strategies

Diagnosis is made by stool culture, but culture for *Aeromonas* species is not part of the standard stool testing, and the clinician should request that the laboratory culture specifically for this organism. *Aeromonas* infection should be suspected in children or immunocompromised patients with diarrhea associated with a history of drinking from untreated water sources.

Management

No controlled trials have been conducted that clearly demonstrate a benefit to antibiotic therapy. In most patients, *Aeromonas* enteritis is mild and self-limited, and antibiotic therapy probably is not warranted. In the case of severe disease, prolonged diarrhea, or an immunocompromised host, susceptibility testing supports the use of quinolones, aminoglycosides, carbapenems, cephalosporins, macrolides, nitrofurans, or tetracycline.[22]

Plesiomonas shigelloides Gastroenteritis

Epidemiology

P. shigelloides is a gram-negative, facultatively anaerobic bacterium of the family Enterobacteriaceae. The organism is found in a variety of settings, including animals, soil, and freshwater and dilute saltwater bodies, including the Gulf of Mexico. Humans usually are infected by contaminated food or water or after contact with colonized animals. Worldwide, *P. shigelloides* enteritis is well documented in the tropical and subtropical areas of Africa, Asia, and Australia. In the United States and Europe, most cases occur after travel to tropical areas or after consumption of raw shellfish, especially oysters.[15] Sporadic diarrheal illness occurs in both normal and immunocompromised hosts. Large outbreaks have occurred, usually resulting from oyster consumption.[15]

Pathophysiology

Evidence supporting a pathogenic role for *P. shigelloides* includes documented outbreaks associated with contaminated shellfish, a very low asymptomatic carrier rate, and recovery from diarrheal illness after antibiotic therapy. The mechanism of disease production remains poorly understood but probably involves enteroinvasion and elaboration of cytotoxins.

Clinical Presentation

The incubation period is only 1 to 2 days. The infectious dose is thought to be high, over 1 million organisms. Abdominal pain is noted in 72% of patients. Diarrhea is watery in 73% of patients and grossly bloody in 24%. Occult blood is noted in 44%, emesis in 38%, and fever in 51%.[24] Symptoms resolve after 1 to 3 days in most cases but occasionally may persist for up to 8 weeks. The duration of illness usually is shorter in children.

Diagnosis of *P. shigelloides* infection should be considered in patients with a typical invasive-appearing diarrhea, especially if the stools are bloody or when the onset of illness occurs shortly after the ingestion of raw shellfish or foreign travel, particularly to Mexico. *P. shigelloides* is increasingly recognized as a pathogen in immunocompromised patients.

Diagnostic Strategies

Definitive diagnosis is obtained by routine stool culture on MacConkey agar. The laboratory should be notified when this organism is considered. Unless oxidase testing is done, *Plesiomonas* may be indistinguishable from other strains in the Enterobacteriaceae family on nonselective culture media. Patients with *Plesiomonas* infections should be evaluated for possible immunodeficiency.

Management

Antibiotic therapy usually is not necessary for *P. shigelloides* enteritis because of the brief duration of illness. In patients who are immunocompromised and those with severe or prolonged symptoms, antibiotic treatment may be of benefit. *P. shigelloides* usually is resistant to ampicillin but susceptible to TMP-SMX, quinolones, cephalosporins, and chloramphenicol. The current recommended treatment regimen is TMP-SMX 160 mg/800 mg twice daily for 3 days; ciprofloxacin 500 mg twice daily; or norfloxacin 400 mg twice daily for 3 days.[3] Follow-up evaluation is not necessary unless the patient is immunodeficient or does not respond clinically.

Bacillus anthracis Infection

Epidemiology

Although gastrointestinal anthrax is rare in developed countries, large outbreaks still occur in agricultural regions throughout the world. Anthrax also has been used as a weapon of bioterrorism in regions not normally susceptible to the disease. As early as the

www.ketabpezeshki.com 66485457-66963820

1930s, groups experimented with anthrax-impregnated chocolate as a weapon against their enemies. Awareness of the spectrum of clinical presentations of gastrointestinal anthrax is important not only for the welfare of the patient but for prompt recognition of potential terrorist activity.[25]

Traditionally, gastrointestinal infection has been estimated at less than 1% of all human anthrax cases. It was thought that 95% of cases involved cutaneous symptoms and 5% were limited to the respiratory tract. However, because gastrointestinal anthrax can cause only mild and self-limited symptoms and occurs in underserved areas, many persons with the gastrointestinal form may not seek medical treatment. Studies of several large outbreaks in Uganda and Thailand suggest that the gastrointestinal form is observed in 74 to 92% of patients who contract anthrax after having eaten the meat of infected herbivores.[25]

Areas endemic for anthrax exist in all continents containing tropical and subtemperate regions. Thailand, India, Iran, Gambia, and Uganda all have reported deaths from gastrointestinal anthrax.[25] Within the United States, naturally occurring anthrax exposure has been documented in several areas, including Minnesota.[25] Although no predilection for time of year in endemic areas has been documented, the disease is more common in animals after substantial rainfall following a period of drought, a pattern known as "anthrax weather."[26]

In the United States, gastrointestinal anthrax has not been reported, although cutaneous anthrax is reported once or twice each year.[27] Populations at risk for naturally occurring anthrax are persons living in rural, agricultural areas who have ingested undercooked meat contaminated with anthrax spores. As with many other organisms, the pediatric population seems to be at greatest risk for serious or fatal illness.

Pathophysiology

B. anthracis is a nonmotile, rodlike, gram-positive anaerobic bacillus that produces central oval-shaped spores. It is introduced into the food chain most often after ingestion by herbivores such as cattle. The animal usually becomes visibly ill, and the meat often is identifiable as abnormal after slaughter, thereby preventing human exposure. Even when the meat reaches a consumer, adequate cooking usually reduces the inoculum to harmless levels. However, if the meat is undercooked, a high rate of infectivity results. Intentional placement of anthrax spores in the food or water supply could theoretically cause outbreaks of gastrointestinal anthrax, although this has not been reported.

When swallowed, anthrax spores stick to the gastrointestinal epithelium, where they germinate and create multiple superficial ulcerations. Lesions have been identified from the oral cavity to the cecum.[25] The vegetative cells may at times migrate into the bloodstream, where they rapidly multiply and can cause septicemia. *B. anthracis* protects itself with an antiphagocytic capsule and produces two exotoxins, lethal and edema toxins.[25]

Clinical Presentation

A minority of patients who ingest anthrax spores remain asymptomatic, and in endemic areas, adults often are thought to have some natural immunity acquired through previous exposure. Of those in whom symptoms do develop, presentation can vary widely, ranging from mild watery diarrhea to fulminant upper and lower gastrointestinal bleeding, septicemia, and death. The incubation period for gastrointestinal symptoms ranges from 1 to 6 days, developing earlier with larger inocula and more severe disease. For disease confined to the oropharynx, patients usually have complaints of sore throat, fever, dysphagia, hoarseness, and painful neck swelling. The swelling results from marked lymphadenopathy and tissue edema and can become severe enough to compromise breathing.[27]

Much information concerning intestinal anthrax has been derived from two large outbreaks in Uganda and Thailand.[25] A majority of the patients had isolated diarrhea. Nausea, vomiting, and severe abdominal pain with distention also developed in a minority of the patients. Most patients were febrile, with temperatures above 39° C (102° F) and blood in both the vomitus and diarrheal stool was common.

With this form of anthrax, lesions throughout the gastrointestinal tract often are surrounded by significant edema and can lead to obstruction, necrosis, and perforation. Intra-abdominal lymphadenopathy and splenomegaly develop as well. The lymphatic tissue often becomes hemorrhagic, and ascites may form, with fluid shifts large enough to cause shock and even death.

In cases of primary gastrointestinal anthrax, the superficial mucosa is always involved, with ulcerations visible on endoscopic examination. These findings are in contrast to those with disseminated infection from pulmonary anthrax, in which the lesions begin submucosally as a result of seeding from the bloodstream. These lesions can then secondarily ulcerate to the surface of the gastrointestinal tract epithelium. Untreated, gastrointestinal anthrax may last weeks and is fatal in over 50% of patients. Appropriate treatment results in a mortality rate less than 40%.[27]

Diagnostic Strategies

Diagnosis of *B. anthracis* infection in cases of oropharyngeal disease is best accomplished by swabbing the oral lesions for culture and PCR. Blood cultures are recommended for all suspected cases of anthrax, but culture results usually are negative in patients with isolated oropharyngeal involvement. A Gram-stained smear from the lesions will demonstrate numerous polymorphonuclear leukocytes and gram-positive bacilli. Studies of acute and convalescent serum antibody to anthrax antigens may confirm the diagnosis, but serologic testing is not widely available.

Diagnosis of the gastrointestinal variant of anthrax relies more on identifying *B. anthracis* DNA by PCR assay and cultures of blood and, if possible, ascitic fluid. Stool or rectal swab should be obtained for culture and PCR as well.[28]

Differential Considerations

Oropharyngeal anthrax lesions are sometimes confused with peritonsillar abscess, although cervical swelling is unusually severe in cases of oropharyngeal anthrax. The marked swelling of the oral lesions is secondary to edema and should not yield pus if incision and drainage are performed. Gastrointestinal anthrax can cause enough upper gastrointestinal bleeding to be confused with variceal rupture. In patients with severe disease manifested as marked ascites and abdominal pain, the clinical presentation may be similar to that in patients with end-stage liver disease with peritonitis.

Management

Traditionally, penicillin has been used to treat gastrointestinal anthrax. Cases of penicillin resistance have been documented, however, and a logical assumption is that a resistant strain would be chosen for use as a weapon of bioterrorism. Therefore, current recommendations from the CDC are to treat gastrointestinal cases in the same manner as cases of respiratory anthrax, with ciprofloxacin 400 mg intravenously (IV) every 12 hours or doxycycline 100 mg IV every 12 hours. Cephalosporins should not be used. Even with aggressive antibiotic therapy, the disease carries a 25 to 60% mortality rate, depending on treatment, host factors, and the size of the inoculum.[28]

www.ketabpezeshki.com 66485457-66963820

Table 94-3 Epidemiologic Aspects of Toxin-Induced Bacterial Enteritis

PATHOGEN OR ILLNESS	SOURCE(S)	INCUBATION PERIOD (I); DURATION (D)	COMMENTS AND FEATURES IF UNTREATED
Preformed Toxins			
Staphylococcus	Food handler related; potato salad, mayonnaise, confections	I: 1-6 hr D: 6-10 hr	Very high attack rates, large outbreaks
Bacillus cereus			
Emetic toxin	Fried rice	I: 2-4 hr D: 10 hr	High attack rate, almost always after consumption of fried rice
Diarrheal toxin	Vegetables; meats, especially gravies	I: 6-14 hr D: 24-36 hr	Food reheated or sitting out for long periods
Scombroid fish poisoning	Mahi mahi, tuna, bluefish	I: 5-60 min D: 6 hr	Peppery or bitter taste, histamine intoxication, high attack rates
Ciguatera fish poisoning: ciguatoxin	Large, predacious coral reef fish	I: 2-6 hr D: 7-14 days	High attack rates, gastrointestinal and neurologic symptoms with paresthesias, cold allodynia, worse with alcohol
Toxins Produced after Colonization			
Clostridium perfringens	Meat, poultry, gravies, "steam table" meats	I: 6-24 hr D: 24 hr	Food reheated or sitting out for long periods
Vibrio	Seafood, especially raw shellfish	I: 24-48 hr D: 6-8 days	Summer months, dehydration common
Escherichia coli	Usually unsanitary drinking water	I: 24-72 hr D: 1-7 days	Travelers; dehydration common in children
Clostridium difficile	Overgrowth of normal flora	I: 5-14 days D: Variable	Antibiotic-associated colitis, cytopathic toxin
Aeromonas	Untreated drinking water	I: 1-5 days D: 2-10 wk	Common and severe in children, chronic watery diarrhea in adults, occasionally mimics inflammatory bowel disease

TOXIN-INDUCED BACTERIAL GASTROENTERITIS

Pathogens associated with toxin-induced bacterial enteritis are summarized in Table 94-3. In general, gastroenteritis caused by toxin-forming bacteria and viral agents will manifest as an acute noninvasive enteritis, with watery diarrhea, minimal fever, little or no abdominal cramping, and absence of fecal leukocytes and erythrocytes. Treatment is primarily supportive, and diagnostic testing generally is not indicated in otherwise healthy patients. A specific diagnosis may be of help in attempting to identify a common source during large outbreaks.

Staphylococcal Food Poisoning

Epidemiology

Staphylococcus-related food poisoning occurs after multiplication of an enterotoxin-forming strain of *Staphylococcus* that is present in the food before ingestion. Food contamination with *Staphylococcus* is extremely common because the organism is ubiquitous in the environment. It can be isolated from the skin, hair, throat, and nasal passages of approximately 50% of persons in the general population. Most protein-rich foods support the growth of staphylococci, especially ham, eggs (even hard boiled), custard-filled pastries, mayonnaise, milk, and salads such as egg, tuna, chicken, potato, and macaroni.[29] Foods that require considerable handling during preparation and are then kept slightly warm after preparation are frequent offenders. Temperatures of 45 to 140° F for only a few hours will allow proliferation of the organism in contaminated food and production of sufficient enterotoxin to cause disease. Foods containing sufficient enterotoxin to produce violent illness usually are normal in appearance, odor, and taste. Large outbreaks are common worldwide, particularly in institutions such as school or hospital cafeterias, military bases, airlines, and restaurants.[29]

Pathophysiology

Although the bacterium itself is killed by cooking at temperatures above 140° F, *Staphylococcus* enterotoxin is heat stable. Thus once it is present in food, reheating or even boiling will not prevent illness. The toxin has no local effect on the digestive tract. It is a potent stimulator of T lymphocytes in the host, stimulating their proliferation and the release of various cytokines. The gastrointestinal effects are believed to be mediated by the release of interleukin 2, tumor necrosis factor beta, and interferon from mast cells.[30] Stool, vomitus and blood can be tested for the presence of the enterotoxin, but this is typically done by local health departments or the CDC during large outbreaks and rarely done in clinical laboratories.[31]

Clinical Presentation

The illness has an explosive onset, beginning 1 to 6 hours after ingestion of the contaminated food. Cramping and abdominal pain, with violent and often-repeated retching and vomiting, are the predominant symptoms. Diarrhea is a variable feature; it usually is mild, occasionally absent entirely, and infrequently profuse. Fever occasionally is present. Staphylococcal food poisoning is short-lived, usually subsiding in 6 to 8 hours and rarely lasting as long as 24 hours. Patients often are recovering by the time they seek medical attention. Attack rates are very high, often greater than 75% of the population at risk.[29] The short incubation

www.ketabpezeshki.com 66485457-66963820

period and multiple cases among persons eating the same meal are highly suggestive of this disease. Examination of the stool is noncontributory, and no practical laboratory test is clinically available to confirm the diagnosis. The epidemiologic circumstances, however, usually provide adequate suggestive evidence.

Management

Rapid, uncomplicated, spontaneous recovery is the rule. Parenteral antiemetic agents help control vomiting. Intravenous fluids should be given to patients with significant dehydration and ongoing vomiting, particularly the very young, elders, and debilitated patients. Antibiotics are of no value because staphylococcal food poisoning is caused by preformed enterotoxin and not by viable microorganisms. Adherence to strict personal hygiene practices by food handlers and immediate refrigeration of foods not intended for immediate consumption are the most important preventive measures. Ordinary refrigerator temperatures prevent production of the enterotoxin. Food should not be allowed to stand at room temperature for long periods before being served.

Clostridium perfringens Food Poisoning

Epidemiology

C. perfringens food poisoning is one of the most commonly reported food-borne illnesses in the United States, with at least 10 to 20 outbreaks reported annually. Most cases occur in large groups, with dozens or even hundreds of persons affected. Illness is caused by the ingestion of meat or poultry heavily contaminated with *C. perfringens* type A heat-resistant spores.[32] The organism also is ubiquitous in the environment and in human and animal feces. Typically, poisoning results from ingesting food that is cooked more than 24 hours before consumption, allowed to cool slowly at room temperature, and then served either cool or rewarmed. During this period of incubation, spores that survived cooking germinate, and clostridia multiply to reach sufficient numbers to constitute an infectious inoculum.

Pathophysiology

Ingestion of live organisms is required to produce disease, but illness is not caused by infection; rather, it is from an enterotoxin produced by sporulation of the organism in the gastrointestinal tract. The enterotoxin is responsible for all the symptoms of *C. perfringens* food poisoning.

Clinical Presentation

Symptoms usually appear within 6 to 12 hours but can occur up to 24 hours after ingestion of the contaminated food. Frequent passage of watery diarrheal stools and moderately severe abdominal cramping are the major symptoms. Fever, nausea, and vomiting are rare. The illness is self-limited and rarely lasts for more than 24 hours.

C. perfringens food poisoning should be considered in a patient who experiences an acute onset of abdominal cramps and watery diarrhea shortly after eating a suspect meat or poultry dish and when others who ate the same meal are similarly ill. Leukocytes and erythrocytes are not present on stool examination.

Complications

A rare type of *Clostridium* food poisoning termed *enteritis necroticans* (also known as “pig-bel”) occurs after the ingestion of foods heavily contaminated with type C strains of *C. perfringens.* The illness is characterized by an acute onset of severe abdominal pain, vomiting, diarrhea, prostration, and shock and may be rapidly fatal. Postmortem examination reveals a diffuse, hemorrhagic, necrotizing enteritis of the jejunum, ileum, and colon.[33]

Management

Occasionally, a patient will need intravenous fluid replacement. Antibiotics are of no value because of the toxigenic nature and brief duration of the disease. Food poisoning from *C. perfringens* can be prevented by avoiding long periods of warming or cooling of foods that have already been cooked.

Bacillus cereus Food Poisoning

Epidemiology

B. cereus is an aerobic, spore-forming, gram-positive rod that is a common cause of food-borne illness. The organism is one of the most frequently isolated soil bacteria. Because of its abundance and the hardiness of its spores, *B. cereus* contaminates nearly all agricultural products and plays a major role in the spoilage of food items, including pasteurized milk and milk products. It commonly is isolated from pasta, rice, dairy and dried milk products, spices, dried foods, meat, chicken, vegetables, seafood, fruits, and grains. Because it is ubiquitous and tolerates extremes of temperature, control of this bacterium in the food-processing environment is very difficult to achieve.[34] It is estimated that *B. cereus* causes more than 27,000 cases of food poisoning in the United States each year.[35]

B. cereus causes two distinct clinical syndromes: an emetic form produced by a heat-stable, *Staphylococcus*-like enterotoxin known as *cereulide,* and a diarrheal form resulting from a heat-labile enterotoxin known as *HBL,* which is similar to that of *E. coli.* The emetic form usually is caused by the ingestion of contaminated fried rice, although beef, poultry, vanilla sauce, pasteurized cream, milk pudding, pasta, potato, cheese and infant formula also have been implicated. The diarrheal syndrome usually is associated with ingestion of HBL in meats or vegetables, but reported outbreaks also have involved fish, vegetables, soups, sauces, and dairy products.[34]

Pathophysiology

The heat-resistant spores of *B. cereus* survive boiling and then germinate when boiled foods such as fried rice are left unrefrigerated. The vegetative forms then multiply and produce toxin. Flash-frying or brief rewarming of the food before serving often is not sufficient to destroy the preformed, heat-stable emetic toxin. Improper holding temperatures for cooked food are the most common feature of *B. cereus* food-borne illness.

Clinical Presentation

The emetic syndrome is clinically indistinguishable from that caused by staphylococcal enterotoxin. After an incubation period of 1 to 5 hours, profound vomiting and abdominal cramping occur in all patients. Diarrhea is present in approximately 25 to 30% of persons affected. The duration is short, usually less than 10 hours, and patients recover uneventfully.

The diarrheal syndrome begins after an incubation period of 6 to 14 hours and is characterized by diarrhea in all patients and by abdominal cramps in approximately 75%. Vomiting occurs in only 20% of cases. The duration of illness ranges from 12 to 36 hours. Symptoms are essentially the same as for food poisoning produced by *C. perfringens,* although vomiting is less common with *C. perfringens.*

www.ketabpezeshki.com 66485457-66963820

B. cereus food poisoning should be suspected whenever an illness localized predominantly to the upper gastrointestinal tract develops less than 6 hours after eating, or whenever a predominantly lower intestinal tract illness occurs 6 to 24 hours after a suspect meal, usually of meats or vegetables.

Diagnostic Strategies

Because of the brief and noninvasive nature of the illness, diagnostic testing typically is not performed. In response to large outbreaks, public health authorities may elect to test common food sources. Isolation of 10^5 colony-forming units per gram from incriminated foods confirms the diagnosis. *B. cereus* enteric infection can also be confirmed via detection of the emetic or diarrheal toxin in stool, emesis, or foods, but this is done only in reference laboratories and only during investigation of large outbreaks.

Management

Both syndromes generally are mild and self-limited. Antibiotics are not indicated because symptoms are mediated by enterotoxins. Parenteral antiemetic agents provide effective relief in patients with violent vomiting. *B. cereus* food poisoning is preventable if boiled rice or cooked foods are promptly eaten or refrigerated and not left to sit at room temperature.

Cholera and Gastroenteritis Caused by Noncholera *Vibrio* Species

Epidemiology

In addition to *V. parahaemolyticus,* other halophilic marine *Vibrio* species have increasingly been determined to be causes of acute gastroenteritis associated with seafood. Their epidemiology is similar to that of *V. parahaemolyticus:* presence in coastal seawater, outbreaks associated with the eating of raw or inadequately cooked shellfish, and an incidence markedly limited to the warmer months of the year.[15] Outbreaks of true cholera continue to occur sporadically along the Gulf Coast of the United States from inadequately cooked crabs or oysters. Other implicated foods include imported seafood, cooked rice, frozen or fresh coconut milk, and commercially prepared cut cantaloupe.[15] Cholera outbreaks in South America, Haiti, the Dominican Republic, Pakistan, and India have led to an increasing number of cases of cholera imported into the United States. The CDC reports approximately 10 U.S. cases annually. Worldwide, an estimated 3 to 5 million cases and 100,000 deaths occur each year, primarily in underdeveloped countries with poor water and sewer sanitation systems.[36]

Pathophysiology

The difference between these species and *V. parahaemolyticus* lies in the mechanism of pathogenesis. *V. parahaemolyticus* produces disease via toxins that cause intestinal mucosal destruction, whereas these strains produce an enterotoxin in vivo that stimulates enterocyte adenylate cyclase, disrupting mucosal fluid absorption, leading to a secretory diarrhea. Therefore symptoms resemble those of other forms of enterotoxin-induced gastroenteritis and not those caused by invasive pathogens. The enterotoxin of the noncholera *Vibrio* species is antigenically similar to *Vibrio cholerae* enterotoxin and produces a similar secretory diarrhea, although it is much less severe.[15]

Clinical Presentation

Patients with classic epidemic cholera experience copious "rice water" diarrhea, abdominal cramps, and often nausea and vomiting within 24 to 48 hours after ingesting contaminated seafood. A low-grade fever may be present. In these severe cases (cholera gravis), rates of diarrheal fluid loss can reach 1 L per hour. Nearly one half lose enough fluids to necessitate hospitalization, and fatality rates can reach 25 to 50% in untreated populations. The median duration of illness is approximately 7 days, quite unlike the 1- to 2-day course of *V. parahaemolyticus* infection.[15] Despite the notoriety of the classic form of cholera, the CDC estimates that only 1 in 20 cases is associated with cholera gravis. A majority of affected patients experience a relatively mild diarrheal illness that may go undocumented.

Another *Vibrio* species, *Vibrio vulnificus,* also is associated with eating raw seafood, especially raw oysters. *V. vulnificus* can cause self-limited gastroenteritis with onset approximately 16 hours after ingestion of contaminated food by healthy persons. In the compromised host, this organism causes serious wound infections after contact of seawater with open wounds, or a syndrome of primary septicemia characterized by hemorrhagic bullae of the skin and rapidly progressive septic shock. *V. vulnificus* infection is the leading cause of death in the United States associated with consumption of seafood. Septicemia carries a mortality rate of approximately 50% in patients with significant underlying disease, particularly chronic liver disease.[15] Approximately 95 cases (including 85 hospitalizations and 35 deaths) are documented in the United States each year. All patients with chronic liver disease, alcoholism, AIDS, other immunodeficiency states, and any significant chronic disease should be advised to avoid all raw shellfish.[37]

Diagnostic Strategies

Because these are noninvasive *Vibrio* species, unlike *V. parahaemolyticus,* stained fecal smears will not show leukocytes or erythrocytes. Stool cultures will quickly identify *V. cholerae* if plated on appropriate TCBS medium.[15] *V. vulnificus* infection can be diagnosed with stool, blood, or wound cultures. The clinical laboratory should be notified when this infection is suspected so that specific culture media can be used.[37]

Management

Patients with classic cholera often will lose enough fluids to require rehydration therapy. The World Health Organization oral rehydration formula has been used successfully to treat cholera worldwide.[8] The use of either oral or intravenous fluid hydration is dictated by the clinical picture. The role of antibiotics in the treatment of intestinal infections caused by noncholera *Vibrio* species is not clearly established. However, appropriate antibiotic regimens have been shown to decrease both the severity and the duration of cholera and may have the same effect on the diarrheal disease caused by these marine vibrios.[15] Antibiotics should be guided by strain-specific sensitivities if available. Typical choices include a single oral dose of ciprofloxacin 1 g, azithromycin 1 g, or doxycycline 300 mg; or a 3-day regimen of double-strength TMP-SMX twice a day or tetracycline 500 mg four times daily or erythromycin 500 mg four times daily.[3,36] Preventive measures include use of bottled water, meticulous attention to handwashing before eating and after use of the bathroom, avoidance of fecal soiled water sources, thorough cooking of food, peeling of fruits and vegetables, and bathing and toileting at least 30 yards away from drinking water sources.[36] Cholera is a nationally reportable infection.

An oral cholera vaccine is licensed and available in other countries. The oral vaccine appears to provide better immunity with fewer adverse effects than the previously available parenteral vaccine. The CDC does not recommend this vaccine for travelers, and it is not available in the United States.[36]

www.ketabpezeshki.com 66485457-66963820

If *V. vulnificus* infection is known or suspected, antibiotics should be initiated immediately, as this improves survival. Wounds should be débrided aggressively, as these progress rapidly and sometimes mandate fasciotomy or amputation. Single-dose antibiotic regimens include levofloxacin or ciprofloxacin. The combination of doxycycline 100 mg orally (PO) or IV plus a third-generation cephalosporin such as ceftazidime 1 to 2 g IV or intramuscularly (IM) every 8 hours is also recommended. Children can be treated with TMP-SMX plus an aminoglycoside.[37]

Scombroid Fish Poisoning

Epidemiology

Scombroid fish poisoning remains one of the most common forms of fish poisoning in the United States. The disease takes its name from the family Scombroidea (e.g., tuna, mackerel, skipjack, bonito, and related species) and results from the ingestion of a wide variety of dark-meat fish, including nonscombroid species such as herring, bluefish, anchovy, sardine, amberjack, black marlin, and mahi mahi. The fish species most commonly implicated are mahi mahi, tuna, and bluefish.[38] Restaurants serve these fish under various names such as mackerel, swordfish, bonito, dolphin, or amberjack, or they may make their appearance in the generic "tuna salad sandwich."

Most U.S. cases occur in Hawaii and Florida, followed in frequency by California, New York, Washington, and Connecticut. However, scombroid poisoning can occur in any location where "fresh fish" are flown in on a regular basis.

Pathophysiology

Implicated species naturally contain unusually high levels of histidine. Scombroid fish poisoning results from the ingestion of heat-stable toxins produced by bacterial action on the histidine present in the dark meat of the fish. The responsible bacteria are normal constituents of the surface marine flora, rather than contaminants. The histidine decarboxylase activity of these organisms produces histamine and histamine-like substances, which cause the symptoms of scombroid fish poisoning. High levels of histamine in the fish correlate directly with the occurrence of the illness. Formation of the scombrotoxins is directly related to improper preservation and refrigeration of the fish from the time they are caught until the time they are cooked. In general, the problem is caused by improper refrigeration by the supplier rather than being the fault of the restaurant serving the fish. Other foods, notably Swiss cheese, contain sufficient amounts of histidine and have also been implicated.

Clinical Presentation

The symptoms of scombroid fish poisoning resemble those of histamine intoxication. While eating the fish, the patient may note a metallic, bitter, or peppery taste, although many affected fish do not have an abnormal odor or taste. Symptoms usually develop abruptly within 20 to 30 minutes and consist of facial flushing, diarrhea, severe and throbbing headache, palpitations, and abdominal cramps. Other manifestations may include dizziness, dry mouth, nausea and vomiting, and urticaria. The facial flushing resembles a sunburn and can extend over the entire skin surface. The conjunctivae usually are injected. The duration of the major symptom complex generally is less than 6 hours, and although weakness and fatigue persist longer, the clinical course usually is benign. The attack rate is very high; most persons sharing the same toxic fish will become ill.

Management

Parenteral antihistamine therapy, such as diphenhydramine 50 mg IM or IV or cimetidine 300 mg IM or IV, usually promptly relieves all symptoms. Rarely, intravenous fluids are necessary. The disease is preventable if fish are properly handled, especially if they are refrigerated early and adequately. This is not an allergic reaction, so patients should not be told they are allergic to these fish, nor should they be prohibited from eating them again in the future.

Ciguatera Fish Poisoning

Epidemiology

Ciguatera fish poisoning is a common public health problem, with appreciable economic significance. It is endemic in tropical regions but is found worldwide. The CDC estimates that 50,000 to 100,000 people per year become ill from ciguatera poisoning worldwide.[38] Fish caught around Hawaii and Florida cause most U.S. cases, but because the responsible ocean fish are now commonly transported inland, cases can be seen virtually anywhere in the country.[38]

Ciguatoxin is produced by the marine dinoflagellate *Gambierdiscus toxicus,* which attaches itself to marine algae and is passed up the food chain. The lipid-soluble toxin accumulates in the tissues of the larger predacious coral reef fish, with the highest concentrations in the liver, intestines, head, and roe. It does not affect the fish in any way. Only humans suffer its ill effect when the toxin is ingested.

More than 400 fish species that frequent coral reefs have been implicated as ciguatoxin carriers, but fewer than 50 are commercially important. Those implicated in ciguatera poisoning include amberjack, barracuda, grouper, king mackerel, parrotfish, sea bass, snapper, sturgeon, surgeonfish, and ulua.[38]

Pathophysiology

Ciguatera fish poisoning results from the ingestion of the ciguatoxin neurotoxin. Ciguatoxin is heat and acid stable, odorless, and tasteless. It is not deactivated by cooking or freezing, nor is it eliminated by drying, salting, smoking, marinating, or pickling. It is not possible to predict whether a fish contains sufficient amounts of the toxin to produce illness.[38] Ciguatoxin has both anticholinesterase and cholinergic properties, but its neurotoxicity is mediated by its effect on sodium channels. Ciguatoxins cause a hyperpolarizing shift of the voltage dependence of channel activation such that sodium channels are open at resting membrane potential. Spontaneous firing of neurons occurs as tetrodotoxin-sensitive sodium channels are activated, giving rise to the typical neurologic signs and symptoms.[39]

Clinical Presentation

Ciguatera fish poisoning most commonly is seen in the spring and summer months. The incubation period is approximately 2 to 6 hours, but a delay of 12 to 24 hours is not unusual. Attack rates are very high; 80 to 90% of persons exposed become ill. Symptoms tend to be related to the amount of toxin ingested and vary considerably in their severity. If not fully recovered from an initial ingestion of ciguatoxin, affected persons are likely to have much more serious symptoms from a second ingestion.[38]

Classically, patients exhibit both gastrointestinal and neurologic symptoms. The gastrointestinal symptoms (e.g., nausea, vomiting, profuse watery diarrhea, crampy abdominal pain, and diaphoresis) tend to appear first and resolve over the first 24 hours. The constellation of neurologic symptoms consists largely of dysesthesias and paresthesias around the throat and the perioral area;

www.ketabpezeshki.com 66485457-66963820

"burning feet," which may resemble alcoholic peripheral neuropathy; "loose, painful teeth"; and sometimes central nervous system changes, such as ataxia, weakness, vertigo, visual hallucinations, and even confusion and coma.[38]

Distortion of temperature perception is vividly described by patients with ciguatera poisoning. *Cold allodynia,* defined as dysesthesia experienced on contact with cold water or cold objects, is almost pathognomonic of ciguatera poisoning and often is incorrectly referred to as "cold-hot temperature reversal." Another classic feature is either a return or a worsening of all of the symptoms after ingestion of alcohol.

Ciguatera poisoning lasts an average of 1 to 2 weeks, but at least one half of its victims are still symptomatic at 8 weeks. The neurologic symptoms, particularly the paresthesias and dysesthesias, tend to persist longer than the gastrointestinal symptoms and have been reported up to years later.

Differential Considerations

Ciguatera fish poisoning should be strongly considered in patients with a combination of gastrointestinal and neurologic symptoms, particularly dysesthesias. Cold allodynia and marked worsening of the symptoms with alcohol ingestion are highly suggestive of ciguatera toxicity.

The disease sometimes is misdiagnosed as acute gastroenteritis with "hyperventilation syndrome" because of the combination of gastrointestinal symptoms and paresthesias, particularly when they occur about the mouth and acral areas. Similarly, manifestations of ciguatera toxicity sometimes have been ascribed to malingering because the paresthesias often are transient and vague and lack traditional dermatome patterns.

Other disorders that should be considered in the differential diagnosis include paralytic or neurotoxic shellfish poisoning, eosinophilic meningitis, botulism, organophosphate insecticide poisoning, and tetrodotoxin poisoning.

Management

Treatment is primarily supportive. Intravenous fluids are given to replace volume losses from vomiting and diarrhea, and analgesics are given as needed. In severe cases, the toxin may exhibit some anticholinesterase activity, manifested as bradycardia and hypotension, which can be treated with atropine and dopamine. Patients should be told to abstain from alcohol in any amount until symptoms have completely resolved.

Pruritus may be managed with a histamine H_1-receptor antagonist such as cetirizine (Zyrtec) at a dose of 10 mg once daily. Amitriptyline 25 mg twice a day can bring about a dramatic reduction in both the pruritus and the dysesthesias, two of the most disturbing and protracted symptoms.

Intravenous mannitol has historically been an accepted treatment for ciguatera poisoning. The rationale for its use was based on data compiled from one uncontrolled study of 24 patients, one nonrandomized study, one nonblinded study, and anecdotal reports. More recently, a controlled, randomized double-blinded study of 50 adults found no difference in symptomatic improvement between patients who received normal saline and those who received mannitol. In addition, studies of ciguatoxin-intoxicated animals showed that mannitol did not reverse the effects of ciguatoxin. On the basis of this information, mannitol is not recommended as therapy for ciguatera poisoning.[38] Recently, the naturally occurring compound brevenal was shown to inhibit ciguatoxin-induced neurosecretion in laboratory studies. This compound may prove beneficial in treating the neurologic sequelae of ciguatera fish poisoning.[39]

Enterotoxigenic *Escherichia coli*

Epidemiology

Enterotoxin-producing *E. coli,* or enterotoxigenic *E. coli* (ETEC), is recognized as a major cause of acute diarrheal disease throughout most of the world. It is a major cause of diarrhea in persons traveling to underdeveloped areas, especially South Asia, sub-Saharan Africa, and South America. The disease has been most intensely studied in North American visitors to Latin America, where it occurs in 17 to 70% of travelers studied, often incapacitating them or forcing a change in their plans.[40] ETEC is increasingly recognized as a cause of food-borne illness in developed countries, including the United States.[41]

Infection is acquired from fecally contaminated food or drink. Unpeeled fruits, leafy vegetables, unsanitary drinking water, and ice prepared from impure water are the most common sources. Most tourists are careful about their food and drink, but there seems to be a poor correlation between individual eating habits and the incidence of traveler's diarrhea. It is likely that the quality of hygiene at a particular food source is the major determinant of risk; travelers should choose locations that have a reputation for excellence in hygiene.

Pathophysiology

For an *E. coli* strain to cause diarrhea, it must possess both a surface factor that allows colonization (although not invasion) of the small intestine and the ability to secrete an enterotoxin that causes the outpouring of fluids and electrolytes into the small bowel lumen. The enterotoxin-induced secretion occurs in the absence of any demonstrable histologic damage to intestinal epithelial cells or to the capillary endothelial cells.[42]

E. coli produces both heat-labile and heat-stable toxins. The heat-labile enterotoxin is similar to cholera toxin in that it binds to specific receptors on the surface of the intestinal epithelial cell, allowing translocation of an A subunit into the cell. The A subunit modifies host cell signals, resulting in the dysregulation of sodium and chloride secretion, disturbances of ion transport, and intestinal water loss. The heat-stable toxin exerts its effect through the stimulation of guanylate cyclase C receptor in mucosal cells and tends to have a more rapid onset of action. Either or both toxins can be produced by any enterotoxic strain of *E. coli.* The intestinal fluid losses are qualitatively identical to those in cholera and other toxigenic diarrheas.[42]

Clinical Presentation

After an incubation period of 24 to 72 hours, an abrupt onset of watery diarrhea occurs. Severity varies, with the illness ranging from a fulminant, cholera-like disease to the much more common and milder *turista,* in which the symptoms of mild, watery diarrhea and abdominal cramps are more troublesome than life-threatening. Fever is unusual. Vomiting occurs in fewer than one half of affected adults and is seldom responsible for significant fluid losses. Even in severe cases, the diarrhea seldom lasts longer than 48 to 72 hours, and the response to either oral or intravenous fluids is uniformly good. Milder disease generally subsides more gradually, occasionally persisting for 1 week or longer. Virtually all persons recover completely without long-term sequelae.

E. coli enterotoxin–induced disease should be suspected when a child or adult has frequent, watery diarrhea and few other symptoms. It often is passed off as mild, nonspecific gastroenteritis and resolves spontaneously. Anyone who acquires toxigenic diarrhea while visiting a developing nation probably has this disease. ETEC is by far the most common cause of traveler's diarrhea.

www.ketabpezeshki.com 66485457-66963820

Diagnostic Strategies

No easy, rapid means of laboratory diagnosis of ETEC infection exists. Methods that rely on identification of specific *E. coli* serotypes are unreliable because *E. coli* is part of the normal colonic flora, and its ability to produce enterotoxin is not restricted to any specific serotype. Methods based on detection of the heat-stable and heat-labile toxins through use of real-time PCR assay have been developed but are generally available only in reference laboratories. Stool preparations show no erythrocytes or leukocytes.

Management

Because ETEC infection is almost always a self-limited disease, no treatment other than maintaining hydration is required. However, if the organism is identified while symptoms are still active, or if the patient is traveling in an endemic area, antibiotics can afford clinical relief. For milder symptoms, a single dose of ciprofloxacin 750 mg by mouth in addition to loperamide should be effective. For more severe symptoms, TMP-SMX 160 mg/800 mg or standard doses of a fluoroquinolone for 3 days should eradicate the organism.[3]

Clostridium difficile Antibiotic-Associated Enterocolitis

Epidemiology

C. difficile is an anaerobic spore-forming gram-positive bacillus that was first linked to enteritis in 1978. It has been associated with a range of illnesses from asymptomatic colonization to severe diarrhea, pseudomembranous colitis, toxic megacolon, intestinal perforation, and death.[43] *C. difficile* can be cultured from the stool of up to 70% of healthy infants and approximately 3% of healthy adults.[43] The disease is unique in that an organism normally found in the colon causes illness primarily during or after the administration of antimicrobial agents that alter bowel flora. Colitis can occur as a result of oral or parenteral administration of most antimicrobial drugs, including quinolones, clindamycin, lincomycin, ampicillin, cephalosporins, tetracycline, penicillin, chloramphenicol, sulfa products, and erythromycin. Other risk factors, in addition to recent use of antimicrobials, include age older than 65 years, severe underlying illness, nasogastric intubation, use of antiulcer medications, and prolonged hospital stay.[43] Infection with this organism occurs primarily in adults but is being seen with increasing frequency in children. Most cases of *C. difficile* colitis occur in patients who are hospitalized or reside in long-term care facilities or in outpatients who were hospitalized in the previous 6 months. Stool carriage rates reach 16 to 35% in hospitalized patients owing to transfer of organisms by the hands of hospital personnel or from patient to patient.[44] Occasional nosocomial infections occur in the absence of antibiotic therapy.[8]

C. difficile has emerged as the most important health care–associated enteric infection of the past three decades. During the past several years, an increase in the incidence and severity of *C. difficile*–associated colitis has been noted, along with recognition of a new strain designated NAP1/027 (toxinotype III, North American pulsed field gel electrophoresis type 1, PCR ribotype 027). This strain has been associated with outbreaks in Canada, Europe, and the United States. Mortality rates in the United States have increased from 5.7 per million in 1999 to 23.7 per million in 2004.[43]

Pathophysiology

C. difficile spores can survive up to 2 years on inanimate objects before ingestion and are able to tolerate the acidic environment of the stomach. After passing into the milder environment of the small bowel, the vegetative form proliferates when the normal bowel flora is substantially reduced by antibiotic therapy. The organisms must then produce sufficient quantities of toxin for the disease to occur. *C. difficile*'s primary virulence factors are known as toxin A and toxin B. Toxin A attracts neutrophils and monocytes, and toxin B disrupts colonic epithelial cells, both leading to watery diarrhea, colitis, and sometimes pseudomembrane formation. In persons who are colonized with *C. difficile* without experiencing colitis, higher levels of antibody to toxin A have been documented, and development of clinical disease is less likely. In those in whom colitis does develop, higher levels of anti–toxin A antibody are associated with a shorter duration of illness and decreased recurrence rate.[44] The incubation period has not been well established.[43]

On histologic examination, the mucosa is hyperemic and edematous. Raised, yellowish-white plaques, loosely adherent to the mucosa, occur in patches, primarily in the rectosigmoid area, but can occur in any part of the colon. The disease was previously named *pseudomembranous enterocolitis* because of these pseudomembrane-like plaques.

Clinical Presentation

Symptoms may appear during the course of antimicrobial therapy or commonly up to 3 or 4 weeks after discontinuation of antibiotics. Of interest, *C. difficile* has been reported to produce illness as late as 6 months after completion of antibiotic therapy. The clinical presentation is highly variable. Most often, patients have mild to moderate nonbloody diarrhea associated with lower abdominal cramping and few systemic symptoms. Because the toxin alters the intestinal mucosa, the illness can manifest more like an invasive diarrhea than a toxigenic one, with fever, nausea, dehydration, severe crampy abdominal pain, distention, and profuse watery stools. Occult blood in the stool may be a feature, although hematochezia is uncommon. Fecal leukocytes usually are present. Persons at extremes of age tend to have more severe infections. The past decade has seen the emergence of a fulminant form in patients older than 65 years. Elders with a leukocyte count greater than 20×10^9 per liter, nosocomial infection, renal failure, and immunosuppression are at increased risk for complications such as toxic megacolon, shock, need for colectomy, and death.[44]

Diagnostic Strategies

A variety of diagnostic tests are available for the detection of *C. difficile*. The historical gold standard modality is the cell cytotoxicity assay, in which stool is cultured on suitable medium and observed for the cytotoxic effect of toxin B. This test is 94 to 100% sensitive but requires 48 to 72 hours for completion. A more rapid method, currently recommended by the Infectious Diseases Society of America, is to screen for the presence of the glutamate dehydrogenase (GDH) ("common") antigen indicative of *C. difficile* and then to test positive samples with EIA for toxin A or B to establish toxigenicity. Although rapid, this method achieves a sensitivity of only 80 to 85%. A rapid PCR assay for the gene coding for the toxin is commercially available and will likely become the gold standard in the near future.[43,44]

Differential Considerations

It is important to differentiate *C. difficile* colitis from simple antibiotic-associated diarrhea. Of all patients treated with antibiotics, 3 to 10%, particularly children, develop diarrhea not associated with *C. difficile* toxin. These patients experience mild, watery diarrhea and no associated constitutional symptoms or evidence of a cytopathic toxin-induced colitis.

www.ketabpezeshki.com 66485457-66963820

Management

In early studies, 15 to 23% of patients who had *C. difficile* colitis experienced spontaneous resolution within 48 to 72 hours of discontinuing the offending antibiotic.[44] If discontinuing the antibiotic does not resolve the diarrhea or if the diarrhea is severe, antibiotic treatment should be started promptly. Either oral metronidazole or oral vancomycin can be used. The dosage of metronidazole is 250 mg orally four times daily for 10 to 14 days. Metronidazole also is effective when administered by the intravenous route. Doses of vancomycin ranging from 125 to 500 mg orally four times daily have been equally effective.[44] Intravenous vancomycin generally is not effective because it does not reach effective intraluminal concentrations.

Initial trials comparing metronidazole and vancomycin found similar response rates of approximately 90%. In more recent studies, approximately 78% of patients treated with metronidazole had an initial response to therapy, and approximately one third of these had recurrence of disease, for an overall response rate of approximately 50%. Because vancomycin is much more expensive than metronidazole and because of concerns about emerging vancomycin resistance, oral metronidazole is the agent of choice for treatment in patients with mild disease, and oral vancomycin is reserved for patients who do not respond to metronidazole therapy or for those who are moderately to extremely ill at the time of presentation. In response to high recurrence and clinical failure rates, additional drugs, including rifaximin, nitazoxanide, OPT-80, and ramoplanin, are being developed.[43]

Patients generally become afebrile and show clinical improvement within 36 to 72 hours; the diarrhea resolves over 5 to 7 days, even though results of toxin assays and stool cultures may remain positive for weeks. From 8 to 50% (average, 25%) of patients experience a relapse regardless of the antibiotic chosen, its dosage, or the duration of treatment, and the recurrence rate is increasing. Risk factors for recurrent disease include new exposure to antibiotics, age older than 65 years, severity of underlying disease, low serum albumin, need for admission to an intensive care unit, and hospital stay of 16 to 30 days. Nearly all of these patients will respond to another course of antibiotic therapy.[44]

Adding the yeast *Saccharomyces boulardii,* 500 mg orally twice daily for 4 weeks, to antibiotic treatment has been shown to dramatically decrease the number of recurrences of *C. difficile*–associated disease in patients with previous episodes. However, no benefit is seen when *S. boulardii* is given to patients with an initial episode.[43] No serious adverse reactions have occurred with the use of *S. boulardii.*

Although toxicity from parenteral vancomycin is common, no adverse effects have been reported with its oral use in the treatment of *C. difficile* colitis. Antimotility or constipating agents are contraindicated in these patients because of the risk of toxic megacolon and the possibility of increasing the level of cytopathic toxin in the colon.[44]

ACUTE VIRAL GASTROENTERITIS

Etiology and Epidemiology

Viral gastroenteritis is the second leading cause of illness in the United States. Although several virus families have been implicated, including caliciviruses, coronaviruses, and parvoviruses, two have predominated in the past decade. Noroviruses, which include the Norwalk virus, are primarily responsible for disease in adults and older children, whereas human reovirus–like agents, also called *rotaviruses,* cause most diarrheal disease in infants and young children. Worldwide, rotavirus infection causes more than 500,000 deaths in children younger than 5 years. In the U.S. prevaccine era, rotavirus infection was the leading cause of hospitalization for gastroenteritis and precipitated 400,000 physician visits, 60,000 admissions, and approximately 20 deaths each year. Rotaviruses also cause epidemics in adults, especially those in contact with sick children.[45]

These viruses have a low infectious dose, and attack rates may reach 50%. The incubation period is short, so explosive outbreaks are common. Norovirus is transmitted by several routes and is relatively stable in the environment, making this infection particularly prone to spread. It is estimated that noroviruses are responsible for 68 to 80% of all outbreaks of gastroenteritis in industrialized countries.[8,46] Both viruses can be transmitted from person to person by the fecal-oral route, but water- or food-borne outbreaks also are common. Sources in large reported outbreaks of norovirus infection have included municipal or semipublic water supplies, bodies of water used in recreational swimming, stored water on cruise ships, cafeteria sandwiches, food handlers, and shellfish.[7,46] The ingestion of raw oysters has caused many large outbreaks. The CDC estimates that 50% of all food-borne outbreaks of gastroenteritis are attributable to noroviruses.[8,46] Nosocomial spread of infection also is common. Astrovirus and picornaviruses are common causes of diarrhea in human immunodeficiency virus (HIV)–infected patients.[8]

Pathophysiology

Viruses distort the absorptive cells of the microvilli of the small bowel, decreasing their absorptive surface and causing diarrhea from decreased absorption of fluid and electrolytes. Viral nonstructural proteins also may act as enterotoxins, promoting active chloride secretion into the bowel lumen. The histologic picture resembles that with tropical sprue, and transient malabsorption of fats and sugars, which may persist for a week or more after infection, occurs in patients with viral gastroenteritis.[45]

Diarrheal stools in viral disease contain more sodium, chloride, and bicarbonate than do normal stools, but these abnormalities are not comparable with the almost isotonic fluid loss of bacterial toxin–induced diarrhea. Potassium loss usually is not significant unless symptoms are prolonged.

Clinical Presentation

Viral gastroenteritis occurs primarily in two epidemiologically distinct clinical forms. Outbreaks caused by rotaviruses usually are sporadic, occasionally are epidemic, and typically occur in the winter months in infants and children 6 to 24 months of age. The incubation period is 24 to 72 hours, followed by abrupt onset of vomiting, watery diarrhea, and low-grade fever but little or no associated abdominal pain. Vomiting is a prominent and constant early manifestation of rotavirus enteritis but rarely persists beyond the first 36 hours. The diarrhea generally lasts for 4 to 7 days and may be followed by steatorrhea in approximately 20 to 40% of patients. Many children become significantly dehydrated, requiring hospitalization and intravenous fluid replacement, but the disease rarely is life-threatening in developed countries.

Overt clinical disease can occur among family and adult contacts of ill children but it is uncommon. Most adults with rotavirus infections are asymptomatic. When symptoms do occur, they usually are mild, perhaps because these episodes represent reinfections; 60 to 90% of older children and adults have antibodies to rotaviruses.[45]

The second clinical entity is characteristically epidemic and is responsible for family and community-wide outbreaks of gastroenteritis among school-aged children, family contacts, and adults. This form generally is caused by the Norwalk virus. After an incubation period of 20 to 36 hours, diarrhea, nausea, and mild abdominal cramps occur. Vomiting is not prominent. Fever typically is absent. Anorexia, headache, malaise, and myalgias may be

www.ketabpezeshki.com 66485457-66963820

present. The illness is self-limited, usually lasting only 24 to 48 hours. Most affected adults have mild symptoms and do not seek medical attention.[7,46]

Diagnostic Strategies

The diagnosis of rotavirus gastroenteritis should be considered in children with significant vomiting, diarrhea, low-grade fever, moderate dehydration, and a normal white blood cell count, especially in those 6 to 24 months of age who become symptomatic during the winter months. An elevated blood urea nitrogen level and a compensated metabolic acidosis are common findings. Serum electrolyte studies indicate that the dehydration usually is isotonic.

In adults, the diagnosis of viral gastroenteritis usually is one of exclusion. Viral enteritis is the likely diagnosis when a patient has mild intestinal symptoms and does not appear ill and further history and physical examination uncover no reason to suspect a bacterial pathogen, inflammatory disease, or any other cause. No investigation beyond the physical examination usually is required. Some of these patients may actually have mild bacterial infections, but these also generally are self-limited, and treatment is not different.

A reference laboratory diagnosis can be made by demonstration of the viruses in stools by electron microscopy or various methods used for the detection of viral antigens, such as latex agglutination, enzyme-linked immunosorbent assay (ELISA), or reverse transcriptase PCR techniques. With rotavirus illness, large numbers of viruses are present in the stools, and these antigen detection methods are quite sensitive and specific. Rotavirus testing is indicated only in more serious cases of diarrhea or in large outbreaks. Fecal leukocytes and erythrocytes are not found in cases of viral gastroenteritis.[8]

Management

The most important aspect of therapy for acute viral gastroenteritis is fluid replacement. Many children require hospitalization for intravenous fluid and electrolyte repletion. No specific antiviral therapy is indicated. Use of antidiarrheal agents is not recommended in children. In adults, they generally are not needed but may provide some symptomatic relief. Because viral spread is primarily by the fecal-oral route, scrupulous handwashing and other hygienic practices are the best preventive measures.

A live tetravalent vaccine against rotavirus was approved for use in infants in 1998 but was withdrawn from the market in 1999 owing to a temporal association with intussusception. RotaTeq is a newer oral, liquid live pentavalent vaccine that was licensed in the United States in 2006 and is given at ages 2, 4, and 6 months. In 2008, Rotarix was licensed as an alternative to RotaTeq and is given at 2 and 4 months of age. Rotavirus vaccination is now part of the annual recommended immunization schedule.

PARASITIC GASTROINTESTINAL INFECTION

Organisms that commonly cause protozoal enteritis are summarized in Table 94-4. As a group, parasitic pathogens are associated with more prolonged illness than that characteristic for bacterial or viral pathogens. The clinician should consider the possibility of a parasitic infection in patients with diarrhea that persists for longer than 2 weeks, especially in immunocompromised persons, travelers, and residents of developing countries.

Coccidial Infections

Cryptosporidium and *Cystoisospora* (formerly *Isospora*) *belli* Infections

Epidemiology. *Cryptosporidium* and *Cystoisospora* are intestinal protozoal parasites that commonly cause diarrhea in the young of many animal species. In humans, cryptosporidiosis is a worldwide problem, most often seen in persons who handle animals, children in daycare centers, healthy homosexual men, and immunocompromised patients.[8,47] *Cryptosporidium* has been the most common cause of chronic diarrhea in persons with AIDS, although the incidence has decreased in the U.S. AIDS population with the use of highly active antiretroviral therapy (HAART).[47] Congenital immunodeficiency and treatment with cancer chemotherapeutics or other immunosuppressive drugs are additional predisposing factors. The organism is highly infectious and is easily transmitted among nosocomial, household, and daycare contacts or in any facility in which personal hygiene is poor.[47] In addition to zoonotic and person-to-person spread, indirect transmission occurs by exposure to fecally contaminated environmental surfaces, toys, food, and recreational water.[47] *Cryptosporidium* oocysts are highly resistant to chlorine and common disinfectants. Large outbreaks have originated from community swimming pools.[47]

Table 94-4 Epidemiologic Aspects of Protozoal Gastroenteritis

PATHOGEN	SOURCES AND RISK FACTORS OR GROUPS	INCUBATION PERIOD	FEATURES
Entamoeba histolytica	Fecally contaminated food and water sources	3 wk to 4 mo	Infection may be commensal or intermittently symptomatic or produce severe dysentery
Giardia lamblia	Water-borne organisms, fecal-oral contact, daycare centers, travelers, backpackers, AIDS, homosexual men	1-3 wk	5-10% of U.S. population, malabsorption syndromes or commensal
Coccidia			
Cryptosporidium and *Cystoisospora*	Fecal-oral contact, water-borne organisms, animals, daycare centers, AIDS	5-10 days	Profuse watery diarrhea, self-limited in the immunocompetent, persistent in the immunocompromised
Cyclospora cayetanensis	Fresh fruit, berries, lettuce, water supply	1 wk	Explosive, protracted, watery diarrhea; fatigue, weight loss
Strongyloides stercoralis	Occupational exposure to soil, travel to endemic areas in United States (Kentucky, Tennessee, West Virginia) or overseas	Weeks to months	Eosinophilia, sepsis, and hyperinfection syndrome in AIDS patients
Enteromonas hominis	Fecal-oral contact, homosexual men	Unknown	Chronic watery diarrhea, especially in children

AIDS, acquired immunodeficiency syndrome.

www.ketabpezeshki.com 66485457-66963820

The oocysts also are small (2 to 6 μm in diameter) and may not be removed from contaminated water by standard filtration systems used in the treatment of public water supplies. Ingestion of as few as 10 to 20 oocysts can cause illness in healthy persons. In a recent report, thousands of people contracted cryptosporidiosis from contamination of filtered public water systems that met federal and state standards for drinking water. Contamination of rivers and streams by *Cryptosporidium* has been reported in a number of states.[47] In children, cryptosporidiosis is more common in the late summer and early fall and often is associated with intestinal infection with other organisms, particularly *Giardia*.

Cystoisosporiasis generally is an opportunistic infection. It occurs primarily in patients with AIDS, especially Haitians with AIDS, and in homosexual men. In the homosexual community, cystoisosporiasis is a sexually transmitted disease similar to giardiasis and amebiasis.[48]

Pathophysiology. The pathophysiology is the same for both *Cryptosporidium* and *Cystoisospora*. Disease is acquired by ingestion of oocysts. Excystation occurs, and sporozoites attach to the surface of intestinal epithelial cells of the terminal ileum and proximal colon; no tissue invasion occurs. Profuse fluid loss results from a combination of active chloride secretion and malabsorption. A specific enterotoxin has not been identified, although upregulation of a variety of proinflammatory cytokines, chemokines, and neuropeptides has been observed. In cryptosporidiosis, a biliary reservoir may contribute to chronicity of the infection and inability to eradicate the organism.[48]

Clinical Presentation. The clinical presentations of cryptosporidiosis and of cystoisosporiasis are indistinguishable and highly variable. After an incubation period of approximately 1 week, symptoms may develop insidiously or suddenly. Infection is characterized by mild to profuse watery diarrhea, crampy abdominal pain, anorexia, nausea, malaise, weight loss, and flatulence. The diarrhea and abdominal pain often are exacerbated by eating. Immunocompromised patients (especially HIV-infected patients with CD4+ counts less than 200/mm^3) can experience enormous stool fluid losses: 3 to 4 L/day is common, and losses may reach 10 to 20 L/day. Physical examination usually reveals only signs of dehydration. Minimal diffuse abdominal tenderness may be elicited by palpation, and fever and leukocytosis are uncommon. Eosinophilia is not a feature. Findings on stool examination for blood or leukocytes are almost uniformly negative in adults but occasionally are positive in children.[47]

The patient's immune status is the primary determinant of whether the infection is self-limited or persistent. Diarrhea in immunocompetent persons usually resolves after 1 to 3 weeks, but it can continue longer or become chronic. In immunodeficient patients, especially those with AIDS, chronic, persistent diarrhea is common, causing significant discomfort and morbidity unless the infection is responsive to treatment.[8,47]

Asymptomatic infections can occur from either *Cryptosporidium* or *Cystoisospora*, and a carrier state has been demonstrated for *Cryptosporidium*.[47] In a U.S. study of immunocompetent patients who underwent upper endoscopy for a variety of reasons, 13% were found to harbor *Cryptosporidium* organisms in the second portion of the duodenum. None of the patients had diarrhea.

Diagnostic Strategies. The diagnosis of coccidial infection with either *Cryptosporidium* or *Cystoisospora* is made by documenting the oocysts in the stool. Yeasts are similar in size and shape to coccidia but are not acid-fast. Before the development of antigen-based assays, acid-fast staining techniques were the preferred means of diagnosis. Such methods are insensitive for the diagnosis of cryptosporidiosis and require a high oocyst concentration and an experienced examiner. Immunofluorescent assays using monoclonal antibodies to the *Cryptosporidium* oocyst are commonly used and are 10 times more sensitive than acid-fast staining. ELISA-based detection kits also are commercially available, highly sensitive, and easy to use. Sensitivities and specificities of 94 to 100% have been documented in several studies. A PCR-based assay for *Cryptosporidium* has been developed but is not yet routinely available in clinical laboratories.[8,47]

Management. In immunocompetent persons, *Cryptosporidium* infection generally is self-limited; symptomatic therapy and fluid replacement are sufficient. Initial management should focus on replacement of fluid and electrolytes, by the oral route if possible. Antimotility agents such as loperamide or the combination agent diphenoxylate-atropine (Lomotil) can decrease stool output in persons with mild to moderate illness. For immunocompetent patients with persistent disease, nitazoxanide 500 mg every 12 hours for three days has been approved by the FDA and has proved to be effective in adults and children older than 1 year.[46] Immunocompetent patients shed oocysts in the stools when symptomatic and continue to do so for up to 6 weeks after resolution of their clinical illness, creating a public health risk. Oocyte shedding resolves more rapidly in those treated with nitazoxanide.[47]

Treatment of cryptosporidiosis in immunocompromised patients is more challenging. The most successful interventions occur when the underlying immunodeficiency can be reversed. In patients taking immunosuppressive agents, immune function generally recovers if the drugs can be discontinued. Patients with AIDS and CD4+ counts below 200/μL sometimes respond dramatically if immune function is restored through institution of HAART.[47] Patients severely infected with *Cryptosporidium* often are fecally incontinent, with large numbers of infectious oocysts in the stool, so strict enteric precautions are necessary to prevent nosocomial spread. If enhancement of the immune system fails and symptoms continue to be severe, nitazoxanide 1 g twice daily for 14 days combined with antidiarrheals may be used, although evidence is lacking for the efficacy of nitazoxanide in HIV-infected patients. Paromomycin (Humatin, 500 to 750 mg three or four times daily) also is sometimes used to ameliorate cryptosporidiosis, particularly in combination with azithromycin, but no good evidence exists that these drugs are routinely effective.[47]

In contrast with cryptosporidiosis, cystoisosporiasis responds promptly to antibiotic therapy. The treatment regimen of choice in immunocompetent adults is TMP-SMX 160 mg, 800 mg twice daily for 10 days. In immunocompromised adults, the dosage is increased to four times daily for 10 days and then extended with twice-daily dosing for 3 weeks. In patients with sulfonamide sensitivity, ciprofloxacin 500 mg twice daily or pyrimethamine 50 to 75 mg daily may be effective.[3] Chronic suppressive therapy with either twice-daily doses of TMP-SMX or daily doses of pyrimethamine often is required, because *Cystoisospora* infection recurs in more than 50% of patients.[3,48]

Patients seen in the ED in whom stool examination for parasites later reveals *Cryptosporidium* or *Cystoisospora* should be contacted for appropriate management. Recovering patients require only an explanation of the diagnosis and its ramifications. Patients who are not recovering and those who are known or thought to be immunosuppressed should receive appropriate treatment and referral for follow-up care. Cryptosporidiosis is a nationally notifiable disease.

Cyclospora cayetanensis Infection

Epidemiology. *Cyclospora* is a coccidial parasite widely distributed throughout tropical and subtropical areas of the world that produces disease similar to that caused by *Cryptosporidium* and *Cystoisospora*. In Nepal, *Cyclospora* organisms have been found in up to 11% of patients with diarrheal disease, with increased rates of 32% in the month of June.[49] North American outbreaks have been

www.ketabpezeshki.com 66485457-66963820

traced to contaminated imported foods, primarily fresh fruit such as raspberries grown in Guatemala, fresh salads containing snow peas from Guatemala, fresh basil preparations, and mesclun lettuce; foreign travel; and contaminated water supplies.[50] *Cyclospora* infects all classes of vertebrates, reptiles, and rodents, and the vast majority of cases occur during the spring and summer seasons, often in large outbreaks.

Pathophysiology. The organism passes from the human gastrointestinal tract as an oocyst that must sporulate in the environment to become infective. Sporulation requires several days to weeks outside the human host; therefore the disease is not transmitted from person to person and is not likely to be transmitted by infected food handlers. Histologic examination shows flattening of the villi and thickening of the basement membrane in the duodenum with intracellular parasites identified in jejunal biopsies.[50] As with other parasitic diseases, immunocompromised patients are affected more frequently than immunocompetent hosts.

Clinical Presentation. The average incubation period is 1 week.[50] Typically, the patient reports an acute onset of explosive watery diarrhea and abdominal cramps. Thirty percent of patients report fever during this initial phase. Severe diarrhea subsides within 1 to 3 days and is followed by a period of intermittent mild diarrhea and marked anorexia and fatigue, which distinguishes this from other parasitic disorders. Weight loss is almost invariable, as is malabsorption of D-xylose.[50] Constitutional symptoms are relatively mild, and fever is uncommon during this phase. Fecal leukocytes are absent. The disease generally is self-limited in immunocompetent persons but may last as long as 2 to 6 weeks, and relapsing diarrhea is common. Sustained fatigue and weight loss are especially characteristic of cyclosporiasis. These findings are noted in approximately 90% of patients and should prompt consideration of the diagnosis in the setting of outbreaks or history of foreign travel.[50]

Diagnostic Strategies. The clinical picture may be suggestive, but finding oocysts in the stool is required to confirm the diagnosis. Stool specimens submitted for ova and parasite testing are not routinely examined for *Cyclospora* unless specifically requested. The oocysts measure 8 to 10 μm in diameter, approximately twice the size of *Cryptosporidium* oocysts. Oocysts can be identified by modified acid-fast stain, yet the inexperienced microscopist may overlook them or find *Cyclospora* difficult to distinguish from *Cryptosporidium.* False-negative and false-positive results on microscopic examination are common. Microscopic examination is greatly facilitated by stool concentration techniques.[50] Cyclospora oocysts are autofluorescent, appearing blue or green under ultraviolet microscopy, and this distinctive feature can facilitate identification. *Cyclospora* also can be identified by stool PCR testing, although this technique is not widely available in U.S. hospitals.

Differential Considerations. The primary confusing organism is *Cryptosporidium,* because the symptoms of infection with the two pathogens often are indistinguishable. *Cryptosporidium* tends to be associated with animal contact, exposure in daycare centers, and immunocompromised status. *A. hydrophila* infection also should be considered in the differential diagnosis.

Management. The disease tends to be self-limited in immunocompetent persons, but treatment with sulfa medications is very effective for cyclosporiasis, in contrast to cryptosporidiosis. The drug regimen of choice consists of double-strength TMP-SMX one tablet twice daily for 7 days in immunocompetent patients, and one tablet four times daily for 10 days, followed by one tablet three times per week, in patients with AIDS. The pediatric dose is TMP 5 mg/kg plus SMX 25 mg/kg twice daily for 7 days. Thorough washing of fresh produce before consumption decreases but does not eliminate the risk of transmission. Irradiation may be a future solution.[3,50] Cyclosporiasis is a reportable disease.

Giardiasis

Epidemiology

Giardia is the most common cause of parasitic diarrheal outbreaks in the United States and worldwide.[8,51] The mode of transmission in large outbreaks is contamination of municipal water supplies with cyst-infested feces from humans or animals, particularly beavers or muskrats, but also dogs, raccoons, and other animals. Campers and backpackers commonly acquire giardiasis, called “backpacker’s diarrhea,” from drinking fecally contaminated water from the “pristine” mountain streams.[51] Only rarely is *Giardia* infection transmitted by contaminated food.

Giardia can be spread by sexual or other close person-to-person contact in which fecal contamination may occur, particularly among homosexual men, and in daycare centers and institutions for the mentally challenged. The prevalence of giardiasis is approximately 2% of adults and 7% of children in developed countries and nearly 33% of residents of developing countries. Infection rates are twice as high in the summer months.[51]

Many cases of acute symptomatic giardiasis in the United States are found in persons returning home from travel elsewhere. Travelers to any developing country can acquire giardiasis, but it is especially feared in those who visit the republics of the former Soviet Union, the Caribbean states, and Latin America, where the water supplies appear to be heavily contaminated with *Giardia* cysts.[52] Small groups traveling to the former Soviet Union, particularly the city of Leningrad, have experienced attack rates approaching 60%, and the disease is ruefully known among its victims as “the Trotskys.” More recently, a Swedish study of giardiasis in returning travelers found that highest attack rates occurred in those returning from the Indian subcontinent, east Africa, and west Africa.[53]

Patients with decreased gastric acidity, for any reason, are more susceptible to *Giardia* infection. Giardiasis also is more frequent in patients with various immunoglobulin deficiencies; a relative deficiency of intestinal immunoglobulin A (IgA) may be the reason.

Pathophysiology

Giardia trophozoites infect the duodenum, jejunum, and upper ileum of humans and more than 40 other mammalian species. Encystation occurs in the gut lumen, and cysts passed in the feces remain viable for long periods. After the cysts have been ingested by the next host, excystation to the active trophozoites occurs in the proximal small bowel, completing the parasite’s life cycle. The trophozoites multiply rapidly. A single diarrheal stool may contain billions of parasites or hundreds of millions of cysts. The trophozoites are capable of superficial invasion of the mucosa, but malabsorption probably causes most symptoms.

Clinical Presentation

Many patients harboring *Giardia* are asymptomatic. The most common symptoms of acute infection are abdominal distention (69%), colicky pain (70%), flatulence (74%), and frequent episodes of explosive diarrhea (89%) producing pale, loose stools that often are offensive smelling. Audible borborygmi is a classic feature. The serum white blood count usually is normal, and eosinophilia is not seen. The onset typically is sudden, following an incubation period of 1 to 3 weeks. Symptoms may resolve within 7 to 10 days or continue intermittently and produce a malabsorption-like illness, particularly in patients with an immunoglobulin deficiency. The infection resolves spontaneously within 6 weeks in 85% of patients.

www.ketabpezeshki.com 66485457-66963820

Diagnostic Strategies

Routine tests (e.g., blood counts, electrolyte panel, radiographic studies) generally are not helpful. Eosinophilia is not seen. Stool examination is the primary means of diagnosis. In the acute phase of *Giardia* infection, rapid bowel transit allows trophozoites as well as the more hardy cystic form of the parasite to appear in the stool. Trained observers using standard stool examination techniques will readily identify *Giardia* in more than 95% of acute cases if three or more stool specimens are studied. Detecting *Giardia* in cases of subacute, chronic, or asymptomatic infection, however, can be difficult. The trophozoites may be passed only intermittently and in small numbers. Concentration techniques should be used to improve the chance of finding the cysts in the stools. Diagnosis may require small bowel sampling techniques, such as duodenal-jejunal aspiration by endoscopy or biopsy of duodenal-jejunal tissue. *Giardia* antigen tests using immunofluorescence ELISA, nonenzymatic immunoassays, or direct fluorescent antibody (DFA) techniques are replacing microscopic examination as the strategy of choice. The per-specimen cost is similar to that for microscopy; sensitivity is 85 to 98%, and specificity 90 to 100%.[51]

Differential Considerations

Enteromonas hominis, a flagellate parasite like *Giardia,* can produce an intestinal infection that mimics giardiasis. *Enteromonas* infection most commonly affects children and homosexual men. Even when all techniques fail to confirm a clinically suspected case of giardiasis, an empirical diagnosis can be supported by a successful trial of appropriate antibiotics.

Management

The treatment regimen of choice has historically been metronidazole, a 5-nitroimidazole drug, 250 mg three times daily for 7 to 10 days for adults, or 5 mg/kg three times daily (maximum 500 mg three times daily) for 7 days for children.[3,51] Metronidazole has an efficacy rate of 80 to 95%. Tinidazole is another 5-nitroimidazole agent that is FDA approved for the treatment of giardiasis. Some experts consider tinidazole a first-line agent because it can be given as single-dose therapy. When given in a single 2-g dose (50 mg/kg in children), tinidazole achieves a cure rate of approximately 90 to 100%. Furazolidone is an alternative drug available as a suspension, which may be helpful in treating children. Its cure rates average only 80%, however. The recommended dosage is 100 mg four times daily for adults or 1.5 mg/kg four times daily for children, up to the adult dose, for a total of 7 to 10 days. Nausea and vomiting are common side effects, and rarely a hemolytic anemia develops in patients with glucose-6-phosphate dehydrogenase deficiency. Other alternatives include nitazoxanide, albendazole, quinacrine and paromomycin.[53]

Treatment of asymptomatic infections is controversial and best determined on a case-by-case basis. Asymptomatic cyst passers, especially children and food handlers, pose a threat of infection to others and are at risk for the development of intermittent chronic symptoms. Treatment of asymptomatic carriers can theoretically reduce the risk of spread. In heavily infected endemic populations, reinfection is practically universal after 3 months, and treatment is not useful or cost-effective. *Giardia* vaccines for veterinary animals are commercially available in the United States, but a human vaccine against *Giardia* has not been developed.[54]

Giardiasis should be considered a family infection. Strict adherence to handwashing is important, especially after using the toilet, playing with pets, or changing diapers. For prevention of reinfections, other household members and sexual contacts should be examined and, if found to harbor the parasite, treated appropriately.

Acute Intestinal Amebiasis

Epidemiology

Entamoeba histolytica is a ubiquitous organism infecting at least 10% of the world's population but originally thought to cause clinical disease in only 10% of persons who carry it. This number probably is an underestimate, however, because studies have confirmed the presence of a morphologically indistinguishable species, *Entamoeba dispar,* as a separate nonpathogenic species that also colonizes the human gut and probably is responsible for a vast majority of asymptomatic infections originally attributed to *E. histolytica.* Distinguishing between the two organisms can be accomplished with ELISA or PCR assay, with PCR testing slightly more reliable.[55] Worldwide, approximately 50 million symptomatic cases occur each year, resulting in 100,000 fatalities. In the United States, high-risk groups include travelers, homosexual men, patients with AIDS, and institutionalized persons. Most cases acquired in the United States are asymptomatic; acute amebic dysentery is rare and most often occurs in travelers returning from developing countries in which the disease is endemic.[56]

E. histolytica exists in trophozoite and cystic forms. The trophozoites infect the colon and may produce symptomatic disease. Infectious cysts are passed in the stool and are highly resistant to environmental factors. Transmission usually occurs through ingestion of cysts present in fecally contaminated food or water. Homosexual men commonly acquire amebic infection from cysts ingested through anal-oral sexual practices. When these patients report diarrhea, a diligent search for other organisms should be completed before symptoms are ascribed to amebic infection. Coinfection with other enteric pathogens occurs frequently in homosexual men.[56]

Pathophysiology

The mechanism behind the virulence of *E. histolytica* has become clearer in recent years and is strongly correlated with the organism's ability to effectively kill and phagocytose host cells. This process involves a sequential model of adherence, cell killing, initiation of phagocytosis, and engulfment that is not observed in commensal species such as *E. dispar.*

Invasive trophozoites characteristically produce colonic ulcerations that on histologic examination are seen to have rounded or punched-out margins and are elevated by a submucosal inflammatory reaction from the advancing trophozoites. The ulcer bases are covered with whitish or yellowish exudate. Usually, no diffuse mucosal inflammation exists in areas between ulcers. Should diffuse inflammation occur, however, the picture becomes indistinguishable from that of idiopathic ulcerative colitis or Crohn's disease. Less than 1% of infections will spread outside the intestines. Gastrointestinal complications can include severe bleeding, toxic megacolon, intussusception, stricture, obstruction, and perforation. Extraintestinal complications include liver and brain infection, as well as pleural or pericardial effusions.[55]

Clinical Presentation

Acute amebic dysentery manifests after an incubation period as short as 1 week or as long as 1 year. The onset is abrupt, with fever; severe abdominal cramps; profuse, bloody diarrhea; and tenesmus. Chronic amebic colitis is the common symptomatic form, for which the onset is gradual. Usually, intermittent diarrhea is present, with two to four foul-smelling stools daily, often containing blood-streaked mucus. Vague abdominal cramps, flatulence,

www.ketabpezeshki.com 66485457-66963820

weight loss, and low-grade fever are present. Symptomatic periods may alternate with asymptomatic periods lasting for months to years. The only physical finding may be slight right lower quadrant tenderness to palpation and occasional tender hepatomegaly. The diagnosis is elusive because cysts or trophozoites are difficult to detect; inflammatory bowel disease is a common misdiagnosis, and steroid therapy may exacerbate the symptoms.[57]

The stools of patients with symptoms contain mucus and leukocytes, although not in large quantity and numbers. Eosinophilia is not seen except in rare cases of ameboma. Liver function test results generally are normal unless the disease is complicated by liver abscess, which is the most common serious complication of amebic colitis.[56]

Diagnostic Strategies

Definitive diagnosis of intestinal amebiasis historically relied on microscopic identification of the organisms in the stools. Microscopic examination limited to a single stool sample can miss almost one half of infections; at least three fresh samples should be submitted. The examination must precede the administration of antibiotics, antidiarrheal agents, antacids, or enemas and the performance of radiographic procedures that use barium sulfate. All of these agents destroy trophozoites or distort cysts, thereby interfering with the recovery of amebas. A rectal biopsy specimen or mucosal exudate obtained at sigmoidoscopy may reveal the amebas, even when multiple previous stool examinations have yielded negative results. To obtain mucosal exudate, a glass or metal pipette must be used, because amebas adhere to cotton swabs. Microscopy cannot distinguish *E. histolytica* from the nonpathogenic *E. dispar.* The presence of amebas on stool microscopy in an asymptomatic patient should suggest the presence of nonpathogenic *E. dispar;* treatment is not indicated.[55]

The diagnosis of amebiasis has been greatly improved by the development of stool antigen assays. Monoclonal antibody–based EIA for *E. histolytica* antigens has a sensitivity and specificity of approximately 95% and can distinguish *E. histolytica* from *E. dispar.* PCR techniques also have been developed but are not widely available in hospital laboratories.[55]

Serologic tests are quite sensitive and specific for active amebic infection. Because administration of steroids to patients with amebic colitis is potentially fatal, and because identification of the parasite in stools is difficult, a serologic test for amebiasis should be done in all newly diagnosed cases of inflammatory bowel disease before initiation of steroid therapy.

Differential Considerations

Amebiasis should be considered in cases of acute dysentery-like colitis and in the differential diagnosis for any chronic diarrhea, especially when the stool contains blood-streaked mucus. Amebiasis also should be suspected in homosexual men with acute or chronic colitis. Among patients with AIDS, however, amebic dysentery is rare.[58] Patients with nondysenteric amebiasis often are misdiagnosed as having irritable bowel syndrome, diverticulitis, or regional enteritis.

Management

Substantial controversy previously existed over whether asymptomatic cyst passers should be treated. Today, however, advances in testing permit distinction between nonpathogenic *E. dispar* and *E. histolytica,* so an accurate diagnosis is now possible. Accordingly, it seems prudent to treat for *E. histolytica* infection in all patients in whom this organism is detected, even asymptomatic carriers. If only *E. dispar* is identified, treatment is unnecessary. When differentiation is not possible and the patient is asymptomatic, treatment is not recommended unless the clinical picture suggests an increased likelihood of *E. histolytica* infection. Such would be the case with patients with high specific antibody titers, a history of close contact with a patient with invasive amebiasis, or a patient with symptoms during an outbreak of amebiasis. In symptomatic patients who are diagnosed with *E. histolytica* or *E. dispar* infection, other pathogens should be ruled out before *E. histolytica* can be assumed to be the cause.[55]

For treatment of benign cyst passers, paromomycin (aminosidine) 500 mg orally three times a day for 7 days should be effective. Other regimens include oral iodoquinol, 650 mg orally three times a day for 20 days, and diloxanide furoate, 500 mg orally three times a day for 10 days. For mild to moderate intestinal infection, metronidazole is added (see Table 94-2). Treatment with metronidazole should precede treatment with aminosidine. Aminosidine can cause diarrhea as a side effect, making it difficult to assess the patient's response to the metronidazole if both agents are given together.[59] Patients with severe infections and systemic illness such as dehydration or hypotension should be hospitalized. Therapy usually is effective, but relapses can occur. Standard precautions to prevent fecal-oral spread are the best preventive measures.

Diarrhea in Patients with AIDS

Epidemiology

Diarrhea is the most common manifestation of gastrointestinal disease in patients with AIDS and may be the presenting symptom or a life-threatening complication of the disease. The occurrence rate is greater than 90% in developing countries and historically 50 to 60% in the United States. With the widespread use of HAART, the incidence of infectious diarrhea has decreased dramatically in the United States and other developed countries, even among those with CD4+ counts less than 200/mm^3. In one study of symptomatic patients undergoing colonoscopy from 1995 to 1998, the prevalence of opportunistic diseases fell from 69 to 13% while the use of HAART increased from 0 to 82% of patients. Most cases of diarrhea in patients with AIDS in developed countries are now noninfectious in nature, most often related to the use of protease inhibitors; hence the clinician should ask about recent changes in the HAART regimen in addition to considering infectious causes.[55,60]

Worldwide, patients who are HIV positive and those with active AIDS are more susceptible to infection both from the usual enteric organisms and from opportunistic organisms. Diarrheal diseases are much more problematic in patients with AIDS because of their diminished immunity and underlying poor nutritional status.[61] A vastly expanded profile of pathogens may potentially cause diarrhea in patients with AIDS compared with immunocompetent persons. Also, the ramifications of the disease are significantly more serious, necessitating a much more aggressive diagnostic evaluation and treatment regimen.

Pathophysiology

The early concept of mucosal transmission of HIV was that it occurred through mucosal trauma that created breaches in the physical barrier of the genital or rectal epithelium, allowing introduction of viral particles directly to the bloodstream. It is now known that infection also occurs after atraumatic inoculation of mucous membranes. With gastrointestinal exposure, virions of certain HIV strains bind to particulate-sampling M cells (membranous epithelial cells) in the gastrointestinal mucosa and undergo receptor-mediated transport from intestinal lumen to the lamina propria, with subsequent infection of CD4+ lymphocytes located in the gut-associated lymphatic tissue. Mucosal biopsy specimens in up to 40% of patients with AIDS demonstrate HIV

www.ketabpezeshki.com 66485457-66963820

virions, with depletion of CD4+ lymphocytes in the lamina propria and apoptosis of both HIV-infected and non–HIV-infected lymphocytes. It also has been observed that in a significant number of HIV-infected patients, diarrhea develops in the absence of an identifiable gastrointestinal pathogen, and that this pathogen-negative HIV-related diarrhea subsides with institution of HAART. These findings suggest that HIV itself can induce a primary enteropathy, although specific mechanisms have yet to be elucidated.[60]

In the population of homosexual men, unprotected receptive anal intercourse and anal-oral contact among multiple partners provide exposure to a diverse spectrum of enteric pathogens. In the heterosexual intravenous drug–abusing population, infection spreads primarily by water- and food-borne transmission of the organisms. Patients with AIDS are unable to combat these intestinal pathogens, probably because of a combination of T lymphocyte functional deficiency and underlying HIV-induced enteropathy.

Etiology

A known enteric pathogen can be identified in approximately 13 to 75% of patients with AIDS who are experiencing diarrhea. Multiple pathogens may be present in as many as 20 to 25% of patients. Homosexual men with AIDS experience diarrhea more often than do other patients with AIDS. Diarrhea also develops more often in patients who do not have access to or are not compliant with HAART and in those infected with resistant strains of HIV than in other AIDS patients. The CD4 lymphocyte count continues to be the best predictor for risk of a particular opportunistic infection.[60]

In HAART-naïve populations, *Cryptosporidium* and cytomegalovirus infections are the two most common causes. The incidence of each is approximately 20%.[61,62] Chronic high-volume watery diarrhea often is indicative of small bowel disease from one of the coccidia *Cryptosporidium* and *C. belli.* Although self-limited in the healthy host, coccidial disease often is persistent in patients with CD4+ counts less than 200/mm^3. Cytomegalovirus and *Mycobacterium avium-intracellulare* also produce a chronic illness in those with CD4+ counts less than 100/mm^3. Fever, weight loss, and abdominal pain are prominent; diarrhea is mild to moderate and sometimes bloody, typical of colonic disease. Many patients die within 6 months of diagnosis. Microsporidia have emerged as a common cause of diarrhea in patients with AIDS in whom CD4+ counts are less than 100/mm^3. Worldwide, these organisms have been identified in 10 to 20% of patients with AIDS who are experiencing diarrhea. In one prospective study in the United States, microsporidia were identified in 39% of patients with AIDS undergoing small bowel biopsy for evaluation of diarrhea.[62]

Salmonella infections, especially with *S.* Typhimurium, are common in immunocompromised hosts.[62] Patients with AIDS who acquire *Salmonella* enteritis are at increased risk for bacteremia and metastatic focal infection compared with normal hosts. *C. difficile* enteritis occurs more commonly in patients with AIDS owing to the common use of prophylactic antibiotic therapy and frequent hospitalizations. It is the most common bacterial enteritis in the AIDS population. Clinical presentation, response rate, and relapse rate are no different from those in the healthy host.[62] Giardiasis occurs with a frequency and severity that are unrelated to the degree of immune compromise.[55]

E. histolytica infection is neither more prevalent nor more severe in HIV-infected patients. When amebae are present, it is rare for these organisms to cause invasive disease in patients with AIDS.[62] For unknown reasons, *Yersinia, V. parahaemolyticus,* viruses (noncytomegalovirus), *Neisseria gonorrhoeae,* and *Chlamydia trachomatis* are relatively unusual causes of diarrhea in patients with AIDS. Shigellosis and campylobacteriosis are more common among male patients with AIDS who have sex with men than among HIV-negative men who have sex with men.

Clinical Presentation

In patients with AIDS, diarrhea manifests in one of three ways. First, at the time of HIV seroconversion, patients usually experience diarrhea, nausea, anorexia, and malaise in association with an acute infectious mononucleosis-like syndrome. Second, diarrhea may be the presenting symptom of full-blown AIDS, with associated fever, malaise, anorexia, and significant weight loss. The most common presentation, however, is for diarrhea to start well after AIDS has become clinically apparent and when the CD4+ count falls below 300/mm^3. In these cases, the patient typically has a chronic debilitating infection that rarely remits spontaneously unless CD4+ counts are normalized with use of HAART. Diarrhea often is accompanied by profound weight loss, major nutritional impairments, and a diminished sense of well-being. Many cases are refractory to antimicrobial treatment and persist until death, or may even be the cause of death.[55,62]

In patients with AIDS, the presenting signs and symptoms generally do not allow consistent classification of diarrheas, as is done for the immunocompetent host. This is so in part because many patients with AIDS have multiple, concomitant enteric pathogens. However, some clinical pictures are typical. Patients with a fulminating clinical course usually have a disseminated infection, such as infection with cytomegalovirus or *Mycobacterium avium* complex. Massive weight loss also is associated with diarrhea caused by infection with those two organisms and the coccidia *Cryptosporidium* and *Cystoisospora.* Voluminous, watery diarrhea usually is a result of one of the coccidial organisms. Patients with a proctocolitis-like picture most often have herpes simplex virus or cytomegalovirus infection. Strongyloidiasis should be considered in any immunocompromised patient who experiences sudden clinical deterioration with eosinophilia, polymicrobial sepsis, meningitis, or adynamic ileus.[62]

Complications

The most common complications are dehydration, electrolyte abnormalities, and malnutrition resulting from both fluid loss and malabsorption. Cytomegalovirus infection can produce gastrointestinal hemorrhage or perforation or toxic megacolon. *M. avium* complex infection often manifests with severe anemia, weight loss, and a rapid downhill course of persistent weakness, malaise, and malabsorption. Bacteremia historically was found in as many as 40 to 45% of patients with AIDS and diarrhea, usually caused by *M. avium* complex or *Salmonella* species. The incidence has decreased markedly over the past decade as the use of HAART has increased.[62]

Diagnostic Strategies

The diagnostic approach to patients with HAART-naïve AIDS who are experiencing diarrhea is entirely different from that to an immunocompetent host. In 80 to 90% of cases, one or more enteric pathogens are found; of the pathogens identified, a majority are susceptible to appropriate antimicrobials.[55,61] Diarrhea in patients with AIDS in whom CD4+ counts are less than 300/mm^3 generally is not self-limited and requires medical intervention to effect resolution. Therefore each patient merits a diagnostic evaluation (Box 94-2). Infectious causes are detected less frequently in patients being treated with HAART.[61]

Patients with AIDS who are experiencing diarrhea should have up to three stool specimens cultured for enteric bacteria, because fecal shedding of pathogenic bacteria can be intermittent. Stool also should be examined for parasites via antigen detection assays

www.ketabpezeshki.com 66485457-66963820

Box 94-2 Diagnostic Protocol for Evaluating Diarrhea in Patients with AIDS

Initial Evaluation

Indicated in all patients.

1. Stool cultures for enteric bacteria—*Salmonella, Shigella, Campylobacter, Yersinia,* STEC
2. Stool examination for *Giardia, Cryptosporidium, Cystoisospora, Cyclospora,* amebas, and mycobacteria; *Clostridium difficile* toxin assay
3. Blood cultures
4. Proctosigmoidoscopy in patients with clinically severe colitis or a proctocolitis picture, especially homosexual men

Further Evaluation

Indicated if initial study results are negative or to look for the presence of multiple organisms if a patient fails to respond to appropriate therapy for an identified pathogen.

1. Repeat stool cultures and examinations, possibly add culture for viruses
2. Colonoscopy or esophagogastroduodenoscopy performed to obtain duodenal fluid and small bowel and colonic biopsy specimens, which are examined as follows:
   a. Duodenal fluid examination for ova and parasites
   b. Duodenal and colonic biopsy specimens cultured for mycobacteria, cytomegalovirus, and herpes simplex virus; colonic biopsy tissue also is cultured for bacterial enteric pathogens (add testing for gonorrhea and chlamydial infection in patients with acute proctitis)
   c. Biopsy specimens examined with use of multiple stains (e.g., acid-fast, hematoxylin-eosin, Giemsa, silver, periodic acid–Schiff) for protozoa, mycobacteria, and cells containing viral inclusion bodies

AIDS, acquired immunodeficiency syndrome; *STEC,* Shiga toxin–producing *Escherichia coli.*

where available or microscopy of multiple samples for ova, parasites, and mycobacteria. The usual bacterial enteric pathogens are readily identified, but the protozoal infections can be difficult to detect if microscopy-based strategies are used. In patients with severe diarrhea from *Cryptosporidium,* the first stool examination usually yields a positive result, but in less severe cases, additional samples may have to be studied to make the diagnosis. Specialized techniques are necessary to detect most of the viral agents.

Blood cultures are a valuable diagnostic adjunct. Bacteremia may be found in up to 43% of patients, and a blood culture may yield a positive result when the stool cultures and examinations fail to reveal a pathogen.[63] The most common organisms detected by means of blood culture are *M. avium* complex, cytomegalovirus, *Salmonella,* and occasionally herpes simplex virus. Most cases of *M. avium* complex bacteremia occur in heterosexual intravenous drug abusers. A routine complete blood cell count demonstrating eosinophilia suggests parasitic infection with *Strongyloides stercoralis* or *Cystoisospora.*[64]

If results of these diagnostic tests are negative, endoscopy should be performed to obtain mucosal biopsy samples from affected areas of the rectum or colon. Rectal biopsy, which can be performed easily even in seriously ill patients, is an indispensable tool in the diagnosis of cytomegalovirus infection. Viral inclusion bodies with clear halos typical of cytomegalovirus can be demonstrated or cytomegalovirus DNA can be detected with use of PCR techniques. Special staining examinations, DNA detection techniques, or culture of the biopsy tissue also may enable diagnosis of *M. avium* complex, *Cryptosporidium,* or *Giardia* infections that were missed on stool examination. Herpes simplex virus infection can be identified microscopically by detection of multinucleated giant cells or through cultures obtained at the time of endoscopy.

Small bowel biopsy and duodenal aspiration are indicated when stool examination, cultures, and sigmoidoscopy fail to yield a definitive diagnosis. Small bowel studies are most helpful for detecting infection with *Cryptosporidium,* cytomegalovirus, *M. avium* complex, *Giardia,* or *C. belli.*[62]

Differential Considerations

Kaposi's sarcoma, even if it involves the bowel, rarely produces diarrhea. Symptomatic oral and esophageal candidiasis is common in patients with AIDS, but diarrhea from *Candida* has not been reported. Diarrhea can be a side effect of antiretroviral drugs used to treat AIDS, especially the protease inhibitor nelfinavir and the combination agent lopinavir plus ritonavir.[55]

Antibiotic-associated colitis from *C. difficile* should be considered when onset of the diarrhea follows antibacterial therapy or hospitalization. Ulcerative colitis can mimic or be mimicked by cytomegalovirus colitis.[62] Aphthous ulceration, particularly of the colon, should be considered when cultures and endoscopy biopsy specimens fail to reveal evidence of infection with common infectious pathogens, herpes simplex virus, or cytomegalovirus. Empirical corticosteroid therapy may lead to dramatic improvement in these patients.[62] Acute proctitis should be differentiated from diarrhea or acute colitis because the investigative evaluation and treatment regimens are distinctly different.

Management

The best strategy for treatment and prevention of acute and chronic infectious diarrhea is maintenance of CD4+ counts through HAART. Treatment of diarrhea in patients with AIDS also includes diet, antimotility agents, and antimicrobial agents. Diets that are lactose-free and low in fat often diminish the diarrhea caused by malabsorption. Patients should avoid intestinal stimulants such as caffeine, raw or inadequately cooked seafood, rattlesnake preparations, and untreated water. Variable success has been reported with standard antimotility agents such as diphenoxylate or loperamide. In patients with cryptosporidiosis, these agents commonly cause a marked increase in crampy abdominal pain; long-acting morphine sulfate derivatives have provided better clinical relief.[46]

Specific antimicrobial therapy can lead to marked symptomatic improvement in 55 to 75% of patients in whom a pathogen has been identified (Table 94-5). Many patients show substantial improvement after therapy, even when the organism has not been eliminated or the diarrhea persists. Antimicrobial therapy should be dictated by the results of the diagnostic evaluation. Empirical use of antimicrobial agents is not indicated; no one antimicrobial agent can possibly provide reasonable coverage for the wide variety of causative organisms found in these patients. The possibility of infection by multiple organisms should always be considered, especially when patients do not respond to antimicrobial agents known to be effective against an identified pathogen.

Ganciclovir, a nucleoside analogue similar to acyclovir, is effective in inducing clinical remission in up to 90% of patients with gastrointestinal cytomegalovirus infection.[65] Foscarnet also is effective and typically is used in ganciclovir-resistant infections. The dosage of both drugs should be reduced in patients with low creatinine clearance. Treatment for the other most common cause of diarrhea in patients with AIDS, cryptosporidiosis, has improved with the use of nitazoxanide: in one study of HIV-positive patients with CD4 counts greater than 50/mm^3, 90% responded to a dose of 2 g/day, compared with 20% of those who received placebo.[46] Infection with *C. belli* and *C. cayetanensis* can be cured with TMP-SMX.[3] *M. avium* complex infection is poorly responsive to therapy, and death generally ensues within 6 to 8 months of diagnosis. Virtually all of the other organisms listed in Table 94-6 are

www.ketabpezeshki.com 66485457-66963820

Table 94-5 Treatment Directed against Pathogens Causing Diarrhea in Patients with AIDS

ORGANISM AND TREATMENT REGIMEN	COMMENTS
Cytomegalovirus	
Foscarnet 90 mg/kg IV q12h × 14-21 days (diluted in 100 mL D_5W, infused over at least 1 hr) Ganciclovir 5 mg/kg q12h IV × 14 days (diluted in 100 mL D_5W, infused over 1 hr)	Effective, but 75% recurrence rate within 8 to 9 weeks; maintenance therapy may be warranted
Cryptosporidium	
Paromomycin 25-35 mg/kg/day PO in 2-4 doses × 4 wk Azithromycin 600 mg PO qd × 4 wk in combination with paromomycin Nitazoxanide 1 g PO bid × 4 wk	Disease generally chronic despite treatment
Cyclospora cayetanensis	
TMP-SMX 160 mg/800 mg qid PO × 10 days, then 1 tab PO 3 times/wk	
Entamoeba histolytica	
Iodoquinol 650 mg PO tid × 20 days Diloxanide 500 mg PO tid × 10 days For severe symptoms, add metronidazole 750 mg PO tid × 10 days Paromomycin 25-35 mg/kg divided tid × 7 days	Treat only if distinguished from *Entamoeba dispar* or for severe symptoms, which warrant search for other causes as well
Giardia lamblia	
Metronidazole 250-750 mg PO tid × 5-10 days Tinidazole 2 g PO as a single dose Furazolidone 100 mg PO qid for 7-10 days	Patient's symptoms may resolve despite continued enteric presence of *Giardia*
***Mycobacterium avium* complex**	
Clarithromycin 500 mg PO bid or azithromycin 500 mg PO qd plus ethambutol 15 mg/kg/day with or without rifabutin 300 mg PO qd until response Levaquin 500 mg PO qd	Mixed results with antituberculosis drugs, more drug-resistant than tuberculous strains of mycobacteria; little evidence that treatment prolongs life
***Salmonella* species**	
Ciprofloxacin 500-750 mg PO bid × 10-14 days *or* azithromycin 1 g day 1, then 500 mg × 10 days *or* ceftriaxone 1-2 g IV q12h × 7-10 days	Bacteremia common; maintenance therapy often required
Herpes simplex virus	
Acyclovir 5 mg/kg PO or IV tid × 7-10 days Famciclovir 250 mg PO tid × 7-10 days Valacyclovir 1 g PO bid × 7-10 days	Proctitis picture, especially in homosexual men
Campylobacter jejuni	
Erythromycin 500 mg bid × 7-10 days *or* azithromycin 500 mg qd × 5-7 days	40% recurrence rate; high rate of fluoroquinolone resistance
Cystoisospora belli	
TMP-SMX 160 mg/800 mg PO qid × 10 days, then bid × 3 wk Pyrimethamine 50-75 mg qd × 10 days	50% recurrence rate; chronic suppressive therapy usually recommended
Aeromonas hydrophila	
Ciprofloxacin 500 mg PO bid × 3 days TMP-SMX 160 mg/800 mg PO bid × 3 days	Associated with drinking untreated water
Enteromonas hominis	
Metronidazole 250-750 mg PO tid × 10 days	Increasingly common in homosexual men, possibly commensal; treatment indicated when no other pathogens found in the presence of appropriate symptoms
Blastocystis hominis	
Metronidazole 750 mg PO tid × 10 days *or* furazolidone 100 mg PO qid × 7-10 days	Possibly more common in children
***Shigella* species**	
Ciprofloxacin 500 mg PO bid × 7 days	Most species resistant to ampicillin, and increasing resistance is found to TMP-SMX
***Yersinia* species**	
Ciprofloxacin 500 mg PO bid × 7 days	Appendicitis-like picture; bacteremia possible
Strongyloides stercoralis	
Ivermectin 200 μg/kg/day × 1-2 days *or* thiabendazole 25 mg/kg PO bid × 2 days	Migration of the larvae through the bowel wall may be accompanied by gram-negative bacteremia and a hyperinfection syndrome in patients with AIDS; in disseminated strongyloidiasis, therapy should be continued for at least 5 days

AIDS, acquired immunodeficiency syndrome; *D_5W,* dextrose 5% in water; *IV,* intravenously; *PO,* orally; *TMP-SMX,* trimethoprim-sulfamethoxazole.

www.ketabpezeshki.com 66485457-66963820

Table 94-6 Causes of Diarrhea in Patients with AIDS

FREQUENCY	ORGANISM
Most common	*Cryptosporidium* Cytomegalovirus
Common	*Entamoeba histolytica* *Giardia lamblia* *Mycobacterium avium* complex *Salmonella* species, especially *Salmonella enterica* subsp. *enterica* serovar Typhimurium* *Aeromonas hydrophila* Microsporidia Astrovirus, picornavirus *Clostridium difficile* *Campylobacter jejuni*
Less common	Viruses—herpes simplex virus, rotavirus, adenovirus, Norwalk agent *Cyclospora* *Cystoisospora belli* *Enteromonas hominis* *Strongyloides stercoralis* *Blastocystis hominis* *Shigella* species *Yersinia enterocolitica*

AIDS, acquired immunodeficiency syndrome.
*Formerly *Salmonella typhimurium.*

Table 94-7 Causes of Traveler's Diarrhea

AGENT	ESTIMATED INCIDENCE (%)*
Bacteria (in Approximately 75% of Cases)	
Enterotoxigenic *Escherichia coli*	45-50
Shigella	8-12
Campylobacter	7-9
Shiga toxin–producing *E. coli* (STEC)	5-6
Salmonella	3-5
Others, such as *Vibrio, Aeromonas, Plesiomonas shigelloides, Yersinia,* other types of *E. coli*	1-5
Viruses (in Approximately 5-10% of Cases)	
Rotavirus	5-10
Norwalk agent and others	0-5
Parasites (in Approximately 5-6% of Cases)	
Giardia lamblia	4-5
Cryptosporidium	3-4
Entamoeba histolytica	0-1
Strongyloides stercoralis	0-1
Unknown	5-10

*Rough estimates, which vary depending on locales visited.

susceptible to the usual therapeutic agents, although higher dosages and longer courses of treatment often are required. Recurrences of diarrhea caused by either the opportunistic organisms or the usual enteric organisms are common. Chronic suppressive antimicrobial therapy may be indicated to prevent relapse or reinfection.[3]

TRAVELER'S DIARRHEA

Epidemiology

It is said that "travel expands the mind and loosens the bowels." Diarrhea is by far the most common health problem among the 12 million people who travel from an industrialized nation to a developing country each year. Travel to high-risk areas (South Asia, followed by sub-Saharan Africa and Latin America) is associated with diarrheal attack rates of 30 to 50%. Among travelers to industrialized countries, however, the development of diarrhea is infrequent. For visitors to the United States, the attack rate is less than 4%.[55]

Traveler's diarrhea is more common in young adults than in elders. Travelers with inflammatory bowel disease, diabetes, or immunocompromise and those taking antacids also are at increased risk.[66]

Pathophysiology

The syndrome is caused by ingesting fecally contaminated food or water. High-risk items include raw leafy vegetables, raw or undercooked meats or seafood, unpeeled fruits, unpasteurized dairy products, tap water, and ice. Overall levels of sanitation at the travel destination and the particular food source are more predictive of acquisition of traveler's diarrhea than the particular food or beverage. Once an organism is ingested, rapid and dramatic change occurs in the traveler's intestinal flora. When the ingested inoculum overcomes host defense mechanisms, diarrhea develops. Most often, the pathomechanism involves elaboration of enterotoxins that produce a secretory diarrhea. When organisms are invasive rather than toxigenic, a typical infectious enteritis results.

Etiology

Pathogens that commonly cause traveler's diarrhea are listed in Table 94-7. Bacterial enteropathogens cause approximately 75% of cases of traveler's diarrhea. Enterotoxigenic *E. coli* is the most common pathogen and can be acquired anywhere in the world, although the incidence of infection is higher in Latin America, the Caribbean, Africa, and South Asia than in Southeast Asia. *Campylobacter* species are the most common isolates in travelers to Southeast Asia but are also found in travelers to South Asia, North Africa, and Central and South America. *V. parahaemolyticus* is an increasingly common cause because of its association with consumption of raw or inadequately cooked seafood. The organism commonly causes diarrhea in persons traveling to Japan or Asia or in those vacationing on cruise ships.[15,55,67]

P. shigelloides typically is associated with uncooked shellfish, especially oysters. It also is associated with travel to Mexico. *Plesiomonas* produces a typical invasive enteritis.[15] *E. coli* O157 : H7 and enteroinvasive *E. coli* each cause up to 5% of cases of traveler's diarrhea.[67] Another type of *E. coli,* enteroadherent *E. coli,* may be the cause of 5 to 30% of the previously undiagnosed cases of traveler's diarrhea. Viral agents (primarily noroviruses and rotavirus) cause up to 20% of cases of traveler's diarrhea.[67] Parasitic pathogens are implicated in approximately 10% of cases of traveler's diarrhea but are more common in returning travelers who seek medical care for diarrhea. *Giardia* is the most common parasite acquired by travelers; travelers to the former Soviet Union, particularly St. Petersburg and Moscow, have a very high risk for acquiring giardiasis. *E. histolytica, Cyclospora,* and *Cryptosporidium* are each implicated in less than 2% of cases.[67,68]

Clinical Presentation

Traveler's diarrhea typically begins abruptly, with production of four or five loose or watery stools per day for 1 to 3 days.

www.ketabpezeshki.com 66485457-66963820

Approximately one third of patients must curtail their activities, and the symptoms last more than a week in 10% of patients.[67] Onset usually is within the first 3 to 4 days of travel but can occur at any time, including after the patient arrives home. Patients may not associate their diarrhea with recent travel because the incubation time for the infection, particularly if it is parasitic, may have been long enough to allow them to return home before the symptoms began.

Associated symptoms include abdominal cramps, nausea, bloating, urgency, and occasionally vomiting, fever, chills, headache, malaise, tenesmus, and bloody stools. Symptoms and signs depend on whether the pathogen is noninvasive or invasive. Traveler's diarrhea may ruin a trip, but it is rarely life-threatening.

Prevention

Diet

Traditionally, instruction regarding food and beverage preparation has been touted to prevent traveler's diarrhea. Most travelers, however, do not follow such advice. Ideally, tourists should eat only foods that are freshly prepared and served piping hot. High-risk destinations and venues with poor sanitation should be assiduously avoided, and travelers should follow the Peace Corps adage of "boil it, cook it, peel it, or forget it." Thirsty travelers should be advised to avoid ice and to drink beverages such as tea and coffee that are made with boiled water, canned or bottled carbonated beverages, and wine.[66,67] Boiling water is by far the most reliable method to make it safe for drinking and brushing teeth. Travelers and outdoor enthusiasts should be advised to bring the water to a vigorous boil and allow it to cool without adding ice. Boiling destroys virtually all bacteria, viruses, and parasitic cysts. A pinch of salt in each quart improves the taste. When boiling is not feasible, water can be chemically disinfected with 2% tincture of iodine drops or tetracycline hydroperiodide tablets, such as Globaline or Potable Aqua, available from pharmacies and sporting goods stores.

Nonantimicrobial Medications

The nonantimicrobial agent most studied in the prevention of traveler's diarrhea is bismuth subsalicylate (e.g., Pepto-Bismol). Taking 525 mg four times per day decreases the incidence of traveler's diarrhea by 65%. This dosage, however, contains the daily equivalent of eight 5-grain aspirin tablets. Bismuth subsalicylate should not be used in patients who are allergic to salicylates, those taking large doses of salicylates for arthritis, or patients taking oral anticoagulants, uricosuric drugs, or methotrexate. Salicylates have antiplatelet effects, inhibit the activity of uricosuric drugs, and increase the toxicity of methotrexate by decreasing its renal clearance. Bismuth subsalicylate also turns the tongue and stool black and may cause mild tinnitus and interfere with the bioavailability of doxycycline.

Antiperistaltic agents such as diphenoxylate and loperamide are not effective prophylactic agents. Controlled studies have indicated that the prophylactic use of diphenoxylate actually increases the incidence of traveler's diarrhea: slowing of the gut allows more time for organisms to colonize and elaborate toxin or produce infection.[67]

Antimicrobials

The risks associated with prophylactic treatment with antibiotics include allergic reactions, skin rashes, photosensitivity reactions, serious hematologic reactions, Stevens-Johnson syndrome, and antibiotic-induced infections such as antibiotic-associated colitis or *Candida* vaginitis.[67] The main argument, however, against the widespread use of prophylactic antibiotics is the risk of emergence of resistant organisms. Resistance to doxycycline is now found in many parts of the world. TMP-SMX resistance is common in tropical areas. The quinolones are the most effective agents, but resistance rates of up to 80% have been reported for some organisms in parts of Southeast Asia.[67,68]

In addition, if the traveler is provided with a prescription for a suitable antibiotic based on regional resistance patterns, taking one dose in combination with loperamide immediately after the onset of diarrhea often will halt symptoms within hours. For these reasons, prophylactic use of antibiotics before the onset of symptoms is no longer recommended, except in cases of significant concurrent illness or immunocompromised status.[67,68]

If prophylaxis is indicated, a single daily dose of prophylactic antibiotics such as ciprofloxacin (500 mg), norfloxacin (400 mg), or rifaximin (200 mg), in combination with bismuth subsalicylate two tablets (262 mg/tablet) or 30 mL four times daily can effectively prevent traveler's diarrhea in up to 90% of persons. The regimen is started on the day before travel and continued until 2 days after the return home. TMP-SMX also can be used but is not recommended as a first-line agent because of significant resistance.

Management

Diet

In most patients, fluid and electrolyte balances can be maintained by drinking potable fruit juices, bottled beverages, or caffeine-free soft drinks.

Nonantimicrobial Medications

Adsorbents such as kaolin or pectin are ineffective for treating traveler's diarrhea. They may give the stools more consistency but have not been shown to decrease cramping or the frequency of stooling, or to shorten the course of an infectious diarrheal illness. Nonantimicrobial agents such as bismuth subsalicylate, paregoric, codeine, diphenoxylate, or loperamide may provide prompt but temporary symptomatic relief.

Loperamide (4 mg followed by 2 mg after each unformed stool for 2 days; total dosage no more than eight 2-mg capsules/day) has been shown to provide significantly more relief than that obtained with bismuth subsalicylate (525 mg every 30 minutes for eight doses on each of 2 days, for a total dose of 240 mL/day).[68] Antimotility agents alone, however, should never be given to patients when an invasive bacterial infection is suspected, and they should be discontinued if symptoms persist longer than 48 hours.

Antimicrobials

Antibiotic therapy can provide prompt relief of symptoms, decrease the rate of stooling, and shorten a typically 1- to 3-day illness to a few hours.[67,68] In cases of mild toxigenic, nondysenteric traveler's diarrhea, a single dose of ciprofloxacin 750 mg PO in combination with loperamide often resolves the symptoms within an hour. When the course is extended to 3 days, response rates of up to 98% are attained. In patients with high fever, bloody stools, or the typical bacterial or invasive picture, the treatment of choice is norfloxacin, 800 mg once daily or 400 mg twice daily, or ciprofloxacin, 750 mg once daily or 500 mg twice daily, in combination with loperamide. The duration of treatment generally is 3 days, although one double dose may be all that is necessary.[67]

Persons with dysentery who fail to respond to one antibiotic should promptly be switched to another. Azithromycin may be effective in cases in which fluoroquinolones either cannot be used

www.ketabpezeshki.com 66485457-66963820

or are ineffective. The quinolone agents are not recommended for use in children and pregnant women.[67]

The antibiotic rifaximin was FDA approved in 2004 for the treatment of traveler's diarrhea in adults and children older than 12 years. It is a nonabsorbable antibiotic that acts by inhibiting RNA synthesis, and the potential for development of bacterial resistance to this agent is believed to be low. Several studies demonstrate that oral rifaximin 200 mg three times daily for 3 days is an effective treatment for traveler's diarrhea.[67]

A summary of current recommendations for the prevention and treatment of traveler's diarrhea is outlined in Box 94-3. Further detailed information on traveler's diarrhea and the other medical problems of travelers can be found at the Travelers' Health section of the CDC's website, wwwnc.cdc.gov/travel/. The CDC's "Yellow Book," *CDC Health Information for International Travel,* can be downloaded for free at wwwnc.cdc.gov/travel/page/yellowbook-2012-home.htm, and the CDC provides up-to-the-minute travel information through its traveler's hotline telephone number, 1-800-CDC-INFO.

Box 94-3 Current Recommendations for the Prevention and Treatment of Traveler's Diarrhea

1. Provide instruction regarding sensible dietary practices and drinking water management.
2. Reserve prophylaxis for patients with special circumstances, including severe concurrent illness or immunosuppression. The basis of this recommendation is threefold: first, the potential for aspirin-related complications; second, the ramifications of widespread use of prophylactic antibiotics in terms of adverse medication reactions or the emergence of resistant organisms; and third, the availability of highly successful treatment strategies.
3. Other patients who request prophylaxis should be steered toward the use of bismuth subsalicylate rather than antibiotics.
4. For those requiring prophylaxis, one of the quinolones—norfloxacin, ciprofloxacin, or rifaximin—is recommended.
5. For all patients requiring prophylaxis, it is reasonable to institute prompt antimicrobial therapy once traveler's diarrhea has occurred.
   a. Toxigenic and nondysentery: loperamide combined with one dose of ciprofloxacin 750 mg orally.
   b. Infectious or dysentery: norfloxacin, ciprofloxacin, or rifaximin—alone or in combination with loperamide twice daily for 3 days.
   c. The rare traveler with persistent symptoms, particularly fever, chills, or blood or mucus in stools, unresponsive to antimicrobial therapy within 24 to 48 hours should seek immediate medical attention.

KEY CONCEPTS

- Contact isolation precautions in the ED should be followed for all patients with significant diarrhea.
- Most otherwise healthy patients with diarrhea do not require laboratory testing or antibiotic therapy.
- Fecal testing should be reserved for patients who are systemically ill, are febrile, have significant comorbid disease, have bloody stools, or report recent antibiotic use, or in whom exposure to a treatable or reportable pathogen is strongly suspected.
- Empirical treatment of diarrhea in adults with a fluoroquinolone or TMP-SMX generally is not recommended but is acceptable for traveler's diarrhea and when severe inflammatory diarrhea is present with a low risk of *E. coli* O157 : H7 as its cause. This indication includes bloody diarrhea in patients with a temperature higher than 38.5° C.
- Milk and other lactose-containing foods should be avoided because gastroenteritis often leads to transient lactose intolerance. Caffeine products also may worsen diarrhea. Bowel rest is not necessary or advantageous.
- Risks of empirical antibiotic treatment include adverse and allergic reactions, possible increase in the risk of HUS in the case of *E. coli* O157 : H7 infection, prolonged shedding of salmonellae of non-Typhi serotypes, and increased organism resistance.
- Treatment should be considered in patients who are still significantly ill when culture results are reported, particularly if they are immunocompromised or have a significant underlying medical illness, or in cases in which the fecal shedding could represent a public health hazard.
- Although risk associated with antimotility agents may be overstated, these agents are still not recommended for treatment of invasive enteritis unless antibiotics also are used.
- In patients with *Y. enterocolitica* gastroenteritis, the abdominal pain and diarrhea usually persist for 10 to 14 days or longer. In many patients, especially adolescents and young adults, an ileocecitis may develop; symptoms may perfectly mimic acute appendicitis.
- Scombroid fish poisoning causes the abrupt onset (20-30 min) of symptoms similar to histamine intoxication. The mainstay of therapy is antihistamine administration.
- Many cases of *C. difficile* antibiotic-associated enterocolitis are self-limited. If stopping the antibiotic does not resolve the diarrhea, or when the diarrhea is severe, empirical antibiotic treatment should be started promptly.
- *Giardia* is the most common cause of water-borne diarrheal outbreaks in the United States The most common symptoms of acute infection are abdominal distention, colicky pain with audible borborygmi, flatulence, and frequent stools. All patients with proven *Giardia* infection should receive treatment even if they are asymptomatic.
- Diarrhea is the most common manifestation of gastrointestinal disease in patients with AIDS, either as a presenting symptom or a life-threatening complication of the disease. Diarrhea in patients with AIDS in whom CD4+ counts are less than 300/mm^3 generally is not self-limiting but requires medical intervention to effect resolution. Therefore each patient deserves a diagnostic evaluation.
- ETEC is responsible for 40 to 50% of all cases of traveler's diarrhea. Prophylactic antibiotics are no longer recommended for otherwise healthy patients, but quick resolution of diarrhea is possible with prompt treatment.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Sherman PM, Ossa JC, Wine E: Bacterial infections: New and emerging enteric pathogens. *Curr Opin Gastroenterol* 2010; 26:1.
2. Centers for Disease Control and Prevention (CDC), National Center for Emerging and Zoonotic Infectious Diseases: Campylobacter. Available at www.cdc.gov/nczved/divisions/dfbmd/diseases/campylobacter/technical.html. Accessed April 16, 2011.
3. Guerrant RL, et al: Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis* 2001; 32:331.
4. Savola KL, Baron EJ, Tompkins LS, Passaro DJ: Fecal leukocyte stain has diagnostic value for outpatients but not inpatients. *J Clin Microbiol* 2001; 39:1.
5. Ternhag A: A meta-analysis on the effects of antibiotic treatment on duration of symptoms caused by infection with *Campylobacter* species. *Clin Infect Dis* 2007; 44:5.
6. Centers for Disease Control and Prevention (CDC): Preliminary FoodNet Data on the Incidence of Infection with Pathogens Transmitted Commonly through Food—10 States, 2009. Available at www.cdc.gov/mmwr/preview/mmwrhtml/mm5914a2.htm. Accessed April 23, 2011.
7. Centers for Disease Control and Prevention (CDC): Salmonella. Available at www.cdc.gov/salmonella/general/technical.html. Accessed April 16, 2011.
8. Dennehy PH: Acute diarrheal disease in children: Epidemiology, prevention and treatment. *Infect Dis Clin North Am* 2005; 19:3.
9. Centers for Disease Control and Prevention (CDC): Shigellosis. Available at www.cdc.gov/nczved/divisions/dfbmd/diseases/shigellosis/. Accessed April 23, 2011.
10. Centers for Disease Control and Prevention (CDC): Shigellosis: Technical Information. Available at www.cdc.gov/nczved/divisions/dfbmd/diseases/shigellosis/technical.html. Accessed April 23, 2011.
11. American Academy of Pediatrics Pediatric Care Online: *Shigella Infections*. Available at www.pediatriccareonline.org/pco/ub/view/RedBook/187302/all/shigella_infections. Accessed April 23, 2011.
12. Cunningham SA, et al: Three hour molecular detection of *Campylobacter, Salmonella, Yersinia,* and *Shigella* species in feces with accuracy as high as that of culture. *J Clin Microbiol* 2010; 48:2929.
13. Centers for Disease Control and Prevention (CDC): *Yersinia enterocolitica*. Available at www.cdc.gov/ncidod/dbmd/diseaseinfo/yersinia_g.htm. Accessed April 23, 2011.
14. Rosner BM, Stark K, Werber D: Epidemiology of reported *Yersinia enterocolitica* in Germany, 2001-2008. *BMC Public Health* 2010; 10:337.
15. Pitout JD, Church DL: Emerging gram negative enteric infections. *Clin Lab Med* 2004; 24:605.
16. Centers for Disease Control and Prevention (CDC): *Vibrio parahaemolyticus:* Technical Information. Available at www.cdc.gov/nczved/divisions/dfbmd/diseases/vibriop/technical.html. Accessed April 24, 2011.
17. Public Health Agency of Canada: *Vibrio parahaemolyticus*. Available at www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/vibrio-parahaemolyticus-eng.php. Accessed May 4, 2011.
18. Centers for Disease Control and Prevention (CDC): Enterohemorrhagic *Escherichia coli* (EHEC). Available at http://www.cdc.gov/ncidod/dbmd/diseaseinfo/enterohemecoli_t.htm. Accessed May 6, 2011.
19. Reference deleted in proofs.
20. Hunt JM: Shiga toxin–producing *Escherichia coli* (STEC). *Clin Lab Med* 2010; 30:21.
21. Gould LH, et al: *Recommendations for Diagnosis of Shiga Toxin–Producing* Escherichia coli *Infections in Clinical Laboratories*. Available at www.cdc.gov/mmwr/preview/mmwrhtml/rr5812a1.htm. Accessed May 6, 2011.
22. Janda J, Abbott S: The genus *Aeromonas:* Taxonomy, pathogenicity, and infection. *Clin Microbiol Rev* 2010; 23:35.
23. Subashkumar R, Thayumanavan T, Vivekanandhan G, Lakshmanaperumalsamy P: Occurrence of *A. hydrophila* in acute gastroenteritis among children. *Indian J Med Res* 2006; 123:61.
24. United States Food and Drug Association: *Bad Bug Book: Foodborne Pathogenic Microorganisms and Natural Toxins Handbook:* Plesiomonas shigelloides. Available at www.fda.gov/Food/FoodSafety/FoodborneIllness/FoodborneIllnessFoodbornePathogensNaturalToxins/BadBugBook/ucm070530.htm. Accessed May, 2011.
25. Beatty M, Ashford D, Griffin P, Tauxe R, Sobel J: Gastrointestinal anthrax. *Arch Intern Med* 2003; 163:2527.
26. Peck RN, Fitzgerald DW: Cutaneous anthrax in the Artibonite valley of Haiti: 1992-2002. *Am J Trop Med Hyg* 2007; 77:806.
27. Shadomy SV: Anthrax. Available at wwwnc.cdc.gov/travel/yellowbook/2010/chapter-5/anthrax.htm. Accessed May 10, 2011.
28. Centers for Disease Control and Prevention (CDC): Recommended Specimens for Microbiology and Pathology for Diagnosis: Inhalation, Cutaneous, and Gastrointestinal Anthrax. Available at http://emergency.cdc.gov/agent/anthrax/lab-testing/recommended_specimens.asp. Accessed May 10, 2011.
29. U.S. Food and Drug Administration: *Bad Bug Book: Foodborne Pathogenic Microorganisms and Natural Toxins Handbook: Staphylococcus aureus*. Available at www.fda.gov/Food/FoodSafety/FoodborneIllness/FoodborneIllnessFoodbornePathogensNaturalToxins/BadBugBook/ucm070015.htm. Accessed May 11, 2011.
30. Gleason B: CBRNE—Staphylococcal Enterotoxin B. Available at http://emedicine.medscape.com/article/830715-overview#a0104. Accessed May 11, 2011.
31. Food-Borne Illnesses Table: Bacterial Agents. Available at www.phsource.us/PH/FBI/FBI_Bacterial.htm. Accessed May 11, 2011.
32. U.S. Food and Drug Administration: *Bad Bug Book: Foodborne Pathogenic Microorganisms and Natural Toxins Handbook:* Clostridium perfringens. Available at www.fda.gov/Food/FoodSafety/FoodborneIllness/FoodborneIllnessFoodbornePathogensNaturalToxins/BadBugBook/ucm070483.htm. Accessed May 11, 2011.
33. Sobel J, et al: Necrotizing enteritis associated with *Clostridium perfringens* type A in previously healthy North American adults. *J Am Coll Surg* 2005; 201:48.
34. U.S. Food and Drug Administration: *Bad Bug Book: Foodborne Pathogenic Microorganisms and Natural Toxins Handbook:* Bacillus cereus *and other* Bacillus *spp*. Available at www.fda.gov/food/foodsafety/foodborneillness/foodborneillnessfoodbornepathogensnaturaltoxins/badbugbook/ucm070492.htm. Accessed May 11, 2011.
35. Mead PS, et al: *Food-Related Illness and Death in the United States*. Available at http://wwwnc.cdc.gov/eid/article/5/5/pdfs/99-0502.pdf. Accessed May 11, 2011.
36. Centers for Disease Control and Prevention (CDC): Cholera. Available at www.cdc.gov/cholera/index.html. Accessed May 12, 2011.
37. Centers for Disease Control and Prevention (CDC): *Vibrio vulnificus:* Technical Information. Available at www.cdc.gov/nczved/divisions/dfbmd/diseases/vibriov/technical.html. Accessed May 12, 2011.
38. Institute of Food and Agricultural Sciences: Ciguatera. Document ENY-741. Available at http://edis.ifas.ufl.edu/in742. Accessed May 16, 2011.
39. Mattei C, et al: Brevenal inhibits pacific ciguatoxin-1B–induced neurosecretion from bovine chromaffin cells. *PLoS One* 2008; 3:e3448.
40. Centers for Disease Control and Prevention (CDC): Travelers' Diarrhea. Available at www.cdc.gov/ncidod/dbmd/diseaseinfo/travelersdiarrhea_g.htm. Accessed May 16, 2011.
41. Centers for Disease Control and Prevention (CDC): Enterotoxigenic *Escherichia coli* (ETEC). Available at www.cdc.gov/ncidod/dbmd/diseaseinfo/etec_g.htm. Accessed May 16, 2011.
42. Taxt A, Aaland R, Sommerfelt H, Nataro J, Puntavoll P: Heat-stable enterotoxin of enterotoxigenic *E. coli* as a vaccine target. *Infect Immun* 2010; 78:1824.
43. Dupont HL, Garey K, Caiero JP, Jiang ZD: New advances in *Clostridium difficile* infection: Changing epidemiology, diagnosis, treatment and control. *Curr Opin Infect Dis* 2008; 21:500.
44. Jaber MR, Olafsson S, Fung WL, Reeves ME: Clinical review of the management of fulminant *C. difficile* infection. *Am J Gastroenterol* 2008; 103:3195.
45. Centers for Disease Control and Prevention (CDC): *Rotavirus: Clinical Information*. Available at www.cdc.gov/rotavirus/clinical.html. Accessed May 17, 2011.
46. Centers for Disease Control and Prevention (CDC): Norovirus. Available at http://www.cdc.gov/norovirus/hcp/clinical-overview.html. Accessed May 17, 2011.
47. Centers for Disease Control and Prevention (CDC): *Parasites—*Cryptosporidium *(Also Known as "Crypto"). Infection—General Public.* Available at www.cdc.gov/parasites/crypto/gen_info/infect.html. Accessed May 17, 2011.
48. Centers for Disease Control and Prevention (CDC): Parasites—Cystoisosporiasis (Formerly Known as *Isosporiasis*). Cystoisosporiasis FAQs. Available at www.cdc.gov/parasites/cystoisospora/faqs.html. Accessed May 17, 2011.
49. Sherchand JB, Cross JH: An epidemiological study of *Cyclospora cayetanensis* in Nepalese people. *J Inst Med* 2007; 29:8-13.
50. Centers for Disease Control and Prevention (CDC): Parasites—Cyclosporiasis (*Cyclospora* Infection). Available at www.cdc.gov/parasites/cyclosporiasis/index.html. Accessed May 18, 2011.
51. Centers for Disease Control and Prevention (CDC): Parasites—*Giardia.* Epidemiology and Risk Factors. Available at www.cdc.gov/parasites/giardia/epi.html. Accessed May 18, 2011.

www.ketabpezeshki.com 66485457-66963820

52. Karanis P: Occurrence of *Giardia* and *Cryptosporidium* in water supplies of Russia and Bulgaria. *Environ Res* 2006; 102:260.
53. Lalle M: Giardiasis in the post-genomic era: Treatment, drug resistance and novel therapeutic perspectives. *Infect Disord Drug Targets* 2010; 10:283.
54. Tian H, Chen B, Wen J: Giardiasis, drug resistance, and new target discovery. *Infect Disord Drug Targets* 2010; 10:295.
55. Goodgame R: A Bayesian approach to acute infectious diarrhea in adults. *Gastroenterol Clin North Am* 2006; 35:249.
56. Sateriale A, Huston C: A sequential model of host cell killing and phagocytosis by *Entamoeba histolytica*. *J Parasitol Res* 2011; 2011:926706.
57. Centers for Disease Control and Prevention (CDC): Parasites—Enterobiasis (Also Known as Pinworm Infection): Disease. Available at www.cdc.gov/parasites/pinworm/disease.html. Accessed May 18, 2011.
58. Bowley DM, Loveland J, Omar T, Pitcher GJ: Human immunodeficiency virus and amebiasis. *Pediatr Infect Dis J* 2006; 25:1192, 2006.
59. Farthing MJ: Treatment options for eradication of intestinal protozoa. *Nat Clin Pract Gastroenterol Hepatol* 2006; 3:436.
60. Wilcox CM, Saag MS: Gastrointestinal complications of HIV infection: Changing priorities in the HAART era. *Gut* 2008; 57:861.
61. Mönkemüller KE, Lazenby AJ, Lee DH, Loudon R, Wilcox CM: Occurrence of gastrointestinal opportunistic disorders in AIDS despite the use of highly active antiretroviral therapy. *Dig Dis Sci* 2005; 50:230.
62. Wilcox CM: Gastrointestinal manifestations of AIDS. *Nutr Clin Pract* 2004; 19:356.
63. Antony MA, Brandt LJ, Klein RS, Bernstein LH: Infectious diarrhea in patients with AIDS. *Dig Dis Sci* 2005; 33:1141.
64. Lin RY, Lugo LA, Smith FB: Protracted diarrhea associated with eosinophilia in an HIV infected patient. *Internet J Asthma Allergy Immunol* 2007; 5:2.
65. Shagil'dian VI: Cytomegalovirus infection of the gastrointestinal tract in patients with HIV infection. *Ter Arkh* 2005; 77:14.
66. Centers for Disease Control and Prevention (CDC), National Center for Emerging and Zoonotic Infectious Diseases: Travelers' Diarrhea: General Information: Frequently Asked Questions. Available at www.cdc.gov/nczved/divisions/dfbmd/diseases/travelers_diarrhea/. Accessed May 18, 2011.
67. Hill DR, Beeching NJ: Travelers' diarrhea. *Curr Opin Infect Dis* 2010; 23:481.
68. Hill DR, Ryan ET: Management of travellers' diarrhea. *BMJ* 2008; 337:863.

www.ketabpezeshki.com 66485457-66963820

Chapter 95

Disorders of the Large Intestine

Michael A. Peterson

IRRITABLE BOWEL SYNDROME

Perspective

Irritable bowel syndrome (IBS) is a chronic non–life-threatening disorder characterized by abdominal pain and alteration in bowel habits. IBS is an extremely common disorder; estimates put the prevalence in the North American population at 10 to 15%, with women affected twice as often as men.[1,2] Although only one third of patients who have the clinical syndrome ever seek medical attention, IBS accounts for more than 10% of all visits to primary care physicians and more than 25% of all visits to gastroenterologists. IBS is said to contribute more impairment to quality of life than either diabetes or renal failure.

No specific physical or laboratory abnormalities defining IBS have been identified. IBS is a functional somatic syndrome that is diagnosed by clinical criteria in the absence of "alarm" symptoms and findings that suggest other, more urgent diagnoses. Diagnosing IBS is problematic in the emergency department (ED), and typically patients are discharged with a diagnosis of "abdominal pain of unclear cause" or the equivalent. Patients with known IBS who are experiencing acute symptoms may also pose a diagnostic challenge. Symptoms of IBS overlap with those of other conditions, including some that are life-threatening, which must be excluded before hospital discharge.

Principles of Disease

Although the cause of IBS is unknown, it is associated with several pathophysiologic findings suggesting that it is a disorder of altered gut motility, gut sensation, and perception of intestinal activity. IBS was originally thought to be primarily a psychiatric disorder because there are no visible anatomic abnormalities and because stress is an exacerbating factor. Physiologic testing has since shown that patients with IBS have disturbances in the rhythmic pattern of electrical activity in the intestine and in how the intestine responds to stimulation. Patients with IBS seem to be more attuned to activity in the abdomen as well, sensing different phases of intestinal motor activity and intestinal content movement to a greater extent than people without IBS.

Psychiatric conditions often coexist with IBS, ranging from generalized anxiety disorder to major depression. IBS has been associated with fibromyalgia, chronic fatigue syndrome, and chronic pelvic pain.[2] An association with previous sexual abuse also has been reported. In women, symptoms often are related to the menstrual cycle, suggesting a hormonal influence. A familial predisposition for the symptoms of IBS has been described, suggesting a genetic component. Bacterial overgrowth and infection have also been associated with IBS.[2]

Clinical Features

The diagnosis of IBS is defined by clinical criteria in a patient whose symptoms have no other organic explanation. Several sets of clinical criteria have been published, one set of which is the Rome III criteria (Box 95-1). Patients with IBS experience symptoms intermittently, with the typical patient averaging symptoms on 1 of every 3 days. Complaints include abdominal pain, bloating, and constipation or diarrhea. Pain typically is relieved with defecation; pain that persists suggests another diagnosis. A mucoid discharge from the rectum often accompanies diarrhea. Upper gastrointestinal symptoms such as nausea and dyspepsia can also occur. Patients may come to the ED with an exacerbation of their previous symptoms or with a new abdominal complaint and often report that they are undergoing a period of stress. Physical examination may reveal either mild focal abdominal tenderness that can vary in location, or diffuse tenderness. IBS is subdivided into three categories: constipation-predominant (IBS-C), diarrhea-predominant (IBS-D), and mixed pattern (IBS-M).[2]

Pain that is progressive or is associated with anorexia or significant abdominal tenderness suggests an alternate diagnosis. Signs and symptoms that point away from the diagnosis of IBS (alarm symptoms) include onset of symptoms after age 50, unintentional weight loss, anorexia, bloody stools, nocturnal diarrhea, or a family history of significant colon disease.[2] In the absence of symptoms suggesting another diagnosis, the clinical criteria have a specificity ranging from 87 to 100%, although sensitivity may be only 60%. In patients determined to have IBS through correct use of the clinical criteria, follow-up evaluation over many years rarely leads to a change in the diagnosis.[2]

A final diagnosis of IBS usually is made in the primary care setting and not in the ED. Studies that are sometimes performed in the evaluation for IBS may include a complete blood count, thyroid studies, stool examination for ova and parasites, evaluation for lactose intolerance, and possibly lower gastrointestinal endoscopy, although current approaches try to limit testing in cases in which the clinical picture is clearly IBS.[3] The ED evaluation seeks to exclude other, more urgent causes for the patient's symptoms. In this setting, testing for pancreatitis, hepatitis, biliary colic, or urologic disorders, including urolithiasis, may be appropriate as indicated by the pattern of the presenting complaints.

Diagnostic Strategies

No specific testing should be done in the ED on individuals who fit the pattern of IBS. In the primary care setting patients may benefit from lactose intolerance or celiac disease testing. Other tests, including colonoscopy, are not found to be helpful.

www.ketabpezeshki.com 66485457-66963820

Box 95-1 Rome III Criteria for Irritable Bowel Syndrome

Recurrent abdominal pain or discomfort at least 3 days per month in the previous 3 months associated with two or more of the following:

1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

From Kahn S, Chang L: Diagnosis and management of IBS. Nat Rev Gastroenterol Hepatol 7:565-581, 2010.

Box 95-2 Differential Diagnosis in Irritable Bowel Syndrome

Constipation—Predominant
Bowel obstruction
Cancer
Adult-onset Hirschsprung's disease
Rectocele
Paradoxical closure of the anus during defecation

Diarrhea—Predominant
Bacterial or parasitic intestinal infection
Inflammatory bowel disease
Lactose intolerance
Malabsorption
Radiation proctocolitis

Painful
Inflammatory bowel disease
Ureteral colic
Bowel obstruction
Diverticular disease
Gastroesophageal reflux or ulcer
Liver or pancreatic disease
Lead toxicity
Porphyria

Differential Considerations

The differential diagnosis of symptomatic IBS depends on the predominant symptoms and includes a host of disorders (Box 95-2). Patients may report pain, constipation, or diarrhea or any combination of the three.

Management

Not all patients with IBS require treatment. It is recommended that therapy be initiated only if symptoms diminish the quality of life.[1] Because no curative therapy is available, treatment is directed toward the relief of symptoms. Diet, behavioral, and pharmacologic therapies all are used in IBS. Specific therapy will be determined by the type of IBS: IBS-C, IBS-D, or IBS-M. Dietary suggestions include a low-fat diet, reduced nondigestible sugars, and avoidance of gas-forming foods, although none of these has any proven benefit. Fiber supplementation may aid IBS-C.

Medications with antispasmodic activity, such as anticholinergics and calcium channel blockers, are used for abdominal cramping, and peripherally acting narcotics, such as loperamide, are used to reduce diarrhea. Osmotic laxatives such as lactulose sometimes are helpful in constipation. Tricyclic antidepressants have been effective in certain classes of patients with IBS. Serotonin receptor antagonists, serotonin receptor agonists, chloride channel activators, and prokinetic agents also are used (Box 95-3), but the serotonin receptor drugs have significant side effects, including adverse cardiovascular events and ischemic colitis, and thus are reserved

Box 95-3 Medications Used in the Treatment of Irritable Bowel Syndrome

Osmotic laxatives
Antidiarrheals
Antispasmodics (anticholinergics and calcium channel blockers)
Tricyclic antidepressants
Serotonin receptor agonist (e.g., tegaserod)
Serotonin receptor antagonists (e.g., alosetron)
Chloride channel activators (e.g., lubiprostone)
Prokinetic agents
Female hormone–modulating agents
Tranquilizers
Rifaximin

for patients with severe symptoms unresponsive to other agents. Nonsteroidal anti-inflammatory drugs (NSAIDs) may worsen symptoms.[3]

Behavioral therapy may benefit patients who are unresponsive to medication, but high-quality evidence of its effectiveness is lacking. A role for nontraditional therapies such as arrowroot, artichoke leaf, and some Chinese traditional herbal medicines is supported by limited scientific evidence.

Disposition

IBS is not a life-threatening disease and can be managed on an outpatient basis as long as other disorders have been excluded. The search for optimal therapy usually involves empirical trials until the correct fit is found. This process is best accomplished through a well-established primary care relationship. The disorder is chronic, but with appropriate therapy, many patients experience significant improvement in their quality of life.

DIVERTICULAR DISEASE

Perspective

Diverticular disease is an affliction of middle age that seems to be a direct consequence of the diet of modern Western civilization. Diverticular disease was virtually unknown in the Western world before the 20th century and is still rare in other cultures. In 1925 only 9% of people older than 50 years of age in the United States had diverticula; by 1968 the percentage had increased to 30%.[4] Today it is estimated that 5 to 10% of people older than 45 years and 80% of people older than 85 years have diverticula. Diverticula are less common in people younger than age 40, representing only approximately 2 to 5% of all patients with the disease. The proliferation of this disease was coincident with the invention and widespread use of the flour rolling mill, which removes the fiber-containing outer part of the wheat kernel. This coincidence has prompted the labeling of diverticulosis as a "modern deficiency disease," which is supported by the fact that adding fiber back into the diet seems to be protective against the development of diverticulosis.[4] In rural Africa and Asia, where the diet is high in fiber, diverticular disease is virtually unknown. Over the last decade the incidence of diverticulitis has increased in the United States, especially in people aged 18 to 44.[5]

Diverticulosis denotes the presence of diverticula in the colon. Most patients with this condition are asymptomatic. *Diverticulitis* denotes inflammation of diverticular tissue, which is usually painful. It is estimated that 10 to 25% of patients with diverticulosis will develop diverticulitis.[5] *Complicated diverticulitis* is defined by the presence of more extensive disease, including abscess formation, peritonitis, intestinal obstruction, or fistula formation.

www.ketabpezeshki.com 66485457-66963820

Principles of Disease

The wall of the colon is penetrated at regular intervals by blood vessels, collectively known as the *vasa recta,* that supply the internal intestinal layers. The site of vessel penetration is apparently the weakest part of the colon wall because it is at these sites that diverticula form. Although the exact pathogenic mechanism is unknown, the current theory is that diverticula form in response to increased intracolonic pressures generated when the colon is processing smaller, non–fiber-containing stools. Patients with diverticular disease exhibit normal resting colonic pressure but higher peak pressure than those without diverticular disease[5]; higher peak pressures lead to a herniation of colonic mucosa through the intestinal wall at the vasa recta, creating small, saclike appendages. These appendages (diverticula) typically measure 5 to 10 mm in diameter but on rare occasions can grow into huge sacs measuring many centimeters across *(giant colonic diverticula).* Diverticula are generally asymptomatic; symptoms are believed to develop when diverticula become obstructed, presumably with inspissated stool. When obstruction occurs, inflammation sets in and microperforations of the sac develop, resulting in inflammation of pericolonic structures and abdominal pain.

In the Western world, most diverticular disease occurs in the left colon, usually the sigmoid. This is not the case in Japan, where right-sided diverticular disease is more common. Japanese-Hawaiians consuming a low-fiber Western diet have a significantly increased incidence of diverticular disease, but it remains in the right colon.[4] This finding suggests that although diet plays a significant role in the formation of diverticula, the location of diverticula is genetically determined.

A spectrum of disease is observed in relation to diverticular inflammation. In *uncomplicated* diverticulitis, only the pericolonic fat is inflamed. With time, a phlegmon, abscess, or gross perforation may develop. Any extension of disease beyond the pericolonic fat is considered to represent *complicated* diverticulitis. The involved colonic segment may fistulize to any adjacent organ, most commonly the bladder. Adjacent bowel may become obstructed by mass effect from an abscess or may incur an inflammatory ileus. Recurrent episodes of diverticulitis can lead to strictures in the colon with subsequent colonic obstruction.

Diverticula can also bleed, presumably from erosion into the mucosal wall by dried stool trapped in the diverticular sac. Severe hemorrhage occurs in 3 to 5% of all patients with diverticulosis and accounts for approximately 40% of all instances of lower gastrointestinal hemorrhage.[4] Bleeding notably occurs in the absence of inflammation and typically is painless. NSAID use is associated with this complication.

Clinical Features

Diverticulosis

Although approximately 75% remain asymptomatic throughout their lifetime,[4,6] patients with diverticulosis sometimes have nonspecific abdominal complaints including bloating, crampy pain, excessive gas, or a change in bowel habits.[7] Diverticulitis will develop in approximately 10 to 30% of patients with diverticulosis.

Diverticulitis

Because most diverticula found in persons in the Western world form in the left colon, the typical presentation of diverticulitis is persistent left lower quadrant pain and tenderness. Pain may be felt first in the hypogastrium before localizing to the left lower quadrant. Referred pain may occur in the penis, scrotum, or suprapubic region. Right-sided diverticulitis may manifest as right lower quadrant pain and is impossible to distinguish clinically from appendicitis. Additional findings suggest various complications: diffuse tenderness is associated with gross perforation or abscess rupture; dysuria, with a colovesical fistula; mass, with an abscess; and vomiting or abdominal distention, with intestinal obstruction. Fecal matter or gas emanating from the vagina suggests a colouterine fistula. Almost any adjacent organ can be involved in the inflammatory process. Patients recently diagnosed with diverticulitis who are being treated on an outpatient basis with oral antibiotics and who visit the ED with continuing or worsening symptoms should be evaluated for the possibility of an abscess.

Special care must be taken with elders or immunocompromised patients because clinical signs and symptoms are much less dramatic, even with more severe disease. Perforation is more common in these patients (up to 40%), manifests with less significant findings, and carries a high mortality rate.[5]

Diagnostic Strategies

Uncomplicated Diverticulitis

The clinical diagnosis of uncomplicated diverticulitis can be made in a patient in the appropriate age range exhibiting focal left lower quadrant pain and tenderness in the absence of symptoms or signs that suggest an alternative diagnosis. No mass or peritoneal irritation should be encountered on examination, and the patient should otherwise appear well. If the patient fits this clinical picture, treatment can be initiated on an empirical basis, and no laboratory tests or diagnostic imaging is required. Ancillary tests are performed primarily to exclude alternative diagnoses or the presence of complicated diverticulitis. When the diagnosis is unclear, studies to exclude gynecologic, renal, hepatic, biliary, or pancreatic disease may be indicated, depending on the patient's presentation and degree of distress. Computed tomography (CT) of the abdomen should be considered for elders and immunocompromised patients to exclude the possibility of a subtle presentation of complicated diverticulitis.

Complicated Diverticulitis

Abdominal Computed Tomography. Abdominal CT is the preferred method of evaluation in complicated diverticulitis. CT has the advantage of evaluating the colon and the structures around it, so it can facilitate the diagnosis of diverticulitis and simultaneous evaluation of the extent of disease. CT can also be used to guide percutaneous drainage of diverticular abscesses. Findings on CT consistent with diverticulitis include the presence of diverticula, inflammation of pericolonic fat, thickening of the bowel wall to more than 4 mm, free abdominal air, and abscesses.[6,8] CT also can help make an alternative diagnosis when diverticulitis is absent. CT is relatively noninvasive and is well tolerated by ill patients. Sensitivity and specificity for diverticulitis range from 69 to 95% and from 75 to 100%, respectively.[8] Negative findings on CT scan cannot absolutely exclude diverticulitis. Small abscesses within the colon or mesocolon can be missed, as can the diverticula themselves. It may also be difficult to differentiate between carcinoma and diverticulitis on CT scan. Marked bowel wall thickening associated with diverticulitis looks like cancer; contrast enema or endoscopy may be required to differentiate the two.

Barium Enema. Although double-contrast barium examination is the standard for the diagnosis of asymptomatic diverticula, it should be avoided in the setting of diverticulitis. The potential for preexisting occult perforation and subsequent risk of barium

www.ketabpezeshki.com 66485457-66963820

peritonitis limits its usefulness. Barium enema may be used after the acute episode to exclude the diagnosis of carcinoma.

Water-Soluble Contrast Enema. Although now rarely used, a water-soluble contrast enema is the preferred method of imaging if a contrast enema study is needed in the acute setting. Water-soluble contrast material shows less detail than barium, but this modality is still useful. Findings consistent with diverticulitis include the presence of diverticula along with extravasation of contrast material into an abscess cavity or into the peritoneum. This study can also show a fistula or evidence of compression of the colon by an extrinsic mass. Because contrast material usually collects only in the intestinal lumen, contrast enemas give less information than CT about the extent of disease outside of the colon.

Ultrasonography. Ultrasound examination can detect various pathologic features characteristic of diverticulitis, including fluid collections around the colon, thickened hypoechoic bowel wall, or hyperechoicity adjacent to the bowel wall that suggests pericolonic inflammation. Tenderness to palpation over an abnormal-appearing colon suggests that the colon is the source of the patient's pain. Diverticula can occasionally be visualized by ultrasound examination. As is often the case, the sensitivity of ultrasound imaging for these findings varies significantly with the experience of the operator. Because gas interferes with ultrasound imaging, adequate visualization of the bowel can be a problem. Currently, the role for ultrasonography in the evaluation of diverticulitis is not well defined.

Endoscopy. Endoscopy is limited in the acute setting by its more invasive nature, the risk of perforation, and the logistics of arranging this procedure emergently.[9,10] Although the endoscope affords visualization of diverticula and other pathologic processes within the lumen of the colon, it does not permit evaluation of the extent of extracolonic disease.

Plain Radiography. Plain radiographs of the abdomen are not likely to be helpful in the diagnosis of diverticulitis unless either intestinal obstruction or perforation is suspected.

Differential Considerations

In a patient with more serious disease, making the correct diagnosis usually poses no great dilemma because more extensive laboratory testing and diagnostic imaging typically have been performed. In a patient with milder disease, in whom a tentative diagnosis of diverticulitis may be based on clinical grounds alone, the differential diagnosis presents more of a challenge. An important consideration is whether or not the patient has colonic carcinoma; however, it usually is safe to wait until after the acute episode has resolved to investigate this possibility. Additional diagnoses to consider include colitis (either inflammatory or ischemic); ureteral stones; inguinal hernia; and pelvic pathology, including ectopic pregnancy or pelvic inflammatory disease, and ovarian pathology with or without ovarian torsion. Appendicitis should be suspected when symptoms are predominantly right sided. Diffuse abdominal pain should prompt an evaluation for other life-threatening problems, including leaking abdominal aortic aneurysm, peritonitis, hemoperitoneum from ectopic pregnancy, and bowel obstruction.

Management

Diverticulosis

All patients diagnosed with diverticulosis should be placed on a high-fiber diet, which has been shown to reduce abdominal symptoms and recurrent bouts of diverticulitis. The common advice to avoid foods that may obstruct diverticula, such as nuts, small seeds, and popcorn, has recently been discredited.[5]

Box 95-4 Oral Antibiotic Therapy for Uncomplicated Diverticulitis

- Trimethoprim-sulfamethoxazole, one double-strength tablet bid, *and* metronidazole 500 mg q6h *or*
- Ciprofloxacin 750 mg bid *and* metronidazole 500 mg q6h *or*
- Amoxicillin-clavulanate extended-release, 1000/62.5 mg, two tablets bid

All oral regimens should be taken for 7 to 10 days.

From Gilbert DN, Moellering RC Jr, Eliopoulos GM, Chambers HF, Saag MS, (eds): The Sanford Guide to Antimicrobial Therapy, 41st ed. Sperryville, Va: Antimicrobial Therapy, 2011.

Box 95-5 Intravenous Antibiotic Coverage for Bowel Flora

Mild to Moderate Infection
- Ticarcillin-clavulanate 3.1 g IV q6h *or*
- Ciprofloxacin 400 mg IV q12h *and* metronidazole 1 g IV q12h

Severe Infection
- Ampicillin 2 g IV q6h *and* metronidazole 500 mg IV q6h *and* (gentamicin 7 mg/kg q24h *or* ciprofloxacin 400 mg IV q12h)
- Imipenem 500 mg IV q6h

From Gilbert DN, Moellering RC Jr, Eliopoulos GM, Chambers HF, Saag MS (eds): The Sanford Guide to Antimicrobial Therapy, 41st ed. Sperryville, Va: Antimicrobial Therapy, Inc; 2011.
IV, intravenously.

Uncomplicated Diverticulitis

Uncomplicated diverticulitis in an immunocompetent, nonelderly patient can be managed on an outpatient basis with oral antibiotics[11] (Box 95-4). Coverage for gram-negative aerobic and anaerobic bacteria is required. Patients may be placed on a liquid diet for comfort, although this is not mandatory. NSAIDs or narcotics are appropriate for pain control, but many experts recommend avoiding morphine sulfate because it increases intraintestinal pressure, which can theoretically precipitate perforation. A high-fiber diet prevents recurrent diverticulitis for 5 years in 70% of patients.

Patients with significant comorbid illness or other problems, including inability to tolerate oral liquids, poor social support, and inability to comply with follow-up in a reasonable time frame (2 to 3 days), should be considered for hospital admission. Hospitalized patients generally are treated with intravenous antibiotics (Box 95-5) and placed on bowel rest, although patients hospitalized for psychosocial reasons can be treated with oral medications.

Complicated Diverticulitis

Patients with complicated diverticulitis should be admitted to the hospital and treated with intravenous antibiotics and bowel rest. Emergent surgical intervention is indicated for all patients with peritonitis or perforation. Newer techniques that use a laparoscopic approach with lavage and biologic glue have supplanted open surgical techniques in some patients.[12] Continuing clinical decline, sepsis resistant to medical management, or a high level of suspicion for carcinoma warrants urgent surgical consultation.[6] Small abscesses (less than 5 cm in diameter) are treated with intravenous antibiotics alone (see Box 95-5), whereas larger abscesses are drained either percutaneously with imaging guidance or surgically.[13] Bowel obstruction during an attack of diverticulitis usually is self-limited and resolves with conservative management. Chronic recurrent diverticulitis can result in stricture, necessitating surgical intervention. Fistulae are usually repaired surgically

www.ketabpezeshki.com 66485457-66963820

but are typically not emergent.[5] A significantly dilated cecum (to greater than 10 cm in diameter) or gas in the bowel wall should prompt early consultation with a surgeon about the possibility of bowel necrosis and impending perforation.

Definitive Management

It is not known whether medical or dietary treatment is of benefit in diverticulitis. The only proven way to eradicate diverticula is to remove the affected segment of colon surgically. Most patients who recover from their first attack of diverticulitis are likely to remain asymptomatic for many years. With subsequent attacks, the likelihood of recurrence increases. Elective resection of diverticula generally is reserved for patients who have had more than one attack of diverticulitis. According to some experts, younger patients (i.e., younger than 40 years) should undergo elective resection after their first bout of diverticulitis because of concerns about a higher risk for a second attack, but this recommendation is controversial, with recent evidence suggesting that outcomes are better without surgery.[6] Most resections can be done laparoscopically with a single-stage procedure (no colostomy). Estimates on recurrence of diverticular disease after resection vary, ranging from 3 to 27%.[7,14]

Disposition

Uncomplicated Diverticulitis

Nonelderly and immunocompetent patients may be sent home on oral antibiotics with referral for follow-up evaluation in 2 to 3 days to determine the success of treatment. Patients are cautioned to return to the ED if their condition worsens. Patients not significantly improved at follow-up should undergo diagnostic imaging to look for an abscess and should be hospitalized for intravenous antibiotic therapy. Of patients treated medically for their first attack of diverticulitis, 95% remain symptom-free for the next 2 years, and 80 to 90% remain symptom-free permanently.[14] Patients with recurrent episodes of diverticulitis should be referred to a surgeon for outpatient consultation for elective resection. All patients should undergo an evaluation for colon cancer when the acute episode has resolved because the incidence of coexistent cancer has been reported to be as high as 9%.[9]

Complicated Diverticulitis

All patients require hospitalization for intravenous antibiotic therapy and bowel rest. Most patients (65-85%) recover with medical management alone; the rest require surgical intervention. Outcomes generally are good, with mortality rates ranging from 1 to 6% for all patients, increasing to 12 to 18% for patients requiring surgery.[4]

LARGE BOWEL OBSTRUCTION

Perspective

Large bowel obstruction (LBO) is much less common than small bowel obstruction, but LBO is a more ominous condition because it is frequently associated with malignant disease. One half of all operative cases involving LBO in the United States are the result of colorectal cancer, and up to 20% of patients with colon cancer will develop acute obstruction.[15] Adhesions, a common cause of small bowel obstruction, cause only a small number of LBOs. Other causes of LBO include volvulus, diverticular disease, fecal impaction, strictures (often related to inflammatory bowel disease [IBD] or chronic colon ischemia), adhesions, hernia, and pseudo-obstruction. Most causes are managed surgically, but pseudo-obstruction responds well to medical management alone.

Principles of Disease

When mechanical obstruction is secondary to an obstructing lesion, either inside the bowel (carcinoma) or outside the bowel (diverticular abscess, volvulus), the bowel becomes increasingly dilated with air and fluid that cannot be passed distally. As the distention increases, the intraluminal pressure increases. When intraluminal pressure approaches systolic blood pressure, blood flow to the bowel wall is compromised and edema sets in, with subsequent transudation of fluid into the lumen. Transudation along with decreased resorption of intraluminal fluid leads to dehydration. Eventually, as arterial flow to the bowel wall is compromised, ischemia and gangrene develop. Translocation of bacteria from compromised bowel can lead to sepsis. Perforation of the bowel wall follows if the process is not interrupted.

Pseudo-obstruction, also called *Ogilvie's syndrome,* occurs through a completely different mechanism. *Pseudo-obstruction* is defined as LBO in which no obstructing lesion can be identified. This condition usually is found in patients with significant acute comorbid conditions.[16] Patients typically have a history of significant spine or retroperitoneal trauma, severe electrolyte disturbances, or narcotic exposure. Although the exact mechanism is unknown, it is believed to involve malfunction of autonomic control of the bowel. Normal balance between parasympathetic and sympathetic input is disrupted, resulting in changes in motility that lead to obstruction. The pathophysiologic changes observed with pseudo-obstruction are the same as those described for mechanical obstruction.

Clinical Features

The typical presenting complaints in LBO are abdominal pain, abdominal distention, obstipation, and vomiting. The time frame within which these symptoms develop varies in accordance with the rapidity of onset of the obstruction. LBO associated with a volvulus can develop rapidly, whereas obstruction from cancer tends to be of gradual onset. Patients seen later in the course of obstruction may be significantly dehydrated. Significant fever or tachycardia should prompt an investigation for gangrene and perforation. A palpable abdominal mass may represent a tumor, an abscess, or simply distended bowel. A rectal examination is helpful to look for an obstructing rectal mass or a large volume of hard stool in the rectal vault consistent with fecal impaction.

Diagnostic Strategies

Electrolyte measurements may be helpful in guiding fluid and electrolyte replacement therapy. A significantly elevated white blood cell (WBC) count should raise suspicion for gangrenous bowel, whereas anemia suggests the possibility of colorectal cancer.

Plain Radiography

A distended colon is the hallmark of LBO (Fig. 95-1), although small bowel may be distended as well if the ileocecal valve is incompetent. In some cases, gas-filled small bowel may obscure visualization of the colon, leading to the misdiagnosis of small bowel obstruction. An abrupt cutoff at the distal end of the obstructed colonic segment suggests a possible pseudo-obstruction. A cecal diameter exceeding 12 cm is of concern because this finding is associated with a higher risk of perforation.[16] The actual location and cause of the LBO are usually not evident on plain films.

www.ketabpezeshki.com 66485457-66963820

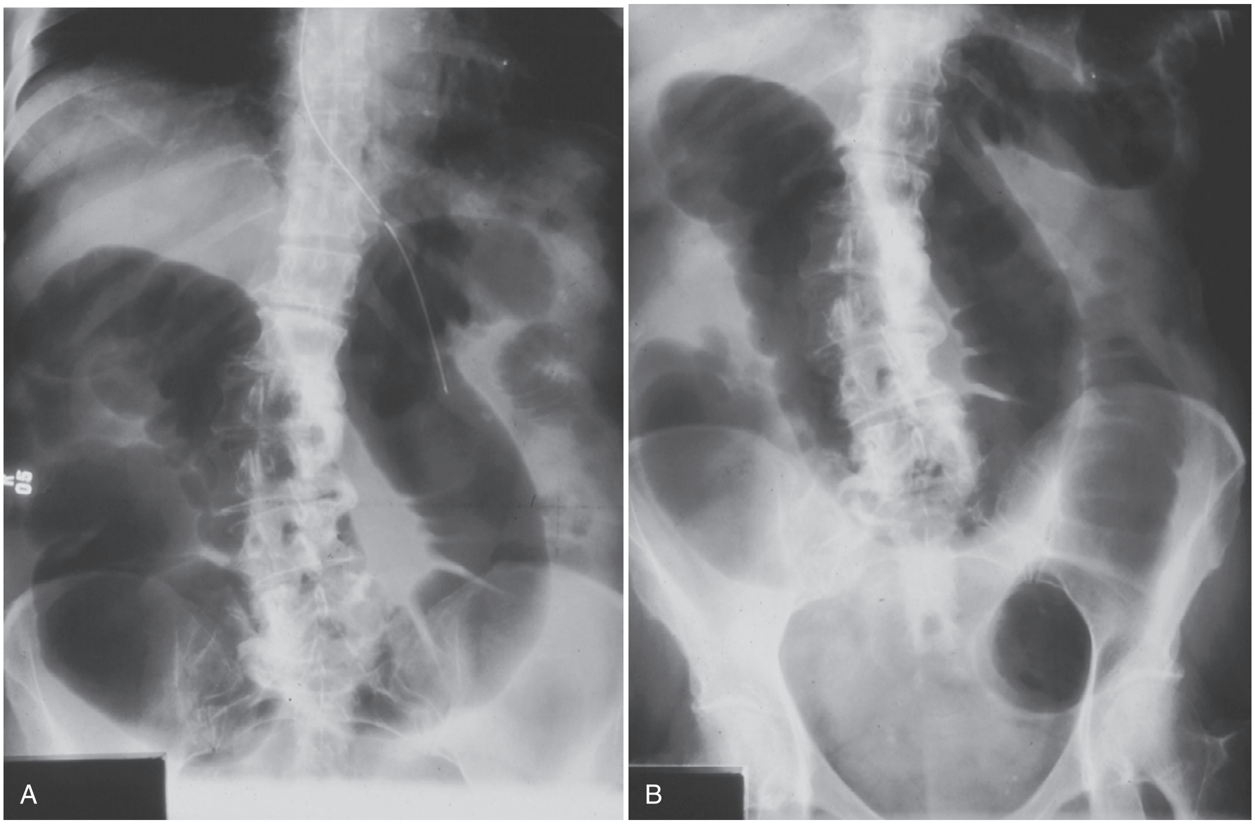


Figure 95-1. Plain radiographs showing large bowel obstruction at the sigmoid colon caused by carcinoma. **A,** Upright view. **B,** Supine view.

Computed Tomography

CT is a valuable tool for determining the cause of the obstruction, especially if the cause is a diverticular abscess or intussusception. CT typically is less helpful in pseudo-obstruction, in which either colonoscopy or a water-soluble contrast enema study is needed to make the diagnosis.

Colonoscopy and Water-Soluble Contrast Enema

Patients in whom the cause of obstruction is not known and who are not candidates for urgent surgical intervention should undergo either a water-soluble contrast enema study or colonoscopy to determine the cause of the obstruction. This diagnostic strategy is much more accurate in ruling out pseudo-obstruction than imaging.

Differential Considerations

The most common causes of LBO are colorectal cancer (53%), volvulus (17%), diverticulitis (12%), and compression from metastatic disease (6%). Other, less common causes are strictures, incarcerated hernia, fecal impaction, adhesions, and pseudo-obstruction.

Management

Management in the ED is directed at relief of symptoms. Rehydration, electrolyte replacement, and pain management are the first concerns. Gastric decompression with a nasogastric tube may be helpful in cases in which vomiting is prominent or when there is evidence of significant fluid or gas buildup in the small intestine. No additional fluid or solids should be administered by mouth. Antibiotics are indicated if gangrene or perforation is suspected (see Box 95-5). Definitive management depends on the cause of the obstruction. Select diverticular abscesses may be drained percutaneously, whereas a sigmoid volvulus or pseudo-obstruction can be decompressed endoscopically. Diverticular disease and sigmoid volvulus eventually necessitate an elective surgical procedure to prevent recurrence, although this often can be delayed. Carcinoma, cecal volvulus, strictures, intussusception, adhesions, and hernias are dealt with primarily surgically. In malignant obstruction of the left colon, placement of a stent can be done palliatively or as a bridge to surgery.[15]

As long as the possibility of perforation is not an immediate concern, pseudo-obstruction is managed for the first 24 hours with bowel rest, hydration, and management of any acute comorbid conditions. If the colon fails to decompress, colonoscopic or pharmacologic intervention (neostigmine) may be attempted, with surgery reserved for refractory cases.[16]

Fecal impaction is generally managed definitively in the ED by digital disimpaction or an enema. Particularly helpful are retention enemas, for which the patient retains the enema fluid in the rectum for 15 minutes or longer. Occasionally, disimpaction is technically difficult enough to warrant general anesthesia.

Disposition

Most cases of LBO require procedural intervention (surgical, endoscopic, or percutaneous abscess drainage) to achieve resolution. All patients require hospitalization and consultation with a specialist capable of performing the appropriate procedure. Emergent surgical consultation is warranted in patients with evidence of gangrenous bowel or perforation.

www.ketabpezeshki.com 66485457-66963820

VOLVULUS

Perspective

Volvulus of the colon occurs when a loop of bowel twists and obstructs the intestinal lumen. If severe enough, the twist may involve and compromise the vascular supply to the loop of colon. The incidence of colonic volvulus is 2.65 cases per 100,000 population per year, accounting for 1 to 7% of all LBOs.[17] Volvulus occurs in all age groups, but older adults are affected most often, with a mean age of 60 to 70 years. One third of cases in the developed world involve institutionalized patients.[17] Most cases are divided roughly equally between the sigmoid colon and the cecum, although volvulus can occur in all other areas of the colon. Sigmoid volvulus typically is a disease of older persons. Mortality rates with sigmoid volvulus exceed 50% in patients with gangrenous bowel. In the absence of gangrenous bowel, the risk of death is less than 5%.[17]

Principles of Disease

Sigmoid Volvulus

The anatomic requirement for a sigmoid volvulus is a long, redundant section of sigmoid that is attached to the abdominal wall by a narrow strip of mesentery. The narrow attachment allows the mesentery to twist on itself, thereby obstructing the intestinal lumen. It is not clear whether this is a congenital condition or occurs as part of the aging process, but the fact that sigmoid volvulus rarely occurs before the third decade suggests it is an acquired condition.[17] After the colon twists on itself, the proximal colon continues to force gas and liquid into the obstructed segment, causing a sometimes massive dilation of the distal colon. Significant electrolyte disturbances can occur secondary to third spacing, and respiratory compromise occasionally occurs from massive abdominal distention. If the condition is left untreated, the vascular supply can become compromised, resulting in gangrene and perforation. In one series, approximately 10% of patients developed gangrene of the affected segment.[18] The exact precipitator of an acute episode of volvulus is not clear. A high-fiber diet has been implicated, because a significant increase in the disease is noted in patients who are switched to a high-fiber diet. Chronic constipation has been associated with volvulus, but it is unclear how the two conditions are related. Residents of long-term care facilities and patients with neurologic or psychiatric diseases also are predisposed to sigmoid volvulus, possibly as a result of alterations in colonic motility. No association with previous surgery has been observed.

Cecal Volvulus

As in sigmoid volvulus, a mobile segment of cecum is a prerequisite to the disease. This mobility seems to be a result of a congenitally incomplete fusion of the cecal mesentery to the posterior abdominal wall. Cadaver studies show that 11 to 25% of the adult population have ceca that are mobile enough to cause torsion.[19] In 10% of the cases, cecal volvulus is a result of a variant called *cecal bascule,* in which the cecum does not twist but merely folds over on itself; symptoms and management are the same. The tendency for cecal volvulus may be related to "maneuvering room" available for the colon within the abdomen. Women seem to be at a higher risk for cecal volvulus during pregnancy, presumably because of crowding of the abdominal cavity by the enlarged uterus. The condition is still rare, however, occurring in approximately one per million pregnancies.[20] Gangrene of the bowel is common with cecal volvulus, occurring in 20% of patients.[18]

Clinical Features

Sigmoid Volvulus

The hallmark of sigmoid volvulus is the triad of abdominal pain, distention, and constipation. The extent to which the sigmoid colon can twist on itself is recognized to vary, so the presentation of sigmoid volvulus will vary accordingly, from subtle to dramatic. The clinical picture may range from one of minor abdominal discomfort that has been present for many days to an acute onset of severe abdominal pain associated with gross abdominal distention and unstable vital signs. Sometimes the diagnosis of sigmoid volvulus is not made until the patient has been hospitalized for some time. In many instances the history may be suggestive of previous episodes of volvulus that self-reduced. Diarrhea may be present in cases with incomplete obstruction.[17]

The physical examination may reveal a distended tympanitic abdomen, often with most of the distention in the upper abdomen but primarily on one side. Patients may look remarkably well for the amount of distention that is encountered. Significant abdominal pain, fever, lack of bowel sounds, peritonitis, or cardiovascular instability suggests gangrenous bowel and should prompt immediate surgical consultation. The absence of these findings does not exclude gangrene, however. The duration of symptoms alone is not predictive of gangrene of the bowel.

Cecal Volvulus

Though the vast majority of patients (90%) have abdominal pain, the clinical triad of abdominal pain, distention, and constipation is inconsistent.[18] Patterns of presentation vary on a spectrum similar to that for sigmoid volvulus.[19] Vomiting is seen in only about 50% of patients.

Diagnostic Strategies

Sigmoid Volvulus

The diagnosis of sigmoid volvulus can be made on the basis of findings on plain radiographs in most cases. A grossly distended loop of colon lacking haustral markings is typical and is seen just as often on the right side of the abdomen as on the left (Fig. 95-2). The bowel may have the appearance of a "bent inner tube." Free air may be seen on an upright chest radiograph or lateral decubitus radiograph of the abdomen in patients who have a perforation. Gas backing up into the rest of the colon may obscure the typical appearance of sigmoid volvulus on plain radiographs, leading to a significant number of nondiagnostic studies. Cecal volvulus and bowel obstruction from other causes may have a similar radiographic appearance. When the diagnosis is in doubt, contrast enema may be helpful. Contrast material fills up the colon to the tapering point of torsion, giving a "bird's beak" appearance to the column of contrast material (Fig. 95-3). Sigmoidoscopy is diagnostic in many cases, visualizing a spiral sphincter-like twist in the colonic mucosa.[21] CT scan, when used, is also highly accurate, but most diagnoses can be made without it.[21,22]

Cecal Volvulus

Plain radiographs often are helpful in establishing a diagnosis of cecal volvulus, but the findings are not definitive in 50% of cases. The cecum should be markedly dilated and may contain an air-fluid level. The small bowel often is distended as well. In contrast with the picture in sigmoid volvulus, the distal colon should have a paucity of gas (Fig. 95-4). The classic "coffee bean" sign, a large oval gas shadow with a line down the middle representing bowel bent over on itself, may be seen in the midabdomen. Free

www.ketabpezeshki.com 66485457-66963820

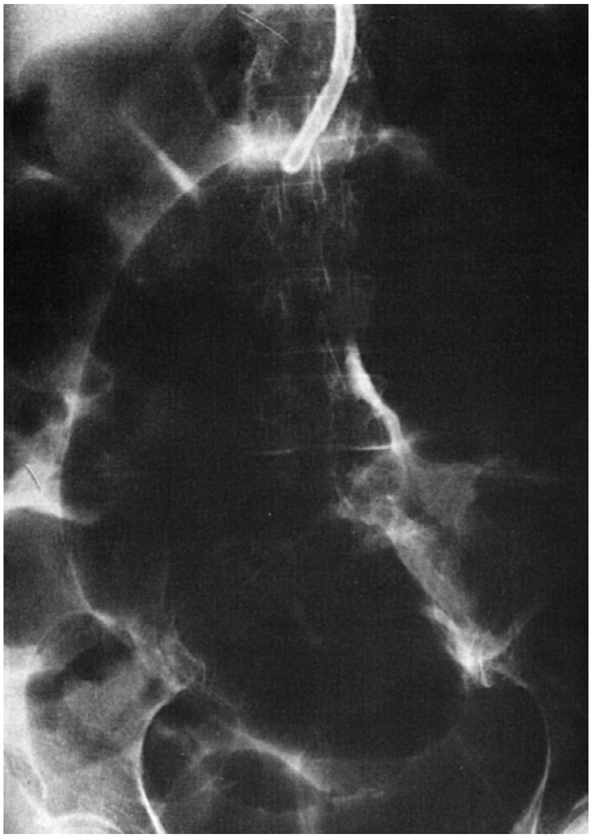


Figure 95-2. Plain film of abdomen shows a large dilated loop characteristic of sigmoid volvulus.

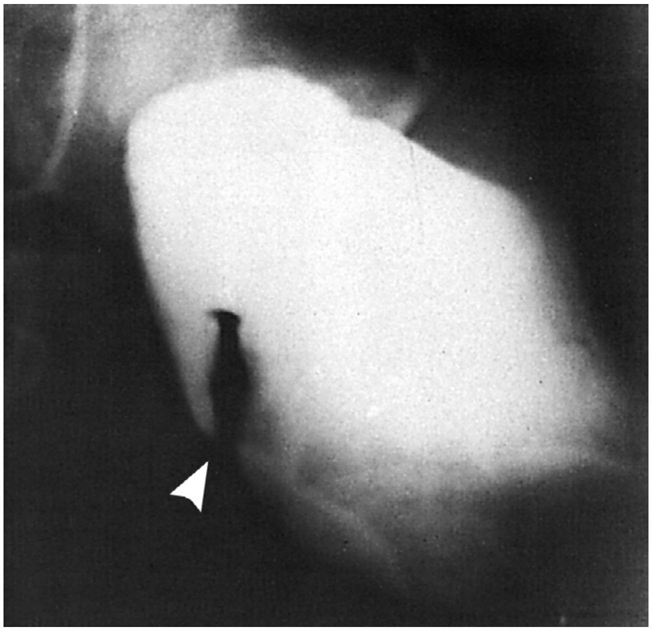


Figure 95-3. Characteristic "bird's beak" sign of volvulus *(arrowhead)* shown on this image from a barium enema study.

air suggests perforation and necessitates emergent surgical consultation. A common mistake is misinterpreting the plain radiograph as showing a sigmoid volvulus. If the diagnosis is unclear, a contrast enema is helpful in showing the site of torsion. Ultrasound imaging generally is unhelpful.[20] On CT, a mesocolon "whirl sign"

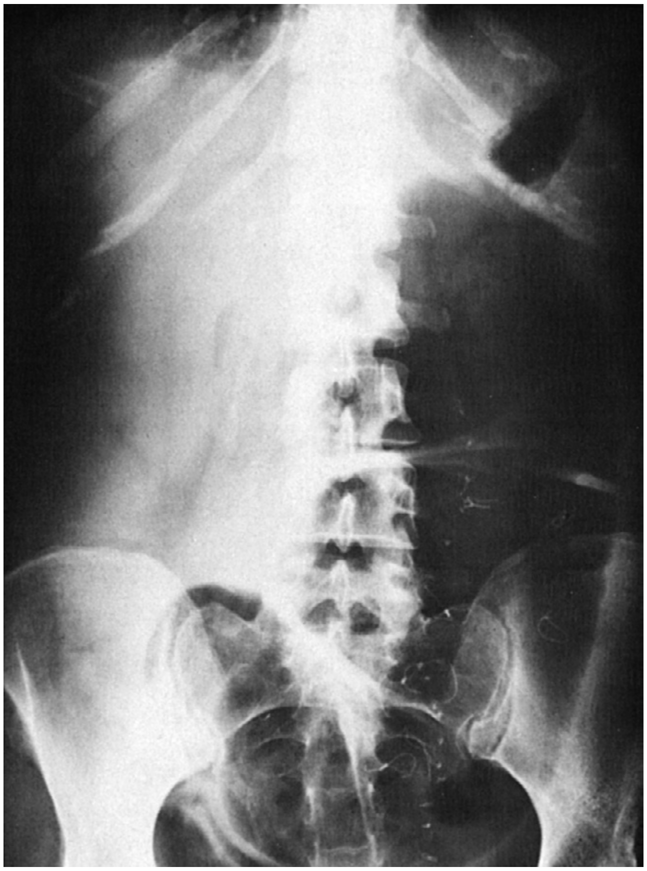


Figure 95-4. Plain radiograph shows distended colon characteristic of cecal volvulus. Note presentation in the left lower quadrant and absence of right-sided gas shadows.

may be seen, indicating a twisted segment of mesentery.[23] In many cases, cecal volvulus is definitively diagnosed only at surgery.[18]

Differential Considerations

Any process that causes LBO may mimic volvulus, including neoplastic disease, paralytic ileus, toxic megacolon, and pseudo-obstruction.

Management

Sigmoid Volvulus

Although spontaneous reduction of a sigmoid volvulus can occur, it is infrequent enough to mandate a proactive approach to treatment. If clinical evidence of gangrenous bowel is lacking, endoscopic detorsion should be attempted by an experienced operator. With the endoscope the bowel is first examined for any signs of gangrene. If the bowel is healthy, the twisted, obstructed proximal end of the bowel lumen is identified, and a lubricated flexible tube is inserted through the obstruction. With decompression of gas and liquid stool, the bowel is able to undergo self-detorsion. Endoscopic decompression is successful in 50 to 90% of cases.[21] If the patient has gangrenous bowel or the volvulus does not respond to endoscopic decompression, surgery is indicated. Recurrence rates are estimated at 60%; as a preventative, elective resection of the redundant sigmoid is recommended after resolution of the acute episode. The mortality rate for sigmoid volvulus is 20% overall and exceeds 50% in the subpopulation of patients with gangrene.

www.ketabpezeshki.com 66485457-66963820

Cecal Volvulus

The proximal nature of the cecum makes it unavailable for endoscopic manipulation; cecal volvulus requires resection of the cecum. Recurrence is rare after resection.[19]

Disposition

All patients with volvulus require hospitalization for surgical intervention.

INTUSSUSCEPTION

Perspective

Intussusception in adults is rare, accounting for only 1 to 5% of cases of adult bowel obstruction.[24] Most adult intussusceptions (80%) are of the small bowel. Although only 10% of children have a pathologic lesion as the cause of the intussusception, 90% of adults do. In the colon, these lesions are malignant 50 to 80% of the time, as opposed to in the small bowel, in which malignant lesions are present approximately one third of the time.[25] In adults, the intussusception is often unsuspected before being revealed on a CT scan or during laparotomy. The condition occurs over a wide variety of ages, with a mean age at presentation of 65 years.[26]

Principles of Disease

The exact mechanism of intussusception is unknown, but it is believed that a lesion (the "lead point") changes the motility properties of the intestine, allowing a proximal segment to invaginate into a more distal segment. As peristaltic activity pushes the invaginated segment along with its mesentery and mesenteric blood vessels distally down the bowel, the blood supply to the segment can be compromised, and ischemia may occur. Edema associated with the intussusception can lead to a mechanical obstruction of the bowel. In 8 to 20% of cases no lead point can be identified.[24]

Clinical Features

Intussusception in adults manifests in one of two patterns. The most common is that of acute partial intestinal obstruction. Less than 20% of intussusceptions cause complete obstruction.[27] With this pattern, the typical presenting complaint is abdominal pain. Vomiting, bleeding, and constipation may be present but often are not. The abdomen may be distended, and bowel sounds often are decreased. A mass is seldom palpated; the classic triad of abdominal pain, mass, and heme-positive stools noted in children is rarely found in adults. The second presentation is much more subtle, with intermittent abdominal pain for months or years. The diagnosis usually is made only when the pain becomes unrelenting or has been recurrent enough to prompt imaging.

DIAGNOSTIC STRATEGIES

Plain Radiography

Plain radiography is a reasonable screening test in a patient suspected of having bowel obstruction, but the radiographs usually show only nonspecific large bowel dilation.

Computed Tomography

Typically used in the evaluation of abdominal pain and bowel obstruction, CT is usually the most useful test in suspected intussusception but may not detect the actual intussusception in as many as one half of cases.[25,26]

Ultrasound Examination

Ultrasonography is helpful in detecting intussusception but is not as useful as CT in excluding other diagnoses. A transverse view of the intussusception has a donut or target shape, with multiple concentric rings. A longitudinal view of the intussuscepted segment has an ultrasound appearance similar to that of a kidney ("pseudo-kidney sign"), with a bright central area surrounded by a darker outer layer.

Barium Enema

Although a barium enema study can demonstrate intussusception and even reduce it, it is a less desirable study than either CT or ultrasound examination for initial diagnosis. In contrast to children, reduction of intussusception in adults is not desirable before surgery because of concerns about spreading malignant cells from potentially malignant lead points. Barium enema should not be performed in patients suspected of having a bowel perforation.

Colonoscopy

Colonoscopy is helpful in defining the lesion causing intussusception but does not usually detect the intussusception itself.

Differential Considerations

The differential diagnosis includes other causes of bowel obstruction.

Management

Surgery is required in most cases. ED care is supportive and aimed at optimizing fluid status, recognizing gangrene or perforation, administering antibiotics if compromised bowel is suspected, and securing surgical consultation in the appropriate time frame. Because of the high incidence of malignancy, reduction often is not attempted in adults before surgical exploration.[26] Occasionally, intussusception may resolve spontaneously, but an evaluation to exclude a pathologic lead point must still be undertaken.

Disposition

Because of the surgical nature of this disease, all patients require hospitalization. Operative mortality tends to be minimal.[25]

INFLAMMATORY BOWEL DISEASE

Perspective

IBD includes two clinically similar but distinct diseases: Crohn's disease (CD) and ulcerative colitis (UC). Both diseases are characterized by chronic and unpredictable relapsing inflammation of the gastrointestinal tract from causes that have not been definitively identified. Significant morbidity occurs from acute exacerbations of inflammation. It is estimated that more than 1 million people in the United States are affected by IBD.[25] Cases are divided approximately equally between CD and UC, with a combined annual incidence of approximately 10 cases per 100,000.[29] The long-term management of IBD is a complex, stepwise process that involves multiple medications and surgery. The goals of ED evaluation are to (1) recognize potential new cases of IBD, (2) consider and exclude serious complications in patients with IBD, and (3) identify those patients with IBD who need in-hospital care. Treatment plans are best developed in consultation with a physician experienced in the long-term management of IBD. Although life

www.ketabpezeshki.com 66485457-66963820

expectancy is slightly decreased for patients with CD, it is normal for patients with UC.[30]

Principles of Disease

Ulcerative Colitis

UC causes inflammation and ulceration throughout the colon and rectum but spares the small intestine. Inflammation is more superficial than that found in CD. Typically the inflammation exists as one continuous lesion originating in the rectum and extending a variable distance into the colon, although more recently cases of discontinuous disease ("skip lesions") similar to that in CD have been reported in UC.[31] The concordance rate between identical twins is low (6 to 14%), suggesting that factors other than genetics are involved in the development of UC.[32] Stress can trigger exacerbations, and cigarette smoking has a protective effect, suggesting environmental factors at work. Appendectomy at an early age is protective, suggesting that the immune system may play a role. In animal models of IBD, the disease does not occur in animals that are devoid of normal bowel flora, suggesting that bowel flora are a necessary ingredient for disease.[33] One unifying theory is that UC represents a genetic predisposition for the development of an inflammatory reaction to normal intestinal flora—in essence, loss of the normal tolerance to these bacteria.

Crohn's Disease

The cause of CD is unknown, but genetic, environmental, immunologic, and infectious processes have all been implicated as possible causative or contributory factors.[29] Concordance between identical twins is 45 to 50%, suggesting a strong genetic predisposition that is modified by other factors.[32] Africans have a low incidence of CD, but African Americans have an incidence similar to that in white Americans.[29] The first genetic mutation associated with CD was described in 2001 and is associated with 10 to 20% of cases of CD.[31] Although the onset of the disease can occur at any time of life, CD affects primarily young patients, with onset of disease typically in the teens and 20s. Inflammation in CD is deep, involving the entire colonic wall. The disease is not limited to the colon and rectum as it is in UC but may affect any part of the gastrointestinal tract. CD most often involves the distal small intestine and colon and less commonly the esophagus, duodenum, or stomach. Because of the transmural nature of the inflammation, the development of intestinal strictures or fistulae to adjacent organs is a potential complication.

Clinical Features

Typical presenting complaints in patients with IBD include abdominal pain, often crampy, and tenesmus with loose or diarrheal stools. Blood may be present in the stool. Patients with CD may have a history of nocturnal diarrhea, a complaint that helps differentiate CD from patients who have IBS. Weight loss is common. The physical examination may reveal significant abdominal tenderness or an abdominal mass representing an abscess. Patients with CD may have fissures, ulcerated hemorrhoids, strictures, or cutaneous abscesses around the anus. Extraintestinal manifestations include inflammatory conditions of the skin, eyes, joints, spine (ankylosing spondylitis), and liver (primary sclerosing cholangitis).[34] In children, growth and sexual development may be affected. Onset of symptoms usually occurs before the age of 30 years,[28] although the diagnosis can be difficult to make in the early stages.

Patients often come to the ED with a known diagnosis of IBD and worsening abdominal symptoms. A common reason for relapse is interruption of the medications that have kept the disease in remission. Many patients become complacent during quiescent periods and stop taking such medications. IBD requires continuous, lifelong maintenance therapy. Adherence to therapy has been shown to reduce the risk of acute attacks and cancer.[28] Common complications of IBD include formation of fistulae, strictures, and abscesses; less common but life-threatening complications include fulminant colitis, toxic megacolon, and intestinal perforation.

Toxic Megacolon

Toxic megacolon is a pathologic dilation of the colon resulting from inflammation of the smooth muscle layers of the intestine. Muscle inflammation leads to paralysis, dilation, and eventually perforation if left untreated. The hallmark of toxic megacolon is colonic dilation in a patient with a known inflammatory condition of the colon who appears systemically toxic. Presence of inflammation and toxicity differentiates toxic megacolon from other disorders that cause colon dilation, including mechanical obstruction, pseudo-obstruction, and congenital or acquired megacolon.

Toxic megacolon is typically associated with IBD or infectious colitis. The triggering event may be recent ingestion of anticholinergics, antimotility agents, narcotics, or antidepressants. Patients usually have experienced symptoms of colitis, often severe, for several days before the onset of toxic megacolon. Abdominal pain, fever, tachycardia, and abdominal distention are present. Plain radiographs are diagnostic and show a colon with a diameter of 6 cm or greater, although this feature may not be present in early stages. Treatment includes aggressive fluid hydration, intravenous corticosteroids, antibiotics covering bowel flora (see Box 95-5), and an evaluation for potential intestinal infections, especially in immunocompromised patients. Hypokalemia or hypomagnesemia should be aggressively corrected if present, as it can exacerbate colonic dilation.[34] The mortality rate has decreased over the past four decades to less than 2% as a result of early recognition and aggressive treatment.

Diagnostic Strategies

No specific laboratory tests to diagnose IBD are available, although recent tests targeting antibodies to *Saccharomyces cerevisiae* or antineutrophil cytoplasm help to differentiate between CD and UC.[30] Laboratory abnormalities may occur for a variety of reasons. Electrolyte abnormalities may be secondary to significant diarrhea, or anemia may occur from bloody stools. The erythrocyte sedimentation rate can be elevated and useful for categorizing the severity of the disease. Stools contain fecal leukocytes, but findings on stool cultures and ova and parasite examinations should be normal.

Plain radiography is not helpful in the diagnosis of uncomplicated disease but may show bowel obstruction, toxic megacolon, or free air from a perforation (Fig. 95-5). The use of plain radiographs should be limited to patients suspected of having these complications. Contrast studies can reveal lesions suggestive of IBD, including ulcerations of the mucosal surface, fistulae, and strictures. In Europe, where ultrasound technicians are more experienced in its application, ultrasonography is used to identify active disease and to look for complications.[31] Ultrasound imaging is used much less commonly in the United States. Magnetic resonance imaging can locate affected bowel segments and identify fistulae, stenoses, and abscesses and has the advantage of no radiation, which is a consideration in individuals likely to get multiple imaging studies over time. CT is the best study routinely available to evaluate extraluminal complications. CT colonography ("virtual colonoscopy"), although good for identifying cancerous lesions of the colon, does not show the typical lesions of IBD.[31] Recently,

www.ketabpezeshki.com 66485457-66963820

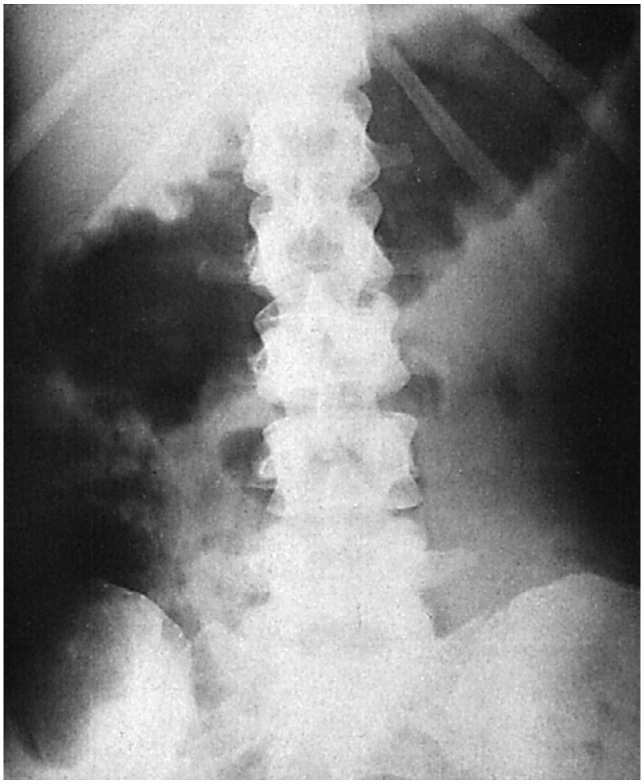


Figure 95-5. Toxic megacolon secondary to ulcerative colitis. The smooth indentations seen along the margin of the colon represent pseudopolyps.

video capsule endoscopy (VCE) has shown promise in finding small bowel pathology missed by other studies. VCE has the drawback that capsules may get stuck at stricture sites and need to be surgically removed.[35] Endoscopic evaluation with biopsy is usually required to confirm the diagnosis.[30]

Differential Considerations

Symptoms and signs are protean and overlap with those of many common abdominal conditions, including appendicitis, infectious colitis, ischemic colitis, radiation colitis, diverticular disease, cancer, and bowel obstruction. Intestinal infections commonly mimic the symptoms of IBD, and in new patients microbiologic studies for bacterial infection, including *Escherichia coli* O157 : H7, *Clostridium difficile,* and amoeba should be considered. Established patients who have recently been hospitalized or on antibiotics should be tested for *C. difficile.* Several assays may be required owing to the high false-negative rate for testing.[34]

Management

Medical management is the mainstay of therapy for most patients with IBD. In general, patients are maintained on 5-aminosalicylic acid (5-ASA) agents while asymptomatic and placed on steroids if symptoms recur. Once remission is achieved, steroids are discontinued and the patient is once more maintained on 5-ASA agents. If remission is not achieved with steroids, other agents such as antimetabolites and immunosuppressants are used (Box 95-6). The choice of agents depends on classification of the disease as mild, moderate, or severe (Box 95-7). Surgery is reserved for patients with severe disease who do not respond to medical therapy or for complications such as obstruction or fistula formation. This classic stepwise approach has recently been challenged by evidence that early initiation of immunosuppressants or antibody therapy leads to a more sustained remission and less need for surgical intervention, although this is still controversial.[36]

5-ASA agents are the first line of therapy for disease that is not severe. These agents can be administered orally, or rectally if the disease is in or near the rectum. Sulfasalazine, one of the original drugs in this category, is limited by sulfa toxicity at higher doses

Box 95-6 Medications Used in the Treatment of Inflammatory Bowel Disease

5-Aminosalicylic Acid Agents
Sulfasalazine
Mesalamine

Antibiotics
Metronidazole
Ciprofloxacin
Rifaximin
Tobramycin

Corticosteroids
Prednisone
Hydrocortisone
Methylprednisolone
Budesonide

Antimetabolites
Azathioprine
6-Mercaptopurine
Methotrexate

Immunosuppressant
Cyclosporine

Anti–Tumor Necrosis Factor Antibody
Infliximab

Box 95-7 Disease Severity Criteria in Inflammatory Bowel Disease

Ulcerative Colitis

Mild Disease
- Fewer than four stools per day
- Stools may contain some blood
- No systemic signs of toxicity (fever, tachycardia, anemia, elevated erythrocyte sedimentation rate)

Moderate Disease
- More than four stools per day
- Minimal signs of toxicity

Severe Disease
- More than six bloody stools per day
- Signs of systemic toxicity

Crohn's Disease

Mild to Moderate Disease
- Patient ambulatory and able to eat
- No dehydration
- No toxicity
- No significant abdominal pain or mass
- Weight loss of 10%

Moderate to Severe Disease (Any of the Following)
- Mild disease that has failed to respond to treatment
- Patient may have some systemic toxicity, significant weight loss, anemia
- Fever, some abdominal pain or tenderness, intermittent nausea or vomiting

Severe Disease
- Persistence of symptoms during corticosteroid or biologic (e.g., infliximab) therapy
- High fever, persistent vomiting
- Intestinal obstruction
- Rebound tenderness
- Cachexia
- Abscess

Adapted from Hanauer SB, Present DH: The state of the art in the management of inflammatory bowel disease. Rev Gastroenterol Disord 3:81, 2003, and Lichtenstein GR, Hanauer SB, Sandborn WJ: Management of Crohn's disease in adults. Am J Gastroenterol 104:465-483, 2009.

www.ketabpezeshki.com 66485457-66963820

and has serious side effects including nausea, vomiting, anorexia, headache, and rarer conditions such as bone marrow suppression, pancreatitis, hepatotoxicity, anemia, and interstitial nephritis. A newer 5-ASA derivative, mesalamine, has less toxicity, allowing higher dosages. When IBD goes into remission after an acute flare, the patient may be continued on 5-ASA derivatives for maintenance therapy.

Antibiotics may be used for the primary treatment of IBD as well, but their use is controversial. Evidence supporting antibiotic use is stronger in CD than in UC. Metronidazole and ciprofloxacin are the most common antibiotics used, with some evidence suggesting that tobramycin or rifaximin may be beneficial as well.[37]

Oral corticosteroids are used in patients with moderate to severe disease or patients whose IBD is unresponsive to a 5-ASA agent. Steroids should be tapered when remission is achieved to avoid typical steroid side effects. Intravenous corticosteroids are reserved for hospitalized patients with severe disease. Budesonide, a newer oral corticosteroid, is degraded on its first pass through the bloodstream and has fewer systemic side effects. Prolonged use of steroids can lead to gastrointestinal mucosal injury, problems with wound healing, osteopenia with fractures, and frank osteonecrosis that may be evident only on MRI.[34]

The immunomodulating drugs azathioprine and 6-mercaptopurine are used in patients resistant to other therapies or to wean steroid-dependent patients. Patients on these medications should be assessed for bone marrow suppression and pancreatitis.[38]

The immunosuppressant agent cyclosporine is used in severe cases, often when patients are not surgical candidates. Although most patients tolerate it well, cyclosporine has significant potential toxicity, including myelosuppression, electrolyte disturbances, and hepatic and nephrotoxicity.[28] Opportunistic infections including *Pneumocystis* pneumonia have been known to occur.[32]

Infliximab, an antibody to human tumor necrosis factor alpha, is useful in advanced cases of IBD. It generally has a benign side effect profile but carries an increased risk of opportunistic infections, including tuberculosis and fungal infections.[29] Of patients receiving infliximab, 1 to 2% will experience serum sickness–like symptoms including arthralgias, myalgias, fevers, and rash.[34] Surgery is reserved for patients with severe disease refractory to medical management and for patients with complications such as intestinal obstruction, significant bleeding, abscess, or fistula. A colectomy is curative for UC and improves quality of life, but there is no curative surgery for CD. Extraintestinal manifestations usually respond to therapy for intestinal disease.[30,39]

Disposition

Consultation with a gastroenterologist is recommended before patient disposition. Most patients with an uncomplicated mild-to-moderate exacerbation of IBD need only restart their maintenance therapy if it was interrupted, or add oral corticosteroids to their regimen. Patients with severe disease or those in whom oral corticosteroids have failed to effect improvement need hospitalization for administration of parenteral corticosteroids.[30] Bowel rest does not seem to be beneficial except as preparation for surgical intervention.[40] Emergent surgical consultation should be sought for life-threatening hemorrhage, evidence of perforation, or toxic megacolon. Urgent (not emergent) surgical intervention is indicated if the bowel is obstructed. Abscesses may be treated percutaneously with imaging guidance or surgically. Chronic fistulae initially are treated medically.[38] After hospital discharge, close follow-up by the physician monitoring the patient's disease is indicated to ensure that remission is achieved in a timely fashion and that the patient complies with the suppressive therapy after the acute event. For patients in remission, endoscopic monitoring for cancer is required on an ongoing basis, although the optimal frequency of examination has not yet been defined.[38] The estimated prevalence of cancer among patients with CD is significant at 2%, and patients with UC have a 15 times greater risk for the development of colorectal cancer than the general population.[32] Up to 25% of patients with UC will eventually require colectomy for uncontrolled disease.[36]

COLONIC ISCHEMIA

Perspective

Colonic ischemia is the most common of the intestinal ischemic disorders and yet remains poorly understood.[41] Estimates place the incidence of colonic ischemia at 1 of every 2000 hospitalizations. Its presentation overlaps with that of many other significant abdominal diseases, and the disorder is difficult to diagnose without endoscopic visualization of the colonic mucosa. Although elders are most at risk, with 90% of cases occurring in those older than 60 years, the condition can occur in all age groups.[42] Both sexes are equally affected. In one study more than 50% of persons admitted with colonic ischemia were initially diagnosed with IBD. Because there is no specific treatment, outcomes usually are good and recurrences are rare; difficulty in making the diagnosis does not result in significant morbidity.

Principles of Disease

The exact cause of colonic ischemia is unknown. Isolated ischemia without small bowel involvement usually is a result of nonocclusive microvascular disease of the colon and not large vessel (mesenteric artery) occlusion. The primary insult is a low–blood-flow state associated with a variety of factors, including congestive heart failure, vasoactive drugs, atherosclerosis, renal failure, and recent cardiac or vascular surgery.[42-44] Factors that have recently been implicated are infections, especially *E. coli* O157 : H7, and thrombophilia.[41] Younger patients may develop colonic ischemia in the setting of collagen vascular disease, hematologic disorders, long-distance running, or cocaine abuse. Medications associated with colonic ischemia through a variety of mechanisms include digoxin, pseudoephedrine, and sumatriptan, among others. The colonic vascular system generally enjoys significant collateral flow, but in some patients this protective mechanism is tenuous, predisposing the affected person to ischemia from low-flow events.[42] In addition, colonic arterioles seem to be particularly sensitive to vasoconstrictive influences, and the rapidly growing intestinal mucosa is especially vulnerable to interruptions in blood flow. High intraluminal pressures that normally develop within the colon can also alter intestinal perfusion significantly. Colonic ischemia can occur in any part of the colon, including the rectum, but for unknown reasons it occurs most often in the left colonic segment.

Colonic ischemia represents a spectrum of disease whose manifestations vary with the extent of the ischemic insult. In most cases the ischemic episode is self-limited, and the condition resolves completely with conservative therapy, but in one third of patients a prolonged or severe insult results in scarring or stricturing of the colon and chronic symptoms.[42] If the ischemia is transmural, gangrene and intestinal perforation are possibilities. Chronic mild inflammation results in intermittent symptoms similar to those of IBD.

Clinical Features

The presentation of colonic ischemia typically involves the acute onset of mild crampy abdominal pain in the left lower quadrant with abdominal distention and almost always blood in the stool.[45] The typical patient has had recent surgery or has a significant medical illness. Some patients do not have pain. Nausea and

www.ketabpezeshki.com 66485457-66963820

vomiting can occur with obstruction secondary to a stricture or an ileus. Tenderness over the affected colon may be present but often is not dramatic. Peritoneal findings, fever, and a significantly elevated WBC count suggest gangrenous bowel and perforation. Toxic megacolon is a recognized complication.

Diagnostic Strategies

No sensitive or specific biochemical markers for colonic ischemia are recognized, although biochemical abnormalities such as elevated serum lactate, phosphate, and alkaline phosphate levels may be present. These abnormalities may be absent in milder disease and are often not observed in more significant disease until after irreversible damage has occurred. A complete blood count to exclude significant anemia and to look for a leukocytosis suggestive of perforation is appropriate. Serum electrolytes should be checked if diarrhea or vomiting has been significant or prolonged. Blood and WBCs in the stool are common findings in several of the entities that present similarly to colonic ischemia, including IBD and infectious colitis. A positive occult stool guaiac test result should ensure that the patient is eventually evaluated for colonic carcinoma. Unfortunately, the definitive diagnosis of colonic ischemia rarely is made in the ED.[42]

Plain Radiography

Plain radiographs often show only nonspecific dilated bowel. Findings specific for colonic ischemia occur in only 20% of patients. The classic findings are intraluminal prominences, known as *thumbprinting*, representing submucosal hemorrhage and swelling. Thumbprinting can also be seen with other disorders, including IBD, colonic infections, and hemorrhage secondary to anticoagulants. Other findings consistent with colonic ischemia include wall thickening and ahaustral segments. Air in the portal venous system or bowel wall suggests imminent intestinal infarction.

Barium Enema

Thumbprinting is detected more often by barium enema than by plain radiography, but barium enemas have largely been replaced by colonoscopy.

Colonoscopy

Colonoscopy with colonic biopsy is the preferred method to diagnose colonic ischemia because it visualizes the abnormal colonic mucosa better than barium enema and affords the opportunity to take biopsy specimens to differentiate between cancer and other nonischemic causes of colitis. Colonoscopy can also detect necrotic bowel by its distinct cyanotic or black appearance. If colonoscopy is delayed, pathologic changes consistent with colonic ischemia may have already improved or resolved. The diagnosis may be missed on colonoscopy in up to one third of cases.[43]

Computed Tomography

Although CT does not allow the definitive diagnosis of colonic ischemia, it can exclude other disorders. CT features suggestive of colonic ischemia include thumbprinting, wall thickening, and luminal narrowing and inner wall hypoperfusion ("double halo sign").[42]

Angiography

Angiography is usually not helpful in either the diagnosis or the management of colonic ischemia. In most cases the blood flow defect is at the microvascular level and has resolved by the time the patient seeks evaluation.[46] The exception is the case in which only the ascending colon is affected, suggesting a superior mesenteric artery thrombosis.

Differential Considerations

The symptoms of colonic ischemia are nonspecific and overlap with those of numerous other disorders including IBD, radiation proctocolitis, infectious colitis, and other causes of nonprofuse lower gastrointestinal bleeding. If strictures are present, the possibility of diverticulitis or colon cancer should be considered.

Management

In the absence of surgical complications, the treatment of colonic ischemia is supportive and includes hospitalization for bowel rest, hydration, and pain management, with some authors recommending antibiotic coverage.[42] NSAIDs are best avoided, as are oral cathartics or bowel preparation regimens that may lead to perforation. Broad-spectrum antibiotics covering bowel flora are indicated for patients with more significant symptoms (see Box 95-5). If colonic ischemia is precipitated by an episode of hypotension, the underlying cause of the hypotension must be sought and treated aggressively, and cardiac output should be maximized.[42] Vasopressors should be avoided to prevent worsening of ischemia; steroids should also be avoided because they may facilitate bowel perforation. Colonic distention, if present, can be relieved acutely through the use of a rectal tube; surgical consultation is recommended in these cases. Decompression of the colon may result in a lowering of transmural pressure and improved colonic perfusion. Sepsis, peritoneal changes, free abdominal air, significant fever, massive bleeding, and a significant leukocytosis suggest bowel necrosis or perforation and should prompt emergent surgical consultation.[42,44]

Disposition

Patients with mild symptoms and no significant abdominal tenderness or bleeding can be managed on an outpatient basis and referred for colonoscopy. Stool studies including cultures for bacteria, microscopy to look for ova and parasites, and a *C. difficile* titer are helpful if the diagnosis is uncertain. Patients with more significant findings, especially if the diagnosis of gangrenous bowel cannot be excluded, require hospitalization. A high mortality rate (60%) is expected for patients undergoing emergent surgery, although deaths before the age of 50 years are rare.[44] Most patients improve without surgical intervention, and only 5% have a recurrence of colonic ischemia. In those with continuing significant symptoms, colectomy is usually curative.

RADIATION PROCTOCOLITIS

Perspective

Radiation proctocolitis is a common side effect of radiation therapy, occurring in 50 to 75% of patients receiving radiation to the pelvis. The disease has two distinct presentations: acute and chronic. Acute radiation proctocolitis begins during or shortly after a course of radiation therapy, is usually easily diagnosed, and is self-limited. Chronic radiation proctocolitis occurs in 5 to 10% of patients who have undergone pelvic radiation therapy and typically begins any time up to 2 years after the end of radiation therapy, although onset of clinical manifestations may be delayed beyond 2 years.[48] Some cases have occurred decades later. Patients with more severe acute radiation proctocolitis seem to be prone to chronic proctocolitis.[49] Because of its nonspecific presentation

www.ketabpezeshki.com 66485457-66963820

and delayed appearance, the diagnosis of chronic radiation proctocolitis can be challenging. Unfortunately there is a paucity of robust research evaluating the best approach to management of this disorder.[50]

Principles of Disease

Radiation causes tissue injury through the creation of oxygen free radicals, which damage cellular DNA. The faster the growth rate of cells, the more DNA damage affects their function. For this reason, radiation is an effective treatment for neoplastic disease, but it also damages rapidly growing normal tissue, such as intestinal epithelium. Radiation damage also may adversely affect anal sphincter function, leading to bowel incontinence.

Acute Radiation Proctocolitis

Intestinal epithelium normally is sloughed and replaced at a rapid rate. After the start of radiation therapy, growth of replacement epithelium is slowed, but sloughing continues at the preexposure rate. This mismatch leads to gaps in the epithelium, which over time coalesce into ulcerations. In addition, edema and inflammatory changes of the submucosa cause excessive mucus secretion and bleeding. When radiation therapy has ended, the cycle of damage stops, and healing occurs over the next few weeks.

Chronic Radiation Proctocolitis

The pathologic mechanism in chronic radiation proctocolitis is entirely different from that in acute radiation proctocolitis. Chronic radiation proctocolitis results from a progressive endarteritis with abnormal tissue collagen deposition. Affected intestine has a decreased microvascular density, with subsequent decreased perfusion.[51] Over time, affected bowel gradually becomes more ischemic, leading to ulceration, scarring, and narrowing of the bowel lumen. Frank necrosis and perforation, although uncommon, can occur. Long-term outcomes in chronic radiation proctocolitis have not been well studied, but it seems that patients in whom fistulae and persistent bleeding strictures develop have the poorest prognosis.[49]

Clinical Features

Acute radiation proctocolitis manifests with abdominal pain, bleeding, and tenesmus. Onset during the course of radiation therapy, typically after several treatments, suggests the diagnosis. Fecal urgency and incontinence can be devastating to quality of life.[51]

Chronic radiation proctocolitis has a more insidious onset with a variety of presentations, including ulcerative disease, stricture with or without obstruction, fistulae, and bowel perforation. Symptoms may be similar to those in acute disease, with tenesmus, diarrhea, and urgency. Bleeding is common but usually is not hemodynamically significant. Decreased caliber of stool with increased straining or constipation suggests a stricture. Fistulae can develop between affected bowel and any adjacent organ, but the most common fistulae are rectovaginal. Some patients may exhibit anal sphincter dysfunction and loss of bowel control. Symptoms tend to have a significant negative impact on the quality of life.[49]

Diagnostic Strategies

The diagnosis of acute radiation proctocolitis is made clinically on the basis of the development of typical symptoms in the setting of radiation therapy. Further evaluation is usually not warranted.

Chronic radiation proctocolitis typically is a diagnosis of exclusion. Endoscopy can be suggestive, revealing pale, thickened, and friable mucosa with prominent telangiectasias. Biopsy specimens often show only nonspecific chronic inflammation. In some cases, endoscopy may be technically difficult because of scarring and reduced mobility of the intestine. Barium enema is an acceptable alternative when endoscopy is problematic, as long as bowel perforation is not a concern.

Differential Considerations

In chronic radiation proctocolitis, the possibility that symptoms are a result of recurrence of the initial malignancy or a new malignancy induced by radiation exposure must be entertained. Symptoms of chronic radiation proctocolitis generally are clinically indistinguishable from those of other causes of bowel inflammation, including IBD, infectious colitis, and ischemic colitis.[52]

Management

Treatment of acute radiation proctocolitis is symptomatic, and a therapeutic plan should be developed in conjunction with the patient's radiation therapist. Steroid enemas to reduce inflammation and water-absorbing stool softeners to reduce mucus-containing diarrhea are helpful. Reduction of the daily radiation dose also can reduce symptoms significantly.

Chronic radiation proctocolitis treatment also is symptomatic. If rectal involvement is significant, stool softeners, analgesics, anti-inflammatory agents (e.g., sulfasalazine, balsalazide), and sucralfate enemas are helpful. Metronidazole is beneficial when added to anti-inflammatory therapy. Continued rectal bleeding can be controlled with topical formalin or laser photocoagulation.[50] Minimally symptomatic strictures can be managed initially with stool softeners and enemas as needed. Some strictures have a reversible edema component, so the extent of narrowing may lessen after treatment. Fistulae and significant strictures generally require surgical repair. Approximately 20% of all patients with chronic radiation injury to the intestinal tract require some type of surgical intervention. Biopsy specimens from ulcerations associated with chronic injury should be obtained to exclude malignancy.

Disposition

Suspected perforation mandates emergent surgical consultation, and signs of bowel obstruction should prompt urgent surgical consultation. Unless symptoms are severe, patients with acute or chronic radiation proctocolitis can usually be managed on an outpatient basis under the care of their radiation therapist or gastroenterologist. With acute disease, symptoms typically resolve several weeks after radiation treatments have been completed. Mild chronic disease typically resolves with medical therapy, but more severe symptoms often require aggressive intervention.

KEY CONCEPTS

- New or atypical symptoms in a patient with known IBS should prompt an evaluation for other abdominal pathology.
- A new diagnosis of IBS should be left to the primary care setting; the purpose of the ED evaluation is to exclude other abdominal disorders.
- A positive result on testing for fecal occult blood should never be assumed to be caused by diverticula. An appropriate investigation to exclude malignancy is essential.
- Uncomplicated diverticulitis can be diagnosed and treated without imaging in many patients.

www.ketabpezeshki.com 66485457-66963820

- An LBO should prompt an evaluation for malignancy.
- Gangrene or perforation should be suspected in any patient with persistent unexplained tachycardia, fever, or remarkable abdominal tenderness that is associated with intestinal disease.
- Volvulus often appears as a nonspecific large bowel obstruction on plain radiographs.
- Although typically a disease of older persons, volvulus can occur at any age.
- Intussusception in adults most commonly is associated with a significant cause, often a malignancy.
- Intussusception in adults usually manifests as a partial small bowel obstruction and rarely is associated with the classic triad of abdominal pain, mass, and heme-positive stool that is seen in children.
- IBD is a lifelong relapsing disorder that can be treated with a variety of therapies. Management decisions are best made in consultation with the physician who will be providing ongoing care for the patient.
- Treatment of uncomplicated IBD depends on the clinical classification of disease severity (see Box 95-7).
- A new diagnosis of IBD in an elderly patient should be made only after the exclusion of colonic ischemia.
- Chronic radiation proctocolitis should be considered in any patient with a history of irradiation of the pelvis or abdomen who has symptoms of gastrointestinal inflammation. This is true regardless of how long ago the radiation therapy was received.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. American College of Gastroenterology Functional Gastrointestinal Disorders Task Force: Evidence-based position statement on the management of irritable bowel syndrome in North America. *Am J Gastroenterol* 2002; 97:S1.
2. Khan S, Chang L: Diagnosis and management of IBS. *Nat Rev Gastroenterol Hepatol* 2010; 7:565.
3. Agrawal A, Whorwell PJ: Irritable bowel syndrome: Diagnosis and management. *BMJ* 2006; 332:280.
4. Mimura T, Emanuel A, Kamm MA: Pathophysiology of diverticular disease. *Best Pract Res Clin Gastroenterol* 2002; 16:563.
5. Hall J, Hammerich K, Roberts P: New paradigms in the management of diverticular disease. *Curr Probl Surg* 2010; 47:680.
6. Janes SE, Meagher A, Frizelle FA: Management of diverticulitis. *BMJ* 2006; 332:271.
7. Fearnhead NS, Mortensen NJ: Clinical features and differential diagnosis of diverticular disease. *Best Pract Res Clin Gastroenterol* 2002; 16:577.
8. Halligan S, Saunders B: Imaging diverticular disease. *Best Pract Res Clin Gastroenterol* 2002; 16:595.
9. Wong WD, et al: Practice parameters for the treatment of sigmoid diverticulitis—supporting documentation. The Standards Task Force. The American Society of Colon and Rectal Surgeons. *Dis Colon Rectum* 2000; 43:290.
10. Buchanan GN, Kenefick NJ, Cohen CR: Diverticulitis. *Best Pract Res Clin Gastroenterol* 2002; 16:635.
11. Rafferty J, et al: Practice parameters for sigmoid diverticulitis. *Dis Colon Rectum* 2006; 49:939.
12. O'Riordan JM, O'Connell PR: Practice parameters for sigmoid diverticulitis. *Dis Colon Rectum* 2007; 50:402.
13. Ambrosetti P, Chautems R, Soravia C, Peiris-Waser N, Terrier F: Long-term outcome of mesocolic and pelvic diverticular abscesses of the left colon: A prospective study of 73 cases. *Dis Colon Rectum* 2005; 48:787.
14. Blair NP, Germann E: Surgical management of acute sigmoid diverticulitis. *Am J Surg* 2002; 183:525.
15. Trompetas V: Emergency management of malignant acute left-sided colonic obstruction. *Ann R Coll Surg Engl* 2008; 90:181.
16. Saunders MD, Kimmey MB: Colonic pseudo-obstruction: The dilated colon in the ICU. *Semin Gastrointest Dis* 2003; 14:20.
17. Raveenthiran V, Madiba TE, Atamanalp SS, De U: Volvulus of the sigmoid colon. *Colorectal Dis* 2010; 12:e1.
18. Lau KC, Miller BJ, Schache DJ, Cohen JR: A study of large-bowel volvulus in urban Australia. *Can J Surg* 2006; 49:203.
19. Habre J, Sautot-Vial N, Marcotte C, Benchimol D: Caecal volvulus. *Am J Surg* 2008; 196:e48.
20. Hogan BA, Brown CJ, Brown JA: Cecal volvulus in pregnancy: Report of a case and review of the safety and utility of medical diagnostic imaging in the assessment of the acute abdomen during pregnancy. *Emerg Radiol* 2008; 15:127-131.
21. Clinical presentation and diagnosis of sigmoid volvulus: Outcomes of 40-year and 859-patient experience. *J Gastroenterol Hepatol* 2009; 24:1154.
22. Selvaraj DR, Palaniswamy C: Sigmoid volvulus. *J Hosp Med* 2010; 5:E36.
23. Madiba TE, Thomson SR: The management of cecal volvulus. *Dis Colon Rectum* 2002; 45:264.
24. Wang N, et al: Adult intussusception: A retrospective review of 41 cases. *World J Gastroenterol* 2009; 15:3303.
25. Zubaidi A, Al-Saif F, Silverman R: Adult intussusception: A retrospective review. *Dis Colon Rectum* 2006; 49:1546.
26. Takeuchi K, et al: The diagnosis and treatment of adult intussusception. *J Clin Gastroenterol* 2003; 36:18.
27. Haas EM, Etter EL, Ellis S, Taylor TV: Adult intussusception. *Am J Surg* 2003; 186:75.
28. Hanauer SB, Present DH: The state of the art in the management of inflammatory bowel disease. *Rev Gastroenterol Disord* 2003; 3:81.
29. Knutson D, Greenberg G, Cronau H: Management of Crohn's disease—a practical approach. *Am Fam Physician* 2003; 68:707.
30. Baumgart DC, Sandborn WJ: Inflammatory bowel disease: Clinical aspects and established and evolving therapies. *Lancet* 2007; 369:1641.
31. Scholmerich J: Inflammatory bowel disease. *Endoscopy* 2003; 35:164.
32. Farrell RJ, Peppercorn MA: Ulcerative colitis. *Lancet* 2002; 359:331.
33. Xavier RJ, Podolsky DK: Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007; 448:427.
34. Kornbluth A, Sachar DB: Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010; 105:501.
35. Lichtenstein GR, Hanauer SB, Sandborn WJ: Management of Crohn's disease in adults. *Am J Gastroenterol* 2009; 104:465.
36. Panaccione R, et al: Review article: Treatment algorithms to maximize remission and minimize corticosteroid dependence in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2008; 28:674.
37. Gionchetti P, et al: Antibiotics and probiotics in treatment of inflammatory bowel disease. *World J Gastroenterol* 2006; 12:3306.
38. Hanauer SB, Sandborn W: Management of Crohn's disease in adults. *Am J Gastroenterol* 2001; 96:635.
39. Cohen JL, et al: Practice parameters for the surgical treatment of ulcerative colitis. *Dis Colon Rectum* 2005; 48:1997.
40. Rizzello F, Gionchetti P, Venturi A, Campieri M: Review article: Medical treatment of severe ulcerative colitis. *Aliment Pharmacol Ther* 2003; 17(Suppl 2):7.
41. Brandt LJ: Colon ischemia: *Respice, adspice, prospice*. *Surgery* 2010; 148:3.
42. Baixauli J, Kiran RP, Delaney CP: Investigation and management of ischemic colitis. *Cleve Clin J Med* 2003; 70:920.
43. Scharff JR, et al: Ischemic colitis: Spectrum of disease and outcome. *Surgery* 2003; 134:624.
44. Acosta S, Ogren M, Sternby NH, Bergqvist D, Björck M: Fatal colonic ischemia: A population-based study. *Scand J Gastroenterol* 2006; 41:1312.
45. Ullery BS, Boyko AT, Banet GA, Lewis LM: Colonic ischemia: An under-recognized cause of lower gastrointestinal bleeding. *J Emerg Med* 2004; 27:1.
46. Brandt LJ, Boley SJ: AGA technical review on intestinal ischemia. American Gastrointestinal Association. *Gastroenterology* 2000; 118:954.
47. American Gastroenterological Association Medical Position Statement: Guidelines on intestinal ischemia. *Gastroenterology* 2000; 118:951.
48. Otchy DP, Nelson H: Radiation injuries of the colon and rectum. *Surg Clin North Am* 1993; 73:1017.
49. Denton A, Forbes A, Andreyev J, Maher EJ: Non-surgical interventions for late radiation proctitis in patients who have received radical radiotherapy to the pelvis. *Cochrane Database Syst Rev* 2002; 1:CD003455.
50. Wong MT, et al: Radiation proctitis: A decade's experience. *Singapore Med J* 2010; 51:315.
51. O'Brien PC: Radiation injury of the rectum. *Radiother Oncol* 2001; 60:1.
52. Leupin N, et al: Acute radiation colitis in patients treated with short-term preoperative radiotherapy for rectal cancer. *Am J Surg Pathol* 2002; 26:498.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 96

DISORDERS OF THE ANORECTUM

Wendy C. Coates

PERSPECTIVE

Patients visit the emergency department (ED) with a variety of anorectal complaints. Such problems may be self-limited or may signify the presence of an underlying medical condition. A high degree of sensitivity and a professional demeanor should be maintained in interactions with these patients, who may find it difficult to discuss historical details openly and to describe physical complaints related to this area of the body and its function.

PRINCIPLES OF DISEASE

The anorectum marks the end of the alimentary canal. From its beginning at the rectosigmoid junction at the level of the third sacral vertebra (S3), the rectum follows the sacral curvature for 12 to 15 cm and then sharply turns posteriorly and inferiorly at the puborectalis muscle (Fig. 96-1). Here the anal canal begins its 4-cm course to the anal verge, the orifice whereby stool exits the body. It is supported by three muscle groups, the levator ani and the internal and external anal sphincters. Anal valves are located 2 cm proximal to the anal verge at the dentate line. Above the valves are the anal crypts, which contain mucous glands to provide lubrication during defecation. These constitute a nidus for abscess formation, if occluded. Proximal to the crypts are the columns of Morgagni, where the epithelium of the anal canal changes from pink columnar (as in the rectum) to squamous.[1]

The superior, middle, and inferior hemorrhoidal arteries provide the blood supply to the anorectum. They arise from the inferior mesenteric, internal iliac, and internal pudendal arteries, respectively. The superior hemorrhoidal veins drain into the portal system, and the inferior hemorrhoidal veins drain into the caval system. Lymphatic drainage is to the inferior mesenteric nodes above the dentate line and to the inguinal nodes from all areas of the anorectum.[1]

Sympathetic and parasympathetic nervous systems function together to retain the contents of the rectum until evacuation is desired. Continence is maintained when sympathetic fibers from L1 to L3 (upper rectum) and presacral nerves (lower rectum) inhibit contraction of rectal smooth muscle and L5 fibers cause the internal sphincter to contract. Elimination occurs when parasympathetic fibers from the anterior roots of S2 to S4 cause the rectal wall to contract and the internal sphincter to relax. Voluntary external sphincter control is mediated by motor branches of the pudendal nerve (S2, S3) and the perineal branch of S4. The levator ani is supplied by the pudendal nerve and pelvic branches of S3 to S4 fibers. Sensory perception of rectal distention involves a signal pathway from extramural receptors to parasympathetic fibers from S2 to S4. The abundant sensory nerve endings of the distal anal epithelium perceive sensations that are transmitted by the pudendal nerve.[1]

Defecation begins as the rectum becomes distended, the internal sphincter relaxes, and stool enters the anal canal. At an appropriate time and place, the external sphincter is relaxed to complete the process of elimination. Sometimes voluntary straining is needed to assist in the passage of stool. When the Valsalva maneuver is performed, the abdominal muscles contract, the rectal angle straightens, and the pelvic floor descends. To postpone defecation, the external sphincter contracts voluntarily. This contraction relaxes the rectal wall and quells the urge to defecate unless there is an underlying sphincter disorder or an overwhelming volume of stool.[1]

CLINICAL FEATURES

History

A complete history of anorectal and gastrointestinal (GI) symptoms and the presence of systemic disease elucidate the diagnosis of most anorectal disorders (Box 96-1; Fig. 96-2). Common complaints include bleeding, swelling, pain, itching, and discharge. Standard historical questions about time and circumstances of onset, duration, quality, and exposure to radiation should be asked. Alterations in bowel habits should be noted. These include changes in color, frequency, or consistency of the stool and the presence of straining, flatus, and incontinence of solid or liquid stool. Persons with underlying GI disorders (e.g., Crohn's disease, cancer, polyps) are predisposed to atypical presentations of anorectal problems. Similarly, those with underlying systemic diseases such as acquired immunodeficiency syndrome (AIDS), cancer, diabetes mellitus, and coagulopathy are prone to develop more serious complications of standard anorectal conditions. Finally, patients should be asked directly about sexual practices involving the anus.[2]

Rectal Bleeding

The color, amount, and relationship to defecation are important factors in establishing the cause of rectal bleeding. Approximately 10 to 20% of the population experiences rectal bleeding at some time.[3] Pain and bright red blood signify anal fissures or hemorrhoids. Fissure pain is sharp, sudden in onset, and not associated with swelling, whereas pain from a prolapsed or thrombosed hemorrhoid is gnawing, continuous, and of more gradual onset. Painless rectal bleeding occurs with internal hemorrhoids, cancer, or precancerous lesions.

www.ketabpezeshki.com 66485457-66963820

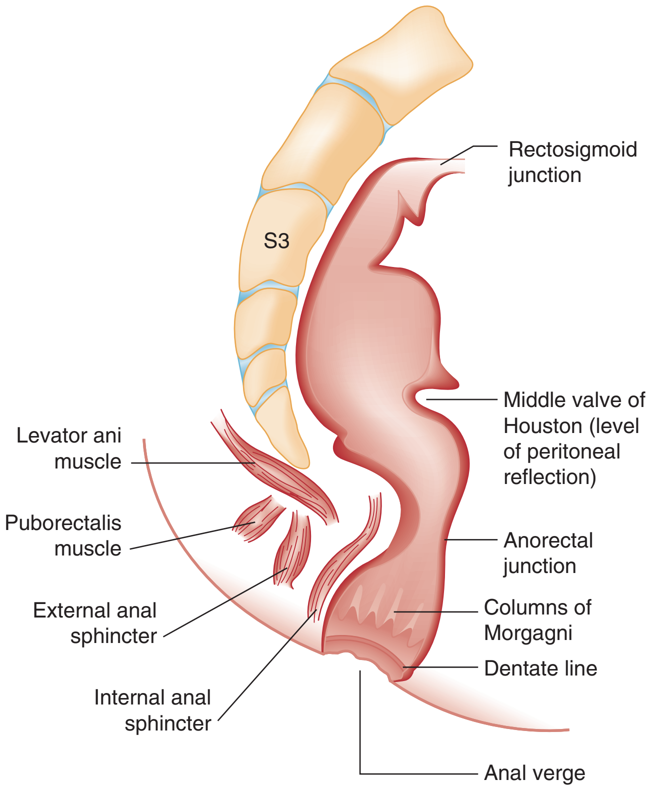


Figure 96-1. Anorectal anatomy.

Box 96-1 Medical History in Diagnosis of Anorectal Disorders

Anorectal History
Pain
Bleeding
Swelling
Itching
Discharge
Urgency

Gastrointestinal History
Change in bowel habits (straining, flatus, color, consistency, frequency)
Nausea or vomiting
Incontinence of stool
Underlying GI disease (Crohn's disease, cancer, polyps)

Systemic Disease History
Diabetes mellitus
Coagulopathy
Cancer
HIV infection

Sexual History of the Anus
Penetration
Known STDs
Assault

GI, gastrointestinal; *HIV,* human immunodeficiency virus; *STD,* sexually transmitted disease.

The relationship of bleeding to defecation is important. Visible blood on the toilet paper usually is caused by anal fissures or external hemorrhoids; however, minute quantities can result from any irritating condition. Bright red blood that drips into the toilet bowl or streaks around the stool is caused by internal hemorrhoids. Blood mixed with stool originates proximal to the rectum, whereas melena indicates a very proximal source. Bloody mucus is associated with cancer, inflammatory bowel disease, and proctitis.[3]

Swelling and Masses

Patients who report a swelling near the anus or have the sensation of rectal fullness often list hemorrhoids as their chief complaint. Painful swellings that bleed usually are thrombosed hemorrhoids, but other painful lesions such as abscesses, pilonidal disease, and hidradenitis suppurativa must be considered. Painless, itchy swellings may be caused by condylomata acuminata or secondary syphilis. A mass protruding through the anal orifice may signal rectal prolapse. Perianal and rectal carcinoma should be considered in older persons and those with long-standing anorectal complaints.[2]

Pain and Itching

Severe, episodic anorectal pain that is not associated with bleeding or swelling may represent proctalgia fugax or levator ani syndrome. Perianal itching (pruritus ani) is caused by any lesion that makes hygiene difficult to maintain or may be attributed to certain foods or medications.

Physical Examination

The physical examination should take place in private, with the patient's modesty respected. The patient can then relax the external sphincter to facilitate a complete examination. The patient is placed in the left lateral decubitus position and covered with a sheet. The buttocks are inspected for dermatologic manifestations of disease and then gently spread apart to expose the anal orifice. Elements of personal hygiene are noted, in addition to anatomic disruptions such as fissures, skin tags, lesions, protruding hemorrhoids, or abscesses. The patient is asked to strain; the integrity of the pelvic floor is assessed, and prolapse of hemorrhoids or rectal mucosa is noted. Next, a well-lubricated gloved finger is placed flat against the anal opening, exerting gentle pressure until the external sphincter relaxes and allows the finger to enter the anus. Anal sphincter tone can be assessed by asking the patient to squeeze the anal muscles against the examining finger. By sweeping the finger in a circumferential manner, accessible areas of the anorectum can be examined for masses and areas of tenderness. The cervix or prostate is palpated through the rectal wall. A bidigital examination reveals masses and tender areas at the distal portion of the anal canal and perineum. On withdrawal, the contents on the glove can be assessed for frank or occult blood, mucus, or pus.

Direct visualization can be accomplished by anoscopy. With the patient positioned as described, the lubricated anoscope is inserted into the anus with the obturator in place. The obturator is removed to allow a circumferential view of the rectal mucosa. Attention is directed to sites of bleeding, hemorrhoids, masses, or abnormal tissue and finally the dentate line and anal epithelium.

SPECIFIC ANORECTAL PROBLEMS

Hemorrhoids

Perspective

When the Philistines defeated the Israelites, the book of I Samuel reports the fate of the avengers: "A deadly panic had seized the whole city, since the hand of God had been very heavy upon it. Those who escaped death were afflicted with hemorrhoids, and the outcry from the city went up to the heavens."[4] In 1815 the

www.ketabpezeshki.com 66485457-66963820

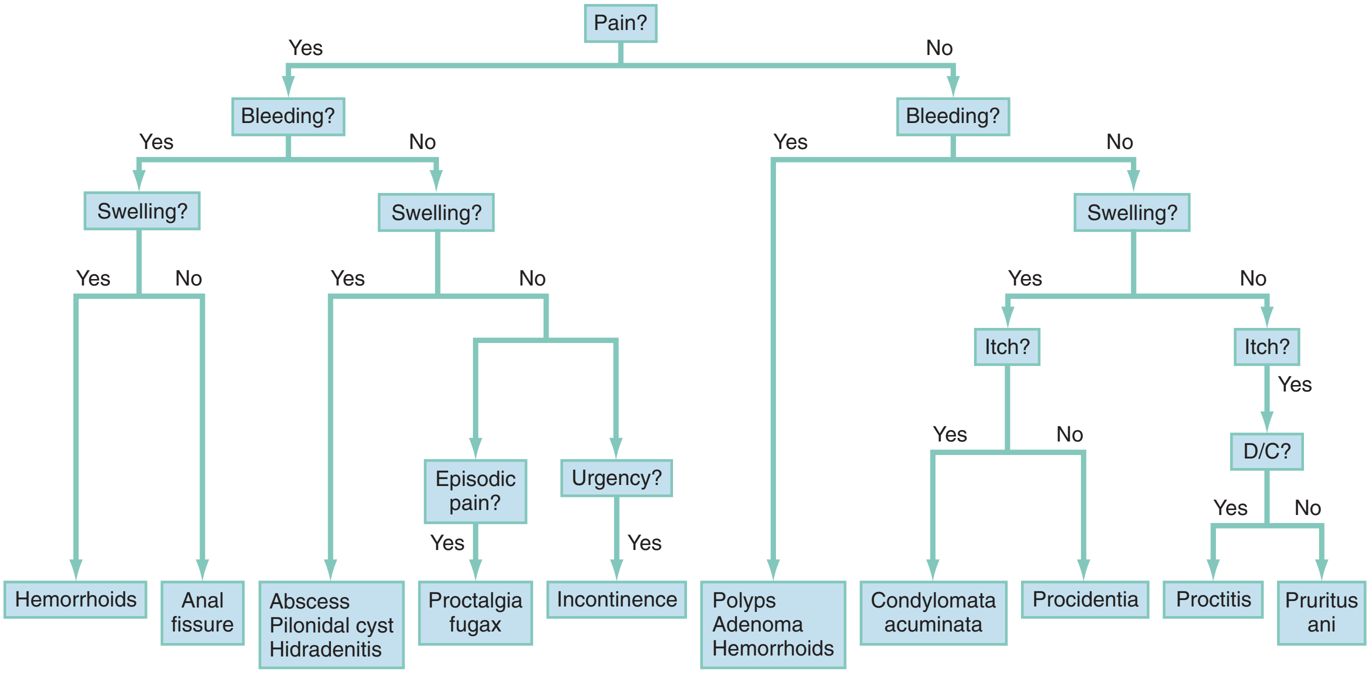


Figure 96-2. Algorithm for anorectal complaints. *D/C,* discharge.

battle of Waterloo marked the defeat of Napoleon's army. Speculation purports that the great leader suffered from hemorrhoids at the time of his defeat.[5] Hemorrhoidal disease continues to afflict modern humans, with a 5% incidence in the U.S. population. Both sexes are affected, and an increased frequency has been documented among whites, rural dwellers, and those of high socioeconomic status.[6]

Principles of Disease

Hemorrhoids occur when the anal vascular cushions become engorged. Rather than forming a continuous ring around the anal canal, the submucosa forms three distinct cushions of tissue that are richly supplied with small blood vessels and muscle fibers. Blood supply to these cushions is from the superior rectal artery, with some contribution from the middle and inferior hemorrhoidal arteries, which explains why hemorrhoidal bleeding is bright red. The muscularis submucosa cushions the anal canal during defecation to prevent injury and to aid in fecal continence.[7]

As the supportive tissue deteriorates, often starting in the third decade of life, venous distention, prolapse, bleeding, and thrombosis may occur. Some controversy exists about whether straining and constipation cause these changes by producing venous backflow when intra-abdominal pressure increases.[7,8] In pregnant women, direct pressure on a hemorrhoidal vein can produce symptomatic hemorrhoids. Up to one third of pregnant women experience hemorrhoids in the last trimester of pregnancy or the postpartum period. An increased incidence of thrombosed hemorrhoids is associated with traumatic deliveries.[9,10] Some familial predisposition is recognized, but whether this is a result of genetics or acquired factors such as diet is unknown.

Hemorrhoids are not varicose veins; they are normal structures that manifest symptoms when the muscularis submucosa weakens and the anal cushions are displaced distally.[7] Conditions that increase sphincter tone correlate with a higher prevalence of hemorrhoids.[8] Portal hypertension does not cause hemorrhoids in adults. The incidence of symptomatic hemorrhoids is similar in patients with and in those without portal hypertension. Rectal bleeding in patients with portal hypertension may be caused by rectal varices, which are vascular communications between the superior and middle hemorrhoidal veins.[6,11] A major exception to this observation occurs in the pediatric population; children with portal hypertension are susceptible to hemorrhoidal exacerbations.[12,13]

Clinical Features

A careful history is needed to confirm the presence of hemorrhoids because many patients use this term to refer to any perianal condition. Bleeding with defecation is the most common complaint, and unless the hemorrhoids are thrombosed, it usually is painless. Patients report variable amounts of bright red blood on the toilet paper or in the toilet bowl. Many complain of swelling, itching, mucoid discharge, or simply the presence of a moist perianal area. Further history should address recent stool patterns, such as diarrhea or constipation; chronic medical problems, such as portal hypertension or bleeding disorders; and a dietary and family history.

Frequent bowel movements, prolonged sitting, heavy lifting, and straining while defecating exacerbate hemorrhoidal symptoms. Although straining is cited as a cause of hemorrhoids, it also may be a result of them when the patient is constipated from delaying defecation because of fear of pain. Physical examination should ascertain the type and degree of hemorrhoids. This can be accomplished by a visual inspection at rest and during straining. Nonprolapsing hemorrhoids can be visualized on anoscopy as a focus of bleeding or as they bulge when the patient is asked to strain while the anoscope is removed. Anoscopy is painful and not useful in cases of prolapsed or thrombosed hemorrhoids.

Hemorrhoids are classified according to their location and severity (Table 96-1). *External* hemorrhoids originate *below* the dentate line and receive their blood supply from the inferior hemorrhoidal plexus. They are covered with modified squamous epithelium (anoderm) and resemble the surrounding skin. Two syndromes are common. First, the veins beneath the skin of the hemorrhoid become dilated and the surrounding subcutaneous tissue becomes engorged, causing swelling or pressure after

www.ketabpezeshki.com 66485457-66963820

Figure 96-3. Thrombosed hemorrhoids. **A,** External. **B,** Internal. Note the engorged external hemorrhoids surrounding the thrombosed internal hemorrhoids. (**A,** Courtesy Michelle Lin, MD, Harbor-UCLA Medical Center; **B,** courtesy Gershon Effron, MD, Sinai Hospital of Baltimore. From Seidel HM, et al: Mosby's Guide to Physical Examination, 4th ed. St Louis, Mosby, 1999.)

Table 96-1 Types of Hemorrhoids

TYPE	ORIGIN	EPITHELIUM
External	Inferior hemorrhoidal plexus Proximal to dentate line	Modified squamous epithelium (anoderm)
Internal	Superior hemorrhoidal plexus Distal to dentate line	Transitional or columnar epithelium (mucosa)
Mixed	Superior and inferior hemorrhoidal plexus	Transitional, columnar, or modified squamous epithelium (mucosa and anoderm)

Table 96-2 Classification of Internal Hemorrhoids by Severity

TYPE	PROLAPSE	MODE OF REDUCTION	TREATMENT
First degree	None	N/A	Medical management
Second degree	During defecation	Spontaneous	Medical management
Third degree	May be spontaneous or during defecation	Manual	Medical management Optional surgical repair
Fourth degree	Permanent	Irreducible	Surgical repair

N/A, not applicable.

Box 96-2 The WASH Regimen for Management of Hemorrhoids

*W*arm water	*S*tool softeners
*A*nalgesic agents	*H*igh-fiber diet

defecation. Painless, bright red bleeding may occur. Second, the veins can become thrombosed as clots form within them (Fig. 96-3A). This produces acute pain and tenderness to palpation. A bluish discoloration often is noted.

Internal hemorrhoids originate *above* the dentate line and receive their blood supply from the superior hemorrhoidal plexus (Fig. 96-3B). They are covered with a mucosal surface consisting of transitional or columnar epithelium that looks very different from the surrounding anoderm. They are classified according to severity (Table 96-2). Symptoms and signs range from mild, painless bleeding with defecation to irreducible prolapse with unremitting and debilitating pain. First-degree internal hemorrhoids protrude into the lumen of the anal canal, causing a feeling of fullness. Because the mucosal wall lacks sensory nerve endings, these lesions do not cause pain. Second-degree internal hemorrhoids temporarily prolapse outside the anal canal during defecation but spontaneously return to their normal position at the end of the bowel movement. Both first- and second-degree hemorrhoids are amenable to medical management. Third-degree internal hemorrhoids prolapse spontaneously or during defecation and remain outside the body until they are manually replaced into the anal canal. A throbbing, pressure-like pain may accompany bleeding and subsides when the hemorrhoids are reduced. Fourth-degree internal hemorrhoids cannot be reduced and are permanently prolapsed. Continued prolapse leads to the formation of a thrombus with possible progression to gangrene. Definitive treatment for the intense pain and thrombosis is surgical.[8,14]

Management

The symptoms of nonthrombosed external and nonprolapsing internal hemorrhoids can be ameliorated by the standard regimen—warm water, analgesics, stool softeners, and high-fiber diet (WASH)—aimed at combating the problems that led to the hemorrhoids' formation (Box 96-2). Anal canal pressures decrease in warm water (40° C). Patients can direct a shower stream at the area for several minutes or take sitz baths. Mild oral analgesic agents reduce the pain. Several over-the-counter preparations are available for the treatment of hemorrhoidal symptoms; however, their use is directed at improved hygiene and temporary symptom relief rather than correction of the condition.[15] The use of topical anesthetics, corticosteroids, astringents (e.g., witch hazel), mineral oils, and cocoa butter is controversial. Prolonged use of topical corticosteroids produces atrophic skin changes and is discouraged.[7] Stool softeners can make the passage of stool easier, to prevent straining. A high-fiber diet (consumption of 20 to 30 g of dietary fiber per day) produces stool that is passed more easily.[16]

Patients with second- or third-degree internal hemorrhoids also benefit from this regimen; however, permanent resolution of their symptoms may require surgical intervention (Table 96-3). These patients can be discharged from the ED with the WASH regimen and referred to a surgeon for banding, sclerotherapy, or elective

www.ketabpezeshki.com 66485457-66963820

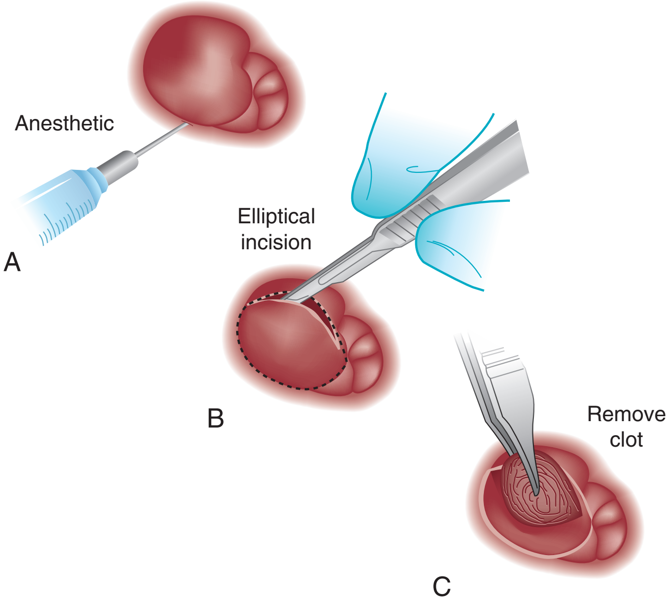


Figure 96-4. Excision of thrombosed external hemorrhoid. **A,** Field block with local anesthetic. **B,** An elliptical incision is made around the hemorrhoid. **C,** The thrombosed hemorrhoid is removed. (From Larson S, et al [eds]: Atlas of Emergency Procedures. St Louis, Mosby, 2001.)

Table 96-3 Surgical Management of Hemorrhoids

CLASSIFICATION	MANAGEMENT
Thrombosed external hemorrhoids	Excision in emergency department
Second- and third-degree internal hemorrhoids	Elective surgical repair Banding Sclerotherapy Hemorrhoidectomy
Fourth-degree hemorrhoids (nonthrombosed)	Nonemergent hemorrhoidectomy
Thrombosed or gangrenous fourth-degree internal hemorrhoids	Emergent hemorrhoidectomy

hemorrhoidectomy. Patients with acute, gangrenous, thrombosed fourth-degree internal hemorrhoids should be referred for emergent hemorrhoidectomy.

Acutely thrombosed external hemorrhoids can be excised (not incised and drained) in the ED to provide prompt relief within the first 48 hours after the onset of symptoms (Fig. 96-4). Incision results in incomplete evacuation of the clot, subsequent rebleeding, swelling, and the formation of a skin tag.[8,17] If not excised, the thrombosed external hemorrhoid resolves spontaneously after several days when it ulcerates and leaks the dark accumulated blood, with relief of associated symptoms. Residual skin tags may persist, making anal hygiene more challenging. In the ED setting, this procedure is not commonly performed in pediatric patients, pregnant women, or immunocompromised patients.

Nonsurgical therapy with topical nifedipine (0.3%) and lidocaine (1.5%) gel has been shown to alleviate symptoms when applied twice daily for 2 weeks. The purported effectiveness of this regimen for treatment of thrombosed hemorrhoids is related to the ability of nifedipine to modulate resting sphincter tone and thereby reduce the associated pain and inflammation. However, this regimen is not widely used.[18]

Figure 96-5. Lateral anal fissure. (Courtesy Gershon Effron, MD, Sinai Hospital of Baltimore. From Seidel HM, et al: Mosby's Guide to Physical Examination, 4th ed. St Louis, Mosby, 1999.)

Anal Fissures

Principles of Disease

The development of an anal fissure is the most common cause of intensely painful rectal bleeding of sudden onset. A superficial tear in the anoderm results when a hard piece of feces is forced through the anus, usually in patients who are constipated. Although anyone can experience an anal fissure, it is most common in the 30- to 50-year age bracket.[19] It is the most commonly encountered anorectal problem in pediatric patients, especially infants.[20,21] Males and females are affected equally. Most fissures occur along the posterior midline, where the skeletal muscle fibers that encircle the anus are weakest. Anterior midline fissures are more common in women than in men. Fissures that occur elsewhere are more likely to be associated with systemic disease such as leukemia, Crohn's disease, human immunodeficiency virus (HIV) infection, tuberculosis (TB), or syphilis.[19] Fissures not treated promptly may become chronic, with development of a classical "fissure triad" of deep ulcer, sentinel pile, and enlarged anal papillae (Fig. 96-5). A sentinel pile forms when the skin at the base of the fissure becomes edematous and hypertrophic. A resolving sentinel pile can form a permanent skin tag and may be associated with a fistulous tract.

Clinical Features

The patient reports sudden, searing pain during defecation that may be accompanied by a small amount of bright red blood in the stool or on the toilet paper. This is followed by a nagging, burning sensation that lasts for a few hours from internal sphincter spasm. Subsequent bowel movements are excruciating, and the external sphincter can exhibit a reflex spasm. Physical examination must be performed cautiously to avoid further spasm and pain. The depth of the fissure, its orientation to the midline, and the presence of a coexisting sentinel pile or edema are noted. Rectal examination during an acute exacerbation often is impossible because of pain and sphincter spasm.[19]

Management

Specific measures for the treatment of anal fissures are summarized in Box 96-3. Treatment with the WASH regimen (see Box

www.ketabpezeshki.com 66485457-66963820

96-2) focuses on eliminating constipation with a bulking agent, stool softener, and high-fiber diet. Warm sitz baths and limited use of topical anesthetics may be helpful. Parental encouragement of pediatric patients helps prevent encopresis, which can result from a fear of painful bowel movements. Most acute, uncomplicated fissures resolve in 2 to 4 weeks. For adult patients with chronic anal fissures, application of various topical agents aimed at reducing sphincter pressures has been effective.[22-24] Hyperbaric oxygen has been used successfully for adjunctive therapy.[25]

Lidocaine ointment is effective in treating chronic anal fissures. In addition, nitroglycerin ointment applied topically to the anoderm two or three times daily has been shown to relieve the pain from anal fissures. Although it was not associated with more rapid healing, patients receiving this therapy have reported a higher level of comfort during the healing process. The typical side effect of a vasodilatory headache may be experienced by some patients.[26]

Nifedipine gel (0.2%) in combination with lidocaine (1.5%) applied to the anal area twice daily is effective in promoting healing and reducing discomfort in the management of anal fissures. The mechanism of healing is thought to be the reduction of anal canal pressures by local calcium channel blockade.[27,28] When the efficacy of calcium channel blockers was compared directly with that of topical nitrates, the rates of healing and recurrence were similar; however, the incidence of side effects was lower in one study.[29]

Injection of botulinum toxin by colorectal surgeons (2.5 to 5.0 units of Botox preparation) is effective in relaxing the sphincter tone by inhibiting acetylcholinesterase release but may cause temporary, reversible fecal incontinence.[24,27,30-33] Injection into the external (rather than internal) sphincter muscles may reduce this undesirable side effect. It has not yet been studied as a primary treatment in the ED or primary care setting. In comparison with the topical treatments, botulinum toxin may provide some advantages in its rate of permanent healing[34]; however, the first line of therapy is still dietary modification and the application of topical agents because of their cost, ease of application, and benign side effect profiles.[24,33] Long-term treatment of recurrent fissures focuses on reducing resting anal pressures and may require anal dilation performed with the patient under anesthesia or surgical correction to reduce the tone of the internal sphincter.[19]

Box 96-3 Treatment of Anal Fissures

- WASH regimen*
- Nitroglycerin ointment (0.4%) bid or tid
- Nifedipine gel (0.2%) bid with lidocaine (1.5%)
- Botulinum toxin (surgical consultation)
- Anal dilation performed with the patient under general anesthesia
- Surgical excision

*See Box 96-2.

Abscesses and Fistulae

Principles of Disease

Anorectal abscesses and fistulae occur in otherwise healthy adults when the mucus-producing glands at the base of the anal crypts occlude. Abscesses are a manifestation of inflammatory bowel disease, trauma, cancer, radiation injury, and infection (TB, lymphogranuloma venereum, actinomycosis). Common causative bacteria are *Staphylococcus aureus, Escherichia coli, Streptococcus, Proteus,* and *Bacteroides.*[35] An increased incidence in infants (85% in male babies) has been reported to be associated with congenital abnormalities.[36]

Management

General Approach. Anorectal abscess is an acute disease that naturally progresses to fistula formation in the body's attempt to drain the infection spontaneously. Symptoms vary depending on the site of infection, but incision and drainage constitute the curative treatment in all cases (Table 96-4). Delay of medical management may allow extension of the infection and eventual compromise of the sphincter mechanism.[37] Adjunctive antimicrobial therapy is indicated in patients who are immunocompromised or diabetic or have valvular heart disease. Tetanus immunization status should be verified. The sites of anorectal abscess formation are depicted in Figure 96-6. The difficulty in diagnosis is that pain often precedes physical findings of a mass or fluctuance. Approximately 34% of patients with AIDS develop anorectal abscesses and fistulae, which may include opportunistic organisms in addition to the usual ones. HIV-infected patients appear to be more likely than their seronegative cohorts to have an incomplete fistulous tract. This condition prevents adequate spontaneous drainage, highlighting the urgency of treating these patients promptly. A small incision is desirable, when possible, because wound healing in general may be impaired.

Treatment of Specific Abscesses

Perirectal and Perianal Abscesses. Perirectal and perianal abscesses are the most common (40-45%) and produce painful swelling at the anal verge that is worsened by defecating or sitting. Most patients are afebrile. Physical examination reveals localized tenderness, erythema, swelling, and fluctuance. ED management by incision and drainage with same-day discharge is possible in patients who do not have comorbidity (e.g., diabetes mellitus, extremes of age, compromised immune status). Some patients

Table 96-4 Types of Abscesses of the Anorectum

FEATURE	PERIANAL	ISCHIORECTAL	INTERSPHINCTERIC	SUPRALEVATOR	POSTANAL
Incidence	40-45%	20-25%	20-25%	<5%	5-10%
Location	Outside and verge	Buttocks	Lower rectum	Above levator ani	Deep to external sphincter
Symptoms	Painful perianal mass	Buttock pain	Rectal fullness	Perianal and buttock pain	Rectal fullness Pain near coccyx
Fever, ↑ WBCs	–	±	±	+	+
Associated fistula	++	+	+++	+++	–
ED incision and drainage	+	±	–	–	–

ED, emergency department; *WBCs,* white blood cells; –, does not occur; ±, occurs sometimes; ++, occurs often; +++, usually occurs.

www.ketabpezeshki.com 66485457-66963820

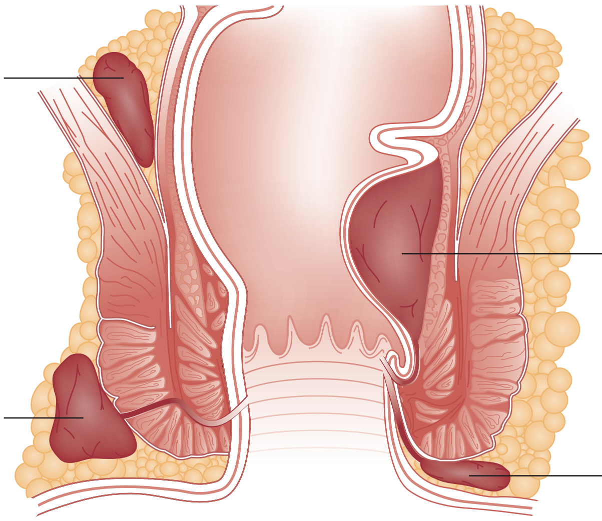


Figure 96-6. Location of common anorectal abscesses. (Adapted from Gordon PH, Nivatvonghs S: Principles and Practice of Surgery for the Colon, Rectum, and Anus. St Louis, Quality Medical Publishing, 1992.)

may be unable to tolerate the procedure without general or regional anesthesia. The WASH regimen (see Box 96-2) may alleviate postprocedure discomfort. Antibiotics are unnecessary in healthy adult patients except in cases involving associated cellulitis.[38,39]

Ischiorectal Abscess. Approximately 20 to 25% of abscesses form outside the sphincter muscles in the buttocks, and patients report severe pain. The diagnosis is obvious if an indurated mass is seen on the buttocks but is more difficult if the abscess is deep. Patients often have fever and leukocytosis. If there is no induration, a needle aspirate can confirm the presence of pus. Although many of these abscesses will require drainage performed with the patient under general anesthesia, superficial abscesses can be treated in the ED as for perianal abscess. If the patient is febrile, a short course of antibiotics, such as cephalexin, may be considered, beginning with a parenteral dose before drainage, followed by 3 to 7 days of an oral agent.[39,40]

Intersphincteric Abscess. One fourth of abscesses form in the space deep to the external sphincter and inferior to the levator ani. The infection tracks cephalad and may appear to be a mass in the rectum and can be confused with a thrombosed internal hemorrhoid. Patients report continuous rectal pressure and a throbbing pain exacerbated by defecation or sitting. They may have fever and leukocytosis. External evidence of inflammation may be lacking, but rectal examination reveals an erythematous, indurated, sometimes draining mass. Associated fistulae and inguinal lymphadenopathy are common. Drainage in the operating room is required so that the entire abscess and fistula network can be evaluated and treated.[35]

Supralevator Abscess. Accounting for less than 5% of abscesses, supralevator abscesses cause perianal and buttock pain associated with fever and leukocytosis. External evidence of this disease usually is absent, which often delays the diagnosis. Approximately 23% of patients with this condition are obese or have diabetes mellitus, and others have concurrent disorders such as Crohn's disease, pelvic inflammatory disease, or diverticulitis. A tender mass may be palpated on rectal or pelvic examination. Emergent surgical treatment is indicated to drain the abscess and excise the fistulous network.[35,39]

Postanal Abscess. Postanal abscesses are uncommon and occur posterior to the rectum, deep to the external sphincter, and inferior to the levator ani. Patients experience severe rectal discomfort and coccygeal pain. They usually are febrile and have continuous pain that does not change with position. Rectal examination is painful, but anal drainage is rare. Many of these abscesses are missed on initial presentation, and the patient may be misdiagnosed as having lumbosacral strain, proctalgia fugax, sciatica, or coccygodynia. Patients often return in a few days with an abscess draining at the skin. Treatment is surgical.

Horseshoe Abscess. Occasionally a large, communicating, horseshoe-shaped abscess forms in the ischiorectal, intersphincteric, or supralevator space. Surgical management is necessary.

Necrotizing Infection. A delay in management of an anorectal abscess may lead to the destruction of tissue, especially in diabetic or immunocompromised patients. Widespread cellulitis, necrotic tissue, and gas on radiography suggest the possibility of necrotizing fasciitis, Fournier's gangrene, or tetanus. Wide surgical débridement, broad-spectrum antibiotics with anaerobic coverage, and tetanus prophylaxis are required.

Treatment of Fistulae

A *fistula* (Latin for "pipe") is a connection between two epithelium-lined surfaces. Anorectal fistulae develop in 50 to 67% of patients with ischiorectal abscesses.[37] Other causes include Crohn's disease, trauma, foreign body reactions, TB, and cancer. Evidence to support these diagnoses should be sought because the anorectal complaint may be the presenting symptom of the underlying disease. Patients notice a recurrent or persistent perianal discharge that becomes painful when one of the openings becomes occluded. Bidigital rectal examination may reveal a tract in the perineum or canal. Probing of fistulous tracts is not recommended because the danger of creating a new tract outweighs the benefit of identifying the path of the existing fistula. Spontaneous resolution of fistula in ano is rare. Although symptoms resolve when antibiotics are administered (e.g., ciprofloxacin, metronidazole), they commonly return as soon as therapy is discontinued. Increasingly, definitive treatment of the fistulous network at the time of incision and drainage of the abscess is advocated to prevent ongoing progression of the disease continuum. Fistulectomy and application of fibrin glue are commonly accepted practices of colorectal surgeons.[35,39,40,41] Nonsurgical treatments that have been proposed for some patients, especially those with Crohn's disease, are administration of infliximab, a monoclonal antibody, or cyclosporine and hyperbaric oxygen therapy.[37]

www.ketabpezeshki.com 66485457-66963820

Pilonidal Disease

Principles of Disease

Little nests of hair in the sacrococcygeal area were first described in 1847 by Anderson (Latin *pilus,* "hair"; *nidus,* "nest"), who originally believed the lesions to be scrofula.[42] More than 150 years later, physicians have yet to agree on the cause and best mode of treatment. Pilonidal abscesses and subsequent sinus tracts afflict young adults with a 4:1 male predominance and are more common in obese and hirsute persons. The disease is rare in people older than 40 years, even among those who were affected in their youth. The lesions arise in the midline of the sacrococcygeal area in the natal cleft and should not be confused with anal fistulae, perirectal abscesses, hidradenitis suppurativa, or granulomatous diseases (syphilis, TB).[43] Much of the current understanding of pilonidal disease comes from the experience in World War II, when the condition was rampant among jeep drivers and was therefore dubbed "jeep-driver's disease."[43,44]

The debate between congenital predisposition and acquired disease seems to favor the latter.[44-46] This theory asserts that bacteria enter the usually sterile hair follicle and produce inflammation and edema, thereby occluding the opening to the skin surface. The contents expand until the hair follicle ruptures, and the material spreads into the subcutaneous fatty tissue, where a foreign body reaction leads to abscess formation. The purulent material subsequently tracks cephalad and drains to the skin through a laterally displaced, epithelialized tract. Diagnosis is made by establishing the presence of a painful, fluctuant area in the presacral skin. In chronic or recurrent disease, visible or palpable tracts 2 to 5 cm in length may be identified with openings approximately 5 cm above the anus. These sinuses usually contain hairs and cellular debris.[43,44]

Management

Treatment options vary, ranging from conservative therapy to extensive surgical excision.[43,44,47] Antibiotics can supplement incision and drainage in cases accompanied by cellulitis but are not effective as the primary mode of treatment. ED management of pilonidal disease involves drainage of the acute abscess for relief of symptoms. To prevent reaccumulation of debris and to minimize inflammation in the midline, a longitudinal incision lateral to the sacral midline should be made. To decrease the usual 40% recurrence rate, the patient can be referred for follicle removal and unroofing of sinus tracts after the acute inflammation subsides (usually 1 week). An alternate noninvasive strategy of shaving the hairs in the natal cleft every 3 weeks has been reported. For patients whose disease is recalcitrant, unroofing and marsupialization or wide excision techniques are used.[47]

Hidradenitis Suppurativa

Perianal hidradenitis suppurativa is an infection of the apocrine glands. It is most common in young adults and is related to poor skin hygiene, hyperhidrosis, obesity, acne, diabetes mellitus, and smoking. The condition commonly is misdiagnosed as pilonidal disease or fistula in ano. Other considerations in the differential diagnosis include sebaceous cysts, furuncles, granulomas (from TB or syphilis), and Crohn's disease. Occluded apocrine ducts may be infected with strains of *Staphylococcus, Streptococcus, E. coli,* or *Proteus.* Extension through the dermis spreads the infection to neighboring ducts, and a network of sinus tracts forms. This cycle leads to extensive scarring.[46,48]

Patients report one or more tender, draining pustules in the perianal area, which may be associated with fever, leukocytosis, and malaise. Local lymphadenopathy and surrounding cellulitis are common. Treatment begins with careful attention to perianal hygiene, warm compresses, and broad-spectrum antibiotics. Recently, infliximab has been found to be effective, resulting in rapid clinical improvement.[49] Drainage of isolated lesions may provide symptomatic relief, but the recurrence rate approaches 40%. Referral to a surgeon for wide excision of tissue involved in advanced chronic disease may be necessary.[50-52]

Proctalgia

Perspective

Anorectal pain (proctalgia) that does not arise from one of the organic disorders described earlier can be severe and difficult to treat.[53,54] The two most common causes are levator ani syndrome and proctalgia fugax. These disorders can be distinguished by their patterns of affliction. Other causes of pelvic pain, such as tumors, cauda equina syndrome, and endometriosis, must be considered.[55]

Levator Ani Syndrome

A constant, dull pressure in the sacrococcygeal region that is precipitated by defecation or prolonged periods of sitting suggests levator ani syndrome. The patient usually has tenderness of the levator muscles, which may be firmly contracted on examination. It affects both men and women. No standard treatment regimen has been studied, but anecdotal reports indicate that sitz baths, levator ani muscle massage, and muscle relaxants can provide some relief.[53,54]

Proctalgia Fugax

Proctalgia fugax is an intensely painful spasm in the rectal area that begins abruptly and lasts for several minutes. It is attributed to a sudden spasm of the levator muscle complex or the sigmoid colon. People who frequently visit the toilet are at greatest risk, and women are more commonly affected than men. A psychogenic predisposition is described by Pilling and colleagues, who found that professionals, managers, and perfectionists are more likely to be affected.[56]

Proctalgia fugax can begin abruptly during sleep, defecation, urination, or intercourse. The nature of the pain has been compared to a "charley horse." It lasts less than 30 minutes and may radiate to the coccyx or perineum. Symptoms during recurrent episodes are consistent for the affected person, and each patient has a unique constellation of symptoms.[53] Treatment often is unrewarding, but recommendations include bowel cleansing regimens, upward manual pressure on the anus, diazepam, and topical nitrates.[54]

Fecal Incontinence

Perspective

Fecal incontinence is an embarrassing condition that affects parous women, elderly persons, and patients with a variety of neurologic or traumatic disorders. The delicate balance among the pelvic floor muscles, sphincters, and anorectal sensation is disrupted in this condition. Complete incontinence is the inability to control passage of solid feces. Partial incontinence is characterized by loss of control of the passage of flatus or liquid feces.

Principles of Disease

Multiple causes of fecal incontinence have been described (Box 96-4).[53,57,58] Injury to muscles and nerves may result from

www.ketabpezeshki.com 66485457-66963820

Box 96-4 Causes of Fecal Incontinence

Traumatic Causes
Iatrogenic (surgical) nerve injury
Spinal cord injury
Obstetric trauma
Sphincter injury

Neurologic Causes
Spinal cord lesions
Dementia
Autonomic neuropathy (e.g., diabetes mellitus)
Obstetric: pudendal nerve damage from stretching during surgery, Hirschsprung's disease

Mass Effect
Carcinoma of anal canal
Carcinoma of rectum
Foreign body
Fecal impaction
Hemorrhoids

Medical Causes
Procidentia
Inflammatory disease
Diarrhea
Laxative abuse

Pediatric Patients
Congenital
- Meningocele
- Myelomeningocele
- Spina bifida

After corrective surgery for imperforate anus
Sexual abuse
Encopresis

Box 96-5 Causes of Pruritus Ani

Dermatitis
Fecal Irritation
Poor hygiene
Anorectal conditions: fissure, fistula, hemorrhoids, skin tags, perianal clefts
Systemic: caffeine, tea, beer, spicy foods, citrus fruits, quinidine, intravenous hydrocortisone, colchicine, tetracycline

Contact Dermatitis
Anesthetic agents, topical corticosteroids, perfumed soap

Systemic Diseases
Dermatologic
Psoriasis, seborrhea
Lichen simplex or lichen sclerosus

Nondermatologic
Chronic renal failure, myxedema, diabetes mellitus, thyrotoxicosis, polycythemia vera
Vitamin A or D deficiency, iron deficiency
Cancers: Bowen's, Paget's, Hodgkin's diseases

Infections
STDs
Syphilis
HSV infection
HPV infection

Other Infectious Processes
Scabies
Pinworm
Bacterial infection
Fungal infection

HPV, human papillomavirus; *HSV,* herpes simplex virus; *STD,* sexually transmitted disease.

accidental trauma or surgery for anorectal disorders. Similarly, injury or stretching during childbirth can cause immediate or delayed problems. Spinal cord and cauda equina lesions and the autonomic neuropathy of diabetes mellitus can cause progressive incontinence. Liquid feces may seep around tumors or foreign bodies of the rectum or anal canal. A common "foreign body" is a large impacted stool, as seen in elderly patients or those with underlying megacolon. Explosive diarrhea from laxative abuse, inflammation, or infection can temporarily overwhelm a normal sphincter mechanism. Partial incontinence after surgery to correct imperforate anus is common.[59] Incontinence is a common feature of congenital neurologic conditions such as meningocele, myelomeningocele, and spina bifida. Encopresis also may develop in young children (4 to 7 years) experiencing emotional stress.[60] In otherwise healthy children, sexual abuse involving the anus must be considered.[61]

Clinical Features

The physical examination should address the local and systemic factors described previously. The anorectum should be assessed for masses, hemorrhoids, evidence of previous surgery, and neuromuscular function. The anocutaneous reflex, or "anal wink," is elicited by touching the skin near the anus with a pin and observing the resulting constriction. Sphincter function is assessed by asking the patient to "squeeze" the examiner's finger.

Management

The approach to management of fecal incontinence depends on the cause. Structural and inflammatory conditions may be diagnosed with anoscopy. In cases of transient incontinence caused by diarrhea, a high-fiber diet along with brief therapy with loperamide or opioids has been shown to solidify stool and enhance rectal compliance.[57]

Neuromuscular causes of fecal incontinence can be diagnosed by anorectal physiologic testing. In addition to conservative treatment measures described for transient incontinence, Kegel exercises, biofeedback training, or surgical repair may be necessary.[57,58,62]

Pruritus Ani

Principles of Disease

Patients with pruritus ani complain of an uncontrollable urge to scratch the perianal area. Approximately 1 to 5% of the population seeks medical attention for this condition during their lifetime. Others rely on self-treatment to soothe less severe symptoms. The period of peak incidence is during the fifth and sixth decades of life, and it occurs more often in men. The condition is more common in the summer months and is more noticeable at night. The sensation of itching arises when the richly innervated perianal skin becomes irritated. Patients scratch vigorously in an effort to relieve the itching, creating a vicious circle that results in greater irritation and excoriation. The causes of pruritus ani are summarized in Box 96-5.

The most common cause is the presence of feces on the perianal skin. Conditions ranging from poor personal hygiene to anatomic disorders of the anorectum allow feces to accumulate in the area. Patients may not clean the area thoroughly after defecation. Disruptions in the anorectal anatomy can lead to uncontrollable fecal accumulation on the perianal skin. Obesity, deep perianal clefts, copious hair, hemorrhoids, posthemorrhoidal skin tags, rectal

www.ketabpezeshki.com 66485457-66963820

mucosal prolapse, anal fissures, and fistulae make the area difficult to clean effectively. Decreased air circulation from wearing tight pants or undergarments of synthetic "nonbreathable" fabric may exacerbate symptoms.[63]

Foods (e.g., caffeine, spicy or citrus foods, tea, beer) and drugs (e.g., quinidine, colchicine, tetracycline, intravenous hydrocortisone) augment the irritant quality of the feces by altering its pH. Perfumed soaps and drugs, especially local anesthetic creams and ointments, can produce a contact dermatitis. Prolonged use of hemorrhoidal preparations containing local anesthetic and topical corticosteroid can exacerbate the symptoms. Other dermatologic conditions include psoriasis, seborrhea, lichen simplex, and lichen sclerosus.

Systemic diseases and local infections can produce perianal itching. Chronic renal failure, diabetes mellitus, thyrotoxicosis, myxedema, polycythemia vera, deficiency of iron or vitamin A or D, and certain cancers (Bowen's disease, Paget's disease, Hodgkin's disease) are systemic causes. Local conditions include pinworms (*Enterobius vermicularis* infection), scabies (*Sarcoptes scabiei* infection), bacterial or fungal infections, and dermatologic manifestations of sexually transmitted diseases (STDs) (e.g., syphilis or herpes simplex virus [HSV], cytomegalovirus, or human papillomavirus infection).

Management

A careful history and physical examination can identify the cause of pruritus ani. Important considerations include hygienic care of the anus, coexisting anorectal or systemic conditions, diet, and sexual practices.

Pinworms can be identified by applying transparent tape to the perianal area and attaching it to a glass slide. Visualization of eggs under the low-power objective of a microscope confirms the diagnosis. The first-line agent is mebendazole (Vermox) 100 mg orally. An alternative agent is pyrantel pamoate (Antiminth) 1 g orally (11 mg/kg, to a maximum of 1 g for pediatric patients). The dose of either may need to be repeated in 2 weeks. Scabies and pediculosis pubis should be treated with 1% lindane lotion or 5% permethrin cream. Dermatitis caused by a fungal infection is characterized by sharply demarcated borders and is treated with clotrimazole or nystatin cream. Definitive treatment of concomitant anorectal conditions (e.g., fissures, fistulae, hemorrhoids, skin tags, rectal prolapse) can prevent recurrence of pruritus ani.[64]

Underlying systemic diseases that have perianal manifestations should be treated. Education on personal hygiene is of the utmost importance. Patients should be instructed to clean the area thoroughly with lukewarm water after each bowel movement and pat (rather than rub) it dry with a tissue or towel that is free of chemical irritants. Loose-fitting underwear and exposure to fresh air may aid in alleviating symptoms. The treatment of acute dermatitis includes a short course of topical corticosteroids,[65] calamine lotion, and systemic antihistamines. Some success with topical application of capsaicin cream has been reported.[62,66] Prevention of recurrent bouts of pruritus ani requires compliance with impeccable anal hygiene and minimizing the factors that caused the initial exacerbation.[63]

SEXUALLY TRANSMITTED DISEASES AND PROCTITIS

General Approach

Anorectal transmission of STDs is of particular concern in the patient with HIV infection. For patients who are sexually active, the history should ascertain whether sexual practices involve anal penetration and whether condoms are used. As a means of public health prevention of disease and patient safety, education regarding transmission of STDs and the efficacy of barrier methods is important.[67-69] Semen has a concentrated viral load, and the damaged epithelium of ulcerated anoderm makes an easy portal for entry of the virus. Syphilis, gonorrhea, and chlamydial infection have been documented among men who have sex with men. For this reason, routine STD screening is indicated.[67] A summary of common infections and treatment guidelines is presented in Table 96-5.

Surgical repair for benign anorectal conditions in HIV-positive patients should be undertaken early in the course of the disease, when potential wound healing and overall patient health are at their best.[68] Empirical therapy is indicated for patients who have recently practiced anal-receptive intercourse and have a rectal discharge. The recommended regimen is a single dose of ceftriaxone 250 mg intramuscularly plus doxycycline 100 mg twice a day orally for 7 days.[67] Patients with anorectal infections should be referred for HIV testing. The possibility of sexual assault should be considered and managed appropriately.[67] The health care provider should report STDs and new diagnoses of HIV infection in accordance with state and local health department regulations.

Treatment of Specific Sexually Transmitted Diseases

Gonorrhea

Gonorrhea is caused by the gram-negative diplococcus *Neisseria gonorrhoeae.* Proctitis (inflammation of the rectum) results from anal intercourse or autoinoculation from vaginal secretions and becomes symptomatic after a 5- to 7-day incubation period. Symptomatic patients report pruritus ani, tenesmus, and bloody or thick, purulent yellow drainage. Anoscopy reveals proctitis and mucus in the anal crypts. Recovery of the organism directly from the crypts doubles the likelihood of identifying the organism on Gram stain. Water should be used to lubricate the anoscope because many lubricants contain an antibacterial agent. Signs and symptoms of disseminated gonococcal infection may include arthritis, skin lesions, perihepatitis, endocarditis, and meningitis.[70]

Chlamydial Infection and Lymphogranuloma Venereum

Infection with *Chlamydia trachomatis,* an intracellular organism that is endemic to the tropics, is a common STD in the United States.[67,70] It causes proctitis in people whose sexual practices include anal intercourse or oral-anal contact. Common signs and symptoms include mucoid or bloody rectal discharge and tenesmus. Some people are asymptomatic carriers of the organism. Lymphogranuloma venereum is a more serious manifestation caused by specific strains of *C. trachomatis* and starts as a painful anal or perianal ulceration. Prominent unilateral lymph nodes coalesce to form a bubo, which must be distinguished from the granuloma of secondary syphilis. Patients often have systemic complaints of fever and malaise. Anoscopic examination reveals an erythematous, friable mucosa. Rectal cultures generally are unreliable because the organism is intracellular. Diagnosis is best achieved by immunofluorescent antibody testing. In the final stage, rectal strictures and rectovaginal fistulae may form.[70]

Herpes Simplex Virus Infection

Herpes proctitis is caused by both HSV-1 and HSV-2, but HSV-2 is responsible for approximately 90% of cases, especially in the HIV-positive population.[67,70] Herpes genital infections occur in people whose sexual practices include oral-anal contact or anal

www.ketabpezeshki.com 66485457-66963820

Table 96-5 Sexually Transmitted Diseases of the Anorectum

DISEASE OR CONDITION (WITH SPECIFIC PATHOGEN WHEN KNOWN)	FINDINGS	TREATMENT
Ulcerative Conditions		
LGV	Unilateral inguinal adenopathy Fever, malaise Mucoid or bloody discharge	Doxycycline 100 mg PO bid × 21 days *For pregnant patients or those allergic to tetracyclines*: Erythromycin 500 mg PO qid × 21 days
HSV infection	Rectal pain, tenesmus, constipation Bloody mucoid discharge Vesicles and ulcerations Fever, malaise, myalgias, paresthesias	*First episode*: Acyclovir 400 mg PO tid 7-10 days *or* Acyclovir 200 mg PO 5×/day × 7-10 days *or* Famciclovir 250 mg PO bid × 7-10 days *or* Valacyclovir 1 g PO daily for 7-10 days
Early (primary) syphilis *(Treponema pallidum)*	Chancre Tenesmus, pain, mucoid drainage Inguinal lymphadenopathy	Benzathine penicillin G 2.4 million units IM once
Chancroid *(Haemophilus ducreyi)*	Inflammatory lesion progresses to ulcer Inguinal adenitis—bubo	Azithromycin 1 g PO once *or* Ceftriaxone 250 mg IM once *or* Ciprofloxacin 500 mg PO bid × 3 days *or* Erythromycin 500 mg PO tid × 7 days
Idiopathic (usually HIV positive)	Eccentric, deep, poor healing, multiple lesions	Symptomatic relief or surgical referral
Nonulcerative Conditions		
Condylomata acuminata (HPV)	Keratinized vegetative growths in anus or skin Asymptomatic, or pruritus ani, or bleeding	Podofilox 0.5% topically, or cryotherapy
Gonorrhea *(Neisseria gonorrhoeae)*	Pruritus ani Tenesmus Purulent yellow discharge	Ceftriaxone 250 mg IM once *or* cefixime 400 mg PO once
Chlamydial infection *(Chlamydia trachomatis)*	Mucoid or bloody discharge Tenesmus	Azithromycin 1 g PO once *or* Doxycycline 100 mg PO twice per day × 7 days
Syphilis (secondary)	Maculopapular rash Condyloma latum	Benzathine penicillin G 2.4 million units IM once

HIV, human immunodeficiency virus; *HPV,* human papillomavirus; *HSV,* herpes simplex virus; *IM,* intramuscularly; *LGV,* lymphogranuloma venereum; *PO,* orally.

intercourse. Symptoms appear 1 to 3 weeks after exposure. Those with proctitis may have severe rectal pain, bloody mucoid discharge, tenesmus, constipation, sacral paresthesias, or urinary difficulties. Systemic complaints may include fever, malaise, and myalgias. Physical examination and anoscopy may be impossible without anesthesia. Single or coalesced vesicles and ulcerations occur in the perianal area and rectum, and anoscopy reveals an erythematous, friable, ulcerated rectal mucosa. Chronic mucocutaneous HSV infection is considered diagnostic for AIDS. Definitive diagnosis with viral or immunofluorescent staining relies on proper collection of fluid and scrapings from the base of the vesicle.[67,70]

Syphilis

Syphilis is caused by *Treponema pallidum,* a motile spirochete. During anal intercourse, the organism enters the rectal mucosa or anoderm and forms an ulcer (chancre) within 2 to 6 weeks. The chancre heralds the primary phase of syphilis and may resemble an anal fissure. Patients may experience discomfort during defecation, tenesmus, mucoid discharge, and inguinal adenopathy. Primary syphilis can be confused with lymphoma, but the diagnosis can be made by visualizing spirochetes on darkfield microscopy from scrapings taken from the base of the ulcer.[70] Serologic testing is useful several weeks after the appearance of the chancre. Treponemal tests such as the fluorescent treponemal antibody test yield a positive result earlier than does the Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (nontreponemal) test. Patients with AIDS have a high incidence of neurosyphilis regardless of the stage of syphilis at the time they seek treatment.[71]

If the chancre goes unnoticed, patients may have secondary syphilis on presentation, marked by a maculopapular rash that characteristically involves the palms and soles. Condyloma latum is a spirochete-laden, weeping, verrucous lesion in the perianal area that emits a foul odor. It is easily distinguishable from condyloma acuminatum, which has a drier, more keratinized appearance. Serologic testing results usually are positive. Tertiary syphilis is rare but may manifest as a rectal gumma with severe perianal pain and paralysis of the sphincters, which may be mistaken for anal cancer.[67]

Chancroid

Chancroid is caused by the gram-negative bacillus *Haemophilus ducreyi* and begins as an inflammatory pustule or macule that ruptures to form an irregularly shaped ulcer. In several days, painful inguinal adenitis develops. Chancroid often is a diagnosis of exclusion.

Condyloma Acuminatum

Condyloma acuminatum, the most commonly encountered anorectal STD, is caused by human papillomavirus. These lesions, also called *genital warts,* most often are found in homosexual men but can be seen in heterosexual men, women, and children. The mode

www.ketabpezeshki.com 66485457-66963820

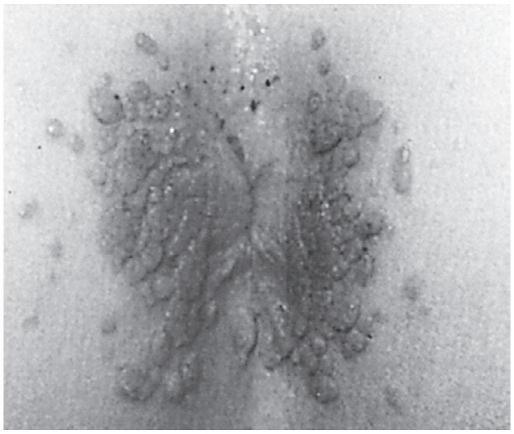


Figure 96-7. Condylomata acuminata in a child.

Figure 96-8. Prolapse of the rectum. (Courtesy Gershon Effron, MD, Sinai Hospital of Baltimore. From Seidel HM, et al: Mosby's Guide to Physical Examination, 4th ed. St Louis, Mosby, 1999.)

of transmission is primarily through sexual intercourse, but transmission can occur through close personal contact, as often happens in pediatric cases in which an infected person is changing a diaper and transmits the virus to the infant because of poor handwashing techniques. It is incumbent on the evaluating physician to consider sexual abuse in such cases.[21] Because one half of HIV-positive patients have anal warts, HIV testing is recommended in patients with this diagnosis.[67]

The pink-to-gray warts are a result of hyperplastic epithelial growth and appear as vegetative papilliform growths (Fig. 96-7). They may coalesce to form a massive patch that obscures the anal verge.[33] Many patients are asymptomatic or report pruritus ani, a "hemorrhoid," or bleeding. Evaluation should include anoscopy because the warts often grow within the anal canal. Failure to treat the internal lesions results in recurrence.[67,70] The differential diagnosis includes the condyloma latum of secondary syphilis and squamous cell carcinoma. Progression to intraepithelial neoplasia has been reported to be related to the level of immunosuppression. Preferred treatment is cryotherapy, but outpatient treatment with 0.5% podofilox solution or gel can be successful in limited cases.[67]

Ulcerative Lesions in the Patient with HIV Infection

The practice of anal intercourse has led to a proliferation of anorectal STDs. Most patients who are HIV seropositive have current or past infection with an STD, which may be the initial reason for seeking medical attention. One third of anorectal complaints in this population fall into three categories: (1) routine proctologic conditions as seen in the general population, (2) STDs, and (3) opportunistic infections (Box 96-6). The treatment of routine conditions and common STDs is similar to that in other patients except that wound healing may be slower in HIV-infected patients.

In immunocompromised patients, the differential diagnosis of ulcerative anorectal lesions should include opportunistic infections, lymphoma, and Kaposi's sarcoma. Patients with AIDS often exhibit idiopathic anal ulcerations with pain and bleeding. Before this diagnosis is made, other possible causes of the lesions must be considered (see Box 96-6). Symptomatic relief can often be achieved with the WASH regimen (see Box 96-2), but recalcitrant lesions may require surgical excision.[67,70]

Radiation Proctitis

Radiation-induced injury of the rectum is often caused by treatment of gynecologic, urologic, and GI malignancies. Immediate radiation proctitis usually is self-limited and responds to symptomatic treatment. Delayed radiation proctitis can manifest up to 2 years after the exposure to radiation and may predispose the patient to subsequent rectal malignancies as a result of damage to DNA.

Signs and symptoms of radiation proctitis include bleeding ranging in severity from spotting to hemorrhage, tenesmus, diarrhea, pain, fistula in ano, and rectal strictures. Diagnosis is achieved by rectal mucosal biopsy, a procedure best performed with the patient under sedation or anesthesia.

Treatment regimens include the use of anti-inflammatory agents, botulinum toxin injection, enemas with short-chain fatty acids, oral sucralfate therapy, hyperbaric oxygen therapy, and sclerosing therapy.[72-75] Supportive therapy can be given for symptoms that the individual patient experiences.

Procidentia

Rectal prolapse, or procidentia, is a disease of persons at the extremes of age. Prolapse is *complete* if all bowel layers protrude and *incomplete* if only the mucosal layer is involved. In adults, complete procidentia is most common among older women with a history of excessive straining while defecating. The cause is a laxity of attachment structures, and the rectal prolapse often is accompanied by uterine prolapse or cystocele. Patients report an anal mass that protrudes during defecation, coughing, or sneezing. Findings may include fecal incontinence, bloody or mucoid discharge, and a foul odor. In some cases the patient is able to reduce the prolapse manually, whereas in others the tissue becomes edematous and a red, ulcerated mass protrudes from the anus (Fig. 96-8). Sphincter tone may be weakened. Reduction may be attempted; when this is successful, the patient should be discharged with agents to relieve constipation. Surgical repair often is necessary.[76,77]

In children up to 4 years of age, procidentia often is associated with chronic constipation or diarrheal disease. However, it may herald the presence of malnutrition, parasitic infection, or cystic fibrosis.[78] Children usually have a mucosal prolapse. The parent reports protrusion during defecation with small amounts of mucus or blood. This condition must be distinguished from a protruding juvenile polyp and intussusception. Gentle reduction may be attempted. Conservative medical management aimed at the cause of procidentia often is successful because of the self-limited nature of the condition in children. Increasing the dietary fiber and fluid intake frequently is successful as a first line of therapy.[77,78]

www.ketabpezeshki.com 66485457-66963820

Box 96-6 Anorectal Lesions in the Patient with HIV Disease

Common Conditions
Anal fissure
Abscess and fistula
Hemorrhoids
Pruritus ani
Pilonidal disease

Common STDs
Gonorrhea
Chlamydial infection
Herpes
Chancroid
Syphilis
Condyloma acuminatum

Atypical Conditions
Infectious
TB, CMV infection, actinomycosis, cryptococcosis

Neoplastic
Lymphoma, Kaposi's sarcoma, squamous cell carcinoma

Other
Idiopathic anal ulcer

CMV, cytomegalovirus; *HIV,* human immunodeficiency virus; *STD,* sexually transmitted disease; *TB,* tuberculosis.

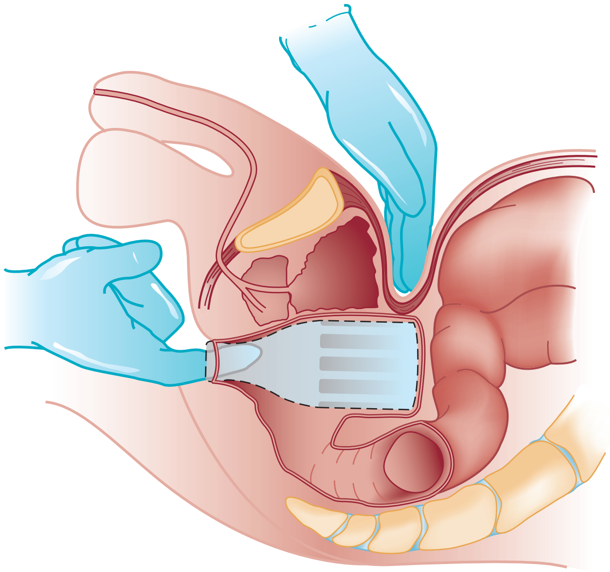


Figure 96-9. Removal of a foreign body from the rectum.

Anorectal Foreign Bodies

Perspective

Anorectal foreign bodies may result from the use of the anus for sexual gratification, although they also are found in children, psychiatric patients, and victims of assault or iatrogenic injury. Most objects are introduced directly into the anus, but some become lodged there after oral ingestion. It is important to identify and remove foreign bodies to prevent mucosal lacerations, intestinal perforation and obstruction, sepsis, and peritonitis.[79,80] In many cases, removal can be done safely in the ED.

Clinical Features

Objects Inserted into the Anus. Rarely, a foreign body such as an enema tip or broken rectal thermometer is introduced iatrogenically. In most cases the foreign body is placed deliberately by the patient or a partner for medicinal or sexual purposes. Objects that are commonly retrieved include fruits and vegetables; household items, especially those whose dimensions resemble the penis; and items purchased specifically with an anal erotic intent.[80,81] By the time patients arrive at the ED, sometimes days after the introduction of the foreign body, they have likely tried to remove it at home. The history of the injury often is reluctantly given or is vague and inconsistent. The initial ED evaluation, conducted in a nonjudgmental manner, attempts to ascertain the type of foreign body involved, how long it has been there, what attempts have been made to remove it, and whether the patient has fever, abdominal pain, or rectal bleeding. The possibility of assault should be considered.[81]

Physical examination of the anorectum begins with an external examination for signs of trauma followed by digital rectal examination and anoscopy, which may reveal the foreign body, a lax sphincter, or a mucosal injury. Abdominal examination may demonstrate signs of perforation or obstruction. The foreign body may be visible on abdominal radiographs, or its presence may be inferred by a nonspecific gas pattern, free air, or signs of intestinal obstruction.[80] If perforation is suspected, water-soluble contrast material can be introduced to delineate radiolucent foreign bodies.

Orally Ingested Foreign Bodies. Some foreign bodies that are ingested orally, especially toothpicks and fish or chicken bones, pass through the GI tract and subsequently become lodged in the rectum or anal crypts.[81] Patients at highest risk for ingested foreign bodies are children, especially those in the first 2 years of life; psychiatric patients; and body packers who ingest condoms containing drugs.

Management

Optimal treatment depends on the location and type of object found.[79] In general, objects that are soft and low-lying (less than 10 cm from the anal verge) can be removed safely in the ED. Large, hard, fragile objects and those that have migrated proximally are difficult to remove without anal dilation and instrumentation to assist in the passage through the sacral curve and sphincters. These are best performed with the patient under general anesthesia.[82] As a rule, however, the patient should remain awake to assist in expulsion by performing the Valsalva maneuver at the appropriate time, and premedication with a benzodiazepine is helpful to relax both the sphincter and the patient.[81] With the patient in the lithotomy position, suprapubic pressure can assist in removal (Fig. 96-9). Other positions may be more appropriate for a particular foreign body.

Several methods are effective for removal. The easiest is to grasp an edge of the foreign body with forceps and apply traction while the patient bears down. Most foreign bodies in the rectum do not have a convenient place to grasp, and other methods are needed. A Foley catheter can be placed beside the foreign body and the balloon inflated proximal to it (Fig. 96-10). This breaks the suction of the rectal wall mucosa and provides a way to guide the object out of the rectal vault. Hollow objects may be filled with plaster of Paris, with an inset, inflated Foley catheter to be used as a handle.[81]

Other creative ways to remove foreign bodies in the ED have been successful, and an individualized strategy for each patient is essential. After the removal of the foreign body, all patients should undergo sigmoidoscopy to look for mucosal tears and perforations. Discharge instructions should warn the patient about signs and symptoms of perforation, peritonitis, and sepsis.[80]

www.ketabpezeshki.com 66485457-66963820

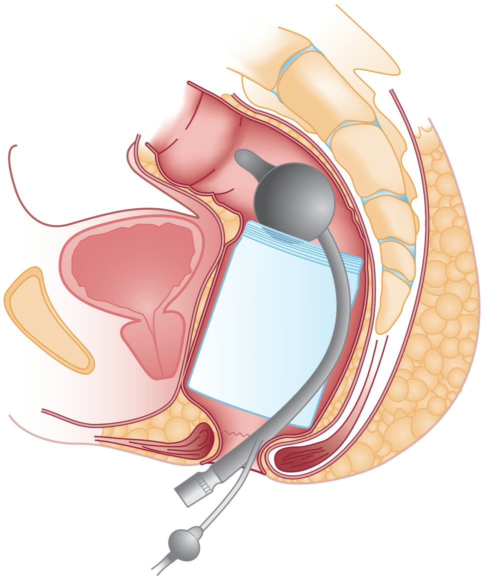


Figure 96-10. Foley catheter–assisted removal of a rectal foreign body.

KEY CONCEPTS

- Patients who seek treatment for nonspecific anorectal complaints should be evaluated for the presence of underlying systemic disease (e.g., cancer, diabetes mellitus, immunodeficiency) because disorders of the anus may herald associated conditions.
- Patients with any STD should be evaluated for HIV infection and questioned about the use of the anus for sexual purposes.
- Anorectal conditions can be differentiated according to an algorithm (see Fig. 96-2) that addresses the presence or absence of pain, bleeding, swelling, and pruritus, in combination with an assessment of the patient's overall health.
- Most anorectal conditions can be symptomatically improved by adherence to the WASH regimen (warm water, analgesics, stool softeners, high-fiber diet).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Barleben A, Mills S: Anorectal anatomy and physiology. *Surg Clin North Am* 2010; 90:1-15.
2. Gopal DV: Diseases of the rectum and anus: A clinical approach to common disorders. *Clin Cornerstone* 2002; 4:34.
3. Tan BK, Tsang CB, Nyam DC, Ho YH: Management of acute bleeding per rectum. *Asian J Surg* 2004; 27:32.
4. New American Bible. New York: Fireside Bible Publishers; 2001.
5. Welling DR, Wolff BG, Dozois RR: Piles of defeat: Napoleon at Waterloo. *Dis Colon Rectum* 1988; 31:303.
6. Sneider EB, Maykel JA: Diagnosis and management of symptomatic hemorrhoids. *Surg Clin North Am* 2010; 90:17-32.
7. Thomson WH: The nature of haemorrhoids. *Br J Surg* 1975; 62:542.
8. Kaidar-Person O, Person B, Wexner SD: Hemorrhoidal disease: A comprehensive review. *J Am Coll Surg* 2007; 204:102.
9. Abramowitz L, et al: Anal fissure and thrombosed external hemorrhoids before and after delivery. *Dis Colon Rectum* 2002; 45:650.
10. Bharucha AE, Wald AM: Anorectal disorders. *Am J Gastroenterol* 2010; 105:786-794.
11. Lorenzo-Rivero S: Hemorrhoids: Diagnosis and current management. *Am Surg* 2009; 75:635-642.
12. Heaton ND, Davenport M, Howard ER: Symptomatic hemorrhoids and anorectal varices in children with portal hypertension. *J Pediatr Surg* 1992; 27:833.
13. Heaton ND, Davenport M, Howard ER: Incidence of haemorrhoids and anorectal varices in children with portal hypertension. *Br J Surg* 1993; 80:616.
14. Acheson AG, Scholefield JH: Management of haemorrhoids. *BMJ* 2008; 336:380-383.
15. Madoff RD, Fleshman JW: Clinical practice committee, American Gastroenterological Association, American Gastroenterological Association technical review on the diagnosis and treatment of hemorrhoids. *Gastroenterology* 2004; 126:1463.
16. Alonso-Coello P, et al: Fiber for the treatment of hemorrhoids complications: A systematic review and meta-analysis. *Am J Gastroenterol* 2006; 101:181.
17. Jongen J, Bach S, Stübinger SH, Bock JU: Excision of thrombosed external hemorrhoid under local anesthesia: A retrospective evaluation of 340 patients. *Dis Colon Rectum* 2003; 46:1226.
18. Perrotti P, et al: Topical nifedipine with lidocaine ointment vs. active control for treatment of chronic anal fissure: Results of a prospective, randomized, double-blind study. *Dis Colon Rectum* 2002; 45:1468.
19. Herzig DO, Lu KC: Anal fissure. *Surg Clin North Am* 2010; 90:33-44.
20. Matt JG: Proctologic problems in infants and children: An analysis of 308 cases. *Dis Colon Rectum* 1960; 3:511.
21. Behrman R, Kliegman RM, Jenson HB, eds: *Nelson's Textbook of Pediatrics*, 17th ed. Philadelphia: WB Saunders; 2003.
22. Collins EE, Lund JN: A review of chronic anal fissure management. *Tech Coloproctol* 2007; 11:209.
23. Dharwan S, Chopra S: Non-surgical approaches for the treatment of anal fissures. *Am J Gastroenterol* 2007; 102:1312-1321.
24. Festen S, Gisbertz SS, van Schaagen F, Gerhards MF: Blinded randomized clinical trial of botulinum toxin versus isosorbide dinitrate ointment for treatment of anal fissure. *Br J Surg* 2009; 96:1393-1399.
25. Cundall JD, Gardiner A, Laden G, Grout P, Duthie GS: Use of hyperbaric oxygen to treat chronic anal fissure. *Br J Surg* 2003; 90:452.
26. Ahmad J, Andrabi SI, Rathore MA: Comparison of topical glyceryl trinitrate with lignocaine ointment for treatment of anal fissure: A randomised controlled trial. *Int J Surg* 2007; 5:429.
27. Nelson R: A systematic review of medical therapy for anal fissure. *Dis Colon Rectum* 2004; 4:422.
28. Sajid MS, Rimple J, Cheek E, Baigi MK: The efficacy of diltiazem and glyceryl trinitrate for the medical management of chronic anal fissure: A meta analysis. *Int J Colorectal Dis* 2008; 23:1.
29. Ezri T, Susmallian S: Topical nifedipine vs. topical glyceryl trinitrate for treatment of chronic anal fissure. *Dis Colon Rectum* 2003; 46:805.
30. Brisinda D, Maria G, Fenici R, Civello IM, Brisinda G: Safety of botulinum neurotoxin treatment in patients with chronic anal fissure. *Dis Colon Rectum* 2003; 46:419.
31. Brisinda G, Maria G: Botulinum toxin in the treatment of chronic anal fissure. *Dis Colon Rectum* 2003; 46:1144.
32. Mitka M: Colon and rectal surgeons are trying Botox treatment, too. *JAMA* 2002; 288:439.
33. Helton WS: 2001 Consensus statement on benign anorectal disease. *J Gastrointest Surg* 2002; 6:302.
34. Sajid MS, Vijaynagar B, Desai M, Cheek E, Baig MK: Botulinum toxin vs glyceryltrinitrate for the medical management of chronic anal fissure: A meta analysis. *Colorectal Dis* 2008; 10:541.
35. Rizzo JA, Naig AL, Johnson EK: Anorectal abscess and fistula-in-ano: Evidence based management. *Surg Clin North Am* 2010; 90:45-68.
36. Murthi GV, Okoye BO, Spicer RD, Cusick EL, Noblett HR: Perianal abscess in childhood. *Pediatr Surg Int* 2002; 18:689.
37. Koutroubakis IE: The patient with persistent perianal fistulae. *Best Pract Res Clin Gastroenterol* 2007; 21:503.
38. Nunoo-Mansah JW, et al: Fistula-in-ano: Do antibiotics make a difference? *Int J Colorectal Dis* 2006; 21:441.
39. Malik AI, Nelson RL, Tou S: Incision and drainage of perianal abscess with or without treatment of anal fistula. *Cochrane Database Syst Rev* 2010; 7:CD006827.
40. Yano T, et al: Prognostic factors for recurrence following the initial drainage of an anorectal abscess. *Int J Colorectal Dis* 2010; 25:1495-1498.
41. Dietz DW: Role of fibrin glue in the management of simple and complex fistula in ano. *J Gastrointest Surg* 2006; 10:631.
42. Anderson AW: Hair extracted from an ulcer. *Boston Med Surg J* 1847; 37:74.
43. Lee PJ, et al: Sacrococcygeal pilonidal disease. *Colorectal Dis* 2008; 10:639-652.
44. Chintapatla S, Safarani N, Kumar S, Haboubi N: Sacrococcygeal pilonidal sinus: Historical review, pathological insight and surgical options. *Tech Coloproctol* 2003; 7:3.
45. Haworth JC, Zachary RB: Congenital dermal sinuses in children—their relation to pilonidal sinus. *Lancet* 1955; 2:10.
46. Billingham RP: Anorectal miscellany: Pilonidal disease, anal cancer, Bowen's and Paget's diseases, foreign bodies, and hidradenitis suppurativa. *Prim Care* 1999; 26:171.
47. Tejirian T, Lee JJ, Abbas MA: Is wide local excision for pilonidal disease still justified? *Am Surg* 2007; 73:1075.
48. Mitchell KM, Beck DE: Hidradenitis suppurativa. *Surg Clin North Am* 2002; 82:1187.
49. Fernandez-Vozmediano JM, Armario-Hita JC: Infliximab for the treatment of hidradenitis suppurativa. *Dermatology* 2007; 215:41.
50. Bocchini SF, Habr-Gama A, Kiss DR, Imperiale AR, Araujo SE: Gluteal and perianal hidradenitis suppurativa: Surgical treatment by wide excision. *Dis Colon Rectum* 2003; 46:944.
51. Slade DEM, Powell BW, Mortimer PS: Hidradenitis suppurativa: Pathogenesis and management. *Br J Plast Surg* 2003; 56:451.
52. Ather S, Chan DS, Leaper DJ, Harding KG: Surgical treatment of hidradenitis suppurativa: A case series and review of the literature. *Int Wound J* 2006; 3:159.
53. Bharucha AE, Wald A, Enck P, Rao S: Functional anorectal disorders. *Gastroenterology* 2006; 130:1510.
54. Jeyarajah S, Chow A, Ziprin P, Tilney H, Purkayastha S: Proctalgia fugax, an evidence-based management pathway. *Int J Colorectal Dis* 2010; 25:1037-1046.
55. Hetrick DC, et al: Musculoskeletal dysfunction in men with chronic pelvic pain syndrome type III: A case-control study. *J Urol* 2003; 170:828.
56. Pilling LF, Swenson WM, Hill JR: The psychologic aspects of proctalgia fugax. *Dis Colon Rectum* 1965; 8:372.
57. Leung FW, Rao SSC: Fecal incontinence in the elderly. *Gastroenterol Clin North Am* 2009; 38:503-511.
58. Mellgren A: Fecal incontinence. *Surg Clin North Am* 2010; 90:185-194.
59. Peña A, Hong AR, Midulla P, Levitt M: Reoperative surgery for anorectal anomalies. *Semin Pediatr Surg* 2003; 12:118.
60. Loening-Baucke V: Encopresis. *Curr Opin Pediatr* 2002; 14:570.
61. Oztürk H, et al: Management of anorectal injuries in children: An eighteen-year experience. *Eur J Pediatr Surg* 2003; 13:249.
62. Norton C, Wilson-Barnett J, Redfern S, Kamm MA: Randomized controlled trial of biofeedback for fecal incontinence. *Gastroenterology* 2003; 125:1320.
63. Markell KW, Billingham RP: Pruritus ani: Etiology and management. *Surg Clin North Am* 2010; 90:125-135.
64. Stermer E, Sukhotnic I, Shaoul R: Pruritus ani: An approach to an itching condition. *J Pediatr Gastroenterol Nutr* 2009; 4:513-516.
65. Al-Ghnaniem R, et al: 1% Hydrocortisone ointment is an effective treatment of pruritus ani: A pilot randomized controlled crossover trial. *Int J Colorectal Dis* 2007; 22:1463.
66. Lysy J, et al: Topical capsaicin—a novel and effective treatment for idiopathic intractable pruritus ani: A randomised, placebo controlled, crossover study. *Gut* 2003; 52:1323.
67. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC): Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep* 2010; 59(RR-12):1-116.

www.ketabpezeshki.com 66485457-66963820

68. Law CL, Qassim M, Cunningham AL, Mulhall B, Grierson JM: Nonspecific proctitis: Association with human immunodeficiency virus infection in homosexual men. *J Infect Dis* 1992; 165:150.
69. Kim AA, Kent CK, Klausner JD: Risk factors for rectal gonococcal infection amidst resurgence in HIV transmission. *Sex Transm Dis* 2003; 30:813.
70. Lee PK, Wilkins KB: Condyloma and other infections including human immunodeficiency virus. *Surg Clin North Am* 2010; 90:99-112.
71. Bordón J, et al: Neurosyphilis in HIV infected patients. *Eur J Clin Microbiol Infect Dis* 1995; 14:864.
72. Henson C: Chronic radiation proctitis: Issues surrounding delayed bowel dysfunction post-pelvic radiotherapy and an update on medical treatment. *Ther Adv Gastroenterol* 2010; 3:359-365.
73. Wong MT, et al: Radiation proctitis: A decade's experience. *Singapore Med J* 2010; 51:315-319.
74. Jones K, Evans AW, Bristow RG, Levin W: Treatment of radiation proctitis with hyperbaric oxygen. *Radiother Oncol* 2006; 78:91.
75. Leiper K, Mossir AI: Treatment of radiation proctitis. *Clin Oncol (R Coll Radiol)* 2007; 19:724.
76. Madbouly KM, et al: Clinically based management of rectal prolapse. *Surg Endosc* 2003; 17:99.
77. Karulf RE, Madoff RD, Goldberg SM: Rectal prolapse. *Curr Probl Surg* 2001; 38:771.
78. Antao B, Bradley V, Roberts JP, Shawis R: Management of rectal prolapse in children. *Dis Colon Rectum* 2005; 48:1620.
79. Rodríguez-Hermosa JI, et al: Management of foreign bodies in the rectum. *Colorectal Dis* 2006; 9:543.
80. Goldberg JE, Steele SR: Rectal foreign bodies. *Surg Clin North Am* 2010; 90:173-184.
81. Johnson SO, Hartranft TH: Nonsurgical removal of a rectal foreign body using a vacuum extractor: Report of a case. *Dis Colon Rectum* 1996; 39:935.
82. Lake JP, et al: Management of retained colorectal foreign bodies: Predictors of operative intervention. *Dis Colon Rectum* 2004; 47:1694.

www.ketabpezeshki.com 66485457-66963820

Section Six

GENITOURINARY AND GYNECOLOGIC SYSTEMS

Chapter 97

Renal Failure

Allan B. Wolfson

EVALUATION OF RENAL FUNCTION

The evaluation of renal disease in the emergency department (ED) requires the intelligent use of urinalysis, serum and urine chemical determinations, and renal imaging studies to assess the degree of renal dysfunction and to take the first steps in determining its cause.

Diagnostic Strategies

Urine Volume

Because urine flow does not diminish until the glomerular filtration rate (GFR) is sharply decreased, urine volume is a poor indicator of renal dysfunction. In fact, urine volume often *increases* as concentrating ability is lost with advancing renal dysfunction; patients with renal failure typically produce urine that is isosmolar with serum. *Oliguria,* defined as a urine volume of 100 to 400 mL/24 hr, may be seen with prerenal (blood flow dependent), intrinsic (intrarenal), or postrenal (obstructive) causes of acute kidney injury (AKI) (previously known as *acute renal failure* [ARF]). Although uncommon, alternating oliguria and anuria (the latter defined as less than 100 mL/24 hr), is a classic indicator of intermittent obstruction, which occurs as urine collects behind an obstructing stone or tumor and then is allowed to flow past as the obstructing material shifts position.

Urinalysis

The standard urinalysis consists of dipstick screening for heme pigment, protein, glucose, ketones, pH, leukocyte esterase, and nitrite and microscopic examination of a spun specimen of freshly voided urine.

Heme

The dipstick detects both free hemoglobin from lysed red blood cells (RBCs) (or myoglobin) and the hemoglobin inside RBCs but is more sensitive to free hemoglobin. Although as few as three RBCs per high-power field can be detected, on any given sample the dipstick may fail to identify 10 to 15% of patients who are otherwise found to have microscopic hematuria, as defined by more than five RBCs per high-power field. A positive result on dipstick testing should prompt microscopic examination of the urine. If red cells are seen, the diagnosis of hematuria is confirmed. If the dipstick result is positive but findings on microscopic examination are negative, pigmenturia (myoglobin or free hemoglobin) is suspected as a potential cause.

Protein

The dipstick test for protein, which uses the color change of tetrabromophenol blue, can detect protein at concentrations of 10 to 15 mg/dL but does not yield reliably positive results until the concentration is greater than 30 mg/dL. Moreover, the relation between color intensity and protein concentration is only approximate. The dipstick reagent is three to five times more sensitive to albumin than to globulins and immunoglobulin light chains (e.g., Bence Jones protein)—an important limitation.[1] False-positive results are caused by alkaline urine, hematuria, or prolonged immersion of the dipstick in the urine. False-negative results are seen with dilute urine.

Microscopic Examination

After dipstick testing of the urine has been completed, 10 mL of urine is placed in a conical test tube and spun at 2000 revolutions per minute for 5 minutes (higher speeds may break up casts). The supernatant is discarded. The sediment is resuspended in the residual urine, and a drop is placed on a slide and covered with a coverslip. Observations are recorded as the number of cells per high-power field. A level of two to three RBCs per high-power field in adult men or two to four RBCs per high-power field in adult women is commonly accepted as normal; in many studies a finding of five RBCs per high-power field is considered to represent the threshold of abnormality.[2]

Casts are formed from urinary Tamm-Horsfall protein, a product of the tubular epithelial cells that gels at low pH and high concentration and when mixed with albumin, or from red cells, tubular cells, or cellular debris in the urine. The composition of a cast thus reflects the contents of the tubule. Casts are described and classified according to their appearance or constituents (e.g., hyaline, red cell, white cell, granular, or fatty casts). Hyaline casts, those that are devoid of contents, are seen with dehydration, after exercise, or in association with glomerular proteinuria. Red cell casts indicate glomerular hematuria, as seen in glomerulonephritis; the presence of even a few red cell casts is significant. White cell casts imply the presence of renal parenchymal inflammation. Granular casts are composed of cellular remnants and debris. Fatty casts, like oval fat bodies, generally are associated with heavy proteinuria and nephrotic syndrome.

Microscopic examination of the urinary sediment can be helpful in establishing the cause of AKI. A sediment without

www.ketabpezeshki.com 66485457-66963820

formed elements or with only hyaline casts is characteristic of prerenal azotemia or obstruction. Red cell casts suggest glomerulonephritis or vasculitis. Fatty casts also suggest glomerular disease. In acute tubular necrosis (ATN), the urinary sediment commonly shows granular casts and renal tubular epithelial cells. Large numbers of polymorphonuclear leukocytes are observed in interstitial nephritis, papillary necrosis, and pyelonephritis. Eosinophil-containing casts (appreciated only after staining of the sediment) are typical of allergic interstitial nephritis. Uric acid crystals suggest uric acid nephropathy but are extremely nonspecific; oxalic acid or hippuric acid crystals may be seen in ethylene glycol ingestion.

Serum and Urine Chemical Analysis

Creatinine and Blood Urea Nitrogen. The normal range for the serum creatinine level extends from 0.5 mg/dL in thin people to 1.5 mg/dL in muscular persons. Spurious elevations (up to 2 mg/dL) can be caused by acetoacetate (which cross-reacts with creatinine in commonly used assays) as well as by certain medications that either cross-react in the assay or reversibly inhibit tubular creatinine secretion despite a normal GFR (generally less than 0.5 mg/dL). Serum creatinine concentration is a function of the amount of creatinine entering the blood from muscle, its volume of distribution, and its rate of excretion. Because the first two are usually constant, changes in serum creatinine concentration generally reflect changes in GFR. The creatinine clearance is commonly estimated by the Cockcroft-Gault equation[3]:

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight}}{72 \times \text{serum creatinine}} \times (0.85 \text{ if female})$$

Table 97-1 Typical Urinary Findings in Prerenal Azotemia and Acute Tubular Necrosis

LABORATORY TEST FINDING	PRERENAL AZOTEMIA	ACUTE TUBULAR NECROSIS
Urinalysis	Normal or hyaline casts	Brown granular casts, cellular debris
Urine sodium concentration (mEq/L)	<20	>40
Fractional excretion of sodium (%)	<1	>1
Urine-to-plasma creatinine ratio	>40	<20

Box 97-1 Causes of High or Low FENa and UNa in Patients with Acute Kidney Injury

UNa <20 mEq/L, FENa <1%	UNa >40 mEq/L, FENa >1%
Prerenal azotemia	ATN (90% of cases)
Acute glomerulonephritis	Chronic obstruction
Acute obstruction	Diuretic drugs
Contrast-induced ATN (some cases)	Osmotic diuresis
Rhabdomyolysis-associated ATN (some cases)	Underlying chronic renal failure
Early sepsis	
Nonoliguric ATN (10% of cases)	

From Kelley WN (ed): Internal Medicine, 2nd ed. Philadelphia, JB Lippincott, 1992.
ATN, acute tubular necrosis; *FENa,* fractional excretion of sodium; *UNa,* urine sodium concentration.

Under steady-state conditions, if the GFR is halved, the serum creatinine doubles. Abrupt cessation of glomerular filtration causes the serum creatinine to rise by 1 to 2 mg/dL per day. Thus a daily increment of less than 1 mg/dL suggests that at least some renal function has been preserved. Rhabdomyolysis releases creatine into the plasma and may cause the serum creatinine to increase by more than 2 mg/dL per day. The blood urea nitrogen (BUN) level also rises with renal dysfunction but is influenced by many extrarenal factors as well. Increased protein intake, gastrointestinal (GI) bleeding, and the catabolic effects of fever, trauma, infection, and drugs such as tetracycline and corticosteroids all increase protein turnover and result in increased hepatic urea production and increased BUN. Conversely, BUN tends to be decreased in patients with liver failure or protein malnutrition.

When glomerular filtrate has been formed, renal urea clearance is largely a function of flow rate. Urea clearance is thus decreased in patients with prerenal azotemia or acute obstruction, despite preservation of tubular function. In such cases the BUN/creatinine ratio usually is greater than the normal value of 10 : 1, whereas this ratio usually is not markedly increased in cases of uncomplicated intrinsic AKI.

Urine Sodium and Fractional Excretion of Sodium. Measurement of the urine sodium concentration provides information on the integrity of tubular reabsorptive function. Normally, urine sodium concentration parallels sodium intake. Low urine sodium concentration thus indicates not only intact reabsorptive function but also the presence of a stimulus to conserve sodium. The urine sodium concentration, as well as the fractional excretion of sodium (FENa), an additional measure of tubular sodium handling, helps distinguish between the two most common causes of AKI: prerenal azotemia and ATN (Table 97-1).

Urinary indices are most helpful in oliguric patients.[4] In general, an oliguric patient with a urine sodium concentration below 20 mEq/L and an FENa below 1% should be considered to have prerenal azotemia, whereas urine sodium concentration above 40 mEq/L and FENa above 1% suggest ATN. Values in patients with prerenal azotemia overlap somewhat with those in patients with nonoliguric ATN, particularly if the renal injury is mild and some capability to retain sodium has been preserved. Thus, intermediate values for urine sodium concentration and FENa are of little help in differentiating between the two conditions. The administration of mannitol or a loop diuretic within the several hours preceding urine collection also may make interpretation of urine values difficult because the urinary sodium will tend to be higher and the urine less concentrated, causing the results in prerenal azotemia to resemble those in intrinsic renal failure (Box 97-1).

In glomerulonephritis, the urinary indices generally reflect intact tubular sodium handling, but the diagnosis is more accurately made by urine microscopy. In obstructive uropathy, the values of the urinary indices depend on the duration of obstruction and cannot be relied on to indicate either the presence or absence of obstruction.

Renal Imaging

Renal imaging is often helpful in evaluation of the patient with kidney dysfunction, particularly when obstruction is suspected. Contrast-enhanced computed tomography (CT) scanning provides an anatomic image of the urinary tract but does not provide an evaluation of renal function. The classic CT findings of obstruction are kidneys that are normal to large in size, nephrograms that become increasingly dense, and delayed opacification of dilated collecting systems. However, contrast-enhanced CT subjects the kidneys of an already azotemic patient to the risk of an additional potential insult from the contrast agent. Thus techniques such as

www.ketabpezeshki.com 66485457-66963820

Figure 97-1. Computed tomography scan of bilateral hydronephrotic kidneys without intravenous contrast medium.

Box 97-2 Causes of Hematuria

Hematologic Causes
Coagulopathy
Sickle hemoglobinopathies

Renal Causes
Glomerular
Primary glomerular disease
Multisystem disease (e.g., systemic lupus erythematosus, Henoch-Schönlein purpura, hemolytic uremic syndrome, polyarteritis nodosa, Wegener's granulomatosis, Goodpasture's syndrome)

Nonglomerular
Renal infarction
Tuberculosis
Pyelonephritis
Polycystic kidney disease
Medullary sponge kidney
Acute interstitial nephritis
Tumor
Vascular malformation
Trauma
Papillary necrosis

Postrenal Causes
Stones
Tumor of ureter, bladder, urethra
Cystitis
Benign prostatic hypertrophy
Prostatitis, urethritis
Foley catheter placement
Exercise
Tuberculosis

ultrasonography and CT that do not involve contrast administration are much preferred in patients with preexisting renal insufficiency (Fig. 97-1).

Computed Tomography. Noncontrast CT may be useful in evaluating some azotemic patients. Hydronephrosis can be recognized without the use of contrast material. Often, dilated ureters also can be seen without contrast enhancement, and the level of obstruction can be determined. Moreover, the cause of obstruction (e.g., bilateral stones, lymphoma, retroperitoneal hemorrhage, metastatic cancer, retroperitoneal fibrosis) often can be delineated as well. Occasionally, obstruction severe enough to result in renal failure may not cause detectable proximal dilation of the urinary tract. Bilateral ureteral obstruction produced by malignancy or retroperitoneal fibrosis is the most important cause of this nondilated obstructive uropathy. When noninvasive studies yield negative results, the diagnosis of obstruction can be made by retrograde pyelography or by antegrade pyelography performed via a percutaneous nephrostomy.

Ultrasonography. Ultrasonography allows accurate measurement of renal dimensions and is a safe and reasonably reliable method of excluding obstruction as a cause of AKI. The normal kidney shows an echo-free renal parenchyma surrounding the echogenic central urothelium of the renal pelvis and calices. The sonographic appearance of the kidney in obstruction is that of an enlarged central sonolucent area that spreads the normal central echo densities. A similar pattern may be produced by renal cysts, but without associated ureteral dilation. Dilation of the collecting system generally is apparent within 24 to 36 hours of the onset of obstruction, but obstruction may not be evident in patients who are evaluated early in the development of obstructive AKI.

HEMATURIA AND PROTEINURIA

Hematuria

Principles of Disease

Microscopic hematuria often is discovered incidentally on routine urinalysis, but as little as 1 mL of blood in 1 L of urine can cause grossly appreciable hematuria. Although not invariably a sign of disease, the finding of hematuria calls for an effort to rule out any treatable underlying disorder. Both gross and microscopic hematuria are caused by similar disorders, but the amount of blood in the urine does not correlate with the severity or the seriousness of the underlying condition.[2]

The causes of hematuria can be divided into hematologic, renal, and postrenal; renal causes may be further classified as glomerular or nonglomerular (Box 97-2). Overall, the most common causes of nontraumatic hematuria, in roughly descending order of occurrence, are kidney stones, urinary tract infection (UTI), carcinoma of the kidney or bladder, urethritis, benign prostatic hypertrophy, and glomerulonephritis. The scope of the differential diagnosis can be narrowed by taking into account the patient's age and sex and by distinguishing between upper and lower urinary tract sources. When gross hematuria is present, cystoscopy can determine whether blood is emerging from one or both ureteral orifices, thereby defining a source in the upper tract. Red cell casts indicate a renal source, as does associated proteinuria (excretion of more than 500 mg of albumin in 24 hours). In differentiating between proteinuria from renal parenchymal disease and that simply produced by admixture of urine with extravasated blood, a useful rule of thumb is that 1 mL of whole blood contains approximately 5 billion RBCs and approximately 50 mg of albumin.

ED evaluation of the patient with gross or microscopic hematuria should begin with a complete history to define the pattern and character of the hematuria. Blood noted only on initiation of voiding suggests a urethral source, whereas blood noted only in the last few drops of urine suggests a prostatic or bladder neck source. Hematuria present throughout urination suggests a source in the bladder, ureter, or kidney. Brown or smoky-colored urine usually has a renal source. Blood clots indicate a nonglomerular renal or lower urinary tract source of bleeding. Hematuria may rarely be cyclic or associated with menses, suggesting endometriosis of the ureter or bladder. Flank pain suggests calculus, neoplasm, renal infarction, obstruction, or infection as the cause. Symptoms of frequency, dysuria, and suprapubic pain suggest cystitis or urethritis; in adult men, perineal pain, dysuria, and terminal hematuria suggest prostatitis.

Other clues to the cause are obtained by careful questioning. Because glomerulonephritis or interstitial nephritis may be caused by a variety of bacterial, viral, and parasitic infections, a history of recent infection is important. Symptoms suggestive of a multisystem disorder (e.g., systemic lupus erythematosus) also should be sought, as should a history of human immunodeficiency virus infection.[5] Because drugs may cause acute interstitial nephritis (AIN), papillary necrosis, or hemorrhagic cystitis, a complete

www.ketabpezeshki.com 66485457-66963820

medication history is elicited. When hematuria is associated with anticoagulant use, significant underlying disease can be identified in about one third of patients.[6] The family history may provide a clue to the presence of polycystic or other familial kidney disease, sickle cell disease, or renal calculi. A history of recent strenuous exercise is important to identify; 15 to 20% of normal persons exhibit hematuria after strenuous exercise. The mechanism is unclear, but the hematuria resolves spontaneously within a few days.

Clinical Features

On physical examination, findings of arthritis, skin lesions, hypertension, or edema suggest underlying glomerulonephritis. Examination of the external genitalia may reveal a urethral meatal lesion that may be the source of bleeding; in adult women, a pelvic examination will reveal vulvovaginal sources of blood. Because endocarditis or atrial fibrillation may cause renal embolism, the patient should be checked for a new heart murmur or an irregular rhythm. Costovertebral angle tenderness suggests pyelonephritis or obstructive stone disease, and a palpably enlarged kidney suggests polycystic kidney disease or renal malignancy. The prostatic examination may offer clues to the presence of prostatitis, benign prostatic hypertrophy, or cancer.

Laboratory Findings

Evaluation of hematuria in the ED setting includes assessment of the blood pressure and measurement of the BUN and serum creatinine levels to gauge the patient's underlying renal function, but urinalysis can be expected to provide more specific information. Red or orange urine that is dipstick negative and free of red cells on microscopy may be caused by ingestion of beets, red berries, or food coloring; by urate crystals; or by drugs such as phenazopyridine (Pyridium) and rifampin. A finding of red cell or other casts, lipiduria, or significant proteinuria in combination with hematuria suggests intrinsic renal disease. Microscopic hematuria usually does not produce a positive dipstick test result for protein, but gross hematuria may contribute enough protein to cause a positive result; thus a finding of proteinuria should be confirmed and the amount quantified with a 24-hour urine collection. Hematuria in combination with pyuria or bacteriuria suggests UTI; the infection should be treated and hematuria reassessed after therapy has been completed. Even if white cells or organisms are not seen on urinalysis, the urine should be cultured to rule out hemorrhagic cystitis, especially when lower tract symptoms are present.

Blood studies should be ordered only as necessary to gauge renal function and to confirm causes suggested by the clinical presentation. In the ED setting, routine ordering of the full gamut of chemical and serologic studies necessary to rule out all possible causes of hematuria is rarely appropriate. In particular, a platelet count and coagulation studies are extremely unlikely to be helpful in the absence of a suggestive history or other specific clinical clues.

Radiography and Ultrasonography

The role of urinary tract imaging studies in the immediate evaluation of hematuria also is limited. Visualization of the urinary tract generally is helpful only when the history suggests renal colic or other disorders of the upper urinary tract (e.g., polycystic kidney disease, tumor, obstruction). CT without contrast is the imaging modality of choice.[7] Ultrasonography can be used to determine kidney size and shape and to detect renal masses or obstruction. Further imaging studies, if indicated, should be planned after urologic consultation.

If no upper tract lesions are identified on initial imaging studies, cystoscopy usually is the next step in evaluation because it is the most effective means of visualizing the bladder and the male urethra. It is the initial study of choice for patients with active gross hematuria not caused by an obvious source (e.g., hemorrhagic cystitis); in fact, some urologists prefer to perform endoscopic procedures promptly during an acute bleeding episode to maximize the chance of localizing the source. In older patients in whom urinalysis shows only hematuria and the findings on the history and physical examination are otherwise unhelpful, urinary cytologic examination also may be undertaken.

Monitoring on an outpatient basis constitutes appropriate management in patients with hematuria who have no other abnormality revealed by urinalysis; who are otherwise asymptomatic; who are not azotemic, hypertensive, or severely anemic; and who have no evidence of intrinsic renal disease. (A possible exception may be the patient who has a known bleeding disorder or who is taking an anticoagulant.) Extensive outpatient evaluation for an isolated episode of hematuria usually is not undertaken in patients younger than 40 years unless hematuria is persistent, but it is generally recommended that most patients older than 40 undergo a thorough evaluation after even a single episode of hematuria.

The cause of hematuria can be determined on initial medical and urologic evaluation in about 70% of cases. In other cases a diagnosis of small calculi, occult bladder tumor, arteriovenous malformation, or early glomerulonephritis is made only after repeated examination or the development of further signs or symptoms. In about 20% of cases no cause can be determined.

Proteinuria

Principles of Disease

Abnormal proteinuria is defined as excretion of more than 150 mg of protein (albumin) per 24 hours in adults, or more than 140 $mg/m^2/24$ hr in children. Patients with mild to moderate degrees of proteinuria commonly are identified incidentally on routine urinalysis; patients with more severe degrees of proteinuria often seek medical attention because of edema or other effects of hypoproteinemia.

With alteration in the glomerular capillary barrier (e.g., with the nephrotic syndrome and the many varieties of primary and secondary glomerulonephritis), albumin and globulins, which under normal circumstances are restricted from the glomerular ultrafiltrate because of their ionic charge and size, are lost into the urine. Persistent proteinuria is a marker for renal disease even in the absence of azotemia or an abnormal urine sediment.

Excretion of more than 2 g of protein in 24 hours is likely to be caused by a glomerular process. In the nephrotic syndrome, protein losses exceed the liver's capacity to synthesize albumin, resulting in hypoalbuminemia. This leads to decreased plasma oncotic pressure and accumulation of edema fluid in the extravascular interstitial space. Increased aldosterone secretion and further retention of salt and water ensue. Thus edema is the clinical hallmark of the nephrotic syndrome and often is the initial complaint of patients who have significant proteinuria. Edema ranges in severity from mild dependent peripheral edema or periorbital swelling to frank anasarca with pleural effusions and ascites. *Nephrotic-range proteinuria* is defined arbitrarily as excretion of more than 3.5 g of protein per 24 hours.

Patients with the nephrotic syndrome are at increased risk for thromboembolic events, including deep vein thrombosis of the lower extremity, renal vein thrombosis, and pulmonary embolism. The reason for this propensity appears to be a hypercoagulable state that is complex and incompletely understood.[8] Hyperlipidemia is another typical feature of the nephrotic syndrome; the

www.ketabpezeshki.com 66485457-66963820

Box 97-3 Causes of the Nephrotic Syndrome

Primary renal disease

Multisystem disease
Diabetes mellitus
Systemic lupus erythematosus
Rheumatoid arthritis
Henoch-Schönlein purpura
Polyarteritis nodosa
Wegener's granulomatosis
Amyloidosis
Cryoglobulinemia

Drugs and toxins
Heroin
Captopril
Heavy metals
Nonsteroidal anti-inflammatory drugs
Penicillamine
Others

Allergens

Infection
Bacterial
- Infective endocarditis
- Poststreptococcal infection
- Syphilis

Viral
- Hepatitis B
- Human immunodeficiency virus infection
- Cytomegalovirus infection

Protozoal
- Malaria
- Toxoplasmosis

Malignancy
Solid tumors
Multiple myeloma
Lymphoma
Leukemia

Miscellaneous
Hereditary nephritis
Preeclampsia
Malignant hypertension
Reflux nephropathy
Renal vein thrombosis
Transplant rejection

mechanism is thought to be related indirectly to hypoalbuminemia and decreased oncotic pressure or viscosity. The major clinical significance of the nephrotic syndrome, however, is that it indicates the presence of an underlying renal process or systemic disease affecting the glomerulus (Box 97-3).

Clinical Features

Evaluation of the patient with proteinuria focuses not only on gauging the severity of proteinuria and the likelihood of complications but also on identifying any associated signs of underlying renal disease or systemic illness. Careful questioning will elicit a history of recent infections or use of medications or drugs or a past history of proteinuria, hypertension, edema, or renal disease. In young female patients, the presence of pregnancy is determined, as pregnancy can exacerbate previously inapparent renal disease; in late pregnancy, proteinuria may be the first sign of preeclampsia. Clues to the presence of systemic diseases that commonly affect the kidneys (e.g., diabetes, collagen vascular disease) should be sought as well. The physical examination includes evaluation of the blood pressure, determination of the presence or absence of edema, and assessment for signs of systemic disease or renal insufficiency.

Laboratory Findings

The laboratory evaluation in the patient with proteinuria includes urinalysis and measurement of the BUN and serum creatinine. Although the finding of isolated proteinuria may or may not be clinically important, proteinuria is almost always significant when it occurs in combination with hematuria. RBCs and red cell casts suggest glomerulonephritis; proteinuria with pyuria may be seen with AIN. The combination of proteinuria and glycosuria suggests diabetic nephropathy. A 24-hour urine collection provides an accurate measure of GFR and will quantify protein excretion.

Abnormal findings on the history, physical examination, or laboratory evaluation greatly increase the probability of the presence of significant renal disease, and early referral to an internist or nephrologist is indicated. However, in the absence of edema, azotemia, hypertension, active urine sediment, or known systemic illness affecting the kidney, patients with proteinuria may be referred to their primary care provider for follow-up. Because transient, mild proteinuria is not uncommon in healthy persons, patients with mild proteinuria as indicated by dipstick testing (particularly if the urine is concentrated) should have dipstick testing repeated at the follow-up visit before further evaluation is undertaken. Persistent proteinuria may necessitate referral to a nephrologist; in some cases, renal biopsy will be necessary to establish a diagnosis and guide management.

Box 97-4 Clinical Features of Acute Kidney Injury

Cardiovascular
Pulmonary edema
Arrhythmia
Hypertension
Pericarditis
Pericardial effusion
Myocardial infarction
Pulmonary embolism

Metabolic
Hyponatremia
Hyperkalemia
Acidosis
Hypocalcemia
Hyperphosphatemia
Hypermagnesemia
Hyperuricemia

Neurologic
Asterixis
Neuromuscular irritability
Mental status changes
Somnolence
Coma
Seizures

Gastrointestinal
Nausea
Vomiting
Gastritis
Gastroduodenal ulcer
Gastrointestinal bleeding
Pancreatitis
Malnutrition

Hematologic
Anemia
Hemorrhagic diathesis

Infectious
Pneumonia
Septicemia
Urinary tract infection
Wound infection

From Brady HR, Brenner BM, Clarkson MR, Lieberthal W: Acute renal failure. In Brenner BM: Brenner and Rector's the Kidney, 6th ed. Philadelphia, Saunders, 2000, pp 1201-1246.

ACUTE KIDNEY INJURY

The hallmark of AKI (formerly known as *acute renal failure* [ARF]) is progressive azotemia, which commonly is accompanied by a wide range of other disturbances, depending on the severity and duration of renal dysfunction. These include metabolic derangements (e.g., metabolic acidosis and hyperkalemia), disturbances of body fluid balance (particularly volume overload), and a variety of effects on almost every organ system (Box 97-4).

The causes of AKI may be divided into those that decrease renal blood flow (prerenal), produce a renal parenchymal insult (intrarenal), or obstruct urine flow (obstructive or postrenal). Identification of either a prerenal or a postrenal cause of AKI generally makes it possible to initiate specific corrective therapy; if these two broad categories of AKI can be excluded, an intrarenal cause is implicated. The renal parenchymal causes of AKI can be usefully subdivided into those primarily affecting the glomeruli, the intrarenal vasculature, or the renal interstitium. The term *acute tubular necrosis* denotes another broad category of intrinsic renal failure that cannot be attributed to specific glomerular, vascular, or interstitial causes (Fig. 97-2).[4]

Principles of Disease

Prerenal Azotemia

Decreased renal perfusion that is sufficient to cause a decrease in the GFR results in azotemia. The possible causes can be grouped

www.ketabpezeshki.com 66485457-66963820

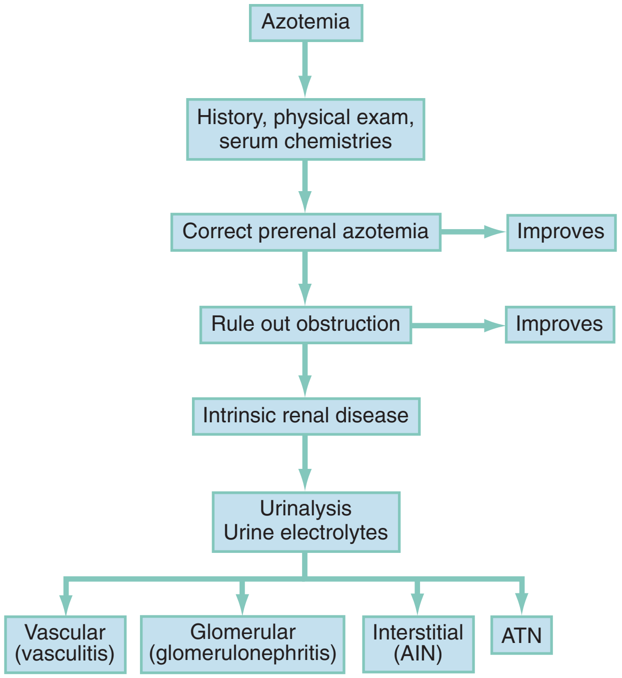


Figure 97-2. Evaluation of azotemia. *AIN*, acute interstitial nephritis; *ATN*, acute tubular necrosis.

Box 97-5 Causes of Prerenal Azotemia

Volume Loss
Gastrointestinal: vomiting, diarrhea, nasogastric drainage
Renal: diuresis
Blood loss
Insensible losses
Third-space sequestration
Pancreatitis
Peritonitis
Trauma
Burns

Cardiac Causes
Myocardial infarction
Valvular disease
Cardiomyopathy
Decreased effective arterial volume
Antihypertensive medication
Nitrates

Neurogenic Causes
Sepsis
Anaphylaxis
Hypoalbuminemia
Nephrotic syndrome
Liver disease

into entities causing intravascular volume depletion, volume redistribution, or decreased cardiac output (Box 97-5). Patients who have preexisting renal disease are particularly sensitive to the effects of diminished renal perfusion.

Prerenal azotemia is characterized by increased urine specific gravity, BUN/creatinine ratio generally between 10 : 1 and 20 : 1, urine sodium concentration less than 20 mEq/dL, and FENa less than 1%. The condition generally can be corrected readily by expanding extracellular fluid volume, augmenting cardiac output, or discontinuing vasodilating antihypertensive drugs. However, severe prolonged prerenal azotemia can eventuate in ATN.

Patients who have congestive heart failure (CHF) or cirrhosis form an important subset of those with prerenal azotemia. These patients often are salt-overloaded and water-overloaded, yet their effective intra-arterial volume is decreased. Administration of diuretics has the potential to decrease intravascular volume further, resulting in decreased glomerular filtration and prerenal azotemia. For some patients with advanced CHF or hepatic disease, a state of chronic stable prerenal azotemia may be the best

Box 97-6 Causes of Postrenal Renal Failure

Intrarenal and Ureteral Causes
Kidney stone
Sloughed papilla
Malignancy
Retroperitoneal fibrosis
Uric acid, oxalic acid, or phosphate crystal precipitation
Sulfonamide, methotrexate, acyclovir, or indinavir precipitation

Bladder
Kidney stone
Blood clot
Prostatic hypertrophy
Bladder carcinoma
Neurogenic bladder

Urethra
Phimosis
Stricture

achievable compromise between symptomatic volume overload and severe renal hypoperfusion.[9]

Glomerular perfusion also may be decreased in patients with normal intravascular volume and normal renal blood flow who take angiotensin-converting enzyme (ACE) inhibitors or, more commonly, prostaglandin inhibitors. All nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, inhibit prostaglandin synthesis. Renal vasodilator prostaglandins are critical in maintaining glomerular perfusion in patients with conditions such as CHF, chronic renal insufficiency, and cirrhosis, in which elevated circulating levels of renin and angiotensin II decrease renal blood flow and GFR. In this setting, a decrease in the production of vasodilator prostaglandins may result in acute intrarenal hemodynamic changes and a reversible decrease in renal function.[10] This phenomenon also is seen with the selective cyclooxygenase-2 inhibitor class of NSAIDs.[11,12] Other risk factors include advanced age, diuretic use, renovascular disease, and diabetes. This entity is distinct from other renal complications of NSAIDs, including interstitial nephritis and papillary necrosis.

Renal insufficiency secondary to NSAIDs generally is reversible after withdrawal of the causative agent. For patients who are at increased risk but require treatment with NSAIDs, a short-acting preparation (e.g., ibuprofen) should be prescribed, and follow-up monitoring of renal function and serum potassium level should begin within days rather than weeks. If renal function is unchanged after a short course of treatment, adverse effects from continuing therapy are unlikely, although other potential mechanisms for the development of renal dysfunction (e.g., interstitial nephritis) should be kept in mind.

Postrenal (Obstructive) Acute Renal Failure

Obstruction is an eminently reversible cause of AKI and should be considered in every patient with newly discovered azotemia or worsening renal function. Obstruction may occur at any level of the urinary tract but most commonly is produced by prostatic hypertrophy or by functional bladder neck obstruction (e.g., secondary to medication side effects or neurogenic bladder) (Box 97-6). Intrarenal obstruction may result from intratubular precipitation of uric acid crystals (e.g., with tumor lysis), oxalic acid (as in ethylene glycol ingestion), phosphates, myeloma proteins, methotrexate, sulfadiazine, acyclovir, or indinavir.[13] Bilateral ureteral obstruction (or obstruction of the ureter of a solitary kidney) may be caused by retroperitoneal fibrosis, tumor, surgical misadventure, stones, or blood clots. A sudden deterioration in renal function in the setting of diabetes mellitus, analgesic nephropathy, or sickle cell disease should suggest papillary necrosis.

Treatment of postrenal AKI consists of relief of the obstruction. In the absence of infection, full renal recovery is possible even after 1 to 2 weeks of total obstruction, although the serum creatinine level may not return to baseline for several weeks. Because the

www.ketabpezeshki.com 66485457-66963820

onset of irreversible loss of renal function with obstruction appears to be gradual, a few days' delay in diagnosis generally is considered acceptable. Still, common sense dictates that obstructions should be detected and relieved promptly.

Intrinsic Acute Renal Failure

Of the specific intrarenal disorders that cause AKI, glomerulonephritis, interstitial nephritis, and abnormalities of the intrarenal vasculature are amenable to specific therapy and are important to consider as possible causes. These entities are responsible for only 5 to 10% of cases of AKI in adult inpatients; most are caused by ATN. In adults in whom AKI develops outside the hospital, the incidence of glomerular, interstitial, and small-vessel disease is much greater. In children, these entities account for approximately one half of the cases of AKI (Box 97-7).[4]

Glomerular Disease. Acute glomerulonephritis may represent a primary renal process or may be the manifestation of any of a wide range of other disease entities (see Box 97-7). Patients may have dark urine, hypertension, edema, or CHF (secondary to volume overload) or may be completely asymptomatic, in which case the diagnosis rests on an incidental finding on urinalysis. The hematuria associated with glomerular disease may be microscopic or gross and may be persistent or intermittent. Proteinuria, although often in the range of 500 mg/day to 3 g/day, not uncommonly is in the nephrotic range. The presence of hematuria, proteinuria, or red cell casts is highly suggestive of glomerulonephritis. In fact, red cell casts are essentially diagnostic of active glomerular disease, although occasionally they are seen with other types of renal disease. Conversely, the absence of red cell casts, proteinuria, and hematuria essentially excludes glomerulonephritis as the cause of AKI.

The specific diagnosis of acute glomerulonephritis caused by primary renal disease often is ultimately made by renal biopsy. However, when glomerulonephritis is secondary to a systemic disease such as systemic lupus erythematosus, the patient's clinical signs and symptoms, in combination with the results of laboratory assessment, aid considerably in narrowing the scope of the differential diagnosis. As a rule, extensive laboratory testing to identify the cause of acute glomerulonephritis is not indicated in the ED setting and is more appropriately performed as part of an inpatient evaluation.

Interstitial Disease. AIN most commonly is precipitated by drug exposure or by infection.[14] Drug-induced AIN is poorly understood, but the absence of a clear relationship to the dose and the recurrence of the syndrome on rechallenge with the offending agent suggests that an immunologic mechanism is responsible. The most commonly incriminated drugs are the penicillins, diuretics, and NSAIDs. AIN has been reported in association with bacterial, fungal, protozoan, and rickettsial infections.

Patients with AIN classically have rash, fever, eosinophilia, and eosinophiluria, but it is common for one or more of these cardinal signs to be absent.[15] Pyuria, gross or microscopic hematuria, and mild proteinuria are observed in some cases. A definite diagnosis sometimes can be made only on renal biopsy. Treatment of AIN is directed at removing the presumed cause; infections should be treated and offending drugs discontinued. Renal function generally returns to baseline over several weeks, although chronic renal failure has been reported to occur.

Intrarenal Vascular Disease. Vascular disease of the kidney can be classified according to the size of the vessel that is affected. Disorders such as renal arterial thrombosis or embolism, which affect large blood vessels, must be bilateral (or affect a single functioning kidney) to produce AKI. Whether to attribute such cases of AKI to prerenal or intrarenal vascular causes is a matter of semantics. The most common cause of thrombosis probably is trauma; thrombosis also may occur after angiography or may be secondary to aortic or renal arterial dissection. Renal atheroembolism is thought to occur commonly—at least on a microscopic level—after arteriography but is an uncommon cause of AKI. Similarly, patients with chronic atrial fibrillation or infective endocarditis may experience embolization of the kidney but rarely develop AKI as a result. Renal arterial embolism can cause acute renal infarction, generally manifested by sudden flank, back, chest, or upper abdominal pain. Urinary findings, including hematuria, are variable. Fever, nausea, and vomiting are not uncommon; in some cases, evidence of embolization to other vessels provides a useful clue. The diagnosis usually is made by renal flow scanning or arteriography. Surgical embolectomy has been reported to restore function when undertaken within several hours of occlusion, but significant return of function has been documented in patients operated on as long as 6 weeks after total occlusion. This outcome presumably is possible because collateral circulation has developed in association with a preexisting partial occlusion.

An interesting but relatively uncommon type of AKI occurs when an ACE inhibitor is given to a patient with underlying bilateral renal artery stenosis (or unilateral stenosis of a solitary functioning kidney). With inhibition of angiotensin synthesis, efferent arteriolar tone is not maintained and GFR decreases. The condition is reversible with cessation of therapy.

Several diseases that affect the smaller intrarenal vessels can cause AKI (see Box 97-7). Patients whose disease is severe enough to cause ARF also generally are found to have hypertension, microangiopathic hemolytic anemia, and other systemic and organ-specific manifestations. Infection with *Escherichia coli* O157:H7 has emerged as a major cause of hemolytic uremic syndrome, an important cause of AKI in children.[16]

Box 97-7 Intrinsic Renal Diseases That Cause Acute Kidney Injury

Vascular Diseases

Large-Vessel Diseases

- Renal artery thrombosis or stenosis
- Renal vein thrombosis
- Atheroembolic disease

Small- and Medium-Vessel Diseases

- Scleroderma
- Malignant hypertension
- Hemolytic uremic syndrome
- Thrombotic thrombocytopenic purpura
- HIV-associated microangiopathy

Glomerular Diseases

Systemic Diseases

- Systemic lupus erythematosus
- Infective endocarditis
- Systemic vasculitis (e.g., periarteritis nodosa, Wegener's granulomatosis)
- Henoch-Schönlein purpura
- HIV-associated nephropathy
- Essential mixed cryoglobulinemia
- Goodpasture's syndrome

Primary Renal Diseases

- Poststreptococcal glomerulonephritis
- Other postinfectious glomerulonephritis
- Rapidly progressive glomerulonephritis

Tubulointerstitial Diseases and Conditions

- Drugs (many)
- Toxins (e.g., heavy metals, ethylene glycol)
- Infections
- Multiple myeloma

Acute Tubular Necrosis

Ischemia

- Shock
- Sepsis
- Severe prerenal azotemia

Nephrotoxins

- Antibiotics
- Radiographic contrast agents
- Myoglobinuria
- Hemoglobinuria

Other Diseases and Conditions

- Severe liver disease
- Allergic reactions
- NSAIDs

HIV, human immunodeficiency virus; *NSAIDs,* nonsteroidal anti-inflammatory drugs.

www.ketabpezeshki.com 66485457-66963820

Malignant hypertension, although much less common since the advent of more effective antihypertensive therapy, has by no means disappeared. Patients with scleroderma (systemic sclerosis) may have "scleroderma renal crisis,"[17,18] characterized by malignant hypertension and rapidly progressive renal failure. Whereas vasculitis associated with glomerular capillary inflammation typically causes gross or microscopic hematuria and formation of red cell casts, vascular involvement of the medium-size vessels, such as that produced by scleroderma, often spares the preglomerular vessels and tends not to produce an active urine sediment. Extrarenal manifestations (rash, fever, arthritis, pulmonary symptoms) are usually evident.

For malignant hypertension, both as a separate entity and as a part of scleroderma renal crisis, appropriate treatment can produce a gratifying remission of AKI. Patients with malignant hypertension have been reported to recover renal function after aggressive antihypertensive therapy, with temporary maintenance with dialysis if necessary.[19] In patients with scleroderma renal crisis, specific therapy with ACE inhibitors has been shown to result in improvement in renal function in a significant proportion of cases.[18]

Acute Tubular Necrosis

The term *acute tubular necrosis* refers to a generally reversible deterioration of kidney function associated with a variety of renal insults. Oliguria may or may not be a feature. The diagnosis is made after prerenal and postrenal causes of ARF and disorders of glomeruli, interstitium, and intrarenal vasculature have been excluded. These discrete categories do overlap in a few disorders. For example, AKI associated with multiple myeloma or ethylene glycol toxicity is associated with both intrarenal obstruction and interstitial disease, as well as a probable direct toxic effect on the renal tubule itself.

The most common precipitant of ATN is renal ischemia occurring during surgery or after trauma and sepsis.[20] The remainder of cases occur in the setting of medical illness, most commonly as a result of the administration of nephrotoxic aminoglycoside antibiotics or radiocontrast agents or in association with rhabdomyolysis. Multiple causes can be identified in some cases; in others a definitive cause is never established.

Decreased renal perfusion results in a continuum of renal dysfunction that ranges from transient prerenal azotemia at one extreme to ATN at the other. Early during the period of renal ischemia, renal function can be restored completely by restoring renal blood flow, but at some point, continued hypoperfusion results in renal dysfunction unresponsive to volume repletion, and ATN will supervene. ATN may occur in the absence of frank hypotension; even modest renal ischemia may result in ATN in susceptible persons. Individual susceptibility to ATN may be related to the balance of prostaglandin-mediated vasopressor and vasodilatory influences on the renal vasculature.

Postischemic ATN can occur in the setting of volume loss from the GI tract (upper or lower), skin, or kidneys or can result from severe hemorrhage or major burns. Heatstroke commonly is associated with the development of ATN, which is thought to result from a combination of volume loss, hyperpyrexia, and rhabdomyolysis. Another cause of ATN is hyperglycemic hyperosmolar nonketotic coma, which can be associated with loss of as much as 25% of total body water. ATN also is seen in the setting of cardiogenic shock, sepsis, and third spacing of fluids in pancreatitis and peritonitis.

ATN is common in postoperative patients, although not all cases can be attributed to intraoperative hypotension or hemorrhage. Concomitant sepsis, increased age, preexisting renal disease, and other comorbid conditions are associated with a worse outcome.[20,21]

Box 97-8 Causes of Pigment-Induced Acute Kidney Injury

Rhabdomyolysis and myoglobinuria	Alcoholism
Vigorous exercise	Hypokalemia
Arterial embolization	Hypophosphatemia
Status epilepticus	Hemoglobinuria
Status asthmaticus	Transfusion reactions
Coma-induced and pressure-induced myonecrosis	Snake envenomation
Heat stress	Malaria
Diabetic ketoacidosis	Mechanical destruction of RBCs by prosthetic valves
Myopathy	G6PD deficiency

G6PD, glucose-6-phosphate dehydrogenase; *RBCs,* red blood cells.

Nephrotoxins constitute the other major cause of ATN. Among the most prominent of these are the endogenous pigments myoglobin and hemoglobin. Rhabdomyolysis and ARF resulting from crush injuries first received widespread attention after their description in survivors of the London blitz during World War II, but many other causes of pigment nephropathy have been reported (Box 97-8). Hypotension secondary to fluid loss into damaged muscle is thought to worsen the effects of myoglobinuria on the renal tubule, as does acidemia. Hemolysis, resulting in the release of hemoglobin into the circulation and hemoglobinuria, can cause ATN but usually only in the presence of coexisting dehydration, acidosis, or other causes of decreased renal perfusion. ATN may be associated with the hemolysis of as little as 100 mL of blood.

ATN associated with rhabdomyolysis is often oliguric; it is characterized by rapid increases in the serum creatinine, potassium, phosphorus, and uric acid levels.[22,23] Creatine released from muscle is metabolized to creatinine, which may result in serum creatinine increases of more than 2 mg/dL/day, in contrast to the increase of 0.5 to 1.0 mg/dL/day typically seen in other forms of AKI. The BUN/creatinine ratio often is less than 10 : 1. Intracellular potassium released from damaged muscle may raise the serum potassium by 1 to 2 mEq/L in several hours. Likewise, phosphate released from muscle may cause dramatic increases in the serum phosphate level. Uric acid, produced by metabolism of purines released from damaged muscle, may accumulate to levels high enough to cause acute uric acid nephropathy.

Urine dipstick testing yields a positive result for heme in only 50% of patients with rhabdomyolysis, because myoglobin is rapidly cleared from the serum and may therefore be undetectable in the urine at the time of presentation. Thus a negative result on urine dipstick testing does not rule out the diagnosis. Serum creatine kinase (CK) is cleared much more slowly, so measurement of serum CK levels is a more sensitive test.

No biochemical parameter can be used to predict which patients who have rhabdomyolysis will experience AKI. In one classic study of patients in whom alcoholism, muscle compression, and seizures were the most common causes of rhabdomyolysis, AKI developed in only one third.[22] Neither the degree of serum CK elevation, the presence (or absence) of myoglobinuria, nor the degree of hyperkalemia correlates well with the development of AKI.

Antibiotics and radiographic contrast agents are other nephrotoxins that commonly are implicated in the development of ATN. Aminoglycosides are the most commonly implicated antibiotics. Higher doses and longer duration of therapy are associated with higher serum drug levels, leading to greater accumulation of drug in the renal parenchyma and a greater likelihood of nephrotoxicity. Increased age, impaired renal function, dehydration, and exposure to other nephrotoxins are additional risk factors. Once-daily administration of a somewhat higher dose is associated with less nephrotoxicity but equal effectiveness.[24,25]

www.ketabpezeshki.com 66485457-66963820

Aminoglycoside-induced ATN typically has a gradual onset. Clinically significant renal dysfunction usually occurs only after several days and often after more than a week of therapy. However, renal failure can develop as late as 10 days after a drug has been discontinued, an observation that appears to be explained by the prolonged tissue half-life characteristic of these agents. Renal function returns to normal after an average of 6 weeks, but the condition occasionally progresses to permanent renal injury.

Radiographic contrast agents constitute a common cause of hospital-acquired renal insufficiency. Renal failure produced by these agents has been defined as an increase in serum creatinine level of 25% over baseline with a temporal relation to contrast medium administration and in the absence of other identifiable causes. Radiocontrast agent–induced ATN encompasses a spectrum ranging from asymptomatic nonoliguric renal insufficiency to severe renal failure requiring dialysis, but most cases are mild. It can occur after any procedure involving intravascular administration of contrast material. Typically, an increase in the serum creatinine level is noted within 3 days of exposure, with a return to normal within 10 to 14 days.

The most important risk factors for radiocontrast agent–induced ATN are preexisting renal insufficiency, diabetes mellitus, multiple myeloma, age older than 60 years, volume depletion, and higher doses of contrast material. Among these, preexisting renal insufficiency is the most important.[26] Diabetic patients with a serum creatinine level less than 1.5 mg/dL are at low risk for the development of radiocontrast agent–induced ATN, whereas those whose serum creatinine is greater than 1.5 mg/dL are at significant risk. Multiple myeloma, particularly in patients who are dehydrated, is another reasonably well-documented risk factor. Advanced age also appears to make ATN more likely, possibly because of decreased renal mass and cortical blood flow. Volume depletion appears to be an independent risk factor, and aggressive volume expansion before contrast exposure has been shown to have a protective effect.[27,28] Finally, large doses and repeated doses of contrast material are associated with increased risk of ATN, particularly if a second study is performed within 72 hours of the first.

N-acetylcysteine in combination with periprocedural hydration appears to decrease the incidence of contrast-associated ATN,[29] although this has not been a consistent finding in published studies.[30] Modest volumes of intravenous normal saline (3 mL/kg over 1 hour, followed by 1.5 mL/kg/hr for 4 hours after contrast exposure) appear to be effective in decreasing the likelihood of nephrotoxicity; sodium bicarbonate does not appear to offer an advantage over normal saline.[30,31] Recent reviews continue to emphasize the importance of appropriately limiting exposure to contrast agents as well as ensuring preprocedural hydration.[27]

Clinical Features

When the presence of azotemia or renal failure has been discovered, the first consideration in the ED evaluation should be the possibility of potentially life-threatening complications (e.g., hyperkalemia, pulmonary edema). Assuming these have been satisfactorily ruled out, the next step is to determine whether the condition represents AKI or is the result of preexisting renal disease. The clinical distinction between AKI and chronic kidney disease (CKD) often is difficult; old records and laboratory results are invaluable. The finding of small kidneys on abdominal radiography or bone changes of secondary hyperparathyroidism on hand films suggests that the renal failure is chronic. Anemia, hypocalcemia, and hyperphosphatemia, on the other hand, should not be relied on to identify patients who have CKD because these abnormalities can develop rapidly in AKI.

In evaluating the patient with azotemia, the clinician uses history, physical examination, and laboratory studies to seek clues to the cause and to identify signs and symptoms of uremia, volume overload, or other complications of renal failure. In attempting to identify the cause of azotemia, the general strategy is to rule out both prerenal and postrenal causes before considering the many intrinsic renal causes. First, potential sources of volume loss and causes of decreased cardiac output are sought in the history, and the patient is questioned about lightheadedness, bleeding, GI fluid loss, abnormal polyuria, or symptoms of CHF. In men a history of nocturia, frequency, hesitancy, or decreased urinary stream suggests prostatic obstruction. A history of lower tract symptoms or of abdominal or pelvic tumor in either sex is determined, as is a history of kidney stones or chronic UTI. A history of acute anuria (defined as the production of less than 100 mL of urine per day) is most often the result of high-grade urinary tract obstruction, although it also may accompany severe volume depletion, severe acute glomerulonephritis, cortical necrosis, or bilateral renal vascular occlusion. Intermittent anuria, on the other hand, is characteristic of obstructive disease.

Medication use and possible exposure to radiographic contrast agents or other exogenous toxins are other key components of the history. A history of hypertension, dark-colored urine, rash, fever, or arthritis suggests intrinsic renal disease or a multisystem disorder. In older patients the presence of symptoms suggestive of multiple myeloma should be elicited.

The physical examination focuses on signs of volume depletion such as tachycardia and decreased skin turgor. Documented short-term changes in body weight offer a valuable clue in assessing volume status, particularly in chronically ill patients. In addition, suspected bleeding should be specifically excluded. Similarly, volume overload is determined by assessment of jugular vein distention and attention to the presence of rales, an S_3 gallop, or edema.

The area of the bladder is palpated and percussed. A distended bladder is percussible when it contains 150 mL of urine, and the dome is palpable abdominally when it contains 500 mL. Ultrasonography can be used to detect bladder distention or postvoid residual volume if there is a question of urinary retention.[32]

Prostate examination in adult men and pelvic examination in adult women are necessary components of the examination. The presence of rash, purpura, pallor, or petechiae is noted, as is arthritis, musculoskeletal tenderness, or findings suggestive of infection or malignancy.

Diagnostic Strategy

Laboratory Findings

The laboratory evaluation begins with a dipstick and microscopic urinalysis and measurement of urine output. BUN, serum creatinine, urine sodium, and FENa levels are determined to help evaluate renal function and to provide clues to the cause of AKI. A complete blood count, serum electrolyte panel (expanded to include calcium, phosphorus, and magnesium determinations), electrocardiogram (ECG), and chest radiograph help to establish the patient's baseline status and to provide information about possible complications. Other studies may be of value in the ED setting when the history or physical findings suggest that they may have a specific role in immediate diagnosis or management.

Prerenal azotemia is suspected in the setting of volume loss, volume redistribution, or decreased effective renal perfusion. It typically is associated with a normal urinalysis, high BUN/creatinine ratio, increased urine osmolality, a urine sodium concentration less than 20 mEq/L, and FENa less than 1%. A rapid response to volume repletion also is characteristic.

Urethral or bladder neck obstruction is documented by the finding of significant amounts of residual urine in the bladder (by catheterization or ultrasound examination) after the patient has

www.ketabpezeshki.com 66485457-66963820

voided or attempted to void spontaneously. An important point is that the ability to void does not rule out obstruction. In fact, the urine volume in the presence of obstruction may range from zero to several liters per day. Flank pain is likewise an insensitive marker for obstruction. Urine indices and the BUN/creatinine ratio tend not to be helpful, although an increase in the latter is common in obstruction. A renal parenchymal disorder often can be diagnosed by its manifestations on microscopic urinalysis or by associated extrarenal manifestations (e.g., with multisystem disease) or the clinical setting (e.g., recent exposure to a new medication). The absence of evidence of prerenal or postrenal causes in a patient with AKI may be taken as presumptive evidence of an intrarenal parenchymal process. Among these, the possibility of an acute or ongoing vascular insult should be kept in mind, because timely intervention may be important in preserving ultimate renal function.

Radiography and Ultrasonography

Significant hydronephrosis usually is readily demonstrable by ultrasonography and may indicate either upper or lower tract obstruction. In questionable cases, or if bilateral ureteral obstruction is strongly suspected on the basis of clinical findings, the next step is retrograde urography performed by a urologist.[33] CT imaging is less useful in this setting; in fact, intravenous radiocontrast material may compound the injury to the kidney.

Management

ED management of AKI is directed at reversing decreases in GFR and urine output (if possible) while minimizing further hemodynamic and toxic insults, maintaining normal fluid and electrolyte balance, and managing other complications of AKI as required. Because renal failure alters the metabolism and action of many drugs, often in ways that are not predictable, great care should be exercised in prescribing all medications. A compendium of guidelines for drug dosage in renal failure, such as the one by Aronoff and colleagues,[34] is of great help for this purpose.

After ensuring that the vital signs are adequate and that the patient is in no immediate danger from volume or metabolic derangements, the next step is to correct prerenal and postrenal factors, if any are identified. Intravascular volume is repleted in hypovolemic patients and maintained in euvolemic patients by matching input to measured and insensible output. Inadequate cardiac output is augmented when possible. Postrenal or obstructive ARF is treated by restoration of normal urine outflow. Bladder outlet obstruction may be relieved by passage of a Foley catheter, whereas upper tract obstruction may require percutaneous nephrostomy.

When prerenal and postrenal factors have been ruled out, the challenge to the emergency physician is to identify the cause of intrinsic renal AKI, keeping in mind the multitude of known possible causes (see Box 97-7). The clinical setting and physical and laboratory findings often allow the scope of the differential diagnosis to be considerably narrowed. The clinical picture is often most consistent with the broad category of ATN.

It has been noted repeatedly that patients who have oliguric AKI have a significantly higher mortality rate and a much greater risk of complications than those who are not oliguric. The difference in prognosis may simply reflect a more severe renal insult in patients who are oliguric, however, and it is not clear that interventions aimed at converting oliguric to nonoliguric AKI have an effect on renal function or mortality.[20] Nevertheless, because nonoliguric patients are easier to manage, an attempt to increase urine flow is warranted.

Use of loop diuretics or mannitol often is effective in increasing urine flow when intravascular volume deficits have been corrected. Furosemide has not been shown to shorten the clinical course or affect mortality. Mannitol appears to be most useful when given at the time of or shortly after the renal insult; the recommended dose is 12.5 to 25 g given intravenously (IV). If urine output does not increase, further doses may cause hyperosmolality and clinically significant intravascular volume overload in patients with impaired renal function.[35]

Dopamine also has been used, with and without furosemide, in an effort to increase urine output, but has not proven effective.

Certain specific considerations apply to toxin-induced ATN. Pigment-induced ATN may be prevented by avoidance of hemolysis and muscle injury and by correction of the factors (e.g., dehydration, acidemia) that are known to predispose patients with pigmenturia to the development of renal failure. When hemolysis or rhabdomyolysis has occurred, treatment is directed at eliminating the cause and preventing the development of renal failure.

Mannitol has been shown to prevent AKI in experimental models of myoglobinuria, presumably by inducing osmotic diuresis and decreasing intratubular deposition of pigment. Furosemide, on the other hand, has not consistently shown a beneficial effect. Other studies have suggested that myoglobin precipitates in an acid urine but not in an alkaline urine. Thus, aggressive volume repletion, alkalinization, and mannitol infusion have traditionally been recommended after crush injuries to reduce the likelihood or severity of AKI.[23] This regimen also helps control hyperkalemia. Other evidence, however, suggests that aggressive volume resuscitation alone may be equally effective.[23] When AKI has occurred, management is similar to that of other forms of AKI, but early dialysis may be required to control rapidly developing hyperkalemia, hyperphosphatemia, and hyperuricemia.

Patients who have radiocontrast agent–induced ATN usually require only supportive therapy but are often hospitalized and seen by a nephrologist. A more significant aspect of ED management is *preventing* the occurrence of contrast nephropathy, particularly by identification of risk factors in patients for whom contrast studies are being considered. BUN and serum creatinine levels should be checked before contrast exposure in patients with risk factors. Moreover, before contrast medium is administered to a high-risk patient, it should be established that there is a compelling reason to perform the contrast study and that there is no adequate alternative to use of a contrast agent. The patient should be volume repleted before the study, the administered dose of contrast agent should be kept as low as possible, and multiple studies should be avoided, as should concomitant use of other nephrotoxins. As noted previously, *N*-acetylcysteine given before and after contrast administration appears to decrease the incidence of contrast nephropathy. Intravenous saline given before and after contrast administration appears to be at least as important in prevention.[27-31]

Volume and Metabolic Complications

In addition to those general measures aimed at minimizing decreases in GFR and increasing urine output, an important component of the management of AKI is the prevention or control of systemic complications. Of particular significance in this regard are metabolic derangements (e.g., hyperkalemia, hypocalcemia, hyperphosphatemia, metabolic acidosis) and complications of volume overload (e.g., hypertension, CHF).

Hyperkalemia, the most common metabolic cause of death in patients with AKI, results from an inability to excrete endogenous and exogenous potassium loads. In oliguric patients the serum potassium level typically increases by 0.3 to 0.5 mEq/L per day, but greater increases occur in catabolic, septic, or traumatized patients and in the presence of acidosis or exogenous potassium loads from diet or medication.

www.ketabpezeshki.com 66485457-66963820

Hyperkalemia results in serious disturbances in cardiac electrophysiology that may culminate in cardiac arrest. Although some hyperkalemic patients note muscular weakness, most generally are asymptomatic until major manifestations of cardiotoxicity appear. Accordingly, detection of hyperkalemia is a primary consideration in these patients. ECG changes correlate only roughly with the serum potassium level. Mild hyperkalemia (serum potassium less than 6.0 mEq/L) may be cautiously observed without specific treatment while all exogenous sources of potassium are eliminated. If the serum potassium level is greater than 6.5 mEq/L, and particularly if ECG changes are present, urgent intervention is necessary. When cardiotoxicity must be reversed immediately (e.g., when there is hemodynamic compromise), intravenous calcium (10 mL of 10% calcium gluconate or calcium chloride infused over 2 minutes and repeated after 5 minutes if necessary) is the treatment of choice. Calcium directly antagonizes the membrane effects of hyperkalemia. Intravenous insulin (given with glucose to prevent hypoglycemia) temporarily shifts potassium to the intracellular space. Bicarbonate appears to be less effective in shifting potassium into cells than once thought.[36] It should be used with caution in patients with renal failure because of its potential to cause volume overload and to provoke hypocalcemic tetany or seizures. The safety and efficacy of beta-agonists in hyperkalemic patients have been well documented; like insulin, inhaled albuterol (in a dose of 10-20 mg) causes potassium to move into cells, thereby controlling hyperkalemia for 2 hours or more.[37,38] Elimination of potassium from the body can be promoted by use of a potassium-binding ion exchange resin (sodium polystyrene sulfonate [Kayexalate]) or, much more effectively, by enhancing urinary potassium excretion or by initiating dialysis.[36] Hypocalcemia is a common feature of AKI and can develop rapidly after its onset. Vitamin D–dependent intestinal absorption of calcium is decreased in AKI because of decreased renal synthesis of 1,25-dihydroxyvitamin D. Another factor promoting hypocalcemia is the complexing of calcium with retained phosphate. Rhabdomyolysis-associated AKI in particular often is associated with the deposition of complexed calcium in muscle and other tissues. Asymptomatic hypocalcemia requires no immediate treatment, but subtle or frank tetany should be treated with intravenous calcium (10-20 mL of 10% calcium gluconate infused over several minutes).

Hyperphosphatemia resulting from decreased renal elimination of phosphate is another common feature of AKI. The serum phosphorus level usually ranges from 6 to 8 mg/dL but may be much higher with rhabdomyolysis or in catabolic states. A calcium-phosphate product greater than 70 may result in metastatic soft tissue calcification. Hyperphosphatemia often is treated with oral calcium-based antacids that bind ingested phosphate in the gut.[39]

Acids produced in normal metabolic processes accumulate in AKI and are buffered in part by serum bicarbonate, resulting in a decrease in the serum bicarbonate level and a high–anion-gap metabolic acidosis. Compensatory hyperventilation may be mistakenly attributed to primary cardiac failure or volume overload. The metabolic acidosis associated with AKI usually is mild, and treatment generally is not necessary if the serum bicarbonate level is greater than 10 mEq/L. Overzealous correction may result in hypokalemia, hypocalcemia, or volume overload.

Hypermagnesemia may complicate AKI when patients are given magnesium-containing antacids or laxatives. Thus these products, as well as magnesium itself (e.g., when given for preeclampsia or for treatment of arrhythmia or wheezing), should be avoided in the setting of AKI.

Disturbances of volume regulation can be expected to occur in most patients with AKI. Some nonoliguric patients excrete enough salt and water that intravascular volume depletion can occur if adequate fluid replacement is not provided. Volume depletion prolongs recovery from AKI. Much more commonly, AKI is complicated by volume overload because sodium and water excretion may be inadequate to match even modest intakes. Volume overload is largely responsible for the hypertension often seen in AKI and commonly leads to CHF and pulmonary edema. Iatrogenic volume overload is particularly common and can be prevented only by careful attention to fluid intake and output with prudent estimates of insensible loss. Volume overload can be treated with diuretics or intravenous nitroglycerin while preparations are being made to initiate dialysis.

Organ System Effects

The clinician should be alert to the numerous other important systemic and organ-specific effects of renal failure. Only the more prominent of these are mentioned here.

Uremia impairs host defenses, particularly leukocyte function, and infection is a significant cause of morbidity and mortality in AKI. Thus patients with fever require prompt investigation and aggressive treatment.

Pericarditis, which has a prevalence of 10 to 20% in dialyzed patients with CKD, also may occur in patients with AKI. Chest pain that is worse in a recumbent position is the most common symptom, and most patients have a pericardial friction rub. Fever is common. The ECG may show ST-T wave elevation, low voltage, electrical alternans, or atrial fibrillation. The presence of pericardial effusion is identified most accurately by echocardiography; tamponade, with typical clinical signs, occurs in some patients. In contrast to the situation in chronic kidney failure, pericarditis or pericardial effusion in the setting of AKI generally is an indication for the urgent initiation of dialysis. Patients who have hemodynamically significant tamponade require surgical drainage of the effusion or, occasionally, emergency pericardiocentesis.

Neurologic abnormalities in AKI may be precipitated by electrolyte abnormalities, medications, or uremia. Common signs and symptoms in uremic patients include lethargy, confusion, agitation, asterixis, myoclonus, and seizures.

Anorexia, nausea, vomiting, gastritis, and pancreatitis also are associated with AKI. Significant GI hemorrhage is seen in about 10% of patients.

Impaired erythropoiesis, shortened RBC survival, hemolysis, hemodilution, and GI blood loss all play a role in the normocytic normochromic anemia that usually accompanies AKI. Although mild thrombocytopenia may be present, it is the qualitative defect in platelet function, which is felt to be caused by the effect of circulating uremic toxins, that is more significant and that contributes to these patients' bleeding tendencies. In patients with active bleeding or those in whom an invasive procedure is being contemplated, the prolonged bleeding time can be corrected pharmacologically.[40] Administration of 1-deamino-8-D-arginine vasopressin (DDAVP) shortens the bleeding time within 30 minutes. Infusion of 10 units of cryoprecipitate normalizes the bleeding time in 1 to 2 hours, with a return to baseline in 24 hours.

Disposition

Patients with new-onset AKI should be hospitalized. If nephrology consultation and dialysis facilities are not available, transfer to another institution is advisable, once volume and metabolic abnormalities have been adequately controlled and the patient is hemodynamically stable.

Decisions regarding dialysis generally are made by the nephrology consultant and take into account many factors, including laboratory test abnormalities and the presence or absence of signs and symptoms of uremia (e.g., nausea, vomiting, change in mental status). Many nephrologists choose to initiate dialysis when the

www.ketabpezeshki.com 66485457-66963820

BUN level exceeds 100 mg/dL or the serum creatinine level exceeds 10 mg/dL. Intractable volume overload and life-threatening hyperkalemia are the two most common indications for emergency dialysis.

CHRONIC KIDNEY DISEASE

In contrast to the typical patient with AKI, the patient with CKD has most commonly experienced a slowly progressive course of decreasing renal function over months or years and is likely to have either slowly progressive symptoms or acute problems brought on by superimposed illness, trauma, or other physiologic stress. The most common problems requiring emergent intervention are severe hyperkalemia and symptomatic volume overload.

Barring renal transplantation, CKD is an essentially irreversible condition generally characterized by a relentless decrease in renal function. Thus, whereas preservation of renal function may be a high priority in the patient with known AKI, management need not as a rule involve efforts to reverse the process presumed to have caused CKD, nor even perhaps efforts to determine the exact cause. On occasion, however, the kidney disease may have a reversible component. In some cases the underlying pathologic process affecting the kidneys may be arrested or treated; more commonly, correctable extrarenal factors (e.g., volume depletion or urinary tract obstruction) may be identified.

In the patient with CKD who has an acute problem, the focus should be the identification and treatment of an intercurrent illness that has caused clinical decompensation, with the goal of returning the patient to a stable, chronically compensated status.

Principles of Disease

The standard terminology for chronic renal failure has changed.[41] *Chronic kidney disease* denotes kidney damage or decreased renal function for 3 months or more and is characterized by irreversible nephron loss and scarring. *Chronic renal insufficiency,* which denotes a condition in which GFR has been moderately reduced but not to a degree sufficient to cause clear-cut clinical symptoms, has been replaced by an indication of the degree to which GFR is reduced. *End-stage renal disease,* now termed *kidney failure,* describes a condition in which renal function has diminished to a low level and in which serious, life-threatening manifestations can be expected to occur without dialysis or transplantation. At this stage the kidneys often are shrunken and diffusely scarred to such a degree that it may be impossible to make an etiologic diagnosis, even on pathologic examination.

The causes of CKD are numerous; their relative frequency depends primarily on the population studied. As with AKI, they can be conveniently classified (Box 97-9) as prerenal (vascular), intrinsic renal (glomerular and tubulointerstitial), or postrenal (obstructive). Glomerular disease accounts for approximately one third to one half of the cases of CKD; in the United States, diabetic nephropathy forms the largest group of these. Hypertensive nephrosclerosis is another important cause, particularly among blacks, in whom it may be the cause of 25% or more of cases of CKD. Among children and adolescents, reflux nephropathy is the most common cause of CKD. Renal failure related to intravenous drug use or to human immunodeficiency virus disease is a major consideration in some populations. Clues to other specific causes may be gained from elements of the history, physical examination, or laboratory and imaging studies. Although determining the underlying cause of CKD can permit the underlying disease to be treated and make possible some improvement in renal function in some cases, this is the exception rather than the rule.

Box 97-9 Major Causes of Chronic Kidney Disease

Vascular Causes
Renal arterial disease
Hypertensive nephrosclerosis

Glomerular Causes
Primary Glomerulopathies
Focal sclerosing glomerulonephritis (GN)
Membranoproliferative GN
Membranous GN
Crescentic GN
IgA nephropathy

Secondary Glomerulopathies
Diabetic nephropathy
Collagen vascular disease
Amyloidosis
Postinfectious
HIV nephropathy

Tubulointerstitial Causes
Nephrotoxins
Analgesic nephropathy
Hypercalcemia or nephrocalcinosis
Multiple myeloma
Reflux nephropathy
Sickle nephropathy
Chronic pyelonephritis
Tuberculosis

Obstructive Causes
Nephrolithiasis
Ureteral tuberculosis
Retroperitoneal fibrosis
Retroperitoneal tumor
Prostatic obstruction
Congenital abnormalities

Hereditary Causes
Polycystic kidney disease
Alport's syndrome
Medullary cystic disease

HIV, human immunodeficiency virus; *IgA,* immunoglobulin A.

Uremia

Progressive loss of renal function eventually results in a recognizable syndrome termed *uremia.* Clinical manifestations do not generally appear, however, until GFR has been reduced to approximately 15 to 20% of normal.

As the patient becomes unable to excrete an ingested salt or water load promptly, external balance of sodium and water is affected; volume overload or hypernatremia or hyponatremia may result. Inability to concentrate the urine is an early manifestation of renal insufficiency and may be manifested as nocturia. Potassium homeostasis is likewise disrupted, and a relatively small potassium load may lead to dangerous hyperkalemia. Acid-base balance is affected, because the kidney fails to clear the daily metabolic acid load owing to a decreased ability to excrete ammonium and phosphate; the result is a non–anion-gap acidosis in the earlier stages of CKD and a superimposed anion-gap acidosis as GFR decreases further. Calcium and phosphate metabolism is affected as well; retention of phosphate and progressive loss of the kidney's capacity to synthesize 1,25-dihydroxycholecalciferol, the active form of vitamin D, lead to hypocalcemia, secondary hyperparathyroidism, and eventually the development of renal osteodystrophy.

Nitrogenous byproducts of protein catabolism retained in the blood are the presumed cause of many of the diverse abnormalities of organ function in renal failure. Most patients with CKD show decreased glucose tolerance, although it is rarely severe enough to require treatment unless the medical history includes established diabetes. In such cases, insulin or other hypoglycemic therapy may need to be continued but generally at a lower dosage than required before the onset of renal failure, because the normal kidney has a major role in insulin degradation. Alterations in lipid metabolism result in elevated low-density lipoproteins and hypertriglyceridemia in many patients with CKD.

Clinical Features

Uremia has specific effects on a variety of organ systems. Many of these manifestations are relieved by dialysis, but others are not. A number have been attributed in some degree to the retention of nitrogenous wastes and to the previously noted derangements in vitamin D and parathyroid hormone metabolism.

www.ketabpezeshki.com 66485457-66963820

Cardiovascular System

The cardiovascular system is perhaps most dramatically affected in CKD.[42-44] Many of the manifestations can be attributed to the effects of chronic volume overload, anemia, hyperlipidemia, alterations in calcium and phosphorus metabolism, and volume- and hormonally mediated hypertension.[44-47] Pericarditis, with or without pericardial fluid accumulation, also is common in CKD, particularly among patients who have not had dialysis.

Pulmonary Effects

Similarly, uremic pleuritis, with or without associated pleural fluid collections, may develop in some patients. So-called "uremic lung," manifested radiographically by "batwing" perihilar infiltrates, represents pulmonary edema and is almost always caused by volume overload or myocardial dysfunction. Noninflammatory pleural effusion caused by volume overload also is fairly common. Of special importance in the ED evaluation is the fact that the radiographic appearance in pulmonary edema may at times be misleading, simulating an infectious lobar infiltrate or even assuming a nodular appearance in some cases.[48]

Neurologic Features

Neurologic dysfunction is common in advanced uremia and usually manifests with lethargy, somnolence, difficulty concentrating, or frank alteration in mental status. Seizures also may occur, although causes other than uremia alone must be ruled out. Uremic encephalopathy also commonly manifests with hiccups, asterixis, or myoclonic twitching. The last should not be confused with tetany caused by hypocalcemia, which also is common in untreated patients with CKD. In the peripheral nervous system, uremia often causes cramps and a distal sensorimotor neuropathy. A troublesome and characteristic complaint is restless legs syndrome, in which persistent neuropathic discomfort in the legs can be relieved only by movement.

Gastrointestinal System

Anorexia, nausea, and vomiting are nearly constant features of uremia. These GI manifestations are thought to be caused by accumulation of nitrogenous wastes because they often are relieved, even in the undialyzed patient, by introduction of a low-protein diet, and seem to correlate roughly with the BUN level.

Dermatologic Features

The skin of patients with CKD has a characteristic yellowish tinge. Uremic frost, the result of deposition of urea from evaporated sweat on the skin, is a classic finding that, like "uremic fetor," is seen only rarely now with the widespread use of dialysis (Fig. 97-3). Diffuse pruritus is often a major source of discomfort for the patient with CKD; in some cases it may be caused by calcium deposition in the skin secondary to derangements in calcium metabolism.

The use of gadolinium-based contrast agents for magnetic resonance imaging (MRI) has been associated with the development of nephrogenic systemic fibrosis, a potentially fatal disorder that occurs in patients with chronic kidney failure.[49]

Musculoskeletal System

The bones and joints are sites of problems for many of these patients, particularly those with long-standing renal disease. The complex disturbances of calcium and phosphate metabolism in CKD result in renal osteodystrophy, a clinical entity encompassing several overlapping varieties of bone disease that can cause bone pain or frank fractures. Patients with CKD generally are treated with long-term oral calcium and vitamin D in an effort to prevent both secondary hyperparathyroidism and uremic osteodystrophy. Occasional patients will have a poor response to therapy and require parathyroidectomy.

A specific type of arthritis caused by deposition of calcium hydroxyapatite or calcium oxalate crystals in joints is seen in some patients, as are periarticular calcium deposition, spontaneous tendon rupture, myopathy, and carpal tunnel syndrome.

Figure 97-3. Uremic frost. Note the fine white powder on the skin of this patient with kidney failure.

Immunologic Considerations

Uremic patients have long been noted to have an increased susceptibility to infection, even when not challenged by the invasive procedures associated with dialysis. Both humoral and cellular immunity have been shown to be affected. The relative importance of each in the pathogenesis of infection in renal failure has not been clarified, but defects in cellular immunity appear to be more significant clinically. Although patients with renal failure should be considered to be immunocompromised, most infections in patients with CKD are caused by common pathogens rather than opportunistic organisms.

Hematologic Effects

A pronounced normochromic normocytic anemia, with a hematocrit commonly in the range of 18 to 25%, is nearly universal in untreated CKD, except among patients with polycystic disease. It is caused primarily by the kidneys' decreased production of erythropoietin, a hormone that stimulates red cell production by the bone marrow. Other contributing factors are increased red cell hemolysis, nutritional deficiencies, and increased bleeding secondary to platelet dysfunction.

Although platelet number generally is normal in uremia, the bleeding time is prolonged because of defective platelet adhesiveness and activation. Numerous ecchymoses, seen in many patients with CKD, is a common manifestation.

Diagnostic Strategies

The patient with CKD, particularly one who is not yet receiving dialysis, is likely to be seen in the ED with one of the

www.ketabpezeshki.com 66485457-66963820

Box 97-10 Causes of Chronic Kidney Disease with Normal or Large Kidney Size

Polycystic kidney disease
Amyloidosis
Diabetic nephropathy
Malignant hypertension
Multiple myeloma
Glomerulonephritis (some cases)
Obstructive uropathy (some cases)

Box 97-11 Reversible Factors and Treatable Causes of Chronic Kidney Disease

Reversible Factors
Hypovolemia
Congestive heart failure
Pericardial tamponade
Severe hypertension
Catabolic state, protein loads
Nephrotoxic agents
Obstructive disease
Reflux disease
Acute interstitial nephritis
Hypercalcemic nephropathy
Multiple myeloma
Vasculitis (e.g., systemic lupus erythematosus, Wegener's granulomatosis, polyarteritis nodosa)
Obstructive nephropathy
Reflux nephropathy

Treatable Causes
Renal artery stenosis
Malignant hypertension

manifestations previously noted. In cases in which the diagnosis of renal failure has not previously been made, patients' complaints most commonly are nonspecific and often of insidious onset, such as generalized weakness, poor appetite, or deterioration of mental functioning. The initial laboratory finding of a reasonably well-tolerated but rather severe anemia may be the first clue to the diagnosis, which is subsequently confirmed by elevated BUN and serum creatinine levels. A prudent next step is to check the ECG for evidence of immediately life-threatening hyperkalemia before further laboratory and radiographic investigations are undertaken.

Once it has been determined that the patient is in no immediate danger, the ED evaluation can establish that renal failure is indeed chronic rather than acute. An explicit history to that effect obtained from previous medical records or from the patient or family provides the most straightforward and reliable confirmation, as does the presence of a dialysis access device on physical examination. If such a history is unavailable, the finding of bilaterally small kidneys (readily detected on plain abdominal films or by ultrasonography) constitutes equally good evidence. However, the converse is not necessarily true—a finding of normal-sized or large kidneys does not rule out CKD (Box 97-10). In such cases, additional diagnostic steps are required to establish the diagnosis. A convincing history of the long-standing presence of the presenting symptoms or of symptoms such as nocturia may be helpful in suggesting chronicity, as may a history of familial kidney disease such as polycystic kidney disease or Alport's syndrome. Laboratory abnormalities such as anemia, acidosis, hyperuricemia, hypocalcemia, and hyperphosphatemia can occur in patients with *acute* kidney failure as early as 10 days after onset. Although urinary findings likewise tend not to be helpful, the presence of broad waxy casts on microscopic examination is suggestive of chronic disease, whereas the finding of an "active" sediment (e.g., red cell casts) is good evidence for an acute process.

Although as a rule chronic kidney failure is irreversible and slowly progressive, an essential component of the ED evaluation is to exclude the possibility of potentially reversible factors (in effect, ruling out "acute on chronic" renal failure) and to ensure that treatable causes of CKD—disorders that if treated might allow for some return of renal function—have not been overlooked. These potentially reversible factors and treatable causes of CKD are important to keep in mind because they represent the only potential opportunity to reverse the patient's disease rather than simply to manage its results (Box 97-11).

Primary among superimposed reversible factors are those that lead to decreased renal perfusion. Of these, the most common is volume depletion. Regardless of the initiating cause, the process is exacerbated by the diseased kidney's impaired ability to conserve sodium and to concentrate the urine appropriately. Decreased renal perfusion caused by cardiac dysfunction of any cause is another extremely common and potentially reversible factor. An uncommonly encountered but important vascular cause of reversible deterioration of renal function is scleroderma renal crisis, a syndrome of accelerated hypertension and severe vasoconstriction in patients with underlying scleroderma that can be reversed by timely treatment with ACE inhibitors.[18]

Increased catabolism caused by infection, trauma, surgery, corticosteroids, or GI bleeding is another reversible factor that often is responsible for worsening azotemia and the development of uremic symptoms.

Drugs and toxins constitute another important group of reversible factors. Not only may these agents exacerbate renal insufficiency by causing intravascular volume depletion (diuretics), decreased renal perfusion (antihypertensive agents), or increased catabolism (tetracycline); they also can cause ATN (radiographic contrast material), AIN (many drugs), or inhibition of renal prostaglandin synthesis (NSAIDs). Particularly noteworthy is the dramatic decrease in renal function produced when an ACE inhibitor is administered to a patient with renal insufficiency caused by bilateral renal artery stenosis (or renal artery stenosis in a solitary kidney).[50]

Postrenal reversible factors also are important because of their frequency, particularly obstructive disease in the older male patient and reflux nephropathy in the child. Papillary necrosis should remain a consideration in the diabetic patient, the patient with sickle cell disease, and the patient with a history of long-term analgesic use. Stone disease, retroperitoneal fibrosis, and even rarer entities such as ureteral tuberculosis also should not be overlooked.

Finally, treatment of the underlying disorder that has caused the CKD can occasionally result in the return of some renal function, most notably in cases of myeloma kidney, some forms of secondary glomerulonephritis, and severe hypertensive disease. Although this consideration should relate to long-term care and follow-up, it is appropriate that ED management address this issue to ensure that appropriate evaluation and disposition are arranged.

Management

Persons with CKD constitute a group of patients who merit special attention in the ED setting. These patients are susceptible to infection, bleeding, and the numerous other complications associated with renal failure, as well as those that may be associated with the underlying causative disorder. Moreover, these patients are more vulnerable to the effects of any intercurrent illness or trauma. Those who are maintained with chronic hemodialysis or peritoneal dialysis are subject to potential complications from the dialysis therapy itself.

Patients with CKD also are uniquely susceptible to iatrogenic illness. First, they are less able to handle fluid and solute loads than are normal persons. Just as important, the presence of renal failure significantly alters the metabolism and action of many drugs, often in ways that are not predictable (Box 97-12). Thus the dose and schedule of every administered agent, even apparently innocuous ones such as antacids, laxatives, antiemetics, or multivitamin preparations, should be carefully considered.[51] For this purpose,

www.ketabpezeshki.com 66485457-66963820

ready access to a compendium such as the one by Aronoff and colleagues or availability of a hospital pharmacist for frequent consultations is invaluable.[34] In general, consultation with the patient's nephrologist is recommended on completion of the initial ED evaluation, because management and follow-up monitoring after the patient has left the ED often are complex.

In the United States, most patients with advancing CKD eventually will require dialysis, but several true emergencies may develop in the patient with CKD before chronic dialysis has been instituted. Specific diagnostic and therapeutic considerations apply to the management of these conditions regardless of whether they occur in dialyzed or undialyzed patients.

Hyperkalemia

Potentially the most rapidly lethal complication of CKD encountered in the ED setting is severe hyperkalemia. As a rule, this condition is clinically silent until it causes potentially life-threatening manifestations. Accordingly, hyperkalemia must be looked for in every patient with CKD. These patients can become severely hyperkalemic when required to handle even modest exogenous and endogenous potassium loads; moreover, even drugs that have only minimal effects on the serum potassium in normal persons, such as beta-blockers and ACE inhibitors, can cause hyperkalemia in these patients. There is concern that the use of succinylcholine in patients with CKD has the potential to cause rapid deterioration in patients who are already hyperkalemic, although this appears to be rare.

An ECG should be obtained whenever hyperkalemia is a possibility, and if signs of hyperkalemia are noted, appropriate therapy should be started immediately, even before laboratory confirmation of a high serum potassium level. ECG changes may be completely absent even when hyperkalemia is severe, however.[52] Thus a normal ECG does not preclude the need for laboratory confirmation of a normal serum potassium level. A potassium level of 6 mEq/L should be considered potentially dangerous, even though many patients with CKD chronically tolerate levels somewhat above this threshold without ECG changes. A patient with CKD who is in cardiac arrest should be assumed to be hyperkalemic and treated accordingly while the usual resuscitative measures are taken.

The most rapidly effective treatment for hyperkalemia is intravenous calcium, which transiently reverses the cardiac manifestations of hyperkalemia without altering the serum potassium level or total-body potassium (Table 97-2). Calcium should be given to buy time until more definitive measures can take effect. It makes little sense to administer calcium in response to an elevated serum potassium level in the absence of manifestations of hyperkalemia on the ECG.

In treating hyperkalemia, it also is important to keep in mind the CKD patient's limited ability to tolerate volume and solute

Box 97-12 Mechanisms of Drug Toxicity in Renal Failure

Excessive drug level
Impaired renal excretion of drug
Impaired renal excretion of active metabolite
Impaired hepatic metabolism
Increased sensitivity to drug
Changes in protein binding
Changes in volume of distribution
Changes in target organ sensitivity
Metabolic loads administered with drug
Misinterpretation of measured serum drug level (i.e., change in therapeutic range)

From Wolfson AB, Singer I: Hemodialysis-related emergencies: Part I. J Emerg Med 5:533, 1987.

Table 97-2 Treatment of Hyperkalemia

AGENT OR MODALITY	DOSE AND REGIMEN	ONSET/DURATION OF ACTION	MECHANISM OF ACTION	COMMENTS
Calcium gluconate (10%) or calcium chloride (10%)	10 mL IV (may repeat × 2 prn every 5-10 min)	1-5 min/~1 hr	Antagonizes membrane effects of K	ECG monitoring required Do not mix with HCO_3^- *Beware:* Hypercalcemia
Albuterol	10-20 mg (nebulized) by inhalation	30 min/2+ hr	Intracellular movement of K	Relatively free of significant side effects; tachycardia
Glucose and insulin	10-20 units regular insulin per 100 g glucose	30 min/while infusion continued	Intracellular movement of K	*Beware:* Hyperglycemia Hypoglycemia Infused volume may be decreased by giving $D_{10}W$, $D_{20}W$, or $D_{50}W$
Sodium bicarbonate	150 mEq/L IV infusion (rate variable)	Approximately 10-15 min/1-2 hr	Possible intracellular movement of K	Sodium bicarbonate
Kayexalate	25 g in 25 mL 70% sorbitol PO q6h ± 50 g in 50 mL 70% sorbitol by retention enema q6h	Hours/while continued	Exchange of K for Na	Slow and modest effect *Beware:* Na overload Enema must be retained × 30-45 min
Dialysis	HD PD	Minutes/while continued	Removal of K from blood	HD may remove 50 mEq/hr (*beware:* K rebound) PD may remove 15 mEq/hr
Intravenous diuretics (intravenous fluid if patient is hypovolemic)		Minutes/while diuresis continued (depending on renal function)	Urinary K excretion	Only in patients with some residual renal function

$D_{10}W$, 10% dextrose in water; *$D_{20}W$,* 20% dextrose in water; *$D_{50}W$,* 50% dextrose in water; *ECG,* electrocardiogram; *HD,* hemodialysis; *IV,* intravenously; *PD,* peritoneal dialysis; *PO,* orally.

www.ketabpezeshki.com 66485457-66963820

loads (see Table 97-2). Thus, sodium bicarbonate infusion risks causing volume overload and precipitating pulmonary edema. Intravenous glucose and insulin treatment also entails some volume administration but is much more effective in any case, and hyperkalemia can be controlled for as long as the infusion is continued. Another effective temporizing measure is the administration of inhaled albuterol to promote movement of potassium into cells while more definitive maneuvers are being instituted.[37,38] To remove potassium from the body, dialysis remains the most rapid and effective intervention. Sodium polystyrene sulfonate (Kayexalate), a resin that exchanges sodium for potassium ions, can be administered orally or rectally but is slow acting and only somewhat effective as a temporizing measure until dialysis (if necessary) can be instituted. In patients who still retain some renal function, the most effective way to treat hyperkalemia may be to administer an intravenous diuretic such as furosemide (if the patient is not hypovolemic) and to give volume if necessary. Large doses of diuretic may be necessary for a satisfactory diuresis to be induced. In light of the potential for ototoxicity with the use of loop-active diuretics, these drugs should be administered by slow infusion rather than by bolus and may be contraindicated in patients who also are receiving other potentially ototoxic agents. During the course of any of these therapeutic interventions, both the ECG and serum potassium levels must be monitored frequently.

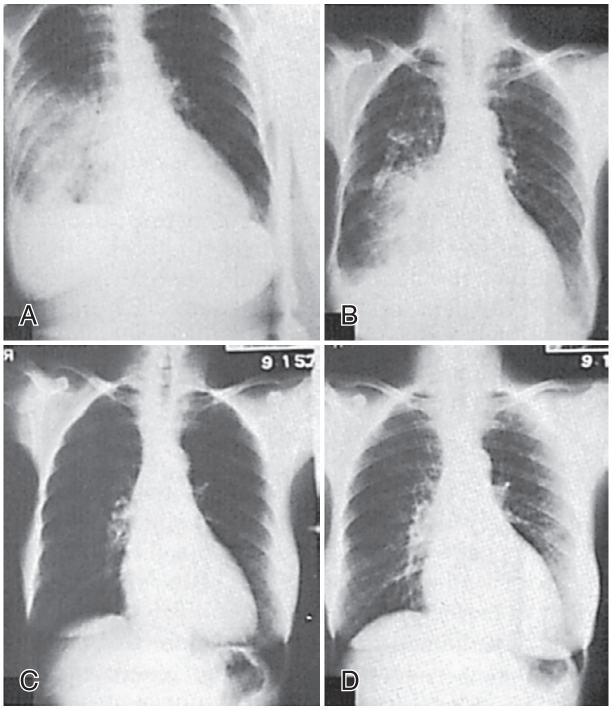


Figure 97-4. Pulmonary edema simulating right lower lobe pneumonia in a dialysis-dependent patient. Marked improvement with decreased infiltrate and return of heart to normal size were evident after dialysis and ultrafiltration. **A,** Chest x-ray film obtained immediately before dialysis shows cardiomegaly and right lower lobe infiltrate interpreted as pneumonia. **B,** Chest x-ray film at 5 hours after initiation of dialysis, with 2-kg weight reduction. The extent of the infiltrate has markedly decreased. **C** and **D,** Lung and heart have returned to normal size. (From Kjellstrand C, et al: In: Drukker W, Parson FM, Maher JF (eds): Replacement of Renal Function by Dialysis. Boston, Martinus Nijhoff, 1983, pp 536-568.)

Pulmonary Edema

Perhaps the most common ED problem in patients with CKD is pulmonary edema secondary to volume overload. Surprisingly, the diagnosis is not always straightforward. A history of increasing dyspnea on exertion or paroxysmal nocturnal dyspnea may be suggestive, but physical examination may not reveal the expected signs of CHF, and even chest radiography may be deceptive (Fig. 97-4).[48] Recent weight gain or a body weight considerably over "dry weight" (typically more than 5 pounds) is the most reliable clue, and in the absence of convincing evidence of another cause for dyspnea, volume overload should be assumed to be the cause, and the patient should be treated accordingly.

Treatment of pulmonary edema in the patient with CKD is of necessity somewhat different from that in other patients (Box 97-13).[53,54] Arrangements for initiation of dialysis should be made as soon as possible because it is the most rapidly effective means to decrease intravascular volume in the absence of renal function. Other immediate measures should be instituted in the meantime. Although such measures may occasionally prove to be effective enough to avoid dialysis temporarily in patients who possess some residual renal function, it should nevertheless be anticipated that the response to even extremely aggressive medical therapy short of dialysis will be inadequate.

Box 97-13 Treatment of Pulmonary Edema in Renal Failure

- Dialysis
  - Hemodialysis
  - Hemofiltration
  - Peritoneal dialysis
- Oxygen
  - Nitroglycerin
  - Nitroprusside
  - Diuretics

The CKD patient with pulmonary edema is placed in the sitting position, and high-flow oxygen is administered by mask. The use of continuous or bilevel positive airway pressure (CPAP or BL-PAP) delivered by face mask has been reported to be a useful adjunct in patients with CKD, as it is in patients without renal failure.[55,56] Sublingual or topical nitroglycerin, or both, can be administered immediately and functions rapidly to reduce both preload and afterload; an intravenous infusion can be begun promptly and titrated to effect. Intravenous nitroprusside may have an advantage in producing more arteriolar dilation if the patient is hypertensive. Diuretics are not expected to be helpful unless the patient has retained a significant level of renal function.

Infection

Because infection is a major contributor to morbidity and mortality among patients with CKD, the possibility of serious infection should be entertained even when the expected classic findings are not all present.[51,57-59] For example, bacteremia may manifest with fever alone, just as in other patients with impaired immunity. Patients with pneumonia may have only vague dyspnea or malaise, symptoms that may be attributed to volume overload or uremia. Thus, all diagnostic possibilities should be pursued, and empirical broad-spectrum antibiotic coverage often is advisable until infection has been ruled out in the hospital. Bacteremia resulting from vascular access infection is quite common in patients receiving hemodialysis, as is peritonitis in patients undergoing peritoneal dialysis.

UTI can occur even in patients with minimal urine output or those with long-standing renal failure. Urinary stasis is undoubtedly a predisposing factor.[59] Upper UTI associated with a clinical picture typical of pyelonephritis or renal colic is seen most commonly in patients with polycystic kidney disease and requires parenteral treatment. A clinical diagnosis can be made presumptively in the ED, but invasive measures sometimes are necessary to document infection and guide therapy. For infected cysts, lipid-soluble antibiotics (e.g., clindamycin, trimethoprim-sulfamethoxazole) offer the best antibiotic penetration; surgical intervention for refractory infection sometimes becomes necessary, however.[61]

www.ketabpezeshki.com 66485457-66963820

Dialysis

Dialysis can normalize fluid balance, correct electrolyte and other solute abnormalities, and remove uremic toxins or drugs from the circulation when the patient's kidneys are unable to do so. Dialysis also can, but generally to a lesser degree, reverse some uremic symptoms and permit better long-term control of hypertension, anemia, and renal osteodystrophy.

The two major dialysis modalities are hemodialysis and peritoneal dialysis. Each is based on a technique whereby the patient's blood comes into contact with a semipermeable membrane on the other side of which is a specially constituted balanced physiologic solution. Water and solutes diffuse across the membrane by moving along concentration and osmotic gradients, effectively normalizing the blood's composition.

Hemodialysis requires special access to the patient's circulation, generally through a surgically created arteriovenous fistula or implanted artificial graft, or through a surgically placed tunneled catheter. The vascular access site must be treated with care because hemodialysis cannot be performed without it. Careless manipulation or puncture can cause bleeding, infection, or thrombosis that may result in loss of the access. The involved arm should not be used for blood pressure determinations, and a tourniquet should not be applied.

In general, blood is drawn and intravenous lines are established in other locations. In exceptional circumstances, if no other site is available and it is essential to obtain blood samples quickly, the fistula or graft may be used, but with precautions: A tourniquet is not applied, the area is cleansed scrupulously before the puncture, and extreme care is taken not to puncture the back wall of the access. After the puncture, firm but nonocclusive pressure is applied for at least 10 minutes. The presence of a thrill both before and after the procedure is documented. Similar precautions are taken in the exceptional cases in which the fistula or graft must be used for intravenous access. If this is done, an automated infusion pump is essential to control the infusion rate into these relatively high-pressure blood vessels.

In *peritoneal dialysis,* the patient's peritoneum functions as the dialysis membrane. Dialysate is infused through a surgically implanted Silastic catheter (Tenckhoff catheter) that penetrates the lower abdominal wall. Fluid exchanges are performed several times per day, typically by the patient at home. As compared with hemodialysis, peritoneal dialysis offers the theoretic advantages of greater patient independence, avoidance of anticoagulation, and smoother control of volume and hypertension without the intermittent rapid shifts of solute typical of hemodialysis. Medications such as insulin and antibiotics can be administered intraperitoneally (IP), allowing smoother absorption and more stable blood levels. The main disadvantage of peritoneal dialysis is a significant incidence of bacterial peritonitis, which is, however, usually readily treatable.

Indications for Dialysis. The decision to initiate chronic dialysis in the patient with CKD generally is made by the patient's nephrologist in the setting of gradually decreasing GFR and slowly progressive manifestations of renal failure. The absolute value of the BUN or serum creatinine generally is used only as a rough guide to when chronic dialysis should be instituted. Provision of vascular or peritoneal access usually has been arranged weeks to months before the anticipated initiation of dialysis, to allow the access site to mature and to minimize any mechanical complications of the procedure.

For patients who come to the ED with AKI, however, as well as for patients with CKD in whom acute problems have developed, it is the emergency physician who must be prepared to make the decision to arrange for dialysis to be provided emergently (Box 97-14). How urgently dialysis must be initiated depends not only on the severity and acuteness of the presenting problem but also on the availability of technical facilities and trained dialysis personnel and the effectiveness of available temporizing measures for the problem at hand.

Box 97-14 Indications for Emergency Dialysis

- Pulmonary edema
- Severe uncontrollable hypertension
- Hyperkalemia
- Other severe electrolyte or acid-base disturbances
- Some overdoses
- Pericarditis (possibly)

The most common problem requiring emergent dialysis, particularly in the patient with CKD, is pulmonary edema secondary to volume overload. In general, the inciting cause is overingestion of fluid and salt in excess of the patient's greatly diminished renal excretory capacity. Despite the effectiveness of temporizing measures, many of these patients require immediate dialysis—either emergency hemodialysis or, in the case of the patient maintained on peritoneal dialysis, intensification of the usual dialysis regimen.

A related problem that may require emergent, or at least urgent, dialysis is malignant hypertension, particularly when associated with hypertensive encephalopathy or cardiovascular decompensation. Because hypertension in most patients with renal failure commonly is volume dependent, correction of volume overload, even if it is clinically not apparent, is a central component of therapy. Temporizing measures such as the administration of intravenous sodium nitroprusside or nitroglycerin often permit hypertension to be controlled sufficiently for dialysis to be delayed for several hours, but prolonged administration of sodium nitroprusside carries an increased risk of thiocyanate toxicity in patients with renal failure. In many cases, hypertension and associated symptoms are difficult to control until dialysis permits volume overload to be corrected. Because the blood pressure often is dramatically responsive to reduction of circulating volume, it is recommended that other antihypertensive agents with more prolonged effects be withheld until after dialysis to avoid hypotension after circulating volume has been acutely reduced.

Severe hyperkalemia is another common indication for emergent or urgent dialysis, particularly in the patient with AKI who is hypercatabolic. In the patient with CKD, hyperkalemia usually is caused by excessive potassium intake, but endogenous causes such as hemolysis or rhabdomyolysis should be kept in mind as well. The available temporizing measures can be used with variable degrees of effectiveness and for different durations to control the serum potassium level, but dialysis remains the most effective means of removing potassium from the body. For rapid control of the serum potassium, hemodialysis, with its high clearance rates, is preferred to peritoneal dialysis.

Other severe electrolyte and acid-base disturbances, including diabetic ketoacidosis,[61] may sometimes necessitate emergent dialysis. Occasional patients with renal failure and severe hypercalcemia uncontrollable by other modalities (e.g., patients with multiple myeloma causing both renal failure and hypercalcemia) may require dialysis. The occasional patient with renal failure in whom severe hypermagnesemia develops after inappropriate therapy or magnesium ingestion may require immediate dialysis to reverse life-threatening paralysis or cardiac dysrhythmia. Severe metabolic acidosis in the setting of renal failure is another indication for emergent dialysis, particularly if volume overload precludes the administration of reasonable amounts of bicarbonate. Of note, bicarbonate also can precipitate tetany and convulsions if administered IV (e.g., to treat acidosis or hyperkalemia) to a patient with hypocalcemia.

www.ketabpezeshki.com 66485457-66963820

A somewhat unusual but related situation is one in which a patient with renal failure has taken an overdose or inadvertently been administered medication that ordinarily is cleared by the kidneys. If the agent is adequately dialyzable and its continued presence in the circulation poses a significant risk to the patient, immediate dialysis can be lifesaving. An example of such a situation is the ingestion of methanol or ethylene glycol by a dialysis patient. Similarly, ill-advised use of magnesium-containing cathartics or phosphate-containing enemas by patients with CKD can lead to dangerous hypermagnesemia and hyperphosphatemia, respectively, and may necessitate urgent dialysis.

The serum creatinine and BUN levels themselves are not considered definitive indications for dialysis. A creatinine of 10 mg/dL or a BUN of 100 mg/dL often is used as a guideline for beginning chronic dialysis in the patient with progressive renal failure. In dialyzed patients, however, the serum creatinine often is considerably greater than 10 mg/dL but is a reflection more of total body muscle mass than the adequacy of dialysis. The BUN is a somewhat better indicator; the level in well-dialyzed persons generally is in the range of 50 to 80 mg/dL and is more than 100 mg/dL in less well-dialyzed patients. Neither blood level, however, correlates more than roughly with uremic symptoms even in undialyzed patients or has any direct bearing on how urgently dialysis should be initiated.

The occurrence of uremic symptoms or signs such as nausea, vomiting, lethargy, or twitching indicates a need for dialysis but does not necessitate immediate initiation of dialysis unless symptoms are severe. Pericarditis, even in the absence of cardiac tamponade, often is considered an indication for urgent dialysis,[62] but it is not uncommon for pericarditis to occur in well-dialyzed CKD patients as well.[63] In a previously undialyzed patient with progressive renal insufficiency, the appearance of pericarditis indicates that it is time to initiate dialysis, although not necessarily on an emergency basis.

Complications of Dialysis Therapy. Optimal ED management of acute problems referred from the dialysis unit, or those occurring at home or in the interdialytic period, requires knowledge of and familiarity with the particular problems associated with CKD and dialysis.[51,57-59] Consultation with the nephrologist or dialysis nurse is important in arranging a consistent care plan for the dialysis patient with an emergent condition and in ensuring appropriate further acute care or follow-up.

Complications of Hemodialysis

Vascular Access–Related Complications

The performance of hemodialysis depends on reliable vascular access, and it is the vascular access device that is responsible for complications of dialysis that most often require evaluation in the ED setting. These problems must be attended to promptly to minimize the risk of losing the patient's dialysis "lifeline."

Bleeding from the dialysis puncture site can occur hours after a hemodialysis treatment, either spontaneously or after inadvertent minor trauma to the site. Such bleeding almost always can be stopped by applying firm pressure to the access site; care should be taken not to occlude and possibly cause thrombosis of the vessel by compressing it too vigorously, and the presence of a thrill immediately after the procedure should be documented in the chart. It may be necessary to keep the patient in the ED for a time to ensure that bleeding does not recur. Recurrent bleeding, especially from an aneurysm or a pseudoaneurysm, is best evaluated by a vascular surgeon.

Similarly, if the patient reports that the thrill in the access has been lost, a vascular surgeon is consulted immediately. Although thrombolytic agents sometimes are used, definitive treatment generally is surgical revision.[57,58] The access device should not be forcefully manipulated or irrigated because rupture of the vessel or venous embolization may result.

Infection of the vascular access is not uncommon and can result in persistent or recurrent bacteremia as well as loss of the access. Infection appears to be a consequence of contamination at the time of puncture for dialysis; most infections are caused by staphylococci typical of skin flora. Infections are more likely to occur in grafts than in native fistulae.[64,65] The signs and symptoms of an access infection—redness, warmth, and tenderness over the site—often are obvious, but in many cases, localizing findings are absent and the patient has only fever or a history of recurrent episodes of fever and documented bacteremia. For this reason, it is common practice to obtain blood cultures for all patients on hemodialysis who have a fever without an obvious source of infection and to treat them presumptively for an access infection.[66] A careful search for other sources of infection is done, however, before nonapparent access infection is concluded to be the cause. Infections such as odontogenic abscess, extremity cellulitis (particularly in diabetics), and perirectal abscess can easily be missed.

Although some nephrologists prefer to admit all dialysis patients with fever to the hospital, management of these patients on an outpatient basis often is possible, provided that they otherwise feel well and do not appear to be septic and provided that they can care for themselves at home and return promptly if their condition worsens. This course is made more practicable by the fact that they can be loaded with intravenous antibiotics that dependably maintain adequate blood levels until the time of the next scheduled dialysis treatment, at which time the culture and sensitivity test results can be checked and therapy adjusted accordingly. Vancomycin 1 to 1.5 g given IV as a single loading dose is the drug of choice in this situation because most access infections are staphylococcal and because this drug is only minimally hemodialyzable and needs to be given only every 5 to 7 days in the chronic dialysis patient. If a gram-negative infection also is thought to be likely, as in a patient who has had recent episodes of gram-negative bacteremia, a loading dose of a second drug (e.g., a third-generation cephalosporin or an aminoglycoside) also can be administered.[66] Patients can be reloaded with these drugs at the end of their next hemodialysis session if culture results prove to be positive.

Non–Vascular Access–Related Complications

The hemodialysis procedure itself, which entails invasion of the vasculature, anticoagulation, and significant shifts of fluid and solutes, often is associated with acute complications such as hypotension, shortness of breath, chest pain, and neurologic abnormalities.

Hypotension

Hypotension that occurs after dialysis most commonly is the result of an acute reduction in circulating intravascular volume and the failure of the patient's homeostatic mechanisms to compensate for it. Because hemodialysis is episodic, each treatment must remove the excess fluid that has accumulated over the period since the last dialysis (generally 2 to 3 days), and patients often are relatively volume-overloaded at the beginning of each treatment. With rapid removal of extracellular fluid, there is inadequate time for transcellular fluid shifts to replace intravascular volume. Antihypertensive medications, particularly beta-blockers, that are required when the patient is in a volume-expanded state can contribute to the hypotension when intravascular volume is normalized.

Most episodes of hypotension that occur during hemodialysis will resolve spontaneously or can be readily managed by either a decrease in blood flow rate or the infusion of small volumes of saline (to effect transient volume expansion) or hypertonic solutions (to reverse transient acute hypo-osmolality). Patients with significant hypotension who do not respond to these maneuvers

www.ketabpezeshki.com 66485457-66963820

Box 97-15 Differential Diagnosis of Hypotension in Hemodialysis Patients

- Hypovolemia
- Excessive fluid removal
- Hemorrhage
- Septicemia
- Cardiogenic shock
- Dysrhythmia
- Pericardial tamponade
- Myocardial infarction
- Myocardial or valvular dysfunction
- Electrolyte disorders
- Hyperkalemia or hypokalemia
- Hypercalcemia or hypocalcemia
- Hypermagnesemia
- Vascular instability
- Drug-related
- Dialysate-related
- Autonomic neuropathy
- Excessive access arteriovenous flow
- Anaphylactoid reaction
- Air embolism

From Wolfson AB, Singer I: Hemodialysis-related emergencies: Part I. J Emerg Med 5:533, 1987.

often are brought to the ED for further evaluation. Patients on dialysis should be considered to be at risk for acute myocardial infarction, acute dysrhythmias, and sepsis. These are common causes of hypotension among all patients in the ED, and consideration should first be given to these entities (Box 97-15).[51]

Dialysis patients are commonly treated with epoetin or darbepoetin to prevent severe anemia, but untreated patients typically have low baseline hemoglobin levels, and acute blood loss may result in symptomatic angina or CHF. Serum levels of clotting factors are normal in CKD, but patients are routinely anticoagulated for each hemodialysis treatment. Although transient thrombocytopenia may occur during the dialysis procedure, the qualitative platelet defect characteristic of renal failure represents the most important factor in bleeding that continues beyond the peridialytic period.[67] This abnormality is only partially reversed by dialysis but can be corrected by administration of DDAVP, which increases release of factor VIII–von Willebrand factor (vWF) polymers from vascular endothelium. DDAVP has been used successfully to normalize the bleeding time in preparation for surgery in patients with CKD. Cryoprecipitate and conjugated estrogen both have been shown to produce similar effects for a longer period.[40]

Overt bleeding from the GI tract, often caused by angiodysplasia or peptic ulcer disease, is common and can be dramatic. Occult hemorrhage in other locations, however, can present a diagnostic challenge because symptoms and signs of volume loss tend to be overshadowed by local manifestations of bleeding into a closed space. Thus, spontaneous retroperitoneal or pleural hemorrhage tends to manifest with flank pain or with chest pain and shortness of breath, respectively.

Occasionally, acute hypotension may be caused by anaphylaxis or an anaphylactoid reaction to some component of the dialyzer or the dialysate; these possibilities should be considered if the history is suggestive. Acute pulmonary embolism and acute air embolism are two less likely possibilities. The former, although it does occur occasionally in dialysis patients, is unusual. The latter, although reported occasionally in the past, has been all but eliminated by improved dialysis monitoring equipment and safety mechanisms.

Two additional entities in the differential diagnosis for hypotension are of particular importance in the patient with CKD—acute pericardial tamponade and severe, life-threatening hyperkalemia. Acute pericardial tamponade may be the result of either sudden pericardial hemorrhage or sudden worsening of a formerly compensated pericardial effusion after acute correction of elevated preload. The clinical features of tamponade in the dialysis patient are similar to those in other populations, but the common preexistence of cardiomegaly may make the chest film difficult to interpret unless it shows the typical "water bottle" shape and a definite increase in heart size from previous examinations.

Similarly, an elevated central venous pressure is of little use in differentiating tamponade from underlying right-sided heart failure. Even a bedside ultrasonographic examination that shows pericardial fluid, although suggestive, is not proof that tamponade is present, because many dialysis patients chronically have pericardial effusions that do not cause hemodynamic compromise.[63] Ultrasonographic demonstration of right ventricular diastolic collapse is more specific, but a definitive diagnosis of tamponade depends on the direct demonstration of equal pressures in the right and left atria on cardiac catheterization.

Emergency pericardiocentesis must occasionally be performed in the ED to relieve acute tamponade, but there often is enough time for the patient to be transported to the catheterization suite or operating room for safer and more definitive therapy in a controlled setting. If immediate pericardiocentesis is believed to be necessary, however, the emergency physician should not hesitate to perform this potentially lifesaving procedure, despite the many potential complications and the increased risk of bleeding in patients with CKD. Similarly, in the case of a dialysis patient who is in cardiac arrest, pericardiocentesis generally should be attempted if initial resuscitative efforts have not been successful.

Severe, life-threatening hyperkalemia, although unusual in a dialyzed patient, can occur in the presence of underlying catabolic illness or with a prolonged period of hypotension and low flow. Patients who are hyperkalemic can have profoundly slow heart rates, particularly if they have been treated with beta-blockers or calcium channel blockers. If a dialysis patient is in cardiac arrest, it should be assumed that hyperkalemia is present, and intravenous calcium should be given immediately.

Shortness of Breath

Shortness of breath in dialysis patients generally is caused by volume overload. In the patient who becomes short of breath while being dialyzed, however, other causes must be sought—primarily sudden cardiac failure, pericardial tamponade, pleural effusion, or pleural hemorrhage. Air embolism and anaphylactoid reactions are unusual causes. Often, pneumonia or underlying reactive airway disease is responsible.

Chest Pain

Chest pain during dialysis must be taken seriously because cardiovascular disease is a leading cause of death in patients with CKD, and most episodes of chest pain occurring during dialysis are likely to be ischemic in origin.[68,69] Most dialysis patients have risk factors for coronary artery disease, related to either CKD itself or the underlying condition that led to renal failure, and many have well-documented coronary artery disease.[42,43] CKD is commonly associated with hypertension, hyperlipidemia, carbohydrate intolerance, and disturbances of calcium and phosphorus metabolism. In addition, dialysis patients may be anemic, and many are chronically volume-overloaded. During hemodialysis, these underlying factors may be added to acute physiologic stresses such as transient hypotension and hypoxemia, which often are associated with the dialysis procedure, thereby increasing myocardial oxygen demand while decreasing oxygen delivery.

In evaluating presumed ischemic chest pain in a patient with CKD, it is important to keep in mind the potentially reversible factors that may have precipitated the episode. Particularly when a patient whose angina has been stable begins to experience more frequent or more severe anginal episodes, it should be determined whether increasing anemia, poorly controlled hypertension, or uncorrected volume overload is a factor. Coronary artery disease appears to become symptomatic with a lesser degree of obstruction than in other conditions.

Patients who repeatedly experience chest pain during dialysis should undergo a complete evaluation so that the extent of their coronary artery disease can be defined and optimal management

www.ketabpezeshki.com 66485457-66963820

planned. After repeated, frequent hospital admission to rule out myocardial infarctions because of chest pain during dialysis, it may be reasonable for the patient's nephrologist and cardiologist to set guidelines regarding further admissions.

The presence of renal failure and its associated electrolyte and acid-base disturbances does not in general obscure the usual ECG changes of angina or acute myocardial infarction. The pattern of the change of serum cardiac enzymes with acute infarction also is not altered by CKD, although the baseline level of these enzymes may be higher than in the general population. Troponin appears to perform best as a marker of infarction in patients with CKD.[70-72] Treatment of ischemic chest pain is the same as for other populations.

Among nonischemic causes of chest pain, pericarditis should always be a consideration, even in the well-dialyzed patient. The presentation is essentially the same as in nonrenal patients; fever, a friction rub, or atrial dysrhythmias may be associated findings, and signs of pericardial effusion or early tamponade should be sought. Indomethacin often is effective in relieving pain, but some patients eventually require further measures, such as pericardiocentesis with corticosteroid instillation or pericardial stripping. Patients with pericarditis often receive more frequent or intensified dialysis because pericarditis is thought to be a marker for inadequate dialysis.[62]

Neurologic Dysfunction

Neurologic dysfunction manifesting during or immediately after hemodialysis often is caused by disequilibrium syndrome, a constellation of symptoms and signs that is thought to result from rapid changes in body fluid composition and osmolality during hemodialysis. It usually occurs only in patients with high BUN levels who are just starting hemodialysis. The syndrome does not occur with peritoneal dialysis. Typically, patients have headache, malaise, nausea, vomiting, and muscle cramps, but features in more severe cases may include altered mental status, seizures, or coma. Symptoms resolve over several hours as fluid and solutes are redistributed across cell membranes.

It is dangerous, however, to attribute an altered mental status to disequilibrium syndrome unless other potential causes have been ruled out (Box 97-16), particularly when symptoms persist, fluctuate, or worsen during a reasonable period of observation. Likewise, when seizures occur during dialysis, it is tempting but unwise to attribute them to disequilibrium syndrome without considering other, potentially serious causes, even in patients who have had seizures in the past. In particular, the finding of any new focal neurologic abnormality calls for, at a minimum, an immediate head CT scan to detect intracranial hemorrhage. Similarly, if fever or other evidence of infection is present, meningitis must be a serious consideration. Other considerations include hyperglycemia and hypoglycemia (especially in the diabetic patient), electrolyte abnormalities, hypoxic states, hypotension of any cause, and other toxic or metabolic causes. The treatment of seizures in patients with CKD is essentially the same as in other populations.

Box 97-16 Differential Diagnosis of Altered Mental Status in Dialysis Patients

Structural Conditions
- Cerebrovascular accident (particularly hemorrhage)
- Subdural hematoma
- Intracerebral abscess
- Brain tumor

Metabolic Conditions
- Disequilibrium syndrome
- Uremia
- Drug effects
- Meningitis
- Hypertensive encephalopathy
- Hypotension
- Postictal state
- Hypernatremia or hyponatremia
- Hypercalcemia
- Hypermagnesemia
- Hypoglycemia
- Severe hyperglycemia
- Hypoxemia
- Dialysis dementia

Complications of Peritoneal Dialysis. As with hemodialysis, most of the complications of peritoneal dialysis are related to the dialysis access device, in this case the peritoneal catheter.[51,57] In contrast to hemodialysis, however, the dialytic process in peritoneal dialysis occasions few immediate difficulties. Whatever volume or metabolic problems develop often are a consequence of the fact that the typical patient maintained on peritoneal dialysis is seen by a doctor or nurse only once a month.

Peritonitis is the most common complication of peritoneal dialysis. Fortunately, it is in general much less severe than other types of peritonitis and can be treated readily on an outpatient basis despite the continued presence of a foreign body—the Tenckhoff catheter—in the peritoneal cavity.[57,73] Occasionally, when an episode of peritonitis responds poorly to antimicrobial therapy or when a patient has repeated episodes of peritonitis caused by the same organism, the catheter must be removed and the patient sustained with hemodialysis until the infection is completely cleared and a new catheter can be placed. Repeated infections do, however, carry the risk of permanently altering peritoneal permeability or effective surface area and necessitating a permanent switch to hemodialysis.

Peritonitis in patients on peritoneal dialysis presumably is caused by inadvertent bacterial contamination of the dialysate or tubing during an exchange, or by extension of an infection of the exit site or the subcutaneous tunnel into the peritoneal cavity. A majority of cases of peritonitis are caused by *Staphylococcus aureus* or *Staphylococcus epidermidis*, and most of the remainder (approximately 30%) by gram-negative enteric organisms.[73] Fungal infections are uncommon but generally are refractory to medical therapy and are often considered an indication for catheter removal. Polymicrobial infection suggests direct contamination from the GI tract and mandates a search for the site of perforation or fistula, although such a source is identified in only a minority of cases. No organism is identified in approximately 10 to 20% of cases of peritoneal dialysis–associated peritonitis.

The diagnosis of peritonitis usually is made by the patient when a cloudy dialysis effluent is noted, corresponding with the appearance of white blood cells (WBCs) in the dialysate. Peritonitis is often, but by no means invariably, accompanied by nonspecific abdominal pain, malaise, or fever. Even in the absence of cloudy fluid, when a patient has fever or abdominal symptoms, it is advisable to consider peritonitis and to check the fluid, because early peritonitis may manifest in an atypical manner. In more severe cases, peritonitis is accompanied by nausea, vomiting, severe pain, and hypotension, necessitating hospitalization and consideration of the possibility of acute surgical disease.

In the ED setting the diagnosis of peritonitis is confirmed by the finding of more than 100 WBCs/mm^3 in the peritoneal fluid, with more than 50% neutrophils, or by a positive result on Gram staining. A sample of fluid is obtained for analysis. If a specialized dialysis nurse is available to obtain the fluid, this may be preferable. If not, the fluid is obtained through use of sterile technique. Fluid is sent for cell count and differential, Gram staining, and culture (with use of blood culture bottles).

Peritoneal dialysis–associated peritonitis is treated with an initial intraperitoneal loading dose of antibiotic, followed by a 10- to 14-day course of intraperitoneal antibiotics that are administered by the patient on an outpatient basis. After the diagnosis has been confirmed, consultation with the patient's nephrologist or dialysis nurse specialist is indicated to determine antibiotic therapy as well as a plan for outpatient management and follow-up evaluation or occasionally, if peritonitis is severe or outpatient management is precluded by psychosocial considerations, for hospitalization.

www.ketabpezeshki.com 66485457-66963820

A common treatment regimen is a loading dose of vancomycin 30 mg/kg given IP, followed by further intraperitoneal doses every 5 to 7 days, plus ceftazidime or cefepime 1 g IP or gentamicin 0.6 mg/kg IP. The last two regimens are given as a loading dose followed by maintenance doses administered IP once daily at the time of an exchange.[73] Heparin 500 to 1000 units also may be added to each bag of dialysate for the first few days of treatment to help reduce the formation of fibrin strands that may obstruct the catheter. Patients should be seen by the dialysis nurse in 24 to 48 hours for assessment of the response to therapy and adjustment of antibiotic therapy as necessary after review of the results of culture and sensitivity testing.

Catheter contamination or leaks from the catheter, tubing, or dialysate bag should be managed in the same fashion as for frank peritonitis. The site and cause of leakage are identified, and damaged elements are promptly replaced. Occasionally, with leakage of peritoneal fluid from around the catheter, surgical correction of the underlying problem will be necessary.

Patients who have severe abdominal pain, vomiting, ileus, chills or high fever, or hypotension require hospital admission and management. Likewise, patients with severe underlying illness and those who cannot reliably perform exchanges or administer antibiotics at home also require inpatient management. Dialysis exchanges are continued on the same schedule. The inpatient antibiotic regimen is essentially the same as that used for outpatients.

Perhaps the most serious potential pitfall in caring for the patient maintained on peritoneal dialysis with abdominal pain or other signs of peritonitis is to overlook other serious intra-abdominal conditions whose presentation may mimic that of peritonitis. Patients on peritoneal dialysis are at increased risk for abdominal wall or inguinal hernia because of chronically increased intra-abdominal pressures; previous abdominal surgery also places them at risk for hernia, as well as for obstruction secondary to adhesions. The manifestations of serious disorders unrelated to dialysis (e.g., acute appendicitis, diverticulitis, cholecystitis, acute pancreatitis, ischemic bowel, perforated viscus) also may be attributed to ordinary peritoneal dialysis–associated peritonitis, with the potential for disastrous consequences. The accessibility of the peritoneal fluid for examination may prove to be helpful in documenting the presence of an inflammatory process, but it also has the potential to mislead ED investigation of its cause. A finding of brownish or fecal material in the peritoneal drainage should suggest a ruptured viscus until proven otherwise, and immediate surgical consultation should be sought. Detection of localized tenderness, a palpable mass, or an incarcerated hernia on physical examination can be extremely helpful in making the diagnosis. Abdominal radiography may be useful for demonstrating the presence of ileus, but pneumoperitoneum may reflect only the introduction of air during a recent fluid exchange rather than a perforated viscus.[74] Thus it is important to keep in mind the possibility that disorders other than peritonitis may underlie the patient's symptoms, and astute clinical judgment rather than specific criteria should dictate requests for surgical consultation or decisions regarding hospitalization of the patient for observation.

Infection of the catheter exit site is another relatively common problem for which the patient on chronic peritoneal dialysis may seek care in the ED.[73] This infection tends to be caused by typical skin flora and manifests with the usual local signs of infection. Although not serious in themselves, exit site infections should be taken seriously because they may lead to infection of the subcutaneous tunnel, which can cause repeated episodes of peritonitis and may ultimately necessitate removal of the catheter. Any visible exudate is cultured and Gram stained, and therapy with an oral antibiotic such as trimethoprim-sulfamethoxazole is started, pending the results of culture and sensitivity testing. The patient is instructed to cleanse the site meticulously several times a day using povidone-iodine or peroxide solution.

Tunnel infections can be difficult to detect on physical examination and may be suspected only after the patient has several bouts of peritonitis caused by the same organism. As with other closed-space infections, tunnel infections tend to be difficult to eradicate unless the tunnel is partially unroofed and drained.

Patients maintained on peritoneal dialysis also may come to the ED with any of several basically mechanical problems, of which the most common is failure of the dialysate to drain completely at the time of an exchange. Occasionally this problem is caused simply by kinking or inadvertent clamping of the external catheter or tubing. More often, though, it is the result of catheter obstruction by fibrinous debris or kinking or migration of the catheter within the peritoneal cavity, often associated with constipation. Catheter position is best assessed initially by plain radiography of the abdomen. Specific intervention may be guided by a contrast "catheterogram." Fibrinolytic agents have been used successfully to open occluded catheters, but surgical intervention for catheter replacement often is required.

Severe metabolic disturbances are much less common among patients on peritoneal dialysis than patients on hemodialysis, because in the former group, dialysis is being performed essentially continuously and the blood remains in near-equilibrium with the dialysate. However, significant disturbances do occasionally occur, usually in association with hypercatabolic states, major dietary indiscretions, or significant GI fluid loss. One interesting derangement that occurs occasionally in diabetic patients receiving peritoneal dialysis is a syndrome of severe hyperglycemia (sometimes even despite continuation of the usual insulin dose) resulting from absorption of glucose from hyperosmolar dialysate, with associated nonspecific symptoms of malaise, weakness, and headache. Although glucose levels may be as high as 1500 mg/dL in these patients, they cannot undergo an osmotic diuresis and remain clinically euvolemic. Correction of hyperglycemia must be undertaken carefully to avoid causing rapid osmolar and volume shifts.

KEY CONCEPTS

Acute Kidney Injury

- The causes of AKI can be classified as prerenal, postrenal, and intrinsic renal disorders.
- Management of AKI is directed first at potentially lethal complications such as hyperkalemia or volume overload and then at reversal of the underlying cause of renal dysfunction. It is important to avoid any further hemodynamic or toxic insults to the kidneys.
- The patient's impaired renal function must be considered when fluid is administered and drugs are prescribed.

Chronic Kidney Disease

- Patients with chronic kidney disease have a limited ability to handle fluid and solute loads and have altered metabolism of many drugs; therefore, as with AKI, fluid administration regimens and drug dosages should be checked carefully.
- The most rapidly lethal complication of chronic kidney disease is hyperkalemia. The possibility of this entity should always be considered, and appropriate diagnostic and therapeutic interventions should be instituted when indicated.
- Patients with renal failure often have varying degrees of volume overload. Volume overload generally is the first diagnostic consideration when dyspnea is the presenting complaint.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Orth SR, Ritz E: The nephrotic syndrome. *N Engl J Med* 1998; 338:1202.
2. Cohen RA, Brown RS: Microscopic hematuria. *N Engl J Med* 2003; 348:2330.
3. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16:31.
4. Singri N, Ahya SN, Levin ML: Acute renal failure. *JAMA* 2003; 289:7473.
5. Kimmel P, Barisoni L, Kopp JB: Pathogenesis and treatment of HIV-associated renal diseases: Lessons from clinical and animal studies, molecular pathologic correlations, and genetic investigations. *Ann Intern Med* 2003; 139:214.
6. Thaller TR, Wang LP: Evaluation of asymptomatic microscopic hematuria in adults. *Am Fam Physician* 1999; 60:1143.
7. Vieweg J, et al: Unenhanced helical computerized tomography for the evaluation of patients with acute flank pain. *J Urol* 2000; 160:1465.
8. Singhal R, Brimble KS: Thromboembolic complications in the nephrotic syndrome: Pathophysiology and clinical management. *Thromb Res* 2006; 118:397.
9. Dagher L, Moore K: The hepatorenal syndrome. *Gut* 2001; 49:729.
10. Ulinski T, Guigonis V, Dunan O, Bensman A: Acute renal failure after treatment with non-steroidal anti-inflammatory drugs. *Eur J Pediatr* 2004; 163:148.
11. Perazella MA, Tray K: Selective cyclooxygenase-2 inhibitors: A pattern of nephrotoxicity similar to traditional nonsteroidal anti-inflammatory drugs. *Am J Med* 2001; 111:64.
12. Whelton A, et al: Effects of celecoxib and naproxen on renal function in the elderly. *Arch Intern Med* 2000; 160:1465.
13. Perazella MA: Drug-induced renal failure: Update on new medications and unique mechanisms of nephrotoxicity. *Am J Med Sci* 2003; 325:349.
14. Baker RJ, Pusey CD: The changing profile of acute tubulointerstitial nephritis. *Nephrol Dial Transplant* 2004; 19:8.
15. Fletcher A: Eosinophiluria and acute interstitial nephritis. *N Engl J Med* 2008; 358:1760.
16. Garg AX, et al: Long-term renal prognosis of diarrhea-associated hemolytic uremic syndrome: A systematic review, meta-analysis, and meta-regression. *JAMA* 2003; 290:1360.
17. Adams BD: Scleroderma renal crisis [letter]. *Ann Emerg Med* 2003; 42:713.
18. Steen VD, Costantino JP, Shapiro AP, Medsger TA Jr: Outcome of renal crisis in systemic sclerosis: Relation to availability of angiotensin converting enzyme (ACE) inhibitors. *Ann Intern Med* 1990; 113:352.
19. Bakir AA, Bazilinski N, Dunea G: Transient and sustained recovery from renal shutdown in accelerated hypertension. *Am J Med* 1986; 80:172.
20. Esson ML, Schrier RW: Diagnosis and treatment of acute tubular necrosis. *Ann Intern Med* 2002; 137:744.
21. Nash K, Hafeez A, Hou S: Hospital-acquired renal insufficiency. *Am J Kidney Dis* 2002; 39:930.
22. Gabow PA, Kaehny WD, Kelleher SP: The spectrum of rhabdomyolysis. *Medicine (Baltimore)* 1982; 61:141.
23. Bosch X, Poch E, Grau JM: Rhabdomyolysis and acute kidney injury. *N Engl J Med* 2009; 361:62.
24. Barza M, Ioannidis JP, Cappelleri JC, Lau J: Single or multiple daily doses of aminoglycosides: A meta-analysis. *BMJ* 1996; 312:338.
25. Hatala R, Dinh T, Cook DJ: Once-daily aminoglycoside dosing in immunocompetent adults: A meta-analysis. *Ann Intern Med* 1996; 124:717.
26. McCullough PA: Contrast-induced acute kidney injury. *J Am Coll Cardiol* 2008; 51:1419.
27. Sinert R, Doty CI: Update: Prevention of contrast-induced nephropathy in the emergency department. *Ann Emerg Med* 2009; 54:e1.
28. Mueller C, et al: Prevention of contrast media-associated nephropathy: Randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med* 2002; 162:329.
29. Kelly AM, Dwamena B, Cronin P, Bernstein SJ, Carlos RC: Meta-analysis: Effectiveness of drugs for preventing contrast-induced nephropathy. *Ann Intern Med* 2008; 148:284.
30. Zoungas S, et al: Systematic review: Sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy. *Ann Intern Med* 2009; 151:631.
31. Brar SJ, et al: Sodium bicarbonate vs. sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography. *JAMA* 2008; 300:1038.
32. Aquilera PA, Choi T, Durham BA: Ultrasound-guided suprapubic cystostomy catheter placement in the emergency department. *J Emerg Med* 2004; 26:319.
33. Lyons K, Matthews P, Evans C: Obstructive uropathy without dilatation: A potential diagnostic pitfall. *Br Med J (Clin Res Ed)* 1988; 296:1517.
34. Aronoff GR, Bennett WM, Berns JS: *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*, 5th ed. Philadelphia: American College of Physicians; 2007.
35. Better OS, Rubinstein I, Winaver JM, Knochel JP: Mannitol therapy revisited (1940-1997). *Kidney Int* 1997; 52:886.
36. Weisberg LS: Management of severe hyperkalemia. *Crit Care Med* 2008; 36:3246.
37. Allon M, Dunlay R, Copkney C: Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. *Ann Intern Med* 1989; 110:426.
38. Montoliu J, Almirall J, Ponz E, Campistol JM, Revert L: Treatment of hyperkalemia in renal failure with salbutamol inhalation. *J Intern Med* 1990; 228:35.
39. Kestenbaum B: Mineral metabolism disorders in chronic kidney disease. *JAMA* 2011; 305:1138.
40. Hedges SJ, Dehoney SB, Hooper JS, Amanzadeh J, Busti AJ: Evidence-based treatment recommendations for uremic bleeding. *Nat Clin Pract Nephrol* 2007; 3:138.
41. Levey AS, et al: National Kidney Foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Ann Intern Med* 2003; 139:137.
42. Luke RG: Chronic renal failure—a vasculopathic state. *N Engl J Med* 1998; 339:841.
43. Shlipak MG, et al: Cardiovascular mortality risk in chronic kidney disease. *JAMA* 2005; 293:1737.
44. Sarnak MJ, et al: Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003; 108:2154.
45. Goodman WG, et al: Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000; 342:1478.
46. Cheung AK, et al: Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. *Kidney Int* 2000; 58:353.
47. Collins AJ, et al: Chronic kidney disease and cardiovascular disease in the Medicare population. *Kidney Int* 2003; 64:524.
48. Kohen JA, Opsahl JA, Kjellstrand CM: Deceptive patterns of uremic pulmonary edema. *Am J Kidney Dis* 1986; 7:456.
49. Agarwal R, et al: Gadolinium-based contrast agents and nephrogenic systemic fibrosis: A systematic review and meta-analysis. *Nephrol Dial Transplant* 2009; 24:856.
50. Hricik DE, et al: Captopril-induced functional renal insufficiency in patients with bilateral renal-artery stenoses or renal-artery stenosis in a solitary kidney. *N Engl J Med* 1983; 308:373.
51. Wolfson AB, Singer I: Hemodialysis-related emergencies: Part I. *J Emerg Med* 1987; 5:533.
52. Szerlip HM, Weiss J, Singer I: Profound hyperkalemia without electrocardiographic manifestations. *Am J Kidney Dis* 1986; 7:461.
53. Gehm L, Propp DA: Pulmonary edema in the renal failure patient. *Am J Emerg Med* 1989; 7:336.
54. Venkat A, Kaufmann KR, Venkat K: Care of the end-stage renal disease patient on dialysis in the ED. *Am J Emerg Med* 2006; 24:847.
55. Huff JS, Whelan TV: CPAP as adjunctive treatment of severe pulmonary edema in patients with ESRD. *Am J Emerg Med* 1994; 12:388.
56. Sacchetti A, McCabe J, Torres M, Harris RL: ED management of acute congestive heart failure in renal dialysis patients. *Am J Emerg Med* 1993; 11:644.
57. Pastan S, Bailey J: Dialysis therapy. *N Engl J Med* 1998; 338:1428.
58. Ifudu O: Care of patients undergoing hemodialysis. *N Engl J Med* 1998; 339:1054.
59. Chaudhry A, Stone WJ, Breyer JA: Occurrence of pyuria and bacteriuria in asymptomatic hemodialysis patients. *Am J Kidney Dis* 1993; 21:180.
60. Gabow PA, Bennett WM: Renal manifestations: Complication management and long-term outcome of autosomal dominant polycystic kidney disease. *Semin Nephrol* 1991; 11:643.
61. Blicker J, Herd AM, Talbot J: Diabetic ketoacidosis in the dialysis-dependent patient: Two case reports and recommendations for treatment. *Can J Emerg Med* 2004; 6:281.
62. Lundin AP: Recurrent uremic pericarditis: A marker of inadequate dialysis. *Semin Dial* 1990; 3:5.
63. Frommer JP, Young JB, Ayus JC: Asymptomatic pericardial effusion in uremic patients: Effect of long-term dialysis. *Nephron* 1985; 39:296.
64. Nassar GM, Ayus JC: Infectious complications of the hemodialysis access. *Kidney Int* 2001; 60:1.
65. Allon M: Dialysis catheter-related bacteremia: Treatment and prophylaxis. *Am J Kidney Dis* 2004; 44:779.

www.ketabpezeshki.com 66485457-66963820

66. Mermel LA, et al: Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 49:1.
67. Eberst ME, Berkowitz LR: Hemostasis in renal disease: Pathophysiology and management. *Am J Med* 1994; 96:168.
68. Bleyer AJ, Russell GB, Satko SG: Sudden and cardiac death rates in hemodialysis patients. *Kidney Int* 1999; 55:1553.
69. Herzog CA: Acute myocardial infarction in patients with end-stage renal disease. *Kidney Int* 1999; 56:S130.
70. Watnick S, Perazella MA: Cardiac troponins: Utility in renal insufficiency and end-stage renal disease. *Semin Dial* 2002; 15:66.
71. McCullough PA, et al: Performance of multiple cardiac biomarkers measured in the emergency department in patients with chronic kidney disease and chest pain. *Acad Emerg Med* 2002; 9:1389.
72. Donnino MW, et al: Prevalence of elevated troponin I in end-stage renal disease patients receiving hemodialysis. *Acad Emerg Med* 2004; 11:979.
73. Li PK, et al: Peritoneal dialysis-related infections recommendations: 2010 update. *Perit Dial Int* 2010; 30:393.
74. Kiefer T, Schenk U, Weber J, Hübel E, Kuhlmann U: Incidence and significance of pneumoperitoneum in continuous ambulatory peritoneal dialysis. *Am J Kidney Dis* 1993; 22:30.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 98

SEXUALLY TRANSMITTED DISEASES

Diane M. Birnbaumer

PERSPECTIVE

More than 300 million new cases of sexually transmitted diseases (STDs) are diagnosed worldwide each year. In the United States, nearly 20 million new cases of STDs are diagnosed annually, and patients with these infections frequently come to the emergency department (ED) for care.[1] Because EDs often are used as a source of primary health care, their role in screening and treating STDs has been debated. One major area of difficulty in use of EDs for this purpose is that many test results are not available during the ED visit. Treatment decisions are therefore made presumptively, inevitably leading to both overtreatment and undertreatment for STDs. As evidence supporting this concern, one third of patients who test positive for STDs in the ED are not treated during the initial visit, and a majority of untreated patients do not return for subsequent treatment.[1] As a result, emergency providers should weigh the cost of overtreatment against the risk of untreated disease. Because these diseases pose a significant public health risk, it is recommended that patients be treated presumptively in the ED unless good follow-up for test results can be ensured. In addition, to help contain these diseases, many states allow expedited partner therapy (EPT) or patient-delivered partner therapy (PDPT), allowing physicians to prescribe treatment not only for the patients being treated but also for their sexual partners. (Information on EPT and PDPT and the states that allow it is available on the Centers for Disease Control and Prevention [CDC] website [www.cdc.gov]).

Although patients with STDs usually have presenting complaints involving the genitalia, they may also have abdominal, dermatologic, musculoskeletal, neurologic, or systemic symptoms. Prompt and accurate diagnosis prevents both the complications and spread of these diseases.

As with most other illnesses, the history and physical examination provide much of the clinical information needed to diagnose STDs. Patients should be questioned about current and previous symptoms and their duration, as well as any previous history of STDs, recent sexual contacts, use of contraceptives (particularly barrier devices such as condoms), and types of sexual practices; women should additionally be questioned about their menstrual history. Physical examination focuses on the symptomatic area, often the genitalia. Evidence of skin lesions and their type as well as presence of discharge should be noted. Examination of the skin and lymph nodes may be an important component of the examination, particularly in the case of syphilis, gonorrhea, or chancroid. Evidence of septic arthritis on examination of symptomatic joints may indicate gonococcal arthritis and disseminated gonococcal infection (DGI).

The STDs can be divided into two broad categories: those that manifest with genital lesions, with or without adenopathy, and those that are nonulcerative, which most frequently cause genital discharge (Table 98-1).

DISORDERS CHARACTERIZED BY GENITAL LESIONS WITH OR WITHOUT ADENOPATHY

STDs are a well-recognized cause of genital lesions. It is important to note, however, that patients with a "sore" on or near the genitalia or anus may be using this term to refer to genital warts, scabies, premalignant lesions, or other conditions. If an STD is the cause, certain components of the history and physical examination can provide crucial information to help narrow the diagnosis to a specific infection (Table 98-2). The history and physical examination should focus on the characteristics of the lesion or lesions, the presence or absence of adenopathy, and the presence or absence of systemic symptoms. With regard to the lesions, it is important to determine whether they are single or multiple, painful or painless, indurated or soft; whether they have irregular or regular borders; and how they began (e.g., as a vesicle or papule). If the patient has lymphadenopathy, examination will determine if they are unilateral or bilateral and whether the nodes are painful or fluctuant.

In the evaluation of a patient with genital ulcerative lesions, herpes simplex virus (HSV) testing and syphilis serologic studies should be performed; if feasible, a darkfield examination of the lesion scrapings also is useful. In addition, patients should either be tested for or referred for human immunodeficiency virus (HIV) testing, because ulcerative genital lesions increase the risk of acquiring HIV infection.

Comprehensive test results often are not available during the patient's ED visit; therefore treatment is considered for the most likely diagnoses based on history and physical examination findings. The most common ulcerative diseases in the United States are herpes and syphilis; herpes occurs vastly more frequently than does syphilis. In rare outbreaks, chancroid may be the cause of the ulceration.

HERPES

In the United States, genital herpes is the most common cause of ulcerative STDs, with 50 million people infected with the virus and 200,000 to 300,000 new symptomatic cases annually.[2] One in five sexually active adults is infected with the virus, many of whom are asymptomatic. Most commonly caused by HSV type 2, genital herpes also can be caused by HSV-1. In pregnant patients, herpes can cause a devastating congenital infection, although the incidence of such infections has decreased. In addition, HSV infection

www.ketabpezeshki.com 66485457-66963820

plays a major role in the transmission of HIV as herpetic lesions increase the risk of both acquisition and transmission of HIV.

Clinically, genital herpes manifests as either primary herpes infection or recurrence. In primary infections the degree of illness depends on whether the patient has preexisting circulating antibodies to either HSV-1 or HSV-2; in cases of initial genital infection, those with antibodies tend to have a milder syndrome than those without. In cases of primary infection in patients without antibodies, symptoms develop after a 2- to 7-day incubation period. The syndrome begins with genital lesions that may start as vesicles and rapidly become painful, shallow, multiple, and grouped ulcers (Fig. 98-1). In women, these lesions may coalesce into large ulcerations on the perineum (Fig. 98-2). Systemic symptoms may include low-grade fever, myalgias, headache, and fatigue. Adenopathy typically develops during the second or third week of the illness and is bilateral, mildly tender, and nonfluctuant. The local symptoms peak at approximately 8 to 10 days, and it takes 2 to 4 weeks for the lesions to completely heal. Viral shedding can last as long as 3 weeks. In some cases, sacral radiculopathy may develop, with urinary retention, constipation, and sensory changes in the perineal region. Aseptic meningitis and transverse myelitis are relatively uncommon complications. In contradistinction to patients without antibodies, patients acquiring an initial herpes genital infection who have circulating antibodies to the herpesvirus have a milder course, often developing only the genital lesions.

As the symptoms of primary infection recede, the virus settles in the spinal cord ganglia and becomes latent, residing there for the lifetime of the patient. Symptomatic recurrences are the rule, occurring in 60 to 90% of patients. In contrast to the prolonged syndrome and systemic symptoms of primary infection, recurrences are much shorter in duration and tend to cause only mild local symptoms. Many patients will be warned of an impending recurrence by a prodrome, usually characterized by paresthesias, burning, or itching at the site of the subsequent lesions. Although it is known that viral shedding can occur during a recurrence, data suggest that in patients infected with HSV-2, shedding occurs during asymptomatic periods as well.[3]

Population screening with serologic tests for HSV-2 suggests that many people become infected with the virus without symptoms or knowledge of having acquired the infection. Patients with only serologic evidence of past infection may be a potential reservoir for transmission of the virus.

Figure 98-1. Genital herpes lesions on the penile shaft.

Table 98-1 Differential Diagnosis for Sexually Transmitted Diseases

ULCERATIVE	NONULCERATIVE
Herpes genitalis	Gonorrhea
Syphilis (primary)	Chlamydial infection
Chancroid	Nongonococcal urethritis
Lymphogranuloma venereum	Secondary or tertiary syphilis
Granuloma inguinale (donovanosis)	Candidal vaginitis
Molluscum contagiosum	Trichomoniasis
Condylomata acuminata (genital warts)	Bacterial vaginosis
Pediculosis	Endometriosis
Scabies	
Pyoderma	
Trauma	
Excoriations	
Behçet's disease	
Fixed drug eruption	
Yeast infection	

Table 98-2 Characteristics of Ulcerative Sexually Transmitted Diseases

DISEASE	NATURE OF GENITAL ULCER	INCUBATION PERIOD	PAINFUL	INGUINAL ADENOPATHY	DIAGNOSTIC TESTS
Syphilis	Indurated, sharply demarcated, with red, smooth base; heals spontaneously	9-90 days; average 2-3 weeks	No	Firm rubbery nodes; nontender	Darkfield examination; serology
Herpes simplex	Multiple small grouped vesicles on a red base, which form shallow ulcers; may coalesce; resolve spontaneously but recurrence is common	2-7 days	Yes	Bilateral, firm, tender	Culture, serology
Chancroid	Irregular, sharply demarcated borders with undermined edges, shallow, often multiple	3-6 days	Yes	Unilateral most common; overlying erythema, fixed and tender; suppuration may occur	Culture
Lymphogranuloma venereum	Usually single lesion, papule or ulcer, transient, frequently not noticed	5-21 days	No	Unilateral most common; firm, tender, matted, fixed; may suppurate or form fistulae	Lymphogranuloma venereum complement fixation (serology)

www.ketabpezeshki.com 66485457-66963820

Figure 98-2. Coalescent primary herpes lesions on the vulva.

Diagnosis

Although the diagnosis of genital herpes usually is made clinically, this diagnostic strategy is both insensitive and nonspecific. Confirmatory testing should be strongly considered, particularly in women of childbearing age. Several methods are available, including viral culture and antigen testing of the lesions, as well as type-specific viral serologic testing of the blood; a positive result on any of these tests is considered definitive. The Tzanck test, used in the past for diagnosis of herpes infection, is no longer recommended because of its lack of sensitivity.

Although viral culture of a lesion has traditionally been the "gold standard" diagnostic modality, this test has a low sensitivity, takes 3 to 10 days to complete, and has false-negative results ranging from 5 to 20%. Polymerase chain reaction (PCR) testing for HSV DNA is more sensitive and is now the preferred method for making the diagnosis.[3] Recently available serologic testing is type-specific, but patients with newly acquired viral infection may take up to 6 weeks to show positive antibodies.[3] This test is most useful in patients with symptoms consistent with herpes but with negative results on culture or antigen testing. In the patient with a new presentation, PCR testing for HSV DNA is the recommended diagnostic test.

Treatment

Although genital herpes is incurable and outbreaks are self-limited, treatment decreases the duration of symptoms in patients with primary infection, can shorten or abort recurrences, and decreases the amount and duration of viral shedding and therefore potential infectivity. In patients with frequent recurrences, suppressive therapy can decrease the number of these episodes by up to 80%.[4] The mainstay of treatment is therapy with one of the antiviral drugs acyclovir, valacyclovir, and famciclovir[5] (Table 98-3). None of these agents can eliminate the virus, but their use can control symptoms, at least while the drug is being taken. Acyclovir has been shown to be safe for up to 6 years' continuous use as a suppressive agent; the other antivirals have been proven safe for 1 year.[6]

Patient education is critical in cases of genital herpes. The importance of testing the patient's sexual partner or partners should be emphasized, and the patient should be told that he or she can potentially transmit the virus and infect a sexual partner even during asymptomatic periods. If the patient is a woman of childbearing age, she should be instructed to inform her physician of her history of genital herpes if she becomes pregnant.

Neonatal herpes is a devastating and potentially fatal infection seen most often in newborns born to women who acquired the infection near delivery, but it can also be transmitted by women with recurrences and even those who lack a history of clinically evident genital herpes. Cesarean section is the preferred method of delivery if the patient has active lesions at the time of onset of labor. Because the antiviral agents used to treat genital herpes have not been proved safe during pregnancy, the decision to use these agents should be made in conjunction with both the patient and her physician.

BARTHOLIN CYST AND ABSCESS

The Bartholin glands are located inferiorly on either side of the vaginal opening and normally secrete fluid through their openings on the sides of the vestibule. The ducts and glands are palpable or visible only when obstructed, infected, or inflamed. When the duct of the gland becomes obstructed, a simple cyst develops, which usually is painless. Patients with a Bartholin gland cyst typically report a lump at the lateral introitus, and on examination an ovoid mass can be palpated on the mucosal surface of the lateral posterior introitus, just above the posterior fourchette. Treatment usually consists of incision and drainage with local anesthesia with Word catheter placement and sitz baths. Simple packing can be used, but the cavity may need repacking multiple times as the area heals.

A Bartholin abscess develops when a Bartholin cyst becomes secondarily infected. A majority of abscesses involve the anaerobic and aerobic bacteria normally found in the vagina. However, infection may also be caused by sexually transmitted organisms such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Other implicated bacteria include *Bacteroides* species, *Escherichia coli*, and other gram-negative organisms. Patients with a Bartholin abscess have swelling and pain at the lower lateral vaginal opening and may report a lump or mass near the affected labium. On examination, patients may have a swollen and painful labium, and a tender, fluctuant mass can be palpated on the posterolateral margin of the vaginal vestibule. Cellulitis may be present with surrounding edema and erythema.

Treatment consists of incision and drainage, with insertion of a Word catheter. The distal end of this small catheter includes an inflatable balloon. This distal portion is placed into the incision, and the balloon is then inflated with 2 to 4 mL of water or saline. Because the catheter needs to be left in place for 6 to 8 weeks to allow epithelialization along the tract, it is preferable to make the incision on the mucosal surface of the vestibule. This location allows for the protruding portion of the catheter to be tucked into the vaginal opening for patient comfort. Although iodoform gauze can be used as a packing material, the multiple changes necessary to keep the area open during the several weeks of healing make this alternative less desirable. Although incision and drainage are adequate for most patients, management of recurrent infections may require surgical marsupialization, creating a permanent fistula that prevents recurrent abscess formation.

Patients are instructed to start sitz baths within 24 hours of ED discharge to promote drainage. Patients should be referred for follow-up for reexamination of the wound within 48 hours. Because some Bartholin abscesses are caused by multiple organisms, abscess drainage should be cultured and routine testing for STDs performed. Antibiotics usually are not necessary unless

www.ketabpezeshki.com 66485457-66963820

Table 98-3 Treatment Guidelines for Sexually Transmitted Diseases

DISEASE	RECOMMENDED TREATMENT REGIMEN	ALTERNATIVE(S)
Chlamydial infection	Azithromycin 1 g PO × 1 *or* Doxycycline 100 mg PO bid × 7 days	Erythromycin base 500 mg PO qid × 7 days *or* Erythromycin ethylsuccinate 800 mg PO qid × 7 days *or* Ofloxacin 300 mg PO bid × 7 days *or* Levofloxacin 500 mg PO qd × 7 days
Gonorrhea,* uncomplicated urethral, cervical, or rectal infection	Ceftriaxone 250 mg IM × 1 *plus* Azithromycin 1 g PO once	May substitute azithromycin with doxycycline 100 mg PO daily for 7 days
Gonorrhea,* pharyngeal	Ceftriaxone 250 mg IM × 1 *plus* Azithromycin 1 g PO once	May substitute azithromycin with doxycycline 100 mg PO daily for 7 days
Gonorrhea,* adult conjunctivitis	Ceftriaxone 1 g IM × 1 Normal saline irrigation *Consider hospitalization*	
Gonorrhea,* disseminated infection	Ceftriaxone 1 g IM or IV every 24 hours *Strongly consider hospitalization*	Cefotaxime 1 g IV q8h *or* Ceftizoxime 1 g IV q8h
Syphilis; primary, secondary or early latent	Benzathine penicillin G 2.4 million units IM single dose	
Syphilis, late latent	Benzathine penicillin G 2.4 million units IM in three doses, 1 week apart	
Herpes simplex, first episode	Acyclovir 400 mg PO tid × 7-10 days *or* Acyclovir 200 mg PO 5×/day × 7-10 days *or* Famciclovir 250 mg PO tid × 7-10 days *or* Valacyclovir 1 g PO bid × 7-10 days	
Herpes simplex, recurrent	Acyclovir 400 mg PO tid × 5 days *or* Acyclovir 800 mg PO bid × 5 days *or* Acyclovir 800 mg PO tid × 2 days *or* Famciclovir 125 mg PO bid × 5 days *or* Famciclovir 1000 mg PO bid × 1 day *or* Famciclovir 500 mg PO once, then 250 mg PO bid for 2 days *or* Valacyclovir 500 mg PO bid for 3 days *or* Valacyclovir 1 g PO qd × 5 days *or* Valacyclovir 500 mg PO bid × 3 days	
Herpes simplex, suppressive	Acyclovir 400 mg PO bid *or* Famciclovir 250 mg PO bid *or* Valacyclovir 500 mg PO qd *or* Valacyclovir 1 g PO qd	
Chancroid	Azithromycin 1 g PO once *or* Ceftriaxone 250 mg IM once *or* Ciprofloxacin 500 mg PO bid × 3 days *or* Erythromycin base 500 mg PO tid × 7 days	
Lymphogranuloma venereum	Doxycycline 100 mg PO bid × 21 days	Erythromycin base 500 mg PO qid × 21 days

IM, intramuscularly; *IV,* intravenously; *PO,* orally.
* Because of resistance, quinolones are no longer recommended for the treatment of gonorrhea. Also, recent increases in cephalosporin resistance led to the removal of the previously recommended cefixime as treatment for uncomplicated gonorrhea.

significant surrounding cellulitis is present. If deemed necessary, patients should be treated with appropriate antibiotic therapy to cover coliforms as well as sexually transmitted infections, including *Chlamydia* and *N. gonorrhoeae.*

SYPHILIS

Syphilis, known as the "Great Imitator," is caused by the spirochete *Treponema pallidum* and earns its nickname from its ability to infect virtually any organ of the body and cause multiple symptoms.

The organism is fragile and does not survive on dry surfaces. Transmission occurs during exposure of moist skin to an infected area. Although transmission usually involves the genitalia, inoculation can occur virtually anywhere on the body. The incidence of primary and secondary syphilis in the United States hovers between 7000 and 10,000 cases per year.[7]

If untreated, syphilis typically progresses through several stages, as follows.

1. *Primary.* The primary lesion, called a *chancre,* occurs after an incubation period that varies from 9 to 90 days, averaging 2 to 4 weeks. This lesion occurs at the site of inoculation and begins as a papule that then ulcerates. Typically the chancre is solitary and painless and has a smooth, slightly raised edge, with sharply defined borders and a clean base (Fig. 98-3); occasionally patients have more than one lesion (Fig. 98-4). Without treatment the chancre lasts for 2 to 6 weeks and resolves spontaneously, and the disease then progresses to the secondary stage. Adenopathy is not a predominant feature of primary

www.ketabpezeshki.com 66485457-66963820

Figure 98-3. Chancre of primary syphilis on the penis.

Figure 98-4. Two lesions of primary syphilis on the penile shaft.

syphilis. If the chancre is on the genitalia, bilateral, painless, nonfluctuant, and slightly enlarged inguinal adenopathy may develop several days after appearance of the primary chancre.

2. *Secondary.* Manifestations of the secondary stage of syphilis begin 5 to 8 weeks after resolution of signs and symptoms of the primary stage. The most common manifestation is a total body rash (Fig. 98-5). This rash

Figure 98-5. The rash of secondary syphilis.

Figure 98-6. Palmar rash caused by secondary syphilis.

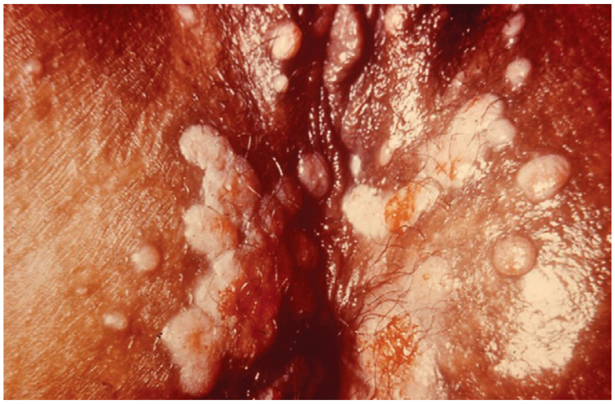


Figure 98-7. Condylomata lata of secondary syphilis.

begins on the trunk as a fine macular rash, which then spreads outward to the arms and legs and may involve the palms and soles (Fig. 98-6). As it progresses, it becomes papulosquamous and may appear slightly annular, often resembling the rash of pityriasis rosea. Mucous patches can be seen on the tongue, which are the oral manifestations of the skin rash. Condylomata lata (Fig. 98-7) can also develop; these lesions are broad-based papules with flat moist tops, occurring in the perineal region, and may involve the anus, the skin between the buttocks, and the labia. Constitutional signs and symptoms are common during this stage, including fatigue, low-grade fever, malaise, headache, arthralgias,

www.ketabpezeshki.com 66485457-66963820

and generalized lymphadenopathy. Adenopathy may occur virtually anywhere in the body, including epitrochlear node involvement. The nodes are discrete, nontender, and rubbery. As with the primary stage, the manifestations of secondary syphilis will resolve spontaneously if the condition goes untreated, and the infection then enters the latent or tertiary stage.

3. *Latent.* After resolution of the clinical manifestations of secondary syphilis, patients enter the latent phase, which is defined as seroreactivity for syphilis without evidence of disease. As there are no clinical signs and symptoms during this stage, laboratory testing is the only means to identify infected persons. Latent syphilis is divided into two categories: *early latent* syphilis, acquired within the preceding year, and *late latent* syphilis, the designation for all other cases of latent syphilis or for latent syphilis of unknown duration.
4. *Tertiary.* In the immunocompetent individual, signs and symptoms of tertiary syphilis may appear after a latent period of at least 3 to 4 years. This stage predominantly involves the cardiovascular and nervous systems. Presenting conditions may include a thoracic aortic aneurysm, meningitis, peripheral neuropathy (tabes dorsalis), or gummatous lesions of the mucous membranes. Although common in the preantibiotic era, tertiary syphilis is now uncommon in the United States.

Diagnosis

The only rapid means of diagnosing syphilis is the darkfield examination. This method involves viewing scrapings or fluid from primary or secondary syphilis lesions under a darkfield microscope to identify the spirochete. Unfortunately, the sensitivity of darkfield microscopy is approximately 80%, and many hospitals and clinics do not have this technique routinely available.[5]

Serologic testing is the current standard for diagnosing secondary, latent, and tertiary syphilis. In primary syphilis, one-time testing is less reliable, and follow-up testing may be necessary to confirm the diagnosis. There are two types of serologic tests: *nontreponemal*—the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests—and *treponemal*—microhemagglutination assay for *T. pallidum* (MHA-TP) and fluorescent treponemal antibody absorption (FTA-ABS) test. Both types of tests are necessary for definitive diagnosis, although the nontreponemal test is used for screening, with treponemal testing used for confirmation. Nontreponemal tests measure nonspecific antibodies in serum from patients with syphilis, and the titers tend to vary with the stage and activity of disease. These tests involve quantitative measurement of antibody and become positive approximately 2 weeks after the primary chancre appears. Titers are used to follow response to treatment. Because these tests are nonspecific for the treponeme and false-positive results can occur, positive test results should be confirmed with the more specific treponemal tests. Treponemal tests measure antibodies specific to the spirochete *T. pallidum.* These tests are more expensive and difficult to perform than the nonspecific tests, and because their titers do not predictably vary with treatment, the main value of these tests is in confirming positive findings on nontreponemal tests.[5]

Treatment

A one-time dose of the long-acting formulation of penicillin G benzathine, 2.4 million units intramuscularly (IM), is the regimen of choice for treating primary and secondary syphilis[5] (see Table 98-3 for treatment of latent and tertiary syphilis). It is crucial that the long-acting form of penicillin G benzathine be used; the half-life of an alternative preparation comprising both penicillin G benzathine and penicillin G procaine (i.e., Bicillin C-R) is too short, which has resulted in treatment failures.[5] Sexual partners need to be evaluated; partners within the last 90 days should be tested but treated presumptively, and partners from more than 90 days before diagnosis should be evaluated and treated if indicated. Because syphilis increases the risk of acquisition of HIV, all patients should be referred for HIV testing. For response to treatment to be ensured, patients should be reexamined clinically and serologically 6 and 12 months after treatment. Successful treatment is confirmed by either a nonreactive nontreponemal test or a fourfold or greater decrease in titers after 6 months. Because syphilis is a reportable disease, patients with positive test results should be reported to the public health department.

Because congenital syphilis can be devastating, pregnant patients with syphilis pose a unique and significant concern. Parenteral penicillin G is the only agent with documented efficacy in these instances. Therefore in pregnant women with a reported penicillin allergy who have syphilis at any stage, treatment with penicillin is still recommended after desensitization.[5]

LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum (LGV) is a chronic STD caused by specific serotypes of *C. trachomatis.* Although this disease is prevalent in many tropical countries, it is rare in the United States and is seen either in patients who have traveled to endemic areas or in localized outbreaks in patient populations such as men who have sex with men. The incubation period ranges from 3 days to 3 weeks. In cases of genital exposure, the initial infection manifests as a transient genital lesion that is small and painless and often goes unnoticed by the patient. Patients typically are seen in the secondary stage with lymphadenitis, characterized by involvement of the lymphatic channels and nodes of the genitalia, pelvis, and rectum. This lymphadenitis begins at 7 to 30 days after the primary lesion disappears. Inguinal lymphadenopathy most often is unilateral, and enlargement of the glands above and below Poupart's ligament gives the characteristic LGV "groove sign." The enlarged nodes often are painful, with overlying erythema, but usually are not fluctuant or at most are minimally so. The nodes either eventually break down, with the formation of multiple draining sinuses, or form a hard inguinal mass without suppuration. The late complication of distal lymphedema results from the blockage of lymphatic channels.

Patients with rectal exposure may have proctocolitis, manifesting with mucoid and/or hemorrhagic rectal discharge with anal pain, fever, constipation, and/or tenesmus. Untreated, these patients may develop colorectal fistulae and strictures.

Diagnosis

Although serologic testing is available, the diagnosis of LGV is usually based on the clinical picture, epidemiologic information, and the exclusion of other causes of inguinal lymphadenopathy and genital ulcers.

Treatment

Treatment is curative and is crucial to prevent permanent tissue damage. The preferred treatment is with doxycycline, 100 mg orally (PO) twice daily for 21 days; erythromycin base 500 mg PO four times daily for 21 days is an alternative regimen.[5] Patients should refer their sexual partners from within the previous 60 days for evaluation and treatment, and all patients should be referred for HIV testing.

www.ketabpezeshki.com 66485457-66963820

Figure 98-8. Ulcerative lesions of the penis from chancroid with accompanying fluctuant, tender, erythematous lymphadenitis (bubo).

CHANCROID

Chancroid is caused by *Haemophilus ducreyi,* a small gram-negative bacterium. This disease is common in developing countries but rare in the United States, with usually less than 100 cases reported annually to the CDC. Despite being relatively rare, outbreaks of chancroid have been reported in the United States, and physicians should be aware of the characteristics of this disease to permit recognition of these occasional outbreaks when they occur.

Clinically, chancroid is characterized by multiple painful genital ulcerations and inguinal bubo formation (Fig. 98-8). After an incubation period of less than 1 week, a short-lived, small, tender red papule appears at the site of inoculation. This lesion rapidly ulcerates, followed by the formation of multiple shallow, painful ulcers with sharply demarcated edges and purulent bases. These lesions last 1 to 2 weeks, and in some patients they may coalesce. Inguinal lymph node involvement is seen in 50% of patients, manifesting 1 week after the ulcers appear. Typically, a unilateral large, painful, fluctuant lymph node (bubo) develops in the groin. Overlying skin is thinned and erythematous, and suppuration is common. These buboes can spontaneously rupture.

On a clinical basis, it may be difficult to distinguish chancroid from genital herpes. The presence of a large, fluctuant bubo strongly suggests chancroid. However, if only ulcers are present, the patient can have either disease. Because herpes is several orders of magnitude more common in the United States than chancroid (which tends to occur in isolated outbreaks), herpes is the first diagnosis to be considered.

Diagnosis

H. ducreyi is difficult to culture, so the diagnosis is based on clinical presentation and often is one of exclusion, after other diseases such as herpes and syphilis have been ruled out by testing. Definitive diagnosis requires isolation and identification of *H. ducreyi,* a fastidious organism requiring a special growth medium that is not routinely available. Because definitive diagnosis can be elusive, a "probable diagnosis" can be made if all of the following criteria are met: (1) The patient has one or more painful genital ulcers; (2) the patient has no evidence of *T. pallidum* infection on dark-field examination or serologic testing at least 7 days after onset of the ulcers; (3) the clinical presentation, appearance of genital ulcers, and, if present, regional lymphadenopathy are typical for chancroid; and (4) results of HSV testing performed on the ulcer exudates are negative.[8] When local outbreaks are known, the microbiology laboratory can prepare the special medium required for growth of the organism to confirm specific cases, as well as to follow containment of the infection.

Any of the following four curative treatment regimens may be used: a single dose of azithromycin 1 g PO, a single dose of ceftriaxone 250 mg IM, ciprofloxacin 500 mg PO twice daily for 3 days, and erythromycin base 500 mg PO three times daily for 7 days (see Table 98-3).[5] Coinfection with syphilis or HSV occurs in approximately 10% of patients who have chancroid acquired in the United States, so patients should be evaluated for these infections. Because chancroid is associated with increased risk of HIV transmission, all patients should be referred for HIV and other STD testing. Sexual partners of patients with chancroid should be examined and treated if sexual contact with the patient occurred during the 10 days preceding the patient's onset of symptoms, even if the partners are asymptomatic. To confirm response to treatment, patients should be referred for reexamination 3 to 7 days after initiation of therapy.

Drainage of buboes is not routinely recommended because appropriate antibiotic treatment typically results in a good clinical response. If deemed necessary, needle aspiration of nodes in the superior cephalic aspect of the fluctuant area can be performed; reaspiration usually is usually not necessary because the adenopathy responds quickly to antimicrobial treatment. On rare occasions, incision and drainage may be necessary.

GRANULOMA INGUINALE

Granuloma inguinale (donovanosis) is caused by *Klebsiella granulomatis* (formerly known as *Calymmatobacterium granulomatis*), an intracellular gram-negative rod. The disease is rare in developed countries but is endemic in tropical and semitropical regions, including India, Papua New Guinea, central Australia, the Caribbean, and southern Africa. The disease is presumed to be sexually transmitted, with an incubation period of 8 to 80 days.

Clinically, the disease manifests as chronic, painless, progressive ulcerative lesions on the genitalia or perineum. The lesions are irregular, clean-based granulomatous ulcers that are highly vascular (giving the classic "beefy red appearance") and bleed easily on contact. The ulcer feels hard when palpated. Regional lymphadenopathy does not occur. As the lesion enlarges, it can be quite mutilating to the genitalia, causing urethral stenosis over a period of months to years. Without adequate treatment, it may result in lymphatic obstruction, producing genital edema and eventually lower extremity elephantiasis. In men the sites of predilection are the prepuce, the coronal sulcus, and the frenulum. In women, lesions typically are found on the labia, but vaginal and cervical lesions also can occur.

Diagnosis is difficult and requires identification of the infectious agent, which appears as short, pleomorphic rods with bipolar staining. Donovan bodies may be seen within histiocytes on microscopy of tissue crush preparation or biopsy specimen. The causative organism is very difficult to culture, so visualization of the organism with appropriate staining is the primary means of diagnosing the disease.

Treatment halts progression of the lesions, but relapse can occur 6 to 18 months after apparently successful treatment. The CDC-recommended regimen is doxycycline 100 mg PO twice daily for at least 3 weeks or until the lesions have healed. Alternative regimens include azithromycin 1 g PO once a week, ciprofloxacin 750 mg PO twice a day, erythromycin base 500 mg PO four times daily, and trimethoprim-sulfamethoxazole, one double-strength (160 mg/800 mg) tablet PO twice daily; each regimen should be continued for 3 weeks or until the lesions have healed.

Clinical follow-up visits are recommended until signs and symptoms have resolved. Persons who have had sexual contact with the patient within 60 days of symptom onset should be examined and offered therapy. Patients should be screened for other STDs.

www.ketabpezeshki.com 66485457-66963820

Figure 98-9. Genital warts from human papillomavirus infection.

CONDYLOMATA ACUMINATA

Anogenital warts are caused by the human papillomavirus (HPV), and more than 40 types of HPV can infect the genital tract. HPV infections most often are sexually transmitted, and lesions are most common at the site of greatest trauma during sexual intercourse. Most cases of HPV infection are asymptomatic or subclinical, with only approximately 1% resulting in clinically apparent warts. Most visible genital warts are caused by HPV types 6 and 11 and are benign. Other HPV types (i.e., 16 and 18) have been associated with external genital squamous intraepithelial neoplasia in both men and women and are considered to be the cause of most cases of cervical cancer.

In clinically apparent cases, warts may be single or multiple (Fig. 98-9). Warts on warm, moist, nonhairy skin tend to be soft and nonkeratinized, whereas those on dry, hairy skin are more firm and keratinized. The lesions can be broad based, pedunculated, or pigmented. Depending on the size and location, warts can be asymptomatic or painful, friable, or pruritic. Warts that are indurated, fixed, ulcerated, and darkly pigmented may require biopsy to rule out carcinoma.

Diagnosis usually is made clinically by visual inspection. In women, a speculum examination is indicated to evaluate the patient for intravaginal and cervical lesions. Occasionally, HPV infections may be confused with the condylomata lata of syphilis. If there is any doubt about the diagnosis, or if warts have high-risk characteristics, biopsy and darkfield microscopy of tissue are indicated, along with serologic testing for syphilis.

Treatment is aimed at removal of symptomatic warts. Although wart-free periods may be achieved, treatment has not been shown to affect the course of disease or to reduce infectivity. If left untreated, visible genital warts may resolve spontaneously, remain unchanged, or increase in number.

Many treatment options are available, although no specific treatment has been proved to be superior to another; all have significant failure and recurrence rates. For patient-applied regimens, the patient should be able to identify and reach the warts to be treated with these methods. Provider-administered regimens often require ongoing treatments on a weekly basis and usually are best administered by a primary care physician, who can monitor the patient's response to therapy. In general, warts located on moist surfaces respond better to topical treatments than do the keratinized warts found on drier surfaces. Patients should be instructed to watch for recurrences, which are most common in the first 3 months after treatment.

Patient preference, available resources, and physician experience should guide treatment. Most of these treatments are administered by the patient's primary care physician and not through the ED. Regimens can be divided into patient-applied and provider-administered treatments.

Patient-applied regimens include the following:

- Podofilox 0.5% solution or gel, applied twice a day for 3 days, followed by 4 days of no therapy—which may be repeated, as necessary, for up to four cycles.
- Imiquimod 5% cream, applied once daily at bedtime, three times a week for up to 16 weeks. The treatment area should be washed with soap and water 6 to 10 hours after application.
- Sinecatechins 15% ointment, applied three times daily with a finger to ensure complete wart coverage with a thin layer of ointment; the ointment is not washed off. Treatment is continued until complete clearance of warts has been achieved, but no longer than 16 weeks.

Provider-administered regimens include the following:

- Cryotherapy with liquid nitrogen or cryoprobe, which may need to be repeated every 1 to 2 weeks
- Podophyllin resin, 10 to 25% in a compound tincture of benzoin
- Trichloroacetic acid (TCA) or bichloroacetic acid (BCA), 80 to 90%
- Surgical removal

Podophyllin and podophyllum resin should be avoided in pregnant patients because of possible teratogenic effects. Imiquimod also is not approved for use during pregnancy. Immunosuppressed patients are more likely to demonstrate a poor response to treatment, increased relapse rates, and dysplasia and need close follow-up. All patients need screening for other sexually transmitted infections. Treatment of partners is not necessary.

In 2006 the U.S. Food and Drug Administration (FDA) licensed the HPV vaccine, which covers the four virus types that are responsible for 70% of cases of cervical cancer and 90% of anogenital warts. The vaccine is virtually 100% effective if administered before first sexual contact. Currently the vaccine is recommended for males aged 9 to 26 years to prevent genital warts and for females aged 11 and 12 years and those aged 13 to 26 years who were not fully vaccinated when they were younger.

MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is a condition characterized by multiple rounded, domed, waxy papules ranging from 2 to 5 mm in size that are often umbilicated. They are caused by a benign virus inoculated on the skin. In adults the virus is commonly sexually transmitted and causes few lesions, often limited to the perineum, genitalia, lower abdomen, or buttocks. It is usually a self-limiting disease in healthy adults and rarely needs specific treatment.

DISORDERS CHARACTERIZED BY GENITAL DISCHARGE

Patients with diseases that fall into the group of disorders characterized by genital discharge tend to have urethral or vaginal discharge and do not have ulcerations or significant lymphadenopathy. These infections include chlamydial infection,

www.ketabpezeshki.com 66485457-66963820

gonorrhea, nongonococcal urethritis, trichomoniasis, bacterial vaginosis, candidiasis, and pelvic inflammatory disease (PID). Bacterial vaginosis and candidiasis are not typically considered to be sexually transmitted conditions but often are diagnosed in patients undergoing evaluation for STDs. Chlamydial infection and gonorrhea can also cause vaginal discharge, especially in the setting of mucopurulent cervicitis, and both tend to cause urethral discharge in men. These two organisms commonly cause coinfections, and clinical manifestations of these two infections are similar. It usually is not possible to distinguish between the two diseases on the basis of signs and symptoms alone, and patients often are appropriately treated presumptively for both infections (see Table 98-1).

CHLAMYDIAL INFECTION

In the United States, chlamydial infection is diagnosed in more than 1 million people annually, making it the most commonly reported STD.[1] The causative organism is *C. trachomatis,* an obligate intracellular organism that infects columnar and pseudostratified columnar epithelial cells. Although infection with *C. trachomatis* can cause a variety of symptoms, including urethritis, cervicitis, epididymitis, proctitis, prostatitis, PID, and perihepatitis (also known as *Fitz-Hugh–Curtis syndrome*), asymptomatic infection is common.

Symptoms appear after an incubation period of 1 to 3 weeks. Although urethritis is the most common manifestation in men, men also can have epididymitis, or both in combination. When symptomatic, women may report symptoms and signs ranging from dysuria to systemic illness related to peritonitis. Often, however, the presenting manifestations in women are vague and nonspecific: dyspareunia, vaginal discharge or bleeding, or abdominal or pelvic pain, or some combination thereof. Unfortunately, infection is commonly asymptomatic; estimates show that up to 75% of infected women and 50% of infected men have no symptoms.[9] The highest rate of infection is in sexually active adolescent females, with infection rates as high as 10% in this group.[9] Of note, PID, with its increased risk of subsequent ectopic pregnancy and infertility, develops in up to 40% of women with untreated chlamydial infection.[5] Because of the high rate of asymptomatic infection and the increased risk for development of PID and its sequelae after chlamydial infection, screening of high-risk patients (e.g., those with multiple sexual partners) for disease may be appropriate in the ED, as long as adequate follow-up is ensured. The CDC recommends *Chlamydia* testing for all women 25 years of age or younger, for older women with risk factors (a new sexual partner or multiple sexual partners), and for all pregnant patients.[5]

In the past the gold standard modality for diagnosing chlamydial infection was cell culture, but it has fallen out of favor as it is labor-intensive, it is fraught with difficulties, and definitive results take days. Although other nonculture techniques (DNA probe and latex agglutination testing) have been used since the 1990s to make the diagnosis of chlamydial infection, the high sensitivity and specificity of nucleic acid amplification techniques (NAATs) has made them the diagnostic methods of choice. All of these techniques amplify nucleic acid sequences specific to the organism being tested and do not require viable organisms. NAATs have sensitivity rates better than those for culture (greater than 90%, versus 60-80%),[10] with specificity greater than 99%,[10] and they are more sensitive than other nonculture tests (DNA probe testing, latex agglutination testing). NAATs can be performed on swabs (endocervical or urethral) and urine. Urine screening with NAATs is adequate for symptomatic male patients, and urethral swabs generally are not necessary[10]; either vaginal or urine specimens are adequate for testing in women.[10]

Treatment of chlamydial infection consists of azithromycin 1 g PO in a single dose or doxycycline 100 mg PO twice daily for 7 days. Coinfection with gonorrhea is common, so unless gonorrhea is definitively ruled out, patients should be treated for both infections. Patients should be instructed to abstain from sexual intercourse for 7 days after completion of treatment (either single-dose therapy or the 7-day regimen of doxycycline). Sexual partners within the previous 60 days (and, if the last sexual encounter was more than 60 days before symptom onset, the most recent sexually partner) need to be evaluated, tested, and treated, and the index patient also should be instructed to abstain from sexual intercourse until all partners have been treated. Follow-up testing for cure is not required unless symptoms persist or reinfection is suspected.

NONGONOCOCCAL URETHRITIS

Nongonococcal urethritis is characterized by urethral discharge, dysuria, or urethral pruritus and, although most commonly diagnosed in men, also can be seen in women. Although the condition is often caused by *C. trachomatis* or *N. gonorrhoeae,* other organisms such as *Mycoplasma* and *Ureaplasma* also may be causative agents. All patients with suggestive symptoms should be evaluated for both gonorrhea and chlamydial infection with NAATs. The diagnosis is confirmed by Gram's stain (more than five white blood cells [WBCs] per high-power field and no gram-negative diplococci), a positive result on the leukocyte esterase test on urinalysis, or more than 10 WBCs per high-power field on urinalysis.

Treatment consists of azithromycin 1 g PO in a single dose or doxycycline 100 mg PO twice daily for 7 days.[5] In women with dysuria, other causes or coinfections should be ruled out, including chlamydial infection, trichomoniasis, and candidiasis. Patients with persistent symptoms despite adequate initial therapy (appropriate regimen and completion of treatment course) should be reevaluated for the accuracy of diagnosis. If the diagnosis was accurate, the patient should be treated with metronidazole 2 g in a single dose or tinidazole 2 g in a single dose; azithromycin 1 g as a single dose should be added if it was not used in the first treatment regimen.[5]

GONORRHEA

After chlamydial infections, gonorrhea is the second most frequently reported STD, with an estimated 300,000 new *N. gonorrhoeae* infections in the United States each year.[1] Because infection involves columnar or transitional epithelium, this organism can affect the urethra, rectum, cervical canal, pharynx, upper female genital tract, and conjunctival sac.

The most common clinical presentation in men is acute urethritis, characterized by dysuria and a penile discharge (Fig. 98-10) starting within 1 to 14 days of exposure. On examination, findings may include urethral meatal erythema and a purulent urethral discharge. Men may also have epididymitis, although this is uncommon.

In women, primary infections are often asymptomatic or produce only vague symptoms, such as vaginal discharge, abnormal vaginal bleeding, abdominal or pelvic pain, dyspareunia or dysuria, and frequency. Patients may not seek treatment until after the emergence of complications such as PID, which develops in up to 20% of women with untreated gonorrhea.[5] Like chlamydial infection, symptomatic and asymptomatic gonococcal infection can cause PID with consequent tubal scarring that may lead to infertility or ectopic pregnancy.

Gonorrhea also can involve the oropharynx and the anorectal area. Gonococcal infection of the pharynx often is asymptomatic, but in symptomatic cases, patients develop sore throat and

www.ketabpezeshki.com 66485457-66963820

Figure 98-10. Purulent urethral discharge in a patient with gonorrhea.

exudative tonsillitis. Most cases are self-limited. Anorectal involvement is more common in persons who engage in receptive anal intercourse but can occur in women from contamination from cervicovaginal secretions. Like pharyngeal infection, it often is asymptomatic. When the condition is symptomatic, patients report rectal discomfort or pain, tenesmus, constipation, dyspareunia, pruritus ani, and purulent or mucoid anal discharge or bleeding. Anoscopy reveals friable mucosa and mucopurulent exudate.

Gonococcal conjunctivitis can be a sight-threatening infection, so recognition of this form of infection is crucial. This infection can occur in newborns, in whom it is acquired during passage through an infected birth canal, and in adults, who often acquire the infection by direct inoculation from organisms on the fingers and then rubbed onto the eye. Symptomatic conjunctivitis is characterized by beefy red conjunctiva, chemosis, and purulent eye discharge that may be copious. If untreated, it can progress to corneal ulceration or, in severe cases, gonococcal endophthalmitis and globe perforation.

DGI results from gonococcal bacteremia and occurs more frequently in women than in men. Typically, it manifests as the arthritis-dermatitis syndrome, characterized by a combination of any or all of the following: fevers, chills, monoarticular or oligoarticular arthritis or arthralgias, rash, and tenosynovitis. The rash of DGI consists of petechial or pustular acral skin lesions, usually found peripherally on the extremities. The lesions are described as necrotic pustules on an erythematous base and are tender to palpation. These lesions represent the consequence of septic emboli to small blood vessels during bacteremia. Joint involvement, the second most common manifestation of DGI, manifests with an acute monoarticular or oligoarticular septic arthritis or arthralgias. The knees are most commonly involved, followed by elbows, ankles, wrists, and small joints of the hands and feet. The involved joint is erythematous and warm, often has an effusion, and is painful on range-of-motion testing. Other manifestations of DGI, which are rare, include hepatitis, myocarditis, endocarditis, and meningitis.

Definitive diagnosis of DGI is confirmed by isolating gonococci from the blood, synovial fluid, or infected skin; unfortunately, cultures from these sites have relatively poor sensitivity. Presumptive diagnosis of DGI is based on the appropriate clinical presentation, plus isolation of gonococci from a source site.

Diagnosis

Diagnostic tests for gonorrhea include Gram staining, culture, and NAATs. Gram staining is most useful in symptomatic men with urethritis and in patients with gonococcal conjunctivitis. In these cases it is an excellent diagnostic test, with a sensitivity and specificity approaching 100%,[5] and results are available rapidly.

Culture for *N. gonorrhoeae* can be used to isolate the organism for antimicrobial testing and determination of antibiotic sensitivities, and is useful in areas of rapidly emerging resistance. The sensitivity of this test may be significantly decreased by improper specimen collection and handling. For the yield of gonococcal culture to be maximized, inoculation of the specimen immediately after collection directly onto the appropriate medium optimizes viability of the organisms. If the specimen is from a sterile site, such as cerebrospinal fluid or synovial fluid, a nonselective medium such as chocolate agar is best. Specimens from nonsterile sites such as the cervix, urethra, rectum, or oropharynx, where normal bacterial flora is present, should be inoculated on selective media such as Martin-Lewis agar. If not transported immediately to the laboratory, specimens should be incubated at 35 to 36.5° C in a carbon dioxide–enriched atmosphere after collection and transported to the laboratory in a carbon dioxide–enriched atmosphere.

NAATs have good sensitivity and excellent specificity for detection of gonorrhea from endocervical, urethral, and urine samples. These tests are approved by the FDA for the detection of *N. gonorrhoeae* in endocervical swabs from women, urethral swabs from men, and urine from both men and women. The sensitivities of NAATs are superior to those of culture but may vary by type of NAAT.

Although NAATs are useful for diagnosis of cervical and urethral gonorrhea, they have not been cleared by the FDA for diagnosis of gonorrheal infection of the rectum, pharynx, or conjunctiva or from synovial fluid and cerebrospinal fluid; culture is required for diagnosis of organisms from these sites. In addition, culture is the diagnostic method of choice if it is necessary to determine the organism's sensitivity to specific antibiotics.

Treatment

The ability of *N. gonorrhoeae* to develop antimicrobial resistance is closely monitored by the CDC's Gonococcal Isolate Surveillance Project (GISP). In 2007, quinolone resistance increased to the point that these agents can no longer be used to treat gonococcal infections in the United States. In 2011, increasing resistance to cephalosporins led to a change in recommended therapy for uncomplicated gonococcal infections (see Table 98-3). In particular, the current recommendation is a two-drug regimen of ceftriaxone 250 mg IM once *plus* azithromycin 1 g PO as a single dose.[5] Use of cefepime is discouraged owing to increasing resistance to this agent, and azithromycin is recommended over doxycycline. This combined regimen will also treat coinfection with *Chlamydia*.

Sexual partners (those within the previous 60 days or, if the last sexual encounter was more than 60 days before onset of symptoms, the last sexual partner) need referral for evaluation, testing, and treatment. Patients should be instructed to avoid sexual activity until therapy has been completed and until they and their

www.ketabpezeshki.com 66485457-66963820

Table 98-4 Characteristics of Vulvovaginitis by Cause

ETIOLOGIC DISORDER	PH	DISCHARGE APPEARANCE	WET MOUNT	TREATMENT
Bacterial vaginosis	>4.5	Gray, white, milky or creamy; amine odor present	Clue cells present	Metronidazole, 500 mg PO bid × 7 days *or* clindamycin cream 2% intravaginally qhs × 7 days *or* metronidazole gel 0.75% intravaginally bid × 5 days
Trichomonas infection	>4.5	Gray, yellow, greenish, or white; often frothy; homogeneous	Trichomonads present	Metronidazole 2 g PO once *or* tinidazole 2 g PO once *or* metronidazole 500 mg PO bid × 7 days
Candida infection	<4.5	White, often curdy	Mycelia present	Fluconazole 150 mg PO once *or* intravaginal agents

PO, orally.

partners are no longer symptomatic. Referral for HIV testing should be offered.

TRICHOMONIASIS

Trichomoniasis is caused by *Trichomonas vaginalis,* a flagellated protozoan. It is the most common nonviral STD in the world. As with other vaginal infections, up to 50% of infected women are asymptomatic. The most common presenting signs and symptoms include dysuria, vulvar irritation or itching, and vaginal discharge, often described as thin, malodorous, and yellow-green (Table 98-4). Affected patients also may report lower abdominal pain or discomfort and dyspareunia. Males are frequently asymptomatic and most often are seen as partners of infected women.

On physical examination, vaginal discharge is noted in up to 70% of patients, ranging in character from thin and scanty to the classic description of thick, frothy, and yellow. Vaginal pH is above 4.5. Punctate mucosal hemorrhages of the cervix ("strawberry cervix") have been described in 2 to 10% of patients. However, the history and physical examination findings are not sensitive or specific enough to make the diagnosis on clinical grounds alone, and testing is indicated.

The diagnosis most often is made by microscopic examination of a wet mount slide, but this method has a sensitivity of only 60 to 70%; sensitivity varies with the skill and thoroughness of the examiner and is optimized by examination of the slide soon after specimen collection. Culture is more sensitive than wet mount but is not widely performed, and culture results are not available in a timely manner for ED diagnosis and treatment. In men, urine sediment can be examined for trichomonads and also can be sent for culture. PCR assay is an alternate method for diagnosis of trichomoniasis. Several PCR primers have been studied, and each has demonstrated higher sensitivity than wet mount or culture.[11] PCR assay also has been found to be highly specific, exceeding 95%.[11] PCR testing is now available for combined point-of-care testing for *Trichomonas* along with gonorrhea and *Chlamydia.*[12]

Either of two single-dose treatments is recommended: metronidazole 2 g PO or tinidazole 2 g PO. Alternative therapy is metronidazole 500 mg PO twice daily for 7 days (see Table 98-4). Because these nitroimidazoles can cause a disulfiram-type reaction in persons who subsequently consume alcohol, patients taking these agents should be advised to avoid imbibing for 24 or 72 hours after the last dose of metronidazole or tinidazole, respectively. Topical metronidazole is available but is less efficacious than oral preparations for treatment of trichomoniasis and is not recommended for this use.

In pregnant women, trichomoniasis has been associated with premature rupture of membranes, premature labor, and low birth weight. Despite this association, treatment has not been shown to reduce these complications, although it may relieve local symptoms in the woman, may decrease the risk of infection of the newborn, and may decrease sexual transmission. Symptomatic pregnant women desiring treatment should be counseled on the risks and benefits. Metronidazole as a single 2-g dose is considered safe in any stage of pregnancy as studies have not shown an association between its use during pregnancy and mutagenic or teratogenic effects in the fetus.[13] Because its safety has not been well evaluated, tinidazole should not be used in pregnant patients.

Sexual partners of patients with *T. vaginalis* should be treated, and patients should be instructed to avoid sexual contact until they and their partners are clinically cured.

CANDIDIASIS

Vulvovaginal candidiasis most often is caused by *Candida albicans* but can be caused by other *Candida* species and other yeasts. It is estimated that 75% of women will have at least one episode of yeast vulvovaginitis in their lifetime, and 40 to 45% will have two or more episodes.

Common presenting signs and symptoms include vulvar itching or soreness, vaginal discharge, dyspareunia, and dysuria. Characteristic examination findings are vulvar erythema, vulvar edema or excoriation, and white curdlike vaginal discharge. Satellite lesions also may be seen. Vaginal pH is normal (less than 4.5) (see Table 98-4). Because none of these symptoms or signs is specific for candidiasis and the history and examination findings are relatively unreliable, diagnostic testing is indicated.

Diagnosis typically is based on wet-mount microscopy with use of potassium hydroxide (KOH) preparation or Gram's stain demonstrating yeast or pseudohyphae. The sensitivity of these tests ranges from 40 to 70%. Culture is more sensitive and is considered the gold standard diagnostic modality but is rarely performed, and 10 to 20% of asymptomatic women harbor *Candida* organisms and other yeasts in the vagina.

Multiple short-course topical preparations are available for treatment and effect an 80 to 95% cure rate in patients who complete therapy (see Table 98-4); many are available over the counter. Self-medication with over-the-counter preparations should be advised only for women who have been diagnosed previously with vulvovaginal candidiasis and experience recurrence of the same symptoms. Unnecessary or inappropriate use of over-the-counter preparations is common, can lead to contact or irritant vulvar dermatitis, and may delay treatment for other causes of vulvovaginitis. In addition, patients should be counseled that vaginal preparations are oil based, which may weaken latex condoms and diaphragms. Fluconazole, 150 mg in a single dose, is the only oral agent that is approved by the FDA for the treatment of candidiasis.

Candidal infections can be divided into complicated and uncomplicated types. Uncomplicated vaginitis is seen in 90% of patients. It is characterized by sporadic or infrequent episodes with mild to moderate symptoms caused by *C. albicans* in a normal host. It responds readily to short-course treatments. Complicated infections, associated with severe or recurrent symptoms (four or more episodes of vulvovaginal candidiasis each year), tend to occur in patients with complicating medical problems

www.ketabpezeshki.com 66485457-66963820

(e.g., immunosuppression, poorly controlled diabetes mellitus) and require longer courses of treatment (e.g., 7 to 14 days of topical therapy or a 150-mg oral dose of fluconazole given in three doses on days 1, 4, and 7).[5] Vulvovaginal candidiasis in HIV-positive patients is not considered complicated and should be treated as for uncomplicated vulvovaginal candidiasis.

Vulvovaginal candidiasis occurs frequently during pregnancy and may be more difficult to cure. Only topical azole therapies, applied for 7 days, are recommended for use during pregnancy; fluconazole is contraindicated.

Evidence to support treatment of asymptomatic sexual partners is lacking. In addition, no direct association has been found between yeast infection and other STDs, and no difference in yeast isolation rates has been observed in patients who have an STD and in those who do not.

BACTERIAL VAGINOSIS

Bacterial vaginosis occurs because of a shift in bacterial flora in the vagina, with replacement of the normal H_2O_2-producing *Lactobacillus* species with high concentrations of a polymicrobial group, including anaerobic bacteria (*Prevotella, Mobiluncus,* and *Bacteroides* species), *Gardnerella vaginalis,* and *Mycoplasma hominis,* and an attendant increase in the vaginal pH from 4.5 to as high as 7.0. Bacterial vaginosis is the most common cause of vaginal discharge and malodor (see Table 98-4). However, up to 50% of women with bacterial vaginosis are asymptomatic.

The most common manifestation is vaginal discharge, often with an offensive vaginal odor, which may be accentuated after coitus (the alkaline pH of semen induces a fishy odor, recognition of which constitutes a physiologic "whiff test"). Vaginal pruritus and irritation are not common complaints. On examination, a thin, white, homogeneous discharge is present.

Diagnosis can be made with the Amsel criteria (see Table 98-4).[5] Three of the four criteria must be present for diagnosis:

1. A thin, white homogeneous discharge that smoothly coats the vaginal walls.
2. Presence of clue cells in microscopic examination. (True clue cells are epithelial cells that are so heavily stippled with bacteria that the cell borders are obscured. Epithelial cells with few bacteria do not classify as clue cells.)
3. A pH of vaginal fluid greater than 4.5.
4. A fishy odor to the vaginal discharge before or after the addition of 10% KOH (whiff test).

Diagnosis also can be made with Gram staining to determine the relative concentrations of bacterial morphotypes (Nugent criteria). Culture isolation of *G. vaginalis* is not useful, because this organism can be cultured from vaginal specimens in more than 50% of healthy women and is therefore not specific. Several other available tests perform acceptably when compared with Gram staining, but these are usually not available in the emergency setting.

All symptomatic women should be treated. Bacterial vaginosis is associated with an increased risk of acute upper genital tract infection by the various organisms recognized as likely pathogens in such infections.[14] It is not known whether treatment of bacterial vaginosis reduces the risk of ascending infection, so screening for and treatment of bacterial vaginosis in asymptomatic women are not recommended.

Recommended treatment regimens for bacterial vaginosis include metronidazole 500 mg PO twice a day for 7 days, metronidazole gel 0.75% 5 g intravaginally every day for 5 days, and clindamycin cream 2% 5 g intravaginally at bedtime for 7 days. The vaginal cream is oil based and may weaken condoms and diaphragms; patients should be advised of this possibility. Alternative regimens include tinidazole 2 g PO once daily for 3 days, dinidazole 1 g PO once daily for 5 days, clindamycin 300 mg PO twice a day for 7 days, or clindamycin ovules 100 mg administered intravaginally once at bedtime for 3 days. Alternative regimens have lower efficacy for treatment of bacterial vaginosis. Patients taking tinidazole and metronidazole should be advised to avoid alcohol for up to several days after treatment to avoid the disulfiram-like reaction that may be seen when these agents are taken. Treatment of sexual partners does not affect response to therapy or recurrence rates and is therefore not recommended.

All pregnant women with symptoms should be treated. Bacterial vaginosis during pregnancy is associated with premature rupture of membranes and preterm labor, preterm birth, and postpartum endometritis. Studies have not consistently demonstrated a benefit of treatment for asymptomatic pregnant patients, but treatment may be considered in women with a previous preterm birth or those who are at high risk for preterm birth.[15] Recommended treatment regimens in pregnancy include metronidazole 500 mg PO twice a day for 7 days, metronidazole 250 mg PO three times a day for 7 days, and clindamycin 300 mg PO twice a day for 7 days. Topical agents are not recommended for use during pregnancy.[5] Metronidazole use during pregnancy has no demonstrated association with teratogenic or mutagenic effects in newborns.

OTHER CAUSES OF GENITAL DISCOMFORT

Many other conditions manifest with vulvovaginal itching or discharge. Considerations in the differential diagnosis include the sexually transmitted and vaginal infections discussed previously, as well as allergic or chemical vaginitis, atrophic vaginitis, scabies, pediculosis pubis (genital lice), and vaginal foreign bodies.

Chemical vaginitis most commonly is associated with the use of douches, scented soaps, or feminine hygiene products. In addition, some women with a latex allergy may report vaginal itching and discomfort after intercourse with a partner who uses latex condoms. Diagnosis is by history, and discontinuing use of the offending agent usually is sufficient treatment.

Atrophic vaginitis occurs when levels of circulating estrogens decrease after menopause. Patients may report increased vaginal itching, vulvar discomfort, and dyspareunia. Other sources of discomfort, such as *Candida* infection, should be ruled out, because relative lack of estrogen predisposes affected women to vaginal and vulvar infections. Treatment typically consists of topical estrogen creams.

The mite *Sarcoptes scabiei* causes scabies infestation, and any part of the body may be affected. Transmission is by skin contact. The main symptom is pruritus, which is caused by a hypersensitivity reaction to mite excrement. The diagnosis is made clinically by identification of characteristic silvery lines seen in the skin where the mites have burrowed. Papules or nodules also may be noted, especially in the genital area. Scrapings viewed under the light microscope contain mites, confirming the diagnosis. Topical treatment for scabies is permethrin cream (preferred agent), lindane, or benzyl benzoate. In infants, permethrin 5% cream is the only indicated therapy. This agent can also be used in children, who may also be treated with benzyl benzoate 12.5%. Ivermectin, the only oral treatment for scabies, is more effective than topical permethrin.

Phthirus pubis is a crab louse transmitted by close body contact. Adult lice infest pubic hair, body hair, and occasionally the eyebrows and eyelashes. Eggs (nits) adhere to the hairs. The main symptom is pruritus caused by hypersensitivity reaction to the feeding lice. Diagnosis is based on finding adult lice or eggs. Treatment includes pyrethrin shampoos and permethrin 1% rinses (available over the counter), permethrin 5%, malathion, lindane, and ivermectin topical.

www.ketabpezeshki.com 66485457-66963820

PELVIC INFLAMMATORY DISEASE

Perspective

PID is a spectrum of disorders of the female upper genital tract, including any combination of endometritis, salpingitis, peritonitis, and tubo-ovarian abscess. Approximately 750,000 cases of PID are diagnosed annually in the United States.[1] The serious complications of PID (infertility, ectopic pregnancy, and chronic pelvic pain) account for a significant proportion of non-HIV STD-related morbidity in the United States and affect approximately 25% of diagnosed patients.[16] PID is reported to be the most common serious infection in women of reproductive age and causes approximately 30% of infertility cases, 50% of ectopic pregnancies, and many cases of chronic pelvic pain.[16]

Principles of Disease

PID is an ascending infection, with the infecting microorganisms spreading from the cervix and vagina to the upper portions of the female genital tract. Although the most commonly implicated organisms are *C. trachomatis* and *N. gonorrhoeae,* the cause of PID often is polymicrobial, and various microorganisms have been recovered in patients with acute PID, including genital mycoplasmas and anaerobic and aerobic bacteria from endogenous vaginal flora such as *Prevotella* species, peptostreptococci, *G. vaginalis, E. coli, Haemophilus influenzae,* and aerobic streptococci. Although organisms that are associated with sexual transmission are those most commonly found with PID, this infection can be caused by nonsexually acquired organisms. Patients diagnosed with PID should be counseled that the infection can be acquired nonsexually and that the diagnosis does not imply that either sexual partner may have had sexual encounters outside the relationship.

Risk factors for the development of PID include young age, multiple sexual partners, cigarette smoking, and menses. Intrauterine contraceptive devices (IUDs) have previously been implicated as a major risk factor for PID; however, IUDs increase the risk of PID only in the 3 weeks after insertion. It should be noted that nearly half of patients with PID do not have identifiable risk factors; a lack of risk factors does not rule out the infection.

Clinical Features

Owing to the wide range of presenting signs and symptoms, acute PID is challenging to diagnose. The most common presenting symptom is lower abdominal pain. Other signs and symptoms include dyspareunia, abnormal bleeding, abnormal cervical or vaginal discharge, abdominal pain, and fever. Physical examination may reveal a fever, abdominal pain, and lower abdominal tenderness, cervical motion, or adnexal tenderness (unilateral or bilateral) on bimanual palpation.

Studies show that many women with PID demonstrate mild, vague, or subtle symptoms, often not recognized as manifestations of PID by either the patient or her physician. Unrecognized PID probably is as common as, if not more common than, clinically apparent disease, and it is estimated that up to two thirds of cases may go unrecognized. *Silent* or *atypical PID* is a term that has been used to describe the underlying disorder in women with documented tubal infertility who have no history of being diagnosed with PID despite confirmed chronic inflammatory residua.

Patients also can report right upper quadrant pain and tenderness, which may be preceded or accompanied by the signs and symptoms of PID. This syndrome, known as *perihepatitis* or *Fitz-Hugh–Curtis syndrome,* has been associated with both gonococcal and chlamydial salpingitis. Transaminases will be normal. Fitz-Hugh–Curtis syndrome may develop in up to 10% of patients with PID, depending on the organisms implicated as the cause.[5]

When compared with laparoscopy as the gold standard for making the diagnosis of PID, the clinical examination has a sensitivity ranging from 65 to 90%.[17] The positive predictive value of the clinical diagnosis depends on the epidemiologic milieu in which the diagnosis is made. There is no single historical, physical, or laboratory finding, or combination of these that is adequately sensitive or specific to permit a definitive diagnosis of PID. With that in mind, and because of the difficulty in making the diagnosis and the serious long-term sequelae of PID, current recommendations call for a low threshold to both consider this clinical entity and to institute appropriate treatment in patients who may have PID.

The CDC recommends empirical treatment for PID in sexually active young women experiencing pelvic or lower abdominal pain if any one of the following minimum criteria is present without other identifiable causes:

- Cervical motion tenderness
- Adnexal tenderness
- Uterine tenderness

Controversy also surrounds what constitutes cervical motion tenderness. Although the traditional "chandelier sign" (pain so severe the patient ends up "swinging from a chandelier") of severe tenderness has been taught as the criterion standard, the patient herself should be questioned about her degree of pain. If it is more than the usual discomfort experienced by the patient during a pelvic examination, this should be considered positive evidence for cervical motion tenderness.

Other criteria that support but are not necessary for the diagnosis of PID include the following:

- Oral temperature greater than 101° F (38.3° C)
- Abnormal cervical or vaginal mucopurulent discharge
- Presence of WBCs on wet mount preparations of vaginal secretions
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein level
- Laboratory documentation of cervical infection with *N. gonorrhoeae* or *Chlamydia*

As more criteria for diagnosis are met, the specificity increases but the sensitivity decreases. The absence of either mucopurulent cervical discharge or WBCs on wet mount preparations makes the diagnosis of PID unlikely; in such cases, other causes of abdominal pain should be sought. Ultrasonography also may be useful in the diagnosis of PID, especially in identifying tubo-ovarian abscess or pyosalpinx. If the diagnosis is unclear, particularly in patients with fever and peritoneal signs, further testing is indicated. In these cases, computed tomography may rule out other causes of peritoneal clinical findings, such as appendicitis or diverticulitis, and in some cases laparoscopy may be necessary to determine the cause of the patient's illness.

Differential Diagnosis

The differential diagnosis of lower abdominal pain in young women is broad in scope. Other common diagnostic considerations include ectopic pregnancy, acute appendicitis, endometriosis, ovarian cysts, and functional abdominal pain.

Management

The goal of treatment in PID is to prevent the chronic sequelae of infection. Treatment regimens should provide broad-spectrum coverage against likely pathogens, including *N. gonorrhoeae, Chlamydia,* anaerobes, gram-negative bacteria, and streptococci. Although endocervical testing is recommended in these patients, negative results do not preclude upper tract infection.

www.ketabpezeshki.com 66485457-66963820

Table 98-5 Treatment for Pelvic Inflammatory Disease

REGIMEN A	REGIMEN B	REGIMEN C
Inpatient		
Cefoxitin 2 g IV q6h *or* Cefotetan 2 g IV q12h *plus* Doxycycline 100 mg PO or IV q12h	Clindamycin 900 mg IV q8h *plus* Gentamicin 2 mg/kg IV or IM load, *then* 1.5 mg/kg IV or IM q8h *or* single daily dose (3-5 mg/kg) can be substituted	
Continue until at least 48 hours after improvement	Continue until at least 48 hours after improvement	
Continue doxycycline 100 mg PO bid for 10-14 days total	Continue doxycycline 100 mg PO bid for 10-14 days total	
	Continue clindamycin 450 mg PO q6h or change to doxycycline	
Outpatient		
Ceftriaxone 250 mg IM once *plus* Doxycycline 100 mg PO bid × 14 days *with or without* Metronidazole 500 mg PO bid × 14 days	Cefoxitin 2 g IM *plus* Probenecid 1 g PO once *plus* Doxycycline 100 mg PO bid × 14 days *with or without* Metronidazole 500 mg PO bid × 14 days	Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) *plus* Doxycycline 100 mg PO bid for 14 days *with or without* Metronidazole 500 mg PO bid × 14 days

IM, intramuscularly; *IV,* intravenously; *PO,* orally.

Delaying treatment may increase the risk of developing long-term sequelae.

In patients with mild-to-moderate disease, no studies have clearly demonstrated differences in efficacy of parenteral versus oral therapy, or of inpatient versus outpatient treatment. The decision to hospitalize a patient should be based on the clinical presentation and other comorbid or complicating factors. The CDC suggests that any of the following criteria constitutes grounds for hospitalization:

- Surgical emergencies such as appendicitis cannot be excluded.
- The patient is pregnant.
- The patient does not respond clinically to oral antimicrobial therapy.
- The patient is unable to follow or tolerate outpatient oral regimens.
- The patient has a severe illness, nausea and vomiting, or high fever.
- The patient has a tubo-ovarian abscess.

Parenteral and oral regimens are listed in Table 98-5. If outpatient treatment is chosen, patients must be reevaluated within 24 to 48 hours to assess response to oral therapy. If there is no response, the patient should be hospitalized for parenteral antibiotic therapy and confirmation of the diagnosis.

Patients should demonstrate significant clinical improvement, such as defervescence, decreased abdominal tenderness, and reduction in uterine, adnexal, and cervical motion tenderness, within 3 days of initiation of therapy. Sexual partners of patients diagnosed with PID should be evaluated and empirically treated for gonorrhea and chlamydial infection. Patients should be counseled to avoid sexual activity until both they and their partners have completed treatment. It is recommended by some specialists that patients with documented gonorrhea and chlamydial infection be reevaluated for test of cure in 4 to 6 weeks after completion of therapy, although this practice is not universal.

KEY CONCEPTS

- Patients with ulcerative genital lesions should be considered to have an STD and should be tested and treated accordingly.
- Patients with suspected gonorrheal infection also should be treated for chlamydial infection.
- Sexually active women with adnexal or cervical motion tenderness should be treated for PID.
- A single dose of azithromycin is inadequate to treat upper female genital tract infection; patients require a 2-week course of antibiotics.
- Asymptomatic women with clue cells on wet mount preparations should not be treated for bacterial vaginosis.
- Pregnant women with bacterial vaginosis should not be treated if they are asymptomatic unless they are at risk for preterm labor or premature birth (i.e., if they have a history of preterm labor, miscarriage, or premature rupture of membranes).
- Patients with sexually transmitted infections are at risk for HIV infection and should be either tested in the ED or referred for HIV testing.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Centers for Disease Control and Prevention (CDC): 2010 Sexually Transmitted Diseases Surveillance. Available at www.cdc.gov/std/stats10.
2. Xu F, et al: Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. *JAMA* 2007; 296:964.
3. Whittington WL, Celum CL, Cent A, Ashley RL: Use of a glycoprotein G–based type-specific assay to detect antibodies to herpes simplex virus type 2 among persons attending sexually transmitted disease clinics. *Sex Transm Dis* 2001; 28:99.
4. Romanowski B, Marina RB, Roberts JN; Valtrex HS230017 Study Group: Patients' preference of valacyclovir once-daily suppressive therapy versus twice-daily episodic therapy for recurrent genital herpes: A randomized study. *Sex Transm Dis* 2003; 30:226.
5. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC): Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep* 2010; 59(RR-12):1.
6. Fife KH, Crumpacker CS, Mertz GJ, Hill EL, Boone GS: Recurrence and resistance patterns of herpes simplex virus following cessation of > or = 6 years of chronic suppression with acyclovir. *J Infect Dis* 1994; 169:1338.
7. Centers for Disease Control and Prevention (CDC): 2010 Sexually Transmitted Diseases Surveillance: Syphilis. Available at www.cdc.gov/std/stats10/syphilis.htm.
8. Lewis D: Chancroid: Clinical manifestations, diagnosis and management. *Sex Transm Infect* 2002; 79:68.
9. Meyers DS, Halvorson H, Luckhaupt S; U.S. Preventive Services Task Force: Screening for chlamydial infection: An evidence update for the U.S. Preventive Services Task Force. *Ann Intern Med* 2007; 147:135.
10. Bachmann LH, et al: Nucleic acid amplification tests for diagnosis of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections. *J Clin Microbiol* 2010; 48:1827.
11. Nye MB, Schwebke JR, Body BA: Comparison of APTIMA *Trichomonas vaginalis* transcription-mediated amplification to wet mount microscopy, culture, and polymerase chain reaction for diagnosis of trichomoniasis in men and women. *Am J Obstet Gynecol* 2009; 200:188.
12. Huppert JS, et al: Rapid antigen testing compares favorably with transcription-mediated amplification assay for the detection of *Trichomonas vaginalis* in young women. *Clin Infect Dis* 2007; 45:194.
13. Caro-Patón T, et al: Is metronidazole teratogenic? A meta-analysis. *Br J Clin Pharmacol* 1997; 44:179.
14. Koumans EH, et al: The prevalence of bacterial vaginosis in the United States, 2001-2004: Associations with symptoms, sexual behaviors, and reproductive health. *Sex Transm Dis* 2007; 34:864.
15. Hauth JC, Goldenberg RL, Andrews WW, DuBard MB, Copper RL: Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis. *N Engl J Med* 1995; 333;1732.
16. Wiesenfeld HC, et al: Comparison of acute and subclinical pelvic inflammatory disease. *Sex Transm Dis* 2005; 32:400.
17. Gaitán H, et al: Accuracy of five different diagnostic techniques in mild-to-moderate pelvic inflammatory disease. *Am J Obstet Gynecol* 2001; 184:856.

www.ketabpezeshki.com 66485457-66963820

Chapter 99

Selected Urologic Problems

Kevin M. Ban andJoshua S. Easter

URINARY TRACT INFECTIONS

Perspective

Background

Urinary tract infection (UTI) describes an inflammatory response of urothelium to microorganisms in the urinary tract, resulting in clinical symptoms including dysuria, frequency, urgency, hematuria, and suprapubic or costovertebral angle discomfort self-reported by the patient or elicited on physical examination. This term does not differentiate between upper and lower tract infections. Traditionally the emphasis has been on distinguishing lower tract from upper tract infections. Although this distinction may seem sensible from an anatomic perspective, it often does not provide additional information for making important management and disposition decisions. *Bacteriuria* is the presence of bacteria in the urine but is not considered to represent a UTI in the absence of clinical manifestations. Bacteriuria accompanied by symptoms should be treated, whereas bacteriuria in the absence of symptoms should be treated only in select patients (e.g., pregnant women, immunosuppressed patients).[1]

It is more useful to designate UTIs as being either uncomplicated or complicated, rather than as lower or upper tract infections. An *uncomplicated* infection is one involving a structurally and functionally normal urinary tract. The causative pathogen generally can be eradicated with a short course of standard antibiotics.[2] This type of infection usually occurs in nonpregnant, sexually active, young women who have no evidence of an obstructive process. *Complicated* infection is that associated with underlying neurologic, structural, or medical problems, all of which may reduce the efficacy of standard antimicrobial therapy. These types of infections often require a prolonged course of antibiotic therapy and a more in-depth approach to testing and anatomic evaluation.

Urethritis refers to the inflammation of the urethra secondary to either an infection or trauma. Frequently, urethritis may be a manifestation of a sexually transmitted disease (STD), such as gonococcal urethritis in *Neisseria gonorrhoeae* infection, but may occur in other clinical scenarios as well. *Cystitis* generally refers to inflammation of the bladder resulting in increased urinary frequency, urgency, dysuria, and suprapubic pain. Cystitis can be separated into bacterial and nonbacterial (e.g., radiation) etiologic categories. Acute pyelonephritis is a UTI of the renal parenchyma and collecting system manifesting with the clinical syndrome of fever, chills, and flank pain. Management and disposition of patients with acute pyelonephritis depend on whether the infection is simple or complicated.

Epidemiology

UTI is a problem that affects all age groups.[3,4] It is considered the most frequently occurring bacterial infection, accounting for 7 to 8 million annual outpatient visits, 1 million annual emergency department (ED) visits, 100,000 annual hospitalizations, and more than one third of all hospital-acquired infections.[1,5] These statistics notwithstanding, gauging the actual extent of the disorder is very difficult because it is not a reportable disease in the United States and the definition of a UTI is not exact.

Women have a 50% chance of experiencing a UTI during their lifetime.[2] The annual incidence of UTIs is 2 to 4% among young, sexually active women and gradually increases to 5 to 10% by the age of 70 years and to approximately 50% by the age of 80 years.

UTIs account for 5 to 14% of pediatric ED visits in the United States. UTI is more common in boys during the neonatal period but becomes more common in girls during infancy and thereafter.[6] When a UTI is seen in preschool boys, it is almost always associated with congenital anomalies of the urinary tract. The overall risk for all children with unexplained fever having a UTI is 7 to 9%.[7]

UTIs in adult men are uncommon unless cystoscopy or catheterization has been performed. The prevalence is less than 1% from childhood through middle age but increases to 1 to 3% by the age of 65 years and to 10% by the age of 80 years. Among institutionalized men and women, prevalence rates for bacteriuria and UTI are increased to approximately 25% and 40%, respectively.[3] UTIs associated with presence of an indwelling catheter constitute the most common nosocomial infection in the United States, accounting for more than 1 million cases annually.[8]

Principles of Disease

Physiology

The urine is sterile along the entire urinary tract from the glomerulus to the external sphincter in men and to the bladder neck in women. The urinary tract maintains its sterility by means of various defenses. A major mechanism is complete emptying. Free, unobstructed flow of urine within the kidney and down the ureter, coupled with complete evacuation of the bladder, is essential. Abnormal anatomy or physiology or the presence of a foreign body may compromise host defense mechanisms and predispose the patient to infection.[5]

In men the distal end of the urethra is inhabited by staphylococci, streptococci, and diphtheroid organisms. Nevertheless, men

www.ketabpezeshki.com 66485457-66963820

generally do not become infected without an underlying obstruction of normal urinary flow.

In women the urethra is short and opens close to the vulvar and perirectal areas. The organisms that cause UTI in women usually arise from the fecal reservoir and initially colonize the vaginal introitus and periurethral area.[4] These factors contribute in part to the much higher incidence of UTI in women.

Pathophysiology

Bacteria most often enter the urinary tract by ascent through the urethra and into the collecting system. Infrequently, bacterial infection of the urinary tract arises from hematogenous or lymphatic sources. This is the usual pathologic mechanism in debilitated and chronically ill patients who are immunosuppressed. Organisms from distal foci of infection such as endocarditis or soft tissue sources may make their way through lymphatic or hematogenous channels, resulting in a UTI. In these patients, it is important to identify and treat the primary source of infection.

Numerous abnormalities of the urinary tract interfere with its innate ability to resist infection. Obstruction from any cause, with resultant stasis of urine, is the major causative factor. Any obstruction or impediment to the free flow of urine or complete bladder emptying results in an increased incidence of infection. Urinary calculi may cause obstruction and increased susceptibility to the development of UTI. It is crucial that obstruction in the setting of infection be relieved promptly.

Vesicoureteral reflux in children plays an important role in the pathogenesis of UTIs, particularly upper tract infections. Reflux caused by congenital abnormalities or by bladder overdistention (as seen in advanced prostatic hypertrophy) also predisposes affected patients to infection. Subgroups of patients who are more susceptible than the normal population to UTIs include diabetic patients, pregnant women, the elderly, patients with spinal cord injury and indwelling urinary catheters, patients with multiple sclerosis, and those with immunodeficiency disorders such as human immunodeficiency virus (HIV) infection.[5]

In young men, asymptomatic bacteriuria is rare and may signify urinary tract disease. UTIs in men generally begin to appear at 50 years of age (concomitant with the onset of prostatic hypertrophy) and slowly increase in incidence.[9] The occurrence of UTIs in men of any age warrants referral to a urologist for further evaluation.

Bacteriology

The organisms that cause UTIs generally come from enteric flora colonizing the perineum and urethra. *Escherichia coli* is the dominant pathogen in more than 80% of first infections in women, men, and children, as well as in 50% of nosocomial UTIs.[10] *Staphylococcus saprophyticus,* a coagulase-negative gram-positive organism, is the second most common pathogen in UTI and accounts for approximately 11% of cases.[5] This species is present in normal skin flora, including the perineal area, but only in low numbers, and it does not appear to be of fecal origin. Occasionally, it is falsely identified as *Staphylococcus albus* or *Staphylococcus epidermidis.* Other, less common bacteria that may be responsible for infection include *Proteus, Klebsiella,* and *Enterobacter.*[5] Unusual microorganisms may be found in institutionalized or hospitalized populations and with complicated UTIs. Such settings and conditions predispose the patient to alterations in the normal gastrointestinal (GI) flora, leading to complex UTIs. The uropathogens in these patients include more resistant strains of *Escherichia, Klebsiella, Proteus,* and *Enterobacter,* as well as *Pseudomonas, Enterococcus, Staphylococcus, Providencia, Serratia, Morganella, Citrobacter, Salmonella, Shigella, Haemophilus, Mycobacterium tuberculosis,* and fungi. Although not necessary with uncomplicated UTIs, urine culture and sensitivity testing are recommended for all patients with complicated UTIs. Antibiotic therapy based on the most likely pathogen should be initiated immediately.

Uropathogenic organisms may elaborate various factors that affect their virulence, including aerobactin, hemolysins, and fimbriae (pili). Fimbriae, also called *adhesions,* are proteinaceous structures that can attach to specialized receptor sites on host cells. Attachment of bacteria to vaginal and uroepithelial cells ultimately leads to a higher incidence of UTI.[11]

Clinical Features

Signs and Symptoms

UTI is suspected in adolescents and adults on the basis of clinical findings, including dysuria, frequency, urgency, and hematuria in the setting of suprapubic or costovertebral angle (CVA) discomfort. Symptoms and signs vary with age. In infants, initial manifestations may include irritability, fever, vomiting, diarrhea, and failure to thrive. Preschool children with UTI have vomiting, diarrhea, generalized abdominal pain, and febrile seizures. History of fever alone is not an adequate indicator of severity of infection in children because it may be historically absent in pediatric patients subsequently found to have significant renal scarring.[12]

In general, clinical signs and symptoms associated with *lower* UTIs are localized to the genitourinary system and include urgency, dysuria, frequency, and suprapubic pain. In addition to these problems, a patient with an *upper* UTI may have back and flank pain as well as constitutional symptoms and signs such as fever, nausea, vomiting, and malaise.

As discussed previously, it is more important to determine if the infection is simple or complex. Simple, uncomplicated infections do not require urine culture, may be treated on an outpatient basis, and may not always necessitate urinalysis when thought to represent isolated cystitis.[10] Complicated infections require urine culture with antibiotic sensitivity and also may necessitate inpatient therapy with further diagnostic evaluation.[13] Distinction between upper and lower tract infections becomes important for understanding the differences in pathology and the pharmacokinetics of antibiotic delivery. Infection of the bladder generally involves only the superficial mucosa, and high urinary concentrations of antibiotics can easily be achieved with a short course of antibiotic therapy. The kidney, by contrast, tends to become infected in the medullary tissue, where achieving therapeutic concentrations of antimicrobial agents is far more difficult. As a result, parenteral antibiotics and longer courses of therapy are needed.

Men who report dysuria must be evaluated for the presence of urethral discharge before urinalysis is performed. In these patients, in whom the diagnosis of UTI is rare, the most likely causative disorder is an STD such as gonococcal or nongonococcal urethritis. If the patient has purulent urethral discharge, he should undergo testing for *Chlamydia trachomatis, N. gonorrhoeae,* and syphilis, as well as empirical treatment for STDs. If the patient does not have urethral discharge and complains predominantly of dysuria, frequency, urgency, and suprapubic or CVA discomfort, a urinalysis with culture should be performed. Male patients who have bacteriuria in the absence of clinical signs of urethritis or prostatitis should be considered to have a complicated UTI and should be treated with antibiotic therapy and undergo urologic follow-up for further evaluation.

Diagnostic Strategies

Laboratory Tests

Urine Collection Methods. The diagnostic value of microscopic examination depends on the quality of the specimen obtained. In neonates and children younger than 6 months, urethral

www.ketabpezeshki.com 66485457-66963820

catheterization is the preferred method of urine collection. Aseptic technique ensures a low risk of introducing bacteria. Before catheterization is attempted in these younger patients, an ultrasound or bladder scanner can be used to confirm the presence of urine in the bladder. Suprapubic bladder aspiration is a reliable method if urine is available to be withdrawn, but it is less commonly used owing to the invasiveness of the procedure. For patients 12 months or younger, ultrasound-guided suprapubic bladder aspiration is a useful method and carries an incidence of adverse effects similar to that of urethral catheterization. Plastic bag collection is a reasonably reliable method, but the perineum (in girls) and the glans (in boys) should be properly cleansed before application of the bag. It is the least invasive method but is useful only if culture results are negative, because of high associated contamination rates. A clean-catch urine specimen is preferred in cooperative and continent male patients.

In older children, a sterile midstream urine sample can be collected from boys. In girls, if the voided specimen is free of cellular elements (epithelial cells), it is acceptable for analysis. Catheterization often is a traumatic experience for children and one that invades their sense of privacy. An alternative approach to catheterization in a young girl with classic symptoms of UTI who has epithelial cells in the urine suggesting contamination is to evaluate the urine for other signs of infection. If the urine contains bacteria, red blood cells (RBCs), and white blood cells (WBCs) and is either nitrite or leukocyte esterase positive, the most likely cause of the symptoms is an uncomplicated UTI, for which antibiotic therapy and referral for follow-up care with the child's pediatrician are indicated. If the clinical picture remains unclear and a definitive diagnosis is mandatory, straight catheterization is performed after examination of the child's bladder with an ED ultrasound machine has confirmed the presence of urine.

Recommendations regarding urine collection methods in women vary widely. Midstream-voided specimens rarely escape perineal contamination, because for most adult women, adequate preparatory self-cleansing of the perineal area is difficult to achieve. It has been shown that in up to 50% of women with sterile bladder urine, a midstream clean-catch specimen grows 1000 to 100,000 bacterial colony-forming units (CFUs) per milliliter. This finding assumes major significance in the ED evaluation, in which accurate, initial supportive evidence for the diagnosis of UTI is crucial.

Sterile catheterization is the quickest and most accurate method of obtaining a urine specimen from an adult woman and may be the best solution for achieving a reliable urinalysis if the patient is actively menstruating. It is safe and relatively atraumatic and carries a remarkably low risk of infection. This risk increases if the patient is pregnant, elderly, or debilitated. If the clinician decides against catheterization, a clean-catch, midstream urine specimen should be sought. A predominance of epithelial cells suggests that the specimen is contaminated. The lower the ratio of leukocytes to vaginal epithelial cells, the more likely it is that the leukocytes are vaginal contaminants.

In men the specimen is not affected significantly by lack of cleansing or by the timing of specimen collection. Therefore it is not appropriate to catheterize an adolescent or adult man simply for the purpose of collecting a urine specimen.

Urinalysis. Urine cultures constitute a majority of cultures performed by microbiology laboratories, and various screening tests have been developed for the purpose of reducing this burden and its attendant costs. The goal of urine screening tests is reliable selection of specimens that will provide negative cultures. This allows the laboratory to focus more appropriately on higher-yield studies.

The most commonly used screening tests measure urinary leukocyte esterase and nitrite. Leukocyte esterase is an enzyme found in neutrophils, and nitrite is produced from urinary nitrate by nitrate reductase, which is present in gram-negative bacteria. Both can be detected by a color change on dipstick testing. The two tests often are combined to improve overall accuracy. Indirect urine dipstick tests for pyuria or bacteriuria are inexpensive and easy to perform and may aid in establishing the diagnosis of UTI. They should be used with caution, however, because they can be less sensitive than microscopic examination of urine (urinalysis). Urine dipstick testing for leukocyte esterase has shown a sensitivity of 75 to 96% in detecting pyuria associated with UTI. By contrast, a meta-analysis of screening tests for UTI in children has demonstrated that dipstick testing for leukocyte esterase and nitrite may be equivalent to microscopic urinalysis for detection of UTI.

Symptomatic patients who have normal host defenses and demonstrate a positive result on leukocyte esterase testing (in the absence of other indications for urine culture) can be treated empirically without culture. In symptomatic patients, a negative result on tests for both leukocyte esterase and nitrite should be followed by urine microscopy. In adults, urine culture should be performed only if findings on the microscopic analysis also are negative or if the patient is at risk for bacteremia.

Urine Microscopy. Urine microscopy is another commonly used method of providing rapid results, thereby reducing the number of urine cultures performed. Up to 96% of infected urine specimens contain 10 or more WBCs per cubic millimeter when counted by a hemocytometer. Various counting chamber methods detect pyuria with an accuracy approaching that of the hemocytometer. Unfortunately, these tests are not widely available, so direct microscopy commonly is used.

The accuracy of direct microscopy is compromised by a lack of standardization of the technique. Common sources of variability include specimen collection and transport, centrifugation speed and duration, decanting and resuspension techniques, staining, and the threshold used for significant numbers of WBCs or bacteria. One method, the slide centrifuge test, avoids many of these sources of error, and high sensitivity and specificity have been reported.

Although no accepted level of pyuria is diagnostic of UTI, on careful quantitation with a hemocytometer chamber, pyuria will be found in nearly all cases of acute UTI caused by coliforms. In patients with a low-count coliform infection, those with fewer than 8 WBCs/mm^3 of urine will have no demonstrable infection. In patients with more than 8 WBCs/mm^3, 85% will have documented infection (by the presence of coliforms, staphylococci, or chlamydiae). Despite these controversies and limitations, microscopic examination of urine to identify bacteria remains the most readily available and reliable test for a presumptive diagnosis of UTI in most patient populations.[14] Any analysis of a urine sample must be performed immediately after collection. Urine specimens that are allowed to sit for longer than 2 hours become alkaline, with subsequent dissolution of the cellular elements and multiplication of bacteria, thus providing the clinician with markedly unreliable results.[15]

Urine Culture. Definitive diagnosis of UTI is based on isolation of significant numbers of bacteria on urine culture. Traditionally, 10^5 CFUs/mL has been used as the statistically significant number for the presence of UTI. However, use of an absolute number is fraught with limitations. The presence of 10^5 CFUs/mL of bacteria in cultures from urine is associated with a 95% likelihood of infection, whereas 10^4 CFUs/mL is associated with a 50% likelihood of infection. It makes best clinical sense to put these results in clinical context regarding the presence of symptoms suggestive of a UTI. The symptom complex of dysuria, frequency, urgency, and suprapubic pain may be caused by a wide variety of infectious organisms in numbers far less than the traditional 10^5 CFUs/mL. In addition, these same symptoms may represent a significant upper tract infection or may be caused by urethritis.

www.ketabpezeshki.com 66485457-66963820

Box 99-1 Patient Groups in Which Urine Culture Is Indicated

- Children
- Adult men
- Immunocompromised patients
- Patients with "treatment failure" (i.e., with persistent urinary symptoms despite recently completed course of antibiotics)
- Patients with duration of symptoms more than 4 to 6 days
- Elderly patients at risk for bacteremia
- Ill-appearing patients with signs and symptoms suggestive of pyelonephritis or bacteremia
- Pregnant women
- Patients with known chronic or recurrent renal infection
- Patients with known anatomic urologic abnormalities
- Patients in whom urinary tract obstruction is suspected (e.g., stones, benign prostatic hypertrophy)
- Patients with serious medical diseases, including diabetes mellitus, sickle cell anemia, cancer, and other debilitating diseases
- Patients with alcoholism or drug dependence
- Recently hospitalized patients
- Patients taking antibiotics
- Patients who recently have undergone urinary tract instrumentation (e.g., cystoscopy, catheterization)

The presence of bacteria on culture in the absence of clinical manifestations does not always indicate infection. Women often carry large numbers of pathogenic bacteria on the perineum, and uncircumcised men may harbor large quantities of uropathogenic bacteria on the foreskin. The presence of bacteria in these regions may contaminate otherwise sterile bladder urine during collection.

The decision to perform a urine culture should be assessed for its relevance to patient care. Patients with frequency, dysuria, urgency, and suprapubic pain should be treated on the basis of symptoms if the infection is thought to be simple, and a urine culture is not required to guide therapy. For women who have host factors (e.g., structural abnormalities) or comorbid conditions (e.g., compromised immune status, pregnancy) necessitating definitive identification of the organism by culture, both urinalysis and culture are necessary. In general, the list of indications for urine culture (Box 99-1) defines high-risk groups. In vitro sensitivity testing contributes little to the general management of patients with uncomplicated UTI. Correlation between the therapeutic response and in vitro testing results often is poor. Culture also represents an additional cost with minimal contribution to the therapeutic plan for most outpatients.

Imaging. The majority of patients with acute cystitis or pyelonephritis do not need emergency imaging of the urinary tract. In certain clinical settings, however, emergency imaging is indicated. Patients with either unusually severe signs and symptoms or an atypical clinical presentation are candidates for genitourinary imaging. For example, a patient with the classic signs and symptoms of pyelonephritis but unremarkable urinalysis findings may have an obstructive process that has prevented the leukocytes and bacteria from reaching the bladder. Another example is that of a patient with a known history of UTI, currently receiving antibiotic therapy, who has persistent fever, chills, and general toxicity. Perhaps one of the most sensitive predictors of a complicated infection (e.g., abscess) is the persistence of fever beyond 72 hours after the institution of antimicrobial therapy. Pyelonephritis with obstruction from any cause can rapidly lead to abscess formation with resultant deterioration of renal function and sepsis. Emergency imaging is indicated to rule out this condition or to identify a suspected renal stone serving as a nidus for infection.

First episodes of UTI in selected patients, such as children younger than 4 years, generally require evaluation after resolution of the UTI. These patients are more likely than those in the general pediatric population to have structural anomalies and, if untreated, are at increased risk for recurrent UTI or for the development of complications such as hydronephrosis, renal scarring, and ultimately renal failure. The female patient with multiple episodes of complex infection, the patient with diminishing renal function, and the patient with renal colic and a possible obstructing stone, which progresses to sepsis, all require imaging.

Several imaging studies may be useful in these patients. Historically, intravenous or excretory urography—typically, intravenous pyelography (IVP)—was used because such studies provide both structural and functional information about the upper urinary tract. Recent work has focused on obtaining this information through safer, less invasive, and less costly methods.[16] Ultrasonography compares favorably with IVP but is inferior to computed tomography (CT).[17] Radionuclide cystograms compare favorably with voiding cystourethrograms in the diagnosis of vesicoureteral reflux and give less ionizing radiation to the gonads by a factor of 50 to 100. Voiding cystourethrography is the traditional method for initial evaluation of the genitourinary tract. CT scan is exceptional for diagnosing upper tract complications such as various degrees of pyelonephritis, abscesses, pyonephrosis, granulomatous infections, and infected cysts. As with IVP, its disadvantages include higher cost, radiation exposure, and potential for contrast-induced reactions.

Ultrasonography. Ultrasonography is useful in the evaluation of patients with potential urinary obstruction. It is a sensitive tool for detecting intrarenal and perinephric abscess and the presence of hydroureter and hydronephrosis. It is less accurate in determining the presence of a partially obstructing ureteral stone. Ultrasound examination also can detect the presence of pyelonephritis and congenital anomalies. Regardless of patient age group, this procedure is relatively inexpensive and avoids the hazards of contrast and radiation exposure.

Intravenous Pyelography. IVP, previously considered one of the mainstays in the evaluation of the genitourinary tract, has been nearly replaced by helical CT scanning and ultrasonography. IVP has higher sensitivity and specificity for determining the presence of obstruction than ultrasound examination but is inferior to CT scanning, and it is not sensitive for detecting the presence of pyelonephritis and renal abscess.[18]

Radionuclide Scans. Radionuclide scans also are gaining popularity for the early evaluation of UTI. A dimercaptosuccinic acid scan is the most sensitive method of identifying pyelonephritis and is the imaging study of choice in infant girls with UTI and fever.

Computed Tomography of the Abdomen. A contrast-enhanced CT scan of the abdomen is perhaps the best test for assessing the kidneys, ureters, and bladder. It has the highest sensitivity for detecting abscess, obstruction, and acute inflammation.[17] Its disadvantages include cost, radiation exposure, and potential for contrast-induced reactions and radiocontrast agent–induced acute kidney injury, which occurs infrequently in patients with a serum creatinine less than 1.5 mg/dL and can be further avoided by intravenous hydration with normal saline. CT without contrast can be performed in patients with renal insufficiency and is the preferred study in patients with clinical concern for urolithiasis.

Complicated Urinary Tract Infection in High-Risk Populations

Pregnancy

UTI during pregnancy represents a special situation. The incidence of UTI in pregnancy is approximately 2 to 7%.[19] Maternal complications include acute pyelonephritis, increased incidence of

www.ketabpezeshki.com 66485457-66963820

postpartum chronic pyelonephritis, preterm delivery, and low newborn birth weight. The physiologic changes that occur within the urinary tract of pregnant women include ureteral and renal pelvis dilation, as well as reduced peristalsis throughout the collecting system. During the last trimester, minimal ureteral contractions occur in many patients.

Unlike bacteriuria in nonpregnant females, bacteriuria in pregnant women, even if they are asymptomatic, should be treated. Complications that may result from untreated bacteriuria in pregnancy include premature labor, perinatal mortality, maternal anemia, and maternal pyelonephritis.

Reasonable antibiotic choices include amoxicillin, cephalexin, and nitrofurantoin. Trimethoprim-sulfamethoxazole (TMP-SMX) may be used before the third trimester. Single-dose therapy is not recommended, because these are not considered simple infections. Hospital admission should be considered in patients who are in their last trimester, who appear ill, or who have evidence of pyelonephritis and would benefit from treatment with parenteral antibiotics and intravenous fluids. Although pregnant patients with UTI are being treated on an outpatient basis more frequently than in the past, conservative treatment and close follow-up are warranted.

Diabetes and Sickle Cell Disease

Diabetic patients with bacteriuria also have an increased risk for the development of pyelonephritis, but treatment of asymptomatic bacteriuria has not been proved to be beneficial and should not be standard therapy at this time.[20] Papillary necrosis, perinephric and renal abscess formation, and emphysematous cystitis represent grave complications for this patient group. Manifestations of these complications may include altered vital signs, systemic signs and symptoms such as nausea and vomiting with dehydration, and a toxic appearance suggesting bacteremia and sepsis. These patients require aggressive fluid resuscitation, intravenous antibiotics, and a thorough diagnostic investigation including CT scanning.

Patients with sickle cell anemia also have shown a predilection for the development of papillary necrosis and generalized renal microvascular compromise. In these patients, compromised renal function is thought to be secondary to microvasculature damage from the chronic sickling of the erythrocytes. The renal damage from a UTI can compound the chronic renal insufficiency, leading to rapid worsening of the condition of these patients. They and all patients with underlying kidney disease or renal compromise should be approached conservatively, with hospitalization as deemed necessary for intravenous hydration and antibiotics.

Indwelling and Temporary Urinary Catheters

Treatment of asymptomatic bacteriuria in patients with indwelling catheters is not indicated. Antibiotic treatment results in the development of resistant microorganisms, whereas removal of the catheter leads to the spontaneous elimination of bacteria in many patients. Treatment of patients with a UTI in whom removal of the catheter is contraindicated includes urine culture and sensitivity, antibiotic therapy, replacement of the catheter, and strong consideration for hospitalization in those who exhibit altered vital signs, systemic symptoms, or a toxic appearance. These patients are at high risk for infection with an unusual pathogen and subsequent bacteremia. Urine culture with antibiotic sensitivity testing will help guide antibiotic therapy in this patient population.

The prevention of catheter-associated urinary tract infections (CAUTIs) has become an area of recent interest in the hospital setting since the Centers for Medicare and Medicaid Services (CMS) identified this condition as one of the six unacceptable diagnoses for payment if UTI was not present on admission.[21] CAUTIs are responsible for more than 80% of nosocomial UTIs and 40% of all nosocomial infections. Less than half of urinary catheters placed in hospitalized elderly patients have been found to be clinically indicated.[22] The most effective strategy for addressing CAUTIs is to prevent the infection from occurring by placing urinary catheters only when indicated and considering the use of intermittent catheterization and condom catheters when appropriate.

Differential Considerations

Bacterial UTI is the most common cause of dysuria with low-count infections. It is important, however, to consider the possibility of acute urethritis or acute vaginitis in these patients, as well as mechanical trauma or irritation (Tables 99-1 to 99-3; Fig. 99-1). Urethritis caused by *Chlamydia* may be seen in patients with acute dysuria; in fact, *C. trachomatis* may be present in up to 20% of women with dysuria. In general, if historical information includes contact with multiple sexual partners, a recent change in sexual partners, or a sexual partner with dysuria or discharge, *C. trachomatis* infection should be strongly considered. A pelvic examination should be performed, and culture specimens should be obtained to detect *C. trachomatis* and *N. gonorrhoeae*. Other causes of acute dysuria include infections with *Trichomonas vaginalis* and herpes simplex virus.

The dysuria of vaginitis most often is described as "external," the sensation being caused by the passage of urine over inflamed introital tissue. Elderly women may report dysuria secondary to atrophic vaginitis. In either case, a pelvic examination may be required. Urinary frequency and urgency are seldom if ever associated with a vaginal cause of dysuria.

Bacterial infection of the bladder is the most likely cause of dysuria in female patients. Most demonstrate positive results on urine cultures, with growth of more than 10^5 CFUs/mL of bacteria. This number is not absolute because 30 to 50% of patients have low-count bacterial infections as a cause of their symptoms. It has been suggested that low bacterial counts may represent an early phase of UTI.

Management

Simple Urinary Tract Infection

Options for treating uncomplicated lower UTI include single-dose therapy, short-course therapy (3-5 days), and the more traditional 7- to 10-day course of therapy (Table 99-4). *E. coli* remains the most common urinary tract pathogen and is susceptible to many antibiotic regimens. Emerging resistance to TMP-SMX has been noted in 15 to 32% of organisms.[23] In some areas of Europe, resistance to TMP-SMX is approaching 50%.[24] Risk factors for UTI from TMP-SMX–resistant *E. coli* include recent use of antibiotics (especially TMP-SMX), recent travel to areas with a high prevalence of resistance, and age younger than 3 years with daycare attendance.

Three days of therapy is more effective than single-dose therapy.[25] Three days of therapy have the advantages of improved compliance, lower cost, and reduced side effects. It currently is the recommended regimen for treatment of uncomplicated lower UTI. Despite emerging resistance, TMP-SMX remains the best first-line agent for 3-day regimens when compared with other commonly used antibacterials, owing to its low cost and effectiveness. Short-course 3-day therapy also is effective for asymptomatic bacteriuria in pregnancy. It is unclear whether this regimen can be used for symptomatic lower UTIs in pregnancy, so longer-course therapy is recommended. A regimen of 7- to 10-day therapy generally offers no benefit over shorter courses in uncomplicated

www.ketabpezeshki.com 66485457-66963820

Table 99-1 Differential Diagnosis of Dysuria Syndromes: Laboratory Findings

SYNDROME OR DISORDER	MICROSCOPIC HEMATURIA OR PYURIA	BACTERIURIA	URINE CULTURE (>10^2 CFUS/ML)	POSITIVE FLUID OR CERVICAL SMEAR	POSITIVE CULTURE OF GENITAL LESIONS, CERVIX, OR URETHRA*
Acute pyelonephritis	+	+	+	–	–
Acute cystitis	+	±	+	–	–
Urethritis caused by sexually transmitted disease					
Herpes simplex virus	+	–	–	±	+
Neisseria gonorrhoeae	+	–	–	+	+
Chlamydia trachomatis	+	–	–	+	+
Vulvovaginitis (bacterial vaginosis, trichomoniasis, yeast, genital herpes simplex)	–	–	–	+	±
Noninflammatory dysuria (trauma, irritant, allergy)	–	–	–	–	–

From Stamm WE: Protocol for diagnosis of urinary tract: Reconsidering the criterion for significant bacteriuria. Urology 32(Suppl 2):6, 1988.
*Positive for herpes simplex virus, *Neisseria gonorrhoeae,* or *Chlamydia trachomatis.*

Table 99-2 Differential Diagnosis of Dysuria Syndromes: Physical Examination

SYNDROME OR DISORDER	VAGINAL OR CERVICAL DISCHARGE, VULVAR LESIONS	SUPRAPUBIC TENDERNESS	FLANK TENDERNESS, FEVER
Acute pyelonephritis	–	±	–
Acute cystitis	–	±	–
Urethritis caused by sexually transmitted disease			
Herpes simplex virus	+	–	–
Neisseria gonorrhoeae	+	–	–
Chlamydia trachomatis	+	–	–
Vulvovaginitis (bacterial vaginosis, trichomoniasis, yeast, genital herpes simplex)	+	–	–
Noninflammatory dysuria (trauma, irritant, allergy)	–	–	–

From Stamm W: Protocol for diagnosis of urinary tract: Reconsidering the criterion for significant bacteriuria. Urology 32(Suppl 2):6, 1988.

Table 99-3 Clinical Differentiation among Major Causes of Dysuria

CAUSE	CLINICAL FEATURES
Urinary tract infection	Internal dysuria Frequency, urgency, voiding small volumes Abrupt onset Suprapubic pain Often associated with diaphragm use Presence of pyuria Presence of hematuria (50% of patients)
Sexually transmitted disease	Internal dysuria Occasional history of frequency, urgency, voiding small volumes Gradual onset History of new or multiple sexual partners Vaginal discharge
Vaginitis	External dysuria Gradual onset Vaginal discharge Vaginal odor Pruritus

From Stamm W: Protocol for diagnosis of urinary tract: Reconsidering the criterion for significant bacteriuria. Urology 32(Suppl 2):6, 1988.

UTIs; however, it remains the standard of care in complicated infections (in patients with pregnancy, diabetes, or sickle cell anemia) for which cure rates are lower with shorter regimens.

The fluoroquinolones are considered first-line agents in regions in which the incidence of TMP-SMX resistance has approached 10 to 20%. Ciprofloxacin is the most commonly used drug and requires twice-daily dosing. Although more expensive than ciprofloxacin, gatifloxacin and levofloxacin offer once-daily administration, have the broadest activity, and have same-dose bioequivalence between oral and parenteral administration. Fluoroquinolones damage developing cartilage in animal studies and should be avoided in children.[26]

Nitrofurantoin and trimethoprim are excellent drugs for the treatment of acute bacterial cystitis. Nitrofurantoin is inexpensive and maintains low serum and high urine levels, with a bacterial resistance pattern that remains unchanged. Adverse reactions are primarily secondary to GI disturbance, but they may be alleviated by use of the macrocrystalline form (Macrodantin). Folate antagonists such as trimethoprim have a broader spectrum of activity than does nitrofurantoin. The addition of sulfamethoxazole further broadens the spectrum to include coverage for *Proteus* and *Klebsiella.* Folate antagonists carry a higher incidence of adverse

www.ketabpezeshki.com 66485457-66963820

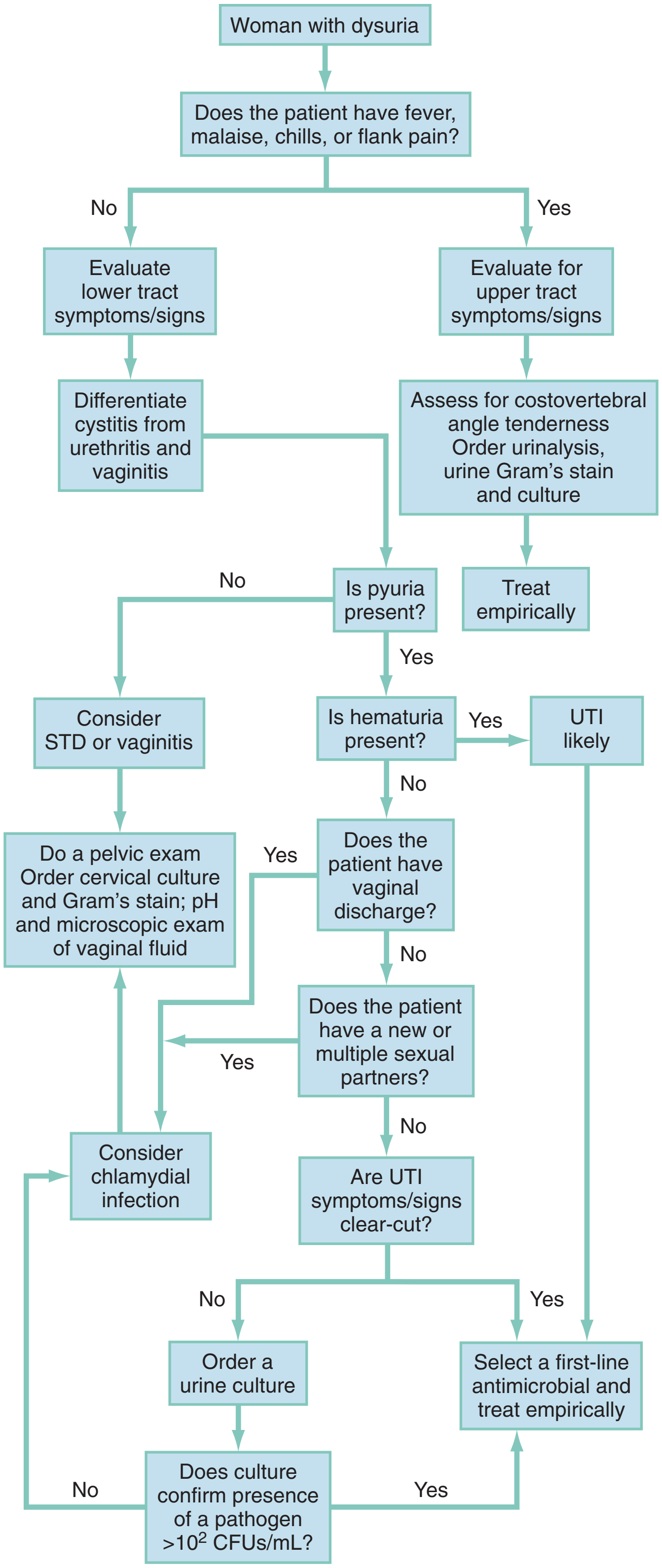


Figure 99-1. Diagnostic protocol for women with dysuria. *CFUs,* colony-forming units; *STD,* sexually transmitted disease; *UTI,* urinary tract infection. (From Stamm WE: Protocol for diagnosis of urinary tract: Reconsidering the criterion for significant bacteriuria. Urology 32[Suppl 2]:6, 1988.)

effects than nitrofurantoin, predominantly GI upset, yeast vaginitis, and rash. Addition of the sulfa component further increases the likelihood of side effects.

Except in pregnancy, ampicillin and amoxicillin should not be used empirically as first-line drugs for the treatment of uncomplicated UTI. Recurrence rates with use against ampicillin-resistant strains are high, and neither agent effectively eradicates the vaginal reservoir of pathogenic bacteria.

A useful adjunctive therapy for UTIs is phenazopyridine (Pyridium). It produces topical analgesia in the urinary tract and helps relieve dysuria. Patients should be cautioned that body secretions and excretions (e.g., tears, urine) will turn orange. This side effect can stain contact lenses and alarm unknowing patients.

Complex Urinary Tract Infection

Mild-to-moderate pyelonephritis can be safely treated on an outpatient basis with a fluoroquinolone for 10 to 14 days (first-line agent) or TMP-SMX (second-line agent) as long as the patient is able to eat and drink, has achieved adequate pain control, and has appropriate social support in the home. In many clinical centers, observation units have evolved to offer a short-stay (less than 24 hours) option for moderate cases in which immediate discharge for outpatient therapy may not be the optimal approach to management.[20]

Severe upper tract UTI necessitating hospitalization initially should be treated with parenteral antibiotics, with transition to oral therapy after the patient has been afebrile for 24 to 48 hours. Oral therapy should be continued for 2 weeks. Because 20% of cultures are resistant to ampicillin, cephalothin, and sulfonamides, antibiotic therapy should be initiated with a fluoroquinolone.

Hospitalization is required in the presence of clinical toxicity (fever, tachycardia, hypotension, vomiting), inability to take oral medications, an immunocompromised state, third-trimester pregnancy, inadequate social circumstances, failure of oral outpatient therapy, or urologic abnormalities or in patients with significant comorbid conditions, including heart failure or renal insufficiency. A subgroup of patients with upper tract UTI do not require immediate hospital admission but may benefit from intravenous hydration and pain and fever control, along with a first dose of an intravenous fluoroquinolone before discharge from the ED. If these patients do not have any contraindications as previously discussed and they improve clinically and are able to tolerate food and drink, they can be safely discharged home on a 10- to 14-day course of an oral fluoroquinolone with close primary physician follow-up. Urine culture with sensitivity testing and further diagnostic evaluation are not necessary in this patient population.

URINARY TRACT INFECTION IN CHILDREN

Perspective

UTI is a major bacterial disease of childhood; it is estimated that 0.8 to 1.5% of children have bacteriuria. The risk for development of UTI before 11 years of age is 3% in girls and 1% in boys.[6] The incidence of UTI in the neonatal period is higher in boys, but the infection becomes more prominent in girls during infancy and thereafter. In children aged 1 to 3 months, UTI is associated with a high incidence of sepsis (30%).[7] After the age of 3 months, the incidence of sepsis associated with UTI decreases (to 5%). Vesicoureteral reflux is a common risk factor for UTI and renal scarring in children.[12] Data suggest that the incidence of scar formation after acute pyelonephritis may be as high as 37%.

www.ketabpezeshki.com 66485457-66963820

Table 99-4 Treatment Regimens for Bacterial Urinary Tract Infections (UTIs)

CONDITION	CHARACTERISTIC PATHOGENS	MITIGATING CIRCUMSTANCE(S)	RECOMMENDED EMPIRICAL TREATMENT*
Acute uncomplicated cystitis in women	*Escherichia coli, Staphylococcus saprophyticus, Proteus mirabilis, Klebsiella pneumoniae*	None	Use 3-day regimens: oral TMP-SMX, trimethoprim, norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, or enoxacin[†]
		Diabetes, symptoms for longer than 7 days, recent UTI, use of diaphragm, age >65 yr	Consider 7-day regimen: oral TMP-SMX, trimethoprim, norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, or enoxacin[†]
		Pregnancy	Consider 7-day regimen: amoxicillin, macrocrystalline nitrofurantoin, cefpodoxime proxetil, or TMP-SMX[†]
Acute uncomplicated pyelonephritis in women	*E. coli*, *P. mirabilis*, *K. pneumoniae*, *S. saprophyticus*	Mild to moderate illness, no nausea or vomiting—outpatient therapy	Oral[‡] TMP-SMX, norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, or enoxacin for 10-14 days
		Severe illness or possible urosepsis—hospitalization required	Parenteral[§] TMP-SMX, ceftriaxone, ciprofloxacin, ofloxacin, or gentamicin (with or without ampicillin) until fever gone; then oral[‡] TMP-SMX, norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, or enoxacin for 14 days
		Pregnancy—hospitalization recommended	Parenteral[§] ceftriaxone, gentamicin (with or without ampicillin), aztreonam, or TMP-SMX until fever gone; then oral[‡] amoxicillin, a cephalosporin, or TMP-SMX for 14 days
Complicated UTI	*E. coli*, *Proteus* species, *Klebsiella* species, *Pseudomonas* species, *Serratia* species, enterococci, staphylococci	Mild to moderate illness, no nausea or vomiting—outpatient therapy	Oral[‡] norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin, or enoxacin for 10-14 days

Adapted from Stamm W, Hooton TM: Management of urinary tract infections in adults. N Engl J Med 329:1328, 1993.

TMP-SMX, trimethoprim-sulfamethoxazole.

*Treatments listed are those to be prescribed before the causative agent is known (Gram staining can be helpful); they can be modified once the agent has been identified. These recommendations are limited to drugs currently approved by the U.S. Food and Drug Administration, although not all of the regimens listed are approved for these indications. Fluoroquinolones should not be used in pregnancy. TMP-SMX, although not approved for use in pregnancy, has been widely used. Gentamicin should be used with caution in pregnancy because of its possible toxicity to eighth nerve development in the fetus.

[†]Multiday oral regimens for cystitis are as follows: TMP-SMX 160-800 mg every 12 hr; trimethoprim 100 mg every 12 hr; norfloxacin 400 mg every 12 hr; ciprofloxacin 250 mg every 12 hr; ofloxacin 200 mg every 12 hr; lomefloxacin 400 mg every day; enoxacin 400 mg every 12 hr; macrocrystalline nitrofurantoin 100 mg four times a day; amoxicillin 250 mg every 8 hr; and cefpodoxime proxetil 100 mg every 12 hr.

[‡]Oral regimens for pyelonephritis and complicated UTI are as follows: TMP-SMX 160-800 mg every 12 hr; norfloxacin 400 mg every 12 hr; ciprofloxacin 500 mg every 12 hr; ofloxacin 200-300 mg every 12 hr; lomefloxacin 400 mg every day; enoxacin 400 mg every 12 hr; amoxicillin 500 mg every 8 hr; and cefpodoxime proxetil 200 mg every 12 hr.

[§]Parenteral regimens are as follows: TMP-SMX 160-800 mg every 12 hr; ciprofloxacin 200-400 mg every 12 hr; ofloxacin 200-400 mg every 12 hr; gentamicin 1 mg/kg of body weight every 8 hr; ceftriaxone 1-2 g every day; ampicillin 1 g every 6 hr; imipenem-cilastatin 250-500 mg every 6-8 hr; ticarcillin-clavulanate 3.2 g every 8 hr; and aztreonam 1 g every 8-12 hr.

Principles of Disease

As in adults, *E. coli* is the predominant pathogen.[6] Age-related differences are recognized: In older boys *Proteus* often is isolated during UTI, whereas in newborn children, *Klebsiella* is more often the causative agent. The route of infection also is age related. It is thought that in the newborn period the bacteria are blood-borne (and often associated with generalized sepsis). In the older age group, as in adults, the ascending urethral route is primarily responsible for generating infection of the urinary tract.

Clinical Features

UTI often is overlooked in children because of inappropriate emphasis on classic signs and symptoms, with little regard to age variables. Nonspecific findings should be considered the rule and not the exception (Table 99-5). Pyelonephritis may be present without overt symptoms. A UTI in a febrile patient usually indicates pyelonephritis. An elevated blood urea nitrogen (BUN) level or hypertension in a child older than 2 months strongly suggests bilateral hydronephrosis or advanced renal parenchymal disease.

Neonates

Generalized septicemia often is the major manifestation of neonatal UTI.[12] Classically, feeding difficulties, irritability, and sluggishness are seen in this age group. Bacteremia is present in nearly 50% of cases.[6]

Table 99-5 Signs and Symptoms of Urinary Tract Infection by Age Group

NEWBORN	INFANT	PRESCHOOLER	SCHOOL-AGE CHILD
Poor feeding Vomiting Jaundice Hypothermia Fever Failure to thrive Sepsis	Poor feeding Vomiting Diarrhea Fever Strong-smelling urine	Abdominal pain Vomiting Strong-smelling urine Fever Enuresis Increased frequency of urination Dysuria Urgency	Fever Enuresis Increased frequency of urination Dysuria Urgency Costovertebral angle tenderness (flank pain)

Age 1 Month to 3 Years

The 1-month to 3-year age group has the most deceptive clinical presentation of UTI. Nonspecific findings are typical: fever, irritability, abdominal pain, vomiting, and failure to thrive. Occasionally, gross hematuria may be present.

www.ketabpezeshki.com 66485457-66963820

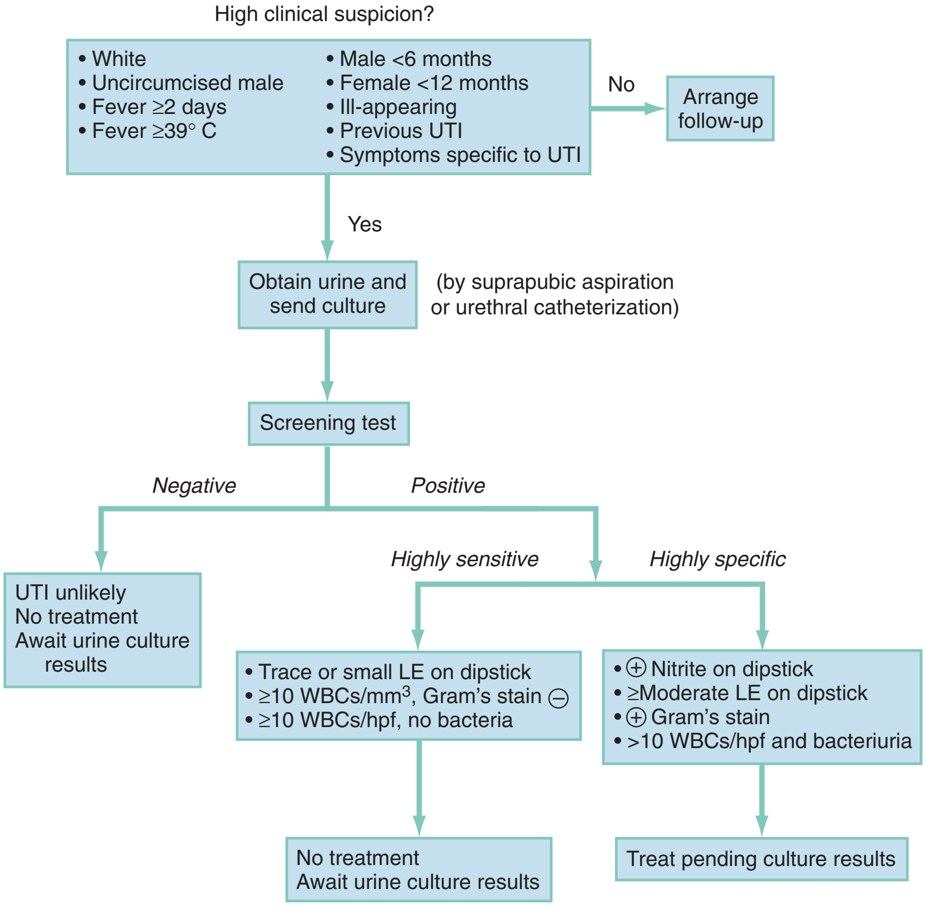


Figure 99-2. Screening for urinary tract infection (UTI) in febrile children (age 2 to 23 months) in the emergency department. *hpf,* high-power field; *LE,* leukocyte esterase; *WBCs,* white blood cells. (From Shaw KN, Gorelick MH: UTI in the pediatric patient. Pediatr Clin North Am 46:1111, 1999.)

Age 3 to 11 Years

In girls, abdominal pain, newly developed enuresis, and irritative voiding symptoms suggest the presence of UTI. In boys, fever is present in association with UTI in more than 50% of cases. Varying degrees of hematuria and irritative symptoms (urgency, dysuria) are present. *Proteus* is a common pathogen in this particular group. Most cases are simple, uncomplicated infections responsive to commonly used antimicrobial agents. The presence of certain signs and symptoms implies the possibility of serious underlying disease of the urinary tract. The most significant factors include a raised or palpable bladder, hypertension, abnormalities in electrolytes, acidosis, elevated BUN level, evidence of dribbling, poor urinary stream, and straining to void. If any of these factors is noted, prompt urologic referral or consultation is indicated. If the clinical picture is suggestive of an underlying obstructive process, emergency imaging is essential.

Diagnostic Strategies

Laboratory studies useful for diagnosing an infection of the urinary tract as previously described also apply to children. However, presumptive treatment may be indicated in high-risk patients based on clinical predictors and screening tests, as shown in Figure 99-2. Additional studies are dictated by the clinical setting and include renal function studies, a complete blood count, serum electrolyte panel, CT scan, voiding cystourethrography, and ultrasonography. Renal cortical scintigraphy is the most sensitive method of detecting pyelonephritis.

As described previously, urine collection often poses a challenge in a child with a suspected UTI. Catheterization or suprapubic bladder aspiration provides the most reliable specimen for determination of UTI.

Management and Disposition

As in adults, many therapeutic options are available for children with UTI. Sulfonamides, nitrofurantoin, TMP-SMX, cephalosporins, and aminopenicillins are effective.[6] Newborns and young infants should be treated with ampicillin and gentamicin on an inpatient basis. Sulfonamides and fluoroquinolones should be avoided in pediatric patients. Traditionally, inpatient treatment with parenteral antibiotics has been the standard of care for young children with suspected pyelonephritis. Oral therapy is acceptable in children with uncomplicated infections. These patients should be managed conservatively, and hospital admission is advised for children who are dehydrated, severely ill, or not tolerating oral fluids and for those with underlying structural abnormalities of the genitourinary system. In addition, family dynamics, which could affect compliance with medication, should be taken into consideration.

The appropriate duration of therapy currently is a subject of debate. Many experts believe that in children with uncomplicated lower UTI, short-course therapy can be used instead of the traditional 10-day regimen. Short-course (3-day) therapy is more widely accepted in adolescent girls. Once the decision to discharge a child has been made, the parents should be advised of signs of toxicity and the importance of compliance with medications.

www.ketabpezeshki.com 66485457-66963820

Parents should bring the child to the ED immediately if signs of toxicity develop and should arrange routine follow-up with the pediatrician if the child improves. The child should be seen for follow-up 2 to 3 days after the ED visit and again 2 to 3 weeks later (or 7 to 10 days after completion of the antibiotic course).

URINARY TRACT INFECTION IN MEN

Perspective

The incidence of UTI is much lower in men than in women. The route of infection in men is usually ascending, from the urethra to the prostate, to the bladder, and then to the kidney. Pathogenic organisms responsible for UTI in men are similar in type, regardless of the site of infection in the genitourinary tract. *E. coli* causes 80% of infections in men. UTI in men should be considered a complicated infection and requires a more extensive evaluation as well as a longer course of antibiotics.

Specific Disorders

Cystitis

Cystitis is rare in male patients in the absence of blunt trauma, prostate pathology, or instrumentation.[3] Chronic prostatitis, prostatic hyperplasia with obstruction, and previous instrumentation are the most common predisposing factors. Lack of circumcision and homosexuality are other recognized risk factors. Commonly, men with cystitis have symptoms of urinary urgency, frequency, dysuria, nocturia, suprapubic pain, and often low back pain. Gross hematuria occasionally occurs, but fever, chills, and flank pain generally are absent. On physical examination, suprapubic tenderness to palpation may be elicited. Pneumaturia may be present and is indicative of an infection with gas-forming bacteria. It also may indicate the presence of a vesicoenteric fistula, which often is caused by diverticulitis, although rectosigmoid carcinoma and regional enteritis are associated diseases as well. If fever and chills are present in association with irritative symptoms and difficulty voiding, acute bacterial prostatitis should be strongly considered. The most common pathogens found in men with cystitis are *E. coli, Proteus,* and *Providencia.*

A voided urine specimen should reveal pyuria, bacteriuria, and a variable degree of hematuria. Urine culture is indicated. If there are no signs of toxicity, the patient can be treated on an outpatient basis with any of the urinary antibacterial agents (TMP-SMX, nitrofurantoins, sulfonamides, or fluoroquinolones).

Three qualifying factors should be addressed in dealing with UTIs in men:

1. *Obstruction.* It is imperative that urinary obstruction be ruled out as a pathogenic mechanism. Infection and obstruction together can be catastrophic and lead to sepsis. Obstruction at the level of the prostate in older men is common and should be considered. Catheterization or bedside ultrasound examination may help to rule out retention. Suggestion of obstruction of the upper tracts based on lack of response to medical therapy necessitates performance of an abdominal noncontrast CT scan or ultrasound.
2. *Genitourinary tract anomalies.* UTIs in men may be secondary to underlying diseases of the genitourinary tract. Therefore all of these patients should be referred to a urologist for diagnostic studies.
3. *Catheterization.* Urethral catheterization should not be used to collect a urine specimen in men unless they are experiencing urinary retention. An inability to produce a specimen in the presence of infectious symptoms should be a major clue regarding the cause of the infection. If retention is suspected, catheterization for collection of residual urine is indicated. Referral for urologic consultation is recommended and hospital admission is prudent for a majority of these patients.

Pyelonephritis

Clinical features in men with acute pyelonephritis include flank and costovertebral angle pain, chills and fever, urinary frequency, urgency, and dysuria. Generalized malaise, nausea, and vomiting are early signs of systemic toxicity, suggesting impending gram-negative sepsis. These patients require hospitalization for intravenous hydration and antibiotic therapy, as well as pain and fever control.

A voided urine specimen usually reveals leukocytes, occasional leukocyte casts, a variable number of RBCs, and bacteria. Urine culture is essential in this patient population. Blood cultures should be performed if the clinical picture suggests sepsis. A complete blood count, renal function studies, and electrolyte studies are recommended. Uncomplicated pyelonephritis should not produce detectable alterations in the BUN level. In males, imaging with ultrasonography or an abdominal CT scan without contrast is required because the cause typically involves obstruction secondary to a stone, prostate pathology, stricture, or tumor. Catheterization for collection of residual urine may be indicated if urinary retention is suspected.

Prostatitis

Bacterial prostatitis is an infection of the prostate caused primarily by gram-negative organisms. More than 80% of cases are caused by strains of *E. coli;* the remainder are caused by *Klebsiella, Enterobacter, Proteus,* and *Pseudomonas* species. Patients with prostatitis may report dysuria and perineal and low back pain associated with fever, chills, and malaise. A rectal examination should be part of the workup in all men with symptoms suggestive of cystitis. Bacterial prostatitis is not a subtle disease, and patients will have an exquisitely tender and boggy prostate.

Acute bacterial prostatitis is an acute febrile illness characterized by chills, low back pain, and perineal pain. Irritative symptoms of voiding, including frequency, urgency, and dysuria, are present, along with various degrees of bladder outlet obstruction and retention. Patients often have constitutional symptoms of arthralgia, myalgia, and generalized malaise. Prostate examination reveals a tender, swollen gland that is firm and warm to touch. Palpation of an acutely inflamed prostate should be limited, to avoid the possibility of precipitating bacteremia or sepsis. Cystitis usually accompanies acute bacterial prostatitis; thus culture of voided bladder urine generally reveals the responsible pathogen.

Antimicrobial therapy has been shown to be beneficial and is recommended.[27] In patients without signs of systemic toxicity, a prolonged course of an antibiotic for 4 to 6 weeks is required. This may need to be repeated if only partial success is achieved. The following list represents an appropriate selection of drugs for *nontoxic* prostatitis:

1. Ciprofloxacin 500 mg orally (PO) twice daily; norfloxacin 400 mg PO twice daily; ofloxacin 400 mg PO twice daily or enoxacin 400 mg PO twice daily for 30 days
2. Trimethoprim with sulfamethoxazole (Bactrim), one double-strength tablet PO twice daily for 30 days

If the patient is toxic appearing with fever, chills, or urinary retention, hospitalization and parenteral antibiotics are warranted. The following antibiotic choices are appropriate for *toxic* prostatitis:

1. Ciprofloxacin 400 mg intravenously (IV) every 12 hours, or levofloxacin 500 mg IV every 24 hours

www.ketabpezeshki.com 66485457-66963820

2. Ceftriaxone 2 g IV every 24 hours with or without gentamicin 3 to 5 mg/kg/day

Some experts have recommended alpha-blocker therapy because the bladder neck and prostate are rich in these receptors and alpha-blockade may improve outflow obstruction and diminish prostatic reflux. Although this may facilitate the patient's recovery course, clinical trials are ongoing and this is not considered standard of care.[28]

If the patient is experiencing painful urinary retention, urethral catheterization should be avoided. Suprapubic needle aspiration or catheterization is much safer and more comfortable than urethral catheterization for initial management. A urologist should be consulted regarding management of all patients requiring suprapubic tube placement.

General support measures for outpatients should include bed rest, analgesics, antipyretics, hydration, and stool softeners.

Chronic Prostatitis

Patients with chronic prostatitis typically visit the ED when they experience an acute exacerbation of the disease. Clinical manifestations vary widely, but most patients report some degree of irritative voiding symptoms (frequency, urgency, dysuria), low back and perineal pain, and occasionally myalgias.[27] Fever and chills are uncommon except during an acute exacerbation of the chronic infection. A history of previous episodes of acute prostatitis may be absent. Findings on the physical examination, including examination of the prostate, often are unremarkable. The hallmark of chronic bacterial prostatitis is relapsing UTI caused by the same organism. Chronic bacterial prostatitis is the most common cause of recurrent UTI in men.

Antimicrobial therapy is recommended for the treatment of chronic prostatitis.[29] Most antimicrobials diffuse poorly from plasma into prostatic fluid. The fluoroquinolones achieve the highest concentrations in the prostate and are the drugs of choice, with cure rates of approximately 64%. The recommended dosages are as follows: ciprofloxacin 500 mg twice daily for 30 days; norfloxacin 400 mg twice daily for 30 days; enoxacin 400 mg twice daily for 30 days; or ofloxacin 300 mg twice daily for 6 weeks. TMP-SMX also is useful, with cure rates of 44 to 50%. The dosage is one double-strength tablet twice daily, but the optimal duration of therapy is unclear and may range from 4 to 16 weeks.

RENAL CALCULI

Perspective

Background

Urolithiasis constitutes a common clinical problem seen in the ED and affects 5 to 15% of the population worldwide, and recurrence rates are close to 50%.[30] From 1994 through 2000, presentations for urolithiasis nearly doubled, and all indicators point to a rise in the incidence of kidney stones in the general population.[31] Renal calculi are seen commonly in young adults and middle-aged men, with nearly 70% of all ureteral calculi occurring in individuals aged 20 to 50 years. Most ureteral calculi originate in the kidney and then pass into the collecting system.

Epidemiology

Various clinical syndromes involve metabolic alterations and are therefore associated with an increased likelihood of stone formation[32] (Box 99-2). Risk factors include age, male gender, and family history. In the United States, prevalence rates for renal calculi are 10% in men and 5% in women.[33]

Box 99-2 Risk Factors for Urolithiasis

Metabolic disease or disturbance
- Crohn's disease
- Milk-alkali syndrome
- Primary hyperparathyroidism
- Hypernitraturia
- Hyperuricosuria
- Sarcoidosis
- Recurrent UTI
- Renal tubular acidosis (type I)
- Gout
- Laxative abuse

Positive family history
Hot arid climates (southeast United States)
Male gender (white men affected more commonly than black men)
Previous kidney stone
Dehydration

UTI, urinary tract infection.

Principles of Disease

Overview

Multiple pathogenic factors interact to cause the formation of renal calculi. Renal calculi can be stratified into the following types: calcium, struvite, uric acid, and cystine.

Most stones (75%) are composed of calcium oxalate, alone or in combination with calcium phosphate. Hyperexcretion of calcium is a major contributor to stone formation and occurs in various clinical settings. The major dietary sources of calcium are cheese and milk, and hypercalciuria may occur in adults who ingest more than 1 quart of milk daily. Many conditions are associated with the development of hypercalciuria with increased risk of stone formation. The most common is hyperparathyroidism, in which calculi develop in 67% of patients. Peptic ulcer disease also may be a predisposing factor. These patients tend to ingest large amounts of calcium with food, in addition to absorbed alkali sources (sodium bicarbonate) and antacids. The other major component of calcium stones, oxalate, is influenced by diet. Hyperoxaluria occurs in the presence of small bowel disease, Crohn's disease, ulcerative colitis, and radiation enteritis.

Magnesium-ammonium-phosphate (struvite) stones account for approximately 15% of all renal calculi. Struvite stones occur almost exclusively in patients with UTI and often are referred to as "infection stones." They form as a result of urea-splitting organisms such as *Proteus, Providencia, Klebsiella, Pseudomonas,* and *Staphylococcus.* Distinctive features of these stones include common occurrence as staghorn calculi and the formation of "coffin-lid" crystals, often in the presence of alkaline urine.

Uric acid stones account for 10% of all stones in the United States. The basic causative factor is excessive excretion of uric acid in urine. Approximately 25% of patients with symptomatic gout have uric acid calculi, and the incidence of uric acid stones increases with the use of uricosuric agents. A distinctive feature of uric acid stones is their radiolucency. These stones infrequently take the form of staghorn calculi.

Cystine stones are rare and account for only 1% of stones. They are caused by an inborn error of metabolism that results in increased secretion of cystine and often occur as staghorn calculi.

Pathophysiology

Impaction along the genitourinary tract is a serious complication of renal calculi and can cause several physiologic changes. Once

www.ketabpezeshki.com 66485457-66963820

obstruction occurs, a rapid redistribution of renal blood flow results in a decrease in the glomerular filtration rate. As glomerular and tubular function decreases, renal excretion shifts to the unaffected kidney. Obstruction also causes a rapid decrease in ureteral peristaltic activity. In the presence of infection, both renal and ureteral function may be impaired. Complete obstruction of the ureters may lead to loss of renal function, with an increased incidence of irreversible damage after 1 to 2 weeks, including rupture of the renal calyx. Partial obstruction is associated with a lower likelihood of renal injury, but it may still result in irreversible damage.

Although calculus size and location are important determinants of the degree of disease, the major cause of progressive renal damage is associated infection. The stone behaves as a foreign body and leads to stasis and obstruction, decreasing host resistance and increasing the incidence of infection. Subsequent infectious complications include pyelonephritis, perinephric abscess, and gram-negative bacterial sepsis.

The three primary predictors of stone passage without the need for surgical intervention are calculus size, location, and the degree of patient pain at discharge. The most important factor that relates to passage of a calculus though the genitourinary tract is its size. Approximately 90% of stones smaller than 5 mm pass spontaneously within 4 weeks. This percentage decreases to 15% for stones 5 to 8 mm. Up to 95% of stones larger than 8 mm become impacted along the genitourinary tract, and lithotripsy or surgical removal may be required. Unless the stone is infected, renal damage is considerable, or there is obstruction of a solitary kidney, surgical intervention can be performed on an outpatient basis, provided the patient is able to tolerate oral intake and has adequate pain control. Spontaneous passage is more frequent with stones located below the midureter than with those located above the midureter. Patients with well-controlled pain on discharge are less likely to require surgical intervention than those who do not have well-controlled pain.

Renal calculi seldom cause complete obstruction. There are five sites along the ureter at which calculi are likely to become impacted (Fig. 99-3). First, a stone may lodge in the calyx of the kidney or pass into the renal pelvis and become lodged at the ureteropelvic junction. The relatively large renal pelvis (1 cm) narrows abruptly at its distal portion, where it is equal in diameter to its adjoining ureter (2-3 mm). The third region is near the pelvic brim where the ureter arches over the iliac vessels posteriorly into the true pelvis. The most constricted area along the ureter, and a common location for impaction, is at the ureterovesicular junction. This location is the site at which the ureter enters the muscular coat of the bladder (intramural ureter). At the time of diagnosis, up to 75% of stones are located in the distal third of the ureter. Finally, calculi may become lodged in the vesical orifice.

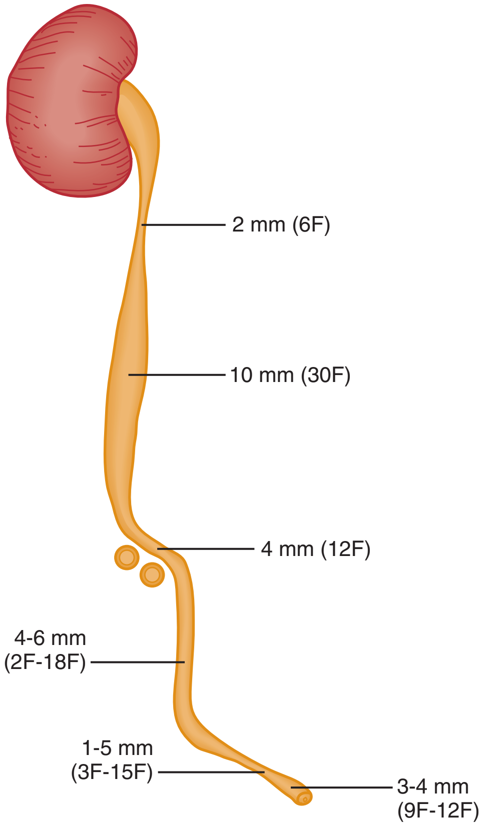


Figure 99-3. Variations in caliber of the ureter. *F,* French catheter size. (Adapted from Eisendrath, Rolnick. From Lich R Jr, et al: Childhood disorders and diseases. In Harrison JH, et al [eds]: Campbell's Urology, vol 1, 4th ed. Philadelphia, WB Saunders, 1978.)

Clinical Features

Signs and Symptoms

The onset of pain usually is abrupt, with a crescendo of extreme pain that begins in the flank, extends laterally around the abdomen, and radiates into the groin. Pain may radiate to the testicles in men and the labia majora in women. A constant, underlying dull ache in the flank is common between episodes of colic. The cause of colicky, severe flank pain is hyperperistalsis of the smooth muscle of the calyces, pelvis, and ureter, whereas the cause of a dull ache can be acute obstruction and renal capsular tension.

Autonomic nerve fibers that serve the kidney, testicle, and ovary are involved in the transmission of pain with renal calculi, and the location of the stone may be suggested by the pattern of pain. A stone located high in the ureter may cause pain that radiates to the testicle (or ovary). As the stone approaches the bladder, the pain may shift to the scrotum or vulva. Symptoms of urinary urgency and frequency often develop as the stone nears the bladder.

GI symptoms of nausea and vomiting are common in patients with renal colic. A third of patients experience gross hematuria, with or without blood clots in the urine. A history of fever and chills strongly suggests superimposed infection; such cases should be regarded as true urologic emergencies.

Physical Examination

A patient with renal colic often is in severe pain and paces or writhes in pain on the stretcher, unable to find a comfortable position. The skin usually is pale, cool, and clammy. Fever generally is not noted but if present strongly suggests infection. The abdominal examination may reveal signs of an early ileus with hypoactive bowel sounds. A decrease in peristalsis often accompanies renal colic, but abdominal tenderness usually is absent and flank tenderness is more common. It is essential that the abdomen be auscultated and palpated in search of bruits and thrills over the abdominal aorta and iliac vessels, because the clinical manifestations of aortic abdominal aneurysms may mimic those of renal colic. Patients commonly have intermittent pain that may nearly resolve between episodes of severe discomfort. The clinical picture may be misleading, with the patient's repeated attempts to secure relief from the pain misinterpreted as drug-seeking behavior, whereas actual pathology requiring medical attention is present.

www.ketabpezeshki.com 66485457-66963820

Diagnostic Strategies

Laboratory Tests

Urinalysis. The initial diagnostic step in the management of suspected renal colic is urinalysis. This simple, noninvasive test provides helpful information on various aspects of the patient's condition. In general, a dipstick test is performed first to evaluate for the presence of blood and infection. If results are abnormal, it is usually followed by microscopic analysis.

Sediment Analysis. RBCs generally are found in the urine of patients with urolithiasis. However, the absence of RBCs in urine does not exclude the diagnosis. From 10 to 20% of patients with documented urolithiasis have no microscopic hematuria.[34] Furthermore, there is no correlation between the degree of obstruction and the absence of hematuria. Although sterile pyuria can occur in the absence of infection as a result of ureteral inflammation, the presence of a UTI should be investigated if other clinical signs of infection are present, such as fever and chills. A urinalysis with culture should be performed to look for pyuria and bacteriuria and to measure nitrites and leukocyte esterase when infection is suspected.

Urinary pH. The kidney will not produce urine with a pH greater than 7.5 under normal conditions, so urinary pH greater than 7.5 should raise suspicion for the presence of urea-splitting organisms such as *Proteus*. Renal tubular acidosis and ingestion of absorbable alkali also may increase urine pH and should be considered in the differential diagnosis. A pH less than 5 often is associated with the formation of uric acid calculi.

Crystalluria. Historically, examination of urine crystals present on microscopic evaluation has provided a clue to the type of stone present. As a result of consolidation of urine testing to a central laboratory in most hospitals, this test is no longer routinely performed in most EDs.

Other Laboratory Tests. Serum uric acid levels are elevated in 50% of all uric acid stone formers, but this determination is not mandatory in the ED evaluation of the patient. Measurement of BUN and serum creatinine levels is not routine but should be done in patients who have a renal calculus with a solitary kidney, a transplanted kidney, or a history of renal insufficiency. A complete blood count may reveal a slightly elevated WBC count in patients with renal calculi that may be a result of demargination, but this is not a sensitive test and should be performed only in patients who are thought to be infected. A WBC count higher than 15,000/mm^3 or a significant left shift on the differential suggests active infection. Serum calcium and phosphorus levels can help screen for hyperparathyroidism, sarcoidosis, and other disorders of calcium metabolism, but this metabolic workup is not a necessary component of the ED evaluation of nephrolithiasis.

Imaging

Imaging is not needed in all patients with renal colic. If the signs and symptoms are atypical, the diagnosis is in question, the patient appears toxic, high-grade obstruction is suspected, or it is the patient's first episode of flank pain, imaging should be performed.

Computed Tomography. Non–contrast-enhanced helical (spiral) CT scanning is the standard imaging modality in the United States. It is sensitive and specific (98% and 100%, respectively, with a negative predictive value of 97%) in detecting both ureteral calculi and ureteral obstruction.[35] Other advantages include its ability to detect calculi as small as 1 mm in diameter and to provide direct visualization of complicating conditions such as hydroureter, hydronephrosis (Fig. 99-4), and ureteral edema. The CT scan is superior to other imaging modalities in its ability to recognize other pathology (malignancy, renal abscess, abdominal aortic aneurysm). It also has the advantage of lack of contrast exposure, short duration of testing, and ease of interpretation.

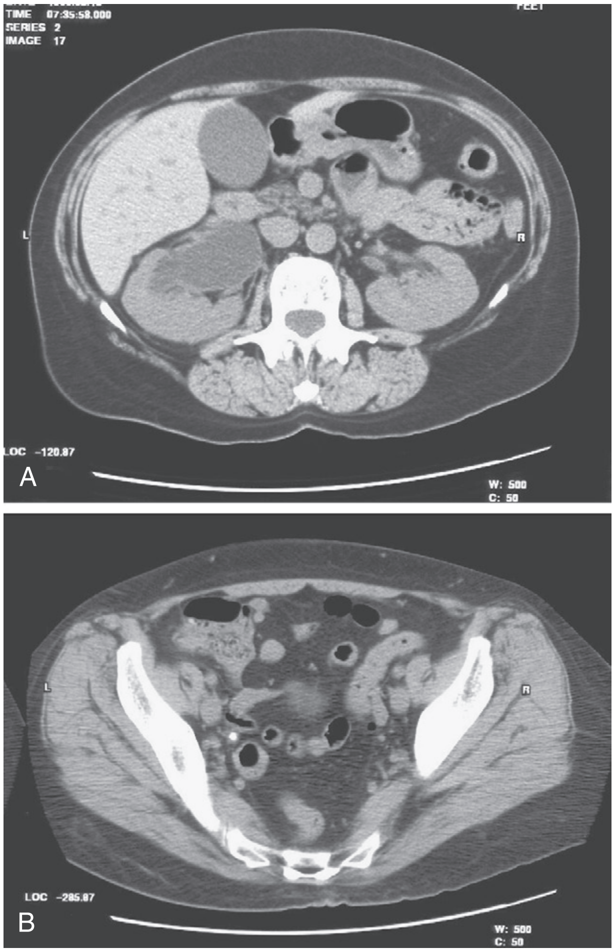


Figure 99-4. Computed tomography images obtained in a patient with renal colic. **A,** Right-sided hydronephrosis. **B,** Right ureteral calculi.

In patients who have signs and symptoms consistent with renal colic without a history of nephrolithiasis, noncontrast CT should be performed to improve diagnostic accuracy and guide management.[36] For unnecessary radiation to be limited and resource usage improved, patients who have a known history of nephrolithiasis and signs and symptoms consistent with renal colic in whom infection is not a concern do not need any form of imaging as long as they improve with medical management. Further imaging is appropriate in patients who have a history of nephrolithiasis who do not improve with treatment, who have a urinalysis showing infection, or in whom a more likely diagnosis than renal colic is suspected.[37]

Contraindications to CT scan imaging are few. Obese patients may be unable to undergo CT scanning if their girth or weight is beyond the capacity of the scanner. CT scanning should be avoided in pregnant patients because of radiation exposure to the fetus, and ultrasonography is the preferred diagnostic modality. CT scans may underestimate the actual size of the stone compared with the scout film from an IVP or kidney, ureter, and bladder (KUB) study. This limitation may adversely affect the management of patients with 5-mm stones, for example, in whom conservative therapy would be chosen on the basis of CT findings, although specific intervention would be more appropriate.[38]

Intravenous Pyelography. IVP is an accurate imaging modality to detect renal stones, but it is seldom used because CT scanning

www.ketabpezeshki.com 66485457-66963820

and ultrasonography have become first-line imaging modalities. It is very sensitive, capable of establishing the diagnosis of calculous disease in 96% of cases, and it can quantify the presence and severity of obstruction. Contraindications to the use of urographic contrast media include renal insufficiency with a serum creatinine greater than 1.5 mg/dL and previous reaction to radiocontrast material. The incidence of serious contrast reactions is extremely low, estimated to be 0.9 per 100,000. The value of IVP also is limited by the complexity and length of time needed to perform the procedure, which can take as long as 2 hours.

Ultrasonography. Ultrasonography is safe and easily performed, but it is much less reliable than CT scanning for detecting small (less than 5 mm in diameter) ureteral and midureteral stones.[39] Although only 37 to 64% sensitive for detecting calculi, ultrasound examination shows hydronephrosis with a sensitivity of 85 to 94% and a specificity of 100% (Fig. 99-5). It is the study of choice for ruling out hydronephrosis in a pregnant patient with pyelonephritis, if obstructive urolithiasis is a concern, or in obese patients who cannot undergo CT scanning.

Radiography of the Kidney, Ureter, and Bladder. A KUB film is the standard initial radiographic study done before injection of contrast medium during IVP. It is of limited usefulness on its own except as a progress film after CT has already identified a radiopaque stone. A KUB film is not reliable for diagnosing urolithiasis because it provides only presumptive evidence of calculi (less than 70% specificity), so it should be followed by a more definitive study or be avoided altogether. The most common radiographic densities seen on KUB films are phleboliths in the pelvic veins, which are spherical with a hollow (lucent) center, whereas calculi usually are irregularly shaped and solid. Calcified mesenteric lymph nodes also may add confusion, although unlike phleboliths, these densities commonly change position on subsequent films.

Most calculi (90%) are radiopaque, including calculi composed of calcium oxalate, cystine, calcium phosphate, or magnesium-ammonium-phosphate (Figs. 99-6 and 99-7). Uric acid stones, blood clots, and sloughed papillae are seen as "negative" shadows on radiographs. The most commonly overlooked calculi lie in the region over the sacrum, where small stones often are obscured by this bony density.

Differential Considerations

A number of significant clinical diseases can produce flank pain (Box 99-3) and should be considered in patients with symptoms suggestive of renal colic. Such conditions include abdominal aortic aneurysm, pyelonephritis, renal abscess, carcinoma, renal tuberculosis, papillary necrosis, and vascular compromise.

Acute pyelonephritis can cause severe renal pain. Urinalysis will aid in the differential diagnosis by demonstrating pyuria and bacteriuria. However, infection also can occur concomitantly with an obstructive stone. This combination constitutes a true urologic emergency and requires imaging (renal CT, ultrasonography, IVP) to rule out hydronephrosis, which may warrant immediate

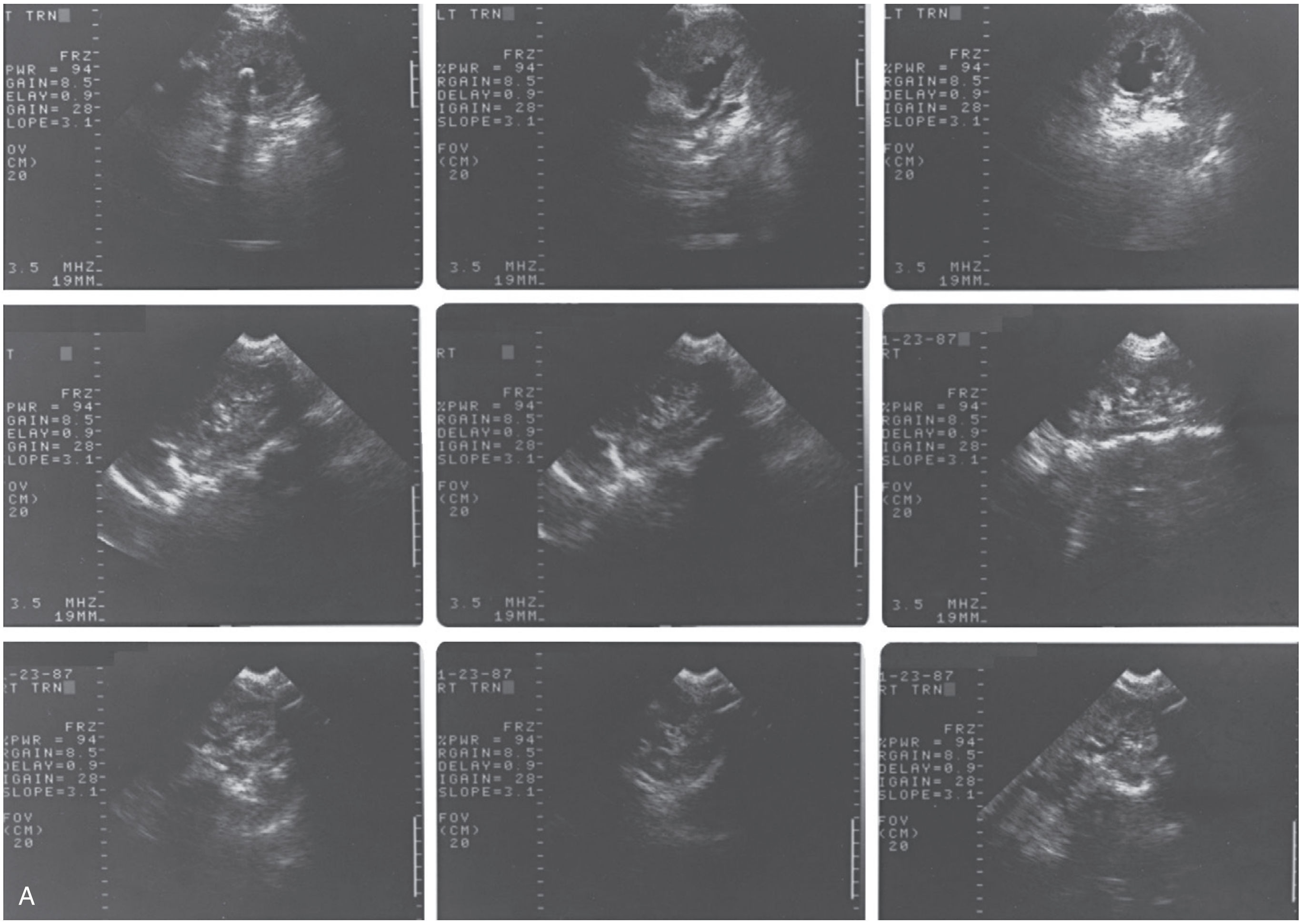


Figure 99-5. Ultrasound images of the kidney in a patient with renal colic. **A,** A long 1-1 axis view demonstrates hydronephrosis.

Continued

www.ketabpezeshki.com 66485457-66963820

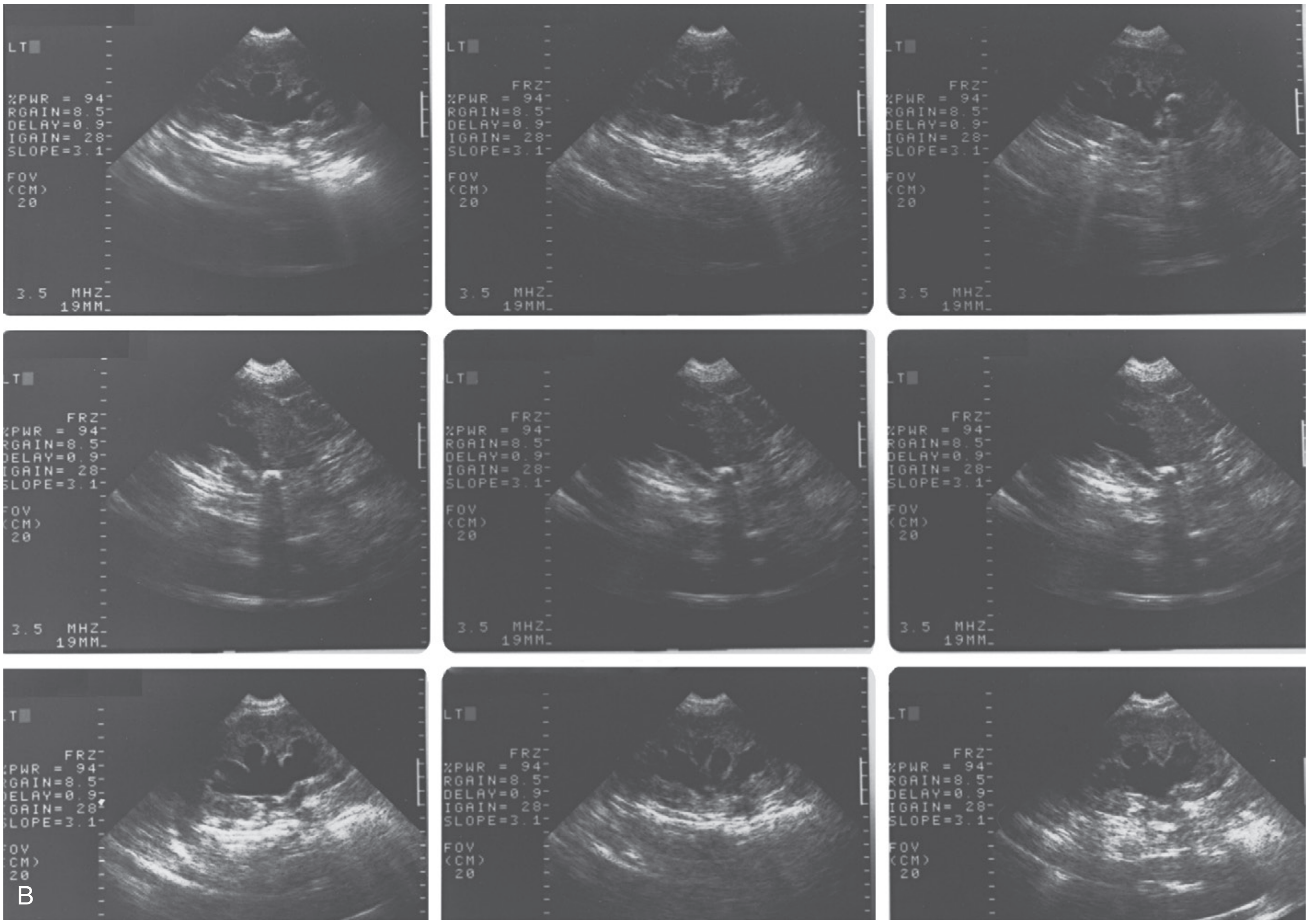


Figure 99-5, cont'd. B, A transverse cut shows a calcification with an acoustic shadow in the renal calyx.

Figure 99-6. In a near-term pregnant woman with an obstructed left kidney, intravenous pyelography demonstrates a delayed nephrogram. The right kidney has physiologic hydronephrosis from ureteral compression by the fetal head.

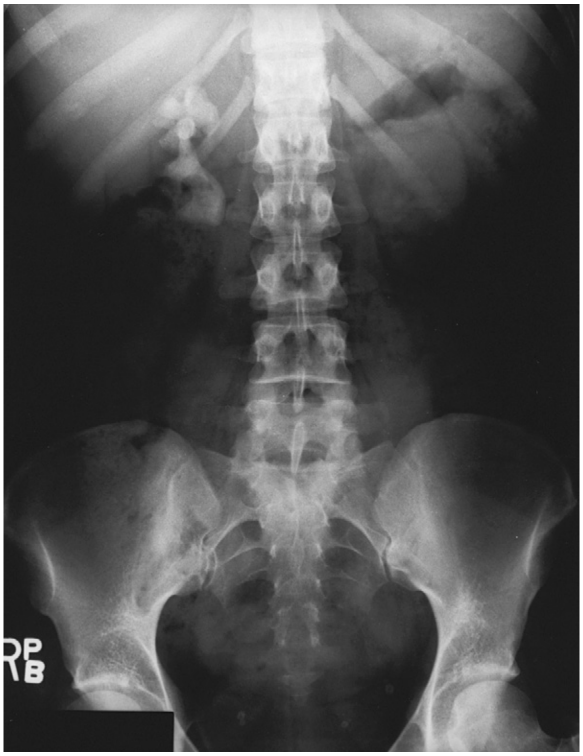


Figure 99-7. In a near-term pregnant woman with an obstructed left kidney, intravenous pyelography demonstrates a delayed nephrogram. The right kidney has physiologic hydronephrosis from ureteral compression by the fetal head.

www.ketabpezeshki.com 66485457-66963820

Box 99-3 Differential Diagnosis for Pain Associated with Urolithiasis

Urologic Disease

Upper Urinary Tract

Renal infarct
Renal parenchymal tumors
Urothelial tumors
Papillary necrosis
Pyelonephritis
Hemorrhage (blood clot)

Ureter

Urothelial tumors
Hemorrhage (blood clot)
Previous surgery (e.g., stricture)
Metastatic tumors

Lower Urinary Tract

Urothelial tumors
Urinary retention

Nonurologic Disease

Intra-abdominal

Peritonitis (especially appendicitis)
Biliary colic
Intestinal obstruction

Vascular

Abdominal aortic aneurysm
Superior mesenteric artery occlusion

Retroperitoneal

Retroperitoneal lymphadenopathy
Retroperitoneal fibrosis
Tumor

Gynecologic

Cervical cancer
Endometriosis
Ovarian vein syndrome

Musculoskeletal

Muscle strain or bony injury

From Lingeman J: Calculous disease of the kidney and bladder. In Harwood-Nuss A [ed]: The Clinical Practice of Emergency Medicine, 2nd ed. Philadelphia, JB Lippincott, 1996.

urologic intervention for placement of ureteral stents or decompression of the renal pelvis by percutaneous nephrostomy.

Renal carcinoma also may produce flank pain, especially if hemorrhage has occurred within the tumor. An abdominal flat-plate radiograph (a KUB film) may demonstrate calcifications overlying the renal shadow, which often are seen in renal neoplasms. IVP may suggest the diagnosis, but CT scanning is the best imaging modality.

Papillary necrosis may cause renal colic as a result of passage of sloughed papillae down the ureter. It is most commonly seen in diabetics and in patients with a history of acute or chronic UTI. Sloughed papillae may be visualized on renal imaging and can be mistaken for an obstructive stone.

Renal pain, either colicky or noncolicky, may be caused by acute vascular compromise of a kidney. The pain of renal infarction is severe and occasionally associated with microscopic or gross hematuria. The acute vascular changes may be secondary to renal artery embolism, renal vein thrombosis, dissection of the renal artery, rupture of a renal artery aneurysm, aortic dissection, or abdominal aortic aneurysm. If a vascular cause is suspected, a contrast-enhanced CT scan or an angiogram should be performed. The most common of these relatively rare processes is renal artery embolism, which most often is of cardiac origin (as with atrial fibrillation, subacute bacterial endocarditis, or mural thrombus). An immediate traditional angiogram or CT angiogram scan is indicated because early diagnosis allows possible salvage of the ischemic kidney. Most renal artery aneurysms are small and seldom produce clinical manifestations. Dissection or rupture of a renal artery aneurysm is rare and causes shock and flank pain. Renal vein thrombosis often demonstrates microscopic hematuria and proteinuria. The KUB film may show an increased renal shadow, and in the early stages, contrast studies show decreased function of the affected kidney. Predisposing factors for renal vein thrombosis include nephrotic syndrome, malignancies, and pregnancy.

A renal or perinephric abscess may cause flank pain, fever, and a palpable mass. Ultrasonography or a CT scan should be performed. A chest radiograph may demonstrate a pleural effusion or elevation of the diaphragm. Both renal and perinephric abscesses require hospitalization for drainage, intravenous fluids, antibiotics, and determination of the underlying cause.

Management

General Approach

Patients with renal stones generally are in severe pain and are unable to find a comfortable position. Often the history and physical examination, combined with the finding of hematuria, allow a presumptive diagnosis to be made and therapy to be initiated. The first priority is adequate pain control. Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line agents, but parenteral administration often is necessary because of nausea and vomiting. Intravenous ketorolac or diclofenac provides rapid effective analgesia with minimal side effects. In addition to their analgesic effects, NSAIDs decrease the pain of renal colic by decreasing ureterospasm and also reduce renal capsular pressure by diminishing the glomerular filtration rate in the obstructed kidney. Accordingly, caution is advised with use of these agents in patients with underlying renal insufficiency or peptic ulcer disease. An antiemetic may be useful if the patient has nausea, and intravenous fluids should be given to the vomiting patient who is unable to tolerate liquids and who is likely to undergo an imaging procedure. There are no definitive studies proving that high-volume fluid therapy in acute renal colic facilitates stone passage or improves outcomes.[40]

Narcotics (morphine sulfate or hydromorphone) also are very effective in providing rapid analgesia, faster than NSAIDs. However, they carry a higher incidence of side effects than that noted with NSAIDs. The combination of NSAIDS and opiates is an acceptable approach that may reduce length of stay in the ED.[41] Little evidence in the literature supports the use of anticholinergics or steroids for the treatment of acute colic.

Outpatient Management

Most patients with nephrolithiasis may be safely discharged from the ED. Current guidelines recommend urologic intervention in patients with symptoms persisting for longer than 2 months.[32] The patient should be instructed to drink a moderate amount of fluids, to take analgesics as needed for pain, and to engage in activity as tolerated.

Medical expulsive therapy (MET) is another potentially useful treatment modality in the management of distal ureteral stones, although initial reports of its efficacy have recently been questioned.[43] Because ureteral smooth muscle contraction is mediated by intracellular calcium and by the autonomic nervous system, it is thought that alpha$_1$-antagonists and calcium channel blockers facilitate distal stone expulsion and decrease the time to spontaneous stone passage.[44] These agents are presumed to work by blocking ureteral smooth muscle contraction and improving antegrade

www.ketabpezeshki.com 66485457-66963820

stone movement. No published studies have addressed the usefulness of medical expulsion therapy with stones larger than 6 mm in the absence of shockwave lithotripsy, and a recent study with over 3000 patients showed that alpha-adrenergic antagonists are more effective than calcium channel blockers, although both forms of MET are acceptable.[45] Although still not considered essential in the treatment of nephrolithiasis, MET therapy seems to be effective in some patients and is safe.

Proper discharge instructions should include work and driving restrictions for patients taking narcotics. In addition, patients with first-time stones or those who have not had chemical analysis of their stones can strain all urine with a strainer manufactured for this purpose. If such a device is not available, patients may simply void into a glass jar; the calculus should be visible at the bottom. The stone can be submitted to the follow-up urologist for analysis. Patients should be instructed to return to the ED immediately for intractable or severe pain, persistent nausea and vomiting, fever or chills, or difficulty voiding. Finally, outpatient urologic evaluation is standard for ED patients with acute ureterolithiasis.

Indications for Hospital Admission

Hospital admission should be sought for patients who are severely dehydrated, are experiencing unrelenting pain or vomiting, or have an underlying urinary infection (Box 99-4). Sepsis and renal damage are risks in the presence of obstruction and infection, so admission to the hospital for symptomatic therapy is inadequate. These patients require urologic consultation to evaluate the need for drainage and for relief of the obstruction. If signs of sepsis (tachycardia, fever, hypotension, shock) are present, antibiotics and fluid resuscitation should be administered pending urologic evaluation. Immediate operative intervention may be indicated to provide drainage and relieve the obstruction.

A patient returning to the ED with persistent colic does not need a second imaging study if the stone was identified previously. In such cases a KUB film may localize the stone. An intervention by the urologist may be necessary if the stone has not progressed along the genitourinary tract. Several interventional strategies are available to the urologist for the management of stones that do not pass spontaneously. Optimal therapy depends on the size, location, and composition of the stone. Extracorporeal shock wave lithotripsy (ECSWL) has proved to be effective for stones located in the kidney, with a greater than 85% clearance rate. Upper ureteral stones also may be cleared with a high success rate when ECSWL is performed after ureteroscopic manipulation of the stone to a more proximal position. Percutaneous nephrolithotomy, which establishes a tract from the skin to the collecting system, is used for stones too large or hard for ECSWL by removing them directly from the renal pelvis.

Box 99-4 Indications for Hospital Admission of Patients with Urologic Symptoms

Absolute
- Obstructing stone with signs of urinary infection
- Intractable nausea or vomiting
- Severe pain requiring parenteral analgesics
- Urinary extravasation
- Hypercalcemic crisis

Relative
- Significant comorbid illness complicating outpatient management
- High-grade obstruction
- Leukocytosis
- Solitary kidney or intrinsic renal disease
- Psychosocial factors adversely affecting home management

BLADDER (VESICAL) CALCULUS

Although calculi generally form in the kidneys, they also may originate in the bladder. Bladder stones are different from renal stones. In the United States, bladder stones occur almost exclusively in elderly men, often as a complication of other urologic disease. The most common cause is infection of residual bladder urine with urea-splitting organisms. The other common cause of vesical stones is an indwelling catheter. Disorders predisposing to the formation of bladder stones include bladder neck obstruction (usually secondary to prostatic hyperplasia), neurogenic bladder, vesical diverticula, damage from irradiation, and schistosomiasis.

The presenting manifestations most often are pain on voiding and hematuria. The patient may report a sudden interruption of the urinary stream, which strongly suggests a vesical stone that intermittently obstructs the bladder outlet. Frequency, urgency, and dysuria are described by up to 50% of patients, and UTI is common. Physical examination is rarely rewarding because signs may be minimal. Rectal examination may reveal an enlarged prostate or a prostatic malignancy. Poor sphincter tone may suggest a neurogenic bladder. Urinalysis generally reveals pyuria, bacteriuria, and hematuria. Plain radiographs of the pelvis reveal a bladder stone in 50% of cases. Contrast scans may demonstrate obstructive changes in the upper tracts or bladder diverticula. Ultrasonography also is useful in the diagnosis of bladder stones.

ACUTE SCROTAL PAIN

Perspective

Several unique disorders encountered in the ED setting produce scrotal pain. It is crucial to determine the exact causative disorder in such cases because testicular torsion, a common cause of scrotal pain, represents a surgical emergency requiring rapid recognition and treatment. Other causes of scrotal pain require less invasive and time-dependent therapies, such as antibiotics for epididymitis and observation for benign masses or torsion of the appendix of the testes.

Principles of Disease

Anatomy

Knowledge of testicular landmarks is essential for examination of the patient with an acute scrotal mass. Figure 99-8 demonstrates the normal anatomy of the scrotum and testis. A normal scrotum is relatively symmetrical, and both testicles are of equal mass and volume. The left testicle often is higher than the right, because its blood flow empties into the large, low-pressure vena cava, whereas the right drains into the relatively smaller, high-pressure renal vein. A normal testis is found in the vertical axis with a slight forward tilt, and the epididymis is above the superior pole in the posterolateral position.

Physical Examination

On examination of the testis, any tenderness to palpation, discrepancies in size, loss of testicular landmarks, or discoloration should be noted. The epididymis is located posterolateral to the testis and is normally nontender and soft. The cremasteric reflex is elicited by stroking or pinching the inner aspect of the thigh; more than 0.5 cm of elevation of the ipsilateral testicle is considered evidence of a normal reflex. This reflex normally is absent in 50% of male infants younger than 30 months of age.

www.ketabpezeshki.com 66485457-66963820

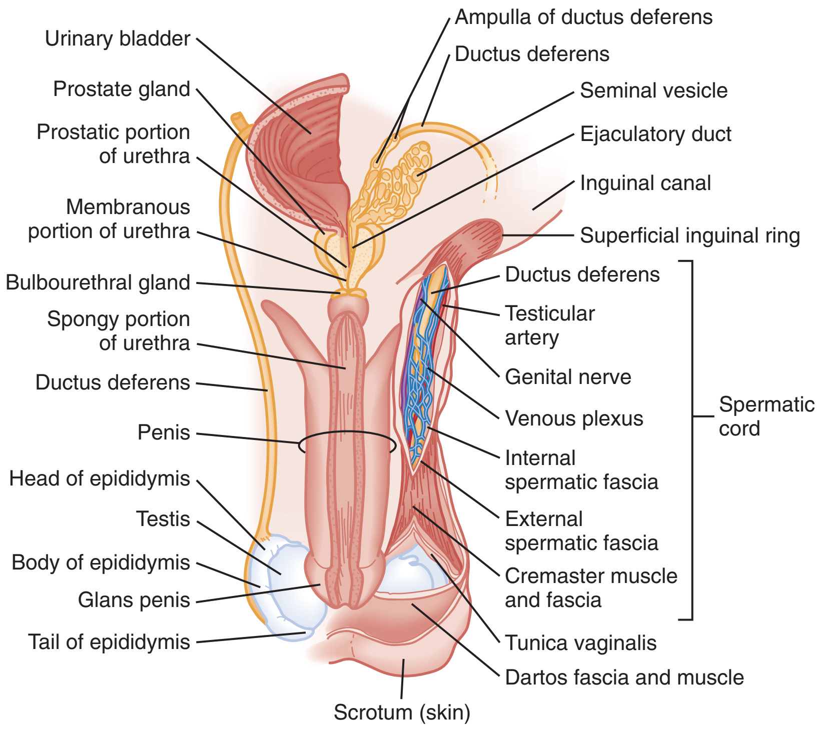


Figure 99-8. Testes, epididymis, ductus deferens, and glands of the male reproductive system. (From Seeley RR, et al [eds]: Anatomy and Physiology. New York, McGraw-Hill, 1989.)

Differential Considerations

Acute scrotal pain can arise with testicular torsion, epididymitis, torsion of the appendix of the testis, testicular tumor, or a hernia. Testicular torsion is the most important causative disorder to be excluded because any delay in treatment of this condition beyond 6 hours is associated with increased risk of testicular loss and infertility (Box 99-5).

Box 99-5 Causes of Acute Scrotal Swelling

Infant
Hernia
Hydrocele

Child
Hernia
Torsion
Epididymitis

Adolescent
Epididymitis
Torsion
Trauma

Adult
Epididymitis
Hernia
Trauma
Tumor torsion

Specific Disorders

Testicular Torsion

Perspective. Most studies suggest that testicular torsion is present in approximately 16 to 42% of patients coming to the ED with scrotal pain.[46] However, this is likely an overestimation resulting from selection bias, as most studies include only patients for whom suspicion of torsion is high, such as those evaluated by a urologist. A more recent retrospective study identified torsion in only 3.2% of all children brought to the ED with scrotal pain.[47] Nevertheless, torsion remains the most common cause of the acute scrotum in prepubertal boys, with a peak incidence in the first year of life. It also has a second peak incidence at puberty, when the rapid increase in testicular volume predisposes the testis to torsion. It can occur in adulthood, as evidenced by a retrospective review of data for 44 patients with torsion, of which 17 were older than 21 years of age.[48] Factors that increase the likelihood of torsion include horizontal lie of the testis, increased length of the spermatic cord in the scrotum, and a history of cryptorchidism. It is interesting to note that low ambient temperature has also been associated with testicular torsion, presumably because it induces contraction of the cremasteric muscles.[49]

Principles of Disease. With torsion, an extravaginal or intravaginal defect of the testis leads to twisting of the spermatic cord and decreased blood supply to the testicle. The cremasteric muscle surrounds the spermatic cord, and in the normal testicle, the testicle does not rotate when the cremasteric muscle contracts. In patients with torsion, however, the anatomic defect allows the tunica vaginalis to insert higher on the testicle, where it encircles the epididymis and distal spermatic cord. When the cremasteric muscle contracts in this abnormal scrotum, there is more room for the testicle to move, and it twists around the spermatic cord. Its movement resembles the ringing of the clapper in a bell—hence the description of a “bell clapper” deformity. By contrast, extravaginal defects occur almost exclusively in neonates and arise because the testicle lies outside of the tunica vaginalis, where it is prone to rotation. Torsion in neonates often is congenital, and by the time the condition is noted at birth, the testicle is not salvageable.

Testicular trauma also has been associated with torsion and has been noted in the literature to occur after motor vehicle collisions, straddle injuries, and athletic injuries. In these instances, the symptoms of torsion often are misattributed to the trauma itself, delaying the diagnosis. As a result, testicular salvage rates are only

www.ketabpezeshki.com 66485457-66963820

40% after groin trauma. To prevent loss of the testicle, scrotal pain persisting for an hour after any traumatic injury should raise suspicion for concomitant torsion of the testis.

As the testicle twists around the spermatic cord in torsion, it initially hinders venous return. Persistent torsion produces arterial obstruction, leading to ischemia and eventual necrosis of the testicle. With increasing degrees of rotation of the cord, ischemia increases, and infarction of the testicle occurs much more rapidly. Unfortunately, no clinical method has been devised for determining the extent of rotation of the testicle and the resultant likelihood of rapid ischemia. The duration of vascular obstruction also affects the ability to salvage the testicle; torsion recognized within 6 hours is associated with testicular salvage rates of 80 to 100%, whereas persistence of symptoms for 24 hours or longer is associated with nearly universal loss of the testicle.[50]

Clinical Features. Patients typically report sudden onset of scrotal pain that awakens them from sleep or develops several hours after physical activity. The pain arises in the scrotum, lower abdomen, or inguinal area. Patients with torsion tend to seek medical attention earlier than those with other causes of acute scrotal pain. However, the mean time of presentation is still 9.5 hours into the disease course, which makes expedient diagnosis and treatment very important for this time-sensitive condition. Up to 29% of patients with testicular torsion describe similar pain in the past, caused by previous intermittent torsion in a predisposed testicle. Patients often report nausea and vomiting or abdominal pain caused by reflex stimulation of the celiac ganglion.[47] Although a history of scrotal trauma reduces a patient's likelihood of having testicular torsion, approximately 10% of patients with testicular torsion report prior acute blunt trauma to the scrotum. There are no historical factors, including nausea, vomiting, abdominal pain, fever, urinary symptoms, or a history of trauma, that accurately or reliably differentiate torsion from other causative disorders (Table 99-6). Similarly, age cannot reliably be used to discriminate between torsion and other causes of acute scrotal pain.[49]

The physical examination is much more reliable than the history in determining the presence of testicular torsion. The most common finding is loss of the cremasteric reflex, observed in nearly 100% of patients older than 30 months with torsion. In a retrospective review of 245 patients with acute scrotal swelling, none of the patients with a cremasteric reflex had torsion.[51] However, a more recent ED-based study identified a normal cremasteric reflex in 19 of 62 patients with testicular torsion.[52] Therefore clinicians cannot rely on the presence of an intact cremasteric reflex to rule out torsion. Moreover, in asymptomatic children younger than 30 months, this reflex is often absent. Patients with torsion frequently have a tender, firm testicle that can be higher than the contralateral testicle (the odds ratio in one study was 58.8 for this finding) owing to shortening of the spermatic cord as it twists.[47] This difference in testicular heights can be difficult to ascertain because many individuals have differential testicular heights at baseline. Twisting also can leave the testicle in the transverse position and displace the epididymis from its usual location along the posterior aspect of the scrotum. Often the patient's scrotum is so swollen and tender that a complete physical examination is impossible. After 24 hours the physical examination is not particularly helpful because many of the aforementioned findings are no longer present. Despite the limitations of the physical examination, any patient with acute onset of scrotal pain and any of the aforementioned physical findings should be considered to have torsion until proven otherwise.

Diagnostic Strategies. In patients in whom the history and physical findings strongly suggest torsion, emergent surgical consultation is warranted. If the diagnosis is equivocal, adjunctive tests should be performed to determine the cause of the pain. Although clinical decision rules may eventually exist to guide imaging decisions, current rules have been based on small populations of children at single EDs and have not been validated.[53] Although urinalysis results suggestive of infection are consistent with epididymitis, such findings also may be noted in patients with torsion and concomitant UTI. Similarly, a complete blood count does not adequately differentiate torsion from alternate causes of the acute scrotum.

Ultrasound imaging for testicular torsion has a sensitivity of 88 to 100% and specificity approaching 90%.[54] With a 7- to 10-mHz high-frequency probe used on the supine patient, the asymptomatic testicle should be examined first, and the optimal settings for visualization and measurement of blood flow should be determined. In contrast to this testicle, the torsed testicle typically will be hypoechoic and enlarged (Fig. 99-9). False-negative findings occur when the testicle is examined early in the course of the disease, when blood flow is still present, and with intermittent torsion. Examination of the spermatic cord for twisting, instead of the testicle itself, has been shown to reduce the frequency of these false negatives. Color Doppler techniques can improve the specificity of ultrasound imaging to 100% by demonstrating reduced blood flow to the affected testicle. Doppler studies can be more difficult to interpret in younger boys because blood flow is physiologically low in the testicles of prepubertal boys. As many

Table 99-6 Differentiation among Causes of the Acute Scrotum

FEATURE	TESTICULAR TORSION	APPENDIX TORSION	EPIDIDYMITIS
Age	<1 yr, puberty	7-14 yr	Adult
Onset	Hours	1-2 days	Days to weeks
Location of pain	Entire testicle	Upper pole	Epididymis
Systemic symptoms	Nausea	None	Fever
Cremasteric reflex	No	Intact	Intact
Pyuria	Rare	No	Yes
Ultrasound findings	Diffusely hypoechoic Asymmetrical testicles Normal or decreased flow Spermatic cord knot	Focally hypoechoic Symmetrical testicles Normal flow	Hypoechoic epididymis Symmetrical testicles Increased flow
Treatment	Surgery	Supportive	Antibiotics; prepuberty: supportive only

Note: No single finding in patients with an acute scrotum can reliably differentiate torsion from other causative disorders. When torsion is a diagnostic possibility, prompt urology consultation is mandatory.

www.ketabpezeshki.com 66485457-66963820

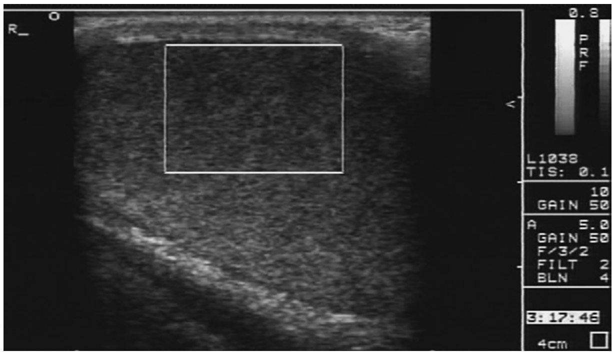


Figure 99-9. Doppler ultrasound image showing a testicle with no flow as a result of torsion. (From Blaivas M, Brannam L: Testicular ultrasound. In Rosen C, Wolfe R [eds]: Ultrasound in Emergency Medicine. Emerg Med Clin North Am 22:730, 2004 [Figure 7].)

as 50% of boys younger than 8 years do not show intratesticular flow.[55] This hypovascularity can result in false-positive diagnoses, which could potentially lead to unnecessary surgical exploration. Comparison with the contralateral testicle can help avoid this misdiagnosis, as in normal patients, blood flow to the two testicles will be similar.

The color Doppler appearance of the testicle depends on the degree of twisting of the spermatic cord. With 180 degrees or less of twisting of the cord, venous flow from the testicle ceases but arterial flow persists. This leads to edema of the testicle on ultrasound that can be misinterpreted as inconsistent with torsion. Although technically more difficult to perform, direct visualization of the spermatic cord for torsion can prevent this misdiagnosis. With torsion, this should reveal a knot in the spermatic cord above the testis, often referred to as a "snail shell" or "whirlpool." A study of 919 children found this sign had a sensitivity and specificity close to 100%. In contrast, with more than 180 degrees of twisting of the cord, arterial flow also ceases, leading to a lack of Doppler signal on ultrasound.[55]

Parenchymal echo texture on ultrasound may help predict the viability of the testicle. Homogenous echo texture of the parenchyma has been associated with higher likelihood of testicular salvage. A retrospective review of 25 cases of testicular torsion found a zero recovery rate in testes with heterogeneous echogenicity.[56] In the future, parenchymal appearance may help determine patients who are appropriate candidates for emergent surgery.

Color Doppler ultrasound imaging has the advantage of being an inexpensive, rapid test, readily performed in the ED setting. It is helpful when it demonstrates torsion in cases with equivocal findings on the history and physical examination, but it does not have sufficient sensitivity to rule out a diagnosis of torsion. A recent analyses of 669 scrotal ultrasounds revealed a 98% negative predictive value for torsion.[57] A urologist should evaluate any patient in whom ultrasound findings are negative but history and physical findings are suggestive of torsion. Moreover, ultrasound examination should never delay evaluation by a urologist in any patient with probable torsion.

Radioisotope scanning has the advantage of improved sensitivity compared with ultrasonography, but it is a time-consuming test inappropriate for use in the ED.

Management. The first step in management of very strongly suspected testicular torsion is immediate consultation with a urologist. The longer the spermatic cord remains twisted, the lower the likelihood of testicular salvage. More than 90% of affected testicles can be saved within 6 hours of symptom onset, but by 24 hours, 100% are lost.[50] In addition, early consultation allows the urologist to accompany the patient to ultrasound—if imaging is obtained—where images can be reviewed in real-time with the radiologist. After consultation, intravenous access is established and analgesia is provided either systemically or with a block of the spermatic cord.

If the urologist is not readily available, then manual detorsion should be attempted as follows. The operator stands at the supine patient's feet and rotates the affected testicle away from the midline, as if turning the pages of a book. If this maneuver is successful, patients should report immediate improvement of symptoms. Most studies suggest that this technique untwists about one fourth of testicles under torsion; other studies, however, have achieved success rates as high as 80%. Some torsions involve rotation through 720 degrees, so continuing the untwisting maneuver past 360 degrees is recommended if no improvement is obtained initially, especially in cases in which torsion is strongly suspected. Analgesics should be administered before this procedure. Regardless of the outcome with manual detorsion, patients still require surgical evaluation. Often urologists will perform bilateral orchiopexy after successful manual detorsion, to prevent recurrence. In addition, evaluation by a urologist should never be delayed to perform this or any other test or maneuver.

Once the diagnosis of testicular torsion has been established, the clinician should determine if emergent removal of the torsed testicle is necessary. Many studies suggest that emergent surgical exploration is unnecessary when symptoms of testicular torsion persist beyond 24 hours because the testicle is not salvageable. Other studies suggest that persistence of symptoms beyond only 10 hours, combined with absence of flow on ultrasound, predicts irreversible testicular necrosis.[58] Unfortunately, in the ED it is difficult to know if torsion is complete, and with incomplete torsion, surgery can achieve salvage beyond 24 hours. In addition, surgical removal of the necrotic testicle reduces pain and the duration of other symptoms.[52] Therefore, emergency clinicians should not rely on the duration of symptoms to determine management; all patients require emergent urologic evaluation.

Disposition. Rapid diagnosis of testicular torsion is essential and should be followed by emergent surgical scrotal exploration and bilateral orchiopexy, if necessary. Loss of the testicle most commonly is a result of delay in seeking medical attention. However, almost 30% of cases of failed testicular salvage have been attributed to misdiagnosis, and another 13% to a delay in treatment after the proper diagnosis was established. Misdiagnosis nearly universally leads to orchiectomy and represents a common source of litigation.[59]

Torsion of Appendages of the Testis

Perspective. A normal scrotum has several vestigial appendages that also can twist and become ischemic, with resultant scrotal pain. This process is most common between 7 and 14 years of age, with a mean age of 10 years. In retrospective analyses, torsion of an appendage rivals testicular torsion as the most common cause of the acute scrotum.

Principles of Disease. The appendix testis, a remnant of the paramesonephric duct, is present in 92% of patients. It is located on the superior aspect of the testicle between the testis and the epididymis. The appendix epididymis, a remnant of the mesonephric duct, is the second most common testicular appendage, found in approximately 23% of patients. It typically is located on the tip of the epididymis (Fig. 99-10). These appendages are prone to torsion owing to their pedunculated shape. After several days of ischemia from torsion, they will undergo necrosis with eventual reabsorption. Their loss does not permanently affect fertility or have any impact on surrounding structures.

Clinical Features. As with testicular torsion, patients with torsion of an appendage complain of scrotal pain but report milder symptoms with a more gradual onset. These patients usually seek

www.ketabpezeshki.com 66485457-66963820

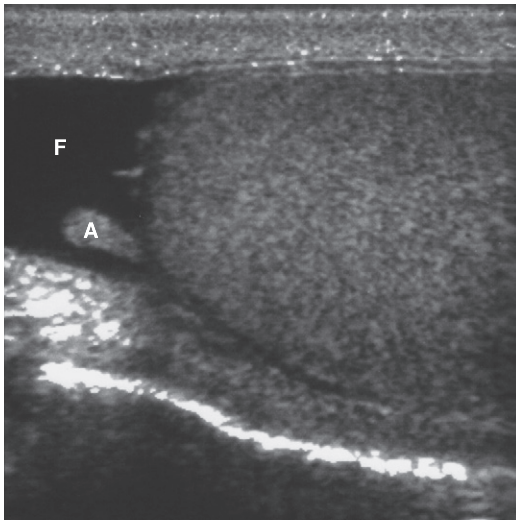


Figure 99-10. Ultrasound image showing the testicular appendage *(A)* surrounded by a hydrocele *(F)*. (From Blaivas M, Brannam L: Testicular ultrasound. In Rosen C, Wolfe R [eds]: Ultrasound in Emergency Medicine. Emerg Med Clin North Am 22:729, 2004 [Figure 6].)

medical attention in the ED later than patients with testicular torsion, commonly after 48 hours of symptoms. Also in contrast to testicular torsion, the pain often can be localized to one point on the testicle. These patients report nausea, vomiting, urinary symptoms, or previous episodes of similar pain less commonly than patients with testicular torsion.[52]

On physical examination, twisting of the appendix testis leads to formation of a hard, tender, 2- to 3-mm nodule at the upper pole of the testicle. Unlike in testicular torsion, the entire testicle is not tender. The testicle also does not change in overall size, and the scrotum typically does not swell until late in the disease process. The cremasteric reflex typically is intact. On transillumination, the ischemic appendage may appear as a blue dot. Although highly specific for torsion of the appendix, this sign is found in as few as 10% of patients. A reactive hydrocele can form during the course of disease, obscuring the physical findings.

Diagnostic Strategies. Urinalysis does not show evidence of infection. On ultrasound imaging, the appendix under torsion will appear hypoechoic. When the appendix then enlarges, the "Mickey Mouse" sign may be apparent on the transverse view, as a result of juxtaposition of the testicle, enlarged appendix, and epididymis. Color Doppler ultrasound can show decreased flow in both normal and torsed appendages. With torsion of the appendix, a hypoechoic spherical nodule with a diameter greater than 5 mm is present over the superior aspect of the testicle.[55]

Differential Considerations. Other diagnostic entities such as testicular torsion, epididymitis, and testicular tumor should be considered and excluded before a firm diagnosis of torsion of an appendage can be made.

Management and Disposition. If testicular torsion is ruled out, surgical excision of the appendix is rarely necessary. Treatment consists of scrotal support, ice, and NSAIDs. Resolution of symptoms can be expected within 7 to 10 days. Surgical excision is reserved for uncontrollable pain.

Epididymitis

Perspective. Epididymitis is the most common intrascrotal inflammatory disease. Nearly one half of the cases arise in young men aged 20 to 29 years, but the disease also has affected patients from 4 months to 76 years of age.[60] If untreated, it can lead to orchitis, testicular abscess, and rarely sepsis.

Principles of Disease. The epididymis is a tightly coiled tubular area along the posterior aspect of the testes, where sperm mature before their transit to the vas deferens. It becomes infected when organisms travel retrograde from the vas deferens. With infection, the testis may become edematous secondary to passive congestion and inflammation. Resolution of epididymitis typically concludes without sequelae, but rarely, men will develop infertility that persists after bacteriologic cure.

Pathophysiology. The particular organisms involved in the infection depend on the sexual activity of the patient. Although the literature classically describes men younger than 35 years of age as prone to *C. trachomatis* and *N. gonorrhoeae* infections, all sexually active men, regardless of age, are at risk for epididymitis from these organisms. *C. trachomatis* is much more common, being identified in 47% of patients younger than 35 years, with *N. gonorrhoeae* seen in 20%.[61] *Ureaplasma* also has been identified in patients with epididymitis, although whether it was the actual causative agent is unclear. In patients with syphilis, infection can spread to the epididymis during the secondary phase. In homosexual men who engage in anal intercourse, coliforms also can lead to sexually transmitted epididymitis.[61]

In men older than 35 years, urinary tract pathogens become the predominant cause of epididymitis. *E. coli* is the most common, occurring in 32 to 55% in this age group.[60] *Pseudomonas aeruginosa* and *Proteus mirabilis* also can infect the epididymis, and although much less common in the industrialized world, *M. tuberculosis* also has been implicated. In immunocompromised patients, fungal and other opportunistic infections have been reported.

Unlike younger patients, older men with epididymitis tend to have urinary tract abnormalities that predispose them to these infections of the epididymis. In one review, over half of men older than 60 years with epididymitis had lower urinary tract obstruction.[62] Older men also are more likely to have undergone recent genitourinary instrumentation, another risk factor for epididymitis. This includes hernia repair, which often can lead to iatrogenic infection of the nearby spermatic cord and epididymis. Acute or chronic prostatitis also may increase the risk of epididymitis. Finally, several authorities have suggested a possible association between indwelling catheters and epididymitis. Each of these factors renders older men prone to epididymitis after they are no longer sexually active.

Epididymitis also occurs in children. Historically, epididymitis was considered uncommon in prepubertal children, but it has been increasingly identified in this age group.[63] In children, epididymitis is most commonly idiopathic, although children can also have congenital genitourinary anomalies that predispose them to recurrent infection. The most commonly associated abnormality is neurogenic bladder, which produces increased pressure during urination and reflex into the ejaculatory ducts. In contrast to older children, in infants, bacterial causes are more common.

Amiodarone also has been implicated as a cause of epididymitis, with nearly 20 case reports in the literature. One study has suggested that amiodarone-induced epididymitis may be more common, arising in as many as 3 to 11% of patients receiving this agent. The effect is dose dependent, typically occurring after at least 4 months of treatment and with doses of 400 mg or more per day.[64] Amiodarone concentrates in the testicle, resulting in lymphocytic infiltration and epididymal fibrosis. Unlike with infectious epididymitis, patients do not have fever, pyuria, or leukocytosis.

Clinical Features. Patients with epididymitis experience scrotal pain of gradual onset, prompting them to come to the ED later in the clinical course than patients with torsion, whose symptoms tend to be more abrupt in onset. Initially, this pain may reside in

www.ketabpezeshki.com 66485457-66963820

the lower abdomen or flank, caused by inflammation of the vas deferens. In patients with STDs, urinary symptoms and urethral discharge are found in 10 to 30%. Nearly three fourths of patients report fever.[65] In the early stages of the disease, tenderness is localized to the epididymis, but it quickly spreads to the ipsilateral testicle. Later in the course the scrotum can become edematous, erythematous, and extremely tender. Although Prehn's sign—decrease in pain with elevation of the scrotum—has been touted as indicative of epididymitis, it has low sensitivity and specificity. Similarly, only 10% of patients with epididymitis from sexually transmitted organisms have urethral discharge on examination. None of these historical factors or physical findings have been shown reliably to differentiate torsion from epididymitis.

Diagnostic Strategies. Urinalysis typically demonstrates evidence of infection, with the finding of pyuria in 50 to 93% of patients with epididymitis (defined as the presence of more than four leukocytes per high-power field).[66] If patients are at risk for STD, a urethral swab or urine sample should be obtained to test for *C. trachomatis* and *N. gonorrhoeae;* polymerase chain reaction (PCR) and other nucleic acid amplification tests have the greatest sensitivity and should be used when available. Studies suggest that this diagnostic regimen is underused, with less than 35% of adults with epididymitis undergoing testing for STDs.[67]

The literature also describes epididymal aspiration, but this diagnostic modality has no role in the ED. It is difficult to use, and studies suggest that all patients with positive epididymal cultures have positive urine cultures. Systemic leukocytosis may be present but is a nonspecific finding and does not differentiate epididymitis from torsion. In prepubertal children, urinalysis and urine culture rarely are positive; a retrospective review of 151 children with epididymitis demonstrated bacteriuria in only one patient.[68] Nevertheless, in these patients, urine cultures should still be obtained to rule out bacterial infection, because untreated bacterial infections may lead to long-term complications.

In patients with an equivocal presentation for epididymitis versus testicular torsion, testicular ultrasound examination should be performed in the ED as rapidly as possible. As noted earlier, historical and physical examination features and laboratory results cannot reliably distinguish torsion from epididymitis or other diseases. With inflammation, the epididymis appears enlarged and hypoechoic (Fig. 99-11). On color Doppler ultrasound images, the affected testicle will show increased vascularity. These findings are 70% sensitive and 88% specific for epididymitis and can help differentiate the condition from torsion.[69] However, a minority of patients with torsion have preserved flow that can appear similar to epididymitis. In these cases, the presence of a spermatic cord knot, indicative of torsion, should be sought.

Finally, prepubertal children with recurrent epididymitis should undergo renal ultrasound and cystography to identify any potential underlying urinary tract abnormalities. These are important to identify to reduce the risk of future inflammation.

Differential Considerations. Three intrascrotal processes are commonly confused with epididymitis: torsion, torsion of the testicular appendage, and tumor of the testicle. Epididymitis is the most common misdiagnosis in patients with torsion, and this error can lead to loss of the testicle.

Management. Empirical antibiotics should be selected in accordance with the patient's age, sexual history, and any previous genitourinary instrumentation (Table 99-7). In patients with a suspected sexually acquired infection, ceftriaxone 250 mg intramuscularly (IM) should be given to treat possible *N. gonorrhoeae* infection. In conjunction, doxycycline 100 mg PO twice daily for 10 to 14 days should be started to treat *C. trachomatis* or *Ureaplasma urealyticum* infection. Although this regimen has never been studied in patients with chlamydial epididymitis, it is presumed to be more successful than the single-dose azithromycin that is used for uncomplicated urethritis. Treatment of sexual partners should be arranged even if the partner's culture demonstrates no growth because female partners of men with epididymitis often harbor *C. trachomatis* infection, including partners of men with negative culture results. A recent retrospective review suggests that only 50% of patients 18 to 35 years of age receive appropriate antibiotic treatment for sexually transmitted causes of epididymitis.[67]

In patients with infection by urinary tract pathogens, ciprofloxacin 500 mg PO twice daily has been shown to be the most successful regimen, with 80% of patients cured after 14 days of treatment. Ofloxacin 200 mg PO twice daily for 14 days is an

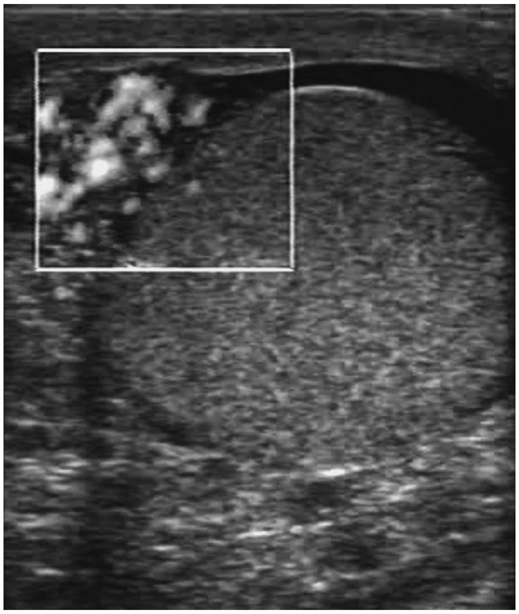


Figure 99-11. Ultrasound of the testicle showing an enlarged epididymis and increased blood flow on Doppler ultrasound imaging *(white box).* (From Blaivas M, Brannam L: Testicular ultrasound. In Rosen C, Wolfe R [eds]: Ultrasound in Emergency Medicine. Emerg Med Clin North Am 22:741, 2004 23 [Figure 23].)

Table 99-7 Treatment of Epididymitis

DRUG OF CHOICE	DOSE AND ROUTE	ALTERNATIVE REGIMEN(S)
Presumed Sexually Acquired Epididymitis		
Ceftriaxone	250 mg IM	Ciprofloxacin 500 mg PO Ofloxacin 400 mg PO
followed by		
Doxycycline	100 mg PO bid × 10 days	
or		
Tetracycline	500 mg qid × 10 days	
Presumed Nonsexually Acquired Epididymitis*		
Trimethoprim-sulfamethoxazole	One double-strength tablet PO bid × 14 days	Ciprofloxacin 500 mg PO bid × 14 days Ofloxacin 400 mg PO bid × 14 days
Prepuberty		
Supportive care only		Obtain urine culture and administer antibiotics only if culture positive

IM, intramuscularly; *PO,* orally.
*Adjust antibacterial therapy according to results of urine culture.

www.ketabpezeshki.com 66485457-66963820

alternative that also will cover sexually transmitted organisms and therefore is the ideal treatment when it is unclear if a patient has sexually acquired or urinary tract pathogens. Treatment can later be adjusted in accordance with the results of the patient's urine culture. In addition to appropriate antibiotics, bed rest, scrotal support, analgesics, sitz baths, and ice packs may be beneficial. A urologist can block the spermatic cord with bupivacaine to provide pain relief. This maneuver also appears to hasten the healing process, perhaps by increasing blood flow to the spermatic cord that was anesthetized. On discharge the patient should be referred to a urologist for follow-up evaluation within 1 week.

In prepubertal boys in whom an idiopathic cause is suspected, antibiotics are not routinely recommended. This contrasts with prior teaching and practice; previously over 90% of boys received antibiotics.[69] Urine cultures should be obtained for these boys, and only if the cultures reveal bacteria should antibiotic therapy be initiated. This graduated treatment approach is supported by studies showing that most epididymitis in boys is idiopathic.[69] Boys should limit activity, elevate the scrotum with ice packs, and reduce inflammation with NSAIDs. In contrast, infants often have bacterial epididymitis and should be treated empirically with antibiotics pending urine culture results.

Typically, symptoms resolve in 2 weeks in patients with sexually acquired disease and in 4 weeks in patients with urinary tract pathogens.[61] Complications are more common in older men, occurring in 39% of patients, and include intratesticular and epididymal abscess, testicular infarction, and late testicular atrophy. In adolescents, infection often reduces spermatogenesis, but the long-term effect on fertility is unclear. Finally, prepubertal children are at risk for developing testicular abscess, necrosis, and infertility.[68]

Disposition. Patients with systemic signs of toxicity (fever, chills, nausea, vomiting) or complications of acute epididymitis should be hospitalized and treated with parenteral antibiotics. Well-appearing patients with uncomplicated epididymitis can be discharged from the ED and should be reassessed within 1 week to ensure that their symptoms are resolving. Spread of infection, continued scrotal edema, ongoing testicular pain, and scrotal wall fixation are indications that outpatient management has failed, and hospitalization and emergent urologic evaluation are required to rule out an alternate diagnosis such as testicular torsion or scrotal abscess. Prepubertal children with evidence of bacterial infection require outpatient urologic evaluation owing to a high incidence of genitourinary tract abnormalities.

Testicular Tumors

Perspective. Tumor of the testis is the most common malignancy in young men but accounts for only 1% of all cancers in men. These tumors are more common in infertile patients and whites. They also occur with increased frequency in the nondescended and descended testicles of patients with cryptorchidism. A number of simplified classification systems have been proposed for categorizing the different types of testicular tumors. Approximately 95% of tumors are germ cell tumors, with half of these being seminomas and the other half being mixed types, including teratomas, choriocarcinomas, and yolk sac tumors. The other 5% of testicular tumors are sex cord stromal tumors. The disease course will depend on the type of tumor present as well as the age of the patient.

Clinical Features. Unlike in torsion and epididymitis, patients with tumor typically have a painless scrotal mass. When pain develops, it most often is from acute hemorrhage within the tumor pushing against the nonpliable tunica albuginea. Presence of pain should be considered unusual with testicular tumor, and in such cases, torsion and epididymitis should be ruled out before a diagnosis of malignancy is considered. Unlike other painless scrotal masses, such as hydroceles and varicoceles, tumors cannot be separated from the underlying testicle. Palpable tumors are more likely to be malignant compared with tumors identified only with imaging. Patients with tumor also can have symptoms related to metastases from a previously undiagnosed testicular cancer; 15% of patients have metastases to regional lymph nodes at the time of diagnosis, and 5% have metastases to the abdomen or pelvis.

Diagnostic Strategies. All patients with a scrotal mass should undergo a scrotal ultrasound examination. This study can reveal a concomitant hydrocele or a homogeneous hypoechoic lesion. Intratesticular tumors are typically hypervascular with irregular branching vessels. Leydig cell tumors are unique, because they show hypervascularity around the lesion but no internal color Doppler flow. Although helpful for staging purposes, CT scans of the chest and abdomen are necessary in the ED only if the patient has complaints related to these parts of the body. Urinalysis findings typically are normal.

Management. Suspicion of a testicular tumor is an indication for urgent referral to a urologist because radical orchiectomy with high ligation of the spermatic cord may be required. The radiosensitive nature of seminomas renders the combined treatment of orchiectomy and radiation therapy highly successful for early-stage disease. The ultimate treatment strategy, however, should be determined by a urologist. Any patient with systemic symptoms should be admitted to the hospital.

Orchitis

Perspective. Orchitis is a rare acute infection of the testis. It is most common in prepubertal boys, with viral infections such as mumps causing a majority of cases. Orchitis rarely develops in prepubertal boys with mumps but is more common in adolescent males with mumps. It tends to arise several days after the onset of parotitis. Although vaccination has significantly reduced the incidence of mumps infection, sporadic outbreaks have occurred. Infections in vaccinated individuals are increasingly common, presumably resulting from vaccine failure or antigenic differences between the infecting and vaccine strains.

Owing to the testes' relatively high threshold of resistance to infection, bacterial orchitis more commonly results from local bacterial spread from the epididymis. The most frequent bacterial pathogens are *N. gonorrhoeae, C. trachomatis, E. coli, Klebsiella,* and *P. aeruginosa.* These organisms tend to infect postpubertal males and men older than 50 years with benign prostatic hypertrophy (BPH).

Clinical Features. A patient with mumps orchitis has testicular pain and swelling that commonly begins 4 to 6 days after the onset of parotitis, although it can develop in the absence of parotitis. The clinical course varies, with adults having more severe symptoms. Clinical resolution generally occurs in 4 to 5 days. More than 50% of testes involved with mumps orchitis develop atrophy; however, this seldom results in infertility.

Patients with bacterial orchitis have fever and scrotal pain. They often have constitutional signs and symptoms including nausea, vomiting, myalgias, and malaise. The affected testicle (the disease is unilateral in 70% of patients) and the scrotum are swollen, tender, and erythematous.

Diagnostic Strategies. As with all causes of scrotal pain, the first priority is to exclude testicular torsion. If the patient clearly has mumps orchitis based on the clinical presentation and a history of preceding parotitis, then no other tests are necessary. For all other patients, urinalysis and urine culture should be performed. Patients in whom the diagnosis is unclear also should undergo color Doppler ultrasound examination to evaluate for torsion or concomitant epididymitis. On ultrasound, orchitis shows hypervascularity, commonly described as a "testicular inferno." Blood

www.ketabpezeshki.com 66485457-66963820

tests are typically not helpful, as false negatives are common with serologic testing, particularly in vaccinated individuals.

Management. In sexually active patients, ceftriaxone and doxycycline should be used as in epididymitis to cover *N. gonorrhoeae* and *C. trachomatis.* In older patients, fluoroquinolones provide the best coverage of gram-negative organisms. Treatment of viral orchitis is supportive only. Although steroids may improve symptoms, they can reduce testosterone levels. All patients should receive local scrotal care as described for epididymitis. Patients with marked pain, high fever, or constitutional symptoms merit hospitalization and parenteral antibiotics.

Testicular Trauma

The most concerning injury associated with trauma involves rupture of the testicle. The presentation can range from a large blood-filled scrotum to minimal swelling with mild pain of the testicle. If there is any concern for rupture, scrotal ultrasound is indicated. Disruption in the echogenic tunica albuginea is 100% sensitive and 65% specific for rupture.[70] Surgical intervention is associated with higher rates of testicular salvage. Hematomas can also form in the testicle without overt rupture. Similar to rupture, these require surgical evaluation unless the tunica albuginea is intact. Trauma can also result in formation of a hematocele with blood accumulating within the tunica vaginalis. This often leads to ecchymosis of the scrotal wall. Ultrasound can also identify this condition. Lacerations of the scrotum that do not violate the dartos fascia can be repaired in the ED.

Inguinal Hernia, Acute Hydrocele, Varicocele, and Spermatocele

Inguinal hernias, hydroceles, varicoceles, and spermatoceles are reasonable considerations in the differential diagnosis of an acute scrotal mass. These clinical entities are typically painless and readily identifiable on physical examination. Most children with inguinal hernias will not have any palpable mass on examination but will report a history of intermittent bulge in the groin that appears with straining or crying. Less commonly an inguinal mass is palpable, and it may extend into the scrotum. If this mass becomes incarcerated, it will be tender, and often the overlying skin will be edematous and erythematous. Children typically will develop irritability, vomiting, or abdominal distention. Incarcerated hernias should be reduced promptly to prevent bowel infarction from strangulation. Reduction can be accomplished by applying gentle pressure to expel the gas and stool in the bowel from the hernia. Pressure is then applied over the distal aspect of the hernia to reduce the bowel. If this technique fails, which is more likely in younger children with prolonged symptoms, then the patient should be placed in the Trendelenburg position, ice applied to the groin, and surgery consulted. After reduction of an incarcerated hernia, children typically require hospitalization and delayed surgical repair. In contrast, acute hydroceles typically are benign, are localized to the scrotum, and transilluminate. Varicoceles are enlarged spermatic cord veins that typically are painless or cause only minimal discomfort. On examination, they are often described as feeling similar to "a bag of worms" just superior to the testicle and decrease in size when the patient is supine. In contrast, a spermatocele is a sperm-containing cyst that is palpated as a nontender mass posterior to the testicle. Ultrasound is diagnostic of both conditions. No emergent treatment is necessary, but patients require outpatient urologic evaluation.

Regardless of the cause of the scrotal swelling, it remains crucial to rule out concomitant pathology by assessing the testicle thoroughly, as each of these conditions is often identified in patients with torsion, epididymitis, and tumors.

ACUTE URINARY RETENTION

Perspective

Acute urinary retention (AUR) is the sudden inability to pass urine voluntarily. In contrast to patients with anuria, in which the kidneys fail to produce urine, patients with AUR have normal renal function but cannot pass urine and typically have a distended bladder. The lifetime risk of AUR increases with age: 10% of men in their 70s and 33% of men in their 80s have experienced AUR.[71] The retention most commonly is secondary to an obstructive lesion but also can be the presenting manifestation of other pathologic processes (Box 99-6). For example, in women it often develops from infrequent voiding leading to an atonic bladder. In younger patients, it often is suggestive of a serious underlying neurologic disease.

The most common cause of AUR seen in the ED is obstruction of the urinary tract distal to the bladder. In men, BPH is the typical precipitant, causing AUR in 53% of patients.[72] Enlargement of the prostate coupled with constriction of the prostatic urethra from heightened alpha-adrenergic tone obstructs urinary output. Prostate cancer also can block the urethra by means of similar mechanisms, and urinary retention develops in 70% of patients with this cancer. Approximately 25% of men seen in the ED with AUR have prostate cancer, and often this cancer diagnosis was not known beforehand.[73] Strictures of the urethra can arise after trauma from manipulation with a Foley catheter, cystoscopy, previous infections, or radiation therapy. Such strictures may then lead to obstructed urinary outflow. Other, less common obstructive causes of AUR include phimosis (inability to retract the foreskin over the glans penis) and paraphimosis (inability to reduce the foreskin over an edematous glans).

In women, the most frequent causes of obstructive AUR are pelvic masses and prolapse of pelvic organs such as the bladder, rectum, or uterus. These structures compress the urethra, thereby creating AUR. In both sexes, bladder neoplasms, fecal impaction,

Box 99-6 Causes of Acute Urinary Retention in Adults

Penis
Phimosis
Paraphimosis
Meatal stenosis
Foreign body constriction

Urethra
Tumor
Foreign body
Calculus
Urethritis (severe)
Stricture
Meatal stenosis (female)
Hematoma

Prostate Gland
Benign prostatic hypertrophy
Carcinoma
Prostatitis (severe)
Bladder neck contracture
Prostatic infarction

Neurologic Causes
Motor Paralytic
Spinal shock
Spinal cord syndromes

Sensory Paralytic
Tabes dorsalis
Diabetes
Multiple sclerosis
Syringomyelia
Spinal cord syndromes
Herpes zoster

Drugs
Antihistamines
Anticholinergic agents
Antispasmodic agents
Tricyclic antidepressants
Alpha-adrenergic stimulators
"Cold tablets"
Ephedrine derivatives
Amphetamines

Psychogenic Problems
Psychodynamic stressors such as lazy bladder syndrome

From Sacknoff EJ, Dretler SP: Urologic emergencies. In Wilkins E [ed]: MCH Textbook of Emergency Medicine. Baltimore, Williams & Wilkins, 1978.

www.ketabpezeshki.com 66485457-66963820

Table 99-8 Presentation and Diagnosis of Acute Urinary Retention

CAUSE	HISTORY	PHYSICAL EXAMINATION FINDINGS	DIAGNOSIS*
Benign prostatic hypertrophy	Frequency, urgency, hesitancy Prior retention	Enlarged, firm prostate	UA
Prostate cancer	Frequency, urgency, hesitancy Previous retention Constitutional symptoms	Enlarged, firm prostate Nodular prostate	UA
Phimosis, paraphimosis	Penile pain	Nonretractable foreskin Edematous penis	Clinical only
Prostatitis	Dysuria, frequency, urgency Fever, chills	Warm, tender, boggy prostate Penile discharge	UA Urine culture
Urethritis, vulvovaginitis	Dysuria, frequency, urgency Itching	Discharge	UA Urine culture Urethral or cervical culture
Pelvic mass	Pelvic pain pressure	Prolapse of rectum, bladder, uterus	UA Ultrasound imaging, CT
Neurogenic bladder	Other neurologic complaints	Neurologic deficits	UA CT, MRI

CT, computed tomography; *MRI,* magnetic resonance imaging; *UA,* urinalysis.
*In the emergency department setting, each of these diagnoses is made primarily by the history and findings on the physical examination. Additional tests are needed as described.

GI masses, foreign bodies, or stones can block urine outflow. Finally, congenital posterior urethral valves are the most common source of AUR in children.

Infection also can cause AUR and should be considered in the differential diagnosis, because treatment of the condition through placement of a catheter will correct the retention but not the underlying infection. The most common infectious causative disorder is acute prostatitis, which usually is a result of infection of the prostate by *E. coli* or *P. mirabilis.* The resulting edema causes AUR, particularly in the setting of BPH or other underlying prostatic disease. Similarly, urethritis from a UTI or sexually transmitted infection can obstruct the urethra, and in women vulvovaginitis also can produce enough urethral edema to create AUR. In Elsberg syndrome, genital herpes involving the sacral nerves leads to AUR. Finally, in pediatric patients UTIs can induce sufficient dysuria that the child refuses to void, with consequent urinary retention.

Pharmacologic agents have been associated with AUR. Anticholinergic agents inhibit detrusor muscle contraction, whereas sympathomimetic agents increase α-adrenergic tone in the prostate. In addition, NSAIDs may inhibit prostaglandin-mediated detrusor muscle contraction, leading to a twofold increase in risk of AUR in men taking these drugs.[74]

Although less common in older patients, neurogenic causes of AUR constitute an important etiologic category. Upper motor neuron lesions create bladder spasticity through a deficit above the micturition center in the sacral cord. They result from spinal cord and cortical lesions caused by multiple sclerosis, trauma, Parkinson's disease, stroke, or neoplasms. Lower motor neuron deficits produce bladder flaccidity with lesions below S1. Such lesions typically are associated with spinal cord tumors, epidural abscesses, spinal trauma, Guillain-Barré syndrome, tabes dorsalis, and multiple sclerosis. Peripheral nerve lesions also can cause AUR. Diabetic peripheral neuropathy is the most commonly encountered peripheral lesion and occurs in 45% of patients with diabetes mellitus.[75]

Numerous alternate causes for AUR are recognized, as listed in Box 99-6. They include intervertebral disk herniation, recent surgery, and psychogenic causes. In the ED these are encountered much less frequently than the aforementioned disorders. Psychogenic urinary retention also is rare and is a diagnosis of exclusion made only after appropriate studies of bladder function have been performed by a urologist.

Box 99-7 Symptoms of Urinary Retention

Obstructive Symptoms

Urinary hesitancy
Straining to void
Decrease in size and force of urinary stream
Interruption of urinary stream
Sensation of incomplete emptying
Previous episode of urinary retention

Irritative Symptoms

Urinary frequency
Urinary urgency
Dysuria (usually secondary to infection)
Nocturia or nocturnal incontinence

Adapted from Lapides J: Fundamentals of Urology. Philadelphia, WB Saunders, 1976.

Clinical Features

Although the potential causes of AUR are many, the history and physical examination can considerably narrow the scope of the differential diagnosis (Table 99-8). Patients with AUR report sudden pain and have a distended bladder that is tender to palpation (Box 99-7). With lesions proximal to the bladder, patients typically note pain in the flank, whereas lesions distal to the bladder can produce pain radiating to the scrotum or labia. This pain is often quite severe, leading to significant distress. By contrast, with slowly developing or chronic obstructions, patients typically are older with multiple comorbid conditions; they have overflow incontinence and report little to no pain.

When obstruction is the cause of AUR, the patient often will recall multiple previous episodes of urinary retention. In addition to this history, patients with BPH report frequency, urgency, hesitancy, nocturia, difficulty initiating the urinary stream, decreased force of the stream, a sensation of incomplete voiding, and terminal dribbling. The prostate is enlarged, firm, and non-nodular.

www.ketabpezeshki.com 66485457-66963820

Normal findings on the prostate examination do not exclude BPH. Patients with prostate cancer can have similar symptoms, but these often are accompanied by weight loss, bone pain, and other constitutional signs and symptoms. These patients generally will have an enlarged, nodular prostate. Examination of the penis also is crucial in men because phimosis will reveal edema of the penis with a nonretractable foreskin. In women with obstruction, pelvic pain and pressure are symptoms commonly associated with AUR. A prolapsed bladder, rectum, or uterus and enlarged ovaries or uterus can be identified on pelvic examination.

Patients with an infectious cause for their symptoms often complain of dysuria, frequency, urgency, hematuria, fever, chills, and low back pain. In acute prostatitis these symptoms can be associated with penile discharge and a tender, warm, and boggy prostate. Despite the obstruction, the patient may nevertheless be able to void small amounts of urine. In vulvovaginitis and urethritis, presenting complaints also may include discharge and pruritus.

Patients with a neurogenic cause for AUR may already have a history of neurologic disease. They require a thorough neurologic examination, focusing on strength, sensation, and reflexes in the lower extremities, for which innervation is similar to that of the bladder. The status of the bulbocavernosus reflex, anal reflex, sphincter tone, and perineal sensation also should be assessed.

Diagnostic Strategies

The only two suggested procedures in the ED for AUR are placement of a Foley catheter and a urinalysis. The urinalysis can reveal infection, whereas presence of hematuria suggests infection, tumor, or calculi. Patients with hematuria require follow-up because the bleeding can arise from prostatic obstruction alone or may have other, more serious causes such as bladder cancer. A basic chemistry panel for assessment of renal function should be obtained only when renal damage or hydronephrosis is a concern. Historically, it was believed that the significant pain associated with AUR prompts patients to come to the ED readily before their creatinine elevates. However, a recent study of patients in the ED with AUR revealed that 24% of patients had an elevated creatinine on presentation and 7% had persistent elevations 1 month later.[76]

Imaging studies are indicated when patients have evidence of concomitant infection or neurologic deficits or when the diagnosis of AUR is unclear. With an equivocal history or physical examination, bedside ultrasound can confirm AUR. Renal and bladder ultrasound studies provide visualization of any obstruction, hydronephrosis, or other causes of upper urinary tract disease. Pelvic ultrasound examination and CT scan evaluate for masses or malignancy causing obstruction. Magnetic resonance imaging of the spine evaluates for disk herniation, cord compression, and cauda equina syndrome. Cystoscopy and retrograde cystourethrogram can depict problems in the lower urinary tract and usually are performed as outpatient procedures.

Several other tests described in the literature provide little benefit in the ED management of patients with AUR. Prostate-specific antigen (PSA) levels frequently are elevated in the setting of AUR, so a PSA assay will not help in differentiating cancer from other causes of retention. Similarly, alternate imaging modalities have rendered IVP unhelpful in the ED.

Management

Immediate placement of a 14F to 18F Foley catheter should provide decompression of the bladder. If this fails, placement of an elbowed catheter (coudé catheter) should be attempted; its curved and firm tip allows it to pass more easily across any obstruction. The curved tip of the coudé catheter should point cephalad during insertion. If both of these techniques prove to be unsuccessful, a urologist should be consulted unless the ED personnel are well versed in the use of filiforms, followers, and metal sounds because such instrumentation without the requisite degree of skill may result in serious tissue damage. In addition, if a patient recently underwent urologic surgery, urethral catheterization should not be performed.

When immediate bladder decompression is required and a urologist is not available or major urethral trauma is present, suprapubic bladder drainage should be performed. With use of ultrasound guidance and sterile technique, a 22-gauge spinal needle should be inserted two fingerbreadths above the symphysis pubis in the midline and directed toward the anus. This needle can be used to administer local anesthetic and should be advanced until urine is aspirated. Return of air suggests that the needle is in the bowel, and the needle should be retracted and moved more cephalad. Once the bladder has been located, the needle is left in place and the syringe is removed. A guidewire is then passed through the needle into the bladder, followed by removal of the needle. A 1-cm skin incision is made, and a dilator and sheath are inserted into the bladder. The guidewire and dilator are removed, and a Foley catheter can then be passed through the sheath. The Foley balloon is inflated and urine drained (Fig. 99-12). Alternatively, an open technique with a trocar can be used. Finally, bladder aspiration without placement of a catheter can also be performed as a temporizing measure pending urology consultation.

Historically, it has been recommended that initial drainage be limited to 1 L to prevent postobstructive diuresis and hypotension. Such postobstructive diuresis is uncommon after AUR. Moreover, limited drainage of the bladder can increase the risk of UTI. Therefore, complete drainage should be performed.

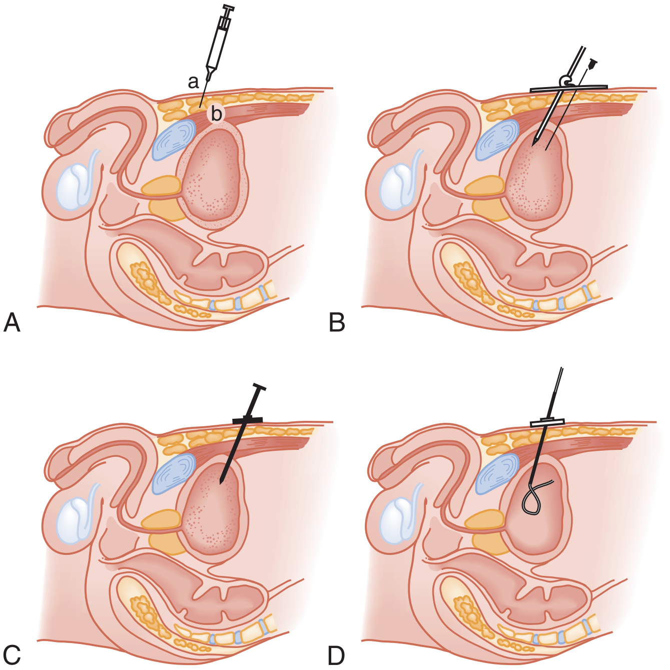


Figure 99-12. Cystostomy tube placement. **A,** Anesthetizing trocar tract. After a skin wheal *(a)* is raised, the suprapubic tract for the trocar is anesthetized, including the rectus fascia *(b)*. Anesthetizing until the bladder is penetrated will ensure total comfort for the patient during insertion of the trocar. **B,** Needle localization of the bladder. A spinal needle may be used even during insertion of the trocar to locate the bladder. **C,** Trocar position. The trocar is advanced until its sheath, as well as the point, is fully in the bladder. **D,** Tubing position. Enough tubing is inserted that it will not pull out of the bladder when the bladder empties. (From Robert JR, Hedges JR: Clinical Procedures in Emergency Medicine. Philadelphia, WB Saunders, 1985.)

www.ketabpezeshki.com 66485457-66963820

Complications

Catheterization has been associated with urethritis, cystitis, prostatitis, bacteremia, and sepsis. These infections are most common in patients with indwelling catheters and elderly debilitated female patients. For each day a catheter remains in place, there is an additional 4% risk of bacterial colonization of the bladder. Placement of a catheter also has been reported to cause postobstructive diuresis and hematuria. Such problems are believed to be related to rapid bladder decompression, so historically, gradual decompression has been recommended to prevent complications such as hematuria, hypotension, and postobstructive diuresis. Although hematuria occurs in 2 to 16% of patients after rapid bladder emptying, no major consequences from this bleeding have been documented.[77] Similarly, postobstructive diuresis can cause transient hypotension, but it is responsive to fluid administration. The side effects of rapid bladder decompression are rare; therefore all patients with AUR should undergo rapid, complete decompression of the bladder.

Rarely, chronic obstruction may lead to development of a salt-wasting nephropathy that requires treatment. The patient's urine output should be observed for 4 hours after catheterization. If output is greater than 200 mL/hour, the patient should be hospitalized for monitoring of blood pressure and sodium concentration.

Disposition

After bladder drainage, healthy and reliable patients can be safely discharged from the ED with an indwelling catheter and education about catheter management. Follow-up with a urologist should be arranged before the patient leaves. Patients with concomitant infection, significant comorbid illnesses, impaired renal function, neurologic deficits, or complications from catheterization require emergent urology consultation and probably admission.

Although the catheter is an inconvenience for the patient, and chronic use has been associated with UTI, trauma, stones, and urethral strictures, early removal of the catheter also is associated with heightened risk for recurrence of AUR. In a study of patients with suspected BPH, if the bladder was drained and a catheter was not left in place, recurrent AUR developed in 70%.[78] In patients in whom the catheter remained in place for 3 days, AUR developed in 49%, and when the catheter was in place for 7 days, AUR recurred in only 38% of patients.[79]

Studies also suggest that initiation of an alpha-adrenergic blocker, such as tamsulosin, at the time of catheter insertion improves the likelihood of spontaneous voiding after catheter removal. In addition, a recent Cochrane review suggests that alpha-blockers may also improve the likelihood that a patient will not require ongoing catheter placement; 48 to 62% of patients on alpha-blockers successfully completed a trial without a catheter, compared with 23 to 28% of patients not treated with alpha-blockers.[80] These medications should be provided only after consultation with the urologist or primary care physician because they increase the risk of orthostatic hypotension, particularly in the elderly. 5-Alpha-reductase inhibitors, another medication typically used for BPH, have not been shown to reduce recurrence of AUR.[81]

Prophylactic antibiotic therapy is not recommended in patients with AUR because although bacteriuria often develops in patients with indwelling catheters, it typically is asymptomatic. Antibiotics only promote resistance among these organisms.

Definitive therapy often requires surgical correction of any underlying obstruction. This should not be performed in the acute setting, as early surgery is associated with increased morbidity.

HEMATURIA

Perspective

Although hematuria is commonly encountered in the ED, the specific underlying disorder often is elusive. Most cases seen in the ED result from detection of asymptomatic microscopic hematuria, as an incidental finding noted on routine examination through microscopic or dipstick analysis of the urine. The bleeding typically is transient and not indicative of serious underlying pathology. After an uneventful workup, patients often are referred for outpatient evaluation; however, the cause of the hematuria remains unknown in 61% of patients evaluated with laboratory and imaging studies.[82] Less commonly, patients come to the ED complaining of gross blood in their urine. Unlike microscopic hematuria, gross blood in the urine often is the presenting symptom of an underlying malignancy. The risk of malignancy is greater in older patients; in those older than 60 years, gross hematuria has a positive predictive value for malignancy of 22.1% in men and 8.3% in women.[83] Regardless of age or visibility of blood in the urine, patients with hematuria require evaluation in the ED to rule out life-threatening diagnoses such as malignancy and abdominal aortic aneurysm.

Principles of Disease

Blood in the urine can be gross or microscopic. As little as 1 mL of whole blood in 1 L of urine can produce gross hematuria, turning the urine red. Multiple other substances and reactions can turn the urine red, and centrifugation of the urine and microscopic analysis differentiate these false positives from true hematuria. After centrifugation, the red color persists only in the urine sediment with hematuria. By contrast, a red supernatant appears bloody but contains no RBCs on microscopic analysis, and the cause typically is a benign condition (Box 99-8). The supernatant should be tested for heme, and if positive suggests hemoglobinuria or myoglobinuria. The supernatant will then contain heme in addition to a red coloring agent.

Microscopic hematuria is the presence of more than three to four RBCs per high-power field in clear urine. The particular cutoff for number of RBCs per high-power field used is arbitrary. Lower numbers of RBCs per high-power field decrease specificity but increase sensitivity, because significant disease can occur with as little as one RBC per high-power field. Urine dipstick testing increases sensitivity to 91 to 100% for the presence of blood, detecting one or two RBCs per high-power field. A negative urine dipstick rules out the presence of hematuria, and urine microscopy is then not necessary. However, the dipstick is less specific, with false positives occurring when sperm are present and with alkaline or extremely concentrated urine.[84] Accordingly, a positive result on urine dipstick testing should trigger at least reflex confirmation with microscopic analysis.

Bleeding from anywhere along the genitourinary tract can produce hematuria. In both the upper and lower portions of the urinary tract, infection, trauma, and renal calculi are the most

Box 99-8 Etiology of Red-Colored Urine without Hematuria

Phenazopyridine	Bromide
Nitrofurantoin	Food coloring
Rifampin	Beets
Chloroquine	Berries
Hydroxychloroquine	Rhubarb
Iodine	

www.ketabpezeshki.com 66485457-66963820

Box 99-9 Most Frequent Causes of Hematuria by Age and Gender

Age 0-20 Years
Acute UTI
Irritation of urethral meatus
Acute glomerulonephritis
Congenital urinary tract anomalies with obstruction

Age 20-40 Years
Acute UTI
Bladder cancer
Urolithiasis

Age 40-60 Years
Women
Acute UTI
Bladder cancer
Urolithiasis

Men
Acute UTI
Bladder cancer
Urolithiasis

Age 60 Years and Older
Women
Acute UTI
Bladder cancer

Men
Acute UTI
Benign prostatic hyperplasia
Bladder cancer

UTI, urinary tract infection.

common causative disorders. Patients also can have more serious causes of hematuria, such as malignancy or vascular lesions (e.g., abdominal aortic aneurysm), and these diagnoses should be excluded. Unfortunately, hematuria has poor specificity for malignancy; an analysis of 156,691 adults with hematuria revealed malignancy in only 0.7% of patients.[85] Malignancy was more common in patients older than 40 years (odds ratio [OR] 17), male patients (OR 4.8), and patients who had more than 25 RBCs per high-power field (OR 4.0). Other, less common risk factors for malignancy include cigarette smoking, occupational exposure to chemicals such as aniline dye and benzidine, and excessive use of analgesics. When another cause for the hematuria, such as UTI or stone, is identified in the ED, close follow-up is still necessary because patients with these risk factors often prove to have an underlying malignancy. In the upper urinary tract, the glomerulus is the most frequent source of bleeding, which may result from glomerulonephritis, immunoglobulin A (IgA) nephropathy, or nephritis. The common causes of hematuria are further divided by patient age and gender in Box 99-9.

Occasionally, hematuria also has been attributed to warfarin use, BPH, and exercise. Supratherapeutic anticoagulant therapy can lead to blood in the urine, but therapeutic anticoagulation does not produce spontaneous hematuria. The incidence of hematuria was not significantly different between controls and 243 patients followed prospectively while receiving warfarin.[86] Similarly, BPH can lead to increased vascularity of the prostate but does not increase the risk of hematuria. High-intensity exercise also can produce hematuria. This bleeding typically is transient and clinically inconsequential. However, a concomitant genitourinary tract lesion can be present, particularly if the bleeding persists for more than 72 hours after exercise. Because warfarin use, BPH, and exercise do not directly cause persistent hematuria, patients in whom these factors are present require evaluation identical to that for other patients.

Table 99-9 Timing of Blood Appearance during Micturition and Disease Location

TIMING OF BLOOD APPEARANCE	LOCATION OF LESION
Beginning of micturition	Urethra
Between episodes of urination	Urethral meatus Distal urethra
End of micturition	Bladder Prostatic urethra
Throughout urination episode	Bladder Ureter Kidney

In children, gross hematuria typically arises from UTI or benign causes such as irritation of the urethral meatus or hypercalciuria without nephrolithiasis.[87] However, when accompanied by trauma, edema, or hypertension, more serious causes should be considered such as rhabdomyolysis, tumors, glomerulonephritis, and hemolytic uremic syndrome.

Clinical Features

The timing and appearance of the blood in the urine can help narrow the scope of the differential diagnosis (Table 99-9). Repeated episodes of bleeding during and after menstruation in women suggests endometriosis of the urinary tract. Gross hematuria suggests lesions in the lower urinary tract. Passage of clots indicates a source below the kidney. Finally, passage of a large amount of congealed blood in the urine suggests malignancy of the kidney.

Several other historical factors also are associated with particular causes of hematuria (Box 99-10). A careful history will identify a benign cause for hematuria, such as menstruation, recent heavy exercise, or sexual activity, as well as the use of agents that can produce red urine without blood (see Box 99-8). Patients may report frequency, urgency, and dysuria in the setting of infection. They may note flank pain with urolithiasis or pyelonephritis. IgA nephropathy arises days after a viral respiratory infection, whereas poststreptococcal glomerulonephritis develops in children 1 to 2 weeks after skin or throat infections.

The physical examination is crucial in establishing the diagnosis. Hypertension occurs with glomerulosclerosis and, in the setting of peripheral edema, suggests nephrotic syndrome. Atrial fibrillation increases the likelihood of embolic disease and renal infarction. An abdominal bruit may be caused by an arteriovenous fistula, whereas a palpable abdominal mass may represent an abdominal aortic aneurysm. Flank pain and tenderness can arise with pyelonephritis or nephrolithiasis. The external genital examination can show evidence of trauma or a tumor, and in children often a reveals a rectal or vaginal source for the bleeding, such as urethral prolapse. It is also important to assess for hypertension and edema in children, which can arise with nephritis.

Diagnostic Strategies

A clean-catch or catheterized urine specimen should be obtained in all patients with hematuria. Catheterization itself induces hematuria in approximately 15% of patients, but the amount of bleeding is inconsequential, rarely exceeding three RBCs per high-power field.[88] Bedside urine dipstick testing of this urine should be performed. If positive for blood, then urine microscopy should be performed. Microscopy will reveal WBCs in addition to RBCs in the presence of infection. Proteinuria and RBC casts are seen with glomerular disease, and the urine is often brown or cola colored. Patients with these disorders do not require further

www.ketabpezeshki.com 66485457-66963820

Box 99-10 Medical History for Patients with Hematuria

- Exclude pseudohematuria—drugs, vegetable dyes, pigments
- Factitious—Munchausen syndrome, narcotic-seeking behavior
- Bleeding diathesis
- Clots—indicate nonglomerular bleeding; large, thick clots (bladder); small, stringy clots (upper tract)
- Gross hematuria—relationship to exercise, infection
- Relationship of gross hematuria to urinary stream—initial (urethra distal to the urogenital diaphragm), total (bladder proper or upper urinary tract), terminal (bladder neck or prostatic urethra)
- Painful hematuria—urinary tract infection or calculus, papillary necrosis, passage of clots, obstruction, loin pain—hematuria syndrome, glomerulonephritis
- Genitourinary history—flank trauma or pain frequency; nocturia; dysuria; previous stones, tissue passage, or infections; vaginal or penile discharge; sexual activity; presence of urinary catheter
- Relationship to menstruation—endometriosis
- Sickle cell disease or trait
- Medications
- Systemic symptoms—fever, rash, joint pain, weight loss
- Infectious cause—night sweats, sore throat, impetigo, recent tooth extraction or other invasive procedure, diarrhea, travel to areas endemic for *Schistosoma haematobium*
- Risk factors for urologic cancer—age older than 40 years, tobacco use, analgesic abuse, pelvic irradiation, cyclophosphamide, *S. haematobium,* occupational exposure to dyestuffs and rubber compounds
- Family history—hematuria, renal disease, sickle cell disease, deafness, bleeding diathesis
- Previous testing—blood pressure, urinalysis, serum chemistries, intravenous pyelogram
- Pregnancies—proteinuria, hypertension (with month of onset)

Box 99-11 Risk Factors Requiring Further Evaluation of Hematuria

Adults
Age older than 40 years
Cigarette smoking
Occupational exposure
Analgesic abuse
Persistent hematuria
Abdominal pain
Trauma

Children
Trauma
Hypertension
Edema
Proteinuria (>2+ on dipstick)
Signs of coagulopathy
Flank or abdominal pain

evaluation in the ED beyond the urinalysis and should be referred to a nephrologist. The exception is glomerular disease in children, which can produce substantial elevations in blood pressure and pulmonary edema with glomerulonephritis or anemia, thrombocytopenia, and renal failure with hemolytic uremic syndrome.

By contrast, any patients with gross hematuria or microscopic hematuria with risk factors for significant disease require thorough evaluation before discharge from the ED (Box 99-11). Renal function should be assessed to rule out the development of renal insufficiency. They also should undergo appropriate imaging tests, although clear consensus is lacking on the appropriate radiographic study. If findings fail to suggest a particular disorder as a cause for the hematuria, a CT scan with contrast or a renal ultrasound study should be performed. If the possibility of an occult stone is a concern, the CT scan should be ordered without contrast. CT scanning is highly sensitive for stones, masses, and other diseases of the upper urinary tract.[89] If contrast CT must be avoided owing to pregnancy, renal insufficiency, or a history of anaphylaxis to contrast medium, then ultrasound imaging is the modality of choice. Ultrasound is less sensitive than a CT scan for detecting stones, small masses, and traumatic causes of hematuria. Although it is not as sensitive as IVP for identifying lesions of the bladder and ureters, ultrasound does provide adequate visualization of the kidney. Ultrasound is the recommended imaging study in children with atraumatic hematuria because there is no radiation exposure and malignancy is less common.

CT is the appropriate imaging modality for both adults and children with traumatic hematuria. Its sensitivity and specificity exceed those of ultrasound. The exact level of hematuria that should trigger imaging is unclear, but it appears that patients without gross hematuria or evidence of coexisting abdominal or pelvic injuries are unlikely to have clinically significant injuries on CT.[90] In patients with hematuria and pelvic fractures, CT cystogram should also be performed to evaluate for bladder injury. In patients with blood at the urethral meatus or straddle injuries, a retrograde urethrogram should be obtained to evaluate for urethral injury. Historically, IVP was commonly used for the evaluation of hematuria in trauma, but its use now should be limited to unstable patients in whom CT is impractical.

IVP, angiography, retrograde pyelography, and cystoscopy should be reserved for outpatient evaluations, when diagnostic imaging in the ED with ultrasonography or CT shows no evidence of disease. Finally, urine cytology can increase the sensitivity of the diagnostic evaluation, particularly for bladder cancer.

Disposition

Patients younger than 40 years, with no risk factors for severe disease and an ED workup not revealing of a particular cause for their microscopic hematuria, can be discharged with outpatient follow-up to ensure resolution of the hematuria. Such transient hematuria is most commonly idiopathic but also can arise with infection, trauma, and exercise. By contrast, patients with known risk factors or gross hematuria require imaging in the ED. If findings on a subsequent workup are negative, urgent outpatient evaluation is essential because within 3 to 4 years a genitourinary malignancy will develop in 1% of older patients with initially negative findings on workup.[91]

KEY CONCEPTS

- Acute scrotal pain should be considered a result of testicular torsion until proven otherwise.
- No historical or physical examination findings accurately and reliably exclude testicular torsion, and therefore patients with concern for this diagnosis should undergo a scrotal ultrasound.
- Sexually active males should receive ceftriaxone and doxycycline to treat epididymitis, whereas in young children, antibiotics are not typically required.
- Scrotal pain or swelling after trauma warrants a scrotal ultrasound to evaluate for testicular rupture.
- Patients with acute urinary retention and concomitant infection or neurologic deficits warrant imaging in the ED.
- Patients with acute urinary retention should have complete drainage of the bladder performed via catheterization or, if this is not possible, by suprapubic bladder aspiration.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. American College of Obstetricians and Gynecologists: ACOG Practice Bulletin No. 91: Treatment of urinary tract infections in nonpregnant women. *Obstet Gynecol* 2008; 111:785-794.
2. Hooton TM, Besser R: Acute uncomplicated cystitis in an era of increasing antibiotic resistance: A proposed approach to empirical therapy. *Clin Infect Dis* 2004; 39:75.
3. Griebling TL: Urologic diseases in America project: Trends in resource use for urinary tract infections in men. *J Urol* 2005; 173:1288-1294.
4. Griebling TL: Urologic diseases in America project: Trends in resource use for urinary tract infections in women. *J Urol* 2005; 173:1281-1287.
5. Foxman B: Epidemiology of urinary tract infections: Incidence, morbidity, and economic costs. *Am J Med* 2002; 113:5S.
6. Baumer JH, Jones RW: Urinary tract infection in children, National Institute for Heal and Clinical Excellence. *Arch Dis Child Educ Pract Ed* 2007; 92:189-192.
7. Conway P, et al: Recurrent urinary tract infections in children: Risk factors and association with prophylactic antimicrobials. *JAMA* 2007; 298:179-186.
8. Nicolle LE: Catheter-related urinary tract infection. *Drugs* 2005; 22:627.
9. Nicolle LE, et al: Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis* 2005; 40:643.
10. Guay DR: Contemporary management of uncomplicated urinary tract infections. *Drugs* 2008; 68:1169-1205.
11. Kucheria R: Urinary tract infections: New insights into a common problem. *Postgrad Med J* 2005; 81:83.
12. Shaikh N, Morone NE, Bost JE, Farrell MH: Prevalence of urinary tract infection in childhood: A meta-analysis. *Pediatr Infect Dis J* 2008; 27:302-308.
13. Neal DE Jr: Complicated urinary tract infections. *Urol Clin North Am* 2008; 35:13.
14. Echevery G, Hortin GL, Rai AJ: Introduction to urinalysis: Historical perspective and clinical application. *Methods Mol Biol* 2010; 641:1-12.
15. Rabinovitch A: *Urinalysis and Collection, Transportation and Preservation of Urine Specimens: Approved Guideline*, 2nd ed. Wayne, Pa: National Committee for Clinical Laboratory Standards; 2001.
16. Andrews SJ, Brooks PT: Ultrasonography and abdominal radiography versus intravenous urography in investigation of urinary tract infection in men: Prospective incident cohort study. *BMJ* 2002; 324:4542.
17. Demertzis J, Menias CO: State of the art: Imaging of renal infections. *Emerg Radiol* 2007; 14:13.
18. Browne RF, Zwirewich C: Imaging of urinary tract infection in the adult. *Eur Radiol* 2004; 14(Suppl 3):E168.
19. Car J: Urinary tract infections in women: Diagnosis and management in primary care. *BMJ* 2006; 332:94-97.
20. Grabe M: *UTIs in renal insufficiency, transplant recipients, diabetes mellitus and immunosuppression*. In: Grabe M, et al, eds: *Guidelines on the Management of Urinary and Male Genital Tract Infections*. Arnhem, The Netherlands: European Association of Urology (EAU); 2008:52-63.
21. Zhan C, et al: Identification of hospital-acquired catheter-associated urinary tract infections from Medicare claims: Sensitivity and positive predictive value. *Med Care* 2009; 47:364-369.
22. Gokula RR, Hickner JA, Smith MA: Inappropriate use of urinary catheters in elderly patients at a midwestern community teaching hospital. *Am J Infect Control* 2004; 32:196-199.
23. McLaughlin SP, Carson CC: Urinary tract infections in women. *Med Clin North Am* 2004; 88:417.
24. Gupta K, Hooton TM, Stamm WE: Increasing antimicrobial resistance and the management of uncomplicated community acquired urinary tract infections. *Ann Intern Med* 2001; 135:41.
25. Wagenlehner FM, Weidner W, Naber KG: An update on uncomplicated urinary tract infections in women. *Curr Opin Urol* 2009; 19:368-374.
26. Committee on Infectious Diseases: The use of systemic fluoroquinolones. *Pediatrics* 2006; 118:1287.
27. Hua VN, Schaeffer AJ: Acute and chronic prostatitis. *Med Clin North Am* 2004; 88:2.
28. Wyllie MG: Promise for prostatitis? *BJU Int* 2005; 96:1137-1138.
29. Wagenlehner FME, Naber KG: Prostatitis: The role of antibiotic treatment. *World J Urol* 2003; 21:105.
30. Moe OW: Kidney stones: Pathophysiology and medical management. *Lancet* 2006; 367:333-344.
31. Pearle MS, Calhoun EA, Curhan GC: Urologic Diseases in America Project: Urolithiasis. *J Urol* 2005; 173:848.
32. Teichman J: Acute renal colic from ureteral calculus. *N Engl J Med* 2004; 350:684.
33. Hall PM: Nephrolithiasis: Treatment, causes, and prevention. *Cleve Clin J Med* 2009; 76:583-591.
34. Luchs JS, et al: Utility of hematuria testing in patients with suspected renal colic: Correlation with unenhanced helical CT results. *Urology* 2002; 59:839.
35. Pfister SA, et al: Unenhanced helical computed tomography vs. intravenous urography in patients with acute flank pain: Accuracy and economic impact in a randomized prospective trial. *Eur Radiol* 2003; 13:2513.
36. Ha M, MacDonald RD: Impact of CT scan in patients with first episode of suspected nephrolithiasis. *J Emerg Med* 2004; 27:225-231, 2004.
37. Abujudeh HH, et al: Abdominopelvic CT increases diagnostic certainty and guides management decisions: A prospective investigation of 584 patients in a large academic medical center. *AJR Am J Roentgenol* 2011; 196:238-243.
38. Dundee P, Bouchier-Hayes D, Haxhimolla H, Dowling R, Costello A: Renal tract calculi: Comparison of stone size on plain radiography and noncontrast spiral CT scan. *J Endourol* 2006; 20:1005.
39. Fowler KA, Locken JA, Duchesne JH, Williamson MR: US for detecting renal calculi with nonenhanced CT as a reference standard. *Radiology* 2002; 222:109.
40. Worster AS, Richards CG: Fluids and diuretics for acute ureteric colic. *Cochrane Database Syst Rev* 2005; 3:CD004926.
41. Larkin GL, Peacock WF 4th, Pearl SM, Blair GA, D'Amico F: Efficacy of ketorolac tromethamine versus meperidine in the ED treatment of acute renal colic. *Am J Emerg Med* 1999; 17:6.
42. Reference deleted in proofs.
43. Ferre RM, Vasielewski JN, Strout TD, Perron AD: Tamsulosin for ureteral stones in the emergency department: A randomized, controlled trial. *Ann Emerg Med* 2009; 54:432-439.
44. Hollingsworth JM, et al: Medical therapy to facilitate urinary stone passage: A meta-analysis. *Lancet* 2006; 368:1171.
45. Ye Z, et al: A multicentre, prospective, randomized trial: Comparative efficacy of tamsulosin and nifedipine in medical expulsive therapy for distal ureteric stones with renal colic. *BJU Int* 2011; 108:276-279.
46. Lewis AG, Bukowski TP, Jarvis PD, Wacksman J, Sheldon CA: Evaluation of acute scrotum in the emergency department. *J Pediatr Surg* 1995; 30:277.
47. Beni-Israel T, Goldman M, Bar Chaim S, Kozer E: Clinical predictors for testicular torsion as seen in the pediatric ED. *Am J Emerg Med* 2010; 28:786-789.
48. Cummings JM, Boullier JA, Sekhon D, Bose K: Adult testicular torsion. *J Urol* 2002; 167:2109.
49. Molokwu CN, Somani BK, Goodman CM: Outcomes of scrotal exploration for acute scrotal pain suspicious of testicular torsion: A consecutive case series of 173 patients. *BJU Int* 2011; 107:990-993.
50. Ringdahl E, Teague L: Testicular torsion. *Am Fam Physician* 2006; 74:1739.
51. Rabinowitz R: The importance of the cremasteric reflex in acute scrotal swelling in children. *J Urol* 1984; 132:89.
52. Waldert M, et al: Color Doppler sonography reliably identifies testicular torsion in boys. *Urology* 2010; 75:1170-1174.
53. Srinivasan A, Cinman N, Feber KM, Gitlin J, Palmer LS: History and physical examination findings predictive of testicular torsion: An attempt to promote clinical diagnosis by house staff. *J Pediatr Urol* 2011; 7:470-474.
54. Kravchick S, et al: Color Doppler sonography: Its real role in the evaluation of children with highly suspected testicular torsion. *Eur Radiol* 2001; 11:1000.
55. Dudea SM, Ciurea A, Chiorean A, Botar-Jid C: Doppler applications in testicular and scrotal disease. *Med Ultrason* 2010; 12:43-51.
56. Chmelnik M, Schenk JP, Hinz U, Holland-Cunz S, Günther P: Testicular torsion: Sonomorphological appearance as a predictor for testicular viability and outcome in neonates and children. *Pediatr Surg Int* 2010; 26:281-286.
57. Yagil Y, et al: Role of Doppler ultrasonography in the triage of acute scrotum in the emergency department. *J Ultrasound Med* 2010; 29:11-21.
58. Cimador M, DiPace MR, Castagnetti M, DeGrazia E: Predictors of testicular viability in testicular torsion. *J Pediatr Urol* 2007; 3:387-390.
59. Bayne AP, et al: Factors associated with delayed treatment of acute testicular torsion—do demographics or interhospital transfer matter? *J Urol* 2010; 184(4 Suppl):1743-1747.
60. Mittemeyer BT, Lennox KW, Borski AA: Epididymitis: A review of 610 cases. *J Urol* 1966; 95:390.
61. Berger RE, Kessler D, Holmes KK: Etiology and manifestations of epididymitis in young men: Correlations with sexual orientation. *J Infect Dis* 1987; 155:1341.

www.ketabpezeshki.com 66485457-66963820

62. Höppner W, Strohmeyer T, Hartmann M, Lopez-Gamarra D, Dreikorn K: Surgical treatment of acute epididymitis and its underlying diseases. *Eur Urol* 1992; 22:218.
63. Karmazyn B, Kaefer M, Kauffman S, Jennings SG: Ultrasonography and clinical findings in children with epididymitis, with and without associated lower urinary tract abnormalities. *Pediatr Radiol* 2009; 39:1054-1058.
64. Sadek I, Biron P, Kus T: Amiodarone-induced epididymitis: Report of a new case and literature review of 12 cases. *Can J Cardiol* 1993; 9:833.
65. Kaver I, Matzkin H, Braf ZF: Epididymo-orchitis: A retrospective study of 121 patients. *J Fam Pract* 1990; 30:548.
66. Hoosen AA, O'Farrell N, van den Ende J: Microbiology of acute epididymitis in a developing community. *Genitourin Med* 1993; 69:361.
67. Tracy CR, Costabile RA: The evaluation and treatment of acute epididymitis in a large university based population: Are CDC guidelines being followed? *World J Urol* 2009; 27:259-263.
68. Graumann LA, Dietz HG, Stehr M: Urinalysis in children with epididymitis. *Eur J Pediatr Surg* 2010; 20:247-249.
69. Santillanes G, Gausche-Hill M, Lewis RJ: Are antibiotics necessary for pediatric epididymitis? *Pediatr Emerg Care* 2011; 27:174-178.
70. Guichard G, et al: Accuracy of ultrasonography in diagnosis of testicular rupture after blunt scrotal trauma. *Urology* 2008; 71:52-56.
71. Fong YK, Milani S, Djavan B: Natural history and clinical predictors of clinical progression in benign prostatic hyperplasia. *Curr Opin Urol* 2005; 15:35-38.
72. Choong S, Emberton M: Acute urinary retention. *BJU Int* 2000; 85:186.
73. Curtis LA, Dolan TS, Cespedes RD: Acute urinary retention and urinary incontinence. *Emerg Med Clin North Am* 2001; 19:591.
74. Verhamme KM, et al: Nonsteroidal anti-inflammatory drugs and increased risk of acute urinary retention. *Arch Intern Med* 2005; 165:1547.
75. Sasaki K, Yoshimura N, Chancellor MB: Implications of diabetes mellitus in urology. *Urol Clin North Am* 2003; 30:1.
76. Shah K, et al: Can bedside ultrasound assist in determining whether serum creatinine is elevated in cases of acute urinary retention? *J Emerg Med* 2010; 39:198-203.
77. Nyman MA, Schwenk NM, Silverstein MD: Management of urinary retention: Rapid versus gradual decompression and risk of complications. *Mayo Clin Proc* 1997; 72:951.
78. Selius BA, Subedi R: Urinary retention in adults: Diagnosis and initial management. *Am Fam Physician* 2008; 77:643.
79. Djavan B, Larson TR, Blute ML, Marberger M: Transurethral microwave thermotherapy: What role should it play versus medical management in the treatment of benign prostatic hyperplasia? *Urology* 1998; 52:935.
80. Zeif HJ, Subramonian K: Alpha blockers prior to removal of a catheter for acute urinary retention in adult men. *Cochrane Database Syst Rev* 2009; 4:CD006744.
81. McConnell JD, et al: The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003; 349:2387-2398.
82. Khadra MH, Pickard RS, Charlton M, Powell PH, Neal DE: A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. *J Urol* 2000; 163:524.
83. Bruyninckx R, Buntinx F, Aertgeerts B, Van Casteren V: The diagnostic value of macroscopic haematuria for the diagnosis of urological cancer in general practice. *Br J Gen Pract* 2003; 53:31.
84. Sutton JM: Evaluation of hematuria in adults. *JAMA* 1990; 263:2475.
85. Jung H, et al: Association of hematuria on microscopic urinalysis and risk of urinary tract cancer. *J Urol* 2011; 185:1698-1703.
86. Van Savage JG, Fried FA: Anticoagulant associated hematuria: A prospective study. *J Urol* 1995; 153:1594.
87. Greenfield SP, Williot P, Kaplan D: Gross hematuria in children: A ten-year review. *Urology* 2007; 69:166-169.
88. Hockberger RS, Schwartz B, Connor J: Hematuria induced by urethral catheterization. *Ann Emerg Med* 1987; 16:550.
89. O'Connor OJ, Fitzgerald E, Maher MM: Imaging of hematuria. *AJR Am J Roentgenol* 2010; 195:W263-W267.
90. Raz O, et al: Use of adult criteria for slice imaging may limit unnecessary radiation exposure in children presenting with hematuria and blunt abdominal trauma. *Urology* 2011; 77:187-190.
91. Murakami S, Igarashi T, Hara S, Shimazaki J: Strategies for asymptomatic microscopic hematuria: A prospective study of 1,034 patients. *J Urol* 1990; 144:99.

www.ketabpezeshki.com 66485457-66963820

Chapter 100

Selected Gynecologic Disorders

Carrie D. Tibbles

PERSPECTIVE

Many women come to the emergency department (ED) with either pelvic pain or vaginal bleeding. After the possibility of pregnancy has been eliminated, a primary goal of the ED evaluation is to recognize the presence of a few conditions, such as ovarian torsion, also known as *adnexal torsion,* that warrant urgent intervention and others, such as new postmenopausal uterine bleeding, that require reliable outpatient follow-up. Most patients also benefit from relief of symptoms and reassurance. This chapter specifically addresses the ED management of ovarian torsion, ovarian cysts, abnormal uterine bleeding, and the provision of emergency contraception. Vaginal bleeding and pelvic pain in pregnant patients and gynecologic infections are discussed in other chapters.

OVARIAN TORSION

Principles of Disease

Ovarian torsion accounts for approximately 3% of gynecologic emergencies.[1] While ovarian torsion can occur in young girls[2] and is increasingly recognized in postmenopausal women, it is still most common in the reproductive years because of the regular development of a corpus luteal cyst during the menstrual cycle.[3] Ovarian torsion is typically caused by a twisting of both the ovary and the fallopian tube on the vascular pedicle.[4] Most cases of torsion (50-80%) are associated with an ovarian tumor, typically a benign neoplasm; with large, heavy cysts, as seen in ovarian hyperstimulation syndrome after in vitro fertilization; or with polycystic ovaries.[1] Torsion may be a complication of pregnancy.[5,6] Torsion of a normal ovary only rarely occurs.[7] A slight predominance of ovarian torsion on the right side has been noted. The reason for this predilection is unclear but may relate to the stabilizing effect of the sigmoid colon on the left side.[4] In ovarian torsion, venous and lymphatic obstruction occurs initially, with subsequent congestion and edema of the ovary, progressing to ischemia and necrosis and eventual infarction of the ovary[1] (Fig. 100-1). Thrombosis of the ovarian vein and artery can occur as well. The ovary is often salvageable if the diagnosis is made before thrombosis occurs.[4] Because of the dual blood supply of the ovary from both the uterine and ovarian arteries, complete arterial obstruction is rare[7] (Fig. 100-2).

Clinical Features

Ovarian torsion can often be challenging to diagnose, because the classic symptoms of severe, sharp unilateral abdominal pain and nausea may not be present.[5,6,8,9] The presence of known risk factors for ovarian torsion such as an ovarian mass or infertility treatments may suggest the diagnosis.[1] Because the presentation can be variable and often subtle, the diagnosis can be difficult to make. In 87 patients with surgically confirmed torsion, the diagnosis was missed on the first visit in almost half of the patients. Patients reported pain from several hours to weeks in duration, most likely from intermittent ischemia, and almost all had some pain on abdominal palpation. Nausea was a symptom in many of the patients. Other series report similar findings.[2-4,6,8]

Diagnostic Strategies

Laboratory Tests

No specific laboratory tests are helpful in the evaluation of a patient for suspected ovarian torsion, except for a pregnancy test to exclude ectopic pregnancy. A small percentage of patients may have an elevated white blood cell count above 15,000/μL,[5] but this is not a reliable indicator of ovarian torsion.[5,8]

Imaging

Ultrasonography. Ultrasound examination is the initial imaging test in the evaluation of patients with pelvic pain suggestive of ovarian torsion.[7] Enlargement of the ovary is the most common ultrasound finding,[4] but the ovary also may have an abnormal position relative to the uterus. Enlargement of an ovary with a heterogeneous stroma and small, peripherally displaced follicles is the classic ultrasound appearance of torsion but is often absent, particularly early in the presentation[4] (Fig. 100-3). The ultrasound study may reveal a mass in the ovary or evidence of hemorrhage[10] (Fig. 100-4). The ultrasound appearance of ischemia can vary depending on the duration of the symptoms.[11] Free pelvic fluid also may be seen.[7] Hemorrhagic cysts and non-neoplastic masses frequently are associated with torsion. These may have a fluid-filled cystic component, exhibit a complex pattern with debris and septations, or be visualized as a solid mass.[10] The characteristic appearance of torsion may be difficult to appreciate if the ovary is obscured by an associated mass.[7]

Doppler Ultrasound Examination. Doppler ultrasound findings are inconsistent in ovarian torsion.[7,12,13] Many cases of surgically proven torsion will have documented blood flow on Doppler examination because the ovary has a dual blood supply from both the ovarian and uterine arteries. Because the torsion may be intermittent, the findings may also vary depending on the time of the examination.[7] If a large mass is present, the examination may be technically difficult to perform.[9] Despite these limitations, the Doppler examination is still useful because detection of abnormal venous flow is particularly important in early cases of torsion[10]

www.ketabpezeshki.com 66485457-66963820

(Fig. 100-5). Visualization of the twisting of the pedicle and the coiled vessels is referred to as a "whirlpool sign."[14,15] Lee and colleagues report an 88% accuracy for torsion when the twisted pedicle or whirlpool sign is visualized.[16] In summary, the combination of ultrasound with Doppler studies is the initial study of choice in considering the diagnosis of ovarian torsion; however, it is important for the clinician to appreciate that many of the findings can be subtle and may be negative, particularly in early presentations.

Computed Tomography. When renal colic and appendicitis also are strong considerations in the differential diagnosis for acute pelvic pain, abdominopelvic computed tomography (CT) may be the best initial study, particularly in patients who have a presentation atypical for torsion.[17] In ovarian torsion, CT findings include fallopian tube thickening, smooth wall thickening of the associated adnexal mass, ascites, and uterine deviation to the twisted side[18,19] (Fig. 100-6). Associated hemorrhage in patients with hemorrhagic infarction can be seen. A retrospective review

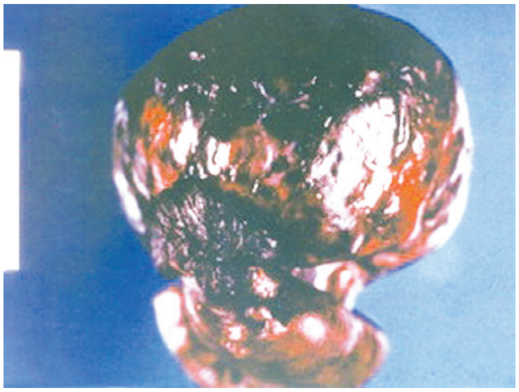


Figure 100-1. Pathology specimen demonstrating ovarian torsion. (From Andreotti RF, Shadinger L, Fleischer A: The sonographic diagnosis of ovarian torsion: Pearls and pitfalls. Ultrasound Clin 2:155, 2007.)

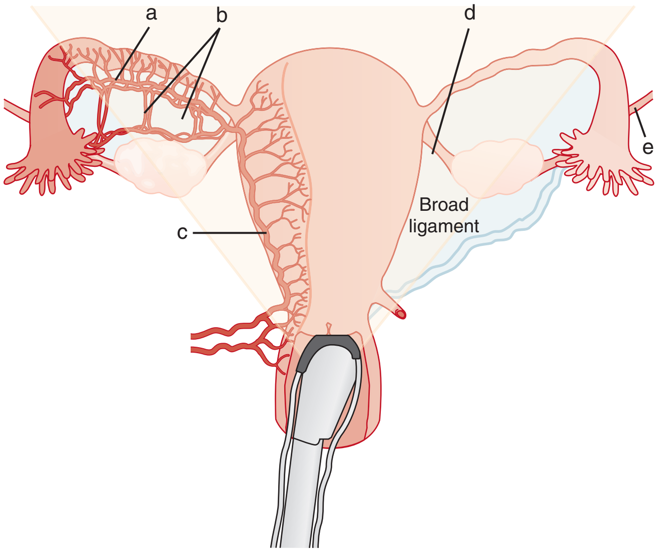


Figure 100-2. Ovarian blood supply: ovarian artery and vein *(a)*, branching arterioles supplying ovary *(b)*, utero-ovarian ligament *(c)*, utero-ovarian ligament *(d)*, infundibulo-pelvic ligament *(e)*. (From Andreotti RF, Shadinger L, Fleischer A: The sonographic diagnosis of ovarian torsion: Pearls and pitfalls. Ultrasound Clin 2:155, 2007.)

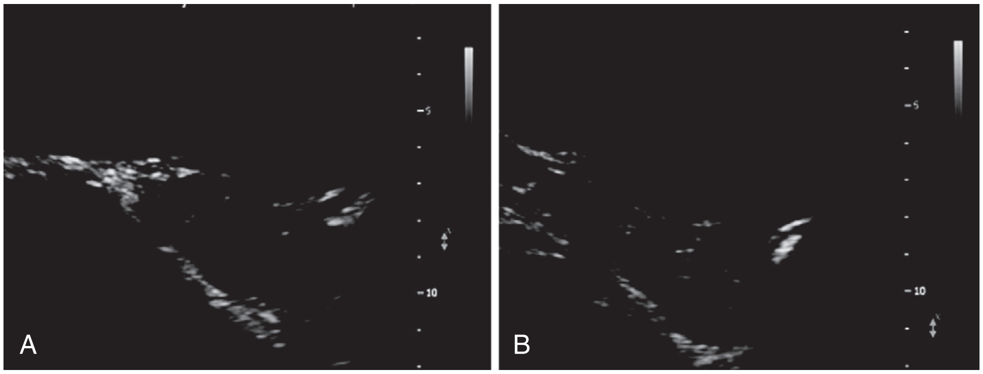


Figure 100-3. Ultrasound appearance of adnexal torsion in a prepubertal girl. (From Andreotti RF, Shadinger L, Fleischer A: The sonographic diagnosis of ovarian torsion: Pearls and pitfalls. Ultrasound Clin 2:155, 2007.)

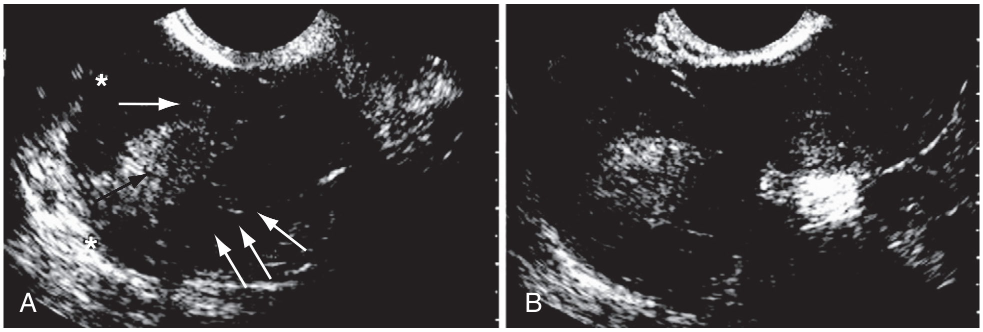


Figure 100-4. Intraovarian hemorrhage (*arrows* in A) in patient with adnexal torsion. (From Andreotti RF, Shadinger L, Fleischer A: The sonographic diagnosis of ovarian torsion: Pearls and pitfalls. Ultrasound Clin 2:155, 2007.)

www.ketabpezeshki.com 66485457-66963820

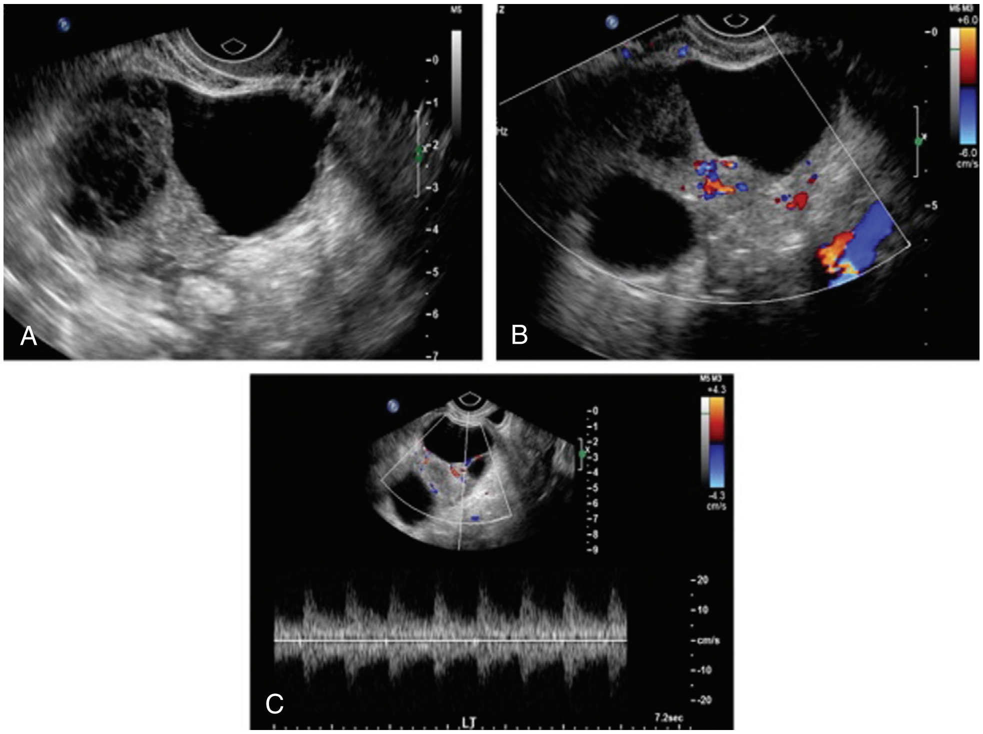


Figure 100-5. Arterial Doppler signal without venous signal in patient with surgically proven torsion. Ultrasound examination also demonstrated an associated hemorrhagic cyst. (From Andreotti RF, Shadinger L, Fleischer A: The sonographic diagnosis of ovarian torsion: Pearls and pitfalls. Ultrasound Clin 2:155, 2007.)

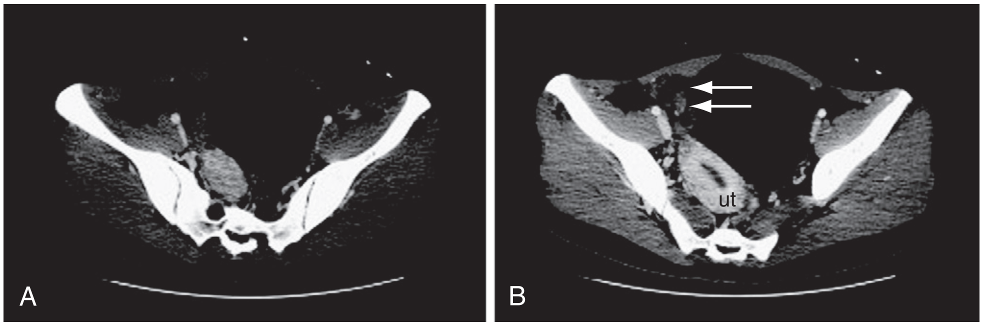


Figure 100-6. Computed tomography scans of the pelvis of a patient with adnexal torsion. Findings include a thickened fallopian tube, associated adnexal mass (arrows in **B**), and deviation of the uterus *(ut)* toward the twisted adnexa. (From Andreotti RF, Shadinger L, Fleischer A: The sonographic diagnosis of ovarian torsion: Pearls and pitfalls. Ultrasound Clin 2:155, 2007.)

of CT scans of patients with confirmed torsion found that every CT scan had evidence of an abnormality, including ovarian enlargement or the presence of a mass or cyst, suggesting that torsion is unlikely if the CT visualized a normal ovary.[20] In contrast, another study of surgically confirmed ovarian torsion cases found that CT correctly diagnosed 5 of 13 cases (38%), as opposed to ultrasonography, which correctly identified 15 of 21 cases (71%).[3] Therefore, negative imaging findings should be interpreted with caution when clinical suspicion is high, but with lower suspicion a normal-appearing ovary on CT scan can be reassuring.

Magnetic Resonance Imaging. Magnetic resonance imaging (MRI) is not typically ordered in the ED but may also demonstrate findings consistent with torsion. It is particularly helpful if the diagnosis is not clear, such as with intermittent pain over days, or when the history is highly suggestive but the ultrasound is not conclusive.[21] Findings on MRI suggestive of torsion are similar to those on CT.[18] Box 100-1 lists the common imaging findings in ovarian torsion.

Laparoscopy. A diagnostic laparoscopy is the gold standard investigative modality in patients in whom clinical suspicion is high despite negative imaging results. In 100 nonpregnant patients with an acute abdomen, only 29 of the 66 laparoscopically proven cases of ovarian torsion were diagnosed preoperatively. Laparoscopy also allowed diagnosis of other unsuspected conditions, including ovarian cysts, appendicitis, and pelvic inflammatory disease.[22]

Differential Considerations

Considerations in the differential diagnosis include other causes of acute lower abdominal pain, such as appendicitis, ovarian cyst, urinary tract infection, renal calculi, pelvic inflammatory disease, diverticulitis, and ectopic pregnancy. A pregnancy test and pelvic

www.ketabpezeshki.com 66485457-66963820

imaging with either ultrasound or CT if necessary can usually distinguish between these possibilities.

Management

Once the diagnosis of ovarian torsion has been made, the patient should be taken to the operating room as soon as possible. Pediatric patients taken to surgery more than 24 hours later have been found to have a zero salvage rate, compared with patients who had the best chance for salvage—those who were taken to the operating room within 8 hours.[23] The ovary often will recover even if black in appearance at the time of surgery because of its dual blood supply, so attempts at ovarian salvage are warranted even if the diagnosis is made late.[24] This is particularly true in adolescent patients. Ovarian function returns in a majority of patients with surgery that saves the ovary.[23] Additional imaging studies, such as MRI, are an option if the diagnosis is not clear. Because torsion of a normal-appearing ovary is very rare, patients with a normal-appearing ovary on CT or ultrasound scan may be discharged from the ED.

Box 100-1 Imaging Characteristics of Adnexal Torsion

Ultrasonography
Enlargement of the ovary
Associated ovarian mass
Loss of enhancement
Edema
Free pelvic fluid
Loss of venous waveforms
Loss of arterial waveforms

Computed Tomography and Magnetic Resonance Imaging
Enlargement of the ovary
Associated ovarian mass
Thickening of the fallopian tube
Free pelvic fluid
Edema of the ovary
Deviation of the uterus to the affected side
Associated hemorrhage

OVARIAN CYSTS AND MASSES

Principles of Disease

Ovarian cysts are the most common cause of gynecologic masses. They occur at any stage of life but are most frequent in the reproductive years because of the cyclic changes of the ovary associated with menstruation (Fig. 100-7). Most ovarian cysts are benign and resolve with no interventions, but on occasion they may be malignant or associated with significant complications such as hemorrhage or torsion.

The most common type of cyst is a simple, follicular cyst. A follicular cyst develops normally during the first half of the menstrual cycle and is considered pathologic when it is greater than 2.5 cm in diameter. It is thin walled and typically filled with clear fluid. A corpus luteum is considered to be a corpus luteal cyst when it attains a diameter greater than 3 cm. Several other types of cystic masses can occur in the ovary, including other types of cysts, non-neoplastic lesions such as benign cystic teratoma, and various types of ovarian malignancy.

Clinical Features

The most common presentation for patients with an ovarian cyst is pelvic pain. Rupture of a follicular cyst may produce transient pelvic pain or be associated with dyspareunia or may be asymptomatic. Because of its thin, fragile wall, a follicular cyst may rupture during sexual intercourse or during the pelvic examination. Follicular cysts are rarely associated with hemorrhage. Presentation of a corpus luteal cyst may range from an asymptomatic mass to dull, chronic pelvic pain to severe pain associated with rupture. Rupture of a corpus luteal cyst is frequently associated with a significant degree of hemorrhage. As with a follicular cyst, rupture may follow a pelvic examination, sexual intercourse, exercise, or trauma. Rupture of a large or complex cyst may result in severe pain and peritoneal signs, particularly if the associated bleeding is considerable. Occasionally a large cyst may be discov-

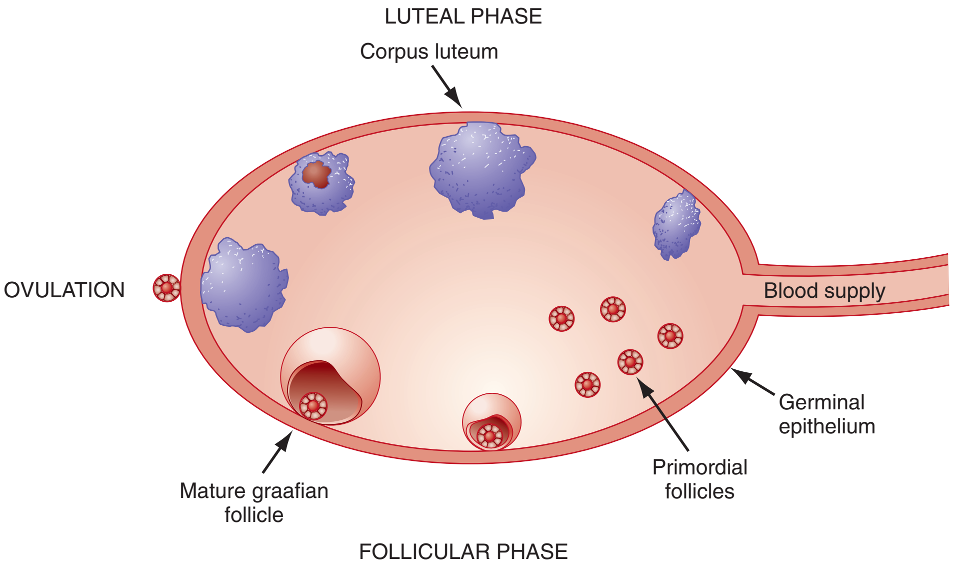


Figure 100-7. Ovarian function during the normal menstrual cycle. (From Lambert MJ, Villa M: Gynecologic ultrasound in emergency medicine. Emerg Med Clin North Am 22:683, 2004.)

www.ketabpezeshki.com 66485457-66963820

ered on a routine pelvic examination as an asymptomatic mass, but this is less common.

Diagnostic Strategies

Laboratory Tests

The initial step in the evaluation of pelvic pain or a pelvic mass is to exclude pregnancy with a urine or serum β-human chorionic gonadotropin (β-hCG) test. A hematocrit may be valuable in the unstable patient as a marker of blood loss.

Imaging

Ultrasonography. Ultrasonography is the standard initial imaging modality used to diagnose and characterize all ovarian pathologic processes and lesions including cysts and masses. Both transabdominal and endovaginal examinations provide useful information. The transabdominal approach permits an overall view of the pelvis and will visualize large masses and pelvic free fluid. Use of the endovaginal probe will provide a detailed picture of the ovary.[10] Figures 100-8 and 100-9 present endovaginal views of a normal ovary, and Figure 100-10 illustrates a simple cyst. Follicular cysts are part of the normal architecture of the ovary, but a cyst is considered to be pathologic if it is larger than 2.5 cm in diameter. Depending on the timing of the scan and the degree of clot formation and lysis, hemorrhage may be seen as well. Ultrasound findings suggestive of malignancy include internal septations, solid elements, internal echoes, daughter cysts, thickened wall, and large amounts of ascites or free fluid.[10]

Computed Tomography. When the differential diagnosis of unilateral pelvic pain is broad, particularly in the patient with associated gastrointestinal symptoms or more diffuse pain, a CT scan may be the initial imaging study. CT scan can also detect a cyst and associated complications including torsion as noted earlier. A follow-up ultrasound examination may be useful in select cases after the CT scan has been obtained, particularly if the cyst is complex. CT findings suggestive of malignancy are cystic-solid mass; necrosis in a solid lesion; cystic lesion with thick, irregular walls, papillary projections, or both; and the presence of ascites, peritoneal metastases, and lymphadenopathy.[25]

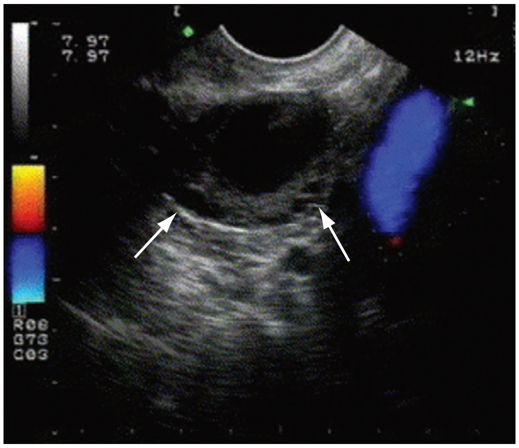


Figure 100-8. Endovaginal ultrasound image of a normal ovary with a dominant follicle *(arrows).* (From Lambert MJ, Villa M: Gynecologic ultrasound in emergency medicine. Emerg Med Clin North Am 22:683, 2004.)

Differential Considerations

It is important to rule out other causes of pelvic pain that require intervention, such as ectopic pregnancy, pelvic inflammatory disease, urinary tract infections, renal colic, appendicitis, and diverticulitis. Cysts range from the benign, simple cyst to ovarian malignancies, so the specific appearance of the cyst is important. Large cysts or masses are a risk factor for ovarian torsion.

Management

Patients with a simple cyst and decrease in their symptoms may be safely discharged with referral for outpatient gynecologic follow-up to ensure resolution of the cyst. Most uncomplicated, simple cysts will resolve within a month. A recent prospective study followed premenopausal patients diagnosed with benign (<6 cm) cysts treated with conservative management for a median of 42 months.[26] Lesions included simple cysts, hemorrhagic cysts, endometriomas, and hydrosalpinx. All the cysts resolved after 2 years, and no patients developed signs and symptoms of ovarian cancer. A complex cyst requires more urgent gynecologic intervention, and these patients may benefit from gynecology consultation in the ED, particularly if reliable follow-up is unlikely or if the patient is particularly symptomatic.

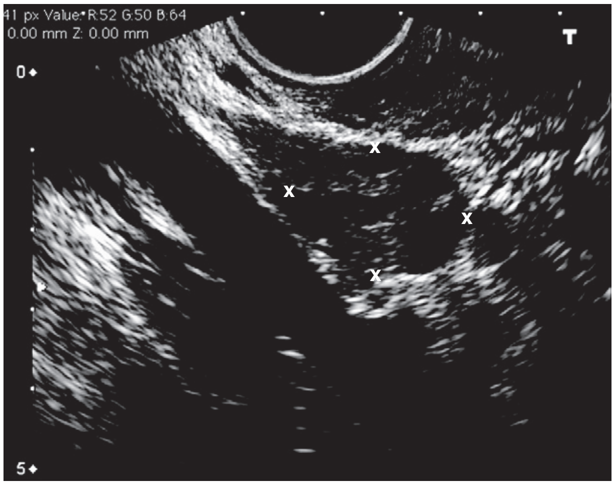


Figure 100-9. Endovaginal ultrasound image of a normal ovary (within Xs). (Courtesy Robert Reardon, MD, Hennepin County Medical Center, Minneapolis, Minnesota; used with permission.)

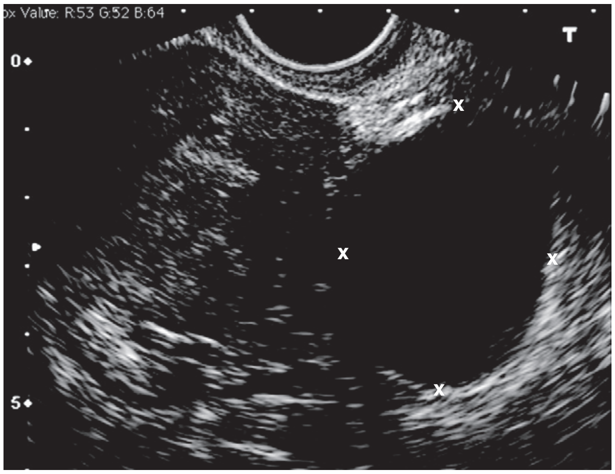


Figure 100-10. Simple ovarian cyst (within Xs). (Courtesy Robert Reardon, MD, Hennepin County Medical Center, Minneapolis, Minnesota; used with permission.)

www.ketabpezeshki.com 66485457-66963820

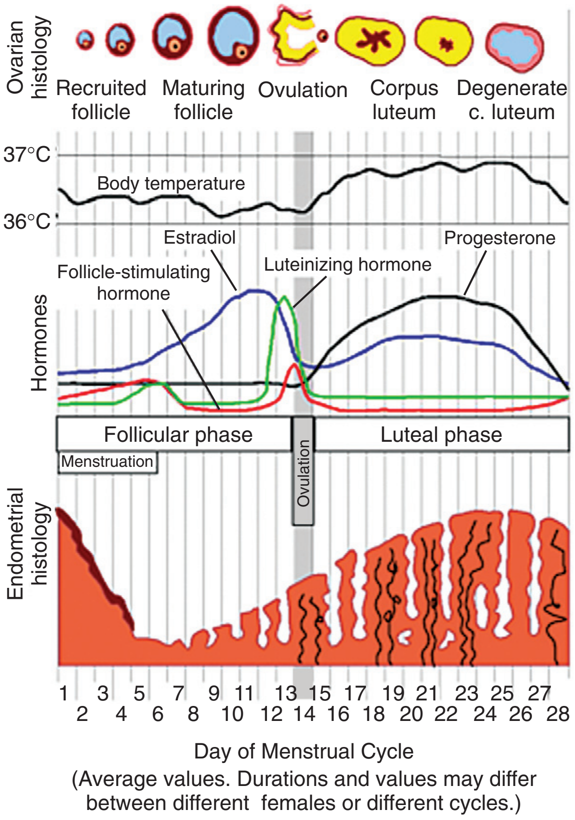


Figure 100-11. Normal menstrual cycle.

ABNORMAL UTERINE BLEEDING IN THE NONPREGNANT PATIENT

Principles of Disease

An understanding of the normal menstrual cycle is invaluable in considering potential causes of abnormal uterine bleeding (Fig. 100-11). The menstrual cycle starts on the first day of menses. During the first part of the menstrual cycle, the endometrium thickens under the influence of estrogen, and a dominant follicle develops in the ovary, releasing an ovum at the midpoint of the cycle. After ovulation, the luteal phase begins and is characterized by production of progesterone from the corpus luteum. Progesterone matures the lining of the uterus, and if implantation does not occur, the corpus luteum dies, accompanied by sharp drops in progesterone and estrogen. These changes typically are followed by menstruation. Menstrual bleeding is usually predictable and cyclic and results from withdrawal of the effects of hormones on the endometrium, which occurs approximately 14 days after ovulation.

Disruption of the hypothalamic-pituitary-ovarian axis from a variety of causes can result in abnormal uterine bleeding. Returning the balance of estrogen and progesterone with oral contraceptives will help many patients regulate the cycle, with reduction in or cessation of abnormal uterine bleeding.[26-30]

Clinical Features

History

Abnormal uterine bleeding is a common presentation in the ED. A large number of possible conditions can cause abnormal uterine bleeding, and a systematic history and physical examination can help narrow the possibilities. Table 100-1 lists terms frequently used to describe abnormal uterine bleeding. (See Chapter 34 for further discussion.)

Table 100-1 Abnormal Uterine Bleeding

TERM	BLEEDING PATTERN
Menorrhagia	Bleeding occurring at regular intervals but with heavy flow (≥80 mL) or duration (≥7 days)
Intermenstrual bleeding	Irregular bleeding between cycles
Amenorrhea	Bleeding absent for 6 mo or more in a nonmenopausal woman
Midcycle spotting	Spotting occurring just before ovulation, typically from declining estrogen levels
Postmenopausal bleeding	Recurrence of bleeding in a menopausal woman at least 1 year after cessation of cycles
Acute emergent abnormal uterine bleeding	Bleeding characterized by significant blood loss that results in hypovolemic shock
Dysfunctional uterine bleeding	Ovulatory or anovulatory bleeding, diagnosed after the exclusion of pregnancy, medications, iatrogenic causes, genital tract pathology, and systemic disease

Vaginal bleeding before the age of menarche is abnormal and is often the result of trauma, such as sexual abuse, or a structural lesion.[31] In a woman of reproductive age, abnormal uterine bleeding includes a change in the duration, frequency, or amount of bleeding, or bleeding between menstrual cycles. In the postmenopausal woman, any bleeding 12 months after the cessation of menses or unpredictable bleeding during hormone therapy should be considered abnormal. The amount and frequency of bleeding and the duration of symptoms, as well as the relationship to the menstrual cycle, should be established.[32] A menstrual cycle that is fewer than 21 days in duration or more than 35 days long or flow for less than 2 days or more than 7 days is classified as abnormal. A pattern of irregular bleeding between cycles or an abrupt change in the previous pattern of bleeding should be determined.[33] Systemic disease, such as liver disease, diabetes, or thyroid disease, may be associated with abnormal uterine bleeding.[34] Endometrial cancer is associated with underlying diabetes mellitus, anovulatory cycles, obesity, nulliparity, and age older than 35 years.[29] Cervical dysplasia or other genital tract pathology may cause postcoital or irregular bleeding.[35] Disruption along the hypothalamus-pituitary-ovarian pathway frequently is the cause of abnormal uterine bleeding. Causes of hypothalamic suppression include excessive exercise, stress, and weight loss.[36] Polycystic ovary syndrome (PCOS) results in excess estrogen production.

According to Dilley and colleagues, 10.7% of patients with heavy menstrual bleeding have an underlying coagulation disorder, most commonly von Willebrand's disease.[37] Although most patients with abnormal uterine bleeding do not require evaluation for coagulopathy, the diagnosis is suggested by a family history of a bleeding disorder, prolonged history of heavy menses, excessive bleeding with surgery or dental procedures, or easy bruising.[38] Box 100-2 lists historical factors that suggest a potential cause for the bleeding.[29] Dysfunctional uterine bleeding is a diagnosis of exclusion in a woman of childbearing age after pregnancy, malignancy, and systemic disease have been ruled out.[29] Dysfunctional uterine bleeding typically is classified as anovulatory or ovulatory. Anovulatory bleeding is much more common, resulting from a disturbance of the normal hypothalamic-pituitary-ovarian axis, and is particularly common at the extremes of the reproductive years.[28]

www.ketabpezeshki.com 66485457-66963820

Box 100-2 Differential Diagnosis for Abnormal Uterine Bleeding

- Pregnancy and pregnancy-related conditions
  - Miscarriage
  - Ectopic pregnancy
  - Placenta previa
  - Placental abruption
  - Trophoblastic disease
- Medications and iatrogenic causes
  - Anticoagulants
  - Oral contraceptives
  - Steroids
  - Antipsychotics
  - Intrauterine devices
  - Thyroid hormone replacement
- Systemic disease
  - Cushing's disease
  - Coagulopathies
  - Liver or renal disease
  - Hypothalamic suppression (excessive exercise, weight loss)
  - Polycystic ovary syndrome
  - Thyroid disease
- Genital tract pathology
  - Cervicitis
  - Endometritis
  - Fibroids (leiomyomata)
  - Adenomyosis
  - Malignancy
  - Trauma
  - Foreign body
- Dysfunctional uterine bleeding

Physical Examination

With prolonged, heavy bleeding, signs of chronic anemia may be noted on the physical examination. PCOS is a common cause of abnormal uterine bleeding. Physical findings suggestive of PCOS include obesity, acne, hirsutism, and acanthosis nigricans, which is hyperpigmentation typically seen in the folds of skin in the neck, groin, or axilla.[39] Other causes of bleeding include vaginal or cervical lesions, which may be visible on the speculum examination. A leiomyoma or fibroid uterus may be palpable on the bimanual examination.[40] Patients with endometrial cancer frequently have an enlarged uterus as well.

Diagnostic Strategies

Laboratory Studies

In evaluating a woman of reproductive age with vaginal bleeding, a urine pregnancy test is the most essential laboratory test. In a patient with excessive bleeding, any hemodynamic instability, or clinical evidence of anemia (e.g., excessive fatigue, pale conjunctiva), a hemoglobin or hematocrit may be helpful. Coagulation studies should be considered in patients with underlying liver disease or other coagulopathies.[38]

Imaging

Ultrasonography. Transvaginal ultrasonography may reveal a fibroid uterus, endometrial thickening, or a focal mass.[41] Endometrium measuring less than 4 mm thick is under the influence of low estrogen—for example, either in the early follicular phase or in menopause. Thickened endometrium may indicate an underlying lesion or excess estrogen[42] (Fig. 100-12). For a majority of nonpregnant patients with abnormal uterine bleeding, these ultrasound findings do not immediately affect ED decision-making. In

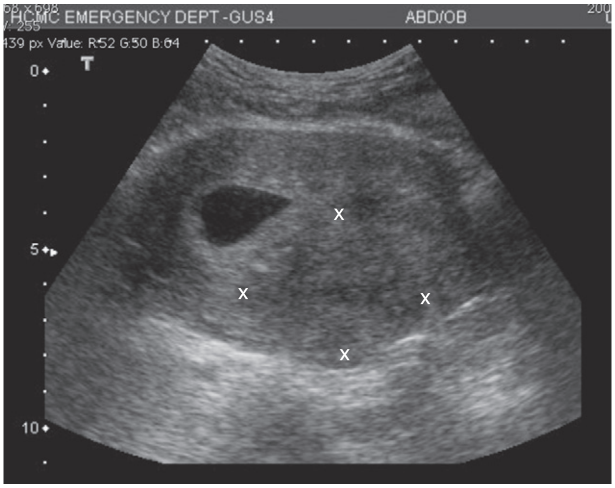


Figure 100-12. Longitudinal view of the uterus with thickened endometrium. (Courtesy Robert Reardon, MD, Hennepin County Medical Center, Minneapolis, Minn.; used with permission.)

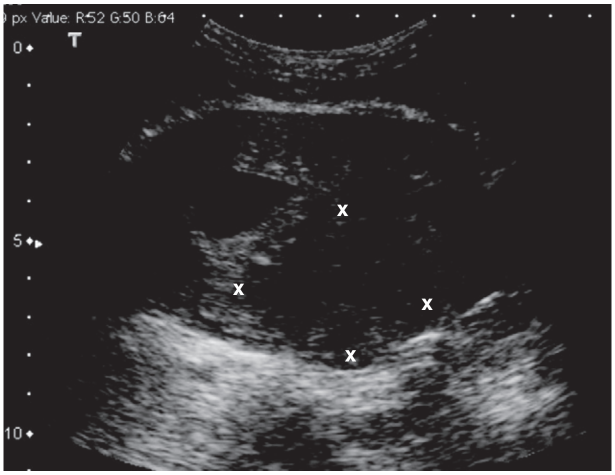


Figure 100-13. Ultrasound image of a uterine fibroid (within Xs). (Courtesy Robert Reardon, MD, Hennepin County Medical Center, Minneapolis, Minn.; used with permission.)

patients who have access to adequate gynecologic services, imaging may be deferred until follow-up evaluation with the gynecologist. The decision to perform ultrasound imaging in the ED will depend on the urgency to determine the cause of bleeding and on the reliability of outpatient follow-up. ED pelvic ultrasound imaging in nonpregnant patients can determine the cause of the bleeding in approximately 60% of cases. Uterine fibroids are by far the most common diagnosis (Fig. 100-13), but in one study 9.6% of patients had endometrial changes suggestive of malignancy,[43] illustrating the importance of arranging follow-up for any patient with new abnormal uterine bleeding.

Differential Considerations

The etiology of abnormal uterine bleeding is extensive and includes systemic disease, structural lesions, such as a fibroid uterus, hormonal abnormalities, and iatrogenic causes, such as medication side effects. A careful physical examination will exclude vaginal or rectal sources of bleeding.

Management

The likely causative disorder, as well as the amount of bleeding, will guide the ED management. Nonsteroidal anti-inflammatory

www.ketabpezeshki.com 66485457-66963820

medications are generally effective for relief of associated cramping pelvic pain.[29] For anovulatory bleeding, combination oral contraceptive pills can help regulate the cycle and also counteract the effects of long-term effects of unopposed estrogen on the endometrium. In a patient who desires contraception and is not heavily bleeding on presentation to the ED, a combination oral contraceptive with 20 to 35 μg of ethinyl estradiol may be prescribed.[28] In the patient with heavy bleeding, an oral contraceptive with 35 μg of estrogen can be taken twice a day for 5 to 7 days until the bleeding stops, at which time the dose is decreased to once a day until the pack is completed.[29] This is often done by prescribing two packs of oral contraceptives and having the patient take one pill from each package until the bleeding stops then continue with one pill daily. Rarely, a patient will have uncontrolled bleeding and signs of significant blood loss on presentation. These patients should receive aggressive resuscitation with saline and blood as with other types of hemorrhagic shock. In these patients, surgical removal of the culprit lesion, if one is present, or an urgent dilation and curettage (D&C) procedure is likely necessary. Alternatively, intravenous conjugated estrogen (Premarin) may be used. The dose is 25 mg intravenously (IV) every 4 to 6 hours until the bleeding stops.[44]

EMERGENCY CONTRACEPTION

Emergency contraception, also commonly known as the *morning-after pill*, consists of therapy to prevent pregnancy after unprotected sexual intercourse. It is estimated that more than 1 million unintended pregnancies could be avoided per year if emergency contraception were used.[45] The most common reasons cited by patients seeking emergency contraception include failure to use contraception and failure of the contraception method, such as a broken condom or missed oral contraceptive pill. A recent survey of 800 women of reproductive age found that only 6% of the women had ever used emergency contraception.[46] Many women are not aware of the availability of this option, are not informed about its safety or use, or do not have access to the medications.[46,47]

Emergency contraception with high-dose estrogen was reported in the early 1960s and began to have widespread use after Yuzpe demonstrated the efficacy of a lower-dose combination of estrogen and progestin to prevent pregnancy in 1974.[45,48,49] At present, levonorgestrel alone, marketed as Plan B in the United States, is more effective and has largely replaced the Yuzpe method.[50] Nausea occurs in 18% of patients using Plan B and in 43% of women taking combination pills.[51] Antiemetics given 1 hour before the combination pills are effective and should be considered with use of these pills. The incidence of nausea is much lower with Plan B, but antiemetics can be offered. The package insert of Plan B recommends taking the 0.75-mg pill as soon as possible and the subsequent dose 12 hours later; however, taking the doses simultaneously is equally effective. Emergency contraception should be administered before 24 hours if possible but can be given up to 120 hours after intercourse. The Yuzpe method is 87 to 90% effective if the regimen is given within 72 hours; this rate drops to 72 to 87% if the pills are given between 72 and 120 hours. Plan B is noted to be 89% effective in preventing pregnancy.[45]

Emergency contraception may be offered after inadequately protected intercourse to any woman who does not desire pregnancy. The typical contraindications to oral contraceptives do not apply to emergency contraception because the duration of therapy is so brief.[52] Emergency contraception has no adverse effects on a developing fetus and does not pose a risk to an established pregnancy.[53] A majority of nonpregnant women experience menses within a week of the expected time, but irregular bleeding may occur.[37] It is still possible for a patient who uses emergency contraception to get pregnant in the same menstrual cycle, so she should be advised to use an alternative form of contraception and to undergo a pregnancy test if menstruation is delayed more than 3 weeks. Advance provision of emergency contraception does not increase the number of unprotected sexual encounters.[54-57]

In 2007, after FDA approval, Plan B became available nationally over the counter without a prescription. Pregnancy rates as well as rates of sexually transmitted diseases and sexual activity have remained unchanged even though the use of emergency contraception has increased.[58] Even though Plan B is available over the counter, follow-up studies highlight ongoing barriers to access, including cost and patient awareness, and highlight the importance of continued education including education on the use of primary contraceptive methods.[59-61]

DISPOSITION

A majority of patients with pelvic pain from ovarian cysts or abnormal uterine bleeding without hemodynamic compromise may be managed with specific therapies to minimize symptoms and should be referred to a gynecologist for definitive management on an outpatient basis. Patients with confirmed or suspected ovarian torsion or severe, acute abnormal uterine bleeding and hemodynamic instability require urgent gynecology consultation and hospitalization. Patients who receive emergency contraception should be counseled regarding birth control and have a follow-up pregnancy test should they miss their next period.

KEY POINTS

- Ovarian torsion is easily missed on initial presentation. This diagnosis should be a consideration in any patient with known risk factors, even if symptoms are subtle or atypical.
- Abnormal uterine bleeding has many structural and hormonal causes. A careful history and physical examination and selected imaging can often allow determination of the likely cause.
- Ultrasound examination may distinguish among the various types of ovarian cysts and identify associated complications such as torsion and hemorrhage.
- Emergency contraception is a safe, effective option to prevent undesired pregnancy. Levonorgestrel (progestin) as Plan B is more effective and is associated with fewer side effects than the traditional Yuzpe method.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Oelsner G, Shashar D: Adnexal torsion. *Clin Obstet Gynecol* 2006; 49:459.
2. Breech LL, Hillard PJ: Adnexal torsion in pediatric and adolescent girls. *Curr Opin Obstet Gynecol* 2005; 17:483.
3. Chiou SY, Lev-Toaff AS, Masuda E, Feld RI, Bergin D: Adnexal torsion: New clinical and imaging observations by sonography, computed tomography, and magnetic resonance imaging. *J Ultrasound Med* 2007; 26:1289.
4. Shadinger LL, Andreotti RF, Kurian RL: Preoperative sonographic and clinical characteristics as predictors of ovarian torsion. *J Ultrasound Med* 2008; 27:7, 2008.
5. Houry D, Abbott JT: Ovarian torsion: A fifteen-year review. *Ann Emerg Med* 2001; 38:156.
6. Mazouni C, Bretelle F, Ménard JP, Blanc B, Gamerre M: [Diagnosis of adnexal torsion and predictive factors of adnexal necrosis.] *Gynecol Obstet Fertil* 2005; 33:102.
7. Andreotti RF, Shadinger L, Fleischer A: The sonographic diagnosis of ovarian torsion: Pearls and pitfalls. *Ultrasound Clin* 2007; 2:155.
8. Bouguizane S, et al: [Adnexal torsion: A report of 135 cases.] *J Gynecol Obstet Biol Reprod (Paris)* 2003; 32:535.
9. Huchon C, Fauconnier A: Adnexal torsion: A literature review. *Eur J Obstet Gynecol Reprod Biol* 2010; 150:8-12.
10. Lambert MJ, Villa M: Gynecologic ultrasound in emergency medicine. *Emerg Med Clin North Am* 2004; 22:683.
11. Smorgick N, Maymon R, Mendelovic S, Herman A, Pansky M: Torsion of normal adnexa in postmenarcheal women: Can ultrasound indicate an ischemic process? *Ultrasound Obstet Gynecol* 2008; 31:338-341.
12. Ben-Ami M, Perlitz Y, Haddad S: The effectiveness of spectral and color Doppler in predicting ovarian torsion: A prospective study. *Eur J Obstet Gynecol Reprod Biol* 2002; 104:64.
13. Pena JE, Ufberg D, Cooney N, Denis AL: Usefulness of Doppler sonography in the diagnosis of ovarian torsion. *Fertil Steril* 2000; 73:1047.
14. Vijayaraghavan SB: Sonographic whirlpool sign in ovarian torsion. *J Ultrasound Med* 2004; 23:1643, quiz 1650.
15. Valsky DV, Esh-Broder E, Cohen SM, Lipschuetz M, Yagel S: Added value of the gray-scale whirlpool sign in the diagnosis of adnexal torsion. *Ultrasound Obstet Gynecol* 2010; 36:630-634.
16. Lee EJ, Kwon HC, Joo HJ, Suh JH, Fleischer AC: Diagnosis of ovarian torsion with color Doppler sonography: Depiction of twisted vascular pedicle. *J Ultrasound Med* 1998; 17:83.
17. Kalish GM, Patel MD, Gunn ML, Dubinsky TJ: Computed tomographic and magnetic resonance features of gynecologic abnormalities in women presenting with acute or chronic abdominal pain. *Ultrasound Q* 2007; 23:167-175.
18. Rha SE, et al: CT and MR imaging features of adnexal torsion. *Radiographics* 2002; 22:283.
19. Hiller N, et al: CT features of adnexal torsion. *AJR Am J Roentgenol* 2007; 189:124-129.
20. Moore C, Meyers AB, Capotasto J, Bokhari J: Prevalence of abnormal CT findings in patients with proven ovarian torsion and a proposed triage schema. *Emerg Radiol* 2009; 16:115-120.
21. Haque TL, Togashi K, Kobayashi H, Fujii S, Konishi J: Adnexal torsion: MR imaging findings of viable ovary. *Eur Radiol* 2000; 10:1954.
22. Cohen SB, et al: Accuracy of the preoperative diagnosis in 100 emergency laparoscopies performed due to acute abdomen in nonpregnant women. *J Am Assoc Gynecol Laparosc* 2001; 8:92.
23. Anders JF, Powell EC: Urgency of evaluation and outcome of acute ovarian torsion in pediatric patients. *Arch Pediatr Adolesc Med* 2005; 159:532.
24. Oelsner G, et al: Minimal surgery for the twisted ischaemic adnexa can preserve ovarian function. *Hum Reprod* 2003; 18:2599.
25. Gatreh-Samani F, Tarzamni MK, Olad-Sahebmadarek E, Dastranj A, Afrough A: Adnexal masses: Accuracy of detection and differentiation with multi-detector computed tomography. *Gynecol Oncol* 2008; 110:22-31.
26. Alcázar JL, Castillo G, Jurado M, García GL: Is expectant management of sonographically benign adnexal cysts an option in selected asymptomatic premenopausal women? *Hum Reprod* 2005; 20:3231-3242.
27. Pitkin J: Dysfunctional uterine bleeding. *BMJ* 2007; 334:1110.
28. Agarwal N, Kriplani A: Medical management of dysfunctional uterine bleeding. *Int J Gynaecol Obstet* 2001; 75:199.
29. Albers JR, Hull SK, Wesley RM: Abnormal uterine bleeding. *Am Fam Physician* 2004; 69:1915.
30. Daniels R, McCuskey C: Abnormal vaginal bleeding in the nonpregnant patient. *Emerg Med Clin North Am* 2003; 21:751-772.
31. Hill NC, Oppenheimer LW, Morton KE: The aetiology of vaginal bleeding in children: A 20-year review. *Br J Obstet Gynaecol* 1989; 96:467.
32. Fraser IS, Critchley HO, Munro MG: Abnormal uterine bleeding: Getting our terminology straight. *Curr Opin Obstet Gynecol* 2007; 19:591.
33. Livingstone M, Fraser IS: Mechanisms of abnormal uterine bleeding. *Hum Reprod Update* 2002; 8:60.
34. Krassas GE: Thyroid disease and female reproduction. *Fertil Steril* 2000; 74:1063.
35. Rosenthal AN, Panoskaltsis T, Smith T, Soutter WP: The frequency of significant pathology in women attending a general gynaecological service for postcoital bleeding. *BJOG* 2001; 108:103.
36. Lazovic G, Radivojevic U, Milicevic S, Milosevic V, Spremovic S: The most frequent hormone dysfunctions in juvenile bleeding. *Int J Fertil Womens Med* 2007; 52:35.
37. Dilley A, et al: von Willebrand disease and other inherited bleeding disorders in women with diagnosed menorrhagia. *Obstet Gynecol* 2001; 97:630.
38. El-Hemaidi I, Gharaibeh A, Shehata H: Menorrhagia and bleeding disorders. *Curr Opin Obstet Gynecol* 2007; 19:513.
39. Fraser IS, Kovacs G: Current recommendations for the diagnostic evaluation and follow-up of patients presenting with symptomatic polycystic ovary syndrome. *Best Pract Res Clin Obstet Gynaecol* 2004; 18:813.
40. Lethaby A, Vollenhoven B: Fibroids (uterine myomatosis, leiomyomas). *Clin Evid (Online)* 2011; Jan 11.
41. Goldstein SR, Zeltser I, Horan CK, Snyder JR, Schwartz LB: Ultrasonography-based triage for perimenopausal patients with abnormal uterine bleeding. *Am J Obstet Gynecol* 1997; 177:102.
42. Tabor A, Watt HC, Wald NJ: Endometrial thickness as a test for endometrial cancer in women with postmenopausal vaginal bleeding. *Obstet Gynecol* 2002; 99:663.
43. Stumpf M, Tibbles CD: Utility of pelvic ultrasound in non-pregnant patients with pelvic pain or vaginal bleeding. *Ann Emerg Med* 2004; 44:S12.
44. DeVore GR, Owens O, Kase N: Use of intravenous Premarin in the treatment of dysfunctional uterine bleeding—a double-blind randomized control study. *Obstet Gynecol* 1982; 59:285.
45. Ranney ML, Gee EM, Merchant RC: Nonprescription availability of emergency contraception in the United States: Current status, controversies, and impact on emergency medicine practice. *Ann Emerg Med* 2006; 47:461.
46. American College of Obstetricians and Gynecologists: ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists, No. 69, December 2005 (replaces Practice Bulletin Number 25, March 2001). Emergency contraception. *Obstet Gynecol* 2005; 106:1443.
47. Abbott J, Feldhaus KM, Houry D, Lowenstein SR: Emergency contraception: What do our patients know? *Ann Emerg Med* 2004; 43:376.
48. Yuzpe AA: Postcoital hormonal contraception: Uses, risks, and abuses. *Int J Gynaecol Obstet* 1977; 15:133.
49. Yuzpe AA, Thurlow HJ, Ramzy I, Leyshon JI: Post coital contraception: A pilot study. *J Reprod Med* 1974; 13:53.
50. Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. Task Force on Postovulatory Methods of Fertility Regulation. *Lancet* 1998; 352:428.
51. Raymond EG, et al: Meclizine for prevention of nausea associated with use of emergency contraceptive pills: A randomized trial. *Obstet Gynecol* 2000; 95:271.
52. Conard LA, Gold MA: Emergency contraceptive pills: A review of the recent literature. *Curr Opin Obstet Gynecol* 2004; 16:389.
53. Zhang L, et al: Pregnancy outcome after levonorgestrel-only emergency contraception failure: A prospective cohort study. *Hum Reprod* 2009; 24:1605-1611.
54. Ellertson C, et al: Emergency contraception: Randomized comparison of advance provision and information only. *Obstet Gynecol* 2001; 98:570.
55. Gold MA, Wolford JE, Smith KA, Parker AM: The effects of advance provision of emergency contraception on adolescent women's sexual and contraceptive behaviors. *J Pediatr Adolesc Gynecol* 2004; 17:87.
56. Jackson RA, Schwarz EB, Freedman L, Darney P: Advance supply of emergency contraception: Effect on use and usual contraception—a randomized trial. *Obstet Gynecol* 2003; 102:8.
57. Lo SS, Fan SY, Ho PC, Glasier AF: Effect of advanced provision of emergency contraception on women's contraceptive behaviour: A randomized controlled trial. *Hum Reprod* 2004; 19:2404.

www.ketabpezeshki.com 66485457-66963820

58. Raine TR, et al: Direct access to emergency contraception through pharmacies and effect on unintended pregnancy and STIs: A randomized controlled trial. *JAMA* 2005; 293:54.
59. Maharaj P, Rogan M: Missing opportunities for preventing unwanted pregnancy: A qualitative study of emergency contraception. *J Fam Plann Reprod Health Care* 2011; 37:89-96.
60. Parrish JW, Katz AR, Grove JS, Maddock J, Myhre S: Characteristics of women who sought emergency contraception at a university-based women's health clinic. *Am J Obstet Gynecol* 2009; 201:22e1-7.
61. Goyal M, Zhao H, Mollen C: Exploring emergency contraception knowledge, prescriptions, practices, and barriers to prescriptions for adolescents in the emergency department. *Pediatrics* 2009; 123:765-770.

www.ketabpezeshki.com 66485457-66963820

Chapter 101

Stroke

Todd J. Crocco and Joshua N. Goldstein

PERSPECTIVE

Background

Stroke is the third leading cause of death in the United States and a leading cause of long-term disability.[1] It affects about 795,000 people per year. On average, someone has a stroke every 40 seconds, and someone dies of a stroke every 4 minutes.[2] Stroke patients have an in-hospital mortality rate of 5 to 10% for ischemic stroke and 40 to 60% for intracerebral hemorrhage (ICH).[3] Only 10% of stroke survivors will recover completely. The remaining survivors will be left with an impairment that will often necessitate rehabilitation.[4] The estimated direct and indirect cost of stroke in the United States in 2010 was $73.7 billion.[2]

Stroke can be defined as any vascular injury that reduces cerebral blood flow (CBF) to a specific region of the brain, causing neurologic impairment. The onset of symptoms may be sudden or stuttering, often with transient or permanent loss of neurologic function. Approximately 87% of all strokes are ischemic in origin, caused by the occlusion of a cerebral vessel.[2] Approximately 13% are hemorrhagic strokes caused by the rupture of a blood vessel into the parenchyma of the brain (ICH) or into the subarachnoid space (subarachnoid hemorrhage [SAH]).[2] Only ischemic stroke and ICH are discussed in this chapter.

Before the development of interventional strategies, treatment for stroke consisted of stabilization, observation, and rehabilitation. More recently, a better understanding of the pathophysiology of neuronal injury and the introduction of new therapies have led to a shift from observation to early evaluation and treatment. Current interventional treatment regimens include blood pressure (BP) management, anticoagulation, thrombolytic therapy, catheter-based interventions, and surgery. The key to success is early identification and treatment of patients with stroke before neurologic deficits become irreversible.

Epidemiology

Ischemic Stroke

An estimated 610,000 "first-ever" ischemic strokes occur each year in the United States.[2] These may result either from in situ thrombosis or embolic obstruction from a more proximal source, usually the heart. In more than one third of these first-ever strokes, no clear cause is identified[5-7] (Table 101-1).

Approximately one third of all ischemic strokes are thrombotic in nature. These can be caused by either large- or small-vessel occlusions. Common areas for large-vessel occlusions are cerebral vessel branch points, especially in the distribution of the internal carotid artery. Thrombosis usually results from clot formation in the area of an ulcerated atherosclerotic plaque that forms in the area of turbulent blood flow, such as a vessel bifurcation. A marked reduction in flow results when the stenosis occludes more than 90% of the blood vessel diameter. With further ulceration and thrombosis, platelets adhere to the region. A clot then either embolizes or occludes the artery.

Lacunae, or small-vessel strokes, involve small terminal sections of the vasculature and more commonly occur in African Americans and patients with diabetes and hypertension.[5] A history of hypertension is present in 80 to 90% of patients who experience lacunar strokes. The subcortical areas of the cerebrum and brainstem often are involved. The infarcts range in size from a few millimeters to 2 cm and are seen most commonly in the basal ganglia, thalamus, pons, and internal capsule. They may be caused by small emboli or by a process termed *lipohyalinosis*, which occurs in patients with hypertensive cerebral vasculopathy. Although nearly 20 lacunar syndromes have been described, the most common of these lacunar syndromes are pure motor strokes, pure sensory strokes, or ataxic hemiparesis. Because they are subcortical and well localized, lacunar strokes do not typically cause cognitive impairment, aphasia, or simultaneous sensorimotor findings.

One fourth of all ischemic strokes are cardioembolic in nature.[5,6] Embolization of a mural thrombus in patients with atrial fibrillation is the most common mechanism, and patients with atrial fibrillation have an approximate fivefold increased risk for development of a stroke.[8] In addition, roughly 45% of all embolic strokes occur as a result of atrial fibrillation.[8] Noncardiac sources of emboli may include diseased portions of extracranial arteries, resulting in an artery-to-artery embolus. One common example is amaurosis fugax, in which emboli from a proximal carotid artery plaque embolizes to the ophthalmic artery, causing transient monocular blindness.

Another cause of stroke is recent myocardial infarction (MI). Approximately 12 ischemic strokes occur per 1000 nonfatal MI patients within 1 month after the index event. Furthermore, 11 ischemic strokes occur per 1000 nonfatal MI patients in the post-MI hospitalization period. Independent predictors of stroke after acute MI are advanced age, diabetes, hypertension, history of previous stroke, anterior location of index MI, previous MI, atrial fibrillation, heart failure, and nonwhite race.[9] The use of aspirin has been shown to reduce the incidence of post-MI stroke by 46%.[10]

Approximately 3 to 4% of all strokes occur in patients aged 15 to 45 years. Although atherosclerosis is the most common cause in older patients, causative disorders and conditions in younger patients often are uncommon and may be reversible. Pregnancy, the use of oral contraceptives, antiphospholipid antibodies (such as lupus anticoagulant and anticardiolipin antibodies), protein S and C deficiencies, sickle cell anemia, and polycythemia all

www.ketabpezeshki.com 66485457-66963820

Table 101-1 Estimated Number per Year of First-Ever Strokes and Transient Ischemic Attacks (TIAs) in the United States

STROKE SUBTYPE	ESTIMATED NUMBER
Large vessel	69,000 (16%)
Small vessel/lacunae	76,000 (17.5%)
Cardioembolic	113,000 (26%)
Stroke of uncommon mechanisms	15,000 (3.5%)
Infarction of unknown cause	157,000 (36.5%)
Total strokes and TIAs	430,000 (100%)

Data from Woo D, et al: Incidence rates of first-ever ischemic stroke subtypes among blacks: A population-based study. Stroke 30:2517, 1999; and Petty GW, et al: Ischemic stroke subtypes: A population-based study of incidence and risk factors. Stroke 30:2513, 1999.

predispose patients to sludging or thrombosis, thereby increasing the risk of stroke. Fibromuscular dysplasia of the cerebral vasculature also may lead to stroke, and in rare instances prolonged vasoconstriction from a migraine syndrome causes stroke. Recreational drugs such as cocaine, phenylpropanolamine, and amphetamines are potent vasoconstrictors that have been associated with both ischemic and hemorrhagic stroke.

Carotid and vertebral dissections often are associated with trauma but may follow such mild events as turning the head sharply. Carotid and vertebral dissections also are seen more frequently in people with underlying pathology of the vessel wall, such as in fibromuscular dysplasia and connective tissue disorders. Alteration in the vessel intima can lead to vessel stenosis, occlusion, or embolism. The patient may report a minor preceding event such as spinal manipulation, yoga, working overhead, coughing, or vomiting. Presenting manifestations may include headache, facial pain, visual changes, cranial nerve (CN) palsies, pain over the affected vessel, Horner's syndrome, amaurosis fugax, SAH, or an ischemic stroke. The headache frequently is unilateral and may occur days before onset of the other neurologic symptoms.[11] Although angiography has been the standard diagnostic study, dissections are increasingly being diagnosed by less invasive modalities such as ultrasonography, magnetic resonance angiography (MRA), and computed tomography angiography (CTA).[12] Medical therapy includes early anticoagulation if SAH is not suspected. If symptoms recur despite anticoagulation, the patient may be eligible for endovascular intervention. Carotid or vertebral dissection is not considered a contraindication to use of tissue plasminogen activator (tPA) in the eligible patient.[13] This entity is considered a major cause of stroke in younger patients.[11,14,15]

A *transient ischemic attack* (TIA) was historically defined as a neurologic deficit with complete resolution within 24 hours. However, advances in neuroimaging suggest that many such events represent minor stroke with resolved symptoms rather than true TIAs.[16] Therefore the American Heart Association (AHA) recommends the following definition: a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.[17]

From 200,000 to 500,000 TIAs per year are diagnosed in the United States, and emergency department (ED) visits for TIA occur at a rate of about 1 visit per 1000 population.[16] TIAs constitute an important warning sign for the future development of cerebral infarction. Approximately 10% of the patients who experience a TIA will experience a stroke within 3 months of the sentinel event, and one half of these occur within the first 2 days.[18]

Box 101-1 Most Common Sites for Hypertensive Intracranial Hemorrhage

Affected Area	Frequency
Putamen	44%
Thalamus	13%
Cerebellum	9%
Pons	9%
Other cortical areas	25%

Hemorrhagic Stroke

Spontaneous ICH causes 10 to 15% of all acute strokes, affecting approximately 65,000 patients per year.[19] It carries a 30-day mortality rate of up to 50%, with one half of patients dying in the first 2 days. Among survivors, only 1 in 5 are living independently at 6 months.[3]

The two major underlying causes of ICH are hypertensive vasculopathy (caused by long-standing hypertension) and cerebral amyloid angiopathy (usually found in elders, the result of amyloid deposition in cerebral vessel walls). Hypertensive hemorrhage results from degenerative changes in the small penetrating arteries and arterioles, leading to lipohyalinosis of small, deep penetrating arteries. Such hemorrhages generally occur in the deep regions including basal ganglia and thalamus. The most common sites for hypertensive hemorrhage are listed in Box 101-1. ICH caused by amyloid angiopathy tends to be lobar in nature and to occur more commonly in elders. Specific apolipoprotein E alleles appear to predispose to the development and recurrence of ICH.

Other factors leading to ICH include underlying vascular malformations, including arteriovenous malformations (AVMs) and aneurysms, drug intoxication (particularly sympathomimetics, such as cocaine), malignant hypertension, saccular aneurysms, blood dyscrasias, venous sinus thrombosis, hemorrhagic transformation of an ischemic stroke, moyamoya disease, and tumors. High-risk features for such secondary forms of ICH include lobar location, presence of intraventricular blood, and younger age.[20]

PRINCIPLES OF DISEASE

Pathophysiology

The cerebral vasculature supplies the brain with a rich flow of blood that contains the critical supply of oxygen and glucose necessary for normal brain function. When a stroke occurs, there are immediate alterations in CBF and extensive changes in cellular homeostasis. The normal CBF is approximately 40 to 60 mL/100 g of brain per minute. When CBF drops below 15 to 18 mL/100 g of brain per minute, several physiologic changes occur. The brain loses electrical activity, becoming electrically "silent," although neuronal membrane integrity and function remain intact. Clinically, the areas of the brain maintaining electrical silence manifest a neurologic deficit, even though the brain cells are viable. When CBF is below 10 mL/100 g of brain per minute, membrane failure occurs, with a subsequent increase in the extracellular potassium and intracellular calcium and eventual cell death. The ischemic penumbra is the area of the brain surrounding the primary injury, which is preserved by a tenuous supply of blood from collateral vessels. This border zone of neuronal tissue is the area of greatest interest to investigators for possible salvage in both ischemic and hemorrhagic stroke. In ischemic stroke, the duration of occlusion plays a critical role in neuronal survival.[21] Increasing the duration of occlusion increases both the irreversibility of deficits and the amount of cerebral infarction. Thus, ischemic stroke trials typically focus on the first few hours after symptom onset.

www.ketabpezeshki.com 66485457-66963820

In ICH, acute vessel rupture is most often caused by underlying small vessel disease, as noted earlier, and causes injury by several mechanisms. First, there is mass effect from the hematoma itself, followed by activation of the coagulation cascade, release of inflammatory cytokines, and blood-brain barrier (BBB) disruption. This leads to perihematomal edema formation and secondary brain injury. Finally, continued bleeding, or hematoma expansion, occurs in many patients—either continued bleeding from the primary source or secondary bleeding at the periphery of the hemorrhage.[19]

Anatomy and Physiology

Blood is supplied to the brain by the anterior and posterior circulations. The anterior circulation originates from the carotid system and perfuses 80% of the brain including the optic nerve, retina, and frontoparietal and anterior-temporal lobes. The first branch off the internal carotid artery is the ophthalmic artery, which supplies the optic nerve and retina. As a result, the sudden onset of painless monocular blindness (amaurosis fugax) identifies the stroke as involving the anterior circulation (specifically the ipsilateral carotid artery) at or below the level of the ophthalmic artery. The internal carotid arteries terminate by branching into the anterior and middle cerebral arteries at the circle of Willis.

The anterior cerebral artery supplies the basal and medial aspects of the cerebral hemispheres and extends to the anterior two thirds of the parietal lobe. The middle cerebral artery feeds the lenticulostriate branches that supply the putamen, part of the anterior limb of the internal capsule, the lentiform nucleus, and the external capsule. Main cortical branches of the middle cerebral artery supply the lateral surfaces of the cerebral cortex from the anterior portion of the frontal lobe to the posterolateral occipital lobe.

Although the posterior circulation is smaller and supplies only 20% of the brain, it supplies the brainstem (which is critical for normal consciousness, movement, and sensation), cerebellum, thalamus, auditory and vestibular centers of the ear, medial temporal lobe, and visual occipital cortex. The posterior circulation is derived from the two vertebral arteries that ascend through the transverse processes of the cervical vertebrae. The vertebral arteries enter the cranium through the foramen magnum and supply the cerebellum by the posterior inferior cerebellar arteries. They join to form the basilar artery, which branches to form the posterior cerebral arteries.

The extent of injury in either an anterior or a posterior stroke depends on both the vessel involved and the presence of collateral blood flow distal to the vessel occlusion. A patient with excellent collateral blood flow from the contralateral hemisphere may have minimal clinical deficits despite a complete carotid occlusion. By contrast, a patient with poor collateral flow may have hemiplegia with the same lesion.

CLINICAL FEATURES

Ischemic Stroke

The signs and symptoms of an ischemic stroke may appear suddenly and without warning or may have a stuttering, insidious onset. Disruption of the flow to one of the major vascular limbs of the cerebral circulation will result in physiologic disruption to the anatomic area of the brain supplied by that blood vessel. Ischemic strokes can be classified as anterior or posterior circulation strokes depending on the vasculature involved. The presence of neurologic deficits is highly dependent on collateral flow. In addition to the vascular supply involved, ischemic strokes can be further described by the temporal presentation of their neurologic deficits. A "stroke in evolution" is one in which focal neurologic deficits worsen over the course of minutes or hours. Approximately 20% of anterior circulation strokes and 40% of posterior circulation strokes will show evidence of progression. Anterior circulation strokes may progress within the first 24 hours, whereas posterior strokes may progress for up to 3 days. Propagation of thrombus is postulated as a likely mechanism for progression. With anterior circulation strokes (involving variously and primarily the carotid, anterior, and middle cerebral arteries), the clinical presentation rarely includes complete loss of consciousness unless the lesion occurs in the previously unaffected hemisphere of a patient who has experienced a previous contralateral stroke. Occlusions in the anterior cerebral artery mainly affect frontal lobe function. The patient has altered mentation coupled with impaired judgment and insight, as well as the presence of primitive grasp and suck reflexes on physical examination. Bowel and bladder incontinence may be features of anterior cerebral artery stroke. Paralysis and hypesthesia of the lower limb opposite the side of the lesion are characteristic. Leg weakness is more pronounced than arm weakness in anterior cerebral distribution stroke. Apraxia or clumsiness in the patient's gait also may be noted.

Marked motor and sensory disturbances are the hallmarks of occlusion of the middle cerebral artery. They occur on the side of the body contralateral to the side of the lesion and usually are worse in the arm and face than the leg. Such disturbances may involve only part of an extremity or the face but almost always are accompanied by numbness in the same region as that of the motor loss. Hemianopsia, or blindness in one half of the visual field, occurs ipsilateral to the lesion. Agnosia, or the inability to recognize previously known subjects, is common, and aphasia may be present if the lesion occurs in the dominant hemisphere. Patients often have a gaze preference toward the affected hemisphere because of disruption of the cortical lateral gaze centers. The clinical aphorism is that a patient looks *at* a destructive lesion (stroke) but *away from* an irritative lesion (seizure focus).

Aphasia, a disorder of language in which the patient articulates clearly but uses language inappropriately or understands it poorly, also is common in dominant-hemisphere stroke. Aphasia may be expressive, receptive, or a combination of both. *Wernicke's aphasia* occurs when the patient is unable to process sensory input such as speech and thus fails to understand verbal communication (receptive aphasia). *Broca's aphasia* refers to the inability to communicate verbally in an effective way, even though understanding may be intact (expressive aphasia). Aphasia should be distinguished from dysarthria, which is a motor deficit of the mouth and speech muscles; the dysarthric patient articulates poorly but understands words and word choices. Aphasia is important to recognize because it usually localizes a lesion to the dominant (usually left) cerebral cortex in the middle cerebral artery distribution. *Aphasia* and *dysphasia* are terms that are used interchangeably but must be distinguished from *dysphagia,* which is difficulty in swallowing.

Pathology in the vertebrobasilar system (i.e., posterior circulation strokes) can cause the widest variety of symptoms and as a result may be the most difficult to diagnose. The symptoms reflect CN deficits, cerebellar involvement, and involvement of neurosensory tracts. The brainstem also contains the reticular activating system, which is responsible for mediating consciousness, and the emesis centers. Unlike those with anterior circulation strokes, patients with posterior circulation stroke can have loss of consciousness and frequently have nausea and vomiting. The posterior cerebral artery supplies portions of the parietal and occipital lobes, so vision and thought processing are impaired. Visual agnosia, the inability to recognize seen objects, may be a feature, as may alexia, the inability to understand the written word. A third nerve palsy may occur, and the patient may experience homonymous hemianopsia. One of the more curious facets of this

www.ketabpezeshki.com 66485457-66963820

syndrome is that the patient may be unaware of any visual problem (visual neglect). Vertigo, syncope, diplopia, visual field defects, weakness, paralysis, dysarthria, dysphagia, spasticity, ataxia, or nystagmus may be associated with vertebrobasilar artery insufficiency. Posterior circulation strokes also demonstrate crossed deficits, such as motor deficits on one side of the body and sensory loss on the other. In anterior circulation strokes, by contrast, abnormalities are always limited to one side of the body.

A focused neurologic examination should assess level of consciousness, speech, CN function, motor and sensory function, and cerebellar function. Level of consciousness and fluency of speech can be rapidly assessed in a dialogue with the patient to determine the presence of dysarthria or aphasia. The head should be evaluated for signs of trauma. Pupillary size and reactivity and extraocular movements provide important information about brainstem function, particularly CN III through CN VI; an abnormal third nerve function may be the first sign of tentorial herniation. Gaze preference suggests brainstem or cortical involvement. Central facial nerve weakness from a stroke should be distinguished from the peripheral causes of CN VII weakness. With a peripheral lesion, the patient is unable to wrinkle the forehead. Assessment of facial sensation, eyebrow elevation and squinting, smiling symmetry, gross auditory acuity, gag reflex, shoulder elevation, sternocleidomastoid strength, and tongue protrusion complete the CN evaluation.

Motor and sensory testing is performed next. Muscle tone can be assessed by moving a relaxed limb. Proximal and distal muscle group strength is assessed against resistance. Pronator drift of the arm is a sensitive sign of motor weakness and can be tested simultaneously by having the patient sit with eyes closed and arms outstretched, with palms toward the ceiling, for 10 seconds. Asymmetrical sensation to pain and light touch may be subtle and difficult to detect. Double simultaneous extinction evaluation tests for sensory neglect and can be easily performed by simultaneously touching the right and left limbs. The patient may feel both the right and left sides being touched individually but may not discern touch on one side when both are touched simultaneously. Similarly, the ability to discern a number gently scratched on a forearm, graphesthesia, is another easily tested cortical parietal lobe function. These tests can help differentiate a pure motor deficit of a lacunar stroke from a sensorimotor middle cerebral artery deficit.

Cerebellar testing and the assessment of reflexes and gait complete the examination. Finger-to-nose and heel-to-shin evaluations are important tests of cerebellar functions. Asymmetry of the deep tendon reflexes or unilateral Babinski's sign may be an early finding of corticospinal tract dysfunction. Gait testing is commonly omitted yet is one of the most informative parts of the neurologic examination. Observing routine ambulation and heel-to-toe walking can assess for subtle ataxia, weakness, or focal cerebellar lesions.

The National Institutes of Health Stroke Scale (NIHSS) is a useful and rapid tool for quantifying neurologic deficit in patients with stroke and can be used in determining treatment options[22] (Box 101-2). NIHSS scores have been shown to be reproducible and valid and to correlate well with the amount of infarcted tissue on CT scan.[23,24] The baseline NIHSS score can identify patients who are appropriate candidates for fibrinolytic therapy as well as those at increased risk for hemorrhage. In addition, it has been used as a prognostic tool to predict outcome and is currently being used by some stroke centers to stratify patients for entry into treatment trials.[22]

Hemorrhagic Stroke

The classic presentation of ICH is the sudden onset of headache, vomiting, severely elevated BP, and focal neurologic deficits that progress over minutes. Similar to ischemic stroke, ICH is often associated with a motor and sensory deficit contralateral to the brain lesion. Almost 40% of patients will demonstrate significant growth in hemorrhage volume within the first few hours.[25]

Although headache, vomiting, and coma are common, many patients do not have these findings, and the clinical presentation can be identical to that of patients with ischemic stroke; the two cannot reliably be differentiated in the absence of neuroimaging (Table 101-2).

Ongoing assessment of airway and mental status is of paramount importance in patients with ICH because precipitous deterioration is always a possibility. Emergency airway management requires careful judgment. On the one hand, airway control can prevent aspiration, hypoxia, and hypercarbia; on the other, sedation and paralysis can make it difficult to follow the neurologic examination, which can help monitor for hemorrhage expansion, elevated intracranial pressure (ICP), seizure activity, and brainstem herniation.

As with ischemic stroke, a careful neurologic examination is important in localizing the region and extent of injury. Baseline NIHSS and Glasgow Coma Scale (GCS) scores can be used to assess stroke severity, although the GCS score may be more feasible to follow for neurologic deterioration (Box 101-3). In addition, serial examinations can detect early changes that may suggest ongoing bleeding during the acute phase.

Poor prognostic indicators for patients with ICH include a decreased level of consciousness on arrival, intraventricular hemorrhage, and large ICH volume, all of which can be assessed in the ED. The ABC/2 technique is a quick and accurate method of measuring ICH volume at the bedside[26] (Fig. 101-1). One validated tool to predict outcome is the ICH score (Box 101-4)[21]: Patients are given 0 to 2 points for GCS score, 1 point for age over 80, 0 to 2 points for ICH volume, 1 point for presence of intraventricular blood, and 1 point for hemorrhage location. This score has been shown to predict short- and long-term mortality.

DIFFERENTIAL CONSIDERATIONS

Ischemic Stroke

Extra-axial collections of blood secondary to trauma can mimic stroke. An epidural or subdural hematoma can cause an altered mental status, focal neurologic signs, and rapid progression to coma. Elders, who represent the age group at highest risk for stroke, can be victims of recurrent falls that lead to chronic subdural hematomas. Carotid dissection may occur after neck trauma or sudden hyperextension and may be associated with focal neurologic signs and symptoms, as with an aortic dissection that extends into the carotid arteries. The diagnosis is supported by a compatible history or relevant findings on computed tomography (CT) imaging or magnetic resonance imaging (MRI).

Other structural lesions that may cause focal neurologic signs include brain tumors and abscesses. Air embolism should be suspected in the setting of marked atmospheric pressure changes, such as in scuba diving or during medical procedures or injuries that may allow air into the vascular system. Seizures, altered mental status, and focal neurologic findings also may be manifestations of air embolism.

Metabolic abnormalities also can mimic stroke syndromes. Hypoglycemia often is responsible for an altered mental status and is a well-known cause of sustained focal neurologic symptoms that can persist for several days. Wernicke's encephalopathy causes ophthalmoplegia, ataxia, and confusion that can be mistaken for signs of cerebellar infarction.

Migraine may present with focal neurologic findings, with or without headache. A seizure followed by Todd's postictal paralysis may mimic stroke. Bell's palsy, labyrinthitis, vestibular neuronitis, peripheral nerve palsy, and demyelinating diseases may all mimic

www.ketabpezeshki.com 66485457-66963820

Box 101-2 National Institutes Of Health (NIH) Stroke Scale Scoring Form

Item	Scoring Definitions	Score
1a. *Level of consciousness (LOC)*	0 = alert and responsive 1 = arousable to minor stimulation 2 = arousable only to painful stimulation 3 = reflex responses or unarousable	
1b. *LOC-related questions:* Ask patient's age and month. Must be exact.	0 = both correct 1 = one correct (or dysarthria, intubated, foreign language) 2 = neither correct	
1c. *Commands:* Open and close eyes, grip and release nonparetic hand. (Other one-step commands or mimic also acceptable.)	0 = both correct (acceptable if impaired by weakness) 1 = one correct 2 = neither correct	
2. *Best gaze:* Horizontal EOM by voluntary or doll's eye maneuver.	0 = normal 1 = partial gaze palsy; abnormal gaze in one or both eyes 2 = forced eye deviation or total paresis that cannot be overcome by doll's eye maneuver	
3. *Visual field:* Use visual threat if necessary. If monocular, score field of good eye.	0 = no visual loss 1 = partial hemianopsia, quadrantanopia, extinction 2 = complete hemianopsia 3 = bilateral hemianopsia or blindness	
4. *Facial palsy:* If patient is stuporous, check symmetry of grimace to pain.	0 = normal 1 = minor paralysis, flat NLF, asymmetrical smile 2 = partial paralysis (lower face = UMN lesion) 3 = complete paralysis (upper and lower face)	
5. *Motor arm:* Arms outstretched 90 degrees (sitting) or 45 degrees (supine) for 10 seconds. Encourage best effort. Indicate paretic limb in score box.	0 = no drift for 10 seconds 1 = drift but does not hit bed 2 = some antigravity effort, but cannot sustain 3 = no antigravity effort, but even minimal movement counts 4 = no movement at all X = unable to assess owing to amputation, fusion, fracture, and so on	L or R
6. *Motor leg:* Raise leg to 30 degrees (from supine) for 5 seconds. Indicate paretic limb in score box.	0 = no drift for 5 seconds 1 = drift but does not hit bed 2 = some antigravity effort, but cannot sustain 3 = no antigravity effort, but even minimal movement counts 4 = no movement at all X = unable to assess owing to amputation, fusion, fracture, and so on	L or R
7. *Limb ataxia:* Check finger-nose-finger, heel-shin position sense; and score only if out of proportion to paralysis.	0 = no ataxia (or aphasic, hemiplegic) 1 = ataxia in upper or lower extremity 2 = ataxia in upper *and* lower extremity X = unable to assess owing to amputation, fusion, fracture, and so on	L or R
8. *Sensory:* Use safety pin. Check grimace or withdrawal if patient is stuporous. Score only stroke-related losses.	0 = normal 1 = mild-moderate unilateral loss but patient aware of touch (or aphasic, confused) 2 = total loss, patient unaware of touch; coma, bilateral loss	
9. *Best language:* Describe cookie jar picture, name objects, read sentences. May use repeating, writing, stereognosis.	0 = normal 1 = mild-moderate aphasia (speech difficult to understand but partly comprehensible) 2 = severe aphasia (almost no information exchanged) 3 = mute, global aphasia, coma; no one-step commands	
10. *Dysarthria:* Read list of words.	0 = normal 1 = mild-moderate; slurred but intelligible 2 = severe; unintelligible or mute X = intubation or mechanical barrier	
11. *Extinction or neglect:* Simultaneously touch patient on both hands, show fingers in both visual fields, ask about deficit, left hand.	0 = normal, none detected (visual loss alone) 1 = neglects or extinguishes to double simultaneous stimulation in any modality (visual, auditory, sensation, spatial, body parts) 2 = profound neglect in more than one modality	

EOM, extraocular movement; *L,* left; *NLF,* nasolabial fold; *R,* right; *UMN,* upper motor neuron.
Modified from online document. Massachusetts General Hospital Stroke Service. NIH stroke scale materials. Scoring form. Available at http://www2.massgeneral.org/stopstroke/pdfs/scoring_form.pdf. Accessed March 6, 2013.

stroke. Ménière's disease may be difficult to distinguish from a posterior circulation stroke or TIA. Dizziness, vertigo, hearing loss, and tinnitus in Ménière's disease are common, whereas difficulties with vision or speech or other focal symptoms are uncommon.

Like stroke, giant cell arteritis is a disease of elders. It may cause severe headache, visual disturbances, and, rarely, aphasia and hemiparesis. Other symptoms include intermittent fever, malaise, jaw claudication, morning stiffness, and myalgias. The diagnosis should be suspected in patients with a very high erythrocyte

www.ketabpezeshki.com 66485457-66963820

Table 101-2 Clinical Findings Associated with Ischemic Strokes, Intracerebral Hemorrhage (ICH), and Subarachnoid Hemorrhage (SAH)

FINDING	ISCHEMIC STROKE	ICH	SAH
Headache	11-17%	33-41%	78-87%
Vomiting	8-11%	29-46%	45-48%
Decreased level of consciousness	13-15%	39-57%	48-68%
Seizure	0.3-3%	6-7%	7%

Data from Bogousslausky J, Van Melle G, Regli F: The Lausanne Stroke Registry: Analysis of 1000 consecutive patients with first stroke. Stroke 19:1083, 1988; Foulkes MA, et al: The Stroke Data Bank: Design, methods, and baseline characteristics. Stroke 19:547, 1988; and Mohr JP, et al: The Harvard Cooperative Stroke Registry: A prospective registry. Neurology 28:754, 1978.

Box 101-3 Glasgow Coma Scale

Eye Opening (E)	Verbal Response (V)	Motor Response (M)
4 = Spontaneous	5 = Normal conversation	6 = Normal
3 = To voice	4 = Disoriented conversation	5 = Localizes to pain
2 = To pain	3 = Words, but not coherent	4 = Withdraws to pain
1 = None	2 = No words; only sounds	3 = Decorticate posture
	1 = None	2 = Decerebrate posture
		1 = None

Total score = E + V + M

Shoestring Graphics. Glasgow coma score. Available at http://www.ssgfx.com/CP2020/medtech/glossary/glasgow.htm. Accessed March 6, 2013.

Figure 101-1. The computed tomography (CT) slice with the largest area of hemorrhage is identified. The largest diameter of the hemorrhage on this slice is measured in centimeters *(A)*. The largest diameter 90 degrees to A on the same slice is measured *(B)*. C is the approximate number of 10-mm slices on which the intracerebral hemorrhage was seen (many centers use 5-mm slices, in which case an adjustment can be made by dividing by 2). The volume of the hemorrhage equals A multiplied by B multiplied by C, divided by 2 (ABC/2).

Box 101-4 Intracerebral Hemorrhage (ICH) Score: Predicting Mortality after Acute ICH

Feature	Points
GCS Score	
3-4	2
5-12	1
13-15	0
ICH Volume	
>30 mL	1
≤30 mL	0
IVH (Intraventricular Blood)	
Present	1
Absent	0
ICH Location	
Infratentorial	1
Supratentorial	0
Age	
≥80 years	1
<80 years	0

30-Day Mortalities for Total ICH Scores

0 = 0%
1 = 13%
2 = 26%
3 = 72%
4 = 97%
5 = 100%
6 = estimated to be 100%; no patients in the study fell into this category

Adapted from Hemphill JC, et al: The ICH Score. Stroke 32:891-897, 2001.
GCS, Glasgow Coma Scale; *IVH,* intraventricular hemorrhage.

sedimentation rate (ESR) and is confirmed by temporal artery biopsy. Collagen vascular diseases such as polyarteritis nodosa, lupus, and other types of vasculitis may cause stroke syndromes.

Venous sinus thrombosis is another cause of focal neurologic symptoms that most commonly affects the superior sagittal sinus and lateral sinuses (see Chapter 105). The diagnosis of cerebral venous thrombosis can be difficult because of the nonspecific nature of symptoms, as well as the variable time frame of symptom onset (from hours to a few weeks). Patients may have generalized headaches, nausea, vomiting, paresis, visual disturbances, depressed level of consciousness, seizures or even symptoms generally ascribed to psychiatric disorders (such as depression).[27] Depending on the location of the thrombus, physical examination of the patient may reveal papilledema, proptosis, or palsies of CNs III, IV, and VI, as well as other focal neurologic signs and symptoms.[27] Multiple risk factors predisposing affected patients to venous sinus thrombosis are recognized, including trauma, infectious processes, hypercoagulable states, low-flow states, compression of the venous sinus, dehydration, various drugs (such as androgens, “ecstasy,” and oral contraceptives), and pregnancy or the postpartum state.

Hemorrhagic Stroke

The differential diagnosis for ICH is similar to that for ischemic stroke; considerations include migraine, seizure, tumor, abscess, hypertensive encephalopathy, and trauma. Hypertensive encephalopathy and migraine also can manifest with headache, nausea, and vomiting, although focal neurologic signs are less common in these entities. With hypertensive encephalopathy, patients usually exhibit marked elevation in BP and other evidence of end-organ injury, such as proteinuria, cardiomegaly, papilledema, and malignant hypertensive retinopathy. These patients usually improve

www.ketabpezeshki.com 66485457-66963820

significantly with treatment of their hypertension. Migraines frequently are associated with an aura, and the patient often has a history of similar headaches.

Once ICH is appreciated on neuroimaging, it can be difficult to determine underlying cause. Primary ICH typically manifests as a parenchymal hematoma with new onset neurologic symptoms. Patients with hemorrhagic transformation of an ischemic stroke may have recurrence or worsening of previously established deficits. Patients with known underlying cancer, or perihematomal edema out of proportion to the hemorrhage, should be considered for hemorrhage into a metastasis or primary tumor. Younger patients with a predominantly lobar location are at higher risk for underlying aneurysm or AVM.[20] Finally, patients with known underlying venous thromboembolic risk factors may have underlying cerebral venous sinus thrombosis (CVST).

DIAGNOSTIC STRATEGIES

Ischemic Stroke

Although clinical data can help establish the diagnosis, cause, and location of the stroke, confirmatory diagnostic tests are often required to establish the final cause or to eliminate other causes for the deficits. The immediate evaluation includes a blood glucose determination, cranial imaging (CT or MRI scan), and an electrocardiogram (ECG).

An emergent noncontrast cranial CT is the standard initial imaging technique for evaluating a patient with a potential stroke. It can quickly differentiate an ischemic stroke from ICH and other mass lesions. This information is crucial to the subsequent therapeutic decisions that must be rapidly made. A CT scan can identify almost all parenchymal hemorrhages larger than 1 cm in diameter. Recent studies have a high sensitivity for the detection of SAH by CT scan.[28] In a majority of ischemic strokes, gross signs of infarction will not appear on routine CT scans for at least 6 to 12 hours, depending on the size of the infarct. However, subtle, early ischemic changes have been noted in up to 67% of noncontrast CT scans within the first 3 hours.[28] These early ischemic changes include the hyperdense artery sign (acute thrombus in a vessel), sulcal effacement, loss of the insular ribbon, loss of gray-white interface, mass effect, and acute hypodensity (Fig. 101-2). In addition, CTA can be used to identify the presence of intravascular thrombosis, vasculature dissection, or stenosis. In cases in which arterial dissection is suspected, imaging with MRA or CTA is indicated.[12]

The clinical importance of early ischemic CT findings with regard to fibrinolytic therapy within 3 hours of symptom onset is questionable because the ability of treating physicians to reproducibly identify these findings is poor and their clinical significance is questionable.[28-30] Only acute hypodensity and mass effect have been shown to be associated with an increased risk of ICH after fibrinolysis (over that in treated patients without these findings). However, these findings do not exclude appropriate patients from fibrinolytic therapy, because the chance for excellent neurologic outcome at 3 months has been found to be better with such therapy than with placebo despite the presence of such abnormalities, and the risk of symptomatic ICH, severe disability, or death at 3 months was no different between treatment groups.[29] Patients with a hyperdense artery sign and acute hypodensity of one third of the middle cerebral artery distribution tend to have a poorer prognosis; however, their outcomes are still better with tPA treatment than without such treatment.[29]

The role of MRI in the evaluation of stroke continues to evolve. MRI can visualize ischemic infarcts earlier and identify acute posterior circulation strokes more accurately than CT. In addition, recent studies suggest that it is as effective as CT in identifying ICH.[28] However, availability, difficulty in accessing critically ill

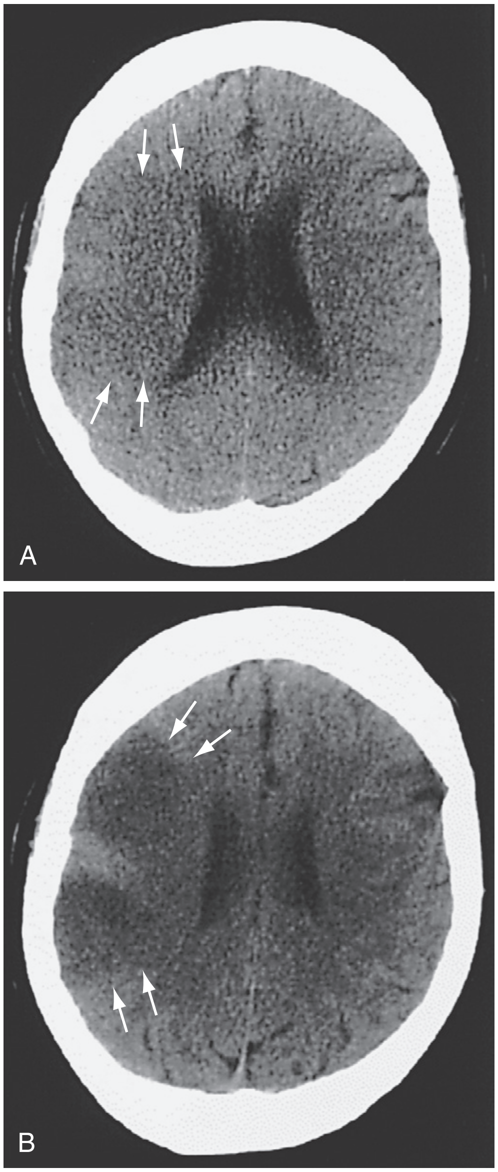


Figure 101-2. **A,** Computed tomography (CT) scan taken 2 hours and 50 minutes after a large right middle cerebral artery occlusion. There are subtle, ultra-early ischemic changes, including loss of the gray-white interface *(arrows)* and subtle evidence of sulcal effacement. **B,** CT scan of same patient approximately 8 hours after symptom onset shows acute hypodensity *(arrows)* and more prominent sulcal effacement.

patients, and scan time limit the use of MRI in acute stroke. Advances in MRA technology have allowed a noninvasive method of demonstrating large-vessel occlusions of the anterior and posterior circulation, though small intracranial vascular occlusions may not be readily apparent. With the improvements in MRI and MRA speed and resolution, some stroke centers are replacing CT protocols with limited "stroke protocol" MRI or MRA as the initial imaging modality of choice. The choice of initial cranial imaging modality is highly dependent on the speed with which these scans can be performed and interpreted at each individual center.

Diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) are MRI techniques that take minutes to perform and may allow differentiation between reversible and irreversible neuronal injury. In one study of patients with DWI-PWI mismatch, 30-day clinical outcomes were better after early reperfusion than without such early reperfusion (56% and 19%, respectively).[31] Of importance, however, early reperfusion in patients without

www.ketabpezeshki.com 66485457-66963820

DWI-PWI mismatch did not result in a favorable outcome. Other potential imaging modalities include CTA and perfusion scans. In CTA, a CT scan is enhanced by an intravenous contrast agent to better define the vasculature of the brain. Areas of vascular stenosis and occlusion can be visualized with this technique. This information can then be used by interventionalists to determine whether a lesion is amenable to intra-arterial thrombolysis or mechanical retrieval. Also requiring intravenous contrast, perfusion CT scans can reveal perfusion deficits within different regions of the brain. In addition, CTA and perfusion CT can differentiate reversible from irreversible ischemic insults.[28]

An ECG is indicated in all patients with acute ischemic stroke because atrial fibrillation and acute MI are associated with up to 60% of all cardioembolic strokes. The hematologic evaluation includes a complete blood count with platelet count, prothrombin time (including international normalized ratio), partial thromboplastin time, and serum glucose measurement. A toxicologic screen and cardiac isoenzyme assay should be considered if appropriate. Elevated blood viscosity, even when hematocrit levels are not frankly polycythemic, can affect blood flow and prognosis. A platelet count can identify thrombocytosis or thrombocytopenia, which may precipitate a thrombosis or hemorrhage. Coagulation studies are especially helpful to guide management for patients in whom anticoagulation is being considered or for patients with a hemorrhagic stroke. Cocaine or amphetamine ingestion should be considered with either an ischemic or hemorrhagic stroke in patients younger than 40 years of age.

Other ancillary diagnostic tests to consider include an echocardiogram, carotid duplex scan, and angiogram. Some centers are performing these studies as part of a TIA observation unit protocol in the ED. An echocardiogram can identify a mural thrombus, tumor, patent foramen ovale, or valvular vegetation in those patients in whom a cardioembolic stroke is suspected. An echocardiogram also should be considered in patients with no obvious cause for their stroke. Carotid duplex scanning may be helpful in patients with known or suspected high-grade carotid stenosis with worsening neurologic deficit or crescendo TIAs.[28,32] These patients may be candidates for heparinization or emergent carotid endarterectomy. Carotid duplex studies can accurately identify carotid artery stenosis with occlusion of more than 60% vessel diameter, but an angiogram is required to distinguish 95% stenosis from a complete occlusion. Finally, angiography can demonstrate stenosis or occlusion of both large and small blood vessels of the head and neck. It can detect subtle abnormalities, such as with dissection, that may not be demonstrated with other imaging techniques.

Hemorrhagic Stroke

The hematologic evaluation for the patient with hemorrhagic stroke should be performed in the same manner as for the patient with ischemic stroke. Particular attention should be directed to uncovering the presence of a coagulopathy. A drug screen should be obtained to evaluate for use of sympathomimetics if substance abuse is suspected. Increased sympathetic outflow secondary to the hemorrhage may lead to an increase in dysrhythmias. Dysrhythmias also may signal impending brainstem compression from an expanding hemorrhage.

As in ischemic stroke, the cranial CT scan is the diagnostic test of choice to evaluate for an ICH.[3] The noncontrast CT scan will reliably diagnose patients with clinically relevant acute ICH. Hemorrhages that are several days old may not be as apparent as acute hemorrhages, and appear as isodense regions.

Also, as with ischemic stroke, advanced neuroimaging modalities are gaining favor in ICH. First, CTA produces high-quality images of the larger arterial vessels and can help exclude secondary causes such as aneurysm, AVM, or fistula. In addition, some patients with primary ICH show contrast extravasation on CTA, and such patients are at particularly high risk of ongoing bleeding and hematoma expansion. Second, a venous phase can be added to this study (CT venography [CTV]) to evaluate for CVST. Third, MRI can help detect underlying lesions such as tumor and may offer better resolution for evaluating perihematomal edema. Use of gradient-echo imaging (GRE) provides the ability to detect white matter hyperintensities and previous small ICHs (microbleeds), which can both guide the clinician as to the underlying cause of ICH and predict risk of future hemorrhage. Fourth, MRA and magnetic resonance venography (MRV) can be used in place of CTA and CTV for appropriate patients. Finally, digital subtraction angiography (DSA) remains (in many centers) the gold standard to rule out an underlying vascular abnormality.

STROKE MANAGEMENT

Ischemic Stroke

With the recent focus on rapid recognition, evaluation, and treatment of stroke, many hospitals have attempted to streamline the care of these patients to meet recommended time goals (Table 101-3). This has led to the development of various stroke protocols, critical pathways, and acute interventional stroke teams that often are deployed in the field before the patient even arrives at the ED.

In the prehospital setting, the focus should be on maintenance of the ABCs (airway, breathing, and circulation), rapid identification, early hospital notification, and rapid transport.[33] Although it is unusual for patients with ischemic stroke to be unresponsive on presentation, their ability to communicate may be altered secondary to dysphasia. After an ischemic stroke, patients usually can maintain their airway unless the brainstem is affected or unless significant cerebral edema is compressing the opposite hemisphere. Patients with intact protective airway reflexes should receive oxygen if they are hypoxic (oxygen saturation less than 95%),[33] and a monitor and intravenous line should be established.

Overhydration should be avoided to prevent cerebral edema. By contrast, dehydration may lead to decreased cerebral perfusion, and saline infusion should be given if dehydration is suspected. Dextrose-containing solutions should be avoided in normoglycemic patients suspected of having had a stroke because elevated blood glucose levels may worsen an ischemic deficit. Out-of-hospital personnel should attempt to rapidly ascertain the patient's blood sugar. If this is not possible, glucose should be given only to diabetic patients in whom hypoglycemia is strongly suspected. Electrocardiographic monitoring is recommended to identify life-threatening arrhythmias and atrial fibrillation.[33]

The circumstances surrounding the stroke as well as concomitant medical conditions should be ascertained. A key part of the

Table 101-3 NINDS-Recommended Stroke Evaluation Targets for Potential Thrombolytic Candidates

MANAGEMENT COMPONENT	TARGET TIME FRAME
Door to doctor	10 min
Door to CT completion	25 min
Door to CT scan reading	45 min
Door to treatment	60 min
Access to neurologic expertise*	15 min
Access to neurosurgical expertise*	2 hr

CT, computed tomography; *NINDS,* National Institute of Neurological Disorders and Stroke.
*By phone or in person.

www.ketabpezeshki.com 66485457-66963820

initial information on stroke patients is the prehospital providers' documentation of the exact time the patient was last seen to be neurologically normal and the level of neurologic functioning. This is especially important because reversible defects may completely resolve by the time the patient has arrived at the hospital. The level of consciousness, gross focal motor deficits, difficulty with speech, clumsiness, facial asymmetry, and any other focal deficits should be noted. Prehospital stroke scales have been developed to assist in differentiating patients who have had a stroke from those who have not and to identify potential candidates for fibrinolytic therapy.[33] Early recognition, notification, and transport by emergency medical services (EMS) and other out-of-hospital personnel have been shown to be valuable in enabling early treatment.[33]

In the ED setting, the ABCs should be reassessed on an ongoing basis, because patients may experience rapid deterioration, even with subacute stroke. Some stroke patients are found at home 1 or 2 days after the event has occurred and may have concomitant illnesses, such as aspiration pneumonia, dehydration, hypothermia, rhabdomyolysis, or myocardial ischemia. Fever necessitates a thorough evaluation to identify the source of infection, followed by prompt institution of appropriate treatment. As supported by strong evidence, even minor degrees of hyperthermia will result in worsening of the neurologic injury.[33]

Blood Pressure Management

The management of BP in patients with acute ischemic stroke and TIA is controversial because of limited data. Current guidelines for the management of hypertension in patients with acute ischemic stroke recommend that antihypertensive treatment be reserved for those with markedly elevated BPs, unless fibrinolytic therapy is planned or specific medical indications are present.[7] These medical indications include (1) acute MI, (2) aortic dissection, (3) true hypertensive encephalopathy, and (4) severe left ventricular failure.

Oral or parenteral agents are withheld unless the patient's systolic pressure is greater than 220 mm Hg, diastolic pressure is greater than 120 mm Hg, or mean arterial pressure (MAP) is greater than 130 mm Hg (Box 101-5). If parenteral agents are used, labetalol or nicardipine is favored because of ease of titration and limited effect on cerebral blood vessels. Sublingual nifedipine or sublingual nitroglycerin is not recommended because either agent can produce a precipitous drop in BP.[7]

If fibrinolytic therapy is planned, stringent control of BP is indicated to reduce the potential for intracranial hemorrhage after the thrombolytic is administered (Box 101-5).[7]

Thrombolytic therapy is not recommended for patients whose systolic pressure is consistently higher than 185 mm Hg or whose diastolic pressure is 110 mm Hg at the time of treatment. Simple measures can be used to try lowering BP below this level. Recommended approaches include the use of nitroglycerin paste and one or two doses of intravenous labetalol 10 to 20 mg. If more aggressive measures are required to reduce BP below 185/110 mm Hg, the use of tPA is not recommended. Once thrombolytic therapy has been initiated, BP must be monitored closely and hypertension treated aggressively.

Just as problematic as high BP can be, low BP can be quite detrimental to patients with ischemic stroke.[7] Normally normotensive stroke patients with low BP or normally hypertensive stroke patients with low or even low-normal BP are given a fluid bolus to try to increase cerebral perfusion. This is especially important in patients in a dehydrated state. If initial fluid challenge is ineffective, the patient may require vasopressor therapy (e.g., with dopamine) to gradually increase MAP and improve cerebral perfusion.[7]

Box 101-5 Emergency Antihypertensive Therapy for Acute Ischemic Stroke

- Indication that patient is eligible for treatment with intravenous rtPA or other acute reperfusion intervention
  - Blood pressure level
    - Systolic >185 mm Hg or diastolic >110 mm Hg
      - Labetalol 10-20 mg IV over 1-2 min, may repeat × 1
      - *or*
      - Nitropaste 1-2 inches
      - *or*
      - Nicardipine infusion, 5 mg/hr, titrate up by 2.5 mg/hr at 5- to 15-min intervals, maximum dose 15 mg/hr; when desired blood pressure attained, reduce to 3 mg/hr
    - If blood pressure does not decline and remains >185/110 mm Hg, do not administer rtPA
- Management of blood pressure during and after treatment with rtPA or other acute reperfusion intervention
  - Monitor blood pressure every 15 min during treatment and then for another 2 hr, then every 30 min for 6 hr, and then every hour for 16 hr
  - Blood pressure level
    - Systolic 180-230 mm Hg or diastolic 105-120 mm Hg
      - Labetalol 10 mg IV over 1-2 min, may repeat every 10-20 min, maximum dose of 300 mg
      - *or*
      - Labetalol 10 mg IV followed by an infusion at 2-8 mg/min
    - Systolic >230 mm Hg or diastolic 121-140 mm Hg
      - Labetalol 10 mg IV over 1-2 min, may repeat every 10-20 min, maximum dose of 300 mg
      - *or*
      - Labetalol 10 mg IV followed by an infusion at 2-8 mg/min
      - *or*
      - Nicardipine infusion, 5 mg/hr, titrate up to desired effect by increasing 2.5 mg/hr every 5 min to maximum of 15 mg/hr
    - If blood pressure not controlled, consider sodium nitroprusside

(Adapted from Adams HP Jr, et al; American Heart Association; American Stroke Association Stroke Council; Clinical Cardiology Council; Cardiovascular Radiology and Intervention Council: Guidelines for the early management of adults with ischemic stroke: A guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke 2007; 38:1655-1711, 2007.)

Acute Drug Therapy

To date, only the use of intravenous tPA has been approved by the U.S. Food and Drug Administration (FDA) for treatment of patients with acute ischemic stroke. These recommendations initially were based on the results of the National Institute of Neurological Disorders and Stroke (NINDS) trial, although subsequent analysis of other studies has supported its use.[34-36] Concern previously emerged regarding the safety of the use of tPA in community practice.[37] However, a meta-analysis of non–trial-related use of tPA (N = 2639) in community practice demonstrates efficacy and safety for tPA similar to that reported in the NINDS trial.[38] The current recommendation for recombinant tPA (rtPA) is that it be administered intravenously at a dose of 0.9 mg/kg to a maximum of 90 mg (10% of the dose given as a bolus followed by an infusion lasting 60 minutes). Although the initial recommended time window for intravenous tPA administration was 3 hours since the patient was last known to be at his or her neurologic baseline, a subsequent study has demonstrated the usefulness of intravenous tPA at 3 to 4.5 hours in a carefully selected subgroup of acute

www.ketabpezeshki.com 66485457-66963820

Box 101-6 Fibrinolytic Therapy for Acute Ischemic Stroke in the 0- to 3-Hour Time Window: Inclusion and Exclusion Criteria

Inclusion Criteria

1. Age 18 years or older
2. Clinical diagnosis of ischemic stroke causing a measurable neurologic deficit
3. Time of symptom onset well established to be less than 180 minutes before treatment would begin

Exclusion Criteria

1. Evidence of intracranial hemorrhage on noncontrast head CT
2. Only minor or rapidly resolving stroke symptoms
3. High clinical suspicion of subarachnoid hemorrhage even with normal CT findings
4. Active internal bleeding (e.g., gastrointestinal or urinary bleeding within last 21 days)
5. Known bleeding diathesis, including but not limited to:
   - Platelet count <100,000/μL
   - Patient has received heparin within 48 hours and had an elevated activated partial thromboplastin time (greater than upper limit of normal for laboratory)
   - Recent use of anticoagulant (e.g., warfarin sodium) and elevated prothrombin time >15 seconds
6. Within 3 months of intracranial surgery, serious head trauma, or previous stroke
7. Within 14 days of major surgery or serious trauma
8. Recent arterial puncture at noncompressible site
9. Lumbar puncture within 7 days
10. History of intracranial hemorrhage, arteriovenous malformation, or aneurysm
11. Witnessed seizure at stroke onset
12. Recent acute myocardial infarction
13. On repeated measurements, systolic pressure >185 mm Hg or diastolic pressure >110 mm Hg at time of treatment, requiring aggressive treatment to reduce blood pressure to within these limits

CT, computed tomography.

Box 101-7 Fibrinolytic Therapy for Acute Ischemic Stroke in the 3- to 4.5-Hour Time Window: Inclusion and Exclusion Criteria

Main Inclusion Criteria

Acute ischemic stroke
Age 18 to 80 years
Onset of stroke symptoms 3 to 4.5 hours before initiation of study-drug administration
Stroke symptoms present for at least 30 minutes with no significant improvement before treatment

Main Exclusion Criteria

Intracranial hemorrhage
Time of symptom onset unknown
Symptoms rapidly improving or only minor before start of infusion
Severe stroke as assessed clinically (e.g., NIHSS score >25) or by appropriate imaging techniques*
Seizure at the onset of stroke
Stroke or serious head trauma within the previous 3 months
Combination of previous stroke and diabetes mellitus
Administration of heparin within the 48 hours preceding the onset of stroke, with an activated partial-thromboplastin time at presentation exceeding the upper limit of the normal range
Platelet count of less than 100,000/mm^3
Systolic pressure greater than 185 mm Hg or diastolic pressure greater than 110 mm Hg, or aggressive treatment (intravenous medication) necessary to reduce blood pressure to these limits)
Blood glucose less than 50 mg/dL or greater than 400 mg/dL
Symptoms suggestive of subarachnoid hemorrhage, even if CT scan was normal
Oral anticoagulant treatment
Major surgery or severe trauma within the previous 3 months
Other major disorders associated with an increased risk of bleeding

Adapted from Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al; ECASS Investigators: Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 359:1317-1329, 2008.
CT, computed tomography.
*A severe stroke as assessed by imaging was defined as a stroke involving more than one third of the middle cerebral artery territory.
NIHSS denotes National Institutes of Health Stroke Scale, in which total scores range from 0 to 42, with higher values reflecting more severe cerebral infarcts.

ischemic stroke patients[39] (Boxes 101-6 and 101-7). Intravenous tPA is not recommended when the time of stroke onset cannot be ascertained reliably, including strokes recognized on awakening. In addition, caution is warranted in treating patients with large strokes (NIHSS score of 20 or higher) or those with early CT changes from a recent major infarction (e.g., acute hypodensity or mass effect) because they are at increased risk for symptomatic hemorrhage.[7,40] A recent study suggests that patients with mild or rapidly resolving symptoms may still benefit from the use of intravenous tPA.[25]

Intra-arterial thrombolysis is an alternative treatment for eligible patients seen beyond the 3-hour time window but within 6 hours of symptom onset.[41,42] In the Prolyse in Acute Cerebral Thromboembolism II (PROACT II) study, patients with middle cerebral artery strokes were 58% more likely than those who received a placebo to have little or no neurologic disability at 90 days when treated with intra-arterial prourokinase up to 6 hours after stroke onset.[41] In addition, the use of intra-arterial thrombolysis in patients with posterior circulation strokes and those unresponsive to initial treatment with intravenous tPA also is being evaluated and has shown favorable outcomes.[7,43-46]

Various mechanical clot retrieval devices are being investigated. The best studied is the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) retrieval device. This corkscrew-like device has been shown to be successful in recanalizing intracranial lesions of the internal carotid artery and has demonstrated improved clinical outcomes and survival when compared with outcomes of patients who do not have successful recanalization of the artery.[47] Successful recanalization has been achieved when performed within an 8-hour window of symptom onset.[48,49] In 2004 the FDA approved the MERCI retrieval device for use in the setting of acute ischemic stroke.

Previous studies have focused on the use of antiplatelet agents in acute ischemic stroke. Data from two large trials involving almost 40,000 patients indicate that early use of aspirin in patients with acute ischemic stroke who were not treated with a fibrinolytic agent was associated with a small but significant reduction in rates of stroke recurrence and mortality.[50] These studies in combination suggest a number needed to treat of 77 (i.e., 77 stroke patients would need to be treated with daily aspirin therapy to prevent a poor outcome, such as death, dependency at discharge, or at 6 months after stroke, in 1 patient). The need for acute administration of aspirin in the ED is unclear, because patients were given aspirin up to 48 hours after stroke onset. Aspirin should not be given for the first 24 hours to patients who have received a fibrinolytic agent.[7]

The use of low-molecular-weight or unfractionated heparin is common in patients with acute ischemic stroke or TIAs, but its value is unclear. It may be that any reduction in risk of subsequent ischemic stroke is balanced by an increased risk of hemorrhagic stroke. To date, no studies have definitively established the efficacy

www.ketabpezeshki.com 66485457-66963820

of anticoagulants in the management of patients with acute ischemic stroke, and current AHA guidelines recommend against the routine use of heparinoids in this population.[7,51,52] However, heparin is sometimes considered in select patients at high risk for stroke progression, including patients with crescendo TIAs or TIA from a cardioembolic source, patients with a high-grade carotid artery stenosis, patients with posterior circulation TIA, and patients with evolving strokes. Heparin is recommended for the treatment of carotid and vertebral artery dissection unless a contraindication such as intracranial extension is present. If a dissection is diagnosed and the patient has no symptoms of ischemia, treatment with antiplatelet therapy alone may be an option.[13] Heparin therapy should not be initiated in patients with suspected endocarditis or in any patient until a CT scan has ruled out intracranial bleeding. Owing to the lack of consistent evidence of efficacy, the most prudent course in the ED setting is to determine the need for heparin therapy in conjunction with the patient's neurologist or the admitting physician.

General supportive care should not be overlooked. Antipyretics should be provided for patients who are febrile (while an infectious source is also sought). Hyperglycemia appears to be neurotoxic, and many patients demonstrate this finding even in the absence of known diabetes; although intensive insulin therapy is not clearly beneficial, some form of glucose control such as with sliding scale subcutaneous therapy is probably warranted.[53,54] Oral medications (and food) should be withheld until some form of swallowing assessment has been performed, given the risk of aspiration in patients with compromised swallowing function.[55] Finally, as mentioned earlier, there is some evidence favoring admission to a stroke unit.[56]

Intracerebral Hemorrhage

Overall, no specific therapy has been demonstrated to improve the outcome of patients with ICH in a phase III clinical trial. However, indirect evidence supports the value of aggressive medical care. Patients admitted to a specialized unit, patients who are expedited to the ICU, those admitted on a weekday, and those treated more aggressively appear to have better neurologic outcomes.[57-61] Therefore, even in the absence of therapies specifically proven in phase III trials, multidisciplinary care by specially trained care teams appears to provide benefit.

The patient with suspected ICH requires rapid assessment and transport to a care center with rapid neuroimaging and intensive care management facilities. Out-of-hospital management is similar to that for ischemic stroke, including determination of time of onset, concomitant medications, and application of a prehospital stroke scale.

Supportive care involving attention to airway management and perfusion is of the highest priority. Patients with hemorrhagic stroke are more likely to have an altered level of consciousness that may rapidly progress to unresponsiveness requiring emergent endotracheal intubation. After intubation, a short-acting medication for sedation should be considered, so that a neurologic examination can be repeatedly performed and the findings evaluated. Standard care includes establishing intravenous access and cardiac monitoring. Evaluation of blood glucose and appropriate dextrose and naloxone administration are essential in any patient with altered mental status.

Patients seen early after symptom onset are at high risk of ongoing bleeding. Approximately 30% of such patients will have significant hematoma expansion on presentation, leading to neurologic deterioration and worse outcome. Major therapies aimed at reducing this risk include BP reduction, anticoagulation reversal, and hemostatic therapy.

BP control is commonly performed after ICH. This intervention is controversial, as hypertension may potentiate further bleeding, but lowering BP in a patient with chronic hypertension may decrease CBF, worsening brain injury. One randomized trial found that lowering systolic BP to below 140 reduced ongoing bleeding, but there was no change in neurologic outcome, suggesting that this therapy may not provide clinical benefit in unselected patients.[62] The current consensus regarding management of ICH is to recommend antihypertensive treatment with parenteral agents for systolic pressures higher than 160 to 180 mm Hg or MAP higher than 130 mm Hg. Agents that are thought to minimize risk of ICP elevation include labetalol, esmolol, nicardipine, and hydralazine.[3]

Many patients are anticoagulated at the time of their ICH. In the absence of clinical trials, most experts believe that emergency anticoagulation reversal can minimize the risk of further bleeding. For patients on warfarin, this can be reversed with intravenous vitamin K, supplemented with either fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC).[3] Whether antiplatelet agents increase ongoing bleeding is controversial[63]; some providers transfuse platelets for those patients taking such agents.

Hemostatic therapy (treatment with procoagulant agents) was promising at one time, with a phase II trial of recombinant factor VIIa showing the ability to reduce hematoma expansion.[64] However, a phase III trial showed no clinical benefit[65]; as a result, there is no current evidence that patients with a normal underlying coagulation system will benefit from such agents.

For patients with clinical or radiographic evidence of elevated ICP, therapies aimed at lowering ICP should be considered. First, neurosurgical consultation is obtained to evaluate the benefits of an external ventricular drain (EVD) placement or hematoma evacuation. Pending consultation, a number of medical therapies aimed at decreasing ICP are available; however, these interventions should not be used prophylactically.[3] Hyperventilation can be a temporizing measure pending more definitive treatment. Mannitol moves fluid from the intracranial compartment, thereby reducing cerebral edema. Hypertonic saline (3% or 23.4%) can be used as an alternative to mannitol or in combination. Other experimental modalities include barbiturate coma and hypothermia.

Seizure activity can cause neuronal injury, elevations in ICP, and destabilization of an already critically ill patient. However, there is observational evidence that prophylactic administration of antiepileptic therapy (AED) may be harmful[3]; therefore AEDs should be reserved for patients with known or suspected seizure (or nonconvulsive seizure).

Surgical evacuation of the hematoma is not beneficial in most cases of noncerebellar ICH.[66] Selected patients with a sizable lobar hemorrhage that is proximal to the cortical surface and associated with progressive neurologic deterioration may benefit from surgical drainage. Recent studies have also suggested that minimally invasive surgery, stereotactic insertion of a catheter, may provide some benefit to selected patients.[19] For patients with cerebellar hemorrhage, surgery can be lifesaving, as the infratentorial space is much more limited and high ICP can disrupt vital brainstem functions. For this reason, many neurosurgeons will consider emergent surgery for patients with cerebellar hemorrhage within 48 hours of onset.

In cases of severe intraventricular hemorrhage or hemorrhages in the posterior fossae, the normal circulation of cerebrospinal fluid (CSF) can become interrupted, leading to the development of hydrocephalus. This condition is characterized by an abnormal rise in CSF volume. In such cases, neurosurgeons will often place a ventricular catheter. Some groups infuse thrombolytic agents through the catheter to help break up the clot and minimize the risk of hydrocephalus.[19]

Finally, as with ischemic stroke, general supportive care should be provided to minimize neuronal injury. This includes treating

www.ketabpezeshki.com 66485457-66963820

hyperthermia (such as with acetaminophen), and treating hyperglycemia with insulin.

DISPOSITION

Ischemic Stroke and Transient Ischemic Attacks

"Stroke center" definitions have been proposed, and a national certification process for primary stroke centers is now underway. In broad terms, institutional certification as a primary stroke center requires the establishment of a stroke infrastructure (such as a stroke team, stroke unit, patient care protocols, and support services including CT scanning and laboratory testing availability), as well as institutional administrative support and strong leadership.[67] In addition, recommendations have been established for comprehensive stroke centers (CSCs). CSCs are expected to have the capability to provide the full spectrum of care to patients with stroke and other cerebrovascular diseases. More specifically, CSCs should offer advanced imaging modalities, perform surgical and endovascular interventions, and maintain a core infrastructure such as a stroke unit and stroke registry.[68] The establishment of primary stroke centers (PSCs) and CSCs is intended to improve outcomes for stroke patients by providing them with a high level of coordinated care.

It has been recommended that patients with symptoms consistent with an acute stroke should be transported to emergency facilities capable of initiating fibrinolytic therapy within 1 hour of hospital arrival. At a minimum, this requires emergent CT capabilities, an institutional "acute stroke protocol," and availability of a physician knowledgeable in the use of thrombolytic therapy. Intensive care monitoring and neurosurgery capabilities should be available within 2 hours of drug initiation, either at the treating hospital or by helicopter or ground transport to an appropriate health care facility.[69]

In most cases, once the diagnosis of an acute stroke or stroke syndrome is established and the patient is stabilized, hospitalization will be necessary for further evaluation and treatment. Patients may deteriorate over the first 24 hours and require close in-hospital monitoring. Most patients can be managed on a general medical or telemetry unit, although there is evidence suggesting a benefit from admission to a stroke-specific unit (see later). Patients with large acute hemispheric strokes (associated with increased risk of herniation) or with significant posterior circulation-related changes and those treated with a fibrinolytic agent should be monitored in a step-down or intensive care unit for at least 24 hours.

Some hospitals have specialized stroke units that provide organized, multidisciplinary care to stroke inpatients. A previous evidence-based medicine review amalgamated the results of 26 trials that compared the outcomes for more than 5500 stroke patients treated in either specialized stroke units or general wards. This review found a 14% reduction in the odds of poststroke mortality for patients treated in a stroke unit compared with patients managed on a general ward (odds ratio [OR] 0.86; 95% confidence interval [CI] 0.76 to 0.98). A similar reduction was found for the composite outcomes of death or institutionalized care (OR 0.82; 95% CI 0.73 to 0.92) and death or dependency (OR 0.82; 95% CI 0.73 to 0.92). All outcomes were independent of age, sex, or stroke severity, and evidence for increase in hospital length of stay by treatment in a stroke unit was lacking.[70]

Patients with new-onset TIAs require expedited evaluation and treatment owing to the substantial short-term risk of stroke and other adverse events.[18] Emergency neuroimaging, vascular imaging (such as with a carotid Doppler study, MRA, or CTA), electrocardiography, and basic blood tests should be performed. A medically or surgically treatable cause for TIAs (e.g., high-grade carotid stenosis, mural thrombus) should be sought, which would require in-hospital treatment such as anticoagulation, stenting, or carotid endarterectomy. In many centers, patients require admission to receive this workup. However, some centers have developed ED observation unit protocols or rapid outpatient TIA clinics to ensure an expedited evaluation.[71] One commonly used tool available to help select which TIA patients are at highest risk (and thus likely should be admitted) versus those at lowest risk (who might therefore be safe for expedited outpatient evaluation) is the ABCD2 score (Box 101-8).[72,73] In addition, most patients without a contraindication will be started on appropriate antithrombotic therapy in the ED after consultation with a neurologist.

Box 101-8 ABCD2 Score

Risk Factor	Points
Age >60 years	1
Initial BP >140/90	1
Unilateral weakness	2
Speech impairment	
Without weakness	1
Symptoms 10-59 min	1
Symptoms ≥60 min	2
History of diabetes	1

Result
0-3 = low risk (1% risk of stroke in 48 hours)
4-5 = moderate risk (4.1% risk of stroke in 48 hours)
≥6 = high risk (8% risk of stroke in 48 hours)

BP, blood pressure.

Hemorrhagic Stroke

The majority of patients with an acute hemorrhagic stroke should be admitted to an intensive care unit in which specialty consultation is available. If this is unavailable at the evaluating institution, the patient should be transported to an appropriate institution.

KEY CONCEPTS

- Patients with signs and symptoms of an acute ischemic stroke within 4.5 hours of the last time they were known to be at their neurologic baseline should be evaluated for thrombolytic therapy with the appropriate inclusion and exclusion criteria for the 0- to 3-hour time window or the 3- to 4.5-hour time window (see Table 101-3).
- Carotid Doppler, MRA, or CTA studies are recommended before discharge of a patient with TIA from the ED.
- Overly aggressive blood pressure management should be avoided in patients with acute ischemic stroke.
- Accurate identification of the last time a patient was known to be at his or her neurologic baseline should be documented in all patients with stroke.
- Assessment of gait is essential to rule out posterior circulation stroke in patients with vertigo.
- The possibility of carotid or vertebral dissection should be considered in young patients with stroke and in patients with headaches and neck pain with acute stroke.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Furie KL, et al: Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011; 42:227-276.
2. American Heart Association: Heart disease and stroke statistics—2010 update. Available at http://circ.ahajournals.org/content/121/7/e46.full.pdf+html.
3. Morgenstern LB, et al: Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2010; 41:2108-2129.
4. Centers for Disease Control and Prevention (CDC): Outpatient rehabilitation among stroke survivors—21 States and the District of Columbia, 2005. *MMWR Morb Mortal Wkly Rep* 2007; 56:504.
5. Woo D, et al: Incidence rates of first-ever ischemic stroke subtypes among blacks: A population-based study. *Stroke* 1999; 30:2517.
6. Petty GW, et al: Ischemic stroke subtypes: A population-based study of incidence and risk factors. *Stroke* 1999; 30:2513.
7. Adams HP Jr, et al: Guidelines for the early management of adults with ischemic stroke: A guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke* 2007; 38:1655-1711.
8. Kannel WB, Benjamin EJ: Status of the epidemiology of atrial fibrillation. *Med Clin North Am* 2008; 92:17.
9. Witt BJ, et al: The incidence of stroke after myocardial infarction: A meta-analysis. *Am J Med* 2006; 119:354.
10. Tran H, Anand SS: Oral antiplatelet therapy in cerebrovascular disease, coronary artery disease, and peripheral arterial disease. *JAMA* 2004; 292:1867.
11. Lang ES: *Vertebral artery dissection: Overview*. Copyright 1994-2012, WebMD LLC. Available at http://emedicine.medscape.com/article/761451-overview.
12. Flis CM, Jager HR, Sidhu PS: Carotid and vertebral artery dissections: Clinical aspects, imaging features and endovascular treatment. *Eur Radiol* 2007; 17:820.
13. Shah Q, Messé SR: Cervicocranial arterial dissection. *Curr Treat Options Neurol* 2007; 9:55.
14. Arauz A, et al: Dissection of cervical arteries: Long-term follow-up study of 130 consecutive cases. *Cerebrovasc Dis* 2006; 22:150.
15. Schievink WI, Roiter V: Epidemiology of cervical artery dissection. *Front Neurol Neurosci* 2005; 20:12.
16. Goldstein JN: *Transient ischemic attack: Background.* Copyright 1994-2012 WebMD LLC. Available at http://emedicine.medscape.com/article/1910519-overview#a0101.
17. Easton JD, et al: Definition and evaluation of transient ischemic attack: A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke* 2009; 40:2276-2293.
18. Johnston SC, Gress DR, Browner WS, Sidney S: Short-term prognosis after emergency department diagnosis of TIA. *JAMA* 2000; 284:2901.
19. Goldstein JN, Gilson A: Critical care management of acute intracerebral hemorrhage. *Curr Treat Options Neurol* 2011; 13:204-216.
20. Delgado Almandoz JE, et al: Diagnostic accuracy and yield of multidetector CT angiography in the evaluation of spontaneous intraparenchymal cerebral hemorrhage. *AJNR Am J Neuroradiol* 2009; 30:1213-1221.
21. Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC: The ICH score: A simple, reliable grading scale for intracerebral hemorrhage. *Stroke* 2001; 32:891-897.
22. Cruz-Flores S: Ischemic stroke in emergency medicine: Background. Copyright 1994-2012 by WebMD LLC. Available at http://emedicinemedscapecom/article/793904-overview.
23. Kasner SE: Clinical interpretation and use of stroke scales. *Lancet Neurol* 2006; 5:603-612.
24. Lyden P, et al: Underlying structure of the National Institutes of Health Stroke Scale: Results of a factor analysis. NINDS tPA Stroke Trial Investigators. *Stroke* 1999; 30:2347-2354.
25. Smith EE, et al: Poor outcomes in patients who do not receive intravenous tissue plasminogen activator because of mild or improving ischemic stroke. *Stroke* 2005; 36:2497-2499.
26. Kothari RU, et al: The ABCs of measuring intracerebral hemorrhage volumes. *Stroke* 1996; 27:1304-1305.
27. McElveen WA: Cerebral venous thrombosis: Background. Copyright 1994-2012 by WebMD LLC. Available at http://emedicine.medscape.com/article/1162804-overview.
28. Latchaw RE, et al: Recommendations for imaging of acute ischemic stroke: A scientific statement from the American Heart Association. *Stroke* 2009; 40:3646-3678.
29. Intracerebral hemorrhage after intravenous tPA therapy for ischemic stroke. The NINDS tPA Stroke Study Group. *Stroke* 1997; 28:2109-2118.
30. Grotta JC, et al: Agreement and variability in the interpretation of early CT changes in stroke patients qualifying for intravenous rtPA therapy. *Stroke* 1999; 30:1528-1533.
31. Albers GW, et al: Magnetic resonance imaging profiles predict clinical response to early reperfusion: The diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. *Ann Neurol* 2006; 60:508-517.
32. Rustemli A, Bhatti TK, Wolff SD: Evaluating cardiac sources of embolic stroke with MRI. *Echocardiography* 2007; 24:301-308.
33. Jauch EC, et al: Part 11: Adult stroke: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010; 122:S818-S828.
34. Wardlaw JM, Murray V, Berge E, Del Zoppo GJ: Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev* 2009; 4:CD000213.
35. Lees KR, et al: Time to treatment with intravenous alteplase and outcome in stroke: An updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010; 375:1695-1703.
36. Hacke W, et al: Association of outcome with early stroke treatment: Pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 2004; 363:768-774.
37. Katzan IL, et al: Use of tissue-type plasminogen activator for acute ischemic stroke: The Cleveland area experience. *JAMA* 2000; 283:1151-1158.
38. Graham GD: Tissue plasminogen activator for acute ischemic stroke in clinical practice: A meta-analysis of safety data. *Stroke* 2003; 34:2847-2850.
39. Hacke W, et al: Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; 359:1317-1329.
40. Generalized efficacy of t-PA for acute stroke. Subgroup analysis of the NINDS t-PA Stroke Trial. *Stroke* 1997; 28:2119-2125.
41. del Zoppo GJ, et al: PROACT: A phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism. *Stroke* 1998; 29:4-11.
42. Wechsler LR, et al: Factors influencing outcome and treatment effect in PROACT II. *Stroke* 2003; 34:1224-1229.
43. Tountopoulou A, Ahl B, Weissenborn K, Becker H, Goetz F: Intra-arterial thrombolysis using rt-PA in patients with acute stroke due to vessel occlusion of anterior and/or posterior cerebral circulation. *Neuroradiology* 2008; 50:75-83.
44. Kim DJ, et al: Rescue localized intra-arterial thrombolysis for hyperacute MCA ischemic stroke patients after early non-responsive intravenous tissue plasminogen activator therapy. *Neuroradiology* 2005; 47:616-621.
45. Sekoranja L, et al: Intravenous versus combined (intravenous and intra-arterial) thrombolysis in acute ischemic stroke: A transcranial color-coded duplex sonography–guided pilot study. *Stroke* 2006; 37:1805-1809.
46. The Interventional Management of Stroke (IMS) II Study. *Stroke* 2007; 38:2127-2135.
47. Flint AC, Duckwiler GR, Budzik RF, Liebeskind DS, Smith WS: Mechanical thrombectomy of intracranial internal carotid occlusion: Pooled results of the MERCI and Multi MERCI Part I trials. *Stroke* 2007; 38:1274-1280.
48. Smith WS, et al: Safety and efficacy of mechanical embolectomy in acute ischemic stroke: Results of the MERCI trial. *Stroke* 2005; 36:1432-1438.
49. Gobin YP, et al: MERCI 1: A phase 1 study of Mechanical Embolus Removal in Cerebral Ischemia. *Stroke* 2004; 35:2848-2854.
50. van der Worp HB, van Gijn J: Clinical practice. Acute ischemic stroke. *N Engl J Med* 2007; 357:572-579.
51. Paciaroni M, Agnelli G, Micheli S, Caso V: Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: A meta-analysis of randomized controlled trials. *Stroke* 2007; 38:423-430.
52. O'Donnell MJ, Berge E, Sandset PM: Are there patients with acute ischemic stroke and atrial fibrillation that benefit from low molecular weight heparin? *Stroke* 2006; 37:452-455.

www.ketabpezeshki.com 66485457-66963820

53. Gray CS, et al: Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: The UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol* 2007; 6:397-406.
54. Van den Berghe G, et al: Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354:449-461.
55. Turner-Lawrence DE, Peebles M, Price MF, Singh SJ, Asimos AW: A feasibility study of the sensitivity of emergency physician dysphagia screening in acute stroke patients. *Ann Emerg Med* 2009; 54:344-348.
56. Schwamm LH, et al: Recommendations for the establishment of stroke systems of care: Recommendations from the American Stroke Association's Task Force on the Development of Stroke Systems. *Stroke* 2005; 36:690-703.
57. Diringer MN, Edwards DF: Admission to a neurologic/neurosurgical intensive care unit is associated with reduced mortality rate after intracerebral hemorrhage. *Crit Care Med* 2001; 29:635-640.
58. Rincon F, et al: Impact of delayed transfer of critically ill stroke patients from the Emergency Department to the Neuro-ICU. *Neurocrit Care* 2010; 13:75-81.
59. Crowley RW, et al: Influence of weekend hospital admission on short-term mortality after intracerebral hemorrhage. *Stroke* 2009; 40:2387-2392.
60. Zahuranec DB, et al: Early care limitations independently predict mortality after intracerebral hemorrhage. *Neurology* 2007; 68:1651-1657.
61. Zahuranec DB, et al: Do-not-resuscitate orders and predictive models after intracerebral hemorrhage. *Neurology* 2010; 75:626-633.
62. Anderson CS, et al: Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): A randomised pilot trial. *Lancet Neurol* 2008; 7:391-399.
63. Thompson BB, et al: Prior antiplatelet therapy and outcome following intracerebral hemorrhage: A systematic review. *Neurology* 2010; 75:1333-1342.
64. Mayer SA, et al: Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005; 352:777-785.
65. Mayer SA, et al: Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008; 358:2127-2137.
66. Mendelow AD, et al: Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): A randomised trial. *Lancet* 2005; 365:387-397.
67. Alberts MJ, et al: Recommendations for the establishment of primary stroke centers. Brain Attack Coalition. *JAMA* 2000; 283:3102-3109.
68. Alberts MJ, et al: Recommendations for comprehensive stroke centers: A consensus statement from the Brain Attack Coalition. *Stroke* 2005; 36:1597-1616.
69. Acker JE 3rd, et al: Implementation strategies for emergency medical services within stroke systems of care: A policy statement from the American Heart Association/American Stroke Association Expert Panel on Emergency Medical Services Systems and the Stroke Council. *Stroke* 2007; 38:3097-3115.
70. Organised inpatient (stroke unit) care for stroke. Stroke Unit Trialists' Collaboration. *Cochrane Database Syst Rev* 2000; 2:CD000197.
71. Ross MA, et al: An emergency department diagnostic protocol for patients with transient ischemic attack: A randomized controlled trial. *Ann Emerg Med* 2007; 50:109-119.
72. Fothergill A, Christianson TJ, Brown RD Jr, Rabinstein AA: Validation and refinement of the ABCD2 score. A population-based analysis. *Stroke* 2009; 40:2669-2673.
73. Johnston SC, et al: Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet* 2007; 369:283-292.

www.ketabpezeshki.com 66485457-66963820

Chapter 102

Seizure Disorders

Jason T. McMullan, Evelyn H. Duvivier, and Charles V. Pollack Jr.

PERSPECTIVE

A *seizure* is the clinical manifestation of excessive, abnormal cortical neuron activity. The physical manifestation depends on the area of brain cortex involved and, to a lesser extent, on the specific underlying abnormality. *Ictal event* is the more general term used to describe the seizure or seizure-like episode. Patients who have recurring seizures without consistent provocation have *epilepsy,* a term that encompasses many disparate clinical syndromes. Seizures may also occur as a predictable response to certain toxic, pathophysiologic, or environmental stresses; these are *reactive* or *secondary seizures,* and patients who experience these do not have epilepsy. In the United States, 10% of people experience at least one seizure in their lifetime; the cumulative incidence of epilepsy is 3%.[1]

More than 1 million patients visit U.S. emergency departments (EDs) every year for seizure care.[2] The evaluation of patients with seizures in the ED can be complex and difficult. A careful history must be elicited to determine the presence of ictal events that represent epilepsy, exposure to ictogenic stimuli (e.g., alcohol, cocaine), significant underlying illness (e.g., meningitis, hypoxemia, hypoglycemia, intracranial mass), or provocative stimuli (e.g., sleep deprivation in an epileptic). The physical examination focuses on the identification of focal neurologic abnormalities, systemic illness, and signs of toxic exposure. If the patient continues to experience seizure activity, airway protection and abortive therapy must be provided.[3] Laboratory and radiographic evaluation are guided by historical and physical findings and may be limited or unnecessary in some cases. Finally, the appropriate disposition of a patient in the ED with a seizure or with a history of a recent seizure requires an understanding of the underlying illness, likelihood of recurrence, indications for maintenance pharmacologic therapy, and state reporting regulations.

In addition to the distinction between primary (epileptic) and secondary (reactive) seizures, many other classifications of ictal events have been proposed.[4-8] Seizures are termed *generalized* or *focal (partial)* depending on the clinical manifestations. Generalized seizures result from an abnormal electrical event that simultaneously involves both cerebral hemispheres and is accompanied by loss of consciousness; in partial seizures, abnormal activity is limited to part of one cerebral hemisphere only. Generalized seizures usually are characterized by rhythmic, tonic-clonic muscle contractions, or *convulsions,* although *nonconvulsive generalized seizures* also occur. Partial seizures can be differentiated further into seizures during which cognition is maintained *(simple partial)* and seizures during which cognition is impaired *(complex partial).* The term *cognition* refers to involvement of at least two of five features—perception, attention, emotion, memory, and executive function—and replaces the previously used term *consciousness,* which is difficult to define and difficult to document.[9,10] Finally, partial seizures may become generalized *(partial with secondary generalization).*

Inexperienced witnesses may provide histories that are insufficient for accurate categorization of seizures. However, when an accurate history is available, secondary *(reactive)* seizures typically are generalized, not partial, in nature. The definitive differentiation among these classifications may require electroencephalogram (EEG) recording *during* the seizure, sometimes in association with simultaneous video recording.[11,12]

Seizures in children, as in adults, are classified as primary *(idiopathic)* and secondary (*symptomatic* or *reactive*). The term *cryptogenic* is used sometimes when seizures are thought to be secondary but no cause has been identified. The history is a vital diagnostic tool in evaluating seizures in children, as the actual seizure activity is usually not observed.

Other important terms to describe ictal events include *status epilepticus,* in which seizures are prolonged or occur serially without an intervening return to a normal neurologic condition; *spasm,* which is a specific, debilitating seizure syndrome that occurs in infants; and *myoclonus,* which refers to rhythmic, shock-like muscle contractions also typical for specific seizure syndromes. The *postictal period* is an interval after a seizure, of variable duration, usually characterized by impaired cognition but sometimes also marked by such diverse physiologic manifestations as self-limited focal motor paralysis *(Todd's paralysis)* or neurogenic pulmonary edema.

PRINCIPLES OF DISEASE

The pathophysiology of seizures at the neuronal level is incompletely understood, with most of what is known coming from animal studies in which either electrical or pharmacologic stimulation is applied directly to brain cortex. To produce generalized ictus, stimuli must be simultaneously applied to both hemispheres. Some studies show the concept of recruitment, which occurs when the initiating neurons' abnormal, increased electrical activity activates adjacent neurons and propagates until the thalamus and other subcortical structures are recruited. The clinical seizure activity typically, but not always, reflects the focus of initiation.[10,13]

What prompts such initiation is unclear. Proposed mechanisms include disruption of normal structure, whether congenital, maturational, or acquired (as with scar tissue), and disruption of local metabolic or biochemical function. The latter mechanism is better understood because the roles of two neurotransmitters—acetylcholine, which is excitatory to cortical neurons, and γ-aminobutyric acid (GABA), which is inhibitory—have been more fully characterized. In sensitive neurons, such as those at an

www.ketabpezeshki.com 66485457-66963820

ictogenic focus, subtle changes in the local concentrations of these neurotransmitters can produce sustained membrane depolarization, ultimately followed by local hyperpolarization and recruitment. Recruitment may follow contiguous paths or extend along diverse integrated circuits that are deep and cross the midline.[10,13]

When the ictal discharge extends below the cortex to deeper structures, the reticular activating system in the brainstem may be affected, altering consciousness. In generalized seizures, the focus often is subcortical and midline, which explains the prompt loss of consciousness and bilateral involvement. Seizures typically are self-limited; at some point, the hyperpolarization subsides and the electrical discharges from the focus terminate. This termination may be related to reflex inhibition, loss of synchrony, neuronal exhaustion, or alteration of the local balance of acetylcholine and GABA in favor of inhibition.[10]

The systemic manifestations of convulsive ictal activity include hypertension, tachycardia, tachypnea, and hyperglycemia from sympathetic stimulation. With more prolonged convulsions, skeletal muscle damage, lactic acidosis, and, rarely, frank rhabdomyolysis may ensue.[10,14,15] Autonomic discharge and bulbar muscle involvement may result in urinary or fecal incontinence, vomiting (with significant aspiration risk), tongue biting, and airway impairment.

CLINICAL FEATURES

Primary Seizures in Adults

Primary ictal events in adults may have a genetic origin or may be idiopathic. Onset is typically during childhood or adolescence, but occasionally idiopathic seizures may begin de novo in adulthood. Because idiopathic seizures are rare, a first-time seizure in an adult requires a thorough evaluation.

Focal seizures in adults may be classified as simple partial or complex partial. Simple partial seizures are limited in electrical focus to one cerebral hemisphere and do not cause loss of cognition. Although the specific function of the initiating neurons determines the clinical manifestation of the ictal event (i.e., motor, somatosensory, special sensory, autonomic, or psychic), such clinical manifestations are not sufficiently specific for anatomic localization without an EEG. Typical features of simple partial seizures include focal clonic movements; paresthesias; visual, auditory, olfactory, or gustatory experiences; sweating and flushing; dysphasia; a sense of déjà vu; or a sense of unwarranted fear.[10,13] Motor signs, which by definition remain ipsilateral in simple partial seizures, may spread contiguously in a stepwise fashion *(Jacksonian march)* as neuron recruitment occurs in the motor cortex. There is generally no postictal state after a simple partial seizure.

Complex partial seizures are ictal events that involve impairment of cognition, either at onset or evolving from focal activity. Amnesia for the ictal event is a consistent feature of complex partial seizures, although during the episode the patient may remain responsive to the surroundings. Complex partial seizures typically involve automatisms that are specific to the affected person, such as lip smacking, repeated swallowing or uttering verbal phrases, or picking at clothing. Complex partial seizures generally are associated with an aura, such as a specific smell, taste, visual hallucination, or intense emotional feeling. In contrast with those experiencing generalized seizures, these patients may continue with ongoing motor activity, such as driving an automobile, riding a bicycle, or playing a musical instrument *(reactive automatisms)*, and they may react to their surroundings in a semi-appropriate manner.[10] Partial seizures may progress rapidly to generalized seizures. A postictal state is common after complex partial seizures and may persist for hours.[13]

Generalized seizures in adults may be convulsive or nonconvulsive. By definition, patients lose consciousness in a generalized seizure, and no aura is present. Some patients may experience a brief, vague prodrome or dysphoric state just before the ictal event. Convulsive generalized seizures are typified by the tonic-clonic, or grand mal, seizure, in which the patient loses consciousness, stiffens with generalized muscular hypertonus, and then rhythmically and violently contracts multiple, bilateral, and usually symmetrical muscle groups. The muscular force may be sufficiently vigorous to result in posterior shoulder dislocation or fractures of thoracic spine vertebral bodies; significant tongue and buccal injuries also may be incurred from biting with repeated jaw muscle contractions. Dysautonomia, including transient apnea, is a potential manifestation of convulsive generalized seizures; urinary incontinence is more common than fecal incontinence. A generalized convulsive seizure generally lasts 1 to 2 minutes and is followed by a postictal state, headache, and drowsiness that may persist for hours. This state must be differentiated from altered consciousness attributable to other causes.

Nonconvulsive generalized seizures include absence, or petit mal, seizures; myoclonic seizures; tonic seizures; and atonic seizures. Absence seizures in adults are subclassified further as *typical* or *atypical.* Typical absence ictus is characterized by the sudden cessation of normal, conscious activity, followed by a nonconvulsive, dissociative state that persists for a few seconds to several minutes before suddenly terminating. Eye movements, blinking, or automatisms may be present. There is no aura and no postictal state. If the seizure occurs midsentence, then the patient typically will resume speaking at precisely the point of interruption without awareness of the intervening event. Absence seizures typically begin in childhood but occasionally develop in adults. Atypical absence seizures are marked by more complicated motor signs, coexistence with other forms of generalized seizures, inconsistent postictal confusion, and irregular EEG abnormalities.[13]

Atonic seizures are characterized by focal diminution of muscle tone (limb or head) or generalized loss of postural tone in which the head falls forward and then the body slumps to the ground ("drop attack"), usually landing buttocks first (although this can vary depending on the axis of gravity at the time of the fall). Recovery occurs immediately, and there is either no loss or an extremely brief loss of consciousness. In *myoclonic-atonic seizures,* a brief (less than 100 msec) myoclonic jerk of muscle groups of variable anatomy occurs before the episode of atonia.[10] Because typically no postictal state is associated with these episodes, an altered level of consciousness in a patient after an atonic or myoclonic-atonic seizure should prompt an investigation for head trauma or a toxic or metabolic abnormality.

Status epilepticus is defined as serial seizure activity without interictal recovery or prolonged, continuous seizure activity. Traditionally, status epilepticus was defined as seizure activity lasting longer than 30 minutes, which is the estimated duration necessary for neuronal injury.[16,17] However, because an isolated tonic-clonic seizure rarely lasts more than a few minutes, an operational definition of status epilepticus as either a continuous seizure lasting more than 5 minutes or more than two discrete seizures without intervening recovery of consciousness has been advocated.[18] Although it is recognized that the underlying cause of status epilepticus is the predominant factor determining morbidity and mortality, prolonged seizure activity does cause neuronal injury and therefore warrants prompt abortive therapy. Furthermore, status epilepticus may become refractory to treatment over time.[17,19,20]

In some cases a patient's first seizure episode will manifest as status epilepticus. The most common cause of status epilepticus is discontinuation of anticonvulsant medication. This situation may be compounded by barbiturate withdrawal when phenobarbital therapy is abruptly discontinued. Many other causes of status epilepticus have been documented (Box 102-1).[14,16,21,22] After prolonged status epilepticus or after incomplete treatment, the patient

www.ketabpezeshki.com 66485457-66963820

Box 102-1 Etiology of Status Epilepticus: Common Causative Disorders

Metabolic Disturbances
Hepatic encephalopathy
Hypocalcemia
Hypoglycemia or hyperglycemia
Hyponatremia
Uremia

Infectious Processes
CNS abscess
Encephalitis
Meningitis

Withdrawal Syndromes
Alcohol
Antiepileptic drugs
Baclofen
Barbiturates
Benzodiazepines

CNS Lesions
Acute hydrocephalus
Anoxic or hypoxic insult
Arteriovenous malformations
Brain metastases
Cerebrovascular accident
Chronic epilepsy
Eclampsia
Head trauma
Intracerebral hemorrhage
Neoplasm
Neurosurgery
Posterior reversible leukoencephalopathy
Remote structural injury

Intoxication
Bupropion
Camphor
Clozapine
Cyclosporine
Flumazenil
Fluoroquinolones
Imipenem
Isoniazid
Lead
Lidocaine
Lithium
Metronidazole
Theophylline
Tricyclic antidepressants

CNS, central nervous system.

may exhibit very subtle manifestations of continued seizure activity, such as small-amplitude twitching of the extremities or jerking of the eyes, or any visible motor activity may cease while seizure activity detectable on the EEG continues.[23-25] Recognition of the latter scenario, termed *nonconvulsive status epilepticus,* requires a high index of clinical suspicion. Prompt treatment is essential to prevent neuronal damage; mortality approaches 30% if the seizure lasts more than an hour.[26] Nonconvulsive status epilepticus may be present in more than 9% of hospitalized patients with prolonged decreased mental status.[27]

All classes of primary seizures may recur sporadically, randomly, or predictably. Cyclic recurrence has been reported with awakening, sleep deprivation, emotional or physical stress, alcohol, and menses, among other factors. Seizures also may be triggered by specific sensory stimuli, the most common of which is visual stimulation in the form of flashing lights, such as strobe lights, television, and video games.[10,28] Seizures also can be caused by auditory, gustatory, tactile, or startle triggers that are specific to the affected person. The most common cause of recurrent primary seizures is medication noncompliance.[13,29]

Reactive Seizures in Adults

Reactive or secondary seizures do not result from genetic or idiopathic causes. The conditions that cause reactive seizures may be static (e.g., anatomic scarring), progressive (e.g., degenerative cortical disorders), or transient (e.g., acute electrolyte derangements).

Seizures Caused by Metabolic Derangements

Hypoglycemia is a common metabolic cause of reactive seizures. Ictal activity can occur when the plasma glucose level is less than 45 mg/dL, although some patients may manifest neurologic disturbances even at higher levels.[30] A rapid bedside glucose test is an integral part of the evaluation of the patient exhibiting seizure activity. Convulsive and nonconvulsive seizures and generalized and partial seizures all may occur during hypoglycemia.[31-34] Patients at the extremes of age are particularly susceptible to glucose stress during acute illness. Hypoglycemia also may result from insulin reaction, a deliberate insulin or hypoglycemic agent overdose, alcoholism, poor nutrition, and sepsis. Hypoglycemic seizures respond to glucose therapy; anticonvulsants and benzodiazepines are unnecessary. At times, however, prolonged seizures may cause hypoglycemia. Seizures that do not cease after correction of low blood glucose deserve further evaluation and treatment.

Cation derangements, notably hypernatremia and hyponatremia, hypomagnesemia, and hypocalcemia, are other common metabolic causes of ictal activity.[35,36] Hypo-osmolar and hyperosmolar states can precipitate seizures. Disorders of sodium, the primary cation in the extracellular fluid compartment and the primary determinant of serum osmolarity, are most common. Hyponatremia is the most frequently identified electrolyte disorder in hospitalized patients, and sodium levels less than 120 mEq/L often are associated with seizures.[37,38] The rate at which the sodium level decreases, and not the absolute magnitude of the decrease, determines the risk for neurologic manifestation.[37] Correcting hyponatremia should be undertaken slowly to avoid osmotic demyelination. If seizures are persistent, administration of hypertonic (3%) saline may be indicated.[37] Hypernatremia will result in cerebral edema and seizures in the setting of rapid elevation of serum sodium to greater than 160 mEq/L or during aggressive correction of subacute hyponatremia.[36,39]

Hypercalcemia reduces neuronal excitability and rarely causes seizures; significant hypocalcemia (below 7.5 mEq/L), however, is associated with ictal activity. Hypocalcemia may result from hypoparathyroidism, renal failure, or acute pancreatitis and typically is associated with hypomagnesemia, which also can precipitate seizures, particularly at serum levels less than 1 mEq/L. Hypomagnesemia is seen most often as a result of poor nutrition, especially in alcoholic patients. Patients with significant hypomagnesemia or hypocalcemia are treated empirically for both disorders.[35,36]

Nonketotic hyperosmolar hyperglycemia can be associated with seizure activity. Partial seizures, including partial status, predominate. These seizures do not respond to anticonvulsants; rather, they are best managed with gradual correction of fluid deficits and glucose excess.[40-42]

Seizures may complicate the course and treatment of renal failure.[43] Ictal activity occasionally complicates uremic encephalopathy, more commonly occurs as a result of acute fluid and electrolyte shifts during dialysis *(dialysis disequilibrium syndrome),* and can be a complication of immunosuppressive therapy after renal transplantation.

www.ketabpezeshki.com 66485457-66963820

Thyroid hormones lower seizure threshold, and consequently Graves' disease and thyrotoxicosis may occasionally manifest as seizures, including status epilepticus.[44] Seizures also occur with hypoparathyroidism as a result of secondary hypocalcemia.[14]

Seizures Caused by Infectious Diseases

Infectious diseases can cause seizures independent of a purely febrile mechanism. These seizures generally result from primary central nervous system (CNS) infections but occasionally arise from other septic sources. The most important ictogenic infections are meningitis, encephalitis, cerebral abscess, cerebral parasitosis, and human immunodeficiency virus (HIV) disease and associated opportunistic infections, with their protean CNS manifestations. Cerebral malaria is a common cause in developing countries.[45]

Seizures may result from the acute inflammatory response that occurs with bacterial or viral meningitis. During the acute course of illness, 15% of patients with bacterial meningitis will have at least one seizure,[46] and surviving patients have an increased risk of epilepsy.[47] Viral meningoencephalitides, the most common of which are caused by the herpes simplex virus, also are associated with seizures. These seizures may be generalized or partial, often recur during the acute phase of the illness, and may persist after the illness has resolved.[48]

The parasitic CNS infection neurocysticercosis is relatively common in areas of the United States where there is a population of immigrants from Latin America. Seizures complicate 50 to 90% of neurocysticercosis cases.[49] Latent syphilis can cause adult-onset seizures. Primary HIV disease of the CNS with its attendant infectious and mass lesion complications constitutes a significant cause of generalized and partial seizures. Common HIV-associated infections and conditions include toxoplasmosis, lymphoma, and the demyelinating infection progressive multifocal leukoencephalopathy.[50] Choosing an antiepileptic drug (AED) for an HIV-infected patient with seizures is done in consultation with infectious disease and neurology specialists because of the well-recognized increase in adverse effects of AEDs and the interactions between AEDs and antiviral medications.

Seizures Caused by Drugs and Toxins

The list of substances reported to cause seizures either as an idiosyncratic side effect of therapeutic use or as a manifestation of toxic overdose is extensive.[22,51] The recognition of this etiologic category is crucial in the ED setting. Seizure activity is a dire sign of toxicity and may herald the onset of life-threatening instability.

Seizures may occur after therapeutic doses of antimicrobials, cardiovascular agents, neuroleptics, and sympathomimetics.[52] Seizures also may result from exposure to plant toxins, insecticides, rodenticides, and hydrocarbons. Certain over-the-counter supplements also have been associated with seizures, either alone or through adverse interactions with prescription medications.[53,54] The most common drug-associated and toxin-associated seizures occur, however, in conjunction with illicit drugs, such as cocaine, amphetamines, and phencyclidine; with overdoses of anticholinergic agents, such as cyclic antidepressants and antihistamines; as a manifestation of withdrawal from ethyl alcohol and sedative-hypnotics; and with toxic levels and deliberate overdoses of diverse medications, including aspirin, theophylline, meperidine, isoniazid, lithium, and anticonvulsants, including phenytoin, carbamazepine, lamotrigine, and topiramate.[51,55] Standard ED therapeutic measures are usually effective for management of toxic seizures. In some cases, specific antidotal therapy is available, such as alkalinization for cyclic antidepressant and salicylate overdoses, and pyridoxine (vitamin B_6) for isoniazid overdose. Hemodialysis is the treatment of choice for serious salicylate and lithium toxicity. Dilantin administration is contraindicated in cases of ingestion because its sodium channel blocking actions can worsen the hemodynamic impact of the ingestion.[3]

Because of its prevalence in urban ED patient populations, cocaine toxicity warrants special mention. Seizures may occur after isolated recreational use or chronic abuse, after overdose, and in "body packers" and "body stuffers."[56] Cocaine-related seizures may be a manifestation of direct CNS toxicity or an indirect result of hypoxemia from cardiac toxicity.[57] Seizures in cocaine-intoxicated patients are managed as part of the overall toxic reaction, which often includes high fever, rhabdomyolysis, and cardiac arrhythmias. A benzodiazepine is the appropriate initial therapeutic agent.

Ethyl alcohol use and abuse are additional common toxic causes of seizures; up to 40% of seizure patients in the ED have alcohol-related seizures.[58] Ictal events may occur with acute inebriation but are more common during withdrawal from alcohol.[59] Withdrawal seizures are typically generalized and recurrent and begin within 6 hours of cessation of or decrease in alcohol consumption. Through a phenomenon termed *kindling,* the risk and severity of seizures increase with each episode of withdrawal. Kindling means that with each episode of alcohol withdrawal, the seizure threshold is lower. Alcoholic patients with seizures should also be evaluated for related, concomitant ictogenic problems (e.g., hypoglycemia, electrolyte derangements, head trauma, coingestion of other toxins, pregnancy). The preferred treatment for alcohol-associated seizures is with benzodiazepines, as these drugs substitute for the GABA-enhancing effect of ethanol in the CNS.

Seizures Caused by Trauma

Post-traumatic seizures can occur acutely as a result of blunt or penetrating head trauma or as a post-traumatic sequela. Immediate post-traumatic seizures occur within 24 hours of injury. Epidural, subdural, and intracerebral hematomas and traumatic subarachnoid hemorrhages all can be acutely ictogenic, particularly as intracranial pressure rises. More often, however, the onset of seizure activity is delayed for at least several hours. Early post-traumatic seizures occur within 1 week of injury, whereas late post-traumatic seizures occur after 1 week. Immediate and early post-traumatic seizures are more common in children than in adults, and children also are more likely than adults to be presented in status epilepticus in the immediate or early post-traumatic phase.[60]

The severity of head injury correlates with the likelihood of post-traumatic seizures. Although seizures rarely occur after mild traumatic brain injury, the incidence approaches 30% in patients with depressed skull fracture.[60,61] Antiepileptic drugs are recommended for prophylaxis against post-traumatic seizures occurring within the first 7 days after severe brain injury in adults; however, they have not been shown to be effective in preventing late post-traumatic seizures.[62,63]

Seizures Associated with Malignancy or Vasculitis

Seizures are a common manifestation of primary and metastatic CNS neoplasms. They also may complicate cancer treatment as a result of postsurgical scarring or chemotherapy-related electrolyte derangements, hematologic abnormalities, or immunosuppression. Although any CNS tumor can be ictogenic, low-grade and slow-growing primary neoplasms (e.g., well-differentiated gliomas and oligodendrogliomas) are implicated most commonly.[64] In such cases, seizures, which most often are partial with secondary generalization, may be the initial clinical manifestation. A new-onset seizure in a patient with a non-CNS primary malignancy, such as melanoma and tumors of the lung, breast, colon, germ

www.ketabpezeshki.com 66485457-66963820

cells, or renal cells, prompts consideration of CNS metastasis and warrants neuroimaging.

Seizures also may be the presenting manifestation of CNS vasculitis in patients with systemic lupus erythematosus and polyarteritis nodosa and are usually complex partial seizures that give a general indication of the acute inflammatory focus. Secondary generalization may also occur.[65]

Seizures Caused by Strokes, Arteriovenous Malformations, Aneurysms, and Migraines

Ischemic or hemorrhagic stroke is the cause of new-onset seizures in 40 to 54% of elderly patients.[66] The overall incidence of seizures with stroke ranges from 4 to 15%; more than one half occur within the first week after stroke. The incidence of epilepsy after stroke is 4 to 9%.[67,68] Seizures that occur acutely with stroke are thought to result from local metabolic alterations in the CNS; these events are transient, and the seizures often are focal and self-limited. Seizures that develop later are more likely to be generalized.

Convulsive seizures occur in 6 to 26% of patients with subarachnoid hemorrhage after aneurysmal rupture; 8 to 15% of patients will experience nonconvulsive seizures.[69] Seizures also occur in conjunction with unruptured cerebrovascular aneurysms and arteriovenous malformations.[70] Arteriography may be required to confirm the diagnosis; unruptured arteriovenous malformations are easier to detect on an enhanced cranial computed tomography (CT) scan than are smaller, unruptured aneurysms.

Seizures also may arise in concert with vascular headaches, either coincidentally, by migrainous activation of an epileptic focus, or after vascular headache has induced cerebral infarction that becomes an epileptic focus.[71]

Seizures Caused by Degenerative Disease of the Central Nervous System

In approximately 3% of patients with multiple sclerosis, focal or generalized seizures develop during the course of their illness. These seizures must be differentiated from the tonic spasms that may occur in multiple sclerosis.[72]

CNS degeneration associated with aging, including dementia and Alzheimer's disease, increases the risk of reactive seizures and epilepsy.[66,73] The elderly also are more likely to have other ictogenic problems (e.g., stroke, brain neoplasm, toxic and metabolic disturbances, blunt head trauma from falls). Maintenance treatment of elder patients with epilepsy often is complicated by drug-drug interactions, and breakthrough seizures may result even when patients are compliant. Although the incidence of unprovoked seizures increases after age 60 years, the management of these patients must include a thorough evaluation for causes of secondary seizures.[66]

Gestational Seizures

Seizures associated with pregnancy are divided into two categories: *gestational epilepsy,* in which hormonal and metabolic changes exacerbate underlying epilepsy or adversely influence serum levels of anticonvulsants, and *eclampsia* or *toxemia,* which is a gestational hypertensive encephalopathy manifesting with seizures, hypertension, coma, proteinuria, and edema. For the former, antiepileptic therapy should be tailored by the patient's neurologist and obstetrician to maximize seizure control and minimize the risk of teratogenic effects.[74]

Convulsive generalized status epilepticus in pregnancy jeopardizes both mother and fetus. The definitive treatment for eclamptic seizures is magnesium sulfate and immediate delivery of the fetus; benzodiazepines are useful adjuncts to magnesium. Simultaneous reduction in blood pressure with use of hydralazine, labetalol, or nifedipine is recommended.[75] Postpartum eclampsia represents 25% of eclamptic seizures, can occur up to 8 weeks after delivery, and can be seen in women without preceding preeclampsia.[76]

Psychogenic Nonepileptic Seizures

Psychogenic seizures, or pseudoseizures, are functional events that may be associated with alterations in cognition, abnormal movements and behaviors, and autonomic changes. They are not the result of abnormal CNS electrical activity. Psychogenic seizures may be primarily motor and mimic convulsive generalized seizures, including refractory status epilepticus, or they may be nonconvulsive and mimic either absence or complex partial seizures. Although certain features of convulsive psychogenic seizures may suggest the diagnosis, no clinical criteria are 100% specific; simultaneous video and EEG recordings may be required to confirm the diagnosis.[77,78]

The ED evaluation of these patients is difficult, because epilepsy and pseudoseizures can coexist in a minority of patients.[79] All but obviously functional abnormalities should be treated as true ictus pending formal neurologic evaluation. Many patients with pseudoseizures are not deliberately attempting to mislead the examining physician. The long-term treatment of patients with confirmed pseudoseizures may include direct confrontation, intensive psychotherapy, and use of a placebo.

Postictal States

The postictal state that follows most generalized seizures typically is characterized by decreased levels of arousal and responsiveness, disorientation, amnesia, and headache. These conditions may persist for only a few minutes or for many hours and may not be consistent from seizure to seizure. The most important consideration in ED management of the postictal state is to monitor and investigate the altered mental status after a seizure; otherwise, dangerous underlying metabolic or toxic abnormalities may be overlooked. At a minimum, airway positioning maneuvers, pulse oximetry, rapid glucose determination, and cardiac rhythm monitoring are necessary.

Two unusual postictal manifestations may provoke particular consternation in the ED: postictal paralysis and neurogenic pulmonary edema. Postictal paralysis, or Todd's paralysis, may follow generalized or complex partial seizures and is a focal motor deficit that may persist up to 24 hours and may be caused by transient focal cerebral hypoprofusion.[80] Weakness of one extremity or a complete hemiparesis may occur; in the latter case the patient should be safely restrained to avoid falls caused by a combination of weakness and diminished responsiveness resulting from the postictal state. Todd's paralysis is associated with a high likelihood of an underlying structural cause for the seizure.

Neurogenic pulmonary edema is a relatively common, although often subclinical, complication of any structural CNS insult, including seizure, trauma, and hemorrhage.[81] Neurogenic pulmonary edema is likely caused by centrally mediated sympathetic discharge and generalized vasoconstriction, coupled with increased pulmonary capillary membrane permeability. After a seizure, neurogenic pulmonary edema can be confused clinically and radiographically with aspiration pneumonia. Otherwise unexplained hypoxia or other clinical evidence of pulmonary congestion after a seizure prompts consideration of neurogenic pulmonary edema. Significant neurogenic pulmonary edema is managed with ventilatory support, including positive end-expiratory pressure.[82,83]

A prolonged postictal state raises clinical suspicion for nonconvulsive status epilepticus. After prolonged tonic-clonic seizures, ongoing cerebral epileptic activity may manifest with subtle motor

www.ketabpezeshki.com 66485457-66963820

movements such as twitching of the digits or face. EEG is the most definitive way to confirm the diagnosis.[26]

DIAGNOSTIC STRATEGIES

First-Time Seizures

The essential components of the seizure evaluation in the ED are discussed in Chapter 18. An accurate and thorough history of the ictal event and information about any known or potential precipitants or exposures and the patient's medical problems are obtained. A thorough physical examination, including a complete neurologic examination, is essential. Any identified focal neurologic deficits must be monitored for progression or resolution. Appropriate ancillary studies may be comprehensive, but if precipitants (e.g., hypoglycemia, intoxication, medication noncompliance) are known, studies may be comparatively limited. Frequently, the cause of the first seizure in an adult cannot be found in the ED.[84]

Although the Academy of Neurology recommends neuroimaging, by either CT or magnetic resonance imaging (MRI), for all adults with an apparently unprovoked first seizure, the usefulness of emergent imaging depends on the clinical situation.[85] An emergent cranial CT scan is indicated when a serious structural lesion is suspected on clinical grounds, including presence of a new focal deficit, persistent altered mental status, fever, recent trauma, persistent headache, history of cancer, anticoagulant use, suspicion or known history of acquired immunodeficiency syndrome (AIDS), age older than 40 years, and partial-complex seizure.[86] A reasonable approach is to obtain a brain CT scan on an outpatient, follow-up basis in patients who have recovered completely from the ictal event and in whom no apparent cause has been elucidated. However, if reliable follow-up care is unlikely or even questionable, the CT scan should be obtained in the ED to ensure its completion. In patients with known epilepsy and recurrent seizures, the same considerations apply, but in addition, epileptic patients with a change in seizure pattern, prolonged postictal state, or persistent abnormal mental status should undergo brain CT scan in the ED.

Children with seizures can be evaluated in a similar manner. Those with febrile seizures are not more likely than those with fever alone to have a serious bacterial infection. Children with afebrile seizures who are well appearing can generally be managed as outpatients. Blood tests and other diagnostics are indicated in children younger than 6 months, those who have had a prolonged seizure or postictal state, and those who have a preexisting metabolic disorder or suspected dehydration. Emergent neuroimaging is indicated for children with significant past medical histories or in cases of focal seizures in children younger than 3 years.[87,88] Children younger than 6 months may have positive, relevant brain CT findings in 50% of cases.[89]

The decision to initiate anticonvulsant therapy after a single seizure depends on the cause of the seizure. Seizures caused by structural lesions, such as stroke, tumor, or head injury, are likely to recur and may warrant antiepileptic medication. However, such patients also are likely to be admitted to the hospital if the lesion is newly discovered. For patients with a single unprovoked seizure, evidence-based recommendations are that antiepileptic therapy should not be initiated; rather, the patient should be discharged with referral for neurologic consultation.[84,86,90,93,94] The rationale for this approach is threefold. First, the diagnosis may be incorrect, especially if the seizure-like activity was not witnessed by experienced medical personnel. It is estimated that 20 to 25% of patients diagnosed as having seizures are eventually determined not to have seizures, with the most frequent alternative diagnoses being cardiovascular and psychopathologic.[95-98] Second, the patient may not have a recurrent seizure. It is estimated that less than 50% of patients who have had a single unprovoked seizure will experience a recurrent seizure within 2 years.[90,99,100] Furthermore, whereas treatment decreases the risk of early recurrent seizure, it does not affect long-term prognosis of epilepsy,[90,101-103] nor does it have an impact on patient quality of life,[104] with the exception of driving limitations, which are prolonged in a patient with recurrent seizure. Third, antiepileptic medications have side effects that may outweigh the benefit of treatment, especially in women of childbearing age, owing to the teratogenic risk of AEDs; in patients with liver, kidney, or hematologic disorders; and in patients already taking multiple medications.

Recurrent Seizures

The initial approach to stabilization of a patient with a known seizure disorder does not differ from that for a patient with new-onset seizure; this includes a rapid blood glucose determination and evaluation for precipitant causes. The most common cause of seizures in a patient with a diagnosed seizure disorder is noncompliance with medications.[29] However, supratherapeutic and toxic levels of some anticonvulsants, such as carbamazepine, phenytoin, lamotrigine, and topiramate, can also *cause* seizures.[105-110] Accordingly, it is prudent to check the serum drug level, if this test is available, before giving a full loading dose of anticonvulsants to patients on long-term therapy. Meanwhile, a thorough history and physical examination focus on intercurrent illness or trauma, drug or alcohol use, potential adverse drug-drug interactions with anticonvulsants, a recent change in anticonvulsant dosage regimens, and any change in ictal pattern or characteristics. Clinical indications dictate the selection of other laboratory or radiographic tests.

DIFFERENTIAL CONSIDERATIONS

Even when a "seizure" is witnessed in the ED, other abnormal movements and states of consciousness can be confused with ictal activity. The most common misdiagnoses are cardiovascular (syncope) and psychogenic, but other considerations in the differential diagnosis include hyperventilation and breath-holding, certain toxic and metabolic states, transient ischemic attacks, narcolepsy, and some movement disorders.[13,96,111-114]

At times the diagnosis can be difficult in a patient who is seen after an unwitnessed fall and unprovoked loss of consciousness. Syncope, whether vasodepressive (e.g., "vagal" or micturition syncope), orthostatic, or arrhythmogenic (e.g., paroxysmal ventricular tachycardia or fibrillation, long QT syndrome), may be confused with ictal events. Differentiating among these may be particularly difficult when episodes are recurrent; hence the consideration "fit versus faint." A tonic phase preceding tonic-clonic activity is not seen with syncope, and the tonic-clonic movements in patients with seizures are much more forceful and are more prolonged than the "twitches" sometimes associated with fainting. Tongue biting and urinary incontinence rarely occur with syncope but are common with seizures. Most seizures are characterized by a postictal state in which patients are confused and may complain of headache, which is not a feature of syncope. Retrograde amnesia also suggests an ictal diagnosis.

Hyperventilation syndrome can be associated with mood disturbances, paresthesias, and posturing movements of the distal extremities. Manifestations of toxic and metabolic disorders that mimic ictus include delirium tremens and alcoholic blackouts, the alteration in consciousness associated with hypoglycemia and acute intermittent porphyria, the buccolingual spasms of phencyclidine intoxication, and the tonic spasms caused by tetanus, strychnine, and camphor.[13] Nonictal CNS events, such as transient ischemic attacks, transient global amnesia, and atypical migraines, may manifest in a manner similar to absence seizures and postictal states such as Todd's paralysis. Carotid sinus hypersensitivity,

www.ketabpezeshki.com 66485457-66963820

which can result even from a tight necktie, may cause sudden falls that mimic drop attacks.[115] Narcolepsy (recurrent irresistible daytime sleepiness), especially when it occurs with cataplexy (sudden falls), may be associated with hallucinations and abnormal movements. It can be differentiated from seizure activity by the history and response to stimulation. Movement disorders, such as hemiballismus and tics, usually are associated with other neurologic problems. Finally, dissociative states such as fugue and panic attacks can be confused with seizures. An EEG is an appropriate diagnostic option in unclear cases.

MANAGEMENT

Immediate Management

The management of a patient experiencing a seizure begins with active, anticipatory airway management. In generalized ictus, the gag reflex is suppressed, and vomiting often is complicated by aspiration of gastric contents. The patient is placed in a left lateral decubitus position to lessen chances of aspiration. Dentures are removed but kept close by, as they may be needed for a good mask seal to be attained if bag-mask ventilation is required. A bite-block can be placed to protect the tongue and allow access for suctioning, but care should be taken to avoid iatrogenic trauma from forceful placement of intraoral devices.

If the patient is persistently apneic or if an unavoidable airway threat is present, endotracheal intubation is warranted for definitive protection. A benzodiazepine can be used as an induction agent in the hope that its action may terminate the seizure or obviate the need for tracheal intubation. Postintubation sedation with benzodiazepine infusion or propofol infusion is also recommended. Trismus may necessitate use of a short-acting neuromuscular blocking agent to facilitate intubation; long-acting paralytics will mask motor manifestations of ongoing seizures.

In general, the first-line pharmacologic agent for treatment of any active seizure is a parenteral benzodiazepine. Because benzodiazepines directly enhance GABA-mediated neuronal inhibition, they affect clinical and electrical manifestations of seizures. Benzodiazepines are effective in terminating ictal activity in a majority of patients and have been shown to be more effective than phenytoin in terminating status epilepticus.[116,117] Although phenobarbital appears to be as effective as the benzodiazepine lorazepam in terminating status epilepticus, the associated high risk of hypoventilation and hypotension limits its use as a first-line agent.[117]

The most commonly used benzodiazepines include diazepam, lorazepam, and midazolam (Table 102-1). All three may be used in patients of any age, and all share the following characteristics: rapid onset (seconds to minutes), relatively short duration of anticonvulsant action, a sedative effect, and the potential for hypotension and respiratory depression. Lorazepam has emerged as the drug of choice for the initial management of convulsions, because it terminates seizures rapidly (within 2 minutes) and has a longer duration of action (4-6 hours, compared with 20 minutes for diazepam), thus necessitating fewer repeat doses.[118-121] For this reason, it also is the preferred agent for control of alcohol withdrawal seizures.[122] Lorazepam is most effective when given intravenously but can also be administered intramuscularly, intranasally, intraosseously, and as a sublingual preparation for out-of-hospital control of seizures in children.[123]

An advantage of diazepam is that it is in liquid form at room temperature and is therefore available premixed in resuscitation kits, and it can be administered quickly and without a need for reconstitution by the intravenous, endotracheal, or intraosseous route. Its onset of action with intravenous administration is within 10 to 20 seconds, but there is a 50% chance of recurrent seizure within 2 hours if diazepam is used.[117] Diazepam can also be administered rectally via suppositories or a rectal gel. Rectal diazepam achieves variable success in seizure cessation, perhaps owing

Table 102-1 Medications Used in the Abortive Treatment of Status Epilepticus in the Emergency Department

MEDICATION	ADULT DOSE	PEDIATRIC DOSE	COMMENTS
Initial Therapy			
Diazepam	10 mg IV or 10-20 mg PR	0.15 mg/kg IV; 0.2-0.5 mg/kg PR (max 20 mg)	May repeat in 5-10 min; monitor respiratory status
Lorazepam	4 mg IV	<13 kg: 0.1 mg/kg IV (max 2 mg); 13-39 kg: 2 mg IV; >39 kg: 4 mg IV	Preferred intravenous benzodiazepine; may repeat in 10 min; monitor respiratory status
Midazolam	10 mg IV, IM, IN, buccally	0.2 mg/kg IV, IN (max 5 mg); 0.5 mg/kg buccal (max 5 mg); <13 kg: 0.2 mg/kg IM (max 5 mg); 13-39 kg: 5 mg IM; >39 kg: 10 mg IM	Preferred intramuscular benzodiazepine; may repeat in 10 min; monitor respiratory status
Second-Tier Treatments			
Phenytoin	20-mg/kg intravenous infusion	20-mg/kg intravenous infusion	May cause hypotension and dysrhythmia
Fosphenytoin	20-mg PE/kg intravenous infusion or 20 mg PE/kg IM	20-mg PE/kg intravenous infusion	
Valproic sodium	20-40 mg/kg IV infusion		Max dose 60 mg/kg/day
Pentobarbital	10- to 20-mg/kg intravenous bolus then 0.5-3.0 mg/kg/hr		Titrate according to EEG; intubation and hemodynamic support required
Phenobarbital	5-15 mg/kg IV bolus then 0.5-5.0 mg/kg/hr		Intubation likely required
Midazolam infusion	0.05-2 mg/kg/hr	0.5-2 mg/kg/hr	Monitor respiratory status
Propofol infusion	1-2 mg/kg intravenous bolus then 20-200 μg/kg/hr infusion		Intubation required
Isoflurane inhalation			Titrate according to EEG; intubation and hemodynamic support required

Brophy GM, et al: Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 17:3-23, 2012.
EEG, electroencephalogram; *ET,* endotracheally; *IM,* intramuscularly; *IN,* intranasally; *IV,* intravenously; *PR,* rectally.

www.ketabpezeshki.com 66485457-66963820

to the dual venous drainage of the rectum. The inferior and middle rectal veins drain into the central circulation via the common iliacs, whereas the superior rectal vein flows into the hepatic portal system. Diazepam placed too deeply into the rectum would undergo first-pass metabolism in the liver, thus limiting bioavailability and clinical effect.

Midazolam's onset of action is within 1 minute; it is available in both intranasal and buccal formulations,[124] and among the benzodiazepines it has the least cardiovascular effect.[121] Midazolam is rapidly and reliably absorbed after intramuscular administration and has been shown to be as effective when given intramuscularly as intravenous lorazepam, making it a preferred medication when intravenous access has not yet been established.[125] Nonintravenous midazolam is as effective as intravenous diazepam, and buccal midazolam is superior to rectal diazepam in achieving symptom control.[126]

Second-line abortive anticonvulsant therapy consists of phenytoin and phenobarbital. Phenytoin reduces the repetitive firing of action potentials through sodium channel blockade, thereby stabilizing neuronal membranes.[10] Phenytoin neither sedates patients nor causes respiratory depression, but rapid intravenous administration of phenytoin in its propylene glycol diluent may cause hypotension and cardiac bradydysrhythmias, as well as local vascular injury, including venous thrombosis and localized tissue necrosis (purple glove syndrome).[127-129] Phenytoin's onset of action is within 10 to 30 minutes, and intravenous administration typically requires at least 20 minutes.[130] The duration of action is approximately 24 hours. Continued benzodiazepine administration is appropriate until phenytoin achieves adequate brain levels. Phenytoin is not recommended in toxin-induced seizures, as it is likely to be ineffective and may be harmful in cases of theophylline or tricyclic antidepressant ingestions.[3]

Fosphenytoin is a water-soluble prodrug form of phenytoin, with a more physiologic pH. Its main advantages are that it is not likely to precipitate during intravenous infusion and that it also can be administered intramuscularly, although the volume required for full loading by the intramuscular route may be in the range of 20 mL or more.[131] Although fosphenytoin can be infused more rapidly, the time to therapeutic concentration of the active drug is the same as for intravenous phenytoin.[132] The hemodynamic advantages of fosphenytoin over intravenous phenytoin have not proven to be significant.[133,134] Fosphenytoin use is most appropriate when intravenous access is not obtainable or when the intravenous line is of small gauge, as is often the case in children and elders.[120]

If the serum drug level of phenytoin is subtherapeutic in a patient already being treated for seizures, a loading dose can be given intravenously or orally in divided doses over 6 hours. Oral loading of phenytoin is associated with fewer adverse events than loading with either intravenous phenytoin or fosphenytoin,[134] but it is inadequate when therapeutic activity is required urgently.

Phenobarbital is similar to benzodiazepines in that it binds to and enhances the inhibitory neurotransmitter GABA, thereby acting as a CNS depressant that decreases ictal and physiologic cortical electrical activity. Sedation and depression of respiratory drive and blood pressure must be anticipated, and for this reason nonsedating phenytoin is preferred.[121] The onset of action of phenobarbital is within 15 to 30 minutes, and the duration of action is 48 hours.

Valproic acid administered intravenously has recently been recognized as a safe and effective treatment for seizures, especially in patients with allergies to phenytoin, the elderly, and patients with cardiorespiratory instability who might be at increased risk of adverse events from phenytoin.[135-137] Valproic acid administered intravenously has been shown to be as effective as phenytoin in patients with benzodiazepine-refractory status epilepticus, with fewer cardiopulmonary side effects.[138] Hyperammonemic encephalopathy after valproic acid loading has been reported and should be evaluated by obtaining the serum ammonia level in a patient who does not regain consciousness after seizure resolution.[21,139] Appropriate ED dosage regimens for the benzodiazepines, phenytoin, fosphenytoin, phenobarbital, and valproic acid are listed in Table 102-1.

While these agents are being given to abort ongoing seizure activity, ED management must include a search for underlying reversible causes. This search may prompt administration of dextrose for hypoglycemia, pyridoxine (vitamin B_6) for isoniazid overdose, sodium for hyponatremia, or magnesium for eclampsia.

Eclampsia complicates 1 in 1000 deliveries in the United States and can occur antepartum (91% of cases occur after 28 weeks of gestation), during the peripartal period, and up to 8 weeks postpartum.[140-142] Abortive treatment for eclamptic seizures is with magnesium sulfate, which is superior to both diazepam and phenytoin in limiting maternal mortality and preventing further seizures in eclampsia.[143,144] The loading dose of magnesium sulfate is 4 to 6 g, followed by an infusion of 2 g/hr for 24 hours.[75,143,144] Because hypermagnesemia may cause respiratory arrest, it is essential to monitor patients for hyporeflexia, which precedes respiratory compromise. In the uncommon event of respiratory compromise resulting from excessive neuromuscular blockade caused by magnesium sulfate, 1 g of 10% calcium gluconate is an effective reversal agent.[75] Simultaneous reduction in blood pressure in the eclamptic patient, with use of hydralazine, labetalol, or nicardipine, is recommended.[75]

Nonpregnant patients who continue having seizures in the ED despite management with benzodiazepines, phenytoin, or phenobarbital are likely to meet the clinical criteria for refractory status epilepticus. Additional therapeutic measures include use of valproate, midazolam infusion, propofol infusion, barbiturate coma, and general inhalational anesthesia. Valproate, which increases GABA concentration, may be given intravenously in status epilepticus (see Table 102-1).[23] Another alternative is the use of propofol, a nonbarbiturate anesthetic agent with hypnotic and anticonvulsant activity. Studies suggest that propofol acts at a location other than the benzodiazepine-binding site and modifies the chloride channel by a mechanism that is different from, and possibly synergistic with, those for benzodiazepines and barbiturates. Propofol usually is administered as an intravenous loading dose, followed by an infusion with continuous EEG monitoring to ensure persistent burst suppression.[145,146]

Barbiturate coma is effective in terminating seizures by acting as a GABA agonist, although it also suppresses all brainstem function. Neurologic consultation is advisable before induction of barbiturate coma in a patient with refractory status epilepticus. Expected consequences of barbiturate coma include respiratory arrest, myocardial depression, and hypotension. At the same time, intracranial pressure may be decreased, thus increasing cerebral perfusion. The preferred agent for barbiturate coma is pentobarbital (see Table 102-1). Patients who are treated with barbiturate coma require intubation and ventilatory support, continuous cardiac monitoring, and invasive hemodynamic monitoring. Pressors may be required to support the blood pressure.[147]

Inhalation anesthetics are one final alternative in the management of refractory ictus. Isoflurane and halothane are the common gases that are available. Halothane is associated with more hemodynamic and hepatotoxic complications. Isoflurane suppresses electrical seizure foci and is easily titratable. Patients managed with inhalational anesthesia require intubation and mechanical ventilation.

The role of newer AEDs, such as lacosamide and levetiracetam, in the management of status epilepticus has not yet been well established.[148,149]

The visible manifestations of convulsive ictus are extinguished by neuromuscular blockade. When a seizing patient is paralyzed

www.ketabpezeshki.com 66485457-66963820

and intubated, it cannot be assumed that pharmacologic therapy has terminated the seizure. Anticonvulsant administration is continued, and EEG monitoring of the patient is arranged. Without EEG, detection of seizure activity in a heavily sedated or paralyzed patient may be impossible.

Long-Term Management

Identifying a new-onset seizure disorder in the ED prompts consideration of the need for further management in the following three areas: pharmacologic, psychosocial, and legal. The primary dilemma is whether or not to initiate prophylactic anticonvulsant therapy after one seizure. The decision to treat should be based on (1) ensuring that the diagnosis of seizure is correct, (2) ascertaining the likelihood of seizure recurrence, (3) assessing the benefit versus risk of anticonvulsant therapy, and (4) discussing with the patient his or her approach to risk.

Even when witnessed in the ED, apparent ictal activity may not be a seizure. Diagnosing a seizure is more difficult when the event resolved before the patient's arrival at the ED and is based on witness reports. In patients diagnosed with a seizure, 20 to 25% are subsequently found to have been misdiagnosed.[150,151]

The risk of seizure recurrence is difficult to estimate in the ED setting. In patients with an initial unprovoked seizure, the 2-year risk of recurrence without treatment generally is considered to be less than 50%.[90,99,100] The presence of EEG abnormalities suggests greater risk, but this information usually is unavailable in the ED setting. Other factors associated with an increased risk of recurrence are partial (versus generalized) ictus, status epilepticus, a history of intracranial surgery or trauma, and the presence of a persistent neurologic abnormality, such as Todd's paralysis.

The presence of specific underlying conditions may affect the decision to institute long-term therapy. For example, it would be reasonable to initiate antiepileptic therapy for an initial seizure in an HIV-positive patient when the seizure is not a result of correctable factors such as drug toxicity or metabolic derangement.[50,90] Alcohol-related seizures are notoriously unresponsive to anticonvulsants. Prophylaxis against post-traumatic seizures beyond the first week after injury probably is unnecessary,[152] but the occurrence of early post-traumatic seizures should prompt at least short-term initiation of therapy.[153] Furthermore, if a patient not receiving antiepileptic therapy arrives in the ED with a second seizure, initiation of treatment is warranted because of the estimated 70% risk of recurrent events.[154]

The side effects of anticonvulsants can be debilitating for the patient (Table 102-2). These effects should be considered before such therapy is initiated, particularly in women of reproductive

Table 102-2 Important Adverse Effects and Drug-Drug Interactions of Antiepileptic Drugs

GENERIC NAME	TRADE NAME	IMPORTANT ADVERSE EFFECTS	P_{450} LIVER ENZYME METABOLIZERS*
Carbamazepine	Tegretol	Rash, leukopenia, hyponatremia, cardiac dysrhythmias (elderly), weight gain	Inducer
Clonazepam	Klonopin	Sedation, ataxia, irritability	No
Ethosuximide	Zarontin	Sedation, ataxia, nausea, anorexia	
Felbamate	Felbatol	Rare fatal aplastic anemia, hepatotoxicity, headache, anorexia, vomiting, insomnia	Inducer
Fosphenytoin	Cerebyx	Nystagmus, ataxia, sedation, headache	Inducer
Gabapentin	Neurontin	Sedation, ataxia, tremor	No
Lamotrigine	Lamictal	Hypersensitivity reaction (risk of renal failure, liver failure, DIC), rash (SJS, TEN), ataxia, headache, nausea	Inducer and inhibitor†
Levetiracetam	Keppra	Emotional lability, sedation, dizziness, infections (colds)	No
Oxcarbazepine	Trileptal	Hyponatremia, rash, dizziness, headache, fatigue	Inducer and inhibitor
Phenobarbital	Luminal	Sedation, depression, cognitive slowing, decline in libido, osteomalacia	Inducer
Phenytoin	Dilantin	Gingival hyperplasia, hirsutism, nystagmus, ataxia, sedation, nausea, osteoporosis, leukopenia, phenytoin hypersensitivity syndrome‡	Inducer
Pregabalin	Lyrica	Weight gain	No
Primidone§	Mysoline	Sedation, depression, cognitive slowing, decline in libido, acute toxicity after first dose	Inducer
Tiagabine	Gabitril	Dizziness, depression, tremor, poor concentration	No
Topiramate	Topamax	Cognitive slowing, anorexia, nephrolithiasis, paresthesias, metabolic acidosis, rare glaucoma	Inducer
Valproate	Depakote	Thrombocytopenia, tremor, weight gain, male-pattern hair loss, rare hepatotoxicity, osteoporosis	No
Zonisamide	Zonegran	Sedation, cognitive slowing, ataxia, anorexia, rash	No

Data from Engel J Jr, Pedley TA (eds): Epilepsy: A Comprehensive Textbook, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2008; Harden CL, Leppik I: Optimizing therapy of seizures in women who use oral contraceptives. Neurology 67:S56, 2006; French JA, et al: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy: Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society [see comment]. Neurology 62:1252, 2004; and Mattson RH: Efficacy and adverse effects of established and new antiepileptic drugs. Epilepsia 36:S13, 1995.
DIC, disseminated intravascular coagulation; *SJS,* Stevens-Johnson syndrome; *TEN,* toxic epidermal necrolysis.
*All inducers of liver enzymes reduce the efficacy of oral contraceptives.
†Oral contraceptive pills also reduce Lamictal serum levels.
‡Phenytoin hypersensitivity syndrome includes rash, fever, hepatitis, lymphoid hyperplasia, and blood dyscrasias. Side effects of intravenous phenytoin include hypotension, arterioventricular block, and purple glove syndrome (edema, pain, and discoloration of the limb distal to the site of infusion).
§Primidone is a congener of phenobarbital.

www.ketabpezeshki.com 66485457-66963820

Table 102-3 Medications Used for Long-Term Anticonvulsant Therapy in Adults

MEDICATION	INDICATIONS	MAINTENANCE DOSE (mg/day)*	ROUTE	THERAPEUTIC RANGE (μg/mL)	NUMBER OF DAILY DOSES
Carbamazepine	Partial and generalized seizures	800-1600	Oral	4-12	2 or 3
Clonazepam	Absence seizures	1.5-8	Oral	20-80	2 or 3
Ethosuximide	Absence seizures	750-1250	Oral	40-100	2
Felbamate	Refractory epilepsy only	2400-3600	Oral	N/A	3 or 4
Gabapentin	Partial seizures	900-3600	Oral	N/A	3
Lamotrigine	Partial, generalized, and absence seizures	100-500	Oral	N/A	2
Levetiracetam	Partial, generalized, and absence seizures	1000-3000	Oral, IV	N/A	2
Oxcarbazepine	Partial and generalized seizures	1200-2400	Oral	N/A	2
Phenobarbital	Partial and generalized seizures	90-150	Oral, intravenous	20-40	2-3
Phenytoin	Partial and generalized seizures	300-400	Oral, intravenous, intramuscular	10-20	1-3
Pregabalin	Partial seizures	150-600	Oral	N/A	2-3
Primidone	Partial and generalized seizures	750-1250	Oral	5-12	3-4
Tiagabine	Partial seizures (adjunct)	32-56‡	Oral	N/A	2-4
Topiramate	Partial and generalized seizures	200-400	Oral	N/A	2
Valproate	Partial, generalized, and absence seizures	1000-3000	Oral, intravenous	50-100	1-3
Zonisamide	Partial, generalized, and absence seizures	100-400	Oral	20-30§	1-2

Data from Engel J Jr, Pedley TA (eds): Epilepsy: A Comprehensive Textbook, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2008; Mattson RH: Efficacy and adverse effects of established and new antiepileptic drugs. Epilepsia 36:S13, 1995; Perucca E: Clinical pharmacology and therapeutic use of the new antiepileptic drugs. Fundam Clin Pharmacol 15:405, 2001; and Drugs for Epilepsy. Treatment Guidelines from the Medical Letter 6:37, 2008.

N/A, not applicable.

*Adjust dose for hepatic or renal disease and with use of other medications.

‡If patient is not taking enzyme-reducing antiepileptic drugs, then daily dose should be halved (16-28).

§Some studies indicate a range of 10-50 mg/L.

age, because many anticonvulsants are teratogenic, and some precipitate failure of oral contraceptives.

In the absence of specific underlying conditions that increase risk of recurrence, evidence does not support the initiation of anticonvulsant therapy from the ED after a single unprovoked seizure in adults.[13,101,104,155] If the seizure was provoked, the decision should be based on whether the provoking factor can be corrected; if it cannot, anticonvulsant therapy should be instituted. The anticonvulsant dosage regimen for a patient with known epilepsy should be modified only in consultation with the patient's physician (Table 102-3).

Drug monotherapy is preferable in anticonvulsant regimens. Choosing the right drug depends on numerous factors, including the type of seizure, comorbid conditions, other medications the patient is taking, and the potential for pregnancy, and it is best determined in consultation with a neurologist, ideally after MRI neuroimaging and an EEG.[85] However, if an anticonvulsant is to be initiated in the ED, then the choice is among the three medications with the strongest evidence of efficacy in the treatment of a tonic-clonic seizure of either generalized onset or partial onset with secondary generalization: carbamazepine, phenytoin, and valproate.[156] It is essential to inform women of childbearing age that carbamazepine and phenytoin decrease the efficacy of oral contraceptive pills, so a second form of contraception should be used pending consultation with a neurologist. Valproate, although not altering the efficacy of oral contraceptives, carries a high risk of teratogenic effects and is therefore not an ideal first-line agent for women of childbearing years.[157,158]

The psychological and social implications of the new diagnosis of a seizure disorder for the patient can be profound. Fear of seizures and stigmatization are common; employability and insurability may be adversely affected. Although the emergency physician is not usually in a suitable position to arrange for counseling, referral to local epilepsy support groups may be helpful.

The diagnosis of a new-onset seizure disorder has legal implications as well. Each state has regulations regarding driving privileges in patients with seizures, and some states require reporting by the physician. Accordingly, ED management must ensure compliance with such regulations, including informing patients about any restrictions. Patients also should be advised to refrain from hazardous or isolated activities until cleared by their primary care physician or neurologist to participate in them. The need for a "medical alert" bracelet or other medical condition identifier should be stressed.

Finally, patients and their families should be counseled about seizure first aid, safety precautions such as avoiding swimming alone and operating dangerous machinery, and triggers for recurrence such as photic stimuli, sleep deprivation, and alcohol.

www.ketabpezeshki.com 66485457-66963820

KEY CONCEPTS

- The possibility of reactive seizures should be considered in all patients in the ED with seizures or recent history of seizures, including patients with a history of epilepsy. The most common cause of reactive seizures is hypoglycemia. The most common cause of recurrent primary seizures is medication noncompliance.
- Seizures may be confused with nonictal states, including syncope, movement disorders, and psychiatric disorders.
- Neuroimaging is recommended for patients with seizures who have head trauma, persistently abnormal mental status, focal neurologic abnormality, or HIV disease.
- Primary abortive therapy for seizures in the ED setting is with a benzodiazepine; second-line agents include phenytoin and phenobarbital.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Martindale JL, Goldstein JN, Pallin DJ: Emergency department seizure epidemiology. *Emerg Med Clin North Am* 2011; 29:15.
2. Pallin DJ, et al: Seizure visits in U.S. emergency departments: Epidemiology and potential disparities in care. *Int J Emerg Med* 2008; 1:97.
3. Sharma AN, Hoffman RJ: Toxin-related seizures. *Emerg Med Clin North Am* 2011; 29:125.
4. Benbadis SR: Epileptic seizures and syndromes. *Neurol Clin* 2001; 19:251.
5. Engel J Jr: A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: Report of the ILAE Task Force on Classification and Terminology. *Epilepsia* 2001; 42:796.
6. Engel J Jr: ILAE classification of epilepsy syndromes. *Epilepsy Res* 2006; 70(Suppl 1):5.
7. Fisher RS, et al: Epileptic seizures and epilepsy: Definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005; 46:470.
8. Seino M: Classification criteria of epileptic seizures and syndromes. *Epilepsy Res* 2006; 70(Suppl 1):27.
9. Blume WT, et al: Glossary of descriptive terminology for ictal semiology: Report of the ILAE task force on classification and terminology. *Epilepsia* 2001; 42:1212.
10. Engel J, Pedley TA: *Epilepsy: A Comprehensive Textbook*, 2nd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
11. Alving J, Beniczky S: Diagnostic usefulness and duration of the inpatient long-term video-EEG monitoring: Findings in patients extensively investigated before the monitoring. *Seizure* 2009; 18:470.
12. Watemberg N, et al: Adding video recording increases the diagnostic yield of routine electroencephalograms in children with frequent paroxysmal events. *Epilepsia* 2005; 46:716.
13. Shneker BF, Fountain NB: Epilepsy. *Dis Mon* 2003; 49:426.
14. Goldberg PA, Inzucchi SE: Critical issues in endocrinology. *Clin Chest Med* 2003; 24:583.
15. Orringer CE, Eustace JC, Wunsch CD, Gardner LB: Natural history of lactic acidosis after grand-mal seizures. A model for the study of an anion-gap acidosis not associated with hyperkalemia. *N Engl J Med* 1977; 297:796.
16. Bassin S, Smith TL, Bleck TP: Clinical review: Status epilepticus. *Crit Care* 2002; 6:137.
17. Lowenstein DH: The management of refractory status epilepticus: An update. *Epilepsia* 2006; 47(Suppl 1):35.
18. Huff JS, Fountain NB: Pathophysiology and definitions of seizures and status epilepticus. *Emerg Med Clin North Am* 2011; 29:1.
19. Pellock JM: Overview: Definitions and classifications of seizure emergencies. *J Child Neurol* 2007; 22(Suppl 5):9.
20. Aranda A, et al: Generalized convulsive status epilepticus management in adults: A cohort study with evaluation of professional practice. *Epilepsia* 2010; 51:2159.
21. Rossetti AO, Hurwitz S, Logroscino G, Bromfield EB: Prognosis of status epilepticus: Role of aetiology, age, and consciousness impairment at presentation. *J Neurol Neurosurg Psychiatry* 2006; 77:611.
22. Thundiyil JG, Kearney TE, Olson KR: Evolving epidemiology of drug-induced seizures reported to a Poison Control Center System. *J Med Toxicol* 2007; 3:15.
23. Lowenstein DH, Alldredge BK: Status epilepticus. *N Engl J Med* 1998; 338:970.
24. Walker MC: Treatment of nonconvulsive status epilepticus. *Int Rev Neurobiol* 2007; 81:287.
25. Meierkord H, Holtkamp M: Nonconvulsive status epilepticus in adults: Clinical forms and treatment. *Lancet Neurol* 2007; 6: 329.
26. Chang AK, Shinnar S: Nonconvulsive status epilepticus. *Emerg Med Clin North Am* 2011; 29:65.
27. Alroughani R, Javidan M, Qasem A, Alotaibi N: Non-convulsive status epilepticus; the rate of occurrence in a general hospital. *Seizure* 2009; 18:38.
28. Takahashi T, Tsukahara Y: Pocket Monster incident and low luminance visual stimuli: Special reference to deep red flicker stimulation. *Acta Paediatr Jpn* 1998; 40:631.
29. Ettinger AB, Manjunath R, Candrilli SD, Davis KL: Prevalence and cost of nonadherence to antiepileptic drugs in elderly patients with epilepsy. *Epilepsy Behav* 2009; 14:324.
30. Weiner WJ, Shulman LM: *Emergent and Urgent Neurology*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 1999.
31. Monami M, Mannucci E, Breschi A, Marchionni N: Seizures as the only clinical manifestation of reactive hypoglycemia: A case report. *J Endocrinol Invest* 2005; 28:940.
32. Buckingham B, et al: Duration of nocturnal hypoglycemia before seizures. *Diabetes Care* 2008; 31:2110.
33. Malouf R, Brust JC: Hypoglycemia: Causes, neurological manifestations, and outcome. *Ann Neurol* 1985; 17:421.
34. Yoshino T, et al: A case of hypoglycemic hemiparesis and literature review. *Ups J Med Sci* 2012; 117:347-351.
35. Castilla-Guerra L, del Carmen Fernández-Moreno M, López-Chozas JM, Fernández-Bolaños R: Electrolytes disturbances and seizures. *Epilepsia* 2006; 47:1990.
36. Riggs JE: Neurologic manifestations of electrolyte disturbances. *Neurol Clin* 2002; 20:227.
37. Adrogué HJ, Madias NE: Hyponatremia. *N Engl J Med* 2000; 342(21):1581.
38. Halperin ML, Bohn D: Clinical approach to disorders of salt and water balance. Emphasis on integrative physiology. *Crit Care Clin* 2002; 18:249.
39. Adrogué HJ, Madias NE: Hypernatremia. *N Engl J Med* 2000; 342(20):1493.
40. Cokar O, Aydin B, Ozer F: Non-ketotic hyperglycaemia presenting as epilepsia partialis continua. *Seizure* 2004; 13:264.
41. Kumar S: Epilepsia partialis continua stopped by insulin. *J R Soc Med* 2004; 97:332.
42. Trence DL, Hirsch IB: Hyperglycemic crises in diabetes mellitus type 2. *Endocrinol Metab Clin North Am* 2001; 30:817.
43. Palmer CA: Neurologic manifestations of renal disease. *Neurol Clin* 2002; 20:23.
44. Song TJ, Kim SJ, Kim GS, Choi YC, Kim WJ: The prevalence of thyrotoxicosis related seizures. *Thyroid* 2010; 20:955.
45. Idro R, et al: Burden, features, and outcome of neurological involvement in acute falciparum malaria in Kenyan children. *JAMA* 2007; 297:2232.
46. van de Beek D, et al: Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med* 2004; 351:1849.
47. Jagaralapudi MKM, Sudesh P: Bacterial meningitis and epilepsy. *Epilepsia* 2008; 49(Suppl 6):8S.
48. Annegers JF, Hauser WA, Beghi E, Nicolosi A, Kurland LT: The risk of unprovoked seizures after encephalitis and meningitis. *Neurology* 1988; 38:1407.
49. Carpio A: Neurocysticercosis: An update. *Lancet Infect Dis* 2002; 2:751.
50. Kellinghaus C, et al: Frequency of seizures and epilepsy in neurological HIV-infected patients. *Seizure* 2008; 17:27.
51. Wills B, Erickson T: Drug- and toxin-associated seizures. *Med Clin North Am* 2005; 89:1297.
52. Mokhlesi B, Corbridge T: Toxicology in the critically ill patient. *Clin Chest Med* 2003; 24:689.
53. Haller CA, Meier KH, Olson KR: Seizures reported in association with use of dietary supplements. *Clin Toxicol (Phila)* 2005; 43:23.
54. Kupiec T, Raj V: Fatal seizures due to potential herb-drug interactions with Ginkgo biloba. *J Anal Toxicol* 2005; 29:755.
55. Zimmerman JL: Poisonings and overdoses in the intensive care unit: General and specific management issues. *Crit Care Med* 2003; 31:2794.
56. Shanti CM, Lucas CE: Cocaine and the critical care challenge. *Crit Care Med* 2003; 31:1851.
57. Goldfrank LR, Flomenbaum N: *Goldfrank's Toxicologic Emergencies*, 8th ed. New York: McGraw-Hill; 2006.
58. McMicken D, Liss JL: Alcohol-related seizures. *Emerg Med Clin North Am* 2011; 29:117.
59. Hillbom M, Pieninkeroinen I, Leone M: Seizures in alcohol-dependent patients: Epidemiology, pathophysiology and management. *CNS Drugs* 2003; 17:1013.
60. Frey LC: Epidemiology of posttraumatic epilepsy: A critical review. *Epilepsia* 2003; 44(Suppl 10):11.
61. Temkin NR: Risk factors for posttraumatic seizures in adults. *Epilepsia* 2003; 44(Suppl 10):18.
62. Chang BS, Lowenstein DH: Practice parameter: Antiepileptic drug prophylaxis in severe traumatic brain injury: Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2003; 60(1):10.
63. Schierhout G, Roberts I: Anti-epileptic drugs for preventing seizures following acute traumatic brain injury. *Cochrane Database Syst Rev* 2001; 4:CD000173.
64. Wen PY, Schiff D: Neurologic complications of solid tumors. *Neurol Clin* 2003; 21:107.
65. Nadeau SE: Neurologic manifestations of connective tissue disease. *Neurol Clin* 2002; 20:151.

www.ketabpezeshki.com 66485457-66963820

66. LaRoche SM, Helmers SL: Epilepsy in the elderly. *Neurologist* 2003; 9:241.
67. Camilo O, Goldstein LB: Seizures and epilepsy after ischemic stroke. *Stroke* 2004; 35:1769.
68. Labovitz DL, Hauser WA, Sacco RL: Prevalence and predictors of early seizure and status epilepticus after first stroke. *Neurology* 2001; 57:200.
69. Gilmore E, Choi HA, Hirsch LJ, Claassen J: Seizures and CNS hemorrhage: Spontaneous intracerebral and aneurysmal subarachnoid hemorrhage. *Neurologist* 2010; 16:165.
70. Raps EC, et al: The clinical spectrum of unruptured intracranial aneurysms. *Arch Neurol* 1993; 50:265.
71. Forderreuther S, Henkel A, Noachtar S, Straube A: Headache associated with epileptic seizures: Epidemiology and clinical characteristics. *Headache* 2002; 42:649.
72. Koch M, Uyttenboogaart M, Polman S, De Keyser J: Seizures in multiple sclerosis. *Epilepsia* 2008; 49:948.
73. Mendez M, Lim G: Seizures in elderly patients with dementia: Epidemiology and management. *Drugs Aging* 2003; 20:791.
74. Katz JM, Pacia SV, Devinsky O: Current management of epilepsy and pregnancy: Fetal outcome, congenital malformations, and developmental delay. *Epilepsy Behav* 2001; 2:119.
75. Sibai BM: Diagnosis, prevention, and management of eclampsia. *Obstet Gynecol* 2005; 105:402.
76. Stead LG: Seizures in pregnancy/eclampsia. *Emerg Med Clin North Am* 2011; 29:109.
77. Kerr MP, et al: International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy. *Epilepsia* 2011; 52:2133.
78. Cragar DE, Berry DT, Fakhoury TA, Cibula JE, Schmitt FA: A review of diagnostic techniques in the differential diagnosis of epileptic and nonepileptic seizures. *Neuropsychol Rev* 2002; 12:31.
79. Duncan R: Psychogenic nonepileptic seizures: Diagnosis and initial management. *Expert Rev Neurother* 2010; 10:1803.
80. Mathews MS, Smith WS, Wintermark M, Dillon WP, Binder DK: Local cortical hypoperfusion imaged with CT perfusion during postictal Todd's paresis. *Neuroradiology* 2008; 50:397.
81. Lim HB, Smith M: Systemic complications after head injury: A clinical review. *Anaesthesia* 2007; 62:474.
82. Baumann A, Audibert G, McDonnell J, Mertes PM: Neurogenic pulmonary edema. *Acta Anesthesiol Scand* 2007; 50:447.
83. Fontes RB, et al: Acute neurogenic pulmonary edema: Case reports and literature review. *J Neurosurg Anesthesiol* 2003; 15:144.
84. Jagoda A, Gupta K: The emergency department evaluation of the adult patient who presents with a first-time seizure. *Emerg Med Clin North Am* 2011; 29:41.
85. Krumholz A, et al: Practice parameter: Evaluating an apparent unprovoked first seizure in adults (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 2007; 69:1996.
86. ACEP Clinical Policies Committee; Clinical Policies Subcommittee on Seizures: Clinical policy: Critical issues in the evaluation and management of adult patients presenting to the emergency department with seizures. *Ann Emerg Med* 2004; 43:605.
87. Hampers LC, Spina LA: Evaluation and management of pediatric febrile seizures in the emergency department. *Emerg Med Clin North Am* 2011; 29:83.
88. Sharieff GQ, Hendry PL: Afebrile pediatric seizures. *Emerg Med Clin North Am* 2011; 29:95.
89. Harden CL, et al: Reassessment: Neuroimaging in the emergency patient presenting with seizure (an evidence-based review): Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2007; 69:1772.
90. Miller LC, Drislane FW: Treatment strategies after a single seizure: Rationale for immediate versus deferred treatment. *CNS Drugs* 2007; 21:89.
91. Reference deleted in proofs.
92. Reference deleted in proofs.
93. Seneviratne U: Management of the first seizure: An evidence based approach. *Postgrad Med J* 2009; 85:667.
94. Wiebe S, Téllez-Zenteno JF, Shapiro M: An evidence-based approach to the first seizure. *Epilepsia* 2008; 49(Suppl 1):50.
95. Josephson CB, Rahey S, Sadler RM: Neurocardiogenic syncope: Frequency and consequences of its misdiagnosis as epilepsy. *Can J Neurol Sci* 2007; 34:221.
96. Zaidi A, Clough P, Cooper P, Scheepers B, Fitzpatrick AP: Misdiagnosis of epilepsy: Many seizure-like attacks have a cardiovascular cause. *J Am Coll Cardiol* 2000; 36:181.
97. Bergfeldt L: Differential diagnosis of cardiogenic syncope and seizure disorders. *Heart* 2003; 89:353.
98. McKeon A, Vaughan C, Delanty N: Seizure versus syncope. *Lancet Neurol* 2006; 5:293.
99. Ramos Lizana J, et al: Seizure recurrence after a first unprovoked seizure in childhood: A prospective study. *Epilepsia* 2000; 41:1005.
100. Berg AT: Risk of recurrence after a first unprovoked seizure. *Epilepsia* 2008; 49(Suppl 1):13.
101. Marsoni A, et al: Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: A randomised controlled trial. *Lancet* 2005; 365:2007.
102. Shinnar S, Hauser WA: Do occasional brief seizures cause detectable clinical consequences? *Prog Brain Res* 2002; 135:221.
103. Marson A, et al: Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: A randomised controlled trial. *Lancet* 2005; 365:2007.
104. Jacoby A, Gamble C, Doughty J, Marson A, Chadwick D: Quality of life outcomes of immediate or delayed treatment of early epilepsy and single seizures. *Neurology* 2007; 68:1188.
105. Chua HC, Venketasubramanian N, Tan CB, Tjia H: Paradoxical seizures in phenytoin toxicity. *Singapore Med J* 1999; 40:276.
106. Craig S: Phenytoin overdose complicated by prolonged intoxication and residual neurological deficits. *Emerg Med Australas* 2004; 16:361.
107. Lofton AL, Klein-Schwartz W: Evaluation of lamotrigine toxicity reported to poison centers. *Ann Pharmacother* 2004; 38:1811.
108. Dinnerstein E, Jobst BC, Williamson PD: Lamotrigine intoxication provoking status epilepticus in an adult with localization-related epilepsy. *Arch Neurol* 2007; 64:1344.
109. Spiller HA, Carlisle RD: Status epilepticus after massive carbamazepine overdose. *Clin Toxicol* 2002; 40:81.
110. Brandt C, et al: Topiramate overdose: A case report of a patient with extremely high topiramate serum concentrations and nonconvulsive status epilepticus. *Epilepsia* 2010; 51:1090.
111. Hindley D, Ali A, Robson C: Diagnoses made in a secondary care "fits, faints, and funny turns" clinic. *Arch Dis Child* 2006; 91:214.
112. Macleod S, Ferrie C, Zuberi SM: Symptoms of narcolepsy in children misinterpreted as epilepsy. *Epileptic Disord* 2005; 7:13.
113. Sethi NK, Labar D, Torgovnick J: Myoclonic epilepsy masquerading as a tic disorder. *Neurol Neurosurg* 2007; 109:509.
114. d'Orsi G, Demaio V, Minervini MG: Myoclonic status misdiagnosed as movement disorders in Rett syndrome: A video-polygraphic study. *Epilepsy Behav* 2009; 15:260.
115. Anpalahan M, Gibson S: The prevalence of neurally mediated syncope in older patients presenting with unexplained falls. *Eur J Intern Med* 2012; 23:48.
116. Treiman DM: Treatment of convulsive status epilepticus. *Int Rev Neurobiol* 2007; 81:273.
117. Treiman DM, et al: A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med* 1998; 339:792.
118. Alldredge BK, et al: A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med* 2001; 345:631.
119. Cock HR, Schapira AH: A comparison of lorazepam and diazepam as initial therapy in convulsive status epilepticus. *QJM* 2002; 95:225.
120. Lowenstein DH: Treatment options for status epilepticus. *Curr Opin Pharmacol* 2005; 5:334.
121. Prasad K, Al-Roomi K, Krishnan PR, Sequeira R: Anticonvulsant therapy for status epilepticus. *Cochrane Database Syst Rev* 2005; 4:CD003723.
122. D'Onofrio G, Rathlev NK, Ulrich AS, Fish SS, Freedland ES: Lorazepam for the prevention of recurrent seizures related to alcohol. *N Engl J Med* 1999; 340:915.
123. Arya R, Gulati S, Kabra M, Sahu JK, Kalra V: Intranasal versus intravenous lorazepam for control of acute seizures in children: A randomized open-label study. *Epilepsia* 2011; 52:788.
124. Mahmoudian T, Zadeh MM: Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children. *Epilepsy Behav* 2004; 5:253.
125. Silbergleit R, et al: Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med* 2012; 366:591.
126. McMullan J, Sasson C, Pancioli A, Silbergleit R: Midazolam versus diazepam for the treatment of status epilepticus in children and young adults: A meta-analysis. *Acad Emerg Med* 2010; 17:575.
127. Bhattacharjee P, Glusac EJ: Early histopathologic changes in purple glove syndrome. *J Cutan Pathol* 2004; 31:513.
128. Burneo JG, Anandan JV, Barkley GL: A prospective study of the incidence of the purple glove syndrome. *Epilepsia* 2001; 42:1156.

www.ketabpezeshki.com 66485457-66963820

129. Chokshi R, Openshaw J, Mehta NN, Mohler E 3rd: Purple glove syndrome following intravenous phenytoin administration. *Vasc Med* 2007; 12:29.
130. Smith BJ: Treatment of status epilepticus. *Neurol Clin* 2001; 19:347.
131. Pryor FM, Gidal B, Ramsay RE, DeToledo J, Morgan RO: Fosphenytoin: Pharmacokinetics and tolerance of intramuscular loading doses. *Epilepsia* 2001; 42:245.
132. Eriksson K, Keränen T, Kälviäinen R: Fosphenytoin. *Expert Opin Drug Metab Toxicol* 2009; 5:695.
133. Coplin WM, et al: Randomized evaluation of adverse events and length-of-stay with routine emergency department use of phenytoin or fosphenytoin. *Neurol Res* 2002; 24:842.
134. Swadron SP, et al: A comparison of phenytoin-loading techniques in the emergency department. *Acad Emerg Med* 2004; 11:244.
135. Limdi NA, et al: Safety of rapid intravenous loading of valproate. *Epilepsia* 2007; 48:478.
136. Peters CN, Pohlmann-Eden B: Intravenous valproate as an innovative therapy in seizure emergency situations including status epilepticus—experience in 102 adult patients. *Seizure* 2005; 14:164.
137. Trinka E: The use of valproate and new antiepileptic drugs in status epilepticus. *Epilepsia* 2007; 48(Suppl 8):49.
138. Agarwal P, et al: Randomized study of intravenous valproate and phenytoin in status epilepticus. *Seizure* 2007; 16:527.
139. Embacher N, Karner E, Wanschitz J, Beer R, Trinka E: Acute encephalopathy after intravenous administration of valproate in nonconvulsive status epilepticus. *Eur J Neurol* 2006; 13:5.
140. Zhang J, Meikle S, Trumble A: Severe maternal morbidity associated with hypertensive disorders in pregnancy in the United States. *Hypertens Pregnancy* 2003; 22:203.
141. Chames MC, Livingston JC, Ivester TS, Barton JR, Sibai BM: Late postpartum eclampsia: A preventable disease? *Am J Obstet Gynecol* 2002; 186:1174.
142. Minnerup J, et al: Late onset postpartum eclampsia: It is really never too late? A case of eclampsia 8 weeks after delivery. *Stroke Res Treat* 2010; 2010:798616.
143. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet* 1995; 345:1455.
144. Duley L, Henderson-Smart D: Magnesium sulphate versus diazepam for eclampsia. *Cochrane Database Syst Rev* 2003; 4:CD000127.
145. Parviainen I, Uusaro A, Kalviainen R, Mervaala E, Ruokonen E: Propofol in the treatment of refractory status epilepticus. *Intensive Care Med* 2006; 32:1075.
146. Rossetti AO, Reichhart MD, Schaller MD, Despland PA, Bogousslavsky J: Propofol treatment of refractory status epilepticus: A study of 31 episodes. *Epilepsia* 2004; 45:757.
147. Claassen J, Hirsch LJ, Emerson RG, Mayer SA: Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: A systematic review. *Epilepsia* 2002; 43:146.
148. Albers JM, et al: Intravenous lacosamide—an effective add-on treatment of refractory status epilepticus. *Seizure* 2011; 20:428.
149. Wheless JW, Treiman DM: The role of the newer antiepileptic drugs in the treatment of generalized convulsive status epilepticus. *Epilepsia* 2008; 49(Suppl 9):74.
150. Perrig S, Jallon P: Is the first seizure truly epileptic? *Epilepsia* 2008; 49(Suppl 1):2.
151. Benbadis S: The differential diagnosis of epilepsy: A critical review. *Epilepsy Behav* 2009; 15:15.
152. Benardo LS: Prevention of epilepsy after head trauma: Do we need new drugs or a new approach? *Epilepsia* 2003; 44(Suppl 10):27.
153. Beghi E: Overview of studies to prevent posttraumatic epilepsy. *Epilepsia* 2003; 44(Suppl 10):21.
154. Hauser WA, Rich SS, Lee JR, Annegers JF, Anderson VE: Risk of recurrent seizures after two unprovoked seizures. *N Engl J Med* 1998; 338:429.
155. Kim LG, Johnson TL, Marson AG, Chadwick DW: Prediction of risk of seizure recurrence after a single seizure and early epilepsy: Further results from the MESS trial. *Lancet Neurol* 2006; 5:317.
156. Glauser T, et al: ILAE treatment guidelines: Evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2006; 47:1094.
157. Harden CL, Leppik I: Optimizing therapy of seizures in women who use oral contraceptives. *Neurology* 2006; 67(12 Suppl 4):56.
158. Patsalos PN, Perucca E: Clinically important drug interactions in epilepsy: Interactions between antiepileptic drugs and other drugs. *Lancet Neurol* 2003; 2:473.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 103

HEADACHE DISORDERS*

Thomas Kwiatkowski and Benjamin W. Friedman

Headache is a common complaint, accounting for approximately 3 million visits to the emergency department (ED) per year in the United States.[1] In addition, many more patients present with headache as part of a constitutional illness, making the symptom of headache one of the most frequent complaints in the ED.[1]

Headache commonly is divided into *primary* and *secondary* disorders.[2] The primary headache disorders include migraine, cluster, and tension-type headaches, which represent the majority of headaches seen in clinical emergency practice.[3-5] Secondary headache disorders include a variety of organic illnesses in which head pain is a symptom of an identifiable, distinct pathologic process. To facilitate a standardized approach to headache management, the International Headache Society published a classification system and diagnostic criteria for headache disorders, cranial neuralgias, and facial pain.[2] This comprehensive and widely accepted system includes 14 major categories of headache disorders and uses specific operational diagnostic criteria to define each headache type (Box 103-1). Most patients presenting to an ED with headache have a benign primary headache disorder requiring only symptomatic treatment and referral. The challenge for the emergency physician is to identify the very small subset of patients who have headache as a symptom of a serious or potentially life-threatening disease.

PRIMARY HEADACHE DISORDERS

Migraine Headache

Principles of Disease

Migraine is a common, chronic, sometimes incapacitating neurovascular disease characterized by recurrent attacks of severe headache, autonomic nervous system dysfunction, and, in some patients, an aura causing visual, sensory, motor, or other neurologic symptoms.[6] It is a primary headache disorder with a genetic basis.[7]

Migraine headaches account for approximately 1 million visits to the ED per year.[8] Migraine attacks typically begin in the second decade of life and peak in prevalence in the fourth decade of life, with a 1-year period prevalence of 7% of men and 24% of women.[9] Overall, migraine is more prevalent among women (18%) than among men (6%).[9] During childhood, however, there is no gender difference in the prevalence of migraine. After menarche, a correlation between migraine and menstruation is noted in half of female migraine sufferers. After menopause, the prevalence of migraine among women decreases.[10]

Historically, migraine headaches have been considered to be vascular in origin. However, this hypothesis is no longer tenable as alterations in cerebral blood flow do not correlate with the various phases of the headache attack or vascular territories and do not explain features of an acute migraine such as premonitory mood disturbances, nausea, and osmophobia. Rather, vascular changes are now thought to be an epiphenomenon to what is a primary neurologic event.[11] Abnormal trigeminal nerve activation, possibly triggered by cortical spreading depression or, less likely, a sterile neuropeptide-induced inflammatory process, leads to pain and sensitization of higher order neurons in the brainstem and thalamus. Descending modulation is likely to be compromised as well. It is not yet known what initiates the pathophysiologic process that leads to a migraine attack. Migraine is commonly thought of in two major categories: migraine without aura, or common migraine, which is the most frequent form of migraine and accounts for approximately 80% of all cases (Box 103-2); and migraine with aura, or classic migraine, which has specific reversible neurologic symptoms that precede the actual headache (Box 103-3) and is seen less frequently.[6]

Clinical Features

Migraine is by definition a chronic and recurrent disease. The headache, characteristically, is unilateral, pulsating in quality, moderate to severe in intensity, and exacerbated by routine activities. The side of the headache can vary with individual attacks, and the headache may be bilateral in 40% of patients. The onset usually is gradual, and the attacks typically last 4 to 72 hours. Headache frequency is variable; those patients with more than 15 headache days per month are considered to have chronic migraine. Associated symptoms and signs include nausea, vomiting, anorexia, photophobia, phonophobia, osmophobia (aversion to odors), blurred vision, lightheadedness, and nasal congestion. Some patients experience premonitory cognitive impairment producing forgetfulness, irritability, and depression. Many patients have dramatic light and sound sensitivity and seek a cool, dark, and quiet room.

The aura of classic migraine consists of focal neurologic symptoms that precede and herald the migraine attack. By definition, the aura is fully reversible and typically lasts 10 to 20 minutes, although it may continue for as long as 1 hour. The most common aura is visual; features may include scintillating scotomas (bright rim around an area of visual loss), teichopsias (subjective visual image perceived with eyes open or closed), fortification spectrums (zigzagged wall of fortress slowly drifting across visual field),

*Dr. Kumar Alagappan was a contributor to this chapter in previous editions.

www.ketabpezeshki.com 66485457-66963820

Box 103-1 International Headache Society Classification of Headache

1. Migraine
2. Tension-type headache
3. Cluster headache and trigeminal autonomic cephalalgias
4. Other primary headaches
5. Headache attributed to head and/or neck trauma
6. Headache attributed to nonvascular intracranial disorder
7. Headache associated with nonvascular intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache associated with noncephalic infection
10. Headache attributed to disorder of homeostasis
11. Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures
12. Headache attributed to psychiatric disorder
13. Cranial neuralgias and central causes of facial pain
14. Other headache, cranial neuralgia, central or primary facial pain

Available at http://ihs-classification.org/en/.

Box 103-2 Migraine without Aura (Common Migraine): International Headache Society Criteria

A. At least five attacks fulfilling criteria in B, C, D, and E
B. Attack lasts 4 to 72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate to severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache, at least one of the following:
   1. Nausea or vomiting (or both)
   2. Photophobia and phonophobia
E. Not attributable to another disorder

Available at http://ihs-classification.org/en/.

Box 103-3 Migraine with Aura (Classic Migraine): International Headache Society Criteria

A. At least two attacks that fulfill criterion B
B. Presence of at least three of the following four characteristics for a diagnosis of classic migraine:
   1. One or more fully reversible aura symptoms indicating focal cerebral cortical or brainstem dysfunction (or both)
   2. At least one aura symptom developing gradually over more than 4 minutes, or two or more symptoms occurring in succession
   3. No single aura symptom lasting longer than 60 minutes
   4. Headache beginning *during* aura or *afterward,* with a symptom-free interval of less than 60 minutes (also may begin *before* aura)
C. Exclusion of related organic diseases by means of an appropriate history, physical examination, and neurologic examination with appropriate diagnostic tests

Available at http://ihs-classification.org/en/.

photopsias (poorly formed brief flashes or sparks of light), and blurred vision. Less common auras include somatosensory phenomena such as tingling or numbness, motor disturbances, and cognitive or language disorders.[6]

Ophthalmoplegic migraine is a rare syndrome associated with paresis of one or more ocular nerves, most commonly the third cranial nerve. Patients typically present with ipsilateral headache associated with extraocular muscle paresis and occasionally pupillary changes. The ophthalmoplegia or pupillary changes may last for days to weeks and rarely may become permanent. Because of the neurologic abnormalities, secondary causes including intracranial aneurysm and mass lesion should be ruled out in the absence of a clear history of recurrent identical episodes.[12]

Hemiplegic migraine is characterized by a motor aura consisting of hemiparesis or hemiplegia. The progression of the motor deficit is gradual and in most cases is accompanied by a visual, sensory, or speech disturbance. The neurologic symptoms last up to 60 minutes, followed by headache. Rarely, the motor deficit is persistent, resulting from a true migrainous stroke.[2] A familial version of hemiplegic migraine is associated with genetic mutations of ion transporters.[7]

Basilar-type migraines arise with an aura referable to the brainstem and are associated with multiple neurologic findings, including visual symptoms (often total blindness), dysarthria, tinnitus, vertigo, bilateral paresthesias, paresis, and altered level of consciousness. The symptoms are stereotypic and resolve spontaneously.[2]

Status migrainosus is a severe migraine headache that persists for more than 72 hours. Associated symptoms are debilitating, and patients require hospitalization for pain management and supportive care if they do not improve after parenteral treatment in the ED.

Many factors can trigger migraine headaches in predisposed persons. Common precipitants include sleep deprivation, stress, hunger, hormonal changes including menstruation, and use of certain drugs including oral contraceptives and nitroglycerin.[13] In addition, some patients report specific food sensitivities to chocolate, caffeine, and foods rich in tyramine, monosodium glutamate, and nitrates. Alcohol, specifically red or port wine, has also been implicated. In others, certain sensory stimuli, such as a strong glare or strong odors, loud noises, and weather changes, can trigger an attack.[6]

Differential Diagnosis

Because of the complexity of the symptoms, migraine headaches may be difficult to distinguish from secondary causes of headache. Other disorders that mimic migraine include nontraumatic subarachnoid hemorrhage caused by ruptured aneurysm or arteriovenous malformation, intracranial mass lesions, giant cell arteritis, cerebrovascular disease, and idiopathic intracranial hypertension.

Diagnostic Evaluation

Routine neuroimaging is not necessary for patients with typical recurrent migraine headaches.[14] An increasing appreciation of medical imaging–induced radiation toxicity warrants prudent use of computed tomography (CT) scanning in younger patients. Neuroimaging should be considered for older or immunocompromised patients with new-onset headaches, headaches with a progressive course, headaches worsened by Valsalva maneuver, headache causing awakening from sleep, or headaches associated with unexplained neurologic abnormalities.[14] Such patients have a higher likelihood of having a secondary cause of headache, such as tumor, arteriovenous malformation, or structural lesion. In addition, patients who present with a thunderclap or abrupt-onset headache require a lumbar puncture to rule out subarachnoid hemorrhage if findings on a CT scan are normal.[15] The description "worst headache of life" may be associated with subarachnoid hemorrhage but suffers from interobserver variability.[16]

Treatment

The pharmacologic treatment of migraine is divided into *abortive* therapies, which attempt to limit the intensity and duration of a

www.ketabpezeshki.com 66485457-66963820

Table 103-1 Selected Medications for Acute Migraine Attacks

MEDICATION	DOSE AND ROUTE ADMINISTERED	COMMENTS
Mild to Moderate		
Acetaminophen	500-1000 mg PO	Gastrointestinal upset
Aspirin	650-1000 mg PO	Gastrointestinal upset
Ibuprofen	600-800 mg PO	Gastrointestinal upset
Naproxen sodium	275-550 mg PO	Gastrointestinal upset
Moderate to Severe		
Dihydroergotamine	1 mg IV or IM; may be repeated in 1 hour	Gastrointestinal upset (pretreat with antiemetic)
Triptans Sumatriptan Sumatriptan Rizatriptan Zolmitriptan Naratriptan	 6 mg SC; may be repeated once in 1 hr if partial response 25-100 mg PO 5-10 mg PO 2.5-5 mg PO 1-2.5 mg PO	Chest pain, throat tightness, flushing Contraindicated with hypertension, coronary artery disease, peripheral vascular disease, and pregnancy Cannot be used within 24 hours of ergot use
Prochlorperazine	10 mg IV or IM; may be repeated in 30 to 60 minutes	Sedation and dystonic reaction
Metoclopramide	10 mg IV	Dystonic reaction
Droperidol	2.5 mg IV	QT prolongation; dystonic reaction
Ketorolac	30 mg IV or 30-60 mg IM	Gastrointestinal upset; avoid this medication in elderly and in patients with renal insufficiency
Morphine	4-8 mg IM or IV	Opioids less efficacious than other treatment modalities
Refractory Attack, Status Migrainosus		
Dihydroergotamine	1 mg IV q8h	Use in conjunction with antiemetic (e.g., metoclopramide, prochlorperazine)
Steroids	Various regimens	Gastrointestinal bleeding, infection, cataracts, aseptic necrosis, memory disturbances

given episode, and *prophylactic* therapies, which are intended to decrease the frequency and intensity of attacks. The goals of acute migraine therapy include rapid pain relief, minimization of headache recurrence and medication side effects, restoration of the patient's ability to function, and minimization of the use of backup and rescue medications.[17]

There are several approaches to treatment of the acute headache episode, depending on the severity of the attack (Table 103-1). The choice of agents depends on the patient's previous response to specific therapies, the existence of comorbid conditions, and the presence or absence of nausea or vomiting. Gastric stasis is common during acute migraine attacks and may limit the effectiveness of oral agents.[18]

For mild to moderate attacks, simple analgesics such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) are often effective.[19,20] In the presence of nausea or vomiting, the addition of an agent such as metoclopramide enhances the absorption and effectiveness of these medications.[21] Appropriate doses and possible side effects are listed in Table 103-1.

For moderate to severe attacks, three classes of medications can be recommended as initial parenteral therapy: the antiemetic dopamine antagonists, such as metoclopramide, prochlorperazine, and droperidol; migraine-specific agents, such as the triptans and dihydroergotamine (DHE); and parenteral nonsteroidals, such as ketorolac.

Dopamine antagonists, such as the neuroleptics prochlorperazine and chlorpromazine, and the antiemetics metoclopramide and droperidol have been shown to be highly effective as monotherapy for acute migraine attacks.[22-24] Because of their efficacy, safety, tolerability, and few contraindications, they are used by many emergency physicians as first-line therapy for many migraine patients. For this class of medication, clinical research has outpaced preclinical work, and thus a compelling mechanism of action is lacking. However, migraine pathogenesis is likely to involve dopamine pathways.[25] The most common side effects after parenteral administration include sedation, postural hypotension, and extrapyramidal symptoms, most notably akathisia, which can be treated with diphenhydramine or midazolam.[26]

DHE is administered intravenously (IV) in a dose of 1.0 mg during 2 minutes; this can be repeated in 1 hour if pain control has not been achieved. Because DHE can cause nausea and vomiting, patients should be pretreated with an antiemetic such as metoclopramide 10 mg IV or prochlorperazine 10 mg IV. Repeated administration of the intravenous form of DHE is effective in patients with status migrainosus.[27] Contraindications to use of DHE include pregnancy, breast-feeding, poorly controlled hypertension, coronary artery disease, and peripheral vascular disease. DHE should not be used if the patient has already taken any drug in the triptan class or if the patient is using macrolides or protease inhibitors.

Sumatriptan, the first-approved medication of the triptan class, a class of selective 5-HT (1B/1D) receptor agonists, is available for subcutaneous administration, and it is the most common triptan preparation used in the ED setting.[8] Other triptans available in the United States include eletriptan, almotriptan, zolmitriptan, naratriptan, frovatriptan, and rizatriptan. The initial dose of sumatriptan is 6 mg given subcutaneously, which may be repeated once in 1 hour if the patient has a partial response to the first dose. Common side effects include tingling, flushing, warm or hot sensations, heaviness in the chest, and initial worsening of the underlying headache.[28] Sumatriptan has contraindications similar to those for DHE and should not be used within hours of administration of an ergotamine-containing medication or DHE. A smaller dose of subcutaneous sumatriptan may limit side effects.[29]

www.ketabpezeshki.com 66485457-66963820

Opioid analgesics such as morphine should be reserved for patients who do not respond to any of the medications listed or have contraindications to all standard migraine therapies. Although opioids are frequently used, they have been shown to be less efficacious than other agents and are associated with frequent ED visits.[30,31]

Recurrence of migraine within 24 hours of ED discharge is common, regardless of medication administered or pain intensity at discharge.[32] Corticosteroids are effective at decreasing the rate of migraine recurrence after ED discharge, although with a number needed to treat (NNT) of 9, these medications are not necessarily indicated for all patients.[33] Oral naproxen 500 mg and sumatriptan 100 mg are reasonable treatment options for the recurrent headache.[34]

On occasion, patients do not respond to initial therapy in the ED and require hospitalization for continued pain control and supportive therapy.

Prophylactic Therapy

Prophylactic therapy is indicated for patients who have frequent attacks (more than two or three functionally disabling episodes per month), prolonged attacks lasting more than 48 hours, or attacks that are severe and debilitating. Several classes of medications are used for the prophylaxis of migraine, including beta-blockers, tricyclic antidepressants, and antiepileptic drugs.[35,36] Prophylactic therapy is best initiated in consultation with the patient's primary care provider or neurologist.

Cluster Headache

Perspective

Cluster headache is the only headache syndrome that is more common in men than in women. It typically occurs in young to middle-aged adults who smoke, with a peak incidence in the late 20s.[37] The headaches tend to occur repeatedly during a defined time interval, hence the term *cluster*. Several attacks can occur in 1 day, and a typical cluster period may last weeks to months. Several precipitating factors have been implicated, most notably the ingestion of alcohol. Stress and climatic changes may also play a role in susceptible persons.

Clinical Features

Cluster headaches occur suddenly with little warning, and multiple episodes can occur within a 24-hour period. Each headache lasts from 15 minutes up to 3 hours. The headache typically begins with a unilateral sharp, stabbing pain in the eye, which may awaken the patient from sleep. The attacks occur exclusively in the territory of the trigeminal nerve.[38] Unlike the migraineur, the patient with cluster headache predictably presents agitated and anxious, rocking, rubbing the head, and pacing. The attack subsides rapidly, often leaving the patient exhausted.

Accompanying the headache are ipsilateral autonomic symptoms such as ptosis, miosis, and forehead or facial sweating. The eye often is injected and tearing, and many patients have unilateral nasal congestion.[2]

Differential Diagnosis

Other headache disorders that mimic cluster headache include carotid artery dissection, trigeminal neuralgia, and the rare trigeminal autonomic cephalalgia paroxysmal hemicrania. Carotid dissection should be excluded as the diagnosis in patients who present with unilateral face or neck pain and Horner's syndrome. With trigeminal neuralgia, the pain peaks within seconds, lasts only a couple of minutes, and can be provoked by specific trigger points on the face or oral mucosa. The trigeminal autonomic cephalalgias are manifested by a brief unilateral headache that recurs dozens of times per day, often accompanied by the same unilateral eye and nasal symptoms as cluster.[2]

Treatment

Cluster headache is brief in duration and may resolve before a patient presents to medical attention. High-flow oxygen should be considered first-line therapy. Delivered through a non-rebreather mask at a rate of 12 L/min, it has been shown to abort the headache within 15 minutes in 78% of patients, with an NNT of 2 compared with patients who breathe room air.[39] Subcutaneous sumatriptan is also an effective therapy for acute cluster headache and should be dosed at 6 mg.[40] Larger doses do not confer much benefit, whereas smaller doses may decrease some of the medication side effects. Alternatively, octreotide or intravenous dopamine antagonists may be effective.[41,42]

Once the acute attack has been relieved, the emergency physician's work is not done. The acute attack is part of an ongoing "cluster" of headaches that likely will recur the following day. Corticosteroids have long been theorized to help break the cluster, although high-quality evidence is not available. A recommended regimen is 60 mg of prednisone daily for 10 days, followed by a 1-week taper. Verapamil, dosed at 120 mg three times a day, will decrease the frequency of attacks by the end of the first week of therapy.[43]

Tension-type Headache

Perspective

Tension-type headache is the most common recurrent headache disorder, affecting more than 50% of the population, but it is an infrequent cause of ED visits.[4,44] Women are affected slightly more frequently than men are, with peak prevalence in the fourth decade of life. These headaches typically do not cause substantial functional disability, and patients are able to continue with their normal daily activities. The median frequency of headaches is six per month, and stress and lack of sleep are implicated as triggering factors.[2,45] By definition, episodic tension-type headache lasts as little as 30 minutes and as long as 7 days.

Little is known about the pathophysiology of tension-type headache. There is no clear evidence that increased muscle activity is present, and the physical examination will reveal tender areas of the scalp and neck with both tension and migraine headaches. Despite different epidemiologic profiles, similar response to many therapeutics suggests that tension and migraine headaches may be part of a continuum with similar pathophysiologic mechanisms.[46,47]

Clinical Features

Patients typically complain of a tight, bandlike discomfort around the head that is nonpulsating and dull. They also may experience tightening of the neck muscles. A majority do not seek medical assistance because the headache usually is mild in intensity and not functionally disabling. On occasion, the discomfort can build up slowly and fluctuate in severity for several days. Unlike in migraine, the headache does not worsen with physical activity, and accompanying symptoms, such as nausea, vomiting, phonophobia, and photophobia, are unusual. Anxiety and depression may coexist with chronic tension headache, which by definition occurs more than 15 days a month and can be daily and unremitting.[2]

www.ketabpezeshki.com 66485457-66963820

Differential Diagnosis

Tension headache is the least distinct of all of the primary headache disorders, and its diagnosis is based mainly on the absence of features that would suggest another headache diagnosis. Because of this lack of specificity, the clinician often may hesitate to make this benign diagnosis without other investigations to exclude organic disease. The most common disorders mimicking tension headache are migraine, idiopathic intracranial hypertension, oromandibular dysfunction, cervical spondylosis, sinus or eye disease, and intracranial masses.[48]

Treatment

For a majority of patients with tension headaches, simple analgesics, such as acetaminophen or an NSAID, are adequate for pain control. Because tension-type headache is more common in sedentary persons, a regular exercise program may help.[37] Antiemetic dopamine antagonists may be useful therapy.[49] Patients with chronic symptoms may exhibit signs of depression or anxiety, and these patients often respond to medications and nonpharmacologic regimens that treat these conditions. Some nonpharmacologic regimens are meditation, massage, and biofeedback.

SECONDARY HEADACHE DISORDERS

Subarachnoid Hemorrhage

Principles of Disease

Subarachnoid hemorrhage (SAH) refers to extravasated blood in the subarachnoid space. Presence of the blood activates meningeal nociceptors, leading to diffuse occipital pain along with signs of meningismus. SAH accounts for up to 10% of all strokes and is the most common cause of sudden death from a stroke.[50]

Approximately 80% of patients with nontraumatic SAH have ruptured saccular aneurysms.[15] Other causes include arteriovenous malformations, cavernous angiomas, mycotic aneurysms, neoplasms, and blood dyscrasias. SAH may be caused secondarily by an intraparenchymal hematoma that dissects its way into the subarachnoid space.

The risk for aneurysmal SAH increases with age; most cases occur between the ages of 40 and 60 years.[51] In children and adolescents, aneurysms are uncommon, and when SAH occurs, it usually is secondary to an arteriovenous malformation. It is estimated that 2% of the general population harbor a berry aneurysm, and the risk of rupture may increase with aneurysmal size.[52] Other risk factors associated with SAH include hypertension, smoking, excessive alcohol consumption, and sympathomimetic drugs.[53] Increased systolic blood pressure values and long-term hypertension before aneurysm rupture seem to predict fatal SAH independently of aneurysm size or the patient's age at the time of rupture; patient gender also does not influence mortality.[54] A familial association of cerebral aneurysms with several diseases, including autosomal dominant polycystic kidney disease, coarctation of the aorta, Marfan syndrome, and Ehlers-Danlos syndrome type IV, has been described.

Of all patients presenting to the ED with a primary complaint of headache, less than 1% have SAH. Many patients with SAH die before reaching the hospital; preadmission mortality rates range from 3 to 26%.[15] Because of the significant morbidity and mortality associated with this condition and the high likelihood of clinical deterioration in patients who initially are misdiagnosed, SAH should be a primary consideration in the initial ED evaluation of all patients with nontraumatic headache. Accordingly, familiarity with its presentation is essential.

Clinical Features

A majority of patients with SAH present with a sudden, cataclysmic thunderclap headache, which often is described as "the worst headache of [their] life." The onset of headache may be associated with exertion, the Valsalva maneuver, or sexual intercourse in up to 20% of patients.[15] The headache of SAH classically peaks in intensity within seconds to minutes. Headaches that take longer to peak in intensity are less likely to be SAH.[55] Associated signs and symptoms include nausea and vomiting in approximately 75% of patients, neck stiffness in 25%, and seizures in 17%.[51] Physical findings depend on the extent of the SAH. Meningismus is present in more than 50% of patients, and up to 20% have focal neurologic abnormalities.[56] Funduscopic examination may reveal retinal or subhyaloid hemorrhages, and patients also may have an isolated third or sixth nerve palsy. Oculomotor (third) nerve compression secondary to an expanding aneurysm leads to pupillary dilation. Approximately 50% of patients with a ruptured aneurysm are restless or have an altered level of consciousness. Although a majority do not have focal neurologic signs, such signs when present may indicate the site of the aneurysm.[57]

The patient's prognosis is related to neurologic status at hospital admission. The Hunt and Hess scale stratifies patients according to their clinical signs and symptoms at the time of presentation and is predictive of outcome (Table 103-2).[58] Patients who present with a grade 1 or grade 2 hemorrhage tend to have a good prognosis. Patients with grade 4 or grade 5 hemorrhage tend to do poorly, and these patients have an altered mental status, ranging from stupor to deep coma, together with focal neurologic signs and symptoms. Patients with grade 3 hemorrhage present with drowsiness or confusion and are at risk for rapid clinical deterioration.

Diagnostic Studies

A non–contrast-enhanced head CT scan is the first-line test for the diagnosis of SAH and should be ordered emergently when this diagnosis is suspected (Fig. 103-1). For acute hemorrhage less than 24 hours old, the sensitivity of CT in identifying hemorrhage is greater than 90%; however, sensitivity decreases to approximately 50% by the end of the first week.[59] Because the sensitivity of head CT is limited, particularly as the duration of headache increases, the cerebrospinal fluid (CSF) should be examined for blood or xanthochromia, the yellowish tinting of CSF by hemoglobin breakdown products, for SAH to be ruled out definitively. A common pitfall in ED diagnostic workups of headache is to overestimate the sensitivity of the CT scan for subarachnoid blood. Alternatively, an appropriate strategy may be to perform lumbar puncture without first performing a CT scan to decrease throughput time in carefully selected young patients who have completely

Table 103-2 Hunt and Hess Clinical Grading Scale for Cerebral Aneurysms and Subarachnoid Hemorrhage

GRADE	CONDITION
0	Unruptured aneurysm
1	Asymptomatic or minimal headache and slight nuchal rigidity
2	Moderate or severe headache, nuchal rigidity, no neurologic deficit other than cranial nerve palsy
3	Drowsiness, confusion, or mild focal deficit
4	Stupor, moderate to severe hemiparesis
5	Deep coma, decerebrate posturing, moribund appearance

www.ketabpezeshki.com 66485457-66963820

Figure 103-1. Cerebral aneurysm. Shown is a computed tomography scan of an aneurysmal subarachnoid hemorrhage in a 55-year-old woman. Subarachnoid blood can be seen within the interpeduncular and ambient cisterns and the right sylvian fissure from a ruptured aneurysm at the junction of the right carotid artery and the posterior communicating artery. (From Brisman JL: Neurosurgery for cerebral aneurysm. Emedicine, updated Sep 23, 2010. Available at http://emedicine.medscape.com/article/252142-overview#a1.)

normal physical examination findings, who are not immunocompromised, and in whom SAH is not strongly suspected.[60] This strategy may be particularly appropriate for patients in whom the differential diagnosis includes other conditions requiring a CSF analysis, such as meningitis. An alternative strategy is to perform a non–contrast-enhanced head CT scan followed by CT angiography rather than the lumbar puncture; this is reasonably sensitive and may be appropriate for patients at lower risk of disease.[59] Concerns of additional radiation exposure and contrast agent toxicity need to be weighed against the pain caused by a lumbar puncture. Finally, several published clinical decision rules can help risk stratify patients.[16,61]

After lumbar puncture is performed, interpretation of the results can be challenging because up to one third of spinal fluid analyses may be falsely positive.[62] To differentiate a traumatic lumbar puncture from SAH, the patient's CSF should be spun and the supernatant observed for xanthochromia. The yellowish pigmentation is secondary to the metabolism of hemoglobin to pigmented molecules of oxyhemoglobin and bilirubin, a process that can take up to12 hours to occur.[63] The method of comparing the red blood cell count in the first and the last tubes of CSF is less accurate, although SAH cannot be ruled out if a substantial numbers of red blood cells persist in tube 4.[15] CSF xanthochromia in association with normal findings on the CT scan is suggestive of SAH. After the diagnosis is established, angiography should be performed to study the vascular anatomy and to identify the source of hemorrhage.

A normal non–contrast-enhanced head CT scan followed by a normal spinal fluid analysis definitively rules out SAH and does not need to be followed with angiography, even in patients at high risk of disease.[64] However, this strategy does not rule out other causes of thunderclap headache that may be in the differential diagnosis, such as carotid artery dissection, cerebral venous sinus thrombosis, and reversible cranial vasoconstrictor syndrome.

Up to 90% of patients with SAH have cardiac arrhythmias or electrocardiographic abnormalities suggestive of acute cardiac ischemia, which may lead to an erroneous primary cardiac diagnosis. Typical electrocardiographic findings include ST-T wave changes, U waves, and QT prolongation.[65]

Treatment

The management of SAH is complex and includes initial resuscitation, stabilization, and emergent neurosurgical consultation. The goals of management are to treat the acute medical and neurologic complications, to prevent recurrent hemorrhage, and to forestall the ischemic complications of vasospasm. Because of an altered level of consciousness, patients with SAH of grade 3 or higher are at risk for respiratory depression and hypercapnia, which can lead to further increases in intracranial pressure (ICP); therefore, these patients may require early endotracheal intubation. Blood pressure also should be closely monitored because of the risk of continued bleeding or recurrent hemorrhage. Nimodipine, a calcium channel blocker, should be started soon after a diagnosis of aneurysmal SAH is made to lessen the likelihood of poor outcome.[66] Because nimodipine may cause transient hypotension in some patients, hemodynamic monitoring is required during its administration. The recommended dose is 60 mg by mouth or nasogastric tube every 4 hours. Antifibrinolytics (e.g., aminocaproic acid) do not improve overall outcome because the reduction in the rate of rebleeding is offset by an increase in poor outcome caused by cerebral ischemia.[67] Similarly, corticosteroids have not been demonstrated to be of benefit.[68]

Blood pressure management should be determined by the patient's clinical status with involvement of the treating neurosurgeon. The typical treatment goal is a systolic blood pressure below 160 mm Hg or a mean arterial pressure below 130 mm Hg unless vasospasm is present.[69]

Analgesics, including opioids, should be used for persistent headache. In patients who are nauseated or at risk for vomiting, antiemetics should be administered. Agitated patients require sedation, and all patients should be placed at bed rest in a quiet and dark environment. Clinically evident seizures should be treated with anticonvulsants, but the prophylactic use of these drugs is controversial.[70] A majority of patients require hemodynamic and ICP monitoring in an intensive care setting. For definitive management, endovascular coil embolization is preferable to neurosurgical clipping, but this decision is based on size, location, and morphologic features of the aneurysm as well as local expertise.[71]

Intracranial Neoplasm

Principles of Disease

Headache, the most common presenting complaint among patients with brain tumor, is reported by approximately 50% of the patients.[72] Headache is less common in older patients with brain tumors, presumably because of age-related atrophy. Headache can be caused by benign or malignant primary neoplasms of the central nervous system as well as by metastatic lesions. The most common causes of metastasis are lung and breast carcinoma, followed by malignant melanoma and carcinomas of the gastrointestinal tract.[73]

The headache of intracranial neoplasms can be caused by several mechanisms, including direct involvement of and traction on pain-sensitive structures such as meninges or larger cerebral vessels, or it may be a symptom of increased ICP. The pain patterns produced are highly variable, depending on the location and size of the mass and the structures involved. Rapidly growing tumors

www.ketabpezeshki.com 66485457-66963820

are more likely to be associated with headache. Headaches often but not always are on the same side as the tumor.[72,74]

Clinical Presentation

The typical patient presents with complaints of a worsening headache that has been present for weeks to months. The headache may have been present initially only on awakening, gradually becoming continuous. The classic triad of brain tumor headache—sleep disturbances, severe pain, and nausea and vomiting—is seen in a minority of patients.[73] Vomiting, when it is present, may be projectile and not preceded by nausea and often can be attributed to increased ICP. If increased ICP is present, the headache often is bilateral and worsened by coughing, sneezing, bending, defecation, and sexual intercourse. Other presentations of intracranial neoplasms include seizures, personality changes, and cognitive difficulties.[73]

Diagnostic Evaluation

The diagnosis of brain tumor may be suspected from the history and neurologic examination. Early in the course, patients present with just a headache and an intact neurologic examination, although the majority of intracranial neoplasms eventually will cause focal neurologic deficits. Neuroimaging with CT or magnetic resonance imaging (MRI) is the most efficient way to confirm the diagnosis. Contrast enhancement on CT often improves the identification of the underlying mass lesion and helps differentiate it from other causes, including abscess, hematoma, and vascular malformation.[75]

Treatment

Management consists of urgent referral to neurosurgery and treatment of any acute complications, including increased ICP and seizures. For patients who present with symptoms suggestive of increased ICP (e.g., headache, nausea, vomiting, confusion, weakness), treatment with steroids has been shown to be beneficial. Dexamethasone is the high-potency steroid used most often to treat edema associated with brain tumors. It has several advantages over other glucocorticoids, including a longer half-life, reduced mineralocorticoid effect, and lower associated incidence of cognitive and behavioral complications.[75] The exact dose of steroids necessary for each patient varies in accordance with histologic features, size, and location of the tumor and the amount of edema present. In general, most patients require between 8 and 16 mg of dexamethasone per day. An appropriate starting dose in the ED is 10 mg IV, followed by 4 mg every 6 hours.

Patients who have a seizure should receive anticonvulsant therapy. A multitude of antiepileptic drugs are available, and none has demonstrated superiority in this population of patients. Newer generation antiepileptics may be more tolerable. The choice of antiepileptic should be made in consultation with the specialist. Empirical or prophylactic treatment does not appear to delay or to prevent the onset of seizure activity and may expose the patient to unnecessary complications and toxicity.[76]

Giant Cell Arteritis

Principles of Disease

Giant cell arteritis, or temporal arteritis, is a systemic inflammatory process of the small and medium-sized arteries. Extracranial branches of the aortic arch and the ophthalmic vessels most commonly are involved, but the process may affect any artery in the body. The mean age at onset is 71 years, and it is rare before the age of 50 years. Women are affected more commonly than men are.[77]

Clinical Presentation

Headache is the most common initial manifestation of giant cell arteritis and occurs in more than 70% of patients with this disorder.[78] The headache often is of 2 to 3 months' duration and can be continuous or intermittent and often worsens at night or on exposure to cold. The pain may be described as sharp, throbbing, boring, or aching and usually is localized to the temporal region but may occur anywhere in the head. The physical examination may reveal tenderness over the scalp in the area of the temporal artery, with exacerbation of the pain by wearing a hat or resting the head on a pillow. Patients also may experience jaw claudication secondary to vascular insufficiency of the masseter and temporalis muscles. Systemic signs and symptoms, including fever, anorexia, and weight loss, often are present. Approximately 40% of patients develop symptoms of *polymyalgia rheumatica,* pain in their large proximal joints, with symptoms referable to the neck, torso, and lower back. Typically, pain and stiffness are worse in the morning and lessen as the day goes on.[78]

The most serious complication of giant cell arteritis is permanent visual loss, which eventually occurs in one third of untreated cases. Amaurosis fugax also can occur before permanent visual loss. Other complications include peripheral neuropathies, transient ischemic attacks, and stroke.[77]

Diagnostic Evaluation

The physical examination may reveal abnormalities of the temporal arteries, including tenderness, reduced or absent pulsations, erythema, and nodularity or swelling, best detected by light palpation just anterior and slightly superior to the tragus of the ear. Visual acuity, visual field testing, and thorough funduscopic examination should be performed.[79]

A majority of patients have a significant elevation of the erythrocyte sedimentation rate (ESR), usually to more than 50 mm/hr and often more than 100 mm/hr, although an elevated ESR is not specific for the disorder and a normal value does not rule out the diagnosis. Other abnormalities on laboratory studies include mild to moderate anemia, elevated C-reactive protein level, liver function abnormalities, and thrombocytosis. Temporal arteritis is substantially less likely in patients with an ESR below 50 mm/hr and a C-reactive protein level below 2.45 mg/dL, although patients in whom there is high suspicion of disease should be referred for biopsy even if both of these biomarkers are normal.[80,81] The diagnosis is confirmed by temporal artery biopsy. Because this is a patchy disease with skip lesions, multiple biopsy specimens of a long segment of the artery may need to be examined.

Treatment

Because of the risk of visual loss, giant cell arteritis constitutes a medical emergency, and treatment should be initiated promptly when the diagnosis is suspected. Steroids are the mainstay of therapy; the recommended initial dose of prednisone ranges from 60 mg/day. Symptomatic response usually occurs rapidly over days, although therapy should be continued for months, with close ESR monitoring.

Carotid and Vertebral Artery Dissection

Principles of Disease

Carotid and vertebral dissections are the most frequent cause of stroke in persons younger than 45 years, accounting for approximately 20% of all cases in this age group.[82] Although dissections may occur spontaneously, careful history taking frequently identifies an association with sudden neck movement or trauma

www.ketabpezeshki.com 66485457-66963820

preceding the event.[83] Reported mechanisms include neck torsion, chiropractic manipulation, coughing, minor falls, and motor vehicle collisions. Early symptoms and signs may be subtle, and delays in diagnosis are common in the absence of neurologic findings. The median delay from symptom onset to diagnosis can be several days.[84,85]

The pathologic lesion is intramural hemorrhage within the media of the arterial wall. The hematoma can be localized or extend circumferentially along the length of the vessel, resulting in partial or complete occlusion. Platelet aggregation and thrombus formation also occur, further compromising vessel patency or causing distal embolization. The timing of these events is variable, and a patient may experience symptoms of cerebral ischemia days to years after dissection.[83]

Clinical Presentation

The typical presentation of the patient with carotid or vertebral dissection is the abrupt onset of pain in the neck or face. Neurologic findings usually occur within the first few hours, but autopsy studies have shown that strokes may occur months later.[82]

Carotid Dissection. The classic triad of symptoms for carotid dissection includes unilateral headache, ipsilateral Horner's syndrome, and contralateral hemispheric findings that may include aphasia, neglect, visual disturbances, or hemiparesis. The headache is often severe and throbbing but may be subacute and similar to previous headaches. Acute severe retro-orbital pain in a previously healthy person with no history of cluster headaches is particularly suggestive of carotid dissection.[86] Most patients eventually develop signs of cerebral ischemia. Warning symptoms include transient ischemic attacks, amaurosis fugax, episodic lightheadedness, and syncope. Spontaneous dissection of the carotid artery has a favorable prognosis and recurrence is uncommon. Factors associated with a worse prognosis include old age, occlusive disease on angiography, and stroke as the initial presenting symptom.[83]

Vertebral Dissection. Vertebral artery dissections are less common than carotid dissections. The classic presentation is that of a relatively young person with severe, unilateral posterior headache and neurologic findings. The majority of patients develop a rapidly progressive neurologic deficit with symptoms of brainstem and cerebellar ischemia. Common findings include vertigo, severe vomiting, ataxia, diplopia, hemiparesis, unilateral facial weakness, and tinnitus. Spontaneous vertebral artery dissection appears to be relatively rare. Approximately 10% of patients who develop a vertebral dissection die during the acute phase, secondary to massive stroke. For patients who survive, the prognosis is usually good.[87]

Diagnosis and Treatment

Identification of patients with dissection is challenging. The emergency physician should consider the diagnosis in any young patient who presents with head or neck pain with focal neurologic findings. A non–contrast-enhanced head CT scan is often normal in uncomplicated dissection. Further imaging studies, such as CT angiography, magnetic resonance angiography, and catheter angiography, are required to confirm the diagnosis.[88] Figure 103-2 shows an example of carotid artery dissection on MRI. Duplex imaging is not sufficiently sensitive to rule out disease.[89] Treatment is aimed at prevention of stroke. It is not yet clear if early anticoagulation offers an outcome benefit over antiplatelet therapy.[90]

Cerebral Venous Sinus Thrombosis

Principles of Disease

Thrombosis of the intracranial veins and sinuses is a rare cause of stroke but tends to affect younger patients without traditional cerebrovascular risk factors.[91] Because of the significant associated morbidity, however, cerebral venous sinus thrombosis (CVST) is an important consideration in the differential diagnosis for headache in patients with suggestive signs and symptoms.

Thrombophilia is usually identified in patients with CVST, including genetic and hypercoagulable disorders, pregnancy and the puerperium, inflammatory systemic disorders including vasculitis, connective tissue disorders, and medications such as oral contraceptives. Other risk factors include head trauma, head and orofacial infections, and neurosurgical procedures.[91]

Figure 103-2. Axial T1-weighted magnetic resonance image demonstrating a crescent sign (*arrow*) in a patient with a left internal carotid artery dissection. (From Kidwell C: Dissection syndromes. Emedicine, updated Sep 19, 2011. Available at http://emedicine.medscape.com/article/1160482-overview.)

Clinical Presentation

The clinical presentation can be variable, depending on the location of the thrombosis. Common symptoms and signs include headache, seizures, decreased level of consciousness that may progress to coma, and focal neurologic deficits. Papilledema is less common with acute presentations. With cavernous sinus thrombosis, the clinical picture is dominated by ocular findings including orbital pain, proptosis, and paralysis of extraocular movements.[91]

Diagnostic Evaluation

An elevated D-dimer level is present in approximately 90% of cases of CVST and along with the clinical findings can be used to exclude the diagnosis in individual patients at low risk of disease.[92,93] The definitive diagnosis of CVST is based on neuroimaging of the area of thrombosis. CT by itself is an insensitive test, but it may reveal nonspecific late lesions, such as an infarct, hemorrhage, or edema. The key to diagnosis is to image the venous system itself. This is best accomplished by a combination of MRI to visualize the thrombosed vessel and magnetic resonance venography to detect nonvisualization of the same vessel.[94] CT angiography and venography may also be used to visualize the cerebral venous system.

Treatment

Specific treatment of CVST includes anticoagulation to prevent propagation of the thrombosis as well as complications (e.g., pulmonary embolism). In patients whose clinical condition worsens despite anticoagulation, thrombolysis or thrombectomy may be

www.ketabpezeshki.com 66485457-66963820

considered in centers with expertise in interventional procedures. Seizures should be treated with anticonvulsants.[95]

The prognosis with CVST is based on the underlying etiology, condition at time of diagnosis, and development of complications. Although overall mortality is low compared with other strokes, victims of this disease tend to be younger and healthier patients.[94]

Idiopathic Intracranial Hypertension

Principles of Disease

Although this disease is sometimes called pseudotumor cerebri or benign intracranial hypertension, the term *idiopathic intracranial hypertension* (IIH) reflects the current incomplete understanding of the pathophysiology and the fact that this disorder is not benign—a substantial minority of patients develop permanent visual loss. Compared with other headache disorders, IIH is a relatively uncommon neurologic disease seen primarily in young obese women of childbearing age. Several predisposing factors have been identified, including the use of oral contraceptives, anabolic steroids, tetracyclines, and vitamin A.[96]

Box 103-4 ICHD-II Criteria for Diagnosis of Idiopathic Intracranial Hypertension

1. Alert patient with neurologic examination that either yields normal findings or demonstrates any of the following abnormalities:
   A. Papilledema
   B. Enlarged blind spot
   C. Visual field defect (progressive if untreated)
2. Increased CSF pressure (>200 mm H_2O in nonobese patients, >250 mm H_2O in obese patients) measured by lumbar puncture in the recumbent position or by epidural or intraventricular pressure monitoring
3. Normal CSF chemistry (low CSF protein acceptable) and cellularity
4. Intracranial disease (including venous sinus thrombosis) ruled out by appropriate investigations
5. No metabolic, toxic, or hormonal cause of intracranial hypertension

Available at http://ihs-classification.org/en/.
CSF, cerebrospinal fluid; *ICHD-II,* International Classification of Headache Disorders, 2nd ed.

Pathophysiology and Clinical Features

The pathophysiologic mechanism of this disease is not understood, but it is often attributed to an imbalance between CSF production and reabsorption. The most prominent symptom is generalized headache, which often is gradual in onset and of moderate intensity. No specific localizing pattern has been documented, although in some patients the headache is worsened by eye movement. It may awaken the patient from sleep and is exacerbated by bending forward and the Valsalva maneuver, both of which impede cerebral venous return.

Visual complaints are common, and patients may experience transient visual obscuration several times a day secondary to ischemia of the visual pathways. These episodes can be followed by prolonged periods of visual loss, which can become permanent in up to 10% of patients. Patients also may complain of nausea, vomiting, dizziness, and pulsatile tinnitus. The physical examination will reveal papilledema and visual field defects, including an enlarged blind spot initially, followed by loss of peripheral vision. On occasion, a sixth nerve palsy is noted.[96]

Diagnosis

The diagnosis of IIH should not be made without neuroimaging and measurement of ICP. Diagnostic criteria are listed in Box 103-4. Venous sinus disease should be excluded in all patients with this diagnosis.[2]

Treatment

Predisposing factors (e.g., discontinuation of implicated medications) should be corrected. Symptomatic treatment often includes lowering of ICP and management of the headache. Evidence-based therapies are lacking. Acetazolamide (a carbonic anhydrase inhibitor) can be used to decrease CSF production alone or with a loop diuretic such as furosemide.[97] Steroids also have been used, although their mechanism of action is unclear. Prolonged therapy is a problem, and rebound headache often occurs when doses are tapered. In patients with impending visual loss or incapacitating symptoms, placement of a ventricular shunt or optic nerve sheath fenestration may be indicated.[96]

Lumbar puncture is commonly performed to alleviate acute symptoms. Anecdotal reports indicate that this procedure alleviates headache, visual disturbances, and tinnitus for prolonged periods. It is unclear if a lumbar puncture can obviate the need for optic nerve sheath fenestration or CSF diversion. It is unclear how much CSF should be removed during the lumbar puncture. A reasonable goal is to remove sufficient CSF so that pressure is normalized.

Post-traumatic Headache

Headache is the most common symptom after minor head injury. It often is part of a complex syndrome that can include dizziness, fatigue, insomnia, irritability, memory loss, and difficulty with concentration. There are approximately 2 million closed head injuries per year, and post-traumatic headache (PTHA) occurs in an estimated 30 to 50% of patients with these injuries.[98] Acute PTHA develops hours to days after the injury and resolves within 3 to 6 months.[99] Chronic PTHA may last several months to years and may mimic other forms of headache, including tension and migraine headaches. The presence of headache, dizziness, or nausea on initial presentation is strongly associated with the development of chronic PTHA.[100]

Patients in whom PTHA develops after minor head injuries have normal findings on neurologic examination and neuroimaging studies. The pathophysiologic mechanism for their symptoms is unclear and may have both anatomic and functional components. Most patients are concerned about the cause of the headache more than about the headache itself.

Treatment is symptomatic. For acute PTHA, analgesics such as acetaminophen or NSAIDs are adequate for pain control. For chronic PTHA, treatment should be individualized by the type of headache and associated symptoms the patient is experiencing. Antidepressants and beta-blockers may be effective in selected patients.

Acute Glaucoma

Patients with acute angle closure glaucoma present with sudden onset of severe pain localized to the affected eye that may radiate to the ear, sinuses, teeth, or forehead. Visual symptoms, including blurriness, halos around lights, and scotomas, typically are present, and many patients also experience nausea and vomiting. The underlying pathophysiologic mechanism is congenital narrowing of the anterior chamber angle that under certain conditions closes, resulting in a significant rise in intraocular pressure. Episodes can

www.ketabpezeshki.com 66485457-66963820

be precipitated by entering a low-light environment such as a movie theater, with resultant pupillary dilation, or by the use of medications such as mydriatics (e.g., for dilated ocular examination), sympathomimetics (e.g., pseudoephedrine), or agents with anticholinergic properties (e.g., antiemetics, antihistamines, antipsychotics, antidepressants).

Physical examination reveals a red eye with a fixed, mid-dilated pupil, corneal clouding, and shallow anterior chamber. The diagnosis is confirmed by demonstration of markedly elevated intraocular pressure in the range of 60 to 90 mm Hg (normal is less than 21 mm Hg).

Treatment includes topical miotics, topical beta-blockers, oral carbonic anhydrase inhibitors (e.g., acetazolamide, 250 mg four times daily), intravenous osmotic agents (e.g., mannitol), and prompt referral to an ophthalmologist. The potential for diagnostic confusion between acute glaucoma, iritis, and cluster headache should be recognized. Although cluster headache may arise with pain, nausea, and a red eye, vision is not affected and the pupil generally is small and the eyelid is ptotic (from an oculosympathetic paresis). Acute iritis also arises with a painful red eye, but only acute angle closure glaucoma is associated with markedly elevated intraocular pressure.[101,102]

Post–Dural Puncture Headache

Principles of Disease and Pathophysiology

Headache is the most common complication of lumbar puncture, occurring in up to 40% of patients.[103] The incidence is highest in the 18- to 30-year age group, but this complication is uncommon in young children and in adults older than 60 years. Although the onset often is immediate, patients may not report symptoms for several days. In a majority of affected persons, the duration of headache is less than 5 days.[103]

The cause of post–dural puncture headache (PDPH) is not entirely clear. The most likely explanation is a persistent CSF leak that exceeds CSF production, resulting in CSF hypotension. If sufficient CSF is lost, the brain descends in the cranial vault when the patient assumes the upright position, leading to increased traction on the pain fibers. Thus the headache is characteristically positional and increases with the upright position and decreases with recumbency. The amount of time a patient remains recumbent after lumbar puncture does not appear to affect the incidence of headache.[104]

Certain factors have been implicated as causes of PDPH, including the size or diameter of the spinal needle, the orientation of the bevel during the procedure, and the amount of fluid withdrawn. Smaller-diameter needles cause less leakage, and it is postulated that insertion of the needle with the bevel up (i.e., bevel pointing up when the patient is in the lateral position) minimizes damage to the dural fibers. Use of atraumatic needles or pencil-point needles (e.g., Whitaker or Sprotte) also has been shown to reduce the incidence of PDPH significantly.[105,106]

Clinical Features

PDPH typically is bilateral, throbbing, and exacerbated by the upright position. Associated signs and symptoms include neck stiffness, nausea, vomiting, auditory disturbances including tinnitus and hearing loss (hypoacusis), and ocular symptoms including blurred vision and diplopia.[103]

Treatment

Most PDPHs resolve spontaneously within a few days with bed rest, adequate hydration, and mild analgesics. For persistent headaches, methylxanthine agents may be useful. Caffeine sodium benzoate (500 mg in 1 L of fluid) may be effective.[107] For severe headaches lasting longer than 24 hours, an epidural blood patch (autologous blood clot) relieves the headache in the majority of patients.[108]

Intracranial Infection

Headache is common among patients with intracranial infections, including meningitis, brain abscess, encephalitis, and acquired immunodeficiency syndrome. The severity and type of headache vary by the specific infection.

With acute bacterial meningitis, the patient often has a severe bursting headache that rapidly increases in severity during a short period. These patients typically have significant meningismus, with both Kernig's and Brudzinski's signs. With viral meningitis, patients also may complain of severe headache and nuchal rigidity, but the course is more indolent than with bacterial meningitis.[109]

The severity of headache associated with encephalitis depends on the type of virus involved. For example, the headache is usually mild with mumps encephalitis. With herpes simplex infection, however, the headache is abrupt and severe and frequently is associated with confusion, fever, altered level of consciousness, seizures, and focal neurologic signs. Patients with brain abscess often have headache as their presenting complaint. As the infection progresses, vomiting, focal neurologic signs, and depressed level of consciousness typically develop.[110]

Headache is a frequent complaint in patients with human immunodeficiency virus infection and can be caused by a number of conditions, including aseptic meningitis, toxoplasmosis, cryptococcal or tuberculous meningitis, and cytomegalovirus encephalitis. Cryptococcal meningitis in particular can be indolent but eventually lethal. Because spinal fluid analysis may be relatively bland, clinicians need to maintain a high index of suspicion for this particular pathogen as T-cell counts dwindle.[111]

In a majority of cerebral infections, the mechanism of head pain includes meningeal irritation and increased ICP. In addition, headache may be a general reaction to fever or the toxic products of the infecting agent.[110]

Hypertensive Headache

Contrary to common belief, hypertension is not an important cause of headache, and the occurrence of headache and hypertension in the same patient is often coincidental. Whether some patients with mild to moderate hypertension suffer from headache caused by elevated blood pressure is uncertain. The rate of blood pressure increase is more important as a cause of headache than the absolute blood pressure value is. Diastolic pressures lower than 130 mm Hg are rarely the cause of headache.[2]

Nonetheless, the association of headache with severe hypertension is well documented. Acute, severe headache is a prominent symptom of hypertensive encephalopathy, and most patients have blood pressure readings in the range of 250/150 mm Hg. Other conditions include headache secondary to toxic agents (e.g., drug-induced hypertension), pheochromocytoma, and eclampsia.[2]

The headache of severe hypertension typically is diffuse and is worse when the patient awakes in the morning and gradually subsides during the course of the day. Treatment is directed at lowering of the blood pressure; in most cases, the headache is relieved within 24 hours. In patients with hypertensive encephalopathy, the headache may persist for days until brain edema has resolved.

www.ketabpezeshki.com 66485457-66963820

Cervicogenic Headache

Cervicogenic headache refers to headache originating from disorders of the neck. Diagnosis is based on the presence of one of the following three distinct sets of symptoms[112]:

1. Unilateral headache triggered by movements of the head or neck or certain head positions
2. Unilateral headache triggered by pressure on the neck
3. Unilateral headache spreading to the neck or possibly the ipsilateral shoulder or arm

Many of these headaches are reported after a whiplash injury. Even though neck structures play a primary role in the pathophysiologic process of some headaches, clinical patterns indicating a neck-headache relationship have not been adequately defined.

Medication-Overuse Headache

Excessive analgesic or antimigraine medication use and withdrawal from these medications can worsen an existing headache disorder in susceptible patients. Medication-overuse headache is underdiagnosed and often difficult to manage. It occurs in patients with a primary headache disorder (e.g., migraine, tension type) who use immediate-relief medications on a near-daily basis, often in excessive quantities. Medications that have been implicated include NSAIDs, aspirin or acetylsalicylic acid, acetaminophen, barbiturate-analgesic combinations, opioids, caffeine, ergotamine, and triptans. Often, patients with this disorder describe preemptive use of drugs, in anticipation of—rather than for—headache. Women are affected more commonly than men are, and the most frequently affected age group is that of persons between 30 and 40 years. The headache itself is variable and may be accompanied by asthenia, nausea, anxiety, depression, and difficulty with concentration. Typically, it is worse on awakening in the morning and after physical exertion.[113]

The symptomatic medication that leads to the development of this disorder initially provides some pain relief to the patient, but tolerance develops over time, and larger doses are required to obtain symptomatic improvement.

Treatment requires complete withdrawal of the medication being overused while preventive therapy is initiated and a new acute headache therapeutic. In addition, these patients require a comprehensive education and follow-up program with pharmacologic, dietary, and behavioral components.[113]

High-Altitude Headache

Headache is one of the cardinal manifestations of acute mountain sickness and can occur at altitudes higher than 5000 feet above sea level in unacclimatized persons. The headache is throbbing in nature, located in the temporal or occipital areas, and probably caused by a mild increase in ICP secondary to brain swelling.[114] It is worse at night or in the early morning and exacerbated by the Valsalva maneuver or bending forward.[115] Other findings associated with high-altitude illness include fatigue, nausea, vomiting, dizziness, insomnia, and altered mental status. Pulmonary edema and cerebral edema develop in severe cases. The treatment of these conditions includes supplemental oxygen and descent to a lower altitude.

Reversible Cranial Vasoconstriction Syndrome

Reversible cranial vasoconstriction syndrome (RCVS) is a disorder of cerebral arteries characterized by segmental areas of vasoconstriction. It causes recurrent thunderclap headache in susceptible patients and is a cause of ischemic or hemorrhagic stroke. The headache is often described as severe and throbbing and is associated with nausea, vomiting, and photophobia. The headache may be provoked by use of vasoactive medications or substances. RCVS has been called by the eponym Call-Fleming syndrome and is the same disease as postpartum angiopathy or migrainous vasospasm. Typically, patients present with a thunderclap headache with neurologic deficits or seizures, and during cerebral vascular imaging, abnormal areas of vasoconstriction, described as sausage on a string, are noted. Repeated vascular imaging within 3 months shows resolution of the areas of vasoconstriction. Treatment with calcium channel blockers has been described, although when to initiate treatment is not clear. The prevalence of this presumably rare disorder is not known. However, many patients who present to an ED with a thunderclap headache cannot be assigned a specific diagnosis. It is possible that the prevalence of this disorder is greater than currently understood.[116,117]

OTHER HEADACHE DISORDERS AND FACIAL PAIN

Nummular Headache

Relatively recently described, nummular headache is a highly localized headache, rarely more than moderately painful, that is felt exclusively in a rounded, 2- to 6-cm area of the head. Epidemiology and pathogenesis are not yet well understood. Nummular headache is usually responsive to nonsteroidals, although a high frequency of headaches may be prevented with tricyclic antidepressants. In patients with new onset of headache, underlying disease of the scalp or dura should be excluded.[118]

Trigeminal Neuralgia

Trigeminal neuralgia is a painful unilateral affliction of the face characterized by brief electric shock–like (lancinating) pains limited to the distribution of one or more divisions of the trigeminal nerve. Pain is commonly evoked by trivial stimuli (e.g., washing, shaving, smoking, talking, or brushing teeth) but also may occur spontaneously. Individual attacks are brief, lasting a few seconds to less than 2 minutes, and are stereotypic in the individual patient. The lightning-like pains and unilateral grimaces characteristic of trigeminal neuralgia led to the designation *tic douloureux*. The diagnosis is straightforward in most patients on the basis of clinical criteria. However, because these symptoms also can be caused by an underlying mass lesion or multiple sclerosis, MRI is indicated in previously undiagnosed patients and when sensory loss or motor dysfunction is present.[119]

Several oral drugs have been effective in treatment of trigeminal neuralgia, including carbamazepine and oxcarbazepine. Phenytoin and baclofen may also be useful. However, approximately 30% of patients fail to respond to medical therapy. In these patients, surgical management, by alcohol or glycerol injection or microvascular decompression, may be indicated. For patients with acute severe pain, parenteral treatment with an antiepileptic drug such as phosphenytoin may be useful.[120]

Coital Headache

Coital cephalgia is a recurrent, benign headache associated with sexual activity and is more common in men than in women. Different types have been described, including headaches that occur before, during, or immediately after orgasm. They typically are

www.ketabpezeshki.com 66485457-66963820

occipital in location and may increase in severity with mounting sexual excitement. Their duration can be minutes to hours. On occasion, some patients experience a sudden, explosive headache that occurs during orgasm. In these patients, SAH should be ruled out.[121,122]

Cough and Exertional Headache

In some patients, severe headache can be provoked by rapid increase in intra-abdominal pressure, such as coughing, sneezing, laughing, heavy lifting or exertion, and Valsalva maneuver. The pain starts within a few seconds of the precipitant and typically is brief when it is associated with cough but can last as long as 24 hours when it is associated with exertion. The headache is bilateral and throbbing in nature and in a majority of patients resolves spontaneously without persistent neurologic symptoms (e.g., neck stiffness or photophobia). In some patients, the headache may be secondary to structural lesions, especially in the posterior fossa[113]; therefore, all previously undiagnosed patients require CT, or preferably MRI, followed by lumbar puncture to rule out intracranial disease, including SAH. For patients with recurrent benign exertional headache, treatment includes avoidance of the underlying triggering mechanism and use of analgesics as necessary. For patients with exertional headache, NSAIDs, including indomethacin, have been effective.[121,122]

KEY CONCEPTS

- Headache is a common presenting complaint in the ED. The goals of evaluation in this setting are (1) to distinguish between benign primary headache disorders and potentially life-threatening secondary causes of headache and (2) to treat the headache pain effectively, and rapidly, without causing undue side effects.
- A majority of patients do not have abnormal neurologic findings; therefore, the key to a successful diagnosis is a thorough and systematic history.
- Patients with the following headache presentations are at risk for serious underlying disease: sudden explosive headache; first or "worst-ever" headache; new-onset headache after the age of 50 years; headache associated with papilledema, alteration in or loss of consciousness, or focal neurologic symptoms; subacute headache with increasing frequency or severity; headache associated with fever, cancer, or immunosuppression; and headache triggered by exertion, sexual activity, or Valsalva maneuver.
- The need for diagnostic studies is dictated by the suspected secondary cause of headache.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. McCaig LF, Nawar EW: National Hospital Ambulatory Medical Care Survey: 2004 emergency department summary. *Adv Data* 2006; 372:1-29.
2. The Classification Subcommittee of the International Headache Society: International Classification of Headache Disorders, 2nd ed. *Cephalalgia* 2004; 24(Suppl 1):1-151.
3. Bigal M, Bordini CA, Speciali JG: Headache in an emergency room in Brazil. *Sao Paulo Med J* 2000; 118:58-62.
4. Friedman BW, et al: Applying the International Classification of Headache Disorders to the emergency department: An assessment of reproducibility and the frequency with which a unique diagnosis can be assigned to every acute headache presentation. *Ann Emerg Med* 2007; 49:409-419.
5. Luda E, Comitangelo R, Sicuro L: The symptom of headache in emergency departments. The experience of a neurology emergency department. *Ital J Neurol Sci* 1995; 16:295-301.
6. Goadsby PJ, Lipton RB, Ferrari MD: Migraine—current understanding and treatment. *N Engl J Med* 2002; 346:257-270.
7. de Vries B, Frants RR, Ferrari MD, van den Maagdenberg AM: Molecular genetics of migraine. *Hum Genet* 2009; 126:115-132.
8. Vinson DR: Treatment patterns of isolated benign headache in US emergency departments. *Ann Emerg Med* 2002; 39:215-222.
9. Lipton RB, et al: Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007; 68:343-349.
10. Brandes JL: The influence of estrogen on migraine: A systematic review. *JAMA* 2006; 295:1824-1830.
11. Sprenger T, Goadsby PJ: Migraine pathogenesis and state of pharmacological treatment options. *BMC Med* 2009; 7:71.
12. Troost BT: Ophthalmoplegic migraine. *Biomed Pharmacother* 1996; 50:49-51.
13. Diamond S, Diamond ML: Emergency treatment of migraine. Insights into current options. *Postgrad Med* 1997; 101:169-172, 175-166, 179.
14. Frishberg BM: The utility of neuroimaging in the evaluation of headache in patients with normal neurologic examinations. *Neurology* 1994; 44:1191-1197.
15. Edlow JA, Caplan LR: Avoiding pitfalls in the diagnosis of subarachnoid hemorrhage. *N Engl J Med* 2000; 342:29-36.
16. Perry JJ, et al: High risk clinical characteristics for subarachnoid haemorrhage in patients with acute headache: Prospective cohort study. *BMJ* 2010; 341:c5204.
17. Lipton RB, Hamelsky SW, Dayno JM: What do patients with migraine want from acute migraine treatment? *Headache* 2002; 42(Suppl 1): 3-9.
18. Aurora S, Kori S, Barrodale P, Nelsen A, McDonald S: Gastric stasis occurs in spontaneous, visually induced, and interictal migraine. *Headache* 2007; 47:1443-1446.
19. Rabbie R, Derry S, Moore RA, McQuay HJ: Ibuprofen with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev* 2010; 10:CD008039.
20. Derry S, Moore RA, McQuay HJ: Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev* 2010; 11:CD008040.
21. Tfelt-Hansen P: The effectiveness of combined oral lysine acetylsalicylate and metoclopramide (Migpriv) in the treatment of migraine attacks. Comparison with placebo and oral sumatriptan. *Funct Neurol* 2000; 15(Suppl 3):196-201.
22. Colman I, et al: Parenteral metoclopramide for acute migraine: Meta-analysis of randomised controlled trials. *BMJ* 2004; 329:1369-1373.
23. Kelly AM, Walcynski T, Gunn B: The relative efficacy of phenothiazines for the treatment of acute migraine: A meta-analysis. *Headache* 2009; 49:1324-1332.
24. Silberstein SD, Young WB, Mendizabal JE, Rothrock JF, Alam AS: Acute migraine treatment with droperidol: A randomized, double-blind, placebo-controlled trial. *Neurology* 2003; 60:315-321.
25. Akerman S, Goadsby PJ: Dopamine and migraine: Biology and clinical implications. *Cephalalgia* 2007; 27:1308-1314.
26. Parlak I, et al: Midazolam vs. diphenhydramine for the treatment of metoclopramide-induced akathisia: A randomized controlled trial. *Acad Emerg Med* 2007; 14:715-721.
27. Raskin NH: Repetitive intravenous dihydroergotamine as therapy for intractable migraine. *Neurology* 1986; 36:995-997.
28. Akpunonu BE, et al: Subcutaneous sumatriptan for treatment of acute migraine in patients admitted to the emergency department: A multicenter study. *Ann Emerg Med* 1995; 25:464-469.
29. Landy SH, McGinnis JE, McDonald SA: Pilot study evaluating preference for 3-mg versus 6-mg subcutaneous sumatriptan. *Headache* 2005; 45:346-349.
30. Friedman BW, Kapoor A, Friedman MS, Hochberg ML, Rowe BH: The relative efficacy of meperidine for the treatment of acute migraine: A meta-analysis of randomized controlled trials. *Ann Emerg Med* 2008; 52:705-713.
31. Colman I, Rothney A, Wright SC, Zilkalns B, Rowe BH: Use of narcotic analgesics in the emergency department treatment of migraine headache. *Neurology* 2004; 62:1695-1700.
32. Ducharme J, Beveridge RC, Lee JS, Beaulieu S: Emergency management of migraine: Is the headache really over? *Acad Emerg Med* 1998; 5:899-905.
33. Colman I, et al: Parenteral dexamethasone for acute severe migraine headache: Meta-analysis of randomised controlled trials for preventing recurrence. *BMJ* 2008; 336:1359-1361.
34. Friedman BW, et al: Treating headache recurrence after emergency department discharge: A randomized controlled trial of naproxen versus sumatriptan. *Ann Emerg Med* 2010; 56:7-17.
35. Linde K, Rossnagel K: Propranolol for migraine prophylaxis. *Cochrane Database Syst Rev* 2004; 2:CD003225.
36. Mulleners WM, Chronicle EP: Anticonvulsants in migraine prophylaxis: A Cochrane review. *Cephalalgia* 2008; 28:585-597.
37. Steiner TJ, Fontebasso M: Headache. *BMJ* 2002; 325:881-886.
38. Mathew NT: Cluster headache. *Semin Neurol* 1997; 17:313-323.
39. Cohen AS, Burns B, Goadsby PJ: High-flow oxygen for treatment of cluster headache: A randomized trial. *JAMA* 2009; 302:2451-2457.
40. Ekbom K, et al: Subcutaneous sumatriptan in the acute treatment of cluster headache: A dose comparison study. The Sumatriptan Cluster Headache Study Group. *Acta Neurol Scand* 1993; 88:63-69.
41. Matharu MS, Levy MJ, Meeran K, Goadsby PJ: Subcutaneous octreotide in cluster headache: Randomized placebo-controlled double-blind crossover study. *Ann Neurol* 2004; 56:488-494.
42. Rozen TD: Olanzapine as an abortive agent for cluster headache. *Headache* 2001; 41:813-816.
43. Leone M, et al: Verapamil in the prophylaxis of episodic cluster headache: A double-blind study versus placebo. *Neurology* 2000; 54:1382-1385.
44. Schwartz BS, Stewart WF, Simon D, Lipton RB: Epidemiology of tension-type headache. *JAMA* 1998; 279:381-383.
45. Iversen HK, Langemark M, Andersson PG, Hansen PE, Olesen J: Clinical characteristics of migraine and episodic tension-type headache in relation to old and new diagnostic criteria. *Headache* 1990; 30:514-519.
46. Cady RK: The convergence hypothesis. *Headache* 2007; 47(Suppl 1):S44-S51.
47. Lipton RB, Cady RK, Stewart WF, Wilks K, Hall C: Diagnostic lessons from the spectrum study. *Neurology* 2002; 58(9 Suppl 6):S27-S31.
48. Crystal SC, Robbins MS: Epidemiology of tension-type headache. *Curr Pain Headache Rep* 2010; 14:449-454.
49. Cicek M, et al: Prospective, randomised, double blind, controlled comparison of metoclopramide and pethidine in the emergency treatment of acute primary vascular and tension type headache episodes. *Emerg Med J* 2004; 21:323-326.
50. Becker KJ: Epidemiology and clinical presentation of aneurysmal subarachnoid hemorrhage. *Neurosurg Clin North Am* 1998; 9:435-444.
51. Locksley HB: Natural history of subarachnoid hemorrhage, intracranial aneurysms and arteriovenous malformations. Based on 6368 cases in the cooperative study. *J Neurosurg* 1966; 25:219-239.
52. Rinkel GJ, Djibuti M, Algra A, van Gijn J: Prevalence and risk of rupture of intracranial aneurysms: A systematic review. *Stroke* 1998; 29:251-256.
53. Broderick JP, et al: Major risk factors for aneurysmal subarachnoid hemorrhage in the young are modifiable. *Stroke* 2003; 34:1375-1381.
54. Juvela S: Prehemorrhage risk factors for fatal intracranial aneurysm rupture. *Stroke* 2003; 34:1852-1857.
55. Linn FH, Rinkel GJ, Algra A, van Gijn J: Headache characteristics in subarachnoid haemorrhage and benign thunderclap headache. *J Neurol Neurosurg Psychiatry* 1998; 65:791-793.
56. Linn FH, et al: Prospective study of sentinel headache in aneurysmal subarachnoid haemorrhage. *Lancet* 1994; 344:590-593.
57. Morgenstern LB: Worst headache and subarachnoid hemorrhage. *Ann Emerg Med* 1999; 33:478.
58. Hunt WE, Hess RM: Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *J Neurosurg* 1968; 28:14-20.
59. McCormack RF, Hutson A: Can computed tomography angiography of the brain replace lumbar puncture in the evaluation of acute-onset

www.ketabpezeshki.com 66485457-66963820

headache after a negative noncontrast cranial computed tomography scan? *Acad Emerg Med* 2010; 17:444-451.
60. Schull MJ: Lumbar puncture first: An alternative model for the investigation of lone acute sudden headache. *Acad Emerg Med* 1999; 6:131-136.
61. Locker TE, Thompson C, Rylance J, Mason SM: The utility of clinical features in patients presenting with nontraumatic headache: An investigation of adult patients attending an emergency department. *Headache* 2006; 46:954-961.
62. Perry JJ, et al: Should spectrophotometry be used to identify xanthochromia in the cerebrospinal fluid of alert patients suspected of having subarachnoid hemorrhage? *Stroke* 2006; 37:2467-2472.
63. Roost KT, Pimstone NR, Diamond I, Schmid R: The formation of cerebrospinal fluid xanthochromia after subarachnoid hemorrhage. Enzymatic conversion of hemoglobin to bilirubin by the arachnoid and choroid plexus. *Neurology* 1972; 22:973-977.
64. Savitz SI, Levitan EB, Wears R, Edlow JA: Pooled analysis of patients with thunderclap headache evaluated by CT and LP: Is angiography necessary in patients with negative evaluations? *J Neurol Sci* 2009; 276:123-125.
65. Lanzino G, Kongable GL, Kassell NF: Electrocardiographic abnormalities after nontraumatic subarachnoid hemorrhage. *J Neurosurg Anesthesiol* 1994; 6:156-162.
66. Dorhout Mees SM, et al: Calcium antagonists for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev* 2007; 3:CD000277.
67. Roos Y, Rinkel G, Vermeulen M, Algra A, van Gijn J: Antifibrinolytic therapy for aneurysmal subarachnoid hemorrhage: A major update of a Cochrane review. *Stroke* 2003; 34:2308-2309.
68. Feigin VL, et al: Corticosteroids for aneurysmal subarachnoid haemorrhage and primary intracerebral haemorrhage. *Cochrane Database Syst Rev* 2005; 3:CD004583.
69. Bederson JB, et al: Guidelines for the management of aneurysmal subarachnoid hemorrhage: A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 2009; 40:994-1025.
70. Riordan KC, et al: Anticonvulsant drug therapy after aneurysmal subarachnoid hemorrhage: A critically appraised topic. *Neurologist* 2010; 16:397-399.
71. van der Schaaf I, et al: Endovascular coiling versus neurosurgical clipping for patients with aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev* 2005; 4:CD003085.
72. Valentinis L, et al: Headache attributed to intracranial tumours: A prospective cohort study. *Cephalalgia* 2010; 30:389-398.
73. Kirby S, Purdy RA: Headache and brain tumors. *Curr Neurol Neurosci Rep* 2007; 7:110-116.
74. Pfund Z, Szapáry L, Jászberényi O, Nagy F, Czopf J: Headache in intracranial tumors. *Cephalalgia* 1999; 19:787-790; discussion 765.
75. Newton HB, Turowski RC, Stroup TJ, McCoy LK: Clinical presentation, diagnosis, and pharmacotherapy of patients with primary brain tumors. *Ann Pharmacother* 1999; 33:816-832.
76. Teall J, et al: Rizatriptan (MAXALT) for the acute treatment of migraine and migraine recurrence. A placebo-controlled, outpatient study. Rizatriptan 022 Study Group. *Headache* 1998; 38:281-287.
77. Nordborg E, Nordborg C: Giant cell arteritis: Epidemiological clues to its pathogenesis and an update on its treatment. *Rheumatology (Oxford)* 2003; 42:413-421.
78. Hellmann DB: Temporal arteritis: A cough, toothache, and tongue infarction. *JAMA* 2002; 287:2996-3000.
79. Smetana GW, Shmerling RH: Does this patient have temporal arteritis? *JAMA* 2002; 287:92-101.
80. Parikh M, et al: Prevalence of a normal C-reactive protein with an elevated erythrocyte sedimentation rate in biopsy-proven giant cell arteritis. *Ophthalmology* 2006; 113:1842-1845.
81. Walvick MD, Walvick MP: Giant cell arteritis: Laboratory predictors of a positive temporal artery biopsy. *Ophthalmology* 2011; 118:1201-1204.
82. Norris JW, Beletsky V: Cervical arterial dissection. *Adv Neurol* 2003; 92:119-125.
83. Schievink WI: Spontaneous dissection of the carotid and vertebral arteries. *N Engl J Med* 2001; 344:898-906.
84. Ahmad HA, Gerraty RP, Davis SM, Cameron PA: Cervicocerebral artery dissections. *J Accid Emerg Med* 1999; 16:422-424.
85. Silbert PL, Mokri B, Schievink WI. Headache and neck pain in spontaneous internal carotid and vertebral artery dissections. *Neurology* 1995; 45(8):1517-1522.
86. Dodick DW, Rozen TD, Goadsby PJ, Silberstein SD: Cluster headache. *Cephalalgia* 2000; 20:787-803.
87. Arnold M, et al: Vertebral artery dissection: Presenting findings and predictors of outcome. *Stroke* 2006; 37:2499-2503.
88. Vertinsky AT, et al: Comparison of multidetector CT angiography and MR imaging of cervical artery dissection. *AJNR Am J Neuroradiol* 2008; 29:1753-1760.
89. Nebelsieck J, et al: Sensitivity of neurovascular ultrasound for the detection of spontaneous cervical artery dissection. *J Clin Neurosci* 2009; 16:79-82.
90. Lyrer P, Engelter S: Antithrombotic drugs for carotid artery dissection. *Cochrane Database Syst Rev* 2010; 10:CD000255.
91. Ferro JM, et al: Prognosis of cerebral vein and dural sinus thrombosis: Results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke* 2004; 35:664-670.
92. Crassard I, et al: A negative D-dimer assay does not rule out cerebral venous thrombosis: A series of seventy-three patients. *Stroke* 2005; 36:1716-1719.
93. Kosinski CM, et al: Do normal D-dimer levels reliably exclude cerebral sinus thrombosis? *Stroke* 2004; 35:2820-2825.
94. Bousser MG, Ferro JM: Cerebral venous thrombosis: An update. *Lancet Neurol* 2007; 6:162-170.
95. Einhäupl K, et al: EFNS guideline on the treatment of cerebral venous and sinus thrombosis in adult patients. *Eur J Neurol* 2010; 17:1229-1235.
96. Friedman DI: Idiopathic intracranial hypertension. *Curr Pain Headache Rep* 2007; 11:62-68.
97. Kesler A, Hadayer A, Goldhammer Y, Almog Y, Korczyn AD: Idiopathic intracranial hypertension: Risk of recurrences. *Neurology* 2004; 63:1737-1739.
98. Packard RC: Epidemiology and pathogenesis of posttraumatic headache. *J Head Trauma Rehabil* 1999; 14:9-21.
99. Linder SL: Post-traumatic headache. *Curr Pain Headache Rep* 2007; 11:396-400.
100. De Kruijk JR, et al: Prediction of post-traumatic complaints after mild traumatic brain injury: Early symptoms and biochemical markers. *J Neurol Neurosurg Psychiatry* 2002; 73:727-732.
101. Amerasinghe N, Aung T: Angle-closure: Risk factors, diagnosis and treatment. *Prog Brain Res* 2008; 173:31-45.
102. Hedges TR: An ophthalmologist's view of headache. *Headache* 1979; 19:151-155.
103. Evans RW: Complications of lumbar puncture. *Neurol Clin* 1998; 1683-1105.
104. Dougados M, et al: Efficacy of celecoxib, a cyclooxygenase 2–specific inhibitor, in the treatment of ankylosing spondylitis: A six-week controlled study with comparison against placebo and against a conventional nonsteroidal antiinflammatory drug. *Arthritis Rheum* 2001; 44:180-185.
105. Richman JM, et al: Bevel direction and postdural puncture headache: A meta-analysis. *Neurologist* 2006; 12:224-228.
106. Thomas SR, Jamieson DR, Muir KW: Randomised controlled trial of atraumatic versus standard needles for diagnostic lumbar puncture. *BMJ* 2000; 321:986-990.
107. Halker RB, et al: Caffeine for the prevention and treatment of postdural puncture headache: Debunking the myth. *Neurologist* 2007; 13:323-327.
108. Duffy PJ, Crosby ET: The epidural blood patch. Resolving the controversies. *Can J Anaesth* 1999; 46:878-886.
109. Attia J, Hatala R, Cook DJ, Wong JG: The rational clinical examination. Does this adult patient have acute meningitis? *JAMA* 1999; 282:175-181.
110. Gladstone J, Bigal ME: Headaches attributable to infectious diseases. *Curr Pain Headache Rep* 2010; 14:299-308.
111. Price RW: Neurological complications of HIV infection. *Lancet* 1996; 348:445-452.
112. Sjaastad O, Fredriksen TA, Pfaffenrath V: Cervicogenic headache: Diagnostic criteria. *Headache* 1990; 30:725-726.
113. Dodick D, Freitag F: Evidence-based understanding of medication-overuse headache: Clinical implications. *Headache* 2006; 46(Suppl 4):S202-S211.
114. Hackett PH, Roach RC: High-altitude illness. *N Engl J Med* 2001; 345:107-114.
115. Harris MD, Terrio J, Miser WF, Yetter JF 3rd: High-altitude medicine. *Am Fam Physician* 1998; 57:1907-1914, 1924-1906.
116. Calabrese LH, Dodick DW, Schwedt TJ, Singhal AB: Narrative review: Reversible cerebral vasoconstriction syndromes. *Ann Intern Med* 2007; 146:34-44.
117. Chen SP, Fuh JL, Wang SJ: Reversible cerebral vasoconstriction syndrome: An under-recognized clinical emergency. *Ther Adv Neurol Disord* 2010; 3:161-171.

www.ketabpezeshki.com 66485457-66963820

118. Grosberg BM, Solomon S, Lipton RB: Nummular headache. *Curr Pain Headache Rep* 2007; 11:310-312.
119. Bagheri SC, Farhidvash F, Perciaccante VJ: Diagnosis and treatment of patients with trigeminal neuralgia. *J Am Dent Assoc* 2004; 135:1713-1717.
120. Cruccu G, et al: AAN-EFNS guidelines on trigeminal neuralgia management. *Eur J Neurol* 2008; 151013-151028.
121. Cutrer FM, Boes CJ: Cough, exertional, and sex headaches. *Neurol Clin* 2004; 22:133-149.
122. Pascual J, Iglesias F, Oterino A, Vázquez-Barquero A, Berciano J: Cough, exertional, and sexual headaches: An analysis of 72 benign and symptomatic cases. *Neurology* 1996; 46:1520-1524.

www.ketabpezeshki.com 66485457-66963820

Chapter 104

Delirium and Dementia

Jeffrey P. Smith and Jennifer Seirafi

PERSPECTIVE

Emergency physicians are frequently presented with patients exhibiting neurobehavioral abnormalities. These can be a harbinger of a serious medical condition, and critical decisions must be made expeditiously about diagnostic evaluation, therapeutic intervention, and disposition. The first critical action is to recognize the presence of the neurobehavioral abnormality. The second is to distinguish delirium from dementia or some other neuropsychiatric condition.

In the past, terms such as acute confusional state, sundowning, and organic brain syndrome have been used to describe a host of abnormal cognitive states that can be observed in the emergency setting. These terms have loosely defined a group of neurobehavioral disorders that are caused by a physiologic disturbance. Organic brain syndrome is a nebulous term that the *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition, text revision) eschews because the "organic" connotation implies that so-called functional mental disorders are without a biologic basis.[1]

Several key features best distinguish delirium from dementia: the time course of disease evolution, the presence of autonomic system involvement, the level of consciousness, and the presence of an underlying disease processes. Delirium is characterized by a fluctuating level of neurobehavioral disturbance typically progressing during minutes to hours to days. Delirium is a direct consequence of an acute systemic or central nervous system (CNS) stressor. Dementia, on the other hand, tends to follow a more gradual course, with evolution during months to years. Although patients with dementia exhibit confusion, disturbance in level of consciousness usually is not a feature, and manifestations of autonomic nervous system abnormalities are minimal or absent.

The evaluation of patients who present to the emergency department (ED) with a disturbance of neurobehavioral state is best conducted in accordance with the following basic guidelines:

1. The first step is to determine whether this state represents delirium or dementia. The clinical findings may be subtle, and establishment of the diagnosis can be challenging, especially because delirium may be superimposed on dementia and dementia remains an independent risk factor for delirium.[2,3] Early symptoms and signs may go unrecognized unless an adequate history is obtained from the patient, family members, and caregivers. A careful examination must include memory and cognitive assessment with a mental status screening examination.
2. Supportive care must be provided. This care may range in extent from aggressive airway and cardiovascular support to pharmacologic or physical restraint to simply placing the patient in a quiet room with appropriate environmental support.
3. A diligent search must be initiated for the underlying precipitating stressors in patients presenting with delirium.

DELIRIUM

Definition and Background

Delirium is a syndrome that can be defined as an acute or subacute state of cognitive dysfunction caused by an underlying physiologic condition. Terms that have been used interchangeably with delirium include acute organic brain syndrome, acute confusional state, reversible cerebral dysfunction, metabolic encephalopathy, toxic encephalopathy, and febrile delirium. The word *delirium* is derived from the Latin *delirare,* which literally means "to go out of the furrow" (in a more modern sense, "to derail"), but it is used figuratively to mean "crazy" or "deranged."

Several key features are necessary for a diagnosis of delirium (Box 104-1). Patients with delirium have disturbances in consciousness, memory, cognition, and perception. These disturbances tend to develop during a short time (hours to days). The disturbance in consciousness may be manifested initially as an inability to focus attention. The fluctuating course of symptoms and inattention are the hallmarks of delirium. Deficiencies in cognition may be manifested by disorientation and memory deficits. Perceptual disturbances include hallucinations and delusions. The delirious patient may be somnolent or agitated, and the thought process may range from mildly disturbed to grossly disorganized. The clinical presentation may be subdued or explosive. The patient's sleep-wake cycle may be altered or reversed; agitation often is present during the night. Historically, delirium referred to a hyperactive state marked by agitation and emotional lability (e.g., delirium tremens). An important point, however, is that delirium has several psychomotor subtypes: hyperactive (mania), hypoactive (depressed), and mixed type.[4]

The exact incidence of delirium in the overall ED population is unknown. However, the prevalence of delirium among elders who present to the ED is approximately 10 to 20%.[5] Geriatric patients are at particularly high risk for the development of delirium. Advanced age, dementia, and underlying medical illness are strongly associated with delirium. Multiple medications, drugs, and alcohol also are associated with delirium.[6] Severe psychological stress and sleep deprivation may facilitate the development of delirium.

www.ketabpezeshki.com 66485457-66963820

Box 104-1 Diagnostic Criteria for Delirium

Four Key Characteristics
- Clouding of consciousness with reduced ability to focus, sustain, or shift attention
- A cognitive change (e.g., memory deficit, disorientation, language disturbance) or perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia
- Development of the disturbance during hours to days, with a tendency to fluctuate in the course of the day
- Evidence from the history, physical examination, or laboratory studies that the disturbance is caused by a general medical condition, medication or other substance exposure, substance withdrawal, or multiple etiologic disorders

Additional features may include psychomotor behavioral disturbances such as hypoactivity, hyperactivity with increased sympathetic activity, and emotional lability.

Modified from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text rev. Washington, DC, American Psychiatric Association, 2000.

Table 104-1 Causes of Delirium: "I Watch Death" Mnemonic

CAUSE	FORM
Infectious	Sepsis, encephalitis, meningitis, syphilis, central nervous system abscess
Withdrawal	Alcohol, barbiturates, sedative-hypnotics
Acute metabolic	Acidosis, electrolyte disturbance, hepatic or renal failure, other metabolic disturbances (↑ or ↓ glucose, magnesium, calcium)
Trauma	Head trauma, burns
CNS disease	Hemorrhage, stroke, vasculitis, seizures, tumor
Hypoxia	Acute hypoxia, chronic lung disease, hypotension
Deficiencies	Vitamin B_{12}, hypovitaminosis, niacin, thiamine
Environmental	Hypothermia, hyperthermia, endocrinopathies (diabetes, adrenal, thyroid)
Acute vascular	Hypertensive emergency, subarachnoid hemorrhage, sagittal vein thrombosis
Toxins or drugs	Medications, street drugs, alcohol, pesticides, industrial poisons (e.g., carbon monoxide, cyanide, solvents)
Heavy metals	Lead, mercury

Modified from Wise MG: Delirium: Differential diagnosis for delirium: Critical items (I WATCH DEATH). In: Yudofsky SC, Hales RE (eds): The American Psychiatric Press Textbook of Neuropsychiatry, 2nd ed. Washington, DC, American Psychiatric Publishing, 1992.

Pathophysiology

At a cellular level, delirium is the result of widespread alteration in cerebral metabolic activity, with secondary deregulation of neurotransmitter synthesis and metabolism. Both the cerebral cortex and the subcortical structures are affected, producing changes in arousal, alertness, attention, information processing, and the normal sleep-wake cycle.

Although the exact pathophysiologic process is not well understood, multiple neurotransmitters have been implicated in causing delirium. One theory is that delirium is associated with a derangement of central cholinergic transmission. Serum anticholinergic activity is increased, and low levels of acetylcholine are seen in older patients with delirium.[7] Increased serotonin levels have been found in hepatic encephalopathy, serotonin syndrome, sepsis, and psychedelic drug ingestion.[8] Some of the disturbances that occur in delirium are deficiencies of substrates for oxidative metabolism (e.g., glucose, oxygen); disturbances of ionic passage through excitable membranes; increase in cytokines; imbalance of normal noradrenergic, serotoninergic, dopaminergic, and cholinergic homeostasis; and, in some cases, synthesis of false neurotransmitters.[9] Drugs and exogenous toxins can produce delirium through direct effects on the CNS. Although the limbic system appears to be particularly vulnerable to the effects of these drugs, the cerebral hemispheres and the brainstem also can be profoundly affected.

Tricyclic antidepressants can cause delirium by cholinergic inhibition; sedative-hypnotics depress activity in the CNS, especially in the limbic system, thalamus, and hypothalamus. Narcotics affect CNS activity primarily by interacting with various opioid receptor sites. Depending on the opioid receptor type affected, the physiologic response may be analgesia, euphoria, sedation, dysphoria, delusions, or hallucinations. Psychedelic drugs probably act as agonists at serotonin receptor sites. Phencyclidine (PCP) inhibits reuptake of dopamine, norepinephrine, serotonin, and α-aminobutyric acid and also may act as a false neurotransmitter.

Hyperthermia and hypothermia can cause delirium, probably as a result of changes in the cerebral metabolic rate. In hypothermia, cerebral metabolism decreases 6 to 7% for each 1° C decrease in temperature from 35 to 25° C. In hyperthermia, cellular damage with uncoupling of oxidative phosphorylation begins to occur at temperatures higher than 42° C. Patients suffering from heatstroke may have cerebral edema, degenerative neuronal changes (especially involving Purkinje cells of the cerebellum), and petechiae in the walls of the third and fourth ventricles. Delirium occurring at temperatures below 40° C is multifactorial in origin and not caused solely by increased core temperature.

Delirium caused by metabolic abnormalities, such as hyponatremia, hypernatremia, hyperosmolarity, hypercapnia, and hyperglycemic disorders, is associated with a variety of metabolic disturbances at the neuronal and astrocyte levels. Such disturbances may include impairments in energy supplies, changes in resting membrane potentials, changes in cellular morphology, and changes in the brain water volume.

Most patients with delirium have reduced cerebral metabolic activity. This reduction in cerebral metabolism is reflected by a decrease in the frequency of background electrical activity on the electroencephalogram (EEG). Exceptions are hyperthermia, sedative-hypnotic withdrawal, delirium tremens, and certain drug-induced states, in which the cerebral metabolism is either normal or increased.

Etiology

The causes of delirium are legion (Table 104-1). Within the geriatric population, medications are a common cause of delirium, whereas drugs (including ethanol) are the most common cause of delirium in the younger adult population. Acute cognitive dysfunction may be secondary to drug overdose, withdrawal syndromes, and adverse or idiosyncratic reactions.

The list of commonly prescribed drugs causing delirium is extensive and includes antibiotics (antifungal, antimalarial, and antiviral agents; numerous antibacterial agents, including the quinolones and macrolides), anticholinergic drugs (antihistamines, antispasmodics, muscle relaxants, tricyclic antidepressants), anticonvulsants, anti-inflammatory agents (corticosteroids, salicylates, and other nonsteroidal anti-inflammatory drugs), various cardiovascular medications (beta-blockers, antidysrhythmics, antihypertensives, cardiac glycosides), sympathomimetics (phenylpropanolamine), sedative-hypnotics, narcotics (transdermal

www.ketabpezeshki.com 66485457-66963820

fentanyl [Duragesic], morphine sulfate [Roxanol], hydromorphone HCl [Dilaudid], oxycodone HCl [OxyContin]), miscellaneous drugs (aminophylline, cimetidine, lithium, chlorpropamide), over-the-counter medications with anticholinergic properties, and caffeine-containing products.[6]

Many "street drugs" with significant abuse potential, such as hallucinogens, amphetamines, PCP, cocaine, and methylenedioxymethamphetamine (MDMA, ecstasy), can cause delirium, as can intoxication with any of the alcohols (e.g., ethanol, methanol, ethylene glycol).

Exposure to industrial chemicals (e.g., carbon disulfide, heavy metals, insecticides, cyanide, carbon monoxide) can cause a wide range of symptoms that include acute delirium. In addition, ingestion of certain plants (e.g., nutmeg, foxglove, jimsonweed, psilocybin-containing mushrooms) can cause delirium.

Delirium can be one of the protean manifestations of a metabolic or nutritional abnormality. The most common metabolic disorder causing acute cognitive changes is diabetes mellitus. Hypoglycemia is the most common and readily reversible cause of acute confusion in the diabetic patient. Other causes of acute cognitive impairment in the diabetic patient are hyperglycemia, hyperosmolarity, and acid-base abnormalities. Severe metabolic abnormalities, including electrolyte disturbances, hypoxemia, hepatic insufficiency, renal insufficiency, and dysfunction of various endocrine glands (hyperthyroidism, hypothyroidism, Cushing's syndrome, hyperparathyroidism, and other endocrine disorders), can cause delirium. Deficiency of niacin, pyridoxine, folic acid, or vitamin B_{12} may be associated with an acute confusional state.

Delirium can be a prominent feature of any systemic infection, particularly in the very young, elders, and immunocompromised patients. Infectious and host factors together determine the degree of cognitive impairment. Extracranial infections that are associated with delirium include sepsis (particularly gram-negative sepsis), subacute bacterial endocarditis, Legionnaires' disease, Rocky Mountain spotted fever, malaria, typhoid fever, toxic shock syndrome, and several viral infections including influenza. Patients with CNS infections, including meningitis, encephalitis, and intracerebral abscess, may have acute cognitive dysfunction.

Another less common cause of delirium is CNS infarction in the distribution of the nondominant middle cerebral artery and the posterior cerebral artery. In patients who have a collagen vascular disease with CNS vasculitis, neuropsychiatric manifestations, including acute delirium, may be prominent. Paraneoplastic syndromes may include encephalopathy, with symptoms of confusion, catatonia, and dementia.

Patients who are immunocompromised may have multiple and unusual causes of acute delirium. Patients with immunosuppression secondary to malignant disease, drugs, or human immunodeficiency virus type 1 (HIV-1) infection may have acute brain dysfunction secondary to infection, complications of drug therapy, or the underlying disease itself.

Acute confusional states have been reported to be a more common herald of the onset of physical illness in the elderly than are fever, pain, and tachycardia.[2,3,10] Factors that predispose elders to delirium include the effects of aging on the brain, reduced capacity for homeostatic regulation, impaired vision and hearing, and age-related changes in the pharmacokinetics and pharmacodynamics of drugs.[11] The etiology of delirium in elders is usually multifactorial.

Clinical Features

The clinical manifestations of delirium are as variable as the causes. The clinical presentation can be so subtle as to go unrecognized or may be dramatic enough to disrupt the entire ED. The natural history of a patient's delirium can progress from apathy to marked agitation in the course of hours (see Box 104-1). Nonspecific prodromal symptoms such as anxiety, restlessness, and insomnia typically emerge during hours to days.

Key aspects of cognitive impairment should become evident during a careful history and examination. Disturbance in attention is central to the diagnosis of delirium. The patient is easily distractible and has difficulty remaining focused on a particular topic or interacting with a single person. Disorientation often accompanies the deficit inattention but is not an invariable feature. The patient usually is disoriented with respect to time and occasionally to place; in extreme cases, disorientation to person also may be noted. Delirium, however, may be present in a patient who is completely oriented to person, place, and time. A mental status examination that consists solely of questions that assess orientation will not detect delirium in these instances.

The patient with delirium always has some degree of memory impairment, with the greatest impact on short-term memory. Thought processes and speech may be disorganized. Disturbance in the sleep-wake cycle often occurs early in the course of delirium. Perceptual disturbances, including misperception of the environment, poorly formed delusions, and hallucinations, are common. The delirious patient may experience visual, auditory, tactile, gustatory, or olfactory hallucinations, in contrast to patients with acute functional psychosis, who typically experience only auditory hallucinations. In addition, the delirious patient has a reduced capacity to modulate fine emotional expression and may demonstrate extreme emotional lability.

The cognitively impaired patient may provide an unreliable history. Valuable information often can be obtained from family, friends, and out-of-hospital personnel. Specific inquiry should be made about the patient's current medical problems and previous medical history, including diabetes, hypertension, kidney or liver disease, and any neurologic or psychiatric problems. It is important to determine whether the patient is immunosuppressed or has risk factors for immunosuppression. A detailed medication history, including the use of prescribed and over-the-counter medications, dietary supplements, and alcohol or other substances, is essential. Out-of-hospital personnel should be able to provide information about the home environment, medication bottles belonging to the patient or found near the patient, and the possibility of trauma.

The physical examination should begin with a careful assessment of vital signs including pulse oximetry and a pain assessment. The delirious patient often exhibits abnormalities on such evaluation, including elevated or decreased pulse, blood pressure, respiratory rate, and temperature. The examination includes assessment of the head for signs of trauma and the pupils for symmetry of light reflex; funduscopic examination for hemorrhage or papilledema; examination of the ears for hemotympanum; evaluation of the neck for nuchal rigidity, bruits, and thyroid enlargement; assessment of the heart and lungs; evaluation of the abdomen for organomegaly and ascites; and examination of the extremities for cyanosis. The skin should be carefully examined for rashes, petechiae, ecchymosis, splinter hemorrhages, and needle tracks. The neurologic examination includes assessment of the cranial nerves, motor strength, sensation, and presence of abnormal movements (e.g., tremor, asterixis, myoclonus). The reflexes are assessed for symmetry and presence of hyperreflexia or hyporeflexia. Findings that typically suggest either a metabolic or a structural neurologic problem are not necessarily specific for that category of disorder. For example, asterixis is a hallmark of metabolic encephalopathy but can be seen in focal brain disease. Likewise, focal neurologic signs that typically are associated with structural CNS lesions also can be present in various metabolic abnormalities, such as hypoglycemia, hyperglycemia, hepatic encephalopathy, uremia, and hypercalcemia.

www.ketabpezeshki.com 66485457-66963820

The physical examination is not often helpful in determining the specific drug or class of drugs causing acute cognitive impairment. The one exception to this rule is toxidromes, which are constellations of signs and symptoms characteristic of intoxication with certain drugs or classes of drugs (see Chapter 147).

A brief mental status examination should be performed in all patients thought to have acute brain dysfunction. Although the concept is rather obvious, few physicians proceed beyond questions about the patient's orientation to person, place, and time when assessing mental status. Failure to diagnose subtle forms of delirium when they are present is directly related to omission of mental status testing.[12]

Several standardized tools for assessment of mental status have been successfully applied in the ED.[12-14] Mental status testing includes assessment of orientation, memory, attention, and concentration; several tests also incorporate assessments of constructional tasks, spatial discrimination, arithmetic ability, and writing. Cognitive functioning can be rapidly assessed in approximately 7 to 10 minutes. Memory assessment requires testing of the patient's ability to repeat short series of words or numbers (immediate recall), to learn new information (short-term memory), and to retrieve previously stored information (long-term memory). Constructional apraxia is assessed by having the patient perform tasks such as drawing interlocking geometric figures or clock faces and connecting dots. Dysnomia (inability to name objects correctly) and dysgraphia (impaired writing ability) are two of the most sensitive indicators of delirium. Almost all acutely confused patients exhibit writing impairments, including spatial disorganization, misspelling, and tremor.[13,15]

No single bedside cognitive test that can be administered quickly is ideal. The Mini-Mental State Examination (MMSE) developed by Folstein and colleagues has been validated more than any other test and most frequently is recommended as a rapid screening tool.[10,13,15,16] For hospitalized patients, this test has a sensitivity of 87% and a specificity of 82% for detection of organic brain syndrome. Some investigators report slightly better results when the test is modified and age is added as a variable in the analysis.[16] The MMSE does not measure executive function and is insensitive for detection of early signs of mild cognitive impairment (without dementia) or early dementia.[17]

The MMSE consists of a short series of questions that test orientation, registration (memory), attention, calculation, recall, and language (Fig. 104-1). The time for the test to be administered can be reduced to 5 minutes by elimination of the writing and drawing components with only a modest reduction in sensitivity. The registration section tests both immediate and short-term memory; the recall section also assesses short-term memory. The ability to recall two of three objects has 81% sensitivity and 74% specificity for exclusion of organic brain syndrome. Asking the patient to subtract "serial sevens" backward from 100 assesses attention, concentration, and arithmetic ability. This test is specific but not sensitive for absence of an organic brain syndrome; up to 40% of nondelirious, nondemented people fail to perform the tasks of this test correctly, reflecting limitations due to language ability and education. A total score of 23 or less is considered markedly abnormal and indicates an organic brain syndrome. As a general rule, patients with mild cognitive impairment have a score of 18 to 26 of 30, those with moderate impairment have a score of 10 to 18, and those with severe impairment have a score of less than 10.

The Quick Confusion Scale represents another attempt to quantify the attention aspects of mental status (see Chapter 17, Fig. 17-2). It has significant correlation with the MMSE, can be administered more quickly, and does not require constructional tasks.[18] Another useful diagnostic tool is the Confusion Assessment Method; it has a sensitivity of 93 to 100% and specificity of 90 to 95%.[19] This simple tool has four key features used for screening of delirium: acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. For a definitive diagnosis of delirium, the first two features and one of the last two must be present. It has proved to be a valuable tool because of its ease and interobserver reliability. In addition, it has been shown to be more sensitive than clinical impression alone.[18,20] The Six-Item Screener is another brief test of cognition that was found to be 94% sensitive and 86% specific in identifying disturbance of cognition in older patients.[15]

All bedside tests of cognition have limitations and can miss mild degrees of impairment. The patient's level of education and general intelligence can substantially affect the outcome. Furthermore, a single bedside test reflects a patient's cognitive functioning at only one point in time. For a diagnosis of delirium (or dementia) to be established, an essential criterion is a documented decline from the patient's baseline level of cognitive functioning,

Maximum Score	Orientation
5	What is the (year)(season)(date)(day)(month)?
5	Where are we (city)(state)(country)(hospital)(floor)?
	Registration
3	Name three objects: one second to say each. Ask the patient for all three after you have said them. Give one point for each correct answer. Repeat them until all three are learned. Count trials and record number.
	Attention and calculation
5	Serial sevens backwards from 100 (stop after five answers). Alternatively, spell WORLD backward.
	Recall
3	Ask for the three objects repeated above. Give one point for each correct answer.
	Language and praxis
2	Show a pencil and watch, and ask subject to name them.
1	Ask the patient to repeat the following: "no ifs, ands, or buts."
3	Three-stage command: "Take this paper in your right hand, fold it in half, and put it on the floor."
1	Read and obey the following: "Close your eyes." (Written on a piece of paper.)
1	Write a sentence. (Must contain a noun and a verb and be sensible. Ignore grammar and punctuation.)
1	Copy this design (interlocking pentagons). Must contain all angles and two must intersect.

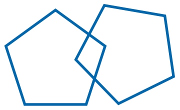


Figure 104-1. Mini-Mental State Examination. (Adapted from Folstein MF, Folstein SE, McHugh PR: "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189, 1975.)

www.ketabpezeshki.com 66485457-66963820

and the sensitivity of these tests increases when they are repeated over time.

Diagnostic Evaluation and Ancillary Studies

Some reversible causes of delirium can be diagnosed by a number of basic, readily available tests. The following laboratory tests can be helpful in evaluation of the delirious patient: a complete blood count (CBC; hemoglobin, leukocyte count with differential, platelet count, and mean corpuscle volume), serum electrolyte values, glucose concentration, calcium concentration, and urinalysis. The CBC may suggest unusual but potentially treatable abnormalities, such as thrombotic thrombocytopenic purpura, megaloblastic anemia, hyperviscosity from myelogenous leukemia, and unsuspected infection. The anion gap should be determined in all patients with altered mental status. An elevated anion gap (>15 mEq/L) may indicate the presence of unmeasured anions, such as sulfate in renal failure; keto acids in diabetic or alcoholic ketoacidosis; lactate in postictal states or associated with hypotension; and exogenous toxins, such as ethylene glycol, methanol, and salicylates. A pulse oximetry measurement should be obtained in all patients to screen for hypoxemia, and an arterial blood gas analysis is warranted in those patients at risk for respiratory failure with carbon dioxide retention. Suspected occult infection warrants urinalysis and chest radiography. In elders, an electrocardiogram should be obtained to exclude a silent acute coronary syndrome. Ammonia level should be considered in patients with cirrhosis, ascites, or asterixis. Despite these diagnostic evaluations, no cause is found for delirium in up to 16% of patients.[6]

Toxicology screens are overused as diagnostic tests and have limited usefulness in the evaluation of most patients with delirium. Additional laboratory studies outside the scope of the ED evaluation that may be appropriate when the cause of delirium remains unknown include thyroid function studies, vitamin B_{12} and folic acid assays, rapid plasma reagin test, measurement of serum antinuclear antibodies, urinary porphobilinogen assay, and screens for heavy metals.

Patients with a history of trauma (especially those taking anticoagulant medications), previous neurosurgical procedures, immunodeficiency, or focal neurologic signs require a head computed tomography (CT) scan to detect structural lesions causing delirium. Early infarctions, small brainstem lesions, meningitis or encephalitis, closed head injuries, sagittal vein thrombosis, and small isodense subdural hematomas may be missed on a CT scan. In addition, approximately 2 to 8% of acute subarachnoid hemorrhages are not detected by head CT scan and require lumbar puncture for diagnosis. The role of magnetic resonance imaging (MRI) in the evaluation of the delirious patient has not been clearly established. MRI is superior to CT for detection of small intercerebral and brainstem lesions, small brain contusions, certain encephalitides, and abnormalities of white matter (e.g., leukoencephalopathy). MRI perfusion scans are more sensitive in detecting an acute vascular event.

Cerebrospinal fluid (CSF) analysis is an essential part of the evaluation in selected patients with delirium. In patients with fever and cognitive dysfunction, even without meningismus, a lumbar puncture should be performed to rule out meningitis. This test is particularly important in the very young, elders, and immunocompromised patients, who are less likely to show classic signs of meningitis. Patients with focal neurologic deficits, immunocompromised states, or evidence of increased intracranial pressure should undergo head CT before lumbar puncture, and they should receive antibiotics before the CT scan.

Although it is rarely practical in the ED setting, the EEG can be a valuable diagnostic tool in determining the presence of delirium. Bilateral diffuse symmetrical electroencephalographic abnormalities are a relatively consistent feature of delirium. In most cases, the changes consist of a nonspecific generalized slowing from the baseline activity and can be useful in distinguishing delirium from other neurobehavioral abnormalities.

Table 104-2 Comparison of Delirium and Acute Psychosis

CHARACTERISTIC	DELIRIUM	ACUTE PSYCHOSIS
Onset	Acute	Acute
Vital signs	Typically abnormal (fever, tachycardia)	Normal
Prior psychiatric history	Uncommon	Common
Course	Rapid, fluctuating	Stable
Psychomotor activity	Variable	Variable
Involuntary activity	Possible asterixis, tremor	Absent
Cognition function		
Orientation	Usually impaired	Occasionally impaired
Attention	Globally impaired	May be disorganized
Concentration	Globally impaired	Impaired
Hallucinations	Visual, visual and auditory	Primarily auditory
Delusions	Transient, poorly organized	Systematized
Speech	Pressured, slow, possibly incoherent	Usually coherent
Course	Typically resolves	Responds to therapy, recurrence common

Differential Diagnosis

Considerations in the differential diagnosis for apparent delirium include functional psychiatric disorders and dementia. Depression, mania, paranoia, and schizophrenia all may resemble delirium. Several clinical features are helpful in distinguishing between organic and functional syndromes (Table 104-2).

Dementia, like delirium, is characterized by global cognitive impairment. Unlike delirium, dementia tends to be an insidious process that develops during months to years with little fluctuation during hours or days. Typically, the patient's vital signs are normal. Dementia occurs primarily in the elderly. A point worthy of emphasis is that patients with dementia are five times more likely to develop delirium.[2,3,5,6]

Management

Delirium constitutes a medical emergency. The outcome depends on the cause of the delirium, the patient's overall health status, and the timeliness of treatment. The presence of hyperactive or hypoactive delirium has some prognostic significance.[2] The hypoactive form of delirium tends to be more common in elders and carries a worse overall prognosis, perhaps because it often goes unrecognized. Acute recognition and management of delirium in elders are essential because delirium in this population is associated with increased risk of long-term institutionalization, development of dementia, and increased overall mortality.[21]

Patients who present with acute delirium should be screened quickly for readily reversible causes, such as hypoglycemia, hypoxia, and narcotic overdose. Acute intoxication from a number of drugs or chemical agents, including tricyclic antidepressants, ethylene glycol, cholinesterase inhibitors, anticholinergic agents, carbon monoxide, and cyanide, requires prompt attention. Although supportive measures are the mainstay of treatment in

www.ketabpezeshki.com 66485457-66963820

most poisonings and intoxications, most of these toxins have specific antidotes.

Other conditions requiring immediate medical intervention include infections. Patients with signs of acute meningitis or sepsis should receive antibiotics within 30 minutes of arrival to the ED along with appropriate fluid resuscitation. Other emergent conditions that may be manifested with delirium and necessitate immediate intervention include severe hypothermia, hyperthermia, and CNS vascular conditions, including hypertensive encephalopathy, acute epidural or subdural hematoma, subarachnoid hemorrhage, and stroke. Patients with Wernicke's encephalopathy require immediate treatment with 100 mg of intravenous thiamine, with titration of additional doses until the ophthalmoplegia resolves. Resistance to thiamine may result from hypomagnesemia because magnesium is a cofactor for thiamine transketolase. Glucose administration in patients with severe thiamine deficiency may precipitate Wernicke's encephalopathy. The specific treatment of delirium tremens (and other alcohol withdrawal syndromes) involves the substitution of a long-acting drug that is cross-tolerant with the alcohol. Benzodiazepines are the agents of choice to induce sedation. Delirium secondary to dehydration, hyponatremia, hypernatremia, hypercalcemia, and hepatic or renal disease gradually resolves during hours to days with appropriate treatment.

Supportive care for all patients with delirium includes provision of an appropriate environment with adequate lighting, minimization of sensory overload, placement of the patient in an area that can be easily observed by staff, and use of stretcher side rails to prevent falls. Use of "sitters" may be necessary because patients may require constant supervision. It is important to protect the patient from self-harm or from injuring other patients or staff. In cases of hyperactive delirium, the patient may need to be initially restrained physically until pharmacologic control takes effect. Restraints should be viewed only as a temporizing action because they can increase agitation and the risk of injury to the patient. Physical restraints in agitated patients have been associated with significant injuries and even death by asphyxiation and are not a substitute for pharmacologic control.[22,23]

Pharmacologic restraint has become the cornerstone of behavioral management. Classes of drugs that have been used for management of delirium include the antipsychotics and benzodiazepines. The ideal sedating drug should have the following characteristics: low toxicity with minimal anticholinergic effects, ease of administration, short half-life, minimal effects on the cardiovascular and respiratory systems, and no effect on the seizure threshold. Antipsychotic medications used to treat delirium include the butyrophenones and the newer atypical antipsychotic agents.[24-29] Although no one drug is ideal, the butyrophenones, specifically haloperidol (Haldol), are considered the agents of choice for control of agitation in acute delirium on the basis of extensive clinical experience.[23,24] Increasing evidence indicates that compared with haloperidol, the newer atypical antipsychotic agents (risperidone, olanzapine, ziprasidone, aripiprazole) may have equal or better efficacy and fewer side effects (especially akathisia and dystonia) for management of acute agitation.[25-29] In addition, the atypical antipsychotic agents received a black box warning from the U.S. Food and Drug Administration (FDA) in 2005 for use in elderly demented patients with agitation because of the increased mortality noted in this special population of patients (although this is associated with long-term use).[30] Phenothiazines and droperidol, a butyrophenone pharmacologically similar to haloperidol, can cause orthostatic hypotension, lower the seizure threshold, and have anticholinergic effects, making them unacceptable for the treatment of delirium. The use of droperidol for management of agitation has been significantly curtailed since the FDA gave this drug a black box warning because of the association of droperidol use with QT prolongation and torsades de pointes; however, many clinicians think that the warning is unjustified.[31,32] The opioids morphine and meperidine (Demerol) are capable of inducing dysphoria and can exacerbate respiratory depression and hepatic encephalopathy and should not be used for behavior control in the agitated delirious patient.

Benzodiazepines are the drugs of choice for management of delirium caused by withdrawal from alcohol or sedative-hypnotics, for which a long duration of action is desirable. Lorazepam, a shorter-acting benzodiazepam that undergoes glucuronide conjugation with rapid renal clearance, is the preferred agent for treatment of withdrawal symptoms. In general, they are not indicated in the management of symptoms of delirium caused by other conditions.[33] Although limited data exist, the benzodiazepines may be helpful with ingestion of stimulants such as hallucinogens, cocaine, and PCP. The benzodiazepine diazepam (Valium) should be avoided as an agent for treatment of agitated behavior in most delirious patients because of its long half-life, respiratory depressant effect, and risk of drug accumulation with repeated dosing. Benzodiazepines can worsen confusion, and use of this class of drugs is an independent risk factor for delirium, especially in the elderly.[34,35]

As the primary drug for control of hyperactive delirium, haloperidol is a potent dopamine-blocking medication with virtually no anticholinergic and minimal hypotensive effects. The main effect of the drug acutely is tranquilization. The drug can be easily titrated with intravenous administration. The incidence of extrapyramidal side effects in patients receiving intravenous haloperidol for management of delirium with agitation is relatively low. Studies of the acute administration of haloperidol report an 8 to 30% incidence of extrapyramidal side effects, with akathisias being most common and acute dystonia occurring in less than 10% of patients.[36] Haloperidol can prolong the QTc interval, but this effect is clinically insignificant in most patients and does not require a pretreatment electrocardiogram. Caution is warranted with use of this agent in patients taking medications that prolong the QTc (e.g., class IA and class III antiarrhythmics, certain antibiotics, inhibitors of the cytochrome P_{450} system) and in patients with acute coronary ischemia, uncompensated congestive heart failure, or hepatic dysfunction.[37] Dosing should vary with the patient's level of agitation, age, weight, and response to treatment. In most patients, 5 to 10 mg intravenously or intramuscularly is well tolerated as an initial dose, and levels can be titrated as needed. Higher doses may be required for younger patients. Daily doses in excess of 200 mg for 15 consecutive days have been given safely to agitated patients in the critical care setting.[35] For elders, a lower initial dose of 0.50 to 1.0 mg is recommended.[38]

Several well-controlled studies have shown that the combination of haloperidol and lorazepam (given by either the intramuscular or intravenous route) can achieve more rapid control of agitated behavior than is possible with haloperidol alone and can reduce the already low incidence of extrapyramidal neuromuscular symptoms.[39,40]

The atypical antipsychotics can be used acutely for management of agitation. These drugs have multiple mechanisms of action including antagonism of alpha$_2$-adrenergic, serotonin, muscarinic, dopamine, and histamine receptors. These drugs block the reuptake of dopamine and serotonin, and the newer drugs also have dopamine agonist effects (aripiprazole).[41-44] Compared with haloperidol, several of these atypical agents (ziprasidone, risperidone, clozapine, and olanzapine) have been shown in nonrandomized case series to control agitation as effectively with less sedation and fewer extrapyramidal side effects.[41-44] Because of the limited dopamine antagonism effect, atypical antipsychotics are the preferred agent for patients with parkinsonism and agitation. Atypical antipsychotic agents for management of acute agitation have been slow to be adopted in clinical practice because of

www.ketabpezeshki.com 66485457-66963820

the limited studies (no randomized controlled studies in the ED setting) and the significant clinical experience with haloperidol and lorazepam.

It is not possible to obtain informed consent for proposed diagnostic and therapeutic interventions from a patient suffering from delirium. In such cases, implied consent exists when a true emergency is present or clinically suspected because common law recognizes that a reasonable person would want to receive treatment in a true emergency even if impaired awareness at the time of treatment precludes giving of informed consent. Thus it is appropriate to render treatment without informed consent to a patient who lacks decision-making capacity in a life-threatening emergency situation unless an advanced directive is available indicating the patient's desire to forgo treatment.[45]

Disposition

Patients with delirium secondary to acute drug intoxication may be discharged from the ED, provided the process readily reverses itself during a short period of observation and the drug has no potentially serious delayed toxicity. For most patients delirious from metabolic, infectious, or CNS processes, admission to the hospital is necessary for further diagnostic evaluation and treatment. The only readily reversible metabolic problem associated with delirium that can be completely managed in the ED is hypoglycemia.

For most patients without significant underlying medical illness who have delirium, the outcome is full recovery. After an episode of acute delirium, younger patients may experience mild cognitive dysfunction that lasts weeks to months. Geriatric patients, on the other hand, often experience persistent decline in their baseline level of functioning, with loss of at least one activity of daily living after acute delirium.[46] Delirium in elders hospitalized without baseline dementia is associated with higher 1-year mortality rates, higher rates of institutionalization, and a greater risk for development of dementia.[21,47] For elders, an episode of delirium, especially for those with baseline cognitive impairment, can have significant long-term consequences despite good supportive multidisciplinary care.[48]

DEMENTIA

Definition and Background

Dementia is not a single disease entity but rather a highly variable clinical syndrome characterized by a gradually progressive deterioration of cognitive function. As with delirium, potential causes are varied and numerous, and the prognosis depends on the underlying cause. A particular dementia can be classified as either potentially reversible or irreversible. Most patients with dementia have an irreversible disease process; during the past several years, the prevalence of reversible dementia has fallen to between 3 and 10%, with depression, hydrocephalus, subdural hematomas, drugs, and alcohol dependence syndrome accounting for a majority of cases.[49,50] The goals of ED evaluation for suspected dementia are (1) to recognize the signs and symptoms of potentially reversible forms of dementia, (2) to identify the manifestations of acute illness in the demented patient promptly, and (3) to assess the findings for congruency with the normal progression of the irreversible dementias.

In 1907, Alzheimer described the clinical history and postmortem findings for a 50-year-old woman with progressive dementia.[51] For decades, Alzheimer's disease was considered to be an uncommon dementia of younger patients known as presenile dementia. The more common dementia of elders was believed to be caused by atherosclerotic cerebrovascular disease and was referred to as senile dementia. During the past several decades, research has shown that the neuropathologic changes in the two entities are identical. Today, these two categories of primary degenerative dementias are collectively referred to as Alzheimer's disease. Alzheimer's disease accounts for 60% of all dementias; vascular dementia (with or without Alzheimer's disease) accounts for 20%, and the remaining 20% of cases are attributable to more than 50 known causes.[52]

Box 104-2 Diagnostic Criteria for Dementia

A. The development of multiple cognitive deficits manifested by both of the following:
   1. Memory impairment (impaired ability to learn new information or to recall previously learned information)
   2. One (or more) of the following cognitive disturbances:
      a. Aphasia (language disturbance)
      b. Apraxia (impaired ability to carry out motor activities despite intact motor function)
      c. Agnosia (failure to recognize or identify objects)
      d. Disturbance in executive functioning (e.g., planning, organization, sequencing, abstracting)
B. The cognitive deficits cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. The deficits do not occur exclusively during the course of a delirium.

Adapted from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text rev. Washington, DC, American Psychiatric Association, 2000.

Worldwide, approximately 24.3 million persons suffer from dementia, and 4.6 million new cases are diagnosed yearly.[52] The prevalence is approximately 1% at the age of 60 years but doubles every 5 years until it reaches 30 to 50% by the age of 85 years. The National Institutes of Health calculates that by 2030 there will be approximately 10 million people with Alzheimer's disease in the United States.[53,54]

The American Psychiatric Association has defined criteria necessary for the diagnosis of dementia (Box 104-2). There must be impairment in both memory and cognitive function. Several clinical features deserve emphasis. Intellectual impairment must involve both short-term and long-term memory. The cognitive impairment commonly involves abstract thinking, judgment, and other higher cortical functions. The cognitive disturbance must significantly interfere with interpersonal relationships, work, and social activities of the affected person. Although mild decline in intellectual functioning can be part of the normal aging process, gross intellectual impairment and confusion should not be considered part of normal aging. Mild cognitive impairment is distinct from early dementia in that impairment involves mild memory deficits; some believe that mild cognitive impairment is a precursor to the development of Alzheimer's disease.[55]

Dementia can be classified according to the degree of cognitive impairment. Mild dementia implies some impairment of work and social activities; however, the capacity for independent adequate personal hygiene and independent living remains intact. With moderate dementia, independent living is hazardous, and some degree of supervision is necessary. With severe dementia, continual supervision and often custodial care are needed.

Demented patients often have longer hospitalizations for the same acute medical illness compared with those without dementia, and the life expectancy of demented patients is 6 to 8 years less than that of nondemented age-matched control subjects.[56]

Etiology

Dementia may be caused by more than 50 different disease states (Box 104-3). Dementia may be broadly classified as either primary

www.ketabpezeshki.com 66485457-66963820

Box 104-3 Classification of Dementias

Primary Cortical Dementias
Alzheimer's disease
Pick's disease

Primary Subcortical Dementias
Huntington's chorea
Parkinson's disease
Progressive supranuclear palsy

Secondary Dementias
Cerebrovascular disease (multi-infarct dementia)
Drug or toxin induced
Metabolic or electrolyte disturbance
Endocrinopathies
Infectious (intracranial) chronic meningitis, encephalitis, abscess, HIV-1 infection, slow virus infection, neurosyphilis
Nutritional
Intracerebral disorders
Head trauma
Mass effect (tumor, hematoma, abscess)
Hydrocephalus
Psychiatric (pseudodementia)
Other (e.g., collagen vascular disease, paraneoplastic syndrome)

HIV-1, human immunodeficiency virus type 1.

degenerative dementia or secondary dementia; the secondary dementia category includes the potentially reversible dementias. Primary degenerative dementias include Alzheimer's disease, dementia with Lewy bodies, subcortical dementias involving the basal ganglia and thalamus (e.g., progressive supranuclear palsy, Huntington's chorea, Parkinson's disease), and dementia of the frontal lobe type, which includes Pick's disease. Dementia with Lewy bodies, clinically manifested by persistent, well-formed visual hallucinations and prominent extrapyramidal movements, has been found to be the third most common type of dementia. With advanced aging, dementia may have mixed causes, with Alzheimer's disease and vascular dementia frequently coexisting. A smaller percentage of dementias are attributable to causes such as anoxic encephalopathy, hepatolenticular degeneration, tumors, and slow virus infections.

Adverse drug reactions and metabolic abnormalities in patients can cause either an acute delirium or a gradual progressive dementia. Drug-induced dementia occurs primarily in elders and can be caused by various psychotropic drugs, antihypertensive medications, anticonvulsants, anticholinergics, and miscellaneous medications such as L-dopa. Dementia also may be caused by heavy metals and other exogenous agents, such as carbon monoxide, carbon disulfide, and trichloroethylene.

Endocrinopathies that can cause secondary dementia include hypothyroidism, hyperthyroidism, parathyroid disease, Addison's disease, Cushing's disease, and panhypopituitarism. Nutritional deficiencies that cause dementia include thiamine deficiency (Wernicke's syndrome), niacin deficiency (pellagra), vitamin B_{12} deficiency, and folate deficiency. Dementia can be caused by intracranial space-occupying lesions and hydrocephalus. Repetitive intracranial trauma resulting from contact sports can produce a chronic organic brain syndrome without evidence of hematoma or significant contusion (dementia pugilistica).[57,58] Intracranial processes that may eventually lead to a chronic organic brain syndrome include infections with slow viruses, HIV-1 infection, chronic meningitis (tubercular or fungal), brain abscess, and neurosyphilis. In addition to primary HIV-1 CNS infection, toxoplasmosis, cryptococcal meningitis, malignant disease, and infections due to herpesvirus, cytomegalovirus, varicella-zoster virus, and papovavirus (progressive multifocal leukoencephalopathy) can cause progressive cognitive impairment in this compromised group of patients and must be excluded.[59]

Depression in elders may closely mimic dementia. Diagnosis of pseudodementia or depression masquerading as dementia can be difficult and may require therapeutic interventions to confirm the clinical diagnosis of depression. Confounding the issue, depression often coexists with dementia; one study found that 40% of patients with dementia were depressed.[60] Depression, anxiety, and apathy are common in the prodrome and course of Alzheimer's disease.[60,61]

Pathophysiology

Alzheimer's disease is the best-understood dementia and involves several characteristic anatomic, pathologic, and neurochemical changes. The predominant change is cortical atrophy most prominent in the temporal and hippocampal regions caused by progressive synaptic and neuronal loss in the cerebral gray matter. This atrophy generally is followed by loss of white matter (subcortical atrophy). Cell loss does occur with the normal aging process but not to the extent seen in dementia. Not all patients with dementia have gross cerebral atrophy. There is no ischemic component to Alzheimer's disease.

Histologic features characteristic of Alzheimer's disease include extracellular deposition of β-amyloid protein and intracellular neurofibrillary tangles contributing to neuron loss. The abnormal processing of β-amyloid protein probably is central to the pathogenesis of Alzheimer's disease. The neurofibrillary tangles are intraneuronal paired helical filaments composed of the abnormally phosphorylated protein tau, the structural protein involved in the regeneration of neurites. In demented patients, these tangles occur in great numbers throughout the cerebral cortex; only limited numbers can be seen in nondemented elders (primarily in the hippocampus region) and in a variety of other diseases. The density of neocortical tangles correlates with the severity of dementia.[56] Mounting evidence suggests that Aβ protein accumulation triggers activation of cysteine aspartyl proteases (caspases) with cleaving of the tau protein, leading to neurofibrillary tangles and apoptosis. Senile plaques are extracellular lesions composed of degenerating neuronal processes and abnormal β-amyloid protein. These plaques are extensively spread throughout the cerebral cortex and do not correlate with the severity of dementia.[62] Other consistent neurohistopathologic changes in Alzheimer's disease include granulovascular degeneration, Hirano bodies, β-amyloid deposition in the small cortical blood vessels, and neuronal loss in the limbic area.[63]

Many biochemical abnormalities have been described in patients with Alzheimer's disease. A decrease in the neurotransmitter acetylcholine is characteristic. Levels of the enzyme choline acetyltransferase, which synthesizes acetylcholine in the brain, can be reduced to 20% of that in age-matched control subjects.[64]

Several risk factors for Alzheimer's disease are recognized, including advancing age, family history, low education level, hypercholesterolemia, and head trauma. The apolipoprotein E epsilon 4 allele on chromosome 19 has been associated with both familial and sporadic late-onset Alzheimer's disease. Apolipoprotein E is responsible for transporting of the cholesterol and phospholipids necessary for dendritic and synaptic repair. There are several allelic variants, but those homozygous or heterozygous for the E4 variant have an increased risk for the development and expression of the disease.[64] Abnormalities on chromosomes 1 and 14 also have been associated with Alzheimer's disease.

The frontotemporal dementias are less prevalent than Alzheimer's disease and are categorized by a frontal and temporal atrophy caused by cell death.[65] The most common histologic finding in the frontotemporal dementias is the combination of prominent cell

www.ketabpezeshki.com 66485457-66963820

loss and gliosis in frontal and temporal regions of the cortex, termed dementia lacking distinctive histology.[66]

Approximately 15 to 20% of dementias are caused by multiple vascular insults to the CNS; the resulting deficit is termed multi-infarct dementia. The multiple infarcts typically involve the cerebral hemispheres and basal ganglia. Multi-infarct dementia often has an earlier age at onset than Alzheimer's disease and occurs more often in adult men and patients who have risk factors for atherosclerosis. Approximately 29% of dementias are a mixed variety, with components of both ischemic cerebrovascular disease and Alzheimer's dementia.[64,67]

Inflammatory conditions of the CNS caused by conventional viruses include subacute sclerosing panencephalitis from measles virus infection, progressive multifocal leukoencephalopathy from infection by the JC virus (a papovavirus), progressive rubella encephalitis, and infection associated with HIV disease. The unconventional viral infections include kuru, Creutzfeldt-Jakob disease (CJD), and variant CJD (which appears to be linked to bovine spongiform encephalopathy, the pathologic process in "mad cow disease") and are associated with minimal inflammatory histopathologic changes in the CNS; these diseases cause a fine vacuolation of the nervous tissue and hence are referred to as subacute spongiform viral encephalopathies.[68]

Slow virus infections of the CNS can cause a progressive dementia that is irreversible. With these infections, months to years pass between infection with the virus and the appearance of clinical illness. Slow virus infections of the CNS are caused by both conventional viruses and unconventional viruslike agents known as prions. A prion is a proteinaceous infectious particle with the apparent ability to start a chain reaction that changes the shape of benign protein molecules into abnormal, slowly destructive forms. Prions are present in CJD and variant CJD.[68]

One of the most prevalent slow virus infections causing progressive dementia is HIV-1 infection. HIV may produce a primary neurotrophic disorder in addition to causing the immunologic compromise that permits other viruses to replicate and damage nervous tissue.

HIV dementia or AIDS dementia complex occurs in approximately one fourth of patients with AIDS. It is believed to be caused by the HIV-1 virus targeting the microglial cells and the macrophages, which may produce cytotoxic substances such as tumor necrosis factor and interleukins. Pathologic changes occur mostly in the hippocampus and basal ganglia and include atrophy, ventricular dilation, and fibrosis.[69,70]

Several of the potentially reversible causes of dementia also are associated with neuropathologic or neurochemical abnormalities. Normal-pressure hydrocephalus generally affects younger people; 50% of patients are younger than 60 years. Most of the conditions that cause hydrocephalus involve a defect in uptake of CSF by arachnoid villi, which results in gradual ventricular dilation.

Chronic, heavy ethanol consumption is associated with dementia. The neurotoxicity of ethanol appears to be independent of thiamine deficiency. Heavy chronic alcohol consumption causes cerebral cortical atrophy, but no single alcohol-related dementia syndrome exists. It is estimated that approximately 20% of chronically demented patients have a history of alcoholism.

Clinical Features

The symptoms, signs, and progression of chronic cognitive impairment rarely are so diagnostic as to permit identification of the specific cause of the dementia. Alzheimer's disease begins insidiously. Signs and symptoms of cognitive dysfunction may be present for months to years before the diagnosis is made. The earliest symptoms and signs of Alzheimer's disease often are vague and nonspecific; patients manifest anxiety, depression, insomnia, frustration, and somatic complaints that often are more prominent than the memory loss. Patients often deny any cognitive deficits and change the subject of the conversation frequently rather than admit their increasing forgetfulness. Physicians often overlook the subtle signs of dementia in this phase of the disease.[71]

Depression often is the initial manifestation of Alzheimer's disease and is present in up to 40% of cases. Early in the illness, short-term memory is affected, with forgetfulness of recent events such as appointments and names of new acquaintances. Patients often repeat questions. The memory impairment may cause them to withdraw from social situations and recreational pursuits. Attempts to perform complex tasks may produce anxiety and confusion. The patient often has difficulty with interpersonal relationships. Affect may be shallow and labile, and minor events may trigger inappropriate laughter or tears. Compensation for early deficits includes excessive orderliness and avoidance of situations in which the defects may be observed. Patients in this early phase who are treated with antidepressants with anticholinergic properties may experience worsening of their symptoms. Sedative-hypnotics prescribed for anxiety also may accelerate cognitive dysfunction.

As the dementia progresses, cognitive deficits are more obvious and should be readily apparent on a mental status examination. Problems with recent memory, impairment of remote memory, language deficits, and difficulty with spontaneous speech may be noted. With moderate severity of the disease, patients have difficulty naming objects (dysnomia). As many as 50% of patients have delusions, usually of the paranoid type. Atypical presentations of Alzheimer's disease include aphasia, visual agnosia, right parietal lobe syndrome, focal neurologic findings, extrapyramidal signs, gait disturbances, and pure memory loss. In the final stage of dementia, patients exhibit marked cognitive impairment, apraxia, and significant personality changes. They often are bedridden and unable to perform any of the routine activities of daily living.

Because Pick's disease dementia affects the frontal and temporal lobes, patients often have frontal lobe release signs, including dramatic behavioral changes of disinhibition and social inappropriateness. Basal ganglia degenerative disorders that have dementia as a prominent feature are Huntington's chorea, Parkinson's disease, and Wilson's disease. One of several features that distinguish cortical from subcortical dementias is a prominent movement disorder, including posturing, ataxia, tremor, and chorea, that tends to occur early in the illness. Other features of these dementias include slowness of speech, hypotonia, and dysarthria, which can progress to mutism.[72]

Patients with vascular dementia have a stepwise deterioration in memory and cognitive function with each cerebrovascular insult. The clinical presentation may follow one of two scenarios. In the more common scenario, the patient suffers several strokes that involve large volumes of cortical and subcortical structures in both hemispheres. The patient then exhibits dementia along with other neurologic disabilities (e.g., focal weakness, hyperreflexia, extensor plantar response). In a second group of patients, the presentation is more subtle. These patients characteristically are hypertensive and suffer multiple tiny infarcts (lacunae) that involve deep subcortical structures. There may be no focal neurologic residua except progressive dementia with psychomotor retardation. Aggressive antihypertensive therapy in the very elderly does not reduce the incidence of dementia.[73]

The clinical manifestations of slow virus CNS infections are protean. After an insidious onset of mental deterioration in subacute sclerosing panencephalitis, a rapid progression ensues that is associated with myoclonic jerks, incoordination, and ataxia. In progressive multifocal leukoencephalopathy, neurologic signs and symptoms reflect diffuse asymmetrical involvement of both cerebral hemispheres. Sporadic CJD, of unknown etiology, tends to affect older people, with a rate of disease among those 50 to 70

www.ketabpezeshki.com 66485457-66963820

years of age of 1 case per million. Among these patients, rapidly evolving dementia with myoclonus is characteristic. The hallmarks of the disorder are mental deterioration, multisystem neurologic signs, myoclonus, and typical electroencephalographic changes that evolve during months. Variant CJD affects younger patients (median age of 24 years), with key features that include early affective symptoms progressing to cognitive impairment and gait disturbances and ultimately leading to progressive neurologic deterioration. The incubation period appears to be in the range of 10 to 15 years, and most patients die within 14 months after the clinical onset of symptoms.[68]

The most common treatable dementia is pseudodementia, or depression. The clinical distinction between depression and dementia is difficult, and the coexistence of depression and dementia is common in people with mild dementia. A number of distinguishing features suggest that the problem is depression rather than dementia: the onset of cognitive changes in pseudodementia often can be pinpointed, and symptoms usually are of short duration before medical help is sought. The progression of symptoms is rapid, and the family usually is aware of the severity of the dysfunction. A history of psychiatric illness is common. Patients with pseudodementia usually complain of cognitive dysfunction and emphasize their failures and disabilities. The affective change often is pervasive, and the patient makes little effort to perform simple tasks. Loss of social skills usually occurs early in the illness, and patients communicate a strong sense of distress and inability to function. Intellectual functioning in pseudodementia often is difficult to assess because of lack of patient cooperation or inconsistent findings on neuropsychometric testing. Attention and concentration often are intact, but patients commonly give answers such as "I don't know" on tests of orientation, concentration, and memory. Memory losses for recent and remote events usually are equally severe, and variability in the performance of tasks with similar degrees of difficulty may be marked. Tasks of high capacity (e.g., testing of delayed memory with distraction) may be helpful in identifying the depressed patient.[74]

The classic triad of progressive dementia, ataxia, and urinary incontinence occurs in patients with normal-pressure hydrocephalus, which typically affects patients who are younger than those with primary degenerative dementia. More than half of the reported cases are in persons younger than 60 years. Hydrocephalus secondary to previous head trauma or infection carries a more favorable prognosis than that for primary hydrocephalus.

In approximately 20% of the reversible cases, dementia is secondary to an intracranial mass. Patients may exhibit focal or nonfocal neurologic signs.[75] Of the reversible dementias, 10 to 15% are secondary to medications or chemical intoxications, frequently compounding a history of heavy alcohol use. Geriatric patients have increased susceptibility to the toxicities owing to polypharmacy and age-related changes in metabolism. The clinical presentation of a patient with a drug-related or toxin-related dementia may be indistinguishable from that of a patient with a primary degenerative process.

Family or friends usually bring the patient to the ED because of a sudden worsening in mental status, a change in the patient's activities (e.g., refusal to eat), or a change in the ability of the caregiver to manage the patient. Presentations vary by the cause of the dementia and the stage of progression. Many elders with dementia have a superimposed delirium on presentation.

Differential Considerations

Subacute or chronic cognitive decline may be secondary to a dementing illness or can be a manifestation of senescent forgetfulness, delirium, or depression. Senescent forgetfulness is an almost inevitable reality of aging. Mild impairment of both short-term and long-term memory is usual. Unlike in dementia, the cognitive disturbance in senescent forgetfulness does not interfere with work or customary social activity. The distinction between senescent forgetfulness and mild cognitive impairment is not well defined.

In most cases, the clinical distinction between delirium and dementia is obvious. As stated previously, the onset of symptoms, progression of signs and symptoms, perceptual disturbances, possible presence of abnormalities on assessment of vital signs, and fluctuations in the level of consciousness are key distinguishing features.

Diagnostic Strategies

The evaluation of the patient with possible dementia should include a focused medical and psychiatric history and medication history plus a collateral history from family and friends. Physical examination should include a detailed neurologic examination with mental status evaluation. Dementia often goes unrecognized in the patient who is alert, pleasant, and cooperative. A validated cognitive evaluation test can play a key role in the early identification of dementia in patients who have maintained social and conversational ability.

Alzheimer's disease is a clinical diagnosis typically made on probability; no routine available laboratory tests have been found to confirm the presence of the disorder (although MRI scan, functional scans looking at regional blood flow or glucose metabolism, assay for specific biomarkers, and CSF analysis can significantly increase the probability of the presence of the disease). The physical examination is rarely helpful in detecting treatable dementias because of the considerable clinical overlap with irreversible dementias. Data clearly supporting or refuting the ordering of "routine" laboratory studies for evaluation of dementia are lacking; however, a number of studies are recommended to exclude treatable causes (Box 104-4). For patients with suspected undiagnosed dementia presenting to the ED, a baseline laboratory evaluation,

Box 104-4 Diagnostic Evaluation for Dementia

- History (patient, family, friends)
- Review of medications
- Physical examination, including neurologic evaluation
- Mental status examination
- Laboratory evaluation
  - Complete blood count
  - Electrolyte and glucose levels
  - Liver and renal function studies
  - Urinalysis
  - Thyroid function studies
  - VDRL and FTA assays
- Radiographic evaluation
  - Chest radiograph
  - Head CT scan
- Additional evaluation
  - Blood and urine screens for drugs and heavy metals
  - Erythrocyte sedimentation rate
  - HIV screen
  - Antinuclear antibody
  - Oxygen saturation, arterial blood gas analysis
  - Serum vitamin B_{12} and folate levels
  - Lumbar puncture
  - MRI head scan
  - Electroencephalogram
  - Neuropsychometric testing
  - Evoked potentials (visual, brainstem auditory, somatosensory)

CT, computed tomography; *FTA,* fluorescent treponemal antibody; *HIV,* human immunodeficiency virus; *MRI,* magnetic resonance imaging; *VDRL,* Venereal Disease Research Laboratory.

www.ketabpezeshki.com 66485457-66963820

including CBC, comprehensive metabolic panel, and urinalysis, is indicated. If neurosyphilis is clinically suspected, a serum fluorescent treponemal antibody absorption test should be performed in addition to a Venereal Disease Research Laboratory (VDRL) test because the serum VDRL assay may yield negative results in patients with tertiary syphilis. The radiologic evaluation should include a non–contrast-enhanced head CT scan. The CT scan is used to diagnose or to exclude the presence of hydrocephalus or space-occupying lesions, and CT findings may support a vascular etiology for the dementia.

Patients require additional laboratory tests on follow-up evaluation; such tests may include determination of serum vitamin B_{12} and folate levels, thyroid function studies, estimation of erythrocyte sedimentation rate, fluorescent antinuclear antibody assay, measurement of urine corticosteroid levels, and, if indicated by history, urine screens for drugs and heavy metals. Selected patients should undergo a lumbar puncture with CSF analysis, MRI, positron emission tomography scan, electroencephalography (in CJD, characteristic slowing and periodic complexes may be electroencephalographic features), neuropsychological testing, and testing of visual evoked potentials, brainstem auditory evoked potentials, and somatosensory evoked potentials. The EEG rarely is helpful in establishing the diagnosis of senile dementia. An MRI finding of medial temporal atrophy suggests Alzheimer's disease but is not specific or sensitive for diagnosis of this disorder.[76]

Treatment and Disposition

Reversible dementias and conditions that cause worsening of baseline dementia require early diagnosis and treatment of the underlying disorder if previous cognitive function is to be restored. Determination of reversible causes of dementia during the ED evaluation occasionally is possible on the basis of the history (including medication history), physical examination, and head CT scan. Patients with acute changes in mental status or a relatively rapid onset of symptoms will require hospitalization for comprehensive evaluation. Patients presenting with recent gradual decline in cognitive function without an underlying acute medical condition can undergo further evaluation on an outpatient basis.

Pharmacotherapy approved by the FDA for the treatment of mild to moderate Alzheimer's disease includes the cholinesterase inhibitors donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne). There are multiple randomized, placebo-controlled, large-scale clinical trials with these drugs establishing efficacy in improving cognitive functions, overall evaluation, and activities of daily living in patients with mild to moderate dementia. These drugs are not considered disease modifying, and there are limited data at present on the benefit of these drugs beyond 2 or 3 years (a significant number of patients discontinue medications because of side effects). The most common side effect of these agents is due to the cholinergic effects, including nausea, vomiting, and diarrhea. In 2003, the FDA approved memantine (Namenda), a disease-modifying agent that helps regulate the excitatory effects of glutamate by antagonizing the *N*-methyl-D-aspartate receptor. Whether this drug alters the underlying disease process is unclear, but short-term studies show improved cognition in patients with moderate and moderate to severe Alzheimer's disease with memantine.[77,78] There are conflicting studies on the effectiveness of other agents, such as gingko biloba, vitamin E, nonsteroidal agents, and statins. Estrogen replacement is not indicated for cognitive improvement or maintenance in women with Alzheimer's disease and can be detrimental. Ultimately, the key to altering the course of the disease is halting neuron loss. In severe dementia, the goal of management is supportive care.

Many therapies currently are under investigation for the modulation and early treatment of Alzheimer's disease. These therapies include antibiotics (directed against *Chlamydophila pneumoniae*), secretase modulators to reduce serum β-amyloid levels, immunization to reduce amyloid plaque burden, chelators to promote dissolution of β-amyloid, nonsteroidal anti-inflammatory medications, supplementation with omega-3 fatty acids, and testosterone.[79,80]

Increasing evidence suggests that certain nonpharmacologic measures, including behavioral methods and avoidance of environmental triggers, may be effective in reducing agitation and anxiety in patients with dementia.[81] On occasion, medications are needed for behavioral symptoms of dementia. Affected patients typically do not improve with anxiolytics. Adverse effects offset the modest advantages in the efficacy of antipsychotic drugs for the treatment of psychosis, aggression, or agitation in many patients with Alzheimer's disease, and these drugs should be avoided when possible.[82,83] However, agitation can be controlled with a small dose of the butyrophenone haloperidol.[84] The cardiovascular toxicity of this drug is minimal, and it is reasonably well tolerated in elders. Clozapine also has been shown to be effective in treating psychosis associated with both Alzheimer- and Parkinson-type dementias.[85] In April 2005, the FDA issued a black box warning that the use of atypical antipsychotics to treat elderly patients with dementia was associated with an increased risk for death compared with placebo. Atypical antipsychotics are relatively contraindicated in this group of patients because of the association with an increased risk of hospitalization and death.[86,87] Agitation may occasionally be due to unrecognized depression in dementia, and a trial of selective serotonin reuptake inhibitors may be warranted.[88] Temazepam (Restoril) is the drug of choice for sleep disturbance. The half-life of temazepam is 8 to 10 hours for patients of all ages, and the drug bypasses the oxidative hepatic enzyme system.

On occasion, patients are brought to the ED because of a crisis due to family stress from continuous care of the person with dementia. A brief nursing home stay or other institutional stay (respite program) may give the family time to mobilize resources to resume the home care regimen. Social workers can play a vital role in attempting to facilitate management of these patients.

KEY CONCEPTS

- Delirium is an acute condition characterized by an altered level of consciousness, disorganized thinking, and inattention. It develops during a short time, and symptoms tend to fluctuate during hours to days. A thorough investigation of possible causes of the delirium should be undertaken in the ED.
- Dementia is a chronic condition characterized by memory loss and cognitive impairment. It is slow in onset and progressive in nature. This disorder has many causes, several of which are reversible with treatment. It is essential to resist the temptation to classify dementia as a "futile" disease, and a search for underlying medical conditions that may be worsening a dementing illness is indicated.
- Patients with either dementia or psychiatric disorders may present with superimposed delirium, often making identification of the underlying cause of their abnormal behavior difficult. When the diagnosis is in doubt, possible causes of delirium should be specifically excluded.
- The clinician should be wary of attributing behavioral disturbances to psychiatric illness in the presence of abnormal vital signs or abnormal sensorium.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. text rev. Washington, DC: American Psychiatric Association; 2000.
2. Inouye SK, Ferrucci L: Elucidating the pathophysiology of delirium and the interrelationship of delirium and dementia. *J Gerontol A Biol Sci Med Sci* 2006; 61:1277-1280.
3. Fick DM, Agostini JV, Inouye SK: Delirium superimposed on dementia: A systemic review. *J Am Geriatr Soc* 2002; 50:1723-1732.
4. Meagher DJ, Trzepacz PT: Motoric subtypes of delirium. *Semin Clin Neuropsychiatry* 2000; 5:75-85.
5. Hustey FM, Meldon SW: The prevalence and documentation of impaired mental status in elderly emergency department patients. *Ann Emerg Med* 2002; 39:248.
6. Elie MJ: Delirium risk factors in elderly hospitalized patients. *J Gen Intern Med* 1998; 13:204.
7. Flacker JM, et al: The association of serum anticholinergic activity with delirium in elderly medical patients. *Am J Geriatr Psychiatry* 1998; 6:31-41.
8. Rivera W, et al: Central nervous system toxicity manifestations of drug toxicity. *Emerg Med Rep* 2003; 24:12.
9. Inouye SK: Delirium in older persons. *N Engl J Med* 2006; 354:1157.
10. Talbot-Stern JK, et al: Psychiatric manifestations of systemic illness. *Emerg Med Clin North Am* 2000; 18:199.
11. Hohl CM, et al: Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. *Ann Emerg Med* 2001; 38:661.
12. Folstein MF, Folstein SE, McHugh PR: "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12:189.
13. Cullen B, O'Neill B, Evans JJ, Coen RF, Lawlor BA: A review of screening tests for cognitive impairment. *J Neurol Neurosurg Psychiatry* 2007; 78:790-799.
14. American Psychiatric Association Practice Guidelines: Practice guidelines for the treatment of patients with delirium. *Am J Psychiatry* 1999; 156(Suppl):5.
15. Wilber ST, et al: An evaluation of two screening tools for cognitive impairment in older emergency department patients. *Acad Emerg Med* 2005; 12:612.
16. Petersen RC: Practice parameter: Early detection of dementia: Mild cognitive impairment (an evidenced-based review). *Neurology* 2001; 56:1133.
17. Duff Canning SJ, et al: Diagnostic utility of abbreviated fluency measures in Alzheimer disease and vascular dementia. *Neurology* 2004; 62:556.
18. Huff JS, et al: The quick confusion scale in the ED: Comparison with the Mini-Mental State Examination. *Am J Emerg Med* 2001; 19:461.
19. Inouye SK, et al: Clarifying confusion: The confusion assessment method: A new method for detection of delirium. *Ann Intern Med* 1990; 113:941.
20. Zou Y, et al: Detection and diagnosis of delirium in the elderly: Psychiatrist diagnosis, confusion assessment method or consensus diagnosis? *Int Psychogeriatr* 1998; 10:303.
21. Witlox J, et al: Delirium in elderly patients and the risk of post-discharge mortality, institutionalization, and dementia: A meta analysis. *JAMA* 2010; 304:443-451.
22. Schmidt P, et al: The effects of positional restraint on heart rate and oxygen saturation. *J Emerg Med* 1999; 17:777.
23. Stratton SJ, et al: Factors associated with sudden death of individuals requiring restraint for excited delirium. *Am J Emerg Med* 2001; 19:187.
24. Lonergan E, Britton AM, Luxenberg J, Wyller T: Antipsychotics for delirium. *Cochrane Database Syst Rev* 2007; 2:CD005594.
25. Seeman P: Atypical antipsychotics: Mechanism of action. *Can J Psychiatry* 2002; 47:27.
26. Daniel DG, et al: Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: A double-blind, randomized trial. *Psychopharmacology (Berl)* 2001; 155:128.
27. Brook S, et al: Intramuscular (IM) ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. *J Clin Psychiatry* 2000; 61:933.
28. Battaglia J, et al: Calming versus sedative effects of intramuscular olanzapine in agitated patients. *Am J Emerg Med* 2003; 21:192.
29. Wright P, et al: Double blind, placebo-controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation. *Am J Psychiatry* 2001; 158:1149.
30. Kales HC, et al: Trends in antipsychotic use in dementia 1999-2007. *Arch Gen Psychiatry* 2011; 68:190-197.
31. Bailey P, Norton R, Karan S: The FDA droperidol warning: Is it justified? *Anesthesiology* 2002; 97:288.
32. Thomas H, Schwartz E, Petrilli R: Droperidol versus haloperidol for chemical restraint of agitated and combative patients. *Ann Emerg Med* 1992; 21:407.
33. Lonergan E, Luxenberg J, Areosa SA, Wyller TB: Benzodiazepines for delirium. *Cochrane Database Syst Rev* 2009; 1:CD006379. DOI: 10.1002/14651858. CD006379.pub2.
34. Pandharipande P, et al: Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006; 104:21.
35. Jacobi J, et al: Clinical practice guidelines for the use of sedatives and analgesics in the critically ill adult. *Crit Care Med* 2002; 30:119.
36. Schillevoort I: Risk of extrapyramidal syndromes with haloperidol, risperidone, and olanzapine. *Ann Pharmacother* 2001; 35:1517.
37. Sharma ND, et al: Torsades de pointes associated with intravenous haloperidol in critically ill patients. *Am J Cardiol* 1998; 81:238.
38. Bergmann MA, Murphy KM, Kiely DK, Jones RN, Marcantonio ER: A model for management of delirious postacute care patients. *J Am Geriatr Soc* 2005; 53:1817.
39. Battaglia J, et al: Haloperidol, lorazepam, or both for psychotic agitation: A multicenter, prospective, double-blind emergency department study. *Am J Emerg Med* 1997; 15:335.
40. Cook IA: *Guideline Watch: Practice Guideline for the Treatment of Patients with Delirium*. Washington, DC: American Psychiatric Association; 2004.
41. Skrobik YK, et al: Olanzapine vs haloperidol: Treating delirium in a critical care setting. *Intensive Care Med* 2004; 30:444.
42. Sipahimalani A, Massand PS: Use of risperidone in delirium: Case reports. *Ann Clin Psychiatry* 1997; 9:105.
43. Ravona-Springer R, et al: Delirium in elderly patients treated with risperidone: A report of three cases. *J Clin Psychopharmacol* 1998; 18:171.
44. Sipahimalani A, Masand PS: Olanzapine in the treatment of delirium. *Psychosomatics* 1998; 39:422.
45. Naess AC: Patient autonomy in emergency medicine. *Med Health Care Philos* 2001; 4:71.
46. Inouye SK, et al: Risk factors for delirium at discharge: Development and validation of a predictive model. *Arch Intern Med* 2007; 167:1406.
47. McCusker J, et al: Delirium predicts 12-month mortality. *Arch Intern Med* 2002; 162:457.
48. Cole MG, et al: Systematic detection and multidisciplinary care of delirium in older medical inpatients: A randomized trial. *CMAJ* 2002; 167:753.
49. Knopman DS, et al: Incidence and causes of nondegenerative nonvascular dementia: A population-based study. *Arch Neurol* 2006; 63:218.
50. Hejl A, Hogh P, Waldemar G: Potentially reversible conditions in 1000 consecutive memory clinic patients. *J Neurol Neurosurg Psychiatry* 2002; 73:390.
51. Alzheimer A: Uber eine eigenartige Erkrankung der Hirnrinde. *Allerg Z Psychiatr* 1907; 64:146.
52. Ferri CP, et al: Global prevalence of dementia: A Delphi consensus study. *Lancet* 2005; 366:2112.
53. National Institutes of Health, National Institute on Aging: *Progress Report on Alzheimer's Disease 1999.* Bethesda, Md: U.S. Department of Health and Human Services; 1999. NIH Publication No. 99-4664.
54. Kukull WA: Dementia epidemiology. *Med Clin North Am* 2002; 86:573.
55. Morris JC, et al: Mild cognitive impairment represents early-stage Alzheimer disease. *Arch Neurol* 2001; 58:397-405.
56. Tschanz JT, et al: Dementia: The leading predictor of death in a defined elderly population: The Cache County Study. *Neurology* 2004; 62:1156.
57. Roberts GW, Allsop D, Bruton C: The occult aftermath of boxing. *J Neurol Neurosurg Psychiatry* 1990; 53:373.
58. Mckee AC, et al: Chronic traumatic encephalopathy in athletes: Progressive tauopathy after repetitive head injury. *J Neuropathol Exp Neurol* 2009; 68:709-735.
59. Belman AL: HIV-1 infection and AIDS. *Neurol Clin* 2002; 20:983.
60. Winblad B: Major depression in a population of demented and nondemented older people: Prevalence and correlates. *J Am Geriatr Soc* 2002; 46:27.
61. Feldman H, et al: Behavioral symptoms in mild cognitive impairment. *Neurology* 2004; 62:1199-1201.
62. Tanzi, RE: Tangles and neurodegenerative disease—a surprising twist. *N Engl J Med* 2005; 353:1835.
63. Gandy S: The role of cerebral amyloid beta accumulation in common forms of Alzheimer disease. *J Clin Invest* 2005; 115:1121.
64. Cummings JL: Alzheimer's disease. *N Engl J Med* 2004; 351:56.

www.ketabpezeshki.com 66485457-66963820

65. Knopman DS: An overview of common non-Alzheimer dementias. *Clin Geriatr Med* 2001; 17:281.
66. Giannakopoulos P, Hof PR, Bouras C: Dementia lacking distinctive histopathology: Clinicopathological evaluation of 32 cases. *Acta Neuropathol (Berl)* 1995; 89:346.
67. Chui HC, et al: Clinical criteria for the diagnosis of vascular dementia: A multicenter study of comparability and interrater reliability. *Arch Neurol* 2000; 57:191.
68. Tyler KL: Creutzfeldt-Jakob disease. *N Engl J Med* 2003; 384:681.
69. Bensalem MK, Berger JR: HIV and the central nervous system. *Compr Ther* 2002; 28:23.
70. Sotrel A, Dal Canto MC: HIV-1 and its causal relationship to immunosuppression and nervous system disease in AIDS: A review. *Hum Pathol* 2000; 31:1274.
71. Finkel SI: Behavioral and psychological symptoms of dementia. *Clin Geriatr Med* 2003; 19:799.
72. Graham NL, Bak T, Patterson K, Hodges JR: Language function and dysfunction in corticobasal degeneration. *Neurology* 2003; 61:493.
73. Peters R, et al: Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): A double-blind placebo controlled trial. *Lancet Neurol* 2008; 7:683-689.
74. Peters KR, et al: Characterizing neuropsychiatric symptoms in subjects referred to dementia clinics. *Neurology* 2006; 66:523.
75. Clarfield AM: The decreasing prevalence of reversible dementia: An updated meta-analysis. *Arch Intern Med* 2003; 163:2219.
76. Barnes J, et al: Measurement of the amygdala and hippocampus in pathologically confirmed Alzheimer disease and frontal lobe degeneration. *Arch Neurol* 2006; 63:1434.
77. Reisberg B, et al: A 24-week open-label extension study of memantine in moderate to severe Alzheimer disease. *Arch Neurol* 2006; 63:49.
78. McShane R, Areosa Sastre A, Minakaran N: Memantine for dementia. *Cochrane Database Syst Rev* 2006; 2:CD003154.
79. Sano M, et al: A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *N Engl J Med* 1997; 336:1216.
80. Siemers ER, et al: Effects of a gamma-secretase inhibitor in a randomized study of patients with Alzheimer's disease. *Neurology* 2006; 66:602.
81. Ayalon L, et al: Effectiveness of nonpharmacological interventions for the management of neuropsychiatric symptoms in patients with dementia: A systemic review. *Arch Intern Med* 2006; 166:2182.
82. Rochon PA, et al: Antipsychotic therapy and short-term serious events in older adults with dementia. *Arch Intern Med* 2008; 168:1090.
83. Kuehn BM: FDA warns antipsychotic drugs may be risky for elderly. *JAMA* 2005; 293:2462.
84. Tariot PN, et al: Pharmacologic therapy for behavioral symptoms of Alzheimer's disease. *Clin Geriatr Med* 2001; 17:359.
85. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. The Parkinson Study Group. *N Engl J Med* 1999; 340:757.
86. Schneider LS, et al: Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med* 2006; 355:1525.
87. Schneider LS, et al: Risk of death with atypical antipsychotic drug treatment for dementia: Meta-analysis of randomized placebo-controlled trials. *JAMA* 2005; 294:1934.
88. Fickle SI, et al: A randomized placebo-controlled study of the efficacy and safety of sertraline in the treatment of the behavioral manifestations of Alzheimer's disease in outpatients treated with donepezil. *Int J Geriatr Psychiatry* 2004; 19:9.

www.ketabpezeshki.com 66485457-66963820

Chapter 105

Brain and Cranial Nerve Disorders

Brian A. Stettler

This chapter discusses cranial nerve problems, cerebral venous thrombosis, and multiple sclerosis—neurologic disorders that often provide significant diagnostic and therapeutic challenges in the emergency department (ED) setting (Table 105-1).

TRIGEMINAL NEURALGIA

Perspective

Trigeminal neuralgia, or tic douloureux, is a syndrome featuring painful paroxysms in one or more distributions of the trigeminal nerve. Trigeminal neuralgia is relatively uncommon, with an annual incidence of 4 to 13 cases per 100,000 population.[1,2] It is more common in women than in men, with a female-to-male ratio of 1.7 : 1. Affected persons typically are between 50 and 69 years of age, and symptoms occur more frequently on the right side of the face.[3]

Pathophysiology

Trigeminal neuralgia is an idiopathic disorder, although significant evidence points to vascular compression of the trigeminal nerve root in many cases. This compression commonly is caused by a tortuous arterial or venous loop in the posterior fossa, an arteriovenous malformation, or rarely a tumor. In surgical case series, vascular compression of the trigeminal nerve root is found in 80 to 90% of cases.[4,5] Of note, however, structural lesions are not found in all patients with trigeminal neuralgia.[6]

Clinical Features

Trigeminal neuralgia is manifested with unilateral facial pain, typically characterized as lancinating paroxysms of pain in the lips, teeth, gums, or chin. The pain of trigeminal neuralgia is commonly associated with physical triggers such as chewing, brushing the teeth, shaving, washing or touching the affected area of the face, swallowing, or exposure to hot or cold temperature in the affected area. The maxillary and mandibular divisions of the trigeminal nerve are most commonly involved; rarely, the ophthalmic division alone is involved. Patients tend to experience the pain in clustered episodes that last a few seconds to several minutes. The attacks can occur during the day or night but rarely arise during sleep.[6,7]

Diagnostic Strategies

A careful history and physical examination should be performed to rule out other painful facial conditions, including odontogenic infections, sinus disease, otitis media, acute glaucoma, temporomandibular joint disease, and herpes zoster. Patients who lack local pathologic findings to explain the painful syndrome require a careful neurologic examination. The presence of a neurologic deficit should prompt suspicion of a structural lesion, such as aneurysm, tumor, or other intracranial lesion (e.g., from multiple sclerosis). Of note, 2 to 4% of patients with trigeminal neuralgia also have multiple sclerosis.[8] Patients with normal findings on the head and neck examination and no neurologic deficits who have episodic, unilateral facial pain associated with nonpainful triggers are likely to have trigeminal neuralgia.

Management

Since the 1960s the treatment of choice for trigeminal neuralgia has been the anticonvulsant medication carbamazepine. The purported effectiveness of this treatment, however, is based on uncontrolled studies, and the mechanism of action of anticonvulsant therapy for trigeminal neuralgia is unclear. The true efficacy of medical therapy is difficult to assess owing to a high rate of spontaneous remission. Nonetheless, carbamazepine appears to be an effective and well-tolerated agent for treatment of trigeminal neuralgia. The initial dosage of carbamazepine is 100 mg twice daily; this dose is then increased to three times daily after 1 week. The dose may be increased by 100 mg/day, up to a maximum of 1200 mg/day. A complete blood count and liver function studies are performed periodically in patients who are taking carbamazepine to monitor for hematologic and hepatic side effects. Additional agents that have been used for treatment of trigeminal neuralgia include phenytoin, baclofen, valproate sodium, lamotrigine, gabapentin, and levetiracetam. None of these drugs has been shown to be more effective than carbamazepine.[7]

Surgical management has been a therapeutic option since the 1950s. Surgical procedures include both peripheral and central procedures. Peripheral strategies include medication injection and cryotherapy techniques designed to temporarily block or permanently ablate branches of the peripheral trigeminal nerve. Although these procedures are relatively effective initially, recurrence is common. Repeated nerve blocks are not recommended because of a high risk of permanent facial anesthesia.

Central procedures can be divided into percutaneous approaches and open approaches. Percutaneous destruction of the trigeminal ganglion can be done by means of radiofrequency ablation, thermal ablation, glycerol injection, or balloon microcompression. These procedures carry the risk of corneal anesthesia, oculomotor paresis, or masticatory weakness.[9]

Open surgical management is the surgical option of choice in many treatment centers. Open surgical procedures include

www.ketabpezeshki.com 66485457-66963820

Table 105-1 The Cranial Nerves: Normal Function and Pathologic Considerations

CRANIAL NERVE	CLINICAL FUNCTION RELEVANT TO EMERGENCY MEDICINE	PATHOLOGIC FEATURES	POSSIBLE CAUSES
Cranial nerve I: Olfactory nerve	Sense of smell	Unilateral anosmia	Trauma: Skull fracture or shear injury interrupting olfactory fibers traversing the cribriform plate Tumor: Frontal lobe masses compressing the nerve
Cranial nerve II: Optic nerve	Vision	Unilateral vision loss	Trauma: Traumatic optic neuropathy *Tumor:* Orbital compressive lesion *Inflammatory:* Optic neuritis (MS) *Ischemic:* Ischemic optic neuropathy
Cranial nerve III: Oculomotor nerve	Extraoculomotor function via motor fibers to levator palpebrae, superior rectus, medial rectus, inferior rectus, inferior oblique muscles Pupillary constriction via parasympathetic fibers to constrictor pupillae and ciliary muscles	Ptosis caused by loss of levator palpebrae function Eye deviated laterally and down Diplopia Dilated, nonreactive pupil Loss of accommodation	*Trauma:* Herniation of the temporal lobe through the tentorial opening, causing compression and stretch injury to the nerve *Ischemic:* Especially in diabetes Microvascular ischemic injury to nerve causes extraocular muscle paralysis but usually is papillary sparing (often painful) *Vascular:* Intracranial aneurysms may press on the nerve, leading to dysfunction Myasthenia gravis can lead to atraumatic ocular muscle palsy
Cranial nerve IV: Trochlear nerve	Motor supply to the superior oblique muscle	Inability to move eye downward and laterally Diplopia Patients tilt head toward unaffected eye to overcome inward rotation of affected eye	Trauma is the most common cause of nerve dysfunction
Cranial nerve V: Trigeminal nerve	Motor supply to muscles of mastication and to tensor tympani Sensory to face, scalp, oral cavity (including tongue and teeth)	Partial facial anesthesia Episodic, lancinating facial pain associated with benign triggers such as chewing, brushing teeth, light touch	*Trauma:* Facial bone fracture may injure one section, leading to area of facial anesthesia Tic douloureux
Cranial nerve VI: Abducens nerve	Motor supply to the lateral rectus muscle	Inability to move affected eye laterally Diplopia on attempting lateral gaze	*Tumor:* Lesions in the cerebellopontine angle Any lesion, vascular or otherwise, in the cavernous sinus may compress nerve *Elevated intracranial pressure (ICP):* Because of its position and long intracranial length, increased ICP from any cause may lead to injury and dysfunction of the nerve
Cranial nerve VII: Facial nerve	Motor supply to muscles of facial expression Parasympathetic stimulation of the lacrimal, submandibular, and sublingual glands Sensation to the ear canal and tympanic membrane	*Hemifacial paresis*: *Lower motor neuron lesion* leaves entire side of face paralyzed *Upper motor neuron lesion* leaves forehead musculature functioning Abnormal taste Sensory deficit around ear Intolerance to sudden loud noises	*Lower motor neuron:* *Infection (viral):* The likely cause of Bell's palsy *Lyme disease:* The most common cause of bilateral cranial nerve VII palsy in areas where Lyme disease is endemic Bacterial infection extending from otitis media *Upper motor neuron:* Stroke, tumor
Cranial nerve VIII: Vestibulocochlear nerve	Hearing and balance	Unilateral hearing loss Tinnitus Vertigo, unsteadiness	*Tumor:* Acoustic neuroma Mimics Ménière's disease, perilymphatic fistula
Cranial nerve IX: Glossopharyngeal nerve	General sensation to posterior third of tongue Taste for posterior third of tongue Motor supply to the stylopharyngeus	Clinical pathology referable to the nerve in isolation is very rare Occasionally painful paroxysms beginning in the throat and radiating down the side of the neck in front of the ear but behind the mandible	Brainstem lesion Glossopharyngeal neuralgia

www.ketabpezeshki.com 66485457-66963820

Table 105-1 The Cranial Nerves: Normal Function and Pathologic Considerations—cont'd

CRANIAL NERVE	CLINICAL FUNCTION RELEVANT TO EMERGENCY MEDICINE	PATHOLOGIC FEATURES	POSSIBLE CAUSES
Cranial nerve X: Vagus nerve	Motor to striated muscles and muscles of the pharynx, larynx, and tensor (veli) palatini Motor to smooth muscles and glands of the pharynx, larynx, thoracic and abdominal viscera Sensory from larynx, trachea, esophagus, thoracic and abdominal viscera	*Unilateral loss of palatal elevation*: Patients complain that on drinking liquids, the fluid refluxes through the nose *Unilateral vocal cord paralysis*: Hoarse voice	Brainstem lesion Injury to the recurrent laryngeal nerve during surgery
Cranial nerve XI: Spinal accessory nerve	Motor supply to the sternocleidomastoid and trapezius muscles	Downward and lateral rotation of the scapula and shoulder drop	Trauma to the nerve
Cranial nerve XII: Hypoglossal nerve	Motor supply to the intrinsic and extrinsic muscles of the tongue	*Tongue deviations*: *Upper motor neuron lesion* causes the tongue to deviate toward the opposite side *Lower motor neuron lesion* causes the tongue to deviate toward the side of the lesion, and the affected side atrophies over time	Stroke or tumor can cause upper motor neuron lesion Amyotrophic lateral sclerosis can cause bilateral lower motor neuron lesion with atrophy Metastatic disease to the skull base may involve the nerve

microvascular decompression of the nerve with or without partial ablation. Although the open microvascular decompression procedure has proved to be effective, with pain relief achieved in 80 to 95% of patients, the surgery is associated with the risk of significant complications, including hearing loss, facial anesthesia, cerebrospinal fluid (CSF) leak, brainstem or cerebellar injury, headaches, meningitis, and death.[10,11] Gamma Knife radiosurgery, a minimally invasive, precision-directed stereotactic radiosurgery, also has been associated with good outcomes. This highly specialized technique requires extremely sophisticated stereotactic radiofrequency equipment and is available only in specialized centers, but in many cases it has similar results for pain relief without the morbidity associated with open procedures in patients who might otherwise be a surgical risk.[12-14]

Disposition

Patients with suspected trigeminal neuralgia should be referred for specialty evaluation. Patients with a neurologic deficit require urgent imaging studies, typically magnetic resonance imaging (MRI), to rule out a mass or vascular abnormality.

FACIAL NERVE PARALYSIS

Perspective

The acute onset of facial nerve paralysis often will prompt an ED visit. Fortunately, early diagnosis and therapy may improve the patient's chance for recovery of function of the facial nerve. Facial nerve paralysis of acute onset affects approximately 20 to 25 persons per 100,000 population per year, without geographic, gender, or race predilection.[15,16]

Principles of Disease

The facial nerve innervates the muscles of facial expression and the muscles of the scalp and external ear in addition to the buccinator, platysma, stapedius, stylohyoid, and posterior belly of the digastric muscles. The sensory portion of the nerve supplies the anterior two thirds of the tongue with taste and sensation to portions of the external auditory meatus, soft palate, and adjacent pharynx. The parasympathetic portion supplies secretomotor fibers for the submandibular, sublingual, lacrimal, nasal, and palatine glands.[17]

The nerve originates from the pontomedullary junction of the brainstem and enters the internal auditory meatus with cranial nerve VIII. Within the temporal bone, the facial nerve has four major branches: the greater and lesser superficial petrosal nerves, the nerve to the stapedius muscle, and the chorda tympani. The facial nerve exits the temporal bone at the stylomastoid foramen and then enters the parotid gland, where it divides to supply the muscles of facial expression.[17,18]

Pathophysiology

The three main causes of facial nerve paralysis that are relevant to emergency medicine are grouped into infectious, traumatic, and neoplastic.

Infection

Bell's Palsy. Bell's palsy, also commonly called idiopathic facial paralysis, has long been postulated to have a viral cause. This disease entity is characterized by an abrupt onset of a lower motor neuron paresis that can progress during 1 to 7 days to complete paralysis. A prodromal illness is described by 60% of patients. Symptoms and signs frequently associated with the facial paresis include ear pain, perception of sensory change on the involved side of the face, decreased tearing, overflow of tears on the cheek (epiphora), abnormally acute hearing (hyperacusis), and impairment or perversion of taste (dysgeusia).[19]

Treatment approaches can be medical or surgical. The primary medical therapies for Bell's palsy center on reducing inflammatory changes to the nerve with corticosteroids and treating the presumed viral cause. If these therapies are unsuccessful, surgical decompression may be considered.

Available evidence now strongly favors the use of corticosteroids for the treatment of Bell's palsy, and earlier treatment is associated with better efficacy and outcomes.[20-24] The rationale for this application of steroid therapy is that edema of the nerve, confined within the facial canal, is thought to cause or contribute to the nerve injury. On the basis of this theory, most experts currently recommend a course of prednisone with an initial dose of 1 mg/kg per day for 7 to 10 days, with or without a short

www.ketabpezeshki.com 66485457-66963820

taper.[15,18,25,26] The most definitive randomized, double-blind, placebo-controlled trial involving 496 patients showed an improvement in complete recovery of facial nerve function at 3 months from 64% with placebo to 83% with the use of prednisolone in a dose of 25 mg by mouth twice daily.[27] Therapy should be started as soon as possible, ideally within the first 24 hours, but it is still recommended for patients without contraindications who seek treatment within 1 week of symptom onset.[25]

A number of studies have supported the contention that Bell's palsy may be caused by herpes virus infection. One study demonstrated herpes simplex virus type 1 DNA in the endoneurial tissue of 11 of 14 patients with Bell's palsy but not in control subjects.[28] In a trial of prednisone and acyclovir in 99 patients, patients treated with prednisone and acyclovir had a more favorable recovery than that observed in patients receiving prednisone alone.[29] A study of 296 patients with Bell's palsy treated with valacyclovir or placebo in addition to a fixed dose of prednisolone found significant benefit to the addition of valacyclovir, particularly in the setting of severe palsy or in those treated within 24 hours of symptom onset.[30] Other studies have found conflicting results. Despite a lack of overwhelming evidence, the addition of an antiviral agent should be considered in the treatment of Bell's palsy, especially with severe loss of function. The most commonly recommended antiviral regimen is valacyclovir, 1000 mg orally two times daily for 10 days. Valacyclovir and famciclovir have better oral absorption, are better tolerated, and are dosed less frequently, resulting in higher compliance than with acyclovir treatment.[18,25,26,28,31] As with steroid therapy, although earlier treatment is preferred, treatment should be considered for patients presenting within 1 week of symptom onset.

Ramsay Hunt Syndrome. Ramsay Hunt syndrome (herpes zoster oticus) is characterized by unilateral facial paralysis, a herpetiform vesicular eruption, and vestibulocochlear dysfunction. The vesicular eruption may occur on the pinna, external auditory canal, tympanic membrane, soft palate, oral cavity, face, and neck as far down as the shoulder. The pain is considerably more severe than that associated with Bell's palsy, and it frequently is out of proportion to physical findings. In addition, outcomes are worse than with Bell's palsy, with a lower incidence of complete facial recovery and the possibility of sensorineural hearing loss. Therapy is similar to that for Bell's palsy. Both prednisone and antiviral therapy for 7 to 10 days are advocated.[18,32,33]

Lyme Disease. Lyme disease is the most frequent vector-borne infection in the United States. It is caused by the spirochete *Borrelia burgdorferi* and is spread by the bite of *Ixodes* genus ticks. Neurologic manifestations can arise in any phase of the disease, and the incidence of facial palsy in patients with neurologic involvement is 35 to 51%. In regions in which Lyme disease is endemic, it has been shown to be the leading cause of facial paralysis in children, responsible for half of all pediatric cases of facial nerve paralysis.[34,35]

Bilateral facial nerve paralysis is rare but can occur with systemic infections. The two diseases most commonly associated with bilateral simultaneous onset of facial paralysis are Lyme disease and infectious mononucleosis. Bilateral facial paralysis should be considered to be a manifestation of Lyme disease until further testing excludes this diagnosis.[26,34-36] The evaluation and treatment of Lyme disease are discussed in Chapter 134.

Bacterial Infections. Facial paralysis can be caused by acute bacterial infections of the middle ear, mastoid, or external auditory canal. In the pre-antibiotic era, facial paralysis was associated with acute otitis media in approximately 2% of cases; today, however, it occurs in only 0.2% of cases. Treatment consists of intravenous antibiotics and myringotomy for decompression. Malignant otitis externa can be associated with facial paralysis. This disease entity is most commonly seen in immunocompromised patients and usually is caused by *Pseudomonas* infection. Treatment involves prolonged intravenous antipseudomonal antibiotic therapy and may require surgical débridement.[26,37]

Trauma

In patients with head trauma, the facial nerve is the most commonly injured cranial nerve. The cause generally is a temporal bone fracture with nerve transection. Surgical exploration is warranted if there is firm evidence that the nerve has been transected, indicated by a sudden onset of complete unilateral facial paralysis, loss of electrical activity, and evidence of a displaced fracture involving the facial canal.

Neoplasm

Tumors of the facial nerve itself or tumors anywhere along the course of the facial nerve that invade or compress the nerve may lead to facial paralysis. The course is typically progressive for at least 3 weeks. A sudden onset of paralysis, however, does not rule out an underlying tumor because facial paralysis secondary to a neoplasm is of sudden onset in approximately 25% of cases.[38] A neoplastic cause should be suspected in patients who suffer from recurrent ipsilateral facial paralysis, significant pain, prolonged symptoms, or any other concomitant cranial nerve abnormality.

Clinical Features and Differential Considerations

The medical history in patients with facial paralysis focuses on onset of the paralysis, concentrating on timing and rapidity of onset and associated signs and symptoms. A rapid onset of facial paralysis with dysgeusia and hyperacusis preceded by a viral prodrome is suggestive of Bell's palsy. A history of recurrent ipsilateral paralysis or slow progression of symptoms is more characteristic of a tumor. Associated cranial nerve abnormalities, although occasionally seen with Bell's palsy, also point to the possibility of a tumor or ischemic insult. The Ramsay Hunt syndrome causes significant pain and a vesicular rash, although the rash may follow the facial paresis by a few days. Significant anatomic abnormalities on visual or otoscopic inspection of the ipsilateral ear will be found with bacterial otitis media and otitis externa. Finally, systemic symptoms or bilateral facial paresis, especially in endemic areas, should raise the possibility of Lyme disease.

Diagnostic Strategies

The diagnostic workup of acute facial nerve paresis is based on whether the clinical picture is suggestive of a disease process other than Bell's palsy. If the clinical history is classic for Bell's palsy, no imaging or laboratory studies are required. Of note, any history of possible exposure warrants serologic evaluation for Lyme disease. Although outpatient testing including electroneurography may ultimately be performed, this usually is not part of the initial evaluation.

The presence of a "central" seventh nerve paralysis (upper face sparing) should prompt imaging with computed tomography (CT) or MRI, and consideration should be given to the possibility of an acute stroke or other hemispheric lesion. History or physical examination findings suggestive of a possible tumor require imaging to rule out a neoplasm. The study of choice will depend on the institution and preferences of the consultant.

Disposition

Most patients who have a seventh nerve paralysis will have a clinical diagnosis of Bell's palsy and may be discharged with referral

www.ketabpezeshki.com 66485457-66963820

for short-term follow-up. Patients with a possible hemispheric process, such as stroke or tumor, require further evaluation and usually hospitalization. Patients thought to have Lyme disease require immediate initiation of appropriate antibiotic therapy.

In patients with a peripheral facial nerve paralysis, the ipsilateral eye should be patched, and consideration should be given to ophthalmologic follow-up because there is a high rate of corneal abrasions and corneal dryness associated with the inability to blink properly or to close the eye completely.

VESTIBULAR SCHWANNOMA

Perspective

Vestibular schwannoma, formally referred to as acoustic neuroma, is a rare but important cause of sensorineural hearing loss. The annual incidence of vestibular schwannoma is 1 case per 100,000 population, with a mean age at the time of detection of 46 to 58 years.[39] The female-to-male ratio is 1.5 : 1. Vestibular schwannoma is rarely bilateral, occurring in this form in approximately 5% of cases and generally associated with type 2 neurofibromatosis. Although histologically benign, vestibular schwannoma can cause neurologic damage by direct compression on the eighth cranial nerve and the other structures in the cerebellopontine angle.[40]

Principles of Disease

Vestibular schwannoma arises from the Schwann cells covering the vestibular branch of the eighth cranial nerve as it passes through the internal auditory canal. The tumor may compress the cochlear (acoustic) branch of the eighth cranial nerve, causing hearing loss, tinnitus, and dysequilibrium. Continued growth of the tumor may result in compression of structures in the cerebellopontine angle, where the facial and trigeminal nerves may be compressed and damaged. Larger tumors may further encroach on the brainstem and if large enough may compress the fourth ventricle, ultimately resulting in signs of increased intracranial pressure (ICP).[41]

Clinical Features

Asymmetrical sensorineural hearing loss is the hallmark of vestibular schwannoma. Up to 15% of patients with this tumor, however, will have normal results on audiometry. These patients typically have symptoms such as unilateral tinnitus, imbalance, headache, fullness in the ear, otalgia, and facial nerve weakness. Thus, patients with asymmetrical symptoms should be further evaluated for vestibular schwannoma even with normal findings on audiometry.[42]

Vestibular schwannomas are extremely slow-growing tumors, averaging an approximately 1-mm increase per year, although many do not grow at all on serial examinations.[43] Symptom onset is therefore generally gradual. In one series of 126 cases, the average time from symptom onset to discovery of a vestibular schwannoma was approximately 4 years.[44]

Diagnostic Strategies

When vestibular schwannoma is suspected, the patient is evaluated by audiometry or gadolinium-enhanced MRI. This imaging technique is extremely sensitive and has led to earlier diagnosis and a decrease in mean size at detection of vestibular schwannoma. CT lacks the necessary sensitivity in the posterior cranial fossa to reliably rule out the presence of vestibular schwannoma. The smaller the tumor at the time of diagnosis, the more options there are for therapy and the better the potential prognosis.[40]

Differential Considerations

A majority of disease entities included in the differential diagnosis for vestibular schwannoma cause symmetrical sensorineural hearing loss. Asymmetrical sensorineural hearing loss has few causes other than vestibular schwannoma. Ménière's disease may present a diagnostic dilemma because it can be asymmetrical. Ménière's disease may be differentiated from vestibular schwannoma in that the tinnitus of Ménière's disease usually is intermittent, whereas the tinnitus of vestibular schwannoma typically is continuous. In addition, patients with Ménière's disease typically describe true vertigo, whereas patients with a vestibular schwannoma are more likely to describe imbalance or dysequilibrium.

Vestibular schwannomas account for 80% of all cerebellopontine angle tumors. Among all other lesions, meningioma is the most common. Meningiomas more frequently cause symptoms of facial palsy or trigeminal nerve abnormality. Of note, however, considerable similarity between the clinical picture of a meningioma and that of vestibular schwannoma in the cerebellopontine angle has been described.[45]

Management

Vestibular schwannoma may be removed surgically or ablated with stereotactic radiation therapy. In general, tumors larger than 3 cm are recommended for microsurgery because radiation treatments, such as with the Gamma Knife or linear accelerator, are less effective for local control and growth arrest in larger masses. Smaller tumors are amenable to use of stereotactic radiation therapy, which has greater salvage rates of facial nerve function and hearing.[46,47] Stereotactic radiation therapy generally has good long-term outcomes of local growth arrest, with nerve salvage approaching 90% or greater. Injuries to the trigeminal, facial, and acoustic nerves and to the cerebellum are possible complications of both procedures. In patients who are minimally symptomatic with small tumors, serial monitoring with MRI is a viable nonsurgical option. All patients should be evaluated by a specialist in the evaluation and treatment of vestibular schwannoma because smaller tumor size at detection is associated with a better long-term outcome.[39,43]

Disposition

Patients with suspected acoustic neuroma should be referred for audiometry or MRI and evaluation by a specialist in either otolaryngology or neurosurgery.

DIABETIC CRANIAL MONONEUROPATHY

Perspective

Cranial mononeuropathies occur uncommonly, usually are a complication of diabetes, and most often affect the extraocular muscles. The oculomotor nerve is most commonly affected, followed in order by the trochlear and abducens nerves. In one large series in Japan, the incidence of cranial nerve palsies was 1.0% among diabetics and 0.1% among nondiabetics.[48,49] Whereas ophthalmoplegia appears to be closely related to diabetes, facial palsy is less strongly correlated with this disease.[48,50]

Principles of Disease

The pathologic basis of diabetic mononeuropathy appears to be ischemia of the affected cranial nerve caused by occlusion of an intraneural nutrient artery serving the nerve. This occlusion leads

www.ketabpezeshki.com 66485457-66963820

to injury located primarily in the center of the nerve because the core fibers are more dependent on the supply from such nutrient arteries. The peripheral fibers are less affected because they also are supplied by collateral vessels. In the oculomotor nerve, the preservation of the circumferentially located parasympathetic fibers explains the pupillary sparing that usually is found in this syndrome. In two studies, the microvascular changes in the intraneural arteries that lead to occlusion were noted in diabetic patients but absent in nondiabetics.[51,52]

Clinical Features

Patients typically describe acute onset of unilateral retro-ocular and supraorbital pain, diplopia, and ptosis.[49] The physical manifestations of a third cranial nerve palsy include the inability to move the eye superiorly and medially, accompanied by ptosis. The pupillary light reflex usually is present. Although it is a less common finding, the fourth and sixth cranial nerves may be affected. Patients with a fourth cranial nerve palsy are unable to move the eye inferolaterally, and those with a sixth cranial nerve palsy are unable to move the eye laterally. Because of the long intracranial course of the sixth nerve, a patient with an isolated sixth nerve palsy should be evaluated for an intracranial lesion or increased ICP.[53]

Differential Considerations

Evaluation of cranial nerve dysfunction requires a thorough history and physical examination and cranial imaging, usually with MRI. Diabetic mononeuropathy should be considered a diagnosis of exclusion. Considerations in the differential diagnosis include trauma, tumor, vertebrobasilar ischemia, aneurysm, and hemorrhage into the brainstem.[54]

Management

Treatment consists of patching of the affected eye and administration of analgesics and antiplatelet therapy. The prognosis is good. If the neuropathy does not begin to resolve within 3 to 6 months or if more than one nerve is affected, another cause should be sought. Complete resolution is expected within the first year. Antioxidant preparations, including α-lipoic acid, have been used therapeutically and have not shown harm, but such agents have yet to be shown to have convincing clinical effect.[55]

CEREBRAL VENOUS THROMBOSIS

Perspective

No exhaustive studies of the epidemiology of cerebral venous thrombosis (CVT) have been performed. In case series, the median patient age is 38 years; women represent 60 to 75% of those diagnosed.[56,57]

Principles of Disease

Cerebral blood is drained by several major veins that lead into the dural sinuses. The major dural sinuses are the superior sagittal sinus, the inferior sagittal sinus, the straight sinus, the lateral sinuses, and the sigmoid sinuses. The variability in symptoms and signs in patients who present with CVT stems from differences in thrombus location and acuity of thrombus formation. Symptoms of intracranial hypertension, especially headache, are present in most patients with sinus thrombosis, whereas those with thrombosis of the cerebral veins are thought to be more prone to hemorrhagic infarction and localizing neurologic deficits.[58] As with venous thrombosis in other locations, multiple causes and predisposing factors for CVT are recognized. Underlying causes are often divided into infectious and noninfectious categories. Infectious causes include local infections, such as sinusitis, otitis media, facial cellulitis, and systemic infections. Noninfectious causes include direct injury to the cerebral venous system from trauma, surgery, dehydration, or any other condition that may predispose the patient to development of a hypercoagulable state, including the presence of a malignant neoplasm or the use of oral contraceptive agents.[59]

Clinical Features

The symptoms and signs associated with CVT are varied. Headache is the primary feature of CVT in 74 to 92% of affected patients.[59,60] Papilledema is noted in 28 to 45% of cases.[57,60,61] Lethargy, decreased level of consciousness, or mental status changes may be noted. Seizures occur in 35 to 50% of patients in the acute phase.[57,59,61,62] In addition to the location and acuity of thrombosis formation, a patient's symptom onset will vary in accordance with the extent of collateral vessel growth in the venous territory. Early thrombotic changes may be well compensated for by the collateral venous drainage. Symptoms will appear only when the compensation for venous thrombosis is no longer sufficient or when hemorrhagic infarction occurs. Variability in collateralization between patients also adds to the variability and time course of symptoms. Two national and international observational studies documented an average time from symptom onset to diagnosis of 7 days, reflecting the difficulty in diagnosis of this rare disease entity.[57,61,63] The reported incidence of focal neurologic signs, including seizures, on clinical examination varies widely between series, ranging from 25 to 71%.[59,60] Because of the broad spectrum of possible clinical features, the diagnosis of CVT may be difficult but should be a consideration in any patient with unexplained headache, especially in combination with focal neurologic deficit, papilledema, or seizures.

Diagnostic Strategies

Cerebral angiography no longer plays a significant role in the diagnosis of CVT. Both MRI and CT scan with venous-phase imaging have been evaluated as both primary and definitive imaging modalities for the diagnosis of CVT. CT scanning is useful in the initial workup of the patient with possible CVT, but non–contrast-enhanced CT is neither sensitive nor specific enough to reliably confirm or exclude the diagnosis. Findings on CT that are consistent with CVT include hyperdensity of a thrombosed sinus or deep vein (referred to as the cord sign or attenuated vein sign, respectively), brain edema, and hemorrhage secondary to venous congestion. Whereas non–contrast-enhanced CT in the diagnosis of CVT has been evaluated only in case series, the published sensitivity and specificity typically range from 65 to 100% when it is evaluated against MRI as the "gold standard."[64]

Similar to CT scanning, MRI also can demonstrate local changes secondary to venous congestion, such as brain edema and hemorrhage. In addition, MRI can demonstrate the possibility of CVT by the lack of a "flow void." On conventional MRI, a flow void indicates the presence of moving blood within the sinus, whereas the absence of a flow void indicates a possible thrombus. Diagnostic accuracy, however, is greatly improved through use of magnetic resonance venography (MRV). This technique takes advantage of the MRI signal characteristics of flowing blood to create images of venous structures. Combination of these imaging techniques further enhances diagnostic accuracy. For imaging of a particular dural sinus, presence of the sinus on conventional MRI and lack of flow on MRV are diagnostic of a sinus thrombosis. This

www.ketabpezeshki.com 66485457-66963820

combined approach has diagnostic sensitivity similar to that of conventional angiography.[59,65]

Several studies show similar sensitivity between MRV and CT venography for the diagnosis of CVT when the CT study is performed on a multidetector row CT scanner. These studies, involving several hundred patients, showed sensitivity of CT venography for CVT that approached 100% and was comparable to that of MRV both in sensitivity and in inter-rater reliablity.[66-69] The sensitivity of CT venography performed by scanners that do not use multidetector row technology is unknown.

Several small studies have attempted to evaluate the usefulness of the D-dimer assay as a screening tool to exclude CVT, particularly when MRI or CT venography is not available. Although the reported sensitivity rates are fair at 83 to 100%, larger prospective studies need to be done to further define the role of D-dimer in the evaluation of CVT because several case reports have noted normal D-dimer levels in the setting of documented CVT.[70-74] In general, although a normal D-dimer level does not exclude the diagnosis of CVT, it does appear to make this diagnosis much less likely, particularly in a patient with symptoms of less than 2 weeks in duration.

Differential Considerations

Considerations in the differential diagnosis of CVT include the conditions that cause patients to present with the new onset of neurologic deficits, alteration in consciousness, or severe headache. A diagnosis of CVT should be considered in a patient with such symptoms when the etiology is unclear, particularly when there is the possibility of a hypercoagulable state and when the head CT scan is normal in appearance or shows subtle signs of CVT.

Management

CVT is a relatively rare disease, and controlled studies evaluating its treatment are lacking. Current therapeutic consensus strongly recommends systemic anticoagulation with low-molecular-weight heparin (LMWH) or unfractionated heparin to prevent further clot formation and to promote recanalization, even in patients with intracranial hemorrhage on initial imaging.[59,60,74,75] In one placebo-controlled randomized trial comprising only 20 patients, anticoagulation with unfractionated heparin demonstrated benefit, even in patients with evidence of intracranial hemorrhage on the pretreatment CT scan.[76] A registry comparing outcomes of patients treated with unfractionated heparin compared with LMWH found more benefit in the LMWH group, although the effect was modest.[77] Two large observational trials also showed improvement in modified Rankin scale at follow-up in the anticoagulated groups, although the trials were not randomized.[57,61] Despite a paucity of randomized controlled trials, expert opinion favors anticoagulation in all groups unless another contraindication is present.[78]

Catheter-based intervention with thrombolysis has been attempted in multiple case series with use of either urokinase or tissue plasminogen activator. Thrombolysis was shown to be relatively safe and relatively successful in very small case series.[75] In one nonrandomized study of 40 patients, 20 received systemic heparin and 20 received catheter-based infusion of urokinase followed by systemic heparin. Despite initially worse neurologic function in the thrombolysis group, a significant difference in neurologic function favoring thrombolysis was observed at discharge.[79] This promising therapy is typically considered only for patients with symptoms of decreased level of consciousness, elevated ICP, or rapid deterioration on neurologic examination.

Disposition

All patients with suspected CVT should be admitted to a unit capable of providing a high level of care with neurologic consultation. Patients should be anticoagulated if no contraindication exists, and catheter-based thrombolysis should be considered in patients with depressed mental status or focal findings on neurologic examination.

MULTIPLE SCLEROSIS

Perspective

Multiple sclerosis (MS) is an inflammatory disease that affects the central nervous system (CNS). Although the exact etiology remains uncertain, the pathologic manifestation of this inflammatory disease is a demyelination of discrete regions (plaques) within the CNS with a relative sparing of axons. The clinical picture is highly variable but is classically characterized by episodes of neurologic dysfunction that evolve in days and resolve during weeks.

MS has an overall prevalence in the United States of 0.1%. The peak age at onset is 25 to 30 years; women are slightly younger than men at onset. The incidence in women exceeds that of men by a ratio of 1.8 : 1. The worldwide prevalence is greatest in the United Kingdom, Scandinavia, and North America. Epidemiologic studies indicate that both genetic and environmental factors are associated with an increased incidence of this disease. MS has a 30% concordance rate between monozygotic twins, and 20% of patients with MS have at least one affected relative. MS is more common in temperate climates. It is rare between 23 degrees north and south latitudes but has a rising incidence above and below 50 degrees north and south latitudes, respectively. Although no exact environmental factor has been identified, if a person emigrates from an area of high prevalence to an area of low prevalence before the age of 20 years, the risk is diminished. MS is rare in Africans and Asians, but African Americans have a higher incidence than their relatives who remain in Africa.[80] In addition, reports of clusters or mini-epidemics support environmental factors. Thus, an environmental cause superimposed on genetic susceptibility appears to be a likely etiologic scenario.[81,82]

Principles of Disease

MS is considered to be an organ-specific autoimmune disease. One theory proposes that genetic factors interact with an environmental trigger or infection to establish pathologically autoreactive T cells in the CNS. After a long and variable latency period (typically 10 to 20 years), a systemic trigger, such as a viral infection or superantigen, activates these T cells. The activated T cells, on reexposure to the autoantigen, initiate the inflammatory response. This sets off a complex immunologic cascade that leads to the demyelination characteristic of MS. This demyelination process releases CNS antigens that are hypothesized to initiate further episodes of autoimmune-induced inflammation. The mechanisms underlying this autoimmunity in MS are unknown.[83]

Clinical Features

The clinical picture in MS is one of marked heterogeneity. The classic clinical syndrome consists of recurring episodes of neurologic symptoms that rapidly evolve during days and slowly resolve. Variability occurs in age at onset, location of CNS lesions, frequency and severity of relapses, and degree and time course of progression.

The clinical features of MS can be divided into areas of specific CNS impairment: cognition; cranial nerves; motor pathways;

www.ketabpezeshki.com 66485457-66963820

sensory pathways; cerebellar pathways; and bowel, bladder, and sexual dysfunction.[80]

Patients with MS have frequent complaints of poor memory, distractibility, and decreased capacity for sustained mental effort. Formal neuropsychological testing suggests that cognitive involvement is common and underreported. Specifically, neuropsychological testing has shown that 43 to 65% of patients with MS have some degree of cognitive impairment.[84,85] Of note, a correlation has been found between the MRI-based total lesion load and presence of cognitive impairment.[86]

Cranial nerve dysfunction is common in MS. The most common associated cranial nerve abnormality is *optic neuritis,* a unilateral syndrome characterized by pain in the eye and a variable degree of visual loss affecting primarily central vision. Within 2 years of an attack of optic neuritis, the risk of MS is approximately 20%, and within 15 years, it is approximately 45 to 80%.[87,88] Optic neuritis often is the first symptom of MS.[89,90]

As a result of lesions in the vestibulo-ocular connections, the oculomotor pathways also may be affected. The deficit may be manifested as diplopia or nystagmus. The nystagmus may be severe enough that the patient may complain of oscillopsia (a subjective oscillation of objects in the visual field). Cranial nerve impairment also may include impairment of facial sensation, which is relatively common. Unilateral facial paresis also may occur. In addition, the occurrence of trigeminal neuralgia in a young person may be an early sign of MS.

Motor pathways also are commonly involved. Specifically, corticospinal tract dysfunction is common in patients with MS. Paraparesis or paraplegia occurs with greater frequency than upper extremity lesions owing to the common occurrence of lesions in the motor tracts of the spinal cord. In patients with significant motor weakness, spasms of the legs and trunk may occur on attempts to stand from a seated position. This dysfunction is manifested on physical examination as spasticity that typically is worse in the legs than in the arms. The deep tendon reflexes are markedly exaggerated, and sustained clonus may be demonstrated. Although these symptoms frequently are bilateral, they generally are asymmetrical.[80]

Sensory manifestations are a frequent initial feature of MS and will be present in nearly all patients at some point during the course of the disease. Sensory symptoms are commonly described as numbness, tingling, "pins and needles" paresthesias, coldness, or a sensation of swelling of the limbs or trunk.[80]

Impairment of the cerebellar pathway results in significant gait imbalance, difficulty with coordinated actions, and dysarthria. Physical examination reveals the typical features of cerebellar dysfunction, including dysmetria, dysdiadochokinesis (an impairment of rapid alternating movements), breakdown in the ability to perform complex movements, intention tremor in the limbs and head, truncal ataxia, and dysarthria.[80]

Impairment of bowel, bladder, and sexual function also is common. The extent of sphincter and sexual dysfunction usually parallels the motor impairment in the lower extremities. Urinary frequency may progress to urinary incontinence as the disease advances. An atonic bladder may develop, which empties by simple overflow and often is associated with the loss of perception of bladder fullness and with anal and genital hypoesthesia. Constipation becomes common in time, and almost all patients with paraplegia require special measures to maintain effective bowel habits. Sexual dysfunction, although frequently overlooked, is common in MS. Approximately 50% of patients become completely sexually inactive as a result of this disease.[80]

Diagnostic Strategies

Although no laboratory tests are diagnostic for MS, one clinical feature remains unique to this disease: *Uhthoff's phenomenon,* temporary worsening of current or preexisting signs or symptoms of MS secondary to small increases in the patient's body temperature. Accordingly, exercise, a hot bath, exposure to a warm environment, or fever can bring about Uhthoff's phenomenon. This phenomenon reflects subclinical demyelination or preexisting injury to nerves without obvious significant clinical involvement before heat exposure or temperature elevation.[80]

MS is described as a relapsing-remitting disorder with symptoms that fluctuate over time. Therefore, the clinical diagnosis rests on occurrence of at least two clinical episodes with different neurologic symptoms at different times.

Findings on CSF analysis are abnormal in 90% of the cases. Fifty percent of patients will have pleocytosis, with more than five lymphocytes per high-power field in the CSF. Approximately 70% of patients will have an elevated gamma globulin level, with immunoglobulin G (IgG) ranging from 10 to 30% of the CSF total protein. Electrophoresis of the CSF demonstrates oligoclonal bands of IgG in 85 to 95% of patients who carry a diagnosis of MS; however, oligoclonal bands of IgG also are seen with neurosyphilis, fungal meningitis, and other CNS infections. Lumbar puncture is recommended for patients with suspected MS, but mass lesions and elevated ICP should be ruled out before lumbar puncture is attempted.[91]

The initial imaging test to aid in the diagnosis of MS is gadolinium-enhanced MRI. MRI is a sensitive test for the detection of lesions consistent with MS and also is useful to assess disease severity.[92] The lesions of MS typically appear hyperintense, or bright white, on T2-weighted or fluid-attenuated inversion recovery (FLAIR) MRI studies. Lesions usually are multiple and commonly are found in the periventricular white matter.[93] In patients with an initial neurologic event consistent with CNS demyelination and an MRI cranial study showing multiple white matter lesions, the 5-year risk for development of MS is 60%. Patients with similar clinical syndromes and a normal MRI appearance have less than a 5% 5-year risk.[94]

Differential Considerations

Other diseases that affect the CNS white matter may be clinically and radiographically similar to MS. Considerable care must be taken to exclude these disease processes before a diagnosis is made. These include CNS tumors (especially lymphomas and gliomas), spinal cord compression, vasculitides, Behçet's disease, neurosarcoidosis, postinfectious and postvaccinal encephalomyelitis, human immunodeficiency virus (HIV) encephalopathy, Lyme disease, and vitamin B_{12} deficiency.

Management

Management of patients with MS has essentially three aspects: (1) therapies aimed at halting the progression of the disease, (2) treatment of acute exacerbations, and (3) therapies designed to modify complications.

Therapies aimed at halting disease progress are based primarily on the use of either interferon-β or glatiramer acetate. The interferons are a group of natural compounds with antiviral and immunomodulatory actions used in therapy for MS. Side effects of the agents interferon-β1a and interferon-β1b include influenza-like symptoms, depression, anxiety, and confusion. In one study, 560 patients with MS were randomly assigned to receive subcutaneous interferon-β1a or placebo (n = 187) three times a week for 2 years.[95] The relapse rate was significantly lower at 1 and 2 years with interferon-β1a than with placebo. The time to first relapse was prolonged significantly and the accumulation of brain lesions on MRI was lower in the treatment group than in the placebo group. The investigators concluded that subcutaneous interferon-β1a is a well-tolerated and effective treatment of

www.ketabpezeshki.com 66485457-66963820

relapsing-remitting MS in terms of relapse rate, defined disability, and all MRI outcome measures.[81] Interferon-β also has been shown to retard progression to clinically definite MS and to decrease the total number of brain lesions seen on subsequent MRI studies in patients who have their first demyelinating episode with MRI abnormalities at initial presentation.[96-99] This finding highlights the importance of early evaluation and treatment.

Glatiramer acetate also has successfully been used in the treatment of MS. This agent is a mixture of synthetic polypeptides designed to mimic myelin basic protein. The mechanism of action by which glatiramer acetate exerts its effect is unknown, but it is thought to modify the immune processes responsible for the pathogenesis of MS. In one study, 251 patients with relapsing-remitting MS were randomized to receive daily subcutaneous injections of glatiramer acetate (previously called copolymer 1) or placebo for 24 months. Patients receiving glatiramer acetate experienced significantly fewer relapses and were more likely to demonstrate neurologic improvement, whereas those receiving placebo were more likely to worsen. This drug generally is well tolerated.[100] Glatiramer acetate has also been shown to slow the progression to clinically definite MS after a first clinical demyelinating episode.[101]

Current recommendations for management of relapsing-remitting MS are to initiate treatment with interferon-β or glatiramer acetate. Such regimens have been demonstrated to decrease the volume of plaques seen on MRI and to diminish relapses.[83] The use of newer disease-modifying agents, such as fingolimod, cladribine, and natalizumab, has shown promise in clinical trials, but each has significant side effect profiles, and appropriate patient selection is still underway.[102-107] At this point, each of these agents is considered second line for severe or refractory patients.

Acute exacerbations of MS also should be targets for therapy. Although most such episodes will resolve without therapy, steroids have been demonstrated to diminish the duration of acute exacerbations. More than 85% of patients with relapsing-remitting MS show improvement with intravenous methylprednisolone. Intravenous steroids have been shown in controlled trials to speed the recovery from the visual loss of optic neuritis compared with placebo. In addition, when patients with acute optic neuritis are treated with high-dose intravenous steroids, the 2-year rate of development of MS is reduced, although this effect diminishes over time.[88,108] Of interest, oral prednisone was not found to be helpful in the optic neuritis trials and was associated with a potential increase in the number of optic neuritis episodes.

The current standard therapy for an acute exacerbation in MS is intravenous methylprednisolone. A typical intravenous dose is 250 to 500 mg every 12 hours for 3 to 7 days. Whether this should be followed by an oral prednisolone taper remains controversial. Potential adverse effects of methylprednisolone therapy include fluid retention, gastrointestinal hemorrhage, anxiety, psychosis, infection, and osteoporosis.

Several therapies directed toward the complications of MS may be helpful. The associated spasticity generally is treated with baclofen. This is a highly effective therapy aimed at reducing the painful flexor and extensor spasms. A major side effect is drowsiness, which generally diminishes with continued use. Higher-dose therapy can cause confusion, especially in the setting of baseline cognitive impairment. For patients with intractable spasticity, baclofen is available for intrathecal administration by either bolus therapy or continuous implanted pump therapy. Additional therapeutic agents for control of spasticity include tizanidine, diazepam, and dantrolene.

The tremor and ataxia associated with MS occasionally are treated with propranolol, diazepam, or clonazepam. The results of these therapies, however, generally are unsatisfactory. Pain often is associated with MS and affects the shoulders, pelvic girdle, and face. The facial pain may be indistinguishable from that of trigeminal neuralgia. Treatment options include carbamazepine, baclofen, and tricyclic antidepressants. Fatigue, which is common, may be ameliorated with amantadine. This agent produces partial relief for a minority of patients. In controlled studies, the effect is only slightly better than placebo.[83]

Disposition

Patients with a history of MS who seek treatment for significant symptoms must first be evaluated to rule out other, non–MS-related pathologic processes. Also, other systemic illnesses, especially infections, which can worsen the symptoms of MS, should be excluded. If the problem is thought to be an exacerbation of MS, most patients will require hospital admission for intravenous steroid therapy. An alternative to hospitalization may be to initiate intravenous steroids in the ED and to arrange for a next-day follow-up visit with the primary care physician or neurologist if outpatient intravenous steroid administration is an option.

Patients with the new onset of symptoms suggestive of MS should be admitted or referred to a neurologist because early treatment has been shown to significantly decrease progression of the disease.

KEY CONCEPTS

Trigeminal Neuralgia

- Patients with unilateral, intermittent, lancinating facial pain without abnormalities on physical examination are likely to have trigeminal neuralgia.
- Carbamazepine is the first-line agent for medical treatment.
- Patients who do not tolerate or whose pain is refractory to medical management may be candidates for microvascular decompression or ablation.

Facial Nerve Paralysis

- Patients with Bell's palsy should be treated early in the course with corticosteroids, and antiviral medication is warranted in patients with severe loss of function.
- Slowly progressive or recurrent facial paralysis is suggestive of a neoplasm. Recurrent unilateral paralysis may occur with Bell's palsy but frequently (30%) is seen in patients with tumor.
- Simultaneous bilateral facial paralysis is suggestive of Lyme disease, especially in endemic regions.
- Patients who have facial muscle paresis with intact forehead movement should be considered to have a central (upper motor neuron) lesion until the diagnostic investigation proves otherwise.

Vestibular Schwannoma

- The onset of unilateral auditory symptoms, especially sensorineural hearing loss, requires evaluation and referral to an ear, nose, and throat specialist.
- Neurologic symptoms of lower cranial nerve dysfunction, ataxia, or raised ICP may be caused by a benign tumor of the cerebellopontine angle.

Diabetic Cranial Mononeuropathy

- Diabetic neuropathy is a diagnosis of exclusion because no definitive diagnostic testing is available.
- Both ischemic and hemorrhagic brainstem lesions must be ruled out in the case of an acute ophthalmoplegia.
- Extraocular mononeuropathy is sufficiently common in patients with diabetes mellitus that its occurrence in isolation warrants evaluation of the patient for previously undiagnosed diabetes.

Cerebral Venous Thrombosis

- The differential diagnosis for CVT includes other conditions that present with new-onset neurologic deficits, alteration in

www.ketabpezeshki.com 66485457-66963820

consciousness, or severe headache. CVT is more likely to be present in such patients when the etiology is unclear, the patient is thought to have a hypercoagulable state, and the head CT is normal in appearance or shows subtle signs of CVT.

- Non–contrast-enhanced CT scanning is not adequate to rule out CVT. MRI with MRV is recommended, although multidetector row CT venography is an acceptable alternative.
- Treatment of most patients with CVT includes systemic anticoagulation, even in the setting of hemorrhagic cerebral infarcts, unless another contraindication exists.

Multiple Sclerosis

- Any patient with a long-term illness, such as MS, must be evaluated to rule out pathologic processes not related to that illness before an exacerbation of the illness can be assumed to be the cause of any problems experienced by the patient.
- Therapy for patients with MS will require consultation with the patient's primary care provider or neurologist to provide consistent disease management.
- Intravenous methylprednisolone effectively promotes earlier resolution of recurrences.
- Intravenous methylprednisolone has been shown to speed the recovery from vision loss from optic neuritis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Bennetto L, Patel NK, Fuller G: Trigeminal neuralgia and its management. *BMJ* 2007; 334:201.
2. MacDonald BK, Cockerell OC, Sander JWAS, Shorvon SD: The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* 2000; 123:665.
3. Katusic CS, Beard M, Bergstralth E, Kurland LT: Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945-1984. *Ann Neurol* 1990; 27:89.
4. Patel NK, et al: How accurate is magnetic resonance angiography in predicting neurovascular compression in patients with trigeminal neuralgia? A prospective, single-blinded comparative study. *Br J Neurosurg* 2003; 17:60.
5. Fukuda H, Ishikawa M, Okumura R: Demonstration of neurovascular compression in trigeminal neuralgia and hemifacial spasm with magnetic resonance imaging: Comparison with surgical findings in 60 consecutive cases. *Surg Neurol* 2003; 59:93.
6. Tenser RB: Trigeminal neuralgia: Mechanisms of treatment. *Neurology* 1998; 51:17.
7. Delzell JE Jr, Grelle AR: Trigeminal neuralgia: New treatment options for a well-known cause of facial pain. *Arch Fam Med* 1999; 8:264.
8. Jensen T, et al: Association of trigeminal neuralgia with multiple sclerosis: Clinical and pathological features. *Acta Neurol Scand* 1982; 65:182.
9. Taha JM, Tew JM: Comparison of surgical treatments for trigeminal neuralgia: Reevaluation of radiofrequency rhizotomy. *Neurosurgery* 1996; 38:865.
10. Chen JF, Lee ST: Comparison of percutaneous trigeminal ganglion compression and microvascular decompression for the management of trigeminal neuralgia. *Clin Neurol Neurosurg* 2003; 105:203.
11. McLaughlin MR, et al: Microvascular decompression of cranial nerves: Lessons learned after 4400 operations. *J Neurosurg* 1999; 90:1.
12. Dhople AA, et al: Long-term outcomes of Gamma Knife radiosurgery for classic trigeminal neuralgia: Implications of treatment and critical review of the literature. *J Neurosurg* 2009; 111:351-358.
13. Kondziolka D, et al: Gamma Knife radiosurgery for trigeminal neuralgia: Results and expectations. *Arch Neurol* 1998; 55:1524.
14. Shetter AG, et al: Gamma Knife radiosurgery for recurrent trigeminal neuralgia. *J Neurosurg* 2002; 97:536.
15. Adour K, et al: The true nature of Bell's palsy: Analysis of 1000 consecutive patients. *Laryngoscope* 1978; 88:787.
16. Hauser W, et al: Incidence and prognosis of Bell's palsy in the population of Rochester, Minnesota. *Mayo Clin Proc* 1971; 46:258.
17. Logan BM, Reynolds PA, Hutchings RT, eds: *McMinn's Color Atlas of Head and Neck Anatomy*, 3rd ed. London: Mosby; 2004.
18. Jackson CG, Doersten PGV: The facial nerve: Current trends in diagnosis, treatment, and rehabilitation. *Med Clin North Am* 1999; 83:179.
19. Marenda S, Olsson J: The evaluation of facial paralysis. *Otolaryngol Clin North Am* 1997; 30:669.
20. Sullivan FM, et al: A randomised controlled trial of the use of aciclovir and/or prednisolone for the early treatment of Bell's palsy: The BELLS study. *Health Technol Assess* 2009;13:iii-iv, ix-xi, 1-130.
21. de Almeida JR, et al: Combined corticosteroid and antiviral treatment for Bell Palsy. *JAMA* 2009; 302:985-993.
22. Salinas RA, Alvarez G, Daly F, Ferreira J: Corticosteroids for Bell's palsy (idiopathic facial paralysis). *Cochrane Database Syst Rev* 2010; 3:CD001942.
23. Yeo SG, Lee YC, Park DC, Cha CI: Acyclovir plus steroid vs steroid alone in the treatment of Bell's palsy. *Am J Otolaryngol* 2008; 29:163-166.
24. Engström M, et al: Prednisolone and valaciclovir in Bell's palsy: A randomised, double-blind, placebo-controlled, multicentre trial. *Lancet Neurol* 2008; 7:993-1000.
25. Knox GW: Treatment controversies in Bell's palsy. *Arch Otolaryngol Head Neck Surg* 1998; 124:821.
26. Ruckenstein MJ: Evaluating facial paralysis: Expensive diagnostic tests are often unnecessary. *Postgrad Med* 1998; 103:187.
27. Sullivan FM, et al: Early treatment with prednisolone or acyclovir in Bell's palsy. *N Engl J Med* 2007; 357:1598.
28. Murakami S, et al: Bell's palsy and herpes simplex virus: Identification of viral DNA in endoneurial fluid and muscle. *Ann Intern Med* 1996; 124:27.
29. Adour KK, Ruboyianes JM, Doersten PGV, Byl FM: Bell's palsy treatment with acyclovir and prednisone compared with prednisone alone: A double-blind, randomized, controlled trial. *Ann Otol Rhinol Laryngol* 1996; 105:371.
30. Hato N, et al: Valacyclovir and prednisolone treatment for Bell's palsy: A multicenter, randomized, placebo-controlled study. *Otol Neurotol* 2007; 28:408.
31. Axelsson S, Lindberg S, Stjernquist-Desatnik A: Outcome of treatment with valacyclovir and prednisone in patients with Bell's palsy. *Ann Otol Rhinol Laryngol* 2003; 112:197.
32. Dickins JRE, Smith JT, Graham S: Herpes zoster oticus: Treatment with intravenous acyclovir. *Laryngoscope* 1988; 98:776.
33. Uri N, Greenberg E, Kitzes-Cohen R, Doweck I: Acyclovir in the treatment of Ramsay Hunt syndrome. *Otolaryngol Head Neck Surg* 2003; 129:379.
34. Dotevall L, Hagberg L: Successful oral doxycycline treatment of Lyme disease–associated facial palsy and meningitis. *Clin Infect Dis* 1994; 28:569.
35. Cook SP, et al: Lyme disease and seventh nerve paralysis in children. *Am J Otolaryngol* 1997; 18:320.
36. Smith V, Traquina DN: Pediatric bilateral facial paralysis. *Laryngoscope* 1998; 108:519.
37. Joseph EM, Sperling NM: Facial nerve paralysis in acute otitis media: Cause and management revisited. *Otolaryngol Head Neck Surg* 1998; 118:694.
38. Jackson CG, Glasscock ME, Hughes G, Sismanis A: Facial paralysis of neoplastic origin: Diagnosis and management. *Laryngoscope* 1980; 90:1581.
39. Myrseth E, Pedersen PH, Moller P, Lund-Johansen M: Treatment of vestibular schwannomas: Why, when and how? *Acta Neurochir (Wien)* 2007; 149:647.
40. The Consensus Development Panel: National Institutes of Health Consensus Development Conference Statement on Acoustic Neuroma, December 11-13, 1991. *Arch Neurol* 1994; 51:201.
41. Selesnick S, Jackler R: Clinical manifestations and audiologic diagnosis of acoustic neuromas. *Otolaryngol Clin North Am* 1992; 25:521.
42. Wright A, Bradford R: Management of acoustic neuroma. *BMJ* 1995; 311:1141.
43. Backous DD, Pham HT: Guiding patients through the choices for treating vestibular schwannomas: Balancing options and ensuring informed consent. *Otolaryngol Clin North Am* 2007; 40:521.
44. Selesnick S, Jackler R, Pitts L: The changing clinical presentation of acoustic tumors in the MRI era. *Laryngoscope* 1993; 103:431.
45. Harvey S, Haberkamp T: Pitfalls in the diagnosis of CPA tumors. *Ear Nose Throat J* 1991; 70:290.
46. Myrseth E, Moller P, Pedersen PH, Lund-Johansen M: Vestibular schwannoma: Surgery or gamma knife radiosurgery? A prospective, nonrandomized study. *Neurosurgery* 2009; 64:654-661.
47. Murphy ES, et al: Long-term outcomes of Gamma Knife radiosurgery in patients with vestibular schwannomas. *J Neurosurg* 2011; 114:432-440.
48. Watanabe K, et al: Characteristics of cranial nerve palsies in diabetic patients. *Diabetes Res Clin Pract* 1990; 10:19.
49. Thomas PK: Clinical features and investigation of diabetic somatic peripheral neuropathy. *Clin Neurosci* 1997; 4:341.
50. Greco D, Gambina F, Pisciotta M, Abrignani M, Maggio F: Clinical characteristics and associated comorbidities in diabetic patients with cranial nerve palsies. *J Endocrinol Invest* 2012; 35:146-149.
51. Asbury AK, Aldredge H, Hershberg R, Fisher CM: Oculomotor palsy in diabetes mellitus: A clinico-pathological study. *Brain* 1970; 93:555.
52. Brown MJ, Asbury AK: Diabetic neuropathy. *Ann Neurol* 1984; 15:2.
53. Clements RS, Bell DS: Diabetic neuropathy: Peripheral and autonomic syndromes. *Postgrad Med* 1982; 71:50.
54. Fujioka T, et al: Ischemic and hemorrhagic brain stem lesions mimicking diabetic ophthalmoplegia. *Clin Neurol Neurosurg* 1995; 97:167.
55. Tankova T, Cherninkova S, Koev D: Treatment for diabetic mononeuropathy with alpha-lipoic acid. *Int J Clin Pract* 2005; 59:645.
56. Wasay M, et al: Cerebral venous thrombosis: Analysis of a multicenter cohort from the United States. *J Stroke Cerebrovasc Dis* 2008; 17:49-54.
57. Ferro JM, Canhão P, Bousser MG, Stam J, Barinagarrementeria F, ISCVT Investigators: Prognosis of cerebral vein and dural sinus thrombosis: Results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke* 2004; 35:664.
58. Stam J: Thrombosis of the cerebral veins and sinuses. *N Engl J Med* 2005; 352:1791.
59. Villringer A, Einhäupl KM: Dural sinus and cerebral venous thrombosis. *New Horiz* 1997; 5:332.
60. Wasson J, Redenbaugh J: Transverse sinus thrombosis: An unusual cause of headache. *Headache* 1997; 37:457.
61. Ferro JM, et al: Cerebral vein and dural sinus thrombosis in Portugal: 1908-1998. *Cerebrovasc Dis* 2001; 11:177.

www.ketabpezeshki.com 66485457-66963820

62. Ferro JM, Canhão P, Bousser MG, Stam J, Barinagarrementeria F, ISCVT Investigators: Early seizures in cerebral vein and dural sinus thrombosis: Risk factors and role of antiepileptics. *Stroke* 2008; 39:1152-1158.
63. Villringer A, Mehraein S, Einhäupl KM: Pathophysiological aspects of cerebral sinus venous thrombosis (SVT). *J Neuroradiol* 1994; 21:72.
64. Linn J, et al: Noncontrast CT in deep cerebral venous thrombosis and sinus thrombosis: Comparison of its diagnostic value for both entities. *AJNR Am J Neuroradiol* 2009; 30:728-735.
65. Provenzale JM, Joseph GJ, Barboriak DP: Dural sinus thrombosis: Findings on CT and MR imaging and diagnostic pitfalls. *AJR Am J Roentgenol* 1998; 170:777.
66. Gratama van Andel HA, et al: Interobserver variability in the detection of cerebral venous thrombosis using CT venography with matched mask bone elimination. *Clin Neurol Neurosurg* 2009; 111:717-723.
67. Gaikwad A, Mudalgi B, Patankar K, Patil J, Ghongade D: Diagnostic role of 64-slice multidetector row CT scan and CT venogram in cases of cerebral venous thrombosis. *Emerg Radiol* 2008; 15:325-333.
68. Linn J, et al: Diagnostic value of multidetector-row CT angiography in the evaluation of thrombosis of the cerebral venous sinuses. *Am J Neuroradiol* 2007; 28:946.
69. Khandelwal N, et al: Comparison of CT venography with MR venography in cerebral sinovenous thrombosis. *AJR Am J Roentgenol* 2006; 187:1637.
70. Kosinski CM, et al: Do normal D-dimer levels reliably exclude cerebral sinus thrombosis? *Stroke* 2004; 35:2820.
71. Talbot K, Wright M, Keeling D: Normal D-dimer levels do not exclude the diagnosis of cerebral venous sinus thrombosis. *J Neurol* 2002; 249:1603.
72. Lalive PH, et al: Is measurement of D-dimer useful in the diagnosis of cerebral venous thrombosis? *Neurology* 2003; 61:1057.
73. Tardy B, et al: D-dimer levels in patients with suspected acute cerebral venous thrombosis. *Am J Med* 2002; 113:238.
74. Preter M, Tzourio C, Ameri A, Bousser MG: Long-term prognosis in cerebral venous thrombosis: Follow-up of 77 patients. *Stroke* 1996; 27:243.
75. Frey JL, et al: Cerebral venous thrombosis: Combined intrathrombus rtPA and intravenous heparin. *Stroke* 1999; 30:489.
76. Einhäupl KM, Villringer A: Heparin treatment in sinus venous thrombosis. *Lancet* 1991; 338:597.
77. Coutinho JM, et al: Unfractionated or low-molecular weight heparin for the treatment of cerebral venous thrombosis. *Stroke* 2010; 41:2575-2580.
78. Stam J, De Bruijn SF, DeVeber G: Anticoagulation for cerebral sinus thrombosis. *Cochrane Database Syst Rev* 2002; 4:CD002005.
79. Wasay M, et al: Nonrandomized comparison of local urokinase thrombolysis versus systemic heparin anticoagulation for superior sagittal sinus thrombosis [editorial comment]. *Stroke* 2001; 32:2310.
80. Francis G, et al: *Inflammatory demyelinating diseases of the central nervous system*. In: Bradley WG, ed: *Neurology in Clinical Practice*. Boston: Butterworth-Heinemann; 1996.
81. Kurtzke JF, Hyllested K, Heltberg A: Multiple sclerosis in the Faroe Islands: Transmission across four epidemics. *Acta Neurol Scand* 1995; 91:321.
82. Hogancamp WE, Rodriguez M, Weinshenker BG: Symposium on multiple sclerosis—part III: The epidemiology of multiple sclerosis. *Mayo Clin Proc* 1997; 72:871.
83. Giovannoni G, Miller DH: Multiple sclerosis and its treatment. *J R Coll Physicians Lond* 1999; 33:315.
84. Winkelmann A, Engel C, Apel A, Zettl UK: Cognitive impairment in multiple sclerosis. *J Neurol* 2007; 254:II35.
85. Rao SM, Leo GJ, Bernardin L, Unverzagt F: Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. *Neurology* 1991; 41:685.
86. Swirsky-Sacchetti T, et al: Neuropsychological and structural brain lesions in multiple sclerosis: A regional analysis. *Neurology* 1992; 42:1291.
87. Wray SH: Optic neuritis: Guidelines. *Curr Opin Neurol* 1995; 8:72.
88. Beck RW, et al: The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis. *N Engl J Med* 1993; 329:1764.
89. Ebers GC: Optic neuritis and multiple sclerosis. *Arch Neurol* 1985; 42:702.
90. Kidd D: Presentations of multiple sclerosis. *Practitioner* 1999; 1:24.
91. Mehta PD: Diagnostic usefulness of cerebrospinal fluid in multiple sclerosis. *Crit Rev Clin Lab Sci* 1991; 28:233.
92. Lee KH, et al: Magnetic resonance imaging of the head in the diagnosis of multiple sclerosis: A prospective 2-year follow-up with comparison of clinical evaluation, evoked potentials, oligoclonal banding, and CT. *Neurology* 1991; 41:657.
93. Neema M, et al: MRI in multiple sclerosis: What's inside the toolbox? *Neurotherapeutics* 2007; 4:602.
94. Morrissey SP, et al: The significance of brain magnetic resonance imaging abnormalities at presentation with clinically isolated syndromes suggestive of multiple sclerosis: A 5-year follow-up study. *Brain* 1993; 116:135.
95. European Study Group on Interferon β-1b in Secondary Progressive MS: Randomised double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis. *Lancet* 1998; 352:1498.
96. Kappos L, et al: Treatment with interferon β-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. *Neurology* 2006; 67:1242.
97. Comi G, et al: Effect of early interferon treatment on conversion to definite multiple sclerosis: A randomised study. *Lancet* 2001; 357:1576.
98. Jacobs LD, et al: Intramuscular interferon β-1a therapy initiated during a first demyelinating event in multiple sclerosis. *N Engl J Med* 2000; 343:898.
99. Stuve O, et al: Pharmacological treatment of early multiple sclerosis. *Drugs* 2008; 68:73.
100. Johnson KP, et al: Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. *Neurology* 1998; 50:701.
101. Comi G, et al: Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): A randomised, double-blind, placebo-controlled trial. *Lancet* 2009; 374:1503-1511.
102. Kappos L, et al: Natalizumab treatment for multiple sclerosis: Recommendations for patient selection and monitoring. *Lancet Neurol* 2007; 6:431-441.
103. Kappos L, et al: A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010; 362:387-401.
104. Cohen JA, et al: Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010; 362:402-415.
105. Giovannoni G, et al: A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med* 2010; 362:416-426.
106. Polman CH, et al: A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; 354:899-910.
107. Rudick RA, et al: Natalizumab plus interferon β-1a for relapsing multiple sclerosis. *N Engl J Med* 2006; 354:911-923.
108. Beck RW, et al: A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group. *N Engl J Med* 1992; 326:581.

www.ketabpezeshki.com 66485457-66963820

Chapter 106

Spinal Cord Disorders

Andrew D. Perron and J. Stephen Huff

PERSPECTIVE

Spinal cord disorders encompass a wide range of pathologic entities and affect all age groups. Some spinal cord disorders may have catastrophic outcomes if they are not recognized early in the clinical course. The ultimate neurologic outcome with many of these disorders may depend on expeditious recognition in the emergency department (ED), with appropriate initial investigations, neuroimaging, management, and consultation for definitive therapy. Early presentations of spinal cord syndromes are frequently subtle, and diagnosis may be difficult if not impossible in the early stages of disease. As with many disease processes affecting the nervous system, correct diagnosis and appropriate management require knowledge of the anatomic organization of the spinal cord and skill in taking the history and in performing the neurologic examination.

This chapter generally is concerned with nontraumatic processes affecting the spinal cord and its vascular supply as well as processes compressing the spinal cord. Spinal cord trauma is discussed in Chapter 43.

PRINCIPLES OF DISEASE

Anatomy

In adults, the spinal cord is approximately 40 cm long and extends from the foramen magnum, where it is continuous with the medulla oblongata, to the body of the first or second lumbar vertebra. Like the brain, the spinal cord is covered by three meningeal layers: the inner pial layer, the arachnoid, and the outer dural layer. At its lower end, the spinal cord tapers into the conus medullaris, where several segmental levels are represented in a small area. The lumbar and sacral nerve roots form the cauda equina as they descend caudally in the thecal sac before exiting the spinal canal at the respective foramina. The non-neural filum terminale runs from the tip of the conus and inserts into the dura at the level of the second sacral vertebra.

Two symmetrical enlargements of the spinal cord contain the segments that innervate the limbs. The *cervical enlargement* (cord level C5 to T1) gives rise to the brachial plexus and subsequently to the peripheral nerves of the upper extremity. The *lumbar enlargement* (L2 to S3) gives rise to the lumbosacral plexus and peripheral nerves of the lower extremity. The space surrounding the spinal cord within the spinal canal is reduced in the area of the enlargements, potentially leaving the cord more vulnerable to compression in these regions. At each segmental level, anterior (ventral) and posterior (dorsal) roots arise from rootlets along the anterolateral and posterolateral surfaces of the cord. At each level, the anterior root conveys the outflow of the motor neurons in the anterior horn of the spinal cord, and the posterior root contains sensory neurons and fibers that convey sensory inflow.

The arterial supply of the spinal cord is derived primarily from two sources. The single anterior spinal artery arises from the paired vertebral arteries. This anterior spinal artery runs the entire length of the cord in the midline anterior median sulcus and supplies roughly the anterior two thirds of the spinal cord. Blood supply to the posterior third of the spinal cord is derived from the smaller paired posterior spinal arteries. The anterior and the posterior spinal arteries receive segmental contributions from radicular arteries, the largest being the radicular artery of Adamkiewicz, which typically originates from the aorta between T8 and L4. The venous drainage of the cord largely parallels the arterial supply.

The internal anatomy of the spinal cord is divided into central gray matter, which contains cell bodies and their processes, and surrounding white matter, where the ascending and descending myelinated fiber tracts are located. These fiber tracts are organized into discrete bundles; the ascending tracts convey sensory information, and the descending tracts convey the efferent motor impulses and visceral innervation.

For clinical purposes, neuroanatomy of the spinal cord may be greatly simplified, as depicted in Figure 106-1. Major ascending sensory tracts are represented on the right side of the figure, with motor tracts on the left side. The posterior columns carry afferent ascending proprioceptive and vibratory information on the ipsilateral side of the cord to the area stimulated; decussation of these fibers occurs in the medulla so that contralateral cortical representation is consistent. The lateral spinothalamic tract conveys afferent information about pain and temperature in a portion of the lateral column of white matter. (Tracts are named with the point of origin first; the spinothalamic tract, for example, arises in the spinal cord and travels to the thalamus.) The tract is laminated so that sacral fibers are represented most laterally. Crossing of fibers from this tract occurs near the level of entry of the spinal nerve; a cord lesion affecting only one lateral spinothalamic tract results in decreased or absent pain and temperature perception below the level of injury on the contralateral side of the body.

For clinical purposes, the major descending motor tract is represented in the lateral corticospinal tract (which, as the name implies, originates in the cortex and descends to the spinal cord). This tract also is anatomically organized, with efferent motor axons to the cervical area located medially and the sacral efferent axons located laterally. Decussation of this descending tract occurs in the medulla. The cell bodies of the lower motor neurons (anterior horn cells) are in the ventral (anterior) portion of the gray matter of the spinal cord.

www.ketabpezeshki.com 66485457-66963820

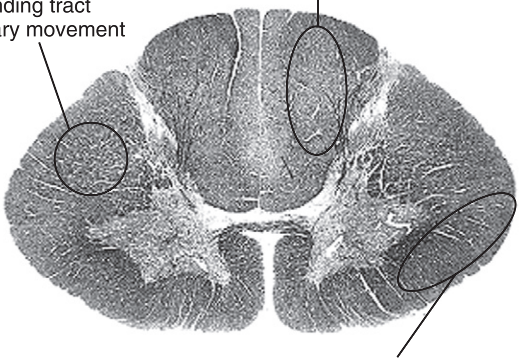


Figure 106-1. Simplified spinal cord anatomy showing clinically essential motor and sensory tracts. (Photomicrograph courtesy John Sundsten, Digital Anatomist Project, University of Washington.)

CLASSIFICATION OF SPINAL CORD SYNDROMES

The anatomic organization of the spinal cord lends itself to a corresponding anatomic-pathophysiologic classification of cord dysfunction. Any of the different anatomic syndromes may be the final clinical picture of a variety of clinical processes. The syndromes frequently exist in partial or incomplete forms, adding to the diagnostic difficulty.

Complete (Transverse) Spinal Cord Syndrome

Complete spinal cord lesions may be manifested as either acute or subacute pathologic processes. A *complete* spinal cord lesion is defined as a total loss of sensory, autonomic, and voluntary motor innervation distal to the spinal cord level of injury. Reflex responses mediated at the spinal level, such as muscle stretch (deep tendon) reflexes, may persist, although they also may be absent or abnormal. Autonomic dysfunction may be manifested acutely with hypotension (neurogenic shock) or priapism. The most common cause of the complete transverse cord syndrome is trauma, although this anatomic syndrome is nonspecific as to etiology.[1,2] Other causes of acute complete cord syndrome include infarction, hemorrhage, and entities causing extrinsic compression. In patients with acute complete transverse syndromes that persist for more than 24 hours, functional recovery does not occur in 99%.[3,4] Any evidence of preserved cord function below the level of injury denotes a partial rather than a complete lesion. Signs such as persistent perineal sensation (sacral sparing), reflex rectal sphincter tone or voluntary rectal sphincter contraction, and even slight voluntary toe movement suggest a partial cord lesion, which usually carries a better prognosis than a complete lesion.[1]

Spinal shock refers to the loss of muscle tone and reflexes with complete cord syndrome during the acute phase of injury. The intensity of the spinal shock increases with affected spinal cord level.[5] Spinal shock typically lasts less than 24 hours but has been reported occasionally to last days to weeks.[5,6] A marker of spinal shock is loss of the bulbocavernosus reflex, which is a normal cord-mediated reflex that may be preserved in complete cord lesions. The bulbocavernosus reflex involves involuntary reflex contraction of the anal sphincter in response to a squeeze of the glans penis or a tug on the Foley catheter. The termination of the spinal shock phase of injury is heralded by the return of the bulbocavernosus reflex; increased muscle tone and hyperreflexia follow later.[1,5,6]

Incomplete Spinal Cord Lesions

Incomplete spinal lesions are characterized by preservation of function of various portions of the spinal cord. Of all incomplete spinal lesions, most can be classified generally as one of three clinical syndromes: central cord syndrome, Brown-Séquard syndrome, or anterior cord syndrome (Table 106-1).

Central Cord Syndrome

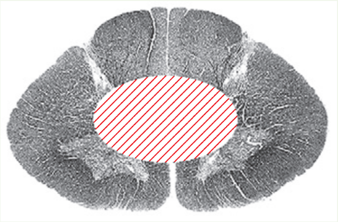
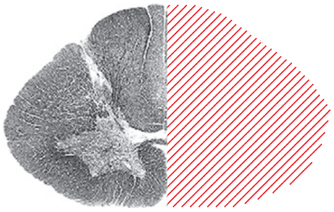
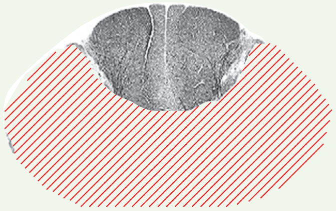
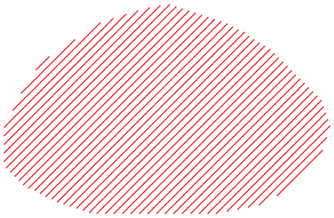
Central cord syndrome, first described by Schneider and colleagues in 1954, is the most prevalent of the partial cord syndromes.[7,8] Because of the anatomic organization of the spinal cord, a central cord injury is characterized by bilateral motor paresis; upper extremities are affected to a greater degree than lower extremities, and distal muscle groups are affected to a greater degree than proximal muscle groups. Sensory impairment and bladder dysfunction are variable features. At times, burning dysesthesias in the upper extremities may be the dominant feature.[9] Central cord injury affects the central gray matter and the central portions of the corticospinal and spinothalamic tracts. It is caused most often by a hyperextension injury; the postulated mechanism is squeezing or pinching of the spinal cord anteriorly and posteriorly by inward bulging of the ligamentum flavum. The most common cause of such injuries is a fall, followed in frequency by a motor vehicle crash.[7,8] The result is contusion to the spinal cord, with the central portion being most affected. This injury often occurs in elders with degenerative arthritis and spinal stenosis in the cervical area but may affect any patient with cervical canal narrowing of any etiology (e.g., congenital narrow canal as seen in achondroplasia or canal narrowing from disk protrusion or tumor). The prognosis with central cord syndrome depends on the degree of injury at presentation and the patient's age.[10,11] In patients younger than 50 years, more than 80% regain bladder continence, and approximately 90% return to ambulatory status. In patients older than 50 years, only 30% regain bladder function, and approximately 50% regain the ability to ambulate.[11]

Brown-Séquard Syndrome

Brown-Séquard syndrome, first described in 1846 by the one physician for whom it is named,[12] is the result of an anatomic or functional hemisection of the spinal cord. Usually associated with penetrating injuries,[13] Brown-Séquard syndrome also may be seen with compressive or intrinsic lesions. The syndrome has been reported in association with spinal cord tumors, spinal epidural hematoma, vascular malformations, cervical spondylosis, degenerative disk disease, herpes zoster myelitis, and radiation injury and as a complication of spinal instrumentation.[13,14] The syndrome in its pure form is characterized by ipsilateral loss of motor function and proprioception or vibration, with contralateral loss of pain and temperature sensation below the spinal cord level of injury. Because fibers associated with the lateral spinothalamic tract ascend or descend one or two spinal cord segments before crossing to the contralateral side, ipsilateral anesthesia (pain and temperature modalities) may be noted one or two segments above the lesion, although this observation is variable. Most patients with Brown-Séquard syndrome incur only partial sensory and motor impairment, and the classic pattern is not seen.[11,13,15] Brown-Séquard syndrome carries the best prognosis of any of the incomplete spinal cord syndromes. Fully 80 to 90% of patients with Brown-Séquard syndrome regain bowel and bladder func-

www.ketabpezeshki.com 66485457-66963820

Table 106-1 Spinal Cord Syndromes

SYNDROME	SENSORY	MOTOR	SPHINCTER INVOLVEMENT
 Central cord syndrome	Variable	Upper extremity weakness, distal > proximal	Variable
 Brown-Séquard syndrome	Ipsilateral position and vibration sense loss Contralateral pain and temperature sensation loss	Motor loss ipsilateral to cord lesion	Variable
 Anterior cord syndrome	Loss of pin and touch sensation Vibration, position sense preserved	Motor loss or weakness below cord level	Variable
 Transverse cord syndrome—complete	Loss of sensation below level of cord injury	Loss of voluntary motor function below cord level	Sphincter control lost
Conus medullaris syndrome	Saddle anesthesia may be present, or sensory loss may range from patchy to complete transverse pattern	Weakness may be of upper motor neuron type	Sphincter control impaired
Cauda equina syndrome	Saddle anesthesia may be present, or sensory loss may range from patchy to complete transverse pattern	Weakness may be of lower motor neuron type	Sphincter control impaired

tion, 75% regain ambulatory status, and 70% become independent in their activities of daily living.[11]

Anterior Cord Syndrome

Anterior cord syndrome is characterized by loss of motor function, pinprick, and light touch below the level of the lesion with preservation of posterior column modalities, including some touch, position, or vibratory sensation. Although most reported cases of anterior spinal syndrome follow aortic surgery,[16] the syndrome also may occur after severe hypotension, infection, myocardial infarction, vasospasm from drug reaction, and aortic angiography.[17] The anatomic lesion may be caused by a cervical hyperflexion injury resulting in a cord contusion or by protrusion of bone fragments or herniated cervical disk material into the spinal canal. Rarely, it is produced by laceration or thrombosis of the anterior spinal artery or a major radicular feeding vessel.[11] Patients present with characteristic mixed motor and sensory neurologic findings as noted before. Functional recovery varies; most improvement occurs during the first 24 hours, but little improvement is expected thereafter.[4] Although anterior cord lesions from ischemia usually are incomplete, patients without motor function at 30 days have little or no likelihood of regaining any motor function by 1 year.[16,18] Overall, only 10 to 20% of patients with this entity regain some muscle function, and even in this group, there is little power or coordination.[11]

Conus Medullaris and Cauda Equina Syndromes

The separation of conus medullaris and cauda equina lesions in clinical practice is difficult because the clinical features of the

www.ketabpezeshki.com 66485457-66963820

disorders overlap. In addition, a combined lesion may occur that masks clear clinical symptoms or signs of either an upper or a lower motor neuron type of injury. The conus medullaris is the terminal end of the spinal cord, located at approximately the L1 level in adults. The conus medullaris syndrome may involve disturbances of urination (usually from a denervated, autonomic bladder that is manifested clinically with overflow incontinence) and sphincter impairment or sexual dysfunction. Sensory involvement may affect the sacral and coccygeal segments, resulting in saddle anesthesia. Pure lesions of the conus medullaris are rare.[19] Upper motor neuron signs, such as increased motor tone and abnormal reflexes, may be present, but their absence does not exclude the syndrome. The conus medullaris syndrome can be caused by central disk herniation, neoplasm, trauma, or vascular insufficiency. Because the conus is such a small structure, with lumbar and sacral segments represented in a small area, a lesion usually causes bilateral symptoms. This finding may help distinguish lesions of the conus from lesions of the cauda equina, which often are unilateral.[19]

The *cauda equina* (Latin for "horse's tail") is the name given to the lumbar and sacral nerve roots that continue on within the dural sac caudal to the conus medullaris. Not a true "cord syndrome," cauda equina syndrome represents dysfunction at the level of nerve roots, but the anatomic clustering of nerve roots within the lumbar dural sac allows injury to several nerve roots to occur simultaneously. The etiologic lesion in the cauda equina syndrome usually is a midline rupture of an intervertebral disk, most commonly at the L4-5 level. Tumors and other compressive masses also may cause the syndrome. As in the conus medullaris syndrome, patients generally present with progressive symptoms of fecal or urinary incontinence, impotence, distal motor weakness, and sensory loss in a saddle distribution. Muscle stretch reflexes also may be reduced. Urinary retention is the most consistent finding, with a sensitivity of 90%.[20] Low back pain may or may not be present.

CLINICAL FEATURES

History

Weakness, sensory abnormalities, and autonomic dysfunction are the cardinal manifestations of spinal cord dysfunction. The tempo and degree of impairment often reflect the disease process. Past medical history is vital because a history of coagulopathy or other systemic processes may be elicited. A history of cancer should suggest the possibility of metastatic disease. Recent trauma raises the possibility of vertebral fracture or disk protrusion.

Physical Examination

The physical examination pertinent to spinal cord dysfunction involves testing in three areas: (1) motor function, (2) sensory function, and (3) reflexes. Each component is best tested with the anatomic organization of the spinal cord in mind to help determine the level of the spinal cord dysfunction.

Motor Function

Testing of motor function encompasses examination of muscle bulk, tone, and strength. Muscle bulk is easily examined in large motor groups, such as the thigh or calf muscles, the biceps, and the triceps. Inspection of the intrinsic hand muscles also may be helpful for determination of muscle bulk; wasting may be evident as hollowed or recessed regions of the hand. Decreased mass, asymmetry, or fasciculations should be noted. Tone is tested with repeated passive knee, elbow, or wrist flexion, with the examiner feeling for abnormally increased or decreased resistance. Rapid pronation-supination of the forearm is another useful method to assess tone. Increased tone may indicate spasticity or an upper motor neuron lesion, whereas decreased tone corresponds with lower motor neuron, motor endplate, or muscle problems. Finally, motor strength is graded in the upper and the lower extremities. Motor grading for the neurologic examination is relatively straightforward. Note that a tremendous gradient of strength is within the fourth grade of the scale. Scored on a scale of 0 to 5, neuromuscular functioning is graded as follows:

0. No firing of the muscle is present.
1. The muscle fires but is unable to move the intended part.
2. The muscle is able to move the intended part with gravity eliminated.
3. The muscle is able to move the intended part against gravity.
4. The muscle is able to move the intended part, but not at full strength.
5. Full muscle strength is present.

A rectal examination is performed to assess voluntary sphincter contraction, resting tone, and, as described previously, the bulbocavernosus reflex. Although it is not commonly thought of as a physical examination maneuver, a post-void residual urine volume may be important for assessment of bladder function. A post-void residual volume of more than 100 to 200 mL in a patient without prior voiding difficulty might suggest bladder dysfunction of neurologic cause.

Sensory Function

Sensory testing requires a cooperative patient and an attentive examiner. The spinal cord–related modalities that may be clinically useful include testing for pinprick and light touch (contralateral lateral spinothalamic tract) and proprioception (ipsilateral posterior column). Assessment of the patient's response to pinprick, light touch, and proprioception in all four extremities is necessary if a neurologic injury is suspected. Testing of sacral dermatomes is an important part of the examination in some patients. As previously noted, sacral sparing is an important finding indicating that spinal cord dysfunction may be incomplete. The sensory fibers from sacral dermatomes are more peripherally located in the ascending fiber bundles; central or partial cord lesions may ablate sensation in the extremities yet allow some perception of sensation in the sacral area.

Reflexes

Muscle stretch (deep tendon) reflexes may be tested rapidly at the bedside. Responses are graded on a scale of 0 to 4+, with 2 being normal. Hyperactive reflexes suggest upper motor neuron disease (affecting the neurons or their outflow from the brain or spinal cord), as do sustained clonus and Babinski's sign. The absence of these reflex changes does not constitute evidence that a myelopathy is not present. In fact, one small series noted a low incidence of extensor plantar responses as well as a lack of hyperreflexia in patients presenting to the ED with acute or progressive cord compression or myelopathies.[21] Reflexes also may be diminished or absent when sensation is lost or when spinal shock is present. Diseases of muscles or neuromuscular junctions also may decrease reflexes. In acute cord injury, reflexes may be diminished in the acute phase. The bulbocavernosus reflex may be helpful in this assessment.

DIAGNOSTIC STRATEGIES

Historical or physical examination findings that suggest spinal cord dysfunction prompt further investigations. The basic strategy is to detect or to exclude extrinsic compressive lesions or other potentially treatable entities. Magnetic resonance imaging (MRI)

www.ketabpezeshki.com 66485457-66963820

Table 106-2 Clinical Characteristics of Neuromuscular Diseases

	HISTORY	STRENGTH	DTR	SENSATION	WASTING
Myelopathy	Trauma, infection, cancer	Normal to decreased	Increased	Normal to decreased	No (yes if chronic)
Motor neuron disease (ALS)	Progressive difficulty with swallowing, speaking, walking	Decreased	Increased	Normal	Yes
Neuropathy	Recent infection Ascending weakness	Normal or decreased Distal > proximal	Decreased	Decreased	Yes
Neuromuscular junction disease	Food (canned goods) Tick exposure Easy fatigability	Normal to fatigue	Normal	Normal	No
Myopathy	Thyroid disease Previous similar episodes	Decreased Proximal > distal	Normal	Normal	Yes

ALS, amyotrophic lateral sclerosis; *DTR,* deep tendon reflex.

has changed the diagnostic approach to patients with suspected spinal cord dysfunction. Plain radiographs and computed tomography (CT) scans may show bone and some soft tissue abnormalities. Conventional radiographs and CT scans are required in patients with trauma or suspected bone involvement by tumor or degenerative processes, but MRI shows many of these abnormalities and defines the spinal cord as well as the soft tissue structures associated with it. Tissue damage patterns within the cord, such as hemorrhage and edema, also may be detected with MRI. CT myelography may be able to answer some of these questions in patients in whom implanted metal precludes MRI but generally does not yield the same level of detail. After imaging studies exclude compressive lesions or other masses affecting the spinal cord, the possibility of inflammatory or demyelinating disorders remains. Lumbar puncture may be useful in diagnosis by revealing an inflammatory cerebrospinal fluid (CSF) formula.

DIFFERENTIAL CONSIDERATIONS

The prime principle in management of spinal cord dysfunction is to consider and exclude potentially treatable clinical conditions. The clinical assessment of spinal cord dysfunction is limited to detection of weakness, sensory alterations, sphincter dysfunction, and perhaps reflex abnormalities. There may be pain in the back, depending on the pathologic process, but generally it is not helpful in formulating a list of considerations for the differential diagnosis. Because potential functional loss and impact on quality of life are great, the detection of a process for which some intervention is possible assumes great importance. A likely diagnosis of spinal cord infarction may be entertained, but the pursuit of a treatable process, such as spinal cord compression from an epidural hematoma, should be seriously considered.[22] This discovery process may involve specialty consultation or studies that may not be readily available in all settings, such as MRI. As a general rule, liberal use of consultation and imaging is recommended when the possibility of spinal cord dysfunction is considered. The history may suggest a specific cause and will guide the tempo of investigation. The caveat is that spinal cord diseases may mimic many other disease processes, and neither the history nor physical examination may allow diagnosis until appreciable neurologic dysfunction has developed.

The picture of a *complete* transverse spinal cord syndrome with paraplegia, sensory loss at a clear anatomic level, and sphincter dysfunction cannot be fully simulated by other anatomic lesions. *Incomplete* or evolving spinal cord syndromes may be imitated by other disease processes. It is always prudent to focus the differential diagnosis on anatomic considerations—the classic "where is the lesion?" approach (Table 106-2). Progressive lower extremity weakness and sensory alteration may represent cord dysfunction but could reflect an intracranial vertex mass with bilateral cortical dysfunction. Ataxia may be a finding in cerebellar disease but also has rarely been reported as an isolated finding with spinal cord compression. Another example is rapidly progressive paralysis in a patient with areflexia and quadriplegia; ascending paralysis (Landry-Guillain-Barré syndrome) at times may mimic an acute cord lesion.

In general, pathologic processes involving the spinal cord may be divided into processes affecting the cord or its blood supply primarily, such as demyelination, infection, or infarction, and processes that compress the cord, most often originating outside the dura (Box 106-1). *Myelitis* is a comprehensive term for spinal cord inflammation with dysfunction, and the potential causes are legion. The clinical presentation is often similar across the variety of entities that may cause cord compression. The tempo of the process may yield a different clinical picture. In chronic compression, muscle wasting and abnormal reflexes may be present, whereas both of these may be lacking in acute compression. A neurologic deficit in concert with back pain strongly suggests a spinal cord lesion causing compression of neural elements, necessitating prompt investigation to identify a specific cause. Atypical presentations for these lesions are the rule, and additional diagnostic studies should be pursued as appropriate.

Box 106-1 Nontraumatic Causes of Spinal Cord Dysfunction

Processes Affecting the Spinal Cord or Blood Supply Directly
Multiple sclerosis
Transverse myelitis
Spinal arteriovenous malformation, subarachnoid hemorrhage
Syringomyelia
HIV myelopathy
Other myelopathies
Spinal cord infarction

Compressive Lesions Affecting the Spinal Cord
Spinal epidural hematoma
Spinal epidural abscess
Diskitis
Neoplasm
  Metastatic
  Primary CNS

HIV, human immunodeficiency virus; *CNS,* central nervous system.

www.ketabpezeshki.com 66485457-66963820

MANAGEMENT

Just as the clinical manifestations of spinal cord dysfunction are nonspecific with respect to etiology, the treatment of many of the disease entities often is nonspecific. Steroid administration had been traditionally recommended as therapy in spinal cord trauma, although currently this use of steroids has been seriously questioned in the medical literature.[23-26] Steroids have also been used with many nontraumatic causes of cord compression, despite the lack of rigorous clinical studies supporting this use. Radiation treatment is recommended for cord compression by tumor. Surgical consultation for decompression may be considered, although the indications for surgery and timing of surgery are controversial.

A specific diagnosis is needed to guide therapy. Accordingly, involvement of appropriate consultants and discussion of what may be understudied therapies are suggested.

SPECIFIC DISEASE PROCESSES

As noted earlier, spinal cord disorders may be grouped into lesions resulting from processes intrinsic to the cord or vasculature and lesions causing extrinsic compression. The order of the following discussion roughly corresponds with the organization of Box 106-1.

Intrinsic Cord Lesions

Multiple Sclerosis

Principles of Disease. Demyelination denotes a disease process with the prominent feature of partial or complete loss of the myelin surrounding the axons of the central nervous system. Multiple sclerosis (MS) is the most common example of such a process; spinal cord involvement may dominate the clinical picture.[27]

Clinical Features. Central nervous system lesions that are "scattered in time and space" are the hallmark of MS, as described in more detail in Chapter 105. The demyelinated segments do not transmit action potentials normally, resulting in a wide variety of spinal cord–related abnormalities, depending on the location and extent of the demyelination. In addition to patchy motor and sensory deficits, patients with MS may complain of bladder dysfunction or tremor or demonstrate evidence of a transverse partial or complete cord syndrome mimicking a compressive spinal lesion.[27, 28] Spinal cord lesions in MS primarily involve the lateral corticospinal tracts, the posterior columns, and the lateral spinothalamic tracts. Motor system dysfunction is the most frequent manifestation of MS involvement of the spinal cord, usually as a result of lesions in the lateral corticospinal tracts.

The examination of patients with MS often reveals paresis, increased muscle tone, hyperreflexia, clonus, and Babinski's response. Spinal cord involvement also may result in dysautonomias.

Diagnostic Strategies. Spinal MRI is the diagnostic imaging modality of choice because it can exclude cord compression and show lesions suggestive of MS.[28-30] CSF testing for myelin basic protein and oligoclonal bands also is a diagnostic option, but no CSF abnormalities are entirely specific for MS.[31,32] Oligoclonal bands in the CSF may aid in the diagnosis, but they are significant only if they are not present in the serum as well.[31]

Differential Considerations. Considerations in the differential diagnosis include systemic lupus erythematosus, Lyme disease, neurosyphilis, human immunodeficiency virus (HIV) myelopathy, and other disorders.

Management. MS exacerbations may be treated with high-dose methylprednisolone, followed by a tapering dose of prednisone.[28] Consultation and referral to a neurologist usually are indicated. Immunosuppressive therapy in patients with the chronic progressive form of the disease has met with variable success.[27,28] Because numerous disorders can mimic MS, the definitive diagnosis of this disease is usually not made in the ED.[33]

Transverse Myelitis

Principles of Disease. Acute transverse myelitis refers to acute or subacute spinal cord dysfunction characterized by paraplegia, a transverse level of sensory impairment, and sphincter disturbance. It describes a heterogeneous group of inflammatory disease processes that can affect the spinal cord by interruption of the ascending or descending pathways in the spinal cord.[34] It is relatively rare, with a reported annual incidence of 1 case per 1.3 million population. The presentation may be mimicked by compressive lesions, trauma, infection, or malignant infiltration. The exact pathogenesis is unknown, although it is noted to follow viral infection in approximately 30% of patients and commonly is termed postinfectious myelitis.[34,35] Other postulated etiologic categories include infectious, autoimmune, and idiopathic.[35-37] No apparent cause of acute transverse myelitis is identified in 30% of the patients.[35] Progression of symptoms usually is rapid, with 66% of the cases reaching maximal deficit by 24 hours.[38] Symptoms may progress, however, during days to weeks. The thoracic cord region is affected in 60 to 70% of cases[38]; the cervical spinal cord is rarely affected.[39]

Clinical Features. In addition to motor, sensory, and urinary disturbances, patients with acute transverse myelitis may complain of back pain and may have low-grade fever, raising concern for spinal epidural abscess. As with MS, the examination may reveal weakness progressing to paresis, hypertonia, hyperreflexia, clonus, and Babinski's response. Spinal cord involvement also can result in dysautonomias.

Diagnostic Strategies. Evaluation for acute transverse myelitis is done primarily with emergent MRI to exclude compressive lesions. Results of CSF studies are normal in 40% of the cases, with only mildly elevated protein level or pleocytosis in the remaining 60%.[40] The most essential aspect of the evaluation is to eliminate a potentially treatable cause, such as spinal epidural abscess, neoplasm, or hematoma.

Differential Considerations. Considerations in the differential diagnosis for transverse myelitis include MS, spinal epidural abscess, spinal neoplasm, and hematoma.

Management. Treatment with steroids is of unknown benefit. Anecdotal reports of improvement after steroid administration exist,[38,41] but some studies have found no benefit to their use.[37] Neurologic consultation is suggested, and hospitalization usually is required.

The clinical course of acute transverse myelitis varies widely, ranging from complete recovery to death from progressive neurologic compromise.[37] Maximal improvement usually is obtained within 3 to 6 months.[42,43] At 5-year follow-up evaluation of one series of patients with this disease, 30% had a good recovery, 25% had a fair recovery, 30% had a poor outcome, and 15% had died as a result of complications of the disease.[43]

Spinal Subarachnoid Hemorrhage

Principles of Disease. Intraspinal hemorrhage is rare and may occur in the same anatomic locations as intracranial hemorrhages; epidural, subdural, subarachnoid, and intramedullary hemorrhages are all possible.[5] Spinal subarachnoid hemorrhage usually is caused by an arteriovenous malformation.[44] Hemorrhage from tumors or cavernous angiomas and spontaneous hemorrhage secondary to anticoagulation therapy also have been reported.[45,46] Bleeding may occur exclusively in the subarachnoid space or within the substance of the spinal cord itself.

www.ketabpezeshki.com 66485457-66963820

Clinical Features. Patients present with excruciating back pain, of paroxysmal onset, at the level of the hemorrhage. This pain also may be in a radicular distribution or extend into the flank. Patients may complain of headache and exhibit cervical rigidity if the blood migrates into the intracranial subarachnoid space, simulating an intracranial subarachnoid hemorrhage. Variable neurologic deficits depend on the magnitude and anatomic location of the hemorrhage. These deficits typically include extremity numbness, weakness, and sphincter dysfunction.[45,47] Nuchal rigidity or signs of meningeal irritation may also be present.

Diagnostic Strategies. The diagnostic study of choice is MRI. Lumbar puncture also can confirm the presence of blood in the CSF.

Differential Considerations. Considerations in the differential diagnosis include epidural abscess, tumor, transverse myelitis, ischemia from aortic dissection, and anterior spinal artery thrombosis.

Management. Treatment depends on the etiology of the hemorrhage. Neurosurgical referral is obtained for further evaluation and for clot evacuation if compression is present. Angiography may be recommended if arteriovenous malformation is suspected.

Syringomyelia

Principles of Disease. Syringomyelia is the presence of a cavitary lesion within the substance of the spinal cord. A syrinx usually is a chronic progressive lesion, and its location within the cord determines the constellation of neurologic findings on examination.

Clinical Features. Headache and neck pain are the most common complaints, followed by sensory disturbance, gait disorder, and lower cranial nerve dysfunction.[48] The classic pattern of sensory deficit involves a loss of pain and temperature sensation in the upper extremities with preservation of proprioception and light touch. This phenomenon is described as a "dissociative anesthesia" because of the discrepant loss of sensory modalities. The sensory deficit often is described as being in a "capelike" distribution over the shoulders and arms. The anatomic basis for the neurologic features of a syrinx is the location near the central canal. Crossing fibers of the lateral spinothalamic tract carrying pain and temperature fibers may be impaired. Crude touch, position, and vibratory sensation typically are unaffected. Sensory fibers from the lower limbs are similarly spared.

The symptoms of syringomyelia develop and progress in accordance with the intracavitary pressure and location of the syrinx. The most common features on physical examination are lower limb hyperreflexia, weakness and wasting in the hands and arms, dissociated sensory loss, and gait disorder. Symptoms may be exacerbated by a sneeze, cough, or Valsalva maneuver.[49] Ninety percent of patients with syringomyelia have Arnold-Chiari I malformation (projection of cerebellar tonsils and medulla into the spinal canal).[50] Syringomyelia also may result from spinal cord trauma (often months to years later) or compressive tumors, or it may follow meningitis.[51]

Diagnostic Strategies. Syringomyelia is best seen on MRI. No other study currently in widespread use is equal to MRI in diagnostic ability.

Differential Considerations. Considerations in the differential diagnosis for syrinx include intrinsic spinal tumor and demyelination.

Management. When the diagnosis of syringomyelia is considered, emergent imaging in the ED is not necessary if follow-up evaluation can be arranged because this condition usually is a slowly progressive process. In patients for whom MRI studies are obtained and the diagnosis is made, referral to a neurosurgeon is indicated because symptoms progress in approximately two thirds of patients.[52]

Idiopathic Spastic Paraparesis

Idiopathic spastic paraparesis is a progressive disorder characterized by progressive weakness and signs of spasticity of the lower extremities. This condition sometimes also is referred to as primary lateral sclerosis, which describes the demyelination pattern in the lateral column of the spinal cord. This disorder typically occurs in older men. A heritable form may sometimes be discovered. It is a diagnosis of exclusion.[53-55]

Human Immunodeficiency Virus Myelopathy

HIV myelopathy typically occurs in patients with advanced HIV disease. Weakness, gait disturbance, sphincter dysfunction, sensory abnormalities, and signs of spasticity are features of this progressive process. This is a diagnosis of exclusion because disorders such as toxoplasmosis, lymphoma, varicella-zoster, and cytomegalovirus infection may produce a similar clinical picture in immunocompromised patients. On pathologic examination, vacuolization of myelin sheaths in the cord may be found. Treatment is directed at the retroviral infection, although there is no proven treatment.[56,57]

Spinal Cord Infarction

Spinal cord infarction is another diagnosis of exclusion. Aortic dissection, surgery, and global ischemia are the more common causes, although this disorder may occur as a complication of systemic lupus erythematosus or may be cryptogenic. An anterior spinal cord syndrome is the most common clinical picture. Some recovery is possible, although it generally is less complete than in cerebral stroke. The site of clinical dysfunction may be distant from the site of vascular occlusion.[58]

Extrinsic Cord Lesions

Spinal Epidural Hematoma

Principles of Disease. Spinal epidural hematoma is a relatively rare condition resulting from a variety of etiologic disorders. Its incidence is 0.1 per 100,000 population.[59,60] The etiology may be traumatic after lumbar puncture, epidural anesthesia, or spinal surgery.[1,5,61] Spinal epidural hematoma is more likely to occur in anticoagulated or thrombocytopenic patients or in patients with liver disease or alcoholism.[62] Spontaneous bleeding is rare but may arise from spinal arteriovenous malformation or vertebral hemangioma. Approximately one fourth to one third of all cases are associated with anticoagulation therapy, including low-molecular-weight heparin.[63,64]

Clinical Features. The patient usually presents with sudden, severe, constant back pain with a radicular component. It may be noted to follow a straining episode. The pain may be worsened by percussion over the spine and maneuvers that increase intraspinal pressure, such as coughing, sneezing, or straining.[65] The pain often causes the patient to seek care before the development of neurologic signs, possibly leading to delays in diagnosis.[5] Neurologic deficits follow and may progress during hours to days.[60] Anticoagulant use or an intrinsic coagulation abnormality may be present.

The patient usually is in significant distress from the pain. Motor and sensory findings depend entirely on the level and size of the hematoma but can include weakness, paresis, loss of bowel or bladder function, and virtually any sensory deficit.

Diagnostic Strategies. MRI, as with virtually all suspected intrinsic spinal disorders, is the diagnostic study of choice.[65]

Differential Considerations. Considerations in the differential diagnosis include abscess, epidural neoplasm, acute disk herniation, and spinal subarachnoid hemorrhage.

www.ketabpezeshki.com 66485457-66963820

Management. Recovery without surgery is rare, and surgical consultation for emergent decompressive laminectomy should be considered. The overall mortality rate is approximately 8%.[60,65] Functional recovery is related primarily to the length of time the symptoms are present. Recovery after 72 hours of symptoms is rare but has been reported even without surgery.[66,67]

Spinal Epidural Abscess

Principles of Disease. Spinal epidural abscess is an infectious process usually confined to the adipose tissue of the dorsal epidural space, where there is a rich venous plexus. It is an uncommon disease, with an overall frequency of 0.2 to 1.2 per 10,000 hospital admissions.[68,69] Major risk factors include diabetes, injection drug abuse, chronic renal failure, alcoholism, and immunosuppression, although the disease can be seen in patients who have none of these conditions.[69-71] Whereas the disease may be manifested in subacute and chronic forms, the acute presentation is seen most frequently in the ED. Thoracic and lumbar sites of infection predominate, with cervical epidural abscess being much less common.[72,73] Infection typically extends over four or five spinal vertebral segments.[74] The dura mater limits the spread of an epidural infection, making subdural or intraspinal spread uncommon. Hematogenous spread of infection to the epidural space is the most common source (seen in 26-50% of cases),[5,68,74] either to the epidural space or to the vertebra with extension to the epidural space. Skin and soft tissue infections are the most frequently reported identified source (in 15%)[70,74]; *Staphylococcus aureus* is the most prevalent organism, being cultured in more than 50% of cases.[68,75] Other frequently identified pathogens include aerobic and anaerobic streptococci, *Escherichia coli,* and *Pseudomonas aeruginosa*. Multiple organisms are identified in approximately 10% of cases; no organism is identified in 40%.[65,72]

Clinical Features. The classic clinical presentation of spinal epidural abscess begins with a backache that progresses to localized back pain often associated with tenderness to percussion. The duration of symptoms is typically a few days but may extend for weeks. Fever, sweats, and rigors are common, being reported in 30 to 75% of patients.[68,75] The classic triad of back pain, fever, and progressive neurologic deficits is present in only a few patients, however, and delayed clinical diagnosis is common.[68] Radicular symptoms may not be present initially but usually develop as the disease progresses.

Without treatment, myelopathic signs will develop, usually beginning with bowel and bladder disturbance. Weakness ensues, followed by paraplegia or quadriplegia. Approximately 10% of patients with spinal epidural abscess present with altered mental status due to encephalopathy.[68,74]

Diagnostic Strategies. MRI is the imaging modality of choice and needs to be performed emergently if the diagnosis is entertained. Other diagnostic testing is nonspecific for spinal epidural abscess, but a complete blood count may support the diagnosis because leukocytosis is commonly present, with a typical white blood cell count of 13,000 to 16,000/μL.[74] The erythrocyte sedimentation rate, although not specific for epidural abscess, is virtually always elevated with this condition.[68,69,74] Plain films usually are normal in appearance unless evidence of osteomyelitis of an adjacent vertebral body is seen. Lumbar puncture is relatively contraindicated with known epidural abscess but is often performed as part of the evaluation for meningitis. CSF findings are consistent with a parameningeal infection, showing elevation of protein and some increase in inflammatory cells.

Differential Considerations. Any compressive spinal lesion, including tumor or hematoma, can mimic spinal epidural abscess.

Management. Urgent surgical consultation for decompression usually is required. Antibiotics effective against the most common pathogens (particularly *S. aureus*) should be started empirically. One such regimen that covers gram-positive and gram-negative organisms consists of a third-generation cephalosporin plus vancomycin, both given intravenously, plus rifampin given orally.

Outcome is usually related to the speed of diagnosis before the development of myelopathic signs. The disease is fatal in 18 to 23% of cases, and patients with neurologic deficit rarely improve if surgical intervention is delayed more than 12 to 36 hours after onset of paralysis.[68,74] Patients operated on before development of neurologic symptoms have an almost universally good outcome.[69,70]

Diskitis

Principles of Disease. Diskitis is an uncommon primary infection of the nucleus pulposus, with secondary involvement of the cartilaginous endplate and vertebral body. It may occur after surgical procedures or spontaneously, the latter being more common in pediatric patients.[76,77] An increased incidence of diskitis has been noted in immunocompromised patients and in patients with systemic infections. Both a chronic disease and a more common acute course have been described.[76]

Clinical Features. Patients present with moderate to severe pain, localized to the level of involvement and exacerbated by almost any movement of the spine. Radicular symptoms are present in 50 to 90% of cases.[76,77] The lumbar spine is the most common site of disease. Elevated temperature is noted in more than 90% of patients.[76] Patients experience pain with range of motion. Neurologic deficits are the exception with diskitis.

Diagnostic Strategies. Plain radiographs usually are not helpful for early diagnosis, but destruction of the disk space is highly suggestive if present. The radiographic findings become abnormal after 2 to 4 weeks of disease. In addition to disk space narrowing, plain films may show irregular destruction of the vertebral body endplates. Often there is a latent period (2 to 8 weeks) between the onset of back pain and the development of other clinical symptoms or abnormalities on the physical examination. MRI is the radiographic study of choice because it can not only diagnose diskitis but also rule out paravertebral or epidural abscess. Laboratory studies often show an elevated erythrocyte sedimentation rate, but the white blood cell count usually is normal.[76,77] *S. aureus* is the most common pathogen, but gram-negative, fungal, and tuberculous infections all have been recognized.

Differential Considerations. Considerations in the differential diagnosis include vertebral osteomyelitis, spinal epidural abscess, neoplasm, and hematoma.

Management. With timely diagnosis and treatment, outcome generally is good, and medical treatment with intravenous antibiotics usually is curative. Surgery often is not necessary.[76,77]

Neoplasm

Principles of Disease. Spinal cord tumors are classified according to their relationship to the dura and spinal cord (extradural, intradural extramedullary, and intradural intramedullary). Spinal cord tumors produce neurologic symptoms by compression, invasion, or destruction of myelinated tracts. The resulting neurologic symptoms are directly related to the growth rate and the location of the tumor. Spinal cord tumors account for 4 to 10% of central nervous system tumors but for only 1% of all cancers. Primary tumors occur with an incidence of 1 per 1 million population.[78] Most tumors affecting the spinal cord are metastatic. Approximately 10% of patients with known cancer are diagnosed with a spinal metastasis at some point in the course of their disease, and 5 to 10% of patients ultimately diagnosed with cancer first present with a spinal metastasis.[2] Lung cancer, breast cancer, and lymphoma represent more than 50% of the primary malignant neoplasms that subsequently develop spinal metastasis, spreading by both the hematogenous route and direct extension. Most

www.ketabpezeshki.com 66485457-66963820

metastases occur in the thoracic spine, and nearly 20% of patients with tumor spread to the spine will be found to have disease at multiple levels.[2,79,80]

Clinical Features. In 95% of patients with spinal neoplasm, the initial complaint is pain, either in the back at the level of the tumor or in a radicular distribution. Pain often is characterized as dull, constant, and aching and commonly is said to worsen with recumbency (in contrast with the pain of herniated disk).[5] Nighttime pain that is severe is characteristic of spinal neoplasm.[81] Any action that increases intraspinal pressure (Valsalva maneuver, sneeze, cough) may be associated with increased pain. Neurologic deficits vary by the location of the lesion. Besides a thorough neurologic examination, a search for possible primary sites should be done on the physical examination.

Diagnostic Strategies. Plain radiographs are usually the initial diagnostic test, and 70 to 85% of patients with spinal column involvement show some abnormality on these films.[81] Patients with neurologic abnormalities and suspicious findings on plain films are candidates for emergent MRI or CT myelography. In patients with a known history of neoplasm and new back pain, some authorities recommend foregoing plain films and proceeding directly to MRI because plain films can be misleading or nondiagnostic.[82]

Differential Considerations. Considerations in the differential diagnosis include any of the compressive lesions (hematoma, infection). Tumor can also mimic intrinsic spinal cord lesions, such as transverse myelopathy and cord infarction.

Management. Acute compressive myelopathy from neoplasm constitutes an oncologic emergency. Immediate treatment is required to preserve function and to prevent deterioration. With onset of paraplegia and incontinence, less than 5% of patients regain ambulatory status.[1,83] Of patients who are ambulatory at the time of diagnosis, 60% remain ambulatory.[5] High-dose steroids, radiotherapy, and surgery all may be necessary acute interventions, and consultation with neurosurgeons, neurologists, oncologists, and therapeutic radiologists may be required.

KEY CONCEPTS

- Spinal cord disorders may be manifested in subtle fashion and with nonspecific clinical signs and symptoms. In the absence of neurologic abnormalities or complaints, diagnosis of these disorders can be extremely difficult.
- Patients with rapid onset and progression of spinal cord symptoms should receive specialized imaging and consultation in the ED.
- MRI frequently is required for a definitive diagnosis of spinal cord syndromes.
- With compressive lesions of the spinal cord, duration of neurologic dysfunction is directly related to ultimate neurologic outcome. The diagnosis should be made expeditiously and definitive therapy begun as soon as possible.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Wagner R, Jagoda A: Spinal cord syndromes. *Emerg Med Clin North Am* 1997; 15:699.
2. Ruckdeschel JC: Early detection and treatment of spinal cord compression. *Oncology* 2005; 19:81.
3. Fredrickson MD: Acute spinal cord injury management. *J Trauma* 2007; 62:S9.
4. McKinley W, et al: Incidence and outcomes of spinal cord injury clinical syndromes. *J Spinal Cord Med* 2007; 30:215.
5. Schiff D: Spinal cord compression. *Neurol Clin* 2003; 21:67.
6. Ditunno JF, et al: Spinal shock revisited: A four-phase model. *Spinal Cord* 2004; 42:383.
7. Harrop JS, Sharan A, Ratliff J: Central cord injury: Pathophysiology, management, and outcomes. *Spine* 2006; 45:292.
8. Schneider RC, Cherry G, Pantek H: The syndrome of acute central spinal cord injury, with special reference to the mechanics involved in hyperextension injury of the cervical spine. *J Neurosurg* 1954; 11:546.
9. Levi ADO, Tator CH, Bunge RP: Clinical syndromes associated with disproportionate weakness of the upper versus the lower extremities after cervical spinal cord injury. *Neurosurgery* 1996; 38:179.
10. Tow AM, Kong KH: Central cord syndrome: Functional outcome after rehabilitation. *Spinal Cord* 1998; 36:156.
11. Kirschblum SC, O'Connor KC: Predicting neurologic recovery in traumatic cervical spinal cord injury. *Arch Phys Med Rehabil* 1998; 79:1456.
12. Brown-Séquard CE: Lectures on the physiology and pathology of the central nervous system and the treatment of organic nervous affections. *Lancet* 1868; 2:593.
13. Gill D, Ifthikharuddin S, Samkoff LM: Acute Brown-Séquard syndrome. *Arch Neurol* 2004; 61:131.
14. Hosaka AI, Nakamagoe K, Watanabe M, Tamaoka A: Magnetic resonance images of herpes zoster myelitis presenting with Brown-Séquard syndrome. *Arch Neurol* 2010; 67:506.
15. Tattersall R, Turener B: Brown-Séquard and his syndrome. *Lancet* 2000; 356:61.
16. McGarvey ML, et al: The treatment of spinal cord ischemia following thoracic endovascular aortic repair. *Neurocrit Care* 2007; 6:35.
17. Rogers FB, et al: Isolated stab wound to the artery of Adamkiewicz: Case report and review of the literature. *J Trauma Injury Infect Crit Care* 1997; 43:549.
18. Weigang E, et al: Thoracoabdominal aortic aneurysm repair: Interplay of spinal cord protecting modalities. *Eur J Vasc Endovasc Surg* 2005; 30:624.
19. Lewandrowski KU, et al: Cord and cauda equina injury complicating elective orthopedic surgery. *Spine* 2006; 31:1056.
20. Jalloh I, Minhas P: Delays in the treatment of cauda equina syndrome due to its variable clinical features in patients presenting to the emergency department. *Emerg Med J* 2007; 24:33.
21. Glick TH, Workman TP, Gaufberg SV: Spinal cord emergencies: False reassurance from reflexes. *Acad Emerg Med* 1998; 5:1041.
22. Kirshblum SC, et al: Spinal cord injury medicine 1: Etiology, classification and acute management. *Arch Phys Med Rehabil* 2002; 83(Suppl 1):S50.
23. Coleman WP, et al: A critical appraisal of the reporting of the National Acute Spinal Cord Injury Studies (II and III) of methylprednisolone in acute spinal cord injury. *J Spinal Disord* 2000; 13:185.
24. Hurlbert RJ: Methylprednisolone for acute spinal cord injury: An inappropriate standard of care. *J Neurosurg* 2000; 93(1 Suppl):1.
25. Canadian Association of Emergency Physicians: Steroids in acute spinal cord injury. *Can J Emerg Med* 2003; 5:9.
26. Kortbeek JB: Advanced trauma life support, 8th edition—the evidence for change. *J Trauma* 2008; 64:1638.
27. Cook SD: Multiple sclerosis: Pathologic, clinical, and imaging updates. *Rev Neurol Dis* 2006; 3:23.
28. Noseworthy JH, et al: Multiple sclerosis. *N Engl J Med* 2000; 343:938.
29. Nielson JM, et al: The role of spinal cord imaging in the diagnosis of multiple sclerosis. *Nat Clin Pract Neurol* 2006; 2:283.
30. Garcia-Merino A, Blasco MR: Confirming the MS diagnosis. *Int MS J* 2007; 14:58.
31. Murray TJ: Diagnosis and treatment of multiple sclerosis. *BMJ* 2006; 332:525.
32. Pender M: CSF testing for multiple sclerosis. *Lancet Neurol* 2005; 4:522.
33. Cohen JA, Rensel MR: *The differential diagnosis and clues to misdiagnosis.* In: Burks JS, Johnson KP, eds. *Multiple Sclerosis: Diagnosis, Medical Management, and Rehabilitation*. New York: Demos Vermande; 2000:127-140.
34. Frohman EM, Wingerchuk DM: Transverse myelitis. *N Engl J Med* 2010; 363:564.
35. Moore AP, Blumhardt LD: A prospective survey of the causes of non-traumatic spastic paraparesis and tetraparesis in 585 patients. *Spinal Cord* 1997; 35:361.
36. Scott TF: Nosology of idiopathic transverse myelitis syndromes. *Acta Neurol Scand* 2007; 115:371.
37. Kalita J, Misra UK, Mandal SK: Prognostic predictors of acute transverse myelitis. *Acta Neurol Scand* 1998; 98:60.
38. Hammerstedt HS, Edlow JA, Cusicj S: Emergency department presentations of transverse myelitis: Two case reports. *Ann Emerg Med* 2005; 46:256.
39. Canellas AR, et al: Idiopathic inflammatory-demyelinating diseases of the central nervous system. *Neuroradiology* 2007; 49:393.
40. Pidcock FS, et al: Acute transverse myelitis in childhood: Center-based analysis of 47 cases. *Neurology* 2007; 68:1474.
41. Greenberg BM, et al: Idiopathic transverse myelitis: Corticosteroids, plasma exchange, or cyclophosphamide. *Neurology* 2007; 68:1614.
42. Bruna J, et al: Idiopathic acute transverse myelitis: A clinical study and prognostic markers in 45 cases. *Mult Scler* 2006; 12:169.
43. Krishnan C, et al: Demyelinating disorders: Update on transverse myelitis. *Curr Neurol Neurosci Rep* 2006; 6:236.
44. Krings T, et al: Spinal vascular malformations. *Eur Radiol* 2005; 15:267
45. Santoro A, et al: Extradural spinal cavernous angiomas: Report of seven cases. *Neurosurg Rev* 2005; 28:313.
46. Cordan T, et al: Spinal subarachnoid hemorrhage attributable to schwannoma of the cauda equina. *Surg Neurol* 1999; 51:373.
47. Kreppel D, Antoniadis G, Seeling W: Spinal hematoma: A literature survey with meta-analysis of 613 patients. *Neurosurg Rev* 2003; 26:1.
48. Larner AJ, Muqit MM, Glickman S: Concurrent syrinx and inflammatory central nervous system disease detected by magnetic resonance imaging: An illustrative case and review of the literature. *Medicine (Baltimore)* 2002; 81:41.
49. Lin JW, et al: Idiopathic syringomyelia: Case report and review of the literature. *Acta Neurochir Suppl* 2006; 99:117.
50. Hankinson TC, et al: Chiari malformations, syringomyelia, and scoliosis. *Neurosurg Clin Norrth Am* 2007; 18:549.
51. Koyanagi I, et al: Clinical features and pathomechanisms of syringomyelia associated with spinal arachnoiditis. *Surg Neurol* 2005; 63:350.
52. Todor DR, Mu HT, Milhorat TH: Pain and syringomyelia: A review. *Neurosurg Focus* 2000; 8:E11.
53. Fink JK: Progressive spastic paraparesis: Hereditary spastic paraplegia and its relation to primary and amyotrophic lateral sclerosis. *Semin Neurol* 2001; 21:199.
54. Gordon PH, et al: The natural history of primary lateral sclerosis. *Neurology* 2006; 66:647.
55. Singer MA, et al: Primary lateral sclerosis. *Muscle Nerve* 2007; 35:291.
56. Portegies P, et al: Guidelines for the diagnosis and management of neurologic complications of HIV infection. *Eur J Neurol* 2004; 11:297.
57. Amayo EO, Kwasa TO, Otieno CF: Herpes zoster myelitis: Report of two cases. *East Afr Med J* 2002; 79:279.
58. Salvador de la Barrera S, Barca-Buyo A, Montoto-Marques A: Spinal cord infarction: Prognosis and recovery in a series of 36 patients. *Spinal Cord* 2001; 39:520.
59. Porterfield WR, Wu CL: Epidural hematoma in an ambulatory surgical patient. *J Clin Anesth* 1997; 9:74.
60. Hejazi N, Thaper PY, Hassler W: Nine cases of nontraumatic spinal epidural hematoma. *Neurol Med Chir* 1998; 38:718.
61. Christie IW, McCabe S: Major complications of epidural analgesia after surgery: Results of a six-year survey. *Anaesthesia* 2007; 62:335.
62. Lonjon M, et al: Nontraumatic spinal epidural hematoma: Report of four cases and review of the literature. *Neurosurgery* 1997; 41:483.
63. Adam M, Leblebici B, Akman MN: Spontaneous spinal epidural hematoma related to warfarin therapy: A case report. *J Back Musc Rehab* 2007; 20:11.
64. Wysowski DK, et al: Spinal and epidural hematoma and low-molecular-weight heparin. *N Engl J Med* 1998; 338:1774.
65. Alexiadou-Rudolf C, et al: Acute non-traumatic spinal epidural hematomas: An important differential diagnosis in spinal emergencies. *Spine* 1998; 23:1810.
66. Liao CC, et al: Experience in the surgical management of spontaneous spinal epidural hematoma. *J Neurosurg* 2004; 100:38.
67. Hentschel SJ, Woolfenden AR, Fairholm DJ: Resolution of spontaneous spinal epidural hematoma without surgery: Report of two cases. *Spine* 2001; 26:E525.
68. Darouiche RO: Spinal epidural abscess. *N Engl J Med* 2006; 355:2012.
69. Rigamonti D, Liem L, Sampath P: Spinal epidural abscess: Contemporary trends in etiology, evaluation, and treatment. *Surg Neurol* 1999; 52:189.

www.ketabpezeshki.com 66485457-66963820

70. Sampath P, Rigamonti D: Spinal epidural abscess: A review of epidemiology, diagnosis, and treatment. *J Spinal Disord* 1999; 12:89.
71. Pereira CE, Lynch JC: Spinal epidural abscess: An analysis of 24 cases. *Surg Neurol* 2005; 63(Suppl 1):S26.
72. Joshi SM, et al: Spinal epidural abscess: A diagnostic challenge. *Br J Neurosurg* 2003; 17:160.
73. Sendi P, Bregenzer T, Zimmerli W: Spinal epidural abscess in clinical practice. *QJM* 2008; 101:1.
74. Pilkington SA, Jackson SA, Gillett GR: Spinal epidural empyema. *Br J Neurosurg* 2003; 17:196.
75. Bluman EM, Palumbo MA, Lucas PR: Spinal epidural abscess in adults. *J Am Acad Orthop Surg* 2004; 12:155.
76. Maiuri F, Laconetta G, Gallicchio B: Spondylodiscitis. Clinical and magnetic resonance diagnosis. *Spine* 1997; 22:1741.
77. Khan AI, Vaccaro AR, Zlotolow DA: Management of vertebral diskitis and osteomyelitis. *Orthopedics* 1999; 22:758.
78. Traul DE, Shaffrey ME, Schiff D: Spinal cord intradural neoplasms. *Lancet Oncol* 2007; 8:35.
79. Schiff D, O'Neill BP, Suman VJ: Spinal epidural metastasis as the initial manifestation of malignancy: Clinical features and diagnostic approach. *Neurology* 1997; 49:452.
80. Jansson KA, Bauer HC: Survival, complications, and outcome in 282 patients operated for neurological deficit due to thoracic or lumbar spinal metastases. *Eur Spine J* 2006; 15:196.
81. Abdu WA, Provencher M: Primary bone and metastatic tumors of the cervical spine. *Spine* 1998; 23:2767.
82. Husband DJ, Grant KA, Romaniuk CS: MRI in the diagnosis and treatment of suspected malignant spinal cord compression. *Br J Radiol* 2001; 74:15.
83. Sciubba DM, Gokaslan ZL: Diagnosis and management of metastatic spine disease. *Surg Oncol* 2006; 15:141.

www.ketabpezeshki.com 66485457-66963820

Chapter 107

Peripheral Nerve Disorders

E. Bradshaw Bunney and E. John Gallagher

PERSPECTIVE

Background

The nervous system is traditionally divided into central nervous system (CNS) and peripheral nervous system (PNS) components. The PNS can be further subdivided into 12 cranial and 31 spinal nerves. Disorders of the cranial nerves are discussed in Chapter 105. Because diseases of the neuromuscular junction and the myopathies are located distal to the neuron itself, they are also considered separately in Chapter 108. Radiculopathies, which are disorders of the roots of the PNS, are so commonly associated with musculoskeletal neck and back pain that they are mentioned only briefly here and are discussed in detail in Chapter 54.

The simplest approach to diseases of the PNS parallels the CNS model of separating focal from nonfocal disease. In the PNS, the first broad category is the focal group, which can be divided into those with evidence of single versus multiple lesions of peripheral nerves, known respectively as *simple mononeuropathies* and *multiple mononeuropathies* (or *mononeuropathy multiplex*). The second broad category, which constitutes the nonfocal group of peripheral neuropathies, contains the polyneuropathies. These tend to produce bilaterally symmetrical symptoms and signs, reflecting the widespread nature of the underlying pathologic process.

The evaluation of PNS disease involves a goal-directed history and physical examination targeted at answering the following three questions, each of which corresponds to a stratum of the algorithm presented in Figure 107-1:

1. Are the sensorimotor signs and symptoms symmetrical or asymmetrical?
2. Are the sensorimotor signs and symptoms distal or both proximal and distal?
3. Is the modality involved exclusively motor, sensory, or mixed sensorimotor?

By systematically combining responses to these questions, one can identify seven discrete categories of peripheral neuropathy, each of which contains a finite set of possible diagnoses. Because pure motor or sensory findings tend to occur mainly in an asymmetrical, distal distribution, this is the only category in Figure 107-1 subdivided into pure motor and pure sensory abnormalities.

Epidemiology

Although Guillain-Barré syndrome (GBS) is the most commonly encountered emergent peripheral neuropathy in developed countries, its annual incidence is just 1 or 2 cases per 100,000 population.[1] In contrast to the acute peripheral neuropathies, several of which are associated with short-term mortality, most peripheral neuropathies seen in the emergency department (ED) are subacute or chronic and are associated not with mortality but with long-term morbidity.

Current estimates suggest that about 1.5% of the U.S. population suffers from peripheral neuropathy.[2] Diabetes mellitus is a leading contributor. More than 7% of the population has diabetes mellitus, with a prevalence rate of 20% in individuals older than 60 years. Roughly 50% of these individuals develop peripheral neuropathy.[3]

PRINCIPLES OF DISEASE

Anatomy

The spinal component of the PNS is shown schematically in Figure 107-2. The anterior and posterior nerve roots exit the spinal cord at each segmental level. Just distal to the dorsal root ganglion they converge to form a mixed (motor and sensory) spinal nerve, of which there are 31 pairs: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal. The spinal nerves immediately bifurcate into anterior (ventral) and posterior (dorsal) rami. The posterior ramus travels to the back. The anterior ramus innervates the anterolateral portion of the body and supplies all peripheral nerves for the upper and lower extremities through the brachial and lumbosacral plexus, respectively. Interweaving of fibers occurs within a plexus, producing a mixed sensorimotor innervation of peripheral nerves exiting the plexus.

In addition to the motor and sensory modalities of the PNS, the autonomic nervous system has a peripheral component. Anatomically and functionally, the autonomic nervous system is divided into two parts: a sympathetic (thoracolumbar) component and a parasympathetic (craniosacral) component. Autonomic dysfunction may cause systemic abnormalities, such as orthostasis, or local problems, such as atrophic, dry skin.

Pathophysiology

The PNS has only three basic responses to a wide array of pathologic stimuli. As shown in Figure 107-2, these are (1) the myelinopathies, in which the primary site of involvement is limited to the myelin sheath surrounding the axon; (2) the axonopathies, in which the primary site of involvement is the axon, with or without secondary demyelination; and (3) the neuronopathies, in which the cell body of the neuron itself is the primary site of involvement, ultimately affecting the entire peripheral nerve. Although overlap occurs, each of these prototypes has a distinctive clinical presentation, electrophysiologic profile, and microscopic appearance.

www.ketabpezeshki.com 66485457-66963820

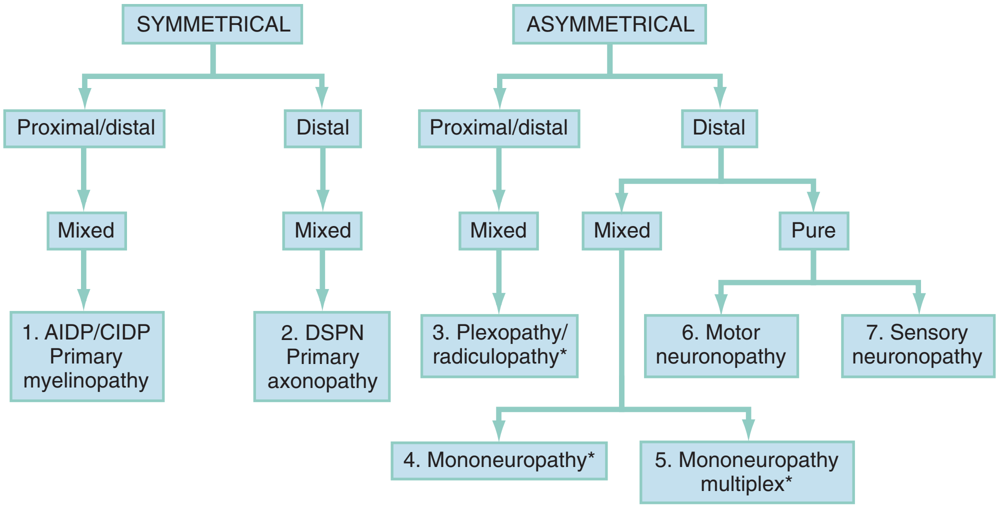


Figure 107-1. An approach to peripheral neuropathy in the emergency department. *AIDP,* acute inflammatory demyelinating polyneuropathy (Guillain-Barré); *CIDP,* chronic inflammatory demyelinating polyneuropathy; *DSPN,* distal symmetrical polyneuropathy. *A proximal distribution of sensorimotor findings may dominate the clinical picture in patterns 3, 4, and 5, depending on the location of the lesions.

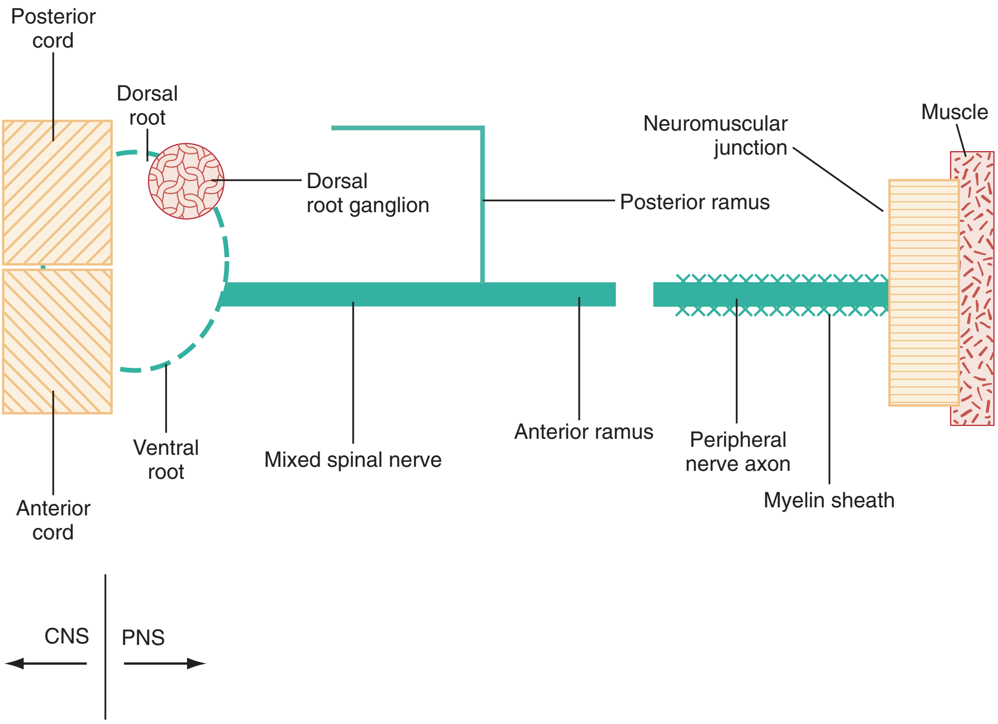


Figure 107-2. Schematic representation of macroscopic and microscopic anatomy of the peripheral nervous system and its interface with the central nervous system. See text for explanation.

Electrophysiologic testing, that is, nerve conduction studies (NCSs) and needle electromyography (EMG), detects underlying pathologic abnormalities. Because neither test is readily available in the acute care setting, they are discussed only briefly here. Information gathered from NCSs and EMG can be used to obtain objective information on the anatomic distribution of involvement (symmetrical vs. asymmetrical and distal vs. proximal and distal) and the modalities involved (sensory, motor, or mixed). NCSs and EMG can also identify the level of the neuraxis affected by the disease process (i.e., root, plexus, or nerve); if the nerve is affected, electrophysiologic testing can help determine whether the lesion is mononeuropathic (either an isolated mononeuropathy or mononeuropathy multiplex) or polyneuropathic. Finally, EMG and NCSs can distinguish axonal from myelin disease, further narrowing the differential diagnosis. Prognosis is determined by the nature of pathologic involvement of the PNS. Primary demyelination spares the axon and thus carries the best prognosis. The prognosis is worse in axonopathies because reestablishment of nerve function is dependent on the much slower process of axonal regeneration. Neuronopathies, which begin with primary destruction of the nerve cell body, produce pure motor or pure sensory syndromes. Eventually the entire nerve is affected, resulting in the worst prognosis of the three.

CLINICAL FEATURES

The differential diagnosis for any patient presenting with sensory, motor, or sensorimotor complaints, particularly if they

www.ketabpezeshki.com 66485457-66963820

Box 107-1 Causes of Acute, Emergent Weakness and Possible Respiratory Compromise

- Autoimmune
  - Demyelinating
    - Guillain-Barré syndrome
    - Chronic inflammatory demyelinating polyneuropathy
  - Myasthenia gravis
- Toxic
  - Botulism
  - Buckthorn
  - Seafood
    - Paralytic shellfish toxin
    - Tetrodotoxin (puffer fish, newts)
  - Tick paralysis
  - Metals
    - Arsenic
    - Thallium
- Metabolic
  - Dyskalemic syndromes
    - Acquired (especially with thyrotoxicosis)
    - Familial
  - Hypophosphatemia
  - Hypermagnesemia
  - Porphyria
- Infectious
  - Poliomyelitis
  - Diphtheria

Table 107-1 Patterns and Prototypes of Peripheral Neuropathies

TYPE	PATTERN DISTRIBUTION	PROTOTYPICAL DISEASE MODALITIES
1	Proximal and distal, symmetrical, sensorimotor polyneuropathy Proximal and distal Motor > sensory	GBS Symmetrical
2	Distal, symmetrical, sensorimotor polyneuropathy Distal Sensory > motor	Diabetic DSPN Symmetrical
3	Proximal and distal, asymmetrical, sensorimotor neuropathy Proximal and distal Sensory and motor	Brachial plexopathy Asymmetrical
4	Distal, asymmetrical, sensorimotor mononeuropathy Distal Sensory and motor	CTS (median mononeuropathy) Asymmetrical
5	Distal, asymmetrical, sensorimotor mononeuropathy multiplex Distal Sensory and motor	Vasculitic mononeuropathy multiplex Asymmetrical
6	Distal, asymmetrical, pure motor neuronopathy Distal Motor	ALS Asymmetrical
7	Distal, asymmetrical, pure sensory neuronopathy Distal Sensory	Pyridoxine toxicity Asymmetrical

ALS, amyotrophic lateral sclerosis; *CTS,* carpal tunnel syndrome; *DSPN,* distal symmetrical polyneuropathy; *GBS,* Guillain-Barré syndrome.

are localized to the extremities, should include a peripheral neuropathy. Within this group, patients with focal weakness are most concerning because they are at greatest risk for respiratory compromise. Box 107-1 lists the causes of acute, emergent weakness that may affect respiration. Although several of the disorders listed are myopathies (see Chapter 108) rather than peripheral neuropathies, they are lumped together because it is important to identify patients at risk for respiratory failure early in the course of evaluation.

As soon as the emergent causes of weakness have been excluded, which is possible in the majority of patients, the individuals with focal weakness should be assessed next to exclude CNS disease (e.g., stroke; see Chapter 101). One can then proceed through the systematic approach to peripheral neuropathy outlined in Figure 107-1. Another way to look at the algorithm displayed in Figure 107-1 is shown in Table 107-1, with the distinguishing features of each of the seven peripheral neuropathic patterns described by distribution and modality and represented by a disease prototype.

Type 1: Demyelinating Polyneuropathies

The pattern of symmetrical weakness, usually worse distally, accompanied by variable sensory findings is characteristic of acute GBS. This pattern is discussed first because it is the most common cause of weakness associated with acute respiratory failure.

Guillain-Barré Syndrome

GBS is a heterogeneous and unpredictable disorder, with marked variation in latency between antecedent infection and symptom onset. The clinical signs, cadence of disease progression, degree of respiratory compromise, laboratory findings, and time required for convalescence are also highly variable. The most common form of GBS is an acute inflammatory demyelinating polyneuropathy, representing 90% of the cases seen in the United States.[1] Less common variants are acute motor axonal neuropathy, acute motor and sensory axonal neuropathy, and the Miller Fisher syndrome. Acute motor axonal neuropathy, which accounts for most of the remaining cases seen in the United States, afflicts those of Asian descent. Miller Fisher syndrome is a rare form of GBS characterized by the triad of ophthalmoplegia, ataxia, and areflexia (Box 107-2).[1,4]

The majority of patients seek treatment days to weeks after resolution of an upper respiratory or gastrointestinal illness, presenting with progressive, symmetrical distal (and usually to a lesser extent proximal) weakness. Signs and symptoms are usually worse in the lower extremities and are associated with diminution or loss of deep tendon reflexes (DTRs), variable sensory findings, and sparing of the anal sphincter. Up to 32% will have all four extremities affected at the time of presentation, but only 10% will have weakness that begins in the upper extremities.[1] The ocular muscles are usually spared. Urinary retention secondary to autonomic dysfunction may occur, contributing to a clinical picture easily mistaken for a spinal cord lesion or conus medullaris syndrome.

The most commonly infectious organisms associated with GBS are *Campylobacter jejuni* (in patients with a history of diarrhea), cytomegalovirus, Epstein-Barr virus, and *Mycoplasma pneumoniae.* Acute inflammatory demyelinating polyneuropathy is caused in part by macrophage invasion of the myelin sheath. The macrophage is believed to detect antigens in the myelin that are nearly identical to the antigens present on certain infectious organisms.[1,5,6]

In practice, patients with symmetrical weakness of relatively acute onset, decreased or absent DTRs, and variable degrees of sensory loss are managed as if they have GBS or one of its variants.

www.ketabpezeshki.com 66485457-66963820

Box 107-2 Demyelinating Polyneuropathies

Guillain-Barré syndrome
- Acute inflammatory demyelinating polyradiculoneuropathy
- Acute motor axonal neuropathy
- Acute motor and sensory axonal neuropathy
- Miller Fisher syndrome

Chronic inflammatory demyelinating polyradiculoplexoneuropathy
Malignant disease
HIV infection
Hepatitis B
Buckthorn
Diphtheria

These patients have a greater risk for respiratory compromise. Conversely, patients with predominantly sensory signs and symptoms are less likely to develop acute respiratory distress and have a more favorable prognosis.[7]

About half of patients with GBS have autonomic dysfunction, experience a peak of disease severity within a week of onset, have some form of cranial nerve involvement (usually VII), and suffer long-term sequelae of their illness. Nearly one third require ventilatory support. Both the mortality and the recurrence rate are about 3%.[8]

In addition to electrophysiologic testing, there are three ancillary tests that may be helpful in the diagnosis of GBS. Cerebrospinal fluid (CSF) analysis is useful when it demonstrates the characteristic picture of markedly elevated protein with only a mild pleocytosis. In the clinical setting of suspected GBS, this finding is highly specific. Early in the disease, however, patients may have normal CSF values. Consequently, a normal CSF value cannot be used to exclude GBS because of the limited sensitivity of this test. Specific protein levels in the CSF (neurofilament NfH) have been shown to correlate with outcomes.[9] The GBS disability score, which combines age, presence or absence of diarrhea, and a score of the patient's ability to ambulate independently at 2 weeks, has been shown to be predictive of prognosis at 6 months, particularly related to independent activity.[10] Tongue weakness has been found to be associated with the development of respiratory compromise and the need for mechanical ventilation in patients with GBS.[11]

Management. Individuals with suspected GBS should have their respiratory function tested. A decrease in forced vital capacity (FVC) has been shown to correlate with the need for intubation in patients with GBS. An FVC of less than 20 mL/kg is associated with pending respiratory failure and the need for intubation, whereas patients with an FVC of more than 40 mL/kg do not usually require intubation.[12,13] Likewise, patients with a negative inspiratory force of less than 30 cm H_2O are more likely to require mechanical ventilation.[13] Other tests, such as the forced expiratory volume in 1 second and peak flow rate, can also be used to assess respiratory function. Patients unable to perform these tests and those with less than 100% of predicted values should have an arterial blood gas sample obtained. Evidence of alveolar hypoventilation (elevated carbon dioxide [P_{CO_2}]) in a patient with an unsecured airway requires a level of intensive monitoring that is impractical in many EDs. Therefore, patients with weakness, carbon dioxide retention, or other evidence of early ventilatory failure should be considered for early, prophylactic intubation.[14]

Among patients with possible GBS who have normal pulmonary function, extensor neck strength can be monitored to predict impending ventilatory failure. Patients with probable GBS should receive neurologic consultation and admission for treatment with either plasma exchange or intravenous immune globulin (IVIG). There is sound evidence that both of these treatments are superior to placebo and that combination or sequential therapy confers no therapeutic advantage over either intervention alone. Plasma exchange is cumbersome and not available at many hospitals. IVIG is more readily available and is usually administered in a dose of 400 mg/kg/day for 5 days. However, IVIG is expensive, costing roughly $50 to $80 per gram.[15,16] Although IVIG is not formally approved by the Food and Drug Administration for this purpose, its use is supported in national treatment guidelines.[17] Corticosteroids are no longer recommended for treatment of GBS.[18] Oral steroids have been shown to delay recovery. Intravenous steroids alone have been shown to impart no benefit, and although the combination of intravenous steroids and IVIG has hastened recovery, there was no effect on long-term outcome.[18-21] The marked elevation in blood pressure seen in some patients with GBS should not be treated because it is typically transient and may be followed by precipitous and unpredictable hypotension.

Compared with adults, children who have GBS have neuropathic pain more often (80%) and require mechanical ventilation less often (13%).[16, 22]

Type 2: Distal Symmetrical Polyneuropathies

Most polyneuropathies are characterized by a pattern of distal, symmetrical sensorimotor findings, worse in the lower than in the upper extremities, with a stocking-glove distribution of sensory abnormalities that gradually diminishes as one moves proximally. Motor weakness and loss of DTRs, which lag behind the sensory features, follow a similar pattern of progression from distal to proximal. The diffuse, distal, symmetrical nature of this pattern is most consistent with a toxic-metabolic disease process, as yet unidentified, that causes a length-dependent axonopathy. Distal symmetrical polyneuropathy (DSPN) is the most common type of peripheral neuropathy. Only the most common causes of DSPN are discussed, with a more complete listing of causes shown in Box 107-3.

Diabetic Distal Symmetrical Polyneuropathy

The preponderance of cases of DSPN occur in diabetics, also termed diabetic polyneuropathy. Initial symptoms usually consist of "positive" sensory complaints (e.g., dysesthesias such as tingling and burning) beginning on the plantar surfaces of both feet. At the early stages of a typical DSPN, there may be some asymmetry. At this juncture, it may be impossible to distinguish a focal neuropathic process such as a mononeuropathy from a polyneuropathy, although in this location, prior probability strongly favors a polyneuropathy. As the process advances, the plantar surfaces of both feet become dysesthetic before the dorsum of either foot is involved. Weakness of dorsiflexion of the big toe is usually the first motor sign, followed by weakness of foot dorsiflexion, footdrop, loss of the Achilles reflex, and later a "steppage gait," in which footdrop causes the toes to point downward and scrape the ground while walking, requiring the patient to lift the leg higher than normal when walking.

Sensory loss continues to move proximally, and before it reaches the knees, the fingertips are usually involved. DTRs are progressively lost, as is proprioception. If loss of proprioception becomes severe, patients may develop sensory ataxia. As the neuropathy continues to progress, sensory abnormalities ultimately involve all modalities and extend to a diamond-shaped periumbilical area. Far-advanced disease may affect sensation over the skull vertex and facial midline structures. Atrophy and areflexia occur as weakness worsens. Severely impaired patients may be unable to ambulate or to grasp objects. These symptoms have a significant impact on the patient's quality of life, affecting not only physical

www.ketabpezeshki.com 66485457-66963820

Box 107-3 Distal Sensorimotor Polyneuropathies

Diabetes mellitus
Alcoholism
Neoplastic or paraneoplastic
Hereditary motor and sensory neuropathies (Charcot-Marie-Tooth)
Cryptogenic sensorimotor polyneuropathies
HIV infection
Toxins
- Organic or industrial agents
  - Acrylamide
  - Allyl chloride
  - Carbon disulfide
  - Ethylene oxide
  - Hexacarbons
  - Methyl bromide
  - Organophosphate-induced delayed polyneuropathy
  - Polychlorinated biphenyls
  - Trichloroethylene
  - Vacor
- Metals
  - Arsenic
  - Gold
  - Mercury (inorganic)
  - Thallium
- Therapeutic agents
  - Amiodarone
  - Antiretrovirals
  - Dapsone
  - Disulfiram
  - Isoniazid
  - Metronidazole
  - Nitrofurantoin
  - Paclitaxel (Taxol)
  - Phenytoin
  - Statins (HMG-CoA reductase inhibitors)
  - Thalidomide
  - Vinca alkaloids (vincristine, vinblastine)

Nutritional
- Beriberi (thiamine or vitamin B_1)
- Pellagra (niacin, B vitamins)
- Pernicious anemia (vitamin B_{12})
- Pyridoxine deficiency (vitamin B_6)

End-organ dysfunction
- Acromegaly
- Chronic pulmonary disease
- Hypothyroidism
- Renal failure (uremic neuropathy)

Paraproteinemias
- Amyloidosis
- Monoclonal gammopathy of unknown significance
- Multiple myeloma
- Waldenström's macroglobulinemia

Porphyria

HMG-CoA, hydroxymethylglutaryl coenzyme A.

functioning but also sleep and emotional and social functioning. Many of these patients display signs of depression or anxiety.[23] Polyneuropathies can be difficult to diagnose and are best approached by the performance of electrodiagnostic studies for patients with a constellation of symptoms and signs suggesting a particular neuropathy.[24]

Management. As with virtually all peripheral neuropathies, referral is indicated for management of diabetic DSPNs. If discomfort is severe, the etiology of the neuropathy seems likely to be diabetic, and if referral is delayed, it may be necessary to provide the patient with some symptomatic relief. Because treatment of neuropathic pain has traditionally been linked to etiology rather than to an underlying mechanism, the choice of pharmacologic agents is empirical, with substantial practice variation in the United States and worldwide. The costs for patients and health plans are considerable; patients will typically spend more than $1000 per year for pain relief from diabetic DSPN.[9] Nonsteroidal anti-inflammatory drugs should not be considered first-line treatment because they have little proven efficacy and a high potential for renal impairment.[3] On the basis of placebo-controlled randomized clinical trials, tricyclic antidepressants and anticonvulsants appear to have the best NNTs (number of patients needed to treat to provide at least 50% relief of symptoms in one patient). These are generally in the range of 3 to 5, with confidence intervals whose upper limits reach 10 in some instances.[25] Imipramine or amitriptyline may be started at a dose of 25 mg at bedtime (10 mg in elders) and titrated slowly up to a dose of 300 mg. Carbamazepine at a dose of 200 to 400 mg every 8 hours and gabapentin at a dose of 900 to 3600 mg/day are also effective treatments.[2,26] Tramadol in two studies has shown an NNT below 5.[24] Although tramadol is a mixed opioid, development of dependence in long-term use appears to be uncommon. Tramadol combined with acetaminophen has been found to be as effective as gabapentin in the treatment of painful diabetic neuropathy.[27] In a recently published guideline, the following medications were recommended for the treatment of neuropathic pain: gabapentin, opioids, tramadol, and tricyclic antidepressants.[3] Pregabalin 150 to 600 mg/day, a more recent treatment option, has a mechanism of action similar to that of gabapentin. Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, has been found effective at a dose of 60 mg/day.[3] Recently, tapentadol ER 100 to 250 mg twice daily was found to provide substantial pain relief in patients with diabetic neuropathy.[28] Topical capsaicin provides relief in some patients, but the burning associated with its application has limited its use. Improving glycemic control can prevent, diminish, or reverse early diabetic DSPNs, and even in diabetic patients with severe peripheral neuropathy, tight glycemic control can improve functionality and pain control.[29]

Alcoholic Distal Symmetrical Polyneuropathy

Although the association between alcoholism and peripheral neuropathy has been well established for centuries, demonstration of a direct neurotoxic effect of alcohol remains elusive. The preponderance of evidence from both observational studies in humans and experimental data from animal models suggests that the association between alcohol and peripheral neuropathy may be confounded by nutritional status (i.e., deficiency states might be the true underlying cause of alcoholic peripheral neuropathy).

The clinical and pathologic picture of alcoholic neuropathy is similar to that of the DSPN of diabetes. However, in alcoholism, severe myopathy and cerebellar degeneration often complicate the clinical picture.[30] Autonomic skin changes with atrophy and hair loss accompany the sensorimotor abnormalities. Often, other systemic effects of alcoholism are so severe that the patient may not notice the neuropathic symptoms. All patients with suspected alcoholic DSPN should receive dietary supplements and referral for outpatient management.

Human Immunodeficiency Virus Neuropathies

With the widespread use of highly active and effective antiretroviral treatment, peripheral neuropathies have become the most common neurologic complication of human immunodeficiency virus (HIV) infection. The typical HIV neuropathy is a DSPN that appears to be triggered by a combination of dideoxynucleoside therapy and poorly characterized immune-mediated mechanisms associated with HIV infection.[31,32] These patients require referral for specialized care. In addition to standard therapies for DSPN,

www.ketabpezeshki.com 66485457-66963820

Box 107-4 Asymmetrical Proximal and Distal Peripheral Neuropathies

Brachial Plexopathy
- Open
  - Direct plexus injury (knife or gunshot wound)
  - Neurovascular (plexus ischemia)
  - Iatrogenic (central line insertion)
- Closed
  - Traction injuries
    - "Stingers"
    - Traction neurapraxia
    - Partial or complete nerve root avulsion
  - Radiation
  - Neoplastic
  - Idiopathic brachial plexitis
  - Thoracic outlet

Lumbosacral Plexopathies
- Open
- Closed
  - Traction injuries
    - Pelvic double vertical shearing fracture
    - Posterior hip dislocation
    - Retroperitoneal hemorrhage
  - Vasospastic (deep buttock injection)
  - Neoplastic
  - Radiation
  - Idiopathic lumbosacral plexitis
  - Infectious
    - Herpesvirus (sacrococcygeal)
    - Herpes simplex 2
    - Herpes zoster
    - Cytomegalovirus polyradiculopathy (HIV infection)

lamotrigine has been shown to be moderately effective in the treatment of HIV-associated painful neuropathies.[33]

Toxic and Metabolic Neuropathies

Many toxic agents and metabolic derangements produce a typical DSPN. Box 107-3 lists some of the most common toxic and metabolic causes of peripheral neuropathy. On the basis of preliminary results from a case-control study, the statins have been added to this list.[34]

Type 3: Asymmetrical Proximal and Distal Peripheral Neuropathies (Radiculopathies and Plexopathies)

Radiculopathies are discussed in detail in Chapter 54. Plexopathies, which are discussed briefly in this chapter, are uncommon and often the result of trauma (Box 107-4). In general, a plexopathy, whether brachial or lumbosacral, is identified by a process of elimination (i.e., a pattern of sensorimotor and reflex abnormalities that fit neither a radicular nor an individual peripheral nerve distribution). Although this approach does not exclude a mononeuropathy multiplex on physical examination alone, a careful history should determine whether the patient is at risk for development of a mononeuropathy or plexopathy on the basis of underlying disease.

Most plexopathies are often the result of blunt trauma and are usually seen in young men after motor vehicle accidents. Most present for evaluation several months after injury because of the need to recover from concurrent injuries. Therapeutic intervention is often delayed to maximize the potential for spontaneous recovery. Several surgical repairs exist, including neurotization and nerve transfer.[35]

Radiation (actinic) plexopathy occurs after a variable period of latency that follows treatment, which may extend to 20 years or more. Almost all series include women who received radiation treatment for breast cancer. Among neoplastic causes, most originate from the lung or breast. Patients with probable neoplastic brachial plexopathy need imaging studies and may require immediate radiation therapy. Pain control is the focus of management.

Thoracic outlet syndrome remains a controversial disorder.[36] Although the pendulum has swung during the past 50 years from a postulated vascular cause to a neurogenic etiology, current evidence supporting the high prevalence of compression of the brachial plexus as a cause of thoracic outlet syndrome is in fact only slightly better than earlier evidence favoring a vascular etiology.[37,38] Nevertheless, the disorder is currently thought to be most commonly due to compression of the medial or lower portion of the brachial plexus by a cervical rib or fibrous band.[39] The syndrome is characterized by gradually progressive weakness and wasting of median and ulnar hand muscles with ulnar forearm and hand sensory signs and symptoms. Patients with this clinical picture should be referred for NCSs and EMG, which are diagnostic.[39] The treatment of true neurogenic thoracic outlet syndrome requires surgical removal of the rib or aberrant fibrous band to decompress the brachial plexus.[39]

Because of the complexity of plexopathies, there is no reason to expect that one can or should do more in the ED than localize the probable pathologic process to the brachial or lumbosacral plexus. Depending on severity and suspected etiology, one should either admit or refer the patient to a neurologist with experience in PNS disease.

Type 4: Isolated Mononeuropathies

The pattern of asymmetrical, sensorimotor, usually distal, peripheral neuropathy is characteristic of a mononeuropathy. Mononeuropathies are of two main types: isolated and multiple. The isolated mononeuropathies are discussed in this section; the multiple mononeuropathies, also termed mononeuropathy multiplex, are discussed in the next section as a type 5 peripheral neuropathy.

Isolated mononeuropathies are usually caused by trauma, either blunt or penetrating (Box 107-5). If the trauma is blunt, the injury may be secondary to compression from an internal or external source. Entrapment neuropathies are a subset of compression neuropathies occurring at anatomic locations where nerves traverse potentially constricting compartments or tunnels. Isolated mononeuropathies may be acute, intermittent, or chronic and continuous. Antecedent peripheral neuropathy may be a risk factor for development of compression neuropathy (so-called double-crush syndrome), particularly in diabetics.

Radial Mononeuropathy

The radial nerve arises from C5-T1 roots. After exiting the brachial plexus, it passes behind the proximal humerus in the spiral groove and takes a lateral (radial) course down the upper arm (Fig. 107-3). At about the level of the antecubital fossa, it bifurcates into the posterior interosseous (pure motor) and superficial radial (pure sensory) nerves.

The radial nerve controls extension of the fingers, thumb, wrist, and elbow (triceps). In contrast to the median and ulnar nerves, the radial nerve provides only *extrinsic* motor innervation to the hand (i.e., it does not supply motor fibers to any muscles that both originate and insert within the hand). In further contrast to the median and ulnar nerves, which supply most of the sensation to the hand, the radial nerve makes a contribution only to a cutaneous dorsal area overlying the first dorsal interosseus muscle,

www.ketabpezeshki.com 66485457-66963820

Box 107-5 Isolated Mononeuropathies

Upper Extremity

Radial nerve
- Axilla
- Humerus
- Elbow (posterior interosseous neuropathy)
- Wrist (superficial cutaneous radial neuropathy)

Ulnar nerve
- Axilla
- Humerus
- Elbow
- Condylar groove
- Cubital tunnel
- Wrist (Guyon's canal)
- Hand
  - Superficial terminal ulnar neuropathy
  - Deep terminal ulnar neuropathy: proximal hypothenar; distal hypothenar

Median nerve
- Axilla
- Humerus (musculocutaneous mononeuropathy)
- Forearm
  - Anterior interosseus
  - Pronator syndrome (?)
- Wrist (carpal tunnel)
- Hand (recurrent motor branch)

Suprascapular mononeuropathy

Axillary mononeuropathy

Lower Extremity

Sciatic nerve

Femoral nerve
- Iliacus compartment (proximal)
- Saphenous mononeuropathy (distal)

Lateral femoral cutaneous (meralgia paresthetica)

Peroneal nerve
- Common peroneal mononeuropathy (fibular head, popliteal fossa)
- Deep peroneal mononeuropathy (anterior compartment)

Tibial nerve
- Popliteal fossa (proximal)
- Tarsal tunnel (distal)

Sural nerve
- Popliteal fossa, calf (proximal)
- Fifth metatarsal base (distal)

Plantar nerve
- Distal to tarsal tunnel
- Interdigital neuropathies (Morton's neuroma)

Obturator mononeuropathy

sometimes extending part of the way up the dorsa of the thumb, index, and long fingers.

Radial mononeuropathy caused by involvement at the level of the axilla is uncommon. When it occurs, it is usually associated with other upper extremity mononeuropathies or a brachial plexopathy. Although improper use of crutches may cause this syndrome, it usually occurs after an extended period of unconsciousness during which the arm is positioned in such a way that prolonged, deep compression is applied to the axilla. Axillary radial mononeuropathy is distinguished from the more common humeral form by the finding of triceps involvement in addition to typical wrist and finger drop. Triceps involvement occurs because the innervation to the triceps is proximal to the point where the nerve is most vulnerable as it winds around the humeral shaft (see Fig. 107-3).

Most radial mononeuropathies are due to so-called Saturday night palsies. The euphemism is derived from the association of radial mononeuropathy with improper positioning of the arm

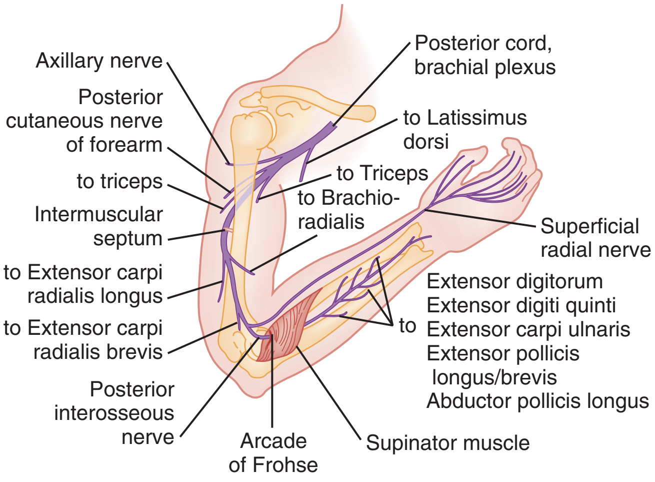


Figure 107-3. Radial nerve, major branches, right arm, lateral view. (From Stewart JD: Focal Peripheral Neuropathies, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2000.)

during deep, commonly inebriated sleep. Consequently, the radial nerve is trapped for a prolonged period between the humeral shaft and some firm surface, causing an external compression mononeuropathy. "Bridegroom's palsy" is another eponym for radial mononeuropathy, so named because the radial nerve may be compressed by the bride's head resting on the bridegroom's arm during sleep.

Because innervation of the wrist and finger extensors occurs distal to this area of the humeral shaft, findings are characterized by wrist and finger drop and mild numbness over the skin of the first dorsal interosseus muscle. Depending on the level, degree, and duration of compression, some fascicles of the nerve may remain functional, resulting in a partial radial mononeuropathy. Thus the superficial radial nerve may remain intact, resulting in no loss of sensation, or loss of wrist and finger extension may be incomplete.

Because the finger drop of radial mononeuropathy places the hand at a mechanical disadvantage, examination of ulnar function by testing of the interossei may produce false-positive findings of weakness. To adjust for this, the examiner should ask the patient to place the palm on a horizontal supporting surface, such as a stretcher. With the fingers extended and no longer "dropped" at the metacarpophalangeal joints, interosseous strength can now be fairly tested. Failure to perform this maneuver may cause misdiagnosis of a simple radial mononeuropathy as a brachial plexopathy in an effort to explain what appears to be radial and partial ulnar nerve involvement.

About 90% of radial nerve palsies occurring during sleep, coma, or anesthesia recover fully, usually within 6 to 8 weeks. Evidence of denervation on EMG studies predicts a slower rate of recovery. Tourniquet injuries to the radial nerve usually recover spontaneously within 2 to 4 months. If axonal degeneration is seen on electrophysiologic testing, recovery may take longer, although virtually all radial mononeuropathies caused by tourniquets eventually resolve. About 75% of radial nerve injuries associated with a closed humeral shaft fracture recover spontaneously. In contrast, surgical intervention is needed to free the nerve from entrapment associated with complex fractures.

While patients are waiting for spontaneous recovery to occur, the hand should be maintained in about 60 degrees of dorsiflexion. Although a simple dorsal plaster or fiberglass splint treats the wristdrop, atrophy and contractures can be minimized and function of the hand can be improved if wide rubber bands anchored to the splint at a point proximal to the wrist are attached to individual fingers to provide passive dorsiflexion.

www.ketabpezeshki.com 66485457-66963820

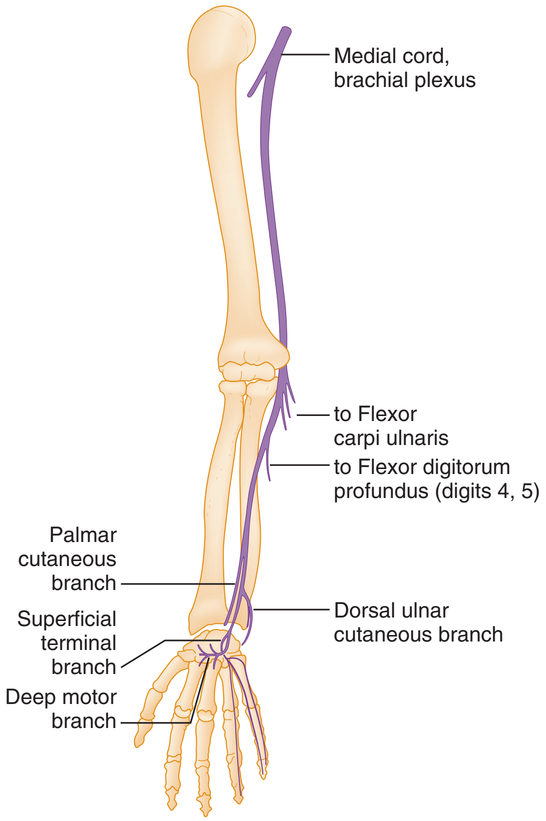


Figure 107-4. Ulnar nerve, major branches, right arm, anterior view. (From Stewart JD: Focal Peripheral Neuropathies, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2000.)

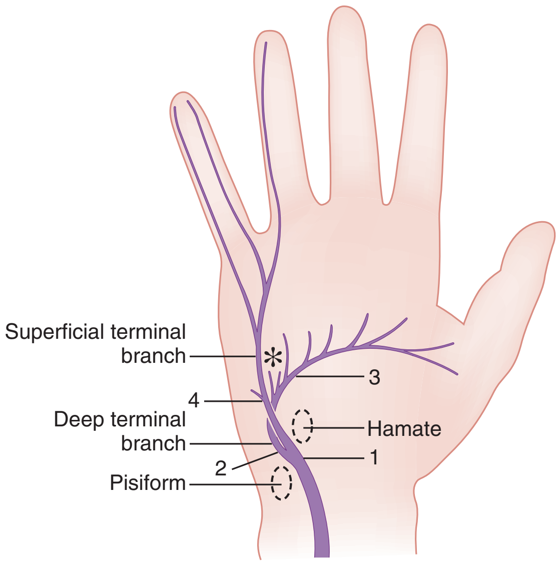


Figure 107-5. Distal ulnar nerve and branches, right hand, palmar view. Numbers indicate four main sites of distal ulnar mononeuropathy in the wrist and hand. *Denotes hypothenar branches. (From Stewart JD: Focal Peripheral Neuropathies, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2000.)

Ulnar Mononeuropathy

The ulnar nerve includes C7-T1 roots and passes through the brachial plexus to descend medially, without branching, to the ulnar (medial) condylar groove at the elbow. It then enters the cubital canal, where it gives off branches to the ulnar wrist flexor and the deep flexors of the fourth and fifth digits.

Just proximal to the wrist, two important sensory branches leave the main trunk to supply cutaneous sensation to part of the hand (Fig. 107-4). These are the palmar and dorsal cutaneous branches, which do *not* pass through Guyon's canal. The palmar branch supplies sensation to the hypothenar eminence and the dorsal branch innervates the ulnar side of the dorsum of the hand, extending out nearly to the tip of the fifth and ulnar half of the fourth digit.

At the wrist, the nerve enters Guyon's canal (Fig. 107-5) between the pisiform and hook of the hamate, then bifurcates into the superficial terminal sensory branch and the deep motor branch.

The superficial sensory nerve supplies ulnar sensation to the palmar side of the fifth and half of the fourth digit (see Fig. 107-5). The deep motor nerve supplies the hypothenar muscles, then crosses to the radial side of the palm to innervate the ulnar intrinsics (all interossei and the ulnar lumbricals of the fourth and fifth digits), terminating in the first dorsal interosseus. The interossei abduct and adduct the fingers and are all innervated by the ulnar nerve. The lumbrical muscles flex the metacarpophalangeal joints and are evenly divided between the ulnar (fourth and fifth) and median (second and third) digits. The ulnar nerve can be thought of as the complement to the median nerve in the hand because it supplies all of the muscles and all palmar sensation not innervated by the median nerve.

The ulnar nerve may be injured at two locations near the elbow: in the ulnar condylar groove and distally in the cubital canal. Because the condylar groove is shallow, the ulnar nerve runs superficially in this location and is vulnerable to injury, usually from external pressure or from a fracture or dislocation. The ulnar nerve has a propensity to develop a "tardy ulnar palsy," occurring years after a traumatic event. Many of these delayed ulnar mononeuropathies can be localized to the elbow on electrophysiologic testing.

Some ulnar mononeuropathies occur secondary to compression just proximal to entry into the cubital canal or are entrapped within the canal itself. Transient symptoms may occur during prolonged flexion or with repeated flexion and extension at the elbow.

Although it is difficult to distinguish a condylar from a cubital ulnar mononeuropathy, it is usually possible to localize the problem to the region of the elbow or the wrist. In addition to prior probability heavily favoring the elbow, the presence of sensory abnormalities in an ulnar distribution in the hand and fingers (i.e., usually including the fifth digit and "splitting" the fourth digit) strongly suggests that the lesion is at the level of the elbow rather than the wrist. The ulnar cutaneous innervation to the hand branches off from the main trunk proximal to the nerve entering Guyon's canal (see Figs. 107-4 and 107-5). Thus a lesion at the wrist should not produce sensory abnormalities, whereas one at the elbow would be expected to do so.

Compression of the ulnar nerve within Guyon's canal is rare. When it does occur, it affects all of the ulnar intrinsics (i.e., the two ulnar [fourth and fifth] lumbricals) and all the interossei. However, the ulnar extrinsics (i.e., the deep flexors of the fourth and fifth digits) are not affected, nor is the ulnar flexor of the wrist. The only sensory abnormalities are those in the distribution of the superficial terminal sensory branch, sparing other areas of ulnar innervation (see Fig. 107-5).

There are three ulnar mononeuropathies that occur distal to Guyon's canal in the hand. The two most common ones involve the deep terminal branch, either proximal or distal to the separation of the hypothenar branches (see Fig. 107-5). If the lesion is proximal, it produces weakness of all the ulnar innervated muscles

www.ketabpezeshki.com 66485457-66963820

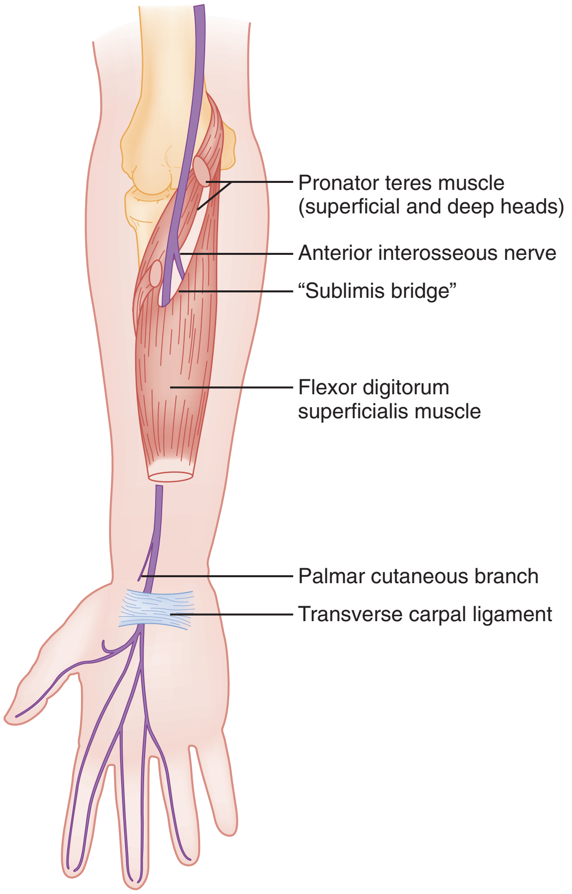


Figure 107-6. Median nerve, major branches, right arm, anterior view. (From Stewart JD: Focal Peripheral Neuropathies, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2000.)

of the hand without sensory loss. If it is distal, the hypothenar ulnar intrinsics are spared, but the picture is otherwise similar. Usually, this occurs secondary to a laceration or repeated compression in the hand from use of certain tools, a cane, or the handle of a crutch.

Involvement of the superficial terminal branch (see Fig. 107-5) produces a pure sensory loss of the palmar surface of the fifth digit and ulnar half of the fourth digit caused by direct compression of this branch just distal to Guyon's canal. The dorsal surface of these two digits should have normal sensation except for the distal tips. This configuration of findings is due to the intact innervation provided by the dorsal and palmar cutaneous branches that enter the hand without passing through Guyon's canal (see Fig. 107-4).

Most ulnar mononeuropathies will spontaneously resolve. However, if muscle atrophy, particularly in the hypothenar area, is detected, surgery may be considered.[40-42]

Median Mononeuropathy

The median nerve arises from C5-T1 spinal nerve roots and exits the brachial plexus through the lower trunk (Fig. 107-6). Median mononeuropathy is usually diagnosed as carpal tunnel syndrome (CTS), which is the most common of all entrapment neuropathies. CTS has a prevalence of 3 to 6% in the U.S. population.[43] Although the patient may complain of bilateral symptoms, a careful history usually reveals that symptoms in one hand preceded those in the other. A common symptom of CTS is awakening at night and shaking the hand. Symptoms are often worsened by activity. For unclear reasons, the pain may spread as high as the arm or shoulder, although the paresthesias are generally confined to the fingers. Many patients on initial questioning state that their entire hand is involved, although this is not supported by careful sensory examination. Patients frequently note that their hands are clumsy or weak, especially when holding a glass or opening a screw-top container. The skin of the fingers innervated by the median nerve may be drier and rougher to the touch than the corresponding ulnar skin, depending on the duration of entrapment.

Box 107-6 Conditions Associated with Carpal Tunnel Syndrome

Acromegaly	Obesity
Amyloid	Pregnancy
Diabetes mellitus	Renal failure
Hypothyroidism	Rheumatoid arthritis

When motor involvement occurs in CTS, it is confined to the median intrinsics, which innervate the *l*umbricals (flexion of the metacarpophalangeal joints) and subserve thumb *o*pposition, *a*bduction, and *f*lexion, known as the LOAF muscles. However, the hallmark of CTS is sensory involvement, with motor abnormalities occurring later. The typical pattern of sensory innervation of the hand by the median, ulnar, and radial nerves shows marked individual variation. The most specific finding for CTS is splitting of the fourth digit (i.e., normal sensation of the ring finger on the ulnar palmar side with abnormal sensation on the median [radial] palmar side of the same finger). The most sensitive finding is abnormal sensation of the distal palmar tip of the index finger. If sensory findings are absent in the presence of motor findings consistent with median nerve involvement, it is highly unlikely that the patient has CTS, and an alternative diagnosis should be sought. Tinel's sign (percussion of the median nerve at the wrist) and Phalen's sign (maximal palmar flexion at the wrist) have been classically taught as provocative tests to reproduce the sensory symptoms of CTS if neither sensory nor motor symptoms are evident on initial examination. However, more recent evaluation has shown that Tinel's and Phalen's signs do not have adequate sensitivity or specificity to determine which patients should be referred for electrodiagnostic studies.[44] Dropping of objects is indicative of severe CTS.[45] As suggested earlier, the best way to examine patients for sensory findings is to touch the distal palmar tips very lightly, asking the patient whether the sensation feels "abnormal."

CTS appears to be associated with the conditions listed in Box 107-6. Of these, the two most common are diabetes mellitus and pregnancy.[46] CTS associated with systemic illness is commonly bilateral. Although CTS in pregnancy may be self-limited, about half the women in one series were still symptomatic at 1-year follow-up.[47] All patients with suspected CTS should be referred for NCSs. However, because of the dissociation between clinical and electrodiagnostic indicators of CTS early in the disease, patients with normal electrodiagnostic findings in the presence of symptoms suggestive of CTS (with or without signs) should have a magnetic resonance imaging (MRI) study or sonographic examination.[48] At present, the sensitivity of MRI is good but its specificity is poor.[49] Ultrasonography has been shown to be useful particularly in patients with symptoms and a normal NCS. This is done by measuring the cross-sectional area of the median nerve at the end of the pisiform.[50] Thus, if all diagnostic studies in a symptomatic patient have normal findings, or if only the MRI result is abnormal, they should be repeated within a few months if symptoms do not resolve. This recommendation is based on the theory that the CTS will progress over time to the point that an objective indicator, such as the NCS, will become positive.

www.ketabpezeshki.com 66485457-66963820

Steroid injection has been shown to be a temporizing measure in treatment of CTS.[51] Because of the possibility of a disabling "median hand" after inadvertent direct injection of the median nerve, it is recommended that emergency physicians defer the injection of the carpal tunnel with steroids to the consulting physician who will provide further care. This physician can decide after NCS whether to recommend splinting, injection, or surgical division of the transverse carpal ligament. Endoscopic repair appears to provide excellent results.[52,53] Noninvasive therapies in all cervicobrachial pain syndromes have yielded mixed results,[54] although smoking of cannabis has been found to improve chronic neuropathic pain.[55]

Sciatic Mononeuropathy

The sciatic nerve includes L4-S3 spinal nerve roots that pass through the lumbosacral plexus and divide into two terminal branches: the common peroneal and tibial nerves. The nerve exits the pelvis through the sciatic notch, passes behind the hip, and remains deep in the thigh until its terminal bifurcation in the proximal popliteal fossa (Fig. 107-7).

Lesions of the sciatic nerve occur with posterior hip dislocation or with virtually any form of penetrating or blunt trauma that causes formation of a buttock hematoma. Other causes include deep gluteal injection and prolonged supine immobilization on a firm surface. Because the sciatic nerve innervates the hamstrings and provides all sensorimotor function distal to the knee, a complete sciatic mononeuropathy is a devastating injury. Ambulation is extremely difficult because of inability to flex the knee and a flail foot (i.e., neither flexion nor extension is possible at the ankle). Fortunately, many sciatic mononeuropathies are incomplete. For unknown reasons, a partial lesion typically involves only the trunk of the sciatic nerve, which subsequently becomes the common peroneal nerve, sometimes making the two difficult to distinguish from one another clinically. On electrophysiologic studies, evidence of involvement of gluteal muscles or of any muscles innervated by the tibial nerve readily distinguishes a partial sciatic mononeuropathy from a lesion of the common peroneal nerve. Treatment of footdrop requires a posterior splint to maintain the ankle at 90 degrees until a brace can be obtained (see later section on common peroneal mononeuropathy).

Lateral Femoral Cutaneous Mononeuropathy

Lateral femoral cutaneous mononeuropathy (meralgia paresthetica) is a common syndrome believed to be caused by injury to this pure sensory nerve as it passes through or over the inguinal ligament, where it may become entrapped or kinked. Along with facial nerve neuropathy, meralgia paresthetica is one of the most commonly reported mononeuropathies associated with HIV infection. External pressure and obesity may also contribute to nerve injury, causing numbness and dysesthesia over the skin of the upper lateral thigh. Regression usually occurs spontaneously, but recurrence is common and may require a release procedure for the inguinal ligament.

Common Peroneal Mononeuropathy

The common peroneal nerve is a continuation of one trunk of the sciatic nerve. It is most vulnerable to injury where it winds around the fibular neck (Fig. 107-8). It then passes through the fibular canal and bifurcates into its terminal branches, the superficial and

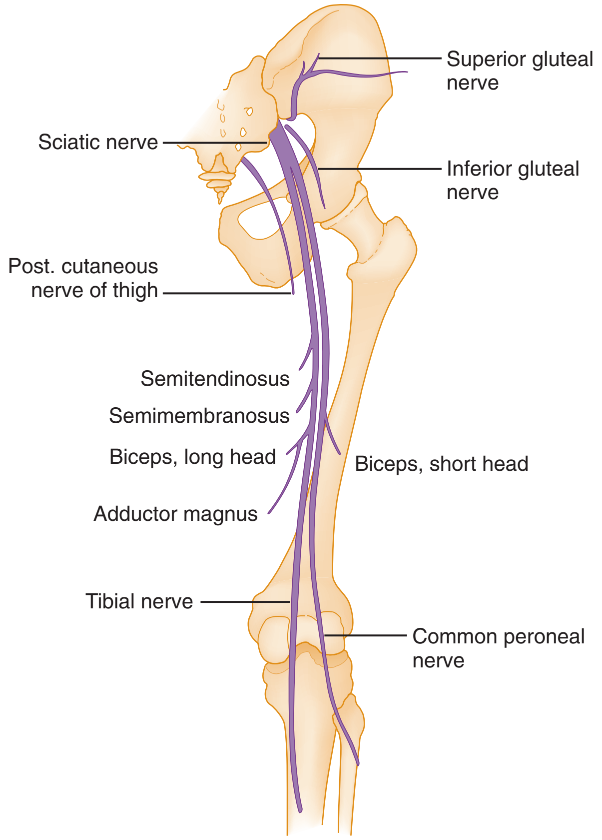


Figure 107-7. Sciatic nerve, major branches, right leg, posterior view. (From Stewart JD: Focal Peripheral Neuropathies, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2000.)

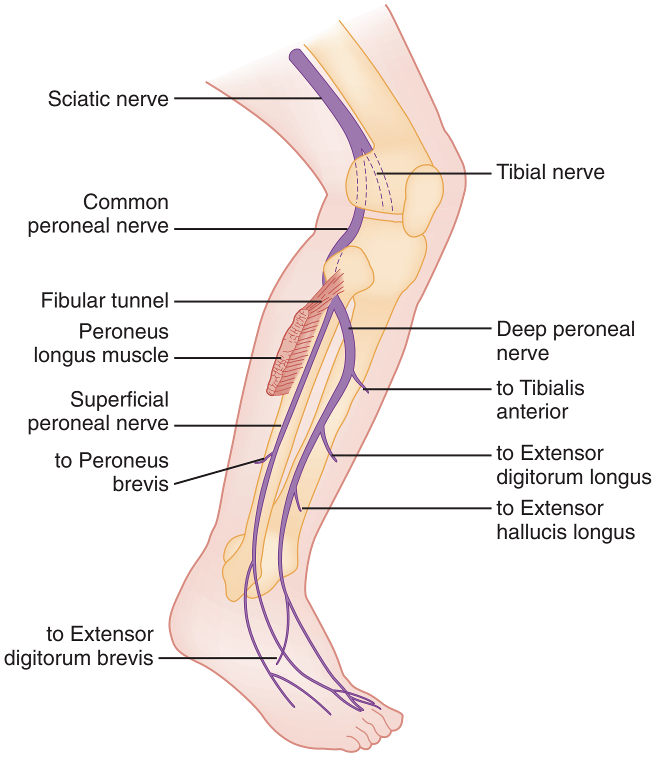


Figure 107-8. Common peroneal nerve, major branches, right leg, anterolateral view. (From Stewart JD: Focal Peripheral Neuropathies, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2000.)

www.ketabpezeshki.com 66485457-66963820

deep peroneal nerves. The superficial peroneal nerve innervates the peroneal muscles (foot everters) and supplies sensation to the lateral, distal lower leg and dorsum of the foot. The deep peroneal nerve traverses the anterior compartment and supplies innervation to the dorsiflexors of the foot and toes plus cutaneous sensation between the first and second toes.

Most common peroneal mononeuropathies are idiopathic and thought to be related to compression where the nerve is superficially located lateral to the fibular neck. Because this common neuropathy is often noted on awakening, it may be secondary to position during sleep. Leg crossing may also be a risk factor for development of this mononeuropathy. The most striking feature of a complete common peroneal mononeuropathy is footdrop caused by weakness of foot dorsiflexion. At testing, the everters of the foot are also weak, but the inverters, which are innervated by the tibial nerve, remain strong. This is the single most reliable clinical feature distinguishing sciatic from common peroneal mononeuropathy. Analogous to radial mononeuropathy in the upper extremity, sensory abnormalities in the leg and foot are inconstant and easily overlooked in peroneal mononeuropathy. Most patients with peroneal palsy recover. Those who do not should be studied electrophysiologically to ensure that the point of compression is not proximal to the fibular neck (i.e., in the popliteal fossa). If the point of peroneal injury appears to be in the region of or distal to the fibular neck on EMG, patients whose footdrop does not resolve should be considered candidates for exploration to determine whether the nerve is compressed within the fibular canal.

Treatment of common peroneal palsy may require a posterior splint to maintain the ankle at 90 degrees until the nerve regenerates. This splinting prevents the foot from falling into sustained equinus (plantar flexion), which in turn allows the intermalleolar distance to narrow, effectively locking the talus out of the ankle mortise.

The treatment of isolated mononeuropathies depends on their etiology, location, and natural history of spontaneous recovery. All penetrating neuropathies should have surgical exploration and repair performed. Blunt trauma may cause a mononeuropathy indirectly by entrapment of a nerve within a fracture, hematoma, or compartment, requiring surgical intervention. Alternatively, nerves may be injured at a point where they are superficial, either by a single direct blow or by sustained pressure caused by immobility (pressure palsies). Most of these resolve spontaneously over time, depending on the severity of injury and length of the nerve. If entrapment can be confirmed by imaging or electrophysiologic studies, a release procedure is indicated. The mononeuropathies that do not require timely surgical exploration should be referred for further workup to confirm the location of the neuropathic lesion.

Type 5: Mononeuropathy Multiplex

Mononeuropathy multiplex is characterized by an asymmetrical, sensorimotor, usually distal pattern of peripheral neuropathy (Box 107-7). As with isolated mononeuropathies, sensory abnormalities tend to be located in the same general anatomic region as the accompanying motor findings. Whether DTRs are affected depends on which nerves are involved. For example, if the process includes the femoral nerve, the patellar reflex is likely to be diminished or absent.

Vasculitis

Mononeuropathy multiplex is strongly associated with vasculitis, which is the most common indication for sural nerve biopsy in most series. However, because diabetes mellitus is far more prevalent than vasculitis, the most common cause of mononeuropathy multiplex among ED patients is diabetes.

Box 107-7 Mononeuropathy Multiplex

- Vasculitis
  - Systemic vasculitis
    - Polyarteritis nodosa
    - Rheumatoid arthritis
    - Systemic lupus erythematosus
    - Sjögren's syndrome (keratoconjunctivitis sicca)
  - Nonsystemic vasculitis
- Diabetes mellitus
- Neoplastic
  - Paraneoplastic
  - Direct infiltration
- Infectious
  - Lyme disease
  - HIV infection
- Sarcoid
- Toxic (lead)
- Transient (polycythemia vera)
- Cryoglobulinemia (hepatitis C)

Diabetes Mellitus

Although the role of ischemia in diabetic neuropathies is controversial, evidence for a vascular cause is stronger in the asymmetrical diabetic multiple mononeuropathies than in the more common DSPNs seen in diabetes.

Lyme Disease

The PNS manifestations of Lyme disease can be divided into early and late. The early PNS syndromes commonly include facial nerve involvement (rarely other cranial nerve palsies) and radiculoneuritis. Late PNS involvement occurs as a DSPN, mononeuropathy multiplex, or radiculoneuropathy. The most common neurologic abnormality in Lyme disease is unilateral or bilateral facial nerve palsy, usually occurring within a month of exposure. Patients may also complain of headache and constitutional symptoms. Early in the course of Lyme disease, severe neuritic pain may develop in a radicular distribution, often in or near the dermatome where the tick bite occurred. There may also be associated sensory changes, motor weakness, and decreased reflexes consistent with nerve root involvement. Patients with chronic Lyme disease present with sensory symptoms, particularly distal paresthesias in the lower extremities. Less commonly, they develop a picture consistent with mononeuropathy multiplex or a radiculopathy, which is much less severe than the early radiculoneuritis of Lyme disease.

The most useful diagnostic tests for patients with suspected Lyme disease are a serum enzyme-linked immunosorbent assay, Western blot, and CSF examination. CSF abnormalities suggestive of Lyme disease are a lymphocytic pleocytosis, elevated protein level, and normal glucose concentration. The CSF is almost always abnormal in early radiculitis, sometimes abnormal with isolated facial palsy, and typically normal in chronic Lyme disease. Facial nerve palsy without CSF abnormalities may be treated with oral doxycycline 100 mg twice a day for 2 weeks. Intravenous ceftriaxone is the drug of choice for all other neurologic syndromes associated with Lyme disease. The adult dosage is 2 g/day, and the pediatric dosage is 75 to 100 mg/kg/day. The standard course of treatment with intravenous ceftriaxone is at least 2 weeks.

www.ketabpezeshki.com 66485457-66963820

Type 6: Amyotrophic Lateral Sclerosis

Although *amyotrophic lateral sclerosis* (ALS) and *motor neuron disease* (MND) are often used synonymously, the latter represents a spectrum of diseases ranging from primary lateral sclerosis, in which degeneration is confined to upper motor neurons, to progressive muscle atrophy, in which only lower motor neurons are involved. ALS, which requires the presence of both upper and lower motor neuron findings, resides in the middle of this spectrum, representing the most common form of MND. The incidence of ALS is 1.5 to 2.5 per 100,000.[56]

In ALS, the primary pathologic process in the PNS component of the disease is a neuronopathy of the anterior horn cell. Because this structure is located proximal to the point where motor and sensory fibers merge to form mixed spinal nerve roots, the signs and symptoms of MND are purely motor (see Fig. 107-2). In the CNS, there is a loss of Betz cells from the motor cortex with secondary degeneration of the corticospinal tracts. Box 107-8 lists some representative upper, lower, and mixed motor signs. Patients typically demonstrate asymmetrical distal weakness without sensory findings. Positive motor phenomena in the form of fasciculations are found in almost all patients at diagnosis but are rarely an initial complaint. Although there is electrophysiologic evidence of autonomic involvement in ALS, this is generally subclinical.

Most patients with an asymmetrical, distal, pure motor neuropathy have ALS, for which only supportive treatment is currently available. However, there are some preliminary studies of recombinant human insulin-like growth factor 1 that have shown marginal improvement in this otherwise fatal disease.[57] All patients in whom this diagnosis is suspected should be referred for electrophysiologic confirmation against standardized criteria. Confirmation is particularly important because multifocal motor neuropathy, a rare disease that masquerades as ALS, responds dramatically to cyclophosphamide and immune globulin administration.

Type 7: Sensory Neuronopathy (Ganglionopathy)

This category of peripheral neuropathy is characterized by a selective or predominant involvement of the dorsal root ganglion,

Box 107-8 Objective Clinical Findings Consistent with Amyotrophic Lateral Sclerosis

Upper Motor Neuron Signs
- Hyperreflexia
  - Sustained clonus, especially at ankle
  - Finger flexors and jaw jerk
- Spasticity, especially of gait
- Presence of Babinski's sign

Lower Motor Neuron Signs
- Positive motor phenomena
  - Fasciculations
  - Cramps
- Negative motor phenomena
  - Asymmetrical distal weakness
  - Atrophy

Combined Upper and Lower Motor Neuron Signs
- Dysarthria
- Dysphagia
- Respiratory compromise

Box 107-9 Sensory Neuronopathies (Ganglionopathies)

- Herpes
  - Herpes simplex 1 and 2
  - Varicella-zoster (shingles)
- Inflammatory sensory polyganglionopathy
- Paraneoplastic
- Primary biliary cirrhosis
- Sjögren's syndrome (keratoconjunctivitis sicca)
- Toxin induced
  - Pyridoxine (vitamin B_6) overdose
  - Metals
    - Platinum (cisplatin)
    - Methyl mercury
- Vitamin E deficiency

Box 107-10 Ancillary Diagnostic Testing in Suspected Peripheral Neuropathy

Obtained in Most Patients
- Complete blood count
- Erythrocyte sedimentation rate
- Glucose
- Creatine kinase
- Creatinine

Obtained Only If Indicated
- Human chorionic gonadotropin
- Magnesium
- Phosphate
- Vitamin B_{12}
- Hemoglobin A_{1c}
- Serum protein electrophoresis with immune fixation electrophoresis
- VDRL (Venereal Disease Research Laboratory) or rapid plasma reagin screen with fluorescent treponemal antibody absorption test, as appropriate
- Thyroid function
- HIV titer
- Lyme enzyme-linked immunosorbent assay and Western blot
- Rheumatoid factor and antinuclear antibody
- Blood, urine, hair, or nails for metal, depending on suspected chronicity of exposure
- Specific serum antibodies to components of peripheral nervous system
- Cerebrospinal fluid for cells, protein, Lyme titer
- Electrodiagnostic testing
  - Nerve conduction studies
  - Electromyography
- Neurodiagnostic imaging
  - Magnetic resonance imaging
  - Computed tomography
  - Sonography
- Quantitative sensory testing
- Nerve biopsy
  - Sural
  - Intraepidermal nerve fiber density

www.ketabpezeshki.com 66485457-66963820

producing a relatively pure sensory syndrome analogous to the pure motor syndrome of ALS. Although all sensory modalities are affected, proprioception is profoundly altered, leading to sensory ataxia and loss of DTRs without weakness. The distribution is typically asymmetrical and distal at the outset, but depending on severity and extent of progression, it may become functionally symmetrical. Sensory ganglionopathies can now be confirmed by MRI of the spinal cord and surrounding areas, showing degeneration of central sensory projections that localize the disease process to the dorsal root ganglion.[58] Some of the more common causes of this type of peripheral neuropathy are listed in Box 107-9.

ANCILLARY DIAGNOSTIC TESTING

Relatively few blood tests contribute to the diagnosis of peripheral neuropathy, and only a small number of these are available in the ED. CSF analysis may be helpful in GBS and Lyme disease. Additional tests that may be indicated in patients referred for evaluation are listed in Box 107-10, along with others that may be ordered selectively, depending on the clinical picture. Expensive batteries of tests purporting to measure a wide variety of antibodies to components of peripheral neuropathies are commercially available but have not been shown to be useful as screening tests.

KEY CONCEPTS

- It is not usually possible to arrive at the diagnosis of a specific peripheral neuropathy in the ED because of the need for confirmatory ancillary testing. One should focus on identifying one of seven categorical patterns of peripheral neuropathy, shown in Figure 107-1 and listed in Table 107-1, after other non-PNS causes have been eliminated.
- One of these seven patterns can usually be identified by combining three clinical features that are readily obtainable from a goal-directed history and physical: (1) right-left symmetry or asymmetry, (2) proximal-distal location, and (3) sensorimotor modalities affected. This approach is summarized as an algorithm in Figure 107-1.
- Identification of one of the seven types of peripheral neuropathy determines the need for ancillary diagnostic testing, therapeutic intervention, disposition, and timing of neurologic referral.
- Respiratory compromise is the primary life-threatening event seen in some peripheral neuropathies; GBS is by far the most common peripheral neuropathic cause of respiratory arrest.
- Any patient with symmetrical weakness, distributed both proximally and distally, with loss or diminution of DTRs and variable sensory abnormalities should be treated as having GBS.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Cosi V, Versino M: Guillain-Barré syndrome. *Neurol Sci* 2006; 27(Suppl 1):47.
2. Moore RA, et al: Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2011; 3:CD007938.
3. Barrett AM, et al: Epidemiology, public health burden, and treatment of diabetic peripheral neuropathic pain: A review. *Pain Med* 2007; 8(Suppl 2):50.
4. Winer JB: Treatment of Guillain-Barré syndrome. *QJM* 2002; 95:717.
5. Tam CC, et al: Guillain-Barré syndrome associated with *Campylobacter jejuni* infection in England, 2000-2001. *Clin Infect Dis* 2003; 37:307.
6. Kieseier BC, Hartung HP: Therapeutic strategies in the Guillain-Barré syndrome. *Semin Neurol* 2003; 23:159.
7. Oh SJ, et al: Sensory Guillain-Barré syndrome. *Neurology* 2001; 56:82.
8. Hughes RA, et al: Pharmacological treatment other than corticosteroids, intravenous immunoglobulin and plasma exchange for Guillain Barré syndrome. *Cochrane Database Syst Rev* 2011; 3:CD008630.
9. Petzold A, et al: CSF protein biomarkers for proximal axonal damage improve prognostic accuracy in the acute phase of Guillain-Barré syndrome. *Muscle Nerve* 2009; 40:42.
10. van Koningsveld R, et al: A clinical prognostic scoring system for Guillain-Barré syndrome. *Lancet Neurol* 2007; 6:589.
11. Orlikowski D, et al: Tongue weakness is associated with respiratory failure in patients with severe Guillain-Barré syndrome. *Acta Neurol Scand* 2009; 119:364.
12. Chevrolet JC, Deleamont P: Repeated vital capacity measurements as predictive for mechanical ventilation need and weaning success in the Guillain-Barré syndrome. *Am Rev Respir Dis* 1991; 144:814.
13. Lawn ND, et al: Anticipating mechanical ventilation in Guillain-Barré syndrome. *Arch Neurol* 2001; 58:893.
14. Wijdicks EF, et al: Emergency intubation for respiratory failure in Guillain-Barré syndrome. *Arch Neurol* 2003; 60:947.
15. Darabi K, et al: Current usage of intravenous immune globulin and the rationale behind it: The Massachusetts General Hospital data and a review of the literature. *Transfusion* 2006; 46:741.
16. Hughes RA, et al: Intravenous immunoglobulin for Guillain-Barré syndrome. *Cochrane Database Syst Rev* 2010; 6:CD002063.
17. Feasby T, et al: Guidelines on the use of intravenous immune globulin for neurologic conditions. *Transfus Med Rev* 2007; 21(Suppl 1):57.
18. Hughes RA, et al: Practice parameter: Immunotherapy for Guillain-Barré syndrome: Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2003; 61:736.
19. Hughes RA, et al: Corticosteriods for Guillain-Barré syndrome. *Cochrane Database Syst Rev* 2010; 2:CD001446.
20. Hughes RA, et al: Intravenous immunoglobulin for Guillain-Barré syndrome. *Cochrane Database Syst Rev* 2006; 1:CD002063.
21. Hughes RA, et al: Immunotherapy for Guillain-Barré syndrome: A systematic review. *Brain* 2007; 130:2245.
22. Korinthenberg R, et al: Clinical presentation and course of childhood Guillain-Barré syndrome: A prospective multicentre study. *Neuropediatrics* 2007; 38:10.
23. Jensen MP, et al: The impact of neuropathic pain on health-related quality of life: Review and implications. *Neurology* 2007; 68:1178.
24. England JD, et al: Distal symmetric polyneuropathy: A definition for clinical research: Report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology* 2005; 64:199.
25. Sindrup SH, Jensen TS: Pharmacologic treatment of pain in polyneuropathy. *Neurology* 2000; 55:915.
26. Wiffen PJ, et al: Carbamazepine for acute and chronic pain in adults. *Cochrane Database Syst Rev* 2011; 1:CD005451.
27. Ko SH, et al: Comparison of the efficacy and safety of tramadol/acetaminophen combination therapy and gabapentin in the treatment of painful diabetic neuropathy. *Diabet Med* 2010; 27:1033.
28. Schwartz S, et al: Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: Results of a randomized-withdrawal, placebo-controlled trial. *Curr Med Res Opin* 2011; 27:151.
29. Perkins BA, et al: Short-term metabolic change is associated with improvement in measures of diabetic neuropathy: A 1-year placebo cohort analysis. *Diabet Med* 2010; 27:1271.
30. Preedy, VR, et al: Alcoholic skeletal muscle myopathy: Definitions, features, contribution of neuropathy, impact and diagnosis. *Eur J Neurol* 2001; 8:677.
31. Luciano CA, et al: Recent developments in the HIV neuropathies. *Curr Opin Neurol* 2003; 16:403.
32. Nicholas PK, et al: Symptom management and self-care for peripheral neuropathy in HIV/AIDS. *AIDS Care* 2007; 19:179.
33. Simpson DM, et al: Lamotrigine for HIV-associated painful sensory neuropathies. *Neurology* 2000; 60:1508.
34. Faist K, et al: Statins and risk of polyneuropathy. *Neurology* 2002; 58:1333.
35. Winfree CJ: Peripheral nerve injury evaluation and management. *Curr Surg* 2005; 62:469.
36. Parziale JR, et al: Thoracic outlet syndrome. *Am J Orthop* 2000; 29:353.
37. Lee GW, et al: Documentation of brachial plexus compression in the thoracic inlet with quantitative sensory testing. *J Reconstr Microsurg* 2000; 16:15.
38. Roos DB: Historical perspectives and anatomic considerations: Thoracic outlet syndrome. *Semin Thorac Cardiovasc Surg* 1996; 8:183.
39. Nannapaneni R, Marks SM: Neurogenic thoracic outlet syndrome. *Br J Neurosurg* 2003; 17:144.
40. Huang JH, et al: Ulnar nerve entrapment neuropathy at the elbow: Simple decompression. *Neurosurgery* 2004; 55:1150.
41. Robertson C, Saratsiotis J: A review of compressive ulnar neuropathy at the elbow. *J Manipulative Physiol Ther* 2005; 28:345.
42. Caliandro P, et al: Treatment for ulnar neuropathy at the elbow. *Cochrane Database Syst Rev* 2011; 2:CD006839.
43. Robinson LR: Electrodiagnosis of carpal tunnel syndrome. *Phys Med Rehabil Clin North Am* 2007; 18:733.
44. Szabo RM, et al: The value of diagnostic testing in carpal tunnel syndrome. *J Hand Surg Am* 1999; 24:704.
45. Pazzaglia C, et al: "Dropping objects": A potential index of severe carpal tunnel syndrome. *Neurol Sci* 2010; 31:437.
46. Padua L, et al: Systematic review of pregnancy-related carpal tunnel syndrome. *Muscle Nerve* 2010; 42:697.
47. Padua L, et al: Carpal tunnel syndrome in pregnancy: Multiperspective follow-up of untreated cases. *Neurology* 2002; 59:1643.
48. Kele H, et al: The potential value of ultrasonography in the evaluation of carpal tunnel syndrome. *Neurology* 2002; 61:389.
49. Jarvik JG, et al: MR nerve imaging in a prospective cohort of patients with suspected carpal tunnel syndrome. *Neurology* 2002; 58:1597.
50. Koyuncuoglu HR, et al: The value of ultrasonographic measurement in carpal tunnel syndrome in patients with negative electrodiagnostic tests. *Eur J Radiol* 2005; 56:365.
51. Lee JH, et al: Effectiveness of steroid injection in treating patients with moderate and severe degree of carpal tunnel syndrome measured by clinical and electrodiagnostic assessment. *Clin J Pain* 2009; 25:111.
52. McNally SA, Hales PF: Results of 1245 endoscopic carpal tunnel decompressions. *Hand Surg* 2003; 8:111.
53. Jarvik JG, et al: Surgery versus non-surgical therapy for carpal tunnel syndrome: A randomized parallel-group trial. *Lancet* 2009; 374:1074.
54. Salt E, et al: A systematic literature review on the effectiveness of non-invasive therapy for cervicobrachial pain. *Man Ther* 2011; 16:53.
55. Ware MA, et al: Smoked cannabis for chronic neuropathic pain: A randomized controlled trial. *CMAJ* 2010; 182:E694.
56. Logroscino G, et al: Descriptive epidemiology of amyotrophic lateral sclerosis: New evidence and unsolved issues. *J Neurol Neurosurg Psychiatry* 2008; 79:6.
57. Mitchell JD, et al: Recombinant human insulin-like growth factor I (rhIGF-I) for amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database Syst Rev* 2007; 4:CD002064.
58. Lauria G, et al: Clinical and magnetic resonance imaging findings in chronic sensory ganglionopathies. *Ann Neurol* 2000; 47:104.

www.ketabpezeshki.com 66485457-66963820

Chapter 108

Neuromuscular Disorders

Peter Shearer and Andy Jagoda

PERSPECTIVE

Disorders of the neuromuscular unit can result in clinical presentations that range from subtle symptoms to acute respiratory failure with significant morbidity and mortality. In most cases, the pathophysiologic mechanism of these disorders is well understood and permits an organization and understanding based on the level of the nervous system affected. This facilitates an approach that interprets signs and symptoms, the findings of which direct the urgency of diagnostic testing and treatment.

PRINCIPLES OF DISEASE

The neuromuscular unit has four components: the anterior horn cells of the spinal cord, the peripheral nerve, the neuromuscular junction, and the muscle innervated. The level of the pathologic process determines associated signs and symptoms (Table 108-1). *Myelopathies* involve the spinal cord; *radiculopathies* involve the nerve roots as they leave the spinal cord; *neuropathies* involve the peripheral nerves; and *myopathies* involve the muscle. The use of physical signs to differentiate these disorders is discussed in Chapter 13.

Neuropathies involve the axon or the myelin sheath of the nerve. Nerve conduction studies can differentiate the locations of involvement. As the conduction along the axon is disrupted, the subsequent delay in transmission first causes symptoms in the muscles controlled by longer nerve axons, resulting in a history of ascending weakness. As the myelin destruction or axonal degeneration progresses, patients usually note a slowly progressive course of symptoms.

The neuromuscular junction is composed of the presynaptic membrane, the postsynaptic membrane, and the synaptic cleft. The neurotransmitter is acetylcholine (ACh). The motor synapse is a nicotinic receptor, whereas muscarinic synapses link the central nervous system with the autonomic nervous system. Disorders of the postsynaptic nicotinic receptors produce weakness. Postsynaptic ACh receptors (AChRs) are continually turned over at a rate that is related to the amount of stimulation. A disorder of transmission often leads to increased production of AChRs. Myasthenia gravis (MG) is the prototype of neuromuscular junction diseases.

CLINICAL FINDINGS

History

The history of patients with complaints of weakness focuses on the acuity and progression of onset and the potential for airway compromise. Any complaint of difficulty in breathing or swallowing raises suspicion of bulbar involvement and concern for life-threatening deterioration. The history must elicit whether the weakness is muscle weakness or nonspecific generalized fatigue. Weakness is the inability to exert normal force, whereas fatigue implies a decrease in force with repetitive use. When muscle weakness exists, the clinician should determine whether it is focal or generalized, proximal or distal. The history of present illness should include the duration of symptoms, exacerbating and mitigating factors, and presence of associated symptoms such as fever, weight loss, and bowel or bladder changes.

Historical elements might explain the presenting complaint: a preexisting neuromuscular disorder that could lead to deterioration; prior episodes or a family history of weakness suggesting periodic paralysis; a recent respiratory or diarrhea illness suggesting a postinfectious, autoimmune process, such as transverse myelitis or Guillain-Barré syndrome (GBS); a cancer history suggesting a metastatic tumor as the cause of a compressive myelopathy; and a food or travel history suggesting botulism or tick exposure.

Physical Examination

The examination should first assess the patient's ability to breathe and ventilate and then evaluate the degree of weakness and the location of the lesion. The presence of swallowing and a strong cough suggest that the patient has sufficient protective and ventilatory reserve. The muscles used to lift the head off the bed may weaken before those of respiration and should be assessed. A patient who is not yet intubated but is complaining of shortness of breath or difficulty in breathing should have frequent measurements of forced vital capacity (FVC). Normal FVC ranges from 60 to 70 mL/kg; when the FVC reaches 15 mL/kg, ventilatory support is necessary. If vital capacity cannot be measured, a maximal negative inspiratory force (NIF) is easily determined. NIF of less than 15 mm Hg suggests the need for intubation. Blood gas analysis is not helpful because functional reserve can be severely diminished by the time a patient has either hypercarbia or hypoxia.

The assessment of vital signs is important because some causes of weakness may result in dysregulation of the autonomic system. A systematic neurologic examination assesses the patient's mental status, cranial nerves, motor function, sensory function, deep tendon reflexes, and coordination, including cerebellar function. The motor examination begins by determining whether the weakness is unilateral or bilateral and which muscle groups are involved. Key components of the examination include motor strength, muscle bulk, and presence of fasciculations. Box 108-1 provides the grading system used in motor strength assessment. Table 108-2 provides the findings used to distinguish upper motor neuron from lower motor neuron processes.

www.ketabpezeshki.com 66485457-66963820

Table 108-1 Clinical Characteristics of Neuromuscular Diseases

DISEASE	HISTORY	STRENGTH	DEEP TENDON REFLEX	SENSATION	WASTING
Myelopathy	Trauma, infection, cancer	Normal to decreased	Increased	Normal to decreased	No
Motor neuron disease (ALS)	Progressive difficulty swallowing, speaking, walking	Decreased	Increased	Normal	Yes
Neuropathy	Recent infection Ascending weakness	Normal or decreased Distal > proximal	Decreased	Decreased	Yes
Neuromuscular junction disease	Food (canned goods) Tick exposure Easy fatigability	Normal to fatigue	Normal	Normal	No
Myopathy	Thyroid disease Previous similar episodes	Decreased Proximal > distal	Normal	Normal	Yes

ALS, amyotrophic lateral sclerosis.

Table 108-2 Distinguishing Upper Motor Neuron from Lower Motor Neuron Involvement

MOTOR NEURON	DEEP TENDON REFLEX	MUSCLE TONE	ATROPHY	FASCICULATIONS	BABINSKI'S RESPONSE
Upper motor neuron	Increased	Increased	No*	No	Present
Lower motor neuron	Decreased	Decreased	Yes	Yes	Absent

* Not significant but can occur.

Box 108-1 Grading Score for Motor Strength

5 = Normal strength
4 = Weak but able to resist examiner
3 = Moves against gravity but unable to resist examiner
2 = Moves but unable to resist gravity
1 = Flicker but no movement
0 = No movement

Differential Consideration

Myelopathies

Myelopathies are spinal cord disorders that are manifested with signs of upper motor neuron dysfunction, such as muscle weakness with increased spinal reflexes, including an extensor plantar reflex (Babinski's response). Muscle tone ranges from normal to slightly increased, eventually leading to spasticity. There may be bladder and bowel involvement. When sensory findings are present, they often define the level of the lesion. The presence of back pain suggests a compressive lesion, such as a herniated intravertebral disk, epidural hematoma, abscess, or tumor. Acute, painless spinal cord lesions include transverse myelitis and spinal cord infarction. Myelopathies are discussed in Chapter 106.

Motor Neuron Disease

The characteristic findings of motor neuron disease combine signs of both upper and lower motor neuron dysfunction, including hyperreflexia, muscle wasting, and fasciculations. Pain is not a component of the clinical picture. Amyotrophic lateral sclerosis, the prototypical motor neuron disease, is a progressive, incurable, neurodegenerative disorder of unclear etiology. It is most common in elders but is seen in people as young as 20 years. Patients may present with upper extremity, lower extremity, or bulbar weakness, which is often initially asymmetrical. The median survival time is 3 to 5 years; most patients ultimately succumb to respiratory failure.

Poliomyelitis affects the anterior horn cells and results in lower motor neuron disease without sensory involvement. The weakness can be symmetrical or more often asymmetrical. Patients initially have a clinical picture similar to that of viral meningitis, with fever and neck stiffness. Currently, most cases follow exposure of an immunocompromised host to the oral polio vaccine, and this should be sought in the history. The cerebrospinal fluid analysis resembles that of viral meningitis.

Neuropathies

Weakness from a neuropathy is often noted first in distal muscles and then ascends. Decreased grip strength and footdrop are common presentations. Muscle tone ranges from slightly diminished to flaccid, and deep tendon reflexes are diminished or absent. Patients exhibit varying degrees of altered sensation, muscle wasting, and fasciculations, depending on the duration of the symptoms. Disorders in the differential diagnosis include GBS, toxic neuropathies, diabetic neuropathy, and tick paralysis (which is caused by inhibition of both nerve conduction and function of the neuromuscular junction). Neuropathies are discussed in Chapter 107.

Diseases of the Neuromuscular Junction

Disorders of the neuromuscular junction cause motor fatigability. The initial depolarization at the nerve endplate stimulates a maximum number of AChRs on the muscle cell, producing a normal or nearly normal strength response. Repeated stimulation leads to diminishing motor strength, which is caused by one of three mechanisms: blockage of the receptors, as in MG; decrease in the amount of ACh released, as in botulism; or inactivation of ACh by irreversible binding, as in organophosphate poisoning.

A decrease in the release of ACh can cause a combination of nicotinic and muscarinic effects. The clinical manifestations of this are anticholinergic findings, such as decreased visual acuity, confusion, urinary retention, tachycardia, low-grade fever, and dry, flushed skin. In the case of Lambert-Eaton myasthenic syndrome, weakness is more pronounced at the beginning of muscle

www.ketabpezeshki.com 66485457-66963820

use and improves with repeated use as more ACh builds up in the synaptic cleft with each stimulation. Diseases of the neuromuscular junction are considered in patients who present with generalized weakness in association with an acute cranial nerve deficit. Muscle tone is generally diminished and sensation is preserved in diseases of the neuromuscular junction.

Myopathies

Myopathies produce generalized, symmetrical weakness. Reflexes are diminished, muscle tone is usually diminished, but sensation is preserved. Myopathies due to inflammatory disorders (polymyositis, dermatomyositis, polymyalgia rheumatica, and viral myositis) cause muscle pain and tenderness. Metabolic disorders affecting muscle strength (e.g., electrolyte and endocrine disorders) are painless in nature.

DIAGNOSTIC STRATEGIES

Laboratory Studies

Serum potassium, calcium, and phosphorus concentrations should be assessed in patients with acute weakness. Thyroid function tests are recommended in cases of suspected myopathies. A creatine kinase (CK) level assesses for muscle inflammation; urinalysis should be performed to test for the presence of myoglobinuria and possible rhabdomyolysis, and renal function studies should be obtained when rhabdomyolysis is present.

Special Studies

Magnetic resonance imaging is the preferred test for suspected cases of acute myelopathy. Computed tomography of the spinal cord with myelography can help differentiate compressive (herniation, abscess, tumor) from noncompressive causes when magnetic resonance imaging is not available. Cerebrospinal fluid analysis is indicated when GBS or transverse myelitis is suspected.

SPECIFIC DISORDERS

Disorders of the Neuromuscular Junction

Myasthenia Gravis

Perspective. MG affects approximately 60,000 Americans.[1] The age at onset is bimodal; women are most commonly affected between the ages of 20 and 40 years and men between 50 and 70 years. Whereas new cases of MG are occasionally diagnosed in the emergency department (ED), it is much more common for patients with established disease to present with exacerbations of their disorder, often caused by precipitating factors.

Principles of Disease. MG results from autoantibodies directed against the nicotinic AChR at the neuromuscular junction or from antibodies against muscle-specific tyrosine kinase. This leads to destruction of AChRs with a decrease in the total number of available receptors. The autoantibodies further compete with ACh for binding at remaining receptors. With repeated stimulation, fewer and fewer receptor sites are available for ACh binding, and fatigue develops.

Fatigability and muscle weakness are the hallmarks of MG. The clinical progression of MG is slow, and the likelihood of short-term complications is low, so the most important aspect of emergency care is early recognition and proper referral for further evaluation when the disease is suspected.

Clinical Features. Patients with MG present with easy fatigability as the result of progressive weakness with repeated activity of affected muscle groups. Ocular symptoms are often the first manifestation of MG; typical symptoms are ptosis, diplopia, and blurred vision. Ocular muscle weakness is the first sign in up to 40% of patients, although 85% of patients with MG eventually have ocular involvement. When ptosis is present, it is often worse toward the end of the day. Respiratory failure is rarely the initial symptom of MG. Even so, up to 17% of patients may have weakness of the muscles of respiration.[2] Bulbar muscles may be involved, producing dysarthria or dysphagia.

Lambert-Eaton myasthenic syndrome is a rare disorder. Almost 50% of cases are associated with small cell carcinoma of the lung. Autoantibodies cause inadequate release of ACh from nerve terminals, affecting both nicotinic and muscarinic receptors. With repeated stimulation, the amount of ACh in the synaptic cleft increases, leading to an increase in strength, the opposite of that seen with MG. The classic syndrome includes weakness that improves with use of muscles, particularly proximal hip and shoulder muscles; hyporeflexia; and autonomic dysfunction, most commonly seen as dry mouth.[3] Management primarily focuses on treatment of the underlying neoplastic disorder, although intravenous immune globulin (IVIG) has been reported to be useful.[4]

Diagnostic Strategies

New-Onset Myasthenia Gravis. The diagnosis of MG is based on clinical findings and a combination of serologic testing, electromyographic testing, and the bedside edrophonium or ice bag test. Serum testing for AChR antibodies is positive in 80 to 90% of patients with MG, but it is not available in the ED setting.

The edrophonium test and ice bag test are similar to perform, and the results are based on their effect on the ptosis seen in patients with suspected MG. The production of edrophonium was discontinued in early 2008, and it will no longer be available once current stores are depleted. Edrophonium is a short-acting acetylcholinesterase-blocking agent that produces an increase of ACh in the synaptic cleft and a reduction in ptosis after intravenous administration. With the ice bag test, cooling decreases symptoms in MG, whereas heat exacerbates symptoms. In both tests, the change in the amount of ptosis is measured before and after administration of edrophonium or application of an ice bag. The distance from the upper to the lower eyelid in the most severely affected eye is measured first. If edrophonium is given, an intravenous test dose of 1 to 2 mg is given first as some patients have a severe reaction. If no adverse reaction is found and the patient does not dramatically improve in 30 to 90 seconds, a second dose of 3 mg is given. If there is still no response, a final dose of 5 mg is given for a total maximum dose of 10 mg.[5] Atropine should be available at the bedside during the test. Because of the potential for cholinergic-induced increased airway secretions, this test should be used with caution in asthmatics and patients with chronic obstructive pulmonary disease. If an ice pack is used, it is applied to the affected eye for approximately 2 minutes, and the distance between the lids is measured again. A prospective evaluation of the ice bag approach found the test result to be positive (an improvement in distance of at least 2 mm) in 80% of patients with MG and no change in patients without MG.[6]

Myasthenic Crisis. Myasthenic crisis is defined as respiratory failure leading to mechanical ventilation. It occurs in 15 to 20% of patients with MG,[7] usually within the first 2 years of disease onset. Although it is potentially life-threatening, the mortality from this complication of MG has declined dramatically with aggressive care in the intensive care unit and the use of plasmapheresis or immunomodulatory therapy with high-dose IVIG and corticosteroids.

Crises are most often precipitated by underlying infection, aspiration, and medication changes, such as stopping anticholinergic

www.ketabpezeshki.com 66485457-66963820

Box 108-2 Drugs That May Exacerbate Myasthenia Gravis

Cardiovascular
- Beta-blockers
- Calcium channel blockers
- Quinidine
- Lidocaine
- Procainamide

Antibiotics
- Aminoglycosides
- Tetracyclines
- Clindamycin
- Lincomycin
- Polymyxin B
- Colistin

Other
- Phenytoin
- Neuromuscular blockers
- Corticosteroids
- Thyroid replacement

medications or taking a new medication that precipitates weakness. Other precipitants can be surgery and pregnancy (Box 108-2). A precipitant may not be identified in up to 30% of cases.[8]

The initial step in managing the patient in crisis is stabilization of the airway. Noninvasive ventilation with biphasic positive airway pressure may be effective in managing patients who need ventilatory support.[9]

All patients with MG who present to the ED should be assessed for signs of myasthenic crisis even when they do not complain of weakness. Many commonly used drugs can adversely affect patients with MG (see Box 108-2). A patient with stable MG who has an acute medical or surgical condition requires a full neurologic examination. The decision to admit or to discharge a patient with MG from the ED should take into account the potential for neurologic deterioration.

Management

Cholinesterase Inhibitors. Pyridostigmine (60-120 mg PO every 4-6 hours) and neostigmine (15-30 mg PO every 4-6 hours) prolong the presence and activity of ACh in the synaptic cleft. They are the backbone of chronic outpatient therapy and provide symptomatic improvement. The most common side effects are those of excessive cholinergic stimulation, such as increased airway secretions and increased bowel motility. At extremes, there may be bradycardia or even worsening of weakness, simulating a myasthenic crisis. These drugs are often used as adjunctive therapy to control symptoms while other therapy is being instituted, after which they are usually discontinued.[10] Cholinergic drug therapy, such as the intravenous administration of pyridostigmine, is not recommended for the treatment of myasthenic crises in the ED because plasmapheresis and IVIG are both safe and highly effective therapies.

Immunosuppressant Drugs. Immunosuppressant drugs are often used for the chronic control of MG. Although they have no role in the acute management of a myasthenic crisis, they may be started before extubation of a patient recovering from a crisis. Cochrane reviews in 2005 and 2007 found support for the use of corticosteroids but only limited evidence that cyclosporine, cyclophosphamide, and azathioprine improve MG.[11,12] Studies suggest that rituximab, a monoclonal antibody that decreases B-cell function, has an emerging role.[13] Of note, the initiation of corticosteroids in patients with moderate to severe weakness may actually precipitate a worsening of weakness or even myasthenic crisis.

Thymectomy. Whereas the association between thymoma and MG is not fully elaborated, it is well known that thymectomy for patients with thymoma can lead to remission of MG or enable a reduction in other medications. Thymectomy for patients with MG without thymoma has been shown to have similar benefits and is recommended by the American Academy of Neurology for patients younger than 60 years, with remission or improvement seen in up to 50% of cases.[14] The onset of improvement after thymectomy is often delayed for 2 to 5 years.

Immunomodulatory Therapy. Plasmapheresis and IVIG can be used for patients with exacerbations of MG or preoperatively in patients with stable MG.

Plasmapheresis removes the AChR antibodies and other immune complexes from the blood. The fall in AChR levels is associated with improvement in symptoms of MG. There is a risk of complications from hypotension or anticoagulation. Although there are no randomized controlled studies, a review yielded many case series with short-term benefit, especially in myasthenic crisis, and it is recommended by the American Academy of Neurology.[15]

A review of IVIG trials found one randomized controlled trial of IVIG versus placebo that demonstrated the benefit of IVIG. Another trial failed to show a difference between IVIG and plasmapheresis.[16] The decision to institute either therapy is based on the input of the consulting neurologist and the resources available at the admitting hospital. If plasmapheresis is not readily available for a patient with myasthenic crisis, IVIG should begin with 1 to 2 g/kg.

Botulism

Principles of Disease. Botulism is a toxin-mediated illness that can cause weakness leading to respiratory insufficiency. In 2009 the Centers for Disease Control and Prevention (CDC) reported 121 cases of botulism in the United States: 9% food-borne, 69% infant botulism, 19% wound botulism, and 3% unknown etiology. *Clostridium botulinum* is an anaerobic, spore-forming bacterium.[17] Three of eight known toxins produced by *C. botulinum* (types A, B, and E) cause human disease. There has been an increase in reported cases of wound botulism in Washington State, California, England, and Germany associated with injection drug use.[18] Botulism is also thought to be a potential agent for bioterrorism. The botulinum toxin works by binding irreversibly to the presynaptic membrane of peripheral and cranial nerves, inhibiting the release of ACh at the peripheral nerve synapse. As new receptors are generated, the patient improves.

Clinical Features. The botulinum toxin blocks both voluntary motor and autonomic functions. Because the disorder is at the neuromuscular junction, there is no pain or sensory deficit. The onset of symptoms is 6 to 48 hours after the ingestion of tainted food. There may or may not be accompanying signs and symptoms of gastroenteritis, with nausea, vomiting, abdominal cramps, diarrhea, or constipation. The classic feature of botulism is a descending, symmetrical, flaccid paralysis. Cranial nerves and bulbar muscles are affected first, causing diplopia, dysarthria, and dysphagia, followed later by generalized weakness. Because the toxin decreases cholinergic output, anticholinergic signs may be seen in the form of constipation, urinary retention, dry skin and eyes, and increased temperature. Pupils are often dilated and not reactive to light. This can be a point of differentiation from MG. Deep tendon reflexes are normal or diminished.

Infantile botulism results from the ingestion of *C. botulinum* spores that are able to germinate and produce toxin in the high pH of the gastrointestinal tract of infants. The same spores are not active in the gut of adults because of the lower pH. The CDC reports approximately 100 cases per year.[19] Botulism spores can survive in honey, so it is recommended that honey not be fed to infants. The clinical presentation includes constipation, poor feeding, lethargy, and weak cry; consequently, this diagnosis must be included in the differential diagnosis of the floppy infant.

Diagnostic Strategies. The diagnosis is made by both clinical findings and exclusion of other processes. The toxin can be identified in serum and stool, but the assay is not commonly available in most hospitals and requires a prolonged turnaround time.

www.ketabpezeshki.com 66485457-66963820

If the suspected food source is available, it should also be tested for the toxin.

Management. Treatment is initially focused on stabilization of the airway and supportive measures. In 2010 the CDC announced a new heptavalent botulinum antitoxin (HBAT) that is now the only antitoxin available in the United States for non-infant botulism. For suspected cases and to obtain HBAT, clinicians should contact their state health departments. The CDC also maintains a botulism duty officer at the CDC Emergency Operations Center (telephone, 770-488-7100).[20] An intravenous human botulism immune globulin (BabyBIG) has been developed for treatment of infantile botulism and is available through the California Department of Public Health Infant Botulism Treatment and Prevention Program on-call physician at 510-231-7600.[21]

Tick Paralysis

Principles of Disease. The pathogenesis of tick paralysis, also known as tick toxicosis, is not fully understood. It is known that a toxin, *ixovotoxin,* is injected while the tick feeds. The toxin appears to decrease the release of ACh at the neuromuscular junction and also reduces nerve conduction velocity. It may also have effects at autonomic ganglia, leading to pupillary signs. Colorado reports on average one case per year, although in 2006 four cases were reported during 1 week.[22]

Clinical Features. Tick paralysis is an acute, ascending, flaccid motor paralysis that can be confused with GBS, botulism, and MG. Symptoms usually begin 1 to 2 days after the female tick has attached and begun to feed, although delays of up to 6 days have been reported.[23] There may be associated ocular signs, such as fixed and dilated pupils, that can help distinguish it from GBS.

Management. The management is supportive care and tick removal. A tick can be removed by use of forceps to grasp it as closely as possible to the point of attachment. Care should be taken not to leave mouth parts in the patient's tissue. Although symptoms may resolve rapidly after removal of the tick, supportive measures such as intubation should not be withheld pending resolution of symptoms.

Disorders of the Muscles

Perspective

Newly acquired weakness originating at the muscle level can be divided into two types: inflammatory and toxic-metabolic. Inflammatory disorders usually produce pain and tenderness, whereas metabolic disorders do not.

Inflammatory Disorders

Principles of Disease. The most common inflammatory myopathies are polymyositis (PM) and dermatomyositis (DM). PM may be idiopathic in nature, occur secondary to infections (viral or bacterial), or be seen in conjunction with other disorders, such as sarcoidosis and hypereosinophilic syndromes. Inflammatory myopathies cause weakness, pain, and tenderness of the muscles involved.

Clinical Features. DM and PM can occur at any adult age, although DM may also affect children. There is a slightly increased incidence in women. They can be associated with various malignant neoplasms, such as of the breast, ovary, lung, and gastrointestinal tract, and lymphoproliferative disorders. Proximal muscle weakness predominates and leads to complaints of difficulty in rising from a seated position or climbing stairs and weakness in lifting the arms over the head. There is often pain and tenderness in these proximal muscles as well. There is a decrease in reflexes that is in proportion to the decrease in strength. Fasciculations are not seen, and atrophy is a very late finding.

DM is similar to PM, but it is also associated with classic skin findings. These are more prominent in childhood but are also found in adults. They include a periorbital heliotrope and erythema and swelling of the extensor surfaces of joints. The facial rash is usually photosensitive and may also involve the exposed areas of the chest and neck.

Diagnostic Strategies. Electrolyte abnormalities must be ruled out and the serum CK level checked. The CK level should be interpreted in light of the entire clinical picture; an elevated CK level does not establish the cause of weakness as a myopathy because some neuropathies can also produce an elevated CK level. Similarly, a normal CK level does not rule out a myopathy as the cause of weakness. Electromyography and muscle biopsy are used to confirm the diagnosis.[24]

Management. PM and DM are usually managed with oral prednisone in a dose of 1 to 2 mg/kg/day. When steroids prove ineffective and during acute exacerbations, cytotoxic drugs such as azathioprine and methotrexate are added. Fortunately, the degree of rhabdomyolysis seen with the inflammatory myopathies is not sufficient to cause renal impairment.

Metabolic Disorders

Perspective. Acute, generalized muscle weakness can be seen with a number of severe electrolyte abnormalities of any cause: hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypomagnesemia, and hypophosphatemia. Acute painless myopathies can also be seen with endocrine disorders involving the thyroid, parathyroid, or adrenal glands.

Of particular interest are several disorders referred to collectively as the periodic paralyses, including familial periodic paralysis (FPP) of the hyperkalemic and hypokalemic forms and thyrotoxic periodic paralysis (TPP), which is similar to hypokalemic FPP except that it is associated with hyperthyroidism.

Periodic Paralysis

Principles of Disease. These are autosomal dominant disorders of ion channels resulting in intermittent attacks of flaccid extremity weakness associated with either hyperkalemia or hypokalemia, although hypokalemia is more common. Periodic paralysis is most often associated with an inherited genetic mutation. Patients usually report a personal and family history of similar episodes.[25]

Clinical Features and Diagnostic Strategies. Patients may suffer either isolated or recurrent episodes of flaccid paralysis. The lower limbs are involved more often than the upper, although both can be affected. Bulbar, ocular, and respiratory muscles are usually not involved. Onset is rapid; a prodrome of myalgias and muscle cramps may occur but is uncommon; mental status and sensory function are typically preserved, but reports of sensory nerve involvement have been documented.[26] Males are more often affected than females, and there is a higher incidence in Asians, particularly Japanese, although it occurs in other ethnic groups.

Attacks may be induced by the injection of insulin, epinephrine, or glucose. The onset of symptoms often follows a high carbohydrate intake (with subsequent insulin rise) and a period of rest. A typical complaint is acute weakness noted on waking the morning after a large meal. The electrocardiogram may demonstrate signs of hyperkalemia or hypokalemia. An immediate determination of potassium level should be obtained; in the hypokalemic form, the potassium level during an attack falls to values below 3.0 mEq/L.

Management. Many cases resolve spontaneously with supportive care alone. The mainstay of management is the treatment of the underlying electrolyte imbalance. In the hypokalemic state, the total body potassium concentration is not depleted but has

www.ketabpezeshki.com 66485457-66963820

shifted intracellularly. Thus, in the repletion of potassium, caution is necessary to prevent overtreatment. For this reason, intravenous potassium should be used sparingly; one or two 10-mEq doses of potassium chloride, during 1 hour, is the maximum intravenous dose. This can be done in parallel with 40 mEq oral potassium repletion and retesting of serum potassium levels. Intravenous hydration helps redistribute the body's potassium stores.

Thyrotoxic Periodic Paralysis. The clinical picture of TPP is almost identical to that of hypokalemic FPP, and indeed a small number of patients with hypokalemic FPP have hyperthyroidism. In TPP, symptoms related to hyperthyroidism are often present at the same time the patient has weakness. The relation of the hyperthyroidism to hypokalemia is probably due to increased sodium-potassium–adenosine triphosphatase activity, which causes a rapid shift of potassium from the extracellular into the intracellular compartment. Treatment of the hyperthyroid symptoms, such as tachycardia, may help the paralysis as well. There are case reports of TPP in which the patient's weakness did not respond to potassium replacement until propranolol was given to treat tachycardia.[27,28] There is probably a genetic feature underlying this disorder because there is a higher incidence of repeated attacks of hypokalemic periodic paralysis among Japanese and Chinese patients with hyperthyroidism. It is important that all patients have thyroid function testing performed after a first episode of hypokalemic paralysis.

KEY CONCEPTS

- The approach to evaluation of patients with acute neuromuscular weakness is facilitated by first determining the location of the lesion (spinal cord, nerve, neuromuscular junction, or muscle) and then considering the most common disorders that affect the area in question.
- In patients with bilateral upper motor neuron signs and a normal mental status, neuroimaging of the spinal cord should be strongly considered.
- In patients presenting with acute neuromuscular weakness, complaints of difficulty in breathing or swallowing should heighten suspicion of bulbar involvement with possible airway compromise. In such patients, FVC of less than 15 mL/kg or maximal NIF of less than 15 mm Hg is a potential indication for mechanical ventilation.
- Botulism usually arises as a painless descending paralysis, often first affecting the cranial nerves and bulbar muscles, without sensory deficits or significant alteration of consciousness. The treatment is airway management and administration of antitoxin.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Phillips LH: The epidemiology of myasthenia gravis. *Semin Neurol* 2004; 24:17.
1a. Thomas CE, et al: Myasthenic crisis: Clinical features, mortality, complications and risk factors for prolonged intubation. *Neurology* 48:1253, 1997.
2. Massey JM: Acquired myasthenia gravis. *Neurol Clin* 1997; 15:577.
3. O'Neill JH, et al: The Lambert-Eaton myasthenic syndrome: A review of 50 cases. *Brain* 1988; 111:577.
4. Fergusson D, et al: Use of intravenous immunoglobulin for treatment of neurologic conditions: A systematic review. *Transfusion* 2005; 45:1640.
5. Seybold ME: The office Tensilon test for ocular myasthenia gravis. *Arch Neurol* 1986; 43:842.
6. Golnik KC, et al: An ice test for the diagnosis of myasthenia gravis. *Ophthalmology* 1999; 106:1282.
7. Thomas CE, et al: Myasthenic crisis: Clinical features, mortality, complications and risk factors for prolonged intubation. *Neurology* 1997; 48:1253.
8. Mayer SA: Intensive care of the myasthenic patient. *Neurology* 1997; 48(Suppl 5):70.
9. Seneviratne J, et al: Noninvasive ventilation in myasthenic crisis. *Arch Neurol* 2008; 65:54.
10. Berrouschot J, et al: Therapy of myasthenic crisis. *Crit Care Med* 1997; 25:1228.
11. Schneider-Gold C, et al: Corticosteroids for myasthenia gravis. *Cochrane Database Syst Rev* 2005; 2:CD002828.
12. Hart IK, et al: Immunosuppressive agents for myasthenia gravis. *Cochrane Database Syst Rev* 2007; 4:CD005224.
13. Maddison P, et al: The use of rituximab in myasthenia gravis and Lambert-Eaton myasthenic syndrome. *J Neurol Neurosurg Psychiatry* 2011; 82:671-673.
14. Gronseth GS, Barohn RJ: Practice parameter: Thymectomy for autoimmune myasthenia gravis (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000; 55:7.
15. Gajdos P, Chevret S, Toyka KV: Plasma exchange for generalised myasthenia gravis. *Cochrane Database of Syst Rev* 2002; 4:CD002275.
16. Gajdos P, Chevret S, Toyka KV: Intravenous immunoglobulin for myasthenia gravis. *Cochrane Database Syst Rev* 2012; 12:CD002277.
17. Centers for Disease Control and Prevention: Botulism Annual Summary, 2009. Available at http://www.cdc.gov/nationalsurveillance/PDFs/Botulism_CSTE_2009.pdf. Accessed April 7, 2011.
18. Centers for Disease Control and Prevention: Wound botulism among black tar heroin users—Washington, DC, 2003. *MMWR Morb Mortal Wkly Rep* 2003; 52:885.
19. Centers for Disease Control and Prevention: Infant botulism—New York City, 2001-2002. *MMWR Morb Mortal Wkly Rep* 2003; 52:21.
20. Centers for Disease Control and Prevention: Investigational heptavalent botulinum antitoxin (HBAT) to replace licensed botulinum antitoxin AB and investigational botulinum antitoxin E. *MMWR Morb Mortal Wkly Rep* 2010; 59:299.
21. Arnon SS, et al: Human botulism immune globulin for the treatment of infant botulism. *N Engl J Med* 2006; 354:462.
22. Centers for Disease Control and Prevention: Cluster of tick paralysis cases—Colorado, 2006. *MMWR Morb Mortal Wkly Rep* 2006; 55:933.
23. Felz MW, et al: A six-year-old girl with tick paralysis. *N Engl J Med* 2000; 342:90.
24. Bartt R: *Autoimmune and inflammatory disorders*. In: Goetz CG, ed: *Goetz Textbook of Clinical Neurology*, 3rd ed. Philadelphia: WB Saunders; 2007:1176.
25. Venance SL, et al; CINCH Investigators: The primary periodic paralyses: Diagnosis, pathogenesis and treatment. *Brain* 2006; 129:8.
26. Inshasi J: Dysfunction of sensory nerves during attacks of hypokalemic periodic paralysis. *Neuromusc Disord* 1999; 9:227.
27. Shayne P, Hart A: Thyrotoxic periodic paralysis terminated with intravenous propranolol. *Ann Emerg Med* 1994; 24:734.
28. Yu T, et al: Potassium chloride supplementation alone may not improve hypokalemia in thyrotoxic hypokalemic periodic paralysis. *J Emerg Med* 2007; 32:263.

www.ketabpezeshki.com 66485457-66963820

Chapter 109

Central Nervous System Infections

William J. Meurer

PERSPECTIVE

Background

Central nervous system (CNS) infections have always been among the most perplexing and devastating illnesses. "Epidemic cerebrospinal fever," classically described by Vieusseux in 1805, was associated with almost universal mortality.[1] The first American epidemic of meningococcal meningitis was recorded in 1806.[2] Since that time, epidemiologic changes have occurred in concert with advances in understanding of disease processes and evolution of effective treatment strategies.

The etiologic spectrum of CNS infection has changed considerably as a result of the development and aggressive use of antibiotics and the epidemic emergence of diseases and conditions that impair the immune system, such as infection with the human immunodeficiency virus (HIV). Some of the research on CNS infections at the cellular and molecular levels has provided insights into pathogenesis, including the role of host mechanisms such as cytokines and other immune components.

Likewise, diagnostic tools have been developed that allow precise pathogen identification, most recently by molecular technologies such as polymerase chain reaction (PCR) tests for viral nucleic acids in cerebrospinal fluid (CSF). The initial treatment methods began by demonstrating the efficacy of antiserum treatment by Flexner in 1913 and of antibiotics by Colebrook and Kenny in 1936.[3,4] Mortality rates in CNS infections were decreased further with the use of high-dose penicillin by Dowling and colleagues in the 1940s.[5] Unfortunately, despite historical advances, the morbidity and mortality of these disorders remain considerable.[6] The use of pneumococcal, *Haemophilus influenzae* type b, and meningococcal vaccines has led to dramatic reductions in the incidence of meningitis caused by these bacteria.[7-10]

Definitions

CNS infections comprise a broad spectrum of disease entities. *Meningitis* is defined as inflammation of the membranes of the brain or spinal cord and is also called *arachnoiditis* or *leptomeningitis*. *Encephalitis* denotes inflammation of the brain itself, whereas *myelitis* refers to inflammation of the spinal cord. The terms *meningoencephalitis* and *encephalomyelitis* describe more diffuse inflammatory processes. Collections of infective and purulent materials may form within the CNS as abscesses. Brain abscesses may be intraparenchymal, in epidural or subdural intracranial locations, or may be found in intramedullary or epidural spinal locations.

This chapter focuses on the more common acute and subacute CNS infections. Infections of the nervous system with HIV or human T-lymphotropic virus, rabies virus, poliovirus, hepatitis viruses, *Borrelia burgdorferi* (Lyme disease), *Treponema* organisms (syphilis), parasites, or *Rickettsia* and the chronic and slow infections of the CNS (subacute sclerosing panencephalitis; progressive multifocal leukoencephalopathy; and the prion-mediated spongiform encephalopathies, such as Creutzfeldt-Jakob disease, bovine spongiform encephalopathy, and kuru) are not addressed in detail. Of note, the incidence of neurocysticercosis is on the rise in the United States.[11]

Epidemiology

Bacterial meningitis is a common disease worldwide. Meningococcal meningitis is endemic in parts of Africa, and epidemics commonly occur in other countries, including the United States. A variety of other pathogens are also causative.[12-16] The overall incidence of bacterial meningitis in the United States is 5 to 10 cases per 100,000 people per year.[17] Men are affected more often than women are.[17] Approximately 80% of cases in the United States are caused by either *Streptococcus pneumoniae* or *Neisseria meningitidis*.[18] In regions where vaccination is common, the epidemiology of bacterial meningitis has substantially changed.[7-10,19] The incidence of bacterial meningitis increases in late winter and early spring, but the disease may occur at any time of the year.

Because most cases go unreported, the actual incidence of viral meningitis is unknown. It is estimated to affect between 11 and 27 individuals per 100,000 people.[20] A prominent increase of cases is seen in summer months, which is concurrent with seasonal predominance of the enterovirus group of the picornaviruses.

The same organisms responsible for viral meningitis may also be associated with encephalitis. Encephalitis is far less common, however, and the ratio of cases of meningitis to encephalitis varies according to the specific pathogen. Arbovirus infection is transmitted by an insect vector, although clinical disease develops in only a small percentage of the people bitten. Before 1999, there were approximately 19,000 hospitalizations in the United States annually for cases of encephalitis. Since then, there has been a rapid increase because of emergence of West Nile virus (WNV). In 2003, more than 8000 additional hospitalizations were required because of WNV alone.[21,22]

Approximately 2000 cases of brain abscess occur in the United States annually.[23] Although CNS abscesses may occur at any age and any time of year, they are seen more commonly in men than in women.[24] CNS abscesses are associated with local contiguous and remote systemic infections, injection drug use, neurologic surgery, and cranial trauma. Brain abscess secondary to otitis media most often occurs in pediatric or older adult populations. When brain abscess is associated with sinusitis, it most often arises among young adults. Increasingly, CNS abscesses are seen

www.ketabpezeshki.com 66485457-66963820

in immunocompromised patients, particularly those with HIV infection, and among bone marrow and solid organ transplant recipients. However, antimicrobial prophylaxis of immunosuppressed patients and more aggressive treatment of otitis and sinusitis have decreased the overall incidence to 0.9 per 100,000 person-years.[23]

PRINCIPLES OF DISEASE

Etiology

Meningitis

Meningeal inflammation may be caused by a variety of disease processes, but the infectious causes predominate. Among the bacterial agents, *Streptococcus pneumoniae* remains the predominant pathogen in adult patients, followed by *Neisseria meningitidis* and *Listeria monocytogenes*.[25] *N. meningitidis* is the predominant organism in adults younger than 45 years. Five major serogroups cause most meningococcal disease worldwide (A, B, C, Y, and W-135). Serogroup A accounts for the majority of cases of meningococcal meningitis in developing nations.[26] A new vaccine for serogroup A may potentially reduce the impact of this disease in nearly half a billion individuals at risk.[27] Serogroup distribution for invasive disease has changed markedly in the United States, with B, C, and Y now most commonly responsible.[28] These pathogens account for the bulk of cases in nontraumatic meningitis, although virtually any organism can be encountered, particularly among patients who are elderly, alcoholic, or immunosuppressed and those who have cancer. Interestingly, higher case fatality has been observed in *N. meningitidis* outbreaks versus sporadic cases, probably because of increased virulence of outbreak-related strains.[29] Causes of aseptic meningitis, simply defined as all cases with CSF cultures negative for bacteria, are listed in Box 109-1.[30]

Meningeal infection may also occur in association with a dural leak secondary to neurosurgery or neurotrauma. *S. pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa*, and coliform bacteria are seen most commonly in this population.

Viral meningitis may likewise be caused by a variety of etiologic agents.[31] Enteroviruses are statistically encountered most commonly.[32] Unfortunately, precise identification of the etiologic agent is often impossible. Fungal and parasitic meningitides are additional concerns, particularly among immunocompromised patients.[14,15] Viral meningitis secondary to herpes simplex virus (HSV) infection is actually relatively benign, especially in comparison with HSV encephalitis.[33]

Noninfectious meningitides include drug-induced meningitis, carcinomatous meningitis, CNS involvement in serum sickness, vasculitis, systemic lupus erythematosus, Behçet's disease, sarcoidosis, and others. The differentiation of noninfectious from infectious causes can often be perplexing.

Encephalitis

Arboviruses and HSV, a human herpesvirus (HHV), are the most common causes of epidemic and sporadic cases of encephalitis, respectively. Children are the most vulnerable to infection with these viruses, although adults are also commonly affected. Epidemics of viral encephalitis have been attributed to a wide variety of viral agents. WNV, a flavivirus, first infected humans in the New York City area and rapidly spread to 47 states by 2003.[15,34] Varicella, herpes zoster, HHV types 6 and 7, and Epstein-Barr virus have been increasingly reported to be the cause of encephalitis in immunocompetent hosts.[35] Vaccinia encephalitis has been recognized in those receiving vaccination for smallpox.[36] Postinfectious encephalomyelitis is also induced by a variety of viral pathogens, most commonly the measles virus.[37] However,

Box 109-1 Causes of Aseptic Meningitis

Infectious Causes

Viruses
- Enteroviruses: polio, Coxsackie, ECHO virus
- Herpes group of viruses
  - Herpes simplex virus types 1 and 2
  - Varicella-zoster virus
  - Cytomegalovirus
  - Epstein-Barr virus
  - Human herpesvirus 6 (HHV-6)
- Respiratory viruses
  - Adenovirus
  - Rhinovirus
  - Influenza virus types A and B
- Arboviruses
- Mumps virus
- Lymphocytic choriomeningitis
- HIV

Bacteria
- Partially treated meningitis
- Parameningeal infection
- Endocarditis
- *Mycoplasma pneumoniae*
- *Mycoplasma tuberculosis*
- Ehrlichiosis
- *Borrelia burgdorferi*
- *Treponema pallidum*
- *Brucella*
- Leptospirosis

Fungi
- *Cryptococcus neoformans*
- *Histoplasma capsulatum*
- *Coccidioides immitis*
- *Blastomyces dermatitidis*
- *Candida*

Parasites
- *Toxoplasma gondii*
- Neurocysticercosis
- Trichinosis
- *Naegleria*
- *Hartmannella*
- *Bartonella henselae*

Rickettsiae
- Rocky Mountain spotted fever
- Typhus

Noninfectious Causes

Postinfectious/postvaccinial
- Rubeola
- Rubella
- Varicella
- Variola
- Rabies vaccine
- Pertussis vaccine
- Influenza vaccine
- Vaccinia
- Yellow fever vaccine

Drugs
- Nonsteroidal anti-inflammatory drugs
- Trimethoprim-sulfamethoxazole, amoxicillin
- Muromonab CD3 (OKT3)
- Azathioprine
- Intravenous immune globulin
- Isoniazid
- Intrathecal methotrexate
- Intrathecal cytosine arabinoside
- Allopurinol
- Carbamazepine
- Sulfasalazine

Systemic disease
- Collagen vascular disorders
  - Systemic lupus erythematosus
  - Wegener's granulomatosis
  - Central nervous system vasculitis
  - Rheumatoid arthritis
  - Kawasaki disease
- Sarcoidosis
- Leptomeningeal cancer
- Post-transplantation lymphoproliferative disorder
- Behçet's disease
- Vogt-Koyanagi syndrome

Neoplastic disorders
- Leukemia
- Carcinomatous meningitis secondary to primary or secondary tumors of the brain

Inflammation of neighboring structures
- Brain abscess
- Epidural abscess

Miscellaneous
- Arachnoiditis
- Migraine
- Urinary tract infection

From Kumar R: Aseptic meningitis: Diagnosis and management. Indian J Pediatr 72:57-63, 2005.

Mycoplasma pneumoniae and idiopathic causes are becoming more common in developed countries.

Central Nervous System Abscess

The causes of CNS abscess are multiple and reflect the primary infective process and the immune state of the human host. A variety of mixed pathogens may be responsible for intracranial abscesses. Streptococci, particularly the *Streptococcus milleri* group, have been identified in nearly 50% of brain abscesses.[38] Anaerobic

www.ketabpezeshki.com 66485457-66963820

Figure 109-1. Central nervous system abscess: computed tomography scan of an intraparenchymal abscess (*arrows*).

bacteria, predominantly *Bacteroides* species, are commonly seen when the primary infectious process is chronic otitis media or pulmonary disease. *S. aureus* and *Propionibacterium* are often identified, particularly after cranial penetration from surgery or trauma.[39] The Enterobacteriaceae are an additional common isolate. Opportunistic fungal and parasitic agents, including *Nocardia* species, are often seen in the immunosuppressed.[40] Culture of epidural and subdural abscesses more often yields a single organism; streptococci are most commonly seen in association with contiguous spread, and *S. aureus* and gram-negative rods are most commonly encountered after neurologic trauma (Fig. 109-1).[15] Etiologic agents in spinal abscess are similarly varied, with *S. aureus* being the most commonly encountered.

Pathophysiology

Bacterial Meningitis

The pathogenetic sequence in bacterial meningitis has been well characterized.[14,15] The first step is nasopharyngeal colonization and mucosal invasion. Although colonization rates vary, virulent microbes use secretion of immunoglobulin A proteases and induce ciliostasis of mucosal cells. After penetration occurs by a variety of mechanisms, bacterial intravascular survival occurs because of evasion of the complement pathway. The varying capsular properties of each organism protect the bacteria. The third step occurs when the bacteria cross the blood-brain barrier to enter the CSF. The dural venous sinuses, cribriform plate area, and choroid plexus have all been implicated as potential sites of invasion. Although the mechanism of invasion is not completely understood, host defense mechanisms within the CSF are often ineffective; there are low levels of complement, immunoglobulin, and opsonic activity. Bacterial proliferation then occurs, which stimulates a convergence of leukocytes into the CSF.

Meningeal and subarachnoid space inflammation is also associated with the release of cytokines into the CSF, most notably tumor necrosis factor and interleukins 1 and 6.[41] This results in increased permeability of the blood-brain barrier, cerebral vasculitis, edema, and increased intracranial pressure. A subsequent decrease in cerebral blood flow leads to cerebral hypoxia. Glucose transport into the CSF is decreased concomitantly with an increased use of glucose by the brain, bacteria, and leukocytes, which depresses CSF glucose concentrations. The increased permeability leads to increased CSF proteins.

Viral Meningitis and Encephalitis

Viruses enter the human host through the skin (i.e., insect vectors); through the respiratory, gastrointestinal, or urogenital tract; or by receipt of infected blood products or donor organs.[42] Viral replication subsequently occurs outside the CNS, most often followed by hematogenous spread to the CNS. Additional routes into the CNS include retrograde transmission along neuronal axons and direct invasion of the subarachnoid space after infection of the olfactory submucosa.[43,44]

Fortunately, most systemic viral infections do not result in meningitis or encephalitis. The development and subsequent magnitude of viral infection depend on the virulence of the specific virus, the viral inoculum level, and the state of immunity of the human host. The tropism of the virus for specific CNS cell types also influences the focality of disease and its manifestations.[43] Particular viruses may preferentially attack cortical, limbic, or spinal neurons, oligodendroglia, or ependymal cells. An example is the tropism of HSV for the temporal lobes and the development of temporal lobe seizures and behavioral changes in afflicted patients.

Fungal Meningitis

Fungal meningitis probably develops in much the same way as bacterial meningitis does, although this has been incompletely studied. Pulmonary exposure followed by hematogenous spread is the primary pathogenic mechanism in most cases. Immune system defects or immunosuppressive medications compromise host defense mechanisms, with ensuing development of CNS infection.

Central Nervous System Abscess

Intraparenchymal brain abscesses, subdural empyema, and intracranial or spinal epidural abscesses form by inoculation of the CNS from contiguous spread of organisms from a sinus, middle ear, or dental infection or metastatic seeding from a distant site, usually from pulmonary infection, endocarditis, or osteomyelitis.[45] The primary infection can be identified in 75 to 85% of cases. These conditions may also follow surgery or penetrating cranial trauma, particularly when bone fragments are retained in brain tissue. Otogenic abscesses occur most commonly in the temporal lobe in adults and the cerebellum in children, whereas sinogenic abscesses typically occur in frontal areas.[38] Multiple brain abscesses suggest hematogenous spread of organisms, although solitary lesions may also occur. The pulmonary system is the most common source of hematogenous spread.[15]

CLINICAL FEATURES

Symptoms and Signs

Numerous host factors have been implicated in the acquisition of meningitis (Box 109-2).[46] Although these factors alone and in combination increase the risk of meningitis, the disease often occurs in patients with none of these factors.

Many patients with meningitis present with advanced disease; in these patients, the diagnosis of acute meningitis is strongly

www.ketabpezeshki.com 66485457-66963820

Box 109-2 Host Factors Predisposing to Meningitis

Age < 5 years
Age > 60 years
Male gender
Low socioeconomic status
Crowding (e.g., military recruits)
Splenectomy
Sickle cell disease
African American race
Alcoholism and cirrhosis
Diabetes
Immunologic defects
Recent colonization
Dural defect (e.g., traumatic, surgical, congenital)
Continuous infection (e.g., sinusitis)
Household contact with meningitis patient
Thalassemia major
Injection drug abuse
Bacterial endocarditis
Ventriculoperitoneal shunt
Malignant disease

suspected. The constellation of symptoms that may classically occur in an acute CNS infection consists of fever, headache, photophobia, nuchal rigidity, lethargy, malaise, altered sensorium, seizures, vomiting, and chills.[13,46]

Unfortunately, more subtle presentations are also common. Immunosuppressed and geriatric patients present a diagnostic challenge because the classic signs and symptoms of meningitis may not be present. Although some degree of fever is present in most patients, as are a headache and neck stiffness, meningitis should be carefully considered in any immunosuppressed patient with symptoms or signs of infectious disease. Often, the only presenting sign of meningitis in elders is an alteration of mental status. However, a meta-analysis suggested that the absence of fever, stiff neck, and mental status change excludes meningitis in immunocompetent adults.[47] A systematic review of prospective data in children found several clinical factors that were useful in influencing the likelihood of bacterial meningitis within suspected cases.[48] There was no combination of factors that could rule in or rule out the disease, which is not surprising given the diversity of presentations in children.

The presentation of fungal meningitis can be obscure even in the healthy adult population. Headache, low-grade fever, lassitude, and weight loss may be present but often to such a mild degree that the correct diagnosis is not initially considered.[13] This is also true of tuberculous meningitis, which often has a protracted course and a vague nonspecific presentation consisting of fever, weight loss, night sweats, and malaise, with or without headache and meningismus.[12]

The physical findings in meningitis vary by the host, causative organism, and severity of the illness. Nuchal rigidity or discomfort on flexion of the neck is common. Kernig's sign (the inability to straighten the leg to a position of full knee extension when the patient is lying supine with the hip flexed to a right angle) and Brudzinski's sign (attempts to flex the neck passively are accompanied by flexion of the hips) are present in approximately 50% of adults.[15] In the evaluation of patients with suspected meningitis, the sensitivity of Kernig's sign, Brudzinski's sign, and nuchal rigidity are 5%, 5%, and 30%, respectively, suggesting that these physical examination findings have little diagnostic value.[49] Deep tendon reflexes may be increased, and ophthalmoplegia may be present, especially of the lateral rectus muscles.

The systemic findings may include an obvious source of infection, such as sinusitis, otitis media, mastoiditis, pneumonia, or urinary tract infection. Various manifestations of endocarditis may be present. Arthritis may be seen with *N. meningitidis* and occasionally with other bacteria.[46] Petechiae and cutaneous hemorrhages are widely reported with meningococcemia but also occur with *H. influenzae* type b, pneumococcal organisms, *L. monocytogenes,* and ECHO virus infections in addition to staphylococcal endocarditis.[46] Endotoxic shock with vascular collapse often develops in severe meningococcal disease, but shock may be present in the advanced stages of any bacterial meningitis. Any determination of a serious systemic infection should encourage rather than dissuade the clinician from considering the possibility of a concomitant CNS infection.

Patients with encephalitis may also have symptoms of meningeal irritation. An alteration of consciousness occurs in virtually all patients. Fever, headache, and a change of personality are also usually present.[44] Hallucinations and bizarre behavior may precede motor, reflex, and other neurologic manifestations by several days, occasionally prompting an initial diagnosis of a psychiatric disorder. Because focal neurologic deficits and seizures occur much more commonly with encephalitis than with meningitis, there may also be diagnostic confusion with a brain abscess. It is difficult to distinguish the etiologic agent in encephalitis clinically, although HSV encephalitis results in a higher incidence of dysphasia and seizures.[50] In some patients, WNV produces a myelitis that affects the anterior horn cells of the spinal column, resulting in a flaccid paralysis with a clear sensorium, similar to findings in poliomyelitis or Guillain-Barré syndrome.[34]

Patients with intracranial abscess may be indistinguishable from those with meningitis or encephalitis. Most patients with intraparenchymal abscess have a subacute course of illness, with symptoms progressing during the course of 2 weeks or more. However, nuchal rigidity and fever are present in less than 50% of cases. Focal neurologic deficits are present in most of these patients. A large number of patients exhibit papilledema, which is a rare finding in meningitis. An abrupt neurologic deterioration that results from uncal herniation or rupture into the ventricular system may occur.

Patients with a subdural or epidural abscess most often have headache, fever, and focal signs, although more subtle presentations are common. Most of the patients with spinal abscess typically present with spinal pain and other symptoms and signs of cord compression but not necessarily with fever.[51]

Complications

Bacterial Meningitis

The immediate complications of bacterial meningitis include coma (with loss of protective airway reflexes), seizures, cerebral edema, vasomotor collapse, disseminated intravascular coagulation, respiratory arrest, dehydration, syndrome of inappropriate secretion of antidiuretic hormone, pericardial effusion, and death (Box 109-3).[16] Various delayed complications include multiple seizures, focal paralysis, subdural effusions, hydrocephalus, intellectual deficits, sensorineural hearing loss, ataxia, blindness, bilateral adrenal hemorrhage (Waterhouse-Friderichsen syndrome), peripheral gangrene, and death.[46]

The case fatality rate for pneumococcal meningitis averages 20 to 25%; higher fatality rates occur in patients with serious underlying or concomitant disease or advanced age.[52] The prognosis is related to the degree of neurologic impairment on presentation. Overall, 20 to 30% of the survivors of pneumococcal meningitis have some residual neurologic deficit.[46] The case fatality rate for *Listeria* meningitis may be as high as 40%.[25]

With the advent of antibiotic therapy, the mortality from meningococcal meningitis has markedly decreased to less than 20%, but it remains substantially higher in elders and those who

www.ketabpezeshki.com 66485457-66963820

Box 109-3 Complications of Bacterial Meningitis

Immediate
Coma
Loss of airway reflexes
Seizures
Cerebral edema
Vasomotor collapse
Disseminated intravascular coagulation
Respiratory arrest
Dehydration
Pericardial effusion
Death

Delayed
Seizure disorder
Focal paralysis
Subdural effusion
Hydrocephalus
Intellectual deficits
Sensorineural hearing loss
Ataxia
Blindness
Bilateral adrenal hemorrhage
Cerebral venous thrombosis
Death

have meningococcemia.[52] Although most of the complications and sequelae are less common than with pneumococcal disease, the incidence of Waterhouse-Friderichsen syndrome is dramatically higher when meningococcemia is present.[46] The overall mortality rate in community-acquired gram-negative meningitis has been less than 20% since the introduction of the third-generation cephalosporins.[14] Hydrocephalus may develop in as many as 5% of patients with community-acquired meningitis; when this is present on admission, the proportion dead or with an unfavorable outcome approaches 50 to 70%.[53] A delayed cerebral venous thrombosis was observed in several adults with an initially excellent recovery from pneumococcal meningitis, suggesting an immunologic vasculopathy.[54]

Viral Meningitis

With rare exceptions, the overall prognosis for complete recovery from viral meningitis is excellent. Various complications related to the systemic effects of the particular virus include orchitis, parotitis, pancreatitis, and various dermatoses. Usually, all of these complications resolve without sequelae.[31] Interestingly, HSV meningitis is often associated with the initial outbreak of genital herpes.[33]

Viral Encephalitis

The outcomes in viral encephalitis are dependent on the infecting agent. Encephalitis caused by Japanese encephalitis virus, Eastern equine virus, and St. Louis encephalitis virus is severe, with high mortality rates and virtually universal neurologic sequelae among survivors.[55] WNV produces encephalitis in only 0.5% of those infected, yet it resulted in 120 deaths in 2003.[22] Western equine virus and California encephalitis virus cause milder infections, and death is rare. The incidence of neurologic sequelae is highly variable and appears to depend on both the host and the infecting agent.[56] Reports have emerged of influenza A H1N1 encephalitis that bears striking resemblance to "encephalitis lethargica," reported as a complication of influenza-like illnesses in the 1920s.[57]

The mortality from HSV encephalitis before the use of acyclovir was 60 to 70%. Acyclovir treatment has reduced the mortality to approximately 30%.[37] Common complications observed among survivors include seizure disorders, motor deficits, and changes in mentation.

Tuberculous Meningitis

Death from tuberculous meningitis in the adult age group ranges from 10 to 50% of cases, with the incidence directly proportional to the patient's age and the duration of symptoms before presentation. Focal ischemic stroke may result from the associated cerebral vasculitis. In advanced disease, up to 25% of patients may require some neurosurgical procedure for obstruction (ventriculoperitoneal shunt or drainage).[58] Some neurologic deficit develops in most patients, but severe long-term sequelae among survivors are unusual.[12]

Fungal Meningitis

Common CNS complications with fungal meningitis include abscesses, papilledema, neurologic deficits, seizures, bone invasion, and fluid collections. Direct invasion of the optic nerve results in ocular abnormalities in up to 40% of patients with cryptococcal meningitis.[13] The mortality rate is high but variable and is related to the timeliness of diagnosis, underlying illness, and therapeutic regimens.

Central Nervous System Abscess

With the early diagnosis afforded by the use of cranial computed tomography (CT), appropriate antimicrobial therapy, and combined management approaches with surgery, aspiration, and medical therapy, the mortality rate from brain abscess has declined dramatically from approximately 50% to less than 20%.[45,59] A seizure disorder is the most common complication of an intracranial abscess, occurring in 80% of patients.[14] Other neurologic findings of intracranial abscesses, including focal motor or sensory deficits and changes in mentation, are common. Complications of spinal abscess primarily result from cord compression, including paralysis, motor and sensory deficits, and bowel and bladder dysfunction. Generalized spread of CNS infection and death may also occur.[51]

DIAGNOSTIC STRATEGIES

Lumbar Puncture

General Considerations

The possibility of the diagnosis of meningitis mandates lumbar puncture (LP) unless the procedure is contraindicated by the presence of infection in the skin or soft tissues at the puncture site or the likelihood of brain herniation.[37] Adherence to this principle prevents a delay in diagnosis, which substantially increases the morbidity and mortality of the disease. Some patients have clinically obvious bacterial meningitis, and CSF examination serves primarily to help identify the organism, thereby facilitating the appropriate treatment. Most patients, however, present more of a diagnostic problem, and analysis of the CSF constitutes the critical step in confirming the presence of CNS infection.

Increased Intracranial Pressure

In most patients with bacterial meningitis, LP may be safely performed without antecedent neuroimaging studies. As this may not be the case in other brain diseases, in many circumstances it is advisable to obtain a CT scan of the head before LP is performed.[60]

www.ketabpezeshki.com 66485457-66963820

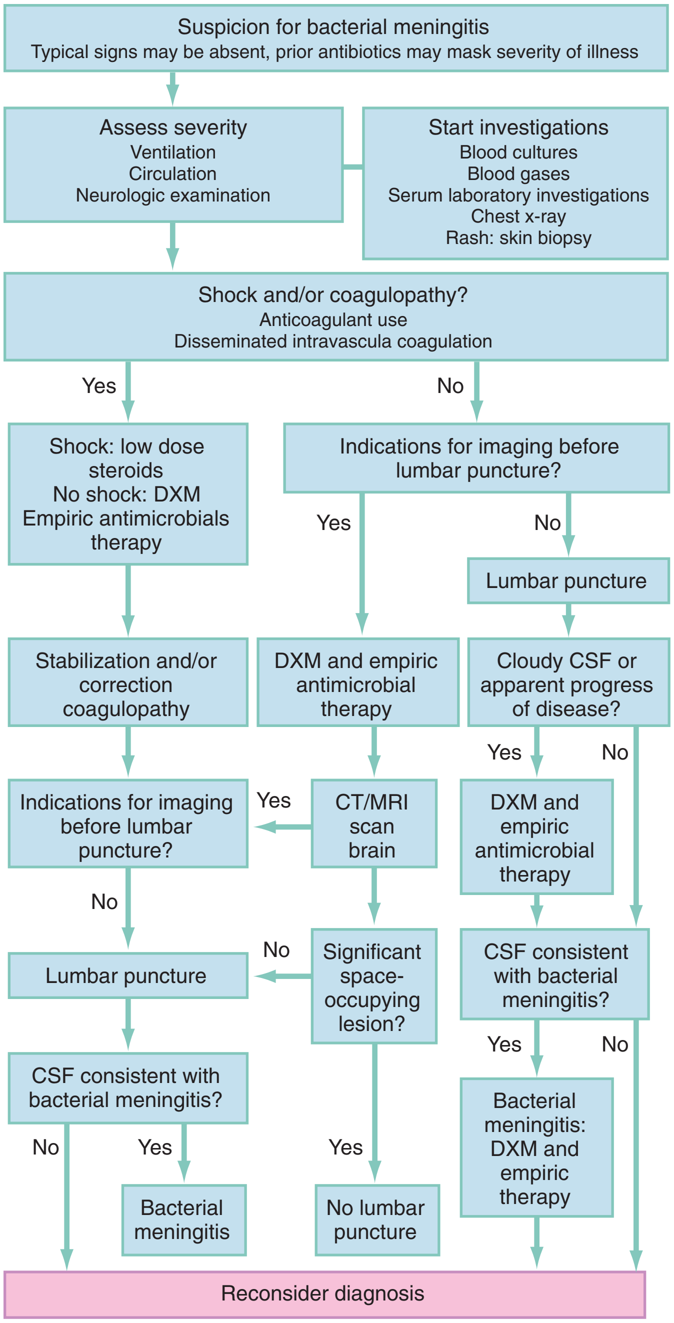


Figure 109-2. Algorithm for diagnostic and therapeutic decision-making when bacterial meningitis is clinically suspected. *CSF,* cerebrospinal fluid; *CT,* computed tomography; *DXM,* dextromethorphan; *MRI,* magnetic resonance imaging.

An algorithm for diagnostic and therapeutic decision-making is presented in Figure 109-2.[61]

It has been conventionally asserted that LP in the presence of increased intracranial pressure may be harmful or fatal to the patient. Although data to address this concern are limited, the presence of focal neurologic signs does appear to be associated with a dramatic increase in complications associated with LP. These patients may deteriorate precipitously during or after the procedure.[62-65]

Patients with a markedly depressed sensorium that precludes careful neurologic examination or those with a focal neurologic deficit, papilledema, seizures, or evidence of head trauma must be considered to be at risk for a herniation syndrome that may be exacerbated by LP. If the presentation is an acute, fulminating, febrile illness and bacterial meningitis is the concerning diagnosis, early initiation of antimicrobial therapy is mandatory because of the association of prognosis and time to treatment.[66] The algorithmic alternatives are therefore (1) immediate LP followed by initiation of antibiotic treatment before the results are obtained and (2) initiation of antibiotic treatment followed by a cranial CT scan and then LP. The latter choice of empirical treatment with antibiotics is now the routine in many institutions, although in some cases a third option could be considered: antibiotics and no LP despite an unremarkable CT scan.[65] This reflects the efficacy of current methods of identification of causative organisms in CSF by means other than bacteriologic cultures that are less likely to be affected by antibiotic administration. The controversy emerging about not performing LP despite a lack of CT findings is based on some reviews and case reports. These describe a fulminant herniation syndrome temporally related to LP in patients with normal CT scans.[63] Raised intracranial pressure may not be reliably detected by CT. Clinical signs of increased intracranial pressure, rapid change in consciousness, and recent seizures were identified as risk factors predicting deterioration despite a normal CT scan.[65] The risks of ongoing empirical treatment with antibiotics without additional information from CSF analysis appears to be low as the yield from blood cultures and other diagnostic techniques such as PCR is relatively high. Therefore, this risk may be less than the risks of performing LP in certain very high-risk patients. In patients who have rapid neurologic deterioration, seizures, or signs of herniation, antibiotics should be given, a CT scan ordered, and the patient moved to intensive care. In this situation, LP may be deferred.

Cerebrospinal Fluid Analysis

Opening Pressure

The normal CSF pressure in an adult varies from 5 to 20 cm H_2O. This value applies only to patients in the lateral recumbent position and may increase substantially when the patient is in the sitting position. The pressure is often elevated in bacterial, tuberculous, and fungal meningitides and a variety of noninfectious processes.[44] Pressure may be falsely elevated when the patient is tense or obese or has marked muscle contraction.

Collection of Fluid

At least three sterile tubes each containing at least 1 to 1.5 mL of CSF are obtained and numbered in sequence. A fourth tube may be desirable should later studies, such as viral cultures or a Venereal Disease Research Laboratory (VDRL) test for syphilis, become necessary. The fluid is sent to the laboratory for immediate analysis of turbidity, xanthochromia, glucose, protein, cell count and differential, Gram's stain, bacterial culture, and antigen testing (Table 109-1). In certain cases an India ink stain, a bacteriologic stain for acid-fast bacilli, or a VDRL test should be obtained. When only a small amount of fluid can be obtained, the most important studies are the cell count with differential, Gram's stain, and bacterial cultures. Ideally, the cell count should be performed on both the first and third or fourth tubes to help differentiate true CSF pleocytosis from contamination of the specimen by a traumatic LP.

Turbidity

The CSF is assessed immediately for turbidity or cloudiness by the person performing the LP. Because normal CSF is completely clear and colorless and is indistinguishable from water, any degree of turbidity is pathologic. Leukocytosis is the most common cause

www.ketabpezeshki.com 66485457-66963820

Table 109-1 Analysis of Cerebrospinal Fluid

TEST	NORMAL VALUE	SIGNIFICANCE OF ABNORMALITY
Cell count	≤5 WBC/mm³ ≤1 PMN/mm³ ≤1 eosinophil/mm³	Increased WBC counts are seen in all types of meningitis and encephalitis; increased PMN count suggests bacterial pathogen
Gram's stain	No organism	Offending organism identified 80% of the time in bacterial meningitis, 60% if patient has been pretreated
Turbidity	Clear	Increased turbidity with leukocytosis, blood, or high concentration of microorganisms
Xanthochromia	None	Presence of RBCs in spinal fluid for 4 hr before lumbar puncture; occasionally caused by traumatic tap (if protein ≥150 mg/dL) or hypercarotenemia
CSF-to-serum glucose ratio	0.6 : 1	Depressed in pyogenic meningitis or hyperglycemia; lag time if glucose given intravenously
Protein	15-45 mg/dL	Elevated with acute bacterial or fungal meningitis; also elevated with vasculitis, syphilis, encephalitis, neoplasms, and demyelination syndromes
India ink stain	Negative	Positive in one third of cases of cryptococcal meningitis
Cryptococcal antigen	Negative	90% accuracy for cryptococcal disease
Lactic acid	≤35 mg/dL	Elevated in bacterial and tubercular meningitis
Bacterial antigen tests	Negative	≥95% specific for organism tested; up to 50% false-negative rate
Acid-fast stain	Negative	Positive in 80% of cases of tuberculous meningitis if ≥10 mL of fluid

CSF, cerebrospinal fluid; *PMN,* polymorphonuclear leukocyte; *RBC,* red blood cell; *WBC,* white blood cell.

of CSF turbidity; counts greater than 200 cells/mm³ usually cause clinically detectable changes in CSF clarity.[67]

Cell Count and Differential

Normal adult CSF contains no more than 5 leukocytes/mm³ with at most one granulocyte (polymorphonuclear [PMN] leukocyte)[46,67,68]; therefore, the presence of more than one PMN or a total cell count of more than 5 cells/mm³ should be considered evidence of CNS infection. In addition, the presence of any eosinophil in the CSF is abnormal, although basophils may occasionally be seen in the absence of disease.[67] Pretreatment with a few doses of antibiotics, although possibly diminishing the yield of Gram's staining and cultures, should not affect the CSF cell counts in meningitis.[14,69,70]

The cell counts in bacterial meningitis are usually markedly elevated, sometimes exceeding 10,000 cells/mm³, and demonstrate a dramatic granulocytic shift.[46] In general, counts exceed 500 cells/mm³, with a preponderance of PMN leukocytes. However, the initial CSF analysis exhibits lymphocytosis (lymphocyte count greater than 50%) in 6 to 13% of all cases of bacterial meningitis. When only the patients with bacterial meningitis with fewer than 1000 cells/mm³ are considered, 24 to 32% have a predominance of lymphocytes.[71,72] In addition, the same population of patients often has only a mild disturbance of CSF glucose and protein levels. In well-established viral meningitis and encephalitis, counts are usually less than 500 cells/mm³, with nearly 100% of the cells being mononuclear.[32] Early (48 hours) presentations may reveal significant PMN pleocytosis and hence be indistinguishable from presentations in early bacterial meningitis.[73]

Similarly, normal cell counts and differentials, although reassuring, do not absolutely exclude bacterial meningitis.[68] Any patient thought to have a clinical syndrome compatible with meningitis requires hospital admission with frequent reevaluation, repeated LP, and antimicrobial therapy. In some patients who have symptoms or signs of meningitis and have a normal initial CSF analysis, CSF pleocytosis may develop within 24 hours; the causative organism may be cultured from the original "normal" CSF.

Brain abscess and parameningeal infections, such as subdural empyema and epidural abscess, usually display CSF cell counts and differentials similar to those of viral meningitis and encephalitis, although the CSF may also be normal.

A traumatic LP is suggested by the presence of a clot in one of the tubes or the clearing of the CSF and a decreasing red blood cell (RBC) count from tubes one to three. In the presence of a traumatic LP, one may estimate the true degree of CSF white blood cell (WBC) pleocytosis with the following formula[67]:

$$\text{True CSF WBC} = (\text{measured CSF WBC}) \times \frac{(\text{CSF RBC}) \times (\text{blood WBC})}{\text{blood RBC}}$$

Alternatively, when peripheral cell counts are normal, the CSF from a traumatic LP should contain about 1 WBC per 700 RBCs.

Gram's Stain

A properly performed Gram's stain of a centrifuged specimen of CSF identifies the causative organism approximately 80% of the time in cases of bacterial meningitis.[70] Gram's stain characteristics of the most commonly encountered organisms are described in Table 109-2. The yield from this procedure is diminished by 20 to 30% when there has been prior treatment with antibiotics.[14]

Table 109-2 Gram's Stain Characteristics of Selected Meningeal Pathogens

PATHOGEN	TYPICAL CHARACTERISTICS
Staphylococci	Gram-positive cocci: singles, doubles, tetrads, clusters
Streptococcus pneumoniae	Gram-positive cocci: paired diplococci
Other streptococci	Gram-positive cocci: pairs and chains
Listeria monocytogenes	Gram-positive rods: single or chains
Neisseria meningitidis	Gram-negative cocci: negative paired diplococci; kidney or coffee bean appearance
Haemophilus influenzae	Gram-negative coccobacilli: "pleomorphic" bacilli
Enterobacteriaceae (including *Escherichia coli*)	Gram-negative rods
Pseudomonas aeruginosa	Gram-negative rods

www.ketabpezeshki.com 66485457-66963820

Misidentification of gram-positive organisms as gram negative is also known to occur more commonly among pretreated patients because organisms with damaged walls stain unpredictably.

Xanthochromia

Xanthochromia refers to the yellowish discoloration of the supernatant of a centrifuged CSF specimen. Xanthochromia is abnormal and results from the lysis of RBCs and release of the breakdown pigments oxyhemoglobin, bilirubin, and methemoglobin into the CSF. This process normally begins within 2 hours, and pigments may persist up to 30 days; therefore, early analysis of the LP specimen is essential. If a traumatic tap has introduced enough plasma to raise the CSF protein level to 150 mg/dL or more, blood pigments may cause xanthochromia. If the CSF protein level is less than 150 mg/dL, however, and systemic hypercarotenemia does not exist, xanthochromia of a centrifuged CSF specimen should suggest that subarachnoid hemorrhage has occurred.[67]

Glucose

When the serum glucose concentration is normal, the CSF glucose concentration is usually between 50 and 80 mg/dL. The CSF glucose concentration is normally in a ratio of 0.6 : 1 to the serum glucose concentration, except with marked systemic hyperglycemia, when the ratio is closer to 0.4 : 1. Therefore, a CSF-to-serum glucose ratio of less than 0.5 in normoglycemic subjects or 0.3 in hyperglycemic subjects is abnormal and may represent the impaired glucose transport mechanisms and increased CNS glucose use associated with pyogenic meningitis.[46,67] Mild decreases in the CSF glucose level may occur with certain viral and parameningeal processes. However, bacterial or fungal meningitis should be presumed to be the cause of low CSF glucose concentration, termed hypoglycorrhachia, until each is clearly excluded.[74] If the serum glucose level has increased rapidly (e.g., after intravenous administration of 50% dextrose in water), equilibration in the CSF may take up to 4 hours, and therefore the interpretation of CSF-to-serum glucose ratios may be unreliable.

Protein

The normal CSF protein level in adults ranges from 15 to 45 mg/dL. An elevated CSF protein level, usually higher than 150 mg/dL, commonly occurs with acute bacterial meningitis.[46] When a traumatic LP has occurred, the CSF protein level can be corrected for the presence of blood by subtracting 1 mg/dL of protein for each 1000 RBCs.[67] Elevated CSF protein concentrations can result from any cause of meningitis, subarachnoid hemorrhage, CNS vasculitis, syphilis, viral encephalitis, neoplasms, and demyelination syndromes.[67] A greatly elevated CSF protein level (>1000 mg/dL) in the presence of a relatively benign clinical presentation should suggest fungal disease.[13]

India Ink Preparation

India ink staining of the CSF should be performed when a diagnosis of cryptococcal meningitis is being considered. The demonstration of budding organisms (Fig. 109-3) is virtually diagnostic for cryptococcal disease but occurs in only one third of the cases.[13] A more definitive diagnostic test is the cryptococcal antigen, which appears to have a similar sensitivity when it is measured in serum, CSF, or urine.[75]

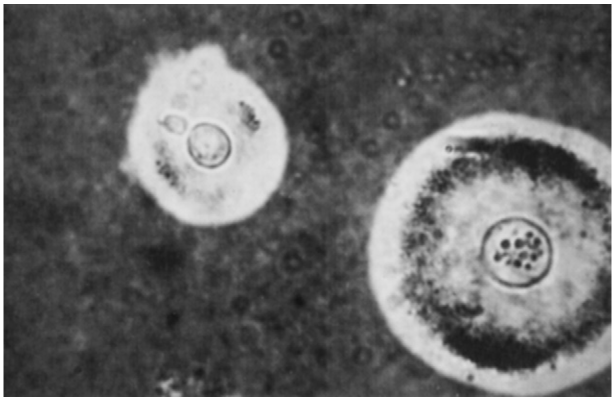


Figure 109-3. India ink staining of cerebrospinal fluid showing cryptococcal meningitis.

Lactic Acid

Although nonspecific, elevations in CSF lactic acid concentrations (>35 mg/dL) are potentially indicative of bacterial meningitis, and lactate may rise before the decline in glucose.[76,77] Normal lactate levels (<35 mg/dL) are usually seen in patients with viral meningitides. A systematic review suggested that with respect to efficacy, CSF lactate outperforms other commonly used laboratory findings (glucose, protein, leukocyte count).[78] The authors did observe that the CSF lactate level is less helpful if it is low but that higher values are highly associated with bacterial meningitis.

Antigen Detection

Counterimmunoelectrophoresis (CIE), latex agglutination, and coagglutination are methods of detecting specific antigens. These tests are particularly useful in patients receiving antibiotic treatment before CSF sampling because the tests depend on the presence of only an antigen and not viable organisms.

The CIE techniques that are performed for the most common bacterial pathogens demonstrate high sensitivity and specificity for bacterial antigens, particularly when they are performed on CSF, blood, and urine simultaneously. Latex agglutination techniques are, however, more rapid and sensitive and are replacing CIE in many facilities. Although reported results vary, the sensitivities of antigen tests are 50 to 90% for *Neisseria* organisms, 50 to 100% for *S. pneumoniae,* and approximately 80% for *H. influenzae.* A specific agglutination test for cryptococcal antigen is also highly sensitive (90%) and specific. Cultures are always indicated because a negative antigen test result does not exclude the possibility of any particular bacterial or fungal etiology.

Antigen and antibody testing is also being used to identify viral and atypical pathogens. These tests have particular utility in HSV encephalitis. Enzyme-linked immunosorbent assays can detect HSV antibody production.[79] Unfortunately, the appearance of antibody in CSF occurs too late to aid in any therapeutic decision analysis. PCR amplification and the identification of HSV DNA have demonstrated a sensitivity of 95 to 100% and a specificity of 100% early in the disease and have markedly decreased the need for diagnostic brain biopsy in this disorder.[80] PCR has improved the diagnosis of tuberculous meningitis, with a sensitivity of 80 to 85% and a specificity of 97 to 100%, and is superior to standard techniques.[81,82] PCR has additionally been shown to be superior in identifying bacteria, enteroviruses, and other viral etiologic agents in both immunocompromised and immunocompetent patients.[83,84] Reported sensitivities of detection in CSF by PCR for *N. meningitidis, H. influenzae,* and *S. pneumoniae* are 88%, 100%, and 92%, with nearly 100% specificity.[85,86] The sensitivities of bacteriologic culture are much lower, especially for *N. meningitidis* at 37 to 55% and *H. influenzae* at 50%.[87,88]

In addition, PCR assays have nearly tripled the yield of viral culture in identifying the etiologic agent.[89] In studies of enteroviral

www.ketabpezeshki.com 66485457-66963820

meningitis, sensitivities and specificities for PCR ranged from 86 to 100% and 92 to 100%, respectively.[90] PCR has been shown to be at least as sensitive as culture technique in detecting cryptococcal meningitis. Quantitative PCR may be of benefit in monitoring response to therapy in some forms of severe disease.[35]

The growing availability of these molecular techniques does not, however, suggest that they should be routinely used as initial diagnostic tests. Most cases of acute bacterial meningitis are readily diagnosed and treated on the basis of the standard Gram's stain and culture. PCR should be reserved for less clear presentations, patients pretreated with antibiotics, and cases in which concern exists for tuberculous, cryptococcal, and treatable viral CNS infections.[91] A reasonable approach is to save the CSF and to consider ordering PCR when acute infection is strongly suspected on the basis of the initial results from the cell count and Gram's stain.

Bacteriologic Cultures

Although results are not available for emergency management, bacteriologic cultures of CSF should be performed. Bacterial culture yields are significantly decreased in patients pretreated with antibiotics. Viral cultures may also be indicated.

Other Tests

A variety of additional, nonspecific tests of CSF have been advocated. These include measurement of CSF lactate dehydrogenase, C-reactive protein, and the limulus lysate test; however, none of these has demonstrated a high degree of clinical usefulness. Likewise, the evaluation of CSF chloride as a diagnostic aid for tuberculous meningitis is no longer clinically relevant.

Neuroimaging Techniques

Cranial CT or magnetic resonance imaging (MRI) is indicated in the evaluation of any patient with presumed CNS infection in whom there is the possibility of an intracranial abscess, intracranial hemorrhage, or mass lesion. In the diagnostic evaluation of acute meningitis, however, a CT scan should not unnecessarily delay LP or antimicrobial therapy. The CT scan may also show hypodense lesions in the temporal lobes in patients with HSV encephalitis, although MRI reveals this abnormality much earlier in the disease process. A contrast-enhanced cranial CT scan or MRI scan is invaluable in the diagnosis of a CNS abscess.[45] MRI is also helpful in the evaluation of other infectious and noninfectious encephalitides.

Additional Investigations

As with other infectious diseases, the complete blood count with differential is a nonspecific adjunct in the diagnostic evaluation of a patient thought to have a CNS infection. The peripheral cell counts are often normal in the presence of significant disease and may even be depressed, particularly in elders or immunosuppressed persons. A "normal" leukocyte count and differential should not dissuade one from performing a diagnostic LP, obtaining a CT scan, or otherwise pursuing the diagnosis of a CNS infection. Serum C-reactive protein is nonspecific, but a negative test result is potentially helpful.[92] Procalcitonin is emerging as a promising serum marker in infectious disease; however, there is not convincing evidence at this point to advocate its use to attempt to rule out bacterial meningitis.[93]

Even when antimicrobial therapy has already been administered, two or three blood culture specimens should be obtained for all patients who are being evaluated for a CNS infection. The blood cultures can improve the identification of the causative organisms, especially with pneumococcus and, to a lesser degree, meningococcus. Although blood cultures are not immediately useful in the initial diagnosis of meningitis, they may be of considerable clinical importance later in management of the disease. The cultures are helpful in identifying a causative organism in only a small minority of cases of brain abscess.

As many as 50% of patients with pneumococcal meningitis also have evidence of pneumonia on an initial chest radiographic study. This association occurs in less than 10% of the cases of meningitis caused by *H. influenzae* type b and *N. meningitidis* and in approximately 20% of cases of meningitis caused by other organisms. The identification of a pulmonary infection on chest radiography may assist in identification of causative organisms and appropriate antimicrobial therapy in approximately 10% of cases of brain abscess.[45]

Other ancillary investigations, such as echocardiography, cultures of other body fluids, and bone scans, may be undertaken as necessary to evaluate coexistent or complicated disease. Serum electrolyte, glucose, urea nitrogen, and creatinine levels should be measured to facilitate the interpretation of the CSF glucose level and to establish the level of renal function and the state of electrolyte balance. Although organism-specific abnormalities are uncommon, hyponatremia has been associated with tuberculous meningitis.

A number of characteristic but not pathognomonic electroencephalographic abnormalities have been associated with HSV type 1 encephalitis. Focal or lateralized electroencephalographic abnormalities in the presence of an encephalitis syndrome should be considered strong evidence supporting a diagnosis of HSV encephalitis.[94]

DIFFERENTIAL CONSIDERATIONS

Patients with meningitis may have symptoms and signs ranging from mild headache with fever to frank coma and shock. To facilitate the discussion of diagnosis and treatment, meningitis may be divided into three clinical syndromes: acute meningitis, subacute meningitis, and chronic meningitis.

Acute meningitis encompasses patients with obvious signs and symptoms of meningitis who are evaluated in less than 24 hours after the onset of their symptoms and who rapidly deteriorate. In many of these patients the diagnosis of meningitis is not in doubt, and the crucial step is to initiate antimicrobial therapy immediately. The most likely pathogens in this syndrome are *S. pneumoniae* and *N. meningitidis*. Although *H. influenzae* has been reported in this context, it is not commonly implicated in the adult population.[16,69]

In the syndrome of subacute meningitis, the symptoms and signs causing the patient to seek care have developed during a period of 1 to 7 days. This syndrome includes virtually all cases of viral meningitis along with most of the bacterial and some of the fungal causes.[14,15] The differential diagnosis depends on the symptoms and signs at presentation. Among elders and immunosuppressed individuals, a change in the patient's mental status may be the only presenting sign in meningitis. Even when a fever is present, the patient's change in mental status may be misattributed to another disease outside the CNS, such as pneumonia or urinary tract infection; neck stiffness may be misattributed to degenerative joint disease. Elders are at high risk for meningitis, and rather than constituting a diagnostic endpoint, the identification of an infection outside the CNS in elders is a clear indication for LP because of the risk of bacteremic seeding by the involved organisms.

The differential diagnosis of encephalitis and brain abscess occurs in the context of the subacute meningitis syndrome. Brain abscess should be considered, especially if fever is minimal or absent or if there are focal neurologic findings. The presence of

www.ketabpezeshki.com 66485457-66963820

fever, altered sensorium, headache, seizures, and personality change is consistent with encephalitis. In addition, diagnoses such as subdural empyema, brain tumor, subarachnoid hemorrhage, subdural hematoma, and traumatic intracranial hemorrhage should be considered. In these circumstances, a cranial CT scan should be obtained before LP is performed.

The spectrum of chronic meningitis includes some of the viral meningitides as well as meningitis caused by tubercle bacilli, syphilis, and fungi. Many of the patients in this group have had symptoms for at least 1 week before presentation and generally have a prolonged indolent course marked by difficult and changing diagnoses and multiple therapies.[12,13] Prediction rules have been both derived and validated and have not yet diffused into widespread practice, probably because of limitations in the models, shifts in the epidemiology of the causative organisms, and relatively small sample sizes.[95]

MANAGEMENT

Assessment and Stabilization

Septic shock, hypoxemia, seizures, cerebral edema, and hypotension resulting from dehydration require aggressive management. When possible, a thorough history should be obtained from the patient, family members, or ambulance personnel with particular emphasis on preexisting conditions that may complicate the patient's disease. Examples include recent neurosurgery, trauma, history of leukopenia, immune suppression, and diabetes mellitus.

Hypotension or shock is treated with isotonic crystalloid infusion, high-flow oxygen, and pressors. Intravenous administration of dextrose may be required for hypoglycemia secondary to depletion of glycogen stores. Alcoholic or nutritionally compromised patients should also receive 50 to 100 mg of thiamine intravenously (IV). In cases of moderate to severe hypotension, central venous pressure monitoring should be initiated on the basis of sepsis guidelines and used to determine additional intravenous fluids or vasopressors. Concern has been raised about brain edema with large amounts of crystalloid fluid in patients with meningitis. However, in children, once fluid volume and vital signs are normalized through resuscitation, there does not appear to be evidence to restrict fluids, and appropriate maintenance fluids should be instituted.[96]

Active airway management with endotracheal intubation may be required in severely ill patients with meningitis, particularly in cases of coma, recurrent seizures, or severe accompanying pulmonary infection. Cardiac monitoring may also be necessary, particularly in elderly patients, those with known coronary disease, and those with an altered mental status. Seizures are a particularly prominent component of the clinical presentation in patients with a brain abscess but may also occur with any CNS infection, especially when an underlying seizure disorder is present.

If acute cerebral edema or an elevated intracranial pressure is present, it is managed by immediate intubation and adequate ventilation. Osmotic agents such as mannitol or diuretics such as furosemide may be used, but caution should be exercised if shock or uncontrolled hypotension is present. If diuretics or osmotic agents are administered, one must ensure that the patient does not become volume depleted and hypotensive.

Definitive Therapy

Bacterial Meningitis

Therapy for bacterial meningitis requires antibiotics that penetrate the blood-brain barrier and achieve adequate CSF concentrations, are bactericidal against the offending organism in vivo, and maintain adequate tissue levels to treat the infection effectively.

Until the pathogenetic organism is identified, broad-spectrum coverage of the most common pathogens is necessary (Table 109-3). Many authorities recommend cefotaxime or ceftriaxone, plus vancomycin to cover potentially resistant organisms.[97] High-dose ampicillin is also added if concern exists about *Listeria*.[97] In patients allergic to penicillin and cephalosporins, meropenem or chloramphenicol plus vancomycin may be effective while the outcome of desensitization techniques is awaited.[97]

After the pathogen is identified, more targeted therapy can be instituted. It is prudent to refer to a current antimicrobial

Table 109-3 Recommendations for Empirical Antimicrobial Therapy for Purulent Meningitis Based on Patient Age and Specific Predisposing Condition

PREDISPOSING FACTOR	COMMON BACTERIAL PATHOGENS	ANTIMICROBIAL THERAPY
Age		
<1 month	*Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes, Klebsiella* species	Ampicillin plus cefotaxime or ampicillin plus an aminoglycoside
1-23 months	*Streptococcus pneumoniae, Neisseria meningitidis, S. agalactiae, Haemophilus influenzae, E. coli*	Vancomycin plus a third-generation cephalosporin*,†
2-50 years	*N. meningitidis, S. pneumoniae*	Vancomycin plus a third-generation cephalosporin*,†
>50 years	*S. pneumoniae, N. meningitidis, L. monocytogenes,* aerobic gram-negative bacilli	Vancomycin plus ampicillin plus a third-generation cephalosporin*,†
Head trauma		
Basilar skull fracture	*S. pneumoniae, H. influenzae,* group A β-hemolytic streptococci	Vancomycin plus a third-generation cephalosporin*,†
Penetrating trauma	*Staphylococcus aureus,* coagulase-negative staphylococci (especially *Staphylococcus epidermidis*), aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*)	Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem
Postneurosurgery	Aerobic gram-negative bacilli (including *P. aeruginosa*), *S. aureus,* coagulase-negative staphylococci (especially *S. epidermidis*)	Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem
CSF shunt	Coagulase-negative staphylococci (especially *S. epidermidis*), *S. aureus,* aerobic gram-negative bacilli (including *P. aeruginosa*), *Propionibacterium acnes*	Vancomycin plus cefepime,‡ vancomycin plus ceftazidime,‡ or vancomycin plus meropenem‡

From Tunkel AR, et al: Practice guidelines for bacterial meningitis. Clin Infect Dis 39:1267-1284, 2004.
* Ceftriaxone or cefotaxime.
† Some experts would add rifampin if dexamethasone is also given.
‡ In infants and children, vancomycin alone is reasonable unless Gram stains reveal the presence of gram-negative bacilli.

www.ketabpezeshki.com 66485457-66963820

reference to guide therapy in all instances, given rapid changes in etiologic spectrum, drug resistance, and available agents. Duration of treatment varies, and in certain situations (namely, epidemics in sub-Saharan African), long-acting chloramphenicol or ceftriaxone is effective.[98]

Corticosteroid treatment is additionally recommended in adult acute bacterial meningitis, although the evidence of efficacy is becoming less compelling over time. Animal studies demonstrate the salutary effects of the administration of corticosteroids in experimental pneumococcal meningitis, including reduced brain edema, CSF pressure, and CSF lactate levels.[99] Earlier resolution of the clinical and CSF stigmata of meningitis and a decrease in long-term hearing loss are observed in infants and children given dexamethasone with cefuroxime or ceftriaxone compared with those receiving the antibiotic alone, particularly when *H. influenzae* is the offending agent.[100] In adult bacterial meningitis, an absolute risk reduction of 10% for unfavorable outcome is seen when dexamethasone is given either 15 minutes before or concomitantly with antibiotics and continued for 4 days at 6-hour intervals.[101] This benefit is greatest in those with *S. pneumoniae*. Subgroup analyses for different causative organisms did not establish a benefit; however, the study was not designed with adequate power to detect improved outcomes. In addition, amoxicillin and penicillin were the most commonly used initial therapy at the time of that study because of the process of health care delivery in Europe, in which nearly all patients were seen initially in an office-based practice. A randomized controlled trial did not demonstrate a benefit of adjuvant dexamethasone in adult patients, even when only those with *S. pneumoniae* were included in a secondary analysis.[102] In the current era of initial empirical parenteral therapy, rising β-lactam resistance, the possibility of the decreased CSF penetration of vancomycin after dexamethasone treatment, and shifts in the likely causative organisms secondary to vaccination campaigns, the true effectiveness of dexamethasone is unclear. The most recent meta-analysis suggests a benefit for patients in the developed (but not developing) world, but the included studies suffer from one or more of the aforementioned limitations.[103] A pooled analysis of patient-level data was less conclusive, suggesting that the benefit of adjunctive dexamethasone for any "subgroup of patients with bacterial meningitis remains unproven."[104] Despite uncertainty from conflicting trials, an initial dose of dexamethasone 10 mg IV is recommended before or concurrent with empirical antibiotics in patients with suspected community-acquired meningitis and without signs of septic shock. Given the potential adverse effects of high-dose corticosteroids in patients with septic shock, the use of low-dose hydrocortisone at 50 mg IV instead of high-dose dexamethasone is a reasonable approach, although it has not been proved in randomized controlled trials of patients with both septic shock and meningitis.[105,106]

In pediatric meningitis, the evidence that adjunctive dexamethasone is helpful is less compelling. Invasive *H. influenzae* type b and pneumococcal infections have drastically been reduced by vaccination.[19] A randomized trial of dexamethasone in childhood meningitis in sub-Saharan Africa did not demonstrate a benefit.[107] A retrospective analysis from U.S. administrative data did not demonstrate any mortality benefit to adjunctive dexamethasone.[108] Current recommendations are organism specific, which presents a major limitation as recommendations are to begin empirical therapy before laboratory results in suspicious cases. For *H. influenzae* type b (Hib): "dexamethasone may be beneficial for treatment of infants and children with Hib meningitis to diminish the risk of neurological sequelae, including hearing loss, if given before or concurrently with the first dose of antimicrobial agent(s). There probably is no benefit if dexamethasone is given more than 1 hour after antimicrobial agent(s)."[109] For *S. pneumoniae:* "for infants and children 6 weeks of age and older, adjunctive therapy with dexamethasone may be considered after weighing the potential benefits and possible risks. Experts do not agree on a recommendation to use corticosteroids in pneumococcal meningitis; data are not sufficient to demonstrate a clear benefit in children. If used, dexamethasone should be given before or concurrently with the first dose of the antimicrobial agent."[110] The implication for frontline physicians caring for children is that unless the causative organism is known before antibiotic treatment, there is probably little role for adjunctive dexamethasone in children.

Viral Meningitis

No specific agents are available to treat most types of viral meningitis. Investigational agents in development may reduce symptoms in enterovirus meningitis[111]; however, with the exception of HSV meningitis, the viral meningitides contracted in the United States are generally characterized by a short, benign, self-limited course followed by a complete recovery. The primary therapeutic consideration in cases of viral meningitis is therefore the validity of the diagnosis. Early cases of viral meningitis may be indistinguishable from bacterial meningitis, and this confusion may not be resolved by CSF analysis; therefore, when any doubt exists about the veracity of the diagnosis, appropriate culture specimens should be obtained and the patient admitted to the hospital. Antimicrobial therapy for presumed bacterial meningitis may be initiated on the basis of the clinical presentation or may be withheld pending the outcome of close clinical observation and repeated LP in 8 to 12 hours.

Viral Encephalitis

Specific therapy for meningoencephalitis from HHV is available. Acyclovir remains the current choice and is capable of substantially improving the patient's outcome. When the diagnosis of herpes meningoencephalitis is suspected or established, acyclovir should be administered in a dose of 10 mg/kg IV every 8 hours.[81] Ganciclovir, foscarnet, and cidofovir are also effective in HHV infections, and pleconaril has been effective in enteroviral disease. Additional antiviral treatments are in development.[34,35,111]

Tuberculous Meningitis

Early chemotherapeutic intervention in acute tuberculous meningitis improves the patient's prognosis. A strong clinical suggestion of this disease is an adequate indication to begin antituberculous therapy. A standard treatment regimen consists of isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin.[97] Corticosteroids have also been shown to decrease secondary complications.[97]

Fungal Meningitis

The treatment of fungal meningitis is complex.[13] Four agents are commonly used: amphotericin B, flucytosine, miconazole, and fluconazole. Of these, amphotericin B, either alone or in combination with flucytosine, is the most commonly recommended initial therapeutic regimen.[97] These diseases are rarely acutely life-threatening but rather are slowly progressive. Prolonged therapy, often with multiple agents, is necessary. The initiation of antifungal therapy is rarely indicated in the emergency department.

Central Nervous System Abscess

The treatment of cerebral abscess is complex, and neurosurgical consultation is indicated. The location, size, and number of abscesses influence the choice of medical management, surgical excision, aspiration, or a combination of these modalities.[38] In

www.ketabpezeshki.com 66485457-66963820

general, small multiple abscesses are more appropriately treated medically, whereas large, surgically accessible lesions should be excised. Empirical antimicrobial therapy before identification of specific organisms by aspiration or surgical excision should be guided by the principles of CSF penetration and the coverage of likely pathogens.

Otogenic and sinogenic abscesses are often treated with cefotaxime or ceftriaxone plus metronidazole.[97] Abscesses with traumatic or neurosurgical causes should have antimicrobial coverage for *S. aureus* or methicillin-resistant *S. aureus*. Patients at high risk for tuberculous, fungal, or parasitic abscess should also receive coverage for the suspected etiologic agent. Corticosteroids should be reserved specifically for management of any attendant cerebral edema; in other circumstances, steroid use is associated with increased mortality. In cases in which the etiology is bacterial endocarditis, valve replacement is often required.[112]

Chemoprophylaxis

Among household contacts, the incidence of transmission of meningococcus is approximately 5%; therefore, it is recommended that household contacts of bacteriologically confirmed cases receive rifampin (adults, 600 mg; children older than 1 month, 10 mg/kg; children younger than 1 month, 5 mg/kg) orally every 12 hours for a total of four doses.[97] In addition, these contacts should be advised to watch for fever, sore throat, rash, or any symptoms of meningitis. They should be hospitalized with appropriate intravenous antimicrobial therapy if there are signs that active meningococcal disease is developing because rifampin is ineffective against invasive meningococcal disease. Intimate, nonhousehold contacts who have had mucosal exposure to the patient's oral secretions should also receive rifampin prophylaxis. Health care workers are not at increased risk for the disease and do not require prophylaxis unless they have had direct mucosal contact with the patient's secretions, as might occur during mouth-to-mouth resuscitation, endotracheal intubation, or nasotracheal suctioning. Ciprofloxacin 500 mg by mouth (adults only) and ceftriaxone 250 mg intramuscularly (125 mg intramuscularly for children younger than 15 years) provide single-dose alternatives.[97]

There is no indication for chemoprophylaxis in pneumococcal meningitis. Rifampin prophylaxis for the contacts of patients with *H. influenzae* type b meningitis is recommended for nonpregnant household contacts when there are children younger than 4 years in the household[97] (adults, 600 mg by mouth; children, 20 mg/kg by mouth daily for 4 days).

Immunoprophylaxis

A quadrivalent vaccine based on the polysaccharide capsule and conferring protection against group A, C, Y, and W-135 meningococci has been in routine use by the U.S. military since the 1980s.[113] However, the capsular polysaccharide vaccines used to immunize adults are neither immunogenic nor protective in children younger than 2 years because of poor antibody response. In addition, no licensed vaccine is currently available against the serogroup B meningococcus.[47] The serogroup B capsular polysaccharide has proved to be poorly immunogenic in both adults and children.[114] The sequence variation of the surface proteins and cross-reactivity of the group B polysaccharide with human tissues have further impeded efforts to develop a successful vaccine. Efforts to enhance the immunogenicity and protective efficacy of meningococcal vaccines have focused on use of conjugate methods that link polysaccharides and carrier proteins. Serogroup C and serogroup C + Y conjugate vaccines have been developed and used effectively.[115] Current recommendations for the quadrivalent vaccine are evolving. The vaccine is recommended in established meningococcal epidemics and for travelers to countries where meningococcal disease is currently epidemic. Elective vaccination of college freshmen has been recommended by the Advisory Committee on Immunization Practices (ACIP) in the United States and public health authorities in the United Kingdom.[116,117] The United Kingdom has also implemented universal childhood immunization with a group C conjugate vaccine.[115]

The development of effective pneumococcal vaccines has been hampered by the large number of serotypes of the organism. A small number of serotypes, however, are responsible for most clinical pneumococcal disease, and a 23-valent vaccine effective against many of these principal serotypes has been developed.[118] The recommendations for this polyvalent pneumococcal vaccine are targeted primarily at prevention of pneumonia, despite a potential beneficial effect for meningitis. A single dose of the vaccine should be considered for elderly or debilitated patients, especially those with pulmonary disease, and for patients with impaired splenic function, splenectomy, or sickle cell anemia.[18] A heptavalent conjugated pneumococcal vaccine has also been developed and is recommended for universal childhood immunization by the ACIP.[119]

A conjugate vaccine effective against *H. influenzae* type b has been developed for use in the pediatric but not the adult population. It appears to be approximately 90% protective and has a very low incidence of adverse reactions.[120] Modern childhood immunization against *H. influenzae* type b has raised the average age of patients afflicted with *Haemophilus* meningitis to 25 years and decreased the incidence of meningitis of any etiology by 55%.[91]

Vaccination is also available to confer immune protection against Japanese encephalitis virus, and it is recommended for people performing extensive outdoor activities or spending more than 30 days in endemic areas during transmission seasons.[121] The reported protective efficacy of the vaccine is approximately 90%. Although there is no current human vaccine for WNV, vaccines for nonhuman mammals have been developed.[34]

DISPOSITION

With the exception of viral meningitis, all but the most chronic CNS infections require initial inpatient evaluation and treatment. Bed rest, analgesics, and the institution of appropriate intravenous antimicrobials are indicated.

Some patients with suspected viral meningitides merit hospitalization. These include patients with more severe disease, immunocompromise, suspicion of HSV meningitis, and potential nonviral causes. Some authorities manage patients with classic presentations of viral meningitis as outpatients and ensure close follow-up within 24 hours. Others admit all patients until the more serious causes, such as early bacterial meningitis and encephalitis, can be excluded with certainty.

www.ketabpezeshki.com 66485457-66963820

KEY CONCEPTS

- CNS infection should be considered in all patients with headache, neck stiffness, fever, altered sensorium, or diffuse or focal neurologic findings.
- Lumbar puncture with sampling of CSF is the only reliable method of assessing the presence or absence of meningitis. In the absence of contraindications, any suspicion of meningitis mandates performance of lumbar puncture.
- Early initiation of antimicrobial therapy is mandatory in any case of suspected acute CNS infection. Antibiotic administration must not be delayed for CSF analysis or performance of neuroimaging studies.
- Antibiotic chemoprophylaxis should be ensured for close contacts of patients with meningitis resulting from *Neisseria meningitidis* or *Haemophilus influenzae*. Single-dose and multiple-dose regimens are available.
- Vaccination against *N. meningitidis* is recommended for certain at-risk populations but does not afford protection against serogroup B infection.
- Concomitant CNS infection should be strongly considered in any patient with another severe systemic infection, such as urinary tract infection or pneumonia.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Vieusseux M: Mémoire sur le maladie qui a régné à Genève au printemps de 1805. *J Med Chir Pharmacol* 1805; 11:163.
2. Roos KL: Acute bacterial meningitis. *Semin Neurol* 2000; 20:293-306.
3. Flexner S: The results of serum treatment in 1300 cases of epidemic meningitis. *J Exp Med* 1913; 17:553.
4. Colebrook L, Kenny M: Treatment of human puerperal infections and experimental infections in mice with prontosil. *Lancet* 1936; 1:1279.
5. Dowling H, et al: The treatment of pneumococcal meningitis with massive doses of systemic penicillin. *Am J Med Sci* 1949; 217:149.
6. Swartz MN: Bacterial meningitis—a view of the past 90 years [see comment]. *N Engl J Med* 2004; 351:1826-1828.
7. Gjini AB, et al: Changing epidemiology of bacterial meningitis among adults in England and Wales 1991-2002. *Epidemiol Infect* 2006; 134:567-569.
8. Albrich WC, et al: Changing characteristics of invasive pneumococcal disease in Metropolitan Atlanta, Georgia, after introduction of a 7-valent pneumococcal conjugate vaccine. *Clin Infect Dis* 2007; 44:1569-1576.
9. Pollard AJ: Global epidemiology of meningococcal disease and vaccine efficacy. *Pediatr Infect Dis J* 2004; 23(12 Suppl):S274-S279.
10. Dubos F, et al: Decline in pneumococcal meningitis after the introduction of the heptavalent-pneumococcal conjugate vaccine in northern France. *Arch Dis Child* 2007; 92:1009-1012.
11. Wallin MT, Kurtzke JF: Neurocysticercosis in the United States: Review of an important emerging infection. *Neurology* 2004; 63:1559-1564.
12. Alvarez S, McCabe WR: Extrapulmonary tuberculosis revisited: A review of experience at Boston City and other hospitals. *Medicine (Baltimore)* 1984; 63:25-55.
13. Salaki JS, Louria DB, Chmel H: Fungal and yeast infections of the central nervous system. A clinical review. *Medicine (Baltimore)* 1984; 63:108-132.
14. Lambert HP, ed: *Infections of the Central Nervous System*. Philadelphia: BC Decker; 1991.
15. Tyler KL, Martin JB, eds: *Infectious Diseases of the Central Nervous System*. Philadelphia: FA Davis; 1993.
16. Durand ML, et al: Acute bacterial meningitis in adults. A review of 493 episodes. *N Engl J Med* 1993; 328:21-28.
17. Fraser DW, Geil CC, Feldman RA: Bacterial meningitis in Bernalillo County, New Mexico: A comparison with three other American populations. *Am J Epidemiol* 1974; 100:29-34.
18. Schuchat A, et al: Bacterial meningitis in the United States in 1995. Active Surveillance Team. *N Engl J Med* 1997; 337:970-976.
19. Scheifele D, et al: Invasive *Haemophilus influenzae* type b infections in vaccinated and unvaccinated children in Canada, 2001-2003. *CMAJ* 2005; 172:53-56.
20. Beghi E, et al: Encephalitis and aseptic meningitis, Olmsted County, Minnesota, 1950-1981: I. Epidemiology. *Ann Neurol* 1984; 16:283-294.
21. Khetsuriani N, Holman RC, Anderson LJ: Burden of encephalitis-associated hospitalizations in the United States, 1988-1997. *Clin Infect Dis* 2002; 35:175-182.
22. West Nile virus activity—United States, October 30–November 5, 2003. *MMWR Morb Mortal Wkly Rep* 2003; 52:1080.
23. Calfee DP, Wispelwey B: Brain abscess. *Semin Neurol* 2000; 20:353-360.
24. Mathisen GE, Johnson JP: Brain abscess. *Clin Infect Dis* 1997; 25:763-779; quiz 780-781.
25. Hussein AS, Shafran SD: Acute bacterial meningitis in adults. A 12-year review. *Medicine (Baltimore)* 2000; 79:360-368.
26. Ahlawat S, et al: Meningococcal meningitis outbreak control strategies. *J Commun Dis* 2000; 32:264-274.
27. Moszynski P: New meningitis A vaccine is a "breakthrough" for 430 million people at risk. *BMJ* 2010; 341:c3552.
28. Summary of notifiable diseases, United States, 1997. *MMWR Morb Mortal Wkly Rep* 1998; 46:ii-vii, 3-87.
29. Brooks R, et al: Increased case-fatality rate associated with outbreaks of *Neisseria meningitidis* infection, compared with sporadic meningococcal disease, in the United States, 1994-2002. *Clin Infect Dis* 2006; 43:49-54.
30. Kumar R: Aseptic meningitis: Diagnosis and management. *Indian J Pediatr* 2005; 72:57-63.
31. Specter S, Bendinelli M, Friedman H: *Neuropathogenic Viruses and Immunity*. New York: Plenum; 1992.
32. Nowak DA, Boehmer R, Fuchs HH: A retrospective clinical, laboratory and outcome analysis in 43 cases of acute aseptic meningitis. *Eur J Neurol* 2003; 10:271-280.
33. Logan SA, MacMahon E: Viral meningitis. *BMJ* 2008; 336:36-40.
34. Solomon T, et al: West Nile encephalitis. *BMJ* 2003; 326:865-869.
35. Redington JJ, Tyler KL: Viral infections of the nervous system, 2002: Update on diagnosis and treatment. *Arch Neurol* 2002; 59:712-718.
36. Thorne CD, et al: Emergency medicine tools to manage smallpox (vaccinia) vaccination complications: Clinical practice guideline and policies and procedures. *Ann Emerg Med* 2003; 42:665-680.
37. Rowland LP, Kneass W: *Merritt's Textbook of Neurology*, 9th ed. Baltimore: Williams & Wilkins; 1995.
38. Wispelwey B, Scheld WM: Brain abscess. *Semin Neurol* 1992; 12:273-278.
39. McClelland S 3rd, Hall WA: Postoperative central nervous system infection: Incidence and associated factors in 2111 neurosurgical procedures. *Clin Infect Dis* 2007; 45:55-59.
40. Carpenter J, Stapleton S, Holliman R: Retrospective analysis of 49 cases of brain abscess and review of the literature. *Eur J Clin Microbiol Infect Dis* 2007; 26:1-11.
41. Quagliarello V, Scheld WM: Bacterial meningitis: Pathogenesis, pathophysiology, and progress. *N Engl J Med* 1992; 327:864-872.
42. Charatan F: Organ transplants and blood transfusions may transmit West Nile virus. *BMJ* 2002; 325:566.
43. Johnson RT: The pathogenesis of acute viral encephalitis and postinfectious encephalomyelitis. *J Infect Dis* 1987; 155:359-364.
44. Whitley RJ, et al: Herpes simplex encephalitis. Clinical assessment. *JAMA* 1982; 247:317-320.
45. Yang SY: Brain abscess: A review of 400 cases. *J Neurosurg* 1981; 55:794-799.
46. Geiseler PJ, et al: Community-acquired purulent meningitis: A review of 1,316 cases during the antibiotic era, 1954-1976. *Rev Infect Dis* 1980; 2:725-745.
47. Attia J, et al: The rational clinical examination. Does this adult patient have acute meningitis? *JAMA* 1999; 282:175-181.
48. Curtis S, et al: Clinical features suggestive of meningitis in children: A systematic review of prospective data. *Pediatrics* 2010; 126:952-960.
49. Thomas KE, et al: The diagnostic accuracy of Kernig's sign, Brudzinski's sign, and nuchal rigidity in adults with suspected meningitis. *Clin Infect Dis* 2002; 35:46-52.
50. Studahl M, Bergstrom T, Hagberg L: Acute viral encephalitis in adults—a prospective study. *Scand J Infect Dis* 1998; 30:215-220.
51. Maslen DR, et al: Spinal epidural abscess. Optimizing patient care. *Arch Intern Med* 1993; 153:1713-1721.
52. Wenger JD, et al: Bacterial meningitis in the United States, 1986: Report of a multistate surveillance study. The Bacterial Meningitis Study Group. *J Infect Dis* 1990; 162:1316-1323.
53. Kasanmoentalib ES, et al: Hydrocephalus in adults with community-acquired bacterial meningitis. *Neurology* 2010; 75:918-923.
54. Schut ES, et al: Delayed cerebral thrombosis after initial good recovery from pneumococcal meningitis. *Neurology* 2009; 73:1988-1995.
55. Anderson JR: Viral encephalitis and its pathology. *Curr Top Pathol* 1988; 76:23-60.
56. Sejvar JJ, et al: Neurologic manifestations and outcome of West Nile virus infection. *JAMA* 2003; 290:511-515.
57. Gadoth A, Aizenstein O, Mosek A: Influenza A/H1N1 encephalitis. *Neurology* 2010; 75:666-667.
58. Kennedy DH, Fallon RJ: Tuberculous meningitis. *JAMA* 1979; 241:264-268.
59. Sennaroglu L, Sozeri B: Otogenic brain abscess: Review of 41 cases. *Otolaryngol Head Neck Surg* 2000; 123:751-755.
60. Hasbun R, Abrahams J, Jekel J, Quagliarello VJ: Computed tomography of the head before lumbar puncture in adults with suspected meningitis. *N Engl J Med* 2001; 345:1727-1733.
61. van de Beek D, et al: Community-acquired bacterial meningitis in adults. *N Engl J Med* 2006; 354:44-53.
62. van Crevel H, Hijdra A, de Gans J: Lumbar puncture and the risk of herniation: When should we first perform CT? *J Neurol* 2002; 249:129-137.
63. Shetty AK, et al: Fatal cerebral herniation after lumbar puncture in a patient with a normal computed tomography scan. *Pediatrics* 1999; 103(6 Pt 1):1284-1287.
64. Greig PR, Goroszeniuk D: Role of computed tomography before lumbar puncture: A survey of clinical practice. *Postgrad Med J* 2006; 82:162-165.
65. Joffe AR: Lumbar puncture and brain herniation in acute bacterial meningitis: A review. *J Intensive Care Med* 2007; 22:194-207.
66. Radetsky M: Duration of symptoms and outcome in bacterial meningitis: An analysis of causation and the implications of a delay in diagnosis. *Pediatr Infect Dis J* 1992; 11:694-698; discussion 698-701.
67. Conly JM, Ronald AR: Cerebrospinal fluid as a diagnostic body fluid. *Am J Med* 1983; 75:102-108.

www.ketabpezeshki.com 66485457-66963820

68. Onorato IM, Wormser GP, Nicholas P: "Normal" CSF in bacterial meningitis. *JAMA* 1980; 244:1469-1471.
69. Luby JP: Infections of the central nervous system. *Am J Med Sci* 1992; 304:379-391.
70. Pickens S, et al: The effects of pre-admission antibiotics on the bacteriological diagnosis of pyogenic meningitis. *Scand J Infect Dis* 1978; 10:183-185.
71. Powers WJ: Cerebrospinal fluid lymphocytosis in acute bacterial meningitis. *Am J Med* 1985; 79:216-220.
72. Arevalo CE, et al: Cerebrospinal fluid cell counts and chemistries in bacterial meningitis. *South Med J* 1989; 82:1122-1127.
73. Huang QS, et al: An echovirus type 33 winter outbreak in New Zealand. *Clin Infect Dis* 2003; 37:650-657.
74. Leonard JM: Cerebrospinal fluid formula in patients with central nervous system infection. *Neurol Clin* 1986; 4:3-12.
75. Saha DC, et al: Detection of *Cryptococcus* by conventional, serological and molecular methods. *J Med Microbiol* 2009; 58:1098-1105.
76. Watson MA, Scott MG: Clinical utility of biochemical analysis of cerebrospinal fluid. *Clin Chem* 1995; 41:343-360.
77. Jordan GW, Statland B, Halsted C: CSF lactate in diseases of the CNS. *Arch Intern Med* 1983; 143:85-87.
78. Huy N, et al: Cerebrospinal fluid lactate concentration to distinguish bacterial from aseptic meningitis: A systemic review and meta-analysis. *Crit Care* 2010; 14:R240.
79. Aurelius E: Herpes simplex encephalitis. Early diagnosis and immune activation in the acute stage and during long-term follow-up. *Scand J Infect Dis Suppl* 1993; 89:3-62.
80. Aslanzadeh J, Skiest DJ: Polymerase chain reaction for detection of herpes simplex virus encephalitis. *J Clin Pathol* 1994; 47:554-555.
81. Kearns AM, Freeman R, Steward M, Magee JG: A rapid polymerase chain reaction technique for detecting *M. tuberculosis* in a variety of clinical specimens. *J Clin Pathol* 1998; 51:922.
82. Rafi A, Naghily B: Efficiency of polymerase chain reaction for the diagnosis of tuberculous meningitis. *Southeast Asian J Trop Med Public Health* 2003; 34:357-360.
83. Read SJ, Kurtz JB: Laboratory diagnosis of common viral infections of the central nervous system by using a single multiplex PCR screening assay. *J Clin Microbiol* 1999; 37:1352-1355.
84. Casas I, et al: Viral diagnosis of neurological infection by RT multiplex PCR: A search for entero- and herpesviruses in a prospective study. *J Med Virol* 1999; 57:145-151.
85. Corless CE, et al: Simultaneous detection of *Neisseria meningitidis, Haemophilus influenzae,* and *Streptococcus pneumoniae* in suspected cases of meningitis and septicemia using real-time PCR. *J Clin Microbiol* 2001; 39:1553-1558.
86. Porritt RJ, Mercer JL, Munro R: Detection and serogroup determination of *Neisseria meningitidis* in CSF by polymerase chain reaction (PCR). *Pathology* 2000; 32:42-45.
87. Richardson DC, et al: Evaluation of a rapid PCR assay for diagnosis of meningococcal meningitis. *J Clin Microbiol* 2003; 41:3851-3853.
88. Singhi SC, et al: Evaluation of polymerase chain reaction (PCR) for diagnosing *Haemophilus influenzae* b meningitis. *Ann Trop Paediatr* 2002; 22:347-353.
89. Hukkanen V, Vuorinen T: Herpesviruses and enteroviruses in infections of the central nervous system: A study using time-resolved fluorometry PCR. *J Clin Virol* 2002; 25(Suppl 1):S87-S94.
90. Romero JR: Reverse-transcription polymerase chain reaction detection of the enteroviruses. *Arch Pathol Lab Med* 1999; 123:1161-1169.
91. Thomson RB Jr, Bertram H: Laboratory diagnosis of central nervous system infections. *Infect Dis Clin North Am* 2001; 15:1047-1071.
92. Gerdes LU, et al: C-reactive protein and bacterial meningitis: A meta-analysis. *Scand J Clin Lab Invest* 1998; 58:383-393.
93. Dubos F, et al: Serum procalcitonin and other biologic markers to distinguish between bacterial and aseptic meningitis. *J Pediatr* 2006; 149:72-76.
94. Lai CW, Gragasin ME: Electroencephalography in herpes simplex encephalitis. *J Clin Neurophysiol* 1988; 5:87-103.
95. Nigrovic LE, et al: Clinical prediction rule for identifying children with cerebrospinal fluid pleocytosis at very low risk of bacterial meningitis [see comment]. *JAMA* 2007; 297:52-60.
96. Oates-Whitehead RM, et al: Fluid therapy for acute bacterial meningitis. *Cochrane Database Syst Rev* 2005; 3:CD004786.
97. Gilbert DN, Moellering RC, Sande MA: *Guide to Antimicrobial Therapy 2003*. Hyde Park, Vt: Antimicrobial Therapy; 2003.
98. Nathan N, et al: Ceftriaxone as effective as long-acting chloramphenicol in short-course treatment of meningococcal meningitis during epidemics: A randomised non-inferiority study. *Lancet* 2005; 366:308-313.
99. Tauber MG, Khayam-Bashi H, Sande MA: Effects of ampicillin and corticosteroids on brain water content, cerebrospinal fluid pressure, and cerebrospinal fluid lactate levels in experimental pneumococcal meningitis. *J Infect Dis* 1985; 151:528.
100. McIntyre PB, et al: Dexamethasone as adjunctive therapy in bacterial meningitis. *JAMA* 1997; 278:925.
101. de Gans J, van de Beek D: Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 2002; 347:1549-1556.
102. Scarborough M, et al: Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. *N Engl J Med* 2007; 357:2441-2450.
103. Brouwer M, et al: Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev* 2010; 9:CD004405.
104. van de Beek D, et al: Adjunctive dexamethasone in bacterial meningitis: A meta-analysis of individual patient data. *Lancet Neurol* 2010; 9:254-263.
105. Annane D, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862-871.
106. Sprung CL, et al: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358:111-124.
107. Molyneux EM, et al: Dexamethasone treatment in childhood bacterial meningitis in Malawi: A randomised controlled trial. *Lancet* 2002; 360:211-218.
108. Mongelluzzo J, et al: Corticosteroids and mortality in children with bacterial meningitis. *JAMA* 2008; 299:2048-2055.
109. *Haemophilus influenzae infections*. In: Pickering LK, et al, eds: *Red Book: 2006 Report of the Committee on Infectious Diseases*. Elk Grove Village, Ill: American Academy of Pediatrics; 2006:310-318.
110. *Pneumococcal infections*. In: Pickering LK, et al, eds: *Red Book: 2006 Report of the Committee on Infectious Diseases*. Elk Grove Village, Ill: American Academy of Pediatrics; 2006:525-537.
111. Rotbart HA, O'Connell JF, McKinlay MA: Treatment of human enterovirus infections. *Antiviral Res* 1998; 38:1-14.
112. Gillinov AM, et al: Valve replacement in patients with endocarditis and acute neurologic deficit. *Ann Thorac Surg* 1996; 61:1125-1129; discussion 1130.
113. Zangwill KM, et al: Duration of antibody response after meningococcal polysaccharide vaccination in US Air Force personnel. *J Infect Dis* 1994; 169:847-852.
114. Morley SL, et al: Immunogenicity of a serogroup B meningococcal vaccine against multiple *Neisseria meningitidis* strains in infants. *Pediatr Infect Dis J* 2001; 20:1054-1061.
115. Soriano-Gabarro M, Stuart JM, Rosenstein NE: Vaccines for the prevention of meningococcal disease in children. *Semin Pediatr Infect Dis* 2002; 13:182-189.
116. *The Changing Epidemiology of Meningococcal Disease in the United States with an Emphasis on College Health Issues*. Englewood, Colo: Postgraduate Institute for Medicine; 1999.
117. Meningococcal disease and college students. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2000; 49:13-20.
118. Butler JC, et al: Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. *JAMA* 1993; 270:1826-1831.
119. Jacobson RM, Poland GA: The pneumococcal conjugate vaccine. *Minerva Pediatr* 2002; 54:295-303.
120. Vadheim CM, et al: Eradication of *Haemophilus influenzae* type b disease in southern California. Kaiser-UCLA Vaccine Study Group. *Arch Pediatr Adolesc Med* 1994; 148:51-56.
121. Zhou B, Jia L, Xu X: A large-scale study on the safety and epidemiological efficacy of Japanese encephalitis (JE) live vaccine (SA14-14-2) in the JE endemic areas [in Chinese]. *Zhonghua Liu Xing Bing Xue Za Zhi* 1999; 20:38-41.

www.ketabpezeshki.com 66485457-66963820

Section Eight
PSYCHIATRIC AND BEHAVIORAL DISORDERS

CHAPTER 110
Thought Disorders

Robert S. Hockberger and John R. Richards

PERSPECTIVE

In the 1800s, Morel introduced the term *dementia praecox* to describe a progressive deterioration of mental functioning and behavior with onset in adolescence to early adult life.[1] In 1911, Bleuler detailed the specifics of this disorder, which he termed *schizophrenia,* or "split-mindedness."[2] Early treatments of schizophrenia included ice water immersion, barbiturates or insulin to induce prolonged narcosis or coma, seizure induction with pentylenetetrazol, electroconvulsive therapy, and frontal leukotomy.[3] The effectiveness of these treatments was marginal at best, and until recent times, most schizophrenic patients were relegated to lifelong institutionalization.

Modern-era pharmacotherapy for schizophrenia, with chlorpromazine and haloperidol, began in the early 1950s. This treatment proved so successful that by the 1960s, most psychiatrists believed that schizophrenia could be successfully managed in the outpatient setting. In 1965, the Community Mental Health Centers Act initiated the release of medicated schizophrenic patients into the community.[4] Unfortunately, inadequate family support, unavailability of jobs and low-cost housing, and lack of funding for social services and outpatient psychiatric care left many of these individuals isolated without the tools needed for resocialization. Currently 20 to 40% of homeless people in the United States have a major mental illness.[5] Emergency departments frequently serve as the primary entry point into the mental health care system for many of these individuals.[6]

PRINCIPLES OF DISEASE

The etiology of schizophrenia is currently believed to be heterogeneous from interaction of biologic and environmental factors. Studies involving adopted twins whose biologic parents have schizophrenia demonstrate a strong genetic basis for the disorder. Although the overall incidence of schizophrenia in the general population is roughly 1%, it is approximately 10% in first-degree biologic relatives of individuals with the disorder.[7] With regard to the pathophysiologic mechanism of schizophrenia, dopaminergic, serotonergic, cholinergic, and glutamatergic systems have been implicated.[8-11]

Schizophrenia is also postulated to be a neurodevelopmental disorder resulting from the influence of environmental factors on genetically predisposed individuals. Disruptions in fetal brain development, caused by perinatal hypoxia, poor nutrition, infection, and other insults, may set the stage for subsequent development of schizophrenia.[1,12] New imaging techniques have documented structural brain abnormalities, most of which appear to be developmental rather than degenerative in nature.[8] Evidence supports the existence of a progressive continuum of psychotic illness, beginning with unipolar depression and progressing to bipolar illness, schizoaffective psychoses, and finally schizophrenia.[1,13,14]

CLINICAL FEATURES

Overt signs of schizophrenia usually become manifested during adolescence or early adult life. Many patients describe a childhood with few interpersonal relationships and a withdrawn, eccentric personality.

Phases of Schizophrenia

The development of schizophrenia involves three phases.[15] The *premorbid phase* is characterized by the development of "negative" symptoms with deterioration in personal, social, and intellectual functioning. Patients progressively withdraw from social interactions and neglect personal appearance and hygiene, which negatively affects their work, school, and home life.

The *active phase* is usually precipitated by a stressful event with development of "positive" symptoms, such as active delusions, hallucinations, and bizarre behavior. Patients may become agitated or exhibit a hypervigilant withdrawal state characterized by rocking or staring. It is during this phase that they are most likely to be brought to the emergency department by family, friends, coworkers, or the police.

In the *residual phase,* patients are left with impaired social and cognitive ability, marked by bizarre ideation, delusions, peculiar behavior, poor personal hygiene, and social isolation. Most schizophrenic patients require a sheltered environment to function adequately. Despite a wide spectrum of severity, the general course for most patients is one of gradual deterioration with periodic episodes of psychotic decompensation.

Criteria for Schizophrenia

The diagnostic criteria for schizophrenia (Box 110-1) are outlined in the *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition, text revision (DSM-IV-TR).[15]

- The patient must exhibit two or more of the following symptoms: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms (such as flattening of affect, poverty of speech, or inability to perform goal-directed activities).
- There must be a sharp deterioration from the patient's prior level of functioning (work, school, self-care, or interpersonal relations), and there must be continuous signs of disturbance for at least 6 months.

www.ketabpezeshki.com 66485457-66963820

Box 110-1 Summary of DSM-IV-TR Criteria for Schizophrenia

A. Presence of two (or more) characteristic symptoms for 1 month (or more) unless treated
   1. Delusions
   2. Hallucinations
   3. Disorganized speech (derailment or incoherence)
   4. Grossly disorganized or catatonic behavior
   5. Negative symptoms: affect flattening, alogia (poverty of speech), avolition (unable to perform goal-directed activities)

   Note: Only one symptom above is required if delusions are bizarre or hallucinations consist of a running commentary.

B. Sharp deterioration from prior level of functioning (i.e., work, self-care, interpersonal relations)

C. Continuous signs of disturbance for 6 months (or more)

D. Schizoaffective disorder and mood disorder with psychotic features have been ruled out

E. Not caused by substance abuse, medication, or a general medical condition

Modified from Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text rev. Washington, DC, American Psychiatric Association, 2000.

- The diagnoses of schizoaffective and mood disorders with psychotic features must be excluded.
- In evaluating these patients, emergency physicians must exclude myriad medical conditions that can mimic or cause psychotic symptoms.

Delusions

The DSM-IV-TR defines *delusions* as "erroneous beliefs that usually involve a misinterpretation of perceptions or experiences."[15] The delusions seen with schizophrenia are most often persecutory, religious, or somatic.

Hallucinations

A *hallucination* is a sensory experience that exists only in the mind of the person experiencing it. Hallucinations associated with schizophrenia may be auditory, visual, olfactory, gustatory, or tactile. Auditory hallucinations (hearing voices) that are pejorative or threatening are especially common.

Disorganized Speech

Patients with schizophrenia experience loosening of associations, with thoughts shifting randomly from one topic to another without a logical connection. Their speech often shows lack of content. *Neologisms* (nonsense words invented by the patient) and *perseverations* (frequently repeated words or phrases) are common. On occasion, the patient's speech may be so severely disorganized that it is totally incoherent, termed *word salad*.

Grossly Disorganized or Catatonic Behavior

Schizophrenic patients have difficulty in formulating and producing goal-directed behavior. They are often found wandering about, disheveled, malnourished, talking to themselves, and exhibiting unpredictable agitation. It is this behavior that usually prompts family members, friends, or the police to bring them to the emergency department. Patients exhibiting catatonia appear to be completely unaware of their environment, maintain a rigid posture, and resist efforts to be moved.

Negative Symptoms

Three negative symptoms—flattening of affect, alogia, and avolition—account for a significant degree of the morbidity associated with schizophrenia. Patients with a *flattened affect* exhibit little facial expressiveness, eye contact, or body language. *Alogia*, or poverty of speech, is manifested by brief, laconic, empty replies to questioning. *Avolition* is characterized by an inability to initiate and to persist in goal-directed activities. Caution should be used in evoking negative symptoms to support a diagnosis of schizophrenia because similar symptoms may be found in patients with severe depression, chronic environmental understimulation, and treatment with neuroleptic medications.

DIAGNOSTIC STRATEGIES

Patients with Known Psychiatric Disorders

Patients with previously diagnosed thought disorders who present with mild to moderate exacerbation of their symptoms do not require extensive laboratory evaluation.[16] Because some of these patients may have coexisting substance abuse or undiagnosed medical disorders, a thorough history, detailed physical examination, and routine toxicology studies are indicated for most patients.[17-19] Patients exhibiting severe exacerbation of symptoms accompanied by marked agitation, violent behavior, or significantly abnormal vital signs should undergo more extensive evaluation.

Patients without Known Psychiatric Disorders

Many toxicologic and medical disorders can mimic schizophrenia. Patients with the apparent new onset of psychosis should receive a medical evaluation to exclude toxicologic and medical disorders.[20-23] Both the DSM-IV-TR and review articles on this topic emphasize that most toxicologic and medical causes of altered mental status that simulate acute schizophrenia are best recognized by patterns of presentation combined with focused testing based on one's index of suspicion for nonpsychiatric disease, rather than the reliance on a broad use of screening tests.

DIFFERENTIAL CONSIDERATIONS

Medical Disorders

Certain medications and medical disorders may affect thought processes, causing patients to exhibit abnormal behavior (Boxes 110-2 and 110-3). This behavior may range from mild personality changes to apparent acute psychosis, even in the absence of an underlying psychiatric disorder.[1] Factors that should alert one to a medical disorder include the following: history of substance abuse or a medical disorder requiring medication; patient's age older than 35 years without previous evidence of psychiatric disease; recent fluctuation in behavioral symptoms; hallucinations that are primarily visual in nature; presence of lethargy; abnormal vital signs; and poor performance on cognitive function testing, particularly orientation to time, place, and person. These and other factors may be helpful in differentiating functional (psychiatric) from organic (medical) causes of abnormal behavior and can be easily recalled with the mnemonic MADFOCS (Table 110-1).[24]

Although the classic textbook differentiation between functional and organic causes of abnormal behavior is straightforward, the evaluation of individual patients may be difficult.[21] A patient with underlying psychiatric disease may develop a medical disorder, which may worsen the patient's behavioral symptoms and

www.ketabpezeshki.com 66485457-66963820

Box 110-2 Pharmacologic Agents That May Cause Acute Psychosis

Antianxiety Agents
Alprazolam
Chlordiazepoxide
Clonazepam
Clorazepate
Diazepam
Ethchlorvynol

Antibiotics
Isoniazid
Rifampin

Anticonvulsants
Ethosuximide
Phenobarbital
Phenytoin
Primidone

Antidepressants
Amitriptyline
Doxepin
Imipramine
Protriptyline
Trimipramine

Cardiovascular Drugs
Captopril
Digitalis
Disopyramide
Methyldopa
Procainamide
Propranolol
Reserpine

Drugs of Abuse
Alcohol
Amphetamines
Cannabis
Cocaine
Hallucinogens
Opioids
Phencyclidine
Sedative-hypnotics

Miscellaneous Drugs
Antihistamines
Antineoplastics
Bromides
Cimetidine
Corticosteroids
Disulfiram
Heavy metals

further cloud the distinction between functional and organic disease. This evaluation is particularly difficult in the emergency department when previous medical or psychiatric history is not available, the patient is uncooperative, and the time frame to make a disposition is brief. When the clinical differentiation between functional and organic disease is unclear on the basis of available information, a patient should be thoroughly evaluated to exclude a toxicologic or medical disorder.

Psychiatric Disorders

A previously undiagnosed patient who presents with an acute functional psychosis may ultimately be given one of several psychiatric diagnoses.[15] A *brief psychotic disorder* involves the sudden onset of psychotic symptoms in response to major stress and lasts several days to 1 month. Patients with *schizophreniform disorder* have similar symptoms that last longer than 1 month but less than 6 months. Whereas one third of individuals initially given the diagnosis of schizophreniform disorder recover within 6 months, the other two thirds retain their symptoms and are diagnosed as having schizophrenia. Patients with mood disorders may develop psychotic symptoms. If these symptoms are present only during periods of mood disturbance, the diagnosis of *mood disorder with psychotic features* is applied; if they persist longer than 2 weeks in the absence of prominent mood symptoms, the diagnosis of *schizoaffective disorder* is made. Patients with *personality disorders* may occasionally develop brief psychotic episodes under stress.

Ganser's syndrome is a symptom complex considered to be emotional in origin in which the patient may appear to have amnesia, hallucinations, or alterations in consciousness, usually in association with physical complaints. An individual with Ganser's syndrome may have psychotic symptoms for no apparent gain except to assume the role of the psychiatric patient.

Persons with a *delusional disorder* experience nonbizarre delusions that may dominate their lives. They may believe that famous people are in love with them (erotomanic type), that they have extraordinary powers with a special relationship to a deity or a famous person (grandiose type), that their sexual partner is unfaithful (jealous type), that they are being malevolently treated in some way (persecutory type), or that they have some physical defect or general medical condition (somatic type). Although patients with somatic delusions may experience tactile or olfactory hallucinations related to the delusional theme (e.g., the sensation of being infested with insects), the other features associated with schizophrenia are not present.

Box 110-3 Medical Disorders That May Cause Acute Psychosis

Metabolic Disorders
Hypercalcemia
Hypercarbia
Hypoglycemia
Hyponatremia
Hypoxia

Inflammatory Disorders
Sarcoidosis
Systemic lupus erythematosus
Temporal (giant cell) arteritis

Organ Failure
Hepatic encephalopathy
Uremia

Neurologic Disorders
Alzheimer's disease
Cerebrovascular disease
Encephalitis (including HIV infection)
Encephalopathies
Epilepsy
Huntington's disease
Multiple sclerosis
Neoplasms
Normal-pressure hydrocephalus
Parkinson's disease
Pick's disease
Wilson's disease

Endocrine disorders
Addison's disease
Cushing's disease
Panhypopituitarism
Parathyroid disease
Postpartum psychosis
Recurrent menstrual psychosis
Sydenham's chorea
Thyroid disease

Deficiency States
Niacin
Thiamine
Vitamin B_{12} and folate

Table 110-1 Factors in Differentiating Organic and Functional Psychosis: MADFOCS

	ORGANIC	FUNCTIONAL
Memory deficits	Recent impairment	Remote impairment
Activity	Psychomotor retardation Tremor Ataxia	Repetitive activity Posturing Rocking
Distortions	Visual hallucinations	Auditory hallucinations
Feelings	Emotional lability	Flat affect
Orientation	Disoriented	Oriented
Cognition	Islands of lucidity Perceives occasionally Attends occasionally Focuses	Continuous scattered thoughts Unfiltered perceptions Unable to attend Unable to focus
Some other findings	Age > 40 years Sudden onset Physical examination findings often abnormal Vital signs may be abnormal Social immodesty Aphasia Consciousness impaired	Age < 40 years Gradual onset Physical examination findings normal Vital signs usually normal Social modesty Intelligible speech Awake and alert

Modified from Frame DS, Kercher EE: Acute psychosis: Functional vs. organic. Emerg Med Clin North Am 9:123, 1991.

www.ketabpezeshki.com 66485457-66963820

MANAGEMENT

General Approach

Patients with thought disorders may be agitated and hyperactive, may be withdrawn but hypervigilant, or may complain of somatic delusions. In addition, they may have paranoid ideation, may be angry they have been brought to the emergency department against their will, or may be frightened because they have been confronted by the police, restrained, and isolated. These patients may be disconcerting to staff because they are often irrational, erratic, and unpredictable in their behavior. Although emergency personnel should remain calm, empathetic, and reassuring in their interactions with patients exhibiting a thought disorder, they must also take steps to ensure staff safety whenever dealing with patients at risk for sudden violence. Such patients include those who have behaved violently before coming to the emergency department, those who physically or verbally threaten staff, and those who have an escalating level of agitation despite verbal attempts to calm them.

Each patient should have a thorough history and physical examination, including a detailed mental status evaluation, to rule out an organic brain syndrome. Valuable information can be obtained from family members, friends, coworkers, neighbors, prehospital personnel, police, and previous medical records (see Table 110-1).[24]

The most important step in evaluating a patient with a suspected thought disorder is the assessment of the patient's thought processes through the initial interview. The goals are to establish a positive physician-patient relationship, to make a correct diagnosis, and to gather enough information for an optimal disposition. The interview should be conducted in a quiet, comfortable room with adequate privacy. The examiner should be sitting, and if possible the interview should proceed to completion without interruption. If the patient is believed to be potentially dangerous but is not in need of immediate restraint, the interview should take place in an open area with security personnel nearby.

The emergency physician should begin with an introduction and should express the desire to be "of help" to the patient. The interview begins with open-ended questions designed to assess the patient's complaint and understanding of the current circumstances. Good opening questions include the following:

Do you understand why you have been brought here today?
You seem to be upset. Can you tell me why?
Do you have any idea why you might be having these symptoms?

The patient's appearance, body language, affect, and speech are observed during the responses to these questions.

A brief mental status examination is then performed. It may be initiated in a nonthreatening manner by stating, "I am now going to ask you a few questions to see how well you are concentrating." The patient is first asked about orientation to time, place, and person as this is the most sensitive test for differentiation of organic from functional disease. Patients who are disoriented require a detailed medical evaluation to exclude the presence of an organic brain syndrome. Patients who are oriented are assessed for attention, memory, intellectual functioning, and judgment in an attempt to determine their specific diagnosis, their potential for danger to themselves or others, and their degree of dysfunction and ability to care for themselves in the outpatient setting.

Rapid Tranquilization

When psychotic patients exhibit behavior that is violent or so disorganized and uncooperative that clinical evaluation is impossible, the temporary use of physical restraints is indicated while rapid tranquilization is initiated (see Chapter 189). The technique of rapid tranquilization involves serial doses of a high-potency antipsychotic agent until target symptoms, such as agitation and excessive psychomotor activity, are improved. The goal is to facilitate cooperation of the patient without causing unnecessary sedation, which inhibits further medical and psychiatric assessment. Oral, intramuscular, or intravenous doses can be given every 30 to 60 minutes until the patient becomes calm and more cooperative. If the patient is willing, an oral concentrate is preferred as it implies consent and takes effect almost as quickly as with intramuscular administration.

Haloperidol (Haldol), a butyrophenone, is widely used for rapid tranquilization in the United States.[25-27] The initial dose is 5 to 10 mg intramuscularly or intravenously for young to middle-aged patients and 0.5 to 2.0 mg intramuscularly or intravenously for elderly patients. Although rapid tranquilization with haloperidol quickly reduces tension, anxiety, and hyperactivity, delusions and hallucinations may not resolve for several weeks. In 2007 the U.S. Food and Drug Administration (FDA) released a non–black box warning about sudden death with the use of haloperidol in large doses or through the intravenous route. Droperidol (Inapsine), another butyrophenone, has also been extensively used for this indication in doses of 2.5 to 5.0 mg intramuscularly or intravenously.[28,29] Compared with haloperidol, droperidol has a faster onset and shorter duration of action and causes slightly more sedation. In 2001 the FDA issued a black box warning because of reports of a potential association between droperidol and prolonged QT interval, torsades de pointes, and sudden death.[30] Despite subsequent studies supporting both the efficacy and safety of droperidol, the FDA warning has resulted in a significant decrease of its use in clinical practice.[31,32] Neuroleptics should not be used for pregnant or lactating women, phencyclidine overdose, or anticholinergic drug–induced psychosis. In addition, although they may be useful to manage agitation in drug or alcohol intoxication, they should not be used as the sole agent in patients with drug or alcohol withdrawal. Newer atypical antipsychotic agents appear to have a broader spectrum of response with fewer side effects than the typical agents. These medications are available in tablet form and should be considered for patients who consent to oral medication. However, oral administration of a pharmacologic agent during an acute episode of agitation and psychosis is usually impossible. Ziprasidone (Geodon), aripiprazole (Abilify), and olanzapine (Zyprexa) are newer atypical antipsychotics currently approved in the United States for intramuscular injection.[33] For ziprasidone, the initial dose is 20 mg intramuscularly, and it can be repeated every 4 hours. It is more effective than haloperidol for sedation and with fewer extrapyramidal side effects, but it is not yet widely used in the emergency department setting.[34,35]

Benzodiazepines are effective in managing agitation in patients who have alcohol or sedative-hypnotic withdrawal, cocaine intoxication, or a contraindication to neuroleptic use. Benzodiazepines are helpful adjuncts to neuroleptic medication in providing rapid tranquilization, particularly for combativeness or severe agitation. Lorazepam (Ativan), 1 to 2 mg, is frequently mixed with haloperidol, 5 mg, in the same syringe and administered intramuscularly or intravenously for this purpose.[27] Benzodiazepines have also been shown to mitigate catatonic signs in schizophrenic patients.[36] Disadvantages of benzodiazepines are the need for repeated dosing and the close monitoring required for potential respiratory depression with large doses.[37]

Outpatient Management

The outpatient treatment of schizophrenia involves maintenance therapy with neuroleptic agents, family counseling, and social rehabilitation. Emergency physicians rarely prescribe outpatient

www.ketabpezeshki.com 66485457-66963820

Box 110-4 Common Neuroleptic Agents

Low Potency
Chlorpromazine (Thorazine)
Chlorprothixene (Taractan)

Intermediate Potency
Acetophenazine (Tindal)
Loxapine (Loxitane)
Mesoridazine (Serentil)
Molindone (Moban)
Perphenazine (Trilafon)
Thioridazine (Mellaril)
Triflupromazine (Vesprin)

High Potency
Droperidol (Inapsine)
Fluphenazine (Prolixin)
Haloperidol (Haldol)
Thiothixene (Navane)
Trifluoperazine (Stelazine)

Atypical
Aripiprazole (Abilify)
Clozapine (Clozaril)
Olanzapine (Zyprexa)
Paliperidone (Invega)
Quetiapine (Seroquel)
Risperidone (Risperdal)
Ziprasidone (Geodon)

neuroleptic medications but should be familiar with complications associated with their long-term use.

Box 110-4 lists the most common neuroleptic medications currently used in the United States.[38-44] The mechanism of action is related to the blockade of dopamine receptors in the central nervous system, particularly dopamine D_2 receptors in the basal ganglia and limbic portions of the forebrain. The earlier, less potent drugs, of which chlorpromazine is the prototype, cause more pronounced sedation, orthostatic hypotension, and cardiovascular toxicity from a combination of anticholinergic, antihistaminic, and anti–alpha-adrenergic effects. More potent agents (e.g., haloperidol) are safer, especially in older patients, because of their relative lack of these adverse effects. However, these more potent drugs are associated with a higher incidence of extrapyramidal symptoms, such as dystonias, akathisia, akinesia, and rigidity.

The high frequency of severe adverse reactions, poor compliance by patients, and the large number of patients with symptoms refractory to traditional antipsychotic agents prompted the development of new alternative agents. These "atypical" neuroleptic agents block serotonin to a greater extent than dopamine does, resulting in a low incidence of extrapyramidal side effects. Clozapine is particularly effective in patients who have not responded to other antipsychotic drugs.[41] However, clozapine is expensive, has a side effect profile similar to that of the low-potency antipsychotic agents, and causes agranulocytosis in approximately 1% of patients.[39] It is recommended only for the treatment of patients with refractory psychosis. Olanzapine, quetiapine, and the newest agent, aripiprazole, are similar to clozapine but have fewer side effects and less risk of agranulocytosis.[38] Risperidone, another newer neuroleptic agent with improved effects on negative symptoms, has been found to be superior to haloperidol in several short-term trials.[42-45] The most recent FDA-approved drug (2006), paliperidone (Invega), is the active metabolite of risperidone. Unfortunately, the expense and unavailability of these newer antipsychotic agents limit their utility for treatment of acute psychosis in the emergency department. Ziprasidone, risperidone, and quetiapine have been associated with QT interval prolongation similar to that seen with droperidol and haloperidol but have not yet been found to be associated with sudden cardiac death.[46]

Because of the high incidence of extrapyramidal symptoms in patients treated with high-potency neuroleptics, it is common practice to administer antiparkinsonian drugs (e.g., benztropine, procyclidine, trihexyphenidyl) at the same time either to treat the adverse effects or to prevent them. Prophylactic treatment is most useful in patients with a history of extrapyramidal symptoms, those receiving large doses of high-potency antipsychotic agents, and those in whom the occurrence of these symptoms is likely to increase the risk of noncompliance.

Noncompliance with antipsychotic medication remains a leading cause of psychiatric hospitalization. Patients with recurrent psychotic relapses caused by noncompliance are candidates for treatment with long-acting injectable antipsychotic drugs, usually given every 2 weeks. Three such agents available in the United States are fluphenazine, risperidone, and haloperidol decanoate.[47]

Complications of Neuroleptic Drug Therapy

Dystonia

Acute dystonia, the most common adverse effect seen with neuroleptic agents, occurs in 1 to 5% of patients. This reaction is caused by a disruption of the dopaminergic-cholinergic balance in the nigrostriatal pathways of the basal ganglia, resulting in cholinergic dominance.[48] Dystonic reactions, which can occur at any point during long-term therapy and up to 48 hours after administration of neuroleptics in the emergency department, involve the sudden onset of involuntary contraction of the muscles of the face, neck, or back. The patient may have protrusion of the tongue (buccolingual crisis), deviation of the head to one side (acute torticollis), sustained upward deviation of the eyes (oculogyric crisis), extreme arching of the back (opisthotonos), and rarely laryngospasm. These symptoms tend to fluctuate, decreasing with voluntary activity and increasing under emotional stress, which occasionally misleads emergency physicians to believe they are factitious.

Dystonic reactions should be treated with intramuscular or intravenous benztropine (Cogentin), 1 to 2 mg, or diphenhydramine (Benadryl), 25 to 50 mg, which usually results in immediate reversal of symptoms. Patients should receive oral therapy with the same medication for 48 to 72 hours to prevent recurrent symptoms.[48]

Akathisia

Akathisia is a state of motor restlessness characterized by a physical need to be moving constantly. It occurs most often in middle-aged patients during the first few months of therapy. Patients usually pace the room and express a sense of inner tension that is not relieved by activity. If asked, they do not want to be constantly moving but feel physically compelled to do so. This reaction can easily be mistaken for a decompensating psychosis, leading to a vicious circle in which more medication is given to treat a side effect caused by the same drug. This misdiagnosis can be avoided by carefully evaluating the patient for the exacerbation of positive psychotic symptoms, which are not increased by akathisia. Akathisia is treated with beta-blockers (e.g., propranolol, 30-60 mg/day) and anticholinergic drugs (e.g., benztropine, 1 mg twice to four times daily). A new potential agent for the treatment of akathisia is glycine, a nonessential amino acid that stimulates glutamatergic neurotransmission.[49] In addition, if possible, the dosage of the antipsychotic agent should be lowered or replaced with another drug.

Pseudoparkinsonism and Akinesia

A clinical picture can occur that may be indistinguishable from Parkinson's disease, particularly in elderly patients during the first month of therapy. Treatment with anticholinergic agents (e.g., benztropine) or antiparkinsonian drugs is usually effective. Akinesia, which is characterized by immobility, withdrawal, and lack of motivation, may be mistaken for a postpsychotic depression. It

www.ketabpezeshki.com 66485457-66963820

is responsive to antiparkinsonian drugs, but symptoms usually resolve gradually over time.

Tardive Dyskinesia

Tardive dyskinesia usually appears after several years of neuroleptic drug treatment and is characterized by involuntary movements, especially of the face and tongue, that are described as writhing, grimacing, and choreoathetoid in nature. The earliest manifestation is often a curling or twisting movement of the tongue. The onset of these symptoms can be falsely attributed to psychological factors because they intensify under emotional stress, fatigue, and voluntary activity and disappear with sleep.

The reported prevalence of tardive dyskinesia ranges from 0.5 to 70%, with a mean of 24%.[48] The incidence of the disorder appears to be directly related to the duration of treatment, total cumulative dosage, evidence of preexisting brain damage, and age of the patient. It is more common in elderly women and patients with associated mood disorders. For patients with mild symptoms, discontinuation or lowering of the dosage of antipsychotic agents, switching to a newer atypical neuroleptic agent, and cotreatment with benzodiazepines may reverse the symptoms. Patients with moderate to severe symptoms are difficult to treat, but some have variable degrees of improvement when they are treated with reserpine or tetrabenazine along with discontinuation of neuroleptic treatment.[48]

Orthostatic Hypotension

All antipsychotic agents can cause orthostatic hypotension, an effect related to alpha-adrenergic blockade. This complication is less common with the more potent agents (e.g., haloperidol). Typically, episodes are mild in severity and brief in duration. Symptomatic patients should be treated with oxygen, Trendelenburg's position, and intravenous fluid administration. Pressor agents (e.g., dopamine) should be used only for severe, symptomatic episodes that fail to respond to the previous measures. Agents with beta-agonist activity (e.g., epinephrine, isoproterenol) are contraindicated in these patients.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a life-threatening complication of neuroleptic drug treatment that affects 0.5 to 1% of patients.[50] It is seen with both typical and atypical neuroleptic agents and usually occurs in the first few weeks after initiation of treatment, but it can also be seen after a recent increase in drug dosage or after parenteral treatment with large doses of neuroleptic agents. NMS is characterized by high fever, severe muscle rigidity, altered consciousness, autonomic instability, and elevated serum creatine kinase levels and can be confused with serotonin syndrome. Additional complications can include respiratory failure, gastrointestinal hemorrhage, hepatic and renal failure, coagulopathy, and cardiovascular collapse.

The pathophysiologic mechanism of NMS is not well understood, but it is thought to be related to dopamine depletion in the central nervous system leading to defective thermoregulation in the hypothalamus. Predisposing factors include exhaustion, dehydration, and the use of long-acting depot neuroleptics. Treatment consists of recognition and discontinuation of the neuroleptic agent, temperature reduction, rehydration with intravenous fluids, and general supportive measures. Dantrolene, a direct-acting muscle relaxant, should be used in severe cases. It can be administered by continuous rapid intravenous push at a minimum initial dose of 1 mg/kg, repeated until symptoms subside or up to a maximum cumulative dose of 10 mg/kg. For severe symptoms, dopamine agonists, such as bromocriptine, levodopa, and amantadine, have shown encouraging results. Because of early recognition and treatment, mortality rates with NMS have decreased from 30% to less than 10%.[51]

DISPOSITION

The ultimate disposition of the acutely psychotic patient depends on the underlying cause of the psychosis, whether the patient is a danger to self or others, and the presence of social support in the community. Hospitalization is indicated for patients experiencing their first psychotic episode, for patients deemed to be a danger to themselves (suicidal) or others (homicidal), for patients who are grossly debilitated, for patients who are moderately debilitated but have no social support system within the community, and for patients with either functional or organic psychosis that does not clear with a brief period of treatment and observation in the emergency department. The decision to hospitalize psychotic patients is complex and imprecise and often must be made in a short period with limited information.

A psychiatric short-procedure unit offers a cost-effective alternative to hospitalization.[52] After stabilization, patients are moved from the emergency department to a separate treatment area, where they are treated for a period of 12 to 24 hours by a small staff of consultants.

KEY CONCEPTS

- In patients exhibiting abnormal behavior, an organic cause is suggested by new onset of symptoms in a patient older than 35 years, rapid onset of symptoms in a previously normal person, visual hallucinations, abnormal vital signs, and lethargy or disorientation.
- Physical restraints should be considered for patients who have violent behavior, verbally threaten staff, or demonstrate escalating agitation despite verbal attempts to calm them. Restraints should be removed after sedation has been achieved.
- Rapid tranquilization is best accomplished with the use of high-potency neuroleptics (e.g., haloperidol, ziprasidone). Benzodiazepines (e.g., lorazepam) are a helpful adjunct for patients with severe agitation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Jones P, Cannon M: The new epidemiology of schizophrenia. *Psychiatr Clin North Am* 1998; 21:1.
2. Tomlinson WK: Schizophrenia: History of an illness. *Psychiatr Med* 1990; 8:1.
3. Tueth MJ: Schizophrenia: Emil Kraepelin, Adolph Meyer, and beyond. *J Emerg Med* 1995; 13:805.
4. Lewis G, et al: Schizophrenia and city life. *Lancet* 1992; 340:137.
5. Opler LA, et al: Symptom profiles and homelessness in schizophrenia. *J Nerv Ment Dis* 1994; 182:174.
6. Kropp S, et al: Characteristics of psychiatric patients in the accident and emergency department (ED). *Psychiatr Prax* 2007; 34:72.
7. Schwab SG, et al: Support for a chromosome 18p locus conferring susceptibility to functional psychoses in families with schizophrenia, by association and linkage analysis. *Am J Hum Genet* 1998; 63:1139.
8. Michels R, Morzuk PM: Progress in psychiatry. *N Engl J Med* 1993; 329:552.
9. Lieberman JA, et al: Serotonergic basis of antipsychotic drug effects in schizophrenia. *Biol Psychiatry* 1998; 44:1099.
10. Tandon R: Cholinergic aspects of schizophrenia. *Br J Psychiatry Suppl* 1999; 37:7.
11. Tamminga CA: Schizophrenia and glutamatergic transmission. *Crit Rev Neurobiol* 1998; 12:21.
12. McGrath JJ, et al: The neurodevelopmental hypothesis of schizophrenia: A review of recent developments. *Ann Med* 2003; 35:86.
13. Harrison PJ: The neuropathology of schizophrenia: A critical review of the data and their interpretation. *Brain* 1999; 122:593.
14. Crow TJ, Harrington CA: Etiopathogenesis and treatment of psychosis. *Annu Rev Med* 1994; 45:219.
15. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed, text rev. Washington, DC: American Psychiatric Association; 2000.
16. Olshaker JS, et al: Medical clearance and screening of psychiatric patients in the emergency department. *Acad Emerg Med* 1997; 4:124.
17. Breslow RE, Klinger BI, Erickson BJ: Acute intoxication and substance abuse among patients presenting to a psychiatric emergency service. *Gen Hosp Psychiatry* 1996; 18:183.
18. Elangovan N, et al: Substance abuse among patients presenting at an inner-city psychiatric emergency room. *Hosp Community Psychiatry* 1993; 44:782.
19. Dhossche D, Rubinstein J: Drug detection in a suburban psychiatric emergency room. *Ann Clin Psychiatry* 1996; 8:59.
20. Tintinalli JE, Peacock FW IV, Wright MA: Emergency medical evaluation of psychiatric patients. *Ann Emerg Med* 1994; 23:859.
21. Henneman PL, Mendoza R, Lewis RJ: Prospective evaluation of emergency department medical clearance. *Ann Emerg Med* 1994; 24:672.
22. Smith ML: Atypical psychosis. *Psychiatr Clin North Am* 1998; 4:895.
23. Hutto B: Subtle psychiatric presentations of endocrine diseases. *Psychiatr Clin North Am* 1998; 21:905.
24. Frame DS, Kercher EE: Acute psychosis: Functional vs. organic. *Emerg Med Clin North Am* 1991; 9:123.
25. Currier GW, Trenton A: Pharmacological treatment of psychotic agitation. *CNS Drugs* 2002; 16:777.
26. Hillard JR: Emergency treatment of acute psychosis. *J Clin Psychiatry* 1998; 59:57.
27. Battaglia J, et al: Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. *Am J Emerg Med* 1997; 15:335.
28. Thomas HA: Droperidol vs. haloperidol for chemical restraint of agitated and combative patients. *Ann Emerg Med* 1992; 21:407.
29. Richards JR, Derlet RW, Duncan DR: Chemical restraint for the agitated patient in the emergency department: Lorazepam versus droperidol. *J Emerg Med* 1998; 16:567.
30. Richards JR, Schneir AB: Droperidol in the emergency department: Is it safe? *J Emerg Med* 2003; 24:441.
31. Chase PB, Biros MH: A retrospective review of the use and safety of droperidol in a large, high-risk, inner-city emergency department patient population. *Acad Emerg Med* 2002; 9:1402.
32. Shale JF, et al: A review of the safety and efficacy of droperidol for the rapid sedation of severely agitated and violent patients. *J Clin Psychiatry* 2003; 64:500.
33. Freudenreich O, et al: The evaluation and management of patients with first-episode schizophrenia: A selective, clinical review of diagnosis, treatment, and prognosis. *Harv Rev Psychiatry* 2007; 15:189.
34. Daniel DG, et al: Intramuscular ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: A double-blind randomized trial. *Psychopharmacology* 2001; 115:128.
35. Marco C, Vaughan J: Emergency management of agitation in schizophrenia. *Am J Emerg Med* 2005; 23:767.
36. Huang T: Lorazepam and diazepam rapidly relieve catatonic signs in patients with schizophrenia. *Psychiatry Clin Neurosci* 2005; 59:52.
37. Martel M, et al: Management of acute undifferentiated agitation in the emergency department: A randomized double-blind trial of droperidol, ziprasidone, and midazolam. *Acad Emerg Med* 2005; 12:1167.
38. Cain JM: Schizophrenia. *N Engl J Med* 1996; 334:34.
39. Alvir JM, et al: Clozapine-induced agranulocytosis: Incidence and risk factors in the United States. *N Engl J Med* 1993; 329:162.
40. Fleischhacker WW: New developments in the pharmacotherapy of schizophrenia. *J Neural Transm Suppl* 2003; 64:105.
41. Breier A, et al: Effects of clozapine on positive and negative symptoms in outpatients with schizophrenia. *Am J Psychiatry* 1994; 151:20.
42. Marder SR, Meibach RC: Risperidone in the treatment of schizophrenia. *Am J Psychiatry* 1994; 151:825.
43. Tran PV, et al: Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. *J Clin Psychopharmacol* 1997; 17:407.
44. Breier AF, et al: Clozapine and risperidone in chronic schizophrenia: Effects on symptoms, parkinsonian side effects, and neuroendocrine response. *Am J Psychiatry* 1999; 156:294.
45. Leucht S, et al: Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo: A meta-analysis of randomized controlled trials. *Schizophr Res* 1999; 35:51.
46. Trenton AJ, Currier GW, Zwemer FL: Fatalities associated with therapeutic use and overdose of atypical antipsychotics. *CNS Drugs* 2003; 17:307.
47. Davis JM, et al: Depot antipsychotic drugs: Their place in therapy. *Drugs* 1994; 47:741.
48. Fernandez HH, Friedman JH: Classification and treatment of tardive syndromes. *Neurologist* 2003; 9:16.
49. Heresco-Levy U, et al: Efficacy of high-dose glycine in the treatment of enduring negative symptoms of schizophrenia. *Arch Gen Psychiatry* 1999; 56:29.
50. Viejo LF, et al: Risk factors in neuroleptic malignant syndrome: A case-control study. *Acta Psychiatr Scand* 2003; 107:45.
51. Caroff SN, et al: Neuroleptic malignant syndrome in the critical care unit. *Crit Care Med* 2002; 30:2609.
52. Mausbach BT, et al: Reducing emergency medical service use in patients with chronic psychotic disorders: Results from the FAST intervention study. *Behav Res Ther* 2008; 46:1.

www.ketabpezeshki.com 66485457-66963820

Chapter 111

Mood Disorders

James L. Young and Douglas A. Rund

PERSPECTIVE

Mood is a subjective emotional state, and fluctuations in mood are expected, especially in response to the joys and sorrows of everyday life. Mood disorders, however, extend beyond these common emotional variations. Patients with mood disorders often present with impairment in functioning, often severe and with threats to life that include suicide, profound self-neglect, and impaired judgment. They are also associated with impaired physical, social, and family functioning as well as with psychological and physical pain and a negative perception of physical health. Patients with mood disorders are most often seen in general medical settings, including the emergency department (ED), often in crisis. One fourth to one third of ED patients screen positive for mood disorders.[1]

The *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition, text revision (DSM-IV-TR), divides mood disorders into four broad categories[2]: (1) depressive disorders, (2) bipolar disorders, (3) mood disorder due to a general medical condition, and (4) substance-induced mood disorder. Because the specific pathophysiologic mechanisms of these disorders are not fully understood, they are categorized by groupings of symptoms that persist for defined lengths of time. As research into the biology, genetics, and treatment of mood disorders advances, we hope to one day be able to more clearly demonstrate the pathophysiologic abnormalities.

EPIDEMIOLOGY

Up to 50% of Americans will meet the criteria for a DSM-IV-TR disorder sometime in their life.[3] Mental health patients are the fastest growing group of patients presenting to the ED.[4] In 2007, 12.5% of the 94 million ED visits in the United States were for psychiatric reasons,[5] which was an increase from 5.4% in 2000.[6] The lifetime prevalence for mood disorders is estimated to be 20.8%.[3]

The World Health Organization ranks major depressive disorder as one of the most prevalent and disabling diseases in the world.[7] The 12-month prevalence for major depressive disorder is 5.28% and the lifetime prevalence is 13.23%.[8] Patients with major depressive disorder frequently have other comorbid mental health issues, including anxiety disorders (36.1% 12-month and 41.4% lifetime prevalence), personality disorders (37.9% 12-month and 30.8% lifetime prevalence), and substance use disorders (4.6% 12-month and 17.2% lifetime prevalence).[8]

Although it is less prevalent than major depressive disorder, bipolar disorder is a serious and potentially life-threatening illness. Up to 80% of patients with bipolar disorder will exhibit suicidal behavior, and 51% will attempt suicide.[9] Suicidal behavior can occur during all phases of bipolar disorder, but patients experiencing a depressed or a mixed episode are at higher risk, especially those with severe depressive symptoms and a sense of hopelessness.[10] Bipolar disorder is diagnosed on a spectrum, decreasing in severity from bipolar disorder type I, consisting of both depressive and manic episodes, to bipolar disorder type II, which has depressive and hypomanic episodes, to subthreshold bipolar disorder, such as cyclothymia and bipolar NOS (not otherwise specified). Bipolar disorder type I has a 0.6% 12-month prevalence and a 1.0% lifetime prevalence, bipolar disorder type II has a 0.8% 12-month prevalence and a 1.1% lifetime prevalence, and subthreshold bipolar disorder has a 1.4% 12-month prevalence and a 2.4% lifetime prevalence.[11]

Most of the disability caused by bipolar disorder occurs during the depressive phase of the illness. On average, patients with bipolar disorder spend 30% of their time in a depressive phase, 10% in a manic phase, and 6% in a mixed phase.[12]

PRINCIPLES OF DISEASE

The pathophysiology of the mood disorders is not well established, but quite a bit is known about the neurophysiology, genetics, and psychosocial aspects of the disorders.

Neurophysiology

The immediate effects of most available antidepressants are to increase the availability and activity of serotonin and norepinephrine in the synapse with subsequent stimulation of the postsynaptic neuron. This is done by direct binding to the presynaptic and postsynaptic receptors, blocking reuptake of the neurotransmitter or inhibiting the enzymatic breakdown of the neurotransmitter. Because norepinephrine and serotonin systems traverse large portions of the brain, one hypothesis is that a monoamine deficiency is a cause of depression. There is a risk in deriving a theory from the mechanism of action of available antidepressants, but there is research to support the monoamine deficiency hypothesis. Positron emission tomography (PET) scans have demonstrated a 30% increase in TPH-2, a brain-specific tryptophan hydroxylase enzyme in some depressed patients.[13] Studies demonstrate that depletion of oral tryptophan and tyrosine, amino acids essential for the production of serotonin and norepinephrine, respectively, can induce a depressive episode in subjects with a history of depression but not in healthy controls.[14] Numerous studies of monoamine metabolite levels in cerebrospinal fluid, plasma, urine, and postmortem brains of patients with depression did not reliably demonstrate a monoamine deficiency, indicating that there could be downstream effects involving

www.ketabpezeshki.com 66485457-66963820

second-messenger systems such as cyclic adenosine monophosphate and phosphatidylinositol.[15]

Other neurotransmitter systems may play a role in the development of depression. A study using magnetic resonance spectroscopy demonstrated decreased levels of both glutamate and γ-aminobutyric acid in the prefrontal cortex of depressed subjects.[16] Intravenous ketamine, an *N*-methyl-D-aspartate (NMDA) antagonist, induces a rapid antidepressant effect[17] and suggests a role for glutamate in the pathophysiologic process of depression. This is important because the excitotoxic effects of glutamate can lead to neuronal loss and atrophy of some brain regions.[18] The brain relies on the actions of protective and regenerative cytokines, such as brain-derived neurotrophic factor (BDNF), and all of the known antidepressants and electroconvulsive therapy raise levels of BDNF and subsequently result in neurogenesis of certain brain regions, such as the hippocampus. Sleep deprivation and light therapy both have antidepressant effects, which suggests circadian rhythm abnormalities as a contributing mechanism for depression.[15,19,20] A novel antidepressant under investigation suggests a role for the melatonergic system and abnormalities in circadian rhythms.[21] Other theories include decreased neurosteroid synthesis, impaired endogenous opioid functioning, monoamine-acetylcholine imbalance, inflammatory effects of cytokines, and dysfunction of specific brain structures and circuits.[15]

The neurophysiology of bipolar disorder is less understood than that of unipolar depression, in part because of the fluctuating mood states and the heterogeneity of the disorder. Bipolar disorder may in part arise from abnormalities in the connections within and between structures in the brain.[22] Specifically implicated are circuits interconnecting the amygdala, hypothalamus, striatum, and subdivisions of the frontal cortex, all of which are involved in both the generation and regulation of emotion.[22]

Neuroanatomy

Neuroimaging studies of the brain suggest that abnormalities in certain areas and the interconnections between those areas may be involved in the mood disorders. A common magnetic resonance imaging (MRI) finding in patients with mood disorders, especially bipolar disorder, is an increased occurrence of subcortical hyperintensities in areas such as the periventricular areas, basal ganglia, and thalamus.[23] High-resolution MRI demonstrates reduced volumes in the hippocampus, orbital cortex, and anterior cingulate. These findings are associated with more severe illness, bipolar disorder, and increased cortisol levels.[23] Volume reduction in the hippocampus is associated with high illness chronicity.[23]

PET scans demonstrate a global reduction of glucose metabolism in the anterior regions of the brain, such as the dorsolateral prefrontal cortex. These findings are mood state dependent and are seen in both unipolar and bipolar depression. Patients in a depressed episode have lower relative functioning on the left side of the brain, and those who are hypomanic or manic have lower relative functioning on the right side of the brain.[23]

The amygdala is a clustering of nuclei that process emotional stimuli, especially fear, anger, and sadness. Functional neuroimaging suggests that amygdala activity is increased when the subject is exposed to emotionally relevant stimuli.[23] It has connections throughout the brain that regulate anticipatory anxiety (bed nucleus of the stria terminalis), cortisol release (hypothalamus), attention and mood (nucleus basalis of Meynert, locus ceruleus, ventral tegmental area), and sympathetic arousal (periaqueductal gray).[18] A decreased amygdala volume has been associated with unipolar depression.[18] There is decreased amygdala volume in children and adolescents with bipolar disorder and increased volume in adults with bipolar disorder.[18]

Endocrine System

The perception of stress in the environment by the cerebral cortex and the amygdala activates circuits and structures in the brain to cause physiologic changes such as increased alertness, decreased appetite, increased heart rate, and activation of the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis may play a role in depression, especially in cases of early childhood and chronic stress.

Activation of the HPA axis releases corticotropin-releasing hormone (CRH) from the hypothalamus. This results in a release of corticotropin (ACTH) from the anterior pituitary, which enters the bloodstream and stimulates release of cortisol from the adrenal glands. Cortisol then provides negative feedback to the hypothalamus and the pituitary to decrease the secretion of CRH and corticotropin, respectively.

There is evidence that CRH and cortisol play a role in depression. Although not specific, patients with depression may have increased levels of free cortisol in the plasma, cerebrospinal fluid, and urine.[24] Increased CRH has been demonstrated in cerebrospinal fluid, and increased levels of CRH messenger RNA and protein have been demonstrated in limbic brain regions.[24] Also, some patients with melancholic or psychotic depression have been shown to have an overactive HPA axis demonstrated by an inability of dosed dexamethasone to suppress cortisol release.[25] Although none of these measures is reliable as a diagnostic tool (e.g., the dexamethasone suppression test has been shown to be 90% sensitive for detection of depression but only 30-50% specific), successful treatment to remission has been shown to reverse some of these abnormalities.[24,26]

Genetics

Genetic vulnerability to mood disorders has not been traced to a single gene. It is likely to be due to the additive effects of many genes and environmental influences on how these genes are expressed.[27]

Major depressive disorder has a heritability of 37 to 38%,[28] lower than the heritability of bipolar disorder.[15] The heritability of major depressive disorder is higher in women than in men[28] and may be higher in early-onset, more severe, and recurrent forms of the disorder.[15] Genetic linkage studies have identified various chromosomal regions that are of interest in major depressive disorder, but not all of these have been consistently replicated.[15] There may also be some environmental factors that could have epigenetic effects.[15] One example of this is the region that codes for 5-HTT, a serotonin transporter protein. Individuals with one or more copies of the short allele of the 5-HTT promoter polymorphism have been shown in some but not all studies to be more prone to depression and suicidality when they are faced with an adverse life event compared with those with only the long allele.[27]

Bipolar disorder is one of the most heritable medical illnesses.[29] Bipolar disorder has a heritability of 80 to 85% and a monozygotic twin concordance of 40 to 45%.[29] There is also considerable overlap between the heritability of bipolar disorder and other DSM-IV-TR diagnoses. First-degree relatives of patients with bipolar disorder have an increased risk for both bipolar disorder and unipolar depression, but first-degree relatives of patients with unipolar depression do not have increased bipolar risk.[29] There is also overlap of genetic risk between bipolar disorder and schizophrenia.[29] Several different genes and linkage studies have been investigated, but the results have been inconsistent.[29]

Psychosocial Factors

The etiology of most psychiatric problems, including the mood disorders, involves complex interactions between both biologic

www.ketabpezeshki.com 66485457-66963820

and psychosocial factors.[30] The complex neural mechanism that regulates mood responds to and is modified by each person's experience, including events in early childhood, reward and punishment during growth and development, interpersonal relationships, and various kinds of loss. Psychosocial theories of mood disorder form the basis for psychotherapy.

Stressful Life Events

Environmental stress and adverse life events, such as parental neglect, sexual and physical abuse, and death of a loved one, have been shown to play a role in the onset of a mood episode as well as in the development and course of the mood disorders.[30] Neuroanatomic changes, such as decreased hippocampal volume and increased amygdala volume, and the correlation between the mechanisms of depression and molecular mechanisms of neuroplasticity suggest that stress has an adverse effect on the brain.[31] This supports the finding that a stressful life event is more likely to precede a first mood episode than subsequent episodes in both major depressive disorder and bipolar disorder.[32] Stressful events that patients perceive as reflections on their self-esteem are more likely to trigger mood episodes. Because many who are exposed to severe stressful life events do not develop mood disorders, it is likely that environmental, psychological, and social factors affect brain neurophysiology in susceptible individuals.[30] This is supported by models such as the activation of the HPA axis and increased susceptibility in those with a short 5-HTT allele described earlier.

Cognitive-Behavioral Theory

The cognitive model was first described by Aaron Beck and is the basis for cognitive-behavioral therapy. The cognitive theory looks at how individuals organize and interpret their experiences. These are called schemas. Those prone to depression develop depressogenic schemata composed of cognitive distortions, such as a tendency to focus on the negative, and overgeneralization. Beck proposed that those with depression have a negative cognitive triad composed of disparaging views about themselves, views of the world as hostile and demanding, and views that that the future will bring further suffering and failure.[32]

The concept of "learned helplessness" was developed on the observation that animals subject to repeated noxious stimuli, such as electric shock, and blocked from escape eventually stop trying to escape. They become apathetic, even when escape becomes available.[33] This concept was later applied to humans and adapted to construct a behavioral mode of therapy for depression.

The Interpersonal Theory

The interpersonal theory of depression emphasizes guilt, disputes between partners and family members, role transitions in families and relationships, and problems with social skills necessary to sustain a fulfilling relationship.

Psychodynamic Theory

The psychodynamic model was first developed by Sigmund Freud and later extended and modified by others, such as Karl Abraham and Melanie Klein. Basic tenets of this theory are that early childhood experiences during key developmental stages can predispose some individuals, depression can be linked to real or imagined loss, introjection of lost objects can be used as a defense against feelings of loss, and feelings of anger can be directed inward toward the self.[32]

Box 111-1 Summary of DSM-IV-TR Criteria for a Major Depressive Episode

A. Five or more of the following symptoms have been present almost every day during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
   Note: Do not include symptoms caused by a general medical condition, and do not include mood-incongruent delusions or hallucinations.
   1. Depressed mood (can be irritable mood in children and adolescents)
   2. Loss of interest or pleasure in activities
   3. Significant weight loss when not dieting or weight gain, or decrease or increase in appetite
   4. Insomnia or hypersomnia
   5. Psychomotor agitation or retardation
   6. Fatigue or loss of energy
   7. Feelings of worthlessness, or excessive or inappropriate guilt
   8. Diminished ability to think or concentrate, or indecisiveness
   9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation, or a suicide plan or attempt

B. Symptoms do not meet criteria for a "mixed episode."

C. Symptoms cause clinically significant distress or impairment in social, occupational, or other functioning.

D. Symptoms are not caused by direct physiologic effects of a substance (e.g., drug of abuse, medication) or a general medical condition (e.g., hypothyroidism).

E. Symptoms are not better accounted for by bereavement; after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Modified from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text rev. Washington, DC, American Psychiatric Association, 2000.

CLINICAL FEATURES

Major Depressive Disorder

Major depressive disorder is characterized by one or more major depressive episodes, as defined by DSM-IV-TR criteria (Boxes 111-1 and 111-2), and a lifelong absence of manic episodes. A major depressive episode is characterized by disturbances in four major areas: mood, psychomotor activity, cognition, and vegetative function.[34] The patient must have at least five symptoms for a minimum of 2 weeks.

Mood Disturbances

Patients in a depressed state often feel profoundly hopeless and helpless. They may describe feeling anguished, sad, gloomy, dejected, unhappy, discouraged, or in low spirits. In addition, they may also experience feelings of anxiety and irritability. Those in a profound state of depression may not have the capacity to feel any emotion at all.

Depression can also be manifested as a decreased capacity to experience pleasure or interest in pleasurable or satisfying activities. Patients may have stopped doing formerly pleasurable activities entirely. This loss of interest and hedonic capacity is known as anhedonia.

The patient must exhibit a depressed mood or anhedonia to meet DSM-IV-TR criteria for a diagnosis of a depressive episode.[2]

www.ketabpezeshki.com 66485457-66963820

Box 111-2 Mnemonics for the Symptoms of Depression and Mania

Mnemonic for the Symptoms of Depression

SIG E CAPS (prescribe energy capsules)
Sleep amount increased or decreased
Interest (anhedonia)
Guilt
Energy level decreased
Concentration decreased
Appetite increased or decreased
Psychomotor activity increased or decreased
Suicidal ideation

Mnemonic for the Symptoms of Mania

DIG FAST
Distractibility
Irritability
Grandiosity
Flight of ideas
Activity increased
Sleeplessness
Thoughtlessness (impulsivity, increased risk taking)

Disturbances in Psychomotor Activity

Physical activity in depression can be either increased or decreased. Psychomotor retardation is a significant slowing of physical activity. The body language of depression may include a slumped posture and creased brow with arms folded, mouth turned down, and eyes closed or downcast. Depressed patients often describe feeling fatigued with a general lack of energy and motivation. Patients may also display psychomotor agitation, which can be manifested as fidgeting, pacing, hand wringing, rubbing of the skin, or restlessness.

Vegetative Disturbances

Vegetative symptoms include disturbances in three major areas: sleep, appetite, and sexual function. Depressed patients may complain of sleeping either too much or too little. Insomnia may be manifested as difficulty in falling asleep, frequent awakenings throughout the night, or early-morning wakening and inability to fall back to sleep. Depressed patients with hypersomnia may report sleeping 12 to 14 hours or more a day. Patients may fluctuate between insomnia and hypersomnia. Either sleep alteration may result in fatigue and decreased arousal. Alterations in appetite and eating patterns can also occur. Patients may eat too much or too little with resulting significant weight gain or loss during a short time. Loss of interest in sexual activity and impaired sexual functioning may also accompany depression, although this is not listed as a DSM-IV-TR criterion.

Thought Process and Content

Depressed patients often describe impaired concentration that may be manifested as diminished mental quickness, difficulty in maintaining attention and focus, and forgetfulness. Executive functioning, such as prioritization, problem solving, and planning, can be impaired. In severe cases, this results in a decreased ability to sufficiently take care of themselves or to perform basic activities of daily living, such as paying bills and the purchase and preparation of food.

Thought content tends to be negatively biased, such as recurrent thoughts of guilt, failure, worthlessness, and self-criticism.

Patients in a depressed episode are at increased risk for suicide. Suicidal thoughts may range from vague notions that life is not worth living to fully envisioned suicide plans with definitive intent to kill themselves. Severely depressed patients must be questioned about suicidal thoughts. Doing so does not increase the likelihood of a future attempt and provides an opening for a dialogue to address the patient's safety. Because patients are not often forthcoming with their thoughts on suicide, a thorough review of risk factors and protective factors needs to form the basis of clinical decisions for providing the necessary level of care.

Patients with severe depression may have psychotic symptoms. The hallucinations and delusions that accompany depression are usually mood congruent, meaning that the themes of the psychotic content are consistent with the depressed mood. An example could be voices saying extremely unpleasant things or punishing the patient for previous wrongs. The patient may report being "already dead" or feeling like "my insides have rotted away." Such hallucinations may suggest the Cotard syndrome, in which patients hold the belief that they do not exist or that they are dead.[35] Mood-incongruent psychotic symptoms do not reflect the mood as clearly and are less likely to occur in a depressed state. Examples are a fear that one is being followed or having one's thoughts controlled by external forces.

Masked Depression

Mood disorders may not be clear at presentation. The depressed patient may have only vague physical symptoms, such as weakness, fatigue, headache, or complaints of pain. Patients may not be aware of their depression and are often heavy users of medical care. Such symptoms may be the presenting features of a masked, or hidden, depression. Clues suggesting mood disturbance include the recent onset of a set of unusual behaviors, trouble at work or job loss, marital difficulties, and self-destructive behavior (e.g., substance abuse, sexual promiscuity).

Special Considerations

Children and Adolescents. Criteria for depression in children and adolescents are the same as for depression in adults. Depression in these age groups can, however, present differently from that in adults and is often misunderstood, masked in its presentation, or simply overlooked. Adequate treatment maximizes the child's potential and minimizes the serious negative impact that depression can have on multiple spheres of development.

Prepubertal children are more likely to have somatic complaints, psychomotor agitation, and mood-congruent hallucinations and less likely to have disturbances in sleep and appetite. Some children are misdiagnosed as having attention deficit disorder, especially if symptoms involve poor concentration, listlessness, agitation, and withdrawal from daily activities.[36]

Adolescents with depression may show increased oppositional behavior and substance abuse and tend to describe more irritability than depressed mood. Other characteristics are social withdrawal, increased rejection sensitivity, and decline in school performance. Some adolescents may be first diagnosed only with depression on receiving treatment for drug and alcohol problems.[36]

The selective serotonin reuptake inhibitors sertraline, fluoxetine, and citalopram are all effective in treating depression in this population. There is some evidence that treatment of adolescents and young adults may lead to increased suicidal ideation, and this has resulted in a Food and Drug Administration (FDA) "black box" warning. It is important that these patients be treated for depression but that the patients be monitored closely for suicidal thoughts, especially shortly after treatment with a selective serotonin reuptake inhibitor has started.[36]

www.ketabpezeshki.com 66485457-66963820

Geriatric. Age is not itself a risk factor for depression. However, depression is more common in older adults because of more frequent occurrences of loss and grief, comorbid health issues, and loss of autonomy. The elderly may have a tendency to report more somatic complaints than younger adults with depression do. They are also more vulnerable to development of melancholic depression, which is characterized by early morning awakening, diurnal variation in mood, low self-esteem, and low mood reactivity.[37]

Older depressed patients can also present with symptoms involving memory loss, inattention, withdrawal from daily activities, confusion, and lapses in personal and social hygiene that suggest dementia rather than depression. When such symptoms are from depression, the condition is called pseudodementia. Serious depression in elders is a highly treatable, reversible condition. It is essential to distinguish it from dementia for further diagnostic and therapeutic follow-up.

Other Depressive Disorders

Seasonal Affective Disorder. Seasonal affective disorder is not a separate mood disorder but a subclassification of major depressive disorder that is diagnosed when major depression occurs during seasons with less daylight (fall and winter), then either resolves or occasionally changes to manic episodes in seasons with more daylight, for at least 2 consecutive years. Melatonin, a hormone secreted in the brain and produced at high levels in the dark, has been implicated in the etiology of this disorder. Symptoms generally include hypersomnia, anergia, weight gain, and craving for carbohydrates. Phototherapy is an effective and safe treatment of seasonal depression.[38] Light exposure to the eyes seems to be essential, but the exact mechanism of action is still unknown.

Postpartum Depression. Symptoms of depression are common in the postnatal period. Up to 65% of mothers report some depressed mood after childbirth, often called postpartum blues. Symptoms are generally mild and transient, although in 10% of mothers, it may lead to a full-fledged episode of major depression. The signs and symptoms of postpartum depression are similar to those of a major depressive disorder, but the onset is within 4 weeks of delivery.[39]

Postpartum depression is more common in those who have a history of mood disorder, experience marital conflict, and have limited assistance with infant care.

Dysthymic Disorder. Dysthymic disorder is a long-standing, fluctuating, low-grade depression. Some features of a major depressive episode may be present, but marked changes in appetite or psychomotor disturbances are not typically observed. Depressed mood typically begins early in life, and the individual may report having always been depressed. Affected individuals generally are able to carry out their work assignments, but they gain little pleasure from the leisure activities others find enjoyable, such as recreation, time with family, or sexual activity. They typically experience significant impairment in interpersonal functioning.

Bipolar Disorders

Bipolar disorder is lifelong, with episodic exacerbation of symptoms and deterioration of function characterized by extreme mood episodes. Patients with bipolar disorder may require different forms and intensities of treatment at different stages of the illness. Bipolar I disorder includes at least one manic episode, and patients have typically had one or more major depressive episodes. Bipolar II disorder involves a hypomanic episode and at least one major depressive episode. A hypomanic episode includes the features of a manic episode without psychosis, marked impairment of function, or the need for hospitalization.

Box 111-3 Summary of DSM-IV-TR Criteria for a Manic Episode

A. Distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 2 weeks (or any duration if hospitalization is necessary).
B. During the period of mood disturbance, three or more of the following symptoms have persisted (four, if the mood is only irritable) and have been present to a significant degree:
  1. Inflated self-esteem or grandiosity
  2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
  3. More talkative than usual or pressure to keep talking
  4. Flight of ideas or subjective experience that thoughts are racing
  5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
  6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
  7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., buying sprees, sexual indiscretions, foolish investments)
C. Symptoms do not meet criteria for a "mixed episode."
D. Mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or social activities or to necessitate hospitalization to prevent harm to self or others, or psychotic features are present.
E. Symptoms are not caused by direct physiologic effects of a substance (e.g., drug of abuse, medication) or a general medical condition (e.g., hyperthyroidism).

Modified from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text rev. Washington, DC, American Psychiatric Association, 2000.

Manic Episode

During a manic episode (Box 111-3), the disturbance in mood must be severe enough to include psychosis, the need for hospitalization, or marked impairment in functioning. Bipolar disorders are much less common than major depressive disorder. The overall prevalence of a manic episode is 1.6% in both women and men.[40]

In many cases, manic patients are brought to the ED by someone else (e.g., family, police, emergency medical services). Patients who are experiencing a manic episode may present as gregarious, humorous, and engaging, which may suddenly alternate with belligerence and irritability. Patients may display pressured speech, in which they keep talking, often rapidly and loudly without pauses between thoughts or sentences, and are difficult to interrupt. The thought process in mania is characterized by illogical associations and flight of ideas. An inflated self-esteem and grandiose delusions may lead them to also be argumentative, impatient, and condescending. Grandiosity often centers on very broad dramatic or universal themes, such as religion or politics. The patient may describe a massive undertaking, such as "uniting the world's churches" or "solving world poverty." These severe symptoms are usually accompanied by a profound lack of insight. Despite obvious altered behavior, impaired judgment, and poor impulse control, the patient may insist that there is nothing wrong or blame problems on others.

Manic patients have decreased or no need for sleep and typically report being awake for days. They may be involved in a massive project (e.g., writing a novel), may completely disregard consequences of actions, may have difficulty with spending (e.g., credit cards revoked), and may engage in risky behavior (e.g., sexual liaisons with strangers, risky driving). Whenever possible, a corroborating history should also be obtained from family or others who know of the patient's behavior.

www.ketabpezeshki.com 66485457-66963820

Manic patients may present to the ED as trauma patients, injured by an action reflecting the patient's grandiosity (e.g., attempting to fly), impulsivity, or belligerence (e.g., fighting, resisting arrest). A manic episode may be punctuated by abrupt periods of tearfulness and profound depression, including suicidal ideation. When depressive and manic features occur concurrently in such a manner, the disorder is termed mixed or bipolar, mixed phase.

Cyclothymic Disorder

Cyclothymic disorder is characterized by a life of mood swings of insufficient severity to meet criteria for a bipolar disorder. Persons with this disorder may have a chaotic life, characterized by frequent subclinical mood episodes, unstable relationships, and uneven school or work performance.

Mood Disorders Caused by a General Medical Condition

Certain medical illnesses have a well-known association with mood disorder (Box 111-4). In Parkinson's disease, electrical stimulation to a certain area of the substantia nigra alleviates symptoms of depression. Stimulation of an area only 2 mm away can cause acute reversible symptoms of depression, such as crying, not wanting to live, and hopelessness.[41] Parkinson's disease has a well-known association with depression, with up to 40% of patients demonstrating major depression.[42]

Certain malignant neoplasms have a well-known association with depression, including pancreatic carcinoma, brain neoplasm, and disseminated malignant disease (e.g., lymphoma).[43] Coronary artery disease,[44] myocardial infarction, stroke, end-stage renal disease, acquired immunodeficiency syndrome, several endocrine diseases, and connective tissue disease are also associated with major depressive disorder.[45] After a myocardial infarction, patients with depression experience a 3.5-fold increase in cardiovascular mortality compared with nondepressed patients.[46] The development of stroke, diabetes, and osteoporosis appears to be more likely in patients with depression than in those who are not depressed.[47,48]

Depression related to medical conditions may be different in some respects from primary depression and responds less favorably than primary depression to antidepressant medication.[49] Two significant issues arise in the assessment of patients with depression who have a serious medical illness. First, symptoms of depression must be distinguished from the symptoms and signs associated with serious medical illness (e.g., weight loss, loss of energy, slowing of activity, sleep disturbance, loss of ability to concentrate). Some experts have proposed that alternative criteria for depression caused by a general medical condition be substituted for DSM-IV-TR neurovegetative symptoms in patients with serious medical illness, such as depressed appearance, social withdrawal, pessimism or self-pity, anhedonia, and nonreactive mood. Second, it is important to determine if mood changes associated with terminal, rapidly progressive, or painful illness should be considered appropriate adjustment and grief. Although patients with such diseases may understandably be sad, most do not have major depression. The treatment of major depression in such patients should be considered and can greatly improve their quality of life.

Mood Disorders Caused by Medications or Other Substances

Certain medications are associated with symptoms of mood disorders (Box 111-5). Intoxication with or chronic heavy use of

Box 111-4 Medical Illnesses Associated with Onset of Depression

Neurologic
Parkinson's disease
Stroke
Multiple sclerosis
Head trauma
Sleep apnea

Neoplastic
Pancreatic carcinoma
Brain tumor
Disseminated carcinomatosis

Endocrine
Hypothyroidism
Hyperthyroidism
Cushing's disease
Addison's disease
Diabetes mellitus

Infectious
Human immunodeficiency virus infection

Cardiac
Coronary artery disease
Myocardial infarction

Renal
End-stage renal disease
Renal dialysis

Connective Tissue
Lupus erythematosus
Rheumatoid arthritis

Box 111-5 Medications That Can Cause Depressive or Manic Symptoms

Depressive Symptoms

Antihypertensives
Beta-blockers
Captopril
Clonidine
Diltiazem
Enalapril
Nifedipine
Prazosin
Thiazide diuretics

Anticonvulsants
Phenytoin
Topiramate
Valproic acid

Hormones
Anabolic steroids
Contraceptives
Corticosteroids
Thyroid hormone

Sedative-Hypnotics
Barbiturates
Benzodiazepines

Antibiotics
Acyclovir
Chloroquine
Interferon
Isoniazid
Norfloxacin
Ofloxacin
Sulfonamides

Other Agents
Amantadine
Bromocriptine
Cyclobenzaprine
Cycloserine
Digitalis
Disopyramide
Levodopa
Metoclopramide
Nonsteroidal anti-inflammatory drugs
Phenylpropanolamine
Theophylline

Manic Symptoms

Psychiatric Agents
Antidepressants

www.ketabpezeshki.com 66485457-66963820

alcohol, sedatives, hypnotics, anxiolytics, narcotics, and other depressants can cause symptoms of a major depressive episode. Stimulants such as cocaine, phencyclidine, hallucinogens, and amphetamines can cause symptoms of a manic episode. Mood disorder symptoms can also develop during withdrawal. To qualify for this diagnosis, the symptoms must not occur exclusively during a course of delirium, must cause significant distress or impairment of functioning, and must develop within a month of either substance intoxication or withdrawal.

When the mood disorder predates the period of substance abuse or lasts longer than 1 month after the period of abuse, the diagnosis may be an underlying mood disorder, such as a major depressive disorder or bipolar disorder, with a comorbid substance abuse or dependence diagnosis.

Substance abuse is often seen in patients with underlying depressive or bipolar conditions.

DIAGNOSTIC STRATEGIES

The initial history and physical examination should focus on the presenting complaints and evaluate the possibility that drug abuse, medications, or a general medical condition may be responsible for the patient's condition. The diagnosis of a mood disorder is based on history and observation of the patient's ability to relate to family and medical staff and style in relating to them. The patient's body language may be helpful. Precipitating events (e.g., loss of job or relationship), accompanying symptoms (e.g., hallucinations, delusions, anxiety disorder, mania), and suicidal ideation or intent should be assessed. The patient's history should be confirmed through interviews with family, friends, or eyewitnesses to the events that precipitated the ED visit. A tentative diagnosis can be established by use of DSM-IV-TR criteria. Laboratory tests to investigate medical conditions may be necessary (see Box 111-4), but no tests can confirm or exclude mood disorders.

DIFFERENTIAL CONSIDERATIONS

Medical disorders, medications, and substance abuse or withdrawal can either cause or mimic mood disorders. The patient who presents with agitation, for example, might have hypoxia, cocaine intoxication, or alcohol-sedative withdrawal. The patient with symptoms and signs of depression may have an unrecognized malignant neoplasm or sedative intoxication.

Patients taking antidepressant medication are often not being treated for depression as antidepressant medications are used to treat a variety of disorders: anxiety, obsessive-compulsive disorder, post-traumatic stress disorder, pain syndromes, smoking cessation, and vasodepressor syncope.

Grief and bereavement are normal human reactions to the acute loss of another person, health, social position, or job. The period of mourning is characterized by sadness, diminished sense of well-being (somatic complaints), sleeplessness, and sadness triggered by thoughts of the loss. Normal grief, however, does not include guilt, loss of self-esteem, feelings of worthlessness, suicidal intent, psychomotor retardation, or occupational dysfunction.

Adjustment disorders are behavioral or emotional disorders that occur in response to an identifiable stress or stressors. The emotional component can involve sadness, low self-esteem, suicidal behavior, hopelessness, helplessness, or other self-threatening behavior. Acute adjustment disorder occurs within 3 months of the stressor and does not last longer than 6 months. The stressors are typically not as severe as those precipitating bereavement reaction, and the responses are often more maladaptive. The teenager who ends a romantic relationship, for instance, may attempt a drug overdose in response to the stress. In such cases, adjustment disorder is a more likely diagnosis than major depressive episode. The pattern of recurrent maladaptive behavioral responses to stress may be lifelong, but the acute episode should resolve within 6 months.

Borderline personality disorder is characterized by unstable personal relationships, unstable self-image, and self-destructive behaviors. The disorder may include chronic feelings of emptiness, which may be misdiagnosed as depression, or lability of mood, which may be mistaken for mania or hypomania. These patients typically live lives of crisis and constant conflict.

Dementia can be confused with depression but is characterized by abnormal mental status, including abnormalities in tests of memory, calculation, and judgment. Delirium with waxing and waning sensorium, hallucinations, and delusions may involve disorganization, agitation, and restlessness, which might be considered features of mania or agitated depression.

Differential considerations for manic symptoms include the manic phase of bipolar disorder, stimulant abuse (e.g., cocaine, amphetamines), hallucinogen abuse, alcohol or sedative withdrawal, delirium, hyperthyroidism, other medical conditions causing agitation, brief reactive psychosis, schizoaffective disorder, and schizophrenia.

MANAGEMENT

Emergency Department Stabilization

The creation of a safe and stable environment for the patient should be the first priority in management. The patient with an acute manic episode may be disruptive, refuse medical evaluation, and make repeated attempts to leave the ED. The initial step in treating such a disruptive patient is to offer assistance in reducing the agitation (placing the patient in a single room, recommending medication). If this approach does not work, the patient may need to be placed in seclusion or restraints for his or her safety and that of others.

Initiation of treatment for a mood disorder is not typically done in the ED. An exception is the acute manic episode (or possibly a severe depressive episode with psychosis) with behavior so extreme that the patient or others are threatened. Such cases may involve significant hallucinations, delusions, and other features of psychoses. In such cases, intramuscular or oral administration of haloperidol with or without lorazepam can calm such patients. A typical regimen for "rapid tranquilization" is an initial dose of 5 mg haloperidol with 2 mg lorazepam intramuscularly and reassessment in 30 to 45 minutes for resolution of "target" symptoms such as agitation. A second dose is administered after 30 to 60 minutes as needed for improvement in hallucinations, delusions, agitation, or violent behavior.[50] Most patients respond after one or two doses. Benztropine (Cogentin), 1 to 2 mg, is often given initially to prevent extrapyramidal symptoms. Despite a black box FDA warning about prolongation of QT intervals and torsades de pointes, droperidol (2.5-5 mg) is a popular antipsychotic drug used effectively for agitation.[50]

The "atypical" antipsychotic medicines, including ziprasidone, risperidone, olanzapine, aripiprazole, and quetiapine, cause fewer of the side effects associated with conventional antipsychotic agents, such as acute dystonia, other extrapyramidal symptoms, and sedation. Oral doses should be offered first, and several agents, including risperidone, olanzapine, and aripiprazole, are available in rapidly dissolving tablet form. Three are available as an intramuscular injection: ziprasidone (Geodon), olanzapine (Zyprexa), and aripiprazole (Abilify). Ziprasidone 10 to 20 mg is effective; however, its use is limited to 40 mg per 24 hours. Olanzapine 2.5 to 10 mg effective but is associated with postural hypotension, and it is not recommended in combination with benzodiazepines because of the risk of hypoventilation. Aripiprazole is the newest agent and at doses of 9.75 to 15 mg seems to be the least sedating of the atypicals, but it is more likely to cause nausea and

www.ketabpezeshki.com 66485457-66963820

Box 111-6 Criteria for Hospitalization of Emergency Department Patient with Acute Psychiatric Episode

Patient demonstrates risk of suicide or homicide or of significant harm to self or others.
Patient lacks the capacity to cooperate with treatment.
Patient has inadequate psychosocial support for safe outpatient treatment and compliance.
Patient has a comorbid condition or complication that makes outpatient treatment unsafe (e.g., acute psychosis, bizarre behavior, need for detoxification).

vomiting.[51-56] Immediate psychiatric consultation should begin during the initiation of rapid tranquilization because patients undergoing rapid tranquilization will generally require hospitalization (Box 111-6).

Long-Term Treatment

Depression

Effective treatment modalities for depression are grouped into three broad categories: antidepressant medication, psychotherapy, and electroconvulsive therapy (ECT).

Antidepressant Therapy

Many effective antidepressants are available for first-episode uncomplicated major depression. After 4 to 6 weeks of therapy, the response rate is usually 60% or greater for all agents. However, 10 to 15% of patients quit medication trials,[57] and many patients in general medical practice are inadequately treated.[46]

Coexistent medical illness, psychotic or bipolar symptoms, substance use, and recurrent or refractory depressive symptoms should be considered in the choice of a medication for treatment of depression. The side effects of tricyclic antidepressants and monoamine oxidase inhibitors, along with strict dietary limitations, have led to the use of selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors for first-line treatment of depression. Side effects of these agents may include dizziness, sedation, peripheral anticholinergic symptoms, weight gain, sexual dysfunction, neurologic symptoms, insomnia, and anxiety. Another antidepressant, lithium, ECT, thyroid hormone, or atypical antipsychotic medication may be an adjunct in patients with treatment-resistant depression.

Psychotherapy

Brief psychotherapy is often initially used in patients with major depression. Interpersonal psychotherapy, psychodynamic psychotherapy, and group or family therapy can be used with some patients. Psychosocial therapeutic support typically includes community-based support groups that focus on specific individual, occupational, or family and marital issues that arise in depression and are amenable to group and supportive intervention.

Depressed patients benefit most from a combination of somatic therapy (medication or ECT) and psychotherapy. All patients with incomplete therapeutic response, recurrent depression, or comorbid conditions (e.g., anxiety or panic, substance abuse) should receive multimodal treatment.[58]

Electroconvulsive Therapy

ECT has a high therapeutic success rate and an excellent safety profile but is not a first-line treatment, in part because of an undeserved reputation among laypersons that ECT causes “permanent brain damage.” Indications for ECT include severe depression with malnutrition, severe psychosis with agitation, continuing significant suicide risk with ongoing suicidal behaviors, prolonged catatonia, and recurrent depression with a previously positive response to ECT. ECT is most often used as a second-line treatment of patients with moderate to severe depression who have not responded to trials of medication or who cannot tolerate the medication because of side effects or concurrent medical conditions.

KEY CONCEPTS

- Patients with apparent mood disorders should be evaluated for a medical disorder, medication effect, or drug use that can mimic both depression and mania.
- Mood disorders should be suspected in patients with multiple, vague, nonspecific complaints and in patients who are frequent, heavy users of medical care.
- The differentiation of depression and dementia in elders can be difficult but is important because depression often responds dramatically to treatment.
- Patients with mood disorders should be assessed for their potential for violence or self-harm before discharge.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Boudreaux ED, Clark S, Camargo CA Jr: Mood disorder screening among adult emergency department patients: A multicenter study of prevalence, associations and interest in treatment. *Gen Hosp Psychiatry* 2008; 30:4-13.
2. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed, text rev. Washington, DC: The American Psychiatric Association; 2000.
3. Kessler RC, et al: Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; 62:593-602.
4. Larkin GL, et al: Mental health and emergency medicine: A research agenda. *Acad Emerg Med* 2009; 16:1110-1119.
5. Chang G, et al: Hospital variability in emergency department length of stay for adult patients receiving psychiatric consultation: A prospective study. *Ann Emerg Med* 2011; 58:127-136.e1.
6. Hazlett SB, McCarthy ML, Londner MS, Onyike CU: Epidemiology of adult psychiatric visits to US emergency departments. *Acad Emerg Med* 2004; 11:193-195.
7. *The World Health Report 2002: Reviewing the Risks, Promoting Healthy Life*. Geneva, Switzerland: World Health Organization; 2002.
8. Hasin DS, Goodwin RD, Stinson FS, Grant BF: Epidemiology of major depressive disorder: Results from the National Epidemiologic Survey on Alcoholism and Related Conditions. *Arch Gen Psychiatry* 2005; 62:1097-1106.
9. Valtonen H, et al: Suicidal ideation and attempts in bipolar I and II disorders. *J Clin Psychiatry* 2005; 66:1456-1462.
10. Valtonen HM, et al: Suicidal behaviour during different phases of bipolar disorder. *J Affect Disord* 2007; 97:101-107.
11. Merikangas KR, et al: Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry* 2007; 64:543-552.
12. Frye MA: Clinical practice. Bipolar disorder—a focus on depression. *N Engl J Med* 2011; 364:51-59.
13. Meyer JH, et al: Elevated monoamine oxidase a levels in the brain: An explanation for the monoamine imbalance of major depression. *Arch Gen Psychiatry* 2006; 63:1209-1216.
14. Ruhe HG, Mason NS, Schene AH: Mood is indirectly related to serotonin, norepinephrine and dopamine levels in humans: A meta-analysis of monoamine depletion studies. *Mol Psychiatry* 2007; 12:331-359.
15. Belmaker RH, Agam G: Major depressive disorder. *N Engl J Med* 2008; 358:55-68.
16. Hasler G, et al: Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. *Arch Gen Psychiatry* 2007; 64:193-200.
17. Zarate CA Jr, et al: A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 2006; 63:856-864.
18. Savitz JB, Drevets WC: *Brain circuits in major depressive disorder and bipolar disorder*. In: Sadock BJ, Sadock VA, Ruiz P, eds: *Kaplan and Sadock's Comprehensive Textbook of Psychiatry*, vol 1, 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:1675-1685.
19. Kundermann B, Hemmeter-Spernal J, Huber MT, Krieg JC, Lautenbacher S: Effects of total sleep deprivation in major depression: Overnight improvement of mood is accompanied by increased pain sensitivity and augmented pain complaints. *Psychosom Med* 2008; 70:92-101.
20. Even C, Schroder CM, Friedman S, Rouillon F: Efficacy of light therapy in nonseasonal depression: A systematic review. *J Affect Disord* 2008; 108:11-23.
21. Srinivasan V, et al: Pathophysiology of depression: Role of sleep and the melatonergic system. *Psychiatry Res* 2009; 165:201-214.
22. Mahon K, Burdick KE, Szeszko PR: A role for white matter abnormalities in the pathophysiology of bipolar disorder. *Neurosci Biobehav Rev* 2010; 34:533-554.
23. Thase ME: *Mood disorders: Neurobiology*. In: Sadock BJ, Sadock VA, Ruiz P, eds: *Kaplan and Sadock's Comprehensive Textbook of Psychiatry*, 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:1664-1674.
24. Carroll BJ, et al: Pathophysiology of hypercortisolism in depression. *Acta Psychiatr Scand Suppl* 2007; 433:90-103.
25. Nemeroff CB: Recent findings in the pathophysiology of depression. *Focus* 2008; 6:3-14.
26. Copolov DL, et al: Specificity of the salivary cortisol dexamethasone suppression test across psychiatric diagnoses. *Biol Psychiatry* 1989; 25:879-893.
27. Joska JA, Stein DJ: *Mood disorders*. In: Hales RE, Yudofsky SC, Gabbard GO, eds. *The American Psychiatric Publishing Textbook of Psychiatry*, 5th ed. Washington, DC: American Psychiatric Publishing; 2008:457-503.
28. Kendler KS, Gatz M, Gardner CO, Pedersen NL: A Swedish national twin study of lifetime major depression. *Am J Psychiatry* 2006; 163:109-114.
29. Barnett JH, Smoller JW: The genetics of bipolar disorder. *Neuroscience* 2009; 164:331-343.
30. *Mental Health: A Report of the Surgeon General, 1999*. Available at www.surgeongeneral.gov/library/mentalhealth/home.html. Accessed April 25, 2011.
31. Pittenger C, Duman RS: Stress, depression, and neuroplasticity: A convergence of mechanisms. *Neuropsychopharmacology* 2008; 33:88-109.
32. *Mood disorders*. In: Sadock BJ, Sadock VA, eds: *Kaplan and Sadock's Synopsis of Psychiatry*, 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2008:527-562.
33. Suomi SJ: Early stress and adult emotional reactivity in rhesus monkeys. *Ciba Found Symp* 1991; 156:171-183; discussion 183-178.
34. Akiskal HS: *Mood disorders: Clinical features*. In: Sadock BJ, Sadock VA, Ruiz P, eds: *Kaplan and Sadock's Comprehensive Textbook of Psychiatry*, 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:1679.
35. Pearn J, Gardner-Thorpe C: Jules Cotard (1840-1889): His life and the unique syndrome which bears his name. *Neurology* 2002; 58:1400-1403.
36. *Mood disorders and suicide in children and adolescents*. In: Sadock BJ, Sadock VA, eds: *Kaplan and Sadock's Synopsis of Psychiatry*, 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2008:1258-1269.
37. *Geriatric psychiatry*. In: Sadock BJ, Sadock VA, eds: *Kaplan and Sadock's Synopsis of Psychiatry*, 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2008:1348-1358.
38. Lam RW, Tam EM, Shiah IS, Yatham LN, Zis AP: Effects of light therapy on suicidal ideation in patients with winter depression. *J Clin Psychiatry* 2000; 61:30-32.
39. Kornstein SG, Sloan DME: *Depression and gender*. In: Stein DJ, Kupfer DJ, Shatzberg AF, eds: *Textbook of Mood Disorders*. Washington, DC: American Psychiatric Publishing; 2006:687.
40. Hendrick V, Altshuler LL, Gitlin MJ, Delrahim S, Hammen C: Gender and bipolar illness. *J Clin Psychiatry* 2000; 61:393-396; quiz 397.
41. Bejjani BP, et al: Transient acute depression induced by high-frequency deep-brain stimulation. *N Engl J Med* 1999; 340:1476-1480.
42. Cummings JL: Depression and Parkinson's disease: A review. *Am J Psychiatry* 1992; 149:443-454.
43. McDaniel JS, Musselman DL, Porter MR, Reed DA, Nemeroff CB: Depression in patients with cancer. Diagnosis, biology, and treatment. *Arch Gen Psychiatry* 1995; 52:89-99.
44. Gonzalez MB, et al: Depression in patients with coronary artery disease. *Depression* 1996; 4:57-62.
45. Evans DL, et al: Depression in the medical setting: Biopsychological interactions and treatment considerations. *J Clin Psychiatry* 1999; 60(Suppl 4):40-55; discussion 56.
46. Gilbody S, Whitty P, Grimshaw J, Thomas R: Educational and organizational interventions to improve the management of depression in primary care: A systematic review. *JAMA* 2003; 289:3145-3151.
47. Pignone MP, et al: Screening for depression in adults: A summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002; 136:765-776.
48. Insel TR, Charney DS: Research on major depression: Strategies and priorities. *JAMA* 2003; 289:3167-3168.
49. Popin MK: *Consultation-liaison psychiatry*. In: Jacobson JL, Jacobson AM, eds. *Psychiatric Secrets*, 2nd ed. Philadelphia: Hanley & Belfus; 2004:381.
50. Nockwitz R, Rund DA. *Psychotropic medications*. In: Tintinalli JE, ed: *Emergency Medicine: A Comprehensive Study Guide*, 6th ed. Columbus, OH: McGraw-Hill; 2003:1918.
51. Daniel DG, Potkin SG, Reeves KR, Swift RH, Harrigan EP: Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: A double-blind, randomized trial. *Psychopharmacology (Berl)* 2001; 155:128-134.
52. Brook S, Lucey JV, Gunn KP: Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. Ziprasidone I.M. Study Group. *J Clin Psychiatry* 2000; 61:933-941.
53. Allen MH, Currier GW, Hughes DH, Reyes-Harde M, Docherty JP: The Expert Consensus Guideline Series. Treatment of behavioral emergencies. *Postgrad Med* 2001; Spec No:1-88; quiz 89-90.
54. Currier GW, Simpson GM: Risperidone liquid concentrate and oral lorazepam versus intramuscular haloperidol and intramuscular lorazepam for treatment of psychotic agitation. *J Clin Psychiatry* 2001; 62:153-157.

www.ketabpezeshki.com 66485457-66963820

55. Citrome L: Atypical antipsychotics for acute agitation. New intramuscular options offer advantages. *Postgrad Med* 2002; 112:85-88, 94-86.
56. Battaglia J, Lindborg SR, Alaka K, Meehan K, Wright P: Calming versus sedative effects of intramuscular olanzapine in agitated patients. *Am J Emerg Med* 2003; 21:192-198.
57. McIntyre JS: *Practice Guideline for Major Depressive Disorder in Adults*. 2nd ed. Washington, DC: The American Psychiatric Association; 2000.
58. Scott J: Treatment of chronic depression. *N Engl J Med* 2000; 342:1518-1520.

www.ketabpezeshki.com 66485457-66963820

Chapter 112

Anxiety Disorders

Rick McPheeters and Joshua L. Tobias

PERSPECTIVE

Acute anxiety and apprehension are common in emergency department (ED) patients. However, many medical conditions mimic anxiety disorders, and up to 42% of patients initially thought to have anxiety disorders are later found to have organic disease. Therefore, emergency physicians should thoroughly assess the anxious patient to identify and distinguish any underlying medical conditions and then appropriately treat that which is determined.[1]

Anxiety is a specific unpleasurable state of tension that forewarns the presence of danger, real or imagined, known or unrecognized, and is often verbalized as an intense feeling of worry. Vigilance is a positive consequence of anxiety that helps people to be alert to imminent danger. This awareness produces a greater ability to experience and manage extreme agitation.[1]

Up to a point, anxiety can improve performance with well-described adrenergic responses to stress that contribute to survival. However, when these responses go beyond a manageable point, further increases in anxiety add to the stress of the patient and lead to deterioration of performance and nonadaptive responses, resulting in pathologic anxiety (anxiety disorder). For instance, the threshold for pain may decrease, or the person may become more aware of body discomfort, with respiratory, cardiovascular, gastrointestinal, genitourinary, and neuromuscular complaints becoming prominent.[1]

The emergency physician should be able to distinguish between the anxiety and the illness and, if necessary, treat both entities. Because an anxiety state makes significant metabolic demands that can actually cause a marginally compensated organ system to fail, one should not assume anxiety to be purely functional; physical discomfort and illness often trigger an anxiety attack.

EPIDEMIOLOGY

Approximately 40 million Americans older than 18 years, nearly 20% of adults, are affected by anxiety disorders each year.[2] Anxiety disorders are among the most prevalent psychiatric disorders and are the most common psychiatric problems seen by primary care physicians, with 20% of these patients experiencing a type of anxiety disorder.[3] Many primary care patients have significant mood and anxiety symptoms, such as panic disorders, generalized anxiety disorders, and depression, but nearly half of these symptomatic patients never receive appropriate treatment.[4] Many patients would rather present with a physical complaint and try to disguise their anxiety than bear the perceived stigma associated with psychiatric complaints.[5] Patients with chronic illness and those who make frequent medical visits have higher rates of anxiety and depression. The prevalence of anxiety disorders surpasses that of any other mental health disorder, including substance abuse. There is a close relationship between alcohol abuse and anxiety disorders; those with anxiety disorders often turn to alcohol and substance abuse as a form of self-medication, and the substance abuser frequently has underlying anxiety in relation to the use of alcohol and drugs.[6]

PRINCIPLES OF DISEASE

The precise mechanisms underlying the development of anxiety have not been fully established. Noradrenergic, serotonergic, and other neurotransmitter systems all play a role in the body's response to stress. The serotonin system and the noradrenergic systems are common pathways implicated in anxiety. It is believed that low serotonin system activity and elevated noradrenergic system activity are involved, and thus selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have become a focus of treatment. The well-established effectiveness of benzodiazepines in the treatment of anxiety has led to the study of the γ-aminobutyric acid (GABA) system and its relationship to anxiety. GABA is the principal inhibitory neurotransmitter in the central nervous system, and benzodiazepines act on the $GABA_A$ receptors. Studies have focused on the role that corticosteroids may play in fear and anxiety. Steroids are thought to induce chemical changes in select neurons that strengthen or weaken certain neural pathways to affect behavior under stress.[7]

Anxiety reactions are also associated with aberrant metabolic changes induced by lactate infusion and hypersensitivity of the brainstem to carbon dioxide receptors. Studies focus on the regulatory centers found in the cerebral hemispheres. The hippocampus and the amygdala regulate emotion and memory and are important areas mediating an individual's response to fear.[8] Family research suggests genetic factors in anxiety, but the precise nature of the inherited vulnerability is unknown. Psychological and environmental factors, as outlined in psychodynamic, behavioral, and cognitive theories, also contribute in the generation of anxiety in biologically predisposed individuals.[8]

CLINICAL FEATURES

Many patients entering the ED experience anxiety, and for some this can be a significant clinical issue. The ED patient encounters many internal and external dangers: assaults on body integrity in the form of uncomfortable procedures and forced intimacy with strangers; the atmosphere of illness, pain, and death; and separation from loved ones and unfamiliar surroundings. In addition,

www.ketabpezeshki.com 66485457-66963820

Box 112-1 Somatic Symptoms of Anxiety

Respiratory
Hyperventilation
Sense of dyspnea

Cardiovascular
Palpitations
Chest discomfort
Awareness of missed beats

Gastrointestinal
Dry mouth
Difficulty in swallowing
Epigastric discomfort
Excessive flatulence
Frequent or loose stools

Genitourinary
Frequent or urgent micturition
Failure of erection
Amenorrhea
Menstrual discomfort

Neuromuscular
Tremor
Aching muscles
Prickling sensations
Headache
Dizziness, tinnitus

the patient may experience uncertainty about his or her illness, the implications that the illness may have on personal relationships and employment, and the financial burden that may accompany the illness.

The anxious patient can be a diagnostic challenge. Anxiety may represent the patient's reaction to medical illness or the medical setting, or it may be a manifestation of the physical disorder itself. The anxiety may also be an expression of an underlying psychiatric disorder. It may be difficult to make the distinction between anxiety as a symptom and anxiety as a syndrome in the ED. There is an overlap between normal situational anxiety and fear, anxiety-like symptoms resulting from a variety of organic disease states and their treatments, and the characteristic presentation of anxiety itself.

The physical symptoms of autonomic arousal (e.g., tachypnea, tachycardia, diaphoresis, lightheadedness) may be the only manifestation of anxiety (Box 112-1). Patients may complain only of overall poor health or vague subjective findings when they visit the physician. Classic panic disorder symptoms of chest pain, shortness of breath, and the sense of impending doom will often lead the patient to the ED, especially if it is the very first episode.[7] Anxiety associated with organic causes is more likely to be manifested with physical symptoms and less likely to be associated with avoidance behavior.[9]

DIFFERENTIAL CONSIDERATIONS

Medical Illness Presenting as Anxiety

Patients with anxiety disorders may present with apparent physical disease, and many physical diseases may be strongly associated with symptoms of anxiety. Somatic symptoms can be so prominent that they occupy most of the patient's attention, making it difficult to differentiate between a primary anxiety disorder and reactive anxiety to a situation or disease. Several factors help distinguish an organic anxiety syndrome from a primary anxiety disorder[10] (Box 112-2). Anxiety disorder classifications, in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV), include anxiety caused by a general medical condition[11] (Box 112-3).

Anxious patients are frequently convinced that their problem is purely physical. The emergency physician should realize that the patient with anxiety is not in control of the symptoms and frequently cannot immediately identify the correct precipitant. Even though the patient may be uncomfortable, uncooperative, impatient, and unreasonable, triage medical personnel should recognize that the patient believes an illness truly exists and is not being consciously manipulative. Because anxiety may be the most obvious symptom of an underlying disease or condition, the patient should be evaluated for exacerbation of known preexisting disease as well as for onset of new illness since anxiety increases the risk of acute medical exacerbation of chronic illness.[12]

The classic scenarios of pulmonary embolism and hyperthyroidism causing anxiety are well documented. Cardiac disease studies indicate poorer outcomes in post–myocardial infarction patients with anxiety than in those without documented anxiety.

Box 112-2 Predictors of Organic Anxiety Syndrome

1. Onset of anxiety symptoms after the age of 35 years
2. Lack of personal or family history of an anxiety disorder
3. Lack of childhood history of significant anxiety, phobias, or separation anxiety
4. Lack of avoidance behavior
5. Absence of significant life events generating or exacerbating the anxiety symptoms
6. Poor response to antipanic agents

Box 112-3 Definitions of Anxiety Disorders

Panic attack is a discrete period in which there is a sudden onset of intense apprehension, fearfulness, or terror, often associated with feelings of impending doom.
Agoraphobia is an anxiety about, or avoidance of, places or situations from which escape might be difficult.
Panic disorder with agoraphobia is characterized by both recurrent, unexpected panic attacks and agoraphobia.
Agoraphobia without a history of panic disorder is characterized by the presence of agoraphobia and panic-like symptoms without a history of unexpected panic attacks.
Specific phobia is characterized by clinically significant anxiety provoked by exposure to a specific feared object or situation, often leading to avoidance behavior.
Social phobia is characterized by clinically significant anxiety provoked by exposure to certain types of social or performance situations, often leading to avoidance behavior. Blushing is the cardinal characteristic symptom.
Obsessive-compulsive disorder is characterized by obsessions that cause marked anxiety or distress and by compulsions that serve to neutralize anxiety.
Post-traumatic stress disorder is characterized by experiencing of an extremely traumatic event, accompanied by symptoms of increased arousal and by avoidance of stimuli associated with trauma.
Acute stress disorder is characterized by symptoms similar to those of post-traumatic stress disorder that occur immediately in the aftermath of an extremely traumatic event.
Generalized anxiety disorder is characterized by at least 6 months of persistent and excessive anxiety and worry.
Anxiety disorder caused by a general medical condition is characterized by prominent symptoms of anxiety that are judged to be a direct physiologic consequence of a general medical condition.
Substance-induced anxiety disorder is characterized by prominent symptoms of anxiety that are judged to be a direct physiologic consequence of a drug of abuse or medication or toxin exposure.
Anxiety disorder not otherwise specified is included for coding (1) disorders with prominent anxiety or phobic avoidance that do not meet criteria for specific anxiety disorders and (2) anxiety symptoms with inadequate or contradictory information.

From American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text rev. Washington, DC, American Psychiatric Association, 2000.

www.ketabpezeshki.com 66485457-66963820

Patients with respiratory diseases, such as asthma and chronic obstructive pulmonary disease, often have anxiety with their long-standing illnesses. In addition, many of the medications used to treat these illnesses may induce anxiety.[5] The most common organic cause of anxiety is alcohol and drug use from either intoxication or, more typically, withdrawal states.

Cardiac Diseases

Various psychiatric conditions may be manifested with complaints of chest pain. Approximately 25% of patients with chest pain who present to the ED have panic disorder. Their disorder often goes undiagnosed, resulting in multiple visits and expensive cardiac evaluations.[13] Some of the symptoms of *myocardial infarction* and *angina pectoris* may include crushing chest pain, shortness of breath, nausea, palpitations, heavy perspiration, and a feeling of impending death. These are also the primary symptoms of acute anxiety, but the pain is usually described as atypical, and patients are generally female and younger.[14] Because of the morbidity and mortality of cardiovascular disease, a patient warrants a full cardiac evaluation when the differentiation between myocardial infarction and acute anxiety is unclear.

Cardiac dysrhythmias can cause palpitations, discomfort, dizziness, respiratory distress, and fainting. An anxious patient with a panic disorder will frequently have similar symptoms. Fortunately, most dysrhythmias can be documented and characterized on cardiac monitors or by electrocardiography. *Mitral valve prolapse* syndrome can be associated with palpitations and panic attacks indistinguishable from a panic disorder. Benzodiazepines can be used to provide symptomatic relief to patients who experience chest pain. Studies have shown that benzodiazepines reduce anxiety, pain, and cardiovascular activation. It is hypothesized that secondary to the reduction in circulating catecholamines, benzodiazepines may cause coronary vasodilation, prevent dysrhythmias, and block platelet aggregation.[15]

Endocrine Diseases

The DSM-IV defines the most common endocrinologic conditions associated with anxiety states as hypoparathyroidism, hyperthyroidism and hypothyroidism, hypoglycemia, pheochromocytoma, and hyperadrenocorticism.[11] Anxiety is the predominant symptom in 20% of patients with *hypoparathyroidism*. Other symptoms include paresthesias, muscle cramps, muscle spasm, and tetany. Most cases are idiopathic or the result of surgical removal of the parathyroid glands during thyroidectomy. Studies indicate a higher incidence of anxiety in the subset of patients with surgically removed glands.[16] The diagnosis of hypoparathyroidism is suggested by a low serum calcium level and a high phosphate level and confirmed by a parathyroid hormone assay.

Anxiety symptoms are seen in up to 40% of diabetics, and 14% of diabetic patients suffer from anxiety disorders. There is evidence that diabetics who are treated with antianxiety medication not only reduce their anxiety but also decrease their glycosylated hemoglobin levels and high-density lipoprotein concentration.[17] Many patients with anxiety, somatoform, or characterologic disorders are convinced that they have *reactive hypoglycemia*. A normal result of a fingerstick blood glucose analysis done during an attack can exclude this diagnosis.

Pheochromocytomas are rare tumors that produce elevated levels of catecholamine in the body. Common symptoms include paroxysmal hypertension, headache, anxiety, sweating, flushing, abdominal and back pain, vomiting, and diarrhea. Pheochromocytoma attacks can be manifested just like panic attacks and can be precipitated by emotional stress. Whereas the sweating associated with pheochromocytoma attacks involves the whole body, the sweating in panic attacks is more likely to be confined to the hands, feet, and forehead. Elevated urinary catecholamine or plasma metanephrine levels can confirm a pheochromocytoma.[18]

Hyperthyroidism is one of the most frequently encountered endocrine diseases associated with anxiety. As with panic disorders, *hyperthyroidism* is associated with acute episodic anxiety. *Thyrotoxicosis* causes anxiety, palpitations, perspiration, hot skin, rapid pulse, active reflexes, diarrhea, weight loss, heat intolerance, proptosis, and lid lag.[19] Psychiatric presentations can be the first sign of *hypothyroidism*, occurring as the initial symptom in 2 to 12% of reported cases along with organic mental deficits. Anxiety and progressive mental slowing associated with diminished recent memory and speech deficits with diminished learning ability are the characteristic initial progression of symptoms. The severity of anxiety disorders in hypothyroid states relates to the rapidity of thyroid hormone level changes more than to the absolute levels. In general, checking of the serum thyroid-stimulating hormone and free thyroxine levels will suffice in the ED to establish the diagnosis of thyroid disease.[20]

Respiratory Diseases

Most conditions causing airway compromise or impairing gas exchange would never be mistaken for a psychiatric disorder. However, in some conditions that cause hypoxemia or hypercarbia, patients may present with significant anxiety, and up to a third of the patients with chronic obstructive pulmonary disease meet the criteria for anxiety disorder.[21]

Asthma is characterized by episodic attacks of dyspnea and often anxiety. Anxiety can also precipitate and prolong asthma attacks. Patients who have severe asthma are twice as likely to have an anxiety disorder and almost five times as likely to have a phobia compared with nonasthmatics. Severe asthmatics are almost five times as likely to have a panic disorder and about four times as likely to have a panic attack. Acute dyspnea from pure panic attack with good air movement and normal lung sounds is easily differentiated from an asthma attack, but studies consistently show that anxiety disorders increase asthma morbidity and mortality.[22]

Shortness of breath is a common complaint in the ED. When it is accompanied by anxiety, panic attacks or anxiety disorders may be high on the differential diagnosis, but so is pulmonary embolism. Acute shortness of breath in any patient should never be dismissed lightly, especially because pulmonary embolus can be manifested with only shortness of breath as the major symptom. The emergency physician can distinguish these patients by paying close attention to history and examination, assessing risk factors for thromboembolic disease, and using basic investigations (e.g., pulse oximetry, electrocardiography, chest radiography, and D-dimer assay) and further tests as indicated.[23]

Neurologic Disorders

Many neurologic conditions are associated with anxiety symptoms.[24-26] *Temporal lobe* seizures, complex partial seizures, tumors, arteriovenous malformation, and ischemia or infarction have been reported with panic attacks. Anxiety often accompanies a *transient ischemic attack* and may be the major symptom on presentation if the episode has resolved by the time the patient reaches the ED. The coexistence of anxiety disorders plays an important role in the prognosis and impairment of patients who have had *cerebral vascular accidents* with neurologic sequelae. Anxiety and depression are associated with left-hemispheric strokes, and anxiety alone is associated with right-hemispheric strokes. Finally, anxiety disorders occur in the aftermath of traumatic brain injury.[27] In *Huntington's disease*, anxiety is the most common prodromal symptom. Anxiety occurs in up to 40% of

www.ketabpezeshki.com 66485457-66963820

patients with *Parkinson's disease* and up to 37% of patients with *multiple sclerosis*. Similarly, anxiety symptoms are common in moderate *Alzheimer's disease*.

Drug Intoxication and Withdrawal States

Amphetamines, cocaine, and *sympathomimetic drugs* are abused for their stimulant and mind-altering properties. Patients often present to the ED agitated, anxious, or aggressive when these drugs are taken in large doses and with prolonged use. *Caffeine* is a common stimulant. Energy drinks and gourmet coffee represent a rapidly growing market in the United States. These drinks are packed with caffeine and the herbal equivalent guarana as well as *Ginkgo biloba*. Studies suggest that 240 to 300 mg of caffeine per day should be the upper limit of healthy consumption. Many energy drinks contain that amount in a single serving.[25] Although lower doses of caffeine can be pleasantly stimulating, higher doses may cause hyperalertness, hypervigilance, motor tension, tremors, gastrointestinal distress, and anxiety. The acute symptoms of caffeine intoxication and generalized anxiety disorder are almost identical. Stimulants such as ephedra and ephedrine-based compounds are found in many dietary supplements and listed by the herbal name of ma huang. Despite the Food and Drug Administration ban on ephedra-containing compounds in 2004, access to these drugs still exists over the Internet.

Many illicit drug users who use *marijuana* believe that the drug reduces their anxiety, but some experience a depersonalization that provokes severe anxiety, fearfulness, and agoraphobic symptoms. Lysergic acid diethylamide (*LSD*), phencyclidine (*PCP*), and *ecstasy* are hallucinogens that can produce anxiety and paranoia from chronic use or "bad trips." Flashbacks affect some users of LSD; the person may experience the symptoms of anxiety and paranoia weeks or months after use.[26]

Sedative-hypnotic drugs (e.g., benzodiazepines, barbiturates) are taken to relieve anxiety or sleeplessness, but their discontinuation can cause sedative withdrawal and rebound anxiety. The severity of the withdrawal syndrome depends on the drug, dosage, duration of use, and speed of elimination. In general, the intermediate-acting sedative-hypnotics (4 to 6 hours) cause the worst withdrawal symptoms. These symptoms include hyperalertness, motor tension, muscle aches, agitation, anxiety, insomnia, hyperactive reflexes, postural hypotension, tremulousness, nausea, vomiting, convulsions, delirium, and even death.

Benzodiazepine withdrawal is rarely fatal but can be very unpleasant. In anxious patients, severe rebound anxiety can occur after a few weeks' use of recommended therapeutic doses. Lorazepam and alprazolam are short-acting agents, and their abrupt discontinuation frequently causes panic attacks within 1 to 2 days. With longer-acting agents, withdrawal symptoms typically peak in about 1 week. Some people may experience this rebound as stimulating. Although antidepressants are rarely abused, their abrupt withdrawal can also cause an abstinence syndrome of insomnia, vivid nightmares, and extreme anxiety.[27]

Alcohol withdrawal, in alcohol-dependent individuals or heavy binge drinkers, can appear 6 to 12 hours after the last drink or significant reduction in consumption of alcohol. Patients often have detectable alcohol still in their systems at this time. Anxiety is one of the first and most prominent symptoms and is seen within 24 to 48 hours of the withdrawal state.[28]

Anxiety in Primary Psychiatric Disorders

Even in patients with known psychiatric illness, a panic disorder is a diagnosis of exclusion because several mental illnesses cause panic attacks as a secondary manifestation. The presence of panic often influences the treatment and outcome of the primary illness. Panic attacks can occur as part of a *bipolar* (*manic-depressive*) *disorder,* in either the manic or the depressed phase. In manic and hypomanic disorders, the patient's predominant affect is usually cheerful and euphoric but may also be dysphoric with irritability and extreme anxiety of panic proportions.[29]

Early in the course of schizophrenia, a patient will often experience panic attacks. Fearfulness, tension, agitation, immobility, disorganized thinking, dilated pupils, extreme insecurity, suspiciousness, and delusions of reference and persecution may characterize schizophrenic panic attacks. The hallucinations often have derogatory accusative content. Social anxiety is a common and disabling condition with schizophrenia that is unrelated to clinical psychotic symptoms.[30]

Patients with *somatoform disorders* report a variety of somatic symptoms, including panic attacks, and 68% report a history of anxiety. Patients claim to have most of the physical symptoms they are asked about, even when evidence excluding illness is presented to the patient. Fear and anxiety initiate, facilitate, and maintain many of the symptoms encountered in the somatoform patient. Patients with "pure" anxiety disorders tend to be hypochondriacal, whereas those with somatization are more likely to improve transiently with active medication or placebo but rarely respond so well that they stop seeking unnecessary medical attention. Patients with panic disorders, however, seek at least as much psychiatric attention as do those with somatoform disorders.[31]

Approximately 50% of patients with a primary panic disorder *major depression* and many others are bothered by some degree of depression in mood. Twenty percent of patients with depression have panic attacks, and the remainder have considerable anxiety. Depression with panic attacks responds less well to treatment. Agitated depression with anxiety and psychosis, sometimes called involutional melancholia, responds well to electroconvulsive therapy. Depression with anxiety and hostility responds well to antidepressants, but benzodiazepines can exacerbate symptoms.[32]

Post-traumatic stress disorder is characterized by the re-experiencing of an extremely traumatic event. The symptoms are closely related to and worsened by reminders of the trauma. The flashbacks, in which patients reexperience the original trauma, can have the same symptoms as panic attacks. These patients often avoid crowds or social situations.[33]

A panic disorder is one of the easier psychiatric diseases to feign because most of the symptoms can be duplicated by intentional hyperventilation. Functional hyperventilation can be distinguished from organic hyperventilation by its irregularity and interruptions by sighs. When there is doubt, formal psychiatric evaluation is indicated, particularly before a potentially dangerous or addictive drug therapy is prescribed.

A *phobia* is an irrational fear that results in avoidance. It is considered normal in children because the objects of fear tend to be things that seem dangerous to a child (e.g., spiders, snakes, enclosed places, the dark). Phobia becomes a disorder when it interferes with day-to-day function in an individual's life. A *social phobia* is characterized by clinically significant anxiety provoked by exposure to a specific feared object or situation, often leading to avoidance behavior. Social phobias prevent a patient from doing such activities as public speaking, performing, visiting, using public showers or restrooms, or eating in public places. *Agoraphobia* is a fear of being alone in public places. Nearly 75% of agoraphobic patients have panic attacks.[34] Those with panic attacks are more likely to seek treatment, whereas those with uncomplicated agoraphobia tend to stay at home. Agoraphobia without panic attacks may not differ fundamentally from other simple phobias. Most panic disorder patients have multiple phobias, including agoraphobia, which is believed to result from the panic patient's increasing attempts to avoid places or situations in which the panic attacks would be particularly inconvenient or difficult to control. Agoraphobic patients particularly avoid places from

www.ketabpezeshki.com 66485457-66963820

which escape would be difficult (e.g., bridges, crowded theaters). When they do attend theaters, they favor seats on the aisle and near the door. Panic attacks in agoraphobic patients are more likely to include fear of losing control, whereas those not associated with agoraphobia are more likely to include dyspnea and dizziness.[35]

An *obsessive-compulsive disorder* (OCD) is characterized by recurrent, obtrusive, unwanted thoughts (obsessions), such as fears of contamination, and compulsive behaviors or rituals (compulsions), such as handwashing or checking. OCD is classified as an anxiety disorder because (1) anxiety or tension is often associated with obsessions and resistance to compulsions, (2) anxiety or tension is often immediately relieved by yielding to compulsions, and (3) OCD often occurs in association with other anxiety disorders. In summary, the obsessions and intrusive thoughts increase anxiety and the compulsions and repetitive behaviors decrease anxiety but with significant disruption of one's life.[9]

MANAGEMENT

Initial Evaluation

The patient should first be placed in a quiet area for evaluation. Some patients calm down when they are removed from the chaotic ED environment. If the emergency physician encounters difficulty in calming the patient, supportive family members may help. A known and trusted face often helps anxious patients make order out of their inner turmoil. Prior discussion and clarification with the family are essential to elicit their support.[1]

Once the patient is calmed, a more formal evaluation can begin. The emergency physician should ask open-ended questions and observe the patient's responses carefully. Questions about drug or alcohol use should be delayed until rapport has been established. Reassurance should not be premature; this important interventional technique is more effective when it is delayed until after the patient's specific concerns are clarified.[1]

The extent of the medical workup for significant anxiety will depend on the age and health status of the patient, the nature of the anxiety, and the range and severity of associated symptoms. The anxiogenic effects of medications, including beta-adrenergic agonists, corticosteroids, thyroid hormones, and sympathomimetics, should be considered. Potential contributory medical illness (e.g., thyroid dysfunction, hypoglycemic episodes in diabetes, hyperparathyroidism, dysrhythmias, chronic obstructive pulmonary disease, seizure disorders), substance use (e.g., caffeine, amphetamines, cocaine), and withdrawal states (e.g., alcohol, sedative-hypnotics) should also be considered.

If a somatic concern is the major component of the acute anxiety attack, a physical examination with particular attention to the area of complaint is important, even when there is overwhelming evidence of a functional etiology to the patient's complaints. Anxiety attacks are stressful experiences in themselves and can cause deterioration in marginally compensated organ systems. Careful evaluation reassures the patient and avoids the problem of a premature "medical clearance." Abnormal vital signs should suggest an organic cause of the anxiety symptoms.[9]

Because of the physical nature of the symptoms, patients with anxiety and panic attacks often seek treatment in the ED rather than in a psychiatric setting. A calm manner and willingness to listen usually relieve some of the patient's initial anxiety. An anxiety or panic reaction may be precipitated by the loss of a significant relationship, a job, a living situation, or self-esteem as well as by physical illness or injury. Once the patient describes a trigger event, the emergency physician should restate it, as if experiencing a similar situation. This gives the patient authoritative approval to express embarrassing feelings. A patient who has frequent anxiety reactions is usually suggestible and will respond to reassurance. Conversely, an anxious or unsympathetic physician will only compound the problem.[1]

Even an apparently calm patient may communicate anxiety through worried looks, nervousness, pressured speech, or covert assaults on the physician's competence. In turn, the physician may empathetically respond to the patient's hidden anxiety by also becoming anxious. This is a strong clue that the patient's anxiety is real and significant. Without this self-awareness, physicians may focus on a patient's physical symptoms rather than on the irrational anxiety. The pressure to see patients quickly and to move them out of the ED expeditiously may result in limited interactions with patients, the misdiagnosis of anxiety disorders, and excessive and unnecessary medical workups. A careful medical evaluation is important, but excessive focus on unlikely purely organic illness suggests to the patient a reason to worry, avoids recognition of crucial psychological factors, and may increase anxiety and the severity of symptoms.

After organic illness, medication effects, and obvious psychiatric causes of the acute anxiety state have been ruled out, the physician should determine whether the anxiety has an external trigger. If the anxiety arises spontaneously without an identifiable stress, is unpredictable, and is accompanied by agoraphobia, an endogenous component is likely to be present, and such patients should be referred to a psychiatrist for evaluation and treatment. If the anxiety appears to be related to an identifiable external event or circumstance, the anxiety is exogenous, and patients should be encouraged to discuss their feelings with a mental health worker. Talking about fears allows anxious patients some sense of mastery and control over events. These patients often require ongoing advice, support, and assistance in mobilizing necessary resources from family members, friends, and social agencies to achieve realistic expectations.

Anxiety is common in the geriatric population; prevalence rates are conservatively estimated at 10%, with higher rates in patients with chronic illness. Anxiety disorders may be the most common psychiatric ailments experienced by elders, but this age group is the least studied of all patients.[36] Older patients with anxiety often have somatic complaints. They require a careful investigation for underlying medical illness, other psychiatric conditions, and use of over-the-counter and prescription drugs.

Pharmacologic Treatment

Before medication is prescribed, education of the patient about the illness is a key component in the treatment of anxiety disorders. Patients are often worried and confused about their illness. Reassurance that they are not alone, education about what to expect and that therapy is available, and involvement of family are all critical in the treatment of anxiety. Use of intravenous medication is rare but may be necessary when an anxiety state renders a patient so helpless and out of control that there is a significant threat to safety of self or others. Intravenous medication is also appropriate for the anxious patient experiencing a significant medical illness or undergoing a medical procedure. Lorazepam in small increments can be helpful in alleviating the anxiety associated with substance withdrawal states. Midazolam reduces anxiety and increases amnesia for ED procedures.

SSRIs have become the first-line treatment of most anxiety disorders because of their broad spectrum of efficacy and good tolerance by most patients. SSRIs have a lower potential for dependence and are safer than the previous classes of antidepressants and anxiolytics. This class of drugs includes fluoxetine, sertraline, fluvoxamine, paroxetine, citalopram, and sertraline. Improvement is usually seen in 3 to 4 weeks, but the medication may have to be adjusted. Initiation of this group of medications is often reserved for the mental health professional as it is important to start the patient with low doses of SSRIs and to arrange for frequent

www.ketabpezeshki.com 66485457-66963820

Table 112-1 Pharmacotherapy for Anxiety Disorders

	SSRIs	TCAs	MAOIs	BDZs	BUSPIRONE	CBT
Panic disorder	+	+	+	+	–	+
GAD	+	+	+	+	+	+
Social phobia	+	–	+	+	–	+
Specific phobia	–	–	–	+/–	–	+
PTSD	+	+/–	+	+/–	–	+
OCD	+	–*	+	+/–†	+/–†	+

*Clomipramine is effective.
†Used adjunctively with serotonergic antidepressant.
BDZs, benzodiazepines; *CBT,* cognitive-behavioral therapy; *GAD,* generalized anxiety disorder; *MAOIs,* monoamine oxidase inhibitors; *OCD,* obsessive-compulsive disorder; *PTSD,* post-traumatic stress disorder; *SSRIs,* selective serotonin reuptake inhibitors; *TCAs,* tricyclic antidepressants.

short-term follow-ups because an initial increase in anxiety may be seen.

The SNRIs were initially developed for the treatment of depression, but certain members of this class have been found to be beneficial in the treatment of anxiety. Venlafaxine is indicated in the treatment of generalized anxiety disorder, panic disorder, and social phobias; duloxetine has an indication for generalized anxiety disorder.

In the past few years, emergency physicians and the public have become increasingly concerned about the growing use of benzodiazepines in the United States. More than 1 million Americans are physically dependent on sedatives. When sedatives are given in place of understanding, support, and intrapersonal therapies, patients are taught to rely on the external support of a pill rather than on inner resources.[8]

Benzodiazepines can be prescribed for motivated patients with acute exogenous anxiety for time-limited stress. Patients who are cooperative, employed, educated, married, and aware that their symptoms have a psychological basis are more likely to respond. Benzodiazepines are an attractive alternative to the delayed response of an SSRI when an immediate reduction of symptoms is desired or a short-term treatment is needed. Benzodiazepines can be given in one or two daily doses to make use of their short half-lives; alternatively, a bedtime dose may minimize daytime sedation and still manifest a daytime anxiolytic effect. Benzodiazepines should not be prescribed for more than a week. Patients who do not improve within a week are unlikely to benefit from the drug. Patients with a history of alcoholism or drug abuse, who are excessively and emotionally dependent, or who become anxious in response to normal stress are at greater risk of drug dependency and are not good candidates for this treatment from an emergency physician. Dependence and abstinence syndromes have been reported to occur with low doses of sedating drugs, especially if they are taken for more than 8 months. Short-acting benzodiazepines (e.g., lorazepam, oxazepam) should be prescribed at low dosages for patients with liver disease or organic brain syndrome and for those taking medications that either depress central nervous system function or inhibit benzodiazepine metabolism and clearance. Withdrawal rebound symptoms are more common with discontinuation of benzodiazepines than with other antianxiety treatments. Short-acting benzodiazepines produce a more severe abstinence syndrome when they are stopped abruptly, and thus many physicians prefer the longer-acting benzodiazepines.[7] For some patients, switching from a short-acting agent (e.g., alprazolam) to a long-acting agent (e.g., clonazepam) can be helpful before initiation of a taper.

Buspirone is a nonbenzodiazepine used in the treatment of generalized anxiety disorder. Buspirone does not appear to cause dependency; it is less sedating than benzodiazepines, and tolerance does not occur at therapeutic doses. It is the therapeutic lag in efficacy of 2 to 3 weeks that has limited the use of buspirone. It has had variable and sometimes disappointing results in clinical practice, particularly when it is used in patients with prior exposure to benzodiazepines.[36]

Monoamine oxidase inhibitors (MAOIs) demonstrate high effectiveness in the treatment of social phobia, panic, generalized anxiety disorders, OCD, and comorbid conditions (e.g., atypical depression). MAOIs (phenelzine and tranylcypromine) may be difficult to tolerate and require discipline and strict dietary restrictions, and thus they are rarely appropriate in the emergency setting.

Tricyclic antidepressants (TCAs) are effective for panic disorders and generalized anxiety disorders but are ineffective for social phobias and, with the exception of clomipramine, are largely ineffective for OCD as well. TCAs have been used effectively for depressive and anxiety symptoms associated with post-traumatic stress disorder. TCAs include imipramine, nortriptyline, desipramine, amitriptyline, and doxepin. The TCAs have been supplanted by the SSRIs and SNRIs as first-line interventions for the treatment of anxiety and depressive disorders.[37]

Patients with endogenous anxiety (panic attacks with or without agoraphobia) should be referred to a psychiatrist to establish a good therapeutic relationship before using anxiolytic medication. Benzodiazepines, tricyclics, SSRIs, SNRIs, and MAOIs are safe and effective in endogenously anxious patients who are under psychiatric care (Table 112-1). Recurrence rates of panic attacks are high when drug therapy is discontinued.[8]

Nonpharmacologic Therapy

Psychotherapies may be helpful for individuals whose psychological makeup, coping style, interpersonal dynamics, and situational stressors contribute to their pathologic anxiety. The use of supportive, insight-oriented family therapy is helpful when these factors appear prominently in the patient's presentation.[8]

Cognitive-behavioral therapy is predicated on the theory that the distress and impairment associated with anxiety and panic are mediated by maladaptive cognitive responses that promote anxiety and avoidance. The core components of cognitive-behavioral therapy for panic disorder include correction of cognitive misperceptions and overreactions to anxiety symptoms, breathing retraining, and muscle relaxation as well as exposure and desensitization to phobic situations. Cognitive-behavioral therapy is very effective but requires commitment from the patient.[8,9]

Meditation (e.g., Zen, yoga, transcendental) has been proposed by many authorities, but few clinical data support its efficacy in

www.ketabpezeshki.com 66485457-66963820

anxiety disorders. *Biofeedback* appears promising for the treatment of generalized anxiety disorder. *Hypnotic suggestion* may be effective because anxious patients tend to be cognitively scattered, unable to focus their attention, and highly suggestible. A hypnotic state can often be induced by specific stimuli.[38]

These nonpharmacologic techniques take anxious patients out of the future, about which they are frightened, and place them into the present. These techniques should be reinforced by the development of a physically and psychologically healthy lifestyle. A significant social support system not only protects against vulnerability to illness but also is highly anxiolytic. Regular exercise (e.g., dancing, swimming, bicycling, walking, jogging) also promotes tranquility. Encouragement of activity that focuses on hand-eye-ear coordination (e.g., painting, playing keyboard, needlework) helps anxious patients regain and maintain control by bringing them into the present.[1]

DISPOSITION

Many patients with anxiety-related symptoms can be effectively treated in the ED by the following approach:

1. Rule out organic illnesses as a cause of anxiety.
2. Evaluate for substance abuse and medications associated with anxiety.
3. Determine whether anxiety is endogenous (without outside trigger) or exogenous (after an outside trigger).
4. Clarify what is currently frightening the patient.
5. Evaluate the patient's capacity for self-awareness.
6. Assess techniques that have worked in the past.
7. Support coping skills.
8. Give the patient as much control over the care plan as feasible.
9. Select patients to start with a short course of benzodiazepines, and educate patients about treatment.
10. Apply adjunctive techniques as appropriate for the patient's personality and the physician's preference (e.g., hypnotic suggestion, breathing exercises).

Patients with a panic disorder associated with suicidal or homicidal ideation or with severe depression require urgent psychiatric attention and admission to the hospital. Other patients with suspected endogenous or severe exogenous anxiety disorders should be referred for psychiatric evaluation. The Anxiety and Depression Association of America can be contacted (240-485-1001) for a national registry of clinicians and treatment programs specializing in anxiety disorders or can be found online at www.adaa.org.

KEY CONCEPTS

- Anxiety may accompany the onset of serious disease, may have significant metabolic demands, and may cause a marginally compensated organ system to fail.
- As many as 42% of patients thought to have anxiety disorders are later found to have organic disease.
- Anxiety caused by physical illness is usually suggested by the patient's physical findings but may require adjunctive testing.
- Anxiety affects at least 10% of elderly patients.
- Intravenous medication may be necessary for patients who are a significant threat to themselves or others and for anxious patients with significant medical illness.
- Limited benzodiazepine therapy may be helpful for select patients with exogenous anxiety.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Kercher EE: Anxiety. *Emerg Med Clin North Am* 1991; 9:161.
2. Kessler RC, et al: Prevalence, severity and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; 62:617.
3. Kroenke K, Spitzer RL, Williams JB, Monahan PO, Löwe B: Anxiety disorders in primary care: Prevalence, impairment, comorbidity, and detection. *Ann Intern Med* 2007; 146:317.
4. Weisberg R, et al: Psychiatric treatment in primary care patients with anxiety disorders: A comparison of care received from primary care providers and psychiatrists. *Am J Psychiatry* 2007; 164:276.
5. Rogers MP, Wolfe DJ: Anxiety in the medical patient. *Psychiatric Times* 2007; 24:29.
6. Grant BF, et al: Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry* 2004; 61:807.
7. Hermida T, Malone D: *Anxiety Disorders*. Disease Management Project, Cleveland Clinic, July 2004. Available at www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/psychiatry/anxiety-disorder.
8. Hollander E, Simeon D, Gorman JM: *Anxiety disorders*. In: Hales RE, Yudofsky SC, Talbott JA, eds. *The American Psychiatric Press Textbook of Psychiatry*, 3rd ed. Washington, DC: American Psychiatric Press; 1999.
9. Pollack MH, Smoller JW, Lee DK: *Approach to the anxious patient*. In: Stern TA, Herman JB, Slavin PL, eds. *Guide to Psychiatry in Primary Care*. New York: McGraw-Hill; 1998.
10. Rosenbaum JF, et al: *Anxiety*. In: Cassem NH, Stern TA, Rosenbaum JF, Jellinek MS, eds. *Massachusetts General Hospital Handbook of General Hospital Psychiatry*, 4th ed. St Louis: Mosby; 1998.
11. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed, text rev. Washington, DC: American Psychiatric Association; 2000.
12. Davies SJ, et al: Association of panic disorder and panic attacks with hypertension. *Am J Med* 1999; 107:310.
13. Huffman JC, Pollack MH, Stern TA: Panic disorder and chest pain: Mechanisms, morbidity, and management. *J Clin Psychiatry* 2002; 4:54-62.
14. Huffman JC, Pollack MH: Predicting panic disorders among patients with chest pain: An analysis of the literature. *Psychosomatics* 2003; 44:222.
15. Huffman JC, Stern TA: The use of benzodiazepines in the treatment of chest pain: A review of the literature. *J Emerg Med* 2003; 25:427.
16. Yudofsky SC, Hales RE: *Neuropsychiatric aspects of endocrine disorders*. In: Yudofsky SC, Hales RE, eds. *The American Psychiatric Publishing Textbook of Neuropsychiatry and Clinical Neurosciences*, 4th ed. Washington, DC: American Psychiatric Publishing; 2002:868.
17. Grigsby AB, et al: Prevalence of anxiety in adults with diabetes: A systematic review. *J Psychosom Res* 2002; 53:1053.
18. Levenson JL: Psychiatric issues in endocrinology. *Prim Psychiatry* 2006; 13:27.
19. Dement MM, et al: Depression and anxiety in hyperthyroidism. *Arch Med Res* 2002; 33:552.
20. Ringel MD: Management of hypothyroidism and hyperthyroidism in the intensive care unit. *Crit Care Clin* 2001; 17:59.
21. Brenes G: Anxiety and chronic obstructive pulmonary disease: Prevalence, impact, and treatment. *Psychosom Med* 2003; 65:963.
22. Goodwin RD, Jacobi F, Thefeld W: Mental disorders and asthma in the community. *Arch Gen Psychiatry* 2003; 60:1125.
23. Mehta TA, Sutherland JG, Hodgkinson DW: Hyperventilation: Cause or effect? *J Accid Emerg Med* 2000; 17:376.
24. Stein DJ, Hugo FJ: *Neuropsychiatric aspects of anxiety disorders*. In: Yudofsky SC, Hales RE, eds. *The American Psychiatric Publishing Textbook of Neuropsychiatry and Clinical Neurosciences*, 4th ed. Washington, DC: American Psychiatric Publishing; 2002.
25. Berigan T: An anxiety disorder secondary to energy drinks. *Psychiatry (Edgmont)* 2005; 2:10.
26. Salomone JA III: Hallucinogen toxicity. *Emedicine,* updated Apr 28, 2011. Available at http://emedicine.medscape.com/article/814848-overview.
27. Sola CL: Sedative, hypnotic, anxiolytic use disorders. *Emedicine,* updated Jun 27, 2011. Available at http://emedicine.medscape.com/article/290585-overview.
28. McKeown NJ: Withdrawal syndromes. *Emedicine,* updated June 4, 2012. Available at http://emedicine.medscape.com/article/819502-overview.
29. Sasson Y, et al: Bipolar comorbidity: From diagnostic dilemmas to therapeutic challenge. *Int J Neuropsychopharmacol* 2003;6:139.
30. Tibbo P, Swainson J, Chue P, LeMelledo JM: Prevalence and relationship to delusion and hallucinations of anxiety disorders in schizophrenia. *Depress Anxiety* 2003; 17:65.
31. Oyama O, Paltoo C, Greengold J: Somatoform disorders. *Am Fam Physician* 2007; 76:1333.
32. Zimmerman M, Chelminski I: Generalized anxiety disorder in patients with major depression: Is DSM-IV's hierarchy correct? *Am J Psychiatry* 2003; 160:504.
33. Howard S, Hopwood M: Post-traumatic stress disorder. A brief overview. *Aust Fam Physician* 2003; 32:683.
34. Preda A: Phobic disorders. *Emedicine,* updated Mar 29, 2011. Available at http://emedicine.medscape.com/article/288016-overview.
35. Craske MG, DeCola JP, Sachs AD, Pontillo DC: Panic control treatment for agoraphobia. *J Anxiety Disord* 2003; 17:321.
36. Roerig JL: Diagnosis and management of generalized anxiety disorder. *J Am Pharmaceut Assoc* 1999; 39:811.
37. Schatzberg AF, Nemeroff CB: *Textbook of Psychopharmacology*, 3rd ed. Washington, DC: American Psychiatric Publishing; 2004.
38. Spiegel MD, Maldonado JR: *Hypnosis*. In: Hales RE, Yudofsky SC, Talbott JA, eds: *The American Psychiatric Press Textbook of Psychiatry*, 3rd ed. Washington, DC: American Psychiatric Press; 1999.

www.ketabpezeshki.com 66485457-66963820

Chapter 113

Somatoform Disorders

Adria Ottoboni Winter

PERSPECTIVE

Patients occasionally present to the emergency department (ED) with myriad physical symptoms in the absence of signs of physical disease. Whereas some harbor underlying medical disorders, many suffer from somatoform disorders, in which they experience and communicate psychological distress as one or more physical symptoms.[1,2] These patients have persistent distress related to the symptoms that inhibits their ability to function. Even when a somatoform disorder is strongly suspected, emergency physicians are reluctant to attribute physical complaints to a psychiatric disorder for fear of missing the subtle presentation of physical disease.

Somatoform disorders are among the most prevalent of psychiatric disorders in the primary care setting, occurring in at least 10 to 15% of primary care patients.[3,4] The annual cost to evaluate these patients medically is estimated at $100 billion.[5]

Somatoform disorders are an enormous source of angst for physicians as they can easily frustrate even the best attempts to place human suffering into well-defined categories based on physical disease. Somatoform disorders are unlikely to be diagnosed in a single visit; in fact, a definitive diagnosis requires multiple visits and an in-depth knowledge of the patient. Nevertheless, proper diagnosis and treatment of patients with a somatoform disorder are essential; misidentification and mismanagement prolong the patient's suffering and add immensely to excess health care costs, with unnecessary diagnostic testing and hospitalization.[5]

CLINICAL FEATURES

Seven somatoform disorders are listed in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV): (1) somatization disorder, characterized by many physical complaints affecting many organ systems; (2) conversion disorder, characterized by one or two neurologic complaints; (3) hypochondriasis, characterized by patients' beliefs that they have a specific disease; (4) body dysmorphic disorder, characterized by a false belief or perception that a body part is defective; (5) pain disorder, characterized by symptoms of pain that are solely due to or exacerbated by psychological factors; (6) undifferentiated somatoform disorder, which includes somatoform disorders not otherwise described that have been present for 6 months or more; and (7) somatoform disorder not otherwise specified, for those somatoform symptoms that do not meet any of the criteria otherwise described and classified.[6]

The general category of somatoform disorders was first explicitly defined in the DSM-III and updated in the DSM-IV; its revision is pending in the DSM-V. The initial criteria were based on descriptions by Briquet and Purtell[7,8]; however, the initial perspectives on hysteria and hypochondriasis have changed markedly and are likely to continue to do so. There is ongoing controversy about whether the somatoform disorders require a reclassification because the diagnosis does not explain the etiology, nor does it predict treatment response.[9]

The phenomenon of somatization extends across a broad spectrum of expression, from mild stress-related symptoms to chronic debilitating presentations that destroy a patient's ability to function socially or occupationally.[10,11] Patients with an underlying somatoform disorder can be particularly frustrating for the emergency physician because they cannot be approached from the practical standpoint of cause and effect, which is the bedrock of training and analysis for most physicians. It is not unusual for physicians to think that patients with somatoform disorders have nonlegitimate disturbances and are using medical care to treat their underlying emotional needs, with the resulting mismatch in the patient-physician relationship.[12]

It is important to recognize when a patient has a somatoform disorder, if only to avoid multiple unnecessary and time-consuming tests; however, the diagnosis itself is typically one of exclusion. In addition, somatizers typically steadfastly insist that their symptoms are caused by serious physical disorders even in the presence of conclusive evidence to the contrary.[13]

Historically referred to as hysteria, somatization disorder was given the eponym Briquet's syndrome by Guze in 1975 to avoid the pejorative connotations associated with the traditional terms.[14,15] *Somatization disorder* is the prototypic somatoform presentation, differing from the other somatoform disorders in the multiplicity of complaints and organ systems affected. As the number of physical symptoms increases, so does the patient's functional impairment and distress.[16] Research has shown that patients with somatization are more likely to be women, nonwhite, and less educated than nonsomatizers.[17]

The diagnosis of somatization disorder requires several criteria (Box 113-1).[6] It can be summarized as a polysymptomatic disorder that begins before the age of 30 years; extends for a period of years; and is characterized by pain, gastrointestinal, sexual, and pseudoneurologic symptoms. Somatization disorder is restrictive and represents only a small subset of patients who have moderate yet clinically significant somatization.[18] Somatization disorder, as currently defined, is present in less than 0.5% of the general population and in 1 to 4% of patients who present in general practice.[19]

Once referred to as hysterical neurosis and originally described by Breuer and Freud,[20] *conversion disorder* is characterized by abnormalities or deficits in voluntary motor or sensory function that are medically unexplained, including pseudoseizures,

www.ketabpezeshki.com 66485457-66963820

Box 113-1 Diagnostic Criteria for Somatoform Disorders

Physical symptoms that are misinterpreted or exaggerated, not accounted for by a diagnosable illness
Symptoms are not intentionally feigned or produced

Somatization Disorder

Unexplained physical symptoms that are manifested before the age of 30 years, that last several years, and that result in treatment being sought with significant impairment in social, occupational, or other important areas of functioning
Presence of the following at any time during the course of the disorder:
Four pain symptoms
Two gastrointestinal tract symptoms
One sexual symptom
One pseudoneurologic symptom

Undifferentiated Somatoform Disorder

One or more physical symptoms that cause significant distress or impairment in functioning, lasting at least 6 months

Conversion Disorder

A single unexplained symptom affecting voluntary or sensory function that suggests a neurologic or general medical condition and is associated with psychological stressors

Pain Disorder

Pain symptom is the predominant focus, causing significant distress or impairment and associated with psychological factors that play a role in the perception and maintenance of pain

Hypochondriasis

Preoccupation with fear of having a serious medical condition

Body Dysmorphic Disorder

Preoccupation with real or imagined physical defect

Somatoform Disorder Not Otherwise Specified (NOS)

Somatoform symptoms that do not meet criteria for other somatoform disorders, including unexplained physical complaints less than 6 months in duration

Modified from Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text rev. Washington, DC, American Psychiatric Association, 2000; and Oyama O, Paltoo C, Greengold J: Somatoform disorders. Am Fam Physician 76:1333-1338, 2007.

Box 113-2 Presentations of Conversion Disorder

1. Motor disturbances
   a. Tremors (that worsen when attention is called to the movements)
   b. Seizures (wild, thrashing, writhing, often mimicking copulation)
   c. Paralysis or paresis (often a monoplegia, stocking-glove weakness, with normal reflexes and limb circumferences)
   d. Aphonia (wherein the patient can whisper and cough normally and vocal cords move normally with respiration)
   e. Coordination disturbances
2. Sensory disturbances
   a. Anesthesia (the patient may not find this symptom disturbing)
   b. Blindness and tunnel vision[16,17]
3. An occasional patient may present with other non-neurologic symptoms, such as vomiting or pseudocyesis.[13]

pseudoparalysis, psychogenic movement disorders, and blindness. Typically, there is a sudden dramatic onset of a single symptom, simulating some nonpainful neurologic disorder for which there is no pathophysiologic or anatomic explanation.[6,21] In contrast to somatization disorder, conversion disorder typically revolves around a single physiologically impossible condition that is not under the patient's voluntary control but probably represents the patient's own perception of neurologic illness. Some symptoms provide gratification for unconscious dependency needs, whereas others may provide escape from painful emotional stimuli (e.g., hysterical paralysis in battle).[22,23] Conversion disorder tends to occur more often in young, naïve, and uneducated women, except for those in military service and industrial accidents.[23] Typical comorbid diagnoses include mood disorders, panic disorder, generalized anxiety disorder, post-traumatic stress disorder, dissociative disorders, social or specific phobias, and obsessive-compulsive disorders. Patients with conversion disorder often have a history of physical or sexual abuse[21,24] (Box 113-2).

According to DSM-IV, *pain disorder* requires psychological factors that are important in the onset, severity, exacerbation, or maintenance of that pain and is characterized by clinically significant pain in one or more anatomic sites.[6] The primary and often exclusive symptom is distressful pain that is not intentionally feigned, is persistent in nature, limits daily function, involves one or more organ systems, and cannot be pathophysiologically explained.[6,25]

The term *hypochondriasis* comes from *regio hypochondriaca,* a Latin term referring to the upper lateral region of the abdomen inferior to the costal cartilages, especially the area of the spleen, which early physicians presumed to be the seat of this disorder. Hypochondriasis is defined as the preoccupation, despite medical evaluation and physician reassurance, that one has a serious disease based on the misinterpretation of symptoms.[6] Patients must have a preoccupation with their symptoms for at least 6 months before the diagnosis can be made. These patients typically have four characteristics: (1) physical symptoms disproportionate to demonstrable organic disease; (2) fear of disease and a conviction that they are sick, leading to "illness-claiming behavior"; (3) preoccupation with their body; and (4) persistent and unsatisfying pursuit of medical care with a history of doctor shopping and an eventual return of symptoms.[26]

These unfortunate patients manifest both a heightened awareness and an unrealistic interpretation of normal physical signs or sensations, such as bowel habits, heartbeat, sweating, or peristalsis. These sensations are perceived as abnormal, noxious, and alarming, a phenomenon known as *amplification.*[27] These aberrant perceptions result in a chronic morbid preoccupation with body functions and a lingering fear of having a disease despite medical reassurance.[6,25,26] A distinguishing feature of hypochondriasis is the presence of real symptoms that are often confirmed by physical examination, but the patient exaggerates and misinterprets them.

Hypochondriasis is relatively common. Its prevalence in general medical practice ranges from 4 to 9%.[6] It has a peak incidence among men in their 30s and women in their 40s, affecting men and women equally.[28-30] Hypochondriacs have an increased sense of responsibility for and place a high value on their personal health and physical appearance. They have an acute sense of body vulnerability and a heightened aversion to death and aging.[31] There is a strong correlation between hypochondriasis and major depression.[32] A milder form of this disorder may be an exaggerated interest in body function and health.[33]

The hypochondriac complains at length and in detail, using medical jargon. Hypochondriacs often believe that they have lost control of their lives and have been described as "experts at defeating doctors in order to feel more powerful."[26] Consequently, physicians perceive hypochondriacal patients as more angry and hostile than other patients.[34] The diagnosis may be suggested when the physician feels "frustration, helplessness, or anger associated with a wish to be rid of the patient."[26,35]

www.ketabpezeshki.com 66485457-66963820

Reactive hypochondriasis, or transient hypochondriasis, is an acute response to a psychosocial stress or life crisis, such as an acute myocardial infarction, terminal illness, or recent loss of a family member. In contrast to true hypochondriasis, this form is reversible and does respond to reassurance.[26,33]

DIAGNOSTIC STRATEGIES

Physicians are often reluctant to include a somatoform disorder in their differential diagnosis when patients present to the ED with unexplained symptoms. Their dramatic presentations and persistent preoccupation with a multitude of symptoms can overwhelm even the most pragmatic diagnostician. Yet repetitive or extensive diagnostic testing rarely excludes organic disease with absolute certainty and may yield false-positive results, which prompts further unneeded testing.[36,37] Unfortunately, somatizing patients are more likely to have morbidity from repeated diagnostic tests than from an undiagnosed physical disease.[38,39] In addition, patients with somatoform disorders often find frustration not only with their symptoms but also with the excessive testing and ineffective treatments that occur concurrently.

Yielding to the temptation to institute further diagnostic procedures or interventions typically leads to a temporary improvement, closely followed by a renewal of symptoms and mutual physician-patient disappointment. This gives rise to inevitable dissatisfaction of the patient with the physician and vice versa, leading to an unsatisfactory parting of ways and a perpetuation of the doctor-shopping cycle.[40]

Managed care and capitated reimbursement have created an additional quandary by restricting the supply of care in a time of rising demands from patients whose symptoms are relatively minor.[41,42] The most effective diagnostic tool with somatizers is the interview. Evaluation starts with a thorough but focused history and, if available, a review of the patient's medical record. This is followed by a careful problem-oriented physical examination, with meticulous inspection of the area of complaint and simple or routine diagnostic testing, when appropriate, until one attains a reasonable level of diagnostic certainty.[42] Further investigations or hospital admissions should be initiated solely on the basis of new objective signs of disease and only after confirming that the tests have not previously been performed. A rule of thumb in considering ancillary tests is to order exactly what would be done if the patient were not a somatizer.[35,42] However, the clinician should resist the impassioned entreaties of the patient when it is clear that further complex or hazardous studies are unlikely to be productive.[28,29,42,43] Multiple medical and surgical consultations generally prove counterproductive. Hypochondriacs perceive this as a test of their claim to illness and respond simply by propagating and demonstrating symptoms with redoubled zeal.[26]

Discussion of the diagnosis of somatoform disorder with these patients is fraught with potential pitfalls, especially in the ED, but it can be managed with some careful forethought. Somatizing patients are keenly aware of diagnostic labels, and all therapeutic alliance will be lost if the physician even hints at the possibility that their symptoms are "all in their head." It is important to discuss the possibility of the disorder with the patient after any underlying medical causation has been ruled out to lay the groundwork for any future psychiatric consultation and treatment.[13,28,44]

DIFFERENTIAL CONSIDERATIONS

Distinguishing between the various somatoform disorders is less important than the diagnosis of treatable organic disease or the detection of anxiety and depression, which are both more common and more likely to respond to treatment. Coexistent depression or anxiety disorder should always be considered.[45,46] Compared with patients with long-standing complaints, patients with a relatively recent onset of somatization are more likely to have underlying but subtle signs of acute psychosis, organic brain syndrome, grief reaction, depression, or anxiety.

Depression

Approximately 50 to 70% of depressed patients consult their physician for various somatic complaints.[47] Depressed patients may not be aware of a depressed mood or may believe that their depression is secondary to the somatic symptoms.[46] As a result, depression is the psychiatric disorder most often mistaken for somatoform disorder.[25]

Although somatoform disorders often coexist with depression, the two conditions must be distinguished if possible. Depression is worse in the morning, better at night, and often associated with a positive family history. The patient is reluctant to describe the symptoms and has vegetative signs of depression (e.g., sleep disturbances, decreased appetite with weight loss, and loss of interest in normally enjoyable activities).[43,48] Pain is a common symptom, particularly headache and pain involving the back, chest, or pelvic area.[46,47] Patients with somatoform disorders, on the other hand, are worse at the end of the day, have a marked propensity to discuss their symptoms, do not usually have a family history, and show no vegetative signs.[26]

In general, elders do not have more physical symptoms than younger patients do. Multiple somatic complaints should not be dismissed as a normal consequence of aging but rather considered a symptom of another underlying problem, usually depression or medical disease. Older patients may communicate somatic complaints as a way of expressing anger and provoking guilt among family members.[30] Depression is discussed in more depth in Chapter 111.

Anxiety

Patients with acute anxiety often hyperventilate and frequently exhibit physical signs of increased sympathetic activity. They may be hypervigilant and irritable and may show signs of muscle tension.[26] They may offer a history of excessive worrying about their health, feeling "on edge" or irritable, having difficulty relaxing, sleeping poorly, or having trouble falling asleep, and report symptoms of headache, tingling, dizzy spells, and diarrhea.[48] Patients with somatoform disorders have a high prevalence of anxiety disorders, especially generalized anxiety disorder.[49] Anxiety disorders are discussed in more depth in Chapter 112.

Physical Illness

When patients with somatization disorder have true organic disease, their presentation is similar to that of other patients, with specific complaints, clear chronology, and objective findings that should be appropriately investigated.[50] Unfortunately, subjective reports of distress are often not dependable in these patients, and the physician should rely on more objective evidence, including physical examination and routine laboratory tests.[35] Multiple physical symptoms starting late in life are frequently the result of physical disease.[6] In addition, patients who have a short duration of symptoms are more likely to have organic disease.

Patients with conversion disorder who present with the acute onset of neurologic symptoms can be particularly challenging. For example, an anxious young woman with apparently severe neuromuscular weakness and findings on neurologic examination that are inconsistent with an identifiable lesion or disorder may be suffering from a conversion reaction or any number of rarely encountered neurologic disorders (Box 113-3). [25] It may, at times,

www.ketabpezeshki.com 66485457-66963820

Box 113-3 Organic Diseases That May Be Mistaken for Somatoform Disorders

Endocrine disorders: hyperparathyroidism, thyroid disorders, Addison's disease, insulinoma, panhypopituitarism
Poisonings: botulism, carbon monoxide, heavy metals
Porphyria
Multiple sclerosis
Systemic lupus erythematosus
Wilson's disease
Myasthenia gravis
Guillain-Barré syndrome
Uremia

require imaging studies and both neurologic and psychiatric consultations to arrive at a clear diagnosis.

Factitious Disorder and Malingering

Patients with somatoform disorders are not deliberately feigning illness; they are exhibiting the result of an unconscious behavior modification. For a subset of patients, secondary gain is unintentionally secured from the sick role in the form of sympathy, encouragement, attention, support, and relief from responsibilities and challenges without significant loss of self-esteem.[33] In contrast, *factitious disorder* and *malingering* are both characterized by the intentional and conscious simulation, exaggeration, or self-induction of illness for an identifiable secondary gain.[51,52] Because such deception is difficult to uncover in the ED, these patients are often mistaken for having a somatoform disorder. Factitious disorder and malingering are discussed in more depth in Chapter 114.

MANAGEMENT

The symptoms of a somatoform disorder may provide a protective coping value for the patient, and the physician should be cautious about removing them without first providing adequate psychological support and treatment. Otherwise, new symptoms may arise to replace old ones. The external precipitating stress or cause of anxiety should be removed if possible. These patients require psychiatric evaluation and management,[28,29] and psychiatric consultation in the ED can be beneficial.[53]

For conversion disorder in particular, recurrence is common, but the prognosis associated with an individual episode is good and the likelihood of recovery from symptoms exceeds that of other somatoform disorders.[6,23,30] Factors associated with a good prognosis include good premorbid health; absence of organic illness or concomitant major psychiatric syndromes; acute and recent onset; definite precipitation by a stressful event; and presenting symptoms of paralysis, aphonia, or blindness.[6]

Reassurance

Young patients with no underlying medical or psychiatric illnesses who present with somatization in response to a clear psychosocial stress can often be reassured successfully with an appropriate explanation of their symptoms. Patients with chronic somatization, however, perceive this as an official denial of their sick role and are almost invariably unwilling to accept reassurance. Because they desire the acknowledgment and recognition that come with the designation of illness, which they think is rightfully theirs, they are disappointed when no pathologic condition is discovered. Conversely, they are elated when given a diagnosis, but they resist recovery because subconsciously the "specter of cure" poses a threat to their sick role.[33] Accordingly, attempts to cure the condition are countered with side effects, allergic reactions, and new symptoms. Such patients require another management strategy.

Legitimization of Symptoms

Most patients with chronic somatization interpret a psychological explanation for their symptoms as an accusation of lying or feeblemindedness. It is important to convince them that the physician believes in their symptoms and will not try to "talk them out of it." The priority is to listen and truly understand what the patient is feeling and trying to convey. Suffering is a subjective phenomenon and, in that sense, is genuine in these patients.[35] The physician should convey empathy for the patient's physical discomfort. If the physician acknowledges the legitimacy of the claim to illness and assures the somatizer of ongoing care, limits may be set on the patient's illness behavior.[26,28,29,42]

Patients should be allowed to tell their story without interruption. They should be told that they have an illness that causes them to experience many symptoms but that these symptoms will not lead to medical deterioration.[38,54] The physician should offer only guarded projections about chances for complete "cure" of the condition. Ironically, this may be better received by these patients than overly optimistic assurances because it serves to safeguard their sick role and shifts the physician away from an adversarial position.[42,43]

Diagnosis

Diagnostic labels are of critical importance for somatizers, but the precise meaning of the term should be clarified for the patient to avoid misinterpretation. Explanations for symptoms that incorporate somatic responses and descriptions, such as hyperventilation, tension headache, muscle tension, muscle strain, chest wall muscle spasm, and stress, may be better accepted than purely psychiatric diagnoses. This reassures the patient that the physician shares the belief that the symptoms result from socially acceptable ailments while allowing more in-depth explanations that incorporate the relationship of body function to psychological stress. This, in turn, serves as a preparation for future psychiatric consultation or psychotropic medication.[13,28,29,43]

At times, the best approach may be to share the diagnostic uncertainty with the patient, using such terms as "atypical pain" or "multiple complaints following injury." On a broader scale, managed care organizations can be encouraged to educate their enrollees about the process of somatization, the negative side effects of medications and other interventions, and the range of body symptoms in healthy people.[41]

Medications

Patients with somatoform disorder have a high affinity for medications and are reluctant to discontinue drugs, even those with no benefit.[26] Physicians should avoid drugs that produce an abstinence syndrome or dependence and those that cannot be safely continued indefinitely.[50] Pain medications, if given, should be prescribed on a regular schedule, not "as needed."[26] Patients with somatoform pain disorder may benefit significantly from treatment with antidepressants, including tricyclic antidepressants.[55] Patients with somatization disorder with major depression may also improve with pharmacologic management of the depression.[32]

Therapy should be kept simple and limited to exercise, diet, physical therapy, and vitamins when possible.[43] Hospitalization and narcotics should be avoided. Benign remedies, such as lotions, nutritional supplements, elastic bandages, and heating pads, may be helpful.[42,35] Drug regimens should be simplified and only the

www.ketabpezeshki.com 66485457-66963820

most distressing symptoms addressed. Before any type of symptomatic drug treatment is started, specific target symptoms should be identified. The goal is to restore function and to make the target symptoms tolerable, not to remove them completely. If patients request an increase in dosage or a stronger medication, they should be told to review their medications with their regular physician before any changes are made. Insistent patients should be informed that long-term opioid use is associated with significant adverse effects, especially constipation, sedation, impaired cognition, and progressive development of tolerance and addiction.[35]

Mental Health Consultation

Patients with somatoform disorders have difficulty in confronting their own emotions, view psychiatric evaluation as threatening to their sick role, and take offense at any suggestion that their fears or beliefs may be unwarranted.[56] They usually resist psychiatric consultation, which they interpret as an attempt to be "dumped on the psychiatrist."[26] Nevertheless, psychiatric consultation may be appropriate to confirm the diagnosis or to discuss medications, when the patient has coexistent manifestations of chronic depression or psychosis, when symptoms suddenly change or become bizarre, when the patient expresses suicidal ideation or severely disruptive behavior, when current management is not working, or when the patient requests psychotherapy.[26,28,29] Favorable prognostic indicators include youth, acute onset, concurrent anxiety or depression, and limited medical comorbidity.[57] Approximately one third of patients with conversion disorder also have major depression, and successful treatment of the depression may lead to improvement or resolution of the conversion disorder.

Many patients accept psychological treatment under the rubric of "stress management" as long as it targets physical symptoms and somatic distress.[42] Group therapy techniques presented as education rather than as psychotherapy have had some limited success.[58] Patients should be reassured that their relationship with the primary physician will continue to avoid the interpretation that the referral is an abandonment.

Physician Attitudes

The key to diagnosis and treatment of patients with somatoform disorder is effective and appropriate communication skills of the physician. Somatizing patients can present a challenge because it is tempting to point out to them that there is nothing "wrong" with them and that their symptoms need no treatment. Physicians caring for these patients predictably react with feelings of uncertainty, helplessness, anger, or guilt when they can find no physiologic process to explain the patient's distress. Patients with somatoform disorders can become as frustrated with their physician as the physician is with them. It is common for a patient with a somatoform disorder to be quickly labeled a "difficult patient" by the physician and staff.[59,60] Unfortunately, the frustration of working with these patients quickly overwhelms the physician's natural tendency toward compassion and can lead to a swift breakdown in communication. Despite the large number of distressing symptoms reported, physicians rarely demonstrate empathy with these patients.[61,62]

Treatment Goals

Somatizing patients, despite lack of objective pathophysiologic changes, are, in fact, patients who are in need of and benefit from tangible and effective help. For some, attaining invalid status enables them to be cared for and nurtured. It offers them a sense of self-importance and respect not otherwise available to them as well as an honorable release from noxious personal and vocational responsibilities and duties.[22] To attempt a cure poses a threat to this role, and unduly positive projections by physicians are therefore understandably met with disappointment, disbelief, and even thinly veiled reproaches about their professional competence.[42,43,63] Thus the goal of therapy should be control of disability and appropriate referrals rather than cure.[30,57] The course of management most likely to prove successful begins with the physician's performing a sympathetic and thorough problem-oriented history and physical examination, then offering the patient the paradoxical reassurance that he or she will probably always be ill. When pain is the dominant feature, the patient should not be promised complete relief; rather, a major task of the patient should be to "learn to live with some pain."[30]

Treatment goals should focus on modification of illness behavior and improvement of functional status.[22] Achievable endpoints include decreased frequency and urgency of medical use, in particular a reduction in ED and unscheduled office visits; avoidance of expensive and hazardous procedures; improved work or school performance; more social activities; and better personal relationships.[25,28,35]

These principles apply equally to children with somatoform disorders. Unnecessary tests and procedures, in addition to placing the patient at risk, may encourage somatization. Physician acknowledgment of the patient's suffering and family concerns, a "rehabilitative" approach emphasizing return to normal activities before definitive symptom relief, rewarding of healthy behavior and discouragement of the sick role, assumption by the patient of responsibility for coping with the symptoms, and treatment of coexistent anxiety or depression are the cornerstones of therapy.[64]

Patients with somatoform disorder have been described as the "least insightful, the least introspective and the least cognitively oriented patients one is likely to encounter."[50] Understanding of the link between emotional and somatic distress need not be a treatment goal for these patients, and insight-oriented psychotherapy is neither productive nor cost-effective.[30,35,42,50] On the other hand, both the physician and the patient can benefit by accepting fundamental alterations in the traditional paternalistic physician-patient relationship. Increasing responsibility for health and disease management should be incrementally turned over to the somatizing patient.[30]

DISPOSITION

Appropriate psychiatric referrals should be provided for the patient. Outpatient tests or hospitalization should be avoided unless clear objective signs indicate a need for diagnostic investigation or therapeutic intervention.[30,50]

As a rule, management is best carried out by a single primary care physician who becomes the gatekeeper for all medical consultation and care.* The patient should be told that no alarming findings have come to light, that further testing and additional medications are not indicated at this time, and that ongoing care and periodic reassessment are indicated and will be arranged. Patients with chronic somatization should initially be seen every 2 to 4 weeks, preferably by the primary care physician, even if their symptoms are stable. The visits should be on a time-contingent, not a need-contingent, basis. For the patient, this severs the association between medical contact and the necessity for worsening or additional symptoms and complaints. It also decreases the patient's fear of abandonment by the physician and permits repeated evaluation for early detection of objective signs of organic disease.[25,30] The patient seems to value the visit to the physician more highly than any treatment.[50]

*References 13, 28, 25, 26, 29, 42, 43, 57.

www.ketabpezeshki.com 66485457-66963820

KEY CONCEPTS

- The differential diagnosis of patients with apparent somatoform disorders includes depression, anxiety, factitious disorder, malingering, and true underlying physical disease.
- Patients with conversion disorder who present with the acute onset of neurologic symptoms can be particularly challenging. It may, at times, require imaging studies and both neurologic and psychiatric consultations to arrive at a clear diagnosis.
- The behavior of patients with somatoform disorders is unconsciously driven. They are not "faking" the symptoms or their distress.
- ED management of known or suspected somatoform disorders includes legitimization of symptoms, communication of compassion, and assurance that ongoing vigilance of the patient's medical condition will be arranged and maintained.
- Long-term cure of somatization disorder is unlikely. However, a steady state of symptom coping with improved function is an achievable goal. This can be done only in the primary care setting, not in the ED.
- In general, laboratory tests, specialty consultations, initiation of medications, and hospitalization should be avoided in patients with known or suspected somatoform disorders unless new objective clinical findings are found.
- Whenever possible, treatment decisions should be deferred to the patient's primary care physician.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Folks DG, Feldman MD, Ford CV: *Somatoform disorders, factitious disorders, and malingering*. In: Fogel B, Greenberg DB, Stoudemire A, eds: *Psychiatric Care of the Medical Patient*, 2nd ed. Oxford, NY: Oxford University Press; 2000:459.
2. Lipowski ZJ: Somatization: The experience and communication of psychological distress as somatic symptoms. *Psychother Psychosom* 1987; 47:160.
3. Ormel J, et al: Common mental disorders and disability across cultures. Results from the WHO collaborative study on psychological problems in general health care. *JAMA* 1994; 272:1741-1748.
4. Kroenke K, Spitzer RL, Williams JBW: The PHQ-15: Validity of a new measure for evaluating the severity of somatic symptoms. *Psychosom Med* 2002; 64:258-266.
5. Barsky AJ, Orav EJ, Bates DW: Somatization increases medical utilization and costs independent of psychiatric and medical comorbidity. *Arch Gen Psychiatry* 2005; 62:903-910.
6. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed, text rev. Washington, DC: American Psychiatric Association; 2000.
7. Briquet P: *Trait clinique et therapeutique a l'hysterie*. Paris: JB Ballière et Fils; 1951.
8. Purtell JJ, Robins E, Cohen ME: Observations on clinical aspects of hysteria. *JAMA* 1951; 146:902-909.
9. Noyes R, Stuart SP, Watson DB: A reconceptualization of the somatoform disorders. *Psychosomatics* 2008; 49:1.
10. Katon W, Lin E: Somatization: A spectrum of severity. *Am J Psychiatry* 1991; 148:1.
11. Servan-Schreiber D, Kolb NR, Tabas G: Somatizing patients: Part I. Practical diagnosis. *Am Fam Physician* 2000; 61:1073-1078.
12. Gordon-Elliott JS: An approach to the patient with multiple physical symptoms. *Med Clin North Am* 2010; 94:1207-1216.
13. Lipowski ZJ: Somatization: The borderland between medicine and psychiatry. *CMAJ* 1986; 135:609.
14. Guze SB: The validity and significance of the clinical diagnosis of hysteria (Briquet's syndrome). *Am J Psychiatry* 1975; 132:138.
15. De Gucht V, Fischler B: Somatization: A critical review of conceptual and methodological issues. *Psychosomatics* 2002; 43:1.
16. Katon W, Lin E, VonKorff M, et al: Somatization: A spectrum of severity. *Am J Psychiatry* 1991; 148:34-40.
17. Gureje O, Simon GE, Ustun T, Goldberg DP: Somatization in cross-cultural perspective: A World Health Organization study in primary care. *Am J Psychiatry* 1997; 154;989-995.
18. Kroenke K: Somatoform disorders and recent diagnostic controversies. *Psychiatr Clin North Am* 2007; 30:593-619.
19. Escobar JI, Burnam MA, Karno M, Forsythe A, Golding JM: Somatization in the community. *Arch Gen Psychiatry* 1987; 44:713-718.
20. Breuer J, Freud S: *Studies on hysteria*. In: Strachey J, ed-trans: *The Standard Edition of the Complete Psychological Works of Sigmund Freud*, vol II. London: Hogarth Press and the Institute of Psycho-Analysis; 1955:vii-xxxi, 1-311; original work published 1893-1895.
21. Stonnington CM, Barry JJ, Fisher RS: Conversion disorder. *Am J Psychiatry* 2006; 163:1510.
22. Quill TE: Somatization disorder: One of medicine's blind spots. *JAMA* 1985; 254:3075.
23. Kent DA, Tomasson K, Coryell W: Course and outcome of conversion and somatization disorders: A four-year follow-up. *Psychosomatics* 1995; 36:138.
24. Ford CV, Folks DG: Conversion disorders: An overview. *Psychosomatics* 1985; 26:371-374, 380-383.
25. Ries RK, et al: The medical care abuser: Differential diagnosis and management. *J Fam Pract* 1981; 13:257.
26. Dubovsky SL, Weissberg MP: *Hypochondriasis*. In: *Clinical Psychiatry in Primary Care*, 3rd ed. Baltimore: Williams & Wilkins; 1986.
27. Barsky AJ, Wyshak G: Hypochondriasis and related health attitudes. *Psychosomatics* 1989; 30:412.
28. Smith RC: A clinical approach to the somatizing patient. *J Fam Pract* 1985; 21:294.
29. Smith RC: Somatization in primary care. *Clin Obstet Gynecol* 1988; 31:902.
30. Ford CV: *The Somatizing Disorders: Illness as a Way of Life*. New York: Elsevier Biomedical; 1983.
31. Morrison J: Histrionic personality disorder in women with somatization disorder. *Psychosomatics* 1989; 30:433.
32. Smith GR: The epidemiology and treatment of depression when it coexists with somatoform disorders, somatization, or pain. *Gen Hosp Psychiatry* 1992; 14:265.
33. Barsky AJ, Klerman GL: Overview: Hypochondriasis, bodily complaints, and somatic styles. *Am J Psychiatry* 1983; 140:273.
34. Kellner R, et al: Anxiety, depression, and somatization in DSM-III hypochondriasis. *Psychosomatics* 1989; 30:57.
35. Servan-Schreiber D, Kolb R, Tabas G: The somatizing patient. *Prim Care* 1999; 26:225.
36. Smith GR: The course of somatization and its effects on utilization of health care resources. *Psychosomatics* 1994; 35:263-267.
37. Smith GR, Monson RA, Ray DC: Patients with multiple unexplained symptoms: Their characteristics, functional health, and health care utilization. *Arch Intern Med* 1986; 146:69-72.
38. Zoccolillo MS, Cloninger CR: Excess medical care of women with somatization disorder. *South Med J* 1986; 79:532.
39. Fink P: Surgery and medical treatment in persistent somatizing patients. *J Psychosom Res* 1992; 36:439-447.
40. Sternbach RA: Varieties of pain games. *Adv Neurol* 1974; 4:423.
41. Barsky AJ, Borus JF: Somatization and medicalization in the era of managed care. *JAMA* 1995; 274:1931.
42. Barsky AJ: A 37-year-old man with multiple somatic complaints. *JAMA* 1997; 278:673.
43. Lichstein PR: Caring for the patient with multiple somatic complaints. *South Med J* 1986; 79:310.
44. McCahill ME: Somatoform and related disorders: Delivery of diagnosis as first step. *Am Fam Physician* 1995; 52:193-204.
45. Rogers MP, et al: Prevalence of somatoform disorders in a large sample of patients with anxiety disorders. *Psychosomatics* 1996; 37:17.
46. Lipowski ZJ: Somatization and depression. *Psychosomatics* 1990; 31:13.
47. Katon W: Depression: Somatization and social factors [editorial]. *J Fam Pract* 1988; 27:579.
48. Goldberg D, et al: Detecting anxiety and depression in general medical settings. *BMJ* 1988; 297:897.
49. Stein DJ: Comorbidity in generalized anxiety disorder: Impact and implications. *J Clin Psychiatry* 2001; 62(Suppl 11):29.
50. Murphy GE: The clinical management of hysteria. *JAMA* 1982; 247:2559.
51. Fishbain DA: Secondary gain concept: Definition problems and its abuse in medical practice. *J Pain* 1994; 3:264-273.
52. McDermott BE, Feldman MD: Malingering in the medical setting. *Psychiatr Clin North Am* 2007; 30:645-662.
53. Dula DJ, DeNaples L: Emergency department presentation of patients with conversion disorder. *Acad Emerg Med* 1995; 2:120.
54. Johns M: Communicating effectively with a patient who has somatization disorder. *Am Fam Physician* 1999; 59:2639.
55. Fishbain DA, et al: Do antidepressants have an analgesic effect in psychogenic pain and somatoform pain disorder? A meta-analysis. *Psychosom Med* 1998; 60:503.
56. Stewart DE: The changing faces of somatization. *Psychosomatics* 1990; 31:153.
57. Barsky AJ: Hypochondriasis: Medical management and psychiatric treatment. *Psychosomatics* 1996; 37:48.
58. Kashner TM, et al: Enhancing the health of somatization disorder patients: Effectiveness of short-term group therapy. *Psychosomatics* 1995; 36:462.
59. Hahn SR, et al: The difficult doctor-patient relationship: Somatization, personality and psychopathology. *J Clin Epidemiol* 1994; 47:647.
60. Hahn SR: Physical symptoms and physician-experienced difficulty in the physician-patient relationship. *Ann Intern Med* 2001; 134:897.
61. Barry CA, Stevenson FA, Britten N, Barber N, Bradley CP: Giving voice to the lifeworld: More humane, more effective medical care? *Soc Sci Med* 2001; 53:487.
62. Schuman AL, Markakis K, Beckman HB, Frankel R: A model of empathetic communication in the medical interview. *JAMA* 1997; 277:678.
63. Gillette RD: Behavioral factors in the management of back pain. *Am Fam Physician* 1996; 53:1313.
64. Campo JV, Fritsch SL: Somatization in children and adolescents. *J Am Acad Child Adolesc Psychiatry* 1994; 33:1223.

www.ketabpezeshki.com 66485457-66963820

Chapter 114

Factitious Disorders and Malingering

Jag S. Heer

PERSPECTIVE

Patients may present to the emergency department with symptoms that are simulated or intentionally produced. The reasons that cause this behavior define two distinct varieties: factitious disorders and malingering.

Factitious disorders are characterized by symptoms or signs that are intentionally produced or feigned by the patient in the absence of apparent external incentives.[1,2] Factitious disorders have been present throughout history. In the second century, Galen described Roman patients inducing and feigning vomiting and rectal bleeding.[3] Hector Gavin sought to categorize this behavior in 1834.[3] These patients constitute approximately 1% of general psychiatric referrals, but this percentage is lower than that seen in emergency medicine because these patients rarely accept psychiatric treatment.[1,4] Of patients referred to infectious disease specialists for fever of unknown origin, 9.3% of the disorders are factitious.[5] Between 5 and 20% of patients observed in epilepsy clinics have psychogenic seizures, and the number reaches 44% in some primary care settings.[6] Among patients submitting kidney stones for analysis, up to 3.5% are fraudulent.[7]

Munchausen syndrome, the most dramatic and exasperating of the factitious disorders, was originally described in 1951.[8] This fortunately rare syndrome takes its name from Baron Karl F. von Munchausen (1720-1797), a revered German military officer and noted raconteur who had his embellished life stories stolen and parodied in a 1785 pamphlet.[3] The diagnosis applies to only 10 to 20% of patients with factitious disorders.[1,9] Other names applied include the "hospital hobo syndrome" (patients wander from hospital to hospital seeking admission), peregrinating (wandering) problem patients, hospital addict, polysurgical addiction, laparotomaphilia migrans, Kopenickades syndrome, Ahasuerus syndrome, and hospital vagrant.[4,10,11]

Munchausen syndrome by proxy (MSBP), an especially pernicious variant that involves the simulation or production of factitious disease in children by a parent or caregiver, was first described in 1977.[12] There are approximately 1200 estimated new cases of MSBP per year in the United States.[3] The condition excludes straightforward physical abuse or neglect and simple failure to thrive; mere lying to cover up physical abuse is not MSBP.[13,14] The key discriminator is motive: the mother is making the child ill so that she can vicariously assume the sick role with all its benefits. The mortality rate from MSBP is 9 to 31%.[14,15] Children who die are generally younger than 3 years, and the most frequent causes of death are suffocation and poisoning.[14] Permanent disfigurement or permanent impairment of function resulting directly from induced disease or indirectly from invasive procedures, multiple medications, or major surgery occurs in at least 8% of these children.[14,16] Other names applied include Polle's syndrome (Polle was a child of Baron Munchausen who died mysteriously),[3,10] factitious disorder by proxy,[17] pediatric condition falsification,[18] and Meadow's syndrome.[2]

Malingering is the simulation of disease by the intentional production of false or grossly exaggerated physical or psychological symptoms, motivated by external incentives, such as avoidance of military conscription or duty, avoidance of work, obtainment of financial compensation, evasion of criminal prosecution, obtainment of drugs, gaining of hospital admission (for the purpose of obtaining free room and board), or securing of better living conditions.[2,19-21] The most common goal among such "patients" presenting to the emergency department is to obtain drugs, whereas in the office or clinic the gain is more commonly insurance payments or industrial injury settlements.[22] Because of underreporting the true incidence of malingering is difficult to gauge, but estimates include a 1% incidence among mental health patients in civilian clinical practice, 5% in the military, and as high as 10 to 20% among patients presenting in a litigious context.[20] The most likely conditions to be feigned are mild head injury, fibromyalgia, chronic fatigue syndrome, and chronic pain.[23]

CLINICAL FEATURES

Factitious Disorders

With a factitious disorder, the production of symptoms and signs is compulsive; the patient is unable to refrain from the behavior even when its risks are known. The behavior is voluntary only in the sense that it is deliberate and purposeful (intentional) but not in the sense that the acts can be fully controlled.[2] The underlying motivation for producing these deceptions, securing the sick role, is primarily unconscious.[9,24,25] Individuals who readily admit that they have produced their own injuries (e.g., self-mutilation) are not included in the category of factitious disorders.[17] Presentations may be acute, in response to an identifiable recent psychosocial stress (termination of romantic relationship, threats to self-esteem), or a chronic life pattern, reflective of the way in which the person deals with life in general.[26] The symptoms involved may be either psychological or physical.

Psychological Symptoms

This disorder is the intentional production or feigning of psychological (often psychotic) symptoms suggestive of a mental disorder. Stimulants may be used to induce restlessness or insomnia; hallucinogens, to create altered levels of consciousness; and hypnotics, to produce lethargy. This psychological factitious condition

www.ketabpezeshki.com 66485457-66963820

is less common than factitious disorders with physical symptoms and is almost always superimposed on a severe personality disorder.[2,17]

Physical Symptoms

The intentional production of physical symptoms may take the form of fabricating of symptoms without signs (e.g., feigning abdominal pain), simulation of signs suggesting illness (e.g., fraudulent pyuria, induced anemia), self-inflicted conditions (e.g., the production of abscesses by injection of contaminated material under the skin), or genuine complications from the intentional misuse of medications (e.g., diuretics, hypoglycemic agents).[21] These patients are predominantly unmarried women younger than 40 years. They typically accept their illness with few complaints and are generally well-educated, responsible workers or students with moral attitudes and otherwise conscientious behavior.[21,27,28] Many are in health care occupations, including nurses, aides, and physicians.

These patients are willing to undergo incredible hardship, limb amputation, organ loss, and even death to perpetuate the masquerade.[21] Although multiple hospitalizations often lead to iatrogenic physical conditions, such as postoperative pain syndromes and drug addictions, patients continue to crave hospitalization for its own sake. They typically have a fragile and fragmented self-image and are susceptible to psychotic and even suicidal episodes.[27] Interactions with the health care system and relationships with caregivers provide the needed structure that stabilizes the patient's sense of self. The hospital may be perceived as a refuge, sanctuary, or womblike environment.[4,21,24,29] Some patients are apparently driven by the conviction that they have a real but as yet undiscovered illness. Consequently, artificial symptoms are contrived to convince the physician to continue a search for the elusive disease process.[21] Factitious illness behavior has even emerged on the Internet. "Virtual support groups" offering person-to-person communications through chat rooms and bulletin boards have been perpetrated by individuals, under the pretense of illness or personal crisis, for the purpose of extracting attention or sympathy, acting out anger, or exercising control over others.[30]

There has been increasing recognition of factitious illness produced by children (distinct from the MSBP described later). These children, ranging in age from 8 to 18 years, are typically "bland, flat and indifferent during their extensive medical interventions . . . depressed, socially isolated and often obese."[31] Among the most common presentations are fever without clear etiology, diabetic ketoacidosis, purpura, and recurrent infections. The prognosis is good if identification and psychotherapeutic intervention can be carried out at a young age.[31]

Munchausen Syndrome

The uncommon patient with true Munchausen syndrome has a prolonged pattern of "medical imposture," usually years in duration. The behavior usually begins before the age of 20 years and is diagnosed between the ages of 35 and 39 years. Twice as many men as women are affected.[4,32] Patients' entire adult lives may consist of trying to gain admission to hospitals and then steadfastly resisting discharge. Their career of imposture usually lasts about 9 years but has continued unabated for as long as 50 years.[4] The quest for repeated hospitalizations often takes these patients to numerous and widespread cities, states, and countries.[2]

These individuals see themselves as important people, or at least related to such persons, and their life events are depicted as exceptional.[32] They possess extensive knowledge of medical terminology. There is frequently a history of genuine disease, and the individual may exhibit objective physical findings.[27]

The symptoms presented are "limited only by the person's medical knowledge, sophistication, and imagination."[2] The alleged illnesses involved have been termed *dilemma diagnoses* in that investigators rarely can totally rule out the disorder, clarify the cause, or prove that it did not exist at one time.[4] Common presentations are those that most reliably result in admission to the hospital, such as abdominal pain, self-injection of a foreign substance,[10,11] feculent urine, bleeding disorders, hemoptysis, paroxysmal headaches, seizures, shortness of breath, asthma with respiratory failure,[4,33] chronic pain,[25] acute cardiovascular symptoms (e.g., chest pain, induced hypertension and syncope),[32] renal colic and spurious urolithiasis,[7] fever of unknown origin (hyperpyrexia figmentatica),[5,11] profound hypoglycemia, and coma with anisocoria.[34] Some self-induced conditions are highly injurious or even lethal.[10]

The patient usually presents during evenings or on weekends so as to minimize accessibility to psychiatric consultants, personal physicians, and past medical records.[11,27] In teaching institutions these patients often present in July, shortly after the change in resident house officers.[4] They relate their history in a precise, dramatic, even intriguing fashion, embellished with flourishes of pathologic lying and self-aggrandizement. *Pseudologia fantastica,* or pathologic lying, is a distinctive peculiarity of these patients. In a chronic, often lifelong behavior pattern, the patient typically takes a central and heroic role in these tales, which may function as a way to act out fantasy.[35] The history quickly becomes vague and inconsistent, however, when the patient is questioned in detail about medical contacts.[2,29] Attempts to manage the complaint on an outpatient basis are adamantly resisted.[25] Once admitted, the patient initially appeals to the physician's qualities of nurturance and omnipotence, lavishing praise on the caregivers. Behavior rapidly evolves, however, as the patient creates havoc on the ward by insisting on excessive attention while ignoring both hospital rules and the prescribed therapeutic regimen.[2] When the hoax is uncovered and the patient confronted, fear of rejection abruptly changes into rage against the treating physician, closely followed by departure from the hospital against medical advice.[10,11,25]

Munchausen Syndrome by Proxy

The diagnosis of MSBP depends on specific criteria (Box 114-1).[14] The presenting complaints typically evade definitive diagnosis and are refractory to conventional therapy for no apparent reason.[14] The symptoms are usually more than five in number, presented in a confused picture; they are unusual or serious and, by design, unverifiable. They invariably occur when the mother is alone with the child or otherwise unobserved.[36] In 72 to 95% of cases, simulation or production of illness occurs while the victim is hospitalized.[14]

Simulated illness, faked by the mother without producing direct harm to the child (e.g., the addition of blood to a urine specimen), is present in 25% of cases. *Produced illness,* which the mother

Box 114-1 Criteria for the Diagnosis of Munchausen Syndrome by Proxy

1. Apparent illness or health-related abnormality that the parent or someone who is in loco parentis has concocted or produced
2. Presentation of the child for medical treatment, usually persistently
3. Failure by the perpetrator to acknowledge the true etiology or the deception
4. Cessation of the acute symptoms and signs of illness when the child is separated from the perpetrator

www.ketabpezeshki.com 66485457-66963820

actually inflicts on the child (e.g., the injection of feces into an intravenous line), is found in 50% of cases. Both simulated and produced illnesses are found in 25% of cases.[14]

MSBP most commonly arises with factitious bleeding, seizures, central nervous system (CNS) depression, apnea, diarrhea, vomiting, fever, and rash.[14] Reported techniques of simulation or production of disease include administration of drugs or toxins (e.g., chronic arsenic poisoning, ipecac, warfarin, phenolphthalein, hydrocarbons, salt, imipramine, laxatives, CNS depressants), caustics applied to the skin, and nasal aspiration of cooking oil.[12,14-16,27,37] Techniques of asphyxiation include (1) covering the mouth or nose with one or both hands, a cloth, or plastic film and (2) inserting the fingers into the back of the mouth. In such instances, even struggling infants may sustain no cutaneous markings.[38] Cases involving seizures are common and may involve third-party witnesses. On personal questioning, however, these witnesses frequently deny the occurrence of seizure activity.[14]

In a variant of MSBP termed *serial Munchausen syndrome by proxy,* there may be a history of similar strange presentations in multiple siblings, although typically only one child is involved at a time.[15,16,38] In 9% of such cases there is a history of siblings who died under mysterious circumstances.[14]

Perpetrator Characteristics. Ninety-eight percent of perpetrators are biologic mothers who come from all socioeconomic groups.[14] Many have a background in health professions or social work, features of Munchausen syndrome themselves, or a past history of psychiatric treatment, marital problems, or suicide attempts.[14,15] Depression, anxiety, and somatization are common, but frankly psychotic behavior by the mother is atypical.[14,16] Perpetrators of MSBP have an inherent skill in manipulating health workers and child protection services.[39] They are pleasant, socially adept, cooperative, and appreciative of good medical care. They often display a peculiar eagerness to have invasive procedures performed on their child.[3] They often choose to stay in the hospital with their child, cultivate unusually close relationships with hospital staff, and thrive on the staff's attention.[12-14,16,37] This affable relationship with the medical team rapidly changes to excessive anger and denial when the perpetrator is confronted with suspicions.[19]

Most of these mothers have had an abusive experience early in life, and they use the health care system as a means to satisfy personal nurturing demands.[36,40] They often cannot distinguish their needs from the child's and satisfy their own needs first. They derive a sense of purpose from the medical and nursing attention gained when their children are in the hospital.[13,14,16,40] Alternatively, the behavior may enable the mothers to escape from their own physical or psychological illnesses, marital difficulties, or social problems.[36]

Victim Characteristics. Victims of MSBP are equally male and female children. The mean age at diagnosis is 40 months, and the mean duration from the onset of signs and symptoms to diagnosis is 15 months.[14] A known physical illness that explains part of the symptoms is common among these children.[40] Most have a history of significant failure to thrive and have been hospitalized in more than one institution. Delays in many areas of performance and learning, difficulty with family relationships, attention deficit disorder, or clinical depression may coexist.[16] Some of these victims may have factitious disorder later in life.[3] Victims of MSBP are also found among the elderly population, although this is uncommon.[41]

Malingering

Malingering is frequently found in association with *antisocial personality disorder*. On questioning, malingerers are vague about prior hospitalizations or treatments. The physicians who previously treated them are usually unavailable. At times, malingerers may be careless about their symptoms and abandon them when they believe no one is watching.[27] In some "patients," such as those seeking drugs, homeless persons seeking hospital admission on a cold night, or prisoners wanting a holiday from incarceration, the secondary gain may be clear. In other persons, the external incentive may be obscure.

In contrast to the person with factitious disorders, the malingerer prefers *counterfeit mental illness* because it is objectively difficult to verify or to disprove. Amnesia is the most common psychological presentation, followed by paranoia, morbid depression, suicidal ideation, and psychosis.[20]

DIAGNOSTIC STRATEGIES

Factitious Disorders

Initial diagnosis is often delayed because the possibility of factitious disease is not considered, physicians may be unfamiliar with this problem, or the patient does not exhibit the type of personality expected with this behavior.[7] Diagnosis may be confounded by genuine medical illnesses predating and coexisting with a factitious disorder. For example, patients with factitious hypoglycemia may have a history of insulin-dependent diabetes mellitus, or factitious skin disorders may be preceded by true dermatologic diseases.[1] Identification of a factitious disorder is usually made in one of four ways: (1) the patient is accidentally discovered in the act, (2) incriminating items are found, (3) laboratory values suggest nonorganic etiology, or (4) the diagnosis is made by exclusion.[17] Wallach[42] provides a useful review of the laboratory diagnosis of factitious disorders, including feigned endocrine, hematologic, genitourinary, gastrointestinal, and infectious disorders.

Suspected MSBP requires a detailed description of the event or illness and a search for caregiver witnesses, who should be interviewed personally. Although it is essential to see the child when the symptoms are present, the parents show great ingenuity at frustrating this effort.[40] Additional history of unusual illness in siblings and parents should be sought. Child victims who are verbal should be interviewed in private about foods, medicines, and their recollection of the symptoms or events. Prior medical records of the victim and, if possible, the siblings should be examined, although parents may impede such data gathering.

The major obstacle to early discovery of MSBP is its omission from the differential diagnosis. When it is considered, the diagnosis is generally made easily and quickly.[14] A suspected diagnosis may be confirmed through separation of the parent from the child (with consequent cessation of symptoms), covert video surveillance during hospitalization, or toxin screens.[16,36,38] In the majority of cases, the caregiver attempts to induce episodes surreptitiously while in the hospital, often during the first day of admission.[14,36]

Malingering

Malingering should be strongly suspected with any combination of certain factors (Box 114-2).[2,43] A definitive diagnosis of malingering is rare and can be established only with the patient's

Box 114-2 Characteristics of Malingering

1. Medicolegal context of the presentation (e.g., the patient was referred by his or her attorney)
2. Marked discrepancy between the person's claimed stress or disability and objective findings
3. Poor cooperation during the diagnostic evaluation or poor compliance with previously prescribed treatment regimens
4. The person exhibits or has a history of antisocial behavior

www.ketabpezeshki.com 66485457-66963820

confession.[44] Because malingering constitutes criminal behavior, documentation of this diagnosis should be made with care.[20] In the absence of proof of wrongdoing, it is best to assume that the patient is not a malingerer but rather a common somatizer.[44] Malingerers who pursue drugs may report an unusually large number of drug allergies to persuade the physician to prescribe their drug of choice or simply insist on a specific drug (e.g., meperidine [Demerol] or hydromorphone [Dilaudid]).[45] Unfortunately, the Internet offers a wide availability of quality medical advice on how to convincingly feign pain and disability.[45]

DIFFERENTIAL CONSIDERATIONS

Patients with factitious disorders are distinguished from malingerers because their desired hospitalization or surgery seems to offer no secondary gain other than to play the sick role.[2,10,22] The clinical presentation of the majority of patients with factitious disorders, unlike those with Munchausen syndrome, is relatively subtle and convincing. The complaints are generally chronic in nature rather than emergent and precipitous, and there are no obvious associated behavioral aberrations.[21] The most important diagnosis to be excluded with a likely factitious disorder is a genuine medical condition that might account for the illness. The chronicity of malingering is usually less than that associated with factitious disorder, and malingerers are more reluctant to accept expensive, possibly painful, or dangerous tests or surgery.[22]

MANAGEMENT

Factitious Disorders

Treatment options for factitious disorders depend on the patient's characteristics. Although it is challenging, management of common forms of factitious disorder can be more rewarding, especially with adolescents, than management of Munchausen syndrome.[1,9,24,29] The prognosis is more favorable for cases with an underlying depression than for those associated with borderline personalities.[27]

The best approach to patients with factitious disorder, other than Munchausen syndrome and MSBP, is controversial. Direct nonaccusatory confrontation has been advocated as "the foundation of effective management" when it is coupled with the assurance that an ongoing relationship with a physician will be provided.[4,21,22,27] This may be the first step in the acceptance of outpatient therapy.[4]

Others point out that confrontation is ineffective in most patients and may even be counterproductive in that it threatens to undermine a needed psychological defense. Enforced recognition of external objective reality, while simultaneously disallowing the patient's subjective experience, may generate even more dysfunction directed at legitimizing and maintaining symptoms and may even place the patient at risk for suicide.[9,17,29,46,47] Some patients may relinquish this defense if they feel safe in doing so and may abandon a claim to disease if some face-saving option is offered. This approach, termed the *therapeutic double bind* or *contingency management,* involves informing the patient that a factitious disorder may exist. The patient is further told that failure to respond fully to medical care would constitute conclusive evidence that the patient's problem is not organic but rather psychiatric. The problem is therefore reframed or redefined in such a way that (1) symptoms and their resolution are both legitimized and (2) the patient has little choice but to accept and respond to a proposed course of action or seek care elsewhere.[9,47]

Individuals with Munchausen syndrome typically demonstrate overt sociopathic traits or a borderline personality disorder and are demanding and manipulative, especially regarding analgesics.[5,9] They have been described as "essentially untreatable," and successful management of this condition is, in fact, considered reportable. Early confrontation or limit setting, especially regarding drug use, is advocated.[9,11,21,25,27] Although Munchausen patients typically do not want to be examined extensively, a thorough physical examination should be performed to rule out physical disease.

MSBP constitutes a form of child (or elder) abuse, and appropriate action to protect the victim, including notification of state social service agencies, should take immediate priority.[38,41] If available, a pediatrician who has expertise in child abuse should assess the case. When the diagnosis has been established and the parents have been confronted, psychiatric care should be made immediately available to the parents because maternal suicide is a significant risk.[14]

Malingering

Malingerers do not want to be treated. Because they are "gaming the system" for personal advantage, the last thing they want is an accurate identification of their behavior and appropriate intervention. The emergency physician should maintain clinical neutrality, offering the reassurance that the symptoms and examination are not consistent with any serious disease.

Some authors have characterized patients' use of medical resources under false pretenses as criminal behavior, and several states have enacted legislation against the fraudulent acquisition of medical services with successful prosecution of such behavior.[48] Conversely, patients with factitious disorders can and do sue. In dealing with such patients, it is advisable to involve hospital administration and risk management. Clandestine searches are inadvisable, and respect for the patient's confidentiality should be maintained.[17]

DISPOSITION

Patients suspected of having a factitious disorder should be referred for primary care follow-up, and if it is acceptable to the patient, psychiatric referral should also be arranged. Referral to other medical specialists or hospitalization should be avoided when possible.

The manner of presentation and the unavailability of past medical history often allow patients with Munchausen syndrome to achieve hospital admission. If the patient is discharged from the emergency department, outpatient primary care follow-up and psychiatric referral should be offered, although both are likely to be refused.[25]

Because perpetrators of MSBP typically induce symptomatic episodes soon after hospitalization, admission of the victims (children or elderly persons) without taking appropriate precautions may actually place them at increased risk.[14] Visits by the suspected perpetrator should be closely supervised, and no food, drink, or medicines should be brought in by the family. Protective services should be notified. Out-of-home placement of children in established cases of MSBP is advisable, and best outcomes are seen among children taken into long-term care at an early age without access to their mother. Children allowed to return home have a high rate of repeated abuse.[39] In 20% of reported deaths, the parents had been confronted and the child sent home to them, subsequently to die.[14]

After courteous but assertive reassurance, suspected malingerers should be offered primary care follow-up if the symptoms do not resolve. These individuals may become threatening when they are either denied treatment or overtly confronted.[19]

www.ketabpezeshki.com 66485457-66963820

KEY CONCEPTS

- Emergency department patients who have consciously synthesized symptoms and signs may be divided into two broad diagnostic categories: (1) those with obvious secondary gain (malingering), who control their actions, and (2) those with a motivation of achieving the sick role (factitious disorders), who cannot control their actions.
- Emergency department management of patients suspected of fabricating disease includes a caring attitude and a search for objective clinical evidence of treatable medical or psychiatric illness.
- Unnecessary tests, medications, and hospitalizations should be avoided in the absence of objective evidence of a medical or psychiatric disease, and patients should be referred for ongoing primary care.
- In cases of suspected MSBP involving children or elderly persons, protection of the victim takes first priority.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Sutherland AJ, Rodin GM: Factitious disorders in a general hospital setting: Clinical features and a review of the literature. *Psychosomatics* 1990; 31:392.
2. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed, text rev. Washington, DC: American Psychiatric Association; 2000.
3. Feldman MD: *Playing Sick? Untangling the Web of Munchausen Syndrome, Munchausen by Proxy, Malingering, and Factitious Disorder*. New York: Routledge; 2004.
4. Burkle FM, Calabro JJ, Parks FB: Munchausen's syndrome presenting as a respiratory failure requiring intubation. *Ann Emerg Med* 1987; 16:203.
5. Aduan RP, et al: Factitious fever and self-induced infection: A report of 32 cases and review of the literature. *Ann Intern Med* 1979; 90:230.
6. Riggio S: Psychogenic seizures. *Emerg Med Clin North Am* 1994; 12:1001.
7. Gault MH, Campbell NR, Aksu AE: Spurious stones. *Nephron* 1988; 48:274.
8. Asher R: Munchausen syndrome. *Lancet* 1951; 1:339.
9. Eisendrath SJ: Factitious physical disorders: Treatment without confrontation. *Psychosomatics* 1989; 30:383.
10. Nichols GR, Davis GJ, Corey TS: In the shadow of the baron: Sudden death due to Munchausen syndrome. *Am J Emerg Med* 1990; 8:216.
11. Scully RE, Mark EJ, McNeely BU: Weekly clinicopathological exercises, case records of the Massachusetts General Hospital. Case 28-1984. *N Engl J Med* 1984; 311:108.
12. Meadow R: Munchausen syndrome by proxy: The hinterland of child abuse. *Lancet* 1977; 1:343.
13. Meadow R: What is, and what is not, "Munchausen syndrome by proxy"? *Arch Dis Child* 1995; 72:534.
14. Rosenberg DA: Web of deceit: A literature review of Munchausen syndrome by proxy. *Child Abuse Negl* 1987; 11:547.
15. Alexander R, Smith W, Stevenson R: Serial Munchausen syndrome by proxy. *Pediatrics* 1990; 86:581.
16. Lacey SR, et al: Munchausen syndrome by proxy: Patterns of presentation to pediatric surgeons. *J Pediatr Surg* 1993; 28:827.
17. Wise MG, Ford CV: Factitious disorders. *Prim Care* 1999; 26:315.
18. Schreier H: Munchausen by proxy defined. *Pediatrics* 2002; 110:985.
19. Dubovsky SL, Weissberg MP: *Hypochondriasis*. In: Dubovsky SL, ed: *Clinical Psychiatry in Primary Care*, 3rd ed. Baltimore: Williams & Wilkins; 1986:18-61.
20. Lipian MS, Mills MJ: *Malingering*. In: Sadock BJ, Sadock VA, eds: *Comprehensive Textbook of Psychiatry*, 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2000:1898-1908.
21. Reich P, Gottfried LA: Factitious disorders in a teaching hospital. *Ann Intern Med* 1983; 99:240.
22. Ries RK, et al: The medical care abuser: Differential diagnosis and management. *J Fam Pract* 1981; 13:257.
23. Mittenberg W: Base rates of malingering and symptom exaggeration. *J Clin Exp Neuropsychol* 2002; 24:1094.
24. Eisendrath SJ: Factitious physical disorders. *West J Med* 1994; 160:177.
25. Fishbain DA, et al: Munchausen syndrome presenting with chronic pain: Case report. *Pain* 1988; 35:91.
26. Goldstein AB: Identification and classification of factitious disorders: An analysis of cases reported during a ten year period. *Int J Psychiatry Med* 1998; 28:221.
27. Ford CV: *The Somatizing Disorders: Illness as a Way of Life*. New York: Elsevier Biomedical; 1983.
28. Krahn LE, Li H, O'Connor MK: Patients who strive to be ill: Factitious disorder with physical symptoms. *Am J Psychiatry* 2003; 160:1163.
29. Spivak H, Rodin G, Sutherland A: The psychology of factitious disorders: A reconsideration. *Psychosomatics* 1994; 35:25.
30. Feldman MD: Munchausen by Internet: Detecting factitious illness and crisis on the Internet. *South Med J* 2000; 93:669.
31. Libow JA: Child and adolescent illness falsification. *Pediatrics* 2000; 105:336.
32. Ludwigs U, et al: Factitious disorder presenting with acute cardiovascular symptoms. *J Intern Med* 1994; 236:685.
33. Bernstein JA, et al: Potentially fatal asthma and syncope: A new variant of Munchausen's syndrome in sports medicine. *Chest* 1991; 99:763.
34. Bretz SW, Richards JR: Munchausen syndrome presenting acutely in the emergency department. *J Emerg Med* 1999; 18:417.
35. Newmark N, Adityanjee, Kay J: Pseudologia fantastica and factitious disorder: Review of the literature and a case report. *Compr Psychiatry* 1999; 40:89.
36. Samuels MP, et al: Fourteen cases of imposed upper airway obstruction. *Arch Dis Child* 1992; 67:162.
37. Fisher GC, Mitchell I: Is Munchausen syndrome by proxy really a syndrome? *Arch Dis Child* 1995; 72:530.
38. Mitchell I, et al: Apnea and factitious illness (Munchausen syndrome) by proxy. *Pediatrics* 1993; 92:810.
39. Davis P, et al: Procedures, placement, and risks of further abuse after Munchausen syndrome by proxy, non-accidental poisoning, and non-accidental suffocation. *Arch Dis Child* 1998; 78:217.
40. Eminson DM, Postlethwaite RJ: Factitious illness: Recognition and management. *Arch Dis Child* 1992; 67:1510.
41. Ben-Chetrit E, Melmed RN: Recurrent hypoglycaemia in multiple myeloma: A case of Munchausen syndrome by proxy in an elderly patient. *J Intern Med* 1998; 244:175.
42. Wallach J: Laboratory diagnosis of factitious disorders. *Arch Intern Med* 1994; 154:1690.
43. Levine SS, Helm ML: An AIDS diagnosis used as focus of malingering. *West J Med* 1988; 148:337.
44. Smith RC: Somatization in primary care. *Clin Obstet Gynecol* 1988; 31:902.
45. McDermott BE, Feldman MD: Malingering in the medical setting. *Psychiatr Clin North Am* 2007; 30:645.
46. Ugurlu S, et al: Factitious disease of periocular and facial skin. *Am J Ophthalmol* 1999; 127:196.
47. Teasell RW, Shapiro AP: Strategic-behavioral intervention in the treatment of chronic nonorganic motor disorders. *Am J Phys Med Rehabil* 1994; 73:44.
48. Feldman MD: Factitious disorders and fraud [letter]. *Psychosomatics* 1995; 36:509.

www.ketabpezeshki.com 66485457-66963820

Chapter 115

Suicide

Stephen A. Colucciello

PERSPECTIVE

Although suicide has occurred in all societies since the beginning of recorded history, attitudes toward suicide have differed dramatically among various eras and cultures. Seneca viewed suicide as the ultimate expression of personal freedom, but later Judeo-Christian religions have routinely condemned it. Shakespeare portrayed suicide sympathetically and expressed either pity or admiration for the victim.[1]

In the United States, suicide is illegal in 49 states, and only since 1994 has assisted suicide of terminally ill patients been sanctioned in Oregon. On the Internet, suicide help groups provide active advice on methods, and numerous bulletin boards condemn them. More than 100,000 sites about suicide now appear on the Internet.[2]

Suicidal patients represent almost 2% of emergency department (ED) visits.[3] Two facts are especially important to remember in approaching potentially suicidal patients. First, many suicide attempts occur during an acute crisis, such as a personal loss or the exacerbation of an underlying psychiatric disorder. This acute crisis is usually time limited and may be resolvable or treatable. Second, except for the acutely psychotic patient, suicidal patients are usually ambivalent about dying. The attitude and approach of the emergency physician can help a patient choose crisis resolution rather than death.

Definitions

The term *suicide,* from the Latin *suicidum* ("to kill the self"), refers to a continuum of thought and action that runs from ideation to completion of the act.[4] *Parasuicide* is used by the British to describe an attempted suicide that is more of a gesture than a serious act. Statistically, there are 10 to 40 suicide attempts for every completed act.[5] *Chronic suicidal behavior* consists of recurrent self-destructive acts, such as heavy drinking in the presence of alcoholic liver disease. *Occult suicide* refers to self-destructive acts disguised as accidents, such as the intoxicated, depressed driver in an apparently accidental car crash. *Silent suicide* describes the act of slowly killing oneself by nonviolent means, such as starvation or noncompliance with essential medical treatment. Silent suicide is most common in elders and frequently goes unrecognized.

A *suicide pact* is an agreement between two people who are intimately involved and accounts for 0.6% of all suicides.[6] *Mass suicide* or *group suicide* involves a number of willing and sometimes not-so-willing persons, such as members of an apocalyptic cult.

Epidemiology

Suicidal ideation is common, and as many as one in three people consider suicide during their lifetime.[7] In 2006, suicide was the eleventh leading cause of death among persons older than 9 years, accounting for 33,289 deaths.[8] This is the equivalent of 89 suicides per day or one suicide every 15 minutes. It is the fourth leading cause of death for adults between the ages of 18 and 65 years. In the United States, there are more than 800,000 suicide attempts per year, many of which do not present to EDs.[9]

In one study performed during a 5-year period, there were approximately 412,000 annual ED visits for attempted suicide and self-inflicted injury. The most common method of injury was poisoning (68%), followed by cutting or piercing (20%). One third were admitted to the hospital, with 31% going to the intensive care unit. A psychiatric diagnosis was assigned for 55% of visits, with depressive disorder accounting for 34% and alcohol abuse for 16%.[10]

The rate of self-harm visits to the ED appears to be increasing. From 1999 to 2004, intentional self-harm episodes increased by 20% with a correspondingly greater increase in hospitalizations for the same.[11] Unemployment and financial troubles may play a role in this rise, and a recent study links suicidal behavior to economic conditions. Longitudinal data show that overall suicide rates rise during recessions and fall during expansions, particularly for patients aged 25 to 64 years.[12] In addition to the recent economic troubles, there are other factors that may play a role in the increasing number of suicide attempters seen in the ED. These include a rise in homelessness and the collapse of the mental health hospital system in most states.[13]

Suicide rates vary with age, gender, race, and marital status. Suicides are highest among older individuals, particularly elderly white men. The case fatality rate also increases tremendously with advancing age, from 5% in youths aged 5 to 14 years to 34% in adults older than 64 years.[14] White men commit 73% of all suicides in the United States. Whites and Native Americans are much more likely to commit suicide than are African Americans, Hispanics, or Asians. Marriage decreases the likelihood of suicide, but the rate of suicide is higher for separated or divorced people than for those who never had a close relationship.

Women attempt suicide three to four times more often than men do, whereas men are three to four times more likely to succeed. In one U.S. study, only 5% of suicide attempts by women were fatal compared with 23% of those by men.[14] In general, men tend to use more lethal methods, such as firearms. Worldwide, Chinese and Indian women have rates of suicide higher than those of women of other nationalities.[15] Pregnant women are at a

www.ketabpezeshki.com 66485457-66963820

Box 115-1 Risk Factors for Suicide

Demographics
White men older than 65 years
Women older than 60 years
Males 15 to 24 years old
American Indian or Native Alaskan 15 to 34 years old

Psychiatric Disorders
Major depression
Bipolar disorder
Schizophrenia
Borderline personality disorder
Panic disorder

Substance Abuse
Alcoholism
Drug abuse (especially cocaine)

Medical History
Prior suicide attempts
Chronic pain or illness
Physical or sexual abuse
Recent psychiatric hospital discharge
Terminal illness (especially cancer and AIDS)
Low intelligence scores (in men)
Lower body mass index
Short stature (in men)
Cosmetic breast augmentation (in women)

Family History
Family violence
Suicide in family

Social Factors
Firearm in home
Living alone
Separated, widowed, or divorced
Unemployed
Homeless
Recent personal loss
Veterans
Recent incarceration
Lack of religious affiliation

Emotional Factors
Hopelessness
Chronic loneliness
Fixation on death

significantly lower risk than are women of childbearing age who are not pregnant. Motherhood seems to protect against suicide, except that postpartum depression is associated with a higher than normal suicide rate.

Most people who attempt suicide have one or more known risk factors (Box 115-1). Individuals with the highest risk include those with psychiatric disorders, alcohol or substance abusers, adolescents, elders, and patients with certain chronic illnesses. In patients hospitalized for psychiatric disorders, the first month after discharge carries a high risk of suicide,[16] and that risk is especially great for patients who are in the first week after discharge from a psychiatric facility.[17] Any prior history of suicide, even in the remote past, is an important risk factor.[18]

A strong association may exist between suicide risk and bisexuality or homosexuality in men.[19] This association is also seen in lesbian, gay, and bisexual adolescents.[20] Unemployment appears to be a risk factor for suicide among 18- to 24-year-old men.[21] Homeless people with mental illness are at particularly high risk for suicidal behavior, in part because of the high prevalence of traditional risk factors. Recent incarceration is also a risk factor for suicide. During the first 2 weeks after release, the risk of death among former inmates is more than 12 times that of the general population. The leading causes of death among former inmates include drug overdose, cardiovascular disease, homicide, and suicide.[22] In general, the risk of suicide in recently released prisoners approaches that in recently discharged psychiatric patients.[23]

Suicide completers and suicide attempters represent separate but overlapping populations.[24] Although 10 to 15% of suicide attempters ultimately complete suicide, 60 to 70% of suicide completers have no prior history of attempts and commit suicide on the first known attempt.[25] In individuals who committed suicide while not in contact with mental health services, nearly one third of cases had no concurrent mental disorder.[26]

PATHOPHYSIOLOGY AND ETIOLOGY

Societal, Psychiatric, and Biologic Factors

There are many motivations to attempt suicide. It may be seen as the only escape from a terminal disease or intense chronic pain. It may be an act of revenge or political protest. Most suicide attempts occur in individuals with intense feelings of hopelessness, guilt, or self-hatred, often compounded by the exacerbation of an underlying psychiatric disorder or by the occurrence or perception of a great personal loss. The underlying causes of suicide are similar for adults and adolescents; however, adolescents tend to romanticize suicide, and "copycat" suicides are frequent after the suicide of celebrities or friends. Regardless of the motivation, most suicide attempters are ambivalent, and their attraction to death is usually counterbalanced by a desire to live. This internal conflict is reflected in the high ratio of attempted to completed suicides and by the fact that most people consult a physician shortly before their death.

Psychoanalysts explain suicide in terms of psychic forces. Freud believed that suicide stems from aggression initially directed toward another person but that ultimately turns against the self. Depression and suicide in the Freudian model represent internalized anger. Many authorities have recognized this association between aggression and suicide. In the United States, more than 1000 deaths each year result from murder-suicides. The perpetrators are usually depressed mothers, despairing elderly men, or young men with intense sexual jealousy. Their victims are usually young children, blood relatives, or female sexual partners. The dual risk for suicide and violence is greatest in alcoholics.[27]

The impulses that lead to suicide differ between violent and nonviolent people. "Suicidality" is correlated with anger, fear, and suspiciousness in violent individuals and with feelings of sadness and despair in nonviolent persons. The psychic roots of suicide may arise from childhood trauma. Chronic loneliness during childhood is associated with subsequent suicide attempts during adolescence, and a history of sexual molestation is linked to suicide attempts in women and adolescents.

Current research suggests a biologic basis for depression and suicide involving the serotonergic and dopaminergic systems. People who attempt suicide have altered serotonin receptor function and low serotonin levels.[28,29] These abnormalities may be regulated through serotonergic-related genes in persons with major depression.[30] The genetic basis of suicide is not clearly understood. The STin2 genetic locus might, at least in part, account for the observed familial aggregation of suicidal behavior.[31] Polymorphisms in the tryptophan hydroxylase gene may affect the synthesis of serotonin. Recent data also indicate that certain genetic markers may be linked to suicidal ideation associated with medications used to treat depression.[32] The genetic susceptibility to suicide, however, may affect individuals only when it is associated with psychiatric illness or stress.[33] The rate of suicide is twice as high in families of suicide victims, and a family history

www.ketabpezeshki.com 66485457-66963820

of suicide predicts suicide independent of severe mental disorder.[34] Relatives of suicide completers are more than 10 times more likely than relatives of comparison subjects to attempt or to complete suicide.[35]

Depressed patients who attempt suicide excrete less homovanillic acid in their urine and produce less dopamine than depressed patients who have not attempted suicide. Low concentrations of dopamine and serotonin metabolites in the cerebrospinal fluid also correlate with suicidal behavior. Suicide attempts in women vary with estrogen levels, with 42% of attempts occurring during the first week of the menstrual cycle.[36]

Neuroanatomy may also influence suicidality; suicide victims have smaller right-sided parahippocampi than control subjects.[37] Although there are no currently available laboratory tests that can identify individuals at increased risk for suicide, research holds promise for biologic markers in the future.

Some drugs, including reserpine, benzodiazepines, and barbiturates, are associated with depression and suicidal behavior. The Food and Drug Administration recently linked suicidal ideation among children and adolescents to selective serotonin reuptake inhibitors (SSRIs) and added a black box warning for SSRI use in all age groups.[38] It is ironic that in both the United States and the Netherlands, SSRI prescriptions for children and adolescents decreased after these regulatory warnings and these decreases were associated with *increases* in suicide rates in both children and adolescents.[39] Patients who commit suicide shortly after the initiation of antidepressant medications are explained by the "mobilization of energy" theory.[40,41] According to this theory, patients who are profoundly depressed may have the energy to attempt suicide only as their condition improves with treatment. Such patients should be monitored very closely during their initial phase of treatment.

Methods of Attempting Suicide

Most completed suicides involve firearms (70%), whereas most attempted suicides involve the ingestion of drugs or poisons (72%).[42] In one large study, poisoning with drugs accounted for 74% of acts but only 14% of fatalities; firearms and hanging accounted for only 10% of acts but 67% of fatalities. Firearms were the most lethal means (91% resulted in death), followed by drowning (84%) and hanging (82%).[14] Episodes involving firearms are 2.6 times more lethal than the second most lethal suicide method, suffocation.[43] In 2005, 17,002 suicides involved firearms in the United States.[44] Guns represent the most common method of suicide in all victim subgroups, especially among older persons and adolescents, and the use of guns has increased dramatically in the past decade, recently replacing ingestion as the major cause of suicide among women.[45] The simple presence of a gun in the home represents an independent risk factor for firearm-related suicide but not by non-firearm means.[46] This is particularly true for adolescents, whose risk for suicide increases 5 to 10 times when there is a gun in the household.[47,48] In general, firearm prevalence is positively related to the suicide rate, even after control for rates of attempted suicide.[49] Suicide by handgun is often associated with drug or alcohol use.[50] The rate of gun-related suicide is 57 times higher in the first week after purchasing of a handgun.[51]

After gun-related deaths, other lethal methods chosen by men include hanging, suffocation, and jumping from a height, whereas women are more likely to commit suicide by poisoning. Antidepressant overdose is the most common cause of suicide by ingestion.[52] Cyclic antidepressants are associated with more deaths because of their widespread use and high potential for lethality. Most patients hospitalized for self-poisoning have ingested drugs prescribed by their physicians for depression.[53] SSRIs, including fluoxetine (Prozac), sertraline (Zoloft), and paroxetine (Paxil), are less lethal when they are taken in overdose and have replaced cyclic antidepressants as the first therapy in depression.

The method of suicide depends on many factors, including psychic issues of self-hate, the desire for a peaceful versus violent death, and the availability of fatal means. Those who jump to their death are more likely to be single, unemployed, or psychotic. Those who use firearms are more likely to be male, to be alcoholic, to have been arrested, or to have an antisocial or borderline personality disorder.[54] Communities with tall buildings and bridges have higher rates of suicide from falls, whereas suicide by gunfire occurs more often in areas where firearms are prevalent.

"Suicide by cop" occurs when a suicidal individual intentionally provokes a police officer by orchestrating a lethal situation in which the officer is forced to shoot in self-defense or to protect other civilians. This may account for as many as 11% of officer-involved shootings in Los Angeles.[55] Certain individuals carry a suicide note; some offer an eerie postmortem apology to the police officer who ultimately kills them.

CLINICAL FEATURES

Psychiatric Illness

Although most psychiatric patients never attempt suicide, most people who commit suicide have either a diagnosable psychiatric illness or alcoholism. Exceptions include those with mental retardation, dementia, and agoraphobia.[56] Patients with an affective disorder, especially major depression, are at highest risk.[57,58] Approximately 15 to 20% of people with major depression commit suicide, usually while under psychiatric care.[59] Individuals who experience hopelessness, anhedonia (loss of ability to experience pleasure), and mood cycling are at highest risk. Impulsive-aggressive personality disorders and alcohol abuse are independent predictors of suicide in major depression.[60]

Approximately 10% of schizophrenic patients will kill themselves. Psychotic patients who commit suicide are most often unmarried white individuals with high intelligence quotient scores.[61] Patients with borderline personality disorders are also predisposed to commit suicide. Women with borderline personality disorder who attempt suicide often have a history of childhood sexual abuse and impulsive behavior. The risk is especially high when patients require hospitalization for psychiatric illness and is greatest the first month after discharge.[62,63]

Approximately 40% of patients with panic disorder attempt suicide at some point in their lives. These patients usually have an additional comorbid psychiatric diagnosis (e.g., borderline personality disorder, substance abuse, emotional instability). However, any preexisting anxiety disorder (including social phobia, simple phobia, generalized anxiety disorder, panic disorder, agoraphobia, obsessive-compulsive disorder) is an independent risk factor for subsequent suicidal ideation and attempts.[64] Post-traumatic stress disorder, sustained by military combat personnel and disaster survivors, is also associated with suicide. Post-traumatic stress disorder frequently coexists with a major depressive episode, and this combined psychopathology enhances the risk for suicidal behavior.[65] In 2005, there were at least 6256 suicides among those who served in the U.S. armed forces, a rate double that of nonveterans. Veterans between the ages of 20 and 24 years who served in Iraq or Afghanistan had the highest suicide rate among all veterans.[66]

Alcoholism and Substance Abuse

Of successful suicides reported by the National Violent Death Reporting System, 33.3% tested positive for alcohol, 16.4% for opiates, 9.4% for cocaine, 7.7% for marijuana, and 3.9% for amphetamines.[67] Other studies show that approximately 25% of all suicides involve alcoholics, and estimates of the lifetime risk

www.ketabpezeshki.com 66485457-66963820

of suicide from chronic alcoholism range from 3 to 25%.[68] Alcoholics who commit suicide usually have multiple risk factors, including major depressive episodes, unemployment, medical illness, and interpersonal loss. In psychiatric patients, the use of alcohol increases depression and suicidal behavior.

Substance abuse among mentally ill patients is increasingly common. Psychoactive substance abuse is associated with a greater frequency, repetitiveness, and lethality in suicide attempts than other medications are.

Nearly half of all adolescents who attempt suicide use drugs shortly before the attempt, and alcohol intoxication is strongly associated with suicide by firearms.[69] Cocaine use is particularly dangerous. In New York City, 20% of all suicide victims younger than 61 years used cocaine within days of their death. Among young Hispanic men, nearly half of the suicide victims have toxicologic screens positive for cocaine.[70] In general, cocaine abusers choose violent means of self-destruction, especially firearms.

Adolescents

Suicide among adolescents has quadrupled during the past 40 years and is now the third leading cause of death (after accidents and homicides) in people between 5 and 24 years of age.[71] Approximately 2 million U.S. adolescents attempt suicide each year, and 19% report serious consideration of suicide in the past year.[72] Although some authorities believe that the rise in adolescent suicide simply corresponds to changing demographics in the United States, others believe that the increase is related to a growing sense of hopelessness, increased economic pressures, and access to firearms. In a survey of high-school students in North Carolina, 24% had seriously considered suicide, 19% had planned suicide, and 9% had actually attempted suicide during a 1-year period.[73]

Adolescent girls are more likely to attempt suicide, whereas adolescent boys are more likely to complete suicide; the ratio of attempted to completed suicides is 25:1 for adolescent girls and 3:1 for boys.[74] Most adolescents who complete suicide have made previous suicide threats.

The majority of youths who kill themselves meet criteria for diagnosable psychiatric disorders, and both alcohol and substance abuse play a significant role in teenage suicide attempts. Adolescents with panic attacks are twice as likely as adolescents without panic attacks to make suicide attempts.[75] Gay, lesbian, bisexual, or “not sure” youths may also be more prone to self-harm.[76] Belonging to the “Goth” subculture is a predictor of self-harm and attempted suicide.[77]

Nearly 40% of youths in runaway programs report prior suicide attempts.[78] Young people may also be influenced by movies or television shows that feature suicide. Teenage suicides typically increase after television broadcasts on the subject.

From 1989 to 1995, suicide by firearm in young people increased dramatically.[79] The firearm-related suicide rate in U.S. adolescents is 11 times higher than the combined rates of 25 other industrialized countries.[80] Having a gun in the home places the troubled adolescent in great danger, and storing the gun in a locked cabinet or separating it from the ammunition does not deter suicide attempts.[81] Surprisingly, up to 23% of adolescents who have attempted suicide report that their families continue to keep firearms and ammunition in the home despite their suicide attempt.

Older Adults

The highest rates of completed suicide occur in elders. Suicide by firearm is the fourth leading cause of injury-related deaths among older U.S. residents.[82] Older Americans use highly lethal methods when attempting suicide and, unlike adolescents, rarely stage an attempt that permits rescue. Self-inflicted gunshot wounds account for 88% of elder suicides.

White men older than 65 years account for approximately 80% of suicide deaths, whereas suicide is rare among elderly people belonging to minority groups.[83] Suicide among older adults is especially common in those with prior suicide attempts or major depression. Severity of depression is the strongest predictor of suicide in elders.[84] Physicians often overlook signs of depression in older patients, even though most who commit suicide see their primary care physician during the month before their death. In one study, almost half of all elders who committed suicide visited a physician in the preceding week.[85] Elders also have more chronic illnesses that predispose to suicide. Perceived poor health, poor sleep quality, and limited presence of a relative or friend to confide in are also associated with suicide among elders.[86]

Chronic Illness

Patients with terminal illnesses may commit suicide to end their suffering and to reduce the emotional and financial burden on their families. Diseases more highly associated with suicide include cancer, stroke, renal failure, congestive heart failure, and chronic lung disease. In elders, cancer, congestive heart failure, chronic obstructive lung disease, seizure disorder, urinary incontinence, anxiety disorders, depression, bipolar disorder, and moderate to severe pain are specific illnesses associated with suicide.[83]

The acquired immunodeficiency syndrome (AIDS) epidemic has also increased suicide rates, and the relative risk of suicide in men with AIDS is nearly 37 times higher than that in uninfected men. Patients who are positive for human immunodeficiency virus but do not have AIDS-defining conditions are more likely to be suicidal than those with active disease.[87]

History

Recognition of Depression and Suicide Potential

Recognition of suicide potential is relatively straightforward in patients who present shortly after a suicide attempt as well as in individuals who complain of depression or express suicidal ideation during their evaluation. The potential for suicide should also be considered in patients with any acute problem related to chronic alcoholism, substance abuse, or any psychiatric disorder. Silent suicide is possible with patients who present to the ED repeatedly because of noncompliance with treatment of their medical disorders. Occult suicide should be suspected in patients who “unintentionally” overdose or have had “accidental” gunshot wounds, lacerated wrists, automobile crashes, or falls from heights.

Patients Who Present after a Suicide Attempt or Have Suicidal Ideation

After a suicide attempt, patients with a normal mental status should be asked about the details of the act after medical evaluation and treatment are initiated. Suicidal patients may give inaccurate histories or may refuse to speak to the physician. Because most people who attempt suicide communicate their intent to others at some point, family, friends, police, and paramedics should be interviewed about the patient’s recent actions and possible motivations. They may also provide information about the specifics of the current suicide attempt. Although some physicians worry that current federal laws regarding patient privacy conflict with the need to obtain information with the family, there is an emergency exception in the Health Insurance Portability and Privacy Act. Section 164.512(j), “Uses and Disclosures to Avert a Serious Threat to Health or Safety,” allows physicians to disclose protected health information without individual authorization

www.ketabpezeshki.com 66485457-66963820

"based on a reasonable belief that use or disclosure of the protected health information was necessary to prevent or lessen a serious and imminent threat to health or safety of an individual or of the public."[88]

Once the patient is medically stable, the presence of risk factors for suicide should be determined. Such factors may include a history of previous suicide attempts or psychiatric care; a history of excessive alcohol or drug use, both acute and long term; family history of suicide; and signs of depression, including a sense of hopelessness. A history of a "near-lethal" prior attempt is particularly worrisome.[89] Patients who have a history of deliberate self-harm (self-poisoning, cutting, burning, or hitting oneself) have a higher risk of suicide, especially male patients.[90] More than 5% of people seen at a hospital after self-harm successfully commit suicide within 9 years.[91]

The patient's marital status and social support are important factors, and the motivation for and the seriousness of the suicide attempt are assessed. Some physicians ask patients to provide their own lists of "reasons why they want to live"—a sort of reverse score for suicidality. If discharge is being considered, patients should be asked whether they would harm themselves if they were released from the ED. Additional demographic information may be helpful (see Box 115-1). The SAD PERSONS mnemonic can be used to document salient points and to facilitate subsequent communications with primary care providers and psychiatrists (Table 115-1).

Patients Suspected of Occult or Silent Suicide Attempts

Patients who are not overtly depressed or suicidal but who exhibit one or more of the high-risk presentations previously described should be assessed in a sympathetic but direct manner in a "graduated" approach. Rapport should first be established during a general medical and psychiatric history, with an evaluation of the patient's home, work, and social situation, followed by specific questions about the signs and symptoms of depression. The physician should ask direct questions about suicide; for example:

Have you ever had the thought that life is not worth living?
Do you have thoughts of killing yourself now?
What plans, if any, have you made to do this?

Patients who are not depressed or suicidal are generally not offended by this approach, and it does not place the concept of suicide into the mind of someone who has not been considering it. Patients who are depressed or suicidal are often thankful and relieved for the intervention.

Physical Examination

Patients should be examined closely for evidence of drug ingestion, trauma, or an associated medical illness. Look at the wrists for evidence of prior cutting attempts. The patient's mental status, vital signs, pupils, skin, and nervous system are helpful in detecting organic conditions, particularly the toxidromes associated with common ingestions. Altered mental status should be assessed to determine whether the condition is caused by an organic (medical) or functional (psychiatric) cause (Table 115-2). Physical findings associated with chronic disease, alcoholism, and substance abuse should be sought. The physical examination is often overlooked or performed in a cursory manner in patients with psychiatric complaints. Up to 50% of patients with an acute psychiatric presentation harbor unrecognized medical illnesses.[92] Patients with evidence of psychosis or auditory hallucinations are at increased risk for suicide, especially those with "command" hallucinations that tell the patients to kill themselves.

DIAGNOSTIC STRATEGIES

Routine toxicologic screening tests are unnecessary in the evaluation of suicidal patients. Nearly all patients with dangerous overdoses and poisonings demonstrate clinical signs within several hours of ingestion. Patients with a suspected overdose may require such testing as an acetaminophen level, electrolyte value determinations, or electrocardiography. Patients with acute depression, particularly if they are newly diagnosed, may need screening tests for underlying medical disorders; however, a primary care physician or psychiatrist can safely perform this evaluation during follow-up.

MANAGEMENT

Out-of-Hospital Care

Out-of-hospital management should focus on the patient's injuries and potential harm from poisoning or overdose. If the patient refuses to be transported to the hospital or becomes aggressive, emergency medical personnel should involve law enforcement officers. All states give police the right to place individuals into protective custody if they are suspected of being a danger to self or others. The presence of law enforcement officers, or even the threat of calling the police for assistance, usually ensures the patient's cooperation during transport. In hospitalized psychiatric

Table 115-1 Modified SAD Persons Scale

FACTOR	POINTS ASSIGNED
Sex (male)	1
Age (≤19 or ≥45 years)	1
Depression or hopelessness	2
Previous attempts or psychiatric care	1
Excessive alcohol or drug use	1
Rational thinking loss	2
Separated, divorced, or widowed	1
Organized or serious attempt	2
No social supports	1
Stated future intent	2

From Hockberger RS, Rothstein RJ: Assessment of suicide potential by nonpsychiatrists using the SAD PERSONS score. J Emerg Med 6:99, 1988.
Five points or fewer, questionable outpatient treatment; 6 or more points, emergency psychiatric treatment or evaluation; more than 9 points, psychiatric hospitalization.

Table 115-2 Factors in Differentiating Organic from Functional Psychosis

	ONSET	AGE AT ONSET	HALLUCINATIONS	ORIENTATION	VITAL SIGNS
Organic	May be acute	Any age	Often visual	Often disoriented	Abnormal
Functional	Subacute to chronic	14-40 years	Usually auditory	Normal	Normal

www.ketabpezeshki.com 66485457-66963820

patients, transportation to the medical facility by police is an independent risk factor for an imminent suicide attempt.[93]

Emergency Department

The clinical assessment of suicide potential requires an empathetic approach. Patients feel more comfortable discussing personal issues when health care personnel are friendly, nonjudgmental, and supportive. Unfortunately, ED staff may be unsympathetic toward patients who attempt suicide because of religious or philosophic beliefs, lack of formal psychiatric training, or inadequate time and personnel to provide appropriate psychiatric evaluation. They may perceive the patient's behavior as abusive or manipulative and may become frustrated with ineffective disposition and follow-up options. Failure to anticipate and to overcome these factors can result in inadequate patient assessment and reinforce these patients' already low self-esteem.

The central goal of suicidal screening is to determine the need for acute psychiatric consultation in the ED or the need to transfer or to admit the patient to a psychiatric facility. Only the low-risk patient should be discharged home without psychiatric evaluation. Whereas some EDs provide on-site psychiatric counseling, there is no evidence that brief therapy can prevent suicide or lower risk.[94]

With the recent collapse of state-wide mental health systems, EDs are treating an increasing number of patients with psychiatric complaints, including depression and suicidal ideation. To assist with this growing burden, many EDs are hiring psychiatric nurses to help in the evaluation and treatment of these patients. Some hospitals provide mental health professionals on-call to the ED to screen patients and to provide disposition and commitment recommendations to the ED physicians.

Medical Clearance

The first priority in managing patients is medical stabilization and treatment of injuries, poisoning, or overdose. The second priority is the identification and treatment of associated medical conditions that may underlie a patient's altered mental status or violent behavior. Patients with significant injury, poisoning, or other medical problems should be hospitalized, sometimes in an intensive care setting, where their medical problems can be treated as they remain under constant observation. Five to 40 inpatients commit suicide for every 100,000 hospitalizations.[95,96]

Suicide Precautions

Suicide of a person in a treatment setting is presently the second most frequently reported type of sentinel event.[97] The ED should ensure the patient's safety and prevent further attempts in the department.

Suicidal patients who are calm and cooperative should be placed in an area where they can be safely observed by staff. Having a dedicated "sitter" to watch the patient is helpful and decreases the need for restraints. The sitter should accompany the patient in leaving the area to use the restroom or to smoke. No potentially suicidal patient should be allowed to leave the ED before an evaluation is completed. The use of family members as sitters is discouraged because they may collude with the suicidal patient to leave or may not intervene if the patient attempts to leave. The use of "wander alert" bracelets, which set off an alarm if a patient wearing one crosses an established threshold, may help in monitoring.

Security personnel should search all potentially suicidal patients early in the ED stay, ideally as soon as the complaint of suicide attempt or suicidal ideation is known. Having the patient change into a hospital gown facilitates removal of weapons, medications, and other possessions that might be used to inflict injury, such as belts, neckties, and long shoelaces. The patient's room should be cleared of all potentially harmful objects, including medications, instruments, and glass objects.

Some EDs have a "secure room" designed and stocked to avoid self-harm. These rooms may contain a lockable "pull-down" wall, like those used on storefronts at night, that cover medical equipment and cabinets when a psychiatric patient is in the room. Suture carts, which may contain scissors, scalpels, or other dangerous objects, should also be kept out of reach.

Use of Restraints

Mechanical and chemical restraint use is based primarily on the physician's judgment of the immediate risk of elopement or subsequent suicide attempt as well as personnel available to contain the patient. Some authorities believe that placement of a depressed patient in mechanical restraints can impair rapport and contribute to the patient's diminished self-esteem. Chemical restraints may calm a violent patient but may make subsequent psychiatric evaluation more difficult in the short term.

Nevertheless, restraints may be essential and even lifesaving for uncooperative, violent, or psychotic patients and for those at high risk for elopement or self-harm. The Joint Commission and state and federal governments have stringent requirements for the use of restraints. A hospital policy that conforms to these guidelines and an approved and consistently used restraint flow sheet are important to comply with these regulations. A timed and dated physician order and frequent rechecks of distal neurovascular function are required for all patients placed in restraints. A restraint flow sheet is essential for documentation.

Determination of Risk

Once a patient has demonstrated suicidal behavior or ideation, the physician should determine whether the risk is imminent (i.e., within 48 hours), short term (i.e., within days to weeks), or long term.[7] The likelihood of an impending repeated attempt will drive disposition: psychiatric hospitalization, emergency psychiatric consultation, or discharge and referral for follow-up. One should consider the potential lethality of the method chosen; for example, ingestion of a handful of birth control pills is less worrisome than shooting oneself or setting oneself on fire. It is also important to consider if the patient believed the attempt would result in death. Even if the method chosen was nonlethal from a medical standpoint (such as ingestion of antibiotics) but the patient believed it was lethal, the patient may be at risk for a future, more lethal attempt. Patients who plan and hide their suicide attempt may be more desperate to die than someone who makes the attempt in front of a family member and is rescued. In depressed patients, an intense sense of desperation is an important predictor of suicide.[98] Another important consideration in the evaluation of the suicidal patient involves the wish to live versus the wish to die. Not surprisingly, those patients with a wish to die are six times more likely to commit suicide than are those who wish to live.[99]

Although one should determine an individual patient's likelihood to commit suicide if discharged, this assessment is far from exact. No single psychological test can accurately predict suicide attempts.[100] In a group of 4800 psychiatric patients who were observed prospectively during 5 years, 44% of all suicides were not foreseen by the psychiatrist, and individuals who complete suicides after evaluation by an emergency psychiatric service have no specific factors that predict imminent suicide.[101,102]

There are at least 31 different English-language scales devised to predict the risk of suicide, but most are not designed for or suitable for use in the ED.[103] Some researchers are even using

www.ketabpezeshki.com 66485457-66963820

"fuzzy logic" and neural networks to achieve computerized prediction models for suicidality.[104] One study evaluated six clinical suicide assessment scales to identify high-risk patients: the Modified SAD PERSONS scale, revised Beck Depression Inventory, Beck Anxiety Inventory, Beck Hopelessness Scale, Beck Scale for Suicidal Ideation, and High-Risk Construct Scale.[105] All of the scales showed 100% sensitivity and negative predictive value but lower specificity (38-90%) and positive predictive value (28-71%). Although scoring systems might help in determining the need for hospitalization, they cannot predict future attempts at self-harm.[106,107] Nevertheless, an attempt to determine a patient's immediate risk of self-harm should occur and, when indicated, be communicated to other health care providers.

The SAD PERSONS mnemonic provides a "suicide score" (see Table 115-1) and is well suited for use in the ED. Two points are given for each of four high-risk factors: (1) complaints of depression or hopelessness, (2) existence of an organic brain syndrome or acute psychosis, (3) presence of a well-conceived plan or life-threatening presentation, and (4) expression of determination or ambivalence about future suicidal behavior. One point is assigned for other important but less significant factors: male gender; age younger than 19 or older than 45 years; a history of previous suicide attempts or psychiatric care; stigmata of chronic alcoholism or substance abuse or the history of recent increased use of these substances; a patient who is separated, divorced, or widowed; and the absence of social support systems, such as close family, friends, job, or active religious affiliation.

A SAD PERSONS score of 6 or more has a sensitivity of 94% and a specificity of 71% compared with formal psychiatric evaluation in identifying the need for hospitalization of patients who present immediately after a suicide attempt.[108] A score of less than 6 has a negative predictive value of 95%. No deaths at 6 to 12 months occurred in patients with low scores.

Another risk assessment tool used for adolescents is the Risk of Suicide Questionnaire.[109] The four most useful questions on the Risk of Suicide Questionnaire were the following:

Are you here because you tried to hurt yourself?
In the past week, have you been having thoughts about killing yourself?
Have you ever tried to hurt yourself in the past?
Has something very stressful happened to you in the past few weeks?

Any positive answer on this rapid screen correlated with potential risk for self-harm compared with a longer Suicidal Ideation Questionnaire, but correlation with actual suicidal outcomes is unknown.

Another simple scoring system is the British Manchester Self-Harm Rule, which uses four clinical correlates to determine future risk of suicide attempts[110]: (1) any history of self-harm, (2) previous psychiatric treatment, (3) benzodiazepine use in this attempt, and (4) any current psychiatric treatment. For 9086 patients, any positive answer on the four-question Manchester Self-Harm Rule had a sensitivity of 94% and specificity of 25% for a repeated attempt. How this rule would perform in a U.S. population with a far greater access to handguns remains unclear.

Suicide assessment should be performed after the patient metabolizes any drugs or alcohol. Intoxicated patients who complain of depression or state ambivalence about their future intentions to commit suicide may disavow these feelings once they are sober (but may still be at risk despite the disavowal). In addition, the information obtained from a potentially suicidal patient is best confirmed with a family member or friend as patients who are determined to commit suicide may give false or misleading information.

The crises that precipitate suicide attempts are often time limited, usually lasting a few hours to a few days. If a crisis has passed or can be adequately addressed, the risk of subsequent suicide is substantially diminished. Hospitalization or emergency psychiatric evaluation should be strongly considered when a patient cannot or will not participate in an evaluation of the current crisis or when the problem is unlikely to be resolved.

Ultimately, the assessment of suicide risk remains a highly individualized process considering the crisis that precipitated the suicide event, the patient's current emotional state, and the presence or absence of a supportive home environment. When emergency physicians are uncertain about the need for hospitalization, they should either admit the patient for psychiatric care or request emergency psychiatric evaluation. A psychiatric social worker or other paraprofessional may assist in gathering information and in making decisions about the need for hospitalization; however, the physician still should make an independent judgment about the patient's suicide risk.[111] Despite the medical-legal threats involved, nearly a quarter of emergency physicians occasionally send patients with suicidal ideation home without any evaluation by a mental health professional.[3]

Some investigators recommend hospitalization for adolescents who have attempted suicide and cannot be adequately monitored at home. However, discharge to home is an option for those with suicidal thoughts if urgent psychiatric follow-up is arranged and the caregivers can adequately supervise and protect the youth. Discharged adolescents should not be actively suicidal, should not have access to lethal methods, should have a supervising adult to closely monitor them, and should have a mental health evaluation before ED discharge whenever feasible.[72]

Involuntary Commitment

Some patients who are severely depressed or suicidal may resist hospitalization. Patients who refuse recommended medical treatment usually do so because of anger or fear. Patients may be angry for being brought to the ED against their wishes or for having to wait for evaluation. Alternatively, they may fear the loss of control associated with hospitalization or the perceived negative stigma associated with a psychiatric disorder. When a patient is reluctant to be hospitalized, the physician should attempt to identify and address the specific concerns. The patient's family and friends may help convince the patient to accept voluntary hospitalization. Involuntary admission may be necessary if the physician believes that the patient may inflict self-harm. Depression alone is not a criterion for involuntary commitment; the accepted legal standard requires the imminent risk of harm to self or others. In some states, even patients who voluntarily agree to hospitalization may need involuntary commitment papers filled out if they are an acute danger to self or others. This is to provide the legal basis for holding them against their will if they change their mind about hospitalization during the trip between the ED and the receiving psychiatric facility.

Civil commitment statutes differ among the 50 states and the District of Columbia. Nearly 85% of the jurisdictions require dangerousness to self to be the result of a mental illness, and only two jurisdictions mandate involuntary commitment if a person is an imminent harm to self.[112]

The efficacy of commitment as a long-term preventive measure is controversial.[99] Involuntary commitment is not proven to prevent future suicide and may even precipitate adverse psychiatric consequences (e.g., increased feelings of hopelessness and dependency) or cause rebellion in some patients. Many authorities believe that people who are determined to kill themselves will probably prevail despite the best efforts of family members and health care professionals.[7] Still, despite the lack of hard data, involuntary commitment remains a primary intervention when patients are deemed acutely suicidal.

www.ketabpezeshki.com 66485457-66963820

Pharmacology

There are no generally accepted or evidence-based protocols for drug treatment of suicidal thoughts in the ED. Antidepressants, lithium, and antipsychotics such as clozapine and olanzapine have been given to suicidal patients, but these are usually prescribed by psychiatrists and their effects occur during many weeks. ED pharmacology is usually directed to the treatment of agitation as needed, with use of a dose or two of a benzodiazepine or short-acting antipsychotic such as haloperidol, risperidone, or ziprasidone.

Ketamine

A number of studies suggest that intravenous (IV) administration of ketamine can rapidly decrease suicidal thoughts in depressed patients.[113-115] In one ED study, 20 patients with suicide ideation were administered a single dose of ketamine (0.25 mg/kg IV bolus during 3 minutes). Ketamine rapidly reduced both suicide ideation and depressive symptoms within hours with an effect sustained for up to a week.[116] Although it is promising, the use of ketamine in the ED to control suicidal impulses warrants further investigation before it can be considered a routine intervention.

DISPOSITION

Most patients at high risk for suicide will need psychiatric evaluation or hospitalization in a psychiatric facility. If patients require transfer to such a facility, they should be protected from self-harm during transport. Deaths from jumping from an ambulance during such transports have been reported.[117]

Many patients who attempt suicide or have symptoms of depression can be safely managed as outpatients if the risk of subsequent suicide is judged to be acceptably low (Box 115-2). Before discharging a patient, one should address the crisis that precipitated the suicide attempt. The patient should also be considered low risk for subsequent suicide (e.g., low SAD PERSONS score). Evaluation by a mental health professional is useful, especially if the safety of outpatient management is in doubt. Some physicians ask the patient to form a verbal or written "contract" with them. This "no harm" agreement usually involves patients' vowing not to hurt themselves and agreeing to return to the ED to seek help if the situation worsens before follow-up. Although the no harm agreement has not been validated, some believe that this is a reasonable approach, whereas others believe that it provides only a false sense of security for the physician. On its own, it will certainly not absolve the clinician from malpractice liability if the patient commits suicide.[118]

If the patient is to be discharged, a family member or friend should agree to stay with the patient or to be immediately available to the patient until follow-up is provided. The patient should be discharged to a stable and supportive home environment that is free of guns and lethal medications. Guns should be removed from the home by a trusted family member; gun locks or cabinets to which the patient has no key access may be a reasonable alternative.

Adequate disposition may include a conversation with the ongoing provider. The follow-up appointment should be scheduled within a few days of discharge and should be specific about the location and time. If possible, the follow-up should occur within 72 hours as suicide risk remains high shortly after discharge from the ED.[119]

Because a significant number of patients do not keep their follow-up appointments, compliance with follow-up may be increased by making a specific appointment for patients.[120] Having the family or friends help ensure that the patient keeps the follow-up appointment is another good strategy. In addition, it may also be helpful to provide a card that indicates how to contact an available physician.[121]

In one study, an ED-based "suicide intervention counselor" coordinated care and long-term follow-up. The counselor was able to decrease hospital readmissions for repeated suicide attempts by almost 10%.[122] Additional interventions that may improve the safety net for patients discharged from the ED include a follow-up phone call in 24 hours and home visits if patients do not keep their first appointment after discharge.[119]

Discharge instructions should include a statement that the patient should seek help immediately for suicidal thoughts. It may also be helpful to provide the phone number for the National Suicide Prevention Hotline resource: 1-800-273-TALK (8255). There is a special option for veterans to press after connecting to this number. The Hotline is a 24-hour, toll-free suicide prevention service, and calls are routed to the closest center. Some EDs provide Crisis Cards that patients can carry in their wallet, listing community resources to call when thoughts of suicide or depression loom.

Box 115-2 Factors for Patients at Low Risk for Suicide

- Few significant risk factors (e.g., low SAD PERSONS score)
- Stable and supportive home environment
- Patient agrees to "no harm" contract and will return to emergency department if situation worsens
- Family member or friend staying with or available to patient
- Phone contact with health care provider responsible for follow-up
- Specific appointment made for follow-up within 24 to 48 hours
- No gun in home
- Young woman who took a nonlethal ingestion or made "hesitation cuts" to wrists
- Patient expresses a strong desire to live

DOCUMENTATION

Documentation is especially important when patients are committed or discharged or when restraints are used. If a patient requires involuntary commitment, one should document why the patient is a danger to self or others. If the patient is discharged, the record should reflect that the patient is low risk and does not intend self-harm after leaving the ED. Documenting that there is no gun in the home is also useful. Preformatted charts may improve documentation.[123] Every time a patient is discharged from the ED after a suicide attempt or evaluation for suicidal ideation, the chart should reflect that the patient is at low risk for suicide.

PREVENTION

During the first 6 to 12 months after discharge from an ED, as many as 17% of suicidal patients reattempt suicide.[124] The incidence of suicide parallels the incidence of alcoholism, drug abuse, and psychiatric disease in society. Although most suicide prevention programs are of mixed value, legislation to control access to lethal drugs and handguns is effective. Laws requiring prescriptions for all sedative and hypnotic drugs in Japan led to a decrease in their use for suicide, with no increase in the use of other methods.[125] In Canada, suicide decreased after gun control laws were tightened.[126] Keeping a gun locked and unloaded and storing ammunition locked in a separate location are each associated with a protective effect against suicide by firearms in children and teens.[127]

Screening for suicidal ideation or depression may be a useful strategy. Physician education in depression recognition and

www.ketabpezeshki.com 66485457-66963820

treatment may reduce suicide rates.[94] Programs that screen for depression in the elderly[128] and school-based programs that screen for suicide risk in teens[129] may decrease suicidal ideation and suicide attempts. Occult suicidality is common in ambulatory ED patients who present for nonpsychiatric problems. In one study, waiting room patients were screened for suicidality with a computerized mental health assessment tool. Eleven percent had passive thoughts of suicide, and another 8% had active thoughts about killing themselves.[130] Whereas screening for occult suicide in all ED patients is an intriguing notion, the implications of referring 20% of all ED patients for psychiatric evaluation are staggering.

Contact of patients by telephone 1 month after their discharge from an ED for deliberate self-poisoning may reduce the number of reattempted suicides during 1 year.[131]

Despite great interest in the prevention of suicide, it is unclear which if any interventions are effective to prevent future attempts at self-harm.[132] No strong evidence suggests that antidepressants prevent self-harm in patients with prior suicide attempts; however, one small study did show an advantage to use of depot flupenthixol in multiple repeaters.[133] In another small study, dialectic behavior therapy was more effective than standard aftercare in preventing further episodes of self-harm.[134]

Suicide attempts correlate with future suicide. In one study of survivors of self-poisoning, the 5-year mortality rate from suicide was 65.5 times greater than expected in the female group (compared with a control group who did not attempt self-harm) and 41.5 times greater in the male group.[135]

KEY CONCEPTS

- Suicide is often provoked by a treatable or reversible short-term crisis.
- Suicidal patients frequently see a physician shortly before their death.
- The most complete information can be elicited with an empathetic approach to the patient and communication with family members, friends, health care providers, and others.
- Suicide precautions in the ED include appropriate use of "sitters" and, when necessary, physical and chemical restraints and involuntary commitment.
- The emergency physician should identify risk factors for suicide, even though determination of suicide risk is not a hard science. The SAD PERSONS score can be of help in documenting this assessment.
- Older men and those who attempt suicide with a firearm are at highest risk for a future completed suicide. Young women, especially those who cut themselves or take a nonlethal ingestion, are generally at lower risk.
- If patients are sent home because their risk of suicide is low, ensure a safe and supportive gun-free environment and early psychiatric follow-up.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Kirkland LR: To end itself by death: Suicide in Shakespeare's tragedies. *South Med J* 1999; 92:660-666.
2. Thompson S: The Internet and its potential influence on suicide. *Psychiatr Bull* 1999; 23:449-451.
3. Baraff LJ, Janowicz N, Asarnow JR: Survey of California emergency departments about practices for management of suicidal patients and resources available for their care. *Ann Emerg Med* 2006; 48:452-458, 458.
4. Brent DA, et al: Risk factors for adolescent suicide. A comparison of adolescent suicide victims with suicidal inpatients. *Arch Gen Psychiatry* 1988; 45:581-588.
5. McAlpine DE: Suicide: Recognition and management. *Mayo Clin Proc* 1987; 62:778-781.
6. Brown M, Barraclough B: Epidemiology of suicide pacts in England and Wales, 1988-92. *BMJ* 1997; 315:286-287.
7. Hirschfeld RM, Russell JM: Assessment and treatment of suicidal patients. *N Engl J Med* 1997; 337:910-915.
8. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, Division of Violence Prevention: *Twenty leading causes of death among persons ages 10 years and older, United States, 2006*. Last updated September 30, 2009. Available at www.cdc.gov/violenceprevention/suicide/statistics/leading_causes.html. Accessed September 15, 2011.
9. McIntosh JL; American Association of Suicidology: *U.S.A. suicide 2007: Official final data*. Last updated May 23, 2010. Available at www.suicidology.org/c/document_library/get_file?folderId=232&name=DLFE-232.pdf. Accessed September 21, 2011.
10. Doshi A, Boudreaux ED, Wang N, Pelletier AJ, Camargo CAJ: National study of US emergency department visits for attempted suicide and self-inflicted injury, 1997-2001. *Ann Emerg Med* 2005; 46:369-375.
11. Claassen CA, et al: Do geographic regions with higher suicide rates also have higher rates of nonfatal intentional self-harm? *Suicide Life Threat Behav* 2008; 38:637-649.
12. Luo F, Florence CS, Quispe-Agnoli M, Ouyang L, Crosby AE: Impact of business cycles on US suicide rates, 1928-2007. *Am J Public Health* 2011; 101:1139-1146.
13. Sharfstein SS, Dickerson FB: Hospital psychiatry for the twenty-first century. *Health Aff (Millwood)* 2009; 28:685-688.
14. Miller M, Azrael D, Hemenway D: The epidemiology of case fatality rates for suicide in the northeast. *Ann Emerg Med* 2004; 43:723-730.
15. Brockington L: Suicide in women. *Int Clin Psychopharmacol* 2001; 16(Suppl 2):S7-S19.
16. Ho TP: The suicide risk of discharged psychiatric patients. *J Clin Psychiatry* 2003; 64:702-707.
17. Qin P, Nordentoft M: Suicide risk in relation to psychiatric hospitalization: Evidence based on longitudinal registers. *Arch Gen Psychiatry* 2005; 62:427-432.
18. Suominen K, et al: Completed suicide after a suicide attempt: A 37-year follow-up study. *Am J Psychiatry* 2004; 161:562-563.
19. Remafedi G, French S, Story M, Resnick MD, Blum R: The relationship between suicide risk and sexual orientation: Results of a population-based study. *Am J Public Health* 1998; 88:57-60.
20. Silenzio VMB, Pena JB, Duberstein PR, Cerel J, Knox KL: Sexual orientation and risk factors for suicidal ideation and suicide attempts among adolescents and young adults. *Am J Public Health* 2007; 97:2017-2019.
21. Blakely TA, Collings SCD, Atkinson J: Unemployment and suicide. Evidence for a causal association? *J Epidemiol Community Health* 2003; 57:594-600.
22. Binswanger IA, et al: Release from prison—a high risk of death for former inmates. *N Engl J Med* 2007; 356: 157-165.
23. Pratt D, Piper M, Appleby L, Webb R, Shaw J: Suicide in recently released prisoners: A population-based cohort study. *Lancet* 2006; 368:119-123.
24. Maris RW: *The relationship of nonfatal suicide attempts to completed suicides*. In: Maris RW, Berman AL, Maltsberger JT, Yufit RI, eds: *Assessment and Prediction of Suicide*. New York: Guilford Press; 1992:362.
25. Kleespies PM, Dettmer EL: An evidence-based approach to evaluating and managing suicidal emergencies. *J Clin Psychol* 2000; 56:1109-1130.
26. Owens C, Booth N, Briscoe M, Lawrence C, Lloyd K: Suicide outside the care of mental health services: A case-controlled psychological autopsy study. *Crisis* 2003; 24:113-121.
27. Greenwald DJ, Reznikoff M, Plutchik R: Suicide risk and violence risk in alcoholics. Predictors of aggressive risk. *J Nerv Ment Dis* 1994; 182:3-8.
28. McBride PA, et al: The relationship of platelet 5-HT2 receptor indices to major depressive disorder, personality traits, and suicidal behavior. *Biol Psychiatry* 1994; 35:295-308.
29. Arango V, Ernsberger P, Sved AF, Mann JJ: Quantitative autoradiography of alpha1- and alpha2-adrenergic receptors in the cerebral cortex of controls and suicide victims. *Brain Res* 1993; 630:271-282.
30. Mann JJ, et al: Possible association of a polymorphism of the tryptophan hydroxylase gene with suicidal behavior in depressed patients. *Am J Psychiatry* 1997; 154:1451-1453.
31. Lopez de Lara C, et al: STin2 variant and family history of suicide as significant predictors of suicide completion in major depression. *Biol Psychiatry* 2006; 59:114-120.
32. Laje G, et al: Genetic markers of suicidal ideation emerging during citalopram treatment of major depression. *Am J Psychiatry* 2007; 164:1530-1538.
33. Roy A, Nielsen D, Rylander G, Sarchiapone M, Segal N: Genetics of suicide in depression. *J Clin Psychiatry* 1999; 60(Suppl 2):12-17.
34. Runeson B, Asberg M: Family history of suicide among suicide victims. *Am J Psychiatry* 2003; 160:1525-1526.
35. Kim CD, et al: Familial aggregation of suicidal behavior: A family study of male suicide completers from the general population. *Am J Psychiatry* 2005; 162:1017-1019.
36. Fourestie V, et al: Suicide attempts in hypo-oestrogenic phases of the menstrual cycle. *Lancet* 1986; 2:1357-1360.
37. Altshuler LL, Casanova MF, Goldberg TE, Kleinman JE: The hippocampus and parahippocampus in schizophrenia, suicide, and control brains. *Arch Gen Psychiatry* 1990; 47:1029-1034.
38. Gibbons RD, Hur K, Bhaumik DK, Mann JJ: The relationship between antidepressant prescription rates and rate of early adolescent suicide. *Am J Psychiatry* 2006; 163:1898-1904.
39. Gibbons RD, et al: Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *Am J Psychiatry* 2007; 164:1356-1363.
40. Gunnell D, Frankel S: Prevention of suicide: Aspirations and evidence. *BMJ* 1994; 308:1227-1233.
41. Birkhead GS, Galvin VG, Meehan PJ, O'Carroll PW, Mercy JA: The emergency department in surveillance of attempted suicide: Findings and methodologic considerations. *Public Health Rep* 1993; 108:323-331.
42. Shenassa ED, Catlin SN, Buka SL: Lethality of firearms relative to other suicide methods: A population based study. *J Epidemiol Community Health* 2003; 57:120-124.
43. Zwerling C, Lynch CF, Burmeister LF, Goertz U: The choice of weapons in firearm suicides in Iowa. *Am J Public Health* 1993; 83:1630-1632.
44. Kung HC, Hoyert DL, Xu J, Murphy SL: Deaths: Final data for 2005. *Natl Vital Stat Rep* 2008; 56:1-120.
45. Meehan PJ, Saltzman LE, Sattin RW: Suicides among older United States residents: Epidemiologic characteristics and trends. *Am J Public Health* 1991; 81:1198-1200.
46. Wiebe DJ: Homicide and suicide risks associated with firearms in the home: A national case-control study. *Ann Emerg Med* 2003; 41:771-782.
47. Killias M: International correlations between gun ownership and rates of homicide and suicide. *CMAJ* 1993; 148:1721-1725.
48. Kellermann AL, Reay DT: Protection or peril? An analysis of firearm-related deaths in the home. *N Engl J Med* 1986; 314:1557-1560.
49. Miller M, Hemenway D, Azrael D: Firearms and suicide in the northeast. *J Trauma* 2004; 57:626-632.
50. Peterson LG, Peterson M, O'Shanick GJ, Swann A: Self-inflicted gunshot wounds: Lethality of method versus intent. *Am J Psychiatry* 1985; 142:228-231.
51. Wintemute GJ, Parham CA, Beaumont JJ, Wright M, Drake C: Mortality among recent purchasers of handguns. *N Engl J Med* 1999; 341:1583-1589.
52. Kapur S, Mieczkowski T, Mann JJ: Antidepressant medications and the relative risk of suicide attempt and suicide. *JAMA* 1992; 268:3441-3445.
53. Prescott LF, Highley MS: Drugs prescribed for self poisoners. *Br Med J (Clin Res Ed)* 1985; 290:1633-1636.
54. de Moore GM, Robertson AR: Suicide attempts by firearms and by leaping from heights: A comparative study of survivors. *Am J Psychiatry* 1999; 156:1425-1431.
55. Hutson HR, et al: Suicide by cop. *Ann Emerg Med* 1998; 32:665-669.
56. Sakinofsky I: Review: Risk for suicide is increased for most mental disorders where patients require treatment in a hospital setting. *Evid Based Ment Health* 1998; 1:27.
57. Henriksson MM, et al: Mental disorders and comorbidity in suicide. *Am J Psychiatry* 1993; 150:935-940.

www.ketabpezeshki.com 66485457-66963820

58. Winokur G, Black DW: Psychiatric and medical diagnoses as risk factors for mortality in psychiatric patients: A case-control study. *Am J Psychiatry* 1987; 144:208-211.
59. Asnis GM, et al: Suicidal behaviors in adult psychiatric outpatients, I: Description and prevalence. *Am J Psychiatry* 1993; 150:108-112.
60. Dumais A, et al: Risk factors for suicide completion in major depression: A case-control study of impulsive and aggressive behaviors in men. *Am J Psychiatry* 2005; 162:2116-2124.
61. Isometsa ET, et al: Suicide in major depression. *Am J Psychiatry* 1994; 151:530-536.
62. Westermeyer JF, Harrow M, Marengo JT: Risk for suicide in schizophrenia and other psychotic and nonpsychotic disorders. *J Nerv Ment Dis* 1991; 179:259-266.
63. Goldacre M, Seagroatt V, Hawton K: Suicide after discharge from psychiatric inpatient care. *Lancet* 1993; 342:283-286.
64. Sareen J, et al: Anxiety disorders and risk for suicidal ideation and suicide attempts: A population-based longitudinal study of adults. *Arch Gen Psychiatry* 2005; 62:1249-1257.
65. Oquendo M, et al: Posttraumatic stress disorder comorbid with major depression: Factors mediating the association with suicidal behavior. *Am J Psychiatry* 2005; 162:560-566.
66. Keteyian A: *Suicide epidemic among veterans*. CBS News Investigates, February 11, 2009. Available at www.cbsnews.com/stories/2007/11/13/cbsnews_investigates/main3496471.shtml. Accessed September 21, 2011.
67. Toxicology testing and results for suicide victims—13 states, 2004. *MMWR Morb Mortal Wkly Rep* 2006; 55:1245-1248.
68. Murphy GE, Wetzel RD, Robins E, McEvoy L: Multiple risk factors predict suicide in alcoholism. *Arch Gen Psychiatry* 1992; 49:459-463.
69. Rich CL, Ricketts JE, Fowler RC, Young D: Some differences between men and women who commit suicide. *Am J Psychiatry* 1988; 145:718-722.
70. Marzuk PM, et al: Prevalence of cocaine use among residents of New York City who committed suicide during a one-year period. *Am J Psychiatry* 1992; 149:371-375.
71. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control: *Injury Prevention & Control: Data & Statistics (WISQARS): Leading causes of death*. Last updated September 9, 2011. Available at www.cdc.gov/injury/wisqars/leading_causes_death.html. Accessed September 21, 2011.
72. Kennedy SP, Baraff LJ, Suddath RL, Asarnow JR: Emergency department management of suicidal adolescents. *Ann Emerg Med* 2004; 43:452-460.
73. Garrison CZ, McKeown RE, Valois RF, Vincent ML: Aggression, substance use, and suicidal behaviors in high school students. *Am J Public Health* 1993; 83:179-184.
74. Rosenberg ML, Smith JC, Davidson LE, Conn JM: The emergence of youth suicide: An epidemiologic analysis and public health perspective. *Annu Rev Public Health* 1987; 8:417-440.
75. Pilowsky DJ, Wu LT, Anthony JC: Panic attacks and suicide attempts in mid-adolescence. *Am J Psychiatry* 1999; 156:1545-1549.
76. Garofalo R, Wolf RC, Wissow LS, Woods ER, Goodman E: Sexual orientation and risk of suicide attempts among a representative sample of youth. *Arch Pediatr Adolesc Med* 1999; 153:487-493.
77. Young R, Sweeting H, West P: Prevalence of deliberate self harm and attempted suicide within contemporary Goth youth subculture: Longitudinal cohort study. *BMJ* 2006; 332:1058-1061.
78. Rotheram-Borus MJ: Suicidal behavior and risk factors among runaway youths. *Am J Psychiatry* 1993; 150:103-107.
79. Cummings P, LeMier M, Keck DB: Trends in firearm-related injuries in Washington State, 1989-1995. *Ann Emerg Med* 1998; 32:37-43.
80. Rates of homicide, suicide, and firearm-related death among children—26 industrialized countries. *MMWR Morb Mortal Wkly Rep* 1997; 46:101-105.
81. Brent DA, et al: The presence and accessibility of firearms in the homes of adolescent suicides. A case-control study. *JAMA* 1991; 266:2989-2995.
82. Suicide among older persons—United States, 1980-1992. *MMWR Morb Mortal Wkly Rep* 1996; 45:3-6.
83. Casey DA: Suicide in the elderly: A two-year study of data from death certificates. *South Med J* 1991; 84:1185-1187.
84. Alexopoulos GS, Bruce ML, Hull J, Sirey JA, Kakuma T: Clinical determinants of suicidal ideation and behavior in geriatric depression. *Arch Gen Psychiatry* 1999; 56:1048-1053.
85. Juurlink DN, Herrmann N, Szalai JP, Kopp A, Redelmeier DA: Medical illness and the risk of suicide in the elderly. *Arch Intern Med* 2004; 164:1179-1184.
86. Turvey CL, et al: Risk factors for late-life suicide: A prospective, community-based study. *Am J Geriatr Psychiatry* 2002; 10:398-406.
87. McKegney FP, O'Dowd MA: Suicidality and HIV status. *Am J Psychiatry* 1992; 149:396-398.
88. Standards for privacy of individually identifiable health information. Office of the Assistant Secretary for Planning and Evaluation, DHHS. Final rule. *Fed Regist* 2000; 65:82462-82829.
89. Joiner TEJ, et al: Worst-point suicidal plans: A dimension of suicidality predictive of past suicide attempts and eventual death by suicide. *Behav Res Ther* 2003; 41:1469-1480.
90. Hawton K, Zahl D, Weatherall R: Suicide following deliberate self-harm: Long-term follow-up of patients who presented to a general hospital. *Br J Psychiatry* 2003; 182:537-542.
91. Skegg K: Self-harm. *Lancet* 2005; 366:1471-1483.
92. Henneman PL, Mendoza R, Lewis RJ: Prospective evaluation of emergency department medical clearance. *Ann Emerg Med* 1994; 24:672-677.
93. King EA, Baldwin DS, Sinclair JM, Campbell MJ: The Wessex Recent In-Patient Suicide Study, 2. Case-control study of 59 in-patient suicides. *Br J Psychiatry* 2001; 178:537-542.
94. Mann JJ, Apter A, Bertolote J, et al: Suicide prevention strategies: A systematic review. *JAMA* 2005; 294:2064-2074.
95. Robertson WD: Poisonings in the United States, 1987. *Am J Emerg Med* 1988; 6:544.
96. Hogarty SS, Rodaitis CM: A suicide precautions policy for the general hospital. *J Nurs Adm* 1987; 17:36-42.
97. Cooke M, Rozovsky F: Suicide assessment and risk mitigation. Last updated 2009. Available at www.awac.com/docs/AlliedWorld_Teleseminar_Suicide_Mitigation_2_09_Final.pdf. Accessed September 21, 2011.
98. Hendin H, Maltsberger JT, Szanto K: The role of intense affective states in signaling a suicide crisis. *J Nerv Ment Dis* 2007; 195:363-368.
99. Brown GK, Steer RA, Henriques GR, Beck AT: The internal struggle between the wish to die and the wish to live: A risk factor for suicide. *Am J Psychiatry* 2005; 162:1977-1979.
100. Maris RW: Suicide. *Lancet* 2002; 360:319-326.
101. Pokorny AD: Prediction of suicide in psychiatric patients. Report of a prospective study. *Arch Gen Psychiatry* 1983; 40:249-257.
102. Harris MR, et al: Completed suicides and emergency psychiatric evaluations: The Louisville experience. *J Ky Med Assoc* 2000; 98:210-212.
103. Brown GK: *A Review of Suicide Assessment Measures for Intervention Research with Adults and Older Adults*. Last updated 2008. Available at sbisrvntweb.uqac.ca/archivage/15290520.pdf. Accessed September 20, 2011.
104. Modai I, Kuperman J, Goldberg I, Goldish M, Mendel S: Fuzzy logic detection of medically serious suicide attempt records in major psychiatric disorders. *J Nerv Ment Dis* 2004; 192:708-710.
105. Cochrane-Brink KA, Lofchy JS, Sakinofsky I: Clinical rating scales in suicide risk assessment. *Gen Hosp Psychiatry* 2000; 22:445-451.
106. Goldstein RB, Black DW, Nasrallah A, Winokur G: The prediction of suicide. Sensitivity, specificity, and predictive value of a multivariate model applied to suicide among 1906 patients with affective disorders. *Arch Gen Psychiatry* 1991; 48:418-422.
107. Maris RW: Suicide and life-threatening behavior. Introduction. *Suicide Life Threat Behav* 1991; 21:1-17.
108. Hockberger RS, Rothstein RJ: Assessment of suicide potential by nonpsychiatrists using the SAD PERSONS score. *J Emerg Med* 1988; 6:99-107.
109. Horowitz LM, et al: Detecting suicide risk in a pediatric emergency department: Development of a brief screening tool. *Pediatrics* 2001; 107:1133-1137.
110. Cooper J, et al: A clinical tool for assessing risk after self-harm. *Ann Emerg Med* 2006; 48:459-466.
111. Armitage DT, Townsend GM: Emergency medicine, psychiatry, and the law. *Emerg Med Clin North Am* 1993; 11:869-887.
112. Werth JLJ: U.S. involuntary mental health commitment statutes: Requirements for persons perceived to be a potential harm to self. *Suicide Life Threat Behav* 2001; 31:348-357.
113. Price RB, Nock MK, Charney DS, Mathew SJ: Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol Psychiatry* 2009; 66:522-526.
114. Krystal JH: Ketamine and the potential role for rapid-acting antidepressant medications. *Swiss Med Wkly* 2007; 137:215-216.
115. DiazGranados N, et al: Rapid resolution of suicidal ideation after a single infusion of an N-methyl-d-aspartate antagonist in patients with treatment-resistant major depressive disorder. *J Clin Psychiatry* 2010; 71:1605-1611.

www.ketabpezeshki.com 66485457-66963820

116. Larkin GL, Beautrais AL, Lippmann L: Rapid treatment of suicide states in the emergency department. *Inj Prev* 2010; 16:A260.
117. Greenwood MJ: Self-inflicted death during interfacility transfer. *Ann Emerg Med* 2006; 47:212.
118. Simon RI: The suicide prevention contract: Clinical, legal, and risk management issues. *J Am Acad Psychiatry Law* 1999; 27:445-450.
119. Knesper DJ; Suicide Prevention Resource Center: *Suicide attempts and suicide deaths subsequent to discharge from an emergency department or an inpatient psychiatry unit: Continuity of care for suicide prevention and research*. Last updated 2011. Available at www.sprc.org/library/continuityofcare.pdf. Accessed September 21, 2011.
120. Granboulan V, Roudot-Thoraval F, Lemerle S, Alvin P: Predictive factors of post-discharge follow-up care among adolescent suicide attempters. *Acta Psychiatr Scand* 2001; 104:31-36.
121. Morgan HG, Jones EM, Owen JH: Secondary prevention of non-fatal deliberate self-harm. The green card study. *Br J Psychiatry* 1993; 163:111-112.
122. Aoun S: Deliberate self-harm in rural Western Australia: Results of an intervention study. *Aust N Z J Ment Health Nurs* 1999; 8:65-73.
123. Crawford MJ, Turnbull G, Wessely S: Deliberate self harm assessment by accident and emergency staff—an intervention study. *J Accid Emerg Med* 1998; 15:18-22.
124. Guthrie E, et al: Randomised controlled trial of brief psychological intervention after deliberate self poisoning. *BMJ* 2001; 323:135-138.
125. Lester D, Abe K: The effect of controls on sedatives and hypnotics on their use for suicide. *J Toxicol Clin Toxicol* 1989; 27:299-303.
126. Lester D, Leenaars A: Suicide rates in Canada before and after tightening firearm control laws. *Psychol Rep* 1993; 72:787-790.
127. Grossman DC, et al: Gun storage practices and risk of youth suicide and unintentional firearm injuries. *JAMA* 2005; 293:707-714.
128. Bruce ML, et al: Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: A randomized controlled trial. *JAMA* 2004; 291:1081-1091.
129. Aseltine RH Jr, DeMartino R: An outcome evaluation of the SOS Suicide Prevention Program. *Am J Public Health* 2004; 94:446-451.
130. Larkin GL, Claassen C: Prevalence and outcomes of occult suicidality in a multiethnic emergency department population. *Ann Emerg Med* 2004; 44(Suppl 4):S22.
131. Vaiva G, et al: Effect of telephone contact on further suicide attempts in patients discharged from an emergency department: Randomised controlled study. *BMJ* 2006; 332:1241-1245.
132. Hawton K, et al: Deliberate self harm: Systematic review of efficacy of psychosocial and pharmacological treatments in preventing repetition. *BMJ* 1998; 317:441-447.
133. Montgomery SA, Roy D, Montgomery DB: The prevention of recurrent suicidal acts. *Br J Clin Pharmacol* 1983; 15(Suppl 2):183S-188S.
134. Linehan MM, Armstrong HE, Suarez A, Allmon D, Heard HL: Cognitive-behavioral treatment of chronically parasuicidal borderline patients. *Arch Gen Psychiatry* 1991; 48:1060-1064.
135. Rygnestad T: Mortality after deliberate self-poisoning. A prospective follow-up study of 587 persons observed for 5279 person years: Risk factors and causes of death. *Soc Psychiatry Psychiatr Epidemiol* 1997; 32:443-450.

www.ketabpezeshki.com 66485457-66963820

Section Nine

IMMUNOLOGIC AND INFLAMMATORY

CHAPTER 116

ARTHRITIS

Nicholas Genes and Bruce D. Adams

PERSPECTIVE

Arthritis and its related disease states represent the most common cause of disability in the United States[1]; this is only expected to increase as the population ages and grows heavier. Because of the pain and limitations associated with joint inflammation, patients with complaints stemming from arthritis present frequently for emergent evaluation. Many of the arthritides are associated with premature mortality, and their treatments are associated with adverse effects. A systematic approach to evaluation of patients with arthritic complaints is important. The inflamed joint may be a diagnostic clue to a serious systemic illness (such as acute rheumatic fever or renal crisis), and unmasking of true arthritis emergencies can prevent or attenuate devastating disability.

Arthritis and related conditions are among the oldest disease states described. Roman, Greek, and Egyptian cultures made reference to gout and rheumatoid arthritis and even associated these maladies with diet and socioeconomic status. Gout was called the disease of kings because of its relationship to alcohol and rich foods.[2]

Many celebrated figures in medicine, such as Hippocrates, Galen, and Sydenham, contributed to the description, classification, and treatment of rheumatic disorders.[2,3] Reiter's syndrome, however, takes its name from a discredited Nazi war criminal (many, including the physician who first bestowed the eponym in the English literature in1942, now advocate for the generic term *reactive arthritis*).[4]

Several world leaders through the ages suffered from arthritis, and some have argued that specific flare-ups have shaped history.[2] Predisposing factors for gout, such as lead levels, may have influenced the rise and fall of civilizations.[5,6]

PRINCIPLES OF DISEASE

As opposed to synarthrotic suture joints of the skull and amphiarthrotic fibrocartilage unions like the pubic symphysis, the joints of concern in acute arthritis are the synovial or diarthrotic (moving) joints. These synovial joints are composed of two ends of subchondral bone covered by articular cartilage, surrounded by a capsule that is lined with a thin synovial membrane and supported by ligaments, tendons, and muscle (Fig. 116-1A).

Articular cartilage is an avascular, aneural tissue composed of a matrix of collagen fibers and proteoglycans synthesized by chondrocytes. The properties of articular cartilage allow tremendous load bearing. Together with the viscous lubricating synovial fluid, an ultrafiltrate of blood supplemented with hyaluronic acid and low-molecular-weight proteins, the cartilage that articulates joint movement is nearly frictionless.

Whereas disease-specific changes receive further detail in subsequent sections, the final common pathway of arthritis is triggered by trauma, infection, or the endogenous cell and humoral inflammation stimulated by infection or autoimmune disease.

The pathologic process of arthritis can unfold during hours or years. Tissue destruction can be mediated by fast-acting catabolic pathways, or long-term changes to the composition of cartilage's extracellular matrix may be brought on by abnormal loading patterns or trauma. The synovium plays a critical role in crystal deposition and inflammatory response (Fig. 116-1B).

CLINICAL FINDINGS

Symptoms and Signs

Pain is the hallmark complaint of patients with joint problems who come to the emergency department (ED) (Table 116-1). The pain may be acute or chronic (traditionally, more than 6 weeks) or an acute episode in a person with chronic disease. The patient may have had similar pain before, so it is important to know whether a diagnosis was previously made and what treatment, if any, was instituted. One must first determine whether the source of the inflammation or pain is articular or periarticular (outside the joint capsule).

True arthritis produces generalized joint pain, warmth, swelling, and tenderness. Discomfort increases with both passive and active motion of the joint because the inflamed synovium is exquisitely sensitive to stretching and because all parts of the joint are involved in the inflammatory process. By contrast, periarticular inflammation (bursitis, tendinitis, or localized cellulitis) tends to be more focal. Tenderness and swelling do not occur uniformly across the joint, and pain is produced only with certain movements, the most common being resisted active contraction and passive stretching of the affected muscles or tendons.

Patterns

If the site of the patient's pain is articular, the next step is to determine whether the arthritis is monarticular or polyarticular. The arthritis may be symmetrical (e.g., rheumatoid or drug induced) or asymmetrical (e.g., rubella, acute rheumatic fever, or gonococcal). In addition, it may also be migratory (e.g., gonococcal or rubella), subsiding in one area before presenting in another, or additive, remaining in the first joint and progressing to additional joints (Box 116-1).

www.ketabpezeshki.com 66485457-66963820

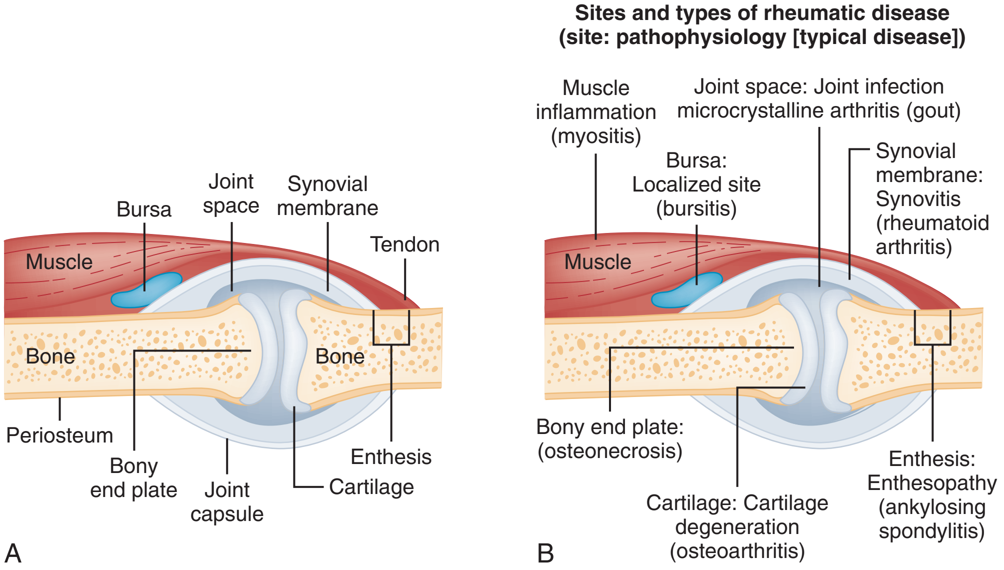


Figure 116-1. Anatomic structures of the joint with location of selected arthritis diseases. (Redrawn from Goldman L, Ausiello DA [eds]: Cecil Medicine, 23rd ed. Philadelphia, Saunders/Elsevier, 2008.)

Table 116-1 Causes of Joint Pain

MONARTICULAR	POLYARTICULAR	PERIARTICULAR
Acute (<6 weeks)		
Acute rheumatic fever	Gout	Bursitis
Lyme disease	Gonococcal arthritis	Tendinitis
Reactive arthritis (Reiter's)	Pseudogout	Cellulitis
Viral arthritis	Septic arthritis Trauma and hemarthrosis	Enthesitis
Chronic (<6 weeks)		
Adult-onset Still's disease	Osteoarthritis	
Relapsing polychondritis		
Rheumatoid arthritis		
Seronegative spondyloarthropathies		

Box 116-1 Differential Diagnosis of Arthritis in the Emergency Department

Monarticular
Septic arthritis
Gout
Pseudogout
Osteoarthritis
Trauma, hemarthrosis
Charcot's joint

Polyarticular
Symmetrical
Gonococcal arthritis
Viral arthritis
Lyme disease
Drug-induced arthritis
Reactive arthritis
Rheumatic fever
Seronegative spondyloarthropathies

Asymmetrical
Gonococcal arthritis
Acute rheumatic fever
Lyme disease
Systemic lupus erythematosus
Immune complex diseases (viral)
Reactive arthritis

Distribution and Associated Symptoms

The distribution of joint involvement may give some clues to the disease: the first metatarsophalangeal (MTP) joint is classically affected in gout; the metacarpophalangeal (MP) joints and proximal interphalangeal (PIP) joints in rheumatoid arthritis (RA); and the distal interphalangeal (DIP) joints and the first carpometacarpal joint in osteoarthritis (OA). Patients with inflammatory arthritis may have low-grade fever; high fever with chills is more suggestive of a septic arthritis. Morning stiffness (gel phenomenon) and improvement of symptoms with activity suggest inflammatory arthritis, whereas improvement with rest suggests mechanical disorders. Concomitant renal stones suggest gout; genital ulcerations occur in Behçet's disease and reactive arthritis; and a purulent urethral discharge suggests gonococcal arthritis or reactive arthritis. The use of isoniazid, procainamide, and hydralazine can precipitate lupus, and thiazides can increase the serum uric acid level, leading to gouty arthritis.

Physical Examination

General Examination. The physical examination searches for evidence of both local and systemic manifestations of rheumatic diseases (Table 116-2).

Joints. Joints are examined for warmth (the dorsum of the hand can detect a difference of 0.5° C), effusion, synovial thickening, deformity, range of motion, pain on actively loaded motion, and tenderness (generalized or localized, articular or periarticular).

Spine. The spine evaluation is best performed with the patient standing; the vertebral column is assessed for abnormal curvature or asymmetry. Although supporting evidence is scant, Schober's maneuver is used to assess for the limitation of the lumbar spine motion that occurs in ankylosing spondylitis.[7]

www.ketabpezeshki.com 66485457-66963820

Table 116-2 Clinical Signs of Arthritis Diseases*

ORGAN SYSTEM	FINDINGS	DISEASES
Airway	Airway obstruction	RA, RP
Cardiac	Pericarditis Murmurs	RA, ARF ARF, RP, AS
Eyes	Iritis, uveitis Conjunctivitis	Spondyloarthropathies Reactive arthritis
Gastrointestinal	IBD Dysentery	Spondyloarthropathies Reactive arthritis
Genitalia	Lesions, urethral discharge	Reactive arthritis, gonococcemia
Hematologic	Aplastic anemia Anemia of chronic disease	Parvovirus Any chronic arthritis disease
Neurologic	Cauda equina syndrome Cervical spine instability	AS AS, RA, OA
Oral mucosa	Ulcerations	Reactive arthritis
Pulmonary	Pleuritis, nodules	RA
Renal	Renal crisis, ARF	Scleroderma
Skin	Plaques on elbows, knees Sclerodactyly, calcinosis Erythema chronicum migrans Tophi Erythema marginatum Subcutaneous nodules	Psoriasis Scleroderma Lyme disease Gout Rheumatic fever Rheumatoid arthritis

*Excludes rheumatic vasculitis diseases.
ARF, acute rheumatic fever; *AS,* ankylosing spondylitis; *IBD,* inflammatory bowel disease; *OA,* osteoarthritis; *RA,* rheumatoid arthritis; *RP,* relapsing polychondritis.

Upper Extremities. Localized tenderness and pain associated with active movement are more likely to be periarticular in origin. A shoulder affected by chronic arthritis or bursitis will have atrophy of the deltoid muscle. Generalized tenderness and pain, both at rest and with active and passive motion, suggest joint involvement.

Early signs of joint inflammation in the elbow are limitation of extension and an increase in the normal angle at which the patient holds the elbow at the side.

The hand and wrist provide many clues to the presence of long-standing rheumatic diseases: MP and PIP joints are affected in RA; and the first carpometacarpal, PIP, and DIP joints are affected in OA. The fingers may be swollen or sausage-like in appearance, an indication of psoriasis or reactive arthritis. Subluxation at the MP joints, ulnar deviation, and swan-neck deformities occur in RA. The nails may have pitting characteristic of psoriatic arthritis.

Assessment of the wrist is difficult because it may not be obviously swollen. Discomfort and decreased range of motion, particularly on extension, may indicate synovial involvement.

Lower Extremities. Inflammation affecting the hip joint can be manifested as pain in the anterior thigh, knee, or groin. A hip joint effusion will cause the patient to hold the hip partially flexed. An externally rotated and abducted leg in a neonate strongly suggests infection.[8] Range of motion of the hip is most easily tested by flexing the hip, bending the knee at a right angle, and rotating the heel medially and laterally to test for external and internal rotation, respectively.

Box 116-2 Radiograph of a Joint Can Be Surveyed by This Systematic Approach

A Alignment: Rheumatoid arthritis is manifested with ulnar deviation.
B Bone mineralization: Osteoporosis is more typical of the inflammatory arthritides; periostitis (reactive bone formation) indicates seronegative spondyloarthropathies or osteoarthritis.
C Calcification: Gouty tophi and typical linear cartilage calcification of CPDD.
D Distribution: Rheumatoid arthritis is typically symmetrical. Specific target sites suggest diagnoses.
E Erosions: Overhanging edges and sclerosis are characteristic of gout.
S Soft tissue: Assess for soft tissue swelling, nail hypertrophy (psoriatic arthritis), and sclerodactyly (scleroderma).

An effusion of the knee joint is relatively easy to detect when it appears as a ballotable fullness medially and laterally. Fullness of the popliteal fossa may indicate Baker's cyst. Passive range of motion may elicit crepitus (suggestive of degenerative joint disease) or clicking (suggesting a meniscal tear). Tibiotalar joint effusions produce swelling under the medial malleolus and make it difficult to palpate the extensor hallucis longus tendon. Tenderness, warmth, and swelling of the great toe MTP joint occur in cases of gout but can also occur with OA and RA. Sausage-like swellings of the toes are seen in reactive arthritis.

DIAGNOSTIC STRATEGIES

Blood Tests

In the ED evaluation of arthritis, blood testing conveys only modest diagnostic value.[9] The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) serum level, white blood cell (WBC) count, and serum uric acid level are best used in the context of evaluating the likelihood of specific forms of arthritis; there are no guidelines or studies supporting the use of blood testing as a general screen of acute undifferentiated arthritis in the ED.

Radiologic Tests

Plain Radiography

Plain radiographs are more helpful in patients with chronic disease than in those with acute arthritis (Box 116-2). Common findings that help distinguish the different forms of arthritis are shown in Table 116-3. For lower extremities, weight-bearing radiographs can better evaluate joint space narrowing.

Computed Tomography, Magnetic Resonance Imaging, and Sonography

Other radiologic modalities are occasionally performed as part of the workup of arthritis in an emergency setting. Ultrasonography compares favorably with plain radiography in the evaluation of joint effusions and synovitis associated with RA, and it is useful to evaluate pediatric hip effusion and to guide arthrocentesis.[10] Magnetic resonance imaging (MRI) is well suited for imaging of cruciate ligaments of the knee, detection of early edema in periarticular structures and fluid collection in tendon sheaths, and determination of the extent of cartilage destruction.[11] MRI is also the study of choice for diagnosis of osteonecrosis and is more sensitive than plain radiography for early osteomyelitis.[12,13]

www.ketabpezeshki.com 66485457-66963820

Table 116-3 Common Radiologic Findings in Arthritis

ARTHRITIS	FINDINGS
Acute arthritis (gout, pseudogout, septic arthritis)	Soft tissue swelling
Late septic arthritis (need at least 8-10 days for changes to be seen)	Subchondral bone destruction Periosteal new bone Loss of joint space Osteoporosis Late joint space narrowing
Late pseudogout (knee, hip; radiocarpal, midcarpal, all MP joints)	Linear calcification in cartilage Asymmetrical joint space narrowing MP "hook spurs" in HHC Osteophyte formation Subchondral cyst formation Lack of osteoporosis
Degenerative arthritis (acromioclavicular, first carpometacarpal, first MTP, DIP joints; knee, hip, cervical spine, lumbosacral spine)	Asymmetrical joint space narrowing Sclerosis of juxta-articular bone Bone spurs and cysts—adjacent to severe cartilage degeneration No osteoporosis
Tuberculous arthritis (knee, hip, shoulder)	Soft tissue swelling Marked demineralization Bone rarefaction Little reactive sclerosis Late bone destruction Joint space preserved
Late rheumatoid arthritis (wrist, MP, PIP, MTP, first IP joints; foot, atlantoaxial joint, glenohumeral joint)	Symmetrical joint space narrowing Osteoporosis of periarticular bone Marginal erosions (no overhanging margins as in gout) Little reactive bone formation

DIP, distal interphalangeal; *HHC*, hereditary hemochromatosis; *IP*, interphalangeal; *MP*, metacarpophalangeal; *MTP*, metatarsophalangeal; *PIP*, proximal interphalangeal.

Arthrocentesis

Arthrocentesis is a crucial diagnostic modality because it is the only method of unequivocal diagnosis of septic arthritis or crystal-induced joint disease.

Indications and Contraindications

The emergency indications for arthrocentesis in the evaluation of joint pain are to obtain joint fluid for analysis, to drain tense hemarthroses in patients with trauma or hemophilia (of the elbows, knees, or ankles and after the appropriate clotting factor replacement), to evaluate whether a laceration communicates with the joint space, and to instill analgesics and anti-inflammatory agents for the treatment of acute and chronic arthritis.

The American College of Rheumatology guidelines recommend arthrocentesis to evaluate patients with an established history of arthritis who present with fever and new joint pain or effusion.[14] Although scant literature on inoculated joint spaces exists, emergency arthrocentesis through overlying cellulitis is relatively contraindicated, and avoidance of the infected area during the puncture is recommended. Coagulopathy is the other relative contraindication, but arthrocentesis can be safely performed with a 20- to 22-gauge needle in the presence of international normalized ratios as high as 4.5.[15] Arthrocentesis of prosthetic joints should be performed only to rule out infection and is best done in consultation with an orthopedic surgeon.

Complications

The primary complications of arthrocentesis are bleeding or infection in the joint space, allergic reaction to anesthetic agents, and long-term corticosteroid-related complications. Dry taps (when no fluid is aspirated after joint puncture) are more common in patients with chronic arthritis because of obstructing tophi or anatomic abnormalities in the synovium and periarticular tissues. Use of a smaller syringe or a larger needle may help in such cases. Many laboratories will accept just a single drop of synovial fluid for use in crystal analysis on a slide mount.

Technique

Successful joint aspirations begin with positioning of patients so they are comfortable, with adequate exposure and cushioned support for the joint. Muscle tension during the procedure can reduce the joint volume, making the procedure more difficult. Carefully palpate the bone landmarks and prepare the skin with an aseptic technique. Adequate local anesthesia is achieved either by use of a vapor coolant or by local infiltration with anesthetic solution, such as 1% or 2% lidocaine. With an 18- or 19-gauge (large joints) or 20- to 22-gauge needle (smaller joints) attached to a syringe, the joint space is punctured and aspirated with care taken to avoid abrasion of the articular cartilage. Excessive suction may bring synovial tissue into the needle, limiting aspiration. After aspiration, a long-acting anesthetic can be instilled to alleviate pain. As a general rule, do not instill steroids unless a septic arthritis has been excluded.

Synovial Fluid Examination

Analysis of synovial fluid is essential for identification of crystalline and suppurative causes of acute arthritis (Table 116-4).

General Appearance. Bedside inspection of synovial fluid for color, clarity, and viscosity can provide diagnostic clues. Normal synovial fluid is clear and colorless, with a viscosity that permits stretching of a "string" of fluid between the thumb and forefinger. Inflamed fluid is more opaque from an elevated WBC count, with a viscosity more like water because of enzymatic breakdown of glycosaminoglycans. Hemarthrosis is manifested after acute trauma or in the presence of coagulopathy, particularly with hemophilia. Lipohemarthrosis indicates ligamentous injury or an intra-articular fracture, and brownish synovial fluid may suggest the rare diagnosis of pigmented villonodular synovitis.

Synovial Fluid Studies. Routine laboratory analysis includes a cell count with differential, Gram's stain, and crystal analysis; synovial glucose and protein concentrations are of little diagnostic assistance.[16] A positive Gram's stain is diagnostic, but a negative result for bacteria does not rule out septic arthritis; culture specimens should also be obtained. Blood culture bottles are more sensitive than other media at identification of pathogens.[17,18]

Synovial White Blood Cell Count. Synovial WBC (sWBC) counts are often used to differentiate classes of synovial fluid; unfortunately, significant overlap exists between inflammatory and septic causes of acute arthritis.[17] A very high fluid sWBC count or polymorphonuclear (PMN) cell pleocytosis indicates infection, but a more modest sWBC count or differential does not exclude it. The likelihood ratio (LR) for septic arthritis increases as the joint WBC count rises. According to one review, sWBC count of less than 25,000/mm^3 = LR of 0.32; sWBC count of more than 25,000/mm^3 = LR of 2.9; sWBC count of more than 50,000/mm^3 = LR of 7.7; and sWBC count of more than 100,000/mm^3 = LR of 28.0.[9] However, low sWBC counts do occur early in infectious arthritis and in partially treated infections; high sWBC counts (>50,000/mm^3) can occur in RA, gout, and pseudogout. Most of

www.ketabpezeshki.com 66485457-66963820

Table 116-4 Synovial Fluid Interpretation

PROPERTY	CLASS I (NONINFLAMMATORY)	CLASS II (INFLAMMATORY)	CLASS III (SEPTIC)	CLASS IV (HEMORRHAGIC)
Color	Clear/yellow	Yellow/white	Translucent/opaque	Opaque, may contain fat droplets (lipohemarthrosis)
Viscosity	High	Variable	Low	
WBCs/mm^3	<2000	2000-100,000	<75,000	
Differential	<25% PMNs	>50% PMNs	>95% PMNs	
Culture	Negative	Negative	Positive	Variable
Leading diagnosis	Osteoarthritis	Inflammatory arthritis	Bacterial arthritis	Trauma, coagulopathy

From Fye KH, Morehead K: Joint aspiration and injection. In Imboden J, Hellman D, Stone J (eds): Current Rheumatology Diagnosis and Treatment. New York, McGraw-Hill, 2007:12.
PMNs, polymorphonuclear cells; *WBCs,* white blood cells.

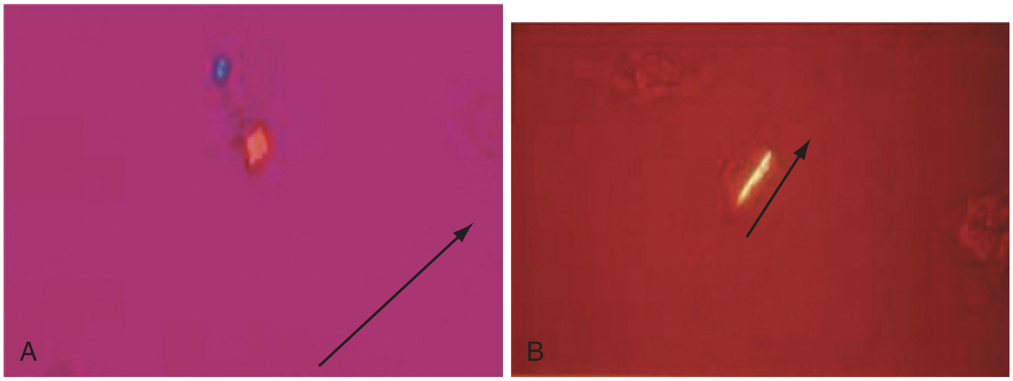


Figure 116-2. Pseudogout (**A,** blue crystal with a more plump structure) and gout (**B,** yellow crystal in parallel refraction with a longer, more needle-like structure) crystals under polarizing light. (From Goldman L, Ausiello DA [eds]: Cecil Medicine, 23rd ed. Philadelphia, Saunders/Elsevier, 2008.)

the cells in both septic and severe inflammatory arthritis are PMN cells.

In summary, cell counts cannot be used to absolutely rule out a septic cause. When in doubt, bacterial cultures sent in blood culture bottles are recommended.

Crystal Analysis. Although there is some variation in study findings, overall there is an acceptable inter-rater reliability in identifying monosodium urate and calcium pyrophosphate dihydrate crystals in acute arthritis.[19] Crystal analysis is best performed by polarizing microscopy of a fresh drop of synovial fluid placed on a slide with cover slip (Fig. 116-2). Monosodium urate crystals are needle shaped and strongly negatively birefringent (yellow when parallel to the compensator and blue when perpendicular), ranging in size from 2 to 10 μm. Calcium pyrophosphate crystals, in contrast, are polymorphic, rhomboid, and positively (although weakly) birefringent. Lipid appears as a spherule with a Maltese cross, and hydroxyapatite is difficult to recognize.

DIFFERENTIAL CONSIDERATIONS AND MANAGEMENT

Monarticular Arthritis: Acute

Inflammatory conditions of the periarticular soft tissues, such as olecranon bursitis, rotator cuff shoulder tendinitis, and prepatellar bursitis, can mimic monarticular arthritis, and classically polyarticular conditions, such as RA and the seronegative spondyloarthropathies, may present initially in only one joint. As a general rule, a patient presenting with monarticular arthritis has a septic arthritis until it is determined otherwise (Fig. 116-3).[20]

Septic Arthritis: Nongonococcal Bacterial

Epidemiology. In two prospective series of patients presenting to the ED with monarticular arthritis prompting arthrocentesis, 8 to 27% of patients had bacterial joint infections.[16,21] The incidence of septic arthritis in the general population is approximately 2 to 10 cases per 100,000 per year, with an age distribution curve for septic arthritis revealing bimodal peaks for young children and adults older than 55 years.[22] Additional risk factors include low socioeconomic status, injection drug abuse (in which joint infections typically involve the axial skeleton but can involve extremities), alcoholism, diabetes, skin infections, advanced human immunodeficiency virus (HIV) infection or other immunocompromised states, chronic arthritis (particularly rheumatoid, crystalline, and degenerative OA), and following intra-articular corticosteroid injections or prosthetic implants.

Pathophysiology. Any diarthrotic joint, whether it is native, chronically diseased, or prosthetic, can develop septic arthritis. Bacterial pathogens infect the joint space most commonly by hematogenous spread, but direct inoculation and contiguous spread from bone or soft tissue infections also occur. Once in the joint, bacteria proliferate essentially unchecked in the highly vascular synovium, which has no limiting basement membrane. Bacterial components and toxins, as well as the inflammatory cascade they induce, trigger synovial proliferation with neovascularization and subsequent enzymatic, cellular, and cytokine degradation of articular cartilage. Septic arthritis, unless it is rapidly recognized and treated, results in serious disabling morbidity, with mortality ranging from 7 to 15% or higher.[17]

Septic arthritis can occur simultaneously with other forms of arthritis, especially RA and gout.[20] The diagnosis of infectious

www.ketabpezeshki.com 66485457-66963820

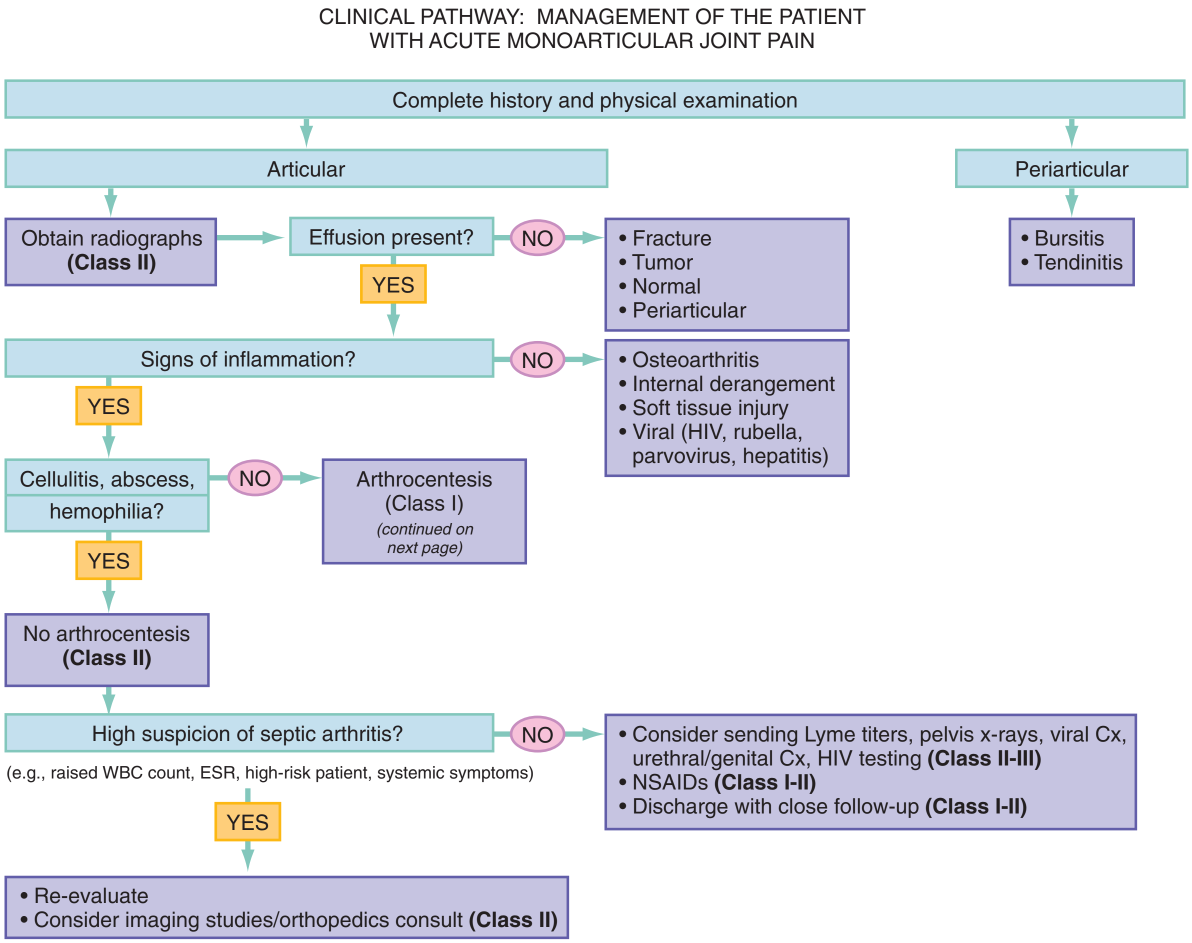


Figure 116-3. An initial approach to the patient with monarticular arthritis. The majority of diagnoses will be determined by the history and physical examination findings. *CBC,* complete blood count; *Cx,* culture; *ESR,* erythrocyte sedimentation rate; *HIV,* human immunodeficiency virus; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *PT/PTT,* prothrombin time/partial thromboplastin time; *WBC,* white blood cell. (Modified from EB Practice LLC. 2004.)

arthritis in a patient with known crystal arthritis can be challenging because acute flare-ups of gout or pseudogout can cause fever, and crystals can emerge from an infected joint. For this reason, Gram's stain and culture should be considered in select cases.

Microbiology. The microbiology of nongonococcal arthritis has remained fairly constant over time, except for the notable decline of *Haemophilus* and pneumococcal species in the postimmunization era.[22] Acute nongonococcal septic arthritis in adults is caused most often by gram-positive organisms (75-90%), followed by gram-negative bacilli (10-20%) and then anaerobes, mycobacteria, and fungal and other unusual organisms.[23] Overall, *Staphylococcus aureus* is still the most common cause of septic arthritis, with the rapid emergence of methicillin-resistant strains.[24] *Neisseria gonorrhoeae* accounts for only 20% of cases of monarticular septic arthritis and more commonly is manifested with polyarthritis; it is discussed separately. Select populations have higher propensities for specific infecting organisms (Table 116-5).

Prosthetic Joint Infection. Prosthetic joint infections are classified as early (within a month of surgery) or late. Late infections can be caused by hematogenous spread from another infection or by indolent organisms introduced at surgery that may not surface for up to a year.[25] Because the joint is literally replaced, antibiotic bioavailability and host immune response are both impaired in the prosthetic environment. A wide range of culprit organisms have been identified[26]; methicillin-resistant *S. aureus* (MRSA) incidence is rising.[27] Arthrocentesis diagnosis of a suspected prosthetic joint infection is best done in consultation with the operating surgeon. A fluid WBC count of more than 1100/mm^3 or a pleocytosis of greater than 64% PMN cells is sensitive and specific for infection in this setting.[28]

Clinical Features. Patients with septic arthritis present with fever, joint pain, and effusion, typically in a single large joint (the knee is most common). Moderate fever occurs in 50% of cases[17] but may be less common in the presence of advancing age or immunosuppressive states.[17] Rigors and chills are reported in only 20% of patients. Polyarticular presentation occurs in 20% of cases, particularly in patients with RA or chronic joint disease, meningococcal infections, or overwhelming sepsis.[17] Other physical signs, such as edema, tenderness, and decreased range of motion, have not been adequately evaluated for their prognostic value.

Diagnostic Strategies. Laboratory evaluation typically includes complete blood cell count, ESR, and CRP level, although in one study a WBC count above 10,000/μL and an ESR above 30 mm/hr only minimally increased the likelihood of septic arthritis.[28] Furthermore, systematic reviews show insufficient evidence for a normal CRP level, ESR, WBC count, or procalcitonin level to rule out septic arthritis.[29,30] Serum blood cultures reveal the causative organism approximately 25 to 50% of the time.[31,32]

Radiographs demonstrate only soft tissue swelling if it is present; the bone changes of septic arthritis are long-term findings and are not usually present on the initial examination. Radiographs are recommended to assess for osteomyelitis or as a baseline for future comparisons.

www.ketabpezeshki.com 66485457-66963820

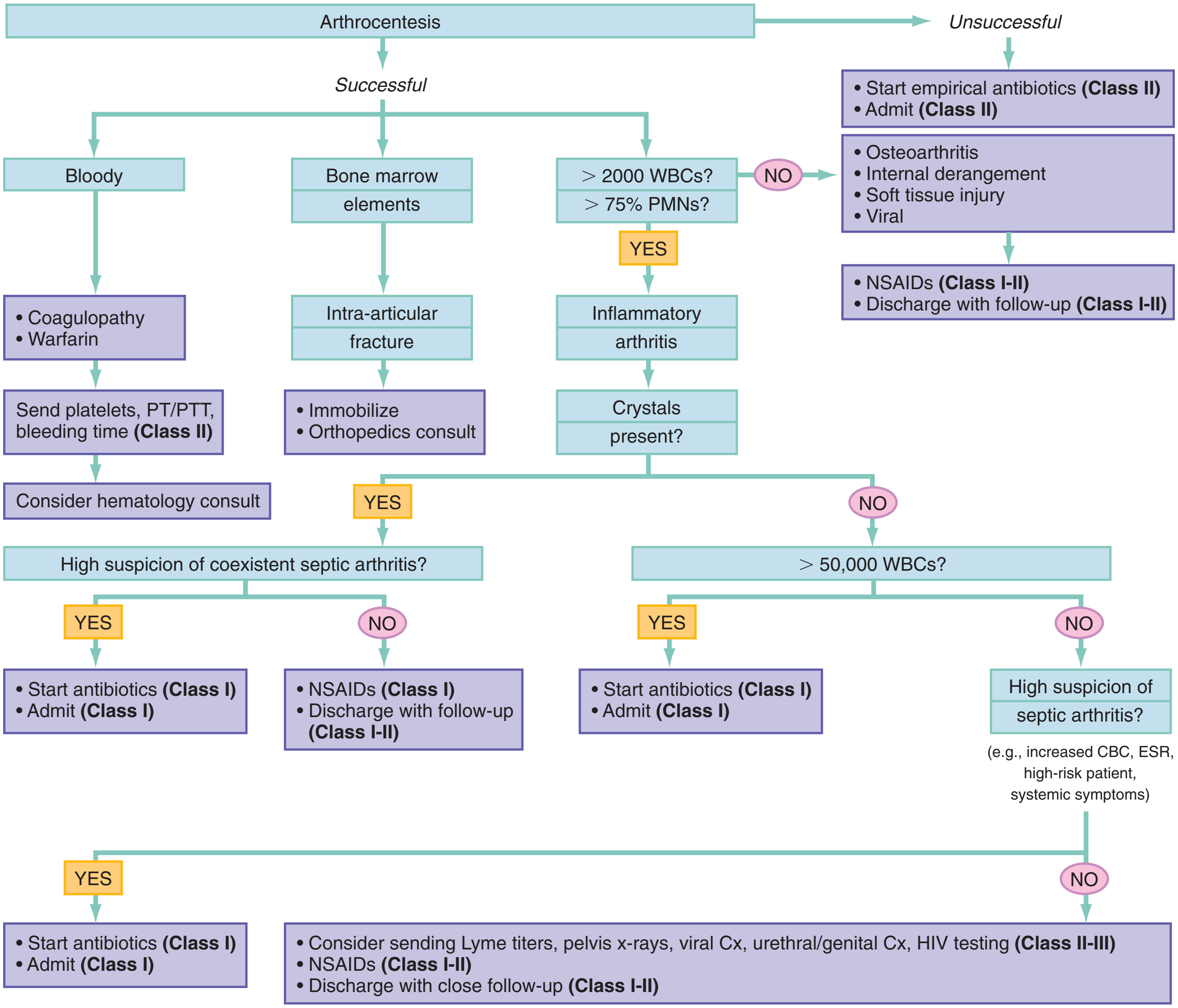


Figure 116-3, cont'd.

Table 116-5 Microbiology of Bacterial Septic Arthritis Related to Patient

PATIENTS	ORGANISMS
Neonates and infants	*Staphylococcus aureus*, group B streptococcus, GNR
Children	*Haemophilus influenzae, S. aureus*
Adolescents and young adults	*Neisseria gonorrhoeae, Chlamydia trachomatis*
Older adults	*S. aureus, Streptococcus*, GNR
Sickle cell anemia	*Salmonella*
Injection drug abusers	*Pseudomonas, S. aureus*, GNR

From Noble J, Greene HL: Textbook of Primary Care Medicine, 3rd ed. St Louis, Mosby, 2001.
GNR, gram-negative rod bacteria.

The only definitive diagnostic test for septic arthritis is synovial fluid analysis. The fluid WBC count is directly proportional to the probability of a septic joint. Polymorphonucleocyte concentrations above 90% are also associated with an increased likelihood for septic arthritis. Synovial lactate levels greater than 5.6 mmol/L have an LR+ of 2.4 to infinity; smaller values make septic arthritis unlikely.[33] Synovial lactate dehydrogenase (LDH) levels above 250 U/L are sensitive for septic arthritis, according to one study,[16] whereas LDH levels below this seem to exclude septic arthritis. Low synovial glucose and high protein concentrations are neither sensitive nor specific for septic arthritis.[32] Gram's stain will show bacteria in 50 to 80% of infected joints.[17] Synovial fluid cultures for both aerobic and anaerobic organisms should be performed.

Management. The key to successful treatment of nongonococcal septic arthritis is early diagnosis. Substantial delays in diagnosis directly worsen prognosis. Empirical antibiotic therapy is based on Gram's stain or the presumptive consideration of likely organisms. Once the diagnosis is made, hospital admission is indicated for administration of intravenous antibiotics and needle, arthroscopic, or open drainage of the affected joint.[34] Whereas the utility of performing or omitting joint drainage has not been prospectively studied, retrospective reviews suggest good cure rates with drainage, with outcomes dependent on initial severity.[35] More severe cases require frequent, potentially daily joint aspirations.

There are no randomized controlled trials of antibiotic regimens in septic arthritis. Antibiotic selection is initially based on

www.ketabpezeshki.com 66485457-66963820

Gram's stain results and then adjusted on the basis of final culture results and sensitivities. For gram-positive organisms, the initial drug of choice is vancomycin 30 mg/kg daily in two divided doses as MRSA is frequently causative.[24] For gram-negative bacilli, use a third-generation cephalosporin, such as ceftriaxone 2 g IV once daily, cefotaxime 2 g IV three times a day, or ceftazidime with gentamicin (especially if *Pseudomonas* infection is suspected). Although no trials of antibiotic duration have been reported, antibiotic therapy is generally continued parenterally for 2 to 4 weeks, depending on the response, and followed with 2 to 6 weeks of oral antibiotic therapy.

The failure to respond to therapy within a few days of hospitalization, the presence of osteomyelitis, the involvement of the hips or shoulders, or the involvement of any prostheses usually mandates open arthrotomy for drainage. Parenteral opioid analgesics and immobilization are recommended for pain and discomfort.

Gonococcal Arthritis

Principles of Disease. Gonococcal arthritis was considered the most common infective arthritis in the United States in the 1970s and 1980s and remains the most common form of joint infection in the sexually active population. In recent years, the incidence has decreased, most likely because of a general decline of *N. gonorrhoeae* prevalence, particularly of the more virulent strains.[36] Host risk factors for dissemination of gonococcal infection to joints include pregnancy, menstruation, and complement deficiency. There is a 4 : 1 female predominance, possibly explained by mucosal infections more often being asymptomatic in women.

Gonococcal arthritis represents a clinical and pathologic course distinctly different from that of other bacterial infections and is less likely to create long-term joint disease.[25]

Clinical Features. Systemic gonococcal infection complicates 0.5 to 3% of mucosal infections and is manifested with two somewhat overlapping musculoskeletal syndromes. The first is a localized septic arthritis, more commonly oligoarthritis than monarthritis, predominantly in the wrist, knee, or ankle. The effusions may be modest. True disseminated gonococcal infection (sometimes termed arthritis-dermatitis syndrome) is manifested with bacteremia, diffuse migratory arthralgias, characteristic skin lesions, and tenosynovitis (Fig. 116-4). A similar syndrome has recently been recognized as a result of *Neisseria meningitidis* infection.[37]

Management. Microbiologic diagnosis is a problem because both synovial and blood cultures are positive for gonococcus in no more than 10 to 50% of cases.[25] The diagnostic yield is higher when specimens are plated on Thayer-Martin medium and even greater with the use of polymerase chain reaction. Synovial fluid often yields a positive Gram's stain result, and the synovial WBC count tends to be lower than in nongonococcal arthritis (40,000-60,000 cells/mm^3). Cervical, urethral, rectal, and pharyngeal cultures are positive in up to 75% of cases, so all mucosal orifices of the patient (and partner, if possible) should be cultured appropriately.[36] In disseminated gonococcal infection, the skin lesions often contain the gram-negative diplococcus.

The current Centers for Disease Control and Prevention (CDC) guidelines recommend hospitalization, especially if etiology or compliance is uncertain, and treatment with intramuscular or intravenous ceftriaxone 1 g every 24 hours or intravenous ceftizoxime or cefotaxime 1 g three times daily, with transition to oral cefixime 400 mg twice daily for at least a week.[38] Partners should be evaluated. Presumptive treatment of *Chlamydia* is also advised.

Repeated therapeutic arthrocentesis need not be as aggressively used in this form of septic arthritis. With prompt antibiotic therapy, residual joint problems are uncommon.

Figure 116-4. Pustular lesion with disseminated gonococcal infection. (From Mandell GL, Bennett JE, Dolin R [eds]: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 6th ed. Philadelphia, Elsevier/Churchill Livingstone, 2005.)

Gouty Arthritis

Epidemiology. Acute intermittent gout typically is manifested in middle-aged men or postmenopausal women, often in the setting of excess alcohol consumption or dietary indiscretion, acute physiologic stressors (such as illness, trauma, or surgery), or new medications. Its prevalence in the United States is estimated at 2.7% of the population. Risk factors include chronic obesity, hypertension, diabetes, thiazide diuretics or cyclosporine use, and lead or radiocontrast exposure. Purine-rich diets (meat; seafood, especially anchovies and shellfish; beer; and legumes) predispose at-risk individuals to attacks; high-fructose corn syrup and soft drinks are also implicated.[39] High dairy and coffee consumption have been shown to decrease risk.[40]

Pathophysiology. Gout results from inflammation caused by the acute precipitation of uric acid crystals from supersaturated extracellular fluid. Uric acid is a normal metabolic end product of purine metabolism. Hyperuricemia results from its underexcretion in the kidney or, less commonly, from systemic overproduction caused by inborn errors of metabolism and myeloproliferative diseases. During an attack of gouty arthritis, the crystals are ingested by PMN cells, resulting in cytokine release and an inflammatory synovial reaction.

Asymptomatic hyperuricemia typically exists for decades, and less than a quarter of these patients have acute manifestations. Furthermore, not all patients with elevated uric acid levels or even joint crystals have acute attacks, and many patients with an acute gouty arthritis have a normal uric acid level.[41]

Clinical Features. Gouty attacks most commonly occur in the great toe MTP joint (*podagra,* up to 75%, with 90% of patients eventually experiencing this joint flare), the knee (*gonagra*), the ankle, and the tarsal joints. Usually only one joint is involved initially, but approximately 20% of patients can experience polyarticular involvement, bursitis, tenosynovitis, or even skin inflammation.[42] The pain is often so exquisite at onset that some patients cannot even tolerate the weight of a sheet on the joint. Systemic symptoms range from absent to dramatically mimicking a picture of septic arthritis. Fever can occur. Without treatment, the attack is self-limited, peaking during 24 to 48 hours and lasting about a week.

Subsequent attacks tend to be closer together, involve more joints, and last longer, eventually morphing into the final stage of chronic gouty arthritis after a decade, if untreated. Long-term sequelae include renal stones and tophi in the musculotendinous units, such as the olecranon bursa, Achilles tendon, ulnar surface

www.ketabpezeshki.com 66485457-66963820

of the forearm, hands and fingers, knees, feet and toes, and even the helix of the ear. The ED patient may present with a first attack or have a known history of gout with a recurrent episode. Cellulitis and septic arthritis need to be excluded, particularly if the knee is involved.

Diagnostic Strategies. During an acute attack, radiographs of the affected joint will show only soft tissue swelling, but long-standing disease produces typical asymmetrical bone erosions slightly removed from the joint (as opposed to RA erosions, which are more proximal to the articular surface). The crystal deposits of gout also cause an overhanging margin of soft tissue by the erosion.[43] Dual-source, dual-energy computed tomography using a mineral composition algorithm has shown promise in a small trial for diagnosis of uric acid collections in joints; blinded radiologists were able to match 12 positive images to 12 positive joint aspirations for gout; specificity was also good.[44]

Whereas higher levels of serum uric acid are commonly seen in gouty patients, this laboratory finding is not helpful in establishing the diagnosis of gout in the acute setting. Urate levels can be transiently normal, a process thought to be mediated by the uricosuric effects of endogenous adrenocorticotropic hormone (ACTH) and epinephrine, released as part of the pain response. Given the association of gout and renal insufficiency and the nephrotoxicity of several therapies, renal function should be checked.

The observation, with a polarizing microscope, of intracellular negatively birefringent crystals in joint fluid aspirate (see Fig. 116-2) remains the "gold standard" for diagnosis of gouty arthritis.

Management. Gout therapies are divided into acute treatment modalities and long-term prophylaxis. Prophylaxis is generally not an emergency consideration, but many patients present with breakthrough attacks. Traditionally, it has been recommended that prophylactic agents such as allopurinol, febuxostat, and probenecid neither be stopped nor initiated during an acute attack.[45]

ED pharmacologic mainstays for acute gout are nonsteroidal anti-inflammatory drugs (NSAIDs, including cyclooxygenase 2–selective agents), corticosteroids (including ACTH), and colchicine. Caution is exercised with use of these agents because hypertension, diabetes, and renal and vascular disease are prevalent in this cohort of patients.

NSAIDs. Whereas NSAIDs, particularly indomethacin, are considered first-line therapy for acute gout attacks, there is little evidence to support their superiority over other agents, and trials between NSAIDs have shown no apparent difference in efficacy.[46,47]

For acute attacks, indomethacin is typically given at 50 mg three times a day, naproxen at 500 mg twice a day, and ibuprofen at 800 mg three or four times a day.[48] If NSAID therapy is initiated promptly, relief occurs rapidly in the first 24 hours. Duration should continue for another 24 hours after the symptoms abate and be tapered quickly; longer durations may be necessary if treatment is delayed.

Colchicine. Colchicine inhibits microtubule formation and impedes the inflammatory response to the presence of crystals in synovial fluid. Its use for gout predates the foundation of the Food and Drug Administration in 1938,[48] but the promise of government-sanctioned market exclusivity has prompted new trials for safety and efficacy. Oral colchicine has been shown to be highly effective for gout in small randomized placebo-controlled trials at a loading dose of 1 mg followed by 0.5 mg orally every 2 hours.[49] However, all patients studied with colchicine at these doses eventually had gas, nausea, vomiting, or diarrhea. In 2010, a prospective double-blind study of an oral loading dose of 1.2 mg colchicine followed by 0.6 mg an hour later demonstrated superior pain relief of colchicine over placebo, and the low-dose regimen demonstrated pain relief similar to that with a high-dose regimen of 4.8 mg administered during 6 hours. The low-dose regimen also had a lower incidence of gastrointestinal complaints. Lower dosing is recommended in elders; in several case reports, dosing of colchicine at 0.6 mg spread over three times a day has been effective for pain relief as well.[49]

Colchicine is also effective in relieving symptoms from other crystal arthritides and therefore is not helpful when it is used for diagnostic purposes.[50]

Colchicine is contraindicated in patients with hematologic, renal, and hepatic insufficiency. Intravenous colchicine is generally not recommended, despite its rapid onset and reduced gastrointestinal toxicity. Intravenous colchicine has a long half-life and narrow therapeutic window; more than 20 iatrogenic deaths have now been reported across a broad spectrum of ages.[51]

Steroids. Once septic arthritis has been excluded, the intra-articular injection of steroids may be effective for individuals with accessible joint involvement; in one series of patients with contraindications to NSAIDs, pain relief was demonstrated within 48 hours of injection of 10 mg triamcinolone acetonide.[52] Triamcinolone acetonide in a dose of 20 to 40 mg for the knee and 5 to 10 mg for smaller joints is recommended.[53]

Systemic steroids, such as oral prednisone (40 mg/day for 3-5 days, with or without a taper), have been used.[54] However, a Cochrane review of three trials of various steroids against other agents failed to demonstrate evidence of efficacy for systemic steroids.[55] The authors of that review undertook a randomized trial of Dutch patients with arthrocentesis-confirmed gout who had not taken pain medications before diagnosis and found similar efficacy for pain relief from oral prednisolone 35 mg daily compared with naproxen 500 mg twice daily during 90 hours.

Adrenocorticotropic Hormone (Corticotropin). Although it is not commonly used (or studied) because of its expense and lack of general availability, synthetic ACTH is a desirable alternative to the preceding agents because of its fast onset of action and decreased toxicity in older patients.[56,57] In one randomized trial, it was found to achieve faster pain relief than indomethacin, with fewer side effects at a dose of 40 IU intramuscularly.[57] It is not considered likely that a single administration of ACTH will cause hypothalamic-pituitary-adrenomedullary axis suppression.

Other Agents. Guidelines for management of acute gout recommend that if the flare occurs while a patient is receiving a diuretic, the diuretic should be stopped if at all possible.[49] Narcotic analgesics and either local or regional anesthetic blocks are potential adjunctive therapy. Clinicians should remember that simple physical modalities, such as rest, elevation, and ice, demonstrate modest benefit and are adjunctive measures for any therapeutic regimen.

Summary. Both NSAIDs and colchicine are considered first-line therapies for gout; the two are often used in tandem in patients without contraindications, particularly renal insufficiency. Best available evidence supports a treatment strategy of prompt initiation of NSAID therapy (e.g., 50 mg of indomethacin three times daily or 500 mg of naproxen twice daily) or colchicine 1.2 mg followed by a 0.6-mg dose an hour later.

Patients for whom NSAIDs or colchicine is contraindicated can be treated with intra-articular injections of triamcinolone or ACTH (corticotropin). Systemic steroids, although commonly used, have a weaker evidence base, but a recent trial suggested that prednisolone 35 mg/day is comparable to naproxen 500 mg twice a day during the course of 4 days.

Follow-up, preferably with a rheumatologist, is recommended for proper prophylaxis against flares and risk mitigation.

Calcium Pyrophosphate Dihydrate Deposition Disease and Pseudogout

Principles of Disease. Calcium pyrophosphate dihydrate deposition disease (CPDD) results when calcium complex crystals form

www.ketabpezeshki.com 66485457-66963820

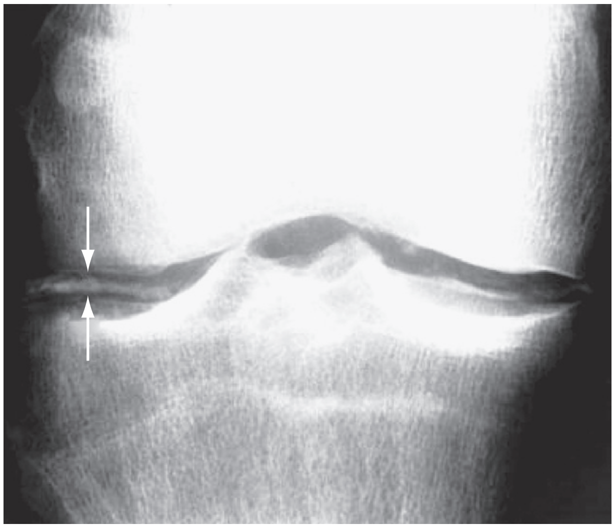


Figure 116-5. Chondrocalcinosis (*arrows*) in calcium pyrophosphate dihydrate deposition disease. (From Mettler FA: Essentials of Radiology, 2nd ed. Philadelphia, Saunders/Elsevier, 2005.)

across articular surfaces, manifested on radiographs as chondrocalcinosis (Fig. 116-5). The pathologic mechanisms are incompletely understood but involve overproduction of chondrocyte pyrophosphate, increased calcium, and histologic changes in the cartilage's extracellular matrix. CPDD is strongly associated with aging and joint surgery, but hemochromatosis, hypothyroidism, hyperparathyroidism, amyloidosis, hypomagnesemia, Wilson's disease, and inflammatory OA have also been implicated. The condition is most often asymptomatic, and its true incidence is unknown, but when precipitating crystals create an inflammatory synovitis, in about a quarter of cases, it is properly termed pseudogout.

Clinical Features. The clinical presentation of CPDD is similar to that of gout, and indeed the two conditions may overlap, thus making a synovial fluid diagnosis important. Pseudogout patients tend to be older than 65 years, and the knee is more commonly involved.

Diagnostic Strategies. Diagnosis of CPDD and pseudogout involves demonstration of the characteristic synovial crystals and radiographic changes. Radiographs demonstrate crystal deposition as punctuate, linear densities within the articular cartilage (such as the knee meniscus) or joint capsules. Joint fluid examination shows the rhomboidal, weakly positive birefringent crystals of CPDD (see Fig. 116-2). As with gout, the patient's symptoms may mimic septic arthritis, and the two conditions can also occur simultaneously.

Management. There are no randomized trials to support any one therapy for a pseudogout attack. Therapy is complicated by the fact that calcium pyrophosphate crystals, once present, cannot be removed. NSAIDs are recommended but with the typical cautions related to gastrointestinal bleeding, renal impairment, and cardiovascular events. Guidelines recommend colchicines,[58] but at a lower dose than for gout: 0.5 mg three or four times a day, with or without a 1-mg loading dose. Intra-articular glucocorticoid injections have expert approval,[58] and a small nonrandomized trial supports a single intramuscular dose of betamethasone (7 mg) or intravenous dose of methylprednisolone (125 mg) over a multiday oral diclofenac regimen.[59] There is some evidence to support oral colchicine as prophylaxis for pseudogout; in a before-and-after trial of 10 patients with recurrent attacks, a dose of 0.6 mg twice daily during a year reduced the rate of new attacks.[60] Treatment of secondary metabolic causes of CPDD, although important, does not appear to influence the course of disease or frequency of acute flares of pseudogout.

Basic Calcium Phosphate Hydroxyapatite Crystal Disease

A variant form of crystalline disease results from basic calcium phosphate hydroxyapatite (BCP) deposits. BCP deposition in synovial fluid is more difficult to detect with light microscopy and is more rapidly progressive and destructive than pseudogout.[61] BCP arthropathy also is manifested with calcific tendinitis, calcific bursitis, and a "pseudopodagra" of the first MTP joint in young women. The Milwaukee shoulder syndrome is characterized by severe bilateral OA of the glenohumeral joint, rapid destruction of the rotator cuff, and BCP crystals, leading to joint instability and upward subluxation.[62] Treatment is often ineffective, but steroid injections and physical therapy provide some benefit.

Acute Calcific Periarthritis

Acute calcific periarthritis results when amorphous calcium hydroxyapatite deposits extravasate into periarticular soft tissue, causing a self-limited, crystal-induced inflammatory reaction.[61,62] It usually occurs in women and most commonly involves the hand or rotator cuff; the symptoms last less than a week, and the radiographic findings resolve after about 3 weeks.[63]

Trauma and Hemarthrosis

Trauma is a common cause of acute monarticular effusion. One prospective series of tense knee hemarthrosis presenting within 12 hours of injury identified complete or partial anterior cruciate ligament tears in 70% of patients and meniscal tears in 16%; synovial disruption was presumed responsible in 5%.[64] An older prospective series of 100 acute trauma patients with knee hemarthrosis in the United Kingdom found that despite normal radiographs and confirmation of hemarthrosis by aspiration, 99 patients had serious pathologic changes, such as anterior cruciate ligament, posterior cruciate ligament, or collateral ligament tears seen with prompt arthroscopy. In both studies, the authors recommended aspiration of a tense effusion and urgent arthroscopy.[65]

Monarticular Arthritis: Chronic

Osteoarthritis (Degenerative Joint Disease)

Principles of Disease. OA, or degenerative joint disease, is the most common form of arthritis among adults, especially in elders and patients who are overweight. As a tissue, cartilage has limited self-repair capability. Mechanical signaling mediates chondrocyte production of extracellular matrix molecules. Perturbations in loading (from trauma or excess weight), combined with biochemical and genetic factors, influence cytokine signaling and matrix composition, ultimately causing subchondral bone overgrowth, cartilage degradation, and synovial membrane inflammation.

Clinical Features. Patients with OA classically describe pain that worsens with activity and improves with rest. The lack of systemic symptoms also helps distinguish OA from RA. In the hands, osteophytic spurs (Bouchard's and Heberden's nodes in the PIP and DIP joints, respectively) may be palpated. The knee, so commonly involved, classically displays crepitus on active and passive ranging.

Radiographs classically show asymmetrical joint space narrowing, although the degree of narrowing often does not correlate with the patient's perception of pain. Radiographs may also show osteophyte formation at joint margins, subchondral cysts.

Synovial fluid is difficult to aspirate in OA but classically is noninflammatory, with fewer than 2000 cells/mm and few PMN cells.

Management. Many nonpharmacologic therapies for knee and hip OA have been endorsed through clinical guidelines and

www.ketabpezeshki.com 66485457-66963820

meta-analyses, such as weight loss, exercise, patient education, and wedge-soled shoes.[66] For the hand, orthotics and splints are also endorsed, although there are few supporting trials.[67]

For pharmacologic therapy, acetaminophen at 4 g/day is supported by a 2006 systematic review of 15 trials, showing superiority to placebo although inferiority to NSAIDs for the hip and knee.[68] However, because the adverse effects of acetaminophen are milder and less likely than with NSAIDs, acetaminophen is considered a first-line therapy in the European League Against Rheumatism (EULAR)[67] and American College of Rheumatology guidelines.[69]

Cyclooxygenase 2 inhibitors (e.g., celecoxib) are associated with less gastrointestinal bleeding risk than traditional NSAIDs in randomized trials, with the same apparent effectiveness.[70] However, subsequent concerns for increased cardiovascular toxicity have limited their use.

Opioid analgesics for OA pain are supported by a meta-analysis for pain reduction and functional improvement.[71] However, the meta-analysis reported that the substantial heterogeneity and attrition due to adverse effects of opioids compared with other agents and placebo limited the validity of the findings.

Therapies involving glucosamine and chondroitin have shown variable benefit. Newer network meta-analysis has revealed no clinically significant improvement with these drugs, alone or in combination, compared with placebo.[72]

Capsaicin is a low-toxicity topical agent that may help after a few weeks of therapy.[66] Intra-articular glucocorticoid injections, such as triamcinolone, have shown pain relief lasting months but uneven efficacy in various joints and no measurable effect on physical function.[67] The dose of triamcinolone is generally 10 mg for hand joints; 20 mg for elbows, ankles, and acromioclavicular joints; and 40 mg for knees, hips, and shoulders. Intra-articular hyaluronic acid injections have demonstrated some improvement in physical function and superior pain relief compared with intra-articular steroid injections (although apparent only after a period of many weeks to months).[73,74]

Management of OA in the ED is geared toward symptom relief; acetaminophen 4 g/day is supported by many reviews for safety and efficacy. NSAIDs and opioids may be superior to acetaminophen for particular kinds of OA but have more adverse effects. In patients resistant to these therapies, intra-articular injections of triamcinolone have demonstrated pain relief in the long term, depending on the joint, but with no impact on physical activities.

Emergency physicians should recommend proven nonpharmacologic therapies for knee and hip OA, such as weight loss, exercise, and wedge-soled shoes, with referral to an orthopedic surgeon for further management.

Polyarticular Arthritis: Acute

The differential diagnosis of polyarticular arthritis is much broader than that of monarticular arthritis (Fig. 116-6). Polyarticular arthritis presentations are classified as either acute (<6 weeks) or chronic (>6 weeks). The acute polyarticular presentations include gonococcal arthritis, viral arthritis (e.g., rubella, hepatitis), Lyme disease, reactive arthritis, and rheumatic fever. Chronic polyarticular presentations are caused by RA, systemic lupus erythematosus, scleroderma, psoriatic arthritis, dermatomyositis, and other autoimmune diseases. The diseases may also be distinguished on the basis of symmetrical or asymmetrical presentations. RA and systemic lupus erythematosus tend to be symmetrical, the others asymmetrical. The spondyloarthropathies (ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and the arthropathy of inflammatory bowel disease) involve predominantly larger joints, but psoriatic arthritis affects the small joints of the hands.

Viral arthritides have varied mechanisms of inflammation (Table 116-6) but typically are manifested as an acute, self-limited, nondestructive polyarticular arthritis.

Lyme Disease

Principles of Disease. *Borrelia burgdorferi* infection causes the multisystem disorder known as Lyme disease, the most common vector-borne illness in the Western world.[75] In the United States, endemic areas for *B. burgdorferi* and its vector tick *Ixodes* include the Northeast, the Upper Midwest, and northern California.[76] More than a quarter-million cases have been reported to the CDC since 1992, with approximately 25,000 cases per year in recent years.[75]

Clinical Features. Lyme disease follows a prescribed pattern of early disseminated disease (weeks to months after a tick bite) and late disease (from several months to years later). Musculoskeletal manifestations of the early stage primarily consist of migratory myalgias and arthralgias without objective evidence of actual arthritis or effusions.[77] Arthritis is the most common manifestation of late Lyme disease. When it is untreated, 50 to 60% of patients will have frank asymmetrical arthritis within 6 months, most commonly in large joints, particularly the knees (although recent series suggest a lower incidence of arthritis).[78] The natural history of Lyme arthritis is intermittent episodes that gradually abate in intensity and frequency during several years, even if it is untreated. Lyme arthritis appears to be autoimmune mediated rather than a direct result of the spirochetal infection, but early antibiotic therapy clearly reduces its incidence. Lyme arthritis seems to be more prevalent in infections in the United States because the endemic *B. burgdorferi* displays stronger arthritogenic properties than other strains.

Diagnostic Strategies. The history of a previous tick bite from an endemic area or the classic erythema migrans rash (although often not remembered by the patient) may aid the clinician in suspecting the diagnosis. Patients have minimal joint pain and usually are afebrile despite large joint effusions. The joint fluid is inflammatory with PMN cell predominance, but *Borrelia* cannot be cultured from it. The differential diagnosis includes gonococcal arthritis, septic arthritis, acute rheumatic fever, RA, and reactive arthritis. Routine blood testing is nonspecific and unhelpful. Confirmatory diagnosis is by immunoglobulin M and immunoglobulin G serologies.

Management. Prophylactic therapy after a tick bite is not generally recommended except for an *Ixodes* attachment of longer than 36 hours in an endemic region; a single doxycycline dose of 200 mg is then recommended by the Infectious Diseases Society of America (IDSA) clinical guidelines[78]; of note, these guidelines have led to an antitrust suit filed by disenfranchised physicians skeptical of the IDSA's statements on post-Lyme syndrome, although the evidence supporting the antibiotic regimens has not been criticized.[79] Lyme arthritis can generally be treated with a 4-week oral course of doxycycline, 100 mg twice daily. Doxycycline is preferred for its excellent oral absorption, low cost, and anti-inflammatory activity as a matrix metalloproteinase inhibitor. Amoxicillin 500 mg three times daily and cefuroxime axetil 500 mg twice daily are acceptable alternatives. Amoxicillin is used instead of doxycycline for pregnant and lactating women and for children younger than 8 years. If Lyme disease is diagnosed at the early stage of erythema migrans, only 2 weeks of treatment is recommended. More expensive intravenous regimens should be reserved for neurologic or cardiac Lyme disease or refractory Lyme arthritis. Antibiotic-refractory Lyme arthritis can be treated with an intravenous regimen or re-treated with an oral regimen of antibiotics, but these problem cases should generally be referred to an infectious disease specialist.

www.ketabpezeshki.com 66485457-66963820

CLINICAL PATHWAY: MANAGEMENT OF THE PATIENT
WITH ACUTE POLYARTICULAR JOINT PAIN

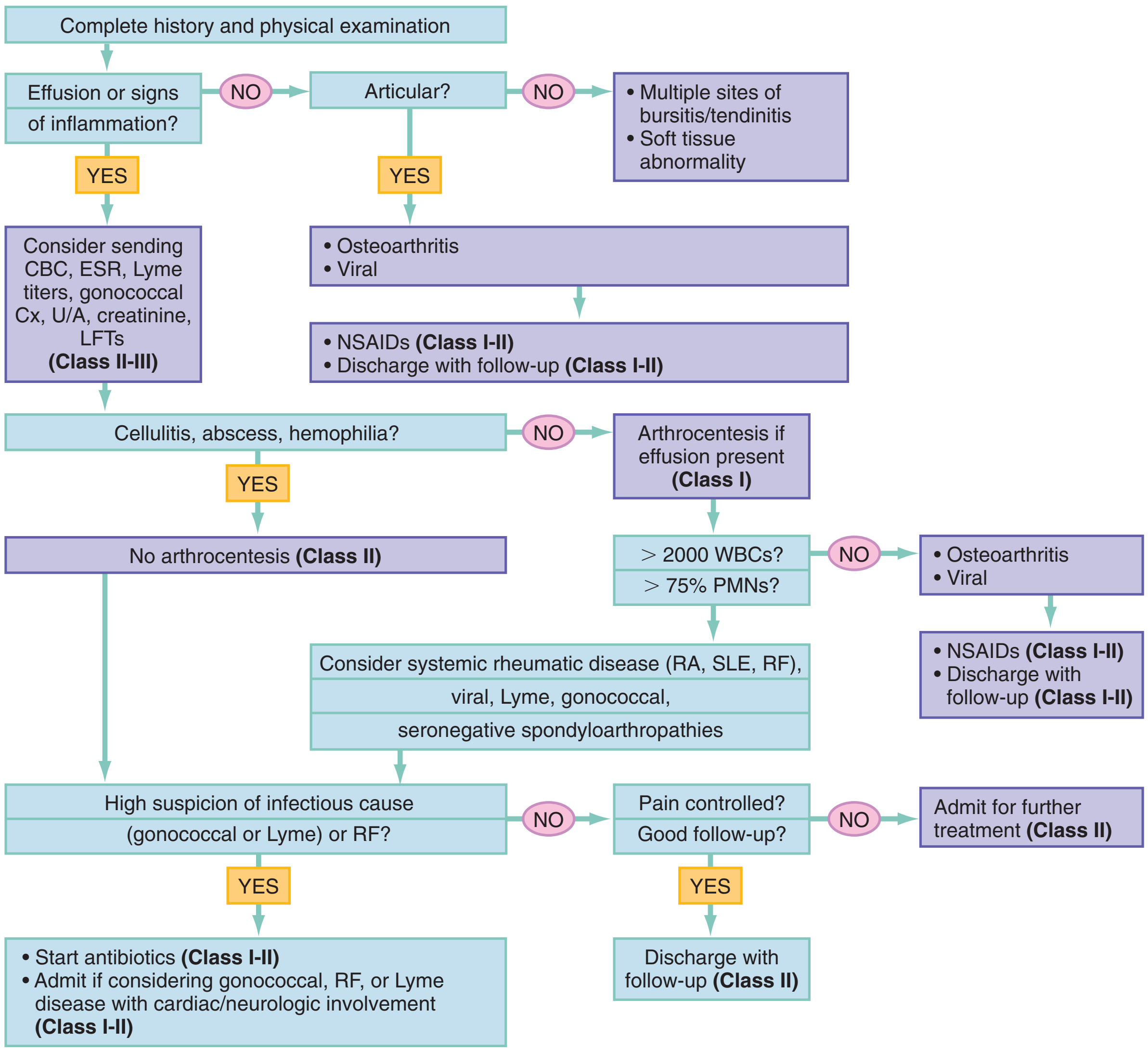


Figure 116-6. An initial approach to the patient with polyarticular joint symptoms. *CBC,* complete blood count; *Cx,* culture; *ESR,* erythrocyte sedimentation rate; *LFTs,* liver function tests; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *PMNs,* polymorphonuclear cells; *RA,* rheumatoid arthritis; *RF,* rheumatic fever; *SLE,* systemic lupus erythematosus; *U/A,* urinalysis; *WBC,* white blood cell. (Modified from EB Practice LLC. 2004.)

Acute Rheumatic Fever

Principles of Disease. Acute rheumatic fever (ARF) is a systemic disease triggered by a complex hyperimmune response in the weeks after group A streptococcal (GAS) pharyngitis. Host cellular and humoral response to GAS infection attacks joint, cardiac, and other tissue, in part through molecular mimicry mechanisms. The incidence of ARF has dramatically declined in recent decades. This success is only partly due to the widespread use of antibiotics; improvements in social hygiene and transformation of GAS strains are probably more important factors.

Clinical Features. The clinical diagnosis of ARF is based on the Jones criteria. The presence of two major criteria (such as erythema marginatum; Fig. 116-7), or one major criterion and two minor criteria, with laboratory evidence of prior GAS infection is required (Box 116-3).

GAS infection–related arthritis, typically migratory, occurs in 75% of patients and mostly affects the large joints. The arthritis lasts 2 to 3 days in each joint and 2 to 3 weeks overall; the axial skeleton is spared. Joints appear modestly inflamed, but the pain is disproportionately excruciating to the patient. ARF arthritis responds so dramatically to salicylate or steroid therapy that the diagnosis can become clouded. Lack of response should promote an alternative diagnosis. Naproxen was shown to be as effective as aspirin and better tolerated in a randomized trial in children.[80]

Poststreptococcal reactive arthritis (PSRA) is another sterile GAS infection–related arthritis recently proposed for patients not fulfilling the Jones criteria for ARF.[81] The arthritis of PSRA tends to be more additive than migratory, with a lower extremity predominance. It typically responds less robustly to salicylates and persists longer than ARF, although a cohort of adults with poststreptococcal reactive arthritis, observed for many years, showed no increased risk of valvular heart disease compared with controls.[82]

Diagnostic Strategies. The diagnosis of ARF is largely clinical. Laboratory workup for suspected ARF is not conducive to ED care. Throat cultures are negative in 75% of patients with systemic manifestations of ARF.[82] Antibody titers to streptolysin O and anti-DNase B may demonstrate antecedent GAS infection.

www.ketabpezeshki.com 66485457-66963820

Table 116-6 Characteristics of Viral Arthritides

VIRUS	ARTHRITIS PRESENTATION	SYMPTOM ETIOLOGY	DURATION OF SYMPTOMS	THERAPY
Hepatitis B	Mimics RA onset with symmetrical, migratory, or additive joint symptoms	Immune complex depositions in prodromal phase affect 10-25% of those with hepatitis B	Subsides with onset of jaundice	Supportive
Hepatitis C	Symmetrical RA-like mimic, or intermittent monarticular arthritis, often associated with salivary inflammation	Hepatitis C–induced mixed cryoglobulinemia	Variable, intermittent	Supportive; RA drugs are often helpful
Human immunodeficiency virus	Often monarticular arthritis, involving feet and ankles, potentially involving tendon, bursae, skin, and muscle inflammation as well	By virus itself or by reactive arthritis, drug-induced myopathy, immune reconstitution syndrome, or opportunistic septic arthritis	Variable	Driven by etiology
Parvovirus	The cause of fifth disease in childhood causes connective tissue syndrome in adults	Symmetrical stiffness in PIP joint, MP joint, without joint erosion	Self-limited, but may recur	Supportive
Rubella virus, rubella vaccine virus	Beyond classic maculopapular rash and lymphadenopathy, 30% of females and 6% of males with rubella show symptoms of arthritis	Virus grows well in synovial tissue, causing arthritis by direct infection	Symptoms appear within 2 weeks of vaccination or a week of rubella infection; self-limited	Supportive
Alphaviruses (Ross River, chikungunya, Mayaro)	Mosquito borne, often seen in epidemics after seasonal rains	Virus persists in synovial macrophages; symptoms arise from triggering of host response	Sometimes abrupt or insidious onset; symptoms can last 3-6 months; some patients have years of discomfort	Largely supportive; corticosteroids were once contraindicated but recently shown to be effective

MP, metacarpophalangeal; *PIP,* proximal interphalangeal; *RA,* rheumatoid arthritis.

Figure 116-7. Erythema marginatum in acute rheumatic fever. The pen mark shows the location of the rash approximately 60 minutes previously. (From Cohen J, Powderly WG: Infectious Diseases, 2nd ed. New York, Mosby/Elsevier, 2004.)

Box 116-3 Jones Criteria for Diagnosis of Acute Rheumatic Fever

Major Manifestations
- Polyarthritis
- Carditis
- Chorea
- Erythema marginatum
- Subcutaneous nodules

Minor Manifestations
- Clinical findings
  - Arthralgia
  - Fever
- Laboratory findings
  - Elevated acute-phase reactants: erythrocyte sedimentation rate, C-reactive protein
- Prolonged PR interval on electrocardiography

Plus supporting evidence of prior group A streptococcal infection (elevated or increasing streptococcal antibody titer, positive rapid streptococcal test or bacterial throat culture results, recent scarlet fever)

From Guidelines for the diagnosis of rheumatic fever. Jones criteria, 1992 update. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association. JAMA 268:2069, 1992.

Synovial fluid is inflammatory in nature and sterile, with a WBC count ranging between 10,000/mm^3 and 100,000/mm^3, a protein level of approximately 4 g/dL, no crystals, and a negative culture.

Management. Successful management of ARF requires three things: rapid eradication of the GAS infection; prophylaxis against recurrent infection; and acute treatment of arthritis, carditis, and chorea. The current recommended treatment of suspected acute GAS infection is benzathine penicillin 0.6 to 1.2 million units intramuscularly or 10 days of oral penicillin (or erythromycin if the patient is penicillin allergic). Long-term prophylactic treatment to prevent recurrences of ARF is provided with either oral or parenteral penicillin or erythromycin. The duration of prophylaxis depends on the age of the patient, the presence of cardiac involvement, the number of previous attacks, and other factors.

Other than antibiotics, ARF treatments were developed well before the era of randomized trials, so their evidentiary basis is suboptimal. High-dose aspirin (50-100 mg/kg/day in four daily doses) for 2 to 4 weeks improves the arthritis and fever but not the symptoms of carditis.[83] Smaller studies have suggested a benefit to oral or intramuscular hydrocortisone over aspirin if carditis is present (1-2 mg/kg/day, slowly tapered during 2-4 weeks).[83,84]

Polyarthritis: Chronic

Rheumatoid Arthritis

Principles of Disease. Although RA is usually considered a chronic and insidious disease, at least 20% of patients have an acute

www.ketabpezeshki.com 66485457-66963820

presentation.[85] RA develops in women two to three times more often than in men, with a peak incidence between the fourth and fifth decades of life. Prevalence is between 0.5 and 1% of Western populations and 5% of women by 70 years of age.[85] There appears to be a genetic predisposition related to the HLA-DR4 haplotype. Immune complexes are formed that stimulate PMN cells to release the enzymes that ultimately cause joint destruction. The synovial cells increase dramatically in number and produce even more inflammatory substances. A pannus of granulation tissue is formed that ultimately destroys the joint.

Clinical Features. Patients commonly see a physician after a prodromal period of fatigue, weakness, and musculoskeletal pain that may last weeks to months. Fever and weight loss may be present. The patient's joints begin to swell in a symmetrical and additive pattern, particularly the hands (MP and PIP joints), wrists, and elbows. The foot may be the initial site of involvement and is affected in more than 90% of patients with RA, particularly the great and little toe MTP joints. Classically, patients describe morning stiffness lasting more than an hour. DIP joints of the fingers are not involved, which helps distinguish RA from OA, reactive arthritis, and psoriatic arthritis.[85]

Acute presentations may have only warm, tender, swollen joints that may be difficult to distinguish from a viral arthropathy. Tenosynovitis can occur with acute RA. Acute pericarditis is not related to the duration of disease and also may be an early presentation.

Long-standing changes of RA include MP and PIP joint swelling, ulnar deviation, swan-neck and boutonnière deformities of the hands, and limitation of dorsiflexion of the wrist. The knee is often affected, in the short term with effusion and in the long term with muscle atrophy and Baker's cysts. Bursae in the retrocalcaneal region are common complications. Extra-articular complications are seen in half of patients with RA and include subcutaneous nodules (associated with more severe disease), vasculitis of the skin, pulmonary fibrosis, mononeuritis multiplex, and Sjögren's and Felty's syndromes. Long-standing RA is associated with atlantoaxial subluxation as well as with laryngeal deviation, requiring anticipation before endotracheal intubation.

Diagnostic Strategies. The emergency workup of the patient with suspected RA is directed at exclusion of other causes of arthritis, particularly septic arthritis. However, the definitive diagnosis of RA is complicated and involves confirmatory serology and a chronicity of 6 weeks or more.[86] ESR and CRP levels may be elevated but are nonspecific and often elevated in other rheumatologic diseases. Rheumatoid factor, an antibody against gamma globulin, is eventually present in approximately 75 to 85% of patients with RA, although it is present in only 50% in the first 6 months.[85]

Early radiographic features of RA are soft tissue swelling and juxta-articular osteoporosis leading to uniform joint space narrowing (Fig. 116-8). Subluxation with loss of joint alignment is a later finding.

Synovial fluid analysis is helpful to rule out infectious or crystalline processes. Arthrocentesis reveals inflammatory fluid with WBC counts between 4000 and 50,000/mm^3 and more PMN cells (75%) than are usually seen with crystal disease.

Management. Excessive movement increases inflammation, so the initial treatment is rest in combination with anti-inflammatory medication.[87] For early mild disease, many clinicians often still use the salicylates or other NSAIDs, which have gastrointestinal and renal toxicities related to their inhibition of cyclooxygenase. Oral prednisone, 5 to 15 mg daily, can effectively control mild inflammation as a bridge to more advanced therapy in early disease.

Because the early months are critical in preventing major joint damage, particularly in moderate to severe disease, the use of disease-modifying antirheumatic drugs (DMARDs) has become extensive and is now recommended by the American College of Rheumatology.[88] Clinical studies support the efficacy of a combination of methotrexate and a tumor necrosis factor blocker in reducing early disease activity. DMARDs are typically prescribed by the consulting rheumatologist, but emergency physicians should be familiar with their potentially life-threatening complications (Table 116-7).

Figure 116-8. Rheumatoid arthritis of the wrist, with osseous erosions shown here including triquetrum, pisiform, scaphoid, and radius. There also are erosions at the ulnar aspect of the distal radius and the ulnar styloid process secondary to involvement of the inferior radioulnar compartment. Diffuse cartilage loss also is evident in the radiocarpal compartment. (From Firestein GS: Kelley's Textbook of Rheumatology, 8th ed. Philadelphia, WB Saunders, 2008.)

Alternatives to DMARDs include combinations of sulfasalazine 1000 mg two or three times daily and hydroxychloroquine 200 to 400 mg/day. NSAIDs (such as ibuprofen 3200 mg daily) are also commonly prescribed. A systematic review concluded that short-term, low-dose steroids (15 mg/day) are significantly more effective than NSAIDs (and placebo) for alleviation of RA symptoms.[89]

Intra-articular glucocorticoid injections have been studied, but often with agents[90] (rimexolone 40 mg) or in regimens (multiple doses of intra-articular betamethasone in conjunction with methotrexate) that are not applicable to emergency medicine practice. A single dose of intra-articular triamcinolone 60 mg (with 2% lidocaine) was shown to be superior to intramuscular triamcinolone (also with lidocaine) in patients with known RA of the knee,[91] but the first baseline evaluation was 1 week after injection.

A systematic review showed no evidence to support the use of resting wrist and hand splints to improve function, symptoms, or quality of life, although patients did prefer the use of splints to nonuse. Extra-depth in-soled shoes were shown to improve walking and pain during several months.[92]

RA management has progressed in recent years, and early use of DMARDs is recommended in moderate to severe disease to prevent joint damage. These drugs are generally best prescribed by rheumatologists or the primary care physician who will be caring for the patient. Emergency physicians should recommend prompt rheumatology follow-up and bridge care by prescribing NSAIDs such as ibuprofen 3200 mg daily as a first-line therapy or, for patients who cannot tolerate NSAIDs, prednisone 15 mg/day.

www.ketabpezeshki.com 66485457-66963820

Table 116-7 Toxicity of Rheumatoid Arthritis Drugs

DRUG	CLASS	MAJOR TOXICITY	PEARL
Methotrexate	Conventional DMARD	Hepatic, bone marrow, lung	Pulse therapy less toxic than daily
Hydroxychloroquine	Antimalarial	Retinal	
Gold salts	Conventional DMARD	Bone marrow	Uncommonly used now
Anakinra	Anti–IL-1	Pneumonia, serious infections, leukopenia	Higher risk in patients with asthma
Abatacept	T-cell modulator		Avoid in COPD
Leflunomide	Pyrimidine antagonist	Diarrhea	Very long half-life
Etanercept	Anti-TNF	Sepsis, pneumonia, tuberculosis	
Infliximab	Anti-TNF	Sepsis, pneumonia, tuberculosis	
Adalimumab	Anti-TNF	Sepsis, pneumonia, tuberculosis	
Rituximab	Anti-CD20 of B-cell lymphocytes	Fatal infusion reactions	Multiple organ collapse typically with first infusion

COPD, chronic obstructive pulmonary disease; *DMARD,* disease-modifying antirheumatic drug; *IL-1,* interleukin-1; *TNF,* tumor necrosis factor.

Intra-articular steroid injections are an option for patients with just one or two joints involved. Splints, joint rest, and supportive care have a role as well.

Adult-Onset Still's Disease

Adult-onset Still's disease (AOSD) is a rare multisystem inflammatory disorder characterized by acute arthritis, characteristic rash, and quotidian or double-quotidian fevers (with the highest temperatures seen in the late afternoon or early evening). The rash is a salmon-colored macular evanescent rash that occurs only with the fever. The protean manifestations of AOSD include sore throat, myalgias, splenomegaly, hepatitis, and pericarditis. The differential diagnosis includes other acute arthritides (especially rheumatic fever) and other causes of "fever of unknown origin." Acute treatment options for AOSD include aspirin, NSAIDs, low-dose corticosteroids, and intravenous immune globulin.[93]

Relapsing Polychondritis

Relapsing polychondritis, a rare multisystem disorder of unknown etiology, is manifested with recurrent severe inflammation of joints, sclera, ears, nose, and vessels of the heart and kidneys. Most patients eventually have unilateral or bilateral external ear swelling and redness. Because of the rarity of this disorder, there are no controlled trials of therapies. In some series, flare-ups are self-limited and well managed with NSAIDs or colchicines (0.6 mg twice daily). However, tracheobronchial cartilage inflammation is possible and can be precipitous, causing respiratory distress and airway compromise. For this, pulse-dose steroids (1 g/day), racemic epinephrine, and sometimes stenting are recommended.[94]

Seronegative Spondyloarthropathies

The seronegative spondyloarthropathies share the characteristics of sacroiliac involvement, peripheral inflammatory arthropathy, absence of rheumatoid factor, pathologic changes around the enthesis (ligamentous and tendinous insertion into bone), and a genetic component related to the HLA-B27 marker. The most important of these chronic polyarthritic inflammatory diseases are ankylosing spondylitis, reactive arthritis, the arthropathy of inflammatory bowel disease (enteropathic arthritis), and psoriatic arthritis. Whereas some clinical overlap exists, each has its distinctive features.

Ankylosing Spondylitis

Clinical Features. Patients with ankylosing spondylitis generally have back discomfort with radiologic evidence of sacroiliitis. There is a male predominance. The classic presentation is chronic, insidious back discomfort of more than 3 months' duration, with morning stiffness that improves with exercise, in someone younger than 40 years. Uveitis is the most common extra-articular manifestation, but life-threatening aortic root disease can rarely occur. The peripheral joints are involved in up to 30% of patients with enthesopathic involvement, such as plantar fasciitis and Achilles tendinitis. On radiologic examination, there is a symmetrical squaring of the margins of the vertebral bodies and later the development of a "bamboo spine." MRI changes occur even earlier at the sacroiliac joint.

Management. The goals of therapy are to control pain, to decrease inflammation, and to begin physiotherapy and strengthening exercises. Recent literature review and consensus with use of Delphi methodology recommend a trial of at least two NSAIDs for symptomatic patients.[95] Anti–tumor necrosis factor, sulfasalazine, methotrexate, and monoclonal antibodies are also options for more severe disability and pain.

Reactive Arthritis (Formerly Reiter's Syndrome)

Clinical Features. Reactive arthritis occurs in genetically susceptible hosts after infection with *Chlamydia trachomatis* in the genitourinary tract or *Salmonella, Shigella, Yersinia,* or *Campylobacter* organisms in the gastrointestinal tract. A number of other microorganisms have also been postulated as causative agents.

Reactive arthritis is generally a disease of patients aged 20 to 40 years, in whom arthritis develops 2 to 6 weeks after an episode of urethritis or dysentery. Because cervicitis is often asymptomatic, the diagnosis is more of a problem in women. The syndrome is predominantly polyarticular and asymmetrical and often additive (Fig. 116-9). The weight-bearing joints of the lower extremities are commonly involved: knees, ankles, and feet, particularly the heels ("lover's heel"; Fig. 116-9B). Other physical signs appear early and may be gone when the musculoskeletal complaints persist. Patients may have conjunctivitis early in the disease, which may progress to uveitis. Up to 10% of patients have initially painless lesions of the oral mucosa and tongue that later develop into shallow painful ulcers.[96] Similar lesions are seen on the glans penis (balanitis circinata), particularly in uncircumcised men (20% of patients). The penile lesions in circumcised men are more psoriatic in appearance. Fingers and toes may swell and appear sausage-like, a phenomenon that also occurs in psoriatic arthritis. In 10% of patients, hyperkeratotic lesions of keratoderma blennorrhagica

www.ketabpezeshki.com 66485457-66963820

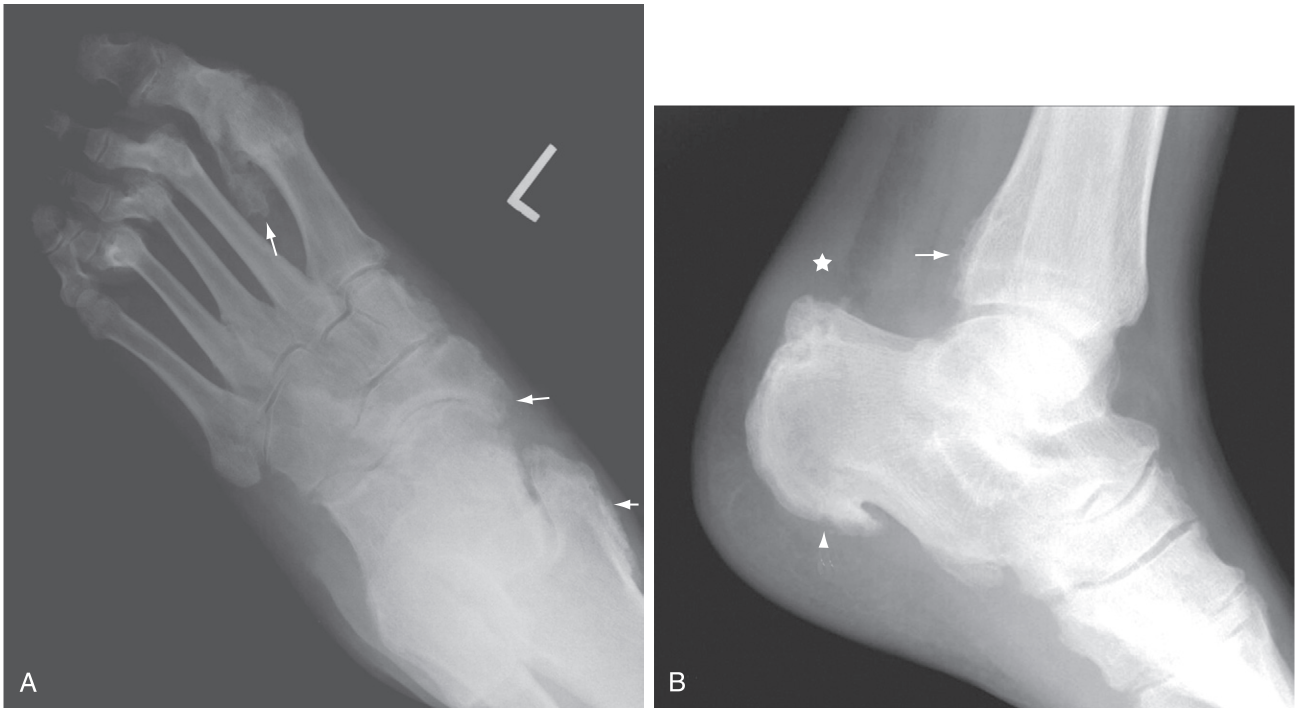


Figure 116-9. Radiographic findings of the foot in reactive arthritis. **A,** Anteroposterior view of the foot reveals erosions and bone proliferation of the first through fourth metatarsophalangeal joints with subluxation. Fluffy bone proliferation is noted along the medial malleolus, midfoot, and sesamoid bones of the first metatarsal head (*arrows*). **B,** Lateral view of the hindfoot shows ill-defined plantar calcaneal enthesophytes (*arrowhead*), periosteal new bone formation along the posterior aspect of the distal tibia (*arrow*), retrocalcaneal bursitis and thickening of the Achilles tendon (*star*), and erosions at the subjacent calcaneus. (From Firestein GS: Kelley's Textbook of Rheumatology, 8th ed. Philadelphia, WB Saunders, 2008.)

(waxy plaques) develop on the palms and soles and look like pustular psoriasis. Patients may have inflammation at the insertion of the Achilles tendon, and up to one third of patients have iliac crest, ischial tuberosity, and sacroiliac joint inflammation, with limitation of vertebral movement on range of motion.

Synovial fluid is inflammatory in nature with a predominance of PMN cells. *Chlamydia, Salmonella,* and *Yersinia* antigens have been found in the synovial membrane and even in the joint fluid, but cultures are sterile. Early x-ray films show an enthesitis where ligaments attach to bone that occurs at the sacroiliac joints, ischial tuberosities, greater trochanter, and Achilles insertion. Patients may have a single episode (the mean length of an episode is 4-7 months) or recurrent episodes of arthritis or a continuous spectrum of disease generally involving the ankles and calcaneus.

Management. Patients with reactive arthritis respond well to NSAIDs, particularly indomethacin, up to 200 mg/day. Antibiotics improve recovery time for patients with *Chlamydia*-triggered reactive arthritis; no benefit has been found for arthritis with a gastrointestinal cause.[96]

Enteropathic Arthritis. Roughly 10 to 22% of patients with inflammatory bowel disease have acute migratory, inflammatory polyarthritis of the peripheral joints, especially the knees. Associated inflammatory sacroiliitis and spondylitis are more common in men. The peripheral arthritis generally correlates with flare-ups of the bowel disease, but the spinal manifestations do not. NSAIDs are first-line therapy for axial and peripheral joint inflammation, although they may exacerbate inflammatory bowel disease. Sulfasalazine and intra-articular glucocorticoid injections are also options for peripheral arthritis.

Psoriatic Arthritis. Psoriatic arthropathy occurs in up to 20% of patients with psoriasis. Several forms exist: asymmetrical oligoarthropathy (with sausage digits), symmetrical polyarthropathy, spondylitis (asymmetrical as in reactive arthritis), DIP joint involvement, and arthritis mutilans (Fig. 116-10).[97] Whereas NSAIDs are considered a cornerstone of therapy, few trials have been performed on psoriatic arthritis; instead, support is derived from trials involving RA, OA, and ankylosing spondylitis. Therapies like sulfasalazine at 2 g/day have shown benefit in large trials, but the duration of therapy (36 weeks) necessitates involvement of a rheumatologist.

Fibromyalgia

Clinical Features. Patients with fibromyalgia commonly present to the ED with diffuse musculoskeletal pain. The encounter is typically difficult for both the patient and the physician because the disease is ill-defined, there may be suspicion of analgesic abuse, and psychiatric comorbidity is common. Current thinking about the pathophysiologic mechanism of this disorder hypothesizes that the patients process normal pain stimuli aberrantly.[98] Patients with fibromyalgia have a history of long-standing, idiopathic, widespread pain (bilateral, upper and lower body, and spine) and an examination showing excessive tenderness of 11 of 18 specific muscle-tendon sites. The differential diagnosis includes the other rheumatic diseases, hypothyroidism, and depression, and more extensive evaluation should be considered with symptoms of short duration. Fibromyalgia is not consistent with the presence of synovitis, fever, or neurologic deficits. Care should be taken before a diagnosis of fibromyalgia is made; many patients are seeking only a reassurance that no emergency condition is present.

Management. Treatment of fibromyalgia in the ED includes ruling out of associated disease, relief of acute pain with anti-inflammatory medications, provision of empathy and education, and referral of the patient to a provider experienced in chronic pain management. For patients in significant distress, the combination of tramadol 75 mg four times daily with acetaminophen

www.ketabpezeshki.com 66485457-66963820

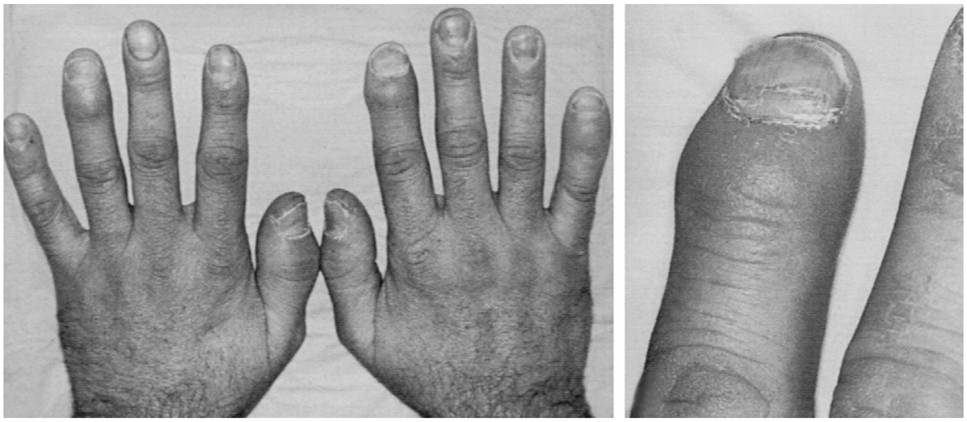


Figure 116-10. Psoriatic arthritis. Note the asymmetry of the distal interphalangeal joint involvement and the associated psoriatic nail disease. (From Firestein GS: Kelley's Textbook of Rheumatology, 8th ed. Philadelphia, WB Saunders, 2008.)

has been shown to be effective.[99] Selective serotonin reuptake inhibitors, low-dose tricyclic antidepressants, and pregabalin have also been shown to improve pain measures and sleep in patients with fibromyalgia.[100]

Polymyalgia Rheumatica

Polymyalgia rheumatica is manifested with musculoskeletal aching and morning stiffness of several weeks' duration, especially of the shoulder and pelvic girdle, almost always in persons older than 50 years.

Physical signs are modest. An elevated ESR can be used to screen for an inflammatory arthritis; a value above 100 mm/hr by Westergren method is thought to be clinically significant, and values below 50 mm/hr make polymyalgia rheumatica unlikely.[101] However, ESR also rises with age and is elevated in infection and paraneoplastic states as well as in pregnancy and hypercholesterolemia. Congestive heart failure and sickle cell disease lower ESR. CRP is an acute-phase protein that can increase within 4 to 6 hours, given sufficient stimulus, with a half-life of 18 hours on resolution of the acute phase. The basal CRP level also rises with age as well as with body mass index. Values above 10 mg/L are indicative of clinically significant inflammation, although scleroderma, polymyositis, and dermatomyositis are not accompanied by CRP elevation.

The disease course is usually self-limited, and most patients will respond to low-dose prednisone (20 mg/day or less). All patients should be referred for evaluation for progression to giant cell arteritis, a closely related disorder.

Scleroderma (Systemic Sclerosis)

Scleroderma has many manifestations discussed in other chapters; musculoskeletal manifestations of scleroderma include morning joint stiffness, tendon friction rubs, symmetrical arthralgias and arthritis, sclerodactyly, and Raynaud's phenomenon. The arthritis seems generally responsive to anti-inflammatory treatment, although cyclophosphamide is the only agent with benefit seen in randomized trials. Scleroderma renal crisis is a feared emergent complication, so screening for renal failure is important, and early use of angiotensin-converting enzyme inhibitors has improved long-term outcomes.

DISPOSITION

Whereas the majority of emergency presentations for arthritis can be followed up satisfactorily in the outpatient setting, the challenge for emergency physicians evaluating acute arthritis is to determine which presentations are rapidly progressive and potentially disabling. Most important, the possibility of septic arthritis must be considered and excluded.

Patients diagnosed with nongonococcal septic arthritis, on the basis of a positive result of Gram's stain or culture or a strong clinical suspicion in the face of a negative Gram's stain result, are admitted for parenteral antibiotics and evaluation for possible arthroscopy or arthrotomy. Patients in whom a disseminated gonococcal infection is suspected are admitted for parenteral antibiotics and orthopedic consultation, except in cases in which the patient is well appearing, the symptoms are mild, and the patient is able to comply with the daily follow-up plans. Patients with noninfectious causes of arthritis can be discharged, assuming their pain is controlled and appropriate follow-up can be arranged.

KEY CONCEPTS

- The most likely cause of emergency arthritis presentations can usually be identified by considering the number of joints involved (monarticular vs. polyarticular), the distribution of joint involvement (large vs. small joints and symmetrical vs. asymmetrical joint involvement), and the time course (a duration of 6 weeks helps differentiate acute arthritides from chronic).
- Consider the possibility of septic arthritis in all patients who present with acute monarticular arthritis.
- There is no combination of examination findings or blood tests that places septic arthritis below the threshold for performance of arthrocentesis in patients presenting with new, hot, swollen joint pain. Synovial fluid analysis is necessary to establish or to rule out the diagnosis of septic arthritis, and delays in treatment worsen outcomes.
- The presence of crystals in synovial fluid or a negative Gram's stain result does not completely eliminate the possibility of septic arthritis. Bacterial arthritis can coexist with gout or pseudogout, and the result of Gram's stain is positive in only 50 to 80% of cases of septic arthritis.
- Many other common arthritides, such as gout, rheumatoid arthritis, and osteoarthritis, can be managed with NSAIDs as a first-line therapy. In those who cannot tolerate or have not improved with NSAIDs, systemic or intra-articular steroid therapy has varying levels of support. Appropriate follow-up is crucial for prophylaxis against future flare-ups.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. The Centers for Disease Control and Prevention: Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation—United States, 2007-2009. *MMWR Morb Mortal Wkly Rep* 2010; 59:1261-1265.
2. Nuki G, Simkin PA: A concise history of gout and hyperuricemia and their treatment. *Arthritis Res Ther* 2006; 8(Suppl 1):1.
3. Low G: Thomas Sydenham: The English Hippocrates. *Aust N Z J Surg* 1999; 69:258.
4. Panush RS, Wallace DJ, Dorff RE, Engleman EP: Retraction of the suggestion to use the term "Reiter's syndrome" sixty-five years later: The legacy of Reiter, a war criminal, should not be eponymic honor but rather condemnation. *Arthritis Rheum* 2007; 56:693-694.
5. Louie JS: *History, the arts, and rheumatic diseases*. In: West SE, ed: *Rheumatology Secrets*, 2nd ed. Philadelphia: Hanley & Belfus; 2002:654.
6. Nriagu JO: Saturnine gout among Roman aristocrats: Did lead poisoning contribute to the fall of the Empire? *N Engl J Med* 1983; 308:660.
7. Sack KE: *Physical examination of the musculoskeletal system*. In: Imboden J, Hellman D, Stone J, eds: *Current Rheumatology Diagnosis and Treatment*. New York: McGraw-Hill; 2007:1.
8. Shah SS: Abnormal gait in a child with fever: Diagnosing septic arthritis of the hip. *Pediatr Emerg Care* 2005; 21:336-341.
9. Imboden J: *Laboratory diagnosis*. In: Imboden J, Hellman D, Stone J, eds: *Current Rheumatology Diagnosis and Treatment*. New York: McGraw-Hill; 2007:22.
10. Tsung JW, Blaivas M: Emergency department diagnosis of pediatric hip effusion and guided arthrocentesis using point-of-care ultrasound. *J Emerg Med* 2008; 35:393-399.
11. Scott WW: *Evaluation of the patient: Imaging*. In: Klippel JH, ed: *Primer on the Rheumatic Diseases*, 13th ed. Atlanta: Arthritis Foundation; 2008:28.
12. Butalia S, Palda VA, Sargeant RJ, Detsky AS, Mourad O: Does this patient with diabetes have osteomyelitis of the lower extremity? *JAMA* 2008; 299:806-813.
13. Nawaz A, Torigian DA: Diagnostic performance of FDG-PET, MRI and plain film radiography (PFR) for the diagnosis of osteomyelitis in the diabetic foot. *Mol Imaging Biol* 2010; 12:335-342.
14. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines: Guidelines for the initial evaluation of the adult patient with acute musculoskeletal symptoms. *Arthritis Rheum* 1996; 39:1-8.
15. Thumboo J, O'Duffy JD: A prospective study of the safety of joint and soft tissue aspiration and injections in patients taking warfarin sodium. *Arthritis Rheum* 1998; 41:736-739.
16. Shmerling RH, Delbanco TL, Tosteson AN, Trentham DE: Synovial fluid tests. What should be ordered? *JAMA* 1990; 264;1009-1014.
17. Margaretten ME, Kohlwes J, Moore D, Bent S: Does this adult patient have septic arthritis? *JAMA* 2007; 297:1478-1488.
18. Font-Vizcarra L, García S, Martínez-Pastor JC, Sierra JM, Soriano A: Blood culture flasks for culturing synovial fluid in prosthetic joint infections. *Clin Orthop Relat Res* 2010; 468:2238-2243.
19. Lumbreras B, et al: Analysis for crystals in synovial fluid: Training of the analysts results in high consistency. *Ann Rheum Dis* 2005; 64:612-615.
20. Yu KH, et al: Concomitant septic and gouty arthritis—an analysis of 30 cases. *Rheumatology (Oxford)* 2003; 42:1062-1066.
21. Jeng GW: Measurement of synovial tumor necrosis factor-alpha in diagnosing emergency patients with bacterial arthritis. *Am J Emerg Med* 1997; 15:626-629.
22. Dubost JJ, et al: No changes in the distribution of organisms responsible for septic arthritis over a 20 year period. *Ann Rheum Dis* 2002; 61:267-269.
23. Ho G: *Infectious disorders: Septic arthritis*. In: Klippel JH, ed. *Primer on the Rheumatic Diseases*, 13th ed. Atlanta: Arthritis Foundation; 2008:271.
24. Frazee BW, Fee C, Lambert L: How common is MRSA in adult septic arthritis? *Ann Emerg Med* 2009; 54:695-700.
25. Gandhi M, Jacobs R: *Septic arthritis and disseminated gonococcal infection*. In: Imboden J, Hellman D, Stone J, eds. *Current Rheumatology Diagnosis and Treatment*. New York: McGraw-Hill; 2007:359.
26. Marculescu CE, et al: Unusual aerobic and anaerobic bacteria associated with prosthetic joint infections. *Clin Orthop* 2006; 451:55-63.
27. Salgado CD, et al: Higher risk of failure of methicillin-resistant *Staphylococcus aureus* prosthetic joint infections. *Clin Orthop* 2007; 461:48-53.
28. Ghanem E: Cell count and differential of aspirated fluid in the diagnosis of infection at the site of total knee arthroplasty. *J Bone Joint Surg Am* 2008; 90:1637-1643.
29. O'Malley A, Svinos H: Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. BET 3: Is the white cell count of the joint aspirate sufficiently sensitive/specific to rule in/out septic arthritis? *Emerg Med J* 2009; 26:435-437.
30. Wang CH, Yen ZS: Best Evidence Topic report. BET 3. Is there a role for serum procalcitonin in the differentiation between septic and non-septic arthritis. *Emerg Med J* 2010; 27:144-145.
31. Weston VC, Jones AC: Clinical features and outcome of septic arthritis in a single UK Health District 1982-1991. *Ann Rheum Dis* 1999; 58:214.
32. Kortekangas P, Aro HT, Lehtonen OP: Synovial fluid culture and blood culture in acute arthritis. A multi-case report of 90 patients. *Scand J Rheumatol* 1995; 24:44-47.
33. Carpenter CR, Schuur JD, Everett WW, Pines JM: Evidence-based diagnostics: Adult septic arthritis. *Acad Emerg Med* 2011; 18:781-796.
34. Chander S, Coakley G: What's new in the management of bacterial septic arthritis? *Curr Infect Dis Rep* 2011; 13:478-484.
35. Stutz G, Kuster MS, Kleinstück F, Gächter A: Arthroscopic management of septic arthritis: Stages of infection and results. *Knee Surg Sports Traumatol Arthrosc* 2000; 8:270-274.
36. Rice PA: Gonococcal arthritis (disseminated gonococcal infection). *Infect Dis Clin North Am* 2005; 19:853-861.
37. Davis BT, Pasternack MS: Case records of the Massachusetts General Hospital: Case 19-2007—a 19-year-old college student with fever and joint pain. *N Engl J Med* 2007; 356:2631-2637.
38. Centers for Disease Control and Prevention: *Sexually transmitted diseases treatment guidelines 2010*. Available at www.cdc.gov/std/treatment/2010/gonococcal-infections.htm. Accessed April 1, 2013.
39. Singh JA, Reddy SG, Kundukulam J: Risk factors for gout and prevention: A systematic review of the literature. *Curr Opin Rheumatol* 2011; 23:192-202.
40. Choi HK, Curhan G: Soft drinks, fructose consumption, and the risk of gout in men: Prospective cohort study. *BMJ* 2008; 336:309-312.
41. Schlesinger N, Norquist JM, Watson DJ: Serum urate during acute gout. *J Rheumatol* 2009; 36:1287-1289.
42. Eggebeen AT: Gout: An update. *Am Fam Physician* 2007; 76:801-808.
43. Edwards NL: *Gout: Clinical features*. In: Klippel JH, ed. *Primer on the Rheumatic Diseases*, 13th ed. Atlanta: Arthritis Foundation; 2008:241.
44. Glazebrook KN, Guimares LS: Identification of intraarticular and periarticular uric acid crystals with dual-energy CT: Initial evaluation. *Radiology* 2011; 261:516-524.
45. Keith MP, Gilliland WR: Updates in the management of gout. *Am J Med* 2007; 120:221-224.
46. Sutaria S, Katbamna R, Underwood M: Effectiveness of interventions for the treatment of acute and prevention of recurrent gout—a systematic review. *Rheumatology* 2006; 45:1422-1431.
47. Schumacher HR Jr, et al: Randomised double blind trial of etoricoxib and indomethacin in treatment of acute gouty arthritis. *BMJ* 2002; 324:1488-1492.
48. Kesselheim AS, Solomon DH: Incentives for drug development—the curious case of colchicine. *N Engl J Med* 2010; 362:2045-2047.
49. Zhang W, et al: EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2006; 65:1312-1324.
50. Terkeltaub RA, et al: High versus low dosing of oral colchicine for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum* 2010; 62:1060-1068.
51. Sussman JS, et al: Accidental intravenous colchicine poisoning. *Ther Drug Monit* 2004; 26:688.
52. Fernández C, Noguera R, González JA, Pascual E: Treatment of acute attacks of gout with a small dose of intraarticular triamcinolone acetonide. *J Rheumatol* 1999; 26:2285-2286.
53. Wise CM: Crystal-associated arthritis in the elderly. *Rheum Dis Clin North Am* 2007; 33:33-55.
54. Janssens HJ, Janssen M, van de Lisdonk EH, van Riel PL, van Weel C: Use of oral prednisolone or naproxen for the treatment of gout arthritis: A double-blind, randomised equivalence trial. *Lancet* 2008; 371:1854-1860.
55. Janssens HJ, Lucassen PL, van de Laar FA, Janssen M, van de Lisdonk EH: Systemic corticosteroids for acute gout. *Cochrane Database Syst Rev* 2008; 2:CD005521.
56. Schlesinger N: Overview of the management of acute gout and the role of adrenocorticotropic hormone. *Drugs* 2008; 68:407-415.

www.ketabpezeshki.com 66485457-66963820

57. Axelrod D, Preston S: Comparison of parenteral adrenocorticotropic hormone with oral indomethacin in the treatment of acute gout. *Arthritis Rheum* 1988; 31:803-805.
58. Zhang W: EULAR recommendations for calcium pyrophosphate deposition. Part II: Management. *Ann Rheum Dis* 2011; 70:571-575.
59. Werlen D, Gabay C, Vischer TL: Corticosteroid therapy for the treatment of acute attacks of crystal-induced arthritis: An effective alternative to nonsteroidal antiinflammatory drugs. *Rev Rhum Engl Ed* 1996; 63:248-254.
60. Alvarellos A: Colchicine prophylaxis in pseudogout. *J Rheumatol* 1986; 13:804-805.
61. McCarthy G: *Calcium pyrophosphate dihydrate, hydroxyapatite, and miscellaneous crystals*. In: Klippel JH, ed. *Primer on the Rheumatic Diseases*, 13th ed. Atlanta: Arthritis Foundation; 2008:263.
62. Genta MS, Gabay C: Images in clinical medicine: Milwaukee shoulder. *N Engl J Med* 2006; 354:e2.
63. Doumas C, et al: Acute calcific periarthritis of the hand and wrist: A series and review of the literature. *Emerg Radiol* 2007; 14:199-203.
64. Maffulli N: Acute haemarthrosis of the knee in athletes. A prospective study of 106 cases. *J Bone Joint Surg Br* 1993; 75:945-949.
65. Casteleyn PP, Handelberg F, Opdecam P: Traumatic haemarthrosis of the knee. *J Bone Joint Surg Br* 1988; 70:404-406.
66. Zhang W, et al: OARSI recommendations for the management of hip and knee osteoarthritis: Part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage* 2010; 18:476-499.
67. Zhang W, et al: EULAR evidence based recommendations for the management of osteoarthritis: Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007; 66:377-388.
68. Towheed TE, et al: Acetaminophen for osteoarthritis. *Cochrane Database Syst Rev* 2006; 1:CD004257.
69. American College of Rheumatology: Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. *Arthritis Rheum* 2000; 43:1905-1915.
70. Silverstein FE, et al: Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: The CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA* 2000; 284:1247-1255.
71. Avouac J, Gossec L, Dougados M: Efficacy and safety of opioids for osteoarthritis: A meta-analysis of randomized controlled trials. *Osteoarthritis Cartilage* 2007; 15:957-965.
72. Wandel S, et al: Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: Network meta-analysis. *BMJ* 2010; 16(341):c4675.
73. Bellamy N, et al: Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* 2006; 2:CD005321.
74. Bannuru RR, et al: Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: A systematic review and meta-analysis. *Arthritis Rheum* 2009; 61:1704-1711.
75. Calabrese LH, Naides SJ: Viral arthritis. *Infect Dis Clin North Am* 2005; 19:963-980.
76. Young NS, Brown KE: Parvovirus B19. *N Engl J Med* 2004; 350:586-597.
77. Hu L: Lyme arthritis. *Infect Dis Clin North Am* 2005; 19:947-961.
78. Wormser GP, et al: The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: Clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; 43:1089-1134.
79. Johnson L, Stricker RB: The Infectious Diseases Society of America Lyme guidelines: A cautionary tale about the development of clinical practice guidelines. *Philos Ethics Humanit Med* 2010; 5:9.
80. Hashkes PJ, et al: Naproxen as an alternative to aspirin for the treatment of arthritis of rheumatic fever: A randomized trial. *J Pediatr* 2003; 143:399-401.
81. van Bemmel JM, et al: No increased risk of valvular heart disease in adult poststreptococcal reactive arthritis. *Arthritis Rheum* 2009; 60:987-993.
82. Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 1992 update. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association. *JAMA* 1992; 268:2069-2073.
83. Shulman S: *Infectious disorders: Rheumatic fever*. In: Klippel JH, ed. *Primer on the Rheumatic Diseases*, 13th ed. Atlanta: Arthritis Foundation; 2008:297.
84. Cilliers AM, Manyemba J, Saloojee H: Anti-inflammatory treatment for carditis in acute rheumatic fever. *Cochrane Database Syst Rev* 2009; 2:CD003176.
85. Tehlirian CV: *Rheumatoid arthritis: Clinical and laboratory manifestations*. In: Klippel JH, ed. *Primer on the Rheumatic Diseases*, 13th ed. Atlanta: Arthritis Foundation; 2008:114.
86. Aletaha D, et al: 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; 62:2569-2581.
87. Oliver AM: *Rheumatoid arthritis: Treatment*. In: Klippel JH, ed. *Primer on the Rheumatic Diseases*, 13th ed. Atlanta: Arthritis Foundation; 2008:133.
88. Saag KG, et al: American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum* 2008; 59:762-784.
89. Gotzsche PC, Johansen HK: Short-term low-dose corticosteroids vs placebo and nonsteroidal antiinflammatory drugs in rheumatoid arthritis. *Cochrane Database Syst Rev* 2004; 3:CD000189.
90. van Vliet-Daskalopoulou E, Jentjens T, Scheffer RT: Intra-articular rimexolone in the rheumatoid knee: A placebo-controlled, double-blind, multicentre trial of three doses. *Br J Rheumatol* 1987; 26:450-453.
91. Konai MS, Vilar Furtado RN, Dos Santos MF, Natour J: Monoarticular corticosteroid injection versus systemic administration in the treatment of rheumatoid arthritis patients: A randomized double-blind controlled study. *Clin Exp Rheumatol* 2009; 27:214-221.
92. Egan M, et al: Splints/orthoses in the treatment of rheumatoid arthritis. *Cochrane Database Syst Rev* 2003; 1:CD004018.
93. Efthimiou P, Paik PK, Bielory L: Diagnosis and management of adult onset Still's disease. *Ann Rheum Dis* 2006; 65:564-572.
94. Kent PD, Michet CJ Jr, Luthra HS: Relapsing polychondritis. *Curr Opin Rheumatol* 2004; 16:56-61.
95. Braun J, Sieper J: Ankylosing spondylitis. *Lancet* 2007; 369:1379-1390.
96. Kim PS, Klausmeier TL, Orr DP: Reactive arthritis: A review. *J Adolesc Health* 2009; 44:309-315.
97. Turkiewicz AM, Moreland LW: Psoriatic arthritis: Current concepts on pathogenesis-oriented therapeutic options. *Arthritis Rheum* 2007; 56:1051-1066.
98. Dadabhoy D: *Musculoskeletal signs and symptoms: The fibromyalgia syndrome*. In: Klippel JH, ed. *Primer on the Rheumatic Diseases*, 13th ed. Atlanta: Arthritis Foundation; 2008:87.
99. Bennett RM, Kamin M, Karim R, Rosenthal N: Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: A double-blind, randomized, placebo-controlled study. *Am J Med* 2003; 114:537-545.
100. Roskell NS, Beard SM, Zhao Y, Le TK: A meta-analysis of pain response in the treatment of fibromyalgia. *Pain Pract* 2011; 11:516-527.
101. Unwin B, Williams CM, Gilliland W: Polymyalgia rheumatica and giant cell arteritis. *Am Fam Physician* 2006; 74:1547.

www.ketabpezeshki.com 66485457-66963820

Chapter 117

Tendinopathy and Bursitis

Michael J. Schmidt and Stephen L. Adams

TENDINOPATHY

Perspective

Emergency physicians may see a wide variety of patients with tendinopathies due to overuse and injury given the increased participation of people in athletics and fitness.[1] Approximately half of all sports participants will be injured at some time, and of these injuries, up to half will involve a tendinopathy. Tendinopathies have been implicated in approximately 40% of tennis injuries, and between 37 and 79% of participants in running will suffer an injury, with most of these injuries related to overuse.[1,2] In the workplace, the incidence of work-related musculoskeletal disorders is higher in occupations that involve repetitive motion, localized contact stress, awkward positions, vibrations, and forceful exertion. Ergonomic and medical intervention programs may reduce the incidence of work-related injuries.[3]

Complicating the acute pain and functional limitations, tendinopathies often become chronic and can be disabling. Patients may have symptoms for extended periods despite appropriate therapy. The management of tendinopathy focuses on identification of the cause of discomfort; elimination of sources of primary tendinopathy; institution of treatment modalities, such as analgesic medication, protection, relative rest, application of ice, compression, and elevation as necessary; modification of behavior to minimize or to eliminate sources of continuing irritation; and, importantly, referral for appropriate follow-up care and early rehabilitation.[4,5]

Principles of Disease

Tendons are collagenous structures that connect muscle to bone. They transmit the forces originating in the muscle to the bone, which enables joint motion. The diagnosis of *tendinitis,* a commonly used term implying an "inflammation of the tendon," has long been attached to many overuse injuries. Many practitioners now advocate use of the term *tendinosis* as a more accurate reflection of the pathologic process, given that histologic findings consistent with inflammation are not clearly evident in pathoanatomic studies. Although it has been noted that reliable, well-conducted epidemiologic studies have not been performed for most tendinopathies, the histopathologic substratum, in many cases, is degenerative.[1] The term *tendinopathy* is used throughout this chapter to refer to the impaired tendon, as it encompasses the variety of pathologic processes.

Mechanical overload and repetitive microtrauma to the musculotendinous unit are thought to be the major precipitating causes of most tendinopathies. This is a result of extrinsic and intrinsic factors that modify the pathophysiologic state. Intrinsic factors, such as age, gender, malalignment, joint laxity, muscle weakness, and imbalance, can result in excessively high or frequent mechanical loads during normal activity. Extrinsic factors, such as ergonomics, abnormal movements, excessive duration of activity, and increased frequency or intensity of activity, can also contribute to the development of a tendinopathy. Many injuries have a multifactorial origin.[6] An increased incidence of tendinopathy and tendon rupture, particularly of the Achilles tendon, is reported in patients taking fluoroquinolone antibiotics, particularly in individuals receiving steroid treatment or those with renal disease.[7]

Under optimal conditions, such as appropriate athletic training, the musculotendinous units are able to adapt to tension overload because of the ability of bone to increase its load-bearing capacity and because of an increase in size and strength by hypertrophy of existing muscle fibers. An enhancement of tendon and ligament strength occurs by an increase in collagen content, collagen cross-linking, and mucopolysaccharide content. Unfortunately, many athletes may not allot sufficient time for this adaptive process to occur. For instance, a runner may increase mileage, intensity, or both with excessive alacrity, not allowing time for the cellular changes that are required to adapt to the increased stresses. Poor technique and improper equipment may also contribute to the development of an overuse syndrome.

The pathophysiologic mechanism of tendon healing has mainly been described in the literature in the context of acute injury (e.g., rupture), and correlation to the healing process in tendinopathies remains unclear. Acutely injured tendons go through several stages in the healing process, and it may take 6 to 12 weeks for structural organization and collagen cross-linking to return the tendon to its preinjured strength.[8] As the healing process ensues, unrestricted activity is generally avoided. However, atrophy associated with immobilization should also be avoided because the strength in healing tendons and ligaments increases faster when controlled forces are applied. Consequently, flexibility forces, eccentric strength training, and a measured return to resistive exercises have been suggested as long as pain is not produced. Most patients with overuse tendinopathies fully recover within 3 to 6 months.[9] In summary, a prescription for good follow-up with proper rehabilitation is important in caring for the patient with tendinopathy. Some areas with common presentations of tendinopathies are diagrammed in Figure 117-1.

Clinical Features

General Tendinopathy

The history of the patient presenting with a tendinopathy can be variable, although certain clinical aspects are characteristic. A

www.ketabpezeshki.com 66485457-66963820

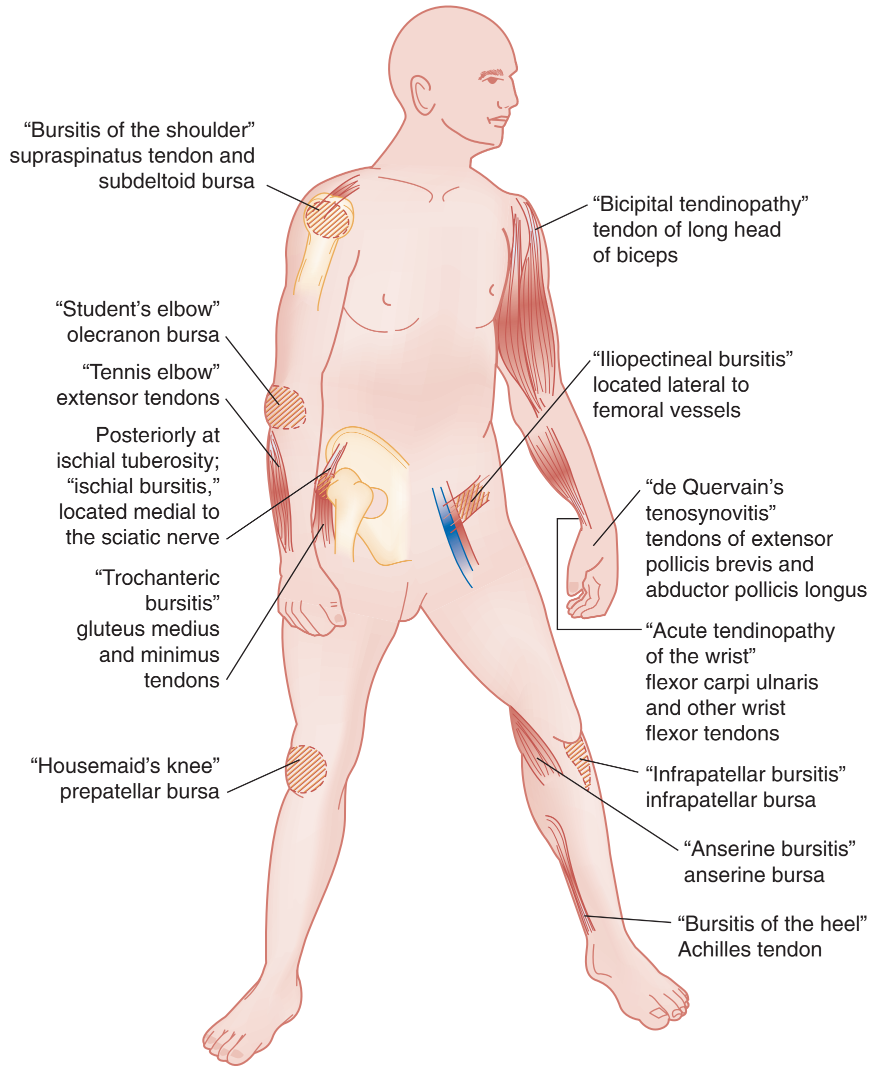


Figure 117-1. Location of common sites for tendinopathy or bursitis. (Modified from Branch WT: Office Practice of Medicine, 2nd ed. Philadelphia, WB Saunders, 1987.)

recent history of repetitive stress may be obtained by inquiring about changes in sports or other recreational activities, work activities, or changes in the workplace. Many patients initially report no such changes, but when they are prompted to consider activities during several weeks or months (including sports equipment used, workplace ergonomic features, protective boots, or other features), a potential inciting change or activity may be elicited. On occasion, no cause is identified for an inciting mechanical overload. A history of fluoroquinolone therapy, infectious disease, or other systemic illness should also be obtained as initial presentations of rheumatologic disorders or infections, such as those from *Mycobacterium,* have been described.[7,10-12]

Pain is the most common symptom of the patient who presents with tendinopathy. Increasing discomfort, nonradiating, at the site of the affected tendon is a general symptom.[4] The discomfort is frequently described as more severe subsequent to periods of rest. Unlike the discomfort of morning stiffness associated with arthritis, the pain of tendinopathy may resolve after initial movement, only to be manifested as a throbbing pain after completion of exercise. The patient may have had prior similar episodes. Continued episodes may be accompanied by an increased severity in pain. Consequently, it may be helpful to know whether a diagnosis was made (and how) and which treatment rendered (if any) was successful.

In the evaluation of the patient with a tendinopathy, a thorough, directed musculoskeletal examination yields important information. Inspection searching for signs of edema, effusion, erythema, atrophy, deformity, symmetry, or trauma can be helpful. Palpation of the tendon, noting warmth or evidence of crepitation on movement, is important. Evidence of tenderness over the tendon, especially localized, reproducing the patient's pain should be elicited.[4] Underlying bone tenderness (and consideration of other differential diagnoses, including avulsion fracture and osteomyelitis) should be assessed as well. Motor function, particularly passive and active range of motion (and symptoms elicited during the examination), strength (and evidence of weakness or pain), and joint involvement and stability should be noted.

In narrowing the diagnosis, it is important to determine whether the source of pain is articular (within the joint capsule) or periarticular (around the joint capsule). In general, arthritis produces generalized joint pain, warmth, swelling, and tenderness. The discomfort of arthritis increases with both passive and active motion of the joint. In contrast, the pain of a tendinopathy tends to be more localized.[4] Tenderness and swelling do not occur uniformly across the joint, and pain may be produced only with certain movements, most commonly with resisted active contraction or passive stretching of the affected muscles or tendons.

www.ketabpezeshki.com 66485457-66963820

Specific Tendinopathies

Shoulder. Tendinopathies of the shoulder joint include impingement syndrome, which includes subacromial bursitis or rotator cuff tendinopathy, bicipital tendinopathy, calcific tendinopathy, and adhesive capsulitis.

Impingement Syndrome and Rotator Cuff Tendinopathies. The shoulder joint is predisposed to soft tissue injury because of its extensive range of motion and unique anatomic structure. Although it is inherently unstable, the muscles of the rotator cuff (supraspinatus, infraspinatus, teres minor, and subscapularis) and the glenohumeral ligaments serve to stabilize the joint. The muscles of the rotator cuff originate from the scapula (hence their nomenclature), and their tendinous insertion is found on the fibrous capsule of the glenohumeral joint after traversing through the subacromial space. The presence of the subacromial bursa, as for all bursae, serves to ensure fluidity of movement, but it may become inflamed as a part of an impingement syndrome.[13] Impingement of the tendons occurs because of their unique position interposed between the humeral head and the acromion, which may predispose to a chronic tendinopathy. The functional arc of the elevated shoulder is forward and in the anterior plane. As a result of this position, the greater tuberosity of the humerus may compress (impinge) the tendons of the rotator cuff (usually the supraspinatus) against the undersurface of the anterior third of the acromion. Because of the insertion of the tendon of the long head of the biceps, it too may be involved as part of the impingement syndrome.[13] Development of this tendinopathy may be a result of overuse of the extremity that leads to microtrauma of the tendinous fibers, or it may be due to individual anatomic differences (congenital or from the process of aging, such as osteophytic changes) that predispose to tendinopathy, or both. Other entities that may coexist and complicate an impingement syndrome include subacromial bursitis, bicipital tendinopathy, and calcific tendinopathy.[14]

More than 30 years ago, Neer noted that 95% of rotator cuff tears are associated with impingement (excluding tears due to a one-time traumatic event). He described three progressive stages of the impingement syndrome as a result of overuse.[15] The first stage is frequently seen in athletes younger than 25 years who participate in sports that require repetitive overhead motions of the shoulder (e.g., swimming and baseball).[15,16] It is characterized by edema and hemorrhage within and around the tendon. The pain is usually described as a dull ache over the anterolateral shoulder, extending from the shoulder to the middle upper arm, often occurring after an activity involving flexion and abduction of the arm. Point tenderness may be elicited over the greater tuberosity. No weakness or loss of motion is generally present. This condition is generally believed to be reversible with appropriate treatment. In the second stage, as mechanical trauma continues, fibrosis and thickening of the tendon and subacromial bursa can occur. This generally affects patients between 25 and 40 years of age. The pain becomes constant and may worsen at night. Active motion may be limited by pain, and any activity involving overhead movement exacerbates the symptoms. Passive range of motion should be preserved, and on physical examination, pain is more diffuse and intense. The third stage has symptoms similar to those of the second stage but may involve a prolonged history of shoulder problems. The range of motion of the shoulder is usually decreased because of either disuse or a partial rotator cuff tear. On pathologic examination, tendon degeneration and attrition may be present. Partial-thickness tears may occur or extend with minor trauma or stress. Complete tears of the rotator cuff, biceps tendon rupture, and osteophytic bone changes are sometimes seen.

Physical examination in the evaluation of a rotator cuff tendinopathy includes maneuvers that can exacerbate the symptoms of impingement.[17] Because the supraspinatus tendon is most often involved, a physical examination sign (sometimes referred to as *Jobe's sign,* after Frank Jobe, team physician of the Los Angeles Dodgers, or the *empty can test,* describing the position of emptying aluminum cans) is helpful in assessing the supraspinatus tendon with resistance testing. With the arms abducted at 90 degrees in the scapular plane (30 degrees anterior to the coronal plane), the arms are internally rotated with the thumbs pointed downward. The examiner places a downward force on the arms, and the patient is instructed to resist the examiner and to keep the arms parallel to the floor. Weakness or pain is considered a positive finding. If the patient is unable to resist the force of the examiner, supraspinatus weakness should be suspected.

Another sign of rotator cuff tendinopathy is elicited by the *Neer test,* which suggests mechanical impingement with decrease of the subacromial space. The examiner forward flexes the arm, which causes impingement of the greater tuberosity of the humerus with the anterior and inferior edge of the acromion. The patient's shoulder should then be fully flexed to 180 degrees. A positive result occurs if there is pain produced at the end range of the arc.

The *Hawkins test,* also indicative of mechanical impingement, is performed by forcibly internally rotating the proximal humerus while the shoulder is forward flexed to 90 degrees and the elbow flexed to 90 degrees. Pain with this maneuver indicates a positive finding.

A complete rotator cuff tear is evaluated by the *drop arm test,* in which the arm is passively abducted at 90 degrees and the patient is asked to maintain the abduction. If the arm drops to the side, a large rotator cuff tear should be considered.[17]

The *shrug sign* is exhibited when a patient with acute macrotrauma to the rotator cuff is asked to abduct the arm at 90 degrees and appears to be giving a shrug with that side. This movement results from the scapula's attempting to abduct the arm without the assistance of the rotator cuff. Although this has historically been associated with rotator cuff disease, it is somewhat nonspecific and can be associated with other shoulder disease.[18] Patients with adhesive capsulitis (frozen shoulder) have limitation of active and passive range of motion.[19]

Bicipital Tendinopathy. The tendon of the long head of the biceps, given its insertion into the humerus in proximity to the rotator cuff, can be associated with the impingement syndrome. The patient with bicipital tendinopathy may report pain in the anterior shoulder that radiates down to the radius. Discomfort occurs when the individual rolls on the shoulder at night or attempts to reach a hip pocket or a back zipper. Focal tenderness can be obtained by palpation in the groove between the greater and lesser tuberosities of the humerus while testing for *Yergason's sign,* which is elicited by having the patient flex the elbow to 90 degrees with the arm against the body and resisting supination of the forearm. Pain in the area of the proximal tendon is considered to be a positive finding and indicative of bicipital tendinopathy.[17]

Another physical examination tool in the diagnosis of bicipital tendinopathy is the *Speed sign*. With the elbow extended and the forearm supinated, the patient is instructed to resist forward flexion of the adducted shoulder at 60 degrees. Pain in the area of the proximal biceps tendon (bicipital groove) is indicative of a positive finding. This may also be suggestive, however, of labral disease.[20]

Calcific Tendinopathy. Calcific tendinopathy is an acute or chronically painful condition associated with deposition of calcium crystals that occurs in or around the tendons of the rotator cuff. The cause is unknown but has been postulated to be related to tissue hypoxia and degeneration due to overuse.[21] Although it can affect any of the rotator cuff tendons, it seems to have a predilection for the supraspinatus. The symptoms are similar to those of an impingement syndrome, and the condition generally affects people older than 40 years. Calcium deposition

www.ketabpezeshki.com 66485457-66963820

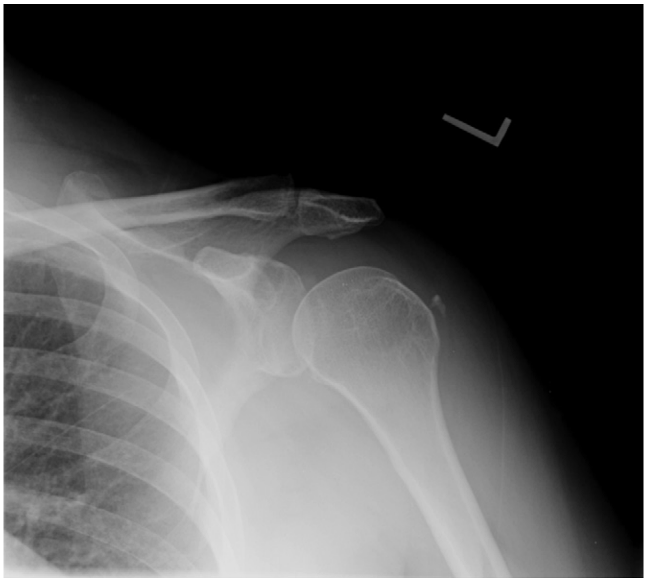


Figure 117-2. Plain radiograph of the shoulder showing calcium deposits of the rotator cuff in a patient with acute shoulder pain, consistent with calcific tendinopathy.

occurs over time and then undergoes spontaneous resorption. This resorptive phase is thought to be the painful aspect, but the severity of the symptoms is not related to the size of the deposit. Pain is believed to be in response to the local chemical pathologic disorder and direct mechanical irritation.[22]

On physical examination, there may be specific tenderness over the greater tuberosity as well as symptoms consistent with impingement. Radiographic evaluation may show evidence of calcification in or around the rotator cuff tendons (Fig. 117-2). The presence of calcium in the tendon does not necessarily affirm the origin of the pain because asymptomatic patients may have evidence of calcification on a routine radiograph.[22]

Elbow. Increasingly, athletes of all ages and skill levels are participating in sports involving overhead arm motions; consequently, elbow injuries are increasingly seen.[23] From an anatomic and functional perspective, the extensors and supinators of the wrist attach to the lateral elbow, and the flexors and pronators attach medially.

Lateral Epicondylitis. Lateral epicondylitis ("tennis elbow") is a painful elbow condition that occurs at the insertion of the common extensor tendon (extensor carpi radialis brevis) onto the lateral epicondyle of the humerus. Although it occurs in many tennis players, epidemiologic studies suggest that less than 5% of patients with such a syndrome actually play tennis. Activities such as driving in screws, use of a wrench, and repetitive work on an assembly line have also been implicated. Symptoms often begin as a dull ache on the outer (lateral) aspect of the elbow.[24,25] The discomfort can be exacerbated by activities that involve extension or supination of the wrist, such as grasping and twisting. *Cozen's test* is performed by having the patient keep the fist clenched while extending the wrist. The examiner grasps the forearm with the left hand while the right hand pulls the patient's hand toward flexion against the patient's resistance. A positive finding is pain at the lateral epicondyle, reproducing the patient's symptoms.[26]

Active extension of the long finger against resistance with the elbow in extension can also reproduce the pain over the lateral epicondyle at the insertion of the extensor carpi radialis brevis. In addition, patients will typically have tenderness to palpation just distal to the lateral epicondyle, over the origin of the extensor carpi radialis brevis.[26]

Radiographs can be helpful in cases with atypical or prolonged symptoms and to rule out other pathologic conditions. Approximately 20% of patients demonstrate tendon calcification or a reactive exostosis at the tip of the epicondyle.[24]

The differential diagnosis of lateral epicondylitis includes posterior interosseus nerve entrapment (motor aspect of radial nerve in forearm). Other associated lesions include plica, synovitis, chondromalacia, and adolescent osteochondral defect.[24]

Medial Epicondylitis. The pain of the less common medial epicondylitis ("pitcher's elbow" or "golfer's elbow") can result from microtrauma at the site of the insertion of the flexor carpi radialis on the medial epicondyle. It is important to differentiate medial epicondylitis from other causes of medial elbow pain, including medial ulnar collateral ligament injury. As a result of repetitive valgus stress placed on the joint, microtraumatic injury and valgus instability at the ligament can occur. With disruption of the medial ulnar collateral ligament, abnormal stress is placed on the articular surfaces, which may lead to degenerative changes and the formation of osteophytes.[27] In the case of medial epicondylitis, patients will generally have tenderness over the flexor-pronator origin slightly distal and anterior to the medial epicondyle. Pain can be reproduced by having the patient attempt wrist flexion and forearm pronation against resistance.[28]

Wrist

de Quervain's Tenosynovitis. The wrist and hand comprise several tendons that pass through thick, fibrous retinacular tunnels. These help prevent subluxation of the tendons and act as a pulley system. Overuse syndromes are thought to result from changes of the synovial lining between these tendons and retinaculum. de Quervain's tenosynovitis involves the synovial lining of the abductor pollicis longus and extensor pollicis brevis. Although the term *tenosynovitis* indicates an inflammation of the tendon sheath, it has been noted that there are many potential forms of tenosynovitis. Classic acute inflammatory changes that are characteristic of tenosynovitis may be related to systemic manifestations of disease (e.g., rheumatoid arthritis and gout); tenosynovitis related to de Quervain's syndrome is referred to by some practitioners as *stenosing tenosynovitis*. The pathologic process of de Quervain's tenosynovitis does not generally involve inflammation because the primary change is thickening of the extensor retinaculum covering the first dorsal compartment of the wrist. It has been suggested that de Quervain's disease is a result of intrinsic degenerative mechanisms rather than extrinsic inflammatory ones.[29]

The history may consist of chronic, repetitive trauma or unaccustomed repetitive efforts, such as firm grasping and movement of the hand in a radial direction. Direct trauma, such as a direct blow or fall, has occasionally been implicated.[30] The discomfort of de Quervain's tenosynovitis can be localized over the radial styloid process. Radiation of pain proximally to the forearm or distally down the thumb has been noted. The pain is generally constant but may be exacerbated by maneuvers that include grasping, abduction of the thumb, and ulnar deviation of the wrist. In most cases of de Quervain's tenosynovitis, the onset is gradual and not associated with a history of acute trauma.

On physical examination, slight swelling may be seen over the radial styloid. Crepitation may be palpable over the tendons with flexion and extension of the thumb. An increase in the tensile load (passive stretching or active contraction) in the abductor pollicis longus or extensor pollicis brevis increases pain. The *Finkelstein test,* which exacerbates the discomfort of de Quervain's tenosynovitis, is the most pathognomonic physical sign. The patient is instructed to hold the affected thumb in the palm by the fingers and then to ulnar deviate the wrist. Pain will occur near the radial styloid, which is also the point of tenderness. Pain with this maneuver is considered to be a positive finding. Radiographs are characteristically normal.

www.ketabpezeshki.com 66485457-66963820

The differential diagnosis includes scaphoid fracture and osteoarthritis of the carpometacarpal joint, which has pain caused by longitudinal traction and compression. Rarely, infections such as tuberculosis or disseminated gonococcal infections can be manifested as tenosynovitis.

Knee

Patellar Tendinopathy. Patellar tendinopathy or "jumper's knee" occurs in sports that have jumping as a part of the activity, although it can also occur as a result of other sporting activities.[31] Patients complain of pain at the inferior pole of the patella. The discomfort may abate with activity early in the tendinopathy but later progresses to the point of discomfort during exercise and at rest. With the knee flexed at 30 degrees, which relaxes the quadriceps, tenderness may be localized to the deep surface of the proximal attachment of the patellar tendon at the inferior pole of the patella. However, healthy active athletes sometimes have tenderness on examination as well.[31,32]

The differential diagnosis includes patellofemoral syndrome, which arises from imbalances in the forces controlling tracking during knee flexion and extension. The patient usually complains of anterior knee pain, described as "behind" or "around" the patella, which is classically worse on ascending or descending stairs or on rising from a seated position. On occasion, there is tenderness of the medial or lateral retinacula or facets.[33]

Imaging with ultrasonography and magnetic resonance imaging (MRI) may reflect collagen degeneration but is generally adjunctive to the distinctive history and physical examination findings. It is noted that some asymptomatic jumping athletes have imaging appearances similar to those of affected individuals and that prognosis and outcome are not predicted by such imaging.[31]

Ankle

Achilles Tendinopathy. Achilles tendinopathy is a common overuse syndrome that typically affects male athletes. The Achilles tendon, named for the mythological Achilles, whose heel was not immersed in the river Styx as his mother dipped him in the river for its protective powers, arises from the medial and lateral heads of the gastrocnemius muscle and the deep layers of the soleus muscle and inserts on the calcaneal tuberosity. A major function is plantar flexion of the foot. It is the strongest and largest tendon in the body and can withstand tensile loads more than 12 times the body's weight during running.[34]

The Achilles tendon is vulnerable to injury from either trauma or overuse. A tendinopathy can also develop as a result of systemic disease (e.g., ankylosing spondylitis, Reiter's syndrome, gout, and pseudogout). The use of fluoroquinolones has also been related to Achilles tendinopathy.[7]

The occurrence of Achilles tendinopathy is highest among individuals who participate in middle- and long-distance running, orienteering, track and field, tennis, badminton, volleyball, and soccer. Some studies have noted an almost 10% annual incidence of Achilles disorders in elite runners.[34] The most common Achilles disorders are tendinopathy (55-66%) and insertional problems, such as retrocalcaneal bursitis and insertional tendinopathy (20-25%).[34] Many cases of Achilles tendinopathy are thought to be multifactorial in origin. Body mechanics and environmental factors (e.g., uneven terrain) may apply valgus or varus stress to the tendon. Technique, equipment, and body mechanics can also contribute to the development of this tendinopathy. Anatomically, the vascular supply to the tendon creates a watershed area approximately 2 to 6 cm above the calcaneal insertion. This is thought to be responsible for clinical symptoms and the pathologic disruption commonly seen at this site.

The patient's history provides most of the information necessary to make the diagnosis of Achilles tendinopathy. Pain, a cardinal symptom of Achilles tendinopathy, may lead the patient to seek medical help. Some practitioners have noted that the patient's symptoms reflect the degree of the tendon abnormality. As with many tendinopathies, pain after strenuous activities is reported in the early phase, whereas pain in the later phase occurs during activity and even at rest. At this point, the patient is often unable to perform sporting activities.[34]

On physical examination, inspect the contour of the muscle-tendon unit and note areas of swelling and erythema. In acute Achilles tendinopathy, the tendon may be diffusely swollen and exhibit tenderness on palpation, usually greatest in the middle third. Typically, in the patient who has acute symptoms of tendinopathy, the area of swelling and tenderness does not move with dorsiflexion of the ankle joint. On palpation, local heat, crepitation, and palpable tendon nodules or defects may be noted. Examination for ankle instability and biomechanical faults should be considered.[34]

Achilles Tendon Rupture. Although rupture of the Achilles tendon most often occurs when it is preceded by tendon damage,[35] it is possible for untrained athletes to apply excessive force and to rupture the tendon in the absence of prior changes of tendinopathy. Partial and complete rupture may occur, most commonly in 30- to 40-year-old men. Complete rupture is more common in the middle-aged recreational athlete. Historically, the patient may note a "popping" sensation followed by acute weakness and inability to continue the exercise or sport. The patient may report that it felt as though someone kicked him or her in the back of the ankle or, if playing a racket sport, as if he or she were struck on the calf by a ball.

On physical examination, a defect in the tendon can sometimes be palpated. If enough time has elapsed to allow hematoma formation, bogginess may be noted over the injured area of the tendon. The ability to plantar flex the foot is not incompatible with a complete rupture of the Achilles tendon. There are multiple plantar flexors of the foot and toes. Muscles such as the tibialis posterior, flexor digitorum longus, flexor hallucis longus, peroneus brevis, and peroneus longus can remain functional and therefore disguise a complete rupture with the ability to plantar flex the foot. The *Simmonds (Thompson) test* can be performed to evaluate for complete rupture. With the patient prone and feet hanging over the edge of the bed, the examiner squeezes the calf muscles at their widest point and looks for passive plantar flexion. The absence of plantar flexion is considered a positive finding, indicative of a complete tear of the Achilles tendon. The presence of plantar flexion does not, however, negate the possibility of a partial tear of the Achilles tendon.

Diagnostic Strategies

The diagnosis of tendinopathy is generally made on clinical grounds. Although plain radiographs may be helpful in excluding bone abnormalities, ultrasonography has been recommended by some practitioners as the modality of choice for evaluation of pathologic tendon conditions.[36] Ultrasonography can be especially useful when other conditions (e.g., gouty arthritis) obscure the findings of concomitant tendinopathy. Although ultrasound imaging is employed in the emergency department (ED), the use of this imaging technique for soft tissue evaluation in this setting is relatively unstudied, and thus it is not frequently used.[37,38] In cases of acute or chronic tendinopathy, one or more of the following features can be seen: loss of the fibrillar echotexture, focal tendon thickening, diffuse thickening, focal hypoechoic areas, extended hypoechogenicity, irregular and ill-defined borders, microruptures, and peritendinous inflammatory edema.[39] Hypoechoic areas surrounding tendons provide evidence for surrounding soft tissue inflammation. In addition to tendinopathy, tendon tears, both partial and complete, can be delineated by ultrasonography.[39]

MRI has been used to visualize pathologic conditions of the tendon. It is able to provide high intrinsic tissue contrast, which

www.ketabpezeshki.com 66485457-66963820

permits the distinction between normal tendons and abnormal tendons, and the high spatial resolution that permits detailed anatomic structures to be identified. MRI has superb resolution of the soft tissue structures and can aid in a variety of tendon disorders. Cost, availability, the need to have the patient be still during examination, and the loss of the interactive and dynamic component compared with ultrasound examination are disadvantages to use of this modality.[40]

Differential Diagnosis

The differential diagnosis for tendinopathy includes tendon ruptures, bursitis, ligamentous injuries, septic and inflammatory arthritis, nerve entrapment syndromes, and bone abnormalities (such as fracture, foreign body, tumor, and osteomyelitis).

Management

General Tendinopathy

The management of tendinopathy focuses on identification of the cause of discomfort; elimination of sources of primary tendinopathy; institution of treatment modalities, such as analgesic medication, protection, relative rest, application of ice, compression, and elevation as necessary; modification of behavior to minimize or to eliminate sources of continuing irritation; and, importantly, referral for appropriate follow-up care.[5]

Cryotherapy (cold treatments, 20 minutes at a time every several hours, for the first 24 to 48 hours) may be beneficial. Nonsteroidal anti-inflammatory drugs (NSAIDs) are also sometimes indicated to provide pain relief, although there is little evidence to support a beneficial effect with their use because tendinopathies tend to represent a degenerative rather than an inflammatory process.[41] Graduated range-of-motion exercises may be useful after the period of immobilization. Although corticosteroid injection is often used, its role for most tendinopathies is unclear.[42,43] The use of corticosteroid injection is controversial. Steroids should not be injected into a major tendon such as the Achilles tendon or the patellar tendon, which may be at risk for spontaneous rupture if it is already weakened.

Specific Tendinopathies

Impingement Syndrome and Rotator Cuff Tendinopathies. The treatment of rotator cuff tendinopathies and the impingement syndrome follows the treatment of tendinopathy in general. Emphasis is placed on physical rehabilitation and strengthening exercises. A significant proportion of patients will improve with conservative management. In those who do not, surgical intervention, such as acromioplasty or repair, may be indicated.[44,45]

Calcific Tendinopathy. The initial treatment of calcific tendinopathy is mainly conservative and consists of analgesia and brief sling immobilization because prolonged immobilization may result in adhesive capsulitis. The use of corticosteroids is controversial. Ultrasonography and extracorporeal shock wave therapy have been used with some success.[22] A small percentage of patients who do not respond to these interventions may need surgery. As well as arthroscopic treatment, localized disruption in the resorptive phase by needle lavage under fluoroscopic guidance or in the operating room has been noted to be an efficacious therapy.[21,22] Follow-up care is important because calcific tendinopathy has been described as the best known cause of reactive cuff failure.

Lateral and Medial Epicondylitis. In up to 95% of patients, epicondylitis will improve with conservative therapy.[24] Initial efforts include making the patient more comfortable with the standard principles of protection, relative rest, cryotherapy, compression, elevation, medication (NSAIDs), and modalities of physical therapy. The term *relative rest* implies the avoidance of abuse and not the absence of activity. Activities that aggravate the pain should be eliminated, and an attempt to protect the tendon through such strategies as a reduction in playing time or intensity should be considered. Control of force loads by bracing, improved performance technique, and use of appropriate equipment should also be considered.[24] Follow-up evaluation should be ensured.

de Quervain's Tenosynovitis. The initial treatment of de Quervain's tenosynovitis consists of immobilization with a thumb spica splint, anti-inflammatory medications, and prompt referral. Corticosteroid injection has been shown to be an effective treatment of de Quervain's disease, and failure to respond may be due to anatomic variation or poor technique.[29,46] Surgical decompression of the first dorsal compartment may be indicated if these treatments fail.[29]

Achilles Tendinopathy and Rupture. In addition to routine conservative treatment, patients with Achilles tendinopathy should be referred for orthopedic evaluation and correction of limb malalignment with the use of orthotics or heel lifts. Eccentric loading exercise and low-energy shock wave therapy are effective therapies for Achilles tendinopathy.[47-49]

The management of Achilles tendon rupture may be either operative or nonoperative, depending on the patient involved. Appropriate consultation with an orthopedist is essential. A conservative approach, including immobilization in a short or long leg cast in the equinus position, may be indicated.[50] Some authors note that complete ruptures in active athletes should be treated surgically in most cases.[51] Although other risks and benefits must be taken into consideration, some studies indicate that early surgery may be indicated because the risk for Achilles tendon re-rupture is less.[50,51]

Disposition

Most patients with tendinopathy are safely discharged home with proper discharge instructions, relative rest of the tendon, analgesia, and appropriate follow-up. The exception is elderly or disabled patients who are rendered unable to perform the activities of daily living by the tendinopathy. Although appropriate rest and analgesia provide symptomatic relief, underlying causes should be sought and modified.

BURSITIS

Perspective

Bursae are closed, round, flat sacs lined by synovium.[52] They occur at areas of friction between skin and underlying ligaments and bone. The bursa permits lubricated movement of soft tissues over areas of potential impingement (e.g., subacromial bursa) and friction (e.g., olecranon bursa and prepatellar bursa). Many bursae are nameless, and new bursae can form as a result of frequent irritation. The two most common identifiably inflamed bursae are the olecranon and the prepatellar. When these bursae are inflamed, they are generally recognizable over the extensor surface of the elbow or the knee, respectively.

Principles of Disease

Many cases of bursitis are idiopathic in nature, but common identifiable causes of inflammation include infection (most often due to *Staphylococcus aureus*), trauma (which may predispose to infection), rheumatologic disorders (e.g., gout, pseudogout, ankylosing spondylitis, and rheumatoid and psoriatic arthritis), and other systemic diseases.

www.ketabpezeshki.com 66485457-66963820

Clinical Features

Olecranon and Prepatellar Bursitis

Less than half of patients who present with olecranon or prepatellar bursitis show signs of an infectious origin.[53,54] Distinguishing septic from nonseptic bursitis is not always straightforward, either on clinical grounds or as a result of diagnostic testing. Patients with septic bursitis generally present earlier in the clinical course and have more pain, tenderness, erythema, and warmth compared with those who have an inflammatory process. The most important predisposing factor in septic bursitis is trauma, which precedes septic bursitis in up to 70% of cases.[52] Other predisposing factors for septic bursitis include chronic illness such as diabetes mellitus or alcohol abuse, chronic skin conditions such as atopic dermatitis, and previous noninfectious inflammation of the bursae such as rheumatoid arthritis or gout.[52] It may also be seen more commonly in people in occupations in which repetitive knee or elbow trauma is common.

The olecranon bursa, on the extensor surface of the elbow, is the only bursa of the elbow joint and is easily traumatized, resulting in inflammation, pain, and swelling. Infection can occur from local trauma (e.g., puncture wound and laceration) but may also be present in the absence of visible trauma. Hematogenous bacterial seeding is rare and is probably due to the limited vascular supply of the bursal tissue.[55]

On physical examination, localized swelling and fluctuance are usually present. Evidence of trauma may or may not be present. Tenderness and warmth are seen in most patients with septic bursitis. Erythema with overlying cellulitis is also common in septic bursitis, and approximately 40% of patients will also have a fever. Whereas tenderness, erythema, and warmth can also be seen in patients with purely inflammatory causes of bursitis, both the frequency and degree of these findings are less, and patients with septic bursitis will usually present earlier in the clinical course.[52,54]

Passive range of motion should not produce much pain, with the exception of full flexion, at which point there may be discomfort as the inflamed bursa is compressed. Evidence of significantly diminished range of motion, generalized joint swelling, or other signs and symptoms of joint involvement (e.g., joint pain, warmth, and joint effusion) should raise a concern for septic arthritis. Although the olecranon and prepatellar bursae generally do not communicate with the joint space, one must consider this possibility in the differential diagnosis, especially if trauma is involved and the integrity of the underlying joint is disrupted. Arthrocentesis to rule out septic arthritis should then be considered.

Diagnostic Strategies

When signs of acute inflammation are present, aspiration of the bursa is indicated to exclude the presence of infection or crystal-induced disease.[52,53] Although a discussion of the technique of bursal aspiration is beyond the scope of this chapter, it should be performed with sterile technique. An 18- to 20-gauge needle can be used to perform this procedure. A lateral approach has been recommended to lower the risk of iatrogenic sinus track formation, although the relation between the two is still somewhat unclear. A distal approach can also be used when the olecranon bursa is aspirated. In cases of septic bursitis, the aspirate usually appears purulent but can occasionally appear serosanguineous or straw colored. In the case of nonseptic bursitis, the aspirate may vary from bloody aspirate to straw colored. The aspirate of an inflamed bursa should be sent for evaluation of white blood cell (WBC) count with differential, microscopy for crystals (if crystalline disease is suspected), Gram's stain, appropriate cultures and sensitivities, and glucose level. A bursal fluid glucose–to–serum glucose ratio of less than 50% is almost exclusively seen in septic bursitis.

Organisms found on either Gram's stain or culture are diagnostic for septic bursitis. There are no definitive guidelines about use of the WBC count to distinguish between septic and nonseptic bursitis. A bursal fluid WBC count higher than $1000/\mu L^3$ is almost always seen, and one higher than $5000/\mu L^3$ suggests bursal fluid infection, even in the presence of a negative Gram's stain, but counts can be much lower in septic bursitis and above this level in nonseptic cases. Culture is the definitive test but will not be available during the initial evaluation. *S. aureus* is by far the most common organism in bursal infection, followed by other staphylococcal and streptococcal species, and this bacteriology has not changed in the last several decades.[56-58]

Because most cases of septic bursitis occur in the olecranon and prepatellar bursae, the diagnosis is made clinically in conjunction with aspiration. MRI can be used to aid in the diagnosis of inflammation or infection of deep bursae.[59,60] Ultrasonography has also been used as a modality for aspiration of deep bursae.[61]

Differential Diagnosis

Conditions that mimic bursitis include underlying fracture and osteomyelitis. Radiography and bone scan or MRI may be necessary to exclude these conditions. Other causes of the nontraumatic, nonseptic bursitis include rheumatoid arthritis, gout, pseudogout, scleroderma, ankylosing spondylitis, systemic lupus erythematosus, hypertrophic pulmonary osteoarthropathy, Whipple's disease, oxalosis, and idiopathic hypereosinophilic syndrome.

Management

Septic Bursitis

The optimal treatment of septic bursitis is uncertain because large-scale clinical prospective trials in this area are lacking. Debate remains about the use of outpatient (oral) versus inpatient (intravenous) administration of antibiotics, duration of therapy, use of needle aspiration and incision and drainage, and use of operative intervention.[54]

Patients who have bursal inflammation with suspicion (clinical or laboratory) of infection should be treated with appropriate antibiotics. Empirical therapy (including coverage for *S. aureus* and *Streptococcus* species) may be indicated until definitive culture results are available. The frequency of methicillin-resistant *S. aureus* (MRSA) in septic bursitis is unclear, although recent literature suggests that rates are low.[56-58] MRSA was found to be the most common cause of community-onset adult septic arthritis in one case series from an ED population, so empirical coverage for this organism in septic bursitis should be considered.[62] A trial of oral antibiotic therapy (up to 14 days) and treatment on an outpatient basis in the patient with uncomplicated bursitis and no underlying disease is reasonable. However, failure rates up to 67% have been reported for outpatient treatment of septic bursitis.[54] One of the largest observational studies on the successful outpatient treatment of septic bursitis showed an admission rate of only 1 of 118 patients, but all patients in this study received sequential intravenous antibiotics for approximately 4 days at an outpatient clinic followed by oral antibiotic therapy.[63] Treatment in an observation unit or inpatient setting with intravenous antibiotics therefore is a consideration for patients with significant symptoms, with overlying cellulitis, or unlikely to receive close follow-up.

Needle aspiration is a commonly used technique for the management of septic bursae. Successful treatment of septic bursitis can be achieved in patients receiving outpatient oral antibiotics

www.ketabpezeshki.com 66485457-66963820

after initial needle aspiration. Laupland and Davies[63] showed no difference between patients who received aspiration (51% of total patients) and those who did not, but the authors conceded that patients who had more severe disease were likely to be selected for drainage. Also, the diagnosis of septic bursitis was confirmed by culture in only 26% of these patients, potentially underestimating the importance of bursal drainage in patients with true septic bursitis.[52] Because needle aspiration is used for the diagnosis of septic bursitis, initial drainage at the same time seems warranted. Those with a purulent aspirate may require repeated aspiration at 1- to 3-day intervals if the effusion persists. In all cases, appropriate follow-up to assess response to therapy should be arranged. Warm soaks and wound care are also indicated. Surgical incision and drainage or bursectomy may also be necessary in severe, recurrent, or refractory cases.[54]

Nonseptic Bursitis

The optimal treatment of nonseptic bursitis has not been clarified. Most cases improve with conservative therapy, although complete recovery can take many months. Aspiration can be considered in the initial treatment of acute nonseptic bursitis. Further conservative therapy includes the administration of NSAIDs and application of a compression dressing with an elastic bandage to prevent recurrent swelling. Systemic causes of bursitis (e.g., crystalline disease) should be treated appropriately. Avoidance of local trauma is important for treatment and successful prevention of bursitis. Recurrent olecranon bursitis may be caused by underlying anatomic disorders such as bone spurs. Steroid injection into a nonseptic bursa has been used as a treatment modality, but multiple complications have been described, including skin atrophy over the bursa, chronic pain, development of septic bursitis, bleeding, postinjection flare as a result of release of microcrystals, and tendon rupture.

Disposition

Patients without underlying medical problems who present with uncomplicated septic bursitis can usually be discharged with appropriate oral antibiotics. Those with underlying diseases (e.g., immunocompromise, leukopenia, and diabetes) and those with systemic toxicity or severe bursal infection (e.g., purulent drainage) are candidates for intravenous antibiotics and inpatient therapy. Patients with a purulent aspirate may need repeated aspiration. Close follow-up is necessary to ensure response to therapy. Patients with presumed nonseptic bursitis require close follow-up as well.

Other Types of Bursitis

Subacromial Bursitis

The subacromial bursa lies between the supraspinatus tendon and the acromion. Subacromial bursitis is thought to be nearly synonymous with supraspinatus tendinopathy and may be involved in the stages of rotator cuff impingement. Pain and tenderness, localized to the lateral aspect of the shoulder, and signs of impingement may be noted on physical examination.[13] Although it is uncommon, septic subacromial bursitis can occur.[61]

Trochanteric Bursitis

The trochanteric bursa has both deep and superficial components. The deep bursa is located between the greater trochanter and the tensor fascia lata; the superficial bursa is located between the greater trochanter and the skin. In general, middle-aged or older women report acute or chronic pain over the bursal area as well as the lateral thigh. Lying on the hip and walking may exacerbate the pain. Trochanteric bursitis can occur as a complication of rheumatoid arthritis. On examination, the pain of superficial bursitis may be reproduced by hip adduction, and the pain of deep trochanteric bursitis may be reproduced with hip abduction. The hip joint has normal examination findings. Septic trochanteric bursitis has been described in the literature.[64]

Ischiogluteal Bursitis

The ischiogluteal bursa is located adjacent to the ischial tuberosity and overlies the sciatic and posterior femoral cutaneous nerves. Inflammation, known as *weaver's bottom,* is described as pain over the center of the buttocks with radiation down the back of the leg. Sitting on a hard surface exacerbates the pain, and palpation over the ischial tuberosity causes discomfort.

Iliopsoas Bursitis

The iliopsoas bursa is the largest bursa around the hip. It lies between the iliopsoas tendon and the lesser trochanter. The pain of iliopsoas bursitis usually is manifested as anterior hip pain that can radiate down the medial thigh to the knee and is increased on hip extension.[65]

Anserine Bursitis

The anserine bursa lies deep to the three tendons (sartorius, gracilis, and semitendinosus) that form the pes anserinus ("foot of the goose") and superficial to the medial collateral ligament. The patient with anserine bursitis usually complains of medial knee pain approximately 2 or 3 cm distal to the joint line. There is usually tenderness to palpation in this area and occasionally swelling. Diabetes mellitus and possibly obesity and osteoarthritis of the knee are risk factors for development of this condition.[66]

KEY CONCEPTS

Tendinopathy

- Mechanical overload and repetitive microtrauma are key underlying mechanisms in the development of tendinopathy. Patients most often present with a history of progressively worsening localized pain after work- or sport-related activities that are repetitive in nature.
- Tendinopathy may also be associated with nonmechanical causes, including systemic manifestations of diseases and the use of fluoroquinolones.
- Most patients with tendinopathy can initially be treated with conservative measures, such as protection, relative rest, application of ice, medication, and elevation. Overuse syndromes can take at least 6 to 12 weeks to heal. Inform patients of this and provide appropriate referral for follow-up.
- Operative treatment may be indicated for selected cases of tendon injury that require primary repair (e.g., rupture of the Achilles tendon) or that have failed to respond to conservative treatment (e.g., impingement syndrome) and are amenable to surgical amelioration.

Bursitis

- Consider the possibility of an infectious cause in all cases of acute bursitis.
- The definitive diagnosis of bursitis is made by aspiration of the bursa and evaluation of the fluid.
- Septic bursitis is most commonly caused by *Staphylococcus aureus*.

www.ketabpezeshki.com 66485457-66963820

- Nonseptic bursitis may be traumatic, rheumatologic (e.g., gout and pseudogout), or idiopathic in nature. Other conditions, such as septic arthritis, osteomyelitis, and underlying fracture, are in the differential diagnosis of bursitis.
- The management of bursitis includes treatment with appropriate medication (antibiotics for septic bursitis, NSAIDs for nonseptic bursitis), rest, application of ice, compression, and elevation as well as prompt referral for appropriate follow-up. Hospitalization is considered for severe local infections, for patients who are immunosuppressed, and in the presence of high fever or systemic toxicity.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Maffulli N, Wong J, Almekinders LC: Types and epidemiology of tendinopathy. *Clin Sports Med* 2003; 22:675-692.
2. Wen DY: Risk factors for overuse injuries in runners. *Curr Sports Med Rep* 2007; 6:307-313.
3. McSweeney KP, Craig BN, Congleton JJ, Miller D: Ergonomic program effectiveness: Ergonomic and medical intervention. *Int J Occup Saf Ergon* 2002; 8:433-449.
4. Khan K, Cook J: The painful nonruptured tendon: Clinical aspects. *Clin Sports Med* 2003; 22:711-725.
5. Rees JD, Maffulli N, Cook J: Management of tendinopathy. *Am J Sports Med* 2009; 37:1855-1867.
6. Magra M, Maffulli N: Genetic aspects of tendinopathy. *J Sci Med Sport* 2008; 11:243-247.
7. Khaliq Y, Zhanel GG: Fluoroquinolone-associated tendinopathy: A critical review of the literature. *Clin Infect Dis* 2003; 36:1404-1410.
8. Sharma P, Maffulli N: Biology of tendon injury: Healing, modeling and remodeling. *J Musculoskelet Neuronal Interact* 2006; 6:181-190.
9. Wilson JJ, Best TM: Common overuse tendon problems: A review and recommendations for treatment. *Am Fam Physician* 2005; 72:811-818.
10. De Simone C, et al: Achilles tendinitis in psoriasis: Clinical and sonographic findings. *J Am Acad Dermatol* 2003; 44:217.
11. Ortiz V, Holgado S, Olive A, Fite E: Achilles tendinitis as the presentation form of Löfgren's syndrome. *Clin Rheumatol* 2000; 19:169.
12. Abdelwahab IF, et al: Atypical extraspinal musculoskeletal tuberculosis in immunocompetent patients. Part II: Tuberculosis myositis, tuberculosis bursitis, and tuberculosis tenosynovitis. *Can Assoc Radiol J* 2006; 57:278.
13. Harrison AK, Flatow EL: Subacromial impingement syndrome. *J Am Acad Orthop Surg* 2011; 19:701-708.
14. Andrews JR: Diagnosis and treatment of chronic painful shoulder: Review of nonsurgical interventions. *Arthroscopy* 2005; 21:333-347.
15. Lim KK, Chang HC, Tan JL, Chan BK: Arthroscopic subacromial decompression for stage-II impingement. *J Orthop Surg (Hong Kong)* 2007; 15:197-200.
16. Rizio L, Uribe JW: Overuse injuries of the upper extremity in baseball. *Clin Sports Med* 2001; 20:453-468.
17. Tennent TD, Beach WR, Meyers JF: A review of the specialized tests associated with shoulder examination. Part I: The rotator cuff tests. *Am J Sports Med* 2003; 31:154-160.
18. Jia X, Ji JH, Petersen SA, Keefer J, McFarland EG: Clinical evaluation of the shoulder shrug sign. *Clin Orthop Relat Res* 2008; 466:2813-2819.
19. Sheridan MA, Hannafin JA: Upper extremity: Emphasis on frozen shoulder. *Orthop Clin North Am* 2006; 37:531-539.
20. House J, Mooradian A: Evaluation and management of shoulder pain in primary care clinics. *South Med J* 2010; 103:1129-1135.
21. Oliva F, Via AG, Maffulli N: Calcific tendinopathy of the rotator cuff tendons. *Sports Med Arthrosc* 2011; 19:237-243.
22. Hurt G, Baker CL Jr: Calcific tendinitis of the shoulder. *Orthop Clin North Am* 2003; 34:567-575.
23. Mariscalco MW, Saluan P: Upper extremity injuries in the adolescent athlete. *Sports Med Arthrosc* 2011; 19:17-26.
24. Nirschl RP, Ashman ES: Elbow tendinopathy: Tennis elbow. *Clin Sports Med* 2003; 22:813-836.
25. Shiri R, Viikari-Juntura E, Varonen H, Heliovaara M: Prevalence and determinants of lateral and medial epicondylitis: A population study. *Am J Epidemiol* 2006; 164:1065-1074.
26. Scher DL, Wolf JM, Owens BD: Lateral epicondylitis. *Orthopedics* 2009; 32:276-282.
27. McCarroll JR: Overuse injuries of the upper extremity in golf. *Clin Sports Med* 2001; 20:469-479.
28. Chen FS, Rokito AS, Jobe FW: Medial elbow problems in the overhead-throwing athlete. *J Am Acad Orthop Surg* 2001; 9:99-113.
29. Ilyas A, Ast M, Schaffer AA, Thoder J: De Quervain tenosynovitis of the wrist. *J Am Acad Orthop Surg* 2007; 15:757-764.
30. Kay NR: De Quervain's disease. Changing pathology or changing perception? *J Hand Surg Br* 2000; 25:65-69.
31. Warden SJ, Brukner P: Patellar tendinopathy. *Clin Sports Med* 2003; 22:743-759.
32. Cook JL, et al: Reproducibility and clinical utility of tendon palpation to detect patellar tendinopathy in young basketball players. *Br J Sports Med* 2001; 35:65-69.
33. Dixit S, DiFiori JP, Burton M, Mines B: Management of patellofemoral pain syndrome. *Am Fam Physician* 2007; 75:194-202.
34. Paavola M, et al: Achilles tendinopathy. *J Bone Joint Surg Am* 2002; 84:2062-2076.
35. Cetti R, Junge J, Vyberg M: Spontaneous rupture of the Achilles tendon is preceded by widespread and bilateral tendon damage and ipsilateral inflammation: A clinical and histopathologic study of 60 patients. *Acta Orthop Scand* 2003; 74:78-84.
36. Rasmussen OS: Sonography of tendons. *Scand J Med Sci Sports* 2000; 10:360-364.
37. Legome E, Pancu D: Future applications for emergency ultrasound. *Emerg Med Clin North Am* 2004; 22:817-827.
38. Dulchavsky SA, et al: Advanced ultrasonic diagnosis of extremity trauma: The FASTER examination. *J Trauma* 2002; 53:28.
39. Grassi W, et al: Sonographic imaging of tendons. *Arthritis Rheum* 2000; 43:969-976.
40. Peduto AJ, Read JW: Imaging of ankle tendinopathy and tears. *Top Magn Reson Imaging* 2010; 21:25-36.
41. Magra M, Maffulli N: Nonsteroidal antiinflammatory drugs in tendinopathy: Friend or foe. *Clin J Sport Med* 2006; 16:1-3.
42. Gaujox-Viala C, Dougados M, Gossec L: Efficacy and safety of steroid injections for shoulder and elbow tendonitis: A meta-analysis of randomised controlled trials. *Ann Rheum Dis* 2008; 68:1843-1849.
43. Koester MC, Dunn WR, Kuhn JE, Spindler KP: The efficacy of subacromial corticosteroid injection in the treatment of rotator cuff disease: A systematic review. *J Am Acad Orthop Surg* 2007; 15:3.
44. Almekinders LC: Impingement syndrome. *Clin Sports Med* 2001; 20:491-504.
45. Gebremariam L, Hay EM, Koes BW, Huisstede BM: Effectiveness of surgical and postsurgical interventions for the subacromial impingement syndrome: A systematic review. *Arch Phys Med Rehabil* 2011; 92:1900-1913.
46. Peters-Veluthamaningal C, Winters JC, Groenier KH, Myboom-DeJong B: Randomised controlled trial of local corticosteroid injections for de Quervain's tenosynovitis in general practice. *BMC Musculoskelet Disord* 2009;10:131.
47. Rompe JD, Nafe B, Furia JP, Maffulli N: Eccentric loading, shock-wave treatment, or a wait-and-see policy for tendinopathy of the main body of tendo Achillis: A randomized controlled trial. *Am J Sports Med* 2007; 35:374-383.
48. Roos EM, Engstrom M, Lagerquist A, Soderberg B: Clinical improvement after 6 weeks of eccentric exercise in patients with mid-portion Achilles tendinopathy—a randomized trial with 1-year follow-up. *Scand J Med Sci Sports* 2004; 14:286-295.
49. Rompe JD, Furia J, Maffulli N: Eccentric loading compared with shock wave treatment for chronic insertional Achilles tendinopathy: A randomized controlled trial. *J Bone Joint Surg Am* 2008; 90:52-61.
50. Bhandari M, et al: Treatment of acute Achilles tendon ruptures: A systematic overview and metaanalysis. *Clin Orthop* 2002; 400:190-200.
51. Schepsis AA, Jones H, Haas AL: Achilles tendon disorders in athletes. *Am J Sports Med* 2002; 30:287-305.
52. Small LN, Ross JJ: Suppurative tenosynovitis and septic bursitis. *Infect Dis Clin North Am* 2005; 19:991-1005.
53. Aaron DL, Patel A, Kayairos S, Calfee R: Four common types of bursitis: Diagnosis and management. *J Am Acad Orthop Surg* 2011; 19:359-367.
54. Wasserman AR, Melville LD, Birkhahn RH: Septic bursitis: A case report and primer for the emergency clinician. *J Emerg Med* 2009; 37:269-272.
55. Lopez FA, Lartchenko S: Skin and soft tissue infections. *Infect Dis Clin North Am* 2006; 20:759-772.
56. Mathieu S, et al: Acute prepatellar and olecranon bursitis: Retrospective observation study in 46 patients. *Joint Bone Spine* 2011; 78:423-424.
57. Perez C, et al: Infectious olecranon and patellar bursitis: Short-course adjuvant antibiotic therapy is not a risk factor for recurrence in adult hospitalized patients. *J Antimicrob Chemother* 2010; 65:1008-1014.
58. Martinez-Taboada VM, Cabeza R, Cacho PM, Blanco R, Rodriguez-Valverde V: Cloxacillin-based therapy in severe septic bursitis: Retrospective study of 82 cases. *Joint Bone Spine* 2009; 76:665-669.
59. Wunderbaldinger P, et al: Imaging features of iliopsoas bursitis. *Eur Radiol* 2002; 12:409-415.
60. Hitora T, et al: Ischiogluteal bursitis: A report of three cases with MR findings. *Rheumatol Int* 2009; 29:455-458.

www.ketabpezeshki.com 66485457-66963820

61. Constantino TG, Roemer B, Leber EH: Septic arthritis and bursitis: Emergency ultrasound can facilitate diagnosis. *J Emerg Med* 2007; 32:295-297.
62. Frazee BW, Fee C, Lambert L: How common is MRSA in adult septic arthritis? *Ann Emerg Med* 2009; 54:695-700.
63. Laupland KB, Davies HD: Olecranon septic bursitis managed in an ambulatory setting. *Clin Invest Med* 2001; 24:171-178.
64. Makki D, Watson AJ: Septic trochanteric bursitis in an adolescent. *Am J Orthop* 2010; 39:E1-E3.
65. Buindo JJ Jr, Irwin RW, Umpierre E: Sports and other soft tissue injuries, tendinitis, bursitis, and occupation-related syndromes. *Curr Opin Rheumatol* 2001; 2:146-149.
66. Alvarez-Nemegyei J, Canoso JJ: Evidence-based soft tissue rheumatology IV: Anserine bursitis. *J Clin Rheumatol* 2004; 4:205-206.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 118

Systemic Lupus Erythematosus and the Vasculitides

Robert T. Arntfield and Christopher M. Hicks

SYSTEMIC LUPUS ERYTHEMATOSUS

Perspective

Systemic lupus erythematosus (SLE) is a multisystem, autoimmune disorder that poses a challenge to the emergency physician with its protean and occasionally dangerous manifestations. Morbidity for SLE patients is typically mediated through organ inflammation and destruction or the consequences of therapeutic immunosuppression. Further complicating lupus is the frequent association with the antiphospholipid syndrome (APS) and its corresponding venous and arterial thromboses. The diagnostic criteria reflective of its complexity and immunologic basis were first described in 1971.[1] Today, the emergency department (ED) is a common venue for the evaluation and treatment of patients suffering from SLE.[2]

Epidemiology

SLE is present in 20 to 70 per 100,000 of the general population.[3] Although great variation in incidence exists worldwide, it is clear that two groups have consistently higher incidences: women, representing 90% of cases; and African Americans.[3] Dramatic rises in incidence of SLE have been described during the past several decades, but it is suspected that this may be due to the implementation of more sensitive diagnostic criteria.[4]

Principles of Disease

The exact etiology of SLE is not understood. It is likely to be related to multiple factors; genetics, environmental factors, race, hormones, medications, and immunology have all been implicated to varying degrees.

With women representing 90% of SLE cases,[5] a strong role for estrogen in disease development has been well supported in large cohort studies.[6-8] The disease also has a strong genetic link, with high rates of monozygotic twin concordance and tremendous genetic overlap at the human leukocyte antigen (HLA) alleles.[9]

Anatomy and Physiology

SLE may cause disease in nearly any organ system in the body through inappropriate immune response to self and is often described as the prototype of all systemic, autoimmune disorders. Like its cause, its exact pathophysiologic mechanism is not completely elucidated. When a cell cycle ends (apoptosis), intracellular contents, including DNA-rich nucleosomes, are released into the bloodstream. For patients with SLE, this cellular debris may be regarded as nonself (i.e., an antigen) by the immune system. After exposure to these self antigens, the familiar immunologic cascade of antigen-presenting cells, T cells, and ultimately B cells and their plasma cell progeny is exacted, and patients form autoantibodies against their own cellular contents.[10] These autoantibodies (which include anti–double-stranded DNA antibody, a commonly ordered rheumatologic assay in evaluation for SLE) may then mediate organ-specific disease and inflammation. This may occur through either direct attack and injury to parenchymal tissue or other mechanisms,[11] such as formation of immune complexes that are deposited in tissue.[12] On the basis of this immunologic understanding of the pathogenesis of SLE, the rationale for immunosuppression as both chronic and acute therapy for SLE can be appreciated.

The pathophysiologic mechanism of SLE may be different for each organ system. Indeed, the organ systems involved in any given patient's disease may be different and may relate to the underlying presence or absence of antigens that resemble tissue from that organ system.

Clinical Features

In general, there are four broad presentations for a patient with SLE: symptoms related to SLE that is not yet diagnosed (e.g., idiopathic pericarditis, new rash); progression or acute deterioration due to known SLE (e.g., progressive nephritis, lupus enteritis); complications of immunosuppression from treatment of SLE (e.g., opportunistic infection); and complaints or disease unrelated to SLE (e.g., trauma, pregnancy).

The Patient with Undiagnosed or Suspected SLE

Although some elements, such as the malar rash, that form the diagnosis of SLE are nearly pathognomonic for SLE, a confident initial diagnosis in the ED may otherwise be rare or difficult. The literature is replete with ED-based case reports of extreme initial presentations with conditions such as Guillain-Barré, cardiac tamponade, and fulminant renal failure that subsequently were confirmed as complications of unrecognized SLE[13-17]; however, in all cases the diagnosis of SLE was applied retrospectively. Because the workup for SLE is commonly conducted in a series of outpatient visits and relies on laboratory investigations that are uncommonly carried out in the ED, establishment of a new diagnosis of SLE in the ED is difficult. If a new diagnosis of SLE is suspected in an otherwise well patient, referral for an expedited workup is reasonable in most circumstances. The American College of Rheumatology classification criteria for SLE are presented in Table 118-1.[18,19]

www.ketabpezeshki.com 66485457-66963820

Table 118-1 American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus[18,19]

CONDITION*	DESCRIPTION
Malar rash	Butterfly-shaped, red rash on the face that spares the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging (atrophic scarring may occur in older lesions)
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Nonerosive arthritis	Two or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	History or clinical evidence of either pericarditis or pleuritis; includes otherwise unexplained pericardial or pleural effusions
Renal disorder	Persistent proteinuria (>0.5 g/day) or cellular casts (red cell, hemoglobin, granular, tubular, or mixed)
Neurologic disorder	Otherwise unexplained seizures or psychosis
Hematologic disorder	Any of: hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia
Immunologic disorder	Positive serology for any of: anti-DNA antibody, anti-Sm antibody, or antiphospholipid antibody (including anticardiolipin antibodies, lupus anticoagulant, or false-positive serology for syphilis)
Positive antinuclear antibody	Abnormal antinuclear antibody titer at any time in the absence of medications that may cause drug-induced lupus

*Patients exhibiting at least 4 of the 11 conditions listed here at any point in time meet the criteria for diagnosis of SLE.

Acute Presentations in the Patient with Known SLE

Emergency physicians are commonly faced with evaluating the acute complaints of patients with an established diagnosis of SLE.[2] The workup of SLE-related complications is based on use of a disease-specific differential diagnosis.

SLE Exacerbation

Even with good medication compliance, SLE patients are prone to exacerbations of their disease, typified by worsening physical symptoms from increased organ inflammation and destruction. These exacerbations may involve organs already affected by SLE or new conditions manifested in previously unaffected organ systems. As a systemic disease, worsening symptoms in one organ system should reasonably prompt evaluation for progressive disease activity in other organs. True to the broad scope of SLE, the most accepted scoring system to grade SLE exacerbations accounts for 20 different markers of disease activity across 9 organ systems.[20] Although such scoring systems have little role in the ED, it is important to identify when overall disease activity is increased as it typically signals the need to initiate or to escalate systemic therapy. In many cases, patients themselves are able to provide direction about the predictable course of their exacerbations and can be helpful in decision-making for therapy and disposition.

Specific Symptoms and Presentations

Fever. Improving survival for patients with SLE during the past several decades has been achieved with the use of improved immunosuppressive regimens. As a result, patients with SLE remain commonly affected by infections mediated by both typical and opportunistic organisms, suffering higher than average death rates from these infections.[21] In one case series, infection was the leading reason for SLE patients to be admitted to the intensive care unit, superseding both renal failure and cardiovascular disease.[22] Whereas absence of fever is insufficient in many cases to rule out infection, the presence of a fever is grounds for concern. Fever may also be due to increased overall disease activity.[23,24] Given the heightened risk for SLE patients with infection, determination that a fever is due strictly to disease exacerbation should be made cautiously.[21] The majority of infections in SLE are due to skin, lung, or urinary sources and are caused by typical organisms. However, largely because of the immunomodulating therapies that form the cornerstone of SLE management, opportunistic diseases are possible; *Pneumocystis (carinii) jiroveci* pneumonia, cryptococcal meningitis, *Listeria* infection, and herpes zoster have all been described.[25]

Neuropsychiatric Presentations. According to the American College of Rheumatology, there are 19 different clinical manifestations of neuropsychiatric SLE, some of which are included in the diagnostic criteria (see Table 118-1).[26] These 19 different presentations range vastly and include seizures, confusion, cranial neuropathies, demyelinating syndromes, myasthenia gravis, depression, psychosis, and anxiety. It may not be possible in the ED to determine whether such manifestations are due to neuropsychiatric SLE or to other, independent pathologic processes.

Headache. In general, headaches in a patient with SLE may be evaluated in a fashion similar to that for headaches in the general population. In one prospective cohort study, for instance, it was found that primary headache disorders, such as migraine and tension headaches, occur with the same frequency in SLE patients as in the general population.[27] This was further supported by an extensive meta-analysis examining the implications of headache in SLE patients.[28] In this study, the authors found no relationship between headache and SLE disease activity. Thus, despite recommendations to consider headache as suggestive of neuropsychiatric SLE or so-called lupus cerebritis,[26] isolated headaches in the context of lupus may be treated in a fashion typical of other primary headache disorders. When a more malignant cause of headache is suspected, as suggested by meningismus, fever, or focal neurologic findings, an aggressive workup is warranted. When concern exists for an infectious cause of headache, consideration for opportunistic infections, such as cryptococcal meningitis, should be made in an immunosuppressed SLE patient.[29] Further, because of common comorbid APS, consider sinus thrombosis in the SLE patient with new-onset focal central nervous system findings and headache.[30]

Seizure. Because of incompletely understood mechanisms, seizures may occur as result of SLE disease activity. In one large series, seizures were observed in 11% of SLE patients, and in the majority of cases, either stroke or comorbid APS was present.[31] Because of the high incidence of seizures, nonconvulsive status epilepticus is a consideration in SLE patients with an acute onset of altered mental status. The workup and management of seizures do not differ between patients with SLE and the general population.

Focal Neurologic Findings. On occasion, the patient with SLE may present with focal motor weakness. In those with SLE who also have APS, there is a significantly increased risk of stroke related to spontaneous arterial thrombosis.[32] Demyelinating disease, such Guillain-Barré and cranial neuropathies, have also been occasionally attributed to SLE from unclear mechanisms.

www.ketabpezeshki.com 66485457-66963820

Table 118-2 Chest Pain and SLE in the Emergency Department: Common Causes, Workup, and Treatment

CONDITION	DIAGNOSTIC TEST IN THE ED	TREATMENT	COMMENT
Pleuritis	Clinical, chest radiography (for commonly associated pleural effusion)	NSAIDs ± steroids	Diagnosis of exclusion
Pulmonary embolism	D-dimer, computed tomography pulmonary angiography	Anticoagulation	Higher incidence in all SLE patients, especially those with APS
Pneumonia	Chest radiography	Antibiotics	Consider opportunistic disease
Pericarditis	Electrocardiography	NSAIDs ± steroids	Echocardiography to rule out effusion; electrocardiographic findings in less than 50%
Coronary artery disease	Electrocardiography, troponin, CK-MB	Aspirin, heparin, percutaneous coronary intervention	++ Increased prevalence in SLE

APS, antiphospholipid syndrome; *CK-MB,* creatine kinase MB fraction; *ED,* emergency department; *NSAIDs,* nonsteroidal anti-inflammatory drugs.

Psychiatric Symptoms. Mood disorders, psychosis, and anxiety are considered potential manifestations of neuropsychiatric SLE.[26] Distinguishing SLE-related from functional causes of psychiatric presentations poses a challenge and may not be possible in the ED. Although psychiatric presentations of SLE in the ED have not been directly studied, in the absence of concern for an organic cause of altered mental status, patients with SLE are approached in the same manner as patients without SLE. Corroboration with the patient's rheumatologist may provide insight to history of similar events or guidance for treatment.

Cardiorespiratory Presentations and Diseases. Chest pain, in the form of either pleuritis or pericarditis, is among the diagnostic criteria for SLE (see Table 118-1). In addition to pericarditis and pleuritis, coronary artery disease (CAD), pulmonary embolism, and musculoskeletal causes are also common. Other forms of cardiac disease that occur without chest pain, such as verrucous (Libman-Sacks) endocarditis and various arrhythmias, may also be present.[15]

Coronary Artery Disease. There is a dramatically increased risk of CAD in the context of SLE. This was demonstrated in a compelling retrospective cohort study of 500 women with lupus compared with age-matched controls from the original Framingham data. In this study, a 52-fold increased risk of myocardial infarction was determined in women between the ages of 35 and 44 years.[33] These findings of increased risk of CAD have been supported by a number of other prospective trials. In one series, patients with SLE were found to be five times as likely to have CAD (based on coronary artery calcium scoring) as patients without SLE.[34] In another series that profiled an even younger subset, it was found that among otherwise low- to moderate-risk women aged 22 to 45 years with complaints of chest pain, dyspnea, or decreased exercise capacity, there was an alarming 82% prevalence of CAD as determined by nuclear imaging. There was a similarly concerning prevalence of 43% of CAD in the asymptomatic "control" group who also had SLE.[35] Further, traditional cardiac risk factors are found less often in patients with SLE who suffer consequences of CAD, suggesting that CAD in patients with SLE cannot be explained by the higher incidence of hypertension or hypercholesterolemia that these patients often exhibit.[36] Thus, whereas there are many considerations for the cause of chest pain in patients with SLE (Table 118-2), CAD must be considered highly, and in fact more highly in patients who would otherwise be deemed to be low risk (young, reproductive age women). It is therefore appropriate to have a low threshold to initiate a workup with electrocardiography, cardiac biomarkers, and stress testing to rule out acute coronary syndromes in patients with chest pain and SLE.

In addition to being at risk for development of CAD, patients with SLE who are treated with percutaneous coronary intervention appear to fare poorly. In one retrospective analysis of 28 patients with SLE receiving percutaneous coronary intervention, reintervention, death, and recurrent myocardial infarction were significantly more likely compared with a similar cohort without SLE.[37]

Pericardial Disease. Pericardial effusion and pericarditis occur commonly in patients with SLE. It is estimated that symptomatic pericarditis occurs in 25% of patients with SLE during the course of their lives and that pericardial effusion occurs even more often, frequently in a silent fashion, in up to 50%.[38] In clinically evident SLE-related pericarditis, dyspnea or pleuritic chest pain is common. Typical electrocardiographic findings (Fig. 118-1) have been shown to be present in less than half of cases, however.[39] Given the increased risk of CAD in patients with SLE, ST elevation of any kind found on an electrocardiogram warrants very careful consideration. When diagnostic uncertainty exists, echocardiography, cardiac enzymes, or cardiac catheterization may be complementary. Treatment of pericarditis includes nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, as discussed later.

Pericardial tamponade, because of its dramatic nature, continues to receive attention as an initial presentation of SLE[40]; however, large case series have shown that this life-threatening presentation occurs in less than 1% of patients with lupus.[41] In large effusions without tamponade, medical management with high-dose glucocorticoids (1-2 mg/kg of methylprednisone) has shown favorable outcomes in averting the need for pericardiocentesis.[39]

Pulmonary Embolism. Pulmonary embolism and deep venous thrombosis occur with increased incidence in patients with SLE. This is especially true for patients with SLE who also carry antiphospholipid (aPL) antibodies. These patients have an estimated 20- to 30-fold increased risk for thrombosis compared with the general population. Patients with SLE who do not have aPL antibodies still have a sixfold greater likelihood for development of pulmonary embolism and deep venous thrombosis compared with patients without SLE.[42,43] Thus, all patients with SLE, regardless of their aPL antibody status, which is often unknown on presentation, should be considered at increased risk for venous thromboembolism.

Pleuritis. Pleuritis, due to autoantibodies acting against the pleura itself, is the most common respiratory condition occurring in SLE.[44] Characterized by pleuritic chest pain with or without a pleural effusion or pleural rub, it has symptoms that overlap with those of other more serious conditions (see Table 118-2). If a pleural effusion is present, analysis of pleural fluid for antinuclear antibodies may be the most accurate method to confirm diagnosis but may be impractical in the ED.[45] A diagnosis of pleuritis should be arrived at only after other causes of pleuritic chest pain in these thrombophilic, immunosuppressed patients have been ruled out.

www.ketabpezeshki.com 66485457-66963820

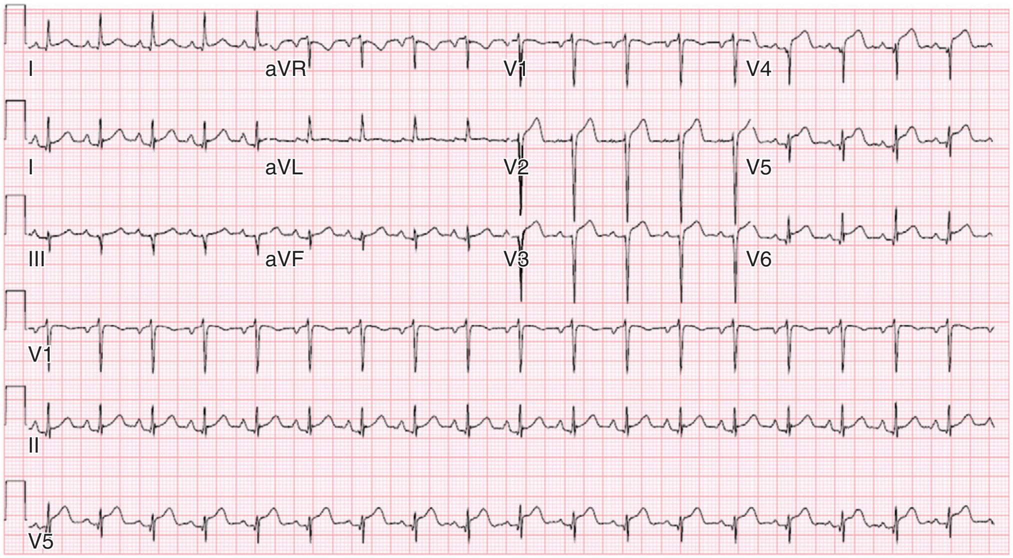


Figure 118-1. Electrocardiogram of a 38-year-old woman with SLE who presented to the ED with seizures and had chest pain while in the ED. Note diffuse ST elevation (with absence of any reciprocal changes) and PR depression (particularly evident in lead II). Q waves anteriorly are related to prior myocardial infarct.

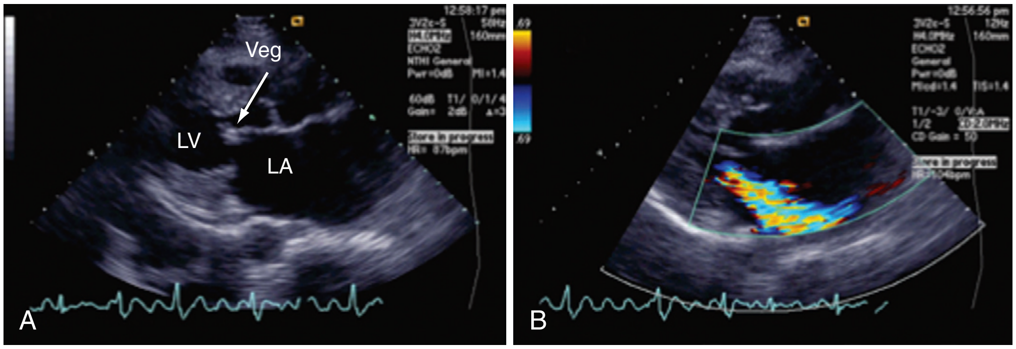


Figure 118-2. Noninfectious endocarditis, known as a Libman-Sacks lesion, in a 56-year-old woman with SLE, a heart murmur, and dyspnea on exertion. **A,** A parasternal long-axis view of the heart; a vegetation is identified (*arrow*) on the mitral valve. **B,** When color flow is superimposed on the valve, moderate to severe mitral regurgitation can be seen as a color jet entering the left atrium during systole. *LA,* left atrium; *LV,* left ventricle. (Courtesy Martin Goldman, MD, Mount Sinai School of Medicine.)

Musculoskeletal Chest Pain. Musculoskeletal chest pain, related to underlying pectoral, intercostal muscle, or costochondral joint inflammation, may also occur in SLE. Similar to pleuritis, the threat of a more malicious underlying cause of pain should prompt the clinician first to seek other causes before arriving at this more benign cause. Treatment with NSAIDs or acetaminophen is generally appropriate.

Pneumonia. Pneumonia is the third most common infection in patients with lupus, after skin and urinary tract infections.[44] Choice of antimicrobial coverage is determined by the severity of the infection and the degree of immunosuppression. For patients receiving long-term glucocorticoids or cyclophosphamide, coverage for organisms such as *Pseudomonas* and *Legionella* generally requires the use of a carbapenem or a fourth-generation cephalosporin in addition to either a respiratory fluoroquinolone or macrolide. There is no evidence to support the routine coverage for *P. jiroveci* in these patients.

Undifferentiated Dyspnea. Mitral valve insufficiency due to noninfectious vegetations, known as Libman-Sacks lesions, may cause a patient to experience dyspnea on exertion or, in rare severe cases, pulmonary edema (Fig. 118-2). Anemia, present in up to 50% of patients with SLE, may lead to a chief complaint of dyspnea. Both anemia of chronic disease and hemolytic anemia are common; hemolytic anemia is more typical in those also carrying aPL antibodies.[46] In cases of severe anemia recognized in the ED, a Coombs test can be diagnostic for immunologic hemolytic anemia. Other less common but noteworthy causes of shortness of breath in a patient with SLE include interstitial lung disease, lupus pneumonitis, diaphragmatic disease (so-called shrinking lung syndrome), and pulmonary hypertension.[47]

Musculoskeletal Presentations. Arthritis commonly afflicts those with SLE, and increasing severity of joint pain may be a marker of increasing disease activity or an SLE flare.[20] Arthritis or arthralgias are typically symmetrical and nonerosive (unlike rheumatoid arthritis) and may involve multiple joints. Arthritis is most commonly present in the hands, wrists, and knees but may be manifested in any joint. Aside from mild tenderness, the joints are often normal to physical examination and rarely experience deformity.[48] Uncommonly, septic arthritis may complicate SLE. In one large retrospective analysis of SLE-related hospitalizations, only 0.3% of admissions were for septic arthritis.[49] Possibly because of immunosuppressant use, including corticosteroids, *Salmonella* is an unusually frequent culprit organism that was isolated in 59% of cases in one study and most commonly found in the hip.[49] An

www.ketabpezeshki.com 66485457-66963820

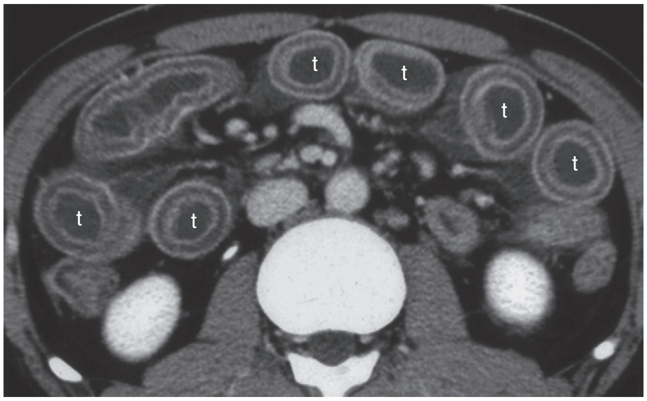


Figure 118-3. CT scan appearance of lupus enteritis. Diffuse bowel wall thickening (*t*) in a 20-year-old patient with lupus enteritis. (From Byun JY, et al: CT features of systemic lupus erythematosus in patients with acute abdominal pain: Emphasis on ischemic bowel disease. Radiology 211:203-209, 1999, with permission).

Figure 118-4. The malar or butterfly rash is the hallmark of SLE. (From Habif TP: Clinical Dermatology, 4th ed. New York, Mosby, 2004:592-606.)

Figure 118-5. Right ear of a patient suffering from chronic discoid lupus. Note pigment change and tissue destruction. (Courtesy Professor Gregory Raugi, University of Washington.)

isolated swollen joint is not typical of SLE and prompts consideration for infectious arthritis. If septic arthritis is suspected, diagnostic arthrocentesis is recommended. Empirical treatment with 1 g of vancomycin and 1 g of ceftriaxone will cover likely organisms, including *Salmonella*. Myalgias are common in SLE and may be an early marker of increasing disease activity for some patients. Generalized muscle pain is typical, but muscle weakness is uncharacteristic.[50] If muscle weakness is present, an underlying myositis or myopathy secondary to steroid use is considered.

Gastrointestinal Presentations. The most common gastrointestinal manifestation of SLE is oral ulceration, which occurs in nearly a third of patients with SLE. Treatment includes local symptom management (chlorhexidine mouthwashes, viscous lidocaine) combined with systemic therapy (hydroxychloroquine) in more severe or refractory cases.[51] Abdominal pain commonly complicates SLE.[52] The causes of abdominal pain, with the exception of lupus enteritis, are largely similar to those in patients without SLE, such as pancreatitis, gastroenteritis, and peptic ulcer disease.[53] Lupus enteritis (also known as mesenteric vasculitis) typically results in diffuse abdominal pain and is the most common cause of acute abdominal pain in SLE.[53,54] The abdominal pain itself may also be associated with nausea, vomiting, and nonbloody diarrhea.[55] Laboratory investigations, such as white blood cell count, hemoglobin level, platelet count, and erythrocyte sedimentation rate (ESR), are not helpful as they do not differ significantly between those with enteritis and those with abdominal pain due to other causes.[53] Although no "gold standard" for the diagnosis of lupus enteritis has been established, computed tomography (CT) is the most useful test to assess for this condition. Several CT scan findings are supportive, including bowel wall thickening (Fig. 118-3), engorgement of mesenteric vessels, and increased attenuation of mesenteric fat.[56]

When lupus enteritis is suspected, early pulse steroids, at a dose of 1 to 2 mg/kg of methylprednisolone per day, should be administered. Surgical consultation should be obtained in severe cases or when bowel necrosis has occurred. With aggressive medical therapy, which may also include cyclophosphamide, the need for surgical management is uncommon.[53] Other, less common gastrointestinal illnesses to which SLE patients are predisposed include protein-losing enteropathy and intestinal pseudo-obstruction.[57] Last, in assessing abdomen pain in patients with SLE, clinicians should be mindful of the effects of chronic steroid use and increased risk for both hollow viscus perforation and peptic ulcers, which may occur in the absence of traditional symptoms.

Dermatologic Presentations. The most characteristic cutaneous manifestation of SLE is the malar rash. The rash has a "butterfly" distribution of raised erythema over the bridge of the nose and malar eminences while sparing nose and nasal-labial folds (Fig. 118-4). The other most common skin lesion found in SLE is the discoid rash. Discoid lesions are circular and raised, scaly lesions that may be commonly found on the face, scalp, and ears, often in association with pigment change, alopecia, and severe scarring (Fig. 118-5). Cutaneous lupus may exist in isolation without systemic involvement. Mild cases of worsening cutaneous lupus are treated topically with 1% hydrocortisone cream. Moderate to severe cases are treated with topical calcineurin inhibitors or even systemic therapy (e.g., hydroxychloroquine) in consultation with the patient's internist or rheumatologist.[58] In nearly all cases of SLE, avoidance of sun exposure is advisable and will help minimize cutaneous disease.

Renal Disease. Renal disease develops in approximately a third of SLE patients.[44] Given a high prevalence and morbidity of renal disease as well as its tendency to carry few if any symptoms, screening urinalysis and assessment of renal function are prudent in nearly all but the most straightforward presentations of SLE to the ED. Lupus nephritis may cause a nephrotic-type disease, primarily characterized by proteinuria (>2 g/day) or a more nephritic

www.ketabpezeshki.com 66485457-66963820

picture with hematuria and increased creatinine concentration.[59] If worsening renal dysfunction is discovered, admission should be considered for hydration and escalation of therapy that may include both pulse steroids and cyclophosphamide.

Complications due to Medications

The remarkable improvements in life expectancy and disease control in SLE carry a cost. Chronic steroid use is associated with a well-known host of consequences, such as increased risk of CAD, osteoporosis, avascular necrosis, psychosis, hyperglycemia, and weight gain, among many others. More potent chemotherapeutic medications, such as cyclophosphamide, methotrexate, and azathioprine, may profoundly influence the patient's immune response and cause increased vulnerability to conventional and opportunistic infections. Chronic NSAID use for the musculoskeletal consequences of SLE may contribute to peptic ulcer disease, especially if they are coadministered with glucocorticoids. Therapy with antimalarials, such as hydroxychloroquine, is common and generally well tolerated; however, retinopathy and both QT interval prolongation and refractory ventricular arrhythmias have been associated with prolonged use.[60]

Diagnostic Strategies

Diagnostic tests will depend on the patient's presentation and whether a diagnosis of SLE is already established or being suspected for the first time.

Laboratory

In all but the most trivial presentations, order a serum creatinine concentration, urinalysis, and complete blood count because renal dysfunction, proteinuria, anemia, or thrombocytopenia may silently complicate SLE and be an important marker of increased disease activity. Leukocytosis, already a nonspecific finding, may be even less contributory in SLE patients taking glucocorticoids. When a new diagnosis of SLE is being entertained, other more specific immunologic assays, such as antinuclear antibody, anti-DNA, anti-Sm antibody, and aPL antibody, can be ordered in the ED with the intent of outpatient follow-up for evaluation of results. Of note, antinuclear antibody is present in nearly all SLE patients but is also present in 50% of people who do not have SLE. Thus, the absence of antinuclear antibody virtually excludes the diagnosis.[61] Unlike in other inflammatory disorders, C-reactive protein does not typically rise in response to increased disease activity in SLE. It does, however, rise in the setting of infection and thus may be a useful laboratory marker to distinguish between a flare and infection. The ESR has less of a role as it has been shown to be elevated in SLE patients experiencing either a flare or an infection.[62] Coagulation profile may show an elevated partial thromboplastin time (PTT) with a normal international normalized ratio (INR) in patients with SLE. In these cases, suspicion for comorbid APS should be raised (see later section on special considerations).

Radiology

Radiography. In SLE, a chest radiograph may point to diagnoses such as pleuritis (pleural effusion); pericardial disease (enlarged cardiac silhouette); pneumonia, including atypical and opportunistic infections (airspace disease); and pulmonary embolism (normal).

Computed Tomography. CT scanning may be of particular value in identifying lupus enteritis in the patient with abdominal pain, and CT pulmonary angiography has become the preferred imaging modality for pulmonary embolism. In both cases, attention to the presence or absence of lupus nephritis must be made to guide the appropriate and safe use of intravenous contrast material.

Special Tests

Bedside echocardiography may be carried out to evaluate the presence of pericardial fluid when pericarditis is suspected on the basis of clinical or electrocardiographic findings. A number of studies have documented the safety and accuracy of emergency physicians' identifying pericardial effusions with point-of-care ultrasound examination.[63]

Nuclear imaging may be helpful to assess for pulmonary embolism in patients with chronic kidney disease due to lupus nephritis.

Differential Diagnosis

In keeping with its highly varied presentations and permutations of disease activity, a number of other diseases may be confused with early SLE before its proper diagnosis. These include undifferentiated connective tissue disease, primary Sjögren's syndrome, primary APS, fibromyalgia with positive antinuclear antibody, idiopathic thrombocytopenic purpura, drug-induced lupus, and early rheumatoid arthritis.[64] For those with an established diagnosis of SLE, chief complaint–driven considerations for acute presentations are listed in Table 118-3.

Management

Nearly all noninfectious consequences of SLE are managed with introduction or escalation of immunomodulatory therapy. In the majority of disease states, a pulse dose of methylprednisolone at 1 to 2 mg/kg is appropriate. See Table 118-4 for additional therapeutic options for escalating disease severity.

For SLE patients presenting with infection who are receiving chronic steroid therapy, consider stress dose glucocorticoids, hydrocortisone 50 to 100 mg intravenously every 8 hours, in addition to appropriate antimicrobial coverage.

Table 118-3 Common or Specific Differential Considerations for Patients with SLE Based on Common Presentations, Comorbidities, or Complications

CHIEF COMPLAINT	CONDITION
Pleuritic chest pain	Pericarditis, pleuritis, pulmonary embolism, pneumonia, musculoskeletal chest wall pain
Delirium	Neuropsychiatric lupus, steroid psychosis
Leg swelling	Deep venous thrombosis, renal failure, right-sided heart failure (pulmonary embolism, pulmonary hypertension), protein-losing enteropathy
Shortness of breath	Pneumonia, anemia, pericarditis or pericardial effusion, pleuritis or pleural effusion, interstitial lung disease, shrinking lung syndrome
Pruritic or painful rash	Discoid SLE, drug reaction, sun exposure
Abdominal pain	Lupus enteritis, peptic ulcer disease, pancreatitis, pseudo-obstruction
Fever	Infection, increased disease activity
Arthritis	Arthralgias (lupus flare), osteoarthritis, septic arthritis, unrelated (gout, fibromyalgia)

www.ketabpezeshki.com 66485457-66963820

Table 118-4 Medications and Typical Dosing Range for Acute Exacerbations of SLE

MEDICATION	MEDICATION CLASS	TYPICAL STARTING DOSE AND ROUTE
Methylprednisolone	Glucocorticoid	1-2 mg/kg IV, once daily
Prednisone	Glucocorticoid	1-2 mg/kg, PO, once daily
Hydroxychloroquine	Antimalarial	200-400 mg PO, once daily
Cyclophosphamide	Alkylating agent	500-750 mg/m^2 IV, once
Azathioprine	Antimetabolite (purine analogue)	25-50 mg/day (IV or PO)

NSAIDs

Much of the pain and morbidity associated with SLE is related to inflammation that is amenable to treatment with NSAIDs. Ibuprofen 400 to 600 mg orally four times a day or naproxen 500 mg orally twice daily is useful for conditions such as pericarditis, pleuritis, arthralgias, myalgias, and fever. Use of NSAIDs in patients with chronic kidney disease due to lupus nephritis or a history of peptic ulcer disease is discouraged. In such patients, acetaminophen is used for mild to moderate pain, and narcotics are recommended for severe pain.

Dermatologic Treatment

In cases of isolated cutaneous findings, topical treatment with corticosteroids is preferable to systemic therapy. Topical therapy may be initiated with 1% hydrocortisone cream to the affected area. In cases in which higher potency topical steroids are necessary, a preparation of 0.05% betamethasone applied once daily to the affected area for 2 weeks is appropriate.[65]

Special Considerations

Antiphospholipid Syndrome

Present in nearly 40% of SLE patients,[66] the antiphospholipid syndrome (APS) is considered when patients both have a clinical history of thrombosis and are carriers of any one of a particular set of aPL antibodies directed against three specific serum proteins.[67] These antibodies include the anticardiolipin antibody, the misleadingly named lupus anticoagulant, and the anti–β_2-glycoprotein I antibody. The most thrombogenic of the antibodies is the lupus anticoagulant, with an odds ratio as high as 16 for the development of venous thromboembolism and 10 for arterial thrombosis (stroke).[32] In addition to being a strong risk factor for both venous and arterial thrombosis, the presence of APS in SLE has been shown to be an independent predictor of more severe disease[68] and to be associated with increased intensive care unit mortality.[44] Whether it is present in the context of SLE or independently, APS is an important cause of morbidity and mortality due to thrombosis.[32,69]

Clinical Features. APS may present with any number of clinical features (Box 118-1), typically related to thrombosis or thromboembolism. A small subset of those with APS may present with multiple thrombotic sites and organ failures simultaneously. This condition is known as catastrophic APS.

Box 118-1 Common Clinical Features of the Antiphospholipid Syndrome

Venous thrombosis
Arterial thrombosis (including stroke and transient ischemic attack)
Recurrent miscarriage
Livedo reticularis
Thrombocytopenia

Diagnostic Strategies. Assays to detect and to measure the presence of aPL antibodies are not generally available in a timely fashion and are impractical for use in the ED setting. However, there are two laboratory findings supportive of APS that may be useful or accidentally discovered during an ED workup:

1. A spuriously elevated PTT in the setting of a normal PT/INR may reflect APS. This in vitro finding, which contradicts the actual in vivo hypercoagulable state of the APS patient, is due to interference of the coagulation study by aPL antibodies. Confirmation of the presence of the interfering antibody is done by carrying out a mixing study. A mixing study requires repeating the PTT with a mixture of the patient's blood and a 50% contribution from normal, control serum. In the presence of an inhibiting antibody, the PTT will remain elevated. If, however, the PTT was elevated for other reasons (most commonly heparin), the addition of normal clotting factors from the control serum will restore the PTT to normal.
2. The VDRL assay to test for syphilis contains cardiolipin and thus will commonly be falsely positive in patients with anticardiolipin antibodies or APS.

Treatment. For acute thrombotic events, anticoagulation with either unfractionated or low-molecular-weight heparin is generally indicated. After an initial thrombotic event, anticoagulation with vitamin K antagonists to maintain an INR between 2.0 and 3.0 is recommended. For patients with arterial thrombotic events (e.g., stroke) or recurrent venous thromboembolic events, anticoagulation is recommended indefinitely.[70] For patients suffering catastrophic APS, in addition to anticoagulation and glucocorticoids, intravenous immune globulin (IVIG), cyclophosphamide, and plasma exchange may all be indicated. Despite aggressive treatment, mortality for catastrophic APS approaches 50%.[71]

Drug-Induced Lupus

Drug-induced lupus is an SLE-like self-resolving illness characterized by arthralgias, myalgias, rash, and serositis; it may be brought on by as many as 80 different medications.[72] Notably, the malar rash and major organ involvement are rare in this condition.[73] In drug-induced lupus, antibodies against the body's own histone proteins are common and purported to be a major mechanism of disease.[74] Although the list of potentially implicated medications is long, those agents with most evidence for causing drug-induced lupus are summarized in Box 118-2. The diagnosis is typically clinical and confirmed by resolution of symptoms with the withdrawal of the offending medication. In addition to cessation of the culprit drug, NSAIDs or steroids for symptom control are indicated.

Disposition

Dispositions for the patient with SLE will vary significantly by clinical presentations. For patients with non–life-threatening presentations, such as increased musculoskeletal symptom burden, simple headache, or cutaneous reactions, discharge with appropriate follow-up is usually appropriate. However, patients with poor insight into their disease, significant comorbidities, or weak social or home supports may require admission.

With disorders characteristic of SLE flares (e.g., progressive lupus nephritis, lupus enteritis), new thrombotic events, and

www.ketabpezeshki.com 66485457-66963820

infectious complications due to immunosuppression, the patient may need admission for initiation of systemic therapy (e.g., glucocorticoids, anticoagulation, antibiotics) and evaluation of response or deterioration. Admission to the intensive care unit is considered for those who, despite initial resuscitation, suffer progressive circulatory or respiratory derangement. Because of the high incidence of CAD in patients with SLE, patients with undifferentiated chest pain who have acute coronary syndrome ruled out in the ED should receive an expedited evaluation with provocative testing (e.g., exercise stress test) in a chest pain unit or on an outpatient basis. If an outpatient workup is pursued, prescribe daily aspirin therapy. The complexity of SLE often challenges physicians not specialized in its many nuances and intricate pathophysiologic changes. Reasons for rheumatologic referral of patients with SLE are presented in Box 118-3.[75]

VASCULITIDES

Perspective

The vasculitides are a heterogeneous group of disorders characterized by inflammatory damage of blood vessels. Arteries and veins of all sizes and their tributaries can be affected to varying degrees. Presentations can range from benign and self-limited to serious and life-threatening. Diagnosis can be challenging as early vasculitis syndromes are nonspecific and can mimic other infectious, inflammatory, or neoplastic conditions. Approximately 1 in 2000 adults are affected by some form of vasculitis, with a higher incidence in adults 65 to 74 years of age.[76] In the United States, the most common vasculitis syndromes are giant cell arteritis, Wegener's granulomatosis, and microscopic polyangiitis.[77]

Box 118-2 Drugs Definitively Implicated in Causing Drug-Induced Lupus[72]

Procainamide	Isoniazid
Hydralazine	Quinidine
Methyldopa	Minocycline
Chlorpromazine	

Box 118-3 Reasons for Rheumatologic Referral for Patients with SLE

- To confirm a diagnosis
- To assess disease activity and severity
- To provide general disease management
- To manage uncontrolled disease
- To manage organ involvement or life-threatening disease
- To manage or prevent treatment toxicities
- Special circumstances: antiphospholipid syndrome, pregnancy, surgery

Modified from Guidelines for referral and management of systemic lupus erythematosus in adults. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. Arthritis Rheum 42:1785-1796, 1999.

Principles of Disease

The cause of most vasculitis syndromes is unknown. Most cases are believed to result from immune complex deposition in blood vessel walls, prompting a complement-mediated inflammatory reaction. This results in vessel wall damage and necrosis, leading to stenosis, occlusion, and subsequent end-organ ischemia. The clinical manifestations are determined predominantly by the size and distribution of blood vessels involved along with the histologic subtype of inflammation.

The most recognized system for classification of the primary vasculitis is by the size of blood vessel involved (Table 118-5). Large-vessel vasculitis involves the aorta and its immediate branches and in some cases the corresponding vessels in the venous system. Medium-vessel disease involves the macrovasculature downstream from the main aortic branches. Small-vessel vasculitis involves capillaries, venules, arterioles, and glomeruli.

Clinical Features

Virtually all vasculitides involve some degree of constitutional symptoms, including fever, malaise, weight loss, and arthralgias. There is substantial overlap in the signs and symptoms associated with the large-, medium-, or small-vessel disorders. Practically, it is more useful to classify the vasculitides according to the pattern of organ system involvement or exposure most evident on presentation: vasculitis presenting with large-vessel occlusive symptoms, vasculitis typified by pulmonary-renal manifestations, vasculitis with characteristic cutaneous manifestations, and syndromes associated with environmental or foreign antigen exposure. This approach assists in refining the differential diagnosis for a given constellation of symptoms and directing initial therapy while awaiting the results of confirmatory tests or tissue biopsy, which are in most cases not readily available in the ED.

Table 118-5 Primary and Secondary Vasculitis: Classification and Associated Features

Predominantly Large Vessel		*Predominantly Medium Vessel*		*Predominantly Small Vessel*	
EXAMPLES	COMMON FEATURES	EXAMPLES	COMMON FEATURES	EXAMPLES	COMMON FEATURES
Giant cell arteritis Takayasu's arteritis	Asymmetrical blood pressures Claudication Aortic disease Renovascular hypertension	Polyarteritis nodosa Buerger's disease Kawasaki disease	Cutaneous nodules Ulcers Mononeuritis multiplex Digital gangrene Microaneurysms Renovascular hypertension	Goodpasture's disease Wegener's granulomatosis Microscopic polyangiitis Churg-Strauss disease Behçet's disease Henoch-Schönlein purpura	Alveolar hemorrhage Glomerulonephritis Purpura Vesiculobullous lesions Uveitis, episcleritis, scleritis
Secondary Forms of Vasculitis					
Connective tissue disorders (rheumatoid vasculitis, lupus erythematous, Sjögren's syndrome, others) Infection (hepatitis B or C virus, human immunodeficiency virus) Inflammatory bowel disease Hypersensitivity (drug induced, others)					

www.ketabpezeshki.com 66485457-66963820

Vasculitis Presenting with Large-Vessel Occlusive Symptoms

Giant Cell Arteritis. Giant cell arteritis (GCA), also known as temporal arteritis, is a systemic vasculitis that affects medium-sized and large vessels. The most recognized symptoms are caused by occlusion of the superficial branches of the carotid artery, although systemic medium- and large-vessel disease involving the carotid, subclavian, aortic, vertebral, and iliac vessels may also be present. The most feared complication of GCA is irreversible visual loss, occurring in up to one third of patients.[78] Early treatment can help prevent this complication, and thus the diagnosis is an important consideration in patients older than 50 years presenting with any combination of constitutional symptoms, headache, visual changes, and jaw claudication.

The incidence of GCA has been increasing steadily during the past 20 to 40 years.[79] The syndrome is tightly coupled to age, with a mean age at onset of 70 years and a range of 50 to 90 years.[80] The incidence increases sharply after the age of 50 years, with an estimated incidence of 33 per 100,000 patients. The disease is twice as common in women than in men, and smoking increases the risk of GCA sixfold in women.

GCA is frequently associated with a spectrum of nonspecific symptoms, such as fever, weight loss, and fatigue. Common presenting complaints include headache, visual symptoms, jaw claudication, and myalgias and associated polymyalgia rheumatica.[80] Headache, the most common presenting symptom, occurs in three quarters of patients with GCA.[81] Although it is classically located in the temporal area and in association with tenderness along the superficial temporal artery, no specific pattern of headache location or severity is predictive of the temporal arteritis, and in untreated patients the headache may improve or disappear, even though active disease is still present.[80,82-84] The presence of tenderness, prominence, or beading of the superficial temporal artery on physical examination is associated with GCA, whereas the absence of any temporal artery abnormality is associated with a modest decrease in the likelihood of disease.[81] Changes in visual acuity occur as a result of occlusive arteritis of the posterior ciliary artery or less commonly retinal artery occlusion. Visual loss may occur in one or both eyes and at times be painless; interruptions in acuity may be partial or complete, transient or permanent.[78,85] The visual deficit is often profound, with 80% of patients unable to appreciate hand waving.[78] Funduscopic findings in patients with acute visual loss include optic disk pallor and edema, in keeping with ischemic optic neuritis. Complete visual loss that is present for more than a few hours is usually irreversible.[78] Diplopia may also occur as a result of ischemic ophthalmoplegia; oculomotor nerve lesions typically spare the pupil.[82]

Thoracic aortic aneurysms are 17 times more likely to occur in patients with GCA compared with age-matched controls.[86] The vertebral-basilar arteries are affected in 75 to 100% of patients, leading to signs of vertebrobasilar insufficiency, including gait disturbance, dizziness or vertigo, and vomiting.[87] The diagnosis of GCA should be considered in elders with signs of vertebrobasilar insufficiency in conjunction with constitutional symptoms and an elevated ESR.

In the presence of symptoms consistent with occlusion of superficial branches of the carotid artery, the diagnosis is usually straightforward. The American College of Rheumatology has developed a scoring system that lends equal weight to each of five diagnostic criteria (Box 118-4).[88] Patients with a score of ≤2 require temporal artery biopsy for the diagnosis to be confirmed; in patients with a score of ≥3, a biopsy adds little information beyond clinical and laboratory appraisal.[89] An ESR of ≥80 mm/hr is common, although approximately 20% of patients with an ESR of <50 mm/hr will go on to have biopsy-proven temporal arteritis. An elevated C-reactive protein level has improved sensitivity over ESR and may actually be the preferred diagnostic test, with a reported sensitivity for GCA of 97.5%.[90] The gold standard for diagnosis remains temporal artery biopsy, with established sensitivity of 90 to 95%.[91] Bilateral biopsies should be considered in patients for whom clinical suspicion is high and initial findings on biopsy are normal. The role of color duplex ultrasonography in the diagnosis of temporal arteritis remains controversial; one study showed no benefit in establishing the diagnosis when it was added to a carefully performed physical examination.[92] High-resolution magnetic resonance imaging may be used alone or as a diagnostic adjunct to biopsy in atypical or challenging cases.[93]

Box 118-4 American College of Rheumatology Classification Criteria for Giant Cell Arteritis

Age ≥ 50 years
New-onset localized headache
Temporal artery tenderness or decreased temporal artery pulse
Erythrocyte sedimentation rate ≥ 50 mm/hr
Abnormal artery biopsy specimen characterized by mononuclear infiltration or granulomatous inflammation

Modified from Hunder GG, et al: The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 33:1125, 1990.

Given the high stakes and morbidity associated with missed or delayed diagnosis, initiate treatment for temporal arteritis as soon as the diagnosis is considered to prevent permanent visual loss. The mainstay of treatment remains high-dose corticosteroids, initiated in the ED and continued until the diagnosis can be confirmed or excluded on subsequent biopsy. A typical initial regimen is oral prednisone 60 to 100 mg daily (or 1 mg/kg) with a temporal biopsy scheduled within 1 week of presentation. More than half of patients treated within 24 hours of presentation will achieve some recovery, compared with only 6% when treatment is delayed beyond this interval.[94] Oral corticosteroids do not alter the sensitivity of temporal artery biopsy when it is performed within 2 weeks of initiation of therapy.[95] Some authors recommend switching to intravenous corticosteroid treatment for 3 days should vision continue to deteriorate despite timely initiation of oral prednisone.[96] Acetylsalicylic acid may be useful as an adjunct to decrease ischemic complications.[97]

Takayasu's Arteritis. Takayasu's arteritis, also known as pulseless disease or occlusive thromboaortopathy, is a systemic large-vessel vasculitis of unknown etiology that primarily affects young women of Japanese and Southeast Asian descent. It is characterized by granulomatous inflammation of the aorta and its branches, leading to massive intramural fibrosis and symptoms of large-vessel stenosis, thrombosis, and aneurysm.

Takayasu's arteritis is a rare disorder worldwide, with a reported incidence of 0.2 to 2.6 cases per million in western Europe and North America, although this number is much higher in Japan.[98] The disease is eight times more common in women than in men; symptoms are first manifested between the ages of 15 and 25 years.[98] The diagnosis should be considered in women younger than 40 years who present with signs and symptoms of large-vessel occlusion, including upper limb claudication, decreased or asymmetrical pulses, and unexplained hypertension accompanied by constitutional symptoms such as fever and weight loss.

The most common presenting symptoms related to vascular occlusion are claudication (most commonly of the upper extremity, 35%), reduced or absent pulse (25%), hypertension (most often associated with renal artery stenosis, 20%), carotidynia (20%), lightheadedness (20%), and asymmetrical arm blood pressures (15%).[99] Cerebrovascular ischemia, stroke, aortic insufficiency, and visual symptoms are present in 10% of patients.[99] Approximately 80% of patients will have an identifiable bruit on physical examination, and 50% will go on to have asymmetrical

www.ketabpezeshki.com 66485457-66963820

Table 118-6 Comparison of the Common Features of Wegener's Granulomatosis, Microscopic Polyangiitis, Goodpasture's Syndrome, and Churg-Strauss Syndrome

FEATURE	WEGENER'S GRANULOMATOSIS*	MICROSCOPIC POLYANGIITIS*	GOODPASTURE'S SYNDROME	CHURG-STRAUSS SYNDROME*	COMMENTS
Pulmonary infiltrates or nodules	+++	++	+++	+++	Asthma and eosinophilia in CSS
Alveolar hemorrhage	++	++	+++	+	
Glomerulonephritis	+++	+++	++	++	Progressive renal failure uncommon in CSS
Upper airway disease	+++	+	–	++	ENT disease favors WG
Purpura	+	+++	+	++	
Peripheral nervous system involvement	++	+	–	+++	Often a prominent feature of CSS
Central nervous system involvement	+	+	–	++	

Data from Firestein GS: Kelley's Textbook of Rheumatology, 8th ed. Philadelphia, WB Saunders, 2008.
*ANCA-associated syndromes.
CSS, Churg-Strauss syndrome; *ENT,* ear, nose, and throat; *WG,* Wegener's granulomatosis.

blood pressures.[99] One third of patients will have cardiac complications, including aortic insufficiency and regurgitation, myocarditis, congestive heart failure, and cardiac ischemia from coronary artery aneurysm.[99] Patients presenting after the age of 40 years or without signs of vascular occlusion pose a diagnostic challenge; only nonspecific constitutional symptoms or fever of unknown origin may initially be manifested, leading to diagnostic and therapeutic delays.

Although an elevated ESR (>80 mm/hr) is suggestive of Takayasu's arteritis, the majority of laboratory investigations are nonspecific, and the diagnosis is almost always secured on the basis of clinical assessment and diagnostic imaging. Patients younger than 40 years who present with symptoms of large-vessel occlusive disease (bruit, absent pulse, claudication) are candidates for axial imaging of the aorta and its major branches; options include CT angiography and magnetic resonance angiography, both of which have largely replaced digital subtraction angiography as the imaging method of choice.[100] Once a diagnosis of Takayasu's arteritis is made, oral corticosteroids (e.g., 0.5 to 1 mg/kg prednisone daily) are indicated and continued for 4 to 12 weeks, followed by a gradual taper. It is a self-limited disorder in 20% of patients; the remainder will go on to have a relapsing-remitting or chronic progressive course requiring long-term corticosteroids.[101] Steroid-sparing agents such as azathioprine, cyclophosphamide, and tumor necrosis factor inhibitors may be added in patients who relapse. Patients should be observed closely by a rheumatologist and vascular surgeon; those who do not respond to corticosteroids may benefit from surgical reperfusion, including bypass grafting and percutaneous transluminal angioplasty. Indications for admission include signs and symptoms of acute end-organ ischemia, aortic insufficiency, myocarditis, and decompensated congestive heart failure. The most common causes of death are congestive heart failure, renal failure, and infectious complications.[102]

Vasculitis Typified by Pulmonary-Renal Manifestations

Vasculitis syndromes in this category are characterized by a predominance of pulmonary and renal manifestations, including dyspnea, cough, pulmonary infiltrates, and renal insufficiency secondary to glomerulonephritis, in addition to a variety of systemic symptoms. Wegener's granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome share a strong association with the presence of antineutrophil cytoplasmic antibodies (ANCA) of various subtypes, including cytoplasmic staining (c-ANCA) and perinuclear staining (p-ANCA), measured in the blood by enzyme-linked immunosorbent assay or direct immunofluorescence.[103] Whether ANCA are involved in pathogenesis or are simply markers of disease is unclear. The absence of ANCA does not rule out an ANCA-associated vasculitis syndrome because between 20 and 50% will have negative assays.[103]

A comparison of the common presenting features of Wegener's granulomatosis, microscopic polyangiitis, Goodpasture's syndrome, and Churg-Strauss syndrome is shown in Table 118-6.

Wegener's Granulomatosis. Wegener's granulomatosis is a c-ANCA–associated systemic necrotizing vasculitis of small and medium-sized blood vessels with a predilection for the upper and lower respiratory tracts and kidneys. The constellation of upper respiratory, pulmonary, and renal disease in patients with constitutional symptoms suggests Wegener's granulomatosis. In the absence of pulmonary or renal symptoms, the diagnosis is extremely challenging and often missed. Wegener's granulomatosis is more common in white individuals but otherwise shows no specific pattern of distribution for age, sex, or geography. The annual incidence is estimated to be 3 per 100,000 people.[104]

Constitutional symptoms including fever, malaise, and weight loss are often evident on initial presentation. Upper airway disease is the most common presenting symptom of Wegener's granulomatosis, with 90% of patients developing upper respiratory tract symptoms in some form.[105] Upper airway manifestations include serous otitis media with or without suppurative infection, hearing loss, sinusitis, nasal mucosal ulcerations and septal perforation, epistaxis, and laryngotracheal disease.[105] Subglottic stenosis is the most common laryngotracheal lesion, present in about 16% of patients, the severity of which can range in presentation from mild dyspnea to acute airway obstruction and respiratory extremis.[105] Nearly 50% of pediatric and adolescent patients will have some degree of subglottic stenosis, with implications for airway management. Lower respiratory symptoms include cough, dyspnea, pleuritis, and hemoptysis. Radiographic studies may demonstrate pulmonary infiltrates and nodules, although the severity of radiographic findings does not always correlate well with symptom severity (Fig. 118-6). A minority of patients present with diffuse alveolar hemorrhage, which has an associated mortality of approximately 50%.[106] Renal embarrassment tends to be a later finding, developing in a subset of patients with generalized disease. Once progressive renal failure has developed, it may evolve rapidly during days to weeks, leading to end-stage renal disease that, if left

www.ketabpezeshki.com 66485457-66963820

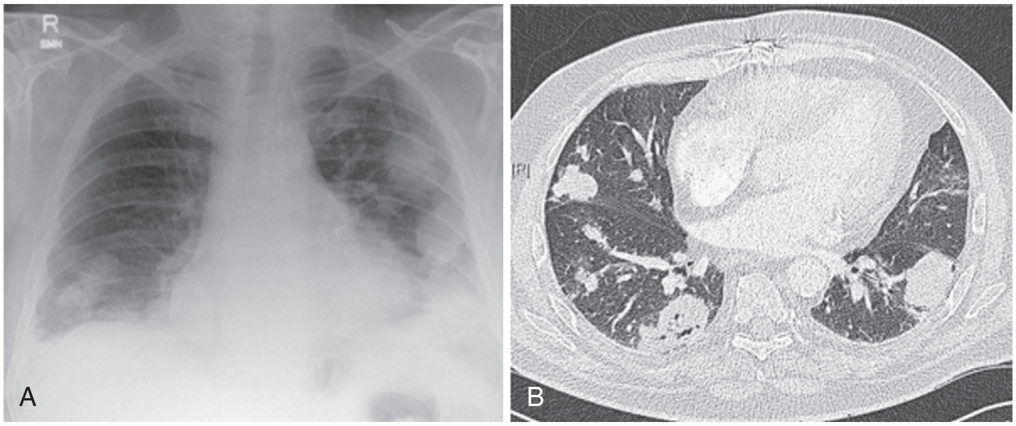


Figure 118-6. **A,** Multiple intrapulmonary nodules on a chest radiograph of a patient with Wegener's granulomatosis. **B,** Pulmonary nodules seen on CT imaging. (From Adam A, Dixon AK: Grainger & Allison's Diagnostic Radiology, 5th ed. Philadelphia, Churchill Livingstone, 2008.)

untreated, is associated with a mean survival of 5 months.[107] Chronic renal insufficiency can develop despite appropriate treatment, with a subset of patients requiring dialysis or renal transplantation.[105]

The list of associated symptoms in Wegener's granulomatosis is myriad and speaks to the systemic nature of the disease. Ophthalmologic (scleritis, episcleritis, uveitis), cutaneous (palpable purpura, subcutaneous nodules, ulcers), neurologic (mononeuropathy and polyneuropathy, cerebral vasculitis, cerebral hemorrhage, or thrombosis), and cardiac (pericarditis, myocarditis) disease may be present to varied degrees.

ED management is directed first toward life-threatening pulmonary hemorrhage and sequelae from acute or decompensated chronic renal insufficiency. The combination of diffuse alveolar hemorrhage and subglottic stenosis represents a "double hit" difficult airway, requiring extreme caution during endotracheal intubation. Although a large endotracheal tube is preferred for the management of massive hemoptysis, selection of a smaller tube size may be required to bypass a narrow subglottic corridor. Fiberoptic intubation through an intubating laryngeal mask airway has been advocated.[108] Combination therapy with corticosteroids and cyclophosphamide is considered the current standard of care for patients with acute flares and has dramatically changed the disease prognosis. Before the use of steroids, 1-year mortality approached 90%; combination therapy with corticosteroids and cyclophosphamide has improved the 5-year survival to nearly 90%, with the majority of patients achieving remission.[105,109,110] Methotrexate plus corticosteroids may be used instead of cyclophosphamide in less severe presentations involving systemic disease.[110] Patients presenting with new or suspected Wegener's granulomatosis and those with severe disease require admission for high-dose intravenous dual-agent therapy. The diagnosis is typically confirmed by open lung biopsy.[105,111] Patients who present with new respiratory symptoms or infiltrates on the chest film should probably be hospitalized and treated for infection until it is proven otherwise, given the morbidity associated with pneumonia in an immunocompromised host.

Goodpasture's Syndrome. Goodpasture's syndrome describes the clinical triad of glomerulonephritis, pulmonary hemorrhage, and circulating anti–glomerular basement membrane (GBM) antibodies. The syndrome is distinct from Goodpasture's disease, which consists of glomerulonephritis and anti-GBM antibodies without pulmonary hemorrhage. Goodpasture's syndrome is not associated with ANCA; anti-GBM autoantibodies target type IV collagen found in the basement membranes of glomeruli and pulmonary alveoli, causing autoimmune damage through a type II hypersensitivity reaction.[112] The disease can affect people of all ages, with white individuals more commonly affected.[112] The incidence is bimodal; one peak occurs in 20- to 30-year-old men and a second in 50- to 70-year-olds of both sexes. The incidence is believed to be about 1 case per 2 million individuals.[113]

There is substantial variation in the presentation of patients with anti-GBM disease. Pulmonary or renal symptoms may exist alone or in combination, although the two are most often present together. Fever, malaise, and weight loss are common early symptoms. Pulmonary symptoms range from dyspnea and cough to hypoxemia and frank pulmonary hemorrhage, which can be massive and life-threatening. Chest radiographic findings may be normal or demonstrate hilar pulmonary infiltrates sparing the apices and costophrenic angles. Renal failure can be insidious or be manifested as rapidly progressive glomerulonephritis with acute kidney injury and volume overload. Urinalysis shows characteristic signs of acute glomerulonephritis, including hematuria, proteinuria, and red cell casts. Definitive diagnosis is made by lung or renal biopsy demonstrating linear deposition of anti-GBM antibodies in the alveolar or glomerular basement membranes, respectively.[112]

Initial management of patients with massive pulmonary hemorrhage is focused on securing a definitive airway and addressing hemodynamic instability. Bronchoscopy or chest radiography can be used to identify the source of hemorrhage, and selective intubation of the contralateral mainstem bronchus or use of a double-lumen endotracheal tube and ventilating with the affected lung in the dependent position may improve oxygenation. High-dose methylprednisone (10-15 mg/kg) and cyclophosphamide are the mainstays of immune suppressive therapy. Therapeutic plasma exchange can be used to decrease the level of circulating anti-GBM antibodies during acute presentations.[114] Patients who have end-stage renal disease may be candidates for renal transplantation, assuming anti-GBM antibodies are undetectable with treatment, else the disease may recur in the transplanted graft.[115] The prognosis has improved in recent years owing in part to the more aggressive use of therapeutic plasma exchange.

Microscopic Polyangiitis. Microscopic polyangiitis was first recognized in a subset of polyarteritis nodosa patients who presented with segmental glomerulonephritis.[116] This systemic small-vessel vasculitis is the most common cause of the pulmonary-renal syndrome, leading to renal failure and pulmonary hemorrhage, the two most clinically relevant features of microscopic polyangiitis. The disease affects men and women equally and typically is manifested in the fourth or fifth decade of life, although it may occur at virtually any age.[117] The annual incidence in the United States is approximately 3.8 cases per 1 million population. The characteristic presentation of rapidly progressive renal failure in

www.ketabpezeshki.com 66485457-66963820

the context of pulmonary alveolar hemorrhage and systemic symptoms occurs in the minority of patients; in many cases the disease presentation is protean, consisting largely of renal insufficiency and constitutional symptoms such as fever, weight loss, and malaise.

Glomerulonephritis with subsequent renal insufficiency is a nearly universal finding in microscopic polyangiitis, and renal failure can be acute and rapidly progressive or chronic and insidious; 25 to 45% of patients require dialysis at some point during the course of the disease.[118,119] The specific renal disease is that of necrotizing glomerulonephritis including elevated serum creatinine and blood urea nitrogen concentrations and a urinalysis demonstrating red cell casts, hematuria, and proteinuria. Pulmonary disease is present in up to 50% of patients, and diffuse alveolar hemorrhage is present in about 12%.[117] Respiratory symptoms range from cough, dyspnea, and pulmonary fibrosis to massive diffuse alveolar hemorrhage requiring active and aggressive resuscitation and airway management. Peripheral neuropathy in the form of mononeuritis multiplex is present in up to 60% of cases. Skin manifestations are common, with about 50% of patients having palpable purpura.[119,120]

It can be difficult to distinguish microscopic polyangiitis from other ANCA-positive syndromes, including Wegener's granulomatosis and Churg-Strauss syndrome, on clinical grounds alone. Microscopic polyangiitis and Wegener's granulomatosis probably exist on a spectrum of illness, and it is usually not required to distinguish between the two in the emergency setting to direct management. The diagnosis is typically secured by tissue biopsy of the lung, kidney, or skin, with demonstration of pulmonary capillaritis, necrotizing glomerulonephritis, or leukoclastic vasculitis, respectively.[120] The priority in patients presenting with acute or decompensated chronic renal insufficiency is to identify and to manage immediate threats, including volume overload, electrolyte disturbances, and refractory acidosis. Admission for renal optimization, intravenous administration of steroids, and possibly dialysis is often required. Airway management is the priority in those presenting with diffuse alveolar hemorrhage, and a difficult intubation should be anticipated. In the presence of serious pulmonary and renal disease, a combination of high-dose glucocorticoid and cyclophosphamide is the treatment of choice, demonstrating superiority over glucocorticoid alone.[121] Mortality in microscopic polyangiitis is approximately 30% during 7 years; morbidity and mortality are the highest in patients with a heavy burden of renal, cardiovascular, or neurologic disease.[121] Plasmapheresis and IVIG are options for refractory cases. Remission is much more common than in Wegener's granulomatosis and is achieved in about 90% of patients, although up to one third will experience flares after remission.[122]

Churg-Strauss Syndrome. Churg-Strauss syndrome, also known as allergic granulomatosis, is an autoimmune vasculitis of medium-sized and small vessels associated with asthma and eosinophilia. The etiology is unknown, although there is a strong association with allergy and atopy. The mean age at onset is typically in the fourth decade of life; men are affected more often than women are. The annual incidence is approximately 2.4 cases per 1 million individuals.[123]

Patients with Churg-Strauss syndrome may present in three distinct stages, although there may be considerable overlap and variance. Most patients with Churg-Strauss syndrome have asthma and allergic rhinitis several years before the onset of vasculitis. Over time, asthma symptoms may actually improve as the vasculitic stage of the disease sets in.[120] The pattern of medium-sized vessels involved determines the clinical picture of the vasculitic phase, although pulmonary, renal, and neurologic symptoms are common. Pulmonary infiltrates, pleural effusion, and alveolar hemorrhage may be seen during the prodromal or vasculitic stage.[120] Renal involvement is less common compared with other ANCA-positive vasculitis syndromes and may preferentially affect the lower urinary tract and prostate gland, leading to obstructive uropathy.[124] Cardiac manifestations, including restrictive pericarditis and cardiomyopathy leading to congestive heart failure, are more common in Churg-Strauss syndrome compared with Wegener's granulomatosis and microscopic polyangiitis.[125] Mononeuritis multiplex, asymmetrical neuropathy, and cranial neuropathies are the most frequently observed neurologic symptoms, seen in up to 80% of patients.[123] Gastrointestinal symptoms include infarction, perforation, and hemorrhage secondary to infiltration of the small bowel or stomach.

Laboratory investigation demonstrates a persistently elevated eosinophil count (>1500 cells/mm^3), although this does not correlate well with the presence of active disease. Myeloperoxidase-ANCA antibodies are seen in about 40% of cases.[126] Pulmonary infiltrates are typically patchy and transient in nature (Löffler's syndrome). The diagnosis of Churg-Strauss syndrome is made by a combination of clinical and histologic features; evidence of necrotizing vasculitis or extravascular granulomas on skin or lung biopsy in conjunction with eosinophilia, asthma, and allergy is highly suggestive of the disease.

Corticosteroids are the mainstay of treatment, although immunomodulating agents such as cyclophosphamide may be added to achieve remission in cases complicated by cardiac, renal, or gastrointestinal involvement.[110,127] The overall survival for patients with Churg-Strauss syndrome approaches 80%, with an increased relative risk of death predicted by the presence of renal and gastrointestinal symptoms.[128]

Vasculitis with Characteristic Cutaneous Manifestations

Cutaneous vasculitis involves inflammation of the blood vessels of the skin. The diseases listed here are associated with cutaneous manifestations that are often characteristic and an important element of disease recognition in the ED. Constitutional signs and symptoms of systemic multisystem disease may also be present.

Erythema Nodosum. Erythema nodosum, a vasculitis of the venules and veins of the skin, is characterized by tender, subcutaneous nodules on the tibial surfaces of the lower legs. Erythema nodosum is presumed to be a hypersensitivity response to systemic diseases or drug therapy, although no clear precipitant can be identified in 30 to 50% of cases.[129] Peak incidence occurs in the spring or fall months among 18- to 34-year-olds, with a male-to-female ratio of approximately 1:4.

The prodromal stage of erythema nodosum consists of nonspecific constitutional symptoms, fever, malaise, and myalgias. The distribution of subcutaneous nodules favors the lower extremities, although lesions may be appreciated on the forearm, trunk, and thigh (Fig. 118-7). The nodules tend to be erythematous, well circumscribed, and exquisitely tender to touch and develop a blue hue as they resolve. Arthralgias may be present in conjunction with or before the cutaneous eruption.

Viral upper respiratory tract infections, streptococcal infection, tuberculosis, and sarcoidosis are common precipitants. Drugs associated with erythema nodosum include penicillins, sulfonamides, oral contraceptive medication, and phenytoin.[129] Less common associations include autoimmune conditions, such as inflammatory bowel disease and SLE; histoplasmosis; *Yersinia, Salmonella,* and *Chlamydia* infections; coccidioidomycosis; and psittacosis.

Management of erythema nodosum is generally supportive and directed toward symptom control and treatment or elimination of the underlying cause. Cutaneous nodules secondary to infection resolve within 6 to 7 weeks; in contrast, 30% of idiopathic cases may persist beyond 6 months. NSAIDs may be useful for

www.ketabpezeshki.com 66485457-66963820

Figure 118-7. Tender subcutaneous nodules associated with erythema nodosum. (From Kliegman R: Nelson Textbook of Pediatrics, 18th ed. Philadelphia, WB Saunders, 2007.)

Figure 118-8. Purpuric lesions associated with Henoch-Schönlein purpura, some of which have coalesced and undergone central necrosis. (From Habif TP: Clinical Dermatology, 5th ed. New York, Mosby, 2009.)

control of arthralgias; corticosteroids and colchicine are reserved for the management of protracted or refractory disease.

Henoch-Schönlein Purpura. Henoch-Schönlein purpura is a small-vessel vasculitis characterized by palpable purpura and gastrointestinal and renal manifestations associated with immunoglobulin A immune complex deposition in blood vessels. The 1990 American College of Rheumatology criteria for Henoch-Schönlein purpura include the presence of two or more of the following: age at onset younger than 20 years, palpable purpura, bowel angina, and vessel wall granulocytes on biopsy (sensitivity of 87.1%, specificity of 87.7%).[130] Although the disease can affect adults, it is most commonly seen in children younger than 5 years.

Henoch-Schönlein purpura usually is manifested 1 to 2 weeks after a viral upper respiratory tract infection with a triad of palpable purpura, arthralgias, and abdominal pain. Purpuric lesions cluster in dependent regions with a predilection for the legs and buttocks (Fig. 118-8). Colicky abdominal pain and bloody stools can occur secondary to gastrointestinal vasculitis. A rare complication of Henoch-Schönlein purpura in children is enteroenteral intussusception (ileoileal, jejunojejunal, jejunoileal), which may be associated with severe abdominal pain, lethargy, bloody diarrhea, and signs of obstruction or perforation.[131] Glomerulonephritis is typically mild and may be manifested as hematuria, red cell casts on urinalysis, and azotemia.

Management in mild disease is generally supportive, and symptoms can intermittently recur for several weeks. NSAIDs control arthralgias in most cases but are avoided if renal impairment is present. Glomerulonephritis is treated more aggressively, with a combination of corticosteroids and cyclophosphamide, azathioprine, or mycophenolate mofetil, and generally demonstrates full resolution with time. Enteroenteral intussusception can be difficult to diagnose with standard approaches (ultrasonography, air-contrast enema), and if the index of suspicion is high, patients should be assessed by a pediatric general surgeon.

Polyarteritis Nodosa. Polyarteritis nodosa is a necrotizing vasculitis of unknown etiology affecting small and medium-sized blood vessels. The disease can involve multiple systems, most commonly the skin, nervous system, and gastrointestinal tract. Necrosis occurs preferentially at arterial bifurcations and branch sites, leading to microaneurysm formation, thrombosis, emboli, organ ischemia, and infarction.[132] Polyarteritis nodosa affects men about twice as often as women, and onset occurs at any age, although the peak is typically the fourth to sixth decade of life. Annual incidence is between 2 and 9 cases per 1 million individuals.[133] Whereas the initial presentation can be nonspecific, the combination of cutaneous lesions and adult-onset hypertension with evidence of systemic illness suggests polyarteritis nodosa.

Cutaneous manifestations occur in one third of patients.[134] Palpable purpura with or without ulceration is recognized in the fingers, ankles, malleoli, and pretibial areas. Digital cyanosis may be seen secondary to ischemia. Splinter hemorrhages and livedo reticularis may also be observed. Renovascular arteritis can cause hypertension, which may at times be severe. Peripheral neuropathies in the form of mononeuritis multiplex or polyneuropathy are present in up to 50% of patients. Mesenteric vasculitis can produce abdominal angina and in rare cases lead to frank mesenteric ischemia, infarction, and perforation, often with devastating consequences.

Treatment generally begins with a corticosteroid (e.g., prednisone 1 mg/kg), and a second immunosuppressive agent is added for severe or extensive disease. Abdominal catastrophes may require surgical intervention; prognosis in these cases is poor. Polyarteritis nodosa is almost always fatal if it is left untreated, although the prognosis has been much improved with the use of

www.ketabpezeshki.com 66485457-66963820

Figure 118-9. Oral aphthae associated with Behçet's disease. (From Firestein GS: Kelley's Textbook of Rheumatology, 8th ed. Philadelphia, WB Saunders, 2008.)

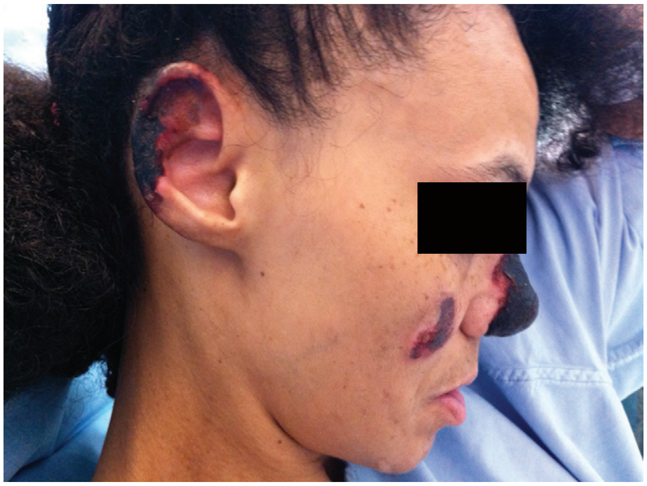


Figure 118-10. Vasculitic lesions caused by crack cocaine containing levamisole. (Courtesy Dr. Christopher Hicks, University of Toronto.)

systemic corticosteroids. In a prospective study, the presence of two or more prognostic factors (azotemia, proteinuria, cardiomyopathy, gastrointestinal involvement, or neurologic signs) predicted a 5-year mortality of 46%; if none was present, the 5-year mortality was 12%.[128]

Behçet's Disease. Behçet's disease is a complex, chronic small-vessel vasculitis that may affect the mucocutaneous, ocular, cardiovascular, renal, gastrointestinal, pulmonary, urologic, musculoskeletal, and central nervous systems. Early descriptions of the disease date to the time of Hippocrates and the third book of endemic diseases.[135] The disease is defined by the presence of aphthous oral ulcers plus two or more of the following: genital aphthae; cutaneous lesions; and neurologic, oral, or rheumatologic manifestations. The exact pathogenesis remains unknown. Behçet's disease is found worldwide, with the highest prevalence in Turkey, Japan, the Middle East, and Mediterranean regions. The disease affects people of all ages, although patients often first present in the second or third decade of life.[136] The male-to-female ratio varies somewhat according to geography; women are more commonly affected than men in northern Europe and the United States, with an estimated prevalence in these regions of about 1 in 150,000 individuals.[137,138]

The triad of recurrent oral aphthous ulcers, genital ulcers, and uveitis in young adults is highly suggestive of Behçet's disease. Oral aphthous ulcers are the defining characteristic of the disease (Fig. 118-9). The lesions are typically found on the tongue, lips, buccal mucosa, and gingiva; the tonsils, palate, and pharynx are less commonly affected. The ulcers are painful, have a yellow, necrotic base, and may appear alone or in crops of three to ten. Genital ulcers appear on the scrotum and penis in men and the vulva or vaginal mucosa in women. Skin lesions include erythema nodosum–like subcutaneous nodules, pyoderma gangrenosum, cutaneous thrombophlebitis, and pustular acne-like folliculitis.[139] Ocular symptoms are common and constitute a major source of morbidity in Behçet's disease. Findings may include uveitis, iritis, and optic neuritis. Hypopyon, once considered a characteristic feature of the disease, is uncommon. Visual symptoms may be bilateral or unilateral and can occasionally lead to permanent vision loss. Neurologic manifestations include brainstem and corticospinal tract syndromes (neuro-Behçet's), aseptic meningoencephalitis, increased intracranial pressure, and cerebral sinus thrombosis complicated by optic nerve ischemia and atrophy.[140] Gastrointestinal ulcers can cause obstruction or ileocecal perforation.[141] Inflammatory oligoarthritis of the ankles, knees, elbows, and wrists is present in 40 to 60% of patients.[137]

The diagnosis of Behçet's disease is made primarily on clinical grounds. The appearance of genital lesions can be ambiguous, and other causes of painful genital ulcers need to be ruled out. Oral and genital ulcerations are often managed successfully with a topical steroid. Management of severe mucocutaneous disease involves systemic corticosteroids (e.g., prednisone, 1 mg/kg), low-dose thalidomide, or methotrexate.[142] Treatment of systemic disease may be accomplished with a corticosteroid alone or in combination with cyclophosphamide or azathioprine.[137] Ocular manifestations, including uveitis, are usually managed with prednisone plus azathioprine and require a rapid referral to an ophthalmologist. The presence of cerebral venous sinus thrombosis is an indication for immediate heparinization. Behçet's disease often has a complicated and protracted course, with morbidity related primarily to ophthalmologic complications. Death can occur from neurologic, cardiovascular, and gastrointestinal sequelae or from complications related to long-term immunosuppressive therapy.

Vasculitis Associated with Environmental or Foreign Antigen Exposure

Vasculitis Caused by Cocaine Adulterated with Levamisole. Levamisole is an immune-modulating agent that has been used to treat autoimmune disorders, various forms of cancer, and the nephrotic syndrome. The drug has been withdrawn from the U.S. drug market owing to the frequency and severity of side effects, including antibody-mediated agranulocytosis and autoimmune vasculitis. Since 2005, the incidence of cocaine cut with levamisole (added at the source of supply to add bulk and weight to the raw product) has been increasing, and some 70% of cocaine seized at U.S. borders contains levamisole to varying degrees.[143] Levamisole is not detected by routine blood and urine toxicology testing, and specialized testing with gas chromatography or mass spectrometry is of limited clinical utility given the short half-life of the drug (5.6 hours); it is unlikely to be detected in the plasma or urine beyond 24 to 72 hours after the last exposure.[143]

The rash associated with levamisole involves tender palpable purpuric plaques with a predilection for the cheeks, nose, and earlobes (Fig. 118-10). Treatment is typically supportive; spontaneous resolution occurs with discontinuation of the offending agent. The agranulocytosis associated with levamisole is transient

www.ketabpezeshki.com 66485457-66963820

Table 118-7 Summary of Buerger's Disease (Thromboangiitis Obliterans), Serum Sickness, and Hypersensitivity Vasculitis

	BUERGER'S DISEASE	SERUM SICKNESS	HYPERSENSITIVITY VASCULITIS
Pathophysiology	Small and medium-sized arteries and veins of the extremities	Immune complex deposition in blood vessel walls	Small vessel
Associated exposures	Heavy cigarette smoking Cold exposure	Foreign protein or serum Penicillin-based antimicrobials Sulfa drugs NSAIDs	β-Lactam antibiotics NSAIDs Diuretics
Common symptoms	Pain, paresthesias Claudication Rest pain	Fever, arthralgias, and diffuse lymphadenopathy Pruritus, skin lesions	Typically confined to the skin (vs. serum sickness)
Physical examination findings	Poorly healing wounds, ulcerations Splinter hemorrhages Digital ischemia and necrosis Distal-to-proximal progression	Urticaria Purpuric skin lesions Scarlatiniform rash Erythema multiforme Azotemia, proteinuria Myocarditis, pericarditis	Palpable purpura in dependent regions, including legs and buttocks Urticarial vasculitis Livedo reticularis Skin nodules and ulcers
Diagnosis	Angiography: demonstrates "corkscrew" pattern of collateral vessels; rule out other causes of ischemia	Clinical	Clinical
Management and outcome	Smoking cessation Meticulous wound care Protection from trauma and thermal injury	Supportive Systemic corticosteroids for severe disease Recovery generally within 4-6 weeks	Supportive Systemic corticosteroids for severe disease
Comments	Up to 50% of patients who continue to smoke will require amputation	Incidence has decreased with modern immunization programs and the use of products derived from human serum	In theory, any medication can cause a hypersensitivity vasculitis syndrome

NSAIDs, nonsteroidal anti-inflammatory drugs.

and fully reversible within a week to 10 days after discontinuation of the offending agent. Patients may present with asymptomatic agranulocytosis detected on routine blood work or with fever, sepsis, or signs of overwhelming infection. Febrile patients are treated aggressively with broad-spectrum antibiotics and a septic workup directed at the likely source of infection, similar to febrile neutropenia associated with chemotherapy. Afebrile patients are also often admitted for investigation and observation until their neutrophil count recovers.

Cryoglobulinemic Vasculitis. Cryoglobulins are immunoglobulins that precipitate from serum at cold temperatures.[144] Damage to small and medium-sized blood vessels occurs when cryoglobulins bind to circulating antigens and deposit in vessel walls, prompting a complement-mediated inflammatory reaction and cryoglobulinemic vasculitis.

Three types of cryoglobulinemic vasculitis syndromes have been identified. Type I is associated with Waldenström's macroglobulinemia and multiple myeloma and produces a syndrome of hyperviscosity with symptoms of presyncope, altered mental status, and stroke. Types II and III are known as the mixed cryoglobulinemias and represent 80% of recognized cryoglobulinemic syndromes. There is a strong association between these subtypes and hepatitis C, Sjögren's syndrome, and SLE. The mixed cryoglobulinemias are manifested with a triad of purpura, arthralgias, and myalgias along with glomerulonephropathy and vasculitic peripheral neuropathy. Purpuric lesions are typically multiple and confluent and appear preferentially in dependent areas and the lower extremities in particular.[144] Renal failure is the most serious consequence of cryoglobulinemia and is present in 20 to 60% of patients.[145]

The diagnosis is based on the presence of serum cryoglobulins accompanied by typical clinical features; the most salient elements of the differential diagnosis include SLE and Henoch-Schönlein purpura . Skin biopsy can be helpful in confirming the diagnosis. Management involves identification and treatment of associated diseases, such as hepatitis C and multiple myeloma. Low-dose corticosteroids are helpful when systemic symptoms are present but should be avoided while antiviral therapy is being initiated. Plasmapheresis may be useful in life-threatening cases related to cryoprecipitation or serum hyperviscosity.

Features associated with Buerger's disease, serum sickness, and hypersensitivity vasculitis are outlined in Table 118-7.

KEY CONCEPTS

Systemic Lupus Erythematosus

- SLE may affect any organ system. Thus, a fundamental understanding of the disease is required to tailor the differential diagnosis and workup.
- A 50-fold increased risk of CAD and up to a 30-fold increased risk of venous thromboembolism in patients with SLE prompt aggressive chest pain workups in the ED, even in young women.
- An elevated C-reactive protein level is more closely linked to infection in SLE patients and is not reflective of SLE disease activity. An isolated elevated PTT in a patient with SLE prompts consideration for antiphospholipid antibody carrier state and, if there is a history of thrombosis, antiphospholipid syndrome.
- Steroids are the mainstay for management of the majority of conditions that are associated with increased SLE disease activity, including musculoskeletal, cutaneous, renal, pleural, and pericardial disease.
- Antiphospholipid syndrome is common in patients with SLE and carries with it a risk of venous (typically deep venous thrombosis or pulmonary embolism) and arterial (most commonly stroke) thrombosis.

www.ketabpezeshki.com 66485457-66963820

- Consultation with a rheumatologist may be helpful in diagnostic, management, and disposition decisions for patients with SLE.

Vasculitides

- Vasculitis syndromes should be considered in the presence of systemic symptoms such as fever, malaise, and weight loss plus pulmonary, renal, or cutaneous manifestations.
- Massive hemoptysis and acute renal failure can occur in Wegener's granulomatosis, Goodpasture's disease, microscopic polyangiitis, and Churg-Strauss syndrome. Tracheal stenosis may be present in Wegener's granulomatosis, further complicating airway management.
- Many patients with established vasculitis are receiving high-dose or combination immune suppressive therapy, making them vulnerable to opportunistic infections and overwhelming sepsis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Cohen AS, et al: Preliminary criteria for the classification of systemic lupus erythematosus. *Bull Rheum Dis* 1971; 21:643-648.
2. Panopalis P, et al: Frequent use of the emergency department among persons with systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2010; 62:401-408.
3. Pons-Estel G, Alarcón G, Scofield L, Reinlib L, Cooper G: Understanding the epidemiology and progression of systemic lupus erythematosus. *Semin Arthritis Rheum* 2010; 39:257-268.
4. Uramoto K, et al: Trends in the incidence and mortality of systemic lupus erythematosus, 1950-1992. *Arthritis Rheum* 1999; 42:46-50.
5. Siegel M, Lee S: The epidemiology of systemic lupus erythematosus. *Semin Arthritis Rheum* 1973; 3:1-54.
6. Sánchez-Guerrero J, Liang M, Karlson E, Hunter D, Colditz G: Postmenopausal estrogen therapy and the risk for developing systemic lupus erythematosus. *Ann Intern Med* 1995; 122:430-433.
7. Sanchez-Guerrero J, et al: Past use of oral contraceptives and the risk of developing systemic lupus erythematosus. *Arthritis Rheum* 1997; 40:804-808.
8. Costenbader K, Feskanich D, Stampfer M, Karlson E: Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. *Arthritis Rheum* 2007; 56:1251-1262.
9. Moser K, Kelly J, Lessard C, Harley J: Recent insights into the genetic basis of systemic lupus erythematosus. *Genes Immun* 2009; 10:373-379.
10. Rahman A, Isenberg D: Systemic lupus erythematosus. *N Engl J Med* 2008; 358:929-939.
11. Michaud J, et al: Focal and segmental glomerulosclerosis in mice with podocyte-specific expression of mutant alpha-actinin-4. *J Am Soc Nephrol* 2003; 14:1200-1211.
12. Berden J, Licht R, van Bruggen MC, Tax W: Role of nucleosomes for induction and glomerular binding of autoantibodies in lupus nephritis. *Curr Opin Nephrol Hypertens* 1999; 8:299-306.
13. Ulas S, Ulger Z, Balkan S, Sozeri B, Ozyurek A: Cardiac tamponade as a first manifestation of possible systemic lupus erythematosus in a 3-year-old female child. *Minerva Pediatr* 2010; 62:319-321.
14. Hsu T, Wang S, Kuo C, Chiu T, Chang Y: Acute inflammatory demyelinating polyneuropathy as the initial presentation of lupus. *Am J Emerg Med* 2009; 27:900.
15. Makaryus J, Catanzaro J, Goldberg S, Makaryus A: Rapid progression of atrioventricular nodal blockade in a patient with systemic lupus erythematosus. *Am J Emerg Med* 2008; 26:967.
16. Muñiz A: Pericardial tamponade presenting as abdominal pain in a patient with systemic lupus erythematosus. *CJEM* 2000; 2:117-120.
17. Waseem M, Alsheikh M, Hana A: Presentation of systemic lupus erythematosus in emergency department. *Pediatr Emerg Care* 2007; 23:238-241.
18. Tan E, et al: The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25:1271-1277.
19. Hochberg M: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40:1725.
20. Bombardier C, Gladman D, Urowitz M, Caron D, Chang C: Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum* 1992; 35:630-640.
21. Goldblatt F, Chambers S, Rahman A, Isenberg D: Serious infections in British patients with systemic lupus erythematosus: Hospitalisations and mortality. *Lupus* 2009; 18:682-689.
22. Williams F, Chinn S, Hughes G, Leach R: Critical illness in systemic lupus erythematosus and the antiphospholipid syndrome. *Ann Rheum Dis* 2002; 61:414-421.
23. Inoue T, et al: Differential diagnosis of fever in systemic lupus erythematosus using discriminant analysis. *Rheumatol Int* 1986; 6:69-77.
24. Stahl N, Klippel J, Decker J: Fever in systemic lupus erythematosus. *Am J Med* 1979; 67:935-940.
25. Iliopoulos A, Tsokos G: Immunopathogenesis and spectrum of infections in systemic lupus erythematosus. *Semin Arthritis Rheum* 1996; 25:318-336.
26. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999; 42:599-608.
27. Fernández-Nebro A, et al: Chronic or recurrent headache in patients with systemic lupus erythematosus: A case control study. *Lupus* 1999; 8:151-156.
28. Mitsikostas D, Sfikakis P, Goadsby P: A meta-analysis for headache in systemic lupus erythematosus: The evidence and the myth. *Brain* 2004; 127(Pt 5):1200-1209.
29. Sivalingam S, Saligram P, Natanasabapathy S, Paez A: Covert cryptococcal meningitis in a patient with systemic lupus erythematous. *J Emerg Med* 2012; 42:e101-104.
30. Vidailhet M, Piette J, Wechsler B, Bousser M, Brunet P: Cerebral venous thrombosis in systemic lupus erythematosus. *Stroke* 1990; 21:1226-1231.
31. Appenzeller S, Cendes F, Costallat L: Epileptic seizures in systemic lupus erythematosus. *Neurology* 2004; 63:1808-1812.
32. Galli M, Luciani D, Bertolini G, Barbui T: Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: A systematic review of the literature. *Blood* 2003; 101:1827-1832.
33. Manzi S, et al: Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: Comparison with the Framingham Study. *Am J Epidemiol* 1997; 145:408-415.
34. Asanuma Y, et al: Premature coronary-artery atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003; 349:2407-2415.
35. Sun S, et al: The role of technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography (SPECT) in the detection of cardiovascular involvement in systemic lupus erythematosus patients with non-specific chest complaints. *Rheumatology (Oxford)* 2001; 40:1106-1111.
36. Rahman P, Urowitz M, Gladman D, Bruce I, Genest J: Contribution of traditional risk factors to coronary artery disease in patients with systemic lupus erythematosus. *J Rheumatol* 1999; 26:2363-2368.
37. Maksimowicz-McKinnon K, et al: Poor 1-year outcomes after percutaneous coronary interventions in systemic lupus erythematosus: Report from the National Heart, Lung, and Blood Institute Dynamic Registry. *Circ Cardiovasc Interv* 2008; 1:201-208.
38. Moder K, Miller T, Tazelaar H: Cardiac involvement in systemic lupus erythematosus. *Mayo Clin Proc* 1999; 74:275-284.
39. Man B, Mok C: Serositis related to systemic lupus erythematosus: Prevalence and outcome. *Lupus* 2005; 14:822-826.
40. Mohseni M, Rogers E: Cardiac tamponade as the initial manifestation of systemic lupus erythematosus. *J Emerg Med* 2010; Aug 11. [Epub ahead of print]
41. Doherty N, Siegel R: Cardiovascular manifestations of systemic lupus erythematosus. *Am Heart J* 1985; 110:1257-1265.
42. Cushman M, et al: Deep vein thrombosis and pulmonary embolism in two cohorts: The longitudinal investigation of thromboembolism etiology. *Am J Med* 2004; 117:19-25.
43. Brouwer J, Bijl M, Veeger N, Kluin-Nelemans H, van der Meer J: The contribution of inherited and acquired thrombophilic defects, alone or combined with antiphospholipid antibodies, to venous and arterial thromboembolism in patients with systemic lupus erythematosus. *Blood* 2004; 104:143-148.
44. Cervera R, et al: Morbidity and mortality in systemic lupus erythematosus during a 10-year period: A comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine (Baltimore)* 2003; 82:299-308.
45. Good J, King T, Antony V, Sahn S: Lupus pleuritis. Clinical features and pleural fluid characteristics with special reference to pleural fluid antinuclear antibodies. *Chest* 1983; 84:714-718.
46. Giannouli S, Voulgarelis M, Ziakas P, Tzioufas A: Anaemia in systemic lupus erythematosus: From pathophysiology to clinical assessment. *Ann Rheum Dis* 2006; 65:144-148.
47. Pego-Reigosa J, Medeiros D, Isenberg D: Respiratory manifestations of systemic lupus erythematosus: Old and new concepts. *Best Pract Res Clin Rheumatol* 2009; 23:469-480.
48. van Vugt RM, Derksen R, Kater L, Bijlsma J: Deforming arthropathy or lupus and rhupus hands in systemic lupus erythematosus. *Ann Rheum Dis* 1998; 57:540-544.
49. Huang J, et al: Septic arthritis in patients with systemic lupus erythematosus: Salmonella and nonsalmonella infections compared. *Semin Arthritis Rheum* 2006; 36:61-67.
50. Isenber D, Snaith M: Muscle disease in systemic lupus erythematosus: A study of its nature, frequency and cause. *J Rheumatol* 1981; 8:917-924.
51. Sultan S, Ioannou Y, Isenberg D: A review of gastrointestinal manifestations of systemic lupus erythematosus. *Rheumatology (Oxford)* 1999; 38:917-932.
52. Rojas-Serrano J, Cardiel M: Lupus patients in an emergency unit. Causes of consultation, hospitalization and outcome. A cohort study. *Lupus* 2000; 9:601-606.

www.ketabpezeshki.com 66485457-66963820

53. Kwok S, et al: Lupus enteritis: Clinical characteristics, risk factor for relapse and association with anti–endothelial cell antibody. *Lupus* 2007; 16:803-809.
54. Lee C, et al: Acute abdominal pain in systemic lupus erythematosus: Focus on lupus enteritis (gastrointestinal vasculitis). *Ann Rheum Dis* 2002; 61:547-550.
55. Chng H, Tan B, Teh C, Lian T: Major gastrointestinal manifestations in lupus patients in Asia: Lupus enteritis, intestinal pseudo-obstruction, and protein-losing gastroenteropathy. *Lupus* 2010; 19:1404-1413.
56. Byun J, et al: CT features of systemic lupus erythematosus in patients with acute abdominal pain: Emphasis on ischemic bowel disease. *Radiology* 1999; 211:203-209.
57. Ebert E, Hagspiel K: Gastrointestinal and hepatic manifestations of systemic lupus erythematosus. *J Clin Gastroenterol* 2011; 45:436-441.
58. Kuhn A, Ochsendorf F, Bonsmann G: Treatment of cutaneous lupus erythematosus. *Lupus* 2010; 19:1125-1136.
59. Sidiropoulos P, Kritikos H, Boumpas D: Lupus nephritis flares. *Lupus* 2005; 14:49-52.
60. Chen C, Wang F, Lin C: Chronic hydroxychloroquine use associated with QT prolongation and refractory ventricular arrhythmia. *Clin Toxicol (Phila)* 2006; 44:173-175.
61. Edworthy S, Zatarain E, McShane D, Bloch D: Analysis of the 1982 ARA lupus criteria data set by recursive partitioning methodology: New insights into the relative merit of individual criteria. *J Rheumatol* 1988; 15:1493-1498.
62. Firooz N, et al: High-sensitivity C-reactive protein and erythrocyte sedimentation rate in systemic lupus erythematosus. *Lupus* 2011; 20:588-597.
63. Mandavia D, Hoffner R, Mahaney K, Henderson S: Bedside echocardiography by emergency physicians. *Ann Emerg Med* 2001; 38:377-382.
64. Calvo-Alén J, et al: Identification of patient subsets among those presumptively diagnosed with, referred, and/or followed up for systemic lupus erythematosus at a large tertiary care center. *Arthritis Rheum* 1995; 38:1475-1484.
65. Rothfield N, Sontheimer R, Bernstein M: Lupus erythematosus: Systemic and cutaneous manifestations. *Clin Dermatol* 2006; 24:348-362.
66. Mok C, Tang S, To C, Petri M: Incidence and risk factors of thromboembolism in systemic lupus erythematosus: A comparison of three ethnic groups. *Arthritis Rheum* 2005; 52:2774-2782.
67. Miyakis S, et al: International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006; 4:295-306.
68. Ruiz-Irastorza G, Egurbide M, Ugalde J, Aguirre C: High impact of antiphospholipid syndrome on irreversible organ damage and survival of patients with systemic lupus erythematosus. *Arch Intern Med* 2004; 164:77-82.
69. Ginsberg J, et al:Antiphospholipid antibodies and venous thromboembolism. *Blood* 1995; 86:3685-3691.
70. Greaves M, Cohen H, MacHin S, Mackie I: Guidelines on the investigation and management of the antiphospholipid syndrome. *Br J Haematol* 2000; 109:704-715.
71. Asherson R, et al:Catastrophic antiphospholipid syndrome: International consensus statement on classification criteria and treatment guidelines. *Lupus* 2003; 12:530-534.
72. Katz U, Zandman-Goddard G: Drug-induced lupus: An update. *Autoimmun Rev* 2010; 10:46-50.
73. Vasoo S: Drug-induced lupus: An update. *Lupus* 2006; 15:757-761.
74. Totoritis M, Tan E, McNally E, Rubin R: Association of antibody to histone complex H2A-H2B with symptomatic procainamide-induced lupus. *N Engl J Med* 1988; 318:1431-1436.
75. Guidelines for referral and management of systemic lupus erythematosus in adults. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. *Arthritis Rheum* 1999; 42:1785-1796.
76. Scott D, Watts R: Systemic vasculitis: Epidemiology, classification and environmental factors. *Ann Rheum Dis* 2000; 59:161-163.
77. Lane S, Watts R, Scott D: Epidemiology of systemic vasculitis. *Curr Opin Rheumatol* 2005; 7:270-275.
78. Miller N: Visual manifestations of temporal arteritis. *Rheum Dis Clin North Am* 2001; 27:781-797.
79. Salvarani C, Gabriel S, O'Fallon W, Hunder G: The incidence of giant cell arteritis in Olmstead County, Minnesota: Apparent fluctuations in cyclic pattern. *Ann Intern Med* 1995; 123:192-194.
80. Salvarani C, Cantini F, Boiardi L, Hunder G: Polymyalgia rheumatica and giant cell arteritis. *N Engl J Med* 2002; 374:261.
81. Smetana G, Shmerling R: Does this patient have temporal arteritis? *JAMA* 2002; 287:92-101.
82. Hellmann D: *Giant cell arteritis, polymyalgia rheumatica, and Takayasu's arteritis*. In: Firestein GS, ed. *Kelley's Textbook of Rheumatology*, 8th ed. Philadelphia: WB Saunders; 2008.
83. Levine S, Hellmann D: Giant cell arteritis. *Curr Opin Rheumatol* 2002; 14:3-10.
84. Solomon S, Cappa K: The headache of temporal arteritis. *J Am Geriatr Soc* 1987; 35:163-165.
85. Mehler M, Rabinowich L: The clinical neuro-ophthalmologic spectrum of temporal arteritis. *Am J Med* 1988; 85:839-844.
86. Evans J, O'Fallon W, Hunder G: Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis: A population-based study. *Ann Intern Med* 1995; 122:502-507.
87. Ruegg S, et al: Bilateral vertebral artery occlusion resulting from giant cell arteritis: Report of 3 cases and review of the literature. *Medicine (Baltimore)* 2003; 82:1-12.
88. Hunder G, et al: The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum* 1990; 33:1122-1128.
89. Varma D, O'Neil D: Quantification of the role of the temporal artery biopsy in diagnosing clinically suspected giant cell arteritis. *Eye (Lond)* 2004; 18:384-388.
90. Parikh M, et al: Prevalence of a normal C-reactive protein with an elevated erythrocyte sedimentation rate in biopsy-proven giant cell arteritis. *Ophthalmology* 2006; 113:1842-1845.
91. Hall S, Hunder G: Is temporal artery biopsy prudent? *Mayo Clin Proc* 1984; 59:793-796.
92. Salvarani C, et al: Is duplex ultrasonography useful for the diagnosis of giant-cell arteritis? *Ann Intern Med* 2002; 137:232-238.
93. Bley T, et al: Diagnostic value of high-resolution MR imagining in giant cell arteritis. *Am J Neuroradiol* 2007; 28:1722-1727.
94. Seo P, Stone J: Large-vessel vasculitis. *Arthritis Rheum* 2004; 51:128-139.
95. Ray-Chaudhuri N, et al: Effect of prior steroid treatment on temporal artery biopsy findings in giant cell arteritis. *Br J Ophthalmol* 2002; 86:530-532.
96. Belliveau M, ten Hove M: Five things to know about: Giant cell arteritis. *CMAJ* 2011; 183:581.
97. Warrington K, Matteson E: Management guidelines and outcome measures in giant cell arteritis (GCA). *Clin Exp Rheumatol* 2007; 25(Suppl 47):137-141.
98. Gonzalez-Gay M, Garcia-Porrua C: Epidemiology of the vasculitides. *Rheum Dis Clin North Am* 2001; 27:729-749.
99. Kerr G, et al: Takayasu arteritis. *Ann Intern Med* 1994; 120:919-929.
100. Andrews J, et al: Non-invasive imaging in the diagnosis and management of Takayasu's arteritis. *Ann Rheum Dis* 2004; 63:995-1000.
101. Liang P, Hoffman G: Advances in the medical and surgical treatment of Takayasu arteritis. *Curr Opin Rheumatol* 2004; 17:16-24.
102. Miyata T, Sato O, Koyama H, Shigematsu H, Tada Y: Long-term survival after surgical treatment of patients with Takayasu's arteritis. *Circulation* 2003; 108:1474-1480.
103. Radice A, Sinico R: Antineutrophil cytoplasmic antibodies (ANCA). *Autoimmunity* 2005; 38:93-103.
104. Cotch M, et al: The epidemiology of Wegener's granulomatosis. Estimates of the five-year period prevalence, annual mortality, and geographic disease distribution from population-based data sources. *Arthritis Rheum* 1996; 39:87-92.
105. Hoffman G, et al: Wegener granulomatosis: An analysis of 158 patients. *Ann Intern Med* 1992; 116:488-498.
106. Travis W, Carpenter H, Lie J: Diffuse pulmonary hemorrhage. An uncommon manifestation of Wegener's granulomatosis. *Am J Surg Pathol* 1987; 11:702-708.
107. Walton E: Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *Br Med J* 1958; 2:265-270.
108. Mahajan R, Gupta R, Sharma A: Wegener's granulomatosis and subglottic stenosis: How to handle the airway? *Acta Anaesthesiol Scand* 2009; 53:412-413.
109. Fauchi A, Haynes B, Katz P, Wolff S: Wegener's granulomatosis: Prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 1983; 98:76-85.
110. Bosch X, Guilabert A, Espinosa G, Mirapiex E: Treatment of antineutrophil cytoplasmic antibody associated vasculitis: A systematic review. *JAMA* 2007; 298:655-669.
111. Travis W, Hoffman G, Leavitt R, Pass H, Fauci A: Surgical pathology of the lung in Wegener's granulomatosis. Review of 87 open lung biopsies from 67 patients. *Am J Surg Pathol* 1991; 15:315-333.

www.ketabpezeshki.com 66485457-66963820

112. Salama A, Levy J, Lightstone L, Pusey C: Goodpasture's disease. *Lancet* 2001; 358:917-920.
113. Kluth D, Rees A: Anti–glomerular basement membrane disease. *J Am Soc Nephrol* 1999; 10:2446.
114. Bolton W: Goodpasture's syndrome. *Kidney Int* 1996; 50:1753-1766.
115. Hudson B, Tryggvason K, Sundaramoorthy M, Neilson E: Alport's syndrome, Goodpasture's syndrome, and type IV collagen. *N Engl J Med* 2003; 348:2543-2556.
116. Davson J, Ball J, Platt R: The kidney in periarteritis nodosa. *Q J Med* 1948; 17:175-202.
117. Duvuru G, Stone J: *Microscopic polyangiitis*. In: Imboden J, ed. *Current Rheumatology Diagnosis and Treatment*, 2nd ed. New York: McGraw-Hill; 2007.
118. D'Agati V, Chander P, Nash M, Mancilla-Jimenez R: Idiopathic microscopic polyarteritis nodosa: Ultrastructural observations on the renal vascular and glomerular lesions. *Am J Kidney Dis* 1986; 7:95-110.
119. Adu D, et al: Polyarteritis and the kidney. *Q J Med* 1987; 62:221-237.
120. Calabrese L, Molloy E, Duna G: *Antineutrophil cytoplasmic antibody–associated vasculitis*. In: Firestein GS, ed. *Kelley's Textbook of Rheumatology*, 8th ed. Philadelphia: WB Saunders; 2008.
121. Gayraud M, et al: Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: Analysis of four prospective trials including 278 patients. *Arthritis Rheum* 2001; 44:666-675.
122. Jayne D: Challenges in the management of microscopic polyangiitis: Past, present and future. *Curr Opin Rheumatol* 2008; 20:3-9.
123. Seo P, Stone J: The antineutrophil cytoplasmic antibody–associated vasculitides. *Am J Med* 2004; 117:39-50.
124. Chumbley L, Harrison EG Jr, DeRemee R: Allergic granulomatosis and angiitis (Churg-Strauss syndrome). Report and analysis of 30 cases. *Mayo Clin Proc* 1977; 52:477-484.
125. Guillevin L, et al: Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore)* 1999; 78:26-37.
126. Sable-Fourtassou R, et al: Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann Intern Med* 2005; 143:632-638.
127. Molloy E, Langford C: Advances in the treatment of small vessel vasculitis. *Rheum Dis Clin North Am* 2006; 32:157-172.
128. Guillevin L, et al: Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome: A prospective study in 342 patients. *Medicine (Baltimore)* 1996; 75:17-28.
129. Mert A, et al: Erythema nodosum: An experience of 10 years. *Scand J Infect Dis* 2004; 36:424-427.
130. Mills J, Michel B, Bloch D, et al: The American College of Rheumatology 1990 criteria for the classification of Henoch-Schönlein purpura. *Arthritis Rheum* 1990; 33:1114-1121.
131. Little K, Danzl D: Intussusception associated with Henoch-Schönlein purpura. *J Emerg Med* 1991; 9:29-32.
132. Stone J: Polyarteritis nodosa. *JAMA* 2002; 288:1632-1639.
133. Cohen R, Conn D, Ilstrup D: Clinical features, prognosis, and response to treatment in polyarteritis. *Mayo Clin Proc* 1980; 55:146-155.
134. Lightfoot RW Jr, et al: The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. *Arthritis Rheum* 1990; 33:1088-1093.
135. Feigenbaum A: Description of Behçet's syndrome in the Hippocratic third book of endemic diseases. *Br J Ophthalmol* 1956; 40:355-357.
136. Kim D, Chang S, Bang D, Lee E, Lee S: Clinical analysis of 40 cases of childhood-onset Behçet's disease. *Pediatr Dermatol* 1994; 11:95-101.
137. Kaklamani V, Vaiopoulos G, Kaklamanis P: Behçet's disease. *Semin Arthritis Rheum* 1998; 27:197-217.
138. Zouboulis C: Epidemiology of Adamantiades-Behçet's disease. *Ann Med Interne (Paris)* 1999; 150:488-498.
139. Ghate J, Jorizzo J: Behçet's disease and complex aphthosis. *J Am Acad Dermatol* 1999; 40:19-20.
140. Saadoun D, et al: Cerebral venous thrombosis in Behçet's disease. *Arthritis Rheum* 2009; 61:518-526.
141. Sakane T, Takeno M, Suzuki N, Inaba G: Behçet's disease. *N Engl J Med* 1999; 341:1284-1291.
142. De Wazieres B, Gil H, Vuitton D, Dupond J: Treatment of recurrent oro-genital ulceration with low doses of thalidomide. *Clin Exp Rheumatol* 1999; 17:393.
143. Wintrobe M, Buell M: Hyperproteinemia associated with multiple myeloma: With report of a case in which an extraordinary hyperproteinemia was associated with thrombosis of the renal veins and symptoms suggesting Raynaud's disease. *Bull Johns Hopkins Hosp* 1933; 52:156.
144. Monti G, Galli M, Invernizzi F, et al: Cryoglobulinaemias: A multi-centre study of the early clinical and laboratory manifestations of primary and secondary disease. GISC. Italian Group for the Study of Cryoglobulinaemias. *QJM* 1995; 88:115-126.
145. Duvuru G, Stone J: *Mixed cryoglobulinemia*. In: Imboden J, ed. *Current Rheumatology Diagnosis and Treatment*, 2nd ed. New York: McGraw-Hill; 2007:303-307.

www.ketabpezeshki.com 66485457-66963820

Chapter 119

Allergy, Hypersensitivity, Angioedema, and Anaphylaxis

T. Paul Tran and Robert L. Muelleman

PERSPECTIVE

The human immune system is an assemblage of cellular and humoral components working together in a highly complex, coordinated, and elegant fashion to achieve the primary goal of protecting the human host (*self*) from harmful offenders (*nonself*). Exposure to *danger* signals activates the various immune mechanisms to bring about immune responses aimed at neutralizing the dangerous nonself while preserving self.[1] The immune system can, however, overreact to otherwise harmless nonself agents, producing inappropriate responses that are harmful to the host, thereby giving rise to allergy or allergic diseases. These hypersensitivity reactions are manifested in clinical symptoms ranging from mildly inconvenient to debilitating to fatal. For practical purposes, the term *allergy* is used in this chapter to refer to mast cell–mediated hypersensitivity reactions. For most allergic diseases to occur, predisposed individuals need to be exposed to allergens through a process called *sensitization*. Substances that elicit an allergic reaction are referred to as *allergens,* and those that elicit an antibody response (activated by B- and T-cell receptors) are called *antigens*.

In this allergic continuum, there are several important allergic syndromes frequently encountered in the emergency department (ED). *Urticaria* is a common allergic reaction to foods, drugs, or physical stimuli and is clinically characterized by a red itchy rash. *Angioedema* is the other important allergic syndrome, mediated by either an allergic mechanism in response to exposure to foods, drugs, or physical stimuli or a nonallergic mechanism (e.g., angiotensin-converting enzyme [ACE] inhibitor). Angioedema is characterized by swelling of the subcutaneous tissues, which can cause airway difficulty if the larynx is involved. At the other extreme of this allergic continuum is *anaphylaxis,* a life-threatening systemic allergic reaction characterized by acute onset and multiorgan involvement. The term *anaphylaxis* is derived from Greek (*ana,* against; *phylax,* guard or protect), meaning "against protection." Mechanistically, anaphylaxis is a type I hypersensitivity reaction (allergic), mediated by immunoglobulin E (IgE). In its most common form, anaphylaxis is precipitated by exposure to allergens in previously sensitized individuals. Timely recognition of the syndrome and proper care are essential to bring about beneficial outcomes for patients with anaphylaxis.

The term *anaphylactoid reaction* refers to a syndrome clinically similar to anaphylaxis that is not mediated by IgE. Its clinical presentation and treatment are identical to those of anaphylaxis. Anaphylactoid reactions appear to result from direct degranulation of mast cells (and basophils) and may follow a single, first-time exposure to certain inciting agents. In this chapter, we use the term anaphylaxis to refer to both IgE- and non–IgE-mediated reactions, obviating the need for the term anaphylactoid reaction.

Epidemiology and Risk Factors

The incidence of anaphylaxis has not been determined with certainty, but recent evidence suggests that it is increasing.[2] There are approximately 100,000 attacks of anaphylaxis in the United States per year, of which approximately 60,000 are first-time events and 1000 to 1500 are fatal.[3]

Factors affecting the incidence of anaphylaxis include time of the year, age, female sex (adults), higher socioeconomic status, northern locations, route of allergen exposure, and history of atopy (Box 119-1).[2,4] Anaphylactic reactions seem to be more common in the summer and early fall, coincident with the outdoor season; in people of higher socioeconomic status; and in people with a history of atopy. In general, anaphylaxis is more common in adults, but in particular, it is more common in women older than 30 years and in boys younger than 16 years. The dose, frequency, duration, and route of administration of a drug also affect the tendency to develop an anaphylactic reaction; the parenteral route is more likely than the oral route to lead to an anaphylactic reaction. One interesting aspect of drug-related anaphylaxis is the constancy of administration. An anaphylactic reaction may not occur in an otherwise susceptible patient as long as a drug is administered at regular intervals. The same patient may, however, experience an anaphylactic reaction if the drug is resumed after an interruption of therapy.[5]

Risk factors for increased severity and mortality of an anaphylaxis reaction include having a recent episode of anaphylaxis, extremes of age, presence of atopy or cardiopulmonary conditions, taking medications that may influence timely recognition of the symptoms or impede the treatment of anaphylaxis, and rapid onset of symptoms after exposure (see Box 119-1).[2,6] The more rapid an anaphylaxis reaction is after an exposure, the more likely it is to be severe and potentially fatal. Whereas anaphylaxis in an infant is a rare event, timely recognition of an anaphylactic reaction in an infant can be difficult because signs of anaphylaxis, such as flushing, vomiting and diarrhea, lethargy, and dystonia after feeding, can be overlooked as minor reactions.[7] Elders, on the other hand, tend to have worse outcomes in anaphylaxis because of their comorbid conditions, notably heart failure, ischemic heart disease, hypertension, and obstructive lung diseases. A history of asthma and atopy is associated with a more severe or fatal anaphylactic reaction. This is particularly true when the allergen is administered by the mucosal route (e.g., food). Atopy does not, however, seem to be a risk factor when the allergen is administered parenterally (e.g., penicillin). Patients with psychiatric disorders and individuals taking medications and drugs that may impede prompt recognition of an anaphylaxis reaction are also at increased risks (e.g., recreational drugs, alcohol, tranquilizers, and hypnotics). In addition, two classes of medications concurrently

www.ketabpezeshki.com 66485457-66963820

Box 119-1 Risk Factors for Having Anaphylaxis and Increased Anaphylaxis Severity and Mortality

Risk Factors for Having Anaphylaxis

Age and sex
- Males < 16 years, females > 30 years

Route of administration
- Parenteral > oral

Higher social economic status

Time of the year
- Summer and fall (the outdoor seasons)

History of atopy

Risk Factors for Increased Anaphylaxis Severity and Mortality

Extremes of age
- Very young (under-recognition)
- Elderly (increased risks of mortality from treatment and venom-induced anaphylaxis)

Comorbid conditions
- Cardiovascular disease (heart failure, ischemic heart disease, hypertension)
- Pulmonary disease (asthma, obstructive airway disease, acute infection)

Others
- Concurrent use of beta-blockers and angiotensin-converting enzyme inhibitors
- Concurrent use of cognition-impairing drugs (e.g., alcohol, recreational drugs, sedatives, tranquilizers)
- Recent anaphylaxis episode

Modified from Lieberman P: Anaphylaxis. Med Clin North Am 90:77-95, 2006, viii; and Simons FE: Anaphylaxis. J Allergy Clin Immunol 125(Suppl 2):S161-S181, 2010.

taken by patients may increase their risks of anaphylaxis severity. ACE inhibitors can cause an accumulation of kinins and bradykinin and thus can exacerbate the angioedema in anaphylaxis. Beta-blockers can oppose the actions of adrenergic agents used in anaphylaxis treatment, potentially leading to protracted hypotension.

Triggers for Anaphylaxis

Virtually any agent that is capable of activating mast cells (or basophils) can potentially precipitate an anaphylactic reaction. In approximately one third of the cases, however, an inciting agent cannot be identified.[8] When a cause can be determined, foods, medications, and insect stings are the most common causes of anaphylactic reactions. Box 119-2 lists most common agents by their proposed immunologic mechanism.[9] Reactions without identifiable causative agents are classified as physically induced or iatrogenic anaphylaxis.

Foods

Foods are the major identifiable causative agents, accounting for approximately one third of the cases of anaphylaxis.[8] A variety of foods have been identified, ranging from the well-known (nuts, shellfish, and eggs) to the obscure (chamomile tea, which may have cross-reactivity with ragweed). Cow's milk, egg, peanut, soy, wheat, fish, shellfish, and tree nuts are foods that most commonly cause anaphylaxis. Even for a person with a known history of food allergy, it may be difficult to avoid foods that may cause allergic reactions because their identity may be obscured in processing (e.g., consuming wine contaminated with Hymenoptera venom).[10] Because allergenic foods are first absorbed transmucosally, symptoms of food anaphylaxis may first appear localized to the upper airway of the respiratory tract. When anaphylactic allergens are administered parenterally, symptoms of anaphylaxis tend to be more cardiovascular and systemic. Allergic reactions to foodstuffs are more common in children, with incidence ranging from 0.3 to 7.5%.[11]

Box 119-2 Etiologic Agents Causing Anaphylaxis by Immunologic Mechanisms

IgE-Dependent Mechanism

Food: egg, peanut, tree nut, milk, fruits, shellfish, shrimp, other crustaceans
Antibiotics: penicillins, cephalosporins, sulfonamides, nitrofurantoin, tetracycline, streptomycin
Insect stings: Hymenoptera venoms, fire ant stings
Natural rubber latex
Hormones: insulin, methylprednisolone, parathormone, estradiol, progesterone, corticotropin
Enzymes: trypsin, streptokinase, chymotrypsin, chymopapain, L-asparaginase
Other therapeutics: NSAIDs (some are IgE independent), methylparaben, human diploid cell rabies vaccine, egg-based vaccines (measles, mumps, rubella), vasopressin, antilymphocyte globulin, heterologous and human sera, local anesthetics (mostly ester family, procaine, tetracaine, benzocaine)
Seminal fluid

IgE-Independent Mechanism (direct mast cell degranulation)

Radiocontrast media
Aspirin and NSAIDs (arachidonic acid metabolism)
Alcohol, opiates, protamine, polysaccharides (some are IgE mediated), curare, D-tubocurarine
Certain food colorants and additives

Immune Complex Mediated

Whole blood (transfusion reaction to formed elements), immunoglobulins

Physical Factors

Exercise
Heat or cold
Sunlight
Ultraviolet radiation

Miscellaneous

Factitious
Undifferentiated somatoform idiopathic anaphylaxis
Idiopathic

Modified from Kemp SF, Lockey RF: Anaphylaxis: A review of causes and mechanisms. J Allergy Clin Immunol 110:341-348, 2002.
IgE, immunoglobulin E; *NSAIDs,* nonsteroidal anti-inflammatory drugs.

Therapeutic and prophylactic use of large quantities of antibiotics is common in the production of beef cattle, swine, fish, poultry, and sometimes vegetables and fruits. Along with antibiotics, sodium and potassium bisulfites and metabisulfites are used as preservatives in foods. Sulfites have been used as antioxidants in the food and restaurant industry to prevent discoloration of vegetables (e.g., salad bars and avocado dips), fruits, and potatoes and to preserve fruit and vegetable juices. They are also used to prevent bacterial contamination and oxidation of wines, beers, and distilled beverages. Sensitivity to ingested sulfites has been well documented, especially among asthmatics.[12] Establishment of a particular foodstuff or preservative as the causative agent of anaphylaxis can be difficult.

Antibiotics

Allergic reactions to common antibiotics, such as benzylpenicillin, semisynthetic penicillin, and cephalosporins, are well documented; allergy to penicillin is perhaps the most commonly reported medication allergy. Because of their low molecular

www.ketabpezeshki.com 66485457-66963820

weights, these antimicrobials themselves do not possess antigenic properties (they are haptens). They become immunologically active (i.e., elicit an immunologic response) only after they bind to a "carrier" host protein. Although patients often report a history of penicillin allergy, this may not stand up to close scrutiny.[13] Studies have shown that up to 90% of individuals with a reported history of penicillin allergy can safely use penicillin; these individuals usually either are mislabeled as penicillin allergic or lose their allergy after years of avoidance.[14] Depending on the studies, the frequency of allergic reactions to penicillin varies from 0.01 to 0.05% (1 to 5 reactions per 10,000), with an anaphylactic reaction rate of less than 0.01% and a fatality rate of less than 0.002% (less than 1 fatality per 50,000 penicillin administrations).[15] Parenterally administered penicillin is responsible for most of the anaphylactic reactions. The extensive use of this drug in unsuspected sources such as foods, in which it is used as a bacteriostatic agent, may make it difficult to ascertain historically that penicillin is not the causative agent.

Cephalosporins share the β-lactam ring structure and side chains of the penicillins, and allergic cross-sensitivity has been incriminated in 1 to 8% of patients.[16] Patients who have urticaria or anaphylactic reactions after taking penicillin are approximately four times more likely to have an adverse reaction to cephalosporins. Even in this setting, the risk of an anaphylactic reaction to cephalosporins is still less than 0.1%, and the first dose of cephalosporin can be administered orally under medical supervision.[17]

Insect Stings

Hymenoptera venoms and fire ant stings are responsible for significant anaphylactic morbidity and mortality.[18] The Hymenoptera venoms are complex mixtures of pharmacologically and biochemically active substances. Honeybee venom contains hyaluronidase, phospholipase A, and other peptides. Yellow jacket venom contains not only phospholipases A and B and hyaluronidase but also kinins. Hornet venom contains acetylcholine in addition to those typical peptides. Fire ant venom is mostly a nonproteinaceous alkaloid suspension containing phospholipase A and hyaluronidase.

Stinging Hymenoptera insects affect up to 13.6 million Americans annually (c. 1999), accounting for approximately 50 to 100 deaths annually.[19] Allergic sensitization to Hymenoptera has been reported in 0.4 to 4% of the general population. The principal offenders (in decreasing order of frequency) are yellow jackets, honeybees, wasps, and yellow and bald-faced hornets. The imported fire ant has become a significant pest responsible for anaphylaxis, spreading from the Atlantic and Gulf coasts inland.[20] The introduction of killer (Africanized) bees in Brazil and their subsequent northern migration make them a significant cause of sting-induced anaphylaxis in areas of Texas, Arizona, and the southwestern United States.[21]

Other Agents

Latex and Medical Products. Latex allergy refers to sensitivity to the proteins or chemicals contained in the latex products. The sensitivity reaction can be delayed (type IV) contact dermatitis or an immediate hypersensitivity (type I) reaction (Box 119-3). The most common symptoms of latex allergy include allergic urticaria, rhinitis, conjunctivitis, and occupational asthma. Although latex allergy used to be more common, with the institution of nonpowdered gloves and nonlatex gloves in hospitals, anaphylactic reaction from latex has become an uncommon event.[22] Anaphylactic reactions have also occurred against ethylene oxide (ETO), which is used to sterilize hemodialyzers. ETO can bind with human proteins such as human serum albumin (HSA), rendering the ETO-HSA complex allergenic.

Box 119-3 Gell and Coombs Classification of Immune Reactions

Type I: Immediate Hypersensitivity
Binding of multivalent antigens to IgE on the surface of mast cells and basophils leads to degranulation of mediators. In previously sensitized individuals, the reaction develops quickly (minutes). This type of hypersensitivity reaction is seen in allergic diseases (e.g., hay fever, allergic asthma, urticaria, angioedema, and anaphylaxis). *Anaphylactoid reaction* refers to the direct release of preformed mediators of mast cells independent of IgE.

Type II: Cytotoxic Antibody Reaction
Antibody (IgM, IgG) binding of membrane-bound antigens leads to cytotoxicity and cell lysis of cells through the complement or mononuclear cell system (macrophages, neutrophils, and eosinophils). This type of reaction is seen in transfusion reaction and Rh incompatibility.

Type III: Immune Complex–Mediated Reaction
Binding of antibody (IgM, IgG) to antigens forms soluble immune complexes, which are deposited on vessel walls, causing a local inflammatory reaction (Arthus reaction) leading to inflammation and tissue injury. This type of reaction is seen in systemic lupus erythematosus and serum sickness (after antithymocyte globulin administration).

Type IV: Cell-Mediated Delayed Hypersensitivity
Sensitized lymphocytes (T_H1 cells) recognize the antigen, recruit additional lymphocytes and mononuclear cells to the site, and start the inflammatory reaction. No antibodies are involved. This type of reaction is seen in contact dermatitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Anesthetic Drugs. Local anesthetics produce occasional adverse reactions.[23] Most of these reactions are not allergic in nature but are related to a direct effect of the medication. True allergic reactions are uncommon and are most commonly seen with local anesthetics from the ester family (e.g., procaine, tetracaine, and benzocaine). Allergic reactions to local anesthetics belonging to the amide family (e.g., lidocaine, bupivacaine, mepivacaine, and dibucaine) are rare. Multidose vials of lidocaine contain the preservative methylparaben, which belongs structurally to the ester family. This preservative has been implicated in allergic reactions in patients with a history of previous lidocaine hypersensitivity.[24] Only pure lidocaine (without the methylparaben preservative) should be used in intravenous applications (as in Bier's block).

Vaccines. Anaphylactic reactions have occurred after the administration of egg embryo–grown vaccines, including the combined measles, mumps, and rubella (MMR), yellow fever, and influenza vaccines. Patients who are able to tolerate eggs orally are likely to tolerate the vaccines.

Blood Products. Anaphylactic-type reactions are an uncommon complication of the administration of whole blood and immunoglobulins. The fixation of antibodies to formed elements such as red blood cells, platelets, and leukocytes and soluble components activates the complement system. This is particularly relevant in IgA-deficient patients exposed to multiple transfusions, who may have produced antibodies to IgA in previous transfusions. With subsequent transfusions, an antigen (IgA)–anti-IgA antibody (IgG) immune complex forms, leading to subsequent activation of the complement cascade.

Opiates. Many of the opioid analgesics can cause anaphylactic reaction through a direct histamine release mechanism, although some are IgE mediated. It is unclear how much cross-sensitivity is present among these agents.[25]

www.ketabpezeshki.com 66485457-66963820

Box 119-4 A Standard Treatment Protocol for Patients with a History of Radiocontrast-Induced Anaphylaxis

Prednisone 50 mg by mouth given 13 hours, 7 hours, and 1 hour before the procedure
Diphenhydramine 50 mg intramuscularly given 1 hour before the procedure
Consider ephedrine 25 mg by mouth given 1 hour before the procedure
Consider an H_2 antagonist such as ranitidine 300 mg by mouth given 3 hours before the procedure

Modified from Lieberman P: Anaphylaxis. Med Clin North Am 90:77, 2006.

Radiocontrast Media. Radiocontrast media (RCM) represent an important class of drugs that can cause an anaphylactic reaction. Approximately 10 million radiologic studies using RCM are performed in the United States annually. Anaphylactic reactions to RCM are largely idiosyncratic, occur within minutes of infusion, and are independent of the dose. The pathophysiologic mechanism of anaphylactic reactions to RCM is unknown, but it is believed to be nonimmunologic. Suggested mechanisms include direct histamine release, alternative complement pathway activation, and activation of the contact system. Risk factors for an anaphylactic reaction include a previous adverse reaction to RCM, a history of atopy or allergic disease, asthma, and certain medications. A history of allergy to fish or shellfish is not a contraindication to the use of RCM, nor does it increase the risk of an adverse reaction to RCM.[26] Clinically, the risk for severe adverse reaction is 0.16% with ionic contrast materials and 0.03% with nonionic contrast materials. The death rate from RCM reactions is estimated at 1 to 3 per 100,000 administrations of contrast material.[27] Protocols have been developed to minimize risks of a serious allergic reaction in patients who have had a previous adverse reaction to RCM but who still require additional radiographic studies with contrast agents (Box 119-4).

Aspirin and NSAIDs. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are believed to cause anaphylaxis (or anaphylactoid reaction) through interruption of arachidonic acid metabolism.[28] The incidence of anaphylaxis to aspirin and NSAIDs varies widely, depending on the population (healthy, atopic, or those with nasal polyps). One study estimated the incidence as 2.1 anaphylaxis cases per 100,000 exposed patients.[15] Desensitization protocols have been suggested for cardiovascular patients with a history of aspirin allergy.[29] For aspirin-induced cutaneous disease, an aspirin desensitization protocol that can be used for cardiovascular patients in the ED is to administer aspirin every 15 minutes, starting with 0.1 mg, up to 325 mg at 135 (FD&C Yellow No. 5), may also cause anaphylaxis through modulation of arachidonic acid metabolism.[31]

Immunotherapy Drugs. Allergen extracts are commonly used in skin testing and in immunotherapy (also known as hyposensitization or desensitization).[32] Exposure to therapeutic pollens, by injection or inhalation, can result in local allergic or systemic anaphylactic reactions. High-dose therapy, too frequent administration, or inadvertent intravascular injection increases the risk of anaphylaxis with immunotherapy.

Steroids. Although corticosteroids are used in the management of acute allergic syndromes and anaphylaxis, adverse reactions to these medications have been observed after parenteral administration.[33] Skin testing may demonstrate the specific class of steroids responsible for hypersensitivity, and substitution of a different class should be considered.

Exercise (Physical)–Induced Anaphylaxis. Thermomechanical and physical factors (heat and cold), especially exercise, have increasingly been recognized as etiologic agents in certain anaphylactic-like incidents.[34] The mechanism is unclear, but release of mediators from mast cells and basophils has been implicated. Patients with exercise-induced anaphylaxis are generally dedicated athletes who may have a personal or family atopic history. Exercise-induced anaphylaxis has been demonstrated in some cases to depend on previous ingestion of food to which the patient may be subclinically sensitive. Provocative foods, if identified, should be avoided. Patients should discontinue the exercise at the onset of rash or pruritus. When exercise is continued beyond this point, clinical deterioration is likely in susceptible individuals. Prophylactic treatment with an antihistamine as a single agent or in combination with other agents may be helpful. Avoidance of precipitating factors, modification of exercise, and use of a self-injectable epinephrine kit are recommended for patients with exercise-induced anaphylaxis.

Idiopathic Anaphylaxis. In the United States, approximately 20,000 to 47,000 patients annually see allergists for signs and symptoms of idiopathic anaphylaxis (IA).[35] The diagnosis of IA is made only after extensive evaluation by the allergist. Although IA may be life-threatening, it is usually responsive to conventional therapies, including antihistamines, sympathomimetics, and especially prednisone.[36] Some cases of IA may appear to be caused by the act of kissing but are in fact caused by food or conversion disorders.[37] The overall prognosis for IA is good, but certain patients may experience recurrent IA despite intensive prophylactic therapy. Sometimes, IA can represent "progesterone" anaphylaxis.[38] Women suffering from this disorder may present with recurrent episodes of anaphylaxis that are temporally related to the menstrual cycle. Other patients may have anaphylactic reactions to injection of medroxyprogesterone or luteinizing hormone–releasing hormone.

PRINCIPLES OF DISEASE

Because allergy is intimately related to immunology, a brief review of immunology is included in this chapter. Immunologic responses to *antigens* in humans are coordinated by two systems: the ancient *innate* immune system, which humans inherited from invertebrates; and the recently evolved *adaptive* immune system, which is present in humans and vertebrates (Fig. 119-1). The innate immune system is considered the first line of defense, characterized by its nonspecific but rapid responses to offending agents or microbes. Its effector components include resident cells (epithelial cells, mast cells, macrophages, dendritic cells, antimicrobial proteins), infiltrative cells (natural killer cells, neutrophils, monocytes, dendritic cells), and various proteins (antimicrobial peptides, complements, cytokines, pathogenic pattern recognition receptor [PRR] system). Encoded in the germline, PRRs can recognize pathogen-associated molecular patterns (PAMPs) extracellularly or intracellularly. PAMPs are evolutionarily conserved molecular patterns that are present in microbes but not in humans (except in mitochondrial DNA).[39] On exposure of the human host to these PAMPs, the PRR and subsequently the innate system and the inflammatory cascade are activated, leading to the clearance of dangerous PAMPs.[40] The innate system responds to the danger signals rapidly and nonspecifically, whereas the adaptive immune system takes time for the antigen-specific cells (B and T cells) to amplify through a process known as *clonal expansion* to mount a specific immune response. In contrast to the innate system, the adaptive immune system is characterized by the delayed response, immune memory, enormous diversity, and exquisite specificity. The effector components of the adaptive system include B and T lymphocytes and cytokines. T and B cells are capable of recognizing myriad antigens through a vast library of antibodies and receptors (up to 10^{15}). This diversity is accomplished by somatic rearrangement of fewer than 400 genes.[41,42]

www.ketabpezeshki.com 66485457-66963820

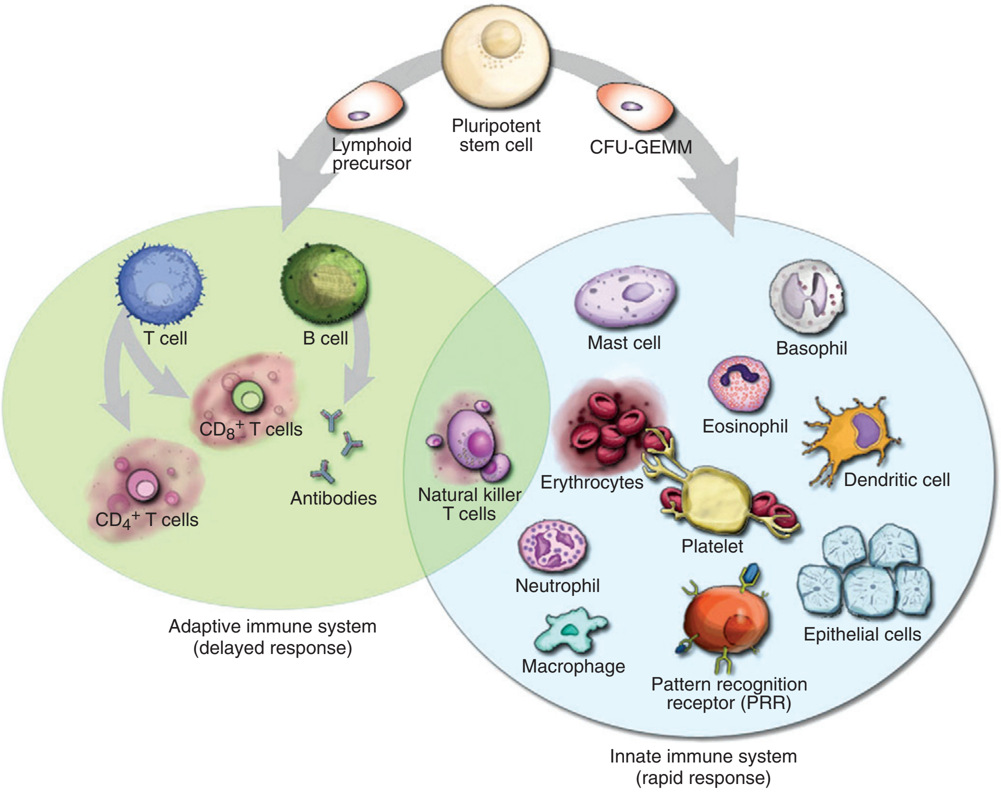


Figure 119-1. Developmental pathways of the immune and hematopoietic systems. *CFU-GEMM,* colony-forming unit for granulocyte, erythroid, myeloid, and megakaryocyte.

Development of the Immune System and Mechanism of Immune-Mediated Injury

The adaptive and innate immune systems originate from the common pluripotential hematopoietic stem cells, which are derived from the yolk sac and later reside in the bone marrow. These stem cells differentiate and develop into the lymphoid precursor cells and the colony-forming unit for granulocyte, erythroid, myeloid, and megakaryocyte (CFU-GEMM) stem cells. The lymphoid precursor cells differentiate into bursa-equivalent lymphocytes (B cells), thymus-derived lymphocytes (T cells), and natural killer cells. The CFU-GEMM cells develop into mast cells, basophils, and others (see Fig. 119-1). When the host encounters a foreign antigen, the cellular components of the adaptive immune system interact with the cellular and protein components of the innate immune system to mount a concerted defense aimed at neutralization of the antigen.

T-Cell Development

Lymphoid precursor cells migrate from the bone marrow into the thymus, where they continue their ontogeny.[43] Under regulation by cytokines and cell-cell interaction, these precursors undergo gene rearrangement and positive and negative selection. In the process, T cells acquire the T-cell antigen receptors and various surface markers. Two types of T cells mature and come out of the thymus: $CD4^+$, also called helper T cells (60-70%), and $CD8^-$, also called suppressor T cells (30-40%). Depending on the type of cytokine produced, T helper cells differentiate into type 1 helper cells (T_H1) and type 2 helper cells (T_H2), with opposing activities. Whereas T_H1 cells inhibit IgE production and IgE isotype switching, T_H2 cells stimulate IgE production and IgE isotype switching. The balance of these stimulatory and inhibitory activities of the T_H1 and T_H2 cells is believed to determine an individual's propensity to develop allergic disease or atopy and may help explain the increased prevalence of allergy in urbanized and Western societies in the past three decades. Early in utero and soon after birth, naïve T lymphocytes in the infant's immune system are dominated by the allergy-prone T_H2 cells and their associated cytokines (interleukins 4, 5, and 13). These cytokines are important inducers for production of IgE antibodies. Later, during infancy through early childhood and adolescence, the nonatopic infant's immune system gradually shifts from this allergy-prone T_H2 environment to an allergy-protective T_H1 environment. The cytokines associated with this T_H1 environment include interleukin-2 and interferon-γ. This shift is thought to be caused by the continual exposure of the young individual's immune system to allergenic stimuli from the surrounding environment, mainly microbes. Features of Western lifestyles, such as changes in infant diets, widespread use of antibiotics, smaller family size, and cleaner childcare, are believed to reduce this stimulatory antigenic exposure in an individual's early years, leading to an environment in which the immune system is dominated by a persistent allergy-prone T_H2 system (the hygiene hypothesis). This imbalance between the two immune systems supposedly ultimately leads to atopy and thus an allergy-prone population.[44]

B-Cell Development and Immunoglobulins

B-cell ontogeny is divided into antigen-independent and antigen-dependent stages.[43] During the antigen-independent stage, B cells mature in primary lymphoid organs (bone marrow and fetal liver), where they undergo gene rearrangement in a stochastic

www.ketabpezeshki.com 66485457-66963820

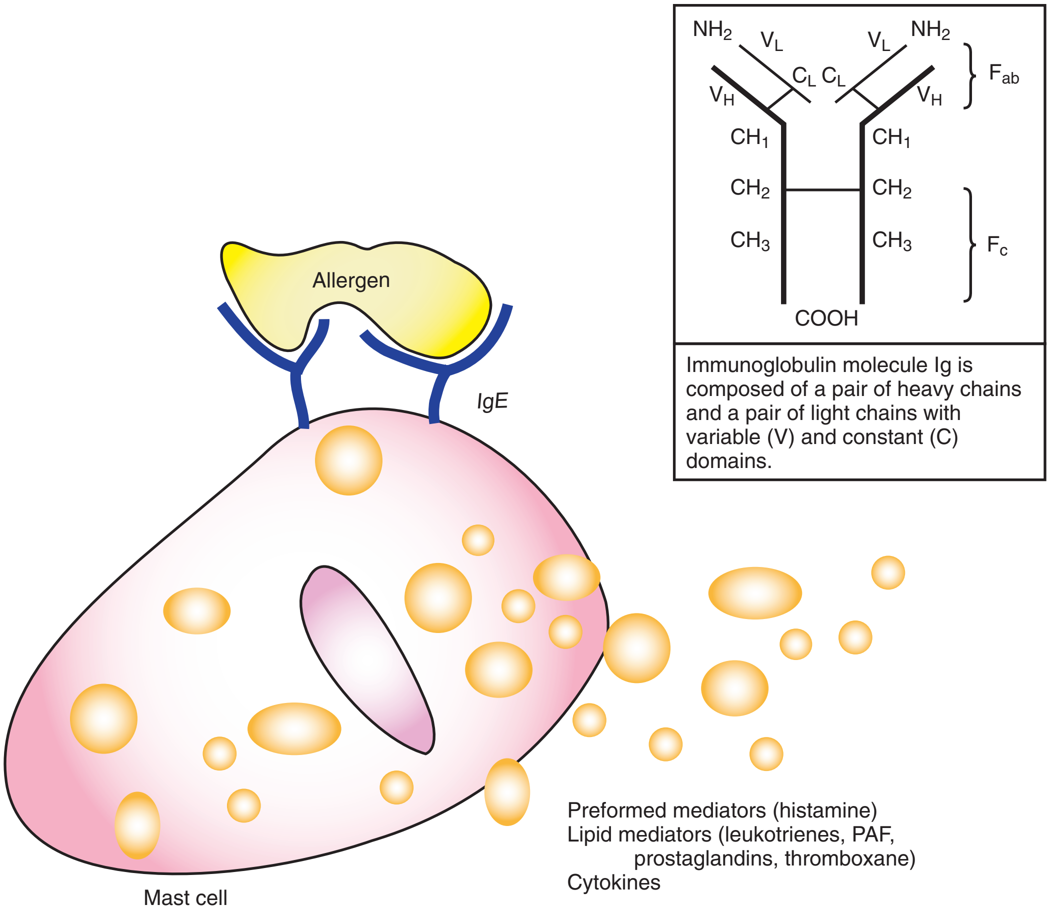


Figure 119-2. Activation of mast cells with degranulation of mast cell mediators by antigen cross-linking of adjacent immunoglobulin E (*IgE*) on the cell surface. *PAF,* platelet-activating factor.

manner and acquire various surface markers. Later during the antigen-dependent stage in the secondary lymphoid organs (lymph nodes and spleen), B cells differentiate into memory B cells and plasma cells and are ready to secrete immunoglobulins. Throughout B-cell ontogeny, B-cell maturation, isotype switching, and immunoglobulin production are driven by activated T cells, cytokines, and interaction with antigen and bone marrow stromal cells.

Immunoglobulins are protein molecules composed of two identical polypeptide heavy chains and two identical polypeptide light chains, covalently linked by disulfide bonds (Fig. 119-2). The heavy (H) chains have one variable domain, V_H, and three or four constant domains, C_H. The light (L) chains have one variable domain, V_L, and one constant domain, C_L. The variable domains of the heavy and light chains together form a pair of identical antigen-binding sites and with the adjacent constant heavy domain pair make up the Fab (antibody-binding fragment) region of the immunoglobulin molecule. The remaining constant domains of the heavy chains together form the Fc (crystallizable fragment) region of the immunoglobulin molecule. The Fc binds to the surface receptors of effector cells, such as mast cells, B cells, or macrophages. There are five isotypes or classes of immunoglobulins, IgG, IgA, IgM, IgD, and IgE; isotype IgG has four subclasses (IgG1, IgG2, IgG3, and IgG4), and IgA has two subclasses (IgA1 and IgA2). The body usually produces IgM antibodies when it first encounters an antigen. Repeated antigenic exposure, however, may cause the constant region of the IgM to switch to another class (IgA, IgG, or IgE), a process also known as isotype switching. Isotype IgE (and IgG4) is the most important antibody in the pathogenesis of allergic disease and anaphylaxis.

Classification of Reactions

The term *allergy* is commonly used to describe clinical illnesses produced by excessive immune responses by a normal immune system to otherwise innocuous allergens. In this chapter, we adapt the classic Coombs and Gell classification to categorize these hypersensitivity reactions (Box 119-5).

Type I reactions (immediate hypersensitivity) are IgE mediated and account for most allergic and anaphylactic reactions observed in humans. Exposure to sensitizing allergens causes mediators from mast cells and basophils to be released through both IgE-dependent and direct mast cell degranulation (IgE-independent) mechanisms. Rhinitis caused by ragweed pollen and anaphylaxis caused by foods are examples of the IgE-dependent mechanism; anaphylactic reaction to aspirin is an example of the IgE-independent mechanism.

Type II reactions (cytotoxic) denote antibody-mediated cytotoxic reaction. Complement-fixing IgG (or IgM) engages cell-bound antigen, activating the classic complement pathway and leading to the fixation of membrane attack complexes on the cell surface and subsequent cell lysis. In the process, anaphylatoxins C3a and C5a cause mast cell mediators to be released, producing the same clinical syndrome seen in allergic anaphylaxis.

Type III reactions (immune complex) are IgG or IgM complex mediated. Circulating soluble antigen-antibody immune complexes migrate from the circulation to be deposited in the perivascular interstitial space, thereby activating the complement system. Anaphylactic reactions to blood transfusions and blood component therapy, including serotherapy (immunoglobulin administration), are examples of the overlap of type II and type

www.ketabpezeshki.com 66485457-66963820

Box 119-5 Clinical Criteria for Diagnosis of Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) *and at least one of the following:*
   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following occurring rapidly (minutes to several hours) after exposure to a likely allergen for that patient:
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

From Sampson HA, et al: Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 119:391, 1996.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and <90 mm Hg from 11 to 17 years.

BP, blood pressure; *PEF,* peak expiratory flow.

III reactivity. They have therefore been classified as complement-mediated or immune complex–mediated anaphylaxis.

Type IV reactions (delayed hypersensitivity) are T-cell mediated and have no documented relationship to the pathogenesis of anaphylaxis.

PATHOPHYSIOLOGY

Mast cells, basophils, and their mediators are the central effectors in allergy and anaphylaxis. Exposure of a genetically predisposed individual to an allergen leads to the synthesis and release of allergen-specific IgE by plasma cells into the circulation. Fixation of this allergen-specific IgE to surface receptors on mast cells (FcεRI) completes the process known as *sensitization*. These IgE-bearing mast cells usually reside in the mucosal surfaces, submucosal tissue (around venules), and cutaneous surfaces, and they are capable of becoming activated on reexposure to a specific allergen. Cross-linking of the FcεRI receptors on the mast cells by a specific multivalent allergen sets off a cascade of conformational and biochemical events, causing the degranulation of preformed mediators, subsequent generation and release of arachidonic acid metabolites, elaboration of cytokines and chemokines, and activation of the cellular components by the innate and adaptive systems. These series of events ultimately lead to the clinical syndrome of allergy and anaphylaxis (see Fig 119-2).

Mediators of Anaphylaxis

The numerous mediators released by mast cells and basophils exert overlapping physiologic effects on target organs and tissues, making it difficult to ascribe specific clinical manifestations to any one mediator. Histamine is the most important mediator and responsible for most of the clinical symptoms (Table 119-1). It is an essential mediator in immediate hypersensitivity and inflammation, and its infusion has been shown to produce the majority of the clinical features of anaphylaxis syndrome.[45] There are three classes of histamine receptors: H_1, H_2, and H_3. H_1 receptor stimulation produces bronchial, intestinal, and uterine smooth muscle contraction; coronary artery spasm; plaque rupture; and acute myocardial infarction (Kounis syndrome).[46] H_1 receptor stimulation also increases vascular permeability, nasal mucus production, eosinophil and neutrophil chemokinesis, and chemotaxis. H_2 receptor stimulation increases the rate and force of ventricular and atrial contraction, gastric acid secretion, airway mucus production, and vascular permeability while also causing bronchodilation and inhibition of basophil histamine release. H_3 receptors are found in neurons (in the central nervous system) and peripheral tissues; these receptors control the synthesis and release of histamine.

In addition to histamine, lipid metabolites elaborated through the prostanoid and leukotriene pathways contribute to the adverse physiologic effects induced by histamine. Prostaglandin D_2 (PGD_2) is the main arachidonic acid metabolite released by activated mast cells (but not by basophils). PGD_2 and thromboxanes are synthesized from arachidonic acid by the cyclooxygenase pathway (through both COX-1 and COX-2). PGD_2 is responsible for hypotension, inhibition of platelet aggregation, and bronchospasm; PGD_2 is approximately 30 times more potent than histamine in causing bronchoconstriction. The cysteinyl leukotrienes LTB_4, LTC_4, LTD_4, and LTE_4 are synthesized from arachidonic acid through the lipoxygenase pathway. LTB_4 and LTC_4 are first synthesized intracellularly in mast cells and basophils and then secreted; LTC_4 is subsequently converted to LTD_4 and LTE_4 in the extracellular space (by γ-glutamyl transpeptidase and dipeptidase). They are involved in cholinergic-independent bronchospasm, increased vascular permeability, and increased mucous gland production. These three leukotrienes have slow onset but potently add to the bronchoconstriction already induced by histamine (LTC_4 and LTD_4 are 1000 times more potent than histamine).

Platelet-activating factor (PAF) is a phospholipid and the most potent compound known to cause aggregation of human platelets. Its other actions include neutrophil activation and chemotaxis and ileal and parenchymal lung strip smooth muscle contraction. PAF produces many of the important clinical manifestations of anaphylaxis, including decreased myocardial contractile force, coronary vasoconstriction, pulmonary edema, and prolonged increase in total pulmonary resistance with a decrease in dynamic compliance.[47,48] Indeed, blockage of PAF with experimental antagonists leads to improved cardiac function, suggesting that PAF may be involved in the late cardiac dysfunction and lethality associated with anaphylaxis.[49]

Recent data have highlighted the important roles that nitric oxide and sphingosine 1-phosphate play in anaphylaxis. Sphingosine 1-phosphate can trigger calcium influx, stimulating synthesis of cytokines and mast cell degranulation. Nitric oxide is synthesized in vascular endothelium and is a sufficiently potent vasodilator to cause hypotension in anaphylaxis. Its action can be increased by histamine, leukotriene, tumor necrosis factor alpha, and PAF.[47,50]

Physiologic Effects

At the organ and tissue level, mediators released from mast cells and basophils account for the overall pathophysiologic effects of anaphylaxis, which variably are manifested clinically as urticaria and angioedema, rhinorrhea, conjunctivitis, chest pain, breathing difficulty, respiratory insufficiency, headache, syncope,

www.ketabpezeshki.com 66485457-66963820

Table 119-1 Mediators in Anaphylaxis and Their Physiologic Actions

MEDIATORS	PHYSIOLOGIC ACTIVITY	CLINICAL MANIFESTATION
Histamine, leukotrienes, thromboxane, prostaglandins, platelet-activating factor, nitric oxide	Vascular permeability, vasodilation, smooth muscle spasm, mucous gland secretion, nociceptor stimulation, myocardial depression	Generalized urticaria and angioedema, pruritus, wheezing, bronchoconstriction, rhinorrhea and bronchorrhea, coryza, conjunctivitis, syncope, tachycardia, hypotension, shock, abdominal pain, nausea, vomiting, diarrhea
Tryptase, carboxypeptidase, chymase, cathepsin G	Activation of complement system, chemoattraction, activation and degranulation of mast cells	Anaphylaxis response is amplified by recruitment and activation of the complement system and further degranulation of mast cell mediators; extent of anaphylaxis may also be limited through opposing effects on conversion of angiotensin I to angiotensin II
Heparin, chondroitin sulfate	Antithrombotic, inhibition of the complement system, chemoattraction, activation of the kinin pathway	Tendency for intravascular coagulation is tempered; activation of the kinin system can exacerbate symptoms of anaphylaxis
TNF-α, cytokines, chemokines, eosinophil chemotactic factors	Induction of anti–platelet-activating factor production, control of migration of eosinophils and other inflammatory cells	May be responsible for the intensity, protracted symptoms, and multiphasic reaction of the anaphylaxis attack

TNF-α, tumor necrosis factor alpha.

hypotension and hemodynamic instability, nausea, vomiting, diarrhea, and other gastrointestinal symptoms (see Table 119-1). Increased vascular permeability caused by histamine leads to urticaria, angioedema, laryngeal edema, nasal congestion, or gastrointestinal swelling with abdominal cramping and vomiting. Vasodilation can lead to flushing, headaches, reduced peripheral vascular resistance, hypotension, and syncope. Contraction of smooth muscle can lead to bronchospasm, abdominal cramping, or diarrhea. Pulmonary vessel vasoconstriction can lead to pulmonary hypertension, pulmonary edema, and decreased cardiac filling pressures. Coronary vasoconstriction can lead to myocardial ischemia and decreased myocardial contractile force. Changes in atrial chronotropy and ventricular and atrial isotropy can lead to cardiac dysrhythmias. In addition to the direct actions on the target tissues, these preformed mediators, lipid-derived mediators, and cytokines activate a number of inflammatory pathways, including the complement system, the clotting and clot lysis systems, and the kallikrein-kinin (contact) system, to add to the clinical manifestations of allergy and anaphylaxis. Deaths in anaphylaxis are caused most commonly by acute respiratory failure from laryngeal angioedema and less commonly by cardiovascular collapse.

Hemodynamic instability in anaphylaxis is typically the result of peripheral vasodilation, enhanced vascular permeability, leakage of plasma, and intravascular volume depletion (the "empty ventricle" syndrome). Up to 50% of intravascular volume can shift to the extravascular space within 10 minutes of exposure.[51] In a number of clinical settings, the hypotension in anaphylaxis is also associated with depressed cardiac index and increased pulmonary vascular resistance. The use of pressors alone in anaphylaxis may not improve hemodynamics. Aggressive volume expansion with crystalloid (2-7 L of normal saline) is needed for hypotension in anaphylaxis.[6]

CLINICAL FEATURES

Anaphylactic reactions vary in duration and severity, affecting organs that are rich in mast cells—the cutaneous, upper and lower respiratory, cardiovascular, neurologic, and gastrointestinal systems. Clinical presentations of anaphylaxis depend on the degree of hypersensitivity; the quantity, route, and rate of antigen exposure; the pattern of mediator release; and the target organ sensitivity and responsiveness. Symptoms of anaphylaxis usually occur minutes after an exposure, although some reactions take longer (>30 minutes). Protracted anaphylaxis may last up to 32 hours.[51] Up to 20% of patients may present with *biphasic anaphylaxis,* in which clinical symptoms may recur 8 to 24 hours after resolution of symptoms from the index event.[52] There are no firmly established factors that can be used to predict which group of patients is at risk for this biphasic attack, although delayed and inadequate administration of epinephrine after the index event and the lack of steroid use have been cited in some studies.[53] Fatal cases of anaphylaxis are usually caused by acute respiratory failure due to laryngeal edema and less commonly by cardiovascular collapse.

The first clinical manifestation of anaphylaxis usually involves the skin (88%), described as generalized warmth and tingling of the face, mouth, upper chest, palms, soles, or the site of antigenic exposure. Pruritus is a nearly universal feature and may be accompanied by generalized flushing and urticaria. Patients presenting with angioedema may complain of swelling and a sensation of burning under the skin but no itchy rash. This may be followed by mild to severe respiratory distress. The patient may describe a cough; a sense of chest tightness, dyspnea, and wheeze from bronchospasm; or throat tightness, dyspnea, odynophagia, or hoarseness associated with laryngeal edema or oropharyngeal angioedema. Hypotension or dysrhythmias may be manifested as lightheadedness or syncope. Seizure activity caused by decreased cerebral perfusion may rarely be observed. Any of these clinical patterns may occur independently or in association with nasal congestion and sneezing; ocular itching and tearing; cramping abdominal pain with nausea, vomiting, diarrhea, and tenesmus; incontinence; pelvic pain and uterine cramping; headache; or a sense of impending doom. Although urticaria and angioedema are the most common presenting symptoms in anaphylaxis (88%), fatal anaphylaxis syndromes with laryngeal edema and circulatory collapse can occur even in the absence of any premonitory warning symptoms or signs or cutaneous manifestations.[6]

The physical examination may reveal tachypnea, tachycardia, and hypotension. Laryngeal stridor, hypersalivation, hoarseness, and angioedema indicate upper airway obstruction, whereas coughing, wheezing, rhonchi, and diminished air flow suggest lower respiratory tract bronchoconstriction. Tachycardia and hypotension suggest cardiac insufficiency. Commonly observed dysrhythmias include sinus tachycardia, premature atrial and ventricular contractions, nodal rhythm, and atrial fibrillation. Other electrocardiographic changes include nonspecific and ischemic ST-T wave changes, right ventricular strain, and intraventricular conduction defects. The patient may have a depressed level of consciousness because of hypotension; rarely, this may be caused

www.ketabpezeshki.com 66485457-66963820

by a postictal state due to seizure activity. Urticaria, angioedema, rhinitis, and conjunctivitis may be evident. A summary of the observed clinical manifestations of anaphylaxis along with their related pathophysiologic changes is presented in Table 119-2.

DIAGNOSTIC STRATEGIES

The diagnosis of anaphylaxis remains clinical. A good history and physical examination offer emergency physicians the best tools in diagnosis of anaphylaxis. The diagnosis of anaphylaxis is "highly likely" in a patient presenting with skin symptoms (itchy urticaria, flushing, and swollen lips, tongue, or throat) *and* either respiratory difficulty (dyspnea, wheezing, and stridor) *or* reduced blood pressure, after an acute exposure (see Box 119-5).[54] Diagnostic laboratory testing is limited and seldom used in the ED. Anaphylaxis can be confirmed by testing for allergen-specific IgE and serum tryptase, serum histamine, or 24-hour urine histamine in select cases. Screening studies are aimed at ruling out of other emergencies (Box 119-6). The initial screening studies can include a complete blood count, complete metabolic panel (hypoglycemia), coagulation panel (prothrombin time, partial thromboplastin time, and international normalized ratio), cardiac enzymes, electrocardiogram, urine analysis, erythrocyte sedimentation rate, and portable chest radiograph. Serum levels of serotonin and urinary 5-hydroxyindole acetic acid, catecholamines, and vanillylmandelic acid are useful to rule out carcinoid syndrome. Serial arterial blood gas analysis may help monitor clinical response. Blood culture, urine culture, computed tomography of the head and lateral soft tissue of the neck, and indirect and direct laryngoscopy can be considered, depending on the clinical situation.

DIFFERENTIAL DIAGNOSIS

The diagnosis of anaphylaxis is readily apparent in a patient presenting with acute rash, respiratory difficulty, or cardiac insufficiency after an allergenic exposure. Considerations for confounders and other diseases with overlapping presentations are shown in Box 119-6.

Urticaria and Angioedema

Generalized urticaria is usually allergic in nature (i.e., mast cell mediated). In half of the cases, it is accompanied by angioedema and may meet the definition for anaphylaxis. Similarly, most cases of angioedema are allergic and usually associated with urticaria. Angioedema caused by bradykinin excess (e.g., hereditary angioedema or ACE inhibitor) usually is manifested without urticaria. The treatment of this "nonallergic" angioedema is rapidly evolving with ongoing clinical trials and new medications approved by the Food and Drug Administration (FDA). Adverse cutaneous drug reactions (ACDR) comprise a spectrum of skin manifestations due to complications from drug therapy. The majority of these ACDRs are minor allergic reactions (e.g., IgE-mediated urticarial rash to penicillin). Severe, life-threatening ACDRs (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug eruption, drug hypersensitivity syndrome) may mimic drug-induced anaphylaxis.

Flush Syndrome

Flush syndrome refers to a group of diverse clinical entities that are characterized by the onset of redness and a feeling of warmth of the face, neck, trunk, and abdomen. Flushing of the face induced by alcohol is common in Asian patients. Monosodium glutamate (MSG) and its cyclization product pyroglutamate are common seasonings in Chinese foods and can provoke flushing. Scombroidosis, a type of histamine poisoning, is caused by the ingestion of spoiled fish that have a high histidine content (generally dark meat fish such as tuna); histamine and *cis*-urocanic acid are produced by histidine-decarboxylating bacteria that cleave histamine from histidine when the fish are not properly stored.

Patients usually present with a frightening flush (sunburn like) but no urticaria, palpitations, syncope, nausea, vomiting, or diarrhea. A number of neoplastic disorders (mastocytosis, carcinoid syndrome, VIPoma, medullary carcinoma of the thyroid) secrete vasoactive substances that are present in anaphylaxis. Harlequin syndrome refers to the hemifacial flushing and sweating induced by exercise.

Respiratory Insufficiency

Epiglottitis, supraglottitis, retropharyngeal and peritonsillar abscess, laryngeal spasm, foreign body aspiration, tumor, obstructive lung diseases such as acute asthma, and status asthmaticus can be manifested with acute respiratory difficulty but are usually not associated with other symptoms and signs of anaphylaxis. Exercise-induced anaphylaxis can be differentiated from exercise-induced asthma as the former is usually accompanied by pruritus and other systemic manifestations of anaphylaxis. Patients with acute pulmonary embolism may present with respiratory difficulty and shock but without the cutaneous stigmata of anaphylaxis.

Shock and Cardiovascular System

Patients with anaphylactic shock may present with urticarial rash, angioedema, respiratory insufficiency, hypotension, vasodilation, and signs and symptoms of end-organ hypoperfusion. This form of shock must be differentiated from early presentations of septic shock (end-organ hypoperfusion, rash, vasodilation, hypotension). A history of recent allergenic exposure is helpful in making the diagnosis of anaphylaxis. Spinal shock also presents with hypotension and vasodilation but usually without the urticarial rash and in the setting of significant spinal injury. In all these forms of shock, the skin is usually moist and warm, suggesting a state of decreased peripheral vascular resistance. Cardiogenic, restrictive, hypovolemic, or hemorrhagic shock, on the other hand, would more likely be seen with signs and symptoms of end-organ hypoperfusion and cold, clammy skin, suggesting a state of heightened peripheral vascular resistance. In addition to history, measurement of central venous pressures may add useful data in teasing out the different forms of shock.

Syncope

Vasovagal syncope is the most common differential diagnosis in the patient arriving with collapse as a result of parenteral administration of an antigen. Classically, the patient has bradycardia, hypotension, and pallor as opposed to the tachycardia, hypotension, and flush skin usually associated with anaphylaxis. The absence of any other clinical manifestations of anaphylaxis, along with history of stress, pain, and previous episodes of simple faints, helps point toward the diagnosis of vasovagal syncope. Other causes of syncope, such as seizure, stroke, hypoglycemia, acute coronary syndrome, and cardiac dysrhythmia, also need to be considered. Ordinary allergic reactions and especially anaphylaxis can precipitate an acute coronary syndrome.

MANAGEMENT

Out-of-Hospital Care

When a susceptible patient is reexposed to an antigen to which there has been a previous reaction, self-administered epinephrine is recommended at the first onset of clinical manifestations of

www.ketabpezeshki.com 66485457-66963820

Table 119-2 Clinical Manifestations of Anaphylaxis and Related Pathophysiologic Changes

ORGAN SYSTEM	REACTION	SYMPTOMS	SIGNS	PATHOPHYSIOLOGIC CHANGES
Respiratory tract				
Upper	Rhinitis	Nasal congestion Nasal itching Sneezing	Nasal mucosal edema Rhinorrhea	Increased vascular permeability Vasodilation Stimulation of nerve endings
	Laryngeal edema	Dyspnea Hoarseness Throat tightness Hypersalivation	Laryngeal stridor Supraglottic and glottic edema	As above, plus increased exocrine gland secretions
Lower	Bronchospasm	Cough Wheezing Retrosternal tightness Dyspnea	Cough Wheeze, rhonchi Tachypnea Respiratory distress Cyanosis	As above, plus bronchiole smooth muscle contraction
Cardiovascular system	Circulatory collapse	Lightheadedness Generalized weakness Syncope Ischemic chest pain	Tachycardia Hypotension Shock	Increased vascular permeability Vasodilation Loss of vasomotor tone Increased venous capacitance
	Dysrhythmias	As above, plus palpitations	ECG changes: Tachycardia Nonspecific and ischemic ST-T wave changes Right ventricular strain Premature atrial and ventricular contractions Nodal rhythm Atrial fibrillation	Decreased cardiac output Decreased mediator-induced myocardial suppression Decreased effective plasma volume Decreased preload Decreased afterload Hypoxia and ischemia Dysrhythmias Iatrogenic effects of drugs used in treatment Preexisting heart disease
	Cardiac arrest		Pulseless ECG changes: Ventricular fibrillation Asystole	
Skin	Urticaria	Pruritus Tingling and warmth Flushing Hives	Urticaria Diffuse erythema	Increased vascular permeability Vasodilation
	Angioedema	Nonpruritic extremity, periorbital and perioral swelling	Nonpitting edema, frequently asymmetrical	Increased vascular permeability
Eye	Conjunctivitis	Ocular itching Increased lacrimation Red eye	Conjunctival inflammation	Stimulation of nerve endings
Gastrointestinal tract		Dysphagia Cramping, abdominal pain Nausea and vomiting Diarrhea (rarely bloody) Tenesmus	Nonspecific	Increased secretion of mucus Gastrointestinal smooth muscle contraction
Miscellaneous central nervous system		Apprehension Sense of impending doom Headache Confusion	Anxiety Seizures (rarely) Coma (late)	Secondary to cerebral hypoxia and hypoperfusion Vasodilation
Hematologic	Fibrinolysis and disseminated intravascular coagulation	Abnormal bleeding and bruising	Mucous membrane bleeding, disseminated intravascular coagulation Increased uterine tone Vaginal bleeding	Mediator recruitment and activation Uterine smooth muscle contraction Bladder smooth muscle contraction
Genitourinary		Pelvic pain Vaginal bleeding Urinary incontinence	Urinary incontinence	

ECG, electrocardiographic.

anaphylaxis (adult dose, 0.2-0.5 mL of 1:1000 [1 mg/mL] intramuscularly; pediatric dose, 0.01 mg/kg of 1:1000 intramuscularly). Delayed administration of epinephrine is associated with increased risks of adverse outcomes.[55] Susceptible patients can use aerosolized epinephrine from a metered-dose inhaler to counteract the effects of laryngeal edema, bronchoconstriction, and other manifestations of anaphylaxis.[56] Multiple inhalations (e.g., 10-20 doses, resulting in the inhalation of 1.5-3 mg of epinephrine) produce therapeutic plasma levels, with the advantages of ease of administration, rapid absorption, and locally high

www.ketabpezeshki.com 66485457-66963820

Box 119-6 Differential Diagnosis of Anaphylaxis

- Acute generalized urticaria
- Allergic and nonallergic angioedema (HAE, ACE inhibitor)
- Adverse cutaneous drug reaction
- Flush syndrome
  - Flushing associated with food
    - Alcohol
    - Monosodium glutamate
    - Sulfites
    - Scombroidosis
  - Carcinoid tumor
  - Medullary carcinoma of thyroid
  - Basophilic leukemia
  - Red man syndrome (vancomycin)
  - Pheochromocytoma
  - Mastocytoses (systemic mastocytosis and urticaria pigmentosa)
  - Vasointestinal peptide tumors
  - Capillary leak syndrome
  - Postmenopausal
  - Hydatid cyst
  - Harlequin syndrome (exercise induced)
  - Auriculotemporal nerve syndrome (Frey's syndrome)
- Respiratory disorders
  - Upper airway disorders (epiglottitis, Ludwig's angina, quinsy, foreign body aspiration, tumor)
  - Status asthmaticus, asthmatic attack
  - Obstructive airway diseases
  - Pulmonary embolism
- Shock syndromes and cardiac
  - Septic shock
  - Hypovolemic shock
  - Cardiogenic shock
  - Distributive shock
  - Acute coronary syndrome
- Miscellaneous
  - Hypoglycemia
  - Neurogenic syncope (vasovagal)
  - Acquired and hereditary angioedema (C1 esterase deficiency)
  - Graft-versus-host disease
  - Progesterone anaphylaxis
  - Neurologic disorders (seizure, stroke, autonomic epilepsy)
  - Vocal cord dysfunction syndrome
  - Panic attacks
  - Undifferentiated somatoform anaphylaxis

Modified from Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology: The diagnosis and management of anaphylaxis: An updated practice parameter. J Allergy Clin Immunol 115(Suppl 2):S483-S523, 2005.
HAE, hereditary angioedema; *ACE,* angiotensin-converting enzyme.

epinephrine levels in the upper and lower airways. Epinephrine should be used with caution in elders and those with a history of cardiovascular disease or hypertension, but it must be stated that there are no absolute contraindications to the use of epinephrine in anaphylaxis.[6] Oral (and parenteral) diphenhydramine (50 mg) can also be administered, but this is only an adjunct therapy.

Out-of-hospital personnel may be required to resuscitate a moribund patient with basic life support. Their first priority is to establish and to maintain ventilation, intravenous access, cardiac monitoring, and administration of supplemental oxygen.

Local measures to decrease antigen absorption from an extremity include dependent positioning of the extremity, ice to vasoconstrict locally, and application of a loose tourniquet to obstruct the venous and lymphatic circulation. The tourniquet should be released for 1 minute of every 10 minutes and should never be applied continuously for more than 2 hours. If an insect stinger remains in the wound, the wound should not be squeezed because the stinger may inject more venom into the patient; the stinger should be removed gently with instruments, avoiding disturbance of the venom apparatus.

Emergency Department

Because most of the morbidity and mortality associated with anaphylaxis are caused by acute respiratory failure or cardiovascular collapse, the treatment of anaphylaxis focuses on the triad of providing a patent airway, expanding intravascular volume with crystalloid (or colloid), and early administration of epinephrine. Antihistamines (H_1 and H_2) and steroids are commonly given in cases of anaphylaxis, although there is no objective evidence that they will improve the outcome.[57,58] Box 119-7 summarizes the treatment algorithm in anaphylaxis.

Airway

Patients at risk of losing their airway are preoxygenated while the airway is assessed. Because upper airway obstruction from laryngeal angioedema can progress rapidly, preparations for a difficult airway, including a surgical airway, must be made early. Premedication with nebulized epinephrine may help maximize visualization. The success rate of intubation is improved when it is performed early, before significant soft tissue swelling from orolaryngeal angioedema occurs.

Volume Expansion

Along with airway preparation, start aggressive fluid resuscitation, which may include 1 to 2 L of normal saline (NS) infused rapidly through large-bore (e.g., 16-gauge) intravenous lines (5 to 10 mL/kg in first 5 minutes). NS is preferred to lactated Ringer's solution, which has the potential to exacerbate metabolic acidosis.[6] The use of a colloid solution (e.g., 5% albumin) in addition to NS may be helpful because of the increased vascular permeability in anaphylaxis. Large volumes of NS (2-7 L) may be required to reverse the fluid lost to extravascular space in anaphylaxis. Patients with heart failure or renal failure should be monitored closely for signs of volume overload.

Epinephrine

Epinephrine is the drug of choice and the first drug to be given at the first suspicion of an anaphylactic reaction.[6] The dose of aqueous epinephrine is 0.2 to 0.5 mL of 1:1000 (1 mg/mL) intramuscularly for adults and 0.01 mg/kg of 1:1000 intramuscularly for pediatric patients, repeated every 5 minutes as needed. The intramuscular route allows shorter time to peak plasma epinephrine concentration (8 minutes) versus subcutaneous administration (34 minutes).[6]

Epinephrine derives its therapeutic value from its combined alpha-adrenergic and beta-adrenergic actions. Its $alpha_1$-adrenergic stimulation increases vasoconstriction, increases peripheral vascular resistance, and decreases mucosal edema. Its $beta_1$-adrenergic stimulation brings about positive inotropic and chronotropic cardiac activity, and its $beta_2$-adrenergic stimulation results in stabilization of mast cells and basophils and bronchodilation.[2] As a result, epinephrine decreases mediator release from mast cells (and basophils), improves hives and bronchospasm, decreases mucosa edema and swelling, and reverses systemic hypotension. Epinephrine therefore works directly to improve the clinical features most commonly observed in a fatal anaphylactic reaction.

Epinephrine can, however, produce untoward side effects, such as palpitations, anxiety, and headache. Excessive alpha-agonist activity (as in overdose) can result in a hypertensive crisis and

www.ketabpezeshki.com 66485457-66963820

Box 119-7 Treatment Options for Anaphylaxis

Emergency Measures (taken simultaneously)

Remove any triggering agent. If the patient had a sting or immunization injection, place a loose tourniquet proximal to the site; if the reaction site is on an extremity, place the extremity in dependent position.
Place patient in the Trendelenburg position if hypotensive.
Begin cardiac monitoring, pulse oximetry, and blood pressure autonomic monitoring; apply oxygen non-rebreather mask, establish large-bore intravenous lines, draw blood, obtain stat electrocardiogram and portable chest radiograph.
Establish a patent airway.
- Open the airway by head tilt/chin lift or jaw thrust as clinically appropriate.
- Be prepared for endotracheal intubation with or without rapid sequence intubation.
  - Be prepared to use adjunct airway technique (laryngeal mask airway, fiberoptic, jet ventilation, surgical airway) as per local custom.
  - Administer racemic epinephrine (L-epinephrine acceptable) 0.5 mL of 2.25% solution in 2.5 mL of NS by nebulizer while awaiting definitive airway management.
- Start rapid infusion of isotonic crystalloid (NS): 500 mL in the first 5 minutes in the adult; several liters of NS may be required.

Antianaphylactic Drugs

Epinephrine is the first-choice drug, to be given simultaneously with the above general emergency measures, at the first suspicion of an anaphylactic reaction.
- Intramuscular (1 : 1000 concentration)
  - Adult: 0.3-0.5 mL every 5 minutes, more often as clinically indicated, titrated to effects
  - Pediatric: 0.01 mL/kg, every 5 minutes as necessary, titrated to effects
  - Alternatively, epinephrine (EpiPen, 0.3 mL; or EpiPen Jr, 0.15 mL) can be administered into anterolateral thigh. Removal of clothing is unnecessary.
- Intravenous (1 : 100,000 concentration; 0.1 mL of 1 : 1000 epinephrine in 10 mL of NS)
  - Continuous hemodynamic monitoring required
  - 10 mL of 1 : 100,000 during 10 minutes, titrated to effects; repeat as necessary

Antihistamines
- Diphenhydramine: intravenous (intramuscular acceptable)
  - Adult: 50 mg, up to 400 mg/24 hr, titrated to effects
  - Pediatric: 1 mg/kg, up to 300 mg/24 hr, titrated to effects
- Ranitidine: intravenous
  - Adult: 50 mg IV (150 mg oral)
  - Pediatric: 1 mg/kg IV or oral

Aerosolized beta-agonists
- Adult
  - Albuterol: 2.5 mg, diluted to 3 mL of NS; may be given continuously
  - Levalbuterol: 0.625-1.25 mg, diluted to 3 mL of NS; may be given continuously
  - Ipratropium: 0.5 mg in 3 mL of NS; repeat as necessary
- Pediatric
  - Albuterol: 2.5 mg, diluted to 3 mL of NS; may be given continuously
  - Levalbuterol: 0.31-0.625 mg, diluted to 3 mL of NS; may be given continuously
  - Ipratropium: 0.25 mg in 3 mL of NS; repeat as necessary

Methylprednisolone
- Adult: 125-250 mg IV
- Pediatric: 1-2 mg/kg IV

Special Situations

Refractory Hypotension

Consider continuous epinephrine drips
- Dilute 1 mg (1 mL 1 : 1000) in 250 mL D_5W to yield a concentration of 4 µg/mL
- Infuse this diluted solution at 1 to 4 µg/min, up to 10 µg/min, titrated to effects

Glucagon: 1-5 mg IV during 5 minutes, followed by 5-15 µg/min continuous infusion
Consider vasopressors:
- Dopamine, 5-20 µg/kg/min continuous infusion and/or dobutamine 5-20 µg/kg/min continuous infusion, titrated to effects
- Norepinephrine: 8-12 µg/min (2-3 mL/min; 4 mg added to 1000 mL of D_5W provides a concentration of 4 µg/mL), titrated to effects
- Phenylephrine, 40-180 µg/min, titrated to effects
- Vasopressin, 2-4 IU/hr, titrated to effects

Patients Receiving Beta-Blockade

Glucagon: 1-5 mg IV during 5 minutes, followed by 5-15 µg/min continuous infusion
Transcutaneous pacing for bradycardia
Atropine for bradycardia
- Adult: 0.3-0.5 mg IV or subcutaneous, to a maximum of 3 mg
- Pediatric: 0.02 mg/kg IV or subcutaneous, to a maximum of 2 mg

D_5W, 5% dextrose in water; *NS,* normal saline.

intracerebral bleeding; worsen myocardial oxygen consumption through increased wall tension, contractility, and chronotropism; and cause myocardial ischemia, myocardial infarction, and pulmonary edema. Increased automaticity and chronotropism can produce hemodynamically significant supraventricular and ventricular tachydysrhythmia. Despite these concerns, the benefits of early administration of epinephrine in anaphylaxis far outweigh any of the stated risks. Serious adverse effects of epinephrine administration, such as myocardial ischemia and pulmonary edema, are usually attributable to an overdose or inappropriately rapid intravenous infusion.[59] There are no absolute contraindications to the use of epinephrine, and it is the drug of first choice in anaphylaxis and anaphylactic shock.[6]

If the patient remains hypotensive after multiple doses of intramuscular epinephrine and aggressive volume expansion, intravenous epinephrine should be considered.[6] Intravenous epinephrine infusion increases the risks of cardiac dysrhythmias, thus requiring continuous cardiac and hemodynamic monitoring. Dilution and slow administration are recommended to reduce untoward effects by epinephrine. The initial intravenous dose is 10 mL of a 1 : 100,000 dilution of aqueous epinephrine during 10 minutes. This is done by dilution of 0.1 mL of 1 : 1000 epinephrine in 10 mL of NS and infusion during 10 minutes (i.e., 100 µg epinephrine infusion given intravenously during 10 minutes at 10 µg/min). If no improvement is observed, a continuous infusion can be set up by mixing 1 mg of epinephrine (i.e., 1 mL of 1 : 1000 epinephrine) in 250 mL of 5% dextrose in water, giving a concentration 4 µg/mL. This solution can be started at 1 µg/min and titrated to effects or 10 µg/min.[6] In children and infants, an infusion rate of 0.1 µg/kg/min is advised, increasing in increments of 0.1 µg/kg/min to a maximum of 1.5 µg/kg/min. A convenient dosing method for pediatric patients is the "rule of 6": 0.6 × body weight (in kilograms) = milligrams of epinephrine to be diluted to 100 mL NS; then 1 mL/hr of this solution delivers 0.1 µg/kg/min.[6] Central line access is usually recommended for intravenous administration of epinephrine because of the risk of tissue necrosis from possible extravasation. Extravasation of epinephrine from peripheral access is treated with phentolamine. In addition to

www.ketabpezeshki.com 66485457-66963820

the intramuscular route of administration for epinephrine, successful administration of epinephrine through the intraosseous, sublingual, intraglossal, and endotracheal routes has been reported anecdotally, although only the parenteral route is recommended in the 2010 anaphylaxis treatment guidelines.[6] The dosage and concentration guidelines for these routes of administration of epinephrine are the same as those for intravenous administration.

Antihistamines

In addition to epinephrine, antihistamines are routinely used in the treatment of anaphylaxis. Through competitive blockade of circulating histamines at target tissue cell receptors, they theoretically decrease symptoms of histaminemia such as itching, flush and rhinorrhea, and myocardial contractility, although they have no role in decreasing mediator release and have no effect on the leukotrienes. Diphenhydramine hydrochloride is the most commonly used H_1 antihistamine (50 mg intravenously or orally every 4 to 6 hours in adults or 1 to 2 mg/kg in children). Ranitidine (50 mg intravenously in adults, 1 mg/kg in children) and cimetidine (300 mg intravenously every 6 hours) are commonly used H_2 blockers. Antihistamines should be not given as lone agents in the treatment of true anaphylaxis.

Corticosteroids

Along with epinephrine and antihistamines, systemic corticosteroids are commonly administered in the treatment of anaphylaxis. A typical regimen involves an initial intravenous loading dose of methylprednisolone (Solu-Medrol, 125 to 250 mg) or oral prednisone (0.5-1 mg/kg). Steroids have an onset of action of approximately 4 to 6 hours after administration and therefore are of limited benefit in the acute treatment. They are most useful for protracted symptoms and may confer theoretic benefits in preventing the biphasic reaction. Rare cases of deterioration after corticosteroid administration may be the result of the patient's hypersensitivity reaction to steroid.

Aerosolized Beta-Agonists

Bronchospasm in anaphylaxis refractory to epinephrine may respond to a nebulized beta-agonist.[6] Continuous nebulization of the beta-agonists (albuterol sulfate, levalbuterol) may be helpful for persistent bronchospasm. The use of anticholinergic therapy with ipratropium bromide (Atrovent, 0.5 mg [2.5 mL of a 0.02% solution]) is an additional option in the management of acute bronchospasm. Anticholinergic medications decrease cyclic guanosine monophosphate levels, thereby decreasing mediator release and reversing the action of mediators on target tissue cells.[6]

Vasopressors

Patients with persistent hypotension despite adequate epinephrine injections require aggressive volume expansion with crystalloid fluids. Large volumes of NS (>2 L) are often infused quickly, at a rate of 5 to 10 mL/kg for the first 5 minutes.[6] Watch for signs of volume overload in patients with a history of reduced cardiac function, renal insufficiency, or congestive heart failure.[6] As a last resort, dopamine, vasopressors (e.g., norepinephrine, phenylephrine), or vasopressin infusion (2-4 IU/hr) should be considered for refractory hypotension.[6,60]

Patients Receiving Beta-Blockade

Glucagon, with positive inotropic and chronotropic cardiac effects mediated independently of alpha and beta receptors, may be helpful in patients who are receiving beta-blockers and who do not respond to epinephrine and other standard treatment modalities.[6] Glucagon is thought to effect positive inotropism by augmenting cyclic adenosine monophosphate synthesis through a nonadrenergic pathway. The initial dose is 1 to 5 mg for adults and 20 to 30 μg/kg (maximum dose 1 mg) for children intravenously, followed by an infusion of 1 to 5 mg/hr.[6] Side effects include nausea, vomiting, hypokalemia, and hyperglycemia. Atropine can be tried as second-line therapy for symptomatic bradycardia.

DISPOSITION

Most patients with anaphylaxis respond to aggressive management and can be safely discharged to home. Patients with mild to moderate anaphylaxis who completely respond to treatment are appropriate for discharge after an observation period (2-6 hours) in the ED. Advise these patients about symptoms of biphasic anaphylaxis and to return to the ED at the earliest onset of symptoms in the next 72 hours.[61] There are established clinical predictors for biphasic response; severity of the initial presentation, hypotension, laryngeal edema, delayed or inadequate dosage of epinephrine, and chronic beta-blocker medication use have been advanced as risk factors for a biphasic attack.[52,62] Patients with these clinical features may thus be candidates for hospital observation. Those going home are commonly prescribed a 7-day course of an oral H_1 antihistamine (either first or second generation, e.g., diphenhydramine hydrochloride 50 mg every 6 hours) and H_2 antihistamine (e.g., ranitidine 150 mg every day).[55] The select patients who present with moderate anaphylaxis symptoms may benefit from outpatient steroid therapy (prednisone 1 mg/kg/day for 7 to 10 days). Consider hospital admission for patients who present with protracted anaphylaxis, hypotension, airway involvement, prolonged bronchospasm, and poor social support and for those who may be at risk for biphasic anaphylaxis.

Prevention

Emergency physicians can take an active role in educating patients under their care about allergy and anaphylaxis, arranging for specialty care follow-up, and prescribing epinephrine for self-administration in case of allergic emergency. The SAFE acronym (Seek support, Allergen identification and avoidance, Follow-up for specialty care, and Epinephrine for emergencies) is a useful reminder tool to use in providing care for patients with anaphylaxis in the ED.[63] Physicians should spend a few minutes to advise patients of risks for future anaphylactic attacks and the need to seek emergency care as quickly as possible at the first signs of another anaphylactic reaction. Discharge planning includes referral to a primary care physician or allergist for further diagnostic workups and allergy management, a prescription for self-injectable epinephrine kits including education on how and when to self-administer, and a recommendation to carry a warning identification stating the hypersensitivity (MedicAlert bracelet or wallet card).

URTICARIA AND ANGIOEDEMA

Clinical Features

Urticaria and angioedema are common allergic presentations encountered in the ED.[64,65] Urticaria (hives) is the clinical manifestation of a wheal and flare (allergic) reaction, appearing as papules or wheals that are nonpitting, edematous, pruritic, slightly erythematous, and raised circular or annular; they range in size from millimeters to several centimeters (Fig. 119-3). The centers of the wheals are usually clear while the borders are erythematous,

www.ketabpezeshki.com 66485457-66963820

Figure 119-3. Acute urticaria. (Copyright © 2001-2003, Johns Hopkins University School of Medicine. http://dermatlas.med.jhmi.edu/derm.)

raised, and serpiginous. The erythema is due to dilation of blood vessels in the dermal layer of the skin, and the edematous wheals are due to transudation from these blood vessels. Urticaria favors the extremities and trunk and is usually transient, with crops of hives spontaneously appearing and resolving as often as every few hours.

Angioedema refers to abrupt vasodilation and edema and resultant swelling of the deeper dermal and subcutaneous layers of the skin. Because the swelling is located in the deeper layers of the skin, the skin may appear normal color (or pink) and pruritus is variable. Instead of itch, patients may complain of pain associated with angioedema. Angioedema commonly involves the face, mouth, lips, tongue, extremities, and genitalia. Angioedema of the larynx can cause an acute upper airway obstruction and is a medical emergency. Recurrent episodes of angioedema and urticaria that last less than 6 weeks are considered *acute* (90%), and those that persist longer than 6 weeks are classified as *chronic* (10%).

Urticaria and angioedema represent clinical symptoms and signs of potentially distinct underlying disease entities. Similar to anaphylaxis, the majority of cases of acute urticaria and angioedema are hypersensitivity reactions, commonly triggered by allergens (e.g., foods, drugs, RCM, Hymenoptera venoms) and, rarely, by physical stimuli (e.g., heat, wet, cold, vibratory, exercise). Angioedema caused by an allergic mechanism is called allergic angioedema. Nonallergic angioedema is caused by bradykinin excess, either by reduced degradation of bradykinin by ACE inhibitors or by excessive bradykinin production by a genetic defect as in hereditary angioedema (HAE). Differentiation of the two forms of angioedema is crucial to successful therapy.

Nonallergic angioedema (angioedema without urticaria and pruritus) is usually kinin related; its causes include HAE, acquired C1 inhibitor deficiency (ACID), and ACE inhibitors. All three result in elevated bradykinin levels.[66] In the case of HAE and ACID, the deficiency of C1 inhibitor causes activation of the kallikrein-kinin system, with consumption of kininogen, and results in increased production of bradykinin. In the case of ACE inhibitor drugs, the inhibition of ACE, one of the main inactivators of bradykinin, results in increased bradykinin levels.[67] Substance P is also thought to play a role in ACE inhibitor–associated angioedema.

HAE affects fewer than 200,000 people in the United States and may account for 15,000 to 30,000 ED visits annually. It is an autosomal dominant condition caused by C1 esterase inhibitor deficiency or functional deficiency, which is biochemically confirmed by low levels of C4 and C1 esterase inhibitor activity.[68] This ultimately results in intermittent elevated bradykinin levels and other mediators, resulting in angioedema. The cardinal symptoms and signs of HAE include edema of the airway, face, genitalia, or extremities and abdominal pain associated with nausea, vomiting, and diarrhea. These clinical manifestations may occur singly or in combination. Trauma and stress are common precipitating factors. There is usually a family history.

ACID is clinically indistinguishable from HAE attacks and is often associated with underlying lymphoproliferative diseases. The underlying disease results in consumption of C1 inhibitor or the development of anti–C1 inhibitor autoantibodies. It is less common than HAE, it typically involves older patients, and a family history is usually absent.

ACE inhibitor–induced angioedema has an incidence of 0.1 to 0.7% and has a predilection for the tongue, lips, and laryngeal soft tissue.[69] The highest incidence occurs in the first month of therapy, but it can occur as many as 10 years after therapy is started. Increased risk factors include African American race, smoking, older age, and female gender. Diabetes decreases the risk. The pathophysiologic mechanism is thought to be related to decreased metabolism of bradykinin and substance P, both of which are potent mediators of tissue inflammation. Most patients who have angioedema while receiving ACE inhibitors should be able to tolerate angiotensin receptor blocker drugs.

The clinical evaluation of angioedema starts with a focused search for emergency conditions, followed by a detailed history aimed at identification of the underlying cause. Life-threatening airway compromise can occur if the angioedema involves the upper airway. HAE, ACID, ACE inhibitors, thermal burn, and local allergic reaction to inhaled drugs (e.g., Quincke's disease) tend to cause glossopharyngeal angioedema, resulting in upper airway obstruction, dysphagia, or both.[70] The detailed history is aimed at eliciting exposures to foods, drugs, physical stimuli, infection (especially viral hepatitis), occupational elements, and insect stings.

Diagnostic Strategies

Diagnostic considerations are vast and include evolving anaphylaxis syndrome, erythema multiforme minor, bullous pemphigoid and dermatitis herpetiformis, urticarial vasculitis, mastocytosis, HAE (C1 esterase deficiency), ACID, ACE inhibitor–associated angioedema, and serum sickness, among others. The constellation of pruritus, urticarial rash or angioedema, hypotension, and wheezing after exercise should raise the possibility of exercise-induced anaphylaxis. Angioedema of the upper extremity raises the possibility of superior vena cava syndrome. Brawny edema and shock raise the possibility of capillary leak syndrome.

Management

Angioedema with Urticaria

Management of allergic angioedema that occurs in conjunction with urticaria (mast cell related) is first focused on stabilization of respiratory insufficiency and hemodynamic instability. Antihistamines (both H_1 and H_2) are the first-line therapeutic drugs. Epinephrine can be considered for moderate to severe cases but should be used with caution in patients older than 35 years to minimize the risk of precipitating an acute coronary syndrome. Steroids may be helpful in preventing recurrence. In the longer term, the most effective treatment of urticaria and angioedema involves removal of the etiologic factors. Second-generation H_1

www.ketabpezeshki.com 66485457-66963820

antihistamines such as cetirizine, loratadine, and fexofenadine, at increased doses (up to fourfold the conventional doses for allergic rhinitis), are the first-line drugs.[71] The older antihistamines (hydroxyzine and diphenhydramine) can be tried when the newer H_1 antihistamines are ineffective. Because 85% of histamine receptors in the skin are H_1 and 15% are H_2, the addition of an H_2 antihistamine (e.g., ranitidine or cimetidine) benefits a histamine-induced urticarial reaction. Besides those common antihistamines, low-dose tricyclics (e.g., doxepin 25-100 mg/day) have both H_1 and H_2 activity and are used as second-line drugs, especially in cases of chronic urticaria.[72] Heavy sedating effects limit the usefulness of doxepin, however. The addition of a short course of corticosteroids (0.5 mg/kg daily, up to 1 week) may shorten the duration of acute urticaria.[71]

Angioedema without Urticaria

Management of angioedema that occurs without urticaria (kinin related) is somewhat more of a problem with fewer therapeutic options.[73,74] Life-threatening acute attacks of kinin-related angioedema do not usually respond satisfactorily to treatment with epinephrine, antihistamines, or steroids.[75,76] Active airway management is the mainstay of treatment. Aerosolized racemic epinephrine (L-epinephrine is acceptable) may help stabilize the airway edema. Several new agents have recently been approved by the FDA for use in the United States; several others either are being used in other countries or are under clinical trial for the treatment of HAE.

For HAE, fresh frozen plasma (FFP), which contains C1 inhibitor, has been reported to be effective in abolishing acute attacks; however, there are rare reports of exacerbation of the angioedema by FFP. Steroids have not been shown to be helpful during acute attacks of HAE and should not be used.[68]

The use of C1 inhibitor replacement protein (C1-INHRP), a product of pooled human plasma, is the recommended treatment of HAE.[73] Currently, two C1-INHRP drugs are approved by the FDA for the treatment of HAE: Berinert (20 units/kg intravenously) and Cinryze (1000 units intravenously for patient weighing 50 to 100 kg).[73] Recombinant C1-INHRP has been developed and is under review in North America for the treatment of HAE. Both types of products have been shown to shorten time to relief of symptoms, but the recombinant product has a shorter half-life.

Ecallantide (Kalbitor, 30 mg subcutaneously) is a small peptide kallikrein inhibitor and prevents the generation of bradykinin.[73] It has been approved for use in the United States since 2009. It should not be used intravenously because of a reported 3.9% risk of anaphylaxis. A bradykinin receptor-2 antagonist (Icatibant) has been approved by the European Medicines Agency for use in the European Union but has not been approved for use in North America.

For ACE inhibitor–induced angioedema, the treatment is mainly supportive. There is a report of FFP being used with success in severe cases of ACE inhibitor–induced angioedema.[77] It is thought that the benefits conferred by FFP are due to the effect of kininase II in breaking down the accumulated bradykinin. Because elevation in bradykinin is observed in both ACE inhibitor–induced angioedema and HAE (among others), perhaps the bradykinin receptor blocker class of drug that is being evaluated for HAE may also be found to be effective in the treatment of ACE inhibitor–induced angioedema.

MASTOCYTOSIS

Mastocytosis is a rare disorder caused by an abnormal proliferation of mast cells (hyperplasia) in the body. There are two forms of mastocytosis. *Cutaneous mastocytosis,* also called urticaria pigmentosa, occurs when mast cell hyperplasia is in the skin. Cutaneous mastocytosis is more common and affects mostly children. *Systemic mastocytosis* refers to the clinical syndrome caused by mast cell hyperplasia in bone marrow, gut mucosa, liver, or spleen. Pathologic fractures, osteoblastic lesions on skeletal radiographs, cutaneous pigmented lesions, abdominal pain, diarrhea, hepatosplenomegaly, lymphadenopathy, headache, flushing, anemia, and, rarely, vascular collapse (from released vasoactive substances) are common clinical findings in systemic mastocytosis. The diagnosis is made by a 24-hour urine collection for histamine or its metabolites, PGD_2, or serum tryptase level. Adjunct diagnostic measures include bone scans, skeletal surveys, and upper gastrointestinal workup (upper gastrointestinal series, small bowel radiograph, computed tomography scan, and endoscopy). A skin or bone marrow biopsy helps confirm the diagnosis. Treatment options include avoidance of agents that precipitate a mediator release (such as aspirin, NSAIDs, opioids, and RCM) and referral to an allergist. Temporizing treatment in the ED includes H_1 and H_2 antihistamines for pruritus, flush, and gastrointestinal symptoms; potent topical steroids (class 1) can also be used for limited cutaneous mastocytosis.

KEY CONCEPTS

- Anaphylaxis is a life-threatening systemic allergic reaction of acute onset and multiorgan involvement; timely recognition and treatment are essential to maximize good outcomes.
- A history of sudden urticarial rash after an exposure, accompanied by either respiratory difficulty or hypotension, strongly favors the diagnosis of anaphylaxis.
- The treatment triad in anaphylaxis includes establishment of a patent airway, early treatment with epinephrine, and aggressive volume expansion with normal saline.
- H_1 and H_2 antihistamines seem helpful in reducing pruritus, rhinorrhea, and the flush syndrome in anaphylaxis. Corticosteroids can be helpful in reducing the risks of a protracted anaphylactic reaction and biphasic anaphylaxis.
- Continuous intravenous infusion of epinephrine may be needed in refractory anaphylactic shock after adequate volume expansion and multiple doses of intramuscular epinephrine. Prolonged treatment with epinephrine or glucagon may be required for patients receiving beta-adrenergic blockade.
- Consider hospitalization or prolonged observation for patients who have experienced hypotension, upper airway involvement, and prolonged bronchospasm.
- The SAFE acronym (Seek support, Allergen identification and avoidance, Follow-up for specialty care, and Epinephrine for emergencies) is a useful framework for discharge planning.
- Nonallergic angioedema is treated with supportive therapy. FFP has been used with varying success in HAE, ACID, and ACE inhibitor–induced angioedema. New drugs, including Berinert and Cinryze, and ecallantide have been approved for use in HAE-induced angioedema.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Matzinger P: Tolerance, danger, and the extended family. *Annu Rev Immunol* 1994; 12:991-1045.
2. Simons FE: Anaphylaxis. *J Allergy Clin Immunol* 2010; 125(Suppl 2):S161-S181.
3. Golden DB: What is anaphylaxis? *Curr Opin Allergy Clin Immunol* 2007; 7:331-336.
4. Lieberman P: Epidemiology of anaphylaxis. *Curr Opin Allergy Clin Immunol* 2008; 8:316-320.
5. Lieberman P: Anaphylaxis. *Med Clin North Am* 2006; 90:77-95, viii.
6. Lieberman P, et al: The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol* 2010; 126:477-480.
7. Simons FE: Anaphylaxis in infants: Can recognition and management be improved? *J Allergy Clin Immunol* 2007; 120:537-540.
8. Kemp SF, Lockey RF, Wolf BL, Lieberman P: Anaphylaxis. A review of 266 cases [see comments]. *Arch Intern Med* 1995; 155:1749-1754.
9. Kemp SF, Lockey RF: Anaphylaxis: A review of causes and mechanisms. *J Allergy Clin Immunol* 2002; 110:341-348.
10. Armentia A, Pineda F, Fernández S: Wine-induced anaphylaxis and sensitization to Hymenoptera venom. *N Engl J Med* 2007; 357:719-720.
11. Castillo R, Delgado J, Quiralte J, Blanco C, Carrillo T: Food hypersensitivity among adult patients: Epidemiological and clinical aspects. *Allergol Immunopathol (Madr)* 1996; 24:93-97.
12. Wuthrich B, Ballmer-Weber BK: Food-induced anaphylaxis. *Allergy* 2001; 56(Suppl 67):102-104.
13. Salkind AR, Cuddy PG, Foxworth JW: The rational clinical examination. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. *JAMA* 2001; 285:2498-2505.
14. Gadde J, Spence M, Wheeler B, Adkinson NF Jr: Clinical experience with penicillin skin testing in a large inner-city STD clinic. *JAMA* 1993; 270:2456-2463.
15. Kaufman DW: Risk of anaphylaxis in a hospital population in relation to the use of various drugs: An international study. *Pharmacoepidemiol Drug Saf* 2003; 12:195-202.
16. Mayorga C, Torres MJ, Blanca M: Cephalosporin allergy. *N Engl J Med* 2002; 346:380-381.
17. Goodman EJ, et al: Cephalosporins can be given to penicillin-allergic patients who do not exhibit an anaphylactic response. *J Clin Anesth* 2001; 13:561-564.
18. Freeman TM: Clinical practice. Hypersensitivity to Hymenoptera stings. *N Engl J Med* 2004; 351:1978-1984.
19. Neugut AI, Ghatak AT, Miller RL: Anaphylaxis in the United States: An investigation into its epidemiology. *Arch Intern Med* 2001; 161:15-21.
20. Rhoades R: Stinging ants. *Curr Opin Allergy Clin Immunol* 2001; 1:343-348.
21. Schumacher MJ, Egen NB: Significance of Africanized bees for public health. A review. *Arch Intern Med* 1995; 155:2038-2043.
22. Decker WW, et al: The etiology and incidence of anaphylaxis in Rochester, Minnesota: A report from the Rochester Epidemiology Project. *J Allergy Clin Immunol* 2008; 122:1161-1165.
23. Fisher M: Anaphylaxis to anaesthetic drugs. *Novartis Found Symp* 2004; 257:193-202.
24. Kajimoto Y, et al: Anaphylactoid skin reactions after intravenous regional anaesthesia using 0.5% prilocaine with or without preservative—a double-blind study. *Acta Anaesthesiol Scand* 1995; 39:782-784.
25. Fisher MM, Harle DG, Baldo BA: Anaphylactoid reactions to narcotic analgesics. *Clin Rev Allergy* 1991; 9:309-318.
26. Huang SW: Seafood and iodine: An analysis of a medical myth. *Allergy Asthma Proc* 2005; 26:468-469.
27. Cochran ST: Anaphylactoid reactions to radiocontrast media. *Curr Allergy Asthma Rep* 2005; 5:28-31.
28. Kong JS, Teuber SS, Gershwin ME: Aspirin and nonsteroidal anti-inflammatory drug hypersensitivity. *Clin Rev Allergy Immunol* 2007; 32:97-110.
29. Ramanuja S, Breall JA, Kalaria VG: Approach to "aspirin allergy" in cardiovascular patients. *Circulation* 2004; 110:e1-e4.
30. Wong JT, Nagy CS, Krinzman SJ, Maclean JA, Bloch KJ: Rapid oral challenge-desensitization for patients with aspirin-related urticaria-angioedema. *J Allergy Clin Immunol* 2000; 105:997-1001.
31. Simon RA: Adverse reactions to food additives. *N Engl Reg Allergy Proc* 1986; 7:533-542.
32. Borchers AT, Keen CL, Gershwin ME: Fatalities following allergen immunotherapy. *Clin Rev Allergy Immunol* 2004; 27:147-158.
33. Butani L: Corticosteroid-induced hypersensitivity reactions. *Ann Allergy Asthma Immunol* 2002; 89:439-445.
34. Robson-Ansley P, Toit GD: Pathophysiology, diagnosis and management of exercise-induced anaphylaxis. *Curr Opin Allergy Clin Immunol* 2010; 10:312-317.
35. Patterson R, Hogan MB, Yarnold PR, Harris KE: Idiopathic anaphylaxis. An attempt to estimate the incidence in the United States. *Arch Intern Med* 1995; 155:869-871.
36. Greenberger PA: Idiopathic anaphylaxis. *Immunol Allergy Clin North Am* 2007; 27:273-293, vii-viii.
37. Fischer A, Groneberg DA, Moehring R, Hallett R, Teuber SS: Kissing and food reactions. *N Engl J Med* 2002; 347:1210.
38. Webb LM, Lieberman P: Anaphylaxis: A review of 601 cases. *Ann Allergy Asthma Immunol* 2006; 97:39-43.
39. Zhang Q, et al: Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature* 2010; 464:104-107.
40. Janeway CA Jr: Approaching the asymptote? Evolution and revolution in immunology. *Cold Spring Harb Symp Quant Biol* 1989; 54(Pt 1):1-13.
41. Delves PJ, Roitt IM: The immune system. Second of two parts. *N Engl J Med* 2000; 343:108-117.
42. Delves PJ, Roitt IM: The immune system. First of two parts. *N Engl J Med* 2000; 343:37-49.
43. Chaplin DD: Overview of the immune response. *J Allergy Clin Immunol* 2010; 125(Suppl 2):S3-S23.
44. Weiss ST: Eat dirt—the hygiene hypothesis and allergic diseases. *N Engl J Med* 2002; 347:930-931.
45. Kaliner M, Shelhamer JH, Ottesen EA: Effects of infused histamine: Correlation of plasma histamine levels and symptoms. *J Allergy Clin Immunol* 1982; 69:283-289.
46. Constantinides P: Infiltrates of activated mast cells at the site of coronary atheromatous erosion or rupture in myocardial infarction. *Circulation* 1995; 92:1083.
47. Incorvaia C, Mauro M, Pravettoni V, Incorvaia S, Riario-Sforza GG: Anaphylaxis: An update on its understanding and management. *Recent Pat Inflamm Allergy Drug Discov* 2010; 4:124-129.
48. Yost CC, Weyrich AS, Zimmerman GA: The platelet activating factor (PAF) signaling cascade in systemic inflammatory responses. *Biochimie* 2010; 92:692-697.
49. Felix SB, et al: Characterization of cardiovascular events mediated by platelet activating factor during systemic anaphylaxis. *J Cardiovasc Pharmacol* 1990; 15:987-997.
50. Peavy RD, Metcalfe DD: Understanding the mechanisms of anaphylaxis. *Curr Opin Allergy Clin Immunol* 2008; 8:310-315.
51. The diagnosis and management of anaphylaxis: An updated practice parameter. *J Allergy Clin Immunol* 2005; 115(Suppl 2):S483-S523.
52. Tole JW, Lieberman P: Biphasic anaphylaxis: Review of incidence, clinical predictors, and observation recommendations. *Immunol Allergy Clin North Am* 2007; 27:309-326, viii.
53. Ellis AK, Day JH: Incidence and characteristics of biphasic anaphylaxis: A prospective evaluation of 103 patients. *Ann Allergy Asthma Immunol* 2007; 98:64-69.
54. Sampson HA, et al: Symposium on the definition and management of anaphylaxis: Summary report. *J Allergy Clin Immunol* 2005; 115:584-591.
55. Simons FE, Simons KJ: Epinephrine (adrenaline) in anaphylaxis. *Chem Immunol Allergy* 2010; 95:211-222.
56. Heilborn H, Hjemdahl P, Daleskog M, Adamsson U: Comparison of subcutaneous injection and high-dose inhalation of epinephrine—implications for self-treatment to prevent anaphylaxis. *J Allergy Clin Immunol* 1986; 78:1174-1179.
57. Choo KJ, Simons E, Sheikh A: Glucocorticoids for the treatment of anaphylaxis: Cochrane systematic review. *Allergy* 2010; 65:1205-1211.
58. Sheikh A, ten Broek V, Brown SG, Simons FE: H_1-antihistamines for the treatment of anaphylaxis with and without shock. *Cochrane Database Syst Rev* 2007; 1:CD006160.
59. Simons FE: Anaphylaxis: Recent advances in assessment and treatment. *J Allergy Clin Immunol* 2009; 124:625-636.
60. Schummer C, Wirsing M, Schummer W: The pivotal role of vasopressin in refractory anaphylactic shock. *Anesth Analg* 2008; 107:620-624.
61. Kemp SF: The post-anaphylaxis dilemma: How long is long enough to observe a patient after resolution of symptoms? *Curr Allergy Asthma Rep* 2008; 8:45-48.
62. Brady WJ Jr, Luber S, Carter CT, Guertler A, Lindbeck G: Multiphasic anaphylaxis: An uncommon event in the emergency department. *Acad Emerg Med* 1997; 4:193-197.
63. Lieberman P, et al: SAFE: A multidisciplinary approach to anaphylaxis education in the emergency department. *Ann Allergy Asthma Immunol* 2007; 98:519-523.
64. Dibbern DA Jr: Urticaria: Selected highlights and recent advances. *Med Clin North Am* 2006; 90:187-209.

www.ketabpezeshki.com 66485457-66963820

65. Kaplan AP, Greaves MW: Angioedema. *J Am Acad Dermatol* 2005; 53:373-388.
66. Cugno M, Nussberger J, Cicardi M, Agostoni A: Bradykinin and the pathophysiology of angioedema. *Int Immunopharmacol* 2003; 3:311-317.
67. Byrd JB, Adam A, Brown NJ: Angiotensin-converting enzyme inhibitor–associated angioedema. *Immunol Allergy Clin North Am* 2006; 26:725-737.
68. Zuraw BL: Clinical practice. Hereditary angioedema. *N Engl J Med* 2008; 359:1027-1036.
69. Slater EE, et al: Clinical profile of angioedema associated with angiotensin converting-enzyme inhibition. *JAMA* 1988; 260:967-970.
70. Kestler A, Keyes L: Images in clinical medicine. Uvular angioedema (Quincke's disease). *N Engl J Med* 2003; 349:867.
71. Zuberbier T, et al: EAACI/GA^{2}LEN/EDF/WAO guideline: Management of urticaria. *Allergy* 2009; 64:1427-1443.
72. Greene SL, Reed CE, Schroeter AL: Double-blind crossover study comparing doxepin with diphenhydramine for the treatment of chronic urticaria. *J Am Acad Dermatol* 1985; 12:669-675.
73. Bowen T, et al: 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol* 2010; 6:24.
74. Bowen T: Hereditary angioedema: Beyond international consensus—circa December 2010. *Allergy Asthma Clin Immunol* 2011; 7:1.
75. Nielsen EW, Gramstad S: Angioedema from angiotensin-converting enzyme (ACE) inhibitor treated with complement 1 (C1) inhibitor concentrate. *Acta Anaesthesiol Scand* 2006; 50:120-122.
76. Caballero T, et al: Consensus statement on the diagnosis, management, and treatment of angioedema mediated by bradykinin. Part I. Classification, epidemiology, pathophysiology, genetics, clinical symptoms, and diagnosis. *J Investig Allergol Clin Immunol* 2011; 21:333-347.
77. Warrier MR, Copilevitz CA, Dykewicz MS, Slavin RG: Fresh frozen plasma in the treatment of resistant angiotensin-converting enzyme inhibitor angioedema. *Ann Allergy Asthma Immunol* 2004; 92:573-575.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 120

Dermatologic Presentations

Boris Garber and Rita K. Cydulka

PERSPECTIVE

Cutaneous eruptions can be manifestations of primary dermatologic disease or signal underlying systemic illness. In addition to medical and family history, three factors are particularly important: onset and evolution of the skin problem, associated symptoms, and prior treatment.

With adequate lighting available, the physical examination is performed with the patient undressed. In general, the dermatologic evaluation includes a thorough evaluation of the scalp, mouth, and nails. Although the examination depends largely on inspection of the skin, palpation helps assess the texture, consistency, and tenderness of the lesions.

Skin lesions are divided into growths and rashes. Growths are subdivided into epidermal, pigmented, and dermal or subcutaneous proliferative processes. Rashes are divided into two groups, depending on whether the epidermis is involved. Lesions and rashes with epidermal involvement are described as being eczematous, scaling, vesicular, papular, pustular, or hypopigmented. Rashes without epidermal involvement are described as being erythematous, purpuric, or indurated.

The diagnosis is aided by the configuration of the lesions and distribution on the body's surface. On occasion, a configuration is specific for a disease; however, the morphologic appearance of the primary lesion is usually given more diagnostic weight (Table 120-1). Finally, many skin diseases have preferential areas of involvement, so the location of the eruption may aid in diagnosis. Several serious dermatologic disorders, such as Stevens-Johnson syndrome, may be manifested initially with lesions on mucous membranes only, thus making an examination of the mucous membranes an important part of a dermatologic evaluation.

Emergency department (ED) management focuses on stabilization (e.g., toxic epidermal necrolysis), symptom control (e.g., acute urticaria and pruritus), flare control (e.g., eczema), and treatment (e.g., skin infections or infestations). A variety of treatment options are available for dermatologic problems, including topical, oral, and intravenous preparations. Vehicles for topical preparations include soaks, creams, ointments, foams, gels, and lotions; use of the proper vehicle is a key component of successful treatment.

Aluminum acetate (Burow's solution), aluminum sulfate–calcium acetate (Domeboro), or oatmeal soaks may provide symptomatic relief of pruritus in patients with conditions with crusting or weeping. Saline wet soaks provide a moist environment and may be used to promote epithelialization of denuded areas; wet-to-dry dressings can be used for lesions requiring débridement. When wet occlusive dressings are applied, the normal skin is protected from maceration by the creation of a lipophilic barrier with an ointment. If a wet dressing is allowed to dry, it can stick to a wound and thus negate its benefit when it is removed.

Creams are a mixture of oil, water, and preservatives that penetrate the skin on application. Creams may cause drying of the skin and are best used for acute conditions. *Lotions* are a mixture of powder and water and may require shaking before application. Lotions may be used on any body surface, especially hair-bearing areas. *Ointments* are emulsions of water and oil that do not penetrate the skin on application; ointments are not usually applied to hairy areas or in natural folds. Ointments are especially useful for treatment of dry lesions. Occlusive dressings are used to increase potency by promoting absorption. *Gels* and *foams* liquefy when they are applied to the skin. They are frequently used for scalp lesions as they penetrate the hair barrier easier than other formulations do. Whenever a potent topical medication is prescribed, patients and caregivers are advised not to use their fingers for application; a cotton-tipped applicator or a plastic spatula is recommended instead.

Topical corticosteroids are commonly used for a variety of inflammatory skin conditions. They induce topical vasoconstriction, depress local immunity, and cause skin thinning with prolonged use. Systemic absorption and side effects are possible. A variety of formulations are available (Table 120-2). The potency of steroids depends on the specific drug, its concentration, and the method of delivery (i.e., whether cream or ointment is used, how often it is applied, whether an occlusive dressing is placed). It is wise for clinicians to familiarize themselves with one or two high-, medium-, and low-potency steroids to limit possible errors. So-called mega potency topical steroids are generally not initiated without consulting a dermatologist. The lowest potency medication available should be used around natural orifices to minimize systemic absorption.

SCALES, PLAQUES, AND PATCHES

Fungal Infection

Principles of Disease

The dermatophytoses are superficial fungal infections that are limited to the skin.[1] A variety of lesions may occur, but the most common are scaling, erythematous papules, plaques, and patches, which often have a serpiginous or wormlike border. Dermatophytes generally grow best in excessive heat and moisture and grow only in the keratin or outer layer of the skin, nails, and hair. Keratin tends to accumulate in body folds, such as between toes and in the inguinal area, the axilla, and the inframammary areas. With the exception of tinea capitis, dermatophyte infections are not markedly contagious.

www.ketabpezeshki.com 66485457-66963820

Table 120-1 Definitions of Skin Lesions

LESION	APPEARANCE
Macule	Flat; color differs from surrounding skin
Patch	A macule with surface changes (i.e., scale or wrinkling)
Papule	Elevated skin lesion <0.5 cm in diameter
Plaque	Elevated skin lesion >0.5 cm in diameter; without substantial depth
Nodule	Elevated skin lesion >0.5 cm in diameter and depth
Cyst	Nodule filled with expressible material
Vesicle	Blisters <0.5 cm in diameter filled with clear fluid
Bullae	Blisters >0.5 cm in diameter filled with clear fluid
Pustule	Vesicle filled with cloudy or purulent fluid
Crust	Liquid debris that has dried on the skin surface; usually moist and yellowish brown
Scale	Visibly thickened stratum corneum; usually white
Lichenification	Epidermal thickening characterized by visible and palpable skin thickening and accentuated skin markings
Induration	Dermal thickening that *feels* thick and firm
Wheal	Papule or plaque of dermal edema; often with central pallor and irregular borders
Erythema	Red appearance of skin caused by vasodilation of dermal blood vessels; blanchable
Purpura	Red appearance of skin caused by blood extravasated from disrupted dermal blood vessels; nonblanchable
Macular purpura	Flat, nonpalpable
Papular purpura	Elevated, palpable

Modified from Lookingbill DP, Marks JG: Principles of Dermatology, 3rd ed. Philadelphia, Saunders, 1993.

Any eruption thought to be a dermatophyte infection can be examined under the microscope in a potassium hydroxide (KOH) preparation. The specimen is examined for the characteristic branching hyphae of the dermatophytes or the short, thick hyphae and clustered spores of tinea versicolor. Affected hair, nail, or scales may be cultured on Sabouraud agar incubated at room temperature for 2 or 3 weeks.

Tinea Capitis

Clinical Features. Tinea capitis is a fungal infection of the scalp. Although it is primarily regarded as a disease of preschool children, tinea capitis is increasingly recognized in adults, infants, and neonates. It is more common among African Americans, although the reasons for this are unknown.[2] Nosocomial transmission of dermatophyte infections, such as *Trichophyton tonsurans,* has also been reported.[3] Recent outbreaks in the United States caused by *T. tonsurans* differ from epidemics of the 1940s and 1950s caused by *Microsporum audouinii* in that many patients have seborrheic-like scaling in the absence of alopecia.[2] Black dots, representing hair broken off near the scalp, may be noted clinically. Hair loss is the result of hyphae growing within the shaft, rendering it fragile, so that the hair strands break off 1 to 2 mm above the scalp. Circular patches of partial baldness may result. The disease may be transmitted by close child-to-child contact and contact with household pets, hats, combs, barber's shears, and similar items. Complications include lymphadenitis, bacterial pyoderma, tinea corporis, pigmenting pityriasis alba, id reaction after treatment, secondary bacterial infection, and scarring alopecia.[2]

Differential Considerations. The differential diagnosis of tinea capitis includes alopecia areata, atopic dermatitis, nummular eczema, bacterial infection, psoriasis, seborrheic dermatitis, "tinea" amiantacea, trichotillomania (hair pulling), and Langerhans cell histiocytosis.

Diagnostic Strategies. A KOH preparation is not helpful in the presence of a kerion or in the absence of alopecia, in which case a fungal culture specimen should be obtained.

Management. Systemic therapy is required for tinea capitis. Treatment usually begins with griseofulvin 20 mg/kg/day, usually not to exceed 1000 mg/day, taken as a single dose with a fat-containing food for a minimum of 6 weeks or 2 weeks after clinical resolution of inflammation. Higher doses may be needed. Griseofulvin can cause sun sensitivity. If treatment is initiated in the ED, refer the patient for a monthly follow-up evaluation. Alternative therapy includes fluconazole 200 mg/day (adults) or 3 to 5 mg/kg/day (children), itraconazole 200 mg daily (adults) or 3 to 5 mg/kg/day (children) for 4 to 6 weeks, oral terbinafine 3 to 6 mg/kg/day (children) or 250 mg/day (adults) for 4 to 6 weeks, and terbinafine cream once a day for 8 weeks. *T. tonsurans* species appear to be more sensitive to newer treatment modalities and require a shorter course of treatment than for *Microsporum* species. Selenium sulfide shampoo, 250 mg twice weekly, decreases shedding of spores. Family members should be evaluated.

Kerion

A kerion is a fungal infection affecting hair follicles that is characterized by intense inflammation with erythematous, boggy lesions often with frank pus. The inflammation is generally uniform and does not display satellite lesions. It usually affects the scalp and is more common in children and in African Americans. Local alopecia and scarring can ensue. Accurate differentiation of lesions with and without superinfection can be challenging, and a bacterial culture may be useful when there is doubt. Kerions tend to be less tense and less tender than bacterial abscesses; however, with superinfection or existing drainage, the distinction becomes less pronounced. A toothbrush, Papanicolaou smear cytology brush, or moistened cotton swab is helpful for quick, painless sampling of large areas of the scalp.

Kerions are treated the same as tinea capitis, with the addition of prednisone 1 mg/kg/day for 1 or 2 weeks to help decrease the inflammatory reaction and subsequent alopecia and scarring. If bacterial superinfection exists, an antibiotic is added. Antibiotic options include oral cephalexin, 500 mg every 6 hours for adults or 50 mg/kg/day divided in four doses not to exceed 500 mg per dose for children, for 1 week; dicloxacillin 100 mg twice a day; and clindamycin 300 mg orally every 6 hours for adults or 8 to 25 mg/kg/day as palmitate in three or four divided doses for children. If intravenous clindamycin is used, the dose is 600 to 900 mg every 6 to 8 hours for adults or 40 mg/kg/day divided three or four times a day for children not to exceed 600 mg per dose. Clindamycin is recommended when community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is a concern, that is, in those cases in which purulent drainage is present. Surgical drainage of kerions is not helpful and should be avoided.

Tinea Corporis

Clinical Features. Tinea corporis is the classic "ringworm" infection. Its characteristic presentation is a sharply marginated, annular lesion with raised or vesicular margins and central clearing (Fig. 120-1). Lesions may be single or multiple; multiple lesions are occasionally concentric. Tinea cruris, which involves the groin, is similar in appearance and may also include the perineum, thighs, and buttocks, but the scrotum is characteristically spared.

www.ketabpezeshki.com 66485457-66963820

Table 120-2 Potency of Topical Steroids

BRAND NAME	GENERIC NAME
Class 1—Superpotent	
Clobex lotion, spray, or shampoo, 0.05%	Clobetasol propionate
Cormax cream or solution, 0.05%	Clobetasol propionate
Diprolene ointment, 0.05%	Betamethasone dipropionate
Olux E foam, 0.05%	Clobetasol propionate
Olux foam, 0.05%	Clobetasol propionate
Temovate cream, ointment, or solution, 0.05%	Clobetasol propionate
Ultravate cream or ointment, 0.05%	Halobetasol propionate
Vanos cream, 0.1%	Fluocinonide
Psorcon ointment, 0.05%	Diflorasone diacetate
Psorcon E ointment, 0.05%	Diflorasone diacetate
Class 2—Potent	
Diprolene cream AF, 0.05%	Betamethasone dipropionate
Elocon ointment, 0.1%	Mometasone furoate
Florone ointment, 0.05%	Diflorasone diacetate
Halog ointment or cream, 0.1%	Halcinonide
Lidex cream, gel, or ointment, 0.05%	Fluocinonide
Psorcon cream, 0.05%	Diflorasone diacetate
Topicort cream or ointment, 0.25%	Desoximetasone
Topicort gel, 0.05%	Desoximetasone
Class 3—Upper Midstrength	
Cutivate ointment, 0.005%	Fluticasone propionate
Lidex-E cream, 0.05%	Fluocinonide
Luxiq foam, 0.12%	Betamethasone valerate
Topicort LP cream, 0.05%	Desoximetasone
Class 4—Midstrength	
Cordran ointment, 0.05%	Flurandrenolide
Elocon cream, 0.1%	Mometasone furoate
Kenalog cream or spray, 0.1%	Triamcinolone acetonide
Synalar ointment, 0.03%	Fluocinolone acetonide
Westcort ointment, 0.2%	Hydrocortisone valerate
Class 5—Lower Midstrength	
Capex shampoo, 0.01%	Fluocinolone acetonide
Cordran cream, lotion, or tape, 0.05%	Flurandrenolide
Cutivate cream or lotion, 0.05%	Fluticasone propionate
DermAtop cream, 0.1%	Prednicarbate
DesOwen lotion, 0.05%	Desonide
Locoid cream, lotion, ointment, or solution, 0.1%	Hydrocortisone
Pandel cream, 0.1%	Hydrocortisone
Synalar cream, 0.03%, 0.01%	Fluocinolone acetonide
Westcort cream, 0.2%	Hydrocortisone valerate
Class 6—Mild	
Aclovate cream or ointment, 0.05%	Alclometasone dipropionate
Derma-Smoothe/FS oil, 0.01%	Fluocinolone acetonide
Desonate gel, 0.05%	Desonide
Synalar cream or solution, 0.01%	Fluocinolone acetonide
Verdeso foam, 0.05%	Desonide
Class 7—Least Potent	
Cetacort lotion, 0.5%, 1%	Hydrocortisone
Cortaid cream, spray, or ointment	Hydrocortisone
Hytone cream or lotion, 1%, 2.5%	Hydrocortisone
Micort-HC cream, 2%, 2.5%	Hydrocortisone
Nutracort lotion, 1%, 2.5%	Hydrocortisone
Synacort cream, 1%, 2.5%	Hydrocortisone

Modified with permission from National Psoriasis Foundation: Topical steroids potency chart. Available at http://www.psoriasis.org/page.aspx?pid=469. Accessed August 16, 2011.

Differential Considerations. The differential diagnosis of tinea cruris includes granuloma annulare, psoriasis, intertrigo with secondary candidiasis, and erythrasma.

Management. Infections of the body, groin, and extremities usually respond to topical measures alone. A number of effective topical antifungal agents are available, including clotrimazole (Lotrimin), haloprogin (Halotex), miconazole (Micatin), tolnaftate (Tinactin), terbinafine, naftifine, and griseofulvin 1%. Two or three daily applications of the cream form of any of these preparations result in healing of most superficial lesions in 1 to 3 weeks.[4] Acute inflammatory lesions displaying oozing or blisters are treated additionally (four times a day) with open, wet compresses of Burow's solution, an aluminum acetate solution that is useful as a soothing wet dressing for inflammatory skin conditions.

Tinea Pedis

Tinea pedis, or athlete's foot, appears with scaling, maceration, vesiculation, and fissuring between the toes and on the plantar surface of the foot. In extensive cases, the entire sole may be involved. A secondary bacterial infection may occur. The vesicular pustular form of tinea pedis should be considered when vesicles and pustules on the instep are noted. The differential diagnosis includes contact dermatitis and dyshidrotic eczema. A KOH preparation is helpful to differentiate between these processes. Interdigital lesions may cause minimal symptoms and serve as a portal of entry for bacterial cellulitis. Treatment options include terbinafine 1% cream twice daily for 2 to 4 weeks; miconazole 2% cream, powder, or spray twice daily for 2 to 4 weeks; and clotrimazole 1% cream, solution, or lotion twice daily for 2 to 4 weeks.[5] For severe disease or if topical treatment has failed, use terbinafine 250 mg orally daily for 2 weeks, fluconazole 150 mg orally weekly for 2 to 4 weeks, or griseofulvin 500 mg orally daily for 2 weeks.

Tinea Versicolor

Clinical Features. Tinea versicolor is a superficial yeast infection caused by *Pityrosporum ovale*. Superficial scaling patches occur mainly on the chest and trunk but may extend to the head and limbs. As the name implies, lesions can be a variety of colors, including pink, tan, and white. The disease may be associated with pruritus, but medical care is often sought because the spots do not tan. On physical examination, a fine subtle scale is noted that may appear hypopigmented (Fig. 120-2). Pale yellow or orange fluorescence under Wood's light is sometimes present. The differential diagnosis includes vitiligo and seborrheic dermatitis. A KOH

www.ketabpezeshki.com 66485457-66963820

Figure 120-1. Tinea corporis. (Courtesy David Effron, MD.)

Figure 120-2. Tinea versicolor. (Courtesy David Effron, MD.)

preparation reveals short hyphae mixed with spores ("chopped spaghetti and meatballs").

Management. Tinea versicolor may be treated with 2.5% selenium sulfide shampoo, imidazole creams, ketoconazole cream or foam, or oral ketoconazole as a single 400-mg dose or 200 mg daily for 5 to 10 days.[6] Fluconazole 150 to 300 mg weekly for 2 to 4 weeks may also be used. Recurrence rates vary from 15 to 50%, and recurrence is considered the rule rather than the exception. Monthly prophylaxis with propylene glycol and water, selenium shampoo, or azole creams can help prevent recurrences. Pigmentation may not return to normal for months. Propylene glycol is inexpensive and effective.

Tinea Unguium (Onychomycosis)

Clinical Features. Tinea unguium results in nails that are opaque, thickened, cracked, and crumbled. Subungual debris is present, and the nail may contain yellowish longitudinal streaks. The nail of the great toe is most commonly involved. Involvement of all of the nails of the hands and feet is rare.

Management. Topical therapy of the nails alone rarely results in a cure because penetration into the nail keratin is poor. Fingernails typically respond more rapidly to therapy than toenails do. Oral griseofulvin and ketoconazole require prolonged courses, with high relapse rates and numerous side effects.[7] Newer agents such as itraconazole, fluconazole, and terbinafine are safer and more effective. They also offer shorter treatment periods, thus improving compliance.[7] The infection may be resistant to this regimen as well, however, and surgical removal of the nail is occasionally required. The choice of specific agent may be best left to a consultant or patient's primary physician, given the long course of treatment and frequency of treatment failure. If therapy is started in the ED, reliable follow-up is needed. Griseofulvin ultramicrosize 375 mg twice daily or ketoconazole 400 mg daily is given for 4 to 6 months. Newer agents are preferred by dermatologists: terbinafine 250 mg/day for 6 to 12 weeks (a longer course is given for toenail involvement) is considered first-line therapy. Recurrence is common.[8]

Candidiasis

Perspective

Infection by *Candida albicans* occurs in patients of all ages. Many conditions predispose to infection, including acquired immunodeficiency syndrome (AIDS), pregnancy, obesity, malnutrition, malignant disease, and diabetes and other endocrine imbalances. Patients treated with corticosteroids, immunosuppressive agents, and antibiotics are also prone to cutaneous fungal infections.

Oral Thrush

Clinical Features. Oral thrush is the most common clinical expression of *Candida* infection. Thrush is common in newborns, with one third being affected by the first week of life. It appears as patches of white or gray friable material covering an erythematous base on the buccal mucosa, gingiva, tongue, palate, or tonsils. Fissures or crust at the corners of the mouth may be present. The differential diagnosis of oral thrush includes lichen planus (which unlike *C. albicans* is not easily scraped off). Oral mucous membrane infection with *C. albicans* is an AIDS-defining illness. If the patient does not use dentures and has not taken antibiotics recently, underlying immunosuppression should be considered.

Management. Treatment of oral thrush involves painting of the mouth with 1 mL to each side of the mouth of oral nystatin suspension (100,000 units/mL) four times a day for infants or 4 to 6 mL four times a day swish and swallow for older children and adults. Treatment is continued for 5 to 7 days after the lesions disappear. A preferable treatment option for adults is clotrimazole troches 10 mg dissolved in the mouth two to five times daily. If topical therapy is not effective or in cases of chronic candidiasis, oral fluconazole 3 mg/kg, 100 to 200 mg/day for 1 to 2 weeks, may be prescribed. If that fails, treatment options include posaconazole suspension, 400 mg twice daily for 3 days, then 400 mg daily for

www.ketabpezeshki.com 66485457-66963820

up to 28 days, or itraconazole 200 mg daily for 2 to 4 weeks.[9] Painting of the oral cavity with small amounts of gentian violet solution 1% has been used in both children and adults for treatment of refractory oral candidiasis. Caution is needed in infants and small children to ensure that only a minimal amount of the solution is swallowed.

Patients with oral candidiasis associated with dentures should soak their dentures overnight in dilute (1:10) sodium hypochlorite solution.

Cutaneous Candidiasis

Clinical Features. Cutaneous candidiasis favors the moisture and maceration of the intertriginous areas—the interdigital web spaces, groin, axilla, and intergluteal and inframammary folds. Lesions appear as moist, bright red macules rimmed with a collarette of scale, which represents the pustule roof with scalloped borders. Small satellite papules or pustules are just peripheral to the main body of the rash. These satellite lesions are the most typical indicators of a *Candida* infection. Intertriginous lesions are prone to bacterial superinfection.

Candidal onychia and paronychia are conditions that occur in those whose hands are frequently immersed in hot water. These infections also occur with thumb sucking by children who have thrush. The paronychial area becomes red and swollen; the nails are thick and brittle, with transverse ridging. Destruction of the nail plate may occur.

Differential Considerations and Diagnostic Strategies. The differential diagnosis of cutaneous candidiasis includes contact dermatitis, tinea cruris, intertrigo, herpes simplex such as herpetic whitlow, and folliculitis. Candidiasis, however, is less sharply demarcated than tinea cruris and brighter red than intertrigo. A KOH preparation of a specimen taken from a pustule and roof of the lesion will reveal hyphae and pseudohyphae.

Management. Treatment of intertriginous lesions requires the removal of excessive moisture and maceration. Lesions should be exposed to circulating air from a fan several times a day. Inflammatory lesions are either soaked in or covered with compresses of cool water or Burow's solution. Topical imidazole creams, such as clotrimazole and miconazole, are applied sparingly to affected areas. Prescription creams, such as econazole, ketoconazole, and sulconazole, are also effective.

Protection of the hands from water is an integral part of the treatment of candidal paronychia. Instruct patients to avoid prolonged immersion and to use gloves with cotton liners to prevent contact with water. Nystatin or clotrimazole cream is applied frequently to the nail folds for 6 to 8 weeks.

A search for an underlying immunocompromising condition is recommended in patients with chronic, recurrent candidiasis. Eczematous dermatitis of the nail folds can lead to the development of chronic paronychia.

Diaper Dermatitis

Clinical Features

Diaper dermatitis is a common disorder that is exacerbated by heat, moisture, friction, and the presence of urine and fecal material. It can affect anyone wearing a diaper. Lesions begin as erythematous plaques in the genital, perianal, gluteal, and inguinal areas. More severe involvement results in moist, eroded lesions that may extend beyond the primary areas of appearance.

Lesions infected with *Candida* are moist, red patches with well-demarcated borders. Papular or pustular satellite lesions are also present.

Diaper dermatitis may reflect the presence of atopic or seborrheic dermatitis in the infant. The presence of lesions elsewhere on the body, particularly on the face in cases of atopic dermatitis or the scalp in cases of seborrhea, alerts the physician to these possibilities. The existence of diaper dermatitis as a true allergic contact dermatitis is rare. Candidal superinfection is common and is manifested with erythematous patches and satellite lesions. Early bacterial cellulitis must also be considered.

Management

Treatment consists primarily of altering the physical environment in which diaper dermatitis thrives. Advise parents to provide continuous air exposure of the area; if this is not possible, diapers should be changed frequently and topical barrier ointments, such as zinc oxide, applied. Treatment includes nystatin or other topical antifungal creams. If exudative lesions are present, treatment with topical, cool, wet compresses of saline or Burow's solution is indicated for 2 or 3 days. Severe contact or seborrheic dermatitis may require the addition of a short course of a low-potency topical corticosteroid, such as 1% hydrocortisone in a cream base.[10] Particularly severe, recurrent, or not improving diaper rash in infants raises the possibility of an immunodeficiency syndrome, diabetes, or caregiver neglect.

SCALY PAPULES

Fungal lesions are typically scaly, as are lesions of secondary syphilis. Additional scaly diseases are discussed in this section.

Pityriasis Rosea

Pityriasis rosea is a mild skin eruption predominantly found in children and young adults. The lesions are multiple pink or pigmented oval papules or plaques 1 to 2 cm in diameter on the trunk and proximal extremities. Mild scaling may be present. The lesions are parallel to the ribs, forming a Christmas tree–like distribution on the trunk. Oral lesions are rare. In children, papular or vesicular variants of the disease may occur.

In half the cases, the generalized eruption is preceded by the appearance of a herald patch. This is a larger lesion, 2 to 6 cm in diameter, that resembles the smaller lesions in other respects. The eruption is usually asymptomatic, although pruritus may be present.

Pityriasis rosea is self-limited, resolving in 8 to 12 weeks. Its cause is unknown, although a virus is suspected. The differential diagnosis includes tinea corporis, guttate psoriasis, lichen planus, drug eruption, Lyme disease, and secondary syphilis. Recurrences are rare. Treatment is usually unnecessary, except for symptomatic alleviation of bothersome pruritus. Direct sun exposure or, alternatively, ultraviolet B therapy to severely affected areas has been recommended; the application of moderately potent topical steroids to severely pruritic areas also has its proponents. The benefits of these treatments are questionable,[11] and ED interventions are usually limited to simple reassurance and close follow-up.

Atopic Dermatitis

Principles of Disease

Atopic dermatitis is a common dermatologic condition often referred to as eczema or chronic dermatitis. Atopic dermatitis is the cutaneous manifestation of an atopic state, and although it is not an allergic disorder, it is associated with allergic diseases such as asthma and allergic rhinitis. Patients with atopic dermatitis are known to have abnormalities of both humoral and cell-mediated immunity.[12] The exact mechanism is unclear, but eosinophil, mast cell, and lymphocyte activation triggered by increased production of interleukin-4 by specific T helper cells seems to be involved.

www.ketabpezeshki.com 66485457-66963820

Increased immunoglobulin E levels are found in most but not all patients with atopic dermatitis, but there is a poor correlation between the severity of the dermatitis and the serum immunoglobulin E level. The course of atopic dermatitis involves remissions and exacerbations. More than 90% of patients have the onset of atopic dermatitis before 5 years of age. New-onset atopic dermatitis in older children or adults should suggest other diagnoses.

Clinical Features

Atopic dermatitis has no pathognomonic skin lesions or unique laboratory parameters. Diagnostic criteria include itchy skin plus three or more of the following: history of flexural involvement, generalized dry skin, history of asthma or hay fever, onset of rash before 2 years of age, and flexural dermatitis.[13] These criteria are sensitive (85%) and specific (96%).

Skin lesions generally appear as inflammatory thickened, papular, or papulovesicular lichenification and hyperpigmentation. The skin is typically dry and may be scaly, but in the acute phase, it may also be vesicular, weeping, or oozing. The distribution of lesions varies with the age of the patient. In infants, inflammatory exudative plaques are seen on the cheeks, on the extensor surfaces, and in the diaper area. Older children and adults have lesions in the antecubital and popliteal flexion areas, neck, face, and upper chest. Infantile atopic dermatitis usually begins in the fourth to sixth month of life and improves by the third to fifth year of life. The childhood form occurs between 3 and 6 years of age and resolves spontaneously or continues into the adult form.

Intense pruritus is a hallmark of atopic dermatitis. During flares, patients may present with complaints of intense itching and failure of routine treatments to control their symptoms. Patients may also present with secondary infections. The itching may be focal or generalized, is worse during the winter, and is triggered by increased body temperature and emotional stress. It may be particularly annoying at night. Excoriations may be prominent, and secondary bacterial infection of excoriated lesions is common. Repeated scratching and rubbing produce lichenification, a condition of hyperpigmentation, thickening of the skin, and accentuation of skin furrows. Lichenification is a common feature of chronic atopic dermatitis.

Differential Considerations

The differential diagnosis of infantile atopic dermatitis includes histiocytosis X, Wiskott-Aldrich syndrome, chronic seborrheic dermatitis, phenylketonuria, Bruton's X-linked agammaglobulinemia, psoriasis, and scabies. Fixed drug eruptions and contact dermatitis round out the differential diagnosis regardless of age. Complications of atopic dermatitis include pyogenic skin infections, otitis externa, cataracts, keratoconus, retinal detachment, and cutaneous viral infections.

Management

The optimal protocol for management in children has not been established. Treatment should be aimed at control of inflammation, dryness, and itching. The use of sedating antihistamines at bedtime can be beneficial in patients with atopic dermatitis who have comorbid allergic conditions and sleep disturbances.

Management includes a careful review of daily skin care with patients or caregivers. General recommendations for all patients include avoidance of nonspecific skin irritants, wool, nonessential toiletries, and detergents and use of cotton clothing as much as possible. Patients should take daily warm baths or showers for approximately 10 to 15 minutes to hydrate the skin, followed by gentle pat drying and immediate application of a topical anti-inflammatory medication on the affected areas and a ceramide-based moisturizer such as Cetaphil, EpiCeram, or CeraVe on the asymptomatic areas. Medium-potency topical corticosteroids may be sufficient to treat moderate flares. Ointment-based medications are usually better tolerated by most patients during an acute flare.

Skin dryness is treated with lubricating ointments such as Vaseline or 10% urea in Eucerin cream (not lotion). Treatment of exudative areas includes the application of wet dressings, which are useful for their moisturizing, anti-inflammatory, and antipruritic actions. Two or three layers of gauze soaked in Burow's solution should be applied for 15 to 20 minutes four times a day for exudative lesions. Antihistamines may be helpful in reducing the pruritus and are also useful for their sedative and soporific effects, although there is no convincing evidence that H_1 antihistamines decrease itching in patients with atopic eczema.

Topical corticosteroids are the cornerstone of therapy and are prescribed in ointment form. When the dermatitis is severe, the application of a fluorinated corticosteroid ointment such as half-strength betamethasone valerate is recommended to affected areas three times a day. Fluorinated corticosteroids should not be used on the face because they can produce permanent cutaneous atrophy. Milder corticosteroid preparations, such as 0.025% triamcinolone ointment, may be used on the face and intertriginous areas. Patients with extremely severe disease may require systemic steroids. Ultraviolet B treatment is moderately effective, although its mechanism of action is not well understood.

Cyclosporine and other immunosuppressant agents are being used with some promising benefit. Further studies are needed to determine ideal dosing and safety profiles for these agents.[13]

Topical calcineurin inhibitors, including tacrolimus ointment and pimecrolimus cream, are nonsteroidal topical immunosuppressants approved in the United States for use on children 2 years or older; they are useful for treatment of lesions on the thinner skin areas (face, groin, and axillae) where repeated applications of topical corticosteroids may result in skin atrophy or striae.[14] A burning sensation at the site of application may occur. Note that the Food and Drug Administration has issued a "black box" warning concerning long-term continuous treatment with topical calcineurin inhibitors and cancer, although there is currently no evidence for a causal link.[15]

Inpatient admission is a consideration for those patients who have generalized erythema and exfoliation (erythroderma) or intractable itching in that skin breakdown and severe secondary bacterial or viral skin infections may occur.

Skin Infections in Patients with Atopic Dermatitis

Patients with atopic dermatitis are susceptible to infection and colonization by a variety of organisms because of their defective skin barrier functions and local skin immunodeficiency. Widespread disseminated viral infections, such as eczema molluscatum, eczema vaccinatum, and eczema herpeticum, and recurrent staphylococcal pustulosis are especially concerning.

Eczema molluscatum is self-limited. Eczema vaccinatum results from exposure of patients to vaccinia virus either by intentional inoculation or through contact with someone recently immunized against smallpox. Therapy for eczema vaccinatum requires prompt administration of intravenous immune globulin, which can be obtained from the Centers for Disease Control and Prevention.[16]

Eczema herpeticum constitutes a medical emergency. Patients present with disseminated eruptions of dome-shaped vesicles that may or may not be superimposed on areas of eczematous rashes, with the head, neck, and trunk commonly affected. Fever, malaise, and local lymphadenopathy are variable, depending on the timing

www.ketabpezeshki.com 66485457-66963820

of presentation and host characteristics. Complications include keratoconjunctivitis, viremia, multiorgan involvement with meningitis, and encephalitis. Clinical suspicion of eczema herpeticum mandates initiation of intravenous acyclovir in conjunction with antistaphylococcal antibiotics for possible bacterial superinfection. Lumbar puncture should not be attempted if infected lesions are present over the lumbar area. Ophthalmology consultation is needed for patients with periocular or suspected eye involvement.

Therapy for bullous impetigo consists of an oral penicillinase-resistant semisynthetic penicillin, such as dicloxacillin, 250 mg four times a day for 5 to 7 days for adults, or erythromycin ethylsuccinate, 250 mg four times a day in adults or 30 to 50 mg/kg/day in children. Azithromycin may also be used, dosed at 500 mg on the first day in adults, followed by 250 mg a day for 4 days; in children, it is dosed at 10 mg/kg given on the first day, followed by 5 mg/kg/day for 4 days more. If the infection is limited to a small area, mupirocin 2% ointment three times a day may be used. Without treatment, impetigo generally heals within 3 to 6 weeks.[17]

PUSTULES

Impetigo

Principles of Disease

Impetigo is a slowly evolving pustular eruption, most common in preschool children. Currently, *Staphylococcus aureus* is the most common pathogen, with group A streptococcus a distant second.[17] Poor health and hygiene, malnutrition, and various antecedent dermatoses, especially atopic dermatitis, predispose individuals to impetigo.

Clinical Features

Streptococcal impetigo (ecthyma) is found most often on the face and other exposed areas. The eruption often begins as a single pustule but later develops multiple lesions. It begins as 1- to 2-mm vesicles with erythematous margins. When these break, they leave red erosions covered with a golden yellow crust. Lesions may be pruritic but usually are not painful. Regional lymphadenopathy is commonly present. Lesions are contagious among infants and young children and less so in older children and adults. Postpyodermal acute glomerulonephritis is a recognized complication of streptococcal impetigo.

Staphylococcal impetigo is differentiated from streptococcal impetigo in that it is more superficial, and there is little surrounding erythema. Other diagnostic considerations are herpes simplex virus (HSV) and inflammatory fungal infections. A Gram stain of the weepy erosion obtained after removal of the crust will reveal gram-positive cocci. MRSA impetigo is increasingly common. Risk factors include prior infection or colonization with MRSA.[18]

Bullous impetigo is caused by phage group 2 staphylococci. It is seen primarily in infants and young children. The initial skin lesions are thin-walled, 1- to 2-cm bullae. When these rupture, they leave a thin serous crust and collarette-like remnant of the blister roof at the rim of the crust. The face, neck, and extremities are most often affected. The differential diagnosis includes contact dermatitis, HSV infection, superficial fungal infections, and pemphigus vulgaris. A Gram stain of the fluid from a bulla reveals gram-positive cocci. Cultures are positive in 95% of cases.

Management

Systemic and topical therapies are equally successful in treating impetigo.[17] For more extensive lesions, systemic treatment is recommended. There is no evidence, however, that systemic antibiotics prevent the development of acute glomerulonephritis. The efficacy is similar for topical mupirocin 2% ointment three times a day, oral erythromycin ethylsuccinate 250 mg four times a day for 10 days in adults or 30 mg/kg/day in children, and cephalexin 50 mg/kg/day not exceed 500 mg per dose three times a day for 7 to 10 days.[17] Mupirocin is avoided when there is concern about methicillin-resistant strains, and care should be taken that it does not get into the patient's mouth.

Folliculitis

Clinical Features

Folliculitis is an inflammation in the hair follicle, usually caused by *S. aureus.* It appears as a pustule with a central hair. The lesions are usually on the buttocks and thighs, occasionally in the beard or scalp, and may cause mild discomfort. The differential diagnosis includes acne, keratosis pilaris, and fungal infection. Gram-negative folliculitis with *Pseudomonas aeruginosa* can occur after exposure to infected hot tubs and swimming pools or in individuals taking antibiotics for acne; it can be differentiated from staphylococcal folliculitis by a Gram stain of the lesion.

Management

Treatment with an antiseptic cleanser such as povidone-iodine or chlorhexidine every day or every other day for several weeks is usually adequate. For patients with extensive involvement, a 7- to 10-day course of doxycycline 100 mg two times a day or dicloxacillin 500 mg four times a day may be added.

Hidradenitis Suppurativa

Hidradenitis suppurativa affects the apocrine sweat glands. Recurrent abscess formation in the axillae and groin resembles localized furunculosis. The condition tends to be recurrent and may be extremely resistant to therapy. Hidradenitis suppurativa may be treated with drainage of abscesses if they are fluctuant, painful, and large. Antistaphylococcal antibiotics are useful if they are administered early and for a prolonged period. Begin treatment for mild disease with topical clindamycin, 10 mg/mL twice daily, for 3 months. In patients with more severe or nonresponsive disease, begin clindamycin, 300 mg twice daily, combined with rifampin, 300 mg twice daily, for 3 to 6 months.[19] Antiandrogen therapy may be considered if antibiotics do not produce improvement. Many cases do not respond, however, and eventually require local excision and skin grafting of the involved area. Sonography will help differentiate abscesses from vascular or lymphoid structures.

Carbuncle

A carbuncle is a large abscess that develops in the thick, inelastic skin of the back of the neck, back, or thighs and usually involves hair follicles. Carbuncles may produce severe pain and fever. Septicemia may accompany the lesions. The diagnosis of skin abscess, furuncle, or carbuncle is usually made clinically. Ultrasonography is often helpful in diagnosis of carbuncles or abscesses that may not appear fluctuant on examination.

Local heat should be applied to furuncles and carbuncles, which should be incised and drained when fluctuant. Antibiotics are unnecessary with incision and drainage unless cellulitis or septicemia is present.

www.ketabpezeshki.com 66485457-66963820

Community-Associated Methicillin-Resistant *Staphylococcus aureus*

Principles of Disease

The incidence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has soared since the first report in 1993. In many major U.S. cities, CA-MRSA is now the most common pathogen cultured from ED patients presenting with skin and soft tissue infections.[20] Concern exists that CA-MRSA may be more virulent than methicillin-sensitive strains, and colonization with CA-MRSA may produce more overt infections.[20]

Hospital-acquired MRSA isolates can survive on a variety of inanimate surfaces, sometimes for weeks. It is unclear whether this is also true for CA-MRSA isolates; if it is true, their presence on such items as clothing, towels, and athletic equipment might contribute to outbreaks. Pets (including dogs and cats), livestock, and birds have been identified as MRSA carriers; their role in MRSA transmission to humans requires further evaluation.[21]

Clinical Features

CA-MRSA infections are most often manifested as skin and soft tissue suppuration, such as an abscess, furuncle, or cellulitis. Lesions frequently exhibit central necrosis and are often confused with spider bites by patients.[22] Clinical features cannot distinguish with certainty skin and soft tissue infections caused by MRSA from those caused by methicillin-susceptible *S. aureus*. Although rare, CA-MRSA infection can also be manifested as necrotizing fasciitis.[23] Recurrences of CA-MRSA cellulitis are common. Contagion among the close household contacts of patients as well as correctional facility, school, and sports team contacts is well recognized.

Management

Several studies have demonstrated excellent outcomes for abscesses caused by CA-MRSA that are treated with incision and drainage alone.[24] If antibiotics are needed, information on local antibiotic resistance patterns can help clinicians assess the likelihood of CA-MRSA infection and guide decisions about empirical treatment. A specimen for culture and susceptibility testing, which was considered to be unnecessary in the pre–CA-MRSA era, may be useful in guiding therapy. Specimens are obtained at the time of incision and drainage of purulent lesions.

In patients with larger abscesses, associated areas of cellulitis, or systemic signs of infection, antimicrobial therapy is needed in addition to incision and drainage. The optimal oral antimicrobial regimen for the treatment of skin and soft tissue infections is not known. The type and route of therapy are guided by the severity of the clinical syndrome.

Clindamycin combines MRSA activity with effectiveness against the majority of other gram-positive organisms. Side effects include diarrhea, *Clostridium difficile* colitis, and increasing rates of clindamycin resistance.[25] Rifamycin has anti-MRSA activity, but resistance readily develops, so it should not be used alone. The advantage of rifamycin is its long half-life, which allows once-a-day administration, and it penetrates well into all tissues and body fluids; its disadvantages include a high potential for drug-drug interactions. Linezolid is active against almost all CA-MRSA isolates and group A streptococci. Disadvantages of its use include high cost, lack of routine availability, hematologic side effects, and potential for resistance among *S. aureus* strains. Prolonged linezolid administration increases the likelihood of resistance.[26]

Trimethoprim-sulfamethoxazole or tetracycline is not recommended as sole empirical therapy for a nonpurulent cellulitis of unknown cause because of group A streptococci resistance to these agents. A β-lactam antibiotic may augment treatment. Cephalosporins and macrolides are ineffective against CA-MRSA. Fluoroquinolones should be avoided because *S. aureus* resistance develops readily.

Patients with large abscesses, abscesses in high-risk locations, fever, signs of systemic infection, young age, or immunodeficiency prompt consideration of hospitalization. Vancomycin is still considered the parenteral drug of choice for patients with invasive *S. aureus* infection, although clinical failures have been reported. It seems reasonable to combine vancomycin with another effective antistaphylococcal agent because many antibiotics have better bactericidal activity. In severely ill patients, carbapenems such as meropenem, panipenem, and ertapenem are recommended because they are active against CA-MRSA and synergistic with vancomycin.[27] Use of parenteral clindamycin (not recommended as monotherapy), trimethoprim-sulfamethoxazole, and linezolid has been described. In addition, daptomycin and tigecycline are now approved for the treatment of skin and soft tissue infections caused by MRSA.[28]

Recurrent infections are generally treated like initial episodes. Some providers recommend "decolonization" strategies, although neither the indications for their use nor their effectiveness in reducing the risk of recurrences is established. Decolonization strategies include the use of intranasal mupirocin to reduce nasal carriage of MRSA; however, eradication of nasal colonization appears to be transient. The efficacy of attempts to eradicate CA-MRSA among household members has not been studied.

Prevention

Common antiseptics appear to retain reasonable activity against CA-MRSA, although the results of studies are somewhat conflicting. Good personal hygiene, including appropriate handwashing techniques, separation of infected patients from other types of patients, and routine cleaning of shared equipment, are essential to limiting CA-MRSA spread.[29]

Gonococcal Dermatitis

Clinical Features

The arthritis-dermatitis syndrome is the most common presentation of disseminated gonococcal disease. It occurs in 1 or 2% of patients with gonorrhea, affecting women primarily.[30] Fever and migratory polyarthralgias commonly accompany the skin lesions. The lesions are often multiple and have a predilection for periarticular regions of the distal extremities. The lesions begin as erythematous or hemorrhagic papules that evolve into pustules and vesicles with an erythematous halo (Fig. 120-3). They closely resemble the lesions of meningococcemia at this stage. They may or may not be tender and may have a gray necrotic or hemorrhagic center. Healing with crust formation usually occurs within 4 or 5 days, although recurrent crops of lesions may appear even after antibiotics have been started.

Diagnostic Strategies

The lesions usually have a negative culture for gonococci, and the Gram stain only occasionally reveals the organisms. A more reliable diagnostic technique is immunofluorescent antibody staining of direct smears from pustules. This method indicates that the lesions may be the result of hematogenous dissemination of nonviable gonococci.

Management

Current treatment of disseminated gonococcal infection is 7 days of ceftriaxone, 1 g intramuscularly (IM) or intravenously (IV)

www.ketabpezeshki.com 66485457-66963820

Figure 120-3. Typical skin lesions of disseminated gonococcal disease. (Courtesy David Effron, MD.)

Figure 120-4. Facial cellulitis. (Courtesy David Effron, MD.)

Figure 120-5. Urticaria (hives). (Courtesy David Effron, MD.)

Figure 120-6. Morbilliform drug eruption. (Courtesy David Effron, MD.)

every 24 hours, or ceftizoxime or cefotaxime, 1 g IV every 8 hours. Patients allergic to β-lactam antibiotics or those with severe penicillin allergies may be treated with spectinomycin 2 g IM every 12 hours. A total of 7 days of antibiotic therapy is required. Parenteral therapy is continued for 24 to 48 hours after improvement is noted and then transitioned to oral cefixime, 400 mg twice a day only if culture demonstrates sensitivity; otherwise, parenteral therapy needs to be continued for 7 days. Ciprofloxacin and ofloxacin are not recommended because of increasing resistance patterns. Hospitalization is recommended for patients with disseminated gonococcal infection.

ERYTHEMA

Cellulitis is an infection of the skin tissue denoted by erythema, swelling, and local tenderness (Fig. 120-4). Erysipelas is a streptococcal infection of the skin and subcutaneous tissue. The involved area is red, indurated, and edematous. Soft tissue skin infections are discussed in more depth in Chapter 137.

RED MACULES

Drug Eruption

Principles of Disease

A given drug can produce a skin eruption of a different appearance in different patients or a different appearance in the same patient on different occasions. The most common eruptions are urticaria (hives) (Fig. 120-5) and, more commonly, morbilliform rashes (Fig. 120-6).

Drug reactions tend to appear within a week after the drug is taken, with the exception of reactions to semisynthetic penicillins, which commonly occur later. Skin lesions may appear after a drug has been discontinued and may worsen if the drug or its metabolites persist in the system. Special note should be made of penicillin because it is the most common cause of drug reaction. Serum sickness and urticaria are the most common manifestations of penicillin allergy. Atopic patients and those with a history of hay fever, asthma, or eczema are at special risk.

On the other hand, a number of drugs in common use rarely produce eruptions. Among these are acetaminophen, aluminum hydroxide (Maalox), codeine, digoxin, erythromycin, ferrous sulfate, meperidine (Demerol), morphine, and prednisone.

www.ketabpezeshki.com 66485457-66963820

Figure 120-7. Purpuric lesions. (Courtesy David Effron, MD.)

Clinical Features

A variety of skin reactions are associated with commonly used drugs, such as aspirin, penicillin, sulfonamides, and phenytoin. *Exanthematous drug eruptions* resemble the skin manifestations of various viral or bacterial infections and are usually widespread symmetric maculopapular eruptions. Severe cases may progress to exfoliative dermatitis.

Eczematous drug rashes resemble those of contact dermatitis but are generally more extensive. They begin as erythematous or papular eruptions that may become vesicular. Prior sensitization to a topical medication is common in cases of this type of eruption.

Vasculitic lesions begin as erythematous papules or nodules but may ulcerate and become gangrenous. Urticarial vasculitis is characterized by persistent urticarial lesions with histologic evidence of leukocytoclastic vasculitis. Wheel-and-flare–like lesions that hurt or burn more than itch, lesions lasting more than 24 hours, and urticarial lesions that leave prolonged pigmentary changes or inflammatory lesions should suggest urticarial vasculitis. Purpuric drug eruptions may be the result of bone marrow suppression, platelet destruction, or vasculitis (Fig. 120-7). Ultimately, a skin biopsy is needed to confirm the diagnosis of vasculitis.

Photosensitive drug reactions require the presence of sunlight and are seen most commonly on sun-exposed areas of skin. This class of reactions is commonly divided into phototoxic and photoallergic. Phototoxic reactions are more common. Sulfonamides, sulfonylureas, thiazide diuretics, and tetracyclines are common causes (see Fig. 120-7). This type of reaction does not primarily involve immunologic mechanisms and occurs in any person taking an adequate quantity of the drug and exposed to sunlight. The lesions usually have the appearance of a severe sunburn but may be bullous or papular. Pruritus is typically minimal or absent.

Photoallergic reactions are the result of antigen formation that results in the formation of sensitized lymphocytes. These reactions therefore represent a delayed immunologic response. A photoallergic reaction occurs only in sensitized individuals, usually 2 weeks or longer after exposure to the drug and sunlight. Its occurrence is not dose related, and the eruption usually appears eczematous and intensely pruritic. Chlorpromazine, promethazine, and chlordiazepoxide are common sensitizers of photoallergic reactions.

Patients who have photoallergic reactions should be withdrawn from the inciting drugs. Patients who are subject to photosensitive drug eruptions may be required to avoid prolonged sunlight exposure; use of a sunscreen containing 5% aminobenzoic acid is recommended for any sun exposure.

Fixed drug eruptions appear and recur at the same anatomic site after repeated exposure to the same drug. The lesions are usually sharply marginated and round or oval. They may be pigmented, erythematous, or violaceous. Pruritus may be prominent.

Differential Considerations

The differential diagnosis of drug eruptions includes viral exanthem, chronic exfoliative erythroderma caused by psoriasis or atopic dermatitis, malignant disease, scarlet fever, staphylococcal scarlatiniform eruptions, and Kawasaki disease.

Management

Treatment of drug eruptions begins with discontinuation of the inciting agent. Warn patients that drug eruptions often clear slowly after discontinuation of the offending agent. Itching may be treated with the application of a drying antipruritic lotion such as calamine. Cool compresses, tepid water baths with colloidal oatmeal (Aveeno) emollient or cornstarch, and diphenhydramine, 50 mg (5 mg/kg/24 hr in children) every 6 hours, are likely to be beneficial.

Staphylococcal Scalded Skin

Clinical Features

Staphylococcal scalded skin syndrome generally occurs in children 6 years of age or younger. It is caused by an infection with phage group 2 exotoxin-producing staphylococci. The illness begins with erythema and crusting around the mouth. The erythema then spreads down the body, followed by bulla formation and desquamation. Mucous membranes are usually not involved, but minimal involvement is occasionally seen. After desquamation occurs, the lesions dry up quickly, with clinical resolution in 3 to 7 days.

Management

Most group 2 toxin-producing organisms are penicillin resistant. Although most patients will recover without antibiotic treatment, intravenous therapy with 50 to 100 mg/kg of nafcillin daily or cephalexin 50 mg/kg/day or dicloxacillin is recommended.[31] Clindamycin, vancomycin, or linezolid may be considered in cases of suspected MRSA.

Toxic Epidermal Necrolysis

Principles of Disease

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are often considered a continuous spectrum of the same disease. Both are true dermatologic emergencies. The main feature of non–staphylococcal-induced TEN, or Lyell's disease, is the separation of large sheets of epidermis from underlying dermis. Drugs that can cause TEN include the long-acting sulfa drugs, penicillin, aspirin, barbiturates, phenytoin, carbamazepine, allopurinol, and nonsteroidal anti-inflammatory drugs. TEN has occurred after vaccination and immunization against poliomyelitis, measles, smallpox, diphtheria, and tetanus. It has also been found in association with lymphoma.

Clinical Features

TEN commonly begins with prodromal symptoms, such as malaise, rhinitis, sore throat, body aches, and fever. These are followed by the abrupt development of a macular rash that may or may not appear as target lesions.[32] Mucous membrane

www.ketabpezeshki.com 66485457-66963820

Figure 120-8. Stevens-Johnson syndrome. (Courtesy David Effron, MD.)

Figure 120-9. Toxic epidermal necrolysis. (Courtesy David Effron, MD.)

involvement commonly precedes the rash in SJS and TEN. The macular exanthem usually starts centrally and then spreads to the extremities. The exanthem becomes confluent, and dermal-epidermal dissociation ensues; Nikolsky's sign (denudation with shear stress) is present, and the skin is commonly painful to the touch (Fig. 120-8).

The patient may be toxic; complain of chills, headache, and malaise; and display fever, tachycardia, and tachypnea. Systemic involvement may occur, with renal, gastrointestinal, or respiratory tract lesions, resulting in hematuria, diarrhea, bronchitis, or pneumonia. Purulent conjunctivitis may be severe enough to cause the eyes to swell shut. Death results from infection and dehydration.

Mucous membrane involvement becomes more apparent during the progression phase. Involvement of the conjunctivae and cornea may lead to permanent scarring and blindness. The full thickness of the epidermis is involved. The two conditions are easily distinguished histologically with a skin biopsy (Fig. 120-9). A mortality rate of 15 to 20% is expected with this condition.

Management

The treatment of SJS and TEN includes discontinuation of the offending agent, fluid replacement, and meticulous attention to infection control. Systemic administration of corticosteroids is controversial. They have little effect on the disease and may mask signs of impending sepsis. High-dose intravenous immune globulin (>2 g/kg) is administered to patients with severe TEN or SJS. Plasmapheresis is considered in consultation with a specialist. The mainstay of treatment is excellent supportive care, prevention of secondary infection, and expert wound management. This is usually best accomplished in a center with burn expertise.

Toxic Shock Syndrome

Principles of Disease

Toxic shock syndrome (TSS) is an acute febrile illness characterized by a diffuse desquamating erythroderma. Classically composed of high fever, hypotension, constitutional symptoms, multiorgan involvement, and rash, the syndrome gained notoriety in the early 1980s because of association with tampon use. However, it is also well known in men and children. Its appearance has often been linked to exotoxin-producing *S. aureus*. Most cases of nonmenstrual TSS occur in the postoperative setting. TSS has also been associated with various staphylococcal and streptococcal infections, including empyema, osteomyelitis, fasciitis, septic abortion, peritonsillar abscess, sinusitis, burns, and subcutaneous abscess.[33]

TSS is associated with severe group A beta-hemolytic streptococcal infections. It has been reported in previously healthy patients, immunocompromised patients, and elders. Fatigue, localized pain, and nonspecific symptoms herald the onset of this disease, followed by septic shock and multisystem organ failure.

Clinical Features

Diagnosis of TSS requires the presence of (1) temperature of at least 38.9° C; (2) hypotension, with a systolic blood pressure of 90 mm Hg or less; (3) rash; and (4) involvement of at least three organ systems. Systemic involvement may include the gastrointestinal tract, muscular system, or central nervous system (CNS) and laboratory evidence of renal, hepatic, or hematologic dysfunction. Headache, myalgias, arthralgia, alteration of consciousness, nausea, vomiting, and diarrhea may be present.

The rash is typically a diffuse, blanching, macular erythroderma. Accompanying nonexudative mucous membrane inflammation is common. Pharyngitis, sometimes accompanied by a "strawberry tongue," conjunctivitis, or vaginitis, may be seen. As a rule, the rash fades within 3 days of its appearance. This is followed by a full-thickness desquamation, most commonly involving the hands and feet.

Management

Initial treatment of TSS consists of intravenous fluid replacement, ventilatory support, pressor agents, antibiotics covering *S. aureus* (including MRSA) and *Streptococcus pyogenes* with addition of clindamycin, and drainage of infected sites. Initial empirical antibiotic regimens include clindamycin 900 mg every 8 hours plus imipenem 500 mg every 6 hours or meropenem 1 g every 8 hours or ticarcillin-clavulanate 3.1 g every 4 hours or piperacillin-tazobactam 4.5 g every 6 hours.

www.ketabpezeshki.com 66485457-66963820

Urticaria

Principles of Disease

Urticaria may occur in isolation or as part of a systemic anaphylactic reaction. The following discussion pertains to urticaria occurring in the absence of systemic symptoms. Anaphylactic reactions and angioedema are discussed in Chapter 119. Approximately 15 to 20% of the population experiences urticaria during their lifetime. Acute urticaria is seen in both sexes and is more likely to have an allergic cause. Chronic urticaria is more common in women in their 40s and 50s. Half of all patients with chronic urticaria have the disease for 5 years and one fourth for 20 years.[34]

Various mediators, including histamine, bradykinin, kallikrein, and acetylcholine, are thought to play a role in urticaria production. Urticaria may be initiated by immunologic or nonimmunologic mechanisms. Hives found in anaphylaxis and serum sickness represent an immunologic reaction. Nonimmunologic urticaria may be produced by degranulation of mast cells, which may be caused by a number of foods and drugs, including aspirin and narcotics.

Substances that can cause urticaria by contact with the skin include foods, textiles, animal dander and saliva, plants, topical medications, chemicals, and cosmetics. The role of drugs in the production of urticaria is discussed in the section on drug eruption. Almost any drug may produce urticaria, although penicillin and aspirin are the most common. Traces of penicillin may be present in dairy products as well as in medications. The mechanism of production of urticaria by aspirin is unknown but is probably nonimmunologic, and the effects of aspirin may persist for a number of weeks after ingestion.

A variety of food allergies, such as fish, eggs, and nuts, may result in urticaria. In addition, foods such as lobster and strawberries can release histamine through a nonimmunologic mechanism. Hereditary forms of urticaria include familial cold urticaria and hereditary angioneurotic edema.

Infections are an uncommon cause of urticaria, except in children, in whom viral infections often cause hives. Occult infections with *Candida,* the dermatophytes, bacteria, viruses, and parasites may trigger hives. Viral infections that produce urticaria include hepatitis, mononucleosis, and Coxsackievirus infections.

The inhalation of pollens, mold, animal dander, dust, plant products, and aerosols may produce urticaria. Respiratory symptoms may accompany the dermatosis, and a seasonal pattern of occurrence may be present. Stings and bites of insects, arthropods, and various marine animals may also produce a urticarial eruption.

On occasion, patients with systemic lupus erythematosus, lymphoma, carcinoma, hyperthyroidism, rheumatic fever, and juvenile rheumatoid arthritis develop a urticarial eruption. The association is uncommon enough that it is not necessary for a urticaria workup to include a search for malignant disease in most cases.

A number of physical agents produce urticaria. Dermatographism is present when firm stroking of the skin produces a urticarial wheal within 30 minutes (Fig. 120-10) and is the most common form of physical urticaria. Pressure urticaria is distinct from dermatographism in that the onset of urticaria is delayed by 4 to 8 hours after the application of physical pressure. There is no other particular significance to this form of urticaria.

Cold urticaria may be either familial or, more commonly, acquired. Cold urticaria may also be associated with underlying illness, such as cryoglobulinemia, cryofibrinogenemia, syphilis, and connective tissue disease. Nonsedating antihistamines, such as rupatadine 10 to 20 mg daily, help suppress primary cold urticaria.[35] Antihistamines taken 30 to 60 minutes before cold exposure may be helpful. Cholinergic urticaria is induced by exercise, heat, or emotional stress. It may be associated with pruritus, nausea, abdominal pain, and headache. The lesions of cholinergic urticaria are wheals 1 to 3 mm in diameter surrounded by extensive erythematous flares and, occasionally, satellite wheals. Nonsedating antihistamines are generally used to treat cholinergic urticaria.[36]

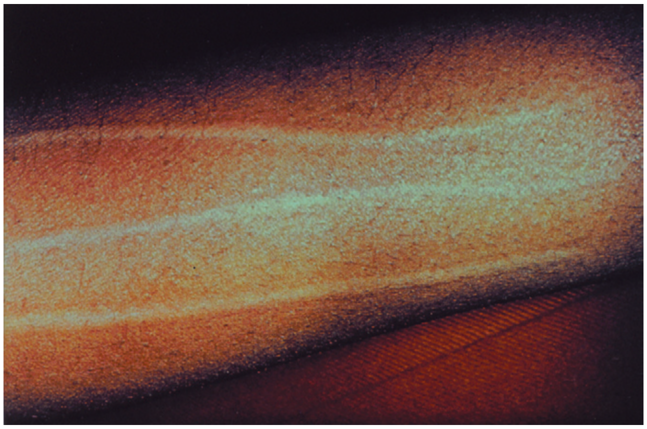


Figure 120-10. Dermatographism. (Courtesy David Effron, MD.)

Heat is a rare cause of hives. Solar urticaria, also uncommon, is confined to sun-exposed areas of skin and clears rapidly when the light stimulus is removed. Extensive sun exposure may cause wheezing, dizziness, and syncope in a susceptible individual. Sunscreens have not been proved to be effective for the prevention of solar urticaria. Phototherapy may be used to induce tolerance.[37]

Clinical Features

Urticaria appears as edematous plaques with pale centers and red borders and is easily recognizable (see Fig. 120-5). Individual hives are transient, lasting less than 24 hours, although new hives may continuously develop, which represents localized dermal edema produced by transvascular fluid extravasation.

Differential Considerations

The differential diagnosis of urticaria includes erythema multiforme, erythema marginatum, and juvenile rheumatoid arthritis.

Management

Treatment of urticaria involves the removal of the inciting factor, when applicable, and the administration of antihistamines or other antipruritics. Hydroxyzine (Atarax and Vistaril) in a dose of 25 to 50 mg (children's dose not to exceed 50 mg/day for children younger than 6 years and 100 mg/day for children older than 6 years) is usually effective in providing symptomatic relief. Alternatives are nonsedating antihistamines, such as loratadine 10 mg to 20 mg once a day or fexofenadine 60 mg twice a day. Prednisone is also effective, but the urticaria can rebound, making cessation of prednisone sometimes difficult. For chronic urticaria, long-term therapy with antihistamines may be needed. Nonsedating antihistamines are preferred, especially during the daytime. Cetirizine 10 to 20 mg/day, fexofenadine 180 mg/day, or loratadine 10 to 20 mg/day can be used. A single dose of an H_2 blocker may be added.

Patients with chronic urticaria may be discharged with a prescription for a combination of an H_1 and H_2 antihistamine. Strong evidence supporting addition of an H_2 blocker is lacking.[38] The use of steroids in management of urticaria is controversial and strong evidence for their use does not exist. Steroids are not indicated for mild cases. Patients with moderate or severe urticaria

www.ketabpezeshki.com 66485457-66963820

may benefit from prednisone 60 mg orally initially, followed by 40 mg daily for 5 days or dexamethasone (Decadron) 6 mg orally initially, followed by another 6 mg orally in 48 hours. Patients with recurrent urticaria may benefit from longer courses of oral steroids (14 to 21 days with a taper). Chronic administration of steroids is not recommended.

EXANTHEMS

Principles of Disease

An exanthem is defined as a skin eruption that occurs as a symptom of a general disease. Approximately 30 enteroviruses, predominantly the Coxsackievirus and echovirus groups, and four types of adenoviruses are known to produce exanthems. Other viruses may do so as well. The exanthems of the Coxsackievirus and echovirus are most thoroughly documented. Most viral exanthems are maculopapular, although scarlatiniform, erythematous, vesicular, and petechial rashes are occasionally seen. The eruptions are variable in their extent, are nonpruritic, and do not desquamate. Oropharyngeal lesions may be present.

Infection with echovirus type 9 may be accompanied by meningitis and a petechial exanthem resembling meningococcemia, although the exanthem also occurs without meningeal involvement. Infections caused by echovirus type 16 (Boston exanthem) and Coxsackievirus group B, type 5, may resemble roseola infantum but are more likely to occur in adults.

Infections caused by Coxsackievirus group A, type 16, cause a distinctive syndrome of vesicular stomatitis and 1- to 4-mm oral vesicles involving the dorsa of the hands and lateral borders of the feet. Disease caused by Coxsackievirus group A, type 9, has been the most extensively studied. It may be associated with meningoencephalitis or interstitial pneumonia. The rash is usually maculopapular, begins on the face or trunk, and spreads to the extremities. A vesicular eruption resembling varicella may occur.

The classic viral exanthems are rubeola (measles), rubella (German measles), herpesvirus 6 (roseola), parvovirus B19 (erythema infectiosum or fifth disease), and the enteroviruses (echovirus and coxsackievirus). Widespread immunization programs have reduced the incidence of rubeola and rubella.

Measles

Clinical Features

Measles is a highly contagious viral illness spread by contact with infectious droplets, with an incubation period of 10 to 14 days. Patients are contagious from 1 or 2 days before onset of symptoms up to 4 days after the appearance of the rash. Symptoms begin with fever and malaise. The fever usually increases daily in a stepwise manner until the temperature reaches approximately 40.5° C on the fifth or sixth day of the illness. Cough, coryza, and conjunctivitis begin within 24 hours of the onset of symptoms.

On the second day of the illness, Koplik's spots, which are pathognomonic of the disease, appear on the buccal mucosa as small, irregular, bright red spots with bluish white centers. Beginning opposite the molars, Koplik's spots spread to involve a variable extent of the oropharynx.

The cutaneous eruption of measles begins on the third to fifth day of the illness. Maculopapular erythematous lesions involve the forehead and upper neck and spread to involve the face, trunk, arms, and finally the legs and feet. Koplik's spots begin to disappear coincident with the appearance of the rash. By the third day of its presence, the rash begins to fade, doing so in the order of its appearance, and the fever subsides.

Complications include otitis media, encephalitis, and pneumonitis. Otitis media is the most common complication. Encephalitis occurs in approximately 1 in 1000 cases of measles and carries a 15% mortality. Measles pneumonia may also be life-threatening.

Management

If bacterial invasion occurs with otitis or pneumonia, the use of antibiotics is indicated. Otherwise, treatment is supportive. Isolation of infected children is of limited value because exposure usually occurs before the appearance of the rash, and the presence of Koplik's spots render the disease diagnosable. Measles is not contagious after the fifth day of the presence of the rash. Infection confers lifelong immunity.

The illness can be modified or prevented by the administration of human immune serum globulin (ISG) in a susceptible person within 6 days of exposure. The recommended dose of ISG is 0.25 mL/kg IM in children. Live measles virus vaccine given within 72 hours of exposure may be effective in preventing measles.[39] The incidence of measles has decreased since the resurgence seen in 1989 to 1991. The patterns observed during outbreaks include a shift from preschool-aged children to older adults and among groups who do not routinely obtain vaccination, such as immigrants.

Rocky Mountain Spotted Fever

Principles of Disease

Rocky Mountain spotted fever is caused by *Rickettsia rickettsii*, an organism harbored by a variety of ticks. The organism is transmitted to humans through tick saliva at the time of a tick bite or when the tick is crushed while in contact with the host. Many patients do not report tick exposure. Although originally described in the Rocky Mountain region, this disease occurs in other areas of North, South, and Central America. Most reported cases are from the southeastern United States.

Clinical Features

The onset of the illness is usually abrupt, with headache, nausea and vomiting, myalgias, chills, and a fever spiking to 40° C. On occasion, the onset is more gradual, with progressive anorexia, malaise, and fever. The disease may last 3 weeks and may be severe with prominent involvement of the CNS and other organ systems (cardiac, pulmonary, gastrointestinal, renal), disseminated intravascular coagulation, or shock.

The rash develops on the second to fourth day or, occasionally, as late as the sixth day of the illness. It begins with erythematous macules that blanch on pressure, appearing first on the wrists and ankles. These macules spread up the extremities and to the trunk and face in a matter of hours. They may become petechial or hemorrhagic. Lesions on the palms and soles are particularly characteristic. Increased capillary fragility and splenomegaly may be present.

Diagnostic Strategies

The Weil-Felix reaction is the best known serologic diagnostic test, but the development of Weil-Felix agglutinins in cases of Rocky Mountain spotted fever is not constant, and more specific immunofluorescent procedures have been developed. Treatment should not await the result of such tests, however, but should begin as soon as the disease is suspected on clinical grounds.

Management

Doxycycline at 2 to 4 mg/kg/day divided twice daily IV or orally is the antibiotic of choice. Doxycycline should not be withheld

www.ketabpezeshki.com 66485457-66963820

from children because significant teeth staining usually occurs only after repeated doses. Failure to administer antibiotics in a timely fashion in this illness dramatically increases morbidity and mortality. Chloramphenicol may be used for patients allergic to tetracycline and in children younger than 9 years; a usual course is 6 to 10 days and should continue for 72 hours after defervescence. A rare but fatal adverse reaction associated with chloramphenicol is aplastic anemia. Sulfa drugs should be avoided because they can exacerbate the illness. Rickettsiae are routinely resistant to penicillins, cephalosporins, aminoglycosides, and erythromycin. Ehrlichiosis may be difficult to differentiate from Rocky Mountain spotted fever clinically and is reliably treated with doxycycline. Chloramphenicol efficacy in this disease is not established.

Roseola Infantum

Roseola infantum, otherwise known as *exanthem subitum* or sixth disease, is a benign illness caused by human herpesvirus 6 and characterized by fever and a skin eruption. A roseola-like illness has occasionally been associated with other illnesses. Ninety-five percent of cases are seen in children 6 months to 3 years of age, and most of these are in infants younger than 2 years. A febrile seizure may occur. The fever typically has an abrupt onset, with temperature rising rapidly to 39° to 41° C, and is present consistently or intermittently for 3 or 4 days, at which time the temperature drops precipitously to normal.

The rash appears with defervescence. The lesions are discrete pink or rose-colored macules or maculopapules 2 or 3 mm in diameter that blanch on pressure and rarely coalesce. The trunk is involved initially, with the eruption typically spreading to the neck and extremities. The eruptions are occasionally limited to the trunk. The rash clears during 1 or 2 days without desquamation.

Despite the presence of a high fever, the infant usually appears well. Encephalitis is a very rare complication. The prognosis is excellent, and no treatment is necessary.

Rubella

Rubella, or German measles, is a viral illness characterized by fever, skin eruption, and generalized lymphadenopathy. It is spread by droplet contact, and peak incidence is in the winter and early spring. The incubation period is typically 14 to 21 days, and the rash heralds the onset of the illness in children. The maximum time of communicability is in the few days before and 5 to 7 days after the onset of the rash. Infants with congenital rubella can shed virus for more than 1 year. In adults, a 1- to 6-day prodrome of headache, malaise, sore throat, coryza, and low-grade fever precedes the rash. These symptoms generally disappear within 24 hours after the appearance of the skin eruption.

The rash of pink to red maculopapules appears first on the face and spreads rapidly to the neck, trunk, and extremities. Those on the trunk may coalesce, but lesions on the extremities do not. The rash remains for 1 to 5 days, classically disappearing at the end of 3 days. Although clearing may be accompanied by fine desquamation, this sign is usually absent.

Lymphadenopathy may begin as early as 1 week before the rash. Although this is generalized, the nodes most apparent are the suboccipital, postauricular, and posterior cervical groups. Palpable adenopathy may be apparent several weeks after other signs and symptoms have subsided.

The major complications of rubella include encephalitis, arthritis, and thrombocytopenia. The most severe complication is fetal damage. A total of 24% of infected fetuses have a congenital defect. A maternal infection may be determined by obtaining serum for hemagglutination inhibition antibody determinations, acutely and in 2 weeks. A fourfold rise in the titer is diagnostic of rubella infection. The routine use of postexposure prophylaxis of rubella in an unvaccinated woman in early pregnancy is *not* recommended.

No treatment is required in many cases of rubella. Antipyretics are usually adequate for the treatment of headache, arthralgias, and painful lymphadenopathy.

Erythema Infectiosum

Erythema infectiosum, or fifth disease, is caused by parvovirus B19 infection. It is characterized by mild systemic symptoms, fever in 10 to 15% of patients, and a characteristic rash. Arthralgia and arthritis occur commonly in adults but rarely in children. The rash is intensely red on the face and gives a "slapped-cheek" appearance with circumoral pallor. A maculopapular lacelike rash, which may be noted on the arms, moves caudally to the trunk, buttocks, and thighs. The rash may recur with changes in temperature and exposure to sunlight. The incubation period is usually between 4 and 14 days.

Parvovirus B19 infection may also result in asymptomatic infection, upper respiratory infection, atypical rash, and arthritis without rash. Rarely, it has been reported to cause hepatitis. Infected immunodeficient patients may experience chronic anemia as a result of this disease. Patients with sickle cell disease or other hemolytic anemias may develop an aplastic crisis lasting 7 to 10 days. Parvovirus B19 infection during pregnancy can cause fetal hydrops and death. No congenital anomalies have been reported. No treatment is required.

Scarlet Fever

Clinical Features

The incidence of scarlet fever has declined in recent years. The illness has an abrupt onset with fever, chills, malaise, and sore throat, followed within 12 to 48 hours by a distinctive rash that begins on the chest and spreads rapidly, usually within 24 hours. Circumoral pallor may be noted. The skin has a rough sandpaper-like texture because of the multitude of pinhead-sized lesions. The pharynx is injected, and there may be erythematous lesions or petechiae on the palate. After the resolution of symptoms, desquamation of the involved areas occurs and is characteristic of the disease.

Complications include the development of a streptococcal infection of lymph nodes, tonsils, middle ear, and respiratory tract. Late complications include rheumatic fever and acute glomerulonephritis (Fig. 120-11).

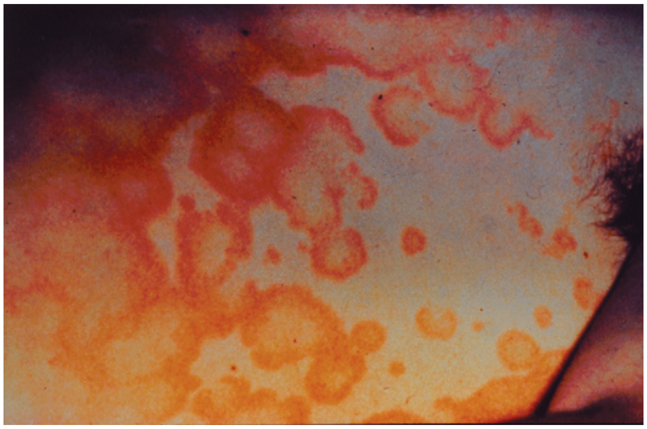


Figure 120-11. Erythema marginatum associated with rheumatic fever. (Courtesy David Effron, MD.)

www.ketabpezeshki.com 66485457-66963820

Management

Treatment is 10 days of oral penicillin VK 50 mg/kg/day (40,000-80,000 units) in four divided doses in children or 250 mg four times a day in adults. IM benzathine penicillin (given as Bicillin C-R) is another option; dosing is 300,000 units in patients weighing less than 30 pounds, 600,000 units in patients weighing 31 to 60 pounds, 900,000 units in patients weighing 61 to 90 pounds, and 1.2 million units in patients weighing more than 90 pounds. In patients allergic to penicillin, the treatment is 10 days of erythromycin, 250 mg four times a day in adults or 40 mg/kg/day in children. Other macrolides and certain other cephalosporins may also be used.

PAPULAR LESIONS

Contact Dermatitis

Principles of Disease

Contact dermatitis is an inflammatory reaction of the skin to a chemical, physical, or biologic agent. The inducing agent acts as an irritant or allergic sensitizer. Allergic contact dermatitis is a form of delayed hypersensitivity mediated by lymphocytes sensitized by the contact of the allergen to the skin. It is less common than irritant contact dermatitis. Caustics, industrial solvents, and detergents are common causes of irritant dermatitis. Dermatitis may result from brief contact with a potent caustic or from repeated or prolonged contact with milder irritants. Latex allergy causing contact dermatitis is of specific interest.

Clothing, jewelry, soaps, cosmetics, plants, and medications contain allergens that commonly cause allergic contact dermatitis. The most common allergens include rubber compounds; plants of the *Toxicodendron* species, including poison ivy, oak, and sumac; nickel, often used in jewelry alloys; paraphenylenediamine, an ingredient in hair dyes and industrial chemicals; and ethylenediamine, a stabilizer in topical medications.

Figure 120-12. Contact dermatitis secondary to nickel. (Courtesy David Effron, MD.)

Figure 120-13. Typical linear lesions of contact dermatitis secondary to poison ivy. (Courtesy David Effron, MD.)

Clinical Features

The primary lesions of contact dermatitis are papules, vesicles, and bullae on an erythematous bed. Streaky, linear, intensely pruritic lesions are characteristic. Atypical or diffuse rash develops with exposure to smoke from burning plants or when power tools are used to cut and mulch brush. Once the plant is touched, urushiol can be transferred to various anatomic locations (face, genitalia) or to other people. Domestic animals can serve as vectors if they are petted shortly after exposure to plants.

Eruptions associated with contact dermatitis can appear as soon as several hours after the exposure or may be delayed for days. Allergy to topical steroid preparations used to treat contact dermatitis can occur.

Management

Treatment of contact dermatitis includes avoidance of the irritant or allergen and treatment of secondary bacterial infection. Oozing or vesiculated lesions should be treated with cool wet compresses of Domeboro or Burow's solutions (aluminum acetate) applied for 15 minutes three or four times a day. Topical baths, available over the counter, may also be comforting. Systemic antihistamines, such as hydroxyzine and diphenhydramine, may help control pruritus; nonsedating antihistamines are preferred for use during the day. Low-potency topical steroid creams may be applied to erythematous areas around natural orifices and medium-potency creams can be used elsewhere. Topical steroids are ineffectual on blistered areas.

Poison Ivy

Clinical Features

Of the allergens, *Toxicodendron* species are the most likely to cause bullous eruptions. Oozing, crusting, scaling, and fissuring may be found along with lichenification in chronic lesions. The distribution of the eruption depends on the specific contact and may be localized, asymmetric linear, or unilateral (Figs. 120-12 and 120-13). Mucous membranes are usually spared unless they are directly exposed to the inciting agent. A history of exposure is the most significant factor favoring the diagnosis. If doubt exists about the diagnosis, the patient should be referred for allergic patch testing. Sensitization to poison ivy results in sensitization to other plants in this family, such as cashew, mango, lacquer, and ginkgo trees.

Management

In addition to the aforementioned treatment regimens for contact dermatitis, a course of systemic corticosteroids is often necessary to treat *Toxicodendron*-associated dermatitis.[10] Prednisone in a dosage of 30 to 80 mg/day (depending on the severity of involvement) can be prescribed initially and then tapered during at least 10 to 14 days and 21 days for poison ivy. The long, slow taper is needed to prevent rebound of the disease. The treatment may be discontinued when a daily dose of 5 mg is reached. In cases of *Toxicodendron* exposure, counsel the patient to wash all clothes

www.ketabpezeshki.com 66485457-66963820

Figure 120-14. Erythema multiforme. (Courtesy David Effron, MD.)

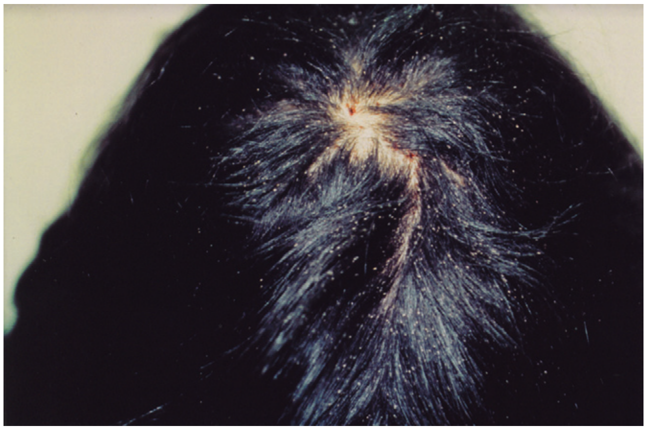


Figure 120-15. Nits as seen in head lice. (Courtesy David Effron, MD.)

that might have contacted the plant because the irritant plant oil can persist. Once the offending agent is reliably removed from the skin and clothes, ongoing outbreak is attributable to the initial contact, not spread from the serous fluid from the bullae. The patient is not contagious to others unless there is direct contact with the plant oil in people who are sensitized.

Erythema Multiforme

Principles of Disease

The most common precipitating factors in erythema multiforme are exposure to drugs and HSV infection. Additional causes include other viral infections, especially hepatitis and influenza A. Less common causes include fungal diseases, such as dermatophytosis, histoplasmosis, and coccidioidomycosis, and bacterial infections, especially streptococcal infections and tuberculosis. Various collagen vascular disorders have been known to precipitate erythema multiforme, particularly rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, and periarteritis nodosa. Pregnancy and various malignant neoplasms have also been associated with erythema multiforme. No provocative factor can be identified in approximately half of all cases. Differential diagnosis includes urticaria, scalded skin syndrome, pemphigus, and pemphigoid and viral exanthems.

Clinical Features

Erythema multiforme is an acute, usually self-limited disease precipitated by a variety of factors. It is characterized by the sudden appearance of skin lesions that are erythematous or violaceous macules, papules, vesicles, or bullae. Their distribution is often symmetric, most commonly involving the soles and palms, the backs of the hands or feet, and the extensor surfaces of the extremities. The presence of lesions of the palms and soles is particularly characteristic.

The target lesion with three zones of color is the hallmark of erythema multiforme. It is a central, dark papule or vesicle that is surrounded by a pale zone, a halo of erythema (Fig. 120-14), and is commonly found on the hands or wrists.

Management

Treatment begins with a search for the underlying cause. Mild forms with no systemic symptoms, lesions limited to extremities, and no mucous membrane involvement resolve spontaneously in 2 or 3 weeks. Patients with lesions on the trunk and patients who are immunocompromised, especially those with multiple lesions, require a course of systemic steroids for 14 to 21 days with a taper and urgent dermatology referral. Patients with mucous membrane involvement, systemic symptoms, or vesicle formation raise concern for SJS.

Pediculosis

Clinical Features

The diagnosis is made by identification of nits or adult lice on microscopic examination of plucked hairs from the symptomatic area. Nits are relatively more common than the adult louse form. Nits attach to the bases of hair shafts and appear as white dots (Fig. 120-15). Adult forms look like blue or black grains. The patient complains of intense itching and scratching. A secondary infection may result from the scratching.

The organisms causing pediculosis corporis reside in the seams of clothing and bedding materials while they feed on the human host. Except for heavily infested individuals, the parasites are absent from the body. Erythematous macules or wheals may be present along with intense pruritus. The treatment consists of laundering or boiling of clothing and bed linen. If nits are found in the body hair, a treatment with lindane lotion may be instituted, but this is not necessary is most cases (Figs. 120-16 and 120-17).

Pediculosis capitis is seen more commonly in small children than in adults. Pruritus is the major symptom and may be confined to the occipital or postauricular scalp. Excoriations commonly result in secondary bacterial infections and regional lymphadenopathy.

Diagnostic Strategies

The diagnosis is made by the identification of nits cemented to hairs at the hair-scalp junction (see Fig. 120-15).

Management

Permethrin (Nix) is the recommended treatment. It remains active for 2 weeks. Lindane (Kwell) lotion or cream is no longer the preferred prescription topical treatment.[40] Cream rinses and conditioning shampoos should not be used during this period because they coat the hairs and protect the lice from the insecticide. Permethrin is applied to the scalp after the hair is shampooed and dried. It is rinsed out with water after 10 minutes. It must be applied when the hair is dry because lice can close down their respiratory airways for up to 30 minutes when immersed in water.

www.ketabpezeshki.com 66485457-66963820

Figure 120-16. Body lice. (Courtesy David Effron, MD.)

Figure 120-17. Body lice. (Courtesy David Effron, MD.)

Higher cure rates are achieved if the dose is repeated 1 week after the initial use.

Other treatments for pediculosis capitis include a single dose of oral ivermectin, 200 µg/kg, repeated in 10 days.[40] The first line of treatment, permethrin or ivermectin, is dependent on the preference of the patient and physician. Lindane is reserved for treatment failures.

Household contacts should be examined for involvement. Because the condition may be spread by sexual contact, sexual

Figure 120-18. Scabies. (Courtesy David Effron, MD.)

partners should also be treated. Other uninfested household members need not undergo a course of therapy. Underclothing, pajamas, and sheets and pillowcases should be machine washed (hot water) and dried, laundered and ironed, or boiled. Pruritus that persists after the course of therapy may result from an irritation of the skin by the pediculicide, sensitization, or anxiety of the patient.

Scabies

Clinical Features

Scabies is a mite infestation characterized by severe itching, which usually worsens at night. The areas of the body most commonly involved are the interdigital web spaces, flexion areas of the wrists, axillae, buttocks, lower back, penis, scrotum, and breasts (Fig. 120-18). The infestation tends to be more generalized in infants and children than in adults. The typical lesions are reddish papules or vesicles surrounded by an erythematous border and scratch marks. Scabies in infants and young children often has generalized involvement of the skin, including the face, scalp, palms, and soles. In infants, the most common presenting lesions are papules and vesiculopustules.

Nodular scabies is a clinical variant in which extremely pruritic nodules are present on the male genitalia, buttocks, groin, and axillary regions. The nodules are reddish to brown, do not contain mites, and are thought to represent hypersensitivity reactions. They can persist for weeks despite adequate scabicidal treatment.

Immunosuppressed patients may develop Norwegian scabies, which is manifested by extensive hyperkeratosis and crusting of the hands, feet, and scalp. It is highly contagious because of excessive mite proliferation.[41] Secondary infections of these lesions are common.

Close personal contact is involved in transmission of scabies. Multiple family members are likely to become infested. The infestation is also transmitted with sexual contact.

Management

Treatment options include crotamiton (Eurax) lotion and cream, permethrin 5% cream (Elimite), and ivermectin (oral or topical). Lindane is not recommended as a first-line therapy; however, it does have a role in treating those cases that fail to respond to first-line therapies. Permethrin 5% cream (Elimite) applied overnight once weekly for 2 weeks over the entire body is the treatment of choice for infants and small children. It is more effective than crotamiton (Eurax) in eliminating the mite, in reducing secondary bacterial infection, and in reducing pruritus. Postscabetic nodules and pruritus may persist for months, even after successful

www.ketabpezeshki.com 66485457-66963820

treatment. Treatment of Norwegian scabies may require repeated treatment with scabicides and sometimes sequential use of several agents.

A single dose of oral ivermectin, 200 μg/kg, may also be used.[42] A second dose given 1 week later has been demonstrated to substantially improve the cure rate. Patients with crusted scabies may require repeated doses of ivermectin (200 μg/kg) along with topical scabicides (full-body application, repeated initially every few days) and keratolytics.

The full benefit of ivermectin becomes evident when eradication of scabies in epidemic or endemic situations is needed because ivermectin leads to reliable disease control.[43] The safety of ivermectin has been documented in millions of people with microfilarial diseases. Although ivermectin does not normally penetrate the blood-brain barrier and there should be no risk of seizures, neurotoxicity has been reported in the elderly. Because of limited safety data, ivermectin should not be used in children younger than 5 years or during pregnancy or lactation.

All family members and sexual contacts should also be treated. Intimate articles of clothing and sheets and pillowcases should be washed and dried by machine (hot water), laundered and ironed, or boiled.

It may take several weeks after therapy for the signs and symptoms to abate. A hypersensitivity state or anxiety may prolong symptoms long after the mites have been destroyed.

Syphilis

Clinical Features

Syphilis is transmitted only by direct contact with an infectious lesion. The causative organism is the spirochete *Treponema pallidum.* After an incubation period of 10 to 90 days, the primary lesion appears, which lasts 3 to 12 weeks and heals spontaneously. In 6 weeks to 6 months after exposure, the disease enters the secondary stage, which involves a variety of mucocutaneous lesions. These lesions also heal spontaneously in 2 to 6 weeks as the disease enters the latent phase. Either a prolonged latent phase or tertiary syphilis follows. Of untreated patients, 25% display at least one relapse of mucocutaneous lesions of the oral cavity or anogenital region.

The chancre is the dermatologic manifestation of primary syphilis. Chancres usually appear as single lesions but may be multiple. They appear at the site of spirochete inoculation, usually the mucous membranes of the mouth or genitalia. The chancre begins as a papule and characteristically develops into an ulcer approximately 1 cm in diameter with a clean base and raised borders. The chancre is painless unless it is secondarily infected, and it may be accompanied by painless lymphadenopathy.

The secondary stage usually follows the primary stage by 6 weeks or more but rarely overlaps primary syphilis. There are a number of cutaneous manifestations of secondary syphilis. Lesions may be erythematous or pink macules or papules, usually with a generalized symmetric distribution (Fig. 120-19). Pigmented macules and papules classically appear on the palms and soles (Figs. 120-20 and 120-21). The lesions may be scaly but are rarely pruritic.

Papular, annular, and circinate lesions are more common in people of color. Generalized lymphadenopathy and malaise accompany the skin lesions. Irregular, patchy alopecia may be seen. Moist, flat, verrucous condyloma latum may appear in the genital area. These lesions are highly contagious.

Diagnostic Strategies

The diagnosis of primary syphilis is made primarily by the identification of spirochetes with darkfield microscopy. Because a darkfield microscope is often not available to the emergency physician, the diagnosis of primary syphilis must be suspected on clinical grounds and the patient referred to a dermatologist or appropriate public agency for diagnosis and treatment. The result of the Venereal Disease Research Laboratory (VDRL) test, the most commonly used diagnostic serologic test, is positive in approximately three fourths of patients with primary syphilis, but the test result tends to be negative early in the course of the disease.

Figure 120-19. Secondary syphilis. (Courtesy David Effron, MD.)

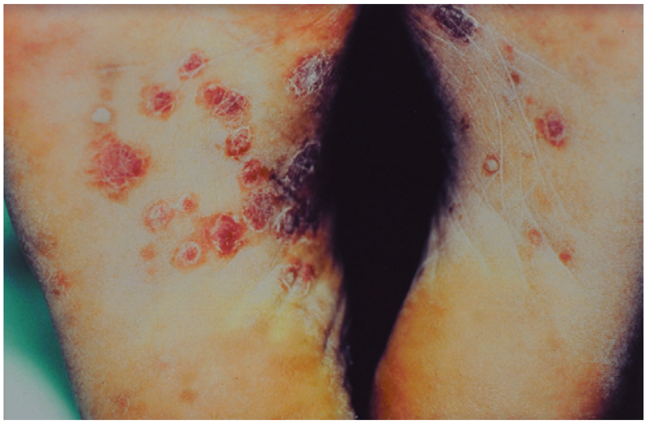


Figure 120-20. Cutaneous manifestation of secondary syphilis on the soles of the feet. (Courtesy David Effron, MD.)

Figure 120-21. Cutaneous manifestation of secondary syphilis on the palms of the hands. (Courtesy David Effron, MD.)

www.ketabpezeshki.com 66485457-66963820

The VDRL test result is invariably positive in cases of secondary syphilis, usually in titers of 1:16 or greater. The findings on dark-field examination of moist lesions may also be positive, but the diagnosis in this stage is based on a positive serologic test result. The most specific and sensitive serologic test is the fluorescent treponemal antibody absorption (FTA-ABS) test.

A biologic false-positive serologic test response for syphilis is defined as a positive VDRL test result with a negative FTA-ABS test result. This situation is seen acutely after vaccination or infections, especially mycoplasmal pneumonia, mononucleosis, hepatitis, measles, varicella, and malaria, and in pregnancy. Chronic biologic false-positive reactions (i.e., those lasting longer than 6 months) may occur with systemic lupus erythematosus, thyroiditis, lymphoma, and narcotic addiction or in elderly patients. Most false-positive reactions are in low titer ranges of 1:1 to 1:4.

Management

Guidelines for syphilis treatment, including in penicillin allergic individuals, are available through www.cdc.gov. Benzathine penicillin (Bicillin L-A) is the preferred agent and is recommended whenever possible. Protocols are available for skin testing and inpatient desensitization if allergy to penicillin is evident. Pregnant patients must be treated with penicillin to prevent transplacental transmission. In penicillin allergic individuals, doxycycline 100 mg twice daily or tetracycline 500 mg four times a day for 14 days can be used. Whereas azithromycin 2 g single dose is usually effective, treatment failures have been reported. Primary and secondary syphilis is treated with benzathine penicillin G in a dose of 2.4 million units IM. HIV-infected patients require more intensive therapy. Patients with latent syphilis are treated the same as patients with primary disease; latent syphilis and tertiary syphilis are treated with benzathine penicillin G, three doses of 2.4 million units IM at weekly intervals for a total of 7.2 million units. Treatment of neurosyphilis requires infusion of aqueous crystalline penicillin, 3 to 4 million units IV every 4 hours for 10 to 14 days.

Treatment may be administered in the ED if the diagnosis can be made on clinical, microscopic, or serologic grounds. If this cannot be done, a serologic sample should be drawn and the patient referred for treatment. The VDRL test response may be expected to return to nonreactive 6 to 12 months after the treatment of primary disease or 1 to 1½ years after the treatment of secondary disease. Patients with tertiary syphilis who are adequately treated may nevertheless retain a positive serologic result. Within 12 hours of receiving therapy, patients may experience a febrile reaction and diffuse rash called the Jarisch-Herxheimer reaction; thus it is best to warn patients of this possibility. The reaction resolves spontaneously, usually within 24 hours.

NODULAR LESIONS

Erythema Nodosum

Clinical Features

Erythema nodosum is an inflammatory reaction of the dermis and adipose tissue that is seen with painful red to violet nodules. Nodules are elevated lesions located deep in the skin, and the skin over the nodules can be moved by palpation. These painful nodules occur most commonly over the anterior tibia but may also be seen on the arms or body. Fever and arthralgia of the ankles and knees may precede the rash. As the lesions evolve, they may turn yellow-purple and resemble bruises (Fig. 120-22). Women are affected three times more often than men are, with the highest incidence in the third to fifth decades of life. Unless lesions quickly resolve, a search for underlying conditions must ensue.

Figure 120-22. Erythema nodosum. (Courtesy David Effron, MD.)

A number of diseases are associated with erythema nodosum; these include tuberculosis, sarcoidosis, coccidioidomycosis, histoplasmosis, ulcerative colitis, regional enteritis, pregnancy, and infections with streptococci, *Yersinia enterocolitica,* and *Chlamydia*. As with erythema multiforme, many cases of erythema nodosum are idiopathic. The relationship of drugs to erythema nodosum was noted in the section on drug eruption. Oral contraceptive agents are a leading cause of drug-induced cases. The differential diagnosis includes traumatic bruises and subcutaneous fat necrosis.

Management

Management begins with treatment of identified underlying conditions. Chest radiography may be considered to rule out sarcoidosis, tuberculosis, or deep fungal infection. Bed rest, elevation of the legs, and wearing of elastic stockings reduce pain and edema. Aspirin in a dosage of 650 mg every 4 hours or other nonsteroidal anti-inflammatory agents may also afford some relief. Erythema nodosum is a self-limited process that usually resolves in 3 to 8 weeks. Patients with severe pain may be treated with 360 to 900 divided three times daily of potassium iodide daily for 3 or 4 weeks. Stopping of therapy before this time may result in a relapse. Potassium iodide may act through an immunosuppressive mechanism mediated by heparin release from mast cells.

VESICULAR LESIONS

Perspective

Vesicles are elevated lesions that contain clear fluid. Vesicles larger than 1 cm are known as bullae. Vesicles may sometimes be associated with red papular lesions, as in contact dermatitis or erythema multiforme.

Pemphigus Vulgaris

Clinical Features

Pemphigus vulgaris is an uncommon but important dermatologic disorder. The mortality rate before the use of steroids was approximately 95%. The current mortality rate is 10 to 15%, related more to steroid-induced complications than to the disease. Pemphigus is a bullous disease, affecting both sexes equally, and is most common in patients 40 to 60 years old. The disease is mostly prevalent in people of Jewish, Mediterranean, or south Asian descent.

www.ketabpezeshki.com 66485457-66963820

Figure 120-23. Bullous pemphigus. (Courtesy David Effron, MD.)

Figure 120-24. HSV-1 infection. (Courtesy David Effron, MD.)

Figure 120-25. Herpetic whitlow. (Courtesy David Effron, MD.)

The typical skin lesions are small, flaccid bullae that break easily, forming superficial erosions and crusted ulcerations (Fig. 120-23). Any area of the body may be involved. Nikolsky's sign is present and characteristic of the disease. Blisters may be extended or new bullae may be formed by firm tangential pressure of a finger on the intact epidermis.

Before the appearance of the skin involvement, mucous membrane lesions occur; 50 to 60% of patients have oral lesions. The oral lesions typically antedate the cutaneous lesions by several months. The most common site is in the mouth, especially the gums and vermilion borders of the lips. Oral lesions are bullous but commonly break, leaving painful, denuded areas of superficial ulceration.

The cause of pemphigus is unknown, although studies suggest an autoimmune mechanism. The development of pemphigus has been associated in a few instances with the use of medications, most notably penicillamine and captopril. A positive Tzanck cytologic test result suggests the diagnosis (i.e., finding acantholytic cells or degenerated, rounded epithelial cells with amorphous nuclei). Acantholytic cells are not specific for pemphigus, however, and the diagnosis must be confirmed by serum immunofluorescence. The differential diagnosis includes bullous pemphigoid, epidermolysis, dermatitis herpetiformis, toxic epidermal necrolysis, bullous scabies, and bullous systemic lupus erythematosus.

Management

Pain control and local wound care are essential components of therapy. Once the diagnosis is made, treatment with oral glucocorticoids in initial doses of 100 to 300 mg of prednisone, or an equivalent drug, should be instituted in conjunction with a dermatologist.[44] Other immunosuppressant drugs may also be used. Despite the condition's localization to the skin and mucous membranes, death was the rule before treatment with steroids, and the mortality rate continues to be substantial. Deaths are related to an uncontrolled spread of the disease, secondary infection, dehydration, and thromboembolism. Other medical illnesses as well as the side effects of high-dosage corticosteroids also contribute to mortality.

Herpes Simplex

Perspective

Two known variants of HSV cause human infection: HSV-1 and HSV-2. HSV-1 primarily affects nongenital sites, whereas lesions caused by HSV-2 are found predominantly in the genital area and are transmitted primarily by venereal contact.

Clinical Features

The hallmark of skin infection with HSV is painful, grouped vesicles on an erythematous base (Fig. 120-24). Those above the waist are usually caused by HSV-1, whereas those below the waist generally result from HSV-2. The lesions are usually localized in a nondermatomal distribution. The skin distribution may become more generalized in patients with atopic eczema and other dermatoses. Adults with HSV infection should avoid contact with children with atopic dermatitis, especially in the first 3 to 5 days of infection.

The mouth is the most common site of HSV-1 infections. Children are affected more commonly than adults are. Small clusters of vesicles appear but are soon broken, leaving irregularly shaped, crusted erosions (Fig. 120-25). The severity of gingivostomatitis varies from the presence of small ulcers to extensive ulceration of the mouth, tongue, and gums accompanied by fever and cervical lymphadenopathy. The infection may be so severe that oral fluid intake is difficult, and dehydration may result. Healing typically

www.ketabpezeshki.com 66485457-66963820

occurs in 7 to 14 days unless a secondary infection with streptococci or staphylococci occurs.

HSV-2 infections in men are seen with either single or multiple vesicles on the shaft or glans penis. Fever, malaise, and regional adenopathy may be present. A prodrome of local pain and hyperesthesia may precede the appearance of the cutaneous lesions. The vesicles erode after several days, become crusted, and heal in 10 to 14 days. Infections in women involve the introitus, cervix, or vagina. Vesicles may be grouped or confluent. Herpetic cervicitis or vaginitis may be the cause of severe pelvic pain, dysuria, or vaginal discharge. Recurrence is common, but recurrent episodes tend to be less severe. A correlation based on serologic and epidemiologic data has been discovered between HSV-2 reproductive tract infections and carcinoma of the cervix.

Management

Recommended treatment for a first clinical episode of genital herpes is with acyclovir (Zovirax) 200 mg orally five times a day for 7 to 10 days, famciclovir 250 mg three times a day, or valacyclovir 1000 mg orally twice a day for 7 to 10 days or until clinical resolution occurs. These agents reduce the duration of viral shedding, accelerate healing, and shorten the duration of symptoms, but they have not succeeded in preventing recurrent episodes. Prophylactic administration of acyclovir may be effective in ameliorating the severity of recurrent genital herpes, but the effects of long-term administration are unknown. Although many episodes of recurrent herpes infection do not benefit from acyclovir therapy, 200 mg five times a day may be given orally for recurrences at the beginning of the prodrome. Famciclovir, 125 mg twice a day for 5 days, and valacyclovir, 500 mg three times a day for 3 days, are equally effective.

Severe initial attacks of genital herpes have been successfully treated with the intravenous infusion of acyclovir. Admission to the hospital is required, however, because such treatment is necessary for several days, especially for the immunocompromised patient. A mucocutaneous herpes infection in such patients is potentially fatal because it has a propensity for generalization and dissemination to the internal organs.

Any vesicular eruption on skin or mucous membranes in a neonate should prompt concern for HSV infection in that there is a high likelihood of dissemination in this group. Unless an alternative diagnosis is established, urgent testing of the vesicle's fluid for HSV along with acyclovir therapy is needed.

Supportive care is important and pain control is a major concern. Systemic analgesics and topical anesthetic agents may be useful. Education of the patient about the prevention or spread of the disease during sexual contact and the birth process is imperative.

Varicella

Clinical Features

Varicella, or chickenpox, is an infection caused by the varicella-zoster virus. After an incubation period of 14 to 21 days, the illness begins with a low-grade fever, headache, and malaise. The exanthem coincides with these symptoms in children and follows them by 1 or 2 days in adults.

The skin lesions rapidly progress from macules to papules to vesicles to crusting, sometimes within 6 to 8 hours. The vesicle of varicella is 2 or 3 mm in diameter and surrounded by an erythematous border (Fig. 120-26). An unusual form of varicella has larger bullae (Fig. 120-27). The drying of the vesicle begins centrally, producing umbilication. The dried scabs fall off in 5 to 20 days.

Figure 120-26. Chickenpox. (Courtesy David Effron, MD.)

Figure 120-27. Bullous chickenpox. (Courtesy David Effron, MD.)

Lesions appear in crops on the trunk, where they are seen in the highest concentration, and on the scalp, face, and extremities. The hallmark of varicella is the appearance of lesions in all stages of development in one region of the body. Extensive eruptions are often associated with a high and prolonged fever.

Complications of chickenpox include encephalitis or meningitis, pneumonia, staphylococcal or streptococcal cellulitis, thrombocytopenia, arthritis, hepatitis, and glomerulonephritis. Varicella pneumonia occurs more commonly in adults than in children.

Management

The illness is self-limited, and treatment is symptomatic only. Salicylates should be avoided in patients with chickenpox to minimize the risk of subsequent Reye's syndrome. Oral acyclovir may be effective if it can be started within 24 hours of development of rash for patients with chronic respiratory or skin disease. Some studies report a diminution in duration and magnitude of fever and number and duration of lesions with the early use of acyclovir.[45]

Isolation of infected patients is often futile because the disease may be transmitted before the diagnosis is clinically evident. Because the disease has the potential to be contagious until all vesicles are crusted and dried, infected persons should be kept at home until this stage is reached.

Varicella-zoster and varicella titers should be checked in pregnant women and immunocompromised patients who are exposed to chickenpox, and if the response is negative, varicella-zoster immune globulin is recommended within 96 hours of exposure.

www.ketabpezeshki.com 66485457-66963820

Figure 120-28. Herpes zoster. (Courtesy David Effron, MD.)

Figure 120-29. Herpes zoster infection. (Courtesy David Effron, MD.)

Fetal infection after maternal varicella in the first or early second trimester of pregnancy may result in varicella embryopathy, a condition characterized by limb atrophy, scarring on extremities, and CNS and ocular manifestations. Maternal varicella that occurs between 5 days before delivery and 2 days after delivery may result in disseminated herpes in the newborn.

The varicella vaccine is a live attenuated virus; it is highly efficacious and very safe.[46] A single dose is effective in children between the ages of 1 and 13 years. For older children, two doses separated by 4 to 8 weeks are recommended. In addition, the incidence of zoster occurring after vaccination appears to be lower than that of naturally acquired disease.

Herpes Zoster

Clinical Features

Herpes zoster, or shingles, is an infection caused by the varicella-zoster virus. It occurs exclusively in individuals who have previously had chickenpox. Before the rash appears, the patient typically develops pain in a dermatomal distribution. This pain precedes the eruption by 1 to 10 days and is variable in intensity; it may be described as sharp, dull, or burning in quality. The rash consists of grouped vesicles on an erythematous base involving one or several dermatomes. The thorax is involved in most cases, and the trigeminal distribution is the next most commonly involved region.

The vesicles initially appear clear and then become cloudy and progress to scab and crust formation. This process takes 10 to 12 days, and the crusts fall off in 2 or 3 weeks (Figs. 120-28 and 120-29). Herpes zoster has a peak incidence in patients 50 to 70 years old and is unusual in children. Although the association with leukemia, Hodgkin's lymphoma, and other malignant neoplasms is well known, rarely does the appearance antedate the diagnosis of such diseases. Most cases of herpes zoster occur in healthy individuals.

Herpes zoster may be transmitted from patients with chickenpox to susceptible individuals. Chickenpox may also be acquired by contact with shingles, although this is less common. It is generally believed, however, that herpes zoster is caused by a reactivation of latent varicella-zoster virus present since the initial infection with chickenpox. During the latent period between the two illnesses, the virus is thought to reside in dorsal root ganglion cells.

Herpes zoster has a very low mortality rate and is rarely life-threatening, except when dissemination to the visceral organs occurs. Complications include CNS involvement, ocular infection, and neuralgia. Meningoencephalitis, myelitis, and peripheral neuropathy have been reported.

Ocular complications occur in 20 to 70% of cases involving the ophthalmic division of the trigeminal nerve. The severity varies from mild conjunctivitis to panophthalmitis, which threatens the eye. Eye involvement may produce anterior uveitis, secondary glaucoma, and corneal scarring. There is a close correlation between eye involvement and vesicles located at the tip of the nose.

Postherpetic neuralgia (pain that persists after the lesions have healed) occurs more commonly in elders and immunosuppressed patients. It may last a number of months and is often resistant to treatment with standard analgesic medications.

Herpes zoster generally tends to be more severe in immunosuppressed patients, especially those with AIDS, Hodgkin's disease, or other lymphomas. Cutaneous dissemination occurs more commonly in these patients than in the general population. Visceral and CNS dissemination is also more likely to occur in these patients; therefore, they should be considered for hospitalization.

Management

Treatment other than analgesia is rarely necessary. Burow's solution compresses diluted 1:20 to 1:40 in water may be applied to hasten drying. Early systemic corticosteroid therapy may shorten the duration of postherpetic neuralgia but does not lessen the severity of pain or the rate of the healing of the lesions.[47] Antiviral chemotherapy, with acyclovir, famciclovir, vidarabine, foscarnet, valacyclovir, and interferon alfa, has been shown to be effective for immunocompromised patients. Postherpetic neuralgia is a complicated problem with few satisfactory solutions. Some success has been achieved with capsaicin cream, but this cannot be applied to inflamed or eroded skin.

Intravenous administration of acyclovir may be of some benefit in the treatment of severe ocular herpes zoster. Treatment includes mydriasis and the application of topical corticosteroids. Unlike the situation with herpes simplex conjunctivitis, eye involvement caused by herpes zoster does not appear to be exacerbated by corticosteroids. Immunization against herpes zoster is recommended in older adults.

Smallpox

The last naturally occurring case of smallpox was in Somalia in 1977. Subsequently, the routine vaccination of the general public was stopped. Except for laboratory stockpiles, the variola virus had been eliminated. Because of recent concerns about biologic agents

www.ketabpezeshki.com 66485457-66963820

Figure 120-30. Smallpox. (From the Centers for Disease Control and Prevention Public Health Image Library [http://phil.cdc.gov].)

Table 120-3 Differentiation of Chickenpox from Smallpox

	CHICKENPOX	SMALLPOX
Prodromal signs and symptoms	Prodromal signs and symptoms absent or mild	1 to 4 days of systemic signs and symptoms before onset of rash
Illness severity	Illness usually not severe unless complications or immunosuppressed	Very ill from onset, may be toxic
Lesion development	Superficial vesicles developing rapidly (1 day) and in multiple stages in each affected area	Hard, circumscribed pustules developing slowly (during days); lesions in same stage in every affected area
Lesion locations	Commonly on face and trunk, *not* palms and soles	Commonly on face and extremities, including palms and soles
Contagiousness	Contagious until all lesions crusted over	Contagious until *all* scabs have fallen off

as weapons, it is important that smallpox be differentiated from chickenpox (Table 120-3; Fig. 120-30).

Cutaneous Anthrax

Cutaneous anthrax begins as a pruritic pustule or vesicle that enlarges and erodes during 1 or 2 days. Subsequently, a necrotic ulcer with central black eschar is formed. The lesion may be painless and may be surrounded by significant edema (Fig. 120-31).

Figure 120-31. Cutaneous anthrax. (From the Centers for Disease Control and Prevention Public Health Image Library [http://phil.cdc.gov].)

SKIN LESIONS ASSOCIATED WITH SYSTEMIC DISEASE

Numerous systemic illnesses have cutaneous manifestations (Table 120-4; Figs. 120-32 to 120-39). Some of the most common illnesses include AIDS, sarcoidosis, diabetes mellitus, connective tissue diseases, and endocrine disorders.

CLINICAL FEATURES OF LESIONS ASSOCIATED WITH INTERNAL MALIGNANT DISEASE

Cutaneous lesions most directly indicative of an internal malignant disease arise from the extension of the tumor to the skin or by hematogenous or lymphatic metastasis. The neoplasms that most commonly produce such a cutaneous extension are lymphomas, leukemias, and carcinomas of the breast, gastrointestinal tract, lung, ovary, prostate, uterus, and bladder. Skin metastases generally signify a poor prognosis.

Acanthosis Nigricans

Acanthosis nigricans is associated with internal malignant disease, despite the fact that most patients do not have tumors. Benign cases may be familial or related to endocrine disease or obesity. The term *malignant acanthosis nigricans* is used to designate the form associated with neoplastic disease. This phrasing is misleading because acanthosis nigricans is only a marker of the underlying disease and is never infiltrated with malignant cells.

The lesion appears as a hyperpigmented verrucous, velvet-like hyperplasia and hypertrophy of the skin accompanied with accentuation of the skin markings. The chief sites of involvement are the body folds, especially the axillae, antecubital fossae, neck, and groin.

More than 90% of cases of malignant acanthosis nigricans are associated with intra-abdominal malignant neoplasms. Regardless of the tumor type, acanthosis nigricans is associated with tumors that are usually highly malignant and metastasize early. The mechanism of this dermatosis in cases of internal malignant disease is postulated to be a result of tumor products that bind to and stimulate insulin-like growth factors in the skin.

Dermatomyositis

The incidence of dermatomyositis with malignant disease ranges from 6 to 55% and is generally higher in older patients. In younger individuals, the appearance of dermatomyositis does not necessarily call for a tumor workup. Tumors commonly associated with dermatomyositis are carcinomas of the breast, ovary, and gastrointestinal and female genital tracts. Polymyositis occurring alone

www.ketabpezeshki.com 66485457-66963820

Table 120-4 Skin Lesions Associated with Systemic Disease

DISEASE	LESIONS	COMMENTS
AIDS	Chronic ulcerative herpes simplex	
	Kaposi's sarcoma (Figs. 120-32 and 120-33)	Diagnostic for AIDS
	Severe herpes zoster	
	Oral hairy leukoplakia	
	Genital warts	
	Molluscum contagiosum (Fig. 120-34)	
	Seborrheic dermatitis, *Pityrosporum*	
	Recurrent staphylococcal abscesses	
	Mycobacterial papules, nodules, abscesses	
	Oral and rectal squamous cell carcinoma	
	Lymphoma	
	Severe psoriasis	
	Acquired ichthyosis	
	Folliculitis	
	Human papillomavirus infection	
	Lichenoid photoeruptions	
Diabetes mellitus	Diabetic dermopathy	Most common
	Necrobiosis lipoidica diabeticorum	Most characteristic
	Cellulitis (Fig. 120-35)	Control of diabetes does not affect presence
	Vascular ulceration (Fig. 120-36)	
	Acanthosis nigricans	
	Bullosis diabeticorum	
	Diabetic thick skin	
	Scleroderma	
Dermatomyositis	Heliotrope discoloration and edema of eyelids	Skin lesions may precede muscle disease
	Scaly erythema of malar prominences	Symmetric proximal weakness, remissions, exacerbations
	Erythematous dermatitis over joint extensor surfaces, especially hands (Fig. 120-37)	Increased creatine kinase and aldolase with active disease
	Raynaud's phenomenon	
Systemic lupus erythematosus	Discoid lesions	Patients with cutaneous discoid lupus generally have benign diseases
	Malar erythema (Fig. 120-38)	
	Hypertrophic or verrucous palm and sole lesions	
	Lupus panniculitis	
	Oral ulcers	
	Raynaud's phenomenon	
Rheumatoid arthritis	Rheumatoid nodules and necrobiosis	
	Vasculitic lesions	
	Pyoderma gangrenosum	
	Urticaria	Still's disease
Hyperthyroidism	Fine, velvety, smooth skin	
	Increased sweating	
	Hyperpigmentation or hypopigmentation	
	Pretibial edema	
	Alopecia	
	Onychosis	
	Urticaria	
Hypothyroidism	Dry, coarse skin	
	Myxedema (Fig. 120-39)	
	Carotene color	
	Pruritus	
	Atopic dermatitis	
	Ichthyosis	
	Erythema nodosum	
	Easy bruising	
	Alopecia (lateral third of eyebrows)	
Ulcerative colitis	Pyoderma gangrenosum	Associated with state of disease
	Erythema nodosum	
	Aphthous stomatitis	

www.ketabpezeshki.com 66485457-66963820

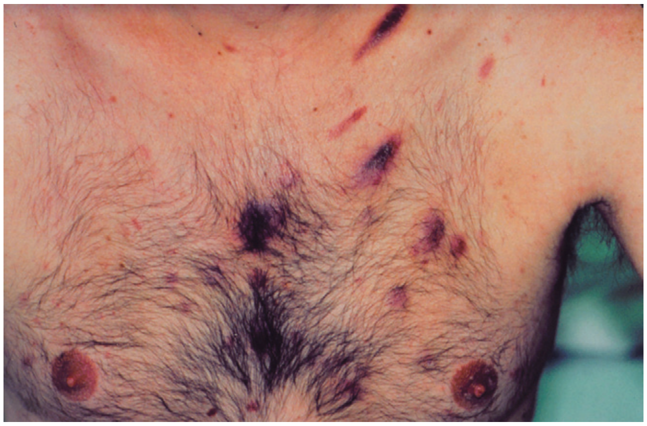


Figure 120-32. Kaposi's sarcoma associated with AIDS. (Courtesy David Effron, MD.)

Figure 120-33. Kaposi's sarcoma in an AIDS patient. (Courtesy David Effron, MD.)

Figure 120-34. Molluscum contagiosum caused by a virus is more prevalent with AIDS. (Courtesy David Effron, MD.)

Figure 120-35. Gangrene of the toe with cellulitis in a diabetic patient. (Courtesy David Effron, MD.)

Figure 120-36. Vascular ulceration secondary to diabetes. (Courtesy David Effron, MD.)

Figure 120-37. Erythematous dermatitis over the joint extensor surfaces, dermatomyositis. (Courtesy David Effron, MD.)

www.ketabpezeshki.com 66485457-66963820

Figure 120-38. Malar erythema in a patient with systemic lupus erythematosus. (Courtesy David Effron, MD.)

Figure 120-39. Severe myxedema in a hypothyroid patient. (Courtesy David Effron, MD.)

Box 120-1 Causes of Purpura

Thrombocytopenic
- Aplastic anemia
- Drug induced
- Idiopathic
- Malignant disease
- Sarcoidosis
- Splenomegaly
- Systemic lupus erythematosus
- Thrombotic
- Tuberculosis

Nonthrombocytopenic
- Drugs
- Infection (meningococcemia, Rocky Mountain spotted fever)
- Qualitative platelet defect
- Vasculitis

without the accompanying skin findings is rarely associated with malignant neoplasms.[48]

Erythema Multiforme

Erythema multiforme may be associated with acute forms of leukemia. It should be differentiated from other skin manifestations of leukemia, such as necrotizing vasculitis.

Erythema Nodosum

Erythema nodosum is another reaction found in association with leukemia and Hodgkin's lymphoma as well as with metastatic carcinoma and inflammatory bowel disease.

Erythroderma

Generalized erythroderma is seen in Hodgkin's disease; it is also a skin manifestation of lymphocytic leukemia. Although less common, it is also seen with other forms of leukemia, carcinoma, and mycosis fungoides. The appearance of erythroderma may precede the diagnosis of internal malignant disease by many years. The skin eruption is invariably accompanied by intractable pruritus.

Acquired Ichthyosis

Acquired ichthyosis is a skin condition manifested as generalized dryness of the skin, scaling, and superficial cracking or as hyperkeratosis of the palms and soles. Hodgkin's disease is the most common malignant disease associated with the nonfamilial form of ichthyosis. Non-Hodgkin's lymphoma and carcinomas of the breast, lung, colon, and cervix have also been associated with acquired ichthyosis.

Pruritus

Itching may be an important indicator of Hodgkin's disease, leukemia, adenocarcinoma or squamous cell carcinoma of various organs, carcinoid syndrome, multiple myeloma, and polycythemia vera. It may appear years before the underlying malignant disease is identified. In cases of Hodgkin's disease, the itching is usually continuous and may be accompanied by a severe burning sensation. Although it is usually generalized, pruritus commonly begins in the feet and may be limited to the lower extremities. It may be intractable and associated with urticaria, erythroderma, excoriation, or lichenification.

The pruritus of leukemia and systemic carcinoma is generally less severe than that found with Hodgkin's disease. Nevertheless, itching associated with internal malignant disease may be difficult to control. Conventional anti-H_1 antihistamines, cimetidine, and cholestyramine have each been used with variable results. On occasion, only the suppression of the tumor is beneficial.

Purpura

Purpura is the most common manifestation of acute granulocytic and monocytic leukemia. It may also be associated with myeloma, lymphoma, and polycythemia vera. Although the most common cause of purpura in these conditions is thrombocytopenia secondary to bone marrow infiltration, in some instances the platelet count is normal and the causative mechanism obscure. Purpura is caused by vascular abnormalities, thrombocytopenia, or other coagulation defects. A variety of diseases and conditions may be the underlying cause, and the treatment should be directed toward this cause whenever possible (Boxes 120-1 and 120-2). Thrombocytopenic and nonthrombocytopenic forms are differentiated by the results of the patient's platelet count. Serious bleeding seldom occurs if the platelet count is higher than 50,000/mm^3. If the platelet count is less than 10,000/mm^3 or serious bleeding is encountered, platelet transfusion should be initiated. Because of the short circulating half-life of infused platelets, transfusion should be used as a short-term measure only.

www.ketabpezeshki.com 66485457-66963820

Box 120-2 Commonly Used Drugs Associated with Purpura

Amitriptyline	Isoniazid
Aspirin	Meprobamate
Cephalothin	Methyldopa
Chloramphenicol	Penicillin
Chlorpromazine	Phenacetin
Chlorpropamide	Phenobarbital
Diazoxide	Phenylbutazone
Digitoxin	Quinidine
Furosemide	Rifampin
Hydrochlorothiazide	Sulfonamides
Indomethacin	Tolbutamide

Figure 120-40. Tracks secondary to intravenous heroin abuse. (Courtesy David Effron, MD.)

Urticaria

Urticaria is occasionally found in Hodgkin's disease and more rarely in leukemia and internal carcinoma. Cold urticaria may occur with multiple myeloma (Table 120-5).

CLINICAL FEATURES OF LESIONS ASSOCIATED WITH NARCOTIC ADDICTION

Individuals who inject opiates and other drugs parenterally develop characteristic skin lesions secondary to such use. Skin lesions have been most extensively described in heroin addicts. Skin tracks, or indurated linear hyperpigmented streaks, are produced by repeated intravenous injection (Fig. 120-40). They follow the course of the superficial veins used in the injection, most commonly in the antecubital fossae and the dorsa of the hands.

Subcutaneous injection results in round or oval hyperpigmented atrophic depressed scars 1 to 3 cm in diameter (Fig. 120-41). Abscesses, which often require drainage, commonly precede the development of such scars. Hypertrophic scarring and keloid formation may also occur. Increased pigmentation may occur in sun-exposed areas and at the site of tourniquet applications.

In addition to the characteristic skin lesions associated with drug injection, people who inject intravenous drugs are prone to sharp foreign body retention, pseudoaneurysm, gram-negative local and systemic infections, wound botulism (associated with the use of black tar heroin), and numerous other illnesses.

Table 120-5 Common Causes of Urticaria

CAUSE	COMMON RESPONSIBLE FACTORS
Bacterial infection	*Streptococcus* *Staphylococcus* *Yersinia* *Mycobacterium*
Viral infection	Herpes simplex virus Epstein-Barr virus Cytomegalovirus Hepatitis viruses (especially B) Many acute viral syndromes (adenovirus, enterovirus)
Other infections	Parasites Coccidioidomycosis Histoplasmosis *Rickettsia* Spirochete (Lyme disease)
Envenomation	Bees Wasps Scorpions Spiders Jellyfish Fleas Mites
Drugs	Penicillin Sulfa Cephalosporins Salicylates Morphine, codeine, other opioids Nonsteroidal anti-inflammatory drugs Barbiturates Amphetamines Blood and blood products
Foods	Nuts Shellfish Eggs Strawberries Tomatoes Milk, cheese Chocolate
Contacts	Chemicals Cosmetics Topical medications Plants Textiles Foods
Inhalants	Dust Pollen Animal dander Chemicals, aerosols Mold spores
Physical agents	Heat Cold Light Pressure (dermatographism) Water
Diseases	Collagen vascular disease Lupus, juvenile rheumatoid arthritis, polyarteritis nodosa, dermatomyositis, Sjögren's syndrome, rheumatic fever Inflammatory bowel disease Crohn's disease, ulcerative colitis Malignant disease Carcinoma, leukemia, lymphoma Miscellaneous Serum sickness, thyroiditis, aphthous stomatitis, Behçet's disease

Data from Edwards L: Dermatology in Emergency Medicine. New York, Churchill Livingstone, 1997; and Weston WL, Badgett JT: Urticaria. Pediatr Rev 19:240, 1998.

www.ketabpezeshki.com 66485457-66963820

Figure 120-41. Scars from subcutaneous illicit drug injection. (Courtesy David Effron, MD.)

KEY CONCEPTS

- Physicians should become familiar with one or two topical steroid preparations of low, medium, and high potency to avoid prescribing errors.
- Fungal infections involving the scalp and toenails require long-term systemic treatment. They do not respond to topical therapy.
- It is essential to consider kerion in the differential diagnosis of inflammatory or purulent scalp lesions as incision is not indicated except in cases complicated with bacterial superinfection.
- Newer nonsedating antihistamines are a useful alternative to older sedating ones to control pruritus and histamine-mediated rashes while allowing the patient to remain active.
- Infection with *C. albicans* can occur normally during infancy and pregnancy and in obese people and elders. In other patients, the following underlying problems should be considered: AIDS and other immunodeficiency states, diabetes and other endocrine imbalances, malignant disease, malnutrition, and other debilitating illnesses.
- Rashes that are associated with mucosal lesions, blisters, or desquamating skin are often caused by significant soft tissue infections, drug eruptions, or immune disorders.
- Purpura results from leaking of blood from vessels into the skin and does not blanch when pressure is applied. Purpuric lesions of less than 3 mm in diameter are called petechiae. Nonpalpable purpuric lesions are often caused by coagulation defects (usually platelet abnormalities), whereas palpable purpuric lesions are usually a sign of vasculitis.
- Diffuse pruritus in the absence of a rash may be a sign of underlying malignant disease or liver disease.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Hainer BL: Dermatophyte infections. *Am Fam Physician* 2003; 67:101.
2. Pomeranz AJ, Sabnis SS: Tinea capitis: Epidemiology, diagnosis and management strategies. *Paediatr Drugs* 2002; 4:779.
3. Shroba J, Olson-Burgess C, Preuett B, Abdel-Rahman SM: A large outbreak of *Trichophyton tonsurans* among health care workers in a pediatric hospital. *Am J Infect Control* 2009; 37:43.
4. Kaur IP, Kakkar S: Topical delivery of antifungal agents. *Expert Opin Drug Deliv* 2010; 7:1303.
5. de Chauvin MF: Novel, single-dose, topical treatment of tinea pedis using terbinafine: Results of a dose-finding clinical trial. *Mycoses* 2008; 51:1.
6. Karakas M, Memisuglu HR: Oral fluconazole in the treatment of tinea versicolor. *J Dermatol* 2005; 32:19.
7. Crawford F, Hollis S: Topical treatments for fungal infections of the skin and nails of the foot. *Cochrane Database Syst Rev* 2007; 3:CD001434.
8. Finch JJ , Warshaw EM: Toenail onychomycosis: Current and future treatment options. *Dermatol Ther* 2007; 1:31.
9. Pappas PG, Kauffman CA, Andes D: Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America . *Clin Infect Dis* 2009; 48:503.
10. Bourke J: Guidelines for the management of contact dermatitis: An update. *Br J Dermatol* 2009; 160: 946.
11. Drago F, Broccolo F, Rebora A: Pityriasis rosea: An update with a critical appraisal of its possible herpesviral etiology. *J Am Acad Dermatol* 2009; 61:303.
12. Leung DY, Bieber T: Atopic dermatitis. *Lancet* 2003; 361:151.
13. Saeki H: Guidelines for management of atopic dermatitis. *J Dermatol* 2009; 36:563.
14. Koo JY: Tacrolimus ointment is safe and effective in the treatment of atopic dermatitis: Results in 8000 patients. *J Am Acad Dermatol* 2005; 53:S195.
15. Fonacier L, et al: Report of the Topical Calcineurin Inhibitor Task Force of the American College of Allergy, Asthma and Immunology and the American Academy of Allergy and Immunology. *J Allergy Clin Immunol* 2005; 115:1249.
16. Wollenberg A, Wetzel S, Burgdorf WH, Haas J: Viral infections in atopic dermatitis: Pathogenic aspects and clinical management. *J Allergy Clin Immunol* 2003; 112:667.
17. George A: A systematic review and meta-analysis of treatments for impetigo. *Br J Gen Pract* 2003; 53:480.
18. Geria AN, Schwartz RA: Impetigo update. *Cutis* 2010; 85:65.
19. Jemec GBE: Hidradenitis suppurativa. *N Engl J Med* 2012; 366:158.
20. Moran GJ, et al: Methicillin-resistant *S. aureus* infections among patients in the emergency department. *N Engl J Med* 2006; 355:666.
21. Leonard FC, Markey BK: Methicillin-resistant *Staphylococcus aureus* in animals: A review. *Vet J* 2007; 175:27.
22. Miller LG, et al: Clinical and epidemiologic characteristics cannot distinguish community-associated methicillin-resistant *Staphylococcus aureus* infection from methicillin-susceptible *S. aureus* infection: A prospective investigation. *Clin Infect Dis* 2007; 44:471.
23. Miller LG, et al: Necrotizing fasciitis caused by community-associated methicillin-resistant *Staphylococcus aureus* in Los Angeles. *N Engl J Med* 2005; 352:1445.
24. Rogers KM: Systemic loxoscelism in the age of community-acquired methicillin-resistant *Staphylococcus aureus*. *Ann Emerg Med* 2011; 57:38.
25. Swartz MN: Cellulitis. *N Engl J Med* 2004; 350:904.
26. Peeters MJ, Sarria JC: Clinical characteristics of linezolid- resistant *Staphylococcus aureus* infections. *Am J Med Sci* 2005; 330:102.
27. Moore MR, Perdreau-Remington F, Chambers HF: Vancomycin treatment failure associated with heterogeneous vancomycin-intermediate *Staphylococcus aureus* in a patient with endocarditis and in the rabbit model of endocarditis. *Antimicrob Agents Chemother* 2003; 47:1262.
28. Rybak MJ: The efficacy and safety of daptomycin: First in a new class of antibiotics for gram-positive bacteria. *Clin Microbiol Infect* 2006; 12:24.
29. Johnson PDR, et al: Efficacy of an alcohol/chlorhexidine hand hygiene program in a hospital with high rates of nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infection. *Med J Aust* 2005; 183:509.
30. Yadav A: Shoulder pain: A presentation of bilateral gonococcal arthritis of the shoulders. *J Emerg Med* 2009; 36:19.
31. Patel NN: Staphylococcal scalded skin syndrome. *Am J Med* 2010; 123:505.
32. Letko E, et al: Stevens-Johnson syndrome and toxic epidermal necrolysis: A review of the literature. *Ann Allergy Asthma Immunol* 2006; 94:419.
33. Lappan E, Fergeson AJ: Gram-positive toxic shock syndromes. *Lancet Infect Dis* 2009; 9:281.
34. Grattan CE, Sabro RA, Greaves MW: Chronic urticaria. *Acad Dermatol* 2002; 46:645.
35. Metz M, et al: Rupatadine and its effects on symptom control, stimulation time, and temperature thresholds in patients with acquired cold urticarial. *Ann Allergy Asthma Immunol* 2010; 104:86.
36. Zuberbier T, et al: EAACI/GA^{2}LEN/EDF/WAO guideline: management of urticaria. *Allergy* 2009; 64:1427.
37. Botto NC, Warshaw EM: Solar urticaria. *J Am Acad Dermatol* 2008; 59:909.
38. Fedorowicz Z, van Zuuren EJ, Hu N: Histamine H_2-receptor antagonists for urticaria. *Cochrane Database Syst Rev* 2012; 3:CD008596. DOI: 10.1002/14651858.CD008596.pub2.
39. Barrabeig I, et al: Effectiveness of measles vaccination for control of exposed children. *Pediatr Infect Dis J* 2011; 30:78.
40. Frankowski BL: American Academy of Pediatrics guidelines for the prevention and treatment of head lice infestation. *Am J Manag Care* 2004; 10: S269.
41. Guldbakke KK: Crusted scabies: A clinical review. *J Drugs Dermatol* 2006; 5:221.
42. Chouela EN, et al: Equivalent therapeutic efficacy and safety of ivermectin and lindane in the treatment of human scabies. *Arch Dermatol* 1999; 135:651.
43. Leppard B, Naburi AE: The use of ivermectin in controlling an outbreak of scabies in a prison. *Br J Dermatol* 2000; 143:520.
44. Yeh SW, Sami N, Ahmed RA: Treatment of pemphigus vulgaris: Current and emerging options. *Am J Clin Dermatol* 2005; 6:327.
45. Arvin AM: Antiviral therapy for varicella and herpes zoster. *Semin Pediatr Infect Dis* 2002; 13:12.
46. Prevention of varicella: Update recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep* 2007; 56(RR-4):1-40.
47. Gnann JW, Whitley RJ: Herpes zoster. *N Engl J Med* 2002; 347:340.
48. Andras C, Ponyi A, Constantin T: Dermatomyositis and polymyositis associated with malignancy: A 21-year retrospective study. *J Rheumatol* 2008; 35:438.

www.ketabpezeshki.com 66485457-66963820

Section Ten
HEMATOLOGY AND ONCOLOGY

CHAPTER 121

Anemia, Polycythemia, and White Blood Cell Disorders

Timothy G. Janz and Glenn C. Hamilton

ANEMIA

Definition

Anemia is an absolute decrease in the number of circulating red blood cells (RBCs). The diagnosis is made when laboratory measurements fall below accepted normal values (Table 121-1).

In emergency medicine, anemia is divided into two broad categories: emergent, having immediate life-threatening complications; and nonemergent, with less imminent danger to the patient. Factors other than the absolute number of circulating RBCs may place the patient in one category or another (e.g., rate of onset and underlying hemodynamic reserve of the patient). Both groups necessitate a sound diagnostic approach, but emergent anemia may require supportive therapy concomitant with or in advance of the definitive diagnosis. Although patients with nonemergent anemia are usually referred to a specialist, they are seen in the hospital often enough to make an understanding of anemia necessary for emergency physicians. The urgency of consultation depends predominantly on the patient's hemodynamic tolerance of the anemia.

Pathophysiology

The major function of the RBC is oxygen transport from the lung to the tissue and carbon dioxide transport in the reverse direction. Oxygen transport is influenced by the amount of hemoglobin, its oxygen affinity, and blood flow. An alteration in any of the major components usually results in compensatory changes in the other two. For example, a decrease in hemoglobin from anemia is compensated by both inotropic and chronotropic cardiac changes that result in increased blood flow and decreased hemoglobin affinity at the tissue level, thereby allowing more oxygen release. These compensatory responses may collapse because of disease severity or underlying pathologic conditions. The result is tissue hypoxia and eventual cell death.

Anemia often stimulates the compensatory mechanism of erythropoiesis controlled by the hormone erythropoietin. Erythropoietin is a glycoprotein produced in the kidney (90%) and the liver (10%). It regulates the production of RBCs by controlling differentiation of the committed erythroid stem cell. It is stimulated by tissue hypoxia and products of RBC destruction during hemolysis. Erythropoietin levels are elevated in many types of anemia.

Bone marrow contains pluripotent stem cells that can differentiate into erythroid, myeloid, megakaryocytic, and lymphoid progenitors. Erythropoietin enhances the growth and differentiation of erythroid progenitors. When the late normoblast extrudes its nucleus, it still contains a ribosomal network, which identifies the reticulocyte (Fig. 121-1). The reticulocyte retains its ribosomal network for approximately 4 days, 3 days of which are spent in bone marrow and 1 day in the peripheral circulation. The RBC matures as the reticulocyte loses its ribosomal network and circulates for 110 to 120 days. The erythrocyte is then removed by macrophages that detect senescent signals.

Under steady-state conditions, the rate of RBC production equals the rate of destruction. RBC mass remains constant because an equal number of reticulocytes replace the destroyed, senescent erythrocytes during the same period.

Common sites of blood loss in trauma include the pleural, peritoneal, pelvic, and retroperitoneal spaces. In nontraumatic circumstances, especially in patients receiving anticoagulants, the gastrointestinal tract, retroperitoneal space, uterus, and adnexa need to be considered.

Causes other than blood loss may be responsible for severe anemia of rapid onset. Certain rare hemolytic conditions can cause rapid intravascular destruction of RBCs (Box 121-1). More common are patients with chronic compensated hemolytic anemia (e.g., sickle cell disease), who decompensate with an acute-onset anemia as a result of decreased erythrocyte production triggered by a viral infection.

Beyond red cell destruction, the status of hemoglobin function should be considered. Impaired hemoglobin transport of oxygen is seen in cases of carbon monoxide poisoning. Methemoglobinemia from nitrates, cyanhemoglobin from cyanide, and sulfhemoglobinemia from hydrogen sulfide may severely decrease functional hemoglobin. These patients often have fatigue, altered mental status, shortness of breath, and other manifestations of hypoxia without signs of RBC loss or volume depletion.

Diagnostic Findings in Emergent Anemia

Clinical Features

The most common cause of clinically significant anemia is blood loss. The clinical manifestation of anemia depends on how rapidly the hematocrit falls and also on the patient's ability to compensate.

Clinical signs and symptoms include tachycardia, decreased blood pressure, postural hypotension, lightheadedness, increased heart rate, and increased respiratory rate. Complaints of thirst, altered mental status, and decreased urine output may also be present. The patient's age, concomitant illness, and underlying hematologic, cerebral, and cardiovascular status tremendously influence the clinical findings. Children and young adults may tolerate significant blood loss with unaltered vital signs until a precipitant hypotensive episode occurs. Pediatric patients may

www.ketabpezeshki.com 66485457-66963820

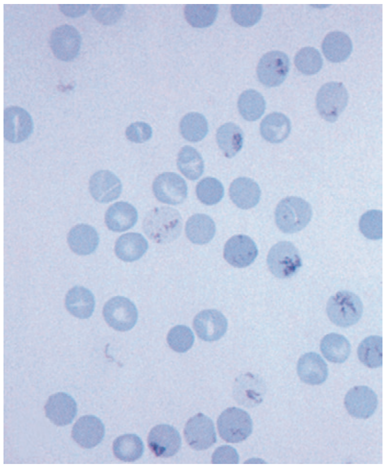


Figure 121-1. Reticulocytes with reticular material after methylene blue staining. (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000:18.)

Table 121-1 Hemogram Normal Values

AGE	HEMOGLOBIN (g/dL)	HEMATOCRIT (mL/dL)	RED BLOOD CELL COUNT ($\times10^6$)
3 months	10.4-12.2	30-36	3.4-4.0
3-7 years	11.7-13.5	34-40	4.4-5.0
Adult man	14.0-18.0	40-52	4.4-5.9
Adult woman	12.0-16.0	35-47	3.8-5.2

Box 121-1 Causes of Rapid Intravascular Red Blood Cell Destruction

Mechanical hemolysis associated with disseminated intravascular coagulation
Massive burns
Toxins (e.g., some poisonous venoms: brown recluse spider, cobra)
Infections such as malaria or *Clostridium* sepsis
Severe glucose-6-phosphate dehydrogenase deficiency with exposure to oxidant stress
ABO incompatibility transfusion reaction
Cold agglutinin hemolysis (e.g., *Mycoplasma* organisms, infectious mononucleosis)
Paroxysmal nocturnal hemoglobinuria exacerbated by transfusion
Immune complex hemolysis (e.g., quinidine)

become markedly tachycardic, physiologically attempting to maintain cardiac output because their ability to increase stroke volume is limited. Elderly patients commonly have underlying disease states that compromise their ability to compensate for blood loss.[1]

Pertinent elements of the history and physical examination of patients with acute anemia are listed in Box 121-2.

Ancillary Evaluation

Stabilization of emergent anemia commonly runs parallel to assessment. If the signs and symptoms suggest potential life-threatening conditions, intravenous lines are placed and samples for the following initial laboratory tests are drawn:

Box 121-2 History and Physical Examination for Clinically Severe Anemia

History

General

Out-of-hospital status, therapy, response to therapy
Bleeding diathesis
Previous blood transfusion
Underlying diseases, including allergies
Current medications, especially those causing platelet inhibition

Trauma

Nature and time of injury
Blood loss at scene

Nontrauma

Skin: petechiae, ecchymoses
Gastrointestinal: hematemesis, hematochezia, melena, peptic ulcer
Genitourinary: last menstruation, menorrhagia, metrorrhagia, hematuria

Physical Examination

Vital Signs Measured Serially

Blood pressure, pulse, respiratory rate, oxygen saturation
Orthostatic blood pressure and pulse (contraindicated with severe hypotension)
Level and content of consciousness

Skin

Pallor
Diaphoresis
Jaundice
Cyanosis
Purpura, ecchymoses, petechiae
Evidence of penetrating wounds

Cardiovascular

Murmurs, S_3, S_4
Quality of femoral and carotid pulses

Abdomen

Hepatosplenomegaly
Pain, guarding, rebound on palpation
Rectal and pelvic examination
Masses
Stool hemoglobin testing

1. Complete blood count and peripheral smear
2. Blood sample for type and crossmatch
3. Prothrombin time and international normalized ratio
4. Partial thromboplastin time
5. Electrolyte levels
6. Glucose level (especially if the patient has altered consciousness)
7. Creatinine level
8. Urinalysis for free hemoglobin
9. Clotting and unclotted blood samples for later testing

If possible, a blood sample is obtained for measurement of hematocrit in the emergency department. Although it may take hours before the hematocrit correctly reflects the degree of blood loss, the initial value is useful in determining a baseline. On occasion, this value reveals an underlying anemia with the acute blood loss superimposed. Depending on severity, a blood sample is sent for type and crossmatch. Peripheral smear interpretation is done on pretreatment blood samples.

Measurements of coagulation status, electrolytes, glucose, blood urea nitrogen, and creatinine are useful in the diagnosis of underlying disease processes that may relate to the patient's anemia. Values of folate, vitamin B_{12}, iron, total iron-binding capacity, reticulocytes, and direct antiglobulin (Coombs' test) are altered by transfusion. Therefore, pretreatment samples are best saved.

www.ketabpezeshki.com 66485457-66963820

Box 121-3 History and Physical Examination for Nonemergent Anemia

History

Symptoms of Anemia
Chest pain, decreased exercise tolerance, dyspnea
Weakness, fatigue, dizziness, syncope

Bleeding Diathesis
Bleeding after trauma, injections, tooth extractions
Spontaneous bleeding, such as epistaxis, menorrhagia
Spontaneous purpura and petechiae

Sites of Blood Loss
Respiratory: epistaxis, hemoptysis
Gastrointestinal: hematemesis, hematochezia, melena
Genitourinary: abnormal menses, pregnancies, hematuria
Skin: petechiae, ecchymoses

Intermittent Jaundice, Dark Urine

Dietary History
Vegetarianism
Poor nutrition

Drug Use and Toxin Exposure, Including Alcohol

Racial Background, Family History

Underlying Disease
Uremia, liver disease, hypothyroidism
Chronic disease states such as cancer, rheumatic or renal disease
Previous surgery

Miscellaneous
Previous treatment of anemia
Weight loss
Back pain

Physical Examination

Skin
Pallor
Purpura, petechiae, angiomas
Ulcerations

Eye
Conjunctival jaundice, pallor
Funduscopic hemorrhage, petechiae

Oral
Tongue atrophy, papillary soreness

Cardiopulmonary
Heart size, murmurs, extra cardiac sounds
Rales, other signs of pulmonary edema

Abdomen
Hepatomegaly, splenomegaly
Ascites
Masses

Lymph Nodes

Neurologic
Altered positions or vibratory sense
Peripheral neuritis

Rectal and Pelvic

Diagnostic Findings in Nonemergent Anemia

Clinical Features

Nonemergent anemias are usually seen in ambulatory patients complaining of fatigue and weakness. Other voiced complaints include irritability, headache, postural dizziness, angina, decreased exercise tolerance, shortness of breath, and decreased libido. When the anemia is of slow onset, the patient may adapt until the hemoglobin is very low. Alternatively, patients with rapid blood loss may experience lightheadedness or syncope even when the measured hemoglobin is not critically low. For patients without evidence of acute bleeding or emergent condition, elements of history and physical examination may help identify the cause (Box 121-3). Most of these patients do not need immediate stabilization and can be further evaluated as outpatients.

Ancillary Evaluation

The initial laboratory evaluation includes a complete blood count with leukocyte differential, reticulocyte count, peripheral smear (Fig. 121-2), and RBC indices, including mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Disposition

Criteria for the admission of patients with nonemergent anemia are shown in Box 121-4.

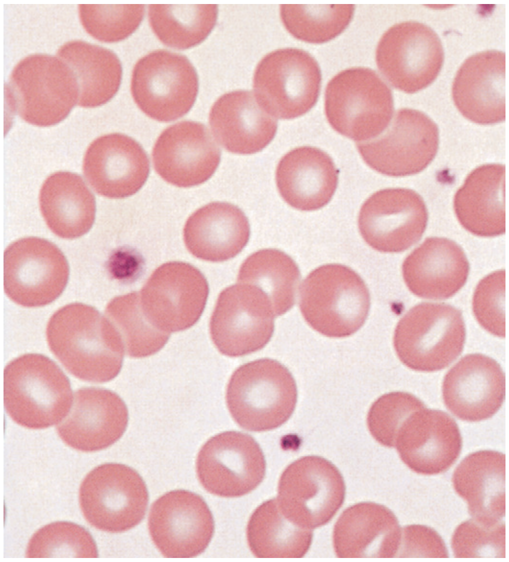


Figure 121-2. Normal smear. (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000:22.)

Differential Diagnosis

The differential diagnosis of anemia is facilitated by classification of the anemia into one of three groups: decreased RBC production, increased RBC destruction, and blood loss. A complementary approach uses RBC morphology and indices. Figure 121-3 presents an algorithm for the evaluation of anemia.

www.ketabpezeshki.com 66485457-66963820

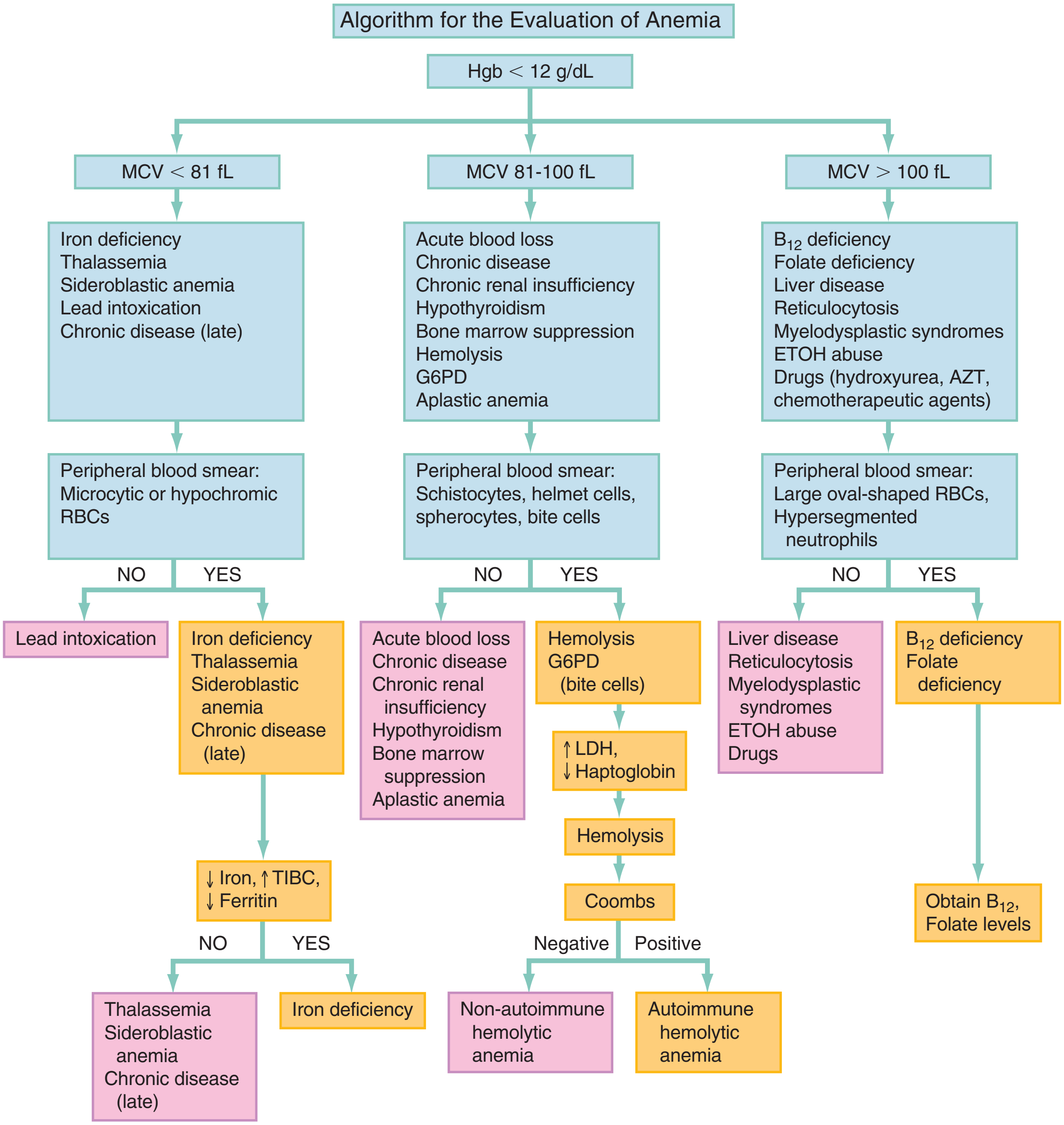


Figure 121-3. Algorithm for the evaluation of anemia. *AZT,* azathioprine; *ETOH,* ethanol; *fL,* femtoliter; *G6PD,* glucose-6-phosphate dehydrogenase; *Hgb,* hemoglobin; *LDH,* lactate dehydrogenase; *MCV,* mean corpuscular volume; *RBCs,* red blood cells; *TIBC,* total iron-binding capacity.

Box 121-4 Admission Criteria for Nonemergent Anemia

- Developing cardiac symptoms, such as shortness of breath or chest pain, or neurologic symptoms
- Initial unexplained hemoglobin value less than 8-10 g/dL or hematocrit less than 25-30%
- Major difficulty in obtaining outpatient care for patients whose hemoglobin levels are significantly low or when comorbidity is present

Decreased Red Blood Cell Production

Anemias caused by decreased RBC production have a natural history of insidious onset and an associated decreased reticulocyte count. A subclassification by indices of anemias caused by decreased RBC production is listed in Box 121-5. The RBC indices and morphology manifested in a peripheral smear are useful in securing the diagnosis. The definitive diagnosis is usually made outside the emergency department and may require bone marrow examination. The emergency physician rarely initiates replacement therapy, except in circumstances that require transfusion. Appropriate diagnostic tests may be initiated, but replacement of iron, vitamin B_{12}, or folate without proof of cause is generally unnecessary and unwise.

RBC indices are useful in classifying anemias caused by a production deficit. Their calculation and normal ranges are provided in Table 121-2. MCV is a measure of RBC size; decreases and increases reflect microcytosis and macrocytosis, respectively. MCH incorporates both RBC size and hemoglobin concentration. It is influenced by both and is the least helpful of the indices. The MCHC index is a measure of the concentration of hemoglobin. Low values represent hypochromia, whereas high values are noted only in patients with decreased cell membrane relative to cell volume, such as in the case of spherocytosis. An additional index is the RBC distribution width (RDW), which is a measure of the

www.ketabpezeshki.com 66485457-66963820

Box 121-5 Differential Diagnosis of Anemias Caused by Decreased Red Blood Cell Production: Subclassification by Red Blood Cell Indices

Hypochromic Microcytic Anemias (Decreased MCV and Hemoglobin Concentration)
Iron deficiency
Thalassemia
Sideroblastic anemia or lead poisoning
Chronic disease (e.g., cancer, renal or inflammatory disease); normochromic and normocytic indices often found

Macrocytic (Elevated MCV)
Vitamin B_{12} deficiency
Folate deficiency
Liver disease
Hypothyroidism

Normocytic (Normal MCV and Hemoglobin Concentration)
Primary bone marrow involvement: aplastic anemia, myeloid metaplasia with myelofibrosis, myelophthisic anemia
Resulting from underlying disease: hypoendocrine state (thyroid, adrenal, pituitary), uremia, chronic inflammation, liver disease

MCV, mean corpuscular volume.

Table 121-2 Calculation of Red Blood Cell Indices and Normal Values

INDEX	FORMULA FOR CALCULATION	NORMAL RANGE
Mean corpuscular volume	Hematocrit (%) divided by red blood cell count ($10^6/\mu L$)	81-100 fL
Mean corpuscular hemoglobin	Hemoglobin (g/dL) divided by red blood cell count ($10^6/\mu L$)	26-34 pg
Mean corpuscular hemoglobin concentration	Hemoglobin (g/dL) divided by hematocrit (%)	31-36%

fL, femtoliter.

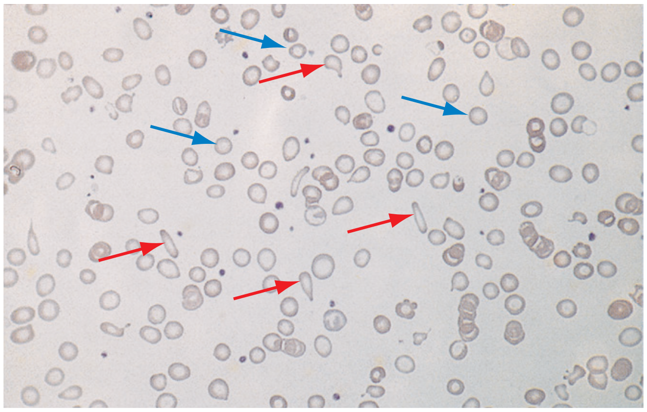


Figure 121-4. Iron deficiency anemia with hypochromic, microcytic cells and poikilocytes (abnormally shaped cells). (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000:44.)

homogenicity of the RBCs measured. RDW is automatically calculated as the standard deviation of MCV divided by MCV multiplied by 100. A normal RDW is 13.5 ± 1.5%. The RDW is usually elevated in anemias caused by nutritional deficiencies; however, it is not specific for any abnormality.

Microcytic Anemias. Hypochromic microcytic anemias are subdivided into deficiencies of the three building blocks of hemoglobin: iron (iron deficiency anemia; Fig. 121-4), globin (thalassemia), and porphyrin (sideroblastic anemia and lead poisoning). Anemia of chronic disease, a secondary iron abnormality, rounds out the differential diagnosis. Not all microcytic anemias are the result of iron deficiency, and routine iron therapy for a patient with a low MCV and MCHC is inappropriate.

Iron Deficiency Anemia. Iron deficiency is a frequent cause of chronic anemia seen in the emergency department. It is the most common anemia in women of childbearing age. In older patients, occult blood loss, especially gastrointestinal, may initially appear as iron deficiency anemia. Because changes in RBC size and hemoglobin content occur only after bone marrow and cytochrome iron stores are depleted, a patient may have early symptoms of iron deficiency (e.g., fatigue) without manifesting changes in RBC structure.

The diagnosis is made by laboratory evaluation of the fasting level of serum iron, serum ferritin, and total iron-binding capacity. The laboratory interpretation and pitfalls are outlined in Table 121-3. A concentrated search for occult blood loss is vital.

Therapy consists of oral iron replacement. A cost-effective form is ferrous sulfate. The dosage is 300 mg for adults (60 mg of elemental iron) or 3 mg/kg/day for children. This medication is generally well tolerated, although it may cause nausea, vomiting, or constipation. Patients should be warned that their stools will be blackened. The patient should also be warned that bleeding from the digestive tract can also be manifested as blackened stool. In rare patients with poor oral tolerance or absorption, parenteral iron therapy may be necessary.

The patient may experience a sense of improvement in as few as 24 hours. Reticulocytosis appears during a 3- or 4-day period in children but may take more than 1 week in adults. The hemoglobin concentration rises on a similar schedule. Explanations for response failures to iron therapy include the following: the patient is noncompliant with the iron supplementation, the blood loss may exceed the replacement, the diagnosis is incorrect, or the diagnosis is partially correct with an additional process complicating the iron deficiency.[2]

Thalassemia. Thalassemia is a genetic autosomal defect reflected by the decreased synthesis of globin chains. The hemoglobin molecule is present as two paired globin chains. Each type of hemoglobin is made up of different globins. For example, normal adult hemoglobin (HbA) is made up of two α chains and two β chains ($\alpha_2\beta_2$). HbA_2 is $\alpha_2\delta_2$, and fetal hemoglobin (HbF) is $\alpha_2\gamma_2$. A separate autosomal gene controls each globin chain. Deletions in this globin gene result in an absence or decreased function of the messenger RNA that codes for the creation of that globin. The various globins (α, β, δ, and γ) may be affected by a number of genetic combinations. The decrease in globin production in thalassemia results in decreased hemoglobin synthesis and ineffective erythropoiesis, which is attributable to increased intramarrow hemolysis with destruction of RBCs before they are released. Normal erythropoiesis has a 10 to 20% incidence of ineffective release, with associated intramarrow RBC destruction. This ineffective release of erythropoiesis may double or triple in patients with thalassemia. The cause is believed to be excess chains of the uninhibited globin precipitating in RBCs.[3]

Although many variations in thalassemia are possible, only three are commonly considered. Homozygous β-chain thalassemia (thalassemia major) occurs predominantly in Mediterranean populations. It represents one of the most common single-gene disorders. The disease is characterized by severe anemia, hepatosplenomegaly, jaundice, abnormal development, and premature death. Patients are transfusion dependent and die as a result of iron deposition in tissues, particularly the myocardium, or infection. Treatment is supportive and consists of transfusion and iron chelation therapy.[4,5]

Heterozygous β-chain thalassemia (thalassemia minor) is manifested as a mild microcytic hypochromic anemia with target cells

www.ketabpezeshki.com 66485457-66963820

Table 121-3 Diagnostic Tests for Iron Deficiency Anemia

TEST	NORMAL RESULT	IRON DEFICIENCY LEVEL	INTERPRETATION
Fasting serum iron	60-180 μg/dL	<60 μg/dL	Diurnal variation (draw in morning); increased by hepatitis, hemochromatosis, hemolytic anemia, and aplastic anemia; decreased in infection
Total iron-binding capacity	250-400 μg/dL	>400 μg/dL	Increased in late pregnancy or hepatitis; decreased in infection
Percentage of saturation (serum iron) of total iron-binding capacity	15-45%	<15%	
Serum ferritin	10-10,000 mg/mL	<10 mg/mL	Reflects iron stores; may increase as an acute-phase reactant in infection
Bone marrow stainable iron	Hemosiderin granules in reticuloendothelial cells	Absent	Standard for assessment of iron stores

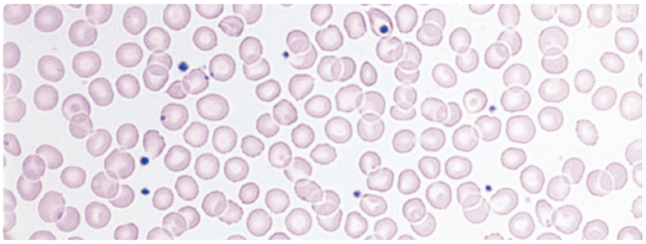


Figure 121-5. β-Thalassemia with microcytic hemochromic red cells and target cells. (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000:96.)

(erythrocytes with central hyperchromic bull's-eye surrounded by pallor) seen on the peripheral smear (Fig. 121-5), an MCV commonly more severely lowered than with iron deficiency anemia, a normal level of serum iron, and an elevated level of HbA_2 ($\alpha_2\delta_2$) on hemoglobin electrophoresis (2-5%). Usually, no treatment is necessary.

α-Thalassemia varies in spectrum from an asymptomatic carrier state to prenatal death. Four gene loci control this range. In the tolerated forms, it is more commonly seen in Asians and African Americans. Microcytosis, hypochromia, target cells, and basophilic stippling are noted on the peripheral smear. The diagnosis is made with hemoglobin electrophoresis and genetic testing.

Screening for carriers is performed by measurement of RBC indices and estimation of the HbA_2 concentration. Prenatal diagnosis can be made by analysis of fetal blood and, more recently, by fetal DNA obtained by chorionic villus sampling.

Therapy consists of blood transfusions, which are based on the clinical severity of the anemia. The goals of transfusion therapy include correction of anemia, suppression of erythropoiesis, and inhibition of increased gastrointestinal iron absorption. Iron chelation therapy is often required to control excess iron stores. Historically, deferoxamine, a subcutaneously administered chelator, was used; however, it has been replaced at many centers with the oral chelator deferasirox (Exjade). Deferasirox is renally cleared; thus dose adjustments may be necessary for chronic renal insufficiency, and it is contraindicated in end-stage renal disease.[6]

Bone marrow transplantation from HLA-identical donors has resulted in disease-free survival in 60 to 90% of recipients, but its role in thalassemia has yet to be determined. Although much interest centers on permanent correction of genetic deficits in thalassemia, gene therapy does not yet exist.[7]

Sideroblastic Anemia. Sideroblastic anemia involves a defect in porphyrin synthesis. The resultant impaired hemoglobin production causes excess iron to be deposited in the mitochondria of the RBC precursor, but some also circulates. The result is increased serum iron and ferritin levels, with transferrin saturation. The defective heme synthesis results in ineffective erythropoiesis, mild to moderate anemia, and a dimorphic peripheral smear with hypochromic microcytes along with normal and macrocytic cells.

Sideroblastic anemia, although found in a rare sex-linked hereditary form, is typically a disease of the elderly. Indeed, the idiopathic form is a common type of refractory anemia in elderly patients. Pallor and splenomegaly may be noted, and iron staining of the peripheral smear may demonstrate iron-containing inclusion bodies in RBCs. Some of these patients are deficient in pyridoxine (vitamin B_6) and respond to treatment with 100 mg of pyridoxine three times a day. Most remain anemic, but a 1- or 2-month pyridoxine trial is acceptable treatment. These patients may be susceptible to iron overload, particularly if long-term transfusion therapy is necessary, but they may respond to iron chelation therapy. Idiopathic sideroblastic anemia is considered a preleukemic state, and acute myelogenous leukemia develops in approximately 5% of these patients.

Secondary causes of sideroblastic anemia include toxins such as chloramphenicol, isoniazid, and cycloserine as well as diseases such as hemolytic and megaloblastic anemia, infection, carcinoma, leukemia, and rheumatoid arthritis. The exact mechanisms of these causative agents and diseases are unknown. Lead poisoning is one reversible cause of sideroblastic anemia. It may be suggested by the appearance of RBC basophilic stippling on the peripheral smear. Elevated blood lead levels are diagnostic. Alcohol abuse may also result in disordered heme synthesis, which can be corrected by alcohol cessation or by parenteral pyridoxal phosphate in cases of continued abuse. Oral pyridoxine may be ineffective because of impaired conversion to the active form in alcoholic patients.

Anemia of Chronic Disease. Anemia of chronic disease is common and typically normochromic, normocytic. It is characterized by low serum iron levels, low total iron-binding capacity, and normal or elevated ferritin levels. Bone marrow is normal, but staining reveals an abnormality in the mobilization of iron from reticuloendothelial cells. This anemia can be differentiated from iron deficiency by total iron-binding capacity, serum ferritin level, bone marrow examination, and nonresponsiveness to a trial of iron therapy. Because the hematocrit is seldom less than 25 to 30%, therapy is not usually required. A complete search for occult blood loss is necessary during the evaluation of this diagnosis because iron deficiency may be superimposed. Disseminated cancer, chronic inflammation, uremia, and infection are common causes.[8]

Macrocytic and Megaloblastic Anemias. In terms of the potential for a therapeutic response, the most important cause of macrocytosis is megaloblastic anemia. Megaloblastic anemia is the hematologic manifestation of a total-body alteration in DNA synthesis.

www.ketabpezeshki.com 66485457-66963820

The defective DNA synthesis is caused by a lack of the coenzyme forms of vitamin B_{12} and folic acid. The deficiency appears clinically in tissues with rapid cell turnover, including hematopoietic cells and those of mucosal surfaces, particularly in the gastrointestinal tract. This deficiency is characterized hematopoietically by ineffective erythropoiesis and pancytopenia. Vitamin B_{12} and folate deficiencies have different developmental histories, but the clinical result may be similar. Differentiation of folate and vitamin B_{12} deficiencies usually depends on measured levels in the laboratory.

Folic acid, absorbed in the duodenum and jejunum, is commonly found in green vegetables, cereals, and fruit. It may be destroyed completely by cooking. The body requires approximately 100 μg/day and usually stores 6 to 20 mg. Therefore, a 2- to 4-month supply is available before megaloblastic changes occur. Causes of folate deficiency are listed in Box 121-6. Most patients with folate deficiency have either an inadequate dietary intake, such as alcoholic patients, or increased use, as in pregnancy.

Vitamin B_{12} is found in foods of animal origin only and is not destroyed by cooking. It is absorbed in the ileum after binding to intrinsic factor. This glycoprotein factor is secreted by the parietal cells of the gastric mucosa and allows low levels of B_{12} to be actively absorbed. The adult requirement is 1 or 2 μg/day, with a body store of 5 mg. Therefore, megaloblastic changes may take up to 4 years to develop after cessation of vitamin B_{12} uptake. The various causes of vitamin B_{12} deficiency are listed in Box 121-7. The most common cause is chronic malabsorption.

Box 121-6 Causes of Folate Deficiency

- Inadequate dietary intake
  - Poor diet or overcooked or processed food diet
  - Alcoholism
- Inadequate uptake
  - Malabsorption with sprue and other chronic upper intestinal tract disorders, drugs such as phenytoin and barbiturates, or blind loop syndrome
- Inadequate use
  - Metabolic block caused by drugs such as methotrexate or trimethoprim
  - Enzymatic deficiency, congenital or acquired
- Increased requirement
  - Pregnancy
  - Increased RBC turnover: ineffective erythropoiesis, hemolytic anemia, chronic blood loss
  - Malignant disease: lymphoproliferative disorders
- Increased excretion or destruction or dialysis

Box 121-7 Causes of Vitamin B_{12} Deficiency

- Inadequate dietary intake
  - Total vegetarianism: no eggs, milk, or cheese
  - Chronic alcoholism (rare)
- Inadequate absorption
  - Absent, inadequate, or abnormal intrinsic factor, as seen in patients with pernicious gastrectomy and anemia. In anemia, autoimmune antibodies act against gastric parietal cells and intrinsic factor.
  - Abnormal ileum, as can occur in sprue and inflammatory bowel disease
- Inadequate use
  - Enzyme deficiency
  - Abnormal vitamin B_{12}–binding protein
- Increased requirement by increased body metabolism
- Increased excretion or destruction

Megaloblastic anemia that is not responsive to folate or vitamin B_{12} is commonly related to antimetabolites used in chemotherapy or rare inherited disorders of DNA synthesis.

Table 121-4 lists a number of the problems associated with megaloblastic anemia and their underlying pathologic states. A unique feature of vitamin B_{12} deficiency is its neurologic involvement. Patients may have paresthesias in their hands and feet, decreased proprioception, or decreased vibratory sense. The insidiously developing classic neurologic complex includes loss of proprioception; weakness and spasticity of the lower extremities with altered reflexes; and variable mental changes, such as depression, paranoid ideation, irritability, and forgetfulness. The last two complaints have also been noted with folic acid deficiency. Vitamin B_{12}–deficient patients have some of the lowest hemoglobin levels seen in any disease state.

Macrocytic anemia is suggested when the MCV is greater than 100 fL, but other criteria need to be met for megaloblastosis to be considered the cause of the macrocytic anemia. On the peripheral smear, large oval red cells (macro-ovalocytes) and hypersegmented polymorphonuclear neutrophils are believed to be diagnostic (Fig. 121-6). A bone marrow aspirate may reveal morphologic changes consistent with megaloblastic erythropoiesis. Other potentially useful laboratory tests include vitamin B_{12} and folate levels, red cell folate, and lactate dehydrogenase (LDH). Laboratory techniques, values, and interpretations are listed in Table 121-5. Once megaloblastic anemia is diagnosed and folate or vitamin B_{12} deficiency determined, standard diagnostic regimens are followed to determine the precise origin of the deficiency.

Because one deficiency may cause gastrointestinal absorption changes that beget other deficiencies, the emergency physician may be forced to initiate therapy before the final diagnosis is made. However, a caution is given to obtain necessary laboratory specimens before this course is pursued. The usual dosage for patients with megaloblastic anemia secondary to folate deficiency is 1 mg of oral folic acid per day. Parenteral administration is generally unnecessary because most cases are due to dietary deficiency. In contrast, malabsorption is the most common cause of vitamin B_{12} deficiency, and parenteral therapy is initiated at 100 μg/day intramuscularly for the first 7 to 10 days. Thereafter, only monthly 100-μg doses are necessary. The response is often dramatic, with reticulocyte counts rising up 30 to 50% and normalization of RBC, white blood cell (WBC), and platelet counts in 6 to 8 weeks. The use of vitamin B_{12} or folate supplements in patients with undiagnosed anemia is to be discouraged. The routine injection of vitamin B_{12} in the elderly has decreased but is still a too common practice.[9]

Macrocytic anemias unrelated to megaloblastic changes are seen frequently. Liver disease, often associated with alcoholism, is

Table 121-4 Clinicopathologic Correlation of Manifestations of Megaloblastic Anemia

CLINICAL FEATURES	PATHOLOGIC CONDITION
Lemon yellow skin	Combination of pallor with low-grade icterus from ineffective erythropoiesis
Petechiae, mucosal bleeding	Thrombocytopenia
Infection	Leukopenia
Fatigue, dyspnea on exertion, postural hypotension	Anemia
Sore mouth or tongue	Megaloblastosis of mucosal surfaces
Diarrhea and weight loss	Malabsorption from mucosal surface change
Paresthesias and ataxia	Related to myelin abnormality in vitamin B_{12} deficiency only

www.ketabpezeshki.com 66485457-66963820

Table 121-5 Serum Tests for Diagnosis and Differentiation of Megaloblastic Anemia

TEST	TECHNIQUE	VALUE	INTERPRETATION
Vitamin B_{12}	Microbiologic or radioisotope	Normal: 300-900 μg/L Deficient: <200 μg/L	Although they may overlap clinically, vitamin B_{12} level is usually normal in folate deficiency.
Folate	Microbiologic or radioisotope	Deficient: <3 μg/L	Vitamin B_{12} deficiency may elevate folate levels by blocking transfer of serum folate to RBCs; hemolysis may elevate folate levels.
Red cell folate	Calculated	Normal: 200-700 μg/L Folate deficiency: <140 μg/L	Index of tissue folate is less influenced by diet and is increased in vitamin B_{12} deficiency because of block.
Lactate dehydrogenase	Spectrophotometric	Normal: 95-200 IU Megaloblastic anemia: 4-50 times normal	Normal in other macrocytic anemias; elevated two to four times normal in hemolytic anemias; isoenzymes may be helpful.

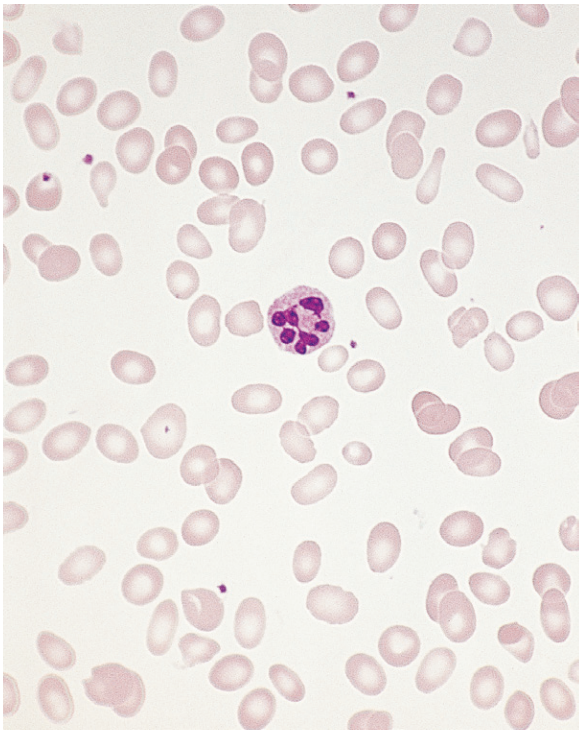


Figure 121-6. Megaloblastic anemia with macrocytic red cells and hypersegmented polymorphonuclear neutrophils. (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000:61.)

the most common cause.[10] Macrocytic target cells may be seen on the peripheral smear in conjunction with this disorder. Hypothyroidism and hemolysis may also be manifested as macrocytic anemia. Screening tests to differentiate between megaloblastic anemia and macrocytic anemia of other causes include a peripheral smear for macro-ovalocytes, hypersegmented polymorphonuclear neutrophils, and the LDH level.

Normochromic and Normocytic Anemias. The origin of normochromic and normocytic anemias secondary to decreased production is not as obvious as that of macrocytic and microcytic anemias because the latter give clues to their origin by alterations in RBC indices. One hematologic parameter that can aid in the diagnosis of normocytic anemia associated with hypoproduction is the corrected reticulocyte count. Reticulocytes reflect RBC production in bone marrow. They are RBCs released from bone marrow every 1 to 3 days and contain residual RNA that can be detected by supravital staining. Reticulocytes have an average MCV of 160 fL and in sufficient numbers can increase the MCV of the total erythrocyte count. The reticulocyte count is expressed as a percentage of

Table 121-6 Aplastic Anemia Caused by Drugs or Chemicals

CAUSE	RELATIVE INCIDENCE (%)
Chloramphenicol	61
Phenylbutazone	19
Anticonvulsants	4
Insecticides	4
Solvents	4
Sulfonamides	3
Gold	3
Benzene	2

From Silver BJ, Zuckerman KS: Aplastic anemia: Recent advances in pathogenesis and treatment. Med Clin North Am 64:607, 1980.

the total RBC population and needs to be related ("corrected") to the RBC count of the patient. Thus the corrected reticulocyte count is equal to the measured percentage of reticulocytes times the patient's hematocrit (%) divided by 45% (taken as the normal hematocrit). The normal range is 1 to 3%.

Normocytic anemia may be classified as being due to primary bone marrow involvement or a secondary marrow response to underlying disease.

Aplastic anemia is rare but may have severe manifestations. It is suspected in anemic patients with normal indices, a low reticulocyte count, and a history of exposure to certain drugs or chemicals (Table 121-6). It is related to drug or chemical exposure in 50% of cases. Viral hepatitis, radiation, and pregnancy have been associated with aplastic anemia. Another group of patients is considered to have an "autoimmune" origin.

The aplastic state may extend to all cell lines and results from destruction by immune-stimulated lymphocytes or failure of the marrow stem cell. On occasion, only one cell line fails, as in RBC aplasia. This condition represents injury occurring at a later stage of cellular differentiation. The precise diagnosis necessitates bone marrow examination, but the causative factor may be difficult to determine.

General treatment of aplastic anemia includes removal of suspected marrow toxins from the environment, avoidance of aspirin, oral hygiene, and suppression of menses. Transfusions are given in life-threatening circumstances only. Bone marrow or peripheral blood stem cell transplantation from a histocompatible sibling can cure the bone marrow failure, with survival rates of 78 to 94% reported.[10] However, because just 30% of patients have suitably matched sibling donors, only a small number undergo allogeneic transplantation. Immunosuppression with antithymocyte globulin, antilymphocyte globulin, and other cytotoxic chemotherapy is used in the majority of patients who are not stem cell

www.ketabpezeshki.com 66485457-66963820

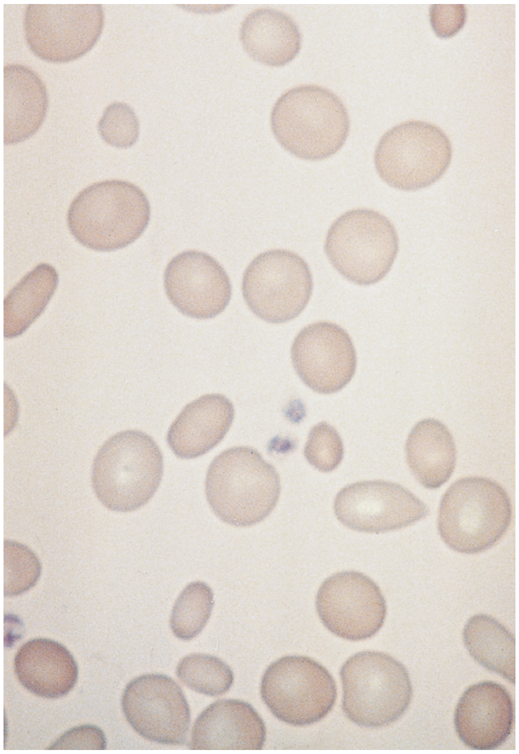


Figure 121-7. Anisocytosis and poikilocytosis. (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000:113.)

transplantation candidates. Unrelated donors are preferred to avoid sensitization of the patient against the non-HLA antigens that are present in bone marrow from a family donor. The disease has a wide range of severity, and the overall 5-year survival rate is 30 to 40%. Given supportive therapy, up to 80% of patients with severe aplastic anemia still die. Bone marrow transplantation before blood product sensitization has resulted in an 80% 5-year survival rate. This is usually combined with immunosuppressive therapy consisting of antilymphocyte globulin. Difficulty is still encountered in finding the correct immunologic match.[11,12]

Myelophthisic anemia is bone marrow failure resulting from replacement by an invading tumor, leukemia, lymphoma, or, rarely, granuloma. A more basic defect or inhibitor may complicate the problem because the degree of anemia cannot always be correlated with the extent of bone marrow invasion. Any patient with oncologic disease may be subject to the development of this type of anemia. Useful clues are signs of extramedullary hematopoiesis, such as hepatosplenomegaly and a leukoerythroblastic peripheral smear that demonstrates immature WBCs, nucleated RBCs, and poikilocytosis (teardrop-shaped red cells) (Fig. 121-7). The final diagnosis is made by bone marrow examination. Therapy is directed at the underlying disorder.

Myelofibrosis of unknown origin is the usual cause of primary bone marrow failure associated with extramedullary hematopoiesis. This myeloid metaplasia occurs in the liver and spleen and imparts a blood picture similar to that of myelophthisic anemia. The diagnosis may be made by bone marrow examination. Treatment is supportive, although splenectomy or the use of alkylating agents may be necessary to treat complications of extramedullary blood cell production, such as hepatosplenomegaly.

The hypoplastic anemias of secondary origin are commonly seen as mild chronic anemias with low reticulocyte counts. They have a normal MCV and RDW. Their diagnosis is made by exclusion. Anemia of chronic disease may have microcytic or normocytic indices. It is associated with chronic inflammation (e.g., rheumatoid arthritis, chronic infections such as tuberculosis and osteomyelitis, and malignant disease). Hypoendocrinism caused by hypothyroidism, hypoadrenalism, or hypopituitarism results in a hypometabolic state in which the bone marrow responds poorly to erythropoietin. Erythropoietin levels may be low. The anemia of chronic renal failure is thought to be caused by a number of factors including decreased erythropoietin production, hemolysis, suppression by dialyzable factors, and increased blood loss caused by platelet abnormalities. If necessary, it may be corrected by erythropoietin replacement therapy.[13]

Increased Red Blood Cell Destruction

The hemolytic anemias are defined by a shortened life span of the erythrocyte. In their acute form, hemolytic anemias can be devastating and require rapid diagnosis and intervention (see Box 121-1). Fortunately, they are relatively rare in comparison to the chronic hemolytic conditions. Chronic disorders may be related to primary blood disorders (e.g., sickle cell anemia) or may be a result of other disease states (e.g., chronic renal failure). These disorders may be manifested as acute hemolytic anemia if the tenuous balance between RBC production and destruction is upset. If the patient can be demonstrated to have a normal hematocrit and reticulocyte count at the same time, differentiation between acquired and inherited hemolytic anemia is possible.

Clinical Features. The clinical signs and symptoms of hemolytic anemia are, in general, caused by either intravascular or extravascular processes. Although it is not a precise representation of the underlying pathophysiologic condition, this division assists in the differential approach in the emergency department.

Intravascular hemolysis is usually associated with an acute process and has a dramatic appearance. Large numbers of RBCs may be lysed within the circulation. The pathologic process primarily involves the handling of released hemoglobin and a compensatory response to an acute decrease in oxygen-carrying capability. Free hemoglobin initially binds to haptoglobin and hemopexin. This complex is transported to the liver, converted to bilirubin, conjugated, and excreted. When this binding and transport system is overwhelmed, free hemoglobin may appear in the blood. Hemoglobin is a large molecule that remains in serum and may tint it pink.

In contrast, myoglobin is a small molecule that is rapidly cleared from serum. Examination of spun whole blood demonstrates clear serum in myoglobinemia, pink serum with free hemoglobin from intravascular hemolysis, and yellow serum from extravascular hemolysis with increased bilirubin production. In severe cases, the last mechanism may also result in free hemoglobin.

The clinical appearance of intravascular hemolysis may vary from mild chronic anemia, as seen in cases of mechanical hemolysis, to prostration, fever, abdominal and back pain, and mental changes, as seen with transfusion reactions. Jaundice, brown to red urine, and oliguria associated with acute renal failure induced by the hemoglobin complex can also occur.

Extravascular hemolysis is more common and usually better tolerated. Splenic blood flow slows as RBCs travel in the sinusoids close to the reticuloendothelial system, which is uniquely designed for removal of older or damaged cells. Primary splenic overactivity, antibody-mediated changes, or RBC membrane abnormalities may cause this normal splenic function to increase to a pathologic degree. Hemolysis may also occur within the bone marrow. As stated previously, normal erythropoiesis is ineffective 10 to 20% of the time. This percentage increases when abnormal RBCs are produced, as in thalassemia, megaloblastic anemia, or some hemolytic anemias.[14]

After hemoglobin is disassembled in the reticuloendothelial cell, globin returns to the amino acid pool, iron is transported by transferrin to the bone marrow or iron stores, and the pyrrole ring

www.ketabpezeshki.com 66485457-66963820

is converted to bilirubin. The unconjugated bilirubin circulates to the liver and is transformed. It is excreted in urine as conjugated bilirubin. The clinical picture of extravascular hemolysis is usually mild to moderate anemia, mild and intermittent jaundice, and enlargement of the spleen. The signs and symptoms vary with the severity and chronicity of the hemolysis.

Ancillary Evaluation. Once hemolysis is suspected, the history and laboratory tests have diagnostic precedence over physical examination. Important historical and physical examination points are listed in Box 121-8.

Laboratory Assessment. Important diagnostic tests for hemolysis are provided in Box 121-9.

The blood smear is often more diagnostic than bone marrow examination. The typical cell seen in intravascular hemolysis is the schizocyte (Fig. 121-8). The classic cell of extravascular hemolysis is the spherocyte (Fig. 121-9). It may be seen in congenital spherocytosis but more commonly indicates splenic activity against an antibody-coated RBC membrane. An increase in macrocytes reflects the presence of younger cells associated with reticulocytosis. The specific diagnosis may be made by a blood smear, as with sickled cells or Heinz bodies in glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Box 121-8 Pertinent Factors in the History and Physical Examination for Hemolytic Anemia

History
- Alteration of color in urine or feces
- Association with drugs, cold, sleep
- Early or recent-onset anemia history with symptoms
- Ethnic background
- Family history of anemia or jaundice
- Drug or toxic exposure
- Disease states associated with hemolysis, such as systemic lupus erythematosus, renal failure, lymphoma, infectious mononucleosis, prosthetic heart valve

Physical Examination
- Jaundice
- Hepatosplenomegaly
- Ulcerations, particularly in the lower extremities
- Enlarged lymph nodes

Box 121-9 Diagnostic Tests for Hemolysis

- Peripheral blood smear
- Corrected reticulocyte index or reticulocyte production index
- Haptoglobin levels
- Plasma free and urinary hemoglobin
- Lactate dehydrogenase level
- Fractionated bilirubin level
- Direct and indirect Coombs' test
- RBC membrane stability (osmotic fragility)

Haptoglobin binds hemoglobin on a molecule-for-molecule basis. Its absence implies saturation and degradation after binding with hemoglobin and is an early finding in hemolysis. It has a normal range of 40 to 180 mg/mL, is decreased in hepatic failure, and increases as an acute-phase reactant. After haptoglobin is bound, hemoglobin binds with hemopexin, transferrin, and albumin before circulating in its free form. Plasma free hemoglobin levels are determined in suspected cases of intravascular hemolysis. The result is considered positive if the level is greater than 40 to 50 mg/dL. Hemoglobin is excreted by the kidney and may be found as a smoky red pigment that is orthotoluidine positive with no associated RBCs. Prussian blue–staining granules of hemosiderin may be found intracellularly in renal tubule cells excreted in urine during chronic hemolytic states.

LDH is released when the RBC is broken down peripherally or in the marrow. It is elevated in hemolytic, thalassemic, sideroblastic, and megaloblastic anemia. It may also be seen in cases of uremia, polycythemia vera, and erythroleukemia. Normal levels of LDH range from 95 to 200 IU and may be fractionated.

In extravascular hemolysis, bilirubin is often delivered to the liver faster than the conjugating mechanism can handle it. Normal total levels are less than 1.5 mg/dL, and the indirect component amounts to less than 0.5 mg/dL. Conjugated or indirect bilirubin may rise as high as 4 or 5 mg/dL even with normal liver function. Higher levels connote some degree of underlying hepatic insufficiency.

The direct antiglobulin (Coombs') test detects antibody or complement on human RBC membranes. It is an essential test in the evaluation of hemolysis. Approximately 90% of patients with autoimmune hemolytic anemia have a positive direct Coombs' test result (warm agglutinin autoimmune hemolytic anemia). The indirect test measures antibody titers in serum (cold agglutinin autoimmune hemolytic anemia). The key to the direct antiglobulin test is the reagent. It contains an antihuman immunoglobulin (Ig) G that is produced in rabbits. This antihuman IgG in its broad-spectrum form reacts with the IgG, IgM, or C3 proteins that may coat RBCs. The reaction causes an agglutination of RBCs that is graded 0 to 4. Agglutinating properties depend on the size of the immunoglobulin. IgM is a large antibody form that can bridge the distance between cells, cause agglutination, and fix complement. The direct antiglobulin test is limited in diagnosis of IgM-mediated hemolysis. It is best in determining IgG or complement on the RBC surface. IgG is not large enough to cause agglutination, and the antihuman globulin attaches to RBC-bound IgG, which allows agglutination. C3 is detected in a similar manner. Both represent possible immunologic causes of hemolysis. This form of hemolysis is usually mediated extravascularly through the

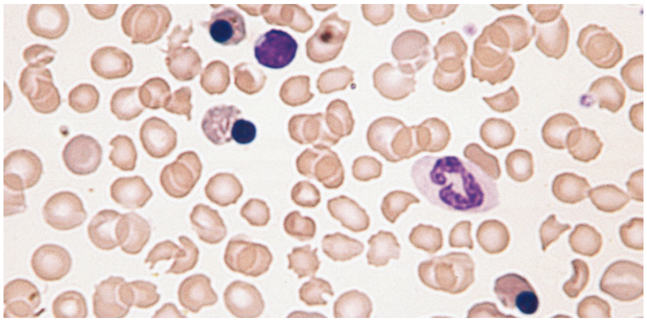


Figure 121-8. Schizocytes (fragmented cell and nucleated red cells). (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000:115.)

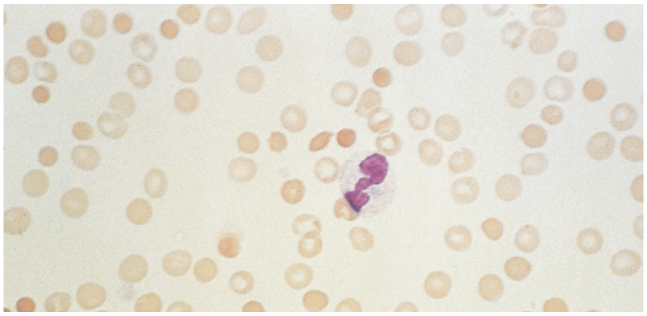


Figure 121-9. Spherocytosis. (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000:115.)

www.ketabpezeshki.com 66485457-66963820

Box 121-10 Classification of Hemolytic Anemia

Intrinsic
Enzyme defect
- Pyruvate kinase deficiency
- Glucose-6-phosphate dehydrogenase deficiency

Membrane abnormality
- Spherocytosis
- Elliptostomatocytosis
- Paroxysmal nocturnal hemoglobinuria
- Spur cell anemia

Hemoglobin abnormality
- Hemoglobinopathies
- Thalassemias (anemias)
- Unstable hemoglobin
- Hemoglobin M

Extrinsic
Immunologic
- Alloantibodies
- Autoantibodies

Mechanical
- Microangiopathic hemolytic anemia
- Cardiovascular, such as prosthetic heart valve disease

Environmental
- Drugs
- Toxins
- Infections
- Thermal

Abnormal sequestrations, as in hypersplenism

Box 121-11 Drugs Associated with Hemolysis in G6PD Deficiency

Analgesics and antipyretics: acetanilid, aspirin, phenacetin
Antimalarials: primaquine, quinacrine, quinine
Nitrofurans
Sulfa drugs: sulfamethoxazole, sulfacetamide, sulfones
Miscellaneous: naphthalene, fava beans, methylene blue, phenylhydrazine, nalidixic acid

G6PD, glucose-6-phosphate dehydrogenase.

spleen because IgG is a poor initiator of the complement system. The direct antiglobulin test evaluates the RBC surface for immunologic markers. The indirect test assumes that IgG or C3 is in the serum and tests for serum antibody activity against RBCs. Positive test results for immunologic markers do not correlate agglutination activity with the severity of hemolysis.[14]

Differential Diagnosis. Hemolytic anemias may be classified as congenital or acquired, Coombs' positive or Coombs' negative, or caused by processes intrinsic or extrinsic to the cell membrane. The last method gives a useful differential classification of hemolysis (Box 121-10).

Intrinsic Enzyme Defects. Eighty-five percent to 90% of the membrane-sustaining energy production of the erythrocyte is through the anaerobic glycolytic pathway. At least eight known enzyme deficiencies are associated with this pathway. The most common is pyruvate kinase deficiency, which is manifested with hemolytic jaundice and is usually diagnosed in infancy.

The remaining 10 to 15% of RBC glycolysis occurs by way of the hexose monophosphate shunt. This bypass mechanism occurs in the early stages of the glycolytic pathway and generates reduced nicotinamide adenine dinucleotide phosphate (NADPH), which is important in maintaining reduced glutathione. Glutathione is essential in the protection of hemoglobin from oxidant injury. A deficiency of the first enzyme in this pathway, G6PD, occurs in 11% of African American men. In this form, the enzyme deteriorates with age, and older RBCs are subject to hemolysis by oxidant stress. G6PD deficiency is sex linked and has a wide range of severity. The most common form in African Americans is self-limited because as the bone marrow responds, younger cells with more normal levels of G6PD predominate and can handle the oxidant stress. The variants in Sicilians, Greeks, and Arabs can be particularly devastating. The clinical manifestation is usually an acute hemolytic episode that may be both intravascular and extravascular in appearance. It occurs 24 to 48 hours after the ingestion of an oxidant drug (Box 121-11) or after acute infections such as viral hepatitis. The anemia induced by oxidant drugs is dose related. The older cells lyse at certain drug levels. The oxidant creates forms of activated oxygen, such as peroxide, that either denature the hemoglobin or destroy cell membranes. The former process produces Heinz bodies, which are clumps of denatured hemoglobin found in RBCs early during an episode. These cells are removed by the spleen. The diagnosis is made by enzymatic screening for G6PD, but this test cannot be performed immediately after the hemolytic episode. A 3-week delay avoids a false-negative result caused by a predominance of young cells. Treatment includes volume and RBC support as necessary. Avoidance of oxidant drugs is the only prevention.

Intrinsic Membrane Abnormality. These abnormalities are manifested in a number of ways. An altered shape is the main feature of autosomal dominant hereditary spherocytosis or elliptocytosis. The spleen sequesters these abnormal cells. Clinical sequelae range from compensated asymptomatic anemia to severe life-threatening acquired aplastic crises. The diagnosis is made by reviewing the family history, blood smear, and osmotic fragility testing. Splenectomy is the treatment of choice for patients requiring therapeutic intervention.

Paroxysmal nocturnal hemoglobinemia is a stem cell defect causing abnormal erythrocyte, neutrophil, and platelet sensitivity to complement. It is most often seen as chronic hemolysis, hemosiderinuria, leukopenia, and thrombocytopenia. The peripheral smear is normal and the direct Coombs' test result is negative. Its major complication is thrombosis, with a predilection for the hepatic vein. Normal activation of complement with the use of sucrose or acid hemolysis (the Ham test) is diagnostic. Transfusion can be a life-threatening hazard in patients with this disease because RBC lysis is caused by donor complement. Because of this danger, only washed packed cells should be used.

Intrinsic Hemoglobin Abnormality. More than 350 types of abnormal hemoglobin have been documented. Problems that may be seen include unstable hemoglobins that appear as Heinz body–positive anemia, M hemoglobins that fix iron in its ferric or methemoglobin state, and hemoglobins with increased oxygen affinity that result in tissue hypoxia and erythrocytosis.

Sickle Cell Disease. Sickle cell disease is the most important hemoglobinopathy with which the emergency physician should be familiar. In hospitals serving a large African American population, it is seen on an almost daily basis. Even experienced physicians may overlook major complications. Clinicians with less experience may fail to recognize the complexity of the disease and the many potential complications.[15]

Pathophysiology. Sickle cell disease is genetically determined. An abnormal allele at the gene loci for hemoglobin β chains produces altered messenger RNA, which in turn results in replacement of glutamic acid by valine at the sixth position from the N-terminal end of the β chain. On the molecular level, this change causes an interlocking of the affected chain with adjacent hemoglobin in the deoxygenated state. This connection causes the formation of bundles of parallel rods called tactoids, polymers that grow to form a *p*-crystalline gel, and then a crystal. Gel formation is facilitated by low pH and reduced by the presence of other hemoglobins, such as HbF. The result is a sickled cell that is less

www.ketabpezeshki.com 66485457-66963820

deformable, an increase in the viscosity and sludging tendency of blood, and the sequestration of RBCs in the spleen and liver. These changes may occur when smaller amounts of polymer do not result in a sickled cell and are associated with an RBC membrane leak. The clinical complex of vaso-occlusive events, chronic hemolysis, thrombosis, and organ injury is derived from this pathologic process. Patients with sickle cell disease generally fall into two phenotypic groups: hemolysis phenotype and vaso-occlusion phenotype. These groups are not genetically determined, and it is still unknown why some people fall into one group versus the other. Patients prone to hemolysis typically do not have pain, stroke, or acute chest syndrome; instead, they typically have pulmonary hypertension and leg ulcers. Their hemoglobin tends to be very low but their LDH is usually high. Patients with the vaso-occlusion phenotype typically have pain, acute chest syndrome, and stroke; they have a higher hemoglobin or high WBC level and lower LDH and indirect bilirubin concentrations.

The globin in hemoglobin is made up of two pairs of identical polypeptide globin chains. Each person has two non–sex-linked gene foci for β-globin chains, one from each parent. Normal individuals express six different types of hemoglobin from varying globin chain combinations: three embryonic hemoglobins, HbA ($\alpha_2\beta_2$), HbA_2 ($\alpha_2\delta_2$), and HbF ($\alpha_2\gamma_2$). Embryonic hemoglobins are expressed only in utero, and after 6 months of age, HbA accounts for more than 95% of hemoglobin in a normal individual. The sickle syndromes result from mutations in the β-globin gene. Instead of HbA ($\alpha_2\beta_2$), an abnormal hemoglobin HbS is produced. Embryonic and fetal hemoglobins do not contain β-globin; thus there are no clinical manifestations in early infancy. As their production declines, normal HbA ($\alpha_2\beta_2$) cannot be produced, and symptoms develop.

In sickle cell trait (HbAS), the patient is heterozygous and only one parent contributes the abnormal S allele. In each cell approximately 40% of the hemoglobin is HbS. Sickle disease (HbSS) is homozygous, and more than 85% of the hemoglobin is HbS. Because a parent may contribute alleles other than S, a wide number of variants can exist. Two clinically important S variants are sickle cell–β-thalassemia and sickle cell–hemoglobin C disease. Therefore, not all hemoglobinopathies that cause sickling are HbS. In addition, HbSS is not limited to the African American population. Up to 10% of patients with various sickling disorders are not ethnically African American.[16,17]

The sickle cell trait is found in 8 to 10% of African Americans. The diagnosis is usually made after sickle cell screening (Sickledex) and a characteristic result on hemoglobin electrophoresis. Most individuals with sickle cell trait are asymptomatic but can present with spontaneous hematuria, renal papillary necrosis, splenic infarction, venous thromboembolism, traumatic hyphema, exertional rhabdomyolysis, and exertional sudden death.[15,18,19] Recent literature suggests that pregnancy in women with sickle cell trait is not associated with an increased risk of adverse events.[20] In patients with sickle cell trait who have eye trauma, serial tonometry and observation are indicated to monitor for ocular complications.

Clinical Features. Sickle cell disease can be a recurrent, painful, and frustrating problem for both patients and physicians. A study suggests that as many as 35% of a sickle cell population are recurrent emergency department users.[21] Sickle cell disease is characterized by two major clinical features, hemolysis and acute vaso-occlusive events. The hallmark manifestation of sickle cell disease and the most common reason for emergency department visits is the painful vaso-occlusive crisis. Preceding infection, cold exposure, and stress such as trauma are all potential precipitating factors. Many episodes are thought to be spontaneous. The painful crisis is believed to have its origin in tissue ischemia caused by increased viscosity, sludging, and microvascular obstruction as a result of irreversibly sickled cells. Sludging and vascular blockage cause stasis, deoxygenation, and local acidosis, which promote the vicious circle of continued sickling. The pain is commonly deep and aching and is most often found in the abdomen, chest, back, and extremities. The disease may mimic an acute abdomen (e.g., cholecystitis), pulmonary embolus, renal colic, or other painful problems. A directed history that relates this pain pattern to previous sickling episodes, a careful repeated physical examination, and specific organ-related laboratory tests are all the physician has to differentiate "uncomplicated" crises from a more serious pathologic condition. Children may be seen more often with skeletal crises leading to bone deformities. In these cases, osteomyelitis and bone infarct needs to be differentiated.[22]

Neurologic complications can occur and include transient ischemic attacks, cerebral infarction, spinal cord infarction, vestibular hearing problems, and hearing loss.[23] Neurologic complications occur in 25% of patients with sickle cell anemia by the time they are 45 years old; 13% demonstrate infarction or ischemia in the absence of symptoms.[24] Transcranial Doppler study may be useful in identifying individuals with sickle cell disease who are at risk for stroke.[25] The use of exchange blood transfusions with the goal of hemoglobin S less than 30% can reduce the risk of cerebrovascular events by 92%.[26] In the setting of an acute stroke, exchange transfusion is recommended with the goals of hemoglobin S of less than 30% and a total hemoglobin level limited to 10 g/dL.[27,28] Tissue plasminogen activator (tPA) should be considered in adult sickle cell disease patients with acute nonhemorrhagic strokes. The use of tPA in this setting is the same as for acute stroke without sickle cell disease.[28]

Acute chest syndrome is the most common pulmonary disease associated with sickle cell disease and one of the most common causes of death.[29] It is a common cause of hospitalization in sickle cell disease, second only to vaso-occlusive crisis. Patients with acute chest syndrome have fever, cough, chest pain, dyspnea, and new infiltrates on the chest radiograph. The pathophysiologic mechanism of the syndrome is not well understood, but it may be a specific form of acute lung injury. The injury is postulated to be related to pulmonary microvascular sludging, infarction of pulmonary parenchyma, and bone marrow fat embolization from infarcted bone. Macrovascular pulmonary embolism and infection may also have a pathogenetic role. Although the causes of acute chest syndrome are uncertain, approximately 54% of the cases are associated with infection, including *Mycoplasma* and *Chlamydia*.[30] The differential diagnosis includes pneumonia, pulmonary embolism, congestive heart failure, and adult respiratory distress syndrome. No definitive diagnostic study is available, and diagnosis is based on the presence of the clinical features and exclusion of other pulmonary causes, as mentioned in the differential diagnosis. Management is primarily supportive and consists of hydration, analgesia, incentive spirometry, maintenance of adequate oxygenation and ventilation, and empirical antibiotics. Approximately 13% of patients will have respiratory failure severe enough to require mechanical ventilation. Antibiotic choice is similar to that for pneumonia in other populations. Exchange blood transfusions, as used in a similar fashion with acute stroke, are often used and have been associated with better gas exchange in acute chest syndrome.[31,32] However, there are no randomized controlled studies demonstrating an improvement in outcome with the transfusions.

Although most of the diagnostic and therapeutic problems of sickle cell disease are related to vaso-occlusive crises, other serious complications should be anticipated. Sickle cell disease is a chronic hemolytic state with reasonably compensated hematocrit values in the 20 to 30% range and elevated reticulocyte counts. This compensated balance may be disrupted by a rare iron deficiency or, more commonly, by folate deficiency. A potentially life-threatening aplastic crisis may be seen as a result of suppression of erythropoiesis by an acute postinfectious condition or folate

www.ketabpezeshki.com 66485457-66963820

Table 121-7 Organ Damage Seen in Sickle Cell Disease

ORGAN OR SYSTEM	INJURY
Skin	Stasis ulcer
Central nervous system	Cerebrovascular accident
Eye	Retinal hemorrhage, retinopathy
Cardiac	Congestive heart failure
Pulmonary	Intrapulmonary shunting, embolism, infarct, infection
Vascular	Occlusive phenomenon at any site
Liver	Hepatic infarct, hepatitis resulting from transfusion, hepatic sequestration, intrahepatic cholestasis
Gallbladder	Increased incidence of bilirubin gallstones caused by hemolysis
Spleen	Acute sequestration
Urinary	Hyposthenuria, hematuria
Genital	Decreased fertility, impotence, priapism
Skeletal	Bone infarcts, osteomyelitis, aseptic necrosis
Placenta	Insufficiency with fetal wastage
Leukocytes	Relative immunodeficiency
Erythrocytes	Chronic hemolysis

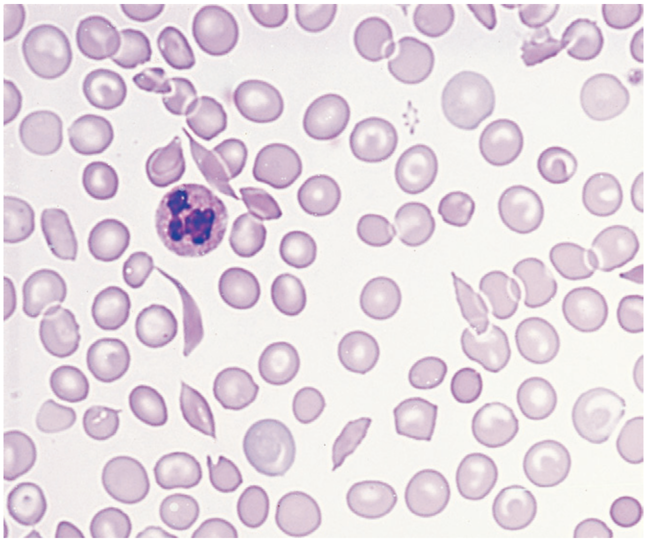


Figure 121-10. Sickle cells. (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000:103.)

deficiency. This aplastic condition is suspected when the hemoglobin level falls 2 g/dL or more from previous stable levels and the reticulocyte count remains low (<2%).

Finally, children may have an acute splenic sequestration syndrome. This syndrome involves acute splenic enlargement from increased intrasplenic sickling and obstruction. The child may demonstrate lassitude and be in shock. Each of these conditions may result in a rapidly falling RBC count and progressive symptoms of anemia. Patients with HbSS are also subject to all other causes of anemia, such as hemolysis from G6PD deficiency. An increased susceptibility to infection is well documented with HbSS.

In infancy, an increased incidence of sudden death may be related to pneumococcal sepsis and meningitis. A WBC count and blood cultures should be performed on all febrile children with sickle cell anemia. HbSS patients who are younger than 2 years and have associated temperatures of 39.5° C or higher and WBC counts greater than 20,000/mm^3 should be given intravenous antibiotics immediately. Adults with fever require careful evaluation and laboratory assessment, including appropriate cultures. Early institution of appropriate antibiotics, such as ceftriaxone 1 to 2 g, adult dose, intravenously or intramuscularly, is necessary in patients with a discernible source of infection. In children and adults, infections with *Staphylococcus* and *Pneumococcus* species and *Haemophilus influenzae* are particularly common.[33] An increased incidence of *Salmonella* osteomyelitis also occurs.[34] The origin of this related immunologic deficiency is believed to be multifactorial, involving functional asplenia, poorly migrating neutrophils, and decreased opsonin production.[34]

Major, chronic organ damage in patients with sickle cell anemia is common. A cross section of these problems is listed in Table 121-7. These associated conditions should be quickly reviewed every time a patient with sickle cell anemia enters the emergency department. The leading causes of death in HbSS patients are cardiopulmonary disease, chronic renal failure, stroke, and infection.[15]

Diagnostically, most patients with HbSS seen in the emergency department are well known with defined pain patterns. Because of a slow but longer growth period caused by the delayed onset of puberty, adult patients with HbSS often have a youthful appearance and long, thin extremities. In a patient with suspected sickle cell disease, inquiry should be made into the family history, previous pain episodes, and symptoms relative to chronic anemia, susceptibility to infection, and ischemic organ damage. Table 121-7 suggests an outline to follow for the physical examination.

Most patients, other than those with mild pain crisis, should have a complete blood count performed, and current blood levels should be compared with those of previous visits. A reticulocyte count is recommended whenever the patient's hemoglobin level has decreased by 2 g/dL from baseline. In sickle cell disease, the typical absolute reticulocyte count is three or four times the upper limit of normal. A reticulocyte count 3% or lower than the patient's usual value may suggest an aplastic crisis. A reticulocyte count greater than 12%, particularly if it is accompanied by numerous nucleated RBCs, may indicate rapid hemolysis. Other laboratory tests are selected on the basis of potential organ complications. Unfortunately, no test is available that detects whether a patient is in a crisis. Currently, this difficult task is based on clinical grounds. In new cases, the peripheral smear may show sickled cells (Fig. 121-10), and a sickle cell screening test with Sickledex may help. Definitive diagnosis of sickle cell disease is aided by hemoglobin electrophoresis.

Management. The antisickling agent hydroxyurea reduces the frequency of painful crises in adults with a history of three or more crises annually. The beneficial effects of hydroxyurea in sickle cell disease are assumed to be due to induction of hemoglobin F, but additional mechanisms may be operative. Hydroxyurea can reduce the incidence of acute painful crisis as well as increase survival in sickle cell disease. However, the effects of hydroxyurea can take weeks to be appreciated, and it is not routinely recommended for acute episodes.[35,36] Other agents, including clotrimazole, magnesium, 5-azacitidine, erythropoietin, and butyric acid, may have a future role in therapy.[37,38] Bone marrow transplantation offers the only current cure for sickle cell disease and is associated with survival rates greater than 90% and disease-free survival rates of 80 to 90%. However, the role of bone marrow transplantation in sickle cell disease remains uncertain because of the inability to predict which patients will benefit, limited patient eligibility as a result of advanced pulmonary and neurologic vasculopathies, and concerns related to transplantation mortality and treatment-induced malignant neoplasms.[37,38]

www.ketabpezeshki.com 66485457-66963820

Current therapies, including rest, adequate nutrition, hydration, oxygenation, analgesia, transfusion, and therapy for infection, are directed toward symptomatic relief and attempts to stop the cycle of deoxygenated sickling and intravascular sludging. Most patients with sickle cell anemia are mildly dehydrated because of difficulty in concentrating urine. Fluid replacement can be oral or intravenous, and the emergency physician should be aware of the potential for congestive heart failure in patients past their second decade. A recommended starting solution is 5% dextrose in half-normal saline at a rate not to exceed 1.5 times maintenance.[15,39] Oxygen through a nasal cannula at 2 to 4 L/min may help hypoxic patients and may be given to any patient with HbSS as a low-risk treatment modality with potential benefit.

Analgesia is a major benefit and essential early therapy for acute sickle cell crisis. Because a small subgroup of patients repeatedly and frequently seek care in the emergency department, emergency department caregivers may become understandably suspicious of needs and motivations. Care protocols are advised to ensure rapid appropriate treatment. Many emergency physicians caring for large populations of sickle cell patients have developed protocols to establish better physician-patient rapport and to lessen the chance of narcotic addiction and manipulation. The following is a protocol for severe pain in adults and children weighing more than 50 kg: patients are evaluated, treated with oxygen and hydration, and given intravenous morphine sulfate, 5 to 10 mg every 2 to 4 hours, or intravenous hydromorphone, 1.5 mg every 3 to 4 hours. For children weighing less than 50 kg, intravenous bolus doses of morphine sulfate, 0.1 to 0.15 mg/kg, can be given every 2 to 4 hours, or intravenous hydromorphone, 0.015 to 0.020 mg/kg, can be given every 3 to 4 hours.[28] At 4 to 6 hours, the patient is allowed to decide whether inpatient or outpatient therapy is desired. Outpatient therapy includes 4 to 6 days of an effective oral analgesic. A 40-mg dose of oral morphine sulfate or equivalent is given 1 or 2 hours before the infusion is stopped. Such a protocol may bring uniformity to the patient's expectations for care and the physician's decisions about therapy and admission. Its major disadvantage has been a tendency to treat patients automatically rather than closely considering the potential acute complications of sickle cell disease. No standard pain management exists for sickle cell disease. A variety of analgesics (nonsteroidal anti-inflammatory drugs, mixed opioid agonist-antagonists, and opiates), dosages, and timing intervals may be chosen. Because many sickle cell disease patients can have varying degrees of hepatic or renal dysfunction, acetaminophen and nonsteroidal anti-inflammatory drugs should be used with caution.[28] Because many patients with acute pain episodes are undertreated, the most important aspect of pain management in these patients is a consistent, thorough, and attentive approach that offers true pain relief.[39]

Blood transfusion has a well-accepted role in sickle cell anemia. Selected use can decrease the chronic transfusion problems of antigen sensitization, iron overload, and hepatitis. Aplastic or splenic sequestration crises may necessitate transfusion. Serial hemoglobin values and reticulocyte counts should be obtained during hospitalization. Whereas the overall goal of simple transfusion therapy for symptomatic anemia is a hemoglobin level no higher than 10 g/dL, transfusion should not be used to treat asymptomatic patients, regardless of hemoglobin value.[40]

Priapism is a painful complication of sickle cell disease and may lead to impotence. First-line therapy for priapism lasting longer than 2 hours is aspiration of blood from the corpus cavernosum and irrigation with an alpha-adrenergic agent (e.g., phenylephrine). Surgical management is reserved for patients who fail to respond to aspiration and irrigation.[41] Aspiration and irrigation of the corpus cavernosum can be difficult and time-consuming. This therapy is best reserved for urologic consultation. The use of exchange transfusions in the treatment of priapism is controversial but appears to have no current role.[41]

Exchange transfusions are recommended for patients, particularly children, with cerebrovascular accidents. Acute symptoms may be reversed and the frequency of recurrence decreased with a regulated 3- or 4-week transfusion program. The goal is to suppress reticulocytosis and to decrease the HbS level to less than 25%. Rarely, transfusions are given for control of bone or visceral crises. This is not an emergency department procedure and is considered only after hematologic consultation. Prophylactic transfusions to dilute HbS levels are also recommended in pregnancy and before major surgery.[40] As discussed before, for stroke in children, acute exchange transfusion is the treatment; for adults, the treatment is tPA.

A number of other therapies are being tested for both prophylaxis and crisis management, including supplemental zinc, induced hyponatremia, gelation inhibitors, membrane-active agents, and gene manipulation. Poloxamer 188 is an artificial surfactant with hemorheologic and antithrombotic properties. Although the mechanism of action of this agent is not fully understood, it improves microvascular blood flow by reducing blood viscosity and adhesive frictional forces. In clinical trials of sickle cell patients with acute painful crisis, poloxamer reduced the total narcotic requirement, duration of pain, and pain intensity.[42]

Sickle Cell–β-Thalassemia. Sickle cell–β-thalassemia disease is seen most commonly in people of Mediterranean descent. The severity of the disease is related to the concentration of HbS in RBCs and the decrease in MCHC. It should be considered in a patient with a low MCV and a positive response on sickle preparation. It is generally a milder form than homozygous HbSS but can be as severe as sickle cell disease. HbSC disease falls between HbSS and HbS-thalassemia in terms of severity. In addition to many of the complications of HbSS, HbSC disease has an increased incidence of eye hemorrhage and pregnancy complications and may cause splenomegaly. The peripheral smear demonstrates a combination of sickled cells and normocytic target cells.

Extrinsic Alloantibodies. Alloantibodies are formed in response to foreign RBC antigens. In the case of the ABO system, these antibodies are preformed. The ABO system is one of the most important RBC wall antigens. ABO incompatibility resulting in donor cell destruction by the recipient's alloantibodies can be a life-threatening reaction. These antibodies are IgM in nature and can act as a hemolysin, both agglutinating RBCs and fixing complement and consequently causing intravascular hemolysis.

The Rh system is another set of antigens on the RBC. This system is unique in that individuals do not have antibodies that correspond to antigens in the Rh system unless they have been sensitized by previous exposure to antigens that they lack. The antibodies produced are IgG in nature, and they accelerate extravascular destruction of RBCs by the spleen and liver. Most autoimmune antibodies are directed toward antigens in the Rh system.

Extrinsic Autoantibodies. Evaluation of autoimmune hemolysis is as complex as its origin. The major feature of autoimmune hemolysis is the production of an IgG or IgM antibody to an antigen present on the RBC membrane. Why the body responds in this manner is unknown. IgM antibodies can agglutinate, fix complement, and act as intravascular hemolysins. IgG antibodies may fix complement to the cell but do not usually complete the hemolysis process. These IgG- or C3-labeled cells undergo accelerated extravascular destruction. The direct antiglobulin test is useful in revealing these labeled cells.[43]

Autoimmune hemolytic anemias are acquired disorders, with 40 to 50% being idiopathic. The remainder are associated with a number of diseases (Box 121-12). Classification of autoimmune hemolytic anemias is based on the optimal temperature at which the antibody reacts with the RBC membrane. Therefore, there are warm-reacting (>37° C) and cold-reacting (<37° C) antibodies.

www.ketabpezeshki.com 66485457-66963820

Box 121-12 Diseases Associated with Autoimmune Hemolytic Anemia

Neoplasms
Malignant: chronic lymphocytic leukemia, lymphoma, myeloma, thymoma, chronic myeloid leukemia
Benign: ovarian teratoma, dermoid cyst

Collagen Vascular Disease
Systemic lupus erythematosus
Periarteritis nodosa
Rheumatoid arthritis

Infections
Mycoplasma
Syphilis
Malaria
Bartonella
Virus: mononucleosis, hepatitis, influenza, Coxsackievirus, cytomegalovirus

Miscellaneous
Thyroid disorders, ulcerative colitis
Drug immune reactions

Box 121-13 Drugs Associated with Immune Hemolytic Anemia

Hapten type with antibodies to the drug
Complement-fixing antibody: quinidine, quinine, phenacetin, ethacrynic acid, *p*-aminosalicylate, sulfa drugs, oral hypoglycemic agents
Non–complement-fixing antibody: penicillin dosages >20 million units/day
Autoimmune type with antibodies to the RBC membrane: D-methyldopa, L-dopa, mefenamic acid, chlordiazepoxide
Cephalosporins at dosages >4 g/day may cause hemolysis by direct membrane injury

Warm-reacting antibodies are characterized by a higher incidence in younger patients (30-60 years), predominance in women, variable complement fixation, and positive direct antiglobulin test result for IgG. Cold-reacting antibodies, or cold agglutinins, are seen predominantly in men and older patients (50-80 years) and with IgM complement fixation. They may also be found in patients with infectious mononucleosis, *Mycoplasma* infection, and lymphoma. Hemolysis may be intravascular and extravascular, and the direct antiglobulin test result is positive for complement.

Clinically, a patient with immune hemolytic anemia has the signs and symptoms of anemia and, often, splenomegaly. Spherocytosis and reticulocytosis are noted in the blood smear. The direct antiglobulin test result is positive in 90% of cases. The strength of the direct antiglobulin test result does not correlate with the severity of the hemolysis because the Coombs' reaction is an antibody function different from hemolysis or stimulation of reticuloendothelial sequestration. In patients with newly diagnosed, reticulocytopenic or severe hemolytic anemia, the emergency physician may need to institute transfusion therapy. Compatible blood may be almost impossible to find because the antibody can react with almost all donors. The most compatible donor cells in terms of the ABO and Rh systems should be transfused with the knowledge that they will be no more compatible than the patient's own blood cells. If emergency blood transfusion is required, type-specific or type O blood (Rh-positive for men; Rh-negative for women of childbearing age) is indicated as well as prednisone or its equivalent in a dose of 1 mg/kg. Prednisone is believed to produce an improvement in 60% of patients with warm antibody reactions. Splenectomy and immunosuppressive therapy are also effective in treating these reactions. Cold agglutinin hemolytic anemia may be self-limited, as after infectious mononucleosis. Other forms respond well to cold avoidance, variably to immunosuppressive agents, but poorly to steroids and splenectomy. Death commonly results from uncontrolled hemolysis, the underlying primary disorder, and pulmonary embolism.[43]

Drug-induced hemolytic anemia may be difficult to diagnose. The emergency physician should know the drugs most often associated with this Coombs'-positive phenomenon and realize that the result of this test is sometimes positive only in the drug's presence. Common drugs and mechanisms of action are listed in Box 121-13.[44]

Extrinsic Mechanical Causes. Hemolysis may be caused by trauma to RBCs. The peripheral smear may demonstrate schizocytes or fragmented cells, which immediately raise the suspicion of traumatic injury (see Fig. 121-8). Microangiopathic hemolytic anemia, cardiac trauma, and exercise-induced hemoglobinemia are the most commonly encountered forms of traumatic hemolysis.

Microangiopathic hemolytic anemia is a form of microcirculatory fragmentation by threads of fibrin deposited in the arterioles. An underlying disease is inevitably present. It may be found in renal lesions such as malignant hypertension and preeclampsia, vasculitis, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, and vascular anomalies. The signs and symptoms are those of intravascular hemolysis. Treatment is directed at the causative disease.

Cardiac trauma to RBCs results from increased turbulence. It may be found in patients with prosthetic valves, traumatic arteriovenous fistula, aortic stenosis, and other left-sided heart lesions. Surgical correction may be necessary. Supportive therapy with an iron supplement is usually required.

March hemoglobinemia is a form of trauma caused by breaking of intravascular RBCs by repetitive pounding. Soldiers, marathon runners, and anyone with repetitive striking against a hard surface may incur this problem. Reassurance and a change in the patient's pattern of activity are the recommended therapy.[45]

Environmental Causes. Hemolysis may be seen in cases of severe burns, freshwater drowning, and hyperthermia. Toxic causes of hemolysis have been documented to be of animal origin, such as brown recluse spider and some snake bites; vegetable origin, such as castor beans and certain mushrooms; and mineral origin, such as copper. Certain infections are associated with hemolytic states, including malaria, *Bartonella* infection, and *Clostridium* sepsis.

Abnormal Sequestration. Hypersplenism may be caused by any disease that enlarges the spleen or stimulates the reticuloendothelial system. An unfortunate cycle can be set up in which the enlarged spleen traps more blood components and grows larger. It is usually seen as splenomegaly with pancytopenia and marrow hyperactivity. Chromium-labeled RBCs may demonstrate increased trapping in the spleen. Therapy for symptomatic or severe disease is splenectomy. Adults usually tolerate splenectomy well, but children should be approached conservatively because the risk of postsplenectomy life-threatening sepsis is increased significantly.

POLYCYTHEMIA

Definition

Polycythemia is a term commonly used for erythrocytosis (i.e., increased number of RBCs). This disorder is seen occasionally in emergency medicine but rarely in a life-threatening manner that requires emergency intervention.

www.ketabpezeshki.com 66485457-66963820

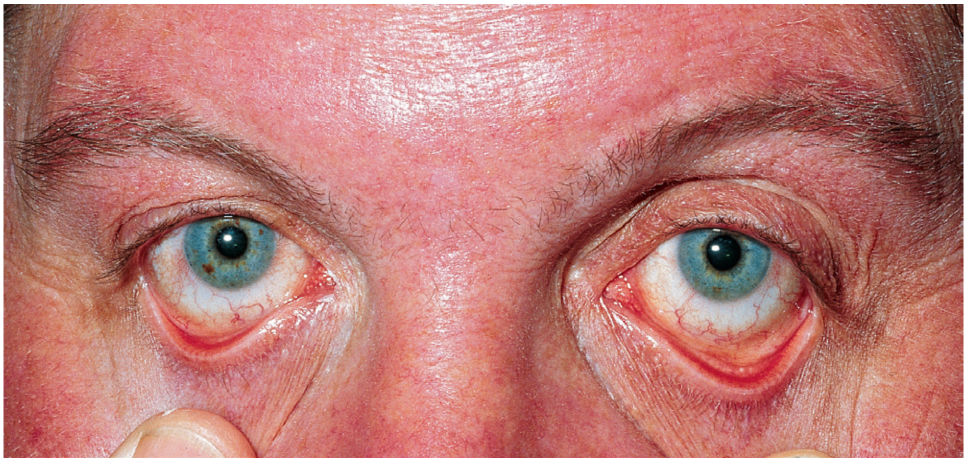


Figure 121-11. Polycythemia vera. Facial plethora and conjunctival suffusion in a 40-year-old woman (hemoglobin, 19.5 g/dL). (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000:248.)

Pathophysiology

Erythropoiesis is controlled by the kidney-produced glycoprotein hormone erythropoietin. It is activated in the liver and regulates the committed erythropoietic stem cell. Its major stimulant is tissue hypoxia. Neoplastic dysfunction of bone marrow may also result in an elevated absolute RBC count.

The major complication of polycythemia is related to the increase in blood viscosity associated with increased RBC numbers. As the hematocrit rises past 60%, viscosity increases in an almost exponential manner. This condition increases the possibility of reduced tissue flow, thrombosis, and hemorrhage. This hazard is usually blunted to a degree by an associated increase in blood volume and some viscosity-reducing vascular dilation.[46]

Clinical Features

The history may range from only mild headaches to a full-blown syndrome of hypervolemia (vertigo, dizziness, blurred vision, and headache), hyperviscosity (venous thrombosis), and platelet dysfunction (epistaxis, spontaneous bruising, and gastrointestinal bleeding).

On physical examination, the skin and mucous membrane manifestations of the elevated RBC count are often readily observed. Plethora, engorgement, and venous congestion are commonly noted (Fig. 121-11). Other systems to be examined include the fundus for venous congestion, the abdomen for evidence of splenomegaly, and the cardiopulmonary system for signs of congestive heart failure. Uterine, central nervous system, renal, and hepatic tumors should be sought in that these are associated with secondary polycythemia. An elevated RBC count, usually greater than the hematocrit, defines the disorder. It results in a low MCV, usually related to low serum iron and iron stores. Specific laboratory testing is discussed in the section on differential diagnosis.

Differential Diagnosis

Polycythemia is classified as apparent, primary, or secondary (Box 121-14). Apparent polycythemia is a decrease in plasma volume such as found with dehydration. The RBC volume does not exceed the upper limit of normal. Although it is a questionable diagnostic entity, "stress" polycythemia is the tendency for an elevated hematocrit and is found in overweight, hypertensive, and overstressed middle-aged men. Increased cigarette smoking with its associated increased carboxyhemoglobin level is considered to be partially responsible. The symptoms are minimal, and treatment is confined to moderation, weight loss, and blood pressure control. The risk of vascular occlusive complications is minimal. The hematocrit is usually less than 60% and RBC mass measurements are normal.[47]

Box 121-14 Causes of Apparent and Secondary Polycythemia

- Appropriately increased erythropoietin caused by tissue hypoxia
  - Congenital heart disease with a right-to-left shunt
  - Pulmonary disease (e.g., bronchial-type chronic obstructive pulmonary disease)
  - Carboxyhemoglobinemia
  - High-altitude acclimatization
  - Decreased tissue oxygen release from hemoglobinopathies with high oxygen affinity
- Inappropriate autonomous erythropoietin production
  - Renal origin: carcinoma, hydronephrosis, cyst
  - Other lesions: uterine fibroids, hepatoma of adrenal origin, cerebellar hemangioma
  - Congenital overproduction
  - Pure or essential erythrocytosis
  - AIDS and zidovudine treatment

Primary polycythemia vera is a myeloproliferative disorder found predominantly in middle-aged or older patients. It may have all the clinical components of polycythemia. Nonspecific symptoms are reported in up to 30% of patients and include headache, weakness, dizziness, excessive sweating, and pruritus. The most serious problems are thrombotic episodes (cerebrovascular accident, myocardial infarction, and deep venous thrombosis), bleeding, and bruising. Primary polycythemia vera is a disease that involves all cell lines—hematopoietic stem, erythroid, granulocytic, and megakaryocytic. Elevated hemoglobin or hematocrit and RBC mass is present in virtually all patients. However, a platelet count above 400,000/μL occurs in 60% and a WBC count above 12,000/μL in 40%. Bone marrow cellularity was increased in 90% of patients, and storage iron was absent from the marrow in 94%. The diagnostic criteria used by the Polycythemia Vera Study Group are listed in Box 121-15.[47]

Polycythemia vera may be satisfactorily treated by phlebotomy as necessary. The reduced hematocrit improves some symptoms, but neither the leukocyte nor the platelet count is decreased. Maintenance of the hematocrit at less than 55% is recommended to decrease hypervolemia and hyperviscosity. Complications necessitating additional therapy include hyperuricemia, refractory

www.ketabpezeshki.com 66485457-66963820

Box 121-15 Diagnostic Criteria for Polycythemia Vera*

Category A
Increased RBC mass
In men: hemoglobin >18.5 g/dL
In women: hemoglobin >16.5 g/dL
Normal arterial oxygen saturation (>92%)
Splenomegaly

Category B
Thrombocytosis: platelets >400,000/mm^3
Leukocytosis: WBC count >12,000/mm^3 (with no fever or infection)
Leukocyte alkaline phosphatase score >100
Vitamin B_{12} >900 pg/mL, unbound vitamin B_{12}–binding capacity <2200 pg/mL

*For polycythemia vera to be diagnosed, either all three criteria in category A or the first two criteria in category A along with any two criteria in category B needs to be present.

increased RBC mass, severe pruritus, excessive splenomegaly, and thrombocytosis. Additional therapy may consist of hydroxyurea, busulfan, chlorambucil, interferon alfa, anagrelide, or radioactive phosphorus (^{32}P). Studies suggest no improvement in long-term survival with the addition of these treatments.[48] The natural history of the disease is that it burns out during a period of 15 to 20 years. However, myelofibrosis with myeloid metaplasia may develop. In 10% of cases, acute leukemia develops with a rapid and poorly responsive downhill course. The 15-year survival for polycythemia vera is 65%.[49] The most common causes of death are thrombosis (29%), hematologic malignant neoplasms (23%), nonhematologic malignant neoplasms (16%), hemorrhage, and myelofibrosis with myeloid metaplasia.

Secondary polycythemia is classified first according to the appropriate erythropoietin response to abnormal tissue oxygen levels. This group of disorders may be ruled out by normal measured arterial oxygen saturation. Second, inappropriate autonomous erythropoietin production is considered. This condition can be assessed with an erythropoietin assay. Because of a strong association with renal pathologic conditions, computed tomography should be used to evaluate a patient with a suspected inappropriate erythropoietin response. Most patients with secondary polycythemia have no central nervous system symptoms or splenomegaly. Because erythropoietin stimulates only the red cell pathway, these patients have normal WBC and platelet counts.

Management

The emergency treatment of any form of symptomatic polycythemia is phlebotomy. Usually, not more than 500 mL of blood is removed as the volume is replaced with a comparable amount of saline. No hemodynamic compromise should occur if this procedure is performed slowly. In true emergencies, up to 1 to 1.5 L of blood may be removed during a 24-hour period. The initial goal is to lower the hematocrit toward 60%. The final goal is a level less than 55%. Low-dose aspirin, 80 to 100 mg/day, has been shown to prevent thrombotic complications in patients with polycythemia vera and can be used in the acute and chronic treatment of this disorder.[50]

Disposition

A number of patients with known polycythemia may be managed by outpatient phlebotomies. Any newly diagnosed or symptomatic patient should be considered for admission to the hospital for full evaluation.

WHITE BLOOD CELL DISORDERS

The WBC count and accompanying differential are the most common laboratory tests ordered in the emergency department. It is essential that the basic physiology, pathophysiology, and clinical evaluation of WBCs be understood.

Physiology and Pathophysiology

The series has three morphologically indistinguishable cell types: B cells (humoral immunity), T cells (cellular immunity), and null cells. Because lymphocytes can freely leave and return to the circulation, the storage pools are less well defined. Only 5% of the total lymphocytes in the body are in the circulation. No marginal pool exists. Leukocytes primarily function extravascularly, and their function is closely integrated with the other types of white cells. WBCs reach their site of action through the circulation. The rate that new cells enter the circulation is usually in equilibrium with the rate of loss in tissues.

Abnormal cell counts are due to changes in production, the marginal pool, or the rate of tissue destruction. Just as in anemia or platelet count abnormalities, the differential diagnosis of increased (leukocytosis) or decreased (leukopenia) WBC counts can be organized by processes altering production, destruction, loss, and sequestration.

The granulocytic and lymphocytic series are the two cell lines of WBCs. The granulocytic series is primarily involved in phagocytic activity. Its origin is the pluripotential stem cells located in the bone marrow. A subset of these cells differentiates and matures into the phagocytic cell lines, which include neutrophils, monocytes, basophils, and eosinophils. Granulocytes are maintained in a series of developmental and storage pools. The most important is the postmitotic storage pool for neutrophils, which represents 15 to 20 times the circulating population. This pool contains metamyelocytes, band neutrophils, and mature neutrophils (polymorphonuclear neutrophils). The pool can be drawn on as a ready reserve during rapid consumption of granulocytes. Circulating neutrophils are subdivided equally into the circulating neutrophil pool and the marginal pool. The marginal pool consists of mature cells adherent to the blood vessel walls. These cells can rapidly enter the circulating pool and cause a substantial increase, even doubling, of the WBC count. This involvement does not alter the maturity pattern of the differential count.[51] The lymphocytic series matures in lymphoid tissues located in the bone marrow, thymus, spleen, lymph nodes, and elsewhere. They are involved in the immune response against foreign substances.

Normal Values and Influences

One unique problem in WBC disorders is the wide variability in normal values and the multiple factors influencing them. WBC counts are generally performed automatically by electrical impedance or optical diffraction techniques. Differential counts are commonly performed by direct examination of 100 to 500 cells with the oil immersion lens of the microscope. Automated techniques for all differential counts are becoming more popular, however. Normal values for the WBC count are listed in Table 121-8. The "normal" count is age dependent until childhood and may be shifted upward by exercise, gender (women), smoking, and pregnancy. Decreases in the total WBC count range by 1000 to 1200 cells/mm^3 have been noted in the African American population.[51] Laboratory errors may be due to improper sample preparation, nucleated RBCs, or platelet clumping. The blood smear differential count may also be influenced by small sample size, improper cell identification, and age group (children). Differential ranges are listed in Table 121-9. One common but easily

www.ketabpezeshki.com 66485457-66963820

corrected error in laboratory reporting is to give the results in terms of the percentage of cell types. Absolute counts for each cell type are more accurate and useful in assessing the risk for infection.

Abnormal Values

Because of the wide range of normal values, all abnormal WBC counts should be interpreted in the context of the patient's condition. A careful history and physical examination, absolute cell counts, and review of the peripheral smear differential count are the starting points to determine the origins of quantitative WBC disorders.

Leukocytosis

Most cases of leukocytosis are caused by increases in the neutrophil or lymphocyte cell lines. Neutrophil leukocytosis (neutrophilia) is an absolute neutrophil count greater than 7500 cells/mm^3 and is commonly associated with infection or inflammation (Box 121-16). Because increased neutrophil destruction is associated with both of these pathologic processes, bone marrow stores are drawn on, and the usual ratio of 1 band to 10 neutrophils increases. This increase is manifested as a "left shift" in the differential count and represents movement of immature neutrophils from the postmitotic pool into the circulation.

WBC counts can increase without a left shift or an increase in band forms by demarginating neutrophils from the vessel walls. It is often seen as a response to stress, exercise, or epinephrine. Severe stress can raise the WBC count to 18,000 to 20,000 cells/mm^3.[51]

Chronic Myeloid Leukemia

One of the myeloproliferative causes of neutrophilic leukocytosis is chronic myeloid leukemia (CML). Although it is the least common of the major leukemias (60% acute, 31% chronic lymphocytic leukemia, and 15% CML), it should be considered in neutrophilia. Patients with CML are usually older than 40 years and have WBC counts greater than 50,000 cells/mm^3. The differential count shows elevated polymorphonuclear neutrophils and metamyelocytes. Less often, the basophil and eosinophil counts are also increased. CML is a stem cell disorder in which the WBC count is elevated and the differential is normal. Mature and intermediate granulocytes are overproduced. Platelets may also be increased, but RBC production is down, thereby resulting in anemia. The patient often complains of fatigue, anorexia, sweating, and weight loss. Physical findings include pallor, sternal pain and tenderness, and splenomegaly (90% of patients; Fig. 121-12). In the laboratory, decreased leukocyte alkaline phosphatase and increased vitamin B_{12} levels are found, which helps differentiate CML from other causes of neutrophilia. The Philadelphia chromosome (Ph^1) is constantly associated with the disease. The chronic phase of CML is treated with an alkylating agent (e.g., busulfan) or an antimetabolite (e.g., hydroxyurea). Selected patients may benefit from bone marrow transplantation.[52]

Table 121-8 Normal Ranges for the Blood Leukocyte Count (cells/mm^3)

AGE	AVERAGE	95% RANGE (AVERAGE VALUE ±2 SD)
1 week	12,200	5,000-21,000
6 months	11,900	6,000-17,500
12 months	11,400	6,000-17,500
4 years	9,100	5,500-15,500
8 years	8,300	4,500-13,500
Adults	7,400	4,500-11,000

Modified from Miale JB: Laboratory Medicine: Hematology, 6th ed. St Louis, Mosby, 1982.

Box 121-16 Causes of Leukocytosis

Neutrophils (absolute count >7500 cells/mm^3)
- Inflammation: rheumatoid arthritis, gout
- Infection: bacterial most common
- Tissue necrosis: cancer, burns, infarctions
- Metabolic disorders: diabetic ketoacidosis, thyrotoxicosis, uremia
- Rapid RBC turnover: hemorrhage, hemolysis
- Myeloproliferative disorders: chronic myeloid leukemia, polycythemia vera
- Malignant disease (e.g., gastrointestinal cancers)
- Stress: exercise, pain, surgery, hypoxia, seizures, trauma
- Drugs: epinephrine, corticosteroids, lithium, cocaine
- Pregnancy
- Heredity or idiopathic disease
- Laboratory error: automated counters, platelet clumping, precipitated cryoglobulin

Lymphocytosis (absolute count >9000/mm^3, ages 1-6 years; >7000/mm^3, ages 7-16 years; >4000/mm^3, adults)
- Viral infection (primary cause): mononucleosis, rubeola, rubella, varicella, toxoplasmosis
- Bacterial infection: pertussis, tuberculosis, hepatitis, cytomegalovirus
- Lymphoproliferative: acute or chronic lymphocytic leukemia
- Immunologic response: immunization, autoimmune diseases, graft rejection
- Endocrine: hypothyroidism
- Relative lymphocytosis associated with granulocytopenia

Modified from Miale JB: Laboratory Medicine: Hematology, 6th ed. St Louis, Mosby, 1982.

Table 121-9 Normal Percentage Ranges for the Leukocyte Differential Count in Blood*

AGE	SEGMENTED NEUTROPHILS	BAND NEUTROPHILS	LYMPHOCYTES	MONOCYTES	EOSINOPHILS	BASOPHILS
1 week	34 ± 15 (4100)	11.8 ± 4 (1420)	41 ± 5 (5000)	9.1 (1100)	4.1 (500)	0-4 (50)
6 months	23 ± 10 (2710)	8.8 ± 3 (1000)	61 ± 15 (7300)	4.8 (480)	2.5 (300)	0-4 (50)
12 months	23 ± 10 (2680)	8.1 ± 3 (990)	61 ± 15 (7000)	4.8 (550)	2.6 (300)	0-4 (50)
4 years	34 ± 11 (3040)	8.0 ± 3 (730)	50 ± 15 (4500)	5.0 (450)	2.8 (250)	0-6 (50)
8 years	45 ± 11 (3700)	8.0 ± 3 (660)	39 ± 15 (3300)	4.2 (350)	2.4 (200)	0-6 (50)
Adult	51 ± 15 (3800)	8.0 ± 3 (620)	34 ± 10 (2500)	4.0 (300)	2.7 (200)	0-5 (40)

Modified from Miale JB: Laboratory Medicine: Hematology, 6th ed. St Louis, Mosby, 1982.
*Numbers in parentheses indicate the average number of cells per cubic millimeter.

www.ketabpezeshki.com 66485457-66963820

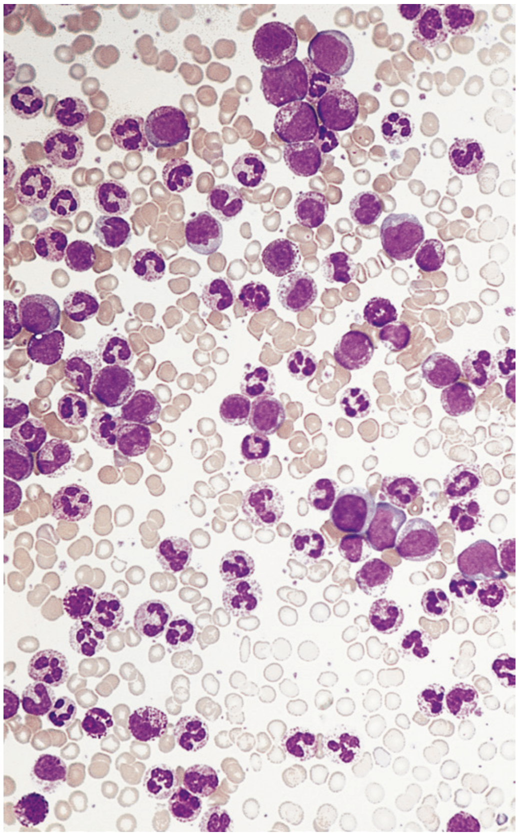


Figure 121-12. Chronic myeloid leukemia. (From Hoffbrand AV, Pettite JE: Color Atlas of Clinical Hematology, 3rd ed. London, Mosby, 2000:169.)

The need for urgent therapy in CML is usually related to hyperuricemia and renal injury or severe anemia and subsequent angina or heart failure. Rarely, hyperleukocytosis occurs, but the more mature, "less sticky" cells in CML do not usually cause problems unless the count exceeds 500,000 cells/mm^3. A higher cell count may cause leukostasis and result in deafness, visual impairment, pulmonary ventilation-perfusion abnormalities, and priapism. Treatment involves hydration, leukapheresis, transfusion as necessary, allopurinol to prevent severe hyperuricemia, and specific chemotherapy (hydroxyurea). Late problems in the natural history of CML involve progressive loss of cell differentiation and response to therapy. The term *blastic crisis* represents the sudden appearance of an acute form of leukemia, which is a rare substage of the evolving deterioration.[52] The condition may occur in lymphoid or myeloid forms. Blast counts greater than 50,000 cells/mm^3 may predispose the patient to the complications of leukostasis.

Leukemoid Reaction

A leukemoid reaction is a nonleukemic reactive granulocytic leukocytosis that resembles CML but has no associated Ph^1 chromosome, no absolute increase in basophils and eosinophils, and an increase in leukocyte alkaline phosphatase. It is difficult to distinguish from CML in the emergency department, and both need to be considered a potential diagnosis in granulocytic leukocytosis. WBC counts are usually greater than 50,000 cells/mm^3. A leukemoid reaction may be seen in tuberculosis, Hodgkin's disease, sepsis, and metastatic tumor, particularly bronchogenic, gastric, and renal carcinoma.[52]

Lymphocytic Leukocytosis

Lymphocytic leukocytosis (lymphocytosis) is an age-dependent definition: 9000 cells/mm^3, ages 1 to 6 years; 7000 cells/mm^3, ages 7 to 16 years; and 4000 cells/mm^3, adults. It is seen in a variety of disorders, primarily infections and lymphoproliferative disease.

In the past, *acute* and *chronic* were descriptive terms applied to lymphocytic neoplasms with respect to survival time of the patient before present therapy was available. The terms *acute* and *chronic* are currently used to describe the cell maturity, rapidity of onset, and aggressiveness of therapy.

Chronic Lymphocytic Leukemia. Chronic lymphocytic leukemia is primarily a B-cell disorder and is the most common type of leukemia in the population 50 years or older. Patients initially complain of fatigue, weight loss, increased susceptibility to infection, rashes, and easy bruising. The lymph nodes are nontender and smooth, and they may appear in only one or two areas. Splenic and hepatic enlargement occurs in more than 50% of patients. Laboratory support of the diagnosis is an absolute lymphocyte count greater than 5000 cells/mm^3 in adults. Anemia, thrombocytopenia, and neutropenia are often found. Autoimmune hemolytic anemia, a positive direct antiglobulin test result, and other altered immune system problems are seen. Early therapy may be directed toward complications of anemia, thrombocytopenia, impaired or accentuated immune response, or enlarged lymph nodes or spleen. Leukostasis is seldom seen in chronic lymphocytic leukemia, but therapy is considered when the total count rises to higher than 200,000/mm^3.[53]

Acute Lymphocytic Leukemia. Acute lymphocytic leukemia is most commonly diagnosed in children younger than 10 years. It is the most frequent malignant neoplasm in children younger than 15 years. The potential for leukostasis increases in acute lymphocytic leukemia when the blast count rises above 50,000 cells/mm^3. Oncologic therapy is based on clinical staging and includes chemotherapy or radiation therapy. Aggressive therapy has improved childhood survival; current 5-year overall survival rates are estimated at 78 to 85%. This response to treatment has not been found to the same degree in adults.[54,55]

Leukopenia

In adults, leukopenia is defined as an absolute blood cell count less than 4000 cells/mm^3. Leukopenia is commonly associated with a reduction in one cell type, the neutrophil, and this decrease has the greatest clinical significance. The absolute neutrophil count is calculated by multiplying the WBC count by the combined percentage of band and segmented neutrophils. The absolute neutrophil count can be classified as mild (1000-1500 cells/mm^3), moderate (500-1000 cells/mm^3), or severe (<500 cells/mm^3) according to the risk for infection. The last is a potentially life-threatening state because the patient is markedly susceptible to overwhelming infection. The physical signs of infection may be minimal in severe neutropenia because there are too few cells to generate a substantial inflammatory or purulent response. Neutropenia may be caused by decreased production, increased destruction, or movement of circulating neutrophils into marginal or tissue pools. Until recently, it was most often caused by a decrease in bone marrow production (Table 121-10). Autoimmune neutropenia is also becoming more commonly diagnosed because it is thought to have a role in acquired immunodeficiency syndrome.[56]

A thorough medication history should be taken in all patients found to have neutropenia. A previous history of neutropenia, a review of recent infection, and a family history are obtained. The review of systems focuses on bleeding problems, fatigue, sweats, weight loss, and autoimmune symptoms. The physical examination is directed toward sites of infection, lymphadenopathy,

www.ketabpezeshki.com 66485457-66963820

Table 121-10 Linkage of Leukopenia to Phases of Neutrophil Maturation

MECHANISM	EXAMPLE
Proliferation in bone marrow	Aplastic anemia, leukemia, cancer chemotherapy (cyclophosphamide, azathioprine, methotrexate, chlorambucil) Drugs: phenothiazines, phenylbutazone, indomethacin, propylthiouracil, phenytoin, cimetidine, semisynthetic penicillins, sulfonamides Infection: viral, tuberculosis, sepsis
Maturation in bone marrow	Folate or vitamin B_{12} deficiency, chronic idiopathic neutropenia Starvation
Distribution	Hypersplenism: sarcoidosis, portal hypertension, malaria
Increased use	Infection: viral most common (mononucleosis, rubella, rubeola), *Rickettsia* organisms, overwhelming bacterial infection Autoimmune disease: systemic lupus erythematosus, AIDS, Felty's syndrome
Laboratory error	Leukocyte clumping, long delay in performing test

hepatosplenomegaly, and underlying disease. In patients with severe neutropenia and fever, a full radiologic and direct examination of commonly involved areas, such as the chest and urine, should be performed, and sputum, urine, and blood culture specimens should be obtained. Basic isolation techniques, early admission, and consultation with another specialist are recommended. Specific therapies may be started after cultures and consultation are completed. A number of empirical antibiotic regimens are recommended for febrile patients with neutropenia.[57,58] Human granulocyte colony–stimulating factor is often used in the setting of neutropenia, but it is best done in consultation with a hematologist.[59] Patients with a clear reversible source or without significant clinical findings and mild to moderate levels of neutropenia may have outpatient follow-up arranged, preferably after discussion with their physician.

RATIONALE FOR SELECTION OF WHITE BLOOD CELL AND DIFFERENTIAL COUNTS

The WBC count has not proved to be a highly sensitive or specific test for the diagnosis of a variety of disease entities. Selected studies suggest some usefulness in certain clinical situations; however, the absence of leukocytosis does not exclude the presence of significant disease. For example, studies evaluating the WBC count for the diagnosis of abdominal pain have found it to be a useful confirming test or helpful in selecting patients for observation.[60] In evaluation of the bacterial infectious potential in febrile children, the WBC and differential counts have demonstrated limited usefulness.[61] Other biomarkers, such as procalcitonin and C-reactive protein, may have more predictive value.[62,63] The test should be viewed as having limited screening value in the acute care setting because multiple agents and conditions can increase the WBC count.

Although the WBC count may be nonspecific and nonsensitive, the differential count may provide helpful information. The absolute neutrophil count may be more helpful than the total WBC count in identifying bacterial infection.[62,63]

KEY CONCEPTS

- Anemia is caused by three basic mechanisms: bleeding, destruction of red blood cells, and decrease in production of red blood cells.
- The use of red blood cell indices and a peripheral blood smear can help determine the mechanism of anemia.
- One of the most important but often overlooked studies in the evaluation of suspected hemolytic anemia is the peripheral blood smear.
- Anemia in the elderly often occurs as an exacerbation of preexisting comorbid diseases.
- Anemia of uncertain etiology should be thoroughly evaluated. If the patient has no adverse hemodynamic consequences, the evaluation can proceed on an outpatient basis.
- Patients with sickle cell disease should be considered to have an acute pain crisis and treated appropriately until it is proved otherwise.
- Acute chest syndrome is one of the most common causes of death in sickle cell disease.
- Acute transfusion therapy is most useful in sickle cell disease associated with acute stroke (in children), acute chest syndrome, and splenic sequestration.
- The white blood cell determination in the emergency department has poor sensitivity and specificity for any specific disease.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Weber P, et al: Anemia in elderly an important diagnostic and therapeutic problem in geriatric medicine. *Adv Gerontol* 2009; 22:662-666.
2. Tefferi A: Anemia in adults: A contemporary approach to diagnosis. *Mayo Clin Proc* 2003; 78:1274-1280.
3. Olivieri NF: The beta-thalassemias. *N Engl J Med* 1999; 341:99-109.
4. Borgna-Pignatti C: Modern treatment of thalassemia intermedia. *Br J Haematol* 2007; 138:291-299.
5. Rund D, Rachmilewitz E: Beta-thalassemia. *N Engl J Med* 2005; 353:1135-1139.
6. Galanello R, Campus S, Origa R: Deferasirox: Pharmacokinetics and clinical experience. *Expert Opin Drug Metab Toxicol* 2012; 8:123-134.
7. Lucarelli G, Gaziev G: Advances in the allogeneic transplantation for thalassemia. *Blood Rev* 2008; 22:53-63.
8. Weiss G, Goodnough LT: Anemia of chronic disease. *N Engl J Med* 2005; 352:1011.
9. Malouf R, Grimley Evans J: Folic acid with or without vitamin B_{12} for the prevention and treatment of healthy elderly and demented people. *Cochrane Database Syst Rev* 2008; 4:CD004515.
10. Locatelli F, et al: Cyclosporin A and short-term methotrexate versus cyclosporin A as graft versus host disease prophylaxis in patients with severe aplastic anemia given allogeneic bone marrow transplantation from an HLA-identical sibling: Results of a GITMO/EBMT randomized trial. *Blood* 2000; 96:1690-1696.
11. Young NS: Acquired aplastic anemia. *Ann Intern Med* 2002; 136:534-538.
12. Marsh JC, et al: Guidelines for the diagnosis and management of aplastic anaemia. *Br J Haematol* 2009; 147:43-50.
13. Jones M, Ibels L, Schenkel B, Zagari M: Impact of epoetin alfa on clinical end points in patients with chronic renal failure: A meta-analysis. *Kidney Int* 2004; 65:757-765.
14. Packman CH: Hemolytic anemia due to warm autoantibodies. *Blood Rev* 2008; 22:17-23.
15. Glassberg J: Evidence based management of sickle cell disease in the emergency department. *Emerg Med Pract* 2011; 13:1-20.
16. Quinn CT, et al: Prediction of adverse outcomes in children with sickle cell anemia: A study of the Dallas Newborn Cohort. *Blood* 2008; 111:544-548.
17. Yanni E, Grusse S, Yang Q, Olney R: Trends in pediatric sickle cell disease–related mortality in the United States, 1983-2002. *J Pediatr* 2009; 154:541-545.
18. Tsaras G, Owusu-Ansah A, Boateng FO, Amoateng-Adjepong Y: Complications associated with sickle cell trait: A brief narrative review. *Am J Med* 2009; 122:507-511.
19. Austin H, et al: Sickle cell trait and the risk of venous thromboembolism among blacks. *Blood* 2007; 110:908-912.
20. Tita AT, Biggio JR, Chapman V, Neely C, Rouse DJ: Perinatal and maternal outcomes in women with sickle cell or hemoglobin C trait. *Obstet Gynecol* 2007; 110:1113-1119.
21. Aisiku IP, et al: Comparisons of high versus low emergency department utilizers in sickle cell disease. *Ann Emerg Med* 2009; 53:587-592.
22. Dampier C, et al: Vaso-occlusion in children with sickle cell disease: Clinical characteristics and biologic correlates. *J Pediatr Hematol Oncol* 2004; 26:785-790.
23. Ohene-Frempong K, et al: Cerebrovascular accidents in sickle cell disease: Rates and risk factors. *Blood* 1998; 91:288-294.
24. Verduzco LA, Nathan DG: Sickle cell disease and stroke. *Blood* 2009; 114:5117-5125.
25. Krejza J, et al: Sickle cell disease and transcranial Doppler imaging. *Stroke* 2011; 42:81-86.
26. Adams RJ, et al: Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med* 1998; 339:5-11.
27. Hulbert ML, et al: Exchange blood transfusion compared with simple transfusion for first overt stroke is associated with a lower risk of subsequent stroke: A retrospective cohort study of 137 children with sickle cell anemia. *J Pediatr* 2006; 149:710-712.
28. The Management of Sickle Cell Disease. Bethesda, Md: National Institutes of Health, National Heart, Lung, and Blood Institute, Division of Blood Diseases and Resources; revised 2004. NIH publication 04-2117.
29. Gladwin MT, Vichinsky E: Pulmonary complications of sickle cell disease. *N Engl J Med* 2008; 359:2254-2259.
30. Vichinsky EP, et al: Causes and outcomes of the acute chest syndrome in sickle cell disease. *N Engl J Med* 2000; 342:1855-1859.
31. Turner JM, Kaplan JB, Cohen HW, Billett HH: Exchange versus simple transfusion for acute chest syndrome in sickle cell anemia adults. *Transfusion* 2009; 49:863-868.
32. Alhashimi D, et al: Blood transfusions for treating acute chest syndrome in people with sickle cell disease. *Cochrane Database Syst Rev* 2010; 20:CD007843.
33. Battersby AJ, Knox-Macaulay HH, Carrol ED: Susceptibility to invasive bacterial infections in children with sickle cell disease. *Pediatr Blood Cancer* 2010; 55:401-406.
34. Syrogiannopoulos GA, McCracken GH, Nelson JD: Osteoarticular infections in children with sickle cell disease. *Pediatrics* 1986; 78:1090-1094.
35. Brawley OW, et al: National Institute of Health consensus development conference statement: Hydroxyurea treatment for sickle cell disease. *Ann Intern Med* 2008; 148:932-937.
36. Steinberg MH, et al: Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: Risks and benefits up to 9 years of treatment. *JAMA* 2003; 289:1645-1651.
37. Vichinsky E: New therapies of sickle cell disease. *Lancet* 2002; 360:629-635.
38. Amrolia PJ, Almeida A, Halsey C, Roberts IA, Davies SC: Therapeutic challenges in childhood sickle cell disease. Part 1: Current and future treatment options. *Br J Haematol* 2003; 120:725-736.
39. Tanabe P, et al: Emergency department management of acute pain episodes in sickle cell disease. *Acad Emerg Med* 2007; 14:419-425.
40. Josephson CD, Su L, Hillyer K, Hillyer C: Transfusion in the patient with sickle cell disease: A critical review of the literature and transfusion guidelines. *Transfus Med Rev* 2007; 21:118-133.
41. Montague DK, et al; Members of the Erectile Dysfunction Guideline Update Panel; American Urological Association: *Priapism. Guidelines on the management of priapism, 2010*. Available at www.auanet.org.
42. Gibbs WJ, Hagemenn TM: Purified poloxamer 188 for sickle cell vaso-occlusive crisis. *Ann Pharmacother* 2004; 38:320-325.
43. Gehrs BC, Friedberg RC: Autoimmune hemolytic anemia. *Am J Hematol* 2002; 69:258-263.
44. Arndt P, Garraty G: The changing spectrum of drug-induced immune hemolytic anemia. *Semin Hematol* 2005; 42:138-142.
45. Kehat I, Shupak A, Goldenberg I, Shoshani O: Long-term hematological effects in Special Forces trainees. *Mil Med* 2003; 168:116-119.
46. Passamonti F, et al: Polycythemia vera in young patients: A study on the long-term risk of thrombosis, myelofibrosis and leukemia. *Haematologica* 2003; 88:13-19.
47. Streiff MB, Smith B, Spivak JL: The diagnosis and management of polycythemia vera in the era since the Polycythemia Vera Study Group: A survey of American Society of Hematology members' practice patterns. *Blood* 2002; 99:1144-1148.
48. Spivak JL: Polycythemia vera: Myths, mechanisms, and management. *Blood* 2002; 100:4272-4290.
49. Passamonti F, et al: Life expectancy and prognostic factors for survival in patients with polycythemia vera and essential thrombocythemia. *Am J Med* 2004; 117:755-761.
50. Squizzato A, Romualdi E, Middledorp S: Antiplatelet drugs for polycythaemia vera and essential thrombocythaemia. *Cochrane Database Syst Rev* 2008; 2:CD006503.
51. Hillman RS, et al: Normal myelopoiesis. In Hillman RS, et al, eds. *Hematology in Clinical Practice*, 5th ed. New York: McGraw-Hill; 2011.
52. Goldman JM, Melo JV: Chronic myeloid leukemia—advances in biology and new approaches to treatment. *N Engl J Med* 2003; 349:1451-1456.
53. Kipps TJ: *Classification and clinical manifestations of lymphocyte and plasma cell disorders*. In: Kaushansky K, et al, eds. *Williams Hematology*, 8th ed. New York: McGraw-Hill; 2010.
54. Ribera JM, Oriol A: Acute lymphoblastic leukemia in adolescents and young adults. *Hematol Oncol Clin North Am* 2009; 5:1033-1045.
55. Pui CH: Treatment of acute lymphoblastic leukemia. *N Engl J Med* 2006; 354:166-171.
56. Jacobson MA, Liu RC, Davies D, Cohen PT: Human immunodeficiency virus–related neutropenia and the risk of hospitalization for bacterial infection. *Arch Intern Med* 1997; 157:1825-1831.
57. Viscoli C, Varnier O, Machetti M: Infections in patients with febrile neutropenia: Epidemiology, microbiology, and risk stratification. *Clin Infect Dis* 2005; 40(Suppl 4):S240-S245.
58. Sepkowitz KA: Treatment of patients with hematologic neoplasm, fever, and neutropenia. *Clin Infect Dis* 2005; 40(Suppl 4): S253-S256.

www.ketabpezeshki.com 66485457-66963820

59. Kuderer NM: Impact of primary prophylaxis with granulocyte colony–stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: A systematic review. *J Clin Oncol* 2007; 25:3158-3162.
60. Deibener-Kaminsky J, Lesesve JF, Kaminsky P: Leukocyte differential for acute abdominal pain in adults. *Lab Hematol* 2011; 17:1-5.
61. Pucell K, Fergie J: Lack of usefulness of an abnormal white cell count for predicting a concurrent serious bacterial infection in infants and young children hospitalized with respiratory syncytial virus lower respiratory tract infection. *Pediatr Infect Dis* 2007; 26:311-315.
62. Kuppermann N, Fleisher GR, Jaffe DM: Predictors of occult pneumococcal bacteremia in young febrile children. *Ann Emerg Med* 1998; 31:679-687.
63. Seigel TA, et al: Inadequacy of temperature and white blood cell count in predicting bacteremia in patients with suspected infection. *J Emerg Med* 2012; 42:254-259.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 122

DISORDERS OF HEMOSTASIS

Timothy G. Janz and Glenn C. Hamilton

PERSPECTIVE

Hemostasis is the process of blood clot formation and represents a coordinated response to vessel injury. It requires an orchestrated response from platelets, the clotting cascade, blood vessel endothelium, and fibrinolysis. Thrombin-stimulated clot formation and plasmin-induced clot lysis are closely related and regulated. This dynamic process is often viewed in phases: formation of a platelet plug, propagation of the coagulation cascade, formation of a clot, and fibrinolysis of the clot.

Most hemostatic abnormalities are acquired and result from drugs (e.g., aspirin or warfarin [Coumadin]), from associated disease (e.g., hepatic insufficiency), or from iatrogenic causes (e.g., multiple transfusions).

PATHOPHYSIOLOGY

Hemostasis depends on normal function and integration of the vasculature, platelets, and coagulation pathway.

Vasculature

Vascular integrity is maintained by a lining of nonreactive overlapping endothelial cells supported by a basement membrane, connective tissue, and smooth muscle. These cells are important in maintaining a barrier to macromolecules and, when injured, in contributing to the metabolic response and local vasoconstriction. The vascular endothelium is an important contributor to hemostasis.[1]

The endothelium contributes to both clot formation and regulation by producing substances such as von Willebrand's factor (vWF), antithrombin III, heparin sulfate, prostacyclin, nitric oxide, and tissue factor pathway inhibitor.

Platelets

Platelets have multiple and ever-expanding roles in our understanding of hemostasis. They are complex cytoplasmic fragments released from bone marrow megakaryocytes under the control of thrombopoietin. Platelets contain lysosomes, granules, a trilaminar plasma membrane, microtubules, and a canalicular system. Granules are an important component of hemostasis and contain platelet factor 4, adhesive and aggregation glycoproteins, coagulation factors, and fibrinolytic inhibitors. Each participates in the process of coagulation. The platelet's role is termed primary hemostasis, and it serves as the initial defense against blood loss.[1,2] A fibrin clot that incorporates coagulation factors usually reinforces a platelet clot. Platelet activity is summarized in Box 122-1. Any of the steps listed may be absent, altered, or inhibited by inherited or acquired disorders.

Coagulation Pathway

The coagulation pathway is a complex system of checks and balances that results in controlled formation of a fibrin clot. Coagulation factors have been given standard Roman numerals matching their order of discovery (Box 122-2).

A simplified version of the coagulation pathway is presented in Figure 122-1. The clotting cascade is traditionally depicted as consisting of intrinsic and extrinsic pathways. The intrinsic pathway is initiated by exposure of blood to a negatively charged surface, such as a glass surface in the activated partial thromboplastin clotting time. The extrinsic pathway is activated by tissue factor exposed at the site of vessel injury or thromboplastin. Both pathways converge to activate factor X, which then activates prothrombin to thrombin. The primary physiologic event that initiates clotting is exposure of tissue factor at the injured vessel site. Tissue factor is a critical cofactor that is required for activation of factor VII. Activated factor VII activates factor X directly as well as indirectly by activating factor IX.

Because of limited amounts of tissue factor and rapid inactivation by tissue factor pathway inhibitor, the extrinsic pathway initiates the clot process. Sustained generation of thrombin and clot formation depend on the intrinsic pathway through activation of factor IX by activated factor VII, which helps explain the bleeding problems associated with hemophilia.[3] Intrinsic, extrinsic, and common pathways function normally for hemostasis to occur, and each may be evaluated with laboratory tests. The clinically important groups of coagulation factors are as follows:

Thrombin-sensitive factors contributing to the metabolic response and local vasoconstriction: I, V, VIII, XIII

Vitamin K-sensitive factors: II, VII, IX, X

Sites of heparin activity: IIa, IXa, Xa (major site), XIa, platelet factor 3

Thrombin-sensitive factors are activated by thrombin and may give rise to a bleeding disorder if defective synthesis occurs. Vitamin K–sensitive factors may also cause bleeding from defective synthesis, as occurs with liver disease and warfarin anticoagulants. Heparin in combination with antithrombin III affects the coagulation pathway at multiple sites.

Coagulation Control

All the components of the coagulation reaction are necessary to prevent excessive bleeding. Hemostasis is a balance between the

www.ketabpezeshki.com 66485457-66963820

excessive bleeding state and thrombosis. Once coagulation is initiated, controls are necessary to prevent local or generalized thrombosis. These controls include the following:

Removal and dilution of activated clotting factors through blood flow, which also mechanically opposes growth of the hemostatic plug
Modulation of platelet activity by endothelium-generated nitric oxide and prostacyclin
Removal of activated coagulation components by the reticuloendothelial system
Regulation of the clotting cascade by antithrombin III, protein C, protein S, and tissue factor pathway inhibitor
Activation of the fibrinolytic system

CLINICAL FEATURES

Out-of-Hospital Treatment

The out-of-hospital treatment of bleeding problems presents no special concerns. Local pressure and volume repletion are the

Box 122-1 Role of Platelets in Hemostasis

Adhesion to subendothelial connective tissue: collagen, basement membrane, and noncollagenous microfibrils; serum factor VIII (von Willebrand's) permits this function; adhesion creates the initial bleeding arrest plug
Release of adenosine diphosphate, the primary mediator and amplifier of aggregation; release of thromboxane A, another aggregator and potent vasoconstrictor; release of calcium, serotonin, epinephrine, and trace thrombin
Platelet aggregation over the area of endothelial injury
Stabilization of the hemostatic plug by interaction with the coagulation system:
- Platelet factor 3, a phospholipid that helps accelerate certain steps in the coagulation system
- Platelet factor 4, a protein that neutralizes heparin
- Pathway initiation and acceleration by thrombin production
- Possible secretion of active forms of coagulation proteins

Stimulation of limiting reactions of platelet activity

Box 122-2 Coagulation Factors

I. Fibrinogens
II. Prothrombin
III. Tissue thromboplastin
IV. Calcium
V. Labile factor (proaccelerin)
VI. Not assigned
VII. Proconvertin
VIII. Antihemophilic A factor
IX. Antihemophilic B factor (plasma thromboplastin component, Christmas factor)
X. Stuart-Prower factor
XI. Plasma thromboplastin antecedent
XII. Hageman factor (contact factor)
XIII. Fibrin-stabilizing factor

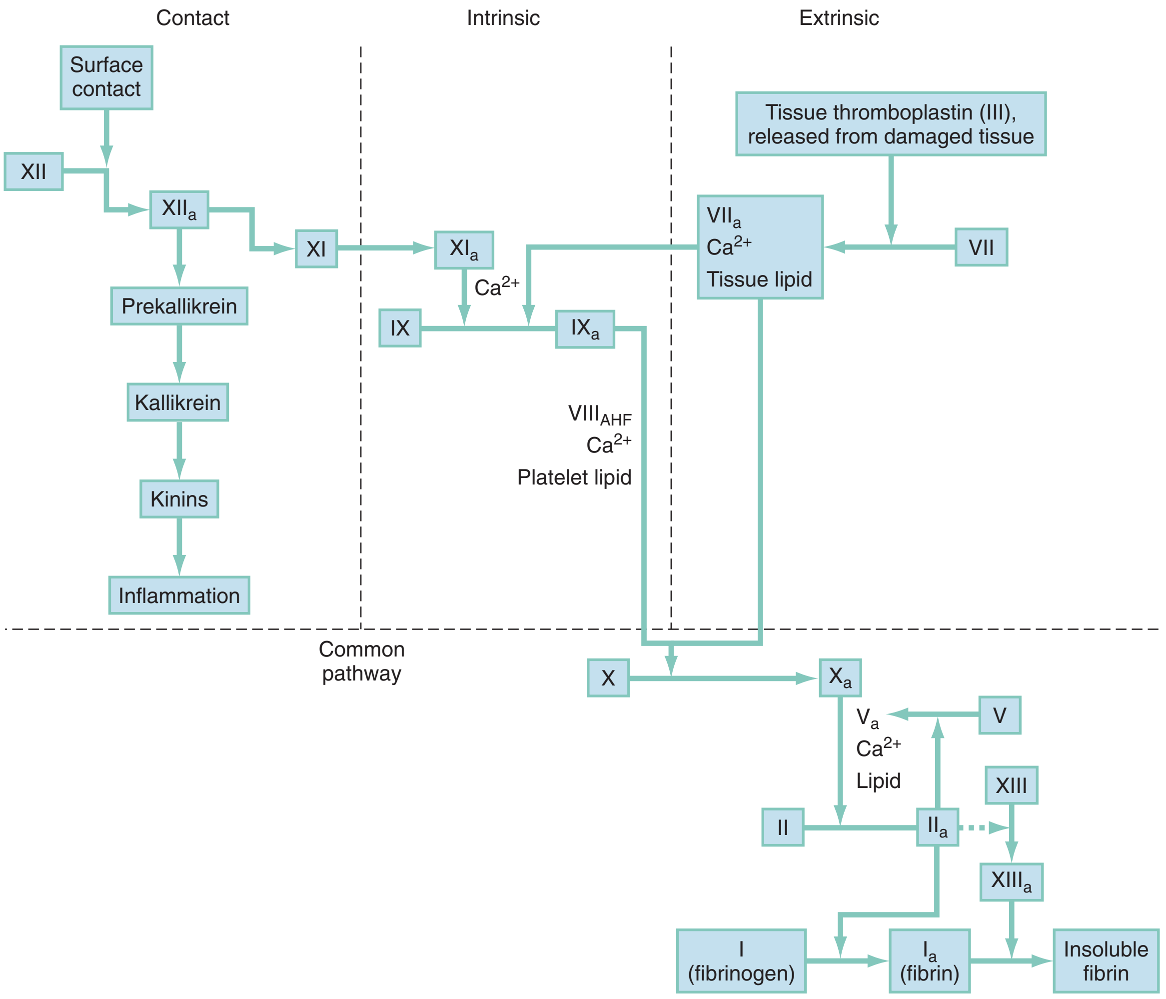


Figure 122-1. Coagulation pathway.

www.ketabpezeshki.com 66485457-66963820

Box 122-3 Clinical Evaluation of a Bleeding Patient

History

Nature of bleeding
- Petechiae
- Purpura
- Ecchymosis
- Significant bleeding episodes

Sites of bleeding
- Skin
- Mucosa: oral or nasal
- Muscle
- Gastrointestinal
- Genitourinary
- Joints

Patterns of bleeding
- Recent onset or lifelong
- Frequency and severity
- Spontaneous or after injury

Challenges to hemostasis
- Tooth extraction
- Operative procedures
- Association with medication, particularly aspirin

Medications

Associated diseases
- Uremia
- Liver disease
- Infection
- Malignant neoplasm

Previous transfusion

Family history

Physical Examination

Vital signs

Skin: nature of bleeding, signs of liver disease

Mucosa: oral or nasal

Lymphadenopathy

Abdomen: liver size and shape, splenomegaly

Joints: signs of previous bleeding

Other sites of blood loss: pelvic, rectal, urinary tract

mainstays of therapy for blood loss. The out-of-hospital team should be aware that inherited coagulopathies may complicate any medical or traumatic problems and that coagulopathy can rapidly develop in critically ill patients. Patients who do not respond quickly to the usual measures of hemostasis either in the field or in the emergency department (ED) should be considered to have a potential bleeding disorder.

History and Physical Examination

An outline of the history and physical examination is presented in Box 122-3. The history alone may be useful in differentiating between platelet and coagulation factor abnormalities. Platelet disorders are usually manifested as acquired petechiae, purpura, or mucosal bleeding and are more common in women. Coagulation problems are commonly congenital, are characterized by delayed deep muscle or joint bleeding, and are seen more often in men.

Ancillary Evaluation

A definitive diagnosis depends on laboratory evaluation. Tests pertinent to the ED are discussed in the following sections and listed in Box 122-4.

Box 122-4 Coagulation Studies

Complete blood count and smear (EDTA—purple top)

Platelet count (EDTA—purple top)

Bleeding time

Prothrombin time (citrate—blue top)

Partial thromboplastin time (citrate—blue top)

Other coagulation studies: fibrinogen level, thrombin time, clot solubility, factor levels, inhibitor screens

As necessary: electrolyte values; glucose, BUN, and creatinine concentrations; type and crossmatch

BUN, blood urea nitrogen; *EDTA,* ethylenediaminetetraacetic acid.

Complete Blood Count and Blood Smear

The complete blood count assesses the degree of anemia associated with the bleeding episode. Reductions in hemoglobin and hematocrit often lag behind the actual loss of red blood cells (RBCs) in acute hemorrhage because of a slow equilibration time. The peripheral blood smear may demonstrate schistocytes or fragmented RBCs in disseminated intravascular coagulation (DIC). Teardrop-shaped or nucleated RBCs may reflect myelophthisic disease. A characteristic white blood cell morphologic condition is seen with thrombocytopenia associated with infectious mononucleosis, folate or vitamin B_{12} deficiency, or leukemia.[4]

Platelet Count

The platelet count may be estimated from the smear. Normally, one platelet is present per 10 to 20 RBCs. Often, the count is automated, the normal range being 150,000 to 400,000/mm^3. Platelet counts less than 100,000/mm^3 define thrombocytopenia. With normal platelet function, the bleeding time increases in direct relation to a decrease in the platelet count below 100,000/mm^3. Levels below 20,000/mm^3 may be associated with serious spontaneous hemorrhage. However, the count gives no information about the functional capability of platelets.

Bleeding Time

Bleeding time is the best test to determine both vascular integrity and platelet function that can be performed in the ED. The test is performed after two standard incisions, 1 mm deep and 1 cm long, are made on the volar aspect of the forearm under 40 mm Hg pressure by a blood pressure cuff with use of a template to ensure appropriate incisions. The time is measured from the incision to the moment when the blood oozing from the wound is no longer absorbed by filter paper. Some institutions have replaced the traditional bleeding time with a platelet function analyzer instrument, which is just as accurate and more convenient. A normal time is 8 minutes, a time of 8 to 10 minutes is borderline, and a time longer than 10 minutes is typically abnormal. Because of the high incidence of drug-induced platelet dysfunction, ask the patient about medications, particularly aspirin and other antiplatelet medications (e.g., clopidogrel). Platelet function testing is independent of the coagulation pathways. As mentioned previously, the bleeding time is prolonged with platelet counts below 100,000/mm^3, but such prolongation does not represent platelet dysfunction. However, a prolonged bleeding time associated with platelet counts above 100,000/mm^3 suggests impaired function.

Prothrombin Time

The prothrombin time (PT) tests the factors of the extrinsic and common pathways. The patient's anticoagulated plasma is

www.ketabpezeshki.com 66485457-66963820

combined with calcium and tissue factor prepared from rabbit or human brain tissue. Sensitivity to factor deficiencies depends on the source of the tissue factor. The PT detects factor deficiencies in fibrinogen, prothrombin (factor II), factor V, factor VII, and factor X. It is used to test the extrinsic pathway. A normal control sample is simultaneously run, and the clotting times of both are recorded. The time in seconds is usually given over the normal control time, for example, 12.5/11.5. A PT of 2 seconds or more above the control time is considered significant. Results are usually reported as the international normalized ratio (INR), which compensates for differences in sensitivity of various thromboplastin reagents to the effects of warfarin. The test is helpful in monitoring the use of coumarin anticoagulants, and the time may be prolonged in patients with liver disease and other abnormalities of vitamin K–sensitive factors.

Partial Thromboplastin Time

The partial thromboplastin time (PTT) tests the components of the intrinsic and common pathways, that is, essentially all factors but VII and XIII in the entire clotting cascade. In this test, a phospholipid source and a contact-activating agent (kaolin) are added to anticoagulated citrate plasma. After an incubation period that allows factor XII to become activated, calcium is added and the clotting time is recorded. A normal control sample is run simultaneously. Normal ranges may vary, and each hospital laboratory should be checked. The average time is 25 to 29 seconds. The sensitivity of the test varies from factor to factor, but factor levels usually are less than 40% before the PTT is prolonged. The test may be altered by clotting factor inhibitors of external origin (e.g., heparin) or internal origin (e.g., anti-VIII antibody). Inappropriately high values may occur if the plasma is too turbid or icteric. The activated PTT is most sensitive to abnormalities in the sequence of the coagulation cascade that precedes activation of factor X.

Fibrinogen

Fibrinogen is present in sufficient concentration to be measured directly. Because it is the final coagulation substrate, its level reflects the balance between production and consumption. It may be decreased by low production, as in severe liver disease, or by overconsumption, as in DIC. Low levels and altered function increase the PT, PTT, and thrombin clotting time. Because fibrinogen is an acute-phase reactant, certain conditions, including malignant disease, sepsis, inflammation, and pregnancy, may alter the test result.

Thrombin Time

Measurement of the thrombin clotting time bypasses the intrinsic and extrinsic pathways by directly converting fibrinogen to fibrin. It is a useful screening test for both qualitative and quantitative abnormalities of fibrinogen and inhibitors such as heparin and fibrin split products.

Clot Solubility

The result of clot solubility testing may be the only abnormality in disorders involving factor XIII deficiency and some abnormal fibrinogen. A washed clot is incubated in acetic acid or urea. If the clot is not properly cross-linked, it dissolves.

Factor Level Assays

Factor levels are determined either by bioassay, in which the ability of the sample of plasma to normalize controlled substrate-deficient plasma is evaluated, or by immunologic assay. Inhibitor screening tests reveal antibodies in plasma that prolong the normal plasma clotting time when mixed.

Box 122-5 Differential Diagnosis of Vascular Disorders

Inherited

Disorders of connective tissue
- Pseudoxanthoma elasticum
- Ehlers-Danlos syndrome
- Osteogenesis imperfecta

Disorders of blood vessels
- Hemorrhagic telangiectasia

Acquired

Scurvy (vitamin C deficiency)
Simple or senile purpura
Purpura secondary to steroid use
Vascular damage
- Infection (meningococcemia)
- Hemolytic-uremic syndrome
- Hypoxemia
- Thrombotic thrombocytopenic purpura
- Snakebite
- Dysproteinemic purpura

DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

When a bleeding disorder is diagnosed or suggested, the assessment initially includes stabilization, which may necessitate volume, RBC, and coagulation factor replacement. If the disorder is known, clinical complications associated with its underlying pathophysiologic condition needs to be considered. If the disorder is unknown, a rapid differential diagnosis must be made. A clinically useful scheme approaches bleeding disorders in terms of three constituents: vascular integrity, platelets, and coagulation factors. This differential diagnostic approach can be further divided into inherited and acquired disorders.

Vascular Disorders

Vascular disorders have signs and symptoms similar to those of thrombocytopenic states. The inherited forms are rare. Acquired forms are usually associated with connective tissue changes or endothelial damage. The differential diagnosis of vascular disorders is listed in Box 122-5.

Platelet Disorders

General Approach

Platelet abnormalities can be caused by congenital disorders, but most are from acquired conditions.[5] The bleeding source is usually capillary, with resultant cutaneous and mucosal petechiae or ecchymosis. Epistaxis, menorrhagia, and gastrointestinal bleeding are common initial symptoms. The bleeding is generally mild and occurs immediately after surgery or dental extractions. Petechiae and purpura may be noted on physical examination, and superficial ecchymoses may be found around a venipuncture site. The purpura associated with platelet disorders is typically asymptomatic and not palpable. This is in contrast to purpura associated with vasculitis, which can burn or itch and is palpable.[6] Deep muscle hematomas and hemarthroses are not aspects of the clinical picture. The bleeding time is prolonged, and the platelet count may be low, normal, or high. The differential diagnosis of platelet disorders is listed in Box 122-6.

www.ketabpezeshki.com 66485457-66963820

Box 122-6 Differential Diagnosis of Platelet Disorders

Thrombocytopenia
Decreased production
- Decreased megakaryocytes secondary to drugs, toxins, or infection
- Normal megakaryocytes with megaloblastic hematopoiesis or hereditary origin
- Platelet pooling and splenic sequestration

Increased destruction
- Immunologic
  - Related to collagen vascular disease, lymphoma, leukemia
  - Drug related
  - Infection
  - Post-transfusion
  - Idiopathic (autoimmune) thrombocytopenic purpura
- Mechanical
  - Disseminated intravascular coagulation
  - Thrombotic thrombocytopenic purpura
  - Hemolytic-uremic syndrome
- Vasculitis

Dilutional secondary to massive blood transfusion

Thrombocytopathy
Adhesion defects such as von Willebrand's disease
Release defects: acquired and drug related
Aggregation defects such as in thrombasthenia

Thrombocytosis
Autonomous (primary thrombocythemia)
Reactive (secondary thrombocythemia)
Iron deficiency
Infection or inflammation
Trauma
Nonhematologic malignant disease
Postsplenectomy
Rebound from alcohol, cytotoxic drug therapy, folate or vitamin B_{12} deficiency

Thrombocytopenia

Decreased Production. Thrombocytopenia from decreased bone marrow production is usually caused by the effects of chemotherapeutic drugs, myelophthisic disease, or direct bone marrow effects of agents such as alcohol or thiazides.

Splenic Sequestration. Splenic sequestration is rare. It is seen primarily with hypersplenism resulting from hematologic malignant disease, portal hypertension, or disorders involving increased splenic RBC destruction, such as hereditary spherocytosis or autoimmune hemolytic anemia.

Increased Destruction

Immune Thrombocytopenia. Thrombocytopenia associated with increased peripheral destruction of platelets and shortened platelet survival caused by an antiplatelet antibody is seen in a number of diseases. In most cases a cause is identifiable.

Collagen vascular diseases, particularly systemic lupus erythematosus, may cause an antiplatelet antibody-related platelet decrease. Similar associations have been noted with leukemia and lymphoma, particularly lymphocytic lymphoma. All evaluations of suggested immune thrombocytopenia should include a complete blood count, peripheral smear, antinuclear antibody test, and bone marrow examination. A number of drugs have been associated with thrombocytopenia of immunologic origin. Quinine and quinidine are common offenders that affect platelets through an "innocent bystander" mechanism. The platelet is coated with a drug-antibody complex, complement is fixed, and intravascular platelet lysis occurs. Because of its relatively high frequency, heparin is an important cause of drug-induced thrombocytopenia in hospitalized patients. Platelets are activated by the formation of an immunoglobulin G (IgG)–heparin complex.

Low-molecular-weight heparin may be associated with less thrombocytopenia than standard, unfractionated heparin is; however, both forms of heparin demonstrate cross-reactivity.[7] Heparin-induced thrombocytopenia (HIT) is a serious immune-mediated side effect associated with heparin.[8,9] A meta-analysis including 7287 patients determined the incidence of HIT to be 2.6% for unfractionated heparin and 0.2% for low-molecular-weight heaprin.[10] It usually occurs 5 to 7 days after the initiation of heparin treatment. Thrombus develops in approximately half the patients with HIT. The thrombotic complications can lead to loss of a limb in up to 20% and death in as many as 30%. The diagnosis is suggested in the presence of absolute thrombocytopenia or a greater than 50% reduction in platelets after the initiation of heparin. The most specific diagnostic tests for HIT are serotonin release assays, heparin-induced platelet aggregation assays, and solid-phase immunoassays. Platelet-associated IgG levels are commonly elevated, but this finding is less specific or sensitive than the other diagnostic tests. More concerning to the emergency physician is delayed-onset HIT. This form of HIT occurs a median of 14 days after the initiation of heparin, but it has been reported to occur up to 40 days after heparin is started.[10] Arterial or venous thrombosis typically develops in patients with HIT after they receive heparin. The administration of heparin can result in the development of antibodies to the heparin and platelet factor 4 complex. The heparin–platelet factor 4–antibody complex is removed from the circulation, resulting in thrombocytopenia; however, this complex also results in the generation of microparticles that have procoagulant properties, which can lead to thrombus formation. Treatment of thrombotic complications in these patients involves the use of direct thrombin inhibitors (lepirudin, argatroban), factor Xa inhibitors (fondaparinux), or heparinoids (danaparoid).[8]

Digitoxin, sulfonamides, phenytoin, and aspirin are other drugs that may be associated with a thrombocytopenia. The patient has usually ingested the medication within 24 hours. An idiopathic thrombocytopenic purpura type of syndrome has been reported in intravenous cocaine users.[11] Clinical trials with platelet glycoprotein IIb/IIIa antagonists suggest that intravenous glycoprotein IIb/IIIa inhibitors may confer an increased risk for associated thrombocytopenia, independent of heparin therapy.[12] The platelet count may fall below 10,000/mm^3 and be complicated by serious bleeding. Laboratory testing may confirm the presence of antibody, especially with the use of quinine and quinidine. After administration of the drug is stopped, the platelet count improves slowly during a period of 3 to 7 days. A short course of corticosteroid therapy, such as prednisone in a dose of 1 mg/kg with rapid tapering, may facilitate recovery.[13,14]

Postinfectious immune thrombocytopenia is usually associated with viral diseases such as rubella, rubeola, and varicella. Although many cases associated with sepsis have a mechanical origin, some immune mechanisms have been demonstrated.[13]

Post-transfusion thrombocytopenia is a rare disorder that causes a precipitous fall in platelets approximately 1 week after the transfusion. In 90% of cases, its origin is linked to the 98% of the population carrying a PLA1 antigen on platelets. Despite the fact that 2% of blood recipients are mismatched with respect to this antigen, it is fortunately a rare occurrence. On transfusion into a PLA1 antigen–negative patient, the platelets with attached PLA1 antibodies provoke an anamnestic response, but the actual mechanism of platelet destruction remains unknown. The platelet count often falls precipitously below 10,000/mm^3, with a significant risk for major bleeding. Intracranial hemorrhage occurs in approximately 10% of such cases. Patients are usually middle-aged women with a history of pregnancy who may have been previously

www.ketabpezeshki.com 66485457-66963820

sensitized to the PLA1 antigen during pregnancy. Plasma exchange therapy is an effective intervention.[13,15]

Idiopathic Thrombocytopenic Purpura. Autoimmune idiopathic thrombocytopenic purpura (ITP) is considered after other causes of thrombocytopenia have been excluded. ITP is associated with an IgG antiplatelet antibody that has proved difficult to detect. The two clinically important forms are acute and chronic.[16]

The acute form of ITP is seen most often in children 2 to 6 years of age. A viral prodrome commonly occurs within 3 weeks of its onset. The platelet count decreases, usually to less than 20,000/mm^3. The course is self-limited, with a greater than 90% rate of spontaneous remission. Morbidity and mortality rates are low, although full recovery may take several weeks. Treatment of acute ITP is supportive. Steroids and intravenous immune globulin therapy are reserved for patients with active bleeding.[13]

The chronic form of ITP is primarily an adult disease found three times more often in women than in men. The onset of chronic ITP is insidious, without a prodrome, and it is manifested as easy bruising, prolonged menses, and mucosal bleeding. The patient may have petechiae or purpura, and platelet counts between 30,000/mm^3 and 100,000/mm^3 are common. Bleeding complications are of unpredictable frequency and severity, although the long-term mortality rate is approximately 1%.[16] Splenomegaly is unusual in either acute or chronic ITP.

Associated diseases, such as lymphoma and systemic lupus erythematosus, needs to be ruled out before the diagnosis of ITP can be made. Quantitative laboratory tests of antiplatelet antibody may differentiate between patients who will favorably respond to therapy and those who will not. Hospitalization is recommended during the initial evaluation because the differential diagnosis is complex and the risk of bleeding is significant. Management includes stopping of all nonessential drugs, particularly those that inhibit platelet function (e.g., aspirin). The initial treatment of chronic ITP is typically corticosteroids (prednisone 1 mg/kg per day). Intravenous immune globulin and anti-D immunoglobulin, in conjunction with steroids, have also been used as first-line therapy. However, these therapies are best used after consultation with a hematologist. Splenectomy, monoclonal antibody therapy, and immunosuppressives are considered in steroid-failure cases.[13] A thrombopoietin-receptor agonist, eltrombopag, has recently been shown in a well-designed trial to increase platelet counts in patients with relapsed or refractory ITP and thus might have a future role in treatment of these patients.[17] Platelet transfusions are used only to control life-threatening bleeding because of increased antiplatelet antibody titers and short-lived hemostatic effect. Although it is rare, life-threatening bleeding is treated with platelet transfusions, intravenous immune globulin (0.7 g/kg), and methylprednisolone (15 mg/kg intravenously).[13] A systematic review of recombinant factor VIIa used in ITP showed that the agent helped stop bleeding, but there are concerns for thrombosis formation.[18]

A similar pattern of thrombocytopenic purpura has been reported in sexually active homosexual men. Although the clinical findings and response to therapy mimic those of ITP, the mechanism is believed to be nonspecific deposition of immune complexes and complement rather than antiplatelet IgG.[19]

Nonimmune Thrombocytopenia. Nonimmune platelet destruction is usually consumptive or mechanical. Consumption occurs as part of the process of intravascular coagulation, although it may be seen at sites of significant endothelial loss. Thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome, and vasculitis all initiate platelet destruction through endothelial damage.[20] The most striking difference between the first two is the age at onset and the prognosis.

Thrombotic Thrombocytopenic Purpura. The pathologic state of TTP is the result of subendothelial and intraluminal deposits of fibrin and platelet aggregates in capillaries and arterioles. Hemolytic-uremic syndrome is considered to be similar to TTP; however, hemolytic-uremic syndrome is associated with less central nervous system and more renal involvement than TTP is. Although the initiating event is unclear, prostacyclin and abnormal platelet aggregation are believed to play a central role in pathogenesis of the disease. The disease may affect patients of any age or sex, but the majority are 10 to 40 years of age, and 60% of cases occur in women. Most cases of TTP are idiopathic. However, TTP can be associated with medications. Quinine is the most common drug associated with the disease. The antiplatelet drugs ticlopidine and clopidogrel, which are used to treat a variety of cardiovascular and cerebrovascular disorders, have also been associated with TTP. It is classically seen as the constellation of thrombocytopenic purpura, microangiopathic hemolytic anemia, fluctuating neurologic symptoms, renal disease, and fever. However, the classic pentad is not commonly seen, and the diagnosis is currently considered for unexplained thrombocytopenia in association with microangiopathic hemolytic anemia.[20]

The platelet count in TTP ranges from 10,000/mm^3 to 50,000/mm^3, and generalized purpura and bleeding complaints are common. Anemia is universal, and hematocrit levels are commonly less than 20%. The hemolysis may cause jaundice or pallor, and the blood smear characteristically contains numerous schistocytes and fragmented RBCs. Neurologic symptoms include stroke, seizures, paresthesias, altered levels of consciousness, and coma, all of which characteristically fluctuate in severity. The renal component varies from hematuria and proteinuria to acute renal failure. Fever is present in 90% of patients.

Before the availability of plasma exchange, TTP followed a progressive and fatal course, with 90% mortality rate 1 to 3 months after diagnosis. Therapy has included corticosteroids, splenectomy, anticoagulation, exchange transfusion, and dextran. However, plasma exchange with fresh frozen plasma (plasmapheresis) is the current treatment of choice and has reduced the mortality to below 20%.[21] In addition to plasma exchange, initial therapy may also include steroids, such as prednisone, and antiplatelet agents, such as aspirin and dipyridamole. If TTP is suspected in the ED, a hematologist should be consulted before any therapy is initiated. With the exception of life-threatening bleeding, platelet transfusion is avoided because platelets may cause additional thrombi in the microcirculation.[21,22]

Dilutional Thrombocytopenia. Dilutional thrombocytopenia occurs in cases of massive transfusion, exchange transfusion, or extracorporeal circulation. Volume replacement with stored bank blood is platelet poor because platelets have a life span of only 9 days. The number of transfusions directly correlates with the degree of thrombocytopenia. Current transfusion practice is to monitor platelet counts for every 10 units of RBCs and to transfuse once the platelet count approaches 50,000/mm^3.[23,24]

Thrombocytopathy

Knowledge of abnormal platelet function as a clinical disorder has grown rapidly in recent years. The drug-induced form may be one of the most commonly seen causes of abnormal bleeding.[14] Defects may occur at any level of platelet function, including adhesion, release, and aggregation.

Adhesion Defects. The representative adhesion disorder is von Willebrand's disease, which is a factor VIII problem more than a platelet deficiency. Platelets are normal in terms of their morphologic condition, number, release, and aggregation. The abnormal adhesion results not from the platelet but from an endothelium-based plasma deficiency of a factor VIII component (vWF) that permits platelet adhesion.[25]

Release Defects. Release defects include "storage pool" syndromes in which release is normal but amounts of adenosine

www.ketabpezeshki.com 66485457-66963820

diphosphate, calcium, and serotonin are decreased. Release defects may be congenital or acquired, as in systemic lupus erythematosus, alcoholism, or lymphoma. Drugs induce the most common release problem. Aspirin and related drugs block the enzyme cyclooxygenase, which participates in thromboxane A_2 formation. Decreased release of thromboxane A_2 results in decreased aggregation and less local vasoconstriction. Both may contribute to an increased risk of bleeding. Testing for this risk has been suggested by development of the post-aspirin bleeding time as a screening test for hemostatic disorders. Aspirin is unique in that it permanently poisons this reaction for the life of the platelet in doses of only 300 to 600 mg. Phenylbutazone and indomethacin affect function only while they are present in the circulation. A similar problem may occur in patients with uremia or dysproteinemia and as a rare inherited form.

Aggregation Defects. Primary aggregation defects are associated with the rare recessive trait thrombasthenia. This platelet membrane abnormality may be detected by the lack of clot retraction during a 2-hour clot retraction test.

Platelet Transfusions. Most platelet function disorders are not treated by platelet transfusion because its efficacy is questionable and alloimmunization may occur. Platelet transfusions are commonly indicated for primary bone marrow disorders (e.g., aplastic anemia or acute leukemia). Assessment of the risk for spontaneous bleeding by platelet counts is an imprecise science. Less mature platelets associated with peripheral consumption or sequestration are less likely to allow spontaneous hemorrhage than are those associated with primary bone marrow involvement. An estimate of functionality is combined with the platelet count for a better predictor of primary hemostasis potential. At counts below 40,000 to 50,000/mm^3, a variable degree of risk exists, especially that associated with trauma, ulcers, or invasive procedures. At counts higher than 50,000/mm^3, hemorrhage caused by platelet deficiency is unlikely. Spontaneous bleeding in the absence of surgery, trauma, or other risk factors may occur in patients with platelet counts below 5000 to 10,000/mm^3, and prophylactic platelet infusions should be reserved for this level of thrombocytopenia.[26]

Thrombocytosis

Thrombocytosis is a platelet count higher than 600,000/mm^3; Box 122-6 presents the list of potential causes. It is often caused by infection or iron deficiency, in which case it is not generally associated with complications related to the platelet count.[27] The primary or autonomous state may be associated with bleeding or thrombosis. It is often an associated finding in patients with polycythemia vera, myelofibrosis, or chronic myelogenous leukemia. Suggested autonomous thrombocytosis requires a full hematologic evaluation.

Disorders of the Coagulation Pathway

The coagulation system accomplishes secondary hemostasis through a complex enzymatic cascade. The clinically significant disorders have a number of characteristic features that help differentiate them from platelet disorders, including the following:

- The bleeding source is often an intramuscular or deep soft tissue hematoma from small arterioles.
- The congenital form of the disease occurs predominantly in men, often as a sex-linked inheritance.
- Bleeding may occur after surgery or trauma but is delayed in onset up to 72 hours.
- Epistaxis, menorrhagia, and gastrointestinal sources of bleeding are rare, whereas hematuria and hemarthrosis are common in severe cases.
- The bleeding time is normal except in patients with von Willebrand's disease.

The PT and PTT are the basic laboratory diagnostic tools for the evaluation of coagulation disorders and can be used to organize the approach to their diagnosis.

Abnormal Prothrombin Time and Other Test Results Normal

An elevated PT reflects an extrinsic pathway abnormality mediated through deficiency of factor VII. The hereditary form is caused by a rare autosomal recessive gene. The acquired form is commonly seen and may be a result of vitamin K deficiency, warfarin use, or liver disease. Because factor VII has the shortest half-life (3-5 hours) of the coagulation factors, it is the first to manifest a deficiency when its active form is underproduced. The PT is a sensitive gauge of hepatic function and the efficacy of warfarin administration. INRs calculate the prothrombin ratio raised to the power of an international sensitivity index for specific thromboplastin reagents. It is recommended with most warfarin therapy that the INR be maintained between 2.0 and 3.0, except in the setting of cardiac valvular disease, in which the target INR is 2.5 to 3.5.

Abnormal Partial Thromboplastin Time and Other Test Results Normal

Two groups of inherited disorders manifest an isolated elevation in the PTT. The first group consists of the contact factors (e.g., XII [Hageman factor]), prekallikrein (Fletcher factor), and high-molecular-weight kininogen. They cause a benign disorder in which the PTT is elevated but the patient has no bleeding diathesis. These deficiencies exist as isolated laboratory abnormalities, and thus they should not be invoked as a cause of the patient's bleeding problem. They may be specifically assayed when a precise diagnosis is necessary.

The second group causes significant bleeding problems resulting from deficiencies of factors within the intrinsic coagulation system. They are the most common inherited abnormalities of the entire clotting system. Deficiencies of factors VIII, IX, and XI account for 99% of inherited bleeding disorders. Patients with active life-threatening bleeding who are thought to have a congenital bleeding disorder can be supported with fresh frozen plasma, 15 mL/kg, while diagnostic studies are being performed. The risk of transmission of hepatitis B or C virus or human immunodeficiency virus (HIV) should be considered.

In a patient with a prolonged PTT and a lifelong history of bleeding, the most important test is assay of factor VIII and factor IX. This test measures the ability of the patient's plasma to correct the prolonged PTT of plasma deficient in factor VIII. This ability is compared with that of normal plasma, and the result is given as a percentage of normal. The test measures the procoagulant activity of factor VIII but does not discriminate between abnormal activity resulting from abnormal factor VIII and low levels of normal factor VIII. The two forms of this deficiency are hemophilia A and von Willebrand's disease.

Hemophilia A. Hemophilia A is caused by a variant form of factor VIII that is present in normal levels but lacks a clot-promoting property. The incidence is 60 to 80 persons per million population. Of known cases, 70% have been found to have a sex-linked recessive nature; that is, the disease is carried on the X chromosome at location Xq28. Factor VIII circulates in plasma in very low concentration and is normally bound to vWF. The source of factor VIII production is uncertain, but the liver is thought to be a significant source because hemophilia A can be corrected by liver transplantation. A female carrier mating with a normal man is predicted to pass the disease to half her sons. Likewise, a male hemophiliac would have all normal sons and all carrier daughters. The remaining 25 to 30% of cases of the disease are believed to

www.ketabpezeshki.com 66485457-66963820

result from a spontaneous genetic abnormality. The familial form has a remarkable consistency of severity from generation to generation, although the degree of severity has considerable variation. This severity may be directly related to the level of factor VIII coagulant (factor VIII:C) activity. Cases with less than 1% activity are severe, with a tendency toward spontaneous bleeding. Cases with 1 to 5% activity are moderate, with rare spontaneous bleeding but increased problems with surgery or trauma. Cases with 5 to 10% activity and above are considered mild, with little risk of spontaneous bleeding but still with hazards after trauma and surgery. A number of hemophiliacs may have activity above 10% but have few problems under normal conditions. The PTT may lack sensitivity for this group because it is significantly prolonged only at factor VIII:C levels less than 35 to 40%.[28,29]

The disease is seen as a disorder of secondary hemostasis with a characteristic pattern of bleeding. Bleeding can occur anywhere, but deep muscles, joints, the urinary tract, and intracranial sites are the most common. Recurrent hemarthrosis and progressive joint destruction are major causes of morbidity in hemophilia. Intracranial bleeding is the major cause of death in all age groups of hemophiliacs. Mucosal bleeding, such as epistaxis and oral bleeding, or menorrhagia is rare unless the disease is associated with von Willebrand's disease or platelet inhibition, such as with aspirin use. Gastrointestinal bleeding is rare unless peptic ulcer disease is also present. Trauma is a common initiator of bleeding in all stages of severity. This potential hazard should be viewed expectantly in all hemophiliacs because late bleeding may occur, usually by 8 hours but potentially up to 1 to 5 days and, rarely, even longer after traumatic injury.[30,31]

Management of Hemophilia A. Comprehensive management of hemophilia involves a team effort of physicians, specialized nurses, physical therapists, social workers, the patient, and the patient's family. The therapeutic responsibility of the emergency physician consists of three areas: preparation for and identification of the problem, initial evaluation, and admission of new bleeders; replacement therapy for bleeding episodes; and anticipation of potential life threats and admission of known bleeders for observation in selected circumstances. At one time, treatment of hemophilia-associated bleeding was a relatively common emergency medicine activity, but since 1975, hemophilia home therapy has increasingly been instituted. Therefore, many hemophiliacs now come to the ED only with complicated problems or trauma-related difficulties, and most are knowledgeable about their disease.

Preparation. ED management of patients with hemophilia is best accomplished with advanced planning that includes protocols developed with a hematologist for ordering and administration of factor VIII and maintenance of a file of known hemophiliacs in the area who are monitored at the hospital. The file should include the primary physician, diagnosis, factor VIII activity level, blood type, presence of antihemophilic factor antibodies, and time of last hospitalization.

Replacement Therapy. The accepted therapy for hemophilia A is factor VIII replacement with cryoprecipitate or factor VIII:C concentrates. These concentrates are exposed to heat treatment or solvent-detergent mixtures to decrease transmission of hepatitis B virus, hepatitis C virus, and HIV. In the past, the concentrate was made from fractionated freeze-dried antihemophilic factor and contained 250 to 1500 IU of factor VIII:C in a reconstituted volume. Factor VIII is also produced by recombinant DNA techniques and is considered to be the replacement product of choice.[32,33] Recombinant-derived factor VIII is comparable to plasma-derived factor VIII in terms of characteristics and control of bleeding, but it has no discernible side effects. Factor VIII:C concentrates are commonly used in severe hemophilia and for home therapy. Cryoprecipitate is the cold precipitable protein fraction derived from fresh frozen plasma thawed at 1 to 6°C. It was once the mainstay of hemophilia A therapy and may be used when noninfectious factor VIII concentrates are not available.[31]

Before 1985, plasma-derived replacement therapies posed risk for transmission of hepatitis C virus, hepatitis B virus, and HIV. However, with the current methods of donor screening, antiviral techniques, and safety testing and with the availability of recombinant clotting factors, the risk of viral transmission is extremely low.[34]

Therapy for a bleeding episode includes a number of considerations: the circumstances in which factor VIII is given, the dosage, the timing of maintenance, the duration of the dosage, the presence of antibodies, and the means of gauging effectiveness. As a general rule, 1 U/kg of factor VIII will increase the circulating factor VIII level by 2%. The dose of factor VIII needed is the desired percentage increase in factor VIII activity × 0.5 × the weight in kilograms. The typical percentage factor VIII activity goals are 25 to 40% for minor bleeding or trauma, greater than 50% for moderate bleeding, and 80 to 100% for serious, life-threatening bleeding or trauma.[35] Tables 122-1 and 122-2 include guidelines for the recommended treatment in a variety of circumstances. Most important, the emergency physician should believe patients who say that they are bleeding and institute early therapy.

The response to therapy can be monitored by clinical improvement, a decreasing PTT, and, optimally, serial factor VIII:C activity levels. The lack of a response to factor VIII administration should raise the possibility of circulating antibodies. All hemophiliacs should be screened for the development of these antihemophilic factor antibodies when they are given in-hospital therapy or if their condition becomes refractory to home therapy. The 7 to 20% of patients in whom these IgG antibodies develop usually have a severe deficiency necessitating multiple factor VIII transfusions. The treatment may be complex, and hospitalization is necessary. A variety of therapies have been considered, including "overwhelming" factor VIII doses, exchange plasmapheresis, immunosuppressive therapy, and the infusion of prothrombin complexes containing activated clotting factors. Other recommended therapies include porcine factor VIII, which has less cross-reactivity with the human product, and recombinant activated factor VIIa.[36,37] Recombinant factor VIIa used in hemophilia complicated by alloantibody inhibitors has been shown to stop bleeding in 93% of cases.[38] Serious or intractable bleeding may be improved in some nonhemophiliac patients with the use of recombinant factor VIIa. However, no improvement in survival has been proved, and the incidence of thromboembolism may be increased.[39] Until more data are available, the role of recombinant factor VIIa in settings outside of congenital coagulation disorders remains to be determined. Acquired IgG antihemophilic factor antibodies may exist in nonhemophiliac patients. They can occur in the postpartum period; as immunologic reactions to penicillin or phenytoin; and in association with systemic lupus erythematosus, rheumatoid arthritis, or inflammatory bowel disease. The diagnosis is made by the occurrence of an acquired hemophilia-like syndrome with positive antibody titers in the appropriate setting.

Desmopressin acetate has been shown to increase levels of factors VIII:C and VIII:Ag in patients with hemophilia A and in some with von Willebrand's disease. It is given intravenously at 0.3 µg/kg per dose. Benefits are primarily noted in patients with mild to moderate disease, and the effects of a single dose last for 4 to 6 hours.[40] Use of desmopressin in the ED is probably best reserved for patients who have been successfully treated with it in the past.

Prophylaxis. The anticipation of delayed bleeding in patients with hemophilia may necessitate admission and observation for a variety of trauma-related injuries. Candidates for prophylactic admission are patients with deep lacerations; those with soft tissue injuries in areas where the pressure from a developing hematoma could be destructive, such as in the eye, mouth, neck, back, and

www.ketabpezeshki.com 66485457-66963820

Table 122-1 Recommended Factor VIII Therapy for Specific Problems in Hemophilia

TYPE OF BLEEDING	INITIAL DOSAGE	DURATION	COMMENT
Skin			
Abrasion	None	None	Treat with local pressure and topical thrombin
Laceration			
Superficial	Usually none; if necessary, treat as minor	None	Local pressure and anesthetic with epinephrine may benefit; watch 4 hours after suturing; reexamine in 24 hours
Deep	Minor bleeding (25 mg/kg)	Single-dose coverage	May need hospitalization for observation; repeated dose may be necessary for suture removal
Nasal epistaxis			
Spontaneous	Usually none; may need to be treated as mild bleeding	None	Uncommon; consider platelet inhibition; treat in usual manner
Traumatic	Moderate bleeding (25 mg/kg)	Up to 5-7 days	Trauma-related bleeding can be significant
Oral			
Mucosa or tongue bites	Usually none; treat as minor if persists	Single dose	Commonly seen
Traumatic (laceration) or dental extraction	Moderate (25 U/kg) to severe (50 U/kg)	Single dose; may need more	Saliva rich in fibrin lytic activity; oral ε-aminocaproic acid (Amicar) may be given at 100 mg every 6 hr for 7 days to block fibrinolysis; check contraindications; hospitalize patients with severe bleeding
Soft tissue or muscle hematomas	Moderate (25 U/kg) to severe (50 U/kg)	2-5 days	May be complicated by local pressure on nerves or vessels (e.g., iliopsoas, forearm, calf)
Hemarthrosis			
Early	Mild (25 mg/kg)	Single dose	Treat at earliest symptom (pain); knee, elbow, ankle more common
Late or unresponsive cases of early hemarthrosis	Mild to moderate (25 U/kg)	3-4 days	Arthrocentesis rarely necessary and only with 50% level coverage; immobilization is critical point of therapy
Hematuria	Mild (12.5 U/kg)	2-3 days	Urokinase, the fibrinolytic enzyme, is in urine; with persistent hematuria, an organic cause should be ruled out
Major or life-threatening bleeding	Major bleeding (50 U/kg)	7-10 days or 3-5 days after bleeding ceases	In head trauma, therapy should be given prophylactically; early computed tomography scan of head is recommended for all

Table 122-2 Dosage of Factor VIII (Antihemophilic Factor)

BLEEDING RISK	DESIRED FACTOR VIII LEVEL (%)	INITIAL DOSE (U/kg)
Mild	5-10	12.5
Moderate	20-30	25
Severe	50 or greater	50

Standard Calculation

1. Patient's plasma volume (50 mL/kg × weight in kg) × (desired level of factor VIII [percent]) – (present level of factor VIII [percent]) = number of units for initial dose.
2. In emergency therapy, the present level of factor VIII is assumed to be zero.
3. One unit is the activity of the coagulation factor present in 1 mL of normal human plasma.
4. Because the half-life of factor VIII is 8 to 12 hours, the desired level is maintained by giving half the initial dose every 8 to 12 hours.
5. Cryoprecipitate is assumed to have 80 to 100 U of factor VIII:C per bag; factor VIII:C concentrates list the units per bottle on the label.

spinal column; and patients with a history of major trauma forces without injury. Head trauma is potentially life-threatening to hemophiliacs, and central nervous system bleeding is the major cause of death for patients in all age groups. Studies find a 3 to 13% risk of intracranial hemorrhage; in a prospectively studied cohort of 37 patients with severe disease who sustained head trauma, no patient given replacement therapy within 6 hours had intracranial bleeding.[41] It is recommended that patients who sustain head trauma but who have normal computed tomography scans have factor VIII therapy initiated to greater than 50% activity level.[42] All hemophiliacs with head trauma should be considered for admission with early hematology consultation.

Gene therapy represents a potential development in the treatment of hemophilia. With cloning of the genes encoding factor VIII, the possibility exists for either a partial or complete cure of hemophilia. The goal of gene therapy is not to restore factor levels to normal but rather to convert from a severe to a mild phenotype and dramatically improve clinical outcomes. Early studies are encouraging. Although genetic testing and counseling are currently available, no genetic therapies for hemophilia A are available at present.[43]

von Willebrand's Disease. To understand von Willebrand's disease, it is helpful to review the nomenclature used to refer to factor VIII in some centers. Factor VIII has at least three activities. First is its antihemophilic, or coagulant, activity, VIII:C. All references to factor VIII in this chapter thus far have been to this activity. A second activity supports platelet adhesion and in vitro aggregation with the antibiotic ristocetin; it is called von Willebrand's factor activity, or VIII/vWF. A third component reacts with rabbit antibodies to factor VIII; it is termed the factor VIII antigen, or VIII:Ag, and relates to the measured plasma level rather than to the activity of factor VIII. The antigen and cofactor activity for platelet function are structurally related.[25] von Willebrand's disease has both decreased factor VIII:Ag levels and decreased VIII:C activity secondary to underproduction. The patient's platelets are normal in number, morphologic condition, and other functions, but in the absence of circulating factor VIII/vWF,

www.ketabpezeshki.com 66485457-66963820

their adhering properties are diminished. von Willebrand's disease is the most common hereditary bleeding disorder, with an estimated prevalence of 1%. The disease occurs in 5 to 10 persons per million population as an autosomal dominant trait with a variable penetrance pattern. A rare X-linked inheritance has been described.[44]

Manifestations of von Willebrand's disease are usually milder and less crippling than those of hemophilia. The factor VIII:C level is in the 6 to 50% range. Bleeding sites are predominantly mucosal (e.g., epistaxis) and cutaneous. Hemarthroses are rare, but menorrhagia and gastrointestinal bleeding are common. Laboratory differentiation from hemophilia A includes abnormal bleeding time, decreased level of factor VIII:Ag, and abnormal platelet aggregation with ristocetin.[25] In patients with severe disease, replacement therapy with factor VIII in the form of intermediate purity factor VIII concentrate is the method of choice. The initial dose is 25 to 50 IU/kg every 12 hours to keep vWF levels at 50% or to control bleeding. A unique response to the transfusion of plasma components in patients with von Willebrand's disease is the stimulation of a progressive increase in VIII:C activity that lasts 12 to 40 hours. After the initial dose, fewer units are necessary, and longer dosage schedules may be followed by a clinical response and a combination of factor VIII:C activity and serial bleeding times. Cryoprecipitate is no longer recommended because of the risk of viral transmission.

In extreme circumstances without alternatives, fresh frozen plasma may be used. A factor VIII concentrate (Humate-P) has also demonstrated sufficient VIII/vWF to treat the disease.[45] Drug therapy with desmopressin is of benefit in patients with mild to moderately severe von Willebrand's disease. It is most useful in the common form of the disease and is ideally given in consultation with a hematologist.[46]

Hemophilia B (Christmas Disease). Hemophilia B is a deficiency of factor IX activity. Its genetic pattern and clinical findings are indistinguishable from those of hemophilia A, but its incidence is only a fifth that of hemophilia A. Factor IX is a vitamin K–dependent glycoprotein. Its deficiency is diagnosed by a factor IX assay, usually after the factor VIII:C assay is found to be normal. The replacement schedule for factor IX is similar to that for hemophilia A, but a purified factor IX concentrate or recombinant factor IX preparation is used. The plasma prothrombin complex (factors II, VII, IX, and X) and fresh frozen plasma are also useful, but they pose a higher risk of viral transmission and venous or arterial thrombosis. The maintenance dosage schedule is increased to every 24 hours because of the longer half-life of factor IX. Clinical concerns and treatment strategies associated with hemophilia A also apply to hemophilia B.[47]

Similar to hemophilia A, gene testing and counseling are available. Gene therapy in animals has demonstrated promising results, and preliminary results from a human study suggest that the severity of hemophilia B can be altered and improved by gene manipulation.[48]

Miscellaneous Coagulation Disorders

A number of other disorders may be caused by a deficiency in the common coagulation pathway. An altered fibrinogen level or abnormal function is a relatively common cause. Patients with this deficiency also have an abnormal thrombin time. The inherited forms are rare. The acquired forms have been related to fibrin-blocking substances and hypofibrinogenemia, which are found most often in cases of DIC and dysfibrinogenemia associated with macroglobulinemia, multiple myeloma, and hepatoma. In the context of emergency medicine, fibrinogen's most important role relates to its activity in DIC.

The other components of the common pathway (factors II, V, and X) have rare inherited deficiencies. The acquired forms are far more common and relate to vitamin K deficiency (decreased factor II, VII, IX, and X activity), warfarin use (same factors as with vitamin K deficiency), hepatic insufficiency (potentially all factors except VIII), and massive transfusion of stored blood (low in factors V and VIII and platelets).

Excessive anticoagulation from warfarin occurs from a number of causes, including interactions between warfarin and other drugs or foods and accompanying diseases that interfere with the absorption or metabolism of warfarin. Management of excessive anticoagulation from warfarin depends on the degree of elevation of the INR and if bleeding accompanies the excessive anticoagulated state. If the INR is below 5.0 and not accompanied with bleeding, treatment consists of withholding of additional warfarin. If the INR is between 5.0 and 9.0 without bleeding, in addition to withholding of additional warfarin, 1.0 to 2.5 mg of oral vitamin K therapy is recommended. Patients presenting with an INR above 9.0 but not bleeding are treated with 5 mg of oral vitamin K. Patients presenting with an elevated INR and bleeding require 10 mg of vitamin K and the administration of fresh frozen plasma.[49] Vitamin K can be administered orally, intravenously, or subcutaneously. A meta-analysis demonstrated that oral dosing is superior to other routes of administration and that subcutaneous dosing is the least desirable method of administration.[50] In cases of excessive anticoagulation with warfarin that is accompanied by serious or life-threatening bleeding, vitamin K is often administered intravenously. Vitamin K given intravenously should be administered as an infusion during 20 to 30 minutes and not given as a bolus injection.[51]

Bleeding from heparin therapy is less of an issue in the ED but still can be a problem. In addition to discontinuation of the heparin, the administration of protamine sulfate can urgently reverse the effects of heparin. The full neutralizing effect of unfractionated heparin is achieved with 1 mg of protamine for every 100 units of heparin. Protamine can also be used to reverse the effects of low-molecular-weight heparin; however, it does not completely abolish the anticoagulant effects as it does with unfractionated heparin. When it is used for bleeding caused by low-molecular-weight heparin, the dose of protamine is 1 mg for every 1 mg of low-molecular-weight heparin. Because rapid injection of protamine results in hypotension, the recommended rate of administration is no more than 50 mg during 10 minutes.[52] Recombinant factor VIIa may be considered in resistant forms of bleeding from anticoagulation; however, it is not a substitute for vitamin K, protamine, or blood product transfusions.[53]

Disseminated Intravascular Coagulation. DIC is a relatively common acquired coagulopathy. Its ubiquitous nature, multiple origins, and potentially devastating sequelae, balanced by an effective mode of therapy, make early diagnosis of this hematologic process critical. It is most often encountered in the critical care setting. Hemostasis is achieved by a fine balance between procoagulants and inhibitors and thrombus formation and lysis. The balance may be disturbed by pathologic processes that result in an out-of-control coagulation and fibrinolytic cascade within the systemic circulation. The following occurs in this abnormal clotting sequence:

Platelets and coagulation factors are consumed, especially fibrinogen and factors V, VIII, and XIII.
Thrombin is formed, and it overwhelms its inhibitor system and acts to accelerate the coagulation process and directly activate fibrinogen.
Fibrin is deposited in small vessels in multiple organs.
The fibrinolytic system by means of plasmin may lyse fibrin and impair thrombin formation.
Fibrin degradation products are released and affect platelet function and inhibit fibrin polymerization.
Coagulation inhibition levels (e.g., antithrombin III, protein C, and tissue factor pathway inhibitor) are decreased.

www.ketabpezeshki.com 66485457-66963820

Table 122-3 Laboratory Diagnosis of Disseminated Intravascular Coagulation

TEST	FINDING	PATHOPHYSIOLOGY
Peripheral smear	Low platelets, schistocytes, red blood cell fragments	Red blood cell fragmentation on fibrin strands; schistocytes not always seen
Platelet count	Low (usually <100,000/mm^3)	Consumed in clotting; lower numbers are reflected in the bleeding time
Prothrombin time	Prolonged	Factors II and IV consumed
Partial thromboplastin time	Prolonged	Factors II, V, and VIII consumed
Thrombin time	Prolonged	Decrease in factor II and fibrin degradation products
Fibrinogen level	Low	Factor II consumed; may be difficult to interpret because it is an acute-phase reactant
Fibrin degradation products (D-dimer)	Zero to large	Dependent on the amount of secondary fibrinolysis
Serum creatinine or urinalysis	May be abnormal	Functional assessment of the organ most commonly injured by fibrin deposition

The clinical consequence of these processes is the life-threatening combination of a bleeding diathesis from loss of platelets and clotting factors, fibrinolysis, and fibrin degradation product interference; small-vessel obstruction and tissue ischemia from fibrin deposition; and RBC injury and anemia from fibrin deposition. The condition needs to be considered in any patient in whom purpura, a bleeding tendency, and signs of organ injury, particularly of the central nervous system and kidney, develop. This broad description is further confused clinically by the variable acuteness and intensity of intravascular clotting, the effectiveness of fibrinolysis, and other systemic manifestations of the initiating disease.[54] The clinical diagnosis of DIC is confirmed by laboratory tests (Table 122-3).

Two conditions that may simulate DIC are severe liver disease and primary fibrinolysis. Liver disease of this severity is usually manifested by clinical jaundice and splenomegaly. Primary fibrinolysis is a rare disorder that affects fibrinogen and fibrin but generally leaves the coagulation components (platelets, factor V, and factor VIII) in the low-normal range. Additional laboratory tests can be used to confirm the diagnosis of primary fibrinolysis, but these are not typical tests obtained in the ED and are best ordered in conjunction with a hematologist.[54]

When planning therapy, the emergency physician needs to remember that DIC is secondary to a serious underlying pathologic process. Once the diagnosis is confirmed, the initial treatment is focused on reversal of the triggering mechanism. Many episodes of DIC are self-limited, such as in a transfusion reaction, or compensated, such as in association with a tumor mass, and do not require intervention other than support.

Replacement therapy is usually instituted simultaneously with attempts to control the primary process. The goal is to avoid depletion of clotting factors. Treatment is partially based on which of the two major pathologic components of DIC dominates the clinical picture. If active bleeding is present, replacement therapy with platelets, fresh frozen plasma, and cryoprecipitate (I, V, VIII) is recommended. Selective replacement therapy can be based on the laboratory and clinical response. Retardation of bleeding, a decrease in fibrin degradation products, and a rise in platelet counts and fibrinogen levels are useful monitors. Normalization of clotting times occurs too late to be of value in monitoring.

Heparin has selective use in the treatment of DIC when fibrin deposition and thrombosis dominate the pathologic picture. Certain disease states are associated more with fibrin deposition, in which case heparin therapy should be considered. Examples include purpura fulminans, retained dead fetus before delivery, giant hemangioma, and acute promyelocytic leukemia. Heparin therapy is of little benefit in cases of meningococcemia, abruptio placentae, severe liver disease, and trauma. Low doses of heparin (300-500 units/hr) as a continuous infusion are currently recommended.[54] Low-molecular-weight heparin may also be used instead of unfractionated heparin. Continuous monitoring of the clinical response, heparin levels, and bleeding status is necessary.

Other therapeutic agents, such as antithrombin III and activated protein C, have been evaluated. However, none has demonstrated an improved outcome in DIC, and only recombinant activated protein C (drotrecogin alfa) has been associated with improved outcomes in septic shock, regardless of whether DIC was present.[55]

The goals of emergency care of patients with DIC include initial recognition, aggressive pursuit of the diagnosis, understanding of potential life-threatening complications, and only rarely initiation of therapy.

DISPOSITION

All patients with bleeding disorders of unknown cause or of a significant degree should be admitted to the hospital for further evaluation. The circumstances in which a patient with a known bleeding disorder may be discharged for home care are discussed in earlier sections on individual disease states. Transfer of these patients may be necessary, particularly if hematologic consultation is not readily available. The standard criteria of hemodynamic stability, appropriate monitoring, and full knowledge and understanding on the part of the family and accepting physician should be met before transfer. Because of the delayed bleeding pattern in hemophiliacs, it may be especially hazardous to transfer them long distances. Therefore, the importance of advance knowledge and preparation is reemphasized. Outpatients are usually treated under the auspices of the hematologic consultant. Early notification and appropriate follow-up arrangements should be made with these specialists.

KEY CONCEPTS

- Although hemostatic disorders are confirmed by specific patterns of laboratory test results, a careful history and focused physical examination are often the key to the diagnosis of hematologic diseases.
- The frequency of hemostatic disorders seen in the ED is unknown; however, they are likely to be more common than thought. Although classic diseases such as hemophilia and DIC are uncommon, the use of antiplatelet and anticoagulation agents is common in other disease states, such as cardiovascular diseases.
- Hemophilia patients are often highly informed about their disease. Patient input should be solicited and respected, and early consultation with the patient's hematologist is encouraged. Early treatment with replacement factor while diagnostic testing proceeds is encouraged.
- Platelet dysfunction is often equated with low platelet counts. Even though critical thrombocytopenia increases the risk of bleeding, particularly with trauma and surgery, dysfunction can occur at normal platelet counts. For example, antiplatelet therapy and renal disease can alter platelet function without reducing blood counts.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Jackson SP: The growing complexity of platelet aggregation. *Blood* 2007; 109:5087.
2. Smyth SS, et al: Platelet functions beyond hemostasis. *J Thromb Haemost* 2009; 7:1759.
3. Furie B, Furie BC: Mechanisms of thrombus formation. *N Engl J Med* 2008; 359:938.
4. Bain BJ: Diagnosis from blood smear. *N Engl J Med* 2005; 353:498.
5. Nachman RL, Rafi S: Platelets, petechiae, and preservation of the vascular wall. *N Engl J Med* 2008; 359:1261.
6. Alexandrescu DT, Gallo RL: *The vascular purpuras*. In: Kaushansky K, et al, eds. *Williams Hematology*, 8th ed. New York: McGraw-Hill; 2010.
7. Smythe MA, Koerber JM, Mattson JC: The incidence of recognized heparin-induced thrombocytopenia in a large, tertiary care teaching hospital. *Chest* 2007; 131:1644.
8. Shantsila E, Lip GY, Chong BH: Heparin-induced thrombocytopenia. A contemporary clinical approach to diagnosis and management. *Chest* 2009; 135:1651.
9. Martel N, Lee J, Wells PS: Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: A meta-analysis. *Blood* 2005; 106:2710.
10. Rice L, Attisha WK, Drexler A, Francis JL: Delayed-onset heparin-induced thrombocytopenia. *Ann Intern Med* 2002; 136:210.
11. Burdy MJ, Martin SE: Cocaine-associated thrombocytopenia. *Am J Med* 1992; 91:656.
12. Aster RH: Immune thrombocytopenia caused by glycoprotein IIb/IIIa inhibitors. *Chest* 2005; 127(Suppl 2):53S.
13. Neunert C, et al: The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 2011; 117:4190.
14. Aster RH, Bougie DW: Drug-induced immune thrombocytopenia. *N Engl J Med* 2007; 357:580.
15. Shtalrid M, et al: Post-transfusion purpura: A challenging diagnosis. *Isr Med Assoc J* 2006; 8:672.
16. Provan D, et al: International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010; 115:168.
17. Cheng G, et al: Eltrombopag for management of chronic immune thrombocytopenia (RAISE): A 6-month, randomized, phase 3 study. *Lancet* 2011; 377:393.
18. Salama A, Rieke M, Kiesewetter H, von Depka M: Experience with recombinant FVIIa in the emergency treatment of patients with autoimmune thrombocytopenia: A review of the literature. *Ann Hematol* 2009; 88:11.
19. Walsh C, et al: Thrombocytopenia in homosexual patients. *Ann Intern Med* 1985; 103:542.
20. George J: Clinical practice. Thrombotic thrombocytopenic purpura. *N Engl J Med* 2006; 354:1927
21. George J: How I treat patients with thrombotic thrombocytopenic purpura: 2010. *Blood* 2010; 116:4060.
22. Hirsh J, Guyatt G, Albers GW, Harrington R, Schünemann HJ: Antithrombotic and thrombolytic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133(Suppl):110S-112S.
23. Abrams CS, Shattil SJ, Bennett JS: *Acquired qualitative platelet disorders*. In: Kaushansky K, et al, eds. *Williams Hematology*, 8th ed. New York: McGraw-Hill; 2010.
24. Allford SL, Hunt BJ, Rose P, Machin SJ: Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anaemias. *Br J Haematol* 2003; 120:556.
25. Nichols WL, et al: von Willebrand Disease (vWD): Evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) expert panel report (USA). *Haemophilia* 2008; 14:171.
26. Schiffer CA, et al: Platelet transfusion for patients with cancer: Clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001; 19:1519.
27. Schafer AI: Thrombocytosis. *N Engl J Med* 2004; 350:1211.
28. White GC, et al: Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost* 2001; 85:560.
29. Franchini M, Favaloro EJ, Lippi G: Mild hemophilia A. *J Thromb Haemost* 2010; 8:421.
30. Mannucci PM, Tuddenham GD: The hemophiliac—from royal genes to gene therapy. *N Engl J Med* 2001; 344:1773.
31. Manco-Johnson MJ: Advances in the care and treatment of children with hemophilia. *Adv Pediatr* 2010; 57:287.
32. Bolton-Maggs PH: Optimal haemophilia care versus the reality. *Br J Haematol* 2006; 132:671.
33. Franchini M, Lippi G: Recombinant factor VIII concentrates. *Semin Thromb Hemost* 2010; 36:493.
34. Soucie JM, et al: Risk factors for infection with HBV and HCV in a large cohort of hemophiliac males. *Transfusion* 2001; 41:338.
35. Hoots WK: *Emergency management in hemophilia*. In: Lee CA, Berntorp EE, Hoots WK, eds. *Textbook of Hemophilia*, 2nd ed. Oxford, UK: Wiley-Blackwell; 2010.
36. Kempton CL, White GC: How we treat a hemophilia A patient with a factor VIII inhibitor. *Blood* 2009; 113:11.
37. Iorio A, et al: Recombinant factor VIIa concentrate versus plasma derived concentrates for the treatment of acute bleeding episodes in people with haemophilia and inhibitors. *Cochrane Database Syst Rev* 2010; 4:CD004449.
38. *Haemophilia*. 2011 Feb 7. doi:10.1111/j.1365-2516.2010.02483.x. [Epub ahead of print].
39. Yank V, et al: Systematic review: Benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. *Ann Intern Med* 2011; 154:529.
40. Franchini M, Zaffanello M, Lippi G: The use of desmopressin in mild hemophilia A. *Blood Coagul Fibrinolysis* 2010; 21:615.
41. Andes WA, Wulff K, Smith WB: Head trauma in hemophilia: A prospective study. *Arch Intern Med* 1984; 144:1981.
42. Witmer CM, et al: The clinical management of hemophilia and head trauma: A survey of current clinical practice among pediatric hematology/oncology physicians. *Pediatr Blood Cancer* 2009; 53:406.
43. Petrus I, Chuah M, VandenDriessche T: Gene therapy strategies for hemophilia: Benefits versus risks. *J Gene Med* 2010; 12:797.
44. Castaman G: von Willebrand's disease diagnosis and laboratory issues. *Haemophilia* 2010; 16(Suppl 5):67.
45. Mannucci PM: Treatment of von Willebrand's disease. *N Engl J Med* 2004; 351:683.
46. Singleton T, Kruse-Jarres R, Leissinger C: Emergency department care for patients with hemophilia and von Willebrand disease. *J Emerg Med* 2010; 39:158.
47. Morfini M, Laguna P, Leissinger C: Factor IX pharmacokinetics: Differences between plasma-derived and recombinant products and the clinical and economic implications: A meeting report. *Haemophilia* 2008; 14:873.
48. Fewell JG: Factor IX gene therapy for hemophilia. *Methods Mol Biol* 2008; 423:375.
49. Dentali F, Ageno W, Crowther M: Treatment of coumarin-associated coagulopathy: A systematic review and proposed treatment algorithms. *J Thromb Haemost* 2006; 4:1853.
50. Dezee KJ, Shimeall WT, Douglas KM, Shumway NM, O'Malley PG: Treatment of excessive anticoagulation with phytonadione (vitamin K): A meta-analysis. *Arch Intern Med* 2006; 166:391.
51. Ansell J, et al: Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133:160S.
52. Hirsh J, et al: Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133:141S.
53. Levi M, Bijsterveld NR, Keller TT: Recombinant factor VIIa as an antidote for anticoagulant treatment. *Semin Hematol* 2004; 41:65.
54. Levi M, et al: Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. *Br J Haematol* 2009; 145:24.
55. Toussaint S, Gerlach H: Activated protein C for sepsis. *N Engl J Med* 2009; 361:2646.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 123

Selected Oncologic Emergencies

Sandra S. Ugras-Rey

PERSPECTIVE

Oncologic emergencies embody an extensive range of illnesses that can occur at any time during the course of malignant disease. Some oncologic emergencies are insidious and develop during months; others are manifested in hours and can lead to paralysis and death.[1] Prompt, accurate diagnosis and appropriate treatment of oncologic emergencies can improve the quality of life dramatically in patients with cancer. With timely intervention, many of these patients can return to their previous level of function and independence. In addition, a reversible life-threatening emergency can occur in a patient with an underlying malignant neoplasm that is otherwise highly treatable or even curable, making identification and management of the oncologic emergency a potentially lifesaving action.

Cancer remains the second leading cause of death in the United States. It is estimated that 1,529,560 men and women (789,620 men and 739,940 women) will be diagnosed with and 569,490 men and women will die of cancer of all sites in 2010.[2] The most commonly diagnosed new cancer is prostate cancer in men and breast cancer in women. The second most commonly diagnosed new cancer in both sexes is lung cancer. The most common cause of cancer death for both sexes is lung and bronchial cancer.[3] Worldwide, the most commonly diagnosed new cancer and most common cause of cancer death is lung and bronchial cancer in men and breast cancer in women.[4] The most common malignant neoplasm of childhood is leukemia, followed by brain tumors and lymphoma.[5]

In 2003, it was estimated that the lifetime risk for development of cancer was 1:2 for men and 1:3 for women.[5] Most cancer patients will experience at least one emergency during the course of their disease, and emergency physicians are increasingly managing complications related to cancer, although definitive therapy for an oncologic emergency is often multidisciplinary, involving surgeons, radiation oncologists, medical oncologists, and other medical and social specialists. Changing trends in cancer have produced an increased number of emergency department (ED) visits secondary to cancer and its complications (Box 123-1).[6] In fact, a study reported that about 40% of cancer patients had visited the ED in the last 2 weeks of life.[7] Therefore, the emergency physician should be well versed in oncologic emergencies. However, many factors can hinder the identification and management of oncologic emergencies in the ED (Box 123-2). This chapter focuses on the most common oncologic emergencies: fever and neutropenia, superior vena cava syndrome, acute tumor lysis syndrome, hyperviscosity syndrome, hyperuricemia, hypercalcemia, neoplastic cardiac tamponade, and spinal cord compression.

FEVER

Fever is defined as a single oral temperature in excess of 38.3°C (101.3°F) or a sustained temperature of 38°C (100.4°F) for more than 1 hour.[8] Fever in the cancer patient can be caused by inflammation, transfusions, antineoplastics, antimicrobials, and tumor necrosis. Although fever can be secondary to malignant disease with a significant tumor burden, fever occurring in cancer patients more commonly has an infectious origin (55-70%). Neutropenia, defined as an absolute neutrophil count (ANC) of less than 500 cells/mm^3 or less than 1000 cells/mm^3 with predicted decrease to less than 500 cells/mm^3, will assist in determining the need for empirical antibiotics and a more aggressive approach to treatment of a febrile cancer patient.[9] ANC can be calculated from white blood cell (WBC) and polymorphonuclear (PMN) cell counts as follows:

$$\text{ANC} = \text{WBCs} + [(\text{PMNs}/100) + (\text{bands}/100)]$$

The risk of infection and morbidity are increased with an ANC of less than 1000/mm^3 and are substantially higher when counts are less than 100/mm^3. In addition to the ANC, the risk of infection is also increased with a more rapid rate of development and a longer duration of neutropenia.

Fever in the neutropenic cancer patient is one of the most common complications related to chemotherapy treatment. It should be presumed to have an infectious origin and thus constitutes a medical emergency. Use of early empirical antibiotic therapy has resulted in a decrease in mortality in patients receiving chemotherapy.[8]

Clinical Features

Because fever is often the first and occasionally the only sign of infection in the neutropenic cancer patient, a careful history and physical examination must be performed; this includes an evaluation of the fundi (looking for *Candida* endophthalmitis), rectum, perineum and groin (for perirectal abscess), skin and mucous membranes (for any lesions suggesting malignant disease or cellulitis), axillae, and catheters. The oral cavity and the perianal area are inspected, although digital rectal examination is discouraged in that it may induce bacteremia. Common infections may be manifested atypically because of lack of neutrophils. In the absence of polymorphonuclear cells, traditional markers of inflammation such as erythema, warmth, and pyuria may be absent or minimal, making it essential to search for subtle signs of inflammation. For example, skin infections may be manifested as a subtle rash or erythema, meningitis may be present without nuchal rigidity,

www.ketabpezeshki.com 66485457-66963820

Box 123-1 Changing Trends in Cancer That Have Produced an Increased Number of Emergency Department Visits Secondary to Cancer and Its Complications

More aggressive and broader use of chemotherapy regimens
Increasing use of bone marrow transplantation
More effective treatment options, increasing cure and survival rates
Increased number of elderly patients receiving chemotherapy
Increased survival for all cancers combined

Box 123-2 Factors That Can Hinder Identification and Management of Oncologic Emergencies

Patient or physician discomfort with the diagnosis of cancer
A voluminous and frequently changing database of chemotherapeutic agents and complex classification systems
Time constraints
Lack of privacy
Lack of an established physician-patient relationship
Inappropriate or premature labeling of the cancer patient as "terminal"
Failure to appreciate that effective treatments are available for oncologic emergencies and many of the cancers that cause them

Box 123-3 Current Recommendations for Antimicrobial Therapy for Fever in Neutropenic Cancer Patients[2,5,10]

An antipseudomonal penicillin + an aminoglycoside ± vancomycin
Ceftazidime ± an aminoglycoside
Ceftazidime ± vancomycin
Cefepime ± an aminoglycoside
Cefepime ± vancomycin
Imipenem-cilastatin
Meropenem

urinary tract infection may be asymptomatic and without pyuria, and a lung infection may be present without pulmonary infiltrates. Conversely, on occasion, a neutropenic patient may not present with fever despite infection; this occurs more commonly in elderly patients and patients receiving corticosteroids.

Many factors predispose the neutropenic patient to infection and sepsis: prolonged bed rest; clinical deterioration; nutritional compromise; disruption of mucous membranes and skin barriers; indwelling catheters; and central nervous system (CNS) dysfunction secondary to cancer, sedatives, opiates, and psychotropic medications. An undetected and untreated infection can be rapidly fatal in this population of patients. Therefore early administration of broad-spectrum empirical antibiotic therapy is recommended in all febrile, neutropenic patients. Consultation with the oncologist and infectious disease specialist will help categorize the risk for patients and aid in the selection of antibiotics based on local resistance patterns (Box 123-3).

Diagnostic Strategies

While antibiotics are being started, diagnostic testing includes a complete blood count with differential cell count, platelet count, prothrombin time, partial thromboplastin time, blood chemistries, urinalysis, and analysis of any accessible sites suggestive of infection. Two sets of blood culture specimens are recommended for aerobic, anaerobic, and fungal growth. If an indwelling catheter is present, at least one set of blood culture specimens should be obtained from the device lumen as well as from a peripheral vein. A routine chest radiograph is obtained at most institutions. However, studies show that a chest radiograph is not necessary in patients with no respiratory symptoms and normal physical examination findings.[9] Urine should be sent for culture even in the absence of pyuria. However, the use of sputum culture and Gram's stain has become controversial because of inconsistencies in collection and preparation that have led to false-negative and false-positive results.

Some oncologists discourage rectal temperature readings for patients with neutropenia because of the risk of tearing the rectal mucosa and establishing a potential nidus for disseminated infection. However, this has not yet become the standard of care and may vary among institutions. An indwelling nasogastric tube predisposes the neutropenic patient to sinusitis. When imaging for suggested sinusitis is required, computed tomography (CT) is preferred to sinus films. A lumbar puncture, preceded by head CT, is indicated when symptoms point to the CNS.[10] Some authorities have recommended surveillance cultures of the stool, nose, and throat. This recommendation is not universally accepted and is generally not indicated in patients with solid tumors.

Despite an intensive and comprehensive evaluation, an infectious cause is initially substantiated in only 30% of febrile, neutropenic patients.[11]

Differential Considerations

Overall, approximately 85% of the initial pathogens isolated in febrile neutropenic patients are bacterial, and of these, 60 to 70% are gram-positive pathogens. Gram-negative bacilli, particularly *Pseudomonas aeruginosa,* were the most common pathogens until the 1980s. However, the administration of prophylactic antibiotics primarily active against gram-negative pathogens during chemotherapy, the widespread use of indwelling venous catheters, and the newer chemotherapy regimens have led to an increase in gram-positive pathogens.[12]

Staphylococcus aureus, Staphylococcus epidermidis, and *Streptococcus epidermidis* are the predominant gram-positive organisms. Once believed to be a skin contaminant, *S. epidermidis* has arisen as a major pathogen and may be resistant to antistaphylococcal penicillins and cephalosporins. *Escherichia coli, P. aeruginosa,* and *Klebsiella pneumoniae* remain the most common gram-negative pathogens.

Fungal, viral, and parasitic infections are also important primary and secondary complications. Fungal infections, especially with *Candida albicans,* can be a major problem in neutropenic febrile patients treated with broad-spectrum antibiotics for protracted periods. Although significant institutional variation has been noted, *Histoplasma, Cryptococcus, Aspergillus,* and Phycomycetes are additional fungal pathogens encountered in the compromised host. In contrast to patients with acquired immunodeficiency syndrome (AIDS), parasitic infections are not a common source of infection in patients with solid tumors. *Pneumocystis jiroveci* (formerly *carinii*), however, may be seen when corticosteroid use or hematologic malignant disease has resulted in lymphocyte dysfunction. Herpes simplex, herpes varicella-zoster, and cytomegalovirus are common viral pathogens. The compromised host is at risk for infection from a large number of individual pathogenic agents, thus further complicating the diagnosis and treatment of these patients.

In an attempt to prevent these infections, oncologists may initiate antimicrobial prophylaxis with trimethoprim-sulfamethoxazole (Bactrim) or quinolones for immunosuppressed patients before development of fever.[11] In addition, recombinant human granulocyte colony-stimulating factor and granulocyte-macrophage

www.ketabpezeshki.com 66485457-66963820

colony-stimulating factor are used to stimulate rapid increase in granulocytes in neutropenic patients in an effort to decrease the duration and degree of neutropenia and immunosuppression.

Fever is occasionally without a source and is believed to arise from the underlying disease, although it is impossible to differentiate by clinical and demographic factors those patients with bacteremia-induced fever from those with unexplained fever. In addition, the absence of physical findings indicative of infection does not exclude a potentially life-threatening septic event because at least 50% of septic patients lack any distinct physical findings.

Management

Local resistance patterns are used to guide treatment. Patients are risk stratified and then treated accordingly. Patients with fever who appear in good condition are considered at low risk. Patients with fever who have severe neutropenia, appear ill, and are expected to have a protracted course are at high risk.[13] In the initial evaluation and management of the febrile cancer patient, one must take into account the particular underlying malignant neoplasm, prior use of antimicrobial therapy, and how the degree of treatment has affected the host's immunologic compromise. For example, in acute leukemia, normal circulating neutrophils and monocytes are largely replaced by blast cells, which do not function well in the phagocytosis and killing of bacterial and fungal agents. Chemotherapeutic agents and irradiation exacerbate or potentiate the underlying defect in already compromised host defenses. Corticosteroids impair granulocyte and mononuclear cell mobilization in leukemic patients. Patients with severely compromised host defenses and those in whom fever is accompanied by an increase in respiratory rate, change in mental status, agitation or apprehensiveness, and hemodynamic instability should be urgently treated.

Once febrile neutropenia is diagnosed, broad-spectrum antibiotic therapy is indicated immediately after culture specimens are obtained regardless of evidence of infection. Afebrile patients with neutropenia and suspicion of infection should also be cultured and should be treated with broad-spectrum antibiotics.

The optimal antimicrobial regimen is synergistic, broad spectrum, and bactericidal with a low potential for toxicity and chosen for efficacy against the most likely causes of systemic and rapidly progressing infection: *S. aureus, S. epidermidis, E. coli, P. aeruginosa,* and *Klebsiella* species. Traditionally, a two-drug regimen was selected because historical studies from the 1980s found that patients with gram-negative bacteremia had a higher survival rate when the isolate was sensitive to and treated with two antibiotics, compared with when the isolate was sensitive to only one of two antibiotics in the combined regimen.

Significant advances in the antimicrobial armamentarium have been made in the past 10 years with the development of broad-spectrum single agents such as the carbapenems (imipenem-cilastatin, meropenem) and the third- and fourth-generation cephalosporins (ceftazidime, cefepime). These agents, when investigated as monotherapy in neutropenic, febrile patients, have been found to be as effective as a dual-drug combination of an antipseudomonal penicillin (ticarcillin, carbenicillin, or piperacillin) plus an aminoglycoside (gentamicin or tobramycin). Furthermore, single-drug therapy is associated with fewer adverse effects.[8] Amikacin is generally reserved as a second-line aminoglycoside for isolates that demonstrate aminoglycoside resistance. Antifungal and antiviral agents are not usually indicated during initial therapy, although they are becoming increasingly prevalent. Antifungal therapy is recommended if there is no improvement within 3 days of treatment.[8] Box 123-3 summarizes current recommendations for antimicrobial therapy for fever in neutropenic cancer patients.

The drug most commonly used for treatment of gram-positive bacteria is vancomycin.[8] Use of empirical vancomycin is indicated in the following circumstances:

- Clinically suspected catheter infections
- Known colonization with penicillin- and cephalosporin-resistant pneumococci or methicillin-resistant *S. aureus*
- Blood cultures positive for gram-positive bacteria before final identification and susceptibility testing
- Hypotension or other evidence of cardiovascular impairment

Neutropenic febrile patients are best admitted to an isolation room, and rapid movement out of a congested waiting room into a private space is a high priority. Handwashing and reverse isolation techniques should be used.

Several clinical trials validate the outpatient management of selected patients older than 16 years with neutropenic fever. These patients must be at low risk for serious infection and must have close follow-up and unrestricted access to health care professionals.[14] The Multinational Association for Supportive Care in Cancer has introduced a prediction tool to assess patients suitable for outpatient therapy that accounts for burden of illness and social factors.[14]

Contraindications to outpatient therapy are as follows:

- History of noncompliance
- Inability to care for oneself
- Lack of caregivers
- No telephone or lack of reliable transportation
- High risk of severe infection

The best-studied outpatient antibiotic regimen for neutropenic fever is a combination of ciprofloxacin (500 mg every 8 hours) and amoxicillin-clavulanate (Augmentin; 500 mg every 8 hours). Daily assessment by a health care professional is recommended for the first 3 days to ensure compliance and tolerability. All decisions involving disposition should be made in concert with the patient's primary care physician, oncologist, or both.

Colony-stimulating factors are used in prophylaxis of neutropenic fever. However, their routine use as an adjunct to antibiotics in the treatment of neutropenic fever is controversial and currently recommended only in select, high-risk patients.[15] Initiation of treatment should be made in consultation with the patient's oncologist.

SUPERIOR VENA CAVA SYNDROME

Epidemiology

Superior vena cava syndrome (SVCS) is an acute or subacute process caused by the obstruction of blood flow through the superior vena cava (SVC) secondary to compression, infiltration, or thrombosis. It occurs in approximately 1500 persons in the United States annually.[16] Malignant disease is the most common cause of SVCS and currently accounts for 60 to 85% of cases.[17] It is estimated that 2 to 4% of all cancer patients will have SVCS; in fact, SVCS is often the initial presenting sign of the tumor, and it is a poor prognostic marker.[18]

The most common cancers associated with SVCS are non–small cell lung cancer (50%), small cell lung cancer (25%), and lymphoma and metastatic lesions (10%).[17] However, benign causes of SVCS, such as intrinsic thrombus, are gradually increasing, accounting for 20 to 40% of all cases owing to more frequent use of intravascular devices.[19] Other common nonmalignant causes are goiter, pericardial constriction, primary thrombosis, idiopathic sclerosing aortitis, tuberculous mediastinitis, fibrosing mediastinitis (histoplasmosis and methysergide treatment), arteriosclerotic or (rarely) luetic aneurysm, nephritic syndrome, and indwelling central venous catheters. In contrast to SVCS in the adult population, SVCS in pediatric patients is most often

www.ketabpezeshki.com 66485457-66963820

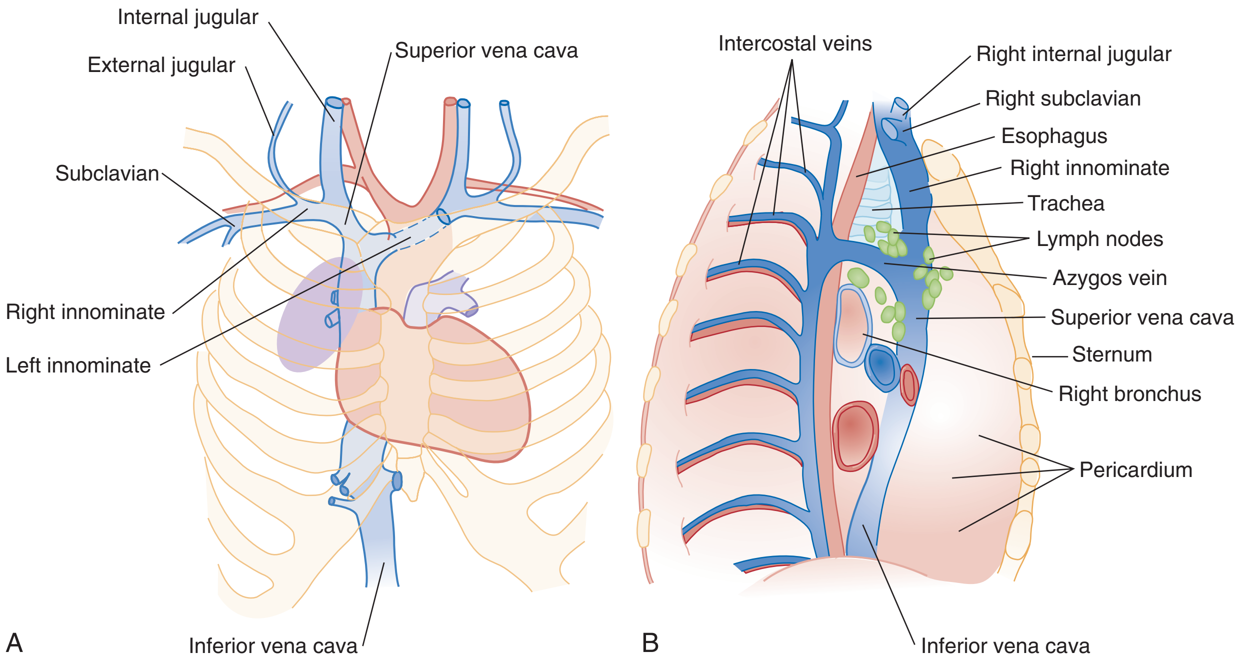


Figure 123-1. Frontal (**A**) and sagittal (**B**) sections of the thorax showing the relationship of the azygos vein to the superior vena cava *(SVC)*, coalescence of innominates to form the SVC at the right second rib, and encasement of the SVC by nodal structures. Shaded area indicates classic site of obstruction. (From Lokich JL, Goodman R: Superior vena cava syndrome. JAMA 231:58, 1975.)

iatrogenic secondary to indwelling catheters, ventriculoperitoneal shunts, and complications of cardiovascular surgical procedures.

Clinical Features

Knowledge of the unique anatomic relationship of the SVC in the anterior superior mediastinum is crucial to understanding of the clinical presentation of SVC obstruction. The SVC is easily compressed by any of its contiguous structures (trachea, heart, aorta, azygos vein, and paratracheal and bronchial lymph nodes). This compression can produce a constellation of symptoms that reveal the likely site of the pathophysiologic process (Fig. 123-1). The SVC arises from the innominate veins, which in turn arise from the internal jugular and subclavian veins. The azygos vein, the last main auxiliary vessel of the SVC, drains blood from the chest wall. As a consequence of this anatomic relationship, if the SVC is blocked above or at the entrance of the azygos, blood may bypass and decompress the obstruction through the chest wall collateral vessels and rejoin the SVC through the azygos. If the obstruction falls below or at the entrance of the azygos, blood must traverse in a retrograde manner down the azygos and other chest wall veins to reach the drainage area of the inferior vena cava and subsequently cause more prominent symptoms.

When the SVC is obstructed, blood flows through a collateral vascular network, but it generally takes weeks for these vessels to sufficiently dilate to accommodate the blood flow of the SVC. The severity of SVCS varies with the rate and degree of obstruction. When the obstruction occurs more slowly and the SVC is less compressed, there is more time for development of collateralization, which results in less severe symptoms.

Because the clinical features of the SVC are characterized by venous hypertension within the area ordinarily drained by the SVC, many of the findings are more noticeably evident in the recumbent or stooped-over position.

SVCS symptoms develop during a period of 2 weeks in about one third of patients and in a longer time in others.[16] SVCS causes edema of the upper body, particularly of the head and neck. Early signs may include periorbital edema, conjunctival suffusion, and facial swelling, which will be most evident in the early morning hours and subside by midmorning. This edema may be significant enough to compromise the lumen of the trachea, causing stridor and dyspnea, or of the esophagus, causing dysphagia. One of the most common presentations in SVCS is dyspnea and swelling of the face, trunk, and upper extremities. Cough, dysphagia, and chest pain are less commonly reported, each occurring in approximately 20% of patients. With increasing impedance to blood flow, the full-blown syndrome begins to be manifested with thoracic and neck vein distention (67% and 59%, respectively), facial edema (56%), tachypnea (40%), tightness of the shirt collar (the Stokes sign), plethora of the face, edema of the upper extremities, and cyanosis.[16] Other concerning symptoms are neurologic, such as headaches, confusion, and even coma, suggesting cerebral edema, ischemia, or both. Although cerebral edema is rare, it can be fatal. The usual course of SVCS is that collaterals develop, and symptoms improve when this occurs.[17]

There is little evidence in the literature to substantiate the notion of untreated SVC obstruction as immediately life-threatening, as was once believed, except when it occurs with respiratory compromise or cerebral edema.[20] Survival in patients with SVCS depends mainly on the course of the underlying disease.

SVCS can occur in conjunction with spinal cord compression (Rubin's syndrome). Venous obstruction usually develops before the spinal cord compression, which is localized in most instances to the lower cervical or upper thoracic spinal cord. This syndrome is most commonly found with malignant neoplasms of lymphoma and lung cancer. Patients with venous obstruction and back pain or peripheral neurologic concerns should be evaluated with magnetic resonance imaging (MRI) of the vertebral spinal cord.

Ancillary Evaluation

The clinical diagnosis of SVC obstruction is mimicked by a few other clinical entities, most noteworthy of which are pericardial tamponade and heart failure; both can usually be excluded by physical examination and bedside cardiac ultrasound

www.ketabpezeshki.com 66485457-66963820

examination. The chest film is abnormal in 84% of patients with SVCS; the most common abnormalities are mediastinal widening (64%) and pleural effusion (26%).[16] It reveals a mass in nearly 10% of patients. When superior mediastinal mass is present, 75% are on the right side, and in approximately 50% of patients, the masses are combined with pulmonary lesions or hilar adenopathy. Pleural effusion is an associated finding in approximately 20 to 25% of patients and is customarily found in the right hemithorax.

CT of the chest with intravenous administration of contrast material is the most useful imaging study to evaluate the SVC.[16] History and physical examination combined with the CT chest scan with intravenous contrast enhancement will help differentiate between intrinsic and extrinsic compression of the SVC. The presence of collateral vessels with compression of the SVC is a reliable indicator of SVCS. Venography is relatively contraindicated because of its concomitant bleeding complications. It is generally warranted only during placement of a stent or surgery. MRI may be useful in patients who cannot receive an intravenous contrast agent. Invasive diagnostic procedures, including bronchoscopy, mediastinoscopy, scalene node biopsy, and limited thoracotomy, are commonly used to establish the diagnosis and extent of the disease.

Morbidity secondary to excessive bleeding from puncture sites has been reported rarely with venous access procedures for SVC. Intravenous injections may be less reliable because of slowing of drug distribution. Low flow rates may result in local irritation with thrombosis or phlebitis. Venous access is preferable on the side contralateral to the obstruction.

Once SVC obstruction is suggested, the appropriate consulting services should be contacted and plans for prompt diagnosis undertaken.

Management

SVCS is considered an immediately life-threatening oncologic emergency only if CNS symptoms are present. If a true emergency exists, a stent can be emergently placed in the SVC or radiation therapy can be used.[21] In all other cases, once the clinical diagnosis is entertained, a tissue biopsy specimen should be obtained promptly before treatment decisions are made. Although supportive therapy may be instituted to alleviate symptoms, definitive therapy is dependent on the histologic diagnosis. The American College of Chest Physicians and the National Comprehensive Cancer Network both recommend consideration of radiation therapy, stent placement, or both. Historically, emergent radiation therapy was the treatment of SVCS. Currently, this is recommended only emergently for patients who present with stridor due to central airway obstruction or severe laryngeal edema. In an attempt to relieve the obstruction, current management uses radiation therapy for cancers responsive to this treatment and chemotherapy in other cancers because of the increased incidence of tumor sensitivity to newer antineoplastic agents. Complete relief of symptoms is achieved with chemotherapy in approximately 80% of patients with non-Hodgkin's lymphoma or small cell lung cancer and in 40% of those with non–small cell lung cancer.[16] However, temporizing measures that alleviate symptoms related to vascular compression should be rapidly instituted.

All management begins with attention to airway. Although no data exist to document its effectiveness, elevation of the head of the bed will theoretically decrease the hydrostatic pressure and thereby the edema with minimal risk. Glucocorticoid therapy (dexamethasone, 4 mg every 6 hours) is not well studied, but case reports do suggest benefit as a temporary measure. Loop diuretics have been used with transient symptomatic relief; they must be used judiciously to avoid hypovolemia, which may result in decreased blood flow.

Other current management approaches include percutaneous transluminal stent placement and bypass surgery.[21] Placement of an intravascular stent to bypass the obstruction is particularly useful in patients requiring urgent intervention before tissue diagnosis because of severe symptoms such as respiratory distress. Stent placement is also useful for patients whose cancer is minimally responsive to chemotherapy or radiation therapy and for those patients with a thrombus associated with an indwelling catheter. Surgical bypass grafting is infrequently used to treat SVCS but may be useful in cancers resistant to chemotherapy and radiation therapy.

The prognosis for patients treated for SVCS depends on the tumor type, with better survival rates in patients with lymphoma than in patients with bronchogenic carcinoma. Median life expectancy of patients with malignant causes of SVCS is 6 months, but this varies widely by the underlying malignant condition.[20]

ACUTE TUMOR LYSIS SYNDROME

Acute tumor lysis syndrome (TLS) refers to the constellation of metabolic disturbances that result from ongoing cell death in a rapidly growing tumor. It also occurs frequently within a few hours to a few days after the initiation of chemotherapy or radiation therapy to treat bulky and treatment-responsive tumors. This syndrome is most commonly seen after chemotherapy of hematologic malignant neoplasms, including acute leukemias and high-grade non-Hodgkin's lymphomas, particularly Burkitt's lymphoma, in which the growth fraction often exceeds 90%. With advances in the effectiveness of chemotherapy, it has also been described after treatment of solid tumors, such as small cell lung carcinoma and germ cell tumors.[22]

The risk of acute TLS increases with the bulk of the tumor, with the presence of hyperuricemia, or with renal impairment before antineoplastic therapy (Box 123-4). Large numbers of neoplastic cells are killed rapidly, leading to release of intracellular ions and metabolic byproducts into the systemic circulation. A correlation between a very high level of blood lactate dehydrogenase and the development of TLS has been observed.[23]

Biochemical hallmarks of this syndrome include hyperuricemia (DNA [nucleic acids—purine] breakdown), hyperkalemia (cytosol breakdown), and hyperphosphatemia (protein breakdown). Hypocalcemia develops secondary to hyperphosphatemia. Acute renal failure, cardiac dysrhythmias, neuromuscular symptoms, and sudden death may result from hyperkalemia or hypocalcemia, and lactic acidosis and metabolic acidosis from acute renal failure may ensue. Early aggressive treatment is crucial.

Clinical Features

Symptoms are related to the underlying malignant neoplasm and the degree of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia that develops. Hyperuricemia with resultant

Box 123-4 Risk Factors for Acute Tumor Lysis Syndrome

Increased lactate dehydrogenase levels (>1500 U/L)
Advanced disease with abdominal involvement
Preexisting renal dysfunction
Post-treatment renal failure
Acidic urine
Concentrated urine
Preexisting volume depletion
Young age

www.ketabpezeshki.com 66485457-66963820

urate nephropathy is the most commonly recognized metabolic cause of renal insufficiency in patients with TLS.[23] The kidney provides the primary mechanism for excretion of uric acid, potassium, and phosphate. Rapid proliferation of tumor cells exacerbated by the rapid destruction of the tumor cells during chemotherapy may exceed the kidney's ability to remove these substances, resulting in toxicity. The integrity of renal function is a critical factor in determining the degree of metabolic derangements. In patients with preexisting renal insufficiency, the metabolic derangements of acute tumor lysis are more likely to be severe. However, even when renal function is normal at the start of treatment, the rapid lysis of certain tumors may overwhelm the excretory capacity of the kidney. Similar to hyperuricemia, hyperphosphatemia may also cause renal failure. A possible mechanism is precipitation of calcium phosphate within the kidney.

Hyperkalemia, along with a contributing hypocalcemia, may result in life-threatening ventricular dysrhythmias. Hypocalcemia may also cause neuromuscular instability with muscle cramps and occasionally tetany. Confusion and convulsions also have been described.

Box 123-5 Criteria for Institution of Hemodialysis

Serum potassium 6 mEq (6 mmol/L)
Serum uric acid 10 mg/dL (590 mol/L)
Serum creatinine 10 mg/dL (880 mol/L)
Serum phosphorus 10 mg/dL (phosphate 3.2 mmol/L) or rapidly rising
To reduce volume overload
Symptomatic hypocalcemia

Management

The main principles of TLS management are (1) identification of high-risk patients with initiation of preventive therapy and (2) early recognition of metabolic and renal complications with prompt supportive care, including hemodialysis. Most of the complications can be readily managed when they are recognized early; however, delay in recognition and in the initiation of treatment of TLS can be life-threatening.

Chemotherapy should be delayed, if possible, until metabolic disturbances, especially prerenal azotemia and hyperuricemia, are corrected. Initial management is aimed at the control of preexisting hyperuricemia with hydration, allopurinol, and alkalinization of the urine to a pH above 7. Diuretics are added if necessary, and frequent monitoring of electrolytes, calcium, and phosphorus is essential.

Hydration

Volume depletion is a major risk factor in TLS and must be corrected vigorously. Rapid intravenous hydration is the single most important intervention. Hydration not only helps correct electrolyte disturbances by diluting extracellular fluid but also increases intravascular volume. Increased volume enhances renal blood flow, glomerular filtration rate, and urine volume, which consequently decreases the concentration of solutes in the distal nephron and medullary microcirculation. Continuous infusion rates as high as 4 to 5 L/day, yielding urine volumes of at least 2 to 3 L/day, should be given unless the patient's cardiovascular status indicates impending volume overload. Ideally, intravenous hydration in high-risk patients is started 24 to 48 hours before initiation of cancer therapy and continued for 48 to 72 hours after completion of chemotherapy.[24]

Hyperuricemia

Allopurinol is a xanthine oxidase inhibitor that reduces the conversion of nucleic acid byproducts to uric acid. It is given in TLS to prevent urate nephropathy and subsequent oliguric renal failure. Because allopurinol inhibits the synthesis of uric acid but has no effect on preexisting uric acid, uric acid levels usually do not fall until after 48 to 72 hours of treatment. The dose of allopurinol is 300 to 600 mg/day orally for prophylaxis and 600 to 900 mg/day for treatment of TLS.

Rasburicase (recombinant urate oxidase) is a newer therapy that can be used when the uric acid levels cannot be lowered sufficiently by standard approaches. It has been approved for the treatment of hyperuricemia in pediatric patients with acute leukemia, lymphoma, and solid tumor malignant neoplasms who are receiving anticancer therapies expected to result in tumor lysis. It works by catalyzing the conversion of poorly soluble uric acid to soluble allantoin, thus rapidly decreasing plasma and urinary uric acid levels. Unlike allopurinol, rasburicase does not increase the excretion of xanthine and other purine metabolites; therefore, it does not increase tubule crystallization of these compounds and decreases the risk of urate nephropathy.[24] Although it is extremely effective in reducing serum uric acid to low levels within a few hours of administration, rasburicase is rarely initiated by emergency physicians because it has not been shown to have an impact on clinical outcomes. It is reserved for severe cases that have failed to respond to traditional prophylactic methods and in which the probability of acute renal failure is very high.

It is generally accepted practice to alkalinize the urine as a prophylactic measure in hyperuricemia to increase the solubility of uric acid. Caution is advised when hyperphosphatemia and hypocalcemia develop because alkalinization favors precipitation of calcium/phosphate complexes in the renal tubules. Furthermore, alkali therapy may aggravate manifestations of hypocalcemia, such as tetany. Although alkalinization may be beneficial, the primary means of uric acid control is hydration and diuresis to maintain adequate urinary flow.

The use of furosemide or mannitol for osmotic diuresis has no proven benefit as in front-line therapy for hyperuricemia. In fact, these modalities may contribute to uric acid or calcium phosphate precipitation in renal tubules in a volume-contracted patient. Instead, diuretics are reserved for the normovolemic patient with hyperkalemia or for the patient with evidence of fluid overload. If TLS develops and is refractory to the previously mentioned treatments, hemodialysis is considered a potentially lifesaving measure. This therapy is effective in lowering of uric acid, potassium, and phosphate levels as well as in control of uremic symptoms. See Box 123-5 for the criteria for institution of hemodialysis.

Aggressive management maximizes the outcomes of patients with TLS, and the prognosis is good in the absence of renal failure. If renal failure develops and hemodialysis is required, the prognosis becomes grave.

HYPERVISCOSITY SYNDROME

Hyperviscosity syndrome (HVS) refers to the clinical sequelae of increased blood viscosity. Viscosity is the resistance that a liquid exhibits to the flow of one layer over another. Excessive elevations in certain paraproteins (circulating immunoglobulins) or cellular blood components (leukocytosis, erythrocytosis, and thrombocytosis) result in elevated serum viscosity and the development of sludging, decreased perfusion of the microcirculation, and vascular stasis. The outcome of these pathophysiologic events leads to the development of HVS, which requires urgent medical therapy to forestall or to reverse the effects of sludging in the microcirculation of the CNS, visual system, and cardiopulmonary system.[25]

www.ketabpezeshki.com 66485457-66963820

Pathophysiology

HVS is most commonly associated with plasma cell dyscrasias (the paraproteinemias) and is due to the large size of the excess immunoglobulin M (IgM) paraproteins in these disorders. Waldenström's macroglobulinemia is the most common cause and accounts for 85 to 90% of cases of HVS. Less frequently, the disease can occur in multiple myeloma (especially with myeloma proteins of the IgA and IgG3 types). Other causes include cryoglobulinemia, a benign hyperglobulinemia of the IgM-IgG type, and leukemias.[26]

The blastic phase of chronic myelogenous leukemia, chronic granulocytic leukemia, and the blast cell crisis of acute lymphoblastic and nonlymphoblastic leukemias also commonly cause HVS. Other more benign causes are leukemoid reaction, polycythemia vera, and the accumulation of abnormal hemoglobins in sickle cell disease. The incidence of HVS in Waldenström's macroglobulinemia is found to be approximately 20%; in IgG myeloma, approximately 4.2%; and in IgA myeloma, as high as 25%.[27]

The inherent physicochemical properties of the dysproteinemias along with extremely high concentrations of these proteins predispose to the development of hyperviscosity. The etiologic factor most responsible for HVS in the leukemias appears to be leukocytosis with white blood cell counts in excess of 100,000, usually accompanied by blast forms exceeding 100,000 in the peripheral smear. The clinical manifestations of HVS become most apparent when the serum viscosity relative to water is greater than 4 to 5, normal serum viscosity relative to water being 1.4 to 1.8.

Clinical Features

The classic presentation of HVS is mucosal bleeding, visual disturbances, and neurologic manifestations. Visual disturbances and, on occasion, visual loss may occur with retinopathy characterized by venous engorgement (e.g., "sausage-link" or "boxcar" segmentation); other findings include microaneurysms, hemorrhages, exudates, and occasionally papilledema. Persistent bleeding diatheses from mucosal surfaces, especially nasal mucosa, the gastrointestinal tract, and sites of minor surgery or trauma, even in the presence of a normal platelet count, are common. Other clinical findings encompass myriad neurologic disturbances, including headache, dizziness, seizures, auditory disturbances (including hearing loss), hypotension, and coma. Constitutional symptoms of somnolence, fatigue, anorexia, and weight loss that are nonspecific early on are commonly associated with the underlying malignant neoplasm or with associated electrolyte disturbances related to the underlying malignant neoplasm. Cardiopulmonary findings include acute respiratory failure and hypoxemia, congestive heart failure, myocardial infarction, and valvular abnormalities. Renal insufficiency and failure may be a complication of the syndrome and will exacerbate existing clinical findings.

The laboratory evaluation of the patient with suggested HVS includes coagulation profile, creatinine and blood urea nitrogen concentrations, electrolyte values, and complete blood count with differential. Serum and urine protein electrophoresis should be done in all cases of suggested dysproteinemias; the diagnosis is supported by a large spike on the serum electrophoresis. A clue to the presence of hyperviscosity may be the inability of the laboratory to perform chemical tests on the blood because of clogging of the analyzers by serum stasis and increased viscosity. Significant hypercalcemia may also occur in multiple myeloma, and with high M-protein fractions, a factitious hyponatremia may be present. The diagnosis may also be entertained when a patient is brought to the ED in a stupor or coma and anemia and rouleaux formation are found on the peripheral smear.[28]

Because HVS is often a presenting characteristic of dysproteinemias and leukemias with blastic transformation and because a history of previously documented disease is often absent, this syndrome should be considered in patients with unexplained somnolence and coma.

Management

Emergency leukapheresis or plasmapheresis is the definitive treatment of HVS. Temporizing measures provided by the emergency physician focus on adequate rehydration and diuresis. An immediate temporizing measure in a patient with frank coma and an established paraproteinemia is a two-unit phlebotomy with replacement of the patient's red blood cells with physiologic saline.[26] Once plasmapheresis or leukapheresis has adequately alleviated the clinical findings, chemotherapeutic modalities can be used.

HYPERURICEMIA

Hyperuricemia is a serious and well-known consequence of certain malignant disorders; its complications can be avoided if it is recognized and treated early. The major source is cell breakdown, and its major excretory pathway is through the kidneys.

Pathophysiology

The pathogenesis of hyperuricemia results from either the increased production or the decreased excretion of uric acid, or both. Uric acid is produced by metabolism, and hyperuricemia results from the rapid dissolution of neoplastic tissues (cell death) after chemotherapy or radiation therapy. It is often seen in the treatment of undifferentiated lymphomas, lymphoblastic lymphomas, and acute lymphoblastic leukemias. In addition, hyperuricemia may be seen with multiple myeloma and occasionally with disseminated metastatic carcinoma. With massive release of precursors, uric acid levels rise precipitously and may reach levels as high as 15 to 20 mg/dL. As a result, uric acid crystals form in the highly concentrated and acidified urine of the distal tubules; intrarenal obstruction follows, leading to acute renal failure.[29]

Chronic, moderately elevated levels of the serum uric acid may result in renal colic, obstructive uropathy, or chronic renal failure. Either uric acid renal calculi or interstitial deposits of sodium urate may develop. This situation is associated with neoplastic overproduction of uric acid precursors. Polycythemia vera, myeloid metaplasia, mast cell disease, and chronic granulocytic leukemia are often associated with this type of hyperuricemia.

Decreased excretion of uric acid may be a result of underlying renal insufficiency or a consequence of urate precipitation in the renal tubules, parenchyma, or ureters. Three types of renal diseases are attributable to hyperuricemia: acute hyperuricemic nephropathy, uric acid nephrolithiasis, and gouty nephropathy.

Clinical Features

Hyperuricemia can occur with or without symptoms. Hyperuricemia precipitated or aggravated by therapy may occur as an isolated metabolic disturbance or may be accompanied by other manifestations of the TLS (see previous discussion of TLS). If an underlying neoplastic disease has been diagnosed, the possibility of hyperuricemia should be investigated before, during, and after chemotherapy or radiation therapy. In patients with urate stones and hyperuricemia, examination of the peripheral blood may provide evidence of an underlying myeloproliferative disorder. Acute oliguria after chemotherapy or radiation therapy suggests the diagnosis of hyperuricemia, and the uric acid level in the blood often far exceeds that associated with acute renal failure.

www.ketabpezeshki.com 66485457-66963820

A number of relatively benign diseases associated with hyperuricemia may coexist with neoplasia. These include hereditary gout, hyperparathyroidism, psoriasis, sarcoidosis, and renal failure of any cause. The long-term administration of certain drugs may lead to elevation of the serum uric acid level. Those most commonly encountered are thiazide diuretics and furosemide. Acute therapy is the same regardless of the etiology.

Management

When possible, hyperuricemia should be treated before chemotherapy or radiation therapy, especially with bulky tumors or if the serum uric acid level is borderline or increased. If a uric acid elevation of more than 9 mg/dL is found, allopurinol, fluids, and alkalinization of the urine should be initiated.

Patients with a history of gouty arthritis are treated with colchicine (0.6 mg orally twice a day) to avoid the acute attacks that can be associated with allopurinol administration. Patients should be kept well hydrated. In patients with acute distal tubular uric acid obstruction, treatment includes the administration of allopurinol together with the fluid and electrolyte management used in other forms of acute renal failure.

If hyperuricemia is secondary to malignant disease, cytolytic therapy is generally stopped. Allopurinol in dosages of 300 to 600 mg/day decreases the serum uric acid level in approximately 3 days, so its administration is started 2 or 3 days before cytolytic therapy, if time permits. Hydration is vital, with a goal of maintaining a urine output above 2 L/day. As discussed before, rasburicase (recombinant urate oxidase) is a newer therapy that can be used when the uric acid levels cannot be lowered sufficiently by standard approaches.

Alkalinization to keep the urine pH above 7 is accomplished by the administration of sodium bicarbonate. Acetazolamide (Diamox) usually alkalinizes the urine temporarily until allopurinol becomes effective. If oliguria occurs, intravenous mannitol may be started with 12.5 g of a 20% solution given during 3 minutes to keep urine output more than 250 mL/hr. The dose of mannitol is limited to avoid clinical features resembling water intoxication. If these measures fail, peritoneal dialysis or hemodialysis or flushing of the ureters through retrograde catheters may be considered. Clearly, prevention of this complication is far better than the need for treatment.

The cancer patient who comes to the ED with renal colic warrants careful evaluation for hyperuricemia. The prognosis depends on the underlying malignant neoplasm and degree of renal failure.

HYPERCALCEMIA

Hypercalcemia occurs in approximately 20 to 40% of cancer patients and is the most common life-threatening metabolic disorder associated with cancer. It affects multiple organ systems and induces a variety of pathophysiologic events that may be more immediate threats to life than the cancer itself. For the purpose of this discussion, we discuss non–parathyroid hormone–mediated hypercalcemia that is associated with malignant disease.[30]

Pathophysiology

Two mechanisms have been proposed to explain the development of hypercalcemia associated with malignant disease. The first mechanism involves patients with metastatic bone involvement, in which case hypercalcemia is associated with the release of calcium and phosphate by increased osteoclastic activity within the bone. The second mechanism involves those patients with no bone disease but who have tumor-produced hormone-like substances that affect bone turnover (e.g., parathyroid hormone, prostaglandins, steroids, and peptides).

Box 123-6 Non-neoplastic Causes of Hypercalcemia

Hyperparathyroidism
Hyperthyroidism
Renal insufficiency (diuretic phase of acute renal failure, after transplantation, secondary hyperparathyroidism)
Drugs (thiazide diuretics, lithium, and calcium carbonate)
Hypervitaminosis (A and D)
Acute adrenal insufficiency
Immobilization (Paget's disease, fracture, paraplegia)
Acromegaly
Myxedema
Milk-alkali syndrome
Sarcoidosis
Benign monoclonal gammopathy
Rarer still are factitious hypercalcemia, idiopathic hypercalcemia of infancy (with elfin facies), familial hypocalciuric hypercalcemia, and hypercalcemia from pheochromocytoma or periostitis

Box 123-7 Common Signs and Symptoms of Hypercalcemia in Malignant Disease

General
Itching

Neurologic
Fatigue, muscle weakness, hyporeflexia, lethargy, apathy, disturbances of perception and behavior, stupor, coma

Renal
Polyuria, polydipsia, renal insufficiency

Gastrointestinal
Anorexia, nausea, vomiting, constipation, abdominal pain

Cardiovascular
Hypertension, dysrhythmias, digitalis sensitivity

Hypercalcemia is a common feature of many malignant neoplasms but most commonly breast, lung, head, and neck cancers as well as multiple myeloma and leukemia. Bone metastases are not a prerequisite for hypercalcemia and are not necessarily the cause of the hypercalcemia. For example, in patients who are hypercalcemic from squamous cell lung cancer, only one in six has bone metastases, whereas in small cell lung carcinoma, hypercalcemia is almost never seen, despite the presence of bone marrow metastases in 20 to 50% of cases. Entities that cause hypercalcemia are listed in Box 123-6.

Clinical Features

The symptoms of hypercalcemia are nonspecific. There is little correlation between serum calcium levels and the presence and severity of symptoms. Acute hypercalcemia results in marked CNS effects ranging from personality changes (depression, paranoia, lethargy, and somnolence) to coma. With chronic hypercalcemia, symptoms include a history of anorexia, nausea, vomiting, constipation, polyuria, polydipsia, and memory loss. The signs, symptoms, and complications of hypercalcemia are summarized in Box 123-7.

In patients with carcinoma, any of these symptoms should suggest the diagnosis of hypercalcemia, but the emergency physician should be particularly alert to the possibility of hypercalcemia in any cancer patient with lethargy or a change in mental status. Many may also have electrolyte abnormalities, such as

www.ketabpezeshki.com 66485457-66963820

hypokalemia and dehydration. Thus evaluation of serum electrolytes should accompany the measurement of serum calcium, phosphorus, albumin, and alkaline phosphate. In general, a serum calcium level above 14 mg/dL constitutes a medical emergency. In chronic hypercalcemia, patients with blood calcium levels as high as 15 mg/dL may be seen with only mild symptoms. With an acute onset, patients may present comatose with a level of only 12 to 13 mg/dL.[31]

Many benign conditions can result in hypercalcemia. The most common are hyperparathyroidism and Paget's disease of bone. Clinical features include a long history of hypercalcemia symptoms, particularly renal stones. Chronic changes on bone films, such as subperiosteal reaction and cysts or a "ground-glass" appearance of the skull, suggest hyperparathyroidism. Diagnosis of Paget's disease rests in biopsy results. Vitamin D excess, milk-alkali syndrome, and adrenal insufficiency are other common causes in the differential diagnosis of hypercalcemia.

The acute onset of severe hypercalcemia or chronic exposure of the renal tubules to elevated calcium levels may reduce the glomerular filtration rate and renal blood flow, resulting in acute renal failure.

Management

The therapeutic modalities for hypercalcemia are numerous, but they should always be used in conjunction with treatment of the underlying malignant disease. The exception to this is breast cancer, in which hormone therapy is generally stopped until hypercalcemia is regulated.

The treatment depends on the clinical status of the patient and on the calcium level in the blood, but the general principles include treatment of the cancer when possible, encouragement of ambulation, correction of dehydration, increase of urinary calcium excretion, inhibition of osteoclastic activity (calcium removal from bone), and reduction of calcium intake.

If serum calcium levels are below 14 mg/dL, oral rehydration and ambulation may suffice. Normal saline solution can be administered if the oral intake is not sufficient. If the serum phosphate level is not elevated, oral phosphates may be used cautiously. Phospho-Soda (5 mL by mouth, two or three times daily) is usually tolerated with mild or no diarrhea. Intravenous phosphates are able to effectively lower the serum calcium level through precipitation of inorganic calcium phosphate salts in bone. This modality of treatment is usually not recommended in view of its serious complications, which include widespread visceral calcifications, shock, and renal failure. However, if it is needed, it is best done in consultation with a nephrologist or oncologist and reserved for hypercalcemia unresponsive to other agents.

Prednisone (60-80 mg) or other corticosteroids may be effective within a few days to a week. They are more useful for long-term treatment than for acute control. Corticosteroids are particularly valuable in breast carcinoma, myeloma, and lymphoma. If the serum calcium level is greater than 14 mg/dL or significant symptoms are present, a more vigorous management should be undertaken. Continuous cardiac monitoring in the ED is necessary, and central venous or pulmonary artery pressure monitoring may be required.

Saline rehydration stimulates renal tubular excretion of calcium and is the most important initial component of the emergency management of hypercalcemia. Dehydration should be corrected within 1 to 2 hours with normal saline solution. When urine flow is adequate, furosemide (40-60 mg intravenously) may be given to increase excretion of calcium. Although the calciuric effect of furosemide is modest, it is also useful in preventing fluid overload in patients predisposed to cardiac failure. Careful attention to fluid input and output to ensure that the patient remains euvolemic is necessary.

Calcitonin is a naturally occurring hormone that inhibits bone resorption and increased excretion of calcium. Calcitonin may be effective in doses of 4 to 8 IU/kg intramuscularly or subcutaneously. This treatment, although relatively safe when renal function is normal, is not generally part of the initial emergency management of hypercalcemia.

Fifty percent of hypercalcemic cancer patients also have hypokalemia. Serum potassium levels should be monitored every 4 hours and potassium chloride (20-40 mEq intravenously or orally) supplemented as necessary to prevent severe hypokalemia.[31]

In the past 10 years, after approval by the Food and Drug Administration, bisphosphonates have become the treatment of choice for management of cancer-induced hypercalcemia, supplanting all other pharmacologic approaches except corticosteroids. Bisphosphonates act by binding to hydroxyapatite in bone and thereby inhibiting the dissolution of crystals. These agents prevent osteoclast attachment to bone matrix and interfere with osteoclast recruitment without inhibiting bone formation and mineralization.

Several agents are now available; pamidronate, etidronate, alendronate, and zoledronate are currently available in the United States, and other more potent bisphosphonates are in development. Pamidronate (90 mg, given as an infusion during 4-24 hours) effectively and safely achieves normocalcemia within a few days (mean 4 days) in more than 90 to 95% of patients.[31] Risedronate is another bisphosphonate that is being evaluated in oral form for the treatment of hypercalcemia. Because of the lag in onset of effect, bisphosphonates should be combined with faster-acting therapeutic modalities mentioned earlier.

NEOPLASTIC CARDIAC TAMPONADE

Although cardiac tamponade resulting from neoplasm is uncommon, it can occur abruptly and result in death if it is not treated quickly. In most cases, neoplastic cardiac tamponade is observed in patients with a previous diagnosis of cancer, typically at late stages of the disease. It is rarely seen as the initial manifestation of an extracardiac malignant neoplasm.

The decompensated state of cardiac function comes from a marked rise in intrapericardial pressure caused by accumulation of fluid within the pericardial sac due to malignant disease or pericardial thickening with scar formation, which results in a thick constrictive neoplastic encasement. This condition, if it is not recognized and decompressed promptly, can lead to circulatory compromise and death. Signs and symptoms are partially affected by the rapidity of development. In the era before diagnostic ultrasonography, this medical-oncologic emergency was often unrecognized in a timely manner. In most instances, pericardial effusion is accompanied by signs and symptoms that presage the development of the clinical picture of tamponade, including dyspnea, apprehension, anxiety, and chest pain. In rare instances, tamponade may be the first manifestation of the malignant disease, solid tumor, or leukemia. Any patient in the ED with a history of cancer, shortness of breath, and hypotension should be suspected of having pericardial tamponade. The diagnoses of pulmonary embolism, congestive heart failure, and anxiety can be mistakenly made in this setting.

Etiology

The most common cause of neoplastic pericardial tamponade is malignant pericardial effusion, often associated with postirradiation pericarditis, fibrosis, and effusion. Only rarely does a tumor or radiation fibrosis cause a neoplastic constrictive pericarditis with resultant tamponade. In most reported cases, cardiac

www.ketabpezeshki.com 66485457-66963820

tamponade represents a clinical progression of neoplastic or post-irradiation pericarditis.

Neoplastic pericarditis can result from any number of benign, malignant, primary, or secondary tumors of the pericardium or mediastinum. The most common benign tumors of the pericardium or mediastinum are fibromas, angiomas, and teratomas. Pericardial mesothelioma can have a clinical course characterized by rapid accumulation of massive quantities of bloody pericardial fluid, eventually leading to tamponade. Secondary involvement of the pericardium may result from either direct invasion from structures or metastases from a distant primary tumor. These metastases are usually multiple rather than solitary lesions. The tumors most commonly associated with pericardial involvement are those of the lung and breast, leukemia, Hodgkin's and non-Hodgkin's lymphomas, melanomas, gastrointestinal primary tumors, and sarcomas. Clinically recognizable symptoms or signs of pericardial disease are difficult to appreciate before death. Less than 30% of patients with autopsy-proven malignant pericardial disease were diagnosed ante mortem.

Radiation pericarditis has been a well-known complication of radiation therapy since the introduction of modern megavoltage techniques. The cardiac effects of radiation therapy may be manifested immediately with acute pericarditis or delayed for months to years, although the majority develop effusion within the first year. The acute forms are inflammatory or effusive, usually self-limited, and subside without residual constriction; the chronic effusive and constrictive types may lead to tamponade and death.

Neoplastic constrictive pericarditis, although rare, may be caused by the invasion of the pericardium by metastatic lesions or indirectly from the complications of radiation therapy with resultant fibrous thickening of the pericardium. Each of these entities can progress to cardiac tamponade because of thickening by tumor or radiation fibrosis, resulting in a decrease in the distensibility of the pericardium, thus reaching the critical point of cardiopulmonary decompensation earlier, despite smaller volumes of slowly accumulating effusion.

The symptoms and signs of neoplastic and radiation pericarditis mimic pericarditis from other causes. Because of the usual insidious onset of the effusion of fibrous pericardial thickening, the condition might be attributed to the underlying malignant disease and not considered until the full-blown picture of cardiac tamponade develops.

Pathophysiology

The severity of cardiac tamponade and eventual cardiopulmonary decompensation increases with more rapid pericardial fluid accumulation, larger fluid volumes, and worsening cardiac function. Clinically, the progressive elevation of intracardiac pressure interferes with ventricular expansion and results in a decrease in the cardiac volume. Intracardiac chamber pressures rise rapidly with subsequent transmission of this pressure peripherally in pulmonary and venacaval beds. In an effort to maintain cardiac output, various compensatory mechanisms come into play (tachycardia, peripheral vasoconstriction, decrease in renal flow with resultant increase in blood volume by sodium and water retention), all to maintain arterial pressure and venous return. When these compensatory mechanisms fail to maintain cardiac output, ventricular end-diastolic pressure increases and subsequent circulatory collapse is impending. The signs and symptoms parallel these pathophysiologic changes. The most common symptoms include extreme anxiety and apprehension, a precordial oppressive feeling, and actual retrosternal chest pain with dyspnea of varying degrees. True orthopnea and paroxysmal nocturnal dyspnea are uncommon; when they occur, the patient assumes a variety of positions to obtain relief from the chest pain and the dyspnea. Other prominent symptoms include cough, hoarseness, hiccups, and occasional gastrointestinal manifestations, such as dysphagia, nausea, vomiting, and epigastric or right upper quadrant abdominal pain that is probably the result of visceral congestion.[32]

Clinical Features

Patients with severe tamponade are acutely ill and may appear ashen, pale, or markedly diaphoretic with an impaired consciousness ranging from mildly confused to unresponsive. Rapid, shallow, and occasionally labored breathing may be present along with peripheral cyanosis and distended jugular veins. Seizures have been reported. Striking facial plethora and a full neck secondary to edema (Stokes collar) can also be seen in SVCS. Pulses are soft and easily compressible. The systolic blood pressure is usually low, with a decreased pulse pressure, although normal systolic, diastolic, and pulse pressures have been reported with moderate degrees of tamponade. Kussmaul's signs (muffled heart sounds, an enlarged cardiomediastinal silhouette, tachycardia, and, most notably, pulsus paradoxus) are extremely useful findings in the physical evaluation of tamponade (Box 123-8). Ascites, hepatomegaly, peripheral edema, and mottling are other findings that reflect the elevation in venous pressure and decrease in cardiac output.[33]

Box 123-8 Physical Evaluation of Neoplastic Cardiac Tamponade

Beck Triad or Acute Compression Triad

Described in 1935, this complex of physical findings refers to increased jugular venous pressure, hypotension, and diminished heart sounds.

These findings result from a rapid accumulation of pericardial fluid. However, this classic triad is usually observed in patients with acute cardiac tamponade.

Pulsus Paradoxus or Paradoxical Pulse

This is an exaggeration (>12 mm Hg, or 9%) of the normal inspiratory decrease in systemic blood pressure.

For measurement of the pulsus paradoxus, patients are often placed in a semirecumbent position; respirations should be normal. The blood pressure cuff is inflated to at least 20 mm Hg above the systolic pressure and slowly deflated until the first Korotkoff sounds are heard only during expiration. At this pressure reading, if the cuff is not further deflated and a pulsus paradoxus is present, the first Korotkoff sound is not audible during inspiration. As the cuff is further deflated, the point at which the first Korotkoff sound is audible during both inspiration and expiration is recorded. If the difference between the first and second measurement is greater than 12 mm Hg, an abnormal pulsus paradoxus is present.

The paradox is that while listening to the heart sounds during inspiration, the pulse weakens or may not be palpated with certain heartbeats, while S_1 is heard with all heartbeats.

A pulsus paradoxus can be observed in patients with other conditions, such as constrictive pericarditis, severe obstructive pulmonary disease, restrictive cardiomyopathy, pulmonary embolism, rapid and labored breathing, and right ventricular infarction with shock.

A pulsus paradoxus may be absent in patients with markedly elevated left ventricular diastolic pressures, atrial septal defect, pulmonary hypertension, and aortic regurgitation.

Kussmaul's Sign

This was described by Adolph Kussmaul as a paradoxical increase in venous distention and pressure during inspiration.

This sign is usually observed in patients with constrictive pericarditis but occasionally is observed in patients with effusive-constrictive pericarditis and cardiac tamponade.

www.ketabpezeshki.com 66485457-66963820

Ancillary Evaluation

Low voltage and the nonspecific findings of pericardial effusion, sinus tachycardia, ST elevation, and nonspecific ST-T wave changes may occur. Electrical alternans is the sinusoidal variation in QRS size—usually in a 2:1 ratio—secondary to the pendular effect of the heart's swinging in the fluid medium of the pericardial sac. It may be observed in patients with myocardial ischemia, acute pulmonary embolism, and tachyarrhythmias. Electrical alternans with 1:1 total atrial-ventricular complexes is an uncommon yet pathognomonic sign of cardiac tamponade.

Radiographic signs of tamponade suggestive of pericardial effusion include an enlarged cardiac silhouette with clear lung fields and normal vascular pattern, although a normal chest radiograph does not exclude tamponade. The typical "water-bottle" appearance of the heart on a plain radiograph is often present. Echocardiography is the simplest and most sensitive of diagnostic tests and can be done at the bedside for confirmation of pericardial effusion. Thoracic CT has also become an important diagnostic tool in diagnosis of pericardial effusions in more clinically stable patients.

Cardiac tamponade should be considered in any cancer patient with dyspnea. Highly suggestive symptoms include clouded sensorium, thready pulse, pulsus paradoxus exceeding 50% of the pulse pressure, low systolic pressure, engorged neck veins with a rising peripheral venous pressure above 130 mm H_2O, falling pulse pressure below 20 mm Hg, and electrical alternans. In this setting, sudden death may occur and emergent pericardiocentesis is indicated.

Management

In the ED, bedside, blind, percutaneous pericardiocentesis resulting in immediate removal of the pericardial effusion is a lifesaving treatment of cardiac tamponade. The procedure carries some risk, including induction of cardiac dysrhythmias and hemorrhage from an injured coronary vessel. Aspiration of as little as 50 to 100 mL of fluid will temporarily alleviate the pathologic process.[34]

Echocardiographically guided pericardiocentesis can also be performed in the ED, but the cardiac catheterization laboratory is a more controlled setting and is preferable. Removal of the maximal amount of fluid is advisable, along with insertion of an indwelling catheter because fluid may reaccumulate during the first 24 hours. Once the pericardial fluid has been obtained, it must be sent for biochemical and cytologic analysis. Neoplastic cardiac tamponade accounts for at least 50% of all reported cases of pericardial fluid collection. Other types of supportive therapy may be needed during the evaluation process while preparing for pericardiocentesis, such as intravenous hydration with normal saline and oxygen therapy. Once the patient has been stabilized, additional therapeutic intervention is planned and initiated by the appropriate admitting services in that reaccumulation of effusion in neoplastic tamponade is not easily managed on a short-term basis. Pericardial windows, radiation therapy, intrapericardial chemotherapy, and pericardiectomy may be justified.

The prognosis after neoplastic cardiac tamponade depends on the underlying type and extent of cancer. The presence of total electrical alternans is an adverse prognostic sign, even when the alternans disappears with pericardiocentesis. Despite a poor prognosis for patients with cancers such as melanoma and non–small cell lung cancer, some patients with treatment-responsive lymphomas have survived long term after neoplastic cardiac tamponade.

NEUROLOGIC EMERGENCIES

Of all patients with cancer, 15 to 20% have neurologic complications.[34] Neurologic symptoms are occasionally the presenting complaint in patients with systemic cancer, but more often symptoms develop in patients known to have cancer. Neurologic emergencies in cancer patients include malignant spinal cord compression, cerebral herniation, seizures, CNS infections, and reversible toxic or metabolic encephalopathies.

Malignant Spinal Cord Compression

Principles of Disease

Malignant spinal cord compression (MSCC) from metastatic cancer is common, serious, and potentially treatable. It occurs in approximately 1 in 12,700 cancer patients in the United States annually.[34] Pretreatment neurologic status is the most significant predictor of function after treatment.[35]

MSCC most commonly occurs when malignant disease metastasized to the spine extends into the epidural space, causing compression of the spinal cord, but it can also occur with direct metastasis of the epidural or dural tissue. Of all osseous sites, the spinal column is the most common site of metastatic deposits.[35] Acute compression causes occlusion of the epidural venous plexus, compromising the blood–spinal cord barrier, resulting in inflammation and vasogenic edema. At this stage, corticosteroids may mitigate the damage. Untreated, spinal cord ischemia, infarction, and irreversible damage result.

Although all tumors can potentially cause MSCC, it is most often caused by breast, prostate, and lung carcinoma.[34] Less common causes of spinal cord compression in patients with cancer include non-Hodgkin's lymphoma, melanoma, myeloma, renal cell carcinoma, vertebral subluxation, spinal epidural hematomas and abscesses, and intramedullary metastasis. Acute myelopathy in patients with cancer may also be caused by radiation, paraneoplastic necrotizing myelitis, ruptured intervertebral disk, and meningeal carcinomatosis with spinal cord involvement. Most cases (68%) of epidural cord compression occur in the thoracic spine, 15% in the cervical spine, and 19% in the lumbosacral spine.[35]

Clinical Features

Back pain, either local or radicular, is the initial symptom in 95% of patients with epidural metastasis and is usually reported to be worse at night.[36] It may be acute in onset or develop insidiously during weeks to months and usually predates other symptoms. The pain may increase during physical examination with spinal percussion, neck flexion, Valsalva maneuver, or straight leg raising; it is usually located at the level of the tumor, although radicular pain is reported if the tumor compresses or invades the nerve roots.[37]

Motor deficits are the second most commonly reported symptoms associated with MSCC, followed by sensory deficits.[36] Other symptoms are usually present at the time of diagnosis and may include weakness (75% of patients) and autonomic or sensory symptoms (50% of patients). Fifty percent of patients are not ambulatory at the time of diagnosis. The neurologic examination usually reveals symmetrical weakness with either flaccidity and hyporeflexia (if the diagnosis is made very early) or spasticity and hyper-reflexia (if the diagnosis is made later). The severity of MSCC can be scored according to several grading systems, some of which include assessment of bowel and bladder function. These are useful in assessing predicted response to therapy.

Diagnostic Strategies

Plain films show evidence of tumor in the vertebral body in 70 to 90% of patients with vertebral metastases.[37] They have a false-negative rate of 10 to 30%, so they should not be used to rule out

www.ketabpezeshki.com 66485457-66963820

compression, nor should obtaining plain films delay MRI or myelography, the study of choice when compression is a consideration. In cases with questionable findings on plain films of the spine, tomograms, coned-down views, or CT may reveal bone metastases not otherwise appreciated.

The "gold standard" for the diagnosis of MSCC is MRI, with a sensitivity of 93%, a specificity of 97%, and an overall accuracy of 95%.[18] If MRI is not available, CT myelography can be used. Lack of neurologic deficits should not inhibit further investigation but may affect the urgency of evaluation. For those patients with back pain only and normal findings on neurologic examination, the spine can be imaged within 72 hours. Those with neurologic deficits need urgent evaluation before nerve damage becomes permanent. Many patients have compression in more than one site of the spine, and therefore the entire spine needs to be imaged.[38] When myelography is used, it can demonstrate a complete or nearly complete obstruction of contrast dye flow at the level of vertebral body involvement.

Management

Because minimal weakness at the time of presentation may progress to profound, irreversible weakness in several hours, rapid initiation of treatment is indicated. Corticosteroids are first-line treatment of most patients with MSCC. Steroids decrease the vasogenic edema and inflammation. In the ED, a loading dose of dexamethasone is recommended. There is still no consensus on the optimal dose, but it is typically given as an intravenous bolus of 10 to 16 mg, followed by 4 to 6 mg every 4 hours with a taper during or immediately after completion of radiation therapy.[38] Immediate oncology and radiation oncology consultations should be obtained. High-dose corticosteroids (e.g., dexamethasone 100 mg) are occasionally administered by an oncologist; however, this is associated with complications, and their use is controversial.[38]

Palliative radiation therapy has been the standard of care for patients with malignant MSCC since the 1950s and is generally initiated after steroid treatment. The prognosis depends on the radiosensitivity of the tumor, the location of the compression, the pretreatment performance status, and the rate of decompensation. The role of surgical decompression has evolved since the 1980s with the advancement of surgical techniques and spinal instrumentation. In 2005, Patchell and colleagues published the first randomized trial that compared direct decompressive and reconstructive surgery, followed by postoperative radiation therapy with radiation therapy alone.[39] This landmark study demonstrated the advantage of a surgical approach in the management of MSCC. However, surgery is not appropriate in all patients, particularly if the patient is not a surgical candidate or has a life expectancy that might be less than necessary for recovery.

Intramedullary metastases are similar in presentation and treatment to epidural cord compression but are associated with a very poor prognosis. A rapidly progressive paraparesis and back pain are seen. MRI or myelography can establish the diagnosis; the treatment is surgical decompression. In cases of thrombocytopenia, platelet transfusions may limit progression of this process.

Encephalopathy

Toxic and metabolic encephalopathies are considerations when patients with cancer have an acute or subacute alteration in mental status. Toxic and metabolic causes should be routinely excluded even when infection or a metastatic complication is suggested. Signs of encephalopathy include confusion, aberrant behavior, and decreased level of consciousness. These may develop acutely or insidiously during days to weeks. Patients with cancer are particularly susceptible to toxic and metabolic encephalopathy because the disease can have multiple organ system involvement and can cause electrolyte and nutritional abnormalities, and the drugs used to treat the disease (especially chemotherapeutic agents and narcotics) can cause encephalopathy even in therapeutic doses. In the ED, encephalopathic patients should first be evaluated carefully for a possible infection or mass lesion, and when these are ruled out, evaluation for toxic and metabolic causes must be pursued. The metabolic workup includes electrolytes; blood urea nitrogen, creatinine, glucose, and calcium levels; arterial blood gas analysis; and liver function tests. Toxicology screens are recommended in possible ingestions and in patients who are unable to give a history. Naloxone and 50% dextrose should be given while the workup is proceeding. Specific treatment is indicated for any abnormalities found during the workup. Hospital admission is usually required unless the cause is easily and rapidly reversible and is unlikely to recur.

KEY CONCEPTS

- Hypercalcemia due to malignant disease is unrelated to bone metastases in 20% of patients and is associated with a poor prognosis independent of therapeutic response. Hydration and use of bisphosphonates (e.g., pamidronate) have become the mainstays of initial treatment.
- Spinal cord compression arises as back pain in more than 95% of patients. The ability to ambulate is maintained in 80% of patients who are ambulatory at the time of diagnosis. MRI has become the diagnostic modality of choice, and high-dose dexamethasone is given to all patients, followed by radiation therapy in most cases.
- Superior vena cava obstruction is rarely life-threatening and requires tissue diagnosis. Although it is caused by malignant disease in 70 to 80% of cases, thrombosis secondary to indwelling central lines is increasing as a cause. Stenting of the SVC has become the approach to SVC obstruction unresponsive to chemotherapy, radiation therapy, or both.
- Fever in the neutropenic cancer patient is a true medical emergency requiring rapid diagnosis, cultures, and treatment with broad-spectrum, bactericidal, synergistic antimicrobials. An aminoglycoside plus an extended-spectrum penicillin and third-generation cephalosporin with or without vancomycin remain the standard combinations in patients without penicillin allergy.
- Neoplastic pericardial effusion can arise insidiously with symptoms such as apprehension, anxiety, dyspnea, and weakness. Bedside ultrasonography has become a rapid, safe imaging modality to establish the diagnosis before the development of clinically apparent tamponade in a critically ill patient.
- Acute TLS, previously limited to hematologic malignant neoplasms, is now being described in patients receiving chemotherapy for solid tumors. It can arise with dyspnea, mental status changes, cardiac dysrhythmia, or seizures. Treatment includes urinary alkalinization and emergency hemodialysis in cases complicated by acute renal failure.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Higdon ML, Higdon JA: Treatment of oncologic emergencies. *Am Fam Physician* 2006; 74:1873-1880.
2. National Cancer Institute: *Estimated New Cancer Cases and Deaths for 2010 All Races, by Sex. SEER Cancer Statistics Review 1975-2007*. Available at http://seer.cancer.gov/csr/ 1975_2007/results_single/sect_01_table.01.pdf.
3. American Cancer Society: *Estimated New Cancer Cases and Deaths by Sex for All Sites, U.S., 2007*. Available at www.cancer.org/downloads/stt/CFF2007EstCsDths07.pdf.
4. American Cancer Society: *Global Cancer Facts & Figures 2007*. Available at www.cancer.org/downloads/stt/Global_Cancer_Facts_and_Figures_2007_rev.pdf.
5. American Cancer Society: *Cancer in Children*. Available at www.cancer.org/cancer/cancerinchildren/detailedguide/cancer-in-children-types-of-childhood-cancers.
6. National Cancer Institute: *Cancer Trends Progress Reports—2007 Update*. Available at http://progressreport.cancer.gov.
7. Barbera L, Taylor C, Dudgeon D: Why do patients with cancer visit the emergency department near the end of life? *CMAJ* 2010; 182:563-568.
8. Hughes WT, et al: 2002 Guidelines for use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002; 34:730-751.
9. Oude Nijhuis CS, et al: Routine radiography does not have a role in the diagnostic evaluation of ambulatory adult febrile neutropenic cancer patients. *Eur J Cancer* 2003; 39:2495.
10. Sipsas NV, Bodey GP, Kontoyiannis DP: Perspectives for the management of febrile neutropenic patients with cancer in the 21st century. *Cancer* 2005; 103:1103-1113.
11. Yoshida M, Ohno R: Antimicrobial prophylaxis in febrile neutropenia. *Clin Infect Dis* 2004; 39:S65.
12. Oude Nijhuis CS, et al: Fever and neutropenia in cancer patients: The diagnostic role of cytokines in risk assessment strategies. *Crit Rev Oncol Hematol* 2002; 44:163-174.
13. Tamura K: Initial empirical antimicrobial therapy: Duration and subsequent modifications. *Clin Infect Dis* 2004; 39:S59.
14. Klastersky J, et al: The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* 2000; 18:3039-3051.
15. Smith TJ, et al: 2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. *J Clin Oncol* 2006; 24:3187-3205.
16. Wilson LD, Detterbeck FC, Yahalom J: Clinical practice: Superior vena cava syndrome with malignant causes. *N Engl J Med* 2007; 356:1862-1869.
17. Rice TW, Rodriguez RM, Light RW: The superior vena cava syndrome: Clinical characteristics and evolving etiology. *Medicine (Baltimore)* 2006; 85:37.
18. Behl D, Hendrickson AW, Moynihan TJ: Oncologic emergencies. *Crit Care Clin* 2010; 26:181-205.
19. Otten T, Stein P, Patel K, Mustafa S, Silbergleit A: Thromboembolic disease involving the superior vena cava and brachiocephalic veins. *Chest* 2003; 123:809-812.
20. Wan JF, Bezjak A: Superior vena cava syndrome. *Emerg Med Clin North Am* 2009; 27:243-255.
21. Nguyen NP, Borok TL, Welsh J, Vinh-Hung V: Safety and effectiveness of vascular endoprosthesis for malignant superior vena cava syndrome. *Thorax* 2009; 64:174-178.
22. Kalemkerian GP, Darwish B, Varterasian ML: Tumor lysis syndrome in small cell lung carcinoma and other solid tumors. *Am J Med* 1997; 103:363.
23. Fojo AT: *Tumor lysis syndrome*. In: DeVita VT, et al, eds. *Cancer: Principles and Practice of Oncology*, 7th ed. Philadelphia: Lippincott-Raven; 2005.
24. Holdsworth M, Nguyen P: Role of i.v. allopurinol and rasburicase in tumor lysis syndrome. *Am J Health Syst Pharm* 2003; 60:2213-2222.
25. Kwaan HC, Bongu A: The hyperviscosity syndromes. *Semin Thromb Hemost* 1999; 25:199.
26. Gertz MA, Kyle RA: Hyperviscosity syndrome. *J Intensive Care Med* 1995; 10:128.
27. Gertz MA, Fonseca R, Rajkumar SV: Waldenström's macroglobulinemia. *Oncologist* 2000; 5:63.
28. Anderson KC, Hamblin TJ, Traynor A: Management of multiple myeloma today. *Semin Hematol* 1999; 36(Suppl 3):3.
29. Flombaum CD: Metabolic emergencies in the cancer patient. *Semin Oncol* 2000; 27:322.
30. Mundy GR, Guise TA: Hypercalcemia of malignancy. *Am J Med* 1997; 103:134.
31. Barri YM, Knochei JP: Hypercalcemia and electrolyte disturbances in malignancy. *Hematol Oncol Clin North Am* 1996; 10:775.
32. Vaitkus PT, Herrmann HC, LeWinteer MM: Therapy of malignant pericardial effusion. *JAMA* 1994; 72:59.
33. Maguire WM: Mechanical complications of cancer. *Emerg Med Clin North Am* 1993; 11:421.
34. Halfdanarson TR, Hogan WJ, Moynihan TJ: Oncologic emergencies: Diagnosis and treatment. *Mayo Clin Proc* 2006; 81:835-848.
35. Sun H: Optimal management of epidural spinal cord compression. *Emerg Med Clin North Am* 2009; 27:195-208.
36. Abrahm JL, Banffy MB, Harris MB: Spinal cord compression in patients with advanced metastatic cancer: "All I care about is walking and living my life." *JAMA* 2008; 299:937.
37. Jeyapalan SA, Batchelor TT: Diagnostic evaluation of neurologic metastases. *Cancer Invest* 2000; 18:381.
38. Cole JS, Patchell RA: Metastatic epidural spinal cord compression. *Lancet Neurol* 2008; 7:459.
39. Patchell RA, et al: Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: A randomized trial. *Lancet* 2005; 366:643.

www.ketabpezeshki.com 66485457-66963820

Section Eleven

METABOLISM AND ENDOCRINOLOGY

CHAPTER 124

ACID-BASE DISORDERS

Reuben J. Strayer

Emergency physicians often manage patients who have an acid-base disorder. Although it is not typically a chief complaint, an acid-base disturbance may be the cause of a patient's symptoms and in some cases represents an immediate life threat. Unlike the supportive therapies for many physiologic derangements, which can be temporized by targeting the effects of the underlying lesion (e.g., supplemental oxygen for pneumonia), the treatment of many acid-base derangements is contingent on identification and treatment of the cause. Emergency physicians must therefore recognize when an acid-base disorder is present and have a diagnostic approach. This chapter presents the essential elements of acid-base physiology, describes the most important causes of acid-base derangements, and highlights key steps in their management.

PRINCIPLES OF DISEASE

Many basic cellular processes are sensitive to small changes in serum pH; the kidneys, lungs, and physiologic buffers therefore defend serum pH, which is normally between 7.36 and 7.44. Serum pH is determined by the relative concentrations of bicarbonate (HCO_3^-) and carbon dioxide ($Paco_2$); when two of these variables are known, the third may be calculated. Most blood gas analyzers measure pH and $Paco_2$ and report a calculated [HCO_3^-]; most laboratories, when they report a serum bicarbonate concentration, are reporting a measured *total carbon dioxide concentration,* which is the sum of the serum bicarbonate and dissolved carbon dioxide. The dissolved carbon dioxide usually contributes negligibly to total carbon dioxide concentration but can become significant in patients with hypercapnia.

An acidosis is a process that lowers HCO_3^- or raises $Paco_2$ and tends to create an acidemia, which exists when serum pH is below 7.36. An alkalosis conversely represents a process that raises HCO_3^- or lowers $Paco_2$ and tends to create an alkalemia, which is present when serum pH is above 7.44. The terms *acidemia* and *acidosis* are not interchangeable; acidosis (or alkalosis) describes a process that pushes serum pH down (or up); acidemia and alkalemia describe the serum pH itself. A patient who is acidemic has at least one acidosis but may have two or more acidoses and may also have one or more alkaloses. Patients with normal serum pH, that is, without acidemia or alkalemia, may have acidoses and alkaloses whose net effect is serum neutrality.

Bicarbonate concentration is predominantly regulated by the kidneys and $Paco_2$ by lung ventilation. Diseases that affect kidney function may therefore produce a metabolic acidosis or alkalosis, for which the lungs will try to compensate by decreasing or increasing $Paco_2$, respectively. Likewise, pulmonary insults cause a respiratory acidosis or alkalosis, for which the kidneys will try to compensate by raising or lowering serum HCO_3^-, respectively.

In the majority of acid-base disturbances, the role of the emergency physician is to identify and manage dangerous causes of the disturbance. Uncommonly, the acid-base disorder is severe enough that the resulting acidemia or alkalemia *itself* is dangerous; serum pH below 6.7 or higher than 7.6 is considered unsustainable and may cause cardiac hypocontractility and irritability, seizures, cerebral edema, and a variety of metabolic disturbances. In these cases, empirical therapy directed at normalization of serum pH may be warranted simultaneously with a search for the underlying process or processes.

A reduced serum bicarbonate concentration defines a metabolic acidosis, which may be the primary disorder or a compensation for a primary respiratory alkalosis; an elevated serum bicarbonate concentration defines a metabolic alkalosis, which may be the primary disorder or a compensation for a primary respiratory acidosis. Likewise, a reduced $Paco_2$ represents a respiratory alkalosis, and an elevated $Paco_2$ represents a respiratory acidosis. When only a primary disturbance and its corresponding compensation are present, it is described as a simple acid-base disorder. A mixed acid-base disorder exists when more than one primary disturbance occurs simultaneously.

Alterations in serum pH are resisted initially by intracellular and extracellular physiologic buffers, followed by specific responses from the lungs and the kidneys. Peripheral and central chemoreceptors adjust pulmonary minute ventilation in response to changes in serum pH. In a primary metabolic acidosis, an increase in minute ventilation lowers $Paco_2$ and pushes the serum pH closer to normal. A primary metabolic alkalosis likewise causes a reduction in minute ventilation to elevate $Paco_2$ in an attempt to restore physiologic serum pH.

The response of the kidneys to alterations in serum pH occurs over hours to days. A sustained acidemia promotes renal excretion of H^+ and retention of HCO_3^-, whereas alkalemia causes renal HCO_3^- excretion and H^+ retention. The kidney transports hydrogen ions in exchange for potassium, whose serum concentration must also be maintained within tight parameters. This may become clinically important when, for instance, correction of alkalemia is attempted: retention of H^+ cannot occur unless potassium stores are sufficient to allow urinary K^+ excretion. Potassium supplementation may therefore be necessary to alkalinize the urine in cases of, for example, heterocyclic antidepressant toxicity.

DIAGNOSTIC STRATEGIES

An acid-base disturbance is often first identified when the results of laboratory tests ordered to evaluate the patient's symptoms demonstrate alterations in bicarbonate, pH, or $Paco_2$. The possibility of an acid-base disorder is suggested by clinical events such

www.ketabpezeshki.com 66485457-66963820

Table 124-1 Categorization of Simple Acid-Base Disorders

	pH	Pa_{CO_2}	HCO_3^-	EXPECTED COMPENSATION
Metabolic acidosis	↓	↓	↓	$\Delta Pa_{CO_2} = 1.2\ \Delta HCO_3^-$
Respiratory acidosis	↓	↑	↑	$\Delta HCO_3^- = 0.10\ \Delta Pa_{CO_2}$ (acute) $\Delta HCO_3^- = 0.35\ \Delta Pa_{CO_2}$ (chronic)
Metabolic alkalosis	↑	↑	↑	$\Delta Pa_{CO_2} = 0.9\ \Delta HCO_3^-$
Respiratory alkalosis	↑	↓	↓	$\Delta HCO_3^- = 0.2\ \Delta Pa_{CO_2}$ (acute) $\Delta HCO_3^- = 0.5\ \Delta Pa_{CO_2}$ (chronic)

as toxic ingestions, severe vomiting, or diarrhea as well as in patients with diseases affecting the organs responsible for maintenance of acid-base balance—primarily the lungs and kidney. All critically ill patients and certainly all patients being mechanically ventilated require an assessment of acid-base status.

When an acid-base disturbance is identified or suspected, elucidation of its underlying cause or causes is central to appropriate management. When the cause of an acid-base disturbance is not evident, the emergency evaluation begins with a full history and physical examination and proceeds with targeted laboratory studies.

Simple acid-base disorders are categorized by the serum pH, Pa_{CO_2}, and HCO_3^- concentrations (Table 124-1). When the primary disturbance is identified, the next step is to determine its etiology and whether an appropriate compensation has occurred. An inappropriate compensation suggests that the process underlying the primary disturbance has hindered an appropriate response or that more than one primary disturbance is present. Simple formulas allow the calculation of an appropriate response once the primary disturbance has been categorized. Compensatory processes generally return pH toward normal but not to normal and never beyond normal; such an exaggerated "compensation" actually represents a second primary disorder.

Blood gas and serum chemistry analysis allows calculation and interpretation of the serum anion gap.

$$\text{Anion gap} = Na^+ - (Cl^- + HCO_3^-)$$

Plasma must remain electrically neutral: the sum of anions and cations must be equal. Because routinely measured cations exceed routinely measured anions, the anion gap represents the concentration of anions other than chloride and bicarbonate in the blood. A variety of these anions are normally present, but serum albumin accounts for most of the physiologic (normal) anion gap, which is usually between 9 and 15. The higher the anion gap, the more likely that one or more *unmeasured anions* is generating a metabolic acidosis. Besides albumin, classic unmeasured anions such as lactate and ketones are now also routinely measured and can be incorporated into a diagnostic pathway (albumin concentration reported in grams per deciliter must be corrected by multiplying by 2.5 to be included in anion gap calculations). Unmeasured cations are also present and may account for an elevated anion gap in cases of hypomagnesemia or hypocalcemia, often in combination with hypokalemia (because serum potassium concentration varies so little, it is usually left out of anion gap calculations and is therefore functionally an unmeasured cation). Elevated concentrations of unmeasured cations may cause a *low* anion gap (<3 mEq/L), such as in cases of lithium toxicity and hypergammaglobulinemia seen in multiple myeloma. Bromide toxicity and hypertriglyceridemia may confound electrolyte measurements and also cause a low or negative anion gap.

Hypoalbuminemia is common and consequential from an acid-base perspective because as albumin is the primary contributor to the "normal" anion gap, significant depression of serum albumin will reduce the anion gap, which could mask the presence of an important unmeasured anion. For example, a chronically malnourished alcoholic may present with alcoholic ketoacidosis but also long-standing hypoalbuminemia, which causes a substantial increase in serum bicarbonate (hypoalbuminemia is in fact a state of metabolic alkalosis). The acute ketonemia therefore reduces serum bicarbonate to "normal," and no anion gap is present. Patients at risk for hypoalbuminemia who present with any significant illness should have serum albumin measured, and if it is low, a normal serum bicarbonate concentration represents a metabolic acidosis. The anion gap can be adjusted to reflect hypoalbuminemia, when albumin is measured in grams per deciliter, by the following formula:

$$\text{Adjusted anion gap} = \text{observed anion gap} + 2.5(4.2 - \text{serum albumin})$$

A normal anion gap does not exclude clinically significant acidosis or high concentrations of unmeasured anions. Direct measurement of compounds that often produce an elevated anion gap (e.g., lactate, ketones, toxic alcohols) should still be pursued when there is clinical concern despite a normal anion gap.

Independent of bicarbonate levels, sodium and chloride play an important role in acid-base status. When $[Na^+] - [Cl^-]$, the so-called strong ion difference, is significantly less than 38, an acidosis is present. An alternative to using the anion gap to identify both the presence and cause of acid-base disorders has the clinician start with the base excess (as calculated by a blood gas analyzer), subtract the sodium chloride effect,* and subtract the albumin effect.† What remains is, in the case of metabolic acidosis, the unmeasured anions (e.g., lactate, ketones, uremic acids, toxic alcohols, or other toxins; see later).[1]

Painful arterial blood sampling is unnecessary for the evaluation of acid-base disturbances. Pa_{CO_2}, HCO_3^-, and pH values taken from peripheral venous, central venous, intraosseous, and capillary blood are all suitable for acid-base assessment.[2-4]

RESPIRATORY ACIDOSIS

Respiratory acidosis occurs when hypoventilation leads to an inappropriately elevated Pa_{CO_2} and resulting acidemia. Any condition that reduces minute ventilation may cause respiratory acidosis (Box 124-1). This commonly occurs acutely in the setting of airway embarrassment, pulmonary insults, major trauma, intracranial catastrophe, or central nervous system (CNS) depressants and chronically in progressive lung disease, neurologic muscle weakness conditions, or obesity hypoventilation syndrome. Respiratory acidosis may be accompanied by hypoxemia, which, depending on its pace and severity, will cause end-organ effects such as headache, ischemic chest pain, altered mental status (usually agitation), bradycardia, and circulatory collapse. When tissue oxygenation is adequate, hypercapnia—which is better tolerated than hypoxemia—tends to produce somnolence and obtundation with cerebral vasodilation and resulting elevation of intracranial pressure.

Beginning 6 to 12 hours after onset of the insult and progressing for 3 to 5 days, the kidneys respond to a respiratory acidosis by retaining bicarbonate; the resulting compensatory metabolic

*Sodium chloride effect = $[Na^+] - [Cl^-] - 38$.
†Albumin effect = 2.5(4.2 − [albumin]).

www.ketabpezeshki.com 66485457-66963820

Box 124-1 Causes of Respiratory Acidosis

Acute
Airway obstruction
Pulmonary disease
- Pneumonia
- Asthma
- Pulmonary edema
- Aspiration pneumonitis

Central nervous system depression
- Recreational drugs (opiates, barbiturates, benzodiazepines, alcohol, γ-hydroxybutyrate [GHB])
- Intracranial catastrophe (intracerebral hemorrhage, subarachnoid hemorrhage, cerebrovascular accident)
- Intravenous sedation

Neuromuscular disorders
- Myasthenia gravis
- Guillain-Barré syndrome

Thoracic trauma
- Pneumothorax
- Flail chest

Chronic
Lung disease
- Chronic obstructive pulmonary disease
- Interstitial lung disease, idiopathic pulmonary fibrosis

Neuromuscular disorders
- Amyotrophic lateral sclerosis
- Muscular dystrophy

Obesity hypoventilation (pickwickian) syndrome

Box 124-2 Causes of Respiratory Alkalosis

Hyperventilation caused by hypoxia
- High altitude
- Severe anemia
- Ventilation-perfusion mismatch

Central hyperventilation
- Voluntary or psychogenic
- Cerebrovascular accident
- Increased intracranial pressure (tumor, hemorrhage, trauma)

Toxic or pharmacologic
- Salicylates
- Caffeine, nicotine
- Catecholamines
- Thyroxine

Pulmonary
- Pulmonary embolism
- Pneumonia
- Pulmonary edema
- Asthma
- Mechanical hyperventilation (iatrogenic)

Endocrine
- Pregnancy
- Hyperthyroidism

Septicemia
Hepatic encephalopathy
Hyponatremia

alkalosis, with an elevated serum bicarbonate level, partially corrects serum pH. Chloride ions are excreted in the urine to increase serum HCO_3^-; patients with chronic respiratory acidosis (e.g., as seen in chronic obstructive pulmonary disease) are therefore often noted to have hypochloremia. An appropriate metabolic compensation for respiratory acidosis is an increase of approximately 3.5 mEq/L in serum HCO_3^- concentration for every increase of 10 mm Hg in $Paco_2$; a patient with chronic respiratory disease resulting in a baseline $Paco_2$ of 60 mm Hg would therefore be expected to have a serum bicarbonate level of approximately 30 mEq/L (and a slight acidemia).

Acute respiratory acidosis is the most immediately dangerous of the acid-base disturbances; fortunately, it is usually also the most readily treatable, as pulmonary ventilation deficits are quickly addressed by therapies commonly used by emergency physicians. Relief of airway obstruction and provision of either noninvasive or mechanical ventilation will often correct imminently dangerous hypoxemia or hypercapnia as treatments directed at the underlying disorder are initiated.

Patients with chronic respiratory acidosis are often hypoxemic at baseline and may be susceptible to further hypoventilation if normal oxygen saturation levels are promptly restored.[5] Typically, a patient with chronic obstructive pulmonary disease being treated for an acute exacerbation receives high-flow oxygen and is later found to be obtunded with profound hypercapnia. It is therefore prudent to target a lower than normal oxygen saturation in patients thought to be so habituated; Spo_2 fractions in the low 90s and high 80s are usually well tolerated in this population.[6] However, supplemental oxygen must not be withheld from patients with dangerously low oxygen saturation or patients with end-organ hypoxic insults, such as myocardial or cerebral ischemia. In these cases, aggressive oxygenation therapies must be instituted, with preparations made to initiate mechanical ventilation if it is needed.

Patients with chronic respiratory acidosis who have been intubated should receive frequent blood gas analyses; standard ventilator settings applied to patients who chronically hypoventilate may precipitate posthypercapnic metabolic alkalosis. Correction of $Paco_2$ to normal levels (40 mm Hg) in this group can cause dangerous alkalemia; clinicians should target a slightly acidemic serum pH (~7.35), which, depending on the severity and chronicity of the patient's baseline respiratory acidosis, may correspond to remarkably high $Paco_2$ levels.

RESPIRATORY ALKALOSIS

Respiratory alkalosis occurs when increased minute ventilation causes a decreased $Paco_2$ and subsequent increase in serum pH. It is often associated with hysterical hyperventilation; however, as always, the emergency physician must consider dangerous conditions before arriving at a psychiatric diagnosis (Box 124-2).

Of particular interest in the differential diagnosis of acute respiratory alkalosis is salicylate toxicity, a dangerous, treatable mixed acid-base disorder (described later) that may be manifested with hyperventilation as its most prominent feature. Suicidal aspirin ingestions often produce the classic syndrome of tinnitus, hyperthermia, confusion, and a variety of metabolic derangements ultimately leading to seizures, coma, and cardiovascular collapse. Chronic salicylism, however, is notoriously subtle in its presentation and occurs in older, sicker patients who have seemingly more likely explanations for their symptoms. Emergency physicians should have a low threshold to obtain a serum salicylate level in cases of unexplained respiratory alkalosis.

Patients with respiratory alkalosis classically complain of lip and extremity paresthesias and may also experience muscle cramps and lightheadedness or even syncope as well as hypocalcemia symptoms, such as carpopedal spasm. The homeostatic response to respiratory alkalosis first involves cellular secretion of H^+ in exchange for K^+; if respiratory alkalosis persists, the kidneys excrete bicarbonate and retain chloride, leading to a compensatory metabolic acidosis with reduced serum HCO_3^-, hypokalemia, and hyperchloremia.

www.ketabpezeshki.com 66485457-66963820

Pregnant women hyperventilate throughout gestation and normally have a $Paco_2$ between 31 and 35 mm Hg, serum pH between 7.46 and 7.50, and serum bicarbonate concentration between 18 and 22 mEq/L. Clinicians should be mindful that eucapnia ($Paco_2$ ~40 mm Hg) in the pregnant patient may represent hypoventilation.[7]

As with other acid-base disorders, management of respiratory alkalosis is directed at the underlying cause. When organic causes of respiratory alkalosis have been excluded, hypocapnia symptoms can be relieved in patients with psychological hyperventilation by reassurance. The technique of using a paper bag to cause rebreathing probably works through the placebo effect rather than by changes in $Paco_2$ and carries the potential danger of inducing hypoxemia.[8]

METABOLIC ACIDOSIS

Metabolic acidosis is defined by a reduced serum bicarbonate concentration. It is a common disorder in emergency department patients and may be a diagnostic challenge for the emergency physician.

Etiology

Metabolic acidosis occurs when acids are added (either by intrinsic processes or from exogenous sources), acid excretion is impaired, or there is inappropriate loss of alkali. Metabolic acidoses are classically divided into *normal anion gap* and *elevated anion gap* to assist the clinician in determining their etiology.

Elevated Anion Gap Metabolic Acidosis

The causes of elevated anion gap metabolic acidosis are classically remembered by the mnemonic *MUDPILES*; however, it is more useful to focus on the identity of the unmeasured anion (Box 124-3). If the cause of an elevated anion gap metabolic acidosis is found to be lactate or ketones, the next step is to determine the cause of the high serum lactate or ketone concentration.

Box 124-3 Causes of Elevated Anion Gap Metabolic Acidosis

Ketoacidosis
Diabetic ketoacidosis
Alcoholic ketoacidosis
Starvation ketoacidosis

Lactic acidosis
Global tissue ischemia
  Shock
  Grand mal seizure (if persistent, consider isoniazid)
Focal end-organ ischemia (limb ischemia, mesenteric ischemia)
Inadequate blood oxygenation
  Hypoxia (from airway or breathing disorder)
  Carbon monoxide, methemoglobinemia
Inability of tissues to use oxygen from cellular poisons
  Cyanide (or nitroprusside therapy), hydrogen sulfide, aspirin, iron
Impaired lactate clearance
  Liver failure
  Metformin or phenformin
  Reverse transcriptase inhibitors (for HIV infection therapy)

Renal failure

Toxins metabolized to acids
Toxic alcohols (methanol, ethylene glycol)
Toluene
Paraldehyde
Aspirin

Severe rhabdomyolysis

Increased production of lactate is a common cause of elevated anion gap metabolic acidosis, and measurement of serum lactate is indicated when another cause is not apparent. When the elevation of the anion gap is accounted for by serum lactate concentration, the clinician next considers the causes of lactic acidosis; these may be divided into hypoxic or hypoperfusion states (most commonly shock) and exogenous cellular toxins, such as cyanide and carbon monoxide. Idiosyncratic causes of lactic acidosis include short gut syndrome (usually after bariatric surgery),[9] reverse transcriptase inhibitor therapy for human immunodeficiency virus (HIV) infection,[10] and metformin therapy. The likelihood of metformin causing lactic acidosis is thought to be enhanced by renal failure (serum creatinine > 1.5 mg/dL), congestive heart failure, coexisting metabolic acidosis, and exposure to intravenous radiologic contrast media.

Common unmeasured anions other than lactate that cause an elevated anion gap metabolic acidosis include keto acids (usually from diabetic ketoacidosis), acidic products of exogenous toxins (most importantly, the toxic alcohols), and organic acids that accumulate in renal failure.

Carbon Monoxide and Cyanide. Exposure to carbon monoxide and cyanide causes lactic acidosis through tissue hypoxia; both are important elements of the differential diagnosis of an elevated anion gap of unknown cause. Although patients extricated from fires have a variety of reasons to have a high lactate concentration, most of these patients, especially if they are obtunded or in cardiac arrest, should be empirically treated for both carbon monoxide and cyanide toxicity. In treatment of cyanide toxicity with suspected coincident carbon monoxide exposure, the nitrite portions of the antidote kit are withheld for concern that the resultant methemoglobinemia will be poorly tolerated given the carboxyhemoglobin burden. Severity of carbon monoxide exposure and treatment requirements may be better predicted by the degree of initial acidemia than by carboxyhemoglobin level.[11]

Diabetic Ketoacidosis. Diabetic ketoacidosis is a common acid-base disorder defined by hyperglycemia, ketonemia, and acidemia. It may occur in type 1 insulin-dependent diabetics or type 2 non–insulin-dependent diabetics. Patients with diabetic ketoacidosis classically complain of progressive polyuria, polydipsia, and malaise, but diabetic ketoacidosis may be manifested atypically with chief complaints of vomiting, abdominal pain, or altered mental status. Sodium concentration is *not* corrected for hyperglycemia when the anion gap is calculated because this dilutional hyponatremia affects other ions in the serum. Diabetic ketoacidosis is often caused by medication noncompliance but may complicate any physiologic stress; when diabetic ketoacidosis is diagnosed, identification of the precipitant is a management priority. Treatment focuses on volume expansion with intravenous fluids, insulin therapy, and careful attention to and replacement of electrolytes, particularly potassium.

Alcoholic Ketoacidosis. Alcoholic ketoacidosis causes an elevated anion gap metabolic acidosis that may be mistaken for the more common diabetic ketoacidosis. Alcoholic ketoacidosis is usually seen when a long-standing ethanol user abruptly stops drinking; ketones are generated by a combination of malnutrition and dehydration. Patients with alcoholic ketoacidosis may demonstrate a high anion gap, but a mixed acid-base disorder can be due to concomitant ethanol withdrawal, which may cause a respiratory alkalosis, and vomiting, which produces a metabolic alkalosis. The resultant serum pH can therefore be acidemic, normal, or alkalemic. Like diabetic ketoacidosis, alcoholic ketoacidosis includes the symptoms of vomiting, abdominal pain, dehydration, altered mental status, prostration, and lethargy; however, alcoholic ketoacidosis patients generally do not demonstrate hyperglycemia or glycosuria. In alcoholic ketoacidosis, the ratio of the keto acid

www.ketabpezeshki.com 66485457-66963820

β-hydroxybutyrate to its metabolites acetoacetate and acetone is double the ratio seen in diabetic ketoacidosis. Urine dipsticks detect acetoacetate but not β-hydroxybutyrate; this causes an apparent worsening of ketonemia as the patient metabolizes β-hydroxybutyrate to acetoacetate, whereas the patient is actually recovering.[12] The treatment of alcoholic ketoacidosis is dextrose-containing fluids; insulin is contraindicated.

Methanol and Ethylene Glycol. Methanol and ethylene glycol, the toxic alcohols, represent an important element of the emergency differential for elevated anion gap metabolic acidosis because their considerable morbidity and mortality can be prevented by timely therapy, and the presence of a wide anion gap may be the most conspicuous sign that this dangerous ingestion has occurred. Toxic alcohols are typically consumed by alcoholics seeking a less expensive drink, by children as an accidental ingestion (usually ethylene glycol, which is sweet), or in a suicide attempt. The first measurable sign of toxic alcohol poisoning is an *osmol gap,* which precedes the elevated anion gap; as the parent compounds are converted to their toxic metabolites, the osmol gap closes and the anion gap widens. Treatment centers on prevention of the enzymatic conversion of methanol and ethylene glycol into their toxic metabolites by use of either ethanol or fomepizole. Many laboratories will report a spuriously elevated lactate concentration in the presence of glycolate, a byproduct of ethylene glycol poisoning. Isopropyl (rubbing) alcohol ingestion causes intoxication, ketosis, and an osmol gap but does not cause acidosis.

Renal Failure. Under normal circumstances, the body generates a net acid load that the kidneys must continuously excrete. Any condition that reduces glomerular filtration rate will undermine this function, and unmeasured anions such as sulfate, phosphate, urate, and hippurate will generate an elevated anion gap metabolic acidosis. Administration of sodium bicarbonate is used as a bridge to renal replacement therapy when uremia-associated metabolic acidosis is severe.

Isoniazid. Grand mal seizures are associated with high lactate levels that typically resolve within 1 hour. Isoniazid (INH) toxicity is usually listed in the differential for metabolic acidosis, but consideration of INH toxicity should primarily be prompted by *intractable seizures* because it is the seizures that cause the lactic acidosis, not INH. INH toxicity is an important consideration in these cases because it causes seizures that do not respond to usual treatments of status epilepticus. Continuous seizure activity, in addition to cardiorespiratory embarrassment, causes a profound, life-threatening acidemia from lactate generation. The initial treatment of status epilepticus related to INH toxicity is the administration of vitamin B_6 (pyridoxine). Specific therapies targeting nonepileptic causes of seizures, such as hypoglycemia, eclampsia, hyponatremia, and cyanide toxicity, should also be considered in the patient with seizures unresponsive to standard therapy.

Salicylate Toxicity. Salicylate toxicity first produces a respiratory alkalosis, as described before. Untreated, the syndrome evolves into a complex acid-base disorder with paradoxical aciduria during the initial respiratory alkalosis, followed by an elevated anion gap metabolic acidosis and hyperthermia due to its interference with cellular metabolism. Serum pH can be normal during the initial phase of the disease—a false reassurance. Dehydration, electrolyte disturbances, fatigue, and lung injury ultimately lead to decompensation with respiratory acidosis—completing the so-called *triple acid-base disturbance*—followed by cardiovascular collapse. Management of aspirin toxicity includes gastrointestinal decontamination, urine alkalinization, meticulous supportive care, and hemodialysis.

Iron. Iron ingestion is a dangerous cause of metabolic acidosis that classically is manifested with prominent vomiting and other gastrointestinal symptoms from gastric irritation, followed by systemic toxicity that includes myocardial depression, liver injury, and lactic acidosis from cellular mitochondrial poisoning. A plain radiograph of the abdomen may provide evidence of an iron ingestion while serum iron concentration is determined. Treatment measures include fluid resuscitation, gastrointestinal decontamination, and chelation with deferoxamine.

Box 124-4 Causes of Normal Anion Gap Metabolic Acidosis

Gastrointestinal HCO_3^- loss
Diarrhea
Colostomy or ileostomy
Enteric fistulas
Ion exchange resins (e.g., sodium polystyrene sulfonate [Kayexalate])

Renal HCO_3^- loss
Renal tubular acidosis
Tubulointerstitial renal disease
Hyperparathyroidism

Rapid normal saline infusion

Urologic procedures
Ureterosigmoidostomy
Ureteroileal conduit

Ingestions
Acetazolamide
Calcium chloride ($CaCl_2$)
Magnesium sulfate ($MgSO_4$)

Other
Hypoaldosteronism
Hyperkalemia
Toluene (after initial elevated anion gap metabolic acidosis)

Normal Anion Gap Metabolic Acidosis

Normal anion gap metabolic acidosis is less likely to be immediately dangerous or caused by an imminently dangerous condition and is therefore of less interest to the emergency physician. The majority of cases encountered in the emergency department are caused by gastric loss of bicarbonate in the setting of diarrhea. A variety of other conditions and medications may cause a normal anion gap metabolic acidosis (Box 124-4), including renal tubular acidosis and bladder-diverting urologic procedures. An important iatrogenic cause of normal anion gap metabolic acidosis is the rapid infusion of large volumes of normal saline; 0.9% normal saline contains 154 mEq/L of sodium and chloride without bicarbonate or any other buffer and is therefore acidic compared with serum. The hyperchloremic acidosis associated with normal saline therapy is generally well tolerated and causes less physiologic derangement than in acidoses of equal magnitude caused by other mechanisms; however, in patients with existing severe acidemia who require aggressive volume resuscitation, use of a more balanced fluid (lactated Ringer's solution, Normosol, Plasma-Lyte), especially after the first several liters of normal saline, may be prudent.

Physiologic Compensation

Physiologic compensation for a metabolic acidosis occurs immediately by the extracellular bicarbonate–carbonic acid system and intracellular protein buffers. Medullary chemoreceptors augment alveolar ventilation to blow off carbon dioxide, partially correcting serum pH. In severe metabolic acidosis (pH < 7.1), hyperventilation is profound and assumes the appearance of Kussmaul's respirations, in which hyperpnea (increase in tidal volume) is seen out of proportion to tachypnea (increase in respiratory rate). In cases of prolonged metabolic acidosis, the kidney generates a compensatory aciduria by secreting H^+ and retaining HCO_3^-.

www.ketabpezeshki.com 66485457-66963820

Management

Management of metabolic acidosis is directed at identification and treatment of the underlying cause while appropriate resuscitative and supportive care is provided. An example of this paradigm is the management of generalized seizures; seizures often cause profound acidemia, but if they are terminated promptly, serum pH normalizes quickly and without sequelae. The treatment of acidemia from seizures is therefore not to treat the acidemia itself but to support the patient through the seizures and terminate the seizures.

When to treat acidemia by actively correcting serum pH, with use of intravenous sodium bicarbonate, is controversial. Theoretic harms of using intravenous sodium bicarbonate to correct acidemia include the following:

- Paradoxical CNS acidosis. Because sodium bicarbonate does not readily cross the blood-brain barrier, serum alkalinizes much faster than the cerebrospinal fluid. As serum pH rises, minute ventilation slows and carbon dioxide, which readily crosses the blood-brain barrier, delivers an additional acid load to the CNS.
- Hypokalemia (which can cause respiratory muscle weakness, impairing respiratory compensation), hypocalcemia, hypernatremia
- Volume overload
- Hyperosmolality
- Overshoot alkalosis

Many authors question the utility of bicarbonate therapy even in cases of severe acidemia, given these potential harms and the absence of demonstrated benefit.[13] However, although evidence is lacking, it is commonly recommended to treat serum pH less than 7.1 empirically with sodium bicarbonate, 1 mEq/kg, unless the underlying acidosis is thought to be quickly responsive to therapy.[14] Many experts will not treat pH above 6.7, however, especially in diabetic ketoacidosis, in which profound acidemia is usually well tolerated while the underlying lesion is corrected. Endpoints of therapy include pH above 7.1 and serum bicarbonate concentration above 10 mEq/L. A bicarbonate drip is prepared by adding 150 mEq sodium bicarbonate (three "crash cart ampules," which are usually 50 mL of 8.4% solution) to 1 liter of 5% dextrose in water and infusing as slowly as the clinical situation permits. Sodium bicarbonate should generally not be added to normal saline for concern of hypertonicity.

An important clinical pitfall is the use of sodium bicarbonate to treat metabolic acidosis without recognizing a concomitant respiratory acidosis. For example, a severe diabetic ketoacidosis patient with profound metabolic acidosis, after hours of respiratory compensation, may tire; the respiratory alkalosis in this case becomes inadequate, which is then considered a primary respiratory acidosis. Providing ventilatory support to address the respiratory acidosis is much more important than bicarbonate therapy. In an appropriate respiratory compensation for metabolic acidosis, the $Paco_2$ drops by the same amount as the serum bicarbonate concentration. It is thought that spontaneous respiration cannot sustainably reduce $Paco_2$ beyond 10 to 12 mm Hg, which is the appropriate compensatory respiratory alkalosis for a metabolic acidosis that drives the pH down to about 7.10. Noninvasive or mechanical ventilation may be required to prevent a more severe acidemia, which is likely to result in multiorgan dysfunction.

Although administration of sodium bicarbonate is unlikely to be beneficial in most cases of acidemia caused by endogenous acid production (lactic acidosis, ketoacidosis), sodium bicarbonate therapy is theoretically more attractive in conditions in which the underlying problem is bicarbonate loss (which generally causes a hyperchloremic or normal anion gap metabolic acidosis) or impairment of acid secretion, such as renal failure. Many of the acidosis syndromes caused by exogenous toxins (aspirin, heterocyclic antidepressants) call for bicarbonate as a specific therapy; these cases are distinct from the empirical use of bicarbonate to treat the acidemia itself.

Bicarbonate has been variously recommended and used as an empirical therapy in cardiac arrest. However, most studies show either no benefit or poorer outcomes in this context, and the 2010 American Heart Association guidelines state that routine use of sodium bicarbonate is not recommended for patients in cardiac arrest.[15]

In summary, sodium bicarbonate should not routinely be used to treat undifferentiated acidemia or acidemia caused by lactic acidosis or ketoacidosis. If the serum pH is so severely depressed that the acidemia itself is thought to be an immediate life threat, bicarbonate therapy is an option. A lower treatment threshold is appropriate in acidemia caused by bicarbonate loss or renal failure, and bicarbonate should not be withheld when it is specifically indicated to treat the underlying cause of an acidosis.

Acidemia causes hyperkalemia as H^+ is brought into cells in exchange for K^+. Clinicians managing patients with acid-base disturbances should therefore carefully monitor serum potassium concentration; as the acidosis resolves, serum potassium level will fall and may require supplementation. This is classically seen in diabetic ketoacidosis patients, who are invariably potassium depleted irrespective of their initial serum potassium concentration.

METABOLIC ALKALOSIS

Metabolic alkalosis occurs from the loss of H^+ or retention of HCO_3^-. Emergency physicians encounter metabolic alkalosis usually as a consequence of prolonged vomiting or nasogastric suction or as a compensation for chronic respiratory acidosis. The differential diagnosis includes a variety of predominantly endocrine and electrolyte disorders (Box 124-5). Patients taking diuretic medications may reduce their plasma volume around a steady concentration of HCO_3^-, causing a *contraction alkalosis*. Contraction alkalosis is often coincident with hypokalemia, which itself causes a metabolic alkalosis as intracellular K^+ is exchanged for H^+.

In the acute phase, the lungs compensate for a metabolic alkalosis by decreasing minute ventilation and retaining carbon dioxide, although from the perspective of an emergency physician, an acute elevation in $Paco_2$ is a primary respiratory acidosis until

Box 124-5 Causes of Metabolic Alkalosis

Volume Contracted (saline responsive)
Vomiting, gastric suction
Diuretics (contraction alkalosis)
Postrespiratory acidosis
Ion-deficient baby formula
Chloride-secreting colonic villous adenomas

Euvolemic/Volume Expanded (saline resistant)
Hyperaldosteronism
Hypercortisolemia
Severe potassium depletion
Adenocarcinoma
Bartter's syndrome

Unclassified
Hypoalbuminemia
Milk-alkali syndrome
Penicillin and related compounds
Hypercalcemia of malignancy
Massive transfusion (from citrate), especially with renal insufficiency

www.ketabpezeshki.com 66485457-66963820

dangerous causes of ventilatory insufficiency have been excluded. Prolonged metabolic alkalosis leads to compensatory renal HCO_3^- excretion.

Metabolic alkalosis rarely causes dangerous alkalemia, and the emergency management of metabolic alkalosis is directed at identification and treatment of dangerous underlying causes. Usual management of patients who have volume loss, vomiting, or hypokalemia will address the resulting *saline-responsive* metabolic alkalosis. Edematous or euvolemic patients with conditions that cause renal Na^+ retention (and accompanying H^+ loss) may have a *saline-resistant* metabolic alkalosis, but this generally does not require emergency therapy. In rare cases, severe metabolic alkalosis may cause hypocalcemic tetany, seizures, altered mental status, or dysrhythmias and require empirical therapy in the emergency department, usually in consultation with nephrology, with either acetazolamide or hydrochloric acid.

MIXED DISORDERS

A simple acid-base disorder is a combination of a primary disturbance and subsequent compensation. Mixed acid-base disorders occur when two or more primary acid-base lesions coincide. These simultaneous conditions may push the serum pH in the same or opposite directions, and each will generate its own compensatory responses; mixed disorders may therefore be difficult to recognize by either clinical or laboratory features. Most often in emergency department patients with mixed acid-base disorders, there is a dominant, precipitating problem that either complicates an existing disease or causes failure of compensatory mechanisms.

Detailed acid-bases analysis is not typically performed in the emergency department; however, knowledge of frequently used acid-base assessment concepts and common conditions that cause a mixed disturbance is valuable. The body usually does not fully compensate for a primary acid-base disorder, so, for example, a primary metabolic acidosis should generate a compensatory respiratory alkalosis, but the serum pH is expected to still be below 7.36. Whether an appropriate respiratory compensation to a metabolic acidosis has occurred can be approximated by comparing the $Paco_2$ to the last two digits of the serum pH. In a primary metabolic acidosis with appropriate respiratory compensation, these two values should be similar, that is, a patient with a serum pH of 7.20 should have a $Paco_2$ of 20 mm Hg. If the serum pH is 7.17 and the $Paco_2$ is 30 mm Hg, the respiratory compensation is less than expected and a *primary respiratory acidosis* is present. This is commonly seen in patients whose dominant condition causes a metabolic acidosis but also impairs respiration, such as sepsis.

The *delta gap* (ΔG) describes the difference between the deviation of the anion gap (AG) from normal and the deviation of the serum bicarbonate concentration from normal:

$$\Delta G = (AG - 12) - (24 - [HCO_3^-]).$$

Conceptually, calculation of the delta gap asks whether the anion gap is accounted for by the change in serum bicarbonate concentration. In patients with an elevated anion gap and a delta gap greater than +6, meaning that serum bicarbonate level is significantly higher than would be predicted by the number of unmeasured anions, a metabolic alkalosis in addition to a metabolic acidosis is likely to be present. This is commonly seen when the dominant acidosis condition causes severe vomiting (e.g., diabetic ketoacidosis). In patients with an elevated anion gap and delta gap more negative than −6, meaning that the serum bicarbonate level is significantly lower than expected given the anion gap, a normal anion gap metabolic acidosis is likely be present in addition to the elevated anion gap metabolic acidosis. This is seen most commonly when a lactic acidosis complicates severe diarrhea.

KEY CONCEPTS

- Patients with an acute severe metabolic acidosis rely on a robust respiratory compensation; in these cases the adequacy of the ventilatory response should be assessed and augmented, with noninvasive or invasive ventilation, if needed.
- Patients who have a chronic respiratory acidosis (e.g., in chronic obstructive pulmonary disease) are at risk for dangerous alkalemia if they are ventilated with routine parameters. Blood gas analysis in these cases should be performed frequently and settings titrated to serum pH.
- Alcoholic ketoacidosis may be manifested similarly to diabetic ketoacidosis but is much less common; insulin is considered contraindicated in alcoholic ketoacidosis.
- When an elevated anion gap is recognized, the initial assessment focuses on identifying its etiology as belonging to one of four causes: ketoacidosis, toxic ingestions, lactic acidosis, and renal failure (typically, only chronic renal failure causes significant acidosis).
- When the cause of an elevated anion gap is determined to be lactate or ketones, diagnostic efforts are directed at identifying the cause of the lactic acidosis or ketoacidosis.
- Sodium bicarbonate is not recommended for the empirical treatment of acidemia; it is an option in cases of severely depressed pH thought to pose an immediate life threat.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Story DA, Morimatsu H, Bellomo R: Strong ions, weak acids and base excess: A simplifed Fencl-Stewart approach to clinical acid-base disorders. *Brit J Anaesth* 2004; 92:54.
2. Kissoon N, et al: Comparison of the acid-base status of blood obtained from intraosseous and central venous sites during steady and low-flow states. *Crit Care Med* 1993; 21:1765.
3. Brandenburg MA: Comparison of arterial and venous blood gas values in the initial emergency department evaluation of patients with diabetic ketoacidosis. *Ann Emerg Med* 1998; 31:459.
4. Harrison AM, et al: Comparison of simultaneously obtained arterial and capillary blood gases in pediatric intensive care unit patients. *Crit Care Med* 1997; 25:1904.
5. Aubier M, et al: Effects of administration of O_2 on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. *Am Rev Respir Dis* 1980; 122:747-754.
6. Stoller JK: Acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 2002; 346:988-994.
7. Landon M: Acid-base disorders during pregnancy. *Clin Obstet Gynecol* 1994; 37:16.
8. van der Hout MA, Boek C, van der Molen GM, Jansen A, Griez E: Rebreathing to cope with hyperventilation: Experimental tests of the paper bag method. *J Behav Med* 1989; 11:303.
9. Uribarri J, Oh MS, Carroll HJ: D-Lactic acidosis: A review of clinical presentation, biochemical features and pathophysiologic mechanisms. *Medicine (Baltimore)* 1998; 77:73.
10. Gérard Y, et al: Symptomatic hyperlactataemia: An emerging complication of antiretroviral therapy. *AIDS* 2000; 14:2723.
11. Turner M, Esaw M, Clark RJ: Carbon monoxide poisoning treated with hyperbaric oxygen: Metabolic acidosis as a predictor of treatment requirements. *J Acad Emerg Med* 1999; 16:96.
12. McGarry JD, Foster DW: *Diabetic ketoacidosis*. In: Rifkin H, Raskin P, eds. *Diabetes Mellitus*, vol 5. Bowie, Md: Robert J. Brady Co; 1981:185.
13. Forsythe S, Schmidt G: Sodium bicarbonate for treatment of lactic acidsosis. *Chest* 2000; 117:260.
14. Kraut JA, Madias NE: Metabolic acidosis: Pathophysiology, diagnosis and management. *Nat Rev Nephrol* 2010; 6:274.
15. Neumar RW, Otto CW, Link MS, et al. Part 8: Adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122(Suppl 3):S729-S767.

www.ketabpezeshki.com 66485457-66963820

Chapter 125

Electrolyte Disorders

Camiron L. Pfennig and Corey M. Slovis

Electrolyte abnormalities are common in emergency medicine and can vary greatly in importance, severity, and symptoms. Asymptomatic electrolyte abnormalities can usually be gradually corrected, but those that cause alterations in consciousness or life-threatening dysrhythmias require immediate therapy to avoid permanent sequelae or death. In some cases, therapy for life-threatening electrolyte disorders may even need to be initiated before laboratory results become available.

HYPERKALEMIA

Principles of Disease

Hyperkalemia, defined as serum potassium level greater than 5.0 mEq/L, is the most dangerous acute electrolyte abnormality, potentially leading to life-threatening arrhythmias and death. Although hyperkalemia may have vague and varied symptoms, it is usually totally asymptomatic, with cardiac arrest as its first "symptom."[1] Thus the diagnosis of hyperkalemia depends on paying specific attention to risk factors for impaired potassium excretion, such as dehydration and renal failure, along with an awareness of medications that cause potassium retention. Evaluation of the electrocardiogram (ECG) of patients at risk for this electrolyte disturbance is critical. Hyperkalemia can be rapidly progressive, and lifesaving interventions must be instituted at the earliest suspicion of toxicity.

Upwards of 98% of potassium in the body is contained intracellularly, whereas less than 2% remains circulating in the blood. Serum potassium concentration is normally between 3.5 and 5.0 mEq/L and is tightly regulated by the kidney. In the healthy state, at least 90% of potassium excretion occurs through the kidney; in the renally impaired state, the gastrointestinal tract may account for roughly 25% of excretion. Hyperkalemia usually develops from impaired renal excretion or increased release from cells; however, in advanced chronic kidney disease or end-stage renal disease, dietary intake of potassium may be a significant factor in its development.[2]

Hyperkalemia causes cardiotoxicity by increasing the resting membrane potential of the cardiac myocyte, causing "membrane excitability" and conversely sluggish depolarization as well as decreasing the duration of repolarization. At very high levels, potassium causes the depolarization threshold to rise, leading to overall depressed cardiac function. Nearly any cardiac arrhythmia can be seen with hyperkalemia, including heart blocks, bradydysrhythmias, pseudoinfarction ST segment elevation, and the classic "sine wave" pattern. As hyperkalemia advances, the end result is cardiac arrest, usually from disintegration into ventricular fibrillation, pulseless electrical activity, or asystole. A serum potassium level of 10.0 mEq/L is usually fatal, but decompensation and death can occur at any level above 7 to 8 mEq/L.

The most common cause of hyperkalemia is spurious elevation due to hemolysis during or after the blood draw. Thus an ECG should be used to assess for true hyperkalemia while another sample is analyzed. Most causes of true hyperkalemia are due to release from cells or renal insufficiency. Renal failure is the most common cause of confirmed hyperkalemia and is often compounded by medications that further impair renal potassium handling. Box 125-1 organizes the most common causes of hyperkalemia. The presence of one of these conditions may be the lone historical clue in hyperkalemia.[3]

Clinical Features

Hyperkalemia remains a difficult clinical diagnosis to make on clinical grounds alone. It is not uncommon for a patient with mild to moderate hyperkalemia to be identified during routine blood sampling for an unrelated condition. Patients with moderate to severe hyperkalemia may have gastrointestinal effects such as nausea, vomiting, and diarrhea often in association with their underlying disease. Neuromuscular findings, including muscle cramps, generalized weakness, paresthesias, tetany, and focal or global paralysis, may be seen in patients with severe hyperkalemia. The signs and symptoms of progressive muscle weakness, paresthesias, dyspnea, and depressed deep tendon reflexes are neither sensitive nor specific, nor do they appear reliably with a particular serum potassium level.[3] Patients with severe hypokalemia may present with hemodynamic instability and cardiac arrhythmias requiring immediate intervention.

Diagnostic Strategies

The ECG is helpful in making the diagnosis of hyperkalemia and can be used in unstable patients to initiate treatment (Figs. 125-1 to 125-3). Classic electrocardiographic changes—the peaked T wave, flattened p wave with prolonged PR interval or a totally absent P wave, wide QRS, and sine wave pattern, portending imminent cardiac arrest—have been well described as appearing sequentially with rising serum potassium levels.[4,5] Peaked T waves usually appear as serum potassium levels exceed 5.5 to 6.5 mEq/L; P wave disappearance and PR prolongation are common with levels above 6.5 to 7.5 mEq/L; and QRS prolongation is seen with potassium levels above 7.0 to 8.0 mEq/L. Although these changes may occur in only half the patients, recognition of these patterns

www.ketabpezeshki.com 66485457-66963820

when they are present is vital to rapid diagnosis and initiation of lifesaving treatment.[6] A serum potassium level above 5.0 mEq/L is diagnostic of hyperkalemia, but the value itself does not always predict electrocardiographic changes or the degree of cardiotoxicity. Subtle electrocardiographic changes consistent with hyperkalemia should not be the sole reason to treat a stable patient not likely to have an elevated potassium concentration until serum levels have returned.[3]

Box 125-1 Five Most Common Causes of Hyperkalemia

Spurious elevation	Hemolysis due to drawing or storing of the laboratory sample or post–blood sampling leak from markedly elevated white blood cells, red blood cells, or platelets
Renal failure	Acute or chronic
Acidosis	Diabetic ketoacidosis, Addison's disease, adrenal insufficiency, type 4 renal tubular acidosis
Cell death	Rhabdomyolysis, tumor lysis syndrome, massive hemolysis or transfusion, crush injury, burn
Drugs	Beta-blockers, acute digitalis overdose, succinylcholine, angiotensin-converting enzyme inhibitors, angiotension receptor blockers, nonsteroidal anti-inflammatory drugs, spironolactone, amiloride, potassium supplementation

Management

Patients with suspected or known hyperkalemia require intravenous access and continuous cardiac monitoring. The treatment of hyperkalemia is based on the clinical scenario combined with the 12-lead ECG and the laboratory potassium value. The treatment strategy consists of three main steps: stabilization of the cardiac membrane, shifting of potassium into the cells, and then removal of potassium from the body. In patients who do not require urgent treatment, lowering of total body potassium may be the only step necessary. A variety of treatment options are considered for the acute management of hyperkalemia, including calcium, insulin, beta$_2$-adrenergic agonists, sodium bicarbonate, resins, and dialysis (Table 125-1).

Intravenous calcium is used to stabilize the cardiac membrane by restoring the electrical gradient. Calcium increases the depolarization threshold and the calcium gradient across the cardiac membrane, quieting myocyte excitability and increasing cardiac conduction speed, thus narrowing the QRS. Calcium does not decrease serum potassium levels, and its effect is rapid but transient. The dose is one ampule, or 10 mL of 10% calcium chloride

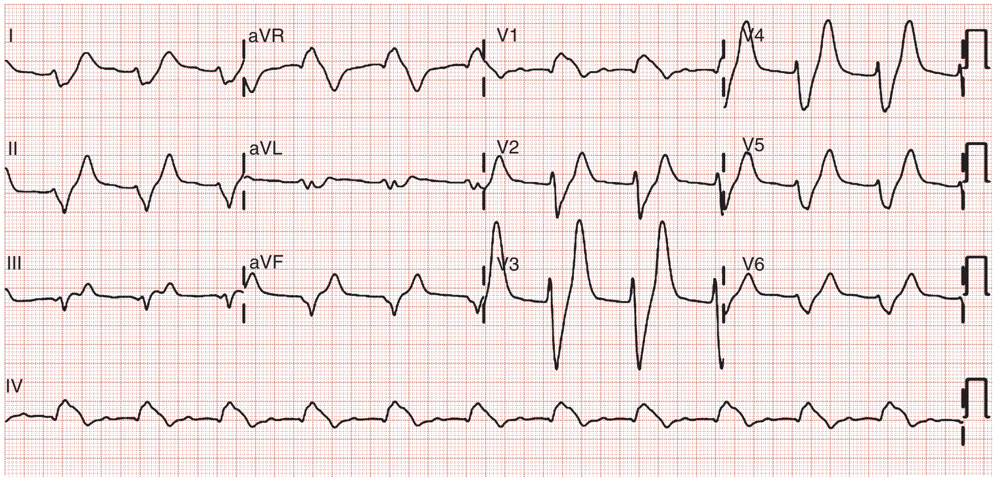


Figure 125-1. Hyperkalemia with QRS widening merging into T wave, absent P wave.

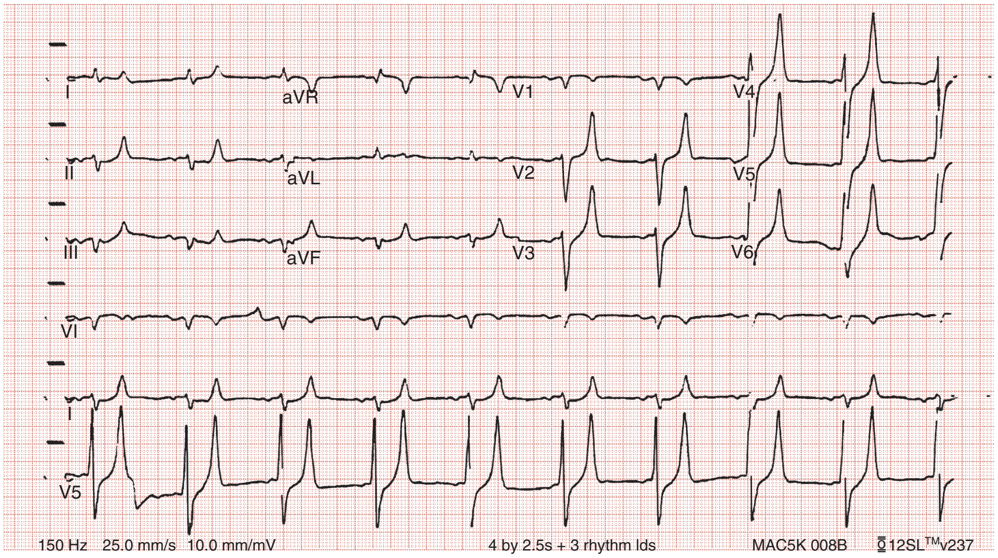


Figure 125-2. Hyperkalemia in the same patient as in Figure 125-1 after potassium-lowering therapy has begun. Tall peaked T waves, decreased P wave.

www.ketabpezeshki.com 66485457-66963820

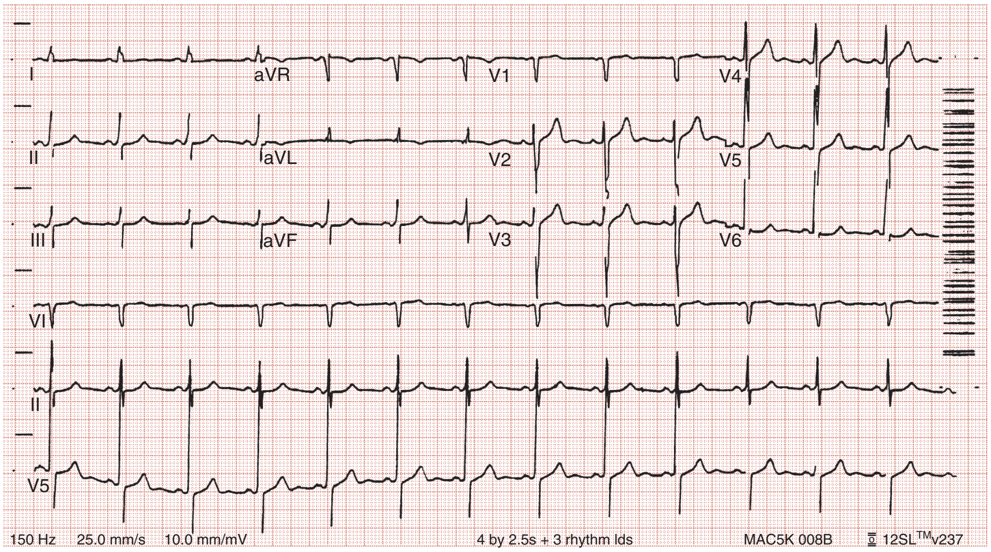


Figure 125-3. The same patient as in Figures 125-1 and 125-2 after dialysis. The electrocardiogram is now normal.

Table 125-1 Treatment of Hyperkalemia

TREATMENT	MEDICATION	FEATURES
Stabilize cardiac membrane	Calcium chloride (10 mL, maximum 20 mL) or calcium gluconate (10-30 mL), IV push	For wide QRS, restores the electrical gradient; does not decrease serum potassium
Shift potassium into cells	Insulin, 10 units, IV push, combined with 100 mL of 50% dextrose, IV push High-dose nebulized albuterol by face mask (15-25 mg by continuous inhalation) Bicarbonate 50-100 mL Normal saline 100-250 mL	If severely acidotic In conjunction with nephrologist if dialysis dependent
Remove potassium from the body	Hemodialysis Normal saline and furosemide Ion exchange resin	Emergently in cardiac arrest, urgently in renal failure; may delay if renal function is normal In patients with rhabdomyolysis or tumor lysis syndrome with intact urine output Not effective acutely

solution. Some authors prefer calcium gluconate rather than calcium chloride on the basis of the reduced risk of tissue necrosis should it extravasate at the injection site.[4,5] More than 10 mL of calcium gluconate will often be required as it contains only one third the calcium contained in calcium chloride. Calcium gluconate is also preferred in pediatric cases as well as in more chronic, less emergent hyperkalemic patients when a slow infusion is desired.

Potassium can be shifted intracellularly with beta$_2$-agonists, insulin, saline, and potentially sodium bicarbonate. Insulin is the most reliable agent to move potassium into cells, but beta$_2$-adrenergic receptor agonists also provide benefit in some patients. Insulin, given intravenously in combination with glucose to prevent hypoglycemia, also shifts potassium into cells by stimulation of the Na^+,K^+-ATPase pump. The onset of action is less than 15 minutes, and the effect is maximal between 30 and 60 minutes, with a maximal drop of 0.6 mEq/L on average.

Nebulized albuterol by face mask is effective in shifting potassium into cells by stimulation of the Na^+,K^+-ATPase pump.[6] Nebulized albuterol begins to take measurable effect after 15 minutes and lowers the serum potassium level by 0.5 to 1 mEq/L, depending on the dose.[7] The effective dose is at least four times higher than that typically used for bronchodilation.[8] Mild tachycardia is the main side effect but is generally well tolerated. The combination of nebulized albuterol and insulin with glucose appears to be additive, lowering serum potassium by a mean of 1.2 mEq/L.[9]

Saline infusions also stimulate the Na^+,K^+-ATPase pump, and only a few hundred milliliters is required for beneficial effects. Saline infusions are given judiciously in anuric patients and usually in consultation with the nephrologist. Sodium bicarbonate is effective only in hyperkalemic patients who are acidotic and has no benefit when it is used for hyperkalemia in nonacidotic patients.[10] Sodium bicarbonate buffers hydrogen ions extracellularly while shifting potassium intracellularly but should be reserved for patients with confirmed acidosis. Although intravenous magnesium also can drive potassium intracellularly, it should never be used in hyperkalemia as most patients with elevated potassium levels are also at risk for concomitant hypermagnesemia.

Potassium can best be removed from the body acutely by hemodialysis. Hemodialysis effectively and reliably decreases serum potassium levels by at least 1 mEq/L in the first hour and another 1 mEq/L during the next 2 hours.[7,11] It is the only reliable method of potassium removal that has been experimentally studied and should be instituted early in the treatment of life-threatening hyperkalemia in patients with renal failure. In patients with intact renal function, medical management alone is usually sufficient, even in extreme cases, and hemodialysis may not be necessary unless multiple medical modalities fail. There are no randomized trials addressing the use of diuretics such as furosemide in the emergent management of hyperkalemia, but in cases such as rhabdomyolysis or tumor lysis syndrome, it may be appropriate to use a normal saline infusion supplemented by furosemide to enhance diuresis and potassium excretion in the urine.

Cation exchange resins, such as sodium polystyrene sulfonate (Kayexalate), have not been shown to decrease the serum

www.ketabpezeshki.com 66485457-66963820

potassium level within the first 4 hours of treatment and should not be used in the acute management of hyperkalemia.[12]

Hyperkalemia is seen in diabetic ketoacidosis (DKA), although most hyperkalemic patients with DKA are actually total body deficient of potassium. In this insulin-deficient and acidotic state, serum potassium levels rise because of cellular shifts. Simply treating the patient's underlying DKA will also treat the hyperkalemia. In fact, the mainstay of treatment of DKA—fluids and insulin—closely mirrors the treatment of hyperkalemia itself.[13]

As hyperkalemia progresses, the end result will be cardiopulmonary arrest due to ventricular fibrillation, pulseless electrical activity, or asystole. In a known or suspected hyperkalemic arrest, an approach beginning with standard advanced cardiac life support combined with the use of multiple potassium-lowering medications is rational.[14,15] Epinephrine has been shown to lower potassium by 0.25 mEq/L.[16,17] Calcium chloride is given immediately by intravenous push, followed by insulin and glucose. Bicarbonate should be given by bolus dose if the patient is believed to be acidotic. Emergent hemodialysis is recommended if it is readily available. Hemodialysis through central venous access can be used during ongoing cardiopulmonary resuscitation to acutely lower the serum potassium level and may result in return of spontaneous circulation with intact neurologic status despite prolonged resuscitative efforts and failure of conventional medications and defibrillation.[18]

HYPOKALEMIA

Principles of Disease

Hypokalemia is the most common electrolyte abnormality encountered in clinical practice. When it is defined as a value of less than 3.5 mEq/L, hypokalemia is found in more than 20% of hospitalized patients and in 10 to 40% of patients treated with thiazide diuretics in the outpatient setting.[19] Although hypokalemia is usually asymptomatic, severe cardiac dysrhythmias and rhabdomyolysis can occur secondary to potassium's effect on the heart and muscle.[20] The five most common causes of hypokalemia are renal losses, increased nonrenal losses, decreased potassium intake, intracellular shift, and endocrine etiologies (Box 125-2). Hypokalemia is often seen in association with hypomagnesemia, and patients with low serum potassium levels should be assumed to be hypomagnesemic also.[20-22]

Increased excretion of potassium, especially coupled with poor intake, is the most common cause of hypokalemia, and patients receiving diuretics represent the single most common patient group encountered in clinical practice. Hypokalemia from thiazide diuretics occurs through increases in distal sodium delivery in the nephron and by activation of the renin-angiotensin-aldosterone system. Thiazide diuretics are more likely than loop or osmotic diuretics to cause hypokalemia, but both the thiazide and loop diuretics block chloride-associated sodium and increase delivery of sodium to the collecting tubules. Hypokalemia is a common adverse effect of treatment with diuretics and may cause fatal arrhythmias and increase the risk of digitalis toxicity.[23] In addition to diuretics, other drugs and disorders can cause significant renal potassium losses, including hyperaldosteronism, steroid excess, metabolic acidosis, DKA, renal tubular acidosis, and alcohol consumption. Penicillin and its synthetic derivatives, when they are given in large doses, promote renal potassium excretion by increasing sodium delivery to the distal nephron.

Individuals with secondary hyperaldosteronism, whether it is due to congestive heart failure (CHF), hepatic insufficiency, or nephrotic syndrome, may also exhibit hypokalemia. Patients with renal tubular acidosis can become hypokalemic because a defect in the distal tubule leads to increased potassium excretion.

Administration of insulin may cause a reduction in serum potassium because of insulin's ability to stimulate the Na^+,K^+-ATPase pump and move potassium intracellularly; hypokalemia can be a dangerous complication with intentional overdoses of insulin and during treatment of DKA. Although most patients with DKA present with high-normal or mildly elevated serum potassium levels, patients are usually 2 to 3 mEq/kg body weight deficient in total body potassium.[24] Failure to appreciate this total body deficit—and to not begin potassium infusion once significant hyperkalemia has been ruled out and intact renal function confirmed—may lead to otherwise unexplained arrhythmias or cardiac arrest in patients hours after their initial therapy has begun.

Hypokalemia can also occur from gastrointestinal and dermal losses. In diarrheal states, large quantities of potassium can be lost as the volume of stool increases and secondary hyperaldosteronism can occur. Although hypokalemia is often seen after protracted vomiting or nasogastric suctions, only 5 to 10 mEq/L of potassium is lost in gastric fluid. The hypokalemia is secondary to the resultant metabolic alkalosis, chloride losses, and hyperaldosteronism. Large doses of laxatives and repeated enemas cause excessive potassium loss in the stool and can cause hypokalemia. On occasion, excessive sweating can lead to hypokalemia from losses of potassium through the skin. In addition, patients with extensive burns can also suffer from hypokalemia because of significant losses from the skin.

Dietary potassium deficiency should be considered in the severely malnourished patient and the chronic alcoholic.[25] When poor potassium intake is combined with increased nonrenal losses, severe hypokalemia can result. Hypokalemia can also result from an acute shift of potassium from the extracellular compartment into cells. This is most commonly seen in patients with metabolic alkalosis, in patients with hyperventilation, and in those patients taking medications such as beta-agonists or decongestants. Beta receptor stimulation can lead to hypokalemia, especially in patients using repetitive and high doses of beta-agonists for chronic obstructive pulmonary disease or asthma. Albuterol-induced hypokalemia can occur even at normal therapeutic doses.[26] A standard dose of nebulized albuterol reduces serum potassium by 0.2 to 0.4 mEq/L, and a second dose taken within 1 hour has the potential to reduce it by almost 1 mEq/L. Patients with starvation or near-starvation may suffer from hypokalemia when they are fed because insulin secretion and increased cellular uptake can cause an acute intracellular migration of potassium.

Box 125-2 Five Most Common Causes of Hypokalemia

Renal losses	Diuretic use, drugs, steroid use, metabolic acidosis, hyperaldosteronism, renal tubular acidosis, diabetic ketoacidosis, alcohol consumption
Increased nonrenal losses	Sweating, diarrhea, vomiting, laxative use
Decreased intake	Ethanol, malnutrition
Intracellular shift	Hyperventilation, metabolic alkalosis, drugs
Endocrine	Cushing's disease, Bartter's syndrome, insulin therapy

Clinical Features

Hypokalemia is usually asymptomatic but can be manifested with nonspecific complaints, including palpitations, skeletal muscle weakness, easy fatigability, depression, and muscle pain.

www.ketabpezeshki.com 66485457-66963820

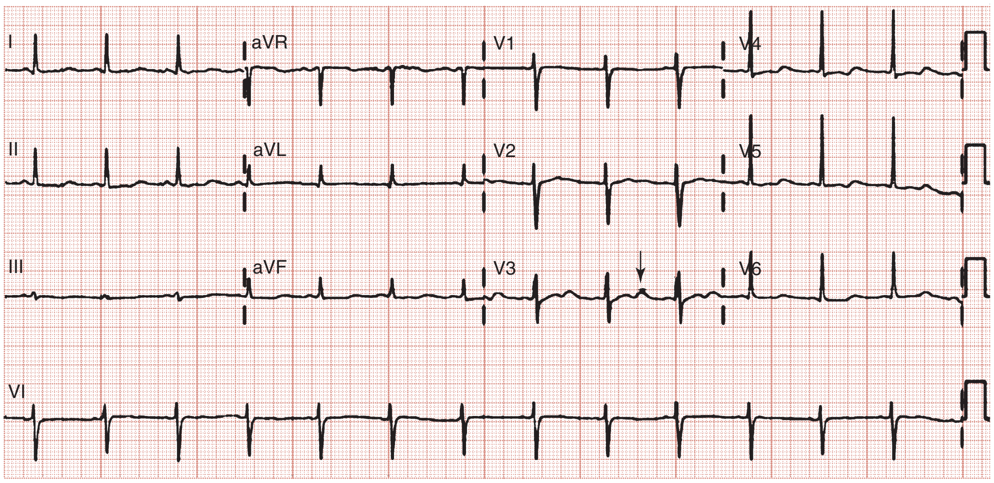


Figure 125-4. Hypokalemic electrocardiographic changes, including flattened T wave, prolonged QT interval, nonspecific ST changes, and prominent U wave *(arrow)*.

Although short periods of mild potassium depletion are typically well tolerated in healthy individuals, severe potassium depletion can result in serious cardiovascular instability, neurologic dysfunction, glucose intolerance, gastrointestinal symptoms, and renal failure as well as affect the acid-base balance in the body.[27] The likelihood of symptoms appears to correlate with the rapidity of the decrease in serum potassium. In patients without underlying heart disease, abnormalities in cardiac conduction are extremely unusual, even when the serum potassium concentration is below 3.0 mEq/L. Paresthesias, depressed deep tendon reflexes, fasciculations, muscle weakness, and confusion can occur when the serum potassium level is less than 2.5 mEq/L. However, in patients with cardiac ischemia or heart failure, even mild to moderate hypokalemia increases the likelihood of cardiac arrhythmias secondary to potassium's effect on the action potential. The data linking hypokalemia with arrhythmias and cardiac arrest in acute myocardial infarction are fairly strong, but the direct myocardial stimulatory effects of increased circulating epinephrine is a possible confounder.[20] Hypokalemia is an independent risk factor contributing to reduced survival of cardiac patients and increased incidence of arrhythmic death. On the basis of available evidence, it appears best to attempt to maintain a serum potassium concentration above 4.5 mEq/L in patients having an acute myocardial infarction. Hypokalemic patients can demonstrate first- and second-degree heart block, atrial fibrillation, ventricular fibrillation, and asystole. Hypokalemia can also promote metabolic acidosis.

Hypokalemic periodic paralysis is a rare disorder characterized by potentially fatal episodes of muscle weakness through the involvement of the respiratory muscles. Life-threatening cardiac arrhythmias are managed by restoration of serum potassium levels into the normal range.[28]

Diagnostic Strategies

Hypokalemia is rarely suspected on the basis of clinical presentation, and the diagnosis is typically made by measurement of the serum potassium concentration during routine laboratory study. If there is any suspicion for hypokalemia or a patient presents with generalized weakness, palpitations, or arrhythmias, an ECG should be obtained. Just as a tall-peaked T wave is characteristic of hyperkalemia, a flattened T wave can be seen in hypokalemia. U waves, which are small deflections after the T wave, may also be seen (Figs. 125-4 and 125-5). The real danger of hypokalemia is that it may also cause a prolonged QT interval. Once the QT interval becomes longer than 500 milliseconds, the risk of malignant ventricular arrhythmias and torsades de pointes increases dramatically.[28] Hypokalemia is also notorious for causing nonspecific ST and T wave changes. In addition, prolonged potassium depletion of even modest proportion can provoke or exacerbate kidney injury or hypertension. A severe degree of hypokalemia with paralysis is a potentially life-threatening medical emergency; measurement of relative urinary potassium excretion and an assessment of the acid-base status might help narrow the differential diagnosis in the emergency setting.

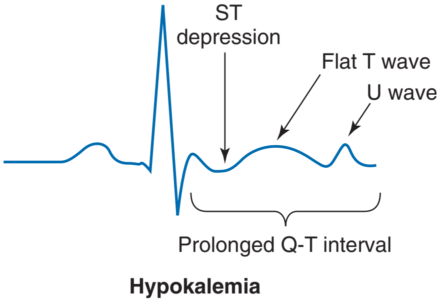


Figure 125-5. Electrocardiographic changes in hypokalemia.

Management

Potassium is an intracellular cation, so a low serum potassium level almost always reflects a significant total potassium deficit. When treating hypokalemia, one should remember that each 0.3 mEq potassium drop below normal correlates with an approximately 100 mEq total body deficit.[29] Patients who have mild or moderate hypokalemia are usually asymptomatic or present with minor symptoms. These patients may only need oral potassium replacement therapy if they do not have nausea or vomiting as the cause of their hypokalemia. Oral replacement is available in liquid, powder, and tablet form. Potassium chloride is the most commonly used supplementation, and 40 to 60 mEq orally every 2 to 4 hours is typically well tolerated. If the cause of hypokalemia is not clear or the hypokalemia is severe and associated with profound weakness, obtain a spot urine potassium level before starting therapy to assess whether the patient's kidneys are inappropriately wasting potassium from a renal or endocrine cause.

www.ketabpezeshki.com 66485457-66963820

Patients in whom severe hypokalemia is suspected should be immediately placed on a cardiac monitor and intravenous access secured.

Treatment of hypokalemia is essential in multiple populations of patients. Hypokalemia is arrhythmogenic, especially in the settings of acute myocardial infarction, high catecholamine states, and hypertrophied or dilated ventricles. Hypokalemia is an important independent risk factor for morbidity and mortality in patients with heart failure. Correction of serum potassium levels to between 4.0 and 5.0 mEq/L is important in these patients.[30]

If intravenous infusion is necessary, potassium chloride at a rate of 10 to 20 mEq/hr is considered safe. Potassium may burn patients with small veins, so small amounts of lidocaine can be added to the intravenous solution. In the rare instance in which intravenous repletion is planned at more than 20 mEq/hr, closely monitor the patient with continuous cardiac monitoring and establish central line access.

Hypokalemia is associated with hypomagnesemia, and the severity of the hypokalemia correlates with a similar degree of hypomagnesemia.[31] Magnesium replacement should usually accompany potassium repletion. Unless the patient receives at least 0.5 g/hr of magnesium sulfate along with potassium replacement, potassium will not move intracellularly and the patient will lose potassium through excretion.[22] Correction of large potassium deficits may require several days, and oral and intravenous replacement can occur simultaneously.

HYPERNATREMIA

Principles of Disease

Hypernatremia is defined as a serum sodium concentration above 145 mEq/ L and is usually associated with a poor prognosis. It is uncommon in previously normal patients, and in adults it is almost exclusively due to a total body water deficit.[32] Most hypernatremic patients have either an impaired sense of thirst or no access to water. Thus elders, infants, patients in coma or with mental impairment, and those who are intubated and paralyzed are at highest risk for this disorder.[33,34] Hypernatremia can be divided into three physiologic pairings (Box 125-3). Diabetes insipidus, a condition that results in insufficient production of or lack of response to antidiuretic hormone, can lead to life-threatening hypernatremia[35] (Box 125-4).

Box 125-3 Three Types of Hypernatremia

Hypernatremia with dehydration and low total body sodium	Heatstroke Increased insensible losses: burns, sweating Gastrointestinal loss: diarrhea, protracted vomiting, continuous gastrointestinal suction Osmotic diuresis: glucose, mannitol, enteral feeding
Hypernatremia with low total body water and normal total body sodium	Diabetes insipidus Neurogenic Elderly with "reset" osmostat Hypothalamic dysfunction Suprasellar or infrasellar tumors Renal disease Drugs (amphotericin, phenytoin, lithium, aminoglycosides, methoxyflurane) Sickle cell disease
Hypernatremia with increased total body sodium	Salt tablet ingestion Salt water ingestion[92] Saline infusions Saline enemas Intravenous sodium bicarbonate Poorly diluted interval feedings Primary hyperaldosteronism Hemodialysis Cushing's syndrome Conn's syndrome

Box 125-4 More Common Causes of Diabetes Insipidus

Central
Idiopathic
Familial disease
Cancer
Hypoxic encephalopathy
Infiltrative disorders
Postsupraventricular tachycardia
Anorexia nervosa

Nephrogenic
Chronic renal insufficiency
Polycystic kidney disease
Lithium toxicity[93]
Hypercalcemia
Hypokalemia
Tubulointerstitial disease
Hereditary
Sickle cell disease

Clinical Features

Hypernatremia is a disease seen predominantly in elders, but it can also be seen in patients who depend on others to provide them with water, including infants, intubated patients, and persons with mental debilitation.[36,37] In addition, patients will also have multifactorial causes leading to severe hypernatremia.[38] Patients may complain of polyuria or polydipsia or have obvious causes of extrarenal fluid losses; others may have no complaints at all.

Hypernatremia should be considered in any patient presenting with altered mental status, especially individuals with severe mental retardation, cerebral palsy, and head injury, as well as in bed-ridden patients who have no access to water.

Diagnostic Strategies

In addition to routine serum chemistries, serum osmolarity and urine sodium concentration and osmolality should be obtained. The degree of hypernatremia almost always equals the total body water deficit in adults. The patient's total body water (TBW) deficit can be estimated by the formula

$$\text{TBW deficit} = \text{TBW} \times (\text{serum Na}^+/140) - 1$$

A patient's total body water is usually calculated by multiplying the patient's body weight in kilograms times 0.6. However, because of percentage body fat differences based on the age and sex of the patient, it is more accurate to use the correction factors listed in Table 125-2.

Management

The treatment of hypernatremia has three interdependent goals: first, to quickly correct underlying shock, hypoperfusion, or significant hypovolemia with normal saline; second, to treat the underlying cause of hypernatremia, such as fever, vomiting, or diabetes insipidus; and third, to carefully lower the serum sodium level, usually by replacement of the body's total water deficit.[39] Until hypoperfusion and hypovolemia are corrected, homeostatic

www.ketabpezeshki.com 66485457-66963820

Table 125-2 Calculation of Body Water

POPULATION	TOTAL BODY WATER
Children and adult men	Body weight (kg) × 0.6
Adult women	Body weight (kg) × 0.5
Elderly men	Body weight (kg) × 0.5
Elderly women	Body weight (kg) × 0.45

mechanisms for sodium balance will promote sodium resorption to maintain intravascular volume, even at the expense of the serum sodium concentration.

The rate of correction in hypernatremia is extremely important to minimize morbidity and mortality. In adult patients who have had hypernatremia during a short time as a result of sodium loading, "rapid correction" at 1 to 2 mEq/hr lowering of serum sodium appears relatively safe.[39,40] However, most adult patients have hypernatremia during days to weeks. In this group of patients, serum sodium concentration should be slowly corrected at no more than 0.5 mEq/hr or 10 to 12 mEq/day.

Normal saline can typically be started for volume replacement until the patient is hemodynamically stable and then changed to half-normal saline at 100 mL/hr once vital signs have normalized. The treatment of central diabetes insipidus with desmopressin (DDAVP) is an effective means of improving polyuria and hypernatremia; initial doses in the acute setting range from 1 to 2 µg.[33]

HYPONATREMIA

Principles of Disease

Hyponatremia, defined as serum sodium concentration of less than 135 mEq/L, is the second most common electrolyte abnormality encountered in clinical practice.[37] It is important to recognize hyponatremia because of its potential morbidity and also because it can be a marker of underlying disease. The most common causes of severe hyponatremia in adults are therapy with thiazides, the postoperative state including transurethral prostatectomy, the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), polydipsia in psychiatric patients, and unintentional water intoxication. Gastrointestinal fluid loss, ingestion of overly dilute formula, accidental ingestion of excessive water, and receipt of multiple tap-water enemas are the main causes of severe hyponatremia in infants and children. Most patients presenting to the emergency department (ED) with hyponatremia are asymptomatic and do not require emergent therapy. If symptoms are present, they are typically based on the degree of hyponatremia and how acutely the hyponatremia developed. Symptoms range from headache, nausea, and vomiting to confusion, seizures, and coma. There are two groups of hyponatremic patients that will require treatment with either normal saline or hypertonic saline: (1) severe but asymptomatic hyponatremia with a sodium level of 110 mEq/L or less and (2) acute symptomatic hyponatremia with a sodium level below 120 mEq/L.

Central nervous system (CNS) damage due to hyponatremia may be caused by cerebral edema and increased intracranial pressure, by osmotic fluid shifts during overly aggressive treatment, or by both. When they are subjected to a hyponatremic environment, neurons become depleted of sodium and potassium in an attempt to limit their own osmolarity to prevent intracellular fluid shifts that would lead to cerebral edema. If fluid therapy raises extracellular sodium levels too quickly, fluids shift out of neurons and diffuse demyelination may occur, leading to flaccid paralysis and often death due to a syndrome most commonly referred to as central pontine myelinolysis, although it is more accurately labeled the osmotic demyelinating syndrome.[41]

Although hyponatremia has many causes, they fall into four general categories: pseudohyponatremia, hyponatremia with dehydration and decreased extracellular volume, hyponatremia with increased extracellular volume, and euvolemic hyponatremia with increased total body water (Box 125-5).

Box 125-5 Causes of Hyponatremia

Pseudohyponatremia	Hyperlipidemia Hyperproteinemia (multiple myeloma, macroglobulinemia)
Dilutional	Hyperglycemia*
Hypovolemic hyponatremia: decreased total body water and sodium, with a relatively greater decrease in sodium	Body fluid losses: sweating, vomiting, diarrhea, gastrointestinal suction Third spacing: bowel obstruction, burns, pancreatitis, rhabdomyolysis Renal causes: diuretics, mineralocorticoid deficiency, osmotic diuresis, renal tubular acidosis, salt-wasting nephropathies
Hypervolemic hyponatremia: increased total body sodium with a relatively greater increase in total body water	Heart failure Chronic renal failure Hepatic failure or cirrhosis
Euvolemic hyponatremia: increased total body water with nearly normal total body sodium	SIADH Drugs causing SIADH (diuretics, barbiturates, carbamazepine, chlorpropamide, clofibrate, opioids, tolbutamide, vincristine) Psychogenic polydipsia Beer potomania Hypothyroidism Adrenal insufficiency MDMA (ecstasy) Accidental or intentional water intoxication

*Hyperglycemia is referred by some as pseudohyponatremia, but hyperglycemia is actually a dilutional hyponatremia.
SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

Pseudohyponatremia

Pseudohyponatremia is a falsely low sodium reading caused by the presence of other osmolar particles in the serum. The phenomenon of pseudohyponatremia is explained by the increased percentage of large molecular particles relative to sodium. These large molecules do not contribute to plasma osmolality, resulting in a state in which the relative sodium concentration is decreased but the overall osmolality remains unchanged. Severe hypertriglyceridemia and hyperproteinemia are two common causes of this condition.[42] Blood draw or laboratory error should also be considered a possible cause of a patient's hyponatremia, especially if the blood sample was drawn near an infusion site using 5% dextrose in water (D_5W) or 5% dextrose in half-normal saline or when a very abnormal sodium level is reported in an otherwise healthy patient.

Hyperglycemia is sometimes considered a cause of pseudohyponatremia; however, it actually causes a dilutional hyponatremia by pulling water into the vascular space by osmosis. Two

www.ketabpezeshki.com 66485457-66963820

different formulas based on the degree of a patient's hyperglycemia are currently used to correct serum sodium levels. One commonly used formula advocates the addition of 1.6 mEq/L to the measured sodium for every 100 mg/dL of glucose above 100. Another formula recommends use of 2.4 mEq as the correction factor because glucose values above 400 mg/dL may lower sodium values by 4 mEq/L per each 100 mg/dL of glucose rise.[40]

Hypovolemic Hyponatremia

Hypovolemic hyponatremia, or hyponatremia in association with dehydration, occurs when there is decreased extracellular volume combined with an even greater loss of sodium. Hyponatremia secondary to body fluid losses must be differentiated from that due to renal losses. Hyponatremia with dehydration due to body fluid losses includes sweating, vomiting, diarrhea, and gastrointestinal suction. Hypovolemic hyponatremia is also seen with "third spacing" in bowel obstruction, burns, and intra-abdominal sepsis. Hypovolemic hyponatremia due to renal causes includes diuretic use, mineralocorticoid deficiency, renal tubular acidosis, and salt-wasting nephropathy. Hypovolemic hyponatremia can be further exacerbated when fluid losses are replaced with hypotonic saline.

Hypervolemic Hyponatremia

Hypervolemic hyponatremia, or hyponatremia with increased extracellular volume, occurs when sodium and water are retained but water retention exceeds sodium retention. Most of these patients present with edema. Hyponatremia with increased total body sodium occurs in patients with heart failure, chronic renal failure, and hepatic failure. The fluid retention in these states is secondary to renal hypoperfusion, resulting in increased aldosterone secretion and a decrease in free water excretion.

Euvolemic Hyponatremia

The final category of hyponatremia is one in which patients are euvolemic but have increased total body water. Causes of this type of hyponatremia include SIADH, psychogenic polydipsia,[43] beer potomania, hypothyroidism, diuretic use in patients with mild CHF, and accidental or intentional water intoxication. These patients do not present with edema because most of the increased body water is intracellular and not intravascular. Hyponatremia without edema has also been described in patients after the use of the recreational drug *N*-methyl-3,4-methylenedioxyamphetamine (MDMA or ecstasy). MDMA-induced hyponatremia is multifactorial and is related to increased free water intake to avoid dehydration and rhabdomyolysis, along with the tendency to be very active while using the drug, leading to sweating and antidiuretic hormone secretion.[41] In addition, there are extensive case reports of significant hyponatremia in endurance athletes.[44]

SIADH is an important cause of hyponatremia that occurs when normal antidiuretic hormone secretion is lost and antidiuretic hormone is secreted independently of the body's need to conserve water. The process results from excess antidiuretic hormone production that causes total body water to increase, diluting the body's sodium and causing the serum sodium to decrease. Patients with SIADH have inappropriately concentrated urine despite a low serum osmolality and normal circulating blood volume. Patients with SIADH have excess total body water but no signs of edema, ascites, or heart failure because most of the increased body water is intracellular, not intravascular. The three most common causes of SIADH are pulmonary lung masses and infections, CNS disorders, and drugs (Box 125-6). Lung cancers (especially small cell cancer), pneumonia, and tuberculosis can lead to SIADH. CNS infections, masses, and psychosis can also cause SIADH. A large number of medications are associated with SIADH, the most common of which are thiazide diuretics, narcotics, lithium, oral hypoglycemics, barbiturates, and antineoplastics. The mainstay of treatment of most patients with SIADH and other causes of euvolemic hyponatremia is free water restriction.

Box 125-6 Three Most Common Causes of SIADH

- Lung masses
  - Cancer (especially small cell)
  - Pneumonia
  - Tuberculosis
  - Abscess
- Central nervous system disorders
  - Infection (meningitis, brain abscess)
  - Mass (subdural, postoperative, cerebrovascular accident)
  - Psychosis (with psychogenic polydipsia)
- Drugs
  - Thiazide diuretics
  - Narcotics
  - Oral hypoglycemic agents
  - Barbiturates
  - Antineoplastics

SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

Diagnostic Strategies

A spot urinary sodium or urinary chloride level is useful to determine if hyponatremia of undetermined origin is renal in etiology. Patients with hypovolemic hyponatremia due to nonrenal causes typically have a low urinary sodium or chloride level (<20 mEq/L) as they try to retain solute. Patients with hypovolemic hyponatremia due to renal causes will have elevated urine sodium and chloride levels above 20 mEq/L as their kidneys cannot retain sodium or chloride. Patients with euvolemic hyponatremia typically have a urinary sodium concentration greater than 20 mEq/L secondary to volume expansion caused by water retention. Patients with hypervolemic hyponatremia secondary to CHF or cirrhosis have urine sodium levels of less than 20 mEq/L because of renal hypoperfusion, whereas those with renal causes of hypervolemic hyponatremia or with SIADH have sodium levels in excess of 20 mEq/L as their kidneys are not able to retain sodium. In interpreting serum sodium levels, consider the possibility of sampling error if the reported value does not seem consistent with the patient's presentation and confirm that a diuretic such as furosemide has not been recently administered, which will increase urinary sodium losses. It is also important to consider adrenal insufficiency when a dehydrated patient has both hyponatremia and hyperkalemia.

Clinical Features

The signs and symptoms of hyponatremia increase as sodium levels decline and also correlate with the rapidity with which hyponatremia develops. Nonspecific signs of hyponatremia include anorexia, nausea, vomiting, and generalized weakness. Acutely hyponatremic patients whose sodium level drops below 120 mEq/L during 24 to 48 hours may present with severe neurologic findings, including confusion, seizures, cerebral edema, coma, and brainstem herniation. Determination of the hydration status of the patient may help establish the etiology of the hyponatremia and help direct subsequent treatment. The diagnosis of hypovolemic hyponatremia is more likely in the patient with diminished skin turgor, increased capillary refill, dry mucous membranes, and orthostasis. On the contrary, the patient with jugular venous distention, peripheral edema, or pulmonary

www.ketabpezeshki.com 66485457-66963820

Table 125-3 Characteristics of Infusates

INFUSATE	INFUSATE SODIUM (mmol/L)	EXTRACELLULAR FLUID DISTRIBUTION (%)
3% Hypertonic saline	513	100
0.9% Normal saline solution	154	100
Lactated Ringer's solution	130	97
Half-normal saline solution	77	73
0.2% Sodium chloride + 5% dextrose in water	34	55
5% Dextrose in water	0	45

congestion is much more likely to have hypervolemic hyponatremia. Patients with SIADH will have no edema and have normal skin turgor.

Management

Treatment of hyponatremia is guided by the patient's clinical presentation, severity of symptoms, estimated duration of illness, fluid status, and underlying cause of the sodium disturbance. Typically, sodium should be corrected during a time course of 48 to 72 hours. Central pontine myelinolysis can occur with too rapid correction of sodium.[43] Most cases of central pontine myelinolysis occur in the alcoholic, malnourished, and elder population, although this devastating side effect can occur in healthy, young patients as well. Patients with central pontine myelinolysis have a flaccid paralysis, dysarthria, dysphagia, and hypotension. If a patient have these symptoms during therapy, stop all sodium-containing fluids and administer D_5W immediately to lower sodium values temporarily.[44] Most patients presenting to the ED with hyponatremia are stable and require no emergent therapy. However, patients who have serum sodium levels of significantly less than 120 mEq/L and those who have acute alterations in mental status, seizures, or new focal findings due to hyponatremia need immediate intervention. Table 125-3 presents the sodium concentration of various infusates, and the following equation is helpful to estimate the effect of 1 liter of any infusate on serum sodium:

$$\text{Change in serum Na}^+ = \text{infusate Na}^+ - \text{serum Na}^+/\text{total body water} + 1$$

There is no consensus regarding the optimal treatment of symptomatic hyponatremia. However, there is agreement that correction should occur at a sufficient pace and magnitude to reverse the manifestations of hypotonicity but not be so rapid and large as to pose a risk for development of osmotic demyelination. For relatively asymptomatic patients with sodium values of 115 to 135 mEq/ L, free water restriction is typically the single most important treatment.

In more severe cases when the sodium value is 120 mEq/L or less and the patient has alterations in mental status, has focal findings, or is seizing, hypertonic saline is indicated.[45-47] Correction of hyponatremia by 4 to 6 mEq/L within 6 hours, with bolus infusions of 3% saline if necessary, is sufficient to manage the most severe manifestations of hyponatremia.[45]

The serum sodium level should be below 120 mEq/L when administration of hypertonic saline is being considered. It is recommended that critically ill hyponatremic patients with seizures, focal findings, or coma receive 100 mL of 3% hypertonic saline during 10 minutes. If a second bolus is required, an additional 100 mL of the 3% solution (513 mEq/L of sodium) may be administered during the next 50 minutes. Increased neurologic stability is highly likely once a symptomatic hyponatremic patient's serum sodium concentration has been raised by about 4 to 6 mEq acutely by the hypertonic saline. To minimize the likelihood of central pontine myelinolysis, it is essential that symptomatic patients with severe hyponatremia not have serum sodium levels rise by any more than a total of 10 to 12 mEq within the first 24 hours.[46,47] Potassium deficits should be replaced aggressively in the treatment of hyponatremic patients with a sodium disorder. If patients are retaining volume and diuresis is not adequate, furosemide can be used; D_5W is infused if the sodium level is rising too quickly.[46] Patients may be able to make full neurologic recoveries from central pontine myelinolysis with the reinduction of hyponatremia in these extreme cases.[44] Demeclocycline in a dosage of 600 to 1200 mg daily is effective in patients with refractory hyponatremia.[48]

Hypovolemic Hyponatremia

Treatment of hypovolemic hyponatremia begins with rehydration. Hypotensive, dehydrated patients are volume resuscitated with normal saline. Once the patient is hemodynamically stable, the infusion rate is slowed. Typically, the normal saline is started at 500 to 1000 mL/hr until the blood pressure is stable and then slowed to 200 mL/hr with frequent sodium checks. If the sodium value is below 120 mEq/L, the sodium concentration should be allowed to rise only by an average of 0.5 mEq/hr or 10 to 12 mEq/day.[47] It is essential to treat the underlying cause of hyponatremia.

Hypervolemic Hyponatremia

Normal saline and hypertonic saline can cause pulmonary edema in the hypervolemic hyponatremic patient. Restriction of fluid and sodium is the preferred treatment of patients with hypervolemic hyponatremia, although loop diuretics can be used in severe cases. Hemodialysis is an alternative in patients with renal impairment and will be required in significantly hyponatremic renal failure patients with volume overload. Patients with CHF will usually benefit from diuretics that will increase water excretion and cause vasodilation to improve cardiac output.[49] In those patients with liver failure, albumin is a consideration, along with diuretics and possibly paracentesis to improve the underlying pathologic process. Water restriction may make the largest impact on the long-term care of these patients.

Euvolemic Hyponatremia

The mainstay of treatment of euvolemic hyponatremia is free water restriction. As the hypo-osmolality in SIADH results from a relative abundance of water in the intracellular and extracellular volumes, maintained by a reduced ability to excrete water, the restriction of free oral water intake is the first recommendation. The use of water restriction is insufficient to treat acute severe hyponatremia and is not recommended as a sole intervention in severely symptomatic hyponatremia, in which a more rapid correction rate is necessary. The only definitive treatment of SIADH is elimination of its underlying cause. Most cases of SIADH caused by malignant disease resolve with effective antineoplastic therapy, and most due to medication resolve promptly when the offending agent is discontinued.[50]

In patients with SIADH, normal saline may cause the serum sodium concentration to decrease even more as free water is retained and hypertonic urine is excreted. If a patient is symptomatic because of a rapid decrease in serum sodium concentration,

www.ketabpezeshki.com 66485457-66963820

Box 125-7 Five Most Common Causes of Hypercalcemia

Malignant disease	Ectopic secretions of parathyroid hormone, multiple myeloma, cancer metastatic to bone Most common: breast, lung, hematologic, kidney, prostate
Endocrine	Hyperparathyroidism, multiple endocrine neoplasias, hyperthyroidism, pheochromocytoma, adrenal insufficiency
Granulomatous disease	Sarcoidosis, tuberculosis, histoplasmosis, berylliosis, coccidioidomycosis
Pharmacologic agents	Vitamins A and D, thiazide diuretics, estrogens, milk-alkali syndrome
Miscellaneous	Dehydration, prolonged immobilization, iatrogenic, rhabdomyolysis, familial, laboratory error

treatment with hypertonic saline is recommended. Demeclocycline and lithium are rarely used in the treatment of SIADH because of their many side effects and nephrotoxicity. Rapid correction of hyponatremia may occur during hemodialysis. To minimize the risks of central pontine myelinolysis, hemodialysis is reserved for patients with documented renal failure and used in a very careful manner.[50] Vaptans, which are oral agents that inhibit the effects of vasopressin, have been studied for treatment of patients with hyponatremia due to SIADH but need further evaluation before becoming standard of care.[46,51]

HYPERCALCEMIA

Principles of Disease

Hypercalcemia is usually defined as a serum calcium level above 10.5 mg/dL; normal levels are usually defined as between 9 and 10.5 mg/dL. Hypercalcemia is considered mild if the total serum calcium level is between 10.5 and 12 mg/dL; levels higher than 14 mg/dL can be life-threatening.

There are five major causes of hypercalcemia (Box 125-7). Primary hyperparathyroidism is the most common cause of hypercalcemia in outpatients, whereas malignant disease is the most common cause in hospitalized patients. Mild hypercalcemia, in an otherwise normal person, may be due to thiazide diuretics with minimal dehydration. Other less common causes of elevated calcium concentration are usually not considered until malignant disease and parathyroid disease are ruled out. Malignancy-associated hypercalcemia occurs in up to 10% of all patients with advanced cancer and generally conveys a poor prognosis. Other causes of hypercalcemia include granulomatous disease, such as sarcoidosis and tuberculosis; medications and pharmacologic agents; and a number of diverse conditions, such as rhabdomyolysis and prolonged immobilization.

Clinical Features

Unfortunately, the clinical presentation of hypercalcemia is often vague and nonspecific. Symptoms include nonfocal abdominal pain, constipation, fatigue, diffuse body aches, anorexia, nausea, and vomiting. Symptom severity depends on the degree of hypercalcemia, the rapidity of onset, and the patient's baseline neurologic and renal function.[52] The diagnosis should be considered in a large number of differential diagnoses. In addition, some patients complain of polyuria or polydipsia. Neuropsychiatric disturbances include anxiety, depression, confusion, and hallucinations. The CNS manifestations that often predominate in more severe cases include lethargy, altered mental status, seizures, and coma. Death due to hypercalcemia is usually related to complications caused by coma, dehydration, or electrolyte disturbances. Cardiac conduction abnormalities may occur; bradydysrhythmias are the most common.[53] Severe hypercalcemia has also been associated with sinus arrest, atrioventricular block, atrial fibrillation, and ventricular tachycardia.

Diagnostic Strategies

The diagnostic evaluation of a patient with suspected hypercalcemia begins with obtaining of electrolyte and renal function tests and an ECG. Calcium is measured by determination of either a total serum calcium level or an ionized calcium level. Ionized calcium is the active form of the total calcium level. It is more accurate in the diagnosis and treatment of hypocalcemia, but it does need to be routinely evaluated in hypercalcemia.[54] The serum total calcium level represents both bound and unbound calcium and thus should be corrected on the basis of the albumin concentration. The adjustment to serum albumin is accomplished by adding or subtracting 0.08 mg/dL to the measured total serum calcium for every 1.0 g/L of albumin below or above 4 g/L albumin, respectively.

A short QT interval can be seen in hypercalcemia and is considered a classic finding. However, although the incidence and duration of QT shortening appear to be correlated with the degree of hypercalcemia, it is not a reliable finding and is not routinely seen in most patients (Fig. 125-6). ST segment elevation may be the least well documented but most consistent electrocardiographic finding, and hypercalcemia should be considered in the differential diagnosis of ST segment elevation caused by conditions other than myocardial infarction.[55,56] In severe cases of hypercalcemia, sinus bradycardia, bundle branch block, and high-degree atrioventricular block may also been seen.

Management

Patients in hypercalcemic crisis are usually dehydrated, often obtunded, and also predisposed to arrhythmias as a result of concomitant electrolyte disturbances; thus they require intravenous access with a normal saline infusion and close monitoring. Normal saline will inhibit proximal tubule reabsorption of calcium and also correct the patient's volume depletion. Normal saline is infused "wide open" until blood pressure and perfusion are normalized. After the initial bolus, the saline infusion is adjusted to a rate of approximately 200 to 300 mL/hr, depending on the patient's age and renal function. Patients with underlying cardiac or renal disease may require lower infusion rates that are carefully titrated. Although the administration of higher volumes of saline may further augment calcium excretion, it is much more likely to result in increased morbidity and mortality from volume overload, pulmonary edema, and myocardial ischemia. The routine use of furosemide in the management of hypercalcemia is no longer recommended. Furosemide was once thought to block the distal reabsorption of calcium, thus complementing saline's proximal tubule effects. However, no modern-day studies have shown furosemide to have significant calcium reabsorption blocking effects. The use of furosemide is reserved to augment saline diuresis and to avoid volume overload during the treatment of hypercalcemia.[57] If it is given to patients who are not yet volume replete, this loop diuretic may worsen the hypercalcemia because of its volume depleting effects and also adversely affect the patient's hemodynamics and renal status. Once calcium excretion by saline infusion has begun, other electrolyte values should be carefully monitored with attention to serum potassium levels.

Osteoclast-inhibiting therapies for severe hypercalcemia are generally considered in consultation with the patient's primary

www.ketabpezeshki.com 66485457-66963820

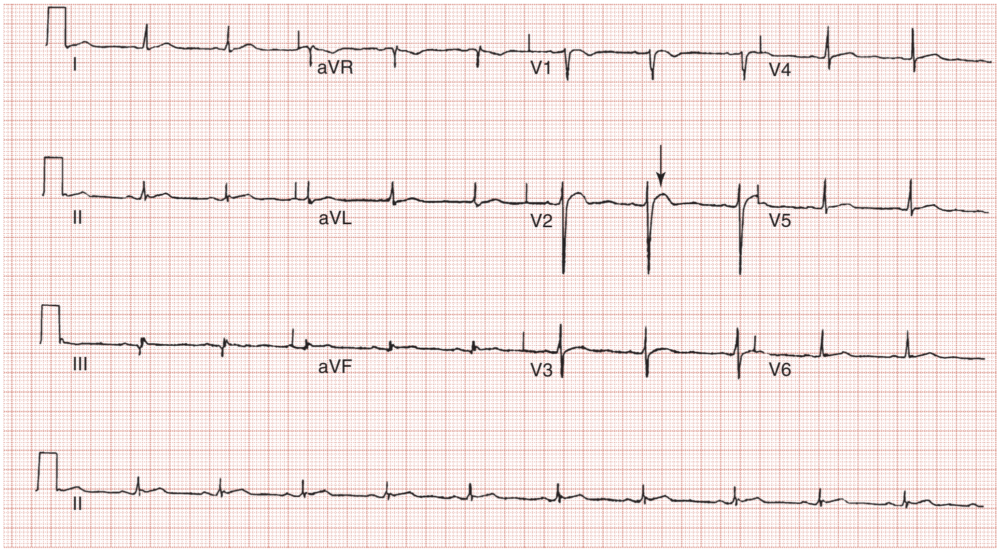


Figure 125-6. Short QT interval *(arrow)* in a patient with multiple myeloma and a calcium level of 14.2 mg/dL. (Courtesy Dr. Barton Campbell.)

physician or oncologist. Drugs that inhibit osteoclast-mediated bone resorption include the bisphosphonates, mithramycin, calcitonin, and glucocorticoids. Intravenous bisphosphonates are the most extensively studied and most efficacious agents for the treatment of malignancy-associated hypercalcemia.[58] Their calcium-lowering effect is achieved predominantly by inhibition of osteoclast function and survival. Zoledronic acid is the bisphosphonate of choice in hypercalcemia of malignancy.[59] The infusion takes 15 minutes, and zoledronic acid may be more effective than other bisphosphonates at keeping the calcium level down over time. The use of intravenous bisphosphonates is restricted to the treatment of acute hypercalcemia associated with serum calcium concentrations above 15 mg/dL and rapid deterioration of CNS, cardiac, gastrointestinal, and renal function.

In the rare case in which a patient has a life-threatening hypercalcemic arrhythmia or heart block, phosphates and hemodialysis are considered.[60,61] In cases of hypercalcemic crisis resulting from primary hyperparathyroidism, urgent parathyroidectomy is potentially curative.

HYPOCALCEMIA

Principles of Disease

Calcium regulation is critical for normal cell function, neural transmission, membrane stability, bone structure, blood coagulation, and intracellular signaling. Total body calcium is controlled by a feedback system in which parathyroid hormone induces the bone and the kidneys to increase serum calcium levels. Vitamin D facilitates intestinal calcium absorption. Conversely, elevated calcium levels normally inhibit parathyroid hormone release.

There are multiple causes of hypocalcemia, of which hypoalbuminemia is the most common (Box 125-8). Because calcium is bound to albumin and other serum proteins, hypoalbuminemia will cause a fall in the measured serum calcium by about 0.8 mg/dL for every 1 g/dL reduction in serum albumin. The active form of calcium is the ionized calcium, which is not affected by changes in albumin.

Hypoparathyroidism is a common cause of hypocalcemia and often develops because of surgery for head and neck cancers. It develops in 1 to 2% of patients after total thyroidectomy. Patients with vitamin D deficiency, including those with malabsorption syndromes, liver disease, malnutrition, and very little sunlight exposure, are at high risk for development of hypocalcemia.[62] Derangements in magnesium and phosphate can also lead to hypocalcemia. Hyperphosphatemic patients often have hypocalcemia because of phosphate's affinity to bind calcium, whereas hypomagnesemia causes end-organ resistance to parathyroid hormone and inhibits the hypocalcemic feedback loop. Patients with sepsis demonstrate hypocalcemia usually associated with hypoalbuminemia.

Box 125-8 Most Common Causes of Hypocalcemia

Hypoalbuminemia
Hypoparathyroidism: inherited, postsurgical, autoimmune, infiltrative
Vitamin D deficiency and vitamin D resistance: malabsorption syndrome, liver disease, malnutrition, sepsis, anticonvulsants, lack of sunlight exposure
Chronic renal failure
Hyperphosphatemia
Hypomagnesemia
Respiratory alkalosis
Severe pancreatitis
Drugs: bisphosphonates, phenytoin, phosphate, calcitonin
Tumor lysis syndrome
Rhabdomyolysis

The most common causes of symptomatic hypocalcemia are massive blood transfusions, toxins, pancreatitis, tumor lysis syndrome, and chronic malnutrition (Box 125-9). Patients receiving massive blood transfusions are at risk for development of hypocalcemia because of citrate toxicity. Rapid blood transfusions and radiocontrast dyes containing citrate should be monitored closely in patients with hepatic failure, CHF, or other low-output states to avoid hypocalcemia.[63]

Hypocalcemia in acute pancreatitis is caused primarily by precipitation of calcium soaps in the abdominal cavity, but glucagon-stimulated calcitonin release and decreased parathyroid hormone secretion may play a role. Toxic exposures to hydrofluoric acid and ethylene glycol can cause profound hypocalcemia secondary to their abilities to complex and chelate with calcium.

When patients are being treated for malignant neoplasms, they are at risk for development of tumor lysis syndrome and multiple

www.ketabpezeshki.com 66485457-66963820

Box 125-9 Five Most Common Symptomatic Causes of Hypocalcemia Seen in the Emergency Department

Hyperventilation	Anxiety, sympathomimetics
Ethanol abuse, chronic malnutrition	Hypoalbuminemia
Massive blood transfusion	More than 10 units
Toxins	Hydrofluoric acid, ethylene glycol
Severe pancreatitis	

secondary electrolyte abnormalities. Hypocalcemia has been attributed to the precipitation of calcium phosphate salts. Finally, one should expect to encounter hypocalcemia in malnourished patients and chronic alcoholics who present to the ED, especially alcoholics with hyperventilation due to alcohol withdrawal.

Clinical Features

Although there are many clinical manifestations of hypocalcemia, neuromuscular and cardiovascular findings predominate. Severe, symptomatic hypocalcemia may result in cardiovascular collapse, hypotension, and dysrhythmias. Clinically evident hypocalcemia generally is manifested in milder forms and is usually the result of a chronic disease state. The patient may complain of muscle cramping, perioral or finger paresthesias, shortness of breath secondary to bronchospasm, and tetanic contractions. More severe symptoms include hypotension, QT prolongation, angina, and CHF. Chronic hypocalcemia may be manifested with cataracts, poor dentition, dry skin, coarse hair, and pruritus. Chvostek's sign may be present: when the examiner taps the facial nerve, facial or eye muscle twitching will be elicited. Trousseau's sign may also be present: when the examiner inflates the blood pressure cuff to 20 mm Hg above the systolic blood pressure for 3 minutes, carpal spasms will be induced because of local ulnar and median nerve ischemia. Trousseau's sign is relatively specific for hypocalcemia, whereas Chvostek's test is less diagnostic.

Diagnostic Strategies

Most cases of hypocalcemia are discovered by clinical suspicion followed by appropriate laboratory testing. A serum calcium level less than 8.5 mg/dL or an ionized calcium level less than 2.0 mEq/L is considered diagnostic. Total serum calcium is approximately 50% free (ionized) and 50% bound, primarily to albumin; thus the serum level must be "corrected" when hypoalbuminemia exists. The ionized calcium level, which is not affected by the albumin level, is more accurate. It is best to perform the whole blood ionized calcium determination rapidly to avoid changes in chelation and pH.[64] In select cases, a parathyroid hormone level may be sent to assist the admitting or consulting physician. Electrocardiography and cardiac monitoring are recommended in suspected hypocalcemia patients to evaluate the QT interval and to provide continuous monitoring for potential dysrhythmias.

Management

Most asymptomatic patients and those with mild symptoms can be treated with oral calcium supplementation, such as calcium carbonate. Intravenous calcium is administered, either as calcium chloride or calcium gluconate, to patients with moderate to severe symptoms; 100 to 300 mg of elemental calcium given during 5 to 30 minutes will raise the ionized calcium level 0.5 to 1.5 mEq. Calcium chloride contains 272 mg of elemental calcium but can be caustic to veins and thus should be given only to critically ill hypocalcemic patients who require calcium urgently. It is best given through a central line. Calcium gluconate contains 92 mg of elemental calcium. Although this is one-third the amount contained in calcium chloride, it is safer to administer and can be given peripherally.[62] Most patients requiring intravenous calcium should be admitted to the hospital for monitoring and treatment of nausea, vomiting, hypertension, and bradycardia. Patients taking digoxin have increased cardiac sensitivity to fluctuations in serum calcium, so intravenous calcium administration is accompanied by continuous electrocardiographic monitoring.[65]

Box 125-10 Five Most Common Causes of Hypermagnesemia

Iatrogenic	Intravenous administration, dialysate
Oral administration	Laxatives, antacids, vitamins, cathartics, dialysate, parental
Impaired elimination: hypomotility	Bowel obstruction, chronic constipation
Impaired elimination: medications	Anticholinergics, narcotics, lithium therapy
Miscellaneous	Hypothyroidism, tumor lysis syndrome, adrenal insufficiency, milk-alkali syndrome, near-drowning in Dead Sea[94]

HYPERMAGNESEMIA

Principles of Disease

Hypermagnesemia is a relatively rare electrolyte abnormality defined as a serum magnesium concentration above 2.2 mg/dL. Hypermagnesemia is most often seen in patients with renal insufficiency who cannot optimally regulate magnesium excretion, especially as their magnesium load increases. There have been reports of fatal and near-fatal cases involving hypermagnesemia in patients receiving magnesium with unrecognized renal failure.[66] Hypermagnesemia can also be caused iatrogenically in patients receiving intravenous magnesium for medical treatment or in patients taking over-the-counter laxatives and antacids.[67] Even though most patients at risk for hypermagnesemia have underlying renal impairment, hypermagnesemia has been reported in patients with normal renal function, especially in elders. Box 125-10 lists the most common causes of increased serum magnesium levels.

Iatrogenic hypermagnesemia most commonly occurs from excessive intravenous infusions of magnesium in patients being treated for preeclampsia or eclampsia, cardiac arrhythmias, or asthma exacerbations. Magnesium administration during eclampsia can also cause fetal hypermagnesemia as magnesium crosses the placental barrier. Hypermagnesemia may also be seen in patients with chronic renal failure on hemodialysis if the dialysate solutions are not closely monitored for magnesium content.

In patients with normal renal function, large amounts of magnesium can be excreted daily in the stool and urine. However, in patients with impaired renal function, hypermagnesemia can be seen even with therapeutic doses of magnesium-containing products. For example, a patient with renal insufficiency should not use magnesium citrate for treatment of constipation. An adult dose of 10 ounces of laxative syrup results in consumption of approximately 2.0 g of elemental magnesium per single dose. A healthy adult can excrete more than 6.0 g of magnesium daily, but renally impaired patients may not be able to tolerate a single dose of laxative syrup. Hypermagnesemia resulting from Epsom salt gargles and salt enemas has been reported.[68,69]

www.ketabpezeshki.com 66485457-66963820

Table 125-4 Clinical Effects of Hypermagnesemia

EFFECT	LEVEL (mg/dL)
Decreased deep tendon reflexes	4-5
Hypotension	5-7
Respiratory insufficiency	10
Heart block	10-15
Cardiac arrest	10-24

Box 125-11 Most Common Causes of Hypomagnesemia

Dietary
Gastrointestinal
Renal
Endocrine or metabolic
Drug induced

Decreased gastrointestinal elimination and increased gastrointestinal absorption of magnesium due to intestinal hypomotility can also result in toxicity. Hypermagnesemia can be seen with bowel obstruction, colitis, gastric dilation, and use of medications that decrease motility, including narcotics and anticholinergics. Other less common causes of hypermagnesemia include rhabdomyolysis, tumor lysis syndrome, adrenal insufficiency, hyperparathyroidism, and hypothyroidism.

Clinical Features

Patients with hypermagnesemia may present with flushing, nausea, vomiting, headache, and diminished deep tendon reflexes. Typically, symptoms begin to be manifested around magnesium levels of 4 mg/dL (Table 125-4). Magnesium is a CNS and neuromuscular depressant and can cause cardiac instability. Magnesium acts as a calcium channel blocker and also blocks potassium channels needed for repolarization. As magnesium levels rise, hypotension and electrocardiographic changes, including QRS widening and QT and PR prolongation, begin to occur. When serum magnesium levels rise above 7 mg/dL, patients can have signs and symptoms of hypotension, respiratory insufficiency, and heart block. Cardiac arrest and death have been reported in patients with serum magnesium levels above 10 mg/dL.[70] Finally, hypermagnesemia causes suppression of parathyroid hormone secretion and can be associated with hypocalcemia.

Diagnostic Strategies

Measured plasma magnesium levels often do not reflect total magnesium content, making it difficult to consistently correlate symptoms to specific magnesium levels. Although there is some question of the role of measuring ionized magnesium in patients with hypomagnesemia, only total body magnesium needs to be followed in hypermagnesemic patients.[71]

Management

Management of hypermagnesemia is dictated by the neuromuscular, cardiovascular, and CNS changes that occur. Most stable or asymptomatic hypermagnesemic patients can be treated with cessation of their magnesium therapy. As symptoms become more pronounced, intravenous isotonic fluids are administered to dilute the extracellular magnesium. Diuretics can be used to promote excretion of magnesium while more definitive treatment is arranged.

In patients with higher levels of serum magnesium or more severe symptoms, renal consultation should be initiated immediately to arrange for dialysis. Intravenous calcium therapy to reverse magnesium toxicity should be reserved for patients with life-threatening symptoms while dialysis is being arranged. Calcium directly antagonizes the neuromuscular and cardiovascular effects of magnesium and is recommended in hypotensive patients with respiratory depression and cardiac instability. In treating life-threatening hypermagnesemia, initially administer 100 to 200 mg of intravenous calcium as either calcium chloride or calcium gluconate (1-2 mL of 10% calcium chloride or 5 mL of 1% calcium gluconate during 2-5 minutes) and then titrate to effect.[72] One can then consider a continuous infusion at 2 to 4 mg/kg/hr if it is needed while dialysis is being arranged.

HYPOMAGNESEMIA

Principles of Disease

Hypomagnesemia is a common electrolyte abnormality that often goes undetected. Normal serum magnesium levels range from 1.5 to 3.0 mEq/L. Symptoms of hypomagnesemia typically begin to be manifested at serum levels below 1.2 mEq/L, although symptoms are often not well correlated with the patient's serum level. This is because most of the body's magnesium is intracellular, and thus a single blood sample with a low serum magnesium level may not accurately reflect total body magnesium or the extent of true hypomagnesemia. Magnesium exists in three states: ionized magnesium, protein bound, and complexed to serum anions. Even though studies show the importance of measuring ionized calcium, most research shows that ionized magnesium can be inferred from total magnesium. Currently, the clinical role of measurement of ionized magnesium is unclear, and measurement of ionized magnesium is not standard practice in the ED; there may be a role for measurement of ionized magnesium in the intensive care setting.[73]

There are many causes of hypomagnesemia (Box 125-11). The following are the five most common ED presentations of hypomagnesemia.

Patients Maintained with Diuretics. Patients using either loop or thiazide diuretics are at increased risk for hypomagnesemia. Both types of diuretics can inhibit magnesium reabsorption. Conversely, potassium-sparing diuretics are also magnesium sparing because they enhance magnesium reabsorption and decrease magnesium excretion. The degree of hypomagnesemia induced by the loop and thiazide diuretics is generally mild, partly because the associated volume contraction will tend to increase proximal sodium, water, and magnesium reabsorption.

Malnourished and Alcoholic Patients. Healthy patients consume enough magnesium in green vegetables, legumes, fruits, shellfish, fresh meat, and cocoa on a regular basis to maintain normal total body magnesium stores. However, hypomagnesemia is common in patients with chronic protein-calorie malnutrition because of an associated lack of essential minerals and vitamins including magnesium. This is especially true in chronic alcoholics, who may not eat foods rich in magnesium.[74] Magnesium losses are further increased in chronic alcoholics because of alcohol's diuretic effects. Hypomagnesemia may also be seen in patients with malabsorption disorders (celiac sprue and short bowel syndrome) and in patients with increased magnesium excretion (chronic diarrhea or inflammatory bowel conditions).

Patients with Hypokalemia. Both potassium and magnesium are critical to help stabilize the membrane potential, to decrease cell

www.ketabpezeshki.com 66485457-66963820

excitability, and for function of the Na^+,K^+-ATPase pump. Approximately 50% of patients with hypokalemia also have concomitant magnesium deficiency. Increasing degrees of hypokalemia are correlated with an increasing likelihood of a magnesium deficit.[21] Hypokalemic patients who are refractory to potassium replacement are likely to also be hypomagnesemic.

Patients with Acute Coronary Artery Disease and Ventricular Arrhythmias. There appears to be a relationship between low serum magnesium levels and the subsequent development of coronary heart disease.[75] Patients who have a myocardial infarction are more likely than controls to be hypomagnesemic. At present, magnesium supplementation is recommended only for those acute coronary syndrome patients who have evidence of hypokalemia, prolonged QT, or known hypomagnesemia. Similarly, patients with acute myocardial infarction who have mild hypomagnesemia appear to have a twofold to threefold increase in the frequency of ventricular arrhythmias in the first 24 hours compared with those with normal magnesium levels.[76] There is controversy about whether magnesium should be administered empirically after acute myocardial infarction.[77] Dysrhythmia is the most common cardiovascular manifestation of hypomagnesemia. Magnesium affects the duration of phase 2 of the action potential, and hypomagnesemia can prolong the QT interval. Magnesium also has effects on phase 4, the resting membrane potential, when it serves to keep the cell more negative by stimulating the sodium-potassium pump. The exact mechanism underlying a possible association between hypomagnesemia and arrhythmias is at present unknown. Arrhythmias are likely to be due to concurrent hypokalemia, hypomagnesemia, or both, resulting in a prolonged QT interval and increases in spontaneous depolarization.

Patients Receiving Specific Medications. In addition to diuretics, many medications are associated with hypomagnesemia. Many nephrotoxic drugs, including aminoglycosides, amphotericin B, cisplatin, and pentamidine, can produce magnesium wasting. The mechanism responsible for hypomagnesemia associated with long-term proton pump inhibitor use is unknown; however, long-term use of proton pump inhibitors may be associated with changes in intestinal absorption of magnesium.[78] Severe hypomagnesemia can also be seen in patients preparing for colonoscopy with polyethylene glycol–based bowel preparations.

Clinical Features

Determination of the clinical consequences of isolated hypomagnesemia is often difficult because patients with hypomagnesemia typically have hypokalemia, hypocalcemia, and hyponatremia. However, many signs and symptoms are reported to correlate with hypomagnesemia, including muscle cramping, diffuse weakness, palpitations, vertigo, ataxia, depression, and seizures. The clinical manifestations most likely seen in the ED typically involve the neuromuscular and cardiovascular systems. Patients may present with hyperactive deep tendon reflexes, muscle cramps, Trousseau's and Chvostek's signs, and dysarthria and dysphagia from esophageal dysmotility. Cardiac conduction abnormalities secondary to magnesium depletion, and often coexisting hypokalemia, can result in PR as well as QT interval prolongation. Dysrhythmias including atrial fibrillation, multifocal atrial tachycardia, premature ventricular complexes, ventricular tachycardia, torsades de pointes, and ventricular fibrillation are the most common cardiovascular manifestations of hypomagnesemia. Women with adequate intakes of magnesium are less likely to be affected by preeclampsia than are those with an inadequate intake.[79]

Diagnostic Strategies

Symptoms of hypomagnesemia begin to be manifested at serum levels below 1.2 mEq/L, but symptoms do not always correlate with the total serum magnesium level. Because most of the total body magnesium is intracellular, the magnesium level alone does not guide therapy. However, the possibility of hypomagnesemia is considered in patients with malnourishment, significant or refractory hypokalemia, and ventricular arrhythmias. Electrocardiographic findings in hypomagnesemia are nonspecific and may be caused by both the hypomagnesemia and concomitant hypokalemia. Hypomagnesemia should be suspected whenever electrocardiographic findings of hypokalemia are noted, including PR and QT interval prolongation, ST segment depression, flattening and widening of the T waves, loss of voltage, and U waves.

Management

The route of magnesium repletion varies with the severity of the clinical manifestations. Parenteral magnesium is recommended for life-threatening conditions. In patients with normal renal function, 1 to 2 g of magnesium sulfate is an appropriate loading dose. A stable patient with hypomagnesemia can be treated with a loading dose of 1 to 2 g of magnesium sulfate during 10 to 60 minutes, followed by a standard maintenance dose of 0.5 to 1 g/hr until symptoms have resolved or a therapeutic effect is obtained. However, patients in cardiac arrest should receive a bolus of 1 to 2 g magnesium sulfate by intravenous push.

Magnesium administration is strongly encouraged for patients receiving intravenous potassium repletion. A dose of 0.5 g/hr is safe in patients who are well hydrated and have normal renal function. There are potential adverse effects to rapid aggressive magnesium replacement at more than 1 to 2 g/hr, including decreased deep tendon reflexes, respiratory depression, and heart block. Magnesium gluconate oral supplementation can be given if the patient is only mildly hypomagnesemic and asymptomatic. When preparing any patient for discharge, physicians can encourage lifestyle changes, including adequate magnesium intake that may benefit blood pressure control, promote weight loss, and improve chronic disease risk.

HYPERPHOSPHATEMIA

Principles of Disease

Hyperphosphatemia is defined as a serum level above 2.5 mg/dL, but it is usually clinically significant only when levels are greater than 5 mg/dL. Although it is rare in the general population, hyperphosphatemia is extremely common in patients with renal insufficiency or renal failure.[80] Almost all patients with renal failure experience hyperphosphatemia at some time during the course of their disease. Hyperphosphatemia can occur because of four major pathways: decreased phosphate excretion, excessive phosphate intake, increased renal tubular reabsorption, and shift of phosphate from intracellular to extracellular space. In addition, physicians must be aware of spurious elevations in phosphate (Box 125-12).

Decreased excretion of phosphate combined with excessive intake is the most common mechanism for the development of hyperphosphatemia. Excessive phosphate intake alone is an uncommon cause of hyperphosphatemia in patients with normal renal function. When patients have glomerular filtration rates below 30 mL/min, the kidneys do not allow excretion of the full amount of ingested phosphate to maintain homeostasis. Exogenous phosphate, including intravenous or oral phosphate administration and phosphate enemas and laxatives can cause a large burden on the kidneys if they do not have normal baseline function.[19]

Hypoparathyroidism, vitamin D intoxication, and thyrotoxicosis increase renal phosphate reabsorption and may cause elevated

www.ketabpezeshki.com 66485457-66963820

Box 125-12 Five Most Common Causes of Hyperphosphatemia

Decreased phosphate excretion	Acute and chronic renal failure
Increased renal tubular reabsorption	Hypoparathyroidism
	Thyrotoxicosis
	Excess vitamin D administration
Excessive phosphate intake	Phosphate enemas or laxatives
	Intravenous or oral phosphate administration
Shift of phosphate from intracellular to extracellular space	Diabetic ketoacidosis
	Tumor lysis
	Rhabdomyolysis
Spurious hyperphosphatemia	Paraproteinemia
	Hyperbilirubinemia
	Hemolysis
	Hyperlipidemia

phosphate levels. Hyperphosphatemia may also occur when there is a large shift of phosphate from the intracellular to the extracellular space and the kidney's ability to excrete phosphate is overwhelmed. This cause of hyperphosphatemia is seen in crush injuries and nontraumatic rhabdomyolysis, tumor lysis syndrome, and DKA.

Hyperphosphatemia can be a spurious finding in cases of hyperproteinemia, such as multiple myeloma, hyperlipidemia, hemolysis, or hyperbilirubinemia. Drawing of a blood sample from a line containing heparin is another cause of a falsely elevated phosphate level.[81]

Clinical Features

Patients with hyperphosphatemia may present with multiple complaints related to associated electrolyte abnormalities, particularly hypocalcemia. Hyperphosphatemia causes hypocalcemia by precipitating calcium out of the blood and decreasing vitamin D production. It is this secondary hypocalcemia that can cause muscle cramping, tetany, and seizures. Chronic hyperphosphatemia can also lead to metastatic calcifications in joints, tissues, and arteries.

Management

Dietary restriction alone may suffice for control of hyperphosphatemia in persons with mild renal insufficiency, but it is inadequate for control in those with overt renal failure. Because most patients presenting with severe hyperphosphatemia also have hypocalcemia, treatment focuses on the correction of both electrolytes. In patients with normal renal function, phosphate excretion can be increased by saline infusion coupled with loop diuretics. Hyperphosphatemia usually resolves in 6 to 12 hours in patients with normal renal function.[82] In patients with hyperphosphatemia with renal failure, hemodialysis or peritoneal dialysis should be considered early in the management. Currently, phosphate control is initiated only when hyperphosphatemia occurs, but a potentially beneficial and simple approach may be to intervene earlier in patients with chronic kidney disease.[83] The optimal method for control of serum phosphate in patients undergoing dialysis is unknown and may involve combinations of dietary modification and enhancement of phosphate clearance through longer dialysis sessions.[84,85]

Box 125-13 Five Most Common Causes of Hypophosphatemia in the Emergency Department

Decreased intake or increased absorptive states	Chronic alcoholism
	Home parenteral nutrition
	AIDS
	Chemotherapy
	Vomiting
	Malabsorption syndromes
	Secretory diarrhea
	Vitamin D deficiency
Hyperventilatory states	Sepsis
	Alcohol withdrawal
	Salicylate poisoning
	Neuroleptic malignant syndrome
	Panic attacks
	Diabetic ketoacidosis
	Hepatic coma
Hormonal and endocrine effects	Insulin loading
	Glucose loading
	Exogenous epinephrine
	Hyperparathyroidism
Medications[19,95]	Diuretics
	Chronic antacid ingestion
	Steroids
	Phosphate binders
	Xanthine derivatives
	$Beta_2$-agonists
Disease states	Trauma
	Severe thermal burns
	Acute renal failure
	Gout

HYPOPHOSPHATEMIA

Principles of Disease

Hypophosphatemia is defined as mild (2-2.5 mg/dL), moderate (1-2 mg/dL), or severe (<1 mg/dL). Mild to moderately severe hypophosphatemia is usually asymptomatic and like hypomagnesemia often goes unrecognized. Although most patients remain asymptomatic, severe hypophosphatemia may result in potentially life-threatening complications. Major clinical sequelae usually occur only in severe hypophosphatemia.

Symptoms of hypophosphatemia typically begin to be manifested at serum levels below 1.0 mg/dL. Acute hypophosphatemia is most commonly due to a rapid intracellular shift, but there are many other causes of clinical manifestations as well.[86] Hyperventilation, glucose, insulin, volume, and resolving acidosis lead to hypophosphatemia by rapid intracellular shift. The many causes of hypophosphatemia include decreased phosphate intake or increased absorptive states, hyperventilatory states, hormonal and endocrine effects, medications, and disease states (Box 125-13). The ED patients most likely to have hypophosphatemia are those who are malnourished with alcohol withdrawal, acute hyperventilation, or sepsis and patients with DKA or alcohol ketoacidosis in whom reintroduction of insulin and glucose causes phosphate uptake into cells.[87,88]

Clinical Features

Mild to moderate hypophosphatemia is usually asymptomatic, but major clinical manifestations can occur with severe hypophosphatemia. Hypophosphatemia can affect a variety of organ systems and cause a wide variety of symptoms because phosphate is an essential component to adenosine triphosphate (Box 125-14).

www.ketabpezeshki.com 66485457-66963820

Box 125-14 Clinical Manifestations of Hypophosphatemia

Central nervous system	Irritability Confusion Paresthesias Depression Dysarthria Seizure Coma
Cardiovascular	Cardiomyopathy Depressed myocardial contractility Arrhythmias
Respiratory	Acute respiratory failure Depressed myocardial contractility
Gastrointestinal	Ileus, dysphagia
Hematologic	Depressed levels of 2,3-diphosphoglycerate and adenosine triphosphate Leukocyte dysfunction Hemolysis Platelet dysfunction
Renal	Acute tubular necrosis Metabolic acidosis Hypercalcemia
Endocrine	Insulin resistance Hyperparathyroidism

Patients with hypophosphatemia may present with nonspecific complaints including joint pain, myalgias, irritability, and depression. Severe hypophosphatemia can be manifested as seizures, arrhythmias, cardiomyopathy, insulin resistance, acute tubular necrosis, rhabdomyolysis, and acute respiratory failure.

Management

Therapy for hypophosphatemia is recommended as levels drop below 1.5 to 2.0 mg/dL, and therapy is essential as levels fall below 1.0 mg/dL. Because hypophosphatemia often is manifested with hypokalemia, phosphate repletion is considered in conjunction with potassium administration. Oral phosphorous, 250 to 500 mg twice daily, can be given to stable or asymptomatic patients. Intravenous preparations are available as sodium phosphate (Na_2PO_4 and $NaPO_4$) or potassium phosphate (K_2PO_4 and KPO_4), and rate of infusion and choice of initial dosage should be based on severity of hypophosphatemia and presence of symptoms. If the serum phosphorus concentration is less than 1.5 mg/dL (0.48 mmol/L), 1.3 mmol/kg of elemental phosphorous (up to a maximum of 100 mmol) can be given in three or four divided doses in a 24-hour period.[89] For routine replacement, give 0.5 mL/hr K_2PO_4; this may be increased to 1 mL/hr in severe symptomatic patients.[87] Each milliliter of K_2PO_4 contains 3 mmol of phosphorus and 4.4 mEq of potassium. Typical replacement therapy provides approximately 1 g of phosphorus per day. Monitoring of patients for the development of hypocalcemia, hyperkalemia, and hyperphosphatemia is required while intravenous phosphate is administered, especially in patients with renal insufficiency. Patients with DKA are initially hypophosphatemic. However, no studies have shown significant benefit to routine phosphate therapy in DKA.[91] Risks of routine treatment with phosphate include hyperphosphatemia, renal failure, hypocalcemia, and hypomagnesemia. In patients with severe malnutrition or significant hypophosphatemia, replacement can be considered, but never administer more than 60 mmol/day without reason.

KEY CONCEPTS

- Asymptomatic electrolyte abnormalities can usually be corrected slowly, but those abnormalities that cause profound mental status changes or life-threatening arrhythmias require immediate correction to avoid cardiac arrest or seizures.
- Intravenous calcium should be used only for hyperkalemic emergencies, defined as the following: widening QRS; sine wave; cardiac arrest believed to be due to hyperkalemia; or rapidly evolving electrocardiographic changes, from normal to development of tall peaked T waves and loss of the P wave. Acute, rapid rises in serum potassium concentration are rare but may be seen in tumor lysis syndrome, rhabdomyolysis, or massive hemolysis.
- After the critical decision about administration of calcium has been made, a $beta_2$-agonist, insulin and glucose, normal saline, and bicarbonate (if the patient is acidotic) can be given to shift potassium intracellularly.
- In treatment of hypokalemia, it is critical that the physician also replace magnesium sulfate, in addition to potassium, or the patient will excrete most of the infused potassium in the urine.
- Low serum potassium levels reflect a much greater total potassium deficit; correction of large deficits can require several days.
- Hypertonic saline should be reserved for severely hyponatremic patients (typically in the 100-110 mEq range) who present with coma, seizures, or focal neurologic deficits. Central pontine myelinolysis can occur if serum sodium concentration is raised rapidly by more than 10 to 12 mEq/day.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Glasziou P: Practice corner: The first symptom of hyperkalemia is death. *ACP J Club* 2004; 140:A13.
2. Whang R, et al: Predictors of clinical hypomagnesemia. Hypokalemia, hypophosphatemia, hyponatremia, and hypocalcemia. *Arch Intern Med* 1984; 144:1794-1796.
3. Wrenn KD, Slovis CM, Slovis BS: The ability of physicians to predict hyperkalemia from the ECG. *Ann Emerg Med* 1991; 20:1229-1232.
4. Ahmed J, Weisberg LS: Hyperkalemia in dialysis patients. *Semin Dial* 2001; 14:348-356.
5. Semple P, Booth C: Calcium chloride; a reminder. *Anaesthesia* 1996; 51:93.
6. Singh BS, et al: Efficacy of albuterol inhalation in treatment of hyperkalemia in premature neonates. *J Pediatr* 2002; 141:16-20.
7. Allon M, Dunlay R, Copkney C: Nebulized albuterol for acute hyperkalemia in patients on hemodialysis. *Ann Intern Med* 1989; 110:426-429.
8. Nair S, et al: A randomized controlled trial to assess the optimal dose and effect of nebulized albuterol in acute exacerbations of COPD. *Chest* 2005; 128:48-54.
9. Allon M, Copkney C: Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients. *Kidney Int* 1990; 38:869-872.
10. Allon M, Shanklin N: Effect of bicarbonate administration on plasma potassium in dialysis patients: Interactions with insulin and albuterol. *Am J Kidney Dis* 1996; 28:508-514.
11. Mahoney A, et al: Emergency interventions for hyperkalaemia. *Cochrane Database Syst Rev* 2005; 2:CD003235.
12. Gruy-Kapral C, et al: Effect of single dose resin-cathartic therapy on serum potassium concentration in patients with end-stage renal disease. *J Am Soc Nephrol* 1998; 9:1924-1930.
13. Kitabchi AE, et al: Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009; 32:1335-1343.
14. Alfonzo AV, et al: Potassium disorders—clinical spectrum and emergency management. *Resuscitation* 2006; 70:10-25.
15. Vanden Hoek TL, et al: Part 12: Cardiac arrest in special situations: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122(Suppl 3):S829-S861.
16. Blumberg A, et al: Effect of various therapeutic approaches on plasma potassium and major regulating factors in terminal renal failure. *Am J Med* 1988; 85:507-512.
17. Roffey P, et al: Implication of epinephrine-induced hypokalemia during cardiac arrest. *Resuscitation* 2003; 58:231.
18. Lin JL, et al: Outcomes of severe hyperkalemia in cardiopulmonary resuscitation with concomitant hemodialysis. *Intensive Care Med* 1994; 20:287-290.
19. Buckley MS, Leblanc JM, Cawley MJ: Electrolyte disturbances associated with commonly prescribed medications in the intensive care unit. *Crit Care Med* 2010; 38(Suppl):S253-S264.
20. Osadchii OE: Mechanisms of hypokalemia-induced ventricular arrhythmogenicity. *Fundam Clin Pharmacol* 2010; 24:547-559.
21. Huang CL, Kuo E: Mechanism of hypokalemia in magnesium deficiency. *J Am Soc Nephrol* 2007; 18:2649-2652.
22. Whang R, Whang DD, Ryan MP: Refractory potassium repletion. A consequence of magnesium deficiency. *Arch Intern Med* 1992; 152:40-45.
23. Hunt SA, et al: 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: A report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines: Developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009; 119:e391-e479.
24. Umpierrez GE, et al: Treatment of diabetic ketoacidosis with subcutaneous insulin aspart. *Diabetes Care* 2004; 27:1873-1878.
25. Finsterer J, et al: Malnutrition-induced hypokalemic myopathy in chronic alcoholism. *J Toxicol Clin Toxicol* 1998; 36:369-373.
26. Udezue E, D'Souza L, Mahajan M: Hypokalemia after normal doses of nebulized albuterol (salbutamol). *Am J Emerg Med* 1995; 13:168-171.
27. Greenlee M, et al: Narrative review: Evolving concepts in potassium homeostasis and hypokalemia. *Ann Intern Med* 2009; 150:619-625.
28. Krahn LE, et al: Hypokalemia leading to torsades de pointes. Munchausen's disorder or bulimia nervosa? *Gen Hosp Psychiatry* 1997; 19:370-377.
29. Gennari FJ: Hypokalemia. *N Engl J Med* 1998; 339:451-458.
30. Coca SG, Perazella MA, Buller GK: The cardiovascular implications of hypokalemia. *Am J Kidney Dis* 2005; 45:233-247.
31. Hamill-Ruth RJ, McGory R: Magnesium repletion and its effect on potassium homeostasis in critically ill adults: Results of a double-blind, randomized, controlled trial. *Crit Care Med* 1996; 24:38-45.
32. Huang WY, et al: Central pontine and extrapontine myelinolysis after rapid correction of hyponatremia by hemodialysis in a uremic patient. *Ren Fail* 2007; 29:635-638.
33. Adler SM, Verbalis JG: Disorders of body water homeostasis in critical illness. *Endocrinol Metab Clin North Am* 2006; 35:873-894, xi.
34. Jacobson J, Bohn D: Severe hypernatremic dehydration and hyperkalemia in an infant with gastroenteritis secondary to rotavirus. *Ann Emerg Med* 1993; 22:1630-1632.
35. Verbalis JG: Diabetes insipidus. *Rev Endocr Metab Disord* 2003; 4:177-185.
36. Palevsky PM, Bhagrath R, Greenberg A: Hypernatremia in hospitalized patients. *Ann Intern Med* 1996; 124:197-203.
37. Price TG, Kallenborn JC: Infant hypernatremia: A case report. *J Emerg Med* 2000; 19:153-157.
38. Holley AD, Green S, Davoren P: Extreme hypernatraemia: A case report and brief review. *Crit Care Resusc* 2007; 9:55-58.
39. Adrogue HJ, Madias NE: Hyponatremia. *N Engl J Med* 2000; 342:1581-1589.
40. Kaplan LJ, Kellum JA: Fluids, pH, ions and electrolytes. *Curr Opin Crit Care* 2010; 16:323-331.
41. Pirzada NA, Ali II: Central pontine myelinolysis. *Mayo Clin Proc* 2001; 76:559-562.
42. Turchin A, Seifter JL, Seely EW: Clinical problem-solving. Mind the gap. *N Engl J Med* 2003; 349:1465-1469.
43. Cheng JC, et al: Long-term neurologic outcome in psychogenic water drinkers with severe symptomatic hyponatremia: The effect of rapid correction. *Am J Med* 1990; 88:561-566.
44. Almond CS, et al: Hyponatremia among runners in the Boston Marathon. *N Engl J Med* 2005; 352:1550-1556.
45. Lien YHH, Shapiro JI: Hyponatremia: Clinical diagnosis and management. *Am J Med* 2007; 120:653-658.
46. Sterns RH, Hix JK, Silver S: Treatment of hyponatremia. *Curr Opin Nephrol Hypertens* 2010; 19:493-498.
47. Verbalis JG, et al: Hyponatremia treatment guidelines 2007: Expert panel recommendations. *Am J Med* 2007; 120(Suppl 1):S1-S21.
48. Janicic N, Verbalis JG: Evaluation and management of hypo-osmolality in hospitalized patients. *Endocrinol Metab Clin North Am* 2003; 32:459-481, vii.
49. Oren RM: Hyponatremia in congestive heart failure. *Am J Cardiol* 2005; 95:2B-7B.
50. Ellison DH, Berl T: Clinical practice. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007; 356:2064-2072.
51. Vaidya C, Ho W, Freda BJ: Management of hyponatremia: Providing treatment and avoiding harm. *Cleve Clin J Med* 2010; 77:715-726.
52. Stewart AF: Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med* 2005; 352:373-379.
53. Ziegler R: Hypercalcemic crisis. *J Am Soc Nephrol* 2001; 12(Suppl 17):S3-S9.
54. Ariyan CE, Sosa JA: Assessment and management of patients with abnormal calcium. *Crit Care Med* 2004; 32(4 Suppl):S146-S154.
55. Nishi SP, Barbagelata NA, Atar S, Birnbaum Y, Tuero E: Hypercalcemia-induced ST-segment elevation mimicking acute myocardial infarction. *J Electrocardiol* 2006; 39:298-300.
56. Littmann L, Taylor L, Brearley WD: ST-segment elevation: A common finding in severe hypercalcemia. *J Electrocardiol* 2007; 40:60-62.
57. LeGrand SB, Leskuski D, Zama I: Narrative review: Furosemide for hypercalcemia: An unproven yet common practice. *Ann Intern Med* 2008; 149:259-263.
58. Drake MT, Clarke BL, Khosla S: Bisphosphonates: Mechanism of action and role in clinical practice. *Mayo Clinic Proc* 2008; 83:1032-1045.
59. Major P, et al: Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: A pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001; 19:558-567.
60. Stewart AF: Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med* 2005; 352:373-379.
61. Koo WS, et al: Calcium-free hemodialysis for the management of hypercalcemia. *Nephron* 1996; 72:424-428.
62. Cooper MS, Gittoes NJ: Diagnosis and management of hypocalcaemia. *BMJ* 2008; 336:1298-1302.
63. Aguilera M, Vaughan RS: Calcium and the anaesthetist. *Anaesthesia* 2000; 55:779-790.
64. Bosworth M, et al: Clinical inquiries: What is the best workup for hypocalcemia? *J Fam Pract* 2008; 57:677-679.
65. Levine M, Nikkanen H, Pallin DJ: The effects of intravenous calcium in patients with digoxin toxicity. *J Emerg Med* 2011; 40:41-46.

www.ketabpezeshki.com 66485457-66963820

66. Schelling JR: Fatal hypermagnesemia. *Clin Nephrol* 2000; 53:61-65.
67. Qureshi T, Melonakos TK: Acute hypermagnesemia after laxative use. *Ann Emerg Med* 1996; 28:552-555.
68. Birrer RB, Shallash AJ, Totten V: Hypermagnesemia-induced fatality following Epsom salt gargles. *J Emerg Med* 2002; 22:185-188.
69. Tofil NM, et al: Fatal hypermagnesemia caused by an Epsom salt enema: A case illustration. *South Med J* 2005; 98:253-256.
70. Slovis CM, Meehan PM: *Electrolyte abnormalities*. In: Roppolo LP, ed. *Emergency Medicine Handbook: Critical Concepts for Clinical Practice*. Philadelphia: Mosby/Elsevier; 2007:1166-1184.
71. Topf JM, Murray PT: Hypomagnesemia and hypermagnesemia. *Rev Endocr Metab Disord* 2003; 4:195-206.
72. Vanden Hoek TL, et al: Cardiac arrest in special situations: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122:S829-S861.
73. Soliman HM: Development of ionized hypomagnesemia is associated with higher mortality rates. *Crit Care Med* 2003; 31:1082-1087.
74. Poikolainen K, Alho H: Magnesium treatment in alcoholics: A randomized clinical trial. *Subst Abuse Treat Prev Policy* 2008; 3:1.
75. Liao F, Folsom AR, Brancati FL: Is low magnesium concentration a risk factor for coronary heart disease? The Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J* 1998; 136:480-490.
76. Agus ZS: Hypomagnesemia. *J Am Soc Nephrol* 1999; 10:1616-1622.
77. ISIS-4: A randomized factorial trial assessing early captopril, oral mononitrate, and intravenous magnesium sulfphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 Collaborative Group. *Lancet* 1995; 345:669.
78. Broeren MA, Geerdink EA, Vader HL, van den Wall Bake AW: Hypomagnesemia induced by several proton-pump inhibitors. *Ann Intern Med* 2009; 151:755-756.
79. Champagne CM: Magnesium in hypertension, cardiovascular disease, metabolic syndrome, and other conditions: A review. *Nutr Clin Pract* 2008; 23:142-151.
80. Kapoor M, Chan G: Fluid and electrolyte abnormalities. *Crit Care Clin* 2001; 17:503-529.
81. Ball CL, Tobler K, Ross BC, Connors MR, Lyon ME: Spurious hyperphosphatemia due to sample contamination with heparinized saline from an indwelling catheter. *Clin Chem Lab Med* 2004; 42:107-108.
82. Slovis CM, Meehan PM: *Electrolyte abnormalities*. In: Roppolo LP, ed. *Emergency Medicine Handbook: Critical Concepts for Clinical Practice*. Philadelphia: Mosby/Elsevier; 2007:1166-1184.
83. Martin KJ, Gonzalez EA: Prevention and control of phosphate retention/hyperphosphatemia in CKD-MBD: What is normal, when to start, and how to treat? *Clin J Am Soc Nephrol* 2011; 6:440-446.
84. Tonelli M, Pannu N, Manns B: Oral phosphate binders in patients with kidney failure. *N Engl J Med* 2010; 362:1312-1324.
85. Culleton BF, et al: Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: A randomized controlled trial. *JAMA* 2007; 298:1291-1299.
86. Subramanian R, Khardori R: Severe hypophosphatemia. Pathophysiologic implications, clinical presentations, and treatment. *Medicine (Baltimore)* 2000; 79:1-8.
87. Miller DW, Slovis C: Hypophosphatemia in the emergency department therapeutics. *Am J Emerg Med* 2000; 18:457-461.
88. Shor R, et al: Severe hypophosphatemia in sepsis as a mortality predictor. *Ann Clin Lab Sci* 2006; 36:67-72.
89. Kraft MD, Btaiche IF, Sacks GS, Kudsk KA: Treatment of electrolyte disorders in adult patients in the intensive care unit. *Am J Health Syst Pharm* 2005; 62:1663.
90. Reference deleted in proofs.
91. Chiasson JL, et al: Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *CMAJ* 2003; 168:859-866.
92. Casavant MJ, Fitch JA: Fatal hypernatremia from saltwater used as an emetic. *J Toxicol Clin Toxicol* 2003; 41:861-863.
93. Trepiccione F, Christensen BM: Lithium-induced nephrogenic diabetes insipidus: New clinical and experimental findings. *J Nephrol* 2010; 23(Suppl 16):S43-S48.
94. Porath A, et al: Dead Sea water poisoning. *Ann Emerg Med* 1989; 18:187-191.
95. Liamis G, et al: Medication-induced hypophosphatemia: A review. *QJM* 2010; 103:449-459.

www.ketabpezeshki.com 66485457-66963820

Chapter 126

Diabetes Mellitus and Disorders of Glucose Homeostasis

Rita K. Cydulka and Gerald E. Maloney, Jr.

DIABETES MELLITUS

Perspective

Diabetes mellitus is the most common endocrine disease. It comprises a heterogeneous group of hyperglycemic disorders characterized by high serum glucose concentration and disturbances of carbohydrate and lipid metabolism. Acute complications include hypoglycemia, diabetic ketoacidosis (DKA), and hyperglycemic hyperosmolar state (HHS). Long-term complications affect multiple organ systems through involvement of the microvasculature and include retinopathy, nephropathy, neuropathy, and angiopathy. As a result, complications such as coronary and cerebral vascular disease, blindness, chronic kidney disease, complicated infections, and amputations are present in a much higher incidence in diabetics than in nondiabetics. Diabetes is frequently ranked as one of the five major chronic diseases that account for a significant proportion of our health care spending. Several trials have shown to varying degrees that tight glucose control can reduce risk of death and several microvascular complications. Patients with diabetes mellitus incur emergency department (ED) costs three times higher than those of nondiabetic patients and are admitted to the hospital four times more often.

Principles of Disease

Normal Physiology

Maintenance of the plasma glucose concentration is critical to survival because plasma glucose is the predominant metabolic fuel used by the central nervous system (CNS). The CNS cannot synthesize glucose, store more than a few minutes' supply, or concentrate glucose from the circulation. Brief hypoglycemia can cause profound CNS dysfunction, and prolonged severe hypoglycemia may cause cellular death. Glucose regulatory systems have evolved to prevent or to correct hypoglycemia.

The plasma glucose concentration is normally maintained within a relatively narrow range, between 60 and 150 mg/dL, despite wide variations in glucose levels after meals and exercise. Glucose is derived from three sources: intestinal absorption from the diet; *glycogenolysis*, the breakdown of glycogen; and *gluconeogenesis,* the formation of glucose from precursors, including lactate, pyruvate, amino acids, and glycerol. After glucose ingestion, the plasma glucose concentration increases as a result of glucose absorption. Endogenous glucose production is suppressed. Plasma glucose then rapidly declines to a level below the baseline.

Insulin. Insulin receptors on the beta cells of the pancreas sense elevations in blood glucose concentration and trigger insulin release into the blood. For incompletely understood reasons, glucose taken by mouth evokes more insulin release than parenteral glucose does. Certain amino acids induce insulin release and even cause hypoglycemia in some patients. Sulfonylurea oral hypoglycemic agents work, in part, by stimulating the release of insulin from the pancreas.

The number of receptor sites helps determine the sensitivity of the particular tissue to circulating insulin. The number and sensitivity of receptor sites are also the primary factors in the long-term efficacy of the sulfonylurea oral hypoglycemic agents. Receptor sites are increased in glucocorticoid deficiency and may be relatively decreased in obese patients.

Under normal circumstances, insulin is rapidly degraded through the liver and kidneys. The half-life of insulin is 3 to 10 minutes in the circulation. Whereas insulin is the major anabolic hormone pertinent to the diabetic disorder, glucagon plays the role of the major catabolic hormone in disordered glucose homeostasis.

Although most tissues have the enzyme systems required to synthesize and to hydrolyze glycogen, only the liver and kidneys contain glucose-6-phosphatase, the enzyme necessary for the release of glucose into the circulation. The liver is essentially the sole source of endogenous glucose production. Renal gluconeogenesis and glucose release contribute substantially to the systemic glucose pool only during prolonged starvation.

The hepatocyte does not require insulin for glucose to cross the cell membrane. However, insulin augments both the hepatic glucose uptake and storage needed for the process of energy generation and glycogen and fat synthesis. Insulin inhibits hepatic gluconeogenesis and glycogenolysis.

Muscle can store and use glucose, primarily through glycolysis to pyruvate, which is reduced to lactate or transaminated to form alanine. Lactate released from muscle is transported to the liver, where it serves as a gluconeogenic precursor. Alanine may also flow from muscle to liver. During fasting, muscle can reduce its glucose uptake, oxidize fatty acids for its energy needs, and, through proteolysis, mobilize amino acids for transport to the liver as gluconeogenic precursors. Adipose tissue can also use glucose for fatty acid synthesis for oxidation to form triglycerides. During fasting, adipocytes can also decrease their glucose use and satisfy energy needs through the beta oxidation of fatty acids. Other tissues do not have the capacity to decrease glucose use on fasting and therefore produce lactate at relatively fixed rates.

Glucose transport across the fat cell membrane also requires insulin. A large percentage of the adipocyte glucose is metabolized to form α-glycerophosphate, required for the esterification of fatty acids to form triglycerides. Although most insulin-mediated fatty acid synthesis occurs in the liver, a very small percentage occurs

www.ketabpezeshki.com 66485457-66963820

in fat cells, with use of the acetyl coenzyme A generated by glucose metabolism. Very low levels of insulin are required to inhibit intracellular lipolysis while stimulating the extracellular lipolysis required for circulating lipids to enter the fat cell.

Glucose Regulatory Mechanisms. Maintenance of the normal plasma glucose concentration requires precise matching of glucose use and endogenous glucose production or dietary glucose delivery. The regulatory mechanisms that maintain systemic glucose balance involve hormonal, neurohumoral, and autoregulatory factors. Glucose regulatory hormones include insulin, glucagon, epinephrine, cortisol, and growth hormone. Insulin is the main glucose-lowering hormone. Insulin suppresses endogenous glucose production and stimulates glucose use. Insulin is secreted from the beta cells of the pancreatic islets into the hepatic portal circulation and has important actions on the liver and the peripheral tissues. Insulin stimulates glucose uptake, storage, and use by other insulin-sensitive tissues, such as fat and muscle.

Counter-regulatory hormones include glucagon, epinephrine, norepinephrine, growth hormone, and cortisol. When glucose is not transported into the cells because of either a lack of food intake or a lack of insulin, the body perceives a "fasting state" and releases *glucagon,* attempting to provide the glucose necessary for brain function. In contrast to the fed state, in the fasting state the body metabolizes protein and fat. Glucagon is secreted from the alpha cells of the pancreatic islets into the hepatic portal circulation. Glucagon lowers hepatic levels of fructose 2,6-bisphosphate, resulting in decreased glycolysis and increased gluconeogenesis, an effect that may be enhanced by ketosis. Glucagon increases the activity of adenylate cyclase in the liver, thereby increasing glycogen breakdown to glucose and further increasing hepatic gluconeogenesis. Glucagon acts to increase ketone production in the liver. Thus, whereas insulin is an anabolic agent that reduces blood glucose concentration, glucagon is a catabolic agent that increases blood glucose concentration. Glucagon is released in response to hypoglycemia as well as to stress, trauma, infection, exercise, and starvation. It increases hepatic glucose production within minutes, although transiently.

Epinephrine both stimulates hepatic glucose production and limits glucose use through both direct and indirect actions mediated by both alpha-adrenergic and beta-adrenergic mechanisms. Epinephrine also acts directly to increase hepatic glycogenolysis and gluconeogenesis. It acts within minutes and produces a transient increase in glucose production but continues to support glucose production at approximately basal levels thereafter. Norepinephrine exerts hyperglycemic actions by mechanisms similar to those of epinephrine, except that norepinephrine is released from axon terminals of sympathetic postganglionic neurons.

Growth hormone initially has a plasma glucose–lowering effect. Its hypoglycemic effect does not appear for several hours. Thus, growth hormone release is not critical for rapid glucose counter-regulation; this is also true for *cortisol.* In the long term, both growth hormone and cortisol may also increase glucose production.

Types of Diabetes

The American Diabetes Association (ADA) defines four major types of diabetes mellitus: type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, and diabetes due to secondary disease processes or drugs. The 1997 National Diabetes Data Group report discontinued the use of the terms *insulin-dependent diabetes mellitus* and *non–insulin-dependent diabetes mellitus* because they are confusing and clinically inaccurate. In addition, use of Arabic numerals (1 and 2) instead of Roman numerals is the standard. The most recent update to the standards of care for diabetes was published in January 2011.[1] The diagnostic criteria for diagnosis of diabetes were changed in 2010 from the previous standards of elevated fasting glucose concentration and abnormal result of the 2-hour oral glucose tolerance test (OGTT) to use of the hemoglobin A_{1c} (HbA_{1c}) value as the preferred confirmatory test.[1] An HbA_{1c} value above 6.5% is now considered diagnostic of diabetes. However, the fasting plasma glucose concentration and 2-hour OGTT are still considered valid, as is the presence of a random glucose measurement of more than 200 mg/dL in a nonfasting patient. In addition, the use of fasting plasma glucose concentration may help identify patients at risk for diabetes (if their glucose concentration is elevated but not crossing the threshold for diagnosis of diabetes).

Type 1 Diabetes Mellitus. Type 1 diabetes is characterized by abrupt failure of production of insulin with a tendency to ketosis even in the basal state. Parenteral insulin is required to sustain life. From 85 to 90% of patients with type 1 diabetes demonstrate evidence of one or more autoantibodies implicated in the cell-mediated autoimmune destruction of the beta cells of the pancreas. Strong human leukocyte antigen (HLA) associations are also found in type 1 diabetes. The autoimmune destruction has multiple genetic predispositions and may be related to undefined environmental insults.

Type 2 Diabetes Mellitus. Patients with type 2 diabetes may remain asymptomatic for long periods and show low, normal, or elevated levels of insulin because of insulin resistance. Ketosis is rare in type 2 disease. Patients have a high incidence of obesity. Hypertriglyceridemia is also frequently noted. No association exists with viral infections, islet cell autoantibodies, or HLA expression. Hyperinsulinemia may be related to peripheral tissue resistance to insulin because of defects in the insulin receptor. Defects in muscle glycogen synthesis have an important role in the insulin resistance that occurs in type 2.

Gestational Diabetes. Gestational diabetes "mellitus" is characterized by an abnormal OGTT result that occurs during pregnancy and either reverts to normal during the postpartum period or remains abnormal. The clinical pathogenesis is thought to be similar to that of type 2. The clinical presentation is usually nonketotic hyperglycemia during pregnancy. Screening is performed around the 24th to 28th week with a 75-g oral glucose load in a woman with no prior history of diabetes.

Diabetes due to Other Causes. Myriad other causes of diabetes have been identified; these include chronic pancreatitis, cystic fibrosis, genetic defects in the beta cell or in insulin receptors, and chemical induced (such as Vacor and chemotherapeutic, antipsychotic, or antiretroviral medications). The management of diabetes due to these conditions is cause specific and depends on whether the underlying pathophysiologic process more closely resembles type 1 or type 2 diabetes.

Impaired Glucose Tolerance. Impaired glucose tolerance (IGT) and its analogue, impaired fasting glucose (IFG), are considered to identify individuals at high risk for development of diabetes. This group is composed of persons whose plasma glucose levels are between normal and diabetic and who are at increased risk for the development of diabetes and cardiovascular disease. The pathogenesis is thought to be related to insulin resistance. Presentations of IGT/IFG include nonketotic hyperglycemia, insulin resistance, hyperinsulinism, and often obesity.

IGT/IFG differs from the other classes in that it is not associated with the same degree of complications of diabetes mellitus. Many of these patients even spontaneously have normal glucose tolerance. One should not be complacent about the patient with IGT because the decompensation of this group into the category of diabetes mellitus is 1 to 5% per year.[1]

Epidemiology

The prevalence of diabetes is difficult to determine because many standards have been used. Regardless, the most recent data

www.ketabpezeshki.com 66485457-66963820

estimate that 8.3% of Americans of all ages and 11.3% of all adults older than 20 years have diabetes.[1] Approximately 215,000 Americans younger than 20 years have diabetes. Of these, 5 to 10% have type 1, and 90 to 95% have type 2; other types account for 1 to 5% of cases.

The peak age at onset of type 1 diabetes is 10 to 14 years. Approximately 1 of every 600 schoolchildren has this disease. In the United States the prevalence of type 1 is approximately 0.26% by the age of 20 years, and the lifetime prevalence approaches 0.4%. The annual incidence among persons from birth to 16 years of age in the United States is 12 to 14 per 1 million population. The incidence is age dependent, increasing from near-absence during infancy to a peak occurrence at puberty and another small peak at midlife.[1]

The morbidity in diabetes is related primarily to its vascular complications. A mortality rate of 36.8% has been related to cardiovascular causes, 17.5% to cerebrovascular causes, 15.5% to diabetic comas, and 12.5% to renal failure.

Pathophysiology and Etiology

Type 1 diabetes results from a chronic autoimmune process that usually exists in a preclinical state for years. The classic manifestations of type 1—hyperglycemia and ketosis—occur late in the course of the disease, an overt sign of beta cell destruction. The most striking feature of long-standing type 1 diabetes is the nearly total lack of insulin-secreting beta cells and insulin, with the preservation of glucagon-secreting alpha cells, somatostatin-secreting delta cells, and pancreatic polypeptide-secreting cells.

Although the exact cause of diabetes remains unclear, research has provided many clues. Studies of the pathogenesis of diabetes mellitus have demonstrated that the cause of the disordered glucose homeostasis varies from individual to individual. This cause may determine the presentation in each patient. Individual patients are currently not studied for the source of their disease except on an experimental basis. The goals of the work in progress, however, are to identify who is susceptible to the development of diabetes and to prevent diabetic emergencies and sequelae or to prevent expression of the disease.

A genetic basis for diabetes is suggested by the association of type 1 disease with certain HLA markers and by the findings of numerous twin and family studies. Families who move from areas with a low frequency of type 1 diabetes to areas with a high frequency have an incidence of disease similar to that in the areas where they reside; this suggests an environmental basis for diabetes. An autoimmune cause has been clearly demonstrated in many type 1 diabetic patients. Islet cell amyloid has also been associated with diabetes. In both types, a variety of viruses have been implicated, most notably congenital rubella, Coxsackievirus B, and cytomegalovirus.

Research has identified two groups of cellular carbohydrate transporters in cell membranes. Sodium-linked glucose transporters are found primarily in the intestine and kidney. The glucose transporter (GLUT) proteins are found throughout the body and transport glucose by facilitated diffusion down concentration gradients. The GLUT-4 transporter, found primarily in muscle, is insulin responsive, and a signaling defect in the protein may be responsible for insulin resistance in some diabetic patients.

Clinical Features

Type 1

The patient with type 1 diabetes is usually lean, younger than 40 years, and ketosis prone. Plasma insulin levels are absent to low; plasma glucagon levels are high but suppressible with insulin, and patients require insulin therapy when symptoms appear. Onset of symptoms may be abrupt, with polydipsia, polyuria, polyphagia, and weight loss developing rapidly. In some cases the disease is heralded by ketoacidosis. Myriad problems related to type 1 diabetes may prompt an ED visit; these include acute metabolic complications, such as DKA, and late complications, such as cardiovascular or circulatory abnormalities, retinopathy, nephropathy, neuropathy, foot ulcers, severe infections, and various skin lesions.

Type 2

The patient with type 2 diabetes is usually middle-aged or older and overweight, with normal to high insulin levels. Insulin levels are lower than would be predicted for glucose levels, however, leading to a relative insulin deficiency. All type 2 patients demonstrate impaired insulin function related to poor insulin production, failure of insulin to reach the site of action, or failure of end-organ response to insulin.

As with type 1 diabetes, research suggests that distinct subgroups of patients fall within the classification of type 2 diabetes. Although most adult patients are obese, 20% are not. Nonobese patients form a subgroup with a different disease, more similar to type 1. Younger patients with type 2 diabetes were previously thought to have a disease with a different course and risk factors, referred to as maturity-onset diabetes of the young. However, one of the fastest-rising subgroups of patients with type 2 diabetes is now young adults and children, who have a disease similar to that seen in older adults and thought to be due to the rise in obesity in this age group.

Symptoms tend to begin more gradually in type 2 diabetes than in type 1. The diagnosis of type 2 is often made by the discovery of an elevated blood glucose level on routine laboratory examination. Hyperglycemia may be controlled by dietary therapy, oral hypoglycemic agents, or insulin administration, depending on the individual. Decompensation of disease usually leads to HHS rather than to ketoacidosis.

Diagnostic Strategies

Serum Glucose

As a rule, any random plasma glucose level above 200 mg/dL, HbA_{1c} value above 6.5%, fasting plasma glucose concentration above 126 mg/dL, or 2-hour postload OGTT is sufficient to establish the diagnosis of diabetes. In the absence of hyperglycemia with metabolic decompensation, these criteria should be confirmed by repeated testing on a different day. Confirmation can be made by the same test or two different tests (fasting plasma glucose and HbA_{1c}, for example). A value of 150 mg/dL is likely to distinguish diabetic from nondiabetic patients more accurately. Formal OGTTs are unnecessary except during pregnancy or in patients who are thought to have diabetes but who do not meet the criteria for a particular classification. The World Health Organization and ADA provide protocols for performance of the OGTT.[1]

Glycosylated Hemoglobin

Measurement of glycosylated hemoglobin (HbA_{1c}) is one of the most important ways to assess the level of glucose control. Elevated serum glucose binds progressively and irreversibly to the amino-terminal valine of the hemoglobin β chain. The HbA_{1c} measurement provides insight into the quality of glycemic control over time. Given the long half-life of red blood cells, the percentage of HbA_{1c} is an index of glucose concentration of the preceding 6 to 8 weeks, with normal values approximately 4 to 6% of total hemoglobin, depending on the assay used. Levels in patients with poorly controlled disease may reach 10 to 12%.

www.ketabpezeshki.com 66485457-66963820

Measurement of glycated albumin can be used to monitor diabetic control during 1 to 2 weeks because of its short half-life but is rarely used clinically. The ADA recommends at least biannual measurements of HbA_{1c} for the follow-up of all types of diabetes. The ADA currently sets an HbA_{1c} value of less than 7% as a treatment goal.

Urine Glucose

Urine glucose measurement methods are basically of two types: reagent tests and dipstick tests. The reagent tests (e.g., Clinitest) are copper reduction tests. They are somewhat more cumbersome and expensive than dipstick methods, use tablets that are caustic and dangerous if accidentally ingested, and may be affected by many substances.

Dipstick tests generally use glucose oxidase, which may also be affected by different substances. Dipsticks are inexpensive and convenient but may vary in their sensitivity and strength of reaction to a given concentration of glucose. Dipstick interpretation can vary significantly, depending on the observer and the type of lighting. Both falsely high and falsely low urine glucose readings can also occur. With the "plus" system, 1+, 2+, 3+, and 4+ have different implications about urine glucose concentrations, depending on the brand of dipstick. The use of reflectance colorimeters to read dipsticks increases accuracy. Urine glucose tests must be interpreted loosely because many factors can affect their results.

Urine Ketones

Urine ketone dipsticks use the nitroprusside reaction, which is a good test for acetoacetate but does not measure β-hydroxybutyrate. Although the usual acetoacetate/β-hydroxybutyrate ratio in DKA is 1 : 2.8, it may be as high as 1 : 30, in which case the urine dipstick does not reflect the true level of ketosis. When ketones are in the form of β-hydroxybutyrate, the urine ketone dipsticks may infrequently yield negative reactions in patients with significant ketosis.

Dipstick Blood Glucose

Dipsticks for testing of blood glucose are clearly more accurate than urine dipsticks as a means of monitoring blood glucose concentration, but they also may be inaccurate. Hematocrits below 30% or above 55% cause unduly high or low readings, respectively, and a number of the strips specifically disclaim accuracy when they are used for neonates. Sensitivity of dipsticks to a variety of factors varies with the particular brand. The largest errors are in the hyperglycemic range. Dipstick readings rarely err more than 30 mg/dL when actual concentrations are below 90 mg/dL. Although specific glucose concentrations may not be accurately represented, blood glucose dipsticks are useful in estimating the general range of the glucose value. Reflectance meters increase the accuracy of the dipstick blood glucose determination. If maximum accuracy is desired, a laboratory blood glucose level should be obtained.

HYPOGLYCEMIA

Hypoglycemia is a common problem in patients with type 1 diabetes, especially if tight glycemic control is practiced; it may be the most dangerous acute complication of diabetes. The estimated incidence of hypoglycemia in diabetic patients is 9 to 120 episodes per 100 patient-years. As significant efforts continue to keep both fasting and postprandial glucose concentrations within the normal range, the incidence of hypoglycemia may increase. The most common cause of coma associated with diabetes is an excess of administered insulin with respect to glucose intake. Hypoglycemia may be associated with significant morbidity and mortality.[2] Severe hypoglycemia is usually associated with a blood glucose level below 40 to 50 mg/dL and impaired cognitive function.

Principles of Disease

Protection against hypoglycemia is normally provided by cessation of insulin release and mobilization of counter-regulatory hormones, which increase hepatic glucose production and decrease glucose use. Diabetic patients using insulin are vulnerable to hypoglycemia because of insulin excess and failure of the counter-regulatory system.

Hypoglycemia has many causes: missing a meal (decreased intake), increased energy output (exercise), and increased insulin dosage. It can also occur in the absence of any precipitant. Oral hypoglycemic agents have also been implicated in causing hypoglycemia, both in the course of therapy and as an agent of overdose.

Hypoglycemia without warning symptoms, or *hypoglycemia unawareness,* is a dangerous complication of type 1 diabetes probably caused by previous exposure to low blood glucose concentrations.[2] Even a single hypoglycemic episode can reduce neurohumoral counter-regulatory responses to subsequent episodes. Other factors associated with recurrent hypoglycemic attacks include overaggressive or intensified insulin therapy, longer history of diabetes, autonomic neuropathy, and decreased epinephrine secretion or sensitivity.

The *Somogyi phenomenon* is a common problem associated with iatrogenic hypoglycemia in the type 1 diabetic patient. The phenomenon is initiated by an excessive insulin dosage, which results in an unrecognized hypoglycemic episode that usually occurs in the early morning while the patient is sleeping. The counter-regulatory hormone response produces rebound hyperglycemia, evident when the patient awakens. Often, both the patient and the physician interpret this hyperglycemia as an indication to increase the insulin dosage, which exacerbates the problem. Instead, the insulin dosage should be lowered or the timing changed.

Clinical Features

Symptomatic hypoglycemia occurs in most adults at a blood glucose level of 40 to 50 mg/dL. The rate at which glucose decreases, however, and the patient's age, gender, size, overall health, and previous hypoglycemic reactions contribute to symptom development. Signs and symptoms of hypoglycemia are caused by excessive secretion of epinephrine and CNS dysfunction and include sweating, nervousness, tremor, tachycardia, hunger, and neurologic symptoms ranging from bizarre behavior and confusion to seizures and coma. In patients with hypoglycemia unawareness, the prodrome to marked hypoglycemia may be minimal or absent. These individuals may rapidly become unarousable without warning. They may have a seizure or show focal neurologic signs, which resolve with glucose administration.

Diagnostic Strategies

The cardinal laboratory test for hypoglycemia is blood glucose concentration. It should be obtained, if possible, before therapy is begun. As noted, dipstick readings are helpful in permitting rapid, reasonably accurate blood glucose estimates before therapy.

Laboratory testing should address any suggested cause of the hypoglycemia, such as ethanol or other drug ingestion. If factitious hypoglycemia is suggested, testing for insulin antibodies or low levels of C peptide may be helpful. A patient who is surreptitiously administering exogenous insulin will have normal to low levels of C peptide and markedly elevated insulin levels.

www.ketabpezeshki.com 66485457-66963820

Management

In alert patients with mild symptoms, oral consumption of sugar-containing foods or beverages is often adequate. In other patients, after blood is drawn for glucose determination, one to three ampules of 50% dextrose in water ($D_{50}W$) is administered intravenously while the patient's airway, breathing, and circulation are assessed and maintained. Augmentation of the blood glucose level by administration of an ampule of $D_{50}W$ may range from less than 40 mg/dL to more than 350 mg/dL. These therapeutic steps are appropriately performed in the field if out-of-hospital care is available. If alcohol abuse is suggested, thiamine is administered. $D_{50}W$ should not be used in infants or young children because venous sclerosis can lead to rebound hypoglycemia. In a child younger than 8 years, it is advisable to use 25% ($D_{25}W$) or even 10% ($D_{10}W$) dextrose. $D_{25}W$ may be prepared by diluting $D_{50}W$ 1:1 with sterile water. The dose is 0.5 to 1 g/kg body weight or, using $D_{25}W$, 2 to 4 mL/kg.

If intravenous access cannot be rapidly obtained, 1 to 2 mg of glucagon may be given intramuscularly or subcutaneously. The onset of action is 10 to 20 minutes, and peak response occurs in 30 to 60 minutes. It may be repeated as needed. Glucagon may also be administered intravenously; 1 mg has an effect similar to that of one ampule of $D_{50}W$. Glucagon is ineffective in causes of hypoglycemia in which glycogen is absent, notably alcohol-induced hypoglycemia.

Families of type 1 diabetic patients are often taught to administer glucagon intramuscularly at home. Of the families so instructed, only 9 to 42% actually inject the glucagon when it is indicated. Intranasal glucagon has not been widely used. Out-of-hospital care providers and emergency physicians should seek a history of glucagon administration because it alters initial blood glucose readings.

All patients with severe hypoglycemic reactions require aspiration and seizure precautions. Although the response to intravenous administration of glucose is generally rapid, older patients may require several days for complete recovery.

Treatment of hypoglycemia secondary to oral hypoglycemic agents depends on the agent. Metformin and the thiazolidinedione agents rarely cause significant or prolonged hypoglycemia, whereas sulfonylureas, which are insulin secretagogues, do cause hypoglycemia. Sulfonylurea oral hypoglycemic agents pose special problems because the hypoglycemia they induce tends to be prolonged and severe. Patients with an overdose of sulfonylurea hypoglycemic agents should have a minimum observation period of 24 hours if hypoglycemia is recurrent in the ED after management of the initial episode. Patients at risk for hypoglycemia from oral sulfonylureas include patients with impaired renal function, pediatric patients, and patients who are naïve to hypoglycemic agents. Although symptoms may occur after an overdose, several case reports in patients with renal failure and pediatric patients describe refractory hypoglycemia after ingestion of a single pill. One case series of pediatric patients presenting with sulfonylurea ingestion who were euglycemic initially demonstrated an average time to onset of 8 hours to the initial hypoglycemic episode.[3] However, onset of symptoms was delayed up to 18 hours in some patients. As a result, we recommend 23 hours of observation for patients with known or suspected ingestion of hypoglycemic agents.

A patient with hypoglycemia from sulfonylureas, in addition to standard glucose replacement, frequently requires treatment with an agent to inhibit further insulin release, such as octreotide, a somatostatin analogue. Several case series have described the use of octreotide in both adult and pediatric patients suffering from sulfonylurea-induced hypoglycemia, frequently reporting successful results with a significant decrease in the number of episodes of recurrent hypoglycemia. A randomized clinical trial concluded that patients receiving octreotide had a decreased glucose supplementation requirement.[4] No single set protocol for use has been described; however, typical adult doses have ranged from 50 to 100 µg intravenously or subcutaneously every 12 hours, and pediatric dosages have ranged from 25 to 50 µg intravenously or subcutaneously. Whereas experience thus far with octreotide has been positive, it does not obviate the need for prolonged observation and serial glucose measurements.

Disposition

Type 1 diabetic patients with brief episodes of hypoglycemia uncomplicated by other disease may be discharged from the ED if a cause of the hypoglycemia can be identified and corrected by instruction or medication. All patients should be given a meal before discharge to ensure their ability to tolerate oral feedings and to begin to replenish glycogen stores in glycogen-deficient patients. Patients who are discharged should receive short-term follow-up for ongoing evaluation. Patients with hypoglycemia caused by long-acting sulfonylurea medications should be observed in the hospital if they have recurrent hypoglycemia after a period of observation in the ED. Other agents, such as metformin, do not typically produce hypoglycemia, although they may have other issues, such as lactic acidosis, that may require admission.

Nondiabetic Patients

Hypoglycemia in the nondiabetic patient may be classified as postprandial or fasting. The most common cause of *postprandial hypoglycemia* is alimentary hyperinsulinism, such as that seen in patients who have undergone gastrectomy, gastrojejunostomy, pyloroplasty, or vagotomy. *Fasting hypoglycemia* is caused when there is an imbalance between glucose production and use. The causes of inadequate glucose production include hormone deficiencies, enzyme defects, substrate deficiencies, severe liver disease, and drugs. Causes of overuse of glucose include the presence of an insulinoma, exogenous insulin, sulfonylureas, drugs, endotoxic shock, extrapancreatic tumors, and a variety of enzyme deficiencies.

Emergency treatment is similar to that of hypoglycemia in the diabetic patient. The determination of inpatient versus outpatient evaluation of hypoglycemia in a nondiabetic patient should be based on the suggested cause and the nature of the episode (i.e., factors such as severity, persistence, and recurrence).

DIABETIC KETOACIDOSIS

Principles of Disease

Pathophysiology

DKA is a syndrome in which insulin deficiency and glucagon excess combine to produce a hyperglycemic, dehydrated, acidotic patient with profound electrolyte imbalance. All derangements producing DKA are interrelated and are based on insulin deficiency (Fig. 126-1). DKA may be caused by cessation of insulin intake or by physical or emotional stress despite continued insulin therapy.

The effects of insulin deficiency may be mimicked in peripheral tissues by a lack of either insulin receptors or insulin sensitivity at receptor or postreceptor sites. When the hyperglycemia becomes sufficiently marked, the renal threshold is surpassed and glucose is excreted in the urine. The hyperosmolarity produced by hyperglycemia and dehydration is the most important determinant of the patient's mental status.[5]

Glucose in the renal tubules draws water, sodium, potassium, magnesium, calcium, phosphorus, and other ions from the

www.ketabpezeshki.com 66485457-66963820

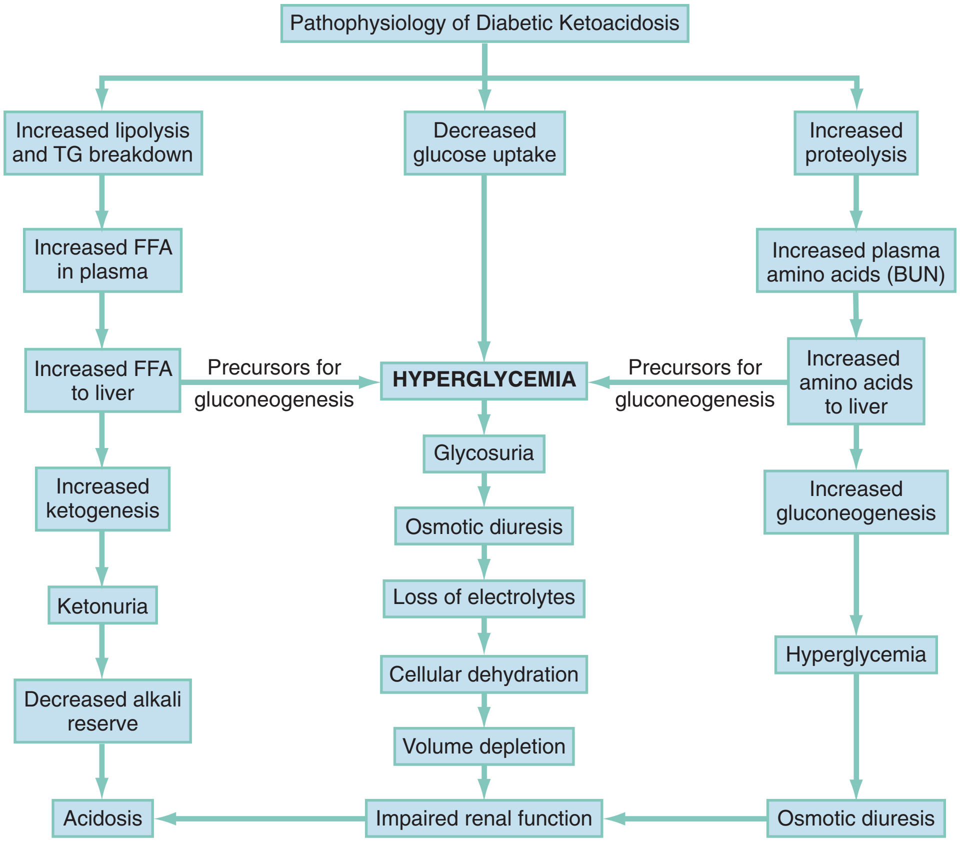


Figure 126-1. Syndrome of diabetic ketoacidosis. *BUN,* blood urea nitrogen; *FFA,* free fatty acids; *TG,* total glucose concentration.

Table 126-1 Average Fluid and Electrolyte Deficits in Severe Diabetic Ketoacidosis*

WEIGHT	WATER (mL/kg)	SODIUM (mEq/L)	POTASSIUM (mEq/L)	CHLORIDE (mEq/L)	PHOSPHORUS (mEq/L)
≤10 kg	100-120	8-10	5-7	6-8	3
10-20 kg	80-100	8-10	5-7	6-8	3
≥20 kg	70-80	8-10	5-7	6-8	3

*Per kilogram of body weight.

circulation into the urine. This osmotic diuresis, combined with poor intake and vomiting, produces the profound dehydration and electrolyte imbalance associated with DKA (Table 126-1). Exocrine pancreatic dysfunction closely parallels endocrine beta cell dysfunction, producing malabsorption that further limits the body's intake of fluid and exacerbates electrolyte loss.

In 95% of patients with DKA, the total sodium level is normal or low. Potassium, magnesium, and phosphorus deficits are usually marked. As a result of acidosis and dehydration, however, the initial reported values for these electrolytes may be higher than actual body stores. Hypokalemia may further inhibit insulin release.

The cells, unable to receive fuel substances from the circulation, act as they do in starvation from other causes. They decrease amino acid uptake and accelerate proteolysis such that large amounts of amino acids are released to the liver and converted to two-carbon fragments.

Adipose tissue in the patient with DKA fails to clear the circulation of lipids. Insulin deficiency results in activation of a hormone-sensitive lipase that increases circulating free fatty acid (FFA) levels. Long-chain FFAs, now circulating in abundance as a result of insulin deficiency, are partially oxidized and converted in the liver to acetoacetate and β-hydroxybutyrate. This alteration of liver metabolism to oxidize FFAs to ketones rather than the normal process of re-esterification to triglycerides appears to correlate directly with the altered glucagon/insulin ratio in the portal blood. Despite the increased pathologic glucagon-mediated production of ketones, the body acts as it does in any form of starvation to decrease the peripheral tissue's use of ketones as fuel. The combination of increased ketone production with decreased ketone use leads to ketoacidosis.

The degree of ketosis has been related to the magnitude of release of the counter-regulatory hormones epinephrine, glucagon, cortisol, and somatostatin. Glucagon is elevated fourfold to fivefold in DKA and is the most influential ketogenic hormone. It is believed to affect ketogenesis by reducing the concentration of malonyl coenzyme A and by inhibiting glycolysis. Epinephrine, norepinephrine, cortisol, growth hormone, dopamine, and thyroxine enhance ketogenesis indirectly by stimulating lipolysis.

Acidosis plays a prominent role in the clinical presentation of DKA. The acidotic patient attempts to increase lung ventilation to rid the body of excess acid with Kussmaul's respiration.

www.ketabpezeshki.com 66485457-66963820

Bicarbonate is used up in the process. Acidosis compounds the effects of ketosis and hyperosmolality to depress mental status directly.

Acidemia is not invariably present, even with significant ketoacidosis. *Ketoalkalosis* has been reported in diabetic patients vomiting for several days and in some with severe dehydration and hyperventilation. The finding of alkalemia, however, should prompt the consideration of alcoholic ketoacidosis, in which this finding is much more common. Whereas these cases are rare, if there is concern for mixed acid-base disorders, an arterial blood gas sample should be obtained instead of a venous gas sample to further delineate the metabolic abnormalities present.

Etiology

Most often, DKA occurs in patients with type 1 diabetes and is associated with inadequate administration of insulin, infection, or myocardial infarction. DKA can also occur in type 2 diabetics and may be associated with any type of stress, such as sepsis or gastrointestinal bleeding. Approximately 25% of all episodes of DKA occur in patients whose diabetes was previously undiagnosed.

Diagnostic Strategies

History

Clinically, most patients with DKA complain of a recent history of polydipsia, polyuria, polyphagia, visual blurring, weakness, weight loss, nausea, vomiting, and abdominal pain. Approximately half of these patients, especially children, report abdominal pain. In children, this pain is usually idiopathic and probably caused by gastric distention or stretching of the liver capsule; it resolves as the metabolic abnormalities are corrected. In adults, however, abdominal pain more often signifies true abdominal disease.

Physical Examination

Physical examination may or may not demonstrate a depressed sensorium. Typical findings include tachypnea with Kussmaul's respiration, tachycardia, frank hypotension or orthostatic blood pressure changes, the odor of acetone on the breath, and signs of dehydration. An elevated temperature is rarely caused by DKA itself and suggests the presence of infection.

Laboratory Tests

Initial tests allow preliminary confirmation of the diagnosis and immediate initiation of therapy (Table 126-2).[4] Subsequent tests are made to determine more specifically the degree of dehydration, acidosis, and electrolyte imbalance and to reveal the precipitant of DKA.

Table 126-2 Typical Laboratory Values in Diabetic Ketoacidosis (DKA) and Hyperglycemic Hyperosmolar State (HHS)

	DKA	HHS
Glucose (mg/dL)	>350	>700
Sodium (mEq)	low 130s	140s
Potassium (mEq)	≈4.5-6.0	≈5
Bicarbonate (mEq)	<10	>15
Blood urea nitrogen (mg/dL)	25-50	>50
Serum ketones	Present	Absent

On the patient's arrival to the ED, check the serum and urine glucose concentrations and ketone level, electrolyte values, and blood gas. If determination of the pH is the sole concern, venous blood gas samples may be used as there is good correlation between arterial and venous pH. If there is concern for the adequacy of respiratory compensation or concern for a mixed acid-base disorder (such as concomitant metabolic alkalosis from vomiting that may confuse the clinical picture), an arterial blood gas sample should be obtained. Glucose is usually elevated above 350 mg/dL; however, euglycemic DKA (blood glucose ≤ 300 mg/dL) has been reported in up to 18% of patients. Blood gas measurement usually reveals a low pH, with the aforementioned rare exception of a concomitant alkalemia that may result in a pseudonormalization of the pH. Metabolic acidosis with an anion gap is primarily the result of elevated plasma levels of acetoacetate and β-hydroxybutyrate, although lactate, FFAs, phosphates, volume depletion, and several medications also contribute to this condition. Rarely, a well-hydrated patient with DKA may have a pure hyperchloremic acidosis with no anion gap. Again, although rare, there are case reports of a normal anion gap in a patient with DKA if the vomiting has been sufficient to cause a concomitant metabolic alkalosis. If an immediate potassium level is not available through blood gas analysis, an electrocardiogram may indicate elevated potassium levels. Despite initial potassium levels that are normal to high, a total potassium deficit of several hundred milliequivalents results from potassium and hydrogen shifts.

Other laboratory tests in DKA are driven by the clinical picture. A complete blood count may be used to rule out other concomitant issues, such as anemia. The white blood cell count has limitations discussed later. Whereas patients with milder degrees of DKA may not have the severe volume deficits seen in the more severe cases, measurement of blood urea nitrogen and creatinine to evaluate renal function is reasonable. Decisions about volume replacement need to be made irrespective of whether an azotemia is noted on blood chemistry testing. DKA has classically been associated with deficits of magnesium and phosphorus; whereas these deficits are not always clinically significant, it is reasonable to check magnesium and phosphorus levels as occasionally profound deficits of these electrolytes have been noted. Urinalysis, in addition to the presence of ketones, may also help confirm a urinary tract infection as a precipitant of DKA. Use of blood or urine cultures should be determined by the clinical picture.

The serum sodium value is often misleading in DKA. Sodium is often low in the presence of significant dehydration because it is strongly affected by hyperglycemia, hypertriglyceridemia, salt-poor fluid intake, increased gastrointestinal and renal losses, and insensible loss. When hyperglycemia is marked, water flows from the cells into the vessels to decrease the osmolar gradient, thereby creating dilutional hyponatremia. Lipids also dilute the blood, thereby further lowering the value of sodium. Newer autoanalyzers remove triglycerides before assay, thus eliminating this artifact.

Hypertriglyceridemia is common in DKA because of impaired lipoprotein lipase activity and hepatic overproduction of very-low-density lipoproteins. In the absence of marked lipidemia, the true value of sodium may be approximated by adding 1.3 to 1.6 mEq/L to the sodium value on the laboratory report for every 100 mg/dL glucose above the norm. Thus, if the laboratory reports a serum sodium value of 130 mEq/L and a blood glucose value of 700 mEq/L, the total serum sodium value is more accurately assessed to be between 137.8 and 139.6 mEq/L.

Acidosis and the hyperosmolarity induced by hyperglycemia shift potassium, magnesium, and phosphorus from the intracellular to the extracellular space. Dehydration produces hemoconcentration, which contributes to normal or high initial serum potassium, magnesium, and phosphorus readings in DKA, even with profound total body deficits. The effect of acidosis on the

www.ketabpezeshki.com 66485457-66963820

serum potassium determination can be corrected by subtracting 0.6 mEq/L from the laboratory potassium value for every 0.1 decrease in pH noted in the arterial blood gas analysis. Thus, if the potassium is reported as 5 mEq/L and the pH is 6.94, the corrected potassium value would be only 2 mEq/L, representing severe hypokalemia. Whereas insulin is administered and the hydrogen ion concentration decreases, the patient needs considerable potassium replacement. Finally, hyperglycemia and the anion gap have significant effects on the plasma potassium concentration, independent of acidosis. No conversion factor has been developed for estimation of true magnesium levels, although initial values may be high.

All laboratory determinations must be interpreted with caution. Serum creatinine determinations made by autoanalyzer may be falsely elevated. Leukocytosis more closely reflects the degree of ketosis than the presence of infection. Only the elevation of band neutrophils has been demonstrated to indicate the presence of infection, with a sensitivity of 100% and a specificity of 80% from a single small retrospective study.[6] Historically, the diagnosis of pancreatitis in a patient with DKA could be confounded by elevation of amylase levels in DKA. Given the strength of the current literature demonstrating greater specificity of lipase for diagnosis of pancreatitis, lipase should be the blood test of choice if pancreatitis is a concern.

Differential Considerations

Alcoholics, especially those who have recently abstained from drinking, with Kussmaul's respiration, a fruity odor to the breath, and acidemic arterial blood gas values may have alcoholic ketoacidosis. These patients may be euglycemic or hypoglycemic, and a large part of their acidosis is often caused by the unmeasured β-hydroxybutyric acid. Alcoholic ketoacidosis accounts for approximately 20% of all cases of ketoacidosis.

Ketoacidosis can also develop with fasting in the third trimester of pregnancy and in nursing mothers who do not eat.

The differential diagnosis for DKA is broad and includes any entity that may cause elevated anion gap acidosis, ketosis, or both. The presence of DKA should not exclude investigation for other causes of anion gap metabolic acidosis, such as sepsis, poisoning, or lactic acidosis, as physiologic stress from one of these other causes can precipitate DKA.

Management

General Measures

The approach to the patient with severe DKA is the same as that to any patient in extremis. The comatose patient, especially if vomiting, requires intubation. Once the patient is intubated, maintain hyperventilation to prevent worsening acidosis. The patient in hypovolemic shock requires aggressive fluid resuscitation with 0.9% saline solution rather than pressors; consider other possible causes of shock (e.g., sepsis or myocardial dysfunction secondary to myocardial infarction). Close monitoring of vital signs is essential. Bedside ultrasonography may be of benefit in excluding other causes of hypotension and evaluating the volume status of an individual patient. For example, use of the Focused Assessment with Sonography for Trauma (FAST) examination to exclude pericardial tamponade or hemoperitoneum, if it is clinically indicated, may be helpful. Likewise, evaluation of myocardial contractility and inferior vena cava diameter can help evaluate cardiac function and volume status noninvasively. Although it is not routinely used in the ED setting, in cases in which the volume status is difficult to ascertain because of complex underlying physiologic derangements, such as congestive heart failure and renal failure, invasive hemodynamic monitoring may be required to guide fluid therapy. Routine use of invasive hemodynamic monitoring is not supported by available evidence.

Box 126-1 Summary of Treatment of Diabetic Ketoacidosis

Identify diabetic ketoacidosis: serum glucose concentration, electrolyte values, ketone level, and arterial blood gas analysis; also obtain complete blood count with differential, urinalysis, chest radiograph, and electrocardiogram, if indicated.
Supplement insulin.
- Insulin replacement: 0.1 unit/kg/hr regular insulin IV
- Change IV solution to D_5W/0.45% NS when glucose concentration is ≤300 mg/dL.

Rehydrate.
- 1-2 L NS IV during 1-3 hours
- Children: 20 mL/kg NS during first hour
- Follow with 0.45% NS

Correct electrolyte abnormalities.
- Sodium: Correct with administration of NS and 0.45% NS.
- Potassium: Ensure adequate renal function. Add 20-40 mEq KCl to each liter of fluid until ketoacidosis is corrected and potassium is normalized.
- Phosphorus: Usually unnecessary to replenish
- Magnesium: Correct with 1-2 g $MgSO_4$. Serum magnesium levels may not correlate with body stores.

Correct acidosis.
- Correction of acidosis is done by administration of IV fluids and insulin.

Search for and correct underlying precipitant.
Monitor progress and keep meticulous flow sheets.
- Vital signs
- Fluid intake and urine output
- Serum glucose, K^+, Cl^-, HCO_3^-, CO_2, pH
- Amount of insulin administered

Admit to hospital or intensive care unit.
- Consider outpatient therapy in children with reliable caretaker *and*
- Initial pH ≥ 7.35
- Initial HCO_3^- ≥ 20 mEq/L
- Can tolerate oral fluids
- Resolution of symptoms after treatment in emergency department
- No underlying precipitant requiring hospitalization

The diagnosis of DKA is generally simple. When hyperglycemia, ketosis, and acidosis have been established, begin fluid, electrolyte, and insulin therapy (Box 126-1).

Insulin

DKA cannot be reversed without insulin, and insulin therapy should be initiated as soon as the diagnosis is certain. There are no randomized trials comparing insulin with placebo or other therapies in DKA. However, the mortality from DKA was 90% in historical controls before development of exogenous insulin and 50% after insulin was introduced; with appropriate supportive therapy, it has reached the current levels of 5 to 7%.[5] In the past, very high dosages of insulin were administered to diabetic patients in DKA because they were thought to be extremely insulin resistant. However, several clinical trials done in the 1970s showed that low-dose insulin therapy is as effective as high-dose therapy.

Whereas the dosing of insulin infusions has been established, the utility of an intravenous bolus before the infusion remains controversial and is no longer routinely recommended. More recently, in selected patients with mild DKA, the subcutaneous or intramuscular administration of insulin has been proved safe and as effective as the intravenous administration of insulin. In selected cases with good outpatient follow-up, treatment of DKA with intermittent bolus dosing of regular insulin by the subcutaneous

www.ketabpezeshki.com 66485457-66963820

or intramuscular routes without admission has also been shown to be safe. However, this strategy has not been used in sicker patients. Poor perfusion may hamper the absorption of intramuscular or subcutaneous insulin, resulting in erratic absorption.[1,5] The current therapy of choice as recommended by the ADA is regular insulin infused at 0.1 unit/kg/hr up to 5 to 10 units/kg/hr, mixed with the intravenous fluids.

Children with DKA pose additional management challenges. Whereas the general principles of fluid and electrolyte repletion in concert with insulin therapy remain the same, controversy exists about the dosing and administration of fluids and insulin because of concerns related to the risk of inducing cerebral edema in children with DKA. Despite frequently voiced concerns about this complication, it remains rare with an overall incidence of 1% in pediatric DKA patients. Virtually all current evidence supporting the contention that the use of higher doses of insulin and aggressive fluid resuscitation contributes to the development of cerebral edema comes from retrospective reviews and small case studies. The best available evidence shows associations only with lower arterial Pco_2 and higher blood urea nitrogen levels, indicating that severity of disease, rather than treatment interventions, plays the most significant role. DKA-related cerebral edema is virtually unheard of in children older than 5 years, and good prospective data are needed to help guide recommendations. Currently, there is an ongoing clinical trial to prospectively assess risk and outcomes (clinicaltrials.gov).

Because the half-life of regular insulin is 3 to 10 minutes, insulin should be administered intravenously by constant infusion rather than by repeated bolus. When the blood glucose concentration has dropped to 250 to 300 mg/dL, add dextrose to the intravenous fluids to prevent iatrogenic hypoglycemia and cerebral edema. In patients with euglycemic DKA, add dextrose to the intravenous fluids at the start of insulin therapy.

Insulin resistance occurs rarely in diabetic patients and requires an increase in dosage for a satisfactory response to be obtained. Resistance may be caused by obesity or accelerated insulin degradation.

Dehydration

The severely dehydrated adult patient is likely to have a fluid deficit of 3 to 5 L. No uniformly accepted formula exists for the administration of fluid in this disorder.

If the patient is in hypovolemic shock, administer normal saline (NS) as rapidly as possible in the adult or in boluses of 20 mL/kg in the child until a systolic pressure of 80 mm Hg is obtained. In the adult who has marked dehydration in the absence of clinical shock or heart failure, 1 L of NS may be administered in the first hour. In general, 2 L of NS during the first 1 to 3 hours is followed by a slower infusion of half-NS solution. DKA patients without extreme volume depletion may be successfully treated with a lower volume of intravenous fluid replacement. NS solution at 20 mL/kg during the first hour is the usual fluid resuscitation therapy for a child. Thereafter, adjust the fluid rate according to age, cardiac status, and degree of dehydration to achieve a urine output of 1 to 2 mL/kg/hr. Data do not support use of colloidal over isotonic crystalloid fluids for resuscitation.

Fluid resuscitation alone may help lower hyperglycemia. Because a low level of circulating insulin may be present even in DKA, increased perfusion may transport insulin to previously unreached receptor sites. In addition, a large volume of glucose may be cleared by the kidneys in response to improved renal perfusion. The mean plasma glucose concentration has been noted to drop 18% after administration of saline solution without insulin.[1] Whereas fluid administration decreases serum glucose concentration and improves acidosis, the underlying insulin deficiency in DKA still requires administration of insulin for correction of ketoacidosis. Thus, fluid resuscitation is an important factor in management of DKA but is not sufficient therapy by itself.

Acidosis also decreases after fluid infusion alone. Increased perfusion improves tissue oxygenation, thus diminishing the formation of lactate. Increased renal perfusion promotes renal hydrogen ion loss, and the improved action of insulin in the better-hydrated patient inhibits ketogenesis.

Potassium

Potassium replacement is invariably needed in DKA. The initial potassium level is often normal or high despite a large deficit because of severe acidosis. Potassium levels often plummet with correction of acidosis and administration of insulin. Administer potassium with the fluids while the laboratory value is in the upper half of the normal range and monitor renal function. In patients with low serum potassium concentration at presentation, hypokalemia may become life-threatening when insulin therapy is administered; therefore, intravenous administration of potassium in concentrations of 20 to 40 mEq/L is required.

It was once believed that there was always a phosphorus deficit in DKA. As a result, after initial potassium administration was completed with potassium chloride, potassium phosphate was used for follow-up potassium administration to correct the phosphorus deficit. There is no scientific evidence to support this practice, and only isolated case reports support concerns about clinically significant hypophosphatemia in DKA. If the measured serum phosphorus is low, it should be replaced with potassium phosphates.

Magnesium

Magnesium deficiency is a common problem in patients with DKA without renal disease. Both the initial pathophysiologic process and the therapy for DKA induce profound magnesium diuresis. Magnesium deficiency may exacerbate vomiting and mental changes, promote hypokalemia and hypocalcemia, or induce fatal cardiac dysrhythmia. The normal person requires 0.30 to 0.35 mEq/kg/day. Thus, it is reasonable to include 0.35 mEq/kg of magnesium in the fluids of the first 3 to 4 hours; further replacement depends on blood levels and the clinical picture. This amounts to 1.0 to 3 g of magnesium sulfate in the 70-kg patient.

Acidosis

Bicarbonate therapy may be indicated in severely acidemic patients ($pH \leq 7.0$). The use of bicarbonate is not warranted in less ill patients for several reasons.

1. Bicarbonate worsens the inhibition of oxygen release from red blood cells caused by the 2,3-diphosphoglycerate deficiency seen in phosphorus-depleted patients with DKA.
2. Overly rapid correction of acidosis is contraindicated because the blood-brain barrier is much more permeable to carbon dioxide than to bicarbonate. Thus, the correction of intravascular acidosis terminates Kussmaul's respiration, further augmenting the blood carbon dioxide available to cross the blood-brain barrier. Slowly, sufficient bicarbonate crosses the blood-brain barrier to provide adequate buffering. In the short term, however, as the blood acidosis is corrected, the acidity of the fluid surrounding the brain increases, causing paradoxical cerebrospinal fluid acidosis. The clinical significance of an acidic cerebrospinal fluid pH is unclear.
3. The administration of bicarbonate increases the potassium requirement, both immediately by driving potassium into the cell and more gradually by affecting the kidney, making iatrogenic hypokalemia more likely. When bicarbonate is

www.ketabpezeshki.com 66485457-66963820

used, serum potassium levels need to be followed even more closely.

4. The overaggressive use of bicarbonate may produce alkalosis, which induces dysrhythmias largely through its effect on the distribution of electrolytes. Alkalemia occurring late in the course of therapy is more common in patients who have received bicarbonate because ketones are metabolized to carbon dioxide, water, and bicarbonate.
5. Evidence suggests that lowered pH produces a feedback mechanism that directly inhibits ketogenesis. Bicarbonate can increase ketonuria and delay the fall in serum ketones compared with saline infusion alone.
6. Patients treated with bicarbonate fare no better and possibly fare worse than patients treated without bicarbonate. Studies indicate that bicarbonate worsens the prognosis even in patients with severe acidosis and pH values in the range 6.9 to 7.1. It is possible to manage severe DKA with fluids and insulin alone. When this is done, pH normalization is similar to that in a bicarbonate control group.

Given this, there is not a scenario in which bicarbonate administration can be recommended. There is no literature that demonstrates any improvement in outcomes from administration of bicarbonate, even in severely acidemic patients.

Complications

The precipitating causes of DKA may have associated morbidity and mortality rates equal to or worse than those of DKA itself. These include iatrogenic causes as well as infection and myocardial infarction. Morbidity in DKA is largely iatrogenic: hypokalemia from inadequate potassium replacement, hypoglycemia from inadequate glucose monitoring and failure to replenish glucose in intravenous solutions when serum glucose concentration drops below 250 to 300 mg/dL, alkalosis from overaggressive bicarbonate replacement, and pulmonary edema from overaggressive hydration.

The mortality rate in treated DKA is approximately 5 to 7%. The primary causes of death remain infection (especially pneumonia), arterial thromboses, and shock. The decrease in mortality rate demonstrates that appropriate therapy can make a difference. Cerebral edema remains an important cause of morbidity and mortality in children with DKA, but its causes remain unclear.

Consider cerebral edema when the patient in DKA remains comatose or lapses into coma after the reversal of acidosis. It generally occurs 6 to 10 hours after the initiation of therapy. There are no warning signs, and the associated mortality rate is currently 90%.[5] Cerebral edema is rare in adults or children older than 5 years and appears to be most strongly associated with severity of illness (acidemia and azotemia). Subclinical cerebral edema in children is probably common. Furthermore, subclinical cerebral edema may either precede or follow the onset of therapy, raising the question of whether this entity is caused by therapy or is simply a manifestation of the basic pathophysiologic mechanism of DKA. The treatment of cerebral edema is largely supportive and outcomes are poor. No large clinical trials have identified effective treatments for this entity, although some authors recommend mannitol. Steroids have not been shown to be effective.

Disposition

Most patients with DKA require hospital admission, often to the intensive care unit. All pregnant diabetic patients in DKA require admission and consultation with an endocrinologist and obstetrician specializing in the care of high-risk pregnancies. Some children (initial pH ≥ 7.35, bicarbonate ≥ 20 mEq/L) with resolution of findings who can tolerate oral fluids after 3 or 4 hours of treatment may be discharged home with a reliable caregiver. Patients who have mild DKA may be treated on an outpatient basis if the patient or parent is reliable, the underlying causes do not require inpatient therapy, and close follow-up is pursued.

HYPERGLYCEMIC HYPEROSMOLAR STATE

HHS represents a syndrome of acute diabetic decompensation characterized by marked hyperglycemia, hyperosmolarity and dehydration, and decreased mental functioning that may progress to frank coma. The terminology has changed recently from the former hyperglycemic hyperosmolar nonketotic coma, as some patients have mild degrees of ketosis and coma is not universally present.[1,5] Ketoacidosis is generally minimal or absent, although metabolic acidosis from another source, such as lactic acidosis from sepsis or uremia from acute renal failure, may be present. Focal neurologic signs may be present, or there may be a global encephalopathy. DKA and HHS may occur together.

Principles of Disease

Pathophysiology

As with DKA, the pathophysiologic mechanism of HHS varies with the particular patient. Because most patients with HHS are elders, decreased renal clearance of glucose produced by the decline of renal function with age often contributes to the illness. As with DKA, decreased insulin action results in glycogenolysis, gluconeogenesis, and decreased peripheral uptake of glucose. The hyperglycemia pulls fluid from the intracellular space into the extracellular space, transiently maintaining adequate perfusion. Soon, however, this fluid is lost in a profound osmotic diuresis, limited finally by hypotension and a subsequent drop in the glomerular filtration rate (GFR). The urine is extremely hypotonic, with a urine sodium concentration between 50 and 70 mEq/L, compared with 140 mEq/L in extracellular fluid. This hypotonic diuresis produces profound dehydration, leading to hyperglycemia, hypernatremia, and associated hypertonicity. Often the patient is prevented from taking in adequate fluids by stroke, Alzheimer's disease, or other diseases, greatly exacerbating the dehydration.

The reason for the absence of ketoacidosis in HHS is unknown. FFA levels are lower than in DKA, thus limiting substrates needed to form ketones. The most likely reason for the blunted counter-regulatory hormone release and lack of ketosis seems to be the continued secretion of tiny amounts of insulin that block ketogenesis.

Etiology

HHS is a syndrome of severe dehydration that results from a sustained hyperglycemic diuresis under circumstances in which the patient is unable to drink sufficient fluids to offset the urinary losses. The full-blown syndrome does not usually occur until volume depletion has progressed to the point of decreased urine output.

HHS is most common in elders with type 2 diabetes but has been reported in children with type 1 diabetes. HHS may occur in patients who are not diabetic, especially after burns, parenteral hyperalimentation, peritoneal dialysis, or hemodialysis.

Clinical Features

The prodrome of HHS is significantly longer than that of DKA. Clinically, extreme dehydration, hyperosmolarity, volume depletion, and CNS findings predominate. If they are awake, patients

www.ketabpezeshki.com 66485457-66963820

may complain of fever, thirst, polyuria, or oliguria. Approximately 20% of patients have no known history of type 2 diabetes. The most common associated diseases are chronic renal insufficiency, gram-negative pneumonia, gastrointestinal bleeding, and gram-negative sepsis. Approximately 85% of patients have underlying renal or cardiac impairment as a predisposing factor. Arterial and venous thromboses are common and often complicate the picture.

The patient often exhibits orthostatic hypotension or frank hypotension, tachycardia, and fever with signs of marked dehydration. The depression of the sensorium correlates directly with the degree and rate of development of hyperosmolarity. Some patients have a normal mental status. Neurologic issues are common in HHS. Whereas decreased level of consciousness is the most common neurologic finding, seizures, stroke syndromes, and movement disorders have been reported in various case series. Whether HHS is the cause of or the result of these disorders is unclear, and there is no evidence currently to recommend use of antiepileptics or antithrombotic agents prophylactically in HHS patients.

Diagnostic Strategies

Laboratory findings usually reveal a blood glucose level above 600 mg/dL and serum osmolarity above 350 mOsm/L. The blood urea nitrogen concentration is invariably elevated. Although patients with HHS do not have a ketoacidosis caused by diabetes, they may have a metabolic acidosis secondary to some combination of lactic acidosis, starvation ketosis, and retention of inorganic acids attributable to renal hypoperfusion.

The patient with HHS typically has a more profound electrolyte imbalance than the patient with DKA. Levels of potassium, magnesium, and phosphorus may seem initially high, even in the presence of marked total deficit. In the absence of acidemia, however, the discrepancy between the initial electrolyte reading and body stores is less than that of DKA. Initial serum sodium readings are inaccurate because of hyperglycemia.

Differential Considerations

The differential diagnosis of HHS is identical to that of DKA. In addition, diabetic patients receiving chlorpropamide are subject to water intoxication with dilutional hyponatremia, which may be manifested as coma without acidosis that is clinically indistinguishable from HHS. The patient with HHS who has a sharply depressed sensorium may not be initially distinguishable from the patient with profound hypoglycemia. When blood glucose concentration cannot be rapidly checked, the immediate administration of one ampule of $D_{50}W$ minimally worsens HHS and may be lifesaving for patients with hypoglycemia.

Management

The fluid, electrolyte, and insulin regimens for the initial resuscitation in HHS are subject to the same controversies as the therapies for DKA (see Box 126-1). There are varying recommendations about which intravenous fluids to administer, generally based on calculations of water deficits. There are no well-done randomized trials comparing isotonic versus hypotonic fluid resuscitation, and use of an isotonic crystalloid is a reasonable choice in the volume-depleted patient. Cerebral edema has been noted in isolated case reports in adults, especially with glucose levels above 700 mg/dL. An association between intravenous fluid resuscitation and cerebral edema has not been shown in the literature; previous reports of this association may have been due to the confounder that it is seen in sicker patients who often receive more aggressive fluid resuscitation.

Dehydration

For patients in coma or hypovolemic shock, initial intravenous fluid infusion is given as rapidly as possible. Add glucose to resuscitation fluids when the blood glucose level drops below 300 mg/dL. Because many HHS patients are elders with coexisting diseases, such as congestive heart failure and renal failure, noninvasive or invasive forms of hemodynamic monitoring may be required to guide fluid administration when there is the clinical suspicion of pulmonary edema or volume overload.

Electrolytes

Measurement of serum electrolytes should be used to guide replacement in the HHS patient. In particular, because the degree of acidosis is generally less, potassium levels more accurately reflect total body stores than they do in DKA.

Insulin

The pathophysiologic mechanism of HHS is different from that of DKA, and there is usually enough basal insulin function to prevent frank ketoacidosis. Therefore, a continuous intravenous insulin infusion is not required in these patients as it is with DKA. However, there are times when the use of an intravenous insulin infusion may be of benefit to help lower glucose concentration in a more controlled fashion, particularly in patients with very high glucose levels (>700 mg/dL) or in those who are severely hypoperfused, in whom intramuscular or subcutaneous insulin absorption may be erratic. If an intravenous insulin infusion is used, it should be done at an infusion rate similar to that for DKA (0.1 unit/kg/hr).

Other Considerations

A vigorous search for the underlying precipitant of HHS should be pursued. Response to therapy should be followed in the manner described for patients in DKA. Phenytoin (Dilantin) is contraindicated for the seizures of HHS because it is often ineffective and may impair endogenous insulin release.[1] Low-dose subcutaneous heparin may be indicated to lessen the risk of thrombosis, which is increased by the volume depletion, hyperviscosity, hypotension, and inactivity associated with HHS.

Complications

Reasons for high morbidity and mortality rates are not always clear, but many patients with HHS are elders who have underlying cardiac and renal disease. Pediatric HHS differs from adult HHS in that children have a much higher incidence of fatal cerebral edema. Other causes of morbidity and mortality are similar to those described for DKA. The mortality rate of treated HHS patients has been 40 to 70% in the past but now ranges from 8 to 25%.[1,5]

Disposition

In general, patients with HHS require hospitalization for intravenous hydration, glucose control, and evaluation of precipitating and complicating conditions.

LATE COMPLICATIONS OF DIABETES

Late complications of diabetes cause significant morbidity and mortality. They develop approximately 15 to 20 years after the onset of overt hyperglycemia. The Diabetes Control and

www.ketabpezeshki.com 66485457-66963820

Complications Trial showed that tight glycemic control significantly reduces the risk of microvascular disease, such as microalbuminuria (the earliest sign of nephropathy), neuropathy, and retinopathy, but at the expense of greatly increasing the risk of recurrent hypoglycemia.[1]

Vascular Complications

Diabetes is associated with an increased risk for atherosclerosis and thromboembolic complications, which are a major cause of morbidity and premature death. The cause of accelerated atherosclerosis is unknown, although it is probably related to oxidated low-density lipoprotein and increased platelet activity. Atherosclerotic lesions are widespread, causing symptoms in many organ systems. Coronary artery disease and stroke are common. Diabetic patients have an increased incidence of "silent" myocardial infarction, complicated myocardial infarctions, and congestive heart failure. Peripheral vascular disease is noted clinically by claudication, nonhealing ulcers, gangrene, and impotence. In addition, standard treadmill stress tests have a decreased sensitivity in the detection of coronary artery disease in diabetics. For this reason, exercise or pharmacologic stress echocardiography or a nuclear medicine imaging study should be considered when a provocative test is needed to evaluate the diabetic patient for acute coronary syndrome.[1]

Diabetic Nephropathy

Renal disease is a leading cause of death and disability in diabetic patients. Approximately half of end-stage renal disease in the United States is caused by diabetic nephropathy. Diabetic nephropathy involves two pathologic patterns: diffuse and nodular. Clinical renal dysfunction does not correlate well with the histologic abnormalities. Disease usually progresses from enlarged kidneys with elevated GFR, to the appearance of microalbuminuria, to macroproteinuria with hypertension, reduced GFR, and renal failure. The appearance of microalbuminuria correlates with the presence of coronary artery disease and retinopathy.

Azotemia generally does not begin until 10 to 15 years after the diagnosis of diabetes. Progression of renal disease is accelerated by hypertension. Meticulous control of diabetes can reverse microalbuminuria and may slow the progression of nephropathy. Blood pressure should be aggressively managed; angiotensin-converting enzyme inhibitors are effective in controlling hypertension and lowering microalbuminuria. Chronic hemodialysis and renal transplantation are unfortunate endpoints for many diabetic patients with renal disease.

Retinopathy

Diabetes is a leading cause of adult blindness in the United States. Approximately 11 to 18% of all diabetic patients have treatable diabetic retinopathy ranging from mild to severe and manifested in many forms. The severity of diabetic retinopathy is clearly related to the quality of glycemic control.

Background (simple) retinopathy is found in most diabetic patients who have prolonged disease. Background retinopathy is characterized by microaneurysms, small-vessel obstruction, cotton-wool spots or soft exudates (microinfarcts), hard exudates, and macular ischemia. The characteristics of proliferative retinopathy are new vessel formation and scarring. Complications of proliferative retinopathy are vitreal hemorrhage and retinal detachment, which may ultimately cause unilateral vision loss. The treatment of diabetic retinopathy is photocoagulation.

Maculopathy is background retinopathy with macular involvement. It results primarily in a deficit of central vision. As with proliferative retinopathy, it is vital that the patient be under the care of an ophthalmologist. Laser therapy in the early stages can dramatically alter the course of this disabling disease.

The diabetic patient may present with complaints ranging from acute blurring of vision to sudden unilateral or even bilateral blindness. Less often, diabetic patients have more gradual vision loss caused by the common senile cataract or the "snowflake" cataract, which may disappear as hyperglycemia is corrected. The associated hyperlipidemia of diabetes may lighten the color of retinal vessels, producing lipidemia retinalis. Anterior ischemic optic neuropathy has been reported.

Diabetic patients with retinopathy should be referred to an ophthalmologist. Even in those with normal vision, ophthalmologic procedures may limit visual loss or prevent crises such as neovascular glaucoma.

Neuropathy

Both autonomic and peripheral neuropathies are well-known complications of diabetes. The prevalence of peripheral neuropathy ranges from 15 to 60%. The cause of the neuropathy is not clearly understood, but evidence suggests several factors in its development. Neuropathy may result from the effects of diabetic vascular disease on the vasa nervorum. Myoinositol, the polyol pathway, and nonenzymatic glycosylation of protein may have roles. All these factors are related to an elevated blood glucose level. On pathologic examination, segmental demyelinization occurs with loss of both myelinated and unmyelinated axons, particularly those affecting the distal part of the peripheral nerve. Neurologic manifestations of diabetes may regress with improved glycemic control.

Several distinct types of neuropathy have been recognized in diabetes. Peripheral symmetrical neuropathy is a slowly progressive, primary sensory disorder manifested bilaterally with anesthesia, hyperesthesia, or pain. The pain is often severe and worse at night. It affects upper and lower extremities, although lower extremities and the most distal sections of the involved nerves are most often affected. There may be a motor deficiency as well. The pain may be very difficult to control; opioid analgesics have been used, but nonopioid medications such as gabapentin, pregabalin, and amitriptyline are preferred. Pregabalin is the newest of these agents and seems to hold the most promise when it is used at higher doses (up to 600 mg/day). Duloxetine at doses of 60 mg/day is also effective. Both pregabalin and duloxetine achieve significant pain control in at least 50% of patients. Gabapentin at 300 mg three times daily has some efficacy, achieving significant pain relief in about a third of patients; amitriptyline 25 mg daily demonstrates similar results. Aldose reductase inhibitors have not proved to be better than placebo. A reasonable approach for the emergency physician is initiation of duloxetine or pregabalin as these have demonstrated the best efficacy in pain control, with the understanding that it may take several days for peak effect to be reached.[7]

Mononeuropathy, or mononeuropathy multiplex, affects both motor and sensory nerves, generally one nerve at a time. The onset is rapid, with wasting and tenderness of the involved muscles. Clinically noted is sudden onset of wristdrop, footdrop, or paralysis of cranial nerves III, IV, and VI.

Diabetic truncal mononeuropathy occurs rapidly in a radicular distribution. In contrast to other mononeuropathies, it is primarily if not exclusively sensory. If it causes pain, it may mimic that of a myocardial infarction or acute abdominal inflammation. Like diabetic mononeuropathy, it may be most bothersome at night and generally resolves in a few months. Whereas diabetic mononeuropathy is often the first clue of diabetes, truncal mononeuropathy is more often found in known diabetic patients.

Autonomic neuropathy occurs in many forms. Neuropathy of the gastrointestinal tract is manifested by difficulty in swallowing,

www.ketabpezeshki.com 66485457-66963820

delayed gastric emptying, constipation, or nocturnal diarrhea. Impotence and bladder dysfunction or paralysis may occur. Orthostatic hypotension, syncope, and even cardiac arrest have resulted from autonomic neuropathy. Diabetic diarrhea responds to diphenoxylate and atropine, loperamide, or clonidine. Orthostatic hypotension is treated by sleeping with the head of the bed elevated, avoidance of sudden standing or sitting, and use of full-length elastic stockings.

The Diabetic Foot. Approximately 20% of hospitalizations in diabetic patients are related to foot problems. Sensory neuropathy, ischemia, and infection are the principal contributors to diabetic foot disease. Loss of sensation leads to pressure necrosis from poorly fitting footwear and small wounds going unnoticed. The most common cause of injury is pressure on plantar bone prominences. Assess all neuropathic foot ulcers for infection, débride devitalized tissue, and obtain radiographs to evaluate for the presence of foreign bodies, soft tissue gas, or bone abnormalities.[8] Weight bearing must be eliminated by total-contact casting.

Not all ulcers are infected. Infection is suggested by local inflammation or crepitation. Conversely, some uninflamed ulcers are associated with underlying osteomyelitis. Most mild infections are caused by gram-positive cocci, such as *Staphylococcus aureus* or streptococci, and may be treated with oral antibiotics with activity against gram-positive organisms, such as trimethoprim-sulfamethoxazole 800/160 mg twice daily, a first-generation cephalosporin such as cephalexin 500 mg four times daily, or clindamycin 300 mg every 6 hours. A strict non–weight-bearing regimen, meticulous wound care, and daily follow-up are also vitally important to wound healing. This approach may not be possible when patients are deemed unreliable, do not have good home support, or do not have ready access to follow-up care.

Deeper, limb-threatening infections—as evidenced by full-thickness ulceration, cellulitis more than 2 cm in diameter with or without lymphangitis, bone or joint involvement, or systemic toxicity—are usually polymicrobial in origin and caused by aerobic gram-positive cocci, gram-negative bacilli, and anaerobes. These patients require hospitalization and, after culture, broad-spectrum intravenous empirical antimicrobial therapy (Table 126-3), strict non–weight-bearing status, tight glycemic control, early surgical intervention for débridement, and meticulous wound care. Consider occult osteomyelitis in all cases of neuropathic ulceration.[8] Hyperbaric oxygen has been shown to have some efficacy in treatment of complicated infection, especially with anaerobic organisms. Up to one third of patients eventually undergo amputation.

Table 126-3 Common Serious Infections in Diabetics and Their Antimicrobial Therapy

INFECTIOUS CONDITION	ANTIMICROBIALS
Diabetic foot infection	Mild: consider trimethoprim-sulfamethoxazole 800/160 twice daily or clindamycin 300 mg q6h Moderate to severe: clindamycin 600 mg IV q6h ± piperacillin-tazobactam (Zosyn) 3.375 g IV q6h and vancomycin 15 mg/kg IV q12h
Malignant otitis externa	Oral: ciprofloxacin 500 mg PO twice daily for 10-14 days IV: ceftazidime 2 g IV q8h ± gentamicin 2 mg/kg IV q8h
Mucormycosis	Amphotericin B 1-1.5 mg/kg/day Posaconazole 400 mg twice daily
Mucocutaneous candidiasis	Ketoconazole 200 mg PO daily; may need several weeks of therapy
Nonclostridial gas gangrene (including Fournier's)	Clindamycin 600 mg q6h + third-generation cephalosporin + vancomycin 15 mg/kg q12h

Infections

Diabetic patients are more susceptible to complications of infections because of their inability to limit microbial invasion with effective polymorphonuclear leukocytes and lymphocytes. They have an increased incidence of extremity infections and pyelonephritis compared with the general population. In addition, they are particularly susceptible to certain other infections, such as tuberculosis, mucocutaneous candidiasis, intertrigo, mucormycosis, soft tissue infections, nonclostridial gas gangrene, osteomyelitis, and malignant *Pseudomonas* otitis externa. Treatment of diabetic patients with infection includes rapid culture and antibiotics (see Table 126-3), glycemic control, and generally hospitalization.

Cutaneous Manifestations

Dermal hypersensitivity is manifested by pruritic, erythematous indurations that occur at insulin injection sites. The declining prevalence of this condition has paralleled the improved purification of insulin. Insulin lipoatrophy likewise seems to be a result of insulin impurities and is manifested as subcutaneous depressions at injection sites. Although lipoatrophy is now more common than dermal hypersensitivity, its prevalence has also declined sharply because of improved insulin preparations. Insulin lipohypertrophy is manifested by raised areas of subcutaneous fat deposits at insulin injection sites. These lesions generally reflect the failure of the patient to rotate injection sites adequately. They resolve spontaneously during months if insulin injection is avoided in the affected areas and sites are properly rotated.

Insulin pumps are often associated with localized skin problems, usually a reaction to the tape securing the tubing and needles. On occasion, sensitivity to the catheters is seen. Skin infections at the site of injection are the most common complication of insulin pumps. Changing the patient to buffered pure-pork from unbuffered beef-pork insulin is the only intervention that seems to reduce the rate of infection. A few patients have been noted to have hard nodules at the injection site. The cause of these nodules is uncertain.

Diabetic patients who use oral hypoglycemic agents may have rashes associated with these medications. After consumption of ethanol, approximately 38% of type 2 patients taking chlorpropamide exhibit a "flush" consisting of redness of the face and neck and a sense of warmness or burning. Patients may demonstrate urticaria in response to both insulin and oral hypoglycemics.

Diabetic skin conditions include fungal infections, acanthosis nigricans, necrobiosis lipoidica diabeticorum, xanthoma diabeticorum, bullosis diabeticorum, and diabetic dermopathy. *Acanthosis nigricans* is characterized by a velvety brown-black thickening of the keratin layer, most often in the flexor surfaces. It is the cutaneous marker for a group of endocrine disorders with insulin resistance. *Necrobiosis lipoidica diabeticorum* begins as erythematous papular or nodular lesions, usually in the pretibial area but in other areas as well. The early lesions may contain telangiectasias. These lesions spread and frequently form a single pigmented area of atrophic skin, often with a yellow and sometimes ulcerated center and an erythematous margin. A history of previous trauma is sometimes found.

The three forms of diabetic thick skin are scleroderma-like skin changes of the fingers and dorsum of the hand associated with stiff joints and limited mobility; clinically inapparent but measurable thick skin; and scleredema adultorum, or increased dermal thickness on the back and posterior upper neck in middle-aged, overweight patients with type 2 diabetes.

www.ketabpezeshki.com 66485457-66963820

Xanthoma diabeticorum is evidence of the hyperlipidemia associated with diabetes. It is similar to the xanthoma found in nondiabetic hyperlipidemic patients. Xanthomas have an erythematous base and a yellowish hue.

Bullosis diabeticorum is a rare occurrence. Bullae are usually filled with a clear fluid and are most often found on the extremities, especially the feet. The fluid is occasionally slightly hemorrhagic. The bullae usually heal spontaneously without scarring.

Diabetic dermopathy, or "skin spots," is the most common finding in diabetes. It arises as discrete, depressed, and brownish lesions generally less than 15 mm in diameter and found in the pretibial area.

Resistant, aggressive *impetigo* or *intertrigo* suggests diabetes.

Insulin Allergy

Insulin allergy is mediated by immunoglobulin E and is manifested by local itching or pain and delayed brawny edema, urticaria, or anaphylaxis. Systemic reactions are usually seen in patients who have previously discontinued insulin and then resumed therapy. Mild reactions may be treated with antihistamines, whereas anaphylaxis must be treated with epinephrine. Patients with significant reactions must be admitted for desensitization.

DIABETES IN PREGNANCY

Before the discovery of insulin in 1922, diabetes in pregnancy was associated with a fetal death rate of 60 to 72% and maternal morbidity of approximately 30%.[9] In 1977, a linear relationship between glycemic control and perinatal mortality was discovered. Strict metabolic control is now a goal in all diabetic pregnancies.[5]

Pregnant patients should be watched extremely closely and aggressively treated for impending or actual DKA. For a variety of reasons, pregnant women have a special predisposition to both glucose intolerance and excess ketone production. Although uncommon, DKA may reduce fetal oxygen delivery and cause perinatal asphyxia. Intellectual deficits in offspring have been associated with maternal ketonuria from any cause.

Pregnancy is associated with progression of retinopathy for unknown reasons. Whether pregnancy worsens diabetic nephropathy or hastens the progression to end-stage renal disease is controversial. Although nephrotic syndrome develops in 71% of pregnancies, blood pressure and proteinuria eventually return to first-trimester values. Diabetic nephropathy is associated with an increased risk of preterm labor, stillbirth, neonatal death, fetal distress, and intrauterine growth retardation; otherwise, the literature is sparse on the effect of pregnancy on diabetic neuropathy. Autonomic neuropathy, particularly gastroparesis, makes adequate nutrition difficult for both mother and fetus. Pregnant women should be referred for parenteral feedings if conservative therapy fails to control vomiting.

Hypoglycemia is common in pregnancy, in part because of intensive insulin treatment to maintain euglycemia. The effects of hypoglycemia on the fetus are unclear. Ketoacidosis is associated with a 50 to 90% fetal mortality rate.[5]

NEW-ONSET HYPERGLYCEMIA

Patients often present to the ED with typical diabetic symptoms such as polyuria, polydipsia, and polyphagia. Many have serum glucose concentrations above 200 mg/dL but are not ketotic. Patients with newly diagnosed hyperglycemia with normal electrolyte values may be treated with intravenous hydration alone or with insulin, often reducing the glucose concentration to 150 mg/dL. In reliable patients whose initial glucose concentration is greater than 400 mg/dL, initiation of oral hypoglycemic therapy may be appropriate, with lifestyle modification. Obtain an HbA_{1c} value before initiation of therapy to confirm a diagnosis of diabetes and to establish a baseline. Initial therapy with sulfonylureas is appropriate; glyburide (2.5-5 mg once daily) or glipizide (5 mg once daily) is recommended.[1,10] Metformin may be initiated as well at a dose of 500 mg daily; however, it lowers blood glucose on average only about 100 mg/dL, and newly diagnosed diabetics frequently require additional agents to control their glucose concentration. Patients with kidney disease may have complications from use of either sulfonylureas or metformin and will likely need insulin therapy. Follow-up should be stressed and warning signs of hypoglycemia discussed.

CONTROL OF DIABETES

The common oral antidiabetic agents are presented in Table 126-4. There are several preparations of insulin available as well. The major recent advances in insulin preparations (in addition to regular insulin and NPH insulin) are ultra-long-acting and ultra-short-acting insulins. These agents are coming into favor because of better basal insulin levels (long acting) and more rapid onset and shorter duration of action (Humalog) to provide more rapid and predictable sliding scale coverage. Other newer agents include the incretin mimetics, such as exenatide, which is used for type 2 diabetes; it is injectable and used in conjunction with oral agents but not with insulin. Amylin analogues, such as pramlintide, are used with insulin but significantly increase the risk of hypoglycemia.

The basic concepts of the diabetic diet remain unchanged, although many studies emphasize foods and medications that alter glucose absorption. Various high-fiber diets have improved glycemic control. The number of supplements or low glycemic index snacks has risen in the past few years. Exercise continues to be a cornerstone of diabetes management, although care must be taken to balance it with appropriate calorie intake and medication use.

Solid organ pancreas transplants have become more common; several centers have performed combined pancreas and kidney transplants in those with end-stage kidney disease due to diabetic nephropathy. Transplantation ameliorates many secondary complications of diabetes, such as nephropathy, neuropathy,

Table 126-4 Common Oral Diabetic Medications

Biguanides (metformin)	Decrease hepatic glycogenolysis	500-1000 mg twice daily
Sulfonylureas (glipizide, glimepiride)	Stimulate pancreatic insulin release	2.5-5 mg daily
Thiazolidinediones (pioglitazone, rosiglitazone)	Insulin sensitizers, decrease hepatic gluconeogenesis	Increased risk of adverse cardiac events
Meglitinides (repaglinide, nateglinide)	Stimulate postprandial insulin release	Take with meals only
Dipeptidyl peptidase 4 inhibitors (sitagliptin)	Decrease insulin degradation and gluconeogenesis	Once a day; can be found in multiple combination medications
α-Glucosidase inhibitors (acarbose, miglitol)	Delay breakdown of carbohydrates in the intestines	Major side effect is diarrhea

www.ketabpezeshki.com 66485457-66963820

gastroparesis, retinopathy, and microvascular changes. The percentage of grafts functioning after 1 year and the 1-year survival rate of patients are greater than 75% in selected medical centers. Rejection, post-transplantation pancreatitis, and graft thrombosis as well as other vascular and immunosuppression problems continue to plague transplant recipients.

KEY CONCEPTS

- Hypoglycemia may be associated with significant morbidity and mortality. When the diagnosis is suggested and, if possible, confirmed by laboratory evaluation, initiate therapy immediately.
- Hypoglycemia caused by sulfonylurea oral hypoglycemic agents may be prolonged. Patients should be observed for an extended period or hospitalized.
- The essential treatment of DKA includes restoration of insulin, correction of dehydration, correction of potassium level, correction of acidosis, and treatment of the underlying cause.
- Use of sodium bicarbonate to correct acidosis in DKA has not demonstrated any benefit and may be associated with worse outcomes.
- Hyperglycemic hyperosmolar state is most commonly seen in elders with multiple comorbid conditions and is distinguished from DKA by lack of ketoacidosis. In addition to fluid resuscitation and correction of hyperglycemia, treatment should address the underlying cause of the state, which includes infection, myocardial infarction, and cerebrovascular accident.
- Diabetic peripheral neuropathy is common and has multiple treatment modalities, including gabapentin, pregabalin, and duloxetine.
- Diabetic foot ulcers and other diabetic soft tissue infections (such as gas gangrene and Fournier's gangrene) are frequently polymicrobial and require broad-spectrum antibiotic therapy covering gram-positives, gram-negatives, and anaerobes.
- Tight glycemic control is considered to be beneficial in reducing the risk of most major complications of diabetes. This is an important point of patient education for diabetics seen in the ED.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. American Diabetes Association: Standards of medical care in diabetes—2011. *Diabetes Care* 2011; 34:S11-S62.
2. Halimi S: Acute consequences of hypoglycaemia in diabetic patients. *Diabetes Metab* 2010; 36:S54-S58.
3. Lung DD, Olson KR: Hypoglycemia in pediatric sulfonylurea ingestion: An 8 year poison center retrospective study. *Pediatrics* 2011; 127:e1558-e1564.
4. Fasano CJ, O'Malley G, Dominici P, Aguilera E, Latta DR: Comparison of octreotide and standard therapy versus standard therapy alone for the treatment of sulfonylurea-induced hypoglycemia. *Ann Emerg Med* 2008; 51:400-406.
5. Kitabchi AE, et al: Thirty years of personal experience in hyperglycemic crises: Diabetic ketoacidosis and hyperglycemic hyperosmolar state. *J Clin Endocrinol Metab* 2008; 93:1541-1552.
6. Slovis CM, et al: Diabetic ketoacidosis and infection: Leukocyte count and differential as early predictors of serious infection. *Am J Emerg Med* 1987; 5:1-5.
7. Lipsky BA, et al: Diagnosis and treatment of diabetic foot infections. *Clin Infect Dis* 2004; 39:885-910.
8. Bril V, et al: Evidence based guideline: Treatment of painful diabetic neuropathy. *Neurology* 2011; 76:1758-1765.
9. Castroino K, Jovanovic L: Pregnancy and diabetes management: Advances and controversies. *Clin Chem* 2011; 57:221-230.
10. Waugh N, et al: Newer agents for blood glucose control in type 2 diabetes: Systematic review and economic evaluation. *Health Technol Assess* 2010; 14:1-248.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 127

Rhabdomyolysis

Ram Parekh

PERSPECTIVE

Rhabdomyolysis is a potentially life-threatening condition characterized by the breakdown of skeletal muscle and the release into the circulatory system of intracellular contents, including creatine kinase, aspartate transaminase, lactate dehydrogenase, aldolase, the heme pigment myoglobin, and electrolytes. The severity of illness ranges from asymptomatic elevations in serum muscle enzymes to life-threatening electrolyte imbalances and acute renal failure.

PRINCIPLES OF DISEASE

Physiology

A healthy 70-kg man has approximately 28 kg of muscle. Skeletal muscle is 80% water and 20% protein, accounting for about half of the total body protein stores, and is the largest organ in the human body.[1] A large amount of adenosine triphosphate (ATP) is required for muscle function, even at rest. ATP generation by muscle accounts for 30% of the body's oxygen consumption at rest and up to 85% at extremes of physical activity.[2] Resting muscle uses fatty acids for ATP generation; muscle then draws on stored ATP for the first 8 seconds of activity, next using the phosphagen (creatine phosphate) stores for an additional 10 to 15 seconds; finally, muscle depends on anaerobic glycogen metabolism to lactate for enough ATP for an additional 30 to 40 seconds of activity. Aerobic ATP production provides the bulk of the energy needed for muscle activity but requires oxygen. Glucose, amino acids, and fatty acids are incorporated into the Krebs cycle to produce much larger quantities of ATP by energy-rich compounds, such as the reduced forms of nicotinamide adenine dinucleotide and flavin adenine dinucleotide.

Myoglobin, like hemoglobin, binds and releases oxygen and delivers it to active skeletal muscle. Unlike for hemoglobin, its ability to deliver oxygen is unaffected by pH, resulting in a relatively increased affinity for oxygen in comparison to hemoglobin and delivery of oxygen to cellular mitochondria at low partial pressures of oxygen.

The integrity of muscle cells is dependent on healthy cell membranes, which rely on ATP for proper membrane ion pump function. The sarcolemma, a thin membrane that encloses striated muscle fibers, contains numerous pumps that regulate electrochemical gradients. Under normal physiologic conditions, the sodium-potassium–adenosine triphosphatase (Na^+,K^+-ATPase) pump located in the sarcolemma maintains intracellular sodium concentrations of 10 mEq/L and intracellular potassium concentrations of 150 to 160 mEq/L by actively transporting sodium from the interior of the cell to the exterior, thereby making the interior of the cell more negative by the efflux of net positive charge (three sodium ions pumped out per two potassium ions pumped in). The electrical gradient then pulls sodium to the interior of the cell through a separate channel in exchange for calcium, effectively removing calcium from the cytoplasm. Low intracellular calcium levels are also maintained by an active calcium exchanger (Ca^{2+}-ATPase pump) that promotes calcium entry into the sarcoplasmic reticulum and mitochondria. As their names indicate, these ATPase pumps depend on ATP as a source of energy.

Under normal physiologic conditions, the concentration of free ionized calcium in the extracellular space is approximately 10,000 times greater than that in the intracellular space.[3] The high concentration of free calcium in the extracellular pool compared with the intracellular compartment and the resulting large electrochemical force on Ca^{2+} are particularly convenient to its role as an intracellular regulator. Even minor changes in the permeability of the plasma membrane to calcium will produce significant fluctuations in the cytosolic concentration with potentially unfavorable consequences for the integrity of the cell.[4,5]

Several transmembrane proteins exist to regulate calcium homeostasis. The plasma membrane transmembrane proteins are the energy-consuming Ca^{2+} channels, the Na^+-Ca^{2+} exchangers, and the Ca^{2+}-ATPase pumps. The last removes Ca^{2+} from the intracellular space by transporting Ca^{2+} out of the cytosol into the extracellular space as well as into the sarcoplasmic reticulum. Plasma membrane Ca^{2+} channels bring Ca^{2+} into the cytosol when activated at the neuromuscular junction. Na^+-Ca^{2+} exchangers are complicated, insofar that the direction of ion movement depends on the chemical and electrical gradients of each ion within the cell, which vary according to the contractile state of the myocyte[3,6] (Fig. 127-1).

Pathophysiology

Whereas the causes of rhabdomyolysis are diverse, the pathogenesis appears to follow a final common pathway: increased cytoplasmic calcium concentration, leading to myocyte destruction with release of muscle components into the circulation. There are two primary mechanisms by which calcium pathologically accumulates in the cell: direct cell membrane damage and ATP depletion.

Membrane damage from trauma and genetic or biochemical factors results in a massive influx of extracellular calcium into the cytoplasm driven by both electrical and chemical gradients.[5] ATP depletion results in failure of cellular transport and increased permeability to sodium ions. Any event that increases cytosolic sodium concentrations, whether it is from increased membrane permeability and inward Na^+ traffic or decreased ATP-dependent

www.ketabpezeshki.com 66485457-66963820

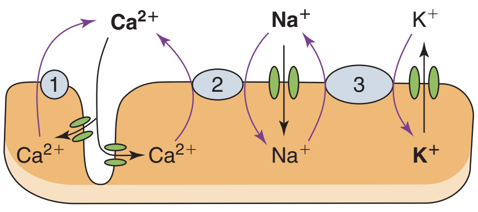


Figure 127-1. Normal membrane ionic pump function of skeletal muscle cell. When ATP supply is impaired, intracellular sodium concentration increases, reversing function of the Na^+-Ca^{2+} exchanger, with subsequent increase in intracellular calcium.

pump removal of intracellular Na^+, results in increased Na^+-Ca^{2+} ion exchanger function and increased cytosolic calcium concentrations. ATP depletion results in dysfunction of energy-dependent ion pumps, such as Na^+,K^+-ATPase and Ca^{2+}-ATPase in the sarcolemma. Na^+,K^+-ATPase pump dysfunction leads to increased intracellular Na^+, causing a temporary increase in Na^+-Ca^{2+} exchanger function and resultant increase in intracellular Ca^{2+}. The Na^+-Ca^{2+} exchanger requires ATP, however, and continued activity of the Na^+-Ca^{2+} exchanger further deprives the cell of ATP, leading to increased Ca^{2+}-ATPase dysfunction and rising intracellular Ca^{2+} levels. The sarcoplasmic reticulum and the mitochondria are also equipped with these same energy-dependent transmembrane calcium transport mechanisms (Ca^{2+}-ATPase) as well as an ATP-dependent Ca^{2+} uniporter, further exacerbating the cell's inability to remove intracellular Ca^{2+} in the low-energy conditions put forth by rhabdomyolysis.

An abrupt increase in cytoplasmic Ca^{2+} leads to a corresponding increase in mitochondrial Ca^{2+} because the mitochondria serve as the Ca^{2+} safety net. In addition to triggering apoptotic cell death by upregulating expression of proapoptotic factors, this mitochondrial Ca^{2+} overload leads to dysfunction of oxidative phosphorylation through structural and functional alterations, disrupting ATP production and further worsening the ATP debt and intracellular homeostasis of Ca^{2+}.

Increased mitochondrial Ca^{2+} also leads to increased production of reactive oxygen species (ROS),[7] which are a broad group of chemical substances that include free oxygen radicals (O_2^-, $OH^\cdot$) and powerful oxidants (hydrogen peroxide, nitric oxide) that lead to free radical production. Free radicals carry extra, unpaired electrons (e^-) that have a strong tendency to pair off, causing oxidation by extraction of electrons from other chemical species. Under normal physiologic conditions, 2 to 5% of oxygen consumed by the mitochondria is transformed during electron transport to ROS that are neutralized by endogenous antioxidants such as glutathione. When the antioxidant capacity of the endogenous system is overwhelmed during times of intense, sustained physical activity or illness such that rhabdomyolysis results, a condition termed oxidative stress ensues. The resulting ROS-induced destruction of lipids and proteins injures the structure of membranes as well as DNA with mutations, leading to disruptions in cellular architecture and mitochondrial respiratory protein integrity. The cumulative effect exacerbates the inability to regulate intracellular Ca^{2+} homeostasis. Whereas ROS may have adaptive physiologic functions in exercising muscles, significant damage to muscle cells occurs when ROS are triggered by pathologic stimuli.

Damage of the sarcoplasmic reticulum and mitochondria during cell death results in the release of stored calcium ions into the cytoplasm. The decreased removal of Ca^{2+} into the extracellular fluid, along with inadequate intracellular storage and increased entry into the cytoplasm, leads to myocytic Ca^{2+} overload and initiation of the cascade of cellular death.

Calcium-induced activation of proteases, phospholipases, and other proteolytic enzymes degrades the protein structure of myofibrils, the cytoskeleton, and membrane composition, leading to further cellular damage. Increased Ca^{2+} leads to sustained contraction of the myofibrils, resulting in severe ATP depletion in the initial stages while leading to myofibrillar breakdown as rhabdomyolysis progresses. Breakdown of the myofibrillar network hastens the disintegration of the myocyte, whereas high Ca^{2+} concentrations within the mitochondria arrest cellular respiration and block ATP production. Diminished ATP production after Ca^{2+}-mediated activation of degradative cellular enzymes, with large metabolic energy requirements of their own, exacerbates the preexisting energy crisis within already ischemic cells.[8] This process releases free fatty acids and lysophosphates that cause direct toxic damage to the sarcolemma, intracellular organelles, and plasma membrane carrier proteins, effecting increased Ca^{2+} entry into the cytosol.

Microelectrode studies of intercostal myocytes show that intracellular calcium concentration rises to 1.27 µmol/L after induction of rhabdomyolysis by exhaustive physical exertion compared with 0.12 µmol/L in normal muscles.[9] That is nearly an 11-fold increase in intracellular calcium concentration. In this study, dantrolene, a known inhibitor of Ca^{2+} release from the sarcoplasmic reticulum, was administered and led to an 83% reduction of cytosolic Ca^{2+} and an improvement in the clinical symptoms of muscle stiffness, rigidity, and pain, highlighting the essential role of increased cytosolic Ca^{2+} in the pathophysiologic process of rhabdomyolysis.

The end result in rhabdomyolysis is muscle cell breakdown, with the release of toxic contents into the extracellular space and damage to adjacent capillaries, resulting in local edema, increased compartmental pressures, and regional ischemia, which further induces energy depletion and destroys more capillaries. Circulating leukocytes adhere to these damaged capillaries, become activated, and transmigrate to the site of myocyte injury, where they release ROS and proteolytic enzymes that further injure the cell.

In instances in which ischemia is the inciting event (e.g., crush syndrome, arterial thromboembolism) of rhabdomyolysis, myocyte destruction primarily takes place not during ischemia but rather during reperfusion[10] (Fig. 127-2).

Etiology

Rhabdomyolysis is classified into four basic pathophysiologic processes:

1. Impairment of the muscle's production or use of ATP at the cellular level. ATP concentrations within the cell fall; energy-dependent mechanisms falter, including, for instance, Na^+,K^+-ATPase pumps, leading to disruption of chemical gradients, sarcolemma and cell membrane compromise, and cell destruction.
2. Disruption in the delivery of oxygen, glucose, and other nutrients to skeletal muscle
3. Increases in metabolic demands beyond the ability of the organism to deliver oxygen and nutrients
4. Direct myocyte damage

Box 127-1 lists the various causes of rhabdomyolysis.

CLINICAL FEATURES

The clinical presentation of rhabdomyolysis is variable because of its many causes. Its course may be mild and subclinical, or it may be severe and life-threatening, depending on the extent of muscle damage and associated complications. It may be evident from the

www.ketabpezeshki.com 66485457-66963820

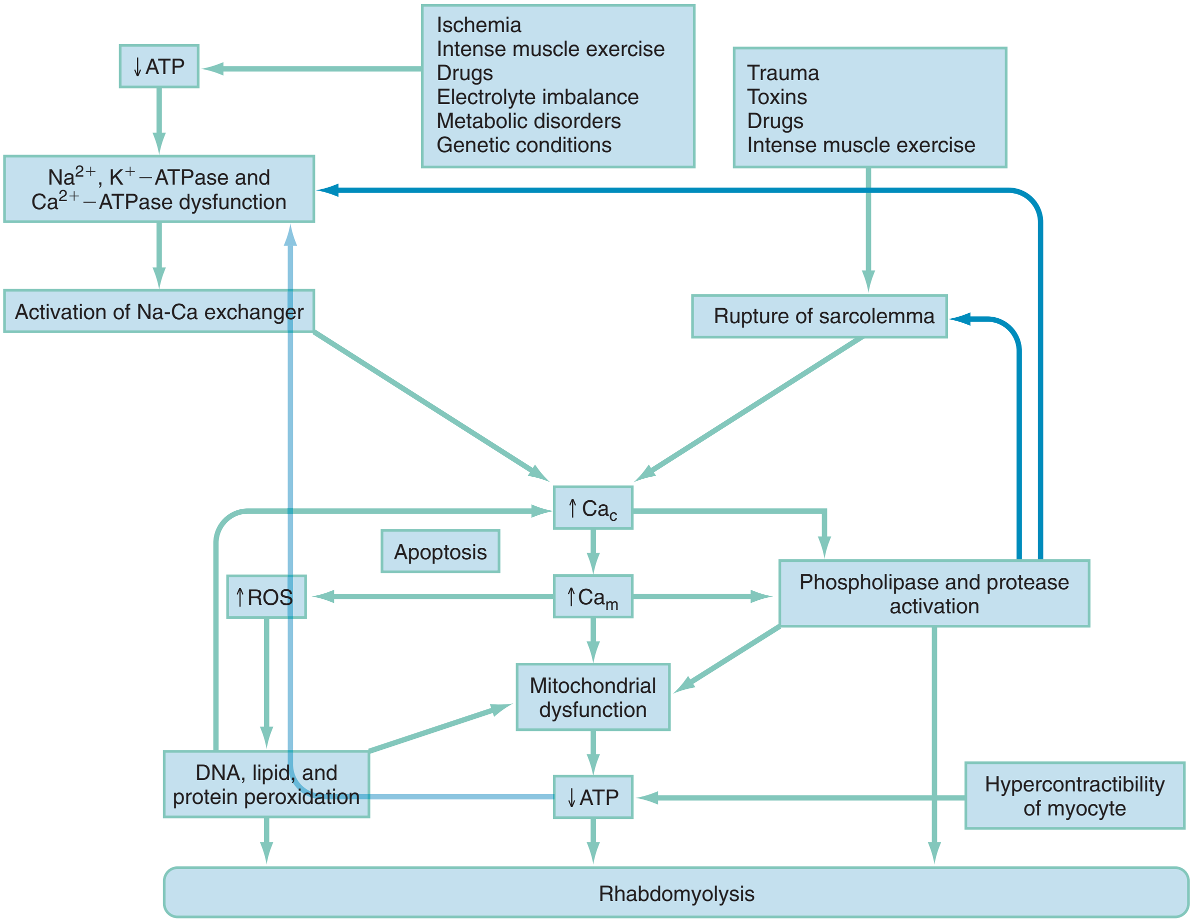


Figure 127-2. Pathophysiology of rhabdomyolysis.

Box 127-1 Differential Diagnosis of Rhabdomyolysis

Prolonged Immobilization

Prolonged immobilization can cause rhabdomyolysis by pressure on gravity-dependent body parts. This pressure-related phenomenon may be enhanced by the underlying cause of the immobilization (e.g., drugs or trauma).

Excessive Muscle Activity

ATP depletion from excessive muscle activity leads to a mismatch of cellular energy needs and ATP supply. This leads to malfunction of ATP-dependent cellular membrane ion pumps, net influx of ionized calcium, and subsequent rhabdomyolysis. Exertion-related cases of rhabdomyolysis have been reported in both sporadic and prolonged muscle activity of both high and low intensity.

Muscle Ischemia

ATP production is limited by interruption of blood perfusion to muscle tissue of any etiology, including arterial occlusion, carbon monoxide poisoning, and external compression. Muscle cell hypoxia leads to muscle damage in as little as 2 hours, with irreversible anatomic and functional changes within 4 hours and muscle necrosis in as little as 6 hours.[52]

Temperature Extremes

Extremes of temperature are known to cause rhabdomyolysis by sarcolemma disruption. The physiologic concept of *thermal maximum* describes the core temperature and duration at which human cells break down. A core body temperature of 42° C for more than 45 to 60 minutes leads to cellular damage. Heat stroke, neuroleptic malignant syndrome, and malignant hyperthermia are conditions known to lead to excess heat and muscle breakdown. Similarly, hypothermia causes sarcolemma membrane dysfunction below critical temperatures necessary for membrane protein structural integrity. Rhabdomyolysis has been attributed to therapeutic hypothermia in a post–cardiac arrest trauma victim.[53]

Electrical Current

Muscle sarcolemma is directly injured by electrical current–induced membrane permeability (electroporation) and thermal injury; high-voltage electrical injury, including lighting, poses the highest risk. Secondary injury by coagulation of blood in muscle capillary beds may lead to localized muscle ischemia. Rhabdomyolysis has also been seen after cardioversion for refractory ventricular tachycardia and fibrillation.[54]

Electrolyte Abnormalities

Hypokalemia by whatever mechanism can cause rhabdomyolysis. Extracellular potassium leads to localized microvascular vasodilation, and low concentrations can lead to focal muscle vasoconstriction and ischemia with subsequent muscle injury. Hypophosphatemia may result in rhabdomyolysis in that phosphate groups are needed for ATP-dependent cell functions.[55] Hyponatremia has been reported to cause rhabdomyolysis in endurance athletes[56] and in psychogenic polydipsia.[57] Hypernatremia may also have direct links to rhabdomyolysis in the absence of other known causative agents.[58]

Illicit Drugs

A number of illicit drugs, such as amphetamines, opiates, ecstasy, and LSD, can result in rhabdomyolysis by either direct or indirect effects, including immobilization with muscle tissue hypoperfusion and hypoxia, psychomotor agitation, direct myotoxicity, and

Continued

www.ketabpezeshki.com 66485457-66963820

Box 127-1 Differential Diagnosis of Rhabdomyolysis—cont'd

electrolyte abnormalities, particularly hypokalemia and hypophosphatemia.

Medications

Statin-induced rhabdomyolysis is well documented. Its precise mechanism is not fully known, but it is hypothesized to be due to membrane instability from inhibition of cholesterol synthesis by hydroxymethylglutaryl–coenzyme A reductase inhibition, impaired intracellular protein messaging from abnormally prenylated proteins, and abnormal mitochondrial respiration from coenzyme Q10 deficiency.[59] Similarly, fibric acid derivatives, which decrease hepatic triglyceride production, have been associated with rhabdomyolysis.[60,61] Many if not most other classes of prescription medications have been associated with rhabdomyolysis, including both the typical and atypical antipsychotics.

Infections

Rhabdomyolysis has been reported after infections with bacterial, viral, fungal, and parasitic agents. Sepsis-induced tissue hypoxia, direct bacterial myocyte invasion, decreased glycolytic and oxidative enzyme activity, lysosomal enzyme activation, and endotoxin-related injury have all been implicated as pathogenetic mechanisms involved in infectious causes of rhabdomyolysis.[62]

Legionella is the most common bacterial etiology of rhabdomyolysis.[63,64] It is unclear if rhabdomyolysis is caused by a common pathway of sepsis-related systemic inflammation or species-specific processes.

Metabolic Myopathies

Inherited disorders are manifested with enzyme deficiencies in carbohydrate and lipid metabolism[65] or myopathies.[66] These lead to defects in glycolysis, gluconeogenesis, fatty acid oxidation, and mitochondrial cellular respiration. These disorders are typically manifested during childhood and are recurrent.

Connective Tissue Disorders

Although rare, cases of rhabdomyolysis have been reported in conditions such as polymyositis, dermatomyositis, and Sjögren's syndrome.

Rheumatologic Disorders

Systemic lupus erythematosus, more commonly associated with mild myositis, has also been reported in a case of fulminant myositis with rhabdomyolysis.[67]

Endocrine Disorders

Hypothyroidism[68] has been reported to cause rhabdomyolysis.

Biologic Toxins

Snakebite,[69] Africanized bee,[70] and honey bee envenomations are known to release myotoxic agents causing rhabdomyolysis.

Other and Unknown

Case reports document the development of rhabdomyolysis after succinylcholine administration to patients with neuromuscular disorders[71] as well as in patients receiving cardiopulmonary resuscitation.[72]

---

patient's primary complaint or found incidentally on laboratory evaluation. The identification of rhabdomyolysis in the trauma patient is straightforward, whereas the nontraumatic causes may pose a diagnostic challenge.

Rhabdomyolysis should be suspected in patients who present with altered mentation and risk factors for the development of rhabdomyolysis (e.g., intoxication, immobility, drug ingestion, electric shock, neuroleptic malignant syndrome). The presence of acute renal failure without any other obvious attributable cause also prompts consideration of rhabdomyolysis.[11]

The classic presentation of rhabdomyolysis includes localizing myalgias, muscle stiffness, cramping, swelling, tenderness, and tea-colored urine. The most frequently involved muscle groups are the thighs, calves, and lower back.[12] Nonspecific constitutional symptoms include malaise, fever, nausea, and vomiting. Unfortunately, the majority of cases do not have characteristic physical signs; up to 50% of patients do not report myalgias or muscle weakness despite serologically proven rhabdomyolysis.[12]

History by first responders or witnesses can be helpful, especially when the patient has an altered mental status. In these cases, the physical examination and high clinical suspicion become increasingly important. Findings may include extremity swelling, tenderness, motor weakness and sensory deficits, pain with passive range of motion, and overlying skin changes, particularly in instances of limb ischemia. Muscle swelling may not become evident until after resuscitation and rehydration with intravenous fluids.

DIAGNOSTIC STRATEGIES

The definitive diagnosis of rhabdomyolysis is reliably made by serologic testing for creatine kinase (CK). This test can assist the clinician in assessing at-risk patients when historical and examination findings are lacking.

Serum Creatine Kinase

Elevated levels of CK are the hallmark of rhabdomyolysis. CK functions as an energy reservoir for ATP:

$$\text{Creatine kinase} + \text{ADP creatine} + \text{ATP}$$

CK has a half-life of 1.5 days; it is elevated in the first 12 hours, peaks during the first 3 days, and normalizes at around 5 days after injury. The degree of CK elevation correlates with the degree of muscle injury,[13] but it remains unclear if the degree of elevation corresponds to the risk for development of acute renal failure.[14] A CK level five times the upper limit of normal (~1000 U/L), without apparent cardiac or brain injury, confirms the diagnosis. Cases have been reported as high as several hundred thousand to even 3,000,000 U/L.[5]

Serum and Urine Myoglobin

Myoglobin is a dark red protein composed of globin and a molecule of heme. Its normal function is to supply oxygen to skeletal and cardiac muscle in times of need. The excretion of myoglobin occurs renally. It is initially filtered at the glomerulus and reabsorbed by endocytosis in the convoluted tubules, where it is broken into its component parts, globin and heme, by proteolytic enzymes. As with all other low-molecular-weight proteins, a small amount is excreted in the urine. The normal concentration of myoglobin in the urine is less than 10 µg/L.

During rhabdomyolysis, myoglobin released by damaged muscle is increasingly filtered at the glomerulus. This leads to an initial increased reabsorptive capacity by glomerular and tubular epithelial cells developed presumably as a protective response to increased filtered myoglobin. When serum myoglobin concentrations exceed 0.3 mg/L and the renal threshold of 1.0 mg/dL is met, this reabsorptive capacity is overwhelmed and excess myoglobin

www.ketabpezeshki.com 66485457-66963820

Table 127-1 Causes and Microscopic Features of Red and Brown Urine

CAUSE	RESULTS FOR BLOOD IN URINE*	SEDIMENT†	SUPERNATANT
Hematuria	+++	Red	Yellow
Myoglobinuria	+++	Normal	Red to brown
Hemoglobinuria	+++	Normal	Red to brown
Porphyria	–	Normal	Red
Bile pigments	–	Normal	Brown
Food and drugs‡	–	Normal	Red to brown

Modified from Bosch X, Poch E, Grau JM: Rhabdomyolysis and acute kidney injury. N Engl J Med 361:62-79, 2009.
*Urine tested with dipstick test.
†Normal refers to white or yellow color.
‡Food and drugs that can cause red urine include beets, blackberries, rhubarb, food coloring, fava beans, phenolphthalein, rifampin, doxorubicin, deferoxamine, chloroquine, ibuprofen, and methyldopa. Those that cause brown urine include levodopa, metronidazole, nitrofurantoin, iron sorbitol, chloroquine, and methyldopa.

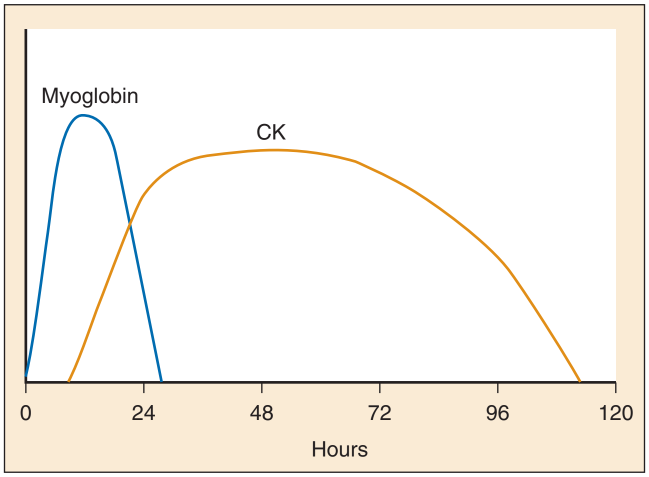


Figure 127-3. Variations of myoglobin and creatine kinase (CK) during the course of rhabdomyolysis. Myoglobin is the first enzyme that increases, but because of its rapid clearance from the plasma, it returns to normal levels within the first 24 hours after the onset of symptoms. CK increases a few hours later than myoglobin, reaches its peak value within the first 24 hours, and remains at these levels for 3 days. CK is considered to be a more useful marker for the diagnosis and assessment of the severity of muscle injury because of its delayed clearance from the plasma.

appears in the urine.[16,17] This is detected by urine dipstick as positive for blood (Table 127-1).

In the past, the diagnosis of rhabdomyolysis was made by serum myoglobin; however, myoglobin has a serum half-life of only 1 to 3 hours and is completely absent after 24 hours.[13] This short window makes serum myoglobin an unreliable diagnostic test. A normal concentration of serum myoglobin is less than 100 µg/L. This also applies to urine myoglobin levels, which depend on the degree of muscle injury, volume status of the patient, and urinary flow rate. A well-hydrated patient with normal renal function can rapidly clear plasma from the body. Although myoglobin is pathognomonic, the absence of plasma or urine myoglobin does not rule out rhabdomyolysis because it is detectable only early in the course of the disease (Fig. 127-3).

Urine Dipstick and Urinalysis

Myoglobinuria causes a positive result for blood in urine dipstick testing. The drawback of this test is its inability to distinguish between heme compounds. Microscopic analysis will, however, show few if any red blood cells, thereby distinguishing between hemoglobin and hemoglobin-rich red blood cells (from hemolysis or hematuria) and myoglobin. In combination with an elevated plasma CK level, myoglobinuria from rhabdomyolysis is confirmed. At plasma concentrations above 100 to 300 mg/L, macroscopic myoglobinuria will be manifested as tea-colored urine.

The urine dipstick test or urinalysis result is generally acidic in rhabdomyolysis, which plays a role in cast and uric acid crystal formation as well as pathologic myoglobin metabolism in tubular epithelial cells. Proteinuria may also be noted because of the detection of the globin component of myoglobin. Urine sediment analysis will show myoglobin casts and dead epithelial cells (see Table 127-1).

Other Laboratory Findings

Hyperkalemia, hyperphosphatemia, and early hypocalcemia followed by late hypercalcemia are common electrolyte disturbances in patients with rhabdomyolysis. Late hypercalcemia is postulated to be due to mobilization of calcium that was initially sequestered in damaged muscle.

Hyperuricemia from the release of muscle nucleic acids is especially common in patients with large muscle mass. Metabolic acidosis typically occurs from the generation of organic acids from damaged muscle, namely, lactate and uric acid. Hypoalbuminemia and anemia result from capillary damage and release into the extracellular space.

Both the blood urea nitrogen (BUN) and creatinine (Cr) concentrations increase but with a characteristic decrease in the BUN/Cr ratio. This is due to large amounts of creatinine released into the serum from damaged muscle. A normal BUN/Cr ratio is 10:1; in rhabdomyolysis, it can be 5:1 or even less.

In severe cases, coagulation disorders such as disseminated intravascular coagulation can ensue, triggered by the released thromboplastin from damaged tissue.

Prognostic Tests in Rhabdomyolysis

Several studies have attempted to predict the likelihood of acute renal failure by means of biochemical and clinical markers. Large variation in study design, small numbers of subjects, variable definitions of acute renal failure, and length of time between insult and measurement make it difficult for conclusions to be drawn.

The presence of myoglobin in urine has been studied as a prognostic factor for the development of acute renal failure in rhabdomyolysis. A systematic review of the literature reports that urine myoglobin is 100% sensitive in predicting acute renal failure, although not very specific, with an unacceptable number of false positives.[18] The authors concluded that urine myoglobin cannot be used to predict acute renal failure; however, acute renal failure is unlikely to develop if sequential, appropriately timed urine myoglobin analyses remain negative.

Whereas the serum CK level correlates well with degree of muscle injury, it does not correlate well with the risk of acute renal failure.[12,15] Multiple retrospective reviews demonstrated that the risk of acute renal failure is greater when the CK level approaches 15,000 U/L.[14,19,20] In one prospective study, no patients with a plasma CK level of less than 5000 U/L developed acute renal failure.[21] Although the plasma CK level is a poor predictor of acute renal failure, one can conclude that if the peak CK level remains below 5000 U/L, the risk of progression to acute renal failure is low.[14,19,20]

www.ketabpezeshki.com 66485457-66963820

COMPLICATIONS

Early Complications

Compartment Syndrome

Most skeletal muscles are encased in compartments formed by bones, fascia, and other structures. The massive influx of calcium and sodium in rhabdomyolysis leads to the accumulation of large amounts of extracellular fluid in the muscle cells, causing local edema and raised intracompartmental pressures, which further leads to increased muscle ischemia. Prolonged ischemia and infarction of muscle tissue can lead to replacement of muscle tissue with inelastic fibrous tissue, resulting in severe contractures (Volkmann's contracture). Intracompartmental pressures above 50 mm Hg or sustained pressures of more than 30 mm Hg during a maximum 6-hour period support the need for fasciotomy.

Electrolyte Disorders and Acidosis

Potassium release by damaged muscle leads to potentially lethal hyperkalemia, which is the most serious complication of rhabdomyolysis. Ninety-eight percent of potassium is found in the intracellular space; 60 to 70% of the total cellular mass of the human body consists of skeletal muscle. Therefore, necrosis of as little as 100 g of muscle mass could increase serum potassium by 1.0 mEq/L. Acidemia contributes to hyperkalemia and can be exacerbated by oliguria. The resulting fluid sequestration or myoglobin-induced kidney injury reduces the kidney's ability to excrete acid. Metabolic acidosis is also induced by the release of organic acids (e.g., lactic acid, uric acid, sulfur-containing proteins).

Disruption of muscle cells releases large amounts of phosphoric components into circulation, leading to hyperphosphatemia and ectopic calcification, typically depositing in necrotic tissue. Calcium phosphate crystal deposition in damaged muscle can lead to early-phase hypocalcemia with potentially fatal dysrhythmias. Hyperkalemia coupled with hypocalcemia predisposes to malignant dysrhythmias. Furthermore, excessively high phosphate levels shut down the enzyme 1α-hydroxylase of the kidneys through negative feedback, decreasing production of the active form of vitamin D, further reducing calcium absorption from the gut and contributing to early hypocalcemia. Late in the course of rhabdomyolysis, the calcium initially deposited in the cytoplasm of necrotic muscle cells can mobilize and reenter the plasma, resulting in late hypercalcemia.

Hypovolemia

There is a movement of fluid from intravascular compartments into the damaged muscle, causing profound intravascular volume depletion. This shift may exceed 15 L.

Hepatic Dysfunction

Large elevations in serum liver enzymes may occur after nontraumatic rhabdomyolysis. The etiology of this finding is not fully understood, but proteases released by muscle cells have been implicated. However, aspartate transaminase elevations may also be of skeletal muscle origin. These derangements are generally reversible.[22]

Late Complications

Myoglobin-Induced Acute Kidney Injury

Experimental evidence suggests that the mechanisms involved in the pathophysiologic process of myoglobinuric acute renal failure are myoglobin cast formation in the distal convoluted tubules, direct cytotoxic action of myoglobin on the epithelial cells of the proximal convoluted tubules, and intrarenal vasoconstriction and ischemia[17,23] (Fig. 127-4).

Myoglobin becomes concentrated along the renal tubules and precipitates in acidic urine along with uric acid to form obstructive casts. This process is enhanced by volume depletion and renal vasoconstriction, which reduces blood flow and glomerular filtration rate (GFR), promoting the accumulation of necrotic epithelial cells into tubular casts and further worsening GFR. Tubule obstruction occurs at the level of the distal tubule, whereas direct tubule cytotoxicity occurs mainly in the proximal tubules. There remains some controversy about the exact mechanism of renal dysfunction in rhabdomyolysis; some experts believe that casts and tubular obstruction are not the cause but rather the consequence of poor tubular clearance.[24]

When the concentration of myoglobin filtered at the glomerulus exceeds the normal level, tubular cells at the proximal convoluted tubule increase their reabsorption capacity to limit the excretion of myoglobin into the urine to protect the kidney from its nephrotoxic effects. At urine pH of 5.6 or lower, myoglobin, an iron-containing heme protein, dissociates into free iron (Fe), ferrihemate (Fe-heme complex), and globin inside the proximal tubular epithelial cell. Free hydroxyl radicals are produced when ferrous oxide in the Fe-heme complex is oxidized by molecular oxygen (O_2) and when free iron reacts with H_2O_2. Free iron may also act as a free radical, although its role in rhabdomyolysis-induced renal injury is unclear.[25-28] Myoglobin itself has been shown to exhibit peroxidase-like enzyme activity. Ferrihemate causes direct nephrotoxic effects along with the resultant increased oxidative stress within the tubular epithelial cell, leading to acute tubular necrosis through lipid, protein, and DNA peroxidation. More recent evidence argues against free iron's role in oxidative stress–induced renal injury and emphasizes the role of ferrihemate-induced lipid peroxidation in cell injury.[29-31]

Fluid shifts and renal dysfunction lead to activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system and production of vasoconstricting molecules such as endothelin 1 and vasopressin. There is also a decreased production of vasodilatory prostaglandins. Nitric oxide (NO), a potent vasodilatory agent, is known to be responsible for maintenance of renal blood flow; myoglobin released from damaged muscle may act as a scavenger of NO in the renal microcirculation, itself reduced by NO buffering against oxidant injury by ferrihemate. When NO is overcome by increased myoglobin concentrations, the kidney is deprived of the ability to autoregulate organ blood flow to maintain adequate perfusion in times of shock, and myoglobin is free to cause damage in proximal tubular epithelial cells (under appropriate acidotic conditions) as described before. Other locally stimulated vascular mediators, such as thromboxane A_2, tumor necrosis factor alpha, and F_2-isoprostanes (which themselves are byproducts of free radical lipid peroxidation), have also been implicated in the reduction of renal blood flow as a result of endothelial disruption and inflammation as well as oxidant injury.[24,32,33]

Disseminated Intravascular Coagulation

Prothrombotic substances, mainly thromboplastin, released from destroyed muscle cells activate the coagulation cascade and can lead to the formation of thrombi in the capillary tufts of the glomeruli.

MANAGEMENT

Management of rhabdomyolysis focuses on treatment of the cause, prevention of renal failure, and management of life- or limb-threatening complications.

www.ketabpezeshki.com 66485457-66963820

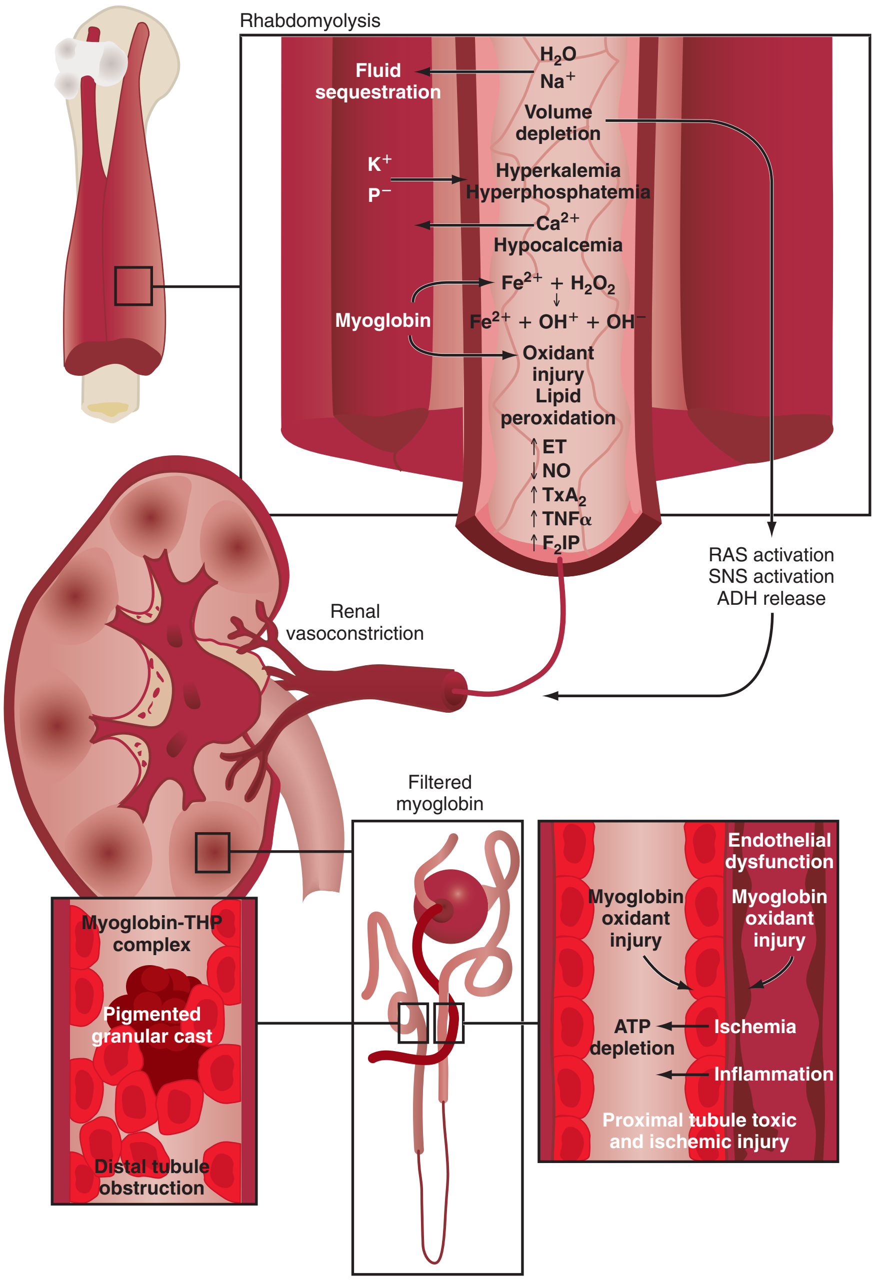


Figure 127-4. Pathophysiologic mechanisms in rhabdomyolysis-induced acute kidney injury. *ADH,* antidiuretic hormone; *ATP,* adenosine triphosphate; *ET,* endothelin; *F_2IP,* F_2-isoprostanes; *NO,* nitric oxide; *RAS,* renin-angiotensin system; *SNS,* sympathetic nervous system; *THP,* Tamm-Horsfall protein; *TNFα,* tumor necrosis factor alpha; *TxA_2,* thromboxane A_2. (Redrawn from Bosch X, Poch E, Grau JM: Rhabdomyolysis and acute kidney injury. N Engl J Med 361:62-72, 2009.)

Fluid Replacement and Urine Alkalinization

Aggressive volume expansion is critical for avoidance of myoglobin-induced acute renal failure. This acts by increasing renal blood flow and therefore glomerular filtration and urination. Patients with rhabdomyolysis typically present with severe dehydration due to fluid sequestration in the affected skeletal muscles. Several case series, mostly from victims of natural disasters (e.g., earthquakes with building collapse), show that some degree of intravascular volume contraction is essentially a prerequisite for the development of acute renal failure. These studies indicated that acute renal failure develops in patients who have a longer delay to supportive therapy; on the basis of these studies, early fluid resuscitation is recommended.[34,35] For victims of mass casualty events with prolonged extrication times, fluid resuscitation should begin before complete extrication.[35,36]

Whereas the need for early aggressive volume expansion is universally accepted, the fluid composition is more controversial, especially regarding the concept of urine alkalinization. The principles of urine alkalinization are derived empirically from animal data and include observations that (1) myoglobin precipitation is increased in acidic urine, (2) reduction-oxidation (redox) cycling of myoglobin and lipid peroxidation, and thus tubule injury, are inhibited by alkaline urine, and (3) myoglobin induces renal vasoconstriction only in an acidic medium.[17] Myoglobin-induced lipid peroxidation occurs at concentrations several orders of magnitude lower than that which leads to precipitation of casts in the distal tubules. The discovery that alkalinization inhibits redox cycling of myoglobin, and lipid peroxidation further lends

www.ketabpezeshki.com 66485457-66963820

credence to its therapeutic utility,[37] although the clinical benefits of alkalinization compared with simple saline volume repletion are not firmly established.

Gleaning of useful information from available comparative studies is difficult. They typically have small sample sizes, vary in the severity of rhabdomyolysis (determined by CK level), and are complicated by the administration of multiple therapeutic measures (e.g., bicarbonate plus mannitol), thereby making it difficult to interpret the impact of any one measure.[17,38-42]

Likewise, one study comparing lactated Ringer's solution and normal saline showed no difference in outcome, although both groups received sodium bicarbonate therapy.[38] One cannot draw a useful conclusion from this study regarding choice of fluids because acute renal failure is not typically present when peak CK levels do not reach 5000 U/L, and peak CK levels in both groups were below 5000 U/L.[39] However, more sodium bicarbonate was needed in the normal saline group than in the group receiving lactated Ringer's solution, probably because of the acidifying effect of normal saline.[38]

Although precise knowledge of potential benefits of alkaline therapy in rhabdomyolysis is not known, what *is* known is the impact of large volumes of normal saline on serum pH. Normal saline contains supraphysiologic concentrations of chloride ion. Massive infusion of normal saline leads to disproportionate increases in serum chloride concentrations, inducing an iatrogenic metabolic (hyperchloremic) acidosis,[43] thereby exacerbating myoglobin precipitation, tubular obstruction, and risk of hyperkalemia-related complications.

The administration of *both* normal saline and sodium bicarbonate, especially in patients with metabolic acidosis, is recommended.[17] If sodium bicarbonate therapy is used, monitor the urine and serum pH and the serum bicarbonate, potassium, and calcium levels. Alkalinize the urine to a pH above 6.5 and serum pH of 7.40 to 7.45. Discontinue the bicarbonate therapy and switch to normal saline if calcium levels become dangerously low (total corrected calcium concentration < 9 mg/dL or ionized calcium concentration < 4.5 mg/dL) or if no improvement in urine pH is noted after 4 to 6 hours. If a saline-only approach is used, monitor the serum chloride and pH levels and discontinue the saline if a hyperchloremic metabolic acidosis is induced iatrogenically. In this instance, a less acidifying solution (e.g., Isolyte or lactated Ringer's solution) can be used. The evidence for this approach is lacking, but it seems reasonable given current experimental and clinical knowledge.

A total of 10 to 20 L of fluid can be expected to be administered in the first 24 hours, depending on the severity of illness, but titration to a urinary output of 3 mL/kg/hr or approximately 200 mL/hr for a 70-kg adult is a reasonable target.[8]

Precise guidelines for the duration of fluid administration are lacking, but intravenous administration of fluids should be continued until plasma CK concentration decreases to less than 1000 U/L.[44]

Diuretics

Mannitol

The use of mannitol remains controversial. Because it is an osmotic diuretic, its theoretic benefit is its ability to increase urinary flow, thereby washing out nephrotoxic agents while at the same time drawing out fluid accumulated in damaged muscle into the intravascular space, improving hypovolemia. It is also a free radical scavenger, although at the concentrations used therapeutically, these antioxidant properties are likely to be irrelevant.[45] Most data on mannitol therapy come from animal studies, which demonstrate the bulk of its therapeutic effect to be attributable to its osmotic diuretic action.[46] In human studies, the addition of mannitol has not been shown to be more beneficial than fluid expansion alone,[40] and no randomized, controlled trials to date have shown any beneficial effect. Large accumulated doses of mannitol may in fact be detrimental by causing renal vasoconstriction and tubular toxicity, a condition known as osmotic nephrosis.[46,47] Mannitol therapy, however, may be beneficial to relieve compartment pressures and to stave off compartment syndrome.[12] If mannitol is used, frequently monitor the plasma osmolality and the osmolal gap; discontinue treatment if adequate diuresis is not achieved or if the osmolal gap rises above 55 mOsm/kg.[47]

Furosemide

Loop diuretics also increase urinary flow, but no study has shown a clear benefit in patients with rhabdomyolysis. Therefore, they are not recommended as prophylaxis against myoglobin-induced renal failure.

Acetazolamide

Carbonic anhydrase inhibitors for urine alkalinization have been used when bicarbonate therapy results in metabolic alkalosis with persistent acidic urine.[48] Acetazolamide has theoretic advantages as it induces bicarbonate diuresis with restorative effects on acid-base status from natriuresis. Case reports show potential benefit, but this has not been confirmed experimentally or clinically and cannot be recommended at this time.

Experimental Therapies

Antioxidants such as glutathione and vitamin E analogues have shown promise in experimental animal models of myoglobin-induced oxidant injury and may have a future role in management.[49]

Renal Replacement Therapy

As with non–rhabdomyolysis-related causes of renal failure, the indications for emergent dialysis or filtration remain uncorrectable metabolic acidosis, life-threatening hyperkalemia and other electrolyte disturbances despite medical management, manifestations of uremia, and anuria or oliguria despite aggressive volume expansion with complications related to fluid overload. Fluid overload is particularly a problem when it results in pulmonary edema or in patients with poor cardiac reserve. Conventional hemodialysis does not filter myoglobin effectively because of its large size. Renal replacement therapy is indicated, with intermittent hemodialysis, which can rapidly correct electrolyte abnormalities. Continuous venovenous hemofiltration or hemodiafiltration has shown promise for the removal of myoglobin in case reports, although outcome data are lacking.[50] The need for renal replacement therapy in the acute setting of rhabdomyolysis does not predict the need for long-term hemodialysis.[51]

DISPOSITION

The need for aggressive fluid resuscitation in rhabdomyolysis and close monitoring of renal function and electrolytes mandates hospital admission in most cases. The type of hospital bed is contingent on the etiology of rhabdomyolysis, presence of comorbidities, and severity of illness at presentation.

PROGNOSIS

Rhabdomyolysis, when it is recognized and treated early, carries an excellent prognosis.

www.ketabpezeshki.com 66485457-66963820

With the exception of hyperkalemia-related death or the rare complication of disseminated intravascular coagulation, acute kidney injury is the most serious complication of rhabdomyolysis, regardless of etiology. Of those patients who have acute renal failure, most will recover full renal function when treatment is instituted in a timely fashion. Mortality data for patients with renal failure vary widely in the literature according to the study population, etiology, presence of multiple causative agents, and comorbidities; however, long-term survival among patients with rhabdomyolysis and acute renal injury tends to be very good when timely management is provided.

KEY CONCEPTS

- Rhabdomyolysis is generally a benign syndrome with potentially fatal complications. Acute renal failure and hyperkalemia are accompanied by high mortality.
- Rhabdomyolysis should be suspected in at-risk patients (see Box 127-1) who present with muscle pain or altered mentation.
- The diagnosis of rhabdomyolysis is confirmed with an elevated serum CK level.
- Survivability hinges on prompt recognition and resuscitation with an aggressive fluid strategy, with or without urine alkalinization.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Heymsfield SB, Arteaga C, McManus C, Smith J, Moffitt S: Measurement of muscle mass in humans: Validity of the 24-hour urinary creatinine method. *Am J Clin Nutr* 1983; 37:478-494.
2. Curry SC, Chang D, Connor D: Drug- and toxin-induced rhabdomyolysis. *Ann Emerg Med* 1989; 18:1068-1084.
3. Guerini D, Coletto L, Carafoli E: Exporting calcium from cells. *Cell Calcium* 2005; 38:281-289.
4. Carafoli E: Intracellular calcium homeostasis. *Annu Rev Biochem* 1987; 56:395-433.
5. Giannoglou GD, Chatzizisis YS, Misirli G: The syndrome of rhabdomyolysis: Pathophysiology and diagnosis. *Eur J Intern Med* 2007; 18:90-100.
6. Green HJ: Cation pumps in skeletal muscle: Potential role in muscle fatigue. *Acta Physiol Scand* 1998; 162:201-213.
7. Brookes PS, Yoon Y, Robotham JL, Anders MW, Sheu SS: Calcium, ATP, and ROS: A mitochondrial love-hate triangle. *Am J Physiol Cell Physiol* 2004; 287:C817-C833.
8. Slater MS, Mullins RJ: Rhabdomyolysis and myoglobinuric renal failure in trauma and surgical patients: A review. *J Am Coll Surg* 1998; 186:693-716.
9. Lopez JR, Rojas B, Gonzalez MA, Terzic A: Myoplasmic Ca^{2+} concentration during exertional rhabdomyolysis. *Lancet* 1995; 345:424-425.
10. Turrens JF, Beconi M, Barilla J, Chavez UB, McCord JM: Mitochondrial generation of oxygen radicals during reoxygenation of ischemic tissues. *Free Radic Res Commun* 1991; 12-13(Pt 2):681-689.
11. Reha WC, Mangano FA, Zeman RK, Pahira JJ: Rhabdomyolysis: Need for high index of suspicion. *Urology* 1989; 34:292-296.
12. Gabow PA, Kaehny WD, Kelleher SP: The spectrum of rhabdomyolysis. *Medicine (Baltimore)* 1982; 61:141-152.
13. Oda J, et al: Analysis of 372 patients with crush syndrome caused by the Hanshin-Awaji earthquake. *J Trauma* 1997; 42:470-475; discussion 475-476.
14. Ward MM: Factors predictive of acute renal failure in rhabdomyolysis. *Arch Intern Med* 1988; 148:1553-1557.
15. Beetham R: Biochemical investigation of suspected rhabdomyolysis. *Ann Clin Biochem* 2000; 37(Pt 5):581-587.
16. Knochel JP: Rhabdomyolysis and myoglobinuria. *Annu Rev Med* 1982; 33:435-443.
17. Bosch X, Poch E, Grau JM: Rhabdomyolysis and acute kidney injury. *N Engl J Med* 2009; 361:62-72.
18. Rodriguez-Capote K, et al: Utility of urine myoglobin for the prediction of acute renal failure in patients with suspected rhabdomyolysis: A systematic review. *Clin Chem* 2009; 55:2190-2197.
19. Mallinson WJ, Green MF: Covert muscle injury in aged patients admitted to hospital following falls. *Age Ageing* 1985; 14:174-178.
20. Veenstra J, Smit WM, Krediet RT, Arisz L: Relationship between elevated creatine phosphokinase and the clinical spectrum of rhabdomyolysis. *Nephrol Dial Transplant* 1994; 9:637-641.
21. Ratcliffe PJ, Ledingham JG, Berman P, Wilcock GK, Keenan J: Rhabdomyolysis in elderly people after collapse. *Br Med J (Clin Res Ed)* 1984; 288:1877-1878.
22. Akmal M, Massry SG: Reversible hepatic dysfunction associated with rhabdomyolysis. *Am J Nephrol* 1990; 10:49-52.
23. Zager RA, Gamelin LM: Pathogenetic mechanisms in experimental hemoglobinuric acute renal failure. *Am J Physiol* 1989; 256:F446-F455.
24. Holt SG, Moore KP: Pathogenesis and treatment of renal dysfunction in rhabdomyolysis. *Intensive Care Med* 2001; 27:803-811.
25. Braun SR, Weiss FR, Keller AI, Ciccone JR, Preuss HG: Evaluation of the renal toxicity of heme proteins and their derivatives: A role in the genesis of acute tubule necrosis. *J Exp Med* 1970; 131:443-460.
26. Paller MS: Hemoglobin- and myoglobin-induced acute renal failure in rats: Role of iron in nephrotoxicity. *Am J Physiol* 1988; 255:F539-F544.
27. Nath KA, Norby SM: Reactive oxygen species and acute renal failure. *Am J Med* 2000; 109:665-678.
28. Halliwell B, Gutteridge JM: Role of free radicals and catalytic metal ions in human disease: An overview. *Methods Enzymol* 1990; 186:1-85.
29. Cooper CE, Green ES, Rice-Evans CA, Davies MJ, Wrigglesworth JM: A hydrogen-donating monohydroxamate scavenges ferryl myoglobin radicals. *Free Radic Res* 1994; 20:219-227.
30. Holt S, Moore K: Pathogenesis of renal failure in rhabdomyolysis: The role of myoglobin. *Exp Nephrol* 2000; 8:72-76.
31. Nath KA, et al: Induction of heme oxygenase is a rapid, protective response in rhabdomyolysis in the rat. *J Clin Invest* 1992; 90:267-270.
32. Holt S, et al: Increased lipid peroxidation in patients with rhabdomyolysis. *Lancet* 1999; 353:1241.
33. Bonventre JV, Weinberg JM: Recent advances in the pathophysiology of ischemic acute renal failure. *J Am Soc Nephrol* 2003; 14:2199-2210.
34. Better OS, Stein JH: Early management of shock and prophylaxis of acute renal failure in traumatic rhabdomyolysis. *N Engl J Med* 1990; 322:825-829.
35. Ron D, et al: Prevention of acute renal failure in traumatic rhabdomyolysis. *Arch Intern Med* 1984; 144:277-280.
36. Better OS: The crush syndrome revisited (1940-1990). *Nephron* 1990; 55:97-103.
37. Moore KP, et al: A causative role for redox cycling of myoglobin and its inhibition by alkalinization in the pathogenesis and treatment of rhabdomyolysis-induced renal failure. *J Biol Chem* 1998; 273:31731-31737.
38. Cho YS, Lim H, Kim SH: Comparison of lactated Ringer's solution and 0.9% saline in the treatment of rhabdomyolysis induced by doxylamine intoxication. *Emerg Med J* 2007; 24:276-280.
39. Brown CV, et al: Preventing renal failure in patients with rhabdomyolysis: Do bicarbonate and mannitol make a difference? *J Trauma* 2004; 56:1191-1196.
40. Homsi E, Barreiro MF, Orlando JM, Higa EM: Prophylaxis of acute renal failure in patients with rhabdomyolysis. *Ren Fail* 1997; 19:283-288.
41. Gunal AI, et al: Early and vigorous fluid resuscitation prevents acute renal failure in the crush victims of catastrophic earthquakes. *J Am Soc Nephrol* 2004; 15:1862-1867.
42. Shimazu T, et al: Fluid resuscitation and systemic complications in crush syndrome: 14 Hanshin-Awaji earthquake patients. *J Trauma* 1997; 42:641-646.
43. Morgan TJ: The meaning of acid-base abnormalities in the intensive care unit: part III—effects of fluid administration. *Crit Care* 2005; 9:204-211.
44. Lane R, Phillips M: Rhabdomyolysis. *BMJ* 2003; 327:115-116.
45. Zager RA: Combined mannitol and deferoxamine therapy for myohemoglobinuric renal injury and oxidant tubular stress. Mechanistic and therapeutic implications. *J Clin Invest* 1992; 90:711-719.
46. Better OS, Rubinstein I, Winaver JM, Knochel JP: Mannitol therapy revisited (1940-1997). *Kidney Int* 1997; 52:886-894.
47. Visweswaran P, Massin EK, Dubose TD Jr: Mannitol-induced acute renal failure. *J Am Soc Nephrol* 1997; 8:1028-1033.
48. Davidov T, Hong JJ, Malcynski JT: Novel use of acetazolamide in the treatment of rhabdomyolysis-induced myoglobinuric renal failure. *J Trauma* 2006; 61:213-215.
49. Abul-Ezz SR, Walker PD, Shah SV: Role of glutathione in an animal model of myoglobinuric acute renal failure. *Proc Natl Acad Sci U S A* 1991; 88:9833-9837.
50. Ronco C: Extracorporeal therapies in acute rhabdomyolysis and myoglobin clearance. *Crit Care* 2005; 9:141-142.
51. de Meijer AR, Fikkers BG, de Keijzer MH, van Engelen BG, Drenth JP: Serum creatine kinase as predictor of clinical course in rhabdomyolysis: A 5-year intensive care survey. *Intensive Care Med* 2003; 29:1121-1125.
52. Tountas CP, Bergman RA: Tourniquet ischemia: Ultrastructural and histochemical observations of ischemic human muscle and of monkey muscle and nerve. *J Hand Surg Am* 1977; 2:31-37.
53. Ciapetti M, di Valvasone S, Spina R, Peris A: Rhabdomyolysis following therapeutic hypothermia after traumatic cardiac arrest. *Resuscitation* 2011; 82:493.
54. Cavusoglu Y, et al: Reversible myoglobinuric renal failure following rhabdomyolysis as a rare complication of cardioversion. *Pacing Clin Electrophysiol* 2003; 26:645-646.
55. Knochel JP: Hypophosphatemia and rhabdomyolysis. *Am J Med* 1992; 92:455-457.
56. Bruso JR, et al: Rhabdomyolysis and hyponatremia: A cluster of five cases at the 161-km 2009 Western States Endurance Run. *Wilderness Environ Med* 2010; 21:303-308.
57. Korzets A, et al: Case report: Severe hyponatremia after water intoxication: A potential cause of rhabdomyolysis. *Am J Med Sci* 1996; 312:92-94.
58. Denman JP: Hypernatraemia and rhabdomyolysis. *Med J Aust* 2007; 187:527-528.
59. Khan FY, Ibrahim W: Rosuvastatin induced rhabdomyolysis in a low risk patient: A case report and review of the literature. *Curr Clin Pharmacol* 2009; 4:1-3.
60. Terrovitou CT, Milionis HJ, Elisaf MS: Acute rhabdomyolysis after bezafibrate re-exposure. *Nephron* 1998; 78:336-337.
61. Smals AG, Beex LV, Kloppenborg PW: Clofibrate-induced muscle damage with myoglobinuria and cardiomyopathy. *N Engl J Med* 1977; 296:942.
62. Friman G, Ilback NG, Beisel WR: Effects of *Streptococcus pneumoniae, Salmonella typhimurium* and *Francisella tularensis* infections on

www.ketabpezeshki.com 66485457-66963820

oxidative, glycolytic and lysosomal enzyme activity in red and white skeletal muscle in the rat. *Scand J Infect Dis* 1984; 16:111-119.
63. McConkey J, Obeius M, Valentini J, Beeson MS: *Legionella* pneumonia presenting with rhabdomyolysis and acute renal failure: A case report. *J Emerg Med* 2006; 30:389-392.
64. Erdogan H, Yilmaz A, Kal O, Erdogan A, Arslan H: Rhabdomyolysis-induced acute renal failure associated with legionnaires' disease. *Scand J Urol Nephrol* 2006; 40:345-346.
65. Lofberg M, Jankala H, Paetau A, Harkonen M, Somer H: Metabolic causes of recurrent rhabdomyolysis. *Acta Neurol Scand* 1998; 98:268-275.
66. Brumback RA, Feeback DL, Leech RW: Rhabdomyolysis in childhood. A primer on normal muscle function and selected metabolic myopathies characterized by disordered energy production. *Pediatr Clin North Am* 1992; 39:821-858.
67. Schubert J, Manschwetus H, Walter GF, Zeidler H, Schmidt RE: Systemic lupus erythematosus (SLE) with panniculitis and rhabdomyolysis [in German]. *Immun Infekt* 1991; 19:58-59.
68. Kisakol G, Tunc R, Kaya A: Rhabdomyolysis in a patient with hypothyroidism. *Endocr J* 2003; 50:221-223.
69. Bush SP, Jansen PW: Severe rattlesnake envenomation with anaphylaxis and rhabdomyolysis. *Ann Emerg Med* 1995; 25:845-848.
70. Bresolin NL, Carvalho LC, Goes EC, Fernandes R, Barotto AM: Acute renal failure following massive attack by Africanized bee stings. *Pediatr Nephrol* 2002; 17:625-627.
71. Tritakarn T, Teeratchanan T: Acute rhabdomyolysis and cardiac arrest following succinylcholine in a patient with Parry-Romberg syndrome. *Anaesth Intensive Care* 2011; 39:135-136.
72. Minor RL Jr, Chandran PK, Williams CL: Rhabdomyolysis and myoglobinuric renal failure following cardioversion and CPR for acute MI. *Chest* 1990; 97:485-486.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 128

Thyroid and Adrenal Disorders

Adhi N. Sharma and David L. Levy

Thyroid dysfunction (hyperthyroidism and hypothyroidism) arguably represents the most common form of endocrine disorder. Together with adrenal insufficiency, these disease states are often manifested with protean symptoms, such as fatigue and weakness, making them a diagnostic challenge. In their advanced states, classic manifestations develop, rendering each disorder more recognizable. Each disorder is also capable of producing life-threatening symptoms when it is untreated or precipitated by other stressors. For patient outcomes to be improved, prompt recognition and therapeutic intervention are critical.

HYPERTHYROIDISM

Perspective

Background and Epidemiology

Hyperthyroidism is a condition caused by overproduction and increased circulation of thyroid hormone. The disorder runs the spectrum from subclinical hyperthyroidism to thyrotoxicosis, a life-threatening event. Thyrotoxicosis is a hypermetabolic condition that results from elevated levels of thyroid hormones (T_4 and T_3). This can occur from hormone overproduction (Graves' disease, toxic multinodular goiter), increased thyroid hormone release from an injured gland (thyroiditis, trauma), or exogenous thyroid hormone (thyrotoxicosis factitia). For the purposes of this discussion, the terms *hyperthyroidism* and *thyrotoxicosis* are used interchangeably.

Recent work has estimated the incidence of thyrotoxicosis at 80/100,000 per year in women and 8/100,000 per year in men.[1] A population-based study in the United Kingdom demonstrated an incidence of 0.9/100,000 in children younger than 15 years. Most cases of thyrotoxicosis (>80%) are due to autoimmune disease.[2] The prevalence of hyperthyroidism is five to ten times less than that of hypothyroidism.

The myriad causes of thyrotoxicosis are listed in Box 128-1. Graves' disease (diffuse toxic goiter) accounts for approximately 80% of all cases. Toxic multinodular goiter occurs most frequently in areas of iodine deficiency. It accounts for approximately 15% of thyrotoxicosis cases. In the United States, the incidence of toxic multinodular goiter is much lower than the global rate. Toxic adenoma is the third major cause of hyperthyroidism, accounting for approximately 3 to 5% of cases. Other less common causes of hyperthyroidism include thyroiditis (traumatic, infectious, or from radiation), ectopic thyroid tissue (lingual thyroid), tumors (pituitary, thyroid), drug induced (lithium, amiodarone), and exogenous thyroid hormone (from therapy or surreptitious consumption of thyroid hormone).[3,4]

Principles of Disease

Anatomy and Physiology

The normal adult thyroid gland is a highly vascular organ overlying the anterior trachea. Its structure is bilobar with a median isthmus and total weight ranging from 10 to 30 g (Fig. 128-1). It receives its blood supply at a rate of 80 to 120 mL/min from the inferior and superior thyroid arteries, which are direct branches of the subclavian and external carotid arteries, respectively. The thyroid's function is to secrete two iodinated hormones: triiodothyronine (T_3) and thyroxine (T_4). Only about 20% of circulating T_3 is directly secreted by the thyroid; the remainder is produced by peripheral conversion of T_4 to the more biologically active T_3. This process occurs predominantly in the liver and in skeletal muscle. The thyroid is the only endocrine gland that stores large quantities of hormone, with enough for about 100 days' supply.

Regulation of hormone production is through a negative feedback loop involving the hypothalamic-pituitary-thyroid axis (Fig. 128-2). As the serum levels of T_4 and T_3 fall, the hypothalamus releases the tripeptide thyrotropin-releasing hormone (TRH), which in turn stimulates the anterior pituitary gland's release of the polypeptide thyroid-stimulating hormone (TSH) from its thyrotroph cells. TSH then binds to epithelial cells on the thyroid gland, stimulating follicular cells to synthesize and secrete the thyroid hormones T_4 and T_3. TRH release may also result from exercise, stress, malnutrition, hypoglycemia, and sleep. The function of thyroid hormone is to influence the metabolism of cells by increasing their basal metabolic rate. It has a role in protein synthesis and function together with other hormones necessary for normal growth and development, such as human growth hormone and insulin.

Pathophysiology

T_4 is a prohormone with only mild intrinsic activity, whereas T_3 is the biologically active hormone. Typically, T_4 deiodination occurs at the outer ring of T_4, forming T_3. However, during systemic illness, deiodination occurs at an inner ring of T_4, resulting in reverse T_3, which is biologically inactive. More than 99.5% of thyroid hormones are protein bound in the serum to thyroxine-binding globulin (TBG) and other proteins, rendering them metabolically inactive. As a result, only free T_4 and free T_3 are clinically relevant.

Whereas iodide is a necessary substrate for thyroid hormone production, excess iodide can have two different effects. In the Wolff-Chaikoff effect, excess iodine inhibits iodide trapping, thyroglobulin iodination, and release of thyroid hormone from the

www.ketabpezeshki.com 66485457-66963820

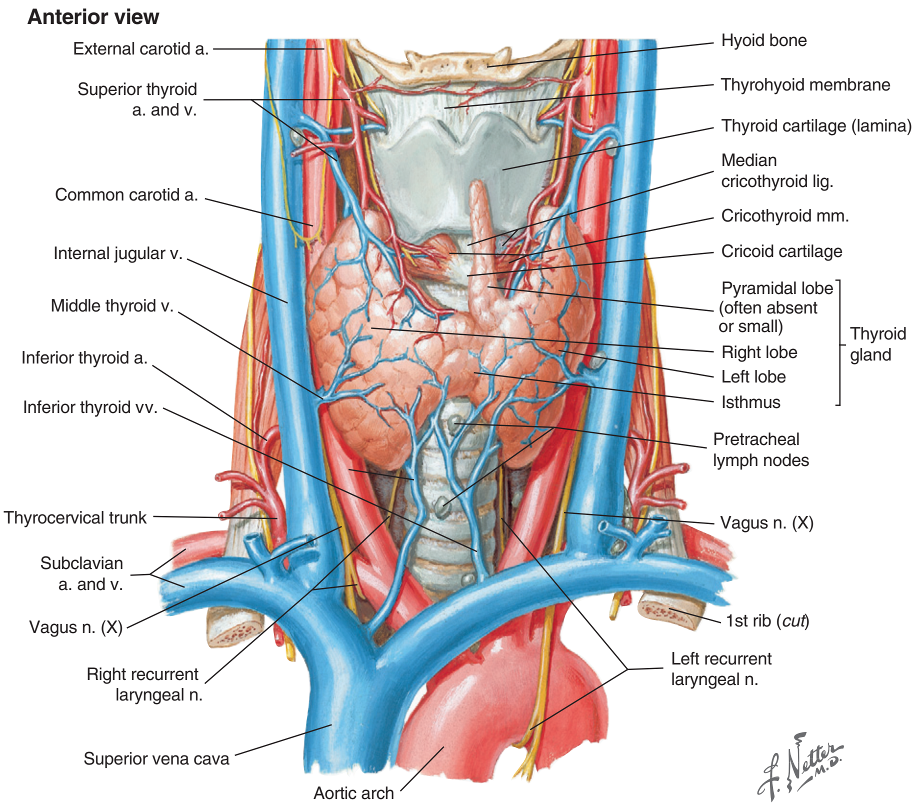


Figure 128-1. Anatomy of the thyroid gland and related structures. (Netter illustration from www.netterimages.com. Copyright Elsevier Inc. All rights reserved.)

Box 128-1 Causes of Thyrotoxicosis

Graves' disease (toxic diffuse goiter)
Toxic multinodular goiter
Toxic adenoma (single hot nodule)
Factitious thyrotoxicosis
Thyrotoxicosis associated with thyroiditis
- Hashimoto's thyroiditis
- Subacute (de Quervain's) thyroiditis
- Postpartum thyroiditis
- Sporadic thyroiditis
- Amiodarone thyroiditis

Iodine-induced hyperthyroidism (areas of iodine deficiency)
- Amiodarone
- Radiocontrast media

Metastatic follicular thyroid carcinoma
hCG-mediated thyrotoxicosis
- Hydatidiform mole
- Metastatic choriocarcinoma
- Hyperemesis gravidarum

TSH-producing pituitary tumors
Struma ovarii

hCG, human chorionic gonadotropin; *TSH,* thyroid-stimulating hormone.

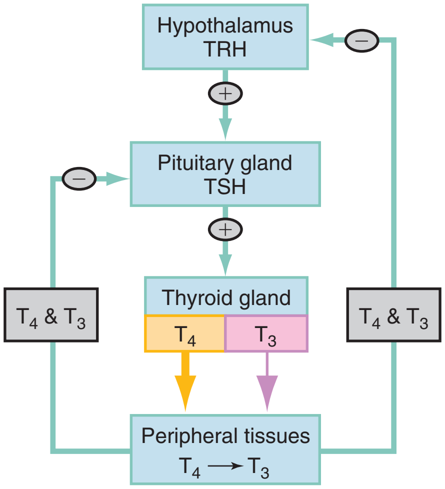


Figure 128-2. Negative feedback loop of thyroid hormone regulation: hypothalamic-pituitary-thyroid axis. Thyroid hormone production is regulated by the hypothalamus and pituitary gland. Hypothalamic thyrotropin-releasing hormone (TRH) stimulates pituitary thyrotropin (TSH) synthesis and secretion. In turn, TSH stimulates production and release of T_4 and T_3 from the thyroid gland. Once released, T_4 and T_3 exert a negative feedback mechanism on the production of TRH and TSH. T_4 is converted to T_3 in the peripheral tissues.

gland. This inhibition is transient, typically lasting only a matter of days. Paradoxically, an iodide load can induce hyperthyroidism (Jod-Basedow effect) in some patients with multinodular goiter and occult Graves' disease.

Thyroid hormone affects the metabolism of all tissues through varied mechanisms. It regulates gene activity by interaction at nuclear receptors and has direct effects on metabolism by interaction with cellular enzymes, like adenosine triphosphatase. Of note, T_3 and T_4 increase the expression and sensitivity of beta-adrenergic receptors, dramatically increasing response to endogenous catecholamines.

Graves' Disease. In the United States, Graves' disease is the most common form of hyperthyroidism. In this autoimmune disorder, autoantibodies are formed to the TSH receptor, where they bind

www.ketabpezeshki.com 66485457-66963820

and stimulate the receptors. The overstimulated gland enlarges and increases thyroid hormone production and release. The triad of goiter, exophthalmos, and pretibial myxedema is diagnostic of Graves' disease. The disease predominantly affects women and those with a family history of hyperthyroidism; it typically occurs between the ages of 20 and 40 years.

Toxic Multinodular Goiter. Toxic multinodular goiter is the second leading cause of hyperthyroidism in the United States. It is characterized by multiple autonomously functioning nodules developing in women older than 50 years. It is rare in youth, except in those with preexisting nontoxic multinodular goiters or living in iodine-deficient regions, such as Central America, South America, the Himalayas, eastern Europe, and central Africa. The hyperthyroidism in toxic multinodular goiter is milder than Graves' disease and is gradual in onset, but acute presentations can occur when iodine replacement is given to an iodine-deficient individual. Graves' disease typically is manifested in the sixth decade of life; cardiovascular manifestations like atrial fibrillation and heart failure predominate, whereas tremors and hypermetabolic features are less pronounced.[5] Muscle wasting and weakness are common, and the patient is often described as apathetic. Obstruction of the airway is a concern as multinodular goiters often extend retrosternally.

Toxic Adenoma. A toxic adenoma is commonly referred to as a hot nodule. This single hyperfunctioning nodule typically affects the same population as toxic multinodular goiter does, but it occurs less commonly.

Thyroiditis. Any inflammatory process that results in thyroid gland inflammation can lead to thyroiditis. The inciting process may be autoimmune, drug induced, infectious, or traumatic. Inflammation leads to follicular cell breakdown, with resultant release of preformed thyroid hormone, causing acute thyrotoxicosis. The most common form of thyroiditis in the United States is *Hashimoto's thyroiditis*, an autoimmune disorder characterized by the presence of thyroid antibodies and lymphocytic infiltration of the thyroid gland. Typically, patients present with a painless goiter and hypothyroidism, but some have transient thyrotoxicosis (hashitoxicosis) that may last for a few months.

Postpartum and Sporadic Thyroiditis. Other autoimmune disorders of the thyroid include postpartum thyroiditis and sporadic thyroiditis. Referred to as painless, or silent, thyroiditis, they are typified by a small nontender goiter and mild symptoms. It is estimated that 5 to 10% of women have postpartum thyroiditis. The diagnostic triad consists of the lack of previous history of thyroid disorder, an abnormal TSH concentration during the first postpartum year, and the absence of TSH receptor antibodies (Graves') or a toxic nodule. Classically, these patients present with thyrotoxicosis 6 weeks to 6 months postpartum, followed by a hypothyroid state lasting up to 6 months; a euthyroid state returns by the end of the first postpartum year. However, the majority of patients present with either hyperthyroidism alone or lone hypothyroidism.[6] The recurrence rate in subsequent pregnancy is estimated at 69%, and some women have permanent hypothyroidism. Sporadic thyroiditis is indistinguishable from postpartum thyroiditis except that it is unrelated to pregnancy. It may account for up to 1% of thyrotoxicosis, and most patients recover; 20% have hypothyroidism.[7]

Subacute Thyroiditis. Subacute thyroiditis (de Quervain's thyroiditis) is thought to be caused by a viral infection of the thyroid, often appearing after an upper respiratory infection. However, a study was unable to detect viral titers in 852 patients with subacute thyroiditis.[8] It is manifested with a typical viral syndrome prodrome (fatigue, myalgias, and pharyngitis), followed by fever and severe anterior neck pain. Pain may radiate to the jaw, ears, or occipital area. The thyroid is exquisitely tender, and pain can occur with head movement or swallowing. During the acute painful phase, a minority of patients have symptoms of hyperthyroidism (diaphoresis, palpitations, and tremor) lasting several weeks. Subacute thyroiditis may account for 2% of thyrotoxic patients; it occurs in the fourth and fifth decades of life and is more common in women than in men.

Suppurative Thyroiditis. Suppurative thyroiditis is a rare but potentially life-threatening infection of the thyroid. Patients present with fever and anterior neck pain, neck swelling, induration, and erythema as well as dysphonia and dysphagia. Infectious causes are overwhelmingly bacterial (aerobic and anaerobic) and very rarely parasitic, mycobacterial, or fungal.[9] Most patients have preexisting thyroid disease and are immunocompromised (AIDS).

Drug-Induced Thyroiditis. Amiodarone contains a high amount of iodine (37%, about 400 times the daily requirement) and as a result has a significant effect on thyroid function. It is estimated that between 5 and 20% of patients treated with amiodarone have thyrotoxicosis (higher in areas of iodine deficiency). Two proposed mechanisms have been described: an iodine-induced hyperthyroidism and a drug-induced destructive thyroiditis.[10] It is thought that the iodine load may unmask hyperthyroidism in patients with multinodular goiter and subclinical Graves' disease. More commonly, the cytotoxic effects of amiodarone destroy thyroid cells, resulting in a release of preformed hormone. An exacerbation of the tachyarrhythmia for which the patient is being treated or heart failure is the typical presentation of a patient with thyrotoxicosis related to amiodarone. Other drugs that may induce thyroiditis include interferon, interleukin-2, granulocyte-macrophage colony-stimulating factor, and lithium. Mechanisms vary, but lithium reportedly induces sporadic thyroiditis by direct toxic effects.

Factitious Thyroiditis. Thyrotoxicosis factitia results from ingestion of thyroid hormone. Although this can be iatrogenic or the result of patient medication error, the majority of cases stem from medical personnel with psychiatric illness who surreptitiously self-administer the medication. Cases of factitious thyrotoxicosis have been reported worldwide as a result of the consumption of bovine thyroid hormone in contaminated beef and from adulterated weight loss products.[11] By contrast, inadvertent acute ingestions of thyroid hormone usually manifest only minor toxicity. Whereas the dose plays a role, the 7-day half-life of T_4 allows physiologic compensation, such as the suppression of T_4 to T_3 conversion, inhibition of endogenous hormone production by negative feedback loops, and downregulation of thyroid hormone receptors.

Clinical Features

Symptoms

The variable presentation of thyrotoxicosis among patients creates a diagnostic challenge (Box 128-2). Hyperthyroidism induces a hypermetabolic state and increases beta-adrenergic activity. The resulting clinical manifestations range from vague constitutional symptoms to more organ-specific symptoms. Thyroid storm, the most severe manifestation of the disease, is a life-threatening state that requires prompt intervention. Variables that affect the severity of disease include age, disease duration, hormone levels and rate of rise, drug interactions, and stress of concurrent illness. Hyperthyroidism in elders often is manifested in subtle ways, mimicking symptoms of aging or masquerading as diseases of the cardiovascular, gastrointestinal, or nervous system.[12] Gradual or long-standing thyrotoxicosis can go unnoticed by the patient, or symptoms may be attributed to other causes like emotional stress, dieting, or physical deconditioning. The clinical manifestations do not necessarily correlate with the degree of biochemical abnormality.

Constitutional and hypermetabolic symptoms are common in thyrotoxicosis. These symptoms include fatigue, generalized

www.ketabpezeshki.com 66485457-66963820

Box 128-2 Symptoms in Thyrotoxicosis

Constitutional: Weight loss despite hyperphagia, fatigue, generalized weakness
Hypermetabolic: Heat intolerance, cold preference, excessive perspiration
Cardiorespiratory: Heart pounding and racing, dyspnea on exertion, chest pains
Psychiatric: Anxiety, restlessness, hyperkinesis, emotional lability, confusion
Muscular: Tremor, difficulty in getting out of a chair or combing hair
Ophthalmologic: Tearing, irritation, wind sensitivity, diplopia, foreign body sensation
Thyroid gland: Neck fullness, dysphagia, dysphonia
Dermatologic: Flushed feeling, hair loss, pretibial swelling
Reproductive: Oligomenorrhea, decreased libido, gynecomastia

weakness, weight loss, heat intolerance, and increased perspiration. Weight loss averaging 15% of baseline can be seen despite increased calorie intake.

Common neuropsychiatric symptoms include anxiety, nervousness, restlessness, tremor, akathisia (inability to sit still), insomnia, memory loss, and poor attention span. Patients are often emotionally labile and irritable. Altered mental status and coma may be seen in thyroid storm. Thyroid myopathy typically affects proximal muscle groups but can also lead to weakness of distal and bulbar muscles. Common presenting symptoms include myalgias, fatigue, and poor exercise tolerance. Patients often report difficulty in combing their hair, climbing stairs, or rising from a seated position. Thyroid myopathy leading to respiratory weakness may be manifested as dyspnea. In the extreme, this condition will require ventilatory support. Thyrotoxic periodic paralysis is manifested as a sudden and profound muscle weakness progressing to flaccid paralysis. It closely resembles familial hypokalemic periodic paralysis.

Palpitations, dyspnea on exertion, and reduced exercise tolerance are common cardiopulmonary complaints. Elders are more prone to cardiac manifestations and often present with new-onset angina, atrial fibrillation, or congestive heart failure as the only manifestations of thyroid disease.[13] Superior vena cava syndrome and dyspnea can occur as a result of compression of vascular and tracheal structures by an enlarged thyroid gland.

An increase in the frequency of bowel movements is the most common gastrointestinal symptom. Dysphagia is also common and can be due to either compression of the esophagus by an enlarged thyroid gland or dysmotility related to thyrotoxic myopathy.

Thyrotoxicosis can cause reproductive endocrine dysfunction in both men and women. Changes in menses can range from amenorrhea to menometrorrhagia. As a result of the increase in estrogen, men may experience gynecomastia, decreased libido, and erectile dysfunction. Infertility related to hyperthyroidism can affect both sexes.

Graves' ophthalmopathy commonly causes eyelid retraction, lid lag, proptosis, and staring eyes. Although these symptoms were previously thought to occur only with Graves' disease, one author suggests that they are present in thyrotoxicosis in the absence of an autoimmune phenomenon, in children and adolescents.[14] Graves' ophthalmopathy is also associated with restrictive extraocular myopathy, exophthalmos, and, less commonly, optic nerve dysfunction.[15] Patients often complain of irritation and excessive tearing as early symptoms; diplopia, retrobulbar discomfort, blurring of vision, and foreign body sensation occur late in the disease.

Box 128-3 Physical Findings in Thyrotoxicosis

Vital signs: Tachycardia, widened pulse pressure, bounding pulses, fever
Cardiac: Hyperdynamic precordium, systolic flow murmur, prominent heart sounds, systolic rub (Means-Lerman scratch), tricuspid regurgitation, atrial fibrillation, evidence of heart failure
Ophthalmologic: Widened palpebral fissures (stare), lid lag, globe lag, conjunctival injection, periorbital edema, proptosis, limitation of superior gaze
Neurologic: Fine tremor, hyperreflexia, proximal muscle weakness
Psychiatric: Fidgety, emotionally labile, poor concentration
Dermatologic: Warm, moist, smooth skin; fine, brittle hair; alopecia, flushed facies; palmar erythema; hyperpigmented pretibial plaques, nodules, or induration that is nonpitting; onycholysis
Neck: Diffuse symmetric thyroid enlargement, sometimes with a bruit and palpable thrill; thyroid with multiple irregular nodules or a prominent single nodule; tracheal deviation, venous prominence with arm elevation (Pemberton's sign)

Physical Signs

Physical examination of the thyrotoxic patient will reveal distinct symptoms that depend on the age of the patient (Box 128-3).[16] Younger patients often appear anxious and fidgety, with a fine tremor of the hands and tongue. Dermatologic changes vary by area of the body. The skin feels warm, smooth, and velvety, especially over the elbows; the face is rosy and blushes readily, and the patient's hands may reveal palmar erythema. Onycholysis (Plummer's nails) may be present and shows separation of the distal portion of the nail from the nail bed. Scalp hair is fine and brittle, and diffuse alopecia may occur. In Graves' disease, about 5% of patients have pretibial myxedema, in which mucopolysaccharide infiltration of the dermis yields marked thickening of the pretibial skin. These lesions are painless, raised nodules and plaques that become confluent over the pretibial area and dorsum of the feet. Hyperpigmentation and induration are present, but pitting is absent, and pretibial myxedema is almost always associated with Graves' ophthalmopathy.[17]

Of the cardiac manifestations, tachycardia is by far the most common finding and is often accompanied by a systolic flow murmur. Other findings include a widened pulse pressure, bounding peripheral pulses, and rarely a friction rub heard along the left sternal border (Means-Lerman scratch). Whereas atrial fibrillation is more common in elders, with a prevalence of 15% in patients older than 70 years, it can be seen at any age, with an overall prevalence of 2%.[13] Patients with subclinical hyperthyroidism have an increase in the prevalence of atrial fibrillation compared with the total population. Dilated cardiomyopathy may develop as a complication of tachycardia and high cardiac output state. Primary pulmonary hypertension, sometimes associated with tricuspid regurgitation and right-sided heart failure, may also be seen.

Increased activity at the sympathetic innervation of the eyelids leads to widening of the palpebral fissures, resulting in the characteristic stare of thyrotoxicosis. Similarly, this also leads to lid lag, noted when the patient looks slowly downward and the lid lags behind the globe. Proptosis of the globe results from mucopolysaccharide infiltration and inflammation of the ocular muscles and soft tissue, leading to exophthalmos. This finding is thought to be unique to Graves' disease and affects about 50% of patients. Early in Graves' ophthalmopathy, conjunctival injection, periorbital edema, and chemosis may be seen. As the disease progresses, patients may experience restriction of upward gaze from

www.ketabpezeshki.com 66485457-66963820

infiltration of the inferior rectus muscle and visual loss from optic nerve involvement (compression by inflamed, enlarged orbital contents). Treatment of hyperthyroidism, especially with radioactive iodine, may paradoxically aggravate Graves' eye disease.[18]

The majority of hyperthyroid patients have an enlarged thyroid gland. The size of the goiter depends on its etiology. Enlargement is common in patients with toxic multinodular goiter or Graves' disease. However, many elders with Graves' disease have a nonpalpable thyroid. In Graves' disease, the thyroid gland is typically symmetrically enlarged (two to three times in size), soft, and smooth (without nodules). Variable enlargement occurs in toxic multinodular goiter, and multiple nodules may be present, resulting in an irregular surface. Retrosternal enlargement can occur, making detection difficult while causing the obstructive symptoms discussed earlier. Facial and neck vein engorgement can be elicited when arms are elevated above the head (Pemberton's sign) (see Box 128-3).

Negligible to moderate thyroid enlargement can be seen in patients with Hashimoto's or painless thyroiditis (postpartum and sporadic). The thyroid gland in subacute thyroiditis is slightly enlarged and exquisitely tender. The addition of overlying erythema or warmth is seen in suppurative thyroiditis. The absence of thyroid enlargement should suggest exogenous (factitious) thyroiditis as well as ectopic hyperthyroidism (struma ovarii).

Thyroid Storm

Thyroid storm is a rare, life-threatening form of severe thyrotoxicosis. Although it can occur as the result of unrecognized or undertreated thyrotoxicosis, more often it is an acute reaction to thyroid or nonthyroid surgery, trauma, infection, iodine load (contrast media or amiodarone), or parturition in patients with preexisting hyperthyroidism. Other precipitants include acute myocardial infarction, pulmonary embolism, and diabetic ketoacidosis (Box 128-4). It affects 1 to 2% of patients with hyperthyroidism and up to 10% of hospitalized thyrotoxic patients. Untreated, mortality approaches 100%, but prompt recognition and aggressive therapy have lowered mortality to 20 to 30%.[19] Nearly all cases are related to Graves' disease or occasionally toxic multinodular goiter and toxic adenoma; it rarely occurs in other causes of thyrotoxicosis.

The typical clinical manifestations of hyperthyroidism are exaggerated in thyroid storm. Marked pyrexia to 104 to 106° F, tachycardia (often in excess of 140 beats/min), and altered mental status (agitation, delirium, or coma) are common features. These findings coupled with the clinical picture of a patient with hyperthyroidism, lid lag, stare, goiter, ophthalmopathy, and tremor should alert the clinician to the diagnosis. Cardiovascular collapse can result in congestive heart failure, hypotension, and cardiac arrhythmias. Hypotension can also result from volume depletion secondary to nausea, vomiting, and diarrhea. Abdominal pain is common; less commonly hepatic failure with cholestatic jaundice occurs, which is an indicator of a poor prognosis.[20]

Hyperthyroidism increases catecholamine receptor expression. As such, an exaggerated response is seen in the face of the adrenergic surge associated with physiologic stressors such as sepsis or trauma, yielding thyroid storm. The clinical picture that ensues should prompt the clinician to the diagnosis; however, no validated diagnostic system exists. Currently, the only tool available is a scoring system developed by Burch and Wartofsky, which can help distinguish between thyrotoxicosis, impending thyroid storm, and frank thyroid storm (Table 128-1).[19]

Box 128-4 Precipitants of Thyroid Storm

Medical
Infection, sepsis
Cerebral vascular accident
Myocardial infarction
Congestive heart failure
Pulmonary embolism
Visceral infarction
Emotional stress
Acute manic crisis

Trauma
Thyroid surgery
Nonthyroid surgery
Blunt and penetrating trauma to the thyroid gland
Vigorous palpation of the thyroid gland
Burns

Endocrine
Hypoglycemia
Diabetic ketoacidosis
Hyperosmolar nonketotic coma

Drug Related
Iodine-131 therapy
Premature withdrawal of antithyroid therapy
Ingestion of thyroid hormone
Iodinated contrast agents
Amiodarone therapy
Iodine ingestion
Anesthesia induction
Miscellaneous drugs (chemotherapy, pseudoephedrine, organophosphates, aspirin)

Pregnancy Related
Toxemia of pregnancy
Hyperemesis gravidarum
Parturition and the immediate postpartum period

Diagnostic Strategies

The diagnosis of hyperthyroidism can be simplified into a two-step process. The initial diagnosis is based on the clinical picture coupled with confirmatory laboratory values. Once the diagnosis of hyperthyroidism is established, if the etiology is unclear, nuclear imaging with radioiodine is generally performed; this second step is a 24-hour test and thus not useful for the emergency physician but rather a tool for further evaluation once the diagnosis of thyrotoxicosis has been established.

Reliable assays for serum TSH and free T_4 have made the laboratory diagnosis of hyperthyroidism straightforward. Measurement of serum TSH is the single best test to assess thyroid function. A normal TSH level excludes hyperthyroidism and an elevated TSH level is generally diagnostic for hypothyroidism. In thyrotoxicosis, serum TSH concentration is depressed or undetectable (values <0.05 μU/mL in third-generation assays). Values above this threshold associated with hyperthyroidism are consistent with subclinical disease.[21] Assessment of thyroid function during acute nonthyroidal illness is difficult, especially in critically ill patients. Severe systemic illness depresses TSH production, leading to low levels of TSH, free T_3, and free T_4. Once referred to as the euthyroid sick syndrome, it appears to be a transient form of central hypothyroidism.[22] It is considered an adaptive response during systemic stress to prevent excessive catabolism. Patients taking dopamine, glucocorticoids, somatostatin, and octreotide may also have depressed TSH levels but not to the degree of patients with hyperthyroidism.[23]

Measurement of thyroid hormone levels can help determine the degree of hyperthyroidism. Because nearly all T_3 and T_4 is bound to TBG, assays measuring total T_3 and T_4 are influenced by changes in TBG and are unreliable. Increases in TBG are seen in pregnancy,

www.ketabpezeshki.com 66485457-66963820

Table 128-1 Diagnostic Criteria for Thyroid Storm

	SCORE
Fever (°F)	
99-99.9	5
100-100.9	10
101-101.9	15
102-102.9	20
103-103.9	25
≥104	30
Tachycardia (beats/min)	
90-109	5
110-119	10
120-129	15
130-139	20
≥140	25
Mental Status	
Normal	0
Mild agitation Delirium, psychosis	10
Extreme lethargy	20
Coma, seizures	30
Congestive Heart Failure	
Absent	0
Mild (edema)	5
Moderate (rales)	10
Pulmonary edema	15
Atrial fibrillation	10
Gastrointestinal and Hepatic Symptoms	
None	0
Nausea, vomiting Diarrhea, abdominal pain	10
Unexplained jaundice	20
Precipitating Event	
None	0
Present	10

Modified from Burch HB, Wartofsky L: Life-threatening thyrotoxicosis: Thyroid storm. Endocrinol Metab Clin North Am 22:263-277, 1993.
Tally the maximum score from each category. A score of 45 or higher suggests thyroid storm, a score of 25-44 suggests impending storm, and a score below 25 is unlikely to represent thyroid storm.

Table 128-2 Thyroid Function Test Interpretation

TSH	FREE T_4	FREE T_3	DISEASE
Normal	Normal	Normal	None
Low	High	High	Hyperthyroidism
Low	Normal	Normal	Subclinical hyperthyroidism
Low	Normal	High	T_3 toxicosis
Low	High	Normal	Thyroiditis, T_4 ingestion, hyperthyroidism in the elderly or with comorbid illness
Low	Low	Low	Euthyroid sick syndrome; central hypothyroidism
High	Normal	Normal	Subclinical hypothyroidism; recovery from euthyroid sick syndrome

T_3, triiodothyronine; *T_4*, thyroxine; *TSH*, thyroid-stimulating hormone.

infectious hepatitis, and drug therapy with estrogens, tamoxifen, methadone, or heroin, with resultant false elevations in total T_3 and T_4 values. By contrast, decreases in TBG are seen in cirrhosis, malnutrition, and nephrotic syndrome as well as in treatment with androgens or glucocorticoids, with subsequent low total T_3 and T_4 values. Last, many drugs inhibit the binding of T_3 and T_4 to TBG, which results in higher free T_3 and free T_4 levels that are not reflected in the measurement of total T_3 and T_4. Such drugs include salicylates, nonsteroidal anti-inflammatories, heparin, furosemide, diphenylhydantoin, carbamazepine, and sulfonylureas. Because of these limitations in the measurement of total hormone levels, only free T_3 and free T_4 assays should be used.

Elevation of free T_4 and free T_3 in conjunction with TSH suppression is diagnostic of thyrotoxicosis. Subclinical hyperthyroidism is likely if TSH is suppressed and free T_4 is normal. T_3 toxicosis occurs in about 5% of patients with thyrotoxicosis, more commonly in toxic multinodular goiter. These patients have an elevated free T_3 level and a normal free T_4 level. When the reverse pattern is present (normal free T_3 level and elevated free T_4 level), the differential includes thyroiditis, exogenous levothyroxine ingestion, and hyperthyroidism in the elderly, often with suppressed T_4 to T_3 conversion due to comorbid illness (Table 128-2).

Additional laboratory abnormalities may be seen in thyrotoxicosis and thyroid storm. Nearly 50% of thyrotoxic patients have hyperglycemia. This is likely to be the result of increased glycogenolysis and catecholamine-mediated antagonism of insulin. Mild hypercalcemia, seen in 10% of patients, is related to hormone-mediated bone resorption and associated with osteoporosis and increased fracture risk.

The results of liver function tests are frequently abnormal in thyrotoxic patients. Mild increases in serum aspartate transaminase, alanine transaminase, lactate dehydrogenase, bilirubin, and alkaline phosphatase may be seen. The elevations in serum bilirubin do not typically result in clinical jaundice. Other frequent laboratory abnormalities include leukocytosis with a leftward shift, mild normocytic normochromic anemia, and low serum cholesterol levels.[21]

In thyroiditis, the diagnostic evaluation is more difficult. An exquisitely tender gland and an erythrocyte sedimentation rate above 100 mm/hr make the diagnosis of subacute thyroiditis likely. The other forms of thyroiditis lack these findings. Doppler ultrasound examination of the thyroid may be helpful in differentiating among the various causes of thyrotoxicosis. A hypervascular enlarged gland is seen in Graves' disease, nodules in toxic multinodular goiter, and decreased Doppler flow in thyroiditis or factitious thyrotoxicosis.[24] If factitious thyrotoxicosis is suspected, low thyroglobulin levels may confirm the diagnosis as these levels are elevated in all other forms of thyrotoxicosis. Furthermore, radioactive iodine uptake is depressed in thyroiditis and factitious thyrotoxicosis but increased in hyperthyroidism.

Differential Considerations

Because of the protean symptoms of hyperthyroidism, the differential diagnosis for the thyrotoxic patient is broad. An anxious patient may be interpreted to be manic or experiencing a panic attack. The hyperadrenergic state may be confused with that seen

www.ketabpezeshki.com 66485457-66963820

in patients with sympathomimetic (cocaine or amphetamine) intoxication, suffering from anticholinergic crisis, or experiencing withdrawal from alcohol or sedative-hypnotics.

The hyperpyrexia and altered mental status seen in thyroid storm may mimic other hyperthermic disorders such as heatstroke, neuroleptic malignant syndrome, serotonin syndrome, bacterial meningitis, and sepsis.

Elders often present with apathetic hyperthyroidism, which lacks the hyperadrenergic features of thyrotoxicosis but is associated with blunted facial expressions and an altered mental status. This is commonly seen in patients older than 70 years with multinodular goiter and can be confused with psychiatric illness. In addition, these patients also present with new-onset atrial fibrillation and congestive heart failure. The elderly are also more prone to hyperthyroidism-induced weight loss, leading to a search for an occult malignant neoplasm.

Management

Management of thyrotoxicosis is based on symptom severity. For those with mild symptoms, outpatient referral and management are appropriate. Patients with moderate to severe symptoms are best managed in the emergency department (ED) setting. Treatment is divided into supportive, symptomatic, and thyroid directed (Box 128-5). In addition, it is important to identify and to treat the precipitating cause of thyroid storm.

Supportive Treatment

Supportive therapy for thyroid storm patients includes aggressive management of hyperthermia with cooling and acetaminophen; aspirin is avoided in thyrotoxic patients as it decreases protein binding of T_4 and T_3, thereby elevating free T_4 and free T_3 concentrations. Agitation is controlled with benzodiazepines. Patients with respiratory compromise or who are significantly altered may require intubation. Aggressive fluid resuscitation is needed to compensate for insensible and gastrointestinal losses; dextrose-containing solutions are helpful as glycogen stores are often depleted. Electrolyte replacement is guided by laboratory values.

Symptomatic Treatment

Symptomatic treatment consists primarily of beta-blockade to diminish the adrenergic response. Traditionally, propranolol has been the beta-blocker of choice as it has the added benefit of blocking conversion of T_4 to T_3; its nonselective effects also improve tremor, hyperpyrexia, and restlessness. Dosage recommendations vary, but most authors suggest 60 to 80 mg, orally every 4 hours.[25] The onset of action after oral dosing is about 1 hour. For rapid beta-blockade, propranolol is administered intravenously (IV) as a bolus dose of 0.5 to 1 mg during 10 minutes. Propranolol dosing can be repeated every 15 minutes, as tolerated, until the desired effect is achieved, then transitioning to 1- to 2-mg boluses every hour. A short-acting agent such as esmolol may be used when concerns about beta-blockade exist. A typical esmolol loading dose is 250 to 500 µg/kg, followed by an infusion of 50 to 100 µg/kg/min. In asthmatics, a beta$_1$-selective drug like esmolol or metoprolol (50 mg every 6-12 hours) may be considered, or if this is contraindicated, reserpine 2.5 to 5 mg intramuscularly every 4 hours is also an option.[25] These patients should be closely monitored for hypotension, regardless of the agent used, because thyrotoxicosis can lower systemic vascular resistance and cause congestive heart failure.[26] In patients with low ejection fraction on echocardiography, angiotensin-converting enzyme inhibitors, diuretics, and digoxin are appropriate alternatives. Atrial fibrillation is often refractory to rate control until antithyroid therapy is administered.

Box 128-5 Management of Thyroid Storm

Beta-adrenergic Blockade

Propranolol 60-80 mg PO every 4 hr
or
Metoprolol 50 mg PO every 6-12 hr
If IV route is required: propranolol 0.5-1.0 mg IV slow push test dose, then repeat every 15 min to desired effect, then 1-2 mg every 3 hr
or
Esmolol 250-500 µg/kg bolus, then 50-100 µg/kg/min infusion
Strict contraindication to beta-blocker: reserpine 2.5-5 mg IM every 4 hr

Inhibition of Thyroid Hormone Synthesis

Propylthiouracil 600-1000 mg loading dose, then 300 mg every 6 hr (maximum daily dose, 1200 mg)
or
Methimazole 20-30 mg initially, then 20-30 mg every 6 hr (maximum daily dose, 120 mg)
(Preferred route: PO or NG. Alternative route: PR. Enema prepared by pharmacy. Same dose for all routes. No IV preparation is available, but IV methimazole can be prepared with the use of a Millipore filter and given 30 mg every 6 hr.)

Inhibition of Thyroid Hormone Release

Saturated solution of potassium iodide (SSKI) 5 gtt by mouth, NG, or PR every 6 hr
or
Lugol's solution 4-8 gtt by mouth, NG, or PR every 6 hr
or
Sodium iodide 500 mg in solution prepared by pharmacy IV every 12 hr
or
If allergic to iodine, lithium carbonate 300 mg by mouth or NG every 6 hr

Administration of Corticosteroids (inhibit T_4 to T_3 conversion, treat relative adrenal insufficiency)

Hydrocortisone 100 mg IV, followed by 100 mg every 8 hr
or
Dexamethasone 2-4 mg IV every 6 hr

Diagnosis and Treatment of Underlying Precipitant

Consider empirical antibiotics if critical

Supportive Measures

Volume resuscitation and replacement of glycogen stores
D_5/0.9 NS 125-1000 mL/hr depending on volume status and CHF
Tylenol with caution
Cooling blanket, fans, ice packs, ice lavage

Miscellaneous

Lorazepam or diazepam as anxiolytic and to decrease central sympathetic outflow
L-Carnitine (block entry of thyroid hormone into cells), 1 g PO every 12 hr
Cholestyramine (blocks enterohepatic recirculation of thyroid hormone), 4 g PO every 6 hr

CHF, congestive heart failure; *D_5/0.9 NS,* 5% dextrose in 0.9% normal saline; *IV,* intravenously; *NG,* by nasogastric tube; *PO,* by mouth; *PR,* in rectum; *T_3,* triiodothyronine; *T_4,* thyroxine.

www.ketabpezeshki.com 66485457-66963820

Thyroid-Directed Treatment

Thyroid-directed therapy has three goals: to reduce thyroid hormone production, to prevent thyroid hormone release, and to block peripheral conversion of T_4 to T_3. Although it is not a specific goal, an additional goal is the avoidance of therapeutic interventions that may worsen thyrotoxicosis. As such, certain drugs should be avoided in the thyrotoxic patient. Amiodarone and iodinated contrast material both contain iodine and can increase thyroid hormone production. Aspirin can increase free thyroid hormone concentrations through its effect on protein binding. Finally, pseudoephedrine, ketamine, and albuterol should be used cautiously as they increase sympathetic tone and can exacerbate the adrenergic effects of thyrotoxicosis.

Reducing Thyroid Hormone Production. Thionamides inhibit oxidation and organic binding of iodine to thyroglobulin, thereby blocking synthesis of thyroid hormone. Either propylthiouracil (PTU) or methimazole can be used. PTU has the additional effect of impairing conversion of T_4 to T_3; methimazole has a longer duration of action. PTU is given as an initial loading dose of 600 to 1000 mg by mouth, followed by 300 mg every 6 hours, to a maximum daily dose of 1200 mg.[27] The recommended dose for methimazole is 20 to 30 mg initially, with the same dose repeated every 4 hours to a maximum daily dose of 120 mg.[27] Both PTU and methimazole may be given by nasogastric tube or by retention enema as needed.[28] There are no intravenous forms of PTU or methimazole; although intravenous administration of methimazole has been attempted, this should be considered only as a last resort.

Inhibiting Thyroid Hormone Release. Despite the blockade of thyroid hormone synthesis by thionamides, release of preformed hormone in the gland is still a concern. Inorganic iodine blocks the release of stored thyroid hormone. However, an iodine load can increase the synthesis of thyroid hormone, so these agents should not be administered until 1 hour after the initiation of PTU or methimazole therapy. Traditionally, oral iodine in the form of potassium iodide (SSKI) 5 gtt every 6 hours or Lugol's solution 4 to 8 gtt every 4 to 6 hours is administered. Like the thionamides, these agents may be given by nasogastric tube or by retention enema as needed. Lithium may be considered an alternative therapy for iodine-allergic patients. The lithium dose is 300 mg every 6 to 8 hours orally to obtain a lithium serum concentration of 0.6 to 1.0 mEq/L.[27] Lithium is also the agent of choice for iodine-induced hyperthyroidism, which is usually the result of the administration of amiodarone or iodinated contrast material.

Side effects of thionamide therapy range from mild to life-threatening. Mild reactions (urticaria or macular rash, arthralgia, and gastrointestinal upset) occur in up to 5% of patients receiving methimazole or PTU. Side effects are dose related for methimazole but not for PTU. Life-threatening side effects are associated with ongoing therapy and occur within the first 90 days of treatment. Agranulocytosis can occur with either drug and should prompt drug discontinuation. PTU-induced hepatotoxicity has earned the drug a black box warning from the Food and Drug Administration. Finally, polyarthritis and vasculitis (drug-induced lupus) can occur; vasculitis is associated with PTU more than with methimazole.

Inhibiting Conversion of T_4 to T_3. Corticosteroids are capable of both inhibiting peripheral conversion of T_4 to T_3 and blocking the release of hormone from the thyroid gland. When steroids are used in conjunction with PTU and iodide, the concentration of T_3 can return to normal within 48 hours. In addition, corticosteroids will treat adrenal insufficiency that can occur concomitantly with thyroid storm. Adrenal insufficiency is usually due to increased clearance of cortisol in thyroid storm and the increased demand for cortisol in these critically ill patients. Hydrocortisone can be administered as an initial bolus of 100 mg IV, then 100 mg every 8 hours for several days. Dexamethasone can also be used in doses of 2 to 4 mg IV.

Miscellaneous Therapies

Cholestyramine, an anion exchange resin, interrupts the enterohepatic recirculation of thyroid hormone by binding it in the bowel lumen. Although it has been shown to result in a more rapid decline in hormone levels compared with thionamides alone, it requires weeks of therapy and as such is reserved for outpatient management.[29] Plasmapheresis, plasma exchange, and dialysis have been used in thyroid storm. They represent an attempt at extracorporeal removal of circulating thyroid hormone. Whereas the literature is split on the benefit of these modalities, plasmapheresis demonstrates the greatest putative benefit and can be initiated when a patient with thyroid storm demonstrates deterioration despite aggressive therapy.

L-Carnitine, given 1 g orally every 12 hours, has been used in thyroid storm. Theoretically, it inhibits entry of thyroid hormone into cell nuclei.[30] Neither radioactive iodine nor surgery plays a role in the management of thyroid storm or thyrotoxicosis until a sustained euthyroid state has been established because these interventions can precipitate storm.[31]

Treatment of subacute thyroiditis generally involves only nonsteroidal anti-inflammatories to control pain. Prednisone is used for refractory cases. Only a minority of patients have thyrotoxicosis, which is typically mild and requires no additional treatment beyond beta-blockers. The same holds true for thyrotoxicosis from exogenous thyroid hormone ingestion. In this situation, the thyroid gland has stopped production from negative feedback, so thionamides and iodine are ineffective. Management of drug-induced hyperthyroidism involves removal of the offending agent (amiodarone, lithium) and symptomatic treatment as needed (Box 128-6).

Box 128-6 Thyrotoxicosis and Thyroid Storm: Special Situations

Congestive Heart Failure

If rate-related, high-output failure
- Beta-blockade is first-line therapy (dose as in Box 128-5)
- ACEI, digoxin, diuretics as needed

If depressed ejection fraction
- Avoid beta-blocker or ¼ dose
- ACEI if blood pressure adequate
- Digoxin and furosemide as needed

If pulmonary hypertension
- Oxygen
- Sildenafil

Atrial Fibrillation

Beta-blocker preferred for rate control (dose as in Box 128-5)
Calcium channel blockers prone to hypotension; diltiazem 10-mg test dose. Avoid verapamil.
Digoxin less effective but may be tried
Amiodarone should be avoided because of iodine load
Refractory to conversion to sinus rhythm unless euthyroid first

Thyroiditis (Subacute)

NSAIDs for inflammation and pain control
Prednisone 40 mg/day if refractory to NSAIDs
Beta-blockade to control thyrotoxic symptoms
No role for PTU, methimazole, or iodides

Factitious Thyrotoxicosis

Beta-blockade for thyrotoxic symptoms
Cholestyramine to block absorption of ingested thyroid hormone
No role for PTU, methimazole, or iodides

ACEI, angiotensin-converting enzyme inhibitor; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *PTU,* propylthiouracil.

www.ketabpezeshki.com 66485457-66963820

Identification and Treatment of the Precipitating Event

Thyroid storm is often precipitated by a physiologic stressor. It is critical to identify the cause to maximize therapeutic benefit. Infections are the most common precipitant. Chest radiography, urinalysis, and blood cultures are part of the routine evaluation. Empirical antibiotics are not recommended without an identified source of infection. Other common stressors include myocardial ischemia, pulmonary embolism, and stroke.

Aggressive management of thyroid storm with PTU, followed by iodine, beta-blockers, corticosteroids, fluid resuscitation, rapid cooling, and treatment of the precipitating illness, can resolve fever, tachycardia, and altered mental status within a 24-hour period. All patients with thyroid storm are candidates for an intensive care unit (ICU) admission. Interruption in therapy should be avoided because it can lead to a sudden recrudescence of symptoms and death.

Disposition and Consultation

Disposition is guided by symptom severity, with ICU admission for patients in thyroid storm. Patients with mild thyrotoxicosis (tremor, tachycardia, nervousness) controlled with first-line medication who are otherwise stable can be managed as outpatients. Admission to the hospital may be appropriate for patients who require more than beta-blockers for symptom control or whose symptoms persist despite therapy. Patients with rapid atrial fibrillation should be admitted to a monitored setting.

Patients managed as outpatients can be sent to a primary care physician or referred to an endocrinologist as appropriate.

HYPOTHYROIDISM

Perspective

Background and Epidemiology

Hypothyroidism is a condition in which the thyroid gland fails to produce or to secrete sufficient circulating thyroid hormone to meet the needs of the peripheral tissues. The condition results from either lack of stimulation of the thyroid gland (central or secondary hypothyroidism) or intrinsic gland dysfunction limiting hormone production (primary hypothyroidism). Hypothyroidism is the most common functional disorder of the thyroid gland.[32]

Hypothyroidism is a relatively common disorder of endocrine dysfunction with an annual incidence affecting approximately 80/100,000 men and 350/100,000 women.[1] Thyroid disorders are the second most common endocrine condition after diabetes mellitus. Higher incidence rates are found in women than in men for all types of autoimmune disorders; the genetic disparity of thyroid disorders is attributed to the higher prevalence of autoimmune disease found in women in general. In the United States, 1 to 2% of women are affected by hypothyroidism. Subclinical hypothyroidism affects 4 to 10% of the population.[33] There is no specific race predilection, but older age groups are at a higher risk for development of hypothyroidism. The incidence of overt and subclinical hypothyroidism in pregnancy is estimated at 0.3 to 0.5% and 2 to 3%, respectively.

Pathophysiology

Primary hypothyroidism from intrinsic gland failure accounts for 95 to 99% of all cases of hypothyroidism. Factors that may result in primary hypothyroidism include autoimmune disorders, infiltrative disorders, congenital thyroid dysfunction, pregnancy, radiotherapy, medications, infection, surgery, inadequate dietary iodine intake, thyroid medication noncompliance, and previous treatment of thyrotoxicosis (Box 128-7). Worldwide, iodine deficiency is the most common cause of hypothyroidism; however, in iodine-replete regions, the primary cause is autoimmune. Hypothyroidism may also be associated with other autoimmune diseases, such as diabetes mellitus, pernicious anemia, Addison's disease, and hyperparathyroidism.

Hashimoto's thyroiditis or chronic autoimmune lymphocytic thyroiditis, first described in 1912 by Hakaru Hashimoto, is one of the most common organ-specific autoimmune diseases and the most common cause of primary hypothyroidism. It is characterized by infiltration of the thyroid gland by lymphocytic inflammatory cells, which is then often followed by hypothyroidism as a result of destruction and eventual fibrous replacement of the gland's follicular tissue. Hashimoto's thyroiditis is the third most common autoimmune disease in the United States and the most frequent cause of hypothyroidism in adults. A systematic review of the literature estimates the annual incidence of Hashimoto's or autoimmune thyroiditis to be 80/100,000 per year (men) and 350/100,000 per year (women).[1]

Neonatal hypothyroidism results from decreased T_4 production in the newborn and is the most preventable cause of intellectual disability.[34] Most infants with congenital hypothyroidism have thyroid dysgenesis, which includes thyroid agenesis, thyroid hypogenesis, and a defect in thyroid migration leading to ectopic

Box 128-7 Causes of Hypothyroidism

Primary Hypothyroidism

- Autoimmune hypothyroidism
  - Hashimoto's thyroiditis (chronic: atrophic thyroid, acute with goiter)
  - Graves' disease (end stage)
- Iatrogenic
  - Radioactive iodine therapy for Graves' disease
  - Thyroidectomy for Graves' disease, nodular goiter, or thyroid cancer
  - External neck irradiation for lymphoma or head and neck cancer
- Iodine related
  - Iodine deficiency (common worldwide but rare in North America)
  - Iodine excess (inhibition of hormone release can unmask autoimmune thyroid disease) (see under drug related)
- Drug related
  - Lithium (inhibits hormone release)
  - Amiodarone (destructive thyroiditis or iodine excess)
  - Interferon alfa (precipitates Hashimoto's thyroiditis)
  - Iodine excess (iodinated contrast media, kelp, amiodarone)
  - Propylthiouracil, methimazole
  - Interference with thyroid hormone absorption in patients receiving replacement therapy (iron, calcium, chromium, phosphate binders, cholestyramine, colestipol)
- Thyroiditis
  - Subacute
  - Silent (sporadic)
  - Postpartum
  - Amiodarone
- Congenital defect in thyroid hormone synthesis

Central Hypothyroidism

- Euthyroid sick syndrome
- Pituitary disease
  - Pituitary adenoma
  - Hemorrhage
  - Infiltrative (amyloid, sarcoid)
- Hypothalamic disease

www.ketabpezeshki.com 66485457-66963820

thyroid tissue most commonly found at the base of the tongue (lingual thyroid). With thyroid dysgenesis, the thyroid tissue, if any, has insufficient function to sustain normal thyroid hormone production. In some cases of a lingual thyroid, patients may have local symptoms of dysphagia, dysphonia, hemorrhage, or upper airway obstruction decades later in life.[35] The longer the diagnosis and treatment of congenital hypothyroidism are delayed, the greater the cognitive deficit will be compared with expected normals.

Previous treatment of hyperthyroidism may lead to iatrogenically induced hypothyroidism as a result of surgical thyroidectomy or radioactive iodine ablation therapy.

Lithium and amiodarone are well-known causes of hypothyroidism. Lithium, commonly prescribed for the treatment of bipolar disorder, has a side effect profile that includes goiter in up to 40% and hypothyroidism in about 20% of patients. The most relevant clinical action of lithium on the thyroid is the inhibition of T_4 and T_3 release. Lithium also increases thyroid autoimmunity if it is present before the initiation of lithium treatment. Treatment with exogenous thyroid hormone is effective and lithium therapy need not be discontinued.[36]

Amiodarone is a class III antiarrhythmic medication that has a chemical structure similar to that of T_4 and contains large amounts of iodine. As such, it inhibits the peripheral conversion of T_4 to T_3, leading to hypothyroidism.[37] In addition, amiodarone is directly cytotoxic to the thyroid, has the intrinsic effect of blocking thyroid hormone entry into cells, and decreases T_3 receptor binding. If amiodarone therapy must be continued for arrhythmia control, patients with amiodarone-induced hypothyroidism may be successfully treated with exogenous thyroid hormone replacement. Screening for thyroid dysfunction is recommended before initiation of therapy and during treatment with these medications.

Tyrosine kinase inhibitors are used as chemotherapeutic agents in the treatment of several types of malignant neoplasms, including thyroid cancer. Some medications in this class have been noted to profoundly alter thyroid function with enough frequency to warrant routine monitoring of thyroid function during treatment.

Insufficient dietary iodine intake leads to reduced T_4 and T_3 production. Although it is uncommon in developed nations, this is still a major concern in areas where the iodine content in the water is low. The compensatory increase in TSH concentration over time results in proliferation of gland cells and enlargement of the gland with a resultant goiter.

Thyroid physiology is altered during pregnancy, when increased circulating estrogen results in a 100 to 150% increase in TBG, which lowers free T_4 levels.[38] Human chorionic gonadotropin (hCG) and TSH have identical subunits, which then both stimulate the release of T_4 and T_3, resulting in a decreased level of TSH at 8 to 14 weeks of gestation. There is iodine transfer to the fetus and an increase in renal iodine clearance. Last, increased peripheral metabolism of thyroid hormone occurs primarily in the second and third trimesters. Women with preexisting hypothyroidism will generally require increased doses of replacement hormone in pregnancy. Management of thyroid dysfunction must meet the maternal needs without compromising the fetal needs.

Data suggest that the presence of thyroid hormone is critical to the development of the fetal brain such that maternal hypothyroidism is known to result in permanent fetal neurodevelopmental disorders.[39] Cretinism is the term used to describe the condition of severely stunted physical and mental growth due to untreated congenital deficiency of thyroid hormones. Well-designed studies have shown that women with hypothyroidism, in comparison to pregnant controls with normal thyroid function, have offspring who score significantly lower than age-matched controls on IQ testing.[39] In subclinical hypothyroidism, the thyroid hormone levels are normal despite an elevated TSH level. The endocrine community has accepted that maternal subclinical hypothyroidism causes a significant decrease in IQ scores of offspring and has advocated routine screening of pregnant women.[40] Contrarily, the American College of Obstetricians and Gynecologists has not embraced this relationship and does not recommend routine testing for thyroid dysfunction unless the pregnant woman has risk factors for the development of hypothyroidism (e.g., past history or family history of thyroid disease; goiter; symptoms of thyroid disease, including hypercholesterolemia, anemia, and hyponatremia; type I diabetes mellitus; autoimmune disorders; infertility; head and neck irradiation; history of miscarriage or preterm delivery) or has symptoms of hypothyroidism.[41]

Other obstetric complications of hypothyroidism include miscarriage, anemia, abruptio placentae, postpartum hemorrhage, low birth weight, and neonatal respiratory distress.

Central causes of hypothyroidism are rare and result from hypothalamic dysfunction in secretion of TRH or pituitary dysfunction in secretion of TSH (see Box 128-7). Pituitary adenoma is the most common cause of central hypothyroidism. Other causes include pituitary hemorrhage (Sheehan's syndrome), pituitary infiltrative processes such as amyloidosis and sarcoidosis, brain injury, and space-occupying mass. Sheehan's syndrome is a result of postpartum pituitary hemorrhage that leads to pituitary ischemia and necrosis. Patients often have lactation failure, amenorrhea, adrenal insufficiency, and central hypothyroidism.

With advancing age, the thyroid gland changes anatomically with a reduction in gland size and weight, an increase in fibrosis with lymphocytic proliferation, and a change in colloid content. These changes do not, however, correlate with gland function. The half-life of T_4 increases with a decrease in T_4 production in the seventh decade of life.

Clinical Features

Signs and Symptoms

Signs and symptoms of hypothyroidism range from asymptomatic to overt organ failure that may lead to death (Box 128-8). Patients with early hypothyroidism often present with vague complaints. As such, clinicians should consider thyroid dysfunction in patients with generalized arthralgias, infertility or menstrual changes, depression, and hypercholesterolemia.

Typical symptoms develop insidiously and include fatigue, weakness, slowing of physical activity, constipation, heavier menstruation, alopecia and brittle hair, weight gain, intolerance to cold, goiter, hypertension, bradycardia, and facial edema. Skin may be dry, coarse, and pale from fluid accumulation and decreased circulation. Paresthesias of hands mimicking carpal tunnel have been described.

As the disease progresses, symptoms may include altered or decreased taste, hoarseness, edema of the hands and feet, slow speech, thickening of the skin, and thinning of the lateral third of the eyebrows. Patients with subclinical hypothyroidism may present with varying nonspecific signs and symptoms similar to those of patients with overt hypothyroidism but less pronounced. Patients with Hashimoto's thyroiditis present typically with an insidiously developed goiter and hypothyroidism.

Subclinical hypothyroidism progresses to clinical hypothyroidism at a rate of 5 to 18% per year in those with elevated TSH levels and detectable thyroid antibodies.[42] Progression may be predicted by the degree of TSH elevation and appears more likely in patients with detectable serum antithyroid antibodies.[43]

Hypothyroidism is responsible for multisystem organ disease. Even mild thyroid failure is a significant risk factor for the development of arterial stiffness from impaired endothelial function and artery intima-media wall thickening. Arterial stiffness is

www.ketabpezeshki.com 66485457-66963820

Box 128-8 Symptoms and Signs of Hypothyroidism

Vital Signs
Systolic blood pressure: normal or low
Diastolic blood pressure: normal or elevated
Slow pulse to sinus bradycardia
Respirations: normal or slow, shallow
Temperature: normal, but prone to hypothermia with stress

Hypometabolic Complaints
Cold intolerance
Fatigue
Weight gain, but decreased appetite

Cutaneous
Coarse, brittle hair
Alopecia
Dry skin, decreased perspiration
Pallor, cool hands and feet
Coarse, rough skin
Yellow tinge from carotenemia
Thin, brittle nails
Lateral thinning of the eyebrows

Neurologic
Slow mentation and speech
Impaired concentrating ability and attention span
Lethargy
Decreased short-term memory
Agitation, psychosis
Seizures
Ataxia, dysmetria
Mononeuropathy
  Carpal tunnel syndrome
  Sensorineural hearing loss
Peripheral neuropathy, paresthesias

Muscular
Proximal myopathy
Pseudohypertrophy
Delayed relaxation of reflexes (hung-up or pseudomyotonic)

Cardiac
Decreased exercise capacity
Dyspnea on exertion
Sinus bradycardia
Long QT with increased ventricular arrhythmia
Chest pain: accelerated coronary disease
Diastolic heart failure (delayed ventricular relaxation)
Pericardial effusion (asymptomatic)
Peripheral edema

Respiratory
Dyspnea on exertion
Obstructive sleep apnea
Primary pulmonary hypertension

Gastrointestinal
Constipation
Ileus
Gastric atrophy

Reproductive
Oligomenorrhea and amenorrhea
Menorrhagia
Decreased fertility
Early abortions
Decreased libido
Erectile dysfunction

Rheumatic
Polyarthralgias
Joint effusions
Acute gout or pseudogout

HEENT
Hoarseness
Deep, husky voice
Macroglossia
Hearing loss
Periorbital swelling
Broad nose
Swollen lips
Goiter

HEENT, head, ear, eyes, nose, and throat.

an important determinant of premature atherosclerosis and changes in arterial wall elasticity. Fortunately, restoration of normal thyroid levels has been shown to improve arterial stiffness and prognosis.

The relationship between thyroid hormone and dyslipidemia has been studied for decades. Subclinical hypothyroidism may result in elevated serum total cholesterol, triglyceride, and low-density lipoprotein concentrations and low serum high-density lipoprotein concentration. Studies have demonstrated a significantly higher incidence of hypothyroidism in patients with hypercholesterolemia than in individuals with normal levels.[44] Although study outcomes vary, there is growing evidence to indicate that subclinical hypothyroidism is associated with lipid abnormalities and subsequently cardiovascular risks.

The thyroid has a fundamental role in maintaining cardiovascular homeostasis in both physiologic and pathologic states, including its influence on cardiac contractility, heart rate, diastolic function, and systemic vascular resistance. Increased peripheral vascular resistance and low cardiac output have been suggested to be additional links between hypothyroidism and impaired blood pressure regulation and resultant hypertension. Vasoconstriction may reflect the absence of the vasodilatory effects of T_3 on vascular smooth muscle. Antihypertensive medications are usually ineffective in noneuthyroid individuals.[45] Hemodynamic effects of subclinical hypothyroidism included impaired left ventricular function with lowered cardiac output and increased peripheral vascular resistance.[46]

The accelerated atherosclerosis in hypothyroidism is ascribed to dyslipidemia, diastolic hypertension, and impaired endothelial function.[47] There is a higher incidence of myocardial infarction in women with subclinical hypothyroidism compared with euthyroid controls; lipid profile abnormalities improve with the treatment of hypothyroidism.[44] In addition, T_3 increases production and secretion of renin. In patients who are hypothyroid, renin levels are found to be low, which plays an important role in the acceleration of atherogenesis.

Subclinical hypothyroidism has been linked to alterations in cerebral perfusion and nerve conduction. Although neuropsychological dysfunction is not easily detected, working memory may become impaired.[48] The Framingham study noted an increased risk of Alzheimer's disease especially in women with subclinical hypothyroidism.[49]

Pulmonary abnormalities in hypothyroidism are primarily related to hypoventilation and hypercapnia. Between 35 and 65%

www.ketabpezeshki.com 66485457-66963820

of patients with pulmonary hypertension have concomitant thyroid dysfunction. Although pulmonary artery pressures normalize after treatment of the thyroid disease, the exact relationship is not known. Because both diseases are associated with autoimmune disorders, they may share a common autoimmune pathophysiologic mechanism.

Changes in skin and hair characteristics may provide an early signal to dysfunction of thyroid hormone production. Cutaneous symptoms found in adults with hypothyroidism include cold, pale xerotic skin often involving the extensor surfaces. Facial changes include periorbital edema, broadened nose, swollen lips, macroglossia, and flat facial expression. Body and scalp hair is brittle and coarse with a high rate of at least some degree of alopecia.

In pregnancy, hypothyroidism may be manifested classically, but it is often subtle and difficult to distinguish from normal changes in pregnancy. The secretion of hCG is greatest in the first trimester of pregnancy and plateaus in the second; hCG has inherent TSH-like activity and results in elevated T_4 and T_3 levels and decreased TSH levels. The fetus begins to produce TSH toward the end of the first trimester; before this time the fetus relies on maternal TSH production. Normal maternal thyroid hormone production is therefore critical to fetal development.

In children, hypothyroidism may affect growth, development, and cognitive capacity. Declining growth velocity noticed during several years might be the first prompt to evaluate for thyroid disorders. This is secondary to retarded skeletal development and growth arrest from epiphyseal dysgenesis. T_4 replacement will induce a rapid growth spurt, although predicted bone maturation size might not be achieved. The resultant height deficit is related to the delay in thyroid hormone replacement.[50] In adults, thyroid hormone functions to regulate and to maintain bone mass. The duration of bone remodeling cycles is increased, with the osteoclastic resorption phase extended twofold and the osteoblastic phase extended fourfold. There is lower bone turnover and overall gain in bone mass and mineralization. Patients with hypothyroidism are at increased risk for fracture, although the underlying mechanism resulting in this association is unclear.

Myxedema Coma

Myxedema coma is the most severe manifestation of hypothyroidism. It is a life-threatening event that is most often precipitated by some stressful occurrence in patients with untreated or undertreated hypothyroidism. Precipitating events may include myocardial infarction, infection, sepsis, stroke, pulmonary embolus, prolonged exposure to cold, or exposure to drugs that suppress the central nervous system (Box 128-9). Patients with myxedema coma have a temperature below 37° C (98.6° F) in 15% of cases, whereas 15% of those patients have a temperature below 29.5° C (85° F). Diagnosis must often be made on the basis of clinical findings (Box 128-10). Treatment of myxedema coma requires potentially toxic doses of thyroid hormone, and mortality rates are high even with optimum therapy; without treatment, the mortality of this condition approaches 100%.[32] Myxedema is associated with a range of severe mental disorders from depression to severe psychoses, sometimes called myxedema madness.

Box 128-9 Myxedema Coma: Aggravating or Precipitating Factors

Infection, sepsis (especially pneumonia)
Exposure to cold
Cerebrovascular accident
Drug effect
- Altered sensorium: sedative-hypnotics, narcotics, anesthesia, neuroleptics
- Decreased T_4 and T_3 release: amiodarone, lithium, iodides
- Enhanced elimination of T_4 and T_3: phenytoin, rifampin
- Inadequate thyroid hormone replacement: noncompliance; interference with absorption (iron, calcium, cholestyramine)

Myocardial infarction
Gastrointestinal bleeding
Trauma, burns
Congestive heart failure
Hypoxia
Hypercapnia
Hyponatremia
Hypoglycemia
Hypercalcemia
Diabetic ketoacidosis

T_3, triiodothyronine; *T_4*, thyroxine.

Box 128-10 Recognition of Myxedema Coma

Patient profile: elderly female in the winter
Known hypothyroidism; thyroidectomy scar
Hypothermia: temperature usually below 95.9° F; below 90° F is a poor prognostic sign; as low as 75° F reported; nearly normal in presence of infection
Altered mental status: lethargy and confusion to stupor and coma, agitation, psychosis, and seizures (myxedema madness)
Hypotension: refractory to volume resuscitation and pressors unless thyroid hormone administered
Slow, shallow respirations with hypercapnia and hypoxia; high risk of respiratory failure
Bradycardia (sinus)/long QT and ventricular arrhythmias
Myxedema facies: puffy eyelids and lips, large tongue, broad nose
Evidence of severe chronic hypothyroidism: skin, hair, reflexes, bradykinesis, voice
Acute precipitating illness (e.g., pneumonia)
Drug toxicity (e.g., sedative, narcotic, neuroleptic)
Hyponatremia

Diagnostic Strategies

Laboratory studies are used to confirm the diagnosis of hypothyroidism. Determination of an elevated TSH level is considered to be the most sensitive and single best screening test to confirm the diagnosis of primary hypothyroidism. TSH levels peak in the evening and are at their lowest in the afternoon but are also affected by physiologic conditions such as physical stress, illness, trauma, and malnutrition.

TSH measurements may be unreliable in severely ill patients. An elevated TSH level with a low T_4 level is indicative of primary hypothyroidism, and a low TSH level with a low T_4 level is associated with central hypothyroidism. The T_3 resin uptake is decreased, and the free T_4 index (T_3 resin uptake × total serum T_4 concentration) is also low. Increased TSH concentration with a normal T_4 level represents subclinical hypothyroidism (Table 128-3). If the TSH level is normal but the T_4 level is low, hypothyroxinemia exists; patients are often asymptomatic, but studies have found that patients with this degree of thyroid dysfunction do experience pathologic effects. The state of subclinical hypothyroidism may frequently progress to overt hypothyroidism in many patients.

A useful confirmatory test is the presence of thyroid antibodies (antithyroglobulin, antimicrosomal). They may help determine the etiology of hypothyroidism or may serve to predict future occurrence. Other laboratory findings may include mild anemia, hypercholesterolemia, elevated hepatic enzymes, elevated prolactin, and hyponatremia secondary to extracellular volume expansion produced by elevated antidiuretic hormone. Blood glucose

www.ketabpezeshki.com 66485457-66963820

Table 128-3 Definitions of Thyroid Dysfunction

FUNCTION	TSH	FREE T_4
Clinical hypothyroidism	Elevated	Low
Subclinical hypothyroidism	Elevated	Normal
Hypothyroxinemia	Normal	Low

Modified from Gyamfi C, Wapner RJ, D'Alton ME: Thyroid dysfunction in pregnancy: The basic science and clinical evidence surrounding the controversy in management. Obstet Gynecol 113:702-707, 2009.
T_4, thyroxine; *TSH*, thyroid-stimulating hormone.

levels may be normal to low as a result of decreased gluconeogenesis and reduced insulin clearance.

The electrocardiogram is nonspecific in hypothyroidism. It might reveal sinus bradycardia with low-voltage complexes and nonspecific ST-T wave changes.

Imaging studies of the thyroid may detect infiltrative disease but are of limited use in hypothyroidism. Fine-needle biopsy of thyroid nodules is recommended. Radioactive iodine uptake and thyroid scanning are not helpful in hypothyroidism because they require a functioning thyroid gland to provide diagnostic information.

Differential Considerations

Differential considerations include other causes of the common clinical presentations of hypothyroidism: congestive heart failure, pulmonary edema, depression, encephalopathy, hypothermia, systemic infection, and shock.

Management

Hypothyroidism

Replacement with levothyroxine (T_4) remains the treatment of choice and resolves most physical and psychological signs and symptoms in most patients. Synthetic levothyroxine is a levo isomer of thyroxine and has activity identical to that of the endogenous hormone. Approximately 80% is absorbed from the gastrointestinal tract, predominantly in the small intestine. T_4 levels peak approximately 2 to 4 hours after ingestion and remain therapeutic for up to 6 hours.[51] T_3 concentration rises more slowly because it is dependent on conversion from T_4. Dose optimization is guided by monitoring of serum T_4 and TSH levels. Patients with normally functioning thyroid glands require an iodine intake of 150 µg/day.

Levothyroxine is the drug of choice for patients with subclinical hypothyroidism and a serum TSH concentration above 10 mIU/L and for patients with a serum TSH concentration between 5.1 and 10.0 mIU/L in whom the decision to treat has been made. The usual daily dose is between 50 and 75 µg. The serum TSH concentration should be checked at 6- to 8-week intervals after initiation of treatment, and once a normal TSH level has been established, the TSH level should be rechecked at 6 months and then annually.[52] In all cases, TSH concentration should be used as the guide to thyroid hormone replacement. Levothyroxine taken at bedtime has been shown to significantly improve TSH levels; however, quality-of-life variables have not been changed.

Studies comparing combination therapy of levothyroxine (T_4) and T_3 (triiodothyronine; Cytomel) with levothyroxine monotherapy alone have not established a significant benefit.[52] However, some reports from combination therapy groups show improvement in depression and anxiety rating scales and lipid profiles but also show increased bone turnover.[53]

Box 128-11 Treatment of Myxedema Coma

Protect the airway, ventilatory support; monitor for alkalosis
Fluid resuscitation
- 0.9 NS or D_5/0.9 NS if hypoglycemia
- Watch for unmasking of CHF

Thyroid hormone replacement
- T_4 alone (elderly and patients with cardiac comorbidity)
  - T_4 300-500 µg IV as initial bolus
  - Or split bolus 200-300 µg IV days 1 and 2
  - Then 50-100 µg IV daily until able to take PO
- T_3 alone (younger patient, no cardiac risks; rapid correction desired)
  - T_3 10-20 µg IV initially, then 10 µg IV every 4 hr for 1 day, then 10 µg IV every 6 hr for 1-2 days

Hydrocortisone
- 50-100 mg IV every 6-8 hr

Hyponatremia
- Consider fluid restriction.
- Avoid hypotonic fluids; use only 0.9 NS or D_5/0.9 NS.
- If <120 mEq/L, consider 3% saline, 50- to 100-mL boluses.

Passive rewarming
- Regular blankets; prevent heat loss
- If heating blankets are considered, pretreat with intravenous fluids and monitor blood pressure closely.
- Avoid mechanical stimulation.

Treatment of any precipitating illness, with special attention to infectious causes

CHF, congestive heart failure; *D_5/0.9 NS*, 5% dextrose in 0.9% normal saline; *IV*, intravenously; *PO*, by mouth; *T_3*, triiodothyronine; *T_4*, thyroxine.

Myxedema Coma

The cornerstone for treatment of myxedema coma is rapid replacement of intravenous thyroid hormones T_4 and T_3 (Box 128-11). In elders and patients with cardiac comorbidities, T_4 may be given as an initial bolus of 300 to 500 µg or as a split bolus of 200 to 300 µg 24 hours apart. Either initial dose is followed by 50 to 100 µg IV daily until the patient can take oral medications. In younger patients or those without cardiac risk factors, T_3 may be administered at an initial dose of 10 to 20 µg IV followed by 10 µg IV every hour for 24 hours, then 10 µg IV every 6 hours for 1 or 2 days. Aggressive thyroid hormone replacement, support of vital functions, and treatment of the precipitating event are necessary. Stress doses of an intravenous glucocorticoid are recommended as there may be concomitant adrenal insufficiency. Hydrocortisone 50 to 100 mg IV is the drug of choice as it has both mineralocorticoid and glucocorticoid effects.

Hypotension may respond to crystalloid infusion, but vasopressors are occasionally required. In patients with initially refractory hypotension, the mere replacement of thyroid hormone may have a beneficial effect on improvement of blood pressure.

Passive rewarming with blankets and removal from the cold are generally sufficient. However, hemodynamically unstable patients with profound hypothermia require active rewarming.

Hyponatremia is largely due to free water retention and should be treated initially with water restriction. Hypertonic saline is indicated in patients with sodium levels below 120 mEq/L or if hyponatremia-induced seizures occur.

Metabolism of sedatives, narcotics, and anesthetics may be slowed, prolonging their effects. Therefore, lower dosages should be considered to prevent untoward effects of these medications, further complicating patient management.

www.ketabpezeshki.com 66485457-66963820

Disposition

Most patients with hypothyroidism may be treated on an outpatient basis. Patients with severe hypothyroidism who require aggressive management or patients with myxedema coma require inpatient care, often in an ICU setting. Overly aggressive replacement of thyroid hormone may precipitate symptoms of hyperthyroidism or, rarely, thyroid storm, which also may require hospital admission.

ADRENAL INSUFFICIENCY

Perspective

Adrenal insufficiency, first described in 1855 by Thomas Addison, remains a potentially life-threatening disease. The clinical manifestations of deficient action or production of glucocorticoids are the result of either primary adrenal failure or secondary adrenal disease from malfunction of the hypothalamic-pituitary-adrenal (HPA) axis in its production of adrenocorticotropin (ACTH). No matter what the etiology, the predominant symptoms are fatigue, generalized weakness, weight loss, and nonspecific gastrointestinal symptoms, such as nausea, vomiting, and abdominal pain. Acute manifestations of disease may result in severe and possibly refractory hypotension.

The estimated prevalence of primary adrenal insufficiency is around 1/10,000 population.[54] Secondary adrenal insufficiency has double the prevalence of primary adrenal insufficiency; the most common cause is exogenous corticosteroid administration.

Principles of Disease

Anatomy and Physiology

The adrenal glands are paired structures that sit in the retroperitoneum, one atop each kidney. They are found at the level of the twelfth thoracic vertebra, and each gland weighs about 4 g. The adrenal gland has two distinct structures, the adrenal cortex and the medulla, which are responsible for the release of the hormone aldosterone, corticosteroids, and catecholamines. The medulla acts in concert with the central nervous system to produce and to secrete the hormones epinephrine and norepinephrine in response to sympathetic stimulation. Anatomically, the adrenal cortex has three distinct zones: the zona glomerulosa, zona fasciculata, and zona reticularis. Functionally, the gland has two regions: the outer cortex, which includes the zona glomerulosa that secretes the mineralocorticoid aldosterone, and the inner medulla, which is composed of the zona fasciculata and zona reticularis that secrete, respectively, the mineralocorticoid cortisol and androgens or sex steroids.

ACTH produced and secreted by the anterior pituitary stimulates the adrenal cortex to predominantly synthesize and produce cortisol, which regulates carbohydrate, protein, and lipid metabolism, and aldosterone, which regulates fluid and electrolyte balance through sodium and potassium homeostasis. Cortisol is the primary glucocorticoid in humans, accounting for approximately 95% of all glucocorticoid activity; it is produced in quantities of about 10 mg/day, which is equivalent to 20 to 30 mg/day of hydrocortisone.

Pathophysiology

Primary adrenal insufficiency, or Addison's disease, is the failure of the adrenal gland to produce cortisol, aldosterone, or both with an intact HPA axis (Fig. 128-3). In developed countries it is most commonly a result of autoimmune destruction.[55] Adrenal insufficiency may occur alone, with other autoimmune diseases (polyglandular autoimmune syndrome type 2 and polygenic inheritance), or with hypoparathyroidism and mucocutaneous candidiasis (polyglandular autoimmune syndrome type 1) due to autosomal recessive inheritance of mutations in the autoimmune regulator (*AIRE*) gene 6. In primary disease, the HPA axis remains intact. Primary adrenal insufficiency is characterized by absent or low cortisol with high levels of circulating ACTH because of reduced negative feedback effects on the anterior pituitary. The increased ACTH concentration results in secretion of other hormones with similar chemical structure. One classic feature exemplifying this relationship is ACTH stimulation of melanocyte-stimulating hormone, which causes melanocytes to form a black pigment and the characteristic skin hyperpigmentation seen in primary adrenal insufficiency.

Secondary adrenal insufficiency is a result of impaired stimulation of the adrenals from disruption of normal secretion of ACTH by the pituitary or corticotropin-releasing hormone (CRH) by the hypothalamus (see Fig. 128-3). It is characterized by a low plasma cortisol level with a low circulating ACTH level. Although CRH in the hypophyseal portal system cannot be measured, it is likely to be increased.

Adrenal insufficiency may be further characterized as acute or chronic (Box 128-12). The most common cause of acute adrenal insufficiency is the exogenous administration of glucocorticoids, which results in suppression of the HPA axis. The degree of suppression varies on the basis of the pharmacokinetics, dose, and duration of the steroid administered. Larger doses of agents with longer half-lives and an extended course of therapy will prolong the suppression of the HPA axis. Adrenal insufficiency has been reported to occur in patients receiving prednisone in doses of as little as 25 mg twice a day for 5 days.[56] It should, however, be anticipated to occur in patients who receive more than 30 mg/day for 3 weeks or more.[56] The time for HPA axis recovery after exogenous suppression is highly variable, with durations ranging from several days to a year.[57]

Adrenal insufficiency may be due to any underlying physiologic stressor, such as surgery, medications, trauma, respiratory distress, hypothermia, myocardial infarction, sepsis, hypoglycemia, pain, depression, and exogenous steroid withdrawal (after suppressed HPA axis). Etomidate, an intravenous imidazole agent, has been associated with acute adrenal insufficiency. Etomidate is a selective inhibitor of adrenal 11β-hydroxylase, the enzyme that converts deoxycortisol to cortisol. For this reason, continuous infusions are not recommended. Bolus administration for rapid sequence intubation is regarded as safe, despite rare case reports of associated acute adrenal insufficiency.

Clinical Features

Clinical manifestations of primary and secondary adrenal insufficiency share some nonspecific features; fatigue, weakness, anorexia, nausea, vomiting, intestinal cramps, and dizziness are common complaints at presentation (Box 128-13). Both also result in hyponatremia from different mechanisms: aldosterone deficiency and sodium wasting in primary adrenal insufficiency, and low cortisol level and free water retention in secondary adrenal insufficiency.

Primary adrenal insufficiency, however, characteristically has more pronounced clinical manifestations than secondary adrenal insufficiency. More specific to primary adrenal insufficiency are skin hyperpigmentation (particularly in areas exposed to the sun or subject to friction or pressure), salt craving, hyperkalemia, and acidosis. In primary adrenal insufficiency, patients have symptoms related to deficiency of glucocorticoids, mineralocorticoids, and androgens. Patients with mineralocorticoid insufficiency may show signs of sodium and volume depletion (e.g., orthostatic hypotension and tachycardia). In secondary adrenal insufficiency,

www.ketabpezeshki.com 66485457-66963820

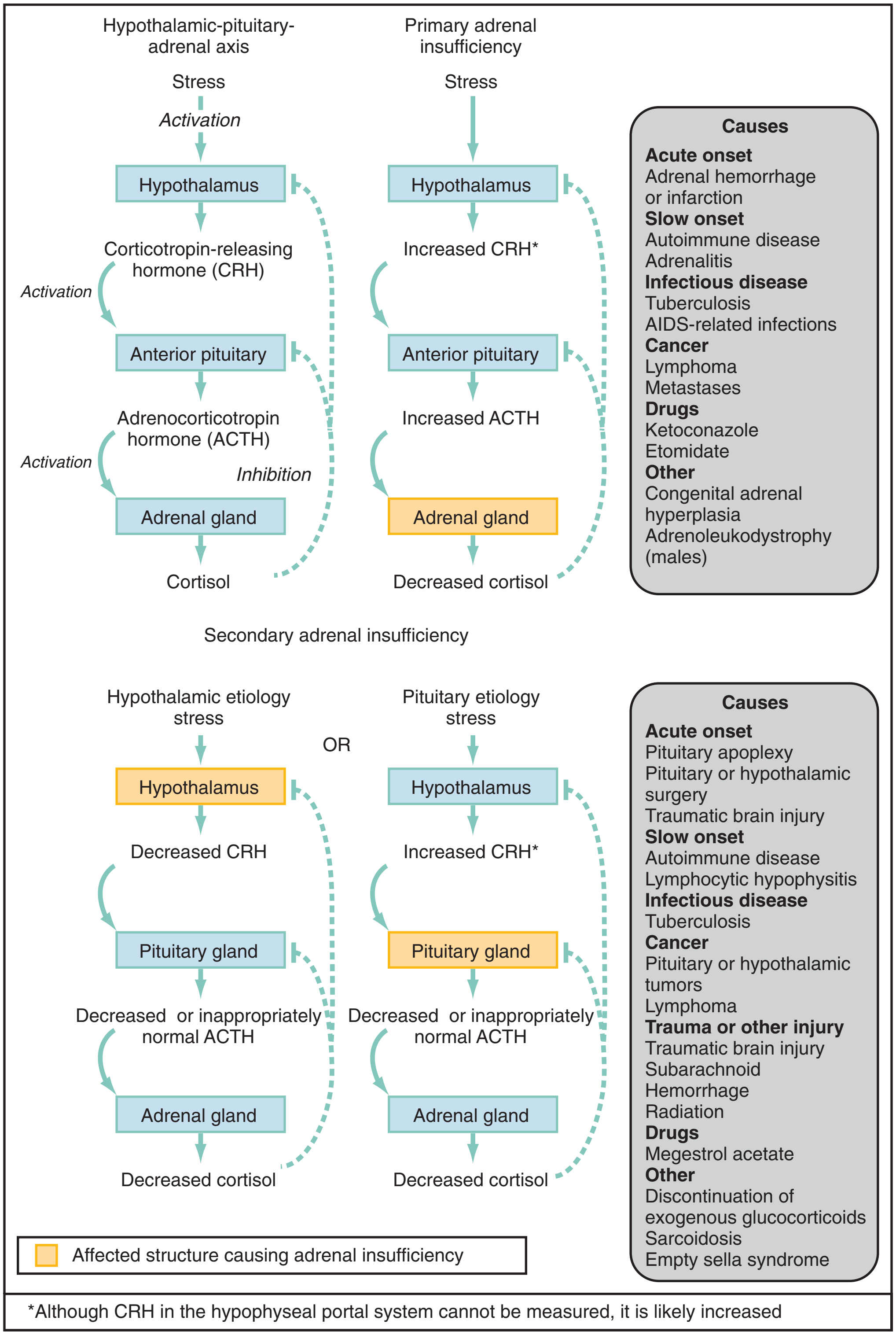


Figure 128-3. Hypothalamic-pituitary-adrenal axis and causes of primary and secondary adrenal insufficiency. (Modified from Wallace I, Cunningham S, Lindsay J: The diagnosis and investigation of adrenal insufficiency in adults. Ann Clin Biochem 46[Pt 5]:351-367, 2009.)

mineralocorticoid production is usually preserved, and patients more often present with pale skin, loss of axillary and pubic hair, decreased libido, and impotence.

With secondary adrenal insufficiency, glucocorticoid deficiency and low ACTH concentrations may result in hypotension and hyponatremia with normal potassium levels. Patients with secondary adrenal insufficiency have normal levels of aldosterone, sex hormones, and catecholamines.

Diagnostic Strategies

Several tests are available to assist in confirming suspected cases of adrenal insufficiency. Whether in screening for chronic disease or in the workup for an acutely ill patient, cortisol measurement is the mainstay for an accurate diagnosis. Measurement of cortisol in the ACTH stimulation test is the standard and most convenient method. The test is based on the inability of the adrenal gland to

www.ketabpezeshki.com 66485457-66963820

Box 128-12 Causes of Adrenal Insufficiency

Primary Adrenal Insufficiency
Chronic
Autoimmune adrenalitis (Addison's disease): isolated or polyglandular deficiency, human immunodeficiency virus (HIV) infection (direct involvement or disseminated cytomegalovirus, *Mycobacterium avium-intracellulare,* tuberculosis, cryptococcosis, histoplasmosis, blastomycosis, toxoplasmosis, Pneumocystis pneumonia)
Tuberculosis and disseminated infections as seen with HIV
Metastatic cancer (breast, lung)
Infiltrative (sarcoid, hemochromatosis, amyloid)
Congenital (adrenal hypoplasia, adrenoleukodystrophy, ACTH resistance)
Bilateral adrenalectomy
Drug toxicity (etomidate, ketoconazole, rifampicin)

Acute
Adrenal hemorrhage
- Meningococcemia and other sepsis
- Anticoagulation (heparins and warfarin)
- Anticardiolipin antibody syndrome
- Trauma

Secondary Adrenal Failure
Chronic
Pituitary tumor (primary or metastatic)
Pituitary surgery or irradiation
Chronic steroid use with functional deficiency
Infiltrative (sarcoid, eosinophilic granuloma, tuberculosis)
Traumatic brain injury
Postpartum pituitary necrosis (Sheehan's syndrome)
Empty sella syndrome

Acute
Pituitary apoplexy (hemorrhage into a pituitary tumor)
Postpartum pituitary necrosis (Sheehan's syndrome)
Traumatic brain injury
Relative adrenal insufficiency (sepsis, hepatic failure, severe acute pancreatitis, trauma)

secrete appropriate amounts of cortisol after administration of corticotropin. The test cannot differentiate between primary and secondary adrenal insufficiency because the HPA axis is bypassed and therefore will not alter endogenous ACTH. Baseline cortisol concentrations are obtained before and 30 and 60 minutes after intravenous or intramuscular administration of ACTH 250 µg. Testing leads to ACTH concentrations of more than 1000 times the normal physiologic peak for adrenal cortex responsiveness.

Random basal serum cortisol concentrations are of limited value for assessment of HPA axis reserve but can confirm an intact adrenocortical reserve if basal morning concentrations are above 500 nmol/L. Cortisol levels peak between 6 AM and 8 AM, which is the appropriate time to draw blood for determination of a cortisol level. With cortisol concentration measurements between 100 and 500 nmol/L, further dynamic testing is indicated. More than 90% of cortisol is protein bound, so changes in protein binding can affect total measured serum cortisol concentrations without affecting free cortisol concentrations.

Mild to moderate hyponatremia with levels typically above 120 mEq/L is seen in primary adrenal insufficiency. Aldosterone deficiency leads to sodium wasting, and decreased cortisol levels lead to increased antidiuretic hormone, resulting in increased water absorption. Hyperkalemia may be seen in primary adrenal insufficiency secondary to low circulating aldosterone concentrations, but it is not seen in secondary causes when aldosterone is not affected.

Box 128-13 Clinical Features of Adrenal Insufficiency

General	
Weakness, fatigue	100%
Anorexia	100%
Gastrointestinal symptoms	92%
Weight loss	100%
Hyponatremia	90%
Blood pressure ≤110/70 mm Hg	88-94%
Fevers (mild)	Common
Depression, apathy	20-40%
Myalgia, arthralgias	6-13%
Auricular calcifications	5%
Primary	
Hyperpigmentation	94-97%
Salt craving	16-22%
Orthostasis, syncope	12-16%
Vitiligo	10%
Hyperkalemia	65%
Hyperchloremia and acidosis	65%
Hypoglycemia	Mild, occasional
Secondary	
Hyperkalemia	Not present
Hyperpigmentation	Not present
Hypoglycemia	More severe, common
Orthostasis, hypotension	Uncommon
Amenorrhea	Common
Axillary and pubic hair loss	Occasional
Decreased libido	Occasional
Crisis	
Refractory hypotension	100%

Differential Considerations

Because of the vague and nonspecific symptoms, the differential diagnosis of hypoadrenalism is extensive. Many of the presenting signs and symptoms resemble other difficult to diagnose conditions as well. The wasting associated with chronic adrenal insufficiency resembles that of anorexia nervosa or an occult carcinoma. The generalized weakness, fatigue, and myalgias can be confused with chronic fatigue syndrome, polymyalgia rheumatica, myopathy, hypothyroidism, or influenza syndromes.

Lack of recognition of acute adrenal crisis with refractory hypotension can result in evaluations for sepsis, gastrointestinal bleeding, myocardial ischemia, or anaphylaxis. Abdominal pain in crisis may be clinically indistinguishable from an acute abdomen, especially if it is precipitated by adrenal hemorrhage. The headache and visual field cuts in pituitary apoplexy may resemble a hemorrhagic stroke. Finally, the constellation of symptoms seen in acute adrenal insufficiency (weakness, malaise, fatigue, nausea, dizziness, and arthralgias) is also present in steroid withdrawal syndrome. Because both can occur with the cessation of chronic glucocorticoid, a proper history is critical to distinguish between the two disease processes.

Management

Patients with adrenal insufficiency require hormone replacement to correct a lack of circulating glucocorticoid and mineralocorticoid without exceeding therapeutic levels. In primary adrenal insufficiency, first-line treatment is hydrocortisone (Box 128-14). In adults, the typical oral dose is 30 mg daily. To mimic natural diurnal adrenal variation, two thirds of the daily dose is usually given in the morning and one third in the late afternoon.

www.ketabpezeshki.com 66485457-66963820

Box 128-14 Treatment of Hypoadrenalism

Maintenance
Hydrocortisone 20 mg AM, 10 mg PM
Fludrocortisone 50-100 µg/day

Maintenance during Minor Illness
Hydrocortisone 40 mg AM, 20 mg PM
Fludrocortisone 50-200 µg daily

Coverage during Procedural Stress
Hydrocortisone 100 mg IV (one time only)

Adrenal Crisis or Relative Adrenal Insufficiency of Critical Illness
Dexamethasone 4 mg IV bolus
or
Hydrocortisone 100 mg IV bolus
0.9 NS 2-3 L in the first few hours
Switch to D_5/NS if hypoglycemia
Treat precipitating illness

D_5/NS, 5% dextrose in normal saline; 0.9 NS, 0.9% normal saline.

Mineralocorticoid should also be replaced in the form of fludrocortisone at 50 to 200 µg/day. In the setting of fever, infection, or intercurrent illness, the dose of hydrocortisone is doubled. In severe illness, it is commonly increased to 75 to 150 mg daily.

Whereas definitive treatment of secondary adrenal insufficiency is directed at replacement of missing hormone (ACTH or CRH) at the level of the hypothalamus or pituitary, simple steroid hormone replacement is administered in the ED setting. Steroid tapering is necessary when gradual downregulation of the HPA axis has been provoked by exogenous glucocorticoids. There is no universally recommended method for tapering of steroids.

In acute disease, emergency management of hypoadrenalism includes recognition and treatment of life-threatening cardiac rhythm disturbances, intravascular volume replacement, correction of electrolyte disturbances, correction of glucose concentration, and administration of glucocorticoids.[58] Dexamethasone 4 mg or hydrocortisone 100 mg is administered as an intravenous bolus.

Disposition

The nonspecific symptoms of hypoadrenalism make diagnosis difficult in the ED. Most patients with mild symptoms who are not acutely ill may be discharged for outpatient evaluation and treatment.

In the severely ill patient, identification of the disease process and any underlying cause is critical. Because the lack of aggressive therapy carries a high mortality rate, admission to an ICU setting is required.

KEY CONCEPTS

Hyperthyroidism

- Thyroid hormone exerts effects on nearly every organ system. A high degree of suspicion is needed to diagnose hyperthyroidism.
- The laboratory evaluation of choice is determination of TSH concentration with free T_4 and T_3 levels. Total T_4 and T_3 levels are of limited utility.
- Thyroid storm is a life-threatening thyrotoxic crisis that requires prompt recognition and aggressive therapy as well as identification and treatment of any precipitating cause, such as infection.
- The order of medication administration in thyroid storm is critical. Iodine can precipitate thyroid storm and must be given a minimum of 1 hour after thionamide therapy (PTU or methimazole) has been administered. As such, the typical order is beta-blocker (propranolol), PTU or methimazole, then iodine (SSKI, Lugol's solution).

Hypothyroidism

- Hypothyroidism results from either lack of stimulation of the thyroid gland (central or secondary hypothyroidism) or intrinsic gland dysfunction limiting hormone production (primary hypothyroidism).
- Signs and symptoms of hypothyroidism range from asymptomatic to overt organ failure, which can lead to death.
- Determination of an elevated TSH level is the most sensitive and single best screening test to confirm the diagnosis of primary hypothyroidism.
- Replacement with levothyroxine (T_4) remains the treatment of choice and resolves most physical and psychological signs and symptoms in most patients.
- Myxedema coma is a life-threatening event that is most often precipitated by some stressful event in patients with untreated or undertreated hypothyroidism. Aggressive treatment with thyroid hormone replacement must be initiated often solely on clinical findings.

Adrenal Insufficiency

- Clinical manifestations of both primary and secondary adrenal insufficiency may be vague and nonspecific and require a high index of suspicion for diagnosis.
- Predominant complaints include fatigue, weakness, dizziness, nausea, vomiting, and other nonspecific gastrointestinal symptoms.
- Patients with primary adrenal insufficiency characteristically have more pronounced clinical manifestations and skin hyperpigmentation. Measurement of cortisol in the ACTH stimulation test is the standard and most convenient method to assist in confirming the diagnosis.
- Refractory hypotension in the acutely ill patient may be the only clue to adrenal insufficiency and is readily treated with the intravenous administration of glucocorticoids (dexamethasone 4 mg or hydrocortisone 100 mg IV).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. McGrogan A, Seaman HE, Wright JW, de Vries CS: The incidence of autoimmune thyroid disease: A systematic review of the literature. *Clin Endocrinol* 2008; 69:687-696.
2. Williamson S, Greene SA: Incidence of thyrotoxicosis in childhood: A national population based study in the UK and Ireland. *Clin Endocrinol* 2010; 72:358-363.
3. Mittra ES, Niederkohr RD, Rodriguez C, El-Maghraby T, McDougall IR: Uncommon causes of thyrotoxicosis. *J Nucl Med* 2008; 49:265-278.
4. Duhig TJ, McKeag D: Thyroid disorders in athletes. *Curr Sports Med Rep* 2009; 8:16-19.
5. Ngo AS, Lung Tan DC: Thyrotoxic heart disease. *Resuscitation* 2006; 70:287-290.
6. Stagnaro-Green A: Recognizing, understanding, and treating postpartum thyroiditis. *Endocrinol Metab Clin North Am* 2000; 29:417-430.
7. Pearce EN, Farwell AP, Braverman LE: Thyroiditis. *N Engl J Med* 2003; 348:2646-2655.
8. Nishihara E, et al: Clinical characteristics of 852 patients with subacute thyroiditis before treatment. *Intern Med* 2008; 47:725-729.
9. Paes JE, et al: Acute bacterial suppurative thyroiditis: A clinical review and expert opinion. *Thyroid* 2010; 20:247-255.
10. Bogazzi F, Bartalena L, Martino E: Approach to the patient with amiodarone-induced thyrotoxicosis. *J Clin Endocrinol Metab* 2010; 95:2529-2535.
11. Poon WT, Ng SW, Lai CK, Chan YW, Mak WL: Factitious thyrotoxicosis and herbal dietary supplement for weight reduction. *Clin Toxicol* 2008; 46:290-292.
12. Diez JJ: Hyperthyroidism in patients older than 55 years: An analysis of the etiology and management. *Gerontology* 2003; 49:316-323.
13. Klein I, Danzi S: Thyroid disease and the heart. *Circulation* 2007; 116:1725-1735.
14. Gruters A: Ocular manifestations in children and adolescents with thyrotoxicosis. *Exp Clin Endocrinol Diabetes* 1999; 107(Suppl 5):S172-S174.
15. Bartley GB: The epidemiologic characteristics and clinical course of ophthalmopathy associated with autoimmune thyroid disease in Olmsted County, Minnesota. *Trans Am Ophthalmol Soc* 1994; 92:477-588.
16. Trivalle C, et al: Differences in the signs and symptoms of hyperthyroidism in older and younger patients. *J Am Geriatr Soc* 1996; 44:50-53.
17. Schwartz KM, Fatourechi V, Ahmed DD, Pond GR: Dermopathy of Graves' disease (pretibial myxedema): Long-term outcome. *J Clin Endocrinol Metab* 2002; 87:438-446.
18. Acharya SH, et al: Radioiodine therapy (RAI) for Graves' disease (GD) and the effect on ophthalmopathy: A systematic review. *Clin Endocrinol* 2008; 69:943-950.
19. Burch HB, Wartofsky L: Life-threatening thyrotoxicosis. Thyroid storm. *Endocrinol Metab Clin North Am* 1993; 22:263-277.
20. Hull K, et al: Two cases of thyroid storm–associated cholestatic jaundice. *Endocr Pract* 2007; 13:476-480.
21. Pimentel L, Hansen KN: Thyroid disease in the emergency department: A clinical and laboratory review. *J Emerg Med* 2005; 28:201-209.
22. Chopra IJ: Clinical review 86: Euthyroid sick syndrome: Is it a misnomer? *J Clin Endocrinol Metab* 1997; 82:329-334.
23. Surks MI, Sievert R: Drugs and thyroid function. *N Engl J Med* 1995; 333:1688-1694.
24. Ota H, et al: Quantitative measurement of thyroid blood flow for differentiation of painless thyroiditis from Graves' disease. *Clin Endocrinol* 2007; 67:41-45.
25. Nayak B, Burman K: Thyrotoxicosis and thyroid storm. *Endocrinol Metab Clin North Am* 2006; 35:663-686.
26. Dalan R, Leow MK: Cardiovascular collapse associated with beta blockade in thyroid storm. *Exp Clin Endocrinol Diabetes* 2007; 115:392-396.
27. Cooper DS: Antithyroid drugs. *N Engl J Med* 2005; 352:905-917.
28. Yeung SC, Go R, Balasubramanyam A: Rectal administration of iodide and propylthiouracil in the treatment of thyroid storm. *Thyroid* 1995; 5:403-405.
29. Tsai WC, et al: The effect of combination therapy with propylthiouracil and cholestyramine in the treatment of Graves' hyperthyroidism. *Clin Endocrinol* 2005; 62:521-524.
30. Benvenga S, Lapa D, Cannavo S, Trimarchi F: Successive thyroid storms treated with L-carnitine and low doses of methimazole. *Am J Med* 2003; 115:417-418.
31. Vijayakumar V, Nusynowwitz ML, Ali S: Is it safe to treat hyperthyroid patients with I-131 without fear of thyroid storm? *Ann Nucl Med* 2006; 20:383-385.
32. McDermott MT: In the clinic. Hypothyroidism. *Ann Intern Med* 2009; 151:ITC61.
33. Razvi S, Weaver JU, Pearce SH: Subclinical thyroid disorders: Significance and clinical impact. *J Clin Pathol* 2010; 63:379-386.
34. Counts D, Varma SK: Hypothyroidism in children. *Pediatr Rev* 2009; 30:251-258.
35. Toso A, Colombani F, Averono G, Aluffi P, Pia F: Lingual thyroid causing dysphagia and dyspnoea. Case reports and review of the literature. *Acta Otorhinolaryngol Ital* 2009; 29:213-217.
36. Lazarus JH: Lithium and thyroid. *Best Pract Res Clin Endocrinol Metab* 2009; 23:723-733.
37. Padmanabhan H: Amiodarone and thyroid dysfunction. *South Med J* 2010; 103:922-930.
38. Fitzpatrick DL, Russell MA: Diagnosis and management of thyroid disease in pregnancy. *Obstet Gynecol Clin North Am* 2010; 37:173-193.
39. Haddow JE, et al: Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 1999; 341:549-555.
40. Gyamfi C, Wapner RJ, D'Alton ME: Thyroid dysfunction in pregnancy: The basic science and clinical evidence surrounding the controversy in management. *Obstet Gynecol* 2009; 113:702-707.
41. Gharib H, Cobin RH, Dickey RA: American Association of Clinical Endocrinologists Position Statement. Subclinical hypothyroidism during pregnancy. *Endocr Pract* 1999; 5:367-368.
42. Huber G, et al: Prospective study of the spontaneous course of subclinical hypothyroidism: Prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. *J Clin Endocrinol Metab* 2002; 87:3221-3226.
43. Diez JJ, Iglesias P: Spontaneous subclinical hypothyroidism in patients older than 55 years: An analysis of natural course and risk factors for the development of overt thyroid failure. *J Clin Endocrinol Metab* 2004; 89:4890-4897.
44. Neves C, Alves M, Medina JL, Delgado JL: Thyroid diseases, dyslipidemia and cardiovascular pathology. *Rev Port Cardiol* 2008; 27:1211-1236.
45. Stabouli S, Papakatsika S, Kotsis V: Hypothyroidism and hypertension. *Expert Rev Cardiovasc Ther* 2010; 8:1559-1565.
46. Galli E, Pingitore A, Iervasi G: The role of thyroid hormone in the pathophysiology of heart failure: Clinical evidence. *Heart Fail Rev* 2010; 15:155-169.
47. Ichiki T: Thyroid hormone and atherosclerosis. *Vascul Pharmacol* 2010; 52:151-156.
48. Jorde R, et al: Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. *J Clin Endocrinol Metab* 2006; 91:145-153.
49. Tan ZS, et al: Thyroid function and the risk of Alzheimer disease: The Framingham Study. *Arch Intern Med* 2008; 168:1514-1520.
50. Gogakos AI, Duncan Bassett JH, Williams GR: Thyroid and bone. *Arch Biochem Biophys* 2010; 503:129-136.
51. Okosieme OE, Marx H, Lazarus JH: Medical management of thyroid dysfunction in pregnancy and the postpartum. *Expert Opin Pharmacother* 2008; 9:2281-2293.
52. Fatourechi V: Subclinical hypothyroidism: An update for primary care physicians. *Mayo Clin Proc* 2009; 84:65-71.
53. Nygaard B, Jensen EW, Kvetny J, Jarlov A, Faber J: Effect of combination therapy with thyroxine (T_4) and 3,5,3′-triiodothyronine versus T_4 monotherapy in patients with hypothyroidism, a double-blind, randomised cross-over study. *Eur J Endocrinol* 2009; 161:895-902.
54. Bornstein SR: Predisposing factors for adrenal insufficiency. *N Engl J Med* 2009; 360:2328-2339.
55. Neary N, Nieman L: Adrenal insufficiency: Etiology, diagnosis and treatment. *Curr Opin Endocrinol Diabetes Obes* 2010; 17:217-223.
56. Streck WF, Lockwood DH: Pituitary adrenal recovery following short-term suppression with corticosteroids. *Am J Med* 1979; 66:910-914.
57. Lamberts SW, Bruining HA, de Jong FH: Corticosteroid therapy in severe illness. *N Engl J Med* 1997; 337:1285-1292.
58. Michalakis K, Ilias I: Medical management of adrenal disease: A narrative review. *Endocr Regul* 2009; 43:127-135.

www.ketabpezeshki.com 66485457-66963820

Chapter 129

Bacteria

Madonna Fernández-Frackelton

DIPHTHERIA

Perspective

Background

In the fifth century BC, Hippocrates provided the first clinical description of what is likely diphtheria, characterized by sore throat, membrane formation, and death through suffocation, but references to the disease date to ancient Syria and Egypt. Epidemics of "throat distemper" occurred throughout the 16th, 18th, and 19th centuries. In 1821, French physician Pierre Bretonneau named the condition *diphtherite,* from the Greek word for leather, to describe the characteristic pharyngeal membrane. Klebs observed the *Corynebacterium diphtheriae* microorganism on smears obtained from pharyngeal membranes in 1883, and 1 year later Löffler isolated the organisms in pure cultures. Löffler subsequently demonstrated that diphtheria is a localized infection and postulated that an elaborated toxin caused its systemic effects. In 1888 Roux and Yersin demonstrated that bacteria-free filtrates of diphtheria culture were able to kill guinea pigs.[1]

In 1890, von Behring and Kitasato first demonstrated diphtheria immunization with a heat- and formalin-treated toxin to make toxoid. One year later they administered the first dose of antitoxin to a human with diphtheria. Schick developed the skin test for diphtheria immunity in 1913. During the 1930s and 1940s, toxoid immunization was routinely used. In the 1950s, Freeman found that only bacteria infected with the B phage produced toxin. Subsequent studies elucidated the toxin genome and the mechanism of toxin activity at the cellular level.[1]

Epidemiology

Humans are the only known reservoir for *C. diphtheriae.* Spread is primarily by person-to-person contact through respiratory droplets or by direct contact with skin lesion exudates. Transmission is associated with crowded living conditions. Individuals may spread the disease when they are actively ill, in the convalescent stage after acute illness, or as asymptomatic carriers. Fomites and foods have occasionally been implicated but do not represent a major route of transmission.[2]

Between 1991 and 1996 the first large-scale epidemic of diphtheria in an industrialized country in three decades occurred in the newly independent states of the former Soviet Union, where the disease had previously been well controlled. During the peak of the epidemic, more than 98,000 cases and 3400 deaths were reported. Several factors contributed to this outbreak, including (1) decreased childhood immunity due to vaccine supply interruption and administration of adult-formulation tetanus-diphtheria toxoids (Td) to children, (2) increased adult susceptibility due to waning immunity, (3) poor socioeconomic conditions and increased population movement, and (4) resurgence of more toxigenic strains of diphtheria.[3] Diphtheria remains endemic in many parts of the world and continues to cause sporadic cases and outbreaks.[2]

Immunization against diphtheria is highly effective (Fig. 129-1). Before widespread immunization programs in the United States, the incidence of diphtheria was in excess of 100 cases per 100,000 population, and the disease predominantly affected children. During this time, 80% of people acquired natural immunity to diphtheria by the age of 15 years, and recurrent exposure to toxigenic strains of the bacteria acted as a booster. Because childhood immunization nearly eliminates these toxigenic strains in a population, adult immunity wanes. Thus more adults in industrialized nations are susceptible to diphtheria.[4] By the 1980s the Centers for Disease Control and Prevention (CDC) reported only 0 to 5 cases per year nationwide. Currently, sporadic cases occur primarily in adults, many of whom are not adequately immunized.[3] Three urban outbreaks of predominantly cutaneous diphtheria occurred in Seattle between 1972 and 1982 among a population of urban alcohol abusers. Outbreaks are associated with poor hygiene, crowding, underlying skin disease, contaminated fomites, pyoderma, and the appearance of new *C. diphtheriae* strains.[1] Even in industrialized nations in which childhood vaccination rates are high, more than 50% of adults older than 40 years lack protective antibodies.[4] The ease of international travel and the epidemic in eastern Europe in the 1990s underscore the importance of aggressive continuation of childhood immunizations and reimmunization of adults.

Principles of Disease

Etiology

Diphtheria is caused by *C. diphtheriae,* an unencapsulated, nonmotile, gram-positive bacillus named for its shape (*korynee,* for "club") and for its characteristic clinical presentation (*diphtheria,* for "leather hide," referring to the appearance of the leathery pharyngeal membrane). When they are viewed on stained smears, the bacteria look like Chinese characters.[1]

Infection by *C. diphtheriae* can occur at various sites of the respiratory tract or the skin. Respiratory diphtheria includes faucial (pharyngeal or tonsillar), nasal, and laryngeal (tracheobronchial) types, named for the primary location of infection. Cutaneous diphtheria can occur as a primary skin infection or as a secondary infection of a preexisting wound.[1]

www.ketabpezeshki.com 66485457-66963820

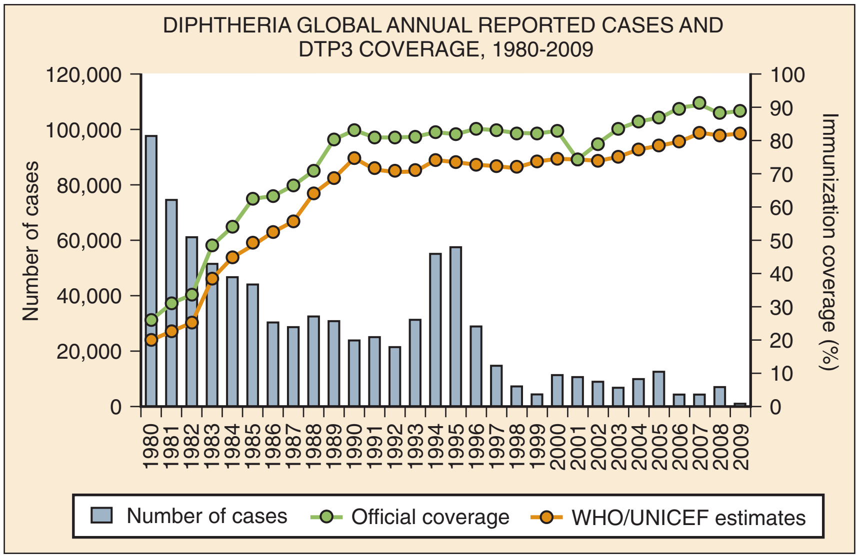


Figure 129-1. Global annual reported cases of diphtheria compared with percentage of immunization coverage. *DTP3,* third dose of diphtheria-tetanus-pertussis vaccine. (From World Health Organization, Department of Immunization, Vaccines and Biologicals: WHO Vaccine-Preventable Diseases: Monitoring System—2010 Global Summary. Geneva, World Health Organization, 2010.)

Pathophysiology

The *C. diphtheriae* bacterium produces an exotoxin that contributes to formation of the diphtheritic membrane and is responsible for the systemic effects of infection. The exotoxin is a 62,000-dalton polypeptide produced by bacterial strains lysogenized by the corynephage B tox$^+$.[1,5] The exotoxin inhibits cellular protein synthesis. Circulating exotoxin most profoundly affects the nervous system, heart, and kidneys.[1] The degree of local and systemic toxicity depends on the location and extent of membrane formation. Pharyngeal diphtheria generally has the greatest toxicity and cutaneous diphtheria the least.

The diphtheritic membrane forms as a result of necrosis caused by the local effects of the exotoxin. The membrane is composed of leukocytes, erythrocytes, fibrin, epithelial cells, and bacteria. Initially, the pharynx appears erythematous, but as necrosis occurs, grayish white patches appear and eventually coalesce. The membrane is accompanied by surrounding edema and cervical adenitis. The initial grayish white, filmy appearance changes to a thick, grayish black membrane with sharply defined borders. This membrane adheres to the underlying tissue, and bleeding occurs if removal is attempted.[1]

Systemic effects of diphtheria infection are caused by the circulating exotoxin's action primarily on the cardiovascular and nervous systems. The exotoxin disrupts cellular protein synthesis and produces a peripheral neuropathy manifested by muscle weakness. About 5% of all patients with symptomatic respiratory infection will have polyneuritis, but 75% of patients with severe disease have some form of neuropathy.[6] The muscles of the palate are usually the first to become paralyzed. Less commonly, other cranial nerves, peripheral nerves, and the spinal cord are affected. Degenerative lesions develop in the dorsal root and ventral horn ganglia of the spinal cord and in cranial nerve nuclei. Cortical cells are spared. Proximal muscle groups are affected first. In severe cases, paralysis may develop in the first few days of illness. In general, the paralysis does not last more than 10 days, and complete recovery during a longer time is the rule.[1]

The extent of cardiac complications correlates with the degree of local infection and membrane formation. Signs of myocardial dysfunction usually appear 1 to 2 weeks after the onset of illness. In more severe cases, cardiac symptoms arise earlier in the course of the illness. The exotoxin directly damages myocardial cells, producing myocarditis. Electrocardiographic changes suggestive of myocarditis occur in up to two thirds of patients, but clinical manifestations of myocarditis are less common (10-25%).[1]

Clinical Features

Symptoms and Signs

The average incubation period of respiratory tract diphtheria is 2 to 4 days but may range from 1 to 8 days. Signs and symptoms are often indistinguishable from those of other upper respiratory tract infections. In a series of 676 patients, fever and sore throat were the most frequent presenting complaints (79% and 69%, respectively). Weakness (42%), dysphagia (35%), headache (20%), change of voice (15%), and loss of appetite (10%) were also common. Cough, shortness of breath, nasal discharge, and neck edema occurred in less than 10% of patients. Fever, although common, is usually low grade. Cervical adenopathy is present in approximately one third of patients, and a diphtheritic membrane is observed in more than half of all patients. Of note, however, one report indicated that shortness of breath and neck edema were present in approximately 40% of patients who died of the disease.[6]

In patients with faucial diphtheria, the extent of the membrane usually parallels the clinical toxicity. If the membrane is limited to the tonsils, the disease may be mild; if the membrane covers the entire pharynx, the onset of illness is usually abrupt and the disease severe. Swelling of the cervical lymph nodes and infiltration of tissues of the neck may be so extensive that the patient has a "bull-neck" appearance. Patients with this form of "malignant diphtheria" usually have high fever, severe muscle weakness, vomiting, diarrhea, restlessness, and delirium.[1,6,7] Death occurs from respiratory tract obstruction or cardiac failure from myocarditis. Nasal diphtheria arises with a unilateral or bilateral serous or serosanguineous discharge from the nose. A diphtheritic membrane may be visible. These patients do not usually have constitutional symptoms. Treatment is important to prevent a persistent carrier state. Laryngeal (tracheobronchial) diphtheria may begin in the larynx or spread downward from a more cephalad primary site. Respiratory tract edema with subsequent upper airway obstruction may develop.

www.ketabpezeshki.com 66485457-66963820

Patients with cutaneous diphtheria generally do not display systemic toxicity. The skin characteristically has an ulcer with a grayish membrane. Wounds from which *C. diphtheriae* is cultured are clinically indistinguishable from other chronic skin conditions.[1]

Complications

The most serious complications of diphtheria are airway obstruction (resulting from membrane formation and edema), congestive heart failure, cardiac conduction disturbances, and muscle paralysis. Mortality in two large series ranged from 2 to 3% overall but was up to 7% in patients with myocarditis and 26% in patients with the malignant form of the disease (with neck swelling).[7] Unimmunized and underimmunized children requiring intensive care have higher mortality rates (78%) from myocarditis and often develop renal failure.[8] Although systemic infection is rare, endocarditis, mycotic aneurysms, osteomyelitis, and septic arthritis have all been described in immunocompromised hosts.[1]

Diagnostic Strategies

When *C. diphtheriae* is suggested, the laboratory should be notified because routine cultures do not identify the organism. Throat or nasopharyngeal swabs should be obtained for respiratory diphtheria, and if it is present, membranous material should be examined. For cutaneous infections, samples should be obtained from skin lesions. Specimens should be collected before antibiotic therapy is initiated and should be transported to the laboratory immediately for rapid inoculation onto tellurite (Tinsdale's) or Löffler's selective culture medium.[1] Immunofluorescent staining of a 4-hour culture may provide a rapid diagnosis, but direct staining is frequently unreliable. Definitive identification is made by use of a combination of colony morphology, microscopic appearance, and fermentation reactions.[1] *C. diphtheriae* isolates should be tested for the production of toxin. The Elek immunoprecipitation test for toxin A is technically demanding and subject to misinterpretation by inexperienced users. Polymerase chain reaction (PCR), which is more reliable but not as readily available, can be used to detect the diphtheria toxin structural gene. Newer methods that rapidly detect the toxin by mass spectrometry are not readily available but may be used in the future.[9] A positive culture for group A beta-hemolytic streptococcus does not exclude diphtheria as a pathogen because up to 30% of patients with diphtheria test positive for streptococcal coinfection or carrier state.

Several laboratory abnormalities, such as leukocytosis, mild thrombocytopenia, and proteinuria, are common but are neither sensitive nor specific for diphtheria. Electrocardiographic changes are nonspecific and include ST-T wave changes, varying degrees of atrioventricular block, and dysrhythmias. An electrocardiogram may be normal even in the presence of myocarditis. An echocardiogram may show dilated or hypertrophic cardiomyopathy. Cardiac enzymes may be elevated, and serum troponin levels correlate with the severity of myocarditis.[10]

Differential Considerations

In the absence of a diphtheritic membrane, it may be difficult to differentiate respiratory diphtheria from many other respiratory conditions, especially in the early phase of infection (Box 129-1). In general, the diphtheritic membrane is darker, grayer, more fibrous, and more firmly attached to the underlying tissues than in other conditions that have a membrane-like appearance. Vincent's angina frequently involves the gingivae, which are unaffected in diphtheria. Acute bacterial epiglottitis generally has a much more rapid onset than diphtheria, and indirect laryngoscopy reveals an erythematous, edematous epiglottis without membrane formation.[1]

Box 129-1 Differential Diagnosis of Respiratory Diphtheria

- Streptococcal or viral pharyngitis
- Tonsillitis
- Vincent's angina
- Acute epiglottitis
- Mononucleosis
- Laryngitis
- Bronchitis
- Tracheitis
- Monilial infection (thrush)
- Rhinitis

Cutaneous diphtheria is difficult to differentiate from other acute and chronic ulcerative skin lesions. *C. diphtheriae* can secondarily infect any of these lesions, especially in high-risk patients such as alcoholic, socioeconomically disadvantaged, and unimmunized or underimmunized people.

Management

Patients with clinical evidence of diphtheria should be placed in respiratory isolation and treated presumptively for *C. diphtheriae* infection. The goals of therapy are to protect the airway, to limit the effects of already produced toxin, and to eliminate future toxin production by terminating the growth of *C. diphtheriae*. Although the likelihood for the development of airway obstruction from diphtheria is remote for a patient in the United States, the management is identical to that for other forms of airway obstruction. Bronchodilators may be useful in symptomatic patients.[10] Patients may be dehydrated from fever and decreased oral intake related to dysphagia or neurologic impairment. Fluid resuscitation should be undertaken cautiously as the toxin's effect on the myocardium may result in congestive heart failure.[1,10]

Equine serum diphtheria antitoxin (DAT) should be administered promptly after the clinical diagnosis of respiratory diphtheria is made and before laboratory confirmation.[10-12] DAT is not licensed by the Food and Drug Administration (FDA) for use in the United States. The CDC is authorized to distribute DAT to physicians as an investigational new drug. DAT can be obtained by contacting the CDC Emergency Operations Center at 770-488-7100. The diphtheria duty officer can also be contacted at 404-639-3158 during duty hours.[12] The size and location of the membrane, the duration of illness, and the patient's overall degree of toxicity determine the dosage of antitoxin. The CDC recommends 20,000 to 40,000 units for pharyngeal or laryngeal involvement of 48 hours' duration, 40,000 to 60,000 units for nasopharyngeal lesions, and 80,000 to 120,000 units for systemic disease of 3 days' duration or more or for diffuse swelling of the neck.[12] After conjunctival or intradermal sensitivity skin testing, the antitoxin is administered intravenously. If the patient exhibits sensitivity to the antitoxin, desensitization should be performed. Active immunization against diphtheria should also be initiated because clinical infection does not necessarily confer immunity.[10]

Antibiotics are beneficial in preventing growth and spread of the organism but are no substitute for antitoxin. Erythromycin 30 to 50 mg/kg/day (up to 2 g) intravenously (IV) or orally in divided doses, aqueous crystalline penicillin 100,000 to 150,000 units/kg/day in four divided doses intramuscularly (IM), and procaine penicillin 25,000 to 50,000 units/kg/day in two divided doses for 14 days given IM are acceptable alternatives.[10] Treatment failures are slightly more common with penicillin than with erythromycin. The newer generation macrolides (azithromycin and

www.ketabpezeshki.com 66485457-66963820

clarithromycin) have activity similar to that of erythromycin in vitro and may result in better compliance. These agents have not yet been adequately tested in clinical disease. An equivalent daily oral therapy may be substituted when the patient is able to swallow. Negative cultures should be documented after treatment.[10]

Myocarditis and neuritis are treated with supportive care and careful monitoring. Patients with electrocardiographic changes of myocarditis have three to four times the mortality rate of those with normal electrocardiograms. The mortality rate for patients with left bundle branch block and atrioventricular block is 60 to 90%. Serial tracings are recommended, and survivors may have permanent conduction abnormalities. No data support the use of steroids.

Cutaneous lesions should be débrided of necrotic tissue and cleansed vigorously. A course of antibiotics is recommended, but the administration of antitoxin for cutaneous lesions is of questionable value. Some experts recommend 20,000 to 40,000 units of antitoxin, but few data support its use in this setting.[1,10]

Carriers of *C. diphtheriae* should receive oral penicillin G or erythromycin for 7 days or intramuscular benzathine penicillin (600,000 units for those weighing less than 30 kg and 1,200,000 units for those weighing more than 30 kg). Active immunization should also be provided to unimmunized and partially immunized carriers. After 2 weeks of therapy is completed, cultures should be obtained; if cultures are positive, erythromycin therapy should be given for 10 additional days.[1]

Individuals who have been in close contact with infected patients should have culture specimens taken, and the patient should be kept under surveillance for 7 days. Previously immunized close contacts should receive a booster of diphtheria toxoid if the last booster was more than 5 years earlier. The vaccine should be diphtheria, tetanus, and acellular pertussis (DTaP), diphtheria-tetanus (DT), or tetanus-diphtheria with a lower dose of diphtheria toxoid (Td) as appropriate for age according to the recommended immunization schedule. Close contacts who are not immunized or whose immunization status is unknown should receive the same antimicrobial therapy as carriers (as previously described), have culture specimens taken before and after therapy, and have active immunization initiated. Close contacts who cannot be kept under surveillance should receive benzathine penicillin intramuscularly to ensure compliance and a Td booster (appropriate for age and immunization history). Some practitioners treat this group with 5000 to 10,000 units of antitoxin intramuscularly (at a site separate from the toxoid booster) after sensitivity testing. This is generally not recommended, however, because of the risk of horse serum allergy.[12]

A universal program of primary immunization along with regular diphtheria boosters every 10 years is the most effective method for control of diphtheria. For this reason, emergency physicians should routinely administer age-appropriate tetanus and diphtheria toxoids as part of wound management.

Disposition

All patients with possible pharyngeal diphtheria should be isolated and admitted. A monitored setting is recommended for the early detection of arrhythmias. A cardiologist should be consulted for patients with evidence of myocarditis. The CDC should be contacted for all suggested or proven cases of diphtheria.

PERTUSSIS

Perspective

Background

Pertussis is an acute respiratory disease that was first described in 1578 when an epidemic swept through Paris. The name *pertussis* was first used by Sydenham in 1670 when he described the illness in infants. Pertussis literally means "violent cough," which is the hallmark of the disease. In China it is known as "the cough of 100 days." It is also called whooping cough because the severe episodes of coughing are followed by forceful inspiration, which creates the characteristic whooping sound. The causative organism was identified in 1906 by Bordet and Gengou.[13] In the prevaccination era, pertussis was a major cause of mortality among infants and children in the United States. A vaccine was developed in the 1940s, but pertussis still remains a significant cause of morbidity and mortality in the United States and worldwide.

Epidemiology

Pertussis is a localized respiratory illness transmitted by aerosolized droplets. It is highly contagious, with attack rates greater than 50% in adults exposed more than 12 years after completion of a vaccination series and up to 90% in susceptible individuals with a household exposure.[14] The average incubation period is 7 to 10 days but may range from less than 1 week to 3 weeks. Neither vaccination nor prior infection confers lifelong immunity.

Pertussis remains prevalent worldwide, with 106,207 cases reported to the World Health Organization in 2009 (Fig. 129-2A). In the United States, annual pertussis rates declined sharply after the introduction of the vaccine and reached a nadir of 1010 cases in 1976. Since then, there has been a steady increase in the incidence of pertussis, with 11,647 cases reported in 2003 and 25,616 in 2005 (Fig. 129-2B).[14] Waning immunity in the adult population and increased reporting of adult cases may be contributing factors. A 1991 report found evidence of a causal relationship between the vaccine and acute encephalopathy. Although there appears to be no causal relationship between the vaccine and long-term neurologic complications, the report resulted in a decline in the use of the whole-cell pertussis vaccine. The acellular pertussis vaccine has been approved in the United States since 1991 for persons 15 months to 64 years and since 1997 for infants.[14]

Although pertussis can occur at any age, it is predominantly a pediatric and adolescent illness. The age-specific attack rates are highest in children younger than 1 year who have not yet received the entire vaccine series. There appears to be a seasonal variation; 50% of cases in the United States occur from June through September.

Principles of Disease

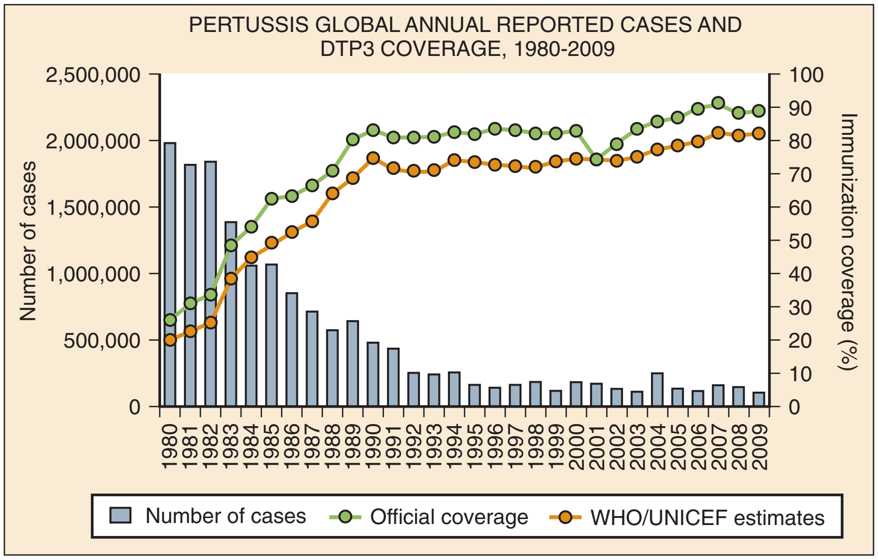
Etiology

Pertussis is caused by organisms of the *Bordetella* genus, which are small, aerobic, gram-negative coccobacilli that occur singly or in pairs. *Bordetella pertussis* and *Bordetella parapertussis* are primarily responsible for disease in humans. The organisms are fastidious and require nicotinamide and an optimal temperature of 35 to 37° C to grow. *Bordetella bronchiseptica,* a flagellated, motile organism, causes illness in animals, including kennel cough, and may rarely cause respiratory infection in immunocompromised humans.[13]

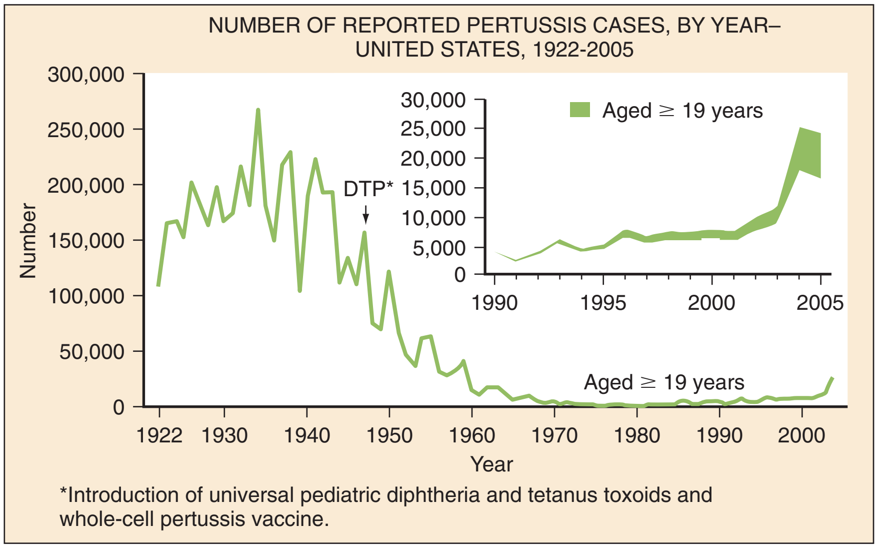
Pathophysiology

The *Bordetella* organism adheres preferentially to ciliated respiratory epithelial cells. *B. pertussis* does not invade beyond the submucosal layer in the respiratory tract and is almost never recovered in the bloodstream. The organism elaborates several toxins that act locally and systemically. These toxins include pertussis toxin, dermonecrotic toxin, adenylate cyclase toxin, and tracheal cytotoxin.[13]

www.ketabpezeshki.com 66485457-66963820



A



B

Figure 129-2. **A,** Global annual reported cases of pertussis compared with percentage of immunization coverage. *DTP3,* third dose of diphtheria-tetanus-pertussis vaccine. (From World Health Organization, Department of Immunization, Vaccines and Biologicals: WHO Vaccine-Preventable Diseases: Monitoring System—2010 Global Summary. Geneva, World Health Organization, 2010.) **B,** Incidence of reported pertussis cases in the United States by year. (From Centers for Disease Control and Prevention National Notifiable Diseases Surveillance System. Reproduced from MMWR Recomm Rep 55:1-33, 2006.)

Local tissue damage consists of inflammatory changes in the mucosal lining of the respiratory tract, primarily congestion and cellular infiltration with lymphocytes and granulocytes. As the infection progresses, secondary pneumonia or otitis media may occur. Systemic effects of pertussis toxin include sensitization to the lethal effects of histamine and increased secretion of insulin. This hyperinsulinemia can cause hypoglycemia, particularly in young infants.[13]

Clinical Features

Symptoms and Signs

Pertussis arises in three distinct sequential clinical stages: the *catarrhal phase,* the *paroxysmal phase,* and the *convalescent phase.* The catarrhal or prodromal phase begins after an incubation period of approximately 7 to 10 weeks and lasts approximately 1 to 2 weeks. Infectivity is greatest during the catarrhal phase, when the disease is clinically indistinguishable from other upper respiratory tract infections. Signs and symptoms include rhinorrhea, low-grade fever, malaise, and conjunctival injection, which are clinically indistinguishable from a common upper respiratory tract infection. A dry cough usually begins at the end of the catarrhal phase.[13]

The paroxysmal phase begins as fever subsides and cough increases and lasts 2 to 4 weeks. Paroxysms of staccato coughing occur 40 to 50 times per day. The patient coughs repeatedly in short exhalations, followed by a single, sudden, forceful inhalation that produces the characteristic "whoop." Only one third of adults with pertussis develop this whoop, and it is rare in young infants, who may present with apneic episodes and no other symptoms. Paroxysms may be spontaneous, occur more frequently at night,

www.ketabpezeshki.com 66485457-66963820

or be precipitated by noise or cold. During the paroxysm, the patient may exhibit cyanosis, diaphoresis, protrusion of the tongue, salivation, and lacrimation. Post-tussive vomiting, syncope, and brief episodes of apnea may occur. Infants may be physically exhausted after a typical paroxysm. Between episodes of coughing, patients do not appear acutely ill.[13]

The convalescent phase is characterized by a residual cough that lasts several weeks to months. Paroxysms of coughing may be triggered by an unrelated upper respiratory infection or by exposure to a respiratory irritant. This recurrence of coughing does not represent recurrence of pertussis infection.

Atypical presentations may occur in young and preterm infants. Fever is usually not present in uncomplicated neonatal pertussis. Tachypnea, apnea, and cyanotic and bradycardic episodes may be the predominant symptoms.[15] Older children and adults who have partial protection from vaccination or previous illness may have a long-lasting intractable dry cough that is frequently misdiagnosed as bronchitis. Post-tussive vomiting in adults is highly suggestive of pertussis.[13]

Physical examination findings are nonspecific. Tachypnea is variably present and may be related to the degree of pulmonary involvement. Low-grade fever is common during the catarrhal phase, as are conjunctival injection and rhinorrhea. The presence of fever during other stages of illness suggests secondary infection. Petechiae above the nipple line, subconjunctival hemorrhages, pneumothorax, and epistaxis may occur because of increased intrathoracic pressure during coughing paroxysms.[13,15] Chest examination may reveal rhonchi or clear lung fields; the presence of rales suggests pneumonia.

Complications

The major complications of pertussis are pneumonia superinfection, central nervous system (CNS) sequelae, otitis media, and complications related to the paroxysm of coughing. Pneumonia complicating pertussis is a leading cause of death, especially in infants and young children.[13-18] Aspiration of gastric contents and respiratory secretions may occur during the paroxysm of coughing, whooping, and vomiting. Secondary pulmonary infection may also be a consequence of decreased respiratory tract clearance related to the actions of the *Bordetella* organism and its toxins on bronchial and lung mucosa. Bacterial (*Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae,* and *Staphylococcus aureus*) and viral (respiratory syncytial virus, cytomegalovirus, and adenovirus) superinfections can complicate pertussis infections. A fever during the paroxysmal phase should alert the physician to a possible superinfection.

CNS complications include seizures and encephalopathy in about 1%.[19] The causes are unclear but may include hypoxia, hypoglycemia, cerebral petechia, effects of a toxin, or secondary infection by neurotropic viruses or bacteria. CNS hemorrhages may occur as a consequence of the increased cerebrovascular pressures generated during the paroxysm of coughing. Sudden increases in intrathoracic and intra-abdominal pressures can result in several other complications (Box 129-2).[13-19]

Box 129-2 Pertussis Complications

Periorbital edema	Pneumothorax
Subconjunctival hemorrhage	Pneumomediastinum
Petechiae	Diaphragmatic rupture
Epistaxis	Umbilical and inguinal hernias
Hemoptysis	Rectal prolapse
Subcutaneous emphysema	

Bradycardia, hypotension, and cardiac arrest can occur in neonates and young infants with pertussis. Severe pulmonary hypertension has increasingly been recognized in this age group and can lead to systemic hypotension, worsening hypoxia, and increased mortality.[15,16] Intensive care monitoring is recommended for these patients, regardless of how well they may appear on admission.

Diagnostic Strategies

The diagnosis of pertussis should be entertained in any patient with prolonged cough with paroxysms, whoops, or post-tussive emesis, regardless of previous vaccination status. Up to 25% of adults in the United States who have a prolonged cough have serologic evidence of pertussis.[13]

Ancillary studies are of limited value in the emergency department. During the late catarrhal and early paroxysmal phases, a marked leukocytosis and a characteristic lymphocytosis are often present. The white blood cell (WBC) count of 25,000 to 50,000/mL is not uncommon and may exceed 100,000/mL in infants.[17] Adults with pertussis frequently do not have the characteristic leukocytosis and lymphocytosis, and some infants and immunocompromised hosts may not be able to mount this response. The chest radiograph may show peribronchial thickening, atelectasis, or pulmonary consolidation.[18]

Laboratory confirmation of the diagnosis is made by nasopharyngeal culture and PCR, if both are available; sputum and throat swabs are inadequate.[13] The *Bordetella* organism is fastidious, and isolation requires a nicotinamide or Bordet-Gengou medium impregnated with antibiotics to reduce overgrowth of competing bacteria. The slow-growing hemolytic colonies of *B. pertussis* take 3 to 7 days to appear. A synthetic culture medium is also available. The sensitivity of pertussis cultures is only 15 to 80% and drops to only 1 to 3% three weeks after the onset of cough. Direct fluorescent antibody techniques are no longer recommended to identify *B. pertussis.* Adults generally come to medical attention late in the disease, at which time cultures are rarely positive (3.6%). PCR is much more likely to identify the organism but has a high false-positive rate. Most laboratories use enzyme-linked immunosorbent assay, which rises 2 to 3 weeks after infection or primary immunization. Paired serologic tests showing a twofold increase are the "gold standard" for diagnosis.[13]

Differential Considerations

The differential diagnosis includes acute viral upper respiratory tract infection, pneumonia, bronchiolitis, cystic fibrosis, tuberculosis, exacerbation of chronic obstructive pulmonary disease, and foreign body aspiration. The marked leukocytosis may suggest the diagnosis of leukemia.

Management

Acute Treatment

Treatment of pertussis is primarily supportive and includes oxygen, frequent suctioning, appropriate hydration, parenteral nutrition if necessary, and avoidance of respiratory irritants. Patients with suggested pertussis and associated pneumonia, hypoxia, or CNS complications or those experiencing severe paroxysms should also be hospitalized. Children younger than 1 year should also be admitted because they are not yet fully immunized and have the greatest risk for morbidity and mortality. Neonates with pertussis should be admitted to an intensive care unit (ICU) as apnea and significant cardiac complications can occur without warning.[15-17]

Antibiotic treatment does not appear to significantly reduce the severity or duration of illness when it is started in the

www.ketabpezeshki.com 66485457-66963820

paroxysmal phase and may have only a minimal effect in the catarrhal phase. The primary goal of antibiotic therapy is to decrease infectivity and carriage. Erythromycin estolate ester is the antibiotic of choice at 40 to 50 mg/kg/day (maximum 2 g/day) in two or three divided doses for 14 days.[13,18-20] Azithromycin (10 mg/kg on day 1, followed by 5 mg/kg on days 2-5), clarithromycin (15 mg/kg/day in two divided doses), and a 7-day course of erythromycin estolate ester are effective alternatives for patients who do not tolerate 14 days of erythromycin.[13,18,19] Trimethoprim-sulfamethoxazole (8 mg/kg/day of trimethoprim) is an alternative for macrolide-allergic patients, but efficacy is unproven. Patients should be considered infectious for 3 weeks after the onset of the paroxysmal phase or until at least 5 days after antibiotics are started.[13] Strict droplet isolation is recommended during this period.

Corticosteroids, especially in young critically ill infants, may reduce the severity and course of illness, but effectiveness is not well established. Beta$_2$-adrenergic agonists do not reduce the frequency or severity of paroxysmal coughing episodes but may be helpful in patients with reactive airway disease. Trials with pertussis immune globulin are limited and to date show no proven benefit.[21] Standard cough suppressants and antihistamines are ineffective.

Postexposure prophylaxis with erythromycin as described previously should be considered for infants younger than 6 months who are household contacts of infected patients.[13] Erythromycin may also be prescribed for any unimmunized person or partially immunized infant with a history of significant exposure to the index case. There is no clinical benefit of prophylaxis for exposed patients older than 6 months, and medication side effects are common.[13,20]

Vaccination

Whole-cell and acellular pertussis vaccines are distributed in combination with diphtheria and tetanus toxoids as DPT and DTaP, respectively. The acellular pertussis vaccines contain inactivated pertussis toxin and one or more other bacterial components. The acellular vaccines are slightly less effective than the whole-cell vaccine but have fewer reported adverse reactions.[22,23] Most recipients have fever, irritability, behavioral changes, and local discomfort at the site of inoculation. Moderately severe reactions are uncommon but include fever with temperature above 40° C, persistent crying, high-pitched crying, and seizures. Severe neurologic complications (prolonged seizures and encephalopathy) occur rarely but led to decreased use of the whole-cell form of the vaccine and the development of DTaP.[23] DTaP has replaced DPT for childhood immunizations, and the whole-cell pertussis vaccine is recommended for use in the United States only when the acellular vaccine is not available.[23] Tdap (with reduced diphtheria toxoid and acellular pertussis) is indicated as a booster vaccine in persons aged 10 to 64 years. There are no Tdap vaccines currently licensed for use in persons older than 65 years. The CDC Advisory Committee on Immunization Practices (ACIP) does, however, recommend that persons older than 65 years who have never received Tdap and anticipate close contact with infants younger than 12 months receive a single dose of Tdap, regardless of interval since last Td vaccination.[24]

Pertussis immunity wanes significantly 3 to 8 years after immunization and 15 years after natural infection, causing an increasing incidence of the disease in people older than 15 years. The acellular pertussis vaccine is safe and effective in adolescents and adults, and routine booster immunization is currently recommended by the CDC ACIP for persons aged 11 to 18 years.[14] Not yet available, a nasal pertussis vaccine may more closely simulate natural infection with the potential of conferring longer immunity.[22]

TETANUS

Perspective

Background

Tetanus is a toxin-mediated disease characterized by severe uncontrolled skeletal muscle spasms. Involvement of the muscles of respiration leads to hypoventilation, hypoxia, and death. Dramatic descriptions of this disease date to ancient Egypt, when physicians recognized a frequent relationship between tissue injury and subsequent fatal spasm.[25]

In 1884, Carle and Rattone produced tetanus in rabbits by injecting material from an acne pustule that came from an infected human. In the same year, Nicolaier isolated the strychnine-like toxin from anaerobic soil bacteria. In 1889, Kitasato obtained pure cultures of spore-forming bacteria that caused tetanus on introduction into animals. One year later, Faber proved that tetanus is a toxin-mediated disease when he induced the illness by injecting animals with bacteria-free filtrates of *Clostridium tetani* cultures. In the 1890s, von Behring and Kitasato discovered tetanus antitoxin in the serum of immune animals and demonstrated its efficacy in preventing disease. Prophylactic injection of this antitoxin provided passive immunity to wounded soldiers during World War I. It was not until 1924 that an effective vaccine was developed by Descombey. Large-scale testing during World War II indicated that the tetanus toxoid confers a high degree of protection against disease.[25-27]

Epidemiology

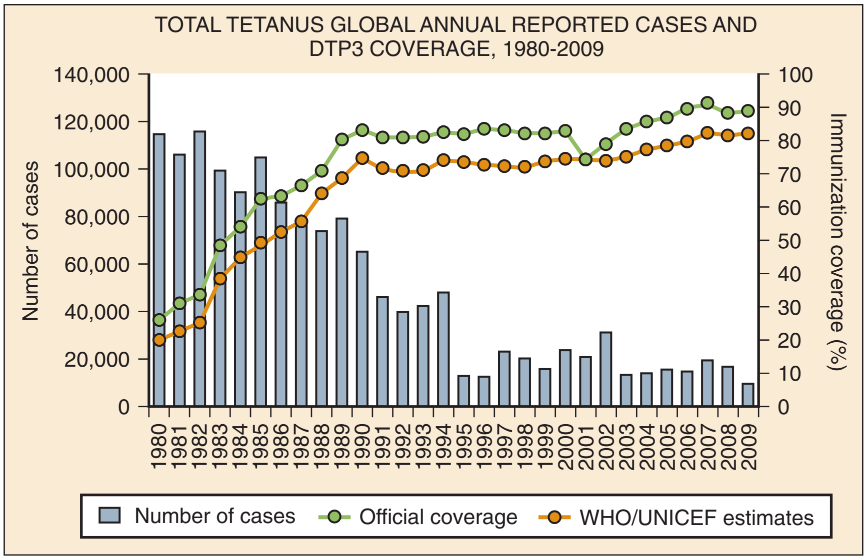
Despite the availability of an effective vaccine, tetanus remains endemic worldwide. It is more common in warm, damp climates and relatively rare in cold regions. The global annual incidence of reported cases of tetanus has declined steadily with the introduction of vaccination programs (Fig. 129-3A). The World Health Organization reported 9836 cases of tetanus in 2009, but it is estimated that 800,000 to 1 million unreported cases occur a year, with half occurring in neonates. Eighty percent of these cases occur in Africa and Southeast Asia because of low immunization rates and poor hygiene.[27]

Since the introduction of vaccination programs in the United States, the incidence of tetanus has steadily declined from 4 cases per million population in the 1940s to 0.095 case per million population in 2005 (Fig. 129-3B).[28] The highest incidence occurs in people older than 65 years (0.23 case per million population), and the incidence in Hispanic Americans is almost twice that in non-Hispanics.[28,29] Fifteen percent of cases occur in injection drug users. The overall case fatality rate is 18% but approaches 50% in patients older than 70 years (Fig. 129-4). Cases have been reported in patients who had been fully vaccinated, but in the eight patients from 1998 to 2000, no deaths occurred.[29]

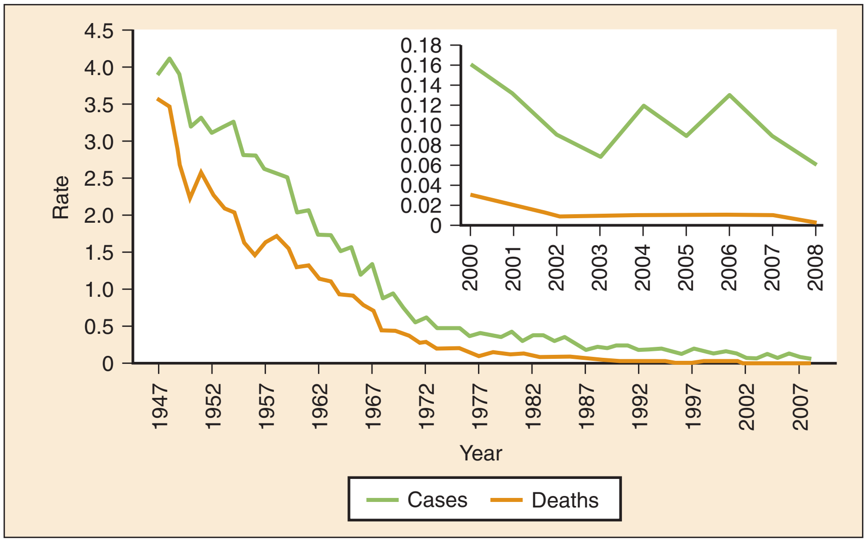
Tetanus typically occurs as a result of a deep penetrating wound. A history of injury is present in more than 70% of patients, but the injury may be trivial in 50% of patients and unapparent in up to 30% of patients.[25-29] The most common portals of entry for the organism are puncture wounds, lacerations, and abrasions. Tetanus has also been reported in association with chronic skin ulcers, abscesses, and otitis media as well as with foreign bodies, corneal abrasions, childbirth, and dental procedures.[26] Postoperative tetanus has been reported in patients who have undergone intestinal operations and abortions. In these cases the source of bacteria is probably endogenous as up to 10% of humans harbor *C. tetani* in the colon.

Inadequate primary immunization and waning immunity continue to be the primary risk factors for tetanus in the United States. As tetanus vaccination of children has improved, older people have accounted for an increasing percentage of reported cases.

www.ketabpezeshki.com 66485457-66963820



A



B

Figure 129-3. A, Global annual reported cases of tetanus compared with percentage of immunization coverage. *DTP3,* third dose of diphtheria-tetanus-pertussis vaccine. (From World Health Organization, Department of Immunization, Vaccines and Biologicals: WHO Vaccine-Preventable Diseases: Monitoring System—2010 Global Summary. Geneva, World Health Organization, 2010.) **B,** Incidence of reported tetanus cases in the United States by year. (From Centers for Disease Control and Prevention National Notifiable Diseases Surveillance System. Reproduced from MMWR Morb Mortal Wkly Rep 60:365-369, 2011.)

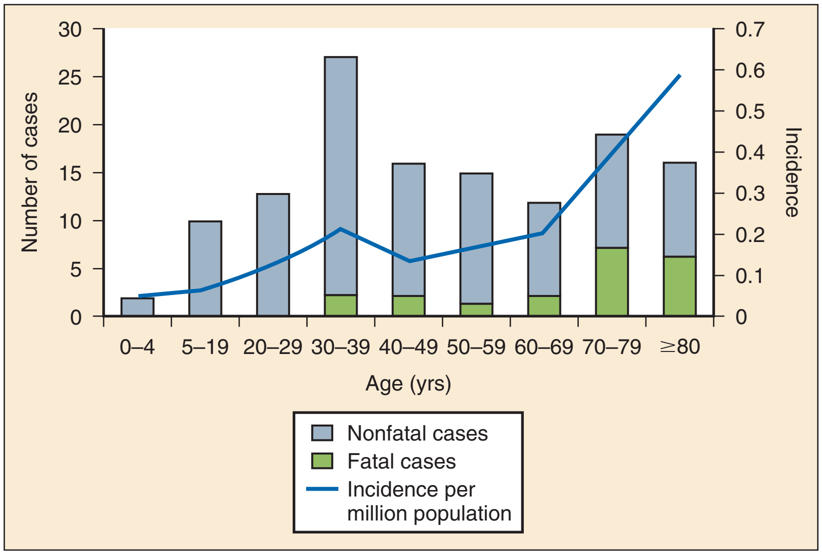


Figure 129-4. Incidence of and mortality from tetanus by age group in the United States, 1998-2000. (From Pascual FB, et al: Tetanus surveillance—United States, 1998-2000. MMWR Surveill Summ 52:1, 2003.)

www.ketabpezeshki.com 66485457-66963820

Etiology

C. tetani is a spore-forming, motile, slender, rod-shaped, obligate anaerobic bacillus. It stains gram positive in fresh culture but has a variable staining pattern in old cultures and tissue samples. The bacillus can form a single spherical terminal endospore that swells the end of the organism to produce a characteristic drumstick appearance. *C. tetani* is ubiquitous in soil and dust and is also found in the feces of animals and humans.[25] Mature bacilli are highly susceptible to heat and other adverse environmental conditions. Spores are resistant to heating and chemical disinfectants and can survive in soil for months to years. When they are introduced into a wound, spores may not germinate for weeks because of unfavorable tissue conditions. When injury favors anaerobic growth, the spores germinate into mature bacilli. Only these mature bacilli produce the tetanus toxin that causes clinical disease.[25-27]

Principles of Disease

C. tetani is a noninvasive organism. The development of clinical tetanus requires a portal of entry for the infecting spores as well as tissue conditions that promote germination and growth in an immunologically susceptible host. Tetanus-prone wounds are those with damaged or devitalized tissue, foreign bodies, or other bacteria. Under these conditions, *C. tetani* produces the neurotoxin that causes clinical illness. Germination and replication of *C. tetani* can occur without clinical signs of a local wound infection.

C. tetani produces the neurotoxin tetanospasmin (TS) at the site of tissue injury. TS first binds the motor nerve ending and then moves by retrograde axonal transport and trans-synaptic spread to the CNS.[30,31] It binds preferentially to inhibitory (GABAergic and glycinergic) neurons and blocks the presynaptic release of these neurotransmitters. Interneurons afferent to alpha motor neurons are affected first.[30] Without inhibitory control, the motor neurons undergo sustained excitatory discharge, resulting in the muscle spasm characteristic of tetanus.[26]

TS may also affect preganglionic sympathetic neurons and parasympathetic centers, resulting in autonomic nervous system dysfunction.[31,32] The clinical manifestations include dysrhythmias and wide fluctuations in blood pressure and heart rate. The binding of TS at the synapse is irreversible; recovery occurs only when a new axonal terminal is produced.[25]

Clinical Features

Symptoms and Signs

The incubation period for tetanus ranges from 1 day to several months. A shorter incubation period portends a worse prognosis.[26] The duration of the incubation period is not useful in making the diagnosis of tetanus because many patients have no history of an antecedent wound. Four types of clinical tetanus have been described.

Generalized Tetanus. Generalized tetanus is the most common form of the disease and results in spasms of agonist and antagonist muscle groups throughout the body. The classic initial presenting symptom of trismus (“lockjaw”) is caused by masseter muscle spasm and is present in 50 to 75% of patients. As the other facial muscles become involved, a characteristic sardonic smile (risus sardonicus) appears. Other early symptoms include irritability, weakness, myalgias, muscle cramps, dysphagia, hydrophobia, and drooling. As the disease progresses, generalized uncontrollable muscle spasms can occur spontaneously or as a result of minor stimuli, such as touch or noise. Spasms may result in vertebral and long bone fractures and tendon rupture. Opisthotonos is a prolonged tonic contraction that closely resembles decorticate posturing. Spasms of laryngeal and respiratory muscles can lead to ventilatory failure and death. Autonomic dysfunction is the major cause of death in patients who survive the acute phase and is manifested by tachycardia, hypertension, temperature elevation, cardiac dysrhythmias, and diaphoresis. The illness is progressive, with an increase in symptoms during the first 3 days, persistence of symptoms for 5 to 7 days, and reduction of spasms after 10 days. If the patient survives, recovery is complete after 4 weeks or more. Throughout the course of this horrific illness, patients remain completely lucid unless they are chemically sedated.[25-27]

Localized Tetanus. Localized tetanus is a form of the disease characterized by persistent muscle spasms close to the site of injury. Symptoms may be mild or severe, but mortality is lower than with generalized tetanus. Local tetanus may progress to generalized disease. This form of illness may probably reflect partial immunity to TS and may be present for weeks to months before resolution.[25]

Cephalic Tetanus. Cephalic tetanus is a rare variant of localized tetanus that results in cranial nerve palsies and muscle spasms. The palsies precede the spasm in 42% of cases, resulting in frequent misdiagnosis. The most commonly involved cranial nerve is the facial nerve (VII), mimicking Bell’s palsy. Most of these cases occur after facial trauma or otitis media. Patients have trismus and palsies of cranial nerve III, IV, VII, IX, X, or XII ipsilateral to the site of local infection. The clinical course is variable. In one third of cases, resolution of symptoms is complete. The remainder progress to generalized tetanus with an overall mortality rate of 15 to 30%.[25-29]

Neonatal Tetanus. Neonatal tetanus is generalized tetanus of the newborn and occurs almost exclusively in developing countries where maternal immunization is inadequate and contaminated material is used to cut and dress umbilical cords. Symptoms begin during the first week of life and include irritability and poor feeding. Mortality approaches 100% because of the high toxin load for body weight and inadequate medical support in developing countries. Even with limited resources, mortality can be reduced to less than 50% with basic medication and experienced medical and nursing personnel.[33] The CDC reported one case of neonatal tetanus in the United States between 1998 and 2000. The infant was born at home to an unimmunized mother. The umbilical cord had been treated with bentonite clay. The child was treated and recovered after 19 days of hospitalization.

Complications

Acute respiratory failure, the main cause of morbidity and mortality in tetanus, results from respiratory muscle spasms or laryngospasms and airway obstruction. If the patient survives the acute onset of illness and has adequate ventilatory support, autonomic dysfunction becomes the leading cause of death. Autonomic instability occurs several days after the onset of generalized spasms. Disinhibition of the sympathetic nervous system predominates and causes dysrhythmias, hypertension, myocarditis, and pulmonary edema.[34] Dysrhythmias and myocardial infarction are the most common fatal events during this phase.

Forceful tetanic muscle spasms can cause vertebral subluxations and fractures, long bone fractures, and shoulder and temporomandibular joint dislocations. Rhabdomyolysis occasionally occurs and can cause acute renal failure. Renal failure may also result from dehydration and sympathetic nervous system hyperactivity. Renal vein thrombosis may cause renal failure in neonatal tetanus.

Secondary infection may occur in the initial inoculating wound or as a complication arising from invasive treatment modalities, such as mechanical ventilation.[35] Hyperthermia may also result from muscle spasms and sympathetic hyperactivity. Prolonged

www.ketabpezeshki.com 66485457-66963820

immobility can lead to deep venous thrombosis and pulmonary embolism. Gastrointestinal complications include peptic ulcers, ileus, intestinal perforation, and constipation. The syndrome of inappropriate secretion of antidiuretic hormone occurs in a small number of patients. Hemolysis has also been reported.

Mortality is a function of the previous immunization status, incubation period, severity and rapidity of onset of symptoms, comorbid disease, age, and sophistication of medical treatment available. With appropriate intensive care treatment, elder patients may fare as well as their middle-aged counterparts.[36] Long-term physical complications in survivors are rare. The most common persistent problem may be psychological trauma related to the disease and its treatment.[25]

Diagnostic Strategies

The diagnosis of tetanus should be made on clinical grounds alone. Wound cultures for *C. tetani* are of little value as they are positive in only one third of cases. Even if a positive culture is obtained, it does not indicate whether the bacterium is a toxin-producing strain. There are no laboratory tests to confirm or to exclude the diagnosis of tetanus.[25] In 1990 the CDC adopted a clinical case definition for the public health surveillance of generalized tetanus: "acute onset of hypertonia or painful muscular contractions (usually of the muscles of the jaw and neck) and generalized muscle spasms without other apparent medical cause (as reported by a health care professional).[29]

Lumbar puncture may be indicated to exclude meningitis in the neonate when the diagnosis of tetanus is uncertain. A computed tomography scan is helpful in assessment for intracranial disease. A serum calcium level is helpful to exclude hypocalcemia. Electromyography may be useful if the diagnosis of cephalic or localized tetanus is in doubt.[25]

The spatula test involves touching of the oropharynx with a tongue blade. With a negative test result, the patient gags and expels the tongue blade. With a positive test result, the patient has reflex masseter muscle spasm and bites the spatula. This test is 94% sensitive and 100% specific for tetanus.[27]

Differential Considerations

Strychnine poisoning is the only clinical condition that truly mimics generalized tetanus. Strychnine, like TS, antagonizes glycine release, but unlike TS, it has no effect on γ-aminobutyric acid (GABA) release. Patients have opisthotonos while remaining alert. The annual incidences of tetanus and strychnine poisoning are similar in the United States, and serum and urine tests for strychnine should be performed when tetanus is considered.[25]

In patients who present with diffuse generalized spasm, the diagnosis of tetanus is less likely to be missed, but ideally the disease should be considered and diagnosed in the early stages to minimize complications and to decrease mortality. Some conditions with clinical similarities to tetanus are listed in Box 129-3. Trismus is most commonly caused by intraoral infections. These can be excluded with careful history and physical examination of the oral cavity and teeth. Mandibular dislocation can be ruled out with appropriate radiographs of the mandible and temporomandibular joints. Dystonic reactions can be differentiated from tetanus by medication history and symptoms that are alleviated by benztropine or diphenhydramine. Patients with encephalitis usually exhibit an altered mental status. Meningitis can be excluded by examination of the cerebrospinal fluid (CSF). Rabies should be considered when there are symptoms of brainstem dysfunction, including dysphagia and respiratory muscle dysfunction. A history of exposure to secretions of an infected animal is the most helpful historical point. In addition, rabies does not cause trismus.

Box 129-3 Differential Diagnosis of Tetanus

Acute abdomen
Black widow spider bite
Dental abscess
Dislocated mandible
Dystonic reaction
Encephalitis
Head trauma
Hyperventilation syndrome
Hypocalcemia
Meningitis
Peritonsillar abscess
Progressive fluctuating muscle rigidity (stiff-man syndrome)
Psychogenic
Rabies
Sepsis
Status epilepticus
Strychnine poisoning
Subarachnoid hemorrhage
Temporomandibular joint syndrome

Cephalic tetanus is especially difficult to diagnose when the cranial nerve palsy precedes trismus. The differential diagnosis of cephalic tetanus also includes Bell's palsy, botulism, cranial nerve palsies, and facial cellulitis with facial nerve compression and ophthalmoplegia.

Management

Acute Treatment

The four treatment strategies for patients with tetanus should be undertaken simultaneously: aggressive supportive care, elimination of unbound TS, active immunization, and prevention of further toxin production.[25-27]

Supportive Care. Supportive care begins with control of the muscle spasms. Reflex spasms can result from stimulation of the patient, such as that caused by any movement of the patient or loud noises. Avoidance of unnecessary stimulation is recommended. Benzodiazepines are the mainstay of symptomatic therapy for tetanus. These drugs are GABA agonists and indirectly antagonize many of the effects of TS. They have no effect on the inhibition of glycine release by TS. Diazepam is the most extensively studied of these agents, but lorazepam and midazolam are equally effective. Diazepam has a rapid onset of action and a wide margin of safety, and it can be given orally, rectally, or intravenously. It is inexpensive and thus available in most parts of the world. It has a long cumulative half-life and active metabolites that can cause prolonged sedation and respiratory depression. The intravenous formulations of diazepam and lorazepam contain propylene glycol, which, at high doses, can produce lactic acidosis. Gastrointestinal delivery of these agents is limited by motility problems associated with tetanus. Midazolam has a short half-life and does not contain propylene glycol, but it should be given by continuous infusion and is cost-prohibitive in most areas of the world. Propofol infusion is effective, but it is also expensive, and patients may not tolerate the lipid vehicle. Neuroleptics, barbiturates, and intrathecal baclofen have no advantage over benzodiazepines. Dantrolene is a direct muscle relaxant without CNS activity. It has been reported as an adjunctive agent for muscle spasms and may decrease the need for mechanical ventilation.[37] Magnesium sulfate infusion has been advocated as both adjuvant and first-line therapy for tetanus. Alone or in combination with other agents, it improves spasm control and may alleviate some of the autonomic instability associated with tetanus toxicity.[38]

www.ketabpezeshki.com 66485457-66963820

If spasm cannot be controlled with these regimens or if any signs of airway compromise develop, the patient should receive neuromuscular blockade and mechanical ventilation. Although succinylcholine can be used in the *initial* phase of the disease, the clinician should be aware of the risk of severe hyperkalemia resulting from its use in any neuromuscular disease. This effect does not begin until about 4 days after the onset of disease.[25] Long-acting nondepolarizing agents are preferred, even in the initial phase. Pancuronium has traditionally been used, but it is an inhibitor of catecholamine reuptake and may worsen autonomic instability.[25] Vecuronium and rocuronium are shorter acting and are without significant cardiovascular side effects but require continuous infusion. Whichever agent is used, adequate sedation should be provided, and neuromuscular blockade should be withheld at least once a day to assess the patient's status. All intubated patients should be considered for early tracheostomy to decrease reflex spasms caused by the endotracheal tube.[32]

Autonomic instability requires monitoring and aggressive treatment. Sympathetic hyperactivity can be treated with combined alpha- and beta-adrenergic antagonists, such as labetalol and propranolol. The use of beta-antagonists alone can lead to unopposed alpha-activity, resulting in severe hypertension.[34] If beta-antagonists are necessary, a short-acting agent such as esmolol should be used.[26] Because the episodes of the autonomic crises in tetanus are due to catecholamine excess, the use of pure beta-antagonism can result in unopposed alpha-agonism. Clonidine has shown variable success at modulation of sympathetic outflow in these cases.[34] Morphine and magnesium sulfate infusions as well as spinal anesthesia and intrathecal baclofen have been shown to improve autonomic dysfunction.[25] Diuretics should be avoided for blood pressure control as volume depletion can worsen autonomic instability. Bradydysrhythmia should be treated with temporary pacing. Atropine and sympathomimetic drugs should be used with caution as the autonomic instability is essentially due to catecholamine excess.[26,27,34]

Elimination of Unbound Tetanospasmin and Active Immunization. Human tetanus immune globulin (HTIG) and Td should be administered as soon as possible to all patients with suspected tetanus. Tetanus immune globulin (TIG) does not neutralize toxin already present in the nervous system, nor does it treat any existing symptoms. HTIG neutralizes any circulating toxin as well as toxin at the site of production and reduces mortality. TIG should be administered at a site separate from the toxoid. Dosage recommendations vary (500-10,000 units of TIG), but multiple injections are stimuli for spasm, and most authorities note that 500 units is as effective as higher doses. Adult and pediatric doses are the same. If the larger doses are used, they should be given in divided injections. Administration of a portion of the TIG proximal to the site of inoculation is often recommended but has not been studied.[25-27] Protective antibody levels are achieved 48 to 72 hours after administration of TIG. Because the half-life of TIG is 25 days, repeated doses are not needed. The preparation of TIG available in the United States is not licensed for intrathecal administration, which is of no proven benefit.[25,27,32]

Prevention of Further Toxin Production. Toxin production is eliminated by treatment of the *C. tetani* infection. Wound débridement and antibiotic administration can cause a transient release of TS, so these measures should be delayed until after the HTIG is administered. Metronidazole (500 mg orally or IV every 6 hours) is the antibiotic of choice for *C. tetani*. Pediatric doses of metronidazole depend on age and weight[26,27]:

Neonates < 1200 g and 0-7 days: 7.5 mg/kg IV or orally every 24 hours
Neonates < 1200 g and 8-28 days: 7.5 mg/kg IV or orally every 12 hours
Neonates > 1200 g and 0-7 days: 7.5 mg/kg IV or orally every 12 hours
Neonates > 1200 g and 8-28 days: 25-30 mg/kg/day IV or orally every 12 hours
Infants and children: 30 mg/kg/day IV divided every 6 hours, maximum 4 g/day

Penicillin has traditionally been used to treat tetanus and has good in vitro and in vivo activity against *C. tetani*, but it also has GABA antagonistic activity and may potentiate the effects of TS. Metronidazole has better penetration than penicillin into devitalized tissue and abscesses and is superior in terms of recovery time and effect on mortality. Macrolides, doxycycline, chloramphenicol, and tetracycline are effective alternatives in metronidazole-allergic patients.[25-27]

Vaccination

Tetanus toxoid is an inactivated form of TS, and vaccination confers protective antibody levels in nearly 100% of people who receive three doses. Immunity wanes between 5 and 10 years after completion of the series. In high-risk patients such as elders, injection drug users, and patients with human immunodeficiency virus (HIV) infection and other causes of immunocompromise, immunity wanes more quickly and the response to vaccine is less brisk.

Adults with an uncertain history of a complete primary immunization series should receive a primary series. The standard vaccination program consists of a primary series of three tetanus toxoid doses, followed by booster doses every 10 years. Age-specific guidelines for tetanus prophylaxis have been developed by the ACIP and published by the CDC (Tables 129-1 and 129-2).

Tetanus vaccination should be updated for all patients who come to the emergency department for management of a wound, even if the presenting complaint is not wound related. Patients with unknown or uncertain immunization status should be considered to have no previous tetanus immunization. Those younger than 7 years should receive diphtheria-tetanus or DTaP. Patients 7 years of age or older should receive Tdap instead of DTaP because adverse reactions from the larger doses of diphtheria toxoid in DTaP are more common in older individuals.

Table 129-1 Routine Diphtheria, Tetanus, and Pertussis Vaccination Schedule for Children and Adults—United States

DOSE	CUSTOMARY AGE	AGE/INTERVAL	PRODUCT
Primary 1	2 months	6 weeks or older	DTaP
Primary 2	4 months	4-8 weeks after first dose†	DTaP
Primary 3	6 months	4-8 weeks after second dose†	DTaP
Primary 4	15-18 months	6-12 months after third dose†	DTaP
Booster	4-6 years, not needed if fourth vaccination administered after birthday*		DTaP
Additional booster	11-18 years		Tdap
Adult booster	>18 years	Every 10 years	Tdap or Td‡

Modified from Recommended childhood immunization schedule—United States, 2011. Available at http://www.cdc.gov/vaccines/recs/acip.
*If primary immunizations are started after the age of 6 years, the series should begin and continue with Tdap.
†Prolonging the interval does not require restarting of the series.
‡Td should be given to adult patients who have previously received Tdap. Tdap can be given regardless of interval since Td.

www.ketabpezeshki.com 66485457-66963820

Table 129-2 Summary Guide to Tetanus Prophylaxis in Routine Wound Management

HISTORY OF ABSORBED TETANUS TOXOID (DOSES)	CLEAN MINOR WOUNDS		ALL OTHER WOUNDS*	
	Tdap† or Td	TIG	Tdap† or Td	TIG
Unknown or less than three	Yes	No	Yes	Yes
Three or more‡	No§	No	No‖	No

Modified from Centers for Disease Control and Prevention: Preventing tetanus, diphtheria and pertussis among adults: Use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine. MMWR Recomm Rep 55:1-33, 2006.
*Such as, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds; avulsions; and wounds resulting from missiles, crushing, burns, and frostbite.
†For children <7 years old, DTaP is preferred. For persons >7 years of age, Tdap is preferred to tetanus toxoid alone. Td is preferable in adults who have previously received one dose of Tdap.
‡If only three doses of fluid toxoid have been received, a fourth dose of toxoid, preferably an adsorbed toxoid, should be given.
§Yes, if >10 years since last dose.
‖Yes, if >5 years since last dose. (More frequent boosters are not needed and can accentuate side effects.)

HTIG prophylaxis (250 units IM) is recommended for unimmunized and underimmunized patients with wounds at high risk for tetanus (>6 hours old, >1 cm deep, contaminated, stellate, denervated, ischemic, infected).[27] When tetanus toxoid and HTIG are given concurrently, separate injection sites should be used. The only contraindication to tetanus and diphtheria toxoids is a history of a neurologic or severe hypersensitivity reaction to a previous dose. Adverse reactions to tetanus toxoid and tetanus-diphtheria toxoids occur commonly and may be the result of the preservative thimerosal. The most common side effects are minor: local swelling, pain, erythema, pruritus, fever, nausea, vomiting, malaise, and nonspecific rash. Local reactions do not preclude future use of toxoid. Serious anaphylactic reactions are rare. If a patient who requires immunoprophylaxis gives a history suggestive of a neurologic or severe anaphylactic reaction, HTIG should be administered alone to protect the patient from development of tetanus as a result of the present injury. HTIG does not confer active immunity, and such patients should be referred to an allergist for measurement of antibody levels, antitoxin desensitization, and immunization. No evidence exists that tetanus and diphtheria toxoids are teratogenic. HTIG is not contraindicated in pregnancy. For inadequately immunized patients of any age, referral should be made to ensure that the patient receives the remainder of the immunizations required.[38]

BOTULISM

Perspective

Background

Botulism is a rare life-threatening paralytic illness caused by neurotoxins produced by *Clostridium botulinum*. The disease typically occurs in one of five forms: food-borne botulism, infant botulism, wound botulism, unclassified botulism, and inadvertent botulism.[39] Since the approval of botulinum toxins A and B by the FDA for cosmetic and therapeutic uses in the United States, cases of iatrogenic botulism have been reported.[40]

In 1820, Kerner, a health officer in Germany, first noted an association between sausage ingestion and a paralytic illness. The term *botulism* comes from the Latin *botulus,* meaning "sausage," because of these early descriptions of the disease. van Ermengem investigated an epidemic of botulism in a group of musicians at a funeral in Belgium in 1897. He isolated the organism from ham and demonstrated that an elaborated toxin produced illness on injection into animals. This toxin was later identified as type A toxin. Type B toxin was discovered in 1904.[39]

Botulism first received attention in the United States during World War I, when housewives were encouraged to preserve fruits and vegetables. The recommended methods for home canning did not destroy the spores of *C. botulinum*. Because these foods were often not adequately heated, epidemics of botulism occurred. Meyer described the circumstances favoring toxin production and the conditions necessary to destroy spores during food processing. Wound botulism was first described in 1943. In 1950 the CDC began surveillance of this form of the disease. Infant botulism, which is now the most common form of the illness, was first described in 1976.[39]

Epidemiology

Seven types of toxin (A through G) are produced by *C. botulinum*. Types A, B, E, and F cause illness in humans, and types C and D cause disease in animals. Type G has been found in soil but has not been definitively linked to human or animal outbreaks. *C. botulinum* spores are found throughout the United States. Type A is found more commonly in the West and type B in the East. Type E is frequently associated with fish products.[39,41] A total of 121 cases of botulism were reported to the CDC in 2009; 9% were food-borne botulism, 69% were infant botulism, and the rest were wound related or unknown.[42] Despite the ubiquitous nature of botulinum spores and the variety of possible routes of toxin entry, the incidence of disease is low.

Typical food-borne botulism results from the ingestion of preformed heat-labile toxin rather than from the ingestion of spores or live bacteria. Food-borne botulism usually results from exposure to home-canned foods that are inadequately preserved and undercooked, but large outbreaks occasionally occur after the ingestion of contaminated food at restaurants or from commercial sources. A variety of preserved foods have been implicated, and botulism has also been reported to result from ingestion of improperly prepared and stored fresh foods.

Infant botulism is the most common form of the illness in the United States. It occurs in children younger than 1 year with a peak incidence between the ages of 6 weeks and 6 months. In contrast to food-borne botulism in adults, infant botulism is caused by the ingestion of spores with in vivo production of toxin. Honey and to a lesser extent corn syrup have been implicated as sources of *C. botulinum* spores in infant botulism. Soil and vacuum cleaner dust have also been implicated, but the source of ingestion remains unknown in most cases. Types A and B botulinum toxins have been responsible for almost all infant cases.[43] Some investigators have explored a possible relationship between infant botulism and the sudden infant death syndrome, but a 10-year prospective study of 248 infants diagnosed with sudden infant death syndrome revealed no cases attributable to *C. botulinum*.[44]

Wound botulism once accounted for approximately one botulism case per year, but the increased use of black tar heroin has resulted in a dramatic increase in cases. In 1994, of the 53 adult botulism cases reported to the CDC, 11 cases were wound botulism. All occurred among injection drug users in California.[45] Toxin type A is the most frequent causative agent.[42]

Unclassified, hidden, or adult infectious botulism is a rare illness that is analogous to infant botulism. The *Clostridium* bacterium produces its toxin in vivo. Patients with compromised gastric acidity, disturbances of gastrointestinal motility, or abnormal gastrointestinal bacterial flora may be susceptible to in vivo production of botulinum toxin. Between 1976 and 1996, 39 cases were reported to the CDC. Toxin types A, B, and F were

www.ketabpezeshki.com 66485457-66963820

identified in these patients. Of the three cases reported in 2009, two were type F.[42]

Inadvertent botulism is an iatrogenic form of the disease that occurs in patients who have been treated with injections of botulinum toxin for dystonia and other movement disorders and for cosmetic purposes. Inadvertent generalized weakness as well as unintentional focal weakness may be seen.[40]

The potential exists for botulinum toxin to be used as an offensive biologic weapon. It is highly potent and easy to produce. The Aum Shinrikyo, responsible for the 1995 sarin gas attack on the Tokyo subway, have produced and dispersed aerosols of botulinum toxin in Japan on at least three occasions between 1990 and 1995. In 1995, Iraq admitted to the United Nations that it had produced 19,000 L of concentrated botulinum toxin and loaded approximately 10,000 L into warheads. These 19,000 L are not fully accounted for and constitute three times the amount needed to kill the entire human population by inhalation.[46]

Principles of Disease

Etiology

C. botulinum is a strictly anaerobic, large, gram-positive, rod-shaped organism. It forms spores that germinate under certain environmental conditions. The bacteria may then produce a potent exotoxin that is responsible for the disease. Each strain of *C. botulinum* produces a specific toxin type—A, B, C, D, E, F, or G. Only types A, B, E, and rarely F produce disease in humans.[39] Botulinum toxins are the most potent known biologic compounds.[46] Doses as small as 0.09 to 0.15 µg IV or 0.7 to 0.9 µg inhaled can cause death in a 70-kg human.[46,47] The toxins are heat labile. Heating at 85° C for 5 minutes destroys any botulism toxin. Consequently, heating of toxin-contaminated food just before ingestion prevents food-borne botulism. Spores are highly heat resistant, however, and can survive at a temperature of 100° C for several hours.[39]

Pathophysiology

Food-borne botulism results from ingestion of food that contains preformed toxin. Toxin-contaminated food may have a normal appearance and taste or exhibit signs of food spoilage caused by proteolytic enzymes produced by the type A and B strains. Because of the tremendous potency, one taste can expose a person to enough toxin to cause clinical illness. Digestive enzymes do not destroy preformed toxin. Infant and adult infectious botulism results from in vivo bacterial elaboration of toxin in the gastrointestinal tract. Achlorhydria and recent antibiotic use predispose the gastrointestinal tract to colonization with *C. botulinum*. Wound botulism results from in vivo bacterial elaboration of toxin in a wound. Inadvertent or iatrogenic botulism results from injection of preformed toxin for medical purposes.[39,40] Primate studies indicate that aerosolized botulinum toxin can also be absorbed systemically through the respiratory tract.[47]

The neurotoxin produced by *C. botulinum* is similar in structure and function to the TS toxin produced by *C. tetani,* but the clinical effects differ dramatically. TS targets inhibitory interneurons in the CNS, causing generalized muscle spasm, whereas botulinum toxin targets peripheral neuromuscular junctions and autonomic synapses, thereby causing a flaccid paralysis. When botulinum toxin is absorbed from the entry site, it circulates until it reaches the neurons.[30,31] The toxin binds to the presynaptic nerve membrane, becomes internalized, and then inhibits the release of acetylcholine, resulting in neuromuscular blockade. This interference with neurotransmission occurs predominantly at the cholinergic synapses of the cranial nerves, autonomic nerves, and neuromuscular junction. Clinically, this is manifested by cranial nerve palsies, parasympathetic blockade, and descending flaccid paralysis. Once it is affected with type A toxin, the nerve is permanently damaged, and recovery requires axonal regeneration and the formation of new synapses, which may take several months. Recovery after type F toxin is substantially faster.[39,41]

Clinical Features

Symptoms and Signs

Food-borne botulism is the prototype for understanding of the clinical signs and symptoms of all forms of botulism. Symptoms begin approximately 18 to 36 hours (range, 6 hours to 8 days) after the ingestion of toxin-containing food. A shorter incubation period is associated with a more severe form of illness. Early symptoms include weakness, malaise, lightheadedness, nausea, vomiting, and constipation. These symptoms are generally not severe and occur in fewer than half of the patients.[39]

Neurologic symptoms may begin at the same time or be delayed in onset for several days. The cranial nerves are first affected. Patients experience diplopia, blurred vision, dysphonia, dysphagia, and dysarthria. Vertigo is also a common symptom. Next, a symmetrical descending muscle weakness occurs, involving the upper and lower extremities and the muscles of respiration. Blockade of the cholinergic fibers of the autonomic nervous system leads to a variety of symptoms. Decreased salivation causes a dry mouth, which may be so severe that the patient complains of a painful tongue and sore throat. Ileus and urinary retention may also occur. In one series of patients with food-borne botulism, all had at least three of the following four symptoms: weakness, dry mouth, double vision, and difficulty speaking. This constellation of symptoms should prompt one to inquire about the ingestion of home-canned or improperly prepared food as well as the presence of similar symptoms in family members or friends.[39,41]

The patient with botulism is usually alert and afebrile unless secondary infection is present. Postural hypotension may be present. Ocular signs are prominent and include ptosis, extraocular palsies, and markedly dilated and fixed pupils; the absence of ocular abnormalities does not exclude the diagnosis. The oropharynx may be erythematous, with dry mucous membranes.[39] The gag reflex is depressed or absent.

Muscle weakness is usually present and varies from mild to severe. Neck muscles are often weak. Upper extremity muscles are affected more than those of the lower extremity. Proximal muscles are weaker than distal muscles. Deep tendon reflexes may be normal, symmetrically decreased, or absent. The sensory examination is normal. The abdomen may be distended with hypoactive or absent bowel sounds. Bladder distention may be apparent on examination. Respirations may be tachypneic and shallow or normal. In advanced illness, signs of respiratory failure may be present.[39]

Atypical presentations of food-borne botulism have been reported, and certain serotypes produce distinct variations in the pattern of symptoms. Type A disease may be more severe and is more commonly associated with bulbar findings and upper extremity weakness. Type A and type B disease may rarely cause a decreased level of consciousness. Type E is associated with a greater incidence of gastrointestinal symptoms.[39]

The presentation of *infant botulism* is different from that of food-borne botulism. Constipation is a common presenting complaint, followed by several days to weeks of poor feeding, weak cry, loss of head control, and hypotonia. On physical examination, patients have decreased muscle tone and depressed deep tendon reflexes. Cranial nerve involvement causes alterations in facial expression, ptosis, and extraocular palsies. Respiratory failure occurs in 50% of patients. Fever is absent unless secondary infection is present.[43,44]

www.ketabpezeshki.com 66485457-66963820

Wound botulism has some notable differences from food-borne botulism. The incubation period is longer, from 4 to 14 days, because the toxin must be produced within the wound after the spores have germinated. If the wound is infected, the patient may be febrile. Gastrointestinal symptoms are notably absent in wound botulism.[39] Recurrent episodes are well described.[45]

The clinical presentation of *unclassified (adult infectious) botulism* is similar to that of food-borne botulism, although the mortality rate is significantly greater. Recovery from botulism is slow, and survivors are hospitalized for several weeks to months.[39,41]

Complications

Complications from botulism are related to respiratory failure and problems associated with prolonged intensive care management. The major cause of death from botulism is respiratory failure resulting from weakness of the respiratory muscles. Aspiration of oral secretions and gastric contents because of loss of protective airway reflexes can occur. In the past 50 years, the overall mortality rate has decreased from 50% to less than 8% with modern intensive care. Mortality rates are higher in wound botulism patients (15-17%) and lower in infant botulism patients (<1%). For those who recover, muscle strength and endurance may not return to normal for up to 1 year, and persistent psychological problems are common.[39,41]

Diagnostic Strategies

The initial diagnosis of botulism is clinical and should be considered in any patient who presents with the constellation of gastrointestinal, autonomic, and cranial nerve dysfunction. Bilateral cranial nerve involvement and the progression of neurologic findings should increase clinical suspicion. Routine laboratory studies are of no value in the diagnosis. If a lumbar puncture is performed, the CSF in patients with botulism is normal or may show a slight elevation of protein.[41]

The diagnosis is confirmed by detection of (1) botulinum toxin in the patient's blood; (2) botulinum toxin or *C. botulinum* in the gastric contents, stool, or wound of the patient; or (3) toxin or organisms in the suspected food source. Because most hospital laboratories are unable to process such specimens, the local health department and CDC should be notified for specific instruction on the handling of specimens. Ideally the specimens should be obtained before administration of antitoxin. Serial measurements of the patient's vital capacity are helpful in recognizing deteriorating ventilatory function.[39,41]

Electromyography can detect electrophysiologic abnormalities consistent with the diagnosis of botulism; it may also be useful in differentiation of botulism from other paralytic illnesses. The electromyographic signature of botulism is decreased amplitude of the compound muscle action potential in response to a supramaximal stimulus and facilitation of the muscle action potential with repetitive nerve stimulation. Not all motor units are affected, and normal test results do not exclude the diagnosis.[39,41]

Differential Considerations

The differential diagnosis of *adult botulism* includes a wide variety of illnesses. Commonly, the first presenting case is misdiagnosed because early symptoms suggest pharyngitis or gastroenteritis, both of which can affect several members of a single household. Only after one or more cases progress to classic botulism is the diagnosis usually suggested.

Botulism should be differentiated from other illnesses that cause paralysis. In Guillain-Barré syndrome, weakness usually starts distally and ascends, paresthesias may be present, and the CSF protein level may be elevated. Tick paralysis is an ascending paralysis, notable for a lack of bulbar involvement and the presence of a tick. In myasthenia gravis, eye signs are also prominent, but pupillary response is preserved, no autonomic symptoms are present, and weakness responds to the administration of edrophonium or ice applied to the affected muscle group. Of note, minimal improvement in weakness after the administration of edrophonium has been reported in botulism.[39,41] Poliomyelitis causes fever, asymmetrical neurologic signs, and CSF abnormalities. Diphtheria can be distinguished by the prolonged interval between pharyngitis and neurologic symptoms. Eaton-Lambert syndrome does not usually involve bulbar muscles. Cerebrovascular accidents of the brainstem have an acute onset and asymmetrical, neuroanatomically localizing signs and symptoms.[39]

Certain toxins should also be considered in the differential diagnosis of botulism. Anticholinergics (atropine, belladonna, jimson weed) cause pupillary dilation and dry, red mucous membranes but also cause delirium with alterations in mental status. Organophosphate insecticides have a characteristic odor, and poisoning causes fever and altered mental status. Dystonic reactions are self-limited and respond to diphenhydramine or benztropine. Neuromuscular blockade from the administration of aminoglycosides is distinguished by the medication history. Heavy metal poisoning produces changes in mental status. Magnesium toxicity may mimic botulism, but the history and serum magnesium levels distinguish these entities.[39,41] In paralytic shellfish poisoning, paresthesias are prominent, a history of shellfish ingestion is present, and recovery occurs within 24 hours.

Infant botulism has a broader differential diagnosis. Common illnesses that mimic the presentation of infant botulism include sepsis, various viral illnesses, dehydration, encephalitis, meningitis, and failure to thrive. Neurologic illnesses such as Guillain-Barré syndrome, myasthenia gravis, and poliomyelitis should also be considered.[41,43,44] Hypothyroidism, hypoglycemia, diphtheria, and toxin exposures are all part of the differential consideration, as are less common conditions such as inborn errors of metabolism, congenital muscular dystrophy, and cerebral degenerative diseases.

Management

The treatment of botulism consists of supportive care and specific treatment with antitoxin and other medications to block the effects of the toxin. All patients with suggested botulism should be admitted to the hospital and placed in an ICU as respiratory failure may develop rapidly and insidiously. When signs of ventilatory failure develop, early endotracheal intubation should be performed. A decrease in vital capacity to less than 30% of predicted or less than 12 mL/kg is an appropriate criterion for intubation of a patient with botulism.[39,41] Ileus should be treated with nasogastric suction and urinary retention with an indwelling urinary catheter. Fortunately, the autonomic dysfunction of botulism is much less severe than that of tetanus and rarely requires any intervention.[39,41]

Saline enemas and cathartics have been recommended by some authors to cleanse the gastrointestinal tract of residual toxin. Cathartics should not be given in the presence of ileus. Magnesium-containing cathartics should be avoided because elevated serum magnesium levels can exacerbate muscle weakness. Special care should be taken with use of gastrointestinal clearance in infants with botulism. Because the source of toxin is outside the gastrointestinal tract in wound botulism, bowel decontamination is not indicated.[39]

Equine trivalent antitoxin contains antibodies to toxin types A, B, and E. It should be administered intravenously as soon as possible after appropriate laboratory specimens have been obtained. It neutralizes only circulating toxin and has no effect on bound toxin. Early administration prevents the progression of illness,

www.ketabpezeshki.com 66485457-66963820

decreases hospital length of stay, prevents respiratory failure, and shortens the duration of respiratory failure in patients with severe disease.[46] Antitoxin can be obtained from the CDC or state health department. After skin testing for hypersensitivity, one 10-mL vial should be given intravenously. This dose results in circulating antitoxin levels capable of binding circulating toxin concentrations many times in excess of those reported in botulism patients. The serum half-life is 5 to 8 days. For these reasons, and contrary to the information in the package insert, only one vial of antitoxin is required. Repeated doses are unnecessary and may increase the risk of hypersensitivity reactions, which occur in approximately 9% of patients.[39,41]

Equine antitoxin is generally not recommended in infant botulism because efficacy has not been demonstrated and because of the risk of anaphylaxis to horse serum.[48] A human botulism immune globulin (BabyBIG) is pooled plasma from immunized adults with high titers of antibodies to toxins A and B. It was approved by the FDA for the treatment of infant botulism in October 2003. BabyBIG shortens hospital length of stay by a mean of 3.1 weeks and mechanical ventilation by a mean of 1.7 weeks. It can be obtained by calling the California Department of Public Health Infant Botulism Treatment and Prevention Program at 510-231-7600 or 510-540-2646.[43]

Antibiotics are not currently recommended for food-borne botulism and may increase cell lysis and promote toxin release.[43] Because the source of toxin is in vivo production within an infected wound, débridement and antibiotic administration should be considered only after antitoxin has been administered. Otherwise, the use of antibiotics should be limited to treatment of secondary infections (e.g., aspiration pneumonia) that may develop. Antibiotic treatment of both infant and wound botulism has no proven benefit. If an antibiotic is used for any reason in a botulism patient, all attempts should be made to avoid the aminoglycosides and tetracyclines because they can impair neuron calcium entry and worsen the effects of botulinum toxin.[39,43]

Guanidine hydrochloride may enhance the release of acetylcholine from terminal nerve fibers. For this reason, it has been recommended as an experimental component of botulism therapy.[39]

Disposition

All patients with possible botulism should be admitted to the hospital and placed in an ICU as respiratory failure may develop rapidly and insidiously. An infectious disease specialist should be consulted for management issues. The CDC should be called for assistance in any case of suggested botulism. The CDC can be reached by calling 404-639-3311 (days) and 404-639-2540 (nights, weekends, and holidays). State and local health departments may also be helpful in investigating and preventing major epidemics. Area emergency departments should be alerted so that subsequent cases can be looked for and diagnosed.

PNEUMOCOCCEMIA

Perspective

Background

More than a century after the identification of *Streptococcus pneumoniae* as a pathogen in human disease and more than 80 years after the discovery of antibiotics, pneumococcus remains a significant cause of morbidity and mortality worldwide. Pneumococcemia is defined as the presence of *S. pneumoniae* in the blood. The clinical presentation ranges from a mild illness to a fulminant, life-threatening, systemic syndrome. *S. pneumoniae* also causes myriad localized infections, including otitis media, pneumonia, meningitis, and, less commonly, endocarditis, septic arthritis, and peritonitis.[49,50]

S. pneumoniae was discovered in 1881 by Sternberg in the United States and simultaneously by Pasteur in France. By the late 1880s it was referred to as pneumococcus because it was the most common cause of lobar pneumonia. In 1884, Friedländer described pneumococcemia. In 1902, Cole published the first case reports of pneumococcemia, including a patient who had meningitis and arthritis without pneumonia. In the early 20th century, Maynard, Lister, Wright, and others demonstrated a decreased incidence of pneumonia after inoculation of miners with killed pneumococci. In the 1920s, Heidelberg and Avery showed that antibodies to the surface capsular polysaccharide conferred immunity to pneumococcal disease. Two routes to bacteremia were described. Wandel described the migration of *S. pneumoniae* from the lung to the bloodstream by way of the lymphatic system. In 1964, Robert Austrian described bacteria passing directly from the upper respiratory tract (middle ear or sinus) to the subarachnoid space, then through the arachnoid villa and into the venous sinus.[50]

An *S. pneumoniae* vaccine was initially developed in the 1940s but was not produced commercially because of the availability of penicillin. The first vaccine was not licensed for use in the United States until 1977. This 14-valent pneumococcal vaccine was replaced in 1983 by a 23-valent vaccine for use in people older than 2 years. The heptavalent conjugate vaccine (Prevnar) is now available and licensed for use in infants younger than 2 years and for other high-risk patients.[51,52]

Epidemiology

S. pneumoniae remains a substantial cause of serious illness despite the availability of antibiotics and vaccines. Pneumococcal infection appears sporadically in normal individuals and in patients with impaired host defenses. Epidemics of pneumococcal infection occur rarely, although bacterial serotypes may cluster by geographic area. Most cases of pneumococcal infections are community acquired, and the peak incidence is in winter.[49]

Invasive pneumococcal disease (IPD) is defined as isolation of *S. pneumoniae* from a normally sterile site, such as blood, pleural fluid, or CSF.[49] In 1997 the CDC estimated 15 to 30 cases per 100,000 population annually in the United States for all people, 50 to 83 cases per 100,000 population annually for those older than 65 years, and 160 cases per 100,000 population annually for children younger than 2 years. Rates were threefold to fivefold higher in black adults (49-58 cases per 100,000 population) than in whites. Rates were even higher among Alaskan natives, at 74 and 624 cases per 100,000 population for adults and children younger than 2 years, respectively. The highest incidence in the United States occurred among Apache Native Americans, with an overall annual incidence of 156 and 2396 cases per 100,000 population for adults and children younger than 2 years, respectively.[53] The introduction of the heptavalent vaccine for infants has decreased the incidence of IPD by 65 to 84% in children younger than 2 years in all populations studied.[49-53] This decline is almost entirely attributable to the fact that the vaccine is 97% effective at providing immunity to the seven serotypes included.[54] The IPD in these studies in almost entirely due to nonvaccine serotypes, with particular concern recently attributed to multidrug-resistant serotype 19A. Ongoing surveillance will determine the need to change the serotypes included in the vaccine.[55,56]

Pneumococcemia occurs in less than 2% of all hospitalized patients with community-acquired pneumonia, but this number increases to 7.3% of patients admitted to the ICU, 11.5% of those with multilobar infiltrates on the chest radiograph, 15% of those with a temperature ≥40° C or ≤35° C, 20% of those with a systolic blood pressure below 90 mm Hg, and 22% of those with HIV infection.[57] Other sources include the meninges (8%) and the

www.ketabpezeshki.com 66485457-66963820

sinuses or middle ear (4%). Bacteremia is primary in 18% of adults but in a much higher percentage of children. People at higher risk for pneumococcemia include those with chronic respiratory or cardiovascular disease; chronic alcohol abusers; patients with cirrhosis, diabetes mellitus, or an absent or functionally impaired spleen (i.e., those with splenectomy or sickle cell disease); those receiving immunosuppressive therapy; and those with chronic renal failure, nephrotic syndrome, organ transplantation, lymphoma, Hodgkin's disease, multiple myeloma, and acquired immunodeficiency syndrome (AIDS).[52] Pneumococcus is spread from person to person by close contact, and crowded living conditions are associated with epidemics.

The mortality rate from pneumococcemia is 10 to 20% for young adults and much higher for elders, those with underlying disease, and those with localized infections such as meningitis.[54] The case fatality rate is significantly lower for children. The overall mortality rate from pneumococcemia may increase in the future because of the increasing number of elders and AIDS patients and the emergence of antibiotic-resistant strains.

Principles of Disease

Etiology

Pneumococcemia is caused by *S. pneumoniae,* an encapsulated, gram-positive, facultative anaerobic coccus that occurs in pairs and chains. Antigenic differences in the polysaccharide capsule separate *S. pneumoniae* into 90 serotypes.[49] In the United States, the seven serotypes present in Prevnar account for 80% of invasive disease in children younger than 6 years and 50% of invasive disease in people older than 6 years. Worldwide, 10 capsular types account for 62% of invasive disease.[54,58]

Pathophysiology

S. pneumoniae enters the blood by one of two routes. (1) It begins as a pulmonary infection and spreads to the mediastinal lymph nodes, into the thoracic duct, and then into the circulation. (2) It colonizes or causes infection in the upper respiratory tract and spreads to the subarachnoid space through the arachnoid villi to the venous sinus and into the blood (with or without meningeal involvement).[54]

S. pneumoniae bacteremia causes a clinical picture that ranges from a minor febrile illness to life-threatening septic shock. Different capsules of *S. pneumoniae* confer varying levels of resistance to phagocytosis, resulting in a spectrum of virulence among these serotypes. Multiple virulence factors contribute to adherence to tissues, inhibition of phagocytosis, activation of complement, and stimulation of cytokines.[50,54]

The diversity of individual clinical reactions to pneumococcemia is not well understood. Host defenses rely heavily on antibody and complement production, and people who have impaired humoral immunity are more susceptible to IPD. In patients with pneumococcal infections, antibodies specific to the capsule serotype develop within several days of onset of infection. This response occurs approximately 30 days after a patient receives the pneumococcal vaccine. Patients who demonstrate substantial host resistance are able to develop active immunity, and it is clear that some children can spontaneously clear culture-proven pneumococcemia.[59]

Clinical Features

Symptoms and Signs

The clinical presentation of pneumococcemia ranges from mild illness to fulminant disease, progressing to death within several hours. Occult bacteremia arises as a febrile illness in which the only direct indication of pneumococcemia is a positive blood culture (most often at 24-48 hours). Sepsis is the systemic response to infection, manifested by two or more of the following: (1) temperature higher than 38° C or lower than 36° C, (2) heart rate above 90 beats/minute, (3) respiratory rate of more than 20 breaths/minute or partial pressure of carbon dioxide in arterial gas of less than 32 mm Hg, and (4) WBC count higher than 12,000/mm^3, below 4000/mm^3, or more than 10% immature (band) forms.[58] Patients may present with lethargy, signs of poor tissue perfusion, cyanosis, and hypoventilation or hyperventilation. Either occult bacteremia or sepsis can occur in conjunction with a localized infection.

The history should include a description of symptoms, including fever, chills, cough, shortness of breath, headache, and rash; a review of systems; and any recent use of antibiotics. The shaking chills and fever that occur with pneumococcemia are believed to be caused by a toxin. There should be an assessment of the patient's social situation, including availability of caregivers, transportation to medical care, and ability to comply with discharge instructions.

In children, the clinical presentation of pneumococcemia is similar to that of other common febrile illnesses. Although signs of focal infection, such as pneumonia, may be present,[60] often the only indication of pneumococcemia is fever or other signs of bacterial toxicity.

Most adult patients have fever or hypothermia. Cough, rigors, pleuritic pain, and gastrointestinal symptoms occur in approximately one third of adult patients. Many patients complain of vague, nonspecific constitutional symptoms similar to those of common viral illnesses. Fever (temperature >38.5° C) occurs in 90% of younger patients but in less than 60% of those older than 65 years. Patients with signs of sepsis have an increased risk for a fulminant course with rapid deterioration. Findings on physical examination vary with the site, if any, of primary infection. A focal primary source of infection is more common in adults than in children.[54] The physician should evaluate for signs of otitis media, sinusitis, and meningitis. Pneumococcemia is considered primary in 18% of adults and 30% of children, so lack of localized infection as a source does not rule out IPD.

Complications

Cardiovascular collapse can occur with fulminant pneumococcal sepsis. Patients who develop severe illness from pneumococcemia may have end-organ damage from inadequate perfusion, disseminated intravascular coagulopathy (DIC), septic emboli, and other complications. These include respiratory failure, meningitis, hypothermia, gastrointestinal bleeding, hepatic coma, renal failure, and myocardial infarction.

Pneumococcemia occasionally results in hematogenous seeding, which causes peritonitis, arthritis, endocarditis, meningitis, and cellulitis.[54] Adults and children with functional or anatomic asplenia may have fulminant pneumococcemia termed overwhelming postsplenectomy infection (OPSI). This is characterized by septic shock, adrenal hemorrhage, and DIC. Although the true incidence of OPSI is unknown, studies demonstrate that it is substantial and that the risk for it does not decrease over time after splenectomy. Most invasive pneumococcal infections occur in the first 2 years after splenectomy, and about two thirds occur between 5 and 20 years. OPSI may initially arise with symptoms indistinguishable from those of common viral illnesses.[61] The 100-fold increased incidence of pneumococcal bacteremia and meningitis in children with sickle cell disease is probably primarily due to splenic dysfunction, but complement abnormalities may also play a role.[62]

www.ketabpezeshki.com 66485457-66963820

Diagnostic Strategies

The only test specific for pneumococcemia is a blood culture that grows *S. pneumoniae*. Ancillary testing of adults with suggested bacteremia should include a complete blood count with differential, blood cultures, urine culture and sensitivity, electrolyte values, glucose concentration, serum creatinine level, and blood urea nitrogen level. A chest radiograph may demonstrate pneumonia as the source of infection. Sputum Gram's stain, culture, and sensitivity testing, if pneumonia is suggested, are of questionable value in the emergency department but may be useful for continued inpatient care. For sputum specimens to be of value, they should be collected before antimicrobial therapy is instituted; however, therapy should not be significantly delayed for the sole purpose of obtaining sputum. Antigen testing of urine for pneumococcal polysaccharide is up to 100% sensitive in IPD.[62]

If the patient appears to be toxic or has signs of respiratory compromise, an arterial blood gas analysis and a coagulation profile should be obtained. If signs of meningitis or alterations in mental status are present, a lumbar puncture should be performed. Gram's stain of the buffy coat may be positive in cases of overwhelming pneumococcal sepsis.[63] The WBC count is usually elevated. A normal or low WBC count is suggestive of more serious disease, as are hypoxemia and hypercarbia. Musher and colleagues demonstrated an increased mortality rate in patients with serum creatinine levels higher than 2.0 mg/dL, bilirubin levels higher than 1.5 mg/dL, and albumin levels below 2.5 g/dL.[64]

Differential Considerations

Pneumococcemia in its more benign presentation should be differentiated from other febrile illnesses, such as viral infections. The combination of clinical findings and culture results enables the emergency physician to distinguish between bacteremia and sepsis of other origins. The presence of fever and shock, with or without a distinct rash, suggests the possibility of sepsis caused by *H. influenzae, Neisseria meningitidis,* and other streptococcus types. The presence of confirmed pneumococcemia does not exclude other diagnoses, such as influenza and lung cancer.[54]

Management

Acute Treatment

Management of pneumococcemia consists of stabilization of life-threatening conditions, eradication of the infection, and treatment of predisposing or coexisting conditions. All septic patients should be managed with early goal-directed therapy (see Chapter 138).[65] The decision to initiate antibiotic therapy for pneumococcemia is often made with limited objective data, which include the clinical findings, age of the patient, underlying conditions, and possible preliminary laboratory studies.

Elimination of the *S. pneumoniae* organism by prompt initiation of antibiotics is essential to reduce the morbidity and mortality of pneumococcal infection. Antibiotic administration should begin in the emergency department. To simplify selection of a treatment strategy, patients can be divided into three groups:

1. *Bacteremia or sepsis is suggested on the basis of clinical findings; however, the organism has not been identified*. The patient in this group is given broad-spectrum antibiotics initially; the selection is based on factors that include the most likely organism or organisms, the patient's age (neonate, child, adult, or elder) and immune status, the presence of coexisting disorders, and the local patterns of antibiotic resistance. The antibiotic regimen is changed to a narrower spectrum drug after positive identification of the organism and its sensitivities.
2. *S. pneumoniae growth is reported from cultures of blood drawn (usually 1-2 days) previously*. The treatment regimen for "occult bacteremia" is guided by the patient's age, history, physical examination, general appearance, and ancillary test results. Often, the antibiotic selected on the initial visit for a localized infection (e.g., amoxicillin) is sufficient to treat the pneumococcal bacteremia subsequently identified by the laboratory. The patient should be reevaluated promptly. Specimens for repeated blood culture should be obtained if the patient has not been taking an antibiotic. For well-appearing children, a 7- to 10-day course of an appropriate oral antibiotic is reasonable. The decision to admit a child for inpatient care is based on the findings at the time of reevaluation.[59]
3. *Bacteremia or sepsis is suggested, and S. pneumoniae is identified from a site of local infection, such as Gram's stain of sputum*. The antibiotic regimen is focused narrowly.

The adult patient with laboratory-proven pneumococcemia may be treated with penicillin G if susceptibility has been documented: 2 to 4 million units every 4 hours IV if local penicillin resistance patterns are still low. Meningitis is treated with 4 million units of penicillin G every 4 hours. In children, the dosage for meningitis is 250,000 units/kg per 24 hours in divided doses every 4 hours IV up to a maximum of 20 million units.

S. pneumoniae susceptible to penicillin in the United States continues to decline.[66] Unless penicillin susceptibility has been documented in a patient's isolate, treatment should begin with either ceftriaxone (1-2 g IV every 12-24 hours; 50-100 mg/kg/day in children) or cefepime (1-2 g IV every 12 hours; 50 mg/kg every 8 hours in children). When meningitis is present, the higher doses should be given. In areas where ceftriaxone resistance has emerged, the addition of vancomycin (1 g IV every 12 hours; 40 mg/kg/day divided every 6 to 8 hours in children) should be considered. An infectious disease consultant may be able to assist with antibiotic selection on the basis of local resistance patterns.

Intramuscular ceftriaxone is commonly administered to children with suggested occult bacteremia who are treated as outpatients while blood culture results are pending. Ceftriaxone (initial dose of 50-100 mg/kg IM or IV, followed by daily dosage of 100 mg/kg in divided doses every 12 hours, up to a maximum of 4 g) and cefotaxime (200 mg/kg/day in divided doses every 6 hours IV, up to a maximum of 12 g) offer the advantage of being excellent antibiotics for *N. meningitidis* and *H. influenzae*. Alternative initial treatment of pneumococcemia in penicillin- or cephalosporin-allergic patients includes vancomycin, imipenem, and chloramphenicol. Chloramphenicol has the associated risk of toxicity and interaction with anticonvulsant medications.

The patient with pneumococcemia may not have an obvious response to treatment for the first 24 to 48 hours of therapy. This may be attributed to the normal course of the disease, an incorrect diagnosis, the underlying illness, or an antibiotic regimen that does not treat the infection sufficiently.

Disposition

Disposition of the patient depends on three factors: the patient's age, the overall clinical condition, and the presence of coexisting illnesses. Toxic-appearing patients of any age should be promptly treated with antibiotics and admitted to the hospital. Patients with underlying or coexisting conditions and those with an unclear course of illness should also be admitted.

Children who are afebrile and appear well at the time of the initial examination are unlikely to have serious sequelae.[57] A large randomized, controlled trial involving 37,868 infants showed that IPD is rare in children who have received the heptavalent pneumococcal vaccine. Children were observed for 3 years. There was only one case of bacteremic pneumonia in a patient who had

www.ketabpezeshki.com 66485457-66963820

Box 129-4 CDC Recommendations for the Use of the 23-Valent Pneumococcal Vaccine, 2010

Immunocompetent adults with chronic illnesses
- Cardiovascular (excluding hypertension)
- Chronic lung disease
- Diabetes mellitus
- Alcoholism
- Chronic liver disease including cirrhosis
- Cerebrospinal fluid leaks
- Those 65 years of age or older

Immunocompromised adults, including those with
- Splenic dysfunction or asplenia, including sickle cell disease and other hemoglobinopathies
- Congenital or acquired immunodeficiencies, including those using immunosuppressive drugs
- Hodgkin's disease, lymphoma, or leukemia
- Multiple myeloma
- Generalized malignant disease
- Chronic renal failure or nephrotic syndrome
- Alcoholism
- Organ transplantation associated with immunosuppression

Adults and children older than 2 years with asymptomatic HIV infections

Children older than 2 years with chronic illness
- Anatomic or functional asplenia (including sickle cell disease)
- Nephrotic syndrome
- Cerebrospinal fluid leak
- Other conditions associated with immunosuppression

Persons living in special environments or social settings with an identified increased risk (e.g., certain Native American populations)

The vaccine is not indicated for children having only recurrent upper respiratory tract disease, such as otitis media and sinusitis

CDC, Centers for Disease Control and Prevention; *HIV,* human immunodeficiency virus.

Box 129-5 CDC and AAP Recommendations for the Use of the 7-Valent Vaccine

All children aged 2-23 months at 2, 4, 6, and 12-15 months

Children aged 24-59 months who are at high risk for pneumococcal disease, including those with
- Sickle cell disease
- HIV infection
- Other immunocompromising medical conditions
- This should be followed by the 23-valent vaccine 2 months after the heptavalent vaccine is given.

Consider for all children aged 24-59 months, with priority given to the following:
- Those aged 24-35 months
- Alaskan natives, Native Americans, and African Americans
- Children who attend daycare

AAP, American Academy of Pediatrics; *CDC,* Centers for Disease Control and Prevention; *HIV,* human immunodeficiency virus.

received all four doses of vaccine and two cases in children who had received one dose; one of these children had acute myelogenous leukemia after entering the study and was receiving immunosuppressive chemotherapy. The heptavalent vaccine contains serotypes responsible for only approximately 85% of pneumococcal disease in infants and children. The decision to treat a febrile child with antibiotics and discharge should be based on clinical findings, medical history, ability of the parents to follow the discharge instructions, and availability of timely follow-up.

Vaccination

The pneumococcal vaccine is effective in preventing infection; the currently available 23-valent vaccine contains the purified polysaccharide antigens of the serotypes that cause 70 to 80% of pneumococcemia infections in the United States. Although the overall protective efficacy of the vaccine is only 39 to 63%, it is safe, inexpensive, and of substantial value for well-defined groups at risk.[52] Unfortunately, the 23-valent pneumococcal vaccine has limited immunogenicity in children younger than 2 years. The heptavalent conjugate vaccine links the polysaccharide to proteins, resulting in an improved immunogenic response in children younger than 2 years.[67]

The CDC recommendations for the use of the 23-valent vaccine are given in Box 129-4.[52] The CDC and the American Academy of Pediatrics (AAP) recommendations for the use of the heptavalent vaccine are listed in Box 129-5.[51]

The ACIP for pneumococcal vaccine and the AAP recommend that revaccination be strongly considered at 2 to 6 years of age or older for people who are most likely to have a rapid decline of pneumococcal antibodies (e.g., patients with renal failure, transplant recipients, and patients with nephrotic syndrome) and for those at risk for fatal infection (e.g., asplenic patients). Children 10 years of age or younger with nephrotic syndrome, sickle cell anemia, or asplenia should be considered for revaccination after 3 to 5 years. Other preventive measures for pneumococcemia include passive immunization with immunoglobulins for patients with congenital or acquired immunodeficiency diseases and daily antibiotic prophylaxis for children with functional or anatomic asplenia.[68]

MENINGOCOCCEMIA

Perspective

Background

Few clinical situations in emergency medicine produce greater anxiety for the physician than meningococcal infection. Virtually all experienced emergency physicians have had a patient who appeared relatively well on initial presentation, only to be moribund and in critical condition with fulminant infection several hours later. "Epidemic cerebrospinal fever" was initially described in 1805 by Vieusseux in Geneva. Weichselbaum identified the causative bacterial agent in 1887. Throughout the 19th and first half of the 20th centuries, epidemics occurred periodically in most regions of the world. "Serum therapy" was introduced in France in 1907 and in the United States in 1913 as the first specific treatment of meningococcal disease. The introduction of sulfonamide therapy in 1937 replaced serotherapy and dramatically improved the outcome of meningococcal infection. Sulfonamide prophylaxis was also effective at eradication of the carrier state and was used to prevent the epidemics that occurred in military barracks. Not surprisingly, in the 1940s, sulfonamide resistance began to emerge. In 1963 an outbreak of resistant meningococcal disease occurred in the United States, which spurred efforts to develop a vaccine for this devastating infection. Subsequent worldwide resistance has resulted in continued efforts to develop safe and effective vaccines.[69]

Epidemiology

Humans are the only reservoir for *Neisseria meningitidis*. As of 2004, 1400 to 2800 cases of meningococcal infection were reported to the CDC annually. The incidence of disease has decreased in the United States since the licensing of the first conjugated meningococcal vaccine in 2005 (Fig. 129-5). Of the more

www.ketabpezeshki.com 66485457-66963820

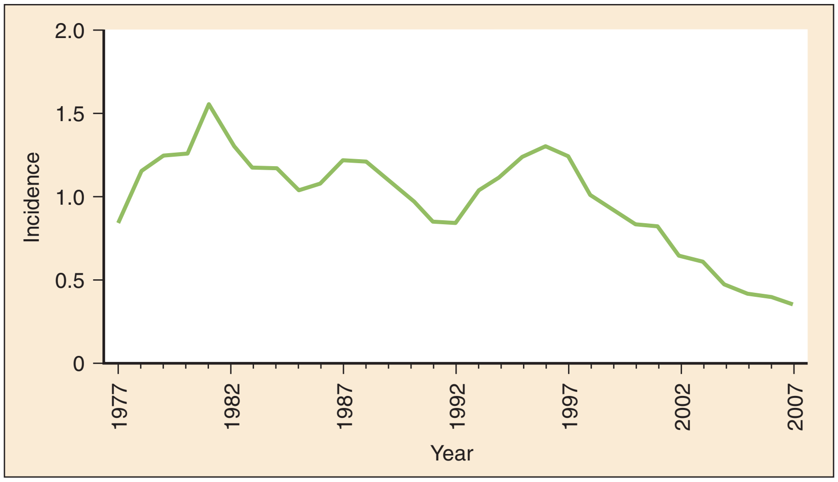


Figure 129-5. Incidence of meningococcal disease in the United States 1974-2007. (From Hall-Baker PA, et al: Summary of notifiable diseases—United States, 2007. MMWR Morb Mortal Wkly Rep 56:1-94, 2009.)

than 13 serogroups, groups A, B, C, Y, and W-135 cause most of the infections. More than 95% of cases occur sporadically, with occasional outbreaks, most notably on college campuses in dormitories or in other crowded living situations. More than half of the cases in infants are caused by serogroup B, for which there is no effective vaccine. Serogroups C, Y, and W-135 cause 35% of meningococcal disease in patients older than 11 years.[70] Although grouping is important for tracking of the disease, all groups are capable of causing the same spectrum of clinical disease.

The incidence of meningococcal disease peaks in the winter and falls in the summer. Superimposed on this annual variation are cyclic peaks of disease every 5 to 15 years. Approximately every 10 years, massive outbreaks of serogroup A occur in sub-Saharan Africa (the "meningitis belt"). The last outbreak was in 2007. During nonepidemic periods, children younger than 5 years have the highest incidence of infection. During epidemics, the incidence increases among children aged 5 to 9 years, an observation that may be of value in predicting the beginning of an epidemic. Crowded living conditions increase the risk for spread of meningococcal disease. The incidence of disease and the carrier state are several times higher among military recruits in the first few weeks of service than in the general public. This is also true of college freshmen, particularly those living in dormitories or residence halls. Other risk factors for development of invasive meningococcal disease include close contact with an infected patient, complement deficiency, properdin deficiency, asplenia, chronic alcohol abuse, active and passive smoking, corticosteroid use, and recent respiratory illness.[69]

The overall mortality rate of meningococcal disease is 40% in the United States. Septicemia without meningitis carries a much higher mortality rate (up to 70%) than meningitis alone (2-10%).[69,71]

Principles of Disease

Etiology

Meningococcal disease is caused by *N. meningitidis,* a fastidious, aerobic, gram-negative diplococcus. *N. meningitidis* is an encapsulated organism classified into at least 13 serogroups on the basis of the capsular polysaccharides.[69]

Pathophysiology

N. meningitidis attaches to nonciliated epithelial cells in the nasopharynx by a number of adhesion factors. Once it is attached, it may either remain on the epithelial surface, causing an asymptomatic carrier state, or produce mild symptoms of an upper respiratory tract infection. In certain patients, the bacteria enter the bloodstream and cause symptoms and signs of localized infection, bacteremia, sepsis, or fulminant infection. The precise host and microorganism characteristics that determine whether clinical disease develops are not fully understood, but the presence of bactericidal antibodies is protective. Complement deficiency may play a role in a host's inability to fight this infection. The capsule is required for *N. meningitidis* to adhere to epithelium, but only unencapsulated meningococci enter epithelial cells; capsular biosynthesis has been shown to stop as the bacteria enter the epithelial cell.[69] The release of lipo-oligosaccharide and endotoxin by autolysis of the *N. meningitidis* cell is the initial event in the development of meningococcal sepsis. The exogenous mediators appear to stimulate the release of endogenous mediators, including tumor necrosis factor, interleukin-1, and the host's complement system. All of the major pathophysiologic events of meningococcal sepsis are caused by the host's inflammatory response to the organism. The complement-activating products and other chemical mediators cause functional and histologic damage to the microvasculature, resulting in increased vascular permeability, pathologic vasoconstriction and vasodilation, loss of thromboresistance, DIC, and profound myocardial dysfunction.[71,72]

After exposure to *N. meningitidis,* protective antibodies develop. Immunity in children is conferred initially by maternal antibodies that pass through the placenta and later by the development of antibodies after exposure to the bacteria. In children, the incidence of meningococcal disease is inversely proportional to the levels of antibodies against *N. meningitidis.*[71]

Clinical Features

Symptoms and Signs

The clinical presentation of meningococcemia ranges from a mild febrile illness to fulminant disease progressing to death within hours. Most patients have fever on presentation. Other initial complaints include headache, irritability, lethargy, myalgias, emesis, diarrhea, cough, and rhinorrhea. Anywhere from 27 to 77% of patients will present with the classic hemorrhagic skin lesions.[72] These patients can rapidly progress to purpura fulminans, with hypotension, adrenal hemorrhage, and multiorgan failure. The following categories detail the five patterns of presentation.

www.ketabpezeshki.com 66485457-66963820

Occult Bacteremia. This condition arises as a febrile illness in which the only direct indication of meningococcemia is a positive blood culture, with results available most often 24 to 48 hours after the clinical evaluation. In its mildest form, meningococcal bacteremia cannot clinically be distinguished from more benign febrile illnesses. Initial diagnoses in these patients include common childhood infections, such as otitis media, acute viral upper respiratory infections, and gastroenteritis. For some patients the illness resolves after treatment with an oral regimen of antibiotics; others experience spontaneous resolution without antibiotic treatment. *N. meningitidis* accounts for less than 1% of occult bacteremia cases,[73] but these patients are much more likely to develop meningitis (up to 58%) than are those with *S. pneumoniae*. Also, despite the total absence of clinical clues to meningococcal infection at initial presentation, some untreated patients subsequently deteriorate rapidly.

Meningococcal Meningitis. Patients with meningococcal meningitis may present similarly to patients with meningitis of other origins, with headache, photophobia, vomiting, fever, and signs of meningeal inflammation. This classic constellation triad of fever, neck stiffness, and altered mental status is present in less than 30% of patients.[69] Infants and small children may present with fever, irritability, and vomiting as the only complaints. More than half of patients with meningococcal meningitis have rash on presentation, and 20% present with seizures. Onset of symptoms is less abrupt (usually during 24 hours) and prognosis is better for patients with meningococcal meningitis than for patients with meningococcemia without clinical signs of meningitis.

Meningococcal Septicemia. Patients with meningococcal septicemia present with lethargy, poor tissue perfusion, cyanosis, and hypoventilation or hyperventilation. Hemorrhagic skin lesions are present in 28 to 77% of patients, but a macular or maculopapular rash may also occur and be mistaken for a variety of viral exanthems. Petechiae generally appear on the extremities and may appear under pressure points, such as the elastic bands of socks and underwear. They may progress to involve almost any body surface, including the mucosa and sclera, but typically spare the palms, soles, and head. Macular lesions may progress to purpura and ecchymoses in fulminant meningococcemia. The purpurae are not a coalescence of petechiae but a distinct entity that more specifically characterizes meningococcemia. *Purpura fulminans,* the most dreaded and advanced form of meningococcal septicemia, occurs most often in children and is usually associated with DIC. This condition is characterized by rapidly spreading ecchymoses and gangrene of the extremities. Evidence of mucosal and gastrointestinal bleeding as well as oozing from intravenous sites may be noted on examination. Clinical signs of meningitis and CSF pleocytosis may not be present, even when diplococci are isolated from the CSF. This is probably because the systemic progression of the disease is so rapid that it precludes a host meningeal inflammatory response to the organism in the CSF. Shock results from both intravascular volume loss and congestive heart failure, probably related to myocarditis. Renal failure, coma, and bilateral adrenal hemorrhage often occur.[69-72]

Fever and a Nonblanching Rash. Up to 30% of patients present without signs of meningitis or septicemia. They are typically admitted for fever and a nonblanching rash and no other specific findings. If they are untreated, meningitis or fulminant septicemia and shock can develop.[74]

Chronic Meningococcemia. This syndrome is characterized by fever, rash, and arthritis in conjunction with a positive blood culture for *N. meningitidis*. Headache and upper respiratory symptoms are often present. This is the rarest form of meningococcal disease, accounting for 1 to 2% of cases. It may progress to meningitis, endocarditis, or fulminant meningococcemia regardless of treatment.[69]

Complications

Myocarditis with congestive heart failure is a common complication of meningococcemia and is the primary cause of death in more than half of patients. Many of the inflammatory mediators released during sepsis cause myocardial dysfunction, and the severity of sepsis is related to the degree of impairment of myocardial contractility. The acidosis, hypoglycemia, hypokalemia, hypocalcemia, hypophosphatemia, and hypoxia that accompany meningococcemia also contribute to the myocardial dysfunction. Treatment with cardiac glycosides is beneficial,[69] but patients may become unresponsive to positive inotropic medications.

Acute respiratory failure occurs from capillary leak in the patient who requires volume resuscitation. It is also likely that intrapulmonary DIC contributes to the pulmonary edema, and patients frequently require mechanical ventilation. Renal failure is common secondary to impaired renal perfusion; acute tubular necrosis may develop. If meningitis accompanies meningococcemia, focal neurologic signs as well as seizures may occur but are less common than with pneumococcal meningitis. Vasculitis in severe cases of meningococcal septicemia may result in skin lesions that necessitate plastic surgery and loss of digits or limbs from gangrene. Purulent or immune complex arthritis and pericarditis with tamponade may also occur.[69,71]

Poor prognostic indicators in meningococcemia include seizures on presentation, hypothermia, hyperpyrexia, total peripheral WBC count of less than 500/mm^3, platelet count of less than 100,000/mm^3, metabolic acidosis (pH < 7.30), development of purpura fulminans, onset of petechiae within 12 hours of admission, absence of meningitis, presence of shock, low sedimentation rate, and extremes of age. In one study, all patients who developed organ system failure had one or more of the following at the time of initial presentation: circulatory insufficiency (hypotension or shock), peripheral WBC count of less than 10,000 cells/mm^3, or a coagulopathy.[75] Herpes labialis occurs in 5 to 20% of patients with meningococcal disease.

Diagnostic Strategies

The tentative diagnosis of meningococcemia is based on clinical findings and confirmed by the isolation of *N. meningitidis* from blood cultures or any other usually sterile site, such as CSF or synovial, pleural, or pericardial fluid. Ideally, blood culture specimens should be obtained before the administration of antibiotics unless this unduly delays the patient's treatment. Blood cultures are positive in approximately 50 to 80% of cases. A lumbar puncture should be performed only in stable patients without evidence of DIC. The CSF shows either gram-negative diplococci on Gram's stain or a positive culture in about 46 to 94% of cases. Even patients without clinical signs of meningitis frequently have the organism grown from the CSF. Gram's stain of petechial scrapings may show gram-negative diplococci in up to two thirds of cases,[72] and the organism can rarely be seen in the peripheral blood buffy coat. Highly specific antigen tests for CSF are available but have a high false-negative rate. PCR of the buffy coat or CSF is more sensitive and specific than any of the preceding tests and is not affected by prior antibiotic therapy.[69,71]

Ancillary laboratory tests are of little value in establishing a specific diagnosis of meningococcal sepsis but may be useful in ruling out other disease, determining prognosis, and monitoring complications. The WBC count may be high, low, or normal, but a bandemia is typically present. The symptoms and signs of CNS infection may be nonspecific in the infant and child younger than 2 years. If meningitis is present, the CSF opening pressure is usually elevated, the protein level is increased, and the glucose concentration is decreased. Pleocytosis is usually present, with a predominance of polymorphonuclear leukocytes. Gram-negative

www.ketabpezeshki.com 66485457-66963820

diplococci may be seen on microscopy. Early in the disease or with fulminant disease, the CSF may be free of inflammatory cells. Serologic evidence of DIC is frequently present.[69,71,72]

A chest radiograph is useful in evaluation for pneumonia and acute respiratory distress syndrome. An echocardiogram helps assess for myocardial dysfunction and pericardial effusion.

Differential Considerations

It is difficult to distinguish the clinical signs of meningococcemia from those of bacteremia caused by *S. pneumoniae,* other streptococcal groups, *H. influenzae,* and *Neisseria gonorrhoeae*. A hemorrhagic rash is more commonly associated with meningococcal disease.[76] The differential diagnosis of meningococcemia also includes viral exanthems, Rocky Mountain spotted fever, typhus, typhoid fever, endocarditis, vasculitis syndromes (polyarteritis nodosa and Henoch-Schönlein purpura), toxic shock syndrome, acute rheumatic fever, dengue fever, drug reactions, idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura.[71]

In one study of 184 children hospitalized with fever and petechiae, 24 (11%) had proven *N. meningitidis*. The remainder showed evidence of viral or other organisms. These data were acquired before the initiation of a vaccination program.[77]

Management

Acute Treatment

Morbidity and mortality in meningococcemia are reduced with prompt recognition and immediate initiation of antibiotic therapy. Delays in initiation of therapy for the completion of diagnostic studies or admission to an inpatient unit should be avoided. To simplify selection of a treatment strategy, patients can be divided into three general groups:

1. *Bacteremia or sepsis is suggested on the basis of clinical findings; however, the organism has not been identified*. These patients should receive broad-spectrum antibiotics; the selection is based on factors that include the most likely organism or organisms, the patient's age and immune status, the presence of coexisting disorders, and the local patterns of antibiotic resistance. A narrower spectrum agent is selected after positive identification of the organism and its sensitivities.
2. *N. meningitidis growth is reported from prior blood cultures*. The treatment regimen for occult bacteremia is guided by the patient's age, history, physical examination, general appearance, and ancillary test results. The antibiotic selected at the time of the initial visit may be sufficient to treat the meningococcal bacteremia subsequently identified by the laboratory. The decision to hospitalize the patient is based on the findings at the time of reevaluation and the risk of sequelae. Regardless of the patient's clinical appearance, most physicians would draw blood for repeated cultures, consider lumbar puncture, and admit the patient to the hospital until results of repeated cultures are obtained.
3. *Bacteremia or sepsis is suggested and N. meningitidis is identified*. The antibiotic regimen is focused narrowly.

The standard antibiotic regimen for laboratory-proven meningococcemia is penicillin G, 4 million units every 4 hours IV for adults, and penicillin, 250,000 to 300,000 units/kg/day in divided doses every 4 hours IV for children, up to a maximum of 20 million units. Penicillin resistance in *N. meningitidis* remains low in the United States but has been reported in Spain and the United Kingdom.[69,71,77]

Although it is appropriate first-line therapy, penicillin is rarely given as the initial agent in patients with suspected meningococcal sepsis or meningitis. Ceftriaxone (initial dose of 100 mg/kg IV, followed by daily dosage of 100 mg/kg in divided doses every 12 hours, up to a maximum of 4 g) and cefotaxime (100 mg/kg/day IV in divided doses every 6 hours, up to a maximum of 12 g) are appropriate initial antibiotics as well. The cephalosporins offer the advantages of safety, rapid onset of action, and excellent coverage for *S. pneumoniae* and *H. influenzae*. Chloramphenicol (50-100 mg/kg/day divided every 6 hours to a maximum of 4 g/day) should be considered in penicillin- and cephalosporin-allergic patients.[69] Intramuscular ceftriaxone is occasionally administered to children with suspected bacteremia who are treated as outpatients while culture results are pending. Several reports have demonstrated the efficacy of ceftriaxone (80-100 mg/kg IV) in a single daily dose; however, twice-daily dosing remains the standard recommendation at this time. In addition to the obvious advantage of extended dosing intervals, ceftriaxone-treated patients have a more rapid sterilization of the CSF and a lower incidence of hearing loss than conventionally treated patients do.

Patients with fulminant meningococcemia require prompt airway management, intravenous fluid resuscitation, and vasopressor support. Fluid requirements may be high because of third spacing of fluid, and in the setting of frequent myocardial dysfunction, intensive cardiovascular monitoring is required. Electrolyte and acid-base abnormalities should be corrected. If the patient is oliguric or anuric, hemodialysis may be necessary to correct these abnormalities. Fresh frozen plasma should be considered for patients with bleeding complications.[69,72]

The role of steroids for the treatment of meningococcemia without meningitis remains controversial. Although corticosteroids were once widely recommended for the treatment of the adrenal insufficiency associated with fulminant meningococcemia, more recent studies demonstrate that adrenal function is not impaired in all patients. If a patient has persistent shock despite vigorous fluid resuscitation and vasopressor therapy, glucocorticoid therapy may be considered and adrenal function tested.[78]

The use of corticosteroids in patients with bacterial meningitis is currently recommended for adults and children but not for neonates. The most recent clinical data show that corticosteroid administration before antibiotic administration decreases mortality rates in adults and long-term neurologic sequelae in adults and children. Dexamethasone (0.4-0.6 mg/kg/day every 6 hours for 4 days) should be given to patients with bacterial meningitis. The first dose should be given before the first dose of antibiotics if possible.[79]

Plasmapheresis, blood exchange, and extracorporeal membrane oxygenation have been described with favorable outcome, but data are limited.[72]

Disposition

All patients with possible or confirmed meningococcemia should be admitted to the hospital, preferably to an ICU because these patients can decompensate rapidly and without warning. A possible exception is the well-appearing child who has culture-proven *N. meningitidis* and has been taking appropriate antibiotics as an outpatient. This child should have a lumbar puncture to determine CSF involvement if one was not performed at the initial evaluation. Antibiotics should be continued on an inpatient basis, but an ICU may not be necessary if the child appears well.

Antibiotic Prophylaxis and Vaccination

Patients with meningococcemia should be placed in respiratory isolation for at least 24 hours. Close contacts should receive antibiotic prophylaxis. Household, nursery school, and daycare

www.ketabpezeshki.com 66485457-66963820

center contacts should receive prophylaxis promptly. Intimate contacts and health care workers with intimate exposure (e.g., mouth-to-mouth resuscitation, intubation, or suctioning) should receive rifampin, 10 mg/kg (up to 600 mg) orally every 12 hours for four doses. The dose for infants younger than 1 month is 5 mg/kg. Patients should be warned that rifampin discolors the urine and secretions; contact lenses should be removed to avoid permanent staining. Intramuscular ceftriaxone (125 mg for children younger than 15 years and 250 mg for those older than 12 years) is effective against group A strains. This is an alternative for pregnant women and for people in whom compliance with an oral regimen cannot be ensured. Ciprofloxacin (500 mg orally) is another alternative for adults.[69,72]

Meningococcal vaccine should be considered an adjunct to prophylaxis in epidemics and for close contacts in sporadic cases if one of the serotypes contained in the vaccine is identified as the causative agent. The currently available vaccine is a quadrivalent vaccine containing purified capsular polysaccharides for groups A, C, Y, and W-135. Unfortunately, the polysaccharides other than A are poorly immunogenic for children younger than 2 years. In addition, no vaccine exists for group B, a serogroup that causes a significant portion of meningococcal infection in the United States. The quadrivalent vaccine is not recommended for routine use but should be administered to children 2 years of age and older in high-risk groups, such as those with functional or anatomic asplenia and those with terminal complement deficiency. In 2000 the CDC ACIP recommended that college students, especially those living in dormitories, and their parents be advised of the risks of meningococcal disease and be offered vaccination. In August 2007 the ACIP recommended that all persons aged 11 to 18 years receive the vaccine. The vaccine is currently administered to U.S. military recruits. Consideration should be given to vaccination of people traveling to endemic areas of the world, such as sub-Saharan Africa.[80]

TOXIC SHOCK SYNDROME

Perspective

Background

Toxic shock syndrome (TSS) is a toxin-mediated systemic inflammatory response syndrome that was first described by Todd and colleagues in 1978. They reported a series of seven children aged 8 to 17 years who had high fever, rash, headache, confusion, conjunctival injection, edema, vomiting, diarrhea, renal failure, hepatic dysfunction, DIC, and shock. *S. aureus* was cultured from various body sites but not from the blood in five of the seven cases.[81]

The disease gained notoriety in the early 1980s when many cases were reported in association with tampon use in young, healthy menstruating women. The term *toxic shock syndrome* was coined to describe the constellation of signs and symptoms. Investigators noted positive vaginal cultures for *S. aureus*, recurrence of illness during subsequent menses, and the value of antistaphylococcal antibiotics in preventing recurrences. In response to the growing concern about TSS, changes were made to reduce the absorbency and composition of tampons. Nonmenstrual cases were also recognized in both men and women as a result of a variety of predisposing conditions, and a case definition was published in 1982 (Box 129-6).[82-84]

In the late 1980s, several reports described group A streptococcus (GAS) infection associated with shock and multisystem organ failure. This has been called *streptococcal toxic shock syndrome* because it shares so many features with staphylococcal TSS. Box 129-7 shows the case definition for streptococcal TSS.[84,85]

Box 129-6 Case Definition of Toxic Shock Syndrome (Revised)

Clinical Case Definition

Fever: temperature >38.9° C (102° F)
Rash: diffuse macular erythroderma
Desquamation 1-2 weeks after onset of illness, particularly of palms and soles
Hypotension: systolic blood pressure <90 mm Hg for adults or below fifth percentile by age for children younger than 16 years, orthostatic drop in diastolic blood pressure >15 mm Hg from lying to sitting, orthostatic syncope, or orthostatic dizziness
Multisystem involvement—*three* or more of the following:
- Gastrointestinal: vomiting or diarrhea at onset of illness
- Muscular: severe myalgia or creatine kinase level at least twice the upper limit of normal for laboratory
- Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
- Renal: BUN or creatinine at least twice the upper limit of normal for laboratory or urinary sediment with pyuria (>5 leukocytes/high-power field) in the absence of urinary tract infection
- Hepatic: total bilirubin, AST, and ALT at least twice the upper limit of normal for laboratory
- Hematologic: platelets <100,000/mm^3
- CNS: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent

Laboratory Criteria for Diagnosis

Negative results on the following tests, if obtained:
- Blood, throat, or CSF cultures (blood culture may be positive for *Staphylococcus aureus*)
- Rise in titer to Rocky Mountain spotted fever, leptospirosis, or rubeola

Case Classification

Probable: a case that meets the laboratory criteria and in which four of the five clinical findings are present
Confirmed: a case that meets the laboratory criteria and in which all five of the clinical findings are present, including desquamation, unless the patient dies before desquamation occurs

ALT, serum alanine transaminase; *AST,* serum aspartate transaminase; *BUN,* blood urea nitrogen; *CNS,* central nervous system; *CSF,* cerebrospinal fluid.

Epidemiology

The peak incidence of TSS occurred in 1980, when 890 cases were reported, 91% of which were associated with tampon use. Since then, the reduction in cases of the menstrual form of TSS has followed an active effort to decrease the absorbency of tampons and to change their composition.[86] Menstruation remains the most common setting for TSS, but nonmenstrual TSS accounts for just under half of the reported cases. TSS has also been reported in association with barrier contraceptives and childbirth. Nonmenstrual TSS occurs in people of all ages and in both sexes. The CDC reported an average of about 200 cases a year (about 1 case per 100,000 population) from 1994 to 2001, with a steady increase in the incidence of streptococcal TSS and a slight decrease in the incidence of staphylococcal TSS.[87] The age and sex distribution reflects the association with menses. In 2003, 294 cases were reported, but a steady decline continues to occur, with 182 cases reported in 2007. Streptococcal TSS accounts for a little more than half of the cases.[88]

Nonmenstrual staphylococcal TSS is associated with superinfection of various skin lesions, including burns, surgical sites, dialysis catheters, and lung (influenza associated). It may also occur in association with staphylococcal respiratory infections or even with colonization by a toxigenic strain of the organism,

www.ketabpezeshki.com 66485457-66963820

Box 129-7 Case Definition of Streptococcal Toxic Shock Syndrome

Clinical Case Definition

Hypotension: systolic blood pressure ≤90 mm Hg for adults or below fifth percentile by age for children younger than 16 years

Multisystem involvement—*two* or more of the following:

- Renal: creatinine >2 mg/dL (177 µmol/L) for adults or more than twice the upper limit of normal for age or more than twofold elevation above baseline for patients with preexisting renal disease
- Hematologic: platelets <100,000/mm^3 or DIC, defined as prolonged clotting times, low fibrinogen level, and the presence of fibrin degradation products
- Hepatic: total bilirubin, AST, and ALT at least twice the upper limit of normal for laboratory, or a twofold increase in patients with preexisting liver disease
- Acute respiratory distress syndrome: defined by acute onset of pulmonary infiltrates and hypoxemia in the absence of cardiac failure or by evidence of diffuse capillary leak manifested by acute onset of generalized edema, or pleural or peritoneal effusions with hypoalbuminemia
- Generalized erythematous maculopapular rash that may desquamate
- Soft tissue necrosis, including necrotizing fasciitis, myositis, or gangrene

Laboratory Criteria for Diagnosis

Isolation of GAS

Case Classification

Probable: a case that meets the clinical case definition in the absence of another identified cause of the illness and with isolation of GAS from a nonsterile site

Confirmed: a case that meets the clinical case definition and with isolation of GAS from a normally sterile site (e.g., CSF or joint, pleural, or pericardial fluid)

ALT, serum alanine transaminase; *AST,* serum aspartate transaminase; *CSF,* cerebrospinal fluid; *DIC,* disseminated intravascular coagulation; *GAS,* group A streptococcus.

without an obvious infectious source. Streptococcal TSS is classically associated with more severe soft tissue infections, such as necrotizing fasciitis and myositis, as well as with pneumonia, peritonitis, myometritis, and osteomyelitis.[84-87]

The mortality rate from staphylococcal TSS has declined since the disease was first described. The case fatality rate in 1980 was 10%, and it was less than 3% in the past several years. Streptococcal TSS remains a highly fatal disease, with a mortality rate of 30 to 70%.[84-87]

Principles of Disease

Etiology

Staphylococcal TSS is caused by colonization or infection with toxigenic strains of *S. aureus*. This strain produces toxic shock syndrome toxin 1 (TSST-1). *S. aureus* has been detected in virtually all cases of both forms of the illness. *S. aureus* has been isolated from the vagina or cervix in 98% of women with menstrual TSS, compared with a colonization rate of less than 10% of unaffected women. Because the organism is often not invasive, the blood cultures are often negative. Streptococcal TSS is caused by invasive infection with toxigenic strains of GAS.[82-84]

Pathophysiology

The shock and multiorgan dysfunction associated with TSS are caused by the effects of various exotoxins produced by *S. aureus* and GAS. *S. aureus* produces TSST-1 and enterotoxin B. TSST-1 is identified in more than 90% of menstrual cases and 60% of nonmenstrual cases. Other toxins may play a role in nonmenstrual TSS. Antibodies to these toxins are protective against disease. GAS produces streptococcal pyrogenic exotoxins A (SPEA) and B (SPEB). These exotoxins are absorbed into the bloodstream through inflamed or traumatized mucous membranes or from areas of focal infection. Absorbed toxins act as superantigens, inducing mononuclear cells to synthesize and to release cytokines, tumor necrosis factor alpha (TNF-α), and interleukins, which begin the cascade of systemic vasculitis and the multisystem manifestations of the disease. Host immune factors are important in the pathogenesis of TSS. GAS is an invasive organism, and circulating GAS organisms induce the production of TNF-α and other cytokines by mononuclear cells.[84,89]

Box 129-8 Risk Factors for Toxic Shock Syndrome

- Use of superabsorbent tampons
- Postoperative wound infections
- Postpartum period
- Nasal packing
- Cancer
- Common bacterial infections
- Ethanol abuse
- Infection with influenza A virus
- Infection with varicella virus
- Diabetes mellitus
- Human immunodeficiency virus infection
- Chronic cardiac disease
- Chronic pulmonary disease
- Nonsteroidal anti-inflammatory use (may mask symptoms rather than be a risk factor)

Clinical Features

Symptoms and Signs

The clinical presentations of streptococcal TSS and staphylococcal TSS are similar. The primary difference is that an identifiable infectious source is virtually always present with streptococcal TSS, and colonization alone may be the source in staphylococcal TSS.

TSS should be considered in any patient who presents with sudden-onset fever, rash, hypotension, and evidence of end-organ damage, such as respiratory failure or altered mental status. Patients may have a prodromal illness with fever, chills, nausea, vomiting (25%), watery diarrhea (14-30%), headache (10%), myalgias, and pharyngitis, which can last 2 to 3 days before progression to frank sepsis and organ dysfunction. Other patients may become abruptly symptomatic within hours. Rapid progression is more typical of streptococcal TSS. Patients may complain of pain at a site of infection more often with streptococcal TSS.[84] Risk factors for TSS are listed in Box 129-8.[84,85]

The fever is usually high and abrupt in onset, although septic patients may have hypothermia on presentation. The classic rash is a nonpruritic, diffuse, blanching, macular erythroderma. It develops in the first few days of the illness and initially may be faint, evanescent, and mistaken for the flush associated with a fever. The rash is usually diffuse but may be localized to the trunk, extremities, or perineum. After about a week, a fine flaking desquamation occurs on the face, trunk, and extremities, followed by full-thickness peeling of the palms, soles, and fingers. This classic rash progression is much more common in staphylococcal TSS and is present in less than 10% of patients with streptococcal TSS.[90] Patients with streptococcal TSS may have a scarlet fever–like

www.ketabpezeshki.com 66485457-66963820

Table 129-3 Comparison of Staphylococcal and Streptococcal Toxic Shock Syndrome

FEATURE	STAPHYLOCOCCAL	STREPTOCOCCAL
Age	Primarily 15-35 years	Primarily 20-50 years
Sex	Greatest in women	Either
Severe pain	Rare	Common
Hypotension	100%	100%
Erythroderma rash	Very common	Less common
Renal failure	Common	Common
Bacteremia	Low	60%
Tissue necrosis	Rare	Common
Predisposing factors	Tampons, packing, NSAID use?	Cuts, burns, bruises, varicella, NSAID use?
Thrombocytopenia	Common	Common
Mortality rate	<3%	30-70%

NSAID, nonsteroidal anti-inflammatory drug.

rash, petechiae, or maculopapular lesions. Mucosal involvement may also occur, including conjunctival and scleral hemorrhages, "strawberry tongue," and mucosal ulceration.[84]

The patient's mental status is frequently abnormal, out of proportion to the degree of hypotension. Confusion, somnolence, agitation, and combativeness are present in 55% of patients with streptococcal TSS and in even more patients with staphylococcal TSS.[84,85]

Other findings on physical examination may include pharyngeal and conjunctival erythema and peripheral edema. Vaginal mucosal erythema and purulent vaginal discharge may be present in menstrual TSS but are not required for the diagnosis to be made. As multiple organ systems become involved, a wide constellation of signs and symptoms may be seen. Gastrointestinal involvement is manifested by vomiting, diarrhea, and severe abdominal pain. Hepatomegaly may be present. Acute respiratory distress syndrome develops in more than half of patients and is manifested by rales on pulmonary examination and hypoxia. Comparisons between staphylococcal and streptococcal TSS are presented in Table 129-3.

Complications

Complications of TSS include acute respiratory distress syndrome (55%), shock (95%), gangrene, DIC, and a constellation of neuropsychiatric symptoms. Renal failure occurs in 80% of patients but is irreversible in 10%. Less common findings in staphylococcal TSS include rhabdomyolysis, seizures, pancreatitis, pericarditis, and cardiomyopathy. Women with the menstrual form of TSS may experience one or more recurrent episodes; recurrences of the nonmenstrual form are rare. Complication rates are higher with streptococcal TSS. Rhabdomyolysis occurs in up to 63% of patients with streptococcal TSS and is usually related to the underlying soft tissue infections.[90]

Diagnostic Strategies

The case definition for TSS does not require a positive culture for *S. aureus,* but isolation of *Streptococcus* organisms is a criterion for diagnosis. These case definitions (see Boxes 129-6 and 129-7) are useful to the clinician, but they are neither specific nor foolproof. Specific tests are not required to exclude other diseases, but if such tests are obtained, the results of these studies should be negative.

No specific laboratory changes are associated with TSS, but many abnormalities are common. Either leukocytosis or leukopenia can occur, but a marked bandemia is common. Elevated creatinine levels and hemoglobinuria occur in most patients. Laboratory evidence of renal dysfunction occurs before hypotension in half of the patients. Hypoalbuminemia (85%) and life-threatening hypocalcemia (79%) are prominent initially and persist throughout the course of the disease. Other abnormalities include anemia, thrombocytopenia, prolonged prothrombin and activated partial thromboplastin times (60-71%), hyperbilirubinemia, elevated transaminase levels (63%), and sterile pyuria.[84,91]

Blood cultures are positive for bacteria in approximately 60% of cases associated with GAS but are rarely positive in staphylococcal TSS. Gram's stains and cultures from wounds may identify the organism. Culture of the cervix or vagina is positive in 90% of menstruation cases associated with TSS even in the absence of local infection.[84]

Chest radiography may reveal evidence of acute respiratory distress syndrome or a pulmonary source of the organism. Plain radiographs of any infected skin or soft tissue site typically show only soft tissue swelling but may reveal evidence of a retained foreign body or air in the soft tissue. A lack of air in the soft tissue does not rule out a necrotizing soft tissue infection.

An electrocardiogram may reveal evidence of ischemia, arrhythmias, and varying degrees of atrioventricular block in association with sepsis. A blood gas analysis may indicate metabolic acidosis secondary to hypotension or hypoxia. A lumbar puncture should be performed in febrile patients with altered mental status to evaluate for meningitis. It is prudent to wait for the results of a coagulation profile before the lumbar puncture is performed because these patients may have DIC at presentation. The CSF is normal in patients with TSS.

Differential Considerations

The differential diagnosis includes any severe febrile illness with exanthems associated with hypotension. Other diseases to consider include heat stroke, cellulitis, Kawasaki disease, staphylococcal scalded skin syndrome, scarlet fever, drug reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), Rocky Mountain spotted fever, clostridial gas gangrene, leptospirosis, meningococcemia, gram-negative sepsis, atypical measles, and viral illnesses.

Kawasaki disease occurs almost exclusively in children, usually does not progress to shock, lacks multisystem involvement, is manifested with a protracted fever, and is associated with thrombocytosis later in its course.[92] Staphylococcal scalded skin syndrome is manifested with a desquamating rash acutely, whereas the desquamation of TSS occurs in the convalescent phase. Staphylococcal scalded skin syndrome does not progress to shock, is not associated with multisystem illness, and lacks mucous membrane involvement. Scarlet fever differs in its clinical course by lack of shock and multisystem involvement, positive cultures for GAS, and a rise in the convalescent titer. Stevens-Johnson syndrome usually occurs after drug administration, has characteristic mucous membrane lesions, and lacks desquamation. TEN may be difficult to distinguish from TSS; TEN patients are typically febrile, are in shock, and can progress to multisystem failure. The desquamation of TEN occurs early in the course of the disease, and it usually occurs after administration of a drug.[93] Rocky Mountain spotted fever occurs after a tick bite, has a distinctive rash, and is associated with a severe headache without an altered mental status or hypotension. Leptospirosis occurs in endemic areas and may be distinguished by positive serologic studies and cultures. The rash of meningococcemia is characterized by petechiae and purpura occurring anywhere on the skin.

www.ketabpezeshki.com 66485457-66963820

Management

Patients with TSS should receive aggressive fluid resuscitation with crystalloids and may require up to 10 to 15 L/day. Supplemental oxygen should be provided to all septic patients, regardless of initial pulse oxymetry. This allows maximum tissue oxygenation and reduces acidosis. Patients should be placed in a monitored setting. Assisted ventilation may be necessary in patients with acute respiratory distress syndrome.

The source of bacteria, such as tampons, nasal packs, and other foreign bodies, should be removed. Prompt surgical consultation should be obtained to débride wounds. If specimens are sent for culture, the laboratory should be informed of the suspected diagnosis.

Patients who do not respond to fluid resuscitation require vasopressors such as norepinephrine, dopamine, phenylephrine, and epinephrine.

Antibiotics should be initiated early in the treatment of TSS as the clinical presentation of the disease is similar whether the source is staphylococcal or streptococcal. For septic patients without an identified organism, broad-spectrum antibiotics should be administered. Although the penicillinase-resistant penicillins (nafcillin, oxacillin) have been widely used in the treatment of TSS, most clinicians recommend clindamycin as a first-line agent. Clindamycin is a potent suppressor of bacterial toxin synthesis; it also facilitates phagocytosis of streptococci by inhibiting M protein synthesis, decreases monocyte synthesis of cytokines, and has a longer postantibiotic effect than the β-lactams. The dose is 600 to 900 mg IV every 8 hours. (The pediatric dose is 20-40 mg/kg/day divided every 6-8 hours.)[84,85]

Patients who do not respond to massive fluid resuscitation, antibiotics, and vasopressors should be considered for intravenous immune globulin treatment, especially if pulmonary edema develops and mechanical ventilation is required. Pooled immune globulin has high titers for antibodies to TSST-1 and other exotoxins, and significant improvement has been reported with its use. If it is used, the recommended dose is 1 to 2 g/kg on day 1 administered intravenously during several hours, followed by 400 to 500 mg/kg/day for up to 5 days.[84,85,94]

The value of corticosteroids in TSS is still unresolved. They are not currently recommended for treatment of staphylococcal or streptococcal TSS but should be given to patients thought to have adrenal insufficiency related to underlying disease or chronic steroid use.[84]

Disposition

All patients thought to have TSS should be admitted to an ICU. Prompt surgical consultation should be obtained for patients with a wound source.[83-85]

KEY CONCEPTS

- All patients appearing septic should be treated with broad-spectrum antibiotics as soon as possible, even before a definitive diagnosis is made.
- A surgeon should be consulted as soon as possible for patients with sepsis and a débridable source of infection.
- Immunity to diphtheria, tetanus, and pertussis wanes significantly in adults. Pertussis should be considered a cause of persistent cough in adults. A tetanus vaccination history should always be obtained from patients with trauma or infection. When there is doubt about the history, the age-appropriate vaccine according to CDC guidelines is administered.
- Neonates with suspected pertussis should be admitted to an intensive care setting.
- Botulism should be kept in the differential for the infant with failure to thrive, constipation, or decreased muscle tone and for the injection drug user with neurologic symptoms.
- Patients with pneumococcemia, meningococcemia, and TSS can decompensate rapidly. Antimicrobial therapy should be initiated promptly, before identification of an organism.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. MacGregor RR: *Corynebacterium diphtheriae*. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia: Elsevier/Churchill Livingstone; 2010:2687-2693.
2. Tiwari TSP: *Diphtheria*. In: *Manual for the Surveillance of Vaccine-Preventable Diseases*, 4th ed. Atlanta, Ga: Centers for Disease Control and Prevention; 2008.
3. Golaz A, et al: Epidemic diphtheria in the newly independent states of the former Soviet Union: Implications for diphtheria control in the United States. *J Infect Dis* 2000; 181(Suppl 1):S237.
4. Galazka A: The changing epidemiology of diphtheria in the vaccine era. *J Infect Dis* 2000; 181(Suppl 1):S2.
5. Mokrousov I: *Corynebacterium diphtheriae:* Genome diversity, population structure and genotyping perspectives. *Infect Genet Evol* 2009; 9:1-15.
6. Kadirova R, Kartoglu HU, Strebel PM: Clinical characteristics and management of 676 hospitalized diphtheria cases, Kyrgyz republic, 1995. *J Infect Dis* 2000; 81(Suppl 1):S110.
7. Rakhmanova AG, et al: Diphtheria outbreak in St. Petersburg: Clinical characteristics of 1,860 adult patients. *Scand J Infect Dis* 1996; 28:37-40.
8. Jayashree M, et al: Predictors of outcome in patients with diphtheria receiving intensive care. *Indian Pediatr* 2006; 43:155.
9. Konrad R, et al: Matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) mass spectrometry as a tool for the rapid diagnosis of potentially toxigenic *Corynebacterium* species in the laboratory management of diphtheria-associated bacteria. *Euro Surveill* 2010; 15:pii:19699. Available at http://eurosurveillance.org/ViewArticle.aspx?ArticleId=19699.
10. Guy AM: Diphtheria in emergency medicine. *eMedicine*, updated Feb 14, 2011. Available at http://emedicine.medscape.com/article/782051.
11. Wagner KS, Stickings P, White JM: A review of the international issues surrounding the availability and demand for diphtheria antitoxin for therapeutic use. *Vaccine* 2010; 28:14-20.
12. Tiwari T: Use of diphtheria antitoxin (DAT) for suspected diphtheria cases. Available at www.cdc.gov/vaccines/vpd-vac/diphtheria/dat/downloads/protocol_032504.pdf.
13. Waters V, Halperin S: *Bordetella pertussis*. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia: Elsevier/Churchill Livingstone; 2010:2955-2964.
14. Centers for Disease Control and Prevention: Preventing tetanus, diphtheria, and pertussis among adults: Use of tetanus toxoid, reduced diphtheria and acellular pertussis vaccine. *MMWR Recomm Rep* 2006; 55:1-33.
15. Hoppe JE: Neonatal pertussis. *Pediatr Infect Dis J* 2000; 19:244.
16. Haberling DL, Holman MS, Paddock CD, Murphy TV: Infant and maternal risk factors for pertussis-related infant mortality in the United States, 1999 to 2004. *Pediatr Infect Dis J* 2009; 28:194-198.
17. Vitek CR, Pascual FB, Baughman AL, Murphy TV: Increase in death from pertussis among young infants in the United States in the 1990s. *Pediatr Infect Dis J* 2003; 22:628-634.
18. Bocka JJ: Pertussis in emergency medicine. *eMedicine*, updated Mar 22, 2012. Available at http://emedicine.medscape.com/article/803186.
19. Guint-Ocampo H: Pediatric pertussis. *eMedicine*, updated Feb 27, 2012. Available at http://emedicine.medscape.com/article/967268.
20. Altunaiji SM, Kukuruzovic RH, Curtis NC, Massie J: Antibiotics for whooping cough (pertussis). *Cochrane Database Syst Rev* 2007; 3:CD004404.
21. Halperin SA, et al: Is pertussis immune globulin efficacious for the treatment of hospitalized infants with pertussis? No answer yet. *Pediatr Infect Dis J* 2007; 26:79.
22. Feunou PF, Kammoun H, Debrie AS, Mielcarek N, Locht C: Long-term immunity against pertussis induced by a single nasal administration of live attenuated *B. pertussis* BPZE1. *Vaccine* 2010; 28:7047-7053.
23. Zhang L, Prietsch SO, Axelsson I, Halperin SA: Acellular vaccine for preventing whooping cough in children. *Cochrane Database Syst Rev* 2011; 1:CD001478.
24. Centers for Disease Control and Prevention: Updated recommendations for the use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine from the Advisory Committee on Immunization Practices, 2010. *MMWR Morb Mortal Wkly Rep* 2011; 60:13-15.
25. Reddy P, Bleck TP: *Clostridium tetani (tetanus)*. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia: Elsevier/Churchill Livingstone; 2010:3091-3096.
26. Hinfey PB: Tetanus. *eMedicine*, updated Sep 28, 2011. Available at: http://emedicine.medscape.com/article/229594.
27. Dire DJ: Tetanus in emergency medicine. *eMedicine*, updated Sep 20, 2011. Available at http://emedicine.medscape.com/article/786414.
28. Tetanus surveillance—United States, 2001-2008. *MMWR Morb Mortal Wkly Rep* 2011; 60:365-369.
29. Pascual FB, et al: Tetanus surveillance—United States, 1998-2000. *MMWR Surveill Summ* 2003; 52:1.
30. Caleo M, Schiavo G: Central effects of tetanus and botulism neurotoxins. *Toxicon* 2009; 54:593-599.
31. Humeau Y, et al: How botulinum and tetanus neurotoxins block neurotransmitter release. *Biochimie* 2000; 82:427.
32. Cook TM, Protheroe RT, Handel JM: Tetanus: A review of the literature. *Br J Anaesth* 2001; 87:477.
33. Roper MH, Gasse FL: Maternal and neonatal tetanus. *Lancet* 2007; 370:1947-1959.
34. Freshwater-Turner D, et al: Autonomic dysfunction in tetanus—what lessons can be learnt with specific reference to alpha-2 agonists? *Anaesthesia* 2007; 62:1066.
35. Sanya EO, et al: A 12-year review of adult tetanus managed at the university college hospital, Ibadan, Nigeria. *Trop Doct* 2007; 37:170-172.
36. Jolliet P, et al: Aggressive intensive care treatment of very elderly patients with tetanus is justified. *Chest* 1990; 97:702.
37. Possamai C, Corbanese U, Casagrande L: Dantrolene infusion in severe tetanus. *Anaesthesia* 1997; 52:610.
38. Attygalle D, Rodrigo N: New trends in the management of tetanus. *Expert Rev Anti Infect Ther* 2004; 2:73-84.
39. Reddy P, Bleck TP: *Clostridium botulinum (botulism)*. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia: Elsevier/Churchill Livingstone; 2010:3097-3102.
40. Crowner BE, Brunstrom JE, Racette BA: Iatrogenic botulism due to therapeutic botulinum toxin A injection in a pediatric patient. *Clin Neuropharmacol* 2007; 30:310-313.
41. Chan-Tack KM: Botulism. *eMedicine*, updated May 19, 2011. Available at http://emedicine.medscape.com/article/213311.
42. Centers for Disease Control and Prevention: Summary of botulism cases reported in 2009. Available at www.cdc.gov/nationalsurveillance/PDFs/Botulism_CSTE_2009.pdf.
43. Brook I: State-of-the-art: Infant botulism. *J Perinatol* 2007; 27:175-180.
44. Böhnel H, Behren S, Loch P, Lube K, Gessler F: Is there a link between infant botulism and sudden infant death? Bacteriological results obtained in central Germany. *Eur J Pediatr* 2001; 160:623-628.
45. Yuan J, Inami G, Mohle-Boetani J, Vugia DJ: Recurrent wound botulism among injection drug users in *California. Clin Iinfect Dis* 2011; 52:862-866.
46. Arnon SS, et al: Botulinum toxin as a biological weapon: Medical and public health management. *JAMA* 2001; 285:1059.
47. Dhaked RK, Singh MK, Singh P, Gupta P: Botulinum toxin: Bioweapon and magic drug. *Indian J Med Res* 2010; 132:489-503.
48. Chalk C, Benstead TJ, Keezer M: Medical treatment for botulism. *Cochrane Database Syst Rev* 2011; 3:CD008123.
49. Lynch JP, Zhanel GG: *Streptococcus pneumoniae:* Epidemiology and risk factors, evolution of antimicrobial resistance, and impact of vaccines. *Curr Opin Pulm Med* 2010; 16:217-225.
50. Lopez R: Pneumococcus: The sugar-coated bacteria. *Int Microbiol* 2006; 9:179-190.
51. Centers for Disease Control and Prevention: Recommended immunization schedule for persons aged 0-18 years—United States, 2011. *MMWR Morb Mortal Wkly Rep* 2011; 60(5).
52. Centers for Disease Control and Prevention, Advisory Committee on Immunization Practices: Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). *MMWR Morb Mortal Wkly Rep* 2010; 59:1102-1106.
53. Lacapa R, et al: Changing epidemiology of invasive pneumococcal disease among White Mountain Apache persons in the area of the pneumococcal conjugate vaccine. *Clin Infect Dis* 2008; 47:476-484.
54. Muench DF: Pneumococcal infections. *eMedicine*, updated Nov 3, 2010. Available at http://emedicine.medscape.com/article/225811.
55. Herz AM, et al: Changing epidemiology of outpatient bacteremia in 3- to 36-month-old children after the introduction of the heptavalent-conjugated pneumococcal vaccine. *Pediatr Infect Dis J* 2006; 25:293.
56. Peters TR, Poehling KA: Invasive pneumococcal disease: The target is moving. *JAMA* 2007; 297:1825-1826.
57. Bordon J, et al: The presence of pneumococcal bacteremia does not influence clinical outcome in patients with community-acquired pneumonia: Results from the Community-Acquired Pneumonia

www.ketabpezeshki.com 66485457-66963820

Organization (CAPO) International Cohort study. *Chest* 2008; 133:618-624.

58. Burdette SD: Systemic inflammatory response syndrome. *eMedicine*, updated Apr 11, 2012. Available at http://emedicine.medscape.com/article/168943.
59. Bachur R, Harper MB: Reevaluation of outpatients with *Streptococcus pneumoniae* bacteremia. *Pediatrics* 2000; 105:502.
60. Steele RW: Pediatric pneumococcal bacteremia. *eMedicine*, updated May 3, 2011. Available at http://emedicine.medscape.com/article/967600.
61. DiSabatino A, Carsetti R, Corazza GR: Post-splenectomy and hyposplenic states. *Lancet* 2011; 378:86-97.
62. Battersby AJ, Knox-Macaulay HH, Carrol ED: Susceptibility to invasive bacterial infections in children with sickle cell disease. *Pediatr Blood Cancer* 2010; 55:401-406.
63. Anjay MA, Anoop P: Diagnostic utility of rapid immunochromatographic urine antigen testing in suspected pneumococcal infections. *Arch Dis Child* 2008; 93:628-631.
64. Musher DM, et al: Bacteremic and nonbacteremic pneumococcal pneumonia. *Medicine (Baltimore)* 2000; 79:210.
65. Daniels R: Surviving the first hours in sepsis: Getting the basics right (an intensivist's perspective). *J Antimicrob Chemother* 2011; 66(Suppl 2): ii11-ii23.
66. Jones RN, Sader HS, Moet GJ, Farrell DJ: Declining antimicrobial susceptibility of *Streptococcus pneumoniae* in the United States: Report from the SENTRY Antimicrobial Surveillance Program (1998-2009). *Diagn Microbiol Infect Dis* 2010; 68:334-336.
67. Black S, et al: Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugated vaccine in children. *Pediatr Infect Dis J* 2000; 19:187.
68. Nuorti JP, Whitney CG; Centers for Disease Control and Prevention: Prevention of pneumococcal disease among infants and children—use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2010; 59:1-15.
69. Apicella MA: *Neisseria meningitidis*. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia: Elsevier/Churchill Livingstone; 2010:2737-2752.
70. Cushing K, Cohn A: *Meningococcal disease*. In: *Manual for Surveillance of Vaccine-Preventable Diseases*, 4th ed. Atlanta, Ga: Centers for Disease Control and Prevention; 2008.
71. Javid MH: Meningococcemia. *eMedicine*, updated Jul 5, 2012. Available at http://emedicine.medscape.com/article/221473.
72. Stephens DS, Greenwood B, Brandtzaeg P: Epidemic meningitis, meningococcaemia, and *Neisseria meningitidis*. *Lancet* 2007; 369:2196-2210.
73. Stoll ML, Rubin LG: Incidence of occult bacteremia among highly febrile young children in the era of the pneumococcal conjugate vaccine: A study from a children's hospital emergency department and urgent care center. *Arch Pediatr Adolesc Med* 2004; 158:671-675.
74. Horino T, et al: Meningococcemia without meningitis in Japan. *Intern Med* 2008; 47:1543-1547.
75. de Jonge RC, van Furth AM, Wassenaar M, Gemke RJ, Terwee CB: Predicting sequelae and death after bacterial meningitis in childhood: A systematic review of prognostic studies. *BMC Infect Dis* 2010; 10:232.
76. Karanika M, et al: Diagnostic clinical and laboratory findings in response to predetermining bacterial pathogen: Data from the Meningitis Registry. *PLoS One* 2009; 4:e6426.
77. Wells LC, et al: The child with a non-blanching rash: How likely is meningococcal disease? *Arch Dis Child* 2001; 85:218.
78. Sprung CL, et al: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358:111.
79. Brouwer MC, McIntyre P, de Gans J, Prasad K, van de Beek D: Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev* 2010; 9:CD004405.
80. Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices: Revised recommendations of the Advisory Committee on Immunization Practices to vaccinate all patients aged 11-18 years with meningococcal conjugate vaccine. *MMWR Morb Mortal Wkly Rep* 2007; 56:794.
81. Todd J, et al: Toxic-shock syndrome associated with phage-group-I staphylococci. *Lancet* 1978; 25:1116.
82. Todd J: Toxic shock syndrome—evolution of an emerging disease. *Adv Exp Med Biol* 2011; 697:175-181.
83. Que YA, Moreillon P: *Staphylococcus aureus (including staphylococcal toxic shock)*. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia: Elsevier/Churchill Livingstone; 2010:2543-2570.
84. Venkataraman R: Toxic shock syndrome. *eMedicine*, updated Jul 16, 2010. Available at http://emedicine.medscape.com/article/169177.
85. Lappin E, Ferguson AJ: Gram-positive toxic shock syndromes. *Lancet Infect Dis* 2009; 9:281-290.
86. Centers for Disease Control: Reduced incidence of menstrual toxic shock syndrome—United States, 1980-1990. *MMWR Morb Mortal Wkly Rep* 1990; 39:421.
87. Centers for Disease Control and Prevention: Summary of notifiable diseases, United States, 2001. *MMWR Morb Mortal Wkly Rep* 2001; 50(53):i-xxiv, 1-108. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/figures/m053a1t8c.gif.
88. Notifiable diseases/deaths in selected cities weekly information. *MMWR Morb Mortal Wkly Rep* 2008; 57:16.
89. Fraser JD, Proft T: The bacterial superantigen and superantigen-like proteins. *Immunol Rev* 2008; 225:226-243.
90. Stevens DL: Invasive streptococcal infections. *J Infect Chemother* 2001; 7:69.
91. Stevens DL: Invasive group A streptococcus infections. *Clin Infect Dis* 1992; 14:2-11.
92. Scheinfeld NS: Pediatric Kawasaki disease. *eMedicine*, updated Jan 5, 2012. Available at http://emedicine.medscape.com/article/965367.
93. Cohen V: Toxic epidermal necrolysis. *eMedicine*, updated Sep 15, 2011. Available at http://emedicine.medscape.com/article/787323
94. Sriskandan S, Ferguson M, Elliot V, Faulkner L, Cohen J: Human intravenous immunoglobulin for experimental streptococcal toxic shock: Bacterial clearance and modulation of inflammation. *J Antimicrob Chemother* 2006; 58:117-124.

www.ketabpezeshki.com 66485457-66963820

Chapter 130

Viral Illnesses

Tenagne Haile-Mariam and Larissa May

Most viral infections are manifested as benign, self-limited upper respiratory tract or gastrointestinal infections, and therapy most often is directed at control of symptoms. Diagnosis of the specific illness is often neither necessary nor possible. On the other hand, emergency health care workers should be able to recognize viral diseases for which specific therapy or postexposure prophylaxis is available. In some cases, recognition of the manifestations of a specific viral illness and prompt institution of therapy or prevention can reduce morbidity and mortality and halt transmission of the disease to vulnerable populations. Examples include the early institution of acyclovir treatment of herpes simplex virus (HSV) encephalitis and the use of rabies vaccine and immune globulin for patients exposed to rabies. An example of how early recognition of disease can prevent widespread transmission was seen in the remarkable worldwide efforts that resulted in the halting of the SARS epidemic.

CLASSIFICATION

Viruses were first distinguished from other microorganisms by their ability to pass through filters of small pore size. Initial classifications of viruses were based on their pathologic properties (e.g., enteroviruses) or epidemiologic features (e.g., arthropod borne). More recently, classification has been based on the genetic relationships of the viruses. The components of the current classification are the type and structure of the viral nucleic acid, the type of symmetry of the virus capsid, and the presence or absence of an envelope (Table 130-1).

The genetic information of viruses is encoded in either DNA or RNA, which can be either single or double stranded and circular (closed ended) or linear (open ended). The genomes of the smallest viruses may code for only three or four proteins, whereas those of the largest viruses encode several hundred. A protein coat, called the capsid, is composed of a repeating series of protein subunits, called capsomeres. The viral nucleic acid and the surrounding protein coat are jointly referred to as the nucleocapsid. The use of repeating protein structures limits the shape of the capsid. All but the most complex viruses are either helically symmetrical or icosahedral. Finally, some virus nucleocapsids are surrounded by a lipid envelope acquired by the virus as it buds from the cell cytoplasm, nuclear membranes, or endoplasmic reticulum. Whereas this classification is important for the study and genetic identification of these organisms, for the purposes of clinical practice it is most useful to group viral illnesses by syndromic complexes based on presenting symptoms or signs.

VIRAL IMMUNIZATIONS

Whereas treatment strategies against most bacterial diseases have focused on eradication of bacteria from the host after disease has developed, the most successful strategies against viral diseases have concentrated on immunization, with the goal of preventing infection or illness. The history of immunization against viral diseases began in 1796, when Jenner injected pustular material from the lesions of cowpox into a child to prevent smallpox.[1] The word *vaccination* is derived from *vaccinia,* referring to the skin reaction at the site of injection of such material for smallpox immunization, and originally meant "inoculation to render a person immune to smallpox." Currently, the terms *vaccination* and *immunization* are used interchangeably to mean the administration of any vaccine. *Immunization* is a broader term that includes administration of immunobiologics such as immune globulins.

Viral vaccines are suspensions of live, attenuated, or inactivated whole viruses or parts of viruses that are administered to induce immunity. Some vaccines, such as the surface antigen of hepatitis B, are highly defined; others, such as live, attenuated viruses, are complex. Immune globulin is an antibody preparation obtained from large pools of human blood plasma. It is given intramuscularly for passive immunization against measles and hepatitis A and intravenously as replacement therapy for antibody deficiency disorders. Specific immune globulins are preparations of monoclonal antibodies or are prepared from special donor plasma pools preselected for high antibody titers against specific antigens, such as those presented by the hepatitis B, varicella-zoster, or rabies viruses. None of the immune globulin preparations, when properly prepared, can transmit infectious viruses.

The modern era of immunization began in 1885, when Louis Pasteur and colleagues injected the first of 14 daily doses of rabbit spinal cord suspensions containing progressively inactivated rabies virus into 9-year-old Joseph Meister, who had been bitten by a rabid dog 2 days earlier.[2] The introduction of the inactivated poliomyelitis vaccine (IPV) in 1955 and the attenuated live oral polio vaccine (OPV) in 1962 has virtually eliminated the threat of paralytic poliomyelitis in the United States and other developed countries.[2,3] Currently, a massive World Health Organization (WHO) campaign to eradicate polio worldwide is under way. As of 2007, in four countries (Pakistan, India, Afghanistan, and Nigeria), polio transmission has never been interrupted, and in several more countries in Asia and Africa, polio has reemerged.[4] Vaccines against measles, mumps, rubella, influenza, and hepatitis B have greatly reduced morbidity and mortality associated with

www.ketabpezeshki.com 66485457-66963820

Table 130-1 Classification of Viruses

FAMILY	EXAMPLES	REPRESENTATIVE DISEASES, COMMENTS
DNA Viruses		
Poxviridae	Variola Orf	Smallpox Contagious pustular dermatitis
Herpesviridae	HSV-1, HSV-2 Cytomegalovirus VZV HHV-6 EBV Kaposi's sarcoma herpesvirus	Mucocutaneous ulcers, herpes encephalitis Pneumonitis in immunocompromised patients Chickenpox, shingles Roseola infantum Mononucleosis Kaposi's sarcoma
Adenoviridae	Adenovirus (50+ species)	Upper respiratory tract infections, diarrhea
Papillomaviridae	Papillomavirus (80+ species)	Warts (e.g., plantar, genital)
Polyomaviridae	JC virus	PML
Hepadnaviridae	Hepatitis B	Hepatitis
Parvoviridae	Parvovirus B19	Aplastic anemia
RNA Viruses		
Reoviridae	Colorado tick fever Rotavirus	Fever and rash Gastroenteritis
Togaviridae	Eastern equine encephalitis Rubella	Epidemic encephalitis German measles
Flaviviridae	Yellow fever Dengue West Nile virus Hepacivirus, hepatitis C	Hemorrhagic fever Dengue hemorrhagic fever West Nile encephalitis Chronic hepatitis
Coronaviridae	Coronavirus SARS-CoV	Upper respiratory tract infections Severe acute respiratory syndrome
Paramyxoviridae	Respiratory syncytial virus Measles Parainfluenza	Bronchiolitis Measles (rubeola), SSPE Croup
Rhabdoviridae	Rabies	Rabies
Filoviridae	Ebola	Hemorrhagic fever
Orthomyxoviridae	Influenza A, B	Influenza
Bunyaviridae	La Crosse Hanta	Encephalitis Hemorrhagic fevers, ARDS
Arenaviridae	Lassa Lymphocytic choriomeningitis virus	Hemorrhagic fever Meningoencephalitis
Retroviridae	HIV	AIDS
Picornaviridae	Poliovirus Coxsackie B Hepatitis A Rhinovirus (115+ species)	Polio Myocarditis Enteric hepatitis Upper respiratory infections
Caliciviridae	Norwalk virus	Gastroenteritis
Unclassified viruses	Hepatitis E	Enteric hepatitis
Subviral Agents		
Satellites	Delta virus	Hepatitis
Prions		Kuru, Creutzfeldt-Jakob disease

AIDS, acquired immunodeficiency syndrome; *ARDS,* acute respiratory distress syndrome; *EBV,* Epstein-Barr virus; *HHV,* human herpesvirus; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *PML,* progressive multifocal leukoencephalopathy; *SARS-CoV,* severe acute respiratory syndrome–coronavirus; *SSPE,* subacute sclerosing panencephalitis; *VZV,* varicella-zoster virus.

these diseases. The worldwide eradication of smallpox in 1977 is a testament to the advances made against viral diseases.

Administration of an immunobiologic agent does not automatically confer adequate immunity. Some preparations require more than one dose to produce an adequate antibody response, or periodic boosters may be needed to maintain protection. The simultaneous administration of immune globulin with a live virus vaccine may result in diminished antibody response to the vaccine. Deviation from the recommended volume or number of doses of any vaccine is strongly discouraged. Significant problems also remain in developing countries that cannot afford vaccines or have problems delivering vaccines to their at-risk populations. Table 130-2 summarizes currently available viral vaccines, their indications, and recommended uses.[5-8] During the past several years,

www.ketabpezeshki.com 66485457-66963820

Table 130-2 Viral Vaccines

VIRUS	VACCINE	TYPE	INDICATION	RECOMMENDED SCHEDULE
Smallpox	Vaccinia	Live	For persons at risk or for emergency responders	Once, before anticipated risk of exposure
Polio	Oral polio vaccine (Sabin)	Live	During outbreaks Unvaccinated travelers	Inactivated polio vaccine preferred in almost all cases
	Inactivated polio vaccine (Salk)	Inactivated	All children	At 2, 4, and 12 to 18 months and at 4 to 6 years
Measles	Measles, mumps, rubella (MMR)	Live	All normal children	At 12-15 months and 4-6 years
Mumps	MMR	Live	All normal children	Same as for measles
Rubella	MMR	Live	All normal children	Same as for measles
Hepatitis A	HAV vaccine	Inactivated	Persons at risk (e.g., travelers, persons living in areas of high prevalence)	Two doses, 6 months apart Immune globulin should be given if travel is imminent
Hepatitis B	HBV vaccine	Inactivated or recombinant	All children	At birth, 1-4 months, and 6-18 months
			Persons at risk of exposure (e.g., health care workers)	Hepatitis B immune globulin (HBIG) should be given in addition in case of high-risk exposure
Influenza A and B	Influenza vaccine	Inactivated	Persons at high risk for complications (e.g., elders) or persons capable of transmitting influenza to high-risk patients (e.g., health care workers)	One dose yearly in the fall or winter
	Intranasal vaccine	Live, cold adapted	As above, for persons 5-49 years of age	As above
Rabies	Human diploid cell vaccine (HDCV)	Inactivated	Postexposure prophylaxis	HDCV, RVA, or PCEC 1.0 mL IM in the deltoid region on days 0, 3, 7, 14, and 28
	Rabies vaccine absorbed (RVA)	Inactivated	Pre-exposure prophylaxis in high-risk groups (e.g., veterinarians)	Rabies immune globulin (RIG) 20 IU/kg should be administered around the wound site, as possible, with the remainder given IM at an anatomically distant site
	Purified chick embryo cell (PCEC)	Inactivated		
Yellow fever	17D virus strain	Live	Persons older than 6 months traveling to endemic areas	Boosters every 10 years
Varicella	Varicella	Live	All healthy children	Persons 1-12 years old should receive one dose
			At-risk adults	Persons older than 13 years should receive two doses 4-8 weeks apart

new vaccines have been developed against rotavirus,[8] a major cause of diarrheal disease in young children worldwide; human papillomaviruses,[9] which are associated with urogenital cancers; and herpes zoster (shingles),[10] which is a major cause of morbidity in mostly elderly patients.

ANTIVIRAL CHEMOTHERAPY

Because most viral illnesses are self-limited, treatment generally is targeted at amelioration of symptoms. The revolution in molecular biology has unlocked pathophysiologic mechanisms of viral diseases and opened up the field of viral chemotherapy. The initial therapeutic armamentarium for viral diseases has been aimed at illnesses associated with significant mortality (e.g., ribavirin for Lassa fever, acyclovir for HSV encephalitis) or those associated with significant end-organ damage (e.g., ganciclovir for cytomegalovirus [CMV] retinitis, acyclovir for ophthalmic zoster) (Table 130-3).

Amantadine and Rimantadine

Amantadine (Symmetrel) and rimantadine (Flumadine) are effective in the prevention and treatment of influenza A but have no activity against influenza B. They prevent or greatly reduce the uncoating of the viral RNA of influenza A after attachment and endocytosis by host cells. When it is initiated before exposure to influenza A, amantadine, 200 mg/day orally, is effective in preventing illness in 50 to 90% of subjects. When it is begun within 2 days after the onset of symptoms of influenza A, amantadine has reduced the duration of fever and systemic symptoms by 1 to 2 days. The drug generally is well tolerated; the most common therapy-limiting toxicities are central nervous system (CNS) effects, such as nervousness, lightheadedness, difficulty in concentrating, insomnia, and decreased psychomotor performance. These reactions occur particularly in elders who have impaired renal function; they should receive no more than 100 mg of amantadine daily. Rimantadine is mostly metabolized before renal

www.ketabpezeshki.com 66485457-66963820

Table 130-3 Drugs for the Treatment of Viral Illnesses

VIRUS	DISEASE	DRUG OF CHOICE	ALTERNATIVE TREATMENT	PROPHYLAXIS OR SUPPRESSIVE
Cytomegalovirus	Retinitis	Ganciclovir 5 mg/kg IV bid for 14-21 days, then 5 mg/kg IV qd Valganciclovir 900 mg PO bid for 14-21 days, then 900 mg PO qd	Foscarnet 90 mg/kg IV bid for 14-21 days, then 90-120 mg/kg IV qd Cidofovir 5 mg/kg weekly IV for 2 weeks, then 5 mg/kg q2wk Ganciclovir implant Ganciclovir, foscarnet, or cidofovir intraocular injections	
	Colitis, esophagitis	Same as for retinitis, but need for maintenance not established	Foscarnet, as above	
	Pneumonitis	Ganciclovir, as above, with or without IV immune globulin Need for maintenance not established		
Hepatitis B (see also Chapter 90)	Chronic hepatitis	Interferon alfa, 5 million units SC or IM qd or 10 million units SC or IM 3 times/week for 16-24 weeks	Lamivudine 100 mg PO qd for 1-3 years Adefovir 10 mg PO qd	Hepatitis B immune globulin (HBIG)
Hepatitis C (see also Chapter 90)	Chronic hepatitis	Peginterferon alfa-2b, 1-1.5 µg/kg SC weekly for 24-48 weeks *or* Peginterferon alfa-2a, 180 µg SC weekly for 24-48 weeks *Either with* Ribavirin 1000-1200 mg PO daily in divided doses	Interferon alfa, 3 million units SC or IM 3 times/ week *with* Ribavirin 1000-1200 mg PO daily in divided doses	
Herpes simplex virus	Genital	Acyclovir 200 mg PO, 5 times/day, or 400 mg PO tid for 7-10 days If severe or complicated by aseptic meningitis, can give acyclovir 5 mg/kg q8h for 5 days	Foscarnet 40-60 mg IV q8h (for acyclovir-resistant HSV)	Acyclovir 200-400 mg PO bid *or* valacyclovir 500-1000 mg PO qd *or* famciclovir 250 mg PO bid
	Mucocutaneous disease in immunocompromised host	Acyclovir 400 mg qid, famciclovir 500 mg tid, or valacyclovir 500 mg bid for 7-14 days	Acyclovir 5 mg/kg q8h for 7-14 days	Variable regimen, depending on length of immunocompromised state
	Neonatal keratoconjunctivitis	Trifluridine 1% ophthalmic solution, 1 drop topically q2h, up to 9 drops daily for 10 days		
	Primary encephalitis	Acyclovir 10 mg/kg q8h for 14-21 days	Foscarnet 40-60 mg IV q8h (for acyclovir-resistant HSV)	
Human immunodeficiency virus (see also Chapter 132)		Combination therapy with: Zidovudine Didanosine Zalcitabine Lamivudine Stavudine Abacavir Tenofovir Emtricitabine Saquinavir Ritonavir Indinavir Nelfinavir Amprenavir Atazanavir Fosamprenavir Nevirapine Delavirdine Efavirenz Enfuvirtide, T-20	See Chapter 132 for dosing and therapeutic combination therapy	
Influenzavirus A	Influenza A	Oseltamivir 75 mg PO bid for 5 days	Zanamivir 2 inhalations bid for 5 days	
Influenzavirus B	Influenza B	Oseltamivir 75 mg PO bid for 5 days	Zanamivir 2 inhalations bid for 5 days	

Continued

www.ketabpezeshki.com 66485457-66963820

Table 130-3 Drugs for the Treatment of Viral Illnesses—cont'd

VIRUS	DISEASE	DRUG OF CHOICE	ALTERNATIVE TREATMENT	PROPHYLAXIS OR SUPPRESSIVE
Lassa fever virus	Lassa fever	Ribavirin 1 g IV q6h for 4 days, then 500 mg IV q8h for 6 days	Treatment for Lassa fever is investigational.	
Papillomavirus	Condyloma acuminatum	Interferon alfa-2b, 1 million units/0.1 mL intralesional injection in up to 5 warts three times/week for 3 weeks Imiquimod 5%, topical application to warts 3 times/week		
Respiratory syncytial virus	Severe bronchiolitis or pneumonia in infants and children	Ribavirin aerosol, 12-18 hours daily for 3-7 days with a 20 mg/mL concentration reservoir		RSV immune globulin can be used for prophylaxis in young children. Palivizumab, a monoclonal antibody, can be given monthly to premature infants.
Varicella-zoster virus	Varicella (chickenpox) Herpes zoster (shingles) Varicella or zoster in an immunocompromised host	Acyclovir 20 mg/kg, up to 800 mg, PO qid for 5 days Valacyclovir 1 g PO tid for 7 days Famciclovir 500 mg PO tid for 7 days Acyclovir 10 mg/kg IV q8h for 7 days	Acyclovir 800 mg PO 5 times/day for 7-10 days Foscarnet 40 mg/kg IV q8h for 10 days (for acyclovir-resistant VZV)	

excretion, and a lower incidence of CNS toxicity is associated with rimantadine than with amantadine. Other side effects include nausea and loss of appetite. Overdose is associated with an anticholinergic syndrome.[11]

Prophylaxis with daily amantadine or rimantadine is indicated for the duration of the influenza season in persons at high risk for contracting influenza in whom the influenza vaccine is contraindicated. When influenza A is reported in a community, appropriate management is to administer the influenza vaccine and to give amantadine for 2 weeks while antibody production is induced. Adults with acute onset of fever, cough, headache, and myalgias may be treated with 200 mg of amantadine, followed by 100 mg for 5 to 7 days.

During the 2005-2006 influenza season, the Centers for Disease Control and Prevention (CDC) recommended that amantadine and rimantadine no longer be used for treatment or prophylaxis of influenza A because of high levels of resistance among H3N2 viruses during that season.[12] In 2008 the Advisory Committee on Immunization Practices updated their recommendations that these antivirals not be used for the treatment or chemoprophylaxis of influenza A in the United States until evidence of their effectiveness had been reestablished among circulating influenza A viruses.[13] It seems unlikely they will come back into use, given persistent findings of adamantane resistance among influenza A viruses, including pandemic H1N1.[14]

Zanamivir and Oseltamivir

Zanamivir (Relenza) and oseltamivir (Flumadine) were approved in 1999 for the treatment of influenza A and B. Both medications act by inhibiting the activity of neuraminidase, an enzyme involved in the release of viral progeny from infected cells. They have been shown to decrease the duration of moderate or severe symptoms of influenza by approximately 1 day. Either medication should be started within 2 days of onset of symptoms if efficacy is to be expected. Zanamivir is administered by inhalation through a novel device (Diskhaler) and is approved for use in patients older than 12 years. The dose is two inhalations twice a day for 5 days. Most of the inhaled dose is deposited in the respiratory tract and cleared unchanged in the urine or stool. The most common side effect is bronchospasm in predisposed patients. Such patients should be given a fast-acting inhaled bronchodilator before receiving zanamivir.[12,15]

Olestamivir is an oral medication approved for patients older than 2 weeks. The dose is 75 mg twice daily for 5 days for adults and children weighing more than 40 kg. For children younger than 1 year, the dose is 3 mg/kg twice daily. For children 1 year or older, the dose varies by weight: 30 mg twice daily for those weighing less than 15 kg, 45 mg twice daily for those weighing 15 to 23 kg, and 60 mg twice daily for those weighing 23 to 40 kg. Initial reports of influenza virus resistance to oseltamivir were followed by a rapid rise in such resistance in H1N1 strains in the United States during the 2008-2009 influenza season.[16] This resistance was not seen in the H3N2 strain that was also circulating during the same season. This resulted in the CDC's issuing interim treatment recommendations in December 2008. If treatment was based on the identification of the infecting virus, zanamivir was recommended as first-line treatment for H1N1 and oseltamivir for H3N2. If such data were not available to the treating physician, the CDC recommended that clinicians review local disease surveillance data to determine which subtype was more likely to be the offending agent and choose treatment accordingly.[13] With the onset of pandemic H1N1, there were initial concerns about the need for treatment and prophylaxis of patients at risk for complications from influenza, which prompted the CDC to create interim guidelines recommending that all hospitalized persons confirmed or thought to be infected with novel H1N1 and all patients at risk for complications be treated with antiviral agents.[16,17] Because of concerns about the development of resistance to oseltamivir and zanamivir in influenza A viruses, recommendations for their use were limited to the population at risk for complications. To date, 0.5% of novel H1N1 viruses submitted to a United States influenza surveillance system were found to be resistant to olsetamivir.[18]

Acyclovir

Acyclovir (Zovirax) is one of the drugs of choice for serious infections caused by HSV or varicella-zoster virus (VZV). Only 15 to

www.ketabpezeshki.com 66485457-66963820

30% of the oral formulation is absorbed, so the intravenous form is required to treat HSV encephalitis, disseminated or ophthalmic zoster, or extensive HSV or VZV infection in the immunocompromised patient. Oral acyclovir has some use in treatment of primary HSV infections and in suppression of frequent recurrences of these infections. In general, the more immunocompromised the patient, the greater the likelihood that he or she will require intravenous acyclovir therapy. Acyclovir rarely is associated with gastrointestinal upset, reversible renal dysfunction, or encephalopathy.[19]

Famciclovir and Valacyclovir

Famciclovir (Famvir) and valacyclovir (Valtrex) are analogues of acyclovir that inhibit herpesvirus DNA synthesis.[20,21] They are much more bioavailable than acyclovir and can be given less frequently. Both are available only as oral formulations and are effective in prevention of recurrent HSV infection.[22,23]

Ganciclovir

Ganciclovir (Cytovene) is used to treat life- or sight-threatening CMV infections in immunocompromised patients. Patients with acquired immunodeficiency syndrome (AIDS) and CMV colitis or esophagitis may also improve with ganciclovir. Some CMV isolates in immunocompromised patients have been found to be or may become resistant to ganciclovir.[24] Ganciclovir also is effective against HSV, but isolates resistant to acyclovir also are resistant to ganciclovir. The most common therapy-limiting toxic effects of ganciclovir are granulocytopenia and thrombocytopenia, which usually are reversible when therapy ceases.

Cidofovir

Cidofovir (Vistide) is a nucleotide agent used to treat CMV retinitis in patients with human immunodeficiency virus (HIV) infection and acyclovir-resistant HSV infections. It is available only for parenteral administration but has a long half-life, allowing a dosing schedule of once per week or less frequent administration. The most common form of toxicity is renal insufficiency, which usually is reversible on discontinuation of the drug.

Foscarnet

Foscarnet (Foscavir, trisodium phosphonoformate hexahydrate, phosphonoformic acid) is an antiviral agent with activity against the human herpesviruses and HIV-1. It has been shown to be effective against CMV retinitis in AIDS patients and in acyclovir-resistant HSV and VZV infections.[25] The main limiting form of toxicity with foscarnet is renal insufficiency, which usually is reversible after the drug is discontinued. Other side effects include malaise, headache, fatigue, nausea, vomiting, anemia, hypomagnesemia, hypophosphatemia, hyperphosphatemia, and hypocalcemia.

Vidarabine

Intravenous vidarabine (Vira-A, adenine arabinoside, Ara-A) can be effective for life-threatening HSV and VZV infections, but because of its potential for toxicity, acyclovir and foscarnet have largely replaced it.

Trifluridine

Trifluridine 1% ophthalmic solution (Viroptic, Trifluorothymidine) is effective for treatment of primary keratoconjunctivitis and recurrent epithelial keratitis caused by HSV. Treatment of ocular infections should be undertaken in consultation with an ophthalmologist. Duration of treatment depends on the lesions' response to the medication.

Interferon Alfa, Recombinant

Interferons are naturally occurring proteins with both antiviral and immunomodulating properties that are produced by host cells in response to an inducer. Injected intralesionally, recombinant preparations of interferon-alpha (interferon alfa-2a [Roferon-A], interferon alfa-2b [Intron A], peginterferon alfa-2b [PegIntron]) are effective in treatment of refractory condyloma acuminatum.[26] Patients with chronic hepatitis B who have lost hepatitis B e antigen with interferon therapy have better long-term outcome with lower rates of end-stage liver disease and its complications.[27] Newer agents for treatment of hepatitis B infection include lamivudine, adefovir, entecavir, and telbivudine. Interferon alfa-2b combined with ribavirin has been shown to induce virologic and histologic response in patients with chronic hepatitis C infection. Therapy is discontinued because of side effects in approximately 20% of patients. The side effects of interferon therapy include fever, malaise, headache, fatigue, alopecia, and bone marrow suppression. Use of newer pegylated interferons is now standard therapy for hepatitis C.[28,29]

Therapy for HIV Infection

More than 30 antiretroviral drugs are currently available for the treatment of HIV infection (see Table 130-3). Treatment regimens usually include at least three of the recommended antiretroviral agents. Treatment of HIV infection is covered in Chapter 132.

Therapy for Hepatitis B Infection

At present, four antiviral agents are licensed for the treatment of chronic hepatitis B: lamivudine, adefovir, entecavir, and telbivudine. In addition, emtricitabine, tenofovir, and their combined tablet, licensed for HIV infection, are off-label options. The treatment of hepatitis B infection is highly specialized. Treatment of hepatitis B infection is covered in Chapter 90.

Vaccine-Preventable Infections of Childhood

Mumps Virus

Principles of Disease. Mumps, or infectious parotitis, is an acute viral illness characterized by fever, swelling, and tenderness of the salivary glands, with the parotid gland most commonly involved. Mumps occurs most commonly in the winter and spring and, since the advent of widespread pediatric immunization, mostly in older children. The virus is spread by way of the respiratory tract and through direct contact with the saliva of infected people. The incubation period is 2 to 4 weeks, and the disease is communicable from 1 week before to 9 days after the onset of parotitis, with a period of maximal infectiousness approximately 2 days before the onset of illness. One third of cases are asymptomatic.

Clinical Features. Nonsuppurative parotid swelling is the hallmark of mumps; the swelling may be unilateral. Trismus sometimes is a feature. In the first 3 days, the patient's temperature may range between normal and 40° C. The most important but less common manifestations are epididymo-orchitis and meningitis. Orchitis occurs in 15 to 25% of postpubertal male patients and usually is unilateral. Although some degree of testicular atrophy is usual, the incidence of sterility is low, especially when the orchitis is unilateral. More than 50% of patients with mumps have a lymphocytic pleocytosis in the cerebrospinal fluid (CSF), and

www.ketabpezeshki.com 66485457-66963820

hypoglycorrhachia is common; symptomatic meningitis occurs in less than 10% of cases. Encephalitis is uncommon, occurring in 1 in 6000 cases, and is the major determinant of mortality. Congenital infection is rare but may result in fetal loss if it occurs in the first trimester. Rare complications of mumps include hydrocephalus, deafness, transverse myelitis, Guillain-Barré syndrome, pancreatitis, mastitis, oophoritis, myocarditis, and arthritis.

Differential Considerations. In children, the diagnosis of mumps is made by a history of infectious exposure and the presence of parotid swelling and tenderness in association with constitutional symptoms. Laboratory confirmation generally is not required. Considerations in the differential diagnosis include other viral infections and other causes of parotid swelling and tenderness, such as bacterial parotitis or sarcoidosis.

A multistate outbreak of mumps was reported in the United States in 2006, with almost 6000 reported cases.[30] Because the likelihood of infection was five times higher in persons who had received only one dose of mumps vaccine as opposed to those who had received two doses of the vaccine, updated recommendations that all persons receive two doses of mumps vaccine were introduced by the CDC's Advisory Committee on Immunization Practices.[31]

Management. Treatment is supportive and should include an analgesic and an antipyretic agent. No data support the use of steroids to prevent complications or to ameliorate the symptoms of orchitis in postpubertal men.

Contacts who have had no history of mumps or of previous vaccination should be immunized. Because there is no risk in vaccinating those who are already immune, serologic screening to identify susceptible people is unnecessary. Long-lasting immunity develops in more than 95% of recipients of the vaccine. Among previously infected people, including those who had asymptomatic disease, long-lasting and possibly lifelong immunity is possible.

Measles Virus (Rubeola)

Principles of Disease. Measles is a highly communicable viral illness acquired as an infection of the respiratory tract. In general, all susceptible people exposed to an active case will acquire infection. After multiplication in the respiratory mucosa, the virus spreads to regional lymphoid cells and then travels in the bloodstream to leukocytes in the reticuloendothelial system. The clinical manifestations appear after a second viremic phase.

Before the availability of an effective vaccine in 1963, measles was a ubiquitous disease. In 2006, measles accounted for approximately 240,000 deaths globally; in view of higher death rates in previous years, it is clear that great strides have been made to decrease measles deaths in many areas of the world. Measles continues to be a leading cause of death in young children, especially those living in developing countries.[32] Endemic measles in the United States has been eradicated, although the disease continues to occur among inadequately vaccinated persons who, in most instances, have been exposed to the disease by someone who has been infected abroad. A recent increase in the number of reported measles cases has been linked to travel abroad and unvaccinated status.[33,34] Measles is a reportable disease, and the local health authority should be contacted. Children should be kept out of school for at least 4 days after the appearance of the rash.

Clinical Features. The incubation period of measles is 10 to 14 days. Cough, coryza, conjunctivitis, and fever precede development of the characteristic rash by 2 to 4 days (Fig. 130-1A). Pinpoint grayish spots surrounded by bright red inflammation (Koplik's spots) typically are found on the lateral buccal mucosa before the appearance of the rash and are considered pathognomonic for measles (Fig. 130-1B). Discrete red macular and papular lesions begin on the head and progress downward during a period

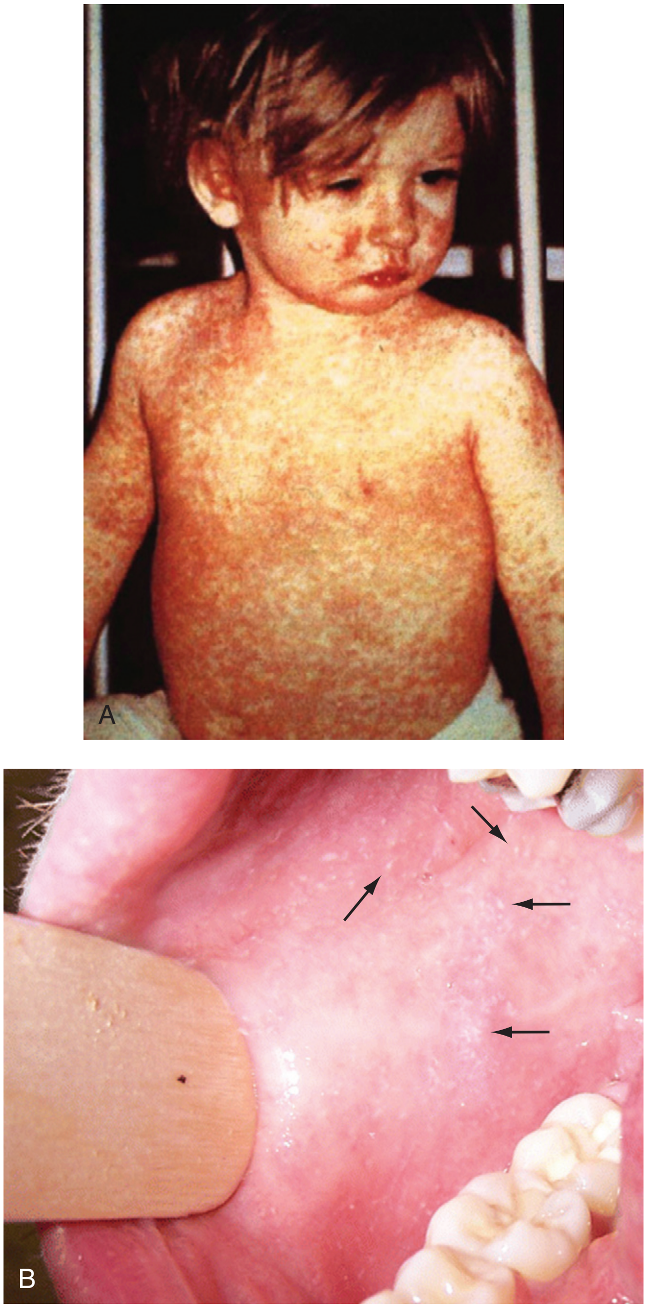


Figure 130-1. A, Measles. B, Koplik's spots due to measles. (From Steichen O, Dautheville S: Koplik spots in early measles. CMAJ 180:583, 2009. © 2009 Canadian Medical Association.)

of 3 days to cover the entire body. Laryngitis, tracheobronchitis, bronchiolitis, and pneumonitis may accompany the disease. Bacterial superinfections occasionally delay recovery. A rare acute encephalomyelitis, associated with a mortality rate of 25%, can complicate recovery. Unlike rubella, measles acquired during pregnancy is not teratogenic but may result in stillbirth or premature delivery.

Among infants and malnourished children, more severe illness is usual. Deaths from pneumonia and diarrhea occur in up to 10% of cases. Measles can exacerbate vitamin A deficiency and lead to blindness.

Measles may be manifested with atypical findings in people who were vaccinated with the inactivated vaccine before its removal from the market in the United States in 1968. An atypical rash, predominantly on the extremities, can accompany pneumonitis,

www.ketabpezeshki.com 66485457-66963820

pleural effusion, and peripheral edema. The current vaccine is a live, attenuated strain available as a single antigen or in combination with rubella vaccine or with mumps and rubella vaccines.

Differential Considerations. The diagnosis is made primarily on the basis of clinical characteristics. Other viral exanthems may at times be manifested with a similar rash.

Management. Treatment of the primary disease is supportive. Immunocompromised children and infants younger than 1 year who are susceptible and have been exposed to measles can be given passive immunization within 6 days of exposure. Healthy infants should receive 0.25 mL/kg of immune globulin intramuscularly, and immunocompromised children should be given 0.5 mL/kg intramuscularly, up to 15 mL.

Subacute Sclerosing Panencephalitis

Principles of Disease. Subacute sclerosing panencephalitis (SSPE) is a degenerative disease of the brain caused by measles virus or a defective variant that persists in the CNS after primary measles. SSPE has virtually disappeared in the United States since the 1970s, approximately 10 years after measles vaccination began.

Clinical Features. SSPE is a subacute encephalitis involving both the white and the gray matter of the cerebral hemispheres and brainstem and follows 1 in 100,000 cases of measles. It generally occurs in patients with a history of an uncomplicated case of primary measles that occurred at a younger than average age. Five to 10 years later, SSPE is manifested with myoclonus and variable focal neurologic deficits. Progressive neurologic degeneration ensues, and death usually occurs within months to years of diagnosis.

Diagnostic Strategies. The disease can resemble other degenerative neurologic disorders, but characteristic electroencephalographic changes and the detection of measles antibodies in the CSF and markedly elevated serum antibodies to measles will confirm the diagnosis.

Management. Treatment is supportive only.

Rubella Virus (German Measles)

Clinical Features. Rubella is a mild febrile illness associated with a diffuse maculopapular rash, fever, malaise, headache, and postauricular, occipital, and posterior cervical lymphadenopathy (Fig. 130-2).

Figure 130-2. Rubella.

Transmission of rubella is through contact with respiratory secretions. The incubation period of rubella ranges from 12 to 23 days. Accompanied by viremia, the rash usually lasts 3 to 5 days. The disease is highly communicable from approximately 1 week before to 4 days after the onset of the rash. The most common complications of rubella are arthropathies, or frank arthritis, predominantly affecting the fingers, wrists, and knees; the arthropathies may persist for several months. Encephalitis and thrombocytopenia are rare complications.

Although the disease generally is a mild, febrile illness in children and adults, the consequences of rubella occurring during pregnancy (congenital rubella syndrome) may be tragic. Severe consequences include fetal death, premature delivery, and a variety of congenital defects, including hearing loss, cataracts, retinopathy, mental retardation, and a variety of cardiac abnormalities. The younger the fetus is at the time of a maternal infection, the more likely it is that the fetus will be affected. During the first 2 months of pregnancy, the fetus has an approximately 90% chance of being affected. The risk decreases to approximately 80% during the third month and to 66% during the fourth month, with no congenital defects reported from infection after the 17th week of pregnancy.

Differential Considerations. The rash associated with rubella (third disease) is one of the classic common exanthems of childhood. It may be similar to the rash of measles (rubeola, or first disease), scarlet fever (second disease), a variant of scarlet fever or toxin-producing staphylococcal disease (fourth disease), erythema infectiosum (fifth disease), and roseola (exanthema subitum, or sixth disease).

Management. Rubella control is required to prevent birth defects in the offspring of women who have the disease during pregnancy. In the United States, vaccination to prevent rubella is recommended for all children at the age of 15 months. Vaccination results in a greater than 95% seroconversion rate. Because of the production of a transient viremia, pregnancy should be delayed for 3 months after a susceptible woman has been vaccinated. No cases of the congenital rubella syndrome attributable to rubella vaccine occurred in more than 300 women inadvertently vaccinated during pregnancy who carried their infants to term.[35] There is no evidence of decreasing immunity with age. Persons with rubella should be cautioned to avoid contact with susceptible women. Because of an increasing failure to vaccinate susceptible persons, a moderate resurgence of rubella and a major increase in the congenital rubella syndrome in the United States occurred in 1990. Since then, a general decline in rubella incidence has been observed, but outbreaks continue to occur, especially among foreign-born adults.

SPECIFIC VIRAL DISEASES BY PRESENTING CLINICAL SYNDROME

Viral Diseases with Significant Dermatologic Manifestations

Poxviridae

Perspective. The elimination from the natural environment of variola virus, the virus that causes smallpox, at one time the most devastating worldwide pestilence, is one of the great medical and public health accomplishments of the past century.[5] The

www.ketabpezeshki.com 66485457-66963820

Figure 130-3. Smallpox.

elimination of smallpox from the natural environment was possible because of the lack of nonhuman reservoirs or human carriers of variola and the availability of rapid diagnostic techniques and an effective vaccine. Global eradication was certified by the WHO in 1980. Other human poxvirus diseases include monkeypox, vaccinia virus infection, molluscum contagiosum, orf, and paravaccinia virus infection. The poxviruses are the largest pathogenic viruses, consisting of complex, brick-shaped capsids and double-stranded DNA.

Variola (Smallpox), Monkeypox, Vaccinia, and Cowpox Viruses. Within the Poxviridae family, the Orthopoxvirus genus contains at least nine homogeneous viruses, including variola, vaccinia, cowpox, and monkeypox viruses. The last naturally acquired case of smallpox occurred in Somalia in October 1977. Two cases occurred in 1978 in Birmingham, England, related to a research laboratory accident.

Principles of Disease. Recently, the possibility that military and research stores of virus could become weaponized and used as tools of terrorism or war has mandated that health care professionals familiarize themselves with the manifestations of smallpox, the clinical manifestations of vaccine-related illness, and the risks and benefits of the vaccine. The CDC has established extensive web-based information and training materials in preparation for the possibility of an outbreak.

Clinical Features. Smallpox is transmitted by infected droplets or close contact with a patient in any stage of illness. The most common manifestation in the unvaccinated host is variola major, which has a fatality rate of approximately 30%. The illness is characterized by a short prodrome of headache, backache, and fever. An ensuing enanthem progresses from small macules to papules and then vesicles during a few days. Lesions begin on the face and limbs and spread in a centrifugal pattern. These develop into 4- to 6-mm firm, deep-seated vesicles or pustules that umbilicate, crust, and then desquamate in the next several weeks (Fig. 130-3). All lesions are at the same stage of development. Modified, milder forms of smallpox can appear in previously vaccinated patients and, more rarely, in nonimmune hosts. There are also two more rare but almost uniformly fatal forms of smallpox: a fulminant, “hemorrhagic” form and “flat type” smallpox, characterized by plaquelike lesions.[36]

Diagnostic Strategies. Major criteria for diagnosis include a prodrome of 1 to 4 days with fever (temperature higher than 38.3° C) and symptoms and signs such as headache and vomiting. Minor criteria include a centrifugal distribution of the rash, lesions on the palms and soles, a toxic appearance, and a rash that develops during several days. Routine laboratory tests are not helpful in the diagnosis. In the prodromal phase, there may be a relative granulocytopenia, but the white blood cell count usually is elevated in the eruptive phase. Laboratory diagnosis can be established by antibody testing, cell culture, or electron microscopy.

Differential Considerations. Smallpox has been confused with other papulovesicular eruptions, including varicella (chickenpox), measles, erythema multiforme, molluscum contagiosum, generalized vaccinia virus infection, and monkeypox. The lesions of chickenpox generally are at different stages of development and healing and often spare the palms and soles.

Management. The CDC guidelines classify suspected cases of smallpox into categories of high, moderate, and low risk. Cases with high or moderate risk should prompt appropriate isolation and consultation with an infectious disease specialist or local health care authority. Quarantine, contact tracing, and immunization efforts are a priority for public health officials, and prompt involvement of the appropriate agencies will be crucial to containment efforts in the event of an outbreak.

Immunization with vaccinia virus was the cornerstone of smallpox containment and eradication efforts. Vaccinia virus immunization has been associated with morbidity and death in vaccinated persons and their close contacts. The decision to vaccinate must balance the risk of smallpox infection against the risk of vaccine-related injury. Pre-event vaccination is contraindicated in several groups of patients, including those who are pregnant, are breastfeeding, have significant immunosuppression, or have eczema. Close household contacts of persons at risk for serious side effects from vaccine should not be vaccinated. There are no absolute contraindications to vaccination for persons who have been exposed to smallpox.

Vaccinia Virus

Perspective. The origin of the vaccinia virus is not well established, but it is the poxvirus that is used to produce the smallpox vaccine. Although primary infection (through live virus vaccination) or secondary infection (from virus shed from an immunized patient) with vaccinia virus is usually well tolerated, severe local reactions from immunization as well as disseminated severe manifestations of primary or secondary infection have been well described. The normal reaction to vaccinia vaccine is a localized inflammatory reaction with scar formation. Viremia is possible, but manifestations are of a mild viral illness. In immunocompromised hosts, such as some young infants or persons with aberrant cell-mediated immunity, a syndrome of multiplying and aggressive necrotic skin lesions called progressive vaccinia can lead to death.

Management. Therapy for this syndrome with vaccinia immune globulin (VIG) and antiviral medications such as cidofovir and ribavirin has been advocated.[37]

Cowpox Virus

Perspective. Edward Jenner, in his *An Inquiry into the Causes and Effects of the Variolae Vaccinae* in 1798, observed that on inoculation into humans, the pustular material from the lesions of cowpox protected them from infection with smallpox.[1] Cowpox virus is similar to vaccinia virus and is found mostly in Europe, countries of the former Soviet Union, and Central Asia. It has natural reservoirs in wild animals but can also cause infection in domesticated animals, including cattle and cats.

Clinical Features. In the immunocompetent human host, the disease is limited to a vesiculopustular, scabbing eruption that is often localized and can be accompanied by an influenza-like syndrome. In immunocompromised hosts and person with eczematous eruptions, the disease is more aggressive and sometimes fatal. There appears to be an increase of cowpox cases in Europe that is thought to be due to waning smallpox immunity and increased exposure to the disease from wild animal reservoirs.[38]

Monkeypox Virus

Clinical Features. The disease of monkeypox is clinically similar to that of smallpox. Most cases have occurred in west and

www.ketabpezeshki.com 66485457-66963820

central Africa, with a case fatality rate of 1 to 10% and higher death rates among children. An outbreak of 72 cases in the Midwest United States in spring 2003 was traced to contact with prairie dogs housed with Gambian giant rats that were imported from Ghana.[39] No deaths were associated with this outbreak. There seems to be an increase in monkeypox cases that could be attributable to decreased cross-immunity from the cessation of smallpox vaccination as well as to increased human exposure to rainforest wildlife from hunting "bush meat." Monkeypox has also been seen as a potential biowarfare agent, but the greater threat for global spread of the disease comes from the illegal international trade of exotic animals.[40]

Parapoxviruses, Molluscum Contagiosum, and Tanapox Viruses

Perspective. Other viruses within the Poxviridae family that cause disease in humans include the parapoxviruses (paravaccinia virus and bovine pustular stomatitis virus) and the molluscum contagiosum and tanapox viruses.

Clinical Features. The milker's node virus, or paravaccinia virus, produces vesicular lesions on the udders or teats in cattle and is transmitted to humans by direct contact. Milker's nodules, which develop on the fingers or hands, are small, watery, painless nodules occasionally associated with lymphadenopathy. The lesions generally resolve completely within 3 to 8 weeks.

Bovine pustular stomatitis, ecthyma contagiosum, and orf viruses cause papillomatous lesions on the mucous membranes and corneas of sheep. Single lesions generally develop in infected persons at the site of an abrasion.

Molluscum contagiosum is a generally benign human disease characterized by multiple small, painless, pearly, umbilicated nodules. They appear on epithelial surfaces, commonly in anogenital regions, and may be spread through close contact or autoinoculation. In immunocompetent persons, the lesions may clear rapidly or persist for up to 18 months. The infection often is seen in patients with HIV infection, in whom the lesions often are not restricted to the genital area and may increase in size and number.[41] Curettage or other forms of local ablation may be helpful in such recalcitrant cases.

Herpesviridae

Principles of Disease. At least eight human herpesviruses are known. Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) are the agents of herpes genitalis, labialis, and encephalitis. Varicella-zoster virus (VZV) is the etiologic agent of chickenpox and herpes zoster. Epstein-Barr virus (EBV) is the agent of infectious mononucleosis and also is associated with nasopharyngeal carcinoma, Burkitt's lymphoma, and other lymphoproliferative syndromes. Cytomegalovirus (CMV) is associated with heterophil-negative infectious mononucleosis and invasive disease in immunocompromised patients. Human herpesvirus 6 (HHV-6) is associated with roseola infantum.[42] The role of human herpesvirus 7 (HHV-7) has not been completely elucidated. Human herpesvirus 8 (HHV-8) is associated with Kaposi's sarcoma,[43] body cavity–based lymphomas, and multicentric Castleman's disease. In addition, a closely related monkey virus, herpesvirus simiae or herpes B virus, has been shown to cause fatal encephalitis in humans.

Herpes Simplex Virus

Principles of Disease. A localized primary lesion, latency, and a tendency for local recurrence characterize infections with HSV-1 and HSV-2 (herpesvirus hominis). The primary lesion with HSV-1 may be mild and inapparent; the first outbreak may occur during childhood. Reactivation of latent HSV-1 infection usually results in herpes labialis (cold sores, fever blisters). Neurologic involvement is not uncommon with HSV-1. Although such involvement usually occurs in association with a primary infection, neurologic signs may appear after a recrudescence and may be manifested as encephalitis. Although it is uncommon, HSV-1 encephalitis is one of the most common causes of encephalitis in the United States, with estimates of several hundred to several thousand cases occurring yearly. HSV-2 most commonly is associated with genital herpes, although either HSV-1 or HSV-2 may infect any mucous membrane, depending on the route of inoculation. HSV-2 is commonly associated with aseptic meningitis rather than with meningoencephalitis. The incubation period for primary herpes infection is 2 to 12 days.[44]

On contact with abraded skin or mucous membranes, HSV replicates locally in epithelial cells, which lyse and cause a local inflammatory response. Thin-walled vesicles on an erythematous base are the characteristic lesions of superficial HSV infection. Multinucleated giant cells with ballooning degeneration and intranuclear inclusions may be seen on a Tzanck preparation of a smear of material obtained from the base of these vesicles. After primary infection, HSV can become latent within sensory nerve ganglia. Emotional stress, sunlight, fever, or local trauma can trigger reactivation of the virus. HSV encephalitis usually involves the temporal lobes, resulting in a necrotizing, hemorrhagic encephalitis.

Clinical Features. Primary HSV-1 often is asymptomatic but may appear as pharyngitis and gingivostomatitis in children younger than 5 years. Associated with fever, pharyngeal edema, erythema, cervical adenopathy, and multiple small vesicles that ulcerate and multiply, the disease generally lasts 10 to 14 days. Recurrences develop in 60 to 90% of people after primary infection but generally are milder than the primary infection. Vesicles generally recur on the vermilion border, usually are small, and crust within 48 hours.

Herpes simplex infections of the eye most often are caused by HSV-1. Primary infections are manifested as follicular conjunctivitis, blepharitis, or corneal epithelial opacities, which usually heal completely within 2 to 3 weeks. Recurrences may result in keratitis. Branching dendritic ulcers, detectable with fluorescein staining, are diagnostic and may result in diminished visual acuity. Deep stromal involvement may result in corneal scarring.

Primary herpetic finger infections (i.e., herpetic whitlow) generally are caused by HSV-1 among medical or dental personnel and by HSV-2 among the general population. The lesions are associated with intense pain and itching but generally resolve in 2 to 3 weeks. Recurrent whitlow with severe local neuralgia may occur.

Primary genital herpes generally is seen in the sexually active population and is caused by HSV-2 in 70 to 95% of cases. The lesions usually involve the shaft or glans of the penis in men and the vulva, perineum, buttocks, cervix, and vagina in women. Primary perianal and anal herpes can be seen in persons who have had receptive anal intercourse. Primary infection may be associated with fever, malaise, anorexia, and inguinal adenopathy. Vaginal discharge is common, and urethral involvement can result in urinary retention. Herpetic sacral radiculomyelitis is uncommon but is associated with urinary retention, myalgias, and obstipation. The lesions of primary genital herpes can last for several weeks before completely clearing. Recurrences of genital herpes generally are shorter and milder than the primary episodes and may be preceded by a prodrome of tenderness, itching, or tingling. Healing of recurrent lesions generally is complete in 6 to 10 days. Minimally symptomatic lesions are often overlooked as recurrent episodes by the patient. Over time, symptomatic recurrences can be expected to diminish in frequency, intensity, and duration, but persons who have diminished immunity, such as those infected with HIV, may suffer with prolonged, frequent, or atypical recurrences.

Neonatal herpes infection occurs in 8 to 60 in 100,000 births, depending on the population of patients studied, and is caused by the transmission of the virus at the time of delivery. Most babies

www.ketabpezeshki.com 66485457-66963820

with neonatal herpes infection are born to asymptomatic mothers, but there appears to be a much higher risk of transmission by a mother who experiences the first genital herpes infection during pregnancy. It is estimated that 50 to 80% of infants with neonatal herpes are born to mothers who acquire genital herpes infection near term. This might indicate that women with long-standing infection transmit antibody to the fetus that decreases disease manifestation after exposure to virus during birth.[45] The use of invasive monitoring and premature delivery also are associated with an increased risk of infection.[46] Infection may be manifested after several days to weeks with vesicles or conjunctivitis; neurologic involvement, with seizures, cranial nerve palsies, lethargy, and coma, is common. Untreated disseminated or CNS disease is fatal in more than 70% of patients.

Encephalitis caused by HSV is uncommon, but it is the most common acute, nonepidemic encephalitis in the United States. Cases do not have a seasonal distribution. Other than in the neonate, HSV-1 is the usual pathogen. The clinical disease begins acutely, with fever and focal neurologic signs, often localized to the temporal lobe. The patient may complain of a bad odor not perceived by anyone else (temporal lobe hallucination). Common clinical manifestations include headache, meningeal signs, lethargy, confusion, stupor, and coma. The mortality rate among untreated patients with CNS disease approaches 80%, and less than 10% of patients are left with no neurologic sequelae. Treatment with acyclovir appears to reduce mortality and to decrease the neurologic sequelae more effectively than treatment with vidarabine.

Diagnostic Strategies. CSF findings are nonspecific, with a moderate mononuclear pleocytosis. Results of culture of the CSF generally are negative for HSV. Localization of the encephalitis within the temporal lobes by electroencephalography, magnetic resonance imaging (MRI), or computed tomography (CT) scan increases the likelihood of a diagnosis of HSV encephalitis. The diagnosis of HSV encephalitis can be made reliably only with a biopsy of the lesion and subsequent isolation or detection of the virus by culture, direct fluorescent antibody tests, or polymerase chain reaction (PCR) assay.

Differential Considerations. The superficial lesions of HSV infection are indistinguishable from those of VZV infection. Pharyngitis and gingivostomatitis in children can mimic streptococcal or diphtheritic pharyngitis, herpangina, aphthous stomatitis, Stevens-Johnson syndrome, Vincent's angina, or infectious mononucleosis. Primary genital herpes can mimic the appearance of chancroid, syphilis, candidiasis, or Behçet's syndrome. In the neonate, in the absence of vesicles, congenital HSV infection can mimic disease caused by rubella, CMV, or *Toxoplasma* organisms. Encephalitis caused by HSV may be clinically indistinguishable from other viral encephalitides, tuberculous and fungal meningitis, brain abscesses, brain tumors, and cerebrovascular accidents.

Management. Oral acyclovir (400 mg three times daily), oral valacyclovir (1 g twice daily), or intravenous acyclovir (5 mg/kg three times daily) is recommended for treatment of primary genital herpes or mucocutaneous herpes in the immunocompromised host, although some authorities use higher dosages in these patients despite no clear evidence.[47] Because of the safety and efficacy of oral acyclovir, there is little indication for use of acyclovir ointment. In people with severe or frequent recurrences, acyclovir, ranging in doses from 200 mg five times daily to 800 mg once daily, can be used as an effective suppressive regimen. Both famciclovir and valacyclovir also are approved for suppressive therapy and daily dosing of the affected partner in an HSV-discordant couple; a 500-mg dose of valacyclovir yielded about a 50% reduction in transmission to the unaffected partner in a recent study.[45]

In the immunocompromised host, acyclovir is effective for both treatment and prophylaxis of recurrent mucocutaneous herpes. Foscarnet has been shown to be effective for the treatment of mucocutaneous herpes that is resistant to acyclovir. Intravenous acyclovir, 10 mg/kg every 8 hours, is the treatment of choice for HSV encephalitis in adults and children. Vidarabine, 30 mg/kg/day intravenously, also is effective in neonatal encephalitis but is rarely used.

Several vaccines against HSV have reached differing phases of development and testing, but none has shown enough promise to become clinically available.[48] Research in this area is ongoing.

Disposition. Patients with cutaneous HSV infections generally can be managed easily. The diagnosis often carries with it a great deal of stigma that should be addressed. Assurance of the generally benign nature of the infection is helpful. Counseling should include cautions about the transmissibility of the virus, even during asymptomatic periods. Women of childbearing age should discuss management of HSV infection during pregnancy and delivery with their obstetricians. It is clear that shedding of HSV occurs when there is no clinical outbreak in persons with a history of recurrent lesions and that persons who have never had recognizable lesions but who have antibody to HSV can also shed virus. With the advent of dependable commercialized serologic tests for HSV-1 and HSV-2, it is hoped that clinicians will be better able to identify persons with asymptomatic infection and to provide counseling on ways to decrease transmission. There are no clear current guidelines for how to decrease such transmission, but the routine use of condoms and suppressive therapy with antiviral medications are reasonable until more research in the field is conducted.

Encephalitis caused by HSV constitutes a treatable medical emergency. Prompt recognition and institution of appropriate therapy in the emergency department (ED) before a definitive diagnosis has been made may decrease the high mortality rate and neurologic sequelae associated with this disease. When HSV encephalitis is suspected, empirical initiation of intravenous acyclovir is indicated in the ED. This approach has minimal toxicity and demonstrable efficacy.

Varicella-Zoster Virus

Principles of Disease. VZV, or human (alpha) herpesvirus 3, is the agent of both chickenpox and herpes zoster, or shingles.

Clinical Features. Chickenpox is an acute, generalized viral disease characterized by sudden onset of fever, malaise, and a skin eruption that initially is maculopapular and then becomes vesiculated for several days before a granular scab is left (Fig. 130-4). Lesions occur in crops, with several stages present at the same time. Lesions can appear anywhere on the skin and mucous membranes. There may be few lesions and mild, inapparent infections.

Figure 130-4. Chickenpox.

www.ketabpezeshki.com 66485457-66963820

Figure 130-5. Herpes zoster.

Most cases occur in children younger than 9 years; adults with the disease may have high fevers and severe constitutional symptoms. Children with acute leukemia are at increased risk for disseminated disease, which carries a case fatality rate of greater than 5%. Neonates in whom varicella develops before 10 days of age and mothers who contract the disease in the perinatal period are at increased risk for generalized infection. Fatal disease in adults, although uncommon, usually is associated with pneumonic involvement. In children, fatal disease usually is associated with septic complications and encephalitis.

Herpes zoster is due to reactivation of VZV that has been latent in a dorsal root ganglion after an episode of chickenpox; it occurs predominantly in older adults and those with an immunocompromised state, such as HIV infection.[49] There are about 1 million cases in the United States annually.[50] The rash is often preceded by tingling or hypesthesia; multiple vesicles on an erythematous base appear in crops along nerve pathways supplied by sensory nerves of a single dorsal root ganglion or an associated group of dorsal root ganglia. The distribution usually is unilateral and dermatomal (Fig. 130-5). The lesions often are extremely painful. Postherpetic neuralgia, which is defined as continued pain for 6 months after lesions have healed, is more likely to occur in elders with larger and more painful rashes. It can last for months or years and is refractory to treatment. Ophthalmic infection, which can occur without other cutaneous lesions, can lead to corneal ulceration. Two relatively rare but often cited facial zoster infections are Hutchinson's sign, which is the appearance of a blister on the tip of the nose with herpes ophthalmicus, and Ramsey Hunt syndrome, which is characterized by localized pain, facial weakness, and a rash of the face or ear canal that can be subtle.[51]

Diagnostic Strategies. Both chickenpox and herpes zoster are often easily diagnosed on physical examination, and laboratory tests generally are not required. Multinucleated giant cells may be seen on Tzanck preparations of material from the base of a lesion but will not allow differentiation of HSV from VZV lesions. Submission of scrapings for a direct fluorescent antigen test is cost-effective and allows differentiation of VZV from HSV infection.

Management. Use of acyclovir for uncomplicated chickenpox in children is safe but only modestly effective. Parents of children with chickenpox should be cautioned not to give their children aspirin or aspirin-containing compounds because of the strong association between this practice and the development of Reye's syndrome.[52] Acetaminophen can be used as an antipyretic. Adults experience increased morbidity and mortality from chickenpox, so treatment of otherwise healthy adults with acyclovir, famciclovir, or valacyclovir frequently is indicated. Patients with pneumonitis or other severe illness should be treated with intravenous acyclovir. In immunocompromised patients, varicella-zoster immune globulin and intravenous acyclovir have been shown to decrease morbidity.

A live, attenuated vaccine that shows a high degree of protection for both normal children and children with leukemia was licensed in the United States in 1995. It is recommended for immunocompetent people older than 12 months. In those older than 12 years, two doses of vaccine are to be administered 4 to 8 weeks apart. It also is recommended for use as postexposure prophylaxis in the nonimmune host. The vaccine is most effective in preventing or attenuating illness in these circumstances if it is administered within the first 3 to 5 days after exposure.[53] The vaccine is a live attenuated virus and not recommended for use in immunocompromised patients.

Uncomplicated herpes zoster generally is treated with supportive measures, especially pain control, and antivirals (acyclovir, famciclovir, or valacyclovir). The currently recommended dosages are 800 mg five times a day for acyclovir, 500 mg three times a day for famciclovir, and 1 g three times a day for valacyclovir. Both famciclovir and valacyclovir are preferred to acyclovir because of increased compliance. In addition, there are data that valacyclovir 1.5 g twice a day yields equivalent therapeutic effect, and one might guess that compliance may be improved with dosing twice a day compared with three times a day, but this regimen is not currently approved for the treatment of herpes zoster.[54] There is good evidence that treatment with antivirals reduces the incidence and severity of postherpetic neuralgia, and treatment should be considered for those most at risk for this complication, such as those with large painful rashes and those 50 years of age or older.[54] Treatment with intravenous acyclovir should be considered for patients with disseminated disease and complicated zoster (involving more than one dermatome). Susceptible immunocompromised patients exposed to infected persons should receive varicella-zoster immune globulin within 72 hours to prevent or to modify clinical illness. Foscarnet is useful for treatment of infections due to acyclovir-resistant VZV in immunocompromised patients.

The use of corticosteroids to decrease the incidence of postherpetic neuralgia is controversial. A recent Cochrane review could not support the practice.[55] Nevertheless, the use of corticosteroids in conjunction with antivirals in persons who are at highest risk for postherpetic neuralgia and do not have contraindications to systemic steroid therapy is condoned by reliable sources. Herpes zoster is estimated to eventually occur in approximately 30% of the population; the introduction of an effective vaccine led to the recommendation that immunocompetent persons older than 60 years be vaccinated with one dose of varicella-zoster vaccine.

Disposition. Chickenpox and herpes zoster are highly contagious. Although these diseases generally are benign, patients should avoid situations that put them in contact with steroid-treated or immunocompromised persons. The incubation period most commonly is 13 to 17 days, and the period of communicability may range from 5 days before to 5 days after the appearance of the vesicles. Susceptible persons should be considered potentially infectious from 10 to 21 days after exposure. Susceptible health care workers should not care for people with varicella or zoster. Health care workers without a well-documented history of chickenpox or herpes zoster should have antibody levels checked before they begin their employment to determine susceptibility to VZV, and they should strongly consider vaccination if they prove to be nonimmune.

Human Herpesvirus 6

Principles of Disease. HHV-6 has been implicated as an agent of roseola infantum (exanthema subitum).

Clinical Features. Roseola infantum is the most common exanthem of children younger than 2 years and occurs most often at approximately 1 year of age. The illness begins abruptly with the acute onset of fever, with temperature often as high as 41°C,

www.ketabpezeshki.com 66485457-66963820

lasting 3 to 5 days. A fine, evanescent, rose-colored maculopapular rash appears on the trunk after lysis of the fever and lasts 1 to 2 days. The rash may spread to the face and extremities. Most cases are self-limited, and despite the fever, the child usually remains active and alert. There is conflicting evidence on the frequency of HHV-6–associated febrile seizures.[56,57] Although secondary cases occur after an incubation period of approximately 10 days, most cases of roseola occur without known exposure.

Differential Considerations. The disease appears similar to other childhood exanthems. The child generally looks well despite the high fever.

Management. Acetaminophen may reduce the fever. Routine supportive measures should be used if febrile seizures occur.

Human Herpesvirus 7. HHV-7 has been associated with a clinical presentation similar to that for HHV-6, but its role in disease has not yet been fully elucidated.[58]

Human Herpesvirus 8. HHV-8 has been implicated as the cause of Kaposi's sarcoma regardless of the HIV serostatus of the affected patient. HHV-8 is also implicated in Castleman's disease, which is also known as angiofollicular lymph node hyperplasia.[59] Mechanisms of disease pathogenesis as well as epidemiology of transmission for this virus remain unclear and continue to be actively investigated.

Herpes B Virus

Principles of Disease. Herpes B virus, or herpesvirus simiae, a close relative of human HSV, is enzootic in macaques and most commonly is associated with rhesus, cynomolgus, or African green monkeys. Like human HSV, herpes B virus produces mild disease in monkeys that is characterized by intermittent reactivation and shedding, particularly during times of stress, such as during handling. Among monkey handlers and those exposed to the animals' saliva or tissues, monkey B virus is a serious occupational hazard and is associated with a high proportion of progressive mucocutaneous disease and fatal encephalitis in infected patients.[60] The first known case of fatal herpes B virus infection, from a mucosal splash exposure, occurred in 1998.

Clinical Features. After a penetrating bite or scratch from an infected monkey, herpetiform vesicles may form at the site of the injury. Giant cells can be seen on a Tzanck preparation. An acute febrile illness with headache and lymphocytosis may follow as late as 3 weeks after the injury. An ascending myelitis ensues, leading to death from respiratory paralysis or encephalomyelitis within 3 weeks of onset of symptoms. The incidence of asymptomatic infection is unknown.

Differential Considerations. The initial skin lesions appear similar to those of herpes simplex. In the context of any exposure to monkey tissues and the appearance of a herpetiform lesion, the diagnosis of herpes B virus infection must be considered because of its associated high mortality rate.

Management. The most important step that can be taken to prevent B virus disease is thorough cleansing of exposed tissues. Current recommendations are that mucous membranes be flushed with sterile saline or water for 15 minutes and that areas of exposed skin be washed for 15 minutes with a detergent or a solution containing disinfectants (such as chlorhexidine or povidone-iodine). Affected tissue (except ocular or mucous membranes) can be initially washed with 0.25% hypochlorite (Dakin's) solution before being washed with a detergent solution.

The decision to initiate postexposure prophylaxis is based on the severity of the exposure and the appropriateness of first aid measures. Postexposure prophylaxis does not need to be initiated if the exposed skin is intact or the exposure is to a nonmacque species of monkey. Valacyclovir, 1 g orally every 8 hours for 14 days, is recommended for postexposure prophylaxis.[60]

Suspected B virus infection constitutes a medical emergency. Anecdotal reports have described successful prevention of disease progression with intravenous acyclovir. The apparent response of the infection to appropriate regimens emphasizes the need for early recognition and treatment. If CNS symptoms are present, ganciclovir is the drug of choice.

Papillomaviridae

Principles of Disease. Human papillomavirus (HPV) infections are common in all human populations and are the cause of a variety of cutaneous and mucous membrane lesions, including common warts, anogenital or venereal warts (condyloma acuminatum), and respiratory or laryngeal papillomas.

More than 70 types of HPVs have been identified. Laryngeal papillomas (most commonly caused by HPV types 6 and 11) and genital warts (most commonly caused by HPV types 16 and 18) can undergo malignant transformation.[61] In addition, HPV has been implicated as a causative agent for oropharyngeal squamous cell carcinomas that have been traditionally attributed mainly to other causative agents, such as cigarettes. This observation has led to the prospect that vaccination against HPV might reverse the increasing incidence of oropharyngeal squamous cell carcinomas attributable to HPV infection.[62] The association between HIV infection and more aggressive forms of HPV infection, including a greater likelihood for malignant transformation of lesions, has been shown.[63]

Clinical Features. Common warts generally are well-circumscribed, hyperkeratotic, painless papules occurring most commonly on the extremities and transmitted by close personal contact. Plantar warts, found on the soles of the feet, may be very painful. Venereal warts, found on the internal or external genitalia or perianal region, are hyperkeratotic, exophytic papules, either sessile or pedunculated, and are sexually transmitted. Laryngeal papillomas in children presumably are acquired during passage through the birth canal. Malignant transformation can occur, particularly in patients receiving radiation therapy.

Differential Considerations. The diagnosis of warts usually is made clinically. Condyloma acuminatum must be distinguished from the condyloma latum of syphilis.

Diagnostic Strategies. Diagnosis of cervical HPV infections can be made during colposcopy with previous application of a 3 to 5% acetic acid solution to the internal genital tract. Flat condylomata appear as shiny white patches with ill-defined borders and irregular surfaces. Acetowhitening also can reveal subclinical vulvar or penile warts.

Management. Genital warts generally regress spontaneously within months or years, and it is unclear whether their removal decreases infectivity or decreases the chance of malignant transformation. Therapy is at the discretion of the patient and the caregiver. Patient-applied therapies use podofilox 0.5% gel or imiquimod 5% cream. Freezing with liquid nitrogen, surgical removal, and intralesional interferons also are effective for most accessible lesions. Combination therapies also can be used. Salicylic acid plasters and curettage are useful for plantar warts. Laryngeal warts require surgery or laser therapy.

Parvoviruses (Erythema Infectiosum)

Principles of Disease. Parvovirus B19 has been implicated as the causal agent in several epidemics of erythema infectiosum or fifth disease. It also is associated with transient aplastic crisis in patients with chronic hemolytic disease, particularly those with sickle cell disease. Infections during pregnancy have been associated with hydrops fetalis and spontaneous abortion.[64] Humans constitute the only reservoir for parvovirus B19. Transmission usually occurs through contact with aerosol or respiratory secretions. Transmission by contaminated blood products has been documented.

Clinical Features. Erythema infectiosum is a mild, usually nonfebrile disease of children between 4 and 10 years of age, characterized by a striking erythema of the cheeks—a

www.ketabpezeshki.com 66485457-66963820

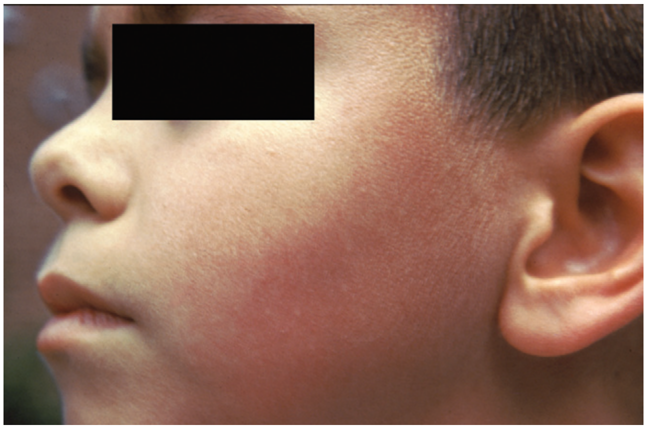


Figure 130-6. Erythema infectiosum.

"slapped-cheek" appearance (Fig. 130-6). The rash usually appears after an incubation period of 4 to 14 days without a prodrome. One to 4 days later, an erythematous rash on the extremities may be seen spreading to the trunk in a lacelike pattern. The rash generally fades within a week but can persist for several weeks, and recrudescence can be precipitated by skin trauma or sunlight exposure. Constitutional symptoms generally are mild in children, but adults with the disease commonly have associated arthralgias and arthritis. Rare cases of encephalitis and pneumonia have been reported.

Parvovirus B19 infects and causes a marked reduction in erythroid cell precursors and is a cause of transient *aplastic crisis* in patients with chronic hemolytic anemia. Recovery is associated with reappearance of reticulocytes in the peripheral smear 7 to 10 days after their disappearance. In patients with AIDS and other immunosuppressive illnesses, parvovirus B19 infection can be manifested as chronic anemia. These patients often have persistent parvovirus infection without an appropriate immunoglobulin response.

Differential Considerations. In children, erythema infectiosum resembles other viral exanthems. The slapped-cheek appearance of the rash is characteristic.

Management. Erythema infectiosum generally is a mild disease, and no treatment is required. Patients with parvovirus B19–associated aplastic crisis may require blood transfusions. Therapy with immune globulin can lessen the need for transfusions in immunosuppressed patients with chronic anemia. Women in whom parvovirus infection develops during pregnancy should be observed closely for the development of nonimmune fetal hydrops. The role of intrauterine blood transfusions in the treatment of this disorder remains controversial.[65]

Mononucleosis and Viral Diseases That Present with Mononucleosis-like Syndrome

Epstein-Barr Virus (Infectious Mononucleosis)

Principles of Disease. EBV, or human herpesvirus 4, most commonly is associated with infectious mononucleosis, an acute viral syndrome characterized by fever, exudative pharyngotonsillitis, lymphadenopathy, and peripheral lymphocytosis with atypical lymphocytes.

EBV infects and transforms B lymphocytes. Infection is common and widespread in early childhood in developing countries, where it usually is mild or asymptomatic. In developed countries, infectious mononucleosis usually is manifested in older children and young adults, commonly among high school and college students. It is transmitted by way of the oropharyngeal route, often by kissing. The incubation period may be as long as 4 to 6 weeks, and pharyngeal excretion can persist for 1 year or more. A chronic form of the disease has been suggested as the cause of chronic fatigue syndrome, but recent data do not support this association.[66]

EBV also has been strongly implicated in the pathogenesis of African Burkitt's lymphoma and nasopharyngeal carcinoma. EBV is also expressed by Hodgkin's lymphoma cells and is more frequently seen in certain groups of patients with Hodgkin's lymphoma, such as children.[67] Other lymphomas in immunocompromised patients, such as renal transplant recipients or persons with AIDS, also have been associated with EBV infection.

Clinical Features. Acute mononucleosis is a mild disease in most children. Those who acquire the disease as adults tend to have more symptomatic disease classically described as a syndrome of severe exudative pharyngitis, fevers, lymphadenopathy, and fatigue. About 95% of young adults have abnormal transaminases and 4% have jaundice. Hepatosplenomegaly is common. The disease generally resolves in 1 to 3 weeks, but malaise and fatigue rarely can persist for several months. On occasion, tonsillar swelling causes respiratory compromise. Splenic rupture is rare but should be considered in patients with left upper quadrant pain and a falling hematocrit. Neurologic complications, including encephalitis, aseptic meningitis, transverse myelitis, Guillain-Barré syndrome, optic neuritis, and peripheral neuropathies, occur in less than 1% of patients.

Diagnostic Strategies and Differential Considerations. Laboratory diagnosis is based on the finding of lymphocytosis (more than 50% of the total white blood cell count) or an elevation in heterophil antibodies (Monospot test). Heterophil antibodies are sensitive and specific antibodies that usually appear early in the illness. Other assays for virus-specific antibodies are available but rarely are needed to diagnose mononucleosis because the patient is heterophil seropositive in 90% of cases.

A presumptive diagnosis can be made on the basis of the finding of significant cervical lymphadenopathy, particularly posterior cervical, and exudative pharyngitis coupled with a lymphocytosis and the presence of atypical lymphocytes on a blood smear. HHV-6, CMV, and *Toxoplasma* can cause syndromes that are clinically and hematologically similar to infectious mononucleosis.

Management. Treatment is supportive only, except when rare complications of organ compromise are present. The use of corticosteroids in uncomplicated illness is controversial. These agents generally are used for impending airway obstruction, hemolytic anemia, or severe thrombocytopenia. Infection confers a high degree of resistance to reinfection. Patients should be cautioned about potential communicability to previously uninfected people.

Cytomegalovirus

Principles of Disease. CMV, or human herpesvirus 5, commonly is associated with heterophil-negative infectious mononucleosis syndrome and is clinically and hematologically similar to EBV-associated mononucleosis. More severe infections with CMV occur in the perinatal period and among immunocompromised patients. Severe CMV infections also are found in transplant recipients when organs from CMV-seropositive donors are transplanted into CMV-seronegative recipients.

Primary infection with CMV often is associated with a vigorous T-lymphocyte response. CMV persists indefinitely, probably within multiple cell types in various organs. Reactivation leading to CMV-associated disease may occur in response to a variety of external stimulants.

Clinical Features. CMV infection in immunocompetent older children and adults generally is subclinical. It is characterized by fever, lymphadenopathy, exudative pharyngitis, and peripheral lymphocytosis, with atypical lymphocytes present on peripheral blood smears. The acute infection resolves in 2 to 4 weeks, but malaise and viral excretion can persist for months. In the perinatal period, severe, generalized infection can occur and may be associated with lethargy, convulsions, jaundice, petechiae, hepatosplenomegaly, chorioretinitis, and pulmonary infiltrates.

www.ketabpezeshki.com 66485457-66963820

Survivors may exhibit various degrees of neurologic impairment. Fetal infection can occur after primary or reactivated maternal infections, with primary infections carrying a much higher risk. Severe, generalized disease can occur in immunocompromised patients and often is associated with severe end-organ disease, such as colitis, esophagitis, pneumonitis, retinitis, and adrenalitis. Retinitis caused by CMV was the most common cause of blindness among people with AIDS in the era before highly active antiretroviral therapy, but its incidence has fallen precipitously. CMV can cause a polyradiculopathy and other, less common neurologic manifestations in patients with AIDS or other conditions of immunocompromise. Therapy with ganciclovir and foscarnet is indicated, but treatment results may be disappointing.

Diagnostic Strategies and Differential Considerations. Mononucleosis caused by CMV may be clinically indistinguishable from syndromes caused by EBV or *Toxoplasma*. In the perinatal period, infants with generalized infections require evaluation for other common perinatal infections, such as toxoplasmosis, rubella, syphilis, and HSV infection. Recipients of organ transplants and other immunocompromised patients with fever and other signs and symptoms of generalized infection require intensive evaluation for bacterial and viral causes of infection. Diagnosis of CMV infection depends on viral isolation, detection of CMV pp65 antigen, or the demonstration of a fourfold rise in antibody to viral antigens.

Management. Only supportive care is indicated for infected immunocompetent adults and children, and they generally can be managed at home. CMV infection in the perinatal period or complicated by impairment of immune function can be life-threatening, and patients in whom such infections are suspected generally require hospitalization for aggressive evaluation, monitoring, and specialized care. Valganciclovir, ganciclovir, foscarnet, and cidofovir are useful in treatment of CMV infections in immunocompromised patients.

Viral Infections Presenting as Nonspecific Febrile Disease

Coxsackieviruses, Echoviruses, and Other Enteroviruses

Principles of Disease. The enteroviruses are spread from person to person by the fecal-oral route. As with poliovirus, inapparent infections greatly outnumber symptomatic cases.

All enteroviruses enter the body through the oropharynx and multiply in the tissues around the oropharynx. The viruses are stable in acid conditions and are capable of passing through the stomach to the intestines.

Clinical Features. Most enteroviral infections are inapparent. The most common clinical presentation is that of a nonspecific febrile illness. Young children may be hospitalized with enteroviral fevers that simulate bacterial sepsis. Coxsackievirus B and some of the echoviruses may cause severe perinatal infection associated with fever, meningitis, myocarditis, and hepatitis.

Febrile diseases with rashes often are associated with enteroviruses. Exanthems resembling rubella occurring during the summer months have been seen with the echoviruses and Coxsackie A viruses. Vesicular lesions are seen, such as with the hand-foot-and-mouth syndrome caused by some Coxsackieviruses A and B. Herpangina, a specific disease characterized by a vesicular rash on the cheeks and soft palate and associated with fever, sore throat, and severe pain on swallowing, is caused by the Coxsackievirus A. Roseola-like exanthems and petechial exanthems also are associated with Coxsackievirus and echovirus infections.

The enteroviruses are the most common causes of viral meningitis. The course generally is benign, but enteroviral infections often can be confused with a bacterial process, particularly in the acute phase, when CSF analysis may show a neutrophil predominance.

Coxsackie B viruses are strongly associated with myocarditis, although echoviruses and Coxsackie A viruses also can cause the disease. Severe cases may lead to dysrhythmias, heart failure, or death.

Enteroviruses cause upper respiratory tract infections similar to other causes of the common cold. Interstitial pneumonias also can occur. Pleurodynia (Bornholm's disease—the "devil's grippe") generally is associated with the Coxsackie B viruses. This disease involves the intercostal muscles and can last for several weeks.

Differential Considerations. Other proven or suggested associations of the enteroviruses and disease include enterovirus 70 with acute hemorrhagic conjunctivitis, Coxsackieviruses and echoviruses with diarrhea and gastroenteritis, Coxsackieviruses and echoviruses with hemolytic-uremic syndrome, and enteroviruses with acute myositis. Other possible associations include chronic cardiomyopathy, aortitis, hepatitis, pancreatitis, orchitis, diabetes mellitus, lymphadenopathy, a mononucleosis-like syndrome, and infectious lymphocytosis. A progressive, dementing, chronic meningitis associated with enteroviruses has been reported in persons with common variable immunodeficiency syndromes.

Management. No specific treatments are available for infections caused by the enteroviruses. Care is supportive. Vaccination against poliovirus and hepatitis A is recommended, and immune serum globulin also can prevent the acquisition of hepatitis A infection.

Colorado Tick Fever

Principles of Disease. Colorado tick fever, or mountain fever, is caused by a coltivirus similar to the orbiviruses that are transmitted to humans through the bite of the hard-shelled wood tick *Dermacentor andersoni*. It occurs primarily in the western United States, but a serotype has been isolated from the *Ixodes ricinus* tick in Germany and from the dog tick, *Dermacentor variabilis,* in Long Island, New York. Illness generally occurs in late spring through summer (see Chapter 134).

Clinical Features. The incubation period for Colorado tick fever is 3 to 6 days, and a history of tick exposure is elicited in 90% of patients. The disease generally occurs in people engaged in activities that bring them into contact with ticks. The fever is biphasic, as indicated by a "saddle-back" curve plotting temperatures over time, with the patient initially acutely experiencing chills, lethargy, prostration, headache, ocular pain, photophobia, abdominal pain, and severe myalgias. The initial fever lasts 2 to 3 days, recedes for a similar period, and then is followed by a second fever lasting approximately 3 days. Rash, occasionally petechial, is uncommon, occurring in 5 to 10% of patients. Meningoencephalitis is a rare but serious complication in children. Convalescence lasts 1 to 3 weeks; half of infected persons are viremic 4 weeks after the onset of illness.[68]

Differential Considerations. Colorado tick fever commonly is misdiagnosed as Rocky Mountain spotted fever. Patients with fever and rash after tick bites in endemic areas should be treated for Rocky Mountain spotted fever. Confirmation of the diagnosis of Colorado tick fever is by mouse inoculation or fluorescent staining of erythrocytes.

Management. Treatment is supportive and symptomatic.

Orbivirus. Six orbiviruses have been implicated in human disease. Changuinola virus is transmitted from *Phlebotomus* flies; Lebombo and Orungo viruses from mosquitoes; and Kemerovo, Lipovnik, and Tribec viruses from ticks. All six have been associated with febrile illnesses and, rarely, encephalitis.

Viruses Associated with Respiratory Infections

Rhinovirus

Principles of Disease. Rhinoviruses are the most common cause of the common cold. More than 100 strains exist. Rhinovirus

www.ketabpezeshki.com 66485457-66963820

transmission generally occurs primarily by hand contact and through inoculation of the eye or nasal mucosa and less commonly by aerosolization of respiratory secretions. Viral replication probably occurs on the epithelial surface of the nasal mucosa.

Clinical Features. After a 1- to 4-day incubation period, the usual signs and symptoms of rhinoviral infection occur, including nasal obstruction, sneezing, sore throat, cough, and malaise. Severe tracheobronchitis and pneumonia occur rarely. Fever and lower respiratory tract infections are more common in children than in adults with rhinovirus infections.

Differential Considerations. Other respiratory pathogens, such as coronaviruses, respiratory syncytial virus (RSV), parainfluenza viruses, influenza viruses, adenoviruses, and enteroviruses, can produce clinical syndromes similar to those produced by the rhinoviruses. The rhinoviruses in general cause less morbidity than that typical for the parainfluenza viruses and RSV.

Diagnostic Strategies. Definitive diagnosis is made by the demonstration of a rise in antibody titer. New commercially available molecular assays include detection of rhinovirus in their viral panel.[69]

Management. Treatment is aimed at relief of symptoms. Routine vaccination appears to be an unlikely prospect because of the number of serotypes. Because hand-to-face inoculation appears to be the predominant means of transmission, frequent handwashing during epidemic periods may decrease the spread of rhinovirus infections.

Adenoviridae

Adenovirus

Principles of Disease. Adenoviruses are the most clinically important viruses because of their capacity to cause upper respiratory tract infections, conjunctivitis, and gastroenteritis. Nevertheless, no drugs or therapeutic measures specifically effective for adenoviral infections are available. Adenovirus is used as a vector in many vaccines that are being studied against viral pathogens (including rotavirus, hepatitis B, RSV, HIV, and Ebola), a growing area of vaccine research.

Clinical Features. Adenoviruses cause respiratory diseases ranging from pharyngitis and tracheitis to fulminant bronchiolitis and pneumonia. Cough, fever, sore throat, and rhinorrhea are the most common symptoms and generally last only a few days. Pneumonitis with interstitial infiltrates is occasionally seen with some strains. Upper respiratory findings may be associated with conjunctivitis (pharyngoconjunctival fever). Adenoviruses may cause an epidemic keratoconjunctivitis, which in severe cases may be associated with conjunctival scarring. Other syndromes associated with adenoviruses include hemorrhagic cystitis, infantile diarrhea, intussusception, encephalitis, and meningoencephalitis.

Differential Considerations. Other pathogens causing similar atypical pneumonia syndromes include influenza and parainfluenza viruses and *Mycoplasma pneumoniae*. Diarrheal syndromes may be similar to those caused by rotaviruses.

Diagnostic Strategies. New molecular diagnostic assays may detect and differentiate adenovirus types (B, E); however, these are not widely available, and confirmatory testing is usually not performed, although it may be helpful for epidemiologic purposes.

Management. Treatment of adenovirus infections is supportive.

Coronaviridae

Coronavirus

Principles of Disease. The severe acute respiratory syndrome (SARS) was first documented in China's Guangdong province in November 2002. By the time the epidemic was contained in July 2003, it had affected approximately 8000 persons in 29 countries, with a case fatality rate of approximately 10%.[70] The causative agent was identified as a novel coronavirus (SARS-CoV).[71,72] Early in the epidemic, astute researchers noted that the illness was more prevalent among restaurant workers and focused attention on live animals that were being sold for human consumption. Their efforts revealed that the virus was transmitted to humans by handling and consumption of wild mammals, such as the civet.[73]

By 2003, 161 cases of SARS had been reported in the United States, but no deaths were reported that were attributable to SARS.[70] Most patients had traveled to an area of documented or suspected SARS transmission.

The SARS epidemic posed a challenge to national and international agency–based medical personnel and public health authorities. Public health measures were implemented to contain the infection and to establish sentinel systems to warn of recurrent outbreaks. Health care practitioners, especially ED personnel, should notify local public health authorities of suspected or confirmed cases of SARS.

Clinical Features. The current CDC case definition for SARS-CoV disease includes the presence of laboratory-confirmed infection or severe respiratory illness in the setting of epidemiologic criteria for likely exposure to SARS-CoV.[70] *Early disease* is defined by the presence of two or more of the following features: fever (which may be subjective), chills, rigors, myalgia, headache, diarrhea, sore throat, and rhinorrhea. *Mild to moderate disease* requires presence of fever with temperature higher than 38° C and evidence of lower respiratory tract illness. *Severe respiratory illness* is defined as noted previously but also includes radiographic evidence of pneumonia or acute respiratory distress syndrome.[74] Laboratory diagnosis of the disease relies on SARS-CoV antibody testing, cell culture, or reverse transcription–PCR (RT-PCR) techniques. Epidemiologic criteria for *possible exposure* include travel within the past 10 days to an area with documented or suspected recent transmission of SARS-CoV or close contact with a symptomatic person who recently engaged in such travel. Epidemiologic criteria for *likely exposure* require that transmission be somehow linked to a person with confirmed disease.[75]

Retrospective analyses of the SARS-CoV infection outbreak suggest an incubation period of 3 to 10 days with an ensuing viral prodrome characterized by headache, malaise, and myalgias. Fever, clinical evidence of upper and lower respiratory infection, dyspnea, and gastrointestinal disturbances also may be features. Chest radiographs are normal in appearance in up to 25% of patients with early infection, despite the presence of fever and respiratory complaints. CT scans may be more useful in identifying early pulmonary involvement. Hypoxemia, with clinical and radiographic evidence of pneumonitis, develops as the disease progresses. In a minority of patients, progressive respiratory failure and acute respiratory distress syndrome may follow. Patients older than 60 years and those with comorbid illness, such as diabetes mellitus, have worse outcomes.[74-76] A Hong Kong study reported reliable results when diagnostic criteria were combined with variables including exposure, history, and laboratory findings.[77]

Diagnostic Strategies. Laboratory findings are nonspecific but include lymphopenia, thrombocytopenia, elevated lactate dehydrogenase, and prolonged activated partial thromboplastin time. Hemolytic anemia and electrolyte disturbances, such as severe hypomagnesemia with associated tetany, have been reported.[78] Serologic testing for antibody to SARS-CoV is most reliable if it is performed more than 21 days after infection, and PCR analysis may be negative early in the course of illness.

Differential Considerations. The clinical features of SARS-CoV mimic those of many community and nosocomial respiratory infections, so the differential diagnosis is broad in scope. The initial workup should include routine laboratory and radiographic evaluations similar to those for other, more common respiratory

www.ketabpezeshki.com 66485457-66963820

infections. A greater level of suspicion for SARS-CoV infection should be entertained on the basis of travel or exposure history. Specific testing for coronavirus can be conducted through the health department.

Several outbreaks of SARS-CoV infection have occurred after exposure of patients or medical staff to a sentinel case or to a clinical specimen.[79] Therefore, effective evaluation and management of suspected or proven cases of SARS-CoV disease should begin with a travel and occupational history, astute clinical observation, appropriate triaging, and patient isolation measures. Quarantine of persons who may be in the incubation period has proved useful in containing outbreaks.[80] Contact and airborne precautions should be instituted, and protective eyewear should be considered. Detailed guidelines for the diagnosis, isolation, treatment, and disposition of patients with suspected or proven SARS-CoV infection are continually being updated by the WHO and the CDC. These guidelines are available at www.cdc.gov and www.who.int; local health officials also can be contacted for guidance.

Management. No therapeutic measures beyond supportive care have been shown to be clearly effective for the treatment of SARS-CoV infection. Patients with signs and symptoms of lower respiratory tract infection should be treated with conventional antibiotic and supportive therapy, even if they are suspected of having SARS-CoV infection.

Disposition. It is not necessary to hospitalize all patients who are thought to have been exposed to or to have a respiratory syndrome that could be attributed to SARS-CoV infection. Persons well enough to be cared for at home should be placed in home quarantine with contact and airborne precautions. Termination of quarantine precautions for suspected SARS-CoV infection should be done in consultation with public health officials. Infection control is of the utmost importance, given the increased risk to health care workers and of nosocomial transmission; particular care must be paid to procedures at high risk for aerosolization of the virus, including intubation and nebulization.[80,81] Expert consultation from an infectious disease specialist and public health authorities is recommended.

Other Coronaviruses

Principles of Disease. Coronaviruses are agents of the common cold in adults and of lower respiratory tract disease in children. More commonly causing epidemic diarrheal disease in pigs and cows, they have recently been implicated in diarrheal disease in children.

Clinical Features. Coronaviruses primarily cause upper respiratory tract disease in adults. Lower respiratory tract infections caused by coronaviruses occur uncommonly in adults and more commonly in children. They appear to cause diarrheal disease in children younger than 1 year.

Differential Considerations. Coronaviruses probably account for 15% of adult colds. Rhinoviruses account for most of the rest, with parainfluenza viruses, influenza viruses, RSVs, adenoviruses, and enteroviruses also causing upper respiratory infections and colds. Rotaviruses, Norwalk viruses, and enteroviruses cause most viral cases of gastroenteritis in children.

Management. Treatment of most coronavirus infections is supportive only, including oral or intravenous fluids.

Paramyxoviridae

Parainfluenza Viruses

Clinical Features. The parainfluenza viruses are the most common causes of croup in children and, along with RSV, are the most common causes of lower respiratory tract infections that require hospitalization in infants.

The virus is passed by way of the respiratory route, and hand–to–mucous membrane transmission is the likely mode of spread. The incubation period most often is 1 to 4 days, and the clinical picture is that of a febrile illness lasting approximately 4 days.

Infection with the parainfluenza viruses does not confer lasting immunity. Parainfluenza virus type 1 is the predominant cause of croup, or laryngotracheobronchitis, occurring during the autumn months in children younger than 3 years. Parainfluenza virus type 2 also is associated with croup, causes less morbidity than type 1, and often occurs in alternate years with type 1. Parainfluenza type 3 infections occur in the spring and are associated with bronchiolitis and pneumonia in infants younger than 1 year, similar to RSV. Parainfluenza type 3 also is associated with croup in children younger than 3 years and with tracheobronchitis in older children. Parainfluenza type 4 is recovered less often but appears to be associated with mild respiratory illness. Severe croup or bacterial superinfection of laryngotracheitis may lead to respiratory compromise.

Differential Considerations. Viruses causing upper respiratory tract infection similar to that caused by the parainfluenza viruses include adenoviruses, rhinoviruses, influenza virus, RSV, echoviruses, Coxsackieviruses, and coronaviruses. Identification of parainfluenza viral infection can be made by demonstrating a fourfold rise in antibody titer between acute and convalescent serum.

Management. Croup may be worse at night; mist inhalation often is helpful. Nebulized racemic epinephrine can be used to treat severe croup, but the relief it affords can be short-lived, and return to pretreatment state can be seen within 2 hours of therapy. Intramuscular steroids have been shown to be helpful, and their use has been associated with a decreased requirement for hospitalization of children with croup.[82] A single dose of oral dexamethasone at 0.6 mg/kg has been shown to reduce return visits to a health care practitioner.[83] The parainfluenza viruses can cause reinfection within months of the primary infection, so prevention of infection is unlikely to be feasible. More aggressive tracheal diseases, such as laryngotracheobronchitis and laryngotracheobronchopneumonitis, may be caused by viruses, but most are often a result of superinfection with bacteria, including *Staphylococcus aureus* and group A streptococci.[84]

Orthomyxoviridae

Influenza Virus

Principles of Disease. Influenza generally is a self-limited infection of the upper respiratory tract associated with fever, cough, coryza, sore throat, and malaise. Three types of influenza are recognized. Type A has been associated with most widespread epidemics and pandemics and is associated with most of the deaths caused by influenza. Influenza B causes regional or widespread epidemics every 2 to 3 years. Influenza C is associated with sporadic cases.[85]

Clinical Features. The usual clinical disease caused by influenza begins 1 to 4 days after exposure to aerosol respiratory secretions. Clinical manifestations include fever accompanied by myalgias, coryza, conjunctivitis, headache, and nonproductive cough. Patchy infiltrates can be seen on the chest radiograph. Signs and symptoms generally last only a few days, but fatigue and malaise may persist for weeks. The most common serious complications of influenza, particularly among elders and persons with chronic diseases, are pneumonia caused by influenza itself and pneumonia attributable to secondary bacterial infections. More than 90% of deaths during seasonal epidemics are due to exacerbation of cardiopulmonary disease in elders.[85] Rare complications of influenza infection include aseptic meningitis, pericarditis, and a postinfectious neuritis that resembles the Guillain-Barré syndrome.

Diagnostic Strategies. Viral culture remains the "gold standard" modality for the laboratory diagnosis of influenza, but

www.ketabpezeshki.com 66485457-66963820

results often are not timely enough to aid in clinical decisions for therapy. Several rapid assays using nasal specimens for the diagnosis of influenza A or B are commercially available. Rapid influenza diagnostic tests are direct antigen tests that provide results in less than 30 minutes. Some can distinguish between type A and B viruses; however, their sensitivity varies from 10 to 70% and may be greater in children and during the first 48 hours of illness when viral shedding is highest.[86] Positive bedside test results are associated with increased use of antivirals and decreased use of antibiotics in both pediatric and adult patients[87,88]; however, because of their low sensitivity, they are best used for screening and for "ruling in" disease, but they cannot reliably exclude influenza in a patient presenting with influenza-like illness.[89] Therefore, clinical decisions should be based on clinical suspicion of influenza-like illness. Real-time PCR assays are now available for confirmation of influenza, with enhanced sensitivity and specificity and the capability of specific influenza type detection, including novel H1N1.[90]

Differential Considerations. The syndromes produced by the influenza viruses overlap with those produced by other viruses, such as the parainfluenza viruses, RSV, adenoviruses, coronaviruses, and echoviruses.

Management. General supportive measures will ameliorate the symptoms of influenza. The neuraminidase inhibitors zanamivir and oseltamivir have been approved for treatment of both influenza A and B. The dose of oseltamivir should be decreased to 75 mg once daily in patients with creatinine clearance less than 30 mL/min. Zanamivir or oseltamivir should be administered within 2 days of onset of symptoms if efficacy is to be expected.[16] Vaccination is recommended yearly for all children 6 months to 5 years of age, adults older than 50 years, and persons at high risk for significant morbidity or death from influenza; these include immunosuppressed patients, those with chronic illnesses, and pregnant women. Vaccination is also recommended for health care workers and persons who are household contacts of infected persons younger than 5 years or older than 50 years. In addition, the CDC recommends annual vaccination for all persons "who want to reduce the risk of becoming ill with influenza or of transmitting influenza to others." Aspirin and aspirin-containing products should be avoided, especially among children and adolescents, particularly during influenza epidemics, because of the association between the use of aspirin during a bout of influenza and the subsequent development of Reye's syndrome.[52]

A highly pathogenic strain of avian influenza virus, H5N1, was first reported in a farmed goose in China in 1996.[91] Since then, the virus has spread among wild birds and poultry across the Asian continent into large parts of Europe and some areas in Africa. H5N1 has yet to be reported among fowl in the Americas or Australia. Human disease attributable to highly pathogenic avian influenza virus has been reported in several countries of Asia, the Middle East, and Africa. Although direct human contact with affected birds appears to be the major mode of transmission, human-to-human spread has been documented, and cases of unexplained transmission indicate that environment-to-human transmission may be possible.[92] The incubation period is less than a week. Clinical disease can range in severity from an asymptomatic or mildly symptomatic viral syndrome to a highly fulminant and deadly illness and includes influenza-like illness, often prominent conjunctivitis, and gastrointestinal manifestations.[93]

Highly pathogenic avian influenza virus infection should be suspected in a person who is at risk for contraction of the illness because of exposure to a known disease reservoir and who has a progressive respiratory illness.[94] Public health officials should be contacted if the disease is suspected, and full infection control measures should be instituted. Early antiviral therapy with oseltamivir at high doses (150 mg twice a day) and possibly with amantadine or rimantadine is recommended along with appropriate supportive care.[95] Oseltamivir-resistant H5N1 has been described.[93] Postexposure prophylaxis and the use of antiviral medication for asymptomatic persons during an outbreak should be prescribed in consultation with disease experts.

As of January 2011, there have been 525 laboratory-confirmed cases with 310 deaths reported by the WHO; actual morbidity and mortality figures probably are higher.[96] Despite aggressive public health measures, such as culling of affected fowl populations, many experts think that avian influenza can become a serious global pandemic.

H1N1 Pandemic Influenza

A novel strain of influenza A, H1N1, emerged in Mexico in April 2009, resulting in a significant outbreak of highly transmissible respiratory illness. The first novel H1N1 case was confirmed in the United States on April 15 and quickly led to spread across the country and worldwide. More than 55 million hospitalizations ensued, including 250,000 hospitalizations and 10,000 deaths in the United States alone.[97] Clinical features were similar to those of seasonal influenza strains, but with increased morbidity among younger adults with comorbidities. An H1N1 vaccine became available in September 2009. On the basis of the epidemiology of this strain, the CDC made recommendations for vaccination priority groups once the vaccine was available to include pregnant women, caregivers and household contacts of children younger than 6 months, health care providers, persons 6 months to 24 years of age, and persons 25 to 64 years of age at high risk for influenza complications (including asthma and other cardiopulmonary disorders, congestive heart failure, and immunosuppressed state, including diabetes mellitus).[98] Guidelines recommend that all hospitalized persons confirmed or thought to be infected with novel H1N1 and all patients at risk for complications be treated with the antiviral agent oseltamivir or zanamivir.[14,15] The experience in the United States and New Zealand indicated a 12 to 25% critical care admission rate, with more than 90% being younger than 65 years.[99] Although the pandemic was declared over by the WHO on August 10, 2010, the virus has continued to circulate seasonally. Although at this time there is no evidence of enhanced virulence, surveillance continues to detect any mutations in the viral strain that could confer changes in disease severity or predilection.

Respiratory Syncytial Virus

Principles of Disease. Infections with RSV occur worldwide, mostly in midwinter to late spring. Infants with pneumonia show marked inflammation in the interstitial tissue and alveoli of the lungs, whereas infants with bronchiolitis show less alveolar involvement but may exhibit marked changes in the bronchioles. Severe disease may result in obstruction of bronchioles with evidence of peripheral airway obstruction or emphysema. Transmission is through contact with respiratory secretions and probably also by hand-to-nose or eye droplet inoculation.

Infections caused by RSV account for up to 18% of ED visits in children younger than 5 years and the largest number of hospitalizations for respiratory infections in infants.[100] Bronchiolitis and pneumonia, the most severe manifestations of RSV infection, commonly occur in children younger than 6 months. Risk factors include prematurity and low birth weight, but most children who acquire the disease are healthy.[101-103] Children older than 1 year are less likely to have lower respiratory tract infection. Older children and adults commonly have upper respiratory symptoms and cough, but older patients may have severe disease. Furthermore, RSV may be an important contributor to adult asthma exacerbations.

Clinical Features. The average incubation time for RSV infections is 2 to 8 days. The most common manifestations are bronchiolitis and pneumonia in infants; tracheobronchitis, croup, and otitis media in young children; and upper respiratory infections in older children and adults. Bronchiolitis in infancy may lead to

www.ketabpezeshki.com 66485457-66963820

an increased risk of asthma and the development of chronic obstructive airway disease in later life. Fatal disease can occur in immunocompromised infants.

Diagnostic Strategies. The diagnosis of RSV infection can be made definitively by culture of the virus or detection of RSV antigens from respiratory secretions, nasal wash specimens, or nasopharyngeal or throat swabs. Commercial viral panels based on molecular technology include testing for RSV; however, these are not readily available in most EDs and may be more useful to determine the need for isolation precautions in patients, particularly infants.

Differential Considerations. The syndromes associated with RSV infections overlap those due to other upper and lower respiratory tract pathogens, including rhinovirus, parainfluenza and influenza viruses, echoviruses, Coxsackieviruses, and coronaviruses. RSV infection can be presumptively diagnosed in an infant with pneumonia or bronchiolitis when no bacterial pathogens are noted. Noninfectious causes of hypoxemia in infants, such as foreign body aspiration and asthma, also should be considered.

Management. Therapy for RSV infection is largely supportive. For infants sick enough to be hospitalized, aerosolized ribavirin has been shown to shorten the duration of illness and to ameliorate hypoxemia in normal infants. Corticosteroids have not been shown to be beneficial. During the winter, high-risk infants can be protected against RSV infection with monthly infusions of human RSV immune globulin or with monthly intramuscular injections of palivizumab, a monoclonal anti-RSV antibody preparation.[104] Palivizumab is recommended in cardiac disease, preterm infants, chronic lung disease, and immunocompromised children and may decrease intensive care unit admission and mortality[105-107]; however, cost-effectiveness analysis suggests that prophylaxis is best used in high-risk groups.[108] Severe disease may occur in immunocompromised infants, and respiratory precautions are required to prevent transmission from patient to patient and staff to patient. After failed attempts at a vaccine in the 1960s, which paradoxically caused exacerbations of RSV disease, efforts are ongoing to create live attenuated virus and purified subunit vaccines, and early results have been encouraging.[109]

Human Metapneumovirus

Principles of Disease. Human metapneumovirus is a recently discovered paramyxovirus associated with respiratory illness during the winter months. It causes lower respiratory tract disease that is typically more severe in infants and young children.[110,111] Initial symptoms are similar to those of the common cold but occasionally can lead to acute respiratory distress syndrome, especially in immunocompromised children.

Diagnostic Strategies. Diagnosis can be made by RT-PCR as part of molecular viral respiratory assays that detect a broad range of pathogens from nose, throat, and nasopharyngeal washes.[112]

Management. Treatment is supportive. Consultation with a pediatric infectious disease or pulmonary specialist is recommended for hospitalized patients.

Viral Infections with Neurologic Manifestations

Principles of Disease. *St. Louis encephalitis* occurs in the summer in most areas of the Western Hemisphere. After an incubation period of 4 to 21 days, infection with the St. Louis encephalitis virus can produce fever and headache, aseptic meningitis, or encephalitis. The mortality rate associated with the encephalitis approaches 10%. The disease commonly affects elders.

West Nile virus causes a febrile illness, with potential for meningoencephalitis. It was first described in the United States in 1999 but also has caused illness in many areas of Africa, Asia, and Europe.[113] In 2003, the CDC confirmed 9858 cases and 262 deaths attributable to West Nile virus, qualifying this epidemic as the largest outbreak of arboviral meningoencephalitis recorded in the Western Hemisphere.[114] However, in 2010, only 1021 cases were reported, suggesting decreasing activity or reporting of this illness in humans.[115] The primary cycle of infection is maintained by vector mosquitoes in bird populations. Humans are infected by cross-feeding mosquitoes. The virus has disproportionately affected certain bird populations in the United States, resulting in bird deaths. Recognition of this phenomenon led to early elucidation of the life cycle and has helped in characterization of the zoonotic activity of the virus.

Non–arthropod-borne human cases from laboratory transmission and person-to-person transmission by blood transfusion, organ transplantation, maternal-fetal transmission, or breast-feeding have been documented. These modes of transmission account for a small number of cases.[113] It is now clear that the virus has established itself in North America, and yearly outbreaks are to be expected. The peak incidence of disease is during the months of July through October; however, as the disease has moved into the southern states, transmission is being reported as early as April and as late as December.[113]

Clinical Features. The incubation period for West Nile virus appears to be 3 to 14 days. West Nile fever will develop in 20% of infected persons, and meningitis or encephalitis will develop in 1 in 150.[116,117] West Nile fever usually is characterized by fever, headache, myalgia, anorexia, and lymphadenopathy; half of infected patients have a maculopapular central rash. West Nile virus meningoencephalitis is characterized by fever, headache, mental status changes, and motor disturbances that range from generalized weakness to myoclonus, tremor, and parkinsonian movement disorders. A poliomyelitis-like syndrome has been described.[118] Cranial nerve and bulbar abnormalities can be seen.[115]

Diagnostic Strategies. Laboratory testing is nonspecific. CSF findings in patients with meningoencephalitis are similar to those with other viral infections: elevated protein level, normal glucose level, and a mild-to-moderate pleocytosis with a lymphocytic predominance. Viremia usually clears by the onset of meningoencephalitis, but immunoglobulin M (IgM) can be detected in the CSF. IgM levels in the serum can remain elevated long after clinical illness has resolved. Imaging studies are nondiagnostic, but the MRI scan can show nonspecific leptomeningeal inflammation.[115]

Disease outcome is related to age of the patient; elders are at significantly higher risk for the development of encephalitis and death from West Nile virus infection.[114,115] Patients with disease severe enough to necessitate hospitalization often have long-term sequelae.

Togaviridae

Alphavirus (Group A Arbovirus)

Principles of Disease. Arboviruses (*ar*thropod-*bo*rne viruses) are transmitted to humans by an arthropod vector; humans usually are an unimportant host in the reproductive cycle of the virus. Most arboviruses are mosquito borne, but ticks, sandflies, gnats, and midges serve as important vectors for some diseases. The alphaviruses and flaviviruses are the most common arboviruses causing disease in humans, but some bunyaviruses, reoviruses, rhabdoviruses, filoviruses, arenaviruses, and orthomyxoviruses also are transmitted by arboviral vectors.

The alphaviruses are transmitted by the bite of a mosquito. The three alphaviruses that cause human disease in the United States are the agents of eastern equine encephalitis, western equine encephalitis, and Venezuelan equine encephalitis. Other important alphaviruses include the chikungunya (Africa, Southeast Asia, Philippines), Mayaro (South America), o'nyong-nyong (Africa), Ross River (Australia, South Pacific), and Sindbis (Africa, Asia, Soviet Union, Australia, and Scandinavia) viruses.

www.ketabpezeshki.com 66485457-66963820

Clinical Features. These arboviruses can cause outbreaks of encephalitis. The few annual cases of eastern equine encephalitis in the United States occur predominantly near freshwater swamps of the eastern seaboard. Although more than 95% of cases are subclinical, the mortality rate among patients presenting with clinical encephalitis approaches 50%. Infections occur most commonly in children younger than 10 years or in elders. The onset of symptoms often is fulminant, with headache, fever, and convulsions progressing rapidly to decreasing level of consciousness and death. Focal neurologic deficits also may develop. Western equine encephalitis is present throughout the United States but occurs mostly in the western and central parts of the nation. Children younger than 1 year and elders are most often affected. More than 99% of cases are inapparent, and the encephalitis usually is mild, with an associated mortality rate of approximately 3%. Venezuelan equine encephalitis is found predominantly in Central and South America, but the disease has been seen in Texas and Florida. Venezuelan equine encephalitis usually is manifested as an influenza-like illness. One third of patients have encephalitis, with a mortality rate of less than 1%, predominantly in children.

Diagnostic Strategies. The white blood cell count in the CSF of persons with eastern equine encephalitis may be very high, and the diagnosis of meningoencephalitis must be considered. Diagnoses can be confirmed by a rise in antibody titers.

Differential Considerations. Other viral causes of encephalitis in the United States include HSV, HIV, St. Louis encephalitis (a flavivirus), California (La Crosse) encephalitis (a bunyavirus), and the recently encountered West Nile–like encephalitis (a flavivirus). Other viruses, such as mumps, rabies, polio, and other enteroviruses, can also be manifested as encephalitides.

Management. Management is supportive only. For people with expected intensive exposure to these viruses, an investigational vaccine may be available from the U.S. Army Medical Research Institute for Infectious Diseases in Fort Detrick, Maryland.

Rhabdoviridae

Within the Rhabdoviridae family of viruses are two genera, Lyssavirus, containing the rabies and rabies-like viruses, and Vesiculovirus, containing the vesicular stomatitis and related viruses. Six lyssaviruses are known, but only the rabies, Duvenhage, and Mokola viruses are known to cause disease in humans. Rabies is discussed further in Chapter 131.

Polyomaviridae

Principles of Disease. JC virus and BK virus are human polyomaviruses that cause ubiquitous but asymptomatic infection in populations worldwide. Progressive multifocal leukoencephalopathy (PML) is a rare, slowly progressive, demyelinating CNS disease associated with JC virus. The demyelinated lesions of PML slowly enlarge to become large plaques, associated with progressive neurologic deterioration, dementia, and eventually death. The disease occurs mostly in severely immunocompromised patients.[119] Similarly, BK virus viruria is relatively common in immunosuppressed patients or pregnant women. Rare, symptomatic infection can be manifested as urethral stenosis in renal transplant recipients and as hemorrhagic cystitis in bone marrow transplant recipients.

Clinical Features. Initial presentations of PML in immunocompromised patients include paresis, personality changes, and impaired higher cortical functioning. The disease generally is rapidly progressive, usually progressing to death within 2 to 4 months of the initial neurologic symptoms. PML commonly is seen in people with advanced AIDS.

Diagnostic Strategies. A lack of enhancement on contrast-enhanced CT and MRI scans is helpful in making the diagnosis. PCR assay identification of JC virus in the appropriate clinical setting with consistent radiographic findings establishes the diagnosis.

Differential Considerations. Considerations in the differential diagnosis include other causes of progressive neurologic disease in immunocompromised patients—toxoplasmic encephalitis, primary CNS lymphoma, HIV encephalopathy, tuberculous meningitis, vascular disease, and others.

Management. No specific treatment of PML is available; the disease generally is rapidly progressive, and ultimate transfer to appropriate nursing care facilities often is necessary. There have been reports of significant improvements in persons with AIDS who have been prescribed potent antiretroviral (anti-HIV) therapy.[120]

Poliovirus

Principles of Disease. Poliomyelitis is an acute viral infection that ranges in severity from an inapparent infection to a nonspecific febrile illness to aseptic meningitis to severe paralysis and death. Since the introduction of polio vaccination in the United States, only a handful of cases of paralytic poliomyelitis have been diagnosed each year, and most of these cases are either imported or vaccine associated. Since OPV was replaced by IPV in 2000, there have been no reports of vaccine-associated paralytic polio in the United States, although rare cases of imported paralytic polio have been reported.[121]

Poliovirus is transmitted during close contact; transmission both by the fecal-oral route and through contact with respiratory secretions has been documented. Susceptibility to poliovirus is universal, but paralytic infections are rare, increasing in incidence with age at the time of infection. At least 95% of infections are inapparent or asymptomatic.

Clinical Features. With paralytic poliomyelitis, the usual incubation period is 7 to 14 days. The disease in children usually is biphasic, with a brief viremic phase lasting 1 to 3 days. After recovery for 2 to 5 days, an abrupt onset of headache, fever, malaise, vomiting, and CSF pleocytosis ensues. This meningitic phase lasts 1 to 2 days before the beginning of weakness and flaccid paralysis. Bulbar paralytic poliomyelitis involves paralysis of the muscle groups innervated by the cranial nerves. The most important complications of paralytic poliomyelitis are respiratory, especially respiratory failure caused by paralysis of the respiratory muscles, aspiration pneumonia, and pulmonary embolism. Myocarditis may rarely occur. Muscle paralysis usually lasts only 1 to 3 days after its onset. A postparalytic paralysis syndrome has been described in which neuromuscular weakness recurs several decades after resolution of the acute poliovirus infection.

Differential Considerations. Paralytic poliomyelitis usually can be recognized on clinical presentation. Other enteroviruses can cause a similar syndrome. Guillain-Barré syndrome and postencephalitic syndromes may resemble paralytic poliomyelitis. Considerations in the differential diagnosis for nonparalytic poliomyelitis include any of the causes of bacterial and viral meningitis and encephalitis. The definitive diagnosis is made by isolation of the virus from fecal material or respiratory secretions.

Management. Specific antiviral treatment of poliomyelitis is not available. Management is supportive, and reporting to local health authorities is mandatory. In the acute phase of paralytic poliomyelitis, patients require hospitalization.

Routine vaccination in the United States has dramatically reduced the number of cases of paralytic poliomyelitis. The Salk IPV is recommended for most indications in the United States. IPV has the advantage of preventing paralytic disease, but it does not protect susceptible contacts by secondary spread. The Sabin OPV protects susceptible contacts, but it is associated with vaccine-associated cases of paralytic disease. In 2000 the CDC recommended that all U.S. children receive four doses of IPV at ages 2, 4, and 6 to 18 months and 4 to 6 years.[5]

www.ketabpezeshki.com 66485457-66963820

Viral Infections with Gastrointestinal Manifestations

Caliciviridae

Caliciviruses and Astroviruses

Principles of Disease. Caliciviruses and astroviruses are small RNA viruses that have been implicated in outbreaks of gastroenteritis, predominantly in children. The noroviruses (which include the Norwalk virus) and the sapoviruses are caliciviruses. The sapoviruses cause gastroenteritis in children, whereas the noroviruses affect people of all ages. Norovirus may peak in the winter months and often is associated with outbreaks in populations living in close quarters (such as cruise ships).[122]

Clinical Features. All age groups are affected and the clinical presentation is that of gastroenteritis. The incubation period probably is 1 to 4 days, and the disease lasts 1 to 3 days. Norovirus is very contagious and is responsible for up to half of all reported gastroenteritis outbreaks.[123] The disease is generally mild and accompanied by low-grade fever, although more prolonged and severe cases can occur among young children and elders. Vomiting appears to be less common with astroviral disease than with calicivirus infections. One third of outbreaks of gastroenteritis can be attributed to a Norwalk virus–like agent. Diarrhea induced by these agents is associated with transient fat malabsorption. Outbreaks have occurred in schools and other institutions and through the ingestion of inadequately cooked shellfish. The mode of transmission is unknown but probably is by the fecal-oral route. Vomiting and diarrhea occur along with myalgias, malaise, headache, and low-grade fever. Severe diarrhea is rare and stools are not bloody. Electron microscopy can make the definitive diagnosis.

Diagnostic Strategies. The majority of clinical virology laboratories perform real-time PCR assays for detection of norovirus; however, these tests are not approved by the Food and Drug Administration. Although there are commercial kits available, they are not widely available. DNA sequencing can be performed on positive specimens to type strains. Enzyme immunoassay results should be confirmed by PCR.[124] In practice, these assays are most useful to confirm an outbreak, but given the lack of specific treatment of norovirus infection, they are not useful in most cases of clinical illness.

Differential Considerations. Other causes of gastroenteritis associated with a similar syndrome include adenoviruses, enteroviruses, and coronaviruses.

Management. Treatment is supportive. The gastroenteritis generally is self-limited and resolves without specific therapy. Oral rehydration solutions generally are adequate; rarely, intravenous therapy is required.

Reoviridae

The family Reoviridae (*r*espiratory *e*nteric *o*rphan viruses) includes four viruses causing human disease: orthoreovirus, orbivirus, coltivirus, and rotavirus. The reoviruses commonly infect humans but infrequently cause human disease. Upper respiratory infections, exanthems, pneumonia, hepatitis, encephalitis, gastroenteritis, and biliary atresia have on occasion been associated with these viruses.

Rotavirus

Principles of Disease. Rotaviruses derive their name from their wheel-like appearance on transmission electron microscopy. These organisms cause severe gastroenteritis in infants and young children, particularly between the ages of 6 months and 2 years; the gastroenteritis is manifested by severe diarrhea and vomiting, which often lead to dehydration and occasionally death. In temperate climates, illness occurs mainly in the winter, commonly is associated with nosocomial infection, and is spread primarily from person to person by the fecal-oral route. The incubation period is approximately 2 days.

Clinical Features. Mucosal epithelial cells of the small intestine appear to be infected selectively, leading to shortening of villi and decreased absorption of salt and water. A secretory diarrhea is produced with impaired D-xylose absorption. Clinical disease ranges from asymptomatic to severe, fatal diarrhea and dehydration. The illness is abrupt in onset with nausea, vomiting, watery diarrhea, low-grade fever, headache, and myalgias. The course of the disease generally is 3 to 5 days in duration. Fatalities are common in developing countries but rare in developed regions of the world.[125] In newborns, rotavirus has been associated with neonatal necrotizing enterocolitis. Infections in adults usually are asymptomatic.

Diagnostic Strategies. Radioimmunoassays, enzyme immunoassays, and latex agglutination methods for detection of antigen are highly reliable and available at most hospital laboratories.

Differential Considerations. Rotavirus enteritis should be suspected in any child with watery diarrhea occurring during the cooler months of the year. Fecal leukocytes and erythrocytes generally are not seen in rotaviral diarrhea. Other enteric viruses can produce a clinical syndrome similar to that due to rotavirus.

Management. Specific treatment of rotaviral infections is not currently available. Intravenous fluids provide effective therapy for dehydration, but if the patient tolerates oral fluids, oral rehydration with packaged oral rehydration salts can be used in the outpatient setting for mild to moderate dehydration. An attenuated human rotavirus vaccine and a human-bovine reassortant rotavirus vaccine have been shown to be both efficacious and safe in trials conducted in both developed and developing countries.[126,127] Currently, the human bovine reassortant vaccine is approved in the United States as a three-dose (at 2, 4, and 6 months of age) orally administered live vaccine. Although there were concerns about the association of intussusception with rotavirus vaccination, a new oral vaccine (Rotarix) has been shown to be effective and not associated with intussusception in Latin America, Europe, Asia, and Africa. A second vaccine, RotaTeq, is also efficacious.[128]

Viral Hemorrhagic Fevers

Flaviviridae

Flavivirus (Group B Arbovirus)

Principles of Disease. More than 60 flaviviruses have been identified, with more than 20 causing human disease. Four of the most common, all transmitted to humans by a mosquito vector, are the agents of yellow fever, dengue, St. Louis encephalitis, and West Nile virus.

Clinical Features. *Yellow fever* is present in tropical South America and Africa. Fever, chills, headache, nausea, and vomiting follow a 3- to 6-day incubation period. The disease may be biphasic, with fever, jaundice, hemorrhage, and characteristic "black vomit" (from the coagulopathy secondary to an affected liver) occurring after a brief period of remission. The case fatality rate is 5%.

Dengue occurs in tropical areas worldwide. Classic dengue fever (breakbone fever) is a nonfatal disease characterized by fever, headache, arthralgias, weakness, nausea, and anorexia after an incubation period of 5 to 10 days. Patients may experience severe bone pain. A generalized macular rash that occasionally desquamates may be seen. The fever lasts 5 to 7 days, but the recovery period may be prolonged. Dengue hemorrhagic fever, characterized by increased vascular permeability and bleeding associated with thrombocytopenia, carries a mortality rate of less than 5% in people who receive good medical care but up to 50% in those

www.ketabpezeshki.com 66485457-66963820

left untreated. Prior exposure to a dengue serotype with the production of cross-reactive antibodies and virulence plays an important role in the pathophysiologic process of dengue hemorrhagic fever.[129] The number of reports of dengue transmission within the United States on the U.S.-Mexico border in Texas and in Hawaii has been increasing.[130,131] Dengue serotype 2 (DENV-2) has been associated with periodic outbreaks of illness in Puerto Rico and the U.S. Virgin Islands, with a high proportion developing dengue hemorrhagic fever, especially among elders.[132] With a population that shows evidence of previous exposure to dengue fever and the continued presence of the *Aedes aegypti* mosquito, the potential for cases of dengue hemorrhagic fever in persons without a recent history of foreign travel certainly exists. The possibility of dengue fever and its hemorrhagic form should be considered in all persons presenting with suggestive symptoms, even if they have not traveled outside the United States.

Diagnostic Strategies. Viral antigen detected in the blood by enzyme-linked immunosorbent assay provides for a rapid diagnosis. Diagnosis of St. Louis encephalitis is made by serology. West Nile virus infection occurs most often in the summer and fall and may be clinically indistinguishable from other arboviral illnesses. CSF IgM antibody testing is the best means of establishing the diagnosis, but results may be falsely positive after other flaviviral infections, such as St. Louis encephalitis, or after immunization against yellow fever.[117]

Differential Considerations. The differential diagnosis for yellow fever is broad in scope; considerations include hepatitis, malaria, typhoid, dengue, and other viral hemorrhagic fevers in endemic areas. The differential diagnosis for dengue is similar to that for yellow fever. Diagnosis is made by viral isolation or serology. St. Louis encephalitis can be manifested like other causes of meningoencephalitis. In elders, it may be misdiagnosed as stroke.

Management. Treatment of these viral diseases is supportive. The diseases are not contagious through person-to-person contact, but the virus generally is transmissible to the mosquito vector during the period of clinical illness. Control of epidemics is achieved by reducing the mosquito vector populations and limiting access of mosquitoes to infected hosts. Persons traveling to endemic areas should be vaccinated for yellow fever.[133]

No recommended therapies are currently available. Several vaccine candidates are under investigation, including a chimeric dengue fever–yellow fever vaccine in phase 3 trials.[134] Physicians should join public health officials in aggressive efforts to educate the public on mosquito control and bite protection measures, such as the use of repellents and protective clothing.

Filoviridae

Marburg and Ebola Viruses

Principles of Disease. Marburg and Ebola viruses cause a systemic febrile illness associated with multiorgan failure. Although the viruses have infected African green monkeys and cynomolgus monkeys, respectively, the infection is fatal to the monkeys, and the natural reservoir is unknown. Recent reports indicate a possible reservoir in certain bat species, but definitive proof is lacking.[135] Monkey-to-human and human-to-human transmission through contact with contaminated tissues or materials has been documented. Aerosol transmission has not been reported.

Clinical Features. The illness is of sudden onset 2 to 10 days after exposure to infected tissue or contact with contaminated materials. Headache, fever, myalgias, arthralgias, and lethargy are early signs. The cardinal sign is diffuse coagulopathy. With both Marburg and Ebola infections, documented mortality rates are greater than 90%. Human infection with Marburg virus was documented in Germany and the former Yugoslavia as a result of contact with imported green monkeys. Human outbreaks also have been documented in the Democratic Republic of the Congo and Angola.[136] More than 1850 cases of Ebola have been documented worldwide, with more than 1200 deaths.[135]

Diagnostic Strategies. Diagnosis is made by isolation of the virus from blood or demonstration of rising antibody titers. New diagnostic strategies include enzyme-linked immunosorbent assays to detect filovirus-specific antibodies[137] as well as RT-PCR.[138]

Differential Considerations. Marburg and Ebola virus diseases may appear clinically similar to other African hemorrhagic fevers, particularly Rift Valley fever, Lassa fever, and yellow fever.

Management. No vaccine or specific treatment exists; treatment is supportive. A number of vaccine candidates are being developed and have been shown to be effective in animal models; however, human studies are thus far lacking.[139]

Bunyaviridae

California Encephalitis and Bunyavirus Hemorrhagic Fevers

Principles of Disease. California encephalitis viruses, including the La Crosse and Johnson Canyon viruses, are transmitted by mosquito bites, predominantly in the northern United States in the summer and fall. Approximately 100 cases are reported yearly. Infection is mostly asymptomatic, but the mortality rate associated with the encephalitis is up to 3%.[140]

The Bunyaviridae family of viruses includes the Crimean-Congo hemorrhagic fever virus, the Rift Valley fever virus, and the hantaviruses, a genus of viruses that cause a hemorrhagic fever with renal syndrome.

Rodents carry hantaviruses; the disease is transmitted by way of aerosols from infected rodent excretions. Hantaviruses can be divided into Old World and New World varieties. Old World hantaviruses, which predominate in Europe and Asia, tend to cause milder disease and have been associated with hemorrhagic fever with renal syndrome. New World hantaviruses occur mainly in the Americas. In 1994, a previously unknown New World hantavirus was found to cause a pulmonary syndrome associated with tachypnea, hemoconcentration, thrombocytopenia, and leukocytosis.[141] Cases occurred predominantly in the southwestern United States and were associated with a mortality rate higher than 50%. The disease was transmitted from the deer mouse, *Peromyscus maniculatus,* and the risk of human infection is likely to be related to a large population of deer mice in concert with human activities.[142] The virus has been designated the Sin Nombre virus.

Several other hantavirus species have been identified in Central and South America that also have been associated with *hantavirus pulmonary syndrome* or *hantavirus cardiopulmonary syndrome.*[143] Rift Valley fever virus is carried by a mosquito and generally produces a nonspecific febrile disease. Up to 100,000 cases occur yearly in Africa. In some patients, a severe retinitis develops that may lead to blindness. Crimean-Congo hemorrhagic fever is a severe, rare, tick-transmitted disease that occurs in Africa and Asia, with a mortality rate approaching 50%.

Management. Treatment of all of these diseases is supportive. The CDC provides intravenous ribavirin for investigational use. Ribavirin is active against Crimean-Congo hemorrhagic fever virus, but it has not been definitively shown to be efficacious in humans.[144]

Arenaviridae

Lymphocytic Choriomeningitis, Lassa, and Hemorrhagic Fever Viruses

Principles of Disease. The arenaviruses are carried by parasites of rodents and probably are passed to humans from contact with infected rodent urine. Four arenaviruses are known to cause human disease. Lymphocytic choriomeningitis (LCM) virus

www.ketabpezeshki.com 66485457-66963820

causes a meningoencephalitis that may be severe but is rarely fatal. Junin and Machupo viruses, from Argentina and Bolivia, respectively, and the Lassa virus, from Africa, cause severe and often fatal hemorrhagic fevers.

Clinical Features. *LCM virus infection* commonly is transmitted from person to person. LCM virus occurs in the Americas, Europe, and Asia and usually is passed from house mice, pet hamsters, or laboratory animals. Influenza-like symptoms follow a 1- to 3-week incubation period, and recovery is generally complete. Meningitis may ensue, but even severe cases are associated with good recovery. Orchitis and parotitis may accompany the disease. LCM virus still poses a hazard in research settings in the United States.[145]

Lassa fever is a highly contagious disease occurring in West Africa, with a case fatality rate of up to 25% in hospitalized patients.[146] The vector is a common rat species. Transmission is thought to occur by contact with the rats or their droppings or by contact with infected persons. In certain areas of Africa, the rate of seropositivity in the general population can be as high as 55%. A gradual onset of fever and malaise after an incubation period of 6 to 21 days is characteristic. The disease is mild or asymptomatic in up to 80% of infected persons, but in approximately 20% it causes high fever, exudative pharyngitis, and diffuse pain (headache, chest pain, abdominal pain) and often is accompanied by vomiting and diarrhea. Worsening disease is characterized by multiorgan failure, mucosal bleeding, coma, and death. Pneumonitis and respiratory distress may develop. Early lymphopenia followed by neutrophilia and elevated transaminases is associated with a poor prognosis.[146]

Argentine hemorrhagic fever, due to the Junin virus, causes a rash and petechiae and is more likely to be hemorrhagic than Lassa fever. The disease is manifested after a 7- to 10-day incubation period with fever, malaise, anorexia, and myalgias. Petechiae and gastrointestinal bleeding occur between days 4 and 6, and shock may follow. Case fatality rates range up to 30%. Bolivian hemorrhagic fever, caused by Machupo virus, is similar to Argentine hemorrhagic fever but occurs much less commonly.

Differential Considerations. LCM virus infection can resemble other viral causes of meningitis or encephalitis. The diagnosis of arenavirus infections requires a fourfold rise in antibody titer.

Management. Only supportive care is required for LCM. Ribavirin has been used effectively to treat Lassa fever and can result in decreased mortality with a low seroconversion rate.[147] Argentine hemorrhagic fever and possibly Bolivian hemorrhagic fever can be successfully treated with convalescent plasma from a recovered patient. Prevention of arenavirus infections is best accomplished by control of the infected vectors. Special care must be taken to prevent person-to-person spread of Lassa fever.

Retrovirus and Viruses Associated with Malignant Neoplasms

Retroviridae

Three subfamilies are described in family Retroviridae: the type C oncoviruses (human T-lymphotropic virus types 1 and 2 [HTLV-1, HTLV-2]), the lentiviruses (e.g., human immunodeficiency viruses types 1 and 2 [HIV-1, HIV-2]), and the spumaviruses. Only the oncoviruses and lentiviruses have been shown to cause disease in humans.

Type C Oncoviruses. The demonstration that RNA could be transcribed into DNA by the reverse transcriptase in RNA tumor viruses laid the groundwork for the discovery of human retroviruses. HTLV-1 was isolated in 1980. In approximately 1% of people infected in childhood with HTLV-1, adult T-cell leukemia-lymphoma develops later in life. HTLV-1 also has been associated with *tropical spastic paraparesis,* also known as *HTLV-1–associated myelopathy*. HTLV-2 was isolated in 1982 and found to be associated with a T-cell variant of hairy cell leukemia.

Human Immunodeficiency Virus

HIV is a slow virus, or lentivirus, related to animal viruses such as the visna virus and feline leukemia virus. A full description of HIV and AIDS is presented in Chapter 132.

Prions

Principles of Disease. The coined term *prion* (*pr*oteinaceous *i*nfectious particle [-*on*]) refers to the transmissible agent putatively responsible for a group of chronic neurodegenerative disorders sharing certain pathologic features. Prions have not been found to contain nucleic acid. Other terms for these agents have included *unconventional virus* and *virino*. The group of diseases caused by these agents, also referred to as *slow virus infections* or simply *slow infections,* includes Creutzfeldt-Jakob disease (CJD), kuru, and Gerstmann-Sträussler syndrome. There is growing evidence that cells infected with prions develop abnormal protein aggregations that force cell apoptosis accompanied by neuronal vacuolation resulting in spongiform encephalopathy.[148]

Bovine spongiform encephalopathy in cattle (sometimes referred to as mad cow disease), or new-variant CJD in humans, occurred primarily in the United Kingdom in the early 1990s and is thought to have been perpetuated in the cattle population by the feeding of bone meal to animals. Although there have been cases of bovine spongiform encephalopathy identified in the United States, there have been only a handful and the last case was identified in 2006.[149] Fortunately, owing to changes in handling of meat byproducts and cattle feed, the incidence of bovine spongiform encephalopathy appears to be decreasing in many of the previously affected countries.

Clinical Findings. CJD is a rare disease, usually manifested in late middle age with a progressive dementia combined with ataxia and myoclonic jerking. Distribution is worldwide and sporadic. CJD has been transmitted from person to person by direct inoculation (e.g., in corneal transplants and dura mater grafts). Kuru and the Gerstmann-Sträussler syndrome are manifested as cerebellar syndromes, with dementia occurring late in the course of the disease. Kuru has been associated with cannibalism confined to a few tribes in the highlands of New Guinea. With both CJD and kuru, progression is rapid, with death usually occurring in less than 1 year. The Gerstmann-Sträussler syndrome follows a more slowly progressive course of up to 10 years.

Diagnostic Strategies. CT and MRI scans usually are nondiagnostic, but the electroencephalogram often shows changes characteristic of CJD.

Differential Considerations. CJD can be confused with Alzheimer's disease or other slowly progressive dementing diseases. Other diseases to consider in the differential diagnosis include multi-infarct dementia, nutritional deficiency syndromes, and primary brain tumors.

KEY CONCEPTS

- New vaccines have been introduced against rotavirus, HPV, and herpes zoster virus.
- Cases of highly pathogenic avian influenza (due to the H5N1 strain of the virus) have been documented.
- Patients who have primary genital herpes or severe or frequent recurrences of infection and patients who are immunosuppressed and have continuous infections should receive acyclovir, famciclovir, or valacyclovir. Herpes simplex encephalitis constitutes a medical emergency requiring rapid diagnosis and treatment with intravenous acyclovir.

www.ketabpezeshki.com 66485457-66963820

- Patients with herpes zoster that is disseminated or that involves more than one dermatome should be treated with intravenous acyclovir.
- West Nile virus infection most severely affects elders. Treatment is supportive; management of the disease requires reporting to public health authorities and control of vector mosquito populations.
- The presentation of SARS-CoV infection mimics that of other community-acquired or nosocomial respiratory infections. Its recognition depends on obtaining a good possible contact history; its control requires prompt initiation of isolation procedures.
- Young children should be routinely vaccinated against influenza A. People at higher risk of becoming infected, those in whom considerable morbidity can be expected, or those who are likely to transmit influenza A to at-risk groups should receive an influenza vaccine annually. In patients with symptoms of influenza, the duration of illness may be shortened by 1 to 2 days if treatment with neuraminidase inhibitors is initiated within 48 hours after symptom onset.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Kennedy RB, Ovsyannikova IG, Jacobson RM, Poland GA: The immunology of smallpox vaccines. *Curr Opin Immunol* 2009; 21:314-320.
2. Centers for Disease Control and Prevention: Poliomyelitis prevention in the United States: Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2000; 49:1.
3. Brady MT, et al; American Academy of Pediatrics Committee on Infectious Diseases: Poliovirus. *Pediatrics* 2011; 128:805-808.
4. Centers for Disease Control and Prevention: Progress toward interruption of wild poliovirus transmission worldwide, Jan 2006–May 2007. *MMWR Morb Mortal Wkly Rep* 2007; 56:27.
5. Centers for Disease Control and Prevention: Recommended immunization schedules for persons aged 0-18 years—United States, 2008. *MMWR Morb Mortal Wkly Rep* 2008; 57:1.
6. Centers for Disease Control and Prevention: Recommended adult immunization schedule—United States, October 2007-September 2008. *MMWR Morb Mortal Wkly Rep* 2007; 56:41.
7. Parashar UD, Alexander JP, Glass RI; Advisory Committee on Immunization Practices (ACIP), Centers for Disease Control and Prevention (CDC): Prevention of rotavirus gastroenteritis among infants and children. *MMWR Recomm Rep* 2006; 55:1-13.
8. Markowitz LE, et al; Centers for Disease Control and Prevention: Quadrivalent human papillomavirus vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2007; 56:1-24.
9. Harper DM, et al; GlaxoSmithKline HPV Vaccine Study Group: Efficacy of a bivalent L1 virus–like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: A randomised controlled trial. *Lancet* 2004; 364:1757-1765.
10. Harpaz R, Ortega-Sanchez IR, Seward JF; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC): Prevention of herpes zoster: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2008; 57:1-30.
11. Oxford JS: Antivirals for the treatment and prevention of epidemic and pandemic influenza. *Influenza Other Respi Viruses* 2007; 1:27-34.
12. Centers for Disease Control and Prevention: High levels of adamantane resistance among influenza A (H3N2) viruses and interim guidelines for use of antiviral agents—United States, 2005-06 influenza season. *MMWR Morb Mortal Wkly Rep* 2006; 55:44-46.
13. Fiore AE, et al; Centers for Disease Control and Prevention: Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2008; 57:1-60.
14. Centers for Disease Control and Prevention: Update: influenza activity—United States, August 30-October 31, 2009. *MMWR Morb Mortal Wkly Rep* 2009; 58:1236-1241.
15. Centers for Disease Control and Prevention: *CDC issues interim recommendations for the use of influenza antiviral medications in the setting of oseltamivir resistance among circulating influenza A (H1N1) viruses, 2008-2009 influenza season*. Distributed via Health Alert Network, Friday, December 19, 2008, 11:50 EST. Available at www2a.cdc.gov/HAN/ArchivesSys/ViewMsgV.asp?AlertNum=00279.
16. Ong AK, Hayden FG: John F. Enders lecture 2006: Antivirals for influenza. *J Infect Dis* 2007; 196:181.
17. Centers for Disease Control and Prevention: *Interim guidance on antiviral recommendations for patients with novel influenza*. Available at www.cdc.gov/h1n1flu/recommendations.htm. Accessed July 24, 2009.
18. Graitcer SB, et al: Characteristics of patients with oseltamivir-resistant pandemic (H1N1) 2009, United States. *Emerg Infect Dis* 2011; 17:255-257.
19. Piret J, Boivin G: Resistance of herpes simplex viruses to nucleoside analogues: Mechanisms, prevalence, and management. *Antimicrob Agents Chemother* 2011; 55:459-472.
20. Mell HK: Management of oral and genital herpes in the emergency department. *Emerg Med Clin North Am* 2008; 26:457.
21. Dworkin RH, et al: Recommendations for the management of herpes zoster. *Clin Infect Dis* 2007; 44(Suppl 1):S1.
22. Spruance SL, et al: High-dose, short-duration, early valacyclovir therapy for episodic treatment of cold sores: Results of two randomized, placebo-controlled, multicenter studies. *Antimicrob Agents Chemother* 2003; 47:1072-1080.
23. Bartlett BL, et al: Famciclovir treatment options for patients with frequent outbreaks of recurrent genital herpes: The RELIEF trial. *Clin Virol* 2008; 43:190-195.
24. Jabs DA, et al: Cytomegalovirus resistance to ganciclovir and clinical outcomes of patients with cytomegalovirus retinitis. *Am J Ophthalmol* 2003; 135:27.
25. Biron KK: Antiviral drugs for cytomegalovirus diseases. *Antiviral Res* 2006; 71:154-163.
26. Ault KA: Human papillomavirus infections: Diagnosis, treatment, and hope for a vaccine. *Obstet Gynecol Clin North Am* 2003; 30:809.
27. Lok AS, McMahon BJ; Practice Guidelines Committee, American Association for the Study of Liver Diseases (AASLD): Chronic hepatitis B: Update of recommendations. *Hepatology* 2004; 39:1.
28. Torriani FJ, et al: Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004; 351:438.
29. Fried MW, et al: Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; 347:975.
30. Centers for Disease Control and Prevention: Brief report: Update, mumps activity, United States. *MMWR Morb Mortal Wkly Rep* 2006; 55:1152.
31. Centers for Disease Control and Prevention: Notice to readers, updated recommendations from the Advisory Committee on Immunization Practices (ACIP) for the control and elimination of mumps. *MMWR Morb Mortal Wkly Rep* 2006; 55:629.
32. WHO Media Centre: *Measles fact sheet 286*, revised December 2009. Available at http://www.who.int/mediacentre/factsheets/fs286/en/. Accessed June 30, 2011.
33. Centers for Disease Control and Prevention: Preventable measles among U.S. residents, 2001-2004. *MMWR Morb Mortal Wkly Rep* 2005; 54:817.
34. Centers for Disease Control and Prevention: Measles—United States, January–May 20, 2011. *MMWR Morb Mortal Wkly Rep* 2011; 60:666-668. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6020a7.htm?s_cid=mm6020a7_w.
35. Centers for Disease Control and Prevention: Control and prevention of rubella: Evaluation and management of suspected outbreaks, rubella in pregnant women, and surveillance for congenital rubella syndrome. *MMWR Recomm Rep* 2001; 50:1-23.
36. Breman J, Henderson D: Current concepts: Diagnosis and management of smallpox. *N Engl J Med* 2002; 346:1300.
37. Bray M, Wright ME: Progressive vaccinia. *Clin Infect Dis* 2003; 36:766-774 .
38. Vorou RM, Papavassiliou VG, Pierroutsakos IN: Cowpox virus infection: An emerging health threat. *Curr Opin Infect Dis* 2008; 21:153-156.
39. Reed KD, et al: The detection of monkeypox in humans in the Western Hemisphere. *N Engl J Med* 2004; 350:342.
40. Nalca A, Rimoin AW, Bavari S, Whitehouse CA: Reemergence of monkeypox: Prevalence, diagnostics, and countermeasures. *Clin Infect Dis* 2005; 41:1765-1771.
41. Tyring SK: Molluscum contagiosum: The importance of early diagnosis and treatment. *Am J Obstet Gynecol* 2003; 189:S12.
42. De Bolle L, et al: Update on human herpesvirus 6: Biology, clinical features and therapy. *Clin Microbiol Rev* 2005; 18:217.
43. Mancuso R, et al: HHV8 a subtype is associated with rapidly evolving classic Kaposi's sarcoma. *J Med Virol* 2008; 80:2153-2160.
44. Kimberlin DW, Rouse DJ: Genital herpes. *N Engl J Med* 2004; 350:1970.
45. Tronstein E, et al: Genital shedding of herpes simplex virus among symptomatic and asymptomatic persons with HSV-2 Infection. *JAMA* 2011; 305:1441-1449.
46. Whitley R, et al: Neonatal herpes simplex virus infection. *Curr Opin Infect Dis* 2004; 17:243.
47. Glenny AM, Fernandez Mauleffinch LM, Pavitt S, Walsh T: Interventions for the prevention and treatment of herpes simplex virus in patients being treated for cancer. *Cochrane Database Syst Rev* 2009; 1:CD006706.
48. Cohen J: Immunology. Painful failure of promising genital herpes vaccine. *Science* 2010; 330:304.
49. Gnann JW Jr: Varicella-zoster virus: Atypical presentations and unusual complications. *J Infect Dis* 2002; 186:S91.
50. Schmader KE, Dworkin RH: Natural history and treatment of herpes zoster. *J Pain* 2008; 9:S3-S9.
51. Wilson JF: zoster. *Ann Intern Med* 2011; 154:ITC31-15.
52. Hurwitz ES, et al: National surveillance for Reye's syndrome: A five-year review. *Pediatrics* 1982; 70:895.
53. Centers for Disease Control and Prevention: Prevention of varicella: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2007; 56:1-40.

www.ketabpezeshki.com 66485457-66963820

54. Madkan VK, et al: Open-label study of valacyclovir 1.5 g twice daily for the treatment of uncomplicated herpes zoster in immunocompetent patients 18 years of age or older. *J Cutan Med Surg* 2007; 11:89-98.
55. He L, Zhang D, Zhou M, Zhu C: Corticosteroids for preventing postherpetic neuralgia. *Cochrane Database Syst Rev* 2008; 1:CD005582.
56. Laina I, et al: Febrile seizures and primary human herpesvirus 6 infection. *Pediatr Neurol* 2010; 42:28-31.
57. Zerr DM, et al: A population-based study of primary human herpesvirus 6 infection. *N Engl J Med* 2005; 352:768-776.
58. Ward KN: Human herpesviruses 6 and 7 infections. *Curr Opin Infect Dis* 2005; 18:247.
59. Sayer R, et al: Can plasma HHV8 viral load be used to differentiate multicentric Castleman disease from Kaposi sarcoma? *Int J STD AIDS* 2011; 22:585-589.
60. Cohen JI, et al; B Virus Working Group: Recommendations for prevention of and therapy for exposure to B virus (cercopithecine herpesvirus 1). *Clin Infect Dis* 2002; 35:1191-1203.
61. Kimberlin DW: Pharmacotherapy of recurrent respiratory papillomatosis. *Expert Opin Pharmacother* 2002; 3:1091.
62. Ramqvist T, Dalianis T: Oropharyngeal cancer epidemic and human papillomavirus. *Emerg Infect Dis* 2010; 16:1671-1677.
63. Hagansee ME, et al: Human papillomavirus infection and disease in HIV-infected individuals. *Am J Med Sci* 2004; 328:57.
64. Corcoran A, et al: Advances in the biology, diagnosis and host-pathogen interactions of parvovirus B19. *J Med Microbiol* 2004; 53:459.
65. Simms RA, et al: Management and outcome of pregnancies with parvovirus B19 infection over seven years in a tertiary fetal medicine unit. *Fetal Diagn Ther* 2009; 25:373-378.
66. Cameron B, et al: Serological and virological investigation of the role of the herpesviruses EBV, CMV and HHV-6 in post-infective fatigue syndrome. *Med Virol* 2010; 82:1684-1688.
67. Cader FZ, Kearns P, Young L, Murray P, Vockerodt M: The contribution of the Epstein-Barr virus to the pathogenesis of childhood lymphomas. *Cancer Treat Rev* 2010; 36:348-353.
68. Klasco R: Colorado tick fever. *Med Clin North Am* 2002; 86:435.
69. Balada-Llasat JM, LaRue H, Kelly C, Rigali L, Pancholi P: Evaluation of commercial ResPlex II v2.0, MultiCode-PLx, and xTAG respiratory viral panels for the diagnosis of respiratory viral infections in adults. *J Clin Virol* 2011; 50:42-45.
70. Centers for Disease Control and Prevention: Revised U.S. surveillance case definition for severe acute respiratory syndrome (SARS) and update on SARS cases—United States and worldwide. *MMWR Morb Mortal Wkly Rep* 2003; 52:1202.
71. Peiris JS, et al: Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet* 2003; 361:1319.
72. Rota PA, et al: Characterization of a novel coronavirus associated with severe acute respiratory syndrome. *Science* 2003; 300:1394.
73. Guan Y, et al: Isolation and characterization of viruses related to the SARS coronavirus from animals in southern China. *Science* 2003; 302:276.
74. Booth CM, et al: Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA* 2003; 289:2801.
75. Lee N, et al: A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med* 2003; 348:1986.
76. Peiris J, et al: The severe acute respiratory syndrome. *N Engl J Med* 2003; 349:2431.
77. Leung L, Rainer T, Lau F, et al: A clinical prediction rule for diagnosing severe acute respiratory syndrome in the emergency department. *Ann Intern Med* 2004; 141:333-342.
78. Avendano M, Derkach P, Swan S: Clinical course and management of SARS in health care workers in Toronto: A case series. *CMAJ* 2003; 168:1649.
79. Svoboda T, et al: Public health measures to control the spread of the severe acute respiratory syndrome during the outbreak in Toronto. *N Engl J Med* 2004; 350:2352.
80. Thiessen RJ: The impact of severe acute respiratory syndrome on the use of and requirements for filters in Canada. *Respir Care Clin North Am* 2006; 12:287-306.
81. Booth CM, Stewart TE: Severe acute respiratory syndrome and critical care medicine: The Toronto experience. *Crit Care Med* 2005; 22(Suppl):S53-S60.
82. Russell KF, Liang Y, O'Gorman K, Johnson DW, Klassen TP: Glucocorticoids for croup. *Cochrane Database Syst Rev* 2011; 1:CD001955.
83. Bjornson C: A randomized trial of a single dose of oral dexamethasone for mild croup. *N Engl J Med* 2008; 351:1306.
84. Cherry J: Croup. *N Engl J Med* 2008; 358:384.
85. Taubenberger JK, Morens DM: 1918 Influenza: The mother of all pandemics. *Emerg Infect Dis* 2006; 12:15-22.
86. Hawkes M, et al: Sensitivity of rapid influenza diagnostic testing for swine-origin 2009 a (H1N1) influenza virus in children. *Pediatrics* 2010; 125:e639-e644.
87. Falsey A: Impact of rapid diagnosis on management of adults hospitalized with influenza. *Arch Intern Med* 2007; 167:354.
88. Bonner A: Impact of rapid diagnosis of influenza on physician decision-making and patient management in the pediatric emergency department: Results of a randomized, prospective, controlled trial. *Pediatrics* 2003; 112:363.
89. Ciblak MA, et al: Sensitivity of rapid influenza antigen tests in the diagnosis of pandemic (H1N1)2009 compared with the standard rRT-PCR technique during the 2009 pandemic in Turkey. *Scand J Infect Dis* 2010; 42:902-905.
90. Yang Y, et al: Evaluation of twelve real-time RT-PCR primer-probe sets for the detection of pandemic influenza A/H1N1 2009. *Clin Microbiol* 2011; 49:1434-1440.
91. World Health Organization: *H5N1 avian influenza: timeline of major events*. Available at www.who.int/csr/disease/avian_influenza/ai_timeline/en/index.html. Accessed June 6, 2008.
92. Kandun IN, et al: Three Indonesian clusters of H5N1 virus infection in 2005. *N Engl J Med* 2006; 355:2186.
93. Abdel-Ghafar AN, et al: Update on avian influenza A (H5N1) virus infection in humans. *N Engl J Med* 2008; 358:261.
94. Sandrock C, Kelly T: Clinical review: Update of avian influenza A infections in humans. *Crit Care* 2007; 11:209.
95. World Health Organization: *Clinical management of human infection with avian influenza A (H5N1) virus*. Available at www.who.int/csr/disease/avian_influenza/guidelines/ClinicalManagement07.pdf. Accessed June 6, 2008.
96. World Health Organization: *Cumulative number of confirmed human cases of avian influenza A/(H5N1) reported to WHO*. Available at www.who.int/csr/disease/avian_influenza/country/cases_table_2011_02_28/en/index.html.
97. Centers for Disease Control and Prevention: *2009 H1N1 flu U.S. situation update*. Available at www.cdc.gov/h1n1flu/updates/us/.
98. Centers for Disease Control and Prevention: Use of influenza A (H1N1) monovalent vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR Recomm Rep* 2009; 58:1-8.
99. The Anzic Influenza Investigators: Critical care services and the 2009 H1N1 influenza in Australia and New Zealand. *N Engl J Med* 2009; 361:1925-1934.
100. Hall CB, Weinberg GA, Iwane MK: The burden of RSV infection in young children. *N Engl J Med* 2009; 360:588-598.
101. Lanari M, Silvestri M, Rossi GA: Respiratory syncytial virus risk factors in late preterm infants. *J Matern Fetal Neonatal Med* 2009; 22(Suppl 3):102-107.
102. Robinson RF: Impact of respiratory syncytial virus in the United States. *Am J Health Syst Pharm* 2008; 65(Suppl 8):53-56.
103. Pezzotti P, Mantovani J, Benincori N, Mucchino E, Di Lallo D: Incidence and risk factors of hospitalization for bronchiolitis in preterm children: A retrospective longitudinal study in children. *BMC Pediatr* 2009; 10:9-56.
104. Fitzgerald GA: Preventing RSV bronchiolitis in vulnerable infants: The role of palivizumab. *Paediatr Respir Rev* 2009; 10:143-147.
105. Samson L: Canadian Pediatric Society Position Statement. Prevention of respiratory syncytial virus infection. *Paediatr Child Health* 2009; 14:521-526.
106. Committee on Infectious Diseases: From the American Academy of Pediatrics: Policy statements—modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. *Pediatrics* 2009; 124:1694-1701.
107. Morris SK, Dzolganovski B Beyene J, Sung L: A meta-analysis of the effect of antibody therapy for the prevention of severe respiratory syncytial virus infection. *BMC Infect Dis* 2009; 9:106.
108. Prescott WA, Doloresco F, Brown J, Paladino JA: Cost effectiveness of respiratory syncytial virus prophylaxis: A critical and systematic review. *Pharmacoeconomics* 2010; 28:279-293.
109. Blanco JC, Boukhvalova MS Shirey KA, Prince GA, Vogel SN: New insights for development of a safe and protective RSV vaccine. *Hum Vaccin* 2010; 6:482-492.
110. Stockton J, Stephenson I, Fleming D, Zambon M: Human metapneumovirus as a cause of community-acquired respiratory illness. *Emerg Infect Dis* 2002; 8:897-901.
111. Su JR: Emerging viral infections. *Clin Lab Med* 2004; 24:773-795.

www.ketabpezeshki.com 66485457-66963820

112. Patel MM, Hall AJ, Vinge J, Parashar UD: Noroviruses: A comprehensive review. *J Clin Virol* 2009; 44:1-8.
113. Hayes EB, et al: Epidemiology and transmission dynamics of West Nile virus disease. *Emerg Infect Dis* 2005; 11:167.
114. Centers for Disease Control and Prevention: *2003 West Nile virus activity in the United States (reported as of April 14, 2004)*. Available at www.cdc.gov/ncidod/dvbid/westnile/surv&control.htm. Accessed May 15, 2008.
115. Centers for Disease Control and Prevention: *Final 2010 West Nile virus human infections in the United States*. Available at www.cdc.gov/ncidod/dvbid/westnile/surv&controlCaseCount10_detailed.htm. Accessed June 29, 2011.
116. Peterson L, Marfin A: West Nile virus: A primer for the clinician. *Ann Intern Med* 2002; 137:173.
117. Peterson L, et al: West Nile virus. *JAMA* 2003; 290:524.
118. Leis AA, et al: A poliomyelitis-like syndrome from West Nile virus infection. *N Engl J Med* 2002; 347:1279.
119. Berenguer J, et al: Clinical course and prognostic factors of progressive multifocal leukoencephalopathy in patients treated with highly active antiretroviral therapy. *Clin Infect Dis* 2003; 36:1047.
120. Antinori A, et al: Clinical epidemiology and survival of progressive multifocal leukoencephalopathy in the era of highly active antiretroviral therapy: Data from the Italian Registry Investigative Neuro AIDS (IRINA). *J Neurovirol* 2003; 9(Suppl 1):47-53.
121. Centers for Disease Control and Prevention: Imported vaccine-associated paralytic poliomyelitis—United States, 2005. *MMWR Morb Mortal Wkly Rep* 2006; 55:97.
122. Carter MJ: Enterically infecting viruses: Pathogenicity, transmission and significance for food and waterborne infection. *J Appl Microbiol* 2005; 88:1354.
123. Patel MM, Hall AJ, Vinge J, Parashar UD: Noroviruses: A comprehensive review. *J Clin Virol* 2009; 44:1-8.
124. Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention: Updated norovirus outbreak management and disease prevention guidelines. *MMWR Recomm Rep* 2011; 60:1-15.
125. Widdowson MA, et al: Rotavirus disease and its prevention. *Curr Opin Gastroenterol* 2005; 21:26.
126. Vesikari T, et al: Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006; 354:23.
127. Ruiz-Palacios GM, et al: Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006; 354:11.
128. Goveia MG, Nelson CB, Ciarlet M: RotaTeq: Progress toward developing world access. *Infect Dis* 2010; 202(Suppl):S87-S92.
129. Kurane I: Dengue hemorrhagic fever with special emphasis on immunopathogenesis. *Comp Immunol Microbiol Infect Dis* 2007; 30:329-340.
130. Centers for Disease Control and Prevention: Dengue hemorrhagic fever—U.S.-Mexico border, 2005. *MMWR Morb Mortal Wkly Rep* 2007; 56:785.
131. Effler PV, et al: Dengue fever, Hawaii, 2001-2002. *Emerg Infect Dis* 2005; 11:742.
132. McElroy KL, et al: Endurance, refuge, and reemergence of dengue virus type 2, Puerto Rico, 1986-2007. *Emerg Infect Dis* 2011; 17:64-71.
133. Cetron MS, et al: Yellow fever vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2002. *MMWR Recomm Rep* 2002; 51:1.
134. Wilder-Smith A, Ooi EE, Vasudevan SG, Gubler DJ: Update on dengue: Epidemiology, virus evolution, antiviral drugs, and vaccine development. *Curr Infect Dis Rep* 2010; 12:157-164.
135. Hensley L: Ebola and Marburg viruses: Pathogenesis and development of countermeasures. *Curr Mol Med* 2005; 5:761.
136. Feldmann H: Focus on research: Marburg hemorrhagic fever—the forgotten cousin strikes. *N Engl J Med* 2006; 355:866.
137. Nakayama E, et al: Enzyme-linked immunosorbent assay for detection of filovirus species-specific antibodies. *Clin Vaccine Immunol* 2010; 17:1723-1728.
138. Ogawa H, et al: Detection of all known filovirus species by reverse transcription–polymerase chain reaction using a primer set specific for the viral nucleoprotein gene. *J Virol Methods* 2011; 171:310-313.
139. Falzarano D, Geisberg TW, Feldmann H: Progress in filovirus vaccine development: Evaluating the potential for clinical use. *Expert Rev Vaccines* 2011; 10:63-77.
140. Haddow AD, Bixler D, Odoi A: The spatial epidemiology and clinical features of reported cases of La Crosse virus infection in West Virginia from 2003 to 2007. *BMC Infect Dis* 2011; 11:29.
141. Centers for Disease Control and Prevention: Hantavirus pulmonary syndrome—Northeastern United States, 1994. *MMWR Morb Mortal Wkly Rep* 1994; 43:54.
142. Calisher CH, Mills JN, Root JJ, Doty JB, Beaty BJ: The relative abundance of deer mice with antibody to Sin Nombre virus corresponds to the occurrence of hantavirus pulmonary syndrome in nearby humans. *Vector Borne Zoonotic Dis* 2011; 11:577-582.
143. Mertz GJ, et al: Diagnosis and treatment of new world hantavirus infections. *Curr Opin Infect Dis* 2006; 19:437.
144. Keshtkar-Jahromi M, et al: Crimean-Congo hemorrhagic fever: Current and future prospects of vaccines and therapies. *Antiviral Res* 2011; 90:85-92.
145. Peters CJ: Lymphocytic choriomeningitis virus—an old enemy up to new tricks. *N Engl J Med* 2006; 354:2208.
146. Richmond K, et al: Lassa fever: Epidemiology, clinical features, and social consequences. *BMJ* 2003; 329:1271.
147. Hadi CM, et al: Ribavirin for Lassa fever postexposure prophylaxis [letter]. *Emerg Infect Dis* 2010; 16:2009-2011.
148. Goldberg AL: On prions, proteasomes, and mad cows. *N Engl J Med* 2007; 357:1150-1152.
149. Centers for Disease Control and Prevention: *BSE (bovine spongiform encephalopathy, or mad cow disease)*. Available at www.cdc.gov/ncidod/dvrd/bse/index.htm. Accessed June 20, 2011.

www.ketabpezeshki.com 66485457-66963820

Chapter 131

Rabies

Prasanthi Govindarajan and Ellen J. Weber

PERSPECTIVE

Rabies is arguably the oldest infection known to humans. The term *rabies* comes from the Sanskrit *rabhas,* which means "to do violence." The Eshmuna Code of Babylon, from the 23rd century BCE, contains one of the earliest regulations regarding rabies: a fine of 40 shekels was levied on the owner of a dog that killed another man through a rabid bite.[1,2]

Today, rabies is a huge public health problem in Third World countries; according to the World Health Organization (WHO), an estimated 55,000 deaths from rabies occur annually worldwide, with 95% of those deaths occurring in Asia and Africa (Fig. 131-1).[3] In the United States and Puerto Rico, however, human rabies is extremely rare as a result of a successful vaccination program for domestic animals that began in 1947. In the prevaccination era, approximately 40 human cases were reported each year. By contrast, in 2009 only four cases of human rabies, of which three were acquired in the United States, were reported to the Centers for Disease Control and Prevention (CDC).[4-7]

EPIDEMIOLOGY

Although it is believed that any mammal can contract rabies, species within the orders Carnivora and Chiroptera (bats) are considered to be the most important reservoirs for maintenance and transmission of the disease.[8-10] Worldwide, dogs are the most commonly infected animal and the most common source of rabies in humans. Dogs are the primary reservoir of rabies in Asia and in many developing countries of Africa. Although dogs were one of the principal reservoirs in South America, major reduction in human and dog rabies has been observed in the last 20 years since implementation of programs to eliminate rabies.[11] In Europe, Canada, and the Arctic and sub-Arctic regions, the principal carrier is the fox; in Puerto Rico, it is the mongoose. Jackals are the main wildlife reservoir of rabies in Africa. Bats are an important source of human rabies in North and South America, western Europe, and Australia. Bats carrying rabies-related lyssaviruses also are found in Africa.

In the United States, more than 90% of all cases of rabies occur in wild animals; the principal reservoirs are raccoons, bats, skunks, and foxes[5] (Fig. 131-2). The only state that remains rabies free is Hawaii, where there are no rabid bats or rabid terrestrial animals.[5] Rabies in terrestrial animals occurs in discrete geographic regions where the virus is transmitted primarily among members of a single species (Fig. 131-3). Each species and location is associated with a unique variant of the rabies virus. In the United States, for example, rabies is endemic in raccoons along the eastern seaboard. A different strain of virus is carried by skunks in the north central states; two additional distinctive strains carried by the skunks in the south central states and rabid skunks endemic to California have been associated with switching of reservoirs from bats to carnivores.[5] Two gray fox reservoirs, each with a unique rabies virus variant, are found in Arizona and in Texas.

Wherever rabies is endemic, other wild carnivores or domestic animals may become infected by contact with the endemic species and will carry the viral variant of the endemic species ("spillover"). The increase in skunk rabies in New England is largely attributable to the raccoon epizootic that has occurred there, although some of the skunk rabies has resulted from spillover from foxes. Although rabies has never been transmitted from a rodent or lagomorph (rabbit or hare) to humans, these animals do contract rabies, usually from the terrestrial reservoir in their region. Most rodent cases are found in larger rodents, such as groundhogs or beavers. In the United States, infected groundhogs generally are found in areas in which raccoon rabies is endemic.[5]

Rabid bats are ubiquitous throughout the United States and North America and account for 24% of all cases of rabies in U.S. animals, making them the second most common source of rabies in the United States after raccoons (Fig. 131-4); 6% of all bats submitted to state health departments tested positive for rabies in 2006. As with terrestrial reservoirs, bats carry viral variants unique to that species, but the geographic associations are less distinct, relating only to where a particular species of bats makes its home. Rabid bats are capable of infecting terrestrial animals as well as humans in any area of the mainland United States. However, spillover appears to be extremely rare.[12]

The association of a unique rabies virus variant with a particular species and locale makes it possible to determine the source of rabies in areas or species that previously were rabies free. In addition, antigenic typing permits identification of the source of human infections when the animal contact is unknown.[13,14]

Wild and Domestic Animal Rabies

Since the 1950s, rabies in U.S. domestic animals has significantly decreased, but the population of rabid wild animals has actually increased (Fig. 131-5). In 2009, rabies was reported in 6195 wild animals, compared with 7364 in 2000.[5,15] In the 1960s and 1970s, a majority of cases of wildlife rabies were found in skunks in the United States. However, in the late 1970s, an epizootic among raccoons began in the mid-Atlantic states and spread north and south to cover the entire eastern seaboard; in 2009, more cases of wildlife rabies in the United States were attributable to raccoons than to any other wild animal (2327 or 34.8%). The likely source of this epizootic appears to be the inadvertent translocation of rabid raccoons from the southeastern states to the mid-Atlantic region by humans to stock the area for hunting, as evidenced by the fact that

www.ketabpezeshki.com 66485457-66963820

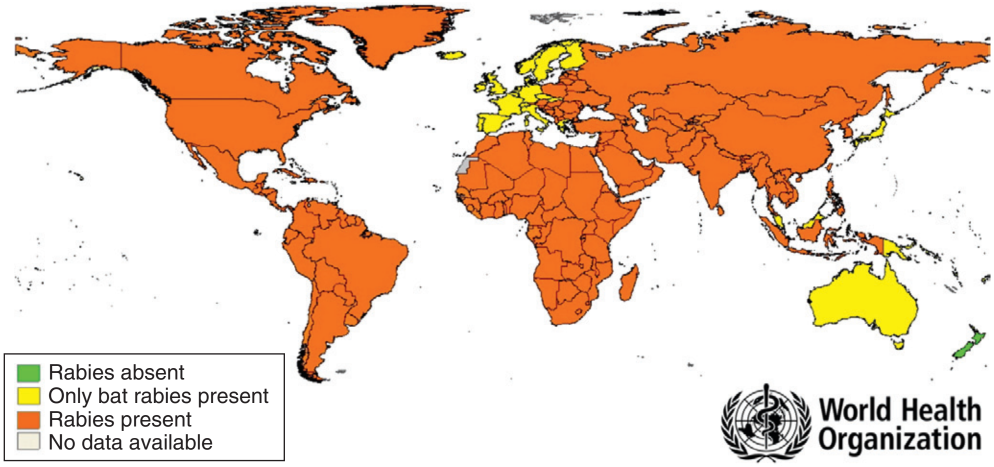


Figure 131-1. Presence or absence of rabies worldwide, 2007. The World Health Organization has been collecting rabies data through the World Survey of Rabies every year. (From RabNet/World Survey of Rabies/OIE/FAO.)

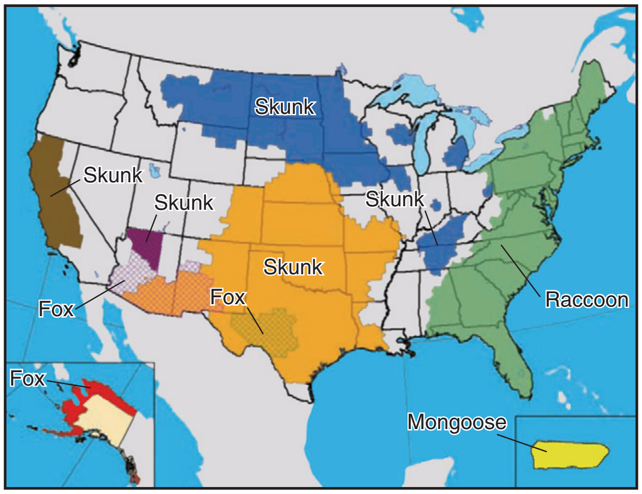


Figure 131-2. Distribution of terrestrial rabies virus variants in the United States and Puerto Rico, 2009. Raccoons were the most frequently reported rabid wildlife species, followed by bats, skunks, and foxes in 2009. (From Blanton JD, Palmer D, Rupprecht CE: Rabies surveillance in the United States during 2009. J Am Vet Med Assoc 237:646-657, 2010.)

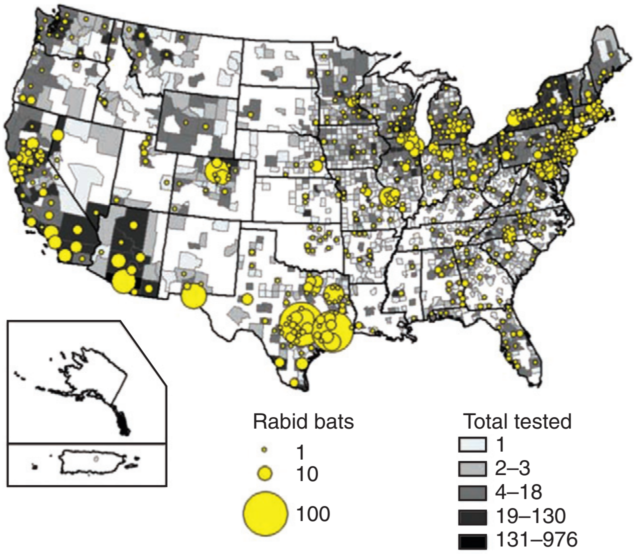


Figure 131-3. Reported U.S. cases of rabies in bats by county, 2009. Rabies in bats accounted for 24% of all cases of animal rabies. (From Blanton JD, Palmer D, Rupprecht CE: Rabies surveillance in the United States during 2009. J Am Vet Med Assoc 237:646-657, 2010.)

rabid raccoons, seen first in the mid-Atlantic states and now along the entire East Coast, carry the same viral variant as those in the southeastern states. The population has spread geographically north and westward. Raccoon rabies is now enzootic in all of the northeastern, mid-Atlantic, and southeastern states.[5,16,17] Of the rabid animal populations in the United States, bats now represent the second most populous (24.3%). A smaller epizootic of coyotes began in the early 1990s in southern Texas; three rabid coyotes were reported in 1990 and 71 in 1993, but the population has since returned to low levels. Eleven cases of coyote rabies were reported in 2009, and they were infected with skunk or gray fox virus variants.[5,18,19]

The number of rabid domestic animals has remained relatively constant for the last decade and accounted for approximately 8% (547 cases) of all rabies in the United States.[5] Cats are the domestic animal most frequently reported as rabid, followed by dogs. An overall slight increase in the number of rabid cattle since 2008 has also been noted.

The median age of rabid cats and dogs is 1 year; most have not been vaccinated or have received only one vaccination.[20] Dogs and cats generally are infected with a strain of rabies virus that is endemic in the terrestrial reservoir in their geographic area. Puerto Rico reported a total of four cases of cat rabies in 2009, which is a presumed spillover from mongoose variant.[5,21] Most owners are unaware of their pets' exposure to wild animals that may carry rabies.

Rabies in Humans

Human cases of rabies in the United States remain low owing to effective animal vaccination programs and availability of human vaccines and immune globulins.[5] Between 2000 and 2010, 31 cases of human rabies were reported to the CDC, 25 of which were acquired from animal sources in the United States. The first ever case of abortive human rabies was reported in 2009 from Texas after exposure to bats.[22] Among the other reported human cases,

www.ketabpezeshki.com 66485457-66963820

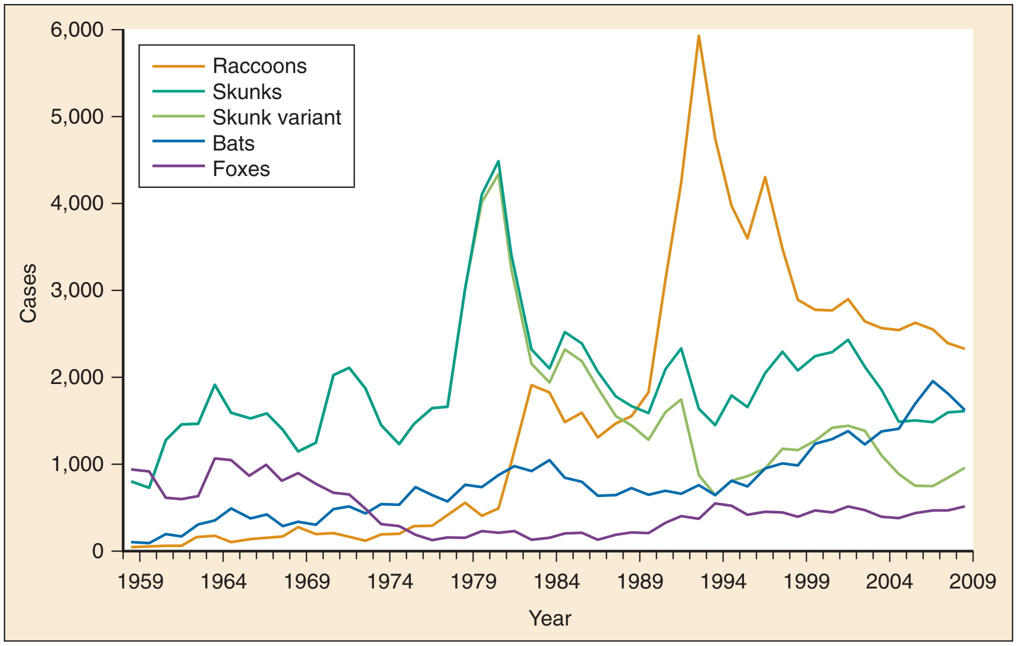


Figure 131-4. Cases of animal rabies, 1959 to 2009. Rabies vaccination campaigns in the 1940s and 1950s resulted in a substantial decrease in rabies in domestic animals. Similarly, elimination of the dog-coyote rabies virus variant and reduction in the gray fox virus variant also have been documented. (From Blanton JD, Palmer D, Rupprecht CE: Rabies surveillance in the United States during 2009. J Am Vet Med Assoc 237:646-657, 2010.)

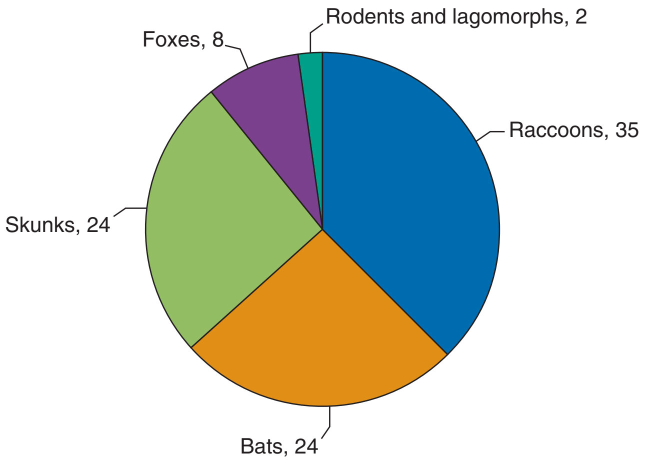


Figure 131-5. Relative proportion of cases of rabies in animals in the United States, 2009. Data for domestic animals are not shown in the pie chart. Numbers may not add up to 100% because of rounding. A total of 2327 cases of rabies in raccoons were reported in 2009, representing a decrease by about 3% from 2008. Decrease was observed in bat rabies, whereas increases also were reported among skunks and foxes in 2009 compared with 2008. (From Blanton JD, Palmer D, Rupprecht CE: Rabies surveillance in the United States during 2009. J Am Vet Med Assoc 237:646-657, 2010.)

one case was associated with the raccoon variant from the eastern United States, one case was due to a dog-mongoose variant in Puerto Rico, and the rest were associated with bats.[5,23-34] Four cases were in transplant recipients, from a donor who died of an unknown encephalopathy, only later identified as rabies.[32] For most bat-associated cases, a history of bat contact was discovered only during hospitalization or determined after the patient's death, when antigenic analysis of the rabies virus infecting the victim revealed a bat variant. In more than half of the cases, the victim was known to have had contact with a bat, although no rabies prophylaxis was sought.* In most other cases, a history of bat exposure was lacking (so-called cryptogenic bat rabies).[24,25,28,31] Although rabies has been found in most of the bat species in the United States, the species most frequently identified with cryptogenic bat rabies in humans is the silver-haired, eastern pipistrelle bat, a solitary, reclusive, tree-dwelling species that is seldom found in buildings and is thought to be rarely encountered by humans. The viral strain associated with this species appears to replicate better and at lower temperatures than a canine rabies variant, suggesting that even a small, superficially administered quantity of virus is sufficient to transmit infection.[9,13]

In 2008 the first case of imported human rabies not associated with canine rabies virus variant was reported from Santa Barbara County, California, in an undocumented immigrant from Mexico. Although the investigations were limited by the subject's linguistic barrier and undocumented status in the United States, laboratory investigations revealed a rabies virus variant most closely related to viruses found in Mexican free-tailed bats.[37] Another case of human rabies was reported in a subject from Virginia who described an encounter with a dog during his visit to India. Postmortem investigations confirmed the presence of an Indian canine rabies variant.[38] Most recently, an 8-year-old girl from rural Humboldt County, California, was reported to have survived a rabies infection. Because the date of exposure was not known, she did not received routine postexposure prophylaxis. Furthermore, although the source animal was thought to be a feral cat, this could not be confirmed as the animal was not available for testing.[39]

PRINCIPLES OF DISEASE

Rabies is caused by a neurotropic rhabdovirus of the genus *Lyssavirus* (from the Greek word *lyssa,* which means "frenzy"). Animals are the natural reservoir for the virus; animals that are infected with the virus become sick and die, usually within 3 to 9

---

*References 23, 26, 27, 29, 30, 32-34, 35, 36.

www.ketabpezeshki.com 66485457-66963820

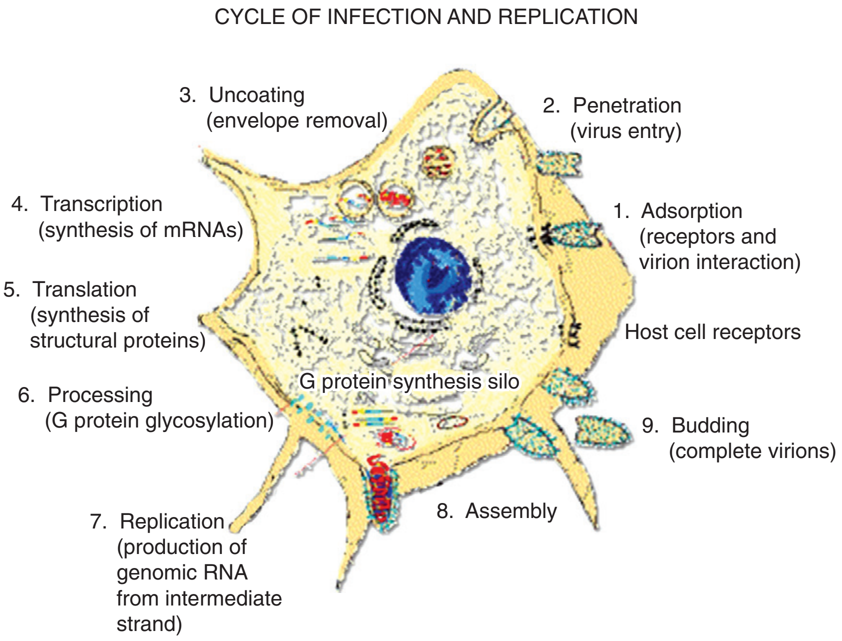


Figure 131-6. Life cycle of the rabies virus within the host cell. (Modified from Centers for Disease Control and Prevention: The rabies virus. Available at www.cdc.gov/rabies/transmission/virus.html. Accessed April 17, 2011.)

days of the time they first begin secreting virus in the saliva.[40] Insectivorous bats may live 10 days; vampire bats, possibly longer.[41,42] Some evidence suggests that dogs can become asymptomatic carriers, but transmission of disease from such an animal to humans has never been documented.[43] A survey of rabid dogs in the United States in 1988 found that all died within 8 days of becoming ill; the median time until death was 3 days.[20]

Animals are capable of transmitting rabies once they start secreting virus in saliva. Most animals with rabies will appear ill before excretion of virus, but some may not become sick for several days after virus can be found in their saliva.[42] The classic picture of a mangy dog foaming at the mouth and wildly running through town is not often seen; clinical signs are invariably present but frequently are more subtle. Indeed, less than half of cases of rabies in domestic animals are initially recognized by veterinarians.[20] The animal may display aggressive behavior, ataxia, irritability, anorexia, lethargy, or excessive salivation; cats are more likely than dogs to demonstrate aggressive or irritable behavior. In a wild animal, however, what may be most apparent is a change in instinctive behavior, for instance, a nocturnal animal may be observed boldly walking through downtown in broad daylight.[44] An unprovoked bite from a domestic animal may be a sign of rabies; however, humans, especially children, often inadvertently provoke a pet by cornering it or competing with it for its natural prey.

Rabies is transmitted when the virus is introduced into bite wounds or open cuts in skin or onto mucous membranes.[45] Almost all documented cases of human rabies have been transmitted by a bite. The risk of transmission by a bite is approximately 50 times that with a scratch[46]; rabies also has been contracted by recipients of corneal and organ transplants from infected donors.[32,45] In animals, rabies is known to be transmitted transplacentally and has been shown to be transmissible experimentally by aerosol under artificial and extreme conditions and by ingestion.[8,47] Other than through transplants, human-to-human transmission has never been confirmed, although two possible cases in family members of rabies victims in Ethiopia that were not laboratory confirmed have been described.[48] Rabies virus has never been isolated from blood.

The virus replicates in muscle cells near the site of the bite, remaining at the site of inoculation for most of the incubation period before entering the peripheral nerve by way of the neuromuscular junction and then rapidly ascending by retrograde conduction along peripheral nerves to the central nervous system. It is estimated that the virus travels along motor and sensory axons at a rate of approximately 8 to 20 mm/day and has a predilection for the thalamus, basal ganglia, and brainstem.[49] Once it is in the central nervous system, the virus creates Negri bodies in the nuclei of neurons, where it manufactures copies of itself that then bud out to infect other neurons (Fig. 131-6). Virus then is transported through the peripheral nerves by antegrade conduction to the salivary glands, where it can be excreted and transmit the disease to a new victim through a bite.[50]

Of interest, the virus does not destroy the neurons; in fact, it prevents cell apoptosis. How rabies actually kills humans has therefore been something of a mystery. Recent theories suggest that in the presence of the rabies virus, there is an outpouring of cytokines and proinflammatory molecules that modify electrical activity in the brain and affect the hypothalamic-pituitary axis and serotonin metabolism, causing the clinical symptoms. The immune reaction recruits T and B cells and results in more cytokine and nitric oxide production. Eventually, cells are depleted of all metabolic pools, and cell death then occurs. Thus the body's own immune reaction may be the actual cause of death. This theory is supported by the fact that persons who have intact T-cell immunity are more likely to have encephalitic rabies and to die quickly, whereas those with impaired immunity are more likely to have paralytic rabies and to live longer.[51]

The risk for development of rabies and succumbing after a bite ranges from 5 to 80% and depends on the type of biting animal, the severity of the exposure, and the location of the bite.[46,52]

CLINICAL FEATURES

Clinical rabies progresses through five stages: incubation, prodrome, acute neurologic illness, coma, and death. The incubation period (bite to first symptom) typically is 20 to 90 days but has been documented to be as short as 10 days and as long as

www.ketabpezeshki.com 66485457-66963820

7 years.[46,52] The duration of the incubation period depends on the amount of viral inoculum, the richness of the peripheral nerve supply, the severity of the bite, the age and immune status of the host, and the proximity of the bite to the central nervous system.[53] Bites on the head and neck result in disease with a shorter incubation period (as short as 15 days) than that for bites on the trunk or lower extremity, most likely because of the rich peripheral nerve supply in the head and neck area.[54] The mortality rate is lower among victims with lower extremity bites.[53]

The prodromal phase can last a day to a week. The clinical manifestations usually are nonspecific and range from numbness or pain at the bite site to generalized influenza-like signs and symptoms, such as low-grade fever, nausea, vomiting, headache, myalgias, sore throat, runny nose, and malaise.

The acute neurologic syndrome that follows the prodromal phase will vary according to the type of rabies that is being manifested. Full-blown rabies has two classic forms: the "furious" or encephalitic form and the paralytic or "dumb" form; another, more recently identified form, "nonclassic," also has been described.[51] Encephalitic rabies is the far more common of the classic forms and is manifested by agitation, hydrophobia, fluctuating consciousness, and extreme irritability; periods of hyperexcitability fluctuate with lucidity or lethargy. Vital signs often are abnormal, with tachycardia, tachypnea, and fever. Hyperactivity is aggravated by light, noise, thirst, and fear. Hydrophobia, so named because of patients' inability to swallow, appears to result from an exaggerated respiratory tract protective reflex that causes a violent, jerky contraction of the diaphragm and accessory muscles of inspiration when the patient attempts to swallow liquids.[49] Overwhelming terror accompanies the phenomenon and may generalize to the sight of water or having water touch the face.[55] Aerophobia, an extreme fear of air in motion, can be elicited in some patients by blowing air across the face. This results in muscle spasms in the neck and pharyngeal regions.[56,57] Signs of autonomic dysfunction, such as excessive salivation and priapism, may be seen. Hyperactive deep tendon reflexes with Babinski's signs and nuchal rigidity often are present. Seizures and focal weakness are rare.

Approximately 20% of cases are manifested as paralytic or dumb rabies, with limb weakness and fever; consciousness initially is spared. Commonly, paralytic rabies has a longer duration of illness; the mean duration of illness before death is 13.4 days versus 7 days in the encephalitic form. Paralytic rabies may be difficult to diagnose because of the lack of the typical irritability and hydrophobia and may be confused with Guillain-Barré syndrome. It also may be difficult to make a distinction between the paralytic form of rabies and Guillain-Barré syndrome on the basis of clinical, pathologic, or electrophysiologic criteria. Features that may suggest paralytic rabies instead of Guillain-Barré syndrome include rapid progression of symptoms involving the central nervous system, asymmetry of limb involvement, persistent fever from the onset of limb weakness, intact sensory function except at the bite site, bladder dysfunction, and percussion myoedema (a mounding of the muscle at the percussion site that lasts a few seconds, most easily elicited on the chest, deltoid, and thigh).[51,54] Neuropathologic findings of motor axon neuropathy in the absence of motor neuron degeneration and inflammation also may help with the recognition of paralytic rabies, although these findings are not unique to rabies.[58] The two forms of classic rabies can overlap or progress from one to the other.

The nonclassic form of rabies is seen with rabies contracted from bats or from dogs in Thailand. This form is characterized by more pronounced motor and sensory deficits than those typical for classic rabies of either form. Commonly seen are brainstem signs such as cranial nerve abnormalities (dysarthria, dysphagia), choreiform movements, ataxia, nystagmus, and vertigo. Seizures are more common in this form of rabies, whereas phobic spasms are rare.

Coma eventually occurs in all forms of rabies, generally 7 to 10 days after the onset of the acute neurologic phase. Hydrophobia persists, accompanied by prolonged apnea and generalized flaccid paralysis. Seizures may ensue, and ultimately the disease culminates in respiratory and vascular collapse. Unless the patient is supported by intensive care, death ensues in 2 to 3 days.[59]

DIAGNOSIS AND MANAGEMENT

In most clinical situations, rabies is not considered until late in the course of the disease. Antemortem diagnosis may involve isolation of virus and detection of viral RNA, antigen, or antibody. Brain biopsy is the definitive method for isolation of virus, but the risks associated with this procedure prohibit its use in most cases. Detection of antigen from the peripheral nerves of a nuchal skin biopsy specimen frequently has been successful and is superior to detection of antigen in corneal epithelium.

Cerebrospinal fluid (CSF) analysis will show a pleocytosis, and in some cases virus can be isolated or viral antibody detected in the fluid. Saliva also may yield virus. Antibody to rabies virus is variably detected in serum and generally is not seen until the second week of illness. Results of direct fluorescent antibody testing for viral antigen in saliva, corneal impressions, and nuchal skin biopsy specimens are variably positive, and such tests should be repeated if the diagnosis remains in doubt. Rabies virus RNA is present in saliva, urine, and CSF, and detection in saliva and urine by reverse transcription–polymerase chain reaction amplification is a promising advance and has been shown to have high reliability and sensitivity.[3,60-62] Magnetic resonance imaging of the brain may be useful in distinguishing rabies from other forms of encephalitis.[63] Because evidence of infection may not be present for many days after the onset of illness, negative findings on antemortem studies do not rule out the disease. Also, antemortem diagnosis is important in limiting contacts with the victim and ascertaining that no others were exposed to the rabies source.

Once it is manifested clinically, rabies is usually fatal within 3 to 10 days; with intensive care unit (ICU) support, survival times are as long as 4 months, but the outcome remains dismal. No clearly effective rabies treatment currently exists; some of the experimental regimens include administration of vidarabine, multisite intradermal vaccination with cell culture vaccines, human leukocyte interferon, rabies immune globulin (RIG) by the intravenous and intrathecal routes, antithymocyte globulin, inosine pranobex, ribavirin, ketamine, and high doses of steroids.* In vitro, high concentrations of ketamine inhibit replication of rabies virus and have been shown experimentally to reduce brain infection. Corticosteroids have been shown to increase the mortality rate in mouse models.[49] Of the total number of eight survivors, only one case of abortive human rabies in which recovery occurred without intensive care treatment was reported from Texas in 2009. The subject presented with headache and nuchal rigidity and was discharged after symptom resolution. A diagnosis of infectious encephalitis was made when her symptoms recurred. However, unlike in other cases of human rabies, she had a short clinical course, recovered from the illness, and was discharged home alive. In this subject, clinical and serologic evidence was supportive of rabies, and no other reason for the patient's clinical condition was identified. In addition, the subject reported an exposure to bats during a camping trip a few months before onset of clinical illness. Although exposure to bats was reported, there was no history of preexposure prophylaxis. After laboratory testing confirmed presence of positive rabies serology, she was given a single dose of

*References 6, 7, 41, 55, 64, 65.

www.ketabpezeshki.com 66485457-66963820

immune globulin and vaccine. Additional doses of vaccines were not given because of concern for adverse effects from boosting of the immune response.

Among other survivors, there are two well-documented cases of survival from rabies in patients who did not receive postexposure prophylaxis.[66] The first, a 15-year-old girl from Minnesota, was treated with ketamine, beta-blockade, antiseizure medications, and neuromuscular blockade. She was not given immune globulin or vaccine to avoid stimulation of an immune response. After 4 months in an ICU, she survived with intact sensorium but significant neurologic sequelae. The second is a rabies survivor from a rural county in California who was managed in the ICU but did not receive postexposure prophylaxis.[39] Unfortunately, two other rabies victims who were treated with the same regimen as the survivor from Minnesota, did not survive.[34] Only five other patients have been reported to have survived clinical rabies, with a satisfactory neurologic status in only one. All five had received some form of preexposure or postexposure prophylactic treatment, and none had rabies virus isolated or antigen detected, raising the question of whether the survivors in fact had the disease.[58]

POSTEXPOSURE PROPHYLAXIS ASSESSMENT

Despite the fact that human rabies is extremely rare in the United States, 20,000 to 39,000 people a year receive postexposure prophylaxis (PEP); direct costs of delivery of prophylaxis are estimated at approximately $2500 per case, with an additional $1100 cost to the patient in the form of lost wages, child care, and transportation.[67,68] From 30 to 60% of treatments are likely to have been avoidable because the exposure was in the low-risk category, no exposure occurred, or animals were not tested or observed appropriately.[69-71] Accordingly, it is imperative that practitioners understand the regional risk of rabies, animal handling procedures, indications for prophylaxis, and recommended treatment measures. The clinical scenario should be discussed with public health officials to reduce unnecessary treatments. Local or state agencies should be contacted first because they are most familiar with the animals in the area. If immediate consultation is required and local agencies are unavailable, clinicians can call the CDC's clinician information line, 877-554-4625 or 800-CDC-INFO, which is available 24 hours a day, 7 days a week.

The decision to begin PEP after a bite depends on a number of factors: the type of exposure, the location of the incident, and the availability of the biting animal (Table 131-1). Treatment decisions may be modified if the animal is available for testing or observation.

Exposure

Bites are considered significant exposures; nonbite exposures that involve contamination of either a mucous membrane or an open wound (one that has bled within 24 hours) with saliva also may necessitate prophylaxis. Petting of a rabid animal and contact with its blood, urine, or feces are not considered exposures.[44] Skunk spray exposure does not require prophylaxis. Dry virus is not infectious.

Biting Animal

In the United States, high-risk animals are raccoons, skunks, foxes, bats, and coyotes. Dogs found along the U.S.-Mexico border and in developing countries also are high-risk animals. Wild carnivores in areas in which rabies is endemic may be infected with rabies; the risk of transmission of rabies to humans from the bites of these animals is approximately 10 times lower than the risk from the predominant reservoir but high enough to warrant prophylaxis.[72] Therefore, bites from most wildlife require immediate prophylaxis; exceptions, as noted later, are lagomorphs and rodents. Significant nonbite exposures to these animals also constitute grounds for initiation of treatment. PEP for the victim may be discontinued if the animal is proved not to be rabid after testing.

Transmission of rabies from bats appears to have occurred from seemingly unimportant or unrecognized bites. Accordingly, the threshold for providing treatment after bat exposures is exceedingly low. The CDC recommends that "postexposure prophylaxis should be considered when direct contact between a human and a bat has occurred, unless the exposed person can be certain bite, scratch, or mucous membrane exposure did not occur."[45] PEP is recommended when a bat is found indoors in the same room with a person who might be unaware that a bite or direct contact had occurred (such as someone sleeping, an unattended child, or a mentally disabled person) and rabies cannot be ruled out by testing of the bat. Prophylaxis would not be recommended for other household members unless contact with the bat had occurred.

Small rodents (squirrels, gophers, rats, chipmunks, and guinea pigs) and lagomorphs (rabbits and hares) are unlikely to carry rabies and thus are low risk. However, in areas in which raccoon rabies is endemic, groundhogs (woodchucks) have been found to

Table 131-1 Guidelines to Determine the Need for Rabies Prophylaxis

ANIMAL TYPE	EVALUATION AND DISPOSITION OF ANIMAL	POSTEXPOSURE PROPHYLAXIS RECOMMENDATIONS
Dogs, cats, and ferrets	Healthy and available for 10-day observation period*	Persons should not begin vaccination unless animal develops clinical signs of rabies.
	Rabid or suspected rabid	Immediately vaccinate.
	Unknown (escaped)	Consult public health officials.
Raccoons, skunks, foxes, and most other carnivores; bats	Regarded as rabid unless animal is proved to be seronegative for rabies by laboratory test†	Consider immediate prophylaxis.
Livestock, horses, rodents, rabbits and hares, and other mammals	Consider individually	Consult public health officials. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other small rodents, and rabbits and hares almost never require rabies postexposure prophylaxis.

Modified from Manning SE, et al: Human rabies prevention—United States, 2008: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 57:1-28, 2008. Available at www.cdc.gov/mmwr/preview/mmwrhtml/rr5703a1.htm#tab3. Accessed April 5, 2011.

For consultation, contact local health officials; if these are unavailable, call the CDC at 877-554-4625.

*During the 10-day observation period, begin postexposure prophylaxis at the first sign of rabies in a dog, cat, or ferret that has bitten someone. If the animal exhibits clinical signs of rabies, it should be euthanized immediately and tested.

†The animal should be euthanized and tested as soon as possible. Holding for observation is not recommended. Discontinue vaccine if immunofluorescence test results for the animal are negative.

www.ketabpezeshki.com 66485457-66963820

be rabid in significant numbers.[5] Current recommendations are to consult state or local health departments before initiation of PEP for cases involving rodents. Bites from rodents outside the United States should receive prophylaxis.

Bites from livestock should be considered individually, and public health officials should be consulted.[45] No human cases of rabies from livestock have ever been reported in the United States.[8]

Domestic animals, particularly urban cats and dogs, are generally low risk, with the exception of dogs at the U.S.-Mexico border. However, domestic animals in endemic areas may be somewhat higher risk. Healthy-appearing domestic animals (dogs, cats, and ferrets) should be observed for 10 days, and PEP for the victim should be withheld unless the animal becomes ill. Public health officials should be contacted if the animal is not available for observation. In nonendemic areas, PEP usually is withheld even if the animal is not available. Rabies has rarely been diagnosed in vaccinated domestic animals and has been reported exclusively in animals that had received only one vaccination in their lifetime.[21,73] Bites from dogs in developing countries should always be considered high risk, and prophylaxis should be given without waiting for test results.

Biting Incident

Animals that are behaving oddly or that bite without provocation have a higher risk of carrying rabies. However, the circumstances of the bite should be taken into consideration only in evaluation of a bite from an otherwise low-risk animal, such as a dog or cat.

Animal in Captivity

Wild animals that have been caught should be sacrificed immediately and the head sent, under refrigeration, to an appropriate laboratory for rabies fluorescent antibody testing. Unless the risk of transmission is low, the victim should begin prophylaxis, which may be discontinued when the results of the test are known. Domestic animals (dogs, cats, ferrets) that are apparently healthy should be observed for 10 days; if the animal does not become ill, the victim does not require treatment. If the animal appears sick or is stray or unwanted, it should be sacrificed and tested immediately and the victim treated accordingly.

POSTEXPOSURE PROPHYLAXIS

Prophylaxis consists of three steps: wound care, passive immunization, and active immunization. No step in this treatment should be omitted. When prophylaxis appears to be indicated, treatment should be begun immediately. Discussions with local public health officials will decrease unnecessary treatment, and advice is available from either state health officials or the CDC 24 hours a day. Prophylaxis should be initiated as soon as possible and delays are not recommended (J. McQuiston, Centers for Disease Control and Prevention, personal communication, 2000).

Wound Care

Although wound care should never be relied on as the only preventive measure, it is an essential part of postexposure rabies prevention, especially because in rare cases rabies subsequently developed in persons who received what was thought to be appropriate immunoprophylaxis. Furthermore, wound treatment may be the only prevention available for a victim in the wild who is days or weeks away from medical care. Rabies virus is easily killed by sunlight, soap, or drying. Experimental studies have shown that the combination of scrubbing and flushing of the wound with benzalkonium chloride, 20% soap solution, or Ivory soap is nearly 100% protective when it is performed within 3 hours of inoculation of virus.[74] For wounds in which rabies transmission is of concern, the CDC recommends immediate and thorough washing with soap and water and also application of a virucidal agent such as povidone-iodine (Box 131-1).[44] Wounds should be scrubbed or swabbed, not simply flushed.[75] After cleansing, the wound is rinsed with water or saline.

Box 131-1 Rabies Wound Treatment

- Early treatment is essential (less than 3 hours after the bite or injury occurred).
- Scrub the wound and its edges with soap and water.
- If the wound is a puncture, swab deeply in the wound and around its edges.
- Follow with application of a virucidal agent:
  1% or 2% benzalkonium chloride.
  or
- Rinse with povidone-iodine.*

*Povidone-iodine has never been tested but is recommended by the Centers for Disease Control and Prevention. Tetanus prophylaxis should be given as indicated by patient's current immunization status.

Immunoprophylaxis

Rabies immunoprophylaxis requires both passive immunization with antibody (immune globulin) and active immunization with vaccine (Box 131-2). It is essential that both parts of this regimen be administered, even when treatment is delayed. Human rabies immune globulin (HRIG), 20 IU/kg, should be administered as soon after the bite as possible but not longer than 7 days after tissue culture vaccine has been given. If it is anatomically feasible, the entire dose of HRIG should be infiltrated into and around the wounds; any remaining volume should be injected intramuscularly at a site distant from the vaccine.[6]

Three cell culture rabies vaccines are licensed in the United States: human diploid cell vaccine (HDCV, Imovax rabies vaccine, Sanofi Pasteur), purified chick embryo cell vaccine (PCECV, RabAvert, Novartis Vaccines and Diagnostics), and rabies vaccine adsorbed (RVA, BioPort Corporation). However, only HDCV and PCECV are available for use in the United States, with HDCV being the most widely used vaccine. According to the new PEP guidelines, only four doses of vaccine need to be administered; the first dose should be administered on the day of the bite; three subsequent injections are required on days 3, 7, and 14. After administration of 1.0 mL of vaccine intramuscularly, an active antibody response takes about 7 to 10 days to develop and lasts several years. The vaccine should be administered in the deltoid rather than in the gluteal region to avoid accidental injection into fat, which will prevent antibody formation.[61,76]

HRIG and HDCV should be given in different anatomic sites and never mixed in the same syringe. All known treatment failures since 1980 have occurred after a deviation from the recommended regimen. Patients did not have their wounds cleansed with soap and water, did not receive HRIG at the wound site, or did not receive rabies vaccine in the deltoid region.[45,64,76-78]

Local reactions (itching, erythema, pain, or swelling) occur in 30 to 74% of PEP recipients; systemic reactions, including headache, myalgia, and nausea, occur in 5 to 40% of recipients, usually those who receive frequent vaccine boosters.[45] Anaphylaxis has occurred in 0.1% of cases; three cases of Guillain-Barré syndrome have occurred after millions of doses given.[45,79] An immune complex type of reaction involving urticaria, arthralgia, arthritis, angioedema, nausea, and vomiting occurs in approximately 6% of patients who receive boosters of HDCV; it is uncommon in those receiving primary vaccination.[45] Two alternative vaccines, RVA and PCECV, also are available in the United States. Both appear

www.ketabpezeshki.com 66485457-66963820

to be associated with fewer hypersensitivity reactions in patients receiving boosters.[80] Although HDCV may be administered intradermally for preexposure prophylaxis, neither RVA nor PCECV is approved for intradermal use.

Patients requiring rabies immunoprophylaxis outside the United States may receive a different regimen and different vaccines from those used within the United States. Some countries still use vaccines derived from nerve tissue, rather than cell cultures, which are poorly immunogenic and carry a greater risk of side effects. In many areas, rabies immune globulin may not be available. The WHO has approved several treatment regimens that reduce cost, with fewer vaccine injections, or use of the intradermal route, which requires less vaccine. In addition, the WHO recommends immune globulin only for severe bites.[80] These regimens are not approved in the United States for PEP. The WHO cautions that intradermal injections should be administered only by medical personnel who have been trained in this technique.[80,81] In addition, because chloroquine has been shown to interfere with the antibody response to vaccine given intradermally, victims of bites who are currently receiving malaria prophylaxis (with any medication) should undergo postexposure rabies prophylaxis only by the intramuscular route.[45,80] Accordingly, bite victims traveling abroad may require additional treatment when they return to the United States. Public health officials should be contacted for advice.

Prophylaxis, including both passive and active immunization, given during pregnancy does not result in an increase in fetal wastage, congenital defects, or side effects and should not be withheld when it is indicated.[82] Corticosteroids, antimalarials, and other immunosuppressives can interfere with the development of active immunity and should be withheld during the course of treatment if possible. Patients who must receive these drugs or those who are immunosuppressed should receive prophylaxis by the intramuscular route and have antibody titers checked at 2 to 4 weeks after completion of the injection series.[45,76] Patients with a history of hypersensitivity should nevertheless be cautiously given immunoprophylaxis in a controlled setting, with antihistamines and epinephrine available.[45] Rabies developed in a patient who was sensitive to equine antirabies immune globulin and was not given passive immunization.[56,83]

Box 131-2 Rabies Postexposure Immunoprophylaxis

Wound cleansing	All postexposure prophylaxis should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as povidone-iodine solution should be used to irrigate the wounds.
Nonimmunized Persons	
Human rabies immune globulin (HRIG)	The dose is 20 IU/kg. If possible, the full dose should be infiltrated around any wound(s), and any remaining volume should be administered IM at an anatomic site distant from vaccine administration. Also, HRIG should not be administered in the same syringe as for vaccine. Because HRIG may partially suppress active production of antibody, **no more** than the recommended dose should be given.
Vaccine	Human diploid cell vaccine (HDCV) or purified chick embryo culture vaccine (PCECV) 1.0 mL, IM (deltoid area), one each on days 0, 3, 7, and 14. For persons with immunosuppression, all 5 doses of vaccine on days 0, 3, 7, 14, and 28 should be administered.
Previously Immunized Persons	
HRIG	HRIG should not be administered.
Vaccine	HDCV or PCECV 1.0 mL, IM (deltoid area), on days 0 and 3

From Centers for Disease Control and Prevention: Resources. Available at www.cdc.gov/mmwr/preview/mmwrhtml/rr57e507a1.htm. Accessed April 5, 2011.

PREEXPOSURE PROPHYLAXIS

For people with frequent exposures to rabies, preexposure prophylaxis may be indicated.[45] Such persons include laboratory personnel working with live rabies virus, veterinarians, animal handlers, and those spending long periods in countries in which rabies is endemic and medical care is difficult to obtain (Table 131-2). Preexposure prophylaxis guarantees protection

Table 131-2 Rabies Preexposure Prophylaxis Guide

RISK CATEGORY	NATURE OF RISK	TYPICAL POPULATION	PREEXPOSURE RECOMMENDATIONS
Continuous	Virus present continuously, often in high concentrations Specific exposures likely to go unrecognized Bite, nonbite, or aerosol exposure	Rabies research laboratory workers Rabies biologics production workers	Primary course Serologic testing every 6 months; booster vaccination if antibody titer is below acceptable level
Frequent	Exposure usually episodic, with source recognized, but exposure also might be unrecognized Bite, nonbite, or aerosol exposure	Rabies diagnostic laboratory workers, spelunkers, veterinarians and staff, and animal control and wildlife workers in rabies enzootic areas All persons who frequently handle bats	Primary course Serologic testing every 2 years; booster vaccination if antibody titer is below acceptable level
Infrequent	Exposure nearly always episodic with source recognized Bite or nonbite exposure	Veterinarians and terrestrial animal control workers in areas where rabies is uncommon to rare Veterinary students Travelers visiting areas where rabies is enzootic and immediate access to appropriate medical care, including biologics, is limited	Primary course No serologic testing or booster vaccination
Rare	Exposure always episodic with source recognized Bite or nonbite exposure	U.S. population at large, including persons in rabies epizootic areas	No vaccination necessary

Modified from Manning SE, et al: Human rabies prevention—United States, 2008: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 57:1-28, 2008. Available at www.cdc.gov/rabies/specific_groups/travelers/pre-exposure_vaccinations.html. Accessed April 5, 2011.

www.ketabpezeshki.com 66485457-66963820

for persons who incur continuous and unapparent exposures (e.g., laboratory workers); it also allows protection when postexposure therapy may be delayed (e.g., in remote areas). After an exposure, patients who have had preexposure prophylaxis do not require HRIG; vaccine is given only on days 0 and 3 (see Box 131-2). However, travelers should be aware that chloroquine prophylaxis for malaria can interfere with antibody response to preexposure vaccination given intradermally; therefore, the vaccination regimen should be completed at least 1 month before initiation of malaria prophylaxis, or the preexposure regimen should be given intramuscularly.[7,45]

KEY CONCEPTS

- The epidemiology of rabies in the United States has undergone a major evolution, with the primary source of this disease now in wild animals rather than in domestic animals.
- Despite an increase in the numbers of terrestrial wild animals with rabies, particularly raccoons, the predominant threat to humans in the United States appears to be contact with bats.
- PEP is indicated for victims of bites or significant nonbite exposures from wild carnivores in endemic areas and bat contact when a bite cannot be ruled out and the bat cannot be tested. In most cases in the United States, healthy domestic animals should be observed before initiation of PEP.
- Discussion with public health officials is highly recommended to guide decisions about PEP and to reduce the number of unnecessary treatments.
- PEP involves three important components: local wound care with soap and water and a virucidal agent, passive immunization with rabies immune globulin, and active immunization with four doses of vaccine. The regimen should be adhered to precisely because treatment failures have occurred when it was not followed.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Fisher DJ: Resurgence of rabies: A historical perspective on rabies in children [see comments]. *Arch Pediatr Adolesc Med* 1995; 149:306.
2. Koprowski H: Visit to an ancient curse. *Sci Am Sci Med* 1995; 2:48.
3. World Health Organization: *Rabies*. Available at www.who.int/mediacentre/factsheets/fs099/en/. Accessed March 26, 2011.
4. World Health Organization: *World survey of rabies no. 34 for the year 1998*. Available at www.who.int/rabies/resources/en/wsr98_a12.pdf. Accessed February 15, 2008.
5. Blanton JD, et al: Rabies surveillance in the United States during 2009. *J Am Vet Med Assoc* 2010; 237:646-657.
6. Anderson L, et al: Human rabies in the United States, 1960 to 1979. *Ann Intern Med* 1984; 100:728.
7. Noah DL, et al: Epidemiology of human rabies in the United States, 1980 to 1996. *Ann Intern Med* 1998; 128:922.
8. Gibbons RV: Cryptogenic rabies, bats, and the question of aerosol transmission. *Ann Emerg Med* 2002; 39:528.
9. Messenger SL, et al: Emerging pattern of rabies deaths and increased viral infectivity. *Emerg Infect Dis* 2003; 9:151.
10. Woldehiwet Z: Rabies: Recent developments. *Res Vet Sci* 2002; 73:17.
11. Pan American Health Organization: *Elimination of dog-transmitted human rabies in Latin America: Situation analysis*. Available at www.paho.org/English/AD/DPC/VP/rabia-sit.htm. Accessed March 26, 2011.
12. Messenger SL, et al: Emerging epidemiology of bat-associated cryptic cases of rabies in humans in the United States. *Clin Infect Dis* 2002; 35:738.
13. Smith JS, et al: Unexplained rabies in three immigrants in the United States: A virologic investigation. *N Engl J Med* 1991; 324:205.
14. Rohde RE, et al: Molecular epidemiology of rabies epizootics in Texas. *Clin Diagn Virol* 1997; 8:209.
15. Eng TR, et al: Rabies surveillance, United States, 1988. *MMWR CDC Surveill Summ* 1989; 38:1.
16. Krebs JW, et al: Rabies surveillance in the United States during 2002. *J Am Vet Med Assoc* 2003; 223:1736.
17. Krebs JW, et al: Rabies surveillance in the United States during 1999. *J Am Vet Med Assoc* 2000; 217:1799.
18. Reid-Sanden F, et al: Rabies surveillance in the United States during 1989. *J Am Vet Med Assoc* 1990; 197:1571.
19. Krebs JW, et al: Rabies surveillance in the United States during 1993. *J Am Vet Med Assoc* 1994; 205:1695.
20. Eng T, Fishbein D: Epidemiologic factors, clinical findings, and vaccination status of rabies in cats and dogs in the United States in 1988. National Study Group on Rabies. *J Am Vet Med Assoc* 1990; 197:201.
21. Blanton JD, Hanlon CA, Rupprecht CE: Rabies surveillance in the United States during 2005. *J Am Vet Med Assoc* 2006; 229:1897.
22. Centers for Disease Control and Prevention: Presumptive abortive human rabies—Texas, 2009. *MMWR Morb Mortal Wkly Rep* 2010; 59:185-190.
23. Centers for Disease Control and Prevention: Human rabies—Texas and New Jersey, 1997. *MMWR Morb Mortal Wkly Rep* 1998; 47:1.
24. Centers for Disease Control and Prevention: Human rabies—Montana and Washington, 1997. *MMWR Morb Mortal Wkly Rep* 1997; 46:770.
25. Centers for Disease Control and Prevention: Human rabies—Virginia, 1998. *MMWR Morb Mortal Wkly Rep* 1999; 48:95.
26. Centers for Disease Control and Prevention: Human rabies—California, Georgia, Minnesota, New York, and Wisconsin, 2000. *MMWR Morb Mortal Wkly Rep* 2000; 49:1111.
27. Centers for Disease Control and Prevention: Human rabies—Tennessee, 2002. *MMWR Morb Mortal Wkly Rep* 2002; 51:828.
28. Centers for Disease Control and Prevention: Human rabies—Iowa, 2002. *MMWR Morb Mortal Wkly Rep* 2003; 52:47.
29. Centers for Disease Control and Prevention: Human rabies—California, 2002. *MMWR Morb Mortal Wkly Rep* 2002; 51:686.
30. Centers for Disease Control and Prevention: Human death associated with bat rabies—California, 2003. *MMWR Morb Mortal Wkly Rep* 2004; 53:33.
31. Centers for Disease Control and Prevention: First human death associated with raccoon rabies—Virginia, 2003. *MMWR Morb Mortal Wkly Rep* 2003; 52:1102.
32. Srinivasan A, et al: Transmission of rabies virus from an organ donor to four transplant recipients. *N Engl J Med* 2005; 352:1103.
33. Centers for Disease Control and Prevention: Human rabies—Mississippi, 2005. *MMWR Morb Mortal Wkly Rep* 2006; 55:207.
34. Centers for Disease Control and Prevention: Human rabies—Indiana and California, 2006. *MMWR Morb Mortal Wkly Rep* 2007; 56:361.
35. Centers for Disease Control and Prevention: Human rabies—Missouri, 2008. *MMWR Morb Mortal Wkly Rep* 2009; 58:1207-1209.
36. Centers for Disease Control and Prevention: Human rabies—Kentucky/Indiana, 2009. *MMWR Morb Mortal Wkly Rep* 2010; 59:393-396.
37. Centers for Disease Control and Prevention: Imported human rabies—California, 2008. *MMWR Morb Mortal Wkly Rep* 2009; 58:713-716.
38. Centers for Disease Control and Prevention: Human rabies-—Virginia, 2009. *MMWR Morb Mortal Wkly Rep* 2010; 59:1236-1238.
39. *Rabies*. UC Health, June 15, 2011. Available at http://health.universityofcalifornia.edu/tag/rabies/. Accessed July 1, 2011.
40. Sikes E: Pathogenesis of rabies in wildlife. 1. Comparative effect of varying doses of rabies virus inoculated into foxes and skunks. *Am J Vet Res* 1962; 23:1041.
41. Roine R, et al: Fatal encephalitis caused by a bat-borne rabies-related virus: Clinical findings. *Brain* 1988; 111:1505.
42. Sikes R: Rabies. In Hubbert W, McCulloch W, Schnurrenberger P, eds: *Diseases Transmitted from Animals to Man*, 6th ed. Springfield, Ill: Charles C Thomas; 1975.
43. Hemachudha T, et al: Latent rabies [letter]. *N Engl J Med* 1991; 324:1890.
44. Thirteenth rabid animal incident of the year. *County of Marin; October 7, 1986.*
45. Human rabies prevention—United States, 1999. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 1999; 48:1.
46. Fishbein D, Robinson L: Rabies. *N Engl J Med* 1993; 329:1632.
47. Afshar A: A review of non-bite transmission of rabies virus infection. *Br Vet J* 1979; 135:142.
48. Fekadu M, et al: Possible human-to-human transmission of rabies in Ethiopia. *Ethiop Med J* 1996; 34:123.
49. Jackson AC: Update on rabies. *Curr Opin Neurol* 2002; 15:327.
50. Rupprecht CE, et al: Rabies re-examined. *Lancet Infect Dis* 2002; 2:327.
51. Hemachudha T, et al: Human rabies: A disease of complex neuropathogenetic mechanisms and diagnostic challenges. *Lancet Neurol* 2002; 1:101.
52. Baer G: Animal models in the pathogenesis and treatment of rabies. *Rev Inf Dis* 1988; 10:S739.
53. Gadre G, et al: Rabies viral encephalitis: Clinical determinants in diagnosis with special reference to paralytic form. *J Neurol Neurosurg Psychiatry* 2010; 81:812-820.
54. Shah U, Jaswal G: Victims of a rabid wolf in India: Effect of severity and location of bites on development of rabies. *J Infect Dis* 1976; 134:25.
55. Case records of the Massachusetts General Hospital: Weekly clinicopathological exercises: Case 21-1998: A 32-year-old woman with pharyngeal spasms and paresthesias after a dog bite [clinical conference]. *N Engl J Med* 1998; 339:105.
56. Frenia ML, et al: Features and treatment of rabies. *Clin Pharm* 1992; 11:37.
57. Centers for Disease Control and Prevention: Human rabies—New Hampshire, 1996. *MMWR Morb Mortal Wkly Rep* 1997; 46:267.
58. Sheikh KA, et al: Overlap of pathology in paralytic rabies and axonal Guillain-Barré syndrome. *Ann Neurol* 2005; 57:768.
59. Jackson AC, et al: Management of rabies in humans. *Clin Infect Dis* 2003; 36:60.
60. Nagaraj T, et al: Ante mortem diagnosis of human rabies using saliva samples: Comparison of real time and conventional RT-PCR techniques. *J Clin Virol* 2006; 36:17.
61. Hemachudha T, Wacharapluesadee S: Antemortem diagnosis of human rabies. *Clin Infect Dis* 2004; 39:1085.
62. De Benedictis P, et al: Lyssavirus detection and typing using pyrosequencing. *J Clin Microbiol* 2011; 49:1932-1938.
63. Laothamatas J, et al: MR imaging in human rabies. *AJNR Am J Neuroradiol* 2003; 24:1102.
64. Shill M, et al: Fatal rabies encephalitis despite appropriate post-exposure prophylaxis. *N Engl J Med* 1987; 316:1257.
65. Warrell MJ, et al: Failure of interferon alfa and tribavirin in rabies encephalitis. *BMJ* 1989; 299:830.
66. Willoughby RE Jr, et al: Survival after treatment of rabies with induction of coma. *N Engl J Med* 2005; 352:2508.
67. Shwiff SA, et al: Direct and indirect costs of rabies exposure: A retrospective study in southern California (1998-2002). *J Wildl Dis* 2007; 43:251.
68. Krebs JW, et al: Causes, costs, and estimates of rabies postexposure prophylaxis treatments in the United States. *J Public Health Manag Pract* 1998; 4:56.

www.ketabpezeshki.com 66485457-66963820

69. Chang HG, et al: Public health impact of reemergence of rabies, New York. *Emerg Infect Dis* 2002; 8:909.
70. Conti L, et al: Evaluation of state-provided postexposure prophylaxis against rabies in Florida. *South Med J* 2002; 95:225.
71. Moran GJ, et al: Appropriateness of rabies postexposure prophylaxis treatment for animal exposures. Emergency ID Net Study Group. *JAMA* 2000; 284:1001.
72. Fishbein D: Rabies. *Infect Dis Clin North Am* 1991; 5:53.
73. Kappus K: Canine rabies in the United States, 1971-1973: Study of reported cases with reference to vaccination history. *Am J Epidemiol* 1976; 103:242.
74. Dean D, et al: Studies on the local treatment of rabies-infected wounds. *Bull WHO* 1963; 28:477.
75. Kaplan M, et al: Studies on local treatment of wounds for the prevention of rabies. *Bull WHO* 1962; 26:765.
76. Wilde H, et al: Failure of rabies postexposure treatment in Thailand. *Vaccine* 1989; 7:49.
77. Lumbiganon P, et al: Human rabies despite treatment with rabies immune globulin and human diploid cell rabies vaccine—Thailand. *JAMA* 1988; 259:25.
78. Wilde H, et al: Failure of postexposure treatment of rabies in children. *Clin Infect Dis* 1996; 22:228.
79. Knittel T, et al: Guillain-Barré syndrome and human diploid cell vaccine [letter]. *Lancet* 1989; 1:1334.
80. Rabies vaccines. *Wkly Epidemiol Rec* 2002; 77:109.
81. Dreesen DW: A global review of rabies vaccines for human use. *Vaccine* 1997; 15(Suppl):S2.
82. Chutivongse S, et al: Postexposure rabies vaccination during pregnancy: Effect on 202 women and their infants. *Clin Infect Dis* 1995; 20:818.
83. Udwadia Z, Udwadia F, Katrak S: Human rabies: Clinical features, diagnosis, complications, and management. *Crit Care Med* 1989; 17:834-836.

www.ketabpezeshki.com 66485457-66963820

Chapter 132

HIV Infection and AIDS

Sukhjit S. Takhar and Kelli N. O'Laughlin

PERSPECTIVE

Background and Epidemiology

The acquired immunodeficiency syndrome (AIDS) is a pandemic caused by the human immunodeficiency virus (HIV). This disease has caused a tremendous degree of human suffering and has had an immeasurable impact on demographics, cultures, economics, and politics in most societies around the globe. There are an estimated 33.3 million people living with HIV infection worldwide, and 35 million people have died of it.[1,2] Significant strides have been made in areas of prevention and treatment, resulting in stabilization of the epidemic, and the annual number of new infections has steadily decreased since the 1990s. Despite this decline in incidence of HIV infection, new infections and the widespread use of highly active antiretroviral therapy (HAART), thus decreasing AIDS-related deaths, have resulted in an increase of the global prevalence of HIV/AIDS (Fig. 132-1).

HIV infection was first recognized in 1981 by clinicians in New York and Los Angeles in previously healthy homosexual men when they noted unusual clusters of *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia (PCP) and Kaposi's sarcoma. Early on, researchers were aware that these patients had a profound defect in their cell-mediated immune system. They discovered that this disease was spread through sexual activity or exposure to blood. Subsequent concerted scientific effort resulted in rapid identification of the infecting organism, prompt understanding of the natural history of the disease, and swift strides in providing therapeutic interventions.[2]

Means of transmission of HIV and the demographic distribution of the virus vary around the globe. Sub-Saharan Africa is the epicenter of the pandemic, with 22.5 million adults and children living with HIV infection (68% percent of the global HIV population). South Africa has the most people living with HIV infection (5.6 million), and Swaziland has the highest prevalence of HIV infection in the world (estimated to be 25.9%).[1] Unprotected heterosexual intercourse with subsequent transmission of HIV to newborns and breast-fed babies (mother-to-child transmission) is the dominant mode of transmission worldwide, accounting for about 85% of all HIV infections.[3] The HIV epidemic in Asia and eastern Europe is largely in people who inject drugs, sex workers and their clients, and men who have sex with men. In the Caribbean, the primary means of transmission is thought to be through unprotected sex between men and women, especially through paid sex. A large portion of the burden of disease in Central and South America is in men who have sex with men. In the Middle East and North Africa, the prevalence of HIV infection is relatively low.[1] The main pattern of transmission in the higher income countries of North America and western and central Europe is in men who have sex with men. Other significant modes of transmission in these regions include injection drug use and paid unprotected sex.[1]

The prevalence of HIV infection in the United States, estimated to be 1,106,400 adults and adolescents in 2009, is currently the highest it has been.[4] The increase in prevalence is likely to be due to a combination of factors, including more people knowing their HIV status and receiving medical therapy, identification of new infections, and fewer people dying of HIV/AIDS. Although the prevalence of HIV/AIDS in the United States continues to rise, the incidence has remained relatively stable since the late 1990s[5] (Fig. 132-2). In the United States, HIV disproportionately affects men who have sex with men, African Americans, Hispanics, and people living in urban areas.[4] Of the estimated 56,300 new HIV infections in the United States each year, 53% are in men who have sex with men, 31% are through high-risk heterosexual contact, 12% are in injection drug users, and 27% are in women.[3,4]

PRINCIPLES OF DISEASE

HIV, a retrovirus from the lentivirus subfamily, is the cause of AIDS. There are two subtypes of HIV: HIV-1 and HIV-2. The most common cause of HIV infection and AIDS throughout the world is HIV-1. HIV-2, a closely related virus, is much less common and is typically seen in West Africa.

The mature HIV virion is a spherical structure with an outer envelope and an inner core (Fig. 132-3). The core contains two copies of the RNA genome, enzymes (reverse transcriptase and integrase), and regulatory proteins.[6] Surrounding the core is the viral membrane, containing the glycoproteins gp41 and gp120, which are responsible for the attachment and entry of the virus into a $CD4^+$ cell.[7]

In a multistep process, the HIV virion invades the host cell and integrates its genetic material into the host's chromosome (Fig. 132-4). The infection begins with binding of the virus to the $CD4^+$ host cell; the interaction is mediated by a high-affinity interaction between the surface proteins gp41 and gp120 with the $CD4^+$ antigen and coreceptors. Different coreceptors, CCR5 and CXCR4, have been identified. The virus enters the cell by fusing its envelope with the target cell membrane. After internalization, reverse transcriptase forms viral DNA from the original RNA. The viral enzyme integrase then transports the newly formed viral DNA into the nucleus, where it integrates with human chromosomal DNA. Viral polyproteins and RNA are formed and subsequently modified and spliced by the viral enzyme protease, and new infectious viral particles are created.[3,8] This cycle continues with HIV infecting more $CD4^+$ cells. Major targets of antiretroviral therapy (ART) include reverse transcriptase, protease, integrase, and the CCR5 coreceptor.

www.ketabpezeshki.com 66485457-66963820

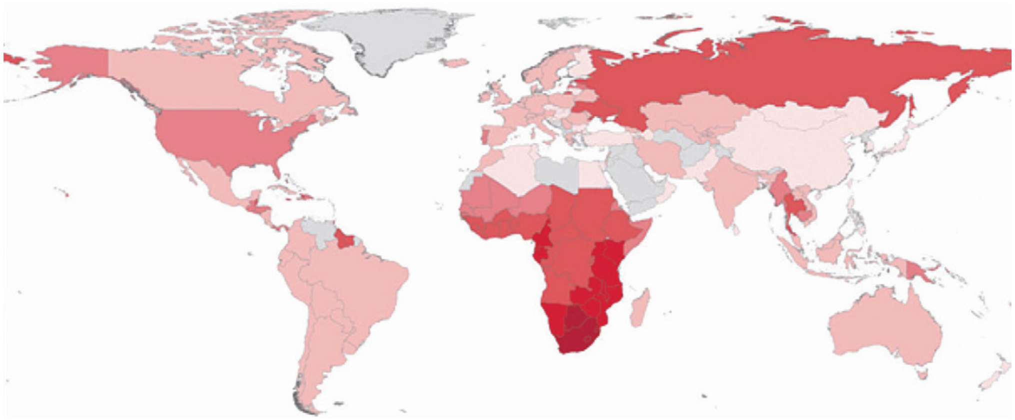


Figure 132-1. The distribution of people living with HIV infection globally. The darker shades represent higher prevalence of HIV infection. (From Joint United Nations Programme on HIV/AIDS: UNAIDS Report on the Global AIDS Epidemic 2010. Available at www.unaids.org/documents/20101123_2010_HIV_Prevalence_Map_em.pdf. Accessed November 25, 2011.)

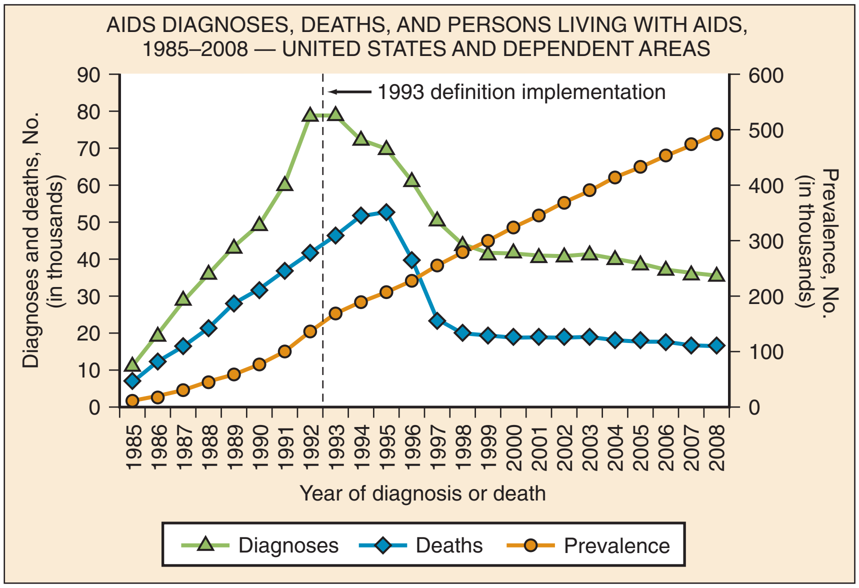


Figure 132-2. AIDS diagnoses, deaths, and persons living with AIDS—United States. (From the Centers for Disease Control and Prevention: AIDS surveillance—trends [1985-2009]. Available at www.cdc.gov/hiv/topics/surveillance/resources/slides/trends/index.htm.)

www.ketabpezeshki.com 66485457-66963820

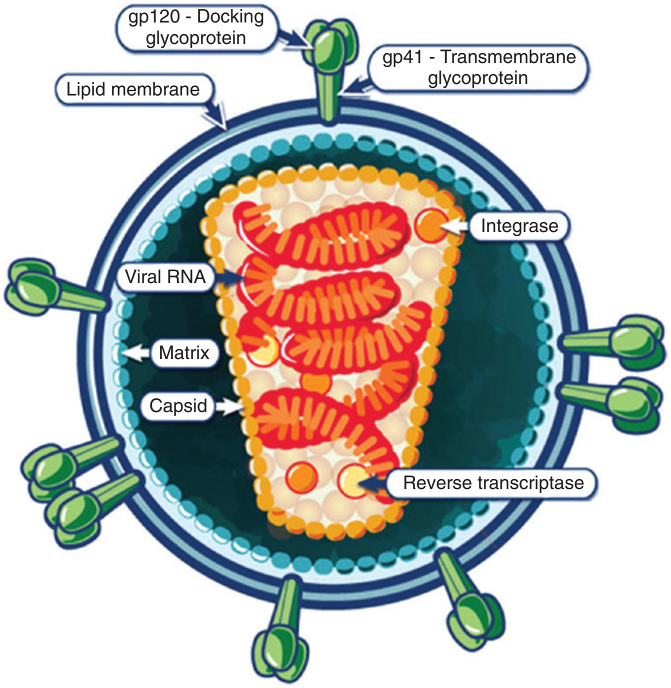


Figure 132-3. The structure of the HIV virion. (From the National Institute of Allergy and Infectious Diseases. Available at http://www.niaid.nih.gov/topics/HIVAIDS/Understanding/Biology/Pages/structure.asPx.)

The hallmark of HIV infection is $CD4^+$ T-cell destruction, leading to a deficient cell-mediated arm of the immune system. The opportunistic infections (PCP and infections due to *Toxoplasma gondii, Mycobacterium avium* complex [MAC], and cytomegalovirus [CMV]) and malignant neoplasms (including Kaposi's sarcoma) of AIDS patients are primarily due to the lack of $CD4^+$ activity. Although it is unclear exactly how HIV depletes $CD4^+$ cells, increased peripheral destruction and decreased production of $CD4^+$ cells occur with the infection. Humoral immunity is also impaired, through B-cell proliferation and production of abnormal antibodies, making HIV-infected individuals more vulnerable to infections by encapsulated bacteria.[2,7]

HIV infection also leads to a chronic immune activation. Ongoing viremia, along with proinflammatory cytokines, B-cell proliferation, and hypergammaglobulinemia, leads to a chronic inflammatory state that contributes to cardiovascular disease, cancer, and other chronic diseases in long-term HIV-infected individuals.[7]

Modes of Transmission

The three predominant modes of transmission of HIV are through sexual intercourse, parenteral transmission, and perinatal transmission. Transmission of HIV through sexual contact, the most common mode of HIV transmission worldwide, occurs in heterosexual intercourse as well as in men who have sex with men. Parenteral transmission (including subcutaneous, intravenous, intramuscular, and intrasternal injections) occurs predominantly among injection drug users but can also be from iatrogenic inoculation, as is the case with the transfusion of contaminated blood or use of contaminated needles by medical providers and traditional healers. Perinatal transmission of HIV, also called mother-to-child transmission, can occur in utero, at birth, or during breast-feeding. The predominant mode of transmission of HIV varies from country to country. High-risk groups include injection drug users and their sex partners, prostitutes, sex partners of HIV-infected persons, men who have sex with men, and heterosexual persons exposed to many sex partners either directly or indirectly.

Risk Factors for HIV Transmission

HIV has been isolated from a wide range of body fluids, including semen, vaginal secretions, lymphocytes, cell-free plasma, cerebrospinal fluid (CSF), tears, saliva, urine, and breast milk. However, only semen, blood, vaginal secretions, and breast milk are significantly infectious. For transmission to occur, these fluids must come into contact with damaged tissue or with a mucous membrane or be directly injected into the bloodstream.

Activities that result in exposure to infectious body fluids increase the likelihood of HIV transmission, and the risk of transmission varies according to the nature of the exposure. The highest risk exposure is transfusion with HIV-positive blood. Other factors associated with increased risk of HIV transmission include exposure to serum with high viral load,[9-12] lack of male circumcision,[13-15] presence of ulcerative sexually transmitted disease,[12] and similarity of HLA class I alleles among discordant couples.[11] The risk of transmission of HIV varies by the type of sexual contact: it is 1 to 30% for receptive anal intercourse; 0.1 to 10% for receptive vaginal and insertive anal intercourse; and 0.1 to 1% for insertive vaginal intercourse.[16,17]

After transmission, the virus replicates in the mucosal surface or lymphoid tissue at the site of entry in lymphocytes and macrophages. If enough cells are infected, the virus spreads to draining lymph nodes and infection is established, usually within 48 to 72 hours.

CLINICAL FEATURES

The clinical manifestations of HIV infection are varied. Patients may present to the emergency department (ED) with acute HIV infection, medication side effects, or unusual opportunistic infections from advanced AIDS. The natural history of the disease has been altered significantly with the advent of HAART. However, there still is no cure. In addition to causing progressive immune dysfunction, chronic HIV infection causes an ongoing inflammatory state, leading to the development of numerous manifestations that have not been classically thought of as HIV disease. These include malignant neoplasms, coronary artery disease, and neurocognitive disorders. The dramatic immune recovery that is seen with modern ART can also cause an inflammatory syndrome that resembles the original opportunistic infection. Overall, the spectrum of HIV infection is changing because of longer life expectancy and better treatment. However, many patients still have undiagnosed HIV infection and present in late stages of disease.

Stages of HIV Infection

The stages of untreated HIV infection are described by the World Health Organization (Box 132-1) and the Centers for Disease Control and Prevention (CDC; Table 132-1). Figure 132-5 also illustrates the natural history of untreated HIV infection.

Primary HIV Infection

Primary infection with HIV often causes an acute, self-limited viral infection. The most common findings are mononucleosis-like symptoms consisting of fever, pharyngitis, and lymphadenopathy. This usually occurs 2 to 6 weeks after transmission. During this time, the virus is actively replicating and antibodies to HIV have not been produced. The virus has many potential targets, and viral loads are often enormous.[18] The diagnosis of

www.ketabpezeshki.com 66485457-66963820

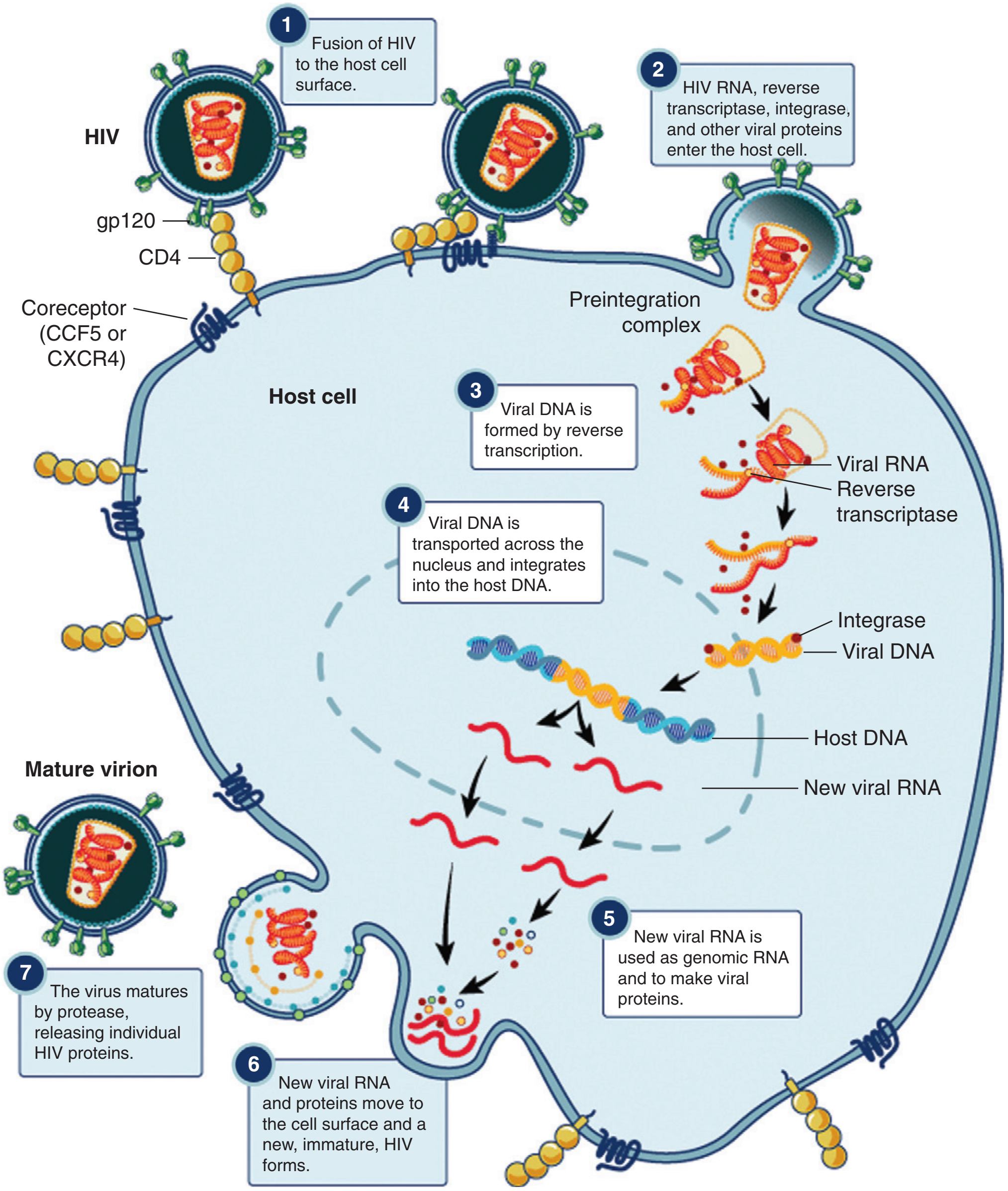


Figure 132-4. Replicative cycle of the HIV virion. (From the National Institute of Allergy and Infectious Diseases. Available at www.niaid.nih.gov/TOPICS/HIVAIDS/UNDERSTANDING/BIOLOGY/Pages/hivReplicationCycle.aspx.)

www.ketabpezeshki.com 66485457-66963820

Box 132-1 Revised World Health Organization Clinical Staging of HIV/AIDS for Adults and Adolescents

Primary HIV Infection
Asymptomatic
Acute retroviral syndrome

Clinical Stage 1
Asymptomatic
Persistent generalized lymphadenopathy

Clinical Stage 2
Moderate and unexplained weight loss (<10% of presumed or measured body weight)
Recurrent respiratory tract infections (such as sinusitis, bronchitis, otitis media, pharyngitis)
Herpes zoster
Recurrent oral ulcerations
Papular pruritic eruptions
Angular cheilitis
Seborrheic dermatitis
Fungal fingernail infections

Clinical Stage 3
Conditions in which a presumptive diagnosis can be made on the basis of clinical signs or simple investigations
Unexplained chronic diarrhea for longer than 1 month
Unexplained persistent fever (intermittent or constant for longer than 1 month)
Severe weight loss (>10% of presumed or measured body weight)
Oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis diagnosed in last 2 years
Severe presumed bacterial infections (e.g., pneumonia, empyema, meningitis, bacteremia, pyomyositis, bone or joint infection)
Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis

Conditions in which confirmatory diagnostic testing is necessary
Unexplained anemia (<80 g/L) and/or neutropenia (<500/µL) and/or thrombocytopenia (<50,000/µL) for more than 1 month

Clinical Stage 4
Conditions in which a presumptive diagnosis can be made on the basis of clinical signs or simple investigations
HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe or radiologic bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital, or anorectal of more than 1 month's duration)
Esophageal candidiasis
Extrapulmonary tuberculosis
Kaposi's sarcoma
Central nervous system toxoplasmosis
HIV encephalopathy

Conditions in which confirmatory diagnostic testing is necessary
Extrapulmonary cryptococcosis, including meningitis
Disseminated nontuberculous mycobacterial infection
Progressive multifocal leukoencephalopathy
Candidiasis of trachea, bronchi, or lungs
Cryptosporidiosis
Isosporiasis
Visceral herpes simplex infection
Cytomegalovirus infection (retinitis or of an organ other than liver, spleen, or lymph nodes)
Any disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis)
Recurrent nontyphoidal *Salmonella* septicemia
Lymphoma (cerebral or B-cell non-Hodgkin's)
Invasive cervical carcinoma
Visceral leishmaniasis

From World Health Organization: Revised WHO clinical staging and immunological classification of HIV/AIDS and case definitions of HIV and related conditions. Geneva: World Health Organization; 2006.

Table 132-1 CDC Surveillance Case Definitions for HIV Infection

STAGE	LABORATORY EVIDENCE
Stage 1	No AIDS-defining condition and either $CD4^+$ T-lymphocyte count of ≥500 cells/µL or $CD4^+$ T-lymphocyte percentage of total lymphocytes of ≥29
Stage 2	No AIDS-defining condition and either $CD4^+$ T-lymphocyte count of 200-499 cells/µL or $CD4^+$ T-lymphocyte percentage of total lymphocytes of 14-28
Stage 3 (AIDS)	$CD4^+$ T-lymphocyte count of <200 cells/µL or $CD4^+$ T-lymphocyte percentage of total lymphocytes of <14 or documentation of an AIDS-defining condition
Stage unknown	No information available on $CD4^+$ T-lymphocyte count or percentage and no information available on AIDS-defining conditions

From Schneider E, et al: Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years—United States, 2008. MMWR Recomm Rep 57:1-12, 2008.
CDC, Centers for Disease Control and Prevention.

acute HIV infection has significant public health benefits. Patients with acute HIV infection transmit the infection disproportionately; these patients often do not know that they are infected, and their viral load may be in the range of millions of RNA copies per milliliter.[19]

Symptoms are nonspecific and often not recognized as signs of HIV infection. The illness usually lasts for less than 2 weeks, although some patients may have a prolonged course. Cases of encephalitis, Guillain-Barré syndrome, and mononeuritis have occurred. $CD4^+$ counts also transiently drop, occasionally to the level at which opportunistic infections can occur. Among others, PCP, toxoplasmosis, CMV infection, and thrush may occur in this stage.

Diagnosis of acute HIV infection requires keeping the constellation of symptoms in mind and understanding the pitfalls of laboratory testing for early infection. The results of routine HIV antibody testing may be negative for several weeks or even months after exposure. The diagnosis of acute HIV infection is confirmed with the presence of high titers of viral RNA and a negative antibody screen. Assay reactivity is dynamic; a plasma RNA test will detect HIV infection approximately 1 week before the ability to detect the p24 antigen and 12 days before antibodies to HIV develop[20] (Table 132-2). A viral load test in the absence of

www.ketabpezeshki.com 66485457-66963820

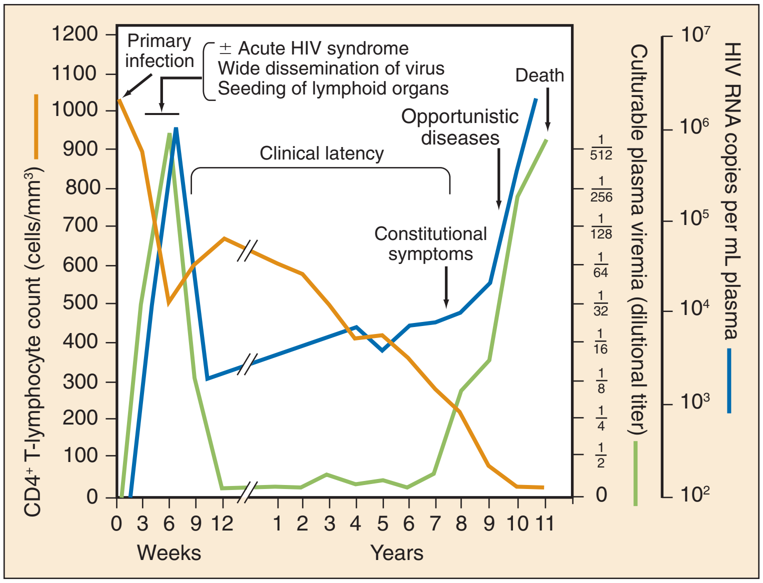


Figure 132-5. Natural history of HIV infection in the absence of therapy in a hypothetical patient. (Modified from Fauci AS, Pantaleo G, Stanley S, Weissman D: Immunopathogenic mechanisms of HIV infection. Ann Intern Med 124:654-663, 1996.)

Table 132-2 HIV Testing by Laboratory Stage

STAGE	LABORATORY MARKER: RNA	p24 Antigen	Third-Generation Antibody (EIA)	Western Blot	HIV STAGE
1	+	–	–	–	Acute HIV infection
2	+++	+	–	–	Acute HIV infection
3	+++	+/–	+	–	Seroconversion
4	+++	+/–	+	Intermediate	Seroconversion
5	++	+/–	+	+	Seroconversion
6	+–+++	+/–	+	+	Chronic HIV infection (all Western blot bands are positive and older antibody tests react)

Modified from Fiebig EW, et al: Dynamics of HIV viremia and antibody seroconversion in plasma donors: Implications for diagnosis and staging of primary HIV infection. AIDS 17:1871-1879, 2003.
EIA, enzyme immunoassay.

symptoms of acute HIV infection is not recommended; false-positive results occur, and the test is costly.[21] Confirmed cases of acute HIV infection should be referred immediately to a specialist, preferably one who actively enrolls patients in clinical trials.

Chronic Infection

After the primary infection, there generally is a prolonged clinical latent period. In this stage, aside from frequent generalized lymphadenopathy, many patients have little or no clinical manifestations of HIV infection. The asymptomatic period is variable; the average onset to AIDS from seroconversion is approximately 8 to 10 years. Certain patients are long-term nonprogressors, and they have remained free of symptoms, without ART, for more than 25 years. Less fortunate individuals have progressed to AIDS within 3 years after transmission. Patients, however, typically lose approximately 80 $CD4^+$ cells/μL a year. HIV RNA levels in the plasma are associated with a rapid $CD4^+$ decline. In addition, there are several host and viral factors that are involved and affect the rate of progression.

AIDS

The CDC definition of AIDS is a $CD4^+$ cell count below 200 cells/μL or the presence of an AIDS-defining condition (Box 132-2). At this level, immune dysfunction is severe, and without ART, survival is short. Those with a $CD4^+$ cell count below 50 cells/μL have advanced AIDS and are at much higher risk for death and for development of opportunistic infections. Some infections are so common in patients with AIDS that primary prophylaxis is indicated and cost effective. Prophylaxis is started for PCP when $CD4^+$ counts are less than 200 cells/μL; for toxoplasmosis, when $CD4^+$ counts are less than 100 cells/μL; and for MAC disease, when $CD4^+$ counts are less than 50 cells/μL (Table 132-3). Isoniazid is given to patients with a positive response to purified protein derivative. The risk of opportunistic infection in relation to the $CD4^+$ cell count is progressive rather than an all-or-none phenomenon.

More pathogenic organisms cause symptoms at a higher $CD4^+$ count. For example, *Mycobacterium tuberculosis* can cause symptoms in patients with normal $CD4^+$ counts; others, such as

www.ketabpezeshki.com 66485457-66963820

Box 132-2 AIDS-Defining Conditions

Bacterial infections, multiple or recurrent
Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month's duration)
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy, HIV related
Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month's duration)
Kaposi's sarcoma
Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex
Lymphoma, Burkitt (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or *Mycobacterium kansasii,* disseminated or extrapulmonary
Mycobacterium tuberculosis of any site, pulmonary, disseminated, or extrapulmonary
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jiroveci pneumonia
Pneumonia, recurrent
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age >1 month
Wasting syndrome attributed to HIV

From Schneider E, et al; Centers for Disease Control and Prevention: Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years—United States, 2008. MMWR Recomm Rep 57:1-12, 2008.

disseminated MAC and CMV, are generally not seen until patients have advanced disease. Some patients have had PCP with $CD4^+$ counts of more than 200 cells/μL.

Initial Evaluation

HIV-infected patients are at risk for some of the same infections and medical problems that noninfected patients have, but they are more vulnerable to opportunistic and unusual infections. Knowledge of the $CD4^+$ count, along with the patient's clinical presentation, is critical in the ED management of the HIV-infected patient. Before HAART, HIV-positive individuals were primarily hospitalized for opportunistic infections. Patients with HIV infection are now dying of diseases that were not traditionally considered AIDS diseases, such as heart disease, liver failure, and non–AIDS-related cancers.[22]

The current $CD4^+$ count is a marker of the degree of immunosuppression and is critical background information for the interpretation of signs and symptoms. However, many patients have undiagnosed HIV infection, and they often present in later stages of disease.[23] Others may not be taking ART because of issues involving access to care, difficulties with medication adherence, or viral resistance to ART. Opportunistic infections such as PCP, disseminated mycobacterial infections, cryptococcal meningitis, and CMV disease do not occur until $CD4^+$ counts are dramatically reduced. A total lymphocyte count may provide a rough surrogate for the absolute $CD4^+$ count; a count between 1000 and 2000 cells/μL appears to be a reasonable surrogate of significant immunosuppression. A cell count of more than 2000 cells/μL makes it less likely that a patient is profoundly immunosuppressed. Acute illness will drop peripheral lymphocyte counts and thus limits the utility of the peripheral lymphocyte count as a diagnostic aid in an acute setting. However, an ED study showed that patients with a peripheral lymphocyte count below 950 cells/μL were highly likely to have AIDS.[24]

Certain clinical features suggest the possibility of a new diagnosis of HIV infection. A careful look at the skin and in the mouth may be revealing; certain skin findings, such as oral hairy leukoplakia and Kaposi's sarcoma, are found almost exclusively in HIV-infected individuals.[25] Unexplained oral candidiasis is often the initial presenting symptom in someone with undiagnosed HIV infection.

Constitutional Disease and Wasting

Patients with late-stage AIDS can present with severe wasting; they may have involuntary weight loss of more than 10%, fevers, fatigue, and diarrhea. There are a number of explanations for the systemic wasting seen in advanced AIDS, including the virus itself. Disseminated MAC disease is another possible inciting factor. Infection with this ubiquitous organism can be manifested as fever, weight loss, anemia, and elevated alkaline phosphatase. Several endemic fungi and parasites can cause severe disease in HIV-infected individuals. In the United States, some patients present with histoplasmosis, coccidioidomycosis, and blastomycosis. Visceral leishmaniasis and *Penicillium marneffei* infection are complications in areas of the world where these organisms are common.

Clinical Manifestations by Organ System

Cardiac

Cardiovascular manifestations of HIV infection vary greatly, depending on the patient's immune status and whether the patient is receiving ART. These medications dramatically affect the rates of opportunistic infections and malignant diseases (non-Hodgkin's lymphoma and Kaposi's sarcoma) that can affect the heart. Patients with advanced HIV infection can have a constellation of cardiac manifestations, including pericarditis, myocarditis, cardiomyopathy, pulmonary vascular disease, pulmonary hypertension, valvular disease, and neoplastic involvement of the heart. Purulent pericarditis and cardiac tamponade are potentially lethal clinical manifestations of cardiovascular disease in patients with AIDS; *M. tuberculosis* is often the causative organism, especially in low-resource countries.

HIV-infected patients have an increased risk of acute coronary syndrome, although it is not fully understood whether this is the result of the HIV infection itself, a complication of ART, or a combination of both. Patients receiving ART suffer from a myriad metabolic abnormalities (hyperglycemia, hyperlipidemia, lipodystrophy) and accelerated atherosclerosis, which may increase their risk for cardiovascular disease and acute coronary syndrome.[26-32] Studies have shown that the virus alone is associated with dyslipidemia,[26] endothelial damage,[33-35] inflammation,[36,37] and hypercoagulability.[38-42] Stopping of ART has been shown to result in systemic inflammation, coagulation cascade activation and an increase in biomarkers associated with endothelial activation,[36,43] and increased risk of major cardiovascular events.[44]

Antiretroviral agents cause varying degrees of dyslipidemia. Protease inhibitors, particularly ritonavir in higher doses, can especially be a problem.[30] Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are associated with increases in low-density

www.ketabpezeshki.com 66485457-66963820

Table 132-3 Prophylaxis to Prevent First Episode of Selected Opportunistic Infections

PATHOGEN	INDICATION	FIRST-CHOICE THERAPY	ALTERNATIVE
Pneumocystis jiroveci pneumonia (PCP)	$CD4^+$ <200 cells/µL or oropharyngeal candidiasis $CD4^+$ <14% or history of AIDS-defining illness $CD4^+$ >200 cells/µL but <250 cells/µL if monitoring is not possible every 1-3 months	TMP-SMZ	TMP-SMZ Dapsone Dapsone + pyrimethamine + leucovorin Aerosolized pentamidine Atovaquone Atovaquone + pyrimethamine + leucovorin
Toxoplasma gondii encephalitis	*Toxoplasma* IgG–positive patients with $CD4^+$ count <100 cells/µL Seronegative patients receiving PCP prophylaxis not active against toxoplasmosis should have *Toxoplasma* serology retested if $CD4^+$ count declines <100 cells/µL Initiate prophylaxis if seroconversion occurred	TMP-SMZ	TMP-SMZ Dapsone + pyrimethamine + leucovorin Dapsone + pyrimethamine + leucovorin Atovaquone ± pyrimethamine + leucovorin
Disseminated *Mycobacterium avium* complex (MAC) disease	$CD4^+$ count <50 cells/µL (after active MAC infection is ruled out)	Azithromycin Clarithromycin	Rifabutin (adjust dose on basis of ART interactions); rule out active TB before rifabutin is started

Modified from Kaplan JE, et al: Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 58:1-207, 2009. Available at www.cdc.gov/mmwr/preview/mmwrhtml/rr5804a1.htm.

ART, antiretroviral therapy; *TB,* tuberculosis; *TMP-SMZ,* trimethoprim-sulfamethoxazole.

lipoprotein cholesterol and total cholesterol but also a significant increase in high-density lipoprotein cholesterol.[45] The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study found that the nucleoside reverse transcriptase inhibitor abacavir was associated with a fourfold increased risk of myocardial infarction and a significant increase in stroke, peripheral vascular disease, and congestive heart failure.[46] Despite the reality that some ART is likely to contribute to the development of coronary artery disease, the benefits of therapy outweigh the risks of accelerated atherosclerosis.

Pulmonary

Pulmonary infections are the leading cause of morbidity and mortality for people living with HIV infection.[47] Noninfectious pulmonary complications are also common. The patient's immune status (as suggested by the last $CD4^+$ count) and the current treatment regimen determine the severity of the presenting illness. The tempo of the illness and geographic risk factors also help guide the diagnostic evaluation and initial therapy.

The most frequent respiratory infections in people with HIV infection are upper respiratory tract infections and acute bronchitis. The incidence of lower respiratory tract infections increases as $CD4^+$ counts decline. Potential causes of lower respiratory tract infections include viruses (influenza, respiratory syncytial, parainfluenza), bacteria, and fungi (*P. jiroveci*) (Table 132-4). Bacterial pneumonia is more frequent in people infected with HIV than in noninfected persons, and the incidence increases as the $CD4^+$ count drops; the most common organism is *Streptococcus pneumoniae*. The incidence of PCP also increases as the $CD4^+$ count drops below 200 cells/µL; the risk of infection progressively increases as immune function worsens.

A number of noninfectious causes of pulmonary disease are associated with HIV infection. Although the incidence is greatly reduced in the era of HAART, pulmonary manifestations of Kaposi's sarcoma and non-Hodgkin's lymphoma can occur. HIV-infected patients also appear to be at increased risk for lung cancer, emphysema, cryptogenic organizing pneumonia, sarcoidosis, drug hypersensitivity, primary effusion lymphoma, foreign body granulomatosis, and lymphocytic interstitial pneumonitis.

Table 132-4 Differential Diagnosis of Respiratory Infections in HIV-Infected Patients by $CD4^+$ Count

$CD4^+$ COUNT AND STAGE	DIFFERENTIAL DIAGNOSIS
Present at any stage	Acute bronchitis Bacterial pneumonia Tuberculosis
>500 cells/µL Early HIV infection	Bacterial pneumonia* PCP* HHV-8–related Kaposi's sarcoma
200-500 cells/µL	Bacterial pneumonia* PCP*
<200 cells/µL AIDS	Bacterial pneumonia* (consider bacteremia) PCP* *Histoplasma capsulatum* or *Coccidioides immitis* pneumonia *Cryptococcus neoformans* pneumonia Extrapulmonary or disseminated tuberculosis*
≤50 cells/µL Advanced HIV infection	Bacterial pneumonia* PCP* *Toxoplasma gondii* pneumonia Pulmonary Kaposi's sarcoma *Histoplasma capsulatum* or *Coccidioides immitis* pneumonia *Mycobacterium avium* complex pneumonia

HHV-8, human herpesvirus 8; *PCP, Pneumocystis jiroveci* pneumonia.
*Occurs more frequently as immune function declines.

Diagnostic evaluation of patients with HIV infection who present with respiratory complaints should be based on their HIV disease stage as well as their clinical presentation (Table 132-5). Evaluation includes pulse oximetry, chest radiography, and complete blood count. Additional tests may include arterial blood gas analysis (to determine the need for corticosteroids in patients

www.ketabpezeshki.com 66485457-66963820

Table 132-5 Pulmonary Manifestations of Disease in HIV-Infected Patients

	PRESENTATION	DIAGNOSTIC EVALUATION	TREATMENT
Bacterial pneumonia	Acute onset (<1 week) Cough Purulent sputum Fevers, chills, rigors	Elevated white blood cell count Chest radiograph: unilateral focal consolidation $CD4^+$ count variable	Antibiotic therapy targeting *Streptococcus pneumoniae* and *Haemophilus influenzae* Also cover atypical bacterial pathogens
Pneumocystis jiroveci pneumonia (PCP)	Gradual onset (>2 weeks) Nonproductive cough Dyspnea Fever	Exercise-induced hypoxia Elevated serum lactate dehydrogenase Chest radiograph: bilateral reticular or interstitial pattern Computed tomography scan: ground-glass opacity (56%) $CD4^+$ <200 cells/μL	Trimethoprim-sulfamethoxazole for 21 days If Pao_2 <70 mm Hg at room air or alveolar-arterial oxygen gradient >35 mm Hg, give prednisone; taper during 21 days
Mycobacterium tuberculosis infection (TB)	Gradual onset (>2 weeks) Cough Fever Night sweats Weight loss Lymphadenopathy	Chest radiograph: alveolar pattern (± cavitation); miliary pattern; nodules; adenopathy; effusions $CD4^+$ count variable	Determine anti-TB therapy with infectious disease consultant Consider possibility of drug resistance Multiple drug interactions exist between TB medications and antiretroviral therapy
Kaposi's sarcoma	Gradual onset (>2-4 weeks) Cough Dyspnea Fever	Chest radiograph: bilateral perihilar nodules, opacities, effusions; adenopathy $CD4^+$ <200 cells/μL	Cryotherapy, radiation therapy Infrared coagulation Sclerosing agents, intralesional vinblastine Systemic chemotherapy

with PCP), serum lactate dehydrogenase (elevated in PCP), serum cryptococcal antigen, urine *Histoplasma capsulatum* antigen, and sputum studies (including Gram's stain, acid-fast bacillus, and staining for *P. jiroveci*). Blood cultures should be considered before antibiotic therapy initiation; an aggressive search for the pathogen is generally recommended in patients with HIV infection.

PCP is one of the most common AIDS-defining opportunistic infections. With the widespread use of HAART as well as chemoprophylaxis against PCP in patients with $CD4^+$ counts below 200 cells/μL, the incidence of PCP in developed countries has greatly decreased during the last several years.[48] The clinical presentation of PCP is characterized by the gradual onset of fever (79-100%), cough (95%), and progressive dyspnea (95%).[49] The cough is nonproductive, although sputum production does not exclude this diagnosis, and patients can be coinfected with a bacterial pneumonia. Some patients, especially those taking nonsystemic prophylaxis (e.g., aerosolized pentamidine), may have extrapulmonary manifestations of PCP, such as hepatosplenomegaly, skin lesions, and ocular lesions. The most common associated laboratory abnormalities are a $CD4^+$ count below 200 cells/μL and an elevated lactate dehydrogenase level. Whereas chest radiographs can be normal, most commonly they show diffuse, bilateral, interstitial, or alveolar infiltrates (Fig. 132-6). High-resolution computed tomography (CT), which has a high sensitivity for PCP, often reveals ground-glass or cystic lesions; a normal scan makes the diagnosis of PCP very unlikely[50] (Fig. 132-7). The definitive diagnosis is made by isolation of the organism, commonly from respiratory specimens obtained by sputum induction, bronchoalveolar lavage, or endotracheal aspiration.

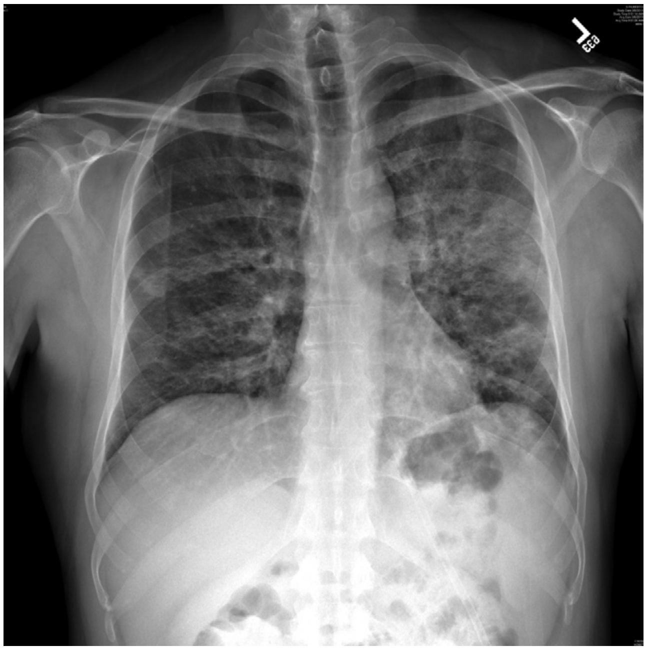


Figure 132-6. Chest radiograph of *Pneumocystis* pneumonia. (From Mocroft A, et al: Decline in the AIDS and death rates in the EuroSIDA study: An observational study. Lancet 362:22-29, 2003.)

The use of primary and secondary prophylaxis greatly diminishes the risk of acquiring PCP. Risk factors for development of PCP include a history of PCP; a $CD4^+$ count below 200 cells/μL (about 95% of the cases occur in people with $CD4^+$ counts below 200); and recurrent fever, night sweats, oropharyngeal thrush, and unintentional weight loss among patients with $CD4^+$ counts above 200 cells/μL. The average $CD4^+$ count at the time of the first episode of PCP for patients not receiving prophylaxis is about 100 cells/μL; and for those receiving prophylaxis, about 20 cells/μL. Double-strength trimethoprim-sulfamethoxazole (TMP-SMZ) administered orally daily is the preferred PCP prophylaxis. TMP-SMZ is also the preferred treatment of PCP; the route is dependent on the severity of disease. There are a number of other possible regimens for those who are intolerant (Table 132-6).

Before initiation of antibiotics, the presence of resting hypoxemia or tachypnea should be assessed to determine whether an arterial blood gas analysis is indicated. Hypoxic patients (partial pressure of oxygen ≤70 mm Hg or an alveolar-arterial oxygen gradient ≥35 mm Hg) receive significant benefit from concurrent corticosteroid treatment. The clinical manifestations of PCP infection are caused by the replication of the organism and

www.ketabpezeshki.com 66485457-66963820

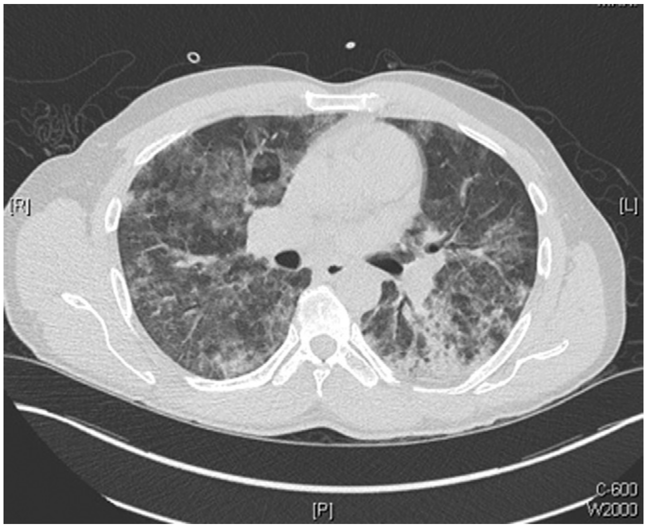


Figure 132-7. Chest computed tomography scan of *Pneumocystis* pneumonia.

Table 132-6 Treatment of *Pneumocystis jiroveci* Pneumonia in Patients with HIV Infection

	PREFERRED THERAPY	ALTERNATIVE THERAPY
Moderate to severe illness	TMP-SMZ intravenously; switch to oral administration after clinical improvement 21-day therapy	Pentamidine Primaquine + clindamycin
Mild to moderate illness	TMP-SMZ	Dapsone + trimethoprim Primaquine + clindamycin Atovaquone

Modified from Kaplan JE, et al: Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 58:1-207, 2009. Available at www.cdc.gov/mmwr/preview/mmwrhtml/rr5804a1.htm.
TMP-SMZ, trimethoprim-sulfamethoxazole.

the host inflammatory response. Fungal death exacerbates the inflammatory response, and hypoxic patients should receive a 21-day prednisone taper in addition to antibiotic therapy.[49]

Concurrent epidemics of HIV infection and tuberculosis (TB) have resulted in significant morbidity and mortality for affected populations, particularly in Africa, where the burden of both diseases is immense. The risk of TB increases with declining immune function[51,52]; it doubles within the first year after HIV seroconverion.[53] Patients with HIV infection are more likely to develop active TB from reactivated latent infection, and HIV infection is a risk factor for accelerated progression of TB.[54] For patients with HIV infection, TB coinfection increases the risk of progression to AIDS or death.[55]

Clinical manifestations and radiographic findings of TB vary by the degree of underlying immunosuppression of the patient. Patients with early HIV infection and TB have presentations similar to those of individuals without HIV infection; they often have classic symptoms of pulmonary TB, such as fever, cough, weight loss, malaise, and night sweats. The typical radiographic findings of cavitation in the upper lung fields are usually present. With worsening immune function, there is less likelihood of pulmonary cavitation. In these cases, atypical radiographs are more common, such as pulmonary infiltrates without preference for the upper lung fields, and normal radiographs have been reported. With advanced HIV infection and severe immunosuppression, there is greater risk of extrapulmonary and disseminated TB.[51,56]

In patients thought to have TB regardless of radiographic findings, diagnostic tests should be pursued, and the patient should be placed in respiratory isolation. Evaluation of extrapulmonary disease includes specimens of suspected areas of involvement (i.e., the CSF, lymph nodes, pleural fluid, pericardial fluid, blood, and urine). Treatment of TB in people with HIV infection is complicated, and drug interactions between ART and anti-TB therapy are severe and common. After initiation of anti-TB therapy, the patient requires close monitoring for assessment of adequate treatment response and for observation of signs of immune reconstitution inflammatory syndrome (IRIS), a complication more common in patients with $CD4^+$ counts below 200 cells/μL.

Although outpatient therapy is possible, the majority of HIV-infected patients with a low $CD4^+$ cell count and respiratory complaints will require hospitalization. Bronchoscopy and high-resolution CT scan of the chest are often required to make the definitive diagnosis. Patients with presumed bacterial pneumonia require treatment with antibiotics that cover the usual community-acquired organisms.

Oropharyngeal and Gastrointestinal

Oropharyngeal and gastrointestinal diseases are often the presenting symptoms of HIV infection. HIV-infected patients with gastrointestinal symptoms may present with common abdominal disease or may have HIV-related infections, malignant neoplasms, or medication side effects. Patients receiving ART may suffer treatment-related adverse gastrointestinal events, including pancreatitis, hepatic steatosis, lactic acidosis, and drug-induced hepatotoxicity. Furthermore, a number of patients with HIV infection have concomitant hepatitis B virus (HBV) or hepatitis C virus (HCV) infection and may have gastrointestinal manifestations of illness from these causes as well. End-stage liver disease is now a common cause of mortality in HIV-infected patients.[57]

As in other organ system disease, patients with higher $CD4^+$ counts tend to be infected by common, more pathogenic bacteria. Patients with $CD4^+$ counts below 100 cells/μL are more likely to have opportunistic infections and hepatobiliary issues, such as acalculous cholecystitis.

Primary HIV infection has a variety of oropharyngeal manifestations, including pharyngitis and severe aphthous ulcers. With progressive immunodeficiency, the pathogens change. Thrush, caused by *Candida,* is an extremely common opportunistic infection (often the first manifestation of HIV infection). The lesions are characterized by white, cheesy plaques that can be scraped off with a tongue depressor; plaques occur most often on the buccal mucosa, soft palate, and tonsils. Oral hairy leukoplakia, caused by Epstein-Barr virus (EBV), is manifested as raised white lesions on the side of the tongue. Unlike in thrush, the lesions cannot be scraped off and are not responsive to topical antifungal agents. Kaposi's sarcoma, which can occur in the mouth, is most commonly found on the palate.

Esophagitis may occur in HIV-infected patients with severe immunosuppression, particularly those with $CD4^+$ counts that are below 100 cells/μL. Patients present with dysphagia or odynophagia. The most common cause of esophagitis in patients with HIV infection is *Candida*; the presence of thrush can be helpful in making the diagnosis of HIV infection (it has a high positive predictive value). Other potential causes include herpes simplex virus, CMV, and deep aphthous ulcers. Confirmation of the underlying cause can be obtained by endoscopy with biopsy. Given that biopsy is invasive, most patients with esophagitis

www.ketabpezeshki.com 66485457-66963820

first undergo a course of fluconazole for empirical treatment of *Candida* infection; clinical response should occur within 5 to 7 days. Gastroesophageal reflux is another common complaint, and the treatment is with antacids. However, certain antiretrovirals, such as atazanavir, require an acidic environment to aid in absorption. Consideration of potential drug interactions is important when new medications are started in HIV-infected patients.

Small or large bowel enteritis, characterized by abdominal pain, cramping, diarrhea, dehydration, and fever, is a common problem in people with HIV infection and can be caused by a number of underlying factors. Bacterial infections are common, and the usual offenders are *Salmonella, Shigella, Campylobacter, Clostridium difficile,* and *Yersinia*. Patients with advanced immunosuppression often have chronic diarrhea, not uncommonly from opportunistic infections with the parasites *Cryptosporidium, Isospora,* and microsporidia. CMV causes large bowel enteritis and generally occurs in severely immunosuppressed hosts with $CD4^+$ counts below 50 cells/μL. In developing countries, TB should also be considered a cause of abdominal disease in patients with HIV infection. Malignant diseases, such as lymphoma and Kaposi's sarcoma, can affect the bowels. Kaposi's sarcoma lesions in the gastrointestinal tract can cause massive bleeding and obstruction. The workup for diarrhea often involves laboratory stool studies (ova and parasite, *C. difficile* toxin, bacterial culture, modified acid-fast staining) and occasionally colonoscopy. The therapy is usually supportive, with a focus on maintaining hydration; symptoms often persist until immune reconstitution.

The routes for transmission of HIV, HBV, and HCV are similar for HIV-infected and noninfected patients. Coinfection is common; approximately 25% of individuals with HIV infection are coinfected with HCV, and another 8% are infected with HBV.[58] Coinfection is more common in patients who are injection drug users or have hemophilia. HCV-HIV coinfection is associated with poor socioeconomic status and substance abuse. Now that HAART has decreased mortality from AIDS-related illness, end-stage liver disease has become a common cause of death in HIV-infected patients in industrialized countries.[58] In addition, concomitant alcohol use contributes to the rapid progression to hepatic failure.

Disseminated opportunistic infections can also involve the liver, including MAC and *Bartonella* infections. AIDS-related cholangiopathy, biliary obstruction from infection-associated strictures of the biliary tract, is seen with severe immunosuppression. However, noninfectious causes, such as cholecystitis, are becoming more common.

Central Nervous System

The differential diagnosis of patients with HIV coinfection who present with headaches, abnormal findings on neurologic examination, or change in mental status varies on the basis of the current status of their immune system and results of neuroimaging. Common problems include *Cryptococcus* meningitis, toxoplasmosis, primary central nervous system (CNS) lymphoma, and progressive multifocal leukoencephalopathy. Many patients with untreated HIV infection, symptomatic or not, will have abnormal CSF findings.

HIV itself is a neurotropic virus, and patients with acute infection can present with aseptic meningitis with complaints of fever, headaches, and meningismus. There usually is lymphocytic-predominant, moderate pleocytosis. Whereas most patients recover spontaneously, this presentation may be an opportunity for ED physicians to diagnose acute HIV infection. Syphilis has also reemerged, and CNS infection can occur at any stage of HIV infection. Meningitis is a common manifestation of primary or, more commonly, secondary syphilis. HIV testing is critical in the evaluation of aseptic meningitis in sexually active patients.

Cryptococcus neoformans is the most common cause of meningitis in patients with AIDS.[59] As with other opportunistic infections, HAART, where it is readily available, has dramatically decreased the incidence of cryptococcal meningitis. However, it remains a leading cause of mortality for people with HIV infection in most of the developing world.[59] It usually affects patients who are profoundly immunosuppressed with $CD4^+$ counts below 100 cells/ μL. The disease is subacute, and patients present with fevers, malaise, and headache. Later in the course, because of increased intracranial pressure, patients experience vomiting and altered mental status. *Cryptococcus* often does not cause a significant inflammatory response, and meningeal signs are frequently absent. The diagnosis is suggested by the presence of cryptococcal antigen (CRAG) in the CSF or the serum and low white blood cell count in the CSF (typically <50/μL in the CSF). A lumbar puncture is diagnostic; elevated opening pressures during lumbar puncture are typical (70% with pressures >200 mm Hg), and evidence of encapsulated yeast forms on staining of the CSF with India ink can be found.[60] Poor prognostic factors for cryptococcal meningitis are altered mental status, absence of CSF pleocytosis, CSF antigen titers greater than 1:1024, and positive serum fungal culture.[59,61] These signs are indicative of a high organism burden, elevated CSF pressure, and lack of an inflammatory response. If it is left untreated, cryptococcal meningoencephalitis is fatal. The therapy involves three phases: induction, consolidation, and maintenance. If the patient can tolerate it, aggressive initial treatment with 2 weeks of amphotericin B and flucytosine is recommended. Fluconazole is used for the consolidation phase, and it is continued until immune reconstitution ($CD4^+$ counts >100 cell/μL for more than a year). Elevated intracranial pressure is treated with repeated lumbar punctures; on occasion, a lumbar drain is needed. Cryptococcal meningitis immune reconstitution syndrome can cause rapid clinical deterioration. Thus, ART is often started after 4 weeks of antifungal treatment.[59]

Patients may present with focal CNS lesions. Severely immunocompromised hosts ($CD4^+$ counts <200 cells/μL) are likely to have opportunistic infections or AIDS-associated tumors (Table 132-7). In developed countries, common causes of mass effect are toxoplasmosis and EBV-related primary CNS lymphoma; in developing countries, the etiology is more likely to be tuberculomas. Toxoplasmosis is caused by reactivation of latent infection by the parasite *Toxoplasma gondii*. The majority of infected patients have a $CD4^+$ count below 100 cells/μL. Patients present with signs of increased intracranial pressure, such as headaches, confusion, lethargy, and seizures. Lesions are typically multiple and ring enhancing on CT. Although the definitive diagnosis is made after a brain biopsy, patients who are serologically positive for toxoplasmosis are usually treated empirically with pyrimethamine and sulfadiazine, keeping in mind that toxoplasmosis is much less common in patients who have been receiving TMP-SMZ prophylaxis for PCP. The majority will show radiographic improvement in 2 weeks; response to treatment will obviate the need for a brain biopsy (Fig. 132-8).

Primary CNS lymphoma often looks identical to toxoplasmosis on magnetic resonance imaging (MRI) or CT. It also occurs with profound immunosuppression ($CD4^+$ counts <50 cells/μL). EBV is the cause of primary CNS lymphoma, and a polymerase chain reaction (PCR) analysis of CSF looking for the virus has become an integral step in the workup of mass lesions.[62] Treatment is with ART and chemotherapy.

Progressive multifocal leukoencephalopathy, caused by the JC virus, is characterized by demyelinating lesions in the CNS. The diagnosis is suggested by nonenhancing, hypodense lesions on CT or MRI with a CSF PCR positive for JC virus. Advanced imaging with positron emission tomography, MRI, and single-photon emission computed tomography can help differentiate

www.ketabpezeshki.com 66485457-66963820

Table 132-7 Differential of Focal Central Nervous System Lesions in Patients with HIV Infection

	COMMON CLINICAL PRESENTATION	IMAGING AND DIAGNOSTIC TESTING
Toxoplasma encephalitis	Fever Headache Altered mental status Focal neurologic findings Seizure Evolves during days to weeks	Ring enhancing (approx. 90% of the time) CNS lesions Frequent edema and mass effect *Toxoplasma* antibodies (reflects past exposure) $CD4^+$ often <100 cells/μL PCR detection of *Toxoplasma gondii*
Primary CNS lymphoma (PCNSL)	Confusion Lethargy Memory loss Hemiparesis Aphasia Seizure Fever Night sweats Weight loss Evolves during months	CNS lesion or lesions (may have mass effect) Solitary lesions are often large (>4 cm) Some ring enhancement may occur but less regular PCR assay for Epstein-Barr virus (associated with PCNSL)
Progressive multifocal leukoencephalopathy (PML)	Progressive focal neurologic deficits (during months) Hemiparesis Visual field defects Ataxia Aphasia Cognitive impairment	Multifocal areas of demyelination primarily involving white matter Less frequent mass effect or ring enhancing PCR assay for the DNA of JC virus (causes PML)
HIV encephalopathy	Memory and psychomotor speed impairment Depressive symptoms Movement disorders	Multiple hyperintense signals in T2-weighted images Often symmetrical; not well demarcated
Cytomegalovirus encephalitis	Delirium Confusion Focal neurologic abnormalities	Magnetic resonance imaging shows multifocal scattered micronodules and ventriculoencephalitis $CD4^+$ <50 cells/μL
Brain abscess	Focal neurologic deficit Headache Bacteremia or craniofacial infection	Often concomitant evidence of disseminated infection
Tuberculoma	Focal neurologic deficit Headache Tuberculosis infection	Single or multiple mass lesions Can be manifested as a focal lesion or meningeal infection

CNS, central nervous system; *PCR,* polymerase chain reaction.

between toxoplasmosis, lymphoma, and progressive multifocal leukoencephalopathy.

The "gold standard" for the diagnosis of CNS mass lesions remains the brain biopsy.[62] Corticosteroid therapy can cause false-negative results on brain biopsies in patients with lymphoma, and therefore the use of corticosteroids should be limited to patients with life-threatening mass lesions.

Renal

Renal disorders in patients with HIV infection are common, occurring in up to 30% of infected patients.[63] HIV-infected individuals often have other high-risk conditions for renal disease, such as hepatitis B and C, opportunistic infections, hypertension, and injection drug use. ART can also affect the kidney. Indinavir, although less commonly used in industrialized countries, is associated with renal calculi. Tenofovir can cause acute renal failure, a Fanconi-like syndrome, and nephrogenic diabetes insipidus.[64] Medications used to treat opportunistic infections can cause acute renal failure; amphotericin, pentamidine, and foscarnet are especially notorious.

HIV-associated nephropathy (HIVAN), a form of focal glomerulosclerosis, usually occurs when the $CD4^+$ count is below 200 cells/μL. Proteinuria, often severe, and elevated creatinine concentration occur. Overall, treated patients with HIVAN are experiencing less mortality, but the treatment is problematic, involving immunosuppressive medications such as steroids and cyclosporine. Some patients recover renal function with HAART, but others progress to end-stage renal disease and require dialysis. Transplantation is now widely accepted for patients with HIV infection, and it is available at certain centers in the United States.[63,65]

Rheumatologic and Orthopedic

HIV-infected patients are susceptible to the same types of orthopedic injuries and musculoskeletal disorders as patients without HIV infection are, but there are certain conditions specific to HIV infection.

Disseminated diseases can be infectious or neoplastic. TB is much more common in HIV-infected patients than in noninfected patients. Although TB primarily involves the lungs, patients with HIV infection are prone to extrapulmonary manifestations; TB can cause septic arthritis, spondylitis, osteomyelitis, and bursitis. In general, however, septic arthritis is relatively uncommon in HIV-infected individuals. Risk factors include injection drug use and hemophilia. The most common organism involved is *Staphylococcus aureus*. Disseminated gonococcus causing septic arthritis is another possibility, especially in sexually active individuals.

Unusual and atypical infections occur in late-stage AIDS. Bacillary angiomatosis is caused by *Bartonella henselae* and *Bartonella quintana*. In addition to causing disseminated disease affecting the skin, lymph nodes, liver, and CNS, the organism is also a common agent of long bone osteomyelitis.[66]

www.ketabpezeshki.com 66485457-66963820

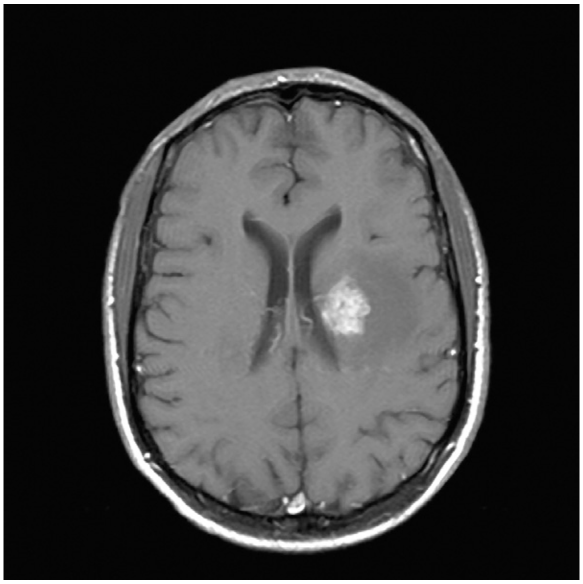


Figure 132-8. Brain magnetic resonance image of a 38-year-old man with AIDS and *Toxoplasma* encephalitis. (From Mandell GL, Bennett JE, Dolin R, eds: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 7th ed. Philadelphia: Elsevier/Churchill Livingstone; 2010.)

Box 132-3 Dermatologic and Mucocutaneous Manifestations of WHO Stage 4 HIV Disease

Chronic herpes simplex virus ulcers
Extrapulmonary tuberculosis
Kaposi's sarcoma
Extrapulmonary cryptococcosis
Disseminated mycosis
Atypical disseminated leishmaniasis
Disseminated nontuberculous mycobacterial infection
Extrapulmonary cryptococcosis including meningitis

WHO, World Health Organization.

Box 132-4 Cutaneous Findings Highly Suggestive of HIV Disease

Any WHO criteria for stage 4 HIV disease
Facial molluscum in an adult
Proximal subungual onychomycosis
Herpes zoster scarring
Oral hairy leukoplakia
Bacillary angiomatosis
Widespread dermatophytosis
Severe seborrheic dermatitis

WHO, World Health Organization.

Patients infected with HIV have lower bone mineral density than that of age-matched controls. Fractures of the hip, spine, and wrist are more common in HIV-infected individuals. Osteonecrosis, especially of the femoral head, is common. Predisposing factors include corticosteroid use, ethanol abuse, and hypertriglyceridemia.[67] Benign and mundane musculoskeletal complaints are common in HIV-infected patients, but osteonecrosis should be considered in HIV-infected patients with severe and persistent joint pain.

HIV-related polymyositis can occur at any stage of infection. These patients may have proximal muscle weakness, myalgias, and fatigue. Medications, especially nucleotide reverse transcriptase inhibitors (NRTIs) such as azidothymidine (AZT), can be toxic to the mitochondria and are common causes of polymyositis. Myopathies, spondylarthritis, pyomyositis, and HIV-associated arthritis are also common musculoskeletal problems.[68] Reactive arthritis and other seronegative arthropathies are common. It is unclear if this relationship is because of sexual activity, generalized immune suppression, or the inflammatory response from the virus itself.

Hematologic

Hematologic disease is common in patients with HIV infection, and HIV infection can cause anemia, thrombocytopenia, and leukopenia. Thrombocytopenia can occur in any stage of HIV infection, and thus its presence in an undiagnosed patient should prompt consideration of screening. The cause is often immune related, presenting as a disease process similar to idiopathic thrombocytopenic purpura, and the treatment is ART. Thrombotic thrombocytopenic purpura is also well described in HIV-infected patients; it tends to occur at later stages of disease.[69]

Anemia and leukopenia tend to occur in later stages of HIV infection. Various medications can cause bone marrow toxicity; AZT, TMP-SMZ, and ganciclovir are common offenders. Systemic fungal infections and mycobacterial disease such as disseminated MAC disease can infect the bone marrow and decrease all three cell lines. Nutritional deficiencies, such as folate and vitamin B_{12}, are common.[69]

AIDS-related lymphoma (Hodgkin's and non-Hodgkin's) occurs more frequently in patients with advanced HIV infection. The majority of non-Hodgkin's lymphomas are of B-cell origin, and they tend to be more aggressive in HIV-infected than in non-infected patients. On occasion, it is the first AIDS-defining illness. CNS lymphomas and Burkitt's lymphoma are nearly always associated with EBV, and primary effusion lymphoma is associated with human herpesvirus 8. The treatment involves standard chemotherapy and ART.[69]

Cutaneous

Dermatologic manifestations of HIV infection are extremely common, and up to 90% of HIV-infected patients will have a skin disorder after seroconversion.[25] Skin findings occur throughout the course of HIV infection. Some skin findings are manifested early in the disease; others, found later, can be suggestive of profound immunosuppression (Box 132-3). Skin problems increase as HIV infection progresses. Recognition of HIV-related dermatologic conditions can lead to early diagnosis and can help the clinician gauge the immune status of the patient (Box 132-4).

Acute HIV infection often is manifested with a generalized maculopapular or morbilliform rash shortly after the onset of fevers. Oral ulcers, lesions on the palms and soles, and mucosal lesions can all be present.[31] Aside from HIV itself, a variety of viruses can involve the skin. An outbreak of herpes zoster can be the first clue that a patient has HIV infection, and affected individuals often have $CD4^+$ counts above 200 cells/µL. Herpes simplex virus infections are often more severe and recur frequently. Chronic ulcerating herpes simplex occurs later in the disease course and is an AIDS-defining opportunistic infection. Other common viral diseases include molluscum contagiosum, human papillomavirus infection, and oral hairy leukoplakia.

Kaposi's sarcoma, a vascular neoplasm, is the most common AIDS-related malignant disease in the United States, and the skin is the most commonly involved organ. Lesions are violaceous patches, nodules, or plaques (Fig. 132-9). Bacillary angiomatosis is manifested with lesions that resemble those of Kaposi's sarcoma.

www.ketabpezeshki.com 66485457-66963820

Figure 132-9. Kaposi's sarcoma lesions.

Box 132-5 CDC-Recommended HIV Testing

HIV Confirmatory

Positive result from a screening test for HIV antibody (e.g., reactive EIA), confirmed by a positive result from a supplemental test for HIV antibody (e.g., Western blot or indirect immunofluorescence assay)

Positive result or a detectable quantity by any of the following HIV virologic (nonantibody) tests:
- HIV nucleic acid (DNA or RNA) detection (e.g., PCR)
- HIV p24 antigen test, including neutralization assay
- HIV isolation (viral culture)

From Schneider E, et al; Centers for Disease Control and Prevention: Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years—United States, 2008. MMWR Recomm Rep 57:1-12, 2008.

CDC, Centers for Disease Control and Prevention; *EIA,* enzyme immunoassay; *PCR,* polymerase chain reaction.

Disseminated fungal infections are often signs of severe immunosuppression, and patients can present with skin manifestations. Disseminated cryptococcosis can be manifested with centrally umbilicated skin lesions resembling molluscum contagiosum. Other fungi (*Histoplasma capsulatum*, *Coccidioides immitis, Blastomyces dermatitidis*, and *Penicillium marneffei*) can cause cutaneous disease and are a significant cause of morbidity and mortality in patients with HIV infection.

Noninfectious skin disorders are common. Seborrheic dermatitis, characterized by greasy, scaly patches that are often located on the nasolabial folds, eyebrows, and scalp, affects up to 85% of HIV-infected patients. Cutaneous drug reactions happen with increased frequency and severity, and TMP-SMZ is responsible for many cases. Severe reactions, such as toxic epidermal necrolysis, occur more frequently in HIV-infected patients. Often the reaction is from sulfa-containing drugs. Abacavir can cause a hypersensitivity reaction that can be fatal if it is not recognized.

DIAGNOSTIC STRATEGIES

HIV Testing

The diagnosis of HIV infection involves the detection of either specific antibodies or viral antigens. Multiple commercial tests are available. Laboratory detection of HIV infection is a two-step process. The first step is a screening test; if the result is positive, a confirmatory test is performed (Box 132-5).

The balance between public health and patient confidentiality has been an issue surrounding HIV testing and reporting. Most states and hospitals have developed policies related to these concerns. Regardless, testing should be done in a confidential manner with appropriate follow-up and counseling. Testing for $CD4^+$ cell levels and HIV viral load is an ill-advised way of circumventing appropriate HIV testing when consent is refused or not attainable; in certain states, there is a requirement to report low $CD4^+$ counts, and this circumvents the patient's right of refusal of formal HIV testing.[70]

Current fourth-generation enzyme-linked immunosorbent assay screening looks for p24 antigen as well as antibodies to the virus. This decreases the time frame needed for detection of acute infection and is an improvement over the previous testing strategies that involved only looking for antibodies.

Emergency Department Testing for HIV

In the past, HIV testing in the ED has been primarily reserved for diagnosis of acute cases of presumed infection; routine screening has not been common practice. Reasons for this include the time it takes to do the test, the risk of not being able to locate the patient after the ED visit to share test results, and the difficulties in providing adequate pretest and post-test counseling.[71-73] With the advent of enhanced testing capabilities as well as the push to diagnose existing cases of HIV infection in difficult-to-reach populations, some experts have started to reevaluate this dogma.[74] Advantages of testing in the ED include increased detection of HIV infection in difficult-to-reach populations and earlier diagnosis of HIV infection, allowing earlier ART implementation and therefore decreased viral transmission.

In 2006, the CDC published revised recommendations for HIV testing in health care settings, including hospital EDs.[75] This report recommends the use of diagnostic HIV testing and opt-out HIV screening in routine clinical care. Routine screening is recommended for 13- to 64-year-old patients, all patients who require TB treatment, those seeking treatment for sexually transmitted diseases, and all pregnant women. Repeated annual screening is recommended for people thought to be at high risk. Providers are to encourage patients to have HIV screening before initiation of sexual relationships and after occupational exposures. Recommendations specify that consent should be obtained for HIV testing, that pretest information should be shared with patients, and that persons responsible for the patient's care should be notified verbally of the planned testing.[75]

Since their publication in 2006, efforts to implement these CDC recommendations and to characterize the implications of these changes to ED practice have been under way.[76-82] Thus far, identified barriers to HIV screening in the ED include insufficient time, burdensome consent processes, lack of knowledge or training, lack of patient acceptance, pretest counseling requirements, competing priorities, and inadequate reimbursement.[71,72,83] Whereas studies of ED providers reflect that the majority of providers are supportive of routine HIV testing,[71,84] it is clear that many gaps remain

www.ketabpezeshki.com 66485457-66963820

in determining how best to implement routine screening into practice.[85-87]

CONSIDERATION OF DIFFERENTIAL DIAGNOSIS

The spectrum of illness in patients with HIV infection is broad, and the differential diagnosis is considerable. HIV infection can affect any organ system, infections can be life-threatening, and nonspecific complaints are common. The illness presenting for ED evaluation may originate from acute HIV infection, opportunistic infections, medication side effects, inflammation, and IRIS. When a patient infected with HIV is evaluated, a knowledge of the patient's $CD4^+$ count, viral load, use of ART, and prior opportunistic infections is extremely useful in management planning. The etiology of illness in patients with a $CD4^+$ count above 200 cells/μL tends to be similar to that in patients without HIV infection (although opportunistic infections can occur, and these patients are more prone to common infections). Patients with advanced AIDS suffer unusual diseases and often have multiple coinfecting pathogens. Often, the diagnosis cannot be made with certainty in the ED.

MANAGEMENT

HAART has led to dramatic reductions in morbidity and mortality from opportunistic diseases and non-AIDS conditions.[87] The goal of therapy is to suppress viral replication and to reconstitute the immune system. Typically in patients receiving appropriate HAART, the viral load is undetectable, and there is a restoration of immune function. Primary and secondary prophylaxis against opportunistic infections can be safely stopped with a return of $CD4^+$ cells. Treatment options in industrialized nations continue to evolve, and the regimens are now easier to tolerate and are less toxic. The best evidence for successful treatment is in those patients with $CD4^+$ counts below 350 cells/μL. However, $CD4^+$ counts below 500 cells/μL indicate that there is an impairment of immune function, and recent guidelines recommend treatment of asymptomatic patients at this level.[88] In addition, even patients with nearly normal $CD4^+$ counts with ongoing viral replication are at elevated risk for a number of conditions, such as cardiovascular disease, kidney and liver disease, and malignant neoplasms. As a result, initiation of treatment for HIV-positive patients at any $CD4^+$ count can be considered.[89]

Antiretroviral therapies target the major viral enzymes (reverse transcriptase, protease, and integrase) and their attachment and fusion sites. HAART involves the use of three active drugs, usually two NRTIs and another agent, often a protease inhibitor or NNRTI. Zidovudine, an NRTI, was the first drug released. Several NRTIs are currently available and approved by the Food and Drug Administration for treatment of HIV infection. Protease inhibitors, released in 1995, revolutionized the treatment of HIV infection and were the beginning of HAART. NNRTIs are also commonly a part of the three-drug regimen. Recently, new classes of antiretroviral therapies have been developed; these include integrase inhibitors and CCR5 inhibitors, allowing further options for patients who suffer side effects or have drug-resistant virus.[88,89] The initial regimen of ART needs to be individualized. Factors to consider in choosing a regimen include tolerability, viral resistance, dosing frequency, cost, and comorbidities.

Antiretroviral treatment failure can occur for many reasons. Commonly, it is from poor medication adherence,[90,91] although studies show exceptional rates of adherence in sub-Saharan Africa.[92] Fixed-dose regimens are thought to increase adherence, and the combination of tenofovir, emtricitabine, and efavirenz is currently available as a once-daily medication. Resistance testing is critical in treatment-experienced patients. Ideally, at least two active medications should be used. Newer therapies, such as advanced-generation NNRTIs (etravirine), integrase inhibitors (raltegravir), CCR5 inhibitors (maraviroc), and new protease inhibitors (darunavir), provide choices for patients.

Side effects from antiretroviral medications are extremely common. Protease inhibitors are notorious for gastrointestinal side effects; most cause nausea and diarrhea. The NRTIs are mitochondrial toxic and can cause pancreatitis and hepatitis. Nevirapine, an NNRTI, can cause hepatic necrosis. Atazanavir causes a Gilbert-like syndrome. Efavirenz is commonly associated with self-limited neuropsychiatric problems (Table 132-8).

Availability of ART to resource-limited countries is an important priority. Presently, of the 15 million people living with HIV/AIDS in low- and middle-income countries, only 5.2 million have access to ART.[1] HAART must be continued for life. The development of an effective vaccine continues to be a top research priority.

Postexposure Prophylaxis

Occupational Exposure

All efforts should be made to minimize the potential for occupational exposure to body fluids. When exposure to body fluids occurs, however, the risk of acquiring HIV infection is low. Before ART, a large study examining HIV transmission from needle-stick injuries to health care workers showed that transmission occurred in only 1 of 300 cases (0.33%), and there were no known cases of transmission through intact skin.[93] Now with postexposure prophylaxis (PEP) using ART, the risk of transmission is thought to be greatly reduced, especially with two or three drugs.

Factors associated with increased risk of transmission from occupational exposure involving needle-stick injuries include depth of injury, injury from a device visibly contaminated with the patient's blood, needle stick into a vein or artery, and terminal illness in the source patient. The last is thought to correlate with high HIV viral load in the body, although data to this effect are limited as viral load measurements are only recently routinely available. People who have been percutaneously inoculated with blood from an HIV-infected source are thought to be at higher risk.

The recommendations for whether to use PEP and which medications to use are based on the type of injury and the body fluid involved. Body fluids of concern include semen, vaginal secretion, and any fluid contaminated with visible blood. Potentially infectious body fluids include CSF and synovial, pleural, peritoneal, pericardial, and amniotic fluids. Unless they contain blood, the following fluids are not considered infectious for HIV: vomitus, feces, nasal secretions, saliva, sputum, sweat, tears, and urine. Low-risk injuries are those involving solid needles (such as suture needles), those that are superficial, and those involving a low-risk source patient or body fluid. High-risk injuries include those involving hollow-bore needles with visible blood and percutaneous injury from a needle that was in an artery or vein of the source patient. Unless a mucocutaneous exposure involves large volumes of blood from a source patient with a plasma HIV viral load of more than 1500 copies/μL, mucocutaneous exposures are considered to be low risk. Transmission is estimated to be as low as 0.09% (1 in 1000) for a splash of infectious body fluid to mucous membranes or broken skin.[94]

As mandated by the Occupational Safety and Health Administration, all U.S. institutions must have a policy indicating how employees should manage occupational exposures. The immediate response should include cleansing of the exposed site; soap and water can be used for intact skin, and virucidal antiseptic agents, such as alcohol-based hand hygiene agents, can be used for small

www.ketabpezeshki.com 66485457-66963820

Table 132-8 Adverse Reactions from Antiretroviral Agents

Antiretroviral Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)	
Class effects: mitochondrial toxicity (lactic acidosis ± hepatic steatosis; most common with d4T, ddI, ddC)	
Abacavir	Hypersensitivity (fever, rash), GI symptoms
Didanosine (ddI)	Pancreatitis, peripheral neuropathy, GI symptoms
Emtricitabine (FTC)	Minimal; headache, GI symptoms
Lamivudine (3TC)	Minimal; headache, GI symptoms
Stavudine (d4T)	Peripheral neuropathy, pancreatitis, lipodystrophy
Tenofovir (TDF)	Renal toxicity (acute renal failure, Fanconi's syndrome)
Zalcitabine (ddC)	Peripheral neuropathy, stomatitis
Zidovudine (AZT, ZDV)	Bone marrow suppression, headache, asthenia, GI symptoms (nausea)
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	
Delavirdine (DLV)	Rash, hepatitis, GI symptoms
Efavirenz (EFV)	Central nervous system symptoms, sleep disturbance, rash; teratogenic
Etravirine (ETR)	Hypertension, rash, GI symptoms
Nevirapine (NVP)	Rash, hepatitis, hepatic necrosis
Antiretroviral Protease Inhibitors	
Class effects: lipodystrophy, hyperlipidemia, GI symptoms, glucose intolerance	
Atazanavir (ATV)	Hyperbilirubinemia, GI symptoms, prolonged QT interval
Darunavir (DRV)	GI symptoms, headache, rash
Fosamprenavir (FPV)	Rash, GI intolerance, headache
Indinavir (IDV)	GI symptoms, nephrolithiasis, hyperbilirubinemia
Lopinavir/ritonavir (LPV/r)	GI symptoms (diarrhea), asthenia, hyperglycemia, prolonged QT interval
Nelfinavir (NVF)	Diarrhea, hyperglycemia, hepatitis
Ritonavir (RTV)	GI symptoms, paresthesia, hepatotoxicity
Saquinavir (SQV)	GI symptoms, QT prolongation, hyperglycemia
Tipranavir (TPV)	Hepatotoxicity, GI symptoms, bleeding
Fusion Inhibitors	
Enfuvirtide (T-20)	Injection site reactions, eosinophilia, GI symptoms
HIV Chemokine Receptor 5 Antagonist (CCR5 Inhibitors)	
Maraviroc (MVC)	Myalgia, hepatotoxicity
HIV Integrase Inhibitor	
Raltegravir (RAL)	Nausea, headache, diarrhea

GI, gastrointestinal.

punctures and wounds. Mucosal surfaces and eyes should be flushed with copious amounts of water. Efforts should be made to document clinical information about the source patient, including risk factors and previous test results for HIV, HBV, and HCV, as well as to provide a description of the exposure and the time it occurred.

Recommendations for PEP are based on the HIV status of the source patient. If the serostatus of the source patient is unknown, PEP should be initiated until the source patient is tested. The source patient may have tested seronegative in the past and could have contracted HIV since the last test; testing of HIV RNA in the source patient should be considered if this is a possibility. If the exposed person is to receive PEP, the goal is to initiate therapy within 1 to 2 hours after exposure; the efficacy of PEP greatly decreases after 24 to 36 hours. Follow-up HIV testing should occur at 6 weeks, 3 months, and 6 months; an additional test at 12 months can be considered for those exposed to source patients coinfected with HIV and HCV.[94]

If the potential benefit of PEP is deemed to outweigh the risk of the medication side effects, persons with low-risk exposures should be treated with two nucleosides. Those with high-risk exposures should be treated with two nucleosides plus a boosted protease inhibitor.[94] The most common two-drug nucleoside regimens are zidovudine and lamivudine (available in a fixed-dose combination) and tenofovir and emtricitabine (available in a fixed-dose, once-daily formulation). For high-risk exposures, the third drug can be ritonavir-boosted lopinavir (lopinavir/r) or an alternative protease inhibitor. The decisions about which medications to use should be made with use of local hospital guidelines and infectious disease specialist consultation, if needed. The patient should be observed closely to monitor for drug toxicity. PEP should be continued for 4 weeks.

Nonoccupational Exposure

Some patients may present to the ED after possible exposure to HIV/AIDS and are concerned about the potential of transmission. Possible means of exposure include sexual contact, injection drug use, and exposure to body fluids through broken skin or mucous membranes. The risk of transmission varies with the means of exposure. For sexual exposures, receptive anal intercourse carries a higher risk of transmission among men who have sex with men compared with other sexual contact exposures because of the potential for mucosal breakdown and rectal bleeding. Similarly, the presence of genital ulcerative disease increases the likelihood of HIV transmission through sexual contact.[17] Among heterosexual contact, the likelihood of HIV transmission is greatest after receptive anal intercourse, followed by receptive vaginal intercourse and insertive vaginal intercourse.[17] Male-to-female transmission of HIV is more common than female-to-male transmission. The risk of transmission after use of injection needles is greater after percutaneous injection of a contaminated needle into an artery or vein. Other important factors influencing the risk of HIV transmission include the HIV status and viral load of the source.

The CDC recommends PEP for persons presenting within 72 hours after an exposure to a source known to be HIV positive if contact of body fluid contaminated with blood (including semen, vaginal secretions, rectal secretions, and breast milk) was made with the vagina, rectum, eye, mouth or other mucous membrane, or nonintact skin or by percutaneous injection.[95] Efforts should be made to determine the current HIV status of the source.

Determination of which ART to use for PEP is based on whether the exposure is considered low or high risk. Evidence for the best choice of antiretroviral medications has been extrapolated from randomized controlled trials looking at prevention of mother-to-child transmission. For low-risk exposures, the use of two NRTIs is appropriate. For high-risk exposures, the dual NRTI therapy is added to either a boosted protease inhibitor (e.g., lopinavir/r) or an NNRTI (e.g., efavirenz). As each of these medications has its side effects and toxicities, the decision of which agents to use should be made in conjunction with an infectious

www.ketabpezeshki.com 66485457-66963820

disease specialist. The patients should be observed closely so their progress can be monitored. The PEP should continue for 4 weeks. Whereas most seroconversions will occur in the first 3 months after the exposure, these patients should be checked for HIV at 6 weeks, 12 weeks, and 6 months.

DISPOSITION

The ED management of patients with HIV/AIDS can be difficult, and the complexities in initiation of treatment and in discerning the appropriate disposition for these patients should not be underestimated. The widespread use of HAART among HIV-positive individuals has dramatically changed the course of the disease; individuals often have sustained and lasting immune reconstitution, living relatively normal lives. Knowledge of their immune status is critical in disposition and treatment; patients with normal or nearly normal $CD4^+$ counts should be treated like non–HIV-infected patients. Drug interactions are common. Patients with AIDS, unlike immunocompetent patients, often suffer from multiple, simultaneous underlying pathologic processes, making workup and treatment decisions even more difficult; a unifying diagnosis is not the norm.[96] These patients are at greater risk of morbidity and mortality from common disease entities as well as from complications of HIV/AIDS. Clinicians who approach these patients with background knowledge of the potential manifestations of HIV/AIDS will be poised to deliver the best emergent care.

KEY CONCEPTS

- Formulation of the differential diagnosis should be guided by the patient's immune status (consider $CD4^+$ count, viral load, current medications, and prior opportunistic infections).
- HIV/AIDS can affect any organ system, and nonspecific complaints are common.
- The presenting illness may originate from acute HIV infection, opportunistic infections, medication side effects, inflammation, and IRIS.
- Consider acute HIV infection in the evaluation of patients with mononucleosis-like syndromes with risk factors.
- Patients with $CD4^+$ counts above 200 cells/μL tend to have illnesses similar to those of individuals without HIV infection.
- Opportunistic infections are more frequent as $CD4^+$ counts decline but can occur at any stage of HIV infection.
- Patients with HIV infection are at greater risk of morbidity and mortality from common disease entities than noninfected patients are.
- Patients with advanced AIDS suffer unusual diseases and often have multiple coinfecting pathogens.
- The current medications used for treatment of HIV infection (especially ART) can interact with many commonly prescribed drugs.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Joint United Nations Programme on HIV/AIDS: *UNAIDS Report on the Global AIDS Epidemic 2010*. Geneva: UNAIDS; 2010.
2. Centers for Disease Control and Prevention: The global HIV/AIDS pandemic, 2006. *MMWR Morb Mortal Wkly Rep* 2006; 55:841-884.
3. Simon V, Ho DD, Abdool Karim Q: HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. *Lancet* 2006; 368:489-504.
4. HIV in the United States: *An Overview*. Atlanta, Ga: Centers for Disease Control and Prevention; 2010.
5. Hall HI, et al: Estimation of HIV incidence in the United States. *JAMA* 2008; 300:520-529.
6. Gomez C, Hope TJ: The ins and outs of HIV replication. *Cell Microbiol* 2005; 7:621.
7. Levy JA: HIV pathogenesis: 25 years of progress and persistent challenges. *AIDS* 2009; 23:147.
8. Stevenson M: HIV-1 pathogenesis. *Nat Med* 2003; 9:853-860.
9. Dorak MT, et al: Transmission of HIV-1 and HLA-B allele-sharing within serodiscordant heterosexual Zambian couples. *Lancet* 2004; 363:2137-2139.
10. Quinn TC, et al: Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med* 2000; 342:921-929.
11. Gray RH, et al: Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1–discordant couples in Rakai, Uganda. *Lancet* 2001; 357:1149-1153.
12. Wawer MJ, et al: Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *J Infect Dis* 2005; 191:1403-1409.
13. Auvert B, et al: Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 Trial. *PLoS Med* 2005; 2:e298.
14. Bailey RC, et al: Male circumcision for HIV prevention in young men in Kisumu, Kenya: A randomised controlled trial. *Lancet* 2007; 369:643-656.
15. Gray RH, et al: Male circumcision for HIV prevention in men in Rakai, Uganda: A randomised trial. *Lancet* 2007; 369:657-666.
16. Landovitz RJ, Currier JS: Clinical practice. Postexposure prophylaxis for HIV infection. *N Engl J Med* 2009; 361:1768-1775.
17. Powers KA, Poole C, Pettifor AE, Cohen MS: Rethinking the heterosexual infectivity of HIV-1: A systematic review and meta-analysis. *Lancet Infect Dis* 2008; 8:553-563.
18. Brenner BG, et al: High rates of forward transmission events after acute/early HIV-1 infection. *J Infect Dis* 2007; 195:951.
19. Pilcher CD, et al: Brief but efficient: Acute HIV infection and the sexual transmission of HIV. *J Infect Dis* 2004; 189:1785.
20. Fiebig EW, et al: Dynamics of HIV viremia and antibody seroconversion in plasma donors: Implications for diagnosis and staging of primary HIV infection. *AIDS* 2003; 17:1871-1879.
21. Roland ME, et al: HIV RNA testing in the context of nonoccupational postexposure prophylaxis. *J Infect Dis* 2004; 190:598-604.
22. Crum NF, et al: Comparisons of causes of death and mortality rates among HIV-infected persons: Analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. *J Acquir Immune Defic Syndr* 2006; 41:194-200.
23. Jean-Jacques M, Walensky RP, Aaronson WH, Chang Y, Freedberg KA: Late diagnosis of HIV infection at two academic medical centers: 1994-2004. *AIDS Care* 2008; 20:977.
24. Napoli AM, et al: Absolute lymphocyte count in the emergency department predicts a low CD4 count in admitted HIV-positive patients. *Acad Emerg Med* 2011; 18:385-389.
25. Garman ME, Tyring SK: The cutaneous manifestations of HIV infection. *Dermatol Clin* 2002; 20:193.
26. Dube M, Fenton M: Lipid abnormalities. *Clin Infect Dis* 2003; 36:S79-S83.
27. Grunfeld C, et al: Preclinical atherosclerosis due to HIV infection: Carotid intima-medial thickness measurements from the FRAM study. *AIDS* 2009; 23:1841-1849.
28. Khunnawat C, Mukerji S, Havlichek D Jr, Touma R, Abela GS: Cardiovascular manifestations in human immunodeficiency virus–infected patients. *Am J Cardiol* 2008; 102:635-642.
29. Tershakovec AM, Frank I, Rader D: HIV-related lipodystrophy and related factors. *Atherosclerosis* 2004; 174:1-10.
30. Friis-Møller N, et al: Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* 2007; 356:1723-1735.
31. Barbaro G: Highly active antiretroviral therapy–associated metabolic syndrome: Pathogenesis and cardiovascular risk. *Am J Ther* 2006; 13:248-260.
32. Grinspoon S, Carr A: Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *N Engl J Med* 2005; 352:48-62.
33. Torriani FJ, et al: Endothelial function in human immunodeficiency virus–infected antiretroviral-naive subjects before and after starting potent antiretroviral therapy: The ACTG (AIDS Clinical Trials Group) Study 5152s. *J Am Coll Cardiol* 2008; 52:569-576.
34. Baker JV, et al: Untreated HIV infection and large and small artery elasticity. *J Acquir Immune Defic Syndr* 2009; 52:25-31.
35. de Gaetano Donati K, et al: Increased soluble markers of endothelial dysfunction in HIV-positive patients under highly active antiretroviral therapy. *AIDS* 2003; 17:765-768.
36. Kuller LH, et al: Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med* 2008; 5:e203.
37. Ross AC, et al: Endothelial activation markers are linked to HIV status and are independent of antiretroviral therapy and lipoatrophy. *J Acquir Immune Defic Syndr* 2008; 49:499-506.
38. Dillmon MS, Saag MS, Hamza SH, Adler BK, Marques MB: Unusual thromboses associated with protein S deficiency in patients with acquired immunodeficiency syndrome: Case reports and review of the literature. *AIDS Res Hum Retroviruses* 2005; 21:753-756.
39. Micieli E, et al: Venous and arterial thrombosis in patients with HIV infection. *Blood Coagul Fibrinolysis* 2007; 18:259-263.
40. Sullivan PS, Dworkin MS, Jones JL, Hooper WC: Epidemiology of thrombosis in HIV-infected individuals. The Adult/Adolescent Spectrum of HIV Disease Project. *AIDS* 2000; 14:321-324.
41. Saber AA, Aboolian A, LaRaja RD, Baron H, Hanna K: HIV/AIDS and the risk of deep vein thrombosis: A study of 45 patients with lower extremity involvement. *Am Surg* 2001; 67:645-647.
42. Lijfering WM, Sprenger HG, Georg RR, van der Meulen PA, van der Meer J: Relationship between progression to AIDS and thrombophilic abnormalities in HIV infection. *Clin Chem* 2008; 54:1226-1233.
43. Calmy A, et al: HIV increases markers of cardiovascular risk: Results from a randomized, treatment interruption trial. *AIDS* 2009; 23:929-939.
44. El-Sadr WM, et al: $CD4^+$ count–guided interruption of antiretroviral treatment. *N Engl J Med* 2006; 355:2283-2296.
45. Fontas E, et al: Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: Are different antiretroviral drugs associated with different lipid profiles? *J Infect Dis* 2004; 189:1056-1074.
46. Strategies for Management of Anti-Retroviral Therapy/INSIGHT; DAD Study Groups: Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS* 2008; 22:F17-F24.
47. Beck JM, Rosen MJ, Peavy HH: Pulmonary complications of HIV infection. Report of the Fourth NHLBI Workshop. *Am J Respir Crit Care Med* 2001; 164:2120-2126.
48. Wolff AJ, O'Donnell AE: Pulmonary manifestations of HIV infection in the era of highly active antiretroviral therapy. *Chest* 2001; 120:1888-1893.
49. Thomas CF Jr, Limper AH: *Pneumocystis* pneumonia. *N Engl J Med* 2004; 350:2487-2498.
50. Hidalgo A, et al: Accuracy of high-resolution CT in distinguishing between *Pneumocystis carinii* pneumonia and non–*Pneumocystis carinii* pneumonia in AIDS patients. *Eur Radiol* 2003; 13:1179-1184.
51. Holmes CB, et al: CD4 decline and incidence of opportunistic infections in Cape Town, South Africa: Implications for prophylaxis and treatment. *J Acquir Immune Defic Syndr* 2006; 42:464-469.
52. Wood R, Maartens G, Lombard CJ: Risk factors for developing tuberculosis in HIV-1–infected adults from communities with a low or very high incidence of tuberculosis. *J Acquir Immune Defic Syndr* 2000; 23:75-80.
53. Sonnenberg P, et al: How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. *J Infect Dis* 2005; 191:150-158.
54. Corbett EL, et al: Human immunodeficiency virus and the prevalence of undiagnosed tuberculosis in African gold miners. *Am J Respir Crit Care Med* 2004; 170:673-679.
55. Lopez-Gatell H, et al: Effect of tuberculosis on the survival of women infected with human immunodeficiency virus. *Am J Epidemiol* 2007; 165:1134-1142.
56. Yang Z, et al: Identification of risk factors for extrapulmonary tuberculosis. *Clin Infect Dis* 2004; 38:199-205.
57. Bica I, et al: Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis* 2001; 32:492-497.
58. Lewden C, et al: Changes in causes of death among adults infected by HIV between 2000 and 2005: The "Mortalité 2000 and 2005" surveys (ANRS EN19 and Mortavic). *J Acquir Immune Defic Syndr* 2008; 48:590-598.

www.ketabpezeshki.com 66485457-66963820

59. Jarvis JN, Harrison TS: HIV-associated cryptococcal meningitis. *AIDS* 2007; 21:2119-2129.
60. Graybill JR, et al: Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID Mycoses Study Group and AIDS Cooperative Treatment Groups. *Clin Infect Dis* 2000; 30:47-54.
61. Perfect JR, et al: Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of America. *Clin Infect Dis* 2010; 50:291-322.
62. Skiest DJ: Focal neurological disease in patients with acquired immunodeficiency syndrome. *Clin Infect Dis* 2002; 34:103-115.
63. Gupta SK, et al: Guidelines for the management of chronic kidney disease in HIV-infected patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis* 2005; 40:1559-1585.
64. Karras A, et al: Tenofovir-related nephrotoxicity in human immunodeficiency virus–infected patients: Three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. *Clin Infect Dis* 2003; 36:1070-1073.
65. Qiu J, Terasaki PI, Waki K, Cai J, Gjertson DW: HIV-positive renal recipients can achieve survival rates similar to those of HIV-negative patients. *Transplantation* 2006; 81:1658-1661.
66. Biviji AA, Paiement GD, Steinbach LS: Musculoskeletal manifestations of human immunodeficiency virus infection. *J Am Acad Orthop Surg* 2002; 10:312-320.
67. Brown P, Crane L: Avascular necrosis of bone in patients with human immunodeficiency virus infection: Report of 6 cases and review of the literature. *Clin Infect Dis* 2001; 32:1221-1226.
68. Reveille JD, Williams FM: Infection and musculoskeletal conditions: Rheumatologic complications of HIV infection. *Best Pract Res Clin Rheumatol* 2006; 20:1159-1179.
69. Sloand E: Hematologic complications of HIV infection. *AIDS Rev* 2005; 7:187-196.
70. Jansen LA: HIV exceptionalism, $CD4^+$ cell testing, and conscientious subversion. *J Med Ethics* 2005; 31:322-326.
71. Arbelaez C, et al: Emergency provider attitudes and barriers to universal HIV testing in the emergency department. *J Emerg Med* 2012; 42:7-14. Epub 2009 Oct 14.
72. Burke RC, et al: Why don't physicians test for HIV? A review of the US literature. *AIDS* 2007; 21:1617-1624.
73. McKenna M: HIV testing: Should the emergency department take part? *Ann Emerg Med* 2007; 49:190-192.
74. Franco-Paredes C, Tellez I, del Rio C: Rapid HIV testing: A review of the literature and implications for the clinician. *Curr HIV/AIDS Rep* 2006; 3:169-175.
75. Branson BM, et al: Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep* 2006; 55:1-17; quiz CE1-4.
76. Arbelaez C, et al: Rapid HIV testing program implementation: Lessons from the emergency department. *Int J Emerg Med* 2009; 2:187-194.
77. Leider J, Fettig J, Calderon Y: Engaging HIV-positive individuals in specialized care from an urban emergency department. *AIDS Patient Care STDS* 2011; 25:89-93.
78. Chen JC, et al: A provider participatory implementation model for HIV testing in an ED. *Am J Emerg Med* 2010; 29:418-426.
79. Haukoos JS, et al: Routine opt-out rapid HIV screening and detection of HIV infection in emergency department patients. *JAMA* 2010; 304:284-292.
80. Brown J, et al: Routine HIV screening in the emergency department using the new US Centers for Disease Control and Prevention Guidelines: Results from a high-prevalence area. *J Acquir Immune Defic Syndr* 2007; 46:395-401.
81. Haukoos JS, et al: Development and implementation of a model to improve identification of patients infected with HIV using diagnostic rapid testing in the emergency department. *Acad Emerg Med* 2007; 14:1149-1157.
82. Lyons MS, Lindsell CJ, Ledyard HK, Frame PT, Trott AT: Emergency department HIV testing and counseling: An ongoing experience in a low-prevalence area. *Ann Emerg Med* 2005; 46:22-28.
83. Ubhayakar ND, et al: Risk, reasons for refusal, and impact of counseling on consent among ED patients declining HIV screening. *Am J Emerg Med* 2011; 29:367-372.
84. Sohoni A, Gordon DM, Vahidnia F, White DA: Emergency department staff satisfaction with rapid human immunodeficiency virus testing. *Acad Emerg Med* 2010; 17:561-565.
85. Millen JC, Arbelaez C, Walensky RP: Implications and impact of the new US Centers for Disease Control and Prevention HIV testing guidelines. *Curr Infect Dis Rep* 2008; 10:157-163.
86. Rothman RE, Merchant RC: Update on emerging infections from the Centers for Disease Control and Prevention. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *Ann Emerg Med* 2007; 49:575-579.
87. Egger M, et al: Prognosis of HIV-1–infected patients starting highly active antiretroviral therapy: A collaborative analysis of prospective studies. *Lancet* 2002; 360:119.
88. Thompson MA, et al: Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society–USA panel. *JAMA* 2010; 304:321.
89. Sax PE, Baden LR: When to start antiretroviral therapy—ready when you are? *N Engl J Med* 2009; 360:1897-1899.
90. Gross R, et al: A simple, dynamic measure of antiretroviral therapy adherence predicts failure to maintain HIV-1 suppression. *J Infect Dis* 2006; 194:1108-1114.
91. Wood E, et al: Impact of baseline viral load and adherence on survival of HIV-infected adults with baseline CD4 cell counts > or = 200 cells/microl. *AIDS* 2006; 20:1117-1123.
92. Mills EJ, et al: Adherence to antiretroviral therapy in sub-Saharan Africa and North America: A meta-analysis. *JAMA* 2006; 296:679-690.
93. Henderson DK, et al: Risk for occupational transmission of human immunodeficiency virus type 1 (HIV-1) associated with clinical exposures. A prospective evaluation. *Ann Intern Med* 1990; 113:740-746.
94. Panlilio AL, Cardo DM, Grohskopf LA, Heneine W, Ross CS: Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. *MMWR Recomm Rep* 2005; 54:1-17.
95. Smith DK, et al: Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States. *MMWR Recomm Rep* 2005; 54:1-20.
96. Hilliard AA, Weinberger SE, Tierney LM Jr, Midthun DE, Saint S: Clinical problem-solving. Occam's razor versus Saint's triad. *N Engl J Med* 2004; 350:599.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 133

PARASITIC INFECTIONS

Bruce M. Becker and John D. Cahill

PERSPECTIVE

Challenge

Parasitology has become increasingly important in the practice of emergency medicine. There has been a dramatic increase in immigration from Southeast Asia, Central and South America, and Africa into the United States during the last few decades. Many of the people in transit have left their countries of origin under dire circumstances, fleeing civil unrest, war, famine, economic hardship, political persecution, and environmental devastation; they often lived in regions where parasitic infections were endemic. Business and adventure travel, including ecotourism, frequently transports immunologically naïve and vulnerable hosts to sites rich in parasitic disease (Fig. 133-1). Patients with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) who travel to countries where parasitic illnesses are endemic are at higher risk of contracting these illnesses. Patients with AIDS who immigrate or travel to the United States or Europe may harbor a number of devastating parasitic illnesses. There is a significant prevalence of endemic parasitic disease in many rural areas of the southeastern and southwestern United States and in some parts of Europe. Often, patients with parasitic illness initially seek treatment in the emergency department (ED).

Correct diagnosis of and prompt chemotherapy for parasitic illness often lead to rapid recovery (Table 133-1); mismanagement can be disastrous. Osler wrote, "Early in the course of disease, diagnosis is difficult and treatment easy; late in the course, diagnosis is easy and treatment difficult." Parasitic illness often begins insidiously; without appropriate treatment, the disease will pursue a chronic course, resulting in damage to the host's end organs, severe morbidity, and even death. To diagnose parasitic infection, the emergency physician must play detective, obtaining a thorough travel history, performing a detailed physical examination, and ordering appropriate laboratory studies. This information must be integrated into a strong understanding of the basic life cycles of parasites, the usual and unusual presentations of infection, and the intersecting geography of the organism and the host.

The incubation period for the development of symptoms for parasitic diseases ranges from days (falciparum malaria) to months (vivax malaria) to years (filariasis). Uncovering parasitic illness depends heavily on Osler's principle—to *make* the diagnosis, the clinician must first *think* of the diagnosis.

Travel History

Parasitic illness should be considered in the differential diagnosis of almost every sign or symptom imaginable, particularly in patients who recently have spent time in areas of the world with endemic parasitic illnesses (Table 133-2). Accordingly, a travel history should be included in the evaluation of most if not all patients presenting to the ED. Some of the most important questions are summarized in Box 133-1. For patients who have recently immigrated to the United States, the history should elicit additional information specific to the country of origin, also summarized in Box 133-1.

PRINCIPLES OF THERAPY

New and more effective antiparasitic agents are continually being developed. The list of drugs used to treat parasitic infestations is large and varied. Table 133-3 includes some of the newest pharmaceutical agents along with other older medications that are still recommended but have become almost obsolete because of toxicity or mediocre efficacy.

The newer antiparasitic drugs are less toxic and more effective. Parasite biochemical pathways are different from those in the human host, permitting selective metabolic interference by using relatively small doses of chemotherapeutic agents. In many instances, single-dose treatment can eradicate an entire parasite burden, leading to implementation of effective mass treatment programs in infected populations in endemic areas. Treatment and disposition in the ED focus on the individual patient and the particular disease entity.

The evolutionary goal of the successful parasite is to live with and at the expense of the living host; a parasite that kills its host has no survival advantage. Most parasitic infections (with certain important exceptions, such as falciparum malaria) pursue a chronic course and are not acutely life-threatening. Nevertheless, alterations in host immune function can change the virulence and morbid course of more benign infections (i.e., strongyloidiasis can become fulminantly disseminated in patients receiving immunosuppressive medication after organ transplantation or after the initiation of long-term steroid therapy). Because of the subacute or chronic nature of most parasitic infections, the clinician should first make a diagnosis and initiate chemotherapy, then arrange careful follow-up and repeated laboratory examinations to ensure that the patient is cured. When the parasites are not eliminated promptly, repeated doses or alternative drugs may be needed because drug resistance among parasitic organisms is becoming increasingly common. In cases of suspected drug resistance, referral to a geographic medicine or infectious disease clinic is indicated. A patient who appears clinically ill or has presumptive falciparum malaria (by symptoms or travel history) will usually require hospitalization for initial diagnosis, treatment, and observation.

www.ketabpezeshki.com 66485457-66963820

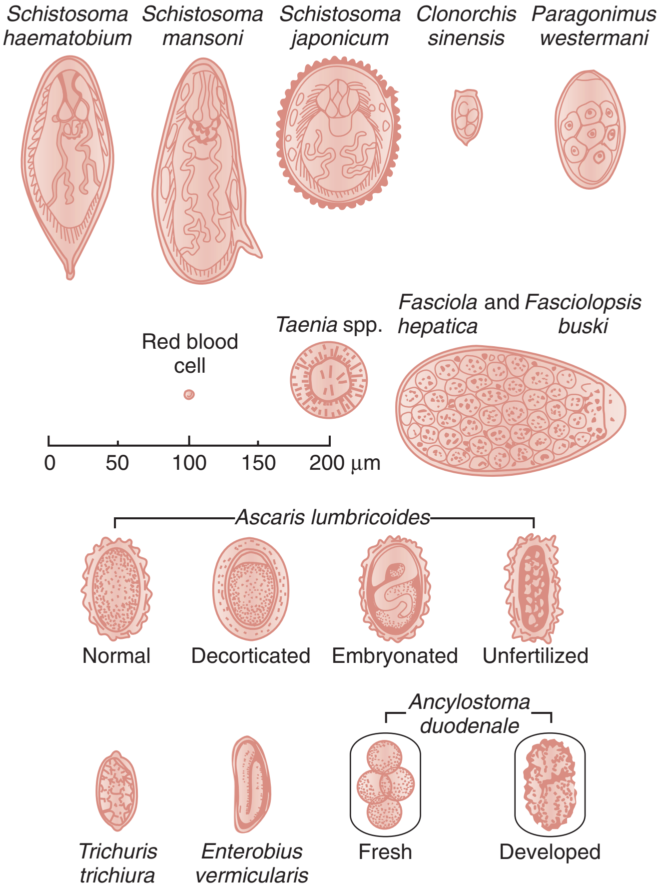


Figure 133-1. Eggs of major parasitic worms causing disease in humans.

Box 133-1 Comprehensive Travel History for Evaluation of Parasitic Disease in the Emergency Department

Questions for All Patients

What were the exact dates of travel?
What countries did the patient visit?
How much time was spent in each country?
What was the patient doing in the country, and where was he or she living?
Was the patient a tourist, an adventure traveler, or a worker?
Did the patient stay in cities or rural villages?
Was the patient sleeping in hotels or tents?
Did the patient engage in protected or unprotected sexual intercourse?
What did the patient eat and drink?
What were the patient's activities (e.g., swimming in fresh water leads to schistosomiasis)?
Did the patient receive prophylactic immunizations before travel?
Did the patient take malaria chemoprophylaxis and comply with the regimen?
Did the patient use mosquito repellent and netting?
Does the patient have underlying chronic medical problems?
What medications does the patient take?
When did symptoms start, and what has been the chronology of symptoms, particularly fever and diarrhea?

Questions for Patients Who Are Recent Immigrants to the United States

When did the patient arrive and from where?
What acute and chronic illnesses did the patient have previously while living in the country of origin?
What treatment did the patient receive there?
If a refugee, what countries did the patient pass through, and what were the living conditions (especially relevant for persons who have lived in numerous refugee camps)?
What was the season during the patient's stay or travel in the countries (e.g., monsoon versus dry)?
What animal exposures and bites has the patient experienced?
Has the patient had exposure to fresh water, in either work or recreational activities?

PRESENTING SYMPTOMS

Fever

Malaria

Principles of Disease. The febrile patient with shaking chills and a time-appropriate history of travel to an endemic region requires evaluation for malaria. *Plasmodium falciparum, Plasmodium ovale, Plasmodium vivax,* and *Plasmodium malariae* are the species responsible for human malaria. More than 41% of the world's population lives in malaria-endemic areas (e.g., parts of Africa, Asia, Oceania, Central America, and South America). Approximately 300 million to 500 million clinical infections occur annually, resulting in 1.5 million to 2.7 million deaths.[1] Approximately 1500 cases of malaria are diagnosed yearly in the United States. The female *Anopheles* mosquito is the arthropod vector that transmits malaria after ingestion of gametocytes from infected persons. After sexual reproduction in the gut of the mosquito, sporozoites are released from the salivary glands into the human host during a blood meal. Sporozoites rapidly penetrate the liver parenchymal cells of their host. The protozoans, now termed cryptozoites or exoerythrocytic schizonts, multiply rapidly. Eventual lysis of the hepatic cells results in the release of merozoites into the bloodstream, which invade erythrocytes. In *P. vivax* and *P. ovale* infection, dormant hypnozoites can reside in hepatocytes; recrudescence of infections can occur many months to years later.

After invading red blood cells (RBCs), the merozoites transform into trophozoites, which feed on the hemoglobin in RBCs. Trophozoites mature into schizonts, which divide asexually into additional merozoites. The RBCs undergo lysis, releasing merozoites into the blood. Although some merozoites are destroyed by the host's immune system, many enter new erythrocytes. After several repetitions of this erythrocytic cycle, the cyclic process changes, and male microgametocytes or female macrogametocytes may develop instead of merozoites. These gametes subsequently complete the reproductive cycle by fusion, which is accomplished sexually within the gut of a new female *Anopheles* mosquito after she has taken a blood meal from an infected host. Most people contract malaria after being bitten by an infected vector mosquito in an endemic region. Other mechanisms of transmission have been reported, including blood transfusions, injection drug use with contaminated syringes, maternal-fetal perinatal transmission, transmission from infected organs after transplantation (worsened by immunosuppression), and so-called airport malaria. *Airport malaria* has been reported in people who have never been in an endemic area but live near or work in an international airport. The infected mosquito is transported from the endemic region and released when the plane arrives at its destination. The mosquito survives long enough to transmit the parasite, although it does not establish itself in the new location.[2]

Clinical Features. Most patients with malaria present with cyclic or irregular fevers. Other signs and symptoms include anemia, headache, nausea, chills, lethargy, abdominal pain, and upper respiratory complaints.[3] The important difference between *P. falciparum* and the other malaria species is the capacity of *P. falciparum* to cause severe organ system damage and death. RBCs infected with P. *falciparum* are rendered "sticky" and

Text continued on p. 1776

www.ketabpezeshki.com 66485457-66963820

Table 133-1 Drug Classes and Modes of Action of Agents Used for Treatment of Parasitic Disease

TYPE OF DRUG	EXAMPLES*	USEFUL IN THE TREATMENT OF	LIKELY TARGET IN THE PARASITE	PROPOSED EFFECTS ON TARGETS
Anthelmintics	Thiabendazole Mebendazole Albendazole	*Ascaris, Enterobius,* hookworm, *Strongyloides, Trichuris,* hydatid disease (long-term therapy)	Tubulin polymerization	Blocks cellular structural integrity and egg production; secondary effects on mitochondrial fumarate reductase and on glucose uptake
	Ivermectin (Stromectol)	Many nematodes of humans (except hookworms) Filariasis Onchocerciasis	GABA-sensitive neuromuscular interface	Flaccidity or contraction (a tight-binding drug effective at low dose)
Trematodicides	Praziquantel (Biltricide)	Schistosomes Most other flukes, such as *Clonorchis, Paragonimus,* Fasciolopsis (many tapeworms of humans)	Surface structure Carbohydrate metabolism	Vacuolization and surface disruption followed by immune attacks by the host; contraction of the muscles due to flooding of calcium through a permeable tegument; initial increase of glucose metabolism followed by shutdown
Antiprotozoals	Metronidazole (Flagyl) Tinidazole Niridazole	Amebiasis Balantidiasis Giardiasis *Schistosoma haematobium*	Molecular electron transport systems Acetylcholine recycling systems	Failure to sustain energy-producing systems Binds to acetylcholinesterase, inactivating normal neuromuscular function
Antimalarials	Chloroquine phosphate (Aralen) Mefloquine Proguanil-atovaquone Doxycycline	Many species of susceptible malaria Many species of susceptible malaria Many species of susceptible malaria Many species of susceptible malaria	Parasite digestive vacuole hemoglobinase Mitochondrial electron transport prevents the normal function of the apicoplast	Local pH is changed so that enzyme becomes inoperative Works on both the erythrocytic and hepatic stages Kills *Plasmodium falciparum*

GABA, γ-aminobutyric acid.
*Some drugs may be available only from the CDC Drug Service, Centers for Disease Control and Prevention, Atlanta, GA 30333; telephone: 404-639-3670 (nights, weekends, and holidays: 404-639-2888).

Table 133-2 Parasites Causing Human Disease: Geographic Location and Portal of Entry

PARASITE	GEOGRAPHIC DISTRIBUTION	COMMON INFECTIVE STAGE AND PORTAL OF ENTRY
Protozoa		
Entamoeba histolytica	Cosmopolitan, especially prevalent in warm climates	Cyst via mouth
Balantidium coli	Warm climates	Cyst via mouth
Giardia lamblia	Found all throughout temperate and warm climates	Cyst via mouth
Trichomonas vaginalis	Cosmopolitan, United States	Trophozoite via vulva or urethra
Leishmania tropica	Mediterranean area to western India	Bite of sandfly introducing promastigote via skin leads to visceral disease
Leishmania infantum	Southern Europe and Mediterranean	Bite of sandfly introducing promastigote via skin leads to visceral disease
Leishmania donovani	China, India, Africa, Mediterranean area, continental Latin America	Bite of sandfly introducing promastigote via skin leads to visceral disease
Leishmania chagasi	South America	Bite of sandfly introducing promastigote via skin leads to visceral disease
Leishmania braziliensis	South America and Central America	Bite of sandfly introducing promastigote via skin leads to cutaneous or mucocutaneous disease
Leishmania major and *L. tropica*	Africa and Asia	Bite of sandfly introducing promastigote via skin leads to cutaneous disease
Leishmania mexicana, L. amazonensis, L. guyanensis, and *L. costaricensis*	Central and South America	Bite of sandfly introducing promastigote via skin leads to cutaneous disease
Trypanosoma gambiense	West and Central Africa	Trypanosome via skin from bite of the tsetse fly

www.ketabpezeshki.com 66485457-66963820

Table 133-2 Parasites Causing Human Disease: Geographic Location and Portal of Entry—cont'd

PARASITE	GEOGRAPHIC DISTRIBUTION	COMMON INFECTIVE STAGE AND PORTAL OF ENTRY
Trypanosoma rhodesiense	Central and East Africa	Trypanosome via skin from bite of the tsetse fly
Trypanosoma cruzi	Continental Latin America	Trypanosome via skin from reduviid bug
Plasmodium vivax	Warm and cooler climates	Sporozoite via skin from *Anopheles* mosquito
Plasmodium ovale	Warm and cooler climates	Sporozoite via skin from *Anopheles* mosquito
Plasmodium malariae	Warm climates	Sporozoite via skin from *Anopheles* mosquito
Plasmodium falciparum	Warm climates	Sporozoite via skin from *Anopheles* mosquito
Nematodes		
Trichinella spiralis	Cooler and temperate climates	Encysted larva in pork or bear via mouth
Trichuris trichiura	Warm, moist climates	Embryonated egg via mouth
Strongyloides stercoralis	Warm, moist climates	Filariform larva via skin
Necator americanus	Common in warm climates	Filariform larva via skin
Ancylostoma duodenale	Common in warm climates	Filariform larva via skin
Enterobius vermicularis	Cosmopolitan, common in the United States	Embryonated egg via mouth
Ascaris lumbricoides	Global distribution, common in the United States	Embryonated egg via mouth
Wuchereria bancrofti	Prevalent in warm climates	Filariform larva via skin from bite of *Anopheles* or *Culex* mosquito
Brugia malayi	Asia	Filariform larva via skin from bite of *Anopheles* or *Culex* mosquito
Onchocerca volvulus	Tropical Africa, Mexico, Central America, and northern South America	Filariform larva via skin from bite of the blackfly
Loa loa	Tropical West Africa	Filariform larva via skin from bite of the *Chrysops* fly
Dracunculus medinensis	Increasingly rare	Ingestion of larva by copepod via mouth
Cestodes		
Taenia saginata	Global distribution, uncommon in the United States	Cysticercus in beef via mouth
Taenia solium	South America, Central America, Mexico, East Africa, India, China, Indonesia	
Adult worm		Cysticercus in pork via mouth
Cysticercus stage		Eggs in human infections via mouth
Echinococcus granulosus	Mediterranean, Russian Federation and neighboring countries, China, Central Asia, North and East Africa, and South America	Eggs from canines via fecal-oral transmission
Echinococcus multilocularis	Central Europe, northern Asia, Alaska	Eggs from foxes, dogs, and cats via fecal-oral transmission
Hymenolepis nana	Warm climates	Eggs in human infections via mouth
Hymenolepis diminuta	Warm climates	Larva in arthropod host via mouth
Diphyllobothrium latum	U.S. Great Lakes region and Alaska, Scandinavia, Russia, Japan, Pacific Coast of South America, and Uganda	Sparganum larva in fish flesh via mouth
Trematodes		
Fasciola hepatica	Sheep-raising countries	Larva on vegetation via mouth
Fasciolopsis buski	Asia	Larva on water nuts
Clonorchis sinensis	Asia	Larva encysted in freshwater fish
Opisthorchis felineus	Europe, Asia	Larva encysted in freshwater fish
Opisthorchis viverrini	Thailand	Larva encysted in freshwater fish
Paragonimus westermani	Primarily Asia, also South America and Africa	Larva encysted in crabs or crayfish via mouth
Schistosoma japonicum	China, Southeast Asia, Philippines	Cercarial larva in water via skin
Schistosoma mansoni	Africa, Latin America, Middle East, Caribbean	Cercarial larva in water via skin
Schistosoma haematobium	Africa, Middle East	Cercarial larva in water via skin

Modified from Beaver PC, et al: Clinical Parasitology, ed 9. Philadelphia, Lea & Febiger, 1984.

www.ketabpezeshki.com 66485457-66963820

Table 133-3 Drug Regimens for Treatment of Parasitic Infections

INFECTION	DRUG*	ADULT DOSAGE	PEDIATRIC DOSAGE
Amebiasis (*Entamoeba histolytica*)			
Asymptomatic			
DRUG OF CHOICE:	Iodoquinol	650 mg tid × 20 days	30 mg/kg/day in 3 doses × 20 days
ALTERNATIVES:	Diloxanide furoate	500 mg tid × 10 days	25-35 mg/kg/day in 3 doses × 7 days
	or Paromomycin	25-30 mg/kg/day in 3 doses × 7 days	25-30 mg/kg/day in 3 doses × 7 days
Mild to moderate intestinal disease			
DRUG OF CHOICE:	Metronidazole (followed by paromomycin or iodoquinol)	750 mg tid × 10 days	35-50 mg/kg/day in 3 doses × 10 days
ALTERNATIVE:	Tinidazole (followed by paromomycin or iodoquinol)	2 g/day × 3 days	50 mg/kg (maximum 2 g) qd × 3 days
Severe intestinal disease, hepatic abscess			
DRUG OF CHOICE:	Metronidazole (followed by paromomycin or iodoquinol)	750 mg IV or PO tid × 10 days	35-50 mg/kg/day in 3 doses × 10 days
Drainage of liver abscess			
ALTERNATIVE:	Tinidazole (followed by paromomycin or iodoquinol)	2 g/day × 5 days	50 mg/kg or 60 mg/kg (maximum 2 g) qd × 3 days
Amebic meningoencephalitis, primary (*Naegleria* spp.)			
DRUG OF CHOICE:	Amphotericin B	1 mg/kg/day IV, uncertain duration	1 mg/kg/day IV, uncertain duration
Anisakiasis (*Anisakis*)			
TREATMENT OF CHOICE:	Surgical or endoscopic removal		
Ascariasis (*Ascaris lumbricoides*): roundworm			
DRUGS OF CHOICE:	Mebendazole	100 mg bid × 3 days	100 mg bid × 3 days
	Albendazole	400 mg × one dose	Older than 6 years, same dose as for adult
	Nitazoxanide	500 mg bid× 3 days	200 mg bid × 3 days
	Ivermectin	150-200 µg/kg for one dose	Should be avoided in young children
Balantidiasis (*Balantidium coli*)			
DRUG OF CHOICE:	Tetracycline	500 mg qid × 10 days	40 mg/kg/day in 4 doses × 10 days (maximum 2 g/day)
ALTERNATIVES:	Iodoquinol	650 mg tid × 20 days	40 mg/kg/day in 3 doses × 20 days
	Metronidazole	750 mg tid × 5 days	35-50 mg/kg/day in 3 doses × 5 days
Cutaneous larva migrans (creeping eruption)			
DRUG OF CHOICE:	Ivermectin	200 µg/kg once daily × 1 or 2 days	
Dracunculus medinensis (Guinea worm)			
DRUG OF CHOICE:	Metronidazole	750 mg tid × 5-10 days	25 mg/kg/day (maximum 750 mg/day) in 2 doses × 10 days
Worm also needs to be extracted			
ALTERNATIVE:	Thiabendazole	50-75 mg/day in 2 doses × 3 days	50-75 mg/kg/day in 2 doses × 3 days
Enterobius vermicularis (pinworm)			
DRUGS OF CHOICE:	Albendazole	A single dose of 400 mg; repeat after 2 weeks	11 mg/kg once (maximum 1 g); repeat after 2 weeks
	Mebendazole	A single dose of 100 mg; repeat after 2 weeks	A single dose of 100 mg; repeat after 2 weeks
Filariasis			
Wuchereria bancrofti, Brugia malayi			
DRUG OF CHOICE:	Diethylcarbamazine	Day 1: 50 mg PO Day 2: 50 mg tid Day 3: 100 mg tid Days 4-21: 6 mg/kg/day in 3 doses	Day 1: 1 mg/kg PO Day 2: 1 mg/kg tid Day 3: 1-2 mg/kg tid Days 4-21: 6 mg/kg/day in 3 doses
Loa loa			
DRUG OF CHOICE:	Diethylcarbamazine	Day 1: 50 mg PO Day 2: 50 mg tid Day 3: 100 mg tid Days 4-21: 9 mg/kg/day in 3 doses	Day 1: 1 mg/kg PO Day 2: 1 mg/kg tid Day 3: 1-2 mg/kg tid Days 4-21: 6 mg/kg/day in 3 doses
Onchocerca volvulus			
DRUG OF CHOICE:	Ivermectin	150 µg/kg PO once, repeated every 3-12 months	150 µg/kg PO once, repeated every 3-12 months

www.ketabpezeshki.com 66485457-66963820

Table 133-3 Drug Regimens for Treatment of Parasitic Infections—cont'd

INFECTION	DRUG*	ADULT DOSAGE	PEDIATRIC DOSAGE
Fluke, hermaphroditic			
Clonorchis sinensis (Chinese liver fluke)			
DRUG OF CHOICE:	Praziquantel	25 mg/kg/day in 4-6 doses × 1 day	25 mg/kg/day in 4-6 doses × 1 day
Fasciola hepatica (sheep liver fluke)			
DRUG OF CHOICE:	Bithionol	30-50 mg/kg on alternate days × 10-15 doses	30-50 mg/kg on alternate days × 10-15 doses
Fasciolopsis buski (intestinal fluke)			
DRUG OF CHOICE:	Praziquantel	25 mg/kg/day in 4 to 6 doses × 1 day	25 mg/kg/day in 4 to 6 doses × 1 day
Opisthorchis felineus			
DRUG OF CHOICE:	Praziquantel	25 mg/kg/day in 4 to 6 doses × 1 day	25 mg/kg/day in 4 to 6 doses × 1 day
Paragonimus westermani (lung fluke)			
DRUG OF CHOICE:	Praziquantel	25 mg/kg/day in 4 to 6 doses × 2 days	25 mg/kg/day in 4 to 6 doses × 2 days
ALTERNATIVE:	Bithionol	30-50 mg/kg on alternate days × 10-15 doses	30-50 mg/kg on alternate days × 10-15 doses
Giardiasis (*Giardia lamblia*)			
DRUG OF CHOICE:	Metronidazole	250 mg tid × 5 to 7 days	15 mg/kg/day in 3 doses × 5 to 7 days
ALTERNATIVES:	Nitazoxanide	500 mg bid × 3 days	200 mg PO bid × 3days (older than 4 years)
	Tinidazole	2 g as a single dose	50 mg/kg as a single dose
Hookworm infection (*Ancylostoma duodenale, Necator americanus*)			
DRUGS OF CHOICE:	Albendazole	400 mg × one dose	
	or Mebendazole	500 mg × one dose	500 mg × one dose
	or Pyrantel pamoate	11 mg/kg (maximum 1 g) × 3 days	11 mg/kg (maximum 1 g) × 3 days
Leishmaniasis (*Leishmania braziliensis, Leishmania mexicana, Leishmania tropica, Leishmania donovani* [kala-azar])			
DRUG OF CHOICE:	Miltefosine	Not indicated in those 12 years or younger	2.5 mg/kg/day PO × 28 days
	or Stibogluconate sodium	20 mg/kg/day IV or IM × 20-28 days	20 mg/kg/day IV or IM × 20-28 days
ALTERNATIVE:	Amphotericin B	0.25-1 mg/kg by slow infusion daily or every 2 days for 8 weeks	0.25-1 mg/kg by slow infusion daily or every 2 days for 8 weeks
Malaria, treatment of (*Plasmodium falciparum, P. ovale, P. vivax,* and *P. malariae*)			
All *Plasmodium* species except chloroquine-resistant *P. falciparum*			
Oral			
DRUG OF CHOICE:	Chloroquine phosphate	600 mg base (1 g), then 300 mg base (500 mg) 6 hr later, then 300 mg base (500 mg) at 24 and 48 hr	10 mg base/kg (maximum 600 mg base), then 5 mg base/kg 6 hr later, then 5 mg base/kg at 24 and 48 hr
Parenteral			
DRUGS OF CHOICE:	Quinine dihydrochloride	20 mg/kg loading dose in 10 mg/kg 5% dextrose during 4 hr, followed by 10 mg/kg during 2-4 hr q8h (maximum 1800 mg/day) until oral therapy can be started	Same as adult dose
	or Quinidine gluconate	10 mg/kg loading dose (maximum 600 mg) in normal saline slowly during 1-2 hr, followed by continuous infusion of 0.02 mg/kg/min for 3 days maximum	Same as adult dose
	or Artesunate for treatment failure or adverse reactions from quinidine or quinine, available from the CDC		

Continued

www.ketabpezeshki.com 66485457-66963820

Table 133-3 Drug Regimens for Treatment of Parasitic Infections—cont'd

INFECTION	DRUG*	ADULT DOSAGE	PEDIATRIC DOSAGE
ALTERNATIVE:	Chloroquine hydrochloride	200 mg base (250 mg) IM q6h if oral therapy cannot be started	0.83 mg base/kg/hr × 30 hr continuous infusion or 3.5 mg base/kg q6h IM or SC
Chloroquine-resistant *P. falciparum*			
Oral			
DRUGS OF CHOICE:	Quinine sulfate	650 mg tid × 3 days	25 mg/kg/day in 3 doses × 3-7 days
	plus Doxycycline	100 mg bid × 7 days	
	or Clindamycin	900 mg tid × 3-5 days	20-40 mg/kg/day in 3 doses × 3-5 days
ALTERNATIVE:	Mefloquine	1250 mg once	25 mg/kg once (<45 kg)
	Atovaquone-proguanil	1000/400 mg qd × 3 days	
	Artemether-lumefantrine	4 tabs bid × 3 days	
Parenteral			
DRUGS OF CHOICE:	Quinine dihydrochloride	Same as above	Same as above
	or Quinidine gluconate	Same as above	Same as above
	or Artesunate	Same as above	Same as above
Prevention of relapses: *P. vivax* and *P. ovale* only			
DRUG OF CHOICE:	Primaquine phosphate	15 mg base (26.3 mg)/day × 14 days or 45 mg base (79 mg)/wk × 8 weeks	0.3 mg base/kg/day × 14 days
Malaria, prevention of			
DRUG OF CHOICE:	Chloroquine phosphate	300 mg base (500 mg salt) PO, once a week beginning 1 week before and continuing for 4 weeks after last exposure	5 mg/kg base (8.3 mg/kg salt) once a week, up to adult dose of 300 mg base, same schedule as for adult
Chloroquine-resistant areas			
DRUGS OF CHOICE:	Mefloquine	250-mg tablet PO once a week × 4 weeks, then every other week, continuing for 4 weeks after last exposure	Same schedule as for adults with the following dosing guidelines: 15-19 kg: ¼tablet 20-30 kg: ½tablet 31-45 kg: ¾tablet >45 kg: 1 tablet
	or Atovaquone-proguanil	250/100 mg qd 1 day before travel, each day in endemic region, and for 1 week afterward	
	or Doxycycline	100 mg daily during exposure and for 4 weeks afterward	>8 yr: 2 mg/kg/day PO, up to 100 mg/day
Schistosomiasis			
Schistosoma haematobium			
DRUG OF CHOICE:	Praziquantel	20 mg/kg/day in 4 to 6 doses × 1 day	20 mg/kg/day in 4 to 6 doses × 1 day
Schistosoma japonicum			
DRUG OF CHOICE:	Praziquantel	20 mg/kg/day in 4 to 6 doses × 1 day	20 mg/kg/day in 4 to 6 doses × 1 day
Schistosoma mansoni			
DRUG OF CHOICE:	Praziquantel	20 mg/kg/day in 4 to 6 doses × 1 day	20 mg/kg/day in 4 to 6 doses × 1 day
ALTERNATIVE:	Oxamniquine	15 mg/kg once	20 mg/kg/day in 2 doses × 1 day
Schistosoma mekongi			
DRUG OF CHOICE:	Praziquantel	20 mg/kg/day in 4 to 6 doses × 1 day	20 mg/kg/day in 4 to 6 doses × 1 day
Strongyloidiasis (*Strongyloides stercoralis*)			
DRUGS OF CHOICE:	Ivermectin	200 µg/kg/day × 1-2 days	200 µg/kg/day × 1-2 days
	or Thiabendazole	50 mg/kg/day in 2 doses (maximum 3 g/day) × 2 days	50 mg/kg/day in 2 doses (maximum 3 g/day) × 2 days
Tapeworm infection, adult (intestinal stage)			
Diphyllobothrium latum (fish), *Taenia saginata* (beef), *Taenia solium* (pork), *Dipylidium caninum* (dog)			
DRUG OF CHOICE:	Praziquantel	5-10 mg/kg once	5-10 mg/kg once
Hymenolepis nana (dwarf tapeworm)			
DRUG OF CHOICE:	Praziquantel	25 mg/kg once	25 mg/kg once

www.ketabpezeshki.com 66485457-66963820

Table 133-3 Drug Regimens for Treatment of Parasitic Infections—cont'd

INFECTION	DRUG*	ADULT DOSAGE	PEDIATRIC DOSAGE
Tapeworm infection, larval (tissue) stage			
Echinococcus granulosus (hydatid cysts)			
DRUG OF CHOICE:	Albendazole	400 mg bid × 28 days, repeated as necessary	15 mg/kg/day × 28 days, repeated as necessary
Echinococcus multilocularis			
TREATMENT OF CHOICE:	Surgical excision		
Cysticercus cellulosae (cysticercosis)			
DRUG OF CHOICE:	Praziquantel	50 mg/kg/day in 3 doses × 15 days	50 mg/kg/day in 3 doses × 15 days
ALTERNATIVE:	Surgery		
Trichinosis (*Trichinella spiralis*)			
DRUGS OF CHOICE:	Steroids for severe symptoms		
	plus Mebendazole	200-400 mg tid × 3 days, then 400-500 mg tid × 10 days	Same as adult dose
Trichomoniasis (*Trichomonas vaginalis*)			
DRUG OF CHOICE:	Metronidazole	2 g once *or* 250 mg tid *or* 375 mg bid PO × 7 days	15 mg/kg/day PO in 3 doses × 7 days
Trichuriasis (*Trichuris trichiura*, whipworm)			
DRUGS OF CHOICE:	Mebendazole	100 mg bid × 3 days	100 mg bid × 3 days
	or Albendazole	400 mg once	400 mg once
Trypanosomiasis			
Trypanosoma cruzi (South American trypanosomiasis, Chagas' disease)			
DRUG OF CHOICE:	Nifurtimox	8-10 mg/kg/day PO in 4 doses × 120 days	1-10 yr: 15-20 mg/kg/day in 4 doses × 90 days 11-16 yr: 12.5-15 mg/kg/day in 4 doses × 90 days
ALTERNATIVE:	Benznidazole	5-7 mg/kg/day × 30-120 days	Same as adult dose
Trypanosoma brucei gambiense, Trypanosoma brucei rhodesiense (African trypanosomiasis, sleeping sickness), hemolymphatic stage			
DRUG OF CHOICE:	Suramin	100-200 mg (test dose) IV, then 1 g IV on days 1, 3, 7, 14, and 21	20 mg/kg on days 1, 3, 7, 14, and 21
ALTERNATIVE:	Pentamidine isethionate	4 mg/kg/day IM × 10 days	4 mg/kg/day IM × 10 days
Late disease with central nervous system involvement			
DRUG OF CHOICE:	Melarsoprol	2-3.6 mg/kg/day IV × 3 days; after 1 week, 3.6 mg/kg/day IV × 3 days; repeat again after 10-21 days	18-25 mg/kg total during 1 month; initial dose of 0.36 mg/kg IV, increasing gradually to maximum 3.6 mg/kg at intervals of 1-5 days for total of 9-10 doses
ALTERNATIVES (*T. b. gambiense* only):	Tryparsamide	One injection of 30 mg/kg (maximum 2 g) IV every 5 days to total of 12 injections; course may be repeated after 1 month	Unknown
	plus Suramin	One injection of 10 mg/kg IV every 5 days to total of 12 injections; course may be repeated after 1 month	Unknown
Visceral larva migrans (toxocariasis)			
DRUG OF CHOICE:	Diethylcarbamazine	6 mg/kg/day in 3 doses × 7-10 days	6 mg/kg/day in 3 doses × 7-10 days
ALTERNATIVES:	Mebendazole	100-200 mg bid × 5 days	Same as adult dose
	or Albendazole	400 mg bid × 3-5 days	400 mg bid × 3-5 days

Modified from Drugs for parasite infections. Med Lett Drugs Ther 37:99, 1995.

*Some drugs may be available only from the CDC Drug Service, Centers for Disease Control and Prevention, Atlanta, GA 30333; telephone: 404-639-3670 (nights, weekends, and holidays: 404-639-2888).

www.ketabpezeshki.com 66485457-66963820

sludge in small arterioles and capillaries, causing ischemia in the host's metabolically sensitive organs. *Acute* falciparum infection may have any of the following manifestations: cerebral malaria with cerebral edema and encephalopathy, hypoglycemia (especially in children), metabolic acidosis, severe anemia, renal failure, pulmonary edema, disseminated intravascular coagulation, and death.

In *chronic* malaria, increased cellularity from the host's exuberant immune response may lead to hepatosplenomegaly. Within the liver, parasites and malarial pigment distend the Kupffer cells. Parasitized RBCs also adhere to the sinusoidal system of the spleen, reducing its immunologic effectiveness. Anemia results from acute and chronic hemolysis. So-called blackwater fever—hemoglobinuria caused by severe hemolysis—may occur in patients with either chronic or acute falciparum malaria.

Diagnostic Strategies. Light microscopic examination of thick and thin blood films is the "gold standard" approach to diagnosis of malaria. The clinician may have to view several slides and multiple fields to make the diagnosis if the parasite burden is small. Peripheral blood smears are stained with Giemsa or Wright stain and examined with ordinary light microscopy. The diagnosis can be made in a simply equipped laboratory. Even if the parasite is not visualized in the smear, treatment of malaria is indicated if the disease is suspected on clinical grounds. The U.S. Food and Drug Administration has approved the use of an antigen-based rapid diagnostic test for screening of patients. Microscopy should still be performed for all patients who have positive antigen test results to determine species and the severity of parasitemia.

Management. In the past, chloroquine phosphate was the treatment of choice for acute, uncomplicated attacks of malaria. Resistance to chloroquine has been steadily increasing, and the drug is now recommended only in regions of known chloroquine sensitivity: Haiti, Dominican Republic, Central America, and limited regions of the Middle East. For uncomplicated malarial infections in patients from chloroquine-resistant regions, oral quinine and doxycycline given together may be used. Another suitable alternative combination is proguanil-atovaquone. For complicated *P. falciparum* infection (e.g., cerebral malaria, involvement of multiple organ systems, inability to tolerate oral medication), intravenous quinine (not available in intravenous form in the United States) or quinidine is used. Rapid infusion of intravenous quinine can cause profound hypoglycemia. Patients should not receive intravenous quinine without cardiac monitoring.

The artemisinin agents are excellent antimalarials and are available in enteral and parenteral preparations. They have a rapid onset of action and are well tolerated. An oral agent known as artemether-lumefantrine (Coartem) is now available for uncomplicated malaria. The other artemisinins are not approved for use in the United States; however, parenteral artesunate is available as an investigational drug for patients who have complicated malaria not responding to quinidine. To obtain this drug, contact the Centers for Disease Control and Prevention (CDC) Malaria Hotline at 770-488-7788 or, during off hours, at 770-448-7100.[4] Primaquine is used to eliminate the hepatic phases of *P. ovale* and *P. vivax* to prevent recrudescent disease. Primaquine therapy is contraindicated in patients with glucose-6-phosphate dehydrogenase enzyme deficiency because it will precipitate severe hemolysis. Untreated falciparum malaria can lead to coma and death; early treatment reduces morbidity and mortality.

Babesiosis

Babesiosis is a malaria-like illness that is becoming increasingly prevalent in the northeastern United States (*Babesia microti*), the northwestern United States (*Babesia gibsoni*), and Europe (*Babesia divergens*). Babesiosis is endemic on Martha's Vineyard and Nantucket and is suspected, along with ehrlichiosis and Lyme disease, in patients on the cape and islands presenting with the "summer flu." The organism is a protozoan, similar in structure and life cycle to the plasmodia. It is transmitted by the deer tick *Ixodes dammini*, the vector of Lyme disease. Several cases have been attributed to transfusions with infected blood.[5] Patients with babesiosis experience fatigue, anorexia, malaise, and emotional lability, with myalgia, chills, high spiking fevers, sweats, headache, and dark urine. Other manifestations include hepatosplenomegaly, anemia, thrombocytopenia, leukopenia, elevated liver enzymes (particularly the transaminases), and signs of hemolysis with hyperbilirubinemia and decreased haptoglobin. In an otherwise healthy person, the disease may remit spontaneously. In asplenic, elderly, and immunocompromised patients (especially patients with AIDS and those taking corticosteroids), up to 85% of RBCs may contain organisms. Clinical syndromes in these patients include massive hemolysis, jaundice, renal failure, disseminated intravascular coagulation, hypotension, and adult respiratory distress syndrome. Diagnosis is based on clinical suspicion, multiple thin and thick blood smears (*Babesia* organisms resemble plasmodia in blood smears), and serologic testing (convalescent titers may not be positive for several weeks after the infection). The treatment of choice consists of quinine plus clindamycin.[6] Patients infected with *B. divergens* tend to be sicker and require more supportive care. Coinfection with *Borrelia burgdorferi*, the agent of Lyme disease, results in more severe and prolonged illness.

Other Parasites Causing Fever

Other parasitic illnesses that commonly cause significant fever include schistosomiasis, fascioliasis, African and American trypanosomiasis, leishmaniasis, toxoplasmosis, and amebic liver abscess. Katayama fever may be the initial phase of schistosomiasis. Infected patients report brief exposures to fresh water in endemic areas. Clinical manifestations include spiking fevers, diaphoresis, and cough. Eosinophilia is common.[7] Fascioliasis, caused by the liver fluke *Fasciola hepatica*, is endemic throughout Asia, the former Soviet Union, southern Europe, and South America. Infection begins with ingestion of the metacercariae often found in watercress. Within 6 weeks, patients exhibit right upper quadrant abdominal pain, fever, and eosinophilia.[8]

American trypanosomiasis (Chagas' disease) is endemic to Central and South America. The vector, the reduviid bug, sheds trypomastigotes in its feces proximal to the bite site. The host responds to local inflammation and infection by excoriating the site, inoculating the wound with trypomastigotes and initiating systemic spread. Acute Chagas' disease begins with a *chagoma*, an infected and swollen bite site, often periorbital, and quickly progresses to fever, malaise, facial swelling, and pedal edema. Parasitization of cardiac muscle leads to the dysrhythmias and ventricular dysfunction that are classically found in late disease (chronic Chagas' cardiopathy).[9] Leishmaniasis is spread to humans by the sandfly and is found in the Middle East, in India, in East Africa, along the Mediterranean coast, and in Brazil. Although leishmaniasis can involve the skin (cutaneous) and the mucosa (mucosal), fever is seen only in visceral leishmaniasis in immunocompetent persons. Signs and symptoms also include massive hepatosplenomegaly, neutropenia, and weight loss.[10] The patient who has amebic liver abscesses from *Entamoeba histolytica* infection presents with high fevers, right upper quadrant pain, and elevated white blood cell count.[11]

Neurologic Symptoms

Cerebral Malaria

Principles of Disease and Clinical Features. Cerebral malaria is a common, life-threatening complication of *P. falciparum* infection.

www.ketabpezeshki.com 66485457-66963820

Parasitized RBCs express malarial cell surface glycoproteins called knobs that are sticky. They adhere to capillary walls, causing sludging in the cerebral microvasculature, localized ischemia, capillary leak, and petechial hemorrhages. Clinical manifestations include fever, altered mentation including obtundation, coma, and occasionally seizures. A careful history and early diagnosis and therapy are essential to prevent severe morbidity and death.

Management. Treatment of cerebral malaria consists of intravenous quinine, quinidine, or artemisinin (if it is available); supportive care, including mechanical ventilation for comatose patients and patients with noncardiogenic pulmonary edema; antiepileptics; and correction of acidosis and hypoglycemia (associated with quinine use and cerebral malaria). The mortality rate is high, especially in children, but if the patient recovers, neurologic sequelae are rare. Corticosteroids, including dexamethasone, provide no benefit and can worsen outcome in cerebral malaria.

Figure 133-2. Hydatid cysts removed surgically.

Figure 133-3. Additional hydatid cysts removed surgically.

Cysticercosis

Principles of Disease. Cysticercosis is caused by the larval form of *Taenia solium,* a common central nervous system (CNS) pathogen in many tropical areas. Cysticercosis is acquired by humans who eat undercooked pork containing the larval cysts. The adult worm matures in the small intestine; the larval forms may penetrate through the gut wall and end up anywhere in the body. They are trophic for the CNS, muscle, and soft tissue.

Clinical Features. In the brain, the cluster of larvae of *T. solium* forms an expanding cyst that induces an intense immunologic reaction from the host, including inflammation, fibrosis, and ultimately calcification. Neurologic abnormalities develop when neural tissue cannot accommodate the enlarging cyst. Seizure activity often is the first indication of cysticercosis, which should be considered in the differential diagnosis of new-onset seizures in adults. The diagnosis of *T. solium* infection is established by the finding of characteristic proglottids (gravid segments) or scolices (worm heads) in stool preparations.

Diagnostic Strategies and Management. Cranial computed tomography (CT) with contrast enhancement or magnetic resonance imaging may reveal an enhancing ring lesion. These lesions can mimic a CNS abscess, metastatic malignant disease, or a primary tumor such as glioblastoma multiforme. Albendazole is the therapeutic agent of choice, and corticosteroids and antiepileptics may be necessary during therapy, particularly if CNS cysts are present.[12,13] Neurosurgical consultation should be sought in the treatment of neurocysticercosis because acute obstructive hydrocephalus can occur.

Echinococcosis

Principles of Disease and Clinical Features. *Echinococcus granulosus* is another tapeworm capable of causing CNS disease. Cerebral hydatid cysts are loculated structures containing *E. granulosus* scolices (heads) and the remains of the germinal epithelium, termed hydatid sand. Common types of exposure include ingestion of food or water contaminated by the ova from feces of sheep or cattle infected by the adult worm and close contact with an infected sheep-herding dog that is shedding ova. Infection results in the liberation of the embryo oncosphere into the small intestine. After penetrating the intestinal wall, the larvae travel through the bloodstream to multiple sites for encystment. The liver is the target organ in nearly two thirds of cases, but 7% of patients have brain involvement; infected patients may present with seizures or focal neurologic signs.

Diagnostic Strategies and Management. The diagnosis of hydatid cyst disease is suggested by the appearance and localization of the cyst on ultrasound examination or CT scan. Serologic evaluation of serum or cerebrospinal fluid (CSF) may help confirm the diagnosis. Aspiration of the cyst should not be attempted because of the risk of seeding the host's body with metastatic cysts. Treatment options include albendazole and surgical resection. Resection of the cyst may cause an anaphylactoid reaction if there is spillage of hydatid sand, which contains parasite antigenic proteins (Figs. 133-2 and 133-3).[14]

African Trypanosomiasis

Principles of Disease. African sleeping sickness is caused by *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense.* This infection is endemic in limited areas of West and East Africa. Several recent cases have been reported in returned travelers who were on safari in East Africa. The motile organisms are transmitted by the bite of the *Glossina* (tsetse) fly, which introduces the infective form of the trypanosome into the host's blood. A small lesion or boil may develop and persist for several days. The flagellated organism travels throughout the bloodstream, invading the lymph nodes and spleen.

Clinical Features. Winterbottom's sign, which is posterior cervical lymphadenopathy, usually is apparent at the time of initial treatment. The patient generally is febrile, and trypanosomes are visible in a thick peripheral blood smear. A maculopapular rash can be seen in fair-skinned people. Once the parasite invades the CNS, cerebral inflammation causes severe headache. Patients may display a change of mental status, psychiatric symptoms, and eventually extreme sleepiness and lethargy. Coma and death from starvation and trypanotoxins are inevitable in untreated patients.[15]

www.ketabpezeshki.com 66485457-66963820

Diagnostic Strategies and Management. An appropriate exposure history and characteristic symptoms should prompt the clinician to obtain diagnostic studies. Trypanosomes in peripheral blood, CSF, or lymph node and bone marrow aspirates establish the diagnosis. The presence of parasites in the CSF indicates advanced progression of the disease. Suramin sodium is the treatment of choice for early infection with *T. b. rhodesiense*. Pentamidine isethionate is the preferred treatment of early *T. b. gambiense* infection. Trivalent arsenicals, such as melarsoprol, which can penetrate the blood-brain barrier, are used in advanced disease with neurologic sequelae.

Other Parasites Causing Neurologic Symptoms

CNS involvement with *Trichinella spiralis* has been reported in severe cases; larval migration of this parasite into the brain and meninges leads to meningitis, encephalitis, seizures, paresis, coma, and death. The pathophysiologic changes may reflect obstruction of small cerebral arterioles by migrating larvae, with subsequent vasculitis or cerebral edema resulting from inflammatory immunologic reaction to the larvae or larval fragments. Therapy for trichinosis with severe muscle or CNS involvement includes mebendazole or thiabendazole as well as steroids, which depress the host's inflammatory response to infection.[16]

Amebic abscess of the brain or meningoencephalitis caused by *E. histolytica* is a rare complication of infection with this intestinal parasite. Infestation occurs after ingestion of amebic cysts. Spread of amebae to the brain or meninges from the colonized large bowel wall is rare but should be considered in any patient with amebiasis and subsequent neurologic impairment. The diagnosis may be made by microscopic identification of trophozoites (motile amebae) in CSF; however, biopsy of affected tissue is more specific. CNS amebiasis is treated with intravenous metronidazole but may require neurosurgical intervention.

Naegleria and *Acanthamoeba* are free-living freshwater amebae that infect patients while they are swimming and diving in ponds and lakes. The amebae invade the CNS through the olfactory neuroepithelium or compromised corneal epithelium that has been violated by abrasion or contact lens wear, leading to amebic meningoencephalitis. The pharmacologic regimen of choice is amphotericin B and miconazole together when these motile amebae are identified in CSF.[17] *Strongyloides stercoralis* infection is a common disease in the tropics. The worm enters through the skin and migrates to the small bowel. Infection with *Strongyloides* is more clinically significant in immunosuppressed patients, who may suffer larval dissemination with subsequent encephalitis and pyogenic meningitis in the CNS. *Strongyloides* infection is treated with thiabendazole or albendazole. Ivermectin has recently been found to be as effective with fewer side effects.[18]

Granulomas may occur in the brain from egg deposition by *Schistosoma*. In general, they do not cause major symptoms; however, several cases of transverse myelitis with paraplegia have been reported when the immunogenic and inflammatory eggs have lodged in the spinal cord of infected patients.

Anemia

Malaria

Malaria infection often is associated with anemia, especially in children younger than 5 years (Fig. 133-4). Anemia may develop quickly, from massive hemolysis in acute infection, or it may have a more insidious onset, developing during months. Mature merozoites lyse parasitized RBCs. Uninfected RBCs undergo immune destruction from cell surface antibodies produced in response to parasite-associated changes in RBC surface proteins. This process of destruction is abetted by increased reticuloendothelial activity. The reticulocyte response in infected persons is blunted by inhibition of erythropoietin secretion. The antimalarial drug primaquine can precipitate hemolysis in patients who have glucose-6-phosphate dehydrogenase deficiency, which is common in many Africans and some Asians.

Figure 133-4. Five-year-old child with severe life-threatening anemia (hematocrit of 9) in association with chronic malaria.

Whipworm and Hookworm

Infestation by the whipworm *Trichuris trichiura* and especially by the two human hookworms *Necator americanus* and *Ancylostoma duodenale* is a major cause of iron deficiency anemia worldwide. Adult worms penetrate into intestinal mucosa and feed, causing significant ongoing luminal blood loss. The host's feces contain eggs that mature in the soil through a rhabditiform larval form to the infective filariform larva. These larvae penetrate the human skin, usually through the feet. In trichuriasis, anemia is seen only with massive parasite infestation. Ova from the whipworm are ingested through stool-contaminated food and water. Diagnosis of these infections requires identification of characteristic ova in the stool. As with most helminthic infections, peripheral eosinophilia is common. Mebendazole or albendazole effectively controls trichuriasis and hookworm infections in adults and children.[19] Anemic patients should receive iron supplementation.

Tapeworm

Infection with the fish tapeworm *Diphyllobothrium latum* is associated with pernicious anemia. This tapeworm competes with the human host for absorption of vitamin B_{12}. When the host ingests raw freshwater fish that contains the embryo plerocercoid larvae in its muscle fibers, the large adult tapeworm develops within the human small intestine. The diagnosis is made by identification of the ova in the feces. Praziquantel is the drug of choice in adults and children.[20]

www.ketabpezeshki.com 66485457-66963820

Peripheral Edema

Elephantiasis

Principles of Disease. Elephantiasis, or filariasis, is manifested in the host by the development of massive peripheral edema with distention and thickening of the overlying epidermis, which acquires the appearance and texture of elephant skin. Elephantiasis is caused by infection with the filarial worm *Wuchereria bancrofti* or *Brugia malayi*. The infection is confined to humans and is widely distributed in the equatorial regions of the world, including Africa, Asia, South America, and Oceania. More than 90% of all infections are found in Asia, where the disease has reached epidemic proportions. Even in endemic regions in which most residents are infected, the disease is rare among travelers. Infected mosquitoes introduce microfilariae into the bloodstream of the human host during a blood meal. After infecting the host, the worms migrate into the lymphatic system and mature into coiled, gravid adults. The adult worm triggers a robust inflammatory reaction in the lymphatic vessels, particularly in the lower extremities and genitalia. The macrophages, lymphocytes, plasma cells, giant cells, and eosinophils migrate to the inflamed and fibrotic lymphatic vessel, which becomes erythematous, edematous, and tender, suggesting the diagnosis of filariasis.

Clinical Features. Chronic manifestations of filariasis include fibrosis of a lymphatic vessel containing a dead or calcified worm. Subsequent mechanical blockage of the lymphatic system leads inevitably to severe lower extremity and genital edema accompanied by thickening of the skin. Recurrent cellulitis is common in these patients; prevention of superinfection requires meticulous skin care.

Diagnostic Strategies and Management. The adult female worm produces microfilariae, which reach the peripheral blood through the lymphatics, whereupon the patient experiences shaking chills and fever. Thick peripheral blood smears may show infection, particularly at night, when the release of microfilariae is most common. Diethylcarbamazine rapidly clears the microfilariae from the peripheral blood and slowly sterilizes the gravid female nematode. Combined therapy with diethylcarbamazine and albendazole, or ivermectin and albendazole, may be more effective.[21] Established elephantiasis of the scrotum can be successfully treated surgically. Chronic lymphatic obstruction of the limbs rarely responds to operative intervention.

Dermatologic Symptoms

Cutaneous Leishmaniasis

Principles of Disease. Cutaneous leishmaniasis is one of the most important causes of painless chronic ulcerating skin lesions in the world. *Leishmania braziliensis* and *Leishmania mexicana* are responsible for New World leishmaniasis; *Leishmania tropica* and *Leishmania major* commonly cause Old World leishmaniasis. The female *Phlebotomus* sandfly transmits the promastigotes during a blood meal, which are ingested by host macrophages and survive in their leishmanial form in the skin.

Clinical Features. Skin papules and nodules are seen early in the course of infection at the site of the insect bite. A raised macule also can appear, which subsequently develops painless central ulceration and a raised border. Lymphocyte and macrophage invasions of the epidermis and dermis cause the induration that occurs at the ulcer border. Secondary bacterial infections of these ulcers increase the associated scarring. *L. braziliensis braziliensis* (subspecies of *L. braziliensis*) attacks the mucocutaneous skin borders (i.e., in tissues of the nose and mouth). Mutilation of the face occurs after massive tissue and nasal cartilage destruction. The larynx and trachea also can be involved, compromising the airway. Disseminated cutaneous leishmaniasis (*L. mexicana amazonensis* in South America and *L. tropica aethiopica* in Ethiopia) is characterized by diffuse nodules and papules resembling those of lepromatous leprosy (Fig. 133-5). Persons with this manifestation of leishmaniasis are thought to have a defect in their cell-mediated immunity response.

Figure 133-5. Cutaneous leishmaniasis.

Diagnostic Strategies and Management. Definitive diagnosis of leishmaniasis is made by direct visualization of the parasite with light microscopy. Diagnosis also can be made by an indirect fluorescent antibody test. Results of intradermal skin testing often are negative during the acute stages of the disease. Many forms of cutaneous leishmaniasis, especially *L. tropica* and *L. mexicana* infection, are self-limited and require no treatment unless the wounds become secondarily infected. Treatment options for advanced disease include sodium stibogluconate, meglumine antimoniate, and amphotericin B. An oral drug, miltefosine, has been used with success for treatment of both the visceral and the cutaneous forms of leishmaniasis.[22] These treatments are rarely initiated in the ED setting.

Dracunculiasis

Principles of Disease and Clinical Features. *Dracunculus medinensis*, the "fiery serpent," appears in the host as the adult worm migrates through the subcutaneous tissues of the leg. The head of the gravid adult female erodes through the skin of the leg and releases larvae into the water when the host wades in a pond or open well. The larvae promptly infect the *Cyclops* water flea. Humans who drink water containing the infected crustacean complete the cycle of infection. The patient may complain of rash, intense pruritus, nausea, vomiting, dyspnea, and diarrhea before the female worm erupts through the skin.

Management. The "classic" treatment in developing countries has been to wind the worm around a stick and slowly extract the parasite from the skin during the course of 1 or 2 days. If the worm breaks while it is being extracted, the patient experiences an intense inflammatory reaction with cellulitis along the worm track. The diagnosis is confirmed when microscopic larvae are found in the fluid of the cutaneous ulcer or when the adult female worm is identified extruding from the skin. The use of metronidazole to shorten the time of extraction is controversial. The World Health Organization set a goal to eradicate this disease through public health awareness: encouraging the covering of wells, filtering well water to remove the fleas, and keeping infected persons with active skin lesions out of potable water. These efforts have had a tremendous impact on the eradication of dracunculiasis from Africa.[23]

www.ketabpezeshki.com 66485457-66963820

Other Parasites Causing Dermatologic Symptoms

Cutaneous larva migrans, the "creeping eruption," occurs in the host's epidermis when the skin is penetrated by *Ancylostoma braziliense* (dog or cat hookworm) larvae. Exposure usually occurs after walking barefoot or lying on beaches or other warm soil contaminated by animal feces. The diagnosis is suggested by the presence of a characteristic meandering erythematous track on the skin surface caused by larval migration. Visceral larva migrans occurs in young children after ingestion of soil containing ova from the dog ascarid *Toxocara canis*. Thiabendazole, ivermectin, or albendazole may be used for treatment of cutaneous larva migrans, and antipruritics give symptomatic relief. Diethylcarbamazine treats visceral larva migrans. An alternative is thiabendazole.[24]

"Swimmer's itch" is a dermatitis that occurs when skin is penetrated by the nonhuman schistosome of avians and mammals, usually from swimming in northern U.S. freshwater lakes. The infection spontaneously resolves when the nonhuman schistosome is destroyed by the human host's immune system. A similar dermatitis also can occur after infection with schistosome species that are trophic for humans. Treatment is symptomatic.

Strongyloides can cause a transient, pruritic rash that may appear and then disappear within hours. *Taenia solium* can cause cysts in the soft tissues and muscles. These cysts often are an incidental finding. Onchocerciasis (from *Onchocerca volvulus*), which is commonplace in West Africa and parts of South America, can cause severe pruritus and the development of nodules on bone protuberances.

Visual Symptoms

Onchocerciasis

Principles of Disease. Onchocerciasis is a major cause of blindness in the world. Ninety-five percent of all cases occur in Africa. The parasite is found only in humans and is transmitted by the bite of the *Simulium* fly. These flies live near rivers, hence the common name of the disease, "river blindness." Microfilariae of *O. volvulus* are released by adult nematodes, which coil in subcutaneous nodules in the infected host; the microfilariae then migrate through the dermis and epidermis. The presence of adult worms stimulates a brisk immune response, including the infiltration of lymphocytes, macrophages, plasma cells, and eosinophils.

Clinical Features. The skin becomes chronically edematous and pruritic; it then atrophies, resulting in loose, thin folds of skin. River blindness is more likely to develop in patients with nodules in proximity to the eyes. When the microfilaria dies during its migration in the eye, the foreign tissue that is deposited in the iris musculature incites an immune sclerosing keratitis, which is the major cause of the ocular destruction and subsequent blindness (Fig. 133-6).

Figure 133-6. Patient with onchocerciasis or "river blindness."

Diagnostic Strategies and Management. The diagnosis of onchocerciasis requires identification of characteristic microfilariae in skin snipped from the patient. Ivermectin is the therapeutic drug of choice. In many countries in which the disease is endemic, the manufacturers of ivermectin have donated the drug in an attempt to eradicate the disease.[25] Surgical excision of the subcutaneous nodules is recommended when they are located on the head.

Loiasis

Principles of Disease and Clinical Features. Another filarial infection that causes ocular problems is loiasis. Loiasis is confined to forest areas in West and Central Africa. Transmission of *Loa loa* occurs through the bite of flies of the genus *Chrysops*. The edema initially associated with migration of the worm is called a Calabar swelling. The disease is caused by migration of the adult worm in the subcutaneous tissue. The adult worm occasionally migrates through the subconjunctival tissues of the eye and can be surgically excised from the conjunctiva. Although it is upsetting to the patient, the disease is generally fairly benign. The adult worm releases sheathed microfilariae into the peripheral bloodstream during the daytime.

Diagnostic Strategies and Management. Microfilariae can be detected in a thick blood smear, securing the diagnosis of loiasis. The treatment of choice for *L. loa* infection is diethylcarbamazine. Corticosteroids or antihistamines should be used to supplement specific chemotherapy because of the intense allergic reaction that occurs when the killed adult worms and microfilariae disintegrate.

Other Parasites Causing Ocular Symptoms

Toxocara canis has a trophism for the host's eyes. Toxocariasis is a roundworm infection found in urban dogs. Humans ingest eggs by the fecal-oral route. The larvae migrate and often enter the retina, where they become trapped. They stimulate an immune response that culminates in granuloma formation. These granulomas can impair vision and sometimes are mistaken for retinal tumors. There is no means of direct diagnosis except tissue biopsy. Although serologic tests are available, results need to be interpreted with caution. Infection is treated with albendazole and steroids; larvae visible in the retina can be destroyed with a laser.

Toxoplasma gondii infection can precipitate a vitreal inflammation with retinal hemorrhages. Immunocompromised patients may have chorioretinitis and optic neuritis with visual field defects and ocular palsies. Erythrocytes with sticky knobs from *P. falciparum* infection can cause retinal vascular congestion and ischemia with hemorrhage, exudate, infarction, and macular destruction. Cerebral malaria can produce cortical blindness. Mucocutaneous leishmaniasis can involve the eyelids, tear glands, retina, or iris and may result in total ocular destruction. *Acanthamoeba* can cause a dangerous keratitis in contact lens wearers. The patient complains of severe pain, tearing, and photophobia. Early infection may be misdiagnosed as herpetic keratitis. The infection may become chronic and necessitate keratoplasty for preservation of vision. Many different worms migrate to or through the eye, causing inflammation, tissue destruction, and blindness. *Echinococcus* and *Cysticercus* can initiate destructive cystic lesions in the eye.

Pulmonary Symptoms

Patients with *P. falciparum* malaria initially may seek treatment for fever and cough. Early in the course of treatment for severe

www.ketabpezeshki.com 66485457-66963820

malaria, noncardiogenic pulmonary edema or acute respiratory distress syndrome may develop, necessitating mechanical ventilation with positive end-expiratory pressure.

E. histolytica can cause sympathetic pleural effusions, pulmonary or pleural involvement by direct extension or rupture of an amebic liver abscess, or direct hematogenous seeding of the lungs, leading to considerable additional morbidity and mortality among patients with underlying amebic infection. *Pneumocystis* pneumonia, caused by *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*), is one of the most common respiratory opportunistic infections in patients with HIV infection in the United States and Europe; surprisingly though, it is responsible for less than 10% of pulmonary opportunistic infections in Africa and the developing world. The reason for this discrepancy is unclear. Many patients with AIDS in these countries die with $CD4^+$ cell counts that are higher than those associated with *P. jiroveci* pneumonia in the United States.[26]

Löffler's syndrome, characterized by persistent and nonproductive cough, substernal chest pain, wheezing, rales, pulmonary infiltrates on the chest radiograph, and marked eosinophilia, often is seen when larvae from the roundworm *Ascaris lumbricoides,* the hookworms *N. americanus* and *A. duodenale,* and the threadworm *S. stercoralis* transit the lungs as part of their developmental cycles. *Ascaris* larvae penetrate the small intestinal wall to gain entry into the small venules of the gastrointestinal tract and then migrate to the lungs. *Strongyloides* and the hookworm filariform larvae penetrate through the skin of the feet, entering small cutaneous venules before migration to the lungs. The pulmonary infiltrates and symptoms are transient, resolving within 2 weeks. Diagnosis depends on discovery of larvae in sputum or gastric aspirates. Negative stool examinations initially are nondiagnostic because eggs do not appear in the stool for at least 1 month after initial infection.

The patient's immune response to the microfilariae of *W. bancrofti* and *B. malayi* is the cause of tropical eosinophilic pneumonia. Affected persons present with malaise, weight loss, new-onset nocturnal wheezing and asthma, shortness of breath, and chest discomfort. Chest radiographs may show nodular or interstitial infiltrates, consolidations, or cavitation. Microfilariae can be seen in lung biopsy material. Untreated infection may result in obstructive or restrictive lung disease. Patients have marked eosinophilia and elevations of serum immunoglobulin E.

Paragonimus westermani and echinococcal species are trophic for the lungs in their human hosts. *P. westermani* eggs are shed in stool, hatch in fresh water, and, as miracidia, infect a snail intermediary. After further development, cercariae are released from the snail, penetrating and encysting in freshwater crabs or crayfish. If the human host consumes raw or undercooked shellfish, the metacercariae excyst within the host's duodenum, penetrating the duodenal wall into the abdominal cavity. The larvae migrate from the peritoneal cavity through the diaphragm into the pleural cavity, finally migrating to the lungs, where they cause hemorrhage, necrosis, and a granulomatous response. Early in the process, patients may have infiltrates and eosinophilia; later disease is marked by bronchiectasis, chronic bronchitis, fever, hemoptysis, and cachexia. Pulmonary nodules and cysts may cavitate. Many of these patients may have a positive result on purified protein derivative testing, and their symptoms and chest radiographic findings may mimic tuberculosis.[27] Sputum often is blood streaked and flecked with dark brown particles containing ova. Finding of ova in sputum is diagnostic. Radiography, stool examination, and immune testing of sputum and blood are all helpful in making the diagnosis. Praziquantel is the therapeutic agent of choice.

E. granulosus causes pulmonary hydatid cyst disease; the host remains asymptomatic until a cyst grows large enough to cause a mass effect, becomes superinfected, or leaks cyst material, which is highly immunogenic and causes a severe anaphylactoid reaction. Pulmonary hydatid cysts also can be associated with cough, expectoration of sandlike material, chest pain, and hemoptysis. Primary hydatid disease in the liver can metastasize to the lungs or brain. A thoracic CT scan may show a unilocular lung cyst; on a plain radiograph, a ruptured cyst is said to resemble a water lily, a pathognomonic finding. Cysts can be treated with careful surgical excision and pharmacotherapy.

Early schistosomal disease, or Katayama fever, can be manifested with fever, cough, eosinophilia, and diffuse pulmonary nodules as the schistosomula pass through the lungs. In long-standing disease, ova shed from worm pairs can lodge in the vasculature of the lungs, causing pseudotubercles, granulomatous lung disease, pulmonary hypertension, and cor pulmonale. In patients with long-standing, latent, and asymptomatic *S. stercoralis* infections who are started on corticosteroids or immunosuppressive therapy, the helminth disseminates widely. Fatal, massive pulmonary infections with radiographic whiteouts and unsupportable respiratory failure have been reported in patients who have received organ transplants; this clinical disaster occurs more commonly in patients who emigrate from developing countries and receive organ transplants and immunosuppressive therapy without being evaluated for *Strongyloides* infection.[28] *Strongyloides* pulmonary infection can cause wheezing and cough, leading to an initial misdiagnosis of bronchospasm and asthma; if the patient is given steroids, the strongyloides may disseminate with markedly increased morbidity and mortality.[28]

Cardiovascular Symptoms

Chagas' Disease

Principles of Disease. *Trypanosoma cruzi* infection often leads to acute and chronic myocarditis. *T. cruzi* is endemic in South and Central America and causes Chagas' disease. The vector is the reduviid bug or "kissing bug" that inhabits the walls and roofs of thatched dwellings built adjacent to forest. Urban transmigration has expanded the epidemiologic scope of Chagas' disease, previously a disease of rural populations. The disease is not seen commonly in travelers. The reduviid bug's bite is no longer the only source of *T. cruzi* infection; transfusion with blood containing live trypanosomes from infected hosts is a growing source of infection. Oral transmission also has been reported.[28]

The reduviid bug bites the patient, often around the eye, and excretes feces containing the trypomastigote of *T. cruzi.* The trypomastigote enters the inflamed bite wound or other mucosal or conjunctival surfaces, causing a local swelling called a chagoma. Romaña's sign (painless unilateral periorbital edema) is pathognomonic but rarely seen. The trypomastigote migrates to trophic tissues, including smooth muscle, cardiac muscle, and autonomic ganglia in the heart, esophagus, and colon, causing local inflammation and tissue destruction.

Clinical Features. Acute infection is heralded by fever, facial and dependent extremity edema, hepatosplenomegaly, lymphadenopathy, malaise, lymphocytosis on peripheral blood smear, and elevated liver transaminases. At this stage, fatal left ventricular dysfunction and dysrhythmias are uncommon. Early illness lasts 1 to 2 months and resolves spontaneously, resulting in a latency known as the indeterminate phase, which can persist throughout the patient's lifetime. In approximately 25% of the cases, the infection progresses to chronic Chagas' disease, principally with cardiomyopathy and gastrointestinal disease. Amastigotes invade cardiac muscle and the cardiac conduction system, causing chronic inflammation, mononuclear cell infiltration, and fibrosis. Patients whose disease involves the conduction system may present with atrial bradydysrhythmias, right and left bundle branch blocks, complete heart block, and ventricular dysrhythmias, including ventricular fibrillation. Cardiac muscle is replaced by fibrosis and

www.ketabpezeshki.com 66485457-66963820

scarring, leading to the development of right and left ventricular dysfunction and dilated cardiomyopathy. Mural thrombi are common. The first indication of long-standing asymptomatic infection can be thromboembolic disease, such as pulmonary embolism, stroke, or peripheral arterial embolism. Congestive heart failure is generally rapidly progressive and fatal within months unless it is aggressively treated with pharmacologic intervention and transplantation.[29]

Diagnostic Strategies. Acute Chagas' disease can be diagnosed by the presence of motile trypomastigotes in anticoagulated blood specimens. The organism also can be cultured in special liquid media. Chronic Chagas' disease can be diagnosed by one of several serologic tests, including complement fixation, enzyme-linked immunosorbent assay (ELISA), and indirect immunofluorescence testing. The assays are nonspecific, cross-reacting with malaria, syphilis, leishmaniasis, and some collagen vascular diseases. Polymerase chain reaction technology is improving and soon will provide the gold standard modality for diagnosis.[30]

Management. Nifurtimox and benznidazole are used for treatment of *T. cruzi* infection. Cure rates rarely exceed 50%. The duration of treatment with nifurtimox is prolonged, and the drug has many serious side effects. Its production has been discontinued; however, it is the only antitrypanosomal medication available in the United States today and can be obtained from the CDC by calling 404-639-2888. Benznidazole has fewer side effects. It is now recommended for indeterminate-phase treatment. Late complications of chronic diseases are modulated by autoimmune activity and do not respond to antiparasitic pharmacotherapy. Chronic Chagas' disease of the heart, esophagus, or colon is treated symptomatically. Automated implantable cardioverter-defibrillators decrease the incidence of sudden death in infected patients.[31] Patients receiving immunosuppressive therapy to prevent rejection after cardiac transplantation have developed recurrent disease in the transplanted myocardium.

Other Causes

Aberrant migration of *Ascaris* to the myocardium, causing myocarditis and pericardial effusions, is well described. *E. histolytica* abscesses of the liver also may cause pericardial effusions if they erode through the diaphragm.

Gastrointestinal Symptoms

Diarrhea

Diarrhea is one of the most common symptoms for which travelers seek medical attention. Gorbach[32] wrote, "Travel expands the mind and loosens the bowels." Diarrhea also is the leading cause of death in children younger than 5 years in developing countries and a major source of morbidity for older children and adults (Fig. 133-7). Most diarrheal disease is viral or bacterial; however, some clinically significant diarrheal disease is caused by parasites.

Figure 133-7. Fecal-oral transmission of diarrheal agents occurring in a developing country.

Cryptosporidium parvum and *Cyclospora cayetanensis* are food-borne and water-borne coccidians that cause watery diarrhea. Both are particularly significant causes of morbidity in malnourished children and patients with AIDS. Cryptosporidial oocysts can be seen in stool when an acid-fast stain is used. ELISA and immunofluorescent assays of stool also are available for this organism. Paromomycin decreases diarrheal frequency in patients with AIDS who have cryptosporidial infections, who would have prolonged, disabling symptoms without treatment. *Cyclospora* oocysts can be detected in stool samples with a Ziehl-Neelsen stain. Trimethoprim-sulfamethoxazole treats this infection.[33]

E. histolytica causes an invasive or inflammatory diarrhea. Patients complain of fever, tenesmus, abdominal pain, and watery stool containing blood and mucus. Untreated disease can progress to widespread colitis and perforation of the bowel wall with peritonitis and death. Stool examination reveals mobile trophozoites containing ingested RBCs. Cysts noted on stool studies do not necessarily reflect active infection as there are nonpathogenic ameba species that can be found in the bowel of healthy adults. Immune assays of stool can now differentiate between *E. histolytica* and these nonpathogenic ameba species. Serologic tests may be useful in an infected patient from a nonendemic region but take a month for results to turn positive. Metronidazole is the drug of choice for treatment of amebiasis. *Balantidium coli* is the other protozoan that can cause invasive diarrhea. It has trophism for the terminal ileum, sometimes resulting in a clinical picture suggestive of appendicitis. Tetracycline and metronidazole are active against *B. coli*.

Giardia lamblia can cause persistent diarrhea, abdominal bloating, cramps, flatulence, and significant weight loss. The organism is ingested and reproduces exponentially in the small bowel. In severe infection, the entire jejunum becomes covered with organisms, and the patient has malabsorption with steatorrhea. The organisms are rarely seen in fresh stool preparations because they quickly break down and become indiscernible. Accordingly, an antigen test often is used to confirm the diagnosis. *Giardia* has many animal reservoirs, including the beaver. Campers who drink unfiltered, "pure" mountain spring water in the United States commonly contract *Giardia* infection. Metronidazole, tinidazole, or nitazoxanide treats the disease.[33]

S. stercoralis, *Capillaria philippinensis*, *T. trichiura*, and *Schistosoma* have been associated with diarrhea. Hyperinfection or dissemination of *Strongyloides* can cause persistent diarrhea, weight loss, and abdominal pain. *Trichuris* causes diarrhea when the parasite load in the intestine is high. Schistosomiasis can cause a chronic granulomatous colitis, which may resemble inflammatory bowel disease, or an acute, bloody, febrile colitis associated with Katayama fever in the immunologically naïve patient.

In chronic schistosomiasis, worm pairs in patients' mesenteric and portal venous systems lay eggs that become ensnared in the liver, causing intense local inflammation and scarring and the classic "pipestem" cirrhosis with periportal fibrosis. Clinical manifestations in these patients include portal hypertension, ascites, and esophageal varices (Figs. 133-8 and 133-9). Upper gastrointestinal bleeding is not as common as in patients with alcoholic cirrhosis; however, a high number of patients are infected with schistosomiasis in endemic regions, so variceal bleeding is an important cause of gastrointestinal hemorrhage in these populations.

www.ketabpezeshki.com 66485457-66963820

Figure 133-8. Pipestem cirrhosis with extensive ascites in a patient with chronic schistosomiasis.

Figure 133-9. Extensive ascites in a child, which may be from schistosomiasis or kala-azar (leishmaniasis).

Abdominal Pain

Several parasites have been identified in pathologic examination of appendices of patients diagnosed with tropical appendicitis. These infections have included enterobiasis, amebiasis, ascariasis, trichuriasis, and taeniasis.[34]

A. lumbricoides can cause significant persistent or recurrent abdominal pain in adults and partial intestinal obstruction in children with significant worm loads. Anthelmintics and conservative, supportive therapy usually eliminate the problem, thereby avoiding surgical intervention. The diagnosis of ascariasis is made by the identification eggs in the stool. Patients with large worm loads may excrete adult worms, especially after therapy is started. Severe intestinal amebiasis can be complicated by colonic perforation and peritonitis.[35]

Angiostrongylus costaricensis, a nematode known as the rat lung worm, is common in Central America. Infected children may appear clinically to have Meckel's diverticulum or acute appendicitis. Manifestations of the infection include nausea, vomiting, fever, abdominal pain localized to the right lower quadrant, and a tender mass. Surgical exploration may uncover abscesses, obstruction, or intestinal infarction. Anisakiasis is characterized by severe abdominal pain after ingestion of raw fish (sushi and sashimi primarily). *Anisakis marina,* a nematode that burrows into the intestine, is the pathogen.

The liver fluke *Fasciola hepatica* causes a syndrome that mimics viral hepatitis: right upper quadrant pain, fever, nausea and vomiting, jaundice, tender enlarged liver, and elevated transaminases. Patients also have eosinophilia and urticaria. Imaging studies, including CT, show the tracks of burrowing flukes. Serologic testing establishes the diagnosis; the patient's stool may not contain eggs for several months after ingestion.[36] The eggs of schistosomes become trapped in the portal venules, where they trigger an inflammatory response, leading to granulomatous liver disease, fibrosis, and cirrhosis. Hepatic granulomas also are seen in disseminated strongyloidiasis and aberrant biliary ascariasis.

E. histolytica can cause hepatic abscesses. Affected patients typically do not have amebic dysentery and do not shed *Entamoeba* in their stool, but results of serologic studies almost always are positive. Patients have fever, weight loss, anorexia, and right-sided abdominal pain but no jaundice. Treatment is with metronidazole or tinidazole and a luminal amebicide, such as iodoquinol.[37] *E. granulosus* produces hydatid cysts of the liver that on CT contain septations and so-called daughter cysts. Pharmacotherapy with albendazole and careful excision remain the treatments of choice. Leaking cyst material can initiate a severe anaphylactoid reaction in the host.

Jaundice may result from hemolysis secondary to direct infection of RBCs with *Plasmodium* or *Babesia* or from biliary obstruction with pigmented stones. *Ascaris* can cause biliary colic, pyogenic cholangitis, pancreatitis, or liver abscess. Dead worms can be the nidus for gallstone formation. Biliary imaging and endoscopic retrograde cholangiopancreatography will show worms in the biliary tree. Mechanical removal by endoscopy combined with anthelminthic therapy is curative. *Clonorchis sinensis* and *F. hepatica* are trophic for the biliary tree. These worms can be present without producing symptoms for years before eventually precipitating cholecystitis, cholangitis, or cholangiocarcinoma.

Pruritus Ani

Enterobius vermicularis, or pinworm, causes pruritus ani, a syndrome of intense perianal itch occurring primarily in children. Autoinfection is common because children (and adults) scratch the pruritic anal area and then bite their nails or put their fingers in their mouth. The worm has a worldwide distribution. Diagnosis is clinical and is confirmed by finding the small adult worms wiggling about on the anal verge. Eggs are rarely seen in the stool but can be visualized by the tape test: transparent tape touched to the perianal region collects eggs, which can be seen with light microscopy. Albendazole or mebendazole is the drug of choice.

PARASITIC COINFECTIONS IN PATIENTS WITH HIV INFECTION AND AIDS

Perspective

HIV infection and AIDS are prevalent in developing countries. Heterosexual transmission and perinatal transmission are common; young children and young adults of both sexes are primarily infected. Patients presenting to the ED may be coinfected with HIV and any other infectious agent, including all of the parasites discussed in this chapter. HIV coinfection may worsen the

www.ketabpezeshki.com 66485457-66963820

symptoms and outcome, alter the presentation, increase the virulence, or assist the infective process.

AIDS causes abnormalities in almost every aspect of a host's immune response to infection; cell-mediated immunity (which is important in combating parasitic infection) is most affected.[37] The diagnosis and response to therapy of many parasitic infections are monitored serologically. HIV infection interferes with this response, rendering many of these tests unreliable. Therapies that are extremely effective in the normal host may be ineffective in a patient with HIV infection. Pharmacologic agents may have to be given for long periods or for the patient's entire life.

Specific Parasitic Infections

Malaria is not an opportunistic infection in patients with AIDS; however, many patients, especially children, with recurrent malaria and anemia from hemolysis have required transfusions from blood supplies not screened for HIV and have become infected.[37] Treatment of febrile patients for malaria in areas in which it is endemic is a common practice. Patients with AIDS have more severe allergic reactions to drugs, especially sulfonamides, that are antimalarials. In patients with AIDS, fever alone is not predictive of malaria; diagnosis should precede therapy. Patients with HIV infection are at greater risk for severe clinical manifestations of babesiosis.[6]

Visceral leishmaniasis is more commonly disseminated and fatal in patients with AIDS. Latent leishmanial infections may be reactivated, and a prolonged febrile illness in an HIV-positive patient with a lifetime history of travel in leishmaniasis-endemic areas of the world should prompt consideration of this coinfection. Cutaneous infection also may become disseminated in these patients. Several clinical trials are currently examining the role of chemoprophylaxis for leishmaniasis in HIV-positive persons who live in endemic regions of the world. Chagas' disease in the indeterminate phase can be reactivated in patients infected with HIV. These patients frequently have CNS involvement with meningoencephalitis and severe myocarditis.[31] Single-drug therapy may be insufficient because benznidazole penetration into the CSF is minimal. *T. gondii* infection is well recognized throughout the world as a common opportunistic infection of patients with AIDS, with a particular trophism for the CNS.

The coccidial organisms *Isospora belli, C. parvum,* and *C. cayetanensis* have been associated with prolonged diarrhea in patients with AIDS. These organisms cause infections that are difficult to treat and are almost impossible to eradicate in these patients. The diarrhea is extremely debilitating and can be as profuse as that seen in cholera. *E. histolytica* has a high prevalence among homosexual men who practice unprotected anal intercourse; however, invasive amebiasis is not an opportunistic infection associated with HIV infection. Schistosomiasis enhances the pathogenesis of HIV infection and is more difficult to treat and to eradicate in patients who are HIV positive. *S. stercoralis* infection is more likely to be manifested as hyperinfection and disseminated disease in patients who are HIV positive.[28] In patients who are at risk for HIV infection and parasitic illness, it is essential to consider coinfection in the differential diagnosis.

KEY CONCEPTS

- Parasitic diseases may be manifested with almost any symptom or constellation of symptoms. Accordingly, a travel history should be obtained in all patients with clinically significant signs and symptoms of unclear etiology. The combination of presenting symptoms and signs and a history of recent travel to specific geographic regions can lead to early diagnosis of most parasitic infections.
- Parasitic coinfections are particularly common in patients with HIV infection and AIDS.
- Acute malaria should be suspected in patients with irregular high fevers associated with headache, abdominal pain, or respiratory symptoms. Patients who are clinically ill or who are suspected of having falciparum malaria should be hospitalized for evaluation and treatment.
- Cysticercosis should be considered in the differential diagnosis for new-onset seizures.
- Giardiasis should be suspected in patients with diarrhea who recently have been camping or drinking unfiltered mountain spring water.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. World Health Organization: *World Malaria Report 2011*. Geneva: World Health Organization; 2011.
2. Martens P, Hall L: Malaria on the move: Human population movement and malaria transmission. *Emerg Infect Dis* 2000; 6:103-109.
3. Cahill J, et al: Malaria in Rhode Island. *J Travel Med* 2000; 7:112.
4. New medication for severe malaria available. *MMWR Morb Mortal Wkly Rep* 2007; 56:769.
5. Cable RG, Leiby DA: Risk and prevention of transfusion transmitted babesiosis and other tick-borne diseases. *Curr Opin Hematol* 2003; 10:405-411.
6. Wormser GP, et al: The clinical assessment, treatment and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: Clinical guidelines from the Infectious Diseases Society of America. *Clin Infect Dis* 2006; 43:1089-1134.
7. Bottieau F, et al: Imported Katayama fever: Clinical and biological features at presentation and during treatment. *J Infect* 2006; 52:339-345.
8. Mas-Coma S, Barques MD, Valero MA: Fascioliasis and other plant-borne trematode zoonoses. *Int J Parasitol* 2005; 35:1255-1278.
9. Prata A: Clinical and epidemiological aspects of Chagas disease. *Lancet Infect Dis* 2001; 1:92-100.
10. Murray HW, Berman JD, Davies CR, Saravia NG: Advances in leishmaniasis. *Lancet* 2005; 366:1561-1577.
11. Haque R, et al: Diagnosis of amebic liver abscess and intestinal infection with TechLab *Entamoeba histolytica* II antigen detection and antibody test. *J Clin Microbiol* 2000; 38:3235-3239.
12. Mahanty S, Garcia HH: Cysticercosis and neurocysticercosis as pathogens affecting the central nervous system. *Prog Neurobiol* 2010; 91:172-184.
13. Hector H, et al: A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. *N Engl J Med* 2004; 350:249.
14. Brunetti E, Kern P, Vuyitton DA: Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. *Acta Trop* 2010; 144:1-16.
15. Ryan ET, Wilson ME, Kain KC: Illness after international travel. *N Engl J Med* 2002; 347:505.
16. Gottstein B, Pozio E, Nöckler K: Epidemiology, diagnosis, treatment and control of trichinellosis. *Clin Micrbiol Rev* 2009; 22:127-145.
17. Visvesvara GS: Amebic meningoencephalitides and keratitis: Challenges in diagnosis and treatment. *Curr Opin Infect Dis* 2010; 23:590-594.
18. Bisoffi Z, et al: Randomized clinical trial of ivermectin versus thiabendazole for the treatment of strongyloidiasis. *PLoS Negl Trop Dis* 2011; 5:e1254.
19. Namwanje H, Kabatereine NB, Olsen A: Efficacy of single and double doses of albendazole and mebendazole alone and in combination in the treatment of *Trichuris trichiura* in school-age children in Uganda. *Trans R Soc Trop Med Hyg* 2011; 105:586-590.
20. Schulz T, Garcia HH, Kuchta R, Wicht B: Update on the human blood tapeworm (*Diphyllobothrium*) including clinical relevance. *Clin Microbiol Rev* 2009; 22:146-160.
21. Fox L, Beach MJ, Lammie PJ: Treatment for lymphatic filariasis and elephantiasis. *JAMA* 2008; 299:632-633.
22. Soto J, et al: Treatment of American cutaneous leishmaniasis with miltefosine. *Clin Infect Dis* 2001; 33:e57-e61.
23. Hopkins DR, Ruiz-Tiben E, Downs P, Withers PC Jr, Maguire JH: Dracunculiasis eradication: The final inch. *Am J Trop Med Hyg* 2005; 73:669-675.
24. Reddy M, et al: Oral therapy for multiple neglected tropical diseases: A systematic review. *JAMA* 2007; 298:1911-1925.
25. Diawara L, et al: Feasibility of onchocerciasis elimination with ivermectin treatment in endemic foci in Africa: First evidence studies in Mali and Senegal. *PLoS Negl Trop Dis* 2009; 3:e497.
26. Stringer J, Beard CB, Miller RF, Wakefield AE: A new name (*Pneumocystis jiroveci*) for *Pneumocystis* from humans. *Emerg Infect Dis* 2002; 8:891.
27. Kanpittaya J, et al: Different chest radiographic findings of pulmonary paragonimiasis in two endemic countries. *Am J Trop Med Hyg* 2010; 83:924-926.
28. Tanton DD, During S, Chambers S: Pulmonary hyperinfection with *Strongyloides stercoralis* in an immunocompromised patient. *J Gen Intern Med* 2002; 17:72-73.
29. Barbosa P, et al: The oral transmission of Chagas' disease: An acute form of infection responsible for regional outbreaks. *Int J Cardiol* 2006; 112:132.
30. Schijman AG, et al: International study to evaluate PCR methods for detection of *Trypanosoma cruzi* DNA blood samples from Chagas disease patients. *PLoS Negl Trop Dis* 2011; 5:e931.
31. Rassi A, et al: Development and validation of a risk score for predicting death in Chagas' heart disease. *N Engl J Med* 2006; 355:799.
32. Gorbach SL: Traveler's diarrhea. *N Engl J Med* 1982; 307:881.
33. Rossignol JF: *Cryptosporidium* and *Giardia*: Treatment options and prospects for new drugs. *Exp Parasitol* 2010; 124:45-53.
34. Okolie BI, et al: Incidence and detection of parasite ova in appendix from patients with appendicitis in South-eastern *Nigeria. World J Agricult Sci* 2008; 4:795-802.
35. Schulze S, Chokshi RJ, Edavettal M, Tarasov E: Acute abdomen secondary to *Ascaris lumbricoides* infestation of the small bowel. *Am Surg* 2005; 71:505-507.
36. Marcos LA, Terashima A, Gotuzzo E: Update on hepatobiliary flukes. *Curr Opin Infect Dis* 2008; 21:523-530.
37. Greenburg AE, et al: The association between malaria, blood transfusions, and HIV seropositivity in a pediatric population in Kinshasa, Zaire. *JAMA* 1988; 259:545.

www.ketabpezeshki.com 66485457-66963820

Chapter 134

Tick-Borne Illnesses

Edward B. Bolgiano and Joseph Sexton

PERSPECTIVE

Ticks are hematophagous parasites of humans and animals, distributed worldwide. They transmit rickettsial, bacterial, spirochetal, viral, and protozoal diseases and cause disease by means of their own toxins (Table 134-1). As vectors of human disease, ticks rank second in importance only to mosquitoes. People who travel during the summer months may return from endemic areas with tick-borne disease. In addition, reports of infection acquired within urban areas emphasize the need to consider tick-borne illness even in the absence of a history of travel to high-risk areas. Tularemia (category A) and Q fever (category B) are now considered by the Centers for Disease Control and Prevention (CDC) to be significant threats during biologic warfare. For this reason, research involving ticks and their diseases has become increasingly important.

Reports on ticks, their feeding habits, and their possible relation to disease can be found from early history. Pliny (CE 77), in *Historia Naturalis,* referred to "an animal living on blood with its head always fixed and swelling, being one of the animals which has no exit [anus] for its food, it bursts with over-repletion and dies from actual nourishment."[1] Tick-borne illness was first recognized on the North American continent by Native Americans. According to legend, Shoshone men avoided the "evil spirits" that caused illness by sending only women into certain areas of the Rocky Mountain region known to be especially hazardous. The etiologic association of the tick vector with Rocky Mountain spotted fever (RMSF) was noted by missionaries and by early settlers, who named the affliction tick fever. Physicians in Idaho and Montana recorded the classic clinical descriptions of the disease in 1899.

PRINCIPLES OF DISEASE

Identification of Ticks

Ticks are arthropods but not insects. They have eight legs instead of six and generally two fusing body parts—a capitulum (head) and an opisthosoma (abdomen)—instead of three. Identification of an arthropod as a tick and subsequent categorization into family and some genera are not difficult (Figs. 134-1 and 134-2). Speciation requires a trained acarologist. However, tick identification has limited importance in clinical decision-making. Color, which varies seasonally, and size, which varies by amount of blood ingested at the time of presentation, are unreliable criteria for identification purposes.

Physiology of Tick Feeding

An understanding of the physiology of feeding in arthropods is more essential than species identification in assessing the risks of transmission of diseases. Blood-sucking arthropods are divided into two groups according to their method of acquiring blood. The solenophagic feeders insert their mouthparts directly into capillaries to obtain blood. Telmophagic feeders insert their mouthparts indiscriminately, lyse tissue along with capillaries, and feed on the resultant pool of blood, extracellular fluid, and tissue. Ticks and deer flies, for example, are telmophagic feeders, whereas mosquitoes are mostly solenophagic.

Argasid ticks (soft bodied) are short, rapid feeders with preformed distensible endocuticles. They therefore need to feed for only minutes to hours to acquire a full meal. As a result, they tend to be found in nests and burrows where their hosts visit frequently. The genus *Ornithodoros* is the vector for relapsing fever. Ixodid ticks (hard bodied) include the genera *Ixodes, Dermacentor, Amblyomma,* and *Rhipicephalus,* which are those responsible for the remainder of human tick-borne diseases discussed in this chapter. These ticks need to form a new exocuticle (phase I of feeding) and thus feed slowly during the first 12 to 24 hours. Once it is fully formed, the new endocuticle allows rapid feeding (phase II) and significant engorgement.

In the capitulum of ticks, the sucking structure, consisting of the chelicerae, is surrounded by a sheath from which it protrudes during feeding. Sense organs on the capitulum, or podomeres, help locate a host by means of chemoreceptors. Hair, or setae, on the legs act as tactile and temperature receptors. A special sensory structure, Haller's organ, is located on the first set of legs and is a humidity and olfactory receptor.

When a suitable location is found, adjacent cheliceral digits incise the skin, and the chelicerae and barbed hypostome are inserted. Two mechanisms prevent the tick from being removed from the skin: the barbed hypostome and a cement-like salivary secretion from the base of the hypostome, composed of lipoproteins and glycoproteins. This allows ixodid ticks to attach for as long as 2 weeks. Because argasids are much faster feeders, they secrete no cement substance.

During a bite, trauma and salivary gland products can cause local inflammation, hyperemia, edema, hemorrhage, and skin thickening. The saliva injected during feeding contains many different substances. Both hard and soft ticks produce a histolytic secretion that liquefies tissue, which is then sucked into the gut. Eventually, the secretion breaks down the walls of the dermal blood vessels and the released blood is ingested. To prevent hemostasis, the saliva contains a thrombokinase inhibitor, apyrase,

www.ketabpezeshki.com 66485457-66963820

Table 134-1 Tick-Borne Illnesses

TYPE	DISEASE	PATHOGEN	ARTHROPOD VECTOR	GEOGRAPHIC DISTRIBUTION
Bacterial (including spirochetal)	Lyme disease	*Borrelia burgdorferi*	*Ixodes scapularis* *Ixodes pacificus* *Ixodes ricinus*	Northeastern United States Upper midwestern United States Pacific Coast Europe
	Tularemia	*Francisella tularensis*	*Ixodes scapularis* *Amblyomma americanum* *Dermacentor variabilis*	Southwest central United States
Rickettsial	Rocky Mountain spotted fever	*Rickettsia rickettsii*	*Dermacentor andersoni* *Dermacentor variabilis* *Rhipicephalus sanguineus*	Predominantly southeastern United States Arizona
	Q fever	*Coxiella burnetii*	*Dermacentor andersoni*	Worldwide
	Human monocytic ehrlichiosis	*Ehrlichia chaffeensis*	*Amblyomma americanum*	South central and southeastern United States
	Human granulocytic anaplasmosis	*Anaplasma phagocytophilum*	*Ixodes scapularis* *Ixodes pacificus*	New England and north central United States Northern California
Parasitic (protozoal)	Babesiosis	*Babesia microti*	*Ixodes scapularis*	Coastal New England
Viral*	Colorado tick fever	Orbivirus	*Dermacentor andersoni*	Mountain areas of western United States and Canada
Miscellaneous	Tick paralysis	Ixobotoxin	*Dermacentor andersoni* *Dermacentor variabilis* *Amblyomma americanum* *Ixodes scapularis* *Ixodes pacificus* *Ixodes holocyclus*	Worldwide

*Many other viruses are transmitted to humans by ticks. In the United States, only Colorado tick fever occurs with any significant frequency.

which prevents platelet aggregation by depleting adenosine diphosphate, prostaglandin E_2, and prostacyclin (prostaglandin I_2) to prevent vasoconstriction, and cytolysins. *Ixodes scapularis* also secretes a carboxypeptidase that destroys other inflammatory mediators, such as anaphylatoxins and bradykinin, as well as anti–complement C3 factor. These other mediators normally would cause further inflammation, which would enhance hemostasis. All infectious agents as well as excretory liquids from some argasids are transmitted through this saliva. Transmission of a disease from *Ixodes* ticks is unlikely if the tick is not yet engorged with blood at the time of removal. Likewise, a tick removed within a few hours after attachment is unlikely to transmit disease. The neurotoxins responsible for tick paralysis also are found in tick saliva.

The local physiologic changes associated with tick feeding produce the characteristic 1- to 4-mm erythematous mark typically seen on the skin after a tick bite. This is a common finding from most blood-sucking arthropods. The mark should not be confused with certain rashes associated with disease progression, for example, erythema migrans. Informing patients of this difference may be reassuring.

LYME DISEASE

Perspective

Lyme disease, the most common vector-borne disease in the United States, is a tick-borne illness caused by the spirochete *Borrelia burgdorferi*. The story of Lyme disease began in 1975, when health officials at Connecticut's State Department of Health and physicians at Yale University were alerted by two skeptical mothers to an unusually large number of cases of apparent juvenile rheumatoid arthritis occurring in their small coastal community of Old Lyme, Connecticut. Investigation led to the description of a "new" entity called Lyme arthritis.[2]

Lyme disease occurs worldwide and has been reported on every continent except Antarctica.[3] It now accounts for more than 95% of all reported cases of vector-borne illness in the United States. The actual overall incidence of Lyme disease is unknown because many cases go unreported. Lyme disease occurs in people of all ages but is more common in children younger than 15 years and in adults 30 to 60 years of age.[4]

Persons at greatest risk live or vacation in endemic areas. In the United States, three distinct endemic foci are recognized: the northeastern coastal, mid-Atlantic, and north central states. During 2000, a total of 17,730 cases of Lyme disease were reported from 44 states and the District of Columbia. Twelve states—Connecticut, Rhode Island, New Jersey, New York, Delaware, Pennsylvania, Massachusetts, Maryland, Wisconsin, Minnesota, New Hampshire, and Vermont—accounted for 95% of cases reported in the nation (Fig. 134-3).[4]

The principal tick vectors are *I. scapularis* in the Northeast and Midwest and *Ixodes pacificus* in the West. Nymphal *Ixodes* ticks satisfy all known epidemiologic requirements for the zoonosis as it exists in nature. There is no compelling evidence for alternative arthropod vectors of infection.

The *I. scapularis* population density depends on that of its preferred hosts: the white-footed field mouse, *Peromyscus leucopus*, for the larval and nymphal forms; and the white-tailed deer, *Odocoileus virginianus*, for the adult form. The white-footed mouse readily becomes infected after being bitten by infected ticks and remains highly infectious for periods that approach its life span in nature, thereby providing an important reservoir for *B. burgdorferi*. Adult *I. scapularis* ticks feed primarily on deer, which are key hosts in the tick life cycle and in whose fur the adult tick may survive the winter. The repopulation of several areas in the United States by white-tailed deer preceded the recent emergence of Lyme disease in those regions.

Although all stages of the tick may feed on humans, the nymph is primarily responsible for the transmission of Lyme disease. It is not surprising that more than two thirds of patients with Lyme disease do not recall a tick bite, in view of the small size (1-2 mm) of nymphs (Fig. 134-4). The nymph feeds in the spring and

www.ketabpezeshki.com 66485457-66963820

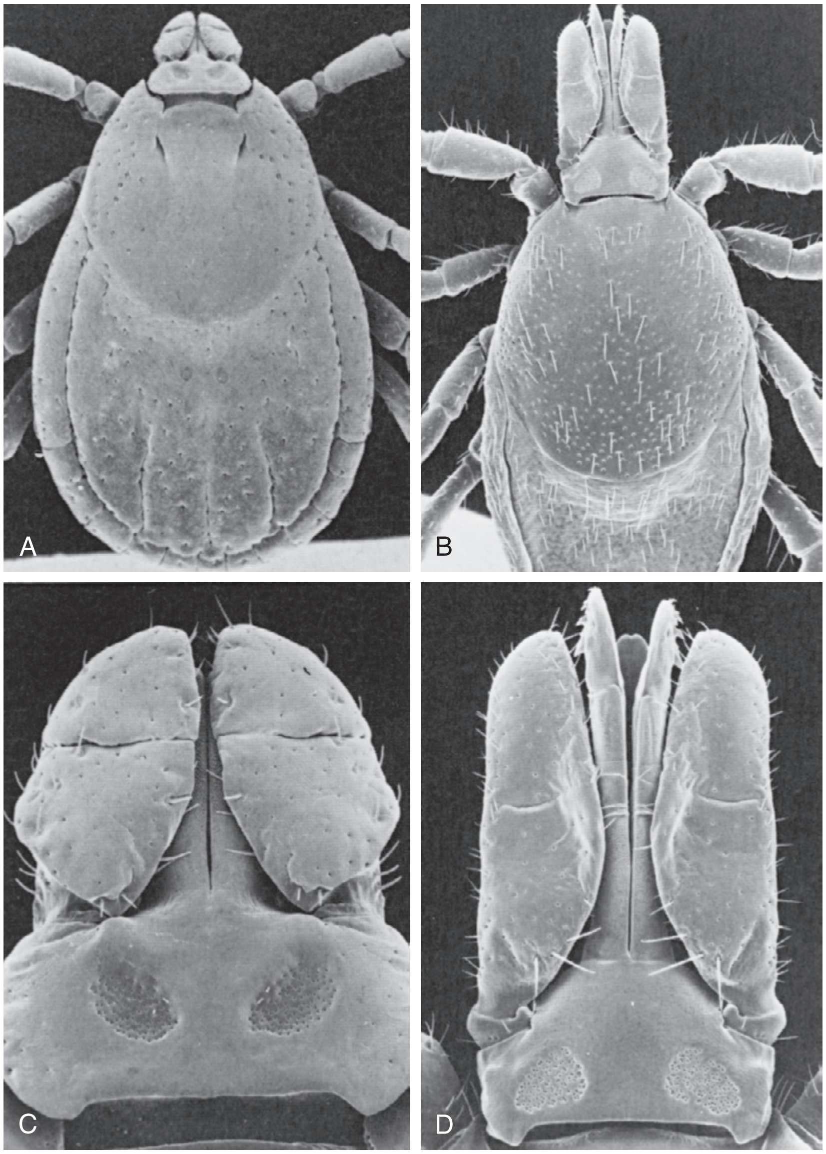


Figure 134-1. Scanning electron micrographs of two tick species. **A,** Dorsal view of adult female *Dermacentor variabilis*. **B,** Dorsal view of adult female *Ixodes scapularis*. **C,** Dorsal close-up view of *D. variabilis* head. **D,** Dorsal close-up view of *I. scapularis* head. (Courtesy Dr. J. E. Keirans, Georgia Southern University, Statesboro, Georgia.)

summer, which correlates with a peak incidence of early Lyme disease occurring between May and August. In addition, recreational and occupational exposure is greatest during this time. Later manifestations of Lyme disease may appear throughout the year.

Principles of Disease

The spirochete *B. burgdorferi* persists and multiplies in the midgut of its tick vector, *I. scapularis*. Transmission of the spirochete to humans occurs during feeding, generally about 2 days after attachment. The mechanism of transmission probably is inoculation with infectious saliva or, alternatively, with tick gut fluids periodically regurgitated during the feeding process.

After an incubation period that lasts several days to several weeks, spirochetemia develops, and *Borrelia* organisms may migrate outward in blood or lymph to virtually any site in the body. The spirochete appears to be tropic for synovial tissue, skin, and cells of the nervous system, but the mechanism of this tropism is not yet understood. Infection by the spirochete itself accounts for early clinical manifestations. It remains unclear whether late disease manifestations require the continued presence of viable spirochetes or whether an ongoing host immune response to initial infection is sufficient to cause some late disease manifestations. Although the exact roles of infecting spirochetes, spirochetal antigens, and host immune responses are unknown, it is likely that persistent live spirochetes are responsible for most later manifestations of the disease. The variable severity of Lyme disease may in part result from genetic variations in the human immune system. Patients with chronic Lyme arthritis have an increased frequency of human leukocyte antigen (HLA) specificity, in particular for HLA-DR4 and, less often, HLA-DR2.

Clinical Features

Lyme disease, a multisystem disorder, can be classified into three stages: early localized, early disseminated, and late disease. Virtually any clinical feature may occur alone or recur at intervals, and some patients who had no early symptoms may have late symptoms. The disorder usually begins with a rash and associated

www.ketabpezeshki.com 66485457-66963820

constitutional signs and symptoms, suggesting a "viral syndrome" (early Lyme disease). Neurologic, joint, or cardiac manifestations may emerge weeks to months later (early disseminated Lyme disease), and chronic arthritic and neurologic abnormalities may appear weeks to years later (late Lyme disease). The time course for the clinical features of untreated Lyme disease is illustrated in Figure 134-5.

Early Lyme Disease

Ticks may attach to human hosts at the initial point of contact (generally around ankle level) or move about until they encounter an obstruction. The groin, popliteal fossae, gluteal folds, axillary folds, and earlobes are common sites of attachment. After transmission of *B. burgdorferi* through a tick bite, the initial site of infection is the skin at the site of the bite. After an incubation period of approximately 1 week (range, 1-36 days), the spirochetes cause a gradually spreading localized infection in skin and a resultant skin lesion, erythema migrans. Erythema migrans is the most

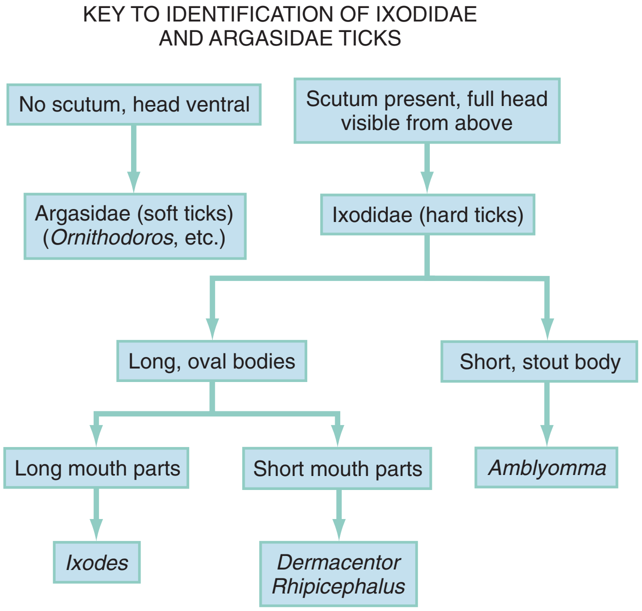


Figure 134-2. Identification scheme for genera within Ixodidae and Argasidae, the two primary disease-transmitting families of ticks.

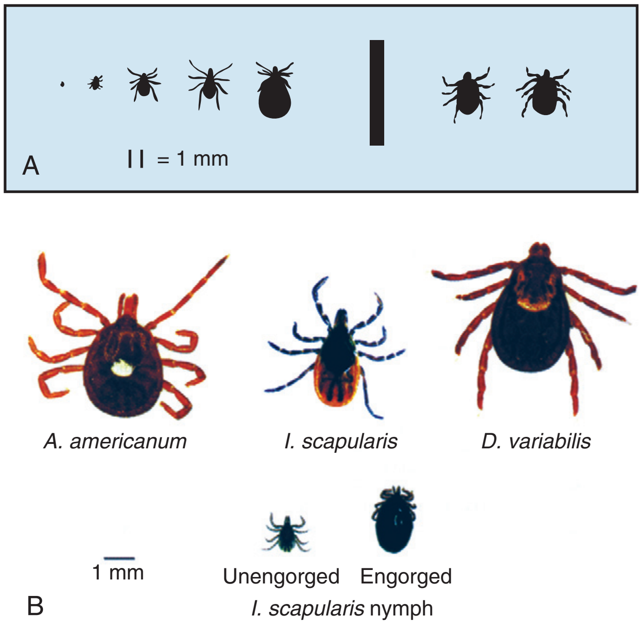


Figure 134-4. A *(left to right),* Larva, nymph, adult male, adult female, and engorged adult female *Ixodes* ticks and adult male and female *Dermacentor* ticks. Actual size. **B,** Adult female *Amblyomma americanum* (Lone Star tick), adult female and nymphal *Ixodes scapularis* (deer tick), and adult female *Dermacentor variabilis* (dog tick). (From Hayes EB, Piesman J: How can we prevent Lyme disease? N Engl J Med 348:2424, 2003.)

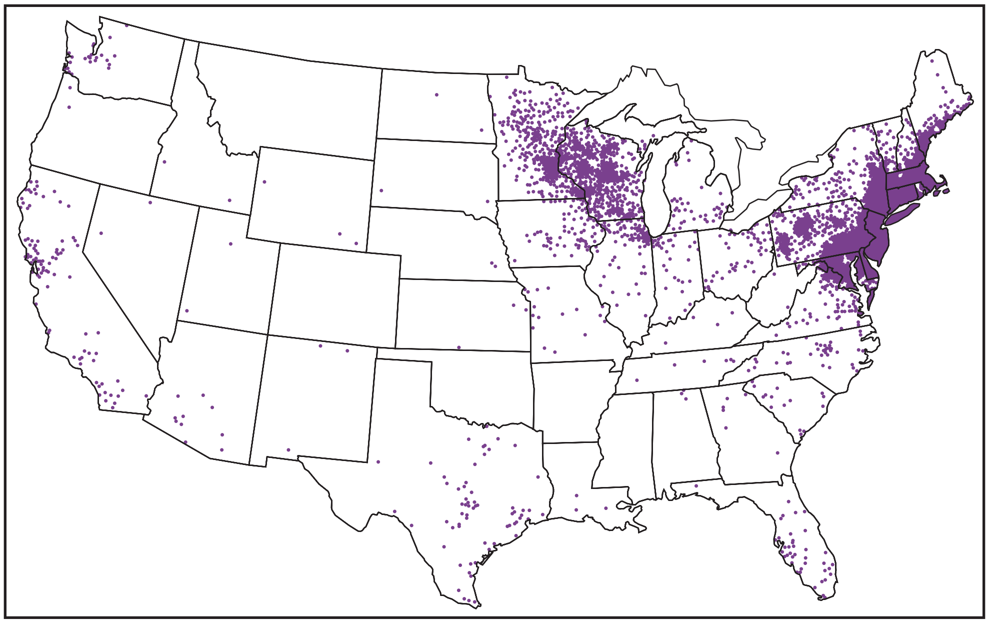


Figure 134-3. Number of newly reported Lyme disease cases, by county in the United States in 2005. *N* = 23,174; the county was unknown for 131 other cases. One dot was placed randomly within the county of patient residence for each reported case. (From Centers for Disease Control and Prevention: Lyme disease—United States, 2003-2005. MMWR Morb Mortal Wkly Rep 56:573, 2007.)

www.ketabpezeshki.com 66485457-66963820

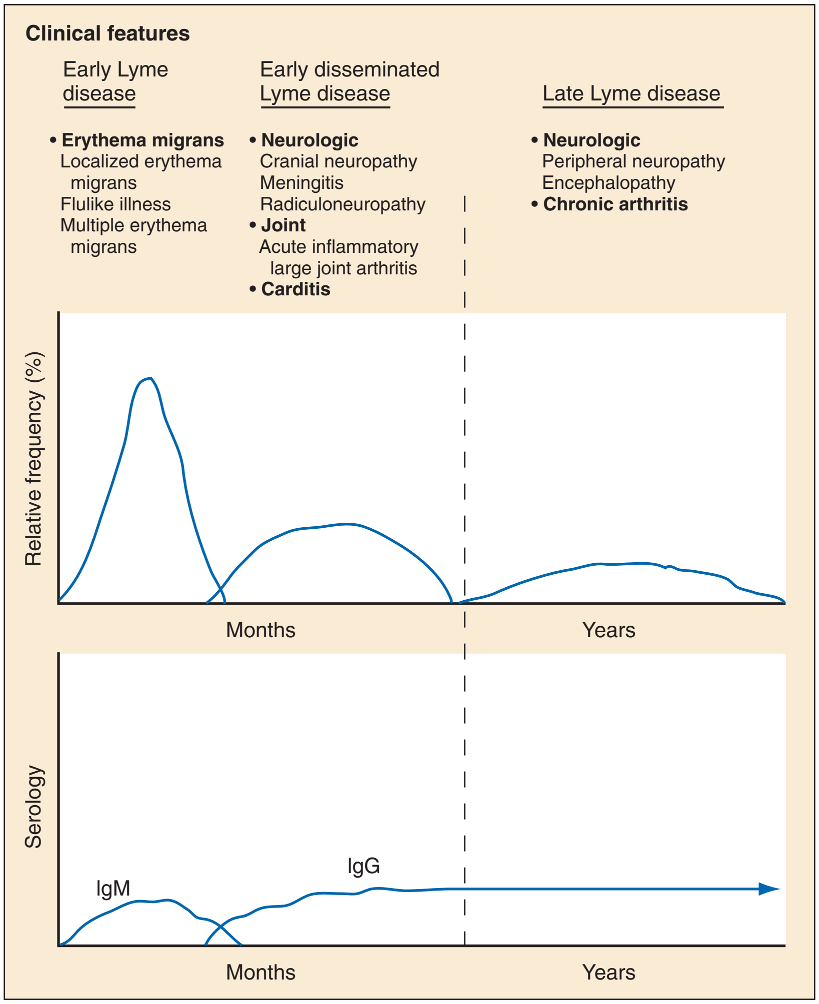


Figure 134-5. Natural history of serologic response, with clinical features, in untreated Lyme disease. *IgG,* immunoglobulin G; *IgM,* immunoglobulin M. (Redrawn from Rahn DW: Natural history of Lyme disease. In Rahn DW, Evans J [eds]: Lyme Disease. Philadelphia, American College of Physicians, 1998, pp 35-48.)

characteristic clinical manifestation of Lyme disease and is recognized in 90% or more of patients. Erythema migrans may go unnoticed if the entire skin surface is not examined.[5] The characteristic rash begins at the site of the tick bite with an erythematous papule or macule. The lesion expands gradually (1-2 cm/day, a rate of expansion slower than that of cellulitis). The patch of erythema may be confluent or may have bands of normal-appearing skin. Central clearing may occur but is not an invariable feature. The lesion borders usually are flat but may be raised. The lesions generally are sharply demarcated and blanch with pressure. Most lesions are oval or round, but triangular and elongated patches may occur. In patients presenting 1 to 7 days after the appearance of lesions, the average lesion size is approximately 8 by 10 cm (range, 2 by 3 cm to 25 by 25 cm). In some cases, the center of some early lesions becomes red and indurated or vesicular and necrotic. The lesion is warm to the touch and may be described by the patient as nontender to minimally tender (Fig. 134-6).

Hematogenous spread of viable spirochetes (not additional tick bites) may result in one or more secondary lesions. These secondary lesions are smaller, migrate less, and typically spare the palms and soles. In all, 10 to 15% of patients have more than 20 such lesions; on rare occasions they may number more than 100. Blistering and mucosal involvement do not occur. The primary and secondary skin lesions generally fade after approximately 28 days (range, 1 week to 14 months) without treatment and within several days of antibiotic therapy. Recurrent lesions may develop in patients who do not receive antibiotic therapy but apparently not in those who receive appropriate antibiotics.

Constitutional signs and symptoms commonly appear in early Lyme disease (Table 134-2). Malaise, fatigue, and lethargy are most common (seen in approximately 80% of patients) and may be severe. Fever typically is low grade and intermittent. Lymphadenopathy usually is regional in the distribution of erythema migrans or may be generalized; splenomegaly may occur. Musculoskeletal complaints, such as arthralgias and myalgias, are common, and the discomfort typically is short-lived and migratory, sometimes lasting only hours in one location. Frank arthritis may occur at this stage but is rare.

Clinical manifestations of meningeal irritation are frequently seen. Headache, the most common symptom, usually is intermittent and localized. Nausea, vomiting, and photophobia occasionally accompany the headache. Kernig's and Brudzinski's signs typically are absent, and neck stiffness usually is noted only on extreme forward flexion. At this stage, the neurologic examination and cerebrospinal fluid (CSF) assessment usually yield normal findings.

Signs and symptoms of hepatitis, including anorexia, abdominal pain, right upper quadrant tenderness, nausea, and vomiting, may be present. Mild pharyngitis also may be present, but other upper respiratory symptoms, such as rhinorrhea, do not occur.

www.ketabpezeshki.com 66485457-66963820

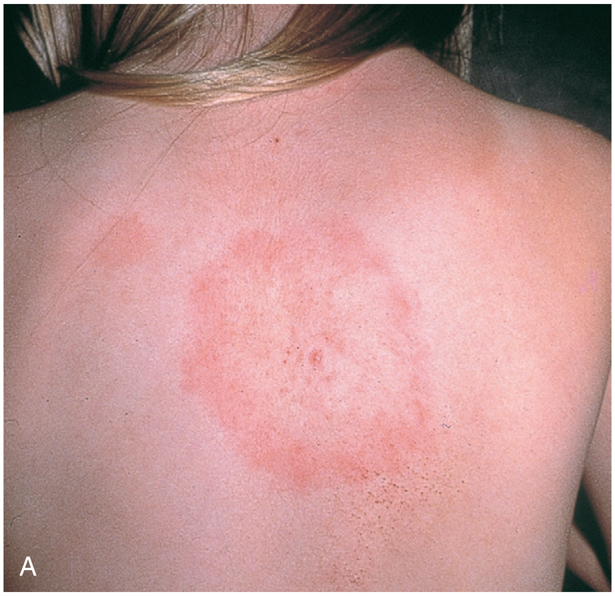


Figure 134-6. Lyme disease usually begins with a slowly expanding skin lesion, erythema migrans, which occurs at the site of the tick bite. **A,** A classic "bull's-eye" or target lesion with partial central clearing, a bright red outer border, and a "target" center. **B,** Expanding erythematous lesion, with central clearing, on trunk. (**A** courtesy Michael O. Murphy, MD. From Malawista SE, Bockenstedt LK: Lyme disease. In Goldman L, et al [eds]: Cecil Medicine. Philadelphia, WB Saunders, 2008, pp 2289-2294; **B** courtesy John Cook, MD. From Goldstein BG, Goldstein AE [eds]: Practical Dermatology, ed 2. St. Louis, Mosby, 1997, p 63.)

Table 134-2 Early Clinical Manifestations of Lyme Disease

MANIFESTATION	NO. OF PATIENTS (%)
Signs	
Erythema chronicum migrans*	314 (100)
Multiple annular lesions	150 (48)
Lymphadenopathy	
Regional	128 (41)
Generalized	63 (20)
Pain on neck flexion	52 (17)
Malar rash	41 (13)
Erythematous throat	38 (12)
Conjunctivitis	35 (11)
Symptoms	
Malaise, fatigue, lethargy	251 (80)
Headache	200 (64)
Fever and chills	185 (59)
Stiff neck	151 (48)
Arthralgias	150 (48)
Myalgias	135 (43)
Backache	81 (26)
Anorexia	73 (23)
Sore throat	53 (17)
Nausea	53 (17)
Dysesthesia	35 (11)
Vomiting	32 (10)

From Steere AC, et al: The early clinical manifestations of Lyme disease. Ann Intern Med 99:76, 1983.
*Required for inclusion in this study.

Although the systemic symptoms of early Lyme disease often are described as "flulike," this term can be misleading because clinically significant cough usually does not occur. Conjunctivitis develops in approximately 10% of patients.

The incidence of Lyme disease without erythema migrans appears to be approximately 10%.[5] Because of the variety of nonspecific signs and symptoms at this stage, in the absence of the characteristic rash or history of tick bite, early Lyme disease may be easily confused with a viral or collagen vascular disease. The intermittent and rapidly changing nature of the early signs and symptoms of Lyme disease may be a helpful distinguishing feature, especially in a patient from an endemic area. In untreated disease, early symptoms usually last for several weeks but may persist for months.

Acute Disseminated Infection

Shortly after disease onset, hematogenous spread can cause a variety of systemic signs and symptoms and result in secondary sites of infection. Organ systems commonly affected are the nervous system, heart, and joints. Less commonly, the eyes, liver, skeletal muscle, subcutaneous tissue, and spleen are infected.

Neurologic Manifestations. A relatively symptom-free interval usually occurs between early and disseminated infection; however, neurologic signs and symptoms may be the presenting manifestations of Lyme disease or may overlap with early or late manifestations. Beginning at an average of 4 weeks (range, 0-10 weeks) after the onset of erythema migrans, neurologic involvement occurs in approximately 15% of untreated patients.

The most common neurologic manifestation of Lyme disease is a fluctuating meningoencephalitis with superimposed symptoms of cranial neuropathy, peripheral neuropathy, or radiculopathy. A triad of meningitis, cranial neuropathies (usually Bell's palsy), and radiculopathy has been described, but each entity may occur alone. Headache of variable intensity usually is present; other signs and symptoms of a mild meningoencephalitis may be noted, including lethargy or irritability, sleep disturbances, poor concentration, and memory loss. At this point, the disease often is misdiagnosed as viral meningitis. As in early disease, Kernig's and Brudzinski's signs are absent and computed tomography findings are normal. Unlike in early disease, however, findings on CSF examination often are abnormal, with a lymphocytic pleocytosis and moderately elevated protein level. CSF glucose concentration usually is normal. Intrathecal *B. burgdorferi* antibody (usually IgG or IgA) is present in 80 to 90% of patients. CSF polymerase chain reaction (PCR) assay results are positive in less than half of

www.ketabpezeshki.com 66485457-66963820

patients,[6] probably reflecting the low number of organisms usually present in spinal fluid. Routine testing of CSF by PCR is not recommended.

Cranial neuropathies are common, occurring in approximately 50% of patients with Lyme meningitis; the seventh nerve is usually involved. Other cranial nerves are affected less often. Bell's palsy is bilateral in approximately one third of patients. Its duration usually is weeks to months, and the condition generally resolves spontaneously without treatment.

Peripheral nervous system manifestations also may occur in early disseminated Lyme disease. The spinal root and plexus and the peripheral nerves may be involved in the form of thoracic sensory radiculitis, brachial plexitis, mononeuritis, and motor radiculoneuritis in the extremities. Patients may complain of weakness, pain, or dysesthesia. Examination may reveal loss of reflexes. Involvement of the extremities usually is asymmetrical, but cervical and thoracic dermatomes may be affected. Other rare neurologic abnormalities described in association with Lyme disease include chorea, transverse myelitis, ataxia, and pseudotumor cerebri. Cerebral vasculitis associated with Lyme disease also has been reported.

Cardiac Manifestations. Cardiac involvement in Lyme disease is uncommon. Estimates of the incidence of carditis in untreated patients who have Lyme disease range from 4 to 10%. The average time from initial illness to the development of carditis typically is 3 to 5 weeks (range, 4 days to 7 months). Direct myocardial invasion has been demonstrated with endomyocardial biopsy. Electrophysiologic testing has demonstrated widespread involvement of the conduction system.

The most common cardiac manifestation of Lyme disease is atrioventricular (AV) block, although conduction defects may involve any level of the conducting system. Myopericarditis, tachydysrhythmias, and ventricular impairment occur less often. In a review of 105 reported cases of Lyme carditis, 49% of cases were third-degree AV block, 16% were second-degree, and 12% were first-degree.[7] The degree of AV block seen in a specific patient may fluctuate rapidly.

A commonly observed feature of AV block in patients with Lyme carditis is its gradual resolution, resembling that occurring after an acute inferior wall myocardial infarction and presumably related to the resolution of inflammation. Assessment of the level of the AV block is important to determine the prognosis of a patient with Lyme carditis. In most cases, block appears to be at or above the level of the AV node; therefore, the prognosis is favorable. However, infranodal AV block does occur and may be characterized by slow escape rhythms of wide QRS pattern, asystole, or fluctuating left and right bundle branch block. Other electrocardiographic findings include nonspecific ST and T wave abnormalities and intraventricular conduction delay.

Patients with high-degree AV block usually are symptomatic. Symptoms include lightheadedness, palpitations, syncope, chest pain, and dyspnea on exertion. Physical examination may reveal flow murmurs and murmurs of mild mitral regurgitation, pericardial friction rub, or evidence of congestive heart failure. Associated left ventricular dysfunction may be present and has been documented by two-dimensional echocardiography and radionuclide studies; in most reported cases, it has been mild and transient.

Arthritis. Although it is classically considered a sign of late Lyme disease, acute arthritis may begin during the acute disseminated stage. Monarticular or oligoarticular arthritis, primarily affecting large joints, especially the knee, may develop weeks to months after the onset of initial illness. In an early study of the natural history of Lyme arthritis, approximately 50% of untreated patients experienced one episode or multiple intermittent attacks of arthritis. Acute arthritis typically is monarticular, with involvement of only one knee. The shoulder, elbow, temporomandibular joint, ankle, wrist, hip, and small joints of the hands and feet are involved less commonly. Episodes of arthritis typically are brief (lasting weeks to months) and separated by variable periods of remission.

Arthrocentesis generally is nondiagnostic, yielding an inflammatory synovial fluid with a mean white blood cell count of approximately 25,000 cells/μL (75% polymorphonuclear leukocytes). Higher white blood cell counts have been reported, simulating septic arthritis. The synovial glucose concentration usually is normal, and protein levels are variable, ranging from 3 to 8 g/dL. Cultures of the fluid rarely identify the causative spirochete. Complement level generally is greater than one third that of serum. Synovial biopsy reveals hypertrophy, vascular proliferation, and a mononuclear cell infiltrate. Findings therefore are similar to those in rheumatoid arthritis, except that rheumatoid factor and antinuclear antibody assays yield a negative result in Lyme arthritis. Radiography may reveal nonspecific abnormalities such as juxta-articular osteoporosis, cartilage loss, cortical or marginal bone erosions, and joint effusions.

Ophthalmic Manifestations. Ocular involvement also may be seen in early disseminated disease; manifestations include conjunctivitis, keratitis, choroiditis, retinal detachment, optic neuritis, and blindness. These findings also may be seen in late disease.

Late Lyme Disease

The chronic phase of Lyme disease is characterized by arthritic and less commonly neurologic symptoms. Transition from a pattern of episodic inflammation in early disease to a more indolent persistent inflammation is observed over time. The term *chronic* (or *late*) *Lyme disease* is used to describe continuous inflammation in an organ system for more than 1 year.

A pattern of exacerbation and remission of arthritis may extend for several years, with a gradual tendency toward less frequent and less severe occurrences. The spontaneous long-term remission rate approximates 10 to 20% annually in untreated patients. However, patients commonly have episodes of periarticular involvement, arthralgias, or fatigue interspersed between attacks of frank arthritis. During the second or third year of illness, attacks of joint swelling sometimes become longer in duration, lasting months rather than weeks. Chronic arthritis eventually develops in approximately 10% of patients.[8]

Late neurologic complications include a wide variety of abnormalities of the central and peripheral nervous systems as well as fatigue syndromes. Diagnosis may be difficult because of the large number of other neurologic conditions that Lyme disease may imitate and because late neurologic symptoms may be the first symptoms of the disease. The manifestations of chronic neuroborreliosis usually appear months to years after the onset of infection.

The most common late neurologic manifestation of Lyme disease is a chronic encephalopathy that is manifested as a mild to moderately severe impairment of memory and learning. Hypersomnolence and mild psychiatric disturbances (depression, irritability, or paranoia) also may develop.[6]

Peripheral nervous system manifestations often are seen in late disease, with involvement of cranial nerves, spinal roots, spinal plexuses, and peripheral nerves. A predominantly sensory polyradiculoneuropathy that is manifested as either radicular pain or distal paresthesia is common. Significant overlap occurs with early symptoms. Less commonly, a demyelinating condition resembling multiple sclerosis may appear in late disease. Symptoms are variable and, as in multiple sclerosis, may undergo exacerbations and remissions. Computed tomography and magnetic resonance imaging may reveal multiple white matter lesions.[9]

Chronic inflammation also may occur in the skin, causing a seldom-recognized late cutaneous manifestation of Lyme disease,

www.ketabpezeshki.com 66485457-66963820

acrodermatitis chronica atrophicans. This condition usually involves the skin of distal extremities at the site of a tick bite. It is characterized in its initial stages by an edematous infiltration, which progresses to an atrophic lesion resembling localized scleroderma in its more established form. *B. burgdorferi* has been demonstrated in the skin of patients with acrodermatitis chronica atrophicans as well as positive findings on serologic studies.

Diagnostic Strategies

The diagnosis of Lyme disease should be considered on the basis of clinical and epidemiologic features. Identification of the disorder often is difficult, especially in the early stage. A history of tick bite is elicited in only approximately one third of cases. Erythema migrans is present in most patients and, in endemic areas, is considered diagnostic. Isolated late symptoms may emerge months after the initial infection, however, and the patient may not recall the rash. The disease should be considered in patients who live in or have visited an endemic area and who present during the summer months with nonspecific symptoms suggesting a viral illness or meningitis. In addition, the development of monarticular arthritis, multiple neurologic abnormalities, or heart block in previously healthy patients should raise the suspicion of Lyme disease.

Results of routine laboratory studies are nonspecific, and such studies generally are not helpful in diagnosis of Lyme disease. Abnormalities may include an elevated erythrocyte sedimentation rate, mild anemia, total white blood cell count in the normal range with a decreased absolute lymphocyte count, microhematuria, proteinuria, and increased alanine transferase level. Cultures of blood, tissue, and body fluids (including CSF and synovial fluid) for *B. burgdorferi* and direct visualization techniques are difficult to perform properly and have such a low yield that they are not clinically useful.[10]

Serologic testing is the most practical and useful means of confirming a clinical diagnosis of Lyme disease, but it is not without limitations. Results of serologic tests should be interpreted cautiously within the clinical context, and such tests should be regarded as only adjuncts in the diagnostic process. Current serologic tests measure host antibody response (for both IgG and IgM) to *B. burgdorferi*. Problems with the performance of these tests and interpretation of findings often result in diagnostic confusion. False-negative and, especially, false-positive results are common. The antibody response to *B. burgdorferi* develops slowly. The peak of IgM titers appears between 3 and 6 weeks after the onset of illness. Earlier in the course of the illness, IgM titers may be negative. IgM antibody usually returns to nondiagnostic levels 4 to 6 weeks after the peak, but elevations may persist. IgG antibody may be detectable 2 months after exposure and peaks at approximately 12 months. Early antibiotic therapy may blunt or even abolish the antibody response.

A two-tier strategy is recommended for serologic testing: a sensitive enzyme-linked immunosorbent assay (ELISA) followed by a Western blot (immunoblot). Positive or equivocal ELISA results should be followed by a Western blot. If the ELISA is negative, no further testing is necessary.

IgM and IgG immunoblots should be obtained if early disease is suspected. If late disease is suspected, IgG Western blot alone should be obtained. Criteria for positive Western immunoblotting (requiring the presence of bands at particular locations) have been adopted by the CDC.[10]

About one third of patients with early localized Lyme disease (erythema migrans) are seropositive at the time of presentation by the two-tier method. Patients with skin lesions typical of erythema migrans do not require confirmatory serologic testing, and the rash itself is sufficient for the diagnosis to be made. If the cause of the rash is uncertain, acute- and convalescent-phase serologic testing may be considered, with the convalescent sample drawn 2 to 4 weeks after the acute sample. In contrast to early localized disease, most patients with early disseminated Lyme disease or late Lyme disease are seropositive.

IgG (and occasionally IgM) antibody may persist for several years after adequate treatment and symptom resolution. Persistent seropositivity is not diagnostic of ongoing infection. Even an IgM response cannot be interpreted as a demonstration of recent infection or reinfection unless the appropriate clinical characteristics are present. IgG antibody developed after natural infection does not always confer immunity against future infection by *B. burgdorferi*. Patients who are treated for erythema migrans may become reinfected; patients with Lyme arthritis, however, usually have high antibody titers to many spirochetal proteins and seem not to become reinfected.[11]

False-positive ELISA results are common. Serologic cross-reactivity can occur between *B. burgdorferi* and other spirochetes, most notably *Treponema pallidum*. False-positive results for Lyme disease also can occur with relapsing fever, gingivitis, leptospirosis, enteroviral and other viral illnesses, rickettsial diseases, autoimmune diseases, malaria, and subacute bacterial endocarditis. In addition, it is estimated that up to 5% of the normal population will "test positive" for Lyme disease by ELISA. Bayes' theorem states that if the pretest likelihood of the disease is low, the positive predictive value is low: a positive test result is more likely to be a false-positive result. For this reason, screening serologic tests are not indicated in the absence of objective clinical evidence of Lyme disease.[12]

Patients suspected of having acute Lyme neuroborreliosis should be evaluated with serologic tests and routine CSF examination. Paired serum and CSF samples should be obtained to evaluate for intrathecal production of antibody, although most patients with neuroborreliosis have positive results on serum serologic testing, thereby making additional laboratory confirmation with CSF serology unnecessary.[12] PCR has low sensitivity when it is performed on CSF and is not routinely recommended.[6] PCR assay is superior to culture for the detection of *B. burgdorferi* in synovial fluid and has a sensitivity of 73% and specificity of 99% in untreated Lyme arthritis.[13]

Differential Considerations

Although Lyme disease is manifested in many ways, each stage has characteristic clinical findings that are helpful in narrowing the scope of a differential diagnosis that at first may seem overwhelmingly broad. Early Lyme disease (erythema migrans and associated constitutional symptoms) may be easily confused with a variety of other diseases, especially if the characteristic rash of erythema migrans is absent. A common clinical presentation is an influenza-like illness with headache, nausea, fever, chills, myalgias, arthralgias, stiff neck, and anorexia, occurring during the summer months. Even in endemic areas during the summer months, most patients with such symptoms do not have Lyme disease. When headache and stiff neck are the predominant symptoms, the principal diagnostic distinction to be made is between Lyme disease and the enteroviral diseases (and other causes of aseptic meningitis). The enteroviral diseases also have their peak incidence during the summer months; however, diarrhea, commonly associated with enteroviral infection, is not a feature of Lyme disease. Abdominal pain, anorexia, and nausea suggest hepatitis; sore throat, adenopathy, and fatigue suggest mononucleosis; and myalgias and arthralgias suggest connective tissue diseases.

The rash of erythema migrans is characteristic of but not pathognomonic for Lyme disease. Some patients are not aware of having had such a rash, and in others, its appearance is atypical. Secondary lesions may be confused with the target lesions

www.ketabpezeshki.com 66485457-66963820

of erythema multiforme, which generally are smaller and nonexpanding. Erythema multiforme also may involve the mucous membranes, palms, and soles; erythema migrans does not. The presence of a malar rash in association with Lyme disease suggests systemic lupus erythematosus. Erythema nodosum generally causes more painful induration than erythema migrans and has a predilection for the extensor surfaces of the legs. Erythema marginatum of acute rheumatic fever also is in the differential diagnosis for erythema migrans; the Lyme disease rash differs in comprising generally fewer, larger, less evanescent lesions that migrate more slowly. Atypical erythema migrans manifesting as a urticarial rash may suggest hepatitis B infection or serum sickness. Other cutaneous entities in the differential diagnosis for erythema migrans include cellulitis, fungal infection, fixed drug eruptions, plant dermatitis, and insect or spider bites. Lyme disease should be considered in a patient with any atypical rash accompanied by a viral syndrome or meningitis-like illness, especially during the months of peak incidence.

Acute rheumatic fever, coronary artery disease, or viral myocarditis may be suggested by the cardiac manifestations of Lyme disease. The carditis of Lyme disease, like the carditis of rheumatic fever, may follow pharyngitis and migratory polyarthritis. Erythema marginatum usually occurs with the onset of arthritis, in contrast with erythema migrans, which usually precedes the carditis. Although some patients with Lyme disease may satisfy the clinical aspects of the Jones criteria for acute rheumatic fever, they lack evidence of a preceding streptococcal infection; in addition, valvular involvement is not a prominent feature of Lyme carditis.

The differential diagnosis of the neurologic manifestations caused by Lyme disease is extensive. Considerations include aseptic meningitis, herpes simplex encephalitis, Bell's palsy of other causes, multiple sclerosis, Guillain-Barré syndrome, dementia, primary psychosis, cerebral vasculitis, and brain tumor. Neurologic symptoms often occur in the absence of any epidemiologic clues or preceding clinical symptoms suggestive of Lyme disease, making the diagnosis particularly challenging.

Lyme arthritis may mimic other immune-mediated disorders. The arthritis of Lyme disease generally is asymmetrical, oligoarticular, and episodic. In contrast to patients with rheumatoid arthritis, those with Lyme arthritis rarely have symmetrical polyarthritis, morning stiffness, a positive result on rheumatoid factor assay, or subcutaneous nodules. Lyme arthritis commonly is mistaken for seronegative rheumatoid arthritis; however, Lyme arthritis is most similar to the spondyloarthropathies, particularly reactive arthritis. Lyme disease and reactive arthritis both commonly cause huge knee effusions, but in Lyme disease, absence of the extra-articular features of reactive arthritis (conjunctivitis, urethritis or cervicitis, balanitis, keratosis blennorrhagica) at the time of the arthritis helps distinguish it from reactive arthritis. In children, Lyme arthritis may mimic juvenile rheumatoid arthritis, but joint involvement in Lyme disease usually occurs in short, intermittent attacks, and iridocyclitis typically is absent. Rheumatoid factor titers will be negative in both juvenile rheumatoid arthritis and Lyme disease. The diseases resemble one another closely enough to have been confused at the time of the initial description of Lyme disease. Other diseases in the differential diagnosis for Lyme arthritis include acute gouty arthritis, septic arthritis, gonococcal arthritis, rheumatic fever, polymyalgia rheumatica, and temporomandibular joint syndrome.

Management

Prompt treatment of early disease can shorten the duration of symptoms and prevent progression to later stages of disease. Most of the various manifestations of Lyme disease can be treated successfully with oral antibiotic therapy, with the exception of neurologic abnormalities, which usually require intravenous therapy. Treatment of Lyme disease is summarized in Table 134-3.

Early Disease

Prompt antibiotic therapy is essential in early Lyme disease because it generally shortens the duration of the rash and associated symptoms and, more important, prevents later illness in most patients. Some patients with severe early disease, however, progress to later stages despite appropriate antibiotic regimens.

The drug of choice for men, nonpregnant and nonlactating women, and children older than 8 years is doxycycline, 100 mg twice daily for 3 weeks.[3] An advantage of doxycycline is that it also is effective for treatment of human granulocytic anaplasmosis, which is transmitted by the same tick that transmits Lyme disease. Pregnant or lactating women and children younger than 8 years should receive amoxicillin, 500 mg orally (20 to 40 mg/kg per day in three doses for children). Cefuroxime axetil has been shown to be as effective as doxycycline and may be used in children of any age, but cephalexin is ineffective in Lyme disease.[14]

Macrolide antibiotics are not recommended as first-line agents for therapy for early Lyme disease.[14] They should be reserved for patients who cannot tolerate doxycycline, amoxicillin, and cefuroxime axetil. Macrolide regimens for adults include azithromycin, 500 mg orally daily for 7 to 10 days[3]; erythromycin, 500 mg orally four times daily for 14 to 21 days; and clarithromycin, 500 mg orally twice daily for 14 to 21 days.

A Jarisch-Herxheimer type of reaction may occur in the first 24 hours of antibiotic treatment, consisting of fever, chills, myalgias, headache, tachycardia, increased respiratory rate, and mild leukocytosis. Defervescence usually takes place within 12 to 24 hours. The pathogenesis of this reaction is controversial, but it probably is caused by the killing of spirochetes with release of pyrogens. The Jarisch-Herxheimer reaction occurs more commonly with penicillin and doxycycline than with erythromycin, probably because of their superior spirocheticidal activity.

Early Disseminated Infection

Neurologic Disease. For patients with relatively mild symptoms (e.g., solitary facial nerve palsy with normal findings on CSF examination), doxycycline or amoxicillin can be used in the same dosage as for early disease, but the duration of therapy should be extended to 28 days. The use of prednisone for facial nerve palsy from Lyme disease has been suggested but is not currently recommended.

For patients with other objective neurologic abnormalities (e.g., meningitis or encephalitis, peripheral neuropathies, cranial neuritis other than facial nerve palsy) or evidence of the spirochete in the CSF, parenteral antibiotic therapy is required. Ceftriaxone, 2 g/day intravenously for 14 days (75 to 100 mg/kg/day for pediatric patients), or penicillin G, 18 to 24 million units daily intravenously for 10 to 14 days, may be used.[14] Ceftriaxone may be more effective than penicillin, and many experts recommend longer courses (e.g., up to 4 weeks). In cases of penicillin or cephalosporin allergy, oral doxycycline for 28 days may be used.

Cardiac Disease. Patients with mild cardiac conduction system involvement (first-degree AV block with a PR interval of less than 0.30 second) and no other significant symptoms usually can be treated safely on an outpatient basis with oral doxycycline or amoxicillin for 21 to 30 days.[14] Patients with higher degrees of AV block, including first-degree block with a PR interval of more than 0.30 second or evidence of global ventricular impairment, should be hospitalized for cardiac monitoring and treatment with parenteral antibiotics. Either penicillin G, 18 to 24 million units

www.ketabpezeshki.com 66485457-66963820

Table 134-3 Treatment of Lyme Disease

SYNDROME/MANIFESTATION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE*
Early Lyme disease	Doxycycline†	100 mg PO bid for 21 days	
	or		
	Amoxicillin	250-500 mg PO tid for 21 days	25-40 mg/kg/day divided tid
	Alternative:		
	Cefuroxime axetil	500 mg PO bid for 21 days	250 mg bid
	or		
	Erythromycin (less effective than doxycycline or amoxicillin)	500 mg PO qid for 14-21 days	
Neurologic disease			
Facial nerve paralysis	With an isolated deficit, oral regimens for early disease, used for at least 28 days, may suffice. For a deficit associated with other neurologic manifestations, intravenous therapy is warranted (see below).		
Lyme meningitis‡	Ceftriaxone	2 g IV by single dose for 14-28 days	75-100 mg/kg/day IV
	Penicillin G	20 million units daily in divided doses for 10-14 days	300,000 units/kg/day IV
	Alternative:		
	Chloramphenicol	1 g IV every 6 hr for 10-21 days	
Cardiac disease			
Mild§	Doxycycline†	100 mg PO bid	
	or		
	Amoxicillin	250-500 mg PO tid	25-50 mg/kg/day divided tid
More severe	Ceftriaxone	2 g IV daily by single dose for 14-21 days	75-100 mg/kg/day IV
	or		
	Penicillin G	20 million units daily in divided doses for 14-21 days	300,000 units/kg/day IV
Arthritis	*Oral:*		
	Doxycycline†	100 mg PO bid for 30 days	
	or		
	Amoxicillin	500 mg PO tid for 30 days	50 mg/kg/day divided tid
	Parenteral:		
	Ceftriaxone	2 g IV by single dose for 14-21 days	75-100 mg/kg/day IV
	or		
	Penicillin G	20 million units daily in divided doses for 14-21 days	300,000 units/kg/day IV

Modified from Treatment of Lyme disease: New drugs for allergic conjunctivitis. Med Lett Drugs Ther 42:37, 2000; and Wormser GP, et al: The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: Clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 43:1089, 2006.

*Pediatric dosage should not exceed adult dosage.

†Tetracycline, 250 to 500 mg PO qid, may be substituted for doxycycline. Neither doxycycline nor any other tetracycline should be used for children younger than 8 years or for pregnant or lactating women.

‡Regimens for radiculoneuropathy, peripheral neuropathy, and encephalitis are the same as those for meningitis.

§Oral regimens are reserved for mild cardiac involvement (see text).

intravenously, or ceftriaxone, 2 g daily for 21 days (50 to 80 mg/kg/day for children), may be used.

The benefit of adjuvant use of aspirin or prednisone in the treatment of Lyme carditis is uncertain. Temporary cardiac pacing may be necessary in patients who have severe heart block with hemodynamic instability. The block generally resolves completely with antibiotic treatment, so the recognition of Lyme carditis in young patients with unexplained heart block is critical for avoidance of unnecessary permanent pacemaker implantation.

Late Infection

Arthritis. In established Lyme arthritis, the response to antibiotic therapy may be delayed for several weeks or months.[3] Thirty-day oral regimens, such as doxycycline, 100 mg orally twice daily, or amoxicillin, 500 mg three times daily, usually are effective and, for reasons of cost and convenience, may be selected as first-line therapy given on an outpatient basis before use of parenteral antibiotic therapy is considered.[14] Persistent or recurrent joint swelling after recommended courses of antibiotic therapy can be treated with another 4-week course of oral antibiotics or with a 2- to 4-week course of intravenous ceftriaxone.[3] A small percentage of patients with Lyme arthritis, particularly those with HLA-DR4 specificity or antibody reactivity with OspA, may have persistent joint inflammation despite treatment with either oral or intravenous antibiotics. Such patients often do not respond to any antibiotic therapy and may require arthroscopic synovectomy.

Neurologic Disease. Patients with late neurologic disease affecting the central or peripheral nervous system should be treated with ceftriaxone (2 g once a day intravenously for 2 to 4 weeks). Alternative parenteral therapy may include cefotaxime (2 g intravenously every 8 hours) or penicillin G (18 million to 24 million units daily, given in divided doses every 4 hours). Response to treatment is usually slow and may be incomplete.

Lyme Disease and Pregnancy

Similar to the spirochetal agents of syphilis and relapsing fever, *B. burgdorferi* can be passed transplacentally. In rare cases, Lyme disease acquired during pregnancy may lead to infection of the fetus and possibly to stillbirth, but adverse effects on the fetus have not been documented conclusively. Counseling the termination of a pregnancy because of maternal Lyme disease is unwarranted.

Lyme disease contracted during pregnancy can be treated and cured. Treatment of pregnant patients can be identical to that of nonpregnant patients with the same disease manifestations, except

www.ketabpezeshki.com 66485457-66963820

that doxycycline should be avoided.[3] Most women give birth to normal infants despite documented Lyme borreliosis during their pregnancies.

Vaccination

No vaccine against Lyme disease is currently available in the United States. The LYMErix vaccine (SmithKline Pharmaceuticals, Philadelphia), initially licensed in 1999, was withdrawn from the market in 2002. The vaccine, directed against the outer surface protein A of *B. burgdorferi* (OspA), was apparently safe and efficacious but required multiple and repeated doses for optimal protection. Ongoing questions about its safety and cost-effectiveness dampened demand for the vaccine.[15]

A history of vaccination with the previously licensed vaccine should not change the approach to management. Because protective immunity produced by the vaccine is short-lived, it is unlikely that previous vaccination will provide any residual protective effect. Vaccination may cause a persistently positive ELISA result but a negative Western blot result.

Prophylaxis and Asymptomatic Tick Bites

Although previous expert consensus has recommended that persons bitten by deer ticks (*I. scapularis*) should not routinely receive antimicrobial chemoprophylaxis,[3] this recommendation should be modified in accordance with the findings of a well-designed trial in which a single 200-mg dose of doxycycline given within 72 hours after tick bite effectively prevented Lyme disease.[15] A single 200-mg dose of doxycycline should be considered for adult patients and children 8 years of age and older (4 mg/kg, up to a maximum dose of 200 mg) when all of the following criteria are met: (1) the tick is an adult or nymphal *I. scapularis,* (2) the tick has been attached for 36 hours or more as indicated by certainty of the time of exposure or the degree of engorgement, (3) prophylaxis can be started within 72 hours after tick removal, (4) the local rate of infection of these ticks with *B. burgdorferi* is 20% or greater, and (5) doxycycline is not contraindicated. Infection rates of 20% or greater of ticks with *B. burgdorferi* generally are reported from highly endemic areas such as New England, parts of the mid-Atlantic region, and parts of Minnesota and Wisconsin. Most other areas of the United States do not have infection rates high enough to warrant prophylaxis.[3]

The efficacy of single-dose doxycycline in patients who present more than 72 hours after removal of a tick is unknown. In children, dosing and efficacy of prophylactic treatment have not been evaluated. The effectiveness of doxycycline for the prevention of other infections transmitted by *I. scapularis* ticks (e.g., babesiosis, human granulocytic anaplasmosis) is unknown and should not be assumed.[15] Other antimicrobial agents that are effective for the treatment of Lyme disease (e.g., amoxicillin) and even other regimens of doxycycline (e.g., 100 mg twice daily) have unknown efficacy for Lyme disease prophylaxis.

Bites from *Dermacentor variabilis* and *Amblyomma americanum* do not require prophylactic treatment. Any patient who has been bitten by a tick should be instructed to seek medical evaluation if symptoms of tick-borne illness develop.

RELAPSING FEVER

Perspective

Relapsing fever is caused by bacteria of the *Borrelia* species, order Spirochaetales. Human *Borrelia* infections occur worldwide, and all are associated with arthropod vectors. The epidemic (louse-borne) form of relapsing fever is caused solely by *Borrelia recurrentis* and is found mostly in Africa, where mortality rates can reach 70% with outbreaks. The endemic form, tick-borne relapsing fever, is caused by a group of closely related *Borrelia* species, their names derived from the species names of *Ornithodoros* tick vectors that carry them. The more common ones in North America are *Borrelia hermsii, Borrelia turicatae,* and *Borrelia parkeri*. *Borrelia burgdorferi* has been recognized as the etiologic agent of the third and most recently described borrelial disease, Lyme disease.

Principles of Disease

Tick-borne relapsing fever is maintained in an animal reservoir consisting primarily of wild rodents, including squirrels, mice, rats, chipmunks, and rabbits. It is found predominantly at altitudes of 2000 to 7000 feet in coniferous forest habitats.[16] The tick vectors are argasids belonging to several species of the genus *Ornithodoros,* which routinely reside in the nests and burrows of their mammalian hosts. Ticks acquire the infection by feeding on a spirochetemic rodent. The borreliae remain viable in the ticks for several years and can be passed transovarially to the next generation; thus the tick is a major reservoir and vector. These soft ticks feed for brief periods (15-120 minutes), usually at night, and their painless bite generally is unnoticed by the sleeping victim. Transmission occurs by injection of infected saliva through the bite site or intact skin. Less common modes of transmission (e.g., by way of venipuncture equipment in injection drug users) have been reported.

In the United States, relapsing fever occurs primarily in the western Mountain and Pacific states, including Montana, Wyoming, Nevada, Colorado, California, and Washington. Persons who come in contact with infected ticks from wild rodents are at greatest risk. Outbreaks have been reported among groups of persons sleeping overnight in hunting cabins inhabited by wild rodents.[16,17]

In tick-borne relapsing fever, the initial febrile episode lasts 3 days. This is followed by an asymptomatic period of variable duration, usually approximately 7 days, during which patients generally feel better and may return to their usual daily activity levels under the assumption that they have recovered from another viral illness. Relapse then occurs, with symptoms that mimic those of the original illness. With tick-borne relapsing fever, this cycle repeats itself three to five times. Each successive relapse usually is less severe. Relapse is caused by the spirochete's unique ability to undergo antigenic variation within the body of the infected host. Each successive antigenic variation is cleared from the bloodstream by specific host antibodies, and a characteristic relapsing febrile course results.

Clinical illness is manifested in two classic stages as each fever episode resolves. The first stage is called the "chill" phase (high fevers with reported temperatures of up to 106.7° F, mental status changes, tachycardia, and tachypnea), lasting approximately 30 minutes, followed by a "flush" phase (rapid temperature decrease, sweats, and hypotension), which can be confused with a Jarisch-Herxheimer reaction.[18]

Clinical Features

After a postbite incubation period of 4 to 18 days, during which time the host concentration of spirochetes increases, fever of abrupt onset occurs, often accompanied by shaking chills, headache, arthralgias, myalgias, nausea, and vomiting. On occasion, a pruritic eschar may be noted at the site of the tick bite, but this usually is absent by the onset of clinical symptoms. Consequently, the nonspecific nature of the clinical presentation often leads to misdiagnosis of the disease as a viral illness. The patient's temperature is high, and generalized muscle weakness and lethargy are common. Hepatomegaly, splenomegaly, and jaundice are sometimes seen. Neurologic involvement is less common but can be

www.ketabpezeshki.com 66485457-66963820

manifested as delirium, nuchal rigidity, peripheral neuropathy, or pupillary abnormalities. Uveitis has been described.[19] A macular or petechial rash, more apparent on the trunk than on the extremities, may be present.

Recent severe cases of tick-borne relapsing fever resulting in acute respiratory distress syndrome (ARDS) in California and Nevada near the Lake Tahoe area and in the state of Washington prompted a comprehensive epidemiologic investigation of cases in those areas during a 10-year period. This study showed that ARDS may be more common than was previously suspected. Reported occurrence rates for Jarisch-Herxheimer reaction were between 6 and 21%; for hypoxia, 16%; for elevated liver function test values, 8%; and for ARDS, 6%. Forty-six percent of the patients required hospitalization.[16]

Diagnostic Strategies

The definitive diagnosis of relapsing fever depends on the demonstration of spirochetes in the peripheral blood during a febrile episode. This is not a typical finding with other spirochetal diseases. In most cases, spirochetes are readily visible on a routine blood smear prepared with Wright or Giemsa stain. Thick or thin blood smears, such as those prepared for malaria evaluation, also are satisfactory. The organisms are seen within the plasma spaces between blood cells or may overlie the blood cells. Several organisms per high-power field typically are visible in smears from febrile patients with relapsing fever.[18] Blood specimens for the smears should be obtained as the temperature curve swings up, and repeated samples may be required before a positive result is observed because sensitivity approaches only 70%. Spirochetes also may be visible in wet mounts with the use of phase contrast microscopy. Culture, although it is the most sensitive diagnostic method available, requires a special medium and does not yield rapid results and so is not commonly performed. Genus-specific PCR testing has now been successfully used and may be higher in sensitivity than either serology or blood smear, especially in the acute phase of disease.[20] Serologic testing offered by the CDC can be accessed through local and state health departments. Nonspecific laboratory findings may include mildly increased bilirubin and liver function levels, thrombocytopenia, and elevated erythrocyte sedimentation rate.[18]

Differential Considerations

On initial presentation, the differential diagnosis is extensive; however, it narrows with the occurrence of relapse. A history of possible soft tick exposure together with recurrent fever should suggest the diagnosis. Other conditions that initially may be considered include malaria, typhus, dengue, yellow fever, Colorado tick fever, and tularemia. Careful examination of blood smears together with clinical data and other laboratory tests will aid in making the correct diagnosis.

Management

Relapsing fever is effectively treated with tetracycline or erythromycin. Tetracycline should be avoided in children younger than 8 years and in pregnant women. Tetracycline or erythromycin should be given in an oral dose of 500 mg for 7 days; single-dose therapy is also effective. Other treatment regimens, including doxycycline and chloramphenicol, have been recommended. Treatment with penicillin G has been associated with an increased rate of relapse. Success with ceftriaxone has been reported in a patient with relapsing fever who did not respond to penicillin. Prophylaxis with doxycycline for tick-borne relapsing fever in exposed subjects in high-risk infested areas has been shown to be effective.[21]

As many as one third of patients experience a Jarisch-Herxheimer type of reaction during treatment with antibiotics. The reaction can be severe, especially with louse-borne relapsing fever. This phenomenon may be related to release of high levels of cytokine intermediaries or endogenous opioids. Approximately 4 hours after antibiotic treatment and coinciding with the clearance of spirochetes from the blood, the patient usually experiences an increase in temperature and severe rigors, accompanied by a drop in leukocyte and platelet counts and onset of hypotension. Anticipation of this reaction is crucial because intravenous volume expansion with saline solution may be required to maintain the blood pressure; the reaction can be more threatening than the disease itself. Meptazinol, an opioid antagonist with agonist properties, has been proposed for use in treatment of this reaction.

Prognosis is good in treated patients with relapsing fever; approximately 95% achieve complete recovery. Poor prognostic signs include the presence of jaundice, high spirochete counts in the blood, and hypotension. Transplacental transmission can occur in infected pregnant women. Perinatal death of the fetus or infant and spontaneous abortions occur in nearly 50% of the cases in pregnant women.[22] Death is rare in tick-borne relapsing fever and is limited to infants and elders.

TULAREMIA

Perspective

Tularemia was first characterized in 1837 by Soken, who described a febrile illness with generalized lymphadenopathy in people who had eaten infected rabbit meat. In 1912, McCoy first isolated *Bacterium tularense,* now known as *Francisella tularensis,* from rodents in Tulare County, California, giving rise to the name of the disease. Edward Francis, for whom the genus *Francisella* was later named, contributed much to the understanding of the bacteriology and epidemiology.[23]

Tularemia occurs worldwide and is endemic between 30 and 71 degrees north latitude. The incidence of tularemia is low. There were 247 reported cases of tularemia in the United States between 2004 and 2005, although it is not a notifiable disease in all states.[24] Tularemia has been seen in every state but is most common in the southwest central region (Arkansas, Louisiana, Oklahoma, Texas, and Mississippi). Fifty-six percent of reported cases have come collectively from Missouri, Oklahoma, South Dakota, and Arkansas. It is more common in men than in women. Persons at increased risk for infection include hunters, trappers, butchers, agricultural workers, campers, sheepherders, mink farmers, and laboratory workers.[25]

Ticks, lagomorphs (hares, rabbits), and rodents (mice, rats) are believed to be the most important sources of transmission to humans; however, the organism has been recovered from animals of more than 100 species. Significant epidemics have been linked to contact with a variety of them, including domestic cats.[23,26]

A large number of commercially distributed prairie dogs from Texas died of tularemia in 2002.[27] The ticks most commonly involved in transmission in the United States are the deer tick (*I. scapularis*), the Lone Star tick (*A. americanum*), and the dog tick (*D. variabilis*), all of which have been associated with other tick-borne illnesses. Whereas mosquitoes are major vectors in many European countries,[28] horse fly and deer fly bites have been implicated in endemic situations in the United States.[29] In 2007, an outbreak in Utah was associated with deer fly bites.[30]

Transmission to humans most commonly occurs through tick bites or handling of infected animals. It also can occur with ingestion of infected food or water, with inhalation of dust or water aerosol, and through insect bites.[29] Nonimmune laboratory workers who work with *F. tularensis* can acquire the disease. Person-to-person transmission is rare. Tularemia has a bimodal

www.ketabpezeshki.com 66485457-66963820

prevalence in the United States; an increased incidence in May to August is associated with tick-borne transmission, and a December to January peak is associated with hunting and skinning of infected mammals (primarily rabbits). *F. tularensis* has been found to coexist in reservoir populations harboring the agent responsible for Lyme disease.[31] Eleven cases of pneumonic tularemia, found to be from aerosolization of contaminated vegetation clippings, were discovered in Martha's Vineyard.[32] Outside of the United States, tularemia has been confirmed in hundreds of cases in Kosovo, through rodent contamination of food. In addition, Sweden has reported a high number of cases, usually associated with aquatic environments and mosquitoes.[23,28,33]

Principles of Disease

F. tularensis is a small pleomorphic gram-negative coccobacillus and is a facultative pathogen of macrophages, neutrophils, and nonphagocytic cells such as hepatocytes and alveolar epithelial cells.[34] Two serologically identical types of *F. tularensis* organisms are responsible for human disease and can be distinguished from each other on the basis of geographic distribution, fermentation reactions, and virulence. Jellison type A (*F. tularensis* biovar *tularensis*), the predominant biovar in North America, is associated with ticks and rabbits and causes severe disease in humans. Strain B (*F. tularensis* biovar *holarctica*) occurs in Asia, Europe, and, to a minor extent, North America; it is associated with rodents and causes milder disease in humans.[35]

Tularemia is manifested in different ways, depending on the portal of entry of the organism. The primary route of infection by *F. tularensis* is through the skin. Entry can occur through hair follicles or through small cuts and abrasions that may be contaminated by exposure to an infected animal; tick exposure can also introduce the bacteria. Because the bacterium has not been isolated from the salivary glands of ticks, it is thought that they transmit the organism through their feces.[29] Scratching after a tick bite introduces the infected feces into the skin. Inhalation or ingestion of the organism or transmission through the conjunctivae also can cause infection. The incubation period is approximately 2 to 6 days, depending on the size of the inoculum.

After penetration of the skin or epithelial membrane, the organism usually spreads to the regional lymph nodes. An erythematous tender papule develops at the primary infection site, followed by inflammation and skin ulceration. The regional nodes enlarge, necrose, and may rupture. The necrotic, purulent, painful lymph node is termed a bubo. In the ulceroglandular form of the infection, the organism may not spread farther than the regional lymph nodes. If the inoculum is sufficiently large or the host defenses are inadequate, bacteremia ensues, with dissemination to phagocytic cells of the reticuloendothelial system.

Pulmonary tularemia may result from inhalation of small-particle aerosols containing *F. tularensis* or may be secondary to hematogenous dissemination. Small areas of localized pneumonitis most commonly are seen, although chest radiographic findings are nonspecific; lobar consolidation or abscess formation is rare. Oculoglandular tularemia occurs when the conjunctiva becomes infected from contact with material from an ulcer or a contaminated finger. Typhoidal tularemia follows systemic spread of *F. tularensis* from the oropharynx and probably the gastrointestinal tract when a large inoculum is swallowed.

Clinical Features

Tularemia has six clinical presentations, depending on whether disease is localized to an entry site and its regional lymph nodes (ulceroglandular, glandular, oculoglandular, and oropharyngeal forms) or is more invasive and generalized (typhoidal and pulmonary forms).

Ulceroglandular tularemia is the most common form of the disease (accounting for approximately 80% of the cases). Typically, a skin lesion on an extremity at the site of primary inoculation begins as an erythematous papule, which then ulcerates 2 to 3 days later. The ulcer is slow to heal and often is still present when the subsequent regional lymphadenopathy and fever develop. The distribution of the regional adenopathy reflects the primary entry site; patients with tick-borne tularemia usually have inguinal or femoral adenopathy, whereas those who acquire rabbit-associated tularemia have axillary or epitrochlear nodal involvement. Generalized lymphadenopathy also may be seen. On occasion, nodes suppurate and drain.[23]

Glandular tularemia, the second most common form, is characterized by the development of lymphadenopathy (usually cervical) without an associated skin ulcer. *Oculoglandular* tularemia is seen in 1 to 2% of cases and is characterized by unilateral conjunctivitis with regional adenopathy involving preauricular lymph nodes. *Oropharyngeal* tularemia is manifested as severe exudative pharyngitis with associated cervical lymphadenitis. It has been known to cause acute glaucoma.[23]

Typhoidal tularemia is a systemic form of the disease in which no obvious entry site can be found; it occurs in approximately 10% of cases. Only 10 to 50 organisms are required to induce disease; incubation time is 2 to 10 days. Symptoms and signs may include fever, chills, constipation or diarrhea, abdominal pain, and weight loss. A 30 to 60% case fatality rate is associated with untreated typhoidal tularemia.[23]

Pulmonary tularemia is common and has symptoms similar to those of other bacterial pneumonias: fever and chills, cough (usually nonproductive), substernal burning, dyspnea, malaise, and prostration. It may result from either direct inhalation of aerosolized organisms or bacteremic spread from another site.

Uncommon complications of tularemia include pericarditis, meningitis, endocarditis, peritonitis, appendicitis, perisplenitis, and osteomyelitis.[23] Guillain-Barré syndrome associated with tularemia also has been reported.

Tularemia is one of the most widely studied diseases with respect to potential biologic warfare. The United States developed an aerosolized form in the 1950s, and the Japanese allegedly contaminated prisoners with the disease in the 1930s.[35] It was removed from the national list of notifiable diseases in 1995 but then was reinstated in view of the heightened biologic weapons threat.[25] It is now classified by the CDC as one of the six category A critical biologic diseases.[36] An aerosolized form of the bacterium would be the most likely delivery mechanism used in biologic warfare.[37] With release of aerosolized particles, disease would be manifested clinically as acute fever, progressive pneumonia, pleuritis, and hilar lymphadenopathy, beginning as early as 3 to 5 days after delivery.[38] Only approximately 55% of emergency departments have been adequately educated on the recognition of and preparedness for tularemia.[39]

Diagnostic Strategies

Diagnosis of tularemia is based on clinical findings and serologic testing. Antibody titers begin to rise approximately 7 to 10 days after exposure and peak in 3 to 4 weeks. In a patient with a clinical presentation suggesting tularemia, an antibody titer of 1:160 or greater in a single specimen is diagnostic. Confirmatory evidence is provided by a fourfold or greater rise in titer in a second sample obtained 2 weeks later. Unfortunately, titers of IgG and IgM can continue to be high for up to 10 years, and cell-mediated immunity can be maintained for up to 25 years.[40] Rapid testing with PCR assay is available.[41-43] A rapid point-of-care test using an immunochromatographic approach is currently being evaluated.[44]

www.ketabpezeshki.com 66485457-66963820

Aspiration of affected lymph nodes for culture is not routinely recommended because of the associated risk to laboratory personnel. If tularemia is suspected, the laboratory should be alerted so that appropriate precautions can be taken in specimen handling and so that enriched culture medium can be used.

Management

Isolation of patients with tularemia is not required. Streptomycin is the drug of choice for treatment of all forms of tularemia. When it is given intramuscularly in a dose of 30 to 40 mg/kg per day in two divided doses every 12 hours, streptomycin usually produces symptomatic improvement and resolution of fever in 1 to 2 days. After the third treatment day, half of the dose is given for a total course of 7 to 14 days.[45] With this regimen, relapses are unusual.

Ulcers and tender lymph nodes usually heal within 7 to 10 days; however, enlarged nodes occasionally develop into fluctuant sterile buboes, requiring incision and drainage after completion of the course of antibiotics. Gentamicin also is effective for treatment (3 to 5 mg/kg/day for 10 to 14 days).[45] Tetracycline and chloramphenicol are effective; however, the risk of relapse is greater than that associated with the aminoglycosides. Imipenem-cilastatin, an antibiotic without nephrotoxicity, has been used successfully to treat pulmonary tularemia in a patient with acute renal failure. Ceftriaxone is not effective against *F. tularensis* infections. Prophylaxis for possible exposure requires doxycycline, 100 mg twice a day for 14 days. Doxycycline or ciprofloxacin prophylaxis is recommended for a large biologic attack.[38] An effective live vaccine strain has been available for vaccination against tularemia for nearly 50 years, but licensure approval has been delayed owing to a lack of understanding of the vaccine's mechanism of action and attenuation. Because of recent interest in biologic warfare, research on tularemia vaccines has resurged.

The overall mortality rate in untreated tularemia ranges from approximately 5 to 30%; the higher figure is associated with severe disease or significant pulmonary involvement. With appropriate antibiotic treatment, death is rare (mortality rate of less than 1%).

ROCKY MOUNTAIN SPOTTED FEVER

Perspective

RMSF is an acute, febrile, systemic tick-borne illness caused by *Rickettsia rickettsii*. The genus *Rickettsia* is divided into the spotted fever group and the typhus group. *R. rickettsii* is considered the typical representative of the spotted fever group; 20 species now exist.[46] One is responsible for Mediterranean spotted fever. RMSF is found in North, South, and Central America and is a nationally reportable disease. All cases are to be registered with the respective state department. As of 2010, reported cases of RMSF are categorized in the broader name of spotted fever rickettsiosis.[47]

The number of reported cases in the United States more than tripled between 2000 and 2007, especially in suburban areas.[48,49] This increase is thought to be due to more widespread use of the new ELISA during this period. However, use of the assay has also resulted in a significantly lower case fatality rate, which could be related to the high cross-reactivity of new serologic tests with more benign rickettsioses.[50] Higher awareness and more aggressive empirical treatment of RMSF may also contribute to the decreased fatality rate. American Indians have the highest incidence of RMSF,[51] and children between the ages of 5 and 9 years have the highest mortality rate.[52]

Since 2004, another rare rickettsiosis has emerged. It is caused by *Rickettsia parkeri* through the Gulf Coast tick, *Amblyomma maculatum*. It is distinguished from RMSF by sometimes causing eschars or a vesicular rash.[53]

RMSF ranges in clinical severity from mild or even subclinical illness to a fulminant disease with vascular collapse and death within several days of onset. It is the only rickettsiosis still associated with significant mortality, causing approximately 40 deaths in the United States each year,[54] with a mortality rate ranging from 3 to 5% despite appropriate treatment. Before tetracycline and chloramphenicol were available, death occurred in as many as 30% of cases in the 1930s.[49] The age-specific incidence is highest in children younger than 10 years, and case fatality rates are highest in persons older than 60 years.[55]

The recorded history of RMSF suggests that the disease was present at least before the European settlement of western North America, among inhabitants of wooded Rocky Mountain regions. Early terms used to name the disease included *tick fever* and *black measles*. In 1899, RMSF was described as "an acute, endemic, noncontagious but probably infectious, febrile disease, characterized by a continuous moderately high fever, severe arthritic and muscle pains, and a profuse petechial or purpuric eruption in the skin, appearing first on the ankles, wrists, and forehead, but rapidly spreading to all parts of the body."[56] In 1906, the causative organism, *R. rickettsii,* was identified by Howard T. Ricketts, who also described the importance of the tick vector in transmission to humans.[57]

Although RMSF was first described in Montana and Idaho, it is now relatively rare in the Rocky Mountain states. Endemic in all 48 contiguous states except Maine, the disease continues to be most prevalent in the southeastern United States. RMSF has been reported in Canada, Central America, Mexico, and South America but never outside the Western Hemisphere. In 1987, four cases of RMSF were reported among residents of the Bronx in New York City; none of the affected persons had recently traveled to an area known for endemic disease, raising the possibility that other urban foci of RMSF may exist.

RMSF also tends to be focally endemic, with clustering of cases within a larger endemic area that may correspond to "islands" of infected ticks. These areas, ecologically distinct from surrounding areas, may be ideally suited to ticks; they usually consist of wild open fields, deciduous forests with thick ground cover and poor water drainage, or uncultivated areas. Geographic clusters of severe disease have been reported.[58] In areas with frequent occurrence of RMSF (Oklahoma, North and South Carolina, Tennessee, and Pennsylvania), an infectivity rate of 2 to 15% of the tick population has been reported. North Carolina and Oklahoma carry the highest incidence rates (35% of all cases) for RMSF.[49]

R. rickettsii organisms are obligate intracellular bacteria with tropism for human endothelial cells. They often occur in pairs and possess a cell wall similar in structure and chemical composition to that of gram-negative bacteria.[59] *R. rickettsii* contain both RNA and DNA and, in contrast with other rickettsial organisms, can invade the nucleus as well as the cytoplasm.

The American dog tick, *Dermacentor variabilis,* and the Rocky Mountain wood tick, *Dermacentor andersoni,* have been the vectors responsible for human RMSF cases in the United States to date[43]; however, the common brown dog tick, *Rhipicephalus sanguineus,* has emerged as a third vector.[60] *R. sanguineus* has been the main RMSF vector in Mexico and Central America. *Amblyomma imitator,* in the genus of the Lone Star tick, has recently been implicated as yet another vector because *R. rickettsii* has been found in its eggs.[61]

Ticks feed on virtually any available warm-blooded animals and humans; the occurrence of *R. rickettsii* in the United States does not depend on the presence of any given order of mammal. Domestic dogs infected with *R. rickettsii* can demonstrate clinical illness similar to that seen in humans. Although dogs do not play an important role in the amplification cycle of RMSF, they can serve as a conduit for infected ticks, carrying them into close contact with pet owners. Dogs may serve as sentinels for RMSF in

www.ketabpezeshki.com 66485457-66963820

humans. A high prevalence of rickettsial antibodies in stray dogs in Arizona is thought to be a major factor in the 70 cases and 8 deaths from RMSF reported in that state between 2003 and 2008.[62]

Communication between physicians and veterinarians is important when cases of zoonotic diseases are detected.[63] Humans serve only as accidental participants in the cycle of infection. A retrospective study revealed that none of 10 recipients of blood products found to be from donors with either confirmed or probable RMSF contracted the disease.[64]

Principles of Disease

After introduction of *R. rickettsii* into the host by the tick vector, the organisms invade and multiply in the vascular endothelial cells. They then enter deeper areas of the vessel walls and infect vascular smooth muscle. Rickettsial organisms move from cell to cell by actin-based motility. Damage to endothelial cells not only exposes subendothelium but also releases tissue plasminogen activator and von Willebrand's factor, thereby causing microhemorrhage, microthrombus formation, and increased vascular permeability. In addition, antibody forms, with antigen activating the complement system (type III immune response), and a cellular response is recruited.

These widespread vascular lesions form the basis for most of the clinical features associated with RMSF. Hypotension, edema, and increased extravascular fluid space result from the increased small-vessel permeability. The early rash results from the vasculitis and the associated changes in permeability; later petechial and hemorrhagic lesions are secondary to the vasculitis and thrombocytopenia. Microinfarcts and focal lesions develop in various organs, including the brain, heart, lungs, kidneys, adrenal glands, liver, and spleen. Rickettsial encephalitis and diffuse microinfarcts are usual features of central nervous system involvement. An interstitial pneumonitis caused by direct lung invasion by the organism may occur, and ARDS can ensue. Acute renal failure and hypovolemic shock, the primary causes of death, can occur as early as the second week of illness.

Table 134-4 Symptoms and Signs in 262 Persons with Rocky Mountain Spotted Fever

SYMPTOM OR SIGN	FREQUENCY DURING ILLNESS (%) Any Time	First 3 Days
Fever (temperature of 37.8-38.9° C [100-102° F])	99	73
Headache, mild to moderate	91	71
Fever (≥102° F)	90	63
Any rash	88	49
Myalgia, mild to moderate	83	57
Rash, maculopapular	82	46
Rash, palms and soles	74	28
Triad of fever, rash, history of tick exposure	67	3
Nausea and vomiting	60	38
Headache, severe	57	40
Abdominal pain	52	30
Rash, petechial and hemorrhagic	49	13
Myalgia, severe	47	25
Conjunctivitis	30	13
Lymphadenopathy	27	13
Stupor	26	6
Diarrhea	19	9
Edema	18	3
Ataxia	18	7
Meningismus	18	5

From Helmick CG, Bernard KW, D'Angelo LJ: Rocky Mountain spotted fever: Clinical, laboratory, and epidemiological features of 262 cases. J Infect Dis 150:480, 1984.

Clinical Features

Children from 5 to 9 years of age are the most common victims of RMSF. Two thirds of all cases are in children younger than 15 years. More than 90% present with a fever and rash. A history of tick bite or presence in possible tick-infested areas is elicited in 60 to 70% of all patients with RMSF, although only 49% of the pediatric population reports a bite.[65] The incubation period ranges from 2 to 14 days, with a mean of 7 days.[49] A short incubation period may indicate a more serious infection. Factors that bring higher risk of death include delayed onset of rash, glucose-6-phosphate dehydrogenase deficiency, hepatomegaly, neurologic deficits, renal insufficiency, increased period between symptoms and antibiotic treatment, and lack of tick bite history.[46]

Onset of symptoms usually is abrupt but is gradual in approximately one third of patients. Early symptoms are nonspecific and similar to those of many acute infectious diseases, making early diagnosis difficult. "Typical" patients experience sudden onset of fever, severe headache, myalgias, prostration, nausea, and vomiting. Tenderness may be noted in large muscle groups (Table 134-4). As many as 80% of patients may have gastrointestinal symptoms secondary to myositis of the abdominal wall. Fever (temperature usually higher than 102° F) is nearly always present during the first 2 to 3 days of illness and may precede other signs by 1 week or more.[49] On occasion, the onset of illness is mild, with lethargy, headache, anorexia, and low-grade fever; these patients may remain ambulatory. Although the triad of fever, rash, and tick exposure traditionally has been seen in only approximately 3 to 18% of cases, newer data show that it is found in up to 45% of children with the disease.[65] An extreme complication of RMSF is gangrene, which probably is induced by small-vessel occlusion.

Cutaneous Manifestations

Vasculitis secondary to rickettsial invasion of vascular endothelial cells causes the rash commonly associated with RMSF; however, the rash reportedly is absent in 4 to 16% of laboratory-confirmed cases, referred to as Rocky Mountain spotless fever. In addition, the rash may go unnoticed in dark-skinned patients. It usually appears on the third to fifth febrile day but can emerge as early as the second and as late as the sixth day. The initial lesions generally are restricted to the ankles and wrists, spreading to the palms and soles. The rash then spreads centripetally to the forearms, arms, legs, thighs, and trunk. Although it is usually spared, the face can be involved. Despite the common belief that the palms and soles are critical for diagnosis, they are not consistently involved (rash on the palms and soles is reported in approximately 50% of cases). Involvement of the scrotum or vulva can be an evasive clue for RMSF.[66] The rash of RMSF typically begins as 1- to 5-mm blanchable pink to bright red discrete macules that may be pruritic (Fig. 134-7). At this initial stage, the lesions fade when pressure is applied and are not palpable. A warm compress applied to the area enhances the rash. After 6 to 12 hours, the rash spreads centripetally. After 2 to 3 days, the rash becomes maculopapular and changes to a deeper red; at this stage, skin changes can be appreciated on light palpation. By approximately the fourth day, the rash

www.ketabpezeshki.com 66485457-66963820

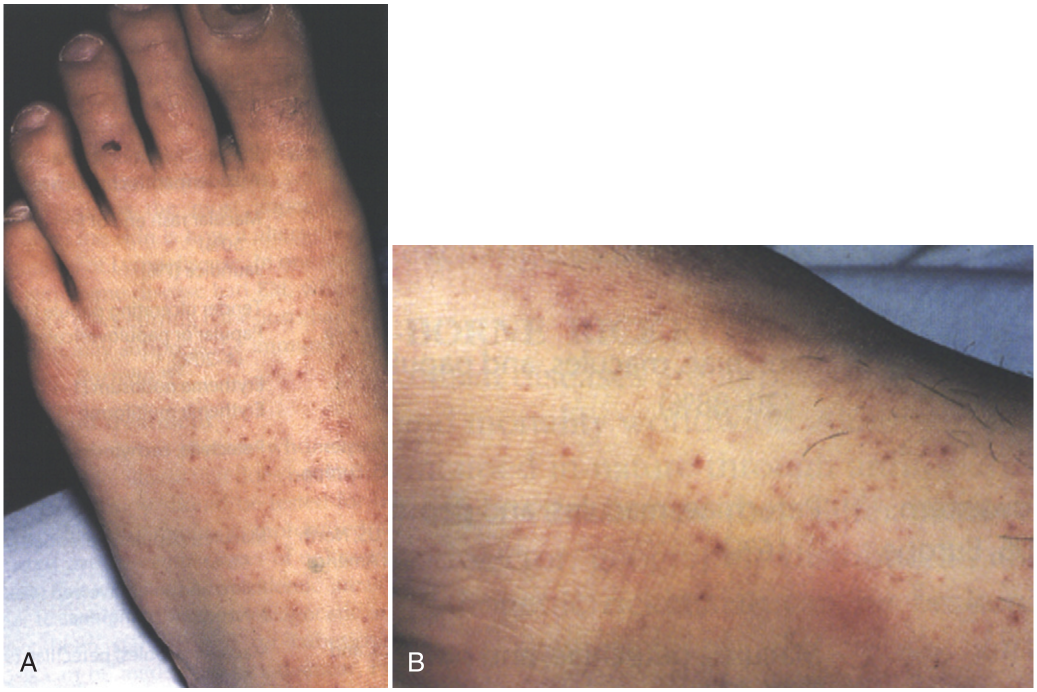


Figure 134-7. **A,** Exanthem of Rocky Mountain spotted fever. **B,** Exanthem of Rocky Mountain spotted fever, close-up view. (From McGinley-Smith DE, Tsao SS: Dermatoses from ticks. J Am Acad Dermatol 49:363, 2003.)

Figure 134-8. Late appearance of the rash of Rocky Mountain spotted fever on the lower extremity. (Courtesy Theodore Woodward, MD.)

becomes petechial and no longer fades with applied pressure. Applying tourniquets for several minutes or taking the blood pressure may cause additional petechiae to form distal to the site of occlusion (Rumpel-Leede phenomenon). The lesions occasionally coalesce to form large ecchymotic areas that may slough and form indolent ulcers (Fig. 134-8).

Prompt institution of specific therapy can cause the initial nonfixed lesions to disappear rapidly, unlike the later fixed lesions. Patients who have had the typical rash may exhibit brownish discolorations at the site during the convalescent period.

Cardiopulmonary Manifestations

Echocardiographic evidence of decreased left ventricular contractility secondary to myocarditis commonly is seen and often is detectable even before clinical signs of RMSF appear. Clinical manifestations of left ventricular dysfunction are uncommon, however, and hypotension and pulmonary edema, when present, usually have noncardiogenic causes. Chest radiographs may demonstrate cardiac enlargement. Electrocardiographic changes include low-voltage, nonspecific ST-T changes, first-degree AV block, dysrhythmias (sinus and nodal tachycardia, paroxysmal atrial tachycardia, atrial fibrillation), and left ventricular hypertrophy. Most cardiac abnormalities are transient, but persistent echocardiographic changes have been described. Decreased systolic function, elevated serum cardiac markers, no finding of vascular lesions, and fourfold rise in antibody titers are consistent with myocarditis from RMSF.[67]

Interstitial pneumonitis and increased pulmonary capillary permeability may result from infection of the pulmonary capillaries with rickettsiae. Nonproductive cough and dyspnea secondary to pneumonitis are sometimes seen on presentation. Chest radiographic abnormalities are identified in approximately 25% of patients. These abnormalities include interstitial infiltrates, patchy alveolar infiltrates, pleural effusions, and cardiomegaly with pulmonary edema. Pulmonary consolidation is rare. In severe cases, progression to noncardiogenic pulmonary edema and ARDS may occur.

Neurologic Manifestations

Neurologic manifestations of RMSF range from mild headache and lethargy to seizures and coma. Acute disseminated

www.ketabpezeshki.com 66485457-66963820

encephalomyelitis has been described. Headache, generally severe, is common, occurring in 50 to 90% of cases. Meningismus is present in 16 to 29% of patients. The CSF may be normal or show slight protein elevation and pleocytosis of both lymphocytes and polymorphonuclear cells (usually 8 to 35 cells/mL). CSF glucose level and opening pressure usually are normal. Resolution of eosinophilic meningitis during RMSF after appropriate antibiotic treatment has been reported. Less than 40% of patients have a positive CSF finding.

Cerebral thrombovasculitis may cause focal neurologic deficits, which usually are transient. Seizures can occur, especially during the acute phase of the illness. Generalized cerebral dysfunction ranging from lethargy to coma can occur secondary to systemic toxicity (fever, hypotension, hyponatremia) or vasculitic lesions involving the central nervous system. Coma is a late finding in patients with severe disease and is seen in less than 10% of cases. Some reports have described patients who remain alert but are amnesic for their illness after recovery.

Other reported neurologic manifestations include transient deafness, tremor, rigidity, athetoid movements, paralysis, ataxia, opisthotonos, aphasia, and blindness.[49,59] In general, neurologic signs abate without residua; permanent neurologic deficits are rare. Behavioral disturbances and learning disabilities have been reported after recovery from RMSF-associated coma in children.

Diagnostic Strategies

Most immediately available laboratory tests provide little help in diagnosis of RMSF. Early in the course of the illness, the diagnosis is based primarily on clinical evidence, so epidemiologic features should be correlated with clinical signs and symptoms. The initial presentation of RMSF is similar to that of many acute febrile infectious diseases, and almost invariably a therapeutic decision must be made on clinical grounds alone, without the luxury of confirmatory laboratory evidence.[68] Abnormalities such as thrombocytopenia, hyponatremia, and acute renal failure may be detected by routine laboratory tests, but they are nonspecific and unhelpful diagnostically. Up to 30% of patients present with anemia. A definitive diagnosis of RMSF requires positive results on one or more of several tests: serologic study, skin biopsy, or direct isolation and identification of the organism (Box 134-1).

Skin Biopsy

Identification by immunofluorescent assay (IFA) and immunoperoxidase staining of *R. rickettsii* in biopsy specimens of the rash from patients with suspected RMSF are the best rapid diagnostic tests currently available.[49] In experienced laboratories, the diagnosis of RMSF can be confirmed as soon as 4 hours after the specimen is obtained. The organisms can be detected as early as day 3 of clinical illness and as late as day 10. Unfortunately, this technique can be used only when a rash is visible for accurate localization of the biopsy site. Biopsy specimens generally are obtained with a 3-mm punch in the center of the skin lesion. Immunofluorescent demonstration of rickettsiae in frozen sections of skin biopsy specimens has a sensitivity of 70%. Results of immunohistochemical staining of tissues at autopsy were positive in all fatal cases in one study, whereas IFA results were negative in the majority of cases. Failure to obtain a biopsy specimen of a rickettsial cutaneous lesion or failure to obtain sections through its center is associated with false-negative results. Treatment with antirickettsial drugs for 24 hours does not appreciably alter the sensitivity of the test; however, after 48 hours, rickettsiae are substantially reduced in numbers.

Box 134-1 Diagnostic Criteria for Rocky Mountain Spotted Fever

Laboratory Criteria

- Serologic evidence of a significant change in serum antibody titer reactive with *Rickettsia rickettsii* antigens between paired serum specimens, as measured by a standardized assay conducted in a commercial, state, or reference laboratory
- Demonstration of *R. rickettsii* antigen in a clinical specimen by immunohistochemical methods
- Detection of *R. rickettsii* DNA in a clinical specimen by the polymerase chain reaction (PCR) assay
- Isolation of *R. rickettsii* from a clinical specimen in cell culture

For confirmed cases, a significant change in titer must be determined by the testing laboratory; examples of commonly used measures of significant change include, but are not limited to, a fourfold or greater change in antibody titer as determined by indirect immunofluorescent antibody (IFA) assay or an equivalent change in optical density measured by enzyme-linked immunosorbent assay (EIA or ELISA).

Case Classification (CDC Case Definition, 2004)

Confirmed: The patient has a clinically compatible illness that is laboratory confirmed.

Probable: The patient has a clinically compatible illness and serologic evidence of antibody reactive with *R. rickettsii* in a single serum sample at a titer considered indicative of current or past infection (cutoff titers are determined by individual laboratories).

From Chapman AS, et al: Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States. MMWR Recomm Rep 55:18, 2006.
CDC, Centers for Disease Control and Prevention.

Serology

Rickettsial infection can be confirmed by demonstration of antibody rise in paired sera. Even with the most sensitive serologic tests, however, elevations in antibody titers do not occur until approximately 5 to 7 days after the onset of initial symptoms. Accordingly, serodiagnosis is retrospective. It is achieved by comparing acute serum, which typically yields negative findings, with convalescent serum, which yields positive results for antibodies. The indirect IFA generally is considered the reference standard for diagnosis of RMSF and is the test currently used by the CDC and most state public health laboratories. It has a high specificity and sensitivity (94%).[66] IFA can be used to detect either IgG or IgM antibodies. An RMSF latex agglutination test that reportedly gives a turnaround result in less than 24 hours is available in selected laboratories.[69]

A study showed a 12% seroprevalence, with antibody titers of 1:64 or greater, in the pediatric population in the southeastern and south central regions of the United States.[65] Accordingly, clinical correlation with titers in these regions is critical.

Convalescent-stage blood samples are best obtained 2 to 3 weeks after the onset of clinical illness. Antibiotic therapy does not affect the time of appearance of antibodies or their ultimate titer if such treatment is begun several days after the onset of illness. However, if antibiotic therapy is initiated earlier in the course of the illness, the rise in titers can be delayed for 4 weeks or more. Under these circumstances, antibody titers should be tested again at 4 to 6 weeks after the onset of illness.

Isolation of Organism

For most pathogenic infections, the standard diagnostic criterion is isolation and identification of the etiologic organism from the patient's blood or tissues. This is seldom attempted in rickettsioses, however, because the isolation procedures are

www.ketabpezeshki.com 66485457-66963820

time-consuming, expensive, and hazardous to laboratory personnel. In addition, primary isolation of rickettsiae by inoculation in the yolk sac of a chick embryo usually fails because of the small number of organisms in the patient's blood.

Differential Considerations

Delayed diagnosis or misdiagnosis is the principal reason for the historically significant mortality associated with RMSF. Clinical diagnosis is difficult, especially early in the course of the illness, because of the nonspecific presentation. For avoidable deaths to be prevented, a diagnosis of RMSF should be considered in any patient with an unexplained febrile illness (with or without a rash and headache), even in the absence of a history of tick bite or travel to an area known to be endemic for the disease.[70] The clinician should remember to routinely ask about recent tick bites, especially when assessing children with unexplained febrile illness, because parents do not always spontaneously provide this important information. An atypical presentation or manifestation of RMSF also should be considered during the differential diagnosis, including (1) absence of a rash (Rocky Mountain spotless fever) or late appearance of a rash, (2) predominant gastrointestinal features or abdominal pain suggestive of an acute condition in the abdomen, (3) cough and pulmonary congestion suggestive of pneumonitis, and (4) meningismus suggestive of viral meningitis.[55] A presumptive diagnosis is advised with the initiation of specific therapy well before specific confirmatory laboratory values are available.

A wide variety of other infections with similar exanthems can be confused with RMSF.[66] The most common include meningococcal infection, measles (rubeola) and atypical measles, gonococcemia, infectious mononucleosis, toxic shock syndrome, and enteroviral infections. Less common diseases include dengue, leptospirosis, murine typhus, and epidemic typhus. The recently described *R. parkeri* rickettsiosis should be considered.

Management

Treatment of RMSF consists of antibiotic therapy, supportive care, and possibly administration of steroids. An understanding of the underlying pathophysiologic changes and an appreciation of the systemic complications that can occur in the patient afflicted with RMSF are necessary for the formulation of a balanced therapeutic regimen. The course of the disease can be complicated by circulatory collapse, coma, renal failure, and electrolyte imbalances. Although these complications are often absent in the mildly ill patient, in whom antibiotic therapy alone usually suffices, they should be anticipated in the seriously ill patient, especially if the patient is first seen late in the disease course.[68]

The most important factor contributing to the persistent case fatality rate of 5% is delayed administration of specific antibiotic therapy. Without appropriate treatment, the fatality rate rises to 25%.[66] For a select group of early-stage, mildly ill patients, outpatient therapy with oral antibiotics can be successful if the patient is reliable and close follow-up observation is arranged. More severely ill patients in whom the diagnosis is uncertain should be hospitalized for administration of intravenous antibiotics.

Antibiotics

Antibiotic therapy is most effective when it is initiated during the early stages of disease, coincident with the initial appearance of the rash. Although data from randomized clinical trials about antibiotic selection for RMSF are lacking, doxycycline is still widely regarded as the therapeutic agent of choice for most patients,[71] including children.[72] Chloramphenicol should be considered only for patients in whom the tetracyclines have caused significant adverse events and for pregnant women (except those who are near term). The recommended doses of doxycycline and chloramphenicol are summarized in Table 134-5.

Table 134-5 Antibiotic Therapy for Rocky Mountain Spotted Fever*

PATIENT	DOXYCYCLINE† (ORAL OR INTRAVENOUS)	CHLORAMPHENICOL‡ (ORAL OR INTRAVENOUS)
Adult	100 mg bid; consider initial loading dose of 200 mg IV for seriously ill patients§	50-75 mg/kg/day, divided q6h
Child (<45 kg)	2.2 mg/kg PO q12h	50-75 mg/kg/day, divided q6h

Data from Dantas-Torres F: Rocky Mountain spotted fever. Lancet Infect Dis 7:724, 2007; and Chapman AS, et al: Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States. MMWR Recomm Rep 55:18, 2006.

*Continue treatment at least 3 days after fever subsides or until unequivocal clinical improvement is seen; minimum course, 5 to 7 days.

†Doxycycline should not be given to pregnant women.

‡Chloramphenicol should not be given to patients with thrombocytopenia; maximum of 1 g/day for children.

§Cunha BA: Clinical features of Rocky Mountain spotted fever. Lancet Infect Dis 8:143, 2008.

Although previous treatment guidelines recommended avoidance of doxycycline in children younger than 8 years, the American Academy of Pediatrics and the CDC currently recommend doxycycline as the agent of choice for treatment of RMSF in children of all ages.[49,70,73] The risk of cosmetically perceptible tooth staining appears to be small for a single course of treatment and is subordinate to the potential lethality of this illness.[68]

The effectiveness of therapy depends on both the duration of therapy and the interval between the onset of illness and the initiation of therapy. Treatment should begin as early as possible and continue for 7 to 10 days or until the patient is afebrile for 2 to 5 days. Patients who are clinically ill should be hospitalized for parenteral antibiotic treatment. Response to treatment, as manifested by decreasing fever and subsiding rash, generally occurs 36 to 48 hours after antibiotic therapy is begun. Resistance to chloramphenicol or the tetracyclines has not been reported.[55] Penicillin, erythromycin, cephalosporins, aminoglycosides, clindamycin, and sulfonamides are ineffective against RMSF. In fact, empirical use of these agents for presumed bacterial infections may potentially permit progression of the illness.

Symptom overlap between early meningococcal infection and RMSF frequently leads to both diagnoses being considered simultaneously. After blood and CSF culture specimens are obtained, empirical antibiotic coverage for both diseases with ceftriaxone plus doxycycline should be administered.

On occasion, secondary bacterial infection from the RMSF rash may occur. Although sulfonamides have recently become a mainstay for empirical treatment of methicillin-resistant *Staphylococcus aureus* skin infections, the use of these agents should be avoided in RMSF patients because their mechanism of inhibiting *p*-aminobenzoic acid may worsen the primary RMSF infection. The role of the new quinolones as potential replacements for doxycycline and chloramphenicol in the treatment of RMSF is as yet unproved. At present, no vaccine is available for RMSF.

Supportive Care

Major complications of RMSF, such as shock, congestive heart failure, disseminated intravascular coagulation, and ARDS, should be anticipated and standard supportive measures instituted when appropriate. Circulatory collapse is common in patients with

www.ketabpezeshki.com 66485457-66963820

severe illness and is a major contributor to morbidity and mortality in RMSF. Hypotension unresponsive to fluid administration may require the use of vasopressors such as dopamine. In the critically ill patient with widespread vasculitis, however, a delicate balance exists between maintenance of effective circulating volume and excessive leakage of fluids into the tissues, including the lungs and brain. Under these circumstances, the excessive administration of intravenous fluids can be catastrophic.[55] Isolation of the patient is unnecessary unless the diagnosis is still uncertain and other highly communicable illnesses, such as meningococcemia and measles, have not been excluded.

Corticosteroids

The use of steroids in RMSF is controversial and is not routinely recommended. However, these agents should be considered for severe cases of RMSF complicated by extensive vasculitis, encephalitis, and cerebral edema.[55] In these critically ill patients, short-term, high-dose steroid therapy is recommended along with concomitant specific antibiotic therapy.

Q FEVER

Perspective

Q fever was first described in 1937 in Australia as an occupational disease of abattoir workers and dairy farmers. Cattle, sheep, goats, and ticks are the primary reservoirs of the causative rickettsia, *Coxiella burnetii,* but many other species may be infected. The disease is now endemic worldwide, although it is rare in Scandinavian countries. The southern area of the Netherlands is presently experiencing a serious outbreak and has reported more than 4000 cases since 2007 and 500 cases with 11 deaths in 2010 alone.[74] France and Australia have significantly more cases than the United States. In the United States, the Midwest states and California currently have the highest incidences of Q fever. More than 30 cases have been seen in U.S. military personnel deployed in Iraq and Afghanistan. Approximately 80% of cases of Q fever occur in males.[75]

Principles of Disease

C. burnetii is extremely infectious for humans and animals; a single inhaled organism is sufficient to initiate infection in guinea pigs and probably in humans as well. The Q fever rickettsiae are extremely resistant to desiccation and to physical and chemical agents and can survive for long periods in an inanimate environment. Consequently, it is classified as a category B biologic warfare agent by the CDC and has been a nationally notifiable disease since 1999.[76] This organism's infectivity and estimated casualty rate have been judged to be comparable with those of anthrax. Humans most commonly are infected by inhalation of aerosolized particles from contaminated environments. Patients with Q fever rarely can recall a history of tick bite. The Rocky Mountain wood tick, *D. andersoni,* is the only currently known tick vector.

Clinical Features

The incubation period of Q fever ranges from 14 to 39 days, with an average of 20 days. Up to 60% of initial infections are asymptomatic.[77] The acute form of the disease includes clinical manifestations such as severe retrobulbar headache, fever with temperatures to 40° C or higher, shaking chills, general malaise, myalgia, and chest pain. Although Q fever is widely regarded as primarily a respiratory disease, the reported incidence of pulmonary involvement varies, ranging from 0 to 90%. The reasons for this reported variation are unclear, but explanations include geographic strain variation, plasmids that may regulate virulence, and the source, route, and dose of the agent. Hepatic involvement may be common, but liver dysfunction is usually minimal. Osteomyelitis in children, acute renal failure, and lymphocytic meningitis secondary to *C. burnetii* have been described.[78]

Q fever also may be a chronic infection, with or without an antecedent acute episode. Clinical syndromes with the chronic form of the disease include granulomatous hepatitis and culture-negative endocarditis. Endocarditis has been documented in up to 68% of patients with chronic Q fever, and the mortality rate for this group approaches 25%. Q fever accounts for 3 to 5% of all cases of endocarditis.[79] Most patients with Q fever in whom endocarditis develops have a history of valvular heart disease, particularly affecting the aortic valve. These patients should be especially cognizant of the potential hazards of Q fever infection and should be restricted from certain at-risk occupational settings. Patients with aneurysms and vascular grafts also are at risk.

Human fetal demise and deaths have been attributed to *C. burnetii* infection. Persons infected with human immunodeficiency virus (HIV) are at increased risk for contraction of Q fever.[80]

Diagnostic Strategies

The diagnosis of Q fever should be suspected in any patient with a severe febrile illness without obvious cause, especially someone who has had recent contact with sheep, cattle, goats, or animal byproducts. Because of the laboratory hazards associated with cultivation of Q fever rickettsiae, isolation of *C. burnetii* is not recommended for routine diagnosis. Rather, serologic studies such as IFA and ELISA are the preferred diagnostic tests, but the results are not identifiable until 2 to 3 weeks after the onset of illness.

C. burnetii displays an antigenic phase variation. In patients with acute Q fever, phase II antibodies dominate the humoral immune response and are detectable by the second week of illness, whereas phase I antibodies are prominent only in patients with chronic Q fever. Confirmation of a Q fever case requires (1) a fourfold increase in IgG titers between acute and convalescent samples or the presence of IgM phase II antibodies, (2) a positive PCR test result, (3) the culture of *C. burnetii* from a clinical specimen, or (4) the positive immunostaining of the organism in tissue.[76] Measurement of IgA and IgG together has been useful in diagnosis of endocarditis. The finding of granulomatous changes on bone marrow biopsy can be characteristic of Q fever in patients with osteomyelitis.[78]

Management

Uncomplicated acute Q fever is treated with doxycycline (200 mg once daily for 2 to 3 weeks). Acute disease with concomitant valvular heart disease is treated with doxycycline (200 mg once daily) plus hydroxychloroquine (600 mg once daily) for 1 year. Chronic sufferers should receive the same regimen for 1.5 to 3 years.[76,81] Combination therapy with both doxycycline and hydroxychloroquine has been shown to be effective for treatment of endocarditis in HIV-infected patients.[80] Strong evidence recommends combination therapy for endocarditis for 18 months and 24 months in patients with native valves and prosthetic valves, respectively, when serologic results are suboptimal.[82] Treatment of pregnant women with Q fever with long-term cotrimoxazole, although not always curative, has been shown to decrease complications to the fetus.[83]

In mass casualty situations, prophylaxis is accomplished with 5 to 7 days of doxycycline.[84] Most acute Q fever infections resolve without treatment, but the risk of chronic infection makes treatment advisable. The mortality rate is less than 1% in untreated patients and lower still in those treated with antibiotics. The

www.ketabpezeshki.com 66485457-66963820

prognosis is worse in those patients with protracted illness and hepatic involvement or endocarditis. Inactivated whole-cell vaccines for Q fever have proved effective for as long as 5 years. Vaccination can afford considerable protection to slaughterhouse and dairy workers and others at risk.[85] Information on handling of suspected or confirmed exposure to *C. burnetii* or bioterrorist threats can be found on the CDC website.

EHRLICHIOSES

Perspective

There are currently two major forms of human ehrlichiosis in the United States: human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA), caused by the bacteria *Ehrlichia chaffeensis* and *Anaplasma phagocytophilum,* respectively. In 2001, restructuring of the *Ehrlichia* phylogenetic branches placed the previously known bacteria of human granulocytic ehrlichiosis into the genus *Anaplasma*, hence the revised name. Both genera, *Ehrlichia* and *Anaplasma,* are now considered to be in the tribe Ehrlichieae, family Anaplasmataceae, but they are still collectively referred to as being in the group of diseases called ehrlichioses.[86,87] Before 1986, *Ehrlichia sennetsu* was the only member of the genus of these organisms thought to infect humans, having been isolated in Japan in 1954 as the causative agent of sennetsu fever, a mononucleosis-like illness. A third species, *Ehrlichia ewingii,* has been shown to cause human disease in the United States. HME was discovered in 1986 and HGA (previously human granulocytic ehrlichiosis) in 1994. Both are identified as emerging diseases by the CDC and are nationally notifiable diseases, reportable through the appropriate state departments.

More than 1220 cases of *E. chaffeensis* were reported in the United States between 1986 and 1997. From 1999 through 2001, the CDC collected a mean number of 81 and 190 cases, respectively, for HME and HGA. Seroprevalence rates up to 13% for *E. chaffeensis* in children in the southeast and south central states and 3 to 15% for *A. phagocytophilum* in adults in New York and Wisconsin strongly suggest that these diseases are highly underdiagnosed or under-reported (or both).[88] Misclassification from failure to confirm *Anaplasma* serologically most likely has led to underreporting of this disease.[89]

Both diseases peak around June through August. High-risk populations are similar to those at high risk for Lyme disease, including those living in endemic areas or with frequent contact with wildlife or rural, wooded areas. HME has been reported predominantly in the south central and southeastern United States; HGA mostly is found in the upper Midwest, New England, parts of the mid-Atlantic states, northern California, and many parts of Europe.[87,88,90]

Principles of Disease

The causative agents in the ehrlichioses are gram-negative, obligate intracellular rickettsia-like coccobacilli. Transmitted from the midgut and salivary glands of their tick vectors, these organisms reside in specific circulating leukocytes in human and other mammalian hosts. Reservoirs include the white-tailed deer and the white-footed mouse. *Ehrlichia canis* is the common pathogenic species in dogs.[91] The species *Ehrlichia equina* has been isolated in California elk. HME, transmitted by the Lone Star tick, *A. americanum,* is caused by the organism *Ehrlichia chaffeensis* (named for Fort Chaffee, Arkansas), which invades monocytes. *Ehrlichia ewingii* and *Ehrlichia muris* are also now known to be causative organisms.[92] *E. chaffeensis* has been isolated from *I. pacificus* ticks in California. *A. phagocytophilum* invades neutrophils (granulocytes), causing HGA, and in the United States is transmitted by the black-legged tick, *I. scapularis*, and its West Coast counterpart, the western black-legged tick, *I. pacificus.*[93] Deer, elk, and wild rodents are the main reservoirs for *Anaplasma*. Both ticks also are the vectors for Lyme disease. *A. phagocytophilum* has now been detected in significant numbers in various *Ixodes* human tick species in mainland Portugal, Italy, and Japan.[94-96] Two cases of HGA in Italy have been reported.[97]

Clinical Features

The clinical presentations of HME and HGA are similar, and for case management, it is not necessary to differentiate between the two illnesses. The average time to onset of symptoms (for HME) from tick discovery is 9 days but ranges from 0 to 34 days. More than 90% of patients with HME report a history of tick bite or tick exposure. Ehrlichiosis characteristically is manifested with abrupt onset of fever, headache, myalgia, and shaking chills. Other, less frequent manifestations include nausea, vomiting, diarrhea, abdominal pain, cough, and confusion. Leukopenia, thrombocytopenia, and elevated liver function test values can be seen in 50 to 90% of patients.[98]

Rashes occur in approximately one third of patients with HME but in only 2 to 11% of those with HGA. In a small series of pediatric patients (average age, 7.4 years) with HME, a rash rate of 67% was found. A majority of these patients suffered permanent cognitive or other neurologic damage.

Ehrlichiosis (HME) also has been associated with optic neuritis.[99] ARDS, meningitis, pancarditis, renal failure, and disseminated intravascular coagulation have been associated with the ehrlichioses. Case fatality rates vary between studies but range between 0.5 and 3% for both diseases, with HGA usually reported as the lower of the two. Approximately 45% of patients with HGA require hospitalization, although almost all recover without residual problems. HME has been associated with hemophagocytic lymphohistiocytosis.[100]

Diagnostic Strategies

For both HME and HGA, the initial diagnosis is based largely on clinical presentation. With most tests, the diagnosis will be retrospective; results rarely are available immediately. The most common mode of diagnosis is confirmation of acute and convalescent antibodies with IFA. Enzyme immunoassay and confirmatory tests with Western blot have been developed. PCR testing for DNA fragments, although not readily available in most hospitals, probably is most reliable in the acute phase of illness (at 1 week after onset of symptoms).[101] Diagnostic serologic testing is available at the CDC through state health departments.

Laboratory criteria required in the CDC's 2008 case definition to establish the presence of either HME or HGA include detection of either *E. chaffeensis* or *A. phagocytophilum,* respectively, through the use of the following diagnostic tests: (1) fourfold change in antibody titer to the organism antigen by IFA in paired serum samples, (2) positive result on PCR assay and confirmation of organism-specific DNA, (3) identification of morulae in leukocytes and a positive titer to the organism antigen, (4) immunostaining of organism antigen in a biopsy or autopsy specimen, or (5) culture of the organism from a clinical specimen. All tests require compatible clinical findings.[102,103] Most patients with acute ehrlichiosis have antibody titers greater than 1:160.[104]

Cytopenia and abnormal liver function usually resolve after the acute phase of illness by 14 to 28 days. Microscopic identification of mulberry-like clusters, called morulae, inside leukocytes on peripheral blood smears is helpful (Fig. 134-9), but this finding usually has disappeared after the first week of illness with HGA, especially if the patient has been treated with doxycycline. Cultures take up to 2 weeks to grow the organisms.

www.ketabpezeshki.com 66485457-66963820

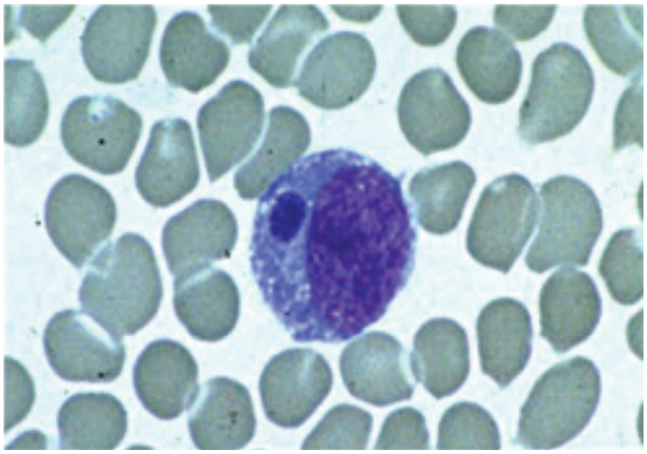


Figure 134-9. Morulae detected in a monocyte on a peripheral blood smear, associated with *Ehrlichia chaffeensis* infection. (From Centers for Disease Control and Prevention: Ehrlichiosis: Symptoms, diagnosis, and treatment, February 7, 2011. Available at www.cdc.gov/Ehrlichiosis/symptoms/index.html. Accessed May 16, 2011.)

Management

Tetracycline, which has been shown to be effective in cases of canine ehrlichiosis, is also effective in cases of human ehrlichiosis. Doxycycline (100 mg twice a day; 2.2 mg/kg body weight given twice a day for children weighing less than 45 kg) and tetracycline regimens for 7 to 14 days are curative. Most patients respond rapidly after treatment is begun, and fever subsides within 24 to 48 hours. Tooth staining is no longer considered a concern for children and should not be a reason to withhold therapy. Rifampin as an alternative has been shown to be effective in children with human ehrlichiosis. Data supporting the use of chloramphenicol are still inconclusive. The same ticks that transmit HGA (*Ixodes* species) also are responsible for Lyme disease and babesiosis. Each disease entity requires a full diagnostic workup because amoxicillin treats Lyme disease but not HGA or babesiosis, and doxycycline alone does not treat babesiosis. Failure of fever to resolve beyond 6 or 7 days of treatment of a suspected tick-borne disease should heighten suspicion of an alternative disease organism.[3]

BABESIOSIS

Perspective

Babesiosis is a tick-borne, malaria-like, acute febrile illness caused by intraerythrocytic protozoal parasites of the genus *Babesia*. Babesiosis has long been recognized as an important veterinary disease and probably was known in ancient times; in fact, it has been proposed that the fifth plague described in the Book of Exodus was actually babesiosis.

The first human cases of babesiosis were reported in Montana in 1904; investigators seeking the cause of RMSF examined blood smears from local inhabitants and described parasitic forms now known to be characteristic of *Babesia*. Since the late 1950s, several widely scattered cases (mostly in Europe) of human babesiosis have been reported in splenectomized persons. *Babesia divergens*, a species primarily infecting cattle, is the most common agent reported in Europe, but other species have been implicated as well, including *Babesia bovis, Babesia equi,* and a single case of *Babesia caucasia* infection. Two strains, WA1, related to a canine pathogen, *Babesia gibsoni,* and MO1, related to *B. divergens,* also have been found to cause disease in humans. In all of these reported cases, the course was fulminant and the disease usually fatal.

Since the late 1960s, more than 350 cases have been documented in the United States. Almost all of these cases were caused by *Babesia microti,* a rodent parasite, and occurred in the coastal regions of southern New England, where *B. microti* is endemic. New Jersey and the eastern part of Long Island recently have been found to be endemic with babesiosis as well.[105,106] Babesiosis also has been reported in Maryland, Virginia, Georgia, Wisconsin, Minnesota, California, and Washington. These cases differ from the European cases in that most (approximately 80%) have occurred in persons with intact spleens. Up to now, significant morbidity has been low in the United States despite lack of specific therapy. Asplenic persons, elders, and otherwise immunosuppressed patients usually have more severe disease.

Principles of Disease

B. microti is associated with deer and mice rather than with cattle. The ecology of *B. microti* is similar to that of *B. burgdorferi,* the etiologic agent of Lyme disease, with the same major vector, *I. scapularis,* and the same mammalian reservoirs: white-footed mice, which host the larval and nymphal stages of the tick, and white-tailed deer, which host the adult ticks.

Human babesiosis results from accidental human intrusion on the natural cycle of infection. The nymphal form of the *Ixodes* tick most commonly transmits the disease to humans, although babesiosis also can be transmitted by the adult tick. *I. scapularis* nymphs measure only 1 to 2 mm long and thus are easily overlooked by the patient (see Fig. 134-4). In more than half of all cases of babesiosis, patients cannot recall tick exposure. As is true for other tick-borne illnesses, the peak incidence of babesiosis is between May and August, coinciding with the nymphal feeding period and also the time of maximal human exposure in endemic areas. Babesiosis acquired through blood transfusion is well documented.

Clinical Features

Babesiosis has an incubation period of 1 to 4 weeks after tick exposure. A nonspecific influenza-like illness, with fever, chills, headache, fatigue, and anorexia, is characteristic. Less common manifestations are nausea, diaphoresis, depression, photophobia, myalgias, arthralgias, dark urine, emotional lability, and hyperesthesias. Unlike in Lyme disease, rash is not a feature of this illness; however, erythema figuratum, a widespread exanthem with well-established annular lesions, has been associated with septic babesiosis.[107] Physical examination usually reveals normal findings, except for fever, which typically is present, and splenomegaly, which occurs in some patients. Meningeal signs are absent. More severe disease occurs in splenectomized patients; hypotension, severe hemolytic anemia, hemoglobinuria, jaundice, renal insufficiency, ARDS, and disseminated intravascular coagulation can be seen in these cases.[106] Some patients with babesiosis are only mildly ill, and asymptomatic infection also may occur, as demonstrated by serologic surveys in endemic areas. The diagnosis of babesiosis should be considered in any febrile patient from an endemic area during the tick season and should be part of the differential diagnosis for post-transfusion infections.

Diagnostic Strategies

The diagnosis may be established through microscopy, antibody detection through IFA staining, or PCR assay. Microscopic examination is done with thick and thin Giemsa-stained blood smears. Characteristic intraerythrocytic forms (piriform, ring, tetrad) may be present. Babesiosis has been known to be misdiagnosed as malaria. Malaria may be excluded by the absence of intracellular pigment granules, schizonts, and gametocytes. The presence of parasites in budding tetrad formation, resembling a Maltese cross,

www.ketabpezeshki.com 66485457-66963820

is more suggestive of babesiosis, although contrary to what is commonly taught, this finding is uncommon. Because parasitemia may vary, serial smears during the course of several days may be necessary in suspected cases. An immunohistochemical assay has been developed that further allows easier microscopic differentiation between babesiosis and malarial organisms.[108]

The diagnosis can be confirmed by serologic studies. IFA antibody to *B. microti* is available through the CDC, and titers usually rise to 1:1024 or greater within the first few weeks of illness. IgM–indirect IFA is sensitive and specific in acute babesiosis. Serologic tests for Lyme disease, which shares a common tick vector with babesiosis, also should be performed; concurrent Lyme disease has been reported in up to 50% of cases of babesiosis.[105] ELISA and IFA sensitivities rise significantly after 5 days of illness, whereas PCR is more useful in the earlier days of sampling.[109]

Parasitemia observed at 1 to 4 weeks after inoculation of blood from infected patients into gerbils or hamsters supports the diagnosis. Other nonspecific laboratory findings include mild to moderate hemolytic anemia, which is present in most patients, and resultant mild elevations in bilirubin and serum lactate dehydrogenase.

Management

Patients who have not undergone splenectomy generally recover without specific therapy, although prolonged malaise and fatigue are common. In patients with severe disease and in those who have had splenectomies, the combination of clindamycin (1.2 g twice daily intravenously or 600 mg three times a day orally) plus quinine (650 mg three times a day orally) has been shown to be effective and is currently the treatment of choice. An alternative regimen that may be better tolerated, especially by children and infants, consists of atovaquone (750 mg twice daily orally) plus azithromycin (500-1000 mg once followed by 250 mg once a day orally); up to 25% of patients may have an adverse effect from quinine. Pediatric doses need to be adjusted accordingly. Therapy should be continued for a minimum of 7 to 10 days.[110-112] Development of resistance during treatment with azithromycin-atovaquone in immunocompromised patients has been described.[113]

Other antimalarial drugs, such as chloroquine and quinacrine, are not effective. Fulminantly ill patients with marked degrees of parasitemia and hemolysis have benefited from exchange transfusion.[106] Effective live vaccines have been developed for bovine babesiosis but not yet for human disease.[114]

COLORADO TICK FEVER

Perspective

Endemic to the Rocky Mountain area, Colorado tick fever is an acute tick-borne viral infection characterized by headache, back pain, biphasic febrile course, and leukopenia. The etiologic agent of Colorado tick fever is a small RNA virus of the genus *Coltivirus,* family Reoviridae. It is one of more than 500 viruses in the heterogeneous group of arthropod-borne viruses (arboviruses). Colorado tick fever has a sharply defined endemic zone encompassing mountainous and highland areas, from an altitude of approximately 4000 feet to more than 10,000 feet, in the Canadian provinces of British Columbia and Alberta and in at least 11 western states (California, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, South Dakota, Utah, Washington, and Wyoming). The largest number of cases has been reported in Colorado. The distribution of the virus coincides with that of its principal tick vector, *D. andersoni,* the Rocky Mountain wood tick. Although RMSF is transmitted by the same vector, that disease is far less common in Colorado. The cases of RMSF are outnumbered at least 20-fold by cases of Colorado tick fever.

Principles of Disease

The Colorado tick fever virus has been isolated from at least eight species of ticks, but *D. andersoni* is the only proven vector for humans. The tick is a significant reservoir for the virus because transstadial transmission (from larva to nymph to adult) of virus occurs, and the tick remains infected and infectious for life (up to 3 years). The primary vertebrate host species for Colorado tick fever virus maintenance are the chipmunk, *Tamias minimus,* and the golden-mantled ground squirrel, *Spermophilus lateralis*; many other vertebrate hosts have been identified as well, including a species of porcupine in Colorado in Rocky Mountain National Park. Larval and nymphal stages of *D. andersoni* ticks are responsible for transmission of Colorado tick fever virus among rodents, and overwintering of the virus is accomplished by nymphal and adult *D. andersoni*. Only adult ticks transmit Colorado tick fever virus to humans.

Several hundred cases per year are reported in the United States. The actual incidence undoubtedly is much higher because many cases are diagnosed as nonspecific viral illness, and other cases may be mild or entirely subclinical. Human susceptibility to Colorado tick fever is universal, but it occurs most commonly in young men, reflecting greater occupational and recreational tick exposure.

Clinical Features

After an incubation period of approximately 3 to 5 days (range, 0-14 days), a moderate to severe influenza-like illness occurs abruptly, with signs and symptoms similar to those in the early stage of RMSF. Fever, chills, headache, retrobulbar pain, myalgia, lethargy, anorexia, and nausea are common; vomiting and abdominal pain occasionally are reported. Early physical findings are nonspecific. A macular or maculopapular rash has been reported in 5 to 12% of patients, but unlike the rash of RMSF, the rash of Colorado tick fever is not a prominent feature of the illness.

A distinct feature of the illness is a biphasic course that occurs in approximately 50% of patients, causing a characteristic "saddle-back" fever curve. Initial symptoms resolve after 2 to 3 days, and the patient feels relatively well for 1 or 2 days, after which the fever, headache, and myalgias return. The second phase may be more intense than the first phase and generally lasts 2 to 4 days. There may even be a third febrile period. Alternatively, a single prolonged febrile illness may occur. Recovery from Colorado tick fever usually occurs within 2 weeks, but convalescence can be prolonged, especially in patients older than 30 years.

Colorado tick fever is a self-limited disease, and virtually all patients recover without sequelae. Reports of severe complications, such as meningoencephalitis and hemorrhagic diathesis, have been limited to children. Only a few fatal cases have been recorded.

Diagnostic Strategies

The peripheral leukocyte count often is depressed during the acute phase of illness to as low as 1000/μL, with a relative lymphocytosis. Transient thrombocytopenia can accompany the leukopenia, and less often a mild anemia can occur. These hematologic abnormalities normalize during convalescence, but persistence of the virus in red blood cells causes a prolonged viremia even when clinical recovery is complete. Transfusion-acquired infection has been reported and is caused by this persistent viremia in asymptomatic blood donors.

The diagnosis of Colorado tick fever can be confirmed by serologic testing (IFA, neutralizing antibody, complement fixation, enzyme immunoassay) of acute and convalescent samples, but serologic study is of little help early on because of the slow rise of

www.ketabpezeshki.com 66485457-66963820

titers. The most rapid confirmation of Colorado tick fever, with corresponding elimination of concern about possible RMSF, is provided by direct immunofluorescent staining of virus in red blood cells in peripheral blood smears. PCR testing is now available for more rapid diagnosis. An ELISA test has shown promising sensitivity in detection of the Colorado tick fever virus.[115]

Management

Treatment of Colorado tick fever is supportive only. Most patients do not require hospitalization, but if RMSF remains a diagnostic possibility, initial treatment with tetracycline or chloramphenicol and a period of observation are necessary until the diagnosis of RMSF can be ruled out.

TICK PARALYSIS

Perspective

Tick paralysis occurs when an adult female tick attaches to a host and releases a neurotoxin that can produce cerebellar dysfunction or an ascending paralysis. Tick paralysis was recognized as early as the beginning of the 19th century. Hovell, while traveling through Australia, wrote in 1824 of "the small insect called the tick, which buries itself in the flesh, and would in the end destroy either human or beast if not removed in time."[116]

Tick paralysis has been reported worldwide, but most cases occur in the southeastern and northwestern regions of the United States, western Canada, and Australia. Cases have been reported to occur in clusters.[117] Forty-three species of ticks have been found to cause tick paralysis in humans, other mammals, or birds. Most cases in North America and Canada are caused by *D. andersoni* (Rocky Mountain wood tick) and *D. variabilis* (American dog tick); species responsible for paralysis cases that also are associated with other tick-borne diseases include *A. americanum* (Lone Star tick), *I. scapularis* (black-legged tick), and *I. pacificus* (western black-legged tick); in Australia, *Ixodes holocyclus* is primarily associated with this disorder. Family Argasidae ticks (soft ticks) also have been implicated. Tick paralysis usually occurs in the spring and summer months, and most reported cases are in children, primarily girls, probably because ticks are more easily concealed in longer hair. Among adults, however, more men than women acquire the disease.

Principles of Disease

Tick paralysis is thought to be caused by a toxin secreted from the salivary glands of the tick during a blood meal. The toxin, ixobotoxin, affects sodium flux across axonal membranes without affecting the neuromuscular junction itself.[118] The mechanism of action of the toxin is poorly understood, but it appears to produce a conduction block in the peripheral branches of motor fibers, resulting in a failure of release of acetylcholine at the neuromuscular junction. Electrophysiologic studies have confirmed a rapid reversal of significant impairment of motor nerve terminal function after tick removal, indicating that the disturbance is not a result of a neuromuscular junction defect.[119] Possible central sites of action of the toxin have been postulated to explain cases in which the clinical picture is dominated by cerebellar dysfunction.

Clinical Features

Onset of symptoms usually occurs 4 to 7 days after the tick attaches. Initial manifestations include restlessness and irritability, followed by ascending flaccid paralysis, acute ataxia, or a combination of the two. Deep tendon reflexes are almost invariably lost. These signs and symptoms can progress rapidly during a few days to bulbar involvement, respiratory paralysis, and ultimately death if the tick is not detected and removed.

The ascending nature of tick paralysis has been noted in most descriptions; however, ataxia and associated cerebellar abnormalities in the absence of muscle weakness may be seen. Thus, tick paralysis may sometimes be manifested as "tick ataxia." Isolated facial paralysis has been reported in patients with ticks embedded behind the ear. Fever, other systemic symptoms, and sensory deficits are unusual. Concomitant infection with Colorado tick fever has been reported.

Diagnostic Strategies

No diagnostic tests to confirm tick paralysis are available other than the combination of the clinical scenario, the presence of a tick, and the improvement after its removal. The Tensilon test yields a negative result in patients with this condition, and CSF is normal.[119]

Differential Considerations

Tick paralysis should be considered in the differential diagnosis for any patient thought to have Guillain-Barré syndrome, Eaton-Lambert syndrome, myasthenia gravis, poliomyelitis, botulism, diphtheritic polyneuropathy, or any disease with an acute onset of ascending flaccid paralysis or acute ataxia. Ocular findings, such as decreased convergence, unresponsive dilated pupils, and nystagmus (horizontal and vertical), seen early in tick paralysis can help distinguish this disease from Guillain-Barré syndrome.[120]

Management

Treatment in the United States consists simply of removing the tick; improvement generally is seen within a few hours and complete recovery within 48 hours. Supportive care, including mechanical ventilation, may be necessary. The mortality rate is approximately 10%; nearly all patients who die are children. The recommended procedure for the removal of any tick (including ticks causing tick paralysis) is summarized in Box 134-2. Traditional methods, such as burning, forceful removal, and application of petroleum, viscous lidocaine, or gasoline, are not consistently successful and do not guarantee removal of mouthparts, where the salivary glands and toxin may remain. Retained mouthparts also may cause infection.

Tick paralysis in Australia often is more devastating than in the United States. Symptoms and signs of illness caused by the

Box 134-2 Recommended Method for Tick Removal

1. Remove an embedded tick by grasping it with blunt forceps or tweezers as close to the point of attachment as possible.
2. Do not use bare fingers to remove ticks from animals or humans; when tweezers are unavailable, fingers should be shielded with a tissue, paper towel, or rubber glove.
3. Apply gentle, steady, upward traction with the forceps; do not twist or jerk the tick. Avoid squeezing or crushing the tick.
4. Do not handle the tick with bare hands. After removal of the tick, thoroughly disinfect the bite site and wash hands with soap and water.
5. Dispose of ticks by placing them in a container of alcohol or flushing them down the toilet.

Modified from Needham GR: Evaluation of five popular methods for tick removal. Pediatrics 75:997, 1985.

www.ketabpezeshki.com 66485457-66963820

Australian tick, *I. holocyclus,* do not resolve and often worsen after tick removal. Hyperimmune serum is available in Australia and often is needed because symptoms may worsen up to 48 hours after removal.

Prophylaxis with Insect Repellents

Insect repellents have long been used to prevent mosquito bites. With recent increased public awareness of and concern about tick-borne illness, especially Lyme disease, skin and clothing repellents are now also being marketed for tick protection.

Three active ingredients in repellants have been shown to be effective against blood-sucking arthropods, including ticks: *N,N*-diethyl-*m*-toluamide or DEET, picaridin in KBR 3023 (known as Bayrepel, Hepidanin, and Autan Repel outside the United States), and *p*-menthane-3,8-diol (PMD) in oil of lemon eucalyptus. The most effective and most studied is DEET. Formulation percentages of DEET vary widely, ranging from 4.75 to 23.8%, giving 1½ to 5 hours of protection, respectively.[121] A long-acting 35% DEET formulation (U.S. Army Extended Duration Topical Insect and Arthropod Repellent [EDTIAR]), available in the United States as Ultrathon (3M), provides protection for 6 to 12 hours. Picaridin is as effective as the 35% DEET formulation.[122] Despite some earlier concerns, toxic and allergic reactions to DEET have been uncommon, and serious adverse effects are rare. Used as directed, concentrations up to 50% appear to be safe even in young children, although toxic encephalopathy rarely can occur.[123] Use on infants younger than 2 months is not recommended.

Permethrin, actually a contact insecticide rather than a repellent, can be used as a clothing spray for protection against ticks. Applied to the clothing as an aerosol, it is nonstaining, nearly odorless, and resistant to degradation by light, heat, or immersion in water. Permethrin is toxic to the nervous system of insects, but in mammals it is poorly absorbed and rapidly inactivated. Reported adverse effects have been limited to the skin and are uncommon.

Both topical DEET and clothing impregnated with permethrin have been shown to be effective in field trials when each is used alone. Wearing of protective clothing treated with permethrin in addition to use of DEET on exposed skin provides the greatest degree of protection against tick bites.[123]

KEY CONCEPTS

- Tick-borne illnesses frequently are misdiagnosed as viral or bacterial infections. Early diagnosis can be facilitated by considering these diagnoses in patients who live in or recently have traveled to endemic areas and by routinely asking for a history of recent tick or insect bites in patients who present with febrile illnesses.
- Lyme disease should be suspected in patients who present with signs of a viral illness, monarticular arthritis, meningitis, multiple neurologic abnormalities, or heart block. Diagnosis can be confirmed with serologic testing of acute and convalescent serum samples. Normal physiologic changes from bites should not be confused with erythema migrans. A significant amount of time of attachment is required for transmission of disease.
- Relapsing fever should be suspected in patients who present with recurrent viral-like illness associated with high fever. The diagnosis can be confirmed by identification of spirochetes on a blood smear obtained during a period of rising temperature.
- Ulceroglandular tularemia should be suspected in patients with slow-healing extremity ulcers associated with large lesions of regional adenopathy (buboes). The diagnosis can be confirmed with serologic testing.
- RMSF should be considered in patients who present with an unexplained febrile illness, even in the absence of a rash or known tick exposure. Delayed diagnosis and late initiation of specific antirickettsial therapy may lead to a fatal outcome. Treatment never should be delayed pending laboratory diagnosis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Arthur DR: Ticks in Egypt in 1500 BC? *Nature* 1965; 206:1060.
2. Steere AC, et al: Lyme arthritis: An epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. *Arthritis Rheum* 1977; 20:7.
3. Wormser GP, et al: The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: Clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; 43:1089.
4. Centers for Disease Control and Prevention: Lyme disease—United States, 2003-2005. *MMWR Morb Mortal Wkly Rep* 2007; 56:573.
5. Wormser GP: Clinical practice: Early Lyme disease. *N Engl J Med* 2006; 354:2794.
6. Halperin JJ, et al: Practice parameter: Treatment of nervous system Lyme disease (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2007; 69:91.
7. van der Linde MR, et al: Range of atrioventricular conduction disturbances in Lyme borreliosis: A report of four cases and review of other published reports. *Br Heart J* 1990; 63:162.
8. Helmick CG, et al: Estimates of the prevalence of arthritis and other rheumatic conditions in the US. *Arthritis Rheum* 2008; 58:15-25.
9. Charil A, et al: MRI and the diagnosis of multiple sclerosis: Expanding the concept of "no better explanation." *Lancet Neurol* 2007; 5:841-852.
10. Centers for Disease Control and Prevention: Notice to readers: Caution regarding testing for Lyme disease. *MMWR Morb Mortal Wkly Rep* 2005; 54:125.
11. Steere AC: Lyme disease. *N Engl J Med* 2001; 345:115.
12. Reed KD: Laboratory testing for Lyme disease: Possibilities and practicalities. *J Clin Microbiol* 2002; 40:319.
13. Dumler JS: Molecular diagnosis of Lyme disease: Review and meta-analysis. *Mol Diagn* 2001; 6:1.
14. Treatment of Lyme disease: New drugs for allergic conjunctivitis. *Med Lett Drugs Ther* 2000; 42:37.
15. Nadelman RB, et al: Prophylaxis with single-dose doxycycline for the prevention of Lyme disease after an *Ixodes scapularis* tick bite. *N Engl J Med* 2001; 345:79.
16. Murphy FK, et al: Acute respiratory distress syndrome in persons with tickborne relapsing fever—three states, 2004-2005. *MMWR Morb Mortal Wkly Rep* 2007; 56:1073.
17. Centers for Disease Control and Prevention: Tickborne relapsing fever outbreak after a family gathering—New Mexico, August 2002. *MMWR Morb Mortal Wkly Rep* 2003; 53:809.
18. Centers for Disease Control and Prevention, Division of Vector-Borne Diseases: Tick-borne relapsing fever: Laboratory testing, February 18, 2008. Available at www.cdc.gov/ncidod/dvbid/RelapsingFever/TBRF_LabTesting.html. Accessed May 12, 2011.
19. Lim L, Rosenbaum J: *Borrelia hermsii* causing relapsing fever and uveitis. *Am J Ophthalmol* 2006; 142:348.
20. Uhlmann EJ, et al: Polymerase chain reaction of tick-borne relapsing fever caused by *Borrelia hermsii*. *Pediatr Infect Dis J* 2007; 26:267.
21. Hasin T, et al: Postexposure treatment with doxycycline for the prevention of tick-borne relapsing fever. *N Engl J Med* 2006; 355:148.
22. Larsson C, et al: Complications of pregnancy and transplacental transmission of relapsing-fever borreliosis. *J Infect Dis* 2006; 194:1367-1374.
23. Sjostedt A: Tularemia: History, epidemiology, pathogen physiology, and clinical manifestations. *Ann N Y Acad Sci* 2007; 1105:1.
24. Provisional cases of selected notifiable diseases, United States, weeks ending December 17, 2005, and December 18, 2004. *MMWR Morb Mortal Wkly Rep* 2005; 54:1289.
25. Levy L, Chiang W: Tularemia—United States, 1990-2000. *MMWR Morb Mortal Wkly Rep* 2002; 51:181.
26. Weinberg AN, Branda JA: Case records of the Massachusetts General Hospital. Case 31-2010. A 29-year-old woman with fever after a cat bite. *N Engl J Med* 2010; 363:1560.
27. Lindley C, et al: Public health dispatch: Outbreak of tularemia among commercially distributed prairie dogs, 2002. *MMWR Morb Mortal Wkly Rep* 2002; 51:688.
28. Eliasson H, et al: The 2000 tularemia outbreak: A case-control study of risk factors in disease-endemic and -emergent areas, Sweden. *Emerg Infect Dis* 2002; 8:956.
29. Tularemia transmitted by insect bites—Wyoming, 2001-2003. *MMWR Morb Mortal Wkly Rep* 2005; 54:170.
30. Calanan RM, et al: Tularemia outbreak associated with outdoor exposure along the western side of Utah Lake, Utah, 2007. *Public Health Rep* 2010; 125:870.
31. Vyrostekova V, et al: Prevalence of coinfection of *Francisella tularensis* in reservoir animals of *Borrelia burgdorferi* sensu lato. *Wien Klin Wochenschr* 2002; 114:482.
32. Feldman KA, et al: Tularemia on Martha's Vineyard: Seroprevalence and occupational risk. *Emerg Infect Dis* 2003; 9:350.
33. Reinties R, et al: Tularemia outbreak investigation in Kosovo: Case control and environmental studies. *Emerg Infect Dis* 2002; 8:69.
34. Conlan JW, Oyston PCF: Vaccines against *Francisella tularensis*. *Ann N Y Acad Sci* 2007; 1105:325.
35. Eachempati SR, Flomenbaum N, Barie PS: Biological warfare: Current concerns for the health care provider. *J Trauma* 2002; 52:179.
36. Centers for Disease Control and Prevention: Emergency preparedness and response: Bioterrorism agents/diseases. Available at www.emergency.cdc.gov/agent/agentlist-category.asp. Accessed May 19, 2011.
37. Stupak HD, et al: Tularemia of the head and neck: A possible sign of bioterrorism. *Ear Nose Throat J* 2003; 82:263.
38. Dennis DT, et al: Tularemia as a biological weapon: Medical and public health management. *JAMA* 2001; 285:2763.
39. Percentage of hospitals with staff members trained to respond to selected terrorism-related diseases or exposures—National Hospital Ambulatory Medical Care Survey, United States, 2003-2004. *MMWR Morb Mortal Wkly Rep* 2007; 56:401.
40. Stralin K, et al: An outbreak of primary pneumonic tularemia. *N Engl J Med* 2002; 346:1027.
41. Johansson A, et al: The development of tools for diagnosis of tularemia and typing of *Francisella tularensis* [abstract]. *APMIS* 2004; 112:898.
42. Johansson A, et al: Comparative analysis of PCR versus culture for diagnosis of ulceroglandular tularemia. *J Clin Microbiol* 2000; 38:22.
43. Maurin M, et al: Real-time PCR for diagnosis of oculoglandular tularemia. *Emerg Infect Dis* 2010; 16:153.
44. Berdal BP, et al: Field detection of *Francisella tularensis*. *Scand J Infect Dis* 2000; 32:287.
45. Tarnvik A, Chu MC: New approaches to diagnosis and therapy of tularemia. *Ann N Y Acad Sci* 2007; 1105:378-404.
46. Chen LF, Sexton DJ: What's new in Rocky Mountain spotted fever? *Infect Dis Clin North Am* 2008; 22:415.
47. Centers for Disease Control and Prevention: Statistics and epidemiology: Annual cases of RMSF in the United States, November 4, 2010. Available at www.cdc.gov/rmsf/stats/. Accessed May 12, 2011.
48. Swerdlow D: *Rocky Mountain spotted fever: Overview*. CDC: Rocky Mountain Spotted Fever: Prevention and Control. Presented at the Infectious Diseases Society of America 45th Annual Meeting, San Diego; October 4-7, 2007.
49. Centers for Disease Control and Prevention: Rocky Mountain spotted fever, January 18, 2011. Available at www.cdc.gov/ncidod/dvrd/rmsf/overview.htm. Accessed May 19, 2011.
50. Raoult D, Parola P: Rocky Mountain spotted fever in the USA: A benign disease or a common diagnostic error? *Lancet Infect Dis* 2008; 8:587.
51. Holman RC, McQuiston JH, Haberling DL, Cheek JE: Increasing incidence of Rocky Mountain spotted fever among the American Indian population in the United States. *Am J Trop Med Hyg* 2009; 80:601.
52. Openshaw JJ, et al: Rocky mountain spotted fever in the United States, 2000-2007: Interpreting contemporary increases in incidence. *Am J Trop Med Hyg* 2010; 83:174.
53. Paddock CD, et al: *Rickettsia parkeri* rickettsiosis and its clinical distinction from Rocky Mountain spotted fever. *Clin Infect Dis* 2008; 47:1188.
54. Paddock CD, et al: Assessing the magnitude of fatal Rocky Mountain spotted fever in the United States: Comparison of two national data sources. *Am J Trop Med Hyg* 2002; 67:349.
55. Treadwell TA, et al: Rocky Mountain spotted fever in the United States, 1993-1996. *Am J Trop Med Hyg* 2000; 63:21.
56. Maxey EE: Some observations of the so-called spotted fever of Idaho. *Med Sentinel* 1899; 10:433.
57. Adjemian JZ, et al: Spatial clustering of disease severity among reported Rocky Mountain spotted fever cases in the United States, 2001-2005. *Am J Trop Med Hyg* 2009; 80:72.
58. Gross D, Schafer G: 100th anniversary of the death of Ricketts: Howard Taylor Ricketts (1871-1910). The namesake of the Rickettsiaceae family. *Microbes Infect* 2011; 13:10.
59. Dantas-Torres F: Rocky Mountain spotted fever. *Lancet Infect Dis* 2007; 7:724.
60. Demma LJ, et al: Rocky Mountain spotted fever from an unexpected tick vector in Arizona. *N Engl J Med* 2005; 353:587.

www.ketabpezeshki.com 66485457-66963820

61. Oliveira KA, et al: *Amblyomma imitator* ticks as vectors of *Rickettsia rickettsii,* Mexico. *Emerg Infect Dis* 2010; 16:1282.
62. McQuiston JH, et al: Evidence of exposure to spotted fever group rickettsiae among Arizona dogs outside a previously documented outbreak area. *Zoonoses Public Health* 2011; 58:85.
63. Elchos BN, Goddard J: Implications of presumptive fatal Rocky Mountain spotted fever in two dogs and their owner. *J Am Vet Med Assoc* 2003; 233:1450.
64. Arguin PM, et al: An investigation into the possibility of transmission of tick-borne pathogens via blood transfusion. Transfusion-Associated Tick-Borne Illness Task Force. *Transfusion* 1999; 39:828.
65. Buckingham SC, et al: Clinical and laboratory features, hospital course, and outcome of Rocky Mountain spotted fever in children. *J Pediatr* 2007; 150:180.
66. Lacz NL, Schwartz RA, Kapila R: Rocky Mountain spotted fever. *J Eur Acad Dermatol Venereol* 2006; 20:411.
67. Doyle A, et al: Myocardial involvement in Rocky Mountain spotted fever: A case report and review. *Am J Med Sci* 2006; 332:208.
68. Masters EJ, et al: Rocky Mountain spotted fever: A clinician's dilemma. *Arch Intern Med* 2003; 163:769.
69. Affiliated Medical Services Reference Laboratory: Lab test directory. Rocky Mountain spotted fever antibody. Available at www.amsreferencelab.com/cgi-bin/test-directory?page=details&item=RMSFA-640. Accessed May 19, 2011.
70. Centers for Disease Control and Prevention: Consequences of delayed diagnosis of Rocky Mountain spotted fever in children: West Virginia, Michigan, Tennessee, and Oklahoma, May-July 2000. *MMWR Morb Mortal Wkly Rep* 2000; 49:885.
71. Donovan BJ, et al: Treatment of tick-borne diseases. *Ann Pharmacother* 2002; 36:1590.
72. Centers for Disease Control and Prevention: *Rocky Mountain spotted fever: Symptoms, diagnosis, and treatment*, November 4, 2010. Available at http://www.cdc.gov/rmsf/symptoms/index.html. Accessed May 18, 2011.
73. *Rocky Mountain spotted fever*. In: Pickering L, ed: *2003 Red Book: Report of the Commission on Infectious Diseases*, 26th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2003.
74. Hartzell JD, et al: Q fever: Epidemiology, diagnosis, and treatment. *Mayo Clin Proc* 2008; 83:574.
75. Centers for Disease Control and Prevention: In the news: Q fever in The Netherlands. Available at wwwnc.cdc.gov/travel/notices/in-the-news/q-fever-netherlands.htm. Accessed May 16, 2011.
76. Centers for Disease Control and Prevention: Q fever: Diagnosis & laboratory guidance for clinicians, September 28, 2007. Available at www.bt.cdc.gov/agent/qfever/clinicians/diagnosis.asp. Accessed May 6, 2011.
77. Raoult D, Marrie T, Mege J: Natural history and pathophysiology of Q fever. *Lancet Infect Dis* 2005; 5:219.
78. Nourse C, et al: Three cases of Q fever osteomyelitis in children and a review of the literature. *Clin Infect Dis* 2004; 39:e61.
79. Gami AS, et al: Q fever endocarditis in the United States. *Mayo Clin Proc* 2004; 79:253.
80. Fenollar F, et al: Risk factors and prevention of Q fever endocarditis. *Clin Infect Dis* 2001; 33:312.
81. Raoult D, et al: Q fever 1985-1998: Clinical and epidemiologic features of 1,383 infections. *Medicine (Baltimore)* 2000; 79:109.
82. Million M, Thuny F, Richet H, Raoult D: Long-term outcome of Q fever endocarditis: A 26-year personal survey. *Lancet Infect Dis* 2010; 10:527.
83. Carcopino X, et al: Managing Q fever during pregnancy: The benefits of long-term cotrimoxazole therapy. *Clin Infect Dis* 2007; 45:548.
84. Kagawa FT, Wehner JH, Mohindra V: Q fever as a biological weapon. *Semin Respir Infect* 2003; 18:183.
85. Gefenaite G, et al: Effectiveness of the Q fever vaccine: A meta-analysis. *Vaccine* 2011; 29:395.
86. Dumler JS, et al: Reorganization of genera in the families Rickettsiaceae and Anaplasmataceae in the order Rickettsiales: Unification of some species of *Ehrlichia* with *Anaplasma, Cowdria* with *Ehrlichia* and *Ehrlichia* with *Neorickettsia,* descriptions of six new species combinations and designation of *Ehrlichia equi* and "HGE agent" as subjective synonyms of *Ehrlichia phagocytophila*. *Int J Syst Evol Microbiol* 2001; 51:2145.
87. Dumler JS, et al: Human granulocytic anaplasmosis and *Anaplasma phagocytophilum*. *Emerg Infect Dis* 2005; 11:1828.
88. McQuiston JH, McCall CL, Nicholson WL: Ehrlichiosis and related infections. *J Am Vet Med Assoc* 2003; 223:1750.
89. Centers for Disease Control and Prevention: Anaplasmosis and ehrlichiosis—Maine, 2008. *MMWR Morb Mortal Wkly Rep* 2009; 58:1033.
90. Centers for Disease Control and Prevention: Summary: Provisional causes of notifiable diseases, United States, cumulative, week ending January 1, 2000. *MMWR Morb Mortal Wkly Rep* 2000; 48:1183.
91. Cohn LA: Ehrlichiosis and related infections. *Vet Clin North Am Small Anim Pract* 2003; 33:863.
92. Centers for Disease Control and Prevention: Ehrlichiosis: Symptoms, diagnosis, and treatment, February 7, 2011. Available at www.cdc.gov/Ehrlichiosis/symptoms/index.html. Accessed May 16, 2011.
93. Krause PJ, Corrow L, Bakken JS: Successful treatment of human granulocytic ehrlichiosis in children using rifampin. *Pediatrics* 2003; 112:e252.
94. Santos AS, et al: Detection of *Anaplasma phagocytophilum* DNA in *Ixodes* ticks (Acari: Ixodidae) from Madeira Island and Setubal District, mainland Portugal. *Emerg Infect Dis* 2004; 10:9.
95. Alberti A, et al: *Anaplasma phagocytophilum,* Sardinia, Italy. *Emerg Infect Dis* 2005; 11:8.
96. Ohashi N, et al: *Anaplasma phagocytophilum*-infected ticks, Japan. *Emerg Infect Dis* 2005; 11:11.
97. Ruscio M, Cinco M: Human granulocytic ehrlichiosis in Italy: First report on two confirmed cases. *Ann N Y Acad Sci* 2003; 990:350.
98. Olano JP, et al: Human monocytotropic ehrlichiosis, Missouri. *Emerg Infect Dis* 2003; 9:1579.
99. Lee MS, Goslee TE, Lessell S: Ehrlichiosis optic neuritis. *Am J Ophthalmol* 2003; 135:412.
100. Hanson D, Walter AW, Powell J: *Ehrlichia*-induced hemophagocytic lymphohistiocytosis in two children. *Pediatr Blood Cancer* 2011; 56:661.
101. Eshoo MW, et al: Detection and identification of *Ehrlichia* species in blood by use of PCR and electrospray ionization mass spectrometry. *J Clin Microbiol* 2010; 48:472.
102. Chapman AS, et al: Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States: A practical guide for physicians and other health-care and public health professionals. *MMWR Recomm Rep* 2006; 55:1. Available at www.cdc.gov/mmwr/preview/mmwrhtml/rr5504a1.htm. Accessed May 19, 2011.
103. Centers for Disease Control and Prevention: Ehrlichiosis and anaplasmosis, February 22, 2011. Available at www.cdc.gov/osels/ph_surveillance/nndss/casedef/ehrlichiosis_2008.htm. Accessed May 16, 2011.
104. IGeneX, Inc: *Tick-borne disease: Ehrlichia*. Available at http://igenex.com/Website/#. Accessed May 19, 2011.
105. Herwaldt BL, et al: Endemic babesiosis in another eastern state: New Jersey. *Emerg Infect Dis* 2003; 9:184.
106. Hatcher JC, Greenberg PD, Antique J, Jiminez-Lucho VE: Severe babesiosis in Long Island: Review of 34 cases and their complications. *Clin Infect Dis* 2001; 32:1117.
107. Gimenez JC, et al: Erythema figuratum in septic babesiosis. *J Eur Acad Dermatol Venereol* 2006; 20:726.
108. Torres-Velez FJ, et al: Development of an immunohistochemical assay for the detection of babesiosis in formalin-fixed, paraffin-embedded tissue samples. *Am J Clin Pathol* 2003; 120:833.
109. Boden K, et al: Diagnosis of acute Q fever with emphasis on enzyme-linked immunosorbent assay and nested polymerase chain reaction regarding the time of serum collection. *Diagn Microbiol Infect Dis* 2010; 68:110.
110. Drugs for parasitic infections. *Med Lett Drugs Ther* 2004; 46:1.
111. Krause PJ, et al: Atovaquone and azithromycin for the treatment of babesiosis. *N Engl J Med* 2000; 343:1454.
112. Raju M, et al: Atovaquone and azithromycin treatment for babesiosis in an infant. *Pediatr Infect Dis J* 2007; 26:181.
113. Wormser GP, et al: Emergence of resistance to azithromycin-atovaquone in immunocompromised patients with *Babesia microti* infection. *Clin Infect Dis* 2010; 50:381.
114. Centers for Disease Control and Prevention: Laboratory Identification of parasites of public health concern: Babesiosis. Available at www.dpd.cdc.gov/DPDx/HTML/Frames/A-F/Babesiosis/body_babesiosis_page2.htm. Accessed March 19, 2009.
115. Attoui H, et al: Coltiviruses and seadornaviruses in North America, Europe, and Asia. *Emerg Infect Dis* 2005; 11:1673.
116. Hovell WH: Journal kept on the journey from Lake George to Port Phillip, 1824-1825. *R Aust Hist Soc* 1921; 7:358.
117. Pape WJ, Gershman K, Bamberg WM: Cluster of tick paralysis cases—Colorado, 2006. *MMWR Morb Mortal Wkly Rep* 2006; 55:933.

www.ketabpezeshki.com 66485457-66963820

118. Pascuzzi RM: Pearls and pitfalls in the diagnosis and management of neuromuscular junction disorders. *Semin Neurol* 2001; 21:425.
119. Vedanarayanan V, Sorey WH, Subramony SH: Tick paralysis. *Semin Neurol* 2004; 24:181.
120. Crawford P, Mitchell D: Tick paralysis as a cause of autonomic dysfunction in a 57-year-old female. *South Med J* 2009; 102:190.
121. Centers for Disease Control and Prevention: Insect repellent use and Safety, February 25, 2010. Available at www.cdc.gov/ncidod/dvbid/westnile/qa/insect_repellent.htm. Accessed May 16, 2011.
122. Scheinfeld N: Picaridin: A new insect repellent. *J Drugs Dermatol* 2004; 3:59.
123. Insect repellents. *Med Lett Drugs Ther* 2003; 45:41.

www.ketabpezeshki.com 66485457-66963820

Chapter 135

Tuberculosis

Peter E. Sokolove and Robert W. Derlet

PERSPECTIVE

History and Epidemiology

Tuberculosis (TB) has plagued humankind throughout recorded history. Hippocrates (460-370 BCE) is credited for providing the first accurate clinical description of TB. He coined the term *phthisis* ("a melting or wasting away") to describe the wasting character of the disease, which he noted also was associated with fever and incurable lung ulcerations. Overcrowded living conditions, widespread poverty, and poor hygienic conditions were ideal for the epidemic spread of the disease throughout western Europe from the early 1600s through the 1800s. TB gradually became a global epidemic as Europeans colonized North America and explored and colonized other parts of the world.[1] The TB epidemic peaked in western Europe in the early 1800s and by 1900 had peaked in the Americas. Globally, the disease still has not reached a peak in some developing countries in Africa and Asia.

Laënnec and Schönlein recognized the tubercle as the fundamental anatomic lesion and named the disease *tuberculosis.* Koch identified the tubercle bacillus in 1882, and Roentgen's discovery of x-rays in 1895 greatly improved the ability to diagnose TB early in the disease course.[2] In 1892 Biggs instituted a comprehensive program of TB control in New York City that served as a model for the U.S. Public Health Service, including public education, systemic surveillance, isolation of patients, nursing follow-up, improved sanitation, and free sputum testing. These types of programs and the subsequent introduction of the antituberculosis drugs led to an impressive decline in the incidence of TB throughout the 20th century. Between 1953 and 1985, TB cases decreased by an average of 5.8% per year. The decline of the infrastructure dedicated to TB control during the late 1980s and early 1990s was compounded by new problems, including the epidemic of human immunodeficiency virus infection and acquired immunodeficiency syndrome (HIV/AIDS), increasing immigration from countries with high TB prevalence, increasing occurrence of TB in institutional living settings, escalating poverty, substance abuse, homelessness, and urban overcrowding. These factors contributed to a resurgence of TB in the United States from 1986 through 2010 and to the emergence of drug-resistant strains of *Mycobacterium tuberculosis* (MTB). TB is currently the world's second leading infectious cause of death, and one third of the world's population has been infected by TB.[3] Each year more than 8 million people acquire active TB infection, and nearly 2 million die of the disease.[4]

Elderly persons who harbor dormant infection that is reactivated constitute an important reservoir of MTB in the United States. Debilitating disease or immunosuppression may predispose the affected person to reactivation. Nursing homes are particularly vulnerable to TB outbreaks because reactivation of disease in remotely infected persons may be followed by epidemic spread among the many susceptible hosts living in close quarters. Emigration from endemic countries is another major factor.[1,3] As recently reported, a majority of U.S. TB cases occur among foreign-born persons.[5] The largest numbers of people with TB originate from Africa and Asia, specifically the Philippines, Vietnam, India, and China, accounting for more than half of all TB cases among foreign-born persons.[6] Homelessness also has contributed to the spread of TB in major urban centers. Homelessness often is associated with conditions that decrease resistance to TB, such as malnutrition, alcoholism, and substance abuse. MTB infection in the homeless population may quickly progress to active TB infection.

The HIV/AIDS epidemic has had the greatest impact on the reemergence of TB in the United States. The pandemic of HIV-related TB has led to an increase in TB cases among non–HIV-infected people owing to the higher numbers of source cases in the community. The rate of TB among patients who are HIV infected and have a positive result of TB skin testing is approximately 200 to 800 times higher than that estimated for the U.S. population overall.[7]

The reemergence of TB also has affected children. Between 1962 and the mid-1980s, the rates of childhood TB in the United States decreased an average of 6% a year. This trend has reversed along with the young urban adult trend, and the number of cases reported in children 4 years of age or younger increased 36% from 1985 through 1992. This increase reflected ongoing transmission of TB in the community because TB in young children must result from recent infection. In 2010, the Centers for Disease Control and Prevention (CDC) reported 11,181 new cases of TB in the United States, a rate of 3.6 cases per 100,000 population. More than half of these cases were in foreign-born persons.[7] Multidrug-resistant TB was reported in 113 cases, and only one case of extensively drug-resistant TB was reported. In contrast, 9 million persons are newly diagnosed with TB each year throughout the world. Approximately 2 million persons die each year in countries outside the United States.[8]

Etiology

One microorganism, *M. tuberculosis,* causes human TB in nearly all cases. Humans constitute the sole known reservoir for MTB. Two other pathogenic mycobacteria, *Mycobacterium bovis* and *Mycobacterium africanum,* have on rare occasions been implicated in causing TB. *M. bovis* is transmitted by drinking of milk from diseased cows, but because pasteurization of milk is now common, it has become a relatively unusual cause of TB. *M. africanum* also is a rare cause of human TB. This mycobacterium is thought to be intermediate in pathogenicity between *M. tuberculosis* and

www.ketabpezeshki.com 66485457-66963820

M. bovis and has been documented to cause human TB, predominantly in Africa. Worldwide, MTB remains the major causative agent.

MTB is an intracellular, aerobic, nonmotile, non–spore-forming bacillus with a waxy lipid coat. This coating makes MTB resistant to decolorization with acid alcohol after staining, hence the term *acid-fast bacillus* (AFB). MTB grows slowly. Its generation time is 15 to 20 hours, compared with less than 1 hour for some common bacteria; cultures take 4 to 6 weeks to grow on standard solid media. MTB produces neither endotoxins nor exotoxins. Its cell components are immunoreactive; some are immunosuppressive, and others are the agents of granuloma formation, macrophage activation, host toxicity, and modification of the immune response.

PRINCIPLES OF DISEASE

Transmission

TB is transmitted with rare exception by the respiratory route, including both droplet spread and as true aerosolization into microparticles. Patients with active disease expel MTB in liquid droplets during coughing, sneezing, and vocalizing. A single cough or 5 minutes of talking can produce 3000 infectious droplets, and sneezing can produce an even higher number.[1] The droplets rapidly evaporate, and the desiccated bacilli circulate airborne for prolonged periods. These infective particles, or droplet nuclei, measure 1 to 5 µm in diameter, contain one to three tubercle bacilli, and, when inhaled , can travel to the distal alveoli. Transmission by nonrespiratory routes, such as direct inoculation, occurs primarily among health care workers.

The susceptible host may become infected when only a few of the droplet nuclei are inhaled. Fomites are not important in the transmission of the disease, and patients' rooms, eating utensils, and bed clothes do not require special decontamination procedures. Because the infectious droplet nuclei are airborne, exchange of contaminated air is the most important environmental control. In addition, MTB is susceptible to ultraviolet radiation, and transmission rarely occurs outdoors because of the dilution of infectious particles and exposure to ultraviolet radiation.

The risk for TB transmission increases when source patients have airway and cavitary disease. Infectivity correlates with the number of organisms seen on sputum smear, the extent of pulmonary disease, and the frequency of cough. After 2 weeks of chemotherapy, patients with initially AFB-negative sputum smears can be considered noncontagious. However, after 2 weeks of treatment, patients who initially were smear positive may still have viable MTB detectable in their post-treatment sputum cultures, and patients with extensive disease may still have AFB detectable on their post-treatment sputum smears; these two groups should be considered contagious. There is currently no clear epidemiologic evidence to better define contagiousness of patients after they have started effective therapy.[9] The CDC has published guidelines requiring presence of three negative smears on different days as the criterion for removal of a patient from respiratory isolation, but debate about this recommendation is ongoing.[9]

Extrapulmonary TB also may be infectious, but only if it is in the oral cavity or an open skin lesion.[9] Transmission of MTB to health care workers caring for patients with skin ulcers and draining tuberculous abscesses has been reported.[10] Irrigation of the abscess may aerosolize the bacilli, forming infectious droplet nuclei.

Pathogenesis

When infectious droplet nuclei are inhaled, the airflow through the bronchial tree tends to deposit them in the midlung zone on the respiratory surface of the alveoli. The deposition launches a complex series of immunologic events. Dannenberg has organized the complex pathogenesis of TB into four stages.[11]

Stage 1

The first stage begins when an alveolar macrophage phagocytoses the recently inhaled bacillus. A macrophage from a resistant host can immediately destroy a less virulent bacillus. In these cases, no tuberculous infection develops and the process ends. If a virulent bacillus can overcome a macrophage's microbicidal capability, the infection may progress to the next stage.

Stage 2

When the alveolar macrophage is unable to destroy the inhaled tubercle bacilli, the bacilli replicate until the macrophage lyses. Circulating monocytes are attracted to the site of infection by the released bacilli, cellular debris, and various chemotactic factors. The monocytes differentiate into macrophages and ingest the free bacilli. Initially, these new macrophages are not activated and cannot destroy or inhibit the mycobacteria. The bacilli multiply logarithmically within macrophages and accumulate at the primary focus of infection, now called a tubercle.[12] The infected macrophages also may be transported through lymphatics to regional lymph nodes, from which they can reach the bloodstream, with subsequent spread. During this lymphohematogenous dissemination, the pathogens tend to distribute preferentially to lymph nodes, kidney, epiphyses of long bones, vertebral bodies, meningeal areas, and apical posterior areas of the lungs. These sites may be favored because of a high oxygen tension or impaired clearance mechanisms from poor lymph flow.

Stage 3

The third stage of TB begins 2 to 3 weeks after the initial infection, with development of the immune response that terminates the unimpeded growth of MTB. Cell-mediated immunity occurs through $CD4^+$ helper T cells. When the T cell encounters mycobacterial antigens, it is activated and produces an expanded population of specific T cells. These T cells secrete cytokines (e.g., interferon-γ [IFN-γ], tumor necrosis factor) that attract and activate monocyte-macrophages. Once activated, the macrophages, containing previously ingested mycobacteria and their progeny, kill the bacilli. The destruction of the mycobacteria is associated with the formation of epithelioid cell granulomas and clearance of the organisms.[12]

Delayed-type hypersensitivity is mediated by cytotoxic $CD8^+$ suppressor T cells. The cytotoxic cells kill nonactivated macrophages laden with mycobacteria and thus cause local tissue destruction. Delayed-type hypersensitivity results in the formation of caseating necrotic granulomas. This stops bacillary growth; mycobacteria, now extracellular, cannot multiply in this acidic, anoxic, extracellular environment. Tubercle bacilli can survive dormant in this solid caseous material for years.[12] The host's resistance determines whether the disease remains dormant or becomes active.

In the immunocompetent host with strong cell-mediated immunity, the primary lesion is effectively walled off by epithelioid cells. Eventually, the caseous center inspissates, and the disease is arrested. Similarly, at sites of lymphohematogenous spread, the mycobacteria are quickly destroyed by a rapid immunologic response. The rapid destruction of the mycobacteria by cell-mediated immunity terminates the infectious process, and the only evidence of the infection is conversion to a positive tuberculin (purified protein derivative [PPD]) skin test result.

www.ketabpezeshki.com 66485457-66963820

This sequence of events from stage 1 to stage 3 represents the pathogenesis of primary TB in the immunocompetent patient. In most cases, primary TB is subclinical and self-limited. In the immunocompromised host, however, clinically active primary disease may develop rapidly after the initial MTB infection.

The less-resistant host with weak cell-mediated immunity relies more on delayed-type hypersensitivity to control the infection. The primary lesion is surrounded by nonactivated macrophages so it is not effectively walled off, and the caseous center expands, compromising more lung tissue. If the infection eventually can be contained by the host, any initial manifestations may go unnoticed, and the infection may be evident only radiographically as healed parenchymal calcifications of the primary or Ghon focus and of the regional lymph nodes. If host defenses are unable to contain the primary infection, however, as can occur in infants and immunosuppressed adults, the primary focus may become an area of advancing pneumonia. This process is called primary progressive TB. In addition, this host may be unable to control the infection at the sites of lymphohematogenous spread, resulting in formation of multiple uncontrolled caseous tubercles and development of disseminated TB.[12] HIV-infected patients are particularly susceptible to primary progressive TB because HIV specifically targets $CD4^+$ cells and macrophages.

Stage 4

The final stage usually occurs months to decades after an apparent recovery from the initial infection. TB may progress to stage 4 even in immunocompetent persons. Usually, host factors lead to decreased resistance and reactivation of dormant foci of MTB. The progression is due to liquefaction and cavity formation.

The liquefied tubercle serves as an excellent growth medium for the mycobacteria. The large numbers of extracellular bacilli stimulate delayed-type hypersensitivity, which secondarily causes local damage. The tubercle eventually erodes through the bronchial wall and drains its contents, forming a cavity. The liquefied caseous material, teeming with mycobacteria, enters other parts of the lung and the outside environment. The spilling of this liquefied material within the lung may produce a caseous bronchopneumonia.[12] The cavity formed at the site of the initial focus remains a significant lesion. Cavities provide optimal conditions for mycobacterial growth. The oxygen tension is increased, and the host's defenses are ineffective at interrupting multiplication of the mycobacteria within a cavity.[12]

CLINICAL FEATURES

Emergency Department Presentation

Patients with TB may present to the emergency department (ED) with either a primary infection or, more commonly, reactivation of an old infection. In either event, a wide variety of symptoms are features of this disease. Common ED presentations include classic infection in previously undiagnosed TB, TB with atypical symptoms, and known TB history with incomplete or complete drug therapy. The ED physician sometimes may be misled and not consider TB in the presentation of ill patients. Therefore, a high index of suspicion should be maintained and TB included in the differential diagnosis of common presenting complaints, such as isolated fever, weakness, weight loss, failure to thrive, and night sweats.[13]

The initial infection with TB most often is asymptomatic in otherwise healthy persons. Mild fever and malaise may develop in association with the immune response at 4 to 6 weeks, but the primary infection is generally insignificant clinically.[14] Conversion to a positive PPD skin test result may be the only means of diagnosis of the infection. Clinically active TB develops in 8 to 10% of otherwise healthy PPD converters who do not take prophylactic agents: 3 to 5% in the first 2 years (acute primary TB) and another 5% during the remainder of life (reactivation TB). By contrast, in persons also infected with HIV, progression to acute primary TB occurs at a rate of 37% within 6 months and then to active TB at a rate of 7 to 10% per year.[5]

Reactivation of dormant foci is responsible for the major clinical manifestations of TB.[14,15] Exogenous reinfection of patients with well-documented previous TB infection causes clinical disease indistinguishable from reactivation TB.[15] Because it may be incorrect to label all late-onset cases as reactivation disease, *postprimary TB* is the preferred term. Postprimary TB is active or chronic disease in a patient previously infected. In the United States and other developed countries, reactivation is thought to be the primary mechanism of postprimary TB. A high index of suspicion should be maintained for elders.[8,16] Exogenous reinfection has played a role in circumstances in which contagion levels are high, as in outbreaks of TB in developing countries, and in immunocompromised hosts.[15,16]

Patient's History

History of Present Illness

Clinically significant pulmonary TB often is indolent, and signs and symptoms are absent or minimal until the disease advances. Systemic reaction, thought to be mediated by cytokines, especially tumor necrosis factor alpha, causes the constitutional symptoms of anorexia, weight loss, fatigue, irritability, malaise, weakness, headache, chills, and, most commonly, fever.[14,17] The fever usually develops in the afternoon; defervescence occurs during sleep, leading to the classic night sweats of TB.[14]

Cough is the most common symptom of pulmonary TB. It may initially be nonproductive, but as caseation necrosis and liquefaction develop, mucopurulent and nonspecific sputum typically is produced.[14,17] Hemoptysis, caused by caseous sloughing or endobronchial erosion, usually is minor but often indicates extensive lung involvement. Many asymptomatic patients present for medical attention because they are alarmed by the hemoptysis.

Patients also may complain of pleuritic chest pain, which is caused by parenchymal inflammation adjacent to the pleural surface. Dyspnea with chest pain may indicate a spontaneous pneumothorax. Shortness of breath from parenchymal lung involvement is unusual, however, and if present indicates extensive parenchymal disease or tracheobronchial obstruction.[14] Table 135-1 shows the frequency of symptoms found in one study of patients with culture-proven pulmonary TB. The clinical manifestation of TB in patients presenting to the ED may be especially confusing. In one study, only one third of ED patients with active pulmonary TB had pulmonary chief complaints, only 64% ever reported a cough, and only 8% had hemoptysis.[18]

Any vague systemic disorder or fever of unknown etiology may represent TB. Atypical presentations are particularly common in infants, elders, and immunocompromised persons. In infants and young children, the development of large hilar lymph nodes is common; such nodes may compress a bronchus, leading to atelectasis and possibly obstructive pneumonia; the child may have a "brassy cough." A node also may erode through the bronchial wall, causing symptomatic endobronchial disease and allowing endobronchial spread of tuberculous pneumonia to other areas of the lungs. By contrast, fewer elders present with respiratory symptoms. The diagnosis may be masked by coexistent disease and nonspecific presenting symptoms.[19] Pulmonary TB should be considered in elderly patients with chronic cough and failure to thrive.[5]

Clinical manifestations of TB in patients coinfected with HIV are even more subtle and nonspecific, especially because these

www.ketabpezeshki.com 66485457-66963820

Table 135-1 Frequency of Symptoms and Signs in Pulmonary Tuberculosis

SYMPTOM OR SIGN	NUMBER AFFECTED	NUMBER EVALUATED	PERCENTAGE AFFECTED
Cough	144	185	78
Weight loss	134	181	74
Fatigue	112	165	68
Tactile fever	109	183	60
Night sweats	98	177	55
Chills	92	180	51
Anorexia	76	167	46
Chest pain	71	179	40
Dyspnea	64	173	37
Hemoptysis	51	181	28
No respiratory symptoms	13	186	7
None of above symptoms	9	187	5

From Barnes PF, et al: Chest roentgenogram in pulmonary tuberculosis: New data on an old test. Chest 94:316, 1988.

Box 135-1 Population Groups with Increased Risk for Tuberculosis

Close contacts of known case
Persons with HIV infection
Foreign born from Asia, Africa, Latin America
Medically underserved, low-income populations
Elders
Residents of long-term care facilities (e.g., nursing homes, correctional facilities)
Injection drug users
Groups identified locally (e.g., homeless, migrant farm workers)
Persons who have occupational exposure

HIV, human immunodeficiency virus.

Box 135-2 Risk Factors for Development of Active Tuberculosis in Previously Infected Persons

HIV infection
Recent tuberculosis infection (within past 2 years)
Chest radiographic findings suggestive of previous untreated tuberculosis
Injection drug use
Diabetes mellitus
Silicosis
Prolonged corticosteroid therapy
Immunosuppressive therapy
Head or neck cancer
Hematologic and reticuloendothelial diseases
End-stage renal disease
Intestinal bypass or gastrectomy
Chronic malabsorption syndromes
Low body weight (10% or more below the ideal)

HIV, human immunodeficiency virus.

patients are vulnerable to opportunistic infections and neoplasms that can cause the same constitutional symptoms as in TB. A synergy between MTB and HIV leads to a greatly increased viral load. Active TB with HIV coinfection has been associated with an increased risk for opportunistic infections and death. Patients with advanced HIV infection also commonly have extrapulmonary involvement (seen in 30%) as well as combined pulmonary and extrapulmonary TB (in 32%).[17]

Risk Factors

All patients in the ED who have been coughing should be screened for the presence of TB risk factors (Box 135-1). One of the most important risk factors is HIV/AIDS with $CD4^+$ levels below 500 cells/μL.[20] Overseas, coinfection with HIV and TB is common and results in increased mortality of TB. Risks for acquiring TB may also be stratified by age. Because infants and toddlers have poorly developed cell-mediated immunity, they have a much higher incidence of TB than adults do. Children 5 to 10 years of age are relatively resistant to TB. Infants and toddlers commonly have extrapulmonary disease and acute lower and midlung bronchopneumonia that rarely progresses to cavitary disease. Young adults show the adult pattern of apical pulmonary disease, including cavity formation, suggesting reactivation. Because of decreased immunocompetence, elders typically have disease manifestations similar to those in young children. Patients with a history of PPD conversion should be asked about the presence of medical conditions associated with increased risk for the development of active postprimary disease through reactivation (Box 135-2). Household contacts also have increased risk of TB infection.[21]

Patients with a history of active TB should be asked about all antituberculosis medications previously or currently being taken and about compliance. Failure to improve after 2 months with an appropriate regimen may signal nonadherence to therapy or the presence of a resistant strain.[22]

Physical Findings

Examination of the chest is unlikely to establish the extent of disease. Over areas of infiltration, rales may be heard when the patient breathes in after a short cough (post-tussive rales), and bronchial breath sounds may be present over areas of lung consolidation. Distant, hollow breath sounds (amphoric breath sounds) may be heard over cavities. One ED study reported abnormal physical examination findings in 80% of patients with active pulmonary TB.[18]

Erythema nodosum or phlyctenular keratoconjunctivitis (severe unilateral inflammation of an eye) may appear with the onset of tuberculin hypersensitivity. These self-limited, allergic manifestations are not common in the United States. The patient's overall appearance and state of health may be the most useful indicators in the evaluation for the potential presence of TB. General signs include pallor secondary to anemia, fever, and cachexia with weight loss.

Complications

Pneumothorax

Spontaneous pneumothorax is not common (affecting less than 5% of patients with severe cavitary disease) but may occur when a tuberculous cavity ruptures and creates a bronchopleural fistula or when a bleb ruptures into the pleural space (Fig. 135-1). Delayed tube thoracostomy and suction result in progressive infection and fibrosis of the pleura that leads to air trapping within affected lung.

Empyema

An empyema, characterized by extensive, progressive parenchymal disease and cavitation, may develop in patients with TB. Although it is rare (with a frequency of 1 to 4%), empyema is more common

www.ketabpezeshki.com 66485457-66963820

Figure 135-1. Chest radiograph demonstrating cavitary tuberculosis with left-sided pneumothorax. The underlying cause of the pneumothorax was later determined to be a bronchopleural fistula. (Courtesy John Pearce, MD.)

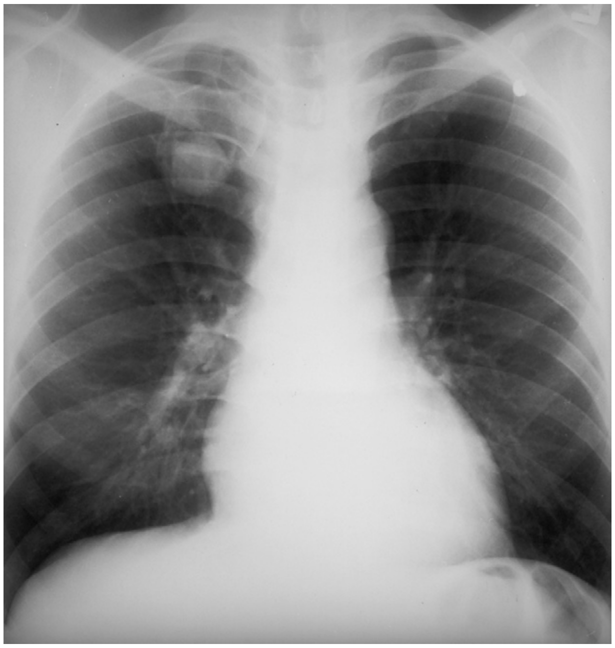


Figure 135-2. Chest radiograph showing superinfection of healed tuberculous cavity. An aspergilloma can be seen in the right upper lung. (Courtesy John Pearce, MD.)

late in the course of the disease in debilitated patients. Rupture of a cavity into the pleural space usually is catastrophic and often is associated with bronchopleural fistula formation. An untreated empyema can result in spontaneous pleurocutaneous fistula formation, presence of a chest wall mass on the radiograph, or rib and vertebra destruction.

Endobronchial Spread

Endobronchial spread is the most common complication of cavitary disease. It is manifested radiographically as 5- to 10-mm, poorly defined nodules clustered in dependent portions of the lungs. These nodules may rapidly coalesce into parenchymal consolidation, so-called galloping consumption.

Airway Tuberculosis

When a cavity drains its highly infectious material into the bronchial tree, the airways not only spread the infection but also develop endobronchial TB. Bronchiectasis commonly complicates endobronchial TB. Bronchial stenosis may result from extensive damage caused by endobronchial TB or from direct extension of infection by tuberculous adenitis or lymphatic dissemination to the airway. Tuberculous bronchostenosis may appear radiographically as persistent segmental or lobar collapse, lobar hyperinflation, and obstructive pneumonia.

Tracheal TB and laryngeal TB are less common than endobronchial TB. Laryngeal disease is the most infectious form of TB; it results from the proximal extension of lower airway disease, pooling of infected secretions in the posterior larynx, or hematogenous dissemination to the anterior larynx. Patients with laryngeal TB also usually have active pulmonary disease.

Superinfection

Extensive TB infection often heals with open cavities and areas of bronchiectasis. Superinfection may occur with a wide variety of organisms, including *Aspergillus fumigatus*.[14] The characteristic finding on chest radiographs is the aspergilloma or "fungus ball" (Fig. 135-2). Aspergillomas are of particular clinical significance because they may cause massive and fatal hemoptysis.[14]

Hemoptysis

Mild hemoptysis is a common complication of acute infection. TB also causes massive hemoptysis. The destruction of lung parenchyma leads to rupture of blood vessels. An uncommon complication is the erosion of a tuberculous lesion or cavity into a pulmonary artery, leading to pseudoaneurysm formation (Rasmussen's aneurysm), with potentially fatal hemoptysis. Alternatively, superinfection of cavities by invasive organisms or tumor development in scarred lung may cause erosion of bronchial or pulmonary vessels, with resultant major hemorrhage. Affected patients often require emergency surgical resection or selective embolization.[23]

Primary Tuberculous Pericarditis

Primary tuberculous pericarditis usually results from direct extension of infection from the tracheobronchial tree, mediastinal or hilar lymph nodes, sternum, or spine. Pericardial involvement also may result from hematogenous spread secondary to acute miliary TB or from another focus elsewhere in the body.[24] In the United States, TB is the leading cause of pericarditis among HIV-infected patients. The predominant symptoms are cough, chest pain, and dyspnea, and the most common signs are cardiomegaly, audible rub, fever, and tachycardia.[25] Complications of pericardial TB include pericardial effusion, constrictive pericarditis, myocarditis, and cardiac tamponade.[24] Cardiac tamponade may result from accumulation of pericardial fluid but also may occur if enlarging lymph nodes rupture into the pericardium. Emergency echocardiography reliably confirms the presence of pericardial fluid.[26]

DIAGNOSTIC STRATEGIES

Laboratory Tests

Routine laboratory studies generally are not useful in suggesting or establishing the diagnosis in the ED.[14] Normochromic normocytic anemia, elevated erythrocyte sedimentation rate and serum

www.ketabpezeshki.com 66485457-66963820

globulin level, hyponatremia, and hypercalcemia can occur in active pulmonary TB, but these findings are nonspecific.[14,27] Tuberculin skin testing is important epidemiologically as a modality for diagnosis of MTB infection but is of limited value for detection of active clinical disease. At least 20% of patients with active TB have false-negative results on tuberculin skin testing.

Diagnostic Imaging

Plain radiography of the chest is the most useful study for a presumptive diagnosis of pulmonary TB to be made. Chest radiographic abnormalities are not limited to the classic upper lobe cavitary infiltrates. Primary TB infection and postprimary disease have distinctive radiographic features. A normal appearance on the chest radiograph has a high negative predictive value and is therefore useful in screening ED patients for active pulmonary TB. However, the small false-negative rate among immunocompetent adults increases significantly among HIV-positive patients. Therefore, depending on the clinical circumstances, absence of specific abnormalities on the chest radiograph does not always exclude active TB, especially in patients with concomitant endobronchial disease and HIV infection.

Primary Tuberculosis

Chest radiographic manifestations of primary disease in adults often are not recognized as TB.[28] Primary tuberculous infiltrates can occur in any lobe. With any age group, a pneumonic infiltrate with enlarged hilar or mediastinal nodes should strongly suggest the diagnosis. The infiltrate usually is homogeneous and most commonly involves a single lobe. Thus primary TB may appear radiographically identical to a bacterial pneumonia, with associated lymphadenopathy, if it is present, being the only distinguishing feature.

Lymphadenopathy is considered the radiologic hallmark of primary TB in children but is seen less commonly in adults. When it is present, adenopathy usually is unilateral and associated with parenchymal infiltrate (Fig. 135-3). It may occur bilaterally or, more rarely, may be an isolated finding on chest radiography.[14] Massive hilar adenopathy is more common in young children. As a result, atelectasis, resulting from airway compression by adjacent enlarged nodes, is a likely finding in children younger than 2 years but is less common among older children and adults.

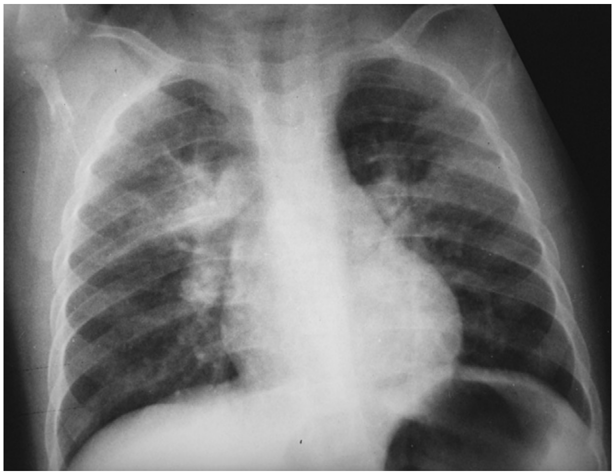


Figure 135-3. Chest radiographic findings in a child with primary tuberculosis. Note the active Ghon focus with associated hilar adenopathy and presence of bilateral infiltrates. (Courtesy John Pearce, MD.)

Other primary TB chest radiographic findings include a moderate to large pleural effusion, which often is an isolated finding whose prevalence increases with age; miliary TB (characterized by the presence of innumerable, 1- to 3-mm noncalcified nodules dispersed throughout both lungs with mild basilar predominance), which is mainly a threat to children younger than 2 years, immunocompromised patients, and elders; and tuberculomas, well-circumscribed nodular lesions of the parenchyma thought to be a result of healed primary TB.[29] When the healed primary focus is visible on the chest radiograph as a calcified scar, it is known as the Ghon focus. Calcified secondary foci of infection are known as Simon's foci. A Ghon focus associated with calcified hilar nodes is called a Ranke complex. A right-sided predominance in the distribution of Ghon foci and Ranke complexes is well recognized and probably reflects the higher statistical probability that an airborne infection will affect the right lung. Calcification seen on the chest radiograph indicates healing, but viable bacilli may still exist in a partially calcified lesion.

When resolution does not occur, the result is progressive primary TB, which appears radiographically as progressive parenchymal consolidation, often including secondary foci in the upper lobes. In some patients, the primary tuberculous pneumonia breaks down into multiple cavitary lesions or a single large abscess. These chest radiographic findings may easily be confused with the findings in postprimary TB.

Postprimary Tuberculosis

Postprimary TB typically appears as an upper lung infiltrate or consolidation, with or without cavitation. The lesion may be small or extensive and usually is located in the apical or posterior segment of the upper lobe but may appear in the superior segment of the lower lobe.[29] Postprimary disease also occurs in the lower lung. In addition, bronchogenic spread can occur, leading to involvement of multiple lobes (Fig. 135-4). The patient with bilateral upper lobe disease is extremely likely to have TB. The other important, recognizable characteristics of postprimary disease are fibrosis and cavitation.

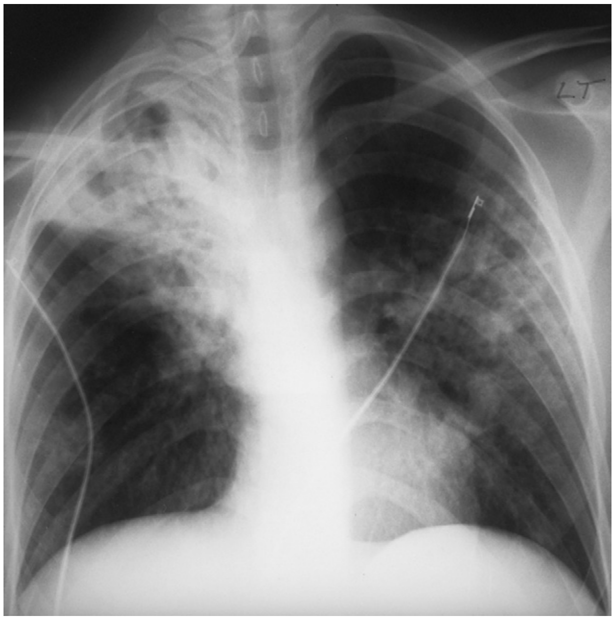


Figure 135-4. Chest radiograph showing evidence of right upper lobe cavitary disease. Also note the left-sided infiltrate, secondary to endobronchial spread.

www.ketabpezeshki.com 66485457-66963820

The initial lesion of postprimary TB is a poorly defined, heterogeneous alveolar opacity called an exudative lesion. These lesions are not purely exudative in that they are associated with a fibrotic pattern of nodules and a few fine, linear densities. Unchecked, the infection may rapidly progress to lobar or complete lung opacification and destruction. Postprimary TB, however, usually runs a chronic course characterized by reactive fibrosis, and in most cases the initial exudative lesions gradually are replaced by more well-defined reticular and nodular opacities or "fibroproductive" lesions.

Fibroproductive lesions often are irregular and angular in contour, have strands extending toward the hilum, and demonstrate calcification of one or more nodules. As fibrosis continues, distortion of normal vascular and mediastinal structures secondary to contraction and shrinkage of the scar may be apparent. Severe fibrosis with upper lobe volume loss may eventually lead to retraction of the interlobar fissure and upward displacement of the hilum. The chest radiographic appearance at this stage has been variably referred to as "old scarring," "no active disease," or "fibrotic, apparently well-healed TB." Many of the patients have positive sputum culture results, and infectivity cannot be accurately assessed by chest radiography. Only serial radiographs can reliably differentiate active from inactive disease. Lack of radiographic changes during a 4- to 6-month interval generally indicates "inactive" or, more precisely, "radiographically stable" disease.

Cavitation should alert ED personnel to the potential high infectivity of the patient and the potential for associated complications, such as bronchogenic spread of TB, when an area of caseous necrosis liquefies, with consequent communication with the bronchial tree (see Fig. 135-4). Cavities usually are multiple and range in diameter from a few millimeters to several centimeters. The walls of the cavities initially are thick and rough and become thinner and smoother with healing (Fig. 135-5). A hazy, parenchymal reaction around a cavity with an ill-defined wall strongly suggests an active lesion. Most cavities heal by obliteration, often leaving a small linear or stellate scar; others remain patent and become thin-walled bullae. Although pulmonary TB usually induces chest radiographic changes, patients with sputum cultures positive for MTB may nevertheless demonstrate normal radiographic findings. Chest radiographs also may be normal in appearance in patients with endobronchial TB.

Figure 135-5. A healed, thin-walled cavity can be seen in the left upper lobe on this chest film. (Courtesy John Pearce, MD.)

Chest radiographs of patients with pulmonary TB and HIV infection may be atypical in approximately one third of cases. However, the radiographic appearance of disease is heavily influenced by the degree of immunocompromise. Patients with late HIV infection more often demonstrate mediastinal adenopathy or atypical infiltrates and less often have cavitation.[30] Severe immunosuppression has been reported to be associated with a miliary pattern of disease on chest radiographs. Conversely, chest radiographs of patients with early HIV infection are more similar to those of patients without HIV infection, with upper lobe infiltrates, more cavitation, and less adenopathy. A normal chest radiographic appearance also is common in patients with HIV infection.

Microbiology

Sputum Studies

If the clinical or chest radiographic findings suggest the diagnosis of pulmonary TB, mycobacteriologic studies of the patient's sputum should be ordered. Spontaneously produced sputum collected under direct supervision is preferred, and early-morning samples are the best diagnostic specimens. Classically, three initial sputum specimens should be obtained on different days. A positive smear supports a presumptive diagnosis, and the number of bacilli seen correlates with infectivity. For patients who are not producing sputum, nebulized induction of sputum and gastric aspiration of swallowed respiratory secretions are the methods of choice for collection of samples.[31] The diagnostic yield is higher for nebulizer-induced sputum samples than for gastric aspirates in adult patients with TB, but in some patients, especially children, gastric aspirates may be the only obtainable specimens. Induction of sputum with nebulization may increase the risk of TB transmission to health care workers and should be performed only in specially ventilated rooms, preferably not in the ED.

When sputum is not diagnostic in adults, fiberoptic bronchoscopy with bronchial washings, brushings, and bronchoalveolar lavage or transbronchial biopsy may be necessary for laboratory diagnosis of TB.[31] In children, sputum obtained by bronchoscopy has a lower culture yield, so this technique is used less often to obtain sputum from pediatric patients.[32]

Direct Microscopy

Direct microscopic examination of a stained sputum specimen for AFB (i.e., an AFB smear) is the most rapid laboratory test widely available to support a presumptive diagnosis of TB (Fig. 135-6), and results usually are available within 24 hours.[33] Although nontuberculous mycobacteria can cause pulmonary disease, they are less common than MTB and vary by geographic location and population of patients. Fluorochrome stains are more sensitive than the traditional Ziehl-Neelsen or Kinyoun methods for the detection of AFB from clinical specimens.[32,33] Negative findings on an AFB smear, however, do not rule out active pulmonary TB because microscopy is relatively insensitive when it is performed on samples with small numbers of bacilli. At least 5000 bacilli/mL of sputum must be present for a positive result by microscopy.[33] Because cavitary disease is associated with great numbers of bacilli, the diagnostic yield of microscopy increases with cavitation. Concentrated smears are prepared by decontamination, liquefaction, and centrifugation of sputum, and such smears may be more sensitive than unconcentrated samples.[4] Overall, AFB smears have a sensitivity of 20 to 80% and a specificity of 90 to 100%.[33] Despite its limitations, microscopy remains an essential diagnostic test

www.ketabpezeshki.com 66485457-66963820

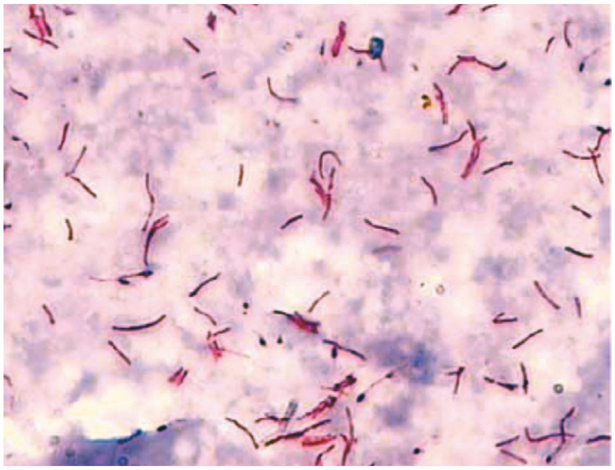


Figure 135-6. Photomicrograph of an acid-fast bacillus smear of *Mycobacterium tuberculosis*. (Courtesy Alfredo Ponce de Leon, MD.)

because of its ease of performance, low cost, rapid turnaround time, and reasonable diagnostic yield.

Culture

Sputum culture is more sensitive than microscopy for detection of MTB and is still considered the "gold standard" diagnostic modality. Liquid culture can detect 10 to 100 bacilli/mL, compared with 5000 to 10,000 bacilli/mL for AFB smear. When the presence of mycobacteria is established, the specific identification of MTB may be accomplished by subjecting the initial mycobacteria to various isolation techniques. These include the detection of pigmentation on solid culture media, various biochemical tests, high-performance liquid chromatography, and nucleic acid probes.[33]

A presumptive diagnosis of TB based on a positive sputum smear usually is confirmed by isolation of MTB by culture. Traditional culture methods using solid media require 3 to 8 weeks for colony formation. The development of liquid culture systems has shortened the detection time to 7 to 14 days. A number of liquid culture systems are available for detection of MTB. For example, the BACTEC (Becton Dickinson, Franklin Lakes, N.J.) method measures carbon dioxide produced by growing mycobacteria when they metabolize the ^{14}C-labeled palmitic acid contained in the system,[14] and the mycobacteria growth indicator tube (MGIT) method measures mycobacterial oxygen consumption with a fluorescence assay.[33]

Drug Susceptibility Testing

Because of the emergence of multidrug-resistant MTB, all initial isolates of MTB should be tested for susceptibility to isoniazid, rifampin, and ethambutol.[34] Further susceptibility testing should be performed when resistance to one of the three agents is detected or if the patient has had previous TB treatment, has been exposed to a drug-resistant contact or source, or has demonstrated a positive result on sputum cultures beyond 3 months of therapy.[34] Conventional susceptibility testing detects selective growth of drug-resistant TB on media containing antituberculosis drugs. For first-line agents, this requires waiting until 4 to 7 days after a positive culture result is obtained; testing for susceptibility to other drugs may require 2 to 3 months. The BACTEC and MGIT systems also can be used for rapid drug susceptibility testing, with results obtained in fewer than 12 days.[33] Other new approaches to susceptibility testing include flow cytometry, genotypic sequence-based methods, and bacteriophage viability testing.[33,35]

Newer Diagnostic Studies

The CDC has recently published guidelines for use of IFN-γ release assays and nucleic acid amplification (NAA) tests for the diagnosis of TB.[36,37]

QuantiFERON Test

The QuantiFERON test is the most widely available IFN-γ release assay available. This test was approved in 2001 by the U.S. Food and Drug Administration (FDA). It uses an enzyme-linked immunosorbent assay (ELISA) to measure the amount of IFN-γ released in response to PPD. IFN-γ is a cytokine associated with cell-mediated immunity. Determination of IFN-γ levels also can be used as a diagnostic test for tuberculous pleural effusions, ascites, and pericardial effusions. Clinical studies have reported sensitivity ranges from 90 to 100%. It can rapidly confirm TB infection in an individual in 2 days. This compares with several weeks for a traditional culture.[36] However, a normal study does not completely exclude TB; therefore, cultures should be sent when persons thought to have TB have a negative QuantiFERON test result.

Nucleic Acid Amplification Tests

NAA tests take only 24 to 48 hours to return results to the clinician. Their overall positive predictive value is about 95%.[37] In some cases, patients with positive TB sputum smears have had negative NAA test results. This is because of inhibitors that may prevent amplification. The best role of NAA is to aid clinicians in decision-making for those patients thought to have active TB. It should not be ordered routinely when the clinical suspicion for TB is low.

Serology

Although ELISAs have been developed for several MTB serum antigens, in practice, no serodiagnostic approach to the diagnosis of TB currently is in widespread clinical use in the United States. Limitations of the ELISA include inadequate accuracy and reproducibility, inability to distinguish active from latent infection, poor discrimination between MTB and other mycobacteria, and relative cost.[32,33]

Tuberculin Skin Test

While newer diagnostic tests undergo development, the tuberculin skin test remains the best tool available for detection of latent MTB infection. The tuberculin test is based on the principle that MTB infection induces sensitivity to certain antigens of the bacillus. These antigens are contained in the tuberculin preparation called PPD. In a person infected with TB, the PPD test result usually turns positive 3 to 8 weeks after the infection, when the immune response is developed. The standard 0.1-mL dose used in skin testing contains 5 tuberculin units (TU). This dose is administered intradermally with the needle bevel up, by the Mantoux technique. A properly placed needle should leave a blanched, distinct wheal 6 to 10 mm in diameter. If the tuberculin dose is incorrectly administered, the test may be repeated immediately at a site several centimeters away. Various types of test kits and applicators are available (Heaf and tine tests); but for diagnostic purposes, the Mantoux test with PPD (5 TU) is preferred.[9,32,33] Test results are read 48 to 72 hours after administration of PPD. The largest diameter of palpable induration is measured and recorded in millimeters; erythema by itself is not measured. The precise measurement that denotes a positive test result depends on the patient's other clinical factors. The current CDC guidelines use

www.ketabpezeshki.com 66485457-66963820

Table 135-2 Criteria for a Positive Tuberculin Skin Test Result

SIZE OF REACTION	PERSONS IN WHOM REACTION IS CONSIDERED POSITIVE
≥5 mm	HIV-infected persons Close contacts of persons with infectious tuberculosis Persons with abnormalities on chest radiograph consistent with previous tuberculosis* Immunosuppressed patients receiving the equivalent of ≥15 mg of prednisone per day for ≥1 month
≥10 mm	Foreign-born persons recently arrived (≤5 years earlier) from a country with a high prevalence of tuberculosis Persons with a medical condition that increases the risk of tuberculosis† Injection drug users Members of medically underserved, low-income populations (e.g., homeless persons) Residents and staff members of long-term care facilities (e.g., nursing homes, correctional institutions, homeless shelters) Health care workers Children <4 years of age Persons with conversion on a tuberculin skin test (increase in induration of ≥10 mm within a 2-year period)
≥15 mm	All others‡

From Jasmer RM, Nahid P, Hopewell PC: Latent tuberculosis infection. N Engl J Med 347:1860, 2002.
HIV, human immunodeficiency virus.
*Chest radiographic abnormalities consistent with previous tuberculosis consist of fibrotic opacities occupying more than 2 cm^2 of the upper lobe; presence of pleural thickening or isolated calcified granulomas is not considered to be suggestive of previous tuberculosis.
†Medical conditions that increase the risk for development of tuberculosis in the presence of latent tuberculosis infection include silicosis, end-stage renal disease, malnutrition, diabetes mellitus, carcinoma of the head and neck or lung, immunosuppressive therapy, lymphoma, leukemia, loss of more than 10% of ideal body weight, gastrectomy, and jejunoileal bypass.
‡These persons should not be screened in the absence of an indication.

Box 135-3 Factors Causing Decreased Ability to Respond to Tuberculin

Factors Related to Person Being Tested

Infections
- Viral (e.g., measles, mumps, chickenpox)
- Bacterial (e.g., typhoid fever, brucellosis, typhus, leprosy, pertussis, overwhelming tuberculosis, tuberculosis pleurisy)
- Fungal (e.g., South American blastomycosis)

Live virus vaccinations (e.g., measles, mumps, polio)
Metabolic derangements (e.g., chronic renal failure)
Nutritional factors (e.g., severe protein depletion)
Diseases affecting lymphoid organs (e.g., Hodgkin's disease, lymphoma, chronic lymphocytic leukemia, sarcoidosis)
Drugs (corticosteroids and many other immunosuppressive agents)
Extremes of age (newborns, elders with "waning" sensitivity)
Recent or overwhelming infection with *Mycobacterium tuberculosis*
Systemic stress (surgery, burn injury, mental illness, graft-versus-host reactions)

Factors Related to Tuberculin Used

Improper storage (exposure to light and heat)
Improper dilutions
Chemical denaturation
Contamination
Adsorption (partially controlled by addition of Tween 80)

Factors Related to Method of Administration

Injection of too little antigen
Delayed administration after antigen has been drawn into syringe
Injection site too close to control

Factors Related to Reading and Interpretation of Test Results

Inexperience of reader
Conscious or unconscious bias
Error in recording

15 mm of induration as a positive test response for people without TB risk factors (Table 135-2).[38]

Some persons with previous TB infection gradually lose their hypersensitivity reaction to PPD and may react weakly or not at all. The PPD test, however, can restimulate or enhance their hypersensitivity, so that a subsequent test does elicit a positive reaction. This phenomenon is called the booster effect. This boosted reaction may be mistaken for a new infection. To eliminate the booster effect as a confounding factor, a two-step testing method is recommended for persons who undergo serial PPD screening (health care workers). If the result of the first test is negative and the person does not have a documented negative PPD test result during the previous 12 months, a second test is done 1 week later with the same dose. If the second test is positive, it most likely represents a boosted reaction and the person should be considered previously infected. If the second test result remains negative, the person is considered uninfected and a positive reaction to a subsequent test indicates new infection.[9]

Infection with nontuberculous mycobacteria may cause a false-positive PPD result. These reactions tend to be smaller than the true-positive reaction to MTB infection. Similarly, bacille Calmette-Guérin (BCG) vaccination may produce a PPD reaction that generally is mild and deteriorates with time. A large reaction to PPD and a long time interval between BCG vaccination and the current skin test make it more likely that the reaction is due to MTB infection.[9] Because the BCG vaccine is imperfect in protecting against MTB infection and because most vaccinated persons come from areas of high TB prevalence, the CDC recommends that tuberculin skin test results be interpreted without regard to BCG vaccination status.[39]

Many conditions can lead to false-negative reactions to PPD testing (Box 135-3). Therefore, the clinical significance of a negative PPD result is best determined by consideration of other clinical factors. Despite some limitations, PPD skin testing remains useful to diagnose individual patients, to screen populations, and to evaluate infected persons for prophylactic treatment (Table 135-3).[38]

DIFFERENTIAL CONSIDERATIONS

Pulmonary Tuberculosis

Bacterial Pneumonia

Segmental or lobar infiltrates on chest radiographs in bacterial pneumonia may easily be confused with those seen in TB, especially primary disease. Compared with TB, however, bacterial pneumonias usually arise with more profound symptoms of systemic toxicity, a more acute onset, and an elevated white blood cell count. In pulmonary TB, there is no prompt response to antibiotics, as seen in bacterial pneumonia.

www.ketabpezeshki.com 66485457-66963820

Table 135-3 Persons at Increased Risk Who Should Be Tested for Latent Tuberculosis Infection

RISK COMPONENT	EXAMPLES OF PERSONS WITH RISK
Increased risk of exposure to infectious cases	Persons with recent close contact with persons known to have active tuberculosis* Health care workers who work at facilities where patients with tuberculosis are treated
Increased risk of tuberculosis infection	Foreign-born persons from countries with a high prevalence of tuberculosis Homeless persons Persons living or working in facilities providing long-term care
Increased risk of active tuberculosis once infection has occurred	HIV-infected persons Persons with recent tuberculosis infection† Injection drug users Patients with end-stage renal disease Patients with silicosis Patients with diabetes mellitus Patients receiving immunosuppressive therapy Patients with hematologic cancers Malnourished persons or those with a recent weight loss of more than 10% of their ideal body weight Persons who have undergone gastrectomy or jejunoileal bypass

From Jasmer RM, Nahid, P, Hopewell PC: Latent tuberculosis infection. N Engl J Med 347:1860, 2002.
HIV, human immunodeficiency virus.
*We define close contact as at least 12 hours of contact with a person with infectious tuberculosis, but well-established criteria for such contact are lacking.
†Persons with recent infection include children younger than 4 years and persons found to have tuberculin conversion, defined as an increase in induration of at least 10 mm on a tuberculin skin test within a 2-year period.

Fungal and Nontuberculous Mycobacterial Infections

Histoplasmosis, coccidioidomycosis, and blastomycosis as well as nontuberculous mycobacterial infections (mainly with *Mycobacterium avium* complex and *Mycobacterium kansasii*) may be radiologically indistinguishable from TB. The incidence of these infections is influenced by geographic location.[40,41] Nontuberculous mycobacterial infection most commonly involves chronic pulmonary infection in HIV-infected patients. Immunocompetent persons also may become infected with MTB, especially patients with chronic lung disease such as cystic fibrosis. Other important risk factors include work in the mining industry, warm climate, advancing age, and male gender.

Pneumonias in Patients with HIV Infection

Bacterial pneumonias including upper lobe *Pneumocystis* pneumonia (due to *Pneumocystis jiroveci*) and, rarely, *Nocardia* and *Rhodococcus* infections may mimic TB in patients with HIV infection.[27]

Cavitary Lesions

Lung abscess or cavitating pneumonia caused by *Klebsiella pneumoniae, Staphylococcus pyogenes,* or aspiration may appear similar to cavitary TB on chest radiographs. In older patients, especially smokers, bronchogenic carcinoma may mimic TB; this is particularly true of squamous cell carcinoma, which tends to cavitate. Because cancer may cause a focus of TB to spread, the two diseases may be present simultaneously.[14] Other causes of nontuberculous cavitary lesions include *M. avium* complex infection in HIV-negative patients, pulmonary infarction secondary to pulmonary embolus, Wegener's granulomatosis, and upper lobe bullous disease secondary to emphysema or neurofibromatosis.[27]

Upper Lobe Infiltrate with and without Fibrosis

A radiographic pattern characterized by presence of an upper lobe infiltrate with or without fibrosis may be seen with atypical mycobacteria, ankylosing spondylitis, silicosis, collagen vascular diseases, lymphomas, and actinomycosis.[27] Upper zone fibrosis and volume loss can occur in the later stages of extrinsic alveolitis, allergic bronchopulmonary aspergillosis, and sarcoidosis. The presence of calcification suggests TB.

Mediastinal Lymphadenopathy

The main considerations in the differential diagnosis for adenopathy include lymphoma and sarcoidosis. In sarcoidosis, lymphadenopathy usually is bilateral, symmetrical, and asymptomatic. Lymphadenopathy tends to be unilateral in TB; if it is bilateral, it is asymmetrical and associated with parenchymal lung disease. Lymphoma tends to involve bulky mediastinal lymphadenopathy.

Extrapulmonary Tuberculosis

Tuberculous infection involving multiple sites most commonly is seen in populations of patients less capable of containing MTB infection, such as infants, elders, and immunocompromised persons.[17] Extrapulmonary TB accounted for roughly 15% of newly diagnosed TB cases in the United States before the HIV epidemic. As reported in 2002, approximately 21% of TB patients in the United States had extrapulmonary disease, and another 7.5% had both pulmonary and extrapulmonary infection.[6] In children younger than 4 years, approximately 25% of TB infections are extrapulmonary.[32] Among HIV-infected persons, extrapulmonary TB infection becomes progressively more common as $CD4^+$ counts fall below 350 cells/μL.[30] One study of patients with TB concurrent with advanced HIV infection reported that 38% had only pulmonary disease, 30% had extrapulmonary TB alone, and 32% had both pulmonary and extrapulmonary TB.[17]

Extrapulmonary TB may occur in multiple sites, with decreasing relative frequencies in lymphatic, pleural, bone or joint, genitourinary, meningeal, peritoneal, and other sites. The lymph nodes are the most common site of extrapulmonary TB for both otherwise normal and HIV-infected patients. Involvement of the meninges is more common in young children than in other age groups (present in approximately 4% of children with TB), and the incidence of TB in the remainder of the extrapulmonary sites increases with age.[25,42] Less commonly involved locations for extrapulmonary TB include the skin, heart, pericardium, thyroid gland, mastoid cells, sclerae, and adrenal glands.

Lymphadenitis

Tuberculous lymphadenitis (scrofula) is the most common form of extrapulmonary TB. Scrofula is common in children but most commonly is seen in young adult women, usually of minority races. The patient usually has an enlarging, painless, red, firm mass in the region of one or more lymph nodes, most commonly in the anterior or posterior cervical chain or the supraclavicular fossa. Early on, the nodes are discrete, rubbery masses that are freely mobile, and the overlying skin is normal. Eventually, the nodes may become matted and harder and the overlying skin inflamed.

www.ketabpezeshki.com 66485457-66963820

Fluctuance as well as an abscess or sinus track may be present if a node erodes through the skin. Systemic signs and symptoms are uncommon, except in HIV-positive patients, in whom lymphadenitis usually is generalized.[17] Pulmonary infection is present in a minority of cases. Considerations in the differential diagnosis include lymphoma, metastatic cancer, fungal disease, cat-scratch disease, sarcoid, toxoplasmosis, reactive adenitis, and bacterial adenitis.

The diagnosis of scrofula usually is made by fine-needle aspiration of an affected lymph node. Although AFB smears are positive in only approximately 20% of cases, granulomatous inflammation may be obvious. Overall, fine-needle aspiration has a sensitivity of 77% and specificity of 93% for TB infection. First-line treatment of scrofula consists of antituberculosis drugs, but surgical excision may be performed when medical therapy has failed or if the diagnosis is unclear. Incision and drainage should not be done because permanent sinuses and prolonged drainage can result.

Pleural Effusion

Pleural extrapulmonary TB may occur early after primary infection with MTB and is manifested as pleurisy with effusion. More rarely, it may occur late in postprimary cavitary disease and arise as an empyema.

Tuberculous pleural involvement often causes no symptoms and resolves spontaneously; however, in untreated patients, a 65% relapse rate has been reported, with development of active pulmonary or extrapulmonary TB within 5 years. In elders, however, the onset may be more insidious and is likely to be confused with congestive heart failure, cancer, or a pulmonary embolus. The diagnosis usually is confirmed by microscopic and chemical examination of pleural fluid or pleural biopsy tissue. White blood cell counts usually range from 500 to 2500 cells/mL. The fluid is an exudate with protein usually exceeding 50% of the serum protein, and the glucose concentration may be normal to low. Because there are few bacilli, AFB smears rarely are positive, and cultures grow MTB for only 25 to 30% of patients known to have the disease. Pleural biopsy can confirm the diagnosis in most patients.

Bone and Joint Infection

Bone and joint TB remains a disease of older children and young adults in developing countries, and it is increasingly a disease of adults in developed countries. Skeletal TB presumably develops from reactivation of dormant tubercles originally seeded during stage 2 of the primary infection or, in the case of spinal TB, from contiguous spread from paravertebral lymph nodes to the vertebrae. In general, spinal TB (Pott's disease) accounts for 50 to 70% of the reported cases; the hip or knee is involved in 15 to 20% of cases, and the ankle, elbow, wrists, shoulders, and other bones and joints account for 15 to 20% of cases.[17] Approximately 50% of patients have a previous history or concurrent case of pulmonary TB, and the chest radiograph is normal in appearance in up to half of the cases.

Patients with Pott's disease may simply complain of back pain or stiffness. Examination may show fever, point tenderness, and decreased range of motion. If the initial radiograph is normal in appearance, the diagnosis may be delayed, allowing the disease to progress. The initial lesion usually spreads to the intervertebral disk and then to the adjacent vertebrae, producing the classic radiographic appearance of anterior wedging of two involved vertebral bodies with destruction of the disk. Early changes of spinal TB can be difficult to detect on plain radiographs and include loss of the "white stripe" of the vertebral endplate subsequent to destruction of subchondral bone. Thus, computed tomography and magnetic resonance imaging should be used when the disease is suspected.[17]

Paraspinal "cold" abscesses develop in 50% or more of cases, with occasional formation of sinus tracks. The abscess can spread the infection up and down the spine, sometimes sparing vertebral bodies along its course, forming the so-called skip lesions.[43] These skip lesions can easily be missed in imaging of the spine for Pott's disease. The main complication of Pott's disease is spinal cord compression.[17]

Medical management includes chemotherapy, modified bed rest, and early ambulation and results in improvement in approximately 90% of patients without neurologic involvement. Surgical treatment usually is reserved for patients with neurologic complications.

Renal Disease

The kidney is well vascularized, and hematogenous dissemination to that organ is fairly common. After the typical tuberculous lesions develop within the parenchyma, infection can spread into the calyces, renal pelvis, ureters, and bladder. As a result, tuberculous granulomas, scarring, and obstruction can occur anywhere along the urinary tract.[42]

The initial presenting signs and symptoms of urinary involvement are nonspecific. Advanced renal disease and destruction may occur before the diagnosis is made. The urinalysis often reveals pyuria, hematuria, and albuminuria. Sterile pyuria is a classic finding in renal TB, but in many cases with this finding, cultures will be positive for other urinary pathogens. The finding of pyuria in an acid urine with no organisms isolated should increase clinical suspicion for TB.[17] In one study of the diagnosis of renal TB, AFB stains were found to be 52% sensitive, and polymerase chain reaction testing was 96% sensitive.[44] Both tests had excellent specificity (97-98%). Mycobacterial cultures should be ordered when genitourinary TB infection is suspected.

Complications of renal TB include nephrolithiasis, ureteral obstruction or reflux, recurrent bacterial infections, hypertension, papillary necrosis, renal insufficiency, autonephrectomy, and, rarely, development of transitional cell cancer.[42,44]

Male Genital Disease

Male genital TB usually is associated with coexistent renal TB. Spread of infection from the kidney may involve the prostate, seminal vesicles, epididymides, and testes. A painless or slightly painful scrotal mass is a typical finding, and the patient may have symptoms of prostatitis, epididymitis, or orchitis.[17] Epididymal or prostatic calcifications may be clues to the diagnosis. TB involvement of the seminal vesicles may lead to infertility.[44]

Female Genital Disease

In women, the disease usually begins with a hematogenous focus in the fallopian tubes. The infection then spreads to the endometrium (in 50%), ovaries (in 30%), cervix (in 5-15%), and vagina (in 1%). Clinical manifestations may include abdominal or pelvic pain, ascites, infertility, menstrual irregularities, and, rarely, vaginal discharge. An ulcerating mass may be present on the cervix. Genital TB may be confused with ovarian or endometrial cancer, Meigs' syndrome, vulvar or vaginal ulcer, pelvic abscess, cervicitis, or cervical carcinoma.[45] Sexual transmission of TB by persons with active genital TB has been described.[46] Women with genital TB who become pregnant are at increased risk for ectopic pregnancy.

Multisystem Disease

Acute disseminated TB refers to active hematogenous spread of MTB to several organs in the body. The term *miliary tuberculosis*

www.ketabpezeshki.com 66485457-66963820

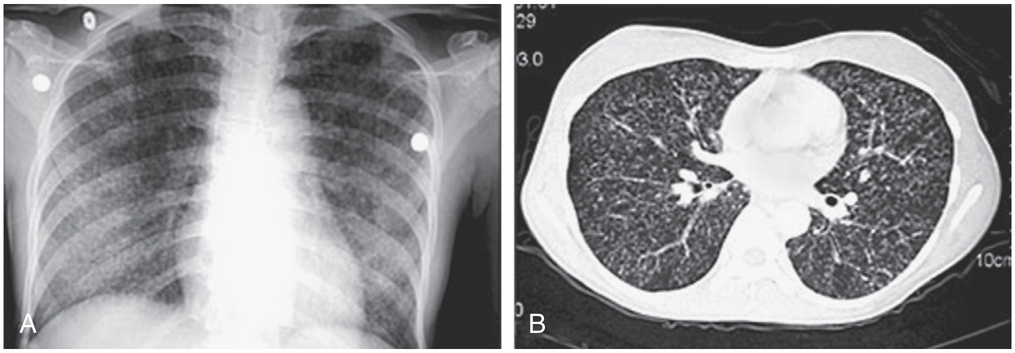


Figure 135-7. Chest radiograph (A) and computed tomography image (B) demonstrate a miliary pattern. (Images reprinted with permission from Golden MP, Vikram HR: Extrapulmonary tuberculosis: An overview. Am Fam Physician 72:1761, 2005. Copyright 2005 American Academy of Family Physicians. All rights reserved.)

was first used to describe the pathologic lesions, which resemble small millet seeds. This term is now used as a clinical term referring to the massive dissemination that leads to generalized systemic illness. Miliary TB occurs when the host is unable to contain either a recently acquired or a dormant TB infection. In the past, miliary TB occurred mainly in young children after primary infection; today, it is more common in elders and in persons infected with HIV.[17]

In infants and young children, the illness generally is acute and severe. In young adults, the acute illness runs a slower course and usually is less severe. Miliary TB often is a subtle disease associated with alcoholism, cirrhosis, neoplasm, pregnancy, collagen vascular disease, or use of corticosteroids or immunosuppressive medications. A presumptive diagnosis can be made rapidly if chest radiographs show a miliary infiltrate (Fig. 135-7). Unfortunately, the classic miliary pattern is absent on radiographs in approximately 50% of cases. Routine laboratory tests generally are not helpful. Hyponatremia from the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is common and often is associated with meningitis. Panculturing usually has a high yield, and HIV-infected patients may have positive results on blood cultures. Transbronchial biopsy can be performed to obtain tissue rapidly for analysis. Other potential biopsy sites include liver, lymph nodes, and bone marrow.

Mortality rates for miliary TB are higher than for the other forms of TB, with one case series reporting a rate of 21%. The high mortality rate often is caused by delay in treatment, which should be initiated immediately on the basis of clinical suspicion and not delayed until confirmation of the diagnosis. A fulminant form of miliary TB may cause the acute respiratory distress syndrome and disseminated intravascular coagulation. In these cases, the addition of corticosteroids (prednisone, 60 to 80 mg/day) is indicated.[34]

Central Nervous System Disease

Approximately 6% of all cases of extrapulmonary TB involve the central nervous system (CNS),[6] and CNS involvement remains a grave consequence of tuberculous infection. The peak incidence of CNS TB is in newborn to 4-year-old children.[17]

Tuberculous Meningitis

Tuberculous meningitis usually results from the rupture of a subependymal tubercle into the subarachnoid space rather than from direct hematogenous seeding of the CNS. When it is a complication of miliary TB, meningitis usually develops within several weeks of infection. In children, it is an early postprimary TB event, usually appearing within 6 months. Tuberculous cerebral involvement is most marked at the base of the brain, and vasculitis of local arteries and veins may lead to aneurysm formation, thrombosis, and focal hemorrhagic infarction. The vessels to the basal ganglia most commonly are involved, leading to formation of lacunar infarcts or deficits associated with movement disorders. Involvement of other vessels, such as the middle cerebral artery, may lead to hemiparesis or hemiplegia.

Tuberculous meningitis begins with a prodrome of malaise, intermittent headache, and low-grade fever. In 2 to 3 weeks, a protracted headache develops. Vomiting, confusion, meningismus and focal neurologic signs, and coma may follow. Nuchal rigidity may be absent. Diplopia resulting from basilar exudate is present in up to 70% of patients. Hyponatremia may be present because SIADH is common. The cerebrospinal fluid (CSF) white blood cell count usually ranges from 0 to 1500 cells/mL, with a predominance of lymphocytes; however, polymorphonuclear cells may predominate early in the course. CSF protein concentration usually is elevated, and CSF glucose concentration typically is low. A single lumbar puncture CSF specimen yields a positive AFB culture result in only 37% of cases, but pooled samples from multiple lumbar punctures yield a positive result in 90% of cases.[2]

The classic triad of neuroradiologic findings in patients with TB meningitis consists of basal meningeal enhancement, hydrocephalus, and cerebral or brainstem infarction. Computed tomography or magnetic resonance imaging also may reveal rounded lesions typical of evolving parenchymal tuberculomas.[47]

Prognosis is influenced by age, duration of symptoms, and presence of neurologic deficits. In children, the overall mortality is 13%, and permanent neurologic deficits develop in approximately half of the survivors.[32] Outcome also is closely linked to the clinical stage at which the disease arises. Complete recovery is the rule in stage 1, wherein the alert patient has no focal neurologic signs and no hydrocephalus. Stage 2 is characterized by confusion and focal neurologic changes, and patients in stage 3 present with stupor or with dense hemiplegia or paraplegia. In contrast with the excellent prognosis for stage 1 disease, approximately half of patients with stage 3 disease either die or are left with severe neurologic disability.

Treatment starts with a four-drug regimen. Isoniazid and pyrazinamide reach increased concentrations in the CSF in the presence of inflamed meninges. Rifampin also crosses the blood-brain barrier. Whereas 6-month regimens are used for most other forms of extrapulmonary TB, the CDC recommends 9 to 12 months of therapy for TB meningitis.[34] Corticosteroids also are recommended by the CDC. Prednisone, 60 to 80 mg, should be given in a daily dose and tapered during 4 to 6 weeks.[34] Ventricular shunting may be needed if hydrocephalus develops.

www.ketabpezeshki.com 66485457-66963820

Figure 135-8. Head computed tomography scan demonstrating tuberculomas in a patient with AIDS.

Spinal Meningitis

Tuberculous spinal meningitis is a complication of CNS infection that usually originates through hematogenous dissemination from an outside source, although tuberculous meningitis may extend caudally and involve the spine. Local extension of bone or disk TB also has been described. Presenting symptoms and signs result from nerve root or cord compression and may include pain, sensory changes, paralysis, or weakness of bladder or rectal sphincters.

Intracranial Tuberculoma

A tuberculoma usually begins in an area of TB cerebritis as a cluster of microgranulomas, which coalesce into a mature noncaseating granuloma.[47] These space-occupying lesions may cause focal or generalized signs or symptoms, such as tonic-clonic seizures. Involvement of the CNS parenchyma also may be accompanied by meningitis. Imaging reveals either solitary or multiple tuberculomas (Fig. 135-8), usually involving the frontal or parietal lobes.[47] Treatment includes chemotherapy before surgical removal. Corticosteroids may reduce edema and decrease the symptoms. If MTB is discovered at the time of surgery, postoperative chemotherapy may prevent the further spread of the disease.

Gastrointestinal Disease

Gastrointestinal TB infection usually is secondary to hematogenous or lymphatic spread but also may result from swallowed bronchial secretions or direct spread from local sites, such as lymph nodes or fallopian tubes.[48] TB may occur in any gastrointestinal location from the mouth to the anus, but lesions proximal to the terminal ileum are rare. The ileocecal area is the most common site of involvement, producing signs and symptoms of pain, anorexia, diarrhea, obstruction, hemorrhage, and often a palpable mass.

The most common clinical manifestations of gastrointestinal TB are abdominal pain, fever, weight loss, anorexia, nausea, vomiting, and diarrhea.[48] The nonspecificity of these findings as well as of those on the physical examination may lead to the misdiagnosis of gastrointestinal TB as appendicitis, intestinal obstruction, or cancer. Approximately 12 to 16% of cases are manifested as an acute abdomen.[48] The signs and symptoms can be so similar to those of other diseases that the diagnosis often is made at surgery.

The clinical manifestations of anal TB include fissures, fistulas, and perirectal abscesses.[17] Antimicrobial treatment of gastrointestinal TB is the same as that of pulmonary disease.[34,48]

Peritonitis

Tuberculous peritonitis may develop from local spread of MTB infection from a tuberculous lymph node, intestinal focus, or infected fallopian tube. In addition, peritonitis can develop from seeding of the peritoneum in miliary TB or from the reactivation of a latent focus.

The patient with tuberculous peritonitis commonly has pain and abdominal swelling associated with fever, anorexia, and weight loss. Diagnosis may be confounded by the similarity of this disease to alcoholic hepatitis and by the fact that this disease often coexists with other disorders, especially cirrhosis with ascites.[17] Paracentesis is thus essential. The peritoneal fluid is exudative, with a cell count of 500 to 2000 cells/mL. Lymphocytes usually predominate, with rare exceptions early in the process, when polymorphonuclear leukocytes may predominate. AFB smears of the fluid have a low diagnostic yield, with a reported sensitivity of no more than 7%, and the culture result is positive in only 25% of the cases. Peritoneal biopsy often is necessary to confirm the diagnosis. Treatment is the same as for pulmonary TB, with a 6-month regimen.[34]

MANAGEMENT

Initial Emergency Department Management

Hemoptysis. The most emergent presentation of pulmonary TB is massive hemoptysis, defined as loss of at least 600 mL of blood in 24 hours. Exsanguination rarely occurs, and the major morbidity is due to asphyxiation from aspirated blood. The airway should be secured with a large-diameter (8-mm) endotracheal tube that can accommodate a fiberoptic bronchoscope. The patient should be positioned with the bleeding lung in a dependent position. Selective main bronchus intubation should be considered to allow ventilation of the unaffected lung and to minimize the spread of blood from the affected lung. Emergent consultation for bronchoscopy, surgical resection, or angiography with selective embolization is required.[23] Patients thought to have active pulmonary TB should be immediately placed in respiratory isolation.

Fever or Wasting. Patients with fever and wasting generally should be admitted for an in-hospital workup. Patients should be placed in respiratory isolation until the diagnosis of TB has been excluded.

History of TB, Therapy Discontinued. In patients with vague symptoms and a history of TB, consideration of reactivation should be raised. If necessary, the local TB health officer or infectious diseases specialist should be consulted.

Medical Therapy

Patients thought to have pulmonary TB whose sputum smears return positive for AFB can be presumptively diagnosed and treated with antituberculosis agents. Consultation with infectious diseases specialists or local TB health officers generally should be made before initiation of treatment in the ED. Exceptions exist, for example, the very ill patient with obvious miliary disease when consultation is not immediately available. In patients with negative findings on a sputum smear but clinical and radiographic findings consistent with pulmonary TB, it also may be appropriate to initiate treatment for presumptive TB.[34] A few days of therapy with antituberculosis agents does not interfere with bacteriologic diagnosis, so severely ill patients with presumed TB should be treated immediately. Local factors, including the prevalence of TB

www.ketabpezeshki.com 66485457-66963820

and available resources, help determine the appropriateness of presumptive therapy.

Antituberculosis Medications

Three basic therapeutic principles govern the treatment of TB: (1) any treatment regimen must contain multiple drugs to which the MTB organism is susceptible, (2) the therapeutic agents must be taken regularly, and (3) the therapy must continue for a sufficient period.[22] In clinical practice, the last is the most problematic.

It is estimated that approximately 33 to 50% of patients with TB fail to follow medical recommendations. Patients at higher risk for noncompliance are those with previous treatment failures; substance abusers; patients with mental, emotional, or physical impairment; and those in whom preventive treatment has failed. The most effective strategy to ensure compliance is directly observed therapy (DOT), which is now the preferred practice in the United States.

The medications used to treat MTB generally are divided into first-line and second-line agents (Tables 135-4 and 135-5).[34] Of these agents, 10 have been approved by the FDA for treatment of MTB. The most commonly used first-line agents are isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB).[34] Agents that are used in special circumstances but are not FDA approved for this purpose include rifabutin, levofloxacin, moxifloxacin, amikacin, and kanamycin.

Table 135-4 Doses of Antituberculosis Drugs for Adults and Children

DRUG	PREPARATION	ADULTS OR CHILDREN	DOSES*† Daily	1×/wk	2×/wk	3×/wk
First-Line Drugs						
Isoniazid (INH)	Tablets (50, 100, 300 mg) Elixir (50 mg/5 mL) Aqueous solution (100 mg/mL) for intravenous or intramuscular injection	Adults (max) Children (max)	5 mg/kg (300 mg) 10-15 mg/kg (300 mg)	15 mg/kg (900 mg) —	15 mg/kg (900 mg) 20-30 mg/kg (900 mg)	15 mg/kg (900 mg) —
Rifampin (RIF)	Capsule (150, 300 mg) Powder may be suspended for oral administration Aqueous solution for intravenous injection	Adults‡ (max) Children	10 mg/kg (600 mg) 10-20 mg/kg (600 mg)	— —	10 mg/kg (600 mg) 10-20 mg/kg (600 mg)	10 mg/kg (600 mg) —
Rifabutin	Capsule (150 mg)	Adults‡ (max) Children	5 mg/kg (300 mg) Appropriate dosing for children is unknown	— Appropriate dosing for children is unknown	5 mg/kg (300 mg) Appropriate dosing for children is unknown	5 mg/kg (300 mg) Appropriate dosing for children is unknown
Rifapentine	Tablet (150 mg, film coated)	Adults Children	— Not approved for use in children	10 mg/kg, continuation phase (600 mg) Not approved for use in children	— Not approved for use in children	— Not approved for use in children
Pyrazinamide (PZA)	Tablet (500 mg, scored)	Adults Children (max)	See Table 135-5 15-30 mg/kg (2 g)	— —	See Table 135-5 50 mg/kg (2 g)	See Table 135-5
Ethambutol (EMB)	Tablet (100 mg, 400 mg)	Adults Children§ (max)	See Table 135-5 15-20 mg/kg (1 g)	— —	See Table 135-5 50 mg/kg (2.5 g)	See Table 135-5
Second-Line Drugs						
Cycloserine	Capsule (250 mg)	Adults (max) Children (max)	10-15 mg/kg/day (1 g in two doses), usually 500-750 mg/day in two doses‖ 10-15 mg/kg/day (1 g/day)	No data to support intermittent administration —	No data to support intermittent administration —	No data to support intermittent administration —
Ethionamide	Tablet (250 mg)	Adults¶ (max) Children (max)	15-20 mg/kg/day (1 g/day), usually 500-750 mg/day in a single daily dose or two divided doses¶ 15-20 mg/kg/day (1 g/day)	No data to support intermittent administration No data to support intermittent administration	No data to support intermittent administration No data to support intermittent administration	No data to support intermittent administration No data to support intermittent administration

www.ketabpezeshki.com 66485457-66963820

Table 135-4 Doses of Antituberculosis Drugs for Adults and Children—cont'd

DRUG	PREPARATION	ADULTS OR CHILDREN	DOSES*† Daily	1×/wk	2×/wk	3×/wk
Streptomycin	Aqueous solution (1-g vials) for intravenous or intramuscular administration	Adults (max)	**	—	—	—
		Children (max)	20-40 mg/kg/day (1 g)	—	20 mg/kg	—
Amikacin or kanamycin	Aqueous solution (500-mg and 1-g vials) for intravenous or intramuscular administration	Adults (max)	**	—	—	—
		Children (max)	15-30 mg/kg/day (1 g) intravenously or intramuscularly as a single daily dose	—	15-30 mg/kg	—
Capreomycin	Aqueous solution (1-g vials) for intravenous or intramuscular administration	Adults (max)	**	—	—	—
		Children (max)	15-30 mg/kg/day (1 g) as a single daily dose	—	15-30 mg/kg	—
p-Aminosalicylic acid (PAS)	Granules (4-g packets) can be mixed with food Tablets (500 mg) are still available in some countries but not in the United States A solution for intravenous administration is available in Europe	Adults	8-12 g/day in two or three doses	No data to support intermittent administration	No data to support intermittent administration	No data to support intermittent administration
		Children	200-300 mg/kg/day in two to four divided doses (10 g)	No data to support intermittent administration	No data to support intermittent administration	No data to support intermittent administration
Levofloxacin	Tablets (250, 500, 750 mg) Aqueous solution (500-mg vials) for intravenous injection	Adults	500-1000 mg daily	No data to support intermittent administration	No data to support intermittent administration	No data to support intermittent administration
		Children	No long-term use††	No long-term use††	No long-term use††	No long-term use††
Moxifloxacin	Tablets (400 mg) Aqueous solution (400 mg/250 mL) for intravenous injection	Adults	400 mg daily	No data to support intermittent administration	No data to support intermittent administration	No data to support intermittent administration
		Children	No long-term use‡‡	No long-term use‡‡	No long-term use‡‡	No long-term use‡‡
Gatifloxacin	Tablets (400 mg) Aqueous solution (200 mg/20 mL, 400 mg/40 mL) for intravenous injection	Adults	400 mg daily	No data to support intermittent administration	No data to support intermittent administration	No data to support intermittent administration
		Children	No long-term use§§	No long-term use§§	No long-term use§§	No long-term use§§

From American Thoracic Society; CDC; Infectious Diseases Society of America: Treatment of tuberculosis. MMWR Recomm Rep 52(RR-11):1-77, 2003.

*Dose per weight is based on ideal body weight. Children weighing more than 40 kg should be dosed as for adults.

†In regimens given in this table, adult dosing begins at age 15 years.

‡Dose may need to be adjusted for patients who also are taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors.

§The drug probably can be used safely in older children but should be used with caution in children younger than 5 years, in whom visual acuity cannot be monitored. In younger children, ethambutol at the dose of 15 mg/kg per day can be used if there is suspected or proven resistance to isoniazid or rifampin.

‖Of note, although this is the dose recommended generally, most clinicians with experience in use of cycloserine indicate that it is unusual for patients to be able to tolerate this amount. Serum concentration measurements often are useful in determination of the optimal dose for a given patient.

¶The single daily dose can be given at bedtime or with the main meal.

**Dose: 15 mg/kg per day (1 g) and 10 mg/kg in persons older than 59 years (750 mg). Usual dose: 750 to 1000 mg administered intramuscularly or intravenously, given as a single dose 5 to 7 days per week and reduced to two or three times per week after the first 2 to 4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.

††The long-term use (for more than several weeks) of levofloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. However, most experts agree that the drug should be considered for children with tuberculosis caused by organisms resistant to both isoniazid and rifampin. The optimal dose is not known.

‡‡The long-term use (for more than several weeks) of moxifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.

§§The long-term use (for more than several weeks) of gatifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.

www.ketabpezeshki.com 66485457-66963820

Table 135-5 Suggested Pyrazinamide and Ethambutol Doses, Using Whole Tablets, for Adults Weighing 40 to 90 kg

DOSING SCHEDULE, UNITS	DOSE BY WEIGHT*		
	40-55 kg	56-75 kg	76-90 kg
Pyrazinamide			
Daily, mg (mg/kg)	1000 (18.2-25.0)	1500 (20.0-26.8)	2000† (22.2-26.3)
Thrice weekly, mg (mg/kg)	1500 (27.3-37.5)	2500 (33.3-44.6)	3000† (33.3-39.5)
Twice weekly, mg (mg/kg)	2000 (36.4-50.0)	3000 (40.0-53.6)	4000† (44.4-52.6)
Ethambutol			
Daily, mg (mg/kg)	800 (14.5-20.0)	1200 (16.0-21.4)	1600† (17.8-21.1)
Thrice weekly, mg (mg/kg)	1200 (21.8-30.0)	2000 (26.7-35.7)	2400† (26.7-31.6)
Twice weekly, mg (mg/kg)	2000 (36.4-50.0)	2800 (37.3-50.0)	4000† (44.4-52.6)

Adapted from American Thoracic Society; CDC; Infectious Diseases Society of America: Treatment of tuberculosis. MMWR Recomm Rep 52(RR-11):1-77, 2003.
*Based on estimated lean body weight.
†Maximum dose regardless of weight.

First-Line Agents

INH demonstrates extremely potent early bactericidal activity and can rapidly decrease the patient's infectiousness. The incidence of INH-induced hepatitis is estimated to be 0.6% when INH is given alone, 1.6% when it is given with other antituberculosis agents (excluding RIF), and 2.7% when it is given with RIF. The risk increases with age and also with underlying liver disease, alcohol use, and administration during the postpartum period. Another adverse effect is peripheral neuropathy. This is uncommon (<0.2%) at standard doses and may be avoided by the coadministration of pyridoxine (25 mg/day). Patients who have conditions associated with neuropathy (e.g., diabetes, HIV infection, alcoholism) and pregnant or breast-feeding women are at increased risk. Supplemental pyridoxine is recommended for such patients.[34]

RIF also demonstrates strong early bactericidal activity. This agent causes orange discoloration of body fluids, including urine, tears, sweat, and sputum. Patients should be warned of this effect before administration of the medication. It is especially important to warn soft contact lens wearers, in whom permanent lens staining may occur. Rifapentine is a rifamycin derivative with excellent activity against MTB. Its long half-life makes it a good candidate for intermittent therapy regimens (given once weekly). Rifabutin is another rifamycin-like antibiotic that most often is used for treatment or prophylaxis of infections with *M. avium* complex; however, it also is effective against MTB. This medication generally is used for treatment of patients who do not tolerate RIF or who are taking medications with known adverse interactions with RIF (e.g., antiretrovirals, oral contraceptives, methadone, warfarin).

PZA works against organisms contained in the acid environment of the macrophage. The chief side effect is hepatotoxicity, but this risk is very low at daily doses of 25 mg/kg or less. Polyarthralgias occur commonly (up to 40% of patients) but usually respond to nonsteroidal anti-inflammatory drugs or aspirin.

EMB is a first-line agent that helps prevent the emergence of RIF resistance during TB treatment. Retrobulbar neuritis can occur, resulting in decreased visual acuity to the point of blindness. Patients who experience visual loss should have EMB stopped immediately. Some patients regain much of their visual acuity, usually during a period of many months, whereas others have permanent visual loss. Thus monitoring of visual symptoms is key to prevention of adverse effects in patients using EMB. Because of the difficulty in visual testing in small children and infants, EMB should be avoided in these populations, except in the cases of adult-type TB or with INH or RIF resistance.[34]

Fixed-Dose Combination Drugs

Fixed-dose combinations are multiple antituberculosis agents packaged into single tablets. They are useful to prevent monotherapy (e.g., when the patient selectively takes only one of the prescribed drugs) and the emergence of drug resistance. Rifater contains INH, RIF, and PZA. Rifamate contains INH and RIF. These preparations are indicated when DOT is not possible.[34]

Second-Line Agents

Streptomycin was once a first-line anti-TB agent, but increasing resistance rates now limit its usefulness. Streptomycin must be given parenterally and has a peak of action 1 hour after the intramuscular dose. The chief side effects of this potentially teratogenic agent are ototoxicity and nephrotoxicity. Amikacin, kanamycin, and capreomycin also are injectable agents used for drug-resistant TB. As with streptomycin, ototoxicity and neurotoxicity are their major adverse effects. TB strains resistant to streptomycin usually are sensitive to both amikacin and kanamycin, and resistance to these last two drugs usually is linked.

Cycloserine, ethionamide, and *p*-aminosalicylic acid (PAS) are oral agents used for treatment of patients with drug-resistant TB when the strain is presumed or known to be sensitive to these agents. Cycloserine also sometimes is used temporarily for patients with acute hepatitis. The main adverse effect of cycloserine is psychosis or seizures (occurring in 3-16% of patients). Ethionamide is similar to INH in both structure and toxicity. Major adverse effects of PAS include gastrointestinal distress (most common), hypothyroidism, and hepatitis.

Fluoroquinolones have played a more recent but limited role in the treatment of TB. They are less effective than the first-line agents and are used mainly in the treatment of drug-resistant disease. They also may be used when first-line agents are not tolerated. If they are used singly, resistance may develop quickly. The agents most active against MTB are levofloxacin, moxifloxacin, and gatifloxacin. Because the long-term experience regarding safety and tolerability is greatest with levofloxacin, this fluoroquinolone is preferred. The main side effects are gastrointestinal upset, minor CNS symptoms, and photosensitivity or rash.[34]

Initial Therapy

Adults

In 2003, the American Thoracic Society, the CDC, and the Infectious Diseases Society of America published a joint statement providing updated evidence-based recommendations for the

www.ketabpezeshki.com 66485457-66963820

Table 135-6 Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

INITIAL PHASE			CONTINUATION PHASE			RANGE OF TOTAL DOSES (MINIMAL DURATION)	RATING† (EVIDENCE)‡	
Regimen	Drugs	Interval/No. of Doses* (Minimal Duration)	Regimen	Drugs	Interval/No. of Doses*§ (Minimal Duration)		HIV⁻	HIV⁺
1	INH RIF PZA EMB	7 days/wk for 56 doses (8 wk) or 5 days/wk for 40 doses (8 wk)‖	1a	INH-RIF	7 days/wk for 126 doses (18 wk) or 5 days/wk for 90 doses (18 wk)‖	182-130 (26 wk)	A (I)	A (II)
			1b	INH-RIF	Twice weekly for 36 doses (18 wk)	92-76 (26 wk)	A (I)	A (II)‖
			1c¶	INH-RPT	Once weekly for 18 doses (18 wk)	74-58 (26 wk)	B (I)	E (I)
2	INH RIF PZA EMB	7 days/wk for 14 doses (2 wk), then twice weekly for 12 doses (6 wk); or 5 days/wk for 10 doses (2 wk),‖ then twice weekly for 12 doses (6 wk)	2a	INH-RIF	Twice weekly for 36 doses (18 wk)	62-58 (26 wk)	A (II)	B (II)‖
			2b¶	INH-RPT	Once weekly for 18 doses (18 wk)	44-40 (26 wk)	B (I)	E (I)
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 wk)	3a	INH-RIF	Three times weekly for 54 doses (18 wk)	78 (26 wk)	B (I)	B (II)
4	INH RIF EMB	7 days/wk for 56 doses (8 wk) or 5 days/wk for 40 doses (8 wk)**	4a	INH-RIF	7 days/wk for 217 doses (31 wk) or 5 days/wk for 155 doses (31 wk)**	273-195 (39 wk)	C (I)	C (II)
			4b	INH-RIF	Twice weekly for 62 doses (31 wk)	118-102 (39 wk)	C (I)	C (II)

From American Thoracic Society; CDC; Infectious Diseases Society of America: Treatment of tuberculosis. MMWR Recomm Rep 52(RR-11):1-77, 2003.

EMB, ethambutol; *INH,* isoniazid; *PZA,* pyrazinamide; *RIF,* rifampin; *RPT,* rifapentine.

*When directly observed therapy is used, drugs may be given 5 days/week and the necessary number of doses adjusted accordingly. Although no studies have compared 5 with 7 daily doses, extensive experience indicates that this would be an effective practice.

†A = preferred; B = acceptable alternative; C = offer when A and B cannot be given; E = should never be given.

‡I = randomized clinical trial; II = data from clinical trials that were not randomized or were conducted in other populations; III = expert opinion.

§Patients with cavitation on initial chest radiograph and positive culture results at completion of 2 months of therapy should receive a 7-month (31 weeks: either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.

‖Not recommended for HIV-infected patients with $CD4^+$ counts below 100 cells/μL.

¶Options 1c and 2b should be used only in HIV-seronegative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial radiograph. For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

**Five-day-a-week administration is given by directly observed therapy. Rating for these regimens is A (III).

treatment of TB.[34] As of early 2013, this document had not been revised. Similar guidelines were published by the World Health Organization in 2006.[49] The goals of therapy are to rapidly kill large numbers of bacilli (bactericidal activity), to prevent emergence of drug resistance, and to prevent relapse by elimination of dormant or slowly dividing bacilli (sterilizing activity). There are four basic recommended regimens (Table 135-6).[34] These are used when the organism is known or presumed to be susceptible to INH, RIF, PZA, and EMB. All begin with a 2-month initial phase, followed by a continuation phase lasting 4 to 7 months (total treatment duration of 6 to 9 months). Therapeutic regimens less than 6 months in duration usually are associated with an unacceptably high relapse rate. Dosing frequency varies, ranging from 1 to 7 days per week. There is also variation in the strength of evidence supporting each regimen, depending on the patient's HIV serostatus. The regimen that is rated as preferred and supported by the strongest evidence (randomized clinical trials) consists of INH, RIF, PZA, and EMB for 8 weeks (5 to 7 days per week), followed by INH and RIF for 18 weeks (2, 5, or 7 days per week). DOT should be used whenever medications are given less often than 7 days per week.[34]

HIV-Seropositive Patients

Adequate treatment of active TB in patients coinfected with HIV is critical. It has been observed that immune activation from TB enhances both systemic and local HIV replication and may accelerate the natural progression of HIV infection. Active TB in HIV-infected patients has been associated with increased risk for opportunistic infections and death. TB treatment alone leads to reduction in viral load in these patients.[50] Untreated or inadequately treated TB may result in increased morbidity and mortality, not only from MTB but also from accelerated AIDS. Furthermore, TB can spread rapidly through immunocompromised populations when a source case remains contagious for a prolonged period.

Current recommendations for treatment of MTB in HIV-infected patients are the same as those for patients who are not HIV infected, with a few important exceptions. The once-weekly INH-RIF dosing for the continuation phase should not be used because of a high relapse rate (17%). The twice-weekly INH-RIF dosing should also not be used in patients with $CD4^+$ counts below 100 cells/μL because of emergence of RIF monoresistance. Treatment duration should be a minimum of 6 months. The duration should be extended to 9 months if sputum cultures remain positive after the 2-month initial phase of treatment.[34]

Significant drug interactions between rifamycins used for TB and antiretroviral drugs (protease inhibitors and non-nucleoside reverse transcriptase inhibitors [NNRTIs]) used for HIV infection complicate the treatment of patients with active TB who are coinfected with HIV. These drug interactions are due primarily to

www.ketabpezeshki.com 66485457-66963820

changes in the metabolism of the antiretrovirals and the rifamycins secondary to induction or inhibition of the hepatic cytochrome CYP450 enzyme system. The currently available rifamycins are inducers of CYP450, with RIF being the most potent, rifapentine intermediate, and rifabutin the least potent.[50] Because all of the protease inhibitors are metabolized by CYP450, coadministration of RIF and the protease inhibitors would cause a marked decrease in the blood concentration of the protease inhibitors, probably reducing their antiretroviral activity as well. For treatment of MTB in patients who are taking protease inhibitors, rifabutin can be used instead of the other rifamycins. Rifabutin provides good activity against MTB without substantially affecting the effectiveness of protease inhibitors.

There are major differences in the actions of NNRTIs on CYP450 and the degree to which they are substrates of CYP450; therefore, their interactions with rifamycins cannot be fully summarized as a class.[50] However, RIF reduces serum concentrations of all three NNRTIs (delavirdine, nevirapine, and efavirenz). Serum concentrations of NNRTIs should be maintained at an optimal steady state to prevent resistant mutations of HIV. When RIF is used in patients taking nevirapine or efavirenz, the NNRTI dose should be increased. Alternatively, rifabutin can be substituted for RIF without NNRTI dose adjustment. Because of the dramatic reduction in serum concentration, none of the rifamycin preparations are acceptable for patients taking delavirdine.[34]

When TB treatment is initiated in HIV-positive patients, a paradoxical reaction to medical therapy may develop in some instances. The reaction is manifested with development of fever, new or enlarging lymph nodes, or worsening of radiographic disease. Other causes of deterioration, such as treatment failure, should be considered when this reaction is suspected. Severe paradoxical reactions may be managed with a 2-week tapering course of prednisone or methylprednisolone.[34]

Children and Adolescents

The treatment of adolescents, children, and infants who are culture positive for MTB is in principle the same as that of adults. Some important differences are recognized, however. In children, active pulmonary TB usually is part of the initial infection. The chest radiograph demonstrates hilar adenopathy and middle or lower lobe infiltrates. Less commonly, the development of "adult-type" infection, which resembles postprimary infection in adults (upper lobe infiltrates, cavitary lesions, sputum production), is seen in this age group. Because the bacillary load of primary infection is lower than with adult-type disease, the recommended regimen for children with primary TB is a three-drug regimen (INH, RIF, PZA) for the 2-month initial phase, followed by INH and RIF for a 4-month continuation phase (for a total of 6 months). For adult-type infection in children, EMB is added to the initial phase. EMB also is added if INH or RIF resistance is suspected. Because it can be difficult to isolate MTB from children, available resistance patterns of the source should be taken into consideration. Visual acuity and color discrimination should be monitored monthly for older children who are treated with EMB. Inability to monitor vision because of young age is not a contraindication to EMB use in adult-type infection or in the case of INH or RIF resistance. Some important points in treatment of children are presented in Box 135-4.

Box 135-4 Treatment of Tuberculosis in Children

Infection with tuberculosis in children younger than 4 years is more likely to disseminate and therefore demands prompt recognition and aggressive management.

Sputum smears are a less reliable diagnostic tool. It may be more appropriate to confirm the diagnosis in a child by use of culture results or results from the adult source. If neither is available, early-morning gastric aspirates, bronchoalveolar lavage fluid, or tissue may be used.

Because of its ocular toxicity, ethambutol should be avoided in this age group. Streptomycin, kanamycin, and amikacin are alternatives.

The primary cause of treatment failure in this population is noncompliance. Therefore, directly observed therapy is preferable, and twice-a-week regimens are an option.

Treat extrapulmonary tuberculosis as described above for pulmonary variety except for infections involving bones or joints, meningitis, and miliary disease, for which therapy may be required for 9 to 12 months.

Hilar adenopathy on chest radiographs may take 2 to 3 years to resolve after treatment.

Drug-Resistant Tuberculosis

Two types of drug-resistant MTB have emerged as a result of spontaneous mutations. *Multidrug-resistant TB* (MDR-TB) is defined as TB in which the mycobacteria are resistant to two or more first-line antituberculosis agents. Multidrug resistance may develop when a single drug is added to a failing regimen, an intervention equivalent to giving monotherapy. *Extensively drug-resistant TB* (XDR-TB) is TB characterized by resistance to both first-line and at least three second-line drugs. Patients with TB who are improperly treated (especially with monotherapy) or who are nonadherent to their treatment regimen present a microbiologic milieu likely to offer the drug-resistant strains a selective advantage. When these strains predominate, "acquired resistance" has occurred. Patients with acquired resistance can transmit drug-resistant organisms to previously uninfected (never treated) persons, a process resulting in primary drug resistance.

Multidrug-Resistant Tuberculosis

Although MDR-TB ultimately can be traced back to suboptimal treatment, it is the transmission of primary drug resistance from person to person that allows rapid dissemination of drug-resistant strains. The spread of primary drug resistance is faster when HIV infection is highly prevalent in a population. Because initial TB infection in HIV-infected patients progresses rapidly to active disease, newly infected persons can quickly become source cases for further transmission of the resistant bacilli. In reports on hospital outbreaks of MDR-TB, more than 90% of patients had coinfection with HIV, and case fatality rates were as high as 70 to 90%. However, patients without HIV infection demonstrate excellent clinical responses when they are treated for MDR-TB.

For the identification of potential cases, health care workers should know the prevalence of drug resistance in their community and the risk factors (Box 135-5) for drug resistance. Rapid identification and prompt isolation of these patients along with other control measures can reduce nosocomial transmission of MDR-TB to patients and health care workers. Failure to control drug resistance may lead to wide dissemination of MDR-TB and to a public health crisis that physicians may confront without effective medications.

Treatment of drug-resistant TB can be challenging and requires familiarity with second-line agents. For MDR-TB, specialist consultation is essential. A general principle that applies in such cases is to use at least three drugs to which the organism is susceptible and that have not been used previously. In general, one of these medications should be an injectable agent. TB infections with strains that are resistant only to INH can be managed with a 6-month course of RIF, PZA, and EMB. Recommended regimens for some other resistance patterns are listed in Table 135-7.

www.ketabpezeshki.com 66485457-66963820

Box 135-5 Risk Factors for Drug-Resistant *Mycobacterium tuberculosis* Infection

Previous unsuccessful antituberculosis treatment
Failure to respond or adhere to a good treatment regimen
Human immunodeficiency virus infection
Injection drug abuse
Close contact with source cases
Recent immigration from area with a high prevalence of drug resistance
Cavitary lung disease
Homelessness
Imprisonment
Drug malabsorption due to gastrectomy or ileal bypass surgery

Data from O'Brien RJ: Drug-resistant tuberculosis: Etiology, management and prevention. Semin Respir Infect 9:104, 1994; and Ellner JJ: Multidrug-resistant tuberculosis. Adv Intern Med 40:155, 1995.

Table 135-7 Potential Regimens for the Management of Patients with Drug-Resistant Pulmonary Tuberculosis

PATTERN OF DRUG RESISTANCE	SUGGESTED REGIMEN	DURATION OF TREATMENT
INH (± SM)	RIF, PZA, EMB (an FQN* may strengthen the regimen for patients with extensive disease)	6 months
INH and RIF (± SM)	FQN, PZA, EMB, IA,† ± alternative agent‡	18-24 months
INH, RIF (± SM), and EMB or PZA	FQN (EMB or PZA if active), IA, and two alternative agents	24 months
RIF	INH, EMB, FQN, supplemented with PZA for the first 2 months (an IA may be included for the first 2-3 months for patients with extensive disease)	12-18 months

From American Thoracic Society; CDC; Infectious Diseases Society of America: Treatment of tuberculosis. MMWR Recomm Rep 52:1, 2003.
EMB, ethambutol; *FQN,* fluoroquinolone; *IA,* injectable agent; *INH,* isoniazid; *PZA,* pyrazinamide; *RIF,* rifampin; *SM,* streptomycin.
*Most experience involves ofloxacin, levofloxacin, or ciprofloxacin.
†May include aminoglycosides (streptomycin, amikacin, or kanamycin) or the polypeptide capreomycin.
‡Alternative agents include ethionamide, cycloserine, *p*-aminosalicylic acid, clarithromycin, amoxicillin-clavulanate, and linezolid.

Extensively Drug-Resistant Tuberculosis

XDR-TB was first recognized in patients coinfected with AIDS in South Africa in 2005.[51] A retrospective analysis of several thousand banked specimens from sources worldwide found that the strain was present in samples every year since 2000 and that it presented a major threat in Africa, Asia, and areas of the former Soviet Union.[52] In that study, up to 17% of patients in the MDR-TB group actually had XDR-TB. The strain has virulence similar to MTB, and disease does not progress faster in the absence of antibiotics.[53,54] As resistance to so many antibiotics has developed, however, this strain has become a major threat, especially in patients with AIDS. Most alarming is a report that as many as 33% of patients with TB coinfected with HIV and MDR-TB had the XDR-TB strain.[55] Mortality rates for this population of patients are high, because few alternative drugs exist. The CDC has reported a handful of cases in several states.[53] EDs could become a major focus for spread of this disease because some U.S. EDs are overcrowded and lack procedures, personnel, and space for recognition and isolation of potentially infected persons. Reports from Africa have shown that XDR-TB can be transmitted directly to health care workers.[56] Of great concern is the potential for transmission of the disease within the ED by a previously undiagnosed patient with XDR-TB, recently arrived from an endemic country, who presents for treatment of TB-related symptoms or an unrelated condition.

Extrapulmonary Tuberculosis

Evidence from clinical trials, including some randomized, controlled trials, indicates that 6- to 9-month regimens provide effective treatment of extrapulmonary TB. An exception is tuberculous meningitis. The CDC recommends 6 to 9 months for bone or joint infection, 9 to 12 months for meningitis, and 6 months for all other forms of extrapulmonary TB.[34]

Corticosteroids

The use of corticosteroids in the treatment of extrapulmonary TB is more common than in pulmonary disease. Corticosteroids may prevent constriction in tuberculous pericarditis and decrease the neurologic sequelae in all stages of tuberculous meningitis, especially if they are given early in the disease.[22] The CDC strongly recommends corticosteroids for MTB pericardial or CNS infections.[34] Corticosteroids may provide some benefit to children with bronchial obstruction caused by enlarged lymph nodes.[32] In addition, in patients with pulmonary TB, prednisone, 20 to 60 mg/day, may benefit those who continue to experience temperature spiking and to lose weight despite a good bacteriologic response to appropriate antituberculosis therapy.

Pregnancy

Treatment of TB during pregnancy poses little risk to the fetus, especially in comparison with untreated disease. INH, RIF, and EMB cross the placenta but have no known teratogenic effects. These three drugs should be used for the initial regimen, followed by a continuation phase of INH plus RIF for an additional 7 months (9 months total). Pyridoxine is recommended for pregnant women receiving INH. The use of PZA in the initial regimen is controversial, mainly because of insufficient data about its safety during pregnancy. When PZA is used, the total treatment duration can be reduced to 6 months. Streptomycin may cause congenital deafness and is contraindicated. Kanamycin, amikacin, and capreomycin should therefore be avoided as well. Fluoroquinolones should be avoided because of the potential for arthropathies (as demonstrated in animal models).[34] Although these chemotherapeutic agents are present in breast milk, they are not harmful to the infant and are not present in high enough concentrations (approximately 20% of the daily dose) to be therapeutic or preventive.[22,34]

Surgical Management

The most common indication for surgery is MDR-TB with severe localized disease. When optimal medical therapy based on drug susceptibility testing is given preoperatively and postoperatively, the outcome appears to improve.[57] In one study of 172 patients who underwent pulmonary resection for MDR-TB, 96% of those with MTB-positive preoperative sputum samples became sputum negative for MTB after surgery.[57] The CDC recommends that surgery be performed after several months of an intensive medication regimen.[34] Other indications for surgery may include bronchopleural fistula, massive uncontrolled hemoptysis, extensive bronchostenosis, destroyed lung, solitary nodule, trapped lung, complicated cavity, and empyema.

www.ketabpezeshki.com 66485457-66963820

Table 135-8 Ratings for Regimens for Treatment of Latent Tuberculosis Infection

DRUGS	DURATION	INTERVAL	RATING* (EVIDENCE)† HIV⁻	HIV⁺
Isoniazid	9 months	Daily Twice weekly	A (II) B (II)	A (II) B (II)
Isoniazid	6 months	Daily Twice weekly	B (I) B (II)	C (I) C (I)
Rifampin-pyrazinamide	2 months 2-3 months	Daily Twice weekly	B (II) C (II)	A (I) C (I)
Rifampin	4 months	Daily	B (II)	B (II)

From Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recomm Rep 49:1, 2000.
*A = preferred; B = acceptable alternative; C = offer when A and B cannot be given.
†I = randomized clinical trial data; II = data from clinical trials that are not randomized or that were conducted in other populations.

Treatment of Latent *Mycobacterium tuberculosis* Infection

After primary infection with MTB, host defenses usually are able to contain the infection within 2 to 10 weeks. This begins the latent period for MTB infection, when affected persons are not contagious and do not have active disease. Preventive therapy is directed at treatment of MTB infection during this latent phase to prevent reactivation and development of active disease. Tuberculin skin testing for the presence of latent MTB infection should be performed in persons who are at increased risk for MTB infection, exposure to infectious cases, or development of active disease (see Table 135-3).

Treatment of latent MTB infection is indicated for persons in whom the risk for development of active TB outweighs the risks associated with the therapy itself. The risk of INH-induced hepatitis increases with age, but age older than 35 years is *not* a contraindication to INH administration. In fact, if a patient belongs to a risk group listed in Table 135-3, age is no longer a factor, and treatment of latent MTB infection is warranted.[38,39] Persons with impaired cell-mediated immunity, such as young children and immunocompromised patients, may not have positive tuberculin skin test results after initial infection with MTB. Thus treatment of latent MTB infection should still be considered for such patients if they have experienced a recent (within 3 months) high-risk exposure to MTB.[38] Continuation of therapy in such cases should be based on tuberculin skin test results at 3 months after the exposure. Exclusion of active TB with chest radiographs and clinical evaluation is a critical step before initiation of therapy for latent MTB infection.

Any of four regimens may be used to treat latent MTB infection (Table 135-8).[39] The preferred regimen is daily INH for 9 months. The dose is 5 mg/kg in adults and 10 to 15 mg/kg for children, with a maximum of 300 mg/day for both populations. INH also may be given twice weekly by DOT. For HIV-positive patients, the recommended regimen is daily INH for 9 months or daily RIF plus PZA for 2 months.[39] DOT is recommended for all intermittent-therapy regimens and for persons at high risk for development of the disease to decrease possible MDR-TB emergence.

DISPOSITION

Most patients with TB can be managed on an outpatient basis. The ideal situation for the patient with newly diagnosed or suspected TB is to be at home, receiving antituberculosis therapy, with the patient's contacts receiving preventive treatment. The CDC strongly recommends DOT to maximize compliance and completion of therapy.[34] The ED discharge instructions should clearly emphasize the importance of adhering to the prescribed treatment regimen and home isolation procedures (avoidance of meeting new contacts). The case should be immediately reported to the health department to ensure that the patient has an adequate source of TB care, that support systems and resources are available to complete the care, and that the patient's contacts are investigated and screened. Two weeks of treatment is widely accepted as the minimum time to be rendered noninfectious as long as the patient has been treated with appropriate medications.

Acutely ill or elderly patients may require hospitalization during the first few days of treatment because adverse reactions to TB chemotherapy are common and may occasionally be life-threatening. In addition, severely ill patients may require parenteral drug administration. Patients with TB have a high rate of HIV coinfection, and the comorbid illnesses associated with HIV infection, the complex synergy between MTB and HIV, and the potentially harmful drug interactions between the antiretroviral agents and the rifamycins may favor inpatient treatment for initial management of these complicated cases.

Hospital admission also is indicated for patients with active MDR-TB. These patients commonly require observation during initiation of therapy because of the complexity of the treatment regimens, the toxicity of the drugs, and the need for close monitoring to ensure adherence to treatment and isolation measures. Finally, social issues such as homelessness, presence of infants or immunocompromised persons in the household, substance abuse, and incapacity for self-care may necessitate hospitalization. The recalcitrant patient constitutes a potential threat to public health, and legal measures for involuntary hospitalization may be required.

PREVENTION OF TRANSMISSION IN THE EMERGENCY DEPARTMENT

EDs often care for patients at increased risk for active pulmonary TB, such as those who are homeless, foreign born, recently incarcerated, or chronically ill. Accordingly, ED workers can be at high risk for occupational TB infection. Increased hospital occupancy and ED overcrowding can lead to extended waiting periods for both ED beds and hospital beds.[58,59] Some EDs may lack an adequate number of TB isolation rooms. Nosocomial transmission risk in the ED setting also is increased because patients with TB often receive care before the diagnosis is suspected; this risk is particularly high with critically ill patients, who by definition require close, intensive contact with multiple emergency care providers.

Early Identification

For the most effective minimization of infectious exposures among health care workers and other patients, all patients with active pulmonary TB would ideally be placed in respiratory isolation when they initially present for care. Not surprisingly, this is difficult to accomplish, and delays in identification and respiratory isolation of such patients are frequent. For early identification of patients who may have TB to be improved, the CDC has recommended screening for TB at triage.[9] Triage screening protocols can detect patients with more classic presentations of TB, but reported protocols are only moderately sensitive and somewhat cumbersome.[60] Immediate respiratory isolation should be considered for patients with high-risk chief complaints, such as

www.ketabpezeshki.com 66485457-66963820

the HIV-positive patient with cough, the person with hemoptysis, or the patient with a history of TB presenting with cough or fever. The best guideline is to initiate respiratory isolation as soon as TB is considered a possible diagnosis. Masks should be placed on such patients *before* chest radiographs are obtained. In addition, the development of policies providing for expedited admission to hospital isolation beds and for improved access to local public health facilities may help decrease TB transmission at virtually no cost.

Isolation and Environmental Control

In addition to triage screening, the use of proper isolation facilities and environmental control measures can help prevent TB exposures. Airflow in the ED plays a central role, and inadequate ventilation has been a contributing factor in many nosocomial outbreaks of TB. Ideally, there should be single-pass airflow from waiting rooms to outside the facility. Within the ED, air should flow from clean areas to less clean areas, rather than vice versa. For EDs that frequently see patients with TB, at least one true respiratory isolation room should be available. The CDC recommends that respiratory isolation rooms have at least 12 air changes per hour and have "negative pressure" (air flows *into* the room from other ED areas). Other engineering approaches to TB infection control include the use of high-efficiency particulate air (HEPA) filters and upper room ultraviolet light irradiation.[9]

Personal Respiratory Protection

ED personnel should be familiar with the appropriate use of respiratory protection against TB. Surgical masks (e.g., string-tie masks) should be placed on potentially contagious patients to decrease the release of infectious droplets into the air.[19] Air can leak around such masks, however, so they may not adequately prevent health care workers from inhaling infectious droplet nuclei. Thus surgical masks are used only for source control, not for health care worker protection. More advanced personal respiratory protection devices include N95 particulate respirators.[61] These masks can filter 1-µm particles with at least 95% efficiency and are the preferred masks for health care workers in the ED. They are available in a variety of shapes and sizes and from various manufacturers. HEPA-filtered masks can also be used for health care worker respiratory protection, and these masks were used more extensively before the development of the N95 masks. Although HEPA-filtered masks are effective, they are more costly and can make breathing uncomfortable.

Preventive Therapy after Inadvertent Exposure

Health care workers who are exposed to patients with active pulmonary TB require referral to their primary care physicians or employee health services for follow-up testing and treatment. Tuberculin skin testing usually is performed within days after exposure to establish whether the health care worker has previously been infected with MTB. If the baseline test result is negative, a follow-up skin test is performed 3 months later to determine whether tuberculin skin test conversion has occurred. Health care workers whose tuberculin skin test result converts to positive (5-mm induration) after an exposure should undergo chest radiography and clinical evaluation to rule out active disease. When active TB infection is excluded, preventive therapy is recommended. The recommendations in Box 135-6 can assist physicians in deciding who should be treated after an exposure. For exposures to MDR-TB, expert consultation is advised for selection of an individualized regimen.

Box 135-6 Guidelines for Management after Accidental Exposure to Tuberculosis

Healthy persons who remain PPD negative after a heavy exposure do not require chemotherapy.
If exposure is discovered immediately, preventive therapy should be started in particularly heavily exposed people who are known to be PPD negative. If the skin test result remains negative after 3 months, therapy can be discontinued.
Persons who seroconvert to a positive PPD test result after the exposure should take preventive therapy regardless of age.
Persons without preexposure PPD results who react positively after the exposure should be treated as converters.
Persons known to be PPD positive before exposure have too slight a risk to warrant preventive therapy.
Persons who are younger than 35 years, have HIV infection, are receiving cancer chemotherapy or long-term corticosteroid therapy, or are otherwise immunocompromised should be considered for preventive therapy, regardless of the exposure.

Modified from Stead WW: Management of health care workers after inadvertent exposure to tuberculosis: A guide for the use of preventive therapy. Ann Intern Med 122:906, 1995.
HIV, human immunodeficiency virus; *PPD,* purified protein derivative.

Tuberculin Skin Testing

Because all ED personnel are potentially exposed to MTB, a skin test program is essential.[9] Skin testing at regular intervals monitors TB transmission among ED personnel and targets staff members who need prophylactic therapy or treatment. Although recommendations for various health care settings depend on the number of TB patients encountered, most ED health care workers should be skin tested every 6 months.[9]

Bacille Calmette-Guérin Vaccine

Although the BCG vaccine has been used since 1921, its overall efficacy, the duration of protective immunity, and the optimal age for administration remain unclear. In the United States, BCG is rarely recommended because of the belief that it may undermine the epidemiologic and diagnostic value of PPD skin testing. However, tuberculin skin tests in patients given previous BCG vaccination usually demonstrate less than 10 mm of induration. Thus, previous BCG vaccination status should be ignored in the interpretation of skin test results.[39]

Institutional outbreaks of TB and the emergence of MDR-TB are sparking reassessment of the BCG issue in the United States. Reports of BCG vaccine efficacy range from 0 to 80%. One meta-analysis reported the efficacy of BCG vaccine to be approximately 50%.[62] Variation in efficacy of the vaccine reported from many studies may be a result of numerous factors. These include differences in strains of BCG associated with the many worldwide production laboratories, study design, and patient age and immunocompetence. A 60-year study in a Native American population showed a 50% reduction in the development of TB in persons receiving BCG vaccine.[63] BCG vaccine is currently recommended in the United States only for tuberculin-negative infants and children who cannot take INH and have ongoing exposure to a persistently untreated or inadequately treated patient with active TB, who are continuously exposed to persons with INH- and RIF-resistant TB, or who belong to groups with rates of new MTB infection exceeding 1% per year.[60] The World Health Organization recommends that all infants in developing countries receive the vaccine.

One decision analysis suggested that BCG vaccination would be more effective than the current annual testing strategy for health care workers.[62] In some European hospitals, health care workers

www.ketabpezeshki.com 66485457-66963820

are required to have received BCG. However, the routine use of BCG vaccine in U.S. heath care workers is still controversial. What is not controversial is that the vaccine is strongly contraindicated in persons with HIV infection or other immunosuppressive disease. New vaccines against MTB are being researched, including those using attenuated strains of the MTB complex, recombinant mycobacteria, and subunit proteins and DNA vaccines.[64]

KEY CONCEPTS

- In the mid-1980s, there was a resurgence of TB cases in the United States. Immigration and the HIV epidemic were important contributing factors. The reemergence of TB has affected both adults and children.
- TB infection starts with primary infection, followed by a latent period in immunocompetent patients. Approximately 10% of infected patients eventually have reactivation of disease.
- Beyond pulmonary manifestations, a variety of extrapulmonary manifestations may occur, including involvement of lymph nodes, pleura, bones or joints, CNS, and genitourinary and gastrointestinal systems.
- TB infection may be more difficult to diagnose in HIV-infected or elderly patients, in whom the clinical presentation often is variable.
- Therapy should be individualized to reflect acuity, sensitivity, system involvement, and underlying conditions. The most commonly used agents are INH, RIF, PZA, and EMB.
- Prevention and screening are fundamental components of any TB control strategy. Patients thought to have active pulmonary TB should be placed in respiratory isolation as soon as possible.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Daniel TM: The history of tuberculosis. *Respir Med* 2006; 100:1862.
2. Das RK: Tuberculosis—historical landmarks. *J Indian Med Assoc* 2000; 98:112.
3. Frieden TR, et al: Tuberculosis. *Lancet* 2003; 362:887.
4. Corbett EL, et al: The growing burden of tuberculosis: Global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003; 163:1009.
5. Centers for Disease Control and Prevention: Trends in tuberculosis incidence—United States, 2006. *MMWR Morb Mortal Wkly Rep* 2007; 56:245.
6. Centers for Disease Control and Prevention: *Reported tuberculosis in the United States, 2002*. Atlanta: U.S. Department of Health and Human Services; 2003.
7. Centers for Disease Control and Prevention: Trends in tuberculosis—United States, 2010. *MMWR Morb Mortal Wkly Rep* 2011; 60:333-337.
8. Lado Lado FL, Tuñez Bastida V, Golpe Gómez AL, Cabarcos Ortiz de Barrón A, Pérez del Molino ML: Tuberculosis in elderly patients. Presentation forms [in Spanish]. *An Med Interna* 2002; 19:111-114.
9. Jensen PA, et al: Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings. *MMWR Recomm Rep* 2005; 54:1.
10. Frampton MW: An outbreak of tuberculosis among hospital personnel caring for a patient with a skin ulcer. *Ann Intern Med* 1992; 117:312.
11. Dannenberg AM Jr: Delayed-type hypersensitivity and cell-mediated immunity in the pathogenesis of tuberculosis. *Immunol Today* 1991; 12:228.
12. Smith I: *Mycobacterium tuberculosis* pathogenesis and molecular determinants of virulence. *Microbiol Rev* 2003; 16:463-496.
13. Long R, Zielinski M, Kunimoto D, Manfreda J: The emergency department is a determinant point of contact of tuberculosis patients prior to diagnosis. *Int J Tuberc Lung Dis* 2002; 6:332-339.
14. de Jong BC, Israelski DM, Corbett L, Small PM: Clinical management of tuberculosis in the context of HIV infection. *Annu Rev Med* 2004; 55:283-301.
15. Geng E, Kreiswirth B, Burzynski J, Schluger NW: Clinical and radiographic correlates of primary and reactivation tuberculosis. *JAMA* 2005; 293:2740-2745.
16. Leung EC, Leung CC, Tam CM: Delayed presentation and treatment of newly diagnosed pulmonary tuberculosis patients in Hong Kong. *Hong Kong Med J* 2007; 13:221-227.
17. Storla DG, Yimer S, Bjune GA: A systematic review of delay in the diagnosis and treatment of tuberculosis. *BMC Public Health* 2008; 8:15.
18. Sokolove PE, Rossman L, Cohen SH: The emergency department presentation of patients with active pulmonary tuberculosis. *Acad Emerg Med* 2000; 7:1056.
19. Rajagopalan S: Tuberculosis and aging: A global health problem. *Clin Infect Dis* 2001; 33:1034.
20. Nsubuga P, et al: Gender and HIV-associated pulmonary tuberculosis: Presentation and outcome at one year after beginning antituberculosis treatment in Uganda. *BMC Pulm Med* 2002; 2:4.
21. Xu C, Hu B: Prevalence of active pulmonary tuberculosis among household contacts of recently diagnosed pulmonary tuberculosis patients with positive sputum-smear. *Zhonghua Liu Xing Bing Xue Za Zhi* 2008; 29:693-695.
22. Faustini A, et al: Treatment outcomes and relapses of pulmonary tuberculosis in Lazio, Italy, 1999-2001: A six-year follow-up study. *Int J Infect Dis* 2008; 12:611.
23. Jean-Baptiste E: Clinical assessment and management of massive hemoptysis. *Crit Care Med* 2000; 28:1642.
24. Reuter H, Burgess LJ, Louw VJ, Doubell AF: The management of tuberculous pericardial effusion: Experience in 233 consecutive patients. *Cardiovasc J S Afr* 2007; 18:20.
25. Trautner BW, Darouiche RO: Tuberculous pericarditis: Optimal diagnosis and management. *Clin Infect Dis* 2001; 33:954.
26. Mandavia DP, et al: Bedside echocardiography by emergency physicians. *Ann Emerg Med* 2001; 38:377.
27. Cohen JN, et al: Presentation, diagnosis and management of tuberculosis in HIV-infected children in the UK. *HIV Med* 2008; 9:277.
28. Day JH, et al: Screening for tuberculosis prior to isoniazid preventive therapy among HIV-infected gold miners in South Africa. *Int J Tuberc Lung Dis* 2006; 10:523.
29. Ors F, et al: High-resolution CT findings in patients with pulmonary tuberculosis: Correlation with the degree of smear positivity. *J Thorac Imaging* 2008; 22:275.
30. Burman WJ, Jones BE: Clinical and radiographic features of HIV-related tuberculosis. *Semin Respir Infect* 2003; 18:263.
31. Drobniewski FA, Caws M, Gibson A, Young D: Modern laboratory diagnosis of tuberculosis. *Lancet Infect Dis* 2003; 3:141-147.
32. Shingadia D, Novelli V: Diagnosis and treatment of tuberculosis in children. *Lancet Infect Dis* 2003; 3:624.
33. Eichbaum Q, Rubin EJ: Tuberculosis. Advances in laboratory diagnosis and drug susceptibility testing. *Am J Clin Pathol* 2002; 118(Suppl):S3.
34. American Thoracic Society; CDC; Infectious Diseases Society of America: Treatment of tuberculosis. *MMWR Recomm Rep* 2003; 52:1.
35. Garcia M, Vargas JA, Castejon R, Durantez A: Flow cytometric assessment of lymphocyte cytokine production in tuberculosis. *Tuberculosis* 2002; 82:37-41.
36. Mazurek GH, et al: Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection—United States, 2010. *MMWR Recomm Rep* 2010; 59:1-25.
37. Centers for Disease Control and Prevention: Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis. *MMWR Morb Mortal Wkly Rep* 2009; 58:7-10.
38. Jasmer RM, Nahid P, Hopewell PC: Latent tuberculosis infection. *N Engl J Med* 2002; 347:1860.
39. Centers for Disease Control and Prevention: Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. *MMWR Recomm Rep* 2000; 49:1.
40. Newman MJ, et al: Culture and sensitivity of mycobacterial isolates from cases of pulmonary tuberculosis classified as treatment failures in a teaching hospital. *West Afr J Med* 2007; 26:131.
41. Marras TK, Daley CL: Epidemiology of human pulmonary infection with nontuberculous mycobacteria. *Clin Chest Med* 2002; 23:553.
42. Eastwood JB, Corbishley CM, Grange JM: Tuberculosis and the kidney. *J Am Soc Nephrol* 2001; 12:1307.
43. De Vuyst D, et al: Imaging features of musculoskeletal tuberculosis. *Eur Radiol* 2003; 13:1809.
44. Lenk S, Schroeder J: Genitourinary tuberculosis. *Curr Opin Urol* 2001; 11:93.
45. Chow TW, Lim BK, Vallipuram S: The masquerades of female pelvic tuberculosis: Case reports and review of literature on clinical presentations and diagnosis. *J Obstet Gynaecol Res* 2002; 28:203.
46. Sutherland AM, Glen ES, MacFarlane JR: Transmission of genito-urinary tuberculosis. *Health Bull (Edinb)* 1982; 40:87.
47. Bernaerts A, et al: Tuberculosis of the central nervous system: Overview of neuroradiological findings. *Eur Radiol* 2003; 13:1876.
48. Sheer TA, Coyle WJ: Gastrointestinal tuberculosis. *Curr Gastroenterol Rep* 2003; 5:273.
49. World Health Organization: *Guidelines for the programmatic management of drug-resistant tuberculosis*, 2006. Available at http://whqlibdoc.who.int/publications/2006/9241546956_eng.pdf. WHO/HTM/TB/2006.361.
50. Burman WJ, Gallicano K, Peloquin C: Therapeutic implications of drug interactions in the treatment of human immunodeficiency virus-related tuberculosis. *Clin Infect Dis* 1999; 28:419.
51. Raviglione MC, Smith IM: XDR tuberculosis: Implications for public health. *N Engl J Med* 2007; 356:656.
52. Centers for Disease Control and Prevention: Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs—worldwide, 2000-2004. *MMWR Morb Mortal Wkly Rep* 2006; 55:301.
53. Centers for Disease Control and Prevention: Extensively drug-resistant tuberculosis—United States, 1993-2006. *MMWR Morb Mortal Wkly Rep* 2007; 56:250.
54. Pillay M, Sturm AW: Evolution of the extensively drug resistant F15/LAM4/KZN strain of *Mycobacterium tuberculosis* in KwaZulu-Natal, South Africa. *Clin Infect Dis* 2007; 45:1409.
55. Singh S, Sankar MM, Gopinath K: High rate of extensively drug resistant tuberculosis in Indian AIDS patients. *AIDS* 2007; 21:2345.
56. Chaisson RE, Martinson, NA: Tuberculosis in Africa—combating an HIV-driven crisis. *N Engl J Med* 2008; 358:1089.
57. Pomerantz BJ, et al: Pulmonary resection for multi-drug resistant tuberculosis. *J Thorac Cardiovasc Surg* 2001; 121:448.
58. Forster AJ, et al: The effect of hospital occupancy on emergency department length of stay and patient disposition. *Acad Emerg Med* 2003; 10:127.
59. Liu S, Hobgood C, Brice JH: Impact of critical bed status on emergency department patient flow and overcrowding. *Acad Emerg Med* 2003; 10:382.
60. Sokolove PE, et al: Implementation of an emergency department triage procedure for the detection and isolation of patients with active pulmonary tuberculosis. *Ann Emerg Med* 2000; 35:327.

www.ketabpezeshki.com 66485457-66963820

61. Lee K, Slavcev A, Nicas M: Respiratory protection against *Mycobacterium tuberculosis:* Quantitative fit test outcomes for five types of N95 filtering facepiece respirators. *J Occup Envir Med* 2004; 1:22-28.
62. Brewer TF: Preventing tuberculosis with bacillus Calmette-Guérin vaccine: A meta-analysis of the literature. *Clin Infect Dis* 2000; 31(Suppl 3):S64-S67.
63. Aronson NE, et al: Long-term efficacy of BCG vaccine in American Indians and Alaska Natives. *JAMA* 2004; 291:2086.
64. Nor NM, Musa M: Approaches towards the development of a vaccine against tuberculosis: Recombinant BCG and DNA vaccine. *Tuberculosis (Edinb)* 2004; 84:102.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 136

Bone and Joint Infections

Neha P. Raukar and Brian J. Zink

PERSPECTIVE

Historically, bone and joint infections have been described in grim terms. *Aids to Surgery,* written in 1919, notes that "acute infective osteomyelitis … is a very fatal disease." With septic arthritis, "the patient becomes exhausted from toxaemia or pyemia," and "ankylosis is the usual most favourable termination."[1] Advances in diagnostic methods, antibiotic therapy, and surgical techniques have resulted in better patient outcomes. In the case of osteomyelitis, treatment with antibiotics and limb salvage protocols is successful in more than 90% of patients with chronic osteomyelitis despite the increase in the number of patients with multiple comorbidities that affect wound healing. However, new challenges are being unveiled. The types of infections that are encountered today are evolving. Host immunity is decreased in many populations, leading to the complexity of the management of bone and joint infections that has never before been encountered. Emergency physicians must consider many subsets of patients who are at increased risk of infection, including injection drug users, patients with acquired immunodeficiency syndrome (AIDS), postsurgical patients, and patients with iatrogenic immune suppression. The emphasis of modern management of bone and joint infections has shifted from prevention of sepsis and death to prompt diagnosis, initiation of treatment, and avoidance of the complications and morbidity associated with chronic bone or joint infections.

The overall occurrence of bone and joint infections appears to have remained constant during the past three decades.[2] The incidence of bone infections in hospitalized patients is approximately 1%. In the United States, the incidence of osteomyelitis in children younger than 13 years is 1 in 5000, whereas the incidence of septic arthritis ranges from 5.5 to 12 per 100,000 individuals.[2] Globally, epidemiologic data for community-acquired bone and joint infections in adults vary significantly, with an overall higher incidence in patients of a lower socioeconomic class in developing countries. However, in the United States, there is no correlation between socioeconomic factors or race and the incidence of bone and joint infections. Both bone and joint infections show a bimodal age distribution, occurring most commonly in people younger than 20 years or older than 50 years. In children, bone and joint infections usually occur in previously healthy individuals, and boys have a slightly increased susceptibility to bone infections.[3] In adults, risk factors can usually be identified in patients who present with either bone or joint infection.

Orthopedic infections can be classified according to the site of involvement and include osseous (osteomyelitis), articular (septic or suppurative arthritis), bursal (septic bursitis), subcutaneous (cellulitis or abscess), muscular (infectious myositis or abscess), and tendinous (infectious tendinitis or tenosynovitis) varieties. The word *osteomyelitis* literally means inflammation of the marrow of the bone, but the term is loosely used to refer to infection in any part of the bone.

Infectious processes can also be categorized by their onset and are generally designated acute, subacute, or chronic. An acute infection is one that lasts less than 2 weeks; a subacute infection is one that lasts 2 to 6 weeks; and chronic infections are those that last longer than 6 weeks. Chronic osteomyelitis is generally defined as a bone infection that fails to respond to a normal course of antibiotic therapy. On histologic examination, chronic osteomyelitis is diagnosed when areas of necrotic bone are identified.

Septic arthritis is defined as an infection of a joint by bacterial or fungal organisms. Bacterial arthritis is sometimes called pyogenic or suppurative arthritis. Reactive arthritis is more common than bacterial arthritis. It is a sterile, secondary inflammation of a joint with no identifiable infecting microorganisms within the synovial fluid. Commonly, reactive arthritis occurs after a systemic infection with a virus,[3] but it can also develop after group A streptococcal infection.

There are many classification systems for osteomyelitis based on the condition of the host, functional impairment caused by the disease, site of involvement, and extent of bone necrosis. For the emergency physician, the most practical way to classify osteomyelitis is as hematogenous osteomyelitis, which is more common, and osteomyelitis secondary to a contiguous focus of infection. Osteomyelitis from a contiguous focus is further subdivided on the basis of the presence or absence of vascular insufficiency. Vascular insufficiency is often secondary to trauma, surgery, or insertion of hardware into the bone, including a prosthetic joint. Recognition of the etiologic mechanism of osteomyelitis assists in the interpretation of diagnostic imaging examinations and helps guide management, including antibiotic therapy and surgical intervention.

Septic arthritis usually results from hematogenous migration of bacteria into the joint, although it can be caused by direct inoculation of bacteria from trauma or joint aspiration or infected foreign material, such as a prosthesis. In some cases septic arthritis may occur concomitantly with osteomyelitis, with infection spreading from bone to joint, and vice versa.

PRINCIPLES OF DISEASE

On the basis of cross-sectional histology, bone tissue can be classified as compact or spongy. Compact bone is dense and without cavities. It forms the shell of most bones and surrounds the trabecular core in the center. It consists of haversian systems, which are made up of concentric rings of osteocytes that synthesize and maintain the bone matrix. The central haversian canals run parallel to the long axis of the bone and contain the blood supply and reticular connective tissue for the haversian system. Spongy bone,

www.ketabpezeshki.com 66485457-66963820

also called cancellous or medullary bone, consists of numerous cavities and is located within the medullary cavity. It consists of extensively connected trabeculae. Spongy bone is more metabolically active.

The gross structure of long bones can be divided into several sections. The diaphysis is the shaft of the bone and contains the compact cortical bone with an overlying periosteum, the medullary canal containing marrow, and a small amount of trabecular bone. The metaphysis is the junctional region between the epiphysis and the diaphysis. The metaphysis contains abundant trabecular bone, but the cortical bone thins here relative to the diaphysis. Finally, the epiphysis is the area at either end of a long bone. The epiphysis is made up of abundant trabecular bone and a thin shell of cortical bone (Fig. 136-1). In general, in the skeletally mature individual, the epiphysis is involved in articulation and is not covered by a periosteum but instead has a thin layer of articulating cartilage.

Joints are enclosed by a synovial capsule, which consists of a dense fibrous connective tissue that offers structural integrity and is lined with synovial cells that secrete synovial fluid. This forms a sleeve around the articulating bones to which it is attached. The ends of the two bones that make up the joint are covered by an articulating cartilage, a very thin layer of secretory cells sitting on a loose fibrous stroma that allows frictionless movement of the bones. In some joints, such as the shoulder, hip, and knee, the synovial membrane extends beyond the epiphysis and attaches to the metaphysis. This anatomic relationship allows bacteria to spread from the metaphysis into the joint.

Osteomyelitis is an infection of the bone and the medullary cavity. Bone is resistant to infection unless it is subjected to trauma, a large inoculum of blood-borne or external microorganisms, or a foreign body. With hematogenous inoculation, the metaphysis is usually the first to be infected because of the slow flow of blood in the sinusoidal blood vessels. Acute inflammatory cells migrate to the area, causing edema, vascular congestion, and small-vessel thrombosis. Acutely, inflammatory fluid spreads into the haversian and vascular channels, raising the intraosseous pressure and compromising blood flow to the bone. Infection may proceed laterally through Volkmann's canals, which are small channels that run perpendicularly to the haversian system, and reach the subperiosteal space. Eventually, blood supply to both the medullary canal and the periosteum is compromised, leading to areas of necrotic bone called sequestra. The presence of necrotic bone is the hallmark of chronic osteomyelitis. Often, the body will try to create new bone around the areas of necrosis. This is called an involucrum. Because there is significantly reduced blood supply to this necrotic bone tissue, bacterial infection is difficult to eradicate with medication alone. Chronic osteomyelitis often requires a combination of surgical débridement and antibiotic therapy.

The variation of the blood flow at the metaphyseal-epiphyseal junction results in the variety of pathologic features of hematogenous osteomyelitis among the different age groups. Also contributing to this are the differences in vascular anatomy as the skeleton ages. In neonates and infants, arterial vessels from the metaphysis perforate the epiphyseal growth plate and terminate in the epiphysis in venous sinusoids. This communication allows osteomyelitis

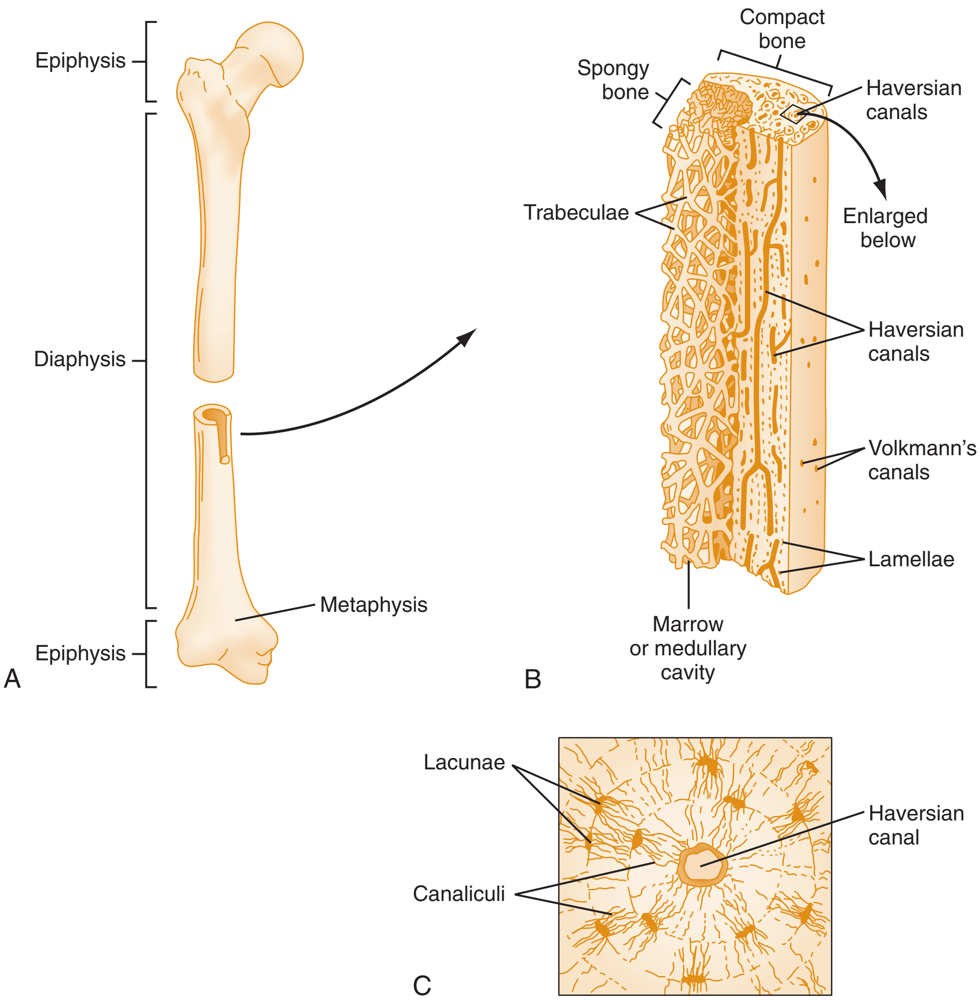


Figure 136-1. Schematic drawing of long bone. **A,** Regions of long bone. **B,** Cross-sectional structure of long bone. **C,** Microscopic structure.

www.ketabpezeshki.com 66485457-66963820

to advance readily from the metaphysis to the epiphysis and adjacent joint space, leading to septic arthritis.

Cortical bone in neonates and infants is thin and loosely attached to the underlying bone. It is composed primarily of woven bone that allows the release of pressure caused by the infection and also permits rapid spread of the infection into the subperiosteum. Because of these structural characteristics of bone in neonates and infants, pressure-related cortical infarction does not usually occur and sequestra are not created. Infection remains trapped in the subperiosteal region and eventually leads to subperiosteal abscess formation. The periosteum is stimulated and vigorous formation of new periosteum occurs, creating an involucrum.

After the first year of life, there is no longer a vascular connection between the metaphysis and epiphysis. The metaphyseal arteries end in loops that abut the growth plate. The epiphyseal growth plate is avascular and inhibits the spread of infection to the epiphysis and joint. Instead of spreading to the joint space, the infection usually spreads laterally through Volkman's canals, breaks through the cortex, and lifts the loose periosteum to form a subperiosteal abscess.[4]

In the adult, after the closure of the epiphyseal plate and resorption of the growth plate, anastomoses form between the metaphyseal and epiphyseal blood vessels, and infection can once again spread from the metaphysis to the epiphysis and eventually into the synovium and joint space. In addition, the periosteum is firmly attached to the underlying bone, limiting subperiosteal abscess formation. Decreased osteoblastic activity in adults limits involucrum formation. However, infection can erode through the periosteum, forming a draining sinus track with more extensive longitudinal diaphyseal spread. Devascularized weakened bone is prone to pathologic fractures. If osteomyelitis proceeds unchecked, ischemic segments of bone may detach from surrounding bone. These separated sections are called sequestra and occur only in advanced or chronic osteomyelitis. The sequestrum can migrate outward from the medullary space through a cortical opening (cloaca) and then to the skin surface through a fistula. Bone infection may also progress into the adjacent soft tissues with abscess formation.

Hematogenous osteomyelitis develops when blood-borne bacteria are deposited in bone. This is most common in prepubertal children and patients older than 65 years. This is also the primary mode of infection in vertebral osteomyelitis. A number of local and humoral factors play a role in determining whether bacteremia progresses to significant skeletal infection. These include the virulence of the infecting organism; the underlying immune status of the host; and the type, location, and vascularity of the bone.

Some sites in the skeletal system are more likely to become colonized by bacteria. Bones containing slow-moving venous systems or venous sinusoids, such as the metaphyses of long bones and the vertebral bodies, have increased susceptibility to hematogenous osteomyelitis. In the metaphysis, a relative lack of phagocytic cells in the venous capillaries and sinusoids may further predispose to infection. In the synovial membrane, the existence of a deep venous plexus that also has sluggish blood flow may invite deposition of bacteria.

Bacteria congregate in a highly structured community, the biofilm, which plays an important role in the pathogenesis of septic arthritis and osteomyelitis.[5] In the biofilm community, bacteria communicate with each other through cell-cell signals and adhere to both inert and living surfaces. Bacterial cells can be released from the biofilm and revert to the individual planktonic state. The biofilm community is more resistant than its planktonic counterparts to the host immune response and antibiotics. First, there is a protective layer on the biofilm, the biofilm matrix, that is difficult to penetrate. Second, the biofilm secretes catalase, which protects the community from hydrogen peroxide, which is used by neutrophils to kill bacteria. Finally, the community is protected by its metabolic variability. Within the biofilm, the bacteria are at varying stages of metabolism; some are active, some are slow growing, and some are dormant. Antibiotics target metabolically active bacteria, such as those in the planktonic state, but bacteria in other stages in the biofilm community may be more resistant to the effects of antibiotics. When bacterial infections form biofilms in bone, in joints, or on artificial implanted devices, fewer free bacteria are available to be aspirated. This helps explain why Gram's stains of aspirated synovial fluid in a suspected septic joint are often negative because Gram's stain will identify only planktonic bacteria. It also helps explain why a definitive diagnosis is made only by a culture of the synovial fluid aspirate or synovial tissue. Biofilm formation is one of the reasons that optimal treatment of a septic joint, especially of prosthetic joints, involves complete surgical débridement.[5]

In joints, the synovium lacks a basement membrane, allowing bacteria to penetrate and to bind to articular cartilage, bone, and even prosthetic devices. Bacteria such as *Staphylococcus aureus,* the most common cause of both hematogenous and contiguous osteomyelitis, have developed mechanisms to increase bone adherence, to increase proteolytic activity, and to increase resistance to host defense mechanisms. In the early stages of osteomyelitis or septic arthritis, *S. aureus* expresses microbial surface proteins called adhesins that help form biofilms by binding to a glycoprotein called fibronectin found in bone and synovium and that can also coat prostheses. Finally, *S. aureus* can surmount host defense mechanisms at both the cellular and matrix levels. For example, *S. aureus* can increase expression of protein A. This interferes with the opsonization and phagocytosis of *S. aureus,* leading to an increase in virulence.

Biomaterials, including the metal and plastic components of prosthetic joints, acrylic bone cement, devascularized bone graft, and synthetic bone substitutes, cause local immune impairment and allow nonpathogenic skin flora, such as coagulase-negative staphylococci, to become significant pathogens. Proteolytic enzymes that are present in noninfected joints are normally inhibited; however, this inhibition is lost in the face of infection, enabling the invading bacteria to persist.

The humoral immune response to bone or joint infection is usually well developed by the time that the infection is clinically apparent. B lymphocytes sense bacterial antigens and release antibodies, and antigen-antibody complex is formed at the site of infection. Through the complement cascade, bacteria are destroyed by neutrophils or macrophages. As with other infections, bacterial toxins may be destroyed directly by bound antibody.

Tissue injury in bone and joint infections can occur by several different mechanisms. Direct tissue destruction by invasive bacteria is the initial insult. After this, the inflammatory response can produce microabscesses and edema in infected tissues and subsequent vascular occlusion and ischemic necrosis. This is especially damaging to the venous capillaries of the metaphysis, where no collateral blood vessels exist to compensate for ischemic injury. If immune complexes become embedded in the bone or cartilage matrix, a prolonged inflammatory response can occur even after the primary infection has been cleared. This prolonged inflammation is particularly a problem in joints. This results in rapid destruction of articular cartilage. A final type of tissue injury caused by infection is abnormal synthesis of bone or joint matrix and cells. Abnormally synthesized bone or cartilage may be structurally unsound and function poorly.

Hematogenous spread of bacteria causes almost all cases of osteomyelitis in children and in the subset of adults who have vertebral osteomyelitis. In children, hematogenous osteomyelitis usually starts in the medullary portion of long bones and progresses outward to involve the surrounding structures. However, in the appendicular skeleton of adults, osteomyelitis occurs more

www.ketabpezeshki.com 66485457-66963820

commonly by either spread of the pathogens from a contiguous source of infection or direct implantation. The direction of contamination for contiguous focus osteomyelitis is from the soft tissues inward into the bone, by dissemination through the haversian and Volkmann's canals and toward the bone marrow. The most common sites of contiguous focus osteomyelitis are in the foot and hand. Other common sites affected by this mechanism are the skull, maxilla, and mandible. Head and neck osteomyelitis is usually caused by sinus disease and odontogenic infections.

Infections from direct implantation of bacteria are caused by deep puncture wounds and tend to occur in the hands and feet. Human and animal bites are another cause of infections that can result in osteomyelitis and septic arthritis. Although cats account for only 10% of animal bites, significant infection results from 20 to 50% of cat bites versus only 5% of dog bites because of the morphology of feline teeth. Most human bite injuries are related to fistfights and contamination of the metacarpophalangeal joints and metacarpals, with infection due to oral flora. Direct implantation of pathogens is also common with open fractures and can also occur during surgical instrumentation. Artificial joints and other implanted surgical materials can serve as sites for colonization of bacteria and formation of biofilms.[6]

Septic arthritis is usually a consequence of hematogenous spread unless there is direct injection of bacteria into the joint. The lack of a basement membrane makes the highly vascular synovium vulnerable to bacterial seeding. Infection occurs first in the synovium, spreads into joint fluid, and finally affects the articular cartilage. Bacterial enzymes and toxins directly damage cartilage. The synovial membrane responds to infection by increasing synovial fluid production, resulting in a large joint effusion. Septic arthritis is a closed space infection; increasing pressure in the joint contributes to a decreased rate of exchange of solutes across the synovial lining and synovial blood flow can be reduced by the increased pressure, resulting in ischemic damage to cartilage. Even a small bacterial load in the joint space elicits a profound and persistent inflammatory and immune response. Bacteria can be cleared from the joint, resulting in a sterile-appearing inflammatory response. In animal models, the injection of isolated bacterial DNA into joints can produce a marked inflammatory arthritis.[7]

In response to infection, synovial cells and polymorphonuclear leukocytes release lysosomal enzymes into joint fluid. These enzymes contain collagenase and elastase, both of which can degrade cartilage. Cytokines also seem to play a key role in the release of metalloproteinases and other harmful enzymes. The most pathologic aspect of septic arthritis is the destruction of articular cartilage, which creates a painful joint with limited motion. Once it is destroyed, hyaline (articular) cartilage is not replaced. Other structures that are enclosed within or adjacent to the synovium, such as bursae, tendons, and bone, may become damaged in septic arthritis.[7]

ETIOLOGY AND MICROBIOLOGY OF BONE AND JOINT INFECTIONS

The pathogenic organisms in osteomyelitis are numerous, and Gram-positive organisms are responsible for most types of osteomyelitis. Even though Gram-negative organisms account for 43% of cases of community-acquired bacteremia, they result in only about 10% of septic arthritis cases. Trauma predisposes patients to osteomyelitis by environmental pathogens. Patients who are wounded or sustain open fractures in fresh water are susceptible to infections with the Gram-negative bacillus *Aeromonas hydrophila.* People who are bitten by animals, particularly dogs and cats, are at risk for development of osteomyelitis from *Pasteurella multocida.*[6] Osteomyelitis caused from human bites is most common in the hand and involves human oral flora, such as *Streptococcus anginosus, Fusobacterium nucleatum,* and *Eikenella* species. In the population of injection drug users, *S. aureus* is the most likely cause of infection, followed by *Pseudomonas* species. *Pseudomonas aeruginosa* is also an important cause of osteomyelitis in puncture wounds, in postsurgical wounds, and in patients with sickle cell anemia.

Certain underlying disease states predispose a patient to acquire bone and joint infections. These conditions include diabetes mellitus, sickle cell disease, AIDS, alcoholism and injection drug use, chronic corticosteroid use, preexisting joint disease (especially rheumatoid arthritis), and other immunosuppressed states. Another subset of patients who are susceptible to bone and joint infections are postsurgical patients, especially those who have implanted prosthetic devices (Table 136-1).

Although most bone and joint infections are bacterial, viruses, fungi, and parasites may be the responsible pathogens. The microbiology of osteomyelitis and septic arthritis is a function of several host and environmental factors. As has been described, age is an important variable in determining the type of bacteria that cause bone and joint infections. A patient's living environment also has some role in determining the incidence of bone and joint infections. For example, people living in crowded conditions where tuberculosis is prevalent are at increased risk for tubercular bone and joint infections. Elder patients in hospitals and institutions may be more susceptible to infections with Gram-negative bacteria. A summary of the organisms that cause osteomyelitis and septic arthritis is given in Table 136-2. The following points deserve special mention:

- In all age groups except neonates, *S. aureus* is the leading cause of osteomyelitis. It also accounts for more cases of septic arthritis than any other bacterium. In neonates, group B

Table 136-1 Microbiology of Bacterial Septic Arthritis as Related to Age of the Patient

ORGANISM	CHILD*	YOUNG ADULT ENGAGING IN HIGH-RISK SEXUAL BEHAVIOR	ADULT	ELDERLY ADULT
Staphylococcus aureus	10-20%	15-20%	60-70%	45-65%
Streptococcus species	5-10%	1-5%	15-20%	10-15%
Gram-negative bacterium	1-5%	Rare	10-15%	15-35%
Haemophilus influenza	Rare†	Rare†	Rare†	Rare†
Neisseria gonorrhoeae	1-5%	60-80%	1-5%	Rare

Reprinted with permission from Esterhai JL Jr, Rao N: The epidemiology of musculoskeletal infections. In Cierny G 3rd, McLaren AC, Wongworawat MD (eds): Orthopaedic Knowledge Update: Musculoskeletal Infection. Rosemont, Ill, American Academy of Orthopaedic Surgeons, 2009, 8. Modified from Liu NY, Giansiracusa DF: Septic arthritis. In Gorbach SL, Bartlett JG, Blacklow NR (eds): Infectious Diseases, ed 2. Philadelphia, WB Saunders, 1998, 1345.

*Ages 6 months to 5 years.

†With widespread immunization.

www.ketabpezeshki.com 66485457-66963820

Table 136-2 Microbiology and Initial (Empirical) Antibiotic Treatment of Bone and Joint Infection

	OSTEOMYELITIS		SEPTIC ARTHRITIS	
AGE GROUP	**Common Organisms**	**Antibiotic Regimen**	**Common Organisms**	**Antibiotic Regimen**
Neonate to <3 months	*Staphylococcus aureus* Group B streptococcus Enterobacteriaceae Gram-negative rods	Ceph 3 PRP + gentamicin Consider vancomycin instead of PRP for MRSA	*Staphylococcus aureus* Group B streptococcus Enterobacteriaceae	PRP + Ceph 3 Alt: PRP + APAG Consider vancomycin instead of PRP for MRSA
3 months to 14 years	*Staphylococcus aureus* Group A streptococcus *Haemophilus influenzae*	PRP + Ceph 3 Alt: vancomycin + Ceph 3, chloramphenicol PRP or Ceph 3 with allergy to penicillin or clindamycin with allergy to penicillin + Ceph 3	*Staphylococcus aureus* Group A streptococcus *Streptococcus pneumoniae* *Haemophilus influenzae*	PRP + Ceph 3 Alt: vancomycin + Ceph 3
14 years to adult	*Staphylococcus aureus*	PRP Alt: vancomycin	*Staphylococcus aureus* Streptococcal sp. Enterobacteriaceae	PRP or Ceph 3 Alt: vancomycin + Ceph 3 or penicillin + aminoglycoside or Ceph 3
Infection Subsets				
Sexually active adolescents or adults with acute arthritis			*Neisseria gonorrhoeae**	Ceph 3 Alt: spectinomycin or penicillin if sensitive
Chronic osteomyelitis and diabetic foot infections	*Staphylococcus aureus* Enterobacteriaceae Anaerobic bacteria	PRP + FLQ + metronidazole Alt: PRP + Ceph 3 + clindamycin		
Infected orthopedic joint prosthesis	*Staphylococcus aureus* *Staphylococcus epidermidis* *Pseudomonas aeruginosa*	Vancomycin + FLQ Alt: imipenem	*Staphylococcus aureus* *Staphylococcus epidermidis* *Pseudomonas aeruginosa*	Vancomycin + FLQ Alt: PRP + APAG
Sickle cell disease	*Staphylococcus aureus* *Salmonella* sp.	PRP + Ceph 3 Alt: FLQ	*Staphylococcus aureus* *Salmonella* sp.	PRP + Ceph 3 Alt: FLQ
Injection drug abuse	*Staphylococcus aureus* *Pseudomonas aeruginosa* Enterobacteriaceae	Ceph 3 + aminoglycoside Alt: Ceph 3	*Pseudomonas aeruginosa* *Staphylococcus aureus* Enterobacteriaceae	PRP + APAG or FLQ Alt: vancomycin + FLQ
Plantar puncture wound	*Pseudomonas aeruginosa*	AP Ceph Alt: FLQ	*Pseudomonas aeruginosa*	AP Ceph Alt: FLQ
Human or animal bites	*Eikenella corrodens* *Pasteurella multocida*	Penicillin ± AC Alt: Ceph 3, TS	*Eikenella corrodens* *Pasteurella multocida*	Penicillin ± AC Alt: Ceph 3, TS

*Concurrent treatment of *Chlamydia trachomatis* infection should be given to patients with suspected *N. gonorrhoeae* septic arthritis.
Alt, alternative antibiotics; *APAG,* antipseudomonal aminoglycoside; *AP Ceph,* antipseudomonal cephalosporin (ceftazidime or cefepime); *Ceph 3,* third-generation cephalosporin (e.g., ceftriaxone, cefotaxime, cefamandole, ceftizoxime, ceftazidime, cefazolin, moxalactam); *FLQ,* fluoroquinolone; *MRSA,* methicillin-resistant *S. aureus*; *PRP,* penicillinase-resistant penicillin (oxacillin, nafcillin, methicillin, amoxicillin-clavulanate [*AC*]); *TS,* trimethoprim-sulfamethoxazole.

streptococci, *Escherichia coli* and other Gram-negative coliforms, and *Staphylococcus epidermidis* are the most common pathogens responsible for bone and joint infections.[8]

- Since the introduction of the vaccine, *Haemophilus influenzae* type b, once a common cause of septic arthritis and osteomyelitis in children younger than 2 years, has essentially disappeared as a pathogen among vaccinated children.[9] Another Gram-negative coccobacillus within the Neisseriaceae family, *Kingella kingae,* in being encountered with increasing frequency. *K. kingae* can be part of the normal flora of the nasopharynx; like *H. influenzae,* it can be spread hematogenously to bones and joints. It is a fastidious organism and may be mistaken for *Haemophilus* or *Neisseria* species.
- *P. aeruginosa* has been reported as a cause of cervical spine osteomyelitis in injection drug users and lumbar spine osteomyelitis in patients with urinary catheters in place for long times. *Pseudomonas* colonizes the rubber and plastic inserts in footwear and is therefore seen in soft tissue infections and osteomyelitis of the foot after a puncture wound.
- In elders and in patients with diabetes, Gram-negative bacteria account for a higher percentage of cases of bone and joint infections.
- Methicillin-resistant *S. aureus* (MRSA), methicillin-resistant *S. epidermidis,* and vancomycin-resistant enterococci have emerged as a significant microbiologic problem in the past decade. Multiresistant enterococci pose the greatest potential danger in that no currently available antibiotic regimen is reliably bactericidal against such organisms.

A typical case of hematogenous osteomyelitis or septic arthritis is caused by a single strain of bacterium, although polymicrobial infection occurs 36 to 50% of the time and is more likely to occur in diabetic foot osteomyelitis, post-traumatic osteomyelitis, and chronic septic arthritis or osteomyelitis. Anaerobic bacteria can complicate polymicrobial infection and may be present in bone and joint infections more often than is commonly recognized because standard culture techniques may be inadequate for isolation of anaerobic bacteria.[10] This is especially important in chronic

www.ketabpezeshki.com 66485457-66963820

osteomyelitis, in which anaerobic bacteria may be present in up to 40% of cases.

Mycobacterium tuberculosis may infect bones and joints, most commonly in the axial skeleton. The two most common forms of skeletal infection are vertebral osteomyelitis (Pott's disease) and tubercular arthritis. The spine is affected in half of cases of tubercular skeletal infection. The arthritis of tuberculosis is a chronic, low-grade inflammatory process that resembles rheumatoid arthritis more than acute septic arthritis.[11]

The prevalence of fungal bone and joint infections is increasing because of the rise in the number of patients with risk factors. Host factors that predispose to fungal infections include immobility, mucositis, use of antibiotics, radiation therapy, immunosuppressive agents, admission to an intensive care unit, malnutrition, and hematopoietic stem cell transplantation.[12] Fungal infection is also a complication of catheter-related fungemia, the use of injection drugs contaminated by *Candida* species, and prolonged neutropenia. *Candida* osteomyelitis occurs through hematogenous spread or as a postoperative wound infection. Fungal bone infection is indolent and may go through periods of activity and remission.[12] *Aspergillus* has been reported to cause osteomyelitis in vertebrae, hip prostheses, and ribs. In adults, the infection is hematogenous. In children, *Aspergillus* osteomyelitis is most common in those with prior granulomatous disease and spreads from a primary pulmonary infection. *Blastomyces* and *Cryptococcus* are two other fungi that may become disseminated and infect the skeleton. Treatment of these infections is difficult, especially because of emerging pathogens that are resistant to common antifungal agents, and therapy needs to be individualized against the specific organism.

Patients with human immunodeficiency virus (HIV) infection and AIDS are predisposed to a variety of common and opportunistic pathogens. Although *S. aureus* is still the most likely cause of bone and joint infections in patients with AIDS, fungal and other atypical organisms should be considered. One unusual but particularly characteristic form of osteomyelitis in HIV-positive patients is bacillary angiomatosis. This infection is caused by a Gram-negative rickettsia-like organism that frequently causes osteolytic bone lesions.

OSTEOMYELITIS

Clinical Features

History and Physical Examination

The symptoms and signs of osteomyelitis in adults are predictable, although not always present. Patients with osteomyelitis often present with fever and rigors and may appear toxic. Fever appears to be present more commonly in children. Systemic complaints of headache, fatigue, malaise, and anorexia are often reported.[13] However, these findings are inconsistently present and are less likely with chronic osteomyelitis. In children with lower extremity osteomyelitis, a sudden limp or inability to bear weight, localized warmth, swelling, and erythema may be reported. A careful review of the patient's past medical history is especially important to identify risk factors that may predispose to bone infection.

The physical examination findings of osteomyelitis are fairly specific. The predominant symptom of osteomyelitis is pain over the affected bone. Palpation of the involved bone usually elicits point tenderness over the infected segment. Palpable warmth and soft tissue swelling with erythema may be present, but these findings are variable. In chronic advanced osteomyelitis, the involucrum or sequestrum may be palpated, and sinus tracks that drain through the skin may be noted. Because osteomyelitis has a propensity to occur in the metaphyses of long bones, it is often difficult to distinguish infection in bone from infection in the neighboring joint. A "sympathetic" effusion in the adjacent joint may develop in some patients with osteomyelitis even when the joint is not infected.

Diagnostic Strategies

Laboratory Data and Diagnostic Imaging

Imaging remains the cornerstone of the initial evaluation process, but bone biopsy and culture are the "gold standard" and definitive tests to confirm the diagnosis and to guide treatment of osteomyelitis.

Laboratory data are not specific and can only suggest the diagnosis of osteomyelitis. In acute osteomyelitis, the white blood cell (WBC) count is often although not always elevated; typical values range from normal to 15,000/mm^3. The WBC count is often normal in chronic osteomyelitis. The erythrocyte sedimentation rate (ESR), a nonspecific measure of inflammation, is more helpful than the WBC count. The ESR represents the rate at which red blood cells fall when anticoagulated blood is placed in an upright tube. When an inflammatory process is present, the high proportion of fibrinogen in the blood causes the red blood cells to form stacks, called rouleaux, which settle faster. This is a sensitive marker for bone infection, and many series report elevated ESRs in patients who have confirmed osteomyelitis. In children, an elevated ESR or C-reactive protein (CRP) level is seen in all cases of osteoarticular infection, and the sensitivity of use of both the ESR and the CRP value is 98%.[14] In the evaluation of a diabetic foot infection, an ESR greater than 70 mm/hr predicts the presence of an underlying bone infection.[15] An elevated ESR in the presence of appropriate physical findings should lead one to suspect osteomyelitis, but a normal or slightly elevated ESR does not eliminate the diagnosis. Other inflammatory conditions, such as cellulitis, can cause an elevated ESR, although the degree of elevation of the ESR is often higher with osteomyelitis.

CRP, another nonspecific marker of inflammation produced by the liver and by adipocytes in response to interleukin-6, also plays a role in the evaluation of patients with bone infections. The CRP value increases within the first 24 hours of infection, peaks within approximately 48 hours, and is usually normal within 1 week of therapy. In children presenting with osteomyelitis, it has been shown that the ESR is elevated in 92%, the CRP level is elevated in 98%, and the WBC count is elevated in 35%.

The ESR and CRP blood tests have a high positive predictive value, and elevated values should increase suspicion for this diagnosis. However, normal values of these nonspecific inflammatory markers cannot be used to rule out the diagnosis of osteomyelitis. The CRP may be a better early indicator of disease, but the ESR is most valuable in following response to treatment.[16] Typically, the ESR falls steadily as osteomyelitis resolves and increases should it recur.

Because conventional radiography is readily available, relatively inexpensive, and useful in differentiation of infection from trauma and tumors, it remains the initial imaging test of choice for suspected osteomyelitis. In addition, plain radiography is often a helpful adjunct to secondary imaging studies. Unfortunately, radiographic evidence of osteomyelitis lags behind the clinical picture, and less than one third of patients have abnormalities on plain radiographs in the first 7 to 10 days after the onset of symptoms. The characteristic early findings on the plain radiograph in osteomyelitis are lucent lytic areas of cortical bone destruction (Fig. 136-2). However, lucency is not detected on radiographs until approximately 50% of bone mineral is lost, and this often takes up to 2 weeks from the onset of infection. Although these findings are often difficult to identify on plain radiographs, soft tissue edema, deep soft tissue swelling, distorted fascial planes, and altered fat interfaces may be present within 3 to 5 days from the

www.ketabpezeshki.com 66485457-66963820

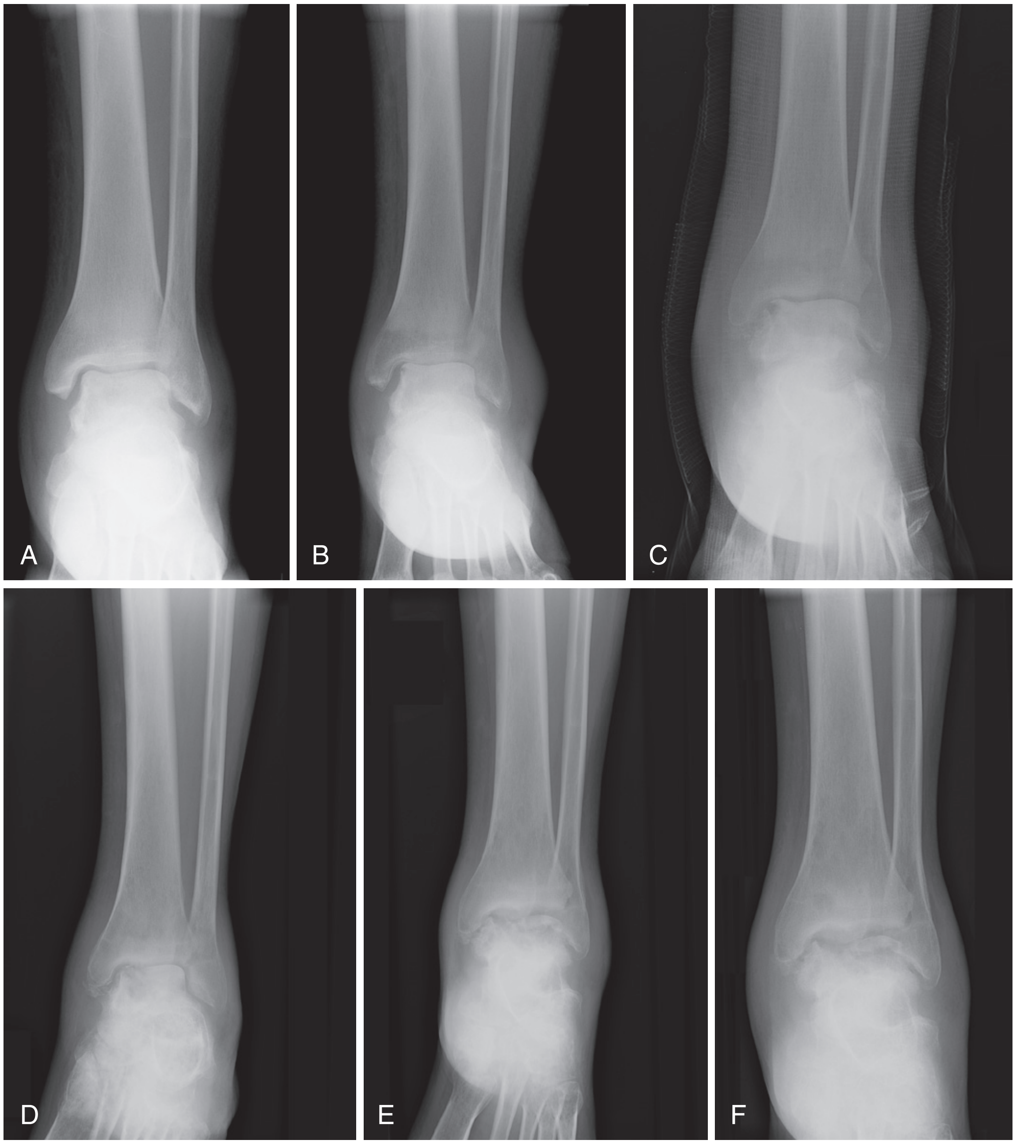


Figure 136-2. Radiographic progression of acute osteomyelitis. **A,** Soft tissue swelling at both the medial and lateral aspects of the ankle with a moderately sized effusion (August 2, 2006). **B,** Large ankle effusion with extensive soft tissue swelling. There is complete loss of the tibiotalar joint space as well as widening of the medial joint space, suggesting chondrolysis. There are lucent areas in the distal tibia and fibula, suggestive of hyperemia, and the talus is diffusely sclerotic (September 11, 2006). **C,** Increased erosion of the medial aspect of the talar dome with increased joint effusion (October 12, 2006). **D,** Talar bone destruction with demineralization involving all of the osseous structures. There is also a small joint effusion (January 2, 2007). **E,** Avascular necrosis of the talus as well as destruction of the articular surfaces of the tibia and talus is present, consistent with chronic osteomyelitis. There is diffuse osteopenia as well as loose bodies within the joint (April 19, 2007). **F,** There is continued irregularity of the articular surface of the tibia as well as collapse of the talus. Loose bodies are still present within the joint, and there is a persistent joint effusion and soft tissue swelling (June 14, 2007). (Courtesy Thomas Egglin, MD, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University.)

onset of infection and can serve as a clue to osteomyelitis in the underlying bone. Periosteal reaction is another early sign. It may appear on radiographs as hypertrophy or elevation of the periosteum creating an involucrum (Fig. 136-3). Because of the thinner periosteum, these early periosteal changes are seen in radiographs in children more commonly than in adults. In advanced disease, the lytic lesions are surrounded by dense, sclerotic bone, and sequestra may be noted. By 28 days from the onset of osteomyelitis, 90% of the plain radiographs are abnormal.[17]

Radionuclide skeletal scintigraphy (bone scanning) is more sensitive than plain radiography in the early diagnosis of osteomyelitis and is especially useful in the presence of prosthetics or other hardware. Radionuclide scans can detect osteomyelitis within 48 to 72 hours after the onset of infection. A radioactive tracer is injected into the bloodstream and given time to bind or to accumulate in body tissues, after which a camera is used to sense released radioactivity. An image is created that is evaluated for increase or decrease in expected uptake of the radionuclide. In the past decade there has been a movement away from skeletal scintigraphy in diagnosis of osteomyelitis. There is a significant radiation burden associated with scintigraphy, and recent recommendations are that children thought to have acute osteomyelitis should have magnetic resonance imaging (MRI) rather than a bone scan.[18]

Computed tomography (CT) may be useful in the diagnosis of osteomyelitis. The bony cortex is particularly well seen on CT, and involucrum and sequestrum formation is easily identified. Non-long bones like the sternum, vertebrae, pelvic bones, and calcaneus are far better imaged with a CT scan than with plain radiographs. CT is most commonly used to detect and to define areas of

www.ketabpezeshki.com 66485457-66963820

Figure 136-3. This right hemipelvis and proximal femur demonstrate permeative moth-eaten changes with resultant femoroacetabular joint space narrowing consistent with osteomyelitis. (Courtesy Peter Evangelista, MD, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University.)

Figure 136-4. Computed tomography scan of osteomyelitis. Diffuse, moth-eaten appearance involving the right hemipelvis as well as the right femoral head with abundant periosteal reaction. (Courtesy Peter Evangelista, MD, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University.)

possible infection in bones with complex anatomy that is difficult to visualize on plain radiographs and bone scans. Osteomyelitis appears as rarefaction, or lucent areas, on the CT scan images (Fig. 136-4). Gas may be seen in bony abscess cavities. The limitation of CT for early diagnosis of osteomyelitis is the same as that for plain radiography in that the disease must be present for more than a week for changes to be apparent. An important role of a CT scan in osteomyelitis is to help localize bone lesions that have been found with other imaging modalities. The CT scan can guide the surgeon in débridement and resection of infected bone and in choosing a site for diagnostic biopsy.[17]

The use of bone scans and CT for detection of osteomyelitis in the emergency department (ED) is decreasing as the availability and image quality of MRI improves while its cost decreases. The anatomic resolution of MRI is far superior to that of bone scans and plain radiographs. MRI findings are often evident before an abnormality is detected by skeletal scintigraphy, plain radiography, or CT because of the earlier detection of bone marrow involvement. MRI can reveal edema and the destruction of the medulla as well as any periosteal reaction, cortical destruction, articular damage, and soft tissue involvement, even when conventional radiographs are still normal. Whereas the presence of ferromagnetic material is a contraindication to MRI, most materials used in orthopedic surgery, such as titanium and chrome cobalt, do not interfere with this imaging modality. One drawback to MRI is the presence of metal in bone, especially prosthetic joints. Metal may cause distortion of the signal in the area adjacent to a joint prosthesis, but this does not exclude MRI in this group of patients.[17] MRI uses a combination of spin echo T1-weighted and T2-weighted images, short tau inversion recovery (STIR) images, and fat-suppressed T2-weighted images. Osteomyelitis produces a diminished intensity of the normal marrow signal on T1-weighted images and a normal or increased signal on T2-weighted images[18] (Fig. 136-5).

Administration of gadolinium as a contrast agent enhances the interface between normal and abnormal marrow and helps distinguish devitalized from normally perfused bone. Gadolinium becomes localized in areas of increased vascularity and blood flow and also helps distinguish soft tissue infections such as abscesses and cellulitis from osteomyelitis. Whereas contrast agents increase reader confidence in the diagnosis of osteomyelitis, they do not increase the sensitivity or specificity of the diagnosis of osteomyelitis.[17] Soft tissue swelling and edema are best detected with fat-suppressed images, in which the resolution is much greater with MRI than with plain radiographs or CT scan. MRI also allows better visualization of subtle bone cortical changes, periosteal reaction, soft tissue edema, abscesses, and sinus tracks.

When it is done with STIR images, MRI has a 100% negative predictive value, and osteomyelitis can be essentially excluded in the presence of a normal MRI study.[17] STIR images have a very low signal from fat, like fat-suppressed images, but still obtain a strong signal from water. The sensitivity of MRI is reported to be between 88 and 100%, with a specificity of 75 to 100%.[17] MRI with gadolinium contrast enhancement has been demonstrated to have higher sensitivity and specificity than radionuclide bone scans in the diagnosis of vertebral osteomyelitis[17,19,20] (Fig. 136-6).

The differential diagnoses for the magnetic resonance findings in acute osteomyelitis are trauma, noninfectious inflammatory and metabolic lesions, histiocytosis, tumors, and cancer. In cases in which a surgical procedure will be done to obtain a microbiologic diagnosis or is needed to treat osteomyelitis, MRI has obvious advantages over a radionuclide bone scan in detailing the anatomy for the surgeon.

Microbiologic Diagnosis

The most direct and often the most effective way to definitively diagnose osteomyelitis is to obtain infected bone by needle aspiration or surgical resection. Culture specimens from this bone will help guide antimicrobial therapy. Culture of draining fistulas or sinus tracks is not an acceptable substitute because the organisms cultured from these sites are often different from those in the underlying infected bone. Because osteomyelitis may be polymicrobial or due to unusual microorganisms, especially in immunocompromised patients, cultures for fungal and anaerobic organisms should be performed.

Particularly in cases of hematogenous osteomyelitis, cultures of blood, urine, cerebrospinal fluid, and pus from other sites of infection can help uncover the infecting bacteria. Blood cultures in patients with acute untreated osteomyelitis are positive for the offending bacteria approximately 50% of the time.[21] In children with hematogenous osteomyelitis, it is not unusual to identify the

www.ketabpezeshki.com 66485457-66963820

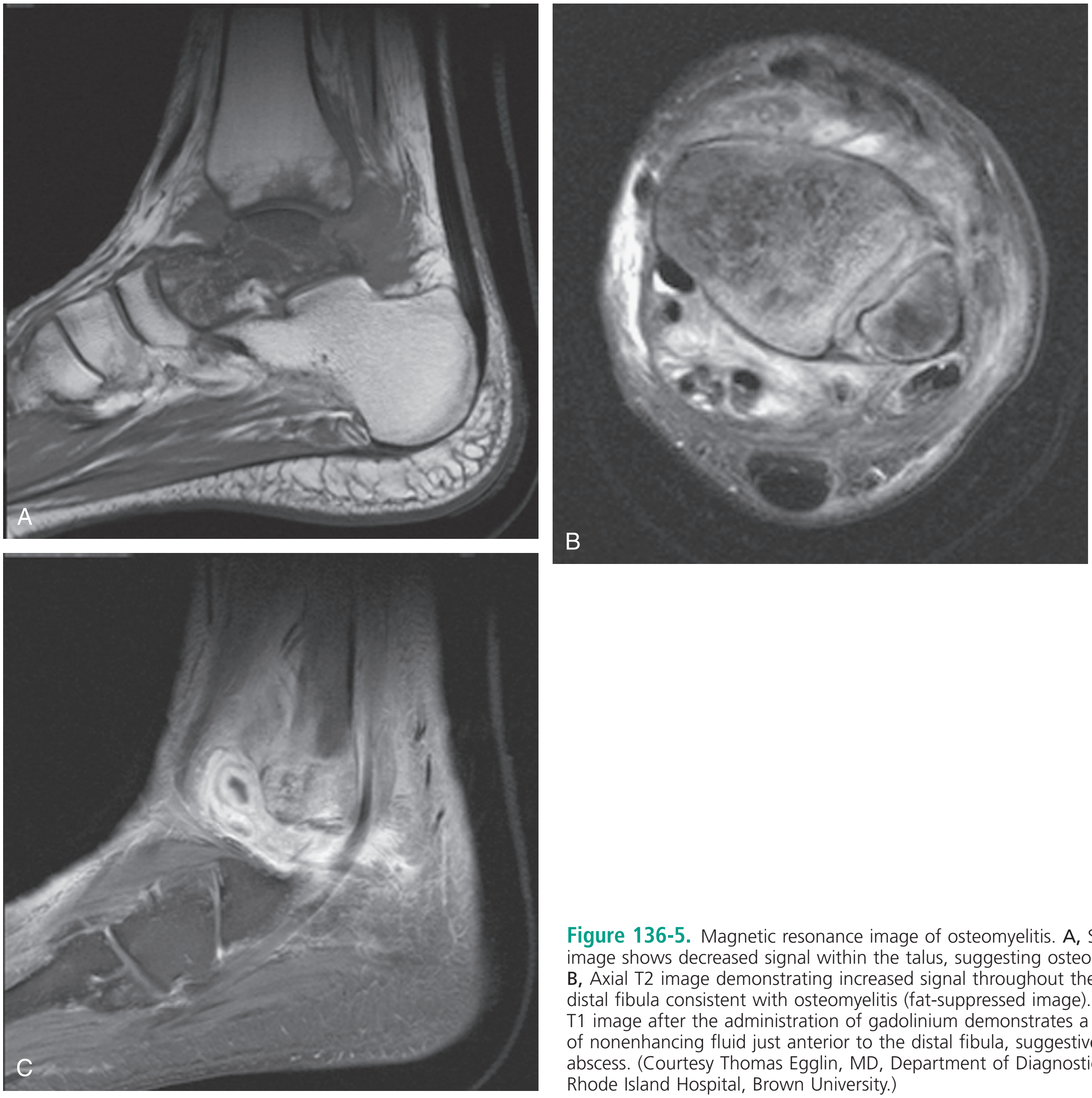


Figure 136-5. Magnetic resonance image of osteomyelitis. **A,** Sagittal T1 image shows decreased signal within the talus, suggesting osteomyelitis. **B,** Axial T2 image demonstrating increased signal throughout the talus and distal fibula consistent with osteomyelitis (fat-suppressed image). **C,** Sagittal T1 image after the administration of gadolinium demonstrates a small focus of nonenhancing fluid just anterior to the distal fibula, suggestive of an abscess. (Courtesy Thomas Egglin, MD, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University.)

infecting organism in other body fluid cultures in addition to blood cultures. In chronic osteomyelitis, blood cultures are almost always negative.[18]

The likelihood of establishing a bacteriologic diagnosis in acute osteomyelitis is 80 to 90%, but in some cases even culture of resected bone yields no organism. Possible reasons for this are poor culture techniques and inadequate preparation of recovered tissue for culture, previous antibiotic treatment, and culture specimens from necrotic ischemic regions that may be devoid of bacteria.[18]

The emergency physician's diagnostic approach in suspected osteomyelitis has become simpler since MRI has largely replaced the use of radionuclide scintigraphy. The algorithm in Figure 136-7 provides a simplified approach to the diagnostic strategy in a patient with suspected osteomyelitis. A few key points should be considered with use of this algorithm:

- Radiographs lag behind the clinical picture.
- When the clinical suspicion for a diagnosis of osteomyelitis is low and the initial bone scan or MRI study is normal, it is extremely unlikely that the patient has osteomyelitis.
- In infants and children, the amount of radiation exposure with imaging techniques must be considered.[18]
- In easily accessible bones, aspiration of the bone is a low-risk procedure that will often help establish a microbiologic diagnosis.
- If the clinical presentation strongly suggests osteomyelitis, a lengthy diagnostic workup should not delay empirical treatment. Culture specimens of blood, urine, and other appropriate sites should be obtained and antibiotic treatment started.[17]
- The cost of imaging tests for osteomyelitis must be considered in deciding how to pursue the diagnosis. Expense must be weighed against the benefit of early diagnosis of osteomyelitis and the prevention of chronic osteomyelitis and the numerous surgeries and increased length of treatment associated with this diagnosis.

Clinical Subsets of Osteomyelitis

Acute hematogenous osteomyelitis (AHO) is the most common form of osteomyelitis, but it has different presentations, diagnosis,

www.ketabpezeshki.com 66485457-66963820

Figure 136-6. Magnetic resonance image of osteomyelitis. **A,** There is diffuse abnormal decreased T1 signal increase. **B,** Increased STIR signal through the T12 and L1 vertebral bodies with loss of the normal disk space and enhancement of these vertebral bodies consistent with osteomyelitis and diskitis. (Courtesy Peter Evangelista, MD, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University.)

and treatment in adults compared with children. The other main type of osteomyelitis, arising from a contiguous focus of infection, has special diagnostic and management features.

Osteomyelitis in Children

Osteomyelitis in children tends to be acute, almost always arises from hematogenous seeding of bone, and can often be treated with antibiotics alone. AHO is seen in children as young as 3 months and as old as 16 years. Bacteremia is the presumed cause of bone infection. *S. aureus* is the most common infecting organism in children of all ages except neonates (see Tables 136-1 and 136-2). As noted before, *H. influenzae* is no longer a common cause of AHO.[18]

AHO has a well-established male preponderance (male-to-female ratio of 2 to 3 : 1) and involves long bones approximately 80% of the time. The site of infection is usually the distal metaphysis because of its increased vascularity, but up to 30% of AHO occurs in other parts of the bone. Children with AHO may have fever, chills, vomiting, dehydration, and malaise; but they usually do not appear toxic. Most children have characteristic pain and limited use of the limb and are point tender. The diagnostic evaluation for AHO is listed in Figure 136-7. Blood cultures are positive for the bacterial cause of osteomyelitis in 60% of patients with AHO. A positive blood culture and a physical examination consistent with osteomyelitis may be sufficient for a diagnosis of AHO to be made. Figures 136-2 and 136-4 show a typical radiographs of AHO.[18]

Neonatal osteomyelitis is difficult to diagnose because of minimal systemic findings. Osteomyelitis in the neonate is more commonly seen after abnormal pregnancies or deliveries and often accompanies other acute illnesses. Multiple sites of bone involvement are found in approximately half the reported cases. Because of the unique vascular anatomy of the neonate, septic arthritis often accompanies osteomyelitis. Osteomyelitis of the flat bones, such as the facial bones, is more common among neonates than any other age group. Group B streptococcus is the leading causative bacterium in neonatal osteomyelitis, but staphylococcal species are still common. Skeletal scintigraphy is of limited value and is not a good option in diagnosis of neonatal osteomyelitis.

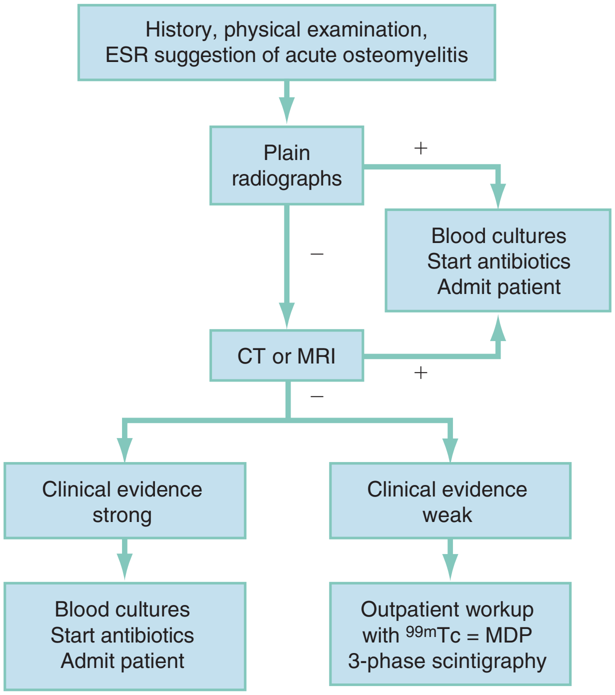


Figure 136-7. An algorithm for use of imaging studies in the emergency department diagnosis of osteomyelitis. *CT,* computed tomography; *ESR,* erythrocyte sedimentation rate; *MRI,* magnetic resonance imaging; *^{99m}Tc-MDP,* technetium Tc 99m–labeled methylene diphosphonate.

Plain radiographs are a good initial test because abnormalities are identified within days of development of neonatal osteomyelitis and are usually abnormal by the time the disease is suspected. In the face of a normal radiograph, the next step for the clinician who suspects neonatal osteomyelitis is MRI.

Two less common forms of osteomyelitis can occur in children: subacute osteomyelitis and chronic recurrent multifocal osteomyelitis (CRMO). Subacute osteomyelitis refers to a form of the

www.ketabpezeshki.com 66485457-66963820

disease in which clinical symptoms and signs are slow to appear and radiographs show small areas of osteomyelitis, usually in the metaphysis of long bones. Cultures of blood and bone are negative more than 50% of the time but usually implicate staphylococcal species when they are positive.

A form of subacute osteomyelitis is Brodie's abscess. This is a localized form of subacute osteomyelitis that also occurs mostly in children. Metaphyseal locations are most common before closure of the growth plates; after closure, a metaepiphyseal abscess is most frequent. The wall of the abscess contains large amounts of dense fibrous tissue. This is demonstrated by pronounced rim enhancement on contrast-enhanced MRI or CT scans. The central portions are pus filled. *S. aureus* is cultured in half of the cases. *Proteus* and *Pseudomonas* species have also been isolated. Symptoms are usually minimal and include localized pain that is often nocturnal, suggesting a tumor. On plain radiographs the lesion is lytic, with a well-defined sclerotic margin. Like subacute osteomyelitis, CRMO usually affects older children (6-10 years) and adolescents. CRMO is characterized by small foci of infection at various sites in the skeleton. The disease is defined by multiple episodes of indolent infection. Diagnosis is made by radiographs; culture of the bone sites is almost always negative. This disease may be associated with a type of psoriasis.

Vertebral Osteomyelitis

Vertebral osteomyelitis usually afflicts older adults in a manner analogous to AHO in children and appears to be increasing in frequency as the population ages and has more chronic medical diseases. Risk factors in elders include intravenous access devices and asymptomatic urinary infections.[22] In young people, risk factors include injection drug abuse. The spine is susceptible to bacterial infection because the venous system surrounding vertebral bodies is valveless (permitting two-way flow of blood) and has transverse and longitudinal anastomoses. Bacteria that reach the spine and enter the venous plexus are more likely to aggregate and to cause infection in this slow-moving system. Infection can readily spread to adjacent vertebral bodies. Vertebral osteomyelitis most often results from hematogenous seeding, direct inoculation at the time of spinal surgery, or contiguous spread from an adjacent infection. A clear source of bacterial hematogenous seeding with positive blood cultures occurs in approximately 40% of cases of vertebral osteomyelitis. *S. aureus* (including MRSA) is the most common offending agent in vertebral osteomyelitis, followed by aerobic Gram-negative rods from urinary or gastrointestinal sources.

Only 10% of patients with vertebral osteomyelitis appear septic or toxic; the rest have a subacute presentation. The majority of patients present with insidious symptoms, leading to possible delays in diagnosis of up to 4 months. Back pain is the most common presenting symptom, seen 86% of the time.[23] In most patients, physical examination will reveal back pain and tenderness over the spinous process. Neurologic deficits are reported in less than 38% of patients with vertebral osteomyelitis and are often an indication of an epidural abscess.[24] Up to 60% of patients with these abscesses present without fever or leukocytosis.[23] On laboratory testing, the ESR and CRP value are highly sensitive and are elevated in 98% and 100% of cases, respectively.[24] Blood culture specimens should be obtained before antibiotic treatment is initiated. Rapid diagnosis and treatment of this medical emergency start with initiation of empirical antibiotics, immediate imaging, and early orthopedic involvement.

The imaging strategy for the diagnosis of vertebral osteomyelitis starts with plain radiographs, which may show disk space narrowing or destruction of the vertebral endplates or the vertebral body. Similar to osteomyelitis in other parts of the body, findings on plain radiographs are not seen until at least the second week of vertebral infection. Bone scintigraphy has been largely replaced by MRI in further imaging of suspected vertebral osteomyelitis. CT is good for defining bone destruction and is often used to assist needle aspiration of the lesion, but if osteomyelitis is still suspected or if the patient has neurologic deficits, MRI is done to look for an epidural abscess and to rule out a herniated disk.[22] MRI has a sensitivity of 90% for vertebral osteomyelitis, with T2-weighted images proving most valuable in establishing the diagnosis.[25] Management of spine infections is usually nonoperative, consisting of immobilization and intravenous antibiotics; surgery is considered after failed nonsurgical management.

The areas most prone to vertebral infections are the lumbar (58%), thoracic (30%), and cervical (11%) spine.[23] Cervical spine osteomyelitis can cause a retropharyngeal abscess; lumbar spine osteomyelitis may be complicated by a psoas muscle abscess. The spinal cord may also suffer ischemic injury if the vertebral infection causes septic thrombosis or compression of local blood vessels.[22] When osteomyelitis affects the thoracic spine, infection can spread to the chest. Paraspinal abscesses, reactive pleural effusions, and empyema have been reported and may mislead the clinician to suspect that the primary problem is not in the spine.[22] The most dreaded complications of vertebral osteomyelitis are the spread of infection into the spinal canal, the development of an epidural abscess, and the progression of the infection to cause spinal cord injury and permanent paralysis. Fortunately, this occurs in less than 15% of cases of vertebral osteomyelitis.[22]

The diagnostic procedure of choice for vertebral osteomyelitis is needle biopsy that can isolate the causative organism. Patients who present with a clinical picture consistent with vertebral osteomyelitis require rapid diagnostic confirmation either through imaging or by direct needle biopsy performed by a surgeon, with or without CT guidance. A delay in the definitive diagnosis of puts the patient at risk for progression of vertebral osteomyelitis to spinal cord compression. Patients who are at increased risk for paralysis include elder patients, those with cervical spine osteomyelitis, and those with serious underlying diseases, such as rheumatoid arthritis and diabetes mellitus.[22]

Patients with vertebral osteomyelitis require antibiotic therapy that is based on the offending microorganism and its susceptibility. Even though AHO can usually be successfully treated with antibiotics alone, surgery may be required for diagnostic purposes, when there is spinal cord compression, for abscess drainage or débridement, for correction of the progressive deformity, and if the infection recurs after adequate treatment.[23] Given evolving resistance patterns for *S. aureus,* intravenous therapy is the standard mode of treatment for Gram-positive bacteria.[24]

Diskitis is a variant of vertebral osteomyelitis. The disk is an avascular structure that depends on nutrient diffusion from adjacent blood vessels in the vertebral metaphysis and endplates. The avascular disk creates a rich environment for the bacteria to flourish. Because of the vascular anatomy, adult pyogenic diskitis coexists with vertebral osteomyelitis. In the pediatric age group, the disk has a more robust vascular supply, and isolated diskitis is more common in this population. This subacute disease is thought to be a low-grade infection (usually *Staphylococcus* species) within the disk, sometimes extending to the adjacent vertebral plates. The patient complains of back pain and may refuse to walk. Although bone scintigraphy may show increased uptake in the disk space, MRI better demonstrates the anatomy of diskitis. CT is used to guide aspiration. Cultures of the disk from needle aspiration are reported to be positive for bacteria 30 to 60% of the time, most commonly for *S. aureus*. The disease typically resolves with nonoperative treatment.[22]

Post-traumatic Osteomyelitis

Post-traumatic osteomyelitis is a form of contiguous focus osteomyelitis that results from open fractures, surgery and invasive

www.ketabpezeshki.com 66485457-66963820

procedures, burns, bites, and puncture wounds. At least 10% of open fractures later develop osteomyelitis, and the tibia is the most commonly affected bone. The fracture site may be contaminated directly from the environment or iatrogenically secondary to emergency procedures or surgery. The intraoperative implantation of prosthetic devices further increases the chance of infection. Severe damage to adjacent soft tissues results in a necrotic nidus of infection that can spread to bone. Polymicrobial infection is more common with this type of osteomyelitis. The imaging of post-traumatic osteomyelitis is complicated by changes induced by surgery and new bone formation in the fracture. Imaging modalities that are best in this situation are MRI and CT.[26]

Osteomyelitis that is due to direct inoculation associated with joint arthroplasty may become evident within 12 weeks after the surgery. These patients generally do not report relief of their pain after the surgery. Patients who have symptoms of infection more than 12 weeks after surgery and who have postoperative improvement of their pain are considered to have a hematogenous source of infection. If either of these presentations is recognized within the first 2 weeks of onset of infectious symptoms, the prosthesis is considered salvageable. After 2 weeks, the chance of eradicating the infection without removal of the prosthesis decreases substantially.[27]

The most common form of postsurgical osteomyelitis is infection of a hip prosthesis, which occurs in 1 to 5% of hip replacement surgeries. Postsurgical osteomyelitis is difficult to diagnose. Fever is often absent, and the patient often presents with a painful, unstable joint on physical examination. *S. aureus* and *S. epidermidis* account for 75% of postsurgical and prosthesis-related osteomyelitis. Radiographs are often normal but may show subtle signs of bone resorption about the prosthetic components. It is difficult to distinguish mechanical from infectious loosening; joint aspiration, synovial fluid analysis, and bone biopsy performed in a sterile, operative setting are undertaken to make a firm diagnosis. Other imaging techniques, such as CT, MRI, and [^{18}F]fluorodeoxyglucose positron emission tomography, are used but are also difficult to interpret because of scatter from the metallic components and postsurgical changes. Systemic antibiotics cannot penetrate the biofilm, and surgical removal of the prosthesis is usually the only way to cure the infection.[28]

Puncture wounds to the feet have approximately a 2% incidence of development of osteomyelitis. The causative organism is usually *S. aureus* or beta-hemolytic streptococcus. *P. aeruginosa* is commonly associated with plantar wounds that occur while wearing a rubber-soled shoe. Other puncture wounds are nosocomial in the form of subclavian venipuncture, fetal scalp monitors, and other invasive procedures.

Diabetic Foot Osteomyelitis

The pathologic changes induced by long-standing diabetes mellitus encourage the development of osteomyelitis. Foot infections are common in diabetics because of their compromised vascularity. The typical patient with diabetic foot osteomyelitis is older than 50 years and has advanced insulin-dependent diabetes. More than 60% of such patients have polyneuropathy, more than 50% have retinopathy, and at least 30% have concurrent cardiovascular disease. The neuropathy leads to repetitive trauma and loss of the protective barrier of the skin and subsequent foot ulcers. Once the skin has been violated and infected, the altered host defenses of diabetic patients make it easier for infection to occur and to spread. The small bones and phalanges are most often affected. Infection spreads first to the periosteum and then to the cortex and may finally disrupt medullary bone. The initial phase of foot infection in diabetic patients may exacerbate preexisting hyperglycemia. This allows bacteria to replicate at an increased rate and impairs leukocyte function, with defective chemotaxis, abnormal phagocytosis, and decreased bactericidal function. Defective antibody synthesis and decreased complement levels also exacerbate osteomyelitis in diabetics.

Local findings in diabetic foot infections consist of swelling, erythema, and sometimes pain. Indolent ulcers and frank cellulitis are seen in more than 50% of cases. Because the process is often chronic, radiographic changes may have sufficient time to develop. Mottled lytic lesions are typical, and air may be present in the soft tissues. The only reliable way for the bacteriologic diagnosis to be made is by surgical culture of the bone; however, if a wound can be probed all the way to the bone, this has an 89% positive predictive value for osteomyelitis.[29] Bone biopsy for diabetic foot osteomyelitis has a reported sensitivity of 94%.[30] Diabetic foot osteomyelitis is usually polymicrobial. The most common organism is *S. aureus*. Other common organisms include streptococci, Enterobacteriaceae, and anaerobes. Surgical treatment is often required, and severe cases commonly lead to amputation of toes or portions of the foot. However, treatment with intravenous followed by oral antibiotics can be successful in some patients. In general, patients are treated with a longer course of about 8 to 10 weeks.[29]

Osteomyelitis in Sickle Cell Disease

Patients with sickle cell disease are at increased risk for hematogenous infection, including osteomyelitis. Macrophage function is impaired in sickle cell patients, rendering them susceptible to infections with encapsulated organisms. AHO in children with sickle cell disease has two major differences from AHO in other children. First, infection in sickle cell disease is usually located in the diaphysis of long bones as opposed to the metaphysis as in other AHO patients. Second, although *S. aureus* is still the most common bacterium in children with sickle cell disease who have osteomyelitis, *Salmonella* species are the next most common infecting organism. Reasons for this are not completely understood, although it is postulated that microinfarcts in the bowel allow *Salmonella* bacteremia to seed the bloodstream and become hematogenous osteomyelitis.[31]

The differentiation of bone infection from bone infarction in sickle cell patients is a challenge. Fever, a toxic appearance, and an elevated ESR are more commonly associated with osteomyelitis than with bone infarction. Plain radiographs are not helpful in distinguishing between the two entities. Whereas skeletal scintigraphy may help make the diagnosis, MRI is proving useful in differentiating between the two.[31] Another approach is to note the response to conservative therapy; bone infarctions usually improve within 24 to 48 hours, whereas bone infection worsens.[32] Antibiotic treatment of osteomyelitis in the sickle cell patient should include coverage against *Salmonella* with a third-generation cephalosporin.

Chronic Osteomyelitis

Most chronic bone infections occur as a complication of post-traumatic infection, surgical procedures, or diabetic foot infections. The inflammatory response to infection triggers bone resorption and cartilage destruction and ultimately leads to bone death (Fig. 136-8). The necrotic bone acts like a foreign material, providing an inanimate surface to which microorganisms adhere.[5] Clinical signs that the infection has become chronic include the formation of sequestra and the presence of draining tracks or fistulas. Chronic infection is almost always polymicrobial and commonly involves anaerobes. Cultures of sinus tracks are not a reliable method to predict which bacteria are active in the underlying bone infection; direct biopsy of bone is the only option for accurate diagnosis of most cases of chronic osteomyelitis. Chronically established infections can be remarkably persistent or evolve

www.ketabpezeshki.com 66485457-66963820

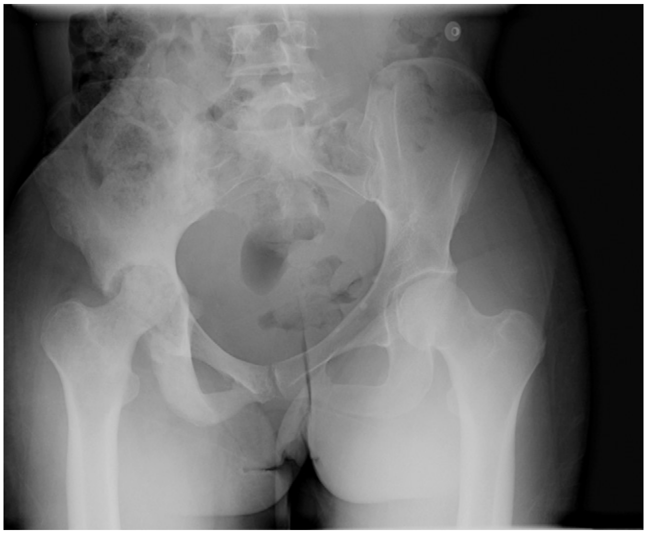


Figure 136-8. Chronic osteomyelitis. Diffuse sclerosis of the right hemipelvis includes the ischium and iliac bone with extension to the right sacroiliac joint. The right acetabulum demonstrates whittling of the femoral head and neck with marked loss of bone stock. Abutting the right symphysis pubis is increased cortical lucency suggestive of subchondral cystic changes. (Courtesy Peter Evangelista, MD, Department of Diagnostic Imaging, Rhode Island Hospital, Brown University.)

even in the face of prolonged antibiotic therapy; therefore, treatment commonly involves surgery.

Complications

In addition to the development of chronic osteomyelitis, several other complications can arise from the acute infection. The bloodstream may become seeded with bacteria or bacterial toxins, resulting in sepsis. Depending on the location of osteomyelitis, local extension of an invasive, suppurative process can lead to septic arthritis, brain abscess, meningitis, spinal cord compression, pneumonia, and empyema. In children, osteomyelitis damages the developing skeleton. If infection involves the epiphysis, permanent growth alterations can occur, resulting in a shorter or deformed extremity on the affected side. Pathologic fractures may occur through sites of osteomyelitis.[33]

Differential Considerations

Many different processes involving bone may masquerade as osteomyelitis. Bone tumors may produce local pain and radiographic changes consistent with osteomyelitis. Tumors most likely to mimic osteomyelitis are osteoid osteomas and chondroblastomas. These produce small, round, radiolucent lesions on radiographs. Ewing's sarcoma is a tumor of bone marrow in children that can be mistaken for osteomyelitis. Metastatic bone tumors and lymphomas should also be considered in the differential diagnosis of osteomyelitis. Trauma can also produce a clinical picture similar to osteomyelitis. In children, when trauma is common and may be occult, the evaluation for osteomyelitis may reveal a buckle fracture.

Management

Once the diagnosis of osteomyelitis is considered, the next step is to rapidly obtain culture specimens and commence treatment. The goal of therapy is to contain the infection before bone death occurs. Cure rates fall dramatically once necrotic bone is present. For osteomyelitis that is characterized by asymptomatic, hematogenous lesions coincidentally discovered during the evaluation of a patient with fever, weight loss, or bacteremia; hematogenous infection caused by sensitive microbacteria or fungi; or hematogenous vertebral osteomyelitis caused by sensitive pathogens, antibiotic treatment and medical management is usually effective.[34] For all other types of osteomyelitis, including contiguous focus osteomyelitis, diabetic foot infections, post-traumatic osteomyelitis, and implant-related infection, definitive care is surgical, and antibiotic treatment should be withheld until intraoperative cultures are obtained. In these cases a discussion about either infectious disease or orthopedic surgery, depending on the scenario and the available services, is appropriate, to plan or initiate surgical and medical therapy. The ideal antibiotic for treatment of osteomyelitis should be bactericidal against the offending bacteria, have low toxicity, be chemically stable at the site of infection, and be relatively inexpensive. The low pH of infected bone may limit the bactericidal action of some antibiotics, particularly the aminoglycosides. Cephalosporins and penicillins are more stable in this environment. In the ED, empirical broad-spectrum treatment of suspected osteomyelitis should be initiated with an awareness of regional resistance patterns.

The antibiotic of choice for osteomyelitis should be active against beta-hemolytic streptococci and staphylococci, including MRSA. Although Gram-negative organisms are uncommon pathogens, the serious consequences of inadequate treatment justify the inclusion of anti–Gram-negative coverage in the initial drug regimen. Once culture results are obtained, the antibiotic regimen can be tailored.[18]

In the case of post-traumatic osteomyelitis, appropriate initial emergency care may help prevent the disease. The proper management of open fractures in the field is to cut away surrounding clothing, to pour sterile saline or water over the exposed bone, and to cover the wound with moist sterile gauze bandages or a sterile sheet. Only in the case of severe vascular compromise to the distal limb should an open fracture site be manipulated or realigned because of the danger of introducing bacteria deeper in the wound. Because wound surface cultures in the emergency setting are not reliable in predicting future pathogens in bone infections, they need not be done as part of emergency care.

Treatment of osteomyelitis often requires a combined medical and surgical approach. This is usually true when osteomyelitis is caused by direct inoculation into bone or spreads from a contiguous focus of infection. If the area of osteomyelitis is small, aspiration or resection of the bone abscess may be both a diagnostic and therapeutic procedure. Acutely, indications for surgery include the presence of an abscess, necrosis, wound dehiscence, and failure to respond to appropriate therapy. In chronic infections, surgery is invariably required for radical cure of infection, and a team with orthopedic and infectious disease expertise may provide the best results.

AHO in children can be treated with antibiotics alone. In other situations, such as diabetic foot osteomyelitis and chronic osteomyelitis, the use of antibiotics with surgical débridement is necessary to eradicate the infection.

The first priority remains adequate treatment of *Staphylococcus* species with a penicillinase-resistant penicillin, such as oxacillin or nafcillin, or a first-generation cephalosporin. In patients with a severe penicillin allergy, vancomycin is an acceptable alternative; however, cure rates with vancomycin are inferior to those with nafcillin or cefazolin. Vancomycin should be reserved for those patients with a real type I penicillin allergy. Nonenterococcal streptococci are usually sensitive to antibiotics used to combat staphylococci. Gram-negative bacteria, including Enterobacteriaceae, *E. coli, Proteus mirabilis,* and *Serratia marcescens,* are rare causes of osteomyelitis. Third-generation cephalosporins, aminoglycosides, imipenem-cilastatin, and ampicillin are the usual choices for broad Gram-negative coverage. Beyond this initial

www.ketabpezeshki.com 66485457-66963820

broad-spectrum therapy, treatment for anaerobic bacteria, *Pseudomonas,* and fungal organisms should be based on clinical suspicion.

The incidence of antibiotic resistance is increasing. Resistance to both penicillinase-resistant penicillins (oxacillin and nafcillin) and fluoroquinolones by staphylococci, vancomycin by enterococci, and imipenem by pseudomonas has been reported. Therefore, if the bacterium is identified or known in the emergency setting, it is important to select the most specific antimicrobial agent on the basis of regional resistance patterns.[18]

The increase in antimicrobial resistance highlights the need for new antibiotics to expand therapeutic options. Second-generation fluoroquinolones, such as ciprofloxacin and lomefloxacin, and third-generation agents, such as levofloxacin, offer excellent bone and joint penetration and are active against a broad spectrum of Gram-positive and Gram-negative organisms. Because the blood concentrations of orally and parenterally administered drugs are similar, development of oral treatment protocols for osteomyelitis is pursued after an initial course of parenteral antibiotics. Successful treatment of osteomyelitis correlates best with serum levels of the antibiotic, not the route of administration. The standard recommendation is that the antibiotic used should achieve a serum level *eight* times greater than its minimum inhibitory concentration. If the serum concentration of an antibiotic is bactericidal, bactericidal levels in bone will almost always be present.[35] Table 136-2 lists common treatment regimens for the variety of bacteria that cause osteomyelitis. The standard recommendation is parenteral antibiotics for 4 to 6 weeks and then an oral course of antibiotics.

Treatment of chronic osteomyelitis is a difficult surgical problem. Instillation of antibiotic-containing beads into infected bone can help eradicate the infection so that bone grafts can be successfully used in chronic osteomyelitis. Hyperbaric oxygen therapy is reported to be effective in treatment of chronic osteomyelitis in noncontrolled clinical case series and may work best in diabetic foot osteomyelitis, although other scenarios are being explored.[36-38]

Disposition of the Patient with Osteomyelitis

Patients with osteomyelitis are admitted for intravenous antibiotic treatment. A subset of these patients will also need operative débridement. Oral antibiotics that have the same bioavailability as their intravenous forms can be used, and some studies have demonstrated good results with outpatient treatment of osteomyelitis. After steady-state serum antibiotic levels have been achieved, patients can receive outpatient intravenous antibiotic therapy.

SEPTIC ARTHRITIS

Clinical Features

Septic arthritis is an orthopedic emergency, and the incidence appears to be increasing. Even with prompt recognition and appropriate care with antibiotics and joint decompression, septic arthritis leads to a loss of function in 25 to 50% of patients.[39] In the United States, the incidence of septic arthritis in native joints ranges from 2 to 10 per 100,000; in patients with rheumatoid arthritis, the incidence jumps to 30 to 70 per 100,000.[40]

Septic arthritis most commonly results from hematogenous migration of bacteria into a joint. Like osteomyelitis, septic arthritis may also result from spread from a contiguous focus of infection or by direct inoculation of bacteria. Direct inoculation can result from penetrating trauma or iatrogenically as a consequence of invasion of the synovium, such as during joint aspiration or injection. Because the synovial membrane extends beyond the epiphysis and attaches to the metaphysis in the knee, hip, and shoulder joints, infection can easily spread from the metaphysis of the femur or humerus into the joint. This explains why septic arthritis may occur concomitantly with osteomyelitis, with infection spreading from bone to joint, and osteomyelitis may also be the result of septic arthritis. The most commonly isolated organism is *S. aureus,* but joint fluid Gram's stain has a 45 to 71% false-negative rate.[41] It is almost always a monarticular process; polyarticular involvement is present in less than 10% of pediatric cases and less than 20% of adult cases.

Septic arthritis is most likely to occur in the joints of the lower extremity. In infants and children, the knee and hip are most often infected. In adults, the knee is the site of septic arthritis 50% of the time, followed by the hip (25%) and shoulder (15%).

History and Physical Examination

Septic arthritis is usually more acute in onset than osteomyelitis. The predominant symptom of septic arthritis is joint pain, exacerbated with range of motion. Many children who have septic arthritis will not use the involved limb at all.[42] If the hip is infected, the patient may present with referred pain to the thigh or knee. Immunosuppressed patients, especially those receiving corticosteroids, may have septic arthritis with minimal joint pain. It is important in obtaining the patient's history to ascertain predisposing factors for septic arthritis. These include underlying joint disease, such as osteoarthritis, gout, rheumatoid arthritis, or joint surgery, and the presence of other conditions, such as chronic systemic diseases, immune deficiency, prolonged steroid use, or a history of injection drug use. In these patients, a careful history may help differentiate chronic joint pain from the acute pain associated with septic arthritis. More than 80% of children and 40% of adults with septic arthritis have a fever on presentation; however, constitutional symptoms such as weakness, malaise, anorexia, nausea, and diffuse myalgias are inconsistently reported.

On physical examination, tachycardia and hypotension may indicate a generalized septic process. Examination of the skin, nose, ears, and pharynx may reveal a focus of infection. In the neonate or infant, there may be "pseudoparalysis" of the affected limb. This can be mistaken for a neurologic problem; however, an isolated true paralysis is far less common than septic arthritis. The inability of a child to bear weight on a lower extremity or to spontaneously move any joint should be considered a sign of septic arthritis, and it should remain on the differential until it is adequately ruled out.[42]

In the older child and adult, signs may be more localized. The extremity will usually be held motionless in the position of greatest comfort, which is slight flexion. Palpation of the septic joint will cause exquisite pain, and any maneuver that stretches the synovium, such as flexion and extension, will cause severe pain. The cardinal signs of inflammation—swelling, erythema, and warmth—are commonly found in the infected joint. Joint pain is 80 to 100% sensitive for septic arthritis, and tenderness is 100% sensitive.[43] Periarticular processes such as bursitis, tendinitis, and cellulitis may produce erythema, warmth, and tenderness, but these processes can usually be differentiated from septic arthritis. Palpation of the joint line and maneuvers that stress the synovium and joint are not usually painful in cellulitis. Periarticular processes also do not commonly produce an effusion. In general, the triad of fever (seen in 45 to 60% of cases), pain (seen in 75% of cases), and impaired range of motion suggests septic arthritis. One caveat with the physical examination is that an increasing number of patients are receiving chronic immunosuppressive drugs, and in these patients the classic history and examination findings may be significantly less dramatic than in their immunocompetent counterparts.

www.ketabpezeshki.com 66485457-66963820

Diagnostic Strategies

Joint Aspiration and Joint Fluid Analysis

Blood tests are not consistently helpful in making a diagnosis of septic arthritis. The ESR is elevated in approximately 90% of cases and along with the CRP level can be used to help diagnose the infection and to track resolution. When low thresholds are used in the ED, the sensitivity of ESR is reported to be 98% with a cutoff of ≥10 mm/hr, and the sensitivity of CRP is 92% with a threshold of ≥20 mg/L.[44] Li demonstrated a sensitivity of 96% for an ESR of greater than 30 mm/hr.[45,46] Procalcitonin is another possible serum marker for septic arthritis, but it is also a nonspecific marker of inflammation and is not likely to provide a definitive diagnosis.[47] Two sets of blood culture specimens should be obtained; however, blood cultures reveal the infecting organism in only 25 to 50% of cases. Serum leukocytosis is both nonspecific and nonsensitive for diagnosis of septic arthritis. Traditionally, a serum WBC count of more than 10,000 cells/mm^3 may suggest a systemic illness but is present in only 50% of patients with septic arthritis, and many sterile inflammatory processes create a similar leukocytosis. Cultures of infectious foci, such as the throat, cervix, and urine, may demonstrate the bacteria responsible for septic arthritis.

The diagnosis of septic arthritis requires joint fluid for culture and analysis. It is fortunate that the knee joint is both the most likely to be infected and the easiest to aspirate. Other joints, such as the hip, are more difficult to aspirate, and aspiration usually requires orthopedic surgical consultation. Ultrasonography and fluoroscopy to guide aspiration are adjunct modalities used to obtain fluid from the joint and may be useful in detection of early, less obvious intra-articular fluid collections. However, the absence of sonographic fluid does not rule out septic arthritis as the cause of joint pain. Septic technique should always be practiced; however, the risk of introducing infection into a joint during intra-articular aspiration or injection has been reported to be between 1 in 2000 and 1 in 15,000 injections and seems to be related to the number of precautions taken to avoid it.[48]

Because joint fluid analysis is not done as often as other diagnostic tests in the ED, a joint fluid protocol is useful to ensure that all necessary tests are prepared and ordered properly. Joint fluid cultures must be inoculated as soon as possible after the fluid is obtained. The laboratory should include special media to test for fastidious organisms such as *Neisseria gonorrhoeae.*[49] Anaerobic and fungal organisms are cultured in patients with risk factors for these infections.

One method that may increase the yield in isolation of bacteria from joint fluid is to inoculate blood culture bottles with joint fluid immediately after joint aspiration. This allows some bacteria, which would normally die before being inoculated on culture media in the laboratory, to survive and grow in the blood culture bottle (brain-heart infusion broth). Synovial Gram's stain results in clinically suspected septic arthritis are negative about a third of the time, probably because the bacteria are usually not in the planktonic state in a joint. This may also be due to an inadequate joint fluid sample, poor culture techniques, presence of fastidious organisms, or misdiagnosis of the joint inflammation. In addition, leukocytes may have cleared bacteria from the joint space; however, the bacteria may still persist in the synovial membrane and may be detected by a synovial biopsy.

The definitive test to determine bacterial arthritis is synovial culture. Other tests of the synovial fluid are commonly performed, but many studies have refuted the efficacy of these additional tests. Gram's stain, synovial WBC count and differential, percentage of polynuclear cells, and joint fluid glucose level have traditionally been used to differentiate bacterial arthritis from other joint diseases. The primary reason for the decreasing utility of these common joint fluid tests is the number of patients who have a chronically activated or suppressed immune response in the infected joint. Traditionally, a synovial fluid leukocyte count of more than 50,000 cells/mm^3 with a predominance of polymorphonuclear leukocytes was used to define septic arthritis, but other processes can produce similar cell counts, and up to 30% of patients with septic arthritis have been documented to have counts below 50,000 cells/mm.[50]

Many other studies support the idea that a specific range of elevation of the synovial fluid leukocyte count can be reliably used to diagnose septic arthritis. One large study found that for a synovial fluid WBC count higher than 17,500 cells/mm^3, the sensitivity was 83% and the specificity was 67%. The positive likelihood ratio at this level was 2.5, with a negative likelihood ratio of 0.25.[46] Another study showed likelihood ratios of 0.32, 2.9, 7.7, and 28 with synovial fluid leukocyte counts of less than 25,000 cells/mm^3, more than 25,000 cells/mm^3, more than 50,000 cells/mm^3, and more than 100,000 cells/mm^3, respectively.[51] A synovial fluid leukocyte differential count with at least 90% neutrophils suggests septic arthritis with a likelihood ratio of 3.4; a count of less than 90% decreases the likelihood ratio to 3.4. There is mounting evidence that one cannot rely solely on the synovial fluid leukocyte count either to exclude or to include the diagnosis of septic arthritis and that this value should be used with the clinical, radiographic, and laboratory findings to help guide therapy as Gram's stain and culture results become available.

The examination of synovial fluid under polarizing microscopy for the presence of crystals may be useful in differentiation of inflammatory from noninflammatory joint disease but is not helpful in the separation of infectious inflammatory joint disease from noninfectious inflammatory joint disease as the two often coexist. The identification of crystals should not deter the physician from continuing to search for an infectious etiology of joint pain.

When only a small volume of synovial fluid is recovered from a joint aspiration, the following tests should be performed. The single most important test is a bacterial culture. Culture of the synovial fluid or of synovial tissue itself (obtained by arthrotomy) is the only definitive method for diagnosis of infective arthritis. If extra fluid is available after a culture specimen is obtained, it can be used to obtain Gram's stain and smear and then a cell count and crystal analysis. A positive result of Gram's stain can be used to guide antibiotic treatment; however, empirical treatment should not be delayed if the result is negative as Gram's stain is less than 60% sensitive for detection of bacteria in synovial fluid.

Plain radiography is not an effective tool for the early evaluation of septic arthritis but may detect surrounding osteomyelitis. In most joints, the small areas of attachment of the synovial membrane to bone are devoid of cartilage. These "bare areas" at the margins of the joint appear as lucencies or erosions early in the course of septic arthritis. Bone beneath the articular cartilage may start to erode 1 to 3 weeks into the disease. Air in the joint may be a sign of infection with gas-forming organisms, but it may be the result of a previous joint aspiration. In patients with existing joint disease, radiographs provide minimal assistance in diagnosis of septic arthritis.

Ultrasonography is a useful modality to detect a joint effusion in suspected septic arthritis and to assist in joint aspiration, particularly of the hip (Fig. 136-9). When synovial fluid aspiration from the hip is attempted under fluoroscopy, a small amount of contrast material should be injected into the joint to confirm that the needle has entered the intra-articular space. CT provides better anatomic images of the joint, and MRI is most useful in visualization of the detailed anatomy of joints and can determine if septic arthritis is complicated by concurrent osteomyelitis.[52] Diagnosis of an effusion on a CT or MRI study is done cautiously. These two modalities can identify joint fluid, but a volumetric analysis cannot be done to assess the amount of fluid.

www.ketabpezeshki.com 66485457-66963820

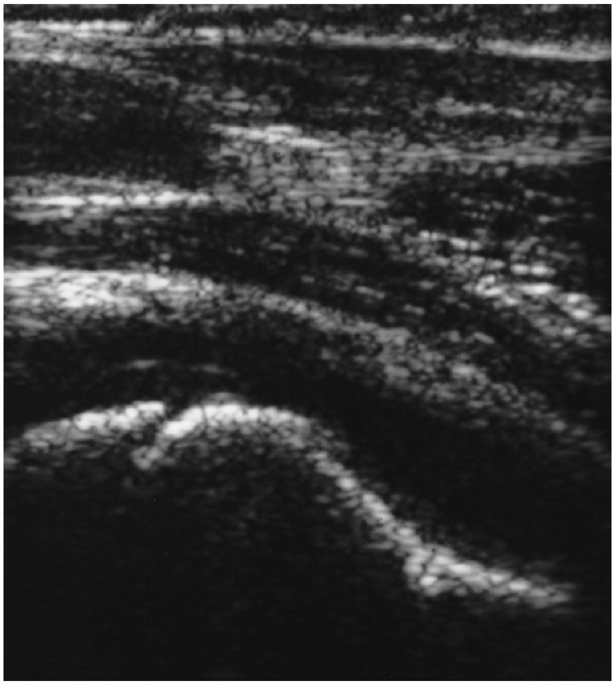


Figure 136-9. Ultrasound image of the right hip in an 8-year-old girl with septic arthritis. A significant joint effusion can be seen just superior to the round contour of the femoral head. Joint aspiration revealed purulent fluid with a white blood cell count of 71,000.

Skeletal scintigraphy has been used in the diagnosis of septic arthritis, but its use is decreasing. The main advantage of skeletal scintigraphy is in detection of septic arthritis earlier than with other imaging techniques. In septic arthritis, scintigraphy shows symmetrical areas of increased uptake on both sides of the joint. In a three-phase ^{99m}Tc scan, all three phases will be "hot" with septic arthritis; however, it may be difficult to distinguish osteomyelitis in the metaphysis of a long bone from septic arthritis in the adjacent joint. In general, skeletal scintigraphy is used only when there is enough uncertainty about the diagnosis to warrant further investigation. This is most common in evaluation of the hip. In joints in which aspiration is easier, skeletal scintigraphy has little role in diagnosis of septic arthritis.

Complications

Septic arthritis leads to two types of serious complications—those involving the joint itself and those that are systemic. The introduction of bacterial DNA into a joint triggers a profound immune response that leads to destruction of the articular cartilage. Bacteria, host synovial cells, chondrocytes, neutrophils, and macrophages all release enzymes and inflammatory chemicals such as collagenase, elastase, hyaluronidase, lipase, and lipoproteinase that may be destructive to the joint. Damaged articular cartilage has limited repair capacity, and a common result of articular cartilage destruction is arthritis or ankylosis, which results in a stiff, immobile joint.

Children are at great risk for epiphyseal damage if the infection extends through subchondral bone. This can result in impaired growth and limb-length discrepancy.[53] Other tissues adjacent to the joint can be invaded. Bursae, tendons, ligaments, and muscles can be destroyed by the suppurative process. Sinus tracks may lead the infection out through the skin. In the hip, the pressure and edema of a septic synovial effusion can occlude blood supply, resulting in avascular necrosis of the femoral head, especially in neonates.[54]

Systemic complications from septic arthritis are less common than joint damage, but the hematogenous spread of bacteria from an infected joint can produce sepsis, septic shock, and death. Seeding of other sites with bacteria is also a possibility, and this can produce endocarditis, pneumonia, and abscesses.[55-57]

Clinical Subsets of Septic Arthritis

Bites

Human mouth flora is polymicrobial with aerobic organisms, such as *Staphylococcus*; oral Gram-negative rods, such as *Eikenella corrodens*; and anaerobes, such as *Fusobacterium*. Therefore, human bites that lead to bone and joint infections can be difficult to treat. Similarly, animal bites also lead to a polymicrobial infection, with *Pasteurella multocida* an important additional organism. Antibiotics should be empirically started, but treatment also requires drainage and débridement.[6]

Septic Arthritis in Infants and Children

Septic arthritis is more common in children than in adults, and the incidence of septic arthritis is twice that of osteomyelitis in children. Of pediatric cases, two thirds occur in children younger than 2 years, and boys are affected twice as often as girls are.[58] The bacterial etiologic agent of septic arthritis varies with age. In the post–*H. influenzae* vaccine era, overall, *S. aureus* (methicillin sensitive more than methicillin resistant) is the most common infecting organism in all pediatric and adult age groups, followed by group A streptococci and *Streptococcus pneumoniae*.[59] In neonates, group B streptococci, *S. aureus,* and Gram-negative enteric bacilli are usual pathogens. *Candida albicans* should also be considered in neonates and premature infants. *Kingella kingae* is an emerging important cause of septic arthritis and osteomyelitis in children younger than 2 years. In children between 3 months and 5 years, concomitant respiratory infection or otitis media is often present. Prior trauma or skin infection may be more common with staphylococcal septic arthritis.

Even with full culture of joint fluid and blood, a causative organism is not discovered in up to 30% of cases of septic arthritis in children. Prior antibiotic treatment in children decreases the yield on synovial fluid cultures from 80 to 38%. In the pediatric population, the hip and knee have equal rates of infection, each accounting for about one third of infections. If the hip joint is infected, delays to diagnosis lead to higher complication rates, and permanent joint damage is more likely. This is especially true in infants, particularly those who have coexisting septic arthritis and osteomyelitis. Hematogenous osteomyelitis is often associated with septic arthritis of the hip in children. Concurrent osteomyelitis is present in 20% of infants and in almost half of all neonates with septic arthritis.[60]

The Kocher criteria can be used to help identify those children with septic arthritis of the hip. However, the sensitivity of the algorithm has been challenged,[61] and it should be used cautiously. The four criteria are fever (temperature ≥38.5° C), nonweightbearing on the affected side, ESR greater than 40 mm/hr, and peripheral blood WBC count of more than 12,000 cells/mm^3 (Table 136-3). Laboratory work, including complete blood count, ESR, and CRP level, are part of the routine evaluation of the limping child but individually do not have adequate sensitivity or specificity to rule in or to rule out the diagnosis; a synovial fluid analysis should also be done if there is any suspicion for septic arthritis.

Gonococcal Septic Arthritis

In the United States, *N. gonorrhoeae* is the most common cause of septic arthritis in sexually active patients. A person with gonorrhea

www.ketabpezeshki.com 66485457-66963820

Table 136-3 Kocher Criteria

NUMBER OF KOCHER CRITERIA MET	LIKELIHOOD OF SEPTIC ARTHRITIS OF THE HIP
1	3%
2	40%
3	93%
4	99%

of the urethra, cervix, rectum, or pharynx has a 1 to 3% chance for development of disseminated gonococcal infection (DGI). More than 75% of the cases of DGI occur in women, possibly because of the increased risk of asymptomatic infection in women.[49] DGI is common during pregnancy or after menstruation when the alkaline vaginal environment makes the organisms more resistant to host defenses in the bloodstream and therefore more likely to disseminate.

The strains of *N. gonorrhoeae* that cause disseminated infection and septic arthritis have characteristics different from those of strains that cause local infection. Those strains that cause disseminated infection contain outer membrane proteins, which make them resistant to serum bactericidal activity. These strains are not more resistant than other types of *N. gonorrhoeae* to antibiotics; however, penicillin-resistant and fluoroquinolone-resistant gonococcal infections appear to be increasing in some parts of the world, including the United States.

The classic triad of gonococcal bacteremia is migratory polyarthritis, tenosynovitis, and dermatitis. Asymmetrical polyarthralgia, which may be migratory, is the most common presenting complaint, occurring in two thirds of cases; 25% of patients have monarthralgia.[49] The arthralgia is usually asymmetrical and most frequently involves the knee, although the elbow, wrist, metacarpophalangeal, and ankle joints are also affected. The sacroiliac and sternoclavicular joints may be involved, although these sites are far less common. Tenosynovitis occurs in about 20% of patients with bacteremia, usually in the hands and fingers, and hemorrhagic pustules on the skin are seen 41% of the time.[49] These are scattered, painless, nonpruritic, small (0.5- to 0.75-cm) papules distributed below the neck that can involve the palms and the soles. These papules can turn into pustules on a broad erythematous base with either a necrotic or hemorrhagic center. There are usually fewer than 50 lesions, distinguishing DGI from the rash of meningococcus.

Septic arthritis develops in approximately 40% of patients with DGI. This is usually a monarticular process , although polyarticular arthritis has been reported. The patient will present with classic signs of a septic joint, including a joint effusion, warmth, tenderness, decreased range of motion, and marked erythema. There is usually no clear progression of DGI and polyarthralgias to purulent monarticular arthritis, and many patients are afflicted with dermatitis and tenosynovitis without the development of true arthritis.[49] Some of the strains of *N. gonorrhoeae* that produce DGI favor the development of tenosynovitis and dermatitis, whereas others favor the development of purulent arthritis.

The diagnosis of gonococcal arthritis is made by synovial fluid culture results; however, gonococci are recovered from synovial fluid in less than 50% of cases. The common finding of sterile joint fluid in DGI, even when mucosal cultures are positive, suggests that the host immune response plays a significant role in the development of purulent arthritis.[49] Joint fluid analysis in gonococcal arthritis reveals some differences in comparison with other types of bacterial arthritis. The synovial fluid WBC count in gonococcal arthritis is often less than 50,000 cells/mm^3. Gram's stains of aspirated joint fluid are positive for bacteria only 25% of the time in gonococcal arthritis, and cultures of the joint fluid are negative in approximately 50% of cases. This may be due to poor culture techniques or because a suppurative reactive process can occur in the joint in DGI even when bacteria are no longer present. When gonococcal arthritis is suspected, cultures of the synovial fluid are plated on prewarmed chocolate agar for the highest yield. To increase the chance of making a firm diagnosis, specimens of the mucosal surfaces for culture of *N. gonorrhoeae* are obtained as these may be the only places where bacteria are readily recovered. Cultures of the genital tract, pharynx, or rectum will be positive in 80% of cases of gonococcal arthritis.[49]

Gonococcal septic arthritis responds rapidly to antibiotic treatment and unlike other types of bacterial arthritis rarely causes permanent damage to the joint. Patients with gonococcal septic arthritis require hospital admission with antibiotic coverage against the likely pathogens until laboratory results are available. With the rise in fluoroquinolone-resistant gonorrhea, the recommended treatment of gonococcal arthritis is a third-generation cephalosporin, such as ceftriaxone, ceftizoxime, or cefotaxime.[62] Patients are given the first dose intravenously or intramuscularly in the ED and admitted until culture results are available. If the diagnosis of gonococcal arthritis can be definitely established in the ED, patients with reliable follow-up can be treated with an intravenous or intramuscular dose of antibiotics and then sent home with an oral regimen that should be continued for 1 week.[49]

Lyme Arthritis

Lyme disease is the most common tick-borne disease in the United States and is caused by infection with a spirochete, *Borrelia burgdorferi.* Transmitted by the *Ixodes* tick, it is an important cause of arthritis in endemic areas and the incidence is on the rise. Lyme disease has been reported in all 50 states, but endemic areas including Maryland, Massachusetts, Minnesota, New Jersey, New York, Pennsylvania, Wisconsin, Connecticut, Delaware, and Rhode Island account for 93% of all cases annually.[63] There is a bimodal age distribution, in children aged 5 to 9 years and adults aged 55 to 59 years. Children infected by *B. burgdorferi* are more likely than adults to have arthritis as the initial manifestation of the disease. Whereas it is important to determine a history of a tick bite, up to 30% of people do not remember being bitten. There are three phases of the infection: early localized, early disseminated, and late.

Arthritis, which is the most distinguishing feature of late-stage Lyme disease, develops in up to 60% of untreated Lyme patients and is manifested months after disease onset.[64] After infection, spirochetes are disseminated and invade synovial joints, resulting in a profound immune response, similar to that seen in bacterial arthritis. Patients with Lyme arthritis present with migratory polyarthralgia involving not only joints but also bursae and tendons. This usually evolves into a monarticular process, although polyarticular processes are reported, and most commonly involves single, large joints. More than 90% of patients report knee inflammation, but other affected joints include the wrist, elbow, ankle, and hip. The Centers for Disease Control and Prevention defines Lyme arthritis as “recurrent, brief attacks (weeks or months) of objective joint swelling in one or a few joints, sometimes followed by chronic arthritis in one or a few joints.”[64,65]

The rash is often overlooked by patients and is generally not present in patients who have arthritis in the later stage of the disease process. Fever is noted in up to half of all children who have Lyme arthritis.[66] Clinically, the arthritis is similar to other inflammatory processes of the joint and includes warmth, erythema, swelling, and pain on motion of the joints; however, the effusion is usually large and out of proportion to the patient's complaints. The effusion also generally recurs after aspiration, even when the joint is appropriately treated.

www.ketabpezeshki.com 66485457-66963820

The most widely used test for diagnosis of Lyme disease is the serum antibody titer, including enzyme-linked immunosorbent assay (ELISA) and Western blot testing, but serum testing does not differentiate between acute and past infection. Synovial fluid analysis is also not helpful in distinguishing Lyme arthritis, but it usually reveals an inflammatory process with WBC counts ranging from 500 to 98,000 cells/μL. Arthrocentesis cannot differentiate between bacterial and Lyme arthritis because serologic analysis is similar. Cultures of synovial fluid in Lyme arthritis are usually nondiagnostic. Testing of synovial fluid with ELISA or Western blot methods for Lyme disease is not recommended as no consensus exists on how to interpret these data.

Lyme arthritis can be successfully treated with oral doxycycline, amoxicillin, or cefuroxime for 30 days. If this is unsuccessful, patients can be re-treated with the same oral regimen for another 30 days, or the antibiotic can be changed to intravenous ceftriaxone for 14 to 30 days.[64]

Fortunately, Lyme arthritis has an excellent prognosis. Up to 95% of children remain asymptomatic after a single course of antibiotics; adults may show an increased incidence of persistent joint swelling months to years after initial infection, even after appropriate antibiotics. A small minority of patients have chronic Lyme disease despite appropriate treatment, with symptoms similar to chronic fatigue syndrome.[64,67]

Periprosthetic Joint Infections

Infections occurring after joint replacement are a challenging and dangerous complication of arthroplasty, with rates reported to be 1 to 2% at 2 years postoperatively in native joints and up to 7% in the patients undergoing joint revision.[68,69] The prosthesis and cement are foreign bodies and are ideal sites for bacterial colonization. The most common infectious agents are *S. epidermidis* (40% of cases), *S. aureus* (20%), and streptococcal species (20%). Risk factors for periprosthetic joint infections have been identified to be rheumatologic disease, preoperative anemia, coagulopathy, diabetes, depression, and socioeconomic status.[69] The most commonly identified organisms are *S. aureus* (methicillin sensitive and methicillin resistant) and *S. epidermidis*. The American Academy of Orthopaedic Surgeons clinical practice guideline summary recommends that patients who present to the ED should initially be stratified to high or low probability for a periprosthetic joint infection. As with many diagnostic maneuvers performed in the ED, a pretest probability helps guide the evaluation.[68]

On history and physical examination, the patient will complain of pain that is constant and present at rest along with impaired function of the joint secondary to loosening of the hardware. Radiographs may also reveal movement of the prosthesis, bone erosion, new subperiosteal bone growth widening, or lucency at the bone-cement interface of more than 2 mm. The investigation starts with laboratory data, including an ESR and CRP level.[70] If both test results are negative, a periprosthetic infection is unlikely (negative likelihood ratio of 0-0.06); when both test results are positive, a periprosthetic infection must be considered (likelihood ratio of 4.3-12.1). However, many inflammatory processes can result in an elevation of the ESR and CRP level, and these are not specific tests. The use of either test alone is less reliable, and no definitive conclusion can be drawn with just one result. In patients with an elevated ESR or CRP level in whom a prosthetic joint infection is suspected, the next step is to obtain fluid from the joint.

If synovial fluid is submitted for analysis, an elevation in the number of neutrophils to 60 to 70% or a synovial WBC count of 1100 to 1700 is a sensitive and specific marker for periprosthetic joint infection in a patient who had a joint implanted more than 6 months earlier and who has no underlying inflammatory joint disease.[71] Aspiration may be more difficult in this situation because of scarring and alteration of the joint space. Consultation with the patient's orthopedic surgeon on the decision to perform joint aspiration in the ED and on the selection and timing of antibiotics in suspected periprosthetic joint infection is advisable. Patients who have received antibiotics within 2 weeks will have a very low yield with intra-articular cultures, even if infection is present. Because of the difficulty in isolation of infectious organisms from the prosthetic joint, even if it is done intraoperatively, orthopedists generally recommended that antibiotics not be started until after culture specimens are obtained.[71]

Septic Arthritis in Patients with Existing Joint Disease

Patients with underlying joint disease are more likely to have septic arthritis than are their counterparts with normal joints.[72] This is especially true for patients with rheumatoid arthritis and crystalline arthritis. If septic arthritis is suspected, laboratory and radiographic evaluation is of lower yield, and antibiotics are started immediately after synovial fluid is sent as these patients have high mortality. In patients with the crystal arthropathies, neutrophil invasion secondary to septic arthritis also leads to increased precipitation and release of crystals. Therefore, the clinician who discovers crystals on joint fluid aspiration should not abandon the search for an infectious agent.[73] The clinical course is variable. With *S. epidermidis* infections, the course is usually indolent. With *S. aureus,* a more aggressive infection occurs, with more pronounced inflammation, effusion, and systemic symptoms.

Septic Arthritis in Atypical Joints

Septic arthritis can be particularly difficult to diagnose and to treat if it occurs in fibrocartilaginous joints, such as the sternoclavicular, acromioclavicular, and sacroiliac joints, and the symphysis pubis. Septic arthritis of the axial skeleton, especially of the sternoclavicular joint, is commonly seen in injection drug users, with *Pseudomonas* a common infecting agent. In patients who do not have other predisposing factors, the most common bacterial causes are *S. aureus* and *S. epidermidis*. The presentation is usually pain and point tenderness over the involved joint. Fever and an elevated ESR are commonly reported, although they are not always present because of the suppressed immune status of the patient. CT and MRI are the preferred imaging techniques and are helpful in diagnosis of septic arthritis in the fibrocartilaginous joints.

Differential Considerations

Many disease processes can be confused with septic arthritis. Metaphyseal osteomyelitis may mimic septic arthritis because the adjacent joint may develop an effusion and the two infections can be concurrent. Juvenile rheumatoid arthritis is usually more gradual in onset and produces polyarticular arthritis in children younger than 16 years but may be manifested as a monarticular process that mimics septic arthritis. Toxic or transient synovitis is another inflammatory process in children that can be confused with septic arthritis. It occurs in the 3-month to 6-year age range, usually affects the hip, and is a self-limited disease with no long-term morbidity. It may be more common after upper respiratory infections. Children with transient synovitis have less pain with passive joint motion than do patients with septic arthritis; they do not usually have a fever or appear ill but tend to favor the unaffected leg as in septic arthritis. Diagnostic evaluation typically reveals a normal WBC count and ESR and no radiographic abnormalities. If fluid is needed for analysis, this is usually obtained under ultrasound guidance.

Other diseases of the hip in children that are included in the differential are Legg-Calvé-Perthes disease (avascular necrosis of

www.ketabpezeshki.com 66485457-66963820

the femoral head) and slipped capital femoral epiphysis; however, these processes are not as acutely disabling as septic arthritis is. Rheumatic fever commonly presents with a migrating polyarthritis and may mimic gonococcal bacteremia. Patients with Lyme arthritis are not as debilitated as those with septic arthritis, but in endemic areas, serum antibody titers should be obtained.

In the adult, osteoarthritis, gout, and pseudogout may produce findings on joint examination that are similar to the findings of septic arthritis. Other arthropathies that should be considered in the differential diagnosis of septic arthritis are psoriatic arthritis, arthritis associated with inflammatory bowel disease, ankylosing spondylitis, crystal-induced arthritis, and drug-induced arthritis. Collectively, these are known as the seronegative spondyloarthropathies. Trauma to the joint can produce synovitis and hemarthrosis, which may be mistaken for septic arthritis. In a patient with hemophilia, hemarthrosis causes joint inflammation and destruction, and there may be superimposed infection.

Reactive arthritis has been traditionally considered a sterile inflammatory response to a distant infection. However, recent data suggest that antigens from the infectious trigger are often present in the joint. Several viral and bacterial microorganisms can produce reactive arthritis. The most recognized syndrome is post-streptococcal reactive arthritis. Some other common organisms to cause reactive arthritis are *Chlamydia, Salmonella, Shigella, B. burgdorferi* (Lyme disease), *Yersinia,* human T-lymphotropic virus type 1 (HTLV-1), rubella virus, hepatitis B virus, adenoviruses, parvovirus, and Epstein-Barr virus. In reactive arthritis, host factors rather than microbial aggression account for most of the inflammatory process. The pathogenesis of reactive arthritis involves deposition of immune complexes in the joint, persistence of organisms in the joint, and stimulation of the immune system. Strong evidence exists to support a link between the susceptibility to reactive arthritis and the HLA-B27 human leukocyte histocompatibility antigen. Reactive arthritis can usually be distinguished from septic arthritis because it tends to involve multiple joints in a migratory pattern. The inflammatory process is also less severe with reactive arthritis. There is less effusion and the joint is not as hot or tender as it is with septic arthritis, and joint fluid cell counts are usually below 50,000 cells/mm^3.

Management

Septic arthritis is an orthopedic emergency, and once synovial fluid is obtained, empirical antibiotics should be promptly administered on the basis of Gram's stain results, when possible, if the diagnosis is strongly suspected (Table 136-4). Whereas most joint infections require surgical joint decompression, there are a few instances in which medical management will suffice. As reviewed before, antibiotics alone can adequately treat gonococcal septic arthritis as well as Lyme arthritis.

Unlike in most other infectious emergencies encountered in the ED, when time to antibiotic administration decreases morbidity and mortality, definitive management for most cases of septic arthritis requires surgical intervention and a prolonged course of antibiotics. Therefore, it is more important to obtain synovial fluid for Gram's stain and culture than to start antibiotics as this will guide long-term antibiotic treatment.

The selection of antibiotics for the treatment of septic arthritis is outlined in Table 136-2. In most cases the emergency physician does not know the identity of the causative organism, but treatment should be tailored to the most likely causative agents on the basis of the patient's age and immune status. *S. aureus* accounts for 44% of cases and remains the predominant pathogen for all age groups. Unless gonococcal arthritis is confirmed, antibiotic selection should always include an antibiotic that has excellent bactericidal activity against *S. aureus*. Empirical antibiotics that are active against MRSA should be considered but based on the prevalence of this pathogen in the community. Risk factors for MRSA include older age, chronic illness, and health care exposure.[74] Group B streptococci have emerged as invasive pathogens in elders, especially those with diabetes mellitus, cirrhosis, and neurologic diseases.[75] Gonococcal septic arthritis is the most common cause of arthritis in young adults. Penicillin- and fluoroquinolone-resistant strains are becoming more prevalent, and a third-generation cephalosporin is the best choice for gonococcal arthritis. Complete recovery without surgical intervention is the rule in gonococcal arthritis. In elders, Gram-negative septic arthritis is more common, and agents such as the third-generation cephalosporins and aminoglycosides are added to the antistaphylococcal regimen. Establishment of good bactericidal serum levels of antibiotics will ensure that the levels in joint fluid are also bactericidal. In pediatrics, there is some evidence to support the early administration of dexamethasone (0.15 mg/kg every 6 hours for 4 days) to accelerate clinical improvement.[76]

Disposition of the Patient with Septic Arthritis

Any patient thought to have septic arthritis requires joint aspiration. In some cases the initial culture results, Gram's stain, and cell counts make the diagnosis of septic arthritis extremely likely. The patient is given an initial parenteral dose of antibiotics in the ED and admitted for continued management. Consultants will then

Table 136-4 Guidelines for Choice of Empirical Antibiotic Based on Gram's Stain

GRAM'S STAIN OR CLINICAL CONDITION	PROBABLE ORGANISMS	PREFERRED ANTIBIOTICS	ALTERNATIVE ANTIBIOTICS
Gram-positive cocci	*Staphylococcus aureus* Streptococci	Nafcillin or cefazolin	Clindamycin Trimethoprim-sulfamethoxazole Vancomycin
Gram-negative cocci or negative stain Healthy, sexually active patient	*Neisseria gonorrhoeae*	Ceftriaxone	Doxycycline
Gram-negative bacilli	*Pseudomonas aeruginosa* Enterobacteriaceae	Piperacillin ± gentamicin	Third-generation cephalosporin
Gram-positive bacilli	*Propionibacterium acnes*	Penicillin G	Nafcillin Vancomycin

Reprinted with permission from Rao N, Esterhai JL Jr: Septic arthritis. In Cierny G 3rd, McLaren AC, Wongworawat MD (eds): Orthopaedic Knowledge Update: Musculoskeletal Infection. Rosemont, Ill, American Academy of Orthopaedic Surgeons, 2009, 159. Modified from Hughes RA, Keat AC: Reiter syndrome and reactive arthritis: A current view. Semin Arthritis Rheum 24:190-210, 1994.

www.ketabpezeshki.com 66485457-66963820

determine the need for further procedures. If Gram's stain of the synovial fluid is negative but the clinical appearance strongly suggests septic arthritis, the patient is treated with appropriate antibiotics and admitted to the hospital while culture results are awaited. If the joint fluid aspirate is not consistent with septic arthritis and clinical findings are equivocal, the patient can be discharged and reevaluated in 24 hours. In immunosuppressed patients, patients with preexisting joint disease, and patients with joint replacements, septic arthritis can be difficult to detect. A conservative approach with in-hospital observation and treatment should be considered if there is any possibility of septic arthritis in these patients.

The prognosis for the patient with septic arthritis is favorable in most cases. From 50 to 75% of afflicted patients can expect to recover completely and to achieve full, painless range of motion of the afflicted joint. In approximately one third of cases there is decreased mobility or ankylosis, pain on joint movement, chronic infection, or overwhelming sepsis and death. Those patients most likely to do poorly include those who have a delay in diagnosis and treatment, patients with underlying joint disease (especially rheumatoid arthritis), those with polyarticular septic arthritis, and those who have positive blood cultures. Despite many advances in diagnosis and treatment, the overall morbidity for patients with septic arthritis has not decreased in the last two decades. A general rule is that if the diagnosis of septic arthritis is made and treatment is initiated within 1 week of the onset of symptoms, the outcome is almost always favorable. Delays to treatment beyond 1 week of symptoms are associated with worse outcomes. Diagnosis and rapid treatment of septic arthritis prove to be most elusive in two groups of patients: infants and people with existing joint disease. In infants and children, early symptoms can be nonspecific and difficult to assess; consequently, children with septic arthritis, especially of the hip, who experience a delay in diagnosis and treatment have a disappointingly high rate of complications. In patients with existing joint disease, septic arthritis may be mistaken for an acute exacerbation of the underlying disease process, so physicians must remain vigilant in their pursuit of the correct diagnosis.

KEY CONCEPTS

- Skeletal infection should be considered in the differential diagnosis of all patients who present with bone or joint pain. In those cases in which a bone or joint infection exists, early diagnosis and treatment can have a potent impact on the long-term morbidity.
- The vascular anatomy of long bones changes throughout life. In infants and adults, vascular connections exist between the metaphysis and epiphysis, which allow extension of bone infection into the joint. In children, the epiphyseal plate prevents this from happening.
- The diagnostic evaluation for septic arthritis includes complete blood count, ESR, and CRP level. Joint aspiration is the definitive diagnostic procedure, and synovial culture is the only reliable joint fluid test in establishing a diagnosis. The diagnosis of osteomyelitis involves an operative culture of the infected bone. MRI has evolved to be the best diagnostic modality to detect osteomyelitis.
- Hematologic evaluation is of little value in diagnosis of bone and joint infections, with the exception of the ESR and CRP level, which are elevated in approximately 90% of cases of bone and joint infections.
- When clinical findings suggest the presence of a bone or joint infection, antibiotic treatment should not be delayed. With suspected septic arthritis, joint fluid and blood culture specimens are obtained before intravenous antibiotics are administered. With suspected osteomyelitis, blood culture specimens are obtained, and intravenous antibiotics are administered while plans are made for further imaging studies or surgical aspiration or resection of bone.
- The most important aspect of antibiotic treatment of suspected bone and joint infections is to provide potent bactericidal activity against *S. aureus* with additional empirical antibiotic coverage aimed at suspected organisms on the basis of age, risk factors, and regional variability.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Cunning J, Joll C: *Aids to Surgery*, 4th ed. New York: William Wood; 1919.
2. Conrad D: Acute hematogenous osteomyelitis. *Pediatr Rev* 2010; 31:464-471.
3. Masuko-Hongo K, Kato T, Nishioka K: Virus-associated arthritis. *Best Pract Res Clin Rheumatol* 2003; 17:309-318.
4. Clarke B: Normal bone anatomy and physiology. *Clin J Am Soc Nephrol* 2008; 3(Suppl 3):S131-S139.
5. Costerton J: *The Biofilm Primer*. New York: Springer; 2007.
6. Kannikeswaran N, Kamat D: Mammalian bites. *Clin Pediatr (Phila)* 2009; 48:145-148.
7. Kapoor M, et al: Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat Rev Rheumatol* 2011; 7:33-42.
8. Mandal S, Berendt A, Peacock S: *Staphylococcus aureus* bone and joint infection. *J Infect* 2002; 44:143-151.
9. Ceroni D, et al: *Kingella kingae* osteoarticular infections in young children: Clinical features and contribution of a new specific real-time PCR assay to the diagnosis. *J Pediatr Orthop* 2010; 30:301-304.
10. Brook I: Joint and bone infections due to anaerobic bacteria in children. *Pediatr Rehabil* 2002; 5:11-19.
11. Mohammadi A, Howell J: Sternal tuberculosis. *J Emerg Med* 2009; 36:342-344.
12. Maschmeyer G: The changing epidemiology of invasive fungal infections: New threats. *Int J Antimicrob Agents* 2006; 27(Suppl 1):3-6.
13. Vazquez M: Osteomyelitis in children. *Curr Opin Pediatr* 2002; 14:112-115.
14. Paakkonen M, et al: Sensitivity of erythrocyte sedimentation rate and C-reactive protein in childhood bone and joint infections. *Clin Orthop Relat Res* 2010; 468:861-866.
15. Cavanaugh P, et al: Treatment for diabetic foot ulcers. *Lancet* 2005; 366:1725-1735.
16. Jurado R: Why shouldn't we determine the erythrocyte sedimentation rate? *Clin Infect Dis* 2001; 33:548-549.
17. Pineda C, Vargas A, Rodríguez A: Imaging of osteomyelitis: Current concepts. *Infect Dis Clin North Am* 2006; 20:789-825.
18. Copley L: Pediatric musculoskeletal infection: Trends and antibiotic recommendations. *J Am Acad Orthop Surg* 2009; 17:618-626.
19. Averill L, et al: Diagnosis of osteomyelitis in children: Utility of fat-suppressed contrast-enhanced MRI. *AJR Am J Roentgenol* 2009; 192:1232-1238.
20. Lalam R, Cassar-Pullicino V, Tins B: Magnetic resonance imaging of appendicular musculoskeletal infection. *Top Magn Reson Imaging* 2007; 18:117-191.
21. Hendrickx L, et al: Candidal vertebral osteomyelitis: Report of 6 patients, and a review. *Clin Infect Dis* 2001; 32:527-533.
22. Tay B, Deckey J, Hu S: Spinal infections. *J Am Acad Orthop Surg* 2002; 10:188-197.
23. Mylona E, et al: Pyogenic vertebral osteomyelitis: A systematic review of clinical characteristics. *Semin Arthritis Rheum* 2009; 39:10-17.
24. Zimmerili W: Vertebral osteomyelitis. *N Engl J Med* 2010; 362:1022-1029.
25. Palestro C, Love C, Miller T: Infection and musculoskeletal conditions: Imaging of musculoskeletal infections. *Best Pract Res Clin Rheumatol* 2006; 20:1197-1218.
26. Gross T, et al: Current concepts in posttraumatic osteomyelitis: A diagnostic challenge with new imaging options. *J Trauma* 2002; 52:1210-1219.
27. Leone J, Hanssen A: Management of infection at the site of a total knee arthroplasty. *Instr Course Lect* 2006; 55:449-461.
28. Hanssen A: Infected hip arthroplasty: "Maximizing its solution: once burned, twice learned". *Orthopedics* 2006; 29:799-800.
29. Lavery L, et al: Probe-to-bone test for diagnosing diabetic foot osteomyelitis: Reliable or relic? *Diabetes Care* 2007; 30:270-274.
30. Zuluaga A, et al: Etiologic diagnosis of chronic osteomyelitis: A prospective study. *Arch Intern Med* 2006; 166:95-100.
31. Ejindu V, et al: Musculoskeletal manifestations of sickle cell disease. *Radiographics* 2007; 27:1005-1021.
32. Wong A, Sakamoto K, Johnson F: Differentiating osteomyelitis from bone infarction in sickle cell disease. *Pediatr Emerg Care* 2001; 17:60-63.
33. Gelfand M, et al: Pathological fracture in acute osteomyelitis of long bones secondary to community-acquired methicillin-resistant *Staphylococcus aureus:* Two cases and review of the literature. *Am J Med Sci* 2006; 332:357-360.
34. Cierny G, Mader JT, Pennick JJ: A clinical staging for adult osteomyelitis. *Clin Orthop Relat Res* 2003; 414:7-24.
35. Levy J, et al: Treatment of bone and joint infections: Recommendations of a Belgian panel. *Acta Orthop Belg* 2000; 66:127-136.
36. Wang C, et al: Hyperbaric oxygen for treating wounds: A systematic review of literature. *Arch Surg* 2003; 138:272-279.
37. Ahmed R, Severson M, Traynelis V: Role of hyperbaric oxygen therapy in the treatment of bacterial spinal osteomyelitis. *J Neurosurg Spine* 2009; 10:16-20.
38. Shields R, et al: Hyperbaric oxygen therapy for chronic refractory osteomyelitis of the sternum. *Ann Thoac Surg* 2010; 89:1661-1663.
39. Nade S: Septic arthritis. *Best Pract Res Clin Rheumatol* 2003; 17:183-200.
40. Smith J, Chalupa P, Shabaz H: Infectious arthritis: Clinical features, laboratory findings and treatment. *Clin Microbiol Infect* 2006; 12:309-314.
41. Faraj A, Omonbude O, Godwin P: Gram staining in the diagnosis of acute septic arthritis. *Acta Orthop Belg* 2002; 68:388-391.
42. Leet A, Skaggs D: Evaluation of the acutely limping child. *Am Fam Physician* 2000; 61:1011-1018.
43. Gallagher E: Evidence-based emergency medicine/editorial. The problem with sensitivity and specificity. *Ann Emerg Med* 2003; 42:298-303.
44. Hariharan P, Kabrhel C: Sensitivity of erythrocyte sedimentation rate and C-reactive protein for the exclusion of septic arthritis in emergency department patients. *J Emerg Med* 2011; 40:428-431.
45. Li S, et al: Laboratory tests in adults with monoarticular arthritis: Can they rule out a septic joint? *Acad Emerg Med* 2004; 11(3):276-280.
46. Li S, et al: Diagnostic utility of laboratory tests in septic arthritis. *Emerg Med J* 2007; 24:75-77.
47. Hügle T, et al: Serum procalcitonin for discrimination between septic and non-septic arthritis. *Clin Exp Rheumatol* 2008; 26:453-456.
48. Charalambous C, et al: Septic arthritis following intra-articular steroid injection of the knee—a survey of current practice regarding antiseptic technique used during intra-articular steroid injection of the knee. *Clin Rheumatol* 2003; 22:386-390.
49. Bardin T: Gonococcal arthritis. *Best Pract Res Clin Rheumatol* 2003; 17:201-208.
50. McGillicuddy D, et al: How sensitive is the synovial fluid white blood cell count in diagnosing septic arthritis? *Am J Emerg Med* 2007; 25:749-752.
51. Margaretten M, et al: Does this adult patient have septic arthritis? *JAMA* 2007; 297:1478-1488.
52. Learch T, Farooki S: Magnetic resonance imaging of septic arthritis. *Clin Imaging* 2000; 24:236-242.
53. Li X, et al: Evaluation of the modified Albee arthroplasty for femoral head loss secondary to septic arthritis in young children: Surgical technique. *J Bone Joint Surg Am* 2011; 93(Suppl 1):54-61.
54. Bytyçi C, Qorraj H, Bytyqi D: Treatment of neonatal septic arthritis sequelae of hip: A case report. *Cases J* 2009; 1:6332.
55. Scillia A, et al: Primary osteomyelitis of the acetabulum resulting in septic arthritis of the hip and obturator internus abscess diagnosed as acute appendicitis. *J Pediatr Surg* 2010; 45:1707-1710.
56. Wang E, et al: Psoas abscess with associated septic arthritis of the hip in infants. *J Pediatr Surg* 2010; 45:2440-2443.
57. Molloy A, et al: The complications of septic arthritis in the elderly. *Aging Clin Exp Res* 2010; 22:270-273.
58. Caksen H, et al: Septic arthritis in childhood. *Pediatr Int* 2000; 42:534-540.
59. Ross J, et al: Pneumococcal septic arthritis: Review of 190 cases. *Clin Infect Dis* 2003; 36:319-327.
60. Forlin E, Milani C: Sequelae of septic arthritis of the hip in children: A new classification and a review of 41 hips. *J Pediatr Orthop* 2008; 28:524-528.
61. Sultan J, Hughes P: Septic arthritis or transient synovitis of the hip in children: The value of clinical prediction algorithms. *J Bone Joint Surg Br* 2010; 92:1289-1293.
62. Centers for Disease Control and Prevention: Update to CDC's sexually transmitted diseases treatment guidelines, 2006: Fluoroquinolones no longer recommended for treatment of gonococcal infections. *MMWR Morb Mortal Wkly Rep* 2007;56: 332-336.
63. Bacon R, Kugeler K, Mead P: Surveillance for Lyme disease—United States, 1992-200. *MMWR Surveill Summ* 2008; 57:1-9.
64. Puius Y, Kalish R: Lyme arthritis: Pathogenesis, clinical presentation, and management. *Infect Dis Clin North Am* 2008; 22:289-300, vi-vii.
65. Lyme disease (Borrelia burgdorferi). Available at www.cdc.gov/ncphi/disss/nndss/casedef/lyme_disease_2008.htm.
66. Milewski M, et al: Lyme arthritis in children presenting with joint effusions. *J Bone Joint Surg Am* 2011; 93:252-260.

www.ketabpezeshki.com 66485457-66963820

67. Feder H, et al: A critical appraisal of "chronic Lyme disease". *N Engl J Med* 2007; 357:1422-1430.
68. Della Valle C, et al: Diagnosis of periprosthetic joint infections of the hip and knee. *J Am Acad Orthop Surg* 2010; 18:760-769.
69. Kurtz S, et al: Prosthetic joint infection risk after TKA in the Medicare population. *Clin Orthop Relat Res* 2010; 468:52-56.
70. Greidanus N, et al: Use of erythrocyte sedimentation rate and C-reactive protein level to diagnose infection before revision total knee arthroplasty: A prospective evaluation. *J Bone Joint Surg Am* 2007; 89:1409-1416.
71. Ghanem E, et al: Cell count and differential of aspirated fluid in the diagnosis of infection at the site of total knee arthroplasty. *J Bone Joint Surg Am* 2008; 90:1637-1643.
72. Edwards C, et al: The importance of the disease process and disease-modifying anti-rheumatic drug treatment in the development of septic arthritis in patients with rheumatoid arthritis. *Arthritis Rheum* 2007; 57:1151-1157.
73. Yu K, et al: Concomitant septic and gouty arthritis—an analysis of 30 cases. *Rheumatology (Oxford)* 2003; 42:1062-1066.
74. Frazee B, Fee C, Lambert L: How common is MRSA in adult septic arthritis? *Ann Emerg Med* 2009; 54:695-700.
75. Farley M: Group B streptococcal disease in nonpregnant adults. *Clin Infect Dis* 2001; 33:556-561.
76. Harel L, et al: Dexamethasone therapy for septic arthritis in children: Results of a randomized double-blind placebo-controlled study. *J Pediatr Orthop* 2011; 31:211-215.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 137

SKIN AND SOFT TISSUE INFECTIONS

Daniel J. Pallin and Denise Nassisi

PERSPECTIVE

Background and Epidemiology

Skin infections are among the most common problems treated by emergency physicians. In 2005 bacterial skin infections accounted for 3% of all emergency department (ED) visits in the United States, with more than 3,400,000 visits in that year alone.[1]

While treating many patients with mild skin infections, the emergency physician is vigilant for the rare occurrence of life threatening variants, such as necrotizing fasciitis. The epidemiology of skin infections has changed in the past decade with the emergence of a new organism, community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA). Unlike most streptococci, *S. aureus* has usually been resistant to penicillin since penicillin was first commercialized because of the production of a β-lactamase (also known as penicillinase) enzyme that cleaves the penicillin molecule.[2] Penicillinase-resistant penicillins typified by methicillin were developed in 1959, but strains of *S. aureus* resistant to these agents (MRSA) were identified by 1960.[2] Resistance is due to an altered bacterial target, the cell wall building enzyme known as penicillin-binding protein.

A new strain was identified in Chicago in the mid-1990s. It was characterized by resistance to methicillin and related antimicrobials but susceptibility to agents ineffective against the older "nosocomial MRSA"; it could not be traced to the hospital environment.[3] The DNA fingerprinting technique known as pulsed-field gel electrophoresis identified the predominant CA-MRSA strain as USA-300.[4] In contrast, the older nosocomial strain of MRSA is known as USA-100.

A large, nationwide, ED-based study found CA-MRSA to be the leading identifiable cause of skin infections among ED patients.[5] The number of ED visits for skin and soft tissue infections increased from 1.2 million in 1993 to more than 3.4 million in 2005; whether this was due to an increase in abscess, cellulitis, or both is unknown.[1] Intriguingly, whereas CA-MRSA is now found in all populations of patients and in health care and community settings alike, the epidemic of skin infections it has caused is most apparent among ED patients for reasons that remain unclear.[6] These data are summarized in Figure 137-1.

PRINCIPLES OF DISEASE

Anatomy and Physiology

The skin is the largest organ in the body and accounts for about 15% of total body weight.[7] It has three layers, the hypodermis, the dermis, and the epidermis (Fig. 137-2). Hair is present throughout except on glabrous skin, which is the heavily keratinized skin found on the palms, soles, and parts of the genitals.

The skin has a rich supply of blood vessels, lymphatics, and nerves, although the epidermis is entirely avascular and relies on the dermis for nourishment. Lymphatics drain interstitial fluid, and their disruption leads to interstitial fluid accumulation and edema. The main cell type in the epidermis is the keratinocyte, which has a cytoskeleton composed of keratin filaments, which are proteins. Also living in the epidermis is the Langerhans cell, a motile macrophage-like antigen-presenting member of the immune system that originates in the bone marrow. Melanocytes in the epidermis produce melanin in response to ultraviolet light–induced DNA damage.

The epidermis contains the pilosebaceous follicles and the sweat glands, known collectively as epidermal appendages. The combination of the hair apparatus and the sebaceous gland is known as a pilosebaceous follicle. The epidermal appendages are important as sites of infection because they provide a break in the otherwise continuous protective layer of keratinocytes and a potential space for bacterial replication. There are two types: sweat glands and follicles. Sweat glands take three forms: eccrine, apocrine, and apoeccrine.

The dermal-epidermal junction is a complex basement membrane whose disruption results in vesicles and bullae. The dermis consists of cells, fibers, and ground substance, which is an acellular material composed of glycoproteins and other macromolecules.[7] The hypodermis, or subcutaneous tissue, is composed largely of adipocytes.

Pathophysiology

Many skin infections arise from breaks in the protective epidermal layer, known as portals of entry. Hematogenous seeding is another common source. Often the source is not clear. When the pilosebaceous follicle becomes obstructed, sebum provides a site for bacterial multiplication, resulting in folliculitis or abscess. Venous blood and lymph drain from the orbits and the skin around them into the cavernous sinuses, and thus bacterial infections in this area can lead to central nervous system infection.

CLINICAL FEATURES

Symptoms and Signs

Most skin infections are present with redness, a symptom, and its corresponding sign, erythema. Erythema is difficult to see in darkly pigmented people. The cause of erythema is microvascular dilation due to the immune response. Confluent erythema is typical of most skin infections; discrete macules and morbilliform (measles-like) eruptions are not typical. Well-demarcated erythema with a raised border, particularly on the face, is typical of

www.ketabpezeshki.com 66485457-66963820

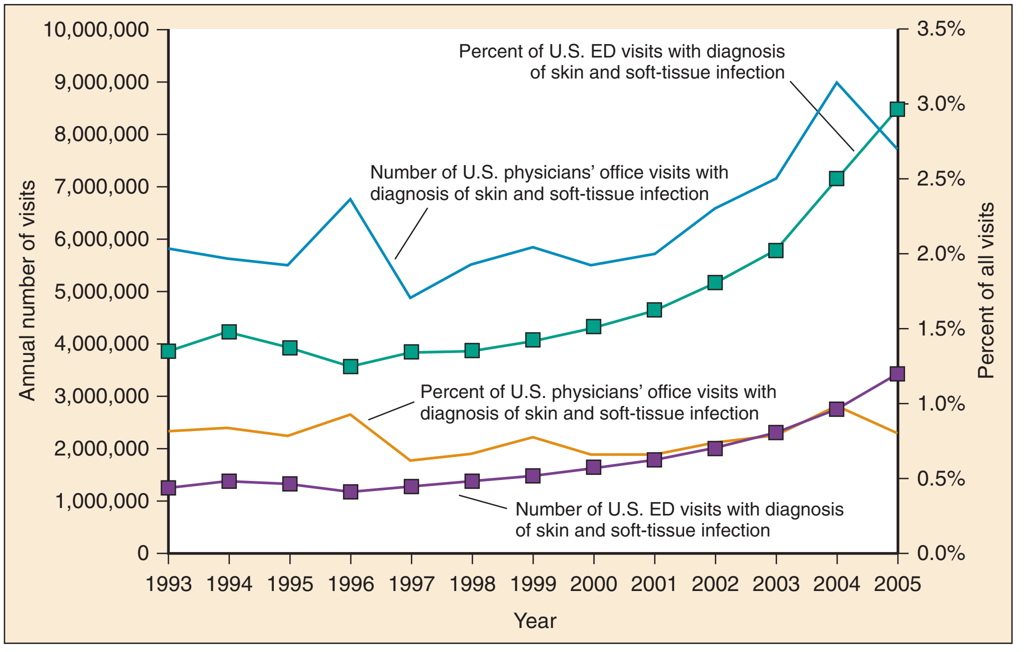


Figure 137-1. Epidemiology of skin and soft tissue infections in U.S. emergency department (ED) and physicians' office visits. Numbers of visits increased in both EDs and offices because of population growth and other factors, but the proportion of all visits attributable to skin infections increased only in EDs. (Modified from Pallin DJ, Espinola JA, Leung DY, Hooper DC, Camargo CA Jr: Epidemiology of dermatitis and skin infections in United States physicians' offices, 1993-2005. Clin Infect Dis 49:901-907, 2009.)

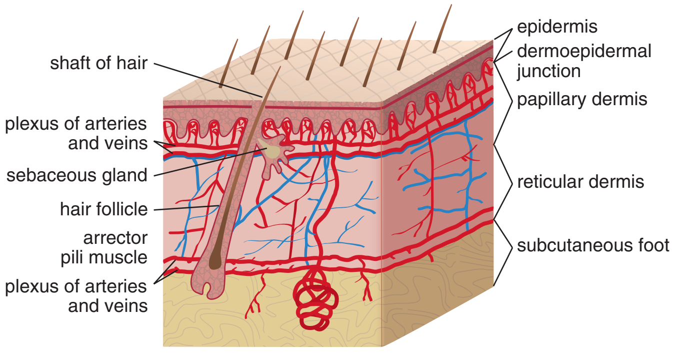


Figure 137-2. Anatomy of the skin. (From Amirlak B: Skin anatomy. Available at http://emedicine.medscape.com/article/1294744-overview#a1. Accessed April 15, 2011.)

erysipelas, a streptococcal cellulitis. Linear erythema tracking from distal to proximal along a vascular pathway suggests lymphangitis or phlebitis and usually represents the action of cytokines involved in combating the infection, although proximal spread of the infection itself is a possibility.

Less common color changes associated with infection stem from small hemorrhages, vasculitis, or septic emboli. Janeway's lesions are painless red, purple, or brown spots, usually seen on the hands or feet, due to septic emboli from infective endocarditis. Painless discolorations of the palms and soles should also trigger concern for secondary syphilis or Rocky Mountain spotted fever. When the diagnosis of infection is not clear, vasculitides such as Kawasaki syndrome in children and Wegener's granulomatosis should be considered. Petechiae and purpura can reveal overwhelming bacterial infection, as with meningococcemia. Vesicles suggest contact dermatitis, herpes simplex, varicella-zoster, or impetigo. Intracutaneous pustules on the palms or soles of the feet are often due to a form of psoriasis called palmoplantar pustulosis, which is troublesome but benign.

Pruritic serpiginous (snakelike) lesions that are not particularly tender suggest an intracutaneous parasite, such as scabies (hands, intertriginous areas), hookworm larvae (feet or buttocks), or strongyloidiasis. Parasitic nematodes (Guinea worm) and insects (botfly) should be considered in the setting of a nodule after exposure to fresh water or insects in developing countries. Induration simply means hardening and is a common finding with many inflammatory lesions of the skin. Skin that is indurated because of cellulitis sometimes becomes engorged with interstitial fluid and takes on the texture of an orange peel. This classic finding is known by the French phrase *peau d'orange,* that is, "orange peel skin."

Fluctuance describes a fluid collection palpated on examination. "Pointing" or "coming to a head" conveys a sense of imminent rupture. Crepitance describes skin that feels crackly when it is palpated and suggests that gas is present in the soft tissues. This suggests necrotizing infection, discussed later.

Fever is present in half of patients with bacterial skin infections presenting to the ED.[1] Febrile skin infections are more common in children; in adults, fever may indicate a more serious infection.

Skin infections can suggest underlying systemic illness. For example, a young man who presents with a first episode of balanitis may have diabetes as the underlying problem. Disseminated varicella (other than a first episode of chickenpox) suggests immunocompromise. Janeway's lesions and splinter hemorrhages suggest endocarditis.

DIAGNOSTIC STRATEGIES

For cellulitis and abscess, the only relevant laboratory test is a wound culture and Gram's stain when pus is present. However, there is debate about the necessity of obtaining culture specimens from skin infections.[8,9] A culture is prudent for complicated purulent infections, such as surgical wound infections that may involve deep structures or abscesses in immunocompromised patients. Uncomplicated skin abscesses are usually caused by CA-MRSA, and the need for culture is debatable. Nonpurulent cellulitis is not routinely cultured because of low yield.[10] A stat Gram's stain can be helpful in the setting of diagnostic uncertainty.

Blood cultures are not indicated in patients with skin infection, with the following exceptions: septic shock, necrotizing infections,

www.ketabpezeshki.com 66485457-66963820

immunocompromise, multifocal infections suggesting hematogenous seeding, and infections complicating lymphedema. Early studies found pediatric facial cellulitis often to be accompanied by *Haemophilus influenzae* bacteremia.[11,12] However, the relevant strain is type b, which is now covered by childhood vaccination. Moreover, this organism is typically be targeted presumptively in treatment of facial cellulitis, and there is no evidence that blood culture is of benefit.

When a foreign body is suspected, plain radiographs are traditional, although they will miss foreign bodies that are small or radiolucent. Plain radiographs may reveal soft tissue gas but do not rule out necrotizing infection. Ultrasonography is promising for detection of foreign bodies associated with infection.[11] Ultrasonography can also identify gas, which suggests necrotizing infection. Ultrasound examination is useful for differentiation of abscess from cellulitis, as discussed later.[12]

Plain radiographs are used to seek evidence of osteomyelitis for chronic skin infections, especially in patients with diabetes, peripheral vascular disease, and secondarily infected nonhealing ulcers. Plain films are not definitive, and bone scanning and magnetic resonance imaging (MRI) have higher sensitivity for osteomyelitis.

Computed tomography (CT) scanning is often used when a necrotizing infection is considered, although its sensitivity has not been quantified. CT is also helpful when there is concern that a skin infection is actually an extension of a deeper infection, such as after surgery or in the case of recurrent perianal abscesses.

Skin scrapings for microscopy are key to the accurate diagnosis of some infections, including scabies, varicella, herpes simplex, tinea, candidiasis, and leishmaniasis. When necrotizing infection is clinically suspected, operative inspection by a surgeon is considered the definitive "rule-out" procedure.

CELLULITIS

Perspective

Cellulitis is an inflammatory abnormality of skin and subcutaneous tissue thought to be the result of bacterial infection.[10] Cellulitis may be purulent or nonpurulent and may occur in the setting of wounds, foreign bodies, or impaired perfusion. Purulent cellulitis drains freely, in contrast to abscesses, which are walled off by fibrous tissue and epidermis. CA-MRSA is the leading cause of purulent skin and soft tissue infections in ED patients, but its role in nonpurulent cellulitis is unknown.[1,5,6,10,13]

Principles of Disease and Clinical Features

The cardinal feature of cellulitis is inflammation due to increased local blood flow. In darkly pigmented patients, inflammation may be subtle. Pain is variable. The inflammation of cellulitis is typically confluent, although it may be patchy. The borders are typically well defined but irregular, and linear or circular lesions should prompt a search for other underlying causes (such as contact dermatitis or Lyme disease). In some cases of cellulitis, there are streaks of inflammation extending proximally from the main area of inflammation, along vascular tracts. This finding is known as lymphangitis and is commonly seen with cellulitis due to streptococci and bite wound–associated *Pasteurella multocida*.

When localized edema becomes severe, separation of epidermal layers can occur, leading to vesicles or bullae. This can make it difficult to distinguish cellulitis from other infectious and noninfectious causes of dermatitis. When the border of an area of cellulitis becomes well demarcated, raised, and palpable, the term *erysipelas* is used. This form of cellulitis is most often caused by *Streptococcus pyogenes*. The bacterial causes of cellulitis vary according to body site, comorbidities, and environmental exposures (see Table 137-2).[10]

Diabetic Foot Infections

Diabetic foot infections are the most common cause of hospitalization for patients with diabetes, and an infected wound precedes two thirds of lower extremity amputations in patients with diabetes.[14] Neuropathy, vascular insufficiency, and hyperglycemia are important factors in the development of diabetic ulcers and foot infections. Nonetheless, it is important to avoid antibiotic overuse, and uninfected ulcers should not be treated with antibiotics.

The most likely organisms in an acute diabetic foot infection are *S. aureus* and streptococci. Chronic wounds are more likely to be polymicrobial with both Gram-positive and Gram-negative organisms as well as anaerobes. Chronic wounds that have previously been treated with antimicrobials are more likely to involve multidrug-resistant organisms.[15] *Pseudomonas* is a traditional concern but is not common.[16] Deep tissue for aerobic and anaerobic culture or bone samples for biopsy should be obtained at the time of débridement if deep tissue infection or osteomyelitis is suspected, but organisms cultured from superficial swabs are not reliable for predicting the pathogens responsible for deeper infection. Osteomyelitis should be considered a potential complication of any deep or extensive ulcer, especially one that is chronic or overlies a bone prominence. In addition to antibiotics, diabetic foot infections require careful wound care and in some cases débridement, revascularization, or amputation.

Bite Wounds

A high proportion of cat bites become infected, and presumptive antibiotic treatment is appropriate in the absence of signs of infection. The typical agent is *P. multocida*. Human bites also become infected frequently, and oral anaerobes are typical. Dog bites become infected infrequently and may be cleansed and observed or treated presumptively; antibiotics are recommended for sutured bites. Amoxicillin–clavulanic acid is an appropriate agent for cat and human bites and for infected or sutured dog bites.

Water-borne Infections

Exposure and travel history are important considerations in the evaluation of skin and soft tissue infections. *Vibrio* species, in particular *Vibrio vulnificus,* are associated with exposure to seawater and can cause severe soft tissue infections.[17] Patients with liver disease, such as cirrhosis, are at risk. Infection occurs from contamination of open wounds by seawater or shellfish and rarely by hematogenous spread from ingestion of contaminated seafood such as raw oysters. *Edwardsiella tarda* is a rare cause of wound infection after seawater exposure; it has been implicated in serious soft tissue infections including myonecrosis, particularly in patients with liver disease. *Erysipelothrix rhusiopathiae* is usually associated with a localized erysipeloid eruption with minor trauma, often on the hands of seafood workers.

Aeromonas myonecrosis is associated with exposure to fresh water by either penetrating trauma or exposure to aquatic animals. It causes rapidly progressive suppurative infections that often require surgical drainage. *Mycobacterium marinum* causes "fish tank granuloma." It typically is manifested weeks after exposure as a papule or nodule that may ulcerate and drain serosanguineous fluid. Multiple nodular lesions may develop along the lymphatics.

Differential Considerations and Diagnostic Strategies

When lymphangitis and fever are present, a bacterial infection is probable. In the absence of these signs, other possibilities include contact dermatitis, ringworm, burns, viral infections, and allergies

www.ketabpezeshki.com 66485457-66963820

Table 137-1 First-Line Oral Antibiotics for Skin and Soft Tissue Infection

DRUG	BACTERIOSTATIC (S), BACTERICIDAL (C), OR VARIABLE (V)	SITE OF ACTION	PEDIATRIC DOSE (mg/kg; adult dose is max)	ADULT DOSE (mg)	FREQUENCY (doses per day)	SPECIAL INSTRUCTIONS
Cephalexin	C	Cell wall synthesis	25	500-1000	4	
Dicloxacillin	C	Cell wall synthesis	10	250-500	4	Empty stomach
Amoxicillin	C	Cell wall synthesis	15	500	3	
Amoxicillin–clavulanic acid	C	Cell wall synthesis	30	875 or 2000 for extended release formulation*	2	
Clindamycin	S	Ribosome	6	300-450	3	
Trimethoprim-sulfamethoxazole	S	DNA synthesis (folate metabolism)	10†	1600	2	
Doxycycline	S	Ribosome	—	100	2	Empty stomach, sun sensitivity

*Dose by amoxicillin component.
†Dose by trimethoprim.
CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus*; *MRSA*, methicillin-resistant *S. aureus*; *MSSA*, methicillin-sensitive *S. aureus*.

including fixed drug eruptions, which can manifest with localized inflammation. Cellulitis must be distinguished from more severe necrotizing infections, discussed later. Consider Lyme cellulitis in endemic areas.

Needle aspiration and even biopsy of cellulitis lesions are unlikely to reveal the etiology and are not recommended.[10] Blood cultures are not recommended except in the presence of a presumed hematogenous source of infection, in septic shock, and in cellulitis complicating lymphedema. Blood cultures are also traditional for facial cellulitis but may be omitted in well-appearing patients who are treated with agents active against *H. influenzae*.[18] The role of high-sensitivity pathogen identification, such as polymerase chain reaction analysis of surface skin swabs, has yet to be determined.

Venous stasis dermatitis is similar to cellulitis but is not infectious in origin. It is typically located above the ankle and is often (but not always) circumferential. When above-the-ankle dermatitis is accompanied by fever, cellulitis may be present, but other causes of fever should be sought, especially if the inflammation is bilaterally symmetrical. Symmetrical venous stasis dermatitis in the afebrile patient should not be confused with cellulitis. When there is inflammation near a joint, the differential includes gout, pseudogout, septic arthritis, tenosynovitis, Baker's cyst, traumatic joint effusion, hemarthrosis, and autoimmune arthritis.

Management

Emergency physicians have changed their prescribing practices dramatically since CA-MRSA was first described.[1] In 1993, antibiotics targeted to CA-MRSA were almost never prescribed for skin and soft tissue infections. By 2005, 38% of antibiotic regimens included an agent typically active against CA-MRSA. Multiple studies have shown that antibiotics do not make a difference in the treatment of abscess, and the effectiveness of agents targeting CA-MRSA in nonpurulent skin infections (i.e., cellulitis) is unknown.

Table 137-1 summarizes relevant antibiotics. Oral agents with activity against CA-MRSA include trimethoprim-sulfamethoxazole, clindamycin, tetracyclines, and linezolid. The common strains of CA-MRSA (i.e., USA-300) are almost universally susceptible to trimethoprim-sulfamethoxazole in vitro. It is well tolerated and causes severe reactions like Stevens-Johnson syndrome no more commonly than do other agents, such as ampicillin. However, it is not considered effective against streptococci. Thus, when CA-MRSA is suspected but streptococci remain a possibility, the best therapy is most likely trimethoprim-sulfamethoxazole plus a β-lactam such as cephalexin or clindamycin monotherapy.[18]

Dicloxacillin is commonly suggested as an agent for treatment of cellulitis because of its appropriate spectrum and high potency. However, it must be taken four times daily on an empty stomach—a very challenging task—and causes gastrointestinal upset. Doxycycline is another option for coverage of CA-MRSA. However, this agent must also be taken on an empty stomach and causes gastrointestinal upset. Moreover, it is not thought to cover streptococci well.[18] As with trimethoprim-sulfamethoxazole, when doxycycline is prescribed for skin and soft tissue infections, a β-lactam should be added to target streptococci unless the etiology of the infection is known. Doxycycline causes photosensitivity, and patients should be warned to avoid sun exposure.

Clindamycin is an important agent because most CA-MRSA isolates are sensitive to it, and it is an excellent agent for streptococci. It can be taken with food. CA-MRSA can become resistant to clindamycin during a single course of treatment. This phenomenon is known as inducible resistance and occurs in about 2% of CA-MRSA isolates.[5,19] Most microbiology laboratories in the United States now test for inducible resistance among MRSA strains that are susceptible to clindamycin in vitro. The test for inducible resistance is known as the D-test. The name comes from a D-shaped pattern of the area of clindamycin's inhibition of bacterial growth, which results from resistance induced by a pellet ("disk") of erythromycin that is placed next to the clindamycin pellet.[20]

Early reports of susceptibility of CA-MRSA to rifampin gave way to later reports of widespread resistance, both inducible and de novo. This agent is not recommended for skin infections.[18]

Vancomycin is the standard parenteral agent for MRSA. Others include linezolid, daptomycin, tigecycline, and telavancin. No penicillin or cephalosporin is active against CA-MRSA, except ceftaroline, a parenteral cephalosporin approved by the U.S. Food

www.ketabpezeshki.com 66485457-66963820

COMMONLY SEEN MAJOR NONALLERGIC CONTRAINDICATIONS	STREPTOCOCCUS	MSSA	CA-MRSA (USA-300)	NOSOCOMIAL MRSA (USA-100)	ANAEROBES	ENTEROBACTERIACEAE
	+	+	−	−	−	±
	+	+	−	−	−	−
	+	+	−	−	±	±
	+	+	−	−	+	+
	+	+	+	±	±	−
Coumadin, glucose-6-phosphate dehydrogenase, or folate deficiency	−	+	+	±	±	±
	±	+	+	±	−	±

and Drug Administration in 2010 and indicated for complicated skin infections.[21]

Nonpurulent cellulitis is treated with coverage for streptococci and methicillin-sensitive *S. aureus*. When the infection is purulent, a culture and Gram's stain may be performed and coverage for CA-MRSA provided. Otherwise, agents effective against CA-MRSA are not recommended except in cases not initially responsive to first-line therapy and when septic shock is present.[18] The first-line agent is cephalexin, which is safe, well tolerated, and well absorbed and need not be taken on an empty stomach. Inadequate dosing and failure to adhere to recommended adjunctive measures may lead to treatment failure. Relatively severe infections may be managed with one or more initial doses of the intravenous equivalent cefazolin, which, like cephalexin, should be given in maximal doses (e.g., 2 g every 8 hours for adults). Nafcillin is an equivalent option. In patients allergic to cephalexin, clindamycin is an excellent choice. Table 137-2 provides further treatment recommendations.

Adjunctive measures are important in the treatment of cellulitis. Extremity cellulitis responds dramatically to compression and elevation. The extremity should be elevated above the level of the heart. A splint is useful as an anchor for elevation and can be hung from an intravenous pole. Patients with cellulitis complicating venous stasis or lymphedema should be educated about the importance of compression not only for the acute infection but also to prevent future episodes. Nonsteroidal anti-inflammatory agents (e.g., ibuprofen) are effective and should not be forgotten.[22] As stated before, many cases of cellulitis treatment failure may be due to failure to adhere to these adjunctive measures rather than antibiotic choice.

Figure 137-3 is a universal treatment algorithm for skin and soft tissue infections. The algorithm assumes no prior treatment and no toxic shock syndrome. Previously treated infections require broader spectrum antibiotic coverage and customized management decisions.

Disposition

Immunocompetent cellulitis patients who can be trusted to adhere to recommended medications and adjunctive measures can be managed as outpatients. In severe cases, one or more initial intravenous doses are often given in the setting of an ED observation unit. Hospitalization is generally required for immunosuppressed patients and patients with diabetic foot infections, infected lymphedema, and multifocal cellulitis or suspected necrotizing infection.

ABSCESS

Principles of Disease and Clinical Features

Historically, abscesses were usually caused by methicillin-sensitive *S. aureus* or mixed flora, but by 2004, CA-MRSA accounted for 61% of abscesses.[5] An abscess begins when bacteria multiply in the lumen of a hair follicle or at other locations beneath the epidermis. Neutrophils are drawn to the site of infection, and various cytokines combine with bacterial toxins to promote development of purulence. The overlying epidermis prevents drainage. A painful red mass is usually seen; it may be tender and often is warm. Skin abscesses are rarely fatal, and most will eventually rupture through the epidermis and drain spontaneously.

Bartholin's cyst abscess is caused by an obstructed Bartholin duct. Bartholin's gland is located at the upper part of the lower third of the labium majus, and its duct opens onto the mucosa in this area, medially, but externally to the labium minus. Bacteria cultured are usually a mixture of aerobic and anaerobic flora from the vagina. *Chlamydia trachomatis* or *Neisseria gonorrhoeae* is isolated approximately 10% of the time.

Differential Considerations and Diagnostic Strategies

The differentiation of abscess from cellulitis can be challenging. Bedside ultrasound examination is the best option.[12] A high-frequency linear probe is used. Abscesses are seen as hypoechoic areas with posterior acoustic enhancement. The hypoechoic areas are pus and may be heterogeneous with some bright signals (Fig. 137-4A). Cellulitis is seen either as a uniformly hyperechoic area or as hyperechoic areas separated by curvilinear hypoechoic areas

www.ketabpezeshki.com 66485457-66963820

Table 137-2 Bacteriology of and First-Line Antibiotic Therapy for Skin Infections

ANATOMIC VARIANT OR PREDISPOSITION	LIKELY BACTERIAL CAUSE	FIRST-LINE THERAPY (NONTOXIC AND IMMUNOCOMPETENT)*
Uncomplicated cutaneous abscess	CA-MRSA, others	Incision and drainage without antibiotics
Nonpurulent bacterial skin infections	Various species in the *Streptococcus* genus, *Staphylococcus aureus*	Cephalexin or clindamycin Adjunctive measures
Purulent cellulitis and wound infections	CA-MRSA, others	Cephalexin plus trimethoprim-sulfamethoxazole, or clindamycin monotherapy Adjunctive measures
Diabetic foot infection	Mixed Gram-positive, Gram-negative, and anaerobes	Amoxicillin–clavulanic acid plus trimethoprim-sulfamethoxazole Avoid antibiotics for uninfected ulcers
Any cat bite or infected dog bite	*Pasteurella multocida*, others	Amoxicillin–clavulanic acid
Human bite (treat presumptively)	Oral anaerobes, others	Amoxicillin–clavulanic acid
Erythema migrans	*Borrelia burgdorferi* (Lyme)	Doxycycline
Puncture wound through sole of shoe (treat presumptively)	*Pseudomonas aeruginosa*	Ciprofloxacin
Buccal cellulitis	*Haemophilus influenzae* type b (vaccine serotype)[10]	Ceftriaxone or ampicillin-sulbactam
Balanitis	*Candida albicans* or group A streptococcus	Fluconazole plus penicillin or amoxicillin Consider diabetes
Liposuction	*Peptostreptococcus* (anaerobe), group A streptococcus	Ampicillin–clavulanic acid ± trimethoprim-sulfamethoxazole
Saltwater exposure	*Vibrio vulnificus*	Doxycycline
Freshwater exposure	*Aeromonas* species	Ciprofloxacin
Butcher, clam handler, veterinarian	*Erysipelothrix rhusiopathiae*	Amoxicillin
Black necrotic eschar with raised border and severe surrounding edema	*Bacillus anthracis* (anthrax)	Ciprofloxacin

*For life- or limb-threatening infections, use intravenous equivalents and add vancomycin.
CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus.*

(Fig. 137-4B). This appearance is known as cobblestoning and results from interstitial edema. The ultrasound probe and the rest of the machine are fomites and should be cleaned carefully.

Necrotizing fasciitis should be considered, although it is rare. Fistula should be considered when perianal or perivaginal infections are evaluated, and the mucosa should be examined digitally. When perirectal abscess recurs, a deep abscess may be the source, and CT scanning should be considered.

The epidermoid cyst represents another diagnostic challenge. These lesions, formerly known as sebaceous cysts, are benign cystic tumors resulting from pathologic accumulation of keratinaceous material. Patients report a long history of a cutaneous mass, often intermittently painful. These lesions become inflamed periodically and sometimes rupture spontaneously. With rupture, they drain a pearly white or yellowish, glistening, waxy material. Pus, which appears dull and viscous rather than waxy, may indicate infection. Isolated mild inflammation of an epidermoid cyst does not contraindicate primary excision by the practiced emergency physician, although a brief course of antibiotics and anti-inflammatories with delayed excision in the ED or by a dermatologist or surgeon is always an option. Primary excision is more difficult during an episode of inflammation. A minimally invasive method of cyst removal has been described.[23]

Vascular aneurysms and malignantly or benignly enlarged lymph nodes can be misdiagnosed as abscesses. Ultrasound examination can be helpful in this regard, and color Doppler study should be used to interrogate perivascular abscesses. When there is doubt, needle aspiration should be used to confirm the presence of pus and the absence of blood, or a surgeon should be consulted.

Inflamed cutaneous nodules and cystic masses in returning travelers and immigrants from developing countries present special diagnostic challenges. Typical staphylococcal abscesses are most common, but parasitic causes, such as dracunculiasis and myiasis, should be considered.[24]

Management

The treatment of abscess is surgical, and antibiotics are not indicated.[18] Exceptions for which antibiotics may be beneficial include the following: severe or extensive disease (e.g., involving multiple sites of infection), severe associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), septic phlebitis, and poor response to incision and drainage alone.

Needle aspiration has not been found to be an adequate alternative to incision and blunt dissection.[25]

Abscess incision and drainage is a nonsterile procedure, but the operator and all environmental fomites should be protected from contamination and transmission of MRSA. The main challenge is to attain adequate analgesia. Injection of local anesthetics into the skin overlying an abscess is difficult because the skin is usually edematous and tense. Also, superficial anesthesia is often inadequate for blunt dissection. An alternative option is to administer procedural sedation. Another excellent option is regional anesthesia (nerve block). Oral analgesia plus a ring block may also provide adequate anesthesia and analgesia. The following medications are safe together and have additive effects: ibuprofen, acetaminophen, oxycodone, and low-dose diazepam. The ring block is performed

www.ketabpezeshki.com 66485457-66963820

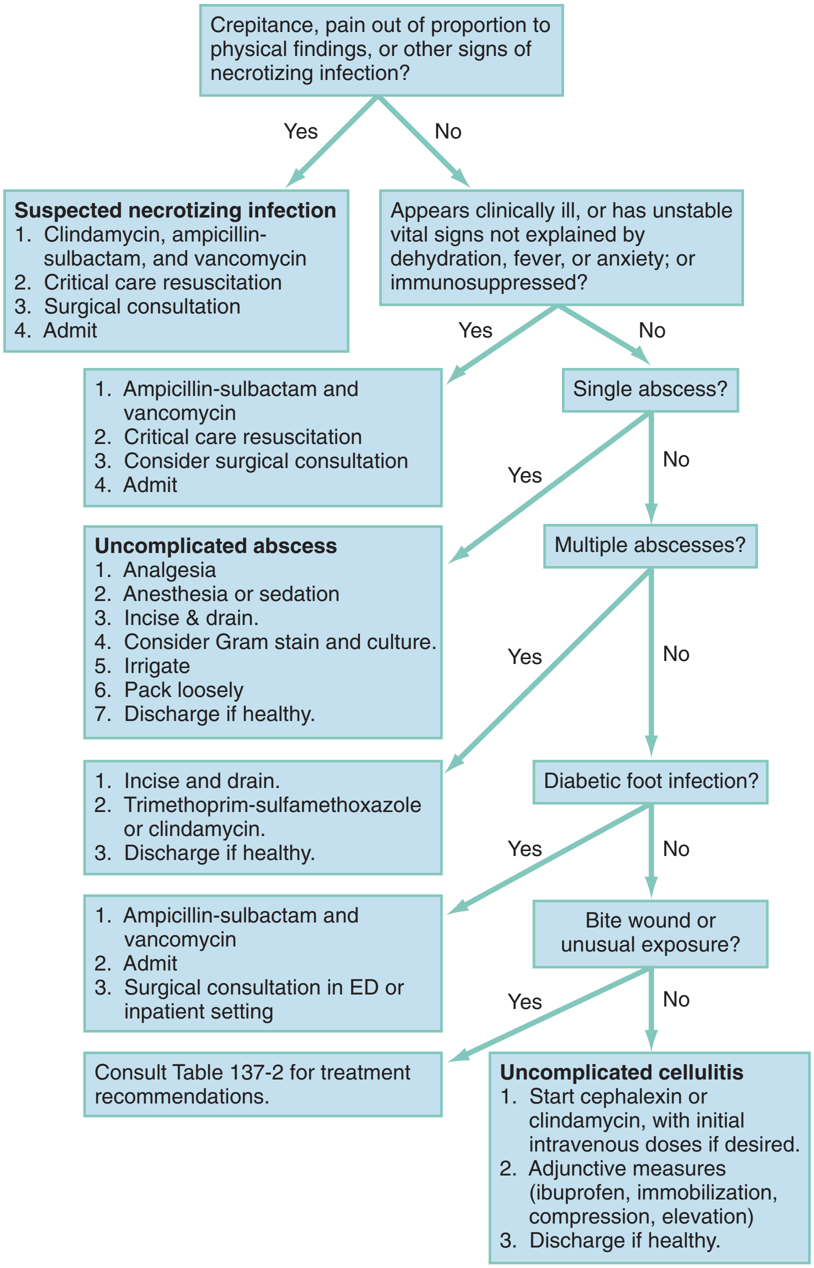


Figure 137-3. Universal algorithm for skin and soft tissue infections (assuming no prior treatment).

with a 25-gauge needle (3.5-inch spinal needle for large areas) to inject bupivacaine in a ring around the abscess, with as few punctures through the skin surface as possible and with care taken that the injection not spread bacteria from infected tissue to healthy tissue. At least 20 minutes should be allowed for this to take effect.

Once anesthesia has been attained, incision and drainage of an abscess involves four steps: incision, blunt dissection to disrupt loculations, irrigation, and packing. The skin is prepared with povidone-iodine (although this is a nonsterile procedure and expensive sterile gloves are not needed). A single incision across the abscess is made; the length of the incision is the same as the dimension of the abscess in the plane being incised. The entire purpose of the procedure is to facilitate drainage; a generous incision is best. Smaller incisions can be used in cosmetically important areas. The incision has less cosmetic effect if it is possible to make it parallel to cutaneous tension lines. A small clamp is used to probe the cavity and to disrupt loculations by opening of the clamp through the loculations. Blunt dissection rarely risks injury to vessels and nerves, but the initial incision should be made with such structures in mind. The drained cavity can be irrigated to further break loculations; saline mixed with a small amount of povidone-iodine or a 1 : 1 dilution of saline and hydrogen peroxide is a reasonable choice for irrigation fluid. The cavity is packed loosely and covered with a loose, absorbent dressing.

Bartholin's abscesses are drained from the mucosal rather than from the cutaneous surface. The Word catheter is a device used to keep the surgical wound from closing (Fig. 137-5) because the abscess will recur if the wound is allowed to close. A very small incision (about 3 mm) is made, and the cavity is drained. Testing for chlamydia or gonorrhea is recommended. The catheter is inserted and inflated with about 4 mL of water or saline. The catheter should be left in place for 4 to 6 weeks so that a sinus tract will have time to form. Sitz baths may help keep the area clean and

www.ketabpezeshki.com 66485457-66963820

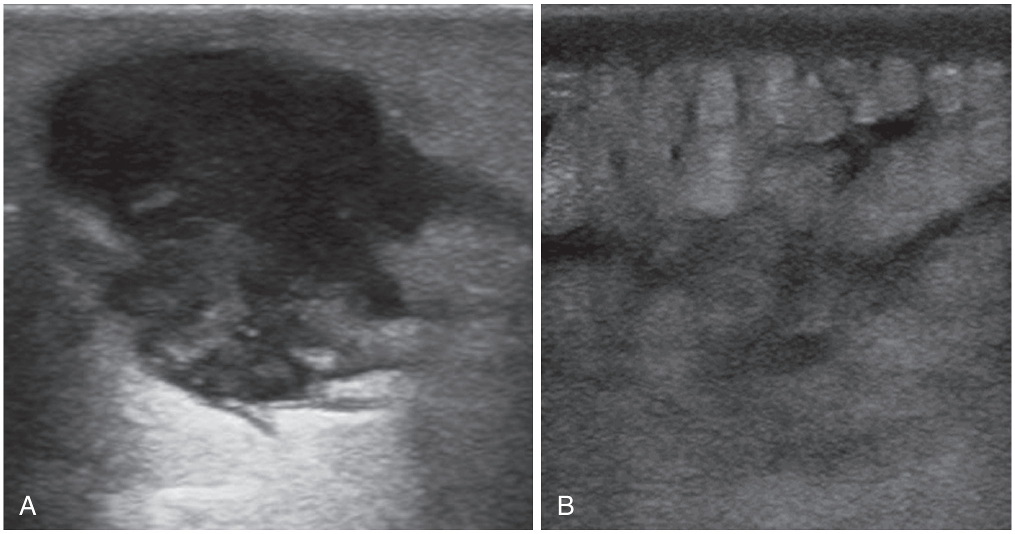


Figure 137-4. Ultrasound examination to distinguish abscess from cellulitis. A, Abscess visualized with 8-MHz linear probe demonstrating dark areas (pus) with posterior acoustic enhancement. B, Cellulitis visualized with 8-MHz linear probe demonstrating cobblestoning. (Courtesy Mark W. Byrne, MD, Department of Emergency Medicine, Brigham and Women's Hospital, Boston, Mass.)

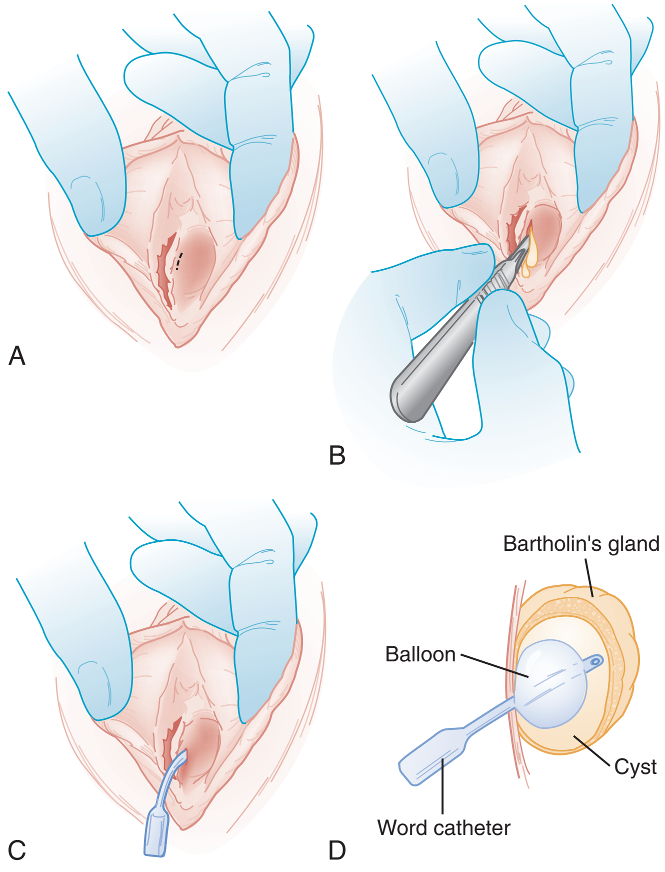


Figure 137-5. Drainage of Bartholin's abscess and use of a Word catheter.

draining. Antibiotics are usually not necessary but should be considered when there is extensive surrounding erythema or induration. Marsupialization is used in recurrent cases to prevent further recurrences. It is usually deferred until the acute inflammation has subsided. A large incision is made, and the interior of the abscess is then sutured to the surrounding mucosa so that the abscess is sutured open.

Disposition

Self-sufficient immunocompetent patients can be discharged to home after incision and drainage of an uncomplicated superficial abscess. It is traditional to schedule one or more visits for "wound checks," but many patients can remove the packing themselves after 2 to 4 days and be instructed to return for reevaluation only in the event of persistent or worsening pain or other symptoms indicative of treatment failure.

IMPETIGO

Perspective

Impetigo is a common superficial skin infection that is most prevalent in children aged 2 to 5 years, but it can occur at any age. It is communicable, spread by both person-to-person transmission and by fomites. It may be manifested as an infection of previously intact skin or may infect skin that has been damaged from minor trauma or atopic dermatitis.

Impetigo rarely progresses to systemic illness. However, most cases of poststreptococcal glomerulonephritis are believed to be caused by impetigo and not pharyngitis. The onset is usually 10 days after the onset of impetigo but may be up to 5 weeks later.

Principles of Disease and Clinical Features

The two main forms of impetigo are nonbullous and bullous. Nonbullous impetigo, or *impetigo contagiosa,* is the most common form. It was believed for many years that group A streptococcus was the primary cause of this disorder, but studies have subsequently shown that most cases are due to *S. aureus*. Approximately one third of cases have *S. pyogenes* isolated, usually in combination with *S. aureus*. The lesions begin as thin-walled vesicles that progress to pustules; subsequent rupture results in the characteristic "honey crusted" lesions. Lesions are typically found on the face or extremities, and associated lymphadenopathy is common.

Bullous impetigo is caused by *S. aureus,* including CA-MRSA.[26] The bacteria produce an epidermolytic toxin that causes separation of the dermal-epidermal junction, resulting in bullae. The lesions in bullous impetigo are fewer and larger (0.5-3 cm) but rupture less readily than the vesicles of the nonbullous form. After rupture, the bullae leave a thin brown crust.

www.ketabpezeshki.com 66485457-66963820

Ecthyma or "deep impetigo" is a less common ulcerative form of impetigo that has extension through the epidermis into the dermis. It is manifested as ulcers with a punched out appearance with raised reddened margins that are covered with thick crust. It has a predilection for the lower extremities. Unlike impetigo, ecthyma leaves scars.

Impetigo can be confused with contact dermatitis, varicella, herpes simplex, bullous pemphigoid, and Stevens-Johnson syndrome. Impetigo does not affect mucous membranes.

Management

Nonbullous impetigo should be treated with topical mupirocin, which is active against most MRSA strains.[27] Systemic antibiotics may be used for nonbullous impetigo when it would be impractical to use topicals because of the extent or location of the infection. Bullous impetigo should be treated with systemic antibiotics active against MRSA and streptococcus. Clindamycin is a good choice. Cephalexin plus trimethoprim-sulfamethoxazole is another option.

INFECTIONS OF THE PILOSEBACEOUS FOLLICLE

Perspective

Folliculitis, furuncle, and carbuncle are purulent infections originating in the hair follicle. They are more likely to occur after damage to the hair follicle, such as from shaving.

Clinical Features and Management

Folliculitis is a superficial inflammation of the hair follicle that is limited to the epidermis. It has many causes, including eosinophilic and drug related, but it is most commonly an infection due to *S. aureus*. The diagnosis is made clinically by its characteristic appearance of a small (2-5 mm), raised, erythematous, painful, tender lesion that is typically pruritic. It can affect any hair-bearing area of the skin. Folliculitis barbae involves the shaved beard area of the face or the shaved scalp.

Hot tub folliculitis is a pruritic condition caused by *Pseudomonas aeruginosa* that develops within 48 hours of bathing in a contaminated hot tub or swimming pool or from use of contaminated sponges. The rash consists of larger pustules and may have well-demarcated margins, typically involving the area of skin that was under the bathing suit.

Candidal folliculitis occurs primarily in immunosuppressed patients and in individuals treated with broad-spectrum antibiotic therapy. Eosinophilic folliculitis is a noninfectious recurrent disorder of unknown etiology. It is more likely in immunocompromised patients and is considered an AIDS-defining illness.

Folliculitis usually resolves on its own but can be treated with warm compresses or topical mupirocin. Multiple sites or a large cluster can warrant systemic antibiotics, although no randomized trials have been conducted on the efficacy of this treatment. Shaving of the involved area should be avoided. Hot tub folliculitis usually resolves on its own without specific treatment, but antihistamines and ciprofloxacin are treatment options. Fungal folliculitis is treated with topical antifungal agents. AIDS-associated folliculitis may be eosinophilic or fungal and may be treated with isotretinoin topically or systemic antifungals, respectively.

Furuncles and Carbuncles

A furuncle or "boil" is an infection of the hair follicle in which suppuration extends through the dermis into the subcutaneous tissue (refer to Fig. 137-2). Furuncles are painful and erythematous and often drain spontaneously. The most common cause is *S. aureus*, both methicillin sensitive and CA-MRSA. Whirlpool baths at nail salons have been implicated in mycobacterial furunculosis. A carbuncle comprises multiple furuncles with loculations and connecting sinuses, often with multiple sites of drainage. Systemic symptoms may occur. Carbuncles are more likely to occur on the back of the neck and are more prevalent in diabetics.

Furuncles and carbuncles are treated in the same manner as skin abscesses, primarily with incision and drainage, although antibiotics with activity against CA-MRSA are treatment options. Small furuncles may be treated initially with a trial of warm compresses to promote drainage.

Acne

Acne results from obstruction of sebaceous glands. It is most common during adolescence because of hormonal stimulation. Acne is treated in the primary care or dermatology clinic, but the emergency physician may choose to initiate therapy with oral doxycycline, topical clindamycin, or topical retinoids.

Hidradenitis Suppurativa (Acne Inversa)

Hidradenitis suppurativa (acne inversa) is an exquisitely painful condition most often seen in the axilla. It may also occur in other apocrine gland–bearing skin, including the perineum, breasts, and inner thighs. It is about three times more common in females than in males. There is some familial predisposition. The typical onset is between puberty and 40 years. It is currently believed to be an acneiform disorder that begins with follicular occlusion, rather than infection of the sweat glands. This has led to suggestions that the term *hidradenitis suppurativa,* which means suppurative inflammation of the sweat glands, be replaced with the term *acne inversa,* which implies an origin of follicular obstruction.[28] The pathophysiologic mechanism remains incompletely understood and is likely to be a complex interaction of hormonal, environmental, and genetic factors.[29]

The clinical course varies from intermittent isolated inflamed nodules to recurrent draining cysts and sinuses that can progress to a chronic and debilitating condition that is difficult to treat. Recurrences can lead to scarring, sinus track formation, and disfigurement. This is a debilitating disease, and patients suffer not only from pain but also from social stigma due to the odor that may accompany the lesions. They may suffer reactive depression.[29]

The diagnosis of abscess is made on the basis of the characteristic clinical presentation. Perianal and vulvar manifestations of Crohn's disease may be similar.

Most emergency physicians manage exacerbations with incision and drainage, although it is uncertain whether this accelerates healing. Certainly, incision of a painful, deep, nondraining abscess that is under pressure may bring symptomatic relief. Systemic antibiotics are usually prescribed and should cover CA-MRSA. Perianal lesions should be treated more broadly, with agents active against CA-MRSA, Gram-negative organisms, and anaerobes. Amoxicillin–clavulanic acid plus trimethoprim-sulfamethoxazole is a good choice.

Long-term treatment is complex and remains a subject of debate.[29] Options include immunomodulators (e.g., steroids, cyclosporine), hormones, and en bloc resection. All patients should be instructed to stop smoking and to keep the area clean and dry. Pain control is essential. Patients rarely show signs of systemic illness and thus can be discharged. They should be referred to a plastic surgeon or dermatologist.

www.ketabpezeshki.com 66485457-66963820

NECROTIZING SKIN AND SOFT TISSUE INFECTIONS

Principals of Disease and Clinical Features

Necrotizing infections progress rapidly, cause extensive tissue destruction, and are often fatal despite aggressive treatment. Clinical manifestations that suggest a necrotizing infection are signs of systemic toxicity, including abnormal vital signs, severe pain or pain out of proportion to physical findings, altered mental status, rapidly advancing infection, crepitus, hemorrhage, sloughing, and blistering.[30] Some patients appear well at presentation, and overlying skin may not be involved initially. Extensive tissue destruction occurs eventually, and the mortality rate is 20%.[31]

Risk factors include diabetes, vascular insufficiency, and immunosuppression, although healthy people are vulnerable. Inciting events include penetrating trauma, recent surgery, varicella infection, injection drug use, burns, and childbirth.

Typical bacterial isolates include group A beta-hemolytic streptococcus, *S. aureus* including CA-MRSA, enterococci, Enterobacteriaceae, and the anaerobes *Bacteroides* and *Clostridium*.[32] Most cases are polymicrobial. The classification schemes historically used for necrotizing infections are less important than the general principles discussed earlier.[30]

Necrotizing fasciitis is an aggressive infection of subcutaneous tissues that spreads rapidly along fascial planes. In the operating room, the fasciae are inflamed and tissue layers separate friably. It is caused by direct extension from a skin lesion in 80% of cases. Type I is polymicrobial, with aerobes and anaerobes; it is more common in diabetics and the immunocompromised.[33] Type II is caused by a single organism, in any age group and among patients who are not chronically ill. Group A streptococcus is most common and is the aggressively virulent agent known in the lay press as flesh-eating bacteria. CA-MRSA is also a cause, although it appears to be less virulent.[34] Initial symptoms may be vague (e.g., malaise, fever, body aches, nausea, and diarrhea). There may initially be diffuse or fusiform swelling of an extremity, or it may appear to be a simple cellulitis or wound infection. Physical findings may not be obvious initially, and pain out of proportion to physical findings is a clue. Eventually the skin turns violaceous or ecchymotic. Anesthesia may develop over the involved tissue because of infarction of superficial nerves. Subsequent inflammation may result in the classic sign of "wooden-hard" subcutaneous tissues.

Skin infections in the perineum warrant extra caution. Fournier's gangrene is the name given to necrotizing polymicrobial infections of the perineum. Fournier's gangrene progresses rapidly to extend to the entire perineum or abdominal wall.

Myonecrosis, myositis, and pyomyositis refer to infections of muscle, which are rare. They may result from local spread of an adjacent infection, penetrating trauma, vascular insufficiency, or hematogenous spread. Clostridial myonecrosis, also known as gas gangrene, has two forms, a more common traumatic form and a rare spontaneous form. The traumatic form typically occurs from an injury that results in an interruption in the blood supply, and crush injuries are often implicated. The infection is most commonly due to *Clostridium perfringens,* a Gram-positive spore-forming bacillus that is ubiquitous in nature, including the normal human body. Inoculation of the organism into tissue with low oxygen tension allows proliferation. Exotoxins destroy tissue, contribute to shock, and may cause intravascular hemolysis with anemia and disseminated intravascular coagulation. Patients present with severe pain. The skin may initially be pale, then bronze, and eventually purplish red. Hemorrhagic bullae may develop. Soft tissue gas may not be present initially. Systemic toxicity and shock ensue when aggressive treatment is not initiated early and sometimes despite aggressive treatment. The spontaneous form of clostridial myonecrosis is very rare and occurs without any inciting wound. It is usually due to *Clostridium septicum* and occurs in patients with bowel disease, such as colon cancer. Synergistic nonclostridial myonecrosis is a related syndrome, most commonly seen in the immunocompromised.

Anaerobic streptococcal myositis usually results from trauma or is a postoperative complication. It resembles clostridial myonecrosis but has a more insidious course. It is caused by anaerobic streptococci, including *Peptostreptococcus,* but the infection may also include group A streptococcus and *S. aureus*.

Spontaneous gangrenous myositis (also known as spontaneous streptococcal gangrenous myositis, group A streptococcal necrotizing myositis, or streptococcal myonecrosis) is rare but aggressive and fatal in most cases. It occurs spontaneously, without trauma, in immunocompetent hosts. It is preceded by a prodromal influenza-like phase. Gangrenous necrosis of skeletal muscle then results in severe pain with tense local swelling.

Pyomyositis is a deep abscess within striated muscle resulting from hematogenous spread of bacteria in the setting of muscle injury. It is usually due to *S. aureus,* including CA-MRSA, and is more common in the immunocompromised.[35] Mortality is less than 10%.[36]

Differential Considerations

The most obvious diagnostic dilemma is distinguishing necrotizing infections from simple cellulitis. A necrotizing infection should be considered when a patient with cellulitis presents with a rapidly progressing course or pain out of proportion to clinical findings or when the patient appears acutely ill or has tachypnea, hypotension, or tachycardia not explained by fever or dehydration. Crepitance or radiographic air is diagnostic of a necrotizing infection unless there is another explanation (such as recent surgery).

Phlegmasia cerulea dolens is iliofemoral vein thrombosis and can be confused with necrotizing fasciitis. Arterial insufficiency causes gangrene, and it may be difficult to determine whether infection is present in severe or chronic cases. Similarly, compartment syndrome can be confused with necrotizing infection or coexist with it.

Diagnostic Strategies

The diagnostic "gold standard" is the characteristic appearance of the tissue by direct visualization in the operating room. Some surgeons may elect to perform a biopsy at the bedside.

A panel of blood tests has been evaluated as a way to differentiate necrotizing infections from other skin infections: the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score.[37] Points are assigned for laboratory abnormalities, and a score of 6 or more is strongly predictive of necrotizing infection, with a positive predictive value of 92% and a negative predictive value of 96%. However, this tool is too preliminary for clinical applicability for several reasons, including methodologic flaws, lack of validation of the findings at other sites, uncertainty about how the score should be implemented in ill-appearing patients, and absence of any data to indicate when the score should be calculated for well-appearing patients.[38] An even simpler decision aid relies on serum sodium concentration and white blood cell count but is similarly lacking in external validation and other criteria needed for clinical application.[39] Necrotizing infections are very rare and other skin infections are common. Diagnosis of necrotizing infection remains clinical, and universal laboratory screening of well-appearing patients is not recommended.

Plain radiographs may show air in the soft tissues, but absence of this finding does not rule out necrotizing infection. Ultrasound examination can visualize the abscess of pyomyositis. CT and MRI may show compelling evidence of a necrotizing infection, but their negative predictive values have not been quantified.

www.ketabpezeshki.com 66485457-66963820

Management and Disposition

Patients with suspected necrotizing infections should be resuscitated aggressively and have coagulation studies and a type and screen performed because emergent surgery may be needed. Renal function should be assessed and goal-directed therapy used to guide resuscitation.

Empirical broad-spectrum antimicrobials should be administered promptly. A good regimen is clindamycin plus a broad-spectrum β-lactam like ampicillin-sulbactam plus vancomycin to cover MRSA. In patients at risk for hospital-acquired infections, drug-resistant *P. aeruginosa* and extended-spectrum β-lactamase–producing Gram-negative bacteria should be considered.

When a necrotizing infection is suspected, a surgeon should be consulted. Repeated operative débridement is often needed. Fasciotomies are often necessary as these syndromes are associated with elevated compartment pressures, which contribute to myonecrosis. The efficacy of hyperbaric oxygen in the management of necrotizing infections is unproven, and a dive should not delay surgery.[40]

TOXIC SHOCK SYNDROMES

Perspective

The principal systemic toxin-mediated bacterial skin syndromes are staphylococcal scalded skin syndrome, streptococcal toxic shock syndrome, and staphylococcal toxic shock syndrome . These syndromes are caused by bacterial exotoxins that are known as superantigens because they cause a severe and pathologic host immune system response by stimulating T-lymphocyte activation and functioning as mitogens in vitro.[41] Systemic disease results from the immune system's response to the toxin, but it may be accompanied by or simply resemble bacteremic septic shock (Table 137-3).

Streptococcal Toxic Shock Syndrome

Streptococcal toxic shock syndrome (TSS) is a severe, toxin-mediated syndrome that rapidly progresses to shock with multiorgan failure and death. Identified in the mid-1980s, this syndrome is caused by group A streptococci, often in the setting of a severe soft tissue infection. Most victims are previously healthy. The syndrome is a rare sequel of disseminated varicella (chickenpox).

Invasive group A streptococcal infections are often due to M-type isolates with potent exotoxins. Signs and symptoms are caused by pyrogenic exotoxins A and B. These act as superantigens and cause overactivation of T cells with massive release of cytokines, including interleukins and tumor necrosis factor.[41] The incidence of streptococcal TSS may be increasing, but it remains rare.

Patients may have an influenza-like prodrome with nausea, vomiting, diarrhea, myalgias, and chills. High fever, hypotension, and tachycardia are typical. Altered mental status with confusion is common. A diffuse rash is sometimes present (10% of cases), which may make differentiation from staphylococcal TSS more difficult.

On presentation, the patient has a severe streptococcal infection; necrotizing fasciitis is present in half of cases. Pain is often out of proportion to physical findings. Most patients present with shock or develop it within 4 to 6 hours. Bacteremia is common, with positive blood cultures in about 60%. Serious multisystem complications are common, including disseminated intravascular coagulation, acute renal failure, and acute respiratory distress syndrome. In contrast to staphylococcal TSS, which is infrequently fatal, about 30 to 80% of patients diagnosed with streptococcal TSS die. Epidermolysis, typical of staphylococcal TSS, is not characteristic of the streptococcal variety.

Staphylococcal Toxic Shock Syndrome

While staphylococcal TSS is not as severe as the streptococcal variety, it remains a life-threatening systemic illness. The classic presentation is of fever, rash, and hypotension, often in patients who were previously healthy. It was first described in 1978, and beginning in 1980 there was an epidemic of cases associated with the use of highly absorbent tampons. Menses-associated cases have since declined dramatically when such tampons were eliminated from the market, although tampon use continues to remain a risk factor.

Nonmenstrual cases, which currently account for about half of cases, are associated with a variety of conditions, including surgical procedures (e.g., rhinoplasty, abortion), nasal packing, burns, injection drug use, and the postpartum state. To the clinician, menstrual and nonmenstrual staphylococcal TSS appear similar, and the source infection is often not readily apparent.

S. aureus exotoxins are superantigens that are able to activate large numbers of T lymphocytes, resulting in the massive release of inflammatory mediators including interleukins, tumor necrosis

Table 137-3 Comparison of Features of Streptococcal TSS, Staphylococcal TSS, and Staphylococcal Scalded Skin Syndrome

	STREPTOCOCCAL TSS	STAPHYLOCOCCAL TSS	SSSS
Organism	*Streptococcus pyogenes*	*Staphylococcus aureus*	*Staphylococcus aureus*
Toxin	Pyrogenic exotoxins	TSST-1; enterotoxins A, B, C	Epidermolytic toxin A or B
Patient	Previously healthy	Tampon use or wound infection	Infant
Source	Necrotizing infection	Nasal or wound packing, tampon Infection not obvious	Skin flora
Rash	Erythematous rash in only 10% Stigmata of necrotizing infection are present Exfoliation weeks later	Initially diffuse erythroderma, with exfoliation after 1-2 weeks Mucosal hyperemia	Tender erythematous rash, localized blisters, extensive exfoliation if no antibodies to toxin Mucosa spared
Systemic illness	Hypotension, shock, multiorgan failure likely	Hypotension, shock, sometimes multiorgan failure	Fever, irritability
Mortality	30-80%	<5%	<5%
Treatment	Critical care resuscitation, operative débridement	Critical care resuscitation	Wound care, hydration

SSSS, staphylococcal scalded skin syndrome; *TSS*, toxic shock syndrome.

www.ketabpezeshki.com 66485457-66963820

factors, and interferon. Toxic shock syndrome toxin 1 (TSST-1) is associated with most menstrual cases. A lack of antibody against this toxin has been demonstrated in patients with menstrual staphylococcal TSS. Episodes of recurrent staphylococcal TSS have been reported in patients who do not mount a long-term antibody response, and it has been postulated that the toxin may interfere with antibody generation against itself.

Patients often have the acute onset of fever, chills, malaise, myalgia, muscle tenderness, and a diffuse blanching macular rash that is not pruritic. There may be nausea, vomiting, or diarrhea. Patients may have altered mental status. Vitals signs usually reveal fever and low blood pressure.

Severe hypotension may ensue as a result of massive vasodilation and fluid shifts out of the intravascular space. Toxic cardiomyopathy may also contribute to the low blood pressure. Hypotension or rhabdomyolysis may cause acute tubular necrosis. Anemia, thrombocytopenia, and leukocytosis are common, and disseminated intravascular coagulation may develop. Desquamation of the skin, including palms and soles, eventually occurs 7 to 14 days after onset. The overall mortality is below 5% with aggressive supportive care.

Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome (SSSS) is a desquamating skin disorder caused by exfoliating toxins produced by *S. aureus*. SSSS was historically known as fourth disease and in newborns as Ritter's disease. A disease of infants, it is rare in older children and adults. It can cause outbreaks in nurseries and daycare centers.[42]

SSSS is caused by certain strains of *S. aureus*, including CA-MRSA, that produce epidermolytic toxin A or epidermolytic toxin B. These toxins probably act as proteases that target the protein desmoglein 1 on the stratum granulosum layer of the epidermis. Whether they meet the T-lymphocyte mitogenic criterion for a superantigen is a subject of debate, and this may be relevant to the prognosis, which is good relative to TSS.[43]

The severity of the disease ranges from a few blisters at the site of infection to exfoliation of most of the body. People with preexisting toxin antibodies develop the localized form, in which toxin is found in the wound periphery; those without develop the generalized form, in which toxin spreads through the bloodstream. Cultures of the bullae are negative unless they are contaminated or secondarily infected.

Typically, a young child presents with fever, irritability, and a tender red rash. The erythema progresses to bullae formation and subsequent exfoliation of the affected skin. The skin exhibits Nikolsky's sign, which is separation of the epidermal layer of skin on gentle stroking. Desquamation may be patchy or sheetlike, leaving the skin denuded with a red moist base and predisposing it to secondary infection. Perioral, perianal, and flexural skin may be affected more severely. Mucous membranes are spared. SSSS is not associated with multisystem illness and typically does not lead to shock. Mortality is 1 to 5% and usually a result of complications from comorbid conditions or superimposed infection.

Early SSSS may be difficult to differentiate from bullous impetigo. The lack of mucosal involvement helps differentiate SSSS from toxic epidermal necrolysis and Stevens-Johnson syndrome. Other differential considerations include Kawasaki syndrome, Rocky Mountain spotted fever, meningococcemia, leptospirosis, and heat stroke.

Diagnostic Strategies

Streptococcal TSS should be suspected in any patient presenting with shock, especially if the patient was previously healthy. Diagnostic criteria for streptococcal TSS include the presence of group A streptococcal infection, hypotension, and two of the following: renal impairment, liver abnormalities, acute respiratory distress syndrome, coagulopathy, necrotic soft tissue infection, and rash. These criteria were developed for epidemiologic purposes; failure to meet all criteria should not exclude the clinical diagnosis in suspicious cases.

Staphylococcal TSS should be considered in any patient presenting with diffuse rash and hypotension. The diagnosis is made on the basis of the clinical presentation. The characteristic rash often raises clinical suspicion and ultimately aids in establishment of the diagnosis. Isolation of *S. aureus* is not necessary for the diagnosis to be made; in fact, blood cultures are positive in a small minority of cases. In severe cases, laboratory abnormalities are those resulting from shock and organ damage.

Management

Both streptococcal and staphylococcal TSS require critical care resuscitation. In streptococcal TSS, immediate surgical consultation for operative débridement of necrotizing infections is critical. In staphylococcal TSS, any potential source of infection should be removed, such as tampons or wound packing, and all postoperative wounds should be explored for infection.

Clindamycin and vancomycin should be administered. Gram-negative coverage should be added when Gram-negative sepsis is in the differential diagnosis.

Intravenous immune globulin has theoretic benefit, but its efficacy has not been shown in clinical trials. It is a reasonable option in cases of presumed staphylococcal TSS unresponsive to intravenous fluids and vasopressors, but this is not standard in the ED setting.[44] There is conflicting evidence on its efficacy in streptococcal TSS.[45,46] SSSS is treated with antibiotics active against *S. aureus*, including MRSA. Wound care and hydration are important.

Disposition

Patients with suspected TSS should be admitted, most often to the intensive care unit, for intravenous fluids, antibiotics, and close monitoring. Patients with necrotizing soft tissue infections associated with streptococcal TSS usually require surgical débridement.

Children with mild SSSS may be considered for outpatient management with oral antibiotics and close follow-up. Those with more severe skin involvement often need admission for pain control as well as for temperature regulation and fluid and electrolyte management. Severely affected patients may need intensive care or burn center care. With proper supportive care and antibiotic treatment, the prognosis is excellent, with an overall mortality of less than 5%. Scarring is rarely severe.

OTHER INFECTIONS WITH SKIN MANIFESTATIONS

Borrelia burgdorferi is the spirochete that causes Lyme disease, endemic in the United States, especially in New England. It produces a characteristic targetoid rash known as erythema migrans, which emerges about a month after the infecting tick bite. The targetoid appearance results from central clearing of the erythema. However, 20% of Lyme disease patients do not report a rash, and the rash does not always have the characteristic round and targetoid appearance (see Chapter 134).

Another spirochete, *Treponema pallidum*, causes a rash that is rare today: syphilis. The primary lesion of syphilis is a painless ulcer at the site of inoculation, known as a chancre, with raised borders and regional lymphadenopathy. The chancre appears days to months after infection and resolves after about a month. Secondary syphilis develops weeks to months later in about a quarter of infected patients. This involves a rash that can take any form

www.ketabpezeshki.com 66485457-66963820

other than vesicular and includes the palms and soles; there is usually diffuse lymphadenopathy. Syphilis is rare in the United States, although about 10,000 cases still occur per year (see Chapter 98).

Rocky Mountain spotted fever, caused by *Rickettsia rickettsii*, is even rarer, diagnosed only about 2000 times each year in the United States. A few days after a bite by a dog tick or wood tick, a nonspecific illness ensues. The characteristic rash begins on the wrists and spreads everywhere, including the palms and soles. It starts macular and becomes petechial and then dusky. The untreated mortality rate approaches 25%, but treated patients do well.[47] Ten percent of those infected never have a rash (see Chapter 134).

Cutaneous anthrax occurs on exposed areas of veterinarians and farmers. A spore of the Gram-positive anaerobe *Bacillus anthracis* enters a break in the skin, and after an incubation period of about a week, a vesicle forms. This ruptures, leaving a shallow-based ulcer with a raised border. The lesion progresses to painless necrosis and the characteristic eschar. Severe surrounding edema is due to bacterial toxins. Unlike with inhalational anthrax, treated cases do well, and even untreated cases have a mortality below 20%. The lesions may be confused with recluse spider bites.

Tularemia is a rare disease resulting from exposure to animals and is endemic in much of the United States, especially the south central states. The ulceroglandular form is most common and involves an influenza-like illness with a single raised ulcer that has mild central eschar formation. The lesion itself is raised, rather than the border (which might suggest anthrax) (see Chapter 134).

The floor of the mouth is a dangerous location for soft tissue infections. Severe infections may progress to Ludwig's angina, in which the floor of the mouth becomes severely indurated, leading to airway compromise and death. Broad-spectrum antibiotics are indicated. Steroids may reduce swelling. Intubation should be considered and a difficult airway anticipated (see Chapter 75).

Scabies is a skin infestation of the parasitic mite *Sarcoptes scabiei*. It is endemic worldwide and can cause institutional outbreaks. Lesions are most prominent on the dorsal hands and in intertriginous areas. It is diagnosed by visualization of characteristic burrows and, in ambiguous cases, by microscopy of skin scrapings. It is treated with topical permethrin or a single dose of oral ivermectin (200 μg/kg). Norwegian scabies, also known as crusted scabies, is an aggressive infestation that occurs in the immunocompromised; it is treated with both permethrin and ivermectin (see Chapter 120).

Cat-scratch disease results from *Bartonella henselae* infection after a cat bite or scratch. Its hallmark is regional lymphadenopathy that appears weeks after a primary lesion at the site of inoculation. Treatment is with a standard 5-day course of azithromycin (with a double dose on day 1).

Strongyloidiasis is caused by infection with the parasitic helminth *Strongyloides stercoralis*. Skin lesions can appear years after infection and are urticarial or serpiginous. A rapidly extending burrow that is pruritic and erythematous is diagnostic; this finding, due to rapid migration of larvae in the skin, is known as larva currens (running larva). Such findings or unexplained eosinophilia in people who have lived in Southeast Asia or tropical Africa should prompt consideration of strongyloidiasis. Diagnosis is by an enzyme-linked immunosorbent assay performed on serum. Detection is important because unlike other nematodes, strongyloides can complete its life cycle in the human host, leading to lifelong infection. When the infected patient becomes immunosuppressed by medications or illness, the strongyloides hyperinfection syndrome can result and is often fatal (see Chapter 133).

Cutaneous larva migrans is another serpiginous skin lesion caused by migrating larvae. In this case, the organism is hookworm, and the site is typically the foot or buttock; it is often seen after a vacation on the beach in Mexico. Treatment is with a single dose of ivermectin 200 mg/kg (see Chapter 133).

Cutaneous leishmaniasis is common in many parts of the world and is found on every continent except Australia and Antarctica. It is caused by protozoans of the genus *Leishmania* and transmitted by sandflies. Lesions are most common on the face and are painless, ulcerative, and disfiguring. Papules in returning travelers and immigrants should raise suspicion of myiasis (botfly) and, rarely, dracunculiasis (Guinea worm).

KEY CONCEPTS

- Skin infections are common and are rarely life-threatening. Deadly necrotizing skin and soft tissue infections are rare, and there is insufficient evidence to motivate screening by laboratory tests.
- Necrotizing infection is suggested by pain out of proportion to physical findings, crepitance, gas seen on imaging studies, or clinical instability. Suspected necrotizing infection is managed aggressively, with broad-spectrum antibiotics, critical care resuscitation, and surgical consultation.
- Emergency physicians should be familiar with toxic shock syndrome and Rocky Mountain spotted fever, which are rare life-threatening skin infection–related syndromes. Lyme disease should be considered in endemic areas.
- For the management of most skin abscesses, antibiotics are not recommended. Adequate analgesia or sedation are essential to good patient care. There is debate about the necessity of wound culture and Gram's stain.
- Current recommendations for the treatment of cellulitis suggest agents effective against streptococci and methicillin-sensitive *Staphylococcus aureus* (e.g., cephalexin at maximal doses). Adjunctive measures are essential to a good treatment response (nonsteroidal anti-inflammatory agents, immobilization, elevation, and compression).
- Clindamycin monotherapy is an excellent choice for treatment of skin infections as it covers streptococci and the great majority of staphylococci, including most CA-MRSA isolates.
- Although they are active against CA-MRSA, trimethoprim-sulfamethoxazole and tetracyclines may not be effective for streptococci and are not recommended for cellulitis monotherapy.
- There is insufficient evidence to recommend measurement of the white blood cell count in patients with skin infections.
- Blood cultures are not necessary for the workup of skin infections, except with septic shock, necrotizing infections, immunocompromise, multifocal infections suggesting hematogenous seeding, infections complicating lymphedema, and perhaps facial cellulitis.
- Skin infection mimics include venous stasis dermatitis and other forms of dermatitis.

ACKNOWLEDGMENT

We are grateful to David A. Talan, MD, for his insightful critique of the manuscript.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Pallin DJ, et al: Increased US emergency department visits for skin and soft tissue infections, and changes in antibiotic choices, during the emergence of community-associated methicillin-resistant *Staphylococcus aureus*. *Ann Emerg Med* 2008; 51:291-298.
2. Chambers HF: Community-associated MRSA—resistance and virulence converge. *N Engl J Med* 2005; 352:1485-1487.
3. Herold BC, et al: Community-acquired methicillin-resistant *Staphylococcus aureus* in children with no identified predisposing risk. *JAMA* 1998; 279:593-598.
4. McDougal LK, et al: Pulsed-field gel electrophoresis typing of oxacillin-resistant *Staphylococcus aureus* isolates from the United States: Establishing a national database. *J Clin Microbiol* 2003; 41:5113-5120.
5. Moran GJ, et al: Methicillin-resistant *S. aureus* infections among patients in the emergency department. *N Engl J Med* 2006; 355:666-674.
6. Pallin DJ, Espinola JA, Leung DY, Hooper DC, Camargo CA Jr: Epidemiology of dermatitis and skin infections in United States physicians' offices, 1993-2005. *Clin Infect Dis* 2009; 49:901-907.
7. Kanitakis J: Anatomy, histology and immunohistochemistry of normal human skin. *Eur J Dermatol* 2002; 12:390-399.
8. Abrahamian FM, Shroff SD: Use of routine wound cultures to evaluate cutaneous abscesses for community-associated methicillin-resistant *Staphylococcus aureus*. *Ann Emerg Med* 2007;50:66-67.
9. Heilpern KL: Skin and soft tissue abscesses: The case for culturing abscess fluid. *Ann Emerg Med* 2007; 50:64-66.
10. Swartz MN: Clinical practice. Cellulitis. *N Engl J Med* 2004; 350:904-912.
11. Nienaber A, Harvey M, Cave G: Accuracy of bedside ultrasound for the detection of soft tissue foreign bodies by emergency doctors. *Emerg Med Australas* 2010; 22:30-34.
12. Squire BT, Fox JC, Anderson C: ABSCESS: Applied bedside sonography for convenient evaluation of superficial soft tissue infections. *Acad Emerg Med* 2005; 12:601-606.
13. Patel Wylie F, Kaplan SL, Mason EO, Allen CH: Needle aspiration for the etiologic diagnosis of children with cellulitis in the era of community-acquired methicillin-resistant *Staphylococcus aureus*. *Clin Pediatr (Phila)* 2011; 50:503-507.
14. Lipsky BA, et al: Diagnosis and treatment of diabetic foot infections. *Clin Infect Dis* 2004; 39:885-910.
15. Kandemir O, Akbay E, Sahin E, Milcan A, Gen R: Risk factors for infection of the diabetic foot with multi-antibiotic resistant microorganisms. *J Infect* 2007; 54:439-445.
16. Citron DM, Goldstein EJ, Merriam CV, Lipsky BA, Abramson MA: Bacteriology of moderate-to-severe diabetic foot infections and in vitro activity of antimicrobial agents. *J Clin Microbiol* 2007; 45:2819-2828.
17. Liu JW, et al: Prognostic factors and antibiotics in *Vibrio vulnificus* septicemia. *Arch Intern Med* 2006; 166:2117-2123.
18. Liu C, et al: Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis* 2011; 52:e18-e55.
19. Lewis JS 2nd, Jorgensen JH: Inducible clindamycin resistance in staphylococci: Should clinicians and microbiologists be concerned? *Clin Infect Dis* 2005; 40:280-285.
20. Siberry GK, Tekle T, Carroll K, Dick J: Failure of clindamycin treatment of methicillin-resistant *Staphylococcus aureus* expressing inducible clindamycin resistance in vitro. *Clin Infect Dis* 2003; 37:1257-1260.
21. Biek D, Critchley IA, Riccobene TA, Thye DA: Ceftaroline fosamil: A novel broad-spectrum cephalosporin with expanded anti–Gram-positive activity. *J Antimicrob Chemother* 2010; 65(Suppl 4):iv9-16.
22. Dall L, Peterson S, Simmons T, Dall A: Rapid resolution of cellulitis in patients managed with combination antibiotic and anti-inflammatory therapy. *Cutis* 2005; 75:177-180.
23. Zuber TJ: Minimal excision technique for epidermoid (sebaceous) cysts. *Am Fam Physician* 2002; 65:1409-1412, 1417-1418, 1420.
24. Freedman DO, et al: Spectrum of disease and relation to place of exposure among ill returned travelers. *N Engl J Med* 2006; 354:119-130.
25. Gaspari RJ, Resop D, Mendoza M, Kang T, Blehar D: A randomized controlled trial of incision and drainage versus ultrasonographically guided needle aspiration for skin abscesses and the effect of methicillin-resistant *Staphylococcus aureus*. *Ann Emerg Med* 2011; 57:483-491.e1.
26. Liu Y, et al: Antimicrobial susceptibility of *Staphylococcus aureus* isolated from children with impetigo in China from 2003 to 2007 shows community-associated methicillin-resistant *Staphylococcus aureus* to be uncommon and heterogeneous. *Br J Dermatol* 2009; 161:1347-1350.
27. Koning S, et al: Interventions for impetigo. *Cochrane Database Syst Rev* 2004; 2:CD003261.
28. Sellheyer K, Krahl D: "Hidradenitis suppurativa" is acne inversa! An appeal to (finally) abandon a misnomer. *Int J Dermatol* 2005; 44:535-540.
29. Shuja F, Chan CS, Rosen T: Biologic drugs for the treatment of hidradenitis suppurativa: An evidence-based review. *Dermatol Clin* 2010; 28:511-521, 523-524; quiz 522-523.
30. Anaya DA, Dellinger EP: Necrotizing soft-tissue infection: Diagnosis and management. *Clin Infect Dis* 2007; 44:705-710.
31. Anaya DA, et al: Predictors of mortality and limb loss in necrotizing soft tissue infections. *Arch Surg* 2005; 140:151-157.
32. Klevens RM, et al: Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. *JAMA* 2007; 298:1763-1771.
33. Sarani B, Strong M, Pascual J, Schwab CW: Necrotizing fasciitis: Current concepts and review of the literature. *J Am Coll Surg* 2009; 208:279-288.
34. Miller LG, Perdreau-Remington F, Rieg G, et al: Necrotizing fasciitis caused by community-associated methicillin-resistant *Staphylococcus aureus* in Los Angeles. *N Engl J Med* 2005; 352:1445-1453.
35. Pannaraj PS, Hulten KG, Gonzalez BE, Mason EO Jr, Kaplan SL: Infective pyomyositis and myositis in children in the era of community-acquired, methicillin-resistant *Staphylococcus aureus* infection. *Clin Infect Dis* 2006; 43:953-960.
36. Sharma A, et al: Clinical characteristics and predictors of mortality in 67 patients with primary pyomyositis: A study from North India. *Clin Rheumatol* 2010; 29:45-51.
37. Wong CH, Khin LW, Heng KS, Tan KC, Low CO: The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: A tool for distinguishing necrotizing fasciitis from other soft tissue infections. *Crit Care Med* 2004; 32:1535-1541.
38. Barie PS: The laboratory risk indicator for necrotizing fasciitis (LRINEC) score: Useful tool or paralysis by analysis? *Crit Care Med* 2004; 32:1618-1619.
39. Wall DB, Klein SR, Black S, de Virgilio C: A simple model to help distinguish necrotizing fasciitis from nonnecrotizing soft tissue infection. *J Am Coll Surg* 2000; 191:227-231.
40. Jallali N, Withey S, Butler PE: Hyperbaric oxygen as adjuvant therapy in the management of necrotizing fasciitis. *Am J Surg* 2005; 189:462-466.
41. Macias ES, Pereira FA, Rietkerk W, Safai B: Superantigens in dermatology. *J Am Acad Dermatol* 2011; 64:455-472; quiz 473-474.
42. El Helali N, et al: Nosocomial outbreak of staphylococcal scalded skin syndrome in neonates: Epidemiological investigation and control. *J Hosp Infect* 2005; 61:130-138.
43. Plano LR, Gutman DM, Woischnik M, Collins CM: Recombinant *Staphylococcus aureus* exfoliative toxins are not bacterial superantigens. *Infect Immun* 2000; 68:3048-3052.
44. Lappin E, Ferguson AJ: Gram-positive toxic shock syndromes. *Lancet Infect Dis* 2009; 9:281-290.
45. Shah SS, Hall M, Srivastava R, Subramony A, Levin JE: Intravenous immunoglobulin in children with streptococcal toxic shock syndrome. *Clin Infect Dis* 2009; 49:1369-1376.
46. Darenberg J, et al: Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: A European randomized, double-blind, placebo-controlled trial. *Clin Infect Dis* 2003; 37:333-340.
47. Paddock CD, Holman RC, Krebs JW, Childs JE: Assessing the magnitude of fatal Rocky Mountain spotted fever in the United States: Comparison of two national data sources. *Am J Trop Med Hyg* 2002; 67:349-354.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 138

Sepsis Syndromes

Nathan I. Shapiro, Gary D. Zimmer, and Adam Z. Barkin

PERSPECTIVE

Background

Sepsis syndrome represents the body's host response to an infection. The causative agent and the host's activated inflammatory cascade overwhelm the body's defenses and regulatory systems, leading to disruption in homeostasis. Tachycardia, tachypnea, fever, and immune system activation are common manifestations. If the body is unable to overcome this insult, cellular injury, tissue damage, shock, multiorgan failure, or death may ensue.

In 1992, the American College of Chest Physicians/Society of Critical Care Medicine issued a consensus statement to establish uniform criteria defining the sepsis syndromes.[1] For the first time, this allowed a common nomenclature for disease classification and systematic comparisons across studies of septic patients. *Systemic inflammatory response syndrome* (SIRS) is defined as two or more of the following: tachycardia, tachypnea, hyperthermia or hypothermia, high or low white blood cell count, or bandemia; *sepsis* is the combination of infection plus SIRS; *severe sepsis* is sepsis plus organ dysfunction; and *septic shock* is severe sepsis plus hypotension, defined as a systolic blood pressure below 90 mm Hg, not responsive to a fluid challenge (Box 138-1). The importance of this nomenclature is to provide clinicians and researchers with a common classification. Efforts to validate this classification scheme in the emergency department (ED) population have demonstrated that the term *sepsis,* when it is characterized by fulfilling of the SIRS criteria alone, is perhaps overly sensitive and nonspecific and does not convey an increased mortality risk, although it should prompt further evaluation.[2] However, organ dysfunction and shock were shown to be significant predictors of adverse outcome. Newer efforts have proposed the PIRO approach, which may help better understand and prognosticate the severity of illness.[3,4] Assessment of *p*redisposing conditions, *i*nfection source, *r*esponse of the host, and *o*rgan dysfunction is proposed to help improve classification. The clinician should approach the septic patient with goals to determine *who* they are (e.g., underlying comorbidities), *what* infection they have, *how* they are responding, and *where/if* organ dysfunction is present.

Bacteremia is often present, but positive cultures are not obligatory in the diagnosis of sepsis. In several prospective studies, only 17 to 27% of patients with sepsis, 25 to 53% of patients with severe sepsis, and 69% of patients with septic shock actually had positive blood cultures.[5-7] Culture-negative and culture-positive septic populations have similar outcomes in patients with similar severity of illness.[8] Pneumonia, abdominal abscess with viscus perforation, and pyelonephritis are common primary causes of sepsis. Gram-positive organisms account for 25 to 50% of infections, gram-negative organisms for 30 to 60%, and fungi for 2 to 10%. The distribution varies with the study and, more important, with host factors such as the status of the host immune system, age of the patient, recent hospitalizations, and presence of indwelling vascular catheters.

The health status of the host is a crucial risk factor in the development and progression of sepsis.[9] Elders and those with multiple comorbidities are overwhelmed more easily by systemic infection. Chemotherapy-induced neutropenia, acquired immunodeficiency syndrome, and steroid dependency increase susceptibility to sepsis. Increased use of indwelling devices such as intravascular catheters, prosthetic devices, and endotracheal tubes contributes to the risk of systemic infection and sepsis.

Epidemiology

Sepsis is now the tenth most common cause of death in the United States.[10] It is estimated that 571,000 cases of severe sepsis present to U.S. EDs each year.[11] Mortality rates from sepsis are estimated between 20 and 50%.[12-14] Sepsis accounts for 4 of 1000 ED visits in the United States.[14] The incidence of sepsis as a reason for hospitalization is rising disproportionately among elders compared with the young (Fig. 138-1). The incidence of sepsis in patients younger than 65 years is less than 5 in 100,000, whereas it is 26 in 100,000 in those 65 years or older.[12] The cost of caring for septic patients is estimated to be $17 billion per year in the United States. Hospital discharge data have shown that the incidence of sepsis is increasing as identification improves and the population ages. Estimates have suggested that the incidence will rise 1.5% per annum or more. The number of ED visits for sepsis has risen proportionally with the rise in ED volume during the past 15 years.[14] Recent research has confirmed the long-held belief that respiratory and genitourinary infections are the most common causes of sepsis.[11]

PRINCIPLES OF DISEASE

Pathophysiology

Sepsis results from the complex interaction of detection molecules, signaling molecules, and numerous inflammatory and coagulation mediators in response to infection. More than 30% of patients with sepsis do not have a definite microbiologic diagnosis.[15] Although our understanding of the pathophysiologic process of sepsis has evolved in the past two decades, it remains incomplete.[16] The initial host response is to mobilize inflammatory cells, particularly neutrophils and macrophages, to the site of infection. These inflammatory cells then release circulating molecules, including cytokines, which trigger a cascade of other inflammatory mediators that result in a coordinated host response.

www.ketabpezeshki.com 66485457-66963820

Box 138-1 Definitions of Sepsis

Bacteremia (fungemia): presence of viable bacteria (fungi) in the blood, as evidenced by positive blood cultures

Systemic inflammatory response syndrome (SIRS): at least two of the following conditions: (1) oral temperature of >38° C or <35° C, (2) respiratory rate of >20 breaths/min or partial pressure of arterial carbon dioxide ($Paco_2$) of <32 mm Hg, (3) heart rate of >90 beats/min, (4) leukocyte count of >12,000/dL or <4000/dL or >10% bands

Sepsis: SIRS that has a proven or suspected microbial source

Severe sepsis: sepsis with one or more signs of organ dysfunction, hypoperfusion, or hypotension, such as metabolic acidosis, acute alteration in mental status, oliguria, or acute respiratory distress syndrome

Septic shock: sepsis with hypotension that is unresponsive to fluid resuscitation plus organ dysfunction or perfusion abnormalities as listed for severe sepsis

Multiple organ dysfunction syndrome (MODS): dysfunction of more than one organ, requiring intervention homeostasis

Data from Bone R, et al: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The APP/SCCM Consensus Conference Committee. Chest 101:1644, 1992.

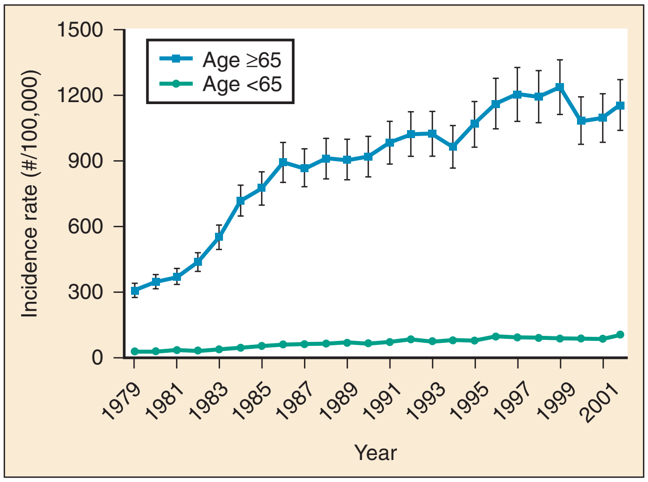


Figure 138-1. Incidence of disease in young and old over time.

Synthesis of the components of the cascade is increased at many steps along the pathway. If these mediators are not appropriately regulated, sepsis will occur. In the setting of ongoing toxin release, a persistent inflammatory response occurs with ongoing mediator activation, cellular hypoxia, tissue injury, shock, multiorgan failure, and potentially death.

Mediators of Sepsis

Host response and pathogen characteristics are both important in the pathogenesis of sepsis. More than 100 discrete markers have been identified and attributed to the sepsis cascade, but the true culprits have not been clearly identified.[1,17] A pathogen is sensed by pattern recognition receptors, most notably toll-like receptors, located on the surface of the white blood cell.[16] The resulting host-pathogen interaction activates the inflammatory and coagulation cascades.[18-21] The subsequent inflammatory signaling occurs through cytokines, chemokines, and other soluble mediators, including increased circulating levels of the interleukins IL-1, IL-6, and IL-8 and tumor necrosis factor alpha (TNF-α). Activation of the clotting cascade results in increased D-dimer levels and decreased circulating levels of protein C.[22]

In benign conditions, a self-limited response helps clear the pathogen. If the innate immune response is inadequate, mediators create a procoagulant state. Coagulation and fibrinolytic components are proinflammatory, precipitating a worsening cycle of procoagulant and proinflammatory mediators. This cascade ultimately creates end-organ damage and disseminated intravascular coagulation (DIC). If it is not effectively reversed, the process leads to cellular hypoxia, organ dysfunction, shock, and death.

The primary mediators are cytokines that are primarily proinflammatory, anti-inflammatory, or growth promoting. The molecular mechanisms by which they are regulated are not well understood. The initial cytokine, TNF-α, is found in serum approximately 90 minutes after the administration of endotoxin to healthy volunteers. IL-6 and IL-8 reach peak levels at approximately 120 minutes. The main proinflammatory cytokines are IL-1, TNF, and IL-8. The primary anti-inflammatory cytokines are IL-10, IL-6, transforming growth factor beta, soluble receptors to TNF, and IL-1 receptor antagonist (IL-1RA). If the resultant inflammatory response is adequate, the infection is controlled and cleared. If the response is deficient or excessive, however, a persistent and worsening cascade is produced, ultimately leading to shock, organ failure, and potentially death.

Instability in vascular tone is becoming increasingly important in understanding of the pathophysiologic mechanism of sepsis. Vasopressin, also known as antidiuretic hormone, is a naturally occurring hormone that is essential for cardiovascular stability. It is produced as a prohormone in the hypothalamus. The hormone is stored in the pituitary gland and released in response to stressors such as pain, hypoxia, hypovolemia, and hyperosmolality.[23] In severe sepsis, there is a brief rise in circulating vasopressin levels followed by a prolonged and severe suppression. This pattern of secretion is different from other forms of shock, in which vasopressin levels remain elevated. Vasopressin has numerous physiologic effects, including vasoconstriction of the systemic vasculature, osmoregulation, and maintenance of normovolemia.

Nitric oxide (NO) is a gas that has an important role in septic shock, regulating vascular tone by an indirect effect on smooth muscle cells. NO also contributes to platelet adhesion, insulin secretion, neurotransmission, tissue injury, and inflammation and cytotoxicity. Its half-life is short (6-10 seconds), and it easily diffuses into cells. Although its mechanisms of action are not well understood, it seems to be a key mediator of sepsis. Animal data show that nitric oxide synthase, the enzyme that produces NO, is upregulated in cases of sepsis.[24] Enhanced NO production is thought to contribute to the profound vasodilation found in patients in septic shock.

In the setting of ongoing inflammatory activation, the mediators of sepsis continue to be produced and the cascade is perpetuated. Unless it is appropriately and rapidly controlled, the ultimate effect is a sequence of events starting with cellular dysfunction and ultimately leading to tissue damage, organ dysfunction, and death.

Organ System Dysfunction

The organ dysfunction that results from sepsis is central to the pathogenesis of the disease. A 3000-patient ED-based study demonstrated that organ dysfunction with septic shock portends increasingly worse outcomes.[2] Patients with suspected infection alone had a mortality rate of 2.1%, whereas the presence of SIRS criteria and suspected infection had a mortality rate of only 1.3% (Fig. 138-2A). However, the mortality rate was 9% for those patients with severe sepsis (sepsis plus organ dysfunction) and 28% for those with septic shock. The risk of death from sepsis approximately doubles for each organ that fails. The mortality rate for patients with no organ dysfunctions was 1%; rates for

www.ketabpezeshki.com 66485457-66963820

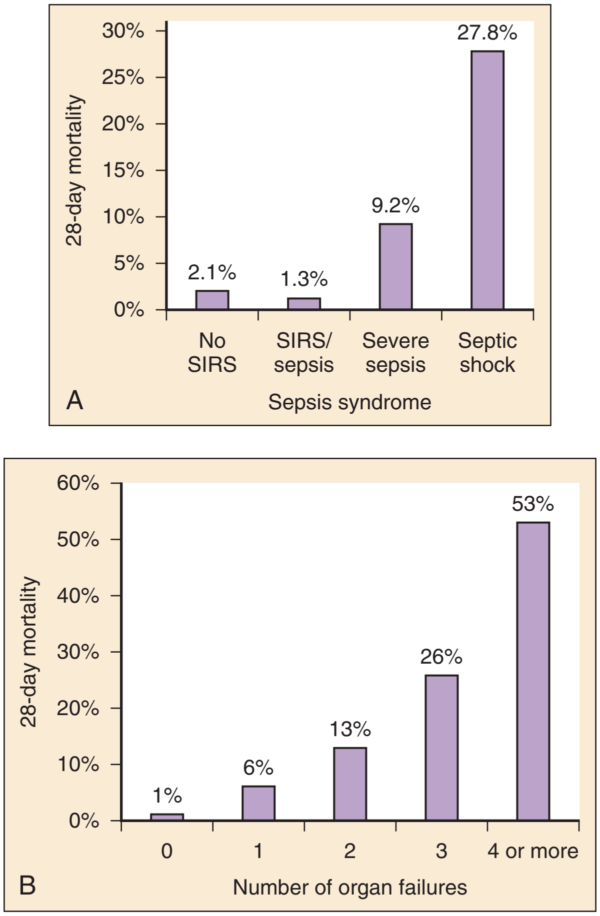


Figure 138-2. Mortality rates by sepsis syndrome (**A**) and number of organ dysfunctions (**B**).

dysfunction of a single organ, two organs, three organs, and four or more organs were 6%, 13%, 26%, and 53%, respectively (Fig. 138-2B).

Neurologic

Patients with sepsis often display neurologic impairment manifested by altered mental status and lethargy, commonly referred to as *septic encephalopathy*. The incidence has been reported between 10 and 70%. The mortality rate in patients with septic encephalopathy is higher than that in septic patients without significant neurologic involvement. One prospective case series showed that a Glasgow Coma Scale score of less than 13 correlated with an increase in mortality rate from 20 to 50%.[25] Although the pathophysiologic process has not been clearly defined, contributing factors include direct bacterial invasion, endotoxemia, altered cerebral perfusion or metabolism, metabolic derangements, multiorgan system failure, and iatrogenic injury. In addition, impaired renal or hepatic function in the absence of overt organ failure has been shown to correlate with encephalopathy.

Cardiovascular

Profound cardiovascular dysfunction is common with sepsis. The cardiovascular dysfunction and failure arise from both direct myocardial depression and distributive shock. Gram-negative, gram-positive, and killed organisms can cause myocardial depression. The direct insults of the toxic mediators as well as the mobilization of host mediators of sepsis produce a distributive shock. Early in sepsis, a hyperdynamic state develops, characterized by increased cardiac output and decreased systemic vascular resistance.[26] Although the cardiac output is increased, it is at the expense of ventricular dilation and decreased ejection fraction. Aggressive fluid resuscitation usually increases preload and, secondarily, ejection fraction, thereby improving the cardiac index, even late in shock. Much of the cardiovascular compromise from septic shock is reversible, and normal cardiovascular function usually returns within 10 days.

Box 138-2 Definition of Acute Respiratory Distress Syndrome

Impaired oxygenation, defined as a ratio of partial pressure of arterial oxygen to fractional inspired oxygen <200, irrespective of how much positive end-expiratory pressure is used
Bilateral pulmonary infiltrates on frontal chest radiograph
Pulmonary artery occlusion pressure ≤18 mm Hg or no clinical evidence of elevated left atrial pressures

Data from Bernard G, et al: The American-European Consensus Conference on ARDS: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149:818, 1994.

Pulmonary

The lung is an early victim of the inflammatory response to sepsis. These effects are apparent irrespective of the primary infection that caused sepsis. Early infiltration with neutrophils, surfactant dysfunction, and edema later give way to monocyte infiltration and fibrosis. Significant right-to-left shunting, arterial hypoxemia, and intractable hypoxemia occur. The resulting morbidity is high and is a common endpoint to sepsis-related deaths.

Sepsis produces a highly catabolic state and places significant demands on the respiratory system. At the same time, airway resistance is increased and muscle function is impaired. Irrespective of whether pneumonia is the cause of sepsis, the common pulmonary endpoint is acute respiratory distress syndrome (ARDS). ARDS is defined clinically (Box 138-2) and correlates with the pathologic finding of diffuse alveolar damage. The development of ARDS occurs 4 to 24 hours after radiographic abnormalities develop. Because of alveolar-capillary membrane damage, fluid accumulates in the alveoli. Rather than being a diffuse disease, ARDS is a heterogeneous process that results in interspersed damaged and normal alveoli.

Gastrointestinal

A shock state causes significant deleterious effects on a hollow viscus and its oxygen supply. A prolonged ileus accompanies hypoperfusion and persists beyond the perfusion deficit. Splanchnic blood flow is dependent on mean arterial pressure because there is relatively little autoregulation. Therefore, hemodynamic dysfunction may have a profound effect on viscus metabolism.

Solid organ involvement is also common. Even in the previously normal host, elevations in aminotransferases and bilirubin are common early in sepsis, although frank hepatic failure is rare. The liver has also been implicated in the pathogenesis of sepsis; some of the mediators of sepsis are produced by the liver.

Endocrine

An absolute or relative adrenal insufficiency is common in sepsis.[27] Depending on the balance of circulating cytokines, augmentation or suppression of the hypothalamic-pituitary axis is possible. IL-1 and IL-6 both activate the hypothalamic-pituitary-adrenal axis. TNF-α and corticostatin depress pituitary function. Other factors that may contribute to adrenal insufficiency in sepsis include decreased blood flow to the adrenal cortex, decreased pituitary

www.ketabpezeshki.com 66485457-66963820

function, and decreased pituitary secretion of adrenocorticotropic hormone due to severe stress. As a result of these interactions, the hypothalamic thermoregulatory mechanism may be reset, and temperature lability may develop.

Hematologic

Sepsis causes abnormalities in many parts of the coagulation system. Endotoxin, TNF-α, and IL-1 are the key mediators. Pathologic activation of the extrinsic (tissue factor dependent) pathway, protein C–protein S, and fibrinolysis lead to consumption of essential factors, causing DIC. The activation of the coagulation cascade produces fibrin deposition and microvascular thrombi. If these depositions are not corrected, they can compromise organ perfusion and contribute to organ failure. Tissue factor expression on monocytes is increased. This results in fibrin deposition and perhaps contributes to an increased incidence of multiorgan failure due to microvascular thrombi.

Protein C has been identified as an important modulator of both inflammation and coagulation in patients with sepsis. Impairment of the protein C–dependent anticoagulation pathway is critical to the development of the thrombotic complications of sepsis.[28] In healthy humans, protein C is activated by a combination of thrombin and thrombomodulin. The activation of protein C results in downregulation of many portions of the coagulation cascade, including release of tissue factor, inactivation of factor VIIIa and factor Va, and stimulation of fibrinolysis.[29] It is possible that protein C activation in early sepsis is impaired because of an inflammatory cytokine–mediated downregulation of thrombomodulin. As a result, a consumptive coagulopathy ensues. This leads to increased fibrin deposition and a resulting upregulation of the fibrinolytic pathway as identified by low plasma levels of the fibrinolytic proteins and increased fibrin split products. This sequence of events leads to consumption of coagulation factors and DIC. In late sepsis, the fibrinolytic system is suppressed.

Novel Concepts

In recent years, there has been increasing evidence that genetics are a risk factor for outcome of sepsis.[30,31] The impact of genetics on future treatment modalities for sepsis remains unclear, but the prospect of customized genetic therapy for sepsis is a promising early development.

CLINICAL FEATURES

Symptoms and Signs

The approach to a patient with sepsis relies on identification of the presence of a systemic infection and localization of the source of the initial infection. This allows appropriate and aggressive treatment directed to the source of infection. Often, the source is not readily apparent, but early identification of the septic state allows implementation of broad-spectrum antibiotics that may be potentially lifesaving.

The septic patient manifests signs of systemic infection through tachycardia, tachypnea, hyperthermia or hypothermia, and, if severe, hypotension. A septic patient will often have flushed skin with warm, well-perfused extremities secondary to the early vasodilation and hyperdynamic state. Alternatively, the severely hypoperfused patient with an advanced shock state may appear mottled and cyanotic. Very early in the patient's presentation, vital sign changes such as tachycardia and tachypnea may be the only early indicators of sepsis. If the patient is in shock, a rapid assessment that excludes other causes, such as hypovolemic or cardiogenic shock, is essential to the proper initial treatment. A complete detailed clinical examination will help the physician determine the cause of the shock state (see Chapter 6). The aforementioned are "classic" signs; however, these findings may not be manifested in a septic patient, and signs and symptoms may be subtle.

Both underlying comorbidities and the etiology of sepsis should be considered. Risk factors such as immunocompromised states (acquired immunodeficiency syndrome, malignant disease, diabetes, splenectomy, and concurrent chemotherapy), older age, debilitation or high-risk environments for iatrogenic infections (such as long-term care facilities), and multiple comorbidities should be considered.

The respiratory system is the most common source of infection in the septic patient. A history of a productive cough, fevers, chills, upper respiratory symptoms, and throat and ear pain should be sought. Both the presence of pneumonia and the findings of tachypnea or hypoxia have been found to be predictors of death in patients with sepsis.[32] Physical examination should also include detailed evaluation for focal infection, such as exudative tonsillitis, sinus tenderness, tympanic membrane injection, and crackles or dullness on lung auscultation. Also, pharyngeal thrush should be noticed as a potential marker of an immunocompromised state.

The gastrointestinal system is the second most common source of sepsis. A history of abdominal pain, including its description, location, timing, and modifying factors, should be sought. Further history, including the time of the last bowel movement and the presence of nausea, vomiting, and diarrhea, should be noted. A careful physical examination, looking for signs of peritoneal irritation, abdominal tenderness, and hyperactive or hypoactive bowel sounds, is critical in identifying the source of abdominal sepsis. Particular attention should be paid to physical findings suggestive of common sources of infection or disease: Murphy's sign indicating cholecystitis, pain at McBurney's point indicating appendicitis, left lower quadrant pain suggesting diverticulitis, or rectal examination revealing a rectal abscess or prostatitis.

The neurologic system is examined by looking for signs of meningitis, encephalitis, or epidural abscess, including nuchal rigidity, fevers, and change in consciousness. A detailed neurologic examination is important. Lethargy or altered mentation may indicate primary neurologic disease or may be the result of decreased brain perfusion from a shock state.

The genitourinary history includes queries about the presence of flank pain, dysuria, polyuria, discharge, Foley catheter placement, and genitourinary instrumentation. A sexual history should assess for the risk of sexually transmitted diseases. Genitalia should be evaluated for ulcers, discharge, and penile or vulvar lesions, looking specifically for the woody induration of Fournier's gangrene. A rectal examination should be performed, looking for a tender, boggy prostate, consistent with prostatitis. A red and friable cervix, cervical discharge, or cervical motion tenderness is consistent with a sexually transmitted disease. Adnexal tenderness in a toxic-appearing woman potentially represents a tubo-ovarian abscess. Also, a pelvic examination in women should also include an inspection to ensure that there is no retained tampon.

Musculoskeletal history includes the presence of any localizing symptoms to a particular joint. Redness, swelling, and warmth over a joint, especially if there is a decreased range of motion in that joint, may be signs of septic arthritis and may mandate arthrocentesis. A patient should be completely exposed and the skin examined for evidence of cellulitis, abscess, wound infection, or traumatic injury. Deep injuries, foreign bodies, and fasciitis may be difficult to identify clinically. The physician should look for crepitus, bullae, or skin edema extending beyond areas of erythema representing the presence of an aggressive, gas-forming organism. Back pain and fever are concerning for an epidural abscess. Local lymphadenopathy, swelling, and streaking should also be noted as signs of an advancing infection. Petechiae and purpura may represent a *Neisseria meningitidis* infection or DIC. Generalized erythroderma and rash may represent an exotoxin

www.ketabpezeshki.com 66485457-66963820

Table 138-1 Mortality in Emergency Department Sepsis (MEDS) Prediction Rule

RISK FACTOR	ODDS RATIO FOR DEATH	MEDS SCORE
Terminal illness (death within 30 days)	6.1	6 points
Tachypnea or hypoxia	2.7	3 points
Septic shock	2.7	3 points
Platelet count < 150,000/mm^3	2.5	3 points
Bands > 5%	2.3	3 points
Age > 65 years	2.2	3 points
Pneumonia	1.9	2 points
Nursing home resident	1.9	2 points
Altered mental status	1.6	2 points

RISK OF DEATH	TOTAL MEDS SCORE (% OF SEPSIS DEATHS)
Very low	0-4 (1.1%)
Low	5-7 (4.4%)
Moderate	8-12 (9.3%)
High	13-15 (16.1%)
Very high	>15 (39%)

from pathogens such as *Staphylococcus aureus* and *Streptococcus pyogenes*.

A history of fevers or chills in the setting of injection drug abuse, an artificial heart valve, or a mitral valve prolapse should increase the suspicion for endocarditis. The clinician should suspect endocarditis in the presence of a murmur or other stigmata of endocarditis (e.g., splinter hemorrhages, Roth's spots, Janeway's lesions).

Clinicians must identify the severity of illness in patients with infection and initiate aggressive resuscitation for those patients with the potential of becoming critically ill. Although a patient may meet SIRS criteria, this alone has little predictive value in determining the severity of illness and mortality.[2] The Mortality in Emergency Department Sepsis (MEDS) score is a method to risk stratify ED patients with sepsis.[33] The MEDS prediction rule assigns point values to specific clinical characteristics (Table 138-1). The total score can be used to assess risk of death. Thus the greater the number of risk factors, the more likely a patient is to die during the hospitalization.

DIAGNOSTIC STRATEGIES

The use of diagnostic testing in patients with sepsis syndromes or suspected syndromes serves two purposes. Diagnostic studies are used both to identify the type and location of the infecting organisms and to define the extent and severity of the infection to assist in focusing therapy. As a result, the diagnostic approach should be tailored to the particular patient.

Hematology

The white blood cell count is a marker of inflammation and activation of the inflammatory cascade. Leukocytosis is associated with infection and is incorporated in the consensus definition of sepsis; however, it is often insensitive and nonspecific, limiting its absolute utility in the ED. The febrile neutropenic patient has been shown to be at increased risk for severe infection. Thus a neutrophil count of less than 500 cells/mm^3 should prompt admission, isolation, and empirical intravenous antibiotics in most chemotherapy patients. A bandemia (≥10% bands on a peripheral smear) represents the release of immature cells from the bone marrow and is considered to be a sign of infection and inflammation. Like the white blood cell count, it is an imperfect indicator of infection. The absence of leukocytosis or bandemia does not preclude the possibility of severe sepsis. The hemoglobin and hematocrit should be determined to ensure adequate oxygen delivery in shock. Platelets are an acute-phase reactant and may be elevated in the presence of infection. Conversely, a low platelet count is a significant predictor of bacteremia in patients with shock. Thrombocytopenia, elevated prothrombin time, elevated activated partial thromboplastin time, decreased fibrinogen, and increased fibrin split products are associated with DIC and severe sepsis syndrome.

Chemistry

Electrolyte abnormalities should be identified and corrected. Low bicarbonate level suggests acidosis and inadequate perfusion. An elevated anion gap acidosis in the setting of sepsis syndrome commonly represents lactic acidosis or diabetic ketoacidosis, but other causes need to be ruled out. Elevated serum creatinine concentration or decreased glomerular filtration rate signals renal dysfunction or failure, which, if it is due primarily to sepsis, indicates organ failure and a worse prognosis. Calcium, magnesium, and phosphorus levels should be checked.

An elevated lactate level is associated with inadequate perfusion, shock, and poorer prognosis. One ED-based study showed a progression in mortality rate with increasing venous lactate level: a lactate level of 0 to 2.5 mg/dL was associated with a 5% mortality rate; a lactate level of 2.5 to 4.0 mg/dL, 9% mortality; and a lactate level greater than 4 mg/dL, 28% mortality.[34] An arterial blood gas assessment may be helpful in identifying and classifying acid-base disturbances. Metabolic acidosis suggests inadequate tissue perfusion. Liver function tests can be used to identify liver failure or dysfunction. An elevated bilirubin level may suggest the gallbladder as a cause of sepsis. An elevated lipase level may represent pancreatitis as the cause of noninfectious SIRS.

Microbiology

Proper blood, sputum, urine, cerebrospinal fluid, and other tissue culture samples are important in guiding therapy. Although the results of culture are not helpful in the initial management, culture samples should be obtained before or soon after the administration of antibiotics in the patient with sepsis syndrome. The initiation of antibiotic therapy should not be delayed while waiting for culture samples to be obtained. The literature suggests that the yield of initial blood cultures is low (5-10%), but this is probably an artifact of the lack of reliable discriminatory guidelines for obtaining blood culture samples in the ED.[6] Among patients with clinical sepsis, only 30 to 60% of patients will have positive cultures.[5,7]

The results of initial microbiologic tests, including Gram's stains whenever possible, will help guide subsequent antibiotic treatment. Initial empirical therapy should be broad spectrum to allow early treatment of all likely organisms.

Special Procedures

The comprehensive protocol of early goal-directed therapy published by Rivers and associates[35] showed that a resuscitation strategy guided by the central venous pressure (CVP), an arterial line, and a central venous catheter with continuous central venous oxygen saturation ($Scvo_2$) monitoring capability can reduce mortality in patients with sepsis. However, whether each of these components is required is unclear. A CVP line may guide fluid

www.ketabpezeshki.com 66485457-66963820

resuscitation, with a low CVP indicating the need for continued fluid repletion. The $Scvo_2$ monitor measures venous blood saturation, which is a marker of tissue metabolism and extraction. It has been suggested that intermittent monitoring of $Scvo_2$ may suffice, although there are no firm data to support this. The goal is to ensure proper tissue oxygenation, which is routinely achieved by adjustment of oxygen delivery, keeping the $Scvo_2$ greater than 70%. An arterial line can be useful for close monitoring of hypotensive patients, especially when one or more vasopressors are being titrated to maintain an adequate blood pressure; however, no evidence exists to show that it is mandatory. Finally, the Swan-Ganz catheter is not a mandatory part of the sepsis management, although the physiologic measurements may be useful in identifying the cause of shock and guiding fluid and inotropic therapy. Low systemic vascular resistance and high cardiac output are most commonly associated with sepsis, although this may vary with the stage of shock and the individual patient. There are data to suggest that the use of Swan-Ganz catheters does not have a substantial impact on mortality.[36]

Radiology

A chest radiograph should be obtained in all patients with suspected sepsis syndrome, looking not only for a focal infiltrate representing pneumonia but also for the fluffy, bilateral infiltrates indicative of ARDS. The pathophysiologic changes of ARDS are often delayed as much as 24 hours after radiographic identification. An upright chest radiograph should be obtained for suspected bowel perforation to detect free air under the diaphragm. The presence of pneumomediastinum is suggestive of esophageal perforation and current or impending mediastinitis.

Soft tissue plain radiographs of infected areas should be obtained, looking for air in the soft tissues associated with necrotizing or gas-forming infection. Periosteal thickening or bone erosion may be seen on plain radiographs of patients with osteomyelitis; a bone scan may be diagnostic. Computed tomography (CT) of superficial infections may be helpful to further quantify the extent of infection and to identify abscesses that are not readily evident on physical examination. A CT scan of the abdomen and pelvis may identify abdominal or pelvic pathologic lesions, provided there is no clear clinical indication for immediate operative intervention. Suspected disease, such as diverticulitis, appendicitis, necrotizing pancreatitis, microperforation of the stomach or bowel, or formation of an intra-abdominal abscess, may be best diagnosed by CT scan. A head CT scan can identify septic emboli from endocarditis or increased intracranial pressure from a mass and should be considered before a lumbar puncture is performed. An abdominal ultrasound examination may be indicated for suspected cholecystitis, and a pelvic ultrasound examination for tubo-ovarian abscess or endometritis. If endocarditis is suspected, a transesophageal cardiac ultrasound study should be obtained for the detection of any valvular vegetations. A magnetic resonance imaging scan can be useful to identify soft tissue infection, such as necrotizing fasciitis or epidural abscess.

DIFFERENTIAL CONSIDERATIONS

The sepsis syndromes represent a spectrum of disease and clinical presentations. SIRS is defined by hemodynamic and laboratory parameters alone, whereas sepsis must include a suspected infectious cause. Often, noninfectious sources can cause a syndrome that mimics sepsis; thus one must keep in mind a broad differential diagnosis when approaching these patients (Box 138-3). A detailed history and physical examination are the first steps in narrowing the differential diagnosis to identify the true source.

Box 138-3 Differential Considerations for Sepsis and Septic Shock

Sepsis
- Dehydration
- Acute respiratory distress syndrome
- Anemia
- Ischemia
- Hypoxia
- Congestive heart failure
- Vasculitis
- Toxicologic
  - Poisonings
  - Overdose
  - Drug induced
- Pancreatitis
- Hypothalamic injury
- Disseminated intravascular coagulation
- Anaphylaxis
- Metabolic
- Hyperthyroidism
- Diabetic ketoacidosis
- Adrenal dysfunction
  - Environmental
  - Burn
  - Heat exhaustion or stroke
- Trauma
  - Blood loss
  - Cardiac contusion
- Neuroleptic malignant syndrome

Septic Shock
- Hypovolemic shock
- Acute blood loss
- Severe dehydration
- Cardiogenic shock
- Pulmonary embolus
- Myocardial infarction
- Pericardial tamponade
- Tension pneumothorax
- Vasogenic shock
- Anaphylaxis
- Paralysis

MANAGEMENT

Early detection and aggressive management can significantly reduce the mortality from sepsis. The primary goal remains antimicrobial therapy and maintenance of adequate tissue oxygenation and perfusion, but the means by which this is achieved has changed substantially in the past years. With the advent of early goal-directed therapy and therapies such as drotrecogin alfa targeting the cascade leading to septic shock,[35,37] there is increasing evidence that the natural history of sepsis can be altered. Initial resuscitation, including appropriate airway management, intravenous access, oxygen, early and appropriate antibiotics, and fluid resuscitation, remains the foundation on which new efforts may be applied.

In the study by Rivers and associates, a protocol for early and aggressive care was used to guide resuscitation in the ED.[35] This randomized, double-blind, placebo-controlled study showed a 16% mortality reduction in patients with severe sepsis and septic shock. The protocol measures targeted "goals" and uses a resuscitation algorithm to facilitate an aggressive and early resuscitation. The use of this strategy has been endorsed by the Surviving Sepsis Campaign, an 11-organization international consensus panel.[38] The recommendation is for the use of goal-directed therapy for all patients who have (1) suspected infection, (2) two or more SIRS criteria, and (3) evidence of hypoperfusion signified by either a systolic blood pressure of less than 90 mm Hg after 20 to 30 mL/kg fluid challenge or a lactic acid level greater than 4 mmol/dL (Fig. 138-3). The theory behind the protocol is to normalize preload and pressure and to prevent tissue hypoxia by matching oxygen delivery with consumption.

Preload

The first step in goal-directed therapy is to provide a proper filling pressure to ensure adequate cardiac preload. Patients with sepsis and septic shock are often in a state of substantial fluid deficit.

www.ketabpezeshki.com 66485457-66963820

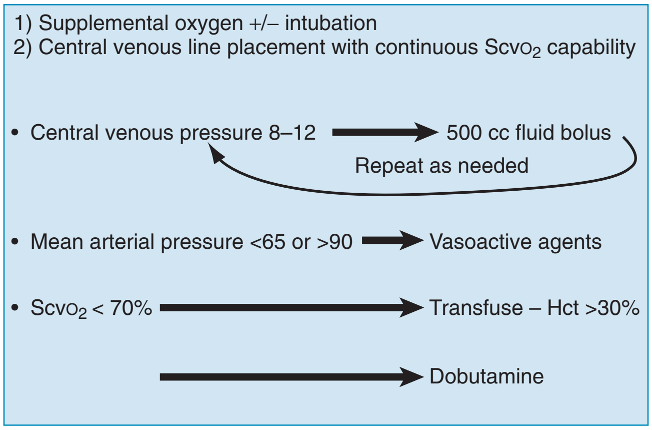


Figure 138-3. Summary of goal-directed therapy protocol.

Table 138-2 Management Recommendations for Hemodynamic Support

Basic Principles
Admission to intensive care unit
Arterial cannulation in patients with shock, although insertion may not be practical in the emergency department
Resuscitation to target tissue perfusion
Central venous or pulmonary arterial catheter placement to assess cardiac filling pressures
Fluid Resuscitation
Fluids are the primary modality to resuscitation[*]
Colloids and crystalloids are equally effective[*]
Invasive monitoring for patients not responding to initial resuscitation with target pulmonary capillary wedge pressure of 12 to 15 mm Hg[†]
Hemoglobin concentrations should be maintained above 8 to 10 g/dL[†]
Vasopressor Therapy
Norepinephrine is the first-line agent in shock unresponsive to aggressive fluid resuscitation[‡]
Dopamine and phenylephrine are alternatives
Epinephrine is reserved for refractory hypotension[†]
Routine low-dose (≤5 µg/kg/min) dopamine is not recommended[‡]
Vasopressin may be considered in refractory shock not responsive to aggressive fluid resuscitation and high-dose conventional vasopressors[§]
Inotropic Therapy
Dobutamine is the first choice for patients with refractory low cardiac index[§]
Dobutamine may improve cardiac index and organ perfusion, but empirical use is not recommended[†]
Vasopressors and inotropes can be titrated separately to maintain mean arterial pressure and cardiac output[†]
Epinephrine and dopamine can be used as inotropes, but splanchnic perfusion may be compromised[*]

Data from Hollenberg S, et al: Practice parameters for hemodynamic support of sepsis in adult patients with sepsis. Crit Care Med 27:639, 1999.
*Supported by small randomized trials with uncertain results.
†Supported by at least one contemporaneous nonrandomized trial.
‡Supported by one randomized, controlled trial with clear results.
§Supported by nonrandomized trials with historical controls and expert opinion or case series.

Rivers and colleagues showed that patients required an average of 5 L of fluids in the first 6 hours of their resuscitation. A CVP measurement should be obtained, and the patients should receive crystalloid or colloid resuscitation to keep the CVP at a level of 8 to 12 mm Hg. In intubated patients with positive-pressure ventilation, pathophysiologic principles support raising the target level to 12 to 16 mm Hg. Whereas CVP monitoring is one approach, other approaches may be used. For example, if cardiac output monitoring is available, an approach of administering intravenous fluids until the point at which cardiac output no longer responds to fluid boluses is certainly reasonable.

Perfusion Pressure

The next step in goal-directed therapy is to maintain an adequate blood pressure. A mean arterial blood pressure (⅔ diastolic + ⅓ systolic) should be kept between 60 and 90 mm Hg. If the mean arterial blood pressure is below 65 mm Hg in the presence of adequate preload, treatment with a vasopressor agent should be started; norepinephrine and dopamine are considered first-line agents.

Oxygen Delivery

The initial management of all critically ill patients should include supplemental oxygen with a goal to maintain a peripheral oxygen saturation of 95% (or the patient's baseline oxygen saturation in the case of preexisting underlying lung disease). Once preload and pressure are normalized, the next focus is on oxygen delivery. A mixed venous saturation or assessment of lactate clearance can be used to guide this aspect of resuscitation. Organ hypoperfusion is a result of global and distributive changes in both systemic blood flow and the microvasculature. As a result of marrow suppression and dilution with crystalloid fluids, many patients with sepsis have a hemoglobin between 8 and 10 g/dL after initial resuscitation. A hematocrit between 27 and 30% has been reported to be most effective,[39] although other authorities have challenged this dogma.[40]

The therapeutic goal is to maintain a mixed venous saturation ($Scvo_2$) greater than 70% or to reduce lactate level by at least 10%. As oxygen demand due to sepsis increases, the $Scvo_2$ starts to fall below 70%. This should be corrected by first ensuring that preload and pressure are adequate.[41] Next, the arterial oxygen saturation should be optimized with non-rebreather oxygen delivery or intubation, as needed. Once these are optimized, one should ensure that the patient has adequate oxygen-carrying capacity by transfusion of the patient to a hematocrit greater than 30%. If this is normalized and the patient is not tachycardic, dobutamine can be added to increase cardiac contractility and to increase cardiac output, resulting in an overall improved oxygen delivery. The protocol should be run continuously with an effort toward normalization of the parameters during the entire resuscitation (Table 138-2).

Respiratory Support

Altered mental status is common in patients in septic shock, and they may require rapid airway protection. Patients with a respiratory rate of more than 30 breaths/minute are likely to develop respiratory collapse, irrespective of arterial oxygenation. In 1999, Wheeler and Gordon reported that 85% of patients with "severe sepsis" required mechanical ventilation during their hospital course.[42] Because patients with impending respiratory failure use a disproportionately large amount of energy for the muscles of respiration, improved oxygen delivery to other organs is achieved by mechanical ventilation, sedation, and paralysis. Although there are no clear intubation guidelines, hypercapnia, persistent hypoxemia, airway compromise, and profound acidosis are valid indicators.

In addition to airway protection, intubation and mechanical ventilatory support provide positive-pressure ventilation. The pattern of injury in ARDS is such that normal lung parenchyma is adjacent to affected tissue. Therefore, increased airway pressures are required to maintain normal oxygen delivery. Current recommendations are to maintain transalveolar pressures (measured as

www.ketabpezeshki.com 66485457-66963820

plateau pressures) below 35 cm H_2O because increased pressures are associated with ventilator-induced lung injury. Maintenance of relatively low transalveolar pressure with increasing end-expiratory pressure is an effective way to increase arterial oxygen delivery.[43] The ARDSNet trial established the benefit of low tidal volumes in acute lung injury (6 mL/kg), which has translated to a recommended approach of lower tidal volumes in mechanically intubated patients to prevent subsequent iatrogenic lung damage.[44]

Cardiovascular Support

Fluid Resuscitation

Patients with sepsis often require large volumes of intravenous fluid to maintain adequate perfusion. The primary reasons for this intravascular hypovolemia are venodilation and diffuse capillary leak. Initial therapy for adults with septic shock should generally be 2 L of isotonic crystalloid. As much as 6 to 10 L of crystalloid may be required in the first 24 hours. Early goal-directed therapy has been shown to be an effective way to guide fluid resuscitation and should be considered in all cases of septic shock. In less critically ill patients, fluid replacement should be titrated to clinical parameters such as heart rate, blood pressure, change in mental status, capillary refill, cool skin, and adequate urine output (0.5-1 mL/kg/hr). Normal (0.9%) saline and lactated Ringer's solution are equally effective and neither worsens lactic acidosis. Colloids are as effective as crystalloids, but they are more expensive. Efforts to identify ways to measure regional perfusion more directly, such as direct measurement of splanchnic blood flow, have been proposed. Even in the absence of global hypoxia and impaired tissue perfusion, there is evidence that regional hypoperfusion and ischemia exist.[45] Although further study is necessary, therapy guided toward maintenance of splanchnic perfusion may decrease the rate of mortality.

Vasopressors

If appropriate fluid resuscitation has failed, vasopressor support may be required (Table 138-3). Only in cases of profound hypotension should vasopressors be started before adequate fluid resuscitation. Use of mean arterial pressure alone as an indicator of overall efficacy of therapeutic intervention is not helpful. A mean arterial pressure of 65 mm Hg has been recommended in otherwise healthy, normovolemic adult patients but must be correlated with other indicators of adequate perfusion, such as mental status and urine output. Patients with previously uncontrolled hypertension may require mean arterial pressures of 75 mm Hg or even higher.

The 2008 Surviving Sepsis Campaign guidelines provide consensus recommendations for treatment of septic shock.[38] Fluid resuscitation remains the fundamental treatment option and should be the initial treatment. Norepinephrine should be used as the initial vasopressor, with the addition of dopamine or vasopressin to norepinephrine as a reasonable adjunct. Vasopressin alone has been shown to be ineffective compared with norepinephrine in the initial treatment of refractory septic shock.[46] Epinephrine should be considered a supplemental agent if dopamine or norepinephrine is ineffective. Dobutamine should be used as the primary inotropic agent if myocardial dysfunction is evident.[38]

Norepinephrine. Norepinephrine is a mixed alpha- and beta-agonist with minimal $beta_2$ activity and primarily functions to increase cardiac output and systemic vascular resistance. In a large study examining patients with shock from multiple causes, norepinephrine was shown to have fewer adverse events (particularly arrhythmias) compared with dopamine, which had a higher mortality rate in those patients with cardiogenic shock.[47] In another meta-analysis, norepinephrine was shown to be superior to dopamine in both in-hospital and 28-day mortality.[48]

Compared with dopamine in septic patients, norepinephrine increases glomerular filtration and urine output equally well. It is an important component of the therapy for septic shock, either as a sole vasopressor or in conjunction with other vasopressors. Recommended doses are 8 to 12 µg/min.

Dopamine. Dopamine is also often used for septic shock that is unresponsive to adequate volume expansion. Dopamine is the immediate precursor of norepinephrine and epinephrine. It is primarily an alpha, $beta_1$, and dopaminergic agonist. Although low doses alone are not effective, they may be effective in combination with other agents. "Renal-dose" dopamine has not been shown to reduce mortality or to decrease dialysis dependence and should not be used.[49,50] Dosages higher than 20 µg/kg/min may produce significant vasoconstriction. Persistent tachycardia, decreased partial pressure of arterial oxygen, and increased pulmonary artery occlusion pressure are common side effects of dopamine use. Dopamine has been shown to increase oxygen delivery better than other catecholamines do. On the basis of its mechanism of action, it is most useful in patients who have depressed cardiac output.

Phenylephrine. Phenylephrine is a selective $alpha_1$-agonist, increasing systemic vascular resistance without significant changes in cardiac output. It can produce a reflexive bradycardia or suppression in cardiac output. A single small study has shown that phenylephrine is effective in restoring perfusion in patients with septic shock refractory to dopamine or dobutamine.[51] Another small study demonstrated that phenylephrine is less effective than norepinephrine in treatment of hypotension in septic patients; however, there was no difference in other measured hemodynamic parameters, including oxygen delivery.[52] Phenylephrine does not impair cardiac and renal function and may be a good choice when significant tachyarrhythmia limits the use of other agents.

Epinephrine. Epinephrine is a potent mixed alpha- and beta-agonist. Epinephrine infusion is also associated with increased oxygen consumption, increased systemic lactate concentrations, and decreased splanchnic blood flow. The rise in lactate is short term, and there is no evidence regarding its long-term effects. As a result of all of the possible adverse effects of epinephrine, it is currently recommended only for those patients who are unresponsive to other vasopressors.

Table 138-3 Dosing of Vasoactive Therapy

DRUG	DOSAGE
Dobutamine	5-15 µg/kg/min
Dopamine	2-20 µg/kg/min
Epinephrine	5-20 µg/min
Norepinephrine	5-20 µg/min
Phenylephrine	2-20 µg/min

Vasopressin

Vasopressin is a naturally occurring nonapeptide that is synthesized as a large prohormone in the hypothalamus. In states of septic shock, there is an early surge of vasopressin followed by a profound drop in circulating vasopressin levels.[23] This is the foundation for use of vasopressin as an adjunct therapy for patients with severe sepsis. Vasopressin should not be used as the sole initial therapy for refractory septic shock. In a well-designed randomized trial, investigators demonstrated no change in mortality for patients with severe sepsis when vasopressin was added to catecholamine vasopressors.[46]

www.ketabpezeshki.com 66485457-66963820

Inotropic Agents

Dobutamine

Dobutamine is a mixed alpha- and beta-agonist. In dosage ranges from 2 to 28 μg/kg/min, cardiac index is increased at the expense of heart rate. In addition, decreased splanchnic blood flow is common. Dobutamine should be used in patients with depressed cardiac index and persistent hypoperfusion in spite of adequate volume expansion and other vasopressor agents. In patients undergoing formal early goal-directed therapy, when preload, perfusion pressure, and oxygen-carrying capacity have been normalized and a low $Scvo_2$ persists, dobutamine is used to increase cardiac output and oxygen delivery. One study suggested that survival in sepsis is associated with the patient's increase in stroke volume in response to dobutamine.[53]

Bicarbonate

Bicarbonate supplementation was previously the standard treatment for patients with presumed lactic acidosis. Current consensus is that it should be reserved for severe acidemia (pH < 7.0-7.2) as there may be a paradoxical decrease in intracellular pH as a result of diffusion of soluble carbon dioxide across the cell membrane. Alternatively, hyperventilation has been suggested to help increase systemic pH.

Antibiotics

Early and appropriate antibiotic therapy should target the nidus of infection; this reduces mortality, perhaps by as much as 30 to 50%.[54] If the patient's condition permits, appropriate culture specimens should be obtained before the administration of broad-spectrum antibiotics (Table 138-4). Surgically correctable conditions, such as intra-abdominal abscesses, perforated viscus, retained products of conception, or retained foreign body (such as a tampon), should be treated concurrently.

In the absence of an obvious source of infection, the use of broad-spectrum antibiotics is recommended. The specific agent depends on many variables, including institutional preference and local resistance patterns. As results from cultures become available, therapy should be modified. There is no consensus about the need for double or triple antibiotic coverage for particular organisms, although it is common practice to double-cover virulent organisms, such as *Pseudomonas aeruginosa,* as well as areas that are commonly infected with multiple organisms, such as the peritoneum. With increasing rates of methicillin-resistant organisms, combinations that include nonpenicillin choices may be warranted.

Novel Therapies

Activated Protein C

After years of unsuccessful, large-scale, multicenter trials of novel therapeutic agents for sepsis, recombinant activated protein C (APC) became the first therapy to be approved by the Food and Drug Administration (FDA) for the treatment of sepsis. In the initial trial, APC was shown to improve survival by 6% in patients with severe sepsis.[29] However, based on subsequent conflicting data in postmarket studies, a confirmatory trial was conducted. In the 1680 patient trial of patients with septic shock, the 28-day mortality rate in the activated protein C group was similar to the placebo group (26.4% versus 24.2%, $p = .31$).[29a] Additionally, there was no significant benefit in meaningful subgroups; thus, based on lack of efficacy, the drug has been withdrawn from the market and is no longer available for use.

Table 138-4 Suggested Initial Antibiotic Management Pending Microbiologic Identification of Organism and Sensitivity

INFECTION	MODIFYING FACTORS	ANTIBIOTIC
Sepsis, unknown source	Immunocompetent	Antipseudomonal cephalosporin *plus* aminoglycoside or fluoroquinolone; *or* antipseudomonal penicillin *plus* aminoglycoside or fluoroquinolone; *or* carbapenem *plus* aminoglycoside or fluoroquinolone
	Anaerobic infection	Add metronidazole or clindamycin to above regimen
	Methicillin-resistant *Staphylococcus aureus* (MRSA)	Add vancomycin to above regimen
	Neutropenia	Antipseudomonal penicillin *plus* aminoglycoside or fluoroquinolone; *or* carbapenem *plus* aminoglycoside or fluoroquinolone
	Splenectomy	Cefotaxime *or* ceftriaxone
	HIV infection	Ticarcillin-clavulanate *plus* tobramycin
Pneumonia	Immunocompetent	Second- or third-generation cephalosporin *plus* second-generation macrolide *or* fluoroquinolone
	Legionella suspected	Azithromycin or fluoroquinolone or high-dose erythromycin
Abdominal infection	Immunocompetent	Ampicillin *plus* aminoglycoside *plus* metronidazole
	Multidrug-resistant organism suspected	Ticarcillin-clavulanate or carbapenem; *or* piperacillin-tazobactam *plus* aminoglycoside
	Urinary tract source	Fluoroquinolone; *or* third-generation cephalosporin; *or* ampicillin *plus* aminoglycoside
Cellulitis	Non-necrotizing fasciitis	Cefazolin *or* nafcillin
	MRSA possible	Vancomycin
	Necrotizing fasciitis (surgical drainage)	Ampicillin-sulbactam; *or* ticarcillin-clavulanate; *or* piperacillin *plus* aminoglycoside *plus* clindamycin; *or* carbapenem
Intravenous catheter infection (remove catheter)	Outpatient acquired	Third-generation cephalosporin
	MRSA suspected	Add vancomycin
	Fungal infection	Amphotericin B
Cerebrospinal infection	Immunocompetent	Ceftriaxone *plus* vancomycin
	Elders or immunocompromised	Add ampicillin
Injection drug abuse	MRSA not suspected	Nafcillin *plus* aminoglycoside
	MRSA suspected	Vancomycin *plus* aminoglycoside

www.ketabpezeshki.com 66485457-66963820

Steroid Therapy

It has been nearly 30 years since the first treatment attempts to block inflammation in sepsis. Because sepsis involves a systemic inflammatory response, corticosteroids are a logical treatment modality as anti-inflammatory agents. Physicians have been working for decades to prove or to disprove their value. For example, Annane and colleagues performed a randomized, double-blind, placebo-controlled study of 300 patients with septic shock that demonstrated benefit when steroids were given to nonresponders in a corticotropin stimulation test.[55] Among nonresponders, those treated with steroids had a 53% mortality rate, compared with 63% in the placebo group, for a 10% absolute benefit. Steroid therapy was not beneficial to those who responded to the corticotropin stimulation test. However, a large-scale multicenter validation failed to show a statistically significant improvement in mortality in both all-comers with septic shock and those with adrenal suppression.[56] Steroids were more effective in reducing the amount of time patients spent hypotensive, but the rates of secondary infection increased, contributing to a null effect overall. At this time, with somewhat conflicting data, the utility of steroids in sepsis remains controversial and should be reserved for cases in which the risk of cardiovascular collapse from refractory hypotension due to adrenal suppression outweighs the risk of increased morbidity and mortality from secondary infection.[55,57]

DISPOSITION

Once ED management is complete, antibiotics are given, and the need for an emergency operative intervention or procedure has been excluded, patients who are deemed at increased risk should be admitted to the hospital. Patients with septic shock should be admitted to an intensive care unit, and those with one of the other sepsis syndromes can be admitted to a monitored floor with close supervision or an intensive care unit, as needed. In certain instances, patients initially meeting sepsis criteria but who are not severely ill (e.g., young patients with pharyngitis) may be appropriate for discharge. However, this should be reserved for stable patients who are unlikely to decompensate.

KEY CONCEPTS

- Sepsis is a progression of disease due to a dysregulated inflammatory cascade, leading to organ dysfunction and circulatory compromise in severe cases.
- Elders, immunocompromised and neutropenic patients, and patients with multiple comorbidities are at increased risk for development of sepsis syndromes.
- Early goal-directed therapy can improve the outcome of patients with sepsis. Treatment should focus on (1) improvement of tissue perfusion (through administration of fluids and vasopressor medications), (2) improvement of tissue oxygenation (through administration of oxygen and positive-pressure ventilation), (3) administration of appropriate antibiotics, and (4) early identification of infections requiring surgical management.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Bone R; American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; 20:864-874.
2. Shapiro NI, et al: The association of sepsis syndrome and organ dysfunction with mortality in emergency department patients with suspected infection. *Ann Emerg Med* 2006; 48:583-590.
3. Howell M, et al: Proof of principle: The predisposition, infection, response, organ failure sepsis staging system. *Crit Care Med* 2011; 39:322-327.
4. Levy MM, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31:1250-1256.
5. Rangel-Frausto M, et al: The natural history of the systemic inflammatory response syndrome (SIRS). *JAMA* 1995; 273:117-123.
6. Bates D, Cook E, Goldman L, Lee T: Predicting bacteremia in hospitalized patients: A prospectively validated model. *Ann Intern Med* 1990; 113:495-500.
7. Brun-Buisson C, et al: Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. *JAMA* 1995; 274:968-974.
8. Perl T, Dvorak L, Hwang T, Wenzel R: Long-term survival and function after suspected gram-negative sepsis. *JAMA* 1995; 274:338-345.
9. Murray S, Bates DW, Ngo L, Ufberg J, Shapiro NI: Charlson Index is associated with one-year mortality in emergency department patients with suspected infection. *Acad Emerg Med* 2006; 13:530-536.
10. Xu J, Kochanek K, Murphy S, Tejada-Vera B: Deaths: Final data for 2007. *Natl Vital Stat Rep* 2010; 58:1-51.
11. Wang H, Shapiro NI, Angus D, Yealy D: National estimates of severe sepsis in United States emergency departments. *Crit Care Med* 2007; 35:1928.
12. Angus D, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303-1310.
13. Martin G, Mannino D, Eaton S, Moss M: The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; 348:1546-1554.
14. Strehlow M, et al: National study of emergency department visits for sepsis, 1992-2001. *Ann Emerg Med* 2006; 48:326.
15. Marshall JC, Reinhart K, Forum IS: Biomarkers of sepsis. *Crit Care Med* 2009; 37:2290-2298.
16. Russell J: Management of sepsis. *N Engl J Med* 2006; 355:1699-1713.
17. Ferreira F, et al: Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001; 286:1754.
18. Akira S, Uematsu S, Takeuchi O: Pathogen recognition and innate immunity. *Cell* 2006; 124:783-801.
19. Schouten M, Wiersinga W, Levi M, van der Poll T: Inflammation, endothelium, and coagulation in sepsis. *J Leukoc Biol* 2008; 83:536-545.
20. Opal S, Huber C: Bench-to-bedside review: Toll-like receptors and their role in septic shock. *Crit Care Med* 2002; 6:125.
21. Zhao B, Bowden R, Stavchansky S, Bowman P: Human endothelial cell response to gram-negative lipopolysaccharide assessed with cDNA microarrays. *Am J Physiol Cell Physiol* 2001; 281:C1587.
22. Toussaint S, Gerlach H: Activated protein C for sepsis. *N Engl J Med* 2009; 361:2646-2652.
23. Holmes CL, Walley KR, Chittock DR, Lehman T, Russell JA: The effects of vasopressin on hemodynamics and renal function in severe septic shock: A case series. *Intensive Care Med* 2001; 27:1416-1421.
24. Beasley D, Schwartz J, Brenner B: Interleukin-1 induces prolonged L-arginine–dependent cyclic guanosine monophosphate and nitrite production in rat vascular smooth muscle cells. *J Clin Invest* 1991; 87:602-608.
25. Eidelman L, Putterman D, Putterman C, Sprung C: The spectrum of septic encephalopathy: Definitions, etiologies, and mortalities. *JAMA* 1996; 275:470-473.
26. Werdan K, et al: Impaired regulation of cardiac function in sepsis, SIRS, and MODS. *Can J Physiol Pharmacol* 2009; 87:266-274.
27. Lipiner-Friedman D, et al: Adrenal function in sepsis: The retrospective Corticus cohort study. *Crit Care Med* 2007; 35:1012-1018.
28. Faust SN, et al: Dysfunction of endothelial protein C activation in severe meningococcal sepsis. *N Engl J Med* 2001; 345:408-416.
29. Bernard GR, et al: Safety and dose relationship of recombinant human activated protein C for coagulopathy in severe sepsis. *Crit Care Med* 2001; 29:2051-2059.

29a. Ranieri VM, et al: Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med* 2012; 366:2055.

30. Sheu C, et al: A large-scale genetic association study identifies different susceptibility loci of sepsis-related and non–sepsis-related ARDS. *Am J Respir Crit Care Med* 2010; 181:A2702.
31. Dolinay T, et al: Gene expression profiling of sepsis patients reveals inflammasome-mediated susceptibility to acute respiratory distress syndrome development. *Am J Respir Crit Care Med* 2011; 183:A2896.
32. Shapiro NI, et al: Mortality in Emergency Department Sepsis (MEDS) score: A prospectively derived and validated clinical prediction rule. *Crit Care Med* 2003; 31:670-675.
33. Sankoff J, et al: Validation of the Mortality in Emergency Department Sepsis (MEDS) score in patients with the systemic inflammatory response syndrome (SIRS). *Crit Care Med* 2008; 36:421-426.
34. Shapiro NI, et al: Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med* 2005; 45:524-528.
35. Rivers E, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368-1377.
36. Shah M, et al: Impact of the pulmonary artery catheter in critically ill patients: Meta-analysis of randomized clinical trials. *JAMA* 2005; 294:1664-1670.
37. Bernard GR, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; 344:699-709.
38. Dellinger RP, et al: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2008; 36:296-327.
39. Czer L, Shoemaker W: Optimal hematocrit value in critically ill patients. *Surg Gynecol Obstet* 1978; 147:363-368.
40. Hebert P, et al: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999; 340:409-417.
41. Pope J, et al: Multicenter study of central venous oxygen saturation ($Scvo_2$) as a predictor of mortality in patients with sepsis. *Ann Emerg Med* 2010; 55:40-46.
42. Wheeler A, Gordon R: Treating patients with severe sepsis. *N Engl J Med* 1999; 340:207-214.
43. Dellinger RP, et al: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Intensive Care Med* 2004; 30:536-555.
44. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342:1301-1308.
45. De Backer D, et al: Does hepato-splanchnic $\dot{V}O_2/DO_2$ dependency exist in critically ill septic patients? *Am J Respir Crit Care Med* 1998; 157:1219-1225.
46. Russell J, et al: Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358:877-887.
47. De Backer D, et al; SOAP II Investigators: Comparison of dopamine and norepinephrine in the treatment of schock. *N Engl J Med* 2010; 362:779-789.
48. Vasu T, et al: Norepinephrine or dopamine for septic shock: A systematic review of randomized clinical trials. *J Intensive Care Med* 2012; 27:172-178.
49. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J: Low-dose dopamine in patients with early renal dysfunction: A placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet* 2000; 356:2139-2143.
50. Kellum JA, M Decker J: Use of dopamine in acute renal failure: A meta-analysis. *Crit Care Med* 2001; 29:1526-1531.
51. Gregory J, et al: Experience with phenylephrine as a component of the pharmacologic support of septic shock. *Crit Care Med* 1991; 19:1395-1400.
52. Morelli A, et al: Phenylephrine versus norepinephrine for initial hemodynamic support of patients with septic shock: A randomized, controlled trial. *Crit Care* 2008; 12:R143.
53. Kumar A, et al: Cardiovascular response to dobutamine stress predicts outcome in severe sepsis and septic shock. *Crit Care* 2008; 12:R35.
54. Aube H, Milan C, Bletery B: Risk factors for septic shock in the early management of bacteremia. *Am J Med* 1992; 93:283-288.
55. Annane D, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862-871.
56. Sprung CL, et al: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358:111-124.
57. Marik PE, Zaloga GP: Adrenal insufficiency during septic shock. *Crit Care Med* 2003; 31:141-145.

www.ketabpezeshki.com 66485457-66963820

Chapter 139

Frostbite

Ken Zafren and Daniel F. Danzl

PERSPECTIVE

Unlike other animals that live outside the tropics, humans are susceptible to peripheral cold injuries. The highest homeostatic priority is to maintain the body's core temperature. This is accomplished through peripheral vasoconstriction and shunting, which prevent adequate heat distribution to the extremities. As a result, failure to achieve adequate protection from the environment results in injuries that are usually preventable.[1-3]

Peripheral cold injuries include both freezing and nonfreezing syndromes, which may occur independently or in conjunction with systemic hypothermia.[4] Frostbite is the most common freezing injury.[5] Trench foot and immersion foot are nonfreezing injuries that result from exposure to wet cold.[6] Nonfreezing injury that usually occurs after exposure to dry cold is termed chilblains (pernio).[7]

The incidence and severity of frostbite correlate with predisposing factors as well as with the degree of cold stress. Most cases of civilian frostbite result from exposure to cold by individuals who have not given due consideration to risk factors for cold injury.[8,9] Well-equipped ascents of the world's highest peaks have been completed without cold injury when appropriate steps have been taken to address these factors.[10,11] An increase in outdoor recreational activities has increased the number of people exposed to severe cold conditions.[12,13] Unsheltered homeless people are no longer the most likely group at risk in areas with moderate climates.[14]

Military history is replete with accounts of the effects of cold injury on combat troops.[15,16] Amputations and time lost to local cold injuries in both world wars and the Korean conflict were extensive. Trench foot was common among Argentine and British forces in the Falkland Islands.[4,17]

Napoleon's Surgeon General, Baron Larrey, first recorded the disastrous effects of the freeze-thaw-refreeze cycle.[18] During the 1812 to 1813 Russian invasion and retreat, soldiers would acutely thaw frozen extremities directly over open fires. The subsequent refreeze further increased tissue destruction. Unfortunately, the resultant gangrene was misattributed to this rapid thawing of frostbite and trench foot injuries. Therefore, gradual thawing, often including friction massage with snow, remained the standard treatment regimen until the 1950s.[19,20] In 1961, Mills ultimately popularized rapid warm immersion rewarming after extensive experience with severe Alaskan frostbite cases.[20,21]

PRINCIPLES OF DISEASE

Physiology

Human cold stress should induce adaptive behavioral reactions such as an attempt to find heat or shelter. In addition, complex endocrinologic and cardiovascular physiologic responses are engaged. Peripheral cooling of the blood activates the preoptic anterior hypothalamus. This central thermostat orchestrates temperature regulation. This dynamic process encompasses catecholamine release, thyroid stimulation, shivering thermogenesis, and peripheral vasoconstriction.

Cutaneous circulation is one of the keys to maintenance of thermoneutrality. Baseline cutaneous circulation greatly exceeds the nutritional requirements. This reflects the skin's "radiator" function to maintain thermostability. Cutaneous blood flow in the euthermic 70-kg human averages 200 to 250 mL/min. Heat stress causes vasodilation that can increase this amount to 7000 mL/min. In contrast, extreme cold-induced vasoconstriction reduces flow tenfold to less than 50 mL/min.

During cold stress, peripheral vasoconstriction limits radiant heat loss. Acral skin structures (fingers, toes, ears, nose) contain a plethora of arteriovenous anastomoses. These arteriovenous anastomoses shut down in the cold, causing drastic reductions in blood flow. This "life-versus-limb" mechanism reflects the homeostatic attempt to prevent systemic hypothermia.

In contrast to heat exposure, humans do not appear to display significant physiologic adaptation to the cold. Exposure of extremities to temperatures down to 15° C results in maximal peripheral vasoconstriction with minimal blood flow. Continued exposure to progressively colder temperatures down to 10° C produces the "hunting response," which is cold-induced vasodilation.[22] These periods of vasodilation, recurring in 5- to 10-minute cycles, interrupt vasoconstriction and serve to protect the extremity. Eskimos as well as Lapps and others of Nordic extraction are capable of stronger cold-induced vasodilation than that in individuals from tropical regions. Measurement of the speed of cold-induced vasodilation may help predict an individual's risk for cold injury.[23] There is evidence of adaptation rather than pure genetic control.[24]

Pathophysiology

The pathologic phases that occur with local cold injury often overlap and vary with the extent and rapidity of the cold response

www.ketabpezeshki.com 66485457-66963820

Box 139-1 Freezing Injury Cascade

Prefreeze Phase
Superficial tissue "cooling"
Increased viscosity of vascular contents
Microvascular constriction
Endothelial plasma leakage

Freeze-Thaw Phase
*Extra*cellular fluid ice crystal formation*
Water diapedesis across cell membrane
*Intra*cellular dehydration and hyperosmolality
Cell membrane denaturation or disruption
Cell shrinkage and collapse

Vascular Stasis and Progressive Ischemia
Vasospasticity and stasis coagulation
Arteriovenous shunting
Vascular endothelial cell damage or prostanoid release
Interstitial leakage or tissue hypertension
Necrosis, demarcation, mummification, or slough

*Extremely rapid cooling produces more initial intracellular than extracellular ice crystallization.

Box 139-2 Predisposing Factors

Physiologic
Genetic
Core temperature
Previous cold injury
Acclimatization
Dehydration
Overexertion
Trauma: multisystem, extremity
Dermatologic diseases
Physical conditioning
Diaphoresis, hyperhidrosis
Hypoxia

Mechanical
Constricting or wet clothing
Tight boots
Vapor barrier, alveolite liners
Inadequate insulation
Immobility or cramped positioning

Psychological
Mental status
Fear, panic
Attitude
Peer pressure
Fatigue
Intense concentration on tasks
Hunger, malnutrition
Intoxicants

Environmental
Ambient temperature
Humidity
Duration of exposure
Wind chill factor
Altitude and associated conditions
Quantity of exposed surface area
Heat loss: conductive, evaporative
Aerosol propellants

Cardiovascular
Hypotension
Atherosclerosis
Arteritis
Raynaud's syndrome
Cold-induced vasodilation
Anemia
Sickle cell disease
Diabetes
Vasoconstrictors, vasodilators

(Box 139-1). Frostbite occurs when the tissue supercools well below 0° C. The required temperature is at least −4° C and may be as low as −10° C.

There are two putative mechanisms of tissue injury: architectural cellular damage from ice crystal formation and microvascular thrombosis and stasis.[25] In the *prefreeze* phase, tissue temperatures drop below 10° C and cutaneous sensation is lost. Before ice crystal formation, microvascular vasoconstriction occurs along with endothelial leakage of plasma into the interstitium. Radiation and conduction of heat from deeper tissues prevent crystallization until the skin temperature drops well below 0° C.[26] In the *freeze-thaw* phase, the timing, location, and rate of ice crystal formation depend on the exposure circumstances. In addition to ambient temperatures, wind and moisture increase the freezing rate.

During usual exposure conditions, ice crystal formation initially occurs extracellularly. This results in diapedesis of water exiting the cell to maintain osmotic equilibrium. Cellular dehydration increases the intracellular osmolarity and electrolyte concentrations. When approximately one third of the cellular volume is lost, cellular collapse and death result. These may occur with or without direct architectural damage from the crystals. Extracellular crystallization also increases the tissue pressure on cell membranes and surrounding vascular structures. Sludging, stasis, and cessation of flow occur at the capillary level.

The third phase, progressive microvascular collapse, first affects venules and then arterioles. Red blood cells sludge and form microthrombi during the first few hours after the tissues are thawed. Factors adversely affecting flow include hypoxic vasospasm, hyperviscosity, and direct endothelial cell damage. Anaerobic metabolism subsequently extends the surrounding injury. Tissues are deprived of nutrients and oxygen. Ultimately, plasma leakage and arteriovenous shunting result in thrombosis, increased tissue pressure, ischemia, and necrosis.

Some direct skin injury is reversible. For example, frozen skin grafted to a normal site can survive. The histopathology of frostbite suggests that some changes in the epidermis are primary and some reflect damage to the endothelial cells. During initiation of rewarming, these tissues are revitalized.

An additional insult, progressive dermal ischemia, is partially mediated by thromboxane.[27] Fluid analysis of clear vesicles identifies prostaglandins. When subdermal vascular plexuses are injured, hemorrhagic blisters develop that also contain these prostanoids. The arachidonic acid breakdown products released from underlying damaged tissue into the blister fluid include both prostaglandins and thromboxane. These mediators produce platelet aggregation, vasoconstriction, and leukocyte immobilization.[28]

The ultimate determinant of progressive tissue damage appears to be injury to the microvasculature. Endothelial cells are the tissue most susceptible to freezing injury. After thawing, the vasculature is patent only temporarily. Platelet and erythrocyte aggregates promptly clog and distort the vasculature. Intense vasoconstriction coupled with arteriovenous shunting occurs at the interface between normal and damaged tissue. The injured viable vasculature remains distorted. Local arteritis, medial degeneration, and intimal proliferative thickening are seen. Nerve and muscle tissues are also more susceptible than connective tissue to cold injury. For example, nonviable hands and feet can be moved after thawing if the tendons are intact.

Edema progresses for 48 to 72 hours after tissue is thawed. Leukocyte infiltration, thrombosis, and early necrosis become apparent as this edema resolves. The dry gangrene carapace of frostbite is superficial in comparison to arteriosclerosis-induced, full-thickness gangrene. Although the historical surgical aphorism was "frostbite in January, amputate in July," advances in imaging modalities can accelerate the identification of the demarcation between viable and nonviable tissue.[21]

Predisposing Factors

The extent of peripheral cold injury is determined by the type and duration of cold contact with the skin (Box 139-2).[29] Predisposing risks include physiologic, mechanical, psychological, environmental, and cardiovascular factors.

Any conditions affecting judgment can jeopardize the physiologically tropical human. In urban settings, cold injuries are often attributed to psychiatric impairment or intoxication, primarily

www.ketabpezeshki.com 66485457-66963820

ethanol intoxication. Ethanol also produces peripheral vasodilation, which increases heat loss. Blunting of self-protective instincts can cause people to fail to undertake appropriate adaptive maneuvers to minimize exposure to cold.

Although air alone is a poor thermal conductor, associated cold and wind (wind chill index) markedly increase heat loss. Direct skin contact with good thermal conductors such as metal, water, and volatile liquids affects the extent and rapidity of tissue destruction. Commercial aerosol spray propellants, such as propane and butane, and carbon dioxide in fire extinguishers are potentially hazardous.[30] Liquid oxygen and Freon can also cause frostbite.[31,32] Overenthusiastic application of standard ice packs in the treatment of soft tissue injuries can also result in tissue loss.[33] Cryotherapy is commonly prescribed in sports medicine. In addition to improper use of cold packs, vapor coolant sprays such as chloroethane can cause frostbite.[34,35]

CLINICAL FEATURES

Symptoms and Signs

"Frostnip" is a superficial cold insult manifested by transient numbness and tingling that resolves after rewarming. This does not represent true frostbite because no tissue destruction occurs.

The symptoms of frostbite usually reflect the severity of the exposure. The most common presenting symptom is numbness, found in more than 75% of patients. All patients have some initial sensory deficiency in light touch, pain, or temperature. Anesthesia is produced by intense vasoconstrictive ischemia and neurapraxia. Acral areas and distal extremities are the usual insensate sites. The distal extremities—the fingers, toes, nose, ears, and penis—are specific locations at risk. Patients often complain of clumsiness and report a "chunk of wood" sensation in the extremity. The history of complete acute anesthesia in a painful cold digit suggests a severe injury.

Classically, the initial presentation of frostbite is deceptively benign. Most patients do not arrive in the emergency department with frozen, insensate tissue. Frozen tissues often appear mottled or violaceous-white, waxy, or pale yellow. In severe cases, the examiner will not be able to roll the dermis over bone prominences. Rapid rewarming results in an initial hyperemia, even in severe cases. After thawing, partial return of sensation should be expected until blebs form.[21]

Favorable initial symptoms include normal sensation, warmth, and color. Soft, pliable subcutaneous tissue suggests a superficial injury. A residual violaceous hue after rewarming is ominous. Early formation of clear large blebs that extend to the tips of the digits is more favorable than delayed appearance of smaller hemorrhagic blebs. These dark vesicles are produced by damage to the subdermal vascular plexuses. Vesicles and large bullae usually form in 1 to 24 hours.

Lack of edema formation suggests significant tissue damage. Post-thaw edema usually develops in less than 3 hours. In severe cases, frostbitten skin forms an early black, dry eschar until mummification and apparent demarcation.

Historically, frostbite, like burns, has been classified into degrees of injury. Anesthesia and erythema are characteristic of first-degree frostbite. Superficial vesiculation surrounded by edema and erythema is considered second-degree frostbite. Third-degree frostbite produces deeper hemorrhagic vesicles. Fourth-degree injuries extend into subcuticular, osseous, and muscle tissues.

Classification by degrees is often incorrect in relation to the actual severity of the frostbite and thus therapeutically misleading. Mills suggests two simple retrospective classifications.[20,21] Superficial or mild frostbite does not entail eventual tissue loss, whereas deep or severe frostbite does result in tissue loss. As a result, it is not feasible to predict, on presentation, the eventual tissue loss. Another classification attempts to establish severity on the basis of clinical features coupled with early bone scan results.[17,36] Significant pain usually accompanies reestablishment of perfusion. With partial tissue destruction, intermittent pain may be noticed during ongoing exposure. The dull continuous ache evolves into a throbbing sensation in 48 to 72 hours. This often persists until tissue demarcation several weeks to months later. Nonfreezing cold injury occurs when tissue fluids have not frozen. Chilblain (pernio) is a mild form of cold injury that often follows repetitive exposure. These "cold sores" appear less than 24 hours after exposure and usually affect facial areas, the dorsa of the hands and feet, and the pretibial areas. Young women with a history of Raynaud's phenomenon or systemic lupus erythematosus or with antiphospholipid antibodies are especially at risk. Persistent vasospasm and vasculitis result in burning, pruritus, erythema, and mild edema. Plaques, blue nodules, and ulcerations can develop and last 1 to 2 weeks.

The other common nonfreezing cold injury is trench foot (immersion foot). This remains a significant threat during recreational activities and military expeditions in cold, wet climates. Trench foot is produced by prolonged exposure to wet cold at temperatures above freezing.[6] It usually develops slowly during several days and results in neurovascular damage in the absence of ice crystal formation. Immersion foot commonly develops while a person is wearing sweat-dampened or neoprene socks, vapor-barrier boots, or constrictive gaiters. Patients who soak their feet for hours each night in cool water for pain relief are also at risk.

The clinical presentation varies. Most patients' symptoms include cool, pale feet that are numb or tingle. Later the feet appear cyanotic, cold, and edematous. Often, numbness and leg cramping are present. The clinical hallmark is that after rewarming, the skin remains erythematous, dry, and very painful to touch. Rubor on dependency and pallor on elevation are caused by vasomotor paralysis. Infrared thermography in response to a cold stress may support the diagnosis and assess its severity.[17]

Bullae that are indistinguishable from those seen with frostbite commonly develop. Vesiculation may proceed to ulceration and liquefaction gangrene in severe cases. Protracted symptoms of pain during weightbearing, cold sensitivity, and hyperhidrosis often last for years. Prevention of trench foot often requires continual drying of socks.

DIAGNOSTIC STRATEGIES

Many ancillary diagnostic imaging techniques attempt to grade the severity of injury. Unfortunately, none consistently and accurately predicts tissue loss at the time of initial examination.

Routine baseline radiographs should be obtained. Follow-up radiographs will begin to demonstrate specific frostbite abnormalities 4 to 10 weeks after injury. Intravenous isotope studies have had mixed success experimentally and clinically.[37,38] In one study, triple-phase bone scans performed 2 days after cold injury demonstrated ischemic tissue at risk.[39,40] Delayed bone scans in 7 to 10 days can image deep tissue and bone infarction. The absence of radionuclide uptake even after 10 days, however, does not reliably predict the eventual need for amputation. The patient should be advised that accurate prediction of eventual tissue loss is difficult. As an ancillary tool, scintigraphy predicts the eventual demarcation line better than thermography does.[41] Scintigraphy as early as day 2 may predict tissue loss and monitor the efficacy of treatment.[42]

Large-vessel angiography does not assess the microvasculature at presentation because of vasospasm. Use of papaverine may help distinguish vasospasm from frostbite sludging and vascular injury. Transitory vascular instability often lasts 2 to 3 weeks. Angiography does facilitate evaluation of associated traumatic or chronic

www.ketabpezeshki.com 66485457-66963820

vascular abnormalities. Doppler ultrasonography and digital plethysmography are insensitive but may help determine the need for sympathetic blockade.

In clinical practice, magnetic resonance imaging and magnetic resonance angiography may be superior to technetium bone scanning. In one study, the clear-cut line of demarcation was noted before clinical demarcation. Magnetic resonance imaging of developing hyaline cartilage can demonstrate physeal injury, which has the largest impact on longitudinal growth.[43]

MANAGEMENT

Field rewarming of frozen tissue is rarely practical. If possible, constricting or wet clothing should be removed and affected areas insulated and immobilized. Friction massage is not efficacious and increases tissue loss. Frozen parts should be kept away from dry heat sources such as heated forced air during transport.

A relationship often exists between the length of time that tissue is frozen and the ultimate extent of cellular damage. Rewarming should not be initiated in the field, however, if there is any potential for interrupted or incomplete thawing. Tissue refreezing is disastrous, and it is preferable to ambulate to safety on frozen extremities if rescue will be delayed.

When evacuation is not possible, rapid field rewarming, preferably in water at 37 to 39° C, may be the only option. Logistic considerations include the risks to the party, the availability of shelter and necessary equipment, and the anticipated mode of eventual transportation.

Box 139-3 Emergency Department Rewarming Protocol

Prethaw
- Assess Doppler pulses and appearance
- Protect part—no friction massage
- Stabilize core temperature
- Address medical and surgical conditions
- Rehydrate patient
- Prevent partial thaw and refreeze

Thaw
- Provide parenteral ketorolac and opiate analgesia as needed
- Administer ibuprofen 400-600 mg every 6 hours orally
- Immerse part in circulating water that is thermometer monitored at 37 to 39° C
- Encourage gentle motion of part

Post-thaw
- Dry and elevate part
- Aspirate or débride clear vesicles
- Débride broken vesicles and apply topical antibiotic or sterile aloe vera ointment every 6 hours
- Leave hemorrhagic vesicles intact
- Consider tetanus and streptococcal prophylaxis
- Provide hydrotherapy at 37° C three times a day
- Consider phenoxybenzamine in severe cases
- Consider imaging, angiography, and thrombolysis
- Obtain admission and serial photographs

Emergency Department

Prethaw

Pertinent history regarding the ambient temperature, wind velocity, and duration of exposure should be obtained. The type of apparel worn, the circumstances surrounding rescue, and the presence of preexisting cardiovascular or neurologic diseases that could affect tissue loss should be noted.[44]

After the core temperature has been stabilized and associated conditions have been addressed, rapid thawing of frostbitten extremities should be initiated. Treatment should not be delayed while the results of laboratory and radiographic studies are awaited. Most patients have some degree of dehydration and benefit from crystalloid administration. Poor oral intake and hypothermia-induced cold diuresis further increase blood viscosity and sludging.

Thaw

Frozen or partially thawed tissue should be rapidly and actively rewarmed by immersion in gently circulating water that is carefully maintained at a temperature of 37 to 39° C by thermometer measurement.[20] Marginal tissue can suffer thermal injury when the water temperature exceeds 42° C. Although a circulating tank is ideal for arms or legs, a large container suffices for the hands or feet. Water warmer than 39° C is less well tolerated and causes more pain. Care should be taken to prevent the frostbitten area from bumping or rubbing against the side of the container.

Rewarming should be continued until the part feels pliable and distal erythema is noted. This usually requires 10 to 30 minutes of submersion. Encourage active gentle motion of the part by the patient during rewarming but avoid direct tissue massage.

Parenteral analgesia is often indicated during rewarming of deep frostbite. Reperfusion may be intensely painful. It produces throbbing, burning pain and tenderness. A common error is premature termination of rewarming, which results in a partial thaw. Sensation is often diminished after thawing until it disappears with bleb formation.

Patients with completely frozen extremities are usually hypothermic and at risk for significant fluid and electrolyte fluxes during rewarming. The acute thawing of large amounts of distal musculature extinguishes peripheral vasoconstriction. This results in the sudden return of cold, hyperkalemic, acidotic blood to the central circulation. This produces "core temperature afterdrop," which is dysrhythmogenic. In the most severe cases, extracorporeal rewarming should be considered for management of these massive metabolic and electrolyte derangements (Box 139-3).

Post-thaw

The injured extremities should be kept elevated to minimize edema formation. Sterile dressings should be applied and involved areas handled gently. Persistent cyanosis in the extremities after a complete thaw may reflect increased fascial compartment pressure. Because of the cold-induced anesthesia, other occult soft tissue injuries are often not appreciated by the patient or physician. Tissue pressures should be monitored carefully, although decompressing fasciotomies are usually not necessary during the initial treatment rendered in the emergency department.

The clinical role of thromboxane inhibition in frostbite seems to be limited. Thromboxane inhibition does not appear to result in additional clinically significant tissue salvage. In one experimental model, methimazole did not improve tissue survival even when therapy was initiated immediately.[45] Progressive secondary dermal ischemia is addressed by attempts to limit the accumulation of the products of arachidonic acid breakdown. Topical aloe vera (Dermaide) every 6 hours is a specific thromboxane inhibitor when it is applied directly to frostbitten areas but has not definitively been proven to salvage tissue.[28] Other alternatives include topical antibiotic ointment. Theoretically, oral ibuprofen appears preferable to oral aspirin. Although both agents inhibit the arachidonic acid cascade, ibuprofen also produces fibrinolysis. Parenteral ketorolac can also be considered.

www.ketabpezeshki.com 66485457-66963820

Figure 139-1. Frostbite with clear vesiculations. (Courtesy Bill Mills, MD.)

Figure 139-2. Severe frostbite with early hemorrhagic vesicles. (Courtesy Bill Mills, MD.)

Frostbite blister management varies widely. Recommended options for large clear blisters include leaving them intact, débridement, and aspiration (Fig. 139-1). Although most clinicians débride broken blisters, many prefer to aspirate intact clear blisters rather than to débride them. In contrast, if hemorrhagic blisters are débrided, secondary desiccation of deep dermal layers appears to extend the injury (Fig. 139-2). In this case, aspiration is preferable to débridement.

In severe cases, parenteral penicillin may be indicated for streptococcal prophylaxis. Cultures and Gram's stains of areas adjacent to the damaged tissue should be performed. Common organisms causing secondary infection include staphylococci, streptococci, and *Pseudomonas* species. Tetanus can also occur after frostbite. Tetanus prophylaxis should follow usual wound care guidelines.

Management of the chilblains syndrome is usually supportive. Nifedipine (20-60 mg daily) is an effective treatment of refractory perniosis.[46,47] Topical or systemic corticosteroids have also been useful. Other options include oral pentoxifylline and limaprost, a prostaglandin E_1 analogue.

Adjunctive Treatment

Numerous ancillary modalities have been suggested for frostbite.[48] Capillary flow ceases early after cold injury, whereas thrombosis proceeds.[10,40] This observation has led to multiple experimental antithrombotic and vasodilation treatment regimens, although most lack adequate controls. Many of these studies were conducted before the elucidation of some of the pathophysiologic consequences of frostbite. Triple-phase bone scans have demonstrated that thrombolytic agents may restore some flow to severely frostbitten limbs.

Thrombolytic Therapy

Thrombolytic therapy may address the primary residual pathophysiologic changes if the cumulative cold-ischemia time (frozen time) and warm-ischemia time (thawed and unperfused) is not excessive. In one retrospective study, intravenous tissue plasminogen activator and heparin reduced predicted digit amputations in severe frostbite.[42] Nonresponders had more than 24 hours of exposure, more than 6 hours of warm ischemia, or multiple freeze-thaw cycles. In another study, intra-arterial tissue plasminogen activator decreased the incidence of amputations when it was administered within 24 hours.[49]

A screening and treatment tool is proposed for thrombolysis.[50,51] If the flow is absent after thawing and both the cold-exposure and warm-ischemia times are each less than 24 hours, angiography is performed with intra-arterial vasodilators. Nitroglycerin and papaverine have both been used successfully. If flow is not reestablished, continuously infuse intra-arterial catheter-directed tissue plasminogen activator to a maximum dose of 1 mg/hr. Heparin is administered concurrently and continued for 72 to 96 hours.[51,52] A second alternative approach combines systemic intravenous thrombolytic therapy with subsequent vascular evaluation by technetium scanning.

Low-molecular-weight dextran may inhibit intravascular cellular aggregation. Animal models suggest that low-molecular-weight dextran is not harmful. Pentoxifylline, a phosphodiesterase inhibitor, may decrease blood viscosity and increase tissue oxygenation.[53] Its ability to increase red blood cell flexibility facilitates revascularization and may enhance tissue survival. The suggested dosage is 400 mg three times daily for 2 to 6 weeks.[54]

Various anti-inflammatory drugs and other agents have not been conclusively evaluated. These include steroids, nonsteroidal anti-inflammatory drugs, dipyridamole, dimethyl sulfoxide, nonionic detergents, and calcium channel blockers.[55,56] A long-acting alpha-blocker, phenoxybenzamine, may decrease vasospasm while increasing peripheral blood flow. The dosage starts with 10 mg/day to a maximum of 60 mg/day. With this agent, adequate hydration is necessary to prevent orthostatic hypotension.

Hyperbaric oxygen produces vasoconstriction and subsequently reduces cutaneous blood flow. A small number of patients report a temporary flush and increased limb motion, but this appears to depend on the elapsed time interval after injury. Hyperbaric oxygen has the potential to accelerate demarcation. There are insufficient data to assess the potential value of hyperbaric oxygen therapy for tissue salvage in severe frostbite.[57,58]

Sympathectomy

The theoretic benefits of sympathectomy include relief of painful vasospasm, decreased edema, and increased tissue salvage. Long-term vasodilation could theoretically protect against repeated cold injury and some of the degenerative sequelae of frostbite. The value of these benefits is speculative. Epidural spinal cord stimulation combined with conventional treatment may reduce pain and conserve tissue.

A chemical sympathectomy results from direct injection of an agent such as reserpine into an artery. Common injection sites include the radial, brachial, and femoral arteries. This injection produces local depletion of arterial wall norepinephrine for 2 to

www.ketabpezeshki.com 66485457-66963820

4 weeks. No significant systemic effects are appreciated with the recommended dose of 0.5 mg. This can be repeated in 2 to 3 days. Parenteral reserpine is not commercially available in the United States. There is angiographic documentation of temporary improvement in perfusion and vasospasm after chemical sympathectomy. When tissue is rapidly thawed, experimental attempts to demonstrate further enhancement of tissue salvage have failed. Intra-arterial reserpine may prove most useful in patients with residual pain after gradual thawing.

Iloprost, a prostacyclin analogue, also has vasodilatory properties that mimic a chemical sympathectomy. The risk of amputation is significantly lower in a controlled trial of patients with severe frostbite who received intravenous iloprost plus aspirin after thawing.[59] Selected patients in this series with severe frostbite were also treated with recombinant tissue plasminogen activator. Forearm nerve blocks also produce in effect a chemical sympathectomy that increases finger skin temperature.[60]

Early results with surgical sympathectomy were encouraging. Bouwman and colleagues performed unilateral surgical sympathectomy on 10 patients with bilateral matched frostbite injuries.[61] Delayed protection against reinjury was one direct benefit. Ultimately, however, there was no increased tissue salvage. Mills observed that surgical sympathectomy produces a smoother initial clinical course but no long-term benefits, with the possible exception of decreased causalgia.[20,21]

Box 139-4 Sequelae of Frostbite

Neuropathic
- Pain
  - Phantom
  - Causalgia
  - "Tabes" burning
  - Chronic
- Sensation
  - Hypesthesia
  - Dysesthesia
  - Paresthesia
  - Anesthesia
- Thermal sensitivity
  - Heat
  - Cold
- Autonomic dysfunction
  - Hyperhidrosis
  - Raynaud's syndrome

Musculoskeletal
- Atrophy
- Compartment syndrome
- Rhabdomyolysis
- Tenosynovitis
- Stricture
- Epiphyseal fusion
- Osteoarthritis
- Osteolytic lesions
- Subchondral cysts
- Necrosis
- Amputation

Dermatologic
- Edema
- Lymphedema
- Chronic or recurrent ulcers
- Epidermoid or squamous cell carcinoma
- Hair or nail deformities

Miscellaneous
- Core temperature afterdrop
- Acute tubular necrosis
- Electrolyte fluxes
- Psychological stress
- Gangrene
- Sepsis

DISPOSITION

Except in minor cases, all patients should be hospitalized to determine the extent of injury. Damaged tissues are best protected with loose sterile sheets and towels rather than with compressive dressings. Feet should be kept elevated under a protective cradle. Sterile cotton pledgets should be placed between the toes, and the hands may rest elevated on the chest.

Whirlpool hydrotherapy with an antiseptic should be performed two or three times daily for 20 to 30 minutes to débride dead tissue and to decrease the amount of bacterial colonization. Range-of-motion exercises should be encouraged during immersion. Severe cases may require position-of-function splinting. Hydrotherapy is continued as the eschar sloughs. During hospitalization, all vasoconstrictive agents, including nicotine, should be avoided. Vacuum-assisted closure therapy attracts wound edges centripetally, reduces tissue edema, and promotes angiogenesis in burns and complex wounds. With frostbite, it could prove beneficial to prevent grafting or amputation.[62]

SEQUELAE

Direct neuronal damage and residual abnormalities in sympathetic tone are responsible for most of the common symptomatic sequelae of frostbite. In a series of military patients with documented frostbite, 65% had long-term residual symptoms. Vasospasm with secondary cold intolerance is the other major sequela.[63]

Intermittent paresthesias resulting from ischemic neuritis are reported after the first week. The severity of this symptom often reflects the extent of tissue damage. Symptoms may persist for many months. Burning electric shock sensations are worse at night, after heat exposure, and on first returning to ambulation. Thermal perception is also altered. Hyperhidrosis suggests an abnormal sympathetic nervous system response and often is both a cause and an effect of frostbite.

Delayed cutaneous findings include nail deformities and pigmentation changes. Squamous and epidermoid cell carcinoma can occur. Osseous reabsorption and subchondral lytic defects develop months after the cold insult. In pediatric patients, concerns include premature fusion, destruction, and fragmentation of epiphyses. Shortening of the distal phalanges is common.[63] Frostbite arthritis also occurs, commonly 3 to 10 years later. Thumb sparing is a characteristic idiosyncrasy. Clenching of the fists can spare both thumbs and metacarpophalangeal joints. Identification of subchondral cysts after bone infarction differentiates frostbite arthritis from osteoarthritis.[64] In severe cases involving extremity muscle compartments, rhabdomyolysis and subsequent renal failure are a concern. Continuous monitoring of serum muscle enzymes and urinalyses is warranted.

Surgical decisions regarding amputation are complex.[63,65] The amount of tissue eventually salvaged often exceeds even optimistic initial estimates. Historically, the natural progression of demarcation, mummification, and eventual sloughing was allowed to occur. Advances in radiologic assessment of tissue viability are facilitating earlier surgical intervention. Free flap tissue transfer to salvage function after earlier débridement of soft tissues should be a consideration.[65,66] Compared with grafts, flaps provide their own vascularity and are less dependent on the recipient bed.[67]

Various neuropathic, musculoskeletal, and dermatologic sequelae of frostbite are listed in Box 139-4.[68]

KEY CONCEPTS

- Premature termination of thawing in 37 to 39° C water is a common error. Reperfusion of completely frozen tissue may be very painful and may require parenteral analgesia.
- The early formation of clear blebs is more favorable than delayed hemorrhagic blebs, which reflect damage to the subdermal vascular plexuses.
- The patient should be advised that accurate prediction of eventual tissue loss is not always possible at presentation, despite imaging.
- Thrombolytic agents may restore some flow to severely frostbitten limbs.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Hamlet MP: Prevention and treatment of cold injury. *Int J Circumpolar Health* 2000; 59:108.
2. Long WB, et al: Cold injuries. *J Long Term Eff Med Implants* 2005; 15:67.
3. Angert D, Schaff EA: Preventing injuries and illnesses in the wilderness. *Pediatr Clin North Am* 2010; 57:683.
4. Thomas JR, Oakley HN: *Nonfreezing cold injury*. In: Pandolf KB, Burr RE, eds. *Textbook of Military Medicine: Medical Aspects of Harsh Environments*, vol 1. Washington, DC: Office of the Surgeon General, Borden Institute; 2002:467.
5. Koljonen V, et al: Frostbite injuries treated in the Helsinki area from 1995 to 2002. *J Trauma* 2004; 57:1315.
6. Atenstaedt RL: Trench foot: The medical response in the first World War 1914-1918. *Wilderness Environ Med* 2006; 17:282.
7. Makinen TM, et al: Occurrence of frostbite in the general population—work-related and individual factors. *Scand J Work Environ Health* 2009; 35:384.
8. Kroeger K, Janssen S, Niebel W: Frostbite in a mountaineer. *Vasa* 2004; 33:173.
9. Ervasti O, et al: The occurrence of frostbite and its risk factors in young men. *Int J Circumpolar Health* 2004; 63:71.
10. Harirchi I, et al: Frostbite: Incidence and predisposing factors in mountaineers. *Br J Sports Med* 2005; 39:898.
11. Subedi BH, et al: Frostbite in a Sherpa. *Wilderness Environ Med* 2010; 21:127.
12. McCauley RL, et al: *Frostbite*. In: Auerbach PS, ed. *Wilderness Medicine*, 5th ed. St. Louis: Mosby/Elsevier; 2007:195.
13. Castellani JW, et al: American College of Sports Medicine position stand: Prevention of cold injuries during exercise. *Med Sci Sports Exerc* 2006; 38:2012.
14. Jurkovich GJ: Environmental cold-induced injury. *Surg Clin North Am* 2007; 87:247.
15. DeGroot D, et al: Epidemiology of U.S. Army cold weather injuries, 1980-1999. *Aviat Space Environ Med* 2003; 74:564.
16. Moran D, et al: Hypothermia and local cold injuries in combat and non-combat situations: The Israeli experience. *Aviat Space Environ Med* 2003; 74:281.
17. Imray C, et al: Cold damage to the extremities: Frostbite and non-freezing cold injuries. *Postgrad Med J* 2009; 85:481.
18. Paton BC: "From Larrey to Mills": The road to rapid rewarming—a commentary. *Wilderness Environ Med* 1998; 9:223.
19. Paton BC: A history of frostbite treatment. *Int J Circumpolar Health* 2000; 59:99.
20. Mills WJ Jr, Whaley R, Fish W: Frostbite: Experience with rapid rewarming and ultrasonic therapy: Part III, 1961. *Alaska Med* 1993; 35:19.
21. Mills WJ Jr: Summary of treatment of the cold injured patient, 1980. *Alaska Med* 1993; 35:50.
22. Brajkovic D, Ducharme MB: Facial cold-induced vasodilatation and skin temperature during exposure to cold wind. *Eur J Appl Physiol* 2006; 96:711.
23. Daanen H, Van Der Struijs NR: Resistance index of frostbite as a predictor of cold injury in arctic operations. *Aviat Space Environ Med* 2005; 76:1119.
24. Keramidas ME, et al: Enhancement of the finger cold-induced vasodilation response with exercise training. *Eur J Appl Physiol* 2010; 109:133.
25. Golant A, et al: Cold exposure injuries to the extremities. *J Am Acad Orthop Surg* 2008; 16:704.
26. Lee CK, Hansen SL: Management of acute wounds. *Surg Clin North Am* 2009; 89:659.
27. Ozyazgan I, et al: Eicosanoids and inflammatory cells in frostbitten tissue: Prostacyclin, thromboxane, polymorphonuclear leukocytes, and mast cells. *Plast Reconstr Surg* 1998; 101:1881.
28. Heggers JP, et al: Frostbite: Experimental and clinical evaluations of treatment. *J Wilderness Med* 1990; 1:27.
29. Geng Q, et al: Temperature limit values for touching cold surfaces with the fingertip. *Ann Occup Hyg* 2006; 8:851.
30. Sever C, et al: Frostbite injury of the foot from portable fire extinguisher. *Dermatol Online J* 2009; 15:10.
31. Uygur F, Sever C, Noyan N: Frostbite burns caused by liquid oxygen. *J Burn Care Res* 2009; 30:358.
32. Sever C, et al: Hand burn caused by Freon gas. *Burns* 2008; 34:1210.
33. Keskin M, et al: Frostbite injury due to improper usage of an ice pack. *Ann Plast Surg* 2005; 55:437.
34. Soyuncu S, Yigit O, Eken C: Frostbite injury related to chlorethane application. *Wilderness Environ Med* 2009; 20:103.
35. Gamble WB, Bonnecarre ER: Coffee, tea, or frostbite? A case report of inflight freezing hazard from dry ice. *Aviat Space Environ Med* 1993; 67:880.
36. Cauchy E, et al: Retrospective study of 70 cases of severe frostbite lesions: A proposed new classification scheme. *Wilderness Environ Med* 2001; 12:248.
37. Kenney A 3rd, Vyas P: Frostbite injury: Appearance on three-phase bone scan. *Clin Nucl Med* 1998; 23:188.
38. Greenwald D, Cooper B, Gottlieb L: An algorithm for early aggressive treatment of frostbite with limb salvage directed by triple-phase scanning. *Plast Reconstr Surg* 1998; 102:1069.
39. Aygit AC, Sarikaya A: Imaging of frostbite injury by technetium-99m-sestamibi scintigraphy: A case report. *Foot Ankle Int* 2002; 23:56.
40. Cauchy E, et al: The value of technetium 99 scintigraphy in the prognosis of amputation in severe frostbite injuries of the extremities: A retrospective study of 92 severe frostbite injuries. *J Hand Surg Am* 2000; 25:969.
41. Bhatnagar A, et al: Diagnosis, characterization and evaluation of treatment response of frostbite using pertechnetate scintigraphy: A prospective study. *Eur J Nucl Med* 2002; 29:170.
42. Twomey JA, et al: An open-label study to evaluate the safety and efficacy of tissue plasminogen activator in treatment of severe frostbite. *J Trauma* 2005; 59:1350.
43. Khanna PC, Thapa MM: The growing skeleton: MR imaging appearances of developing cartilage. *Radiol Clin North Am* 2009; 47:899.
44. Biem J, et al: Out of the cold: Management of hypothermia and frostbite. *CMAJ* 2003; 168:305.
45. Goldberg BD, Robinson WA, Watson WA: Impact of delayed presentation on the efficacy of thromboxane inhibition in the treatment of frostbite. *J Wilderness Med* 1994; 5:325.
46. Parlette EC, Parlette HL III: Erythrocyanotic discoloration of the toes. *Cutis* 2000; 65:223.
47. Simon TD, Soep JB, Hollister JR: Pernio in pediatrics. *Pediatrics* 2005; 116:e472.
48. Petrone P, Kuncir EJ, Asensio JA: Surgical management and strategies in the treatment of hypothermia and cold injury. *Emerg Med Clin North Am* 2003; 21:1165.
49. Bruen KJ, et al: Reduction of the incidence of amputation in frostbite injury with thrombolytic therapy. *Arch Surg* 2007; 142:546.
50. Sheridan RL, et al: Case 41-2009: A 16-year-old boy with hypothermia and frostbite. *N Engl J Med* 2009; 361:2654.
51. Saemi AM, Johnson JM, Morris CS: Treatment of bilateral hand frostbite using transcatheter arterial thrombolysis after papaverine infusion. *Cardiovasc Intervent Radiol* 2009; 32:1280.
52. Bruen KJ, Gowski WF: Treatment of digital frostbite: Current concepts. *J Hand Surg Am* 2009; 34:553.
53. Purkayastha SS, et al: Immediate treatment of frostbite using rapid rewarming in tea decoction followed by combined therapy of pentoxifylline, aspirin and vitamin C. *Indian J Med Res* 2002; 116:29.
54. Hayes DW Jr, et al: Pentoxifylline: Adjunctive therapy in the treatment of pedal frostbite. *Clin Podiatr Med Surg* 2000; 17:715.
55. Muelleman RL, Grandstaff PM, Robinson WA: The use of pegorgotein in the treatment of frostbite. *Wilderness Environ Med* 1997; 8:17.
56. Teixeira F, et al: Use of antioxidants for the prophylaxis of cold-induced peripheral nerve injury. *Mil Med* 2002; 167:753.
57. Finderle Z, Cankar K: Delayed treatment of frostbite injury with hyperbaric oxygen therapy: A case report. *Aviat Space Environ Med* 2002; 73:392.
58. McCrary BF, Hursh TA: Hyperbaric oxygen therapy for delayed frostbite injury. *Wounds* 2005; 17:327.
59. Cauchy E, Cheguillaume B, Chetaille E: A controlled trial of a prostacyclin and rt-PA in the treatment of severe frostbite. *N Engl J Med* 2011; 364:189.
60. Chandran GJ, et al: The hyperthermic effect of a distal volar forearm nerve block: A possible treatment of acute digital frostbite injuries? *Plast Reconstr Surg* 2010; 126:946.
61. Bouwman DL, et al: Early sympathetic blockade for frostbite: Is it of value? *J Trauma* 1980; 20:744.
62. Poulakidas S, Cologne K, Kowal-Vern A: Treatment of frostbite with subatomospheric pressure therapy. *J Burn Care Res* 2008; 29:1012.
63. Su CW, Lohman R, Gottlieb LJ: Frostbite of the upper extremity. *Hand Clin* 2000; 16:235.
64. Kahn JE, Lidove O, Laredo JD, Blétry O: Frostbite arthritis. *Ann Rheum Dis* 2005; 64:966.

www.ketabpezeshki.com 66485457-66963820

65. Leonard LG, et al: Salvage of a vascular bone from frostbite with free tissue transfer. *Ann Plast Surg* 2001; 46:431.
66. Classen DA: Free flap coverage of bilateral frostbite of the feet. *Plast Reconstr Surg* 2000; 106:1316.
67. Delgado-Martinez J, et al: Skin coverage in frostbite injuries: Experimental study. *J Plast Resconstr Aesthet Surg* 2010; 63:713.
68. Oumlish OY, Parish LC: Marching in the army: Common cutaneous disorders of the feet. *Clin Dermatol* 2002; 20:445.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 140

ACCIDENTAL HYPOTHERMIA

Daniel F. Danzl and Ken Zafren

PERSPECTIVE

The "reanimations" of profoundly cold victims in prolonged cardiac arrest and the emergence of therapeutic hypothermia after cardiac arrest help explain the contemporary allure of hypothermia. A 29-year-old Norwegian physician was successfully resuscitated from accidental hypothermia at 13.7° C after a 9-hour resuscitation.[1] This included cardiopulmonary resuscitation initiated at the scene and 179 minutes of cardiopulmonary bypass.[2]

Medical uses of cold were not scientifically evaluated until the 18th century, although it has been used for medical purposes for millennia. The hemostatic, analgesic, and therapeutic effects of cold were well known. Accidental hypothermia was also common and its treatment controversial. Biblical references cite truncal rewarming of King David by a damsel, and various remedies, including rubbing of the extremities with hot oil, were mentioned by Hippocrates, Aristotle, and Galen.

Cold weather has had a major impact on military history.[3,4] Hannibal lost nearly half of his army of 46,000 while traversing the Alps in 218 BCE. The winter of 1777 took its toll on Washington's troops at Valley Forge. Napoleon's chief surgeon, Baron Larrey, reported that only 350 of the 12,000 men in the 12th division survived the cold during their retreat from Russia in 1812. Those soldiers who were rapidly rewarmed closest to the campfire died. The French subsequently suffered heavy losses in the Crimean War (1845-1855). These lessons were relearned during both world wars. Many pilots and U-boat crews perished from the cold water in the North Atlantic. Approximately 10% of the U.S. casualties in Korea were cold related.

Innumerable cold-related tragedies affect both military personnel and civilians, in particular hunters, sailors, skiers, climbers, boaters, swimmers, and survivors of some natural disasters. Widespread participation in outdoor winter sports increases the number of patients who have hypothermia. Hypothermia is geographically and seasonally pervasive.[5-7] Most cases occur in urban settings. "Primary" hypothermia fatalities are classified as accidental, homicidal, or suicidal. Death certificate data, however, underreport secondary hypothermia deaths, in which cold complicates many systemic diseases. The effect of cold on mortality from cardiovascular and neurologic disorders is greatly underestimated.[8]

Hypothermia is defined as a core temperature below 35° C. Many variables contribute to the development of accidental hypothermia. Exposure, age, health, nutrition, medication, and intoxicants can decrease heat production, increase heat loss, or interfere with thermostability.[9] The healthy individual's compensatory responses to heat loss through conduction, convection, radiation, and evaporation are often overwhelmed by exposure. Medications can also interfere with thermoregulation. Central nervous system (CNS) problems commonly decrease the efficiency of thermoregulation.[10]

PRINCIPLES OF DISEASE

Physiology of Temperature Regulation

Human basal heat production increases with food ingestion, muscle activity, fever, and acute cold exposure. Cold stress increases preshivering muscle tone, potentially doubling heat production. Maximal heat production lasts only a few hours because of fatigue and glycogen depletion.

Shivering thermogenesis increases the basal metabolic rate two to five times. Shivering, which markedly increases oxygen consumption, is modulated by the posterior hypothalamus and the spinal cord.

The preoptic anterior hypothalamus orchestrates nonshivering heat conservation and dissipation. Serotonergic and dopaminergic neurons are pivotal. They exert immediate control through the autonomic nervous system and delayed control through the endocrine system. Thermal suppression or activation of the sympathetic nervous system with cold-induced release of norepinephrine also occurs. Cold stimulates the hypothalamus to release thyrotropin-releasing hormone. This activates the anterior pituitary gland, which releases thyroid-stimulating hormone and results in the release of thyroxine from the thyroid gland.[11]

Heat loss occurs through five mechanisms: radiation, conduction, convection, respiration, and evaporation. Assuming an average basal metabolic rate in a normally clothed person at room temperature, 55 to 65% of this loss is through radiation. Heat loss by radiation is greatest when one is spread out nude and least when one is curled up and insulated. Radiative heat loss depends on the temperature gradient between the environment and the exposed body surface area. Conduction normally accounts for only approximately 2 to 3% of the heat loss, but this may increase up to five times in wet clothing. Convection in cold water can increase heat loss by a factor of 25.

Close correlation exists between subcutaneous fat thickness and cooling rates. Individuals with greater insulation lose heat more slowly. Conduction and convection normally account for about 15% of the body's heat loss, but convective losses increase with shivering. Respiration and evaporation account for the remainder of the loss, with 2 to 9% lost in heating of inspired air and 20 to 27% lost to insensible evaporation from the skin and lungs.

Cutaneous and respiratory heat loss is markedly influenced by the ambient temperature, air motion, and relative humidity. Greater losses occur in a cool, dry, windy environment (windchill index). When the body is not perspiring, most heat loss is through

www.ketabpezeshki.com 66485457-66963820

radiation and convection. Convective losses become significant in immersion-induced hypothermia. Children cool faster than adults do because of the elevated ratios of surface area to mass. Chronic cold exposure may result in gradual evolutionary adaptations and thermal acclimation (Fig. 140-1).

When core temperature is between 37 and 32° C, vasoconstriction, shivering, and nonshivering basal and endocrinologic thermogenesis generate heat. From 30 to 24° C, a progressive depression of the basal metabolic rate occurs without shivering thermogenesis. At temperatures below 24° C, autonomic and endocrinologic mechanisms for heat conservation become inactive.

Pathophysiology

The physiologic characteristics of hypothermia are described in Table 140-1.

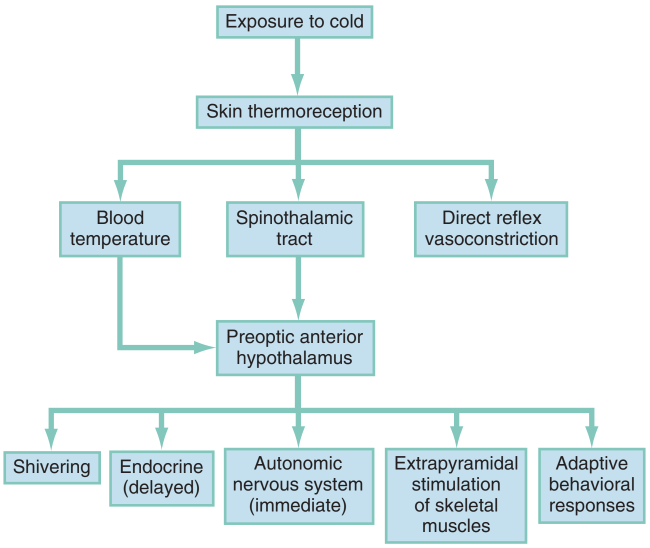


Figure 140-1. Physiology of cold exposure.

Cardiovascular

After initial tachycardia, progressive bradycardia develops. The pulse usually decreases by 50% at 28° C. If an observed tachycardia is inconsistent with a patient's temperature, associated conditions such as hypoglycemia, drug ingestion, and hypovolemia should be considered.

The bradycardia of hypothermia results from decreased spontaneous depolarization of the pacemaker cells. As a result, the bradydysrhythmia is refractory to atropine. The electrocardiographic features of hypothermia are unique.[12,13] Initially described by Tomaszewski in 1938, the Osborn (J) wave is seen at the junction of the QRS complex and ST segment (Fig. 140-2). J waves are potentially diagnostic but not prognostic. They may appear at any temperature below 32° C. The size of the J wave is not related to arterial pH but does increase with temperature depression.

J waves are normally upright in the aVL, aVF, and left precordial leads.[14] The J deflection may be a result of hypothermic ion flux alterations, with delayed depolarization or early repolarization of the left ventricular wall. It can also be seen during local cardiac ischemia and with sepsis or CNS lesions, hypercalcemia, and the Brugada syndrome.

Some J waveform abnormalities simulate a myocardial injury current. Hypothermic electrocardiographic changes are not easily recognized by computer programs. Reliance on computer interpretations can result in mistaken thrombolysis, which would be expected to exacerbate preexistent coagulopathies.[15]

All atrial and ventricular dysrhythmias are common in moderate or severe hypothermia. Reentrant dysrhythmias result from decreased conduction velocity with increased myocardial conduction time and a decreased absolute refractory period. Because the conduction system is more sensitive to the cold than the myocardium is, cardiac cycle prolongation occurs. Fluctuations of available oxygen, pH, electrolytes, and nutrients also alter conduction. As hypothermia worsens, the PR interval, then the QRS interval, and finally (and most characteristically) the QTc interval become prolonged. In the absence of obvious shivering, thermal muscle tone may obscure P waves or produce artifacts.

Atrial fibrillation is common when the core temperature is below 32° C. Other rhythms are sinus, atrial, or junctional. Atrial

Table 140-1 Physiologic Characteristics of the Four Zones of Hypothermia

STATE	CORE TEMPERATURE ° C (° F)	CHARACTERISTICS
Mild	35 (95)	Urine temperature 34.8° C; increased shivering thermogenesis; increase in metabolic rate
	34 (93.2)	Amnesia and dysarthria develop; normal blood pressure; maximum respiratory stimulation
	33 (91.4)	Ataxia and apathy develop
Moderate	32 (89.6)	Stupor; 25% decrease in oxygen consumption
	31 (87.8)	Decreased shivering thermogenesis
	30 (86)	Atrial fibrillation and other dysrhythmias; poikilothermia; pulse and cardiac output two-thirds normal; insulin ineffective
	29 (85.2)	Progressive decrease in level of consciousness, pulse, and respiration; pupils dilated
Severe	28 (82.4)	Ventricular fibrillation susceptibility; 50% decrease in oxygen consumption and pulse
	27 (80.6)	Losing reflexes and voluntary motion
	26 (78.8)	Major acid-base disturbances; no reflexes or response to pain
	25 (77)	Cerebral blood flow one-third normal; cardiac output 45% normal; pulmonary edema may develop
	24 (75.2)	Significant hypotension
	23 (73.4)	No corneal or oculocephalic reflexes
	22 (71.6)	Maximum risk of ventricular fibrillation; 75% decrease in oxygen consumption
Profound	20 (68)	Lowest resumption of cardiac electromechanical activity; pulse 20% of normal
	19 (66.2)	Flat electroencephalogram
	18 (64.4)	Asystole develops
	14.2 (57.6)	Lowest accidental hypothermia survival in an infant[113]
	13.7 (56.7)	Lowest accidental hypothermia survival in an adult[2]
	9 (48.2)	Lowest therapeutic hypothermia survival[107]

www.ketabpezeshki.com 66485457-66963820

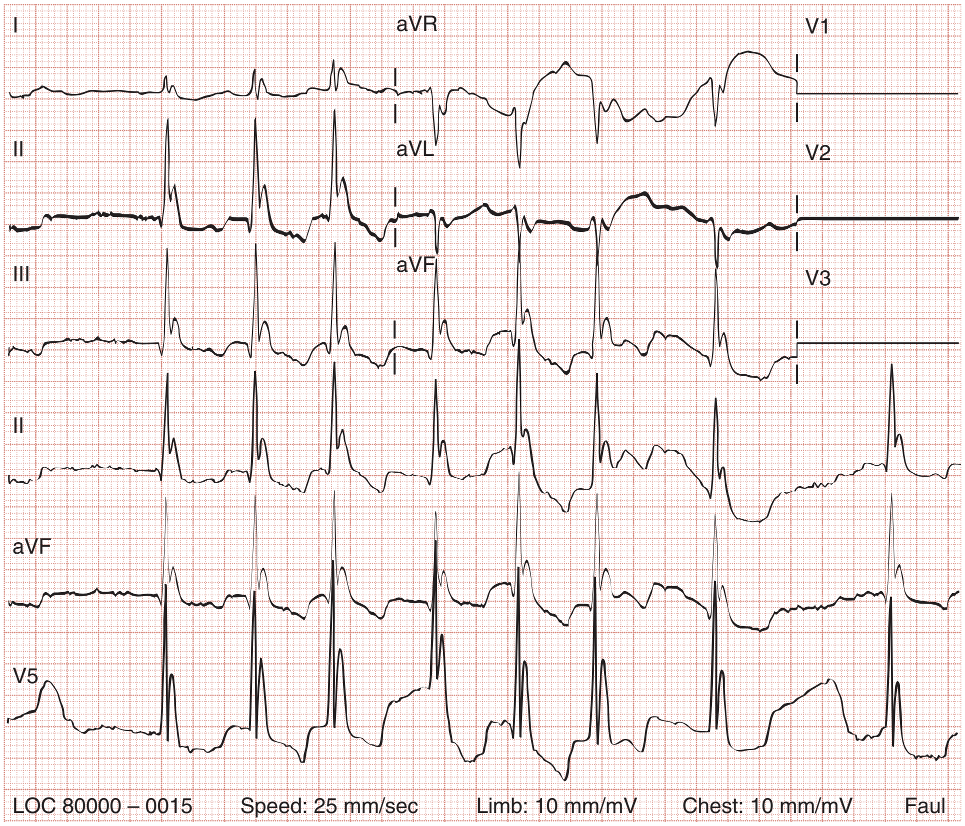


Figure 140-2. Hypothermic J waves.

fibrillation usually converts spontaneously during rewarming, but mesenteric embolization is a hazard.

The development of ventricular fibrillation (VF) or asystole in hypothermia is multifactorial. Putative explanations include tissue hypoxia, physical jostling, electrophysiologic or acid-base disturbances, and autonomic dysfunction. Asystole and VF can occur spontaneously when the core temperature falls below 25° C.[16,17] Hypothermia causes a decrease in transmembrane resting potential, which in turn decreases the threshold for ventricular dysrhythmias. VF can also result from an independent focus or a reentrant phenomenon. When the heart is cold, a large dispersion of repolarization exists, which facilitates the development of a conduction delay. The action potential is also prolonged.

The term *core temperature afterdrop* refers to a further decline in an individual's core temperature after removal from the cold. The two processes that contribute to afterdrop are simple temperature equilibration across a gradient and circulatory changes. Countercurrent cooling of the blood, which is perfusing cold tissues, results in a temperature decline until the gradient is eliminated.[18]

Active external rewarming of the extremities obliterates peripheral vasoconstriction and reverses arteriovenous shunting. This was most vividly demonstrated by Hayward, who measured his own esophageal, rectal, tympanic, and cardiac temperatures (by use of a flotation tip catheter) after cooling in 10° C water on three different days.[19] Warm bath immersion rewarming caused a 30% fall in mean arterial pressure coupled with a 50% decline in peripheral vascular resistance.

Core temperature afterdrop is a clinically relevant consideration in the treatment of patients with a large temperature gradient between the core and the periphery. This is common in patients who are dehydrated after chronic exposure. Major afterdrop can also occur in severely hypothermic patients if frostbitten extremities are thawed before thermal stabilization of the core.

Central Nervous System

Hypothermia progressively depresses the CNS. Significant alteration of the brain's electrical activity begins below 33.5° C. The electroencephalogram silences at 19 to 20° C.

Cerebral autoregulation is maintained with an increase in vascular resistance until 25° C. In cases of severe hypothermia, there is a disproportionately higher redistribution of blood flow to the brain. Like the heart, the brain has a critical period of tolerance to hypothermia. There are temperature-dependent neural enzyme systems that are unable to function at temperatures that are well tolerated by the kidney.

Renal System

Simple exposure to cold induces a diuresis regardless of an individual's state of hydration. Hypothermia depresses renal blood flow, reducing it by 50% at 27 to 30° C. The kidneys then excrete a large amount of dilute urine, termed cold diuresis. Cold diuresis is essentially glomerular filtrate, which does not clear nitrogenous waste products. Severe hypothermia causes an initial relative central hypervolemia as a consequence of peripheral vasoconstriction. Cold diuresis may act as a volume regulator to diminish the vasoconstriction-induced capacitance vessel overload. Cold-water immersion can further increase urinary output by 3.5 times. Ethanol doubles that increase.[20]

Respiratory System

Hypothermia initially stimulates respiration. This is followed by a progressive decrease in the respiratory minute volume. Carbon dioxide production decreases 50% with an 8° C fall in temperature. The normal stimuli for respiratory control are altered in severe hypothermia, and carbon dioxide retention with

www.ketabpezeshki.com 66485457-66963820

Box 140-1 Factors Predisposing to Hypothermia

Decreased Heat Production
Endocrinologic failure
Hypopituitarism
Hypothyroidism
Diabetes
Insufficient fuel
Hypoglycemia
Malnutrition
Marasmus
Kwashiorkor
Extreme exertion
Neuromuscular inefficiency
Age extremes
Impaired shivering
Inactivity
Lack of adaptation

Increased Heat Loss
Environmental
Immersion
Nonimmersion
Induced vasodilation
Pharmacologic
Toxicologic
Erythrodermas
Burns
Psoriasis
Ichthyosis
Exfoliative dermatitis
Iatrogenic
Emergency deliveries
Cold infusions
Heatstroke treatment

Impaired Thermoregulation
Peripheral failure
Neuropathies
Acute spinal cord transection
Diabetes
Central failure, neurologic
Central nervous system trauma
Cerebrovascular accident
Toxicologic
Metabolic
Subarachnoid hemorrhage
Pharmacologic
Hypothalamic dysfunction
Parkinson's disease
Anorexia nervosa
Cerebellar lesion
Neoplasm
Congenital intracranial anomalies
Multiple sclerosis

Miscellaneous Associated Clinical States
Recurrent hypothermia
Episodic hypothermia
Sepsis
Pancreatitis
Carcinomatosis
Cardiopulmonary disease
Vascular insufficiency
Uremia
Paget's disease
Giant cell arteritis
Sarcoidosis
Shaken baby syndrome
Multisystem trauma
Shapiro's syndrome
Wernicke-Korsakoff syndrome
Hodgkin's disease

respiratory acidosis can occur. Hypercapnia increases core temperature cooling during snow burial.[21]

Numerous other pathophysiologic factors adversely affect the respiratory system. These include viscous bronchorrhea, decreased ciliary motility, and noncardiogenic pulmonary edema.

Predisposing Factors

Predisposing factors that contribute to the pathophysiologic changes accompanying core temperature depression can be categorized as those that decrease heat production, increase heat loss, or impair thermoregulation (Box 140-1).

Decreased Heat Production

Decreased thermogenesis is often secondary to an endocrinologic failure, such as hypopituitarism, hypoadrenalism, or myxedema. Myxedema coma is several times more common in women; up to 80% of these persons are hypothermic. Hypothyroidism is often occult in this setting. There is usually no available history of lassitude, dry skin, arthralgias, or cold intolerance.

Hypoglycemia with central neuroglycopenia also predisposes to hypothermia. Another cause of decreased heat production is malnutrition, which causes a decrease in subcutaneous fat. Severe malnutrition, as with marasmus, contributes to heat loss. Kwashiorkor is less commonly associated with hypothermia because of the insulating effect of the hypoproteinemic edema.[11]

The young and the old are commonly at risk. The neonate has a large surface area–to–mass ratio, a relatively deficient subcutaneous tissue layer, and an inefficient shivering mechanism. Neonates lack behavioral defense mechanisms.

Acute neonatal hypothermia is common after emergency deliveries or resuscitations. Many neonates are lethargic, fail to thrive, and have a weak cry. Half have deceptively rosy cheeks. Late-onset hypothermia, which occurs after 72 hours of life, is commonly a result of septicemia. Hypothermia can occur in the shaken baby syndrome and may be a factor in some cases of apparent sudden infant death syndrome.

Homeostatic capability progressively decreases with aging. Thermal perception is altered and elderly people manipulate the indoor ambient temperature less precisely. Most elderly patients are capable of normal thermoregulation but are prone to conditions, including immobility and systemic diseases, that interfere with heat production and conservation. Inability to sense cold, abnormal adaptive behavioral responses, and decreased peripheral blood flow reflect geriatric autonomic dysfunction.[22]

Increased Heat Loss

Patients with erythrodermas, including psoriasis, exfoliative dermatitis, ichthyosis, eczema, and burns, can have increased peripheral blood flow. Iatrogenic causes of heat loss include exposure during resuscitations, massive cold or room temperature infusions, overcooling of patients with heat stroke, and overzealous burn treatment.

Ethanol is metabolized at a slower rate in hypothermic individuals and interacts with every putative thermoregulatory neurotransmitter. It may directly suppress the activity of the posterior hypothalamus and the mammillary bodies. Cutaneous heat loss increases through vasodilation, and shivering thermogenesis is decreased.[23]

Ethanol is the most common cause of excessive heat loss in urban settings.[7,16] Intoxicated persons often lack protective adaptive behavior to avoid the cold. "Paradoxical undressing," which is the removal of clothing in response to a cold stress, is common.[24] Aging is associated with an increased sensitivity to the hypothermic actions of ethanol. Hypothermic alcoholic ketoacidosis also occurs. Hypothermia is common in patients with Wernicke's encephalopathy. Hypothermia can mask the usual clinical triad of ophthalmoplegia, confusion, and truncal ataxia. Intravenous thiamine can be both diagnostic and therapeutic.

Impaired Thermoregulation

Thermoregulation can be impaired centrally, peripherally, or metabolically. Skull fractures, particularly basilar fractures, and chronic subdural hematomas are implicated in central impairment. Other causes include cerebrovascular accidents, neoplasms, anorexia nervosa, and Hodgkin's and Parkinson's diseases. The final common pathway in these disorders may be centrally mediated vasodilation. Cerebellar lesions produce choreiform, less efficient shivering.

In therapeutic or toxic doses, antidepressants, antimanic agents, antipsychotics, anxiolytics, and general anesthetics interfere with thermoregulation by impairing centrally mediated vasoconstriction. Overdosage of these medications and others (e.g., the organophosphates, heroin, glutethimide, and carbon monoxide) predisposes to hypothermia.[25]

Peripheral thermoregulatory failure classically occurs in neurogenic shock after acute spinal cord transection. The interruption of the autonomic nervous system eliminates vasoconstrictive

www.ketabpezeshki.com 66485457-66963820

control. The patient effectively becomes poikilothermic and can rapidly become hypothermic. Neuropathies and diabetes are additional peripheral causes of heat loss. An abnormal plasma osmolality may explain hypothalamic interference in uremia, lactic acidosis, diabetic ketoacidosis, and hypoglycemia.[26]

Miscellaneous Causes

Hypothermia occurs in conjunction with several infections, most commonly overwhelming gram-negative sepsis, pneumonia, meningitis, and encephalitis. Other associated infections include bacterial endocarditis, brucellosis, malaria, syphilis, typhoid, miliary tuberculosis, and trypanosomiasis.

Medical conditions associated with hypothermia include carcinoma, pancreatitis without secondary infection, peritonitis, and severe cerebrovascular disease. Low cardiac output resulting from a myocardial infarction can induce hypothermia. Fetal and maternal bradycardia and hypothermia may result from magnesium sulfate infusion during preterm labor. Delayed recovery from neuromuscular blockade may also result from unrecognized hypothermia.

Traumatic Factors

After trauma, hypotension and hypovolemia jeopardize thermostability.[27] In patients with major injuries, a fall in core and skin temperature with no compensatory shivering thermogenesis occurs. Thermoregulation is impaired, and heat production decreases.

Hypothermia may exacerbate blood loss by inducing a coagulopathy through three mechanisms: the coagulation cascade of enzymatic reactions is impaired, plasma fibrinolytic activity is enhanced, and platelets are sequestered and poorly functional.[28]

Traumatic injuries may be overlooked if hypotension or neurologic findings such as areflexia or paralysis are misattributed to hypothermia. Major risk factors for hypothermia in trauma patients include age, type of injury, level of intoxicants, transfusion requirements, and elapsed time spent in the field, emergency department, and operating room.

Hypothermia can protect the brain from ischemia only when it is induced before shock develops. This reduces adenosine triphosphate (ATP) use while the ATP stores are nearly normal. In traumatized patients, the ATP stores are already depleted.[29]

CLINICAL FEATURES

Appreciation of subtle presentations helps facilitate the early diagnosis of mild to moderate hypothermia. Vague symptoms include hunger, nausea, confusion, dizziness, chills, pruritus, and dyspnea (Box 140-2). During outdoor activities, individuals may simply become uncooperative, uncoordinated, moody, or apathetic. Indoors, elderly patients may exhibit confusion or simply become less communicative and display lassitude or a peculiar “flat” affect. Subtle progression of mental deterioration or motor skill impairment may mimic dementia. Symptoms such as slurred speech and ataxia may resemble symptoms of a cerebrovascular accident or intoxication.[26]

Some elderly people have a decreased ability to sense cold and thus fail to take appropriate adaptive action. The maladaptive phenomenon of paradoxical undressing is not uncommon.[24] This last preterminal effort of the victim may be related to the peripheral vasoconstrictive changes of profound hypothermia. The patient can be mistaken for a victim of sexual assault.

In urban settings, hypothermia is most commonly associated with ethanol ingestion or underlying illness. Other common causes include strokes, overdoses, psychiatric emergencies, and coexistent major trauma.[16]

Box 140-2 Presenting Signs of Hypothermia

Head, Eye, Ear, Nose, Throat
- Mydriasis
- Decreased corneal reflexes
- Extraocular muscle abnormalities
- Erythropsia
- Flushing
- Facial edema
- Epistaxis
- Rhinorrhea
- Strabismus

Cardiovascular
- Initial tachycardia
- Subsequent bradycardia
- Dysrhythmias
- Decreased heart tones
- Hepatojugular reflux
- Jugular venous distention
- Hypotension

Respiratory
- Initial tachypnea
- Adventitious sounds
- Bronchorrhea
- Progressive hypoventilation
- Apnea

Gastrointestinal
- Ileus
- Constipation
- Abdominal distention or rigidity
- Poor rectal tone
- Gastric dilation in neonates or in adults with myxedema

Genitourinary
- Anuria
- Oliguria
- Polyuria
- Testicular torsion

Neurologic
- Depressed level of consciousness
- Ataxia
- Hypesthesia
- Dysarthria
- Antinociception
- Amnesia
- Initial hyper-reflexia
- Anesthesia
- Hyporeflexia
- Areflexia
- Central pontine myelinolysis

Psychiatric
- Impaired judgment
- Perseveration
- Mood changes
- Peculiar flat affect
- Altered mental status
- Paradoxical undressing
- Neuroses
- Psychoses
- Suicide
- Organic brain syndrome

Musculoskeletal
- Increased muscle tone
- Shivering
- Rigidity or pseudo–rigor mortis
- Paravertebral spasm
- Opisthotonos
- Compartment syndrome

Dermatologic
- Erythema
- Pernio
- Pallor
- Frostnip
- Cyanosis
- Frostbite
- Icterus
- Popsicle panniculitis
- Sclerema
- Cold urticaria
- Ecchymosis
- Necrosis
- Edema
- Gangrene

Neurologic manifestations vary widely. A progressive decrease in the level of consciousness is usually proportional to the degree of hypothermia. Some patients, however, continue to be verbally responsive and display intact reflexes at 27 to 25° C.

Eye movement abnormalities and extensor plantar responses do not correlate directly with the degree of hypothermia. Cranial nerve signs may be seen with bulbar damage from central pontine myelinolysis. Above 22° C, it should be assumed that nonreactive dilated pupils reflect inadequate tissue perfusion and not hypothermia.

The rest of the neuromuscular examination may suggest the diagnosis. The patient’s posture ranges from stiff to pseudo–rigor mortis to opisthotonos. Reflexes are usually hyperactive down to 32° C, then become hypoactive until they disappear around 26° C. Cremasteric reflexes are absent because the testicles are already retracted. The plantar response usually remains flexor until 26° C. The knee jerk is the last reflex to disappear and the first to reappear with rewarming. The diagnosis of an antecedent CNS disorder, including spinal cord lesions, may be obscured by hypothermia.

www.ketabpezeshki.com 66485457-66963820

Between 30 and 26° C, both contraction and relaxation phases of the reflexes are equally prolonged. If it is intact, the ankle jerk is helpful in diagnosis of hypothermic myxedema. Myxedema prolongs the relaxation phase more than the contraction phase.

No psychiatric disorder improves when the patient is cold. Mental status alterations include anxiety, perseveration, neurosis, and psychosis. Many individuals who are functional in temperate climates decompensate in colder weather. Hypothermia-induced psychiatric presentations and suicide attempts are commonly misdiagnosed.[11]

DIAGNOSTIC STRATEGIES

Laboratory Evaluations

Acid-Base Balance

Blood gas analyzers warm blood to 37° C, which increases the partial pressure of dissolved gases. This results in an arterial blood gas report showing higher oxygen and carbon dioxide levels and a lower pH than the patient's in vivo values.[30-32] In fact, attempting to maintain a corrected pH at 7.4 and arterial partial pressure of carbon dioxide ($Paco_2$) at 40 mm Hg during hypothermia depresses cerebral and coronary blood flow and cardiac output and increases the incidence of VF.[33] The ideal acid-base strategy is the ectothermic alpha-stat approach.[10] Simply put, the goal is an uncorrected pH at 7.4 and $Paco_2$ at 40 mm Hg.

Cold blood buffers poorly. In normothermia, when the $Paco_2$ increases 10 mm Hg, the pH decreases 0.08 unit. At 28° C, the decrease in pH doubles. Because the neutral point of water at 37° C is a pH of 6.8, the normal 0.6-unit pH offset between blood and intracellular water should be maintained at all temperatures (Fig. 140-3).

Intracellular electrochemical neutrality ensures optimal enzymatic function at all temperatures.[31] Relative alkalinity affords myocardial protection and improves the heart's electrical stability.[33] Carbogen could prove valuable in the treatment of accidental hypothermia because it flattens and shifts the oxyhemoglobin dissociation curve to the right.

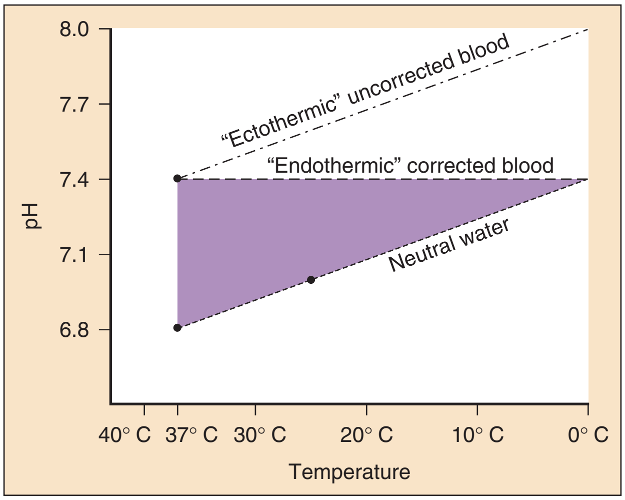


Figure 140-3. Neutrality reflects the pH of water at any given temperature. The pH of water is 6.8 at 37° C and 7.0 at 25° C. The physiologically ideal intracellular to extracellular 0.6-unit pH offset will be maintained if the arterial pH is kept uncorrected for temperature at 7.42.

Hematologic Evaluation

A patient's hematocrit can be deceptively high as the result of the decreased plasma volume. The hematocrit level increases 2% for every 1° C fall in temperature. A low-normal hematocrit level in a moderately to severely hypothermic patient should suggest acute or chronic blood loss.

A normal white blood cell count never excludes infection, especially if the patient is debilitated, alcoholic, myxedematous, or at either age extreme. Splenic, hepatic, and splanchnic sequestration in hypothermia decreases leukocyte and platelet counts.

Frequent evaluation of serum electrolytes during rewarming is essential. There are no safe predictors of their values or trends.[16] Changes occur in membrane permeability and in the sodium-potassium pump. The patient's preexisting physiologic status, the severity and chronicity of hypothermia, and the method of rewarming alter the serum electrolyte values.

The plasma potassium level is independent of the primary hypothermic process. Hyperkalemia is often associated with metabolic acidosis, rhabdomyolysis, or renal failure. An important caveat is that hypothermia enhances the cardiac toxicity of hyperkalemia and obscures the premonitory electrocardiographic changes associated with it.

Hypokalemia is most common with chronic hypothermia. It results from potassium's entering muscle, not a kaliuresis. A discrepant decline in serum potassium level despite a decreasing serum pH is caused by intracellular pH fluxes greater than extracellular pH fluxes.

Conditions associated with hypokalemia include preexisting diabetic ketoacidosis, hypopituitarism, inappropriate secretion of antidiuretic hormone, previous diuretic therapy, and alcoholism. If the potassium level is less than 3 mEq/L, supplementation may be necessary during rewarming.

The blood urea nitrogen and creatinine levels are elevated with preexisting renal disease or decreased clearance. Because of hypothermic fluid shifts, the hematocrit and blood urea nitrogen levels are poor indicators of a patient's actual fluid status.

The blood glucose level may also provide a subtle clue to the type of hypothermia. Acute hypothermia initially elevates blood glucose levels through catecholamine-induced glycogenolysis, diminished insulin release, and inhibition of cellular membrane glucose carrier systems. On the other hand, subacute and chronic hypothermia produce glycogen depletion, leading to hypoglycemia. Symptoms of hypoglycemia can be masked by hypothermia. A cold-induced renal glycosuria does not imply hyperglycemia or guarantee normoglycemia.[26]

When hyperglycemia persists during rewarming, one should suspect hemorrhagic pancreatitis or diabetic ketoacidosis. Patients with diabetic ketoacidosis should be actively rewarmed past 30° C because insulin is ineffective below that temperature. Correction of hypoglycemia corrects the level of consciousness only to that of the corresponding level of hypothermia.

Severe hypothermia also causes serum enzyme elevation because of the ultrastructural cellular damage. Rhabdomyolysis is commonly associated with cold exposure.

Ischemic pancreatitis may result from the microcirculatory shock of hypothermia. The decreased pancreatic blood flow then activates proteolytic enzymes.[7]

Hypothermic Coagulation

A physiologic increase in coagulation occurs with hypothermia, and a disseminated intravascular coagulation type of syndrome occurs. The cause may be catecholamine or steroid release, simple circulatory collapse, or release of tissue thromboplastin from cold, ischemic tissue.[28,34]

www.ketabpezeshki.com 66485457-66963820

Hypothermic patients also have coagulopathies because the enzymatic nature of the activated clotting factors is depressed by the cold. The clotting prolongation is proportional to the number of steps in the cascade. Because the kinetic tests of coagulation are performed in the laboratory at 37° C, the physician will see a disparity between the in vivo, clinically evident coagulopathy and the deceptively "normal" prothrombin time, partial thromboplastin time, or international normalized ratio reported by the laboratory. The only effective treatment is rewarming, not administration of clotting factors.[35] In vitro, desmopressin partially reverses hypothermia-induced coagulopathy.[36]

The leukopenia and thrombocytopenia usually reverse with rewarming. Clinically significant coagulopathies occur, particularly in association with trauma. Cold-induced thrombocytopenia may be from either direct bone marrow suppression or splenic and hepatic sequestration. Platelet thromboxane B_2 production is also temperature dependent. Thrombocytopenia is more common at both age extremes.

The elevated viscosity seen with hypothermia may be exacerbated in patients with cryoglobulinemia or cryofibrinogenemia, especially in elderly patients. Cryofibrinogen, which is a cold-precipitated fibrinogen, is associated with the collagen vascular diseases, carcinomas, and coliform sepsis. The pathophysiologic changes of cold hemagglutination result from cold agglutinins that produce either hemolysis or agglutination with thrombosis. This could explain the increase in coronary and cerebral thromboses in winter.

In summary, except in mild cases, the immediate laboratory evaluations should include the following: glucose concentration; arterial blood gas values uncorrected for temperature; complete blood cell count; comprehensive metabolic panel, including serum calcium, serum magnesium, and serum amylase or lipase levels; and coagulation studies. Baseline serum blood urea nitrogen and creatinine tests are indicated because renal failure may occur after rewarming in patients with chronic hypothermia.

A toxicologic screen may be helpful by history or when the depression of the level of consciousness is inconsistent with the degree of hypothermia. Thyroid function studies, cardiac markers, and serum cortisol levels have selective utility.

The indications for radiography should be liberalized from normothermia. If the patient is not alert, spinal radiographs should be obtained if there is any possibility of trauma. Bedside ultrasonography or computed tomography may show pancreatic calcifications, unsuspected pneumoperitoneum, small bowel dilation from hypothermia-induced mesenteric vascular occlusion, or colonic dilation associated with myxedema coma.[26]

MANAGEMENT

Patients who are cold, stiff, and cyanotic, with fixed pupils and inaudible heart tones, without visible thoracic excursions, continue to be successfully resuscitated.[2] Embarrassingly, some patients still recover completely in the morgue.

An adequate history includes available pertinent information about preexisting cardiac, pulmonary, neurologic, or endocrinologic disease. The duration of exposure, circumstances of discovery, associated injuries, and predisposing conditions should be documented. Initial management should emphasize the prevention of further heat loss.[37] The goals of prehospital care are to rescue, to examine, to insulate, and to gently transport in a horizontal position.[38,39]

If the patient is unresponsive and not shivering, presume that the hypothermia is severe. At temperatures below 32° C, one should expect an irritable myocardium, a temperature gradient between the core and periphery, and relative hypovolemia.

In the emergency department, hypothermia should be confirmed and monitored with continuous core temperature evaluation. Clinically, the rectal temperature is the most widely used; however, it can lag behind core changes and is influenced by lower extremity temperatures and probe placement. The probe should be inserted to 15 cm and not placed in cold feces.

The epitympanic temperature equilibrates most rapidly with the core temperature and is closest to the hypothalamic temperature but is not widely available. Infrared thermography (tympanic temperature) should not be used alone in the setting of suspected hypothermia because the reliability of commercially available devices remains uncertain. If the patient is tracheally intubated, an esophageal probe is the ideal method for continuous core temperature monitoring, although it can read falsely high with heated inhalation.

A Doppler measuring device may be necessary to establish the presence of a spontaneous pulse or blood pressure. Focused ultrasound evaluation of the hypothermic heart should precede chest compressions.[40,41] The accuracy of pulse oximetry during conditions of poor perfusion and hypothermia is uncertain, and it is often impossible to obtain an adequate plethysmograph.[42] Similarly, end-tidal carbon dioxide measurements accurately assess tissue perfusion and tracheal tube placement only at normal temperatures. Commercially available devices do not function with humidified air used for airway rewarming.

Endotracheal intubation may be necessary unless the patient is alert or has intact protective airway reflexes.[6,16] Cold depression of ciliary activity allows secretory accumulation, with the production of frothy sputum and chest congestion. Failure to differentiate between this bronchorrhea and pulmonary edema may explain the conflicting reports of the association of hypothermia with pulmonary edema. Nasotracheal intubation is a noninvasive option when cold-induced trismus is present, unless there is a significant coagulopathy.

In a multicenter survey, endotracheal intubation was performed on 117 patients by multiple operators in various settings.[16] No induced dysrhythmias were recognized. Factors commonly precipitating dysrhythmias include failure to preoxygenate, mechanical jostling, acid-base changes, and electrolyte fluctuations.

A nasogastric tube is indicated in patients with moderate and severe hypothermia after endotracheal intubation. Decreased gastric motility and gastric dilation occur commonly. Physical examination of the abdomen is unreliable because the cold can induce rectus muscle rigidity. A large percentage of moderately and severely hypothermic patients have decreased or absent bowel sounds. It is important to evaluate the patient carefully for an associated ileus, pancreatitis, or occult trauma.

In cases of moderate and severe hypothermia, indwelling bladder catheters with urine meter bags are essential to monitor urinary output and to help determine the severity of vascular fluid shifts.

Cardiac monitoring should be continued. Insertion of a central venous pressure catheter tip into the heart can precipitate dysrhythmias and should be avoided. Arterial catheters for continuous monitoring of intra-arterial blood pressure may rarely be necessary in selected profoundly hypothermic patients. The clinician should avoid placement of pulmonary artery catheters that risk perforation of the cold, stiff pulmonary artery.

Volume Resuscitation

Patients with moderate or severe hypothermia are usually volume depleted, and they are also prone to thromboembolism resulting from the increased viscosity. During rewarming, a relatively high total plasma volume and low circulatory plasma volume are often present. As hypothermia develops, other effects include increased peripheral vascular resistance with a decreased circulatory volume.

Rapid volume expansion is critical. In hypothermic neonates, the mortality risk is dramatically lessened. Adult patients with

www.ketabpezeshki.com 66485457-66963820

moderate or severe hypothermia should initially receive a 500-mL fluid challenge of heated 5% dextrose in normal saline solution pending laboratory analyses. Lactated Ringer's solution should be avoided because the cold liver inefficiently metabolizes lactate.

Fluids administered intravenously should be heated to 40 to 42° C.[43] There are many commercially available fluid and blood warmers. If these are not available, another option is to microwave intravenous fluids in plastic containers. A 1-L bag of crystalloid requires an average of 2 minutes on high power. The fluid should be shaken before administration to avoid hot spots. Rapid central venous administration, which may produce myocardial thermal gradients, should also be avoided. Another option in vasoconstricted patients is the intraosseous route.

Countercurrent heat exchangers effectively heat crystalloids and blood from 10 to 35° C. There can be significant conductive heat loss through intravenous tubing. Long lengths of tubing increase heat loss, especially at slow flow rates.

Normally, hypothermia induces an increased natriuresis. Preexisting gastrointestinal losses or previous diuretic treatment can also contribute to sodium loss. Patients with normal sodium and osmolality values may have preexisting sodium overload as a result of cirrhosis, nephrosis, or congestive heart failure; however, most patients will be free water depleted, which elevates their sodium and osmolality values.

Hemoconcentration resulting from decreased plasma volume, fluid shifts, and increased vascular permeability usually is present. Hemodilution can occur from parenteral crystalloid administration, but a low hematocrit can also result from acute hemorrhage or preexisting anemia.

Advanced Life Support

Blood flow during cardiopulmonary resuscitation (CPR) in patients with hypothermia differs from that during normothermia, in which some flow results from phasic alterations in the intrathoracic pressure and not necessarily from direct cardiac compression.[44,45] During hypothermic cardiac arrest in swine, the cardiac output and cerebral and myocardial blood flows average 50%, 55%, and 31%, respectively, of those achieved during normothermic closed chest compressions.[46] Metabolic demands, however, are also less during hypothermia.

In hypothermia, the heart is a passive conduit. The "thoracic pump" concept notes that the phasic alterations in the intrathoracic pressure are exerted equally on all cardiac chambers. The mitral valve remains patent during systole, and blood continues to circulate through the left side of the heart. This explains the observation of Althaus and associates,[47] who noted that in one of three survivors at thoracotomy, "the heart was found to be hard as stone and it is hardly conceivable how effective external cardiac massage could have been." There are innumerable neurologically intact survivors after prolonged closed chest compressions.[2,48,49]

Chest wall elasticity and pulmonary compliance are decreased with cold. Therefore, more force is needed to depress the chest wall sufficiently to generate intrathoracic pressure gradients. Pneumatic-powered thoracic compression devices are useful during prolonged resuscitations pending decisions about extracorporeal rewarming.[50] Apparent rigor mortis, dependent lividity, and fixed, dilated pupils are not always reliable criteria for withholding of CPR in the hypothermic patient. Because intermittent flow may provide adequate support during evacuation, CPR should not be withheld just because continuous compressions cannot be ensured.

In a multicenter survey of 428 cases, 9 of the 27 patients receiving CPR initiated in the field survived, as did 6 of 14 patients with CPR initiated in the emergency department.[16] Rescuers should initiate CPR in cases of accidental hypothermia unless do-not-resuscitate status is documented and verified, obviously lethal injuries are present, chest wall depression is impossible, signs of life are present, or rescuers are endangered by evacuation delays or altered triage conditions. If possible, verify with Doppler ultrasound examination that there is no spontaneous mechanical cardiac activity before chest compressions are initiated.

PHARMACOLOGY

The efficacy of most medications is temperature dependent. Protein binding increases during hypothermia, and liver metabolism is decreased. Overmedication could be required to achieve a therapeutic response, and subsequent toxic levels would develop with rewarming. In severe hypothermia, consider withholding of medications until the patient is warmer or longer intervals between doses. No medication should be given orally because of decreased gastrointestinal motility; none should be given intramuscularly because of poor absorption from vasoconstricted sites.

Cardiovascular

The effects of hypothermia on the autonomic nervous system vary. In primate studies, the sympathetic nervous system responds rapidly to cooling from 37 to 31° C. It then switches off around 29° C, which suggests that modest catecholamine support might be useful below that temperature.[51]

In general, pharmacologic manipulation of the pulse and blood pressure should be avoided. Vasoconstrictors may be dysrhythmogenic while having a minimal effect on the maximally constricted peripheral vasculature. Epinephrine and other vasoconstrictors should generally be avoided. The indications for vasopressors are unclear.[41] Of note, in controlled animal models, the return of spontaneous circulation after induced VF below 30° C is higher after administration of vasopressor medications.[52]

Inotropes usually are not necessary to support the blood pressure. Low-dose (2-5 μg/min) dopamine infusions should be considered in disproportionately hypotensive patients who do not maintain a mean arterial pressure of 60 mm Hg in response to crystalloids, colloids, and rewarming. To facilitate perfusion of a vasoconstricted cardiovascular system while the patient is receiving dopamine, some investigators add an infusion of low-dose nitroglycerin.

Dysrhythmia Treatment

Preexisting chronic premature ventricular contractions can be suppressed during hypothermia and recur during rewarming. Most hypothermia-induced dysrhythmias convert spontaneously during rewarming. Asystole that develops during rewarming is *not* a more ominous rhythm than VF. Biphasic defibrillation should be attempted at 2 Wsec/kg up to 200 Wsec. A successful reestablishment of electromechanical activity has been reported at 20° C.[53] If the defibrillation attempt is unsuccessful, active rewarming should be initiated with available equipment while CPR is continued. Defibrillation attempts are usually unsuccessful until the core temperature is well above 28 to 30° C. If the defibrillation attempt is unsuccessful, the core temperature should be raised above 30° C before further reattempts.[41]

Virtually all atrial dysrhythmias are common below 32° C and are associated with a slow ventricular response. Atrial fibrillation is common and considered innocent. It usually converts spontaneously during rewarming. Digitalization and calcium channel blockade are not warranted.

The ideal approach to ventricular dysrhythmias is unresolved. Lidocaine and propranolol have minimal hemodynamic effects during hypothermia. Their efficacy in treatment of ventricular dysrhythmias appears limited.

www.ketabpezeshki.com 66485457-66963820

Bretylium tosylate is not available in the United States but was extremely effective in several animal studies when it was given before invasive maneuvers performed *after* induction of hypothermia. Several clinical chemical defibrillations with bretylium in cases of severe hypothermia are reported.[26] In a canine model of severe hypothermic VF, neither amiodarone nor bretylium was effective.[54] Amiodarone can cause torsades de pointes through QT prolongation, and its safety during both accidental and induced hypothermia is unknown.[54,55]

In cases of normothermia, group I ventricular antidysrhythmics directly decrease conduction velocity and possess indirect anticholinergic activity. In cases of hypothermia, at least one agent in this group, procainamide, increases the incidence of VF. Another drug in the group, quinidine, can prevent VF during induced profound hypothermia and during cardiac manipulation at 25 to 30° C.

Transvenous intracardiac pacing is hazardous for hypothermia-induced bradydysrhythmias. External noninvasive pacing by means of large low-resistance electrodes may be a successful alternative to emergency transvenous pacing in the rare setting of a profoundly disproportionate bradycardia.[56] Transcutaneous pacing in two perfusing patients with blood pressure below 60 mm Hg facilitated continuous arteriovenous rewarming.[57] Other active rewarming techniques, however, do not require specific pressure gradients.

Failure to Rewarm

Cold exposure normally induces adrenal unresponsiveness to adrenocorticotropic hormone. A false diagnosis of decreased adrenal reserve is possible. The increase in adrenocorticotropic hormone level seen in hypothermic individuals may be a neurogenic or emotional response to the cold.

Acute cold stress initially stimulates cortisol secretion. The patient may already have a very high level as a result of an underlying stress. In clinical series, serum cortisol levels are commonly elevated. The percentage of cortisol bound to protein is increased with hypothermia, and therefore the active free fraction is decreased.

If a patient fails to rewarm, the historian should search for evidence of adrenocortical insufficiency or steroid dependence. At that juncture, administration of 100 mg intravenous hydrocortisone should be considered.

Empirical treatment with thyroxine should be reserved for patients thought to be myxedematous. Thyroid hormone replacement is recommended if a history of hypothyroidism is present, a suggestive neck scar is present, or a failure to rewarm occurs. After thyroid function study samples are drawn, 250 to 500 µg of levothyroxine should be administered cautiously intravenously during several minutes. Daily injections of 50 to 100 µg are necessary for 5 to 7 days. Hydrocortisone (100-200 mg) should be added to the first several liters of crystalloid fluid.

The absorption of levothyroxine is variable when it is administered orally or intramuscularly. Administration intravenously results in a smooth effect after the onset of action at 6 to 12 hours. This is evidenced by improvement in the vital signs and the rewarming rate. Half the dose is converted by the peripheral tissues into L-triiodothyronine (T_3). An underlying infection also compromises thermogenesis.[58] In an urban setting, infection is the leading cause of failure to rewarm and of mortality.

Septicemia

Hypothermia compromises host defenses and predisposes to infection. The usual signs of infection, including fever, are absent. Shaking chills from sepsis may be mistaken for shivering. If a patient's mental status remains altered despite rewarming, CNS injury or infection should be suspected.

Diminished bone marrow release and circulation of neutrophils, along with impaired neutrophil migration and bacterial phagocytosis, is a factor contributing to infection. In children younger than 3 months, empirical antibiotics after culture are indicated. No reliable clinical or laboratory indicators of infection exist, but bradycardia, anemia, uremia, and serum glucose levels as well as leukocyte abnormalities are common clues.

The role of empirical antibiotics in adults is less clear. Although gram-negative septicemia may be the cause of hypothermia, coexistent infections from gram-positive cocci, Enterobacteriaceae, and oral anaerobes are common.

Elderly patients with thermoregulatory failure have a high risk of mortality and should be considered septic until proven otherwise. Routine empirical antibiotics in hypothermic adults, unlike in elderly patients and in children, does not appear warranted. Antibiotics should be administered if the clinical picture is consistent with septic shock, if there is failure to rewarm, or if aspiration has occurred. Cellulitis, myositis, bacteriuria, or infiltrates present on chest radiographs warrant immediate antimicrobial therapy.[11]

REWARMING

Because no controlled studies comparing rewarming methods in hypothermia exist, rigid treatment protocols would not be evidence based.[38,59-63] As a result, the clinician should consider the advantages, disadvantages, indications, contraindications, and specific guidelines for the various reported techniques of rewarming that follow.[64]

Passive External Rewarming

Spontaneous passive external rewarming is noninvasive and is the treatment of choice for most patients with mild hypothermia. The patient should be able to generate sufficient heat metabolically to maintain an acceptable rate of spontaneous rewarming. Elderly patients are commonly glycogen depleted, centrally hypovolemic, and not capable of normal cardiovascular or metabolic homeostasis.

The normal processes of heat dissipation are minimized by passive external rewarming. Cessation of evaporation and convection is coupled with insulation against further radiation of heat. This technique simply involves covering the patient with an insulating material in a favorable atmospheric condition. The ambient temperature should exceed 21° C. When the air is stationary, less heat is lost to conduction, convection, and radiation.

Below 30° C, humans are functionally poikilothermic. No shivering thermogenesis occurs. Shivering is the thermoregulatory neuromuscular response to cold that increases heat production from 250 to 1000 kcal/hr. Without shivering, endogenously generated metabolic heat is insufficient to raise the core temperature. When the core temperature exceeds 32° C, the major source of heat production is shivering thermogenesis, unless complete glycogen depletion occurs.

Recommended rewarming rates vary between 0.5 and 2.0° C/hr. The rewarming rate should be rapid enough to avoid prolonged exposure to dysrhythmias.

Active Rewarming

Active rewarming is the direct transfer of exogenous heat to the patient. It can be accomplished by either external or internal techniques.

Cardiovascular instability and decompensation require rapid elevation of the core temperature (Box 140-3). Defibrillation is rarely successful at temperatures below 28 to 30° C. Active

www.ketabpezeshki.com 66485457-66963820

Box 140-3 Indications for Active Rewarming

Cardiovascular instability
Moderate or severe hypothermia (≤32.2° C)
Inadequate rate of rewarming or failure to rewarm
Endocrinologic insufficiency
Traumatic or toxicologic peripheral vasodilation
Secondary hypothermia impairing thermoregulation

rewarming is indicated with cerebrovascular accidents and other conditions that impair CNS control of thermoregulation. Active rewarming is also indicated in patients when endogenous thermogenesis is insufficient or when glycogen depletion is present. These diseases are usually endocrine and include hypopituitarism, adrenal insufficiency, hypothyroidism, and Wernicke's encephalopathy. Active rewarming is also indicated if diabetic ketoacidosis is present because the core temperature must be elevated well above 30° C before insulin becomes effective.[65]

Pharmacologically induced peripheral vasodilation or acute spinal cord transection renders a patient incapable of sufficient thermogenesis. Such patients should be actively rewarmed. Active rewarming in patients with moderate or severe hypothermia is also indicated because of the potential for cardiovascular decompensation or ventricular irritability. Patients with severe hypothermia and a sustained perfusing rhythm do not necessarily require invasive extracorporeal rewarming techniques.[66]

Aggressive treatment of hypothermia in infants is also indicated. Rapid rewarming may be advantageous because it minimizes energy expenditures.[67] Vigorous monitoring for infectious, respiratory, hematologic, and metabolic complications is needed.

Active External Rewarming

Early concern with active external rewarming (AER) was voiced by Duguid and colleagues in 1961,[68] when 20 of their 23 patients died. Retrospective analysis of numerous clinical series notes widely varying mortality rates with AER.[6,16,65]

Various methods are available to conduct heat directly to the skin. Rewarming options include plumbed garments that recirculate warm fluids, hot-water bottles, heating pads, forced-air warming systems, and radiant sources. Thermal injury to vasoconstricted hypoperfused skin is a common hazard with local heat application.[69]

Forced air warming systems efficiently transfer heat.[70] The Bair Hugger circulates hot air through a "blanket." The air exits apertures on the patient's side of the cover, which allows a convective transfer of heat. In one study in which accidental hypothermia victims were rewarmed in the emergency department, rewarming shock and core temperature afterdrop were not noted.[71] Both groups of patients were also treated with heated inhalation and warmed intravenous fluids. The use of forced-air warming systems is most practical in the emergency department.[72] Although these devices decrease shivering thermogenesis, afterdrop is minimized and heat transfer can be significant. Another option is the use of a temperature regulation device traditionally used for therapeutic hypothermia in patients after cardiac arrest.[73] In addition, a thermoregulatory system that circulates warm water through energy transfer pads is available.[74]

Arteriovenous anastomosis (AVA) rewarming is another noninvasive AER technique.[75] Exogenous heat is provided by immersion of the lower parts of the extremities (hands, forearms, feet, calves) in 44 to 45° C water. The heat opens the AVAs. These organs are 1 mm below the epidermal surface in the digits.[76] As a result, there is an increased flow of warmed venous subcutaneous blood returning directly to the heart. The forearms and calves must be included for this technique to be effective. A permutation of AVA rewarming is negative-pressure rewarming. In combination with localized heat application, the application of subatmospheric pressure distends the venous rete and increases flow through the AVAs. The clinical practicality and efficacy of AVA rewarming is unclear; with vasoconstricted extremities, burns are a real hazard.

Optimal candidates for AER are previously healthy patients with acute hypothermia. In these patients, minimal dehydration and pathophysiologic circulatory changes have occurred. If AER is chosen and the extremities are vasoconstricted, the heat source should preferentially be applied to the thorax and not to the extremities. Application of heat to the extremities increases the cardiovascular load by increasing the metabolic requirements of the peripheral musculature. The depressed cardiovascular system may not be able to meet the demands, and cardiovascular collapse can occur.

Combining of truncal AER with core rewarming can also be successful. The provision of heated humidified oxygen and warmed intravenous fluids in addition to AER may anticipate and avert hypoxia, metabolic acidosis, core temperature afterdrop, and hypotension. If AER is chosen as the method of treatment for moderate or severe hypothermia, it should be combined with one of the active core rewarming techniques.

Active Core Rewarming

Numerous alternatives achieve active rewarming of the core. These techniques minimize rewarming collapse in patients with temperatures below 32° C.

Airway Rewarming. Airway rewarming as an adjunctive active core rewarming technique has been explored since it was first suggested by Lloyd.[20] This simple technique is indicated in all cases of moderate or severe hypothermia.[16,77]

Advantages of heated humidified oxygen include noninvasiveness, cost, simplicity, assurance of adequate oxygenation, and avoidance of afterdrop. Additional benefits are the stimulation of pulmonary cilia, a decrease in pulmonary secretion viscosity, and a reduction of cold-induced bronchorrhea. Pulmonary absorption occurs without adverse effects on surfactant or increased pulmonary congestion.

The respiratory tract is a limited site for heat exchange. Nevertheless, both the oxygen content and the temperature in the pulmonary vasculature rise. The myocardium is perfused by warmer oxygenated blood, stabilizing against intermittent temperature gradients.

A sufficient respiratory minute volume and complete humidification are necessary for maximal heat delivery. Because of the low thermal conductivity of dry air, ventilation with warm dry air provides negligible heat. Depending on the technique used, one should expect a rewarming rate between 1 and 2.5° C/hr.[6,16] The higher rates are with endotracheal intubation; the lower rates are with the use of a mask. Heated mask ventilation is also of interest. A thermal countercurrent heat exchanger exists in the cerebrovascular bed of humans. This system, known as the rete mirabile, could preferentially rewarm the brainstem. Another option is heated inhalation through face mask with continuous positive airway pressure.

Maintenance of sufficient oxygenation is also critical in moderate and severe cases. Fisher[78] considered the effects of hypothermia, pH, Pa_{CO_2}, and level of 2,3-diphosphoglycerate on the left shift of the oxyhemoglobin dissociation curve. In patients on cardiopulmonary bypass cooled to 28 to 30° C, the capacity of hemoglobin to unload oxygen to the tissue is less than half that found in normothermic patients. Despite lower metabolic requirements, this decrease in "functional" hemoglobin combined with a

www.ketabpezeshki.com 66485457-66963820

depressed respiratory minute volume results in minimal oxygen reserves.

Some patients maintain a level of spontaneous respiration appropriate to the depressed carbon dioxide production. This is not the case in patients with coexisting toxicologic, traumatic, or metabolic depression of their respiratory centers. During spontaneous or assisted ventilation with heated ventilation, there is the flexibility to alter the fraction of inspired oxygen (FiO_2), to monitor airway pressure, and to deliver continuous positive airway pressure or positive end-expiratory pressure.

The technique for patients with spontaneous respirations requires a heated cascade nebulizer. An immersion heater can be connected to a hose with a warming wire. Because patients with a depressed level of consciousness do not complain of pain, it is essential to check the temperature of the inspired air frequently with an in-line temperature probe. The gas temperature should be maintained at 42 to 45° C. Most heater modules require modification to allow the temperature to reach 42 to 45° C and should be so labeled to avoid routine use.

Most humidifiers are manufactured in accordance with the International Standards regulations. The humidifier will not exceed 41° C close to the patient outlet with a 6-foot tubing length. Strategies to circumvent the 41° C ceiling include reduction of tubing length, addition of more heat sources, disabling of the humidifier safety system, and placement of the temperature probe outside the patient circuit.[79] Because of the modest clinical benefit in stable patients, it is probably not worth the effort to circumvent the 41° C ceiling. The only report of thermal airway injury is in a patient ventilated by endotracheal tube for 11 hours with 80° C inhalant. Complete airway protection decreases the risk of aspiration. Hypothermia is associated with ileus, bronchorrhea, and depressed protective airway reflexes. Although the airway rewarming technique provides less heat than other forms of active core rewarming do, it is safe, noninvasive, and practical.

Peritoneal Dialysis. This technique delivers dialysate at 40 to 45° C to the peritoneal cavity. Heat is conducted directly to the intraperitoneal structures, through the posterior parietal peritoneum to the solid viscera and through the hemidiaphragms to the heart and lungs.

A double-catheter system can increase the rate of rewarming with suction at the outflow. The usual clinically attainable rate is 6 L/hr. Two liters are infused, retained for 20 minutes, and then aspirated. Rewarming rates average 1 to 3° C/hr, depending on gradients and flow rates and dwell times.

An additional benefit of this invasive technique is hepatic rewarming, which reactivates depressed detoxification and conversion enzymes. Peritoneal dialysis can exacerbate preexistent hypokalemia; therefore, serum electrolyte levels should be carefully monitored. Peritoneal lavage rewarming should not be selected routinely for stable patients. It should be considered in severe cases and in combination with all available rewarming techniques for patients without spontaneous perfusion.[26]

Heated Irrigation. Heat transfer from irrigation fluids is usually limited because the surface area available for heat exchange is minimal. Gastric or colonic irrigation can cause fluid and electrolyte fluxes. These techniques are rarely indicated.

Closed thoracic lavage in accidental hypothermia is another option.[80,81] Two large-bore thoracostomy tubes are inserted into one or both hemithoraces. One is inserted anteriorly in the second or third intercostal space at the midclavicular line. The other is inserted between the fifth and sixth intercostal space in the posterior axillary line. Normal saline solution is heated to 40 to 42° C and sterilely infused into either tube and drained.[82] The dwell time for thermal transfer will be longest if the fluid is infused into the inferior tube. One should leave the inferior tube for drainage after rewarming. Left-sided tube insertion in perfusing patients risks causing VF.

The efficiency of heat transfer varies with the flow rate and dwell times. Pleural adhesions prevent adequate infusion rates and can result in a tension hydrothorax. Adequate drainage should be ensured to prevent intrathoracic hypertension.

Thoracic lavage should be reserved for the severely hypothermic patient who does not respond to standard techniques or the patient with another indication for a chest tube. It should be combined with all other available rewarming modalities in potentially salvageable cardiac arrest patients.[83,84] The rate of rewarming averages 3° C/hr.[81]

Mediastinal irrigation and direct myocardial lavage should be considered only in patients without spontaneous perfusion. The procedure requires a standard left lateral thoracotomy incision. The pericardium is not incised unless an effusion or tamponade is present. The heart is bathed in 1 to 2 L of an isotonic solution heated to 40° C for several minutes. The fluid is then removed and the lavage repeated. Internal defibrillation is attempted at intervals of 2° C after the myocardial temperature exceeds 26 to 28° C. When a perfusing rhythm is achieved, lavage is continued until the myocardial temperature exceeds 32° C. A median sternotomy approach allows ventricular decompression in addition to direct defibrillation. Open cardiac massage of a cold, rigid, and contracted heart may not generate flow.[45,47]

Endovascular Rewarming. Another active core rewarming option uses endovascular warming devices that are used for therapeutic cooling and subsequent rewarming of comatose resuscitated cardiac arrest patients.[85] These systems involve femoral vein catheterization with a closed-loop catheter that has a temperature control element at the tip. If the core temperature is below 30° C, the fail-safe feature on the console must be circumvented to allow rewarming.[86]

Diathermy. Truncal diathermy involves the conversion of energy waves into heat. Large amounts of heat can be delivered to deep tissues with ultrasonic and low-frequency microwave irradiation. Frostbite, burns, significant edema, and the presence of all types of metallic implants and pacemakers contraindicate diathermy.

Regional heating of hypothermic dogs after immersion does not damage tissue at 4 to 6 W/kg and rapidly elevates the core temperature. Zhong[67] rewarmed 16 piglets with microwave irradiation "until they squealed and suckled." In a subsequent experiment, 20 of 28 human infants were successfully rewarmed with microwave irradiation at 90 to 100 W. Diathermy is still experimental.

Extracorporeal Blood Rewarming. The four common techniques to rewarm blood are venovenous rewarming, hemodialysis, continuous arteriovenous rewarming, and cardiopulmonary bypass (Table 140-2).[87,88]

Extracorporeal venovenous rewarming is an option for warming and recirculation of the blood. With this technique, blood is removed (usually by a central venous catheter), heated to 40° C, and returned through a second central or large peripheral venous catheter. Flow rates are 150 to 400 mL/min.[89-91] The circuit is not complex and is more efficient than many other nonbypass modalities. There is no oxygenator, and because the method does not provide full circulatory support, volume infusion is the only option to augment inadequate cardiac output.[92]

Standard hemodialysis is a widely available and practical rewarming technique.[93] It is portable and efficient and should be considered in patients with electrolyte abnormalities, renal failure, or intoxication with a dialyzable substance. Two-way flow catheters allow cannulation of a single vessel. A Drake Willock single-needle dialysis catheter can be used with a portable hemodialysis machine and external warmer. After central venous cannulation, exchange cycle volumes of 200 to 250 mL/min are possible.[94] Although heat exchange is less than with standard two-vessel hemodialysis, the ease of percutaneous subclavian vein placement is a major advantage. Hemodialysis by two separate single-lumen

www.ketabpezeshki.com 66485457-66963820

Table 140-2 Extracorporeal Blood Rewarming Options

OPTIONS	CONSIDERATIONS
Venovenous circuit	Central venous catheter to central venous or peripheral catheter rewarming No oxygenator/circulatory support Flow rates 150-400 mL/min Rate of rewarming 2-3° C/hr
Hemodialysis circuit	Single- or dual-vessel cannulation Stabilizes electrolyte or toxicologic abnormalities Exchange cycle volumes 200-500 mL/min Rate of rewarming 2-3° C/hr
Continuous arteriovenous rewarming circuit	Percutaneous 8.5F femoral catheters Requires blood pressure of 60 mm Hg systolic No perfusionist/pump/anticoagulation Flow rates 225-375 mL/min Rate of rewarming 3-4° C/hr
Cardiopulmonary bypass circuit	Full circulatory support with the pump and oxygenator Perfusate-temperature gradient (5-10° C) Flow rates 2-7 L/min (average 3-4 L/min) Rate of rewarming up to 9.5° C/hr

From Danzl DF: Hypothermia and frostbite. In Fauci AS, et al (eds): Harrison's Principles of Internal Medicine, 17th ed. New York, McGraw-Hill, 2008.

catheters placed in the femoral vein can achieve continuous blood flow at 450 to 500 mL/min.

Continuous arteriovenous rewarming is another option if the blood pressure is at least 60 mm Hg. Continuous arteriovenous rewarming involves the use of percutaneously inserted femoral arterial and contralateral femoral venous catheters.[27,95] The Seldinger technique is used to insert the 8.5F catheters. Heparin-bonded tubing circuits obviate the need for systemic anticoagulation. The blood pressure of spontaneously perfusing traumatized hypothermic patients creates a functional arteriovenous fistula by diverting part of the cardiac output out the femoral artery through a commercially available countercurrent heat exchanger. The heated blood is then returned with admixed heated crystalloids through the femoral vein. Continuous arteriovenous rewarming does not require the specialized equipment and perfusionist necessary for cardiopulmonary bypass. The average flow rates are 225 to 375 mL/min, resulting in a rate of rewarming of 3 to 4° C/hr. Because the catheters are 8.5F, the patient should weigh at least 40 kg.

Cardiopulmonary bypass uses the standard femoral-femoral circuit and includes arterial and venous catheters, a mechanical pump, a membrane or bubble oxygenator, and a heat exchanger.[96-98] A 16F to 30F venous cannula is inserted through the femoral vein to the right atrium–inferior vena cava junction. The tip of the shorter 16F to 20F arterial cannula is inserted 5 cm or just proximal to the aortic bifurcation. Transesophageal echocardiography can help evaluate ventricular load and valve function.[99] There are techniques to decrease the need for intravenous anticoagulation that previously limited clinical applicability. Heparin-coated perfusion equipment and the use of nonthrombogenic pumps can be coupled with the enhanced physiologic fibrinolysis seen in the first hour of cardiopulmonary bypass.[100,101] Heated, oxygenated blood is returned through the femoral artery. Femoral flow rates of 2 to 3 L/min can elevate the core temperature 1 to 2° C every 3 to 5 minutes. In one review, the mean temperature increase was 9.5° C/hr.[100] Most pumps can generate full flow rates up to 7 L/min.

The optimal temperature gradient and bypass rewarming rates are unknown. An excessive temperature gradient between brain tissue and circulant can adversely affect electroencephalographic regeneration. The electroencephalogram is a surrogate marker of brain recovery. The other concern is the possibility of increased bubbling if high perfusate temperature gradients are used. Most investigators use 5 to 10° C gradients.[102] Extracorporeal rewarming by extracorporeal membrane oxygenation appears to reduce the risk of intractable cardiorespiratory failure after rewarming.[103]

The major advantage of cardiopulmonary bypass in perfusing patients is the preservation of flow if mechanical cardiac activity is lost during rewarming. Other candidates for cardiopulmonary bypass are patients who do not respond to less invasive rewarming techniques, those with completely frozen extremities, and those with rhabdomyolysis accompanied by major electrolyte disturbances. One proposed algorithm suggests direct transfer of the patient to the operating suite to shorten door-to-reperfusion time with hypothermic cardiac arrest without obvious major trauma.[104]

Of note, rapid acceleration of the rate of rewarming does not necessarily improve survival rates. Complications of rapid rewarming in severe hypothermia include disseminated intravascular coagulation, pulmonary edema, hemolysis, and acute tubular necrosis. Percutaneous cardiopulmonary bypass can provide cardiovascular support in perfusing but hemodynamically unstable patients.[105]

Extracorporeal blood rewarming should be considered in hypothermic cardiac arrest patients when no contraindications to CPR exist. A realistic assessment of the risk-benefit ratio for debilitated patients with secondary hypothermia should be made.[106] The lowest temperature in a survivor of induced hypothermia was 9° C.[107] Extracorporeal blood rewarming is unlikely to succeed below 5 to 10° C.[108] Resuscitation should be discontinued if frozen or clotted intravascular contents are identified.

DISPOSITION

Otherwise healthy patients who have mild primary accidental hypothermia (35-32.2° C) usually rewarm easily. They can be safely discharged if a warm environment is available.

Patients with more severe hypothermia (<32.2° C) generally require admission.[109] These patients should be evaluated for the presence of underlying medical disorders (see Box 140-1). Cardiac monitoring should be considered in patients with persistent toxicologic or metabolic abnormalities. This is essential for those patients displaying cardiovascular instability or an inadequate rate of rewarming. Transfer of patients to tertiary care centers is generally not necessary; however, some severely hypothermic patients are best managed in facilities with cardiopulmonary bypass capabilities.

OUTCOME

In the past, the treatment dictum was that "no one is dead until they are warm and dead." Some patients are cold and dead, and it would be useful and humane if they could be safely identified.[110] Because of the variability of human physiologic responses, outcome is difficult to predict.[108,111,112] The type and severity of the underlying or precipitating disease process are the major determinants.[113] Age of the patient is not an independent predictor of mortality.

Trauma, infection, and toxin ingestions also affect survival unpredictably.[29,114] Outcome prediction based on the Glasgow Coma Scale score is unreliable. Significant predictors of outcome include asphyxia, prehospital cardiac arrest, low or absent blood pressure, elevated blood urea nitrogen level, and need for either endotracheal or nasogastric intubation in the emergency department.[88,115]

www.ketabpezeshki.com 66485457-66963820

The search for a valid triage marker of death continues.[116-118] Grave prognostic indicators include evidence of intravascular thrombosis (fibrinogen < 50 mg/dL), cell lysis (hyperkalemia > 10-12 mEq/L), and ammonia levels greater than 250 mmol/L.[104,119]

KEY CONCEPTS

- Indications for active rather than passive rewarming include cardiovascular instability, temperature below 32° C, poor rate of rewarming, endocrinologic insufficiency, and vasodilation.
- One should consider hypoglycemia, hypovolemia, or an overdose if there is a tachycardia disproportionate to the temperature.
- The efficacy of most medications is temperature dependent. Overmedication to achieve an effect when the patient is cold could cause toxicity during rewarming.
- Kinetic laboratory tests of coagulation are performed at 37° C. Despite a clinically obvious coagulopathy, the values will be deceptively "normal."
- There are no safe predictors of serum electrolytes. Hypothermia enhances the cardiac toxicity of hyperkalemia and obscures premonitory electrocardiographic changes.
- Failure to rewarm despite good technique should suggest infection, endocrinologic insufficiency, or a futile resuscitation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Jurkovich GJ: Environmental cold-induced injury. *Surg Clin North Am* 2007; 87:247.
2. Gilbert M, et al: Resuscitation from accidental hypothermia of 13.7°C with circulatory arrest. *Lancet* 2000; 355:375.
3. Moran DS, et al: Hypothermia and local injuries in combat and non-combat situations: The Israeli experience. *Aviat Space Environ Med* 2003; 74:281.
4. Davis PR, Byers, M: Accidental hypothermia. *J R Army Med Corps* 2005; 151:223.
5. Danzl DF, Pozos RS: Accidental hypothermia. *N Engl J Med* 1994; 331:1756.
6. Miller JW, Danzl DF, Thomas DM: Urban accidental hypothermia: 135 cases. *Ann Emerg Med* 1980; 9:456.
7. White JD: Hypothermia: The Bellevue experience. *Ann Emerg Med* 1982; 11:417.
8. Centers for Disease Control and Prevention: Hypothermia-related deaths—United States, 1999-2002 and 2005. *MMWR Morb Mortal Wkly Rep* 2006; 55:282.
9. Afanasieva R, Bobrov A, Sokolov S: Cold assessment criteria and prediction of cooling risk in humans: The Russian perspective. *Ind Health* 2009; 47:235.
10. Kempainen RR, Brunette DD: The evaluation and management of accidental hypothermia. *Respir Care* 2004; 49:192.
11. Giesbrecht GG: Cold stress, near drowning and accidental hypothermia: A review. *Aviat Space Environ Med* 2000; 71:733.
12. deSouza D, et al: Electrocardiographic changes by accidental hypothermia in an urban and a tropical region. *J Electrocardiol* 2007; 40:47.
13. Aizawa Y, et al: Osborn wave in accidental hypothermia. *Intern Med* 2006; 45:333.
14. Nolan J, Soar J: Images in resuscitation: The ECG in hypothermia. *Resuscitation* 2005; 64:133.
15. Danzl DF, O'Brien DJ: The ECG computer program: Mort de froid. *J Wilderness Med* 1992; 3:328.
16. Danzl DF, et al: Multicenter hypothermia survey. *Ann Emerg Med* 1987; 16:1042.
17. Grueskin J, et al: A pilot study of mechanical stimulation and cardiac dysrhythmias in a porcine model of induced hypothermia. *Wilderness Environ Med* 2007; 18:133.
18. Giesbrecht GG, Johnston CE, Bristow GK: The convective afterdrop component during hypothermic exercise decreases with delayed exercise onset. *Aviat Space Environ Med* 1998; 69:17.
19. Hayward JS, Eckerson JD, Kemna D: Thermal and cardiovascular changes during three methods of resuscitation from mild hypothermia. *Resuscitation* 1984; 11:21.
20. Lloyd EL: Accidental hypothermia. *Resuscitation* 1996; 32:111.
21. Grissom CK, et al: Hypercapnia effect on core cooling and shivering threshold during snow burial. *Aviat Space Environ Med* 2008; 79:735.
22. Mallet ML: Pathophysiology of accidental hypothermia. *QJM* 2002; 95:775.
23. Sheridan RL, et al: Case 41-2009: A 16-year old boy with hypothermia and frostbite. *N Engl J Med* 2009; 361:2654.
24. Kibayashi K, Shojo H: Accidental fatal hypothermia in elderly people with Alzheimer's disease. *Med Sci Law* 2003; 43:127.
25. Udy AA, Ziegenfuss MD, Fraser JF: Deep accidental hypothermia during the Queensland summer. *Crit Care Res* 2007; 9:341.
26. Danzl DF: Hypothermia. *Semin Respir Crit Care Med* 2002; 23:57.
27. Gentilello LM, et al: Is hypothermia in the victim of major trauma protective or harmful? A randomized, prospective study. *Ann Surg* 1997; 226:439.
28. Cosgriff N, et al: Predicting life-threatening coagulopathy in the massively transfused trauma patient: Hypothermia and acidoses revisited. *J Trauma* 1997; 42:857.
29. Walpoth BH, et al: Outcome of survivors of accidental deep hypothermia and circulatory arrest treated with extracorporeal blood warming. *N Engl J Med* 1997; 337:1500.
30. White FN: Reassuring acid-base balance in hypothermia: A comparative point of view. *West J Med* 1983; 138:255.
31. Baraka AS, et al: Effect of alpha-stat versus pH-stat strategy on oxyhemoglobin dissociation and whole body oxygen consumption during hypothermia cardiopulmonary bypass. *Anesth Analg* 1992; 74:32.
32. Delaney KA, et al: Assessment of acid-base disturbances and their physiologic consequences. *Ann Emerg Med* 1989; 18:72.
33. Kroncke GM, et al: Ectothermic philosophy of acid-base balance to prevent fibrillation during hypothermia. *Arch Surg* 1986; 121:303.
34. Eddy VA, Morris JA Jr, Cullinane DC: Hypothermia, coagulopathy and acidosis. *Surg Clin North Am* 2000; 80:845.
35. Watts DD, et al: Hypothermic coagulopathy in trauma: Effect of varying levels of hypothermia on enzyme speed, platelet function and fibrinolytic activity. *J Trauma* 1998; 44:846.
36. Ying CL, Tsang SF, Ng KF: The potential use of desmopressin to correct hypothermia-induced impairment of primary haemostasis—an in vitro study using PFA-100. *Resuscitation* 2008; 76:129.
37. Mills WJ Jr: Field care of the hypothermic patient. *Int J Sports Med* 1992; 1(Suppl):199.
38. Samuelson T: Experience with standardized protocols in hypothermia, boom or bane? The Alaska experience. *Arctic Med Res* 1991; 50:28.
39. Grief R, et al: Resistive heating is more effective than metallic foil insulation in an experimental model of accidental hypothermia: A randomized controlled trial. *Ann Emerg Med* 2000; 35:337.
40. Breitkreutz R, Walcher F, Seegar FH: Focused echocardiographic evaluation in resuscitation management: Concept of an advanced life support–conformed algorithm. *Crit Care Med* 2007; 35:150.
41. Vanden Hoek TL, et al: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 12.9: Cardiac arrest in accidental hypothermia. *Circulation* 2010; 122(Suppl 3):S829.
42. Macleod DB, et al: The desaturation response time of finger pulse oximeters during mild hypothermia. *Anaesthesia* 2005; 60:65.
43. Platts-Mills TF, et al: An experimental study of warming intravenous fluid in a cold environment. *Wilderness Environ Med* 2007; 18:177.
44. Headdon WG, Wilson PM, Dalton HR: The management of accidental hypothermia. *BMJ* 2009; 338:2085.
45. Danzl DF: Blood flow during closed chest compressions in hypothermic humans. *Wilderness Environ Med* 1991; 7:12.
46. Maningas PA, et al: Regional blood flow during hypothermic arrest. *Ann Emerg Med* 1986; 15:390.
47. Althaus U, Aeberhard P, Schupbach P: Management of profound accidental hypothermia with cardiorespiratory arrest. *Ann Surg* 1982; 195:492.
48. Lexow K: Severe accidental hypothermia: Survival after 6 hours 30 minutes of cardiopulmonary resuscitation. *Arctic Med Res* 1991; 50:112.
49. Hughes A, Riou P, Day C: Full neurological recovery from profound (18.0°C) acute accidental hypothermia: Successful resuscitation using active invasive rewarming techniques. *Emerg Med J* 2007; 24:511.
50. Wik L, Kiil S: Use of an automatic mechanical chest compression devise (LUCAS) as a bridge to establishing cardiopulmonary bypass for a patient with hypothermic cardiac arrest. *Resuscitation* 2005; 66:391.
51. Weiss SJ, et al: The physiological response to norepinephrine during hypothermia and rewarming. *Resuscitation* 1998; 39:189.
52. Wira CR, et al: Anti-arrhythmic and vasopressor medications for the treatment of ventricular fibrillation in severe hypothermia: A systematic review of the literature. *Resuscitation* 2008; 78:21.
53. DaVee TS, Reineberg EJ: Extreme hypothermia and ventricular fibrillation. *Ann Emerg Med* 1980; 9:100.
54. Stoner J, et al: Amiodarone and bretylium in the treatment of hypothermic ventricular fibrillation in a canine model. *Acad Emerg Med* 2003; 10:187.
55. Khan JN, Prasad N, Glancy J: Amiodarone use in therapeutic hypothermia following cardiac arrest due to ventricular tachycardia and ventricular fibrillation. *Europace* 2009; 11:1566.
56. Dixon RG, et al: Transcutaneous pacing in a hypothermic dog model. *Ann Emerg Med* 1997; 29:602.
57. Ho JD, Heegaard WG, Brunette DD: Successful transcutaneous pacing in 2 severely hypothermic patients. *Ann Emerg Med* 2007; 49:678.
58. Delaney KA, et al: Rewarming rates in urban patients with hypothermia: Prediction of underlying infection. *Acad Emerg Med* 2006; 13:913.
59. Rogers I: Which rewarming therapy in hypothermia? A review of the randomized trials. *Emerg Med* 1997; 9:213.
60. Epstein E, Anna K: Accidental hypothermia. *BMJ* 2006; 332:706.
61. Van der Ploeg G, et al: Accidental hypothermia: Rewarming treatments, complications and outcomes from one university medical centre. *Resuscitation* 2010; 81:1550.
62. Soar J, et al: European Resuscitation Council Guidelines for Resuscitation 2010 Section 8. Cardiac arrest in special circumstances: Electrolyte abnormalities, poisoning, drowning, accidental hypothermia, hyperthermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution. *Resuscitation* 2010; 81:1400.
63. Prendergast HM, Erickson TB: *Procedures pertaining to hypothermia and hyperthermia*. In: Roberts JR, Hedges JR, eds. *Clinical Procedures in Emergency Medicine*, 5th ed. Philadelphia: Saunders/Elsevier; 2010:1235.

www.ketabpezeshki.com 66485457-66963820

64. Mulcahy AR, Watts MR: Accidental hypothermia: An evidence-based approach. *Emerg Med Pract EBMedicine.net* 2009; 11:1.
65. Gregory RT, Doolittle WH: Accidental hypothermia. II. Clinical implications of experimental studies. *Alaska Med* 1973; 15:48.
66. Roggla M, et al: Severe accidental hypothermia with or without hemodynamic instability: Rewarming without the use of extracorporeal circulation. *Wien Klin Wochenschr* 2002; 114:315.
67. Zhong H, Qinyi S, Mingjlang S: Rewarming with microwave irradiation in severe cold injury syndrome. *Chin Med J* 1980; 93:19.
68. Duguid H, Simpson RG, Stowers JM: Accidental hypothermia. *Lancet* 1961; 2:1213.
69. Hamilton RS, Paton BC: The diagnosis and treatment of hypothermia by mountain rescue teams: A survey. *Wilderness Environ Med* 1996; 7:37.
70. Giesbrecht GG, Bristow GK: Recent advances in hypothermia research. *Ann N Y Acad Sci* 1997; 813:676.
71. Steele MT, et al: Forced air speeds rewarming in accidental hypothermia. *Ann Emerg Med* 1996; 27:479.
72. Ittner KP, et al: Convective air warming is more effective than resistive heating in an experimental model with a water dummy. *Eur J Emerg Med* 2004; 11:151.
73. Cocchi MN, Giberson B, Donnino MW: Rapid rewarming of hypothermic patient using arctic sun device. *J Intensive Care Med* 2012; 27:128.
74. Vince SC, Flint NJ, Hall AP: A novel non-invasive warming technique in severe accidental hypothermia. *Resuscitation* 2008; 77:144.
75. Vangaard L, et al: Arteriovenous anastomoses (AVA) rewarming in 45° C water is effective in moderately hypothermic subjects. *FASEB J* 1998; 12:A90.
76. Ducharme MG, et al: Forced-air rewarming in −20° C simulated field conditions. *Ann N Y Acad Sci* 1997; 813:676.
77. Weinberg AD: The role of inhalation rewarming in the early management of hypothermia. *Resuscitation* 1998; 36:101.
78. Fisher A, et al: Oxygen availability during hypothermic cardiopulmonary bypass. *Crit Care Med* 1977; 5:154.
79. Wallace W: Does it make sense to heat gases higher than body temperature for the treatment of cold water near-drowning or hypothermia? A point of view paper. *Alaska Med* 1997; 39:75.
80. Kjaergaard B, Bach P: Warming of patients with accidental hypothermia using warm water pleural lavage. *Resuscitation* 2006; 68:203.
81. Plaisier BR: Thoracic lavage in accidental hypothermia with cardiac arrest: Report of a case and review of the literature. *Resuscitation* 2005; 66:99.
82. Hall KN, Syverud SA: Closed thoracic cavity lavage in the treatment of severe hypothermia in human beings. *Ann Emerg Med* 1990; 19:204.
83. Brunette DD, et al: Comparison of gastric and closed thoracic lavage in the treatment of severe hypothermia in dogs. *Ann Emerg Med* 1987; 16:1222.
84. Iverson RJ, et al: Successful CPR in a severely hypothermic patient using continuous thoracostomy lavage. *Ann Emerg Med* 1990; 19:1335.
85. Willekes T, Naunheim R, Lasater M: A novel method of intravascular temperature modulation to treat severe hypothermia. *Emerg Med J* 2006; 23:56.
86. Laniewicz M, Lyn-Kew K, Silbergleit R: Rapid endovascular warming for profound hypothermia. *Ann Emerg Med* 2008; 51:160.
87. Gregory JS, et al: Comparison of three methods of rewarming from hypothermia: Advances of extracorporeal blood rewarming. *J Trauma* 1991; 31:1247.
88. Farsted M, et al: Rewarming from accidental hypothermia by extracorporeal circulation: A retrospective study. *Eur J Cardiothorac Surg* 2001; 20:58.
89. Heise D, Rathgeber J, Burchardi H: Severe, accidental hypothermia: Active rewarming with a simple extracorporeal veno-venous warming-circuit. *Anaesthetist* 1996; 45:1093.
90. Alfonzo A, et al: Survival after 5-h resuscitation attempt for hypothermic cardiac arrest using CVVH for extracorporeal rewarming. *Nephrol Dial Transplant* 2009; 24:1054.
91. Komatsu S, et al: Severe accidental hypothermia successfully treated by rewarming strategy using continuous venovenous hemodiafiltration system. *J Trauma* 2007; 62:775.
92. Brauer A, et al: Severe accidental hypothermia: Rewarming strategy using a venovenous bypass system and a convective air warmer. *Intensive Care Med* 1999; 25:520.
93. Caluwe R, Vanholder R, Dhondt A: Hemodialysis as a treatment of severe accidental hypothermia. *Artif Organs* 2010; 34:237.
94. Sultan N, et al: Treatment of severe accidental hypothermia with intermittent hemodialysis. *CJEM* 2009; 11:174.
95. Gentilello LM, et al: Continuous arteriovenous rewarming: Experimental results and thermodynamic model simulation of treatment for hypothermia. *J Trauma* 1990; 30:1436.
96. Walpoth BH, et al: Accidental deep hypothermia with cardiopulmonary arrest: Extracorporeal blood rewarming in 11 patients. *Eur J Cardiothorac Surg* 1990; 4:390.
97. Binnema R, et al: Treatment of accidental hypothermia with cardiopulmonary bypass: A case report. *Perfusion* 2008; 23:193.
98. Oberhammer R, et al: Full recovery of an avalanche victim with profound hypothermia and prolonged cardiac arrest treated by extracorporeal re-warming. *Resuscitation* 2008; 76:474.
99. Saxena P, et al: Role of extracorporeal circulation in the management of accidental deep hypothermia. *Heart Lung Circ* 2009; 18:416.
100. von Segesser LK, et al: Reduction and elimination of systemic heparinization during cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1992; 103:790.
101. Kirkpatrick AW, et al: Use of a centrifugal vortex blood pump and heparin-bonded circuit for extracorporeal rewarming of severe hypothermia in acutely injured and coagulopathic patients. *J Trauma* 2003; 55:407.
102. Splittgerber FH, et al: Partial cardiopulmonary bypass for core rewarming in profound accidental hypothermia. *Am Surg* 1986; 52:407.
103. Ruttmann E, et al: Prolonged extracorporeal membrane oxygenation–assisted support provides improved survival in hypothermic patients with cardiocirculatory arrest. *J Thorac Cardiovasc Surg* 2007; 134:594.
104. Brodmann Maeder M, et al: The Bernese Hypothermia Algorithm: A consensus paper on in-hospital decision-making and treatment of patients in hypothermia cardiac arrest at an alpine level 1 trauma centre. *Injury* 2011; 42:539.
105. Seiji M, et al: The efficacy of rewarming with a portable and percutaneous cardiopulmonary bypass system in accidental deep hypothermia patients with hemodynamic instability. *J Trauma* 2008; 65:1391.
106. Bolgiano E, Sykes L, Barish RA: Accidental hypothermia with cardiac arrest: Recovery following rewarming by cardiopulmonary bypass. *J Emerg Med* 1992; 10:427.
107. Niazi SA, Lewis FJ: Profound hypothermia in man: Report of a case. *Ann Surg* 1958; 147:264.
108. Danzl DF, Lloyd EL: *Treatment of accidental hypothermia*. In: Pandolk KB, Burr RE, Wenger CB, Pozos RS, eds. Medical Aspects of Harsh Environments, vol 1. Washington, DC: Office of the Surgeon General; 2001:491.
109. Vionnet M, Mueller X, von Segesser LK: Unusual complications after rewarming for deep accidental hypothermia. *Thorac Cardiovasc Surg* 2004; 52:185.
110. Silfvast T, Pettilä V: Outcome from severe accidental hypothermia in Southern Finland—a 10 year review. *Resuscitation* 2003; 59:285.
111. Vassal T, et al: Severe accidental hypothermia treated in an ICU: Prognosis and outcome. *Chest* 2001; 120:1998.
112. Megarbane B, et al: Hypothermia with indoor occurrence is associated with a worse outcome. *Intensive Care Med* 2000; 25:1943.
113. Dobson JAR, Burgess JJ: Resuscitation of severe hypothermia by extracorporeal rewarming in a child. *J Trauma* 1996; 40:483.
114. Hildebrand RL, et al: Pathophysiologic changes and effects of hypothermia on outcome in elective surgery and trauma patients. *Am J Surg* 2004; 187:363.
115. Danzl DF, et al: Hypothermia outcome score: Development and implications. *Crit Care Med* 1989; 17:227.
116. Locher T, et al: Accidental hypothermia in Switzerland (1980-1987): Case reports and prognostic factors. *Schweiz Med Wochenschr* 1991; 121:1020.
117. Pillgram-Larsen J, et al: Accidental hypothermia: Risk factors in 29 patients with body temperature of 30° C and below. *Tidsskr Nor Laegeforen* 1991; 111:180.
118. Schaller MD, Fischer AP, Perret CH: Hyperkalemia: A prognostic factor during acute severe hypothermia. *JAMA* 1990; 264:1842.
119. Hauty MG, et al: Prognostic factors in severe accidental hypothermia: Experience from the Mt. Hood tragedy. *J Trauma* 1987; 27:1107.

www.ketabpezeshki.com 66485457-66963820

Chapter 141

Heat Illness

Melissa Platt and Salvator Vicario

PERSPECTIVE

Humans have been plagued by heat illness throughout recorded history, often as the result of military exercises, athletic events, or recreational activities. When environmental heat stress is maximal, strenuous exercise is not required to produce heat illness. The ancient Greeks named a disease that resembled heatstroke *siriasis* after the dog star Sirius, which accompanies the summer sun. The U.S. Army reported at least 125 deaths from heatstroke during basic training in the years 1941 to 1944.[1] Modern military organizations continue to encounter heat illness because of the requirement to train unacclimatized troops with forced heavy physical exercise. Furthermore, athletes are prone to heat illness; heat stroke is the third leading cause of death among all U.S. athletes. In particular, football has the greatest number of heat stroke fatalities and a 10 times higher rate for heat illness, resulting in time lost from high school athletic activities.[2,3]

The elderly and poor, often lacking adequate air conditioning and nutrition, and those with preexisting disease are prone to heat illness during environmental extremes. In heat wave years in the United States, approximately 10 times as many deaths are reported as during non–heat wave years. It is also estimated that at least 10 times as many heat-aggravated illnesses occur because of myocardial infarction, cerebrovascular accident, and other causes. More than 700 excess deaths were caused by the heat during the 1995 heat wave in Chicago. The heat wave during the summer of 2003 is estimated to have caused 14,800 deaths in France, and climate models suggest an increase in both frequency and intensity of heat waves in temperate areas in the future.[4]

PRINCIPLES OF DISEASE

Physiology of Heat

Heat Production

Humans can be considered biochemical "furnaces" that burn food to fuel a complex array of metabolic functions. These chemical reactions consume substrate, generate usable energy, and produce byproducts that must be eliminated for continued operation of the system. Water and carbon dioxide are produced and eliminated in large quantities, as are urea, sulfates, phosphates, and other chemical products. All of these reactions are exothermic and combine to produce a basal metabolic rate that amounts to approximately 100 kcal for a 70-kg person. In the absence of cooling mechanisms, this baseline metabolic activity would result in a 1.1° C hourly rise in body temperature.

Heat production can be increased up to 20-fold by strenuous exertion. Rectal temperatures as high as 42° C are recorded without ill effects in trained marathon runners. Metabolic factors, such as hyperthyroidism and sympathomimetic drug ingestion, can dramatically increase heat production. Environmental heat not only adds to the heat load but also interferes with heat dissipation. The physics of heat transfer as it relates to human physiology involves four mechanisms: conduction, convection, radiation, and evaporation.[5]

Conduction. Conduction is the transfer of heat energy from warmer to cooler objects by direct physical contact. Air is a good insulator; therefore, only approximately 2% of the body heat loss is by conduction. In contrast, the thermal conductivity of water is at least 25 times that of air.

Convection. Heat loss to air and water vapor molecules circulating around the body is termed convection. As ambient temperature rises, the amount of heat dissipated by convection becomes minimal, and once air temperature exceeds the mean skin temperature, heat is gained by the body. Convective heat loss varies directly with wind velocity. Loose-fitting clothing maximizes convective (and also evaporative) heat loss.

Radiation. Radiation is heat transfer by electromagnetic waves. Although radiation accounts for approximately 65% of heat loss in cool environments, it is a major source of heat gain in hot climates. Up to 300 kcal/hr can be gained from radiation when a person is directly exposed to the hot summer sun.[6]

Evaporation. Evaporation is the conversion of a liquid to the gaseous phase. Evaporation of 1 mL of sweat from the skin cools the body by 0.58 kcal. As ambient temperature rises, evaporation becomes the dominant mechanism of heat loss. Panting mammals such as dogs have an oropharyngeal countercurrent flow mechanism (carotid rete mirabile) that results in selective cooling of the brain. In humans, respiratory and countercurrent mechanisms are minimal sources of heat loss, and the dominant mode of cooling in hot conditions is evaporation of sweat from the skin.

Heat Regulation

The regulation of body temperature involves three distinct functions: thermosensors, a central integrative area, and thermoregulatory effectors.

www.ketabpezeshki.com 66485457-66963820

Thermosensors. Temperature-sensitive structures are located both peripherally in the skin and centrally in the body. Skin temperature changes, however, correlate poorly with changes in the rate of heat loss.[7] Thermosensitive neurons are in the preoptic anterior hypothalamus. They are activated when the temperature of the blood circulating through that area exceeds a "set point."

The skin temperature affects heat loss because a person resting in a warm environment initiates sweating, even though the core temperature remains constant. In contrast, changes in core temperature are more potent than skin temperature changes in producing heat-dissipating responses.[8]

Central Integrative Area. The central nervous system (CNS) interprets information received from the thermosensors to properly instruct thermoregulatory effectors. The concept of a central thermostat by which an alteration shifts effector thresholds in the same direction fits a variety of clinical situations. For example, fever, the circadian rhythm of temperature variation, and the 0.5° C difference in rectal temperature after ovulation can be explained by variation of a thermal set point.

Thermoregulatory Effectors. Sweating and peripheral vasodilation are the major mechanisms by which heat loss can be accelerated. In a warm environment, evaporation of sweat from the skin is the most important mechanism of heat dissipation. Heat loss from the skin by convection and radiation is maximized by increased skin blood flow to facilitate sweating.

Humans possess apocrine and eccrine sweat glands. Apocrine glands are concentrated in the axillae and produce milky sweat rich in carbohydrate and protein. They are adrenergically innervated and respond to emotional stress as well as to heat. Most glands producing "thermal sweat" are eccrine glands. These are cholinergically innervated and distributed over the entire body, with the largest number on the palms and soles. Eccrine sweat is colorless, odorless, and devoid of protein. Individuals exercising in hot environments commonly lose 1 or 2 L/hr of sweat; loss of 4 L/hr for short periods is possible.

Cooling is best achieved by evaporation from the body surface; sweat that drips from the skin does not cool the body, and sweat evaporated from clothing is considerably less efficient. Each liter of completely evaporated sweat dissipates 580 kcal of heat. The ability of the environment to evaporate sweat is termed atmospheric cooling power and varies primarily with humidity but also with wind velocity. As humidity approaches 100%, evaporative heat loss ceases.

The vascular response to heat stress is cutaneous vasodilation and compensatory vasoconstriction of splanchnic and renal beds. These vascular changes are under neurogenic control and allow heat to be dissipated quickly and efficiently, but they place a tremendous burden on the heart.[9] For blood pressure to be maintained, cardiac output increases dramatically. For this reason, saunas and hot tubs may be dangerous for patients with cardiac disease. Cardiovascular and baroreceptor reflexes also affect skin blood flow. Reduced forearm sweating and vasodilation are observed in severely dehydrated subjects exercising in a warm environment.[10]

Acclimatization

Acclimatization is defined as "a constellation of physiologic adaptations that appear in a normal person as the result of repeated exposures to heat stress." Daily exposure to work and heat for 100 min/day results in near-maximal acclimatization in 7 to 14 days. This is characterized by an earlier onset of sweating (at a lower core temperature), increased sweat volume, and lowered sweat electrolyte concentration. Acclimatization is hastened by modest salt deprivation and delayed by high dietary salt intake. As acclimatization proceeds, the sweat sodium concentration decreases while the volume increases.[11]

The cardiovascular system plays a major role in both acclimatization and endurance training, largely resulting from an expansion of plasma volume.[12] Heart rate is lower and associated with a higher stroke volume. Other physiologic changes include earlier release of aldosterone, although acclimatized individuals generate lower plasma levels of aldosterone during exercise heat stress. Total body potassium depletion of up to 20% (500 mEq) by the second week of acclimatization can occur as a result of sweat and urine losses coupled with inadequate repletion.[12]

Although many similarities exist between thermoregulatory responses to heat and exercise, the well-conditioned athlete is not necessarily heat acclimatized. For heat and exercise-induced adaptive responses to be maintained, heat exposure needs to continue intermittently at least on 4-day intervals. Plasma volume decreases considerably within 1 week in the absence of heat stress.[12]

PATHOPHYSIOLOGY

Predisposing Factors for Heat Illness

Elderly patients, psychiatric patients, or those with chronic diseases who are taking medications predisposing to heat illness are prone to classic heatstroke during periods of high ambient heat and humidity. Adequate fluid intake is essential. Elderly patients sometimes dress inappropriately for hot weather; heat loss is maximized by light, loose-fitting garments.

Exertional heatstroke is most likely to occur in young, healthy people involved in strenuous physical activity, especially if they have not acclimatized to environmental factors that overwhelm heat-dissipating mechanisms. Fluid intake is the most critical variable. Dehydration can be minimized by education on work-rest cycles and fluid consumption and through provision of cool, pleasantly flavored fluids.

The goal is to maximize voluntary fluid intake and gastric emptying so that fluid can rapidly enter the small intestine, where it is absorbed. Gastric emptying is accelerated to 25 mL/min by large fluid volumes (500-600 mL) and cool temperatures (10-15.8° C). High osmolality inhibits gastric emptying; osmolality of less than 200 mOsm/L is optimal. Most commercially available electrolyte solutions contain excessive sugar. Hydration can be monitored by measurement of body weight before and after training or athletic competition. An athlete with a loss of 2 or 3% body weight (1.5-2 L in a 70-kg man) should drink extra fluid and be permitted to compete only when body weight is within 0.5 to 1 kg (1 or 2 pounds) of the starting weight on the previous day. A weight loss of 5 or 6% represents a moderately severe deficit and usually is associated with intense thirst, scanty urine, tachycardia, and increase in rectal temperature of approximately 2° C. Such athletes should be restricted to light workouts after hydration until they return to normal weight. A loss of 7% or more of body weight represents severe water depletion; participation in sports should not be permitted until the athlete is examined by a physician. Wrestlers frequently fast, restrict food and fluid intake, and exercise vigorously wearing vapor-impermeable clothing to lose weight quickly so that they can compete in a lower weight class.[13]

The administration of salt tablets during strenuous exercise can cause delayed gastric emptying, osmotic fluid shifts into the gut, gastric mucosal damage, and hypernatremic dehydration. A 6-g sodium diet is sufficient for successful adaptation for work in the heat, with sweat losses averaging 7 L/day. Excessively high salt intake in relation to salt losses in sweat during initial heat exposure can impair acclimatization because of inhibition of aldosterone secretion. Excessive salt ingestion can also exacerbate potassium depletion.

Evaporative cooling can be lost when clothing inhibits air convection and evaporation. Loose-fitting clothing or ventilated fishnet jerseys allow efficient evaporation. Light-colored clothing

www.ketabpezeshki.com 66485457-66963820

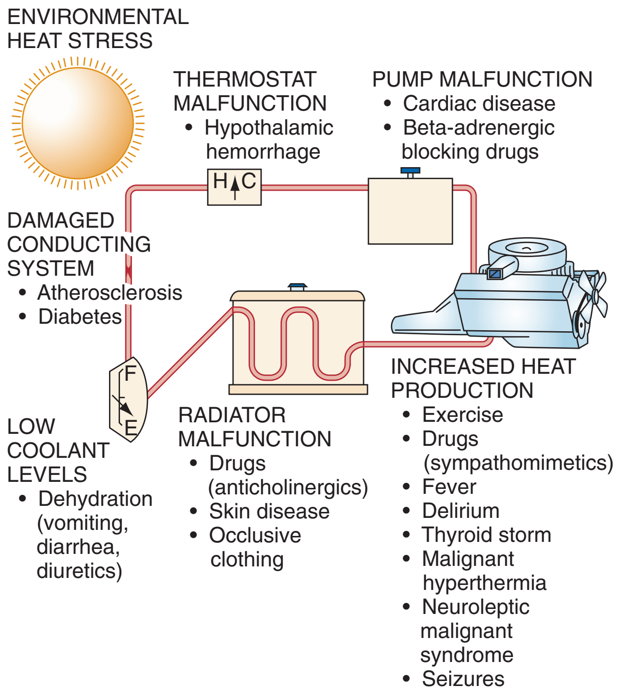


Figure 141-1. Predisposing factors for heat illness: an automotive analogy.

reflects rather than absorbs light. Water evaporated from clothing is much less efficient for body cooling than is water evaporated from the skin.[14,15]

The body's heat dissipation mechanisms are analogous to the cooling system of an automobile (Fig. 141-1). Coolant (blood) is circulated by a pump (heart) from the hot inner core to a radiator (skin surface cooled by the evaporation of sweat). Temperature is sensed by a thermostat (CNS), which alters coolant flow by a system of pipes, valves, and reservoirs (vasculature). Failure of any of these components can result in overheating.

Effective circulation requires both an intact pump and adequate coolant levels. Individuals with cardiac disease or those taking beta-adrenergic blocking agents or calcium channel blockers may be unable to increase their cardiac output sufficiently to produce the necessary peripheral vasodilation to dissipate heat. Dehydration caused by gastroenteritis, diuretics, or inadequate fluid intake predisposes to heat illness. Individuals working in the heat seldom voluntarily drink as much fluid as they lose and replace only approximately two thirds of net water loss ("voluntary dehydration"). Dehydration alone increases body temperature at rest by increasing the work of the sodium-potassium adenosine triphosphatase pump, which accounts for 25 to 45% of basal metabolic rate. This is particularly true in cases of hypernatremic dehydration. The pipes and valves of the coolant system may be abnormal in diabetic or elderly patients with extensive atherosclerosis.

Radiator function depends on the skin and sweat glands. Occlusive, vapor-impermeable clothing hinders evaporative and convective cooling. Anticholinergic medications and some drugs of abuse interfere with sweating and produce heat illness.[11] Various skin diseases, including miliaria (prickly heat rash), extensive burns, scleroderma, ectodermal dysplasia, and cystic fibrosis, are risk factors. Anhidrosis can be secondary to either central or peripheral nervous system disorders as well.

Increased heat production causing heat illness most often accompanies exercise in hot, humid environments. Athletes and military recruits are commonly affected. When heat and humidity are extreme, exertion is not necessary to produce heat-related

Box 141-1 Wet Bulb Globe Temperature

$$WBGT = 0.7T_n + 0.2T_g + T_a$$

T_n "Natural" wet bulb temperature; the temperature achieved by a thermometer covered with a moistened white wick and left exposed to the ambient environment
T_g Globe temperature; the temperature inside a blackened hollow copper sphere exposed to the ambient environment
T_a Ambient temperature
These measurements can be done manually or automatically calculated with the help of computer algorithms.

WBGT, wet bulb globe temperature.

problems. Several indices help objectify heat strain. The indices can be divided into two categories: heat scales that are based on meteorologic parameters only and heat scales that combine environmental and physiologic parameters.[16]

The wet bulb globe temperature heat index is an excellent meteorologic measure of environmental heat stress (Box 141-1). It includes the effects of temperature, humidity, and radiant thermal energy from the sun. When climatic conditions exceed 25° C wet bulb, even healthy people are at high risk if they choose to exercise. Above 28° C, exercise and strenuous work should be avoided or limited to extremely short periods.[17]

The heat strain index is widely accepted as an example of an index that includes environmental and physiologic factors. There are several variations and modified heat strain indices in existence, with varying ease of use and accuracy (Fig. 141-2).[16]

Before the advent of air conditioning, mortality increased threefold to fivefold in nursing homes and threefold in the general population during heat waves. Mortality in geriatric patients correlates with average weekly peak air temperature. Most deaths in the 2003 European heat wave occurred in elderly patients. Microclimates conducive to heat illness are produced in the interiors of automobiles, tanks, and tents in the sun as well as in engine rooms, hot tubs, and saunas.[4] Children are more susceptible to heat stressors because the higher surface area–to–mass ratios allow increased absorption of heat. They also have lower sweat rates per gland.[18]

Endogenous factors, such as hyperthyroidism and pheochromocytoma, can also drastically increase heat production. An overdose of sympathomimetics or stimulants, such as amphetamines, cocaine, and phencyclidine, can cause fatal hyperpyrexia. High ambient temperature is associated with a significant increase in mortality from cocaine overdose. Many younger patients who die of hyperthermia test positive for cocaine.[19] Heatstroke can occur with delirium resulting from ethanol withdrawal.[20] There are also reports of heatstroke occurring in well-trained military soldiers or athletes who ingest dietary supplements containing ephedrine or the ergogenic aid creatine.[21,22]

Certain patients undergoing general anesthesia rapidly experience severe hyperthermia, muscle rigidity, and acidosis. This syndrome, termed malignant hyperthermia, is the result of a genetically determined instability of skeletal muscle sarcoplasmic reticulum that allows inappropriate intracellular calcium release. Dantrolene, which lowers myoplasmic calcium, is effective in the prevention and treatment of this syndrome.[23]

Malignant hyperthermia is rarely seen in outpatient settings, but a clinically similar entity, neuroleptic malignant syndrome, is often encountered. This syndrome is induced by antipsychotic medications and is characterized by muscle rigidity, severe dyskinesia or akinesia, hyperthermia, tachycardia, dyspnea, dysphagia, and urinary incontinence. Although the lead-pipe rigidity and hyperthermia are reminiscent of malignant hyperthermia, the putative mechanism is different. Dopamine receptor blockade in

www.ketabpezeshki.com 66485457-66963820

NATIONAL WEATHER SERVICE
HEAT INDEX CHART

	Heat index F° (C°)												
	Relative humidity (%)												
Temp.	40	45	50	55	60	65	70	75	80	85	90	95	100
110 (47)	136 (58)												
108 (43)	130 (54)	137 (58)											
106 (41)	124 (51)	130 (54)	137 (58)										
104 (40)	119 (48)	124 (51)	131 (55)	137 (58)									
102 (39)	114 (46)	119 (48)	124 (51)	130 (54)	137 (58)								
100 (38)	109 (43)	114 (46)	118 (48)	124 (51)	129 (54)	136 (58)							
98 (37)	105 (41)	109 (43)	113 (45)	117 (47)	123 (51)	128 (53)	134 (57)						
96 (36)	101 (38)	104 (40)	108 (42)	112 (44)	116 (47)	121 (49)	126 (52)	132 (56)					
94 (34)	97 (36)	100 (38)	103 (39)	106 (41)	110 (43)	114 (46)	119 (48)	124 (51)	129 (54)	135 (57)			
92 (34)	94 (34)	96 (36)	99 (37)	101 (38)	105 (41)	108 (42)	112 (44)	116 (47)	121 (49)	126 (52)	131 (55)		
90 (32)	91 (33)	93 (34)	95 (35)	97 (36)	100 (38)	103 (39)	106 (41)	109 (43)	113 (45)	117 (47)	122 (50)	127 (53)	132 (56)
88 (31)	88 (31)	89 (32)	91 (33)	93 (34)	95 (35)	98 (37)	100 (38)	103 (39)	106 (41)	110 (43)	113 (45)	117 (47)	121 (49)
86 (30)	85 (29)	87 (31)	88 (31)	89 (32)	91 (33)	93 (34)	95 (35)	97 (36)	100 (38)	102 (39)	105 (41)	108 (42)	112 (44)
84 (29)	83 (28)	84 (29)	85 (29)	86 (30)	88 (31)	89 (32)	90 (32)	92 (33)	94 (34)	96 (36)	98 (37)	100 (38)	103 (39)
82 (28)	81 (27)	82 (28)	83 (28)	84 (29)	84 (29)	85 (29)	86 (30)	88 (31)	89 (32)	90 (32)	91 (33)	93 (34)	95 (35)
80 (27)	80 (27)	80 (27)	81 (27)	81 (27)	82 (28)	82 (28)	83 (28)	84 (29)	84 (29)	85 (29)	86 (30)	86 (30)	87

Figure 141-2. National Weather Service Heat Index Chart. Key: ■ extreme danger ■ danger

the corpus striatum caused by butyrophenones and similar agents produces severe muscle spasticity and dystonia, leading to overproduction of heat. Some antipsychotics also cause suppression of thirst recognition. Other miscellaneous risk factors include obesity.[24] Individuals with a history of heatstroke, with or without an inherent aberration that predisposed them to the initial episode, are at increased risk for a recurrence.

Fever versus Hyperthermia

It is both diagnostically and therapeutically important to identify patients suffering from a febrile response rather than heat illness. For many years, fever was attributed to pyrogens released by bacteria or viruses (exogenous pyrogens) or to cells undergoing autolysis after phagocytic activity (endogenous pyrogens).[25] These circulating pyrogens would directly affect the thermoregulatory control center. It now appears that fever is the result of triggering by pyrogens of pathways involving cytokine receptors or other signals to reset the thermal set point in the preoptic area of the anterior hypothalamus to a new level above 37° C.[25]

Once this temperature is established, the thermoregulatory center uses all available heat-regulatory servomechanisms to maintain the new temperature. Thus a patient with fever in an environment previously believed to be thermally comfortable begins to feel cold and chooses a warmer environment. This behavioral drive is coordinated with the autonomic mechanisms, such as shivering, to increase body temperature to the new set point. In most circumstances, temperature elevation is not a significant problem, and therapy is directed at the underlying disease state. Fever does not cause primary pathologic or physiologic damage to humans and does not require primary emphasis in the therapeutic regimen, which is directed at the underlying disease state. If temperature-related physiologic changes, such as febrile seizures and tachycardia, compromise a patient with marginal cardiac reserve, temperature must be artificially regulated.

Because fever is the product of a molecular interaction that establishes a new physiologic thermal set point, therapeutic attempts to lower temperature are opposed by body mechanisms that attempt to maintain the new set point. Thus attempts at whole-body cooling produce violent shivering and discomfort.[26] The use of agents to block the causative molecular interaction is the most clinically effective approach. Antipyretics block the action of the pyrogen at hypothalamic receptor sites through inhibition of prostaglandin synthesis.[27] These antipyretics are not

www.ketabpezeshki.com 66485457-66963820

effective against and should not be used to control environmental hyperthermia.

MINOR HEAT ILLNESS

Heat Cramps

Physiology

Heat cramps are brief, intermittent, and often severe muscle cramps occurring typically in muscles that are fatigued by heavy work. Heat cramps appear to be related to a salt deficiency. Heat cramps occur most commonly during the first days of work in a hot environment and develop in persons who produce large amounts of thermal sweat and subsequently drink copious amounts of hypotonic fluid.[28]

Clinical Factors

Athletes, roofers, steel workers, coal miners, field workers, and boiler operators are among the most common victims of heat cramps. Heat cramps tend to occur after exercise when the victim stops working and is relaxing (Box 141-2). In this respect, they differ from the cramps experienced by athletes during exercise, which tend to last for several minutes, are relieved by massage, and resolve spontaneously.

Heat cramps are occasionally confused with hyperventilation tetany, which can occur during heat exhaustion. Hyperventilation tetany can be distinguished by the presence of carpopedal spasm and paresthesias in the distal extremities and perioral area. Heat cramps accompanied by systemic symptoms may be part of salt depletion heat exhaustion. Heat cramp victims exhibit hyponatremia, hypochloremia, and low serum sodium and chloride levels. Rhabdomyolysis or resultant renal damage is not present with isolated heat cramps.

Management

Heat cramps are usually rapidly relieved by salt solutions. Commercially available flavored electrolyte solutions are commonly ingested. Mild cases without concurrent dehydration are treated orally with 0.1 or 0.2% salt solution (two to four 10-grain salt tablets [56-112 mEq] or ¼ to ½ teaspoon of table salt dissolved in a quart of water), which is the general limit of palatability. Severe cases respond rapidly to intravenous isotonic solution (0.9% NaCl). Salt tablets are gastric irritants, delay gastric emptying, and are not recommended.[29]

Heat Edema

Physiology and Clinical Features

Swollen feet and ankles are often reported by nonacclimatized individuals, especially the elderly, who encounter climatic stresses of tropical and semitropical areas. Such individuals often have no underlying cardiac, hepatic, venous, or lymphatic disease. They commonly have assumed rigorous schedules with long periods of sitting or standing. The edema is usually minimal, is not accompanied by any significant impairment in function, and often resolves after several days of acclimatization.

It is presumed that hydrostatic pressure and vasodilation of cutaneous vessels, combined with some degree of orthostatic pooling, lead to vascular leak and accumulation of interstitial fluid in the lower extremities. Simultaneously, aldosterone increases in response to the heat stress and perceived central volume deficit.

Awareness of this clinical presentation prevents overly vigorous diagnostic and therapeutic intervention. Brief diagnostic evaluation to rule out thrombophlebitis, lymphedema, or congestive heart failure is appropriate, but invasive diagnostic techniques or vigorous pharmacologic therapy is not indicated.

Management

Diuretic therapy is not effective. Rather, simple leg elevation or thigh-high support hose should be used. In most individuals, the problem resolves either through adequate acclimatization or with the individual's return to a temperate climate.

Heat Syncope

Physiology and Clinical Features

Heat syncope is a perplexing disorder in which a host of serious and an even larger number of nonserious underlying mechanisms can also result in temporary loss of consciousness. The elderly have a special predilection for this disorder. Individuals adapt to a hot, humid environment by dilation of cutaneous vessels to deliver heat to the body surface. Thus an increased portion of the intravascular pool is located in the periphery at any given time. Increasing blood flow to compliant cutaneous veins raises skin vascular volume at the expense of thoracic blood volume. Individuals who stand for protracted periods tend to pool blood in the lower extremities. Combined with volume loss and peripheral vasodilation, this pooling can result in inadequate central venous return, a concomitant drop in cardiac output, and cerebral perfusion inadequate to maintain consciousness.

Management

The disorder is self-limited because assumption of a horizontal position is curative. Individuals at risk for heat syncope should be warned to move often, to flex leg muscles repeatedly when standing stationary, to avoid protracted standing in hot environments, and to assume a sitting or horizontal position when prodromal warning symptoms or signs occur. These include scintillating scotomas, tunnel vision, vertigo, nausea, diaphoresis, and weakness.

Prickly Heat

Physiology and Clinical Features

Prickly heat, also known as miliaria rubra, lichen tropicus, and heat rash, is an acute inflammatory disorder of the skin that occurs in tropical climates. It is the result of blockage of sweat gland pores by macerated stratum corneum and secondary staphylococcal infection. The acute phase is characterized by vesicles in the malpighian layer of the skin caused by dilation and rupture of the obstructed sweat gland ducts.

Clinically, this initially produces intensely pruritic vesicles on an erythematous base. The rash is confined to clothed areas, and the affected area is often completely anhidrotic. During approximately the next week, a keratin plug arises and fills these vesicles, causing a deeper obstruction of the sweat gland duct. The obstructed duct then ruptures a second time, producing a deeper

Box 141-2 Heat Cramps: Essentials of Diagnosis

Cramps of most worked muscles
Usually occur after exertion
Copious sweating during exertion
Copious hypotonic fluid replacement during exertion
Hyperventilation not present in cool environment

www.ketabpezeshki.com 66485457-66963820

Figure 141-3. Prickly heat. (From Habif TP: Clinical Dermatology: A Color Guide to Diagnosis and Therapy, 3rd ed. St Louis, Mosby, 1996.)

vesicle within the dermis. This is known as the profunda stage, and it can persist for weeks. Profunda vesicles are not pruritic and closely resemble the white papules of piloerection; chronic dermatitis is a common complication (Fig. 141-3).

Management

Chlorhexidine in a light cream or lotion is the antibacterial treatment of choice during the acute phase. Salicylic acid, 1%, can be applied three times daily to localized, affected areas to assist in desquamation, but it should not be used in children or over large areas because of possible salicylate intoxication. For diffuse or pustular rashes, erythromycin can be helpful.

Prickly heat can be prevented by wearing of light, loose-fitting, clean clothing and the avoidance of situations that produce continuous sweating. Routine use of talcum or baby powder should be avoided.

HEAT EXHAUSTION

Physiology

Heat exhaustion (heat prostration) is a clinical syndrome characterized by volume depletion that occurs under conditions of heat stress. Two types of heat exhaustion are classically described: water depletion and salt depletion.

Water depletion heat exhaustion results from inadequate fluid replacement by individuals working in a hot environment, usually laborers, athletes, military personnel, and incapacitated individuals without free access to water. Those working in the heat seldom drink as much as they lose and replace only approximately two thirds of net water loss. This voluntary dehydration results in progressive hypovolemia. Left untreated, water depletion heat exhaustion will progress to heatstroke.

Salt depletion heat exhaustion takes longer to develop than the water depletion form. It occurs when large volumes of thermal sweat are replaced by water with too little salt. It differs from heat cramps in that systemic symptoms occur. This syndrome is characterized by hyponatremia, hypochloremia, and low urinary sodium and chloride concentrations. Symptoms are similar to those seen in water depletion heat exhaustion; body temperature usually remains nearly normal.

Box 141-3 Heat Exhaustion: Diagnosis

- Vague malaise, fatigue, headache
- Core temperature often normal; if elevated, below 40° C (104° F)
- Mental function essentially intact; no coma or seizures
- Tachycardia, orthostatic hypotension, clinical dehydration (may occur)
- Other major illness ruled out
- If in doubt, treat as heatstroke

Clinical Features

The symptoms and signs associated with both types of heat exhaustion are variable and nonspecific and include weakness, fatigue, frontal headache, impaired judgment, vertigo, nausea and vomiting, and occasionally muscle cramps (Box 141-3). Orthostatic dizziness and syncope can occur. Sweating persists and may be profuse. The core temperature is only moderately elevated, usually below 40° C, and signs of severe CNS dysfunction are not present.

Mild heat exhaustion and full-blown heatstroke represent extremes of the spectrum of heat illness, and intermediate cases may prove difficult to differentiate. Nevertheless, heat exhaustion should not be diagnosed in the presence of major CNS dysfunction (seizures and coma) or severe hyperthermia (40.5° C). If uncertainty exists, measurement of hepatic transaminases may prove helpful. Elevations to several thousand units can be seen in patients with heat exhaustion or in healthy runners after a marathon, whereas in patients with heatstroke, such levels are usually in the tens of thousands after 24 hours.[30,31]

Management

Pure forms of either type of heat exhaustion are rare, and most cases of heat exhaustion involve mixed salt and water depletion. Heat exhaustion is primarily a volume depletion problem, and rapid recovery generally follows fluid administration. Decisions regarding the type of fluid and electrolyte replacements should be based on serum electrolyte measurements and the estimation of hydration status by clinical and laboratory parameters.

Patients with significant volume depletion or electrolyte abnormalities require intravenous fluids. If the patient is orthostatic, normal saline should be administered until the patient is hemodynamically stable. Free water deficits should be replaced slowly during 48 hours to avoid a decrease of serum osmolality more than 2 mOsm/hr. Overly rapid correction of hypernatremia is associated with seizures caused by cerebral edema.

Disposition

Young, otherwise healthy patients who do not have significant laboratory abnormalities and who respond rapidly to hydration do not require hospitalization. These patients can be discharged with instructions to drink plenty of fluids and to avoid heat stress for 24 to 48 hours. Older patients, particularly those with cardiovascular disease or other predisposing factors described in Figure

www.ketabpezeshki.com 66485457-66963820

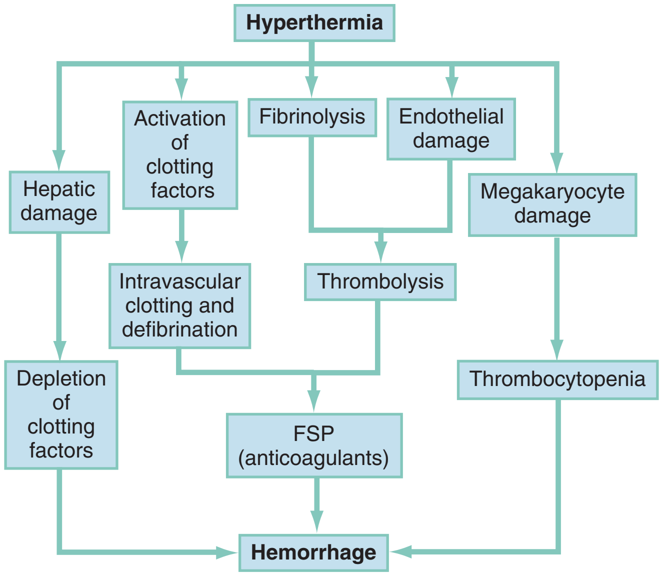


Figure 141-4. Pathogenesis of hemorrhage. *FSP,* fibrin split products.

141-4, require more cautious inpatient fluid and electrolyte replacement and frequent reassessment (Box 141-4).

Box 141-4 Heat Exhaustion: Treatment

Rest
Cool environment
Assess volume status (orthostatic changes, blood urea nitrogen level, hematocrit, serum sodium concentration)
Fluid replacement: normal saline to replete volume if the patient is orthostatic; replace free water deficits slowly to avoid cerebral edema
Healthy young patients are usually treated as outpatients; consider admission if the patient is elderly, has significant electrolyte abnormalities, or would be at risk for recurrence if discharged

Box 141-5 Heatstroke: Diagnosis

Exposure to heat stress, endogenous or exogenous
Signs of severe central nervous system dysfunction (coma, seizures, delirium)
Core temperature usually above 40.5° C (105° F), but may be lower
Hot skin common, and sweating may persist
Marked elevation of hepatic transaminases

HEATSTROKE

In the previously discussed forms of heat illness, although the body temperature rises, homeostatic thermoregulatory mechanisms remain intact. Heatstroke is the catastrophic life-threatening emergency that occurs when these mechanisms fail. This failure results in elevation of body temperature to extreme levels, usually higher than 40.5° C (105° F), producing multisystem tissue damage and organ dysfunction.

Physiology

As heatstroke develops, energy will be insufficient to sustain thermoregulatory mechanisms, resulting in dramatic increases in core temperature and the clinical manifestations of heatstroke.[32] An exact temperature at which cellular damage begins to occur in an individual patient varies. Credible reports exist of full recovery despite rectal temperatures of 44.4 to 46.5° C.[33] Damage is a function not only of temperature but also of the exposure time.[34] The resultant damage to tissues is a function of a complex interaction of body temperature, exposure time, workload, tissue perfusion, and individual factors, which vary markedly.

Neurologic dysfunction is a hallmark of heatstroke, and cerebral edema is common. Other pathologic changes include petechiae in the walls of the third and fourth ventricles and marked cerebellar Purkinje cell damage.[35] Interestingly, the hypothalamus, the predominant site of central thermoregulatory control, is usually not damaged.

Heat stress creates tremendous demands on the cardiovascular system, and patients who succumb to heatstroke show signs of circulatory failure. Although such pathologic changes are common, cardiac damage alone is not lethal.

Prolonged heat stress produces impressive increases in skin blood flow (peripheral vasodilation) and a reduction of the thermal gradient between the core and the skin (Fig. 141-5). Functional hypovolemia is avoided by compensatory vasoconstriction of the splanchnic and renal vasculature. The resulting splanchnic and renal ischemia may explain the nausea, vomiting, and diarrhea observed in runners after a marathon. Hepatic damage is such a consistent feature of heatstroke that its absence should cast doubt on the diagnosis. This is manifested pathologically by centrilobular necrosis with extensive cholestasis.

If severe heat stress continues, compensatory splanchnic vasoconstriction will eventually fail. Failure to perfuse the skin with heated blood from the core results in a dramatically increased rate of heat storage. This produces elevated intracranial pressure, which in combination with a reduction in mean arterial pressure caused by failure of compensatory splanchnic vasoconstriction, conspires to produce a decrease in cerebral blood flow. This results in the major CNS dysfunction characteristic of heatstroke.

Clinical Features

Heatstroke versus Heat Exhaustion

The onset of heatstroke is sudden, and the patient's level of consciousness is altered.[35] Prodromal symptoms lasting minutes to hours occur in approximately 20% of cases. These are nonspecific and may include weakness, dizziness, nausea, vomiting, anorexia, frontal headache, confusion, drowsiness, disorientation, muscle twitching, ataxia and signs of cerebellar dysfunction, and psychiatric symptoms ranging from anxiety and irritability to psychosis.[36,37]

These prodromal symptoms are reminiscent of the description of heat exhaustion. Heat exhaustion, particularly the water depletion variety, can progress to heatstroke if it is untreated. These two syndromes should be considered extremes on a spectrum of responses to heat stress. Heatstroke occurs when the thermoregulatory responses are overwhelmed and fail. If the patient is evaluated as this is occurring, differentiation between heat exhaustion and heatstroke is difficult. If heatstroke cannot be excluded, efforts to cool the patient should begin immediately.

The usual manifestations of heatstroke include hyperpyrexia above 40.5° C, profound CNS dysfunction, and hot skin (Box 141-5). Persistent sweating can be observed in patients with rectal temperatures of 41.5 to 42.4° C with heatstroke. In one large series of exertional heatstroke victims, sweating persisted in 50% of cases.[38] Therefore, the cessation of sweating is not the cause of heatstroke, and continued sweating does not preclude the diagnosis.

www.ketabpezeshki.com 66485457-66963820

Table 141-1 Usual Characteristics of Heatstroke

EXERTIONAL	CLASSIC
Healthy	Predisposing factors or medications
Younger	Older
Exercise	Sedentary
Sporadic	Heat wave occurrence
Diaphoresis	Anhidrosis
Hypoglycemia	Normoglycemia
DIC	Mild coagulopathy
Rhabdomyolysis	Mild CK elevation
Acute renal failure	Oliguria
Marked lactic acidosis	Mild acidosis
Hypocalcemia	Normocalcemia

CK, creatine kinase; *DIC*, disseminated intravascular coagulation.

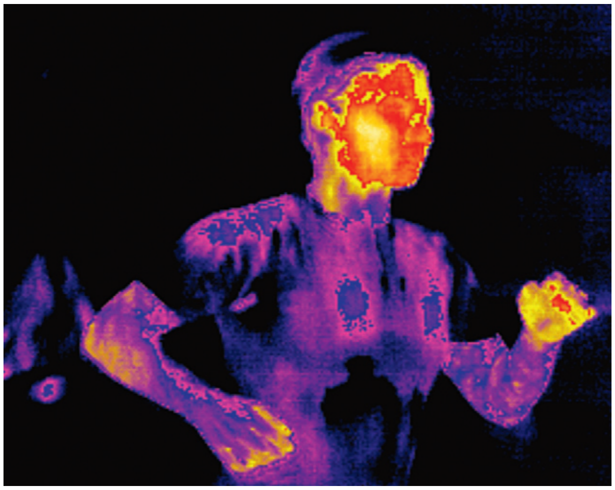


Figure 141-5. Human infrared image. Note that the palms and the face are substantially warmer than the rest of the body. (From Auerbach PS: Wilderness Medicine, 5th ed. Philadelphia, Mosby/Elsevier, 2007.)

Although in heatstroke the core temperature is elevated above 40.5° C, significant cooling may occur in the out-of-hospital phase, and the first temperature obtained in the emergency department (ED) may not represent the original maximum core temperature.

Classic Heatstroke versus Exertional Heatstroke

The two forms of heatstroke have significantly different presentations and manifestations: classic (epidemic) heatstroke (CHS) and exertional heatstroke (EHS) (Table 141-1).

CHS occurs during periods of sustained high ambient temperatures and humidity, such as during summer heat waves. Victims are often elderly and poor and live in underventilated dwellings without air conditioning. Debilitated patients who have limited access to oral fluids may develop water depletion heat exhaustion, which progresses to heatstroke if it is untreated. Victims of CHS commonly suffer from chronic diseases, alcoholism, or schizophrenia, which predisposes to heat illness. Such patients are often prescribed medications (e.g., diuretics, antihypertensives, neuroleptics, and anticholinergics) that impair the ability to tolerate heat stress. Sweating ceases in the majority of CHS patients. Factors such as advanced age, hypotension, altered coagulation status, and the necessity for endotracheal intubation on arrival at the ED predict a poor outcome despite successful cooling measures.[39] In contrast, patients with EHS are usually young and healthy individuals whose heat-dispelling mechanisms are overwhelmed by endogenous heat production. Athletes and military recruits are typical victims.[40-42] Rhabdomyolysis and acute renal failure, rarely seen in patients with CHS, are common in patients with EHS.[43] Sweating is present in half the cases of EHS. Hypoglycemia may occur as the result of increased glucose metabolism and hepatic damage, resulting in impaired gluconeogenesis. Coagulopathy is common. Hyponatremia with serum sodium levels of less than 130 mmol/L has been detected in summer hikers in the Grand Canyon; many present with neurologic symptoms or seizures.[41] Signs of profound CNS dysfunction dominate the early course of heatstroke. Delirium or coma is characteristic, but virtually any neurologic abnormality, including bizarre behavior, opisthotonos, hallucinations, decerebrate rigidity, oculogyric crisis, and cerebellar dysfunction, can be seen.[38] Convulsions occur in up to 75% of patients and can be precipitated by therapeutic cooling maneuvers. Profound muscle rigidity with tonic contractions, coarse tremor, and dystonic movements can mimic seizures. Pupils may be fixed and dilated, and the electroencephalogram may be isoelectric. All these changes are potentially reversible, although permanent damage, including cerebellar deficits, hemiplegia, dementia, and personality changes, is common in severe cases. Patients with heatstroke usually have hyperdynamic cardiovascular systems with low peripheral vascular resistance, tachycardia (up to 180 beats/min), and elevated cardiac index.[9] Elevation of cardiac troponin I is not uncommon with CHS; however, it is rarer in EHS.[44,45] The central venous pressure (CVP) is usually elevated. The combination of elevated CVP with right-sided cardiac dilation suggests right-sided heart failure, which is also seen after shock or sepsis.[46] These changes are expected because skin blood vessels dilate to dissipate heat; however, this low peripheral vascular resistance has persisted in patients after reduction of body temperature to nearly normal.

Respiratory alkalosis is a physiologic response to active or passive heating and may be severe enough to produce tetany. Although most patients with CHS have respiratory alkalosis, those with EHS usually have a relatively pure lactic acidosis. Lactic acidosis is associated with a poor prognosis in cases of CHS but not necessarily in cases of EHS. Both CHS and EHS cause the hemoglobin-oxygen dissociation curve to shift to the right. An increase in the temperature denatures the bond between oxygen and hemoglobin, decreasing the concentration of oxyhemoglobin. Aberrations in coagulation are common in patients with severe heatstroke, and their presence is a poor prognostic sign.[47] Abnormal hemostasis is manifested clinically by purpura, conjunctival hemorrhage, melena, bloody diarrhea, hemoptysis, hematuria, myocardial bleeding, or hemorrhage into the CNS.[48]

Hepatic damage is so consistently featured in heatstroke that its absence should cast doubt on the diagnosis. Hepatic injury is evidenced by markedly elevated levels of hepatic aminotransferases (serum aspartate transaminase and alanine transaminase).[47] Jaundice typically appears 24 to 72 hours after the onset of severe heatstroke and gradually recedes if the victim survives. Survivors generally have no permanent impairment of liver function. Hypoglycemia with a serum glucose level of less than 65 mg/dL is common in cases of EHS. Renal damage is common. The initial urine specimen, usually obtained by catheterization, is a scanty, brownish, turbid fluid resembling machine oil. Microscopic examination reveals proteinuria with abundant granular casts and red blood cells. Acute oliguric renal failure complicates 25 to 30% of EHS cases and 5% of CHS cases. Glomerular filtration rate, renal plasma flow, urine flow, and sodium excretion diminish markedly

www.ketabpezeshki.com 66485457-66963820

during exercise. Heavy physical exertion in hot climates produces acidic and maximally concentrated urine, which can result in acute oliguric renal failure in combination with hypotension and myoglobinuria.[28] Cocaine use is also associated with rhabdomyolysis and hyperthermia.[49] Diarrhea, probably caused by intense splanchnic vasoconstriction, is commonly seen. Cooling aggravates the diarrhea, creating an unpleasant treatment problem. Pancreatitis is described with elevated serum amylase and lipase levels.

Diagnostic Strategies

Thermometry

Unfortunately, most standard measurements of body temperature vary significantly from the actual core temperature. Oral thermometry is affected by mouth breathing and is a poor approximation of the core. Rectal thermometry is less variable but responds to changes in core temperature slowly. Thermistors that are inserted 15 cm into the rectum offer continuous monitoring of temperature and less variability. Although rectal measurements are slower to respond to changes in core temperature than tympanic temperature readings, rectal measurements are not biased by head skin temperature. An esophageal thermistor positioned adjacent to the heart is another option.

Placement of a tympanic temperature sensor directly on the tympanic membrane is difficult and is not used clinically. Commercially available infrared thermometers do not physically contact the tympanic membrane and are unreliable in detection of hyperthermia.[50] Only after the initial assessment and cooling have begun is the differential diagnosis relevant. When a history of collapse under conditions of heat stress is present, rapid improvement in mental status and blood pressure with cooling eliminates alternative diagnoses. If, however, the temperature does not respond and the patient does not recover neurologically, other causes of fever and coma should be considered (Box 141-6).

The history may be helpful; shaking chills suggest fever with an altered hypothalamic set point rather than heat illness. Meningitis and encephalitis can masquerade as heatstroke. In patients with heatstroke, the spinal fluid should be crystal clear, with occasional lymphocytic pleocytosis and elevated protein levels. Cerebral falciparum malaria, which presents a clinical picture of high fever and encephalitis, is seen in tropical areas where heat illness can also occur.

In patients with thyroid storm, the clinical symptoms resemble those of heatstroke. It should be suspected if the thyroid gland is enlarged or nodular, but a normal thyroid gland does not exclude the diagnosis. Thyroid function test results are elevated, but these are not available on an emergency basis. Fortunately, thyroid storm is rare, and some critical aspects of treatment, such as rapid cooling, coincide with those for heatstroke.

Drug-induced heat illness is an important consideration, particularly anticholinergic poisoning. Differentiation may be difficult because both heatstroke and anticholinergic poisoning produce hyperpyrexia, hot and dry skin, tachycardia, and abnormal mental status. Constricted pupils are present in many heatstroke patients.[51] Mydriasis should be present in patients with anticholinergic poisoning, and its absence argues strongly against this diagnosis. Typhoid fever, typhus, delirium tremens, and hypothalamic hemorrhage all produce a symptom complex similar to that of heatstroke.

Malignant hyperthermia and neuroleptic malignant syndrome are characterized by lead-pipe rigidity. The serotonin syndrome can also mimic heatstroke because of the elevated body temperature tremors and CNS alterations that occur. Serotonin syndrome is classically a triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities secondary to increased CNS serotonergic activity. A history of recent exposure to illicit or therapeutic medication is an important clue.

Hepatic transaminase elevations may be diagnostically helpful. In most febrile states that include altered mental status or coma, these enzymes will be normal or minimally elevated, although they are usually dramatically elevated early in the course of heatstroke.

Box 141-6 Differential Diagnosis of Heatstroke

- Central nervous system hemorrhage
- Toxins, drugs
- Seizures
- Malignant hyperthermia
- Neuroleptic malignant syndrome
- Serotonin syndrome
- Thyroid storm
- High fever, sepsis
- Encephalitis, meningitis

Management

It does not take long either to boil an egg or to cook neurons.
David Hamilton[52]

Cooling

Immediate cooling is the cornerstone of treatment. Mortality correlates with the temperature and the number of dysfunctional organ systems, with an increased risk of death if patients present with anuria, coma, or cardiovascular failure.[53] Patients who present to the hospital with heat stroke have high mortality rates ranging from 21 to 63%,[4,54] and mortality increases significantly when cooling is delayed.[34,55] Cooling efforts take precedence over any time-consuming search for the cause. In the out-of-hospital setting, cooling should be initiated after removal of the patient from the hot environment. When the patient arrives at the hospital, clothes should be removed, a thermistor probe should be inserted, and the temperature should be continuously monitored.

The ideal method of evaporative cooling uses a body cooling unit on which the patient lies suspended on a net surface while being sprayed with atomized 15° C water from above and below.[56] Air warmed to 45 to 48° C is blown over the skin surface at 3 m/min. The unit, not widely available, maximizes evaporative cooling by maintaining cutaneous vasodilation and avoiding heat generation caused by shivering.

Less complex equipment can also be used to maximize evaporative cooling, which is the most widely used cooling method. The combination of atomized tepid water at 40° C from a spray bottle and standing fans cools at rates comparable to both body cooling unit and immersion.[57] Other evaporative techniques, including the use of downdraft from a helicopter, can be applied successfully.[58] Immersion in ice water results in a rapid reduction of core temperature to below 39° C within 10 to 40 minutes but complicates the resuscitation.[55] Vigorous skin massage to maintain cutaneous circulation has been advocated, but there is no objective evidence that this is efficacious. When the body temperature reaches 39° C, cooling measures should be discontinued to avoid hypothermic overshoot. Continuous monitoring is necessary to maintain the core temperature at 37 to 38° C.

Military studies of EHS patients treated with ice water immersion have reported no fatalities or permanent sequelae.[40] A mortality rate of 14% was reported in a study of 28 patients with CHS treated by immersion.[51] Immersion is technically difficult in the ED. Vasoconstriction from ice water immersion may be beneficial

www.ketabpezeshki.com 66485457-66963820

Box 141-7 Cooling Modalities to Lower Body Temperature in Heatstroke

Preferred
Evaporative cooling with large circulating fans and skin wetting
Ice water immersion

Adjuncts
Ice packs to axillae and groin
Cooling blanket
Peritoneal lavage (unproven efficacy in humans)
Rectal lavage
Gastric lavage
Cardiopulmonary bypass

to hypotensive patients and may be better than evaporative cooling for victims in shock who have poor peripheral circulation.[59]

Cooling modalities other than evaporation and immersion should be considered adjunctive treatments (Box 141-7). Application of ice packs to high heat transfer areas (neck, groin, and axillae) is commonly used. Cooling blankets may be a useful adjunct but will not produce rapid cooling if they are used exclusively. Peritoneal dialysis with cold fluids, although successful in a canine model, is invasive. Cold-irrigant gastric or rectal lavage will not provide significant heat exchange if it is used as the primary cooling modality.

Resuscitation

Aspiration and seizures are common in patients with heatstroke, and airway control is essential.[60] Hypoxemia may occur because of aspiration, pneumonitis and pulmonary infarction, hemorrhage, or edema. Metabolic demands are high, and normal pulmonary ventilation may be inadequate in this setting.

Circulatory fluid requirements are modest in some cases, averaging 1200 mL of isotonic crystalloid solution in the first 4 hours. Pulmonary edema occurs in patients with heatstroke and can be exacerbated by overzealous fluid administration. The use of a CVP catheter to monitor fluid resuscitation may be deceptive. Most patients have a hyperdynamic circulation with high cardiac index, low peripheral vascular resistance, and elevated CVP as a result of right-sided heart failure. These patients may require only modest intravenous fluids because cooling produces vasoconstriction and increases blood pressure.[61] Nevertheless, crystalloid resuscitation is essential.

Hypotension is common in patients with heatstroke and is usually caused by peripheral vasodilation resulting in high-output cardiac failure in addition to dehydration.[9] Blood pressure usually rises with cooling. If this does not occur, or if the patient monitored invasively has a low CVP, a fluid challenge of 250 to 500 mL of 0.9% saline should be given rapidly while blood pressure, pulse, and urine output are monitored. If the blood pressure rises, more fluids are given with careful monitoring of the CVP. Aggressive fluid replacement is continued until the blood pressure reaches 90/60 mm Hg or the CVP exceeds 12 mL H_2O. On occasion, patients exhibit hypodynamic responses with low cardiac index, elevated CVP, and hypotension. These patients may be cyanotic, whereas patients with hyperdynamic circulation are initially pink. This clinical observation can be helpful in identifying patients who may respond to catecholamines.

A variety of tachyarrhythmias commonly occur during heatstroke. These usually resolve with cooling, and electrical cardioversion should be avoided until the myocardium is cooled. The use of alpha-adrenergic agents such as norepinephrine is not recommended because they promote vasoconstriction without improving cardiac output or perfusion, decrease cutaneous heat exchange, and may enhance ischemic renal and hepatic damage. Atropine and other anticholinergic drugs that inhibit sweating should be avoided.

Because the pathophysiologic processes of heatstroke and fever differ, antipyretics are not indicated and may be harmful. Salicylates, particularly in large doses, can worsen hyperthermia by uncoupling oxidative phosphorylation and aggravate coagulopathies. Large doses of acetaminophen can result in further hepatic damage. The efficacy of dantrolene is not established.[62] If rhabdomyolysis is present, maintenance of urinary output of at least 2 mL/kg/hr is required.[63] Urinary alkalinization higher than 6.5 should be considered early in patients with acidemia, dehydration, or underlying renal disease. After volume repletion, administration of mannitol may be considered to increase intravascular volume and to increase glomerular filtration rate. Mannitol should not be used in an oliguric patient.[64] Persistent anuria, uremia, or hyperkalemia is an indication for consideration of hemodialysis.

Hematologic evaluation should include arterial blood gas determination; complete blood cell count and platelet counts; electrolyte values and blood urea nitrogen, glucose, creatinine, aspartate transaminase, alanine transaminase, lactate dehydrogenase, creatine kinase, uric and lactic acid, and calcium levels; prothrombin and partial thromboplastin times; international normalized ratio; and fibrin degradation products and hepatic enzymes. Serum cardiac troponin I levels should be obtained. Acidosis is common, especially in patients with EHS. Lactate levels are usually elevated; this may persist or even worsen with improved extremity perfusion.[53]

Cooling modalities that drastically lower skin temperature may induce violent shivering; this increases metabolic heat production and may impede cooling. Intravenous benzodiazepines are the treatment of choice for shivering. Neuroleptics, like chlorpromazine, have anticholinergic properties that can interfere with sweating and cause hypotension or, rarely, precipitate seizures; therefore, they should be avoided. Many patients are extremely agitated during the initial cooling period. Short-acting benzodiazepines can be used for sedation and to control seizures. Barbiturates are less desirable for treatment of seizures because metabolism is altered by hepatic dysfunction.

Coagulopathies can occur during the first day of illness but are more common on the second and third days. Initial treatment after cooling should include replacement therapy with fresh frozen plasma and platelets.[48] The clinician should monitor the laboratory signs of disseminated intravascular coagulation (hypofibrinogenemia, elevated fibrin split products, prolonged prothrombin time, and thrombocytopenia).[48] The bleeding diathesis in patients with heatstroke may be the result of fibrinolysis. Although α-aminocaproic acid can impede fibrinolysis, administration of this compound is associated with rhabdomyolysis, and its use is not recommended in patients with heatstroke.

KEY CONCEPTS

- Antipyretics are ineffective and should not be used to control environmental hyperthermia.
- The symptoms and signs of heat exhaustion often mimic those of viral illnesses.
- Patients with exertional heatstroke are commonly diaphoretic.
- Rapid (evaporative) cooling of the potential heatstroke patient should be initiated before the differential diagnosis is firmly established.
- Heatstroke can cause right-sided cardiac dilation and elevated CVP, clinically resemble pulmonary edema, and yet require vigorous crystalloid resuscitation.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Dickenson JG: Heat illness in the services. *J R Army Med Corps* 1994; 140:7.
2. Centers for Disease Control and Prevention: Heat illness among high school athletes—United States, 2005-2009. *MMWR Morb Mortal Wkly Rep* 2010; 59:1009.
3. Mueller FO, Colgate B: Annual survey of football injury research, 1931-2009. Available at www.unc.edu/depts/nccsi/2009AnnualFootball.pdf.
4. Argaud L, et al: Short- and long-term outcomes of heatstroke following the 2003 heat wave in Lyon, France. *Arch Intern Med* 2007; 167:2177.
5. Bouchama A, Knochel JP: Heat stroke. *N Engl J Med* 2002; 346:1978.
6. Gisolfi CV, Wenger CB: Temperature regulation during exercise: Old concepts, new ideas. *Exerc Sport Sci Rev* 1984; 12:339.
7. Charkoudian N: Skin blood flow in adult human thermoregulation: How it works, when it does not, and why. *Mayo Clin Proc* 2003; 78:603.
8. Rowell LB: *General principles in vascular control*. In: Rowell LB, ed: *Human Circulation: Regulation during Physical Stress*. New York: Oxford University Press; 1986.
9. Wilson TE, Crandall CG: Effect of thermal stress on cardiac function. *Exerc Sport Sci Rev* 2011; 39:12.
10. Nadel ER, Fortney SM, Wenger CB: Effect of hydration state of circulatory and thermal regulations. *J Appl Physiol Respir Environ Exerc Physiol* 1980; 49:715.
11. Hajat S, O'Connor M, Kosatsky T: Health effects of hot weather: From awareness of risk factors to effective health protection. *Lancet* 2010; 375:856.
12. Appenzeller O: *Physical training, heat acclimatization and diet*. In: Khogali M, Hales JRS, eds. *Heat Stroke and Temperature Regulation*. New York: Academic Press; 1983.
13. Centers for Disease Control and Prevention: Hyperthermia and dehydration-related deaths associated with intentional rapid weight loss in three collegiate wrestlers—North Carolina, Wisconsin, and Michigan, November-December 1997. *MMWR Morb Mortal Wkly Rep* 1998; 47:105.
14. Pascoe DD, Bellingar TA, McCluskey BS: Clothing and exercise: II. Influence of clothing during exercise/work in environmental extremes. *Sports Med* 1994; 18:94.
15. Bernard T, et al: Critical heat stress evaluation of clothing ensembles with different levels of porosity. *Ergonomics* 2010; 53:1048.
16. Moran DS, Shitzer A, Pandolf KB: A physiological strain index to evaluate heat stress. *Am J Physiol* 1998; 275:129.
17. Olshaker JS, Tek D: Environmental emergencies. *Emerg Med Clin North Am* 1992; 10:299.
18. Falk B: Effect of thermal stress during rest and exercise in the pediatric population. *Sports Med* 1998; 25:221.
19. Marzuk PM, et al: Ambient temperature and mortality from unintentional cocaine overdose. *JAMA* 1998; 279:1795.
20. Martinez M, Devenport L, Saussy J, Martinez J: Drug-associated heat stroke. *South Med J* 2002; 95:799.
21. Oh RC, Henning JS: Exertional heatstroke in an infantry soldier taking ephedra-containing dietary supplements. *Mil Med* 2003; 168:129.
22. Bailes JE, Cantu RC, Day AL: The neurosurgeon in sport: Awareness of the risks of heatstroke and dietary supplements. *Neurosurgery* 2002; 51:283.
23. Ester EA, Harrison J, Stasiewicz ED, Wang D: Malignant hyperthermia in an adult trauma patient. *Am Surg* 2002; 68:883.
24. Chung NK, Pin CH: Obesity and the occurrence of heat disorders. *Mil Med* 1996; 161:739.
25. Dinarello CA: Infection, fever, and exogenous and endogenous pyrogens: Some concepts have changed. *J Endotoxin Res* 2004; 10:4.
26. Kashmeery AMS: Physiological studies on heat exhaustion victims among Mecca Pilgrims: Response to relevant hormones, and effect of cold IV infusion on recovery. *Acta Med Austriaca* 1995; 22:16.
27. Saper CB, Breder CD: Endogenous pyrogens in the CNS: Role in the febrile response. *Prog Brain Res* 1992; 93:419.
28. Noakes TD: Fluid and electrolyte disturbance in heat illness. *Int J Sports Med* 1998; 2:5146.
29. Brake DJ, Bates GP: Fluid losses and hydration status of industrial workers under thermal stress working extended shifts. *J Occup Environ Med* 2003; 60:90.
30. Schiff HB, et al: Myoglobinuria, rhabdomyolysis and marathon running. *Q J Med* 1978; 47:463.
31. Shibolet S, et al: Heat stroke: Its clinical picture and mechanism in 36 cases. *Q J Med* 1967; 36:525.
32. Hubbard RW, et al: Novel approaches to the pathophysiology of heatstroke: The energy depletion model. *Ann Emerg Med* 1987; 16:1066.
33. Slovis CM, Anderson GF, Casolaro A: Survival in a heat stroke victim with a core temperature in excess of 46.5° C. *Ann Emerg Med* 1982; 11:269.
34. Sithinamsuwan P, et al: Exertional heatstroke: Early recognition and outcome with aggressive combined cooling—a 12-year experience. *Mil Med* 2009; 174:496.
35. McLaughlin CT, Kane AG, Auber AE: MR imaging of heat stroke, external capsule and thalamic T1 shortening and cerebellar injury. *Am J Neuroradiol* 2003; 24:1372.
36. Khogali M, Hales JRS, eds: *Heat Stroke and Temperature Regulation*. New York: Academic Press; 1983.
37. Bark N: Heat stroke in psychiatric patients: Two cases and a review. *J Clin Psychiatry* 1982; 43:377.
38. Austin MG, Berry JW: Observations on one hundred cases of heat stroke. *JAMA* 1956; 161:1525.
39. Vicario SJ, Okabajue R, Haltom T: Rapid cooling in classic heatstroke: Effect on mortality rates. *Am J Emerg Med* 1986; 4:394.
40. Beller GA, Boyd AE III: Heat stroke: A report of 13 consecutive cases without mortality despite severe hyperpyrexia and neurologic dysfunction. *Mil Med* 1975; 140:464.
41. Backer HD, et al: Exertional heat illness and hyponatremia in hikers. *Am J Emerg Med* 1999; 17:532.
42. Porter AM: Collapse from exertional heat illness: Implications and subsequent decisions. *Mil Med* 2003; 168:76.
43. Phillips RA: The relationship between proinflammatory mediators and heat stress induced rhabdomyolysis in exercising marines. *Crit Care Nurs Clin North Am* 2003; 15:163.
44. Hausfater P, et al: Elevation of cardiac troponin I during non-exertional heat-related illnesses in the context of a heatwave. *Crit Care* 2010; 14:R99.
45. Whitcar R, Laba D, Smith S: Exertional heat stroke in a young man with a documented rise in troponin I. *Emerg Med J* 2008; 25:283.
46. Shahid MS, et al: Echocardiographic and Doppler study of patients with heatstroke and heat exhaustion. *Int J Card Imaging* 1999; 15:279.
47. Varghese GM, et al: Predictors of multi-organ dysfunction in heatstroke. *Emerg Med J* 2005; 22:185.
48. al-Mashhadani SA, et al: The coagulopathy of heat stroke: Alterations in coagulation and fibrinolysis in heat stroke patients during the pilgrimage (Haj) to Makkah. *Blood Coagul Fibrinol* 1994; 5:731.
49. Roth D: Acute rhabdomyolysis associated with cocaine intoxication. *N Engl J Med* 1988; 319:673.
50. Hansen RD, et al: Infrared thermometry in the diagnosis and treatment of heat exhaustion. *Int J Sports Med* 1996; 17:66.
51. Hart GR, et al: Epidemic heat stroke: Clinical characteristics and course of 28 patients. *Medicine (Baltimore)* 1982; 61:189.
52. Hamilton D: The immediate treatment of heatstroke. *Anaesthesia* 1976; 31:270.
53. Pease S, et al: Early organ dysfunction course, cooling time and outcome in classic heatstroke. *Intensive Care Med* 2009; 35:1454.
54. Dematte JE, et al: Near fatal heat stroke during the 1995 heat wave in Chicago. *Ann Intern Med* 1998; 129:173.
55. Costrini A: Emergency treatment of exertional heatstroke and comparison of whole body cooling techniques. *Med Sci Sports Exerc* 1990; 22:15.
56. Smith JE: Cooling methods used in the treatment of exertional heat illness. *Br J Sports Med* 2005; 39:503.
57. Graham BS, et al: Nonexertional heat stroke: Physiologic management and cooling in 14 patients. *Arch Intern Med* 1986; 146:87.
58. Poulton TJ, Walker RA: Helicopter cooling of heatstroke victims. *Aviat Space Environ Med* 1987; 58:358.
59. Bouchama A, et al: Cooling and hemodynamic management in heatstroke: Practical recommendations. *Crit Care* 2007; 11:R54.
60. Al-Khawashki MJ, et al: *Clinical presentation of 172 heat stroke cases seen at Mina and Arafat—September 1982*. In: Khogali M, Hales JRS, eds: *Heat Stroke and Temperature Regulation*. New York: Academic Press; 1983:99-108.
61. Atar S, Royner E, Rosenfeld T: Transient cardiac dysfunction and pulmonary edema in exertional heat stroke. *Mil Med* 2003; 168:671.
62. Krause T, et al: Dantrolene–a review of its pharmacology, therapeutic use and new developments. *Anaesthesia* 2004; 59:364.
63. Curry SC, Chang D, Connor D: Drug- and toxin-induced rhabdomyolysis. *Ann Emerg Med* 1989; 18:1068.
64. Malinoski DJ, Slater MS, Mullins RJ: Crush injury and rhabdomyolysis. *Crit Care Clin* 2004; 20:171.

www.ketabpezeshki.com 66485457-66963820

Chapter 142
Electrical and Lightning Injuries

Timothy G. Price and Mary Ann Cooper

PERSPECTIVE

Electrical Injury

The first recorded death caused by electrical current from an artificial source was reported in 1879 when a carpenter in Lyons, France, inadvertently contacted a 250-V alternating-current generator.[1] The first U.S. fatality occurred in 1881 when an inebriated man passed out on a similar generator in front of a crowd in Buffalo, New York.

In the United States, electrical burns account for 4 to 6.5% of all admissions to burn units and approximately 1000 fatalities per year.[2] Occupational electrical incidents are uncommon but account for nearly 6% of all occupational fatalities annually.[3] Children have a predisposition to injuries from low-voltage sources, such as electric cords, because of their limited mobility within a relatively confined environment. During adolescence, a more active exploration of the environment leads to more severe high-voltage injuries or death. At the time of presentation, documentation of injuries is important not only for the immediate resuscitation of the victim but also for medicolegal reasons. Many electrical injuries eventually involve litigation for negligence, product liability, or worker's compensation.

Lightning Injury

The incidence of injury and death from lightning is unknown because no agency requires the reporting of lightning injuries, and some victims do not seek treatment at the time of their injury. The incidence of lightning-related deaths in the United States has declined to an average of 39 people annually.[4] Lightning is fatal in 1 of 10 lightning strike victims. In typical years, lightning kills more people in the United States than any storm phenomenon except floods, and it is consistently among the top four storm-related killers (Fig. 142-1). In 2009-2010, most of those killed in the United States were within 50 to 100 feet of safety, either seeking safe shelter too late or returning to their outdoor activities before the end of the storm.[4] In developing countries, particularly those in the tropics, lightning is a much bigger risk both because it is more common and because agricultural, mining, and construction continue to be labor-intensive, resulting in high exposure to the workers.[5] The lack of safe housing and metal vehicles expose entire families and schools to injury whenever a thunderstorm occurs.[6]

PRINCIPLES OF DISEASE

Physics of Injury

The exact pathophysiologic mechanism of electrical injury is not well understood because of the numerous variables that cannot be measured or controlled when an electrical current passes through tissue. With high voltage, most of the injury is thermal, and histologic studies reveal coagulation necrosis consistent with thermal injury.[7,8] The theory of *electroporation* is that electrical charges insufficient to produce thermal damage cause protein configuration changes that threaten cell wall integrity and cellular function.[9]

The nature and severity of electrical burn injury are directly proportional to the current strength, resistance, and duration of current flow (Box 142-1).[10] Factors that may determine the severity of an electrical injury are summarized in Box 142-2. Unfortunately, none of these can be used to predict or to explain the damage that any individual may suffer.

Type of Circuit

One of the factors affecting the nature and severity of electrical injury is the type of circuit involved, either direct current (DC) or alternating current (AC). High-voltage DC contact tends to cause a single muscle spasm, often throwing the victim from the source. This results in a shorter duration of exposure but increases the likelihood of traumatic blunt injury. Brief contact with a DC source can also result in disturbances in cardiac rhythm, depending on the phase of the cardiac cycle affected.

AC exposure of the same voltage tends to be three times more dangerous than DC. Continuous muscle contraction, or tetany, can occur when the muscle fibers are stimulated between 40 and 110 times per second. The standard frequency of electrical transmission in the United States is 60 Hz (cycles per second) versus 50 Hz in most other countries. This is near the lowest frequency at which an incandescent light appears to be continuously lit.

The terms *entry* and *exit* are commonly used to describe electrical injury patterns; however, the terms *source contact point* and *ground contact point* are more appropriate in referring to AC injuries. The hand is the most common source contact point with a tool that is in contact with an AC electrical source. The flexors of the upper extremity are much stronger than the extensors, causing the hand grasping the current source to pull the source even closer

www.ketabpezeshki.com 66485457-66963820

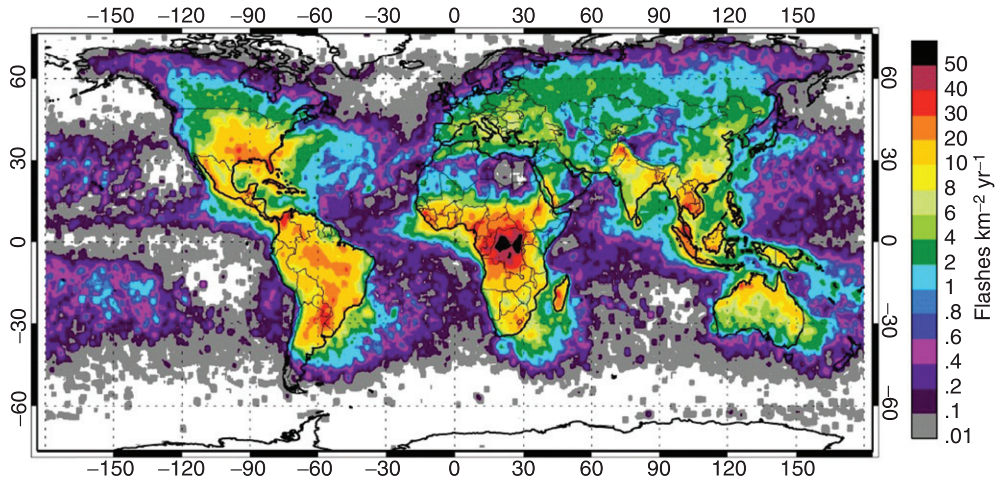


Figure 142-1. Global lightning frequency map. Available at http://thunder.msfc.nasa.gov/data/query/mission.png.

Box 142-1 Electrothermal Heating Formulas

$$P = I^2Rt$$

and

$$I = V/R$$

where
P = thermal power (heat), in joules
I = current, in amperes (A)
R = resistance, in ohms (Ω)
t = time, in seconds
V = potential, in volts (V)

Box 142-2 Factors Determining Electrical Injury

Type of circuit
Duration
Resistance of tissues
Voltage
Amperage
Pathway of current

to the body. Currents greater than the "let-go threshold" (6-9 mA) can prevent the victim from releasing the current source, which prolongs the duration of exposure to the electrical current.

Voltage

Voltage is a measure of the difference in electrical potential between two points and is determined by the electrical source. Electrical injuries are conventionally divided into low or high voltage; 1000 V is the most commonly used divider. Although both can cause significant morbidity and mortality, high voltage tends to have a greater potential for tissue destruction and major amputation.

No fatalities are recorded from contact with the low voltages associated with long-distance communication lines (24 V) or telephone lines (65 V). Fatalities are reported, however, with exposure to 110-V household current, especially in special environmental circumstances decreasing resistance of skin.

Box 142-3 Resistance of Body Tissues

Least
Nerves
Blood
Mucous membranes
Muscle

Intermediate
Dry skin

Most
Tendon
Fat
Bone

Resistance

Resistance is the tendency of a material to resist the flow of electrical current. It varies for a given tissue, depending on its moisture content, temperature, and other physical properties. The higher the resistance of a tissue to the flow of current, the greater the potential for transformation of electrical energy to thermal energy. Nerves, designed to carry electrical signals, and muscle and blood vessels, because of their high electrolyte and water content, have a low resistance and are good conductors. Bone, tendon, and fat, which all contain a large amount of inert matrix, have a high resistance and tend to heat and coagulate rather than to transmit current. The other tissues of the body are intermediate in resistance (Box 142-3).[11]

Skin is the primary resistor to the flow of current into the body. Skin on the inside of the arm or back of the hand has a resistance of approximately 30,000 Ω/cm². Thick, hardened skin can have 20 to 70 times greater resistance (Table 142-1).[8] This high resistance may result in a significant amount of energy being expended at the skin surface as the current burns its way through deep callus, resulting in greater thermal injury to the skin. As the duration of contact increases, however, the skin begins to blister and offer decreased resistance. A surge of current internally can cause extensive deep tissue destruction. Moisture also lowers resistance. Sweating can decrease the skin's resistance to 2500 to 3000 Ω/cm², and immersion in water causes a further reduction to 1200 to 1500 Ω/cm².

www.ketabpezeshki.com 66485457-66963820

Table 142-1 Skin Resistance

TISSUE	RESISTANCE (Ω/cm²)
Mucous membranes	100
Vascular areas	
Volar arm, inner thigh	300-10,000
Wet skin	
Bathtub	1200-1500
Sweat	2500
Other skin	10,000-40,000
Sole of foot	100,000-200,000
Heavily calloused palm	1-2 million

Table 142-2 Physical Effects of Different Amperage Levels at 50 to 60 Hz

PHYSICAL EFFECT	CURRENT (mA)
Tingling sensation	1-4
Let-go current	
Children	4
Women	7
Men	9
Freezing to circuit	10-20
Respiratory arrest from thoracic muscle tetany	20-50
Ventricular fibrillation	60-120

Amperage

Current, expressed in amperes, is a measure of the amount of energy that flows through an object. As defined by Joule's law, the heat generated is proportional to the amperage squared. Amperage depends on the source voltage and the resistance of the conductor. The voltage of the source is often known. Resistance varies according to the involved tissues and may change markedly during the exposure, rendering predictions of amperage difficult for any given electrical injury.

The physical effects vary with different amperages at 50 to 60 Hz, which is the AC frequency used in European countries and the United States (Table 142-2). A narrow range exists between the threshold of perception of current (0.2-0.4 mA) and let-go current (6-9 mA). Thoracic tetany can occur at levels just above the let-go current and result in respiratory arrest. Ventricular fibrillation may occur at an amperage of 60 to 120 mA. Although the 120-V household source usually causes minimal injury across dry skin, amperage delivered to the heart when the resistance of the skin is decreased by sweat or submersion in water can result in current sufficient to cause electrocution with cardiac arrest but without apparent external injury.

Duration of Contact

In general, the longer the duration of contact with high-voltage current, the greater the electrothermal heating and degree of tissue destruction. As carbonization of tissue occurs, the resistance to current flow increases.

The physics differ with lightning. The extremely short duration and extraordinarily high voltage and amperage of lightning result in a short flow of current internally, with little if any skin damage and almost immediate flashover of current around the outside of the body.

Pathway

The pathway of low, high, or lightning voltages determines the tissues at risk, the type of injury, and the degree of conversion of electrical energy to heat. Current passing through the heart or thorax can cause dysrhythmias and direct myocardial damage. Cerebral current can result in respiratory arrest, seizures, and paralysis. Current with ocular proximity can cause cataracts.

Current density is the amount of current flow per area of tissue.[10] As current density increases, any tendency to flow through the less resistant tissues is overcome. Eventually it flows through tissues indiscriminately, as if the body were a volume conductor, with the potential to destroy all tissues in the current's path. Because the current is often concentrated at the source and ground contact points, current density and the degree of damage are greatest there. Nevertheless, extensive deep destruction of the tissues may exist between these sites with high-voltage injuries, and the surface damage is often only "the tip of the iceberg." Damage to the internal structures of the body may be noncontiguous, with areas of normal-appearing tissue adjacent to burned tissue and with damage to structures at sites distant from the apparent contact points.

The pathway between contact points is a major determinant of the electrical field strength, which is the voltage per unit of length over which it is applied. For a given current, the shorter the distance between contact points, the greater the electrical field strength. Current from a 20,000-V power line passing from head to toe (approximately 2 m) results in an electrical field strength of 10,000 V/m. Approximately the same electrical field strength is created when "low"-voltage 120-V household current passes between two close contact points on the mouth of a child chewing on a power cord (120 V/0.01 m). Although the electrical field strengths are similar, there is a tremendous difference in the amount of at-risk tissue in the respective pathways.[12,13]

Although lightning is governed by the same physical laws as artificial electricity is, the rapid rise and decay of the energy complicate predictions of the extent of lightning injury more than with artificial electrical injury. The most important difference between lightning and high-voltage electrical injuries is the duration of exposure to the energy.[14]

Lightning is neither a direct current nor an alternating current but rather a unidirectional massive current impulse. The cloud-to-ground lightning impulse results from the breakdown of a large electrical field between a cloud and the ground that is measured in millions of volts. When connection is made with the ground, this voltage difference between the cloud and ground disappears, and a large current flows impulsively for a brief instant.[14]

Mathematical modeling of a lightning flow on the human body, substantiated in animal models, has included only direct strikes that account for only 3 to 5% of lightning injury to people.[15,16] After a direct strike meets the body, current is transmitted internally for less than a millisecond before external "flashover" occurs.[17] Although lightning current may flow internally for an instant and disrupt electrical systems, it seldom results in significant thermal injury or tissue destruction, and less than one third of lightning survivors have any signs of burns or skin damage. Muscle damage and myoglobinuria from lightning are rare. It is unknown whether the most serious manifestations of lightning injury, cardiac and respiratory arrest, vascular spasm, neurologic damage, and autonomic instability, result from induced electrical changes, current through highly conductive tissues, concussive injury, or other mechanisms.

Lightning tends to cause asystole rather than ventricular fibrillation. Although cardiac automaticity may reestablish a rhythm, the duration of the respiratory arrest may cause secondary deterioration of the rhythm to refractory ventricular fibrillation and asystole.[14,18] Other injuries caused by blunt trauma or ischemia

www.ketabpezeshki.com 66485457-66963820

from vascular spasms, such as myocardial infarction and spinal artery syndromes, also occur.[19-22]

Mechanisms of Injury

Electrical Injury

The primary electrical injury is the burn. Secondary blunt trauma results from falls or being thrown from the electrical source by an intense muscle contraction or the explosive force that may occur with electric flashes from circuit box or transformer accidents. Electrical burns are classified into four different types (Box 142-4).

Heating of tissues secondary to current flow and tissue resistance causes electrothermal burns. Severe electrothermal burns most commonly occur when a person comes in contact with a high-voltage conductor. The prolonged flow of current can result in significant burns anywhere along the current path. Typically, the skin lesions of electrothermal burns are well-demarcated, deep, partial-thickness to full-thickness burns.

The most destructive indirect injury occurs when a victim becomes part of an electrical arc. An electrical arc is a current spark formed between two objects of differing potential that are not in contact with each other, usually a highly charged source and a ground. The temperature of an electrical arc is approximately 2500° C, and the electrical arc causes deep thermal burns at the point where it contacts the skin.[12] With electrical arcs, burns may be caused by the heat of the arc, electrothermal heating due to current flow, or flames that result from the ignition of clothing.

Burns may occur from radiated thermal injury when an electrical explosion occurs, similar to gas explosions. Instead of becoming part of the arc, current may appear to jump the gap by splashing across a large part of the body. These splash burns are generally only partial thickness because the person did not become part of the arc itself.[23]

At the time of presentation it is often difficult to determine the mechanism of injury that caused an electrically injured patient's burns. Electrothermal heating is the main cause of muscle damage and is seen almost exclusively in high-voltage accidents with prolonged (seconds) contact and current flow.[23]

The histologic change in muscle injury that results from direct contact with an electrical source is coagulation necrosis with shortening of the sarcomere.[8,11] Muscle damage can be erratic, so areas of viable and nonviable muscle are often found in the same muscle group. Periosteal muscle damage may occur even though overlying muscle appears to be normal. Similar to muscle damage, serious vascular damage usually occurs only after a high-voltage accident.

Vascular damage is greatest in the media, predisposing to delayed hemorrhage when the vessel eventually ruptures.[11] Intimal damage may result in either immediate or delayed thrombosis and vascular occlusion as edema and clots form on the damaged intimal surface of the vessel during a period of days. The injury is usually most severe in the small muscle branches, where blood flow is slower.[24] This damage to small muscle arteries combined with mixed muscle viability that is not visible to gross inspection creates the illusion of progressive tissue necrosis. Veins, having more sluggish flow, are more prone to thrombosis than arteries are, and significant distal edema can result.

The absence of a pulse on initial examination may be a result of immediate arterial thrombosis or transient vascular spasm. Pulselessness resulting from vascular spasm should resolve within a few hours. If pulselessness persists after this time, serious vascular injury is likely.

Damage to neural tissue also may occur by several mechanisms. An immediate decrease in neural conductivity occurs with coagulation necrosis similar to that observed in muscle. In addition, it may suffer indirect damage as its vascular supply or myelin sheath is injured or from pressure as progressive edema results in a compartment syndrome. Evidence of neural damage may develop immediately or be delayed hours to days.

The hands, feet, and skull are the most common contact points. Histologic studies of the brain reveal focal petechial hemorrhages in the brainstem, cerebral edema, and widespread chromatolysis (the disintegration of chromophil bodies of neurons).[11]

Box 142-4 Types of Electrical Burns

Direct contact
Electrothermal heating
Indirect contact
Arc
Flame
Flash

Lightning Injury

Lightning injury may occur by electrical mechanisms and by secondary concussive or blunt trauma.[16,25] Whereas direct strike is most commonly described as the mechanism of injury, studies show that it accounts for a very small proportion of injuries and deaths (Table 142-3).

Injury from contact occurs when the person is touching an object that is part of the pathway of lightning current, such as a tree, metal fence, indoor plumbing, or wiring. Side flash or splash occurs as a portion of lightning jumps from its primary strike object to a nearby person on its way to the ground.[11,14,16,19,26] Step voltage, a difference in electrical potential between a person's feet, may occur as lightning current spreads radially through the ground.[14,16] A person who has one foot closer than the other to the strike point has a potential difference between the feet so that a portion of the lightning current flows through the legs and body rather than the ground. This ground current is a common killer of large livestock such as cattle and horses because of the greater distance between their hind legs and forelegs, with the heart lying in the pathway.

People may also be injured by upward streamers.[25] Cloud-to-ground lightning approaches the earth as a downward stepped leader. As the leader approaches, the large electrical field induces opposite charges that surge through trees, buildings, people, and any other object near the thunderstorm. If one of these upward streamers connects with a downward leader, a completed lightning strike occurs. Individuals in the path of an upward streamer may be injured even in the absence of a completed lightning strike.

Table 142-3 Distribution of Lightning Injury Mechanisms

MECHANISM	PERCENT
Direct strike	3-5%
Contact injury	3-5%
Side splash/flash	30-35%
Ground current	50-55%
Upward streamer	10-15%
Blunt injury	Unknown

From Cooper MA, Holle RL: Mechanisms of lightning injury should affect lightning safety messages. Presented at the 3rd International Lightning Meteorology Conference, Orlando, Fla, April 2010.

www.ketabpezeshki.com 66485457-66963820

Ball lightning is a mobile, luminous, spheroidal, floating or bouncing ball that lasts a few seconds before suddenly vanishing or exploding. These glowing orbs are observed traveling down power lines and aisles of aircraft and even entering buildings through open doors.[27] Although ball lightning has been described by multiple reputable observers for many years, the origin, chemical makeup, and physics are still a mystery.

Blunt injury from lightning can occur from at least two mechanisms. First, the person may be thrown a considerable distance by the sudden, massive contraction caused by current passing through the body. Second, a concussive injury caused by explosive or implosive force occurs as the lightning pathway is instantaneously superheated then rapidly cooled after the passage of the lightning.[14] This concussive injury or barotrauma is associated with tympanic membrane rupture, contusions of various organs, and pneumothorax.[28-33] Blunt or concussive injury can also accompany electrical injury.

CLINICAL FEATURES

Patients with high-voltage injury commonly present with devastating burns. Patients with lightning injury and low-voltage injury may have little evidence of injury or alternatively may be in cardiopulmonary arrest.[14] After the initial resuscitation of lightning and low-voltage injuries, other conditions may be identified. These patients may have significant residual morbidity from pain syndromes or central nervous system dysfunction.

Head and Neck

Electrical Injury

The head is a common point of contact for high-voltage injuries, and the patient may exhibit burns and neurologic damage. Cataracts develop in approximately 6% of patients with high-voltage injuries, especially whenever electrical injury occurs in the vicinity of the head.[34,35] Although cataracts may be present initially or develop soon after the accident, they more typically appear months after the injury. Visual acuity and funduscopic examination should be performed at presentation. Hearing loss is much less common.[36]

Lightning Injury

Lightning strikes may cause skull fractures and cervical spine injury from associated blunt trauma.[14,19,21] Tympanic membrane rupture is commonly found in lightning victims and may be secondary to the shock wave, a direct burn, or a basilar skull fracture. Although most patients recover without serious sequelae, disruption of the ossicles and mastoid, otorrhea, hemotympanum, perilymphatic fistulas, and permanent deafness may occur.[28-31]

Ocular injuries include corneal lesions, uveitis, iridocyclitis, hyphema, vitreous hemorrhage, optic atrophy, retinal detachment, and macular holes. Dilated, unreactive pupils are not a reliable indicator of death. As with electrical injuries, cataracts may develop in some patients.[37,38]

Cardiovascular System

Electrical Injury

Cardiac arrest, either from asystole or from ventricular fibrillation, is common in electrical accidents.[39] Other electrocardiographic findings include sinus tachycardia, transient ST segment elevation, reversible QT segment prolongation, premature ventricular contractions, atrial fibrillation, and bundle branch block. Acute myocardial infarction is relatively rare.[40]

Lightning Injury

There are many proposed mechanisms of cardiac injury from lightning.[14,39,41] Numerous dysrhythmias occur in the absence of cardiac arrest.[13,14,39,41] Nonspecific ST-T wave segment changes and prolongation of the QT interval may occur, and serum levels of cardiac markers may be elevated. Hypertension is commonly present after lightning injury but usually resolves without treatment within a few hours.[14]

Skin

Electrical Injury

Other than cardiac arrest, the most devastating injuries are burns, which are most severe at the source and ground contact points. The most common sites of contact with the source are the hands and the skull. The most common areas of ground contact are the heels. A patient may have multiple source and ground contact points. Burns in severe electrical accidents often appear as painless, depressed, yellow-gray, punctate areas with central necrosis, or the areas may be mummified.[11] High-voltage current may flow internally to create massive muscle damage. If contact is brief, minimal flow may have occurred, and the visible skin damage may represent nearly all of the damage. Prediction of the amount of underlying tissue damage from the amount of cutaneous involvement is not possible.

A peculiar type of burn associated with electrical injury is the “kissing burn,” which occurs at the flexor creases (Fig. 142-2).[11] As the current causes flexion of the extremity, the skin of the flexor surfaces at the joints touches. Combined with the moist environment that often occurs at the flexor areas, the electrical current may arc across the flexor crease, causing arc burns on both flexor surfaces and extensive underlying tissue damage.

Electrical flash burns are usually superficial partial-thickness burns, similar to other flash burns. Isolated thermal burns may also be seen when clothing ignites. The total body surface area affected by burns in electrical injury averages 10 to 25%. Severe burns to the skull and occasionally to the dura may occur.

The most common electrical injury seen in children younger than 4 years is the mouth burn that occurs from sucking on a household electrical extension cord. These burns usually represent local arc burns, may involve the orbicularis oris muscle, and are especially worrisome when the commissure is involved because of the likelihood of cosmetic deformity. A significant risk of delayed bleeding from the labial artery exists when the eschar separates. Damage to developing dentition and facial bones can occur, and referral to an oral surgeon familiar with electrical injuries is recommended.[42]

Figure 142-2. Kissing burn. (Courtesy Mary Ann Cooper, MD.)

www.ketabpezeshki.com 66485457-66963820

Figure 142-3. Feathering burn. (Courtesy Mary Ann Cooper, MD.)

Lightning Injury

Deep burns occur in less than 5% of lightning injuries.[14,18,43] Patients may exhibit one or more of the following four types of superficial burns or skin changes: linear, punctate, feathering, or thermal burns.[9,14,18] Linear burns tend to occur in areas where sweat or water accumulates, such as under the arms or down the chest. These are superficial burns that appear to be caused by steam production from the flashover phenomenon. Punctate burns appear as multiple, small cigarette-like burns, often with a heavier central concentration in a rosette-like pattern. They range from a few millimeters to 1 cm in diameter and seldom require grafting. Feathering burns are not true burns because there is seldom significant damage to the skin.[14] These transient lesions are rare but when present are pathognomonic for lightning injury (Fig. 142-3) and seldom require any therapy.[14] Thermal burns occur if the clothing is ignited or may be caused by metal that the person is wearing or carrying during the flashover.[14,23]

Extremities

Electrical Injury

In high-voltage injuries, muscle necrosis can extend to sites distant from the observed skin injury, and compartment syndromes occur as a result of vascular ischemia and muscle edema. Decompression fasciotomy or amputation is often necessary. Massive release of myoglobin from the damaged muscle may lead to myoglobinuric renal failure.

Joint areas may exhibit more severe injury than the muscle along the long bone portions of an extremity. Burn injury becomes concentrated at joints because there is less cross-sectional area of muscle to conduct the energy than at long bone portions. There is also a much lower proportion of muscle versus more poorly conductive tendons that cross a joint surface. In addition, as the energy is concentrated in these areas, it may cause skin surface burns, particularly where skin surfaces touch, such as the antecubital fossae.

Vascular damage from the electrical energy may become evident at any time.[24] Neurovascular checks should be assessed frequently in all extremities. Because the arteries are a high-flow system, heat may be dissipated and cause little initial apparent damage but result in subsequent deterioration. In contrast, the veins are a low-flow system, allowing the heat energy to heat blood rapidly, with resulting thrombosis. Consequently, an extremity may initially appear edematous or ischemic; with severe injuries, the entire extremity may appear mummified when all tissue elements, including the arteries, experience coagulation necrosis.

Damage to the vessel wall at the time of injury may result in delayed thrombosis and hemorrhage, especially in the small arteries to muscle.[24] These ongoing vascular changes can cause a partial-thickness burn to progress into a full-thickness burn as the vascular supply diminishes to the area. Progressive loss of muscle because of vascular ischemia downstream from damaged vessels may require repeated deep débridement.[21]

Lightning Injury

Lightning injury may cause transient vasospasm so severe that the extremities appear cold, blue, mottled, and pulseless. This condition usually resolves within a few hours and rarely requires vascular imaging or surgical intervention.[18,44,45]

Skeletal System

As with electrical injury, numerous types of fractures, dislocations, and soft tissue blunt trauma are reported with lightning injury. Fractures of the long bones are possible secondary to the trauma associated with electrical injury. Posterior and anterior shoulder dislocations caused by tetanic spasm of the rotator cuff muscles are reported but are rare. Spinal fractures and ligamentous injury may occur.

Nervous System

Electrical Injury

In high-voltage injuries, loss of consciousness is usually transient unless there is a significant concomitant head injury. Prolonged coma with eventual recovery also occurs. Patients may exhibit confusion, flat affect, and difficulty with short-term memory and concentration. Electrical injury to the central nervous system may cause a seizure, either as an isolated event or as part of a new-onset seizure disorder. Other possible causes of seizures, such as hypoxia and traumatic brain injury, should be considered. Neurologic symptoms may improve, but long-term disability is common. Even with low voltage, electrical injury may result in neurologic and psychological sequelae, many of which are nonspecific and delayed in onset.[46-48]

In high-voltage exposures, spinal cord injury may result from fractures or ligamentous disruption of the cervical, thoracic, or lumbar spine.[49-52] Patients with immediate damage have symptoms of weakness, and paresthesias develop within hours of the insult. Lower extremity findings are more common than upper extremity findings. These patients have a good prognosis for partial or complete recovery. Delayed neurologic damage may be manifested days to months after the insult.[50-52] Clinical presentations include ascending paralysis and transverse myelitis.[49-52] Motor findings predominate. Sensory findings are also common and may be patchy and not match motor levels of impairment. Although recovery is reported, the prognosis is usually poor. Significant autonomic system dysfunction may complicate the postinjury recovery.[51-53]

Lightning Injury

Whereas high-energy electrical injury is primarily a burn injury, lightning is primarily a nervous system injury. On initial presentation, two thirds of seriously injured lightning patients have *keraunoparalysis,* which is a unique temporary paralysis secondary to lightning strike. It is characterized by lower and sometimes upper extremities that are blue, mottled, cold, and pulseless. These findings are secondary to vascular spasm and sympathetic nervous system instability.[18,45] In general, this condition clears within a few

www.ketabpezeshki.com 66485457-66963820

hours, although some patients may be left with permanent paresis or paresthesias.

Paraplegia, intracranial hemorrhages, seizures, and electroencephalographic changes may occur after lightning injuries.[45,51,52,54-56] Loss of consciousness for varying periods is common, and confusion and anterograde amnesia are almost universal findings. Peripheral nerve damage is also common, and recovery is usually poor. A lightning strike to the head can cause a visual cortex defect that results in complex visual hallucinations.[57]

Other Viscera

Electrical Injury

Injury to the lungs may occur because of associated blunt trauma but is rare from electrical current. Injury to visceral organs is also rare, although damage to the pancreas, liver, small intestine, large intestine, bladder, and gallbladder can occur.

Lightning Injury

Pulmonary contusion, pneumothorax, and hemorrhage are seen with lightning injury.[18,32,33] Blunt abdominal injuries occur rarely. None of the other intra-abdominal catastrophes commonly associated with high-voltage electrical injury, such as gallbladder necrosis or mesenteric thrombosis, is seen with lightning injury.

Other Low-Voltage Injuries

An accurate history is essential to ensure that an apparent low-voltage injury was not caused by the discharge from a capacitor (as in the repair of a television, microwave oven, or computer monitor) or other high-voltage source. Although burns from low-voltage sources are usually less severe than burns from high-voltage sources, patients still may complain of paresthesias for an extended period, experience cardiac dysrhythmias, or have cataracts develop if the shock occurs close to the face or head.

Conducted electrical weapons (such as the Taser and stun guns) are now commonly used by law enforcement. These devices deliver brief pulses of electrical energy that incapacitate the target subject. The majority of people subdued with these devices do not receive medical evaluation. When they present, the evaluation should focus on the patient's organic or psychiatric conditions that prompted the officers' use of the device, wounds or retained fragments caused by the probes, and secondary injuries associated with the severe muscle spasm and induced fall.[58]

COMPLICATIONS

Electrical Injury

Cardiac arrest generally occurs only at the initial presentation or as a final event after a long and complicated hospital course.[39-41] Many of the complications are similar to those of thermal burns and crush injuries, including myoglobinuria, infection, and clostridial myositis.[23,59] The incidence of acute myoglobinuric renal failure has decreased since the widespread adoption of aggressive alkalinized fluid resuscitation. Fasciotomies or carpal tunnel release may be necessary for the treatment of compartment syndromes.[23,60] Tissue loss and major amputations are common with severe high-voltage injuries and result in the need for extensive rehabilitation.

Neurologic complications, such as loss of consciousness, peripheral nerve damage, and delayed spinal cord syndromes, may occur.[49-52,61] Damage to the brain may result in a permanent seizure disorder. Long-term neuropsychiatric complications include depression, anxiety, inability to continue in the same profession, aggressive behavior, and suicide.[47,48,51,52] Stress ulcers are the most common gastrointestinal complication after burn ileus.

Lightning Injury

Complications of lightning injury fall into three categories: (1) those that could be reasonably predicted from the presenting signs, such as hearing loss from tympanic membrane rupture or ossicular disruption, and paresthesias and paresis from neurologic damage; (2) long-term neurologic deficits and endocrine dysfunction similar to those associated with blunt head injury and chronic pain syndromes; and (3) iatrogenic complications that are secondary to overaggressive management.[44,49-52,54-56,62]

In the past, patients with lightning injuries were often treated similarly to patients with high-voltage electrical injuries. These injuries, however, are distinctly different.[14,18] The acute treatment of lightning victims almost never requires massive fluid resuscitation, fasciotomies for compartment syndromes, alkalinization of the urine and diuresis, amputations, or repeated débridement of large areas.[14,18,59]

DIFFERENTIAL CONSIDERATIONS

Electrical Injury

Electrical injuries are historically self-evident except in bathtub accidents, instances when no burns occur, or foul play. Alterations in consciousness or seizures can be caused by the electrical injury, associated traumatic brain injury, or underlying neurologic or metabolic disease.

Lightning Injury

The differential diagnosis of lightning injury is more complex, especially if the incident is unobserved.[14,18,63,64] It includes many of the causes of unconsciousness, paralysis, or disorientation of unclear etiology. Evidence of a thunderstorm or a witness to the lightning strike may not be available, particularly when victims are alone when they are injured. The presence of typical burn patterns, such as feathering, may be helpful.[65] The most helpful sign is often the damage to the clothes as they are burst off or singed and have punctate holes, or brass zippers and grommets may show signs of melting with cuprification as the zinc component is evaporated.[11,14,63,64]

MANAGEMENT

Out-of-Hospital

Securing the Scene

On first reaching the scene, prehospital personnel should secure the area to prevent bystanders and rescuers from sustaining additional injuries. For high-voltage incidents, the power source must be turned off. Accidents involving discrete electrical sources that are disconnected easily through a circuit box or switch are easier to manage, although rescuers should still ensure that the power is off before approaching the victim. The use of electrical gloves by emergency medical service personnel is dangerous and discouraged. A microscopic hole in a glove can result in an explosive injury to the hand as thousands of volts from the circuit concentrate there to enter the glove.

Although a line may be on the ground and appear to be de-energized, it may have substantial current flowing from it to the ground, making the surrounding area dangerous. This ground current spreads out in a circle along and just below the surface of the ground.

www.ketabpezeshki.com 66485457-66963820

During lightning incidents, nonhospital medical personnel are at risk of lightning injury if thunderstorms remain active in the area.[14,66] Counter to folklore belief, lightning can strike the same place twice.[14,66]

Triage Considerations

Field evaluation of patients may involve triage of multiple victims. Traditional rules of mass casualty triage do not apply to lightning victims.[14,66] Cardiorespiratory arrest is the major cause of death in lightning injuries.[14,18] In the absence of cardiopulmonary arrest, victims rarely die in the field or afterward.[14,66] Triage of lightning victims should concentrate on victims who appear to be in cardiorespiratory arrest and delay the evaluation of victims who are breathing as their survival is likely. Although intrinsic cardiac automaticity may ensue, the respiratory arrest caused by central nervous system injury often persists.[14,18,66] If the victim is adequately ventilated during the interval, perfusion may be maintained.

Initial Out-of-Hospital Resuscitation

Electrical injury victims may require a combination of cardiac and trauma care because they often have blunt injuries and burns and possible cardiac damage. Spinal immobilization is indicated whenever associated spinal trauma is suspected. Fractures and dislocations should be splinted and burns covered with clean, dry dressings. All patients with substantial conductive injury should receive a bolus of 20 mL/kg of isotonic fluid.

Emergency Department

Assessment

Cardiac arrest and airway compromise, including burns, are the most serious initial complications. For patients suffering circumferential burns to the chest that limit chest excursion or to the extremities causing compartment syndromes, fasciotomy and escharotomy may be necessary.[23,60]

The history obtained from bystanders and the nonhospital medical personnel regarding the type of electrical source, duration of contact, or environmental factors may be helpful. An electrical injury should be treated similarly to a crush injury rather than a thermal burn because of the large amount of tissue damage that is often present under normal-appearing skin. As a result, none of the formulae for intravenous fluids based on percentage of burned body surface area are reliable.[14,66] Standard crystalloid resuscitation in anticipation of myoglobinuria should be maintained. Cardiac monitoring is indicated for severely injured patients and those who have the indications listed in Box 142-5.[13,61,62] All patients with high-voltage injury and also patients with low-voltage injury and cardiorespiratory complaints should have an electrocardiogram (ECG) and cardiac biomarker determinations. Although electrocardiographic changes and dysrhythmias are common with electrical injuries, anesthesia and surgical procedures performed in the first 48 hours of care can be accomplished without cardiac complications.[61]

Most lightning victims behave as though they have had electroconvulsive therapy or a severe concussion, with confusion and amnesia for several days. If any altered mentation or neurologic deterioration occurs after an electrical injury, a computed tomography (CT) scan is indicated to assess for intracranial hemorrhage.[14,18]

Lightning victims who do not experience cardiopulmonary arrest at the time of the strike generally do well with supportive therapy. Patients who have cardiopulmonary arrest may have a poor prognosis, particularly if there is hypoxic brain damage.[14,44,51,52,54-56]

Box 142-5 Indications for Electrocardiographic Monitoring

- Cardiac arrest
- Documented loss of consciousness
- Abnormal electrocardiogram
- Dysrhythmia observed in out-of-hospital or emergency department setting
- History of cardiac disease
- Presence of significant risk factors for cardiac disease
- Concomitant injury severe enough to warrant admission
- Suspicion of conductive injury
- Hypoxia
- Chest pain

Ancillary Tests

Electrical Injury

Patients sustaining an electrical injury should receive cardiac monitoring in the emergency department (ED) and an ECG despite the source voltage.[39-41,67-69] The following laboratory tests may be considered in patients with evidence of conductive injury or significant surface burns: complete blood count; electrolyte levels; serum myoglobin, blood urea nitrogen, and serum creatinine concentrations; and urinalysis. Patients with severe electrical injury or suspected intra-abdominal injury should also have pancreatic and hepatic enzymes measured and a coagulation profile obtained. Arterial blood gas analysis is indicated if the patient needs ventilatory intervention or alkalinization therapy. Patients should be evaluated for myoglobinuria, a common complication of high-voltage electrical injury. If new urine is pigmented or the dipstick examination of the urine is positive for blood and no red blood cells are seen on microscopic analysis, the patient should be assumed to have myoglobinuria.

Creatine kinase (CK) levels and isoenzyme analysis should be performed. Whereas high CK levels may be gross indicators of muscle injury, need for amputation, and length of hospitalization, CK elevations are not linear and the clinical value of a single level in the acute setting is not established. Less specific cardiac biomarkers should be interpreted with care in the diagnosis of myocardial infarction in the setting of electrical injury. The peak CK level is not indicative of myocardial damage in electrical injury because of the large amount of injured skeletal muscle cells, which can contain a 20 to 25% CK-MB fraction. CK-MB fractions, electrocardiographic changes, and angiography correlate poorly in acute myocardial infarction after electrical injury. Elevations in the more specific cardiac biomarkers (e.g., troponin) may indicate myocardial injury and should prompt further monitoring and evaluation.[39,62,63]

Radiographs of the spine should be obtained if spinal injury is clinically suspected or when patients cannot be assessed adequately because of altered mentation or the presence of other painful injuries. Angiography is not routinely indicated to plan débridement or amputations. CT or magnetic resonance imaging (MRI) may be useful in the evaluation of associated trauma and is essential for evaluation of possible intracranial injuries.[14,44,51,52,54-56]

Lightning Injury

In patients injured by lightning, an ECG should be obtained.[39,41] Serum biomarkers for cardiac injury are indicated only in patients with chest pain, abnormal ECGs, or altered mentation. The severity or nature of the injuries may require other laboratory studies. Radiographic studies, particularly cranial CT or MRI evaluation,

www.ketabpezeshki.com 66485457-66963820

may be indicated, depending on the patient's level of consciousness at presentation and throughout the evaluation and treatment.*

Specific Therapies

Rhabdomyolysis

Victims of electrical injury who have heme pigment in the urine usually have myoglobinuria. Alkalinization of the urine increases the solubility of myoglobin in the urine, increasing the rate of clearance. In an adult, urine output should be maintained at 1 to 1.5 mL/kg/hr until all traces of myoglobin have cleared from the urine, while the blood is maintained at a pH of at least 7.45 with use of sodium bicarbonate. Furosemide or mannitol may be used to cause further diuresis. In contrast to high-voltage injuries, rhabdomyolysis and myoglobinuria are rare with lightning injuries.

Burn Wound Care

Cutaneous burns should be dressed with antibiotic dressings, such as sulfadiazine silver. Electrical burns are especially prone to tetanus, and patients should receive tetanus toxoid and tetanus immune globulin on the basis of their immunization history. Prophylactic administration of high-dose penicillin to prevent clostridial myonecrosis is controversial.[23,59]

Extremity Injuries

Management of electrical injuries of the extremities entails surgical management, which includes early fasciotomy, carpal tunnel release, or amputation of an obviously nonviable extremity. Extremities should be splinted in a functional position to minimize edema and contracture formation.[23,60]

DISPOSITION

Electrical Injuries

Admission

Indications for admission for electrocardiographic monitoring are listed in Box 142-5.[13,61,62] In general, when truncal conduction is suspected, the patient should be admitted for 12 to 24 hours of cardiac monitoring. Most patients with significant electrical burns should be stabilized and transferred to a regional burn center for burn care and extensive occupational and physical rehabilitation.

Outpatient Management

Asymptomatic patients with normal physical examination findings after low-voltage exposure can be reassured and discharged without any ancillary tests being performed.[47] Patients with cutaneous burns or mild persistent symptoms can be discharged if they have a normal ECG and no urinary heme pigment. Outpatient referral should be provided in the event that current symptoms persist or new symptoms develop.

Electrical injury during pregnancy from low-voltage sources may result in fetal demise. A prospective cohort study of electric shock in pregnancy suggested that electric shock usually does not pose a major fetal risk.[13,69] Nevertheless, obstetric consultation is advisable for all pregnant patients reporting electrical injury, regardless of symptoms at the time of presentation. Placental abruption, the most common cause of fetal death after blunt trauma, may result from even minor trauma, such as may be associated with electrical injuries. Patients in the last half of pregnancy should receive fetal monitoring if there is even minor blunt trauma and be considered high-risk patients for the remainder of their pregnancy.[13] First-trimester patients should be informed of the remote risk of spontaneous abortion and, if no other indications for admission exist, may be discharged with instructions for threatened miscarriage and close obstetric follow-up evaluation. The prognosis for fetal survival after lightning strike is most dependent on the extent of the mother's injuries. Fetal demise occurs in 50% of cases.[71]

Pediatric patients with oral burns may be safely discharged if close adult care is ensured.[42] There is no evidence that an isolated oral burn correlates with cardiac injury or myoglobinuria. In general, these patients require surgical and dental consultation for oral splinting, eventual débridement, and occasionally reconstructive surgery. After appropriate consultation, if hospitalization is not deemed necessary, the child's parents should be warned about the possibility of delayed hemorrhage and receive instructions to apply direct pressure by pinching the bleeding site and to return immediately to the ED.

Lightning Injuries

Most lightning survivors who appear well can be safely discharged. In reality, many survivors never seek emergency care, and overall mortality is only about 10%.[14,18,72] Many of the more severe signs of lightning injuries, such as lower extremity paralysis and mottling, confusion, and amnesia, resolve with time.[14,18] Spinal cord and intracranial processes should be excluded.

Consultation with other specialists may be indicated for otic and ophthalmic damage. More severely injured patients require trauma surgeon and cardiologist consultation, although medical conditions predominate with lightning injuries. If there is a history of a loss of consciousness or if the patient exhibits confusion, hospital admission and observation are suggested. After evaluation, if the ECG is normal, asymptomatic patients (including patients with feathering burns) may be discharged home with referral for follow-up from an ophthalmologist and other specialists as indicated.

KEY CONCEPTS

- High-voltage electrical injury causes significant tissue and organ damage along the path between the entrance and exit wounds. As a result, victims are often more severely injured than they initially appear to be. Injury assessment should be detailed, fluid requirements during resuscitation are much greater than one would calculate from the surface burns alone, and extensive tissue débridement is often necessary.
- Victims of lightning injury may appear to have significant injuries, but symptoms (extremities that are cold and pulseless, mottled skin, paralysis, and confusion) usually resolve with time. Keraunoparalysis is transient paralysis induced by a lightning strike. After spinal cord and intracranial injuries are excluded, observation is the mainstay of treatment.
- Patients with low-voltage electrical injury who have only minor cutaneous burns or persistent minor symptoms may be discharged safely if they have a normal ECG and no urinary heme pigment.
- With electrical injury, sensory findings may be patchy and not match motor levels of impairment.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

*References 14, 44, 51, 52, 54-56, 70.

www.ketabpezeshki.com 66485457-66963820

References

1. Jex-Blake A: The Gulstonian lectures on death from electricity in the late nineteenth century. *Med Instrum* 1975; 9:267.
2. Lee R: Injury by electrical forces: Pathophysiology, manifestations, and management. *Curr Probl Surg* 1997; 34:677.
3. Fordyce T: Thermal burn and electrical injuries among electric utility workers, 1995-2004. *Burns* 2007; 33:209.
4. NOAA, National Weather Service, Office of Climate, Water, and Weather Services: Weather fatalities. Available at www.nws.noaa.gov/om/hazstats.shtml.
5. NOAA, National Weather Service, Office of Climate, Water, and Weather Services: Lightning safety. Available at www.lightningsafety.noaa.gov.
6. Cooper MA, Ab Kadir MZA: Lightning injury continues to be a public health threat internationally. Presented at the 3rd International Lightning Meteorology Conference, Orlando, Fla, April 2010. Available at www.vaisala.com/Vaisala%20Documents/Scientific%20papers/5.Cooper,%20Zainal.pdf.
7. Childbert M, et al: Measure of tissue resistivity in experimental electric burns. *J Trauma* 1985; 25:209.
8. Puschel K, Brinkman B, Lieske K: Ultrastructural alteration of skeletal muscles after electrical shock. *Am J Forensic Med Pathol* 1985; 6:246.
9. Lee R, et al: Role of cell membrane rupture in the pathogenesis of electrical trauma. *J Surg Res* 1998; 44:709.
10. Barkana BD, Gupta N, Hmurcik LV: Two case reports: Electrothermal (aka contact) burns and the effects of current density, application time and skin resistance. *Burns* 2010; 36:e91.
11. Wright RK, Gantner GE: *Electrical injuries and lightning*. In: Froede RC, ed: *Handbook of Forensic Pathology*. Northfield, Ill: College of American Pathologists; 1990.
12. Capelli-Schellpfeffer M, et al: Advances in the evaluation and treatment of electrical and thermal injury emergencies. *IEEE Trans Ind Appl* 1995; 31:1147.
13. Fish R: Electric injury: Part III. Cardiac monitoring indications, the pregnant patient, and lightning. *J Emerg Med* 2000; 18:181.
14. Cooper MA, Andrews CJ, Holle RL, Blumenthal R: *Lightning injuries*. In: Auerbach PS, ed: *Wilderness Medicine*, 6th ed. Philadelphia: Elsevier/Mosby; 2012.
15. Ishikawa T, et al: Experimental study on the lethal threshold value of multiple successive voltage impulses to rabbits simulating multi-stroke lightning flash. *Int J Biometeorol* 1986; 29:157.
16. Cooper MA, Holle RL: Mechanisms of lightning injury should affect lightning safety Messages. Presented at Proceedings of the 3rd International Lightning Meteorology Conference, Orlando, Fla, April 2010. Available at www.vaisala.com/Vaisala%20Documents/Scientific%20papers/11.Cooper,%20Holle.pdf.
17. Ohashi M, Kitagawa N, Ishikawa T: Lightning injury caused by discharges accompanying flashover: A clinical and experimental study of death and survival. *Burns* 1986; 12:496.
18. Cooper MA: Lightning injuries: Prognostic signs for death. *Ann Emerg Med* 1980; 9:134.
19. Woods J: Spinal atrophic paralysis following lightning stroke. *S Afr Med J* 1952; 26:92.
20. Buechner H, Rothbaum J: Lightning stroke injury: A report of multiple casualties from a single lightning bolt. *Mil Med* 1961; 126:775.
21. Leys K: Spinal atrophic paralysis case following lightning stroke. *Edinburgh Med J* 1942; 49:657.
22. Zack F, Hammer U: Myocardial injury due to lightning. *Int J Legal Med* 1997; 110:326-328.
23. ten Duis H: Acute electrical burns. *Semin Neurol* 1995; 15:381.
24. Hunt J, et al: Vascular lesions in acute electrical injuries. *J Trauma* 1974; 14:461.
25. Cooper MA: A fifth mechanism of lightning injury. *Acad Emerg Med* 2002; 9:172.
26. Arden G, et al: Lightning accident at Ascot. *BMJ* 1956; 1:1453.
27. Fox MR, Gubler C: Struck dysphagic. *Gastroenterology* 2009; 137:9.
28. Offiah C, et al: Lightning strike: A rare cause of bilateral ossicular disruption. *Am J Neuroradiol* 2007; 28:974.
29. Sun G, et al: Bilateral perilymphatic fistulas from a lightning strike: A case report. *Laryngoscope* 2006; 116:1039.
30. Gluncić I, Roje Z, Gluncić V, Poljak K: Ear injuries caused by lightning: Report of 18 cases. *J Larnygol Otol* 2001; 115:4.
31. Wright JW: *Acoustic and vestibular defects in lightning survivors*. Presented at the meeting of the Middle Section of the American Laryngological, Rhinological and Otological Society, Kansas City, Mo, January 19, 1974.
32. Soltermann B, Frutiger A: Lightning injury with lung bleeding in a tracheotomized patient. *Chest* 1991; 99:240.
33. Halldorsson A, Couch MH: Pneumomediastinum caused by a lightning strike. *J Trauma* 2004; 57:196.
34. Benlier E, et al: Isolated uveitis: A rare complication of electrical injury. *J Burn Care Res* 2008; 29:856.
35. Lakosha H, Tremblay F, De Becker I: High-voltage electrical trauma to the eye. *Can J Ophthalmol* 2009; 44:605.
36. Liew L, Morrison G: Bilateral hearing loss following electrocution. *J Laryngol Otol* 2006; 120:65.
37. Cazabon S, Dabbs TR: Lightning-induced cataract. *Eye (Lond)* 2000; 14(Pt 6):903.
38. Dinakaran S, Desai SP, Elsom DM: Ophthalmic manifestations of lightning strikes. *Surv Ophthalmol* 2002; 47:292.
39. Cooper MA, Holle R, Andrews C: *Electrical current and lightning injury*. In: Field J, ed: *The Textbook of Emergency Cardiovascular Care and CPR*. Philadelphia: Lippincott Williams & Wilkins; 2009:498-511.
40. Celebi A, et al: Myocardial infarction after an electric shock: A rare complication. *Cardiol J* 2009; 16:362.
41. Johnson SA, Cooper MA: *Cardiopulmonary resuscitation and early management of the lightning strike victim*. In: Ornato JP, Peberdy MA, eds: *Cardiopulmonary Resuscitation*. Totowa, NJ: Humana Press; 2005.
42. Alexander W: Composite dysplasia of a single tooth as a result of electrical burn. *J Am Dent Assoc* 1961; 69:589.
43. Bartholome C, Jacoby W, Ramchand S: Cutaneous manifestations of lightning injury. *Arch Dermatol* 1975; 111:1466.
44. Cherington M: Neurologic manifestations of lightning strikes. *Neurology* 2003; 60:182.
45. ten Duis H, Klasen H, Reenalda PE: Keraunoparalysis, a “specific” lightning injury. *Burns* 1985; 12:54.
46. Singerman J, Gomez M, Fish JS: Long-term sequelae of low-voltage electrical injury. *J Burn Care Res* 2008; 29:773.
47. Ramati A, et al: Alteration in functional brain systems after electrical injury. *J Neurotrauma* 2009; 26:1815.
48. Ramati A, et al: Prevalence of psychiatric morbidity following electrical injury and its effects on cognitive functioning. *Gen Hosp Psychiatry* 2009; 31:360.
49. Levine N, et al: Spinal cord injury following electrical accidents: Case reports. *J Trauma* 1975; 15:459.
50. Erkin G, et al: Delayed cervical spinal cord injury after high voltage electrical injury: A case report. *J Burn Care Res* 2007; 28:905.
51. Cherington M: Central nervous system complications of lightning and electrical injuries. *Semin Neurol* 1995; 15:233.
52. Cherington M: Neurorehabilitation of the multifaceted and complicated neurologic problems associated with lightning and electrical injuries. *Neurorehabilitation* 2005; 20:1.
53. Kanjwal K, et al: Postural orthostatic tachycardia syndrome: A rare complication following electrical injury. *Pacing Clin Electrophysiol* 2010; 33:e59.
54. Baker R: Paraplegia as a result of lightning injury. *BMJ* 1978; 2:1464.
55. Cherington M: Spectrum of neurologic complications of lightning injuries. *Neurorehabilitation* 2005; 20:3.
56. Cherington M, Yarnell P, Lammereste D: Lightning strikes: Nature of neurological damage in patients evaluated in hospital emergency departments. *Ann Emerg Med* 1992; 21:575.
57. Kleiter I, et al: A lightning strike to the head causing a visual cortex defect with simple and complex visual hallucination. *J Neurol Neurosurg Psychiatry* 2007; 78:423.
58. Strote J, et al: Conducted electrical weapon use by law enforcement: An evaluation of safety and injury. *J Trauma* 2010; 68:1239.
59. Yost J, Holmes F: Myoglobinuria following lightning stroke. *JAMA* 1974; 228:1147.
60. Pannucci CJ, et al: Early fasciotomy in electrically injured patients as a marker for injury severity and deep venous thrombosis risk: An analysis of the National Burn Repository. *J Burn Care Res* 2010; 31:882.
61. Purdue G, Hunt J: Electrocardiographic monitoring after electrical injury: Necessity or luxury? *J Trauma* 1986; 26:166.
62. Orbak Z, Kara IS: Unusual complication in a child with lightning strike: Cerebral salt wasting. *Childs Nerv Syst* 2010; 22:1125.
63. Blumenthal R: “When thunder roars—go indoors!” Lightning autopsy guidelines. *S Afr Med J* 2006; 96:38.
64. Wetli CV: Keraunopathology—an analysis of 45 fatalities. *Am J Forensic Med Pathol* 1996; 17:89.
65. Cherington M, Olson S, Yarnell PR: Lightning and Lichtenberg figures. *Injury* 2003; 34:367.
66. Cooper MA: Myths, miracles, and mirages. *Semin Neurol* 1995; 15:358.
67. Rivera J, et al: Severe stunned myocardium after lightning strike. *Crit Care Med* 2007; 35:280.

www.ketabpezeshki.com 66485457-66963820

68. Garcia C, et al: Electrical injuries in a pediatric emergency department. *Ann Emerg Med* 1995; 26:604.
69. Einarson A, et al: Accidental electric shock in pregnancy: A prospective cohort study. *Am J Obstet Gynecol* 1997; 176:678.
70. Cherington M, Yarnell P, Hallmark D: MRI in lightning encephalopathy. *Neurology* 1993; 43:1437.
71. Gutierrez J, et al: Lightning injuries in a pregnant woman: A case report and review of the literature. *Burns* 2005; 31:1045.
72. Cherington M, et al: *Closing the gap on the actual numbers of lightning casualties and deaths*. American Meteorological Society 11th Conference on Applied Climatology, Dallas, Texas, January 10-15, 1999.

www.ketabpezeshki.com 66485457-66963820

Chapter 143

Scuba Diving and Dysbarism

Richard L. Byyny and Lee W. Shockley

PERSPECTIVE

Underwater free diving to salvage wrecks and to harvest seafood, sponges, coral, and mother-of-pearl has been practiced for more than 5000 years.[1] Historically, divers also used breathing tubes, such as hollow reeds; however, it is nearly impossible to use these at depths of more than 3 feet because of the restriction of inspiration by underwater pressure. Subsequent inventions from the 16th to the 19th centuries, including diving dresses, allowed divers to remain underwater for prolonged periods at depths of up to 12 fathoms (72 feet).[2] The first diving dress (1715) was a reinforced, leather-covered barrel with watertight armholes and a viewing porthole.[2]

With the advent of these technologies, the symptoms of diving-related illness began to be recognized. Colonel William Pasley, the officer in charge of a unit of the British Royal Engineers that salvaged the sunken warship HMS *Royal George* in 1840, observed symptoms in his divers.[3] At approximately the same time, similar symptoms and even fatalities were observed among caisson workers.* The ailment became known as caisson disease, but the construction workers on the Brooklyn Bridge (built from 1870 to 1883) attached the name "the bends," characterizing the symptoms that often caused the victim to bend forward in pain.[3] The first clinical description of caisson disease was by Paul Bert in 1878.[3] He correctly attributed the disease to nitrogen gas coming out of solution in the tissues during decompression. This led to the recommendation of slow ascents for pressurized workers and the development of the first recompression chambers.

The significant breakthrough allowing diving at depth was the invention of the aqua-lung by Jacques-Yves Cousteau and Emile Gagnan in 1943.[2] The lighter and less expensive equipment, widely known by its acronym SCUBA (self-contained underwater breathing apparatus), does not require a surface supply of air or the support personnel that are necessary for helmet diving. This innovation allowed widespread deep-sea diving, and millions of divers have become certified to date.

Most amateur divers use compressed air, open-circuit scuba equipment at depths of less than 130 feet of seawater (fsw). Systems with artificial mixtures of various gases, however, are used to extend the depths to which divers can descend. Some of these are used in sport diving, but their use is uncommon and is primarily limited to commercial applications (Table 143-1).

Other variations of supplying air for divers are closed-circuit and semiclosed-circuit diving apparati ("rebreathers") that use calcium hydroxide to absorb expired carbon dioxide. Oxygen is then added to the decarboxylated gas before rebreathing. The advantages of rebreathers over compressed air scuba are that they are more efficient (less gas is used for a given time), allow deeper dives and longer bottom times, and generate few if any bubbles.

The total number of diving-related injuries is unknown, but the absolute numbers of patients with decompression-related illnesses, one of the most serious dive-related injuries, continue to climb as the number of divers has increased despite the rate per 10,000 dives remaining relatively constant since 2001.[4] This rate varies somewhat on the basis of the type of diver: 0.015% for scientific divers, 0.01 to 0.019% for recreational divers, 0.030% for U.S. Navy divers, and 0.095% for commercial divers.[5] The rate of mortality in diving varies between 1.5 and 9 per 100,000 dives. With the popularity of diving and the relative ease of rapid travel from distant destinations, it behooves even the land-locked emergency physician to be aware of diving-related illnesses.

PRINCIPLES OF DISEASE

Scuba divers may encounter emergencies common to environmental exposures (e.g., hypothermia, sunburn, and physical trauma) or aquatic activities (e.g., submersion accidents, motion sickness, and marine envenomations), but they are also subject to the unique injuries related to dysbarisms and barotrauma. The pathophysiologic mechanism of these conditions primarily results from volume-pressure changes within the air-filled cavities of the body or from increased dissolution of gases, particularly nitrogen, in body tissues.

Atmospheric pressure varies with altitude and weather patterns, but 760 mm Hg (14.7 psi or 1 atm) is the standard used at sea level. Water is far denser than air. A mountain climber would need to ascend to 18,000 feet to reduce atmospheric pressure by 50% from sea level, but a diver needs to descend only 33 feet in seawater (34 feet in fresh water) to double the atmospheric pressure, an increase of 23 mm Hg per foot of depth.

To understand the pathophysiologic processes of dysbarisms and barotrauma, one should be familiar with several of the laws of physics that define the behavior of liquids and gases (Table 143-2; Figs. 143-1 to 143-5). The human body is composed mostly

*Caissons are construction chambers filled with pressurized air that permit working in a dry environment. They have been used in the construction of bridge footings and tunnels in places that would otherwise have been underwater.

www.ketabpezeshki.com 66485457-66963820

of water and behaves like a liquid subject to Pascal's law, which states that a pressure applied to any part of a liquid is transmitted equally throughout. Pressure changes, however, do alter the volume within the air-filled spaces of the body, including the lungs, bowel, sinuses, and middle ear, according to Boyle's law. This law states that at constant temperature, the absolute pressure and the volume of gas are inversely proportional ($PV = k$). In other words, as pressure increases (with descent), the gas volume is reduced; as the pressure is reduced (with ascent), the gas volume increases.

Temperature also affects the pressure and volume of a gas as described by Charles' law. At a constant pressure, the volume of a gas is directly proportional to the change in the absolute temperature ($V_1/T_1 = V_2/T_2$). Thus with heat the volume increases, and with cold the volume decreases. The general gas law ($P_1 \cdot V_1/T_1 = P_2 \cdot V_2/T_2$) combines Boyle's and Charles' laws to predict the behavior of a given quantity of gas when any of these factors change.

Barotrauma results when a diver is unable to equalize the pressure within air-filled structures to the ambient pressure of the

Table 143-1 Mixed Gas Diving

	OXYGEN	NITROGEN	HELIUM	OTHER
Air	21%	78%	Trace	1%
Nitrox I (EAN32 or Nitrox32)*	32%	68%	Trace	<1%
Nitrox II (EAN36 or Nitrox36)*	36%	64%	Trace	<1%
Normoxic trimix (e.g., trimix 19/30)†	19%	51%	30%	<1%
Hypoxic trimix (e.g., trimix 10/50)‡	10%	40%	50%	<1%

*Enhanced air nitrox, oxygen enriched air, nitrox, EANx, SafeAir, "devil gas," "voodoo gas."
†A normoxic mix, such as 19/30, is used in the depth range of 30 m (100 feet) to 60 m (200 feet).
‡A hypoxic mix, such as 10/50, is used for deeper diving, as a "bottom" gas only; it cannot safely be breathed at shallow depths where the oxygen partial pressure is less than 0.18.

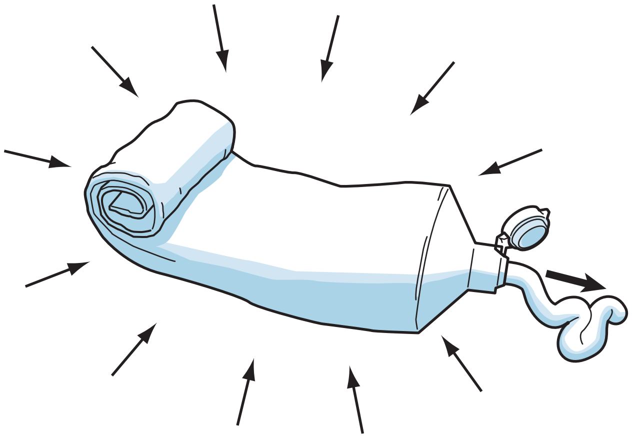


Figure 143-1. Pascal's law. A pressure applied to any part of a liquid is transmitted equally throughout.

Table 143-2 Laws of Physics

GAS LAW	FORMULA	SIGNIFICANCE
Pascal's law: A pressure applied to any part of a liquid is transmitted equally throughout.	$\Delta P = \rho g\,(\Delta h)$ ΔP is the hydrostatic pressure. ρ is the fluid density. g is acceleration due to gravity. Δh is the height of fluid.	Pressure increases in a contained space are transmitted throughout; significant for inner ear barotrauma and middle ear barotrauma (see Fig. 143-1)
Boyle's law: At a constant temperature, the absolute pressure and the volume of gas are inversely proportional. As pressure increases, the gas volume is reduced; as the pressure is reduced, the gas volume increases.	$P_1 \cdot V_1 = P_2 \cdot V_2$	Relates to change in the volume of a gas caused by the change in pressure due to depth, which defines the relationship of pressure and volume in breathing gas supplies (see Fig. 143-2)
Charles' law: At a constant pressure, the volume of a gas is directly proportional to the change in the absolute temperature.	$V_1/T_1 = V_2/T_2$	Increasing pressure (filling a scuba tank) causes heat; cooling a tank decreases the pressure (see Fig. 143-3)
The *general gas law* combines these concepts to predict the behavior of a gas when the factors change.	$P_1 \cdot V_1/T_1 = P_2 \cdot V_2/T_2$ P_1 is the initial pressure. V_1 is the initial volume. T_1 is the initial temperature. P_2 is the final pressure. V_2 is the final volume. T_2 is the final temperature.	A means of relating pressure, volume, and temperature together in one equation when variables are not constant
Dalton's law: The total pressure exerted by a mixture of gases is equal to the sum of the pressures (partial pressures) of each of the different gases making up the mixture, with each gas acting as if it alone is present and occupies the total volume.	$P_{Total}\ 3\ P_1 + P_2 + P_3 + \ldots + P_n$	Nitrogen under pressure acts as if other gases are not present (see Fig. 143-4)
Henry's law: The amount of a gas that will dissolve in a liquid at a given temperature is directly proportional to the partial pressure of that gas.	$e^p = e^{kc}$ e is approximately 2.7182818 (the base of the natural logarithm). p is the partial pressure of the solute above the solution. c is the concentration of the solute in the solution. k is the Henry's law constant.	More nitrogen is taken into solution (e.g., serum) at high pressures than comes out of solution at lower pressures (see Fig. 143-5)

www.ketabpezeshki.com 66485457-66963820

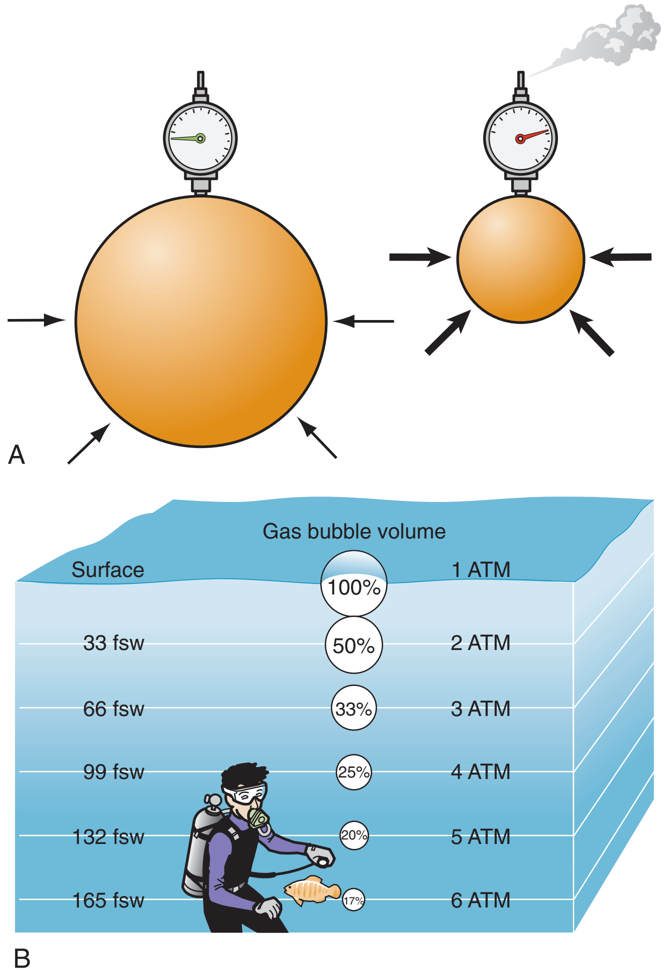


Figure 143-2. Boyle's law. **A,** At a constant temperature, the absolute pressure and the volume of gas are inversely proportional. **B,** As pressure increases, the gas volume is reduced; as the pressure is reduced, the gas volume increases.

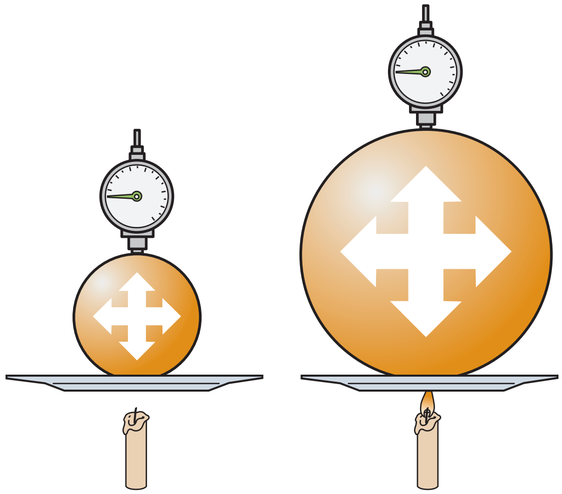


Figure 143-3. Charles' law. At a constant pressure, the volume of a gas is directly proportional to the change in the absolute temperature.

environment during ascent or descent. The fractional changes in volume are greater near the surface. Thus the greatest risk for barotrauma is in shallow water, where the proportional pressure changes are also the greatest.

Dalton's law states that the total pressure exerted by a mixture of gases is equal to the sum of the pressures (partial pressures) of

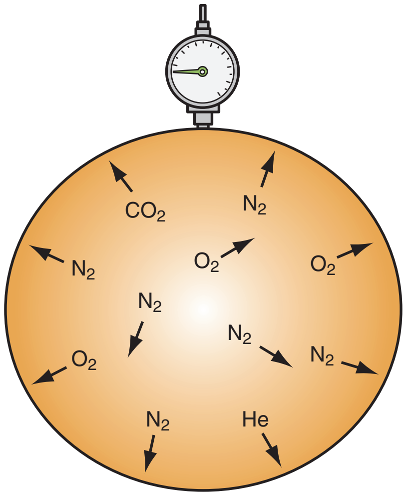


Figure 143-4. Dalton's law. The total pressure exerted by a mixture of gases is equal to the sum of the pressures (partial pressures) of each of the different gases making up the mixture, with each gas acting as if it alone is present and occupies the total volume.

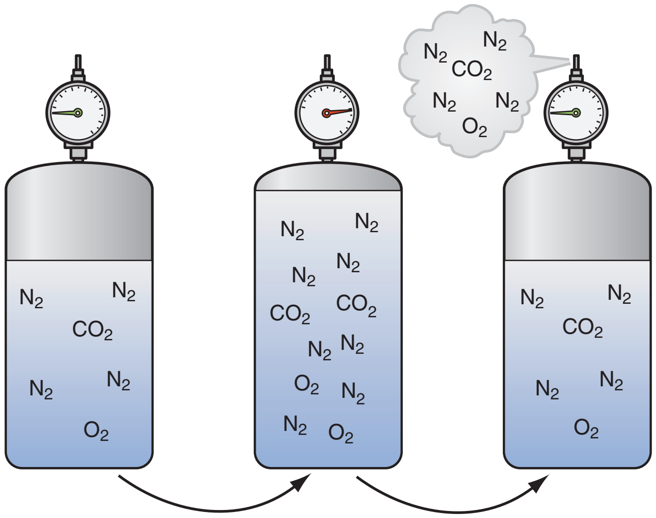


Figure 143-5. Henry's law. The amount of a gas that will dissolve in a liquid at a given temperature is directly proportional to the partial pressure of that gas.

the individual gases making up the mixture, with each gas acting as if it alone is present and occupies the total volume ($P_{total} = P_1 + P_2 + P_3 + \ldots + P_n$). Henry's law states that the amount of any gas that dissolves in a liquid at a given temperature is directly proportional to the partial pressure of that gas. At higher ambient pressures, the concentration of each component of air in solution with blood and tissues increases until a new steady-state concentration is achieved.

The gases in a diver's breathing mixture are dissolved into the body in proportion to the partial pressure of each gas in the mixture. The length of time the diver is breathing the gas at the increased pressure and the inherent solubility of the gas also govern the quantity of a particular gas that dissolves. The dissolved gas remains in solution as long as the pressure is maintained. As the diver ascends, however, increasingly more of the dissolved gas comes out of solution. A rapid ascent may reduce the pressure at a rate higher than the body can accommodate, and the bubbles (particularly nitrogen) may accumulate and disrupt body tissues and systems, a phenomenon termed decompression sickness (DCS). This is similar to the way that rapid opening of a bottle of

www.ketabpezeshki.com 66485457-66963820

soda allows bubbles of carbon dioxide to come out of solution rapidly.

If the ascent rate is controlled (i.e., through the use of the safe decompression tables or submersible dive computers), the gas is carried to the lung vascular bed and is exhaled before it accumulates to form significantly large or numerous bubbles in the tissues, similar to how opening of a soda bottle slowly reduces the bubbling of the contained carbonated liquid.

CLINICAL FEATURES

Disorders Related to Descent

Middle Ear Barotrauma

Middle ear barotrauma (MEBT), also known as barotitis or "ear squeeze," is the most common complaint of scuba divers. It is experienced by 30% of novice scuba divers and 10% of experienced divers.[6,7] The middle ear is an air-filled space with solid bone walls except for the tympanic membrane (Fig. 143-6). The eustachian tube is the only anatomic passage to the external environment.

As the diver descends, the water exerts increasing pressure against the intact tympanic membrane. Typically, the diver performs various maneuvers to force air into the middle ear through the eustachian tubes in an attempt to maintain equal pressure across the tympanic membrane. If the diver fails, the floppy medial third of the eustachian tube collapses shut, making any further attempts at equalization futile. This is typically painful and can be associated with tinnitus; some patients develop transient vertigo.

Further descent can cause the tympanic membrane to rupture. The pain may or may not resolve as the tympanic membrane ruptures. The ruptured tympanic membrane can cause caloric stimulation by exposure of the middle ear to cold water, inducing a transient nystagmus and vertigo. The pressure of the water in the middle ear may lead to a facial palsy in certain individuals where the seventh cranial nerve passes unexposed through this space. On occasion, this disorder can be life-threatening during a dive as the subject becomes disoriented and can drown.

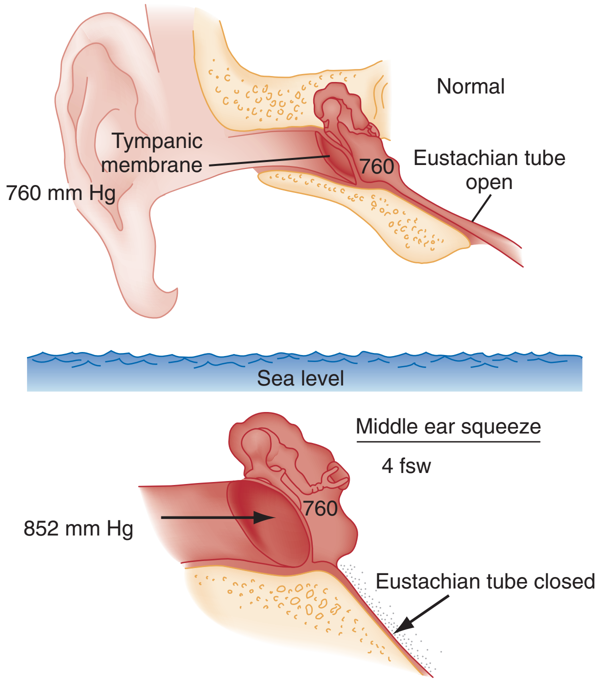


Figure 143-6. Anatomy of the ear and middle ear trauma. *fws,* feet of seawater. (From Kizer KW, Van Hoesen KB: Diving medicine. In: Auerbach PS (ed): Wilderness Medicine, 5th ed. St Louis, Mosby, 2007, p 1612.)

External Ear Barotrauma

External ear barotrauma is less common than MEBT and results from the outward bulging of the tympanic membrane during descent. Normally, the external auditory canal is filled with water during descent. Obstruction of the external auditory canal because of cerumen, stenosis, earplugs, or a tight-fitting wet suit hood can trap air, causing a relative negative pressure. This may lead to localized pain. Patients may have hemorrhages in the wall of the external auditory canal on examination, but the symptoms are typically self-limited.[8]

Inner Ear Barotrauma

Inner ear barotrauma (IEBT) results in damage to the cochleovestibular apparatus. It is much less common than MEBT but is associated with greater morbidity. A large negative pressure gradient develops in the middle ear if the diver is unable to equalize pressure during descent, similar to MEBT. Inward deflection of the tympanic membrane is transmitted to the oval window of the cochlea through the ossicles. Movement of the oval window creates a pressure wave within the perilymph of the cochlea, which causes an outward distention of the round window into the middle ear. Sudden equilibration of pressure in the middle ear or a vigorous Valsalva maneuver may rupture the round window, lead to hemorrhage into the inner ear, or tear the labyrinthine (Reissner's) membrane.[9-11]

Symptoms associated with IEBT include variable hearing loss, severe vertigo, nausea, tinnitus, and fullness in the affected ear. Signs include severe nystagmus, positional vertigo, ataxia, and vomiting. The degree of sensorineural hearing loss is variable. Distinguishing IEBT from inner ear DCS (a type of DCS II) can be challenging but should not delay recompression in a patient in whom the diagnosis is in doubt.

Barosinusitis

Obstruction of the sinus ostia by mucosal thickening, polyps, pus, or deviated septum predisposes to sinus barotrauma, the second most common complaint among divers.[8,9] The air-filled maxillary, frontal, and ethmoidal sinuses are susceptible to volume-pressure changes on ascent or descent; the most commonly affected is the maxillary sinus, followed by the frontal.[11] The most common symptom is facial pain; epistaxis is common.

Facial Barotrauma

As water pressure increases during descent, a negative pressure develops within the dive mask over the eyes and nose, which must be equalized by forced exhalation through the nose. When this is not adequately performed, the large negative pressure gradient may lead to facial and conjunctival edema, diffuse petechial hemorrhages on the face, and subconjunctival hemorrhages.[8] Very rarely, optic nerve damage can result from severe facial barotrauma.

Disorders Arising at Depth

Nitrogen Narcosis

Nitrogen narcosis, known as rapture of the deep, results from the intoxicating effects of increased tissue nitrogen concentration at depth. Symptoms include euphoria, false feeling of well-being,

www.ketabpezeshki.com 66485457-66963820

confusion, loss of judgment or skill, disorientation, inappropriate laughter, diminished motor control, and tingling and vague numbness of the lips, gums, and legs.[3] With breathing of compressed air, symptoms typically begin to occur at approximately 100 feet and often become profound at depths of more than 150 feet.[3] Because of these dangers, the use of compressed air is not recommended for sport diving to depths of more than 120 feet. Although the effects of nitrogen narcosis resolve with ascent to shallower depths and are variable between individuals, the diver may drown because of poor judgment or seriously impaired motor skills in the presence of a dive emergency.

Oxygen Toxicity

At elevated partial pressures for extended periods, oxygen can be toxic to the central nervous system (CNS) or lungs. Oxygen becomes toxic to the CNS when its partial pressure exceeds 1.6 ATA. Oxygen partial pressures below 1.4 ATA are unlikely to produce CNS toxicity. A diver breathing compressed air would attain a partial pressure of 1.6 ATA of oxygen at a depth of 218 fsw. This far exceeds the depth to which sport divers would go. Deep divers prevent oxygen toxicity by breathing mixed gases with decreased oxygen content (e.g., hypoxic trimix).

Pulmonary oxygen toxicity (low-pressure oxygen poisoning) can occur after 24 hours of exposure to partial pressures of oxygen in excess of 0.6 ATA. The symptoms of pulmonary oxygen toxicity include a burning sensation or pain on inspiration and coughing. Pulmonary function gradually becomes normal after the exposure is terminated, but pneumonitis and permanent fibrosis are possible. It is extremely unlikely that a sport diver would ever be exposed for the duration that is required to produce toxicity; however, long exposures to higher levels of oxygen, such as those administered for certain recompression protocols, may lead to pulmonary oxygen toxicity.

Contaminated Air

Rarely, other gases, such as carbon monoxide and carbon dioxide, can contaminate the air that is compressed into a tank. This can happen, for example, if the compressor intake is placed too close to the compressor's engine exhaust. As in the case of oxygen and nitrogen, the partial pressure of these contaminants in the tissues increases dramatically with depth, potentiating their clinical effects. The symptoms of hypercarbia or carbon monoxide poisoning are more severe at elevated partial pressures. Hypercarbia increases a diver's susceptibility to CNS oxygen toxicity.[3]

Rebreathers release microscopic calcium hydroxide or "soda lime" dust particles into the apparatus.[12] These particles are small enough and have geometric characteristics that allow them to be deposited in the alveoli. When soda lime comes into contact with water, it forms a caustic liquid. In the event of a hose rupture allowing seawater contamination of the circuit, caustic burns to the mouth, throat, and airways may result. Chronic exposure to soda lime dust may contribute to long-term effects on respiratory function.

Disorders Arising on Ascent

Alternobaric Vertigo

Alternobaric vertigo (ABV) results from an inability to equalize pressure within the middle ear during ascent. Although equalization during descent requires active maneuvers to maintain eustachian tube patency, air normally exits the middle ear without difficulty during ascent because the pressure within the middle ear exceeds ambient pressure. In the setting of mucosal edema or thickening within the eustachian tube, however, the passage of air may be impeded. The problem is typically unilateral. When the pressure gradient within the middle ear reaches 60 cm H_2O, increased labyrinthine discharge produces nystagmus. Clinically, the patient experiences a profound but transient sense of vertigo during ascent that may be associated with nausea and vomiting. Unlike those of IEBT, the symptoms are self-limited.

Barodontalgia

On occasion, air that is trapped beneath a poorly filled dental cavity expands on ascent, leading to dental pain. This condition is relatively benign and self-limited.

Gastrointestinal Barotrauma

Serious gastrointestinal barotrauma is a rare condition in scuba divers. It results from the expansion of bowel gas in the small intestine and colon on ascent after diving. Predisposing factors include consumption of carbonated beverages, large meals, or gas-producing foods before diving as well as performance of the Valsalva maneuver in the head-down position. Symptoms include eructation, flatulence, bloating, and crampy abdominal pain. In divers with inguinal or other hernias, the potential for expansion of trapped gas within the hernia exists, and expansion may result in incarceration or strangulation.[13,14] Gastric rupture is a rare complication.[14] Although gastrointestinal barotrauma is a rare entity, it should be suspected in the diver-patient with a provocative history and abdominal pain.

Pulmonary Barotrauma

Without continuously expiring on ascent, a scuba diver who takes a full breath at 33 fsw will have twice the lung volume at the surface (Boyle's law). Because the volume expansion of the alveoli is limited, the increase in pressure either forces gas bubbles across the alveolar-capillary membrane or causes the wall of the alveoli to rupture. A differential pressure of only 80 mm Hg between the alveoli and chest wall, corresponding to a change in depth of 3 to 4 feet, is all that is required to force air bubbles across the alveolar-capillary membrane.

The greatest risk for pulmonary barotrauma occurs in less than 10 feet of water. It is therefore important for the clinician to evaluate patients with symptoms that are consistent with disease entities related to pulmonary barotrauma even after exposure to shallow depths. Pulmonary barotrauma can result in the following four conditions: pneumothorax, pneumomediastinum, subcutaneous emphysema, and alveolar hemorrhage. Risk factors elicited from the dive and medical history may suggest the diagnosis of pulmonary barotrauma. In most cases, fast ascent, panic, problems in regulating buoyancy, or running out of air is noted.

Asthmatics have a twofold increased risk for pulmonary barotrauma compared with the general diver population.[15] There are six mechanisms that contribute to the increased risk in asthmatics:

1. Bronchospasm and mucus plugging predispose local regions of lung to injury.
2. When air is compressed, it becomes denser. This may contribute to greater turbulent flow through narrow airways.
3. During scuba diving, there is a reduction in breathing capacity related to the effects of immersion. At 33 feet underwater, the maximum breathing capacity of a normal scuba diver is only 70% of the surface value. At 100 feet underwater, the reduction is approximately 50%.
4. When compressed air (from the scuba tank) expands in the regulator before delivery to the lungs, it cools (Charles' law). Breathing of chilled air may trigger bronchospasm in

www.ketabpezeshki.com 66485457-66963820

asthmatics who have a cold-induced component of their disease.
5. Scuba diving takes some effort; asthmatics who have an exercise-induced component of their disease may experience bronchospasm.
6. Compressed air may be contaminated by pollen and other allergens.

Traditionally, asthmatics were advised not to dive. Several experts, however, propose more liberal guidelines.[16-18] The risk of diving is probably acceptable if the diving candidate with asthma demonstrates normal pulmonary function at rest (forced vital capacity [FVC], midexpiratory flow, forced expiratory volume in 1 second, and forced expiratory flow between 25 and 75% of FVC) and after strenuous exercise. Asthma severity can wax and wane. Because symptoms may worsen for 4 to 6 weeks after an upper respiratory infection or during certain seasons, asthmatics should refrain from diving until they are completely free of symptoms despite the pulmonary function criteria.

Pneumomediastinum and subcutaneous emphysema result when air crosses the alveolar endothelium and dissects into the pulmonary interstitium. Most commonly, the air then travels into the neck, mediastinum, or pericardium. The manifestations of pneumomediastinum may include fullness in the neck, palpable subcutaneous crepitance, and a change in voice quality or timbre. Unless evidence of either hemodynamic instability or airway compromise exists, interstitial air or subcutaneous emphysema is not a life-threatening condition.

Pneumothorax may occur when the air that escapes from alveoli as a result of pulmonary barotrauma crosses the visceral pleura. A tension pneumothorax is a rare complication. The symptoms and signs of a pneumothorax secondary to pulmonary barotrauma are typical for a pneumothorax of any cause.

Pulmonary barotrauma can also cause alveolar hemorrhage.[19,20] Patients may present with hemoptysis coincident with chest pain and dyspnea. Chest radiography may reveal an interstitial infiltrate.

Decompression Sickness

The term *decompression sickness* (DCS) refers to a spectrum of clinical illnesses resulting from the formation of small bubbles of nitrogen gas in the blood and tissues on ascent.[21,22] The clinical expression of DCS depends on the location, destination, and degree of nitrogen bubble formation in blood and tissues. Small, asymptomatic venous gas emboli are common in the ascending diver and are filtered by the lungs without apparent permanent damage.[23,24] Persistent intravascular bubbles, however, elicit inflammatory cascades, cytokines, the complement system, platelet aggregation, and thrombosis.[25] Furthermore, the bubbles can cause mechanical obstruction, ischemia, and tissue hypoxia. Nitrogen is highly fat soluble, and the heavily myelinized white matter of the CNS is at particular risk for DCS.

The incidence of DCS is estimated to be 2.8 cases per 10,000 dives.[4] The potential for development of DCS increases with the length and depth of a dive. Other risk factors include age, obesity, fatigue, heavy exertion, dehydration, fever, cold ambient temperatures after diving, diving at high altitude, and flying after diving. Tobacco and ethanol use may also increase susceptibility to DCS. The risk of DCS is 2.6 times greater for men than for women.[26] This difference is possibly due to risk-taking behaviors. There appears to be no increase in DCS in women who are taking oral contraceptive agents or menstruating during diving.

A patent foramen ovale (PFO) is a risk factor for increased susceptibility to DCS.[27,28] Sixty-five percent of divers who present with serious DCS have a PFO.[27,29] Brain lesions occur in 27% of sport divers.[30] This percentage is roughly the same as the prevalence of PFO or other right-to-left shunts in the general population. These multiple brain lesions may be caused by bubbles in the venous circulation that are not filtered by the vasculature of the lungs but enter the arterial circulation, even in the absence of other DCS symptoms.[31] Most sport divers do not undergo screening for PFO with echocardiographic bubble studies; some PFOs may open only at increased ambient pressures so that bubble studies conducted at 1 ATA would be normal.[32]

The U.S. Navy dive tables estimate the amount of nitrogen that accumulates in the body during a dive to a particular depth and duration.[3] The tables calculate a maximal dive time, called the no-decompression limit. If the no-decompression limits are exceeded, underwater decompression stops are recommended. Many sport scuba divers use submersible dive computers to calculate maximum dive times in lieu of the tables. These computers use mathematical algorithms to model nitrogen saturation in human tissues. Although they remove human calculation errors, such computers also tend to extend no-decompression times to their maximum limits.

These tables and computers are meant to reduce the likelihood of exceeding the solubility of nitrogen at sea level to produce DCS. The diver still must ascend in a slow, controlled manner to allow the gradual release of nitrogen. Off-gassing continues after the diver has surfaced. Repetitive dives within several hours result in accumulation of tissue nitrogen and shorter no-decompression limits. Because dive tables are based on several assumptions about nitrogen elimination, even strict adherence to these tables does not ensure that DCS will not occur.[3] The risk of DCS increases as a diver approaches the no-decompression time limits and almost never occurs after dives to less than 6 meters and rarely at less than 10 meters.[33] It is critical for the evaluating physician to realize that divers can develop DCS even when they are within any calculated no-decompression limits.

DCS typically is manifested within hours after surfacing. The *U.S. Navy Diving Manual* notes that 42% of symptoms occur within 1 hour after diving, 60% within 3 hours, 83% within 8 hours, and 98% within 24 hours.[34] Flying shortly after diving or ascending to altitude, however, may cause symptoms in patients later than expected, and some patients present days after diving with DCS.[34,35]

Traditionally, DCS has been divided into two categories, type I and type II. Type I DCS affects the musculoskeletal system, skin, and lymphatic vessels. Type II DCS involves any other organ system. The more inclusive "decompression-related illness" is now also used to encompass DCS I, DCS II, and arterial gas embolism (AGE). This terminology is adapted to aid clinicians in remembering that the distinction is irrelevant in the selection of treatment. All types of decompression illness require recompression.[35] DCS I, DCS II, and AGE can coexist. The symptoms of DCS may be subtle and resolve by the time of evaluation. A distribution of the most common symptoms and the first symptoms is presented in Figure 143-7.

Type I DCS can be experienced as variable and periarticular pain in the arms and legs. The elbow and shoulder joints are most commonly affected. Local tenderness and erythema are uncommon. The placement of a blood pressure cuff inflated to 150 to 200 mm Hg on an affected joint produces relief of pain and confirms the diagnosis; however, the sensitivity of this maneuver was as low as 61% in one study.[30] Skin marbling, known as cutis marmorata (patchy cyanotic marbling of the skin), results from venous stasis. It may begin as severe pruritus and progress into an erythematous rash and then skin mottling. Cutis marmorata does not follow a dermatomal distribution and commonly involves the trunk and torso. Lymphatic obstruction by air bubbles can also occur, causing extremity edema.

Type II DCS includes symptoms beyond those described for type I. These symptoms can involve the CNS, the inner ear, and the lungs. The CNS is particularly susceptible to decompression

www.ketabpezeshki.com 66485457-66963820

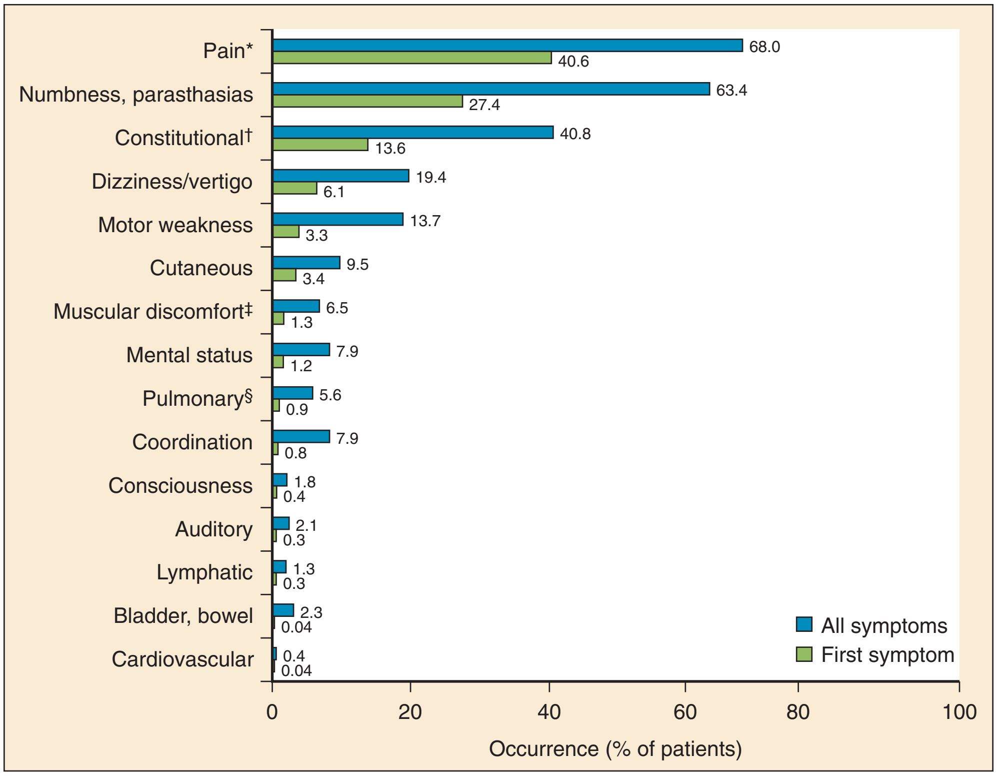


Figure 143-7. Classification of initial and of all eventual manifestations of decompression illness in 2346 recreational diving accidents reported to the Divers Alert Network from 1998 to 2004. *For all instances of pain, 58% consisted of joint pain, 35% muscle pain, and 7% girdle pain. Girdle pain often portends spinal cord involvement. †Constitutional symptoms included headache, lightheadedness, inappropriate fatigue, malaise, nausea or vomiting, and anorexia. ‡Muscular discomfort included stiffness, pressure, cramps, and spasm but excluded pain. §Pulmonary manifestations included dyspnea and cough. (From Vann RD, Butler FK, Mitchell SJ, Moon RE: Decompression illness. Lancet 377:153-164, 2011.)

illness because of its high lipid content. The spinal cord, especially the upper lumbar area, is more often involved than cerebral tissue. Symptoms of spinal DCS include limb weakness or paralysis, paresthesias, numbness, and low back and abdominal pain. Limb symptoms often begin as a distal prickly sensation that advances proximally, followed by progressive sensory or motor loss. A dermatome sensory level occurs in some spinal DCS patients, often at the T12 to L1 dermatomes. Bladder symptoms, fecal incontinence, and priapism may occur. Unlike patients with spinal cord trauma, patients experiencing DCS may have patchy or unequally distributed sensory and motor findings.

Spinal DCS can occur alone or in combination with cerebral, inner ear, or pulmonary symptoms. Cerebral symptoms include mild to moderate headache, blurred vision, diplopia, dysarthria, unusual fatigue, inappropriate behavior, and a sense of detachment. Loss of consciousness in CNS DCS is rare (in marked contrast to AGE).[36] Magnetic resonance imaging, computed tomography (CT), and single-photon emission CT with technetium (Tc-99m)–labeled hexamethylpropyleneamine can identify the bubbles of CNS DCS. No imaging studies are sensitive enough to exclude DCS, however, and normal imaging results should not delay transfer for definitive therapy.

Inner ear DCS is commonly called the staggers. The symptoms of inner ear DCS are the same as those of IEBT and include nausea, dizziness, vertigo, and nystagmus. This can usually be distinguished from IEBT because the onset happens during ascent or after surfacing.

Pulmonary DCS is called the chokes. All divers are exposed to some degree of microbubble emboli to the lungs on ascent. The progression to symptoms depends on the number and volume of bubbles. The deposition of venous gas emboli in the pulmonary arterial circulation produces progressive dyspnea, cough, and chest pain. The cough may progress to paroxysmal fits with worsening pain.

The physical examination of patients suffering from pulmonary DCS may reveal cyanosis and hypotension in association with increased central venous pressure and pulmonary arterial pressure, right-sided strain on an electrocardiogram, and decreased end-tidal carbon dioxide level. The condition may progress to respiratory arrest. Ancillary tests for pulmonary DCS not only are insensitive but also lead to unnecessary treatment delays. Even after ascent from very shallow saturation dives, microbubbles in the venous circulation can be routinely detected by M-mode ultrasonography; however, their presence does not necessarily correlate with symptoms.[37-40]

DCS may be particularly dangerous to a developing fetus of a scuba diving mother because the majority of the fetal circulation bypasses the pulmonary bed through the foramen ovale and the ductus arteriosus. This bypass prevents the fetal lungs from acting as a filter for microbubbles. In addition, venous gas emboli may appear in the fetal circulation before they are apparent in the maternal circulation.[41,42] Data on the effects of diving on pregnant women suggest a higher incidence of low-birth-weight infants, prematurity, congenital malformations, stillbirths, and spontaneous abortions.[43,44] There are no safe-diving tables that would protect a fetus from DCS; therefore, pregnant women should be advised to refrain from scuba diving.

Arterial Gas Embolism

AGE results when air bubbles are forced across the alveolar-capillary membrane, escape into the pulmonary venous circulation, and proceed through the left atrium and ventricle into the arterial circulation. It is one of the most common causes of death

www.ketabpezeshki.com 66485457-66963820

in divers.[4,20,35] Clinical symptoms and signs are in part the result of mechanical obstruction by gas bubbles. AGE can also result from a right-to-left shunt of venous bubbles, such as in a diver with a PFO. AGE may occur alone or in conjunction with DCS.[35]

Although air bubbles may embolize to any organ, the coronary and cerebral arteries are associated with the most serious consequences. Emboli to the coronary arteries may cause cardiac ischemia, myocardial infarction, dysrhythmias, or cardiac arrest. Dysrhythmias are also indirectly caused by centrally mediated autonomic dysfunction from cerebral emboli.[45,46] Mechanical occlusion of the cerebral vasculature from emboli, most commonly to the anterior and middle cerebral arteries, causes a variety of symptoms and signs similar in appearance to an acute stroke.

The clinical manifestations of AGE may be sudden, dramatic, and life-threatening. Divers who have supposedly “drowned” may actually have lost consciousness during ascent as a result of cerebral gas emboli. Any diver breathing compressed air at any depth underwater and who surfaces unconscious or who loses consciousness within 10 minutes of reaching the surface should be assumed to be suffering from AGE. The most common presentation of AGE includes a global alteration of consciousness, headache, dizziness, convulsions, and visual changes. Other common presenting symptoms and signs include cranial nerve symptoms, unilateral weakness, unilateral or bilateral sensory loss, ataxia, and speech changes.[20] Pulmonary symptoms, including dyspnea, pleuritic chest pain, and hemoptysis, occur in 25 to 50% of cases.[47]

Pulmonary Edema

Pulmonary edema while scuba diving was first reported in 1981.[48] An increase in afterload (from vascular hyper-reactivity, possibly triggered by cold) combined with an increase in preload (from the hyperbaric underwater environment) may be the cause.

DIAGNOSTIC STRATEGIES

Focused questions concerning the dive profile, including the depth and length of the dive and a careful assessment of when the symptoms first occurred, may provide important diagnostic clues (Box 143-1). A physician unfamiliar with the specifics of scuba diving may rely on the assessment of members of the dive group to determine whether maximum dive limits were approached. In making the diagnosis of a dive injury, it is helpful to think of the injuries in terms of occurring during descent, while at depth, or during ascent (Fig. 143-8). Because recompression therapy is time sensitive, it is important to concentrate on treatment decisions rather than on securing an absolute diagnosis. The primary question to address is whether this dive injury is likely to be helped by recompression. Early consultation with a hyperbaric specialist is recommended.

Box 143-1 Focused Dive History

- When was the first onset of symptoms?
- What type of equipment was used? compressed air, mixed gas, enriched air, rebreather? What was the source of the gas?
- Did the dive approach or exceed decompression limits? Was a dive computer used?
- What were the number, depth, bottom time, total time, and surface intervals for all dives in the 72 hours preceding symptoms (the dive “profiles”)?
- Were decompression stops used? Was in-water decompression attempted?
- What was the time delay from the last dive to air travel?
- Did the diver experience difficulty with ear or sinus equilibration? Did the pain occur on descent or ascent?
- Was the diver intoxicated? dehydrated? working strenuously?
- How long after the dive did symptoms present? Were they present at surfacing? delayed? progressive?
- Is a medical history of ear or sinus infections or abnormalities present? emphysema or asthma? coronary artery disease? patent foramen ovale? neurologic illness?

DIFFERENTIAL CONSIDERATIONS

Most diving injuries have limited differential diagnoses that include medical disorders and trauma unrelated to dysbarism. The differential diagnosis of IEBT includes inner ear DCS, ABV, and isolated MEBT with a rupture of the tympanic membrane. It is relatively easy to distinguish IEBT from MEBT and ABV because the vestibular symptoms associated with the last two entities are transient and self-limited. When IEBT occurs simultaneously with MEBT, the presence of both may be documented by an audiogram, which demonstrates both a conductive and a sensorineural hearing loss (Table 143-3).

The differentiation of IEBT from inner ear neurologic DCS is crucial because the treatments differ. An IEBT is more likely when symptoms begin during descent or the diver relates a history of difficulty equilibrating or performing a vigorous Valsalva maneuver. If the dive profile is examined and the no-decompression limits are approached and symptoms began soon after surfacing, inner ear DCS is more likely.[49] A history of difficulty in equalizing the ears on descent, or the onset of symptoms early in the dive, suggests barotrauma. A history of a dive that approaches decompression limits, or the onset of symptoms during or soon after ascent, and the presence of other neurologic findings suggest DCS. A trial of recompression therapy is prudent if concerns for DCS exist.

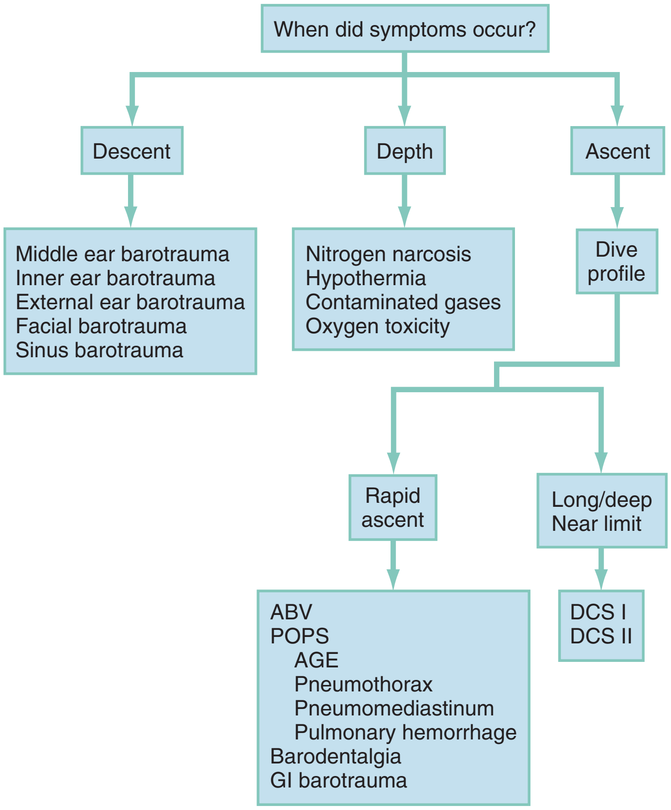


Figure 143-8. The approach to the injured diver. *ABV,* alternobaric vertigo; *AGE,* arterial gas embolism; *DCS,* decompression sickness; *GI,* gastrointestinal; *POPS,* pulmonary overpressure syndrome.

www.ketabpezeshki.com 66485457-66963820

Table 143-3 Middle Ear Barotrauma, Inner Ear Barotrauma, and Alternobaric Vertigo

	MEBT	IEBT	ABV
Symptoms	Ear pain during descent Hearing loss Possible transient vertigo	Ear pain during descent Hearing loss Severe vertigo and nausea	Ear pain during ascent Transient hearing loss Nausea
Signs	Conductive hearing loss TM injury Unilateral face paralysis	Nystagmus Emesis Ataxia Romberg's sign Neural hearing loss	Nystagmus Emesis TM injury

ABV, alternobaric vertigo; *IEBT,* inner ear barotrauma; *MEBT,* middle ear barotrauma; *TM,* tympanic membrane.

Table 143-4 Decompression Sickness versus Arterial Gas Embolism

DECOMPRESSION SICKNESS	ARTERIAL GAS EMBOLISM
Dive History	
Depth and length dependent Decompression limits approached Flying after diving Diving at altitude	Independent of dive profile Rapid ascent Inexperience Out of air
Risk Factors	
Fatigue Dehydration Fever, hypothermia Obesity Strenuous activity	Obstructive lung disease Emphysema Mucus plugging Patent foramen ovale
Symptoms and Signs	
Progressive onset Spinal symptoms predominate Headache Unusual fatigue Limb weakness or paralysis Paresthesias Abdominal pain Urinary retention Fecal incontinence Periarticular joint pain Skin marbling Vertigo or nystagmus	Rapid onset Cerebral symptoms predominate Headache Loss of consciousness Confusion Convulsions Motor or sensory loss Cardiac dysrhythmias or arrest
Treatment	
Recompression	Recompression

The differential diagnosis of pulmonary DCS includes AGE (Table 143-4). Although the treatment of both requires recompression therapy, they may be differentiated by the timing of the onset of symptoms. Almost all cases of AGE present within the first 10 minutes of surfacing, whereas DCS presents more typically after 10 minutes: 42% of pulmonary DCS symptoms begin within 1 hour of surfacing, 60% within 3 hours, 83% within 8 hours, and 98% within 24 hours.[3]

MANAGEMENT

Patients with stable vital signs and suspected dive injuries should receive 100% oxygen until the clinician can exclude pulmonary barotrauma or decompression illness. Patients with unstable vital signs or in cardiac arrest should be treated according to advanced cardiac life support (ACLS) guidelines. The clinician should take a thorough history, including elements in Box 143-1, and then perform a thorough physical examination. Diving-related illnesses are diagnosed and treated on the basis of the history and physical examination, and several invaluable resources are available for advice. The Divers Alert Network (DAN), located at Duke University in Durham, North Carolina, is a membership association that provides courses on diving-related emergencies and publishes data on diving accidents and fatalities. Clinicians may obtain treatment advice by calling DAN. DAN provides a 24-hour medical emergency hotline at 1-919-684-9111 (collect calls are accepted) and a nonemergency advisory line Monday through Friday, 8:30 AM to 5 PM Eastern time, at 1-919-684-2948 or 1-800-446-2671. In addition, DAN international contacts are in Europe, Brazil, Japan, Asia Pacific, and southern Africa. DAN maintains a website with links to key information at www.diversalertnetwork.org. DAN uses a telephone intake form, the DAN On-Site Neurological Assessment for Diver's History (Fig. 143-9); familiarity with this form may facilitate the emergency physician's communications with DAN.

The U.S. Navy has its current diving manual (revision 6) available at its website, www.usu.edu/scuba/navy_manual6.pdf. This manual, updated in 2008, contains a wealth of information about diving principles, equipment, operations, and recompression.

Box 143-2 Diving Disorders That Require Recompression Therapy

Decompression sickness type I
Decompression sickness type II
Arterial gas embolism
Contaminated air (carbon monoxide poisoning)

Diving Disorders Requiring Recompression Therapy

Diving disorders that require recompression therapy are listed in Box 143-2.

Treatment with 100% oxygen replaces inert gases in the lungs with oxygen. By establishment of a large gradient from the tissues to the alveoli, removal of the inert gases is enhanced and bubble size is reduced.[50] In addition, oxygen administration treats the tissue hypoxia caused by gas bubbles. Normobaric oxygen treatment during preparation for recompression therapy is associated with a need for fewer recompressions.[51]

Dehydration can increase the seriousness of DCS.[52] Hydration decreases bubble formation after decompression.[53] It also decreases the endothelial inflammation and damage associated with hemoconcentration and hemodynamic instability seen in dehydrated DCS patients.[54,55] Therefore, intravenous fluids should be administered to divers suspected of having nonpulmonary ("chokes") DCS. Overly aggressive hydration in divers with pulmonary DCS may worsen pulmonary edema. Similarly, fluid overload should be avoided in patients with cerebral or spinal cord edema. There is no clear consensus that the best fluid is crystalloid (normal saline or lactated Ringer's solution) or colloid; many experts, however, advise against dextrose in water without electrolytes (e.g., D_5W). Fluids should be given to ensure a urinary output of 0.5 mL/kg/hr.

The intravenous fluid treatment recommendations differ in AGE. Divers with AGE are less likely to be dehydrated than are divers with DCS. This may be because of a shorter period of immersion or because they experience less bubble-induced endothelial damage.[3] Further, CNS injuries in AGE may be worsened

www.ketabpezeshki.com 66485457-66963820

DAN On-Site Neurological Assessment for Diver's History

Last Name: ______________ **First Name:** ______________ **MI:** ____

Date: (mm/dd/yy): ______________ **Time: (hh:mm)** ______________

COMPLETED BY: ______________

How do you feel? ______________

Symptoms? ______________

Did symptoms start during descent, on bottom, during ascent, or after surfacing? ______________

Dive profile, breathing gas, ascent and time of surfacing, recent dive history ______________

Unusual features of dive (e.g., out of air, rapid ascent) ______________

Decompression computer, table ______________

Difficulty with middle ear equalization? ______________

Numbness, tingling? Where? ______________

Pain? Where? What makes it better or worse? ______________

Rate the pain on a scale of 0 (no pain) to 10 (the worst pain imaginable) ______________

Shortness of breath? ______________

Ringing or buzzing in ear? ______________ Decreased hearing? ______________

Dizziness? Vertigo? ______________

"Vertigo" implies a sensation of the world spinning around. Vague "dizziness" is not vertigo.

Weakness? ______________

Difficulty walking? If so, is this due to difficulty with balance or leg weakness? ______________

Nausea, vomiting? ______________ Able to urinate? ______________

From "observer" (e.g., dive buddy, companion) ______________

Confirm dive profile ______________

His/her version of events ______________

Did the diver breach safe procedures (e.g., ascent rate, out of air, was he/she breathing during ascent)?

____

Has the diver been acting inappropriately? ______________

Was there loss of consciousness, seizure? ______________

Figure 143-9. The DAN On-Site Neurological Assessment for Diver's History.

by cerebral edema. Therefore, large-volume fluid resuscitation is not recommended in divers with AGE after a short, shallow dive.[56]

The goals of recompression therapy are to reduce the mechanical obstruction of air bubbles, to facilitate the washout of nitrogen by increasing the tissue-blood nitrogen gradient, and to increase oxygen delivery to ischemic tissue. Recompression is the only definitive treatment of DCS and AGE. Treatment of DCS or AGE should not be withheld even if a significant time delay in transfer to a hyperbaric chamber is unavoidable. Although delayed recompression is less effective than immediate recompression in serious cases, the time beyond which recompression offers no benefit is unknown.[57]

Hyperbaric therapy for AGE should be initiated as soon as possible, although there are cases of significant improvement even in the face of long delays until recompression.[58] Patients with AGE who are recompressed within 5 minutes of surfacing have a mortality rate of 5%, and there is an extremely low risk of morbidity among the survivors.[32] If recompression is delayed by 5 hours or more, the mortality rate increases to 10%, with 50% morbidity.[32] Although spontaneous resolution of symptoms may occur in patients with AGE, all patients should be recompressed. The rationale is that although microbubbles may clear from the cerebral circulation, secondary capillary edema and swelling may result in a delayed recurrence of symptoms. Furthermore, more subtle

www.ketabpezeshki.com 66485457-66963820

symptoms may be appreciated only after the resolution of more prominent ones. Finally, minor symptoms may progress, and the relapse rate is high in untreated cases.

Similarly, the prognosis for DCS when it is treated with recompression is generally good but depends on the severity of symptoms at onset and the delay to recompression. A delay to definitive recompression treatment is associated with a worse outcome in cases of severe DCS. Patients can obtain some benefit from recompression, however, even if treatment is initiated more than 24 hours after the dive. Recompression therapy for DCS may be initiated as late as 10 to 14 days after exposure if necessary.[59]

Recompression for DCS and AGE is most often performed in a multiplace chamber with one or more in-chamber attendants. DCS and AGE have also been successfully treated in monoplace chambers.[60] Monoplace chambers are compact, lightweight, and more widely available than multiplace chambers. Unfortunately, because of their design, most cannot be pressurized beyond 3 ATA (100 fsw) or deliver air-oxygen mixtures. The most common recompression schedule is U.S. Navy treatment (or an equivalent procedure); the diver is compressed to 2.8 bar (60 fsw pressure) while breathing 100% oxygen. The time to complete treatment is 4 hours 45 minutes, not including descent time.

Ground transport to a hyperbaric facility is preferred to air transportation, if feasible, because an increase in altitude lowers the ambient pressure and allows microbubbles to expand. If air transportation must be used, it is important to maintain cabin pressure at less than 1000 feet. Commercial aircraft are typically pressurized to a cabin altitude of 5000 to 8000 feet in cruise flight (30,000 feet). Many of these aircraft are capable of near–sea level cabin pressures if flying no higher than 15,000 to 20,000 feet. Because helicopters are not pressurized, it is recommended that they maintain an altitude of no more than 500 feet above the departure facility.

In addition to recompression therapy, several adjunctive treatments are proposed in the treatment of DCS and AGE. The treatment or prevention of hypothermia may increase tissue perfusion and off-gassing. The nonsteroidal anti-inflammatory drug tenoxicam (Mobiflex) decreases the number of recompressions required for symptom resolution in DCS but does not change the ultimate outcome.[61] Aspirin therapy (as a platelet aggregation inhibitor) has previously been recommended for DCS and AGE. Because of the lack of studies demonstrating safety and efficacy for DCS or AGE treatment, however, it cannot be recommended.[3,35] Steroids have previously been advocated clinically for neurologic DCS and AGE. No significant improvements in neurologic sequelae are now demonstrated; however, the elevated blood glucose levels associated with steroid treatment may worsen the outcome of CNS injury.[56]

Anticoagulants should not be used routinely in the treatment of DCS. The one exception is in divers with lower extremity paralysis caused by neurologic DCS or AGE. Low-molecular-weight heparin (e.g., enoxaparin, 30 mg, subcutaneously every 12 hours; dose adjustment should be made for patients with renal impairment) after recompression therapy may be used in patients with inability to walk to prevent venous embolic disease. Intermittent pneumatic compression devices are alternatives.[3,35]

Lidocaine is not effective in DCS but may have neuroprotective effects in patients with AGE and serious neurologic symptoms. It is administered as an intravenous bolus of 1 mg/kg, followed by a drip infusion of 2 to 4 mg/min.[56,62]

Cardiac dysrhythmias may be refractory to standard treatments until the diver is recompressed. Defibrillation in a hyperbaric environment may be a fire hazard and is not recommended. Seizures may be managed with benzodiazepines; however, mannitol should be avoided. Spinal DCS patients often develop urinary retention requiring bladder catheterization. Of note, endotracheal tube and urinary catheter balloons should be inflated with sterile saline (not air) before recompression therapy is initiated. Nitrous oxide should be avoided because it can increase the size of tissue bubbles by inward diffusion.[63]

Although the head-down position (Trendelenburg) has previously been advocated to prevent migration of intra-arterial bubbles to the brain, it is not effective and may result in worsening cerebral edema and intracranial pressure.[64] Transport of the patient with AGE in a flat supine position is recommended to maximize arterial-venous flow.

There is limited experience with carbon monoxide poisoning from contaminated air supplies in a diving environment. This condition should be treated immediately with normobaric 100% oxygen and may require hyperbaric oxygen therapy. Consultation with a hyperbaric specialist or toxicologist is recommended.

Diving Disorders Not Requiring Recompression Therapy

Diving disorders that do not require recompression therapy are listed in Box 143-3.

Prevention of MEBT requires that the diver equalize the pressure in both middle ears. Any diver who cannot clear both ears on the surface should not dive. The diver should never perform a forceful Valsalva maneuver during descent or ascent to clear the ears because of the risk of ABV, round or oval window rupture (descent), or pulmonary barotrauma (ascent). The prophylactic use of pseudoephedrine (60 mg taken 30 minutes before diving) or oxymetazoline nasal spray may reduce the incidence and severity of MEBT.[7] The use of these medications to facilitate diving with symptoms of an upper respiratory infection, however, is not recommended. Antihistamines should be avoided before diving. Sinusitis and upper respiratory infections increase the likelihood of suffering barotitis. Diving should be avoided for 2 weeks after the resolution of an upper respiratory infection.[65]

Treatment of uncomplicated serous otitis from MEBT includes topical nasal vasoconstrictors, such as phenylephrine and oxymetazoline hydrochloride, and repeated Frenzel maneuvers to displace the fluid through the eustachian tube. The Frenzel maneuver is performed by pinching the nose, placing the tongue on the roof of the mouth, as far forward as possible, and gently moving the back of the tongue upward, as when starting to swallow; this is repeated as many times as necessary until equalization occurs. If the physical examination reveals a ruptured tympanic membrane, prophylactic treatment should also include an oral antibiotic. Oral steroids (prednisone) may speed recovery when a seventh nerve palsy is diagnosed in conjunction with a perforated tympanic membrane, although this disorder is typically self-limited. Diving must also be suspended until the tympanic membrane heals to prevent calorically induced vertigo.

Box 143-3 Diving Disorders That Do Not Require Recompression Therapy

- Middle ear barotrauma
- External ear barotrauma
- Inner ear barotrauma
- Barosinusitis
- Facial barotrauma
- Nitrogen narcosis
- Oxygen toxicity
- Pneumothorax
- Pneumomediastinum
- Subcutaneous emphysema
- Alveolar hemorrhage
- Alternobaric vertigo
- Barodontalgia
- Gastrointestinal barotrauma
- Avascular osteonecrosis

www.ketabpezeshki.com 66485457-66963820

Treatment of external ear barotrauma includes cleaning of the external canal and removal of foreign bodies. Earplugs should never be worn when diving.

A conservative treatment approach to IEBT includes bed rest for 5 to 7 days with the head elevated, avoidance of straining and the Valsalva maneuver, and decongestants to facilitate drainage of the middle ear. Early surgical intervention may benefit patients with total or near-total hearing loss but not isolated high-frequency hearing loss. All patients with IEBT should be referred to an otolaryngologist because IEBT suggests significant injury to the cochleovestibular system.

Treatment of barosinusitis is typically conservative, including the use of decongestants and, occasionally, antibiotics. If symptoms persist, referral for antrostomy should be considered, particularly to prevent future recurrences. The patient should be advised not to dive until any underlying respiratory infection or acute inflammatory process has resolved.

The victim of facial barotrauma may have a dramatic appearance, but the condition is usually benign and requires no specific treatment. The patient should be advised not to resume diving until facial edema resolves.[66]

Nitrogen narcosis symptoms should resolve on surfacing when the partial pressure of nitrogen decreases. Seemingly persistent symptoms should prompt a search for other causes, such as DCS, cerebral AGE, contaminated air, and near-drowning.

With the exception of AGE, none of the pulmonary barotrauma disorders (pneumothorax, pneumomediastinum, subcutaneous emphysema, and alveolar hemorrhage) requires recompression therapy. Treatment with 100% oxygen may aid in the resolution of the disorders. Although tube thoracostomy may not be required for the treatment of a small pneumothorax, a tube should be placed if the diver is to undergo recompression therapy for concomitant AGE or DCS to prevent a tension pneumothorax. Catheter aspiration of the pneumothorax is an acceptable alternative to tube thoracostomy if the patient will not receive positive-pressure ventilation or recompression therapy.

The evaluation and management of pneumomediastinum include serial chest radiographs to ensure that no coexisting pneumothorax develops. One hundred percent oxygen therapy may hasten the resolution of symptoms. In the rare case of respiratory compromise, tracheal intubation may be required. Most important, the presence of interstitial pulmonary emphysema should alert the physician to the possible coexistence of more severe forms of pulmonary barotrauma. The need for a surgical decompressive treatment of subcutaneous emphysema alone is extremely unlikely. Supportive therapy to correct hypoxia is indicated in the treatment of alveolar hemorrhage.[19]

Careful equalization during a slow ascent can prevent the occurrence of ABV. Oral and intranasal decongestants may be indicated if symptoms persist. Myringotomy is occasionally required.[67]

DISPOSITION

Decompression tables are based on the premise that the diver returns to an ambient pressure of 1 atm on surfacing. However, with ascent in altitude after diving or on diving at altitude, a further reduction in ambient pressure occurs. Commercial airliners may be pressurized to a cabin altitude of 5000 to 8000 feet in cruise flight. Many cases of DCS have a delay in the onset of symptoms in divers who fly after diving even if they are symptom free before departure. Divers who experience DCS symptoms before departure but nevertheless fly are more likely to have type II DCS, less likely to achieve complete relief after recompression, and more likely to have residual symptoms for at least 3 months.

The recommended postdive preflight surface interval (PFSI) before ascending to higher altitudes (or flying) depends on the diver's repetitive group designator (residual nitrogen time). The relative risk for development of DCS increases with greater residual nitrogen times and shorter PFSI (Fig. 143-10).[34] For example, the risk for development of DCS is seven times greater for PFSIs of 12 hours after a dive to 130 fsw than for PFSIs of 24 hours after a dive to 60 fsw.[34] Long PFSIs (up to 48 hours) may be necessary to reduce the risk of DCS after deep, multiday repetitive diving, particularly if the dives required decompression stops (exceeding the no-decompression limits).[68] Some dive computers calculate time-to-flight intervals, which tend to be somewhat shorter than most guidelines based on residual nitrogen timetables. Flying should be delayed for at least 12 hours after diving if less than 2 hours of total dive time was accumulated in the preceding 48 hours. For multiple-day, unlimited diving, flying should be delayed for at least 24 hours. It is prudent to admit all recompressed patients or to advise them to remain within 60 minutes of the hyperbaric facility for 24 hours. Patients recompressed after DCS or AGE should not fly for 72 hours.

The U.S. Navy's guidelines recommend that the patient not return to diving for 7 days after recompression for type I DCS and

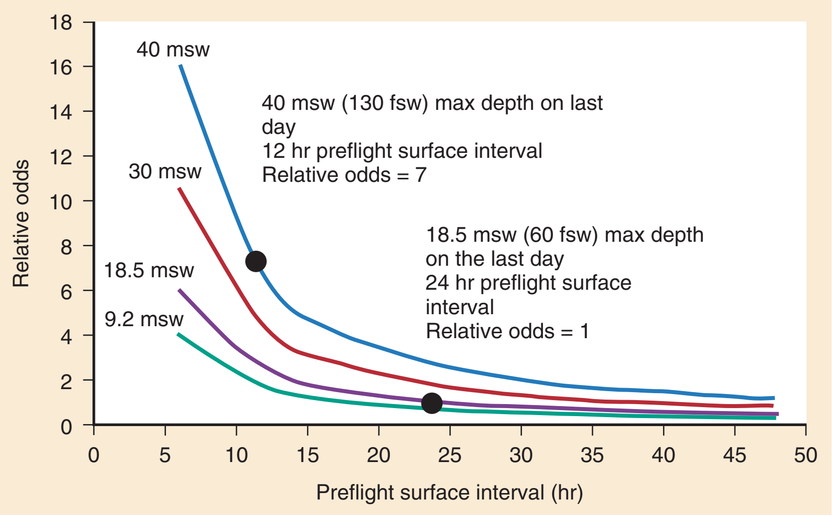


Figure 143-10. The risk of decompression sickness relative to flying. *fsw,* feet of seawater; *msw,* meters of seawater. (From Freiberger JJ, et al: The relative risk of decompression sickness during and after air travel following diving. Aviat Space Environ Med 73:983, 2002.)

www.ketabpezeshki.com 66485457-66963820

for 4 weeks after type II DCS.[3] The sport diver who experiences DCS type II symptoms or AGE should probably never dive again.

After treatment for pulmonary barotrauma, evaluate the diver with a spiral volumetric chest CT scan to determine whether there are any preexisting pathologic conditions (e.g., bullae) that could put the diver at risk for recurrence before further diving.[69] Chest CT is not recommended in routine medical screening before participation in scuba diving without a history of pulmonary barotrauma.

Echocardiography to assess for a PFO is often recommended for divers with severe or recurrent neurologic DCS.[70,71] A substantial amount of venous gas must embolize through the PFO for significant symptoms to occur; that is unlikely to happen in conservative depth-time profiles. A diver with a diagnosed PFO should weigh the risks of continuing to dive and the risks of surgical repair.

KEY CONCEPTS

- Treatment with 100% oxygen is the initial therapy for all diving emergencies until the diagnoses can be determined. It has been demonstrated to reduce the morbidity and mortality related to decompression illness and can be helpful in patients with pneumothorax.
- Intravenous hydration is important for DCS but may not be as important for AGE.
- The Trendelenburg position, once thought to reduce arterial gas cerebral embolization, is no longer recommended.
- The majority of dive injuries are diagnosed on the basis of the focused dive history and physical examination alone and are best differentiated into disorders of descent, disorders of depth, and disorders of ascent. The *U.S. Navy Diving Manual* and the Divers Alert Network (DAN) are valuable resources for the clinician presented with a diving emergency. DAN provides a 24-hour medical emergency hotline at 1-919-684-9111 (collect calls are accepted) and a nonemergency advisory line Monday through Friday, 8:30 AM to 5 PM Eastern time, at 1-919-684-2948 or 1-800-446-2671. Imaging and laboratory studies are not useful for ruling in decompression and should not delay definitive recompression therapy.
- With the exception of DCS, AGE, and possibly carbon monoxide poisoning from contaminated air, most dive-related disorders can be treated without recompression therapy. Recompression treatment is recommended for patients with DCS and AGE.
- Before initiation of recompression therapy, ensure that endotracheal tube and urinary catheter balloons are not inflated with air.
- After multiple-day unlimited diving, flying should be delayed for at least 24 hours.
- Unlike patients with spinal cord trauma, patients experiencing DCS may have patchy or unequally distributed sensory and motor findings. If inflation of a blood pressure cuff to 150 to 200 mm Hg relieves joint pain, type I DCS is suggested.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Brylske A: A brief history of diving: Part I. *Dive Training* 1994.
2. Brylske A: A brief history of diving: Part II. *Dive Training* 1994.
3. *U.S. Navy Diving Manual Revision 6*. Washington, DC: U.S. Department of the Navy; 2008.
4. Pollock NW, ed: *Diver's Alert Network: Annual Diving Report*. Durham, NC: Diver's Alert Network; 2008.
5. Bove AA, Davis JC: *Bove and Davis' Diving Medicine*, 4th ed. Philadelphia: WB Saunders; 2004.
6. Green SM, Rothrock SG, Green EA: Tympanometric evaluation of middle ear barotrauma during recreational scuba diving. *Int J Sports Med* 1993; 14:411-415.
7. Brown M, Jones J, Krohmer J: Pseudoephedrine for the prevention of barotitis media: A controlled clinical trial in underwater divers. *Ann Emerg Med* 1992; 21:849-852.
8. DeGorordo A, Vallejo-Manzur F, Chanin K, Varon J: Diving emergencies. *Resuscitation* 2003; 59:171-180.
9. Melamed Y, Shupak A, Bitterman H: Medical problems associated with underwater diving. *N Engl J Med* 1992; 326:30-35.
10. Moon RE: Treatment of diving emergencies. *Crit Care Clin* 1999; 15:429-456.
11. Cheshire WP Jr, Ott MC: Headache in divers. *Headache* 2001; 41:235-247.
12. Neubauer B, Mutzbauer TS, Tetzlaff K: Exposure to soda-lime dust in closed and semi-closed diving apparatus. *Aviat Space Environ Med* 2000; 71:1248-1251.
13. Landon CW: Gastrointestinal barotrauma in scuba divers. *West J Med* 1981; 135:242.
14. Cramer FS, Heimbach RD: Stomach rupture as a result of gastrointestinal barotrauma in a SCUBA diver. *J Trauma* 1982; 22:238-240.
15. Neuman TS, Bove AA, O'Connor RD, Kelsen SG: Asthma and diving. *Ann Allergy* 1994; 73:344-350.
16. Coetmeur D, Briens E, Dassonville J, et al: [Asthma and scuba diving: Absolute contraindication? in all asthma patients?]. *Rev Mal Respir* 2001; 18(Pt 1):381-386.
17. Harrison D, Lloyd-Smith R, Khazei A, Hunte G, Lepawsky M: Controversies in the medical clearance of recreational scuba divers: Updates on asthma, diabetes mellitus, coronary artery disease, and patent foramen ovale. *Curr Sports Med Rep* 2005; 4:275-281.
18. British Thoracic Society Fitness to Dive Group, Subgroup of the British Thoracic Society Standards of Care Committee: British Thoracic Society guidelines on respiratory aspects of fitness for diving. *Thorax* 2003; 58:3-13.
19. Balk M, Goldman JM: Alveolar hemorrhage as a manifestation of pulmonary barotrauma after scuba diving. *Ann Emerg Med* 1990;19:930-934.
20. Kizer KW: Dysbaric cerebral air embolism in Hawaii. *Ann Emerg Med* 1987; 16:535-541.
21. Masurel G: [The value of ultrasonic detection of circulating bubbles in animal and man—the contribution to physiopathogenesis of a decompression accident]. *Schweiz Z Sportmed* 1989; 37:41-44.
22. Baj Z, Olszanski R, Majewska E, Konarski M: The effect of air and nitrox divings on platelet activation tested by flow cytometry. *Aviat Space Environ Med* 2000; 71:925-928.
23. Spencer MP, Clarke HF: Precordial monitoring of pulmonary gas embolism and decompression bubbles. *Aerospace Med* 1972; 43:762-767.
24. Butler BD, Hills BA: The lung as a filter for microbubbles. *J Appl Physiol* 1979; 47:537-543.
25. Brubakk AO, Neuman TS: *Bennett and Elliott's Physiology and Medicine of Diving*, 5th ed. Philadelphia: WB Saunders; 2003.
26. St Leger Dowse M, Bryson P, Gunby A, Fife W: Comparative data from 2250 male and female sports divers: Diving patterns and decompression sickness. *Aviat Space Environ Med* 2002; 73:743-749.
27. Lairez O, et al: Risk of neurological decompression sickness in the diver with a right-to-left shunt: Literature review and meta-analysis. *Clin J Sport Med* 2009; 19:231-235.
28. Gempp E, Blatteau JE: Decompression sickness with a right-to-left shunt. *Clin J Sport Med* 2009; 19:512-513; author reply 513.
29. Moon RE, Camporesi EM, Kisslo JA: Patent foramen ovale and decompression sickness in divers. *Lancet* 1989; 1:513-514.
30. Reul J, Weis J, Jung A, Willmes K, Thron A: Central nervous system lesions and cervical disc herniations in amateur divers. *Lancet* 1995; 345:1403-1405.
31. Knauth M, et al: Cohort study of multiple brain lesions in sport divers: Role of a patent foramen ovale. *BMJ* 1997; 314:701-705.
32. Tomassoni AJ: Cardiac problems associated with dysbarism. *Cardiol Clin* 1995; 13:266-271.
33. Van Liew HD, Flynn ET: Direct ascent from air and N_2-O_2 saturation dives in humans: DCS risk and evidence of a threshold. *Undersea Hyperb Med* 2005; 32:409-419.
34. Freiberger JJ, et al: The relative risk of decompression sickness during and after air travel following diving. *Aviat Space Environ Med* 2002; 73:980-984.
35. Vann RD, Butler FK, Mitchell SJ, Moon RE: Decompression illness. *Lancet* 2011; 377:153-164.
36. Dick AP, Massey EW: Neurologic presentation of decompression sickness and air embolism in sport divers. *Neurology* 1985; 35:667-671.
37. Bayne CG, Hunt WS, Johanson DC, Flynn ET, Weathersby PK: Doppler bubble detection and decompression sickness: A prospective clinical trial. *Undersea Biomed Res* 1985; 12:327-332.
38. Eckenhoff RG, Olstad CS, Carrod G: Human dose-response relationship for decompression and endogenous bubble formation. *J Appl Physiol* 1990; 69:914-918.
39. Ikeda T, Okamoto Y, Hashimoto A: Bubble formation and decompression sickness on direct ascent from shallow air saturation diving. *Aviat Space Environ Med* 1993; 64:121-125.
40. Ikeda T, Suzuki S, Shimizu K, Okamoto Y, Llewellyn ME: M-mode ultrasonic detection of microbubbles following saturation diving: A case report and proposal for a new grading system. *Aviat Space Environ Med* 1989; 60:166-169.
41. Fife WP, Simmang C, Kitzman JV: Susceptibility of fetal sheep to acute decompression sickness. *Undersea Biomed Res* 1978; 5:287-292.
42. Stock MK, et al: Responses of fetal sheep to simulated no-decompression dives. *J Appl Physiol* 1980; 48:776-780.
43. Bolton ME: Scuba diving and fetal well-being: A survey of 208 women. *Undersea Biomed Res* 1980; 7:183-189.
44. Turner G, Unsworth I: Intrauterine bends? *Lancet* 1982; 1:905.
45. Cales RH, Humphreys N, Pilmanis AA, Heilig RW: Cardiac arrest from gas embolism in scuba diving. *Ann Emerg Med* 1981; 10:589-592.
46. Evans DE, Kobrine AI, Weathersby PK, Bradley ME: Cardiovascular effects of cerebral air embolism. *Stroke* 1981; 12:338-344A.
47. Ball R: Effect of severity, time to recompression with oxygen, and re-treatment on outcome in forty-nine cases of spinal cord decompression sickness. *Undersea Hyperb Med* 1993; 20:133-145.
48. Wilmshurst PT, Nuri M, Crowther A, Webb-Peploe MM: Cold-induced pulmonary oedema in scuba divers and swimmers and subsequent development of hypertension. *Lancet* 1989; 1:62-65.
49. Adkisson GH, Meredith AP: Inner ear decompression sickness combined with a fistula of the round window. Case report. *Ann Otol Rhinol Laryngol* 1990; 99(Pt 1):733-737.
50. Hyldegaard O, Moller M, Madsen J: Effect of He-O_2, O_2, and N_2O-O_2 breathing on injected bubbles in spinal white matter. *Undersea Biomed Res* 1991;18:361-371.
51. Longphre JM, Denoble PJ, Moon RE, Vann RD, Freiberger JJ: First aid normobaric oxygen for the treatment of recreational diving injuries. *Undersea Hyperb Med* 2007; 34:43-49.
52. Fahlman A, Dromsky DM: Dehydration effects on the risk of severe decompression sickness in a swine model. *Aviat Space Environ Med* 2006; 77:102-106.
53. Gempp E, Blatteau JE, Pontier JM, Balestra C, Louge P: Preventive effect of pre-dive hydration on bubble formation in divers. *Br J Sports Med* 2009; 43:224-228.
54. Brunner FP, Frick PG, Buehlmann AA: Post-decompression shock due to extravasation of plasma. *Lancet* 1964; 1:1071-1073.
55. Trytko B, Mitchell S: Extreme survival: A deep technical diving accident. *SPUMS J* 2005; 35:23-27.
56. Moon R: *Adjunctive Therapy for Decompression Illness*. Kensington, Md: UHMS Research Foundation; 2003.
57. Gempp E, Blatteau JE: Risk factors and treatment outcome in scuba divers with spinal cord decompression sickness. *J Crit Care* 2010; 25:236-242.
58. Tirpitz D, Schipke JD: Delayed recompression after SCUBA diving–induced barotrauma: A case report. *Aviat Space Environ Med* 1996; 67:266-267.
59. Myers RA, Bray P: Delayed treatment of serious decompression sickness. *Ann Emerg Med* 1985; 14:254-257.
60. Cianci P, Slade JB Jr: Delayed treatment of decompression sickness with short, no-air-break tables: Review of 140 cases. *Aviat Space Environ Med* 2006; 77:1003-1008.
61. Bennett M, Mitchell S, Dominguez A: Adjunctive treatment of decompression illness with a non-steroidal anti-inflammatory drug (tenoxicam) reduces compression requirement. *Undersea Hyperb Med* 2003; 30:195-205.

www.ketabpezeshki.com 66485457-66963820

62. Mitchell SJ: Lidocaine in the treatment of decompression illness: A review of the literature. *Undersea Hyperb Med* 2001; 28:165-174.
63. Acott CJ, Gorman DF: Decompression illness and nitrous oxide anaesthesia in a sports diver. *Anaesth Intensive Care* 1992; 20:249-250.
64. Moon RE, Sheffield PJ: Guidelines for treatment of decompression illness. *Aviat Space Environ Med* 1997; 68:234-243.
65. Parell GJ, Becker GD: Conservative management of inner ear barotrauma resulting from scuba diving. *Otolaryngol Head Neck Surg* 1985; 93:393-397.
66. Rudge FW: Ocular barotrauma caused by mask squeeze during a scuba dive. *South Med J* 1994; 87:749-750.
67. Becker GD: Recurrent alternobaric facial paralysis resulting from scuba diving. *Laryngoscope* 1983; 93:596-598.
68. Sheffield PJ: Flying after diving guidelines: A review. *Aviat Space Environ Med* 1990; 61:1130-1138.
69. Tetzlaff K, Neubauer B, Reuter M, Warninghoff V: Pulmonary barotrauma of a diver using an oxygen rebreathing diving apparatus. *Aviat Space Environ Med* 1996; 67:1198-1200.
70. Germonpre P, Dendale P, Unger P, Balestra C: Patent foramen ovale and decompression sickness in sports divers. *J Appl Physiol* 1998; 84:1622-1626.
71. Harrah JD, O'Boyle PS, Piantadosi CA: Underutilization of echocardiography for patent foramen ovale in divers with serious decompression sickness. *Undersea Hyperb Med* 2008; 35:207-211.

www.ketabpezeshki.com 66485457-66963820

Chapter 144

High-Altitude Medicine

Michael Yaron, Ryan D. Paterson, and Christopher B. Davis

EPIDEMIOLOGY

High-altitude illness represents a spectrum of clinical entities that have hampered the activities of mountaineers, merchants, military forces, aviators, and explorers throughout time. This illness is seen clinically in one of several forms that overlap and share a common pathophysiologic mechanism. Acute mountain sickness (AMS) is the relatively benign and self-limited presentation, whereas high-altitude pulmonary edema (HAPE) and high-altitude cerebral edema (HACE) represent the potentially life-threatening manifestations of high-altitude illness.

Worldwide, it is estimated that approximately 40 million individuals live above 8000 feet, and 25 million live above 10,000 feet.[1] Rather than these high-altitude residents, the groups at risk for acute altitude illnesses are those who ascend into mountainous regions. Mountain sports activities and tourism are attracting increasing numbers of participants each year. This, combined with the rapid ascent, made possible by air transportation results in more unacclimatized individuals at risk for high-altitude illness. More than 1 million visitors travel annually to the remote high mountain ranges of Asia, Africa, and South America.[1] Approximately 35 million visitors travel annually to high-altitude recreation areas in the western United States.[1]

The incidence of high-altitude illness depends on many variables, including the rate of ascent, previous altitude exposure, and individual genetic susceptibility.[2,3] Sleeping altitude, final altitude reached, and duration of stay at altitude are also risk factors for AMS development.[4] AMS is common (67% incidence) among mountain climbers on Mt. Rainier who ascend quickly (1 or 2 days) to 14,410 feet.[5] Trekkers who fly into the Khumbu region to explore the Mt. Everest area have a higher incidence of AMS (47%) compared with those who walk (23%).[6] Skiers who visit resorts in the western United States from sea level generally fly or drive to the region but sleep at relatively lower altitudes than the other groups mentioned. Among this population, AMS occurs in approximately 25%.[7] Given the large number of visitors (approximately 25 million) in Colorado each year, this is not a trivial matter. The incidence of HAPE varies from 0.01 to 2% in most studies but has reached 15.5% among soldiers flown directly to 14,500 feet without a chance to acclimatize at a lower altitude.[6,8] The incidence of HACE is lower, and although it frequently occurs with HAPE, it can be seen as an isolated entity. Both HAPE and HACE are more common with a longer duration of visit and higher sleeping altitude.

Age may be a relative risk factor. Most studies of children suggest that they have the same incidence of AMS as adults do.[9-12] One small study of tourists in Chile evaluated children 4 to 48 months old and found higher AMS scores and lower oxygen saturations compared with those of their parents.[13] Younger individuals (<20 years old) are more likely to have HAPE, although HAPE is extremely rare in children younger than 2 years. Gender does not affect the incidence of AMS[2]; however, women may have less risk for development of HAPE.[6,7,14,15] No relationship appears to exist between AMS development and the menstrual cycle.[16]

The number of older travelers visiting mountain resorts is increasing. Many of these individuals have underlying health problems, including lung disease (10%), heart disease (25%), and hypertension (30%). Despite these conditions, the risk for AMS development in adults older than 50 years may be less than in younger age groups.[2,17] One study found no difference in the incidence or severity of AMS in climbers older than 50 years compared with a matched cohort of younger climbers.[18] Nevertheless, there are indications that elders may not react well to acute high-altitude exposure. Pulmonary vital capacity decreases almost one third in elders ascending from sea level to 14,000 feet for 1 week, producing a large decrease in both oxygen saturation and maximal oxygen uptake during exercise.

DEFINITIONS

Moderate altitude is between 8000 and 10,000 feet of elevation. Although most people do not experience significant arterial oxygen desaturation until they reach higher altitudes, high-altitude illness is common with rapid ascent above 8000 feet, and individuals with underlying medical problems may be predisposed to development of altitude illness at lower levels.

High altitude is between 10,000 and 18,000 feet. Most serious altitude illness occurs at these levels. The pathophysiologic effects of high altitude begin when the oxygen saturation of the arterial blood begins to fall below the 90% level. The sigmoidal shape of the oxyhemoglobin dissociation curve prevents a significant fall of arterial oxygen saturation ($Sa{O_2}$) in most individuals until an altitude of approximately 12,000 feet. At this altitude, the steep portion of the curve is encountered, and marked oxygen desaturation may occur with relatively small increases in altitude (Fig. 144-1). Some predisposed individuals may desaturate to less than 90% at altitudes as low as 8000 feet.

www.ketabpezeshki.com 66485457-66963820

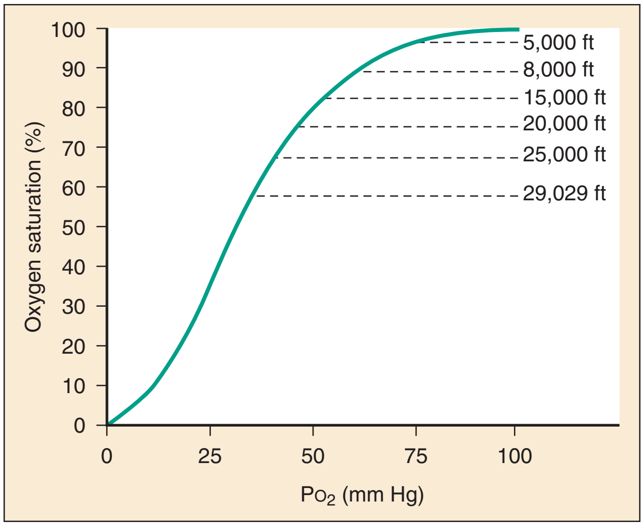


Figure 144-1. Oxygen-hemoglobin dissociation curve. Approximate oxygen saturations are marked for several altitudes. *PO_2*, partial pressure of oxygen. (Data for 15,000-29,029 feet from Sutton JR, et al: Operation Everest II: Oxygen transport during exercise at extreme simulated altitude. J Appl Physiol 64:1309, 1988.)

Extreme altitude is above 18,000 feet. At this height, complete acclimatization generally is not possible, and long visits above this level result in progressive deterioration.

ENVIRONMENTAL CONSIDERATIONS

Barometric pressure decreases logarithmically as the altitude rises. The partial pressure of oxygen (PO_2) in the atmosphere also decreases as altitude rises, but it remains a constant 20.93% of the barometric pressure. The shape of the earth is slightly flat at the poles and bulging at the equator. The atmospheric envelope that surrounds the earth has a similar shape; therefore, the barometric pressure is lower at higher latitudes than it is at the equator. For example, it has been calculated that it would be impossible for a climber to reach the summit of Mt. Everest without supplemental oxygen if the mountain happened to be in a more northern latitude.[19]

The atmospheric envelope also undergoes a seasonal tide that causes a variation in its local thickness. This results in barometric pressures that are lower and "relative altitudes" that are higher during the winter season. Local weather can also have a significant effect on barometric pressure from day to day. A low-pressure front can reduce the barometric pressure 12 to 40 mm Hg (500-2500 feet) and result in a significant temporary increase in relative altitude.

ACCLIMATIZATION

The term *acclimatization* refers to the series of integrated adaptations that take place at high altitude, which tend to restore the oxygen pressures within the tissues toward normal sea-level values despite the lowered PO_2 of the atmosphere. These processes occur gradually and involve multiple systems from protein synthesis to respiratory, cardiovascular, and hematologic adjustments. Gradual ascents made by mountaineers during several weeks have allowed the successful summiting of many of the world's highest peaks, including Mt. Everest (29,029 feet), without supplemental oxygen. Without this gradual approach to allow acclimatization, however, rapid exposure to extreme altitude results in loss of consciousness, and death may occur in a matter of minutes.

Box 144-1 Alveolar Gas Equation

$$PAO_2 = PIO_2(PACO_2/R)$$

PAO_2	Partial pressure of oxygen in alveolus
PIO_2	Partial pressure of oxygen in inspired air
$PACO_2$	Partial pressure of carbon dioxide in alveolus
R	Respiratory quotient

Acclimatization begins at the altitude that causes the oxygen saturation of arterial blood to fall below sea-level values. The altitude at which this occurs depends on the rate of ascent, the duration of exposure, and the individual's physiology. People with preexisting conditions that reduce oxygen saturation or content may have a decreased altitude tolerance. Of particular importance are both acute and chronic cardiac and respiratory illnesses. Most healthy, unacclimatized visitors to high altitude will not desaturate significantly (to less than 90%) until they reach elevations higher than 8000 feet.[1]

The risk of high-altitude illness also depends on an individual's inherent ability to acclimatize. Some people acclimatize easily without having any clinical symptoms. Others may transiently have AMS during acclimatization, and a few have marked reactions to altitude exposure, developing severe altitude illness. This variability involves many genetic and epigenetic factors that moderate the process of acclimatization.[3,20] Previous successful acclimatization may be predictive of future responses for adults in similar conditions, but this may not be the case for children.[21]

One of the most important physiologic changes that occurs during acclimatization is an increase in minute ventilation, causing a decrease in the partial pressure of carbon dioxide ($PACO_2$). The alveolar gas equation states that as the $PACO_2$ decreases, a corresponding increase in PAO_2 occurs, thereby increasing arterial oxygenation (Box 144-1). Thus the level of ventilation determines alveolar oxygen for a given inspired oxygen tension.

When a person arrives at high altitude, the peripheral chemoreceptors in the carotid bodies respond to a decrease in PAO_2 and signal the respiratory control center in the medulla to increase ventilation. This increase in ventilation is known as the hypoxic ventilatory response (HVR), which may be inhibited or stimulated by numerous factors, including ethanol, sleep medications, caffeine, cocoa, prochlorperazine, and progesterone. The magnitude of the HVR varies among individuals and may be genetically predetermined.[22]

As ventilation increases, a respiratory alkalosis occurs that acts as a negative feedback system on the central respiratory center, limiting any further increase in ventilation. Within 24 to 48 hours of ascent, the kidneys excrete bicarbonate in an effort to compensate for the alkalosis. As the pH normalizes, ventilation rises slowly, reaching a maximum after 6 to 8 days. This process is enhanced by acetazolamide. The ability to achieve an adequate HVR varies and is related to the ability to acclimatize. A low HVR and relative hypoventilation are implicated in the pathogenesis of both AMS and HAPE.[23] For the majority of people with intermediate HVRs, however, ventilatory drive probably has no predictive value for AMS development.[24]

The release of catecholamines on ascent stimulates the circulatory system to increase cardiac output. This is manifested by an elevation in heart rate, blood pressure, cardiac output, and venous tone.[25] Except at extreme altitudes, acclimatization results in the gradual return of the resting heart rate to near sea-level values. Resting relative tachycardia is evidence of poor acclimatization. As the altitude increases, a decrease in maximal heart rate capacity occurs, and at the limits of acclimatization, maximal and resting heart rates converge.

www.ketabpezeshki.com 66485457-66963820

The hematopoietic response to high-altitude acclimatization consists of an increase in both hemoglobin and the number of red blood cells. An early increase of up to 15% occurs in mean corpuscular hemoglobin concentration after rapid ascent to high altitude. This is primarily a result of a fluid shift into the extravascular space. Long-term acclimatization leads to an increase in plasma volume and total blood volume. Erythropoietin is secreted in response to hypoxemia within hours of ascent, which in turn stimulates the production of red blood cells, leading to new circulatory red blood cells in 4 or 5 days.[26] During the next 2 months, red blood cell mass increases in proportion to the degree of hypoxemia.[27]

Hypoxemia also results in an increase in 2,3-diphosphoglycerate, causing a rightward shift of the oxyhemoglobin dissociation curve, which favors a release of oxygen from the blood to the tissues. This is counteracted by the leftward shift of the oxyhemoglobin dissociation curve caused by the respiratory alkalosis from hyperventilation. The result is a net null change in the oxyhemoglobin curve and an increase in oxygen-hemoglobin binding in the lung, which raises Sao_2.[28,29] Some individuals with mutant hemoglobin and high oxygen-hemoglobin affinity are found to acclimatize more efficiently than their normal counterparts at moderate altitudes.[30]

PATHOPHYSIOLOGY

The clinical syndromes of high-altitude illness are not discrete entities but represent a spectrum of intertwined pathophysiologic mechanisms. AMS and HACE appear to represent differing manifestations of altitude illness on the same continuum, whereas HAPE appears to have a somewhat independent pathophysiologic mechanism.

The symptoms of AMS develop several hours after arrival at high altitude, whereas the development of HAPE and HACE generally requires several days of altitude exposure. Because hypobaric hypoxemia occurs within minutes of arrival, it cannot be the direct cause of high-altitude illness. Instead, it appears to be the initiating factor for a complex pathologic process that leads to the development of the various clinical syndromes. The proposed mechanisms for the development of AMS, HAPE, and HACE are represented schematically in Figure 144-2.

A poor HVR resulting in relative hypoventilation may be due to either the individual's genetic predisposition or extrinsic factors, such as medications, that decrease the ventilatory drive. Whenever the HVR is decreased, the protective effects of hyperventilation are lost and the hypoxemia of high-altitude exposure is exacerbated.

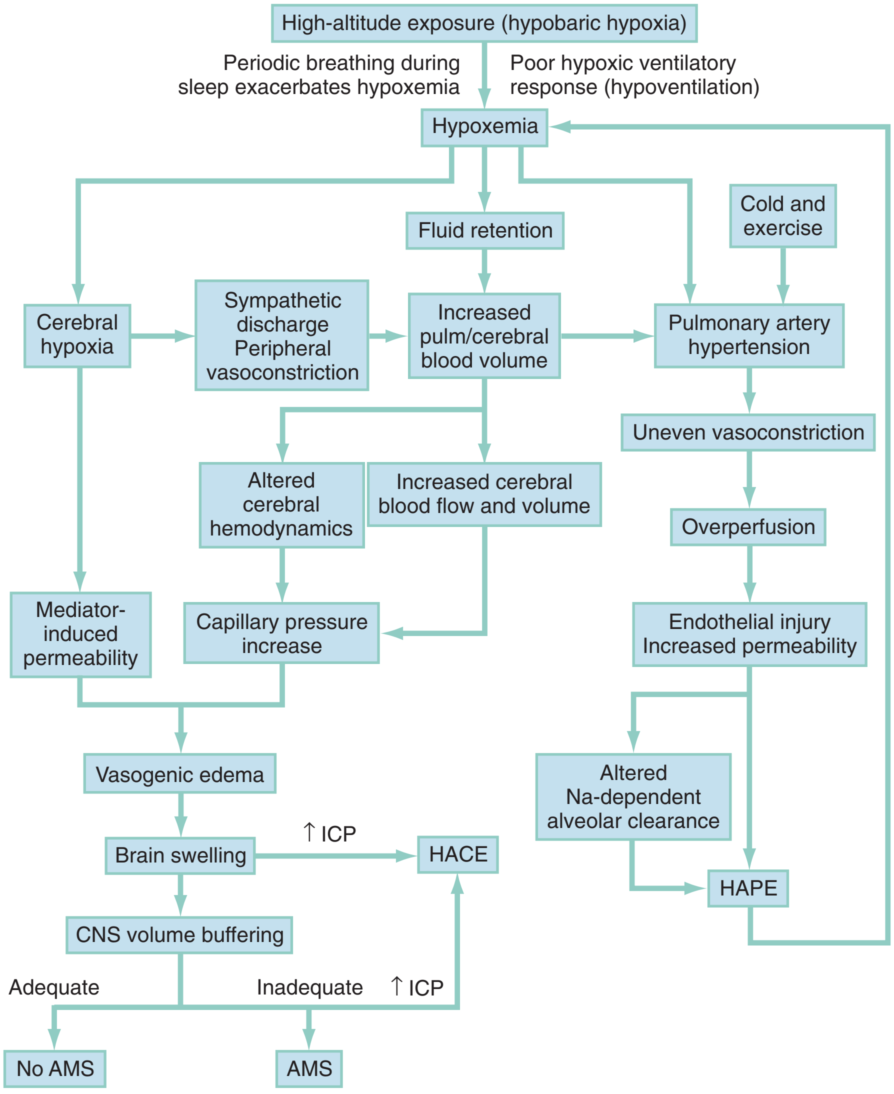


Figure 144-2. Proposed mechanisms for the development of acute mountain sickness (*AMS*), high-altitude pulmonary edema (*HAPE*), and high-altitude cerebral edema (*HACE*). *CNS,* central nervous system; *ICP,* intracranial pressure.

www.ketabpezeshki.com 66485457-66963820

The centrally mediated periodic breathing associated with high-altitude exposure may result in periods of apnea during sleep, causing severe arterial oxygen desaturation, which further exacerbates hypoxemia.[31] Significant hypoxemia initiates multiple systemic responses that involve the circulatory, pulmonary, endocrine, and central nervous systems.

Hypoxemia alters fluid homeostasis, resulting in a generalized fluid retention followed by the shift of fluid into the intracellular spaces. This is manifested by peripheral edema, decreased urinary output, and increased body weight in patients with AMS. Several different mechanisms may account for these fluid shifts, including arginine vasopressin levels and sympathetic stimulation that may be centrally mediated.[32,33] Arginine vasopressin levels are elevated in some cases of AMS and HAPE and decreased in others.[34,35] Aldosterone, plasma renin, and atrial natriuretic levels are higher in people with AMS.[35-37]

The hypoxemia that results from high-altitude exposure also causes an increase in pulmonary artery resistance, leading to pulmonary hypertension and elevated capillary pressures that play the cardinal role in the development of HAPE. Exercise and cold stress at altitude may increase hypoxemia and exacerbate pulmonary hypertension.[38,39] Pulmonary blood volumes and pulmonary hypertension are increased by sympathetic nervous system stimulation and catecholamine release.[40,41] In HAPE-susceptible individuals, pulmonary hypertension becomes severe, and an uneven distribution of pulmonary vasoconstriction results in overperfusion, increased capillary pressures, distention, and leakage in the remaining vessels.[42-45] This explains the patchy nature of the infiltrate seen on a chest radiograph with HAPE (Fig. 144-3). The mechanism for the uneven vasoconstriction in HAPE may be due to decreased nitric oxide bioavailability at the pulmonary tissue level, also leading to increased endothelial leakage and extracellular edema.[46-48] Overperfusion of a restricted vascular bed as the pathogenesis of HAPE is supported by the observation that people born with congenital unilateral absence of a pulmonary artery are susceptible to HAPE.[49] These individuals deliver their entire cardiac output to one lung, predisposing them to overperfusion injury.

The importance of the excessive rise in pulmonary artery pressure in HAPE is emphasized because lowering of the pressure during ascent prevents HAPE.[50] This implicates increased vascular pressure rather than inflammation as the primary cause of the vascular leak. The resultant mechanical shear forces lead to endothelial damage and changes in membrane permeability.[48] Inflammatory mediators appear to be a secondary response to the mechanical injury caused by overperfusion.[44,51] Once the vascular leak occurs and alveolar fluid accumulates, a defect in transepithelial sodium transport impairs the clearance of alveolar fluid and contributes to HAPE development.[52-54] Alveolar fluid clearance is upregulated by beta-adrenergic agonists, and inhaled beta-agonists may successfully prevent and treat HAPE.[54,55]

Preexisting inflammation may also be a risk factor for HAPE. A preexisting respiratory infection during ascent to high altitude increases susceptibility to HAPE, particularly in children.[56] Inflammation may "sensitize" the pulmonary endothelium to mechanical injury and increase susceptibility to alveolar fluid accumulation and HAPE during ascent.

The clinical manifestations of AMS and HACE are the result of central nervous system dysfunction. The mechanistic theories involve altered cerebral hemodynamics and inflammatory mediators.[57,58] It is known that the vasodilatory response to hypoxemia causes an increase of cerebral blood flow and volume.[59,60] The resulting hypoxemia leads to impaired vascular autoregulation, causing increased pressure transmission to the brain's capillary beds.[33,61,62] In addition, systemic hypertension from strenuous exercise at high altitude may overwhelm the brain vasculature, resulting in transcapillary leakage and vasogenic edema. In susceptible individuals, these hemodynamic changes are likely to contribute to clinical manifestations of AMS and HACE.[63-65]

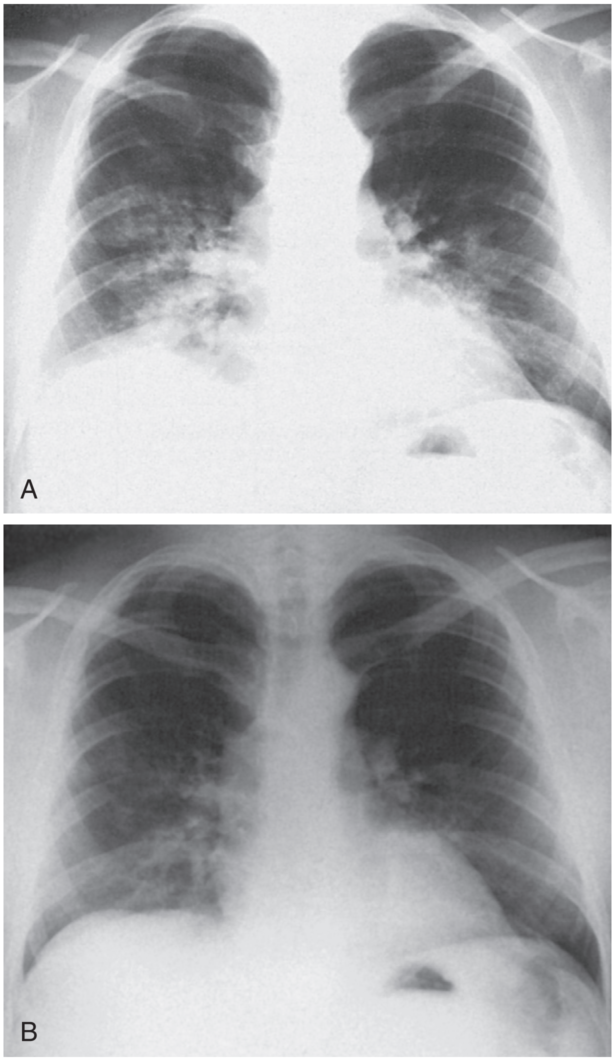


Figure 144-3. Chest radiograph of a patient with high-altitude pulmonary edema. A, Before treatment. B, After treatment. (Courtesy Richard Nicholas, MD.)

Additional circumstances, however, may be necessary for the development of vasogenic edema and clinical symptoms. Inflammatory mediators may contribute to edema formation. Vascular endothelial growth factor, the inducible form of nitric oxide synthase, reactive cytokines, and free radical formation may mediate brain endothelial permeability. The roles that these play in the pathophysiologic process of altitude illness remain unclear.[57,66-69]

Whereas vasogenic edema has been implicated in the origin of AMS, magnetic resonance imaging (MRI) reveals signal changes present in subjects with and without clinical AMS. Thus the significance of vasogenic edema in AMS is questioned.[70] In patients with HACE, MRI studies reveal white matter changes consistent with vasogenic edema that correlate with symptoms.[71] Despite the unclear role of vasogenic edema, a breakdown of the blood-brain barrier remains the leading theory in AMS and HACE pathophysiology and is most likely due to a combination of mechanical factors and biochemical mediation of permeability.[59,72]

MRI data do reveal that cytotoxic edema is also present in severe AMS.[73,74] Cytotoxic edema results from hypoxic cell damage most often associated with ischemic hypoxic insults. Failure of the adenosine triphosphate–dependent sodium pump allows sodium to

www.ketabpezeshki.com 66485457-66963820

accumulate within the cells, increasing intracellular water to maintain the osmotic equilibrium. Cytotoxic intracellular water accumulation may not be the primary mechanism for the development of HACE but rather the result of the increased cell ischemia initially caused by hemodynamic changes, vasogenic edema, biochemical mediators, and increased ratios of brain volume to intracranial space.[71,75]

Hypobaria also appears to play a role in the development of AMS. Sea-level experiments that expose subjects to hypoxia alone do not result in AMS; however, when hypoxia is combined with hypobaria, AMS does occur.[76,77] Although microbubble formation and fluid retention may be a mechanism, the exact pathophysiologic role of hypobaria in altitude illness is unclear.[77]

These responses to hypoxia and altitude exposure occur in both susceptible individuals and those who remain free of AMS. Thus there must be an overall factor in a subject at risk for AMS that fails to compensate for the changes associated with altitude exposure. The "tight fit" hypothesis is proposed to explain AMS development and its inherent individual susceptibility.[59,78] This theory suggests that the development of AMS and HACE is due to a lack of intracranial space to accommodate increasing volume from brain swelling and edema that develop at altitude.[58] The adequacy of the space to buffer changes in brain and cerebrospinal fluid (CSF) volume plays a key role in determining which individuals have symptoms of altitude illness. As brain volume increases from increased cerebral blood volume, the volume-buffering capacity of the central nervous system may prevent an immediate rise of intracranial pressure. As brain volume increases, the intracranial CSF is displaced through the foramen magnum into the space available in the spinal canal. Increased absorption of CSF by the arachnoid villi and decreased CSF production also occur. Individuals with less intracranial and intraspinal CSF buffering capacity have less compliance and become more symptomatic (i.e., develop AMS) from mild brain swelling. This tight fit hypothesis is supported by lumbar puncture, MRI, and computed tomography studies.[59,78-80]

ACUTE MOUNTAIN SICKNESS

Clinical Presentation

The symptoms of mild AMS are similar to those of a viral syndrome, an ethanol "hangover," or simple physical exhaustion. The vague nature of this presentation results in many misdiagnoses. In the setting of recent high-altitude exposure, these symptoms warrant a presumptive diagnosis of AMS until it is proven otherwise.

For the diagnosis of AMS, a patient must be in the setting of a recent gain in altitude, be at the new altitude for at least several hours, and report a headache *plus* at least one of the following symptoms: gastrointestinal upset (anorexia, nausea, or vomiting), general weakness or fatigue, dizziness or lightheadedness, or difficulty in sleeping (Box 144-2).[81] The headache may vary from mild to severe, is generally bitemporal and throbbing in nature, and is worse during the night and on awakening or on suddenly becoming upright. Anorexia and nausea, with or without vomiting, are common, and the other symptoms described can range in severity from mild to incapacitating. The disturbance of sleep caused by periodic breathing is common in all visitors to high altitudes but is exacerbated in the setting of AMS. The symptoms of AMS develop within a few hours after arrival at high altitude and generally reach maximum severity between 24 and 48 hours, followed by a gradual resolution. Most individuals become symptom free by the third or fourth day. Those who do not resolve their symptoms should descend because they may develop more serious manifestations of altitude illness, especially if they continue to ascend.

Box 144-2 Acute Mountain Sickness

Incidence: 12 to 67%, varies with rate of ascent and individual susceptibility; rare below 8000 feet, most common with rapid ascent to altitudes above 10,000 feet
Symptoms and signs: Headache, anorexia, nausea, fatigue, dizziness, difficulty sleeping
Treatment: Mild cases are usually self-limited and do not require treatment; discontinue ascent, rest; for moderate case, administer acetazolamide; ibuprofen, aspirin, or acetaminophen for headache; prochlorperazine for nausea; supplemental oxygen if available; descend if persistent or severe; add dexamethasone in severe cases
Prevention: Gradual ascent to allow acclimatization; high-carbohydrate diet, avoidance of ethanol or smoking; acetazolamide if ascent is rapid or known history of recurrent acute mountain sickness

Among infants and very young children, AMS is manifested by increased fussiness, decreased playfulness, decreased appetite, and sleep disturbance.[10] In most cases of AMS in very young children, all of these symptoms are present. In children, many of the symptoms manifested by AMS can also result from the disruption of normal routine. A change in environment, sleeping accommodation, or eating habits can result in a fussy, unhappy child. In addition, the occurrence of an acute illness can also mimic AMS in young children. If occult bacteremia or another serious illness is suspected in a young child, descent to lower altitude is recommended to eliminate the confounding variable of altitude illness.

There are no diagnostic physical findings in cases of mild AMS. Although dyspnea on exertion is universal at high altitudes, dyspnea at rest is an early indication of HAPE, and a careful examination for pulmonary edema is indicated. Similarly, any evidence of cerebellar dysfunction, such as mild ataxia or alteration in mentation, mandates descent because of early evidence of HACE.

Ultrasonography is emerging as an early, noninvasive diagnostic tool to assess intracranial pressure.[82] Studies have demonstrated that elevated intracranial pressure is associated with AMS and HACE. Increasing intracranial pressure correlates directly with optic nerve sheath diameter.[83] It is possible to demonstrate that subjects with symptoms and signs of AMS or HACE have enlarged optic nerve sheath diameters, which may be a useful adjunct in the diagnosis of AMS and HACE.[84,85]

Management

The management of AMS should include strict adherence to the principle that after the symptoms of altitude illness occur, further ascent to a higher sleeping altitude is contraindicated. Halting of ascent or activity to allow further acclimatization may reverse the symptoms; however, continuation of the ascent exacerbates the underlying pathologic processes and may lead to disastrous results. The presence of neurologic abnormalities (e.g., ataxia or altered mentation) or evidence of severe pulmonary edema mandates immediate descent because these signs indicate a progression of AMS to the more dangerous forms of altitude illness.

Most mild AMS is treated by stopping of further ascent and waiting for acclimatization. This may take 1 to 4 days. AMS that becomes worse or does not respond to maintenance of altitude, rest, and pharmacologic intervention necessitates descent. A descent of 1500 to 3000 feet effectively reverses high-altitude illness in most cases. Descent should be continued until improvement is seen, and efforts to minimize exertion should be instituted during the descent.

www.ketabpezeshki.com 66485457-66963820

Supplemental oxygen administration relieves AMS symptoms, including small amounts (1-2 L/min) during sleep. In the wilderness, oxygen tanks are heavy and are usually unavailable in adequate amounts; therefore, oxygen therapy is usually reserved for the more serious manifestations of high-altitude illness. In resort settings, oxygen may be readily available for use in the hotel or condominium. Hyperbaric therapy that simulates descent is also effective.

Treatment of headache, nausea, and insomnia can be beneficial during the course of mild AMS. Aspirin, ibuprofen, and acetaminophen are useful for the treatment of high-altitude headache. Narcotic analgesics should be avoided because of depression of the HVR and respiratory drive during sleep. For nausea and vomiting, prochlorperazine, unlike other antiemetics, stimulates the HVR.[86] Periodic breathing causes insomnia, which is best treated with the respiratory stimulant acetazolamide.[87] Doses of acetazolamide as low as 62.5 to 125 mg at bedtime may prevent periodic breathing and eradicate insomnia. Benzodiazepines and other sedative-hypnotics should be avoided because of their tendency to decrease ventilation during sleep. Some climbers experience unusual reactions to diazepam at high altitudes, including agitation, hallucinations, and disorientation. These reactions can occur in individuals who have previously used diazepam at lower altitudes without any difficulties.[88] Some studies suggest that low doses of benzodiazepines alone or in combination with acetazolamide are safe at high altitude.[89-92] Nonbenzodiazepine sleep agents (zolpidem and zaleplon) do not depress ventilation and may prove useful in AMS-related insomnia.[93]

Acetazolamide accelerates acclimatization and, if it is given early in the development of AMS, rapidly resolves symptoms. A dose of 250 mg of acetazolamide at the onset of symptoms and repeated twice daily is effective therapy for AMS.[94,95] The treatment of AMS in children is not formally studied, but anecdotal experience supports the use of acetazolamide in children.[96] The dose for children is 2.5 mg/kg/dose given twice daily to a maximum of 250 mg.

Acetazolamide is a carbonic anhydrase inhibitor that induces a renal bicarbonate diuresis, causing a metabolic acidosis that increases ventilation and arterial oxygenation. This respiratory stimulation improves sleep when the hypoxemia caused by periodic breathing is eradicated by acetazolamide. The diuretic effects attenuate fluid retention common in patients with AMS. This agent also lowers CSF volume and pressure, which may play an additional role in its therapeutic and prophylactic use. Non–carbonic anhydrase inhibitory effects of acetazolamide include chemoreceptor effects on ventilatory drive, alterations of cerebral blood flow, relaxation of smooth muscles, and upregulation of fluid resorption in the lungs.[97,98]

The most common adverse reactions to acetazolamide are paresthesias and polyuria. Less common reactions include nausea, drowsiness, tinnitus, and transient myopia. Carbonic anhydrase inhibition at the tongue causes dysgeusia, altering the flavor of carbonated beverages, including beer. Acetazolamide is a nonantibiotic sulfa compound that carries a low risk of cross-reactivity for individuals with an allergy to sulfa antibiotics.[99] Those with known sulfonamide allergy may consider administration of a trial dose of acetazolamide in a controlled environment before ascent. A history of anaphylaxis or severe skin reactions to any sulfa-containing medication makes the use of acetazolamide contraindicated. Acetazolamide should be avoided in breast-feeding mothers and pregnant women.

Dexamethasone is an effective alternative treatment of AMS. An initial dose of 8 mg is followed by 4 mg every 6 hours.[100] No significant adverse reactions are reported; however, symptoms can recur when the treatment is withdrawn. Although dexamethasone can resolve the symptoms of AMS, it does not play a role in acclimatization. Concurrent use with acetazolamide is advocated by some to promote acclimatization.[101,102] It is known to have anti-inflammatory properties, possibly to reduce cerebral blood flow,[103] and to block the action of vascular endothelial growth factor.[66] Reduction of AMS symptoms with the use of dexamethasone may be the result of these or its euphoric effects. We believe that dexamethasone should generally be reserved for use in the setting of acetazolamide intolerance or in more advanced cases of AMS, especially to help facilitate descent.

Individuals with AMS may resume their ascent after their symptoms resolve. Reascent with acetazolamide in these individuals is recommended. Caution in these susceptible individuals requires their understanding that should their symptoms recur, further ascent should be halted.

Prevention

Most of the symptoms of mild AMS are benign and well tolerated. These symptoms, however, can be unpleasant and debilitating to the point that travel, business, or vacation plans should be interrupted. Up to 50% of individuals with AMS report a decrease in activity.[7]

Slow ascent, allowing adequate time for acclimatization, is the best method of prevention; however, the time constraints of many vacationers often make slow ascent unrealistic. The major concern lies in the sleeping altitude during any individual ascent. Ideally, the first night should not be spent at an altitude higher than 9200 feet, with a subsequent increase (to a new sleeping altitude) of not more than 1600 feet each night. One extra night of acclimatization (at the same sleeping altitude) should be added for every 3000 to 5000 feet of altitude gain above 10,000 feet. Excursions during the day to higher altitudes with a return to a lower sleeping altitude aid in acclimatization.

Altitude preexposure regimens in artificially hypoxic environments have been evaluated to facilitate acclimatization. It appears that little protection from subsequent altitude exposure occurs with preexposure regimens lasting less than 8 to 12 hours.[104,105]

Mild to moderate exercise is thought to aid in acclimatization; however, overexertion can contribute to the development of AMS.[38] Maintenance of adequate hydration is also recommended. Guidelines for adequate hydration should target relatively clear (unconcentrated) urine and normal volume of urine output. Recommendations for hyperhydration are frequently given in the lay literature, yet no evidence supports this advice.[106,107] Drinking of excessive amounts of free water may lead to hyponatremia and possibly complicate altitude illness.

The rate of ascent and prior history of altitude illness should be considered in the assessment of the risk for development of altitude illness and the choice of prevention strategies (Table 144-1). Individuals in low-risk situations should not need medications for prophylaxis, and ascent should be gradual to prevent illness. In some cases, such as arrival at a high-altitude airport or the immediate dispatch of rescue personnel to high altitude, a slow ascent is impossible. Mountain climbers commonly ascend at rates that are higher than recommended, and some individuals continue to suffer AMS symptoms despite gradual ascent. Individuals who have a known susceptibility to the development of AMS and those for whom slow ascent is impractical fall into the moderate- and high-risk categories and should consider prophylactic medication in addition to gradual ascent.[4]

Numerous studies demonstrate the effectiveness of acetazolamide in prevention of AMS in adults.[5,6,108] Lower dosages provide prophylaxis similar to that of higher dosages with fewer adverse reactions. Many studies demonstrate that 250 mg twice daily starting 24 hours before ascent and continuing for the first 2 days at high altitude is effective. For avoidance of side effects, a dose of 125 mg given twice daily is effective.[4] Although it is unstudied, the recommended dosage of acetazolamide for AMS prophylaxis for children is 2.5 mg/kg/dose up to 125 mg total given twice daily,

www.ketabpezeshki.com 66485457-66963820

Table 144-1 Risk Categories for Acute Mountain Sickness

RISK CATEGORY	DESCRIPTION
Low	Individuals with no prior history of altitude illness and ascending to ≤9200 ft Individuals taking ≥2 days to arrive at 8200-9800 ft with subsequent increases in sleeping elevation <1600 ft/day
Moderate	Individuals with prior history of AMS and ascending to 8200-9200 ft in 1 day No history of AMS and ascending to >9200 ft in 1 day All individuals ascending >1600 ft/day (increase in sleeping elevation) at altitudes above 9800 ft
High	History of AMS and ascending to ≥9200 ft in 1 day All individuals with a prior history of HAPE or HACE All individuals ascending to >11,500 ft in 1 day All individuals ascending >1600 ft/day (increase in sleeping elevation) above >11,500 ft Very rapid ascents (e.g., Mt. Kilimanjaro)

Modified from Luks AM, et al: Wilderness Medical Society consensus guidelines for the prevention and treatment of acute altitude illness. Wilderness Environ Med 21:146-155, 2010.

AMS, acute mountain sickness; *HACE*, high-altitude cerebral edema; *HAPE*, high-altitude pulmonary edema.

Altitudes listed in the table refer to the altitude at which the person sleeps. Ascent is assumed to start from elevations <4000 ft. The risk categories described pertain to unacclimatized individuals.

and this weight-based approach may reduce side effects in smaller adults. Ibuprofen compared with acetazolamide is equally efficacious in preventing headache.[109]

Dexamethasone also prevents AMS.[103] The lowest effective dosage is 2 mg every 6 hours or 4 mg every 12 hours.[4,110] Some patients experience the rapid onset of AMS after dexamethasone is discontinued. Dexamethasone does not facilitate acclimatization but rather reduces nausea and enhances mood. In most cases, dexamethasone use should be reserved for treatment of AMS rather than for prophylaxis. Military or rescue personnel rapidly ascending to high altitude and individuals with acetazolamide intolerance are candidates for prophylaxis with dexamethasone. The combination of acetazolamide and dexamethasone may be more effective than either drug alone.[101]

Because of its antioxidant properties, *Ginkgo biloba* was proposed for preventive therapy of AMS. The results of several studies are mixed, with some supporting the use of ginkgo and others showing no evidence to support a role in AMS management.[111,112] These contradicting findings may be due to the variability of composition among commercially available ginkgo products, and thus determination of its clinical usefulness in the prevention or treatment of AMS is difficult.[113] Acetazolamide remains the compound of choice for AMS prophylaxis.

Oxygen is an effective prophylactic modality for rescue personnel. Adequate supplies should be available to ensure the safety of all team members for the entire duration of the rescue. Air drops of oxygen can be lifesaving when weather or terrain prevents the immediate arrival of rescue personnel.

HIGH-ALTITUDE PULMONARY EDEMA

HAPE is the most common fatal manifestation of severe high-altitude illness (Box 144-3). Although HAPE is uncommon below 10,000 feet, it can occur and even be fatal at altitudes as low as 8000 feet. Episodes occurring between 8000 and 10,000 feet are usually related to heavy exercise; but at higher altitudes, pulmonary edema can also occur at rest or with light activity.[42]

Box 144-3 High-Altitude Pulmonary Edema

Incidence: 0.01 to 15%, varies with rate of ascent; rare below 8000 feet and more common above 14,500 feet; usually occurs 2-4 days after arrival at high altitude

Symptoms and signs: Dyspnea at rest, cough, fatigue, headache, anorexia, cyanosis, rales, tachypnea, tachycardia

Treatment: Patients with mild cases may recover with bed rest; moderate cases can be treated with bed rest and supplemental oxygen if clinical monitoring is available; severe cases require oxygen and descent; use hyperbaric therapy if available; if oxygen or descent is unavailable, then nifedipine 30 mg slow-release every 12 hours; consider tadalafil 10 mg every 12 hours (unstudied)

Prevention: Gradual ascent and recognition of early AMS symptoms so that ascent is stopped before HAPE develops; with previous HAPE history, use nifedipine 30 mg slow-release every 12 hours during ascent, then continue for 3 days (monitor for hypotension)

AMS, acute mountain sickness; *HAPE,* high-altitude pulmonary edema.

Some individuals are susceptible and experience HAPE with each ascent to altitude. Rarely, the congenital absence of a pulmonary artery exaggerates the pulmonary vascular response to hypoxia, resulting in recurrent HAPE at elevations lower than expected.[49] Many patients, however, have a single episode of HAPE and subsequently are able to return to high altitude without a recurrence. Conversely, those with previously uneventful high-altitude exposures may have HAPE develop in a future ascent.

Individuals who have been residents at high-altitude locations for extended periods may have pulmonary edema develop on reascent from a trip to low altitude. This phenomenon has been termed reentry HAPE. The incidence of reentry HAPE is not established; however, there seems to be an increased risk for children and young adults and possibly a greater incidence compared with HAPE experienced by low-altitude residents during their initial ascent.[114,115] This apparent increased susceptibility among children for development of HAPE is probably the result of developmental changes in pulmonary vascular reactivity and tone.

Clinical Presentation

The initial symptoms of HAPE usually begin insidiously 2 to 4 days after arrival at high altitude. Most cases occur during the second night, but HAPE may develop rapidly, with early symptoms apparent after just a few hours at high altitude. Marked dyspnea on exertion, fatigue with minimal-to-moderate effort, prolonged recovery time, and dry cough are early manifestations of the disease. The symptoms of AMS usually occur concurrently with the development of HAPE.

As the HAPE patient deteriorates, usually through the night, the dyspnea intensifies with effort and is unrelieved by rest. Dyspnea at rest should be recognized as a red flag that warns of the development of a serious pulmonary problem. The cough becomes productive of copious amounts of clear, watery sputum, and hemoptysis may be seen in severe cases. As the condition intensifies, cerebral edema or simply severe hypoxemia causes central nervous system dysfunction, such as ataxia and altered mentation. Coma may follow and precede death in a few hours if oxygen therapy or descent is not instituted.

The physical examination reveals a few rales in patients with mild HAPE, usually found in the region of the right middle lobe, progressing to unilateral or bilateral rales and then to diffuse bilateral rales and also rhonchi and gurgles audible without the stethoscope. Cyanosis of the nail beds alone may progress to severe central cyanosis. Tachypnea and tachycardia become more

www.ketabpezeshki.com 66485457-66963820

pronounced as severity increases. Elevated temperatures are common, and a concurrent respiratory tract infection is occasionally seen, especially in children.[56]

Ancillary Tests

Chest radiographs can help elucidate the nature of the illness. The infiltrates seen in HAPE victims are alveolar and patchy in distribution, with areas of clearing between the patches. Unilateral infiltrates may be present in mild cases; however, bilateral infiltrates are seen in more advanced cases, with involvement of the right midlung field being most common (see Fig. 144-3). Pleural effusion is rare but may be present in severe cases. The extent of the edema on the chest radiograph roughly parallels the clinical severity. Of note, the radiographic findings of cardiomegaly, bat-wing distribution of infiltrates, and Kerley B lines, which are typical of cardiogenic pulmonary edema, are absent in cases of HAPE.

Radiographic evidence of HAPE clears rapidly after initiation of treatment; some mild cases may clear in 4 to 6 hours, and most clear by 24 hours. Radiographs of patients with severe HAPE may reveal infiltrates that persist for as long as 2 weeks, even though the clinical symptoms have resolved.

An electrocardiogram reveals tachycardia and evidence of right-sided heart strain, including right axis deviation, P wave abnormalities, tall R waves in the precordial leads, and S waves in the lateral leads.[42] Hemodynamic studies reveal increased pulmonary vascular resistance, elevated pulmonary artery pressures, and normal pulmonary wedge pressures. Echocardiographic studies demonstrate high estimated pulmonary artery pressures, pulmonary vascular resistance, and normal left ventricular function.[41]

Ultrasonography to estimate pulmonary artery pressure is an emerging modality in the early detection and diagnosis of HAPE. Demonstration of high pulmonary artery pressures with normal left ventricular function is associated with HAPE and HAPE susceptibility.[41,116] Ultrasound lung comet tails, indicating extravascular water, may also be seen to support a HAPE diagnosis.[117,118]

Differential Diagnosis

Pneumonia can be misdiagnosed in the setting of HAPE because the symptoms and signs of pneumonia are similar to those of HAPE. The incidence of pneumonia and the common organisms responsible for pneumonia at high altitude are unknown, but visitors to high altitudes may be predisposed to acquire bacterial infections because of impaired T-lymphocyte function.[119] Patients who present with symptoms compatible with pneumonia at high altitude should be treated for HAPE. If any doubt exists about the diagnosis of HAPE versus pneumonia, empirical antibiotic therapy should be initiated. Because of the mild immunosuppression coincident with high-altitude exposure, the treatment of any serious pulmonary infection at high altitude requires oxygen, descent, and antibiotics.

High-altitude bronchitis and pharyngitis are common problems among climbers. They may result from the increased ventilation of cold, dry air across the upper airway mucosa, causing mucosal inflammation. Copious sputum production is sometimes seen, and antibiotic therapy usually is not helpful. Coughing spasms may be severe and require treatment with antitussives. Other therapeutic measures include hydration, lozenges, and steam inhalation.

Death from pulmonary embolism at high altitude is described.[120] Hypercoagulability may result from altitude effects and hyperviscosity caused by elevation in hematocrit and dehydration. Venous stasis, caused by immobility when the individual is confined to a sleeping bag inside a tent, is also a predisposing factor for deep venous thrombosis. The symptoms and signs of pulmonary embolism can mimic those of HAPE; however, embolic disease tends to have a more rapid onset, and pleuritic chest pain is a more prominent feature.

Management

In remote settings, where oxygen and medical expertise may be unavailable, immediate descent is a lifesaving measure after diagnosis of HAPE. Delay of descent while HAPE progresses or waiting for rescue personnel to initiate evacuation can prove fatal. Descents of 3000 feet are generally adequate for a rapid recovery; however, descent should continue until symptoms resolve.

Warmth and rest are also important in HAPE therapy for avoidance of cold- or exercise-induced pulmonary hypertension. Mild cases of HAPE can be treated without descent or oxygen with 1 or 2 days of bed rest. Oxygen administration increases the rate of improvement. Moderate cases can be treated without descent if bed rest and adequate supplies of supplemental oxygen are available. Any treatment plan that does not include descent necessitates serial examinations by clinicians with experience in management of high-altitude illness.

On difficult terrain or in weather conditions that hamper efforts to descend, oxygen administration (or hyperbaric therapy) can be a lifesaving measure. Rescue personnel should air drop oxygen supplies if immediate evacuation to lower altitudes will be delayed. High-flow rates of oxygen (6-8 L/min) by mask should be delivered initially to victims with severe HAPE until improvement is seen. Flow rates can then be lowered until recovery or descent is completed. Delivery of oxygen with a continuous positive airway pressure mask is more efficacious than normal oxygen delivery and may improve alveolar fluid clearance.[121]

Hyperbaric therapy simulates descent without the administration of supplemental oxygen.[122] Several portable, lightweight (approximately 15 pounds), fabric hyperbaric chambers are available and pressurized manually (Fig. 144-4). These chambers generate 103 mm Hg (2 psi) above the ambient pressure. This simulates a descent of 4000 to 5000 feet at moderate altitudes, and at the summit of Mt. Everest it would simulate a descent of approximately 9000 feet. These devices can be lifesaving in patients with HAPE and HACE. Some nonambulatory patients are able to descend under their own power after a few hours in hyperbaric chambers.[123]

In treatment of HAPE, medications that lower pulmonary artery pressure, pulmonary blood volume, and pulmonary vascular resistance or enhance alveolar fluid clearance are useful but not as effective as oxygen and descent. Diuretic therapy is no longer recommended in the treatment of HAPE as it may result in a profound volume loss in patients who are already intravascularly

Figure 144-4. Gamow bag *(left)* and Certec bag *(right)*: lightweight, portable hyperbaric chambers. Note the attached foot-operated pressure pump. (Courtesy Thomas Dietz, MD.)

www.ketabpezeshki.com 66485457-66963820

depleted.[4,124] Some investigators argue that during the state of antidiuresis found with severe AMS, however, no documented deleterious effects from diuretic therapy exist.[125]

The advent of pulmonary vasodilators has displaced the use of diuretics for HAPE. Nifedipine, a pulmonary vasodilator, is especially useful when oxygen is unavailable or descent is impossible.[41,126] Nifedipine does not improve pulmonary hemodynamics as much as oxygen or descent does, and it does not have an additive effect when it is administered with oxygen.[41] Treatment with 30 mg of a slow-release nifedipine preparation administered twice daily is effective.[127] Patients should be monitored for the development of hypotension during nifedipine administration.

Phosphodiesterase type 5 inhibitors are less likely to produce hypotension. Although they are known to be useful for HAPE prevention, only anecdotal reports of treatment exist, and they remain unstudied for HAPE therapy.[55] Alveolar fluid clearance is upregulated by beta-adrenergic agonists in animal models, and inhaled beta-agonists have been used anecdotally for therapy of HAPE (salmeterol 125 µg inhaled twice daily).[53,54]

No evidence exists that the concurrent use of these medications with oxygen has any benefit beyond the use of oxygen alone. The mainstay of treatment remains immediate oxygen if it is available and descent. Should these treatments not be available, nifedipine should be initiated.

Disposition

Mild to moderate cases of HAPE can be treated with oxygen, rest, and careful monitoring. Resort physicians at moderate altitudes observe HAPE patients receiving oxygen therapy to ensure adequate oxygenation. These patients are then discharged to their hotel with supplemental oxygen and monitored for improvement or deterioration. In severe HAPE or milder cases that do not improve with therapy, descent is warranted. Rapid recovery is usually seen after descent to lower altitudes, and observation of the patient in the emergency department to ensure adequate room air oxygenation is generally adequate. On occasion, admission to the hospital is indicated to maintain the Sao_2 greater than 90%. In the hospital, continuous positive airway pressure improves gas exchange in HAPE patients. Hypocapnia, alkalosis, and radiographic evidence of HAPE may persist for several days. After oxygen saturation remains greater than 90% on room air and clinical improvement is apparent, the patient can be discharged. If the patient requires air travel to return home (cabin pressures equal approximately 8000 feet), additional recovery time before travel or arrangement for supplemental oxygen administration is advised. Detection of a heart murmur in a patient with HAPE should lead to an evaluation searching for cardiac structural anomalies that may increase pulmonary vascular resistance. An evaluation for underlying congenital heart disease is warranted after an episode of HAPE in a young child.

The recovered victim may be able to reascend (generally in 2-3 days) when symptoms resolve and oxygen levels remain acceptable off supplemental oxygen at rest and with mild exercise. Reascent with pulmonary vasodilator medication should be considered.

Prevention

As with all forms of serious altitude illness, a gradual ascent that allows time to acclimatize and immediate cessation of further ascent at the onset of symptoms are the most effective means of prevention. Individuals with a prior history of HAPE should also avoid extreme exertion during the first 2 days at altitude. With a prior history of HAPE, prophylactic therapy should be considered.[128-130] The preferred medication for HAPE prevention is the nonspecific pulmonary vasodilator nifedipine, 30 mg (controlled-release) two times daily before ascent and continued at altitude for 3 days.[4,131] Less evidence exists to support the routine use of other pulmonary vasodilators for HAPE prevention.

Phosphodiesterase type 5 inhibitors are selective pulmonary vasodilators that increase cyclic guanosine monophosphate availability. Sildenafil (40 mg every 8 hours) and tadalafil (10 mg every 12 hours) are effective in preventing HAPE.[50,132-134] The phosphodiesterase type 5 inhibitors have the added benefit that they are less likely than calcium channel blockers to induce systemic hypotension. A few additional medication options may be considered for prevention. Minimal data demonstrate that dexamethasone (8 mg every 12 hours) started 2 days before ascent also prevents HAPE. Unpublished data from animal models revealed that dexamethasone decreases pulmonary capillary leakage through downregulation of the inflammatory cascade, decreasing alveolar fluid accumulation.[102] To enhance alveolar clearance, salmeterol 125 µg inhaled twice daily may be used as an adjunct to nifedipine in patients with a clear history of HAPE recurrence, although side effects are common at this high inhaled dose.[4] Finally, clinical experience suggests that acetazolamide aids in acclimatization and prevents HAPE, and it has utility in reduction of hypoxic pulmonary vasoconstriction.[128-130]

HIGH-ALTITUDE CEREBRAL EDEMA

HACE is the least common but most severe form of high-altitude illness. Death from HACE at as low as 8200 feet is reported, although most cases occur above 12,000 feet. Mild AMS can progress to severe HACE with coma in as few as 12 hours. Although the usual time course is 1 to 3 days for the development of severe symptoms, it may occur in 5 to 9 days (Box 144-4).[135,136]

Clinical Presentation

HACE is characterized by evidence of global cerebral dysfunction. The symptoms of severe AMS (headache, fatigue, and vomiting) as well as those of HAPE (cough and dyspnea) are often present. HACE-specific signs include ataxia, generalized seizures, slurred speech, rarely focal neurologic deficits, and altered mentation, which can range from mild emotional lability or confusion to hallucinations and decreased levels of consciousness that may proceed to coma and death.[135] MRI of patients with HACE reveals white matter changes consistent with vasogenic edema (Fig. 144-5).[71]

Altered consciousness and cerebellar ataxia are the most sensitive signs for early recognition of HACE.[137] The early appearance of ataxia reflects the particular sensitivity of the cerebellum to hypoxia. Ataxia alone is an indication for immediate descent. Retinal hemorrhages are common but often occur as an isolated finding. Papilledema and occasionally cranial nerve palsy also occur in the setting of increased intracranial pressure. Differentiation between HACE and stroke may be difficult. Although it is rare, the occurrence of cerebral thrombosis and transient ischemic attacks, in the absence of high-altitude illness, is documented at

Box 144-4 High-Altitude Cerebral Edema

Incidence: Lower than 1 or 2%, uncommon as a pure entity; usually associated with the presence of severe AMS and HAPE
Symptoms and signs: Ataxia, severe headache, nausea and vomiting, altered mentation, seizures, coma
Treatment: Immediate evacuation to a lower altitude; oxygen, bed rest, dexamethasone, and hyperbaric therapy while awaiting descent

AMS, acute mountain sickness; *HAPE,* high-altitude pulmonary edema.

www.ketabpezeshki.com 66485457-66963820

high altitude.[138,139] The absence of any other evidence for high-altitude illness or the persistence of signs despite adequate treatment of high-altitude illness suggests the presence of a vascular lesion.

Management

Early recognition and initiation of descent are the keys to successful therapy for HACE. High-flow oxygen should be administered if it is available because oxygen alone reduces intracranial blood flow at high altitude.[58] Steroid therapy is recommended and may result in recovery from HACE without neurologic deficits. The initial dose of dexamethasone is 8 mg parenterally or orally in mild cases, followed by 4 mg every 6 hours.

Patients with severely altered levels of consciousness require tracheal intubation. Hyperventilation, diuretics (e.g., furosemide), and hypertonic solutions (e.g., mannitol) may be used to manage severely elevated intracranial pressure. Caution is warranted because many patients with HACE are already volume depleted from poor fluid intake; diuretic use could compromise adequate intravascular volume and reduce cerebral perfusion pressure.

Hyperbaric treatment of HACE is also effective and may result in temporary improvement and allow self-rescue. Conversely, coma may persist for several days after descent to lower altitudes, so placement of HACE patients in a hyperbaric device may only delay the more comprehensive care available in the hospital setting.

Long-term neurologic deficits, such as ataxia and cognitive impairment, are reported after recovery from acute episodes of HACE. Both transient and long-lasting neurobehavioral impairments can occur in mountaineers after climbing to extreme altitude without experiencing clinical HACE.[140] Some of these sequelae can persist for 1 year. Because of the potential for long-lasting neurologic injury, the clinician who treats high-altitude illness should be extremely sensitive to the early manifestations of HACE. Early treatment of HACE generally results in good outcomes, but after coma is present, the mortality rate exceeds 60%.[141]

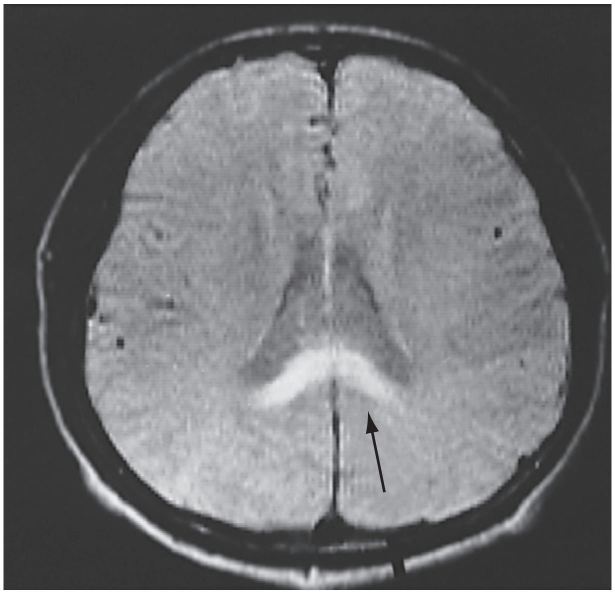


Figure 144-5. Axial proton-weighted magnetic resonance image of a mountain climber with high-altitude cerebral edema. The arrow demonstrates the markedly increased signal (edema) in the splenium of the corpus callosum. (Courtesy Peter Hackett, MD.)

HIGH-ALTITUDE RETINAL HEMORRHAGE

High-altitude retinal hemorrhage (HARH) is the most common type of retinopathy in visitors to high altitude.[142] These hemorrhages are common at altitudes above 17,500 feet, although they can occur at lower levels.[143]

The exact incidence of HARH is unknown because most patients are asymptomatic, with HARH noted only on retinoscopy. HARH is not generally related to the presence of mild AMS but does seem to be related to strenuous exercise at high altitude. At any altitude, in the setting of severe HAPE or HACE, retinal hemorrhages are commonly noted, but the mechanism remains unclear.[143,144]

Hemorrhages usually spare the macula (Fig. 144-6). Retinal hemorrhages usually resolve without treatment in 2 or 3 weeks. With macular involvement, central scotomas may be noticed for several years, gradually resolving. In some cases, however, these visual defects are permanent. HARH is more likely to occur among individuals with a previous history of these hemorrhages, but the underlying risk remains unclear. This usually does not pose a contraindication to return to high altitude unless the macular region is involved.

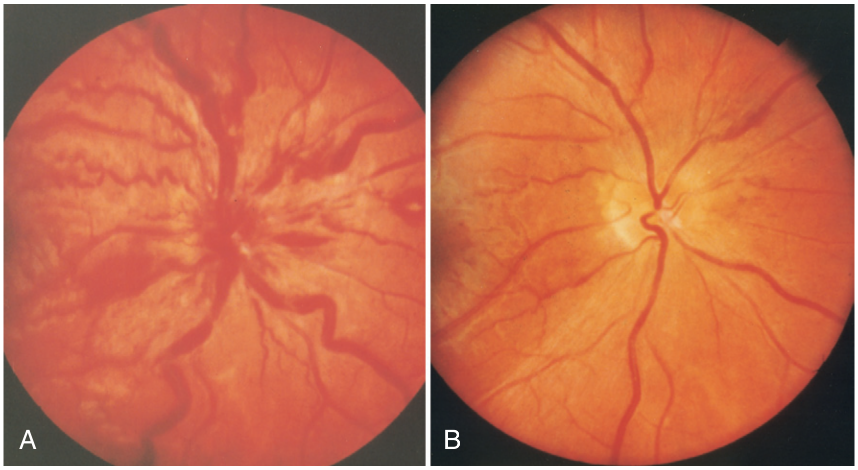


Figure 144-6. High-altitude retinal hemorrhages. **A,** Acute. **B,** After 1 week of resolution. (Courtesy Charles Houston, MD.)

www.ketabpezeshki.com 66485457-66963820

CARBON MONOXIDE TOXICITY

Carbon monoxide (CO) poisoning can occur at altitude from the use of fires and combustion stoves to keep warm and to prepare food in the high-altitude environment. If CO poisoning occurs at altitude, it can be more devastating because of the lower oxygen pressures and the body's baseline hypoxic state. CO binds to hemoglobin and prevents oxygen release to the body's tissues that are already, relative to sea level, hypoxic. It is easy to confuse the symptoms and signs of CO poisoning and AMS as both include headache, nausea, dizziness, dyspnea, and lassitude.[145,146] If there is doubt, a person should leave the enclosed space and descend or use supplemental oxygen if it is available.[147-149]

ALTITUDE AND UNDERLYING MEDICAL CONDITIONS

Individuals with diseases such as moderate to severe chronic obstructive pulmonary disease (COPD) and coronary artery disease may have a more difficult time acclimatizing because these disease states are often aggravated by the hypoxic atmosphere at higher elevations. They may predispose these individuals to the development of high-altitude illness. Table 144-2 describes the risk associated with travel to altitude in individuals with a variety of underlying comorbidities.

Table 144-2 Risk Associated with Travel to Altitude in Individuals with a Variety of Underlying Comorbidities

ADVISABILITY OF EXPOSURE TO HIGH ALTITUDE FOR COMMON CONDITIONS (WITHOUT SUPPLEMENTAL OXYGEN)
Probably No Extra Risk
Young and old
Fit and unfit
Mild obesity
Diabetes
Previous coronary artery bypass grafting (without angina)
Mild chronic obstructive pulmonary disease (COPD)
Asthma
Low-risk pregnancy
Controlled hypertension
Controlled seizure disorder
Psychiatric disorders
Neoplastic diseases
Inflammatory conditions
Caution
Moderate COPD
Asymptomatic pulmonary hypertension
Compensated congestive heart failure
Morbid obesity
Sleep apnea syndromes
Troublesome arrhythmias
Stable angina or coronary artery disease
High-risk pregnancy
Sickle cell trait
Cerebrovascular diseases
Any cause of restricted pulmonary circulation
Seizure disorder (not taking medication)
Radial keratotomy
Contraindicated
Sickle cell anemia (with history of crises)
Severe COPD
Symptomatic pulmonary hypertension
Uncompensated congestive heart failure

Modified from Hackett PH, Roach RC: High altitude medicine. In Auerbach P ed: Wilderness Medicine. Philadelphia, Elsevier, 2007, p 2-36.

Respiratory Illnesses

Travelers with COPD to moderate altitudes have underlying anatomic and physiologic changes that predispose them to development of hypoxemia, sleep apnea, pulmonary hypertension, and ventilation disorders. COPD is a risk factor for the development of AMS.[7] Although oxygen saturation remains more than 90% in a healthy, awake individual until an altitude of 8000 feet, patients with COPD may desaturate below 90% at lower altitudes. Travel to 5000 feet did not result in significant desaturation below 90% in one group of COPD patients and did not produce significant adverse effects on the systemic circulation in another group at 8000 feet.[150] High altitude increases hypoxic pulmonary vasoconstriction and may potentiate the development of cor pulmonale, which is known to adversely affect survival at sea level.[151] Colorado, for example, has a relatively low incidence of COPD but a higher mortality rate than expected from emphysema.[152] Individuals with chronic COPD should be advised of the potential need for oxygen supplementation when traveling to moderate altitude, especially if they are already using oxygen at sea level or if dyspnea or fatigue becomes worse. Use of a pulse oximeter can guide the need for increased oxygen supplementation.

Patients with asthma, on the other hand, may have fewer problems at altitude because of decreased allergens and pollutants and decreased airflow turbulence. There are no descriptions of asthma exacerbations due to altitude, although oxygen saturations might be lower at elevation. Even those with exercise-induced bronchospasm do not have worsening symptoms while exercising at 5000 feet.[153] In addition, AMS incidence is not increased in asthmatics.[153] People with asthma traveling to higher elevations should continue their usual medications and carry a rescue supply of bronchodilators and steroids.

Patients who ascend to high altitude with preexisting primary or secondary pulmonary hypertension should be considered HAPE susceptible, and those with primary pulmonary hypertension should be considered at increased risk for HAPE.[154] Patients with known pulmonary hypertension should be advised against travel to higher elevations. If travel cannot be avoided, supplemental oxygen should be used. Prophylactic nifedipine SR, 30 mg twice daily for the duration of the stay at altitude, can prevent HAPE.[126] Phosphodiesterase type 5 inhibitors and steroids may also be used.[50]

Cardiovascular

Individuals with a history of congestive heart failure, coronary artery disease, dysrhythmias, or coronary bypass surgery are rarely studied in the high-altitude setting. In theory, people with diseased myocardium should be advised to avoid high altitude because of decreased environmental oxygen availability. No studies report increased mortality in visitors to these locations. To the contrary, long-term residents at high altitude may be protected from coronary artery disease by increased collateral vessel formation or a decrease in the development of atherosclerosis.[155-157]

Many elderly people with known or suspected coronary artery disease have been safely exposed to acute hypoxia at altitude while breathing low oxygen mixtures or when being placed in a hypobaric chamber.[158] In contrast, another investigation of elderly people with known coronary disease does demonstrate some risk.[159]

Patients with heart disease have increased sympathetic activity during the first 3 days at altitude, as do all travelers. The resultant increase in heart rate and blood pressure increases cardiac work and myocardial oxygen consumption, and this could increase dysrhythmias. Although both cardiac rhythm abnormalities and ST segment and T wave electrocardiographic changes are reported, none of these changes are associated with any clinical evidence of

www.ketabpezeshki.com 66485457-66963820

myocardial ischemia.[158,160] Limited data suggest no increased risk for sudden cardiac death or myocardial infarction at altitudes up to 8000 feet.

The small increase in heart rate and blood pressure that occurs on first visiting altitude might exacerbate angina in patients with known disease. Even when individuals with stable angina are exercised, there is conflicting evidence for the probability of inducing malignant dysrhythmias.[159,161] In a study of 22 patients with recent percutaneous coronary intervention or coronary artery bypass graft with a submaximal exercise routine at 11,400 feet, there is no evidence of myocardial ischemia or significant arrhythmias despite an elevated oxygen demand, heart rate, and lactate level.[162] Travelers with heart disease who ascend to moderate altitudes do not appear to have an increased incidence of AMS.[7,17]

Travelers with mild stable coronary artery disease should be advised to ascend gradually, to limit activity especially in the first few days at elevation, and to continue antianginal and antihypertensive medications. Individuals who have more severe, symptomatic coronary disease or those in a high-risk group (low ejection fraction, abnormal stress test results, and high-grade ventricular ectopy) should avoid travel to high altitudes. Ascent to moderate elevations can be suggested on an individual basis with the previously mentioned precautions. Individuals with heart failure who travel to altitude may require increased use of diuretics to promote diuresis and acclimatization. Acetazolamide prophylaxis may be useful to speed acclimatization and to prevent AMS and its accompanying fluid retention.[130] If the anticipated workload at altitude is greater than the individual is accustomed to at sea level, exercise stress testing at this increased workload before ascent should be considered.[163]

Hypertension

High-altitude travel produces a mild increase in blood pressure and heart rate in healthy individuals because of increased catecholamine activity and resultant sympathetic tone. This increase begins in the first few days after ascent, is maximal at 2 or 3 weeks, and returns to baseline values over time because of a downregulation of adrenergic receptors if one stays at high altitude or on descent to sea level.[164,165] No studies demonstrate an increased predisposition for altitude illness in patients with underlying hypertension.[166]

The incidence of hypertension in sea-level dwellers traveling to high altitude is 10 to 25%.[167] Although there is no difference in blood pressure readings in either normotensive or hypertensive individuals when blood pressure is measured at low altitudes (3000 feet), significant increases occur in both blood pressure and heart rate at altitudes above 9800 feet.[168] This suggests that people with severe hypertension should travel only to moderate altitudes. For individuals who have mild hypertension while traveling at altitude, treatment is not routinely necessary because the hypertension will rarely become dangerously high and will improve on descent. Although individual variability exists, patients with hypertension should be monitored frequently in the first few days at altitude and antihypertensive medications continued. For hypertensive patients with a rapid rise in blood pressure and who will be staying for several weeks, an alpha-blocker, nifedipine, or angiotensin-converting enzyme inhibitor should be considered.[169]

Seizures

Travel to altitude is implicated as a precipitant for seizure activity. There are numerous reports of altitude-provoked seizures, but epidemiologic data are lacking. Seizures attributable to high altitude are typically generalized tonic-clonic in nature.[170] A focal seizure at altitude should prompt a thorough workup for a space-occupying lesion. Several pathophysiologic mechanisms are implicated. These include sleep deprivation from periodic breathing, hyperventilation, and the direct effect of hypobaric hypoxia.[170] These mechanisms are postulated to induce a metabolic state that lowers the seizure threshold. Seizures not responding to supportive care can be treated with benzodiazepines. Should an epileptic who is already taking seizure medicine experience a breakthrough seizure at altitude, standard seizure evaluation is warranted, and acetazolamide at 250 mg twice daily may be added. Acetazolamide itself has antiepileptic properties and may ameliorate the altitude-related metabolic derangements.[171]

Sickle Cell Disease

Patients with sickle cell disease are affected by the hypoxemia occurring at low to moderate altitudes (5000-6500 feet). Up to 20% of patients with hemoglobin sickle cell and sickle cell–thalassemia disease may experience a vaso-occlusive crisis, even under pressurized aircraft conditions.[172] Oxygen is therefore advised for air travelers who have sickle cell disease.

Although most people with sickle cell trait remain asymptomatic, this subgroup can experience the development of left upper quadrant pain as a result of splenic ischemia or infarction. Nonblacks, usually of Mediterranean origin, who have sickle cell trait may be more prone to the development of splenic infarctions than are blacks.[173,174]

Pregnancy

Studies of permanent high-altitude residents in Colorado and Peru show an increased incidence of complications in maternal, fetal, and neonatal life.[1,175,176] Infants born at high altitude have a lower birth weight compared with infants born at sea level because of a combination of factors, including altitude-related effects on fetal growth, changes in uterine blood flow, and increased premature births.

Pregnancy-induced hypertension, proteinuria, and peripheral edema (manifestations of toxemia and preeclampsia) are more common at high altitudes and may also be related to maternal and uterine hypoxemia.[177,178] Although hypertension in pregnancy is more common at high altitudes, no evidence exists for an increase in spontaneous abortions, abruptio placentae, or placenta previa.

Travel by pregnant women to moderate altitudes appears to be safe, but caution is advised for lowland women with normal pregnancies who wish to travel above 13,000 feet, for pregnant women who wish to remain at high altitude for a prolonged period, and for women with complicated pregnancies.

Radial Keratotomy

Although it is currently less popular, radial keratotomy may cause individuals to experience hyperoptic (farsighted) visual changes with ascent above 9000 feet.[179] This results from corneal swelling from ambient hypoxia because the cornea is markedly sensitive to both systemic and ambient oxygen tension.[180] In normal corneas, this swelling is uniform. After radial keratotomy, the swelling is exacerbated and inconsistent secondary to the pattern of the incisions.[181] Photorefractive keratotomy and LASIK, which use laser techniques that do not produce incisions but instead shave the cornea and corneal stroma, respectively, do not result in similar problems.[179,182]

ACKNOWLEDGMENT

The authors would like to acknowledge Dr. Benjamin Honigman for his contributions to previous editions of this chapter.

www.ketabpezeshki.com 66485457-66963820

KEY CONCEPTS

- The symptoms of AMS can resemble a viral syndrome and include headache, nausea, anorexia, fatigue, and insomnia.
- The management of altitude illness must include adherence to the principle that after the symptoms occur and until symptoms resolve, further ascent is contraindicated.
- Dyspnea at rest is an early symptom of HAPE. As the HAPE patient's condition deteriorates, the dyspnea intensifies with effort and is unrelieved by rest.
- Altered consciousness and cerebellar ataxia must be recognized as early signs of HACE, and descent is mandatory.
- Effective prophylaxis options for altitude illness include acetazolamide for AMS and nifedipine for HAPE. Phosphodiesterase type 5 inhibitors are selective pulmonary vasodilators that increase cyclic guanosine monophosphate availability. Sildenafil (40 mg every 8 hours) and tadalafil (10 mg every 12 hours) are effective in preventing HAPE.[50,132-134]
- Narcotic analgesics should be avoided because of depression of the HVR and respiratory drive during sleep. For nausea and vomiting, prochlorperazine, unlike other antiemetics, stimulates the HVR.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Moore LG: Altitude-aggravated illness: Examples from pregnancy and prenatal life. *Ann Emerg Med* 1987; 16:965-973.
2. Schneider M, Bernasch D, Weymann J, Holle R, Bärtsch P: Acute mountain sickness: Influence of susceptibility, preexposure, and ascent rate. *Med Sci Sports Exerc* 2002; 34:1886-1891.
3. MacInnis MJ, Koehle MS, Rupert JL: Evidence for a genetic basis for altitude illness: 2010 update. *High Alt Med Biol* 2010; 11:349-368.
4. Luks AM, et al: Wilderness Medical Society consensus guidelines for the prevention and treatment of acute altitude illness. *Wilderness Environ Med* 2010; 21:146-155.
5. Larson EB, Roach RC, Schoene RB, Hornbein TF: Acute mountain sickness and acetazolamide. Clinical efficacy and effect on ventilation. *JAMA* 1982; 288:328-332.
6. Hackett PH, Rennie ID, Levine HD: The incidence, importance, and prophylaxis of acute mountain sickness. *Lancet* 1976; 2:1149-1154.
7. Honigman B, et al: Acute mountain sickness in a general tourist population at moderate altitudes. *Ann Intern Med* 1993; 118:587-592.
8. Singh I, Kapila CC, Khanna PK, Nanda RB, Rao BD: High altitude pulmonary oedema. *Lancet* 1965; 1:229-234.
9. Yaron M, et al: Physiologic response to moderate altitude exposure among infants and young children. *High Alt Med Biol* 2003; 4:53-59.
10. Yaron M, Waldman N, Niermeyer S, Nicholas R, Honigman B: The diagnosis of acute mountain sickness in preverbal children. *Arch Pediatr Adolesc Med* 1998; 152:683-687.
11. Theis MK, et al: Acute mountain sickness in children at 2835 meters. *Am J Dis Child* 1993; 147:143-145.
12. Wu T: Children on the Tibetan plateau. *ISSM Newslett* 1994; 4:5-7.
13. Moraga FA, Osorio JD, Vargas ME: Acute mountain sickness in tourists with children at Lake Chungara (4400 m) in northern Chile. *Wilderness Environ Med* 2002; 13:31-35.
14. Sophocles AM: High-altitude pulmonary edema in Vail, Colorado, 1975-1982. *West J Med* 1986; 144:569-573.
15. Cremona G, Asnaghi R, Baderna P, et al: *High altitude pulmonary edema at 4559 m: A population study* [abstract]. In: Roach RC, Wagner PD, Hackett PH, eds: *Hypoxia: Into the Next Millennium*. New York: Kluwer Academic/Plenum Publishers; 1999:375. Advances in Experimental Medicine and Biology, vol 474.
16. Riboni K, Maes DP, Loeppky JA, Icenogle M, Roach RC: *Women at altitude: No gender or menstrual cycle effects on acute mountain sickness (AMS)* [abstract]. In: Roach RC, Wagner PD, Hackett PH, eds: *Hypoxia: Into the Next Millennium*. New York: Kluwer Academic/Plenum Publishers; 1999:423. Advances in Experimental Medicine and Biology, vol 474.
17. Roach RC, et al: How well do older persons tolerate moderate altitude? *West J Med* 1995; 162:32-36.
18. Stokes S, et al: Age is no barrier to success at very high altitudes. *Age Ageing* 2010; 39:262-265.
19. West JB: Barometric pressures on Mt. Everest: New data and physiological significance. *J Appl Physiol* 1999; 86:1062-1854.
20. Macinnis MJ, Wang P, Koehle MS, Rupert JL: The genetics of altitude tolerance: The evidence for inherited susceptibility to acute mountain sickness. *J Occup Environ Med* 2011; 53:159-168.
21. Rexhaj E, et al: Reproducibility of acute mountain sickness in children and adults: A prospective study. *Pediatrics* 2011; 127:e1445-e1448.
22. Weil JV, et al: Hypoxic ventilatory drive in normal man. *J Clin Invest* 1970; 49:1061-1072.
23. Matsuzawa Y, Kobayashi T, Fujimoto K, Kubo K, Sekiguchi M: *Hypoxic ventilatory response and pulmonary gas exchange during exposure to high altitude in subjects susceptible to high altitude pulmonary edema (HAPE)*. In: Sutton JR, Houston CS, Coates G, eds: *Hypoxia and the Brain*. Burlington, Vt: Queen City Press; 1995:331.
24. Roach RC: *The role of the hypoxic ventilatory response in performance at high altitude*. In: Wood SC, Roach RC, eds: *Sports and Exercise Medicine*. New York: Dekker; 1994:211-221.
25. Asano K, Mazzeo RS, McCullough RE, Wolfel EE, Reeves JT: Relation of sympathetic activation in man at 4300 meters altitude. *Aviat Space Environ Med* 1997; 68:104-110.
26. Semenza GL: Regulation of erythropoietin production. New insights into molecular mechanisms of oxygen homeostasis. *Hematol Oncol Clin North Am* 1994; 8:863.
27. Pugh LG: *High altitudes*. In: Edholm OG, Bacharach AL, eds: *The Physiology of Human Survival*. New York: Academic Press; 1965:121-152.
28. Winslow RM: *High altitude polycythemia*. In: West JB, Lahiri S, eds: *High Altitude and Man*. Bethesda, Md: American Physiological Society; 1984:163-172.
29. Samaja M, di Prampero PE, Cerretelli P: The role of 2,3-DPG in the oxygen transport at altitude. *Respir Physiol* 1986; 64:191-202.
30. Hebbel RP, et al: Human llamas: Adaptation to altitude in subjects with high hemoglobin oxygen affinity. *J Clin Invest* 1978; 62:593-600.
31. Sutton JR, Gray GW, Houston CS, Powles AP: *Effects of acclimatization on sleep hypoxemia at altitude*. In: West JB, Lahiri S, eds: *High Altitude and Man*. Bethesda, Md: American Physiological Society; 1984:141-146.
32. Swenson ER: *High altitude diuresis: Fact or fancy*. In: Houston CS, Coates G, eds: *Hypoxia: Women at Altitude*. Burlington, Vt: Queen City Publishers; 1997:272-283.
33. Krasney JA: A neurogenic basis for acute altitude illness. *Med Sci Sports Exerc* 1994; 26:195-208.
34. Bärtsch P, et al: Enhanced exercise-induced rise of aldosterone and vasopressin preceding mountain sickness. *J Appl Physiol* 1991; 71136-71143.
35. Bärtsch P, et al: *Aldosterone, antidiuretic hormone and atrial natriuretic peptide in acute mountain sickness*. In: Sutton JR, Coates G, Houston CS, eds: *Hypoxia and Mountain Medicine*. Burlington, Vt: Queen City Press; 1992:73-81.
36. Bärtsch P, Shaw S, Franciolli M, Gnadinger MP, Weidmann P: Atrial natriuretic peptide in acute mountain sickness. *J Appl Physiol* 1988; 65:1929-1937.
37. Westendorp RG, et al: Atrial natriuretic peptide improves pulmonary gas exchange in subjects exposed to hypoxia. *Am Rev Respir Dis* 1993; 148:304-309.
38. Roach RC, et al: Exercise exacerbates acute mountain sickness at simulated high altitude. *J Appl Physiol* 2000; 88:581-585.
39. Durand J, Coudert J, Guieu JD, Mensch-Dechene J: *Hypoxic pulmonary vasoconstriction and ambient temperature*. In: Brendel W, Zink RA, eds: *High Altitude Physiology and Medicine*. New York: Springer-Verlag; 1982:263-265.
40. Duplain H, et al: Augmented sympathetic activation during short-term hypoxia and high-altitude exposure in subjects susceptible to high-altitude pulmonary edema. *Circulation* 1999; 99:1713-1718.
41. Hackett PH, Roach RC, Hartig GS, Greene ER, Levine BD: The effect of vasodilators on pulmonary hemodynamics in high altitude pulmonary edema: A comparison. *Int J Sports Med* 1992; 13:S68-S71.
42. Hultgren HN: *High altitude pulmonary edema*. In: Staub NC, ed: *Lung Water and Solute Exchange*. New York: Dekker; 1978:437-469.
43. Scherrer U, et al: Inhaled nitric oxide for high-altitude pulmonary edema. *N Engl J Med* 1996;334:624-629.
44. Maggiorini M, et al: High altitude pulmonary edema is initially a hydrostatic, not a permeability edema. *Circulation* 2001;103:2078-2083.
45. Dehnert C, et al: Magnetic resonance imaging of uneven pulmonary perfusion in hypoxia in humans. *Am J Respir Crit Care Med* 2006;174:1132-1138.
46. Berger MM, et al: Hypoxia impairs systemic endothelial function in individuals prone to high-altitude pulmonary edema. *Am J Respir Crit Care Med* 2005; 172:763-767.
47. Duplain H, et al: Exhaled nitric oxide in high-altitude pulmonary edema: Role in the regulation of pulmonary vascular tone and evidence for a role against inflammation. *Am J Respir Crit Care Med* 2000; 162:221-224.
48. Dehnert C, Berger MM, Mairbäurl H, Bärtsch P: High altitude pulmonary edema: A pressure-induced leak. *Respir Physiol Neurobiol* 2007; 158:266-273.
49. Hackett PH, et al: High altitude pulmonary edema in persons without the right pulmonary artery. *N Engl J Med* 1980; 302:1070-1073.
50. Maggiorini M, et al: Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: A randomized trial. *Ann Intern Med* 2006; 145:497-506.
51. Swenson ER, et al: Pathogenesis of high-altitude pulmonary edema: Inflammation is not an etiologic factor. *JAMA* 2002; 287:2228-2235.
52. Scherrer U, et al: High-altitude pulmonary edema: From exaggerated pulmonary hypertension to a defect in transepithelial sodium transport. *Adv Exp Med Biol* 1999; 474:93-107.
53. Mairbäurl H: Role of alveolar epithelial sodium transport in high altitude pulmonary edema (HAPE). *Respir Physiol Neurobiol* 2006; 151:178-191.
54. Sartori C, Matthay MA: Alveolar epithelial fluid transport in acute lung injury: New insights. *Eur Respir J* 2002; 20:1299-1313.
55. Fagenholz PJ, Gutman JA, Murray AF, Harris NS: Treatment of high altitude pulmonary edema at 4240 m in Nepal. *High Alt Med Biol* 2007; 8:139-146.
56. Durmowicz AG, Noordeweir E, Nicholas R, Reeves JT: Inflammatory processes may predispose children to high-altitude pulmonary edema. *J Pediatr* 1997; 130:838-840.

www.ketabpezeshki.com 66485457-66963820

57. Bärtsch P, Bailey DM, Berger MM, Knauth M, Baumgartner RW: Acute mountain sickness: Controversies and advances. *High Alt Med Biol* 2004; 5:110-124.
58. Hackett PH, Roach RC: High altitude cerebral edema. *High Alt Med Biol* 2004; 5:136-146.
59. Hackett PH: High altitude cerebral edema and acute mountain sickness. A pathophysiology update. *Adv Exp Med Biol* 1999; 474:23-45.
60. Lassen NA: Increase of cerebral blood flow at high altitude: Its possible relation to AMS. *Int J Sports Med* 1992; 13:S47-S48.
61. Levine BD, Zhang R, Roach RC: Dynamic cerebral autoregulation at high altitude. *Adv Exp Med Biol* 1999; 474:319-322.
62. Van Osta A, et al: Effects of high altitude exposure on cerebral hemodynamics in normal subjects. *Stroke* 2005; 36:557-560.
63. Sanchez del Rio M, Moskowitz MA: High altitude headache. Lessons from headaches at sea level. *Adv Exp Med Biol* 1999; 474:145-153.
64. Bärtsch P, Roach RC: *Acute mountain sickness and high-altitude cerebral edema*. In: Hornbein TF, Schoene RB, eds: *High Altitude: An Exploration of Human Adaptation*. New York: Marcel Dekker; 2001:731-776.
65. Kilgore D, et al: *Corpus callosum (CC) MRI: Early altitude exposure* [abstract]. In: Roach RC, Wagner PD, Hackett PH, eds: *Hypoxia: Into the Next Millennium*. New York: Kluwer Academic/Plenum Publishers; 1999:396. Advances in Experimental Medicine and Biology, vol 474.
66. Schoch HJ, Fischer S, Marti HH: Hypoxia-induced vascular endothelial growth factor expression causes vascular leakage in the brain. *Brain* 2002; 125(Pt 11):2549-2557.
67. Bailey DM, et al: Free radical–mediated damage to barrier function is not associated with altered brain morphology in high-altitude headache. *J Cereb Blood Flow Metab* 2006; 26:99-111.
68. Clark IA, Awburn MM, Cowden WB, Rockett KA: *Can excessive iNOS induction explain much of the illness of acute mountain sickness?* [abstract]. In: Roach RC, Wagner PD, Hackett PH, eds: *Hypoxia: Into the Next Millennium*. New York: Kluwer Academic/Plenum Publishers; 1999:373. Advances in Experimental Medicine and Biology, vol 474.
69. Schilling L, Wahl M: *Mediators of cerebral edema*. In: Roach RC, Wagner PD, Hackett PH, eds: *Hypoxia: Into the Next Millennium*. New York: Kluwer Academic/Plenum Publishers; 1999:123-141. Advances in Experimental Medicine and Biology, vol 474.
70. Bailey DM, Bärtsch P, Knauth M, Baumgartner RW: Emerging concepts in acute mountain sickness and high-altitude cerebral edema: From the molecular to the morphological. *Cell Mol Life Sci* 2009; 66:3583-3594.
71. Hackett PH, et al: High-altitude cerebral edema evaluated with magnetic resonance imaging: Clinical correlation and pathophysiology. *JAMA* 1998; 280:1920-1925.
72. Krasney JA: *Cerebral hemodynamics and high altitude cerebral edema*. In: Houston CS, Coates G, eds: *Hypoxia: Women at Altitude*. Burlington, Vt: Queen City Publishers; 1997:254-267.
73. Schoonman GG, et al: Hypoxia-induced acute mountain sickness is associated with intracellular cerebral edema: a 3 T magnetic resonance imaging study. *J Cereb Blood Flow Metab* 2008; 28:198-206.
74. Kallenberg K, et al: Magnetic resonance imaging evidence of cytotoxic cerebral edema in acute mountain sickness. *J Cereb Blood Flow Metab* 2007; 27:1064-1071.
75. Baneke A: What role does the blood brain barrier play in acute mountain sickness? *Travel Med Infect Dis* 2010; 8:257-262.
76. Roach RC, Loeppky JA, Icenogle MV: Acute mountain sickness: Increased severity during simulated altitude compared with normobaric hypoxia. *J Appl Physiol* 1996; 81:1908-1910.
77. Loeppky JA, et al: Role of hypobaria in fluid balance response to hypoxia. *High Alt Med Biol* 2005; 6:60-71.
78. Ross RT: The random nature of cerebral mountain sickness. *Lancet* 1985; 1:990-991.
79. Zavasky D, Hackett P: Cerebral etiology of acute mountain sickness MRI findings. *Wilderness Environ Med* 1995; 6:229-230.
80. Wilson MH, Milledge J: Direct measurement of intracranial pressure at high altitude and correlation of ventricular size with acute mountain sickness: Brian Cummins' results from the 1985 Kishtwar expedition. *Neurosurgery* 2008; 63:970-974; discussion 974-975.
81. Roach RC, Bärtsch P, Oelz O, Hackett PH: *The Lake Louise acute mountain sickness scoring system*. In: Sutton JR, Houston CS, Coates G, eds: *Hypoxia and Molecular Medicine*. Burlington, VT: Queen City Press; 1993:272-274.
82. Fagenholz PJ, et al: Evidence for increased intracranial pressure in high altitude pulmonary edema. *High Alt Med Biol* 2007; 8:331-336.
83. Kimberly HH, Shah S, Marill K, Noble V: Correlation of optic nerve sheath diameter with direct measurement of intracranial pressure. *Acad Emerg Med* 2008; 15:201-204.
84. Fagenholz PJ, et al: Optic nerve sheath diameter correlates with the presence and severity of acute mountain sickness: Evidence for increased intracranial pressure. *J Appl Physiol* 2009; 106:1207-1211.
85. Sutherland AI, Morris DS, Owen CG, Bron AJ, Roach RC: Optic nerve sheath diameter, intracranial pressure and acute mountain sickness on Mount Everest: A longitudinal cohort study. *Br J Sports Med* 2008; 42:183-188.
86. Olson LG, Hensley MJ, Saunders NA: Augmentation of ventilatory response to asphyxia by prochlorperazine in humans. *J Appl Physiol* 1982; 53:637-643.
87. Hackett PH, Roach RC, Harrison GL, Schoene RB, Mills WJ Jr: Respiratory stimulants and sleep periodic breathing at high altitude. Almitrine versus acetazolamide. *Am Rev Respir Dis* 1987; 135:896-898.
88. Abernathy C, Meehan RT: *Valium at high altitude. The Genet effect* [abstract]. In: Sutton JR, Jones NL, Houston CS, eds: *Hypoxia: Man at Altitude*. New York: Thieme-Stratton; 1982:204.
89. Nickol AH, et al: Temazepam at high altitude reduces periodic breathing without impairing next-day performance: A randomized cross-over double-blind study. *J Sleep Res* 2006; 15:445-454.
90. Dubowitz G: Effect of temazepam on oxygen saturation and sleep quality at high altitude: Randomised placebo controlled crossover trial. *BMJ* 1998; 316:587-589.
91. Goldenberg F, Richalet JP, Onnen I, Antezana AM: Sleep apneas and high altitude newcomers. *Int J Sports Med* 1992; 13:S34-S36.
92. Bradwell AR, Coote JH, Smith P, Milles JJ, Nicholson A: *The effect of temazepam and diamox on nocturnal hypoxia at altitude* [abstract]. In: Sutton JR, Houston CS, Coates G, eds: *Hypoxia and Cold*. New York: Praeger; 1987:543.
93. Beaumont M, et al: Zaleplon and zolpidem objectively alleviate sleep disturbances in mountaineers at a 3,613 meter altitude. *Sleep* 2007; 30:1527-1533.
94. Grissom CK, Roach RC, Sarnquist FH, Hackett PH: Acetazolamide in the treatment of acute mountain sickness: Clinical efficacy and effect on gas exchange. *Ann Intern Med* 1992; 116:461-465.
95. Maggiorini M, Merki B, Pallavicini E, Bärtsch P: *Acetazolamide and almitrine in acute mountain sickness (AMS) treatment* [abstract]. In: Sutton JR, Houston CS, Coates G, eds: *Hypoxia and the Brain*. Burlington, Vt: Queen City Press; 1995:330.
96. Pollard AJ, Niermeyer S, Barry P, et al: Children at high altitude: An international consensus statement by an ad hoc committee of the International Society for Mountain Medicine, March 12, 2001. *High Alt Med Biol* 2001; 2:389-403.
97. Leaf DE, Goldfarb DS: Mechanisms of action of acetazolamide in the prophylaxis and treatment of acute mountain sickness. *J Appl Physiol* 2007; 102:1313-1322.
98. Swenson ER, Teppema LJ: Prevention of acute mountain sickness by acetazolamide: As yet an unfinished story. *J Appl Physiol* 2007; 102:1305-1307.
99. Kelly TE, Hackett PH: Acetazolamide and sulfonamide allergy: A not so simple story. *High Alt Med Biol* 2010; 11:319-323.
100. Levine BD, et al: Dexamethasone in the treatment of acute mountain sickness. *N Engl J Med* 1989; 321:1707-1713.
101. Bernhard WN, Schalick LM, Delaney PA, Bernhard TM, Barnas GM: Acetazolamide plus low-dose dexamethasone is better than acetazolamide alone to ameliorate symptoms of acute mountain sickness. *Aviat Space Environ Med* 1998; 69:883-886.
102. Chao J, Viets Z, Donham P, Wood JG, Gonzalez NC: Dexamethasone blocks the systemic inflammation of alveolar hypoxia at several sites in the inflammatory cascade. *Am J Physiol Heart Circ Physiol* 2012; 303:H168-H177.
103. Johnson TS, et al: Prevention of acute mountain sickness by dexamethasone. *N Engl J Med* 1984; 310:683-686.
104. Muza SR, Beidleman BA, Fulco CS: Altitude preexposure recommendations for inducing acclimatization. *High Alt Med Biol* 2010; 11:87-92.
105. Fulco CS, et al: Effect of repeated normobaric hypoxia exposures during sleep on acute mountain sickness, exercise performance, and sleep during exposure to terrestrial altitude. *Am J Physiol Regul Integr Comp Physiol* 2011; 300:R428-R436.
106. Aoki VS, Robinson SM: Body hydration and the incidence and severity of acute mountain sickness. *J Appl Physiol* 1971; 31:363-367.
107. Nerin MA, Palop J, Montano JA, Morandeira JR, Vazquez M: Acute mountain sickness: Influence of fluid intake. *Wilderness Environ Med* 2006; 17:215-220.
108. Ellsworth AJ, Meyer EF, Larson EB: Acetazolamide or dexamethasone use versus placebo to prevent acute mountain sickness on Mount Rainier. *West J Med* 1991; 154:289-293.

www.ketabpezeshki.com 66485457-66963820

109. Gertsch JH, et al: Prospective, double-blind, randomized, placebo-controlled comparison of acetazolamide versus ibuprofen for prophylaxis against high altitude headache: The Headache Evaluation at Altitude Trial (HEAT). *Wilderness Environ Med* 2010; 21:236-243.
110. Rock PB, et al: Dexamethasone as prophylaxis for acute mountain sickness. Effect of dose level. *Chest* 1989; 95:568-573.
111. Gertsch JH, Basnyat B, Johnson EW, Onopa J, Holck PS: Randomised, double blind, placebo controlled comparison of ginkgo biloba and acetazolamide for prevention of acute mountain sickness among Himalayan trekkers: The prevention of high altitude illness trial (PHAIT). *BMJ* 2004; 328:797.
112. Leadbetter G, et al: Ginkgo biloba does—and does not—prevent acute mountain sickness. *Wilderness Environ Med* 2009; 20:66-71.
113. Tissot van Patot MC, Keyes LE, Leadbetter G 3rd, Hackett PH: Ginkgo biloba for prevention of acute mountain sickness: Does it work? *High Alt Med Biol* 2009; 10:33-43.
114. Hultgren HN, Marticorena E: High altitude pulmonary edema: Epidemiologic observations in Peru. *Chest* 1978; 74:372-376.
115. Scoggin CH, Hyers TM, Reeves JT, Grover RF: High-altitude pulmonary edema in the children and young adults of Leadville, Colorado. *N Engl J Med* 1977; 297:1269-1272.
116. Dehnert C, Grunig E, Mereles D, von Lennep N, Bärtsch P: Identification of individuals susceptible to high-altitude pulmonary oedema at low altitude. *Eur Respir J* 2005; 25:545-551.
117. Pratali L, Cavana M, Sicari R, Picano E: Frequent subclinical high-altitude pulmonary edema detected by chest sonography as ultrasound lung comets in recreational climbers. *Crit Care Med* 2010; 38:1818-1823.
118. Fagenholz PJ, et al: Chest ultrasonography for the diagnosis and monitoring of high-altitude pulmonary edema. *Chest* 2007; 131:1013-1018.
119. Meehan RT: Immune suppression at high altitude. *Ann Emerg Med* 1987; 16:974-979.
120. Shlim DR, Papenfus K: Pulmonary embolism presenting as high-altitude pulmonary edema. *Wild Environ Med* 1995; 6:220-224.
121. Schoene RB, Roach RC, Hackett PH, Harrison GL, Mills WJ Jr: High altitude pulmonary edema and exercise at 4400 meters on Mt. McKinley: Effect of expiratory positive airway pressure. *Chest* 1985; 87:330-333.
122. Kasic JF, Yaron M, Nicholas RA, Lickteig JA, Roach R: Treatment of acute mountain sickness: Hyperbaric versus oxygen therapy. *Ann Emerg Med* 1991; 20:1109-1112.
123. Taber RL: Protocols for the use of a portable hyperbaric chamber for the treatment of high altitude disorders. *J Wilderness Med* 1990; 1:181-192.
124. Basnyat B, et al: Spironolactone does not prevent acute mountain sickness: A prospective, double-blind, randomized, placebo-controlled trial by SPACE Trial Group (spironolactone and acetazolamide trial in the prevention of acute mountain sickness group). *Wilderness Environ Med* 2011; 22:15-22.
125. Hackett PH, Roach RC: Medical therapy of altitude illness. *Ann Emerg Med* 1987; 16:980-986.
126. Oelz O, et al: Prevention and treatment of high altitude pulmonary edema by a calcium channel blocker. *Int J Sports Med* 1992; 13:S65-S68.
127. Oelz O, et al: Nifedipine for high altitude pulmonary edema. *Lancet* 1989; 2:1241-1244.
128. Hohne C, et al: Acetazolamide prevents hypoxic pulmonary vasoconstriction in conscious dogs. *J Appl Physiol* 2004; 97:515-521.
129. Berg JT, Ramanathan S, Swenson ER: Inhibitors of hypoxic pulmonary vasoconstriction prevent high-altitude pulmonary edema in rats. *Wilderness Environ Med* 2004; 15:32-37.
130. Hackett PH, Roach RC: *High altitude medicine*. In: Auerbach P, ed: *Wilderness Medicine*, 5th ed. Philadelphia: Mosby/Elsevier; 2007:2-36.
131. Bärtsch P, et al: Prevention of high-altitude pulmonary edema by nifedipine. *N Engl J Med* 1991; 325:1284-1289.
132. Perimenis P: Sildenafil for the treatment of altitude-induced hypoxaemia. *Expert Opin Pharmacother* 2005; 6:835-837.
133. Richalet JP, et al: Sildenafil inhibits altitude-induced hypoxemia and pulmonary hypertension. *Am J Respir Crit Care Med* 2005; 171:275-281.
134. Ghofrani HA, et al: Sildenafil increased exercise capacity during hypoxia at low altitudes and at Mount Everest base camp: A randomized, double-blind, placebo-controlled crossover trial. *Ann Intern Med* 2004; 141:169-177.
135. Houston CS, Dickinson JG: Cerebral form of high altitude illness. *Lancet* 1975; 2:758-761.
136. Yarnell PR, Heit J, Hackett PH: High-altitude cerebral edema (HACE): The Denver/Front Range experience. *Semin Neurol* 2000; 20:209-217.
137. Dickinson JG: High altitude cerebral edema: Cerebral acute mountain sickness. *Semin Respir Med* 1983; 5:151-158.
138. Song S-Y, et al: Cerebral thrombosis at altitude: Its pathogenesis and the problems of prevention and treatment. *Aviat Space Environ Med* 1986; 57:71-76.
139. Wohns RN: Transient ischemic attacks at high altitude. *Crit Care Med* 1986; 14:517-518.
140. Hornbein TF, Townes BD, Schoene RB, Sutton JR, Houston CS: The cost to the central nervous system of climbing to extremely high altitude. *N Engl J Med* 1989; 321:1714-1719.
141. Clarke C: High altitude cerebral oedema. *Int J Sports Med* 1988; 9:170-174.
142. Frayser R, Houston CS, Bryan AC, Rennie ID, Gray GW: Retinal hemorrhage at high altitude. *N Engl J Med* 1970; 282:1183-1184.
143. Honigman B, Noordewier E, Kleinman D, Yaron M: High altitude retinal hemorrhages in a Colorado skier. *High Alt Med Biol* 2001; 2:539-544.
144. Seth RK, Adelman RA: High-altitude retinopathy and optical coherence tomography findings. *Semin Ophthalmol* 2010; 25:13-15.
145. Foutch RG, Henrichs W: Carbon monoxide poisoning at high altitudes. *Am J Emerg Med* 1988; 6:596-598.
146. Keyes LE, Hamilton RS, Rose JS: Carbon monoxide exposure from cooking in snow caves at high altitude. *Wilderness Environ Med* 2001; 12:208-212.
147. Lipman GS: Carbon monoxide toxicity at high altitude. *Wilderness Environ Med* 2006; 17:144-145.
148. Roscoe C, et al: Investigating carbon monoxide exposure on Denali. *Wilderness Environ Med* 2006; 17:75-80.
149. Roscoe C, et al: Carbon monoxide exposure on Denali: Comparing the 2004 and 2005 climbing seasons. *Wilderness Environ Med* 2008; 19:15-21.
150. Berg BW, Dillard TA, Derderian SS, Rajagopal KR: Hemodynamic effects of altitude exposure and oxygen administration in chronic obstructive pulmonary disease. *Am J Med* 1993; 94:407-412.
151. Coultas DB, Samet JM, Wiggins CL: Altitude and mortality from chronic obstructive lung disease in New Mexico. *Arch Environ Health* 1984; 39:355-359.
152. Moore LG, Rohr AL, Maisenbach JK: Emphysema mortality is increased in Colorado residents of high altitude. *Am Rev Respir Dis* 1985; 126:225-228.
153. Matsuda S, Onda T, Iikura Y: Bronchial responses of asthmatic patients in an atmosphere-changing chamber. *Int Arch Allergy Immunol* 1995; 107:402-405.
154. Luks AM, Swenson ER: Travel to high altitude with pre-existing lung disease. *Eur Respir J* 2007; 29:770-792.
155. Mortimer EA, Monson RR, MacMahon B: Reduction in mortality from coronary heart disease in men residing at high altitude. *N Engl J Med* 1977; 296:581-585.
156. Morton WE: Coronary heart disease at high altitudes [letter]. *N Engl J Med* 1977; 297:60.
157. Ostadal B, Kolar F: Cardiac adaptation to chronic high-altitude hypoxia: Beneficial and adverse effects. *Respir Physiol Neurobiol* 2007; 158:224-236.
158. Yaron M, Hultgren HN, Alexander JK: Low risk of myocardial ischemia in the elderly visiting moderate altitude. *Wildern Environ Med* 1995; 6:20-28.
159. Levine BD, Zuckerman JH, deFilippi CR: Effect of high-altitude exposure in the elderly: The Tenth Mountain Division study. *Circulation* 1997; 96:1224-1232.
160. Halhuber M, Humpeler E, Inama K, Jungman H: *Does altitude cause exhaustion of the heart and circulatory system?* In: Rivolier J, Cerretelli P, Foray J, Segantini P, eds: *High Altitude Deterioration*. Basel, Switzerland: Karger; 1985:192-202. Medicine and Sport Science, vol 19.
161. Morgan BJ, Alexander JK, Nicoli SA, Brammell HL: The patient with coronary heart disease at altitude: Observations during acute exposure to 3100 meters. *J Wilderness Med* 1990; 1:147-153.
162. Schmid JP, et al: Safety and exercise tolerance of acute high altitude exposure (3454 m) among patients with coronary artery disease. *Heart* 2006; 92:921-925.
163. Alexander JK: Coronary heart disease at altitude. *Tex Heart Inst J* 1994; 21:261-266.
164. Mazzeo RS, Wolfel EE, Butterfield GE, Reeves JT: Sympathetic response during 21 days at high altitude (4,300 m) as determined by urinary and arterial catecholamines. *Metabolism* 1994; 43:1226-1232.
165. Mirrakhimov MM, Khamzamulin RO, Murataliev TM: Changes in hemodynamics in mountain hypoxia. *Hum Physiol* 1978; 4:375-380.
166. Luks AM: Should travelers with hypertension adjust their medications when traveling to high altitude? *High Alt Med Biol* 2009; 10:11-15.

www.ketabpezeshki.com 66485457-66963820

167. Kamat SR, Banerji BC: Study of cardiopulmonary function on exposure to high altitude. Acute acclimatization to an altitude of 3500 to 4000 meters. *Am Rev Respir Dis* 1972; 106:404-413.
168. Palatini P, et al: Effects of low altitude exposure on 24-hour blood pressure and adrenergic activity. *Am J Cardiol* 1989; 64:1379-1382.
169. Hultgren HN: Effects of altitude upon cardiovascular diseases. *J Wilderness Med* 1992; 3:301-308.
170. Maa EH: How do you approach seizures in the high altitude traveler? *High Alt Med Biol* 2011; 12:13-19.
171. Reiss WG, Oles KS: Acetazolamide in the treatment of seizures. *Ann Pharmacother* 1996; 30:514-519.
172. Mahoney BS, Githens JH: Sickling crisis and altitude: Occurrence in the Colorado patient population. *Clin Pediatr* 1979; 18:431-438.
173. Lane PA, Githens JH: Splenic syndrome at mountain altitudes in sickle cell trait: Its occurrence in nonblack persons. *JAMA* 1985; 253:2252-2254.
174. Mairbäurl H: Red blood cell functions at high altitude. *Ann Sport Med* 1989; 4:189-195.
175. Moore LG: Fetal growth restriction and maternal oxygen transport during high altitude pregnancy. *High Alt Med Biol* 2003; 4:141-156.
176. Moore LG, et al: Maternal hypoxic ventilatory response, ventilation, and infant birth weight at 4,300 m. *J Appl Physiol* 1986; 60:1401-1406.
177. Moore LG, Hershey DW, Jahnigen D, Bowes W: The incidence of pregnancy-induced hypertension is increased among Colorado residents at high altitude. *Am J Obstet Gynecol* 1982; 144:423-429.
178. Browne VA, et al: High-end arteriolar resistance limits uterine artery blood flow and restricts fetal growth in preeclampsia and gestational hypertension at high altitude. *Am J Physiol Regul Integr Comp Physiol* 2011; 300:R1221-R1229.
179. Mader TH, Tabin G: Going to high altitude with preexisting ocular conditions. *High Alt Med Biol* 2003; 4:419-430.
180. Bosch MM, et al: New insights into changes in corneal thickness in healthy mountaineers during a very-high-altitude climb to Mount Muztagh Ata. *Arch Ophthalmol* 2010; 128:184-189.
181. Mader TH, White LJ: Refractive changes at extreme altitude after radial keratotomy. *Am J Ophthalmol* 1995; 119:733-737.
182. Mader T: Refractive changes during 72-hour exposure to high altitude after refractive surgery. *Ophthalmology* 1996; 103:1188-1195.

www.ketabpezeshki.com 66485457-66963820

Chapter 145

Drowning

David B. Richards and Gabrielle A. Jacquet

PERSPECTIVE

Unintentional drowning is the sixth most common cause of accidental death, accounting for 4086 deaths (1.4 per 100,000) in the United States in 2007.[1] Among children 1 to 4 years of age, drowning is the leading cause of injury mortality; for 10- to 14-year-olds, it is second only to motor vehicle crashes.[1-3]

Each year an estimated 500,000 people die worldwide after drowning, which exceeds mortality due to war.[4] Low- and middle-income countries account for 97% of all drowning deaths.[5] A study of drowning deaths in South Africa indicated a death rate of 12 per 100,000 for all ages in 2004.[6]

The incidence of drowning with nonfatal outcomes is unknown. The Centers for Disease Control and Prevention estimates that for every child who dies by drowning in the United States, another four receive emergency department (ED) care for a submersion event, and half of these children require hospitalization.[7] Among all age groups, an estimated one to four hospitalizations secondary to nonfatal submersions occur for every drowning death.[8-10] The economic implications of drowning injuries are profound. In Australia, drowning has the highest average lifetime cost (US $40,071) of any injury type.[11]

Submersion injuries occur in domestic settings such as swimming pools, hot tubs, bathtubs, large buckets, and rainwater tanks and in all forms of natural bodies of water. A review of all drowning deaths among individuals younger than 20 years in the United States during a 1-year period revealed that 55% of infants younger than 1 year drown in bathtubs, and nearly 16% drown in large household buckets.[12] Most (56%) children 1 to 4 years old drown in artificial pools, whereas most (63%) deaths among older children occur in natural bodies of fresh water.[12]

Because of the recent natural disasters, the incidence of drowning injuries and fatalities is rising. In disasters such as floods and tsunamis, older populations are disproportionately affected. A study from hurricane Katrina found that 49% of fatalities were in people 75 years of age or older.[13]

PRINCIPLES OF DISEASE

Definitions

Traditionally, the terminology describing submersion injuries has been confusing and impractical. In the past, *drowning* referred to death within 24 hours of suffocation from submersion in a liquid, whereas *near-drowning* described victims who survived at least 24 hours past the initial event regardless of the outcome. In 2005 the World Health Organization (WHO) published a new policy defining drowning to clarify documentation and to better track submersion injuries worldwide. Drowning was defined as "the process of experiencing respiratory impairment from submersion/immersion in liquid." Furthermore, the WHO policy stated, "Drowning outcomes should be classified as: death, morbidity, and no morbidity. … the terms wet, dry, active, passive, silent, and secondary drowning should no longer be used."[4] The term *near-drowning* should not be used, and the association of the term *drowning with a fatal outcome* should be abandoned.

Immersion syndrome refers specifically to syncope resulting from cardiac dysrhythmias on sudden contact with water that is at least 5° C lower than body temperature. The risk is proportional to the difference between body temperature and water temperature. Wetting of the face and head before entrance into the water may prevent the inciting sequence of events. Putative mechanisms for the syndrome are vagal stimulation leading to asystole and ventricular fibrillation secondary to QT prolongation after a massive release of catecholamines on contact with cold water. The resultant loss of consciousness leads to secondary drowning.[2]

Risk Factors

Age, gender, and race affect incidence of drowning. Toddlers and older teenagers are at greatest risk of death by drowning, with annual incidences of 2.46 and 1.47 per 100,000, respectively.[1] Boys account for almost 80% of victims older than 1 year.[1] Black males between 15 and 19 years of age have the highest annual incidence of drowning mortality (3.92 per 100,000), and black children between the ages of 5 and 14 years drown at nearly three times the rate of white children of the same age.[1,7,12] The risk of death by drowning within the American Indian population is twice as high as it is for the white population.[1]

Ethanol consumption in proximity with water is a major risk factor for submersion injury or death. Acute ethanol intoxication may be a contributing factor in 30 to 50% of drownings among adults and adolescents.[8] In one study of boating fatalities, most of which were due to drowning, an association was established between blood ethanol concentration (BEC) and risk of death from drowning while using watercraft. Odds ratios of fatality from drowning followed a trend from 2.8 for a BEC of 1 to 49 mg/dL

www.ketabpezeshki.com 66485457-66963820

to 37.4 for a BEC of 150 mg/dL or greater compared with sober case controls.[14]

Drowning in the United States follows clear temporal patterns. Two thirds of pediatric deaths occur between May and August, and most submersion injuries occur on weekends between noon and 8 PM.[8] Submersion victims older than 20 years are most often participating in water sports or using watercraft.

The relationship between swimming ability and the risk of drowning is unclear. No direct evidence exists to suggest that inexperienced swimmers are more likely to drown. On the contrary, skilled swimmers have greater exposure to water and may be more prone to submersion incidents.[15]

Numerous medical conditions confer an increased likelihood of drowning or submersion injury. Seizure disorders increase the chance of drowning among children and adolescents nearly 20 times.[16] Autism and other developmental and behavioral disorders increase risk in children as well.[17-19] Prolonged QT syndrome is also a risk factor for drowning. Laboratory studies show that immersion in cold water extends the QT interval. Interrogation of the automated internal cardiac defibrillator of a 12-year-old girl with prolonged QT syndrome who had a cardiac arrest on diving into the ocean revealed immediate further prolongation of the QT interval, followed by a premature ventricular complex and subsequent ventricular tachycardia within 5 seconds.[20,21] This phenomenon may account for a significant proportion of immersion syndrome events and otherwise unexplained submersion injuries.

Pathophysiology

Unexpected submersion triggers breath-holding, panic, and a struggle to surface. Air hunger and hypoxia develop, and the victim begins to swallow water. As breath-holding is overcome, involuntary gasps result in aspiration. The quantity of fluid aspirated, rather than the composition, determines subsequent pulmonary derangement.

The historical emphasis on pathophysiologic differences between freshwater and saltwater aspiration with respect to resultant electrolyte imbalance, hemolysis, and fluid compartment shifting was based on animal studies conducted in the early 20th century. Subsequent investigations revealed that significant intravascular abnormalities do not occur until the amount of aspirated water exceeds 11 mL/kg of body weight; autopsy studies show that most drowning victims aspirate less than 4 mL/kg.[22] In one review of the hospital treatment of 91 submersion victims, no patient required emergent intervention for a significant electrolyte abnormality.[23] Aspiration of 1 to 3 mL/kg of either fresh water or salt water destroys the integrity of pulmonary surfactant, leading to alveolar collapse, atelectasis, noncardiogenic pulmonary edema, intrapulmonary shunting, and ventilation-perfusion mismatch.[2] Profound hypoxia and metabolic and respiratory acidoses ensue, leading to cardiovascular collapse, neuronal injury, and ultimately death.

The classic hypothesis was that 10 to 15% of drowning victims die without aspiration of a significant amount of water. Death from such *dry* drowning putatively results from severe laryngospasm causing hypoxia, convulsion, and death without entry of fluid into the lungs. An exhaustive review of the literature failed to corroborate this hypothesis.[24] *Dry drownings* more appropriately reflect deaths from causes other than simple submersion.

Many factors may influence the pathophysiologic sequence of events in submersion injury and affect the chance of survival, including age, water temperature, duration and degree of hypothermia, diving reflex, and effectiveness of resuscitative efforts. Because of a lower ratio of body mass to surface area, children have hypothermia more quickly and to a greater degree after immersion in cold water than adults do. Hypothermia lowers cerebral metabolic rate and is neuroprotective to some extent for victims of submersion injury.[25] Despite dramatic case reports of patients surviving prolonged submersion in cold water with full neurologic recovery, hypothermia is generally a poor prognostic finding. Cold-water immersion speeds the development of exhaustion, altered consciousness, and cardiac dysrhythmia. The *diving reflex* may also play a protective role in infant and child submersions. Activation of the diving reflex by fear or immersion of the face in cold water shunts blood centrally to the heart and brain. Apnea and bradycardia ensue, prolonging the duration of submersion tolerated without central nervous system damage.[26]

CLINICAL FEATURES

Symptoms and Signs

Many submersion injuries are witnessed. Toddler drownings are an important exception, however, often occurring because of a lapse in supervision. On occasion, the history of coughing, choking, or vomiting in a patient found near a body of water suggests the diagnosis. Signs of *pulmonary injury* may be obvious in a submersion victim who is hypoxic, cyanotic, and in obvious respiratory distress or arrest. More subtle clues, such as increased respiratory rate and audible rhonchi, rales, or wheezes, should alert the clinician to evolving respiratory compromise. Submersion victims swallow a significantly greater volume of water than is aspirated, and gastric distention from positive-pressure ventilation during rescue is common. As a result, 60% of patients vomit after a submersion event.[2] Aspiration of gastric contents greatly compounds the degree of pulmonary injury and increases the likelihood that acute respiratory distress syndrome will ensue. In addition, aspiration of particulate contaminants such as mud, sewage, and bacteria may obstruct the smaller bronchi and bronchioles and greatly increase the risk of infection (both bacterial and fungal in nature).[27]

Victims with *central nervous system injury* may present with symptoms ranging from mild lethargy to coma with fixed and dilated pupils. Central nervous system injury results from the initial hypoxic or ischemic insult and from the cascade of reperfusion injury that follows reestablishment of cerebral blood flow after an arrest. The release of inflammatory mediators and the generation of oxygen free radicals in the postresuscitative period contribute to cytotoxic cerebral edema, compromise of the blood-brain barrier, and increased intracranial pressure. Cerebral arteriolar vasospasm and enhanced platelet aggregation impede cerebral perfusion at the macrocirculatory and microcirculatory levels.[26]

Cardiac dysrhythmias may incite a submersion injury or develop as its consequence. Hypoxemia, acidosis, and, potentially, hypothermia are the primary factors responsible for dysrhythmias ranging from ventricular tachycardia and fibrillation to bradycardia-asystole. Electrolyte disturbances are rarely significant enough to be dysrhythmogenic.[23]

Other clinical sequelae of submersion injury may include acute *renal impairment,* present in approximately 50% of patients as the result of lactic acidosis; prolonged hypoperfusion; and, in some instances, rhabdomyolysis.[28] *Coagulopathy* as a consequence of associated hypothermia or disseminated intravascular coagulation may also occur.

Prognostic Factors

Many factors help predict patients who will survive a submersion injury neurologically intact. Hypoxia, which is usually dependent on submersion time, is the most important factor related to outcome and subsequent quality of life in drowning victims.[29] Submersion victims who arrive in the ED alert with normal hemodynamics are unlikely to experience neurologic impairment. Circumstantial variables that portend a poor outcome include victim

www.ketabpezeshki.com 66485457-66963820

age younger than 3 years, submersion for longer than 5 to 10 minutes, and initiation of cardiopulmonary resuscitation (CPR) more than 10 minutes after rescue.[2,30] Adverse neurologic findings on initial presentation do not preclude full neurologic recovery, although in general, patients whose duration of submersion or resuscitation exceeds 25 minutes have an unfavorable outcome.[31] With the exception of victim age, however, such measurements are generally either unknown or inaccurately estimated at the time of a patient's arrival in the ED. On arrival, objective findings associated with an unfavorable prognosis include hypothermia, severe acidosis, unreactive pupils, a Glasgow Coma Scale score of 3, and asystole or the need for ongoing CPR.[2,32-35] Neurologically intact survival is reported for individual patients even with several of these factors present; none of several proposed scoring systems using combinations of these variables has 100% predictive power.[30,33,36,37]

A retrospective study of submersion injury in children noted that all patients who present with an abnormal head computed tomography (CT) scan within the first 24 hours eventually die. Furthermore, an abnormal head CT scan at any time is associated with poor outcome (death or persistent vegetative state).[38]

DIFFERENTIAL CONSIDERATIONS

The precipitants of a submersion injury, such as drug or ethanol intoxication, cardiac arrest, hypoglycemia, seizure, and attempted suicide or homicide, should be considered in patients found unresponsive in the water. For pediatric victims, child abuse or neglect should also be considered a potential cause.

Potential head or cervical spine injury is an important consideration in submersion associated with trauma. A review of 2244 cases of submersion injury in Washington State identified only 11 (0.5%) patients with a cervical spine injury. Each patient had either clinical signs of serious trauma or a history of motor vehicle crash, fall from height, or diving into the water.[39] Unless such factors are present, routine cervical spine immobilization for submersion victims is not warranted.

DIAGNOSTIC STUDIES

Cardiac monitoring and an electrocardiogram should be obtained to determine the presence of significant dysrhythmias, QT prolongation, or ischemia. Hypothermia resulting from drowning may cause vasoconstriction and coronary vessel spasm and may be responsible for cardiac ischemia and myocardial injury.[40] Pulse oximetry, capnography, and arterial blood gases should be monitored closely in all submersion victims for signs of hypoxemia, hypercarbia, and acidosis. Blood glucose, serum creatinine, and electrolyte values should be obtained, although serum creatinine concentration and electrolyte levels are usually normal on initial presentation. Similarly, complete blood count is often normal with the exception of leukocytosis. Toxicologic screening may be appropriate, depending on the circumstances of the submersion. Subsequently, evidence of renal failure, hepatic dysfunction, and disseminated intravascular coagulation may be noted on laboratory testing.

The initial chest radiograph may underestimate the severity of pulmonary injury, although infiltrates or pulmonary edema may be evident within hours. Cranial CT is rarely initially contributory unless significant trauma or other pertinent injury is suspected. Magnetic resonance imaging of the brain may predict neurologic outcome after submersion injury, but its prognostic value is not optimal until 3 or 4 days elapse.[37,41]

MANAGEMENT

Salient details of the events surrounding the accident should be ascertained rapidly. Resuscitation of pulseless and apneic patients should be attempted initially in most cases because bystander estimates of total submersion time are often inaccurate. The clinical presentation of severe hypothermia often mimics death, and case reports exist of functional recovery for individuals submerged for 66 minutes.[42,43]

For a victim without vital signs, outcome depends on the interval preceding CPR. Mouth-to-mouth assisted ventilation should begin immediately, even before the victim is extricated from the water. Chest compressions are impractical before extrication but should be initiated as soon as the individual is placed on a solid surface. Maneuvers such as those proposed by Heimlich and Patrick to remove fluid from the lungs are ineffective and dangerous in a victim at risk for aspiration and may delay ventilation. Use of such maneuvers is not recommended unless there is reason to suspect airway occlusion by a foreign body.[44]

On arrival in the ED, cardiac monitoring and continuous pulse oximetry should be established. A core temperature obtained with a low-reading probe is indicated for any unstable or lethargic patient. Values obtained by use of infrared ear thermometry are unreliable.[45] Rewarming of a hypothermic patient may suffice for hemodynamic stabilization and improvement in mental status. Bedside blood glucose measurement and empirical naloxone administration are warranted. A spontaneously breathing patient should be monitored for signs of developing pulmonary injury. Initial chest radiographs are often unremarkable even in the setting of serious and evolving pathologic processes. Frequent arterial blood gas measurements are indicated to monitor rapidly changing respiratory function.

Clinical impression and objective determination of the adequacy of oxygenation and ventilation should determine the decision for tracheal intubation. Apparent or developing respiratory distress, absence of protective airway reflexes, and significant associated head or chest injuries are indications. A $Paco_2$ greater than 50 mm Hg should prompt strong consideration of intubation and mechanical ventilation. Patients unable to maintain oxygen saturation greater than 90% or with a Pao_2 greater than 60 mm Hg on high-flow oxygen require positive airway pressure to increase functional residual capacity, to decrease intrapulmonary shunting, and to reduce ventilation-perfusion mismatch. In awake patients, this may be accomplished by face or nasal mask (continuous positive airway pressure), but the risk of potential gastric distention, vomiting, and aspiration should be considered. Otherwise, tracheal intubation and mechanical ventilation with positive end-expiratory pressure are necessary. The hemodynamic consequences of positive end-expiratory pressure should be monitored carefully because increased intrathoracic pressure may compromise venous return and cardiac output. Decreased cranial venous return may impede cerebral perfusion.

No consensus exists with regard to the appropriate length of resuscitative effort for hypothermic submersion victims in the ED. The safest parameter is to continue until the core temperature reaches at least 32 to 35° C because cerebral death cannot be diagnosed accurately in hypothermic patients with temperatures below this level. This parameter may not always be practical, however, because brain-dead patients are often poikilothermic.

The administration of corticosteroids in the setting of submersion injury and potential acute respiratory distress syndrome does not improve outcome.[2,37] Barbiturate-induced coma, aggressive diuresis, neuromuscular blockade, and hyperventilation do not improve neurologic outcome and, particularly in the case of hyperventilation, may be harmful.[26] Similarly, empirical antibiotics do not increase survival and should be administered only to the rare patient who was submerged in grossly contaminated water or who shows signs of infection or sepsis.[2]

Interventions such as induced or permissive hypothermia aimed at attenuation of reperfusion injury after anoxic brain insult are the focus of intense investigative effort. A case report of twin toddlers with identical submersion injury and subsequent

www.ketabpezeshki.com 66485457-66963820

prolonged cardiac arrest indicated that therapeutic hypothermia may be a factor in influencing a good neurologic outcome. One twin was treated with therapeutic hypothermia for 72 hours and had a return to normal neurologic status. The other twin was not cooled and survived, but with significant neurologic impairment.[46] Drowning victims in cardiac arrest are usually colder than 30° C and require warming. Comatose patients who have been resuscitated after reasonable submersion time regardless of rhythm should not be rewarmed above 34° C. Case reports suggest that rewarming only up to 34° C followed by a 24-hour mild hypothermic treatment before normothermia is reached may be advantageous because of decreased pulmonary reperfusion injury and reduced secondary brain injury.[47,48] Reports such as these and studies in the resuscitation literature indicate an emerging role for therapeutic hypothermia in drowning victims.

DISPOSITION

Symptomatic patients should be admitted for treatment. Patients with a history of apnea, unconsciousness, or hypoxia and any patients who manifest dysrhythmia or an abnormal chest radiograph also require admission. Patients who are asymptomatic on presentation to the ED, maintain a normal room air oxygen saturation, and have no chest radiograph or arterial blood gas abnormalities can be discharged safely after an observation period of 6 hours.[37,49] Careful instructions about symptoms or signs of delayed pulmonary complications are necessary, and the patient should be discharged in the care of a competent adult.

Preventive Efforts

The mortality rate from drowning is decreasing since the 1990s in the United States.[1,3,37] A similar downward trend in submersion injuries is reported in Great Britain.[50] Although the exact causes of this decline are unknown, an increased public awareness of preventive measures and an emphasis on public education with regard to CPR and the dangers of ethanol use in conjunction with water-related activities are contributing significantly to the reduction in fatalities. A longitudinal study of drownings during a 21-year period in Washington State noted that the incidence of death attributable to ethanol use has decreased by 81%.[2]

Parental education about the danger of pediatric drowning is an important focus of preventive effort. Inadequate supervision of children playing in or near water is one of the most common causes of pediatric submersion death, underscoring the importance of increasing awareness of the need for constant oversight of children in this setting.[10,51] Most pediatric submersion injuries in swimming pools occur at the victim's home.[10] In most cases, the child is last seen in the house, is left unattended for a moment, and enters the pool on an unfenced side closest to the home with no audible splash or screaming.[12] Adequate and fully circumferential fencing of residential pools is a current recommendation of the American Academy of Pediatrics. A meta-analysis of the literature regarding the efficacy of this preventive step reported an odds ratio of 0.27 for drowning or submersion in a properly fenced compared with a nonfenced pool.[51,52] In Australia, safety legislation is associated with a 30% reduction in drowning rates in young children.[53] Some areas require fencing of pools and other artificial bodies of water. Unfortunately, legislation requiring appropriate fencing is poorly adhered to, and one study revealed that only 40% of households are compliant.[54] Even though bodies of water can be fenced in high-income countries, the fencing of all waterways, ponds, and ditches would be unrealistic in low- and middle-income countries. In these countries, swimming education programs are an attractive alternative.

Pool covers are inadequate and potentially dangerous as barriers. Solar blankets do not support the weight of a child and can enmesh and obscure a struggling victim from view. A rigid pool cover may convey a false sense of stability to a child tempted to walk across its surface and is considered an insufficient substitute for effective four-sided fencing.[51]

Medical care providers are a vital resource for enhancement of public awareness of the importance of these measures. The literature supports the concept that education in the ED about drowning prevention can have a positive impact on patient and family awareness of steps to lessen the likelihood of catastrophic drowning or submersion injury.[55,56]

KEY CONCEPTS

- The fluid medium in which a submersion injury occurs (fresh water versus salt water) is usually of little clinical relevance; all significant submersions induce pulmonary injury and hypoxia by the amount of water aspirated and the duration of submersion, not the water content.
- Aggressive pulmonary support is essential to optimization of the victim's chances for a favorable outcome.
- In submersion incidents, the Heimlich maneuver is reserved for patients with a suspected airway occlusion by a foreign body.
- No prognostic scale or clinical presentation accurately predicts long-term neurologic outcome; normal neurologic recovery is documented in patients with prolonged submersions, persistent coma, cardiovascular instability, and fixed and dilated pupils.
- Hyperventilation, steroids, dehydration, barbiturate coma, and neuromuscular blockade do not improve outcome.
- Comatose patients who have been resuscitated after reasonable submersion time regardless of rhythm should not be rewarmed above 34° C.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. National Center for Injury Prevention and Control, Centers for Disease Control and Prevention: *WISQARS (web-based injury statistics query and reporting system)* [database]. Available at www.cdc.gov/ncipc/wisqars. Accessed April 25, 2011.
2. Orlowski JP, Szpilman D: Drowning: Rescue, resuscitation, and reanimation. *Pediatr Clin North Am* 2001; 48:627.
3. Cummings P: Trends in unintentional drowning: The role of alcohol and medical care. *JAMA* 1999; 281:2198.
4. Van Beeck EF, et al: A new definition of drowning: Towards documentation and prevention of a global public health problem. *Bull World Health Organ* 2005; 83:853.
5. Peden MM, McGee K: The epidemiology of drowning worldwide. *Inj Control Saf Promot* 2003; 10:195-199.
6. Meel BL: Drowning deaths in Mthatha area of South Africa. *Med Sci Law* 2008; 48:329.
7. National Center for Injury Prevention and Control, Centers for Disease Control and Prevention: *Water-related injuries* [fact sheet]. Available at www.cdc.gov/ncipc/factsheets/drown.htm. Accessed April 25, 2011.
8. Brenner RA; American Academy of Pediatrics Committee on Injury, Violence, and Poison Prevention: Prevention of drowning in infants, children, and adolescents. *Pediatrics* 2003; 112:440.
9. Ellis AA, Trent RB: Hospitalizations for near drowning in California: Incidence and costs. *Am J Public Health* 1995; 85:1115.
10. Quan L, et al: Ten-year study of pediatric drownings and near-drownings in King County, Washington: Lessons in injury prevention. *Pediatrics* 1989; 83:1035.
11. Hyder A, et al: Childhood drowning in low- and middle-income countries: Urgent need for intervention trials. *J Paediatr Child Health* 2008; 44:221-227.
12. Brenner RA, et al: Where children drown, United States, 1995. *Pediatrics* 2001; 108:85.
13. Brunkard J, et al: Hurricane Katrina deaths, Louisiana, 2005. *Disaster Med Public Health Prep* 2008; 2:215-223.
14. Smith GS, et al: Drinking and recreational boating fatalities: A population-based case-control study. *JAMA* 2001; 286:2974.
15. Brenner RA, Saluja G, Smith GS: Swimming lessons, swimming ability, and the risk of drowning. *Inj Control Saf Promot* 2003; 10:211.
16. Bell GS, et al: Drowning in people with epilepsy. *Neurology* 2008; 71:578-582.
17. Diekema DS, Quan L, Holt VL: Epilepsy as a risk factor for submersion injury in children. *Pediatrics* 1993; 91:612.
18. Shavelle RM, Strauss DJ, Pickett J: Causes of death in autism. *J Autism Dev Disord* 2001; 31:569.
19. Brehaut JC, et al: Childhood behavior disorders and injuries among children and youth: A population-based study. *Pediatrics* 2003; 111:232.
20. Ackerman MJ, Tester DJ, Porter CJ: Swimming: A gene-specific arrhythmogenic trigger for inherited long QT syndrome. *Mayo Clin Proc* 1999; 74:1088.
21. Baktra AS, Silka MJ: Mechanism of sudden cardiac arrest while swimming in a child with the prolonged QT syndrome. *J Pediatr* 2002; 141:283.
22. Modell JH, Davis JH: Electrolyte changes in human drowning victims. *Anesthesiology* 1969; 30:414.
23. Modell JH, Craves SA, Ketover A: Clinical course of 91 consecutive near-drowning victims. *Chest* 1976; 70:231.
24. Modell JH, Bellefleur M, Davis JH: Drowning without aspiration: Is this an appropriate diagnosis? *J Forensic Sci* 1999; 44:1119.
25. Biggart MJ, Bohn DJ: Effect of hypothermia and cardiac arrest on outcome of near-drowning accidents in children. *J Pediatr* 1990; 117:179.
26. Sachdeva RC: Near drowning. *Crit Care Clin* 1999; 15:281.
27. Ender PT, Dolan MJ: Pneumonia associated with near-drowning. *Clin Infect Dis* 1997; 25:896.
28. Spicer TS, et al: Acute renal impairment after immersion and near-drowning. *J Am Soc Nephrol* 1999; 10:382.
29. Ballesteros MA, et al: Prognostic factors and outcome after drowning in an adult population. *Acta Anaesthesiol Scand* 2009; 53:935-940.
30. Suominen P, et al: Impact of age, submersion time, and water temperature on outcome in near-drowning. *Resuscitation* 2002; 52:247.
31. Jacinto SJ, Gieron-Korthals M, Ferreira JA: Predicting outcome in hypoxic-ischemic brain injury. *Pediatr Clin North Am* 2001; 48:647.
32. Habib DM, et al: Prediction of childhood drowning and near-drowning morbidity and mortality. *Pediatr Emerg Care* 1996; 12:255.
33. Christensen DW, Jansen P, Perken RM: Outcome and acute care hospital costs after warm water near drowning in children. *Pediatrics* 1997; 99:715.
34. Graf WD, Cummings P, Quan L: Predicting outcome in pediatric submersion victims. *Ann Emerg Med* 1995; 26:312.
35. Zuckerman GB, Gregory PM, Santos-Damiani SM: Predictors of death and neurologic impairment in pediatric submersion injuries: The Pediatric Risk of Mortality Score. *Arch Pediatr Adolesc Med* 1998; 152:134.
36. Gonzalez-Luis G, et al: Use of the Pediatric Risk of Mortality Score as predictor of death and serious neurologic damage in children after submersion. *Pediatr Emerg Care* 2001; 17:405.
37. Ibsen LM, Koch T: Submersion and asphyxial injury. *Crit Care Med* 2002; 11:S402.
38. Rafaat KT, et al: Cranial computed tomographic findings in a large group of children with drowning: Diagnostic, prognostic, and forensic implication. *Pediatr Crit Care Med* 2002; 9:567-572.
39. Watson RS, et al: Cervical spine injuries among submersion victims. *J Trauma* 2001; 51:658.
40. Chen LB, Lai YC: Case report: Myocardial infarction after near drowning. *Am J Emerg Med* 2008; 26:635.e3-635.e5.
41. Dubowitz DJ, et al: MR of hypoxic encephalopathy in children after near drowning: Correlation with quantitative proton MR spectroscopy and clinical outcome. *AJNR Am J Neuroradiol* 1998; 19:1617.
42. Bolte RG, et al: The use of extracorporeal rewarming in a child submerged for 66 minutes. *JAMA* 1988; 260:377.
43. Hughes SK, et al: Neurodevelopmental outcome for extended cold water drowning: A longitudinal case study. *J Int Neuropsychol Soc* 2002; 8:588.
44. Rosen P, Stoto M, Harley J: The use of the Heimlich maneuver in near drowning: Institute of Medicine report. *J Emerg Med* 1995; 13:397.
45. Muth CM, et al: Infrared ear thermometry in water-related accidents—not a good choice. *J Emerg Med* 2010; 38:417-421.
46. Hein OV, et al: Mild hypothermia after near drowning in twin toddlers. *Crit Care* 2004; 8:R353.
47. Coskun KO, et al: Extracorporeal circulation for rewarming in drowning and near-drowning pediatric patients. *Artif Organs* 2010; 34:1026-1030.
48. Guenther U, et al: Extended therapeutic hypothermia for several days during extracorporeal membrane-oxygenation after drowning and cardiac arrest: Two cases of survival with no neurological sequelae. *Resuscitation* 2009; 80:379-381.
49. Causey AL, Tilelli JA, Swanson ME: Predicting discharge in uncomplicated near-drowning. *Am J Emerg Med* 2000; 18:9.
50. Sibert JR, Lyons RA, Smith BA: Preventing deaths by drowning in the United Kingdom: Have we made progress in 10 years? Population-based incidence study. *BMJ* 2002; 324:1070.
51. American Academy of Pediatrics, Committee on Injury, Violence, and Poison Prevention: Prevention of drowning in infants, children, and adolescents. *Pediatrics* 2003; 112:437.
52. Thompson DC, Rivara FP: Pool fencing for preventing drowning in children. *Cochrane Database Syst Rev* 2000; 2:CD001047.
53. Pearn JH, et al: Safety legislation, public health policy and drowning prevention. *Int J Inj Control Saf Promot* 2008; 15:112-123.
54. Stevenson MR, et al: Childhood drowning: Barriers surrounding private swimming pools. *Pediatrics* 2003; 111:2.
55. Quan L, et al: Do parents value drowning prevention information at discharge from the emergency department? *Ann Emerg Med* 2001; 37:382.
56. Barkin S, Gelberg L: Sink or swim—clinicians don't often counsel on drowning prevention. *Pediatrics* 1999; 104:1217.

www.ketabpezeshki.com 66485457-66963820

Chapter 146

Radiation Injuries

Christopher B. Colwell

HISTORICAL PERSPECTIVE AND EPIDEMIOLOGY

The technology of the 20th and 21st centuries has ushered in the nuclear age. Nuclear energy has significant peaceful industrial and medical uses, but it poses great potential danger as well. Although the safety record involving the use of radiation and radioisotopes is excellent overall, the possible hazards involved are well known. The earthquake and subsequent tsunami in Japan on March 11, 2011, is yet another reminder of the dangers associated with nuclear energy. The near-disaster that occurred at Three Mile Island in Pennsylvania in 1979, the disastrous accident at the Chernobyl Nuclear Power Station in the former Soviet Union in 1989, and the potential for disaster that occurred at a uranium processing plant in Tokaimura, Japan, in 1999 are further reminders of this very real risk.[1,2] The potential contamination of large numbers of people will continue to stress the capabilities of existing emergency medical systems.

The only wartime use of atomic and nuclear energy was the detonation of atomic bombs over Hiroshima and Nagasaki in 1945. Many nations now have nuclear weapons in their arsenals, however, and the possibility for terrorist groups to obtain and to use such weapons does exist. Because the spent fuel from a nuclear power reactor can be reprocessed into plutonium, which can be used to produce nuclear weapons, more countries have now acquired the necessary raw materials to produce these weapons. The technology is available for the production and use of small, low-yield, tactical nuclear weapons and for megaton-yield, strategic nuclear weapons.

Although the proliferation of nuclear weapon technology along with the growth of global terrorism raises new concerns about a rogue nation or terrorist group, a more likely scenario is the production and detonation of a "dirty bomb." In contrast to a nuclear weapon, which would be difficult to produce, a dirty bomb can be produced and detonated with relative ease. The greatest threat from such a bomb lies in its potential to cause widespread terror from fear of radioactive contamination. Although the number of deaths and injuries resulting from a dirty bomb should not exceed those of a conventional explosion, the panic over radioactivity and evacuation measures and the prolonged cleanup efforts that would ensue could wreak prolonged havoc.

A dirty bomb can be produced from existing strontium-90 or cobalt-60 radioactive materials, such as radium and cesium-137 isotopes that are used in some forms of cancer therapy. These are found in many hospitals or university laboratories. Such a weapon can be produced by combining radioactive materials in solid or powder form with a conventional explosive that on detonation would send radioactive material into the area of the explosion and downwind. Although negligible or no harm would be likely from these sources of radiation, there could be tremendous psychological effects.[3,4]

It is technically much more difficult to produce a nuclear weapon than it is to manufacture a chemical or a biologic weapon. Use of a nuclear weapon by terrorists is highly unlikely unless they obtain such a weapon from existing stockpiles, which would include sources that may have been lost from governmental control in developing countries and areas of the former Soviet Union.

Injury from a nuclear explosion initially involves the mechanical effects of the blast wave that result in large-scale conventional types of blunt and penetrating trauma. Thermal or burn effects follow. The effects of ionizing radiation injury occur in proportion to the blast and thermal effects. In addition, radioactive fallout results from a nuclear weapon detonation on or above the ground. Detonation of a nuclear weapon could produce devastation and injury from its immediate and long-term effects (Table 146-1).[5]

Accidents involving peacetime nuclear energy include exposure to and contamination by radioactive sources. Medical, industrial, and laboratory accidents can expose people to unacceptably high doses of radiation. Increased commercial transport of such materials results in an increased risk of accidents during transport. Emergency physicians are concerned primarily with the acute effects of exposure and contamination. The long-term effects continue to be studied in the populace exposed to radiation as a result of the Chernobyl accident.[1]

Nuclear Reactor Incidents

A nuclear weapon, as distinguished from a nuclear reactor, is designed to be autocatalytic (i.e., rather than being self-sustaining, the power grows without bounds after the chain reaction is initiated). The water-cooled nuclear reactors in U.S. power plants are designed to operate in their most reactive configuration. Any material or geometric change (except for removal of the control rods) renders them subcritical. In the graphite-moderated, steam-cooled reactors operating in the former Soviet Union, a nuclear excursion or accident can occur because of loss of coolant, as at Chernobyl.[6]

Every nuclear reactor should be housed within a containment structure to prevent the accidental release of radioactivity. The Three Mile Island reactor has five defense layers. Thus the accident in 1979 resulted in very little radiation release into the environment. At Chernobyl, however, the containment structure failed, and all the radioactive material from the core of the reactor escaped into the environment. Although the amount of radioactive material released at Chernobyl was only approximately three times the Three Mile Island release, failure of containment resulted in a 5000 times greater dose of radiation within a 10-mile radius

www.ketabpezeshki.com 66485457-66963820

Table 146-1 Approximate Distance from the Detonation Site at Which a 50% Fatality Rate Might Be Expected, According to the Size of a Nuclear Weapon

YIELD (kt)	SHOCK WAVE	THERMAL RADIATION (m)	IONIZING RADIATION Initial	IONIZING RADIATION Residual*
0.01	60	60	350	1270
0.1	130	200	460	2750
1	275	610	790	5500
10†	590	1800	1200	9600

Data from the National Council on Radiation Protection and Measurements: Management of Persons Accidentally Contaminated with Radionuclides. Washington, DC, National Council on Radiation Protection and Measurements, 1980. NCRP Report No. 65.
*Data are for residual radiation (mostly fallout) in the first hour.
†At yields exceeding 10 kt, the lethal range of the fireball extends several times farther than the lethal range of either the blast or the initial radiation.

of Chernobyl (40,000 mrem compared with 8 mrem from Three Mile Island).[1] Adding to the tragedy, the large amount of radioactive material released into the atmosphere at Chernobyl was carried aloft by prevailing winds.

As a result of human error at a uranium processing plant in Tokaimura, Japan, 49 people were exposed to radiation, two of whom received a potentially lethal dose. Enriched uranium was mixed with nitric acid in an open vessel, resulting in Cherenkov radiation. This radiation is released when the speed of a charged particle in a transport medium is so high that it exceeds the velocity of light in that medium. A visible flash results from radiation emitted when the uranium reaches a critical mass and triggers an uncontrolled chain reaction for 20 hours.

Finally, a terrorist attack on a nuclear reactor could result in an atmospheric plume of radioactive iodine and noble gases released through a breach in the reactor core. These gases could have immediate health effects nearby, and long-term effects from radioactive iodine could occur at great distances from the reactor.

Radon Exposure

Radon gas is the major source of radiation exposure to the general public. Radon and its breakdown products are in the decay chain of uranium-238. Because uranium-238 has a long half-life and is distributed throughout the earth's rocks and soil, its decay products are ubiquitous. The decay scheme of radon results in the production of four heavy metal isotopes with short half-lives termed radon daughters (Fig. 146-1). These isotopes include alpha-emitting solids that can be inhaled and deposited in the tracheobronchial tree.

Radon-222 is a colorless, odorless, natural radioactive gas that moves by diffusion and pressure flow into basements and lower levels of buildings, where concentrations may reach hazardous levels. Radon daughters can be collected on filters, and alpha activity can be measured. The major source of radon gas is soil containing high levels of radon, such as uranium tailings, which are waste byproducts, used for landfill beneath buildings. Sealing of basement cracks can decrease radon gas entry, and its removal can be enhanced by proper ventilation systems.[7]

Because radon and radon daughters result from the decay of uranium-238, uranium miners sustain some of the highest levels of occupational exposure. These individuals have an increased incidence of lung cancer and interstitial pulmonary fibrosis secondary to radon progeny exposure from inhalation of alpha

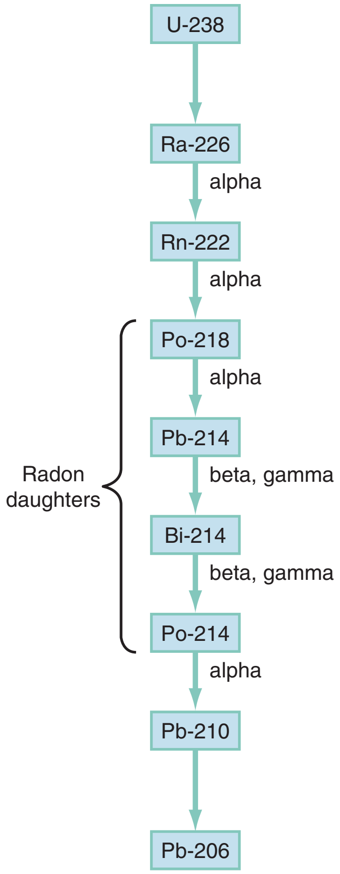


Figure 146-1. Radon and radon daughters in the major decay path of uranium-238. (Redrawn from Hart BL, Mettler FA Jr, Harley NH: Radon: Is it a problem? Radiology 172:593, 1989.)

particles.[8] It is estimated that radon exposure accounts for up to 33,000 lung cancer deaths in the United States each year. Radon is the second-leading cause of lung cancer after cigarette smoking. Each year, 15,000 lung cancer deaths in the United States may result from indoor radon exposure.[9]

PATHOPHYSIOLOGY OF RADIATION EXPOSURE

The electromagnetic spectrum (Fig. 146-2) encompasses a range from microwaves to gamma rays; it includes long-wavelength, low-frequency, low-energy forms of nonionizing radiation and progresses to short-wavelength, high-frequency, high-energy forms of ionizing radiation. The frequency and length of these waves determine the energy, measured in units called *photons*. *Frequency* is the number of times per second the crest of a wave passes a given point, whereas *wavelength* is the distance between crests.

Ionizing versus Nonionizing Radiation

Radiation is the transfer of energy in the form of waves, rays, or particles. The term *radioactivity* refers to the loss of particles (e.g., alpha, beta, or neutrons) or energy (e.g., x-rays and gamma rays) from an unstable atom that is spontaneously decaying. The spontaneous transformation of an unstable isotope to a stable one is referred to as *decay,* and it may involve the release of ionizing radiation. Understanding of the effects of radiation exposure on humans requires a distinction between ionizing and nonionizing

www.ketabpezeshki.com 66485457-66963820

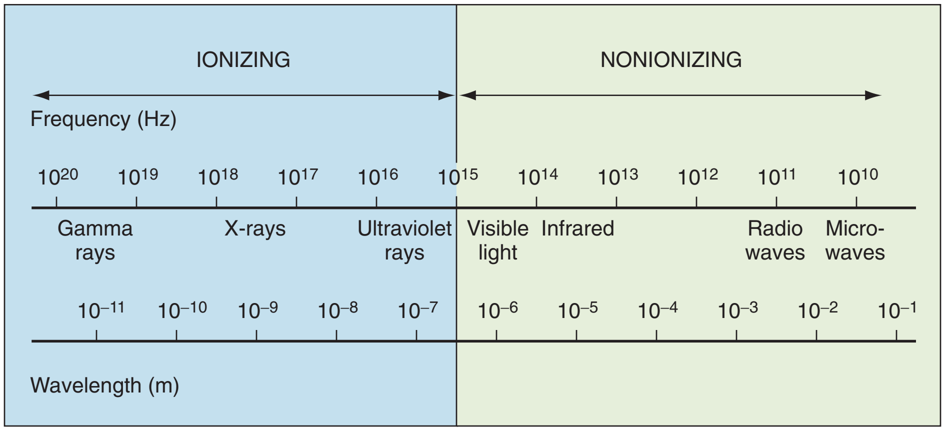


Figure 146-2. Electromagnetic spectrum.

radiation. *Nonionizing radiation* refers to all forms of the electromagnetic spectrum, with the exception of x-rays and gamma rays. Nonionizing (in contrast to ionizing) radiation has a long wavelength, low frequency, and low energy. As such, it does not carry enough energy to remove an electron from an atom and therefore does not produce charged ions on passing through matter. Examples of nonionizing radiation include visible light, radar, radio and television broadcasting, garage door openers, microwave ovens, relay stations, medical diathermy, and satellite communications.

The primary adverse effects of nonionizing radiation are related to local heat production because the energy of nonionizing radiation is essentially all expended in heat. This effect depends directly on the intensity of the source, the distance from the source to the person exposed, and the duration of exposure.[5] Long-term exposure to microwave irradiation at some distance from the source has received extensive study. The most thorough example involves U.S. State Department employees exposed to long-term microwave irradiation in the U.S. chancery in Moscow. This building was subjected to a direct beam that resulted in exposed rooms having a higher power density than that usually found on the ground near transmission towers. After extensive study, it was concluded that no adverse health effects occurred from this exposure. This and other studies performed on various groups of workers exposed to radiofrequency radiation concluded that the present exposure levels (including microwaves) do not cause significant adverse health effects to the general public. Specifically, there is no evidence of either decreased longevity or an increased incidence of cancer. The possibility of hazardous health effects resulting from low-level microwave exposure is an area of ongoing study.[10]

A microwave oven generates 2450-MHz microwaves. This megahertz wavelength can produce hyperthermia above a 25-mW level with a penetration of several centimeters. If a microwave oven has a door leak, a person can be exposed to the thermal effect of microwaves only by placement of a body part in direct contact with the area. Electromagnetic waves dissipate at a rate directly related to the square of the distance from the source. In other words, exposure is cut to one fourth at twice the distance from the source. No thermal effect exists at a distance of several feet, but a potential exists for deleterious effects on electronic devices that are sensitive to the wavelength of this electromagnetic radiation.

Ionizing radiation has a short wavelength, high frequency, and high energy. The photons of ionizing radiation carry 1 billion times more energy than the photons of nonionizing radiation. Ionizing radiation induces injury by directly causing cell death or by damaging DNA and other components and interrupting the cellular reproductive process. This in turn can lead to cellular dysfunction or death. Ionizing radiation is emitted in the form of alpha and beta particles, gamma rays, and x-rays.

Irradiation versus Contamination and Incorporation

Irradiation

A radioactive substance is one that emits ionizing radiation. It is referred to as a radionuclide or radioisotope. If such radiation passes through a nearby object, the object is said to have been irradiated. With the exception of the situation in which there is direct exposure to neutrons, the object that is irradiated does not become radioactive. When a person is irradiated but not contaminated, such as the post–radiation therapy patient, no hazard exists to medical personnel, and the patient may be handled like any other emergency patient.

Contamination

Radioactive contamination is essentially radioactive particulate matter (alpha and beta particles) on an exposed surface. Contamination is not an acute threat to the life of the patient or the provider, and its presence should not preclude institution of lifesaving measures. This radioactive particulate matter may emit radiation with an effect that is directly related to the time of exposure, distance from the source, and type of contamination. The four types of radiation that exist with the potential to contaminate are alpha, beta, gamma, and neutron radiation, and each presents different hazards (Fig. 146-3).

Alpha radiation consists of particles that are highly charged and composed of two protons and two neutrons. *Alpha particles* dissipate their energy quickly and travel only a few centimeters in the air. They cannot even penetrate paper and are therefore easily shielded. When they directly contact skin, penetration is limited to the thickness of the epidermis. Alpha radiation therefore presents a significant biohazard only when it is internalized. Alpha particles are produced by alpha emission from many of the heavy radioactive elements, such as plutonium and uranium decay. Newer Geiger-Mueller counters are able to detect alpha particles and are excellent for detection of beta and gamma radiation. *Beta particles* have a smaller mass and charge than alpha particles and tend to have a greater velocity. They have a tissue penetration of approximately 8 mm and can cause significant skin burns, although these burns are not generally visible immediately after the exposure. Because clothing effectively shields covered areas, the primary danger is to exposed skin. Standard skin cleansing

www.ketabpezeshki.com 66485457-66963820

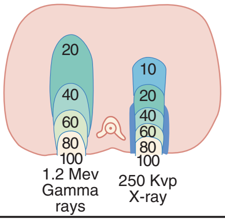
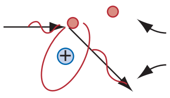
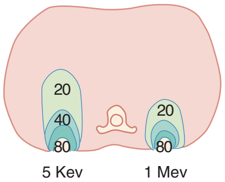
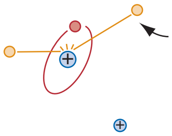
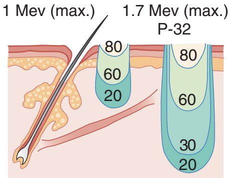
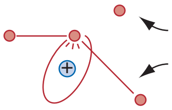
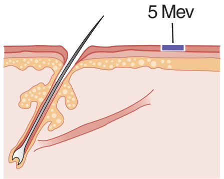
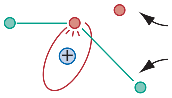
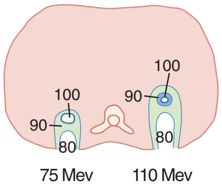
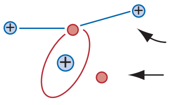
TYPE OF RADIATION	SYMBOL	USUAL SOURCE	PENETRATION OF EXTERNAL RADIATION		PRINCIPAL TYPES OF INTERACTION	
X-rays Gamma rays	x γ	X-ray machines and accelerators Most radioisotopes emit a gamma ray following beta decay		X- and γ rays penetrate deeply, for only a fraction of the rays interact with each layer of tissue		Ejected electron loses energy by causing additional ionization Deflected x- or γ ray may interact again some distance away Ionized atom formed after electron ejection
Neutrons	n	Neutrons are generally produced by critical assemblies, nuclear reactors, or accelerators		Neutrons penetrate deeply, for only a fraction of the neutrons interact with each layer of tissue		Deflected neutron may interact again some distance away Recoil proton loses energy by causing ionization
Beta particles	β	Most radioisotopes decay by beta emission, usually followed by gamma emission		Penetration depends on energy of beta but is usually limited to less than 8 mm in tissue		Ejected electron loses energy by causing additional ionization Deflected electron or beta particle causes additional ionization Ionized atom formed after electron ejection
Alpha particles	α	Many of the heavy radioactive elements such as plutonium decay by alpha particle emission		Penetration is limited to about the thickness of the epidermis		Ejected electron loses energy by causing additional ionization Deflected alpha goes on to cause additional ionization Ionized atom formed after electron ejection
Protons	p	Energetic protons are found only near particle accelerators		Penetration depends on energy of the proton		Deflected proton causes additional ionization Ejected electron loses energy by causing additional ionization Ionized atom formed after electron ejection

Figure 146-3. Types of radiation and possible external hazards. (Redrawn from Andrews GA, Cloutier RJ: Accidental acute radiation injury: The need for recognition. Arch Environ Health 10:499, 1965.)

procedures remove most of this contamination. The only means of detection is a radiation-sensing instrument (Geiger-Mueller counter). If exposure to beta particles is allowed to continue, significant exposure to gamma radiation can occur because most radioisotopes decay by beta radiation followed by gamma emission.

Gamma rays are electromagnetic waves with no mass and no charge that travel quickly and penetrate tissue deeply, with a fraction of the rays interacting with every layer of tissue. Gamma rays are the most penetrating type of ionizing radiation and travel several meters in air and many centimeters into tissue. Gamma rays are emitted from radioisotopes after beta decay and are the primary cause of the acute radiation syndrome.

Neutrons are unique. When they are stopped, or "captured," after emission, they commonly cause a previously stable atom to become radioactive. This is the source of radioactive fallout. A surface burst of a thermonuclear weapon instantly vaporizes tons of surface soil, transforming it into highly radioactive material by the intense neutron bombardment. This cloud rises with the fireball and is carried away by the prevailing winds at high altitudes. Its radioactive particles ultimately descend as fallout.

Some gamma exposure also occurs with neutron exposure. In peacetime, significant neutron exposure is likely to occur only around nuclear reactors and accelerators. Quantization of the radioactive material induced by neutron irradiation is helpful in estimating neutron exposures and, sometimes indirectly, the dose of gamma radiation. The induced radioactivity is primarily sodium-24, which can be detected by a whole-body counter or in blood samples. If neutron exposure is suspected, all feces and urine should be refrigerated and saved when possible. All clothing, especially items containing metal parts, such as belt buckles, should also be saved for analysis of neutron-induced radioisotopes.

Incorporation

Incorporation occurs when a radioactive material is ingested, inhaled, or absorbed through an open wound.

www.ketabpezeshki.com 66485457-66963820

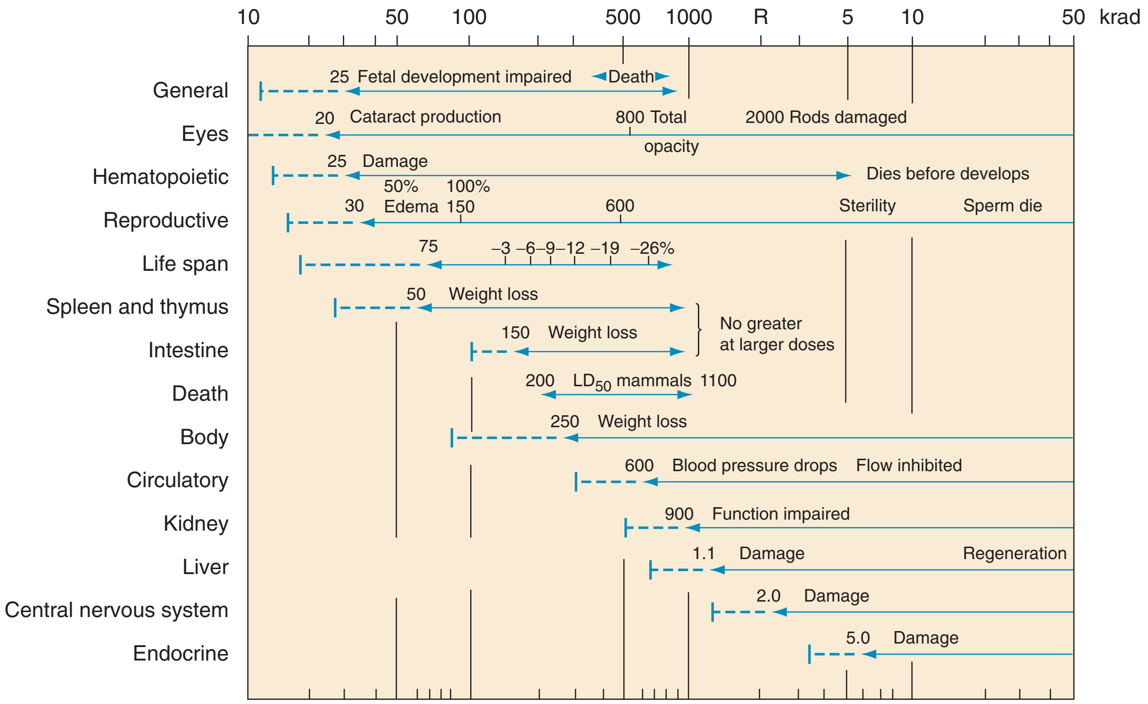


Figure 146-4. Organ and tissue sensitivity in mammals. The dose values are for whole-body, acute, x-ray, or gamma ray exposures. For low-intensity or fractionated exposure, the lines would be moved toward the right (higher doses). Radiosensitivity is directly related to the proliferative rate of the cells of the organs. (Redrawn from Auerbach PS, Gehr EC: Management of Wilderness and Environmental Emergencies. New York, Macmillan, 1983.)

TYPES OF EXPOSURE

- *External radiation* exposure results from partial-body or whole-body irradiation from an outside source. The patient may have received a lethal dose but presents no radioactive hazard to other people or the environment. Examples include accidental irradiation of personnel working with fissionable materials in laboratories or with nuclear reactors in nuclear power plants.
- *Incorporation and internal contamination* generally result from inhalation or ingestion of radioactive substances but can also occur from absorption of radioactive substances through open wounds. When this occurs, even alpha particles, which normally present no real health hazard with external exposure, can have long-term effects, including the development of lung cancer. The treatment of this type of exposure is often similar to that of acute poisoning with heavy metals.
- *External contamination* involves surface exposure to radioactive materials that remain in contact with the skin, such as dirt or liquids. Care must be taken to confine this contamination. Emergency treatment consists of removal of clothing and careful cleansing of exposed parts.
- *Wound contamination* involves exposure of an open wound to radioactive material that results in some degree of internal contamination.

Combinations of these types of radiation exposure can occur. The traumatic blast effects of a thermonuclear explosion could result in exposure to all types of radioactivity in addition to causing radioactively contaminated wounds.

CLINICAL FEATURES AND DIAGNOSTIC STRATEGIES

Symptoms and Signs

Radiation injury is caused by deposition of energy in tissue. This energy can lead to damage of cellular structures such as DNA from free radical formation. Cellular repair mechanisms will be less effective with more rapid delivery of higher doses of radiation. *Acute radiation syndrome* is a symptom complex that occurs after whole-body irradiation. It varies in nature and severity by dose, dose rate, dose distribution, and individual susceptibility. This syndrome can result from external or internal exposure to radiation during a short time. The patterns of symptoms and signs of acute radiation syndrome overlap and contain many variables (Fig. 146-4).

The principal units used to express the dose of radiation absorbed in living tissue are the *gray* (Gy; 1 Gy = 1 joule of radiation absorbed per kilogram of tissue) and the *radiation absorbed dose* (rad; 1 rad = 0.01 Gy, so 1 Gy = 100 rad). The *roentgen equivalent man* (rem) is the dosage of ionizing radiation equal to 1 rad of x-radiation (1 rad = 1 rem). A chest radiograph equals 45 mrem, and flying 3000 miles in a jet at 35,000 feet results in 4 mrem of exposure.

The relative sensitivity of organ systems exposed to the radiation determines the clinical symptoms. Because it is often impossible to accurately quantitate the absorbed dose of radiation, the symptoms and signs determine the diagnosis, therapy, and prognosis. An excellent screening tool to detect those who require more urgent medical investigation is the presence and time at onset of nausea and vomiting.[11] Symptoms may occur at doses as low as 0.75 Gy.[12] When the time to emesis is less than 4 hours after exposure, the effective whole-body dose is likely to be at least 3.5 Gy. If the time to emesis is less than 1 hour, the whole-body dose is likely to exceed 6.5 Gy and the outcome may be fatal. In most radiation accidents, exposed individuals are not wearing a monitoring device that can measure high doses of radiation. The radiation dose should be estimated from its biologic effects. The earliest indicator of a significant radiation exposure is the decrease in the absolute lymphocyte count, which can occur within 48 hours after exposure (Table 146-2).[5]

Tissues with greater rates of cellular division, particularly the hematopoietic and gastrointestinal systems, are the most radiosensitive (see Fig. 146-4). With intense irradiation exposure,

www.ketabpezeshki.com 66485457-66963820

Table 146-2 Prognosis According to the Lymphocyte Count within the First 48 Hours after Acute Exposure to Penetrating Whole-Body Radiation

MINIMAL LYMPHOCYTE COUNT (per mm^2)	APPROXIMATE ABSORBED DOSE (Gy)	EXTENT OF INJURY	PROGNOSIS
1400-3000 (normal range)	0-0.4	No clinically significant injury	Excellent
1000-1499	0.5-1.9	Clinically significant but probably nonlethal	Good
500-999	2-3.9	Severe	Fair
100-499	4-7.9	Very severe	Poor
100	8	Most severe	High incidence of death even with hematopoietic stimulation

however, central nervous system (CNS) symptoms can result, even though the CNS has a low cellular turnover rate. Invariably, all organ systems are involved in whole-body irradiation. At doses less than 1 Gy (100 rem), most cells survive but may be susceptible to radiation-induced cancer. Leukemia can develop as quickly as 2 years after exposure, whereas solid tumors are more likely to develop during several decades.[5,13,14]

The LD_{50} or median lethal whole-body dose (the dose that is lethal for 50% of test subjects), assuming proper medical care, is estimated to be approximately 4.5 Gy.[6] Whole-body exposure of 10 Gy is the maximal survivable dose even with the best medical therapy.[5] Doses greater than 20 Gy commonly produce CNS symptoms. These symptoms occur immediately after exposure and include headache, altered mental status, prostration, vertigo, tinnitus, and sensory and motor changes. If the individual is exposed to a nonuniform dose and the gastrointestinal and hematopoietic systems are spared, there is a chance of survival after resolution of the CNS symptoms. If more than 20 Gy of whole-body exposure occurs, however, fulminating gastrointestinal and CNS symptoms ensue, sometimes within 30 minutes. This indicates a supralethal dose of radiation, and for triage purposes, the death of these patients should be classified as "impending" or "expectant." If medical resources are scarce, sedation and analgesia should be the only therapies. With whole-body exposure of more than 10 Gy, mortality approaches 100%. If the patient survives the CNS and gastrointestinal system insults, hematopoietic complications are lethal.

The gastrointestinal syndrome occurs regularly at doses higher than 1 Gy. In general, the higher the absorbed dosage, the sooner the onset of symptoms. In its mildest form, nausea and vomiting are short-lived. More protracted nausea and vomiting are seen with higher exposures. The onset of high fever and persistent bloody diarrhea are ominous signs. Death from hematopoietic system failure may result despite aggressive fluid and electrolyte therapy.

A latent period lasting 2 days to 4 weeks from the time of exposure often occurs before the signs of hematopoietic system involvement develop. The earliest sign is often pancytopenia resulting from marrow suppression. This hematopoietic syndrome includes leukopenia and thrombocytopenia with fever, increased susceptibility to infection, petechiae, and hemorrhagic diatheses. The absolute lymphocyte count 48 hours after exposure is a good predictor of hematopoietic system involvement (see Fig. 146-4). If the absolute lymphocyte count is greater than 1200 cells/µL, it is unlikely that the patient has received a clinically significant dose of radiation. If the absolute lymphocyte count falls between 100 and 500 cells/µL at 48 hours, a significant or even lethal dose of radiation should be suspected. A level in this range is an indication for protective isolation. Levels less than 500 cells/µL suggest procedures such as the use of hematopoietic growth factors.[5,15] If a patient is symptomatic, serial complete blood counts should be performed. Hemorrhagic complications should be treated with platelet concentrates and whole blood or fresh frozen plasma when necessary. Anemia resulting from erythropoietic suppression is not generally of clinical significance.

Erythema from skin burns may be delayed in onset. When skin burns are secondary to penetrating radiation, they indicate high exposure. Severe skin burns may be a result of nonpenetrating radiation, such as beta particle contamination without accompanying systemic symptoms. These burns can be prevented or tempered by early decontamination. When present, they should be treated like any thermal or chemical burn.

Skin changes that occur can help quantify radiation exposure. Epilation occurs after exposure to 3 Gy, erythema is seen after exposure to 10 Gy, wet desquamation occurs after 20 Gy, and necrosis occurs after 30 Gy of localized skin exposure.[5] These responses are similar to those of severe chemical burns.

A key historical point in the evaluation of a suspicious burn is whether the patient had contact with a hot object or caustic chemical. If the patient does not give a history that clearly explains the burn, particularly if there is a history of carrying a bright metal object that may have been a radioisotope source, the possibility of a radiation burn should be considered.

MANAGEMENT

Out-of-Hospital Care

The history obtained from field personnel is crucial. The exact type of exposure (external versus internal, whole body versus partial body) should be ascertained. If internal exposure is suspected, the portal of entry (inhalation, ingestion, or absorption) and the radioactive material involved should be investigated.

Reducing Exposure

The protection of providers involves reducing exposure to levels that are as low as reasonably achievable. The three classic and effective methods to reduce radiation exposure can be summarized as *time, distance,* and *shielding*. The absorbed dose is directly proportional to time. In addition, radiation exposure follows the inverse square law, and it decreases to one fourth at twice the distance from the source. Effective shielding varies from a sheet of paper for alpha particles to less than an inch of aluminum for beta particles and several inches of lead for gamma rays.

Decontamination

If the patient's condition permits, decontamination should usually be initiated at the scene because many communities lack an emergency department (ED) designed for this procedure. In an industrial or laboratory accident, each facility should have a specific protocol and equipment available to initiate the decontamination process. All out-of-hospital personnel should be trained in the decontamination process. Universal precautions, including rubber gloves, shoe covers, and respirators if airborne contamination is suspected, are effective in protecting personnel and the work area from contamination. The only variation from normal universal precautions is a recommendation to wear two sets of

www.ketabpezeshki.com 66485457-66963820

gloves and to change the outer pair when appropriate to avoid cross-contamination.[16]

The patient's clothing should be removed and placed in plastic bags. If possible, soap and water cleansing of exposed skin should be performed. All materials, including wash water, should be placed in containers and labeled as radioactive waste. Performance of these tasks at the scene minimizes contamination of the ambulance and the ED.

If the patient is unstable, rapid and partial decontamination procedures, such as clothing removal, should be initiated at the scene before expeditious transportation to an ED. Radio contact with the receiving hospital should be provided to the ED to facilitate preparations. If the community disaster plan has a designated hospital for radiation-contaminated victims, they should be transported directly to that facility. Physicians wishing to establish a comprehensive plan to manage radiation accident victims are referred to the National Council on Radiation Protection and Measurements.[17]

Emergency Department

Every ED designated a decontamination facility should have a radiation accident protocol. An excellent prototype is that published by Leonard and Ricks.[18] This protocol should be included in the policies and procedures manual and posted in the decontamination facility.

Preparation

The chaos that ensued in the wake of the Three Mile Island experience suggests that a community disaster plan should be developed with a predetermined individual empowered to make decisions about evacuation and other issues concerning the at-risk population. On notification of the numbers and types of patients involved in a radiation exposure accident, a decision should be made about implementation of a full disaster plan versus a limited response. The *radiation control officer,* usually a radiologist or pathologist, should be contacted immediately. The radiation control officer should monitor all patients and medical personnel with a radiation counter and should supervise the "cleanup" and the routing of patients to minimize "tracking," or spread, of contamination. The role of informational services is critical. Timely and accurate information and instructions should be given to a public relations person for dissemination to the news media to minimize the chaos and paranoia that inevitably result from such incidents.

Decontamination

Contaminated patients should be decontaminated in the field. If they arrive at the ED contaminated, they should enter through a separate, protected entrance or be isolated until a decontamination tent can be erected. Because the risk to staff from radioactive contamination is minimal with universal precautions, medical stabilization and treatment of the patient supersede decontamination efforts in a radiologic emergency.

There is a significant distinction between patients contaminated with radioactive material and those who arrive contaminated with chemical or biologic agents, for which decontamination may need to take precedence. All medical personnel should wear protective, disposable clothing, including surgical gloves and shoe covers. Respirators are not required at the hospital but should be used by first responders who are entering a highly contaminated area.[5] The emergency suite should contain all equipment necessary for a major resuscitation. If decontamination occurs inside the ED, it must have a contained drainage and ventilation system to prevent the spread of water-borne or airborne radioactive contamination. In some hospitals, the only area equipped with such facilities is the autopsy room or morgue. The radiation disaster plan may necessitate taking resuscitation equipment to this area and providing decontamination and initial care there if this cannot be done in a decontamination facility outside of the ED. As opposed to chemical and biologic hazards, radioactive contamination is relatively easy to detect with commonly available survey meters, such as a Geiger-Mueller instrument, often referred to as a Geiger counter. This should be available in any ED that may receive patients exposed to radioactive contamination. Although historically survey meters have not been able to detect alpha radiation, many of the newer devices can detect even small amounts of radioactive contamination and will typically be capable of distinguishing alpha, beta, and gamma radiation.

The patient should be undressed immediately and all clothing placed in sealed containers labeled "radioactive waste." Removal of clothing can reduce contamination on the patient by 90%.[19] Exposed skin should be cleansed with soap and water. Overly aggressive skin washing should be avoided because abraded skin openings could allow increased absorption of radioactive material. Hair should be shampooed. All wastewater, washcloths, and towels should be saved in properly labeled containers. The cleansing process should be repeated as frequently as necessary until the area measures less than twice the background reading on the Geiger-Mueller survey meter or until there is no significant reduction in the level of contamination between washes.[16] Long hair may need to be trimmed. The nails should be trimmed and meticulously scraped to remove contamination.

Wound Management and Treatment

If the patient has open wounds, the surrounding skin should be decontaminated by scrubbing with soap and water. Adhesive, disposable surgical drapes should be applied, and the wounds should be prepared and irrigated with copious amounts of saline. Frequent monitoring for radioactive contamination determines when irrigation can be discontinued. Surgical débridement should be performed according to the usual indications of dirt and nonviable tissue or continued high readings of radioactive contaminants. The normal principles of wound closure should be followed for contaminated wounds. The wounds in patients who have received whole-body radiation greater than 1 Gy should be closed primarily to prevent infection.[5]

Because there is minimal risk to providers using universal precautions, emergency surgery or other necessary procedures should not be delayed by contaminated skin or wounds. Surgical interventions should be performed within 48 hours of the injury when possible in patients who have suffered high-level radiation exposure and trauma. Acute radiation syndrome may be complicated by fluid and electrolyte disturbances. After 48 hours, surgical interventions may need to be delayed until hematopoietic recovery occurs.[16]

Treatment

The indications for pain management and antiemetics should be liberalized. Treatment of acute radiation syndrome should also focus on the prevention of infection. Neutropenia and fever should be managed with antibiotics, although routine enteric prophylaxis is not indicated.[20]

Internal Contamination

Oral ingestion of radionuclides presents special challenges. After ingestion, there is usually a variable time before cellular absorption and uptake. Therapy with blocking or chelating agents is determined by the elements involved. A *blocking agent* is a chemical that saturates a tissue with a nonradioactive element, reducing

www.ketabpezeshki.com 66485457-66963820

Table 146-3 Medication Options for Internal Contamination

MEDICATION	RADIOACTIVE ISOTOPE
Ferric hexacyanoferrate (Prussian blue)	Cesium-137, thallium
Ca- and Zn-diethylenetriaminepentaacetate (DTPA)	Plutonium, americium, curium
Potassium iodide	Radioiodine
Penicillamine	Radioactive heavy metal poisoning (lead)

the uptake of the radionuclide. An example is potassium iodine (KI), which reduces the uptake of radioactive iodine in the thyroid. The American Thyroid Association currently suggests that KI pills be distributed to households within 50 miles of a nuclear power plant and be available to those within a 200-mile radius for the purpose of protection from radioactive fallout during evacuation efforts in the event of a nuclear accident.[21]

Chelating agents bind metals into complexes, which prevents tissue uptake and allows urinary excretion. Two examples of chelating agents are calcium disodium edetate and penicillamine, both of which treat radioactive lead poisoning. Ideally, these agents should be administered soon after exposure, before significant uptake of the radionuclide can occur. A poison information center should be contacted for recommendations about the dosages of chelating and blocking agents and other treatment modalities, including induced emesis, cathartics, activated charcoal, and lavage.[22] All excretions (urine, feces, emesis, and lavage fluid) should be saved in specially labeled containers for dosimetry and proper disposal. The decision to treat suspected internal contamination should not be delayed for sample analysis, which typically will take 24 hours. Medications that may be administered to patients thought to be internally contaminated with some radioactive isotopes are listed in Table 146-3.

Acute inhalation of radionuclides is a problem. Emergent bronchopulmonary lavage may be effective in partial removal of the radioactive contaminants. Nasal swabs subsequently tested for radioactivity may help determine if inhalation of radioactive material has occurred. Chelating and blocking agents may be used if significant inhalation is suspected. Chronic low-level inhaled contaminants are more common, and long-term sequelae occur. Extensive cutaneous radiation fibrosis occurred in some survivors of the Chernobyl accident, and interferon therapy is of benefit.[23]

Triage Classification, Further Treatment, and Disposition

Triage is facilitated by presenting symptoms into three categories: survival probable, survival possible, and survival improbable. The *survival probable group* consists of patients having either no initial symptoms or mild symptoms that subside within a few hours. Radiation exposure in this group is usually less than 2 Gy (200 rem or rad). The initial laboratory studies and serial complete blood counts reveal no depression of the leukocyte count.

The *survival possible group* includes patients in whom nausea and vomiting are relatively brief (lasting 24-48 hours), followed by an asymptomatic (latent) period. After the initial symptoms, these patients exhibit the typical hematologic changes of thrombocytopenia, granulocytopenia, and lymphopenia. The severity of these changes depends on individual susceptibility and the level of the initial radiation dose. These patients should be admitted for fluid and electrolyte therapy if vomiting is severe. Antiemetics may be ineffective. Also, protective isolation precautions are indicated, particularly if there is significant granulocytopenia at 48 hours.

The exposure dosage range for patients in the survival possible group is estimated to be 2 to 10 Gy, with the LD_{50} approximately 3 to 5 Gy. The LD_{50} varies by the vigor of supportive therapy. In mass casualty situations, the LD_{50} is in the range of 3.5 to 4.5 Gy. The concept of calculating the LD_{10} versus LD_{90} for human radiation exposure helps determine what level of therapeutic intervention is indicated. A patient who has received an LD_{90} exposure may survive only if hematopoietic growth factors are used, whereas a patient with an LD_{10} exposure may need only low-risk supportive care, such as reverse isolation and intravenous fluids.

The therapy for the survival possible group is based on the exact hematologic derangements. Platelet concentrates are recommended if the count falls below 25×10^3 cells/μL. Appropriate broad-spectrum antibiotics should be considered only if clinical signs of infection appear. Prophylactic antibiotics may be indicated if serious gastrointestinal symptoms, such as vomiting and diarrhea, are present. Recommended approaches for antibiotic and myeloid cytokine use (for both prophylaxis and treatment) after radiation exposure largely follow algorithms for the treatment of chemotherapy-associated neutropenia.[24,25] Prophylactic antifungal agents, such as amphotericin B, may also be indicated. Acyclovir may be useful for oral herpes simplex infection. Colony-stimulating factors (cytokines) that induce bone marrow hematopoietic cells to proliferate may have substantial benefit, with little risk in victims predicted to have moderate or severe bone marrow failure.

Filgrastim (granulocyte colony-stimulating factor) and sargramostim (granulocyte-macrophage colony-stimulating factor), both used in treatment of patients with neutropenia resulting from myelosuppressive chemotherapy, are useful in radiation accident victims and may hasten recovery of neutrophil counts. Cytokine therapy (filgrastim 5 μg/mg/day, subcutaneously (SC) and sargramostim 5-10 μg/mg/day [200-400 $\mu g/m^2$/day]) is recommended in healthy individuals with no other injuries who receive exposures estimated to be in excess of 3 Gy and in patients with multiple injuries or burns who receive exposures in excess of 2 Gy. These myeloid cytokines may be beneficial even several weeks after exposure. Intravenous hyperalimentation may be necessary for the successful treatment of the gastrointestinal syndrome.

The third group is the *survival improbable group*. The exposed dose range in this group is estimated to be greater than 10 Gy whole-body exposure. These patients experience rapid onset of fulminating nausea, vomiting, and diarrhea. Aggressive fluid and electrolyte and hyperalimentation therapy may initially stabilize these patients. They later experience bone marrow aplasia and pancytopenia that is generally fatal. If CNS symptoms appear early, the patient has received a very large dose of radiation. In mass casualty situations, these patients should be triaged into the impending or expectant death category and provided comfort care. In the situation in which a sufficient dose of radiation causes irreversible bone marrow damage, allogeneic hematopoietic stem cell transplantation (HSCT) has the potential to restore hematopoietic function. Whereas HSCT demonstrates a survival benefit in animal models, there is no evidence that HSCT improves survival in humans exposed to nontherapeutic radiation.[26]

Consultative Resources

The U.S. Department of Health and Human Services launched the *Radiation Emergency Medical Management* (REMM) website in March 2007 as a resource for radiation exposure training, communication, and pre-event and postevent information. The goals of REMM are to guide health care providers in the diagnosis and treatment of radiation emergencies and to provide evidence-based information for those without formal radiation medicine

www.ketabpezeshki.com 66485457-66963820

expertise. The website is www.remm.nlm.gov/.[27] For questions about radiation exposure and injuries, the U.S. Department of Energy can be contacted 24 hours a day at the Radiation Emergency Assistance Center/Training Site (REAC/TS) in Oak Ridge, Tennessee (telephone, 865-576-1005; interactive website, www.orau.gov/reacts). For information about the training of physicians, REAC/TS can be contacted at 865-576-3131. The *Medical Management of Radiological Casualties Handbook* is available online at www.afrri.usuhs.mil. The Chemical/Biological Hotline of the National Response Center is 800-424-8802.

KEY CONCEPTS

- Contaminated patients are "radioactive"; irradiated patients are not.
- No danger to medical personnel from contaminated patients exists with proper precautions and decontamination procedures.
- Decontamination should not delay or impede the stabilization of the patient in radiation emergencies.
- Careful evaluation of initial symptoms and signs is the most reliable indicator of the radiation dose received and the patient's prognosis.
- Most therapy is supportive and symptomatic except for exposures involving the ingestion or inhalation of radioactive material, when specific therapy with blocking or chelating agents may be indicated.
- Detonation of a "dirty bomb" would cause psychological terror and little or no radiation injuries.
- Formal consultation is available 24 hours a day and should be obtained when any patient with radiation injuries is evaluated.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Gale RP, Thompson MA, Crawford MA: Recent radiation accidents. Chernobyl and Goiania: Their impact and global implications. *Ala J Med Sci* 1988; 25:439.
2. International Atomic Energy Agency: *One Decade after Chernobyl, Summing up the Consequences of the Accident*. Proceedings of an International Conference, Vienna, April 8-12, 1996. Vienna: International Atomic Energy Agency; 1996.
3. Council on Foreign Relations: *Terrorism: Questions and answers: Dirty bombs*, revised June 23, 2003. Available at www.cfr.org/publication/9548.
4. Centers for Disease Control and Prevention: *Radiation emergencies—dirty bombs*, revised March 2005, reviewed May 2006. Available at http://emergency.cdc.gov/radiation/dirtybombs.asp.
5. Mettler FA, Voelz G: Major radiation exposure: What to expect and how to respond. *N Engl J Med* 2002; 346:20.
6. Champlin HE, Kastenberg WE, Gale RP: Radiation accidents and nuclear energy: Medical consequences and therapy. *Ann Intern Med* 1988; 109:730.
7. Hart BL, Mettler FA Jr, Harley NH: Radon: Is it a problem? *Radiology* 1989; 172:593.
8. Archer VE, Renzetti AD, Doggett RS: Chronic diffuse interstitial fibrosis of the lung. *J Occup Environ Med* 1998; 40:460.
9. American Cancer Society online. Available at www.cancer.org. Accessed January 2008.
10. Goldsmith JR: Epidemiologic evidence relevant to radar (microwave) effects. *Environ Health Perspect* 1997; 105:1579.
11. Koenig KL, et al: Medical treatment of radiological casualties: Current concepts. *Ann Emerg Med* 2005; 45:643.
12. Coleman CN, et al: Triage and treatment tools for use in a scarce resources–crisis standards of care setting after a nuclear detonation. *Disaster Med Public Health Prep* 2011; 5:S111.
13. United Nations Scientific Committee on the Effects of Atomic Radiation: *Sources and Effects of Ionizing Radiation: UNSCEAR 2000 Report to the General Assembly, with Scientific Annexes*. New York: United Nations; 2000.
14. Pierce DA, Preston D: Radiation-related cancer risks at low doses among atomic bomb survivors. *Radiat Res* 2000; 154:178.
15. MacVittie TJ, Weiss JF, Browne D, eds: *Advances in Treatment of Radiation Injuries*. New York: Pergamon; 1996. Advances in the Biosciences, vol 94.
16. Bushberg JT, et al: Nuclear/radiological terrorism: Emergency department management of radiation casualties. *J Emerg Med* 2007; 32:71.
17. National Council on Radiation Protection and Measurements: *Management of Persons Accidentally Contaminated with Radionuclides*. Washington, DC: National Council on Radiation Protection and Measurements; 1980. NCRP Report No. 65.
18. Leonard RB, Ricks RC: Emergency department radiation accident protocol. *Ann Emerg Med* 1980; 9:462.
19. Armed Forces Radiobiology Research Institute: *Medical Management of Radiological Casualties*, 2nd ed. Bethesda, Md: Armed Forces Radiobiology Research Institute; 2003. Available at www.afrri.usuhs.mil. Accessed January 2008.
20. Waselenko JK, et al: Medical management of the acute radiation syndrome: Recommendations of the Strategic National Stockpile Radiation Working Group. *Ann Intern Med* 2004; 140:1037.
21. American Thyroid Association: Questions and answers about potassium iodide (KI). Available at www.thyroid.org/professionals/publications/statements/ki/02_04_ki_qa.html. Accessed April 25, 2011.
22. National Council on Radiation Protection and Measurements: *Management of Internally Deposited Radionuclides*. Report No. 65. Bethesda, Md: National Council on Radiation Protection and Measurements; 1985. Report No. 65.
23. Peter RU, et al: Interferon gamma in survivors of the Chernobyl power plant accident: New therapeutic option for radiation-induced fibrosis. *Int J Radiat Oncol Biol Phys* 1999; 45:147.
24. DiCarlo AL, et al: Radiation injury after a nuclear detonation: Medical consequences and the need for scarce resources allocation. *Disaster Med Public Health Prep* 2011; 5:S32-S44.
25. Gourmelon P, et al: European consensus on the medical management of acute radiation syndrome and analysis of the radiation accidents in Belgium and Senegal. *Health Phys* 2010; 98:825-832.
26. Ledney GD, Elliott TB: Combined injury: Factors with potential to impact radiation dose assessment. *Health Phys* 2010; 98:145-152.
27. Bader JL, et al: Radiation event medical management (REMM): Website guidance for health care providers. *Prehosp Emerg Care* 2008; 12:1-11.

www.ketabpezeshki.com 66485457-66963820

Chapter 147

General Approach to the Poisoned Patient

Ken Kulig

PERSPECTIVE

Most poisoned patients seen in the emergency department are adults with acute oral drug overdoses. Other common clinical scenarios include accidental poisoning in children; drug abuse through smoking, snorting, or injection; chronic poisoning from drug abuse or from environmental, industrial, and agricultural chemical exposure; medication reactions or interactions; and envenomation. Management requires both a general supportive approach and specific actions directed at the particular toxin or toxins involved, as outlined in the various chapters in this section. Clinical studies have modified the management of poisoned patients, such as the use of gastric decontamination, but much of the toxicology literature, especially with unusual poisonings, remains case based. Regional poison centers and medical toxicologists have a concentrated experience in management of poisoned patients and can be called on for advice and assistance.

INITIAL APPROACH TO THE POISONED PATIENT

Patients who are contaminated with an agent that might injure health care personnel require decontamination before treatment to avoid disabling of the hospital staff or the entire health care facility. Except for specific lifesaving antidotes against certain toxins, most poisoned patients require only supportive therapy for recovery. The initial workup should determine whether a specific patient has been exposed to an agent for which an antidote (or other specific treatment) exists.[1] A thorough poisoning history and toxicologic physical examination may be followed by the selective use of laboratory tests.

After initial stabilization of a critically ill patient, specific antidote therapy is administered while a more detailed history and physical examination are performed. Hypoglycemia should be considered in a patient with altered mental status or seizures and should be evaluated by bedside glucose testing. *Naloxone* can be given to patients with suspected opioid overdose and respiratory depression while preparations are made to secure the airway because a positive response may obviate the need for intubation. *Flumazenil* is not indicated in an undifferentiated overdose patient, and its use should be limited to confirmed acute benzodiazepine overdose in a patient who is not a chronic benzodiazepine user (e.g., an adolescent who impulsively ingests a parent's benzodiazepine). Indiscriminate use may cause a chronic benzodiazepine user to have severe benzodiazepine withdrawal. The patient may have ingested tricyclic antidepressants or other drugs likely to cause seizures. In either case, the use of flumazenil can carry a substantial risk of seizures. *Thiamine* should be administered when dextrose is given to nutritionally compromised, alcoholic patients with altered mental status (100 mg in the maintenance intravenous line is sufficient and safe).[2] It is common to give alcoholic patients intravenous multivitamins ("yellow bag") containing thiamine, folate, and B_{12}. However, serum levels of these vitamins are usually normal in alcoholic patients, and the practice is not justified.[3]

A complete *overdose history* may be time-consuming but is important (Box 147-1). Valuable clues often come from unexpected sources, such as the patient's previous medical records, the pharmacy where prescriptions were filled, online regulatory databases, or the prescribing physician as listed on the patient's prescription bottles. Whenever possible, prehospital personnel should bring the patient's medications and other available medications from the patient's residence to the hospital with them. If the ingested agent is a hazardous chemical (e.g., pesticide) that might endanger hospital personnel, it should be brought to the hospital in an airtight container or secured at the scene. Precise product identification information should be obtained so that a hazardous materials reference system can be consulted. When it is suspected that the contents of the container are not the original product, the substance should be checked against the product label. It is easy to confuse the different types of chemical agents with agents with similar names found in many homes, and some may have specific properties that affect treatment. In rare cases, overdose patients may deliberately attempt to deceive caregivers by hiding the ingested agents.

Accurate vital signs, including pulse oximetry, are important in the diagnosis of poisoning and should be repeated as indicated. At least one measurement of temperature should be included. Respirations should be counted, not estimated. A cardiac monitor or 12-lead electrocardiogram should be evaluated for QRS and QT intervals, morphology, and rhythm. The physical examination in a comatose patient should ensure that concomitant treatable conditions (e.g., trauma, intracranial hemorrhage, central nervous system [CNS] infection) are not missed. Focal neurologic findings could be possible indicators of intracranial disease or severe head trauma.

The pupillary examination may give misleading information. Some opioid agonists, especially propoxyphene and pentazocine, may not produce the characteristic miosis of opioid intoxication. When multiple drugs are ingested, the expected pupillary findings related to any particular agent may be modified or absent.

Physical stigmata of injection drug use (track marks) should be sought in both usual (e.g., antecubital fossa) and unusual (e.g., under the tongue and top of the feet) locations.

Signs of infection (sepsis, abscess, endocarditis) should be investigated in patients suspected of injection drug abuse.[4] A patient may be critically ill as a result of "body packing" or "body

www.ketabpezeshki.com 66485457-66963820

Box 147-1 Obtaining an Overdose History

- Obtain all prescription bottles and other containers when possible. Perform a pill count. Be sure that the bottles contain the medications listed. Identify any unknown tablets.
- Contact the prescribing physician or the pharmacy as listed on the bottles to determine previous overdoses or other medications that the patient may have available. Identify underlying medical and psychiatric disorders and medication allergies. Review past medical records.
- Talk to the patient's family and friends in the emergency department. If necessary, call the patient's home to ask questions of others. The persons providing the important elements of the history should be identified in the chart.
- Search the patient's belongings for drugs or drug paraphernalia. A single pill hidden in a pocket, for example, may provide *the* most important clue to the diagnosis.
- Have family members (or the police) search the patient's home, including the medicine cabinet, clothes drawers, closets, and garage; such searches may also provide clues that make the diagnosis. This has the added benefit of involving the family in the patient's care.
- Look for track marks on the patient. Consider body packing or body stuffing.

Table 147-1 Odors in Overdose History

ODOR	POSSIBLE INTOXICANT
Bitter almonds	Cyanide
Carrots	Water hemlock (cicutoxin)
Fishy	Zinc or aluminum phosphide
Fruity	Ethanol, acetone, isopropyl alcohol, chlorinated hydrocarbons (e.g., chloroform)
Garlic	Arsenic, dimethyl sulfoxide (DMSO), organophosphates, yellow phosphorus, selenium, tellurium
Glue	Toluene, other solvents
Pears	Chloral hydrate, paraldehyde
Rotten eggs	Disulfiram, hydrogen sulfide, *N*-acetylcysteine, dimercaptosuccinic acid (DMSA)
Shoe polish	Nitrobenzene
Wintergreen	Methyl salicylate

stuffing," complicated by rupture of packets of cocaine, heroin, or amphetamines (see Chapters 154 and 162).[5] Rectal, vaginal, and radiographic examination of the abdomen should be performed in these circumstances.

Another important physical finding is evidence of aspiration or noncardiogenic pulmonary edema on chest auscultation. Bowel sounds may be increased or decreased if agents affecting the cholinergic nervous system have been ingested. A rectal examination to detect melena or hematochezia may also provide evidence of a coagulopathy (e.g., ingestion of anticoagulant medication). Skin examination may reveal evidence of skin popping, cyanosis (hypoxia or methemoglobinemia), or pressure marks if the patient has been unconscious.

Unusual odors of the patient's breath, skin, clothing, vomitus, or nasogastric aspirate may also provide useful diagnostic clues (Table 147-1).[6] The absence of such odors, however, should not be taken as evidence that the agents listed are not present.

Table 147-2 Common Toxic Syndromes (Toxidromes)

Anticholinergic	
Common signs	Delirium with mumbling speech, tachycardia, dry flushed skin, dilated pupils, myoclonus, slightly elevated temperature, urinary retention, decreased bowel sounds. Seizures and dysrhythmias may occur in severe cases.
Common causes	Antihistamines, antiparkinsonians, atropine, scopolamine, amantadine, antipsychotics, antidepressants, antispasmodics, mydriatics, muscle relaxants, many plants (e.g., jimson weed, *Amanita muscaria*)
Sympathomimetic	
Common signs	Delusions, paranoia, tachycardia (or bradycardia with pure alpha-agonists), hypertension, hyperpyrexia, diaphoresis, piloerection, mydriasis, hyper-reflexia. Seizures, hypotension, and dysrhythmias may occur in severe cases.
Common causes	Cocaine, amphetamine, methamphetamine and its derivatives, over-the-counter decongestants (phenylpropanolamine, ephedrine, pseudoephedrine). In caffeine and theophylline overdoses, similar findings, except for the organic psychiatric signs, result from catecholamine release.
Opioid/Sedative/Ethanol	
Common signs	Coma, respiratory depression, miosis, hypotension, bradycardia, hypothermia, pulmonary edema, decreased bowel sounds, hyporeflexia, needle marks. Seizures may occur after overdoses of some narcotics (e.g., propoxyphene).
Common causes	Narcotics, barbiturates, benzodiazepines, ethchlorvynol, glutethimide, methyprylon, methaqualone, meprobamate, ethanol, clonidine, guanabenz

TOXIC SYNDROMES AND ANTIDOTES

The term *toxidrome* refers to a syndrome or constellation of physical findings attributed to a specific class of toxins that can provide important clues to narrow the differential diagnosis.[1] The general rules outlined here have many exceptions, and polydrug overdoses may result in overlapping and confusing mixed syndromes. Nevertheless, this approach may confirm the history, provide the clinician with a starting point for management, and suggest useful laboratory tests. The most common toxidromes are the anticholinergic syndrome, sympathomimetic syndrome, opioid/sedative/ethanol syndrome, cholinergic syndrome, and serotonin syndrome (Table 147-2).

The *anticholinergic syndrome* occurs frequently because many common medications and plants have anticholinergic properties. Anticholinergic CNS poisoning causes mild temperature elevation and acute delirium with mumbling speech and typical "picking movements" of the fingers. Suppression of cholinergic inhibition of the heart rate leads to tachycardia. Inhibition of the secretory functions of the integument causes dry mouth and skin, and the face is typically flushed. Unopposed sympathetic drive of the ciliary apparatus causes wide pupillary dilation. Most patients

www.ketabpezeshki.com 66485457-66963820

Box 147-2 Toxins Causing Delirium

Alcohol and alcohol withdrawal	Muscle relaxants
Anticholinergics	Mushrooms with muscimol or ibotenic acid
Anticonvulsants	Opiates
Antidepressants	Phencyclidine
Antihypertensives	Salicylates
Antiparkinson medications	Sedative withdrawal
Antipsychotics	Solvents
Cardiac medications	Steroids
Cocaine	Sympathomimetics (cocaine, amphetamines)
Lithium	
Monoamine oxidase inhibitors	

recover with supportive therapy, but the delirium may last a day or more. *Physostigmine* may be a useful antidote in carefully selected patients; this is discussed in detail in Chapter 150.

The *sympathomimetic syndrome* is usually seen after acute or chronic abuse of cocaine, amphetamines, or decongestants (e.g., phenylephrine). Patients may be delusional; methamphetamine, in particular, may cause complicated, intricate, and paranoid delusions. Seizures may occur, and the postictal state can contribute to the altered mental status. Blood pressure is usually elevated, the pulse is rapid (except with pure alpha-adrenergic agonists, which can cause reflex bradycardia), the pupils are dilated, and piloerection may be seen. In massive overdoses of sympathomimetic agents, cardiovascular collapse can occur with the development of shock and wide-complex dysrhythmias. This clinical picture can mimic that of overdose of cardioactive drugs or cyclic antidepressants. In contrast to the dry skin seen with anticholinergic syndrome, diaphoresis would be expected with the sympathomimetic syndrome.

An extreme presentation of sympathomimetic excess can be excited delirium (Box 147-2). In this state, patients are agitated, hyperthermic, and violent and possess "superhuman strength." Frequently, many security personnel are required to control these individuals. These individuals may have a severe metabolic acidosis and hyperkalemia, which can cause sudden cardiovascular collapse. It is critical to sedate these patients and to control hyperthermia aggressively while treating their acidosis and hyperkalemia simultaneously. Dantrolene has been reported to be effective in treatment of MDMA-related hyperpyrexia.[7]

All sedative-hypnotic agents, when they are taken in sufficient dosage, cause general anesthesia with a complete loss of awareness and reflex activity. The CNS depressant (opioid/sedative/ethanol) syndrome is the most common toxic syndrome seen in the emergency department, and a depressed sensorium is its hallmark. Mixing agents in this class (e.g., ethanol and benzodiazepines) is common. As the drugs are absorbed at higher doses, the patient becomes increasingly obtunded, the deep tendon reflexes diminish, and finally the vital signs deteriorate as medullary drive of respiration and cardiovascular function is attenuated.

Respiratory depression is particularly pronounced with opioid overdose, and the respiratory rate is often diminished before decreases in blood pressure or pulse occur. The diagnosis of opioid overdose is confirmed by the use of naloxone (Narcan) or nalmefene (Revex) in adequate doses. Management of opioid overdose is discussed in Chapter 162. Comatose patients often present without a history and need to be managed aggressively, with securing of the airway when it is needed. These patients may need basic laboratory tests and a head computed tomography scan if their presentation or course is suggestive of stroke, infection, or head trauma while consideration is given to a drug overdose alone or in combination with one of these medical conditions. A serum or breath ethanol level that is not commensurate with the level of CNS depression raises suspicion of intracranial injury, hemorrhage, or infection.

The *cholinergic syndrome* is uncommon, but it is important to recognize it because lifesaving treatment is available. Cholinergic syndrome causes the patient to be "wet," as opposed to the anticholinergic syndrome, which causes the patient to be "dry." The wetness is manifested by profuse sweating and excessive activity of virtually the entire exocrine system, often accompanied by vomiting, diarrhea, diaphoresis, and urinary incontinence. The mnemonic SLUDGE is used to recall the specific elements of the syndrome: *s*alivation, *l*acrimation, *u*rination, *d*efecation, *g*astrointestinal cramping, and *e*mesis. The CNS (e.g., confusion, coma, and seizures) and the skeletal muscles (e.g., weakness and fasciculations) can also be involved. The pupils are often miotic. Cholinergic syndrome is most frequently caused by organophosphate or carbamate pesticide exposure, which may be through unsuspected dermal contamination. Anticholinergic agents are also the foundation of "nerve agents" such as sarin, which was used in the Tokyo subway attack. Recognition of the syndrome led to the use of atropine and cholinesterase regenerators, with a subsequent good outcome in many patients.[8]

Serotonin syndrome ensues when there is a drug interaction involving the selective serotonin reuptake inhibitors (SSRIs) or an overdose of an SSRI.[9] Fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), and citalopram (Celexa) are commonly used SSRIs. Other drugs inhibit the reuptake of other neurotransmitters and are also serotonin reuptake inhibitors (SRIs) that can cause the syndrome. These drugs include venlafaxine (Effexor), nefazodone (Serzone), and mirtazapine (Remeron). Drug interactions between many drugs can cause the serotonin syndrome described in Chapter 151. These drugs include the SSRIs, SRIs, monoamine oxidase inhibitors (MAOIs), tryptophan, sympathomimetics, tricyclic and other antidepressants, meperidine, dextromethorphan, and lithium. Because of the long-lasting effects of the SSRIs, the syndrome can occur when one of the active agents is ingested even weeks after use of an SSRI has been discontinued.

Serotonin syndrome is characterized by altered mental status, fever, agitation, tremor, myoclonus, hyper-reflexia, ataxia, incoordination, diaphoresis, shivering, and sometimes diarrhea.[7] The diagnosis relies on the drug history, and it is difficult to distinguish serotonin syndrome from an overdose of cocaine, lithium, or MAOIs and from the neuroleptic malignant syndrome or thyroid storm. Patients may deteriorate slowly and become critically ill after an apparently benign manifestation.

As possible toxidromes are investigated, the use of specific antidotes should be considered (Table 147-3).

A relatively new antidote, Intralipid, for the treatment of cardiotoxicity from local anesthetics has been reported to be lifesaving in some cases. It has been successfully used for beta-blocker, calcium channel blocker, and tricyclic antidepressant poisoning and many other mostly lipophilic drugs.[10-12] The American College of Medical Toxicology has recently published guidelines for its use.[13]

TOXICOLOGY LABORATORY

A toxicology screen (usually urine, sometimes blood and urine) may identify the class of drugs ingested but may also be misleading.[14-17] The typical urine toxicology screen (U-tox) does not screen for many substances, even commonly ingested agents that are capable of causing critical illness (Box 147-3).[18] Some drugs, such as γ-hydroxybutyrate (GHB), are present relatively briefly in blood and urine, and therefore findings may be negative in samples collected even on the same day. Conversely, drugs found on screening may not be those currently responsible for the toxidrome, and drugs ingested therapeutically and not in overdose

www.ketabpezeshki.com 66485457-66963820

Table 147-3 Antidotes Used in the Emergency Department

TOXIN USED FOR	ANTIDOTE	DOSE AND COMMENTS
Acetaminophen	*N*-Acetylcysteine	140 mg/kg PO, then 70 mg/kg q4h for up to 17 doses OR 150 mg/kg IV load during 1 hour with 50 mg/kg during 4 hours followed by 100 mg/kg during 16 hours
Anticholinergics	Physostigmine	1-2 mg IV in adults, 0.5 mg in children during 2 minutes for anticholinergic delirium, seizures, or dysrhythmias
Arsenic, lead, and mercury	BAL D-Penicillamine	3-5 mg/kg IM only 20-40 mg/kg/day; 500 mg tid in adults; may cross-react with penicillin in allergic patients
Benzodiazepines	Flumazenil	0.2 mg, then 0.3 mg, then 0.5 mg, up to 5 mg; not to be used if patient has signs of TCA toxicity; not approved for use in children but probably safe
Black widow spider bite	*Latrodectus* antivenin	One vial by slow IV infusion is usually curative; may cause anaphylaxis
Beta-blockers	Glucagon Insulin and glucose Intralipid 20%	5-10 mg in adults, then infusion of same dose per hour 1 unit/kg regular insulin IV push followed by 1-10 unit/kg/hr; blood glucose should be checked frequently; D10 at 100 mL/hr with boluses of D50 if hypoglycemia occurs 1.5 mL/kg during 2-3 minutes followed by infusion of 0.25 mL/kg/min Reported to be effective for highly protein bound drugs with large volumes of distribution, such as local anesthetics, beta-blockers, calcium channel blockers, and tricyclic antidepressants
Calcium channel blockers	Calcium Glucagon Insulin and glucose	1 g calcium chloride IV in adults, 20-30 mg/kg/dose in children, during a few minutes with continuous monitoring; repeat as needed 5-10 mg in adults, then infusion of same dose per hour Same dose as for beta-blockers
Cyanide	Hydroxycobalamin	5 mg in 100 mL of NS during 15 minutes; repeat if necessary
Cyanide, hydrogen sulfide	Sodium thiosulfate Sodium nitrite Hydroxycobalamin	50 mL of 25% (12.5 g; 1 ampule) in adults; 1.65 mL/kg IV in children 10 mL of 3% (300 mg; 1 ampule) in adults; 0.33 mL/kg slowly IV in children 5 g in 100 mL of NS given during 15 minutes
Digitalis glycosides	Digoxin-specific Fab	10-20 vials if patient is in ventricular fibrillation; otherwise dose fragments on the basis of serum digoxin concentration or amount ingested
Ethylene glycol	Fomepizole Pyridoxine Thiamine	15 mg/kg × 1, then 10 mg/kg q12h × 4, until ethylene glycol < 20 mg/dL; adjust dose during dialysis 100 mg IV daily 100 mg IV
Hydrofluoric acid	Calcium gluconate	3.5 g in 5 oz of KY jelly topical; apply liberally to affected skin
Iron	Deferoxamine	15 mg/kg/hr IV; higher doses reported to be safe
Isoniazid, hydrazine, and monomethylhydrazine	Pyridoxine	5 g in adults, 1 g in children, if ingested dose unknown; antidote may cause neuropathy in very large doses
Lead	DMSA (succimer) EDTA	Reported useful for arsenic and lead as well; one 100-mg capsule per 10-kg body weight tid for 1 week, then bid, with chelation breaks 75 mg/kg/day by continuous infusion; watch for nephrotoxicity, best done in hospital
Local anesthetics and others	Intralipid 20%	1.5 mL/kg during 2-3 minutes followed by infusion of 0.25 mL/kg/min Reported to be effective for highly protein bound drugs with large volumes of distribution, such as local anesthetics, beta-blockers, calcium channel blockers, tricyclic antidepressants, and others
MDMA-related hyperpyrexia	Dantrolene	2.5 mg/kg IV Lower doses have also been reported to be effective
Neuroleptics	Dantrolene	2.5 mg/kg IV for neuroleptic malignant syndrome
Methanol	Folate or leucovorin Ethanol Fomepizole	50 mg IV q4h in adults while patients have serious toxicity Loading dose, 10 mL/kg of 10%; maintenance dose, 0.15 mL/kg/hr of 10%; double rate during dialysis 15 mg/kg × 1, then 10 mg/kg q12h × 4, until methanol < 20 mg/dL; adjust dose during dialysis
Methemoglobin-forming agents	Methylene blue	1-2 mg/kg IV, one 10-mL dose of 10% solution (100 mg) is typical for an adult without anemia
Opioids	Nalmefene Naloxone	0.5-1 mg; much longer half-life than naloxone 2 mg; less to avoid narcotic withdrawal, more if inadequate response; same dose in children

Continued

www.ketabpezeshki.com 66485457-66963820

Table 147-3 Antidotes Used in the Emergency Department—cont'd

TOXIN USED FOR	ANTIDOTE	DOSE AND COMMENTS
Organophosphates and carbamates	Atropine	Test dose, 1-2 mg IV in adults, 0.03 mg/kg in children; titrate to drying of pulmonary secretions
	Protopam	Loading dose, 1-2 g IV in adults, 25-50 mg/kg in children; adult maintenance, 500 mg/hr or 1-2 g q4-6h
Rattlesnake bite	CroFab antivenin	Five vials minimum dose by infusion in normal saline; increase is rate dependent on patient's tolerance; may cause anaphylaxis
Serotonin syndrome	Cyproheptadine	4 mg PO or by nasogastric tube as needed; no parenteral form available; antidote may cause anticholinergic effects
Sulfonylureas	Octreotide	50 µg SC q12h, 5-10 µg/kg/24 hr IV
Tricyclic antidepressants	Bicarbonate	44-88 mEq in adults, 1-2 mEq/kg in children; best used by IV push and not by slow infusion
	Intralipid 20%	1.5 mL/kg during 2-3 minutes followed by infusion of 0.25 mL/kg/min Reported to be effective for highly protein bound drugs with large volumes of distribution, such as local anesthetics, beta-blockers, calcium channel blockers, and tricyclic antidepressants
Valproic acid	Carnitine	100 mg/kg IV or PO loading dose with 25 mg/kg q6h

BAL, British anti-Lewisite; *DMSA*, dimercaptosuccinic acid; *EDTA*, ethylenediaminetetraacetic acid; *TCA*, tricyclic antidepressant.

Box 147-3 Drugs, Chemicals, and Groups *Not Detected* by a Comprehensive Toxicology Screen

- Ammonia
- Anesthetic gases
- Antibiotics
- Anticoagulants
- Beta-blockers
- Borates
- Bromides
- Caustics and corrosives
- Colchicine
- Cyanide
- Digitalis glycosides
- Disulfiram
- Ergot alkaloids
- Ethylene glycol
- Fentanyl and its derivatives
- Fluorides
- H_2 antagonists
- Hallucinogens (e.g., LSD)
- Herbicides
- Household products
- Hypoglycemics
- Insect repellents
- Isoniazid
- Laxatives
- Lithium
- Metals
- Monoamine oxidase inhibitors
- Most antihypertensives
- Most cardiac medications
- Muscle relaxants
- Mushrooms
- Newer antidepressants (e.g., fluoxetine, sertraline, paroxetine, bupropion, buspirone)
- Nitrates and nitrites
- Nonsteroidal anti-inflammatory drugs
- Paraquat
- Pesticides
- Phenol
- Plants
- Solvents
- Thyroid hormone
- Vitamins

(e.g., Adderall containing amphetamine) and foods (e.g., poppy seeds containing morphine and codeine) can cause a misleading positive U-tox result.[19]

Drugs with a large volume of distribution or high fat solubility may be detected in urine long after the last dose. Most street drugs are detected in urine for days and marijuana for weeks (in rare cases even for months) after the last exposure.[19] Screening results rarely change the immediate clinical management of patients but may help document substance abuse or class of drugs responsible for the current clinical condition, as long as clinicians remember that false-positive or false-negative U-tox results occur. Quantitative serum measurements of certain drugs (e.g., acetaminophen, aspirin) may be helpful. In the agitated or seizing patient, elevated salicylate or lithium levels would significantly alter the management.

Electrolyte levels help identify metabolic acidosis by the carbon dioxide content ("bicarbonate level"); the determination should be repeated if it is low to ensure that the acidosis is resolving. A persistent, unexplained metabolic acidosis should prompt urine examination for oxalate crystals (suggestive of ethylene glycol poisoning), serum osmolality, serum salicylate level, and methanol and ethylene glycol levels. A normal arterial blood gas or electrolyte measurement does not rule out such ingestion because metabolic acidosis is delayed and does not appear until after metabolism of the acids from ethylene glycol and methanol or until after erratic and slow absorption of salicylate. Co-oximetry will confirm carboxyhemoglobin and methemoglobinemia, which will not be detected by pulse oximetry.

Rhabdomyolysis should be suspected when there is severe agitation or hyperthermia or if the patient is thought to have been unresponsive for a prolonged time (i.e., by history of presence or pressure sores). A urine dipstick test for blood (myoglobin) and determination of a serum creatine kinase concentration should be performed. Rhabdomyolysis and its treatment are discussed in Chapter 127. Noncardiogenic pulmonary edema on a chest radiograph suggests opioid or salicylate overdose. Some drugs are radiopaque (e.g., heavy metals, phenothiazines, potassium, calcium, and chlorinated hydrocarbons such as chloral hydrate), but radiography is rarely helpful in the evaluation of a poisoned patient except to monitor the decontamination of iron, lead, or body packets.

DECONTAMINATION

Gastric decontamination should not be undertaken routinely as it may result in morbidity, and patients often present too late for it to be effective.[20-24] Gastric lavage is rarely if ever indicated. In the rare circumstances in which gastric lavage is performed, a large (30-F or larger) orogastric tube is used, and specially designed lavage systems with large-bore tubes are available for this purpose.

Although activated charcoal may decrease drug absorption even if it is given hours after ingestion, it has not been proved to improve outcome. It might be considered in selected high-risk cases (such as with calcium channel blockers or salicylates) to prevent absorption when the patient is still likely to have a toxic amount of a drug or chemical in the gastrointestinal tract that is known to be absorbed by charcoal.

Whole-bowel irrigation with a polyethylene glycol solution is sometimes recommended by poison centers for overdose of metals such as iron and lead, in patients with ingestion of

www.ketabpezeshki.com 66485457-66963820

sustained-release formulations, or for the evacuation of drug packets from body packers or body stuffers.[25] It usually but not always requires placement of a small nasogastric tube. The scientific evidence that this procedure improves outcomes is lacking.

Exposure of the eye to caustic chemicals and irritants requires immediate irrigation with large amounts of water or readily available fluid, as outlined in Chapter 64. Irrigation is begun immediately after exposure, before transfer to the emergency department. Exposure to a gas does not require decontamination because the patient and rescuers are not at risk once the patient is removed from the toxic environment. The exception is when the patient's skin or clothing is contaminated with a liquid that is evaporating. The most important intervention to limit dermal exposure is to remove all clothing as soon as possible, ideally at the scene. Skin should be irrigated with warm water, with special attention to skin folds and other areas that might be missed. This includes the axilla, beneath nails, behind the knees, the genitalia, and in the scalp. For hydrocarbons or solvents, soap can be added. The skin should not be abraded with overly aggressive scrubbing, which could increase skin absorption. Ideally, skin decontamination occurs as soon as possible after exposure, at an out-of-hospital site before transport.

DISPOSITION AND CONSULTATION

The decision to admit a patient is not difficult when the patient manifests serious toxicity. When the patient is minimally symptomatic but has ingested a potentially dangerous substance, the decision is more difficult. Identification of an agent that causes a particular risk for the patient, especially cardiovascular instability, seizures, or respiratory depression, generally suggests admission to the hospital or to an observation unit in the emergency department. For benign medications, such as nonsteroidal anti-inflammatory drugs, observation is not necessary. For others, a 6-hour period of observation usually is sufficient to determine whether there is any significant toxicity. For extended-release preparations of toxic medications (e.g., beta-blockers), a longer observation period is warranted if drug effect is not subsiding by 6 hours. Patients with cardiac dysrhythmia, conduction disturbance, altered mental status requiring intubation, or the need for frequently titrated agents (e.g., pressors) should be admitted to a monitored bed or the intensive care unit. If the patient is acutely suicidal, a sitter or secure environment may be required.

Recognition of drug-induced prolongation of the QTc presents a disposition challenge. Many drugs have been reported to cause QTc prolongation, a known risk factor for torsades de pointes.[26-28] If the QTc is longer than 500 msec, even in a relatively asymptomatic drug overdose patient, monitoring is indicated until the QTc is decreasing.

Regional poison centers use a single nationwide toll-free number (1-800-222-1222) and can provide specific, current advice, especially for more esoteric or unfamiliar poisons. Consultation with a medical toxicologist is particularly helpful when an uncommon agent has been ingested, the patient is not following the anticipated clinical course, or specific interventions (such as administration of antidote therapy or dialysis) are contemplated.

KEY CONCEPTS

- A thorough history from multiple sources is often the key to toxicologic diagnosis.
- Common toxidromes should guide selective use of antidotes.
- Extensive laboratory investigation is usually unnecessary.
- Activated charcoal and other forms of gastric decontamination are not indicated in most poisoned patients. Gastric lavage is unlikely to be beneficial even if it is done soon after an oral drug overdose.
- Poison center and medical toxicologist consultations can be extremely helpful in diagnosis and management of the poisoned patient.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Kulig K: Initial management of ingestion of toxic substances. *N Engl J Med* 1992; 326:1677.
2. Wrenn K, Murphy F, Slovis C: A toxicity study of parenteral thiamine hydrochloride. *Ann Emerg Med* 1989; 18:867.
3. Li SF, Jacob J, Feng J, Kulkarni M: Vitamin deficiencies in acutely intoxicated patients in the ED. *Am J Emerg Med* 2008; 26:792-795.
4. Kaushik KS, Kapila K, Praharaj AK: Shooting up: The interface of microbial infections and drug abuse. *J Med Microbiol* 2011; 60:408-422.
5. Mandava N, et al: Establishment of a definitive protocol for the diagnosis and management of body packers (drug mules). *Emerg Med J* 2011; 28:98-101.
6. O'Malley GF, Deitch KR, Dominici P, Young M: A modified Goldfrank sniffing bar improves accuracy in identifying simulated toxins in a case-based teaching model. *J Med Toxicol* 2008; 4:11-15.
7. Grunau BE, Wiens MO, Brubacher JR: Dantrolene in the treatment of MDMA-related hyperpyrexia: A systematic review. *CJEM* 2010; 12:4335-4342.
8. Suzuki T, et al: Sarin poisoning in a Tokyo subway. *Lancet* 1995; 345:980.
9. Boyer EW, Shannon M: The serotonin syndrome. *N Engl J Med* 2005; 352:1112.
10. Felice KL, Schumann HM: Intravenous lipid emulsion for local anesthetic toxicity: A review of the literature. *J Med Toxicol* 2008; 4:184-191.
11. Jamaty C, et al: Lipid emulsions in the treatment of acute poisoning: A systematic review of human and animal studies. *Clin Toxicol (Phila)* 2010; 48:1-27.
12. Di Gregorio G, Neal JM, Rosenquist RQ, Weinberg GL: Clinical presentation of local anesthetic systemic toxicity. A review of published cases, 1979-2009. *Reg Anesth Pain Med* 2010; 35:181-187.
13. American College of Medical Toxicology: ACMT Position Statement: Interim guidance for the use of lipid resuscitation therapy. *J Med Toxicol* 2011; 7:81-82.
14. Rentsch KM: Laboratory diagnostics in acute poisoning: Critical overview. *Clin Chem Lab Med* 2010; 48:1381-1387.
15. Wu AH: Limitations of point-of-care testing in the ED or ICU: A role for regional centralized toxicology laboratories. *Clin Pharmacol Ther* 2010; 88:295-298.
16. Moeller KE, Lee KC, Kissack JC: Urine drug screening: Practical guide for clinicians. *Mayo Clin Proc* 2008; 83:66-76.
17. Tenore PL: Advanced urine toxicology testing. *J Addict Dis* 2010; 21:436-448.
18. Kulig K: *The appropriate utilization of toxicology screens*. In: Cantrill SV, Karas SJ, eds. *Cost-Effective Diagnostic Testing in Emergency Medicine*. Dallas, Tex: American College of Emergency Physicians; 2000.
19. Medical Review Officer Certification Council, Swotinsky R, Smith D: *The Medical Review Officer's Manual. MROCC's Guide to Drug Testing*, 4th ed. Beverly Farms, Mass: Occupational and Environmental Medicine (OEM) Press; 2010.
20. Chyka PA, Seger D: Position statement: Single-dose activated charcoal. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol* 2005; 2:51-87.
21. Vale JA: Position statement: Gastric lavage. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol* 2004; 42:933-943.
22. Jurgens G, Hoegberg LCG, Graudal NA: The effect of activated charcoal on drug exposure in healthy volunteers: A meta-analysis. *Clin Pharmacol Ther* 2009; 85:501-505.
23. Bond GR: The role of activated charcoal and gastric emptying in gastrointestinal decontamination: A state-of-the-art review. *Ann Emerg Med* 2002; 39:273.
24. Heard K: The changing indications of gastrointestinal decontamination in poisonings. *Clin Lab Med* 2006; 26:1.
25. Tennenbein M: Position statement: Whole bowel irrigation. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol* 2004; 42:843-854.
26. Woosley RL: *Drugs that prolong the QT interval and/or induce torsades de pointes*. Available at www.torsades.org. Accessed July 16, 2002.
27. Pickham D, et al: How many patients need QT interval monitoring in critical care units? Preliminary report of the QT in Practice study. *J Electrocardiol* 2010; 43:572-576.
28. Waring WS, et al: Evaluation of a QT nomogram for risk assessment after antidepressant overdose. *Br J Clin Pharmacol* 2010; 70:881-885.

www.ketabpezeshki.com 66485457-66963820

Chapter 148

Acetaminophen

Robert G. Hendrickson and Nathanael J. McKeown

PERSPECTIVE

Acetaminophen is one of the most commonly used antipyretic and analgesic agents throughout the world. Acetaminophen is found as an isolated product or in combination medications for the treatment of cold symptoms, pain, and headache. In 2010, an intravenous (IV) formulation was approved in the United States (an IV formulation was available in Europe and Australia previously) for the treatment of pain[1-3] and as an antipyretic.[4] Given the widespread use and availability of acetaminophen, toxicity is a concern in all intentional ingestions as well as with repeated supratherapeutic dosing and drug abuse. Acetaminophen toxicity is one of the leading causes of hospital admission, antidote use, and fatalities from oral poisonings in the United States.[5]

Protocols have been established for the assessment and management of acute acetaminophen ingestion through decades of research and experience. However, controversy continues to exist, and with new formulations recently approved, the management of acetaminophen exposures continues to evolve.

PRINCIPLES OF DISEASE

Acetaminophen is absorbed rapidly, with peak plasma concentrations generally occurring within 1 hour and complete absorption within 4 hours. Once it is absorbed, acetaminophen inhibits prostaglandin E_2 (PGE_2) synthesis, leading to antipyresis and analgesia. Inhibition of PGE_2 synthesis is by either direct cyclooxygenase-2 inhibition or inhibition of membrane-associated prostaglandin synthase.[6,7]

In therapeutic doses, acetaminophen is primarily metabolized by conjugation with glucuronide (40-67%) and sulfate (20-46%) into nontoxic metabolites that are excreted in the urine[8] (Fig. 148-1). A small percentage (<5%) is oxidized by cytochrome P_{450} 2E1 (CYP2E1) (and to a lesser extent 1A4 and 3A4) to a highly cytotoxic metabolic intermediary, *N*-acetyl-*p*-benzoquinone imine (NAPQI).[9,10] In therapeutic doses, NAPQI is short-lived, combining rapidly with glutathione and other thiol-containing compounds to form nontoxic metabolites that are excreted in the urine. With typical therapeutic acetaminophen dosing, glutathione stores and the ability to regenerate glutathione easily keep up with NAPQI production.

After large ingestions or repeated supratherapeutic ingestions, the amount of NAPQI produced begins to outstrip glutathione stores and the liver's ability to regenerate glutathione, leading to unbound NAPQI. The highly reactive electrophile NAPQI covalently binds to cell proteins in the liver, which initiates a cascade of events that lead to hepatic cell death. Renal injury may also occur with or without liver injury[11] and may be mediated by renal CYP enzymes or activation of prostaglandin synthase.

Acetaminophen-induced liver damage initially occurs in hepatic zone III (centrilobular) because oxidative metabolism is concentrated in this area. With severe toxicity, necrosis of the entire liver parenchyma may occur. The clinical effects of severe acetaminophen toxicity are the result of severe fulminant liver failure rather than a direct acetaminophen effect. These effects include multiorgan failure, systemic inflammatory response syndrome, hypotension, cerebral edema, and death.[12]

The principal therapy for acetaminophen toxicity is *N*-acetylcysteine (NAC), which is effective by two separate mechanisms. Soon after overdose, NAC serves as a glutathione precursor and a sulfur-containing glutathione substitute (see Fig. 148-1), binding to and thereby detoxifying NAPQI and avoiding subsequent hepatotoxicity. In addition, NAC may decrease NAPQI formation by enhancing acetaminophen conjugation with sulfate to nontoxic metabolites.

Even after acetaminophen hepatotoxicity is evident, NAC acts as a free radical scavenger and an antioxidant and alters hepatic microcirculation and oxygen delivery.[13] In patients with acetaminophen-induced hepatic failure, IV administration of NAC decreases the rates of cerebral edema, hypotension, and death even when no acetaminophen remains.[12]

CLINICAL FEATURES

Early after acute acetaminophen ingestion, patients may be asymptomatic or have mild nonspecific symptoms (e.g., nausea, vomiting, anorexia, malaise, diaphoresis) (Table 148-1). Liver injury becomes evident after a period of 8 to 36 hours as an elevation in aspartate transaminase (AST).[14] Once liver injury has begun, patients may have right upper quadrant pain or tenderness, vomiting, and jaundice. AST concentrations continue to rise rapidly[14] and usually peak in 2 to 4 days, corresponding to maximal liver injury. Alanine transaminase (ALT), prothrombin time, and bilirubin typically begin to rise and peak shortly after AST values. With severe toxicity, AST, ALT, and the prothrombin time may all be elevated within 24 hours (Fig. 148-2).[14] With maximal liver injury, patients have signs and symptoms consistent with fulminant liver failure, including metabolic acidosis, coagulopathy, and hepatic encephalopathy. Death may occur from hemorrhage, adult respiratory distress syndrome, sepsis, multiorgan failure, or cerebral edema. The risk of renal injury increases with the severity of hepatic injury; renal injury occurs in less than 2% of patients without hepatotoxicity and in 25% of patients with severe hepatotoxicity.

If patients recover, transaminases return to baseline concentrations during a 5- to 7-day period, although complete histologic resolution of liver injury may take months. Once histologic recovery is complete, there are no long-term sequelae to the

www.ketabpezeshki.com 66485457-66963820

liver, and patients are not at increased risk for chronic hepatic dysfunction.

DIAGNOSTIC STRATEGIES

The goals of patient assessment after acetaminophen ingestion are the determination of the patient's risk, diagnostic testing, and treatment with the antidote NAC when appropriate.

Acetaminophen exposures may be classified as acute or chronic, and each type requires different testing and risk assessment. An acute ingestion is a single ingestion or a series of ingestions that are arbitrarily defined to occur within an 8-hour period. All other ingestions, including accidental repeated supratherapeutic ingestions and intentional ingestions spread for longer than 8 hours, can be considered to be chronic.

Risk Assessment with Acute Acetaminophen Ingestion

The initial diagnostic strategy of an acute ingestion is well established. The first step is to determine the patient's risk of acute acetaminophen exposure. Patients who report an acute intentional ingestion of acetaminophen should have laboratory risk stratification regardless of the reported amount ingested. It is likely that significantly more than 150 mg/kg must be acutely ingested before significant liver toxicity occurs; however, history alone may not be reliable. A serum acetaminophen concentration should be considered in all intentional overdoses because approximately 1.4 to 8.4% of patients with intentional ingestions who deny acetaminophen ingestion actually have a detectable but usually subtoxic concentration.[15-17]

Once a suggested exposure to acetaminophen is established, the next step is to establish a time of ingestion. If possible, this information should be corroborated by others. If no accurate time of ingestion can be determined, a worst-case scenario should be considered (e.g., the last time the patient was seen before the ingestion).

Once a patient is determined to be at risk and a time of ingestion has been established or estimated, the next step is to determine a serum acetaminophen concentration 4 hours after ingestion or as soon as possible after 4 hours. The serum acetaminophen concentration and the time of ingestion determine the need for antidotal therapy by plotting of the serum acetaminophen concentration against the time since ingestion on the treatment nomogram (Fig. 148-3), an adaptation of the Rumack-Matthew nomogram. If the serum acetaminophen concentration is on or above the treatment line (that starts at 150 µg/mL (990 µmol/L) at 4 hours and decreases to 4.7 µg/mL (31 µmol/L) at 24 hours), treatment with NAC should be initiated. If the serum acetaminophen concentration is below the treatment line and the most severe possible scenario has been taken for the time of ingestion,

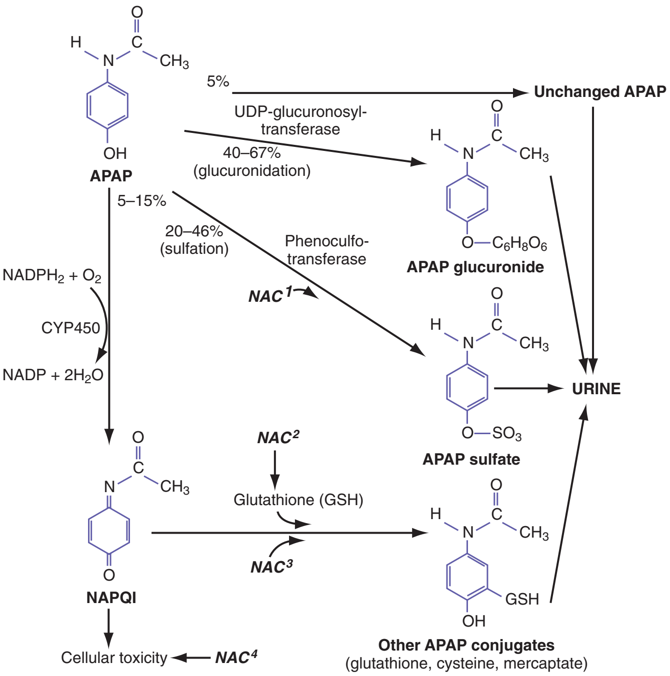


Figure 148-1. Acetaminophen (APAP) metabolism and *N*-acetylcysteine (NAC) mechanisms of action. NAC[1] enhances sulfation; NAC[2] serves as a glutathione (GSH) precursor; NAC[3] is a GSH substitute; NAC[4] may reduce systemic toxicity. *NAPQI, N*-acetyl-*p*-benzoquinone imine. (Modified from Smilkstein MJ: Acetaminophen. In Goldfrank LR, et al (eds): Goldfrank's Toxological Emergencies, ed 6. Stamford, Conn, Appleton & Lange, 1998, p 547.)

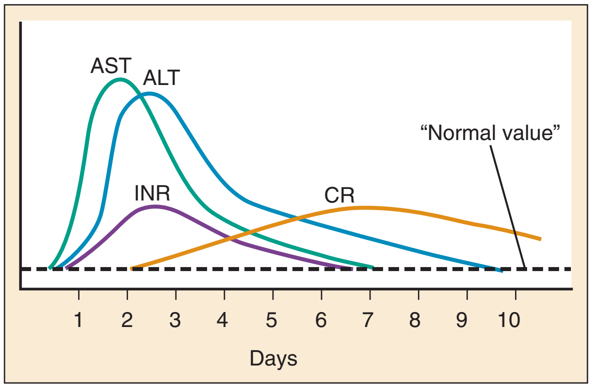


Figure 148-2. A typical time course of rise, peak, and fall of laboratory values in patients with acetaminophen-induced hepatic dysfunction who survive. Peaks are not proportional. Not all laboratory abnormalities occur in all patients, and significant individual variation may occur. *ALT,* alanine transaminase; *AST,* aspartate transaminase; *CR,* creatinine; *INR,* international normalized ratio. (Modified from Robert G. Hendrickson, MD. ©)

Table 148-1 Time Course and Clinical Stages of Acetaminophen Toxicity

STAGE	TIME COURSE	NAME	SYMPTOMS	SIGNS
1	0-12 (up to 24-36) hr	Preinjury	Nausea, vomiting, anorexia, malaise	Elevated serum acetaminophen concentration
2	8-36 hr	Liver injury	Nausea, vomiting, right upper quadrant abdominal tenderness	Transaminitis (AST begins to rise 8-36 hr after ingestion)
3	2-4 days	Maximum liver injury	Liver failure (encephalopathy, coagulopathy, hemorrhage, acidosis)	Hemorrhage, ARDS, sepsis/SIRS, multiorgan failure, cerebral edema
4	>4 days	Recovery	None	Complete hepatic histologic recovery

ARDS, acute respiratory distress syndrome; *AST,* aspartate transaminase; *SIRS,* systemic inflammatory response syndrome.

www.ketabpezeshki.com 66485457-66963820

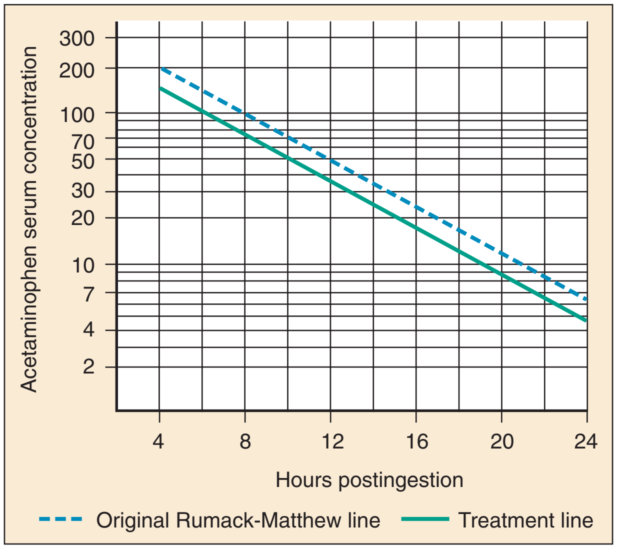


Figure 148-3. Treatment nomogram for acute overdose. The lower treatment line should be used for treatment decisions. (Modified from Rumack BH, Matthew H: Acetaminophen poisoning and toxicity. Pediatrics 55:871, 1975.)

Table 148-2 Indications to Initiate Testing for Serum Acetaminophen Concentration and AST in Chronic Acetaminophen Ingestions[26]

Age ≥6 years	Ingestion of >10 g/day or >200 mg/kg/day (whichever is smaller) during a 24-hr period
or	Ingestion of >6 g/day or >150 mg/kg/day (whichever is smaller) during a 48-hr period or longer
or	Symptomatic (e.g., RUQ pain or tenderness, jaundice, vomiting)
Children <6 years	Ingestion of >200 mg/kg/day during a 24-hr period
or	Ingestion of >150 mg/kg/day during a 48-hr period
or	Ingestion of >100 mg/kg/day during a 72-hr or longer period
or	Symptomatic (e.g., RUQ pain or tenderness, jaundice, vomiting)

AST, aspartate transaminase; *RUQ,* right upper quadrant.

the patient requires no antidote.[18] The treatment nomogram is a highly sensitive approach and may be used for all acute ingestions. Alternative approaches in patients with alcoholism,[19] in patients with coingestions of antimuscarinic agents,[20,21] in patients with unknown ingestion times,[22] and after the administration of IV formulations[23] have been suggested, but these remain controversial and unvalidated. Strict adherence to the approach described here is recommended.

Measurement of serum acetaminophen concentration before 4 hours is typically not necessary. It is likely that a serum acetaminophen concentration less than 10 μg/mL (66 μmol/L) between 1 and 4 hours after ingestion excludes significant ingestion of acetaminophen; however, there are few data on which to base this conclusion. Absorption of acetaminophen may not be complete before 4 hours, and any serum acetaminophen concentration greater than 10 μg/mL (66 μmol/L) is difficult to interpret. Finally, serum acetaminophen concentrations measured before 4 hours cannot be plotted on the treatment nomogram. Fortunately, there is little need to treat patients before 6 to 8 hours after ingestion; patients treated with NAC up to 6 hours after ingestion, even after very large doses, have no increased risk of hepatotoxicity regardless of their serum acetaminophen concentration.[24] For most overdose patients, the risk of hepatotoxicity does not significantly increase unless NAC is delayed for 8 hours or longer after ingestion.[24] This is generally enough time for a serum acetaminophen concentration to be determined at 4 hours and the laboratory evaluation to be completed. For patients at risk whose serum acetaminophen concentration cannot be obtained before 8 hours after ingestion, a loading dose of NAC should be considered.

There are few data for development of a strategy of risk assessment after a large IV acetaminophen overdose. Several pharmacokinetic factors suggest that some alteration of the typical nomogram-based assessment may be necessary. After infusion, IV acetaminophen generates serum concentrations that are significantly higher than an equivalent oral dose. In addition, the nomogram that is used for acute ingestions takes into account an absorptive period that is not necessary for an IV infusion. These and other factors suggest that an alternative approach may be necessary, but experience is limited. We adhere to a conservative approach, which suggests that patients be treated with NAC if they either (1) are treated with more than 60 mg/kg IV acetaminophen in one dose or (2) they have a serum acetaminophen concentration that is above 50 μg/mL (330 μmol/L) at 4 hours after the infusion stops.[25]

Risk Assessment with Chronic Ingestion

If the ingestion is a repeated or chronic exposure, risk assessment is more complex, and the treatment nomogram cannot be used. The initial steps include determining whether the patient is at risk for hepatotoxicity, evaluating the patient by measuring a serum acetaminophen concentration and AST, and initiating therapy with NAC.

The risk of hepatotoxicity from chronic ingestion of acetaminophen is increased with both an increasing total dose of acetaminophen and a longer duration in which it has been ingested in supratherapeutic quantities. With this in mind, laboratory testing for serum acetaminophen concentration and AST should be initiated in any patient who fits the criteria in Table 148-2.[26]

Ingestion of therapeutic amounts of acetaminophen appears to be safe.[27,28] However, rare reports of transaminitis and liver injury during therapeutic dosing suggest that some patients may be at increased risk for liver injury, possibly because of genetic variation or specific risk factors.[29] Patients who chronically ingest isoniazid or ethanol may have increased CYP2E1 activity and theoretically be at higher risk for chronic acetaminophen toxicity. Similarly, patients who have prolonged fasting (e.g., malnourished, AIDS, severe prolonged vomiting) and children with febrile illnesses[30-32] have reason to be at higher risk. All of these risk factors are controversial and require additional study. Given that we are unable to accurately predict the rare patient at high risk, patients who have symptoms consistent with liver injury (e.g., right upper quadrant pain or tenderness, jaundice) after taking acetaminophen merit risk determination regardless of the amount that they reportedly ingest.

Once serum acetaminophen concentration and AST are determined, further risk assessment is necessary. Conceptually, patients with chronic ingestions may benefit from antidotal therapy if they have evidence of liver injury *or* if they have evidence of acetaminophen excess that may lead to liver injury. With this in mind, patients with chronic supratherapeutic acetaminophen exposure with significant elevations of AST (e.g., >50 IU/L) should be treated with NAC regardless of their serum acetaminophen concentration.[33,34] A higher cutoff for AST (e.g., twice normal, or >120 IU/L) has been suggested but is unstudied.[35,36] In patients with an AST that is not elevated (e.g., <50 IU/L), NAC should be initiated if the serum acetaminophen concentration is higher than expected. After a typical therapeutic dose of acetaminophen, serum acetaminophen concentration peaks below 30 μg/mL (199 μmol/L) and is less than 10 μg/mL (66 μmol/L) at 4 hours.

www.ketabpezeshki.com 66485457-66963820

All patients who do not require antidotal therapy should be instructed to return to the emergency department if they have signs of hepatotoxicity (e.g., right upper quadrant abdominal pain, vomiting, jaundice).

Risk Assessment in Pregnant Women

Fetal acetaminophen toxicity is rare, but adverse outcomes have been reported in all stages of pregnancy.[37] Acetaminophen crosses the placenta and may be present in concentrations in the fetus that are as high as or higher than those in the mother.[37] In the early gestational period, acetaminophen toxicity can be associated with fetal death.[37] CYP enzymes appear in the fetus during the second trimester, and activity increases with gestational age, which may put the maturing fetus (e.g., third trimester) or newborn at risk of toxicity.

The risk assessment for and diagnostic approach to pregnant women, however, are the same as those for nonpregnant women. In acute overdoses, a serum acetaminophen concentration should be determined and plotted on the treatment nomogram. NAC therapy should be initiated if the serum acetaminophen concentration plots above the treatment line. With chronic exposure, if either the AST is above 50 IU/L or the serum acetaminophen concentration is above expected, NAC therapy should be initiated.

MANAGEMENT

The mainstays of management are to provide supportive care and to initiate NAC therapy when it is indicated. Emergency physicians may consult with a regional poison center (1-800-222-1222) as the management of acetaminophen exposures is continually changing.

Limiting Gastrointestinal Absorption

Activated charcoal effectively binds acetaminophen in vitro[38] and limited studies have suggested some efficacy,[39,40] but there is no evidence that administration of activated charcoal to patients translates into improved clinical outcomes.

N-Acetylcysteine

When it is indicated, NAC should be administered as early as possible. Delay of NAC administration for more than 8 hours after ingestion increases the risk of hepatotoxicity (Fig. 148-4).

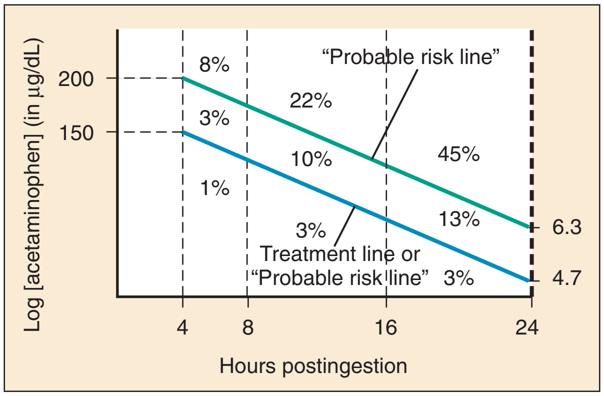


Figure 148-4. Risk of liver injury (alanine transaminase > 1000 IU) based on initial acetaminophen concentration and time to oral administration of *N*-acetylcysteine. (Modified from Rumack BH: Acetaminophen hepatotoxicity: The first 35 years. J Toxicol Clin Toxicol 40:3, 2002.)

NAC can be administered by the oral (PO) or IV route, with advantages and disadvantages for each. All formulations of NAC (PO and IV) are effective when they are started within 8 hours of ingestion.[24,41-44] The main role of early NAC administration is to prevent hepatotoxicity by detoxifying NAPQI and decreasing NAPQI production. The risk of liver injury (i.e., AST > 1000 IU/L) in this group with treatment with NAC is less than 4%, and the mortality rate approaches zero[41,44] (see Fig. 148-4).

Both PO and IV NAC are equally effective in treating patients who present 8 to 24 hours after ingestion, although the overall rate of liver injury (i.e., AST > 1000 IU/L) in this group is significantly higher (approximately 30%).[41,42,45]

Once liver failure (e.g., coagulopathy, encephalopathy) is evident, however, the IV route is the only route that has been systematically studied.[12] IV NAC decreases the risk of hypotension, cerebral edema, and death in patients with acetaminophen-related hepatic failure.[12] Oral NAC should be used only if IV NAC is not available.

The main differences between IV and PO NAC are in their side effect profiles (Table 148-3). Approximately 2 to 6% of patients treated with IV NAC have anaphylactoid reactions,[43,46-48] although rates of up to 30% have been reported in prospective trials.[49,50] The majority of these symptoms are mild and consist of transient skin rashes and flushing. More severe reactions have been reported in less than 1% of patients and include angioedema, bronchospasm, hypotension, and at least one death.[47-51] Symptoms typically occur within 30 minutes of the start of the loading infusion. These anaphylactoid reactions are dose, rate, and concentration dependent.[46,47]

Anaphylactoid reactions are much less frequent with PO NAC. Skin rash, serious systemic reactions, and anaphylactic reactions are rarely reported with the PO formulation. However, approximately 23% of patients receiving PO NAC vomit, delaying timely antidotal delivery.[52] PO NAC is extremely unpalatable, largely because of a "rotten egg" odor and taste. Palatability may be improved by administering NAC diluted with either soda or juice and serving it in a covered container through a straw. Any dose that is vomited within 1 hour of administration should be repeated. Antiemetics (e.g., ondansetron, metoclopramide) are advisable before PO NAC dosing, but there are few data about effectiveness of this approach.

Anaphylactoid reactions to IV NAC are typically mild (e.g., flushing) and occur during the initial 15- to 60-minute infusion. Mild reactions can be managed with antihistamines (e.g., IV diphenhydramine) without stopping the infusion. Serious reactions can be managed by slowing or pausing the infusion, giving a fluid bolus, and administering diphenhydramine or glucocorticoids intravenously if necessary.[53] Epinephrine is rarely required. Although these reactions require close observation and treatment as necessary, they do not preclude subsequent doses.[53]

Table 148-3 Side Effect Profile for *N*-Acetylcysteine Formulations

NAC FORMULATION	COMMON SIDE EFFECTS	SEVERE SIDE EFFECTS
PO NAC	Vomiting (23%)[52]	Very rare
IV NAC	Mild anaphylactoid reactions (e.g., rash, flushing, pruritus, vomiting), 2-18%[46-49,53]	Severe anaphylactoid reactions (e.g., hypotension), <1%[43,46-49]

IV, intravenous; *NAC*, *N*-acetylcysteine; *PO*, by mouth.

www.ketabpezeshki.com 66485457-66963820

Table 148-4 Inpatient Predictors of the Severity of Illness in Patients with Acetaminophen Toxicity

SCORE	PREDICTIVE VARIABLES	OUTCOME PREDICTED	NOTES
Modified King's College Criteria	pH < 7.3 *or* *All three:* Cr > 3.3 mg/dL (292 mmol/L) *and* INR > 5 (or PTT > 100s) *and* Encephalopathy > grade III (patient comatose)	Death or transplantation	Arterial pH is measured *after* fluid resuscitation.
APACHE II[56]	APACHE II score > 20	Death or transplantation	Confounders include coingested medications that may alter the APACHE II score.
Lactate[57]	Lactate > 3.5 mmol/L before resuscitation	Death or transplantation	A specimen for lactate measurement was drawn a mean of 55 hr after ingestion. The predictive ability of an early draw is unknown.

APACHE II, Acute Physiology and Chronic Health Evaluation II; *Cr,* creatinine; *INR,* international normalized ratio; *PTT,* partial thromboplastin time.

N-Acetylcysteine in Pregnancy

Treatment of the mother with NAC is safe and effective,[54] and NAC effectively crosses the placenta.[55] Administration of IV NAC to the mother has the theoretic advantage of increased NAC delivery to the fetus compared with PO NAC. IV administration circumvents first-pass metabolism, presumably exposing the fetal circulation to higher maternal serum concentrations. On the basis of large published studies, we recommend continuation of therapy for 72 hours.[37]

Duration of Therapy

There are two well-established protocols for NAC administration: a 72-hour PO protocol and a 21-hour IV protocol. At the completion of these protocols, NAC may be discontinued if the metabolism of acetaminophen is complete (i.e., serum acetaminophen concentration > 10 µg/mL [66 µmol/L]) and there is no evidence of liver injury (normal AST concentration). The endpoint does not rely solely on the predetermined length of a protocol, and all protocols should be extended if there is significant liver injury (AST concentration greater than normal) *or* acetaminophen metabolism is incomplete (serum acetaminophen concentration > 10 µg/mL [66 µmol/L]). If it is extended, NAC therapy may be discontinued once evidence of liver injury has resolved (e.g., encephalopathy and coagulopathy have resolved and AST is decreasing and is less than 1000 IU/L) and acetaminophen is undetectable.

Supportive Care

Supportive care includes management of coingestions and the nausea and vomiting, hepatic injury, and renal dysfunction related to acetaminophen poisoning. Treatment of these problems is based on general treatment principles and is not acetaminophen dependent (see Chapter 90).

DISPOSITION

Asymptomatic patients who fit the criteria for treatment should be treated with NAC and can be admitted to a medical inpatient unit or emergency department observation unit. The motivation behind any ingestion needs to be evaluated, and psychiatric consultation may be obtained when it is appropriate.

Patients showing evidence of severe hepatotoxicity and those at risk for fulminant hepatic failure may need to be admitted to a monitored bed, often in an intensive care unit. These patients require frequent neurologic checks, monitoring of vital signs, and laboratory studies.

If a patient presents with established hepatotoxicity, transfer to a higher level center that specializes in the care of patients with liver failure may be advisable, as is the case for any other patient presenting with liver failure. Clinical predictors of severe hepatic failure are listed in Table 148-4.[56,57]

KEY CONCEPTS

- Acetaminophen concentration should be measured in cases of unknown or mixed overdoses. Acetaminophen is relatively clinically silent until serious hepatotoxicity ensues.
- Repeated supratherapeutic dosing of acetaminophen can lead to life-threatening toxicity.
- The acetaminophen concentration on the nomogram at 4 hours or more after ingestion is used to determine whether NAC therapy is indicated for acute ingestions.
- For maximum benefit, NAC treatment should not be delayed beyond 8 hours after ingestion. If more than 8 hours has passed since ingestion, treatment should be started with ongoing assessment of the amount of ingestion and likelihood of hepatotoxicity.
- Late or prolonged administration of NAC is beneficial even with low acetaminophen concentrations if hepatotoxicity is evident.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Sinatra RS, et al: Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. *Anesthesiology* 2005; 102:822.
2. Wininger SJ, et al: A randomized, double-blind, placebo-controlled, multicenter, repeat-dose study of two intravenous acetaminophen dosing regimens for the treatment of pain after abdominal laparoscopic surgery. *Clin Ther* 2010; 32:2348.
3. Grissa MH, et al: Paracetamol vs piroxicam to relieve pain in renal colic. Results of a randomized controlled trial. *Am J Emerg Med* 2011; 29:203.
4. Walson PD, Jones J, Chesney R, Rodarte A: Antipyretic efficacy and tolerability of a single intravenous dose of the acetaminophen prodrug propacetamol in children: A randomized, double-blind, placebo-controlled trial. *Clin Ther* 2006; 28:762.
5. Bronstein AC, et al: 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 27th Annual Report. *Clin Toxicol (Phila)* 2010; 48:979.
6. Aronoff D, Neilson E: Antipyretics: Mechanism of action and clinical use in fever suppression. *Am J Med* 2001; 111:304.
7. Graham GG, Kieran FS: Mechanism of action of paracetamol. *Am J Ther* 2005; 12:46.
8. Schenker S, Speeg K, Perez A, Finch J: The effects of food restriction in man on hepatic metabolism of acetaminophen. *Clin Nutr* 2001; 20:145.
9. Manyike PT, Kharasch ED, Kalhorn TF, Slattery JT: Contribution of CYP2E1 and CYP3A to acetaminophen reactive metabolite formation. *Clin Pharmacol Ther* 2000; 67:275.
10. Hazai E, Vereczkey L, Monostory K: Reduction of toxic metabolite formation of acetaminophen. *Biochem Biophys Res Comm* 2002; 291:1089.
11. Boutis K, Shannon M: Nephrotoxicity after acute severe acetaminophen poisoning in adolescents. *J Toxicol Clin Toxicol* 2001; 39:441.
12. Keays R, et al: Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: A prospective controlled trial. *Br Med J* 1991; 303:1026.
13. Jones AL: Mechanism of action and value of *N*-acetylcysteine in the treatment of early and late acetaminophen poisoning: A critical review. *J Toxicol Clin Toxicol* 1998; 36:277.
14. Green TJ, et al: When do the aminotransferases rise after acute acetaminophen overdose? *Clin Toxicol (Phila)* 2010; 48:787-792.
15. Lucanie R, Chiang WK, Reilly R: Utility of acetaminophen screening in unsuspected suicidal ingestions. *Vet Hum Toxicol* 2002; 44:171.
16. Ashbourne JF, Olson KR, Khayam-Bashi H: Value of rapid screening for acetaminophen in all patients with intentional drug overdose. *Ann Emerg Med* 1989; 18:1035.
17. Hartington K, Hartley J, Clancy M: Measuring plasma paracetamol concentrations in all patients with drug overdoses: Development of a clinical decision rule and clinicians willingness to use it. *Emerg Med J* 2002; 19:408.
18. Hendrickson RG: *Acetaminophen*. In: Goldfrank L, et al, eds: *Goldfrank's Toxicologic Emergencies*, 9th ed. New York: McGraw-Hill; 2010.
19. Ali FM, Boyer EW, Bird SB: Estimated risk of hepatotoxicity after an acute acetaminophen overdose in alcoholics. *Alcohol* 2008; 42:213.
20. Hendrickson RG, McKeown NJ, West PL, Burke CR: Bactrian ("double hump") acetaminophen pharmacokinetics: A case series and review of the literature. *J Med Toxicol* 2010; 6:337-344.
21. Klein-Schwartz W, Doyon S: Intravenous acetylcysteine for the treatment of acetaminophen overdose. *Expert Opin Pharmacother* 2011; 12:119.
22. Sivilotti ML, et al: Multiplying the serum aminotransferase by the acetaminophen concentration to predict toxicity following overdose. *Clin Toxicol (Phila)* 2010; 48:793.
23. Beringer RM, Thompson JP, Parry S, Stoddart PA: Intravenous paracetamol overdose: Two case reports and a change to national treatment guidelines. *Arch Dis Child* 2011; 96:307.
24. Sivilotti ML, et al: A risk quantification instrument for acute acetaminophen overdose patients treated with *N*-acetylcysteine. *Ann Emerg Med* 2005; 46:263.
25. Gray T, Hoffman RS, Bateman DN: Intravenous paracetamol—an international perspective of toxicity. *Clin Toxicol (Phila)* 2011; 49:150.
26. Dart RC, et al: Acetaminophen poisoning: An evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila)* 2006; 44:1.
27. Dart RC, Bailey E: Does therapeutic use of acetaminophen cause acute liver failure? *Pharmacotherapy* 2007; 27:1219.
28. Lavonas EJ, Reynolds KM, Dart RC: Therapeutic acetaminophen is not associated with liver injury in children: A systematic review. *Pediatrics* 2010; 126:e1430.
29. Watkins PB, et al: Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: A randomized controlled trial. *JAMA* 2006; 296:87.
30. American Academy of Pediatrics, Committee on Drugs: Acetaminophen toxicity in children. *Pediatrics* 2001; 108:1020.
31. Caravati EM: Unintentional acetaminophen ingestion in children and the potential for hepatotoxicity. *J Toxicol Clin Toxicol* 2000; 38:291.
32. Mohler CR, et al: Prospective evaluation of mild to moderate pediatric acetaminophen exposures. *Ann Emerg Med* 2000; 35:239.
33. Daly FF, O'Malley GF, Heard K, Bogdan GM, Dart RC: Prospective evaluation of repeated supratherapeutic acetaminophen (paracetamol) ingestion. *Ann Emerg Med* 2004; 44:393.
34. Wolf SJ, Heard K, Sloan EP, Jagoda AS: Clinical policy: Critical issues in the management of patients presenting to the emergency department with acetaminophen overdose. *Ann Emerg Med* 2007; 50:292.
35. Kozer E, Greenberg R, Zimmerman DR, Berkovitch M: Repeated supratherapeutic doses of paracetamol in children—a literature review and suggested clinical approach. *Acta Paediatr* 2006; 95:1165.
36. Alhelail MA, Hoppe JA, Rhyee SH, Heard KJ: Clinical course of repeated supratherapeutic ingestion of acetaminophen. *Clin Toxicol (Phila)* 2011; 49:108.
37. Riggs BS, et al: Acute acetaminophen overdose during pregnancy. *Obstet Gynecol* 1989; 74:247.
38. Offerman SR: The clinical management of acetaminophen poisoning in a community hospital system: Factors associated with hospital length of stay. *J Med Toxicol* 2011; 7:4.
39. Buckley NA, Whyte IM, O'Connell DL, Dawson AH: Oral or intravenous *N*-acetylcysteine: Which is the treatment of choice for acetaminophen (paracetamol) poisoning? *J Toxicol Clin Toxicol* 1999; 37:759.
40. Spiller HA, Winter ML, Klein-Schwartz W, Bangh SA: Efficacy of activated charcoal administered more than four hours after acetaminophen overdose. *J Emerg Med* 2006; 30:1.
41. Buckley NA, Whyte IM, O'Connell DL, Dawson AH: Oral or intravenous *N*-acetylcysteine: Which is the treatment of choice for acetaminophen (paracetamol) poisoning? *J Toxicol Clin Toxicol* 1999; 37:759.
42. Prescott L: Oral or intravenous *N*-acetylcysteine for acetaminophen poisoning? *Ann Emerg Med* 2005; 45:409.
43. Whyte IM, Francis B, Dawson AH: Safety and efficacy of intravenous *N*-acetylcysteine for acetaminophen overdose: Analysis of the Hunter Area Toxicology Service (HATS) database. *Curr Med Res Opin* 2007; 23:2359.
44. Rumack BH: Acetaminophen hepatotoxicity: The first 35 years. *J Toxicol Clin Toxicol* 2002; 40:3.
45. Kanter MZ: Comparison of oral and i.v. acetylcysteine in the treatment of acetaminophen poisoning. *Am J Health Syst Pharm* 2006; 63:1821.
46. Horowitz BZ, Hendrickson RG, Pisarro-Osilla C: Not so fast! *Ann Emerg Med* 2006; 47:122.
47. Kao LW, et al: What is the rate of adverse events after oral *N*-acetylcysteine administered by the intravenous route to patients with suspected acetaminophen poisoning? *Ann Emerg Med* 2003; 42:741.
48. Yarema MC, et al: Comparison of the 20-hour intravenous and 72-hour oral acetylcysteine protocols for the treatment of acute acetaminophen poisoning. *Ann Emerg Med* 2009; 54:606.
49. Kerr F, Dawson A, Whyte IM: The Australasian Clinical Toxicology Investigators Collaboration randomized trial of different loading infusion rates of *N*-acetylcysteine. *Ann Emerg Med* 2005; 45:402.
50. Sandilands EA, Bateman DN: Adverse reactions associated with acetylcysteine. *Clin Toxicol (Phila)* 2009; 47:81.
51. Appelboam AV, Dargan PI, Knighton J: Fatal anaphylactoid reaction to *N*-acetylcysteine: Caution in patients with asthma. *Emerg Med J* 2002; 19:594.
52. Bebarta VS, et al: A multicenter comparison of the safety of oral versus intravenous acetylcysteine for treatment of acetaminophen overdose. *Clin Toxicol (Phila)* 2010; 48:424-430.
53. Bailey B, McGuigan MA: Management of anaphylactoid reactions to intravenous *N*-acetylcysteine. *Ann Emerg Med* 1998; 31:710.
54. McElhatton PR, Sullivan FM, Volans GN: Paracetamol overdose in pregnancy analysis of the outcomes of 300 cases referred to the Teratology Information Service. *Reprod Toxicol* 1997; 11:85.
55. Horowitz RS, et al: Placental transfer of *N*-acetylcysteine following human maternal acetaminophen toxicity. *J Toxicol Clin Toxicol* 1997; 35:447.
56. Larson AM, et al: Acetaminophen-induced acute liver failure: Results of a United States multicenter, prospective study. *Hepatology* 2005; 42:1364.
57. Bernal W, Donaldson N, Wyncoll D, Wendon J: Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: A cohort study. *Lancet* 2002; 359:558.

www.ketabpezeshki.com 66485457-66963820

Chapter 149

Aspirin and Nonsteroidal Agents

Donna L. Seger and Lindsay Murray

ASPIRIN

Perspective

The incidence of aspirin (acetylsalicylic acid [ASA]) overdose and related childhood deaths has decreased significantly in recent years. Reasons include pediatricians' preference for acetaminophen preparations, the Food and Drug Administration's mandate limiting 36 tablets of baby aspirin to each bottle, and the use of child-resistant caps.

Unfortunately, the severity of this poisoning may be underestimated because of the lack of familiarity with the clinical picture. Salicylate toxicity can cause metabolic acidosis, seizure, hyperthermia, pulmonary edema, cerebral edema, renal failure, and death. Morbidity and mortality are increased by delayed diagnosis in elderly patients with chronic medical problems and in young patients diagnosed with an acute illness.[1]

Principles of Disease

Pharmacokinetics

Salts of salicylic acid are rapidly absorbed intact from the gastrointestinal tract, with appreciable serum concentrations occurring within 30 minutes. Two thirds of a therapeutic dose is absorbed in 1 hour, and peak levels occur in 2 to 4 hours. Large ingestions frequently delay gastric emptying, and ingestions of enteric capsules may cause a prolonged absorption with rising serum levels for 12 hours or more.[2]

In the intestinal wall, liver, and red blood cells, aspirin is hydrolyzed to free salicylic acid, which reversibly binds to albumin (which contains a genetically determined variable number of salicylate-binding sites). In the liver, salicylate is conjugated with glucuronic acid and glycine (Fig. 149-1). A small fraction is hydroxylated. Free salicylate and its conjugates are eliminated by renal excretion. At therapeutic salicylate concentrations, elimination follows first-order kinetics, and excretion is proportional to salicylate concentration. When serum salicylate concentrations are greater than 30 mg/dL, however, elimination follows zero-order kinetics, and the metabolic rate is constant. The metabolic pathways become saturated, and the pH-sensitive urinary excretion of salicylic acid determines the half-life, which becomes prolonged and may approach 15 to 30 hours with toxic doses.[3]

Pathophysiology

Acid-Base Disturbances and Metabolic Effects. Salicylate stimulates the medullary respiratory center early and increases the sensitivity of the respiratory center to pH and carbon dioxide partial pressure (P_{CO_2}). Hyperventilation develops early, then subsequently becomes a compensatory mechanism to the metabolic acidosis. Prolonged high serum concentrations eventually depress the respiratory center. Respiratory alkalosis is compensated by the buffering of the hemoglobin-oxyhemoglobin system, the exchange of intracellular hydrogen ions for extracellular cations, and the urinary excretion of bicarbonate. Loss of bicarbonate decreases buffering capacity and intensifies the metabolic acidosis.[4,5]

Toxicity results primarily from salicylate interference with aerobic metabolism by uncoupling of mitochondrial oxidative phosphorylation. Inhibition of the Krebs dehydrogenase cycle increases production of pyruvic acid and increases conversion to lactic acid. Increased lipid metabolism increases production of ketone bodies. Metabolic rate, temperature, tissue carbon dioxide, and oxygen consumption are increased. Tissue glycolysis predisposes to hypoglycemia. (Hepatic gluconeogenesis and release of epinephrine may cause the less common hyperglycemia.) Inefficiency of anaerobic metabolism results in less energy being used to create adenosine triphosphate, and energy is released as heat, causing the hyperthermia frequently seen in salicylate poisoning.[4]

Only nonionized particles can cross the lipophilic cell membrane and accumulate in the brain and other tissues. Because ASA has a low pK_a,[3,5] the majority of salicylate is ionized, and little salicylate enters tissues at the physiologic pH of 7.4. However, as pH decreases, more particles become un-ionized and cross the cell membrane and blood-brain barrier, markedly increasing the movement of salicylate into the tissues and central nervous system (CNS).[4,5]

Fluid and Electrolyte Abnormalities. Significant potassium loss in salicylate toxicity is caused by vomiting, secondary to stimulation of the medullary chemoreceptor trigger zone; increased renal excretion of sodium, bicarbonate, and potassium as a compensatory response to the respiratory alkalosis; salicylate-induced increased permeability of the renal tubules with further loss of potassium; intracellular accumulation of sodium and water; and inhibition of the active transport system, secondary to uncoupling of oxidative phosphorylation. The net result is rapid depletion of potassium stores.[4]

A salicylate-induced decrease in renal blood flow or direct nephrotoxicity may cause acute nonoliguric renal failure. Salicylate-induced secretion of inappropriate antidiuretic hormone may also affect renal function.[6]

Pulmonary and Cerebral Edema. The exact mechanism by which salicylates increase alveolar capillary membrane permeability is unknown. Theories include inhibition of prostacyclin, changes in platelet-vessel interaction, and neurogenic influences. In adults, the risk factors for salicylate-induced pulmonary edema include age older than 30 years, cigarette smoking, chronic salicylate

www.ketabpezeshki.com 66485457-66963820

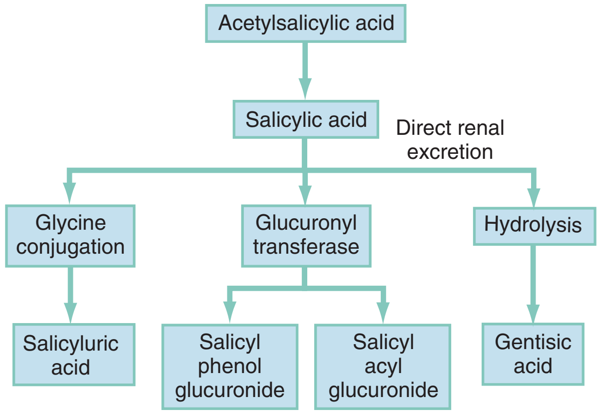


Figure 149-1. Aspirin metabolism.

ingestion, metabolic acidosis, neurologic symptoms, and serum salicylate concentration greater than 40 mg/dL. Risk factors in children include high serum salicylate levels, large anion gap, decreased serum potassium concentration, and low P_{CO_2}.[7]

Any alteration in sensorium is evidence of cerebral edema and is a grave prognostic sign. Factors causing cerebral edema are unknown. Patients with cerebral or pulmonary edema require immediate dialysis.

Chronic Ingestion Physiology. Physiologic changes of aging predispose elderly patients to toxicity from chronic therapeutic ingestion. Decreased liver blood flow rates decrease biotransformation of salicylate, and decreased renal function decreases salicylate clearance. Chronic ingestion allows salicylates more time to pass through the blood-brain barrier. In addition, chronic ingestion of aspirin decreases albumin binding, increasing the free salicylate that can enter the cell. This causes significant clinical illness with a relatively low serum salicylate concentration. A patient with chronic salicylate toxicity and a serum concentration of 40 mg/dL may be more ill than a patient with an acute ingestion and serum concentration of 80 mg/dL.[8]

Pediatric salicylism from supratherapeutic dosing may be more serious than acute ingestion. Sweating, fever, and tachycardia caused by salicylism may be attributed to underlying infection. Other sources of salicylate exposure include breast milk, teething gels, and percutaneous absorption of skin ointments, which have high concentrations of methyl salicylate.

Clinical Features

A toxic dose of aspirin is 200 to 300 mg/kg, and ingestion of 500 mg/kg is potentially lethal. The initial manifestations of acute salicylate toxicity include early hyperventilation, vomiting, and dehydration and later tinnitus, impaired hearing, and hyperthermia. Salicylate-induced hyperpnea may be manifested as increased respiratory depth without commensurate increase in rate. Hyperventilation is more common in adults, who usually have an initial respiratory alkalosis. Young children are predisposed to toxicity from the metabolic acidosis, which increases tissue and CNS salicylate concentrations. Vomiting can occur 3 to 8 hours after ingestion. Serious dehydration can occur from hyperpnea, vomiting, and hyperthermia. CNS manifestations are usually associated with acidemia.

Shortness of breath and altered sensorium are caused by pulmonary and cerebral edema, respectively. Noncardiac pulmonary edema may be more common in children than scattered case reports suggest.[9] Failure to recognize salicylate toxicity as the cause of pulmonary edema increases the likelihood of morbidity and mortality in these patients.

Box 149-1 Symptoms of Salicylate Toxicity

Asymptomatic: Occasional subjective but no objective manifestations
Mild: Mild to moderate hyperpnea, tinnitus, sometimes with lethargy
Moderate: Severe hyperpnea, prominent neurologic disturbances such as marked lethargy or agitation, but no coma or convulsions
Severe: Severe hyperpnea, coma, sometimes with convulsions

Diagnostic Strategies

Initial Evaluation

After the primary survey, a general physical examination is conducted to assess vital signs (including oxyhemoglobin saturation and a counted respiratory rate and reliable temperature). Chest auscultation may provide evidence of pulmonary edema, and mental status may suggest CNS toxicity. Early arterial blood gas determinations in symptomatic patients rapidly assess acid-base and compensatory status. A serum salicylate concentration should be measured with a second sample obtained 2 hours later. If the second concentration is greater than the first, serial concentrations should be obtained to monitor continued absorption, which may be prolonged.

Prognosis and treatment of the acutely poisoned patient should be determined by the serum salicylate concentration; the dose of salicylate ingested; and the patient's age, clinical features, and acid-base status. Acid-base status can change quickly, and frequent monitoring of arterial pH is necessary to guide treatment. The outdated Done nomogram should not be used to determine prognosis or treatment.

Low pH and bicarbonate level portend severe disease. The pH begins to drop when the patient is unable to compensate for the acidosis. Lactic acid accumulates, and serum bicarbonate is consumed. When pH is less than 7.4 and both P_{CO_2} and bicarbonate level are low, the patient begins to decompensate hemodynamically. In the intubated patient or the acidotic patient with low P_{CO_2} and bicarbonate level, hemodialysis should be undertaken.[10]

Differential Considerations

The symptoms of salicylism (hyperthermia, altered mental status or coma, pulmonary edema, and shock) mimic sepsis and the symptoms of many other diseases (Box 149-1). This is especially true with chronic ingestion; serum salicylate concentration is relatively low, and the severity of the poisoning is not recognized.[11] Death is caused by CNS depression and cardiovascular collapse.

Management

Intubation is indicated for patients with refractory shock, pulmonary or cerebral edema, or other manifestations of severe salicylate poisoning. Dialysis is indicated because positive-pressure ventilation cannot maintain the hyperventilation and respiratory rate required, and hemodynamic instability and worsening acid-base status usually follow intubation.

Specific treatment of salicylate toxicity has two main objectives: (1) to correct fluid deficits and acid-base abnormalities and (2) to increase excretion (Box 149-2). Electrolyte values are helpful to guide replacement and to assess renal function necessary to excrete salicylates. Serum salicylate levels should be repeated until they are decreasing to measure the effectiveness of treatment and to guide the decision for dialysis.

www.ketabpezeshki.com 66485457-66963820

Box 149-2 Treatment of Acute Salicylate Poisoning

Treat dehydration; maintain urine output at 2-3 mL/kg/hr with 5% dextrose (D_5) in lactated Ringer's solution or normal saline.
Correct potassium depletion.
Alkalinize urine.
- Obtain baseline arterial blood gas values.
- If pH is <7.4, administer sodium bicarbonate to obtain pH of 7.4 (50 mL bicarbonate increases serum pH by 0.1 in an adult).
- Infuse intravenous fluids: D_5 with bicarbonate 100-150 mEq/L.
- Monitor serum pH; do not cause systemic alkalosis.
- Do not attempt forced diuresis.

Monitor for dialysis indications.
- Coma, seizure
- Renal, hepatic, or pulmonary failure
- Pulmonary edema
- Severe acid-base imbalance
- Deterioration in condition
- Serum salicylate concentration ≥ 100 mg/dL after acute ingestion
- Serum salicylate concentration ≥ 40 mg/dL after chronic ingestion

Activated Charcoal

Although activated charcoal (AC), in a single dose or multiple doses, somewhat reduces salicylate absorption and has been recommended in the past, there is no evidence of outcome benefit. Whereas there is no evidence that AC in general decreases toxicity or alters therapy or course of the illness, this has not been specifically examined for salicylates.[12] In chronic salicylate poisoning, because the presentation is long after absorption, AC would not be expected to be of any benefit.

Intravenous Fluids

Dehydration occurs early in salicylate intoxication because of the hypermetabolic state and should be treated with intravenous fluid. Potassium depletion must be corrected. Fluid administration should be guided by the patient's apparent deficit to maintain urine output of 2 to 3 mL/kg/hr and should not exceed the estimated replacement because overly excessive fluid administration can worsen cerebral and pulmonary edema. Intravenous fluid should contain dextrose, and the serum glucose level should be frequently monitored to prevent hypoglycemia. In animal studies, hypoglycemia consistently occurs with death.

Urine Alkalinization

Because salicylates have a low pK_a and are renally excreted, alkaline urine traps the salicylate ion and increases excretion. Urine alkalinization is advisable in patients with salicylate levels greater than 35 mg/dL, significant acid-base disturbance, or increasing salicylate levels. A urine pH of 7.5 to 8.0 is necessary to increase excretion. Sodium bicarbonate (1-2 mEq/kg) can be administered during 1 to 2 hours, with subsequent dosage adjustment determined by urine and serum pH.

Urine alkalinization is difficult to achieve because the excretion of salicylic acid in the urine decreases urine pH. In addition, potassium depletion must be corrected to attain an alkaline urine. Alkaline urine should not be produced at the cost of systemic alkalemia. Forced diuresis does not significantly increase salicylate excretion and may potentiate cerebral and pulmonary edema. Salicylate clearance varies in direct proportion to flow rate but increases exponentially with pH.[13]

Hemodialysis

Hemodialysis is indicated for patients with the following: serum salicylate levels greater than 100 mg/dL in acute and 50 mg/dL in chronic salicylate poisoning; altered mental status, including coma; seizure; endotracheal intubation other than for coingestants; renal or hepatic failure; pulmonary edema; severe acid-base imbalance; rapidly rising serum salicylate level; and failure to respond to more conservative treatment. Exchange transfusion can be considered in young infants or unusual cases of congenital salicylism.[14]

Pregnancy

Greater salicylate concentration on the fetal side of the placenta and relative fetal acidemia contribute to fetal distress from maternal salicylate poisoning. Salicylate poisoning during pregnancy is associated with fetal demise, and delivery of the distressed fetus should be considered if the fetus is viable.[15]

Disposition

In patients with acute intoxication, hospital admission is required for pulmonary edema, CNS symptoms (other than tinnitus), seizures, acidosis, electrolyte disorders, dehydration, renal insufficiency, or increasing serum levels during serial testing. In patients with chronic intoxication, remarkably low serum salicylate concentrations may accompany severe salicylism. Any indication of infant salicylism requires hospital admission. The mortality rate for chronic salicylate intoxication is 25%, compared with a mortality rate of 1% after acute salicylate intoxication.

In patients with acute ingestion, repeated serum salicylate measurement is essential to determine that the serum concentration is decreasing before the patient is discharged. With any case of intentional overdose, psychiatric evaluation is essential.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Perspective

The nonsteroidal anti-inflammatory drugs (NSAIDs) are a heterogeneous group of agents with variable analgesic, anti-inflammatory, and antipyretic activities. They are usually classified according to chemical structure, although classification based on cyclooxygenase (COX) selectivity may be more clinically relevant. NSAIDs are widely prescribed for a variety of conditions. Ibuprofen and naproxen are available in over-the-counter and prescription strengths.

Principles of Disease

Physiology

The therapeutic anti-inflammatory effect of the NSAIDs is achieved by inhibition of COX and consequent blockade of prostaglandin production. Of the two discrete COX isoenzymes, COX-1, the constitutive enzyme, is concentrated in platelets, vascular endothelial cells, gastric mucosal cells, and renal collecting tubules. It is a physiologic maintenance enzyme, producing the prostaglandins critical for the autocrine-paracrine responses to circulating hormones and the maintenance of normal renal function, gastric mucosal integrity, and hemostasis. COX-2, the inducible enzyme, is expressed only in response to certain inflammatory stimuli. The benefits of NSAIDs are believed to result from COX-2 inhibition, whereas the principal gastrointestinal and renal adverse effects are attributed to inhibition of COX-1.

www.ketabpezeshki.com 66485457-66963820

Traditional NSAIDs are nonselective and inhibit both COX-1 and COX-2. Newer, specific COX-2 inhibitors (e.g., celecoxib, rofecoxib, parecoxib, meloxicam) have fewer side effects than traditional NSAIDs while maintaining analgesic and anti-inflammatory efficacy. However, COX-2 inhibitors permit unopposed thromboxane A_2 production by platelets, thereby potentiating platelet aggregation, thrombosis, and vasoconstriction.[16] Therapeutic use of rofecoxib, particularly at higher doses, was associated with increased risk of myocardial infarction and stroke, and it has subsequently been withdrawn from the market.[17,18]

Pharmacokinetics

The NSAIDs are almost completely absorbed from the upper small intestine after oral administration. The presence of food may alter the site and timing of drug uptake. As weak organic acids (p*K*a, 4-5), NSAIDs are largely nonionized in the stomach and readily diffuse across the bipolar layer lipid membrane of gastric lining cells. Once it is intracellular, the drug can become ionized again at the relatively high pH of normal cytoplasm and become trapped within the mucosal cell. This relatively high local concentration of drug contributes to the frequent gastrointestinal symptoms associated with NSAIDs.

The NSAIDs are highly bound to plasma proteins, mainly albumin, and therefore have small volumes of distribution (0.10-0.17 L/kg). They are eliminated by hepatic biotransformation, principally oxidation and glucuronidation, with the metabolites being excreted in the urine. Metabolites are inactive, except for those of sulindac, nabumetone (inactive parent drugs metabolized to active agent in vivo), and phenylbutazone. Plasma half-lives are short (1-4 hours), except for naproxen (12-15 hours), oxaprozin (25-50 hours), piroxicam (45 hours), and phenylbutazone (50-100 hours). Elimination half-lives are not substantially prolonged in overdose.[19]

Clinical Features

Most NSAID overdoses, even with large amounts, are asymptomatic or cause only minor CNS or gastrointestinal disturbances. Significant toxicity has not been reported after overdose of the newer COX-2 inhibitors. Of all isolated celecoxib exposures reported to the Texas poison control centers during a 5-year period, no more than minor effects were reported and then in only 12% of cases.[20]

Ibuprofen is the most common NSAID ingested in overdose and is representative of the propionic acid derivatives. Despite rare case reports of coma, seizure, hypotension, hypothermia, upper gastrointestinal tract bleeding, acute renal failure, and metabolic acidosis, most ibuprofen overdoses follow a benign, rapidly self-limited course. About 50% of adults and 7% of children have symptoms. Symptomatic overdose occurs only after ingestion of at least 100 mg/kg, and all those who develop symptoms do so within 4 hours of ingestion. Life-threatening symptoms or signs are rare, and most toxicity is a mild gastrointestinal or CNS disturbance that resolves in 24 hours.[21-25] Less common clinical effects include mild metabolic acidosis, muscle fasciculations, mydriasis, chills, diaphoresis, hyperventilation, mildly elevated systolic blood pressure, asymptomatic bradycardia, hypotension, dyspnea, tinnitus, and rash.

Renal dysfunction is seen only after massive acute overdose and in association with a period of relative hypovolemia with hypotension.[21-26] It is reversible and usually responds to supportive measures, but rare deaths have been reported.[27] Serum ibuprofen concentrations do not predict toxicity.[21]

Overdose with mefenamic acid, a fenamate, is associated with a relatively high incidence of seizures, which occur 2 to 7 hours after ingestion.[28] Rapid recovery is the rule with supportive care and intravenous benzodiazepines. Serum mefenamic acid concentrations correlate with seizures but do not aid in acute management.

Phenylbutazone, a pyrazolone, is now rarely used because of its association with aplastic anemia and agranulocytosis. Although phenylbutazone overdose is rare, it is much more severe than overdose with other NSAIDs.[29] Mild poisoning consists of nausea, abdominal pain, and drowsiness. Severely poisoned patients have early onset of abdominal pain, nausea, vomiting, hematemesis, diarrhea, restlessness, dizziness, coma, convulsions, hyperpyrexia, electrolyte disturbances, hyperventilation, alkalosis or acidosis, respiratory arrest, hypotension, cyanosis, edema, electrocardiographic abnormalities, or cardiac arrest. Late sequelae of severe poisoning (2-7 days) include renal, hepatic, and hematologic dysfunction.[29,30] The clinical course is prolonged compared with that of other NSAID poisoning, reflecting the prolonged elimination half-lives of phenylbutazone and its principal metabolite, oxyphenbutazone.[30]

Diagnostic Strategies

The diagnosis and assessment of severity and risk are based on history and clinical features. Plasma NSAID concentrations are not useful, but screening for unsuspected acetaminophen should be done. Serum electrolyte levels, renal and hepatic function tests, serum salicylate level, urinalysis, and chest radiograph are usually not necessary but should be undertaken as indicated by specific clinical concerns.

Management

The management of NSAID overdose is supportive, and there is no specific antidote. Pyrazolone (e.g., phenylbutazone) and fenamate (e.g., mefenamic acid) overdoses are associated with significantly higher morbidity and may require more aggressive supportive care measures, including control of seizures, fluid resuscitation, correction of electrolyte disturbances, and ventilatory support.

Children with ingestions of less than 100 mg/kg of ibuprofen do not require medical evaluation. Those who ingest more than 300 mg/kg should be evaluated. With ingestion of 100 to 300 mg/kg, children need treatment only if symptoms develop. All patients with pyrazolone and fenamate ingestions should be evaluated in the emergency department. For other agents, home observation is adequate unless the amount ingested is more than five times the maximum daily therapeutic dose, the patient is symptomatic, or a suicide attempt is suggested.

There is no evidence supporting the use of gastric emptying or AC for NSAID overdose. All patients with nontrivial overdoses should be observed until 4 hours after ingestion and until symptoms are noted to be mild or improving. Hypotension, if it occurs, is managed with intravenous crystalloid solution. Although it is rarely indicated and not studied, extracorporeal membrane oxygenation has successfully managed refractory hypotension after massive ibuprofen overdose.[30]

Because of high protein binding and rapid metabolism, urine alkalinization, hemodialysis, or hemoperfusion is not clinically useful. Enhanced elimination with plasmapheresis has been attempted in severe phenylbutazone poisoning.[31]

Disposition

Patients who are only mildly symptomatic or asymptomatic for more than 4 hours after an NSAID overdose do not require further medical care. Patients who have ingested a pyrazolone or fenamate require longer observation for possible seizures and admission to

www.ketabpezeshki.com 66485457-66963820

the emergency department observation unit until 8 hours after ingestion. Patients who have CNS symptoms, acidosis, or renal insufficiency and who require supportive care should be admitted to the hospital or an emergency department observation unit for ongoing medical treatment. Patients with only gastrointestinal or neurologic symptoms may be observed in the emergency department until they are asymptomatic or improving. Patients for whom the ingestion represents a suicidal gesture should undergo psychiatric assessment.

KEY CONCEPTS

- ASA intoxication, especially chronic salicylism, should be considered in the differential diagnosis of altered mental status in the elderly.
- Potassium stores are rapidly depleted in patients with salicylate intoxication.
- The acute toxic dose of ASA is 300 mg/kg, and 500 mg/kg is potentially lethal.
- Acidosis signifies severe salicylism as unbound salicylate is moving into the cell.
- Signs of pulmonary or cerebral edema, coma, seizures, hepatic failure, renal failure, circulatory collapse, and refractory acidosis or acute levels greater than 100 mg/dL and chronic levels of 40 mg/dL require immediate hemodialysis.
- Hyperthermia, altered mental status, coma, pulmonary edema, and shock may be presenting signs of salicylism.
- Serial salicylate concentrations should be obtained after acute ingestion until the salicylate concentration is decreasing.
- NSAID overdose, other than ASA, is usually self-limited, with predominantly gastrointestinal toxicity, except for pyrazolones and fenamates, which can cause seizures.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Chapman BJ, Proudfoot AT: Adult salicylate poisoning: Deaths and outcome in patients with high plasma salicylate concentrations. *Q J Med* 1989; 72:699.
2. Drummond R, Kadri N, St-Cyr J: Delayed salicylate toxicity following enteric-coated acetylsalicylic acid overdose: A case report and review of the literature. *CJEM* 2001; 3:44.
3. Roberts LJ, Morrow JD: *Analgesic-antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout*. In: Hardman J, Limbird L, eds: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. New York: McGraw Hill; 2001:687-729.
4. O'Malley G: Emergency department management of the salicylate-poisoned patient. *Emerg Med Clin North Am* 2007; 25:333.
5. Dromgoole S, Furst D: *Salicylates*. In: Evans WE, Schentag JJ, Jusko WJ, eds: *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring*. Vancouver, Wash: Applied Therapeutics; 1992.
6. Pemeger TV, Whelton PK: Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1994; 331:1675.
7. Gonzolea E, et al: Recurrent ARDS in a 39-year-old woman with migraine headaches. *Chest* 1998; 114:919.
8. Gaudreault P, Temple AR, Lovejoy FH: The relative severity of acute versus chronic salicylate poisoning in children: A clinical comparison. *Pediatrics* 1982; 70:566.
9. Fisher CJ, Albertson TE, Foulke GE: Salicylate-induced pulmonary edema: Clinical characteristics in children. *Am J Emerg Med* 1985; 3:33.
10. Greenberg MI, Henderson RG, Hoffman M: Deleterious effects of endotracheal intubation in salicylate poisoning. *Ann Emerg Med* 2003; 4:231.
11. Lamesh RA: Accidental chronic salicylate intoxication in an elderly patient: Major morbidity despite early recognition. *Vet Hum Toxicol* 1993; 35:34.
12. Chyka PA, Seger D, Krenzelok EP, Vale JA; American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists: Position paper: Single-dose activated charcoal. *Clin Toxicol (Phila)* 2005; 43:1.
13. Proudfoot A, Krenzelok EP, Brent J, Vale JA: Does urinary alkalinization increase salicylate elimination? If so, Why? *Toxicol Rev* 2003; 3:29.
14. Lund B, Seifert SA, Mayersohn M: Efficacy of sustained low-efficiency dialysis in the treatment of salicylate toxicity. *Nephrol Dial Transplant* 2005; 7:1483.
15. Palatnick W, Tenenbein M: Aspirin poisoning during pregnancy: Increased fetal sensitivity. *Am J Perinatol* 1998; 15:39.
16. Wright JM: The double-edged sword of COX-2 selective NSAIDs. *CMAJ* 2002; 167:1131.
17. Graham D, et al: Risk of myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: Nested case-control study. *Lancet* 2005; 365:475.
18. Levesque L, Brophy J, Zhang B: The risk for myocardial infarction with cyclooxygenase 2 inhibitors: A population study of elderly adults. *Ann Intern Med* 2005; 142:481.
19. Hall AH, et al: Ibuprofen overdose: 126 cases. *Ann Emerg Med* 1986; 15:1308.
20. Forrester MB: Celecoxib exposures reported to Texas poison control centers from 1999 to 2004. *Hum Exp Toxicol* 2006; 25:261.
21. McElwee NE, et al: A prospective, population-based study of acute ibuprofen overdose: Complications are rare and routine serum levels not warranted. *Ann Emerg Med* 1990; 19:652.
22. Perry SJ, Streete PJ, Volans GN: Ibuprofen overdose: The first two years of over-the-counter sales. *Hum Toxicol* 1987; 6:173.
23. Halpern SM, Fitzpatrick R, Volans GN: Ibuprofen toxicity: A review of adverse reactions and overdose. *Adverse Drug React Toxicol Rev* 1993; 12:107.
24. Hall AH, et al: Ibuprofen overdose in adults. *J Toxicol Clin Toxicol* 1992; 30:23.
25. Le HT, Bosse GM, Tsai Y: Ibuprofen overdose complicated by renal failure, adult respiratory distress syndrome, and metabolic acidosis. *J Toxicol Clin Toxicol* 1994; 32:315.
26. Perazella MA, Buller GK: Can ibuprofen cause acute renal failure in a normal individual? A case of acute overdose. *Am J Kidney Dis* 1991; 18:600.
27. Holubek W, et al: A report of two deaths from massive ibuprofen ingestion. *J Med Toxicol* 2007; 3:52.
28. Balali-Mood M, et al: Mefenamic acid overdosage. *Lancet* 1981; 1:1354.
29. Court H, Volans GN: Poisoning after overdose with non-steroidal anti-inflammatory drugs. *Adverse Drug React Acute Poisoning Rev* 1984; 3:1.
30. Marciniak KE, et al: Massive ibuprofen overdose requiring extracorporeal membrane oxygenation for cardiovascular support. *Pediatr Crit Care Med* 2007; 8:180.
31. Virji MA, Venkataraman S, Lower DR, Rao KN: Role of laboratory in the management of phenylbutazone poisoning. *J Toxicol Clin Toxicol* 2003; 41:1013.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 150

ANTICHOLINERGICS

Larissa I. Velez and Sing-Yi Feng

PERSPECTIVE

Anticholinergic agents are divided into three main groups: *antimuscarinics,* affecting the muscarinic acetylcholine (ACh) receptors; *neuromuscular blockers,* blocking nicotinic ACh receptors; and *ganglionic blockers,* affecting ACh sympathetic and parasympathetic nicotinic ganglia (Fig. 150-1). This chapter refers only to antimuscarinic agents, and the terms *anticholinergic* and *antimuscarinic* are used interchangeably. The prototypical anticholinergic agents are the naturally occurring belladonna alkaloids—atropine (racemic mixture of D- and L-hyoscyamine), scopolamine (L-hyoscine), and hyoscyamine—found in many plant members of the Solanaceae family. Atropine is the major alkaloid of *Atropa belladonna,* an important pharmaceutical source of that drug. *Datura stramonium,* or Jimson weed, contains scopolamine, grows in almost all climates, and is often involved in plant-related belladonna poisoning.[1,2] Other plants that have antimuscarinic agents include henbane (*Hyoscyamus niger*) and mandrake (*Mandragora officinarum*).

Physicians (and Renaissance-era Italian women) have used belladonna alkaloids for hundreds of years as mydriatics (Box 150-1).[3] The belladonna alkaloids and their synthetic congeners are used today as pupillary dilators (atropine, homatropine, tropicamide, cyclopentolate), as antispasmodics (dicyclomine), to decrease gastric secretions (propantheline), to prevent motion sickness (scopolamine), and to treat asthma (ipratropium, tiotropium) and bradycardia (atropine). Atropine and glycopyrrolate are used to dry airway secretions and to block vagal responses to laryngoscopy and endotracheal intubation. The significant central nervous system (CNS) effects of scopolamine also facilitate the induction of perioperative amnesia.

The anticholinergic antiparkinsonian agents are synthetic tertiary amine congeners of atropine and include benztropine and trihexyphenidyl. They are used as second-line antiparkinsonian agents and to counteract the extrapyramidal side effects of neuroleptics. These agents readily cross the blood-brain barrier and thus exhibit central antimuscarinic effects.

Tolterodine and oxybutynin are anticholinergic agents used for the management of urinary incontinence and bladder spasms. They have special selectivity for the muscarinic receptors of the urinary bladder. These agents do not penetrate the blood-brain barrier and thus do not cause significant CNS effects.

Many other drugs with anticholinergic activity cause side effects in addition to their main pharmacologic action. Some examples are the tricyclic antidepressants, drugs that are structurally related to the tricyclics (such as carbamazepine and cyclobenzaprine), the phenothiazines, and the antihistamines (H_1 blockers). In patients with significant toxicity from any of these drugs, these antimuscarinic side effects provide valuable diagnostic clues (Box 150-2; see also Box 150-1).

Accidental and intentional poisoning by anticholinergic drugs occurs commonly with over-the-counter antihistamines such as diphenhydramine and cyclizine. Poisoning from drugs with only anticholinergic effects rarely results in death when adequate supportive care is provided. However, the impaired sweating with an anticholinergic overdose may result in fatal hyperthermia in the agitated or seizing patient.[4,5] Patients taking therapeutic doses of anticholinergics are at increased risk of death from heatstroke when they are exercising or exposed to heat. Finally, deaths from trauma or drowning caused by perceptual distortion are also attributed to anticholinergics.[6]

Poisonings with belladonna alkaloids are common. Deliberate ingestions of seeds or teas brewed from the leaves of the ubiquitous Jimson weed for their hallucinogenic effects occur in many cultures,[1] and it remains popular as a recreational stimulant among teenagers.[7] Commercially available herbal teas contaminated with atropine and smoking of herbal cigarettes cause inadvertent poisoning.[8,9] A cluster of poisonings occurred in Oslo when the difficult-to-detect drug scopolamine was disguised as Rohypnol tablets and given to known illicit drug users.[10] The tainting of heroin with anticholinergics leading to a complex toxidrome has also been reported in drug users in several eastern states of the United States.[4,5] Although the reason for this tainting was never explained, it may have been an attempt to reproduce an old combination of scopolamine and morphine used in obstetric anesthesia called the twilight sleep.[11]

PRINCIPLES OF DISEASE

Atropine and atropine-like drugs inhibit muscarinic ACh receptors both centrally and peripherally at the end-organ sites of the parasympathetic nervous system (see Fig. 150-1). Although the term *anticholinergic* is commonly used, the most precise term to describe the pharmacologic action of these drugs is *antimuscarinic*. These drugs do not block the effects of ACh on nicotinic receptors in the ganglia or at the neuromuscular junction, with the exception of the synthetic quaternary amines. Muscarinic receptors affect smooth muscle function in the eye, intestinal tract, and bladder and also regulate sweat, salivary, and mucosal gland activity. Cardiac cholinergic receptors associated with vagal nerve fibers affect heart rate and conduction through the atrioventricular node. Muscarinic receptors in the CNS appear to be involved in new information storage, general perceptive and cognitive functions, and motor coordination.[12-14]

Generalized inhibition of muscarinic receptors by atropine results in tachycardia, pupillary dilation, loss of accommodation,

www.ketabpezeshki.com 66485457-66963820

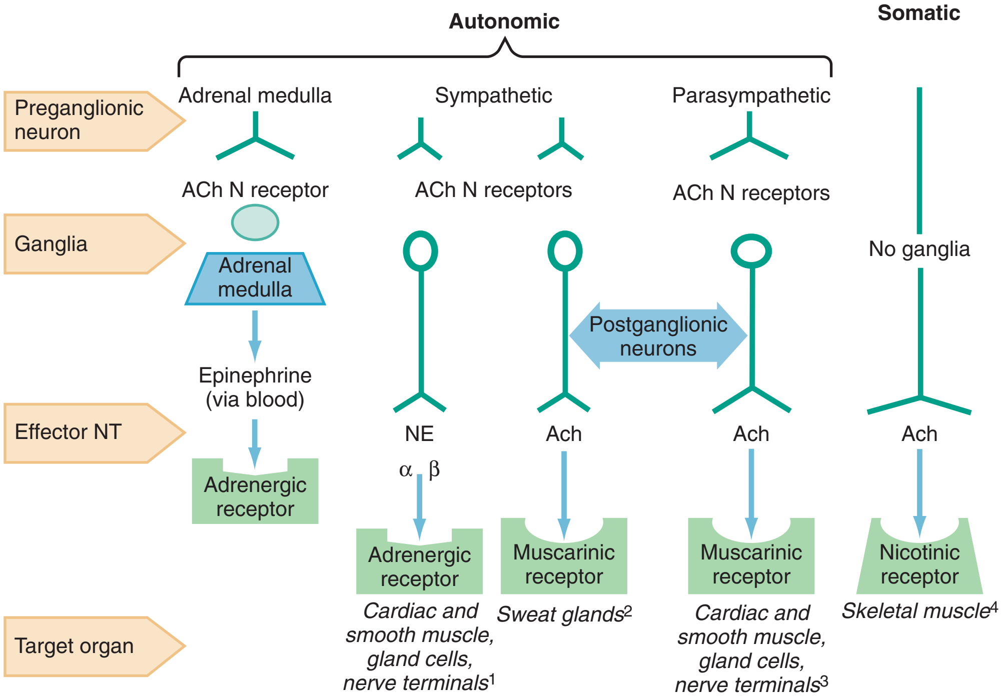


Figure 150-1. The sites of nicotinic and muscarinic acetylcholine receptors. *Ach,* acetylcholine; *N,* nicotinic; *NE,* norepinephrine; *NT,* neurotransmitter. [1]Causing tachycardia, hypertension, diaphoresis, mydriasis. [2]Causing diaphoresis. [3]Causing bradycardia, diarrhea, diaphoresis, urination, miosis, bronchospasm, bronchorrhea, lacrimation, salivation. [4]Causing fasciculations.

Box 150-1 Drugs Exhibiting Primarily Anticholinergic Toxicity

Belladonna Alkaloids and Representative Synthetic Congeners
Atropine
Scopolamine
Homatropine
Cyclopentolate
Tropicamide
Propantheline (Pro-Banthine)
Ipratropium (Atrovent)

Antiparkinsonians
Benztropine (Cogentin)
Trihexyphenidyl (Artane)
Procyclidine (Kemadrin)
Biperiden (Akineton)
Ethopropazine (Parsidol)

Prototypical H_1 Receptor Blockers
Diphenhydramine (Benadryl)
Chlorpheniramine (Chlor-Trimeton)
Brompheniramine (Dimetane)
Cyclizine (Marezine)
Meclizine (Antivert)
Hydroxyzine (Atarax, Vistaril)
Dimenhydrinate (Dramamine)

Phenothiazine
Promethazine (Phenergan)

Box 150-2 Drugs Exhibiting Anticholinergic Effects as Part of Toxic Manifestations

Tricyclic Antidepressants or Related Drugs
Cyclobenzaprine (Flexeril)
Carbamazepine (Tegretol)
Amitriptyline
Imipramine
Doxepin
Amoxapine
Desipramine
Nortriptyline
Glutethimide (Doriden)

Phenothiazines
Chlorpromazine (Thorazine)
Prochlorperazine (Compazine)
Mesoridazine (Serentil)
Thioridazine (Mellaril)

inability to sweat, drying of mucosal surfaces, gastrointestinal paralysis, and urinary retention. In the CNS, muscarinic inhibition causes stimulation, seizures, coma, choreoathetosis, memory impairment, and perceptual and cognitive dysfunction.[12-17] The mnemonic "hot as a hare, red as a beet, blind as a bat, dry as a bone, mad as a hatter" describes the more florid manifestations of the antimuscarinic syndrome. With increasing doses, CNS depression follows the initial CNS stimulation. In adults, CNS depression can predominate without an initial CNS stimulation. Antimuscarinic effects occur in a predictable order with salivation, bronchial secretions, and sweating suppressed first, followed by mydriasis and tachycardia. The organs least sensitive to antimuscarinic drugs are the bladder and the gastrointestinal tract. Patients with anticholinergic toxicity often do not exhibit all the signs and symptoms described in the toxidrome. Instead, many patients present with just a few symptoms; tachycardia (68% of patients) and decreased secretions (75% of patients) are the most common.[18]

Poisoning by anticholinergics has been reported after ingestion, smoking, and topical absorption.[19] Systemic absorption is common after use of eye drops.[19,20] Anticholinergics are generally rapidly absorbed and widely distributed throughout the body. However, with plant and seed ingestions or after an overdose, the onset of symptoms can be delayed. Prolonged anticholinergic toxicity is also reported, which may indicate slowed gastrointestinal

www.ketabpezeshki.com 66485457-66963820

absorption of the ingested drug or residual drug in the gastrointestinal tract.[21,22]

CLINICAL PRESENTATION

The diagnosis of acute anticholinergic poisoning is suggested by the characteristic anticholinergic toxidrome. Mydriasis, dry mucous membranes, absence of axillary sweat, flushed skin, fever, tachycardia, decreased or absent bowel sounds, and urinary retention suggest muscarinic blockade.[18,23] The patient is often alert but may be nonsensical, agitated, or incoherent. Violent agitation is rare. Visual hallucinations are common. Central motor effects may be manifested as myoclonus or choreoathetoid movements. Children are more sensitive than adults to the CNS stimulant effects and more likely to have seizures, typically preceded by signs of CNS irritability or depression. Massive ingestions in both adults and children are associated with coma and cardiovascular collapse,[22,24] but wide-complex tachycardia due to sodium channel blockade is rare.[25,26]

The agitated patient may have an elevated temperature due to increased motor activity and impaired heat exchange. In such cases, death from hyperthermia supersedes the morbidity of the anticholinergic drug itself.[27] The hyperthermic patient may have hepatic necrosis, rhabdomyolysis with myoglobinuric renal failure, cerebral edema, and disseminated intravascular coagulation.

Patients with chronic anticholinergic poisoning are more difficult to diagnose. They have organic mental symptoms that may be incorrectly attributed to dementia or underlying psychiatric illness.[16,28,29] Significant peripheral anticholinergic signs are typically absent. Two likely settings for chronic anticholinergic toxicity are (1) the elderly patient taking anticholinergic drugs for parkinsonism or other chronic diseases and (2) the psychiatric patient receiving neuroleptic therapy and prescribed another anticholinergic drug.[12,16] Resolution of behavioral or cognitive symptoms after withdrawal of the offending drug confirms the diagnosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the comatose, psychotic, delirious, or febrile patient is extensive, and serious alternative diagnoses should be considered and excluded.[30,31] Diagnoses to consider include toxicity and withdrawal from a variety of drugs, metabolic disorders, CNS infections, and other neurologic diseases.[31]

The physical examination findings can help refine this broad differential diagnosis. Patients with excessive sympathetic stimulation from cocaine or amphetamines exhibit hyperthermia, tachycardia, and dilated pupils but classically have diaphoresis compared with the “dry” anticholinergic effects; diaphoresis can be absent in severely dehydrated patients. Marked nystagmus, diaphoresis, small pupils, and extreme agitation suggest phencyclidine poisoning. Lithium or monoamine oxidase inhibitor toxicity usually has tremors and significant hyper-reflexia or clonus, which are not characteristic of anticholinergic poisoning.[32] Patients with serotonin syndrome often present with agitation but often have diaphoresis, rigidity, and a tremor that is more prominent in the lower extremities.[33,34] Neuroleptic malignant syndrome and malignant hyperthermia can also be similar, but these patients display rigidity and hyperthermia as prominent physical examination features.[34,35]

The nontoxicologic differential diagnosis of acute agitated delirium includes metabolic, endocrine, infectious, neurologic, and neurosurgical emergencies. Nuchal rigidity or focality on neurologic examination, physical signs of systemic infection, hepatic failure, thyroid disease, hypoglycemia, hypoxia, uremia, or calcium abnormalities suggest a nontoxic diagnosis.

Except for sinus tachycardia, electrocardiographic abnormalities from a pure anticholinergic overdose are unusual and suggest a cardiotoxic agent, such as a tricyclic antidepressant, carbamazepine, or a phenothiazine, for which the antimuscarinic side effects are of less importance. Rarely, diphenhydramine ingestions have been associated with sodium channel blockade, causing prolonged QRS on the electrocardiogram and possibly leading to ventricular arrhythmias.[25,26] Peaked T waves from hyperkalemia due to rhabdomyolysis can occur.[36]

DIAGNOSTIC STRATEGIES

Mildly symptomatic patients with well-established histories and consistent symptoms do not need routine laboratory testing. In the seriously poisoned patient, serum electrolyte values, renal function, and creatine kinase and glucose concentrations may be abnormal. Arterial blood gas measurements document disorders of oxygenation and ventilation and detect metabolic acidosis but usually are not needed. Blood glucose and oxygen saturation measurements are important in the initial assessment of any patient with altered mental status.[37-39] An electrocardiogram should be performed early because certain anticholinergic medications, such as tricyclic antidepressants and diphenhydramine, can block sodium channels to cause QRS widening.[40]

Urine toxicologic screening is rarely useful in the acute setting, although it may retrospectively confirm a diagnosis in a seriously ill patient. Patients with significant infectious or neurosurgical problems often have evidence of an incidental toxin, so a positive toxicology screen should not distract the physician from ruling out a more serious diagnosis. Serum acetaminophen levels should be obtained, especially because many over-the-counter antihistamine products contain acetaminophen and cause anticholinergic symptoms.

Computed tomography of the brain and a lumbar puncture are not necessary unless the patient deteriorates or fails to improve or if the history or examination suggests an alternative diagnosis, such as subarachnoid hemorrhage, meningitis, or encephalitis.

MANAGEMENT

In the emergency department, many patients with anticholinergic poisoning have no clear history of exposure. The patient is often unable to provide a history because of the delirium. The diagnosis is often suggested solely on the basis of the findings on physical examination fitting the antimuscarinic/anticholinergic toxidrome (Box 150-3). The general treatment of these poisoned patients proceeds with consideration of the broader differential diagnosis of the acutely agitated, febrile, or comatose patient and meticulous supportive care.[30]

Agitation

The need for titrated sedation with a benzodiazepine, cooling, and hydration takes precedence over specific toxicologic concerns in critically ill patients. Physical restraint alone is detrimental and is used only briefly to permit rapid pharmacologic intervention.[41] Agitation is best controlled by titration of intravenous benzodiazepines. Intramuscular lorazepam or midazolam should be used only when an intravenous route is not available and attempts to establish that route may result in needle sticks or other injuries. Haloperidol and droperidol may facilitate intravenous placement but theoretically lower the seizure threshold and have additional anticholinergic effects.[42,43] Pharmacologic restraint prevents self-injury, worsening of the hyperthermia, and development of myoglobinuric renal failure from muscle injury as well as permits a more thorough physical examination and diagnostic procedures. Paralysis and intubation should be undertaken if other clinical imperatives (e.g., refractory shock, coingestants) require it.

www.ketabpezeshki.com 66485457-66963820

Box 150-3 Differential Diagnosis of Delirium

Toxic
Steroids
Lithium
Salicylates
Anticholinergics
Sympathomimetics (cocaine, amphetamines)
Phencyclidine
Mushrooms containing muscimol/ibotenic acid (*Amanita* spp.)
Monoamine oxidase inhibitors
Solvents
Carbon monoxide
Sedative-hypnotic withdrawal

Metabolic
Sodium disorders
Hypoglycemia
Hypercarbia
Hypoxia, severe anemia
Calcium disorders
Uremia
Thyrotoxicosis
Hepatic encephalopathy
Hypertensive encephalopathy
Shock
Sepsis

Infectious or Inflammatory
Meningoencephalitis
Meningitis
Vasculitis

Neurologic or Neurosurgical
Cerebrovascular accident
Subarachnoid hemorrhage
Subdural or epidural hematoma
Frontal contusion
Postictal state
Temporal lobe seizures

Hyperthermia

Deaths of agitated patients can be associated with unrecognized hyperthermia. The patient's core temperature should be measured with a flexible rectal probe. Aggressive temperature reduction with ice water or evaporative cooling with mist and fans should be the first priority in the severely hyperthermic patient. Antipyretic agents and simple cooling blankets are ineffective. Intravenous benzodiazepines should be used to prevent shivering, which can hinder adequate cooling. Dantrolene, a drug that decreases rigidity caused by abnormal calcium fluxes in muscle tissue in malignant hyperthermia, has no role in treatment of hyperthermic patients who do not have muscle rigidity.[44]

Seizures

Seizures should be treated as usual with intravenous benzodiazepines. In the absence of intravenous access, intramuscular lorazepam or midazolam or rectal diazepam can be used, especially in children. Phenytoin is not effective for most toxin-induced seizures. The second-line agents for the management of toxin-induced seizures should be barbiturates. Status epilepticus is rare in anticholinergic poisoning and should strongly suggest an alternative diagnosis.

Drug Removal

Routine decontamination of the patient with anticholinergic poisoning is not necessary.[45] Activated charcoal does adsorb diphenhydramine and phenothiazines; however, there is no evidence that it improves outcome, and it should not be used to decontaminate patients poisoned with a relatively benign drug.[45]

Physostigmine as an Antidote

Physostigmine is a naturally occurring acetylcholinesterase inhibitor, like neostigmine, pyridostigmine, and edrophonium. These agents block the degradation of ACh, which then accumulates in the synaptic space and overcomes the effects of ACh receptor blockade. Physostigmine, as a tertiary amine, is the only agent that can cross the blood-brain barrier and overcome both central and peripheral muscarinic blockade.

The role of physostigmine in the management of anticholinergic overdoses has been controversial.[46] In the absence of anticholinergic blockade, physostigmine itself can precipitate cholinergic excess, causing seizures, muscle weakness, bradycardia, bronchoconstriction, lacrimation, salivation, bronchorrhea, vomiting, and diarrhea. Even in documented cases of anticholinergic toxicity, seizures have been reported after the rapid administration of physostigmine.[47] Asystole has occurred after physostigmine for tricyclic antidepressant overdose,[48] so a conduction delay (QRS > 0.10 second) or suggestion of tricyclic antidepressant ingestion is generally considered a contraindication to physostigmine administration.[49,50]

Physostigmine reverses delirium in 87% and agitation in 96% of patients with anticholinergic overdose.[51] Whereas benzodiazepines controlled agitation in 24% of patients, they do not reverse delirium.[51] Physostigmine is primarily used for patients with anticholinergic signs and symptoms with suspected anticholinergic overdose who have a normal QRS on the electrocardiogram.[23,52] The reversal of coma or severe agitation and normalization of mental status obviate the need for further diagnostic evaluation.

To minimize toxicity, physostigmine should be infused during 5 minutes in an initial dose of 1 to 2 mg for adults and 0.02 mg/kg (max. 0.5 mg) for children. This dose can be repeated in 10 to 15 minutes until a clinical response is obtained because the onset of action is within minutes. Atropine should be available at the bedside to reverse cholinergic side effects, and the physostigmine infusion should be immediately stopped if signs of cholinergic excess develop. If atropine needs to be used, it should be administered at half the dose of physostigmine. Because physostigmine has a relatively short duration of action of 1 hour, repeated doses may be required if clinical relapse occurs.

Physostigmine has been used to treat anticholinergic delirium with a host of pharmaceuticals for which the anticholinergic effect is a side effect and not the main pharmacologic action of that drug and with other ingestions, such as benzodiazepines, γ-hydroxybutyrate (GHB), and narcotics. Currently, its use for nonanticholinergic presentations is not recommended and potentially dangerous.[53,54] Relative contraindications include reversible airway disease, peripheral vascular disease, bladder or intestinal obstruction, intraventricular conduction delays, and atrioventricular blocks. There is little information on its use during pregnancy.

DISPOSITION

Most patients with anticholinergic overdoses recover rapidly with sedation, temperature control, hydration, and observation. Patients with hyperthermia, agitation, coma, or seizures should be admitted to an intensive care unit.

Patients who are alert or have symptoms and vital signs that normalize during observation in the emergency department do not require hospital admission. The onset of symptoms after most anticholinergic ingestions is rapid, and 4 hours of observation is adequate to exclude significant toxicity in an asymptomatic

www.ketabpezeshki.com 66485457-66963820

patient. Patients who have ingested *D. stramonium* seeds should be observed for 8 hours because of delayed absorption.[55] Predischarge measures can include psychiatric assessment; exclusion of other toxins, including documentation of a nontoxic acetaminophen level; and assessment of a child's home situation.

KEY CONCEPTS

- Anticholinergic effects from medications and plants are extremely common.
- Lack of sweating is common with an anticholinergic and rare in a sympathomimetic toxidrome.
- Hyperthermia and agitation should be treated with cooling and benzodiazepines.
- Physostigmine has intrinsic toxicity and is not necessary in most cases of anticholinergic poisoning.
- Physostigmine is contraindicated in cases of tricyclic antidepressant toxicity or with sodium channel blockade effects (as evidenced by a wide QRS).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Spina SP, Taddei A: Teenagers with Jimson weed (*Datura stramonium*) poisoning. *CJEM* 2007; 9:467-468.
2. Al-Shaikh AM, Sablay ZM: Hallucinogenic plant poisoning in children. *Saudi Med J* 2005; 26:118-121.
3. Nickalls RW, Nickalls EA: The first use of physostigmine in the treatment of atropine poisoning. A translation of Kleinwachter's paper entitled "Observations on the effect of Calabar bean extract as an antidote to atropine poisoning." *Anaesthesia* 1988; 43:776-779.
4. Hamilton RJ, et al: A descriptive study of an epidemic of poisoning caused by heroin adulterated with scopolamine. *J Toxicol Clin Toxicol* 2000; 38:597-608.
5. Wang HE: Street drug toxicity resulting from opiates combined with anticholinergics. *Prehosp Emerg Care* 2002; 6:351-354.
6. Gowdy JM: Stramonium intoxication: Review of symptomatology in 212 cases. *JAMA* 1972; 221:585-587.
7. Bronstein AC, et al: 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 27th Annual Report. *Clin Toxicol (Phila)* 2010; 48:979-1178.
8. Cheng SW, et al: Anticholinergic poisoning from a large dose of *Scopolia* extract. *Vet Hum Toxicol* 2002; 44:222-223.
9. Göpel C, Laufer C, Marcus A: Three cases of angel's trumpet tea–induced psychosis in adolescent substance abusers. *Nord J Psychiatry* 2002; 56:49-52.
10. Vallersnes OM, et al: Epidemic of poisoning caused by scopolamine disguised as Rohypnol tablets. *Clin Toxicol (Phila)* 2009; 47:889-893.
11. From the Centers for Disease Control and Prevention: Scopolamine poisoning among heroin users—New York City, Newark, Philadelphia, and Baltimore, 1995 and 1996. *JAMA* 1996; 276:92-93.
12. Katz IR, et al: Screening for cognitive toxicity of anticholinergic drugs. *J Clin Psychiatry* 1985; 46:323-326.
13. Tune L, et al: Association of anticholinergic activity of prescribed medications with postoperative delirium. *J Neuropsychiatry Clin Neurosci* 1993; 5:208-210.
14. Tune LE, et al: Serum levels of anticholinergic drugs and impaired recent memory in chronic schizophrenic patients. *Am J Psychiatry* 1982; 139:1460-1462.
15. Drachman DA: Memory and cognitive function in man: Does the cholinergic system have a specific role? *Neurology* 1977; 27:783-790.
16. Moreau A, Jones BD, Banno V: Chronic central anticholinergic toxicity in manic depressive illness mimicking dementia. *Can J Psychiatry* 1986; 31:39-41.
17. Potamianos G, Kellett JM: Anti-cholinergic drugs and memory: The effects of benzhexol on memory in a group of geriatric patients. *Br J Psychiatry* 1982; 140:470-472.
18. Patel RJ, et al: Prevalence of autonomic signs and symptoms in antimuscarinic drug poisonings. *J Emerg Med* 2004; 26:89-94.
19. Alpay A, et al: The local vasoconstriction of infant's skin following instillation of mydriatic eye drops. *Eur J Clin Pharmacol* 2010; 66:1161-1164.
20. Lim DL, Batilando M, Rajadurai VS: Transient paralytic ileus following the use of cyclopentolate-phenylephrine eye drops during screening for retinopathy of prematurity. *J Paediatr Child Health* 2003; 39:318-320.
21. Fahy P, et al: Serial serum drug concentrations and prolonged anticholinergic toxicity after benztropine (Cogentin) overdose. *Am J Emerg Med* 1989; 7:199-202.
22. Freedberg RS, et al: Cardiogenic shock due to antihistamine overdose. Reversal with intra-aortic balloon counterpulsation. *JAMA* 1987; 257:660-661.
23. Sopchak CA, et al: Central anticholinergic syndrome due to Jimson weed physostigmine: Therapy revisited? *J Toxicol Clin Toxicol* 1998; 36:43-45.
24. Krenzelok EP, Anderson GM, Mirick M: Massive diphenhydramine overdose resulting in death. *Ann Emerg Med* 1982; 11:212-213.
25. Jang DH, et al: Status epilepticus and wide-complex tachycardia secondary to diphenhydramine overdose. *Clin Toxicol (Phila)* 2010; 48:945-948.
26. Sharma AN, et al: Diphenhydramine-induced wide complex dysrhythmia responds to treatment with sodium bicarbonate. *Am J Emerg Med* 2003; 21:212-215.
27. Torline RL: Extreme hyperpyrexia associated with central anticholinergic syndrome. *Anesthesiology* 1992; 76:470-471.
28. Moore AR, O'Keeffe ST: Drug-induced cognitive impairment in the elderly. *Drugs Aging* 1999; 15:5-28.
29. Leentjens AF, van der Mast RC: Delirium in elderly people: An update. *Curr Opin Psychiatry* 2005; 18:325-330.
30. Jones J, Dougherty J, Cannon L: Diphenhydramine-induced toxic psychosis. *Am J Emerg Med* 1986; 4:369-371.
31. Perrone J, Band RA, Mathew R: Agitation complicating procedural sedation with etomidate. *Am J Emerg Med* 2006; 24:511-512.
32. Waring WS: Management of lithium toxicity. *Toxicol Rev* 2006; 25:21-30.
33. Isbister GK, Buckley NA, Whyte IM: Serotonin toxicity: A practical approach to diagnosis and treatment. *Med J Aust* 2007; 187:361-365.
34. Nisijima K, Shioda K, Iwamura T: Neuroleptic malignant syndrome and serotonin syndrome. *Prog Brain Res* 2007; 162:81-104.
35. Hadad E, Weinbroum AA, Ben-Abraham R: Drug-induced hyperthermia and muscle rigidity: A practical approach. *Eur J Emerg Med* 2003; 10:149-154.
36. Akhtar S, et al: Atropine-induced rhabdomyolysis: An uncommon and potentially fatal adverse drug reaction. *J Postgrad Med* 2010; 56:42-43.
37. Olsen RQ, Regis JT: Delirious deficiency. *Lancet* 2010; 376:362.
38. Lee DC, et al: Low plasma thiamine levels in elder patients admitted through the emergency department. *Acad Emerg Med* 2000; 7:1156-1159.
39. Li SF, et al: Vitamin deficiencies in acutely intoxicated patients in the ED. *Am J Emerg Med* 2008; 26:792-795.
40. Boehnert MT, Lovejoy FH Jr: Value of the QRS duration versus the serum drug level in predicting seizures and ventricular arrhythmias after an acute overdose of tricyclic antidepressants. *N Engl J Med* 1985; 313:474-479.
41. Hick JL, Smith SW, Lynch MT: Metabolic acidosis in restraint-associated cardiac arrest: A case series. *Acad Emerg Med* 1999; 6:239-243.
42. Holubek WJ, Dodge K, Hoffman RS: Management of acute undifferentiated agitation in the emergency department. *Acad Emerg Med* 2006; 13:585; author reply 586-587.
43. Rossi J, Swan MC, Isaacs ED: The violent or agitated patient. *Emerg Med Clin North Am* 2010; 28:235-256, x.
44. Amsterdam JT, et al: Dantrolene sodium for treatment of heatstroke victims: Lack of efficacy in a canine model. *Am J Emerg Med* 1986; 4:399-405.
45. Buckley NA, Eddleston M: The revised position papers on gastric decontamination. *Clin Toxicol (Phila)* 2005; 43:29-30.
46. Teoh R, Page AV, Hardern R: Physostigmine as treatment for severe CNS anticholinergic toxicity. *Emerg Med J* 2001; 18:412.
47. Newton RW: Physostigmine salicylate in the treatment of tricyclic antidepressant overdosage. *JAMA* 1975; 231:941-943.
48. Pentel P, et al: Late complications of tricyclic antidepressant overdose. *West J Med* 1983; 138:423-424.
49. Schmidt W, Lang K: Life-threatening dysrhythmias in severe thioridazine poisoning treated with physostigmine and transient atrial pacing. *Crit Care Med* 1997; 25:1925-1930.
50. Suchard JR: Assessing physostigmine's contraindication in cyclic antidepressant ingestions. *J Emerg Med* 2003; 25:185-191.
51. Burns MJ: The pharmacology and toxicology of atypical antipsychotic agents. *J Toxicol Clin Toxicol* 2001; 39:1-14.
52. Arnold SM, et al: Two siblings poisoned with diphenhydramine: A case of factitious disorder by proxy. *Ann Emerg Med* 1998; 32:256-259.
53. Rupreht J, et al: Physostigmine versus naloxone in heroin-overdose. *J Toxicol Clin Toxicol* 1983; 21:387-397.
54. Bania TC, et al: Jimson weed extract as a protective agent in severe organophosphate toxicity. *Acad Emerg Med* 2004; 11:335-338.
55. Salen P, et al: Effect of physostigmine and gastric lavage in a *Datura stramonium*–induced anticholinergic poisoning epidemic. *Am J Emerg Med* 2003; 21:316-317.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 151

ANTIDEPRESSANTS

Michael Levine and Anne-Michelle Ruha

Depression is one of the most common medical conditions in the United States, with a lifetime prevalence of 16.2%.[1] Whereas many treatment strategies are used in the management of depressed patients, pharmacotherapy remains a cornerstone of modern practice. Modern antidepressant therapy hinges on the 50-year-old monoamine hypothesis, which suggests that depressive symptoms are mediated through an imbalance of the dopaminergic, noradrenergic, and serotonergic systems.[1,2] As a result, numerous antidepressant classes have emerged in an attempt to increase synaptic monoamine concentrations.

In the early 1950s, isoniazid and iproniazid were introduced for the treatment of tuberculosis. Shortly after, it was noted that these patients had improved mood, which was attributed to the ability of iproniazid to inhibit monoamine oxidase. Iproniazid, a derivative of isoniazid, subsequently became the first drug marketed specifically as an antidepressant.[3] This led to the advent of other monoamine oxidase inhibitors (MAOIs). In 1956, the antidepressant effect of imipramine, a tricyclic agent, was recognized, and it was marketed the following year.[4] The MAOIs and tricyclic antidepressants (TCAs) became the mainstay for treatment of depression for several decades until the advent of the safer selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

Antidepressant overdose is highly lethal. It accounts for only 3.7% of human exposures reported to U.S. Poison Control Centers but is involved in 10.5% of all poisoning fatalities.[5]

MONOAMINE OXIDASE INHIBITORS

Principles of Disease

Monoamine oxidase (MAO) is located on the outer mitochondrial membrane and is responsible for breakdown of cytoplasmic catecholamines. Type A (MAO-A) primarily deaminates serotonin and norepinephrine; type B (MAO-B) primarily deaminates phenylethylamine.[6] Tyramine and dopamine are metabolized equally by both isoenzymes.[3] Whereas most tissues contain both isozymes, MAO-A is primarily found in the placenta, sympathetic nerve terminals, and intestinal mucosa; MAO-B is found primarily in platelets and the basal ganglia.[3]

Drugs targeting the monoamine oxidase system can act as specific or nonspecific inhibitors. The first-generation MAOIs are nonselective and irreversible. Drugs belonging to this class include phenelzine, isocarboxazid, and tranylcypromine. The second-generation MAOIs can preferentially inhibit either MAO-A or MAO-B.

Although MAOIs have fallen out of favor for treatment of depression, their use in treatment of Parkinson's disease is increasing. Drugs that selectively inhibit MAO-B disproportionately increase dopamine concentrations in the striatum.[7] Selegiline is an irreversible MAO-B inhibitor used in the treatment of Parkinson's disease. Although it is marketed as a selective inhibitor of MAO-B, at high doses its receptor specificity is lost, and it can cause inhibition of MAO-A as well.[8] Rasagiline is also an irreversible inhibitor of MAO-B but appears to be more potent than selegiline.[6] Furthermore, unlike selegiline, which is metabolized to L-methamphetamine, rasagiline is not metabolized to an amphetamine derivative.[6]

In addition to its antibiotic properties, linezolid, an oxazolidinone class antibiotic, is a reversible inhibitor of monoamine oxidase. Specifically, linezolid can produce significant inhibition of MAO-A.

As a class, MAOIs are rapidly absorbed from the gastrointestinal tract and are bound extensively to plasma proteins. With overdose, the MAOIs initially stimulate release of neurotransmitters from the presynaptic neuron but later inhibit their release.

Clinical Features

Patients have MAOI toxicity as a result of an acute overdose or as a consequence of a food or drug interaction. Depending on the scenarios that lead to toxicity, the clinical presentations may be very different.

After an overdose, patients may have symptoms within several hours or may be asymptomatic for up to 24 hours before significant, possibly life-threatening toxicity develops. After this asymptomatic period, hyperadrenergic symptoms, including tachycardia, hypertension, and hyperthermia, can develop. Seizures, rhabdomyolysis, coma, and ultimately cardiovascular collapse can occur once presynaptic catecholamines are depleted. Laboratory abnormalities are nonspecific but can include hyperglycemia, leukocytosis, and elevated creatine kinase.

Patients who take nonselective MAOIs in therapeutic doses are at risk for food-drug interactions. Tyramine is an indirectly acting sympathomimetic amine that is present in aged cheeses, red wine, smoked or pickled and aged meats, and other foods. Usually, tyramine is metabolized in the gut and liver by monoamine oxidase, rarely causing systemic effects. When MAO-A is inhibited, tyramine is absorbed systemically and enters presynaptic vesicles, ultimately causing release of norepinephrine and serotonin into the synapse, leading to a hypertensive crisis.[9] This *tyramine syndrome,* which can occur within minutes to hours of ingestion of foods with high tyramine content, is characterized by headache, hypertension, flushing, and diaphoresis. This syndrome can occur up to 3 weeks after discontinuation of a nonselective MAOI. Although it is theoretically possible, this syndrome is rare with therapeutic use of MAO-B inhibitors.[10]

www.ketabpezeshki.com 66485457-66963820

A drug-drug interaction may result when MAOIs are combined with other agents that have serotonergic effects. A variety of prescription and over-the-counter medications may interact with MAOIs to produce a constellation of symptoms referred to as *serotonin syndrome* (see later section). This syndrome may be life-threatening, so use of medications with serotonin-potentiating activity should be avoided in patients taking MAOIs.

Diagnostic Strategies

Obtaining a thorough medication history is key to establishment of the diagnosis of MAOI toxicity. After overdose, an asymptomatic period followed by delayed toxicity can be a diagnostic clue. Immunoassay urine drug screens that are commonly used in the emergency department do not detect MAOIs, and even gas chromatography–mass spectroscopy of urine may fail to detect the presence of an MAOI. Patients taking selegiline will test positive for methamphetamine because methamphetamine is a metabolite.

Symptomatic patients presenting after an MAOI overdose should have an electrocardiogram with measurement of serum glucose and electrolytes if they are obtunded (see Chapter 147 for general management).

Differential Considerations

The differential diagnosis for MAOI toxicity includes drug abuse or other sympathomimetic, anticholinergic, and methylxanthine toxicity. Nontoxicologic causes to consider include environmental hyperthermia, febrile illness, pheochromocytoma, carcinoid syndrome, thyroid storm, meningitis, and hypertensive emergency.

Management

Even if they are initially asymptomatic, all patients presenting after an MAOI overdose should be admitted or observed in a monitored setting until 24 hours after the ingestion because of the risk of delayed, rapid deterioration. As with most intoxications, supportive care is paramount. Central nervous system (CNS) excitation should be treated with intravenous administration of benzodiazepines, such as lorazepam and diazepam, in usual titrated doses. Hyperthermia should be treated with external cooling. Mild hypertension should not be treated, but severe hypertension is best managed with a rapid, short-acting agent, such as phentolamine or nitroprusside. Hypotension should first be managed by aggressive volume resuscitation. Persistent or severe hypotension requires treatment with infusion of a direct-acting catecholamine, such as norepinephrine or epinephrine. Because hypotension and cardiovascular collapse after MAOI overdose are due to catecholamine depletion, the use of indirect-acting agents, such as dopamine, is not likely to be beneficial. Extracorporeal elimination is also unlikely to be beneficial because of extensive protein binding and large volume of distribution of MAOIs. Because of the potential for intracranial hemorrhage in the setting of severe MAOI-induced hypertension, patients with a seizure or significant neurotoxicity should undergo a non–contrast-enhanced head computed tomography (CT) scan.

Patients presenting with a tyramine reaction may have spontaneous resolution of symptoms during 6 hours. Severe hypertension higher than 200 mm Hg systolic with symptoms may be treated with phentolamine or nitroprusside. Patients with persistent severe headache and hypertension should have a head CT scan to look for intracranial hemorrhage. Patients with chest pain should be evaluated for myocardial infarction (see Chapter 26).

Treatment of suspected serotonin syndrome is supportive (see later section).

Disposition

Patients presenting with an MAOI overdose should be admitted or observed in a monitored setting until 24 hours after ingestion for development of hyperadrenergic symptoms. Asymptomatic patients chronically taking an MAOI who present out of concern for a possible drug-food interaction can be discharged after 6 hours if no signs of toxicity develop.

TRICYCLIC ANTIDEPRESSANTS

Principles of Disease

In the 1950s, imipramine became the first tricyclic antidepressant (TCA) used for the treatment of depression. Until the introduction of the SSRIs, TCAs remained the primary agents for treatment of depression. The therapeutic benefit of TCAs results from monoamine reuptake inhibition.[11] Whereas use of TCAs for treatment of depression has waned, use for other conditions, including nocturnal enuresis, attention-deficit/hyperactivity syndrome, trigeminal neuralgia, and migraines, has increased.

Clinical Features

Cyclic antidepressant toxicity can result from overdose of a TCA or drug-drug interactions. Overdose is more commonly associated with life-threatening toxicity, but toxic effects can also occur when a TCA is combined with drugs that impair its metabolism through cytochrome P450. Tertiary amine TCAs, such as amitriptyline, imipramine, and clomipramine, are substrates of CYP2C19 and CYP1A2. Doxepin is also a substrate for CYP2D6. Drug-induced inhibition of these enzymes as well as genetic polymorphisms can decrease metabolism of these drugs, resulting in unexpectedly high serum concentrations and clinical toxicity.[12] Conversely, inhibition of CYP2D6 and other P_{450} enzymes by these TCAs can also lead to increased serum concentrations of other drugs metabolized by the same enzymes. Because desipramine and nortriptyline are only weak CYP2D6 inhibitors, they cause fewer drug-drug interactions. Another drug interaction that occurs with TCAs is the serotonin syndrome, which occasionally results when a TCA is combined with another serotonergic drug, such as MAOI or SSRI.

After an overdose of a TCA, symptoms typically begin within 1 to 2 hours. With smaller ingested amounts, symptoms may be minimal and resolve quickly; patients who take large amounts may deteriorate rapidly soon after ingestion. All seriously poisoned patients have symptoms within 6 hours of an overdose. Early TCA poisoning is characterized primarily by anticholinergic effects. Patients typically present with tachycardia, flushed and dry skin, mydriasis, and altered level of consciousness. They may be alert and confused, severely agitated, mute, hallucinating, or even deeply comatose. Speech is often rapid and mumbling in character. Urinary retention is common. Seizures may occur and are likely to be multifactorial, resulting from increased synaptic monoamines, sodium channel inhibition, and possibly γ-aminobutyric acid (GABA) receptor antagonism. Early hypertension is common from the anticholinergic effects of the TCA and excess norepinephrine in the synapse from blockade of norepinephrine reuptake, but hypotension may also be due to alpha-receptor antagonism and also norepinephrine depletion. Later myocardial depression resulting from severe sodium channel antagonism may also lead to hypotension and bradycardia.[13,14] Significant sodium channel blockade is associated with widening of the QRS interval. TCAs also block potassium efflux, which leads to a prolonged QT interval.[15] With severe poisoning, the combined effects of the TCA on various receptors and ion channels lead to

www.ketabpezeshki.com 66485457-66963820

depressed level of consciousness, seizures, hypotension, and wide-complex cardiac arrhythmias.

Chronic toxicity from drug-drug interactions or decreased ability to metabolize the drug because of genetic polymorphism may be manifested in a more subtle fashion. Confusion, urinary retention, and prolonged QTc interval are common. Chronic toxicity presents more gradually and should be considered in any confused patient taking therapeutic doses of a TCA.

Diagnostic Strategies

After overdose, the electrocardiogram can yield prognostic information. Early anticholinergic effects cause sinus tachycardia, which occurs virtually uniformly before other effects. Whereas the serum tricyclic concentrations are not particularly beneficial in predicting adverse events, the electrocardiogram is prognostic. A QRS duration longer than 100 milliseconds is predictive of seizures, whereas a QRS duration longer than 160 milliseconds is predictive of ventricular dysrhythmias.[16] Additional findings on the electrocardiogram include a rightward shift of the terminal 40 milliseconds of the QRS complex seen as an R wave in aVR longer than 3 milliseconds.[17] QT prolongation is less important clinically than the QRS duration. Urine drug of abuse screens commonly test for the presence of TCAs, but a positive test result suggests only use of a TCA or another xenobiotic that cross-reacts with the screen. Serum tricyclic levels do not correlate with severity of illness.[16] General management (see Chapter 147) suggests other supportive care measures.

Differential Considerations

Other agents with anticholinergic properties produce a similar early clinical presentation. In addition, sympathomimetic toxicity, serotonin syndrome, and hypoglycemia should be included in the differential diagnosis. Other toxins causing sodium channel blockade, a wide QRS, and subsequently intraventricular conduction delay include Vaughn-Williams class IA antidysrhythmics (e.g., procainamide, disopyramide, quinidine) and class IC antidysrhythmics (e.g., flecainide, encainide, and propafenone), amantadine, carbamazepine, cocaine, diphenhydramine, mesoridazine, and thioridazine. In addition, propoxyphene and propranolol can also cause an intraventricular conduction delay by sodium channel blockade but typically cause a bradycardic rhythm rather than a tachycardic rhythm. The constellation of early anticholinergic symptoms, decreased level of consciousness followed by seizures, wide QRS, and cardiovascular collapse is highly suggestive of acute TCA overdose.

Management

Ensuring stability of the airway, breathing, and circulation is of primary importance. There are no randomized controlled trials demonstrating improved patient-oriented outcomes (e.g., improved mortality) with activated charcoal in patients with cyclic antidepressant overdose. Nonetheless, because of the high lethality of the acute overdose, a patient who presents within 1 hour after ingestion and who is awake and alert can be given activated charcoal, if it is recommended by the regional poison center consultant and if the patient will readily drink it. It should not be administered to patients who are unwilling or unable to voluntarily consume it and is contraindicated if the patient has any decreased level of consciousness because charcoal aspiration may pose a greater risk to the patient than the benefit, if any, of charcoal administration. There is no role for gastric lavage.

Patients with sinus tachycardia alone do not need specific treatment but should be monitored to detect QRS widening early. Early hypertension should not be treated. Hypotensive patients should first receive fluid resuscitation with an isotonic crystalloid.[13] Patients who remain hypotensive should be treated with direct-acting vasopressors, such as norepinephrine and epinephrine.[13,14] There are some data that epinephrine may be superior to norepinephrine in this setting.

Hypertonic sodium bicarbonate should not be given prophylactically and should be given only to treat specific evidence of sodium channel blockade, such as a wide QRS and ventricular dysrhythmias. Recommendations vary about how to administer this therapy. A conservative approach is to administer a bolus of 1 to 2 mEq/kg hypertonic sodium bicarbonate if the QRS interval exceeds 100 milliseconds. This dose may be repeated in a few minutes if the QRS does not narrow. A sodium bicarbonate infusion can be used to maintain a pH between 7.50 and 7.55.[13] This can be done by administration of 5% dextrose in water with 150 mEq of sodium bicarbonate and 40 mEq of potassium added to each liter of fluid at a rate of twice maintenance starting at 35 mEq/hr and titrating to pH. Alternatively, infusions of 1 mEq sodium bicarbonate per milliliter of fluid may be used if volume overload is a concern. Additional boluses of sodium bicarbonate may be necessary if the QRS widens or if adequate alkalinization is not achieved with infusion alone. Figure 151-1 demonstrates a 12-lead electrocardiogram from a patient poisoned with a TCA before and after sodium bicarbonate therapy. If ventricular dysrhythmias persist despite maximal alkalinization ($pH > 7.55$), 200 mL of 3% hypertonic saline (in an adult) can be used.[18] Class IA and IC antidysrhythmics can worsen cardiac toxicity and should be avoided.[13] Seizures are treated with lorazepam or diazepam and with phenobarbital if they are refractory to benzodiazepines. Because seizure leads to acidosis and worsens the cardiac status, seizing patients who do not respond quickly should be rapidly paralyzed and intubated if necessary to prevent increasing acidosis.

Asystole has occurred after physostigmine use, and this agent is considered by many experts to be contraindicated in the management of TCA overdose. Whereas physostigmine should not be administered to any patient with QRS or QTc prolongation after TCA overdose, it may be used in patients with delirium of unknown etiology who are therapeutically taking TCAs and in whom chronic toxicity is suspected, but only if their QRS and QTc intervals are normal. Physostigmine should be given with caution in a monitored setting because it may produce seizures and bradycardia, and it is relatively contraindicated in patients with reactive airway diseases.

Intravenous lipid emulsion (ILE) therapy has gained interest recently for reversal of toxicity caused by lipophilic drugs, including TCAs. Although the exact mechanism of ILE is not known, it probably involves redistribution of a lipophilic drug from the tissue receptors back into the vascular compartment in the context of a large bolus of concentrated lipid solution, the so-called lipid sink phenomenon.[19,20] Other mechanisms also are possible. Because of the potential for iatrogenic harm, its use is currently reserved for life-threatening toxicity that remains refractory to sodium bicarbonate. There are several different dosing strategies. One approach is to give 1.5 mL/kg of a 20% lipid solution during 2 to 3 minutes. This bolus can be repeated once in 5 minutes if there is no clinical improvement. If clinical improvement does occur, the bolus should be followed by an infusion of 0.25 mL/kg/min for 15 to 30 minutes.[21]

Disposition

If no sinus tachycardia, decreased level of consciousness, or seizures have developed within 6 hours of an overdose, it is unlikely that toxicity will occur,[22] and the patient can be medically cleared from the emergency department for psychiatric disposition, if needed. Patients with signs of cyclic antidepressant toxicity should be admitted to an intensive care unit.

www.ketabpezeshki.com 66485457-66963820

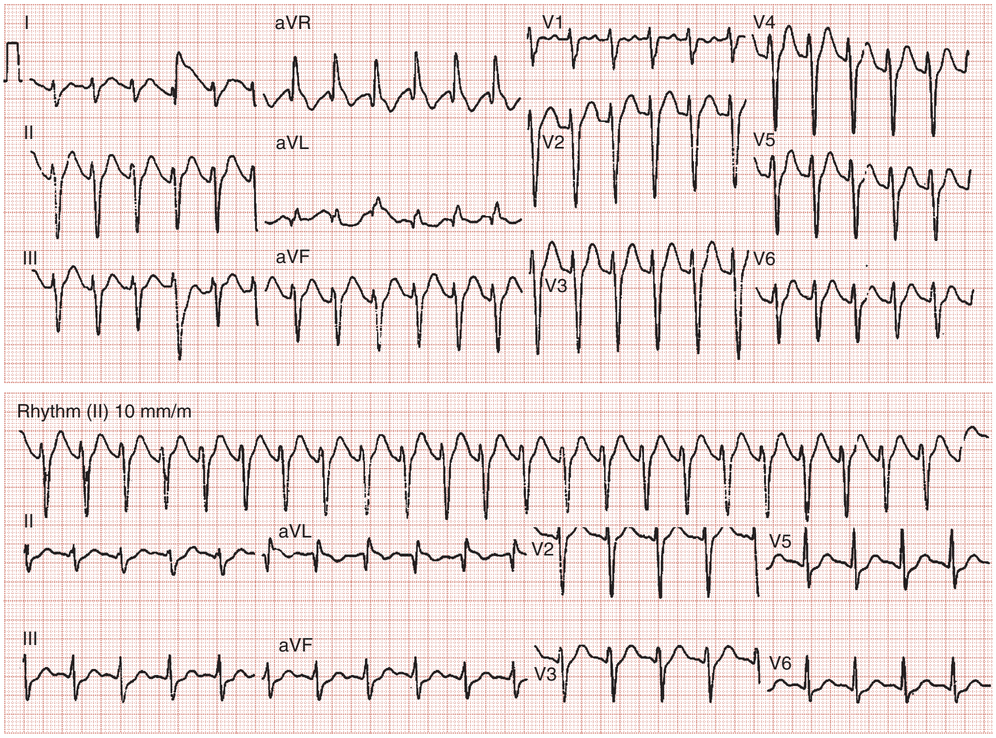


Figure 151-1. *Top,* Initial 12-lead electrocardiogram demonstrating substantial intraventricular conduction delay (QRS 146 milliseconds). *Bottom,* Repeated electrocardiogram after bicarbonate therapy.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Principles of Disease

In recent years, the selective serotonin reuptake inhibitors (SSRIs) have become the mainstay for treatment of depression. As implied by their name, these drugs prevent the presynaptic reuptake of serotonin without affecting the synaptic concentration of other monoamines. Some of the more commonly used SSRIs available today include escitalopram and its enantiomer citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. Some SSRIs are coformulated with other agents in a single pill, like the combination of fluoxetine and olanzapine.

SSRIs have a wide therapeutic index.[23] Although they are safer in overdose than MAOIs and TCAs, they do have therapeutic limitations, such as the long delay until onset of antidepressant effect.[24] The SSRIs undergo hepatic metabolism. There is considerable variability in their half-life; however, paroxetine has one of the shortest half-lives (17 hours) compared with fluoxetine, which has one of the longest half-lives (53 hours for parent drug, 240 hours for active metabolite).[25]

Clinical Features

Overdose of SSRIs is usually well tolerated and rarely fatal, with ingestions of up to 30 times the daily dose associated with few or no symptoms. Gastrointestinal upset and mild CNS depression can occur with large overdoses. Coma and seizures are rare, with incidences of approximately 2.4 and 1.9%, respectively.[23] The incidence of serotonin syndrome after SSRI overdose is variable, up to 14%,[23] but most other series report a much lower incidence.

Citalopram overdose deserves special mention because of a higher rate of QTc prolongation and seizures compared with other SSRIs.[26-28] Furthermore, onset of QTc prolongation may be delayed for up to 13 hours.[29] Despite being the active enantiomer of citalopram, escitalopram appears to be less toxic than citalopram, with a lower incidence of seizure and QTc prolongation.[26]

Therapeutic administration of SSRIs may be associated with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).[30,31] Most cases of hyponatremia develop within 1 month and frequently within the first 2 weeks.[31] The overall incidence is not clear; however, in one small study, 12.5% of elderly patients taking an SSRI had SIADH, with an additional 12.5% of patients having mild asymptomatic hyponatremia.

Diagnostic Strategies

Diagnosis of SSRI toxicity is often dependent on obtaining a history of overdose. Clinical features of toxicity are similar to those seen after overdose of many other toxicants, and urine drug of abuse screens do not detect SSRIs. An electrocardiogram can assess for conduction disturbances, especially QT prolongation. See Chapter 147 for other general management strategy. Specific SSRI levels are not performed by most hospital laboratories and do not influence management. They may help confirm overdose retrospectively.

Management

Treatment of an SSRI overdose is largely supportive. Only rarely will patients require tracheal intubation because of loss of airway reflexes. Magnesium sulfate can be administered when the QT interval is prolonged. Intravenous administration of benzodiazepines should be used to treat seizures.

Disposition

Patients who overdose with an SSRI who are asymptomatic after 6 hours of monitoring are unlikely to have toxicity. Some authors

www.ketabpezeshki.com 66485457-66963820

advocate for 13 hours of observation[29] after the ingestion of more than 1000 mg of citalopram or escitalopram. Symptomatic patients should be admitted to a monitored care setting.

SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

Principles of Disease

Duloxetine, venlafaxine, desvenlafaxine, and milnacipran are collectively referred to as serotonin-norepinephrine reuptake inhibitors (SNRIs). Desvenlafaxine, venlafaxine, and duloxetine are marketed in the United States for treatment of depression. Milnacipran, although it is used as an antidepressant in Europe, is currently approved in the United States only for treatment of fibromyalgia. In addition to the treatment of depression, duloxetine is commonly used in the management of diabetic neuropathy, fibromyalgia, and urinary stress incontinence.[32] Venlafaxine and its active metabolite desvenlafaxine are both available medicinally. The SNRIs may also produce dose-dependent inhibition of sodium channels.[33]

Clinical Features

Duloxetine overdose produces CNS depression.[34] Most fatal overdoses of duloxetine described thus far have involved coingestants.[32] Thus, ascribing causality to duloxetine in these fatal cases is difficult.[32]

Venlafaxine and desvenlafaxine overdoses can result in neurologic, muscular, and cardiovascular toxicity.[35] Common findings include CNS depression, seizures, and tachycardia. Ventricular arrhythmias and QRS prolongation on the electrocardiogram may also occur.[33,36,37] After venlafaxine overdose, rhabdomyolysis can develop independently or as a result of seizures.[35,38] Both serotonin syndrome and *takotsubo* cardiomyopathy occur with venlafaxine overdose.[39]

Experience with milnacipran overdose is limited. Expected toxic effects include CNS depression and tachycardia. Acute, reversible cardiomyopathy,[40] serotonin syndrome, and at least one fatal intoxication have been described after overdose.[40-42]

Diagnostic Strategies

Diagnosis of SNRI ingestion depends on history before onset of symptoms. Specific drug levels are not rapidly available and do not aid management. An electrocardiogram can detect QRS or QT interval prolongation. SNRIs are not detected by urine drug of abuse screens, but venlafaxine is associated with a false-positive phencyclidine screen.[43,44]

Differential Considerations

Differential diagnoses of seizure, decreased level of consciousness, and tachycardia include sympathomimetic toxicity, cyclic antidepressant toxicity, anticholinergic toxicity, and serotonin syndrome.

Management

Care of the patient with an SNRI overdose is supportive, with focus on ensuring airway patency and oxygenation. Hypotension is treated with crystalloid fluid resuscitation; if hypotension persists, direct-acting vasopressors such as norepinephrine should be used. Intraventricular conduction delay should be treated with sodium bicarbonate. First-line treatment of seizures is the intravenous administration of lorazepam or diazepam.

Disposition

Patients who are asymptomatic with a normal 12-lead electrocardiogram after an observation period of 6 hours can be cleared for discharge. Symptomatic patients should be admitted to a monitored care setting. Those patients with conduction delay and coma should be admitted to an intensive care unit.

MISCELLANEOUS ANTIDEPRESSANTS

Bupropion

Bupropion is a monocyclic antidepressant that is structurally related to amphetamine.[45] In addition to its use as an antidepressant, it is used to assist in smoking cessation.[46,47] Its primary mechanism of action is inhibition of dopamine and norepinephrine reuptake, but it also acts as a noncompetitive inhibitor of nicotinic acetylcholine receptors.[47]

Seizures are a dose-dependent phenomenon and can occur with therapeutic dosing or overdose of bupropion.[48] At doses of 300 to 450 mg/day, the incidence of seizures is approximately 0.4%. Doses of 450 to 600 mg/day, however, are associated with a tenfold increased incidence of seizures.[48] Among sustained-release preparations, doses less than 450 mg/day are associated with a seizure incidence of 0.1%.[48]

Sinus tachycardia, tonic-clonic seizures, and agitation are common after overdose.[45,49,50] Intraventricular conduction delay is rare.[45] Because of the risk of delayed seizures, patients with intentional overdoses of extended-release bupropion should be admitted for 24 hours of observation.[51]

Treatment is primarily supportive. Patients with large overdoses may require endotracheal intubation because of CNS depression. Lorazepam and diazepam should be used to treat seizures. If seizures persist, phenobarbital or other GABA agonists may be used.

Trazodone

Trazodone is an atypical antidepressant with a mechanism of action that includes antagonism of the 5-hydroxytryptamine type 2A (5-HT_{2A}) receptor and $alpha_1$ receptor. Its use as an antidepressant has been somewhat limited by adverse effects, such as orthostatic hypotension, priapism, and sedation.[52]

Priapism is probably a result of trazodone's alpha-antagonism, with an incidence of 1/100 to 1/10,000. Whereas many drugs are associated with priapism, particularly those with alpha-antagonism or inhibition of type 5 phosphodiesterase, trazodone is responsible for a disproportionate number of reported cases.

After overdose, sedation and hypotension due to vasodilation are expected. Priapism is not typically associated with overdose of trazodone. Management is supportive, with airway protection, intravenous fluid resuscitation, and use of alpha-adrenergic agonists, such as norepinephrine, as needed for refractory hypotension.

Nefazodone

Nefazodone, a phenylpiperazine antidepressant, is structurally similar to trazodone. It acts as an antagonist at the 5-HT_{2A} receptor, and chronic administration is associated with receptor downregulation. Nefazodone is associated with weak inhibition of norepinephrine and serotonin reuptake. It is metabolized to several active metabolites. After overdose, most patients remain asymptomatic. Antagonism of the $alpha_1$ receptor is responsible for the orthostatic hypotension that can occur. Treatment is supportive.

www.ketabpezeshki.com 66485457-66963820

Table 151-1 Xenobiotics Commonly Implicated in Serotonin Syndrome

Analgesics: tramadol, meperidine, pentazocine
Drugs of abuse: cocaine, amphetamine derivatives (e.g., methylenedioxymethamphetamine), lysergic acid diethylamide (LSD)
Monoamine oxidase inhibitors (e.g., isocarboxazid, linezolid, phenelzine, moclobemide, selegiline)
Miscellaneous: dextromethorphan, lithium, metoclopramide, St. John's wort
Selective serotonin reuptake inhibitors (e.g., milnacipran, venlafaxine)
Serotonin-norepinephrine reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)
Tricyclic antidepressants (e.g., amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline)

SEROTONIN SYNDROME

Principles of Disease

Serotonin syndrome is a potentially lethal condition resulting from excess serotonin accumulation in the synaptic cleft. This syndrome occurs after an isolated overdose of an SSRI, but it is more commonly a result of drug-drug interactions, especially with drug combinations that raise synaptic serotonin concentrations by different mechanisms.[53] Agonism of the 5-HT_{2A} receptor appears to be largely responsible for this condition in humans.[53-55]

Whereas numerous xenobiotics have been implicated in causing serotonin syndrome, some of the most common are the SSRIs, SNRIs, TCAs, MAOIs, dextromethorphan, amphetamines, and designer amphetamines, including methylenedioxymethamphetamine ("ecstasy"), cocaine, meperidine, lithium, tramadol, buspirone, lysergic acid diethylamide (LSD), and linezolid[53,56-60] (Table 151-1). Serotonin syndrome is more likely to develop when drugs from different classes are combined, resulting in increased serotonin in the synaptic cleft from different mechanisms (e.g., increased release and impaired uptake).

Clinical Features

Serotonin syndrome is described as a triad of mental status changes, autonomic instability, and increased neuromuscular activity, but the condition exists along a spectrum; some patients have only mild tremor and diarrhea, whereas others exhibit life-threatening manifestations.[53] Clinical features may include tremor, akathisia, gastrointestinal illness, clonus (inducible or spontaneous), rigidity, fever, seizures, and autonomic instability. The clonus is typically more pronounced in the lower extremities than in the upper extremities.

After an acute overdose of a serotonergic agent, symptom onset typically begins within several hours. With proper treatment, symptoms usually resolve within 24 hours but can persist for several days in severe cases.

Diagnostic Strategies

There is no "gold standard" for the diagnosis of serotonin syndrome. Laboratory studies cannot be used to confirm or to exclude the diagnosis of serotonin syndrome. Rhabdomyolysis and hyperkalemia can occur as a result of increased neuromuscular activity, and these should be screened for as indicated on the basis of the clinical examination.

The Sternbach criteria were developed in 1991 and became the first widely used diagnostic algorithm.[61] Additional criteria, including the Hunter criteria[62] and the Boyer and Shannon criteria,[53] have been developed. The Hunter criteria (Table 151-2) appear to be more sensitive than the Sternbach criteria, with fewer false positives.[62]

Table 151-2 The Hunter Criteria for Serotonin Syndrome[62]

In the setting of exposure to a known serotonergic agent, serotonin syndrome can be diagnosed by the presence of any of the following:
Spontaneous clonus
Inducible clonus *and* agitation or diaphoresis
Ocular clonus *and* agitation or diaphoresis
Tremor and hyper-reflexia
Hypertonic with temperature > 38° C *and* ocular clonus or inducible clonus

In general, a history of overdose or of recently starting an additional serotonergic agent along with clinical findings consistent with this diagnosis should raise the concern for serotonin syndrome.

Differential Considerations

The differential diagnosis of serotonin syndrome includes neuroleptic malignant syndrome, malignant hyperthermia, sympathomimetic toxicity, anticholinergic toxicity, strychnine toxicity, bupropion toxicity, and GABA withdrawal. Nontoxicologic considerations include thyroid storm, meningitis, idiopathic seizure, intracranial hemorrhage, and hypoglycemia.

Management

Management is supportive, with removal of the offending agents being paramount. Mild cases may require only discontinuation of the offending agent and low-dose benzodiazepines for rigidity. More severe cases may require intravenous fluid resuscitation and large doses of benzodiazepines or other sedative-hypnotic agents to gain control of symptoms. A trial of cyproheptadine, a 5-HT_{2A} antagonist, is an appropriate adjunctive therapy for more severe cases,[53,63] but there are no randomized controlled trials demonstrating improved benefit with cyproheptadine over supportive care and benzodiazepines alone.[64] Patients with hyperthermia that does not respond promptly to sedation with benzodiazepines should receive a nondepolarizing neuromuscular blocking agent after endotracheal intubation.

Disposition

Patients with all but the mildest forms of serotonin syndrome should be admitted to a monitored care setting. Those with unresponsiveness and rigidity should be admitted to an intensive care unit.

DISCONTINUATION SYNDROMES

After the abrupt discontinuation of certain antidepressants, patients can experience a withdrawal, or discontinuation, syndrome. Unlike potentially life-threatening GABA withdrawal from ethanol or benzodiazepines, the discontinuation syndrome from antidepressants is rarely life-threatening but can result in significant discomfort. One notable exception involves neonates born to mothers using TCAs[65] or SSRIs, who can have serious, potentially life-threatening withdrawal. Antidepressant discontinuation syndrome does not always develop, but when it does, it typically starts within the first 3 days after therapy is stopped.[66] This syndrome is difficult to distinguish from recurrence of the underlying depression, which has overlap of some symptoms.

Antidepressant discontinuation syndrome was first described in the 1950s with imipramine, but it has been described with all major classes of antidepressants.[66] Withdrawal from SSRIs involves both physical and psychological symptoms, most

www.ketabpezeshki.com 66485457-66963820

commonly nausea, lethargy, headache, and dizziness. The symptoms can be divided into six general categories: dysequilibrium (e.g., dizziness, ataxia), sleep disturbances, gastrointestinal symptoms, affective symptoms (e.g., irritability, anxiety), sensory symptoms (e.g., electric shock–like sensation, paresthesias), and general somatic symptoms (e.g., headache, tremor, anorexia, diaphoresis).[66] The syndrome is more common after discontinuation of drugs with shorter half-lives (e.g., paroxetine) than of drugs with longer half-lives (e.g., fluoxetine). TCA withdrawal is similar to SSRI withdrawal, although sensory abnormalities and equilibrium disturbances are rare with TCA discontinuation. Non–life-threatening arrhythmias are rare after discontinuation of the TCAs.

Patients with mild withdrawal symptoms do not require any specific therapy. For those patients with more severe symptoms, treatment involves restarting of the antidepressant, followed by a gradual taper.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Bostwick JM: A generalist's guide to treating patients with depression with an emphasis on using side effects to tailor antidepressant therapy. *Mayo Clin Proc* 2010; 85:538-550.
2. Lee S, Jeong J, Kwak Y, Park SK: Depression research: Where are we now? *Mol Brain* 2010; 10:8.
3. Youdim MB, Weinstock M: Therapeutic applications of selective and non-selective inhibitors of monoamine oxidase A and B that do not cause significant tyramine potentiation. *Neurotoxicology* 2004; 25:243-250.
4. Lopez-Munoz F, Alamo C: Monoaminergic neurotransmission: The history of the discovery of antidepressants from 1950s until today. *Curr Pharm Des* 2009; 15:1563-1586.
5. Bronstein AC, et al: 2010 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th Annual Report. *Clin Toxicol (Phila)* 2011; 49:910-941.
6. Chen JJ, Ly AV: Rasagiline: A second-generation monoamine oxidase type B inhibitor for the treatment of Parkinson's disease. *Am J Health Syst Pharm* 2006; 63:915-928.
7. Youdim MB, Bakhle YS: Monoamine oxidase: Isoforms and inhibitors in Parkinson's disease and depressive illness. *Br J Pharmacol* 2006; 147:S287-S296.
8. Gerlach M, Youdim MB, Reiderer P: Pharmacology of selegiline. *Neurology* 1996; 47(6 Suppl 3):S137-S145.
9. Stahl SM, Felker A: Monoamine oxidase inhibitors: A modern guide to an unrequited class of antidepressants. *CNS Spectr* 2008; 13:855-870.
10. LeWitt PA: MAO-B inhibitor know-how: Back to the pharm. *Neurology* 2009; 72:1352-1357.
11. Preskorn SH: CNS drug development. Part I: The early period of CNS drugs. *J Psychiatr Pract* 2010; 16:344-349.
12. Gillman PK: Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *Br J Pharmacol* 2007; 151:737-748.
13. Kerr GW, McGuffie AC, Wilkie S: Tricyclic antidepressant overdose: A review. *Emerg Med J* 2001; 18:236-241.
14. Bradberry SM, Thanacoody HK, Watt BE, Thomas SH, Vale JA: Management of the cardiovascular complications of tricyclic antidepressant poisoning: Role of sodium bicarbonate. *Toxicol Rev* 2005; 24:195-204.
15. Alvarez PA, Pahissa J: QT alterations in psychopharmacology: Proven candidates and suspects. *Curr Drug Saf* 2010; 5:97-104.
16. Boehnert MT, Lovejoy FH Jr: Value of the QRS duration versus the serum drug level in predicting seizures and ventricular arrhythmias after an acute overdose of tricyclic antidepressants. *N Engl J Med* 1985; 313:474-479.
17. Liebelt EL, Francis PD, Woolf AD: ECG lead aVR versus QRS interval in predicting seizures and arrhythmias in acute tricyclic antidepressant toxicity. *Ann Emerg Med* 1995; 26:195-201.
18. McCabe JL, Cobaugh DJ, Menegazzi JJ, Fata J: Experimental tricyclic antidepressant toxicity: A randomized, controlled comparison of hypertonic saline solution, sodium bicarbonate, and hyperventilation. *Ann Emerg Med* 1998; 32:329-333.
19. Jamaty C, et al: Lipid emulsions in the treatment of acute poisoning: A systematic review of human and animal studies. *Clin Toxicol (Phila)* 2010; 48:1-27.
20. Harvey M, Cave G: Intralipid outperforms sodium bicarbonate in a rabbit model of clomipramine toxicity. *Ann Emerg Med* 2007; 49:178-185.
21. American College of Medical Toxicology: Interim guidance for the use of lipid resuscitation therapy, 2010. Available at: http://www.acmt.net/_Library/Membership_Documents/Lipid_resuscitation_G_4F9E49_-_for_member_comment.pdf. Accessed December 29, 2011.
22. Woolf AD, et al: Tricyclic antidepressant poisoning: An evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila)* 2007; 45:203-233.
23. Isbister GK, Bowe SJ, Dawson A, Whyte IM: Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose. *J Toxicol Clin Toxicol* 2004; 42:277-285.
24. Olver JS, Burrows GD, Norman TR: Third-generation antidepressants: Do they offer advantages over the SSRIs? *CNS Drugs* 2001; 15:941-954.
25. O'Donnell JM, Shelton RC: *Drug therapy of depression and anxiety disorders*. In: Brunton LL, Chabner BA, Knollman BC, eds: *Goodman and Gilman's the Pharmacological Basis of Therapeutics*, 12th ed. New York: McGraw-Hill; 2011:397-415.
26. Hayes BD, Klein-Schwartz W, Clark RF, Muller AA, Miloradovich JE: Comparison of toxicity of acute overdoses with citalopram and escitalopram. *J Emerg Med* 2010; 39:44-48.
27. Jimmink A, Caminada K, Hunfeld NG, Touw DJ: Clinical toxicology of citalopram after acute intoxication with the sole drug or in combination with other drugs: Overview of 26 cases. *Ther Drug Monit* 2008; 30:365-371.
28. Catalano G, Catalano MC, Epstein MA, Tsambiras PE: QTc interval prolongation associated with citalopram overdose: A case report and literature review. *Clin Neuropharmacol* 2001; 24:158-162.
29. Isbister GK, Friberg LE, Duffell SB: Application of pharmacokinetic-pharmacodynamic modeling in management of QT abnormalities after citalopram overdose. *Intensive Care Med* 2006; 32:1060-1065.
30. Jacob S, Spinler SA: Hyponatremia associated with selective serotonin-reuptake inhibitors in older adults. *Ann Pharmacother* 2006; 40:1618-1622.
31. Kirby D, Ames D: Hyponatremia and selective serotonin re-uptake inhibitors in elderly patients. *Int J Geriatr Psychiatry* 2001; 16:484-493.
32. Vey EL, Kovelman I: Adverse events, toxicity, and post-mortem data on duloxetine: Case reports and literature survey. *J Forensic Leg Med* 2010; 17:175-185.
33. Bosse GM, Spiller HA, Collins AM: A fatal case of venlafaxine overdose. *J Med Toxicol* 2008; 4:18-20.
34. Kruithof MK, Bruins NA, van Roon EN: Coma after overdose with duloxetine. *Ann Pharmacother* 2011; 45:e5.
35. Pascale P, Oddo M, Pacher P, Augsburger M, Liaudet L: Severe rhabdomyolysis following venlafaxine overdose. *Ther Drug Monit* 2005; 27:562-564.
36. Isbister GK: Electrocardiogram changes and arrhythmias in venlafaxine overdose. *Br J Clin Pharmacol* 2009; 67:572-576.
37. Howell C, Wilson AD, Waring WS: Cardiovascular toxicity due to venlafaxine poisoning in adults: A review of 235 consecutive cases. *Br J Clin Pharmacol* 2007; 64:192-197.
38. Wilson AD, Howell C, Waring WS: Venlafaxine ingestion is associated with rhabdomyolysis in adults: A case series. *J Toxicol Sci* 2007; 32:97-101.
39. Christoph M, et al: Broken heart syndrome: Tako Tsubo cardiomyopathy associated with an overdose of the serotonin-norepinephrine reuptake inhibitor venlafaxine. *Eur Neuropsychomarmacol* 2010; 20:594-597.
40. Levine M, Truitt CA, O'Connor AD: Acute cardiomyopathy complicating a milnacipran overdose. *J Med Toxicol* 2011; 7:312-316.
41. Yacoub HA, Johnson WG, Souayah N: Serotonin syndrome after administration of milnacipran for fibromyalgia. *Neurology* 2010; 74:699-700.
42. Fanton L, et al: Fatal intoxication with milnacipran. *J Forensic Leg Med* 2008; 15:388-390.
43. Santos PM, et al: False positive phencyclidine results caused by venlafaxine. *Am J Psychiatry* 2007; 164:349.
44. Bond GR, Steele PE, Uges DR: Massive venlafaxine overdose resulted in a false positive Abbott AxSYM urine immunoassay for phencyclidine. *J Toxicol Clin Toxicol* 2003; 41:999-1002.
45. Curry SC, Kashani JS, LoVecchio F, Holubek W: Intraventricular conduction delay after bupropion overdose. *J Emerg Med* 2005; 29:299-305.
46. McNeil JJ, Piccenna L, Ioannides-Demos LL: Smoking cessation—recent advances. *Cardiovasc Drugs Ther* 2010; 24:359-367.
47. Damaj MI, et al: Enantioselective effects of hydroxyl metabolites of bupropion on behavior and on function of monoamine transporters and nicotinic receptors. *Mol Pharmacol* 2004; 66:675-682.
48. Dhillon S, Yang LP, Curran MP: Bupropion: A review of its use in the management of major depressive disorder. *Drugs* 2008; 68:653-689.
49. Belson MG, Kelley TR: Bupropion exposures: Clinical manifestations and medical outcome. *J Emerg Med* 2002; 23:223-230.
50. Shepherd G, Velez LI, Keyes DC: Intentional bupropion overdoses. *J Emerg Med* 2004; 27:147-151.
51. Starr P, et al: Incidence and onset of delayed seizures after overdoses of extended-release bupropion. *Am J Emerg Med* 2009; 27:911-915.
52. Mendelson WB: A review of the evidence for the efficacy and safety of trazodone in insomnia. *J Clin Psychiatry* 2005; 66:469-476.
53. Boyer EW, Shannon M: The serotonin syndrome. *N Engl J Med* 2005; 352:1112-1120.
54. Nisijima K, Shioda K, Yoshino T, Takano K, Kato S: Memantine, an NMDA antagonist, prevents the development of hyperthermia in an animal model for serotonin syndrome. *Pharmacopyschiatry* 2004; 37:57-62.
55. Sun-Edelstein C, Tepper SJ, Shapiro RE: Drug-induced serotonin syndrome: A review. *Expert Opin Drug Saf* 2008; 7:587-596.
56. Quinn DK, Stern TA: Linezolid and serotonin syndrome. *Prim Care Companion J Clin Psychiatry* 2009; 11:353-356.
57. Schwartz AR, Pizon AF, Brooks DE: Dextromethorphan-induced serotonin syndrome. *Clin Toxicol (Phila)* 2008; 46:771-773.

www.ketabpezeshki.com 66485457-66963820

58. Adan-Manes J, Novalbos J, Lopez-Rodriguez R, Ayuso-Mateos JL, Abad-Santos F: Lithium and venlafaxine interaction: A case of serotonin syndrome. *J Clin Pharm Ther* 2006; 31:397-400.
59. Devlin RJ, Henry JA: Clinical review: Major consequences of illicit drug consumption. *Crit Care* 2008; 12:202.
60. Bijl D: The serotonin syndrome. *Neth J Med* 2004; 62:309-313.
61. Sternbach H: The serotonin syndrome. *Am J Psychiatry* 1991; 148:705-713.
62. Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM: The Hunter Serotonin Toxicity Criteria: Simple and accurate diagnostic decision rules for serotonin toxicity. *QJM* 2003; 96:635-642.
63. Rusyniak DE, Sprague JE: Toxin-induced hyperthermic syndromes. *Med Clin North Am* 2005; 89:1277-1296.
64. Graudins A, Stearman A, Chan B: Treatment of the serotonin syndrome with cyproheptadine. *J Emerg Med* 1998; 16:615-619.
65. Cowe L, Lloyd DJ, Dawling S: Neonatal convulsion caused by withdrawal from maternal clomipramine. *Br Med J (Clin Res Ed)* 1982; 284:1837-1838.
66. Haddad PM: Antidepressant discontinuation syndromes: Clinical relevance, prevention and management. *Drug Saf* 2001; 24:183-197.

www.ketabpezeshki.com 66485457-66963820

Chapter 152

Cardiovascular Drugs

Jon B. Cole and David J. Roberts

Cardiovascular drugs are a common cause of poisoning in the United States; in 2010, 97,336 exposures to cardiovascular drugs were reported to U.S. Poison Control Centers.[1] Cardiovascular drugs are the second most common cause, accounting for more than 10%, of all poisoning deaths in the United States. Of the scores of cardiovascular drugs, three classes—cardioactive steroids (primarily digoxin), beta-adrenergic blockers, and calcium channel blockers—account for the majority of fatalities.

CARDIOACTIVE STEROIDS (DIGOXIN)

Perspective

Digoxin is derived from the Balkan foxglove plant, *Digitalis lanata* (Fig. 152-1), and the trade name for digoxin (Lanoxin) is derived from the Latin name of this plant.[2] Digitoxin, which is no longer in clinical use, comes from *Digitalis purpurea*.[2] Although William Withering was the first to describe the medicinal use of the foxglove plant,[3] the ancient Egyptians reference medicinal use of foxglove. Despite centuries of experience with digitalis, chronic and acute poisonings still occur. Controversy about the therapeutic benefit of cardioactive steroids is not new. Benjamin Rush wrote in 1797, "I suspect the cases in which [digitalis preparations] were useful to have been either so few or doubtful and that the cases they had done harm were so much more numerous and unequivocal as justly to banish them from the *Materia Medica*."[4] Medication errors and toxic effects account for the most common causes (44%) of preventable iatrogenic cardiac arrests.

Principles of Disease

Pathophysiology

Digoxin is used therapeutically (1) to increase the force of myocardial contraction to increase cardiac output in patients with heart failure and (2) to decrease atrioventricular (AV) conduction to slow the ventricular rate in atrial fibrillation. The basis for its first effect is inhibition of membrane sodium-potassium–adenosine triphosphatase (Na^+,K^+-ATPase), which increases intracellular sodium and extracellular potassium concentrations. This increase in intracellular sodium concentration results in dysfunction of the sodium-calcium ion exchanger, which normally extrudes intracellular calcium after systole. This subsequent increase in intracellular calcium concentration results in a larger amount of calcium pumped into the sarcoplasmic reticulum, so that on calcium-induced calcium release during subsequent action potentials, a larger amount of calcium is released into the cell, causing a more powerful contraction and thus increased cardiac output. Any molecule with this effect is classified as a cardioactive steroid. Cardiac glycosides (such as digoxin) are merely cardioactive steroids with additional sugar moieties attached to their steroid nucleus. At therapeutic doses, the effects of digoxin on serum electrolyte levels are minimal. With toxic levels, digoxin paralyzes the Na^+,K^+-ATPase pump, potassium cannot be transported into cells, and serum potassium concentration can rise as high as 13.5 mmol/L.[5]

Digoxin exerts direct and indirect effects on sinoatrial (SA) and AV nodal fibers. At therapeutic levels, digoxin indirectly increases vagal activity. At toxic levels, digoxin can directly block the generation of impulses in the SA node, depress conduction through the AV node, and increase the sensitivity of the SA and AV nodes to catecholamines. Catecholamines, whether endogenous or administered to treat bradydysrhythmias or hypotension, probably play an important role in digoxin toxicity. Because bradydysrhythmias and tachydysrhythmias can appear and alternate in the same patient, administration of drugs to treat tachycardias may later contribute to more refractory bradycardias and AV block.

Digoxin also exerts three primary effects on Purkinje fibers: (1) decreased resting potential, resulting in slowed phase 0 depolarization and conduction velocity; (2) decreased action potential duration, which increases sensitivity of muscle fibers to electrical stimuli; and (3) enhanced automaticity resulting from increased rate of phase 4 repolarization and delayed afterdepolarizations. These mechanisms account for an increase in premature ventricular contractions, the most common manifestation of digoxin toxicity. At toxic extremes, these effects result in a dangerous sensitivity to mechanical and electrical stimulation. Interventions with pacemaker wires, catheters, and cardioversion can result in asystole, ventricular tachycardia, and ventricular fibrillation.[6]

Unlike most cardiovascular drugs, digoxin can produce virtually any dysrhythmia or conduction block, and bradycardias are as common as tachycardias (Box 152-1). Unfortunately, none is unique to digoxin, and because they can all occur in the setting of ischemic and other heart disease, digoxin toxicity remains a clinical rather than an electrocardiographic diagnosis.

The volume of distribution (V_d) of digoxin is 5 L/kg for adults but varies from 3.5 L/kg in premature infants to 16.3 L/kg in older infants.[7] This indicates that only a small fraction of digoxin remains in the intravascular space, and the drug is highly concentrated in cardiac tissue. The myocardial-to-serum ratio at equilibrium ranges from 15:1 to 30:1. The V_d for digitoxin is only 0.5 L/kg, giving it a different pharmacokinetic profile.

The elimination half-life of digoxin, which is primarily excreted in the urine, is 36 hours, and the half-life of digitoxin, which is metabolized in the liver, is 7 days. Whereas digoxin undergoes only a small enterohepatic circulation, that for digitoxin is large, and

www.ketabpezeshki.com 66485457-66963820

Figure 152-1. The Balkan foxglove plant, from which digoxin is derived.

Box 152-1 Dysrhythmias Associated with Digitalis Toxicity

Nonspecific
PVCs, especially bigeminal and multiform
First-, second- (Wenckebach's), and third-degree AV block
Sinus bradycardia
Sinus tachycardia
Sinoatrial block or arrest
Atrial fibrillation with slow ventricular response
Atrial tachycardia
Junctional (escape) rhythm
AV dissociation
Ventricular bigeminy and trigeminy
Ventricular tachycardia
Torsades de pointes
Ventricular fibrillation

More Specific but Not Pathognomonic
Atrial fibrillation with slow, regular ventricular rate (AV dissociation)
Nonparoxysmal junctional tachycardia (rate 70-130 beats/min)
Atrial tachycardia with block (atrial rate usually 150-200 beats/min)
Bidirectional ventricular tachycardia

AV, atrioventricular; *PVCs,* premature ventricular contractions.

multiple-dose activated charcoal treatment has been used for digitoxin.

Protein binding varies from 20 to 30% for digoxin to 95% for digitoxin. The significant protein binding and large volumes of distribution suggest that hemodialysis, hemoperfusion, and exchange transfusion are ineffective. The long half-lives suggest that temporizing measures such as pacemakers, atropine, and antidysrhythmic drugs would cost more time, money, and lives than simply giving Fab fragments initially.

Multiple drugs and disease states can negatively alter absorption, V_d, protein binding, and elimination and render the heart more susceptible to digoxin toxicity. The factors listed in Box 152-2 are especially important risk factors in chronic intoxication.

Clinical Features

The symptoms and signs of chronic digoxin toxicity are nonspecific. The most common symptoms, in more than 80% of cases, are nausea, anorexia, fatigue, and visual disturbance, but a variety of gastrointestinal, neurologic, and ophthalmic disturbances also occur (Box 152-3). Digoxin intoxication should be considered in any patient receiving maintenance therapy who has consistent symptoms, especially with new conduction disturbances or dysrhythmias.

There are significant differences between acute and chronic toxicity (Table 152-1). Chronic poisoning has an insidious onset and is accompanied by a higher mortality rate that is probably due in part to underlying heart disease and chronic accumulation of the

Box 152-2 Factors Associated with Increased Risk of Digitalis Toxicity

Renal insufficiency
Heart disease
- Congenital heart disease
- Ischemic heart disease
- Congestive heart failure
- Myocarditis

Electrolyte imbalance
- Hypokalemia or hyperkalemia
- Hypomagnesemia
- Hypercalcemia

Alkalosis
Hypothyroidism
Sympathomimetic drugs
Cardiotoxic coingestants
- Beta-blockers
- Calcium channel blockers
- Tricyclic antidepressants

Drug interactions
- Quinidine, amiodarone
- Erythromycin
- Verapamil, diltiazem, nifedipine
- Captopril

Elderly woman

Box 152-3 Noncardiac Symptoms of Digitalis Intoxication

General
Weakness
Fatigue
Malaise

Gastrointestinal
Nausea and vomiting
Anorexia
Abdominal pain
Diarrhea

Ophthalmologic
Blurred or snowy vision
Photophobia
Yellow-green chromatopsia (also red, brown, blue)
Transient amblyopia, diplopia, scotomas, blindness

Neurologic
Dizziness
Headache
Confusion, disorientation, delirium
Visual and auditory hallucinations
Paranoid ideation, acute psychosis
Somnolence
Abnormal dreams
Paresthesias and neuralgia
Aphasia
Seizures

www.ketabpezeshki.com 66485457-66963820

Table 152-1 Chronic versus Acute Digitalis Intoxication

CHRONIC	ACUTE
Higher mortality (LL_{50} 6 ng/mL)	Lower mortality
Ventricular dysrhythmias more common	Bradycardia and atrioventricular block more common
Usually elderly patients	Usually younger patients
Often need Fab fragment therapy	Often do well without Fab (*Caution:* many exceptions)
Underlying heart disease increases morbidity and mortality	Absence of heart disease decreases morbidity and mortality

toxin. In cases of chronic intoxication, the LL_{50} (the level with a 50% mortality) is only 6 ng/mL.[8] The LL_{50} for acute intoxication is not known, but it is certainly much higher, especially in children. The association of hyperkalemia with acute toxicity is obvious given the mechanism of digoxin; either hypokalemia or hyperkalemia may occur with chronic toxicity.

Diagnostic Strategies

Diagnosis and management rely heavily on serum digoxin levels, but it is the steady state, rather than peak concentration, that correlates with tissue toxicity and is used to calculate antidote dosages. Peak concentrations after an oral dose of digoxin occur in 1.5 to 2 hours, with a range of 0.5 to 6 hours.[9] Steady-state serum concentrations are not achieved until after distribution, or 6 to 8 hours after a dose or overdose, and may be only one fourth to one fifth of the peak concentration. The ideal serum digoxin concentration for patients with heart failure is considered to be 0.7 to 1.1 ng/mL,[10] although laboratory "normals" are often reported up to 2.0 ng/mL. Serum steady-state digoxin levels of 1.1 to 3.0 ng/mL are equivocal; that is, levels as low as 1.1 ng/mL have been associated with increased mortality,[11] and patients with levels up to 3.0 ng/mL can be asymptomatic.[12] The incidence of digoxin-incited dysrhythmia reaches 10% at a level of 1.7 ng/mL and rises to 50% at a level of 2.5 ng/mL. Determination of a level too soon after the last maintenance dose falsely suggests toxicity, especially in cases of chronic intoxication, in which significant morbidity and mortality can occur at levels of 2 to 6 ng/mL.[10] After an acute massive overdose in a patient who is rapidly becoming symptomatic, however, it may be impractical to wait 6 to 8 hours for the first reading.[13] It is unlikely that early levels exceeding 10 to 20 ng/mL will fade to clinical insignificance at 6 to 8 hours after ingestion.

Differential Considerations

No sign or symptom, including dysrhythmia, is unique to digoxin poisoning, so the differential diagnosis is broad. Intrinsic cardiac disease as well as other cardiotoxic drugs should be considered. Central nervous system (CNS) depression or confusion may be due to various depressant drugs and toxins as well as infection, trauma, inflammation, and metabolic derangements. Visual disturbances should be binocular and are often not reported by the patient. Gastrointestinal disturbances are common and nonspecific and may be misdiagnosed as gastritis, enteritis, or colitis.

Management

Fab Fragments (DigiFab)

The treatment of significant digoxin poisoning is the administration of digoxin-specific fragment antigen-binding (Fab) antibodies (DigiFab); all other interventions are considered complementary.

The mortality rate before Fab fragment therapy was 23% despite all of the interventions described.[14] Fab fragment treatment is well established in both chronic and acute poisonings, with a 90% response rate.[15] Nonresponders usually receive too little antibody or receive it too late. Other nonresponders are compromised by underlying heart or multisystem disease.

Digitalis antibodies are derived from sheep, but allergic reactions occur in less than 1% of cases.[15] Reactions have included erythema, urticaria, and facial edema, all of which are responsive to the usual treatment. Other expected reactions when Fab fragments neutralize digitalis include hypokalemia, exacerbation of congestive heart failure, and increase in ventricular rate with atrial fibrillation. Two Fab fragment preparations were previously available; however, Digibind has been discontinued, leaving DigiFab as the only available product in the United States. If vials of Digibind are still available at a given institution, they require a 0.22-µm membrane filter for proper use; such a filter is not required for DigiFab.

Fab fragment treatment is best reserved for cases of serious cardiovascular toxicity rather than for routine or prophylactic administration with higher than expected serum levels. In acute poisoning, antibody treatment should be used for a serum potassium level above 5.0 mEq/L or unstable dysrhythmias, such as symptomatic sinus bradycardia, ventricular dysrhythmias, or second- or third-degree heart block unresponsive to atropine. Although toxicity increases with greater body load, there is no clear correlation with amount ingested, especially in children, and many patients with large ingestions or high serum levels become only mildly symptomatic.[8] Fab fragment therapy should be used before transvenous pacing, which carries significant risk.

The median time to initial response is 19 minutes after completion of the Fab infusion, but complete resolution of digitalis toxic rhythms may require hours.[16,17] Late administration of Fab fragments has resuscitated 54% of patients who have suffered cardiac arrest.[18] This antidote should be considered whenever hemodynamic compromise attends a digitalis toxic dysrhythmia or heart block (Box 152-4).[19]

Current formulas for calculation of DigiFab doses are found in the package insert. There are at least three approaches. The first is empirical. A patient has a history of digitalis ingestion, consistent symptoms, and life-threatening dysrhythmias. There is no time to assess serum digoxin levels, and 10 vials should be administered over 30 minutes for the average acute ingestion, 4 to 6 vials for the average chronic ingestion. In cardiac arrest, 20 vials can be administered undiluted by intravenous bolus. The second approach uses a simple calculation when the ingested dose is known with reasonable certainty. One vial of Digibind or DigiFab contains 38 mg or 40 mg, respectively, of Fab fragments, which bind 0.5 mg of digoxin or digitoxin (Box 152-5). A third approach is to base the dosage on the steady-state serum digoxin or digitoxin level after 6 to 8 hours (Boxes 152-6 and 152-7). Because most assays measure both bound and unbound drug, digoxin levels will be elevated for up to 1 week, with values often greater than 100 ng/mL once Fab fragments have been administered. Newer methods can measure free digoxin, but it is more meaningful to follow the patient clinically.

Electrolyte Correction

In cases of chronic toxicity, which may be exacerbated by hypokalemia, maintenance of the serum potassium level to at least 3.5 to 4 mEq/L is an important early treatment. Potassium can be administered orally (which is safer) or intravenously (IV) at a rate of less than 40 mEq/hr.

www.ketabpezeshki.com 66485457-66963820

In acute poisoning, serum potassium concentration may begin to rise rapidly within 1 to 2 hours of ingestion. Potassium should be withheld, even if mild hypokalemia is measured initially. The initial serum potassium concentration may in fact be a better predictor of mortality than the initial digoxin concentration. In a study of 91 patients with acute digoxin poisoning, nearly 50% of the patients with serum potassium concentrations between 5.0 and 5.5 mmol/L died. No patients with a potassium level of less than 5.0 mEq/L died, and all 10 patients with serum potassium concentrations exceeding 5.5 mmol/L perished.[20] Because of these findings, a serum potassium concentration greater than 5 mmol/L alone warrants treatment with Fab fragments. Even with Fab fragments, severe hyperkalemia should be treated with intravenous administration of glucose, insulin, and sodium bicarbonate as needed.

The decision to administer calcium to patients with hyperkalemia and digoxin poisoning represents a clinical dilemma. Classic teaching is that in the setting of the increased intracellular calcium concentration from digoxin poisoning, administration of exogenous calcium will result in "stone heart" from excessive intracellular calcium.[21] This concept has been in the literature since 1927,[22] based on animal studies.[23] Documented cases of cardiac arrest after calcium administration are exceedingly rare in the literature, and the temporal relationship is dubious.[24] More recent data indicate that the intravenous administration of calcium can be safe for hyperkalemia in the setting of digoxin toxicity.[25] Unequivocally, however, the best treatment of hyperkalemia due to acute digoxin toxicity is Fab fragments. The treatment of hyperkalemia in the setting of chronic digoxin toxicity and renal failure is less clear; however, the evidence that calcium salts will be harmful is dubious at best. Calcium salts should be administered during several minutes through a secure peripheral intravenous site or through a central venous catheter. Indications are identical to those for hyperkalemia, including but not exclusive to a widened QRS duration on the electrocardiogram. A reasonable starting dose would be 3 g of calcium gluconate or 1 g of calcium chloride. Calcium salts should be followed immediately with other pharmacologic measures to lower serum potassium concentration.

Many patients receiving diuretic therapy are also magnesium depleted, even when the measured serum magnesium level is normal. If significant magnesium depletion is suspected (e.g., if electrocardiographic changes such as QTc prolongation are present), 1 to 2 g of magnesium sulfate can be given during 10 to 20 minutes (child: 25 mg/kg), followed by a constant infusion of 1 to 2 g/hr. Patients should be closely monitored for respiratory depression, which is usually preceded by progressive loss of deep tendon reflexes. Hypermagnesemia can exacerbate digitalis toxicity, but magnesium has been reported to reverse digoxin-induced tachydysrhythmias.[26] It is prudent to infuse magnesium slowly and to stop the infusion if heart block or bradycardia develops. Avoid magnesium in patients with renal failure. The role of magnesium in bradydysrhythmias and conduction blocks is less clear but probably dangerous because hypermagnesemia can impair impulse formation and AV conduction.

Atropine

Atropine is generally used for severe bradycardia and advanced AV block, with mixed results. Standard dosing (0.02 mg/kg in children with a minimum of 0.1 mg; 1 mg IV in adults) should be used. In general, an external or transvenous pacemaker should be readied when bradycardia or AV block appears.

Pacing

Transvenous pacing has been a mainstay of treatment for several decades, but the catheter may induce ventricular

Box 152-4 Recommendations for Administration of Digitalis Antibody Fragments

Adults

1. Ventricular dysrhythmias more severe than premature ventricular contractions
2. Progressive and hemodynamically significant bradydysrhythmias unresponsive to atropine
3. Serum potassium level above 5.0 mEq/L
4. Rapidly progressive rhythm disturbances or rising serum potassium level
5. Coingestion of cardiotoxic drugs such as beta-blockers, calcium channel blockers, or tricyclic antidepressants
6. Ingestion of plant known to contain cardiac glycosides *plus* severe dysrhythmias (rare)
7. Acute ingestion of more than 10 mg *plus* any one of factors 1 through 6 above
8. Steady-state serum digoxin concentration above 6 ng/mL *plus* any one of factors 1 through 6 above

Children

1. Ingestion of more than 0.1-0.3 mg/kg or steady-state digoxin concentration above 5 ng/mL *plus* rapidly progressive symptoms or signs of digitalis intoxication *or* potentially life-threatening dysrhythmias or conduction blocks *or* serum potassium concentration above 6 mmol/L
2. Coingestion of other cardiotoxic drugs with additive or synergistic toxicity
3. Ingestion of plant known to contain cardiac glycosides *plus* severe dysrhythmias (rare)

Box 152-5 Sample Calculation of Digibind or DigiFab Based on Ingested Dose of Digoxin or Digitoxin*

Case: A toxic-appearing 40-year-old woman has ingested fifty 0.25-mg digoxin tablets.

Body load = amount ingested × 0.8 (bioavailability of digoxin tablets)
= 12.5 mg × 0.8 = 10 mg

Dose of digoxin Fab fragments (in vials) = 10 mg ÷ 0.5 mg bound per vial
= 20 vials

*Formula from GlaxoSmithKline, 2008.

Box 152-6 Sample Calculation of Digibind or DigiFab Based on Steady-State Digoxin Concentration*

Case: A toxic-appearing 4-year-old child weighing 20 kg has a digoxin level of 16 ng/mL 8 hours after ingestion of an unknown number of digoxin tablets.

Dose (in number of vials) = (serum digoxin concentration × weight in kg) ÷ 100
= (16 × 20) ÷ 100
= approximately 3 vials

*Formula from GlaxoSmithKline 2008; assumes V_d = 5 L/kg.

Box 152-7 Calculation of Digibind or DigiFab Based on Steady-State Digitoxin Concentration*

Case: A toxic-appearing 70-year-old man weighing 80 kg has a digitoxin level of 200 ng/mL (therapeutic = 10 to 35 ng/mL).

Dose (in number of vials) = (serum digitoxin concentration × weight in kg) ÷ 1000
= (200 × 80) ÷ 1000
= 16 vials

*Formula from GlaxoSmithKline 2008; V_d = 5 L/kg.

www.ketabpezeshki.com 66485457-66963820

tachydysrhythmias in a myocardium made irritable by digoxin. Iatrogenic accidents of cardiac pacing are frequent (14 of 39, 36%) and often fatal (5 of 39, 13%).[27] We recommend avoidance of transvenous pacing unless external pacing fails. Pacing usually is required only temporarily while waiting for Fab fragments to take effect. Cardioversion for tachydysrhythmia also may be hazardous in the setting of digoxin intoxication. If it is deemed necessary, such as when the tachydysrhythmia is thought to be causing severe hypotension, we recommend use of lower than usual energy settings, such as 25 to 50 J, although there is no proof that this is less hazardous.

Carotid Sinus Massage

Carotid sinus massage may result in bradyasystole and cardiac arrest in the setting of digoxin toxicity and is rarely if ever indicated.

Phenytoin and Lidocaine

Phenytoin and lidocaine are believed to be the safest of the antidysrhythmic drugs for control of tachydysrhythmias in the setting of digoxin toxicity. Indications include unstable tachydysrhythmias when Fab fragments are unavailable and unstable tachydysrhythmias that occur while waiting for Fab fragments to take effect. Phenytoin may enhance AV conduction. Phenytoin has been infused at 25 to 50 mg/min to a loading dose of 15 to 20 mg/kg; it may also be administered in 100-mg boluses every 5 minutes until arrhythmias improve or 1000 mg is administered. Lidocaine can be given initially at a dosage of 1 to 1.5 mg/kg during several minutes, followed by an infusion of 1 to 4 mg/min (30-50 μg/kg/min).[28] Most other cardiac drugs (isoproterenol, procainamide, amiodarone, beta-blockers, calcium antagonists) may worsen dysrhythmias or depress AV conduction. Digoxin immune Fab fragments are the preferred therapy for dysrhythmias.

Pediatric Considerations

Children at greatest risk are those receiving chronic digoxin therapy for heart disease. Children with healthy hearts can tolerate massive acute oral ingestions without Fab treatment.[28] This excludes therapeutic errors, children who are taking digoxin therapeutically, and children with heart disease.

Dosage calculation and administration errors account for more pediatric digoxin intoxication and death than does accidental oral ingestion. Therapeutic errors, especially accidental intravenous overdoses, often result in death within 1 to 4 hours.

Signs and symptoms in children with digoxin poisoning are somewhat different (Table 152-2). Vomiting, somnolence, and obtundation are more common than in adults.[18] CNS depression, in the absence of a history, might lead the clinician to suspect narcotic or sedative-hypnotic overdose or nontoxicologic causes, such as head injury, metabolic disorder, and CNS infection. Conduction disturbances and bradycardias are more common than ventricular dysrhythmias in children, especially with acute ingestion.[9,18]

Table 152-2 Age Differences in Digitalis Intoxication

ADULT	PEDIATRIC
Toxic at lower levels	Asymptomatic at higher levels
Nausea, fatigue, and visual disturbances most common	Obtundation and vomiting more common than in adults
Tachydysrhythmias as common as blocks and bradydysrhythmias	Bradydysrhythmias and blocks most common
Allergic reactions to Fab fragments uncommon (<1%)	Allergic reactions extremely rare
V_d less variable (5-7.5 L/kg)	V_d more variable (3.5-6.0 L/kg in premature infants, 8.0-16.3 L/kg in infants 2-24 months)

Disposition

All patients who are symptomatic for digoxin toxicity with hyperkalemia, dysrhythmia, AV block, or significant comorbidity should be admitted to an intensive care unit or coronary care unit after treatment with Fab. Asymptomatic patients reporting an acute ingestion of a large quantity of digoxin should be admitted to an intensive care unit or coronary care unit for at least 12 hours of continuous cardiac monitoring to determine the need for Fab.

BETA-ADRENERGIC BLOCKERS

Perspective

Beta-adrenergic blocking drugs became widely used in Europe in the 1960s for treatment of dysrhythmias. Their antihypertensive effects were later appreciated, and, by the 1970s, they were one of the most widely prescribed classes of drugs in the United States. Current indications include supraventricular dysrhythmias, hypertension (although the drugs have fallen out of favor for this indication), angina, thyrotoxicosis, migraine, and glaucoma. Of the numerous beta-blockers available, propranolol is the most deadly. In 2010, U.S. Poison Control Centers received more than 23,000 calls regarding beta-blocker exposures.[1]

Principles of Disease

Pathophysiology

Beta-blockers structurally resemble isoproterenol, a pure beta-agonist. They competitively inhibit endogenous catecholamines such as epinephrine at beta-adrenergic receptors, blocking the catecholamine effects on augmentation of myocardial contraction (inotropy), enhancing cardiac conduction (dromotropy), and accelerating heart rate (chronotropy). These are all beta$_1$ effects. Complex beta$_2$ effects include vascular (smooth muscle relaxation and vasodilation), liver (glycogenolysis, gluconeogenesis), lung (bronchodilation), adipose tissue (release of free fatty acids), and uterus (smooth muscle relaxation) effects. Equally important properties, which vary from one beta-blocker to another, include cardioselectivity (beta$_1$ selectivity), membrane-stabilizing effect (fast cardiac sodium channel blocking properties), lipophilicity, and intrinsic sympathomimetic activity (Table 152-3). Although cardioselectivity is lost in overdose, cardioselective beta-blockers such as atenolol, metoprolol, and esmolol still have a lower mortality rate than that of propranolol.

Beta-blockers are rapidly absorbed after oral ingestion, and the peak effect of normal-release preparations occurs in 1 to 4 hours. Hepatic metabolism on first pass results in significantly less bioavailability after oral dosing than with intravenous injection (e.g., 1:40 for propranolol). Because volume of distribution for most beta-blockers generally exceeds 1 L/kg, hemodialysis is not efficacious for most beta-blockers. Protein binding varies from 0% for sotalol to 93% for propranolol. Elimination half-lives vary from 8 to 9 minutes for esmolol to as long as 24 hours for nadolol and others (see Table 152-3).

www.ketabpezeshki.com 66485457-66963820

Table 152-3 Selected Characteristics of Common Beta-Blockers

	V_d (L/kg)	ISA	ELIMINATION HALF-LIFE (hr)	LIPOPHILIC	PROTEIN BINDING (%)	MSE	COMMENTS
Nonselective Beta-Blockers							
Propranolol	4	0	4	+	93	+	Most fatalities
Nadolol	1.9	0	10-20	0	20	0	Dialyzable
Timolol	1.4-3.5	0	3-5	+	10	0	Dialyzable
Pindolol	3-6	+	3-4	+	51	+	
Labetalol	10	0	4-6	0	50	+	Alpha-blockade also
Oxprenolol	1.3	+	2	+	78	+	
Sotalol	1.6-2.4	0	7-18	+	0	0	Class III and class II antidysrhythmic; torsades de pointes; dialyzable
Carvedilol	1.5-2	0	6-10	+	95	0	
Selective Beta-Blockers							
Metoprolol	5.5	0	3-4	+	12	0	
Atenolol	0.7	0	5-8	0	5	0	Dialyzable
Esmolol	2	0	0.13	0	55	0	
Acebutolol	1.2	+	2-4	+	26	+	QT prolongation, VT, dialyzable
Practolol	1.6	+	10-11	+		0	
Bisoprolol	2.9	0	10-12	0	30	0	
Betaxolol	5-13	0	12-22	0	55	0	

ISA, intrinsic sympathomimetic activity; *MSE,* membrane-stabilizing effect; *VT,* ventricular tachycardia.

Box 152-8 Manifestations and Complications of Beta-Blocker Overdose in Order of Decreasing Frequency*

1. Bradycardia (65/90 cases)
2. Hypotension (64/90)
3. Unconsciousness (50/90)
4. Respiratory arrest or insufficiency (34/90)
5. Hypoglycemia (uncommon in adults)
6. Seizures (common only with propranolol, 16/90)
7. Symptomatic bronchospasm (uncommon)
8. VT or VF (6/90)
9. Mild hyperkalemia (uncommon)
10. Hepatotoxicity, mesenteric ischemia, renal failure (rare or single case reports)

VF, ventricular fibrillation; *VT,* ventricular tachycardia.
*Intoxication with beta-sympatholytics.

Clinical Features

The most common initial sign remains bradycardia, which should suggest the possibility of cardiac drug overdose. Hypotension and unconsciousness are the second and third most common signs (Box 152-8). Much of propranolol's unique toxicity derives from its lipophilic nature, which allows it to penetrate the CNS, causing obtundation, respiratory depression, and seizures. Seizures probably result from a combination of hypotension, hypoglycemia, hypoxia, and direct CNS toxicity. Other beta-blockers are not lipophilic and do not have these effects. Surprisingly, bronchospasm is rarely a problem in cases of beta-blocker overdose, even with nonselective beta-blockers. The few cases of symptomatic bronchospasm respond to the usual bronchodilator nebulizations.

Propranolol, nadolol, betaxolol, and acebutolol have a membrane-stabilizing effect that impairs SA and AV node function and leads to bradycardia and AV block. Ventricular conduction is also depressed, leading to QRS widening, occasional ventricular dysrhythmias such as ventricular tachycardia and ventricular fibrillation, and cardiogenic shock. The intrinsic sympathomimetic activity of some beta-blockers, such as pindolol, oxprenolol, acebutolol, and carteolol, can lead to some unusual manifestations, such as ventricular dysrhythmias and sinus tachycardia instead of bradycardia. Labetalol and carvedilol also block $alpha_1$-adrenergic receptors, giving an additional mechanism for hypotension and distributive shock. However, labetalol's beta-blockade is three (oral route) to seven (intravenous route) times more potent than its alpha-blockade. Nebivolol is a cardioselective beta-adrenergic blocker that also causes vasodilation through a unique mechanism: induction of endothelium-dependent vasodilation by stimulation of nitric oxide bioactivity.

In contrast to digitalis, beta-blocker toxicity has a more rapid onset; life-threatening CNS and cardiovascular effects can occur 30 minutes after oral overdose. Patients ingesting delayed-release preparations may remain asymptomatic for several hours, affording a valuable therapeutic window.

Diagnostic Strategies

Diagnosis and management depend entirely on the clinical picture. Blood levels of beta-blockers correlate poorly with severity of intoxication and are not readily available. Most urine toxicology screens do not identify antidysrhythmic drugs and are not helpful.[29] Hypoglycemia is common in children, and bedside determination of glucose concentration should be done if CNS depression is noted. Known access of the patient to a beta-blocker and consistent clinical features such as obtundation, seizures, hypotension, bradydysrhythmias, and occasionally tachydysrhythmias should lead the clinician to consider beta-blocker intoxication. Whereas some authors believe that a serum lactate concentration can help predict mortality in overdose patients,[30] this has not held true in pure beta-blocker ingestions.[31]

www.ketabpezeshki.com 66485457-66963820

Differential Considerations

The combination of bradycardia and hypotension suggests beta-blockade or calcium channel blockade. Centrally acting $alpha_2$-adrenergic agonists, such as clonidine and tizanidine, or imidazolines, such as tetrahydrozoline and oxymetazoline, may also cause this constellation of symptoms. Without a history of beta-blocker ingestion, the diagnosis can be challenging, especially when noncardiac effects such as CNS depression and seizures predominate. Sodium channel poisoning with QRS widening can occur, suggesting other antidysrhythmic drugs or cyclic antidepressants. The differential diagnosis also includes sedative-hypnotic drug overdose, hypoglycemic drug ingestion, opiate overdose, CNS injury or infection, endocrine-metabolic disorder, sepsis, and acute myocardial infarction.

Management

Immediate measures include intravenous fluids, supplemental oxygen, and monitoring of cardiac rhythm and respirations. Activated charcoal has been used in the first hour after overdoses as a theoretic but unproven treatment, but theoretic advantages should be weighed against the very real risk of aspiration if obtundation or seizure ensues. Management of dysrhythmias and hypotension should not be delayed by administration of charcoal. Evidence for improved outcome is also lacking, but whole-bowel irrigation has been commonly used for sustained-release preparations with a polyethylene glycol solution (GoLYTELY), administered orally or by nasogastric tube at 2 L/hr in adults or 20 mL/kg initially in children. Again, risks and benefits make a clear recommendation impossible. Gastric lavage also carries procedural risks, and yet morbidity and mortality from beta-blockers are high and consideration of lavage in patients who present within 1 hour of ingestion is reasonable. With currently available evidence, gastric decontamination by activated charcoal, whole-bowel irrigation, or gastric lavage can neither be recommended nor criticized. Onset of toxicity is so uniformly early that absence of symptoms 4 hours after ingestion implies a low risk for subsequent morbidity unless a delayed-release preparation is involved.

Hypotension, Bradycardia, and Atrioventricular Block

The first step in the treatment of beta-blocker overdose is bolus administration of crystalloid fluids. In hypotensive patients, 20 to 40 mL/kg of normal saline or lactated Ringer's solution can be infused and repeated. Atropine at standard doses may be used for bradycardia but is rarely effective. Infusion of more potent drugs or cardiac pacing is usually necessary. Atropine should be given before vagal stimuli, such as tracheal or gastric intubation. Early placement of a central venous catheter may be prudent as these patients frequently require central venous pressure monitoring, additional intravenous access, and administration of medications necessitating central access.

Calcium

Because the final common pathway for stimulation of adrenergic receptors is an increase in intracellular calcium concentration and deleterious effects on calcium transport may contribute to beta-blocker toxicity, intravenous administration of calcium has been suggested for treatment of hypotension. One gram of calcium gluconate contains 4.5 mEq of elemental calcium, whereas 1 g of calcium chloride contains 13.6 mEq of elemental calcium. Calcium chloride is an acidifying salt and can cause significant tissue damage and necrosis if extravasation occurs. Thus it should be administered through a central venous catheter or a secure large-bore antecubital peripheral line. Indications for calcium include hypotension and bradycardia. We recommend an initial dose of 13 to 25 mEq of calcium in adults (1-2 g calcium chloride, 3-6 g calcium gluconate) during 10 minutes. Patients in extremis may receive the initial dose during 1 minute. If a response is observed, repeated doses may be given every 20 minutes, or a constant infusion may be started at 0.5 mEq/kg/hr. It is prudent to raise the total serum calcium level no higher than 14 mg/dL, which the endocrine and oncology literature defines as the threshold of "severe" hypercalcemia; if ionized calcium is measured, we recommend not to exceed twice-normal levels. Children can receive 0.15 to 0.3 mEq/kg of calcium IV initially (10 to 30 mg/kg [0.1-0.3 mL/kg]) of 10% calcium chloride or 30-60 mg/kg calcium gluconate). The serum calcium level can be as high as 18.2 mg/dL within 15 minutes after a bolus of just 5 mL of 10% calcium chloride, so levels should be measured later during the constant infusion.

Glucagon

Because glucagon has both inotropic and chronotropic effects and does not depend on beta receptors for its action, it has long been used for beta-blocker toxicity. It stimulates the production of intracellular cyclic adenosine monophosphate independently of the beta-adrenergic receptor.[32] Furthermore, it helps counteract the hypoglycemia induced by beta-blocker overdose. The dosing of glucagon is not well studied, but the drug is frequently used as a 5- to 10-mg IV bolus (0.05-0.1 mg/kg for children). If a response occurs to glucagon, the "response dose" should be started as an infusion at a rate of response dose during 1 hour. Glucagon has a very short (20-minute) half-life, and unfortunately its effect is often transient. Vomiting is a common complication of glucagon, so the airway should be secured or monitored closely to prevent aspiration. With cumulative large doses, glucagon should be diluted in 5% glucose in water for constant infusion. Side effects also include hypokalemia and allergic reactions. The response to glucagon alone is often inadequate, and glucagon is likely to be less effective than high-dose insulin.[33] Furthermore, hospitals may not be adequately stocked for treatment beyond a few hours.[34] From clinical experience, we find glucagon most useful as a transient therapy to bridge patients to high-dose insulin.

High-Dose Insulin

Despite glucagon's longer history for treatment of beta-blocker toxicity, high-dose insulin (HDI) is probably a better agent. HDI is not a vasopressor; it is a profound inotrope[35] with vasodilating properties.[36,37] The mechanism for HDI is not fully known, but it probably involves both optimization of the use of carbohydrates for fuel by cardiac myocytes and modulation of intracellular calcium.[38] HDI improves cardiac output significantly in beta-blocker toxicity from an increase in stroke volume more than heart rate. Dosing of HDI is not agreed on; dosing in humans successfully treated with HDI has ranged from 0.5 to 21.8 U/kg/hr.[39] In the largest human case series to date of patients receiving HDI for poison-induced cardiogenic shock, 11 of 12 patients survived; the only death occurred when HDI was terminated early because of a protocol violation.[40] Mean maximal HDI dosing in this series was 8.7 U/kg/hr. Previous recommendations for dosing of HDI were a bolus of 1 U/kg of regular insulin IV, followed by a drip at 1 U/kg/hr.[40] On the basis of animal data,[41] some authors start HDI at 10 U/kg/hr in severely toxic patients with the belief that the glucose use from insulin saturates before the inotropic effect. Regardless of HDI dosing, patients should receive a bolus of dextrose before insulin and a dextrose infusion should be started thereafter, such as a bolus of 25 g glucose (1 traditional "amp" of D50) if the serum glucose concentration is below 200 mg/dL

www.ketabpezeshki.com 66485457-66963820

(11.1 mmol/L), followed by concentrated dextrose solutions (such as D25, D50, or even D70) through a central line because patients receiving HDI therapy are at risk of fluid overload. Glucose concentration should be monitored as frequently as every 10 minutes until a steady state of glucose use is achieved. Potassium concentration should also be monitored closely and potassium replaced as needed because patients may become hypokalemic.[40]

Sodium Bicarbonate

Sodium channel blockade from beta-blockers with membrane-stabilizing activity, such as propranolol, occasionally causes QRS widening, which should respond to sodium bicarbonate. Bicarbonate should be dosed at 1 to 2 mmol/kg IV as a bolus repeated every 3 to 5 minutes until the QRS narrows.

Vasopressors and Other Inotropes

If hypotension or bradycardia persists, other cardioactive drugs are indicated. The use of vasopressors is not without risk; HDI is probably safer.[37] Vasopressors may be useful to transiently maintain mean arterial pressure (MAP) high enough to ensure adequate cerebral perfusion pressure (CPP). A MAP of 65 mm Hg is often quoted as the minimum MAP required to ensure adequate CPP.[42] If the patient is not intubated and has a normal mental status, lower MAP readings are probably adequate. The more difficult situation of an intubated patient with a MAP slightly below 65 mm Hg represents a clinical dilemma. It is our practice to accept an MAP of 60 mm Hg if all other signs point to adequate organ perfusion.

A single drug of choice after HDI and glucagon has not emerged, but some clinicians favor isoproterenol (isoprenaline in Europe), dopamine, or epinephrine.[28] Other catecholamines that have been successfully used include norepinephrine, dobutamine, and phenylephrine. Often, norepinephrine or dopamine is added to beta-agonists such as isoproterenol that lack vasopressor activity. In the selection of cardioactive medications to supplement HDI and glucagon, we recommend early assessment of systemic vascular resistance and cardiac output by either indirect measurements with a pulse contour analysis–based hemodynamic monitoring tool such as the FloTrac device (Edwards Lifesciences; Irvine, Calif.) or Swan-Ganz catheter and choosing of appropriate drugs if either cardiogenic (inotropic drugs such as norepinephrine, dobutamine, dopamine) or distributive shock (pressors such as norepinephrine, phenylephrine, vasopressin) exists. Refractory cases of bradycardia may respond to an external or transvenous pacemaker. A pacemaker is particularly useful when the heart rate is the predominant cause of decreased cardiac output.

Intravenous Fat Emulsion (Intralipid)

Intravenous fat emulsion (IFE) is a promising new therapy for poison-induced cardiogenic shock. This therapy was first described for treatment of toxicity from local anesthetics such as bupivacaine.[43] IFE is proposed to work by three separate mechanisms: (1) the lipid sink, (2) modulation of intracellular metabolism, and (3) activation of ion channels.[44] The lipid sink theory posits that fat-soluble drugs are soaked up and removed from the site of toxicity, effectively increasing the volume of distribution for a fat-soluble drug. This is the predominant theory behind the use of IFE. A second theory involves optimization of cardiac metabolism. The heart under physiologic circumstances prefers free fatty acids; in times of stress it switches to glucose metabolism for energy. A dose of IFE theoretically provides a large supply of free fatty acids to optimize energy use in the heart. The final proposed mechanism involves direct activation of cardiac calcium channels. Animal evidence exists to support the use of IFE for both lipid-soluble beta-blockers (such as propranolol)[45] and non–lipid-soluble beta-blockers (such as atenolol).[46] Dramatic human case reports of successful resuscitations exist for propranolol,[47] nebivolol,[39] and metoprolol.[48] Although IFE was originally indicated for patients in cardiac arrest only, in 2011 the American College of Medical Toxicology released a position statement stating that "in circumstances where there is serious hemodynamic, or other, instability from a xenobiotic with a high degree of lipid solubility, lipid resuscitation therapy (IFE) is viewed as a reasonable consideration for therapy, even if the patient is not in cardiac arrest."[49] Dosing for IFE is not agreed on. We recommend an initial bolus of 1.5 mL/kg of 20% lipid solution given during 2 to 3 minutes, followed immediately by an infusion of 0.25 mL/kg/min.[49] The bolus can be repeated up to two additional times for refractory patients. Response is typically within minutes of the bolus. We use IFE in patients with persistent bradycardia or hypotension not responding to intravenous fluids, calcium, and HDI.

Ventricular Dysrhythmias

Although it is uncharacteristic, ventricular tachydysrhythmias do occur sometimes. Cardioversion and defibrillation are indicated for ventricular tachycardia and ventricular fibrillation, respectively, following American Heart Association guidelines. Pulsatile ventricular tachycardia or frequent ventricular ectopy can most safely be treated with lidocaine. Other antidysrhythmic drugs, especially of classes IA and IC, should be avoided; they may potentiate AV block or be prodysrhythmic because of an additive membrane-stabilizing effect. Sotalol, unlike other beta-blockers, has class III as well as class II effects; that is, it prolongs the QT interval and can cause torsades de pointes and other ventricular dysrhythmias. Overdrive pacing with isoproterenol or a pacemaker and magnesium sulfate are specific therapies for torsades de pointes.

Extracorporeal Elimination and Circulatory Assistance

Hemodialysis or hemoperfusion may be beneficial for atenolol, acebutolol, nadolol, sotalol, and timolol, the beta-blockers with lower V_d, lower protein binding, and greater hydrophilicity.[50]

Unlike overdoses of acetaminophen and iron, overdoses of cardiovascular drugs do not destroy tissue, and if circulation can be supported, complete recovery can be expected. An intra-aortic balloon pump or cardiopulmonary bypass can be lifesaving in cases of refractory hypotension.[51,52] A percutaneous left ventricular assist device, although it has not been studied in beta-blocker toxicity, may also be useful. The relatively short half-lives (hours rather than days) of beta-blocking and calcium-blocking drugs fall within the temporal range of such interventions. To be successful, such heroic measures should be taken before prolonged hypotension leads to multiorgan ischemic injury (Box 152-9). Because most patients recover with just supportive care, these expensive and invasive interventions should be reserved for drugs and circumstances, such as propranolol, verapamil, and mixed cardiotoxic overdoses, that are associated with higher rates of mortality.

Pediatric Considerations

Severe pediatric beta-blocker poisonings are rare. In the cases reported, CNS, cardiac, and metabolic toxicities are similar.[53] Symptomatic hypoglycemia, however, is much more common in children and occurs even after therapeutic doses. Therefore, serum glucose concentration should be measured in children. Risk factors include young age, fasting state, and diabetes mellitus. Obtunded children should receive empirical glucose, 1 to 2 mL/

www.ketabpezeshki.com 66485457-66963820

Box 152-9 Treatment of Beta-Blocker Poisoning

Phase 1 (Resuscitation)
Boluses of intravenous isotonic fluids, calcium, atropine, glucagon

Phase 2 (Stabilization)
Infusions of
- High-dose insulin/glucose
- Glucagon
- Catecholamines (epinephrine, norepinephrine, isoproterenol, dobutamine, dopamine, metaraminol)
- Phosphodiesterase inhibitors (amrinone)

Early cardiac pacing if no prompt response to chronotropic or dromotropic drugs
Peripheral arterial and pulmonary artery catheter monitoring if refractory hypotension
Consider hemodialysis of hydrophilic beta-blockers with low protein binding and low V_d

Phase 3 (Salvage Therapies)
Intravenous fat emulsion (e.g., Intralipid)
Intra-aortic balloon counterpulsation
Consider percutaneous left ventricular assist device or cardiac bypass

kg of 25% glucose IV. In general, 5% glucose infusions have been sufficient to maintain euglycemia, especially with concomitant use of glucagon and catecholamines, which stimulate glucose release. Because glycogen mobilization is a $beta_2$ effect, hypoglycemia may be less common with the cardioselective ($beta_1$) blockers.

Seizures also occur in cases of pediatric beta-blocker overdose, but hypoglycemia is probably an important contributing factor. They are more common with the lipid-soluble beta-blockers propranolol and oxprenolol. Benzodiazepines are generally effective.

Children generally fare well after beta-blocker ingestion, with symptoms in only 8 of 378 (2%) potential beta-blocker exposures in children.[50]

Disposition

Patients who remain completely asymptomatic for 6 hours after an oral overdose of normal-release preparations can be safely referred for psychiatric evaluation, with medical consultation for the first 24 hours. Patients ingesting sustained-release preparations should be admitted to a monitored bed, but those who remain asymptomatic 8 hours after ingestion are very unlikely to have toxicity. Those who have been hypotensive, who have more than first-degree heart block, or who have hemodynamically significant dysrhythmias should be admitted to an intensive care unit.

CALCIUM CHANNEL BLOCKERS

Perspective

Verapamil and nifedipine, the earliest calcium channel antagonists, were introduced in Europe in the 1970s and in the United States in the early 1980s. Calcium antagonists have found many clinical applications: angina pectoris, hypertension, supraventricular dysrhythmias, hypertrophic cardiomyopathy, and migraine prophylaxis. Most fatalities occur with verapamil, but severe toxicity and death have been reported for most drugs of this class. In 2010, U.S. Poison Control Centers received more than 10,000 calls about calcium channel blockers.[1]

Pathophysiology

Calcium channel antagonists block the slow L-type calcium channels in the myocardium and vascular smooth muscle, leading to coronary and peripheral vasodilation. They also reduce cardiac contractility, depress SA nodal activity, and slow AV conduction. In cases of overdose, verapamil has the deadliest profile, combining severe myocardial depression and peripheral vasodilation. Both verapamil and diltiazem act on the heart and blood vessels, whereas dihydropyridines such as nifedipine cause primarily vasodilation and subsequent reflex tachycardia. As with beta-blockers, selectivity is lost after overdose, and toxicity is fourfold; the calcium antagonists have negative effects on heart rate, contractility, conduction, and vascular tone, with the exception of dihydropyridines, which tend to result in tachycardia even in severe toxicity.[54]

All calcium channel blockers are rapidly absorbed, although first-pass hepatic metabolism significantly reduces bioavailability (Table 152-4). Onset of action and toxicity ranges from less than 30 minutes to 60 minutes. Peak effect of nifedipine can occur as early as 20 minutes after ingestion, but peak effect of sustained-release verapamil can be delayed for many hours. High protein binding and V_d greater than 1 to 2 L/kg make hemodialysis or hemoperfusion ineffective. Fortunately (except with sustained-release preparations), their half-lives are relatively short, limiting toxicity to 24 to 36 hours.

Clinical Features

Severe calcium antagonism eventually affects multiple organ systems, but cardiovascular toxicity is primarily responsible for morbidity and mortality. Hypotension and bradycardia occur early, and other rhythm disturbances include AV block of all degrees, sinus arrest, AV dissociation, junctional rhythm, and asystole. Dihydropyridines, such as nifedipine, often cause reflex sinus tachycardia from peripheral vasodilation. Calcium channel blockade has little effect on ventricular conduction, so QRS widening is not seen early on. Ventricular dysrhythmias are also uncommon.

Diagnostic Strategies

Serum levels of calcium antagonists are not readily available, nor do urine toxicology screens reliably detect this class of drugs. Glucose and electrolytes (including calcium and magnesium) should be measured. Hyperglycemia secondary to insulin inhibition occurs occasionally, but the elevation is usually mild (150-300 mg/L), is usually short-lived (<24 hours), and generally requires no treatment. Some authors suggest that hyperglycemia is a predictor of poor outcomes in verapamil and diltiazem toxicity.[55] A metabolic (lactic) acidosis occurs with hypotension and hypoperfusion.

An electrocardiogram should be promptly obtained, with special attention to atrial and ventricular rates and PR, QRS, and QT intervals.

Differential Considerations

Differential diagnosis is similar to that of beta-blocker cases. Until characteristic rhythm disturbances supervene, many other toxic, metabolic, traumatic, and cardiovascular disorders can cause hypotension but less commonly cause bradycardia. Like the beta-blockers, calcium antagonists cause early toxicity, and symptoms can be expected within 6 hours of ingestion of normal-release preparations. Toxicity can be delayed 12 to 24 hours with sustained-release preparations.

As with beta-blockade, CNS depressive effects are common and include lethargy, confusion, and coma. Unlike beta-blockers,

www.ketabpezeshki.com 66485457-66963820

Table 152-4 Selected Characteristics of Some Calcium Channel Blockers

	V_d (L/kg)	HALF-Life (hr)	PROTEIN BINDING (%)	COMMENTS
Verapamil	4	3-12	90	Most fatalities; impairs contractility and cardiac conduction more than most other calcium antagonists
Diltiazem	1.7-5.3	3-7.9	70-80	Suppression of atrioventricular node similar to verapamil; myocardial depression otherwise less
Nifedipine	1.4-2.2	1-5	92-98	Vasodilation greatest effect
Nicardipine	0.64	8-9	95	Vasodilation
Nimodipine	0.94-2.3	1-2	95	Vasodilation
Amlodipine	21	30-50	98	Vasodilation
Bepridil	8	33-42	99	Class I as well as class IV antidysrhythmic; prolongs QT: torsades de pointes
Felodipine	10	10	99	Vasodilation
Isradipine	3	1.9-16	95	Vasodilation
Nisoldipine	4-5	7-12	99	Vasodilation

Box 152-10 Manifestations of Calcium Channel Blocker Poisoning

Cardiovascular: Hypotension, sinus bradycardia, sinus arrest, AV block, AV dissociation, junctional rhythm, asystole; ventricular dysrhythmias uncommon except with bepridil
Pulmonary: Respiratory depression, apnea; pulmonary edema; adult respiratory distress syndrome
Gastrointestinal: Nausea, vomiting, bowel infarction (rare)
Neurologic: Lethargy, confusion, slurred speech, coma; seizures (uncommon); cerebral infarction (rare)
Metabolic: Metabolic (lactic) acidosis; hyperglycemia (mild); hyperkalemia (mild)
Dermatologic: Flushing, diaphoresis, pallor, peripheral cyanosis

AV, atrioventricular.

calcium antagonists seldom induce seizures. Pulmonary effects include noncardiogenic pulmonary edema, and apnea can also occur. As with digitalis and beta-blocker overdose, nausea and vomiting are common (Box 152-10).

Management

Initial management includes rapid establishment of vascular access, supplemental oxygen, cardiac monitoring, and frequent blood pressure measurement. Gastrointestinal decontamination is controversial. For this class of highly lethal overdoses, activated charcoal at 1 g/kg can be considered if the airway is secure and if the patient presents in less than 1 or 2 hours. Multidose activated charcoal can be considered for sustained-release preparations and if a bezoar is suspected. Some authors have argued against the use of whole-bowel irrigation[56]; however, calcium channel blockers cause significant morbidity and mortality, and risks should be weighed against potential benefits. Gastric lavage may be considered for patients presenting early, but pills are often large, and safe performance of this procedure requires a secure airway. No evidence exists that gastrointestinal decontamination improves mortality in general overdoses or in calcium channel blocker toxicity. With the lack of currently available evidence, gastric decontamination can neither be recommended nor criticized and has its proponents and detractors.

Hypotension and Bradycardia

Hypotension can be caused by myocardial depression, inadequate heart rate, or peripheral vasodilation. Atropine can be administered in the standard doses. Atropine's effect has often been disappointing and short-lived, and multiple doses risk anticholinergic poisoning. A bolus of crystalloid fluid (20-40 mL/kg or more) should also be infused early. Intravenous calcium salts have traditionally been given to most patients. Their effect on contractility is considerable, but their effect on bradycardia, AV block, and peripheral vasodilation is often poor. The optimal dose of calcium is unknown. See the earlier discussion of calcium in the section on beta-blockers for our dosing recommendations. Adverse effects of hypercalcemia include lethargy, coma, anorexia, nausea, vomiting, pancreatitis, polyuria, dehydration, and nephrocalcinosis. Most of these effects have been reported after weeks or months of hypercalcemia from malignant disease or hyperparathyroidism. It is doubtful that hours or days of acutely induced hypercalcemia would be detrimental in the setting of massive calcium channel blockade. However, with *rapid* intravenous injection in animals and humans, bradycardia, AV block, AV dissociation, junctional tachycardia, ventricular ectopy, and ventricular fibrillation have been reported.

As with beta-blocker poisoning, a monotherapeutic approach will probably succeed only for trivial overdoses. If patients treated with isotonic fluids, calcium, and atropine have persistent hypotension or bradycardia, we next recommend HDI. HDI is thought to act by improving myocardial carbohydrate metabolism, thereby augmenting myocardial contraction. Serum glucose and potassium levels should be checked frequently to ensure that normal levels are maintained, although transient hyperglycemia is acceptable. Enthusiasm for HDI treatment is growing, and this therapy may prove safer and more efficacious than vasopressors.[57] See the earlier discussion for our dosing recommendations.

Most severely poisoned patients require the addition of catecholamines to accelerate the heart rate (chronotropy), to enhance AV conduction (dromotropy), and to restore tone to peripheral vessels (vasotropy). As with beta-blocker toxicity, in the selection of cardioactive medications to supplement HDI and glucagon, we recommend early assessment of systemic vascular resistance and cardiac output by either indirect measurements with a pulse contour analysis–based hemodynamic monitoring tool such as the FloTrac device (Edwards Lifesciences) or Swan-Ganz catheter and choosing of appropriate drugs for cardiogenic (epinephrine, norepinephrine, dopamine, dobutamine) or distributive shock (phenylephrine, vasopressin). Dosing of catecholamines in calcium channel blocker toxicity is not different from that in other clinical situations requiring their use. As long as dysrhythmias are not induced, catecholamine infusions should be aggressively titrated to effect (Box 152-11).

www.ketabpezeshki.com 66485457-66963820

Box 152-11 Treatment of Calcium Channel Blocker Intoxication

Phase 1 (Resuscitation)
Boluses of intravenous isotonic fluids, calcium, atropine

Phase 2 (Stabilization)
Calcium infusion
High-dose insulin/glucose infusion
Catecholamine infusions
Transcutaneous or transvenous cardiac pacing
Invasive monitoring

Phase 3 (Salvage Therapies)
Intravenous fat emulsion (e.g., Intralipid)
Intra-aortic balloon counterpulsation
Consider percutaneous left ventricular assist device or cardiac bypass

Glucagon has also been used for its inotropic and chronotropic effects in doses similar to those advocated for beta-blocker poisoning. Anecdotal human cases exist of calcium channel blocker poisonings responding to glucagon.[58] No controlled human studies exist. It is our practice to omit the use of glucagon in the treatment of calcium channel blocker toxicity.

IFE (e.g., Intralipid) has been described in the use of calcium channel blockers. The proposed mechanisms are discussed earlier. Animal evidence exists that IFE may be effective especially for the treatment of verapamil toxicity.[59] Dramatic human case reports exist of successful resuscitation of toxicity from diltiazem[48] and verapamil.[60] Dosing and indications are identical to those for beta-blocker toxicity.

Pediatric Considerations

Nifedipine and probably other drugs in its class join the short list of medications that can kill a child with ingestion of a single tablet.[61] Seizures may be more common in children than in adults and should be treated with diazepam, lorazepam, or calcium.

Overall, death after calcium antagonist ingestion in children is rare. The intravenous route of administration, as with digitalis, is much more dangerous. Even therapeutic doses of intravenous verapamil are considered contraindicated in infants with supraventricular tachycardia because of case reports of cardiovascular collapse and cardiac arrest after injection.[62]

Hyperglycemia occasionally occurs in children, but the elevation is usually short-lived. Although insulin has been administered in a handful of cases, it is generally not necessary unless HDI is being used therapeutically because the hyperglycemia usually resolves spontaneously within 24 to 36 hours.

A small number of children in refractory shock secondary to drug toxicity have been treated with intra-aortic balloon counterpulsation or cardiac bypass. Circulatory support during the day or two required for hepatic or renal elimination of the drug is potentially beneficial for a drug that does not cause irreversible damage. Aside from the differences previously noted, the presentation in children is similar to that in adults: rapid onset of toxicity with CNS depression, bradydysrhythmias, hypotension, and metabolic acidosis.

Disposition

Because the peak effect of normal-release calcium channel blockers commonly occurs in 90 minutes to 6 hours, patients who are totally asymptomatic for 6 hours after an ingestion of immediate-release medication can be safely discharged according to psychiatric needs. Symptomatic patients or those who ingested delayed-release preparations should be admitted to a medical or toxicology service for at least 24 hours of continuous cardiac monitoring.

NITRATES AND NITRITES

Nitrates (nitroglycerin, isosorbide mononitrate and dinitrate) are widely used as vasodilators in the treatment of heart failure and ischemic heart disease. They augment coronary blood flow as well as reduce myocardial oxygen consumption by reducing afterload. At lower doses nitrates primarily dilate veins, but at higher doses they also dilate arteries. Hypotension is a common complication but usually responds to supine positioning, intravenous fluids, and reduction of dose. Hypotension is usually transient. Low-dose pressors are occasionally needed, but it is best to avoid them in the setting of acute coronary syndromes.

Intravenous nitroglycerin infusions are being used commonly in patients with acute pulmonary edema for afterload reduction. Infusions are usually initiated at 5 to 10 μg/min, but rates as high as 200 to 300 μg/min may be used. These doses may be beneficial in patients with pulmonary edema accompanied by acute hypertension, but hypotension may develop suddenly. Intravenous nitroglycerin has a rapid offset of action, so excessive fall in blood pressure usually responds to reduction or termination of the infusion. Use of nitrates is contraindicated in patients who have recently taken sildenafil (Viagra). Sildenafil and related drugs (vardenafil [Levitra] and tadalafil [Cialis]) inhibit type 5 phosphodiesterase, relaxing vascular smooth muscle. These agents can prolong and intensify the vasodilating effects of nitrates, resulting in severe hypotension. If blood pressure does not rise with intravenous fluids, dopamine should be cautiously titrated, beginning at 5 μg/kg/min.

Nitrates are occasionally found in rural well water contaminated by livestock or fertilizer runoff. Oral nitrates may be converted to nitrites in the gastrointestinal tract, especially in infants, whose hemoglobin is also more susceptible to oxidation. However, most exposures are encountered in young adults, usually male, who inhale various alkyl nitrites (amyl, butyl, isobutyl, or ethyl nitrite) in the hope of enhancing or prolonging sexual pleasure. Because of the sound they make when broken open, these products are best known to abusers as poppers. The popularity of poppers has waned in recent years as sales of sildenafil and related products have soared. Nitrites and nitrates are both potent vasodilators, and excessive use can cause headache, skin flushing, and orthostatic hypotension. Nitrites are also oxidizing agents that convert hemoglobin to methemoglobin, impairing oxygen delivery. Although most exposure is by inhalation, unintentional ingestion may occur because nitrites are also used legitimately as food preservatives. A family of five had methemoglobinemia after consuming a meal seasoned with sodium nitrite mislabeled as table salt.[63]

Patients with glucose-6-phosphate dehydrogenase deficiency are especially susceptible to the oxidative stress of nitrite exposure, and they may even have hemolysis. When methemoglobin levels exceed 15%, a venous blood sample appears chocolate brown, and the skin appears blue even while patients look remarkably comfortable. Unlike in most cases of cyanosis, supplemental oxygen does not improve the patient's color. Pulse oximetry is not reliable, and the partial pressure of oxygen remains normal in mild to moderate cases. This rare complication can be treated with intravenous administration of methylene blue, but this antidote is usually not needed unless methemoglobinemia approaches 30% or the patient has clinical signs of distress, such as tachypnea, tachycardia, acidosis, and hypotension. The usual dose of methylene blue in adults is 1 to 2 mg IV during 5 minutes.

www.ketabpezeshki.com 66485457-66963820

KEY CONCEPTS

Digitalis

- Consider digoxin intoxication in any patient with gastrointestinal or visual disturbance and a new dysrhythmia or conduction disturbance.
- Dose digitalis Fab antibody fragments by body load of digitalis, not by body weight of the patient.
- Use digitalis Fab fragments before pacing or other antidysrhythmic drugs.
- Hyperkalemia in digitalis toxicity is best treated with Fab fragments. Conventional treatment with sodium bicarbonate, insulin, and glucose as well as with calcium is also appropriate, especially when Fab fragment preparations are not immediately available.

Beta-Adrenergic Blockers

- Beta-blocker intoxication usually causes bradydysrhythmias and occasionally AV block.
- Noncardiac symptoms such as obtundation, seizures, and hypoglycemia may predominate, especially early in the course and particularly with propranolol.
- Volume expansion, atropine, calcium, and glucagon are early treatment measures, but absent a response, begin a high-dose insulin/glucose infusion.

Calcium Channel Blockers

- Signs and symptoms of calcium channel blocker intoxication occur early after overdose.
- CNS depression is common; seizures are not.
- AV block and bradydysrhythmias predominate, except with bepridil.
- Volume expansion, calcium, and vasopressors have been the mainstays of treatment, but high-dose insulin/glucose infusion probably offers the most therapeutic benefit in cases of severe intoxication.

Nitrates and Nitrites

- Hypotension and methemoglobinemia are common presentations.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Bronstein AC, et al: 2010 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 27th Annual Report. *Clin Toxicol (Phila)* 2011; 49:910-941.
2. Hollman A: Drugs for atrial fibrillation. Digoxin comes from *Digitalis lanata*. *BMJ* 1996; 312:912.
3. Withering W: An account of the foxglove and some of its medical uses: With practical remarks on dropsy and other diseases. *Med Classics* 1937; 2:295-443.
4. Rush B: *Medical Enquiries and Observations*. Philadelphia: T Dobson; 1797.
5. Reza MJ, Kovick RB, Shine KI, Pearce ML: Massive intravenous digoxin overdose. *N Engl J Med* 1974; 291:777-778.
6. French JH, Thomas RG, Siskind AP, Brodsky M, Iseri LT: Magnesium therapy in massive digoxin intoxication. *Ann Emerg Med* 1984; 13:562-566.
7. Wells TG, Young RA, Kearns GL: Age-related differences in digoxin toxicity and its treatment. *Drug Saf* 1992; 7:135-151.
8. Ordog GJ, Benaron S, Bhasin V, Wasserberger J, Balasubramanium S: Serum digoxin levels and mortality in 5,100 patients. *Ann Emerg Med* 1987; 16:32-39.
9. Lewander WJ, et al: Acute pediatric digoxin ingestion: A ten-year experience. *Am J Dis Child* 1986; 140:770-773.
10. Rahimtoola SH: Digitalis therapy for patients in clinical heart failure. *Circulation* 2004; 109:2942-2946.
11. Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM: Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* 2003; 289:871-878.
12. Smith TW, Haber E: Digoxin intoxication: The relationship of clinical presentation to serum digoxin concentration. *J Clin Invest* 1970; 49:2377-2386.
13. Piergies AA, Worwag EM, Atkinson AJ: Pharmacoepidemiology and drug utilization: A concurrent audit of high digoxin levels. *Clin Pharmacol Ther* 1994; 55:353-358.
14. Antman EM, Wenger TL, Bulter VP Jr, Haber E, Smith TW: Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments: Final report of a multicenter study. *Circulation* 1990; 81:1744-1752.
15. Hickey AR, et al: Digoxin immune Fab therapy in the management of digitalis intoxication: Safety and efficacy results of an observational surveillance study. *J Am Coll Cardiol* 1991; 17:590-598.
16. Weinstein RS, Cole S, Knaster HB, Dahlbert T: Beta-blocker overdose with propranolol and with atenolol. *Ann Emerg Med* 1985; 14:161-163.
17. Louis WJ, McNeil JJ, Drummer OH: Pharmacology of combined alpha-beta blockade I. *Drugs* 1984; 28:16-34.
18. Schaumann W, Kaufmann B, Neubert P, Smolarz A: Kinetics of the Fab fragments of digoxin antibodies and of bound digoxin in patients with severe digoxin intoxication. *Eur J Clin Pharmacol* 1986; 30:527-533.
19. Woolf AD, Wenger T, Smith TW, Lovejoy FH Jr: The use of digoxin-specific Fab fragments for severe digitalis intoxication in children. *N Engl J Med* 1992; 326:1739-1744.
20. Bismuth C, Gaultier M, Conso F, Efthymiou ML: Hyperkalemia in acute digitalis poisoning: Prognostic significance and therapeutic implications. *J Toxicol Clin Toxicol* 1973; 6:153-162.
21. Khatter JC, Agbanyo M, Navaratnam S, Nero B, Hoeschen RJ: Digitalis cardiotoxicity: Cellular calcium overload a possible mechanism. *Basic Res Cardiol* 1989; 84:553-563.
22. Gold H, Edwards DJ: The effects of ouabain on the heart in the presence of hypercalcemia. *Am Heart J* 1927; 3:45-50.
23. Nola GT, Pope S, Harrison DC: Assessment of the synergistic relationship between serum calcium and digitalis. *Am Heart J* 1970; 79:499-507.
24. Bower JO, Mengle HAK: The additive effect of calcium and digitalis. *JAMA* 1936; 106:1151-1153.
25. Levine M, Nikkanen H, Pallin DJ: The effects of intravenous calcium in patients with digoxin toxicity. *J Emerg Med* 2011; 40:41-46.
26. Kinlay S, Buckley NA: Magnesium sulfate in the treatment of ventricular arrhythmias due to digoxin toxicity. *J Toxicol Clin Toxicol* 1995; 33:55-59.
27. Taboulet P, Baud FJ, Bismuth C, Vicaut E: Acute digitalis intoxication—is pacing still appropriate? *J Toxicol Clin Toxicol* 1993; 31:261-273.
28. Hazinski MF, Cummins RO, Field JM, eds: *Handbook of Emergency Cardiovascular Care for Healthcare Providers*. Dallas: American Heart Association; 2002.
29. Maurer HH: Identification of antiarrhythmic drugs and their metabolites in urine. *Arch Toxicol* 1990; 64:218-230.
30. Manini AF, Kumar A, Olsen D, Vlahov D, Hoffman RS: Utility of serum lactate to predict drug-overdose fatality. *Clin Toxicol (Phila)* 2010; 48:730-736.
31. Mégarbane B, Deye N, Malissin I, Baud FJ: Usefulness of the serum lactate concentration for predicting mortality in acute beta-blocker poisoning. *Clin Toxicol (Phila)* 2010; 48:974-978.
32. Bailey B: Glucagon in β-blocker and calcium channel blocker overdoses: A systematic review. *J Toxicol Clin Toxicol* 2003; 41:595-602.
33. Kerns W, Schroeder D, Williams C, Tomaszewski C, Raymond R.: Insulin improves survival in a canine model of acute beta blocker toxicity. *Ann Emerg Med* 1997; 29:748-757.
34. Dart RC, et al: Expert consensus guidelines for stocking of antidotes in hospitals that provide emergency care. *Ann Emerg Med* 2009; 54:386-394.
35. Gradinac S, Coleman GM, Taegtmeyer H, Sweeney MS, Frazier OH: Improved cardiac function with glucose-insulin-potassium after aortocoronary bypass grafting. *Ann Thorac Surg* 1989; 48:484-489.
36. Anderson EA, Hoffman RP, Balon TW, Sinkey CA, Mark AL: Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. *J Clin Invest* 1991; 87:2246-2252.
37. Holger JS, et al: Insulin versus vasopressin and epinephrine to treat beta blocker toxicity. *Clin Toxicol (Phila)* 2007; 45:396-401.
38. Ablorh N-A, Nitu F, Engebretsen KE, Thomas DD, Holger JS: Insulin-dependent rescue from cardiogenic shock is not mediated by phospholamban phosphorylation. *Clin Toxicol (Phila)* 2009; 47:296-302.
39. Stellpflug SJ, Harris CR, Engebretsen KM, Cole JB, Holger JS: Intentional overdose with cardiac arrest treated with intravenous fat emulsion and high-dose insulin. *Clin Toxicol (Phila)* 2010; 48:227-229.
40. Holger JS, Stellpflug SJ, Cole JB, Harris CR, Engebretsen KM: High-dose insulin: A consecutive case series. *Clin Toxicol (Phila)* 2011; 49:653-658.
41. Cole JB, et al: 10 U/kg/hr of high dose insulin is superior to 1 U/kg/hr in a blinded, randomized, controlled trial in poison-induced cardiogenic shock [abstract 1]. *Clin Toxicol (Phila)* 2011; 49:515.
42. Rivers E, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368-1377.
43. Rosenblatt MA, Abel M, Fischer GW, Itzkovich CJ, Eisenkraft JB: Successful use of a 20% lipid emulsion to resuscitate a patient after presumed bupivacaine-related cardiac arrest. *Anesthesiology* 2006; 105:217-218.
44. Jamaty C, et al: Lipid emulsions in the treatment of acute poisoning: A systematic review of human and animal studies. *Clin Toxicol (Phila)* 2010; 48:1-27.
45. Cave G, Harvey MG, Castle CD: The role of fat emulsion therapy in rodent model of propranolol toxicity: A preliminary study. *J Med Toxicol* 2006; 2:4-7.
46. Cave G, Harvey M: Lipid emulsion may augment early blood pressure recovery in a rabbit model of atenolol toxicity. *J Med Toxicol* 2009; 5:50-51.
47. Dean P, Ruddy JP, Marshall S: Intravenous lipid emulsion in propranolol overdose. *Anaesthesia* 2010; 65:1148-1150.
48. Stellpflug SJ, Fritzlar SJ, Cole JB, Engebretsen KM, Holger JS: Cardiotoxic overdose treated with intravenous fat emulsion and high-dose insulin in the setting of hypertrophic cardiomyopathy. *J Med Toxicol* 2011; 7:151-153.
49. ACMT Position Statement: Interim guidance for the use of lipid resuscitation therapy. *J Med Toxicol* 2011; 7:81-82.
50. Saitz R, Williams BW, Farber HW: Atenolol-induced cardiovascular collapse treated with hemodialysis. *Crit Care Med* 1991; 19:116-118.
51. Lane AS, Woodward AC, Goldman MR: Massive propranolol overdose poorly responsive to pharmacologic therapy: Use of the intraaortic balloon pump. *Ann Emerg Med* 1987; 16:1381-1383.
52. McVey FK, Corke CF: Extracorporeal circulation in the management of massive propranolol overdose. *Anaesthesia* 1991; 46:744-746.
53. Belson MG, Sullivan K, Geller RJ: Beta-adrenergic antagonist exposures in children. *Vet Hum Toxicol* 2001; 43:361-365.
54. Schoffstall JM, Spivey WH, Gambone LM, Shaw RP, Sit SP: Effects of calcium channel blocker overdose–induced toxicity in the conscious dog. *Ann Emerg Med* 1991; 20:1104-1108.
55. Levine M, et al: Assessment of hyperglycemia after calcium channel blocker overdoses involving diltiazem or verapamil. *Crit Care Med* 2007; 35:2071-2075.
56. Cumpston KL, Aks SE, Sigg T, Pallasch E: Whole bowel irrigation and the hemodynamically unstable calcium channel blocker overdose: Primum non nocere. *J Emerg Med* 2010; 38:171-174.
57. Kline JA, Tomaszewski CA, Schroeder JD, Raymond RM: Insulin is a superior antidote for cardiovascular toxicity induced by verapamil in the anesthetized canine. *J Pharm Exp Ther* 1993; 267:744-750.

www.ketabpezeshki.com 66485457-66963820

58. Doyer S, Roberts JR: The use of glucagon in a case of calcium channel blocker overdose. *Ann Emerg Med* 1993; 22:1229-1233.
59. Bania TC, Chu J, Perez E, Su M, Hahn IH: Hemodynamic effects of intravenous fat emulsion plus standard therapy in a model of severe verapamil toxicity. *Acad Emerg Med* 2007; 14:105-111.
60. Young AC, Velez LI, Kleinschmidt KC: Intravenous fat emulsion therapy for intentional sustained-release verapamil overdose. *Resuscitation* 2009; 80:591-593.
61. Passal DB, Crespin FH Jr: Verapamil poisoning in an infant. *Pediatrics* 1984; 73:543-545.
62. Ralston M, et al, eds: *Pediatric Advanced Life Support Provider Manual.* Dallas: American Heart Association; 2006.
63. Methemoglobinemia following unintentional ingestion of sodium nitrite—New York. *MMWR Morb Mortal Wkly Rep* 2002; 51:293.

www.ketabpezeshki.com 66485457-66963820

Chapter 153

Caustics

Paul M. Wax and Amy Young

PERSPECTIVE

Caustic or corrosive agents have the potential to cause tissue injury on contact with mucosal surfaces. Agents capable of causing chemical injury include alkaline and acidic corrosives. Alkalis accept protons, resulting in the formation of conjugate acids and free hydroxide ions. Lye is an example of an alkali caustic and refers to both sodium hydroxide (NaOH) and potassium hydroxide (KOH). Ammonia (NH_3) is another common alkaline corrosive. Acids are proton donors, as they dissociate into conjugate bases and free hydrogen ions in solution. Acidic caustics include hydrochloric acid (HCl) and sulfuric acid (H_2SO_4). The injury from caustic agents typically increases with a pH below 3 or above 11. Other chemicals that have caustic properties include phenol, formaldehyde, iodine, and concentrated hydrogen peroxide. This chapter discusses oral exposure. Dermal and inhalational exposures are discussed in Chapter 64 and Chapter 159, respectively.

Most caustic exposures are intentional for the purpose of self-harm. About 75% of reported caustic ingestions are intentional.[1] Accidental ingestions occur typically among the pediatric and elderly populations. Transfer and storage of cleaners in alternative containers that may not be "child proof," such as soda bottles and jars, contribute to unintentional ingestion. Intentional ingestions may have a greater degree of oropharyngeal sparing because of rapid swallowing but have a higher likelihood of serious injury.[2] More than half of suicidal patients who ingest caustic agents have a history of psychiatric illness.

Before 1950, strong lye with concentrations greater than 50% made up a major portion of caustic ingestions in the United States, leading to poor outcomes. To control the frequency of caustic ingestions especially in children, the Federal Caustic Act was passed in 1927, followed by the Federal Hazardous Substance Labeling Act of 1960 and the Safe Packaging Act of 1970.[3] Still, more than 40,000 exposures involving caustic agents occur in the United States every year.[1]

Some household products, such as liquid drain cleaners, continue to have high concentrations of alkali (30% KOH) or acid (93% H_2SO_4) (Table 153-1). These products often do not have concentration or content information available on the label, making it difficult for physicians to determine the severity of exposure.[4] Commercial industries, farms (dairy pipeline cleaners containing liquid NaOH and KOH in concentrations of 8-25%), and swimming pool chemicals also contain caustics in high concentrations.

Crystals and solid particles can have prolonged tissue adherence, causing more severe burns. These ingestions are limited by immediate oral pain, usually causing them to be spit out sooner than a liquid agent. The ingestion of granular automatic dishwashing detergents can be associated with devastating injuries. Crystal drain cleaners have lye concentration as high as 74% NaOH and may cause proximal esophageal injury. Liquid dishwashing detergents and laundry detergents have a pH higher than 12, but because the titratable base content is significantly less, there is less risk of injury after ingestion.

Liquid household bleach typically contains dilute (5.25%) sodium hypochlorite (NaHClO), and ingestion rarely causes consequential injury. Industrial-strength bleach, however, contains significantly higher concentrations of NaHClO, which would more likely cause esophageal necrosis. Toilet bowl cleaners contain hydrochloric acid as high as 26% HCl. General-purpose anticorrosive cleaners, such as 31% muriatic acid (HCl), are sold in gallon containers for home use and as swimming pool cleaners.

The alkali powder in air bags can cause ocular burns. Perfume accidentally sprayed into the eyes can be caustic. Cement is alkaline and causes topical burns, typically on the knees.[5] Although hair relaxer creams contain NaOH and have a pH of 11.2 to 11.9, injuries after ingestion are usually limited.[3]

Caustic ingestions may occur when methamphetamine is produced from over-the-counter medications and household chemicals. Sulfuric acid, hydrochloric acid, NaOH, ammonium hydroxide, anhydrous ammonia, and metallic lithium are all used in the clandestine production of methamphetamine.[6] Severe caustic injuries in these situations can cause stricture formation, esophageal resection, and the need for colonic interposition.

More than 70 different pills can cause damage when they come in contact with esophageal mucus for prolonged periods. Patients who take medications in the supine position or who take pills without water are at higher risk. Pills most likely to adhere are doxycycline, tetracycline, potassium chloride, and aspirin. Potassium chloride is particularly dangerous and has caused perforation into the aorta, left atrium, and bronchial artery.[7]

PRINCIPLES

Factors that influence the extent of injury from a caustic exposure include type of agent, concentration of solution, volume, viscosity, duration of contact, pH, and presence or absence of food in the stomach. The titratable alkaline reserve of an alkali or acid correlates with the ability to produce tissue damage. Concentrated forms of acids and bases generate heat, resulting in superimposed thermal injury.[8]

Acidic compounds desiccate epithelial cells and cause coagulation necrosis. An eschar is formed that limits further penetration. Because acids tend to have a strong odor and cause immediate pain on contact, the quantity ingested is usually limited. Because of resistance of squamous epithelium to coagulation necrosis, acids are thought to be less likely to cause esophageal and pharyngeal injury,[9] although severe esophageal and laryngeal burns still

www.ketabpezeshki.com 66485457-66963820

Table 153-1 Household Cleaning Products That Contain Caustic Chemicals

APPLICATION	PRODUCT (MANUFACTURER), CHEMICAL
Drain cleaner, liquid	Heavy Duty Liquid Drain Opener (Share), H_2SO_4 93% Drain Out Extra (Iron Out), KOH 30% Liquid-Plumr (Clorox), NaOH 0.5-2%, NaOCl 5-10% Maximum Strength Drain Opener (Enforcer), KOH 1-10%, NaOCl <5% Drain Care Professional Strength Drain Opener, NaOH 5-15%
Drain cleaner, crystals	Heavy Duty Crystal Drain Opener (Roebic), NaOH 100% Crystal Drain Opener (Rohyme), NaOH 74% Crystal Drain Out (Iron Out), NaOH 30-60% Drano Pipe Cleaner (Johnson), NaOH 54%
Oven cleaner	Easy-Off Heavy Duty Oven Cleaner (Reckitt), NaOH 4-6%
Rust remover	Rust Remover/Carpet Care (Johnson Wax Professional), HCl 10% Rust Stain Remover (Whink), hydrofluoric acid 2.5-3% Rust Stripper (Certified), NaOH 50-75% Naval Jelly Rust Dissolver (Loctite), phosphoric acid 25-30%
Toilet bowl cleaner	Instant Power Toilet Bowl Cleaner (Scotch), HCl 26% Bowl and Porcelain Cleaner (Cleanline), HCl 0.10% Bowl/Tile/Porcelain Cleaner (Share), phosphoric acid 15-25% Husky 303 Toilet Bowl Cleaner, HCl 23% Misty Bolex Bowl Cleaner, HCl 26%
Swimming pool cleaner	Muriatic acid, Aqua Chem (Recreational Water), HCl 31%

occur. Acids can be absorbed systemically, causing metabolic acidosis as well as damage to the spleen, liver, biliary tract, pancreas, and kidneys from perforation and direct local contact.

Alkaline contact causes liquefaction necrosis, fat saponification, and protein disruption, allowing further penetrance of the alkaline substance into the tissue. The depth of the necrosis depends on the concentration of the lye. A concentration of 30% NaOH in contact with tissue for 1 second results in a full-thickness burn. Alkalis are colorless and odorless, and unlike acids, they do not cause immediate pain on contact. Alkaline ingestions typically involve the squamous epithelial cells of the oropharynx, hypopharynx, and esophagus. The narrow portions of the esophagus, where pooling of secretions can occur, are also commonly involved. Alkalis may also cause gastric necrosis (Figs. 153-1 and 153-2), intestinal necrosis, and perforation. The esophagus can also be injured (Fig. 153-3). Burns below the pylorus carry a 50% mortality compared with 9% for burns above the pylorus.[10]

Caustic damage occurs in four phases. Initially, necrosis occurs, with invasion by bacteria and polymorphonuclear leukocytes. Vascular thrombosis follows, increasing the damage. During the next 2 to 5 days, superficial layers of injured tissue begin to slough. The tensile strength of the healing tissue may be low for up to 3 weeks after the caustic exposure, greatly increasing the chance of delayed perforation in some cases. Between 1 week and several months, granulation tissue forms, collagen is deposited, and reepithelialization occurs in the burn area. Esophageal stricture may form during a period of weeks to years from contraction of the scar.

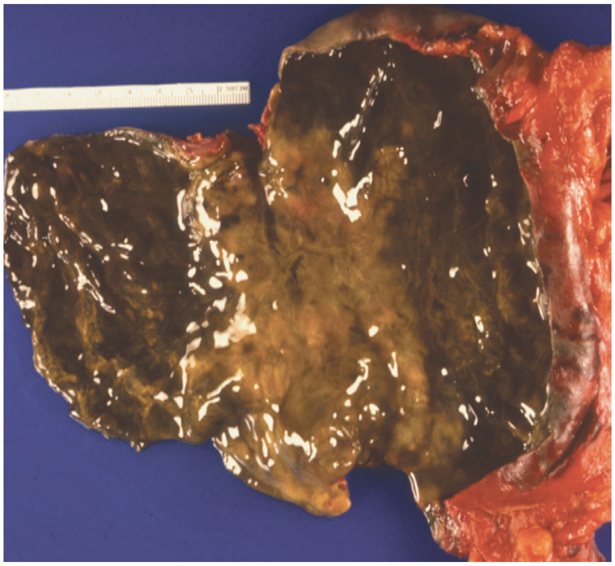


Figure 153-1. Gastric mucosa after ingestion of 35% potassium hydroxide.

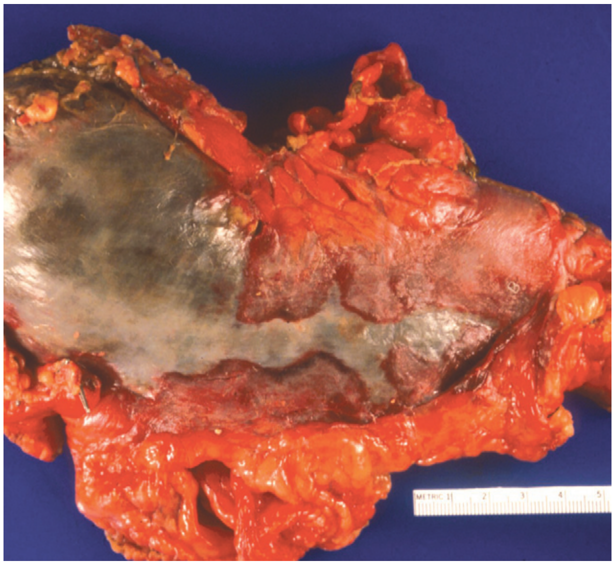


Figure 153-2. Gastric serosa after ingestion of 35% potassium hydroxide.

Figure 153-3. Esophagus after ingestion of 35% potassium hydroxide.

www.ketabpezeshki.com 66485457-66963820

Caustic injury is categorized as first, second, and third degree, similar to a thermal burn, by appearance on endoscopy. The initial depth of injury found on esophagoscopy correlates with the risk of stricture formation. First-degree burns (also known as grade 1) consist of edema and hyperemia. Second-degree burns (grade 2) can be further divided into 2a, which are noncircumferential, and 2b, which are nearly circumferential. Overall, second-degree burns are characterized by superficial ulcers, whitish membranes, exudates, friability, and hemorrhage. Third-degree burns (grade 3) are associated with transmural involvement with deep injury, necrotic mucosa, or frank perforation of the stomach or esophagus. Although grade 1 injuries do not progress to stricture, 15 to 30% of all grade 2 burns and up to 75% of circumferential grade 2 injuries of the esophagus develop strictures. With full-thickness third-degree burns (grade 3), up to 90% result in stricture; however, the formation of strictures is decreasing for both second- and third-degree burns, possibly because of the type and caustic intensity of the substance ingested.[11] Whether heat from the exothermic reaction increases the injury has never been quantified, but it has led to concerns about initial dilution or gastric lavage.[12]

CLINICAL FEATURES

Airway edema and esophageal and gastric perforation are the most emergent issues. Laryngeal edema occurs in a matter of minutes to hours. Systemic toxicity, hypovolemic shock, and hemodynamic instability with hypotension, tachycardia, fever, and acidosis are ominous findings. Small ingestions of potent substances can be as serious as larger ingestions. More than 40% of patients reporting to have "only taken a lick" have esophageal burns.[13] Patients present with oral pain (41%), abdominal pain (34%), vomiting (19%), and drooling (19%).[14] Patients can have wheezing and coughing, stridor, and dysphonia. Chest pain is common. Visible burns to the face, lips, and oral cavity may be seen (Fig. 153-4). Skin burns can occur from spillage or secondary contamination after vomiting. Peritoneal signs suggest hollow viscus perforation or contiguous extension of the burn injury to adjoining visceral areas. Tracheal necrosis is one of the most frequent causes of death after caustic ingestion.[15]

Studies present conflicting data correlating clinical symptoms with the severity of esophageal burns.[14] Oropharyngeal burns alone do not appear predictive of more distal injury, but prolonged drooling and dysphagia predict significant lesions with 100% sensitivity and 90% specificity.[15] Vomiting and stridor also suggest burn injury.

Dysphagia usually subsides in 3 to 4 days. Patients with significant esophageal burns, particularly those that are circumferential, may have esophageal stricture; 80% of strictures become apparent in 2 to 8 weeks. Symptoms include dysphagia and food impactions. Strictures that become symptomatic early are generally more severe. In one study of 86 adults admitted to the hospital after caustic ingestion, 18 had complications and 6 died.

Figure 153-4. Lip burn after exposure to 35% potassium hydroxide.

Patients have an increase in esophageal cancer (1000-fold to 3000-fold increases) that develops 40 to 50 years after the caustic ingestion. Long term, 1.8% of patients who ingest caustic soda have esophageal cancer,[16] and nearly 3% of esophageal cancer patients have a history of caustic ingestion.

Significant acid ingestions may be devastating and result in a higher mortality rate than alkali ingestions. The fulminant course of some acid ingestions may be due to systemic absorption of the acid, resulting in metabolic acidosis (which may also be the result of extensive tissue necrosis), hemolysis, and renal failure. Ingestion of glacial acetic acid (80% acetic acid) is common among certain ethnic populations as a suicidal gesture or accidental ingestion during food preparation, resulting in systemic complications, including renal and hepatic insufficiency, hemolysis, and disseminated intravascular coagulation.[17] Ingestion of sulfuric and hydrochloric acid typically does not cause these systemic complications.[18]

DIAGNOSTIC STRATEGIES

The goal is to identify the extent and severity of the burn. In evaluation of a patient, the history should include the time, amount, type of product ingested, and presence of suicidal intent, if any. Patients who are suicidal may minimize their symptoms or understate the trauma. Product labels are important in confirming the concentration of the chemical. If a sample is obtained, call the poison center for product information, look up the contents, or test the pH with litmus paper. Early and continuous hemodynamic monitoring is essential. The patient should be examined for evidence of dermal and ocular caustic exposures.

Patients with chest and abdominal pain should have a chest radiograph and decubitus or upright abdominal studies to look for peritoneal and mediastinal air, denoting perforation or pleural effusion, and suggestion of abdominal involvement should prompt abdominal computed tomography or ultrasonography. In the suicidal patient, the physical examination and chest radiograph do not "rule out" pneumoperitoneum. Radiographs have low negative predictive values for detection of free air.[10]

Arterial blood gas analysis may be useful after significant acid ingestions to monitor systemic metabolic acidosis. In cases of intentional overdose, coingestants should be considered.

Hydrofluoric acid exposures, whether by inhalation, ingestion, or dermal contact (hand size or larger), are notorious for the effect of absorbed fluoride and require immediate cardiac monitoring to assess for QTc prolongation, torsades de pointes, or other ventricular dysrhythmias. Rapid cardiac deterioration can occur in these unusual cases.[19] Serum calcium and magnesium levels should also be determined.

The depth of burns cannot be predicted on the basis of signs or symptoms. Noninvasive techniques (barium swallow) do not gauge the depth of burn injury. Patients with signs and symptoms (vomiting, drooling, stridor, or dyspnea) of intentional ingestion should undergo endoscopy within 12 to 24 hours to define the extent of the disease, but endoscopy is contraindicated in patients with possible or known perforation. Endoscopy performed too early may miss the extent or depth of tissue injury. Wound softening in the subacute phase when the likelihood of perforation is greatest makes late endoscopy (after 24 hours) more hazardous. Flexible endoscopy is safer than the older rigid instruments, with fewer perforation complications. However, the endoscopy should terminate at the level of the most proximal circumferential burn.[20]

www.ketabpezeshki.com 66485457-66963820

A soft feeding tube or silk string can be placed in the esophagus, when burns are present, for future dilation.

MANAGEMENT

After a caustic ingestion, little can be done to attenuate the severity of the tissue injury. Early endotracheal intubation or upper airway endoscopic examination is warranted when there are indications of upper airway injury: hoarseness or muffling of the voice, odynophagia, drooling, or tongue or pharyngeal edema. If significant exposure has occurred, intubation is undertaken early in the course of evaluation, before edema and secretions both threaten the airway and make intubation difficult or impossible. Blind nasotracheal intubation is contraindicated. When oral intubation is anticipated to be difficult or impossible because of edema and anatomic distortion, awake fiberoptic or video intubation or primary surgical cricothyrotomy may be necessary.

Hypoxia and an increased arterial-alveolar gradient warrant early bronchoscopy. Patients should have vigorous intravenous fluid resuscitation. In alert patients who are not vomiting and can tolerate liquids, small volumes (1-2 cups) of water or milk can be considered within the first few minutes after ingestion. Because injuries occur almost immediately, later dilution is not warranted. Forcing of fluids is never indicated. Attempts to neutralize the ingested corrosive with weak acids or alkalis can cause possible thermal reactions and worsen the injury.

Induction of emesis, administration of activated charcoal, and performance of gastric lavage are not indicated. Careful nasogastric aspiration may decrease the amount of acid absorbed and be useful in the setting of significant acid ingestions presenting immediately after the event, given the ominous natural history of many of these cases and the lower risk of esophageal perforation compared with alkali ingestion.

In the acute phase, barium swallow is of little use because it delays and obscures endoscopy and does not reveal first- or second-degree mucosal burns.[21] Thoracoabdominal computed tomography can be useful in assessing the degree of esophageal damage after caustic ingestions.[22]

Surgical exploration is indicated for free air, peritonitis, increasing and severe chest and abdominal pain, and hypotension. Contaminated clothing should be treated as hazardous waste and disposed of with proper precautions.

Different treatment modalities in stricture prevention have been discussed, including antibiotics, corticosteroids, total parenteral nutrition, nasogastric tube, and antacids, but none has been proved to be effective, and optimal management remains controversial.[23,24] Although the use of systemic corticosteroids has been recommended in the past, it has not statistically significantly decreased stricture after grade 2 esophageal burns.[25] Moreover, steroid therapy in grade 2 and grade 3 burns includes the risk for brain abscess, hemorrhage, pneumonia, severe esophagogastric necrosis, osteoporosis, and prepyloric ulcer formation.[26] Steroids can also mask early signs of inflammation and inhibit resistance to infection. Prophylactic antibiotics may potentially mask evidence of impending perforation.

DISPOSITION

Surgical intervention is required in cases of hollow viscus perforation; early exploration may also be warranted in cases of suggested full-thickness burns. Asymptomatic patients can undergo endoscopy in the emergency department or be discharged home with close follow-up monitoring. Children with a questionable history of ingestion should be observed even if they are asymptomatic and have no oropharyngeal burns. They can have a liquid diet. Symptomatic patients, particularly those with potential for airway compromise, require admission to the intensive care unit. If endoscopy is unavailable, the patient should be transferred to a facility where it can be performed. Psychiatric evaluation is indicated in patients with intentional or possibly intentional ingestion.

SPECIAL CASES

Ocular alkali exposures are true ophthalmologic emergencies. Immediate and aggressive lavage with at least 2 L of normal saline per eye is indicated in almost all cases except frank perforation. Management is described in Chapter 71.

Dermal caustic exposures can also result in significant burn injuries (see Chapter 64). Clothing removal, copious irrigation, and local wound débridement are the most important initial treatment measures. Hydrofluoric acid burns warrant special attention. Although this is a relatively weak acid compared with HCl or H_2SO_4, the dissociated fluoride anion is a problem because of its extreme electronegativity. Deaths from hydrofluoric acid exposure have occurred after ingestion; after skin contact in areas as small as 1% of the body surface area, the size of the palm of the hand, with concentrated hydrofluoric acid; and after inhalation of hydrofluoric acid vapor.[27] Systemic toxicity is characterized by profound hypocalcemia and dysrhythmias; cardiac monitoring and serum calcium and magnesium monitoring are warranted in all but the most limited fingertip exposures.[28] Sudden fatal deterioration can occur despite an initially normal serum calcium level, but oral treatment of hydrofluoric acid ingestion with $CaCl_2$ and $MgSO_4$ has not increased survival.[29] Empirical intervention with high-dose intravenous calcium chloride or magnesium sulfate should be administered for QTc prolongation and life-threatening dysrhythmias and with serum hypocalcemia and hypomagnesemia. Further management is discussed in Chapter 64.

Povidone-iodine (Betadine) is used as a surgical scrub and is not a caustic agent, but ingestion of tincture of iodine can cause severe gastrointestinal injury and is potentially life-threatening. Gastric irrigation with starch or milk in these cases may convert iodine to the much less toxic iodide.

Ingestion of phenol or formaldehyde can also cause severe caustic injury to the gastrointestinal tract. Both phenol and formaldehyde are general protoplasmic poisons and can cause protein denaturation and coagulation necrosis. Systemic symptoms, including dysrhythmias, hypotension, seizures, and coma, may also result from phenol ingestion. Acidosis may be prominent after formaldehyde ingestion because of its metabolism to formic acid. Phenol is well absorbed through the skin, and dermal exposure may result in burns and systemic toxicity. Although dermal decontamination of phenol exposures with low-molecular-weight polyethylene glycol has been suggested, irrigation with water may prove just as useful.

Ingestion of concentrated hydrogen peroxide (H_2O_2) may cause gastrointestinal burn injury and the formation of gas emboli. Radiographic evaluation for the presence of gas in the chest or abdominal cavities, including the portal system, should be performed in symptomatic patients or those who ingest concentrated H_2O_2. Hyperbaric oxygen has been used successfully to treat gas emboli from H_2O_2 ingestion.

Button (disk) batteries and conventional alkaline cylindrical batteries pose potential obstructive and chemical hazards if they are ingested. Ingestion of large 25-mm wafer-sized button batteries was a common problem in the past, but the smaller button batteries of today are less likely to cause esophageal obstruction. Button batteries are usually made of a metallic salt (lithium, mercury, nickel, zinc, cadmium, or silver) bathed in NaOH or KOH. Obstruction can cause pressure necrosis, caustic injury due to leakage of alkaline medium, or electrical injury. Ulceration, perforation, and possible fistula formation occur but are uncommon. Heavy-metal toxicity in this setting has not been reported.[30]

www.ketabpezeshki.com 66485457-66963820

Evaluation of button battery ingestions includes radiography to assess the position of the foreign body. Batteries lodged in the airway or esophagus require expeditious removal. Gastric or intestinal batteries can be treated with watchful waiting.[30] Checking the stool for passage of the batteries is recommended. Follow-up radiographs should be obtained in 1 week if the battery has not passed.

KEY CONCEPTS

- All symptomatic patients should undergo endoscopy and be considered for admission.
- Asymptomatic patients can undergo endoscopy in the emergency department or be discharged with close follow-up monitoring.
- Gastric emptying or decontamination is not indicated for caustic ingestion.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Bronstein AC, et al: 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System. *Clin Toxicol (Phila)* 2010; 48:979.
2. Kay M, Wyllie R: Caustic ingestion and the role of endoscopy. *J Pediatr Gastroenterol Nutr* 2001; 32:8.
3. Aronow SP, et al: Hair relaxers: A benign caustic ingestion? *J Pediatr Gastroenterol Nutr* 2003; 36:120.
4. Baskm D, et al: A standardised protocol for the acute management of corrosive ingestion in children. *Pediatr Surg Int* 2004; 20:824.
5. Spoo J, Elsner P: Cement burns: A review 1960-2000. *Contact Dermatitis* 2001; 45:68.
6. Farst K, et al: Methamphetamine exposure presenting as caustic ingestions in children. *Ann Emerg Med* 2007; 49:341.
7. John SK, et al: Life-threatening hyperkalemia from nutritional supplements: Uncommon or undiagnosed? *Am J Emerg Med* 2011; 29:1237.e1-2.
8. Bertinelli A, et al: Serious injuries from dishwasher powder ingestions in small children. *J Paediatr Child Health* 2006; 42:129.
9. Cordero, B, Savage R: Corrosive ingestions. *Pediatr Rev* 2006; 27:154.
10. Palmer M, et al: A, B, Cs of caustic ingestions in suicidal adults. *Ann Emerg Med* 2007; 49:246.
11. Bicakci U, et al: Minimally invasive management of children with caustic ingestion: Less pain for patients. *Pediatr Surg Int* 2010; 26:251.
12. Homan CS, et al: Thermal characteristics of neutralization therapy and water dilution for strong acid ingestion: An in-vivo canine model. *Acad Emerg Med* 1998; 5:286.
13. Andreoni B, et al: Esophageal perforation and caustic injury: Emergency management of caustic ingestion. *Dis Esophagus* 1997; 10:95.
14. Gorman RL, et al: Initial symptoms as predictors of esophageal injury in alkaline corrosive ingestions. *Am J Emerg Med* 1992; 10:189.
15. Nuutinen M, et al: Consequences of caustic ingestions in children. *Acta Paediatr* 1994; 83:1200.
16. Mamede RC, de Mello-Filho FV: Ingestion of caustic substances and its complications. *Sao Paulo Med J* 2001; 119:10.
17. Kim SJ, et al: CT imaging of gastric and hepatic complications after ingestion of glacial acetic acid. *J Comput Assist Tomogr* 2007; 31:564.
18. Poley J, et al: Ingestion of acid and alkaline agents: Outcome and prognostic value of early upper endoscopy. *Gastrointest Endosc* 2004; 60:372.
19. Kao WF, et al: Ingestion of low-concentration hydrofluoric acid: An insidious and potentially fatal poisoning. *Ann Emerg Med* 1999; 34:35.
20. Arévalo-Silva C, et al: Ingestion of caustic substances: A 15-year experience. *Laryngoscope* 2006; 116:1422.
21. Riffat F, Cheng A: Pediatric caustic ingestion: 50 consecutive cases and a review of the literature. *Dis Esophagus* 2009; 22:89.
22. Ryu HH, et al: Caustic injury: Can CT grading system enable prediction of esophageal stricture? *Clin Toxicol (Phila)* 2010; 48:137.
23. Bicakci U, et al: Minimally invasive management of children with caustic ingestion: Less pain for patients. *Pediatr Surg Int* 2010; 26:251.
24. Lee M: Caustic ingestion and upper digestive tract injury. *Dig Dis Sci* 2010; 55:1547.
25. Fulton J, Hoffman R: Steroids in second degree caustic burns of the esophagus: A systematic pooled analysis of fifty years of human data: 1956-2006. *Clin Toxicol (Phila)* 2007; 45:402.
26. Huang YC, Ni YH, Lai HS, Chang MH: Corrosive esophagitis in children. *Pediatric Surg Int* 2004; 20:207.
27. Blodgett DW, et al: Fatal unintentional occupational poisonings by hydrofluoric acid in the U.S. *Am J Ind Med* 2001; 40:215.
28. Bjornhagen V, et al: Hydrofluoric acid–induced burns and life-threatening systemic poisoning: Favorable outcome after hemodialysis. *J Toxicol Clin Toxicol* 2003; 41:855.
29. Heard K, Delgado J: Oral decontamination with calcium or magnesium salts does not improve survival following hydrofluoric acid ingestion. *J Toxicol Clin Toxicol* 2003; 41:789.
30. Litovitz T, Schmitz BF: Ingestion of cylindrical and button batteries: An analysis of 2382 cases. *Pediatrics* 1992; 89:747.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 154

Cocaine and Other Sympathomimetics

Rama B. Rao and Robert S. Hoffman

PERSPECTIVE

Cocaine, a naturally occurring plant-derived alkaloid, has been used for centuries as a medicinal product. For thousands of years in South America, the leaves of the coca plant (*Erythroxylon coca*) have been chewed for treatment of various ailments. In 1860, the pure alkaloid form was isolated and became a popular constituent of various beverages, pharmaceuticals, and therapeutic tonics, but it was banned from these products in the United States in 1914. At the peak of the cocaine epidemic in the early 1990s, it was estimated that 5 million people used cocaine regularly in the United States.[1] The drug is still popular, with up to 1.6 million current users of cocaine reported as of 2009.[2] This is a decrease from 2.3 million users in 2003,[3] but the consequences of recreational cocaine use are still profound. Cocaine is implicated in violent deaths and was detected in 25% of autopsies of fatal injuries in adults aged 15 to 44 years.[4] In 2009, 39% of drug misuse deaths were due to cocaine.[5] According to the Drug Abuse Warning Network, there were more than 423,000 cocaine-related emergency department (ED) visits representing 52% of drug abuse or misuse cases.[6] As of 2009, cocaine ranked within the top three causes of illicit drug–related deaths at various cities across the United States.[7]

Amphetamines are stimulants originally designed for use as decongestants and dietary aids that became popular as recreational drugs in the mid-20th century. By modification of the amphetamine molecule, illicit "designer" amphetamines are inexpensively produced. The enhanced effects from these alterations add to the popularity of drugs such as 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamines. Cocaine, amphetamines, and derivatives of amphetamines are called *sympathomimetics* (Box 154-1). These agents cause central nervous system (CNS) stimulation and a cascade of adrenergic physiologic effects. As of 2009, there were 502,000 methamphetamine current users in the United States.[2]

PRINCIPLES OF DISEASE

Pathophysiology of Cocaine

Acute cocaine use causes release of dopamine, epinephrine, norepinephrine, and serotonin. These neurotransmitters act on different receptor subtypes to cause many effects, but the most important is adrenergic stimulation by norepinephrine and epinephrine (see Box 154-1). Norepinephrine causes vasoconstriction by stimulation of alpha-adrenergic receptors on vascular smooth muscle. Epinephrine increases myocardial contractility and heart rate through stimulation of beta$_1$-adrenergic receptors. In addition to catecholamine release, the reuptake of these stimulatory neurotransmitters from synaptic clefts is inhibited, altering the normal balance between excitatory and inhibitory tone in the CNS. Subsequent stimulation propagates peripheral catecholamine release (Fig. 154-1). Reuptake of serotonin is similarly inhibited and can cause serotonergic excess as well.

Cocaine also is a local anesthetic agent, slowing nerve impulses from neuronal pain fibers by blocking the inward movement of sodium across cell membranes (phase 0 of the action potential).[8] Sodium channel blockade across myocardial cells, similar to the class IA antidysrhythmics, is responsible for the occasional conduction abnormality with acute cocaine toxicity.

Cocaine metabolism occurs in the liver and the plasma. In the liver, the drug is metabolized primarily to the active metabolite norcocaine, which potentiates the parent drug. In the plasma, cocaine is metabolized to ecgonine methyl ester through pseudocholinesterase (plasma cholinesterase). This difference may account for the differences in duration of action with different routes of administration.[9] Ecgonine methyl ester may be protective because it is a vasodilator. Genetic differences in the phenotypic expression of plasma cholinesterases may account for individual differences in susceptibility to cocaine toxicity.[10]

Benzoyl ecgonine, a metabolite found in the plasma, is produced primarily from nonenzymatic reactions. It is the metabolite identified by urine toxicology screens. Methylecgonidine and its metabolite ecgonidine are products of cocaine pyrolysis (crack). Although it is less commonly assayed, methylecgonidine also can be identified in the urine. The use of ethanol with cocaine forms cocaethylene, a metabolite that may potentiate the drug's stimulatory effects and lengthen the duration of its effects.[11]

Cocaine Formulations

Unpurified cocaine paste is converted to usable forms of cocaine. The crystallized freebase of the cocaine alkaloid is known as crack cocaine. It is inhaled with use of a special "crack pipe" designed to tolerate the high temperature required to volatilize pure cocaine. The high lipid solubility and rapid transport from the lungs into the brain contribute to crack's rapid onset of action (Table 154-1). The water-soluble salts of cocaine (cocaine hydrochloride and cocaine sulfate) are available as a white crystalline powder that is insufflated intranasally or dissolved and injected intravenously. Oral administration is rare except for patients who are smuggling or concealing drugs.

CLINICAL FEATURES

The primary clinical effect of cocaine is the excitation of the sympathetic nervous system. Patients with moderate toxicity are alert and awake but may have diaphoresis, tachycardia, mydriasis, and

www.ketabpezeshki.com 66485457-66963820

hypertension without organ damage. A more severely toxic patient may be agitated, combative, and hyperthermic. End-organ damage is rare but may be manifested as an acute hypertensive emergency. Patients may present with focal acute pain syndromes, circulatory abnormalities, delirium, or seizures.

The clinical presentation depends on the dose, route of administration, and time to presentation after drug use. Additives, contaminants, or other drugs may alter the classic signs of acute cocaine toxicity. Patients who are "speedballing," using intravenous heroin and cocaine together, may be initially sedated, and administration of naloxone may precipitously reveal the underlying cocaine intoxication.

Death due to acute cocaine overdose is significantly higher on days with ambient temperatures higher than 88° F.[12,13] The profound diaphoresis associated with cocaine may be absent or limited in cooler environments or if the patient is excessively salt and water depleted.

Initial assessment and treatment should focus on rapidly fatal complications, specifically hyperthermia, hypertensive emergencies, and cardiac dysrhythmias.

Box 154-1 Clinical Effects of Sympathomimetics

- Hypertension
- Hyperthermia
- Tachycardia
- Mydriasis
- Diaphoresis
- Central nervous system excitation

Hyperthermia

Acute psychomotor agitation with delirium increases the risk of hyperthermia.[14] Cocaine toxic patients have increased motor tone and generate heat. Vasoconstriction and salt and water depletion can compromise cooling, resulting in life-threatening hyperthermia with core temperatures exceeding 106° F (41.1° C). Delay in recognition and management increases the likelihood of death. Even with a normal temperature, increased motor tone can release intramuscular creatine kinase, with rhabdomyolysis and its attendant renal and electrolyte complications.[15]

Hypertensive Emergencies

Acute cocaine-induced hypertension can seriously injure the cardiovascular system and CNS. Reported sequelae include aortic

Table 154-1 Cocaine Pharmacology by Route of Administration

ROUTE	FORMULA	ONSET OF ACTION	PEAK EFFECT	DURATION
Inhalation	"Crack"	8 s	2-5 min	10-20 min
Intranasal	Cocaine HCl	2-5 min	5-10 min	30 min
Intravenous	Cocaine HCl	Seconds	10-20 min	60-90 min
Oral	Cocaine HCl	30-60 min	60-90 min	Unknown
"Skin popping"	Cocaine HCl	Unknown	Unknown	Unknown

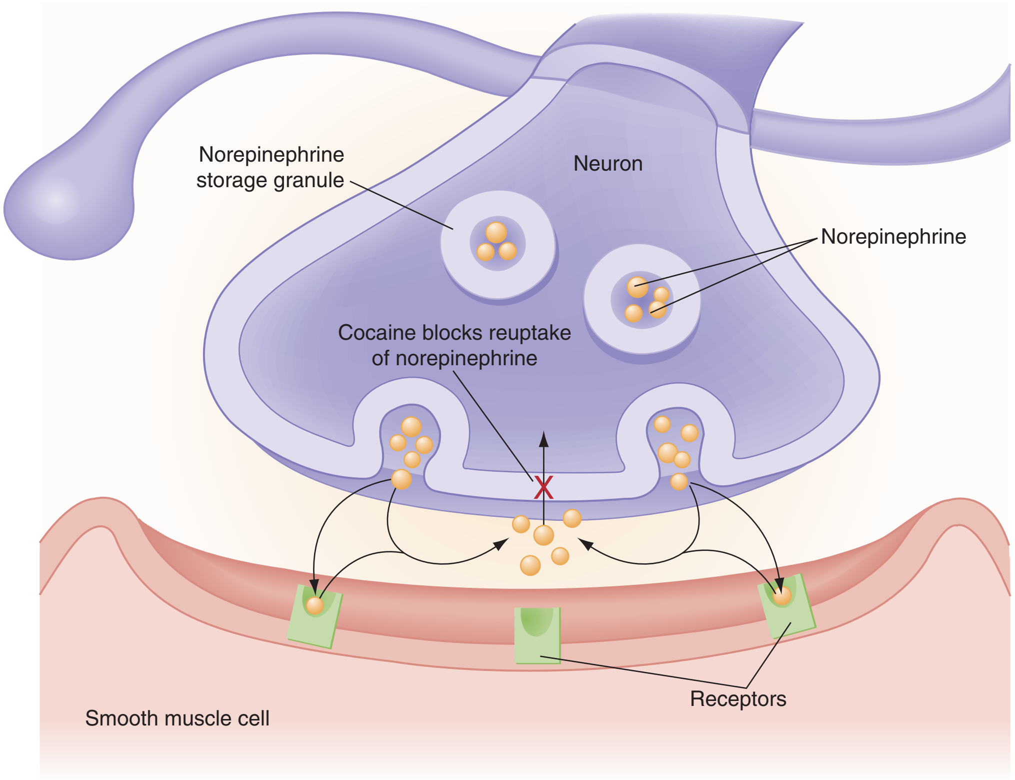


Figure 154-1. How cocaine increases sympathetic tone by increasing neurotransmitters in the synapse.

www.ketabpezeshki.com 66485457-66963820

dissection,[16] pulmonary edema,[17] myocardial ischemia and infarction,[18] intracranial hemorrhage,[19] strokes,[20] and infarction of the anterior spinal artery.[21] Vasospasm can also compromise perfusion to various organs. Intestinal infarctions and mesenteric ischemia can occur, particularly in body packers with large oral ingestions.[22,23] Other local ischemic events include retinal vasospasm, renal infarctions, and placental insufficiency and infarction in the gravid uterus.[24]

Cardiac Dysrhythmias

Although sinus tachycardia is most common, atrial fibrillation and other supraventricular tachycardias can occur as a result of the surge in catecholamines. A life-threatening dysrhythmia may not be noted until cardiac output abruptly diminishes and the patient suddenly loses consciousness. Torsades de pointes[25] or wide-complex tachycardias from blockade of fast sodium channels on the myocardium may deteriorate into poorly perfusing or fatal ventricular rhythms.[8] Transient conduction abnormalities consistent with a Brugada-type pattern are associated with cocaine.[26,27] Hyperkalemia from rhabdomyolysis and myocardial ischemia can also cause dysrhythmias.

Other Complications

People who binge with continuous use for an extended time have a prolonged state of arousal, which causes catecholamine depletion, salt and water depletion, and poor nutrition. After the acute effects of cocaine have subsided, these patients with “cocaine washout” are profoundly sleepy but arousable and oriented, with normal vital signs or a mild sinus bradycardia.

A patient occasionally has “crack dancing,” a transient choreoathetoid movement disorder probably related to abnormalities in dopaminergic tone.[28] Deep venous thrombosis is reported with cocaine use, probably secondary to effects on coagulation. Paranoia, either drug induced or from underlying psychiatric illness, may occur even after the acute effects of the drug subside. The neuropsychiatric effects of cocaine can alter behavior and judgment, increasing the risk of violent injuries.

Complications also arise from the route of administration of cocaine. Inhalation of crack cocaine may cause oropharyngeal burns from the high temperature required to volatilize the drug.[29] Pneumothorax, pneumopericardium, and pneumomediastinum occur from inhalational barotrauma.[30] Intranasal cocaine use is associated with sinusitis and nasopalatine necrosis or perforation.[31] Intravenous users have a high risk of infection with bloodborne viruses, local abscesses, and systemic bacterial infections, including botulism and endocarditis.[32] Transdermal injection of cocaine, or “skin popping,” has similar types of complications, especially of skin abscesses. For a chronic user, addiction, or psychological dependence, is mediated through specific dopaminergic neurotransmitter pathways. Although there are no well-defined syndromes constituting cocaine withdrawal, patients have strong cravings for the drug or a general feeling of dysphoria that is not physiologically life-threatening.[33]

In 2009, as much as 69% of cocaine imported into the United States contained levamisole, a veterinary anthelmintic agent.[34] Agranulocytosis, vasculitis with thrombosis, dermal ulcers, and purpura, often affecting the earlobes, occurred as a result of the unintentional exposure to levamisole.[34-37] The reason for this adulteration of cocaine with levamisole is not clear.

DIAGNOSTIC STRATEGIES

Urine drug screening is unlikely to change treatment because it measures a cocaine metabolite (benzoyl ecgonine) that persists for at least 3 days after last use. In a few circumstances, however, urine drug screening may be beneficial to document possible abuse or neglect in a child with suggested exposure, to confirm cocaine as the unknown substance in body packers, and to differentiate paranoia from drug-induced or psychiatric causes.

An electrocardiogram (ECG) screens for dysrhythmias and conduction abnormalities from ischemia, hyperkalemia, or, more precipitously, QRS prolongation from sodium channel blockade. This blockade slows myocardial depolarization and results in a wide-complex tachycardia. The axis may be indeterminate or have a terminal rightward axis deviation similar to cyclic antidepressant toxicity. Cyclic antidepressants and cocaine share class IA antidysrhythmic effects. Evaluation of chest pain is challenging because ST segment elevation is confounded by the presence of early repolarization.[38,39] Serial ECGs may be helpful.

Creatine kinase (CK), a nonspecific marker for muscle injury, is often elevated with cocaine use. The serum CK-MB fraction, troponin I, and troponin T are more specific in patients with atherogenic coronary disease but less certain in patients with cocaine-related chest pain.[33,39,40] Some patients with elevations in CK-MB have normal troponin I or troponin T levels.[40] Patients presenting with positive troponin I and chest pain after cocaine use have a higher incidence of angiographic findings,[41] but up to 18% of patients may have normal angiograms in the setting of positive biomarkers for myocardial infarction (MI).[42] Although the sensitivity and specificity of troponin and other serum enzyme markers are still being investigated for cocaine-related chest pain, cardiac enzymes should be measured as is done for other cardiac patients. Data regarding the role of coronary computed tomography angiography (CTA) to identify patients with cocaine-related coronary disease are evolving.[43,44] Until it is further studied, coronary CTA cannot be routinely recommended.

Severe, persistent headache despite normalization of blood pressure may occur with a subarachnoid hemorrhage and warrants head computed tomography and, if the scan is normal, lumbar puncture. Urine should be checked for myoglobin to screen for rhabdomyolysis.

In the rare event that a patient presents with agranulocytosis or vasculitis suggestive of levamisole, a special laboratory evaluation for urine levamisole by gas chromatography–mass spectrometry may be requested. The sample is ideally obtained within 48 hours after last use.[37] Other infectious or rheumatologic causes of this presentation should also be considered.

DIFFERENTIAL CONSIDERATIONS

A differential diagnosis of acute cocaine toxicity includes the many causes of agitated delirium (Box 154-2). A thorough assessment of mental status, vital signs, and physical examination can help direct and narrow the differential diagnosis. Conditions that may be indistinguishable from cocaine toxicity include sedative-hypnotic withdrawal, toxicity from amphetamines and amphetamine derivatives, and heatstroke. Phencyclidine toxicity may be distinguished by the presence of multidirectional nystagmus, but the treatment is similar. Patients with anticholinergic poisoning typically have urinary retention, dry skin, and minimally reactive pupils as distinguishing factors. Infection should be considered in all hyperthermic patients.

MANAGEMENT

A severely poisoned patient is combative and unable to cooperate in assessment of vital signs. Actions taken during these first stages of the encounter are crucial (Box 154-3). Because the cause of the patient's state often is not clear, the initial priority is to recognize and treat the life-threatening agitated delirium.

Patients may transiently require physical restraints for complete vital signs to be obtained and intravenous access to be secured. If

www.ketabpezeshki.com 66485457-66963820

Box 154-2 Differential Diagnosis of Agitated Delirium

- Metabolic causes
  - Electrolyte abnormalities
  - Hypoglycemia
  - Hypoxia
  - Uremia, hyperammonemia
- Structural lesions of the CNS
  - Trauma
  - Stroke
  - Hemorrhage
  - Mass
- Endocrine disease
  - Thyrotoxicosis
- Infections
  - Bacterial or viral meningitis or encephalitis
- Toxicologic causes
  - Sympathomimetics, stimulants
    - Cocaine
    - Amphetamines and derivatives
    - Caffeine
    - Phencyclidine, ketamine
  - Anticholinergics
    - Serotonin syndrome
    - Sedative-hypnotic withdrawal
- Heatstroke
- Postictal state

CNS, central nervous system.

Box 154-3 Initial Evaluation of Patients with Sympathetic Stimulation

- Rapid assessment of vital signs, especially core temperature
- Rule out hypoxia, hypoglycemia
- Pharmacologic sedation with benzodiazepines
- Electrocardiogram
- Urinalysis
- Serum creatine kinase

a chest restraint is used, a mesh vest is preferred to a jacket to help limit hyperthermia. The patient should have assessment with a bedside blood glucose monitor. Immediate pharmacologic sedation with intramuscular (IM) or intravenous (IV) administration of benzodiazepines may be necessary (see next section), which, in adequate doses, restores inhibitory tone to the CNS and decreases excessive sympathetic outflow to peripheral tissues. Sedation also facilitates measurement of vital signs (particularly core temperature), continuous electrocardiographic monitoring, and completion of the physical examination.

Pharmacologic Sedation

In adults, diazepam can be administered intravenously in increments of 10 mg every 5 minutes until sedation is achieved. Diazepam has a rapid onset of action, is easily titratable, and has active metabolites for a sustained effect. Persistently increased motor tone reflects an inadequate diazepam dose, even if the patient appears sleepy. In wildly agitated patients in whom 20 to 30 mg of diazepam has no notable effect, diazepam dosing may be increased by 10 mg with each subsequent dose with close monitoring until adequate sedation is achieved. For a patient in whom intravenous access is not possible because of agitation, IM midazolam 10 mg can be administered to facilitate subsequent interventions. Benzodiazepines also treat the choreoathetoid movements of crack dancing. Most cocaine toxic patients have salt

Box 154-4 Management of Stimulant-Induced Hyperthermia

- Early identification of elevated core temperature
- Large-bore intravenous access with rapid infusion of crystalloid
- Sedation and muscle relaxation with benzodiazepines
- Rapid cooling within 20 minutes*
- Foley catheterization to monitor output
- Laboratory analysis for organ function
  - Serum chemistries, creatinine, CK
  - Liver function
  - PT, PTT, fibrin split products
  - Bacterial cultures†
- Urinalysis for myoglobinuria
- Paralysis and intubation if necessary

CK, creatine kinase; *PT,* prothrombin time; *PTT,* partial thromboplastin time.
*Ideally with ice water immersion.
†Consider lumbar puncture or antibiotic therapy, especially in injection drug users.

and water depletion and require vigorous intravenous crystalloid replacement. If the cause of delirium is unclear, careful attention to the patient's respiratory status avoids the respiratory depression caused by excessive benzodiazepine administration in the presence of other sedative-hypnotic agents, such as ethanol.

Phenothiazines, droperidol, and haloperidol have a rapid onset with intramuscular injection, and CNS sedation is achieved. However, the anticholinergic effects of these agents can theoretically limit cooling by impeding diaphoresis, and they may also have associated dysrhythmic effects that theoretically may be additive to cocaine, and so benzodiazepines are preferred.

Hyperthermia

Cocaine-induced hyperthermia must be treated with rapid cooling (Box 154-4). Patients who sustain elevated core temperatures above 106° F (41° C) for more than 20 minutes are likely to stabilize transiently and subsequently have fatal multisystem organ failure, often heralded by disseminated intravascular coagulation. Patients should have continuous monitoring of core temperature with a rectal probe. Heat generated by agitation and increased muscle tone can be terminated by aggressive use of benzodiazepines, with neuromuscular paralysis and intubation as required. Succinylcholine is relatively contraindicated because of hyperthermia and muscle breakdown, and its shared metabolism (plasma cholinesterase) with cocaine is likely to prolong the effects of both drugs. It is crucial to reduce core temperature to 102° F (38.8° C) within 20 minutes. Cooling blankets are insufficient. Ice water, wet sheets with large fans, and packing of the entire body in ice with continuous monitoring of core temperature can be used. These patients often require aggressive fluid resuscitation.[45]

Hypertensive Emergencies

The goal in hypertensive emergencies is to promptly reverse the vasoconstriction of norepinephrine at peripheral alpha-adrenergic receptors. Benzodiazepines restore the CNS inhibitory tone on the peripheral nervous system. With evidence of end-organ damage, intravenous nitroglycerin can be used.[46] Phentolamine, a direct alpha-adrenergic antagonist, is the antihypertensive of choice. It can be titrated slowly by repeated intravenous doses of 1 mg every 3 minutes with blood pressure monitoring. If adequate reduction in therapy by at least two thirds of mean arterial pressure is not achieved after two doses, phentolamine dose can be escalated by 1 mg every 3 minutes up to 5 mg/dose until adequate vasomotor control is achieved. Phentolamine effect will last roughly 45 minutes. Other antihypertensives that can be used

www.ketabpezeshki.com 66485457-66963820

include hydralazine and short-acting intravenous calcium channel antagonists (see Chapter 84). Data for ideal vasodilators in this setting are lacking. In contrast to chronic hypertension, individuals with acute cocaine hypertension often have a normal blood pressure in the absence of the drug, and unless the patient's history suggests otherwise, a normal systolic and diastolic blood pressure should be the endpoint of therapy.

Beta-adrenergic antagonists may cause paradoxical hypertension with cocaine.[47,48] Patients undergoing cardiac catheterization show decreased coronary artery diameter in the presence of cocaine and beta-adrenergic antagonists.[48,49] The use of beta-adrenergic antagonists in cocaine toxicity or cocaine-related chest pain syndromes should be avoided while their role is investigated.[50-52] The treatment of cocaine-induced subarachnoid hemorrhage, MI, or aortic dissection differs from treatment of other causes of the same conditions. The combined use of phentolamine and beta-adrenergic antagonists may result in profound hypotension and is inadequately investigated. Likewise, data on the use of labetalol are disappointing. Because 1-year outcomes in younger low-risk patients presenting with chest pain are generally good,[53,54] the benefits attributed to beta-adrenergic antagonists in older patients with documented coronary artery disease may not be comparable. The 2008 American Heart Association guidelines consider beta-adrenergic antagonists potentially harmful and advise against their routine use.[52]

Dysrhythmias

Dysrhythmias from cocaine may be atrial or ventricular. Atrial fibrillation and supraventricular tachycardias are likely to be due to sympathetic stimulation and often respond to benzodiazepines. Beta-adrenergic antagonists should be avoided. Calcium channel blockers can be used if rapid atrial rhythms fail to respond to sedation, cooling, and volume resuscitation.

Important considerations in the differential diagnosis of a wide-complex tachycardia include hyperkalemia, direct sodium channel blockade, and ischemic ventricular dysrhythmia. In cocaine body packers or patients presenting with cocaine-induced adrenergic toxidrome, abrupt development of a wide-complex tachycardia with a pulse should be treated with empirical sodium bicarbonate, 1 to 2 mEq/kg IV bolus, with closely recorded cardiac monitoring to observe for QRS narrowing. If the patient does not respond with both QRS narrowing and hemodynamic stabilization, treatment by advanced cardiac life support should be instituted. Data regarding the ideal antidysrhythmic agent in this setting are limited. Fluid and electrolytes should be assessed and corrected as indicated. Close monitoring is required for patients with a Brugada-type conduction pattern.[26,27]

Cocaine-Related Chest Pain

The causes of cocaine-related chest pain are diverse (Box 154-5). A chest radiograph may identify aspirated foreign bodies or pneumothorax or pneumomediastinum from inhalational barotrauma. Fever and shortness of breath should prompt consideration of pneumonia, pulmonary infarction,[55,56] or endocarditis with septic pulmonary emboli in intravenous drug abuse.

Cocaine acutely induces coronary vasoconstriction while increasing myocardial oxygen demand. Platelet aggregation is enhanced through thrombogenic and antifibrinolytic pathways.[57] These cumulative effects can result in coronary insufficiency. Cigarette smoking acutely exacerbates these conditions. Chronic cocaine use may accelerate atherogenesis and induce left ventricular hypertrophy. All of these factors contribute to myocardial ischemia or infarction. Of nonfatal MIs in patients aged 18 to 45 years, 25% were attributed to cocaine, even after adjustment of other known cardiac risk factors.[58]

Box 154-5 Causes of Stimulant-Induced Chest Pain

- Noncardiac
  - Pneumothorax
  - Pneumomediastinum
  - Pneumopericardium
  - Aortic dissection
  - Pulmonary infarction
  - Infection
- Foreign body aspiration
- Cardiac chest pain
  - Endocarditis
  - Pericarditis
  - Left ventricular apical ballooning
  - Ischemia, infarction
    - During acute intoxication
    - After acute intoxication
- Coronary stent thrombosis

Identification of a patient with a cocaine-related coronary syndrome is difficult. Patients may present hours to days after use, possibly because of vasoactive metabolites.[59] The patient may deny drug use and have atypical chest pain. Almost one third of cocaine-using patients with elevated serum enzymes have pleuritic chest pain.[60] There are no clear predictors for patients at risk because age, route of drug use, time to presentation, and preexisting risk factors for coronary artery disease are inadequate to identify patients sustaining MI.[60] In the setting of cocaine-related chest pain, risk stratification by TIMI score may not adequately identify patients at risk for 30-day adverse outcomes.[61] However, cocaine history alone in low-risk, asymptomatic patients assessed by coronary CTA was not associated with increased risk of coronary artery disease.[43] Patients with positive serum enzymes for MI often have significant angiographic stenosis.[41] Of patients without positive serum markers, 18% have significant disease by angiography.[41] Other predictors of significant disease in this group included elevated cholesterol concentration and prior diagnosis of coronary disease or MI.[41] Patients with previous coronary stent placement are at a high risk of thrombosis with cocaine use.[62]

As for most complications of cocaine use, benzodiazepines decrease myocardial oxygen demand by limiting peripheral stimulation and should be given early.[63] Aspirin and nitrates should be administered.[57,59] In patients meeting electrocardiographic criteria for MI with persistent chest pain and hypertension and a clear history of acute cocaine intoxication, coronary vasodilation with intravenous phentolamine (1 mg) can be given slowly during 3 minutes. This dose can be repeated, if needed, as long as the patient's blood pressure remains stable. Morphine sulfate can be used to treat pain.[64] Patients with persistent chest pain and ST segments strongly suggestive of MI can be considered for percutaneous intervention or thrombolytic therapy, assuming there are no contraindications, such as uncontrolled severe hypertension.

In contrast to non–cocaine-induced myocardial ischemia or infarction, beta-adrenergic antagonists, including labetalol, are contraindicated during acute cocaine toxicity because coronary vasoconstriction may worsen.[47-51] In patients with cocaine-related coronary syndromes who are not acutely toxic, alpha-adrenergic vasoactive metabolites may be responsible. Administration of beta-adrenergic antagonists on discharge is controversial, especially if cocaine use is likely to continue, and we advise against this practice.[50,51,53,65-67] Heparin can be given, but fibrinolytic therapy is not well studied. Some mechanisms of cocaine-induced MI would be expected to respond to fibrinolytic agents. Patients failing to respond to vigorous treatment with nitrates and phentolamine who have known coronary artery disease or a previous ECG

www.ketabpezeshki.com 66485457-66963820

confirming new ST segment elevations are candidates for cardiac catheterization or fibrinolysis if necessary. The same contraindications apply as for non–cocaine-induced MI. Nuclear imaging studies also may provide more diagnostic information.[18,38,54]

Antiplatelet and glycoprotein IIb/IIIa inhibitors and calcium channel antagonists seem to be of benefit to some patients with MI or ischemia of atherosclerotic origin. Theoretically, these agents may counter some of the platelet aggregation enhanced by cocaine, but data investigating their use are lacking. Patients with cocaine-related chest pain without other risk factors who have normal ECGs and cardiac enzymes are at low risk for MI. The role of provocative testing in these patients is not well established.[52]

In summary, cocaine-induced coronary ischemia is managed with vasodilators and benzodiazepines and avoidance of beta-adrenergic antagonists. In cooperative patients, aspirin, heparin, antiplatelet agents and calcium channel blockers, and interventional therapy can be used as they might be in patients with ischemic chest pain.

Interventions to cease cocaine use are warranted. For patients with documented coronary artery disease, cessation of cocaine use is imperative. Cocaine users presenting with chest pain who continued cocaine use after ED discharge were more likely to have recurrent ED visits than were those who stopped.[53]

Cocaine Body Packers

Before crossing international borders, "body packers" ingest cocaine that has been wrapped tightly into condoms or other latex products and sometimes coated in wax. Each packet can contain approximately 10 g of cocaine, and packers may swallow as many as 150 packets.[22,68] On arrival at the patient's destination, a cathartic is taken to stimulate gastrointestinal passage of the contraband for subsequent delivery and distribution. Body packers are likely to know the exact number of packets they ingested but may be reluctant to share that information.

A body packer may present without symptoms to the ED. The body packer should be placed immediately on continuous cardiac monitoring, with large-bore intravenous access. Diagnosis is made by history. An abdominal radiograph may confirm foreign bodies but cannot be used to count packets because plain radiographs have limited sensitivity in detecting an isolated or small number of packets. When uncertainty persists, a contrast study is warranted.[22]

Body packing also is used to transport heroin and other illicit substances. Although heroin body packing rarely requires surgical intervention, an asymptomatic patient may refuse to identify the packet's contents. A urine toxicology screen may be useful because small quantities of drug may be ingested in swallowing of the contraband. Rupture of a single cocaine packet can result in death because each packet contains almost 10 times the lethal dose. These patients may die suddenly. All cocaine body packers should be admitted to a monitored setting and given nothing to eat or drink except decontamination medications. Patients with bowel obstruction or a leaking or poorly secured packet who become symptomatic satisfy absolute criteria for immediate surgical removal of packets. Because of the large quantity of pure drug in one packet, patients with packet leaks are likely to die without prompt intervention. When evidence of cocaine toxicity is manifested, rapid transportation to the operating room may be the only way to save these patients. Benzodiazepines, neuromuscular blockade, or sodium bicarbonate administration may be required en route.

It is reasonable to administer activated charcoal (1 g/kg body weight) to an asymptomatic body packer whose airway is intact. Whole-bowel irrigation with polyethylene glycol solution facilitates gastrointestinal passage of the packets and cleanses the bowel in the event of emergent transport to the operating room.[22] Subsequent contrast studies may be required to evaluate for remaining packets. Computed tomography and contrast abdominal radiography may fail to detect isolated packets that contain potentially fatal quantities of cocaine. Patients suggesting that they swallowed a larger number of packets than are passed or who refuse to reveal the number ingested can have continued bowel irrigation, observation, and repeated studies. Endoscopic retrieval is generally discouraged because of concern for packet rupture during the procedure, but it has been done on occasion.[22,69]

All packets passed in the stool, through endoscopic procedures, or in the operating room should be counted carefully and promptly given to law enforcement officials. When law enforcement is not yet involved, hospital legal counsel or risk management and the hospital ethics committee may be helpful in determining the disposition of the packets and ultimately of the patient when he or she is medically cleared.[22]

Body Stuffers

A "body stuffer" is an individual who attempts to conceal evidence of cocaine possession by swallowing the drug while being pursued by law enforcement officials. These ingestions are usually unplanned events with generally small quantities of drug that were initially intended for personal use. The drugs are often swallowed in poorly sealed vials or glassine packets that may not be evident on radiographs. In general, patients ingest nonlethal doses and are asymptomatic. Activated charcoal (1 g/kg) can absorb any potentially released drug. Monitoring and whole-bowel irrigation should be performed if the quantity ingested is of concern or if signs of toxicity develop.[70] Body stuffers rarely have fatal events, but these patients usually have symptoms in the first 8 hours.

Levamisole-Related Complications

Patients with agranulocytosis, vasculitis, or other dermatologic manifestations require supportive care, evaluation for other potential causes,[36] and abstinence from further levamisole exposure. Reporting to the local department of health or poison control center can help track these cases.[34]

DISPOSITION

Acutely toxic patients who need only observation or who respond quickly to sedation and do not have complications can be discharged after the acute intoxication resolves. These patients may be extremely lethargic from catecholamine depletion, and it is best to discharge them with a responsible adult. Patients may be open to drug counseling and referral while in the ED.

Patients with chest pain (Box 154-6) who are acutely toxic and who show dynamic changes on the ECG, dysrhythmias, or congestive heart failure and patients requiring vasodilators or reperfusion should be admitted. These patients require further evaluation

Box 154-6 Admission Criteria for Cocaine-Related Chest Pain

Persistent chest pain
Electrocardiographic changes
Dysrhythmias or conduction abnormalities
CHF, cardiogenic shock
Elevated enzymes
Requiring vasodilation
Preexisting CAD or stent placement
Multiple risk factors for CAD

CAD, coronary artery disease; *CHF,* congestive heart failure.

www.ketabpezeshki.com 66485457-66963820

of the extent of preexisting reversible ischemia and intervention to encourage cessation of drug use.

The disposition of patients with chest pain who are not acutely toxic is less clear. Admission is warranted for patients with complications or electrocardiographic changes and patients requiring pharmacologic intervention with vasodilators. Other patients may be admitted for short-term observation to an ED observation unit or discharged, depending on the level of concern about underlying coronary artery disease.

Young patients who present after resolution of chest pain with normal and unchanging ECGs, no dysrhythmias, and few or no risks of coronary artery disease are likely to have a good outcome.[54] Complications such as congestive heart failure and ventricular dysrhythmias typically are manifested within the first 4 hours.[18] After a 12-hour monitored observation period, patients with a benign clinical course and negative serum enzyme markers can be discharged.[54,71]

Body packers need to be observed until all packets have passed. Ideally, these patients have had three packet-free stools, a reliable packet count consistent with the ingestion, and a normal contrast radiographic study.[22] Body stuffers who receive activated charcoal, have normal ECGs, and remain asymptomatic with normal vital signs after 6 to 8 hours of observation may be discharged.

OTHER STIMULANTS

Amphetamines

Amphetamines enhance release of catecholamines from presynaptic nerve terminals by altering the pH of presynaptic vesicles. Amphetamines are usually taken as pills but are occasionally crushed and injected. The subsequent CNS stimulation results in sympathomimetic effects nearly identical to those from cocaine but not with the same frequency or intensity (see Box 154-1). Patients are at risk for hyperthermia, hypertensive emergencies, dysrhythmias, myocardial ischemia, and hyperkalemia associated with rhabdomyolysis. In contrast to cocaine, amphetamines do not block sodium channels and only minimally affect presynaptic reuptake of catecholamines. Although urine drug screens can identify amphetamines, they are of little utility in treatment of a toxic patient. The management follows the same guidelines as for cocaine (see Box 154-3), although the duration of toxicity is longer for amphetamines.

Methylenedioxymethamphetamine

Methylenedioxymethamphetamine (MDMA, ecstasy, XTC, Adam) is a chemically modified amphetamine originally taken orally at all-night dance parties or "raves." Patients describe the euphoria allowing "closeness to others," so it is sometimes called the love drug. The molecular structure of MDMA confers some serotoninergic properties that may account for the "shimmering" visual effects reported.

Along with the usual complications of amphetamines, MDMA can precipitate a life-threatening hyponatremia. MDMA or its metabolite may alter release of endogenous stores of vasopressin.[72] Although the exact mechanism is not understood, patients with MDMA-induced hyponatremia have concentrated urine samples with a relatively high urine sodium concentration, similar to the syndrome of inappropriate secretion of antidiuretic hormone. Unless seizures or other neurologic events are present, patients can be treated supportively with fluid restriction. Urine can be tested for specific gravity, and a sample should be sent to the laboratory for electrolyte analysis and osmolality. Normal saline or other crystalloids may worsen the hyponatremia because these patients are likely to retain more free water than sodium. Their fluid intake should be restricted unless severe hypovolemia exists, and they should be treated with hypertonic saline for neurologic impairment. A newer treatment of hyponatremia includes vasopressin V_2-receptor antagonists,[73] but it has not been described for these patients. In contrast to other amphetamines, chronic MDMA use causes potentially irreversible neurologic damage to serotoninergic neurons.[74] Other MDMA variants, such as 3,4-methylenedioxyethamphetamine (Eve), may cause similar complications (see Chapter 156).

Methamphetamine

Methamphetamine, known as crank and crystal meth, is a fat-soluble, smokable, designer amphetamine. Complications from methamphetamine use are similar to those from other sympathomimetics. The duration of action can be significantly longer, however, with some paranoid delusions persisting for 15 hours. The production of methamphetamines requires a variety of metal salts, and lead toxicity from inappropriately produced drug is reported.[75] Injuries during illicit methamphetamine production or police raids include exposure to anhydrous ammonia, hydrochloric acid, sodium hydroxide, ether, and ephedrine as well as burns and explosions.

Ephedrine and Ephedra

Ephedrine is another illicitly used amphetamine-like agent associated with complications of excessive sympathomimetic stimulation. Ephedra, a plant-derived product, also known as a Chinese herbal product, ma huang, has been associated with strokes and deaths in adolescent users.[76] The U.S. Food and Drug Administration has banned all ephedra-containing dietary supplements.

Khat and Methcathinone

Khat is a stimulant agent naturally occurring in the leaves of the plant *Catha edulis*.[77] These leaves are chewed to extract the active compounds, cathinone and methcathinone, which are stimulants with sympathomimetic effects.[78] Management and disposition follow the same guidelines as for cocaine. Smoking of khat does not typically result in clinical effects because the agent degrades with pyrolysis. Illicitly manufactured methcathinone is known as cat. Some methcathinone users experienced an extrapyramidal syndrome associated with elevated manganese levels, probably resulting from an inadvertent contaminant during production or inadequate purification. The role of chelation therapy for elevated manganese levels is uncertain.[79]

Other Stimulants

Substances vended as bath salts and labeled "not for human consumption" contain similar substances, including the methcathinone derivative mephedrone and the cathinone derivative methylenedioxypyrovalerone. These are exploited for an adrenergic "high"[80,81] and have no pharmacologically approved medical indications in the United States. Treatment is identical to that of cocaine and amphetamine toxicity.

www.ketabpezeshki.com 66485457-66963820

KEY CONCEPTS

- Rapid sedation with an intravenous benzodiazepine is the key for most symptoms from cocaine and other stimulants.
- Hyperthermia is a high-risk sign, and body temperature must be reduced rapidly.
- Beta-adrenergic blockade may cause paradoxical hypertension and increase coronary vasoconstriction and is contraindicated in acute toxicity.
- Wide-complex rhythms secondary to cocaine may respond to intravenous bicarbonate therapy.
- Cocaine body packers who become symptomatic need immediate surgery.
- Amphetamine symptoms and effects last longer than those produced by cocaine.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. *National Household Survey on Drug Abuse: Population Estimates, 1991*. Rockville, Md: National Institute of Drug Abuse, Department of Health and Human Services; 1992. DHHS-ADM-92-1887.
2. Results from the 2009 National Survey on Drug Use and Health: Volume I. Summary of National Findings. Rockville, Md: Office of Applied Studies, Substance Abuse and Mental Health Services Administration; 2010. NSDUH Series H-38A, HHS Publication No. SMA 10-458Findings.
3. *The National Survey on Drug Use and Health*. Rockville, Md: Substance Abuse and Mental Health Services Administration, Department of Health and Human Services; Available at www.samhsa.gov. Accessed December 6, 2011.
4. Marzuk PM, et al: Fatal injuries after cocaine use as a leading cause of death among young adults in New York City. *N Engl J Med* 1995; 332:1753.
5. *The DAWN Report: Highlights of the 2009 Drug Abuse Warning Network (DAWN) Findings on Drug Related Emergency Department Visits*. Rockville, Md: Center for Behavioral Health Statistics and Quality (formerly the Office of Applied Studies), Substance Abuse and Mental Health Services Administration; December 28, 2010. Available at www.oas.samhsa.gov/2k10/DAWN034/EDHighlights.htm.
6. *Drug Abuse Warning Network, 2007: National Estimates of Drug-Related Emergency Department Visits*. Rockville, Md: Office of Applied Studies, Substance Abuse and Mental Health Services Administration; 2010.
7. *Drug Abuse Warning Network, 2008: Area Profiles of Drug-Related Mortality*. Rockville, Md: Office of Applied Studies, Substance Abuse and Mental Health Services Administration; 2010.
8. Bauman JL, et al: Cocaine-related sudden cardiac death: A hypothesis correlating basic science and clinical observations. *J Clin Pharmacol* 1994; 34:902.
9. Javaid J, Musa M, Fischman MW: Kinetics of cocaine in humans after intravenous and intranasal administration. *Biopharm Drug Dispos* 1983; 4:9.
10. Hoffman RS, et al: Association between life-threatening cocaine toxicity and plasma cholinesterase activity. *Ann Emerg Med* 1991; 21:247.
11. Perez-Reyes M: Subjective and cardiovascular effects of cocaethylene in humans. *Psychopharmacology (Berl)* 1993; 113:144.
12. Marzuk PM, et al: Ambient temperature and mortality from unintentional cocaine overdose. *JAMA* 1998; 279:1795.
13. Bohnert AS, Prescott MR, Vlahov D, Tardiff KJ, Galea S: Ambient temperature and risk of death from accidental drug overdose in New York City, 1990-2006. *Addiction* 2010; 105:1049-1054.
14. Merigian KS, Roberts JR: Cocaine intoxication: Hyperpyrexia, rhabdomyolysis and acute renal failure. *J Toxicol Clin Toxicol* 1987; 25:135.
15. Herzlich BC, et al: Rhabdomyolysis related to cocaine abuse. *Ann Intern Med* 1988; 109:335.
16. Fisher A, Holroyd BR: Cocaine-associated dissection of the thoracic aorta. *J Emerg Med* 1992; 10:723.
17. Kline JN, Hirasuna JD: Pulmonary edema after freebase cocaine smoking—not due to an adulterant. *Chest* 1990; 97:1009.
18. Hollander JE, et al: Cocaine associated myocardial infarction: Mortality and complications. *Arch Intern Med* 1995; 155:1081.
19. Seaman ME: Acute cocaine abuse associated with cerebral infarction. *Ann Emerg Med* 1990; 19:34.
20. Mody CK, et al: Neurologic complications of cocaine abuse. *Neurology* 1988; 38:1189.
21. Daras M, et al: Neurovascular complications of cocaine. *Acta Neurol Scand* 1994; 90:124.
22. Traub SJ, Hoffman RS, Nelson LS: Current concepts: Body packing—the internal concealment of illicit drugs. *N Engl J Med* 2003; 349:2519.
23. Sudhakar CB, Al-Hakeem M, MacArthur JD, Sumpio BE: Mesenteric ischemia secondary to cocaine abuse: Case reports and literature review. *Am J Gastroenterol* 1997; 92:1053-1054.
24. MacGregor SN, et al: Cocaine use during pregnancy: Adverse perinatal outcome. *Am J Obstet Gynecol* 1987; 157:686.
25. Bauman JL, DiDomenico RJ: Cocaine-induced channelopathies: Emerging evidence on the multiple mechanisms of sudden death. *J Cardiovasc Pharmacol Ther* 2002; 7:195.
26. Bebarta VS, Summers S: Brugada electrocardiographic pattern induced by cocaine toxicity. *Ann Emerg Med* 2007; 49:827.
27. Ortega-Carnicer J, et al: Aborted sudden death, transient Brugada pattern, and wide QRS dysrhythmias after massive cocaine ingestion. *J Electrocardiol* 2001; 34:345.
28. Daras M, Koppel BS, Atos-Radzion E: Cocaine-induced choreoathetoid movements ("crack dancing"). *Neurology* 1994; 44:751.
29. Meleca RJ, et al: Mucosal injuries of the upper aerodigestive tract after smoking crack or freebase cocaine. *Laryngoscope* 1997; 107:620.
30. Maeder M, Ullmer E: Pneumomediastinum and bilateral pneumothorax as a complication of cocaine smoking. *Respiration* 2003; 70:407.
31. Blanksma CJ, Brand HS: Cocaine abuse: Orofacial manifestations and implications for dental treatment. *Int Dent J* 2005; 55:365.
32. Chambers HF, Morris DL, Tauber MG, Modin G: Cocaine use and the risk for endocarditis in intravenous drug users. *Ann Intern Med* 1987; 106:833.
33. Mendelson JH, Mello NK: Management of cocaine abuse and dependence. *N Engl J Med* 1996; 334:963.
34. Centers for Disease Control and Prevention (CDC): Agranulocytosis associated with cocaine use—four states, March 2008-November 2009. *MMWR Morb Mortal Wkly Rep* 2009; 58:1381-1385.
35. Farhat EK, et al: Levamisole-induced cutaneous necrosis mimicking coagulopathy. *Arch Dermatol* 2010; 146:1320-1321.
36. Waller JM, et al: Cocaine-associated retiform purpura and neutropenia: Is levamisole the culprit? *J Am Acad Dermatol* 2010; 63:530-535.
37. Bradford M, et al: Bilateral necrosis of earlobes and cheeks: Another complication of cocaine contaminated levamisole. *Ann Intern Med* 2010; 152:758-759.
38. Hoffman RS, Hollander JE: Thrombolytic therapy in cocaine-induced myocardial infarction [editorial]. *Am J Emerg Med* 1996; 14:693.
39. Wang K, Asinger RW, Marriot HJL: Current concepts: ST-elevation in conditions other than acute myocardial infarction. *N Engl J Med* 2003; 349:2128.
40. Hollander JE, et al: Effect of recurrent cocaine use on specific cardiac markers for the diagnosis of acute myocardial infarction. *Am Heart J* 1998; 135:245-252.
41. Kontos MC, Jesse RL, Tatum JL, Ornato JP: Coronary angiographic findings in patients with cocaine-associated chest pain. *J Emerg Med* 2003; 24:9.
42. Mohamad T, et al: Spectrum of electrographic and angiographic coronary artery disease in patients with cocaine associated myocardial infarction. *Coron Artery Dis* 2009; 20:332-336.
43. Chang AM, et al: Relationship between cocaine use and coronary artery disease in patients with symptoms consistent with acute coronary artery syndrome. *Acad Emerg Med* 2011; 18:1-9.
44. Bamberg F, et al: Presence and extent of coronary artery disease by cardiac computed tomography and risk for acute coronary syndrome in cocaine users among patients with chest pain. *Am J Cardiol* 2009; 103:620-625.
45. Crandall CG, Vonpatanasin W, Victor RG: Mechanism of cocaine induced hyperthermia in humans. *Ann Intern Med* 2002; 136:785.
46. Brogan WC, et al: Alleviation of cocaine-induced coronary vasoconstriction by nitroglycerin. *J Am Coll Cardiol* 1991; 18:581.
47. Haynes S, et al: Beta-adrenergic blockade in cocaine toxicity [letter]. *J Emerg Med* 1995; 13:537.
48. Lange RA, et al: Cocaine-induced coronary-artery vasoconstriction. *N Engl J Med* 1989; 321:1557.
49. Boehrer JD, et al: Influence of labetalol on cocaine-induced coronary vasoconstriction in humans. *Am J Med* 1993; 94:608.
50. Dattilo PB, et al: β-Blockers are associated with reduced risk of myocardial infarction after cocaine use. *Ann Emerg Med* 2008; 51:117.
51. Hoffman RS: Cocaine and β-blockers: Should the controversy continue? *Ann Emerg Med* 2008; 51:127.
52. McCord J, et al: Management of cocaine-associated chest pain and myocardial infarction: A scientific statement from the American Heart Association Acute Cardiac Care Committee of the Clinical Cardiology Council. *Circulation* 2008; 117:1897.
53. Cunningham R, et al: One-year medical outcomes and emergency department recidivism after emergency department observation for cocaine-associated chest pain. *Ann Emerg Med* 2009; 53:310-320.
54. Hollander JE, et al: Cocaine associated chest pain: One year follow-up. *Acad Emerg Med* 1995; 2:179.
55. Delaney K, Hoffman RS: Pulmonary infarction associated with crack cocaine use in a previously healthy 23-year-old woman. *Am J Med* 1991; 91:92.
56. Haim DY, Lippman ML, Goldberg SK, Walkenstein MD: The pulmonary complications of crack cocaine: A comprehensive review. *Chest* 1995; 107:233.
57. Rinder HM, et al: Platelet alpha granule release in cocaine users. *Circulation* 1994; 90:1162.

www.ketabpezeshki.com 66485457-66963820

58. Qureshi AI, Suri MF, Guterman LR, Hopkins LN: Cocaine use and the likelihood of nonfatal infarction and stroke, data from the National Health and Nutrition Examination Survey. *Circulation* 2001; 103:502.
59. Hollander JE: Management of cocaine-associated myocardial ischemia. *N Engl J Med* 1995; 333:1267.
60. Hollander JE, et al: Prospective multicenter evaluation of cocaine-associated chest pain. *Acad Emerg Med* 1994; 1:330.
61. Chase M, et al: Application of the TIMI risk score in ED patients with cocaine-associated chest pain. *Am J Emerg Med* 2007; 25:1015-1018.
62. McKee SA, et al: Cocaine use is associated with an increased risk of stent thrombosis after percutaneous coronary intervention. *Am Heart J* 2007; 154:159.
63. Honderick T, et al: A prospective, randomized, controlled trial of benzodiazepines and nitroglycerine or nitroglycerine alone in the treatment of cocaine associated acute coronary syndromes. *Am J Emerg Med* 2003; 21:39.
64. Saland KE, et al: Influence of morphine sulfate on cocaine induced coronary vasoconstriction. *Am J Cardiol* 2002; 90:810.
65. Mohamad T, et al: Cocaine-induced chest pain and β-blockade: An inner city experience. *Am J Therapeutics* 2008; 15:531-535.
66. Rangel C, et al: Beta-blockers for chest pain associated with recent cocaine use. *Arch Intern Med* 2011; 170:874-879.
67. Freeman K: Cocaine myocardial infarction and beta blockers: Time to rethink the equation? *Ann Emerg Med* 2008; 51:130-134.
68. McCarron MM, Wood JD: The cocaine body packer syndrome. *JAMA* 1983; 250:1417.
69. Macedo G, Ribeiro T: Esophageal obstruction and endoscopic removal of a cocaine packet. *Am J Gastroenterol* 2001; 96:1656-1657.
70. June R, Aks SE, Keys N, Wahl M: Medical outcome of cocaine body stuffers. *J Emerg Med* 2000; 18:221.
71. Weber JE, et al: Validation of a brief observation period for patients with cocaine associated chest pain. *N Engl J Med* 2003; 348:510.
72. Henry JA, et al: Low-dose MDMA (“ecstacy”) induces vasopressin secretion. *Lancet* 1998; 351:1784.
73. Greenberg A, Verbalis JG: Vasopressin receptor antagonists. *Kidney Int* 2006; 69:2124.
74. Ricaurte GA, et al: Aminergic metabolites in cerebrospinal fluid of humans previously exposed to MDMA: Preliminary observations. *Ann N Y Acad Sci* 1990; 600:699.
75. Alcott JV, Barnhart RA, Mooney LA: Acute lead poisoning in two users of illicit methamphetamine. *JAMA* 1987; 258:510.
76. Perotta DM, et al: Adverse events associated with ephedrine-containing products—Texas, December 1993 to September 1995. *MMWR Morb Mortal Wkly Rep* 1996; 45:689.
77. Kalix P: Pharmacological properties of the stimulant khat. *Pharm Ther* 1990; 48:397.
78. Glennon RA, et al: Methcathinone: A new and potent amphetamine-like agent. *Pharmacol Biochem Behav* 1987; 26:547.
79. Stepens A, et al: A parkinsonian syndrome in methcathinone users and the role of manganese. *N Engl J Med* 2008; 358:1009.
80. Brandt SD, et al: Analyses of second-generation “legal highs” in the UK: Initial findings. *Drug Test Anal* 2010; 2:377.
81. Prosser JM, Nelson LS: The toxicology of bath salts: A review of synthetic cathinones. *J Med Toxicol* 2012; 8:33-42.

www.ketabpezeshki.com 66485457-66963820

Chapter 155

Toxic Alcohols

Suzanne R. White

METHANOL

Perspective

Methanol is a colorless, volatile, slightly sweet-tasting alcohol. It is a product of natural fermentation and originally was manufactured from the distillation of wood, but currently, methanol is almost all synthetically produced. Certain products found in the home may contain high concentrations of methanol; these include antifreeze, windshield washer fluid, carburetor fluid, duplicator fluid, hobby engine fuel, gasohol, dry gas, Sterno, glass cleaners, cleaning agents, and thinners for shellacs, lacquers, adhesives, and inks. Methanol is a precursor in the manufacture of plastics, films, and dyes. Methanol is also found in formalin and embalming fluid. Illicit alcohol production remains a global source of methanol poisoning from products such as *chang'aa* (Kenya), *raki* (Turkey), and *tuica* (Romania).

Although epidemic poisonings from methanol are reported occasionally, most exposures are sporadic. In 2009, of the 2162 cases of methanol poisoning reported to American poison centers, 77% were unintentional, 6% had moderate to major complications, and 10 were fatalities. Treatment delay is associated with increased morbidity, making early recognition of clinical and laboratory clues crucial.

Principles of Disease

Pharmacology and Metabolism

Methanol is absorbed rapidly from the gastrointestinal tract, and blood levels peak 30 to 60 minutes after ingestion.[1] Transdermal and respiratory tract absorption also has resulted in toxicity, especially in infants. Certain occupations, including painting, glazing, varnishing, lithography, and printing, are high risk for inhalational exposure to methanol. Inhalational abuse of methanol is a recent trend that can result in toxic serum levels.[2]

At low serum concentrations, the elimination of methanol follows first-order kinetics; but at concentrations after overdose, zero-order kinetics predominate. This produces a prolonged half-life of 24 to 30 hours, which may be extended even further by the concurrent ingestion of ethanol. First-order elimination prevails at high levels (>300 mg/dL), possibly as a result of enhanced pulmonary elimination. Small amounts of ingested methanol may be exceptionally toxic. In adults, the smallest lethal dose reported is 15 mL of 40% methanol, and 4 mL of pure methanol has led to blindness. With appropriate and timely treatment, however, survival without loss of eyesight has been reported despite extremely high levels. From a pediatric perspective, the ingestion of only 1.5 mL of 100% methanol in a toddler (0.15 mL/kg) is sufficient to produce a toxic blood level of 20 mg/dL. Any suspected pediatric methanol ingestion warrants aggressive evaluation and treatment.

Methanol itself has little toxicity, producing less central nervous system (CNS) depression and inebriation than ethanol. Metabolites of the parent alcohol are extremely toxic, however. Although small amounts of methanol are eliminated by renal and pulmonary routes, 90% is metabolized in the liver. Methanol is oxidized by alcohol dehydrogenase (ADH) to formaldehyde, which is rapidly converted by aldehyde dehydrogenase to formic acid (Fig. 155-1). Formic acid is the primary toxicant and accounts for much of the anion gap metabolic acidosis and ocular toxicity peculiar to methanol ingestion.[3] Through a folate-dependent pathway, formic acid is degraded to carbon dioxide and water.

Pathophysiology

Optic neuropathy and putaminal necrosis are the two main complications of severe methanol poisoning. Long-term morbidity takes the form of visual impairment, including blindness, and parkinsonian motor dysfunction, characterized by hypokinesis and rigidity. Formic acid has a high affinity for iron and inhibits mitochondrial cytochrome oxidase, halting cellular respiration.[4] Methanol metabolism in the cytosol and mitochondria may account for a second mechanism of adenosine triphosphate depletion.[5] Lactate accumulation resulting from hypotension or seizures further compounds the metabolic acidosis predominantly caused by formate. Other mechanisms of toxicity involve increased lipid peroxidation, free radical formation, and impaired protective antioxidant reactions.[4,6] Severe dysfunction of subcellular metabolism from methanol also has been linked to significant disturbance in proteolytic-antiproteolytic balance.[7]

The primary sites of ocular injury are the retrolaminar optic nerve and retina. Selective myelin damage to the retrolaminar optic nerve has been seen at autopsy after methanol toxicity. Müller cells, the principal glial cells of retinal neurons and photoreceptors, have been proposed as the initial target in methanol-induced visual toxicity. It seems that they alone harbor the enzymes necessary to metabolize methanol to formate. Histopathologic correlates suggest that retinal cells develop intra-axonal swelling, calcium influx, mitochondrial destruction, and microtubular disruption. Ultimately, this interferes with transport of essential proteins from the retinal neuron cell body to the nerve fiber axoplasm. Oligodendrocyte involvement causes myelin degeneration and leads to visual decrements. Acidosis may accelerate this process by enhancing nonionic diffusion of formic acid into neurons and further increasing lactate production.[4] This self-perpetuating cycle of acidosis, termed *circulus hypoxicus,*[8] underscores the need for

www.ketabpezeshki.com 66485457-66963820

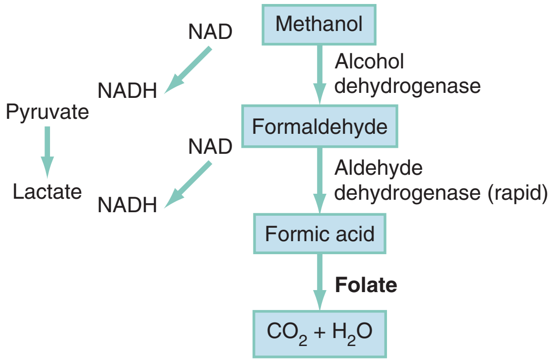


Figure 155-1. Metabolism of methanol. *NAD,* nicotinamide adenine dinucleotide; *NADH,* reduced form of nicotinamide adenine dinucleotide.

aggressive correction of pH to accomplish ion trapping of formate outside the CNS.

Methanol adversely affects other areas of the CNS, specifically the basal ganglia. Bilateral, symmetrical putaminal hypodensities, hemorrhages, or cystic lesions are characteristic, occurring in 13.5% of patients. Necrosis is described in the subcortical white matter, spinal cord anterior horn cells, and cerebellum.[9] Acute signs and symptoms may be lacking or may take several days to develop despite the presence of these radiographic findings. The cellular mechanisms of injury may be similar to the mechanisms of the ophthalmologic injury, but the reason for localization of neurologic damage to the basal ganglia is unknown. Quantitative neuropathologic studies conflict as to whether concentrations of formic acid within the putamen are higher than levels in the blood or other tissues. Massive edema adjacent to the putamen shown by magnetic resonance imaging (MRI) suggests a possible localized disruption of the blood-brain barrier. Other proposed mechanisms for the vulnerability of this region include the unique pattern of arterial blood supply and venous drainage and greater metabolic activity.

Clinical Features

With individual cases of methanol poisoning, the history may be unobtainable or unreliable. The diagnosis should be considered in patients with altered mental status, visual complaints, or metabolic acidosis and in patients with occupations that put them at high risk for exposure. Because methanol is a poor substrate for ADH, a latency period exists between the time of ingestion and metabolism to the formate that causes visual or metabolic disturbance. The typical 12- to 24-hour latency may be shorter when large amounts are consumed or longer when ethanol is coingested (range, 40 minutes to 72 hours).[1] Formic acid accumulation may be ongoing, with risk for significant toxicity, in patients who present early despite being initially asymptomatic. When symptoms are manifested, they are primarily neurologic, gastrointestinal, or ocular.

Although methanol is less inebriating than ethanol, early symptoms of methanol poisoning include depressed mental status, confusion, and ataxia. Nonspecific complaints of weakness, dizziness, anorexia, headache, and nausea develop; in severe cases, coma and seizures may be seen. Although vomiting and abdominal pain commonly result from mucosal irritation, the absence of gastrointestinal complaints does not rule out a serious ingestion.[1] Abdominal tenderness, however, may be so severe that it suggests an acute surgical abdomen.[1] This may result from pancreatitis, and elevation of serum amylase is relatively common, but increased salivary amylase isoenzyme can occur without pancreatic inflammation.

Visual disturbances are seen in 50% of patients, and their development may precede or parallel that of other symptoms.[8] Patients may complain of cloudy, blurred, indistinct, or misty vision or may note yellow spots or, rarely, photophobia. The most common acute field defect is a dense central scotoma.[10] Some patients compare their visual symptoms with "stepping out into a snowstorm," a complaint unique to methanol ingestion. Patients can have a complete lack of light perception and total loss of vision. Visual acuity should be determined. On examination, optic disc hyperemia is seen at 18 to 48 hours after ingestion. Peripapillary retinal edema follows, is most striking in the nerve fiber layer along the vascular arcades, and only rarely involves the macula.[5,10] Sluggishly reactive or fixed and dilated pupils indicate a poor prognosis. Pallor and cupping, indicative of optic atrophy, are late findings suggesting a poor prognosis for visual recovery. On occasion, the fundus may appear normal, even in patients with visual symptoms.

Compensatory tachypnea heralds the onset of metabolic acidosis, which often may be severe, with reported serum bicarbonate concentrations of less than 5 mEq/L and an arterial pH less than 7.0. Early tachycardia has been noted, but in general, cardiovascular abnormalities are rare.[1] Hypotension and bradycardia, when present, are preterminal findings.[11] Historically, death is associated with a peculiar, abrupt cessation of respiration rather than with cardiovascular collapse.[1] Multiple organ failure is rare.[11]

Prognosis after methanol ingestion seems to correlate with the degree of acidosis, time to presentation, and initiation of treatment within 8 hours of exposure.[1,12] Poor prognosis is associated with coma, seizures, or arterial pH less than 7.0.[11] A large outbreak was associated with a fatality rate of 44%.[13] Patients surviving the acute phase of toxicity may be left with permanent blindness or neurologic deficits, such as parkinsonism, toxic encephalopathy, polyneuropathy, cognitive dysfunction, transverse myelitis, primitive reflexes, or seizures.[14]

Diagnostic Strategies

A severe anion gap metabolic acidosis is the hallmark of methanol poisoning. In some cases, this sign may be the only diagnostic clue. Because the onset of acidosis may be delayed 12 to 24 hours, a normal anion gap does not rule out methanol exposure. Absence of high anion gap acidosis has been described in cases with concomitant ethanol, lithium, or bromide ingestion. In methanol toxicity, this anion gap is due primarily to the presence of formic acid, with a variable contribution from lactic acid. Another classic laboratory finding in methanol toxicity is an elevated osmol gap. The osmolal gap is defined as follows:

$$\text{Osmol gap} = \text{measured serum osmolarity} - \text{calculated serum osmolality}$$

Serum osmolality depends on the presence of low-molecular-weight solutes, primarily sodium, chloride, glucose, and blood urea nitrogen (BUN). One formula for calculation of osmolality attributable to these solutes is as follows:

$$\text{Calculated serum osmolality (mOsm/kg)} = 2(Na^+) + [BUN/2.8] + [glucose/18] + [ethanol (mg/dL)/4.6]$$

The "normal" osmol gap is often cited to be less than 10 mOsm/kg when the preceding equation is used. This is an arbitrary number, and there is considerable variability in baseline osmolal gaps in patients, particularly children. An osmol gap significantly greater than 10 mOsm/kg may be a useful aid in the diagnosis of toxic alcohol ingestion. In addition to methanol, ethylene glycol, and isopropanol, other low-molecular-weight solutes, such as

www.ketabpezeshki.com 66485457-66963820

ethanol, acetone, propylene glycol, mannitol, glycerol, and ethyl ether, may cause elevated osmol gaps. Caution should be taken, however, in ruling out toxic alcohol ingestion with a normal osmol gap for several reasons. First, calculated serum osmolality results may vary among laboratories and must be done by the freezing point depression method. Also, delayed presentation after toxic alcohol ingestion may be associated with prior metabolism of most of the parent alcohol. Because only the parent compound is osmotically active and because the charged metabolites are electrically balanced by sodium, there may be little or no osmol gap elevation in this setting. Finally, a toxic level of either methanol or ethylene glycol may be present with a gap of only 10 mOsm/kg. If there is clinical suspicion of toxic alcohol ingestion, direct measurement of the serum toxic alcohol level is necessary, and if it is not readily available, empirical treatment is warranted.[15] Rhabdomyolysis, pancreatitis, and metabolic derangements, such as hypomagnesemia, hypokalemia, and hypophosphatemia, are also described with methanol poisoning.

Computed tomography may be indicated in an intoxicated patient with altered mental status. The characteristic finding of bilateral putaminal lesions suggests methanol poisoning, but this finding also may be seen with Leigh's syndrome, Wilson's disease, hypoxic-ischemic insult, encephalitis, and certain metabolic disorders. Ischemic necrosis, cerebral edema, or brain hemorrhages also may be noted. Follow-up scans may have prognostic value because parkinsonian features are unlikely to develop in patients whose putaminal lesions resolve within a short time frame.[16] MRI may also detect putaminal aberrations or optic neuropathy from methanol intoxication.

Differential Considerations

Methanol and ethylene glycol cause inebriation and are ingested as ethanol substitutes. The differential diagnosis of a patient with altered mental status includes hypoglycemia, head trauma, postictal state, carbon dioxide narcosis, hypoxia, infection, hepatic encephalopathy, other metabolic disorders, thiamine deficiency, endocrinopathy, drug abuse, and other poisoning. For patients who present with severe abdominal pain and altered mental status, the differential diagnosis could include a long list of intraabdominal entities. When an anion gap acidosis is identified, however, the differential diagnosis should be tapered toward entities that cause this, and a primary decision should be made as to whether the acidosis is a result of an ingested toxin or some other cause (e.g., mesenteric ischemia, diabetic ketoacidosis). Toxic alcohol ingestion should be included in the differential diagnosis for patients with depressed mental status of unknown cause. Causes of an elevated anion gap in patients without evidence of renal failure, hypotension, hypoxemia, diabetes, seizures, or alcoholism include methanol, ethylene glycol, paraldehyde, isoniazid, iron, salicylates, toluene, and lactic acidosis from myriad toxicants, including metformin, carbon monoxide, cyanide, and cocaine. Isopropanol does not cause an increased anion gap. Ethylene glycol and methanol may cause a "double gap" (i.e., an osmol gap in addition to the anion gap). Other substances that contribute to an elevated osmol gap include isopropyl alcohol, ethanol, propylene glycol, mannitol, glycerol, and ethyl ether. Other situations in which double-gap acidosis may be encountered include diabetic ketoacidosis; alcoholic ketoacidosis; acetonitrile, methanol, ethylene glycol, and propylene glycol toxicity; multiple organ failure; chronic renal failure; and critical illness. Hyperlipidemia and hyperproteinemia, by decreasing the measured sodium concentration, can increase the osmolal gap.

Certain unique characteristics of methanol and ethylene glycol intoxication may lead to the specific diagnosis. The presence of ocular complaints unique to methanol poisoning is a valuable clue. Ethylene glycol ingestion often is associated with calcium oxalate crystalluria, which is not seen in methanol ingestion. Ultimately, a definitive diagnosis requires the documented presence of the parent alcohol through laboratory tests that may not be routinely available. It is often necessary to start treatment on the basis of clinical suggestion alone. Because the initial treatment for methanol and ethylene glycol is almost identical, identification of the specific toxic alcohol is not crucial to the initiation of therapy.

Management and Disposition

See the discussion on management in the following section on ethylene glycol.

ETHYLENE GLYCOL

Perspective

Ethylene glycol is a viscous, colorless, odorless, slightly sweet-tasting liquid. Because it lowers the freezing point of water, its primary utility is as a commercial antifreeze or coolant. Other sources include airplane deicing solutions, hydraulic brake fluids, and industrial solvents and precursors; it also is a component of certain paints, lacquers, and cosmetics. Most ethylene glycol poisonings occur with the ingestion of antifreeze. Unusual poisoning scenarios are described, including an epidemic after the contamination of water supplies and the intentional poisoning of an infant, manifested as an inherited metabolic disorder. In 2009, the American Association of Poison Control Centers reported 5977 exposures to ethylene glycol. Of those exposures, 72% were unintentional, and 11% resulted in moderate or severe effects with 19 fatalities. If it is treated early and aggressively, ethylene glycol poisoning is unlikely to result in death. Conversely, failure to treat ethylene glycol ingestion may result in multiorgan failure and death within 24 to 36 hours.[17]

Principles of Disease

Pharmacology and Metabolism

Absorption of ethylene glycol is rapid after ingestion. It distributes evenly to tissues with a volume similar to that of body water. Peak blood levels are reached within 1 to 4 hours after ingestion. In contrast to methanol and isopropanol, ethylene glycol is nonvolatile at room temperature, so absorption by inhalation is unlikely. Reported half-lives range from 3 to 8.6 hours.[18] When metabolism is blocked by fomepizole or ethanol, the half-life increases to 11 to 15 hours or 17 hours, respectively.[19] The toxic and lethal doses of 100% ethylene glycol have been reported as 0.2 mL/kg and 1.4 mL/kg. At the other extreme, with modern treatment, patients who have ingested 3000 mL have survived. Twenty-seven percent of ethylene glycol is excreted unchanged by the kidneys. The remainder is oxidized through hepatic ADH and other oxidative enzymes to various toxic organic aldehydes and acids (Fig. 155-2).

Pathophysiology

Unmetabolized ethylene glycol has limited toxicity, yet all metabolites are toxic. In humans, 2.3% of a dose of ethylene glycol ultimately is converted to oxalic acid, most of which is excreted in the urine. A fraction of oxalic acid combines with calcium to form calcium oxalate crystals, which precipitate in renal tubules, brain, and other tissues. Studies have shown definitively that the accumulation of calcium oxalate monohydrate crystals in kidney tissue produces renal tubular necrosis that leads to kidney failure.[20] Other authors suggest that glycolate levels correlate better with disruption of CNS metabolism, development of renal failure, and

www.ketabpezeshki.com 66485457-66963820

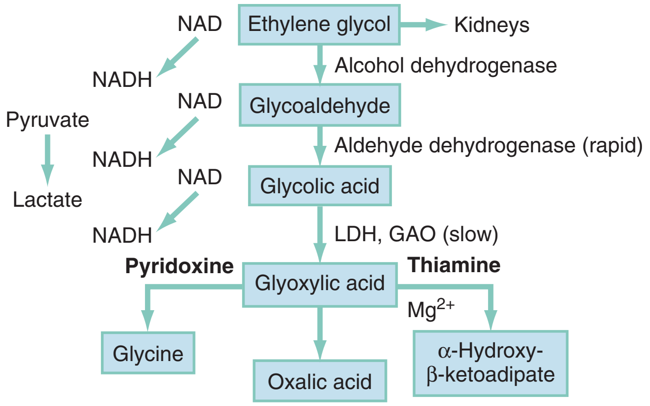


Figure 155-2. Metabolism of ethylene glycol. *GAO,* glycolic acid oxidase; *LDH,* lactate dehydrogenase; *NAD,* nicotinamide adenine dinucleotide; *NADH,* reduced form of nicotinamide adenine dinucleotide.

mortality.[21] Because the intermediate metabolite, glyoxylic acid, theoretically can be shunted toward pyridoxine-dependent or thiamine-dependent pathways to generate the nontoxic products glycine and α-hydroxy-β-ketoadipate (see Fig. 155-2), both pyridoxine and thiamine are routinely used in therapy.

On histologic examination, proximal renal tubular dilation with hydropic change and vacuolar degeneration, intratubular crystal deposition, and edema of the interstitium are seen. Relative sparing of the glomeruli is typical, although glomerular interloop space crystal deposition may occur. Glomerular function is preserved, but tubular dysfunction manifesting as protein leak is noted.[22] Neuropathologic changes induced by ethylene glycol include diffuse calcium oxalate deposition with petechial hemorrhages in the retina, brain, vessel walls, and perivascular spaces, with evidence of cerebral edema and chemical meningoencephalitis. Similar changes also have been noted in the liver, spleen, pancreas, pleura, lungs, pericardium, and blood vessel walls throughout the body. Myonecrosis occurs in skeletal and myocardial muscle, and rhabdomyolysis and myocardial dilation occur. Fatty liver with focal necrosis has been noted.

The metabolism of ethylene glycol results in a profound anion gap metabolic acidosis, caused mainly by glycolic acid. Elevated lactate, triggered by the altered redox potential within cells and inhibition of the citric acid cycle by products of glyoxylate metabolism, is a minor contributing factor to the severe acidosis.

Clinical Features

The clinical syndrome with ethylene glycol ingestion is divided into four stages: (1) acute neurologic stage, (2) cardiopulmonary stage, (3) renal stage, and (4) delayed neurologic sequelae stage. The severity of illness in each stage and the progression through stages may vary. Stages may be skipped and patients may die in any stage of ethylene glycol poisoning. Poor prognostic factors include hyperkalemia, severe acidosis, seizures, and coma. Metabolic acidosis and symptoms typically occur within 4 to 8 hours but may be delayed for 12 hours or longer if ethanol has been coingested.

Stage I, the *acute neurologic stage,* occurs 30 minutes to 12 hours after ingestion. The parent alcohol causes approximately the same degree of inebriation as ethanol does, with CNS depression, slurred speech, nystagmus, ataxia, and vomiting. With large ingestions, more dramatic neurologic findings, such as hallucinations, seizures, and coma, may be present during the early phase of intoxication. Ocular findings including decreased pupillary reflexes, decreased visual acuity, optic disc blurring, papilledema, and loss of color discrimination have been reported, but methanol exposure was not ruled out in most of these case reports.

Stage II, the *cardiopulmonary stage,* occurs 12 to 24 hours after ingestion. Often, the patient exhibits mild hypertension and tachycardia. Tachypnea may reflect the underlying profound metabolic acidosis or may herald the onset of cardiogenic or noncardiogenic pulmonary edema.[8] The mechanism of acute respiratory distress syndrome (ARDS) is unclear but may be related to the toxicity of glycolic and glyoxylic acids and to the deposition of calcium oxalate crystals within the lungs. Pulmonary infiltrates are described during this phase. Circulatory collapse may occur as a result of myocardial depression. Hypocalcemia, rarely associated with tetany or cardiac dysrhythmia, occurs in 30% of patients as a result of systemic chelation of calcium by oxalate. Myositis with muscle tenderness and creatine kinase (CK) elevation results from skeletal muscle inflammation and necrosis.

Stage III, the *renal stage,* occurs 24 to 72 hours after ingestion. In one epidemic of 36 patients, renal damage was noted in 67%. Awake patients may complain of flank pain or have costophrenic angle tenderness. Calcium oxalate monohydrate or dihydrate crystalluria is seen in only 50% of cases. Hematuria and proteinuria are common, however. As with other causes of acute tubular necrosis, oliguria is not always present, but it may develop 12 hours after ingestion and may progress to frank anuria. The outcome has not been well studied in patients who have renal failure. Prolonged hemodialysis may be necessary, although recovery of renal function has been reported. Delayed onset of ARDS has been reported to occur during this stage, but it is more typically seen in stage II. The degree of acidosis, delay in presentation, and glycolate levels correlate better than ethylene glycol levels with the development of renal failure.[23]

Stage IV, the *delayed neurologic sequelae stage,* occurs 6 to 12 days after ingestion and typically is manifested as cranial neuropathy.[24] All cases have been associated with renal failure. Facial diplegia, occasionally with deafness, is most frequently encountered. Other reported findings include dysarthria, dysphagia, tongue deviation, visual deterioration, and internal ophthalmoplegia. Delayed and persistent cognitive and motor deficits, such as ataxia, chorea, coma, and late personality changes, are also reported. Total paralysis from severe axonal peripheral polyneuropathic degeneration with oxalate deposition[25] and polyradiculopathy from nerve root (not distal) disease are also reported. Although some improvement in neurologic status has been noted at follow-up, most patients are left with residual neurologic deficits. Some authors have coined the term *facial auditory nerve oxalosis* for this delayed syndrome on the basis of heavy calcium oxalate crystal deposition along the subarachnoid portions of the seventh and eighth cranial nerves seen at autopsy. Whether calcium oxalate deposition is a cause is unclear. Direct mechanical injury from crystals, inflammatory response triggered by ethylene glycol metabolites, meningitis, and pyridoxine deficiency have been proposed as mechanisms. Because the syndrome has been reported only since 1978, it is possible that the advent of hemodialysis has allowed more patients with potentially lethal ingestions of ethylene glycol to survive to display delayed neurologic complications.

Diagnostic Strategies

Useful laboratory tests for evaluation of a patient with potential ethylene glycol toxicity include serum electrolyte values; calcium, BUN, creatinine, and serum glucose concentrations; serum osmolality; blood ethanol level; arterial blood gas analysis; ethylene glycol level; electrocardiogram; and urinalysis. Although crystalluria is considered the hallmark of ethylene glycol ingestion, its absence does not rule out the diagnosis because less than half of patients have this finding. Crystalluria may take the form of

www.ketabpezeshki.com 66485457-66963820

envelope-shaped calcium oxalate dihydrate crystals or needle-shaped calcium oxalate monohydrate crystals, which are occasionally mistaken for hippurate crystals.[8] Other crystal shapes and composites have been noted so that in the setting of combined anion and osmolal gap elevation, the presence of *any* type of crystalluria warrants a search for ethylene glycol. Monohydrate crystals are thought to be more specific for ethylene glycol poisoning. Irrigating the urinary bladder with 50 to 100 mL of saline, centrifuging the irrigant, and examining the sediment for crystals may yield the diagnosis in patients who are already anuric. Other findings reflecting tubular dysfunction include decreased specific gravity, proteinuria, microscopic hematuria, pyuria, and cylindruria. Falsely elevated ethylene glycol levels may be seen in the face of elevated lactate or lactate dehydrogenase with certain enzymatic assays.

Freshly voided urine can be examined for fluorescence with Wood's lamp. Sodium fluorescein is added to antifreeze to aid in the detection of radiator leaks. Urinary fluorescence may be seen 6 hours after ingestion of fluorescein-containing antifreeze. Gastric contents and the patient's skin or clothing also may fluoresce under Wood's lamp. The lack of fluorescence does not rule out ethylene glycol ingestion, however, because examiner sensitivity, specificity, and inter-rater reliability are low.[26] One study found urinary fluorescence in all specimens from children evaluated for conditions unrelated to poisoning.[27] Specimens should be collected in borosilicate glass test tubes or deposited directly onto gauze or filter paper because many plastic specimen containers and some glass tubes are fluorescent. The urine pH also should be checked and adjusted to 4.5 or higher before Wood's lamp examination.

Leukocytosis may be seen in ethylene glycol poisoning, with a typical white blood cell count of 10,000 to 40,000/μL, but it is neither a sensitive nor a specific finding and is not of diagnostic value. The hematocrit and platelet counts are normal. One third of patients have hypocalcemia, which is most likely caused by calcium precipitation with oxalate. QT prolongation on the electrocardiogram leads to the early diagnosis of hypocalcemia. Rarely, profound hypocalcemia resulting in seizures and tetany may occur. The CK level can be elevated as a result of toxic effects of ethylene glycol metabolites on muscle tissue.

Similar to methanol, ethylene glycol often causes a profound anion gap metabolic acidosis when the metabolites glycolic acid and glyoxylic acid (and, to some extent, lactic acid) accumulate. False elevations of lactic acid levels may occur in the presence of glycolate with certain analyzers.[28] Similar to methanol toxicity, an elevated osmolal gap as measured by freezing point depression can be a clue, but lethal concentrations can be associated with a normal or only slightly elevated osmolal gap. The cerebrospinal fluid may be normal or have a cloudy or bloody appearance, with increased protein or, most commonly, a polymorphonuclear pleocytosis.

Imaging studies show cerebral edema with decreased attenuation in the mediobasilar portions of the brain, typically with a return to isodensity within 1 week; this does not correspond to the clinical picture.[8] MRI in one patient with delayed cranial neuropathy showed gadolinium enhancement of cranial nerve V bilaterally, possibly secondary to calcium oxalate deposition. Electroencephalographic findings have been nonspecific.

Differential Considerations

Classically, patients who ingest ethylene glycol appear intoxicated without the odor of ethanol and have an anion gap metabolic acidosis, increased osmolal gap, and calcium oxalate crystalluria. Without evidence of alcoholic ketoacidosis or diabetic ketoacidosis, the differential diagnosis of the double gap should include methanol and ethylene glycol. The hallmark finding with late presentation is renal toxicity. Toxicant-induced acute renal failure is extensively reviewed elsewhere; substances commonly implicated include antimicrobials, nonsteroidal anti-inflammatory drugs, acetaminophen, halogenated hydrocarbons, radiocontrast media, metals, antineoplastic agents, and myoglobin. Hypocalcemia and a prolonged QT interval are important diagnostic clues. Toxicant-induced hypocalcemia is unusual and may be related to aminoglycosides, calcitonin, cisplatin, loop diuretics, interferon alfa, mithramycin, pentamidine, and phosphate infusions. Healthy individuals with dietary excesses of vitamin C or foods rich in oxalate, such as tomatoes, garlic, spinach, rhubarb, cocoa, and tea, may exhibit calcium oxalate crystalluria.

Management

Methanol and ethylene glycol ingestions are treated essentially in the same manner, and the following recommendations apply to both. As in any overdose, resuscitation and stabilization are paramount, including naloxone, bedside glucose determination, and thiamine, if indicated. Specific blood levels that confirm the presence of these substances may not be readily available, and a delay in therapy can lead to irreversible organ damage or death. For any significant history of exposure, treatment should be initiated pending a confirmatory toxic alcohol blood level.

Methanol and ethylene glycol are absorbed rapidly from the gastrointestinal tract; because gastric emptying has not been shown to alter clinical course or outcome and may be associated with complications, its use is restricted to possible nasogastric suction for patients who have ingested more than a swallow and arrive in the emergency department within 30 to 60 minutes of ingestion.[29] Even in these cases, it is of unproven value. Forced diuresis is of no value and may cause pulmonary edema and ARDS. Early intubation may be indicated to protect the airway against aspiration and in anticipation of further deterioration in mental status.

Three treatment goals exist for patients with methanol or ethylene glycol toxicity: (1) correction of metabolic acidosis with bicarbonate; (2) ADH enzyme blockade, which inhibits the metabolism of methanol and ethylene glycol to toxic metabolites; and (3) removal of the parent alcohol and its metabolites by hemodialysis. The acidic metabolites of methanol and ethylene glycol can cause a profound bicarbonate-resistant metabolic acidosis, with several hundred milliequivalents of excess acid produced per hour. In contrast to lactic acid, these acids are not metabolized to bicarbonate, and massive amounts of bicarbonate may be necessary merely for partial correction of the acidosis.[8] Early correction of metabolic acidosis may be beneficial in reversing methanol-induced visual impairment,[30] most likely related to the induction of a larger fraction of dissociated formic acid, which should decrease the amount of formic acid entering the CNS. Depending on the severity of the patient's acidosis, bicarbonate can be administered intravenously by intermittent boluses, by an initial bolus followed by an infusion, or by infusion alone. Boluses of 1 to 2 mEq/kg to attain a target serum pH of 7.45 to 7.50 followed by an infusion of 150 mEq/L of sodium bicarbonate in 5% dextrose at 1.5 to 2 times the maintenance fluid rate are suggested. With ethylene glycol, the potential for worsened hypocalcemia during the administration of large amounts of sodium bicarbonate should be considered.

To prevent further production of the toxic and acidic metabolites of methanol and ethylene glycol, metabolism of the parent compounds by the enzyme ADH must be blocked by either ethanol or fomepizole (Antizol). As experience has been gained with fomepizole, it is generally thought to be more advantageous than ethanol from a safety and convenience perspective. ADH blockade should be carried out in any adult or child with symptoms or with methanol or ethylene glycol levels greater than

www.ketabpezeshki.com 66485457-66963820

Table 155-1 Standard Range of Therapeutic Doses of Ethanol Based on Average Pharmacokinetic Values

	AMOUNT ABSOLUTE ETHANOL*	VOLUME (43% ORAL SOLUTION)†	VOLUME (10% IV SOLUTION)‡
Loading dose§	600 mg/kg	1.8 mL/kg	7.6 mL/kg
Standard maintenance dose (nondrinker)	66 mg/kg/hr	0.2 mL/kg/hr	0.83 mL/kg/hr
Standard maintenance dose (chronic drinker)	154 mg/kg/hr	0.46 mL/kg/hr	1.96 mL/kg/hr
Maintenance dose during dialysis (nondrinker)	169 mg/kg/hr	0.5 mL/kg/hr	2.13 mL/kg/hr
Maintenance dose during dialysis (chronic drinker)	257 mg/kg/hr	0.77 mL/kg/hr	3.26 mL/kg/hr

Modified from Barceloux DG, Krenzelok EP, Olson K, Watson W: American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning. Ad Hoc Committee. J Toxicol Clin Toxicol 37:537, 1999.
*Specific gravity 0.79.
†Equivalent to 86 proof undiluted liquor (34 g/dL of ethanol).
‡Equivalent to 7.9 g/dL of ethanol.
§Assumes that initial ethanol concentration is zero; dose is independent of chronic drinking status.

20 mg/dL, even if the patient is asymptomatic. If ethanol is used to block ADH, the goal is to maintain the blood ethanol level between 100 and 150 mg/dL, which completely saturates ADH.[8] The affinity of ADH for ethanol is 10 to 20 times greater than for methanol and 100 times greater than for ethylene glycol. When the metabolism of methanol and ethylene glycol is blocked by ethanol, their half-lives increase to more than 30 hours and 17 hours, respectively. Prevention of methanol and ethylene glycol metabolism by ethanol explains the delayed toxicity seen in patients who ingest ethanol in combination with either of these substances. In dosing of ethanol, it also is important to measure the patient's initial blood ethanol level. If it is greater than 100 mg/dL, a loading dose is unnecessary, and a maintenance infusion can be started (Table 155-1). The required maintenance dose of ethanol may nearly triple during hemodialysis because ethanol also is efficiently removed. Ethanol may be given orally or intravenously. Potential side effects of intravenous administration include CNS and respiratory depression, hypotension, vomiting, hypoglycemia, and thrombophlebitis, although even in children, adverse effects are limited.[31] Oral ethanol loading may be associated with gastritis. Initial close monitoring of serum ethanol and glucose levels every 1 to 2 hours is essential until a steady-state level of 100 to 150 mg/dL is achieved. Levels should be checked every 2 to 4 hours thereafter. Monitoring of ethanol therapy ideally is accomplished in the intensive care unit.

Similar to ethanol, fomepizole blocks the metabolism of methanol and ethylene glycol by ADH and prevents the formation of toxic metabolites.[19,32] When the metabolism of methanol and ethylene glycol is blocked by fomepizole, their half-lives increase to an average of 52 hours and 17 hours, respectively.[33] Although fomepizole is a pregnancy category C drug and not approved for pediatric use, it has been used in children.[31] Advantages of fomepizole over ethanol include ease of administration, predictable pharmacokinetics, improved patient safety profile, standardized and less complicated dosing regimen that does not require direct observation or frequent blood monitoring, longer duration of action, and lack of CNS depression.[34] Nonetheless, simply blocking toxic alcohol metabolism does not alter the toxicity of preformed metabolites. The use of neither fomepizole nor ethanol supplants the need for hemodialysis. The main disadvantage of the use of fomepizole is its cost. The dosing regimen for adults and pediatric patients is 15 mg/kg, followed by 10 mg/kg every 12 hours for four doses. After five doses, the dose increases to 15 mg/kg every 12 hours until the ethylene glycol concentration is undetectable or less than 20 mg/dL *and* the patient is asymptomatic with a normal arterial pH. Dosing changes are required during hemodialysis. Side effects of fomepizole include headache, nausea, dizziness, inflammation at the site of infusion, rash, eosinophilia, and mild reversible transaminase elevation. A single case of hypotension and bradycardia related to the rapid infusion has been described.[35] No prospective clinical trials have compared the relative efficacy, safety, or cost of fomepizole and ethanol in the treatment of ethylene glycol or methanol toxicity; however, a 10-year review of adverse events in patients showed fomepizole to be safer than ethanol.[36]

Rapid removal of the methanol or ethylene glycol through hemodialysis before it has been metabolized remains the cornerstone of therapy. In addition, hemodialysis, preferably with use of a dialysate high in bicarbonate, corrects acidosis and uremia, aids in fluid management and cardiovascular stabilization, and removes the toxic metabolites in late presenters. Hemodialysis decreases the half-life of methanol and ethylene glycol to 2.5 to 3.5 hours. Peritoneal dialysis and hemoperfusion are much less effective.[36]

Indications for hemodialysis in patients with methanol or ethylene glycol toxicity are controversial. In general, hemodialysis is indicated for patients who have metabolic acidosis, renal insufficiency, deterioration despite intensive care, electrolyte disturbance, or visual disturbances with methanol.[8] In addition, a blood level of either substance greater than 50 mg/dL usually calls for dialysis,[35,37] but in patients with normal kidneys, prolonged fomepizole treatment alone has been used without hemodialysis.[38,39] For ethylene glycol, a glycolic acid level greater than 8 mmol/L, an anion gap greater than 20 mmol/L, or an initial pH less than 7.30 predicts renal failure and the need for hemodialysis.[40] Methanol and ethylene glycol levels should be interpreted in the context of the clinical status and the time after ingestion. An acidotic patient with a low blood level after a delayed presentation requires more aggressive treatment than an asymptomatic patient with a high level.

The endpoint for hemodialysis is an undetectable serum ethylene glycol or methanol concentration and the disappearance of acid-base abnormalities and signs of systemic toxicity. Resolution of the anion gap also may serve as an endpoint for hemodialysis in situations in which levels are not available or reliable (i.e., in patients with delayed presentation).

In methanol poisoning, the rate of the final degradation reaction of formic acid to carbon dioxide and water depends on the cofactor folate in primates (see Fig. 155-1), so 50 mg of leucovorin (folinic acid) should be given intravenously (IV) every 4 hours to adults with methanol toxicity. Likewise, the cofactors thiamine and pyridoxine have theoretic benefit on the basis of their use in humans with primary hyperoxaluria, although no clinical trials have studied their efficacy in the treatment of ethylene glycol toxicity. Adequate cofactor levels minimize oxalic acid production by favoring the production of other, less toxic metabolites (see Fig. 155-2). The recommended adult doses are thiamine, 100 mg IV every 6 hours, and pyridoxine, 50 mg every 6 hours for 2 days. With symptomatic hypocalcemia, IV calcium should be supplemented, albeit cautiously, to avoid further precipitation of calcium oxalate crystals in tissues. Asymptomatic hypercalcemia need not be treated. Magnesium is a cofactor along with thiamine for the detoxification of glycolic acid and should be replaced in patients who are deficient.

www.ketabpezeshki.com 66485457-66963820

Disposition

Admission is generally necessary for patients undergoing treatment for ethylene glycol or methanol exposure. In addition, all patients with clinical or laboratory findings consistent with these ingestions should be admitted, even when the history is lacking or unavailable. Early consultation with a nephrologist for possible hemodialysis is necessary in the management of suggested toxic alcohol ingestion. If such services are not available, the patient should be given an ADH inhibitor and transferred to a setting where dialysis is available. A regional poison center (800-222-1222) or medical toxicologist may be contacted to guide management. An ophthalmologist can evaluate visual injury fully in patients with methanol poisoning. Neurologic consultation and follow-up monitoring of patients with either methanol or ethylene glycol toxicity are prudent given the potential for delayed or persistent neurologic sequelae.

Prevention

The bittering agent denatonium benzoate (Bitrex) has been added to consumer automotive products containing 10% or more ethylene glycol or 4% or more methanol, but the effect of this effort has not yet decreased the frequency or severity of pediatric antifreeze poisoning.[41] Another opportunity for prevention is the substitution of less toxic glycols, such as propylene glycol, into commercial antifreezes.

ISOPROPYL ALCOHOL

Perspective

Isopropyl alcohol (isopropanol) is a clear, colorless liquid with a slightly bitter taste. It is the second most commonly ingested alcohol after ethanol. In 2009, the American Association of Poison Control Centers reported 20,902 isopropanol exposures: 83% were unintentional, and 3% involved moderate or major effects; there was one fatality. Rubbing alcohols, which contain 70 to 91% isopropanol or ethanol, are frequent sources of exposure and may be tinted green or blue. Other sources include skin and hair products, nail polish removers, disinfectants, window and pine household cleaners, and antifreeze. Children experience toxicity most commonly from accidental ingestion, but inhalation and transdermal absorption during sponge bathing may occur. Isopropanol and its major metabolite acetone cause twice the CNS depression of ethanol, so intentional ingestion as an alcohol substitute is encountered frequently in adults. Isopropanol is not associated with the toxicity of ethylene glycol or methanol poisoning, and death after exposure is rare. The typical fatality involves a chronic, older alcoholic with mixed ethanol-isopropanol intoxication after a drinking binge.[42]

Principles of Disease

Pharmacology and Metabolism

Absorption of isopropanol is rapid and complete; 80% of a dose is absorbed within 30 minutes of ingestion. The kidneys excrete 20% as unchanged isopropanol. A small portion is re-secreted into the stomach and saliva; the remaining 80% is metabolized in the liver to acetone by ADH (Fig. 155-3). Acetone is excreted primarily by the kidneys, with small amounts expired through the lungs.

Isopropanol blood levels peak 30 minutes to 3 hours after ingestion, and elimination follows first-order kinetics, with a half-life of 3 to 7 hours. In children, the half-life may be slightly shorter.

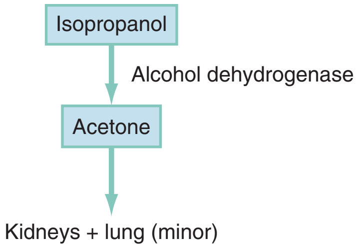


Figure 155-3. Metabolism of isopropanol.

Acetone is eliminated more slowly, with a half-life of 22 hours. The rate of elimination of isopropanol may be increased by chronic ethanol abuse and decreased by hepatic damage.[42] A potentially lethal dose in adults is 150 to 240 mL (2-4 mL/kg), but adults have survived ingestions of 1 L (8-15 mL/kg).

Pathophysiology

Isopropanol is a potent CNS depressant, but the mechanism of action is unclear. Acetone is also a CNS depressant, and it has been suggested that coma may be prolonged by the extended elimination of this metabolite. The extent to which acetone contributes to coma is brought into question by the report of a patient who was awake and conversant with acetone levels of 200 mg/dL. In large doses, isopropanol causes hypotension from peripheral vasodilation and direct myocardial depression. Topical effects include corneal de-epithelialization and dermal burns, described in premature infants as a result of skin de-esterification. Acetone does not seem to be shunted into the formation of acetoacetate or β-hydroxybutyrate; the finding of ketosis without acidosis is characteristic of isopropyl ingestion. No pathognomonic postmortem features are seen in isopropanol intoxication. Pulmonary congestion at autopsy is nonspecific and typical of deaths involving drug-induced CNS depression.

Clinical Findings

Gastrointestinal and CNS complaints predominate clinically. Intoxication may be suggested by apparent inebriation with the odor of acetone rather than of ethanol detected on the breath. The patient may have headache or dizziness and may exhibit neuromuscular incoordination, confusion, and nystagmus. Severe ingestions may result in deep coma, which is prolonged compared with ethanol. Respiratory depression or failure may occur. Patients may have a loss of deep tendon, corneal, or protective airway reflexes and have an extensor response to plantar reflex testing. Pupillary size varies, but miosis is most common.[43] Because isopropanol is a gastrointestinal irritant, the patient may complain of abdominal pain, nausea, and vomiting. Gastritis can occur with dermal and oral exposure.[44] Hematemesis and upper gastrointestinal bleeding stem from gastritis but are rare.

Hypotension, although rare, signifies severe poisoning, with a mortality rate of 45%. One case series found mortality only when coma and hypotension were present.[43] Sinus tachycardia is common, but other atrial and ventricular dysrhythmias are rare and generally found only with confounding hypoxia, acidosis, or shock. Hypothermia is frequent.[43] Rarely, myoglobinuria, acute tubular necrosis, hepatic dysfunction, and hemolytic anemia have been reported. A distinguishing feature is that metabolic acidosis is not present with isopropanol intoxication unless it is accompanied by hypotension, gastrointestinal bleeding, or coingestants. Hyperglycemia may be noted, but hypoglycemia has not previously been described, even though it should be sought in patients who have altered mental status.

www.ketabpezeshki.com 66485457-66963820

Diagnostic Strategies

Most of these patients do not need any laboratory testing unless they are severely ill. The laboratory tests primarily are used to exclude other ingestions and include serum electrolyte values, BUN and creatinine concentrations, osmolality, serum and urine ketones, and arterial blood gas analysis. Peak isopropanol levels occur soon after ingestion, whereas acetone levels peak later at 4 hours after ingestion.[43] The most common laboratory abnormality is ketosis with little or no acidosis and normal blood glucose levels. The ketosis is from the metabolite acetone, which can be detected in the blood 15 minutes after ingestion and in the urine 3 hours after ingestion.[43] Acetone is uncharged, so it does not elevate the anion gap. Isopropanol and acetone contribute to the increased osmol gap. In theory, an increase of 1 mg/dL in blood isopropyl alcohol concentration should result in an increase of 0.17 mOsm/kg in serum osmolality.

One early laboratory clue to the diagnosis of isopropanol ingestion is "pseudo–renal failure," or isolated false elevation of creatinine with a normal BUN concentration. This condition results from interference of acetone and acetoacetate by the colorimetric method of creatinine determination. Creatinine is expected to increase 1 mg/dL for every 100 mg/dL of acetone. A CK level may detect coma-induced myoglobinuria and rhabdomyolysis.

Differential Considerations

Patients who ingest significant amounts of isopropanol appear intoxicated or have depressed consciousness, and the differential diagnosis includes all of the causes of altered mental status in an alcoholic patient, as discussed previously. The presence of ketosis warrants a search for diabetic ketoacidosis, alcoholic ketoacidosis, salicylism, cyanide, or starvation ketosis. A distinguishing feature of isopropanol ingestion is the presence of ketosis without acidosis. An increased osmolal gap with acidosis should lead to a search for other toxic alcohols. In the setting of a high or rising creatinine concentration and normal BUN concentration, acute rhabdomyolysis also should be considered. Other substances that falsely elevate creatinine are cimetidine, nitroethane, and nitromethane, often mixed with methanol in formulating radio-controlled vehicle fuel.[45] Detection of isopropanol in acetonemic patients not exposed to isopropanol (i.e., the conversion of acetone to isopropanol in vivo) is well described.

Management and Disposition

Neither gastric emptying nor activated charcoal administration is warranted. Intubation is indicated if the patient is unable to protect the airway; it may also be indicated on the basis of coingestants or if the patient's mental status is poor and deteriorating. In contrast to methanol and ethylene glycol ingestion, ADH blockade with ethanol or fomepizole is not indicated. Hypotension should be managed with fluids and vasopressors as needed. If the patient remains hypotensive or has further vital sign deterioration despite these measures, dialysis is indicated. Some authors also recommend dialysis for isopropanol serum levels greater than 400 mg/dL. Coma itself is not an indication for dialysis but may necessitate mechanical ventilation. Peritoneal dialysis and hemodialysis have been successful, but hemodialysis is much more effective and is preferred. Because of isopropanol's rapid absorption, patients who are hemodynamically stable without coma during the first 6 hours are at low risk for development of significant sequelae and generally do not require extracorporeal removal of isopropanol. The development of altered mental status within 2 hours is a clinical predictor of toxic blood isopropanol levels in children.[46] Care is otherwise supportive and includes rewarming, evaluation for hypoglycemia, and monitoring for gastrointestinal bleeding.

KEY CONCEPTS

- Small doses (single swallows) of methanol and ethylene glycol may cause toxicity.
- A latent period before the development of symptoms is characteristic of ethylene glycol and methanol toxicity, especially when ethanol has been coingested.
- A double-gap acidosis (anion gap and osmol gap) should suggest methanol or ethylene glycol toxicity.
- Toxic alcohol exposure cannot be ruled out by a "normal" osmol gap.
- Therapy should begin on the basis of clinical suspicion of exposure to ethylene glycol or methanol. Acidosis should be corrected rapidly with bicarbonate, cofactors should be administered, and ADH should be blocked with ethanol or fomepizole.
- Because acidosis in the setting of exposure to either substance indicates toxic metabolite accumulation, immediate consultation for hemodialysis should be made, even before laboratory confirmation of toxic ethylene glycol or methanol levels.
- The presence of an osmol gap without acidosis is characteristic of isopropanol ingestion. Prolonged coma may be seen, and hypotension portends a poor prognosis but is not treated with ADH blockade.

ACKNOWLEDGMENT

The author would like to thank Deborah Mouzon for her assistance with the preparation of this chapter.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Bennett IL, Cary FH, Mitchell GL: Acute methyl alcohol poisoning: Review based on experiences of an outbreak of 323 cases. *Medicine (Baltimore)* 1953; 32:431.
2. Wallace EA, Green AS: Methanol toxicity secondary to inhalant abuse in adult men. *Clin Toxicol (Phila)* 2009; 47:239.
3. Martin-Amat G, et al: Methanol poisoning: Ocular toxicity produced by formate. *Toxicol Appl Pharmacol* 1978; 45:201.
4. Liesivuori J, Savolainen H: Methanol and formic acid toxicity: Biochemical mechanisms. *Pharmacol Toxicol* 1991; 69:157.
5. Martinasevic MK, et al: Folate and 10-formyltetrahydrofolate dehydrogenase in human and rat retina: Relation to methanol toxicity. *Toxicol Appl Pharmacol* 1996; 141:373.
6. Sandhir R, Kaur K: Influence of ethanol on methanol-induced oxidative stress and neurobehavioral deficits. *J Biochem Mol Toxicol* 2006; 20:247.
7. Skrzydlewska E, Szmitkowski M, Farbiszewski R: Activity of cathepsin G, elastase, and their inhibitors in plasma during methanol intoxication. *J Toxicol Environ Health* 1999; 57:431.
8. Jacobsen D, McMartin KE: Methanol and ethylene glycol poisonings: Mechanism of toxicity, clinical course, diagnosis and treatment. *Med Toxicol* 1986; 1:309.
9. Jacobsen D, McMartin KE: Antidotes for methanol and ethylene glycol poisoning. *J Toxicol Clin Toxicol* 1997; 35:127.
10. Sanaei-Zadeh H, Zamani N, Shadnia S: Outcomes of visual disturbances following methanol poisoning. *Clin Toxicol (Phila)* 2011; 49:102.
11. Brent J: Fomepizole for ethylene glycol and methanol poisoning. *N Engl J Med* 2009; 360:2216.
12. Hassanian-Moghaddam H, Pajoumand A, Dadgar SM, Shadnia SH: Prognostic factors in methanol poisoning. *Hum Exp Toxicol* 2007; 26:583.
13. Paasma R, Hovda KE, Tikkerberi A, Jacobsen D: Methanol mass poisoning in Estonia: Outbreak in 154 patients. *Clin Toxicol (Phila)* 2007; 45:152.
14. Paasma R, Hovda KE, Jacobsen D: Methanol poisoning and long term sequelae—a six years follow-up after a large methanol outbreak. *BMC Clin Pharmacol* 2009; 9:5.
15. Glaser DS: Utility of the serum osmol gap in the diagnosis of methanol or ethylene glycol ingestion. *Ann Emerg Med* 1996; 27:343.
16. Hantson P, Duprez T, Mahieu P: Neurotoxicity to the basal ganglia shown by magnetic resonance imaging (MRI) following poisoning by methanol and other substances. *J Toxicol Clin Toxicol* 1997; 35:151.
17. Jacobsen D: New treatment for ethylene glycol poisoning. *N Engl J Med* 1999; 340:879.
18. Eder AF, et al: Ethylene glycol poisoning: Toxicokinetic and analytical factors affecting laboratory diagnosis. *Clin Chem* 1998; 44:168.
19. Baud FJ, et al: Treatment of ethylene glycol poisoning with intravenous 4-methylpyrazole. *N Engl J Med* 1988; 319:97.
20. McMartin KE: Are calcium oxylate crystals involved in the mechanism of acute renal failure in ethylene glycol poisoning? *Clin Toxicol (Phila)* 2009; 47:859.
21. Brent J, et al: Fomepizole for the treatment of ethylene glycol poisoning. *N Engl J Med* 1999; 340:832.
22. Niederstadt C, Lerche L, Steinhoff J: Proteinuria in ethylene glycol–induced acute renal failure. *Nephron* 1996; 73:316.
23. Sabeel AI, Kurkaus J, Lindholm T: Intensified dialysis treatment of ethylene glycol intoxication. *Scand J Urol Nephrol* 1995; 29:125.
24. Reddy NJ, Sudini M, Lewis LD: Delayed neurological sequelae from ethylene glycol, diethylene glycol and methanol poisonings. *Clin Toxicol (Phila)* 2010; 48:967.
25. Tobe TJM, Braam GB, Meulenbelt J, et al: Ethylene glycol poisoning mimicking Snow White. *Lancet* 2002; 359:444.
26. Wallace KL, Suchard JR, Curry SC, et al: Diagnostic use of physicians' detection of urine fluorescence in a simulated ingestion of sodium fluorescein–containing antifreeze. *Ann Emerg Med* 2001; 38:49.
27. Casavant MJ, Shah MN, Battels R: Does fluorescent urine indicate antifreeze ingestion by children? *Pediatrics* 2001; 107:113.
28. Manini AF, Hoffman RS, McMartin KE, Nelson LS: Relationship between serum glycolate and falsely elevated lactate in severe ethylene glycol poisoning. *J Anal Toxicol* 2009; 33:174.
29. Caravati EM, Erdman AR, Christianson G, et al; American Association of Poison Control Centers: Ethylene glycol exposure: An evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila)* 2005; 43:327.
30. Chew WB, et al: Alkali treatment of methyl alcohol poisoning. *JAMA* 1946; 130:61.
31. Brent J: Fomepizole for the treatment of pediatric ethylene and diethylene glycol, butoxyethanol and methanol poisoning. *Clin Toxicol (Phila)* 2010; 48:401.
32. McMartin KE: Antidotes for alcohol and glycol toxicity: Translating mechanisms to treatment. *Clin Pharmacol Ther* 2010; 88:400.
33. Hovda KE, Andersson KS, Urdal P, Jacobsen D: Methanol and formate kinetics during treatment with fomepizole. *Clin Toxicol (Phila)* 2005; 43:221.
34. Barceloux DG, Krenzelok EP, Olson K, Watson W: American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning. Ad Hoc Committee. *J Toxicol Clin Toxicol* 1999; 37:537.
35. Lepik KJ, et al: Bradycardia and hypotension associated with fomepizole infusion during hemodialysis. *Clin Toxicol (Phila)* 2008; 46:570.
36. Lepik KJ, et al: Adverse drug events associated with the antidotes for methanol and ethylene glycol poisoning: A comparison of ethanol and fomepizole. *Ann Emerg Med* 2009; 53:439.
37. Barceloux DG, Bond R, Krenzelok EP, Cooper H, Vale JA: American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. *J Toxicol Clin Toxicol* 2002; 40:415.
38. Sivilotti ML, Burns MJ, McMartin KE, Brent J: Toxicokinetics of ethylene glycol during fomepizole therapy: Implications for management. *Ann Emerg Med* 2000; 36:114.
39. Mégarbane B, et al: Treatment of acute methanol poisoning with fomepizole. *Intensive Care Med* 2001; 27:1370.
40. Porter WH, Rutter PW, Bush B, Pappas AA, Dunnington JE: Ethylene glycol toxicity: The role of serum glycolic acid in hemodialysis. *J Toxicol Clin Toxicol* 2001; 39:607.
41. White NC, et al: The impact of bittering agents on pediatric ingestions of antifreeze. *Clin Pediatr (Phila)* 2009; 48:913.
42. Alexander CB, McBay AJ, Hudson RP: Isopropanol and isopropanol deaths: Ten years' experience. *J Forensic Sci* 1982; 27:541.
43. LaCouture PG, et al: Acute isopropyl alcohol intoxication: Diagnosis and management. *Am J Med* 1983; 75:680.
44. Dyer S, et al: Hemorrhagic gastritis from topical isopropanol exposure. *Ann Pharmacother* 2002; 36:1735.
45. Cook MD, Clark RF: Creatinine elevation associated with nitromethane exposure: A marker of potential methanol toxicity. *J Emerg Med* 2007; 33:249.
46. Stremski E, Hennes H: Accidental isopropanol ingestion in children. *Pediatr Emerg Care* 2000; 16:238.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 156

HALLUCINOGENS

Binh T. Ly and Saralyn R. Williams

The term *hallucinogen* has been used to describe the clinical effect of a variety of xenobiotics; however, most drugs do not produce actual hallucinations. The drugs that are classified as hallucinogens are more likely to cause misperceptions of real objects, which are more accurately termed *illusions*. Some drugs are called psychedelics, a subset that alters cognition and perception. This chapter describes serotonergic agents, sympathomimetic amines (entactogens), dissociative agents, and selected plants and fungi.

SEROTONIN-LIKE AGENTS

Perspective: Background and Epidemiology

Serotonin-like agents are a broad category of compounds that share chemical similarities with serotonin (5-hydroxytryptamine [5-HT]) or enhance serotonergic tone within the body. These agents include various lysergic acid derivatives and tryptamines. Serotonin-like agents produce changes in thought, mood, perception, and consciousness. Orientation to person, place, and time is usually preserved, but severe intoxication may cause confusion. Patients present to the emergency department because of acute panic reactions, massive ingestions, or accidental ingestions (e.g., children or adults who have ingested the drugs unknowingly). There is no addictive component in psychedelics and no euphoria-dysphoria cycle, as with cocaine. The rapid development of tolerance also limits the effect of repeated doses.[1]

LSD

Lysergic acid diethylamide (LSD), or acid, is the most potent psychoactive drug. Doses of 1 to 1.5 μg/kg produce psychedelic effects. The typical dose taken for an acid "trip" is approximately 25 to 100 μg. LSD is sold in tablets (microdots), liquid, powder, gelatin squares (window panes), and "blotter" acid. Sheets of blotting paper are sprayed with LSD, dried, and perforated into small squares. Graphics are incorporated onto the blotting paper in designs that include cartoon characters (e.g., Felix the Cat) and geometric designs (Fig. 156-1). Each sheet is composed of hundreds of squares that are placed sublingually or eaten whole. Massive ingestions are rare.

In addition to synthetic LSD, several plants contain alkaloids similar in structure and action to LSD. These plants include Hawaiian baby woodrose (*Argyreia nervosa*), Hawaiian woodrose (*Merremia tuberosa*), morning glory (*Ipomoea violacea*), and ololiuqui (*Rivea corymbosa*). Intoxication may result after ingestion of the seeds or an extract.[2]

Tryptamines

Substances in the tryptamines category are both naturally occurring and synthesized. For centuries, Native Central and South Americans have used tryptamine-containing beverages, *ayahuasca,* in their religious ceremonies. This plant-derived drink, which contains dimethyltryptamine (DMT) and 5-methoxydimethyltryptamine (5-MeO-DMT), has gained popularity in Europe and North America. Designer tryptamines can be synthesized and possess the psychotropic effects of the naturally found compounds.

Psilocybin and psilocin are naturally occurring tryptamines found in some species of *Psilocybe* (Fig. 156-2), *Panaeolus,* and *Conocybe* mushrooms.[3] Psilocybin remains active even when the mushrooms are dried or cooked. Street psilocybin sold as pills or capsules is usually substituted with phencyclidine (PCP) or LSD. Misidentification of other poisonous species is a danger of consuming mushrooms.

Naturally occurring tryptamines are found not only in plants and fungi but also in the parotid glands of the *Bufo* toad species. The venom of the Sonoran Desert or Colorado River toad (*Bufo alvarius*) contains the hallucinogenic substance 5-MeO-DMT, found in the drink *ayahuasca*. Smoking of the dried venom results in psychoactive effects similar to those of 5-MeO-DMT.[4]

In addition to the tryptamines that occur in nature, designer tryptamines have been synthesized and are orally active.[5] Included in this group are α-methyltryptamine, diisopropyltryptamine, and diisopropyl-5-methoxytryptamine, which is also known on the streets as "foxy" or "foxy methoxy".[6] The effects of these synthetic derivatives are similar to those of naturally occurring tryptamines.

Principles of Disease: Pharmacology and Pathophysiology

Evidence indicates that these drugs act on serotonergic neurons, particularly the 5-HT_{2A} subtype class of serotonin receptors.[1,7] The onset of action of the psychoactive effects of LSD is usually within 30 minutes, with peak effects in 3 or 4 hours. The duration of effects may be approximately 12 hours. During the last half of the 12-hour effect, irritability, increased muscle tension (especially in the face), and paranoia can be present. Psilocybin effects begin within 30 minutes of ingestion, with the psychedelic phase lasting 30 minutes to 2 hours. The effects then wane, with resolution by 4 to 6 hours.

www.ketabpezeshki.com 66485457-66963820

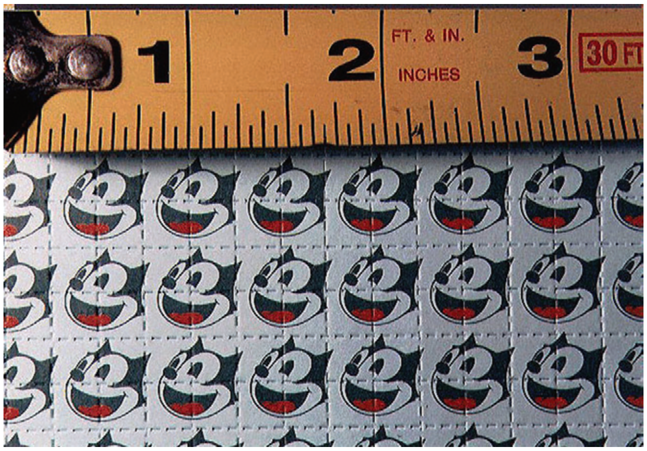


Figure 156-1. LSD blotters. (Copyright © 2001 Blotterart.com. Accessed at www.erowid.org.)

Figure 156-2. *Psilocybe cubensis* mushroom. (Copyright © 2003 Erowid.org. Accessed at www.erowid.org.)

Clinical Features

In Western society, psychoactive agents are taken for internal mental exploration or more commonly for "recreation." Changes include loss of boundaries between the user and the environment; the sensation that colors and sounds are distorted and intensified; and the perception that usual objects appear novel, fascinating, or awe inspiring. This state differs from the confusional and dissociative state produced by PCP. Users are usually aware that they are under the influence of the drug. A sense of euphoria is typical, but it may alternate with an intense dysphoric experience that is accompanied by suffering (e.g., that of dying or being born).

Acute panic reaction is the most common adverse reaction to psychedelics. Paranoid delusions and fear of impending death may be present. Behavior is either agitated or, occasionally, withdrawn. Sympathomimetic effects include dilated, reactive pupils and moderate increases in blood pressure, heart rate, and, rarely, temperature. Mydriasis seems to parallel the intensity of the trip. In contrast to PCP, nystagmus, ataxia, muscle rigidity, and increased secretions are not present.

The individual's altered perceptions may result in lack of awareness of dangers in the environment, resulting in injury. Psychosis after LSD trips is reported, and schizophrenia (overt and borderline) may worsen. Transient depression sometimes occurs after LSD use. Flashbacks, or post-hallucinogen perceptual disorder, are transient episodes of altered consciousness that occur months or years after an LSD trip. However, LSD use and these episodes have not been shown convincingly to have a cause-and-effect relationship.

Massive ingestions may result in a person's becoming comatose and unresponsive to pain. The person may also be hyperactive with marked auditory and visual hallucinations. Fixed and dilated pupils, diaphoresis, vomiting, bleeding complications, and seizures may result.[8]

Euphoria and a distortion of reality usually occur after ingestion of one to five *Psilocybe cubensis* mushrooms. In contrast to peyote, vomiting is unusual. Larger doses (5-20 *P. cubensis* mushrooms) produce visual hallucinations. Few adverse reactions occur, and the incidence of "bad trips" or panic reactions is lower than with LSD. There are reports of seizures, coma, and hyperthermia after psilocybin use.

Diagnostic Strategies

Because most patients are either in a panic or brought in by a worried companion, the drug is usually known. Although mass spectrometry can identify psychedelics in serum, urine, or gastric contents, it is not available in the clinical setting, so diagnosis and treatment are based on clinical grounds. Even when tests are available, however, the results are delayed and useful only to confirm or to document the event.

Differential Considerations

Other drugs and mixed ingestion are a possible source of the patient's symptoms, especially with coma or marked physiologic changes. Cocaine, PCP, anticholinergic drugs, and amphetamines should be considered because their effects may require specific treatment. Acute psychosis may appear similar to psychedelic ingestion at first, but detailed evaluation of the patient will clearly differentiate the two conditions.

Management

The basic principle of out-of-hospital care is reassurance and supportive care. If the patient is a danger to himself or herself or others, the patient may need to be sedated or restrained temporarily to permit sedation. There is no specific antagonist to the effects of serotonergic agents. Empathic reassurance in a calm, quiet environment is an effective therapeutic modality. The drug effect lasts for hours, but when it wears off, the patient feels normal again.

Benzodiazepines, such as lorazepam (1 or 2 mg intravenously, then titrated to effect), can be given to decrease agitation. Phenothiazines should be avoided in case the symptoms are actually caused by an anticholinergic drug and not a psychedelic. Butyrophenones, such as haloperidol and droperidol, are quickly effective and may be given by intramuscular or intravenous injection in doses titrated to clinical response if the patient is violent and must be sedated. Monitoring for QT prolongation is recommended, if possible, when a butyrophenone is used.

Disposition

Patients with anxiety or panic reactions can be talked down and sent home with responsible family or friends. Patients who persist with confused or paranoid behavior should be admitted. If the diagnosis is in question, the patient should be observed for several hours for significant changes in the condition. Follow-up evaluation should be recommended with a psychiatrist, primary care

www.ketabpezeshki.com 66485457-66963820

physician, or drug counseling facility. Patients with massive ingestions or having incurred injuries or medical complications (rhabdomyolysis) may need admission to a monitored setting for serial reassessments.

ENTACTOGENS

Perspective: Background and Epidemiology

Hallucinogenic stimulants, also called entactogens, are structural analogues of amphetamine, mescaline, and *N*-substituted piperazines. These agents share effects in varying degrees of true stimulants and the serotonin-like hallucinogens.

Designer Amphetamines and Cathinones (Bath Salts)

New designer amphetamines appear in drug communities each year. This class of chemicals usually has a structural base of a phenylalkylamine with addition or substitution of side chains or rings. Agents include 3,4-methylenedioxymethamphetamine (MDMA, ecstasy, XTC, or Adam), 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxyethamphetamine (Eve), paramethoxyamphetamine (PMA or death), 4-methyl-2,5-dimethoxyamphetamine (serenity, tranquility, and peace [STP]), 2,5-dimethoxy-4-iodoamphetamine (DOI), 2,5-dimethoxy-4-bromoamphetamine (DOB), and others.[9]

MDMA is the best known of these agents. It was first synthesized in 1914 as an appetite suppressant. Recreational and psychotherapeutic use began in the late 1970s and has remained ubiquitous. MDMA and MDA have been called love drugs because of claims from users that sexual pleasure and feelings are heightened, but the sympathomimetic effects of these drugs may produce erectile dysfunction. MDMA can produce euphoria and increase emotional awareness, and it has been reported to improve interpersonal communications. The psychedelic and stimulant effects of MDMA are preferred to MDA by most users. Overt hallucinations of the type experienced with LSD are rare; however, sensory enhancement and distortion and illusions can occur. Because of these effects, these drugs are called entactogens (i.e., enabling the user to "touch within"). MDMA was classified as a Schedule I drug by the Drug Enforcement Agency (DEA) in 1985.

Entactogens are predominantly used in three main settings: (1) as "psychotherapeutic adjuncts," (2) recreationally in small groups or by couples, and (3) at dance clubs or "rave" parties. Herbal ecstasy, known as ma huang or ephedra, is sometimes substituted for MDMA at these gatherings when MDMA is scarce. Although this herb contains ephedrine, its effects are not as psychedelic as those of MDMA. Ecstasy tablets may also contain other chemicals, such as amphetamine, methamphetamine, caffeine, and ketamine. MDMA is widely available and is sold in clubs, on the street, and at raves (usually 30-150 mg/pill), with a typical dose of 1 or 2 mg/kg.[10] The continuous muscle activity required during these parties in combination with the psychostimulants may produce rhabdomyolysis and hyperthermia. Nine deaths in Canada associated with paramethoxyamphetamine (PMA) were originally reported in 1974, but clusters of multiple deaths in association with PMA exposure have occurred in Europe and Australia.[11,12] Signs and symptoms of adrenergic excess occur before death, but whether PMA is more toxic in equipotent dosages than other amphetamines is not known.

Designer cathinones may be advertised and distributed as "bath salts" or "plant food" in packaging that suggests the actual intent of the product even though it might be labeled "not for human consumption." These synthetic cathinones sold unregulated over the Internet initially contained mephedrone, but their content rapidly changed to include methylone, ethylone, butylone, pyrovalerone, methylenedioxypyrovalerone (MDPV), methcathinone, ethcathinone, and numerous others. These products may be ingested, inhaled, or injected and result in severe agitation, sympathomimetic effects, or even death.[13] Detection of these cathinones is more difficult as their structures are dissimilar enough to classic amphetamines and methamphetamines that routine urine drug testing is not able to detect them.

Figure 156-3. *Lophophora williamsii* (peyote cactus). (Photo by Christopher B. Copyright © 2000 Erowid.org. Accessed at www.erowid.org.)

Mescaline

Mescaline is usually consumed in the form of peyote buttons, which are derived from the small blue-green cacti *Lophophora williamsii* and *Lophophora diffusa* (Fig. 156-3). The cacti grow in the deserts of the southwestern United States and Mexico. Peyote buttons are the round fleshy tops, which are removed and dried. Mescaline is the active hallucinogenic alkaloid found in the buttons of the cactus.

Peyote has been used in religious ceremonies for 8000 years. Mescaline is also contained in the San Pedro cactus (*Trichocereus pachanoi*) of South America and is used ritualistically by Andean Native Americans.[1] These cacti contain many other alkaloids, some of which are also psychoactive. The use of peyote is legal for members of the Native American Church in some states. Adverse reactions (e.g., panic) to peyote are rare in this structured religious use. Mescaline has an onset of action of 45 to 60 minutes with a duration of 4 to 8 hours. The central nervous system (CNS) and physiologic effects of mescaline use are similar to those of LSD, but more vivid hallucinations can occur. Nausea and vomiting are pronounced and almost always precede the hallucinogenic effects.

Piperazines

N-Substituted piperazine compounds such as 1-benzylpiperazine (BZP or A2), 1-(trifluoromethylphenyl)piperazine (TFMPP or Molly), and 1-(chlorophenyl)piperazine (CPP) have emerged as drugs of abuse and have been sold as safe, legal alternatives to MDMA; they are referred to as Legal E or Legal X on Internet websites.[14,15] Although BZP was originally synthesized as a potential anthelmintic agent, there are currently no therapeutic applications for BZP or its congeners. Both in vitro and animal studies demonstrated that these piperazine compounds stimulate release of serotonin and other monoamines but are less potent in comparison to MDMA.[15] In 2002, both BZP and TFMPP were classified as Schedule I drugs because of their potential for abuse and

www.ketabpezeshki.com 66485457-66963820

hazard to the public. There are no deaths directly attributed to these piperazines, but fatalities occur in association with their use.[14]

Nutmeg

Nutmeg is a spice derived from the seed of the nutmeg tree, *Myristica fragrans*. Use of nutmeg as a natural and legal psychotropic agent was popularized in the 1960s. Despite lack of any in vivo human studies, myristicin and elemicin have been suggested as the agents responsible for intoxication because their chemical structures resemble that of mescaline. Reports of intoxication are uncommon.[16,17] Ingestion of 5 to 30 g (1-4 tablespoons) of the spice is said to induce euphoria and hallucinations but is more likely to cause gastroenteritis.

Principles of Disease: Pathophysiology

The psychoactive effects of MDMA and other entactogens are thought to result from alterations in catecholamine neurotransmission at postsynaptic and presynaptic sites, particularly affecting 5-HT. These agents cause a release of serotonin, dopamine, and norepinephrine from nerve terminals as well as inhibit catecholamine reuptake. Release of epinephrine and norepinephrine may produce the cardiovascular effects. MDMA and possibly other entactogens are serotonergic neurotoxins.[18,19] When MDMA is administered to nonhuman primates and laboratory animals, serotonin is released initially from serotonergic neurons followed by degradation of 5-HT projections. Magnetic resonance imaging shows significant neurodegeneration.[19] These effects may persist for weeks or longer after a single dose.[20] The significance of this neurotoxic effect for humans at the doses taken is unknown.[21]

Psychostimulant-associated hyperthermia is well described in humans. Animal models exposed to entactogens develop hyperthermia in the absence of physical exertion but are less capable of regulating core body temperature in response to environmental hyperthermia.[22] In addition, increasing body temperature in the presence of MDMA or other entactogens seems to enhance serotonergic neurotoxicity.[23]

Hyponatremia resulting in seizures, stupor, and death is another complication of MDMA use not described as commonly with other amphetamines. Two hypotheses suggested for the hyponatremia are (1) excessive intake of free water because users of MDMA are advised to keep well hydrated by drinking lots of water and (2) MDMA-mediated release of antidiuretic hormone.[24-26]

Clinical Features

MDMA effects last 3 to 5 hours. Blood pressure increases during the first hour and gradually returns to baseline within 6 hours. CNS effects of MDMA may persist for 6 to 12 hours. Larger doses or greater frequency dosing of MDMA may lead to more frequent unpleasant side effects, such as agitation and confusion. Recreational users rarely report dysphoria.

Clinical effects expected from the entactogens would be similar to clinical effects of other amphetamine derivatives (see Chapter 154). Use of recreational doses of MDMA at rave parties may result in seizures, hyperthermia, and death. MDMA may precipitate a hypertensive crisis in patients taking monoamine oxidase inhibitors, and it may precipitate serotonin syndrome in combination with other serotonergic agents[10] (see Chapter 151). MDMA and its analogues also have contributed to fatal overdoses.[27]

Diagnostic Strategies

Urine screening with immunoassay techniques can detect entactogens that are similar in structure to the phenylalkylamine structure of amphetamines. Small doses may not be detected, but larger doses may test positive for amphetamine and methamphetamine. As the structure of the designer amphetamine becomes less similar to phenylalkylamine, detection of the drug is less likely. Designer amphetamines, including MDMA, and their metabolites may be detectable with thin-layer chromatography methods.[28]

Differential Considerations

All sympathomimetic compounds, including cocaine, amphetamine derivatives, PCP, and LSD, can cause agitated behavior, convulsion, coma, and any combination of sympathomimetic signs and symptoms. Many of these reactions may be not from overdose but rather from idiopathic and unpredictable toxic reactions. Initial management is consistent for each of these compounds.

Management

Patients with panic reactions or violent episodes should be placed in a quiet environment and reassured. Diazepam, 2 to 10 mg, or lorazepam, 1 or 2 mg, can be administered orally to cooperative patients. Repeated doses of diazepam, 5 to 10 mg (intravenously), or lorazepam, 2 to 4 mg (intramuscularly or intravenously), can be used in violent subjects. Butyrophenones, such as haloperidol and droperidol, may also be used intramuscularly. Hypertension and tachycardia should be treated with benzodiazepines as described earlier. Liberal use of benzodiazepines reduces the likelihood that the hypertension will need additional therapy, such as vasodilators. Dysrhythmias should be treated in the usual manner.

Because hyperthermia is a common complication, a core temperature should be obtained. If the patient's temperature is higher than 40 to 42° C, multiple organ damage often ensues. Active evaporative cooling measures should be instituted to reduce the core temperature because the clinical outcome strongly correlates with the magnitude and duration of the hyperthermia (see Chapter 141). Treatment of hyponatremia should proceed in the usual manner. Antiemetic medications, such as intravenous ondansetron, 4 to 8 mg, may be necessary if nausea and vomiting persist, as typically occurs with peyote and nutmeg ingestions.

Disposition

Most patients with a toxic reaction or overdose to an entactogen who are not hyperthermic or do not have abnormal cardiac rhythms resolve their symptoms in several hours. Psychiatric assessment may be necessary if psychotic or abnormal thoughts or actions persist longer than this time. Although urine screening will not guide treatment decisions, it may aid the psychiatrist in counseling.

Patients with ongoing or severe toxicity to these agents require admission to the hospital. Seizures, cardiac dysrhythmias, myoglobinuric renal failure, hepatic damage, and heat-related problems should be monitored in an intensive care unit or step-down unit. Direct sympathomimetic toxicity resolves during 24 hours, but sequelae may require prolonged hospitalization.

DISSOCIATIVE AGENTS

Perspective: Background and Epidemiology

PCP and ketamine are the two main agents included in the class of dissociative agents. Dextromethorphan abuse may also give a similar presentation. They are similar in chemical structure and

www.ketabpezeshki.com 66485457-66963820

pharmacologic effect and cause dissociation of the patient from the environment. They have analgesic and amnestic activity but do not cause respiratory or cardiovascular depression.

Phencyclidine

PCP was initially marketed for use as a general anesthetic; however, severe emergence reactions rapidly led to its recall. In the 1960s, PCP was sold as the "PeaCe Pill," which was consumed orally, but the effects were often unpredictable and unpleasant. In the mid-1970s, PCP was the most common cause of recreational drug–related emergencies. Its popularity decreased because of unpredictable effects, long clinical course, dysphoria, and association with violence. In 1978, PCP was classified as a Schedule I drug.

Ketamine

Ketamine is known as "vitamin K," "special K," "kit kat," and "cat valium"; however, preparations available on the street are often adulterated with various stimulants. The most common use of street ketamine is insufflation, but subcutaneous and intramuscular injection and even rectal infusion are done to achieve a level of intoxication or "high" known as the K-hole.

Dextromethorphan

Dextromethorphan is not truly a dissociative agent but does share a similarity in structure to PCP and its binding to the PCP site of the *N*-methyl-D-aspartate (NMDA) receptor. With the availability of concentrated pill formulations, abusers of dextromethorphan are able to ingest large doses without having to drink large volumes of the less palatable cough syrup formulation. Particularly popular in the adolescent community, dextromethorphan is known as "DXM," "robo," "skittles," triple C," and "red hots."[29]

Principles of Disease: Pharmacology and Pathophysiology

Despite being simple molecules, PCP and ketamine have a complex pharmacology, including the NMDA receptor, dopamine-norepinephrine-serotonin reuptake pump, sigma opioid receptor, and cholinergic receptors.[30] PCP is well absorbed from any oral, nasal, or rectal mucous membrane and can be insufflated or smoked. It can be injected intramuscularly, subcutaneously, or intravenously. Ingested PCP is well absorbed with onset between 15 and 60 minutes. When it is smoked, PCP produces symptoms within 5 minutes, with peak activity in 15 minutes.[31] Intoxication with PCP usually lasts 8 to 16 hours, but it can be prolonged in chronic users. Although enterohepatic recirculation has been proposed, a more likely cause is either gastrointestinal concretion or delayed release from lipid stores.[32]

Ketamine is only approximately one tenth as potent as PCP.[30] With ketamine, the intensity of intoxication is less pronounced, although in larger doses the effects may parallel those of PCP. Duration of action of ketamine is typically shorter, with symptoms lasting approximately 1 hour after insufflation but up to 4 to 8 hours after an oral dose. PCP and ketamine are highly lipid-soluble agents that undergo extensive metabolism in the liver and are eventually excreted in the urine.

Although dextromethorphan is typically classified as an opioid, it has a complex pharmacology. Dextromethorphan is the dextrorotatory isomer of the synthetic opioid levorphanol. At high dosages, dextromethorphan is an agonist at the sigma opiate receptor, and naloxone has been reported to reverse intoxication.[33] Dextromethorphan antagonizes the NMDA receptor, which results in its dissociative effects. It also inhibits the uptake of serotonin, and drug interactions with selective serotonin reuptake inhibitors and monoamine oxidase inhibitors are reported.[29]

Clinical Features

Patients with PCP intoxication have a wide spectrum of findings, with autonomic signs and symptoms similar to those with other sympathomimetic agents. Behavior may be bizarre, lethargic, agitated, confused, or violent. A blank or catatonic stare is common. Vertical, horizontal, and rotatory nystagmus is often present. Moderate hypertension and tachycardia may be present. Pupils usually are midsized and reactive, although there may be miosis or mydriasis. Bizarre posturing, grimacing, and writhing may be seen.[34]

Other variable findings include ataxia, muscle rigidity, increased deep tendon reflexes, increased secretions, bronchospasm, hyperthermia, and seizures. The percentage of violent patients ranges from 10 to 40% for PCP, and control of these patients may be the most challenging problem in the emergency department. "Superhuman" strength is possible because of the dissociative action of PCP. Although mild hypertension in PCP intoxication is common, hypertension requiring antihypertensive treatment is rare. Severe hypertension with PCP overdose has caused intracerebral hemorrhage but less often than with cocaine or amphetamine.[35]

Hyperthermia can range from mild to life-threatening. Core temperatures of PCP victims can exceed 40°C and often go undetected for prolonged periods in the emergency department. Severe hyperthermia with temperatures above 42°C resembles heatstroke and is often associated with multiple organ damage.[36] High-output congestive heart failure has been reported. Rhabdomyolysis and acute myoglobinuric renal failure are the most common serious medical complications. The presumed mechanism is muscle damage from seizures, extreme muscle activity such as struggling against restraints, or prolonged immobility. Renal function returns after several weeks in most cases. Among the most lethal complications of PCP are respiratory depression, apnea, and cardiac arrest.[34]

Although dextromethorphan has activity at opioid receptors, the typical triad of opioid intoxication (miosis, respiratory depression, and mental status depression) is not generally encountered.[37] Similar to meperidine, dextromethorphan may result in mydriasis through paralysis of the ciliary body with intoxication.[38] More typical clinical findings are lethargy, agitation, slurred speech, ataxia, diaphoresis, hypertension, and nystagmus. With larger doses, nausea and vomiting are common, and intoxication resembles that of LSD with euphoria and hallucinations.

Diagnostic Strategies

Most hospital laboratories use radioimmunoassays that can detect urinary PCP with a detection limit of 5 ng/mL. Urine may be positive for PCP for 2 to 4 days after use, but it can be positive for more than 1 week after chronic exposure. Serum screening for PCP is of little clinical benefit because levels correlate poorly with symptoms. Several substances, including dextromethorphan, may cross-react with urine screens for PCP because of their structural similarities. Chlorpromazine, methadone, mesoridazine, ketamine, diphenhydramine, venlafaxine, meperidine, and tramadol may also cross-react with some assays.[39] Because dextromethorphan is typically formulated as a hydrobromide salt, chronic use may result in spurious hyperchloremia with a low or negative anion gap due to interference of chloride analysis by the bromide ion in the laboratory autoanalyzer.[40]

Differential Considerations

PCP, ketamine, and dextromethorphan intoxications can mimic such diverse entities as head trauma, meningitis, catatonia, and

www.ketabpezeshki.com 66485457-66963820

heatstroke. Sympathetically mediated vital sign changes can be found with numerous other agents, including cocaine, amphetamine, and LSD. Antimuscarinic (anticholinergic) compounds, such as diphenhydramine, benztropine, and tricyclic antidepressants, can also simulate the tachycardia and altered mental status found with PCP or ketamine. Salicylate poisoning, thyrotoxicosis, and sepsis should be considered. Meningitis, intracerebral hemorrhage, and viral encephalitis can be manifested with altered mental status of unclear etiology. Even with a urine screen positive for PCP, the diagnosis is not certain unless a definite history of recent PCP, ketamine, or dextromethorphan use is obtained and other conditions have been eliminated.

Management

Out-of-Hospital Care

Life-threatening complications, such as apnea and seizures, should be stabilized before transport. The threat of violence to nonhospital care providers from patients with PCP intoxication makes it dangerous for only two or three nonhospital care providers to restrain these patients until additional help arrives. Oxygen and glucose testing should be deferred until the patient is controlled. Violent patients under the influence of PCP may have traumatic injuries.

Emergency Department

Patients with PCP toxicity can have unpredictable, violent behavior. Sudden complications, such as cardiac arrest and seizures, may occur but are not common. Violent behavior, although possible, is less common with ketamine. Most patients with minor intoxication are alert, oriented, and neurologically normal after 4 to 6 hours.[35] All patients with signs of trauma or struggle should be evaluated for injuries. Reliable assessments of these individuals are difficult, and sedation and restraint are often necessary before diagnostic tests or examinations can be performed.

Chemical sedation or restraint is preferred to physical restraint in cases of PCP or ketamine intoxication, although temporary physical restraint may be necessary to ensure the patient's safety, to establish intravenous access, and to administer benzodiazepines intravenously (IV). Butyrophenones can be given intramuscularly (IM) with a rapid response, avoiding the danger of intravenous establishment. Haloperidol, 5 to 20 mg IM or IV, or droperidol, 2.5 to 10 mg IM or IV (noting the Food and Drug Administration black box warning), is usually effective but can be titrated at 10- to 15-minute intervals until the patient is calm. These agents may antagonize CNS receptor sites that are responsible for much of the violent behavior in these individuals. Benzodiazepines, such as lorazepam, 2 to 4 mg IV or IM, or diazepam, 5 to 10 mg IV, may be used to calm patients with all types of sympathomimetic poisonings. A well-coordinated team may be needed to apply hard restraints simultaneously to all four extremities and the body. Assessment of mental status may not be as reliable after chemical sedation, but the benefits of protecting the staff and patient far outweigh the disadvantages.

Comatose patients or patients with a questionable airway should be intubated to ensure adequate ventilation. Although PCP intoxication can cause mild hypotension, profound hypotension is unusual and represents blood loss from trauma, a mixed-drug ingestion, or another underlying medical problem, and the patient should be resuscitated with fluids as evaluation ensues. Seizures should be treated with intravenous benzodiazepines (see Chapter 102). Tachycardia does not require additional treatment except for sedation.

Hyperthermia (temperature of 40°C) is common in severe cases of PCP poisoning. All patients with significant symptoms, psychosis, or history of violent behavior should have core temperatures measured. Individuals with hyperthermia should be treated with active, evaporative cooling measures (see Chapter 141).

Renal status and creatine kinase level should be monitored to detect rhabdomyolysis and myoglobinuric renal failure. Urinary acidification had been used in the past to trap PCP in urine and to aid in elimination, but its use has been abandoned because of the insignificant renal clearance of the drug (10%) and the potential adverse impact of acid urine on myoglobin in renal tubules that is often present after PCP intoxication. Activated charcoal is of no value in acute intoxication. If patients have never been hyperthermic and have no signs of trauma, laboratory or other diagnostic tests are not needed.

Dextromethorphan poisoning can be managed with supportive care and measures to prevent injury to the patient. Sedation with a benzodiazepine may be used for agitation. Respiratory depression may respond to intravenous administration of naloxone; however, the dissociative effects do not typically respond to naloxone. The patient should improve during 4 to 6 hours. Many dextromethorphan cough and cold preparations also contain acetaminophen, so acetaminophen levels should be measured.

Disposition

For nonviolent patients with PCP intoxication, a quiet holding room is ideal for 4 to 6 hours of observation. Patients with violent behavior or obtundation often require admission to the hospital, where close observation and treatment of potential life-threatening complications can be accomplished. Serial chemistry evaluations, including serum creatinine and creatine kinase, should be monitored. Most of these patients can be medically cleared the next day.

MARIJUANA AND MISCELLANEOUS PLANTS AND FUNGI

Marijuana and Synthetic Cannabinoids

Perspective: Background and Epidemiology

Marijuana is the most common illegal drug in the United States. It was used medicinally in ancient times for conditions such as colic and asthma and has been illegal since 1937, but 16 states have legalized medical marijuana and 7 states allow dispensaries to distribute the drug in 2011. Recreational use of marijuana continues to be common.

Cannabis sativa and *Cannabis indica* plants are some of the earliest plants grown by humans. Bioactive substances derived from these plants are collectively called cannabinoids. The seedless flowering tops of the female plant are referred to as sinsemilla and are the commonly grown form of marijuana in the United States. The resin from the flowers is made into hashish. Marijuana is smoked or eaten blended into foods, such as brownies.

Principles of Disease: Pharmacology and Pathophysiology

Δ^9-Tetrahydrocannabinol (THC) is the main active agent of the more than 61 cannabinol compounds and approximately 300 other substances present in the cannabis plant. Marijuana smoke also contains carbon monoxide, cyanide, acetone, and phenol but not nicotine.[41] The most efficient route of THC delivery is by inhalation. Fifty percent of smoked THC is absorbed compared with 6% by ingestion. Experienced users may be able to absorb larger doses with breath-holding techniques. Peak blood levels occur within 8 minutes of inhalation, with rapid distribution into

www.ketabpezeshki.com 66485457-66963820

tissues, especially tissues with high lipid content.[42] The duration of perceived effects is usually 2 to 4 hours when it is smoked and 6 to 12 hours when it is ingested.

Since the turn of the 21st century, various products containing synthetic "designer" cannabinoids have been gradually emerging and are collectively known as spice. These products are marketed as novelty herbal incense and labeled "not for human consumption." They typically come in 1- to 3-g resealable foil packages and contain various plant leaves sprayed with a solvent mixture of one to several synthetic cannabinoid compounds. Examples of products include Spice (Diamond, Gold, Silver), K2 Summit, Banana Cream Nuke, Yucatan Fire, Genie, and many others. Because these products are also marketed with an emphasis on being "legal highs," the DEA issued an order in March 2011 to list five synthetic cannabinoids (JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol) into Schedule I of the Controlled Substances Act (CSA) to avoid an imminent hazard to the public safety.[43] Previously, only one synthetic cannabinoid (HU-210), a structural analogue of THC, was listed as such. Because numerous synthetic cannabinoids are available, producers of spice products can simply replace a scheduled cannabinoid with others that remain "legal," which minimizes the impact of scheduling by the DEA on long-term availability because the demand for the spice products remains high.

Until the first cannabinoid receptor (CB1R) was isolated and cloned in the late 1980s, the effects of cannabis were not thought to be receptor mediated. Subsequently, a second cannabinoid receptor (CB2R) was identified in the early 1990s. Interestingly, CB2Rs are primarily expressed in immune cells peripherally, whereas CB1Rs are found mostly in the CNS in densities similar to γ-aminobutyric acid (GABA) receptors. Because very few CB1Rs are located in the brain stem, which governs basic physiologic functions, the toxicity of THC and synthetic cannabinoids seems to be relatively low with typical recreational use. Discovery of these cannabinoid receptors has renewed interest in further exploration of the therapeutic potential of cannabinoids[44] (Fig. 156-4).

Clinical Features: Acute Signs and Symptoms

Smoking of marijuana leads to rapid and predictable signs and symptoms. Ingestion can cause delayed and sometimes unpredictable effects. The most common effects from smoking of marijuana include alteration of mood and usually relaxation and euphoria. The only reliable physiologic effects are a mild increase in heart rate and conjunctival injection. Pupillary changes usually do not occur. Other acute peripheral changes include urinary retention, decreased testosterone levels, and decreased intraocular pressure.[45] Short-term memory is impaired, and the ability to perform complex tasks may be adversely affected. Many users report excessive appetite after marijuana use.

Even when "high-potency" marijuana is smoked continuously for hours, adverse effects are rarely seen. Users become more sedated as they continue to smoke but do not become unarousable. No deaths have been solely attributed to marijuana. Pediatric exposures to marijuana may lead to hypothermia, ataxia, nystagmus, tremor, tachycardia, injected conjunctiva, and labile affect.[46,47] Oral ingestion of potent marijuana in children can produce rapid onset of drowsiness, hypotonia, and lethargy, which can lead to coma and airway obstruction.[46,48]

Whereas intoxications with marijuana and spice compounds may be similar in some respects, significant differences have been described.[49] The most common adverse reactions include anxiety, panic, paranoia, and acute psychosis, particularly with novice users or individuals with preexisting psychiatric disease. These episodes are unusual and transient with marijuana but may be more common and pronounced with the synthetic cannabinoids. Nausea and vomiting, which are not typical with marijuana, have been reported with a synthetic JWH-018–containing product.

Diagnostic Strategies

Marijuana screening is not helpful in the emergency department. Urinary metabolites of THC are detectable within 1 hour after smoking of marijuana, but a positive urine test result does not correlate with acute intoxication. A single marijuana cigarette can be detected for 72 hours when a cutoff level of 100 ng/mL is used, and positive urine levels may persist for 3 months after chronic marijuana use.[50] Inadvertent or passive exposure to marijuana may produce positive urine test results, depending on cutoff levels used.[51] False-positive urine screen results may be produced by efavirenz, ibuprofen, and naproxen.[52]

Of the synthetic cannabinoids, only HU-210 is expected to trigger a positive THC immunoassay screen as a result of structural homology. Many other synthetic cannabinoids are structurally distinct from THC and do not result in positive THC

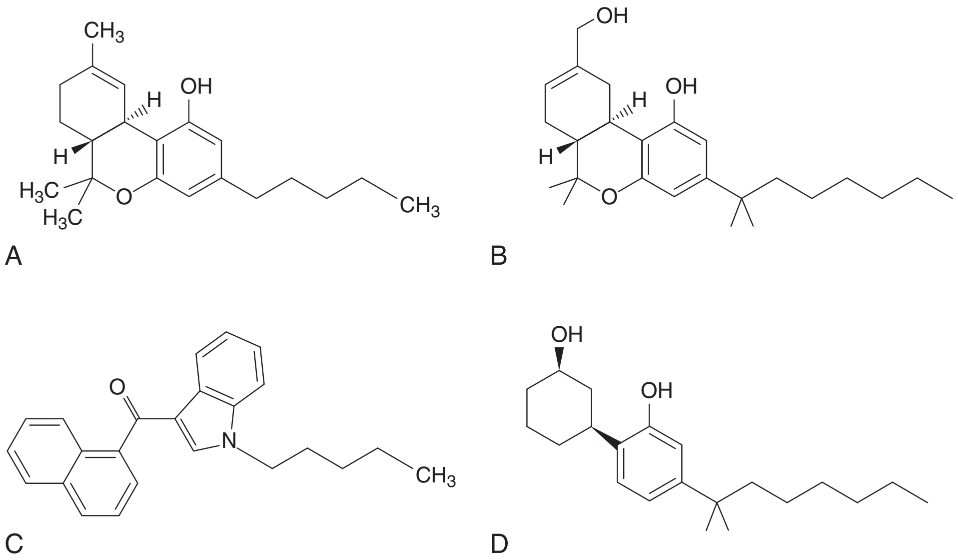


Figure 156-4. Cannabinoid structures. **A,** Δ^9-Tetrahydrocannabinol. **B,** HU-210. **C,** JWH-018. **D,** CP-47,497.

www.ketabpezeshki.com 66485457-66963820

immunoassay screens. Some reference laboratories are beginning to offer confirmatory testing for several synthetic cannabinoids, but the results are not available to the emergency physicians to guide clinical decision-making.

Differential Considerations

The presentation that most closely resembles marijuana and spice intoxication is acute psychosis. Some individuals with underlying and preexisting psychiatric disorders may progress to overt psychosis after heavy or first-time marijuana use. Because marijuana is so readily available, it is commonly a cointoxicant used with ethanol and other psychotropic agents. Rarely, marijuana can be adulterated with other substances, such as lead.[53]

Management and Disposition

Care of patients intoxicated from marijuana and spice consists of prevention of injury and reassurance of those who have panic reactions. An extremely agitated patient can be sedated with oral or parenteral administration of benzodiazepines. Antiemetics may be used to treat nausea and vomiting associated with the synthetic cannabinoids. Children who are significantly symptomatic may require admission.

Salvia

Salvia divinorum, a perennial herb cultivated well outdoors in mild climates, is a member of the mint (*Lamiaceae*) family.[54] Common names for *S. divinorum* are diviner's sage, mystic sage, magic mint, sage of the seers, Sally-D, and ska Maria Pastora. Although the plant has been used for divination and shamanism by the Mazatec Indians of Oaxaca, Mexico, *S. divinorum* has become popular in the past decade for recreational purposes because of its recognized hallucinogenic properties; it continues to be sold legally by online vendors and "smoke" or "head" shops. In 2004, the DEA listed *S. divinorum* as a "drug of concern," but to date, it remains unscheduled under the CSA. Several states, however, have instituted or are considering legislation making possession, cultivation, and use of *S. divinorum* or its extracts illegal. Internationally, regulatory controls have been implemented in Australia and a number of European countries; however, *S. divinorum* and salvinorin A are not currently controlled under the CSA in the United States.[55] Although many states have decided to independently enact legislation with varying degrees of restriction, *Salvia* remains readily available.

The active ingredient in *S. divinorum* is salvinorin A (also known as divinorin A), a neoclerodane diterpene with selective agonist activity for kappa opioid receptors, but it does not bind to delta or mu opioid receptors. Salvinorin A is the first naturally occurring non-nitrogenous kappa opioid receptor agonist with psychotropic properties and is the most potent plant hallucinogen discovered to date. The threshold dose of salvinorin A to produce hallucinations is comparable to that of synthetic LSD and 4-bromo-2,5-dimethoxyphenylisopropylamine. Stimulation of kappa opioid receptors in the brain and spinal cord produces psychomimetic and analgesic effects, respectively. However, salvinorin A is distinct from more traditional hallucinogens because it does not bind to the 5-HT_{2A} serotonin receptors, as is the case with LSD.[56]

Salvia is usually chewed and either spit out or swallowed, and it seems to be absorbed better from the oral mucosa than from the rest of the gastrointestinal tract. Effects produced as a result of oral mucosal absorption may persist for 1 hour. Dried leaves also can be smoked. Inhalation of smoke can produce symptoms within 1 minute that subside during 20 to 30 minutes. Sensations experienced are variable but include distortions of color and vision as well as auditory, visual, gustatory, and olfactory synesthesias that are confusions of the senses, such as seeing sounds, hearing touches, or smelling visions. *S. divinorum* is often used in conjunction with other agents, such as marijuana and MDMA.

Salvinorin A is not detected and is not known to cause interference with routine drug screens used in the clinical setting. Management of intoxication from *S. divinorum* is mainly supportive with emphasis on injury prevention. Use of naloxone, a nonspecific opioid-receptor antagonist, may theoretically be helpful in reversal of psychotropic manifestations.[57]

Kratom

Mitragyna speciosa Korth., or kratom, is a tree indigenous to Thailand but is also found in tropical and subtropical regions of Asia and Africa. Its extracts have been used in Thailand and Malaysia for their euphoric effect as a substitute for opium or to moderate opium use by addicts.[58] The popularity of kratom has grown because of reports of its successful use to attenuate symptoms of opioid withdrawal. Because kratom remains easily obtainable from Internet sources, individuals are able to self-administer the perceived remedy, obviating the need for physician supervision.[59] The safety of such practice is unknown.

Although kratom extract contains more than 25 alkaloids, mitragynine is the most abundantly found in the plant. Mitragynine is an indole alkaloid with structural analogy to yohimbine and has agonist activity at mu and delta opioid receptors, producing euphoric, analgesic, and respiratory depressant effects. Despite its structural similarity to yohimbine, a selective antagonist of presynaptic $alpha_2$-adrenergic receptors, animal studies suggest that mitragynine is also an agonist at postsynaptic $alpha_2$-adrenergic receptors and blocks 5-HT_{2A} receptors.[57]

Typically, kratom leaves are chewed, smoked, or brewed into a tea. Psychotomimetic effects occur within 5 to 10 minutes of use and may persist for 1 hour, with stimulatory effects at lower doses and opioid effects at higher doses. Opioid properties include analgesic, antitussive, antidiarrheal, and emetogenic effects. Reports in the medical literature include intrahepatic cholestasis after abuse for 2 weeks.[60,61]

Currently, there are no diagnostic tests available to detect the presence of kratom alkaloids. Treatment of intoxication is supportive. Although opioid activity has been demonstrated with kratom, the effectiveness of opioid antagonists in reversing effects is inconsistent. A withdrawal syndrome characterized by anxiety, restlessness, and nausea treated with an opioid agonist and lofexidine (an $alpha_2$-agonist related to clonidine) has also been reported.[62]

Iboga

Ibogaine is a naturally occurring indole alkaloid found in the roots of the African rain forest shrub *Tabernanthe iboga*. For many centuries, iboga has been ingested by indigenous peoples of western Africa as a remedy for fatigue, hunger, and thirst and as a psychopharmacologic sacrament in religious ceremonies, and it is believed to enable contact with deceased ancestors. As with many plant-derived agents, ibogaine's physiologic effects are highly complex and may involve opioid, dopaminergic, serotonergic, glutaminergic, GABAergic, glutamatergic, adrenergic, and cellular ion channel signaling systems.

Although iboga in Western culture is used to ease opioid withdrawal and to diminish craving of other abused drugs, the potential for abuse is high because the hallucinogenic effect is extremely vivid. The intensity of visual hallucinations from ingestion of iboga, in contrast to other hallucinogens, is described to be pronounced with closed eyes.[63] There are no clinical tests, and diagnosis is dependent on a history of exposure because clinical

www.ketabpezeshki.com 66485457-66963820

findings are largely nonspecific and management is principally supportive. Since the first report in 1990, there have been 11 reported fatalities within 72 hours of ibogaine use with a hypothesized cardiac etiology.[63]

Absinthe

Absinthe is a bitter, emerald green liqueur derived from an extract of the wormwood tree, *Artemisia absinthium*. The liqueur was popular in the 19th century, particularly among artists, poets, and playwrights, but has been illegal in most countries since the early 20th century. The legal sale of absinthe has resumed in several European countries and Japan, and with the Internet, there has been resurgence in its use and popularity.

In addition to ethanol, the active ingredient of absinthe is thought to be thujone, an aromatic terpenoid related to camphor and turpentine. Although the mechanism is not clear, thujone is thought to antagonize the inhibitory $GABA_A$ receptor, which may explain the clinical effects observed with absinthe.[64] The acute clinical effects of absinthe are reported to be beyond those of ethanol alone and include confusion, delirium, euphoria, and hallucinations (auditory and visual). However, some doubt the plausibility of consuming a dose of thujone adequate to achieve the aforementioned neurotoxic effects given the low concentrations of the toxin present in spirits.[65] Nonetheless, thujone is a known proconvulsant in animals and may cause generalized clonic followed by tonic seizure activity. Ingestion of an essential oil of wormwood has been reported to cause seizures complicated with renal failure secondary to rhabdomyolysis.[66] Treatment is supportive.

Figure 156-5. *Amanita muscaria* mushroom. (Photo by Mark Shubert. Copyright © 2004 Erowid.org. Accessed at www.erowid.org.)

Isoxazole Mushrooms

Isoxazole-containing mushrooms include *Amanita muscaria*, *Amanita pantherina*, *Amanita gemmata*, and *Amanita cothurnata*. *A. muscaria* has a red or yellow cap with white warty structures on its surface and grows in forests of aspen, birch, fir, or pine trees (Fig. 156-5). It has been used by Siberians for centuries and is often described in folklore and fairy tales. Pharmacolinguistic evidence indicates that several modern religions began as *A. muscaria* cults.

The active ingredients are the isoxazole derivatives ibotenic acid and its decarboxylation product, muscimol, which are structural analogues of the endogenous neurotransmitters glutamic acid (excitatory) and GABA (inhibitory) and thought to act at these respective receptor sites.[67] The excitatory effects characterized by elation, giddiness, hyperactivity, muscle tremors, and distortion of space-time begin approximately 30 minutes to 2 hours after ingestion and are likely to be mediated by ibotenic acid. Following is a phase of tiredness and deep "sleep," in which it may be difficult to arouse the patient. During this phase, vivid hallucinations and manic excitement may oscillate with periods of deep sleep. The duration of effect is up to 12 hours. Management of the excitatory phase is similar to that of other hallucinogens previously described in this chapter. Prolonged sleep with *A. muscaria* ingestion requires only observation or supportive care. Tonic-clonic seizures are reported, but occurrences are rare.[68]

Because elements of isoxazole poisoning resemble manifestations of anticholinergic toxicity, these mushrooms have also been referred to as anticholinergic mushrooms; however, belladonna alkaloids are not present. Paradoxically, there has been a high incidence of mistreatment of *A. muscaria* ingestion with atropine because the name implies that it contains muscarine, a cholinergic toxin. However, the amount of muscarine is miniscule. Many textbooks recommend the use of atropine, but atropine may exacerbate the anticholinergic effects associated with isoxazole mushrooms. It is important to differentiate isoxazole-containing *Amanita* mushrooms from the deadly hepatotoxic cyclopeptide-containing *Amanita* mushrooms, of which *Amanita phalloides* is a member.

KEY CONCEPTS

- Hallucinogens include many types of drugs and chemicals with different associated effects.
- Diagnosis and management are based primarily on the history and physical examination.
- Screening tests for drugs of abuse are of limited utility in acute management of intoxicated patients.
- Overreliance on drug of abuse screening may cause the clinician to mistakenly attribute another acute medical condition to drug intoxication.
- Aggressive sedation is necessary in agitated and violent patients.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Nichols DE: Hallucinogens. *Pharmacol Ther* 2004; 101:131.
2. Gertsch JH, Wood C: Case report: An ingestion of Hawaiian Baby Woodrose seeds associated with acute psychosis. *Hawaii Med J* 2003; 62:127.
3. Schwartz RH, Smith DE: Hallucinogenic mushrooms. *Clin Pediatr* 1988; 27:70.
4. Weil AT, Davis W: *Bufo alvarius*: A potent hallucinogen of animal origin. *J Ethnopharmacol* 1994; 41:1.
5. Shulgin AT: *N,N*-Diisopropyltryptamine (DIPT) and 5-methoxy-*N,N*-diisopropyltryptamine (5-MeO-DIPT): Two orally active tryptamine analogs with CNS activity. *Commun Psychopharmacol* 1980; 4:363.
6. Meatherall R: Foxy, a designer tryptamine hallucinogen. *J Anal Toxicol* 2003; 27:313.
7. Glennon RA: Do classical hallucinogens act as 5-HT_2 agonists or antagonists? *Neuropsychopharmacology* 1990; 3:509.
8. Klock JC, et al: Coma, hyperthermia and bleeding associated with massive LSD overdose: A report of eight cases. *J Toxicol Clin Toxicol* 1975; 8:191.
9. Hill SL, Thomas SH: Clinical toxicology of newer recreational drugs. *Clin Toxicol (Phila)* 2011; 49:705.
10. Hall AP, Henry JA: Acute toxic effects of “Ecstasy” (MDMA) and related compounds: Overview of the pathophysiology and clinical management. *Br J Anaesth* 2006; 96:678.
11. Voorspoels S, et al: Resurgence of a lethal drug: Paramethoxyamphetamine deaths in Belgium. *J Toxicol Clin Toxicol* 2002; 40:203.
12. Byard RW, et al: Death and paramethoxyamphetamine—an evolving problem. *Med J Aust* 2002; 176:496.
13. Prosser JM, Nelson LS: The toxicology of bath salts: a review of synthetic cathinones. *J Med Toxicol* 2012; 8:33-42.
14. Elliott S, Smith C: Investigation of the first deaths in the United Kingdom involving the detection and quantitation of the piperazines BZP and 3-TFMPP. *J Anal Toxicol* 2008; 32:172.
15. Baumann MH, et al: *N*-Substituted piperazines abused by humans mimic the molecular mechanism of 3,4-methylenedioxymeth amphetamine (MDMA, or “Ecstasy”). *Neuropsychopharmacology* 2005; 30:550.
16. McKenna A, Nordt SP, Ryan J: Acute nutmeg poisoning. *Eur J Emerg Med* 2004; 11:240.
17. Forrester MB: Nutmeg intoxication in Texas, 1998-2004. *Hum Exp Toxicol* 2005; 24:563.
18. Easton N, Marsden CA: Ecstasy: Are animal data consistent between species and can they translate to humans? *J Psychopharmacol* 2006; 20:194.
19. Ricaurte GA, et al: (+/−)3,4-Methylenedioxymethamphetamine selectively damages serotonergic neurons in nonhuman primates. *JAMA* 1988; 260:51.
20. Ricaurte GA, et al: Toxic effects of MDMA on central serotonergic neurons in the primate: Importance of route and frequency of drug administration. *Brain Res* 1988; 446:165.
21. Gouzoulis-Mayfrank E, Daumann J: Neurotoxicity of methylenedioxyamphetamines (MDMA; ecstasy) in humans: How strong is the evidence for persistent brain damage? *Addiction* 2006; 101:348.
22. Malberg JE, Seiden LS: Small changes in ambient temperature cause large changes in 3,4-methylenedioxymethamphetamine (MDMA)–induced serotonin neurotoxicity and core body temperature in the rat. *J Neurosci* 1998; 18:5086.
23. Farfel GM, Seiden LS: Role of hyperthermia in the mechanism of protection against serotonergic toxicity: II. Experiments with methamphetamine, *p*-chloroamphetamine, fenfluramine, dizocilpine and dextromethorphan. *J Pharmacol Exp Ther* 1995; 272:868.
24. Hartung TK, et al: Hyponatraemic states following 3,4-met hylenedioxymethamphetamine (MDMA, “ecstasy”) ingestion. *QJM* 2002; 95:431.
25. Henry JA, et al: Low-dose MDMA (“ecstasy”) induces vasopressin secretion. *Lancet* 1998; 351:1784.
26. Holden R, Jackson MA: Near-fatal hyponatraemic coma due to vasopressin over-secretion after “ecstasy” (3,4-MDMA). *Lancet* 1996; 347:1052.
27. Randall T: Ecstasy-fueled “rave” parties become dances of death for English youths. *JAMA* 1992; 268:1505.
28. Zhao H, et al: Profiles of urine samples taken from Ecstasy users at rave parties: Analysis by immunoassays, HPLC, and GC-MS. *J Anal Toxicol* 2001; 25:258.
29. Boyer EW: Dextromethorphan abuse. *Pediatr Emerg Care* 2004; 20:858.
30. Javitt DC, Zukin SR: Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry* 1991; 148:1301.
31. Cook CE, et al: Phencyclidine and phenylcyclohexane disposition after smoking phencyclidine. *Clin Pharmacol Ther* 1982; 31:635.
32. Young JD, Crapo LM: Protracted phencyclidine coma from an intestinal deposit. *Arch Intern Med* 1992; 152:859.
33. Schneider SM, et al: Dextromethorphan poisoning reversed by naloxone. *Am J Emerg Med* 1991; 9:237.
34. McCarron MM, et al: Acute phencyclidine intoxication: Incidence of clinical findings in 1,000 cases. *Ann Emerg Med* 1981; 10:237.
35. McCarron MM: Phencyclidine intoxication. *Dig Emerg Med Care* 1985; 5:4.
36. Barton CH, et al: Rhabdomyolysis and acute renal failure associated with phencyclidine intoxication. *Arch Intern Med* 1980; 140:568.
37. Wolfe TR, Caravati EM: Massive dextromethorphan ingestion and abuse. *Am J Emerg Med* 1995; 13:174.
38. Pender ES, Parks BR: Toxicity with dextromethorphan-containing preparations: A literature review and report of two additional cases. *Pediatr Emerg Care* 1991; 7:163.
39. Ly BT, Thornton SL, Buono C, Stone JA, Wu AH: False-positive urine phencyclidine immunoassay screen result caused by interference by tramadol and its metabolites. *Ann Emerg Med* 2012; 59:545.
40. Ng YY, et al: Spurious hyperchloremia and decreased anion gap in a patient with dextromethorphan bromide. *Am J Nephrol* 1992; 12:268.
41. Nahas GG: Cannabis: Toxicological properties and epidemiological aspects. *Med J Aust* 1986; 145:82.
42. Wall ME, et al: Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. *Clin Pharmacol Ther* 1983; 34:352.
43. Rules and regulations. *Fed Regist* 2011; 76(40):11075-11078.
44. Seely KA, Prather PL, James LP, Moran JH: Marijuana-based drugs: Innovative therapeutics or designer drugs of abuse? *Mol Interv* 2011; 22:36.
45. Heishman SJ, et al: Acute and residual effects of marijuana: Profiles of plasma TCH levels, physiological, subjective and performance measures. *Pharmacol Biochem Behav* 1990; 37:561.
46. Renier S, Messi G, Orel P: Acute cannabis poisoning in a female child. *Minerva Pediatr* 1994; 46:335.
47. Weinberg D, Lande A, Hilton N: Intoxication from accidental marijuana ingestion. *Pediatrics* 1983; 71:848.
48. Macnab A, Anderson E, Susak L: Ingestion of cannabis: A cause of coma in children. *Pediatr Emerg Care* 1989; 5:238.
49. Schneir AB, Cullen J, Ly BT: Spice girls: Synthetic cannabinoid intoxication. *J Emerg Med* 2011; 40:296.
50. Ellis GM, et al: Excretion patterns of cannabinoid metabolites after last use in a group of chronic uses. *Clin Pharmacol Ther* 1985; 38:572.
51. Cone EJ, et al: Passive inhalation of marijuana smoke: Urinalysis and room air levels of delta-9-tetrahydrocannabinol. *J Anal Toxicol* 1987; 11:89.
52. Rossi S, et al: Characterization of interference with 6 commercial Δ^9-tetrahydrocannabinol immunoassays by efavirenz (glucuronide) in urine. *Clin Chem* 2006; 52:896.
53. Busse F, et al: Lead poisoning due to adulterated marijuana. *N Engl J Med* 2008; 358:1641.
54. Valdes LJ: *Salvia divinorum* and the unique diterpene hallucinogen, Salvinorin (divinorin) A. *J Psychoactive Drugs* 1994; 26:277.
55. Salvia divinorum. Available at www.justice.gov/dea/concern/salvia_divinorum.html. Accessed July 1, 2011.
56. Cunningham CW, Rothman RB, Prisinzano TE: Neuropharmacology of the naturally occurring K-opioid hallucinogen Salvinorin A. *Pharmacol Rev* 2011; 63:316.
57. Babu KM, McCurdy CR, Boyer EW: Opioid receptors and legal highs: *Salvia divinorum* and Kratom. *Clin Toxicol (Phila)* 2008; 46:146.
58. Chittrakarn S, et al: Inhibitory effects of kratom leaf extract (*Mitragyna speciosa* Korth.) on the rat gastrointestinal tract. *J Ethnopharmacol* 2008; 116:173.
59. Boyer EW, Babu KM, Macalino GE: Self-treatment of opioid withdrawal with a dietary supplement, Kratom. *Am J Addict* 2007; 16:352.
60. Kapp FG, Maurer HH, Auwarter V, Winkelmann M, Hermanns-Clausen M: Intrahepatic cholestasis following abuse of powdered Kratom (*Mitragyna speciosa*). *J Med Toxicol* 2011; 7:227.
61. Nelsen JL, Lapoint J, Hodgman MJ, Aldous KM: Seizure and coma following Kratom (*Mitragyna speciosa* Korth) exposure. *J Med Toxicol* 2010; 6:424.

www.ketabpezeshki.com 66485457-66963820

62. McWhirter L, Morris S: A case report of inpatient detoxification after Kratom (*Mitragyna speciosa*) dependence. *Eur Addict Res* 2010; 16:229.
63. Alper KR, Lotsof HS, Kaplan CD: The ibogaine medical subculture. *J Ethnopharmacol* 2008; 115:9.
64. Höld KM, Sirisoma NS, Ikeda T, Narahashi T, Casida JE: α-Thujone (the active component of absinthe): γ-Aminobutyric acid type A receptor modulation and metabolic detoxification. *Proc Natl Acad Sci U S A* 2000; 97:3826.
65. Padosch SA, Lachenmeier DW, Kröner LU: Absinthism: A fictitious 19th century syndrome with present impact. *Subst Abuse Treat Prev Policy* 2006; 1:14.
66. Weisbord SD, Soule JB, Kimmel PL: Poison online—acute renal failure caused by oil of wormwood purchased through the Internet. *N Engl J Med* 1997; 337:825.
67. Michelot D, Melendez-Howell LM: *Amanita muscaria:* Chemistry, biology, toxicology, and ethnomycology. *Mycol Res* 2003; 107:131.
68. Berger KJ, Guss DA: Mycotoxins revisited: Part II. *J Emerg Med* 2005; 28:175.

www.ketabpezeshki.com 66485457-66963820

Chapter 157

Heavy Metals

Larissa I. Velez and Ellen J. O'Connell

IRON

Iron, which is essential to the function of hemoglobin, myoglobin, many cytochromes, and many catalytic enzymes, can be extremely toxic when levels are elevated after an overdose or from accumulation in disease states.[1] The acute ingestion of iron is especially hazardous to children. Ingestions of pediatric multivitamin formulations are the most common iron exposures. These occur in children younger than 6 years and are minimally toxic. Life-threatening toxicity is associated with ingestion of potent adult preparations, such as prenatal vitamins. Serious iron ingestions in adults are usually associated with suicide attempts.[2]

Principles of Disease

Pharmacology

Under normal conditions, approximately 10% of ingested iron is absorbed from the intestine and subsequently bound to transferrin, using only 15 to 35% of the iron-binding capacity of transferrin. Normal serum iron levels range from 50 to 150 µg/dL. The total iron-binding capacity (TIBC), a crude measure of the ability of serum proteins—including transferrin—to bind iron, ranges from 300 to 400 µg/dL. It is higher than the serum iron level because of a low degree of saturation. When iron levels rise after a significant iron overdose, transferrin becomes saturated so that excess iron circulates as free, unbound iron in the serum. This unbound iron is directly toxic to target organs.

In assessment of the severity of an iron exposure, it is important to refer to the amount of elemental iron ingested because the toxicity of an iron compound depends on the amount of elemental iron it contains (Table 157-1). Different formulations of iron salts contain different percentages of elemental iron. The total amount of elemental iron ingested can be approximated by multiplying the estimated number of tablets by the fraction of elemental iron contained in the tablet. Manufacturers are also required to list the amount of elemental iron per tablet. Ingestions of less than 20 mg/kg of elemental iron usually cause no symptoms. Ingestion of 20 to 60 mg/kg results in mild to moderate symptoms, and ingestion of more than 60 mg/kg may lead to severe morbidity and mortality. Although the dose of elemental iron associated with 50% mortality (LD_{50}) is 200 to 250 mg/kg, doses as small as 130 mg of elemental iron have been lethal in children.[3] Newer forms of iron are carbonyl iron and iron polysaccharide; both are non-ionic and associated with lower toxicity. Neither form is directly corrosive, and the conversion to the iron ion, which is responsible for toxicity, is very slow. There are no reported cases of serious toxicity or death from the ingestion of these compounds.[4,5]

Pathophysiology

Iron has two distinct toxic effects: (1) it causes direct caustic injury to the gastrointestinal mucosa, and (2) it impairs cellular metabolism, primarily of the heart, liver, and central nervous system (CNS). The caustic effects of iron on the gut cause the initial symptoms of vomiting, diarrhea, and abdominal pain. Hemorrhagic necrosis of gastric or intestinal mucosa can lead to bleeding, perforation, and peritonitis.[3] Unbound (free) iron moves into cells and localizes near the mitochondrial cristae, resulting in uncoupling of oxidative phosphorylation and impairment of adenosine triphosphate synthesis. Cell membranes are injured by free radical–mediated lipid peroxidation.[3,6]

Iron increases capillary permeability and both arteriolar dilation and venodilation, resulting in hypotension. Direct myocardial toxicity decreases cardiac output. Hydration of the iron molecule creates an excess of unbuffered protons, worsening metabolic acidosis.[3] These effects, combined with severe gastrointestinal fluid losses, can lead to shock, cardiovascular collapse, and death.[3]

Clinical Features

The clinical effects of acute iron poisoning occur in five stages. Not every patient goes through every phase. Phase I reflects the corrosive effects of iron on the gut. Vomiting occurs within 80 minutes of ingestion in more than 90% of symptomatic cases. Diarrhea, which can be bloody, soon follows. Phase II represents an apparent (but not complete) recovery that lasts less than 24 hours but can extend up to 2 days. Most patients recover after this point. Phase III is characterized by the recurrence of gastrointestinal symptoms, severe lethargy or coma, anion gap metabolic acidosis, leukocytosis, coagulopathy, renal failure, and cardiovascular collapse. Serum iron levels may have fallen to normal during this phase because of distribution of iron into the tissues. Metabolic derangements due to iron poisoning include hypoglycemia, leukocytosis, and severe lactic acidosis from hypoperfusion and interference with cellular respiration. Early coagulation defects are probably related to direct effects of iron on vitamin K–dependent clotting factors.[7] Later coagulation defects are due to hepatic failure. Hypoglycemia and elevations of bilirubin and aspartate and alanine transaminases are other markers of hepatotoxicity. Phase IV, characterized by fulminant hepatic failure, occurs 2 to 5 days after ingestion. This is relatively rare, appears to be dose related, and is usually fatal.[8] Phase V represents the consequences of healing of the injured gastrointestinal mucosa. It is characterized by pyloric or proximal bowel scarring, which is sometimes associated with obstruction.

www.ketabpezeshki.com 66485457-66963820

Table 157-1 Common Iron Preparations

COMPOUND	PERCENTAGE OF ELEMENTAL IRON
Ferrous sulfate	20
Ferrous fumarate	33
Ferrous gluconate	12
Ferric pyrophosphate	30
Ferrocholinate	14
Ferroglycine sulfate	16
Ferrous sulfate, dried	33
Ferrous carbonate, anhydrous	38
Carbonyl iron	100
Iron polysaccharide	46

Table 157-2 Toxicity of Iron by Amount Ingested and Peak Serum Levels

ELEMENTAL IRON (mg/kg)	PEAK SERUM IRON LEVEL (μG/DL)	TOXICITY
<20	50-150	None
20-40	150-300	Mild
40-60	300-500	Moderate
>60	>500	Severe

Figure 157-1. Radiopaque iron tablets *(arrow)* seen on abdominal radiograph. (From Craig SA: Radiology. In Ford MD, Delaney KA, Ling LJ, Erickson T [eds]: Clinical Toxicology. Philadelphia, WB Saunders, 2001, p 62.)

Diagnostic Strategies

The presence of gastrointestinal symptoms suggests a potentially serious ingestion, whereas their absence is reassuring.[5] A serum iron level measured at its peak, 3 to 5 hours after ingestion, is the most useful laboratory test to evaluate the potential severity of an iron overdose. Sustained-release or enteric-coated preparations may have erratic absorption, so a second level 6 to 8 hours after ingestion should also be checked. Peak serum iron levels below 350 μg/dL are generally associated with minimal toxicity; 350 to 500 μg/dL, with moderate toxicity; and above 500 μg/dL, with potentially severe toxicity (Table 157-2).[5] Because iron is rapidly cleared from the serum and deposited in the liver, the level of iron after a substantial ingestion may be deceptively low if it is measured after its peak. TIBC is a crude test and is not useful to gauge the severity of iron poisoning.[9]

When serum iron levels are not immediately available, elevations of the serum glucose level above 150 mg/dL and leukocyte count above 15,000 are 100% specific for prediction of serum iron levels of more than 300 μg/mL. However, a sensitivity of only 50% limits their sole use as indicators of toxicity.[10]

Most tablets that contain a significant amount of elemental iron are radiopaque, although a false-negative radiograph may occur with chewable, liquid, and completely dissolved iron compounds. The presence of tablets on a radiograph correlates with the severity of the ingestion (Fig. 157-1).[11,12] Repeated radiographs can also demonstrate the efficacy of gastrointestinal decontamination efforts.

Management

Gastric Emptying

Decontamination may prevent absorption of additional iron from the gastrointestinal tract and can be performed concomitantly with interventions that address drug that has already been absorbed (see later section on deferoxamine). Activated charcoal does not bind iron, and neither gastric lavage nor ipecac effectively removes large numbers of pills. Iron tablets clump together as their outer coatings dissolve, often forming large pharmacobezoars. Whole-bowel irrigation is generally the preferred method of decontamination for significant iron ingestions.[13] This recommendation is supported by the position statement of the American Academy of Clinical Toxicology and the European Association of Poison Centres and Clinical Toxicologists; it is based on case reports and the lack of effective alternative decontamination techniques for this potentially deadly toxin.[14]

For significant ingestions (>20 mg/kg of elemental iron), especially when tablets are identified on the abdominal radiograph, whole-bowel irrigation with a polyethylene glycol–electrolyte lavage solution (PEG-ELS; CoLyte, NuLytely, or GoLytely) should be initiated.[14] The solution is either taken orally or, more often, administered through a small nasogastric tube.[15] The usual rate of administration of PEG-ELS is 20 to 40 mL/kg/hr in young children and 1.5 to 2 L/hr in teenagers or adults, continued until the rectal effluent is clear and there is no radiographic evidence of pill fragments. This technique has been used in children, adolescents, and pregnant women without serious complications or electrolyte disturbances.[13,16,17] Common side effects include nausea, vomiting, abdominal cramping, and bloating. Whole-bowel irrigation is contraindicated in the presence of bowel obstruction, perforation, or ileus.[14]

Hemodialysis and hemoperfusion are not effective in the removal of iron because of its large volume of distribution. Early exchange transfusions have been recommended for severely symptomatic patients with serum iron levels exceeding 1000 μg/dL.[18,19]

Deferoxamine

Deferoxamine chelates iron to form the water-soluble compound ferrioxamine, which is renally excreted and can be dialyzed;

www.ketabpezeshki.com 66485457-66963820

100 mg will chelate 9.35 mg of elemental iron.[3] Deferoxamine may also limit the entrance of iron into the cell and chelate intracellular iron. Because of its short half-life, it is administered as a continuous infusion at 15 mg/kg/hr for up to 24 hours.[20] The maximum rate of administration is 35 mg/kg/hr. Rapid administration of deferoxamine can lead to hypotension, which resolves by reducing the initial rate of the infusion and slowly increasing it to the desired rate. Pregnancy is not a contraindication to deferoxamine.[4,21,22] However, the pre-pregnancy weight should be used to calculate the dose. Deferoxamine can falsely lower serum iron levels, so measurements should be taken before its administration.[23]

The presence of ferrioxamine turns the urine a "vin rosé" color, which reflects the excretion of chelated iron. The deferoxamine challenge test, which relied on detection of this color change, has been used to detect the presence of free iron in the serum. However, the color change is difficult to detect, especially when the urine is dilute, with false-negative results even in cases of serious poisoning.[24]

Deferoxamine has been associated with acute respiratory distress syndrome and also with *Yersinia* sepsis. The pulmonary complications are usually related to high-dose deferoxamine for durations longer than 24 hours.[20] The presence of fever and sepsis in a patient who has recently been treated for iron poisoning should prompt suspicion for *Yersinia* sepsis.[25,26]

Disposition

The asymptomatic patient who is reliably known to have ingested less than 20 mg/kg of elemental iron and has a normal abdominal radiograph can be observed without further therapy. The patient can be discharged if he or she remains asymptomatic after 6 hours of observation.[5]

The patient who has ingested more than 20 mg/kg of elemental iron or has pills visible on an abdominal radiograph should receive whole-bowel irrigation.[23] Follow-up abdominal radiographs can verify adequate gastrointestinal decontamination. The serum iron concentration should be checked 3 to 5 hours after ingestion. A second iron level 6 to 8 hours after ingestion should be decreasing. If peak levels are less than 300 µg/dL and are not rising and the patient is asymptomatic during 6 hours of observation, the patient can be discharged home. Moderate gastrointestinal toxicity can be expected with peak levels of 300 to 500 µg/dL. Deferoxamine should be used if these patients have symptoms of systemic toxicity evidenced by metabolic acidosis, repetitive vomiting, toxic appearance, lethargy, hypotension, or signs of shock. Patients with a serum iron level above 500 µg/dL require chelation with deferoxamine regardless of symptoms.[4] If serum iron levels are not available, a normal serum glucose level and leukocyte count suggest a low iron level; if there are no signs or symptoms of toxicity during the 6-hour postingestion period and the abdominal radiographs do not show pills in the gastrointestinal tract, the patient can be sent home.

Patients with large ingestions demonstrated by abdominal radiographs should be treated with whole-bowel irrigation until subsequent radiographs show a clean gastrointestinal tract.

LEAD

Lead poisoning is a disease of industrialization and has become the most common environmental toxicologic problem in the United States.[27] Most exposures are from inhalation of lead dust or fumes or ingestion of contaminated substances, such as paint chips. Less often, it results from direct skin contact with organic lead compounds or from retained bullets in or near joints.[28] Approximately 3 to 4 million children (1 in 20) in the United States have toxic blood lead levels (BLLs), defined currently as levels exceeding 10 µg/dL.[29] Although the addition of lead to household paint and gasoline was banned in the United States in the 1970s, residual lead-based paint is still found in 30 million homes.[29] Other sources of toxic lead ingestions include curtain weights, buckshot, fishing weights, lead-contaminated soil or water, bootleg whiskey ("moonshine"), food or beverages stored or prepared in lead-soldered cans, lead-glazed pottery, and lead crystal decanters.[30] Herbal and folk remedies, toys, and numerous products imported from Asia and Mexico can also contain dangerous amounts of lead.[31,32] This has resulted in multiple drug and toy recalls in the United States. Lead found in buckshot can cause toxic effects in those who eat wild game.[33]

Children typically present to the emergency department (1) after an ingestion of lead, (2) symptomatic with a possible exposure history, or (3) referred for management of an elevated BLL. Lead toxicity in adults most often results from inhalational exposure in the workplace as well as from hobbies and related activities. It is estimated that more than 3 million workers in the United States are at risk for toxic lead exposure in industries such as lead smelting, battery manufacture, radiator repair, bridge and ship construction or demolition, soldering or welding, cable or tin can production, stained glass manufacture, lead-glazed or crystal pottery making, glass production, firing range operation, and lead-based paint abatement. Hobbies at risk include making glazed pottery, target shooting at indoor firing ranges, soldering lead, smelting lead in the preparation of buckshot and fishing sinkers, repairing cars or boats, and remodeling homes. Lead toxicity should be considered in adults with compatible symptoms associated with these exposures.

Principles of Disease

Pharmacology

Lead is generally poorly absorbed from the gastrointestinal tract, but its absorption is highest in malnourished children (approximately 40%) and in pregnant women. Although 90 to 95% of lead is stored in cortical bone and teeth, it is also found in the brain, liver, and kidneys. Approximately 75% of the absorbed lead is eliminated by the kidneys; the remainder is excreted through the skin, hair, sweat, nails, and gastrointestinal tract.

Pathophysiology

There is no known physiologic need for lead. Lead binds to sulfhydryl groups and other ligands and interferes with critical enzymatic reactions.[12] Its toxic effects are most prominent in the hematopoietic, neurologic, and renal systems.[34]

Anemia, the classic manifestation of hematopoietic toxicity, may be either normochromic or hypochromic. The severity of the anemia correlates directly with the BLL. Inhibition of heme biosynthesis results in the accumulation of heme precursors, such as D-aminolevulinic acid and protoporphyrin. In the peripheral nervous system, segmental demyelination and degeneration of motor axons result in peripheral neuropathies. Wristdrop and footdrop are characteristic of adult lead poisoning. Lead toxicity also causes a host of neuropsychiatric disorders. In children, elevated BLL is associated with decreased intelligence (IQ) scores, hyperactivity, decreased attention span, overaggressive behavior, learning disabilities, and criminal behavior.[35-38] It has also been associated with subclinical sensorineural hearing loss.[39] Lead nephropathy is characterized by fibrosis in the proximal tubules, with relative sparing of the glomeruli. Hyperuricemic gout ("saturnine gout") can result from increased reuptake of uric acid by the tubular cells.[40] Lead poisoning also correlates with hypertension.[41] Adults and children with severe acute toxicity may present

www.ketabpezeshki.com 66485457-66963820

with lead encephalopathy associated with increased capillary permeability and cerebral edema.[42,43]

Clinical Features

Symptoms of chronic, mild lead poisoning are slow in onset and nonspecific. The diagnosis is suspected by obtaining an accurate and comprehensive history of exposure to lead.

Acute exposure to lead can result in symptomatic poisoning. "Lead colic" is characterized by cramping abdominal pain with nausea, vomiting, constipation, and, occasionally, diarrhea.[43] Other characteristic symptoms and signs of acute toxicity include fatigue, anemia, peripheral neuropathy, renal impairment, and hepatic and CNS dysfunction. The CNS toxicity may be manifested as mild headache or personality changes to full-blown encephalopathy with coma, convulsions, and papilledema. Permanent neurologic and behavioral sequelae may occur.

Diagnostic Strategies

Although capillary lead levels correlate well with BLLs, the most informative biomarker is a BLL.[44-46] The Centers for Disease Control and Prevention has defined a chronic BLL of more than 10 μg/dL as toxic for a child. Acute exposure can result in levels above 100 μg/dL (Table 157-3). Other ancillary data include findings on complete blood cell count, serum glucose level, blood urea nitrogen and creatinine concentrations, electrolyte levels, and urinalysis. A peripheral smear may show basophilic stippling. Markers of hepatic injury may be elevated after acute exposure. Because lead-containing paints and objects are radiopaque when lead is present in sufficient quantities, radiographs can confirm acute ingestion and also monitor the effectiveness of whole-bowel irrigation. In cases of altered mental status, seizures, or coma, a computed tomography scan of the head will show cerebral edema associated with acute lead encephalopathy and rule out other causes of these symptoms. In children, plain radiographs of the wrist and knees may show increased metaphyseal activity manifested as "lead bands" or "lead lines" that are characteristic of chronic exposures.

Table 157-3 Serum Lead Levels and Symptoms

	SYMPTOMS	
LEVEL (μg/dL)	Adults	Children
10	None	Decreased IQ Decreased hearing Decreased growth
20	Increased protoporphyrin No symptoms	Decreased nerve conduction velocity Increased protoporphyrin
30	Increased blood pressure Decreased hearing	Decreased vitamin D metabolism
40	Peripheral neuropathies Nephropathy Infertility (men)	Decreased hemoglobin synthesis
50	Decreased hemoglobin synthesis	Lead colic
70	Anemia	Anemia Encephalopathy Nephropathy
100	Encephalopathy	Death

Management

Acute Lead Encephalopathy

Acute lead encephalopathy can be rapidly fatal. The initial goals in management are identification and treatment of all life-threatening conditions, followed by prevention of further exposure to lead, minimization of ingested lead absorption, enhancement of its elimination, and prevention or reversal of pathologic cell changes. Standard measures to control cerebral edema, including intubation and neurosurgical consultation for invasive monitoring of intracranial pressure, are indicated. When a severe poisoning is associated with recent ingestion or if radiopacities are seen on the radiograph, decontamination with whole-bowel irrigation should be considered.[47,48] This intervention has not been prospectively studied but has been successful in case reports.[14] Activated charcoal does not adsorb lead and should not be used.

Chelation Therapy

The use of chelation in cases of acute lead poisoning is guided by the patient's clinical status and the BLL. Any patient with a BLL above 70 μg/dL or with signs suggestive of encephalopathy will require admission for parenteral chelation therapy. For these seriously poisoned patients, dimercaprol (or British anti-Lewisite [BAL]) should be the first chelator given. The dosage for treatment of lead encephalopathy is 75 mg/m^2 deep intramuscular injection every 4 hours for 5 days for children or 4 mg/kg every 4 hours for adults. Dimercaprol forms complexes that undergo both renal and biliary excretion. Adverse reactions to dimercaprol include nausea, vomiting, urticaria, pyrexia, hypertension, and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.[49] Because dimercaprol is diluted in peanut oil, it is contraindicated in patients allergic to peanuts.[49] Dimercaprol is followed by calcium disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$), a highly effective lead chelator. Because of concerns that the chelated lead can cross the blood-brain barrier and worsen encephalopathy, the first dose of $CaNa_2EDTA$ is administered with the second dose of dimercaprol. The dosage of $CaNa_2EDTA$ for patients with acute lead encephalopathy is 1500 mg/m^2/day (approximately 50-75 mg/kg/day) given by continuous intravenous infusion. Adverse reactions include renal tubular injury and chelation of other metals, especially iron and zinc. $CaNa_2EDTA$ should be given only with adequate urine flow or with hemodialysis in the patient with renal failure.[50] It is important that $CaNa_2EDTA$ not be confused with sodium EDTA. The administration of sodium EDTA has been associated with hypocalcemia and death from arrhythmias.[51]

The need for parenteral chelation therapy in asymptomatic or minimally symptomatic children is guided by the BLL. A BLL of more than 69 μg/dL is an indication for hospitalization and parenteral chelation therapy. For less seriously poisoned patients, the dosage of $CaNa_2EDTA$ is 50 mg/kg/day or 1000 mg/m^2/day, given in two to four divided doses for up to 5 days.

Serum lead levels of 45 to 69 μg/dL in patients without vomiting or CNS symptoms can be managed in the outpatient setting with oral succimer (2,3-dimercaptosuccinic acid [DMSA]; Chemet). The initial dose of DMSA is 10 mg/kg every 8 hours for 5 days, then 10 mg/kg every 12 hours for 14 days. The most common adverse reactions include nausea, vomiting, diarrhea, and transient elevations in liver transaminase levels. Although DMSA has been approved only for children, it is effective and also used for adults.[44,52,53] Oral D-penicillamine is less efficacious than succimer and has more adverse reactions; it should be used only in patients who do not tolerate succimer. The usual oral dose of

www.ketabpezeshki.com 66485457-66963820

Table 157-4 Chelators

CHELATOR	DOSE	INDICATIONS	CONTRAINDICATIONS
Deferoxamine	15 mg/kg/hr up to 24 hr (titrate up slowly because of hypotension)	Iron level >500 g/dL or systemic symptoms	
Dimercaprol (British anti-Lewisite, BAL)	Lead encephalopathy: 75 mg/m^2 deep intramuscular (IM) injection every 4 hr for 5 days in children or 4 mg/kg every 4 hr for adults Arsenic (severe): no established regimen; consider 3 mg/kg IM every 4 hr for 48 hr, then twice daily for 7-10 days Mercury: 5 mg/kg IM first, then 2.5 mg/kg every 12-24 hr	Lead level >70 g/dL or encephalopathy Arsenic: symptomatic patient with known exposure Mercury: inorganic	Peanut allergy Organic mercury poisoning
$CaNa_2EDTA$	1500 mg/m^2/day continuous intravenous infusion 50 mg/kg/day or 1000 mg/m^2/day in 2-4 divided doses for up to 5 days if less severe symptoms	Lead: given after first dose of BAL for blood lead level above 70 g/dL or encephalopathy	
Succimer (DMSA)	10 mg/kg q8h × 5 days, then q12h for 14 days	Lead level of 45-69 g/dL Arsenic: if tolerated orally for subacute and chronic toxicity Mercury: acute and chronic	
D-Penicillamine	25 mg/kg q6h × 5 days	Lead level of 45-69 g/dL, succimer not tolerated Arsenic: only if BAL and DMSA are unavailable Mercury: if BAL and DMSA are unavailable or not tolerated	Penicillin allergy
DMPS (investigational)	5 mg/kg/dose IM q6-8h day 1, q8-12h day 2, q12-24h day 3 and until 24-hr urine is <50 µg/L	Lead (chronic) Arsenic Mercury	

Note: Indications for chelation and dosing regimens may change. Consult with a toxicologist or poison control center for the most up-to-date recommendations.

D-penicillamine is 25 mg/kg every 6 hours for 5 days. Penicillin allergy is a contraindication to the use of D-penicillamine. Another oral chelator is 2,3-dimercapto-1-propanesulfonic acid (DMPS), which, like succimer, is similar to BAL. At this time, it is experimental, although it can be considered in chronic lead poisoning.[54,55] Table 157-4 summarizes available chelating agents with indications and doses.

Evidence indicates no need for chelation for children with a BLL lower than 45 µg/dL.[43] A BLL between 20 and 44 µg/dL in a patient who is asymptomatic or minimally symptomatic requires a medical and environmental evaluation. Children with lead levels of 10 to 19 µg/dL require family counseling about the symptoms and sources of lead exposure and careful follow-up, with frequent screening of BLLs. The key to management of chronic lead toxicity is the identification and reduction of sources of primary exposure, which can often be arranged with the local public health department. Any patient treated on an outpatient basis should be discharged to a lead-free environment.

The treatment of adults with chronic poisoning is based primarily on symptoms and is less aggressive than treatment of children with the same BLL. If gastrointestinal symptoms or CNS problems are present, hospitalization with parenteral chelation therapy is indicated. In the asymptomatic adult or the adult with only mild clinical problems, the only intervention needed is cessation of exposure. According to the Occupational Safety and Health Administration lead standard, workers with serum lead levels above 50 µg/dL should be removed from work.

Pregnant women should be treated in accordance with adult treatment guidelines. Lead does cross the placenta and may accumulate in the fetus, and the newborn may require chelation as well.

Disposition

Patients who have ingested a single lead foreign body (e.g., fishing sinker) will usually pass it harmlessly.[56] If the foreign body remains in the gastrointestinal tract after 2 weeks, removal should be considered to prevent systemic lead toxicity. Gunshot victims with too many lead buckshot pellets to remove may be at risk for elevated BLL and require follow-up lead levels. Asymptomatic children and adults should be counseled on how to avoid further exposure and have a repeated BLL checked in 2 weeks to ensure decreasing levels.

Patients who are significantly symptomatic with CNS symptoms after an acute lead exposure and children with a BLL of 69 µg/dL or higher require hospitalization and chelation therapy. Patients discharged home with oral chelation therapy should not return to a contaminated environment. The health department should conduct an environmental assessment so that the primary source of lead exposure can be identified and further exposure prevented. Follow-up should be arranged with an experienced pediatrician, toxicologist, or occupational medicine physician.[57]

ARSENIC

Arsenic, a tasteless, odorless substance that looks like sugar, has an infamous history as an agent of homicide. Arsenic has also been implicated in many epidemic poisonings. Currently, arsenic exposure is primarily environmental and occupational. It is found in smelters and electric power plants that burn arsenic-rich coal. It is used in industry as a wood preservative and in the production of glass and microcircuits. Inorganic arsenicals are also used in rodenticides, fungicides, insecticides, paint, and tanning agents and as defoliants in the cotton industry. Arsenic is still used for medicinal purposes in the treatment of trypanosomiasis,

www.ketabpezeshki.com 66485457-66963820

amebiasis, and leukemia. It has also been found as a contaminant in herbal remedies and drugs such as opium.[58] There are widespread reports of chronic poisoning associated with arsenic-contaminated drinking water in underdeveloped countries.[59] Arsenic poisoning should be suspected if compatible symptoms occur with the use of these products or these possible exposures.

Principles of Disease

Pharmacology

Arsenic has no metabolic or biologic function. The elemental metal (As) is poorly water soluble and is considered nontoxic. Of the two inorganic forms, trivalent arsenite (As^{3+}) is highly lipid soluble and is 5 to 10 times more toxic than the pentavalent arsenate (As^{5+}) form. The more toxic trivalent arsenite form has a lower gastrointestinal absorption but is well absorbed by the skin. The pentavalent arsenate form, although less toxic, is water soluble and readily absorbed from the gastrointestinal tract. Absorbed arsenic is bound by hemoglobin, leukocytes, and plasma proteins. It is cleared from the intravascular compartment within 24 hours and concentrates in the liver, kidneys, spleen, lungs, and gastrointestinal tract. Arsenic crosses the placenta and can also accumulate in the fetus. Its affinity for sulfhydryl groups in keratin makes arsenic detectable in the hair, skin, and nails.[60] Arsine (AsH_3), a colorless and almost odorless gas, is extremely toxic.[61] It is immediately lethal at 250 ppm.

The excretion of arsenic and its metabolites occurs mainly through the kidneys.

Pathophysiology

Arsenic binds avidly to sulfhydryl groups, inhibiting critical enzymes such as lactate dehydrogenase and glyceraldehyde-3-phosphate dehydrogenase, a critical step in glycolysis. It also disrupts oxidative phosphorylation by replacing phosphorus in the formation of high-energy phosphate bonds (arsenolysis).[59] Arsine causes massive hemolysis, but the exact mechanism for this is poorly understood.[62,63]

Clinical Features

Acute exposure to arsine gas is characterized by severe hemolysis that is also associated with renal tubular injury. Gastrointestinal symptoms are common, and CNS and liver dysfunction can occur; the mortality rate is 25 to 30%.[64] Exchange transfusions and plasma exchange have been used to remove arsine, which is tightly bound to the erythrocytes.[64] Urinary alkalinization can be used to decrease renal deposition of hemoglobin and subsequent renal failure.

Acute gastrointestinal effects (nausea, vomiting, abdominal pain, and diarrhea) predominate as the initial manifestations of acute exposure to arsenic salts.[65,66] These symptoms can be so severe as to be manifested with hematemesis and hematochezia. Within 30 to 60 minutes of exposure, patients complain of a metallic or garlicky taste. The patient can also have encephalopathy with seizures and coma, respiratory failure associated with acute respiratory distress syndrome, and dysrhythmias associated with cardiac conduction disturbances.[67-69] In cases of severe poisoning, cardiovascular collapse and death ensue.[70] Less common complications include hepatitis, rhabdomyolysis, hemolytic anemia, renal failure, unilateral facial nerve palsy, pancreatitis, pericarditis, pleuritis, and fetal demise (Box 157-1).[66] The early arsenic poisoning syndrome may be misdiagnosed as gastroenteritis or sepsis.

Weeks to months after the initial symptoms, chronic effects of arsenic poisoning appear, including characteristic lines in the nails (Mees lines), painful sensorimotor neuropathy, and hyperkeratosis of the palms and soles. Arsenic poisoning should also be considered in any patient with a history of severe or recurrent gastroenteritis or abdominal pain and unexplained dermatologic lesions associated with peripheral neuropathy. Finally, arsenic is a known human carcinogen.

Box 157-1 Acute Effects of Arsenic Poisoning

Gastrointestinal
Violent gastroenteritis; hematemesis or hematochezia
Jaundice
Pancreatitis
Dysphagia
Hepatomegaly

Cardiovascular
Third spacing with shock
Sinus or ventricular tachycardia
Prolonged QT interval, ST depression, T wave inversion
Torsades de pointes
Pericarditis

Respiratory
Respiratory failure
Acute respiratory distress syndrome
Pulmonary edema
Pneumonia

Renal
Proteinuria
Hematuria
Oliguria
Renal failure

Neurologic
Headache
Drowsiness
Delirium
Coma
Encephalopathy
Seizures

Diagnostic Strategies

Normal arsenic levels are 5 µg/L or less in blood or less than 50 µg/day in a 24-hour urine collection, which is the best way to diagnose the poisoning. Any urine level above 100 µg/day or 50 µg/L necessitates treatment. A spot urine sample may be falsely low because urinary excretion of arsenic is intermittent. Seafood contains arsenobetaine, which can increase urinary arsenic excretion to as high as 1700 µg/L.[71] Arsenobetaine, however, does not result in arsenic toxicity. For this reason, patients should refrain from eating seafood, specifically shellfish, before testing, or the laboratory should be asked to speciate the type of arsenic measured.[72]

Other laboratory results may suggest arsenic poisoning in the right clinical setting. Anemia, leukocytosis or leukopenia, and erythrocyte basophilic stippling are seen in the complete blood cell count. The results of renal function tests may be abnormal, demonstrating proteinuria, hematuria, and pyuria. The alanine transaminase, aspartate transaminase, and bilirubin levels may be elevated. In cases of chronic arsenic poisoning, the serum and urine arsenic levels may be undetectable, whereas hair and nail specimens can confirm the diagnosis.

Arsenic in the gastrointestinal tract is radiopaque and can appear on a radiograph, although sensitivity is limited by its rapid absorption and the ensuing gastroenteritis.

www.ketabpezeshki.com 66485457-66963820

Management

The initial management should address life-threatening conditions with supportive management of shock, dysrhythmias, and seizures. Activated charcoal does not adsorb arsenic and is of no value. Although there is no evidence for improved outcomes, orogastric lavage or whole-bowel irrigation should be considered for recent (<1 hour) ingestions or if radiopaque material is visualized on an abdominal radiograph. This recommendation is based on two case reports demonstrating clearance of radiopaque material on the abdominal radiographs of patients who had ingested arsenic. There are no studies demonstrating clinical efficacy of this intervention. Hemodialysis removes arsenic in the setting of acute renal failure.[69] Exchange transfusions or plasma exchange can be considered early after an arsine exposure.[64]

With a known history of exposure in a symptomatic patient, chelation should start as early as possible without waiting for laboratory confirmation of the arsenic levels, which may take some time. Intramuscular dimercaprol is the preferred chelator in patients who are critically ill as described for lead poisoning. DMSA is a water-soluble analogue of dimercaprol that can be given orally.[72,73] The use of DMSA is often limited by the violent gastroenteritis resulting from arsenic poisoning. D-Penicillamine has a high side effect profile, and its ability to chelate arsenic is inferior to that of dimercaprol and DMSA. Therefore, it should be used only when *both* dimercaprol and DMSA are unavailable. All patients receiving chelation for acute arsenic toxicity should be admitted. Chelation is not useful for arsine exposures. Workers should modify their habits to avoid further absorption, and repeated monthly 24-hour urine collections can follow arsenic excretion.

Table 157-4 summarizes available chelating agents with indications and doses.

MERCURY

Mercury is a silver-white metal, familiar to most as the only metal that is liquid at room temperature. It has a long history of medicinal uses as an antiparasitic, a diuretic, a cathartic, an antiseptic, and a preservative in many vaccines. Significant poisoning in the home has occurred when relatively small amounts of spilled mercury, such as that contained in a sphygmomanometer, were aerosolized by vacuuming (which should be avoided) or when mercury was heated on the kitchen stove to extract gold from ore.[74,75] Various other sources of mercury have also been implicated in intoxication. Because of many industrial uses that include the manufacture of fluorescent lights, batteries, polyvinyl chloride, and latex paint, mercury is a common pollutant of air and water. This has led to restrictions in the consumption of fish caught in many local waters, especially by pregnant women and children.[76,77]

Principles of Disease

Pharmacology

The most familiar form of mercury is elemental or metallic mercury, also known as quicksilver. A common route of exposure to elemental mercury is the inhalation of volatilized vapor.[78] Aspiration of elemental mercury and intentional subcutaneous and intravenous injections also cause poisoning.[79] After inhalation, 74% of the metallic mercury is retained in the lungs. This can result in severe pneumonitis and acute respiratory distress syndrome.[80] Aspiration of elemental mercury results in primary pulmonary toxicity in addition to CNS and renal toxicities.[81] Elemental mercury is not absorbed by the gastrointestinal tract, so ingestion does not normally lead to systemic toxicity unless it becomes trapped in diverticula. Mercury is absorbed through the skin at 1% of the rate of inhaled mercury and is not a concern.

Inorganic mercury salts have two different valences, Hg^{1+} (*mercurous*) and Hg^{2+} (*mercuric*). Ingestion of either salt leads to significant gastrointestinal and renal toxicity.

The organic mercury compounds are categorized as either short chain (*alkyl*) or long chain (*aryl*). The major route of exposure to this type of mercury is through ingestion, but these compounds are also readily absorbed through the skin. These organic forms classically result in delayed neurotoxicity with prominent ataxia, tremor, dysarthria, and tunnel vision.[76,82]

Pathophysiology

Mercury has no known physiologic role. Mercury binds covalently to sulfhydryl groups, disturbing multiple cellular enzyme functions. Nephrotoxicity results from both direct damage and an immune reaction in the kidney.[74] Inorganic salts have a direct corrosive effect on the gastrointestinal tract with third spacing and hemorrhage. Skin changes associated with mercury poisoning are also caused by an immune reaction. Mercury increases catecholamine levels by inhibition of catechol-*O*-methyltransferase, resulting in hypertension and tachycardia.[83,84] Atrophy of the cerebellum, postcentral gyri, and calcarine areas of the brain correlates with the symptoms of ataxia and sensory and visual field disturbances.[85]

Clinical Features

The clinical manifestations of mercury poisoning depend on the acuity of the exposure, the route of exposure, and the chemical form of mercury. Inhalation of elemental mercury vapor results in the rapid onset of shortness of breath, fever, and chills that progress to pneumonitis and respiratory distress.[75,80,86] Aspiration of liquid metallic mercury during medical procedures results in the rapid onset of tracheobronchial hemorrhage.

Acute ingestion of inorganic salts typically causes a corrosive gastroenteritis with third spacing and hemorrhage. Patients may have a metallic taste in the mouth and a grayish discoloration of the mucous membranes. Massive fluid loss results in shock and acute tubular necrosis. The manifestations of subacute or chronic inorganic mercury poisoning are neurologic (e.g., neurasthenia and erethism), renal (ranging from proteinuria to the nephrotic syndrome), and gastrointestinal (e.g., metallic taste, gingivostomatitis, loose teeth sensation, burning sensation in mouth, hypersalivation, and nausea).[74,87]

Exposure to organic mercury compounds is not associated with acute toxicity. Neurologic symptoms develop during weeks to months. The neurologic and teratogenic effects of chronic exposure to methylmercury were well illustrated by the tragic poisoning of the population of Minamata, Japan, by eating of fish caught in mercury-polluted water. Slowly progressive fatal CNS injury was described after a minor topical exposure to dimethylmercury in a laboratory researcher (Table 157-5).[76,82,88]

Diagnostic Strategies

Measurement of 24-hour urine mercury levels is the most helpful test in confirming exposure and monitoring the effectiveness of chelation. For organic mercury compounds, which undergo little urinary excretion, serum levels should be used to confirm the diagnosis. "Normal" mercury levels are considered to be less than 10 µg/L in the blood or less than 20 µg/L in the urine. Blood levels above 35 µg/L and urine levels above 150 µg/L require intervention. No information is available on chelation at levels between 20 and 150 µg/L. Fish can be contaminated with mercury, especially larger fish and those from certain bodies of water known by state

www.ketabpezeshki.com 66485457-66963820

Table 157-5 Mercury Intoxication Syndromes

TYPE OF MERCURY AND ROUTE OF EXPOSURE	SIGNS AND SYMPTOMS
Inhalation of metallic mercury	Hypoxemia, dyspnea, chest tightness Fever, chills Burning in mouth and throat Nausea, vomiting, bloody diarrhea Renal tubular necrosis
Aspiration of metallic mercury	Aspiration pneumonitis, ARDS
Subacute or chronic inhalation of metallic mercury	Metal fume fever Neuropsychiatric symptoms Renal dysfunction Skin changes
Ingestion of inorganic mercury salts	Severe hemorrhagic gastroenteritis, shock, hypovolemia, third spacing Acute tubular necrosis in 24 hr, with albuminuria and hematuria
Subacute or chronic inhalation of inorganic mercury	Neurasthenia, erethism, acrodynia
Organomercury exposure (methyl-, diethyl-)	Delayed neurologic problems (ataxia, tremor, dysarthria), visual field constriction, hearing loss, spasticity, hyper-reflexia

ARDS, acute respiratory distress syndrome.

health departments to be most polluted. Individuals eating these locally caught fish will have elevated mercury levels. Metallic mercury is radiopaque on plain radiographs, which can be ordered in cases of injection or ingestion of metallic mercury.[79]

Management

Initial management in the acutely poisoned patient is supportive. Gastric lavage with protein-containing solutions (e.g., milk and egg whites) has been suggested; however, no data exist to support this practice, and it is not recommended. Similarly, whole-bowel irrigation or any other gastric decontamination is without evidence of benefit. Charcoal adsorbs very little mercury and is not recommended unless another serious coingestant is suspected. Ingested metallic mercury is generally harmless unless its passage is impaired by entrapment in a diverticulum or the appendix.[89]

For acute inhalational exposures, the patient should be removed from the source and supportive management provided. There is no role for prophylactic antibiotics or steroids. Suction and postural drainage are indicated in cases of acute aspiration of metallic mercury. Self-injection of metallic mercury often requires surgical débridement of infiltrated tissue.[79]

Help in the management of mercury spills can be obtained from the local hazardous materials team and the local health department.[78] Information on handling of mercury spills or compact fluorescent light bulb breakage can also be found at the Environmental Protection Agency websites at www.epa.gov/hg/spills/index.htm and www.epa.gov/cfl/cflcleanup.html, respectively. Sand or mercury decontamination kits that contain calcium polysulfide, which converts mercury to mercuric sulfide, should be used for elemental mercury spills. Absorbable surfaces such as carpets should be removed. Attempts to remove mercury by vacuuming should be avoided as this can volatilize the mercury and precipitate acute inhalational toxicity. Small spills, such as the contents of a home thermometer or a fluorescent bulb (amount = 30 mL or two tablespoons), can be scooped up with a stiff card or aspirated into a dropper placed onto a damp paper towel, sealed in a plastic bag, and disposed of as hazardous waste. Mercury placed in household trash is incinerated, is spread as an airborne contaminant, contributes to soil and water pollution, and ultimately accumulates in the food chain.

Chelation Therapy

Chelating agents have thiol groups that compete with the enzyme sulfhydryl groups that bind mercury. BAL is used for clinically significant acute inorganic mercury intoxication. Because it increases brain mercury levels in patients with methylmercury poisoning, BAL is contraindicated for patients poisoned with organic mercury compounds.[90] Although DMSA is not currently approved by the U.S. Food and Drug Administration for this indication, it is used for both acute and chronic mercury poisoning and may be the best chelator for methylmercury. D-Penicillamine is also used but should be administered only after thorough gastrointestinal decontamination because mercury absorption from the intestinal lumen is enhanced by the penicillamines. DMPS may also be considered if other options are unavailable or contraindicated. Table 157-4 summarizes available chelating agents with indications and doses.

Disposition

In general, in cases of acute intoxication, the most toxic forms are the inorganic mercurials. Suicidal patients with such ingestions require decontamination and admission for supportive treatment. Patients who self-inject metallic mercury often need admission for surgical débridement. Patients with signs of neurotoxicity from an organomercurial also need admission. Most asymptomatic individuals and fish eaters should abstain from eating locally caught fish and can be observed closely with monthly urine testing as outpatients.

KEY CONCEPTS

- Acute ingestion of the salts of most metals causes severe gastrointestinal pain and emesis.
- Chelation with acute iron ingestion is guided by symptoms and at least two serum iron levels measured between 3 and 8 hours after ingestion.
- Patients with symptomatic acute lead exposures require immediate chelation. Asymptomatic or minimally symptomatic children with elevated BLLs require close follow-up and possible outpatient (oral) chelation. Parenteral chelation is indicated in children with BLLs above 69 μg/dL.
- Patients with a possible chronic heavy metal exposure and compatible symptoms should have further investigation to eliminate exposure and close follow-up testing.
- There is no evidence, beyond case reports, supporting gastric lavage and whole-bowel irrigation in any heavy metal toxicity case. Whole-bowel irrigation should be considered primarily if unabsorbed metal is present, as evidenced by abdominal radiographs.
- Activated charcoal has no role in decontamination of heavy metals.
- The recommendations for chelation are variable, and these patients should be treated under the guidance of a clinical toxicologist whenever possible.

ACKNOWLEDGMENT

The authors want to acknowledge the contributions of Dr. Kathleen Delaney to the previous versions of this chapter.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. van Eijk HG, de Jong G: The physiology of iron, transferrin, and ferritin. *Biol Trace Elem Res* 1992; 35:13-24.
2. Fine JS: Iron poisoning. *Curr Probl Pediatr* 2000; 30:71-90.
3. Robotham JL, Lietman PS: Acute iron poisoning. A review. *Am J Dis Child* 1980; 134:875-879.
4. Madiwale T, Liebelt E: Iron: Not a benign therapeutic drug. *Current Opin Pediatr* 2006; 18:174-179.
5. Manoguerra AS, et al: Iron ingestion: An evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila)* 2005; 43:553-570.
6. Aisen P, Cohen G, Kang JO: Iron toxicosis. *Int Rev Exp Pathol* 1990; 31:1-46.
7. Evensen SA, Forde R, Opedal I, Stormorken H: Acute iron intoxication with abruptly reduced levels of vitamin K–dependent coagulation factors. *Scand J Haematol* 1982; 29:25-30.
8. Robertson A, Tenenbein M: Hepatotoxicity in acute iron poisoning. *Hum Exp Toxicol* 2005; 24:559-562.
9. Siff JE, Meldon SW, Tomassoni AJ: Usefulness of the total iron binding capacity in the evaluation and treatment of acute iron overdose. *Ann Emerg Med* 1999; 33:73-76.
10. Lacouture PG, Wason S, Temple AR, Wallace DK, Lovejoy FH Jr: Emergency assessment of severity in iron overdose by clinical and laboratory methods. *J Pediatr* 1981; 99:89-91.
11. Chyka PA, Butler AY: Assessment of acute iron poisoning by laboratory and clinical observations. *American J Emerg Med* 1993; 11:99-103.
12. Ng RC, Perry K, Martin DJ: Iron poisoning: Assessment of radiography in diagnosis and management. *Clin Pediatr* 1979; 18:614-616.
13. Tennebein M, Wiseman N, Yatscoff RW: Gastrotomy and whole bowel irrigation in iron poisoning. *Pediatr Emerg Care* 1991; 7:286-288.
14. Position paper: Whole bowel irrigation. *J Toxicol Clin Toxicol* 2004; 42:843-854.
15. Tenenbein M: Whole bowel irrigation in iron poisoning. *J Pediatr* 1987; 111:142-145.
16. Velez LI, Gracia R, Mills LD, Shepherd G, Feng SY: Iron bezoar retained in colon despite 3 days of whole bowel irrigation. *J Toxicol Clin Toxicol* 2004; 42:653-656.
17. Kaczorowski JM, Wax PM: Five days of whole-bowel irrigation in a case of pediatric iron ingestion. *Ann Emerg Med* 1996; 27:258-263.
18. De Palma G, et al: Toxicokinetics and toxicodynamics of elemental mercury following self-administration. *Clin Toxicol (Phila)* 2008; 46:869-876.
19. Movassaghi N, Purugganan GG, Leikin S: Comparison of exchange transfusion and deferoxamine in the treatment of acute iron poisoning. *J Pediatr* 1969; 75:604-608.
20. Tenenbein M, Kowalski S, Sienko A, Bowden DH, Adamson IY: Pulmonary toxic effects of continuous desferrioxamine administration in acute iron poisoning. *Lancet* 1992; 339:699-701.
21. Khoury S, Odeh M, Oettinger M: Deferoxamine treatment for acute iron intoxication in pregnancy. *Acta Obstet Gynecol Scand* 1995; 74:756-757.
22. Tran T, Wax JR, Philput C, Steinfeld JD, Ingardia CJ: Intentional iron overdose in pregnancy—management and outcome. *J Emerg Med* 2000; 18:225-228.
23. Wythe E, Osterloh J, Becker C: The reliability of serum iron levels after deferoxamine treatment: An in vitro study. *Vet Hum Toxicol* 1986; 28:478.
24. Proudfoot AT: Antidotes: Benefits and risks. *Toxicol Lett* 1995; 82-83:779-783.
25. Gallant T, Freedman MH, Vellend H, Francombe WH: *Yersinia* sepsis in patients with iron overload treated with deferoxamine. *N Engl J Med* 1986; 314:1643.
26. Mazzoleni G, deSa D, Gately J, Riddell RH: *Yersinia enterocolitica* infection with ileal perforation associated with iron overload and deferoxamine therapy. *Dig Dis Sci* 1991; 36:1154-1160.
27. Warniment C, Tsang K, Galazka SS: Lead poisoning in children. *American Fam Physician* 2010; 81:751-757.
28. Akhtar AJ, Funnyé AS, Akanno J: Gunshot-induced plumbism in an adult male. *J Natl Med Assoc* 2003; 95:986-990.
29. Markowitz G, Rosner D: "Cater to the children": The role of the lead industry in a public health tragedy, 1900-1955. *Am J Public Health* 2000; 90:36-46.
30. Morgan BW, Barnes L, Parramore CS, Kaufmann RB: Elevated blood lead levels associated with the consumption of moonshine among emergency department patients in Atlanta, Georgia. *Ann Emerg Med* 2003; 42:351-358.
31. Tait PA, Vora A, James S, Fitzgerald DJ, Pester BA: Severe congenital lead poisoning in a preterm infant due to a herbal remedy. *Med J Aust* 2002; 177:193-195.
32. Lin CG, Schaider LA, Brabander DJ, Woolf AD: Pediatric lead exposure from imported Indian spices and cultural powders. *Pediatrics* 2010; 125:e828-e835.
33. Renner R: Sick picnic—evaluating the legacy of lead ammunitions. *Environ Sci Technol* 2010; 44:853-854.
34. Garza A, Vega R, Soto E: Cellular mechanisms of lead neurotoxicity. *Med Sci Monit* 2006; 12:RA57-RA65.
35. Lidsky TI, Schneider JS: Lead neurotoxicity in children: Basic mechanisms and clinical correlates. *Brain* 2003; 126(Pt 1):5-19.
36. Canfield RL, et al: Intellectual impairment in children with blood lead concentrations below 10 μg per deciliter. *N Engl J Med* 2003; 348:1517-1526.
37. Nevin R: Understanding international crime trends: The legacy of preschool lead exposure. *Environ Res* 2007; 104:315-336.
38. Chiodo LM, et al: Blood lead levels and specific attention effects in young children. *Neurotoxicol Teratol* 2007; 29:538-546.
39. Park SK, et al: Cumulative lead exposure and age-related hearing loss: The VA Normative Aging Study. *Hear Res* 2010; 269:48-55.
40. Ekong EB, Jaar BG, Weaver VM: Lead-related nephrotoxicity: A review of the epidemiologic evidence. *Kidney Int* 2006; 70:2074-2084.
41. Cheng Y, Schwartz J, Sparrow D, et al: Bone lead and blood lead levels in relation to baseline blood pressure and the prospective development of hypertension: The Normative Aging Study. *Am J Epidemiol* 2001; 153:164-171.
42. Nevin R: How lead exposure relates to temporal changes in IQ, violent crime, and unwed pregnancy. *Environ Res* 2000; 83:1-22.
43. al Khayat A, Menon NS, Alidina MR: Acute lead encephalopathy in early infancy—clinical presentation and outcome. *Ann Trop Paediatr* 1997; 17:39-44.
44. Graziano JH: Validity of lead exposure markers in diagnosis and surveillance. *Clin Chem* 1994; 40(Pt 2):1387-1390.
45. Gordon JN, Taylor A, Bennett PN: Lead poisoning: Case studies. *Br J Clin Pharmacol* 2002; 53:451-458.
46. Centers for Disease Control and Prevention: Interpreting and managing blood lead levels <10 μg/dL in children and reducing childhood exposures to lead. Recommendations of CDC's Advisory Committee on Childhood Lead Poisoning Prevention. *MMWR Recomm Rep* 2007; 56:1-14.
47. McNutt TK, Chambers-Emerson J, Dethlefsen M, Shah R: Bite the bullet: Lead poisoning after ingestion of 206 lead bullets. *Vet Hum Toxicol* 2001; 43:288-289.
48. Roberge RJ, Martin TG: Whole bowel irrigation in an acute oral lead intoxication. *Am J Emerg Med* 1992; 10:577-583.
49. Vilensky JA, Redman K: British anti-Lewisite (dimercaprol): An amazing history. *Ann Emerg Med* 2003; 41:378-383.
50. Chisolm JJ Jr: Safety and efficacy of meso-2,3-dimercaptosuccinic acid (DMSA) in children with elevated blood lead concentrations. *J Toxicol Clin Toxicol* 2000; 38:365-375.
51. Centers for Disease Control and Prevention: Deaths associated with hypocalcemia from chelation therapy—Texas, Pennsylvania, and Oregon, 2003-2005. *MMWR Morb Mortal Wkly Rep* 2006; 55:204-207.
52. Torres-Alanis O, Garza-Ocanas L, Pineyro-Lopez A: Effect of meso-2,3-dimercaptosuccinic acid on urinary lead excretion in exposed men. *Hum Exp Toxicol* 2002; 21:573-577.
53. Safety and efficacy of succimer in toddlers with blood lead levels of 20-44 μg/dL. Treatment of Lead-Exposed Children (TLC) Trial Group. *Pediatr Res* 2000; 48:593-599.
54. Chisolm JJ Jr: BAL, EDTA, DMSA and DMPS in the treatment of lead poisoning in children. *J Toxicol Clin Toxicol* 1992; 30:493-504.
55. Aposhian HV, et al: Human studies with the chelating agents, DMPS and DMSA. *J Toxicol Clin Toxicol* 1992; 30:505-528.
56. Durback LF, Wedin GP, Seidler DE: Management of lead foreign body ingestion. *J Toxicol Clin Toxicol* 1989; 27:173-182.
57. American Academy of Pediatrics Committee on Environmental Health: Lead poisoning: From screening to primary prevention. *Pediatrics* 1993; 92:176-183.
58. Saper RB, et al: Heavy metal content of ayurvedic herbal medicine products. *JAMA* 2004; 292:2868-2873.
59. Lubin JH, Beane Freeman LE, Cantor KP: Inorganic arsenic in drinking water: An evolving public health concern. *J Natl Cancer Inst* 2007; 99:906-907.
60. Daniel CR 3rd, Piraccini BM, Tosti A: The nail and hair in forensic science. *J Am Acad Dermatol* 2004; 50:258-261.
61. Song Y, et al: Severe acute arsine poisoning treated by plasma exchange. *Clin Toxicol (Phila)* 2007; 45:721-727.

www.ketabpezeshki.com 66485457-66963820

62. Pakulska D, Czerczak S: Hazardous effects of arsine: A short review. *Int J Occup Med Environ Health* 2006; 19:36-44.
63. Rael LT, Ayala-Fierro F, Bar-Or R, Carter DE, Barber DS: Interaction of arsine with hemoglobin in arsine-induced hemolysis. *Toxicol Sci* 2006; 90:142-148.
64. Bonastre Blanco E, Domingo Garau A, Cols Roig M, Panzino Occhiuzzo F, Vilar Escrigas P: Accidental iron poisoning [in Spanish]. *An Pediatr (Barc)* 2010; 73:373-375.
65. Cullen NM, Wolf LR, St Clair D: Pediatric arsenic ingestion. *Am J Emerg Med* 1995; 13:432-435.
66. Roses OE, et al: Mass poisoning by sodium arsenite. *J Toxicol Clin Toxicol* 1991; 29:209-213.
67. Beckman KJ, Bauman JL, Pimental PA, Garrard C, Hariman RJ: Arsenic-induced torsade de pointes. *Crit Care Med* 1991; 19:290-292.
68. Bolliger CT, van Zijl P, Louw JA: Multiple organ failure with the adult respiratory distress syndrome in homicidal arsenic poisoning. *Respiration* 1992; 59:57-61.
69. Mathieu D, et al: Massive arsenic poisoning—effect of hemodialysis and dimercaprol on arsenic kinetics. *Intensive Care Med* 1992; 18:47-50.
70. Hantson P, Haufroid V, Buchet JP, Mahieu P: Acute arsenic poisoning treated by intravenous dimercaptosuccinic acid (DMSA) and combined extrarenal epuration techniques. *J Toxicol Clin Toxicol* 2003; 41:1-6.
71. Arbouine MW, Wilson HK: The effect of seafood consumption on the assessment of occupational exposure to arsenic by urinary arsenic speciation measurements. *J Trace Elem Electrolytes Health Dis* 1992; 6:153-160.
72. Kales SN, Huyck KL, Goldman RH: Elevated urine arsenic: Un-speciated results lead to unnecessary concern and further evaluations. *J Anal Toxicol* 2006; 30:80-85.
73. Shum S, Whitehead J, Vaughn L, Shum S, Hale T: Chelation of organoarsenate with dimercaptosuccinic acid. *Vet Hum Toxicol* 1995; 37:239-242.
74. Kazantzis G: Mercury exposure and early effects: An overview. *Med Lav* 2002; 93:139-147.
75. Rennie AC, McGregor-Schuerman M, Dale IM, Robinson C, McWilliam R: Mercury poisoning after spillage at home from a sphygmomanometer on loan from hospital. *BMJ* 1999; 319:366-367.
76. Kulig K: A tragic reminder about organic mercury. *N Engl J Med* 1998; 338:1692-1694.
77. Kondro W: Mercury disposal sole health concern with fluorescent lights. *CMAJ* 2007; 177:136-137.
78. Cherry D, Lowry L, Velez L, Cotrell C, Keyes DC: Elemental mercury poisoning in a family of seven. *Fam Community Health* 2002; 24:1-8.
79. Soo YO, Wong CH, Griffith JF, Chan TY: Subcutaneous injection of metallic mercury. *Hum Exp Toxicol* 2003; 22:345-348.
80. Solis MT, Yuen E, Cortez PS, Goebel PJ: Family poisoned by mercury vapor inhalation. *Am J Emerg Med* 2000; 18:599-602.
81. Lech T, Goszcz H: Poisoning from aspiration of elemental mercury. *Clin Toxicol (Phila)* 2006; 44:333-336.
82. Nierenberg DW, et al: Delayed cerebellar disease and death after accidental exposure to dimethylmercury. *N Engl J Med* 1998; 338:1672-1676.
83. Wossmann W, Kohl M, Grüning G, Bucsky P: Mercury intoxication presenting with hypertension and tachycardia. *Arch Dis Child* 1999; 80:556-557.
84. Torres AD, Rai AN, Hardiek ML: Mercury intoxication and arterial hypertension: Report of two patients and review of the literature. *Pediatrics* 2000; 105:E34.
85. Siegler RW, Nierenberg DW, Hickey WF: Fatal poisoning from liquid dimethylmercury: A neuropathologic study. *Human Pathol* 1999; 30:720-723.
86. Taueg C, Sanfilippo DJ, Rowens B, Szejda J, Hesse JL: Acute and chronic poisoning from residential exposures to elemental mercury—Michigan, 1989-1990. *J Toxicol Clin Toxicol* 1992; 30:63-67.
87. Rosenman KD, Valciukas JA, Glickman L, Meyers BR, Cinotti A: Sensitive indicators of inorganic mercury toxicity. *Arch Environ Health* 1986; 41:208-215.
88. Clarkson TW, Magos L, Myers GJ: The toxicology of mercury—current exposures and clinical manifestations. *N Engl J Med* 2003; 349:1731-1737.
89. McKinney PE: Elemental mercury in the appendix: An unusual complication of a Mexican-American folk remedy. *J Toxicol* 1999; 37:103-107.
90. Baum CR: Treatment of mercury intoxication. *Curr Opin Pediatr* 1999; 11:265-268.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 158

HYDROCARBONS

David C. Lee

PERSPECTIVE

Human exposure to hydrocarbons (HCs) is a common problem. In 2010, U.S. poison centers reported 43,000 exposures to HCs, with the majority of cases managed in an outpatient setting.[1] Exposure to HCs of patients who present to the emergency department (ED) can generally be classified into four types. The first is the accidental ingestion involving children younger than 5 years. This is the most common scenario causing fatality, and it usually involves significant pulmonary injury. Second is the intentional inhalational abuse of volatile HCs. Recreational abuse has been a medical problem since solvent inhalation became popular during the late 1800s. Fatalities in this group will typically occur within distinct demographic groups (Native Americans, homosexual men, and teenagers).[1-3] Third is the accidental inhalational or dermal exposure to HCs in the household or workplace setting. The fourth type is massive oral ingestion of HCs in a suicide attempt.

PRINCIPLES OF DISEASE

Definitions and Terminology

HCs are a diverse group of organic compounds that contain hydrogen and carbon (Table 158-1). Most HCs (e.g., gasoline) are byproducts of crude oil and are therefore called petroleum distillates. Some products, such as turpentine, are derived from pine oil, not petroleum. HCs can also be classified by their structure. The two main categories are straight chain HCs (aliphatic, such as propane) and those containing a benzene ring structure (aromatic, such as toluene). HCs can also have multiple nonorganic side chains. For example, halogenated HCs usually will have one or more bromide, chloride, fluoride, or iodide moieties (e.g., carbon tetrachloride). Finally, HCs are used as the solvent base for many toxic chemicals, such as insecticides and metals, that in turn can cause a separate distinct syndrome of poisoning. Although the range of toxicity of HCs can vary widely, the majority of human exposures are confined to petroleum distillates.

Pathophysiology

Acute HC toxicity usually affects three main target organs: the lungs, the heart, and the central nervous system (CNS). Although certain HCs can enter the body through the skin or gastrointestinal tract, HCs cause the most damage through the lungs. Despite the fact that there are thousands of different types of HCs, their potential for acute toxicity depends on four characteristics[4,5]:

1. Viscosity is the capacity to resist flow or change. Low viscosity allows a substance to spread rapidly, and low-viscosity HCs spread easily into the airway and lungs. Viscosity is measured in Saybolt seconds universal (SSU), and substances with an SSU of less than 60 have the highest potential risk of aspiration. Lubricants and mineral oil have high viscosity and low toxicity, whereas furniture polish has low viscosity and high pulmonary toxicity.
2. Volatility is the ease for a liquid to turn into a gas. High volatility often has a detectable odor. HCs with high volatility can displace alveolar oxygen and cause hypoxia. Butane and propane are types of HCs with high volatility.
3. Surface tension is the capacity for a substance to collect on a liquid surface. Low surface tension enables a substance (e.g., turpentine) to disperse easily.
4. Chemical side chains often increase potential toxicity. These toxic side chains include metals (e.g., arsenic), halogens (e.g., carbon tetrachloride), and aromatic structures (e.g., toluene).

Pulmonary Pathophysiology

The primary target organ for toxicity is the lung. Fatalities after ingestion usually occur with an accompanying aspiration. A small amount of HC in the trachea can be devastating, whereas a much larger amount of the same compound in the stomach remains benign.[1,5,6]

HCs affect the lungs through several mechanisms. HCs are usually poorly water soluble and penetrate into the lower airways, producing bronchospasm and an inflammatory response. Second, volatized HCs can displace oxygen in the alveolar space, causing hypoxia. Third, HCs can cause direct injury to pulmonary alveoli and capillaries, producing distinct uniform lesions. Autopsy findings of these lesions include hyperemia, diffuse hemorrhagic exudative alveolitis with granulocytic infiltration, and microabscesses. Finally, HCs can inhibit surfactant function, leading to alveolar instability and collapse. These mechanisms lead to alveolar dysfunction, ventilation-perfusion mismatch, hypoxemia, and respiratory failure.[5,6]

Central Nervous System Pathophysiology

Certain HCs cause CNS depression (i.e., toluene, benzene, gasoline, butane, and chlorinated HCs). After respiratory exposure, most HCs passively diffuse through the pulmonary alveolus and are highly absorbed in blood and tissues. These HCs can cause euphoria, disinhibition, confusion, and obtundation. With an isolated single exposure, these effects usually have a rapid onset of intoxication and rapid recovery. For these reasons, substance abusers seek these HCs for recreational use. Inhalation of these substances avoids hepatic first-pass metabolism and generates high concentrations in the CNS. Chronic use of inhaled HCs can

www.ketabpezeshki.com 66485457-66963820

Table 158-1 Spectrum of Hydrocarbon Toxicity

TYPE	EXAMPLE	USE	PATHOPHYSIOLOGY	COMMENTS
Aliphatic petroleum distillates	Methane Propane Butane Gasoline Kerosene Mineral spirits Mineral oil Naphtha Mineral seal oil Diesel oil *n*-Hexane	Fuels Liquid fuels Solvents Furniture polish Degreasers Multiple uses in chemical industry	Asphyxiants causing hypoxia and CNS depression Abused inhalants Pneumonitis when aspirated CNS depression from fumes *n*-Hexane causes peripheral neuropathy	Sudden death from intentional inhalation Viscosity and volatility determine spectrum of toxicity Mineral seal oil has high aspiration potential Poor gastrointestinal absorption
Aromatic petroleum distillates	Toluene Xylene Benzene	Used in plastics, pharmaceutical, rubber, chemical, and solvent industries Degreasers	Highly volatile, lung aspiration Absorbed from gastrointestinal tract Abused inhalants	Inhaled toluene causes renal tubular acidosis Benzene causes aplastic anemia, leukemia
Wood distillates	Turpentine Pine oil	Solvent Household disinfectants	Well absorbed from gastrointestinal tract	Gastrointestinal and CNS toxicity
Halogenated hydrocarbons	Methylene chloride Chloroform Carbon tetrachloride Trichloroethylene Freon Methylbromide Lindane DDT	Solvents Cleaning fluids Degreasers Fire extinguishers Paint strippers Fumigants	Multisystem toxicity (CNS, renal, hepatic, cardiac) Inhalant abuse Highly lipid soluble	Methylene chloride metabolized to carbon monoxide Carbon tetrachloride is radiopaque Insecticides absorbed through skin
Related chemicals	Phenol Creosols	Disinfectants	Very corrosive	Phenol causes severe skin burns

CNS, central nervous system; *DDT,* dichlorodiphenyltrichloroethane.

cause severe abnormalities in nervous system function, which include peripheral neuropathy, cerebellar degeneration, neuropsychiatric disorders, chronic encephalopathy, and dementia. More than 50% of patients who abuse toluene for more than 10 years will have cerebral cortical atrophy with histologic changes that include loss of neurons, diffuse gliosis, and axonal degeneration.[3,7]

Cardiac Pathophysiology

HCs can precipitate sudden death, especially after intentional inhalation. These compounds are thought to produce myocardial sensitization of endogenous and exogenous catecholamines, which then precipitates ventricular dysrhythmias and myocardial dysfunction. This is particularly true for halogenated and aromatic HCs (e.g., difluoroethane found in computer keyboard cleaning canisters).[2,8]

Other Pathophysiology

Various HCs have been reported to be toxic to other organ systems. Certain recognized syndromes include toluene-induced renal tubular acidosis, benzene-induced bone marrow toxicity and leukemia, methylene chloride–induced carbon monoxide poisoning, and chlorinated HC–induced centrilobular hepatic necrosis and renal failure. Direct skin exposure of certain HCs can cause extensive chemical burns.[5] HCs are often used as solvents for other chemicals that may have their own significant inherent toxicity.

CLINICAL FEATURES

After oral ingestion, severe poisoning is related to aspiration, which is manifested with early respiratory symptoms, including cyanosis, coughing, grunting (small children), noisy respirations, or repeated bouts of vomiting. A patient may initially have mild symptoms and then develop tachypnea, dyspnea, bronchospasm, wheezing, rales, and fever during several hours.[9-12] A change in mental status can be a manifestation of hypoxia or hypercapnia, but it is also a direct effect of HCs. In extreme cases, patients may have frank respiratory failure. Various additives or solutes can produce symptoms independently (e.g., seizures from camphorated HCs or cyanosis from nitrite-induced methemoglobinemia). Pesticides are often dissolved in an HC base. With pesticide exposures, it can be difficult to distinguish acute respiratory distress syndrome induced by HC aspiration from pulmonary edema induced by organophosphate exposures (see Chapter 163). Ingestion or injection of HC as a mechanism for deliberate self-harm is exceedingly rare.

The second scenario for HC toxicity is with solvent abuse. Solvent abuse is associated with various paraphernalia, such as plastic bags used for "bagging" (a method of pouring HCs in a bag or container and then inhaling deeply) and HC-soaked cloth used for "huffing" (a method in which abusers inhale through a saturated cloth). Patients often have the distinctive odor associated with organic HCs. A characteristic rash may be present over the mouth and nose ("glue-sniffer's rash") (Fig. 158-1). These patients can also present to the ED with CNS intoxication with euphoria, agitation, hallucinations, confusion, or bizarre behavior. This may progress to CNS depression and seizures. In the extreme case, these patients will be in cardiac arrest. This typically involves an individual who has inhaled solvents, performed some type of physical activity, such as running, and then suddenly collapsed. This is thought to be due to cardiac sensitization by endogenous catecholamine and the ensuing development of dysrhythmias.[2-6] Drug abusers who chronically inhale HCs may be brought to medical attention not specifically for treatment of their drug abuse

www.ketabpezeshki.com 66485457-66963820

Figure 158-1. Presentation of paint sniffer ("huffer") with paint around the face and sedation. (Courtesy Chris Tomaszewski, MD.)

but rather for behavioral problems or nonspecific medical symptoms caused by their abuse. The long-term chronic abuser may clinically appear similar to the long-term "skid row" alcoholic, with peripheral neuropathy, cerebellar degeneration, and encephalopathy.[7,13,14]

A third common scenario is the accidental dermal or inhaled (nonaspiration) respiratory exposure to HCs in the workplace or home. Such exposures are rarely life-threatening. Most cases do not present for medical care or are handled primarily through lay discussion with consultants at local poison control centers.[1] The few patients who present to the ED typically will be asymptomatic or have transient nonspecific symptoms, such as headache, dizziness, or nausea. Those with significant respiratory exposure may have persistent pulmonary complaints and physical findings such as coughing, wheezing, and cyanosis. Patients with significant acute dermal exposures may have pain and evidence of chemical burns consisting of erythema, swelling, blistering, and dermal destruction.

The patient who intentionally ingests or intravenously injects HCs in a suicide attempt is rare. However, these patients often ingest other substances. In the absence of aspiration or coingestion of another toxic substance, the massive oral ingestion of most commonly available HCs is not associated with significant morbidity or mortality. These patients risk aspiration if they vomit.

DIAGNOSTIC STRATEGIES

The diagnosis is usually self-evident, supported by history and the patient's characteristic odor. Ideally, a prehospital provider, police officer, school official, or family member brings the offending agent to the ED. The local poison control center may help identify and verify substances containing HCs. When verification of an unknown substance is required, a reference laboratory is usually needed. Laboratory identification of HCs is usually time-consuming and does not help ED management.

History and examination should focus on possible aspiration. These symptoms include cough, difficulty breathing, and shortness of breath. Signs of a significant exposure include tachypnea, tachycardia, wheezing, and hypoxemia. Patients with a significant HC exposure should have a chest radiograph taken. Radiographic changes can occur within 30 minutes of ingestion and may identify pathologic processes not recognized by auscultation in more than 50% of cases.[5] Hypoxemia noted on pulse oximetry or arterial blood gas measurement provides supportive evidence for aspiration.

Patients who chronically abuse HCs may present to the ED for behavioral problems or nonspecific symptoms caused by their drug addiction. Similar to patients with alcoholism, these patients require evaluation for underlying medical disease. For example, serum electrolyte analysis will identify distal renal tubular acidosis associated with chronic toluene abuse.

DIFFERENTIAL CONSIDERATIONS

Organophosphate, salicylate, and paraquat poisonings can mimic the signs and symptoms of HC aspiration. In the scenario of the recreational abuser, multiple drugs of abuse are often present. Behavioral disorders and confusion can be caused by hypoxia and respiratory compromise as well as by the drugs themselves. In the chronic abuser, it can be difficult to differentiate between a functional and an organic confusional state.

MANAGEMENT

Dermal exposures to HCs can cause extensive burns, and exposed patients require early decontamination. Contaminated clothing should be removed, and the skin should be washed with soap and copious lukewarm water. Gastrointestinal decontamination should be avoided. The aphorism "the safest place in the body for hydrocarbons is the duodenum" holds true for most HCs regardless of the volume ingested. HCs are much more toxic to lungs than to the gastrointestinal tract, where they have a low potential for systemic absorption. In rare situations, gastrointestinal decontamination may be considered, in consultation with a regional poison center, but there is no sound evidence supporting gastric emptying, even in such cases. CHAMP is a long-standing mnemonic used to help identify the most serious ingestions for which toxicity of the HCs or additives is potentially life-threatening:

C camphor, which can cause seizures and status epilepticus
H halogenated HCs, which can cause dysrhythmias and hepatotoxicity
A aromatic HCs, which can cause bone marrow suppression and cancer
M metals (e.g., arsenic, mercury, and lead)
P pesticides, which can cause cholinergic crises, seizures, and respiratory depression

If gastric emptying is desired, the use of a small-caliber nasogastric tube to evacuate stomach contents is recommended.

Because HC toxicity can cause rapid decompensation of a patient's pulmonary, cardiac, and CNS functions, all patients should be in a well-observed area with cardiac monitoring and pulse oximetry. In severe cases, early intubation for airway control and positive end-expiratory pressure has been advocated to minimize aspiration risks and to counteract HC-induced alveoli collapse. However, no studies have proved this to be more beneficial than standard respiratory care. High-frequency jet ventilation, surfactant therapy, and extracorporeal membrane oxygenation have been attempted as treatments of children with respiratory failure secondary to aspiration,[1,5,15] but no studies have been done to demonstrate benefit. Corticosteroids and antibiotics have not been shown to be beneficial in HC aspiration, but the differentiation between bacterial and chemical pneumonia may be difficult. More than 50% of children with significant HC poisoning will have a fever and leukocytosis.[5] Theoretically, exogenous catecholamine might cause dysrhythmias in HC-sensitized myocardium, so most toxicologists recommend avoidance of cardiac-active catecholamines, such as epinephrine.

In most cases of HC ingestion or inhalation, supportive care and close observation and monitoring are the cornerstone of management. Currently, there are no specific antidotes for HCs.

www.ketabpezeshki.com 66485457-66963820

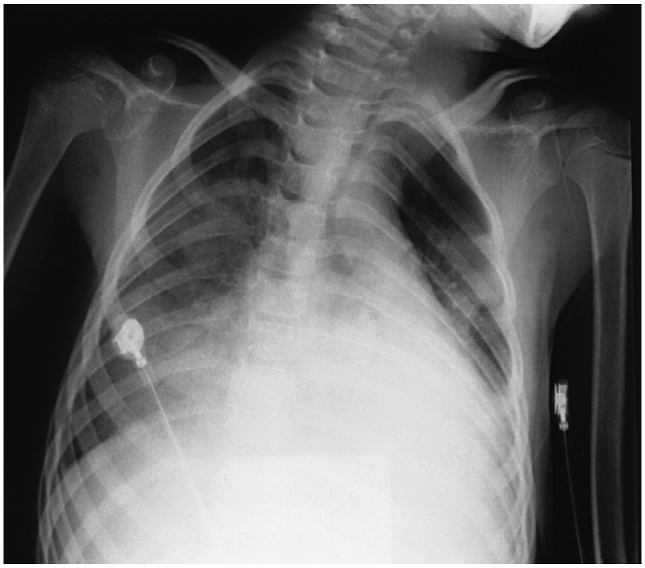


Figure 158-2. Chest radiograph of a patient with hydrocarbon ingestion 6 hours after exposure.

DISPOSITION

Patients with exposures to known, relatively benign HCs should have a 4- to 6-hour period of observation. If no signs of pulmonary or systemic toxicity develop during the observation period, the patient is discharged to home, with advice for follow-up evaluation if symptoms develop on a delayed basis. If pulmonary symptoms develop, a chest radiograph will show developing pneumonitis (Fig. 158-2), requiring hospital admission for prolonged observation.

Patients who present after an episode of recreational inhalation of HCs should be observed until clinical symptoms are improving or resolved, usually 1 to 3 hours.

KEY CONCEPTS

- Aspiration is the major toxic risk of HC poisoning.
- Gastrointestinal decontamination is potentially harmful in cases of HC ingestion and should be avoided.
- Symptoms of toxicity, especially aspiration, can be delayed, so asymptomatic patients should be observed for 4 to 6 hours and given clear instructions to return if symptoms develop after discharge.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Bronstein AC, et al: 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 27th Annual Report. *Clin Toxicol (Phila)* 2010; 48:979-1178.
2. Kurtzman TL, Otsuka KN, Wahl RA: Inhalant abuse by adolescents. *J Adolesc Health* 2001; 28:170-180.
3. Schaumburg HH: *Toluene*. In: Spencer PS, Schaumburg HH, eds: *Experimental and Clinical Neurotoxicology*, 2nd ed. New York: Oxford University Press; 2000.
4. Cobaugh DJ, Seger DL, Krenzelok EP: Hydrocarbon toxicity: An analysis of AAPCC TESS data. *Przegl Lek* 2007; 64:194.
5. Gummin DD, Hryhorczuk DO: *Hydrocarbons*. In: Goldfrank L, ed: *Goldfrank's Toxicologic Emergencies*, 8th ed. New York: McGraw-Hill; 2006.
6. Holubek WJ: *Solvents*. In: Biller J, ed: *The Interface of Neurology and Internal Medicine*. Philadelphia: Lippincott Williams & Wilkins; 2008.
7. Win-Shwe T, Fujimaki H: Neurotoxicology of toluene. *Toxicol Lett* 2010; 198:93-99.
8. Avella J, Wilson JC, Lehrer M: Fatal cardiac arrhythmia after repeated exposure to 1,1-difluoroethane (DFE). *Am J Forensic Med Pathol* 2006; 27:58.
9. Bond GR, et al: A clinical decision rule for triage of children under 5 years of age with hydrocarbon (kerosene) aspiration in developing countries. *Clin Toxicol (Phila)* 2008; 46:222.
10. Jayashree M, Singhi S, Gupta A: Predictors of outcome in children with hydrocarbon poisoning receiving intensive care. *Indian Pediatr* 2006; 43:715.
11. Lifshitz M, Sofer S, Gorodischer R: Hydrocarbon poisoning in children: A 5-year retrospective study. *Wilderness Environ Med* 2003; 14:78.
12. Shotar AM: Kerosene poisoning in childhood: A 6-year prospective study at the Princess Rahmat Teaching Hospital. *Neuroendocrinol Lett* 2005; 26:835.
13. Borne J, Riascos R, Cuellar H, Vargas D, Rojas R: Neuroimaging in drug and substance abuse part II: Opioids and solvents. *Top Magn Reson Imaging* 2005; 16:239.
14. Costa LG, Guizzetti M, Burry M, Oberdoerster J: Developmental neurotoxicity: Do similar phenotypes indicate a common mode of action? A comparison of fetal alcohol syndrome, toluene embryopathy and maternal phenylketonuria. *Toxicol Lett* 2002; 127:197.
15. Horoz OO, Yildizdas D, Yimaz HL: Surfactant therapy in acute respiratory distress syndrome due to hydrocarbon aspiration. *Singapore Med J* 2009; 50:e130-e132.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 159

INHALED TOXINS

Lewis S. Nelson and Robert S. Hoffman

Many airborne toxins produce local noxious effects on the airways and lungs as irritants. The respiratory tract can also serve as a portal of entry for systemic poisons as simple or systemic asphyxiants. Inhalational exposure can be covert and indolent (as in occupational exposure to asbestos or urban exposure to photochemical smog) or fulminant and obvious. The circumstances and location of the exposure, the presence of combustion or odors, and the number and condition of victims assist in the diagnosis. Despite the array of possible toxic inhalants, identification of a specific inhalant is generally unnecessary because therapy is based primarily on the clinical manifestations (Table 159-1).

SIMPLE ASPHYXIANTS

Perspective

Most simple asphyxiations are workplace related and usually occur during the use of liquefied gas while the employee is breathing through an airline respirator or working in a confined space.[1] Since the advent of catalytic converters, most deaths from the intentional inhalation of automotive exhaust result from simple asphyxiation, due to hypoxia, and not from carbon monoxide (CO) poisoning.[2]

Principles of Disease

Most simple asphyxiants are inert and produce toxicity only by displacement of oxygen and lowering of the fraction of inspired oxygen (FIO_2). Exposed patients remain asymptomatic if the FIO_2 is normal. Carbon dioxide and nitrogen, both constituents of air, produce narcosis at elevated partial pressures, but their predominant toxicologic effect is simple asphyxiation.

Clinical Features

Acute effects occur within minutes of onset of hypoxia and are the manifestations of ischemia. A fall in the FIO_2 from normal, 0.21 (i.e., 21%), to 0.15 results in autonomic stimulation (e.g., tachycardia, tachypnea, and dyspnea) and cerebral hypoxia (e.g., ataxia, dizziness, incoordination, and confusion). Dyspnea is not an early finding because hypoxemia is not as potent a stimulus for this sensation, or for breathing, as are hypercarbia and acidosis. Lethargy from cerebral edema is expected as the FIO_2 falls below 0.1 (10%), and life is difficult to sustain at an FIO_2 below 0.06 (6%).[3] Because removal from exposure terminates the simple asphyxiation and allows restoration of oxygenation and clinical improvement, most patients present with resolving symptoms. However, failure to improve suggests complications of ischemia (e.g., seizures, coma, and cardiac arrest) and is associated with a poor prognosis.

Diagnostic Strategies and Differential Considerations

A consistent history, an appropriate spectrum of complaints, and a rapid resolution on removal from exposure are generally sufficient to establish the diagnosis. Minimally symptomatic or asymptomatic patients do not require chest radiography or arterial blood gas (ABG) analysis. Definitive diagnosis ultimately requires scene investigation by a trained and suitably outfitted team. Determination of the exact nature of the gas is of limited clinical value but may have important public health implications. Because the presenting complaints offered by most exposed patients are nonspecific and protean (e.g., dizziness, syncope, and dyspnea), the differential diagnosis is extensive.

Management and Disposition

Management rarely requires specific therapy other than removal from exposure, supportive care, and possibly administration of supplemental oxygen. Neurologic injury or cardiorespiratory arrest should be managed with standard resuscitation protocols. Patients with manifestations of mild poisoning who recover after removal from the exposure can be observed briefly and discharged. Patients at risk for complications of hypoxia, such as those presenting with significant symptoms (e.g., coma) or with exacerbating medical conditions (e.g., cardiac disease), should be observed for the development or progression of posthypoxic complications.

PULMONARY IRRITANTS

Perspective

The pulmonary irritant gases are a large group of agents that produce a common toxicologic syndrome when they are inhaled in moderate concentrations. Although many of these agents can be found in the home, significant poisoning from consumer products is uncommon because of restrictions designed to reduce their toxicity. However, catastrophes such as the 1984 release of methyl isocyanate in Bhopal, India, which resulted in more than 2000 fatalities and 250,000 injuries, remain as an environmental risk. On a different scale, industrialization has increased ambient levels of sulfur dioxide, ozone, and oxides of nitrogen. These irritant gases frequently exacerbate chronic pulmonary disease.

www.ketabpezeshki.com 66485457-66963820

Table 159-1 Common Inhaled Toxins

INHALANT	SOURCE OR USE	PREDOMINANT CLASS
Acrolein	Combustion	Irritant, highly soluble
Ammonia	Fertilizer, combustion	Irritant, highly soluble
Carbon dioxide	Fermentation, complete combustion, fire extinguisher	Simple asphyxiant; systemic effects
Carbon monoxide	Incomplete combustion, methylene chloride	Chemical asphyxiant
Chloramine	Mixed cleaning products (e.g., hypochlorite bleach and ammonia)	Irritant, highly soluble
Chlorine	Swimming pool disinfectant, cleaning products	Irritant, intermediate solubility
Chlorobenzylidene malononitrile (CS), chloroacetophenone (CN)	Tear gas (Mace)	Pharmacologic irritant
Hydrogen chloride	Tanning and electroplating industry	Irritant, highly soluble
Hydrogen cyanide	Combustion of plastics, acidification of cyanide salts	Chemical asphyxiant
Hydrogen fluoride	Hydrofluoric acid	Irritant, highly soluble; systemic effects
Hydrogen sulfide	Decaying organic matter, oil industry, mines, asphalt	Chemical asphyxiant; irritant, highly soluble
Methane	Natural gas, swamp gas	Simple asphyxiant
Methylbromide	Fumigant	Chemical asphyxiant
Nitrogen	Mines, scuba diving (nitrogen narcosis, decompression sickness)	Simple asphyxiant; systemic effects
Nitrous oxide	Inhalant of abuse, whipping cream, racing fuel booster	Simple asphyxiant
Noble gases (e.g., helium)	Industry, laboratories	Simple asphyxiant
Oxides of nitrogen	Silos, anesthetics, combustion	Irritant, intermediate solubility
Oxygen	Medical use, hyperbaric conditions	Irritant, free radical; systemic effects
Ozone	Electrostatic energy	Irritant, free radical
Phosgene	Combustion of chlorinated hydrocarbons	Irritant, poorly soluble
Phosphine	Hydration of aluminum or zinc phosphide (fumigants)	Chemical asphyxiant
Smoke (varying composition)	Combustion	Variable, but may include all classes
Sulfur dioxide	Photochemical smog (fossil fuels)	Irritant, highly soluble

Principles of Disease

Irritant gases dissolve in the respiratory tract mucus and alter the air-lung interface by invoking an irritant or inflammatory response. When these gases are dissolved, most of them produce an acid or alkaline product, but several generate oxygen-derived free radicals that produce direct cellular toxicity (Fig. 159-1). The clinical effects of pulmonary irritants can be predicted by their water solubility (see Table 159-1).

Clinical Features

Highly water-soluble gases have their greatest impact on the mucous membranes of the eyes and upper airway. Exposure results in immediate irritation, with lacrimation, nasal burning, and cough. Although their pungent odors and rapid symptom onset tend to limit significant exposure, massive or prolonged exposure can result in life-threatening laryngeal edema, laryngospasm, bronchospasm, or acute respiratory distress syndrome (ARDS) (formerly known as noncardiogenic pulmonary edema).[4] Poorly water-soluble gases do not readily irritate the mucous membranes at low concentrations, and some have pleasant odors (e.g., phosgene's odor is similar to that of hay). Because there are no immediate symptoms, prolonged breathing in the toxic environment allows time for the gas to reach the alveoli. Even moderate exposure causes irritation of the lower airway, alveoli, and parenchyma and causes pulmonary endothelial injury after a 2- to 24-hour delay. Initial symptoms consistent with acute respiratory distress syndrome may be mild, only to progress to overt respiratory failure and acute respiratory distress syndrome during the ensuing 24 to 36 hours.[5]

Gases with intermediate water solubility tend to produce syndromes that are a composite of the clinical features manifested with the other gases, depending on the extent of exposure. Massive exposure is most often associated with rapid onset of upper airway irritation and more moderate exposure with delayed onset of lower airway symptoms.[6]

Diagnostic Strategies and Differential Considerations

The evaluation of upper airway symptoms is usually done through physical examination but may require laryngoscopy. After exposure, swelling may occur rapidly or may be delayed, so normal findings on oropharyngeal or laryngeal evaluation may not exclude subsequent deterioration. Radiographic and laboratory studies have little role in the evaluation of upper airway symptoms.

Oxygenation and ventilation are assessed by serial chest auscultation, pulse oximetry, and capnometry supplemented as needed by chest radiography and ABGs in patients with cough, dyspnea, hypoxia, or abnormal findings on physical examination. No clinical test can identify the specific irritant, and identification is not generally necessary for patient care, although knowing the causative agent may allow refinement of the observation period.

www.ketabpezeshki.com 66485457-66963820

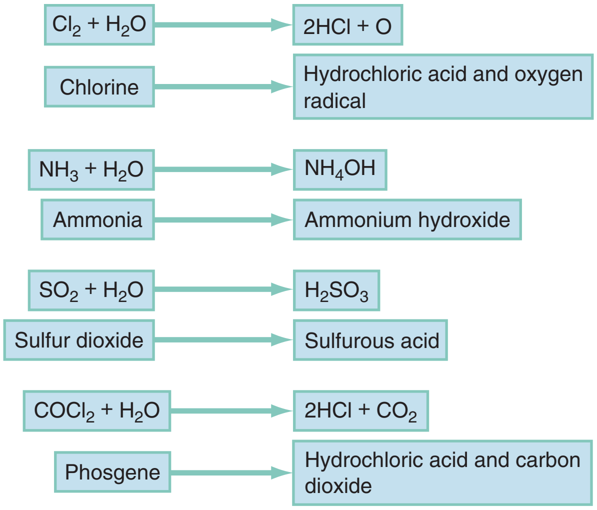


Figure 159-1. Sample reactions of pulmonary irritants reacting with water in the lung.

Bronchospasm, cough, chest tightness, and acute conjunctival irritation frequently follow allergen exposure, but the history generally suggests the diagnosis. ARDS occurs after many physiologic insults, including trauma and sepsis, highlighting the need for accurate history taking.[5]

Management

Signs of upper airway dysfunction (e.g., hoarseness and stridor) mandate direct visualization of the larynx and immediate airway stabilization, if necessary. Given the potential rapidity of airway deterioration, early and frequent reassessment should be performed.

Bronchospasm generally responds to inhaled beta-adrenergic agonists; the role of ipratropium is not yet defined. Other than as a standard treatment of a comorbid condition, such as asthma, there is no clear indication for corticosteroids.[7]

Patients exposed to chlorine or hydrogen chloride gas receive symptomatic relief from nebulized 2% sodium bicarbonate solution.[6] Because the inflammatory cascade is not altered, however, the component of lung injury mediated by free radicals probably continues and causes delayed deterioration. Patients receiving inhalational bicarbonate therapy require extensive discharge instructions for signs and symptoms of pulmonary irritation or admission to the hospital.

Diagnosis of acute respiratory distress syndrome indicates the need for aggressive supportive care, including manipulations of the patient's airway pressures (e.g., continuous positive airway pressure and positive end-expiratory pressure). Exogenous surfactant and nitric oxide may have a beneficial role in toxin-induced acute respiratory distress syndrome, despite little support for use in other forms of the syndrome.

Disposition

Patients exposed to highly water-soluble gases can be discharged if they are asymptomatic or improve with symptomatic therapy. After exposure to intermediate or poorly water-soluble gases, asymptomatic patients should be observed for increasing dyspnea for several hours before final disposition. Patients with substantial exposure to these agents or those in high-risk situations (e.g., underlying pulmonary disease, extremes of age, and poor follow-up) should be observed for 24 hours and may require hospitalization. All patients should be instructed to return if symptoms recur.

SMOKE INHALATION

Perspective

Annually, approximately 4000 people are injured or die in residential fires in the United States. Many of these casualties do not suffer serious cutaneous burns but rather die of smoke inhalation. This is a variant of irritant injury in which heated particulate matter and adsorbed toxins injure normal mucosa, similar to other irritant gases. In addition, CO and cyanide are systemic toxins often discussed with the smoke inhalation syndrome because of their common origin.

Principles of Disease

Even at temperatures between 350 and 500° C, air has such a low heat capacity that it rarely produces lower airway damage. However, the greater heat capacity of steam (approximately 4000 times that of air) or heated soot suspended in air (i.e., smoke) can transfer heat and cause injury deep within the respiratory tract.

The nature of the fuel determines the composition of its smoke, and because fires involve variable fuels and burning conditions, the character of fire smoke is almost always undefined to the clinician. Irritant toxins produced by the fire are adsorbed onto carbonaceous particles that are deposited in the airways. The irritant substances damage the mucosa through mechanisms similar to those of the irritant gases, including generation of acids and free radical formation.

Clinical Features

Most smoke-associated morbidity and mortality relate to respiratory tract damage. Thermal and irritant-induced laryngeal injury may produce cough or stridor, but these findings are often delayed. Soot and irritant toxins in the airways can produce early cough, dyspnea, and bronchospasm. Subsequently, a cascade of airway inflammation results in acute lung injury with failure of pulmonary gas exchange. The time between smoke exposure and the onset of clinical symptoms is highly variable and dependent on the degree and nature of the exposure. Singed nasal hairs and soot in the sputum suggest substantial exposure but are neither sufficiently sensitive nor specific to be practical.[8]

CO inhalation should be routinely considered in these patients. Patients who are exposed to filtered or distant smoke (e.g., in a different room) or to relatively smokeless combustion (e.g., engine exhaust) inhale predominantly CO, cyanide, and metabolic poisons and do not sustain smoke exposure.

Diagnostic Strategies and Differential Considerations

With the obvious exposure history, the differential diagnosis is limited. Although it is often unclear whether inhalational injuries are thermal or irritant, the differentiation is clinically irrelevant. CO and cyanide should be considered in every case.

Early death is caused by asphyxia, airway compromise, or metabolic poisoning (e.g., CO). Airway patency should be evaluated early. If evidence of significant airway exposure is present, such as carbonaceous sputum or hoarse voice, the airway should be examined by direct or fiberoptic laryngoscopy. Simply observing the patient for deterioration can result in airway compromise requiring rapid and, by then, very difficult airway intervention. Signs of alveolar filling or hyperinflation on chest radiography, abnormal flow-volume loop or diffusing capacity for

www.ketabpezeshki.com 66485457-66963820

CO on pulmonary function testing, or abnormal distribution and clearance of radiolabeled gas on ventilation scans can help predict lower airway injury.[9]

Metabolic acidosis, particularly when it is associated with a serum lactate level greater than 10 mmol/L, suggests concomitant cyanide poisoning.[10] Oxygenation should be assessed by co-oximetry because blood gas analysis and pulse oximetry may be inaccurate in CO-poisoned patients (see later).

Management

The acute management of smoke inhalation is identical to that of other irritant inhalational injuries. Rapid assessment of the airway and early intubation, as indicated, are critical because deterioration may be occult and rapid. Inhaled beta-adrenergic agonists are widely used but without evidence supporting their benefit. Optimal supportive care and maintenance of adequate oxygenation (e.g., suctioning and pulmonary toilet) are the most important aspects of care. Bronchoscopy with bronchoalveolar lavage is frequently recommended to clear debris and toxins from the distal airways. Corticosteroids, whether they are inhaled or administered systemically, are not demonstrated to be helpful and are potentially harmful in patients with cutaneous burns.[11] Ibuprofen, antioxidants, exogenous surfactant, and high-frequency ventilation yield variably improved survival in experimental and clinical trials; none is considered standard care. Antibiotics should be used only in patients with suspected infection.

Disposition

After the airway is examined and stabilized, patients with worrisome clinical findings (e.g., hoarseness and respiratory distress) and those at high risk of substantial exposure (e.g., closed-space exposure and carbonaceous sputum) should be admitted to a critical care unit or transferred to a burn center. This decision will vary on the basis of local resources, such as hospital capabilities and availability of a burn referral center.

CYANIDE AND HYDROGEN SULFIDE

Perspective

Inhalation can be the route of exposure for systemic poisons. Instead of directly affecting the airway and lungs, these poisons cause effects at the cellular level. Hydrogen cyanide is a gas with many commercial uses, particularly in synthetic fiber manufacture and fumigation. Hydrogen cyanide is occasionally noted to have the odor of bitter almonds. Cyanide in its salt form (e.g., sodium or potassium) is important in the metallurgic (e.g., jewelry) and photographic industries and is much safer to work with because of its low volatility. Cyanide salts do not have an odor under dry conditions. When cyanide salts are dissolved in water, hydrogen cyanide can leave the surface, particularly under acidic conditions. Cyanide is metabolically released in vivo from precursors (cyanogens) such as amygdalin, found in apricot and other *Prunus* species pits, and from nitriles, a group of chemicals with many commercial uses.

Hydrogen sulfide poisoning most often occurs in petroleum refinery and sewage storage tank workers. An Internet-derived means of suicide involves generation of hydrogen sulfide from sulfur-containing products, such as detergent, mixed with acids in an enclosed space, such as an automobile. On occasion, well-intentioned but hasty would-be rescuers become victims, emphasizing the need for proper training and equipment. Hydrogen sulfide has a noxious odor similar to rotten eggs, which becomes unnoticeable with extremely high concentrations or prolonged exposure (*olfactory fatigue*).[12]

Principles of Disease

Gaseous cyanide is rapidly absorbed after inhalation and is immediately distributed to the oxygen-using body tissues. Inhibition of oxidative metabolism by binding to complex IV of the electron transport chain within mitochondria occurs within seconds. The poisoned tissue rapidly depletes its adenosine triphosphate reserves and ceases to function (Fig. 159-2). Cyanide has no evident effect on other oxygen-binding enzyme systems, most notably hemoglobin. This is probably explained by the oxidation state of its iron moiety; cyanide binds only to oxidized iron (Fe^{3+}), whereas deoxyhemoglobin contains reduced iron (Fe^{2+}).

Hydrogen sulfide exerts its toxic effects both as a pulmonary irritant and as a cellular poison.[12] Its deadly metabolic effects are produced by a mechanism identical to that for cyanide poisoning. However, hydrogen sulfide's spontaneous dissociation from the mitochondrial cytochrome complex IV is rapid, allowing many patients to survive after brief exposure.

Clinical Features

Tissue hypoxia occurs within minutes, with the exact onset dependent on the route, dose or concentration, and nature of the exposure. Dysfunction of the heart and the central nervous system—the organ systems most sensitive to hypoxia—is characteristic of cyanide poisoning, manifested as coma, seizures, dysrhythmias, and cardiovascular collapse. Metabolic acidosis develops as a result of diffuse cellular dysfunction and is associated with an elevated serum lactate concentration. Cyanosis is not characteristic but can be present in profoundly poisoned patients. Given the extreme toxicity of cyanide, mild acute poisoning is uncommon. Patients with acute hydrogen sulfide poisoning have similar clinical manifestations, although many are recovering by the time of arrival in the emergency department.

Because cyanide and hydrogen sulfide prevent tissue extraction of oxygen from the blood, the oxygen content of venous blood remains high, approaching that of arterial blood. Clinically, this may appear as the "arterialization" or brightening of venous blood to resemble arterial blood. A comparison of the measured venous (ideally but impractically mixed venous) and arterial oxygen contents may assist in the diagnosis of cyanide poisoning.[13] A low arterial-venous oxygen difference is suggestive of cyanide poisoning but is neither exclusionary nor pathognomonic for the diagnosis.

Patients surviving cyanide or hydrogen sulfide poisoning may have persistent or delayed-onset neurologic syndromes identical to those noted in patients with CO poisoning or cardiac arrest.[14]

Diagnostic Strategies and Differential Considerations

The result of a blood cyanide determination is usually too delayed to be of use in the emergency department, but it can be useful for confirmation and documentation purposes. Technology exists for immediate cyanide determination but is not widely available. Rapid tests for hydrogen sulfide are not available.

In practice, the diagnosis is based on the circumstances of exposure and a corroborative physical examination. Rapid cardiovascular collapse, hypotension, bradycardia, ventricular dysrhythmias, and seizures in a fire victim should suggest cyanide poisoning but are also consistent with severe CO poisoning.[10] An elevated carboxyhemoglobin concentration in a fire victim may also suggest concomitant cyanide poisoning. However, the presence of these dramatic clinical findings with a low carboxyhemoglobin level is

www.ketabpezeshki.com 66485457-66963820

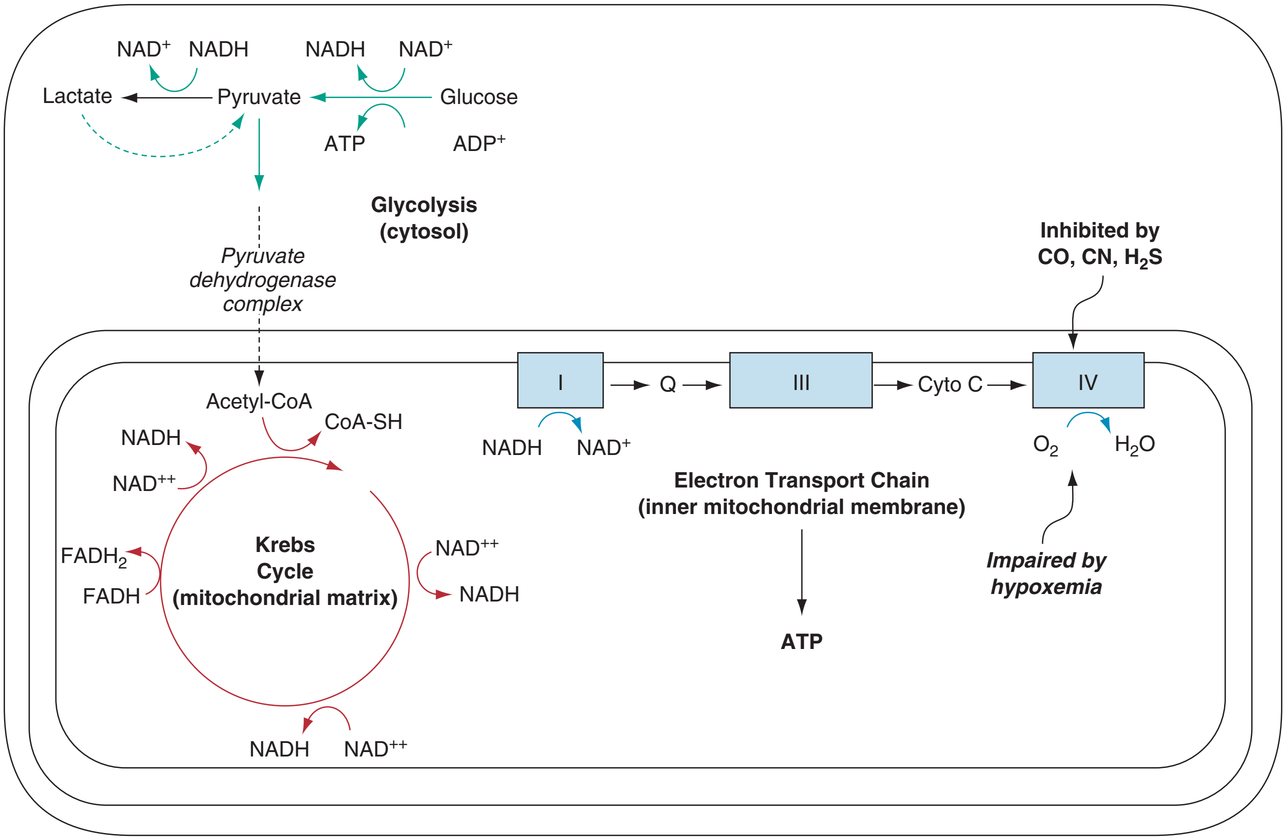


Figure 159-2. The complete metabolism of a molecule of glucose to energy is complex but occurs in two broad steps. The first step, anaerobic glycolysis, which occurs in the absence of oxygen, generates pyruvate, NADH, and adenosine triphosphate (ATP). Pyruvate then enters the Krebs cycle to create potential energy in the second step, through the reduction of NAD^+ to NADH and FADH to $FADH_2$. Similarly, fatty acid metabolism and protein metabolism produce $FADH_2$ and NADH, which also requires conversion to ATP. These conversions occur in the mitochondrial membrane, where oxidative phosphorylation is linked to the electron transport chain, the last phase of which involves the transfer of electrons to molecular oxygen to form water. Cyanide (CN), hydrogen sulfide (H_2S), and carbon monoxide (CO) bind to and inhibit the last step, the Fe^{3+}-containing cytochrome-aa_3 in complex IV, preventing further oxidation of NADH. This in turn hinders the Krebs cycle because the required regeneration of NAD^+ does not occur, and glucose metabolism is forced to end at pyruvate. For energy production to continue, NADH donates its electrons to pyruvate, creating lactate, and sufficient NAD^+ is regenerated for glycolysis to progress. Ultimately, energy failure and end-organ damage occur. *CoA,* coenzyme A; *FAD,* flavin adenine dinucleotide; *NAD,* nicotinamide adenine dinucleotide.

also concerning for cyanide poisoning. Pulse oximetry and ABG analysis are accurate in cases of isolated cyanide or hydrogen sulfide poisoning. An increased anion gap metabolic acidosis and elevated serum lactate concentration are usually present. A lactate concentration greater than 10 mmol/L in a fire victim is highly predictive of cyanide poisoning.[10] However, the carboxyhemoglobin level and other laboratory test results may take too long to be obtained, and the delay has important implications for the treatment of cyanide poisoning.

Management

Patients exposed to cellular poisons, including hydrogen cyanide and hydrogen sulfide, require individualized and specific therapy. The diagnosis usually cannot be confirmed rapidly, and therapy is almost always empirical. Treatment should not be delayed in patients with suspected acute cyanide poisoning, and antidotal therapy should be administered immediately.

Hydrogen Cyanide

The accepted goal of therapy is to reactivate the cytochrome oxidase system by providing an alternative binding site for the cyanide ion. There are two types of antidotal therapy for cyanide. The cyanide antidote kit produces a high-affinity source of ferric ions (Fe^{3+}) for cyanide to bind. The kit has three components, and although the best results are likely to be attained when the entire kit is used, this may be impractical or dangerous, particularly for nonhospital providers. Because animal models and clinical evidence in humans demonstrate that sodium thiosulfate alone (the "third" part of the kit), in combination with oxygen and sodium bicarbonate, offers substantial protection, this should be the initial therapy administered by paramedics and during mass poisoning events. Antidotes should not completely replace other resuscitation measures, including high-flow oxygen.

Methemoglobin (MetHb) formation is the goal of the first two parts of the kit. Inhaled amyl nitrite and intravenous sodium nitrite are both effective, but amyl nitrite should be administered to patients only before intravenous access. Caution should be taken to minimize the provider's exposure to the volatile amyl nitrite because dizziness, hypotension, or syncope may occur. The dose of sodium nitrite for a previously healthy adult is 300 mg (10 mL of a 3% solution) given during 2 to 4 minutes, and dosing instructions for anemic patients and children are supplied with the kit. Sodium nitrite is a vasodilator, and hypotension may complicate a rapid infusion. Cyanide has a high affinity for MetHb and readily leaves cytochrome oxidase to form cyanmethemoglobin. Both free serum cyanide and cyanmethemoglobin are converted

www.ketabpezeshki.com 66485457-66963820

by sulfur transferase (*rhodanese*) to thiocyanate, which is renally eliminated. Because the rate of rhodanese function increases with the availability of sulfur donor, the third part of the antidote kit is the sulfur-containing compound sodium thiosulfate. The adult dose is 12.5 g intravenously (IV), which is provided as 50 mL of a 25% solution (2 mL/kg of 25% sodium thiosulfate up to an adult dose in children). In general, few if any adverse effects are associated with proper doses. The nitrite components of the cyanide antidote kit should be avoided in fire victims with possible simultaneous CO and cyanide poisoning because both CO and MetHb reduce oxygen delivery to the tissues. The use of the thiosulfate component alone in this subset of patients is recommended.

Hydroxocobalamin is another antidotal therapy that takes advantage of the high affinity of cobalt for cyanide. On binding of cyanide, cyanocobalamin, or vitamin B_{12}, is formed. The initial dose is 5 g IV during 15 minutes for adults and 70 mg/kg IV for children, up to an adult dose.[15] Thiosulfate, 12.5 g, can be coadministered if it is available. The known adverse effects of hydroxocobalamin are mild and include hypertension in those not cyanide poisoned and a bright red discoloration of the patient's skin. The drug's red color can interfere with certain spectrophotometric laboratory tests, including carboxyhemoglobin and possibly serum lactate, and blood samples should be obtained before the administration of the first dose of hydroxocobalamin.

There are insufficient clinical data to fully support the use of one cyanide antidote over the other.[16] However, hydroxocobalamin has been used for years and is largely replacing the cyanide antidote kit in the United States because of its ease of use and theoretic safety in CO-poisoned fire victims. Direct comparison to thiosulfate alone in this population has not been and likely never will be performed.[17]

Hyperbaric oxygen (HBO) therapy has been advocated but is of no proven benefit and is not routinely indicated for cyanide poisoning. In selected cases, when it is immediately available, its apparent value may lie in its ability to superoxygenate plasma and tissues, thus permitting higher levels of methemoglobinemia, particularly when CO poisoning is also present.

Hydrogen Sulfide

Because the bond between hydrogen sulfide and cytochrome oxidase is rapidly reversible, removal from exposure and standard resuscitative techniques are usually sufficient to reverse hydrogen sulfide toxicity. Use of the nitrite portion of the cyanide antidote kit is suggested to create MetHb for patients with severe or prolonged toxicity.[12] Sodium thiosulfate is unnecessary because hydrogen sulfide is not detoxified by rhodanese. There is no defined role for hyperbaric oxygen therapy in cases of hydrogen sulfide toxicity.

Disposition

All patients with symptomatic cyanide or hydrogen sulfide poisoning should be admitted to a critical care unit and observed for complications of tissue hypoxia. All patients should be observed for delayed neuropsychiatric findings.

CARBON MONOXIDE

Perspective

CO is the most common cause of acute poisoning death in developed nations and the most common cause of fire-related death.[18] CO is generated through incomplete combustion of virtually all carbon-containing products. Structure fires (e.g., wood), clogged vents for home heating units (e.g., methane), and use of gasoline-powered generators indoors are examples of the myriad means through which patients are poisoned by CO. Appropriate public health authorities (e.g., fire department and Department of Health officials) should be informed immediately about any potential public health risks that are identified during the care of a CO-exposed patient.

Principles of Disease

CO interacts with deoxyhemoglobin to form carboxyhemoglobin (COHb), which cannot carry oxygen. Hemoglobin binds CO tightly and forms a complex that is only slowly reversible. This allows the exposed individual to accumulate CO, even with exposure to low ambient concentrations. Although binding of hemoglobin is historically described as the mechanism of CO poisoning, it is relevant only in profoundly CO-poisoned patients because a simple reduction in oxygen-carrying capacity due, for example, to anemia would not cause similar symptoms. However, for pregnant patients, the fetus is at risk because it is relatively hypoxic compared with the mother. In muscle, CO binds myoglobin, preventing its normal function, and this probably explains the development of atraumatic rhabdomyolysis.

Most important, CO affects cellular oxygen use at the tissue level. CO, similar to cyanide, inhibits the final cytochrome complex involved in mitochondrial oxidative phosphorylation. This results in a switch to anaerobic metabolism and ultimately in cellular death.

Delayed-onset neurologic complications may be a manifestation of the hypoxic insult, although reperfusion injury and lipid peroxidation related to platelet-induced nitric oxide release may play a significant role.[19] By alteration of the platelet-associated nitric oxide cycle, the microvascular endothelium of the central nervous system undergoes free radical–mediated injury, resulting in localized inflammation and dysfunction. Animal models and human reports suggest that loss of consciousness during CO exposure may be necessary and is certainly a risk factor for the development of delayed neurologic sequelae.[20]

Clinical Features

Severe CO toxicity and cyanide poisoning have identical clinical presentations of asphyxia: altered mental status, including coma and seizures; extremely abnormal vital signs, including hypotension and cardiac arrest; and metabolic acidosis. Unlike cyanide poisoning, however, mild CO poisoning occurs frequently, with headache, nausea, vomiting, dizziness, myalgia, and confusion as common presenting complaints. The neurologic assessment in these patients may yield normal findings or may demonstrate focal findings or subtle perceptual abnormalities. The often-touted cherry-red skin color in patients with cyanide or CO poisoning is a postmortem finding and is not noted in living patients.

Delayed neurologic sequelae are a well-documented phenomenon after CO exposure, although the frequency varies from 12 to 50%, depending on the definition and the sensitivity of the test used for their detection.[21] Patients have a variety of neurologic abnormalities after an asymptomatic period ranging from 2 to 40 days.[20] The delayed neurologic effects can be divided into those with readily identifiable neurologic syndromes (e.g., focal deficits and seizures) and those with primarily psychiatric or cognitive findings (e.g., apathy and memory deficits). Although the delayed neuropsychiatric sequelae require formal neuropsychiatric testing to be detected, the impact of these abnormalities on the patient's daily function may be significant. Risk factors that predict the development of delayed neurologic sequelae include age and loss of consciousness. Because most CO-poisoned patients reaching the emergency department survive, prevention of delayed neurologic and neuropsychiatric sequelae is the major goal of therapy.

www.ketabpezeshki.com 66485457-66963820

Diagnostic Strategies and Differential Considerations

Suspicion of CO poisoning relies on the history and physical examination findings. Co-oximetry, an inexpensive and readily available spectrophotometric laboratory method that can distinguish between the normal hemoglobins and COHb (and MetHb), confirms exposure to CO. Other laboratory tests only exclude other diagnoses. Severity of poisoning may not correlate with COHb levels because prolonged exposure to low levels can be fatal with a low measured COHb, but a brief, high-concentration exposure can produce a high COHb level with minimal symptoms.

The ABG analysis is a poor screening test for CO poisoning other than to identify the presence of a metabolic acidosis and a normal partial pressure of oxygen (Po_2). CO decreases oxygen bound to hemoglobin but does not affect the amount of oxygen dissolved in blood. Because the Po_2, a measure of dissolved oxygen, is normal in patients with CO poisoning, the calculated oxygen saturation will be normal even in the presence of significant CO poisoning. Most pulse oximeters are unable to detect CO poisoning because COHb essentially is misinterpreted as oxyhemoglobin. Newer pulse co-oximeters are capable of noninvasively detecting COHb as well as methemoglobinemia, but the exact clinical utility of this test is not yet fully defined.[22]

Mild to moderate CO poisoning is a difficult diagnosis to establish clinically, and patients are easily misdiagnosed as having a benign headache syndrome or viral illness. CO poisoning should be suspected in every patient with persistent or recurrent headache, especially if a group of people have similar symptoms or if the headache improves soon after the person leaves an exposure site.

Patients with severe CO poisoning may present with coma or cardiovascular collapse, both of which have a broad toxicologic, metabolic, infectious, medical, and traumatic differential diagnosis. Many diagnoses are excluded by the medical history, physical examination, or standard laboratory testing. Given the relatively protean manifestations of CO poisoning, when it is being seriously considered, it should be excluded by co-oximetry of an arterial or venous blood sample or by newer pulse co-oximetry. Misdiagnosis can be catastrophic, particularly if the patient returns to the poisoned environment.

Management

Treatment begins with oxygen therapy, which serves two purposes. First, the half-life of COHb is inversely related to the Po_2; it can be reduced from approximately 5 hours on room air to 1 hour by providing supplemental 100% oxygen. Hyperbaric oxygen (HBO) therapy further reduces the half-life to approximately 30 minutes. Alteration of the kinetics of COHb is applicable only to patients with extremely elevated COHb levels (e.g., 50%). Even then, only a minority of patients can be treated sufficiently rapidly for the HBO to be lifesaving. Second, a sufficient Po_2 can be achieved with HBO to sustain life in the absence of adequately functioning hemoglobin, but this is helpful only when the COHb is extremely elevated. Thus, the primary indication for HBO is not to prevent mortality but rather to prevent delayed neurologic sequelae.

There is controversy regarding the benefit of HBO because the effect is not immediate (as with life and death) but requires close follow-up and sophisticated testing. Several evidence-based reviews have suggested a limited role for HBO, although this conclusion is disputed.[23-25] A decrease of delayed neurologic sequelae from approximately 12% to less than 1% is associated with HBO.[21] When HBO administration is delayed more than 6 hours after exposure, its efficacy appears to decrease,[26] suggesting the need for rapid decision-making. Evidence also suggests that HBO positively affects the development of the delayed neuropsychiatric and delayed neurologic sequelae after CO poisoning.[27-29] A randomized, double-blind study found that HBO therapy was superior to normobaric oxygen therapy at reducing the incidence of delayed neurologic sequelae at both 6 weeks and 1 year after poisoning.[27] However, another found no benefit of HBO on the development of delayed neurologic sequelae compared with extensive normobaric oxygen.[28] In this study, however, the majority of patients were suicidal and possibly depressed, which would interfere with performance on the neuropsychiatric testing needed to differentiate the two groups of patients. A recent trial found that in comatose patients, one HBO session was superior to two sessions; however, in patients with transient loss of consciousness (i.e., syncope), outcome after HBO therapy was equivalent to 6 hours of normobaric oxygen therapy.[30]

Given the implications of poor tissue oxygenation with COHb and the relative safety of HBO, a patient with a neurologic abnormality or cardiovascular instability (e.g., syncope, altered mental status, myocardial ischemia, and dysrhythmias) is a candidate for HBO. This should be tempered by the need for transport, sometimes long distances, for HBO therapy to be obtained. The decision about HBO therapy should not be strictly based on the COHb level, which correlates only weakly with toxicity. For example, patients with prolonged low-level exposure have a “soaking” phenomenon, in which extremely high tissue concentrations of CO occur with low COHb levels. Thus, patients with consequential clinical findings that are considered to be related to CO poisoning should receive HBO even though their COHb level is relatively low.

In addition to use of HBO in patients with obvious signs of tissue hypoxia, some institutions have set a conservative COHb level of 25% at which asymptomatic or minimally symptomatic patients will be referred for HBO therapy. Some institutions use COHb levels of 40%, and others refrain from specifying a number. The decision to perform HBO therapy should be considered in light of the transport and other medical requirements. Special consideration is given to pregnant women because of the relative hypoxia of the fetus. Because fetal CO poisoning is associated with dysfunction and death and HBO therapy appears to be safe in pregnancy, many institutions initiate HBO therapy in a pregnant woman to a COHb level of 15%.[31]

Further study is still needed to define the optimal duration, pressure, and frequency as well as the cost-benefit and risk-benefit relationships of HBO therapy. At this time, discussion with a regional HBO center or poison control center is advisable. Patients with elevated COHb levels who do not require HBO should be treated with normobaric oxygen delivered by a tight-fitting nonrebreather face mask until the symptoms resolve and the COHb levels fall. The total duration of such therapy is undefined, and although 3 days was suggested in one study,[28] most mildly CO-poisoned patients probably require no more than 6 hours of therapy.[32]

Simultaneous Carbon Monoxide and Cyanide Poisoning (Fire Victim)

Concurrent toxicity from CO and cyanide is widely reported and a major factor in the mortality associated with smoke.[10,33] Smoke inhalation victims who present with coma and metabolic acidosis can have severe CO poisoning, cyanide poisoning, or both. Nitrite-induced methemoglobinemia, which further reduces the tissue oxygen delivery, may be detrimental to patients with elevated COHb levels or otherwise impaired oxygen delivery.

Sodium thiosulfate, administered without nitrites,[34] or hydroxocobalamin should be given to all smoke inhalation victims with coma, hypotension, severe acidosis, or cardiovascular collapse in whom cyanide poisoning cannot be rapidly excluded. If the COHb level is known to be low and the patient has persistent acidosis or

www.ketabpezeshki.com 66485457-66963820

hemodynamic instability, the complete cyanide antidote kit, including the nitrites, can be administered. Patients with high COHb levels undergoing HBO therapy can also receive nitrite therapy while pressurized with little concern of decreasing the oxygen-carrying capacity. Alternatively, hydroxocobalamin, with or without sodium thiosulfate, can be administered in either of these last two situations.

Disposition

The decision to transfer a patient to an HBO facility must consider the time delay to therapy, patient issues (e.g., burns and age), and potential transport-related complications.[35] At a minimum, prolonged normobaric oxygen therapy should be administered, although the benefit of this remains undefined. Admission decisions should be based on the patient's clinical condition. All patients exposed to CO require close follow-up for delayed neurologic sequelae.

KEY CONCEPTS

Simple Asphyxiants

- Any gas can be a simple asphyxiant if it displaces sufficient oxygen from the breathable air.
- Appropriate therapy for simple asphyxiation includes removal from exposure, supplemental oxygen, and supportive care.

Pulmonary Irritants

- Highly water-soluble gases produce rapid irritation and predominantly upper respiratory tract symptoms, such as bronchospasm.
- Poorly water-soluble gases often produce delayed lower respiratory tract findings, such as acute respiratory distress syndrome.

Smoke Inhalation

- Smoke inhalation injury is typically irritant in nature.
- Early assessment, often including visualization of the airway, is essential. Early intubation before deterioration is critical if damage is present.
- Consider carbon monoxide and cyanide in patients with smoke inhalation.

Cyanide and Hydrogen Sulfide

- An antidote for cyanide poisoning optimally be administered early.
- The sodium thiosulfate portion of the cyanide antidote kit and hydroxocobalamin are safe for empirical administration in any patient in whom cyanide poisoning is possible, including fire victims.
- Patients with hydrogen sulfide poisoning generally respond to removal from exposure and ventilatory support.

Carbon Monoxide

- Carbon monoxide poisoning is common and has important public health implications.
- Carbon monoxide poisoning can be covert and difficult to diagnose; it should be investigated with co-oximetry.
- Because the role of hyperbaric oxygen therapy in carbon monoxide poisoning is controversial, consultation with a hyperbaric oxygen facility, poison control center, or medical toxicologist may be helpful.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Gill JR, Ely SF, Hua S: Environmental gas displacement: Three accidental deaths in the workplace. *Am J Forensic Med Pathol* 2002; 23:26.
2. Studdert DM, Gurrin LC, Jatkar U, Pirkis J: Relationship between vehicle emissions laws and incidence of suicide by motor vehicle exhaust gas in Australia, 2001-06: An ecological analysis. *PLoS Med* 2010; 7:e1000210.
3. DeBehnke DJ, et al: The hemodynamic and arterial blood gas response to asphyxiation: A canine model of pulseless electrical activity. *Resuscitation* 1995; 30:169.
4. White CW, Martin JG: Chlorine gas inhalation: Human clinical evidence of toxicity and experience in animal models. *Proc Am Thorac Soc* 2010; 7:257-263.
5. Tsushima K, et al: Acute lung injury review. *Intern Med* 2009; 48:621-630.
6. Traub SJ, Hoffman RS, Nelson LS: Case report and literature review of chlorine gas toxicity. *Vet Hum Toxicol* 2002; 44:235.
7. Peter JV, et al: Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: Meta-analysis. *BMJ* 2008; 336:1006.
8. Clark WR, Bonaventura M, Myers W: Smoke inhalation and airway management at a regional burn unit: 1974-1983. Part I: Diagnosis and consequences of smoke inhalation. *J Burn Care Rehabil* 1989; 10:52.
9. Lin WY, Kao CH, Wang SJ: Detection of acute inhalation injury in fire victims by means of technetium-99m DTPA radioaerosol inhalation lung scintigraphy. *Eur J Nucl Med* 1997; 24:125.
10. Baud FJ, et al: Elevated blood cyanide concentrations in victims of smoke inhalation. *N Engl J Med* 1991; 325:1761.
11. Greenhalgh DG: Steroids in the treatment of smoke inhalation injury. *J Burn Care Res* 2009; 30:165-169.
12. Reiffenstein RJ, Hulbert WC, Roth SH: Toxicology of hydrogen sulfide. *Annu Rev Pharmacol Toxicol* 1992; 32:109.
13. Johnson RP, Mellors JW: Arteriolization of venous blood gases: A clue to the diagnosis of cyanide poisoning. *J Emerg Med* 1988; 6:401.
14. Snyder JW, et al: Occupational fatality and persistent neurological sequelae after mass exposure to hydrogen sulfide. *Am J Emerg Med* 1995; 13:199.
15. Borron SW, et al: Hydroxocobalamin for severe acute cyanide poisoning by ingestion or inhalation. *Am J Emerg Med* 2007; 25:551.
16. Rodgers GC Jr, Condurache CT: Antidotes and treatments for chemical warfare/terrorism agents: An evidence-based review. *Clin Pharmacol Ther* 2010; 88:318-327.
17. Erdman AR: Is hydroxocobalamin safe and effective for smoke inhalation? Searching for guidance in the haze. *Ann Emerg Med* 2007; 49:814.
18. King M, Bailey C: Carbon monoxide–related deaths, United States, 1999-2004. *MMWR Morb Mortal Wkly Rep* 2007; 56:1309-1312.
19. Weaver LK: Clinical practice. Carbon monoxide poisoning. *N Engl J Med* 2009; 360:1217-1225.
20. Choi IS: Delayed neurologic sequelae in carbon monoxide intoxication. *Arch Neurol* 1983; 40:433.
21. Thom SR, et al: Delayed neuropsychiatric sequelae following CO poisoning. *Ann Emerg Med* 1994; 23:612.
22. Touger M, et al: Performance of the RAD-57 pulse CO-oximeter compared with standard laboratory carboxyhemoglobin measurement. *Ann Emerg Med* 2010; 56:382-388.
23. Juurlink DN, Stanbrook MB, McGuigan MA: Hyperbaric oxygen for carbon monoxide poisoning. *Cochrane Database Syst Rev* 2005; 1:CD002041.
24. Wolf SJ, Lavonas EJ, Sloan EP, Jagoda AS; American College of Emergency Physicians: Clinical policy: Critical issues in the management of adult patients presenting to the emergency department with acute carbon monoxide poisoning. *Ann Emerg Med* 2008; 51:138.
25. Logue CJ: An inconvenient truth? *Ann Emerg Med* 2008; 51:339.
26. Goulon M, et al: Intoxication oxy carbonee et anoxic aique par inalation de gaz de charbon et d'hydvocarbure. *Ann Med Interne (Paris)* 1969; 120:335 [English translation, *J Hyperbaric Med* 1986; 1:23].
27. Weaver LK, et al: Hyperbaric oxygen for acute carbon monoxide poisoning. *N Engl J Med* 2002; 347:1057.
28. Scheinkestel CD, et al: Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: A randomized controlled clinical trial. *Med J Aust* 1999; 170:203.
29. Hardy KR, Thom SR: Pathophysiology and treatment of carbon monoxide poisoning. *J Toxicol Clin Toxicol* 1994; 32:613.
30. Annane D, et al: Hyperbaric oxygen therapy for acute domestic carbon monoxide poisoning: Two randomized controlled trials. *Intensive Care Med* 2011; 37:486-492.
31. Elkharrat D, et al: Acute carbon monoxide intoxication and hyperbaric oxygen in pregnancy. *Intensive Care Med* 1991; 17:289.
32. Raphael JC, et al: Trial of normobaric and hyperbaric oxygen for acute carbon monoxide intoxication. *Lancet* 1989; 2:414.
33. Alarie Y: Toxicity of fire smoke. *Crit Rev Toxicol* 2002; 32:259.
34. Ivankovich AD, et al: Cyanide antidotes and methods of their administration in dogs: A comparative study. *Anesthesiology* 1980; 52:210.
35. Sloan EP, et al: Complications and protocol considerations in carbon monoxide–poisoned patients who require hyperbaric oxygen therapy: Report from a ten-year experience. *Ann Emerg Med* 1989; 18:629.

www.ketabpezeshki.com 66485457-66963820

Chapter 160

Lithium

Oliver Hung

PERSPECTIVE

Lithium has been used as a medicinal agent since the mid-1800s, when lithium salts were popularized as a treatment of gout (lithium carbonate and lithium citrate), a sedative for manic patients (lithium bromide), and a treatment of epilepsy (lithium bromide). In 1929, the soft drink 7UP, whose original name was Bib-Label Lithiated Lemon-Lime Soda, included lithium citrate (an ingredient until 1950) and was marketed as a patent medicine to cure hangovers. In the late 1940s, lithium chloride was used as a salt substitute for patients requiring low-salt diets. However, in 1949, the Food and Drug Administration (FDA) banned the use of lithium because of several patient deaths attributed to lithium toxicity. Ironically, in the same year, the Australian psychiatrist John Cade convincingly demonstrated the efficacy of lithium for the treatment of bipolar disorder. Use of lithium was prohibited in the United States until 1970, when the FDA reversed the ban on lithium and approved its use for the treatment of bipolar disorder. Despite the introduction of newer and safer medications, lithium remains the most effective long-term treatment to prevent recurrences of mania and bipolar disorder.[1] Lithium treatment also appears to substantially decrease the risk of suicide and suicide attempts.[1] According to U.S. Poison Control Centers data, in 2009, there were 6396 reported lithium exposures with 134 major outcomes (life-threatening or significant residual disability) and 3 deaths.[2] A very low mortality was also described in a retrospective study from 2003 to 2007 of lithium exposure cases reported to the California Poison Control System. The study identified 629 toxic exposures: 44 acute exposures, 124 acute-on-chronic overdoses, and 282 chronic overdoses. Of these patients, 69 patients required hemodialysis, and 4 died.[3]

PRINCIPLES OF DISEASE

The precise mechanism of action of lithium as a mood-stabilizing agent is still not fully understood. Lithium increases serotonin release and serotonin receptor sensitivity and also inhibits norepinephrine and dopamine release from nerve terminals. Postulated mechanisms have begun to focus on cellular pathways, including intracellular signaling, neuronal plasticity and neurogenesis, and gene expression. These mechanisms include the inositol depletion hypothesis, glycogen synthase kinase 3 inhibition, and the arachidonic acid cascade hypothesis. In the inositol depletion hypothesis, lithium inhibits inositol monophosphatase, which depletes brain cell myoinositol and dampens phosphoinositide signaling.[4-6] Lithium's neuroprotective properties are attributed to its ability to inhibit glycogen synthase kinase 3. Finally, in the arachidonic cascade hypothesis, lithium reduces the amount of arachidonic acid recycled in brain cells. Bipolar disorder is thought to result from a hyperactive arachidonic acid cellular signaling cascade.

Immediate-release lithium is rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations occur 0.5 to 3 hours after a single oral dose, with complete absorption within 8 hours. Sustained-release lithium preparations exhibit variable absorption, with a delayed peak of 6 to 12 hours. Ingestion of a single 300-mg lithium carbonate tablet increases the serum lithium level by approximately 0.1 mmol/L. After absorption, lithium distribution follows an open two-compartment model. Lithium is initially distributed in the extracellular fluid and then gradually is redistributed in various tissue compartments (preferentially the brain, kidney, thyroid, and bone). Brain lithium distribution may take up to 24 hours after absorption. Approximately 95% of a single dose of lithium is excreted by the kidney. Lithium is freely filtered by the glomerulus, with 80% of filtered lithium reabsorbed by the proximal renal tubule. Lithium renal elimination is increased by factors that decrease glomerular filtration rate (e.g., dehydration) or sodium concentration (e.g., hyponatremia). Medications such as nonsteroidal anti-inflammatory drugs, diuretics, and angiotensin-converting enzyme inhibitors may increase lithium levels by interfering with renal lithium elimination.

Chronic lithium therapy is also associated with the development of nephrogenic diabetes insipidus, resulting in hyponatremia and dehydration and increased lithium levels. Fluid resuscitation and lithium cessation are usually sufficient to reverse the effects of diabetes insipidus permanently. Lithium also inhibits the synthesis and release of thyroid hormone, but hypothyroidism is a rare complication (5% of all patients) of chronic lithium therapy. Finally, lithium causes a temporary leukocytosis and was once investigated as a potential treatment of chemotherapy-induced neutropenia.

CLINICAL FEATURES

Clinical manifestations of lithium poisoning can be classified on the basis of whether the poisoning is due to acute toxicity, chronic toxicity, or acute-on-chronic toxicity.

Acute toxicity represents an overdose of lithium in a patient without any lithium body stores. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea are the earliest and most common presentation of toxicity. Lithium also causes electrocardiographic effects, including bradycardia, T wave flattening or inversion, and QT prolongation. Several case reports have also reported lithium-induced Brugada-type electrocardiographic changes. Fortunately, significant cardiac dysrhythmias after lithium poisoning are rare. Neurotoxicity is delayed because of the time required for lithium to be distributed to the brain.

www.ketabpezeshki.com 66485457-66963820

In chronic toxicity, the patient, who takes lithium regularly and has significant lithium body stores, develops toxicity because of increased absorption or, more commonly, decreased lithium renal elimination (e.g., dehydration, drug interactions, and renal insufficiency). Neurotoxicity is the predominant presentation. Mild toxicity may be manifested as a worsening tremor. Progressively more severe signs of neurotoxicity include drowsiness, hyperreflexia, confusion, clonus, coma, seizures, and extrapyramidal signs. The syndrome of irreversible lithium-effectuated neurotoxicity (SILENT) is described as neurologic dysfunction attributed to lithium toxicity persisting for 2 months after lithium cessation.[7] Typical SILENT presentations include cerebellar dysfunction, persistent extrapyramidal syndromes, brainstem dysfunction, and dementia. The presence of fever is considered a poor prognostic sign and possible precipitant of SILENT.[7]

Finally, in acute-on-chronic toxicity, a patient who is already taking lithium ingests an additional quantity of lithium in excess of the prescribed dosage. The clinical presentation includes signs and symptoms of both acute and chronic toxicity, including gastrointestinal and neurologic symptoms.

Lithium use has also been implicated in the development of both neuroleptic malignant syndrome and serotonin syndrome. Serotonin syndrome usually results from the combination of serotonergic agents. Consequently, lithium should not be used in conjunction with serotonin agonists (e.g., monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, dextromethorphan, buspirone, and meperidine). Lithium use is also considered a risk factor for neuroleptic malignant syndrome. The signs and symptoms of neuroleptic malignant syndrome, serotonin syndrome, and lithium toxicity are similar, with considerable overlap of symptoms (fever and neurologic deterioration). Fortunately, the initial treatment of lithium toxicity, serotonin syndrome, and neuroleptic malignant syndrome is the same and includes supportive care and discontinuation of the involved medication.

DIAGNOSTIC STRATEGIES

Because the signs and symptoms of lithium toxicity are nonspecific and are often delayed after acute overdose, a serum lithium level should be obtained in any patient thought to have acute or chronic lithium poisoning. It may be helpful in patient management to obtain serum electrolyte values. Increased serum sodium concentration may indicate lithium-induced nephrogenic diabetes insipidus, whereas the serum creatinine level may help determine whether dialysis is required. Thyroid function studies should also be obtained if clinical thyroid disease is suspected. Finally, for acute, intentional ingestions, electrocardiography and determination of a serum acetaminophen level should be considered to evaluate for the presence of coingestants.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for lithium poisoning is extremely broad because of its nonspecific signs and symptoms. Consideration of an alternative diagnosis can be based on whether the clinical presentation represents acute versus chronic lithium poisoning. Acute lithium poisoning typically is manifested with initial, prominent gastrointestinal symptoms similar to those of other drug overdoses. These include other metal salts (e.g., iron, arsenic, or mercury), salicylates, cardioactive steroids (e.g., digoxin), and, rarely, theophylline. Other illnesses causing nausea and vomiting include gastroenteritis and other abdominal maladies. Chronic lithium poisoning, with its predominant neurologic symptoms, should raise concern for other neurologic conditions causing tremor or confusion and for central nervous system toxins, including central nervous system depressants, drugs that cause seizures, hypoglycemic agents, carbon monoxide, neuroleptic malignant syndrome, and serotonin syndrome.

MANAGEMENT

There is no antidote for lithium poisoning; consequently, the management of lithium toxicity includes selected gastrointestinal decontamination (for acute overdose only), techniques to increase the elimination of lithium (renal and extracorporeal) from the body, and supportive care.

Gastrointestinal Decontamination

Both oral activated charcoal and gastric lavage are ineffective in the management of lithium poisoning. Lithium is poorly adsorbed by activated charcoal.[8] Gastric lavage is ineffective for several reasons. The immediate-release lithium preparations are usually absorbed from the gastrointestinal tract too quickly for lavage or whole-bowel irrigation to be effective. Lithium-induced emesis typically occurs soon after an ingestion of immediate-release lithium, thereby limiting its own gastrointestinal absorption and making any attempt at gastric lavage potentially hazardous. Finally, sustained-release lithium tablets are too large to fit through an orogastric tube.

Whole-bowel irrigation with polyethylene glycol is the recommended gastrointestinal decontamination treatment for any overdose of sustained-release lithium preparation. It has not been studied in overdose but has been demonstrated to safely eliminate lithium in humans.[9] The recommended initial rate of administration is 2 L/hr in adults and 500 mL/hr in children through a gastric tube until the rectal effluent is clear (4-6 hours), but the rate may be decreased for vomiting.

Sodium polystyrene sulfonate (Kayexalate), a cationic exchange resin used to treat hyperkalemia, has been investigated as a gastrointestinal decontamination method for lithium poisoning. In animal models and in two human case reports (one volunteer and one overdose patient), administration of oral sodium polystyrene sulfonate (30 g every 6 hours for five doses) is effective in decreasing serum lithium levels.[8,10] However, it also significantly lowers serum potassium concentrations.[11,12] Because of limited patient experience and concerns about life-threatening hypokalemia, sodium polystyrene sulfonate is not recommended.

Techniques to Increase Elimination

Lithium can be removed by increasing renal elimination as well as by extracorporeal methods.

Fluid resuscitation with sodium chloride (normal saline) to correct hyponatremia and dehydration is the recommended method to maximize renal lithium elimination. Unless there are contraindications to aggressive volume expansion (e.g., renal insufficiency, congestive heart failure), administration of intravenous normal saline at a twice maintenance rate is recommended. Overly aggressive hydration, known as forced diuresis, is not recommended because of the risk of causing hypernatremia and because of its unpredictability in increasing renal lithium elimination. Urinary alkalinization by intravenous sodium bicarbonate is also not recommended because it does not significantly increase renal lithium elimination more than volume expansion by sodium chloride (normal saline) and because of the additional risk of hypokalemia and alkalemia.

The most effective technique to eliminate lithium from the body is hemodialysis. Endogenous lithium renal clearance is approximately 15 to 20 mL/min, whereas hemodialysis lithium clearance is approximately 100 mL/min.[13] Although hemodialysis substantially increases lithium elimination, its effect to decrease mortality or to treat or to prevent SILENT has never been

www.ketabpezeshki.com 66485457-66963820

demonstrated.[13-16] Consequently, there is no evidence-based consensus to define the indications for hemodialysis for lithium poisoning. Hemodialysis is primarily used for clinical deterioration (e.g., seizures and decreased level of consciousness), inadequate endogenous lithium clearance (e.g., renal insufficiency), or inability to enhance renal elimination through volume expansion (e.g., congestive heart failure, cirrhosis, pancreatitis, and sepsis). Although it may not correlate directly with toxicity, hemodialysis is often recommended for a serum lithium level above 4.0 mEq/L for acute toxicity and above 2.5 mEq/L for chronic toxicity, but dialysis is most efficient when the drug is still in the vascular space before distribution to tissues. Continuous renal replacement therapies (e.g., continuous venovenous hemodialysis) have also been successfully used to treat lithium-poisoned patients.[17] Although their clearance rates are inferior to hemodialysis, they can be used in place of hemodialysis in hemodynamically unstable patients as well as in conjunction with hemodialysis in stable patients.

Because of the two-compartment model of lithium distribution in the body, serial lithium levels need to be monitored repeatedly for increases after treatment because of redistribution from intracellular stores. In chronic lithium toxicity, rising lithium levels from the large tissue stores occur after hemodialysis, necessitating multiple hemodialysis treatments.

DISPOSITION

Hospital admission should be considered for any patient with suspected lithium poisoning with abnormal neurologic signs (e.g., increased tremor, hyper-reflexia, clonus, altered sensorium, or seizure) or for any asymptomatic patient after acute overdose with increasing lithium levels or decreasing renal function. In addition, hospitalization at a center with emergency dialysis capability is preferable.

KEY CONCEPTS

- Lithium toxicity can be acute, chronic, or acute-on-chronic and presents with nonspecific gastrointestinal and neurologic signs and symptoms.
- Consider lithium poisoning in any patient who is taking lithium and presents with an altered sensorium.
- Medications that impair renal function or environmental factors that lead to dehydration increase the risk of lithium toxicity.
- Consider hemodialysis in patients with worsening tremor, confusion, decreased consciousness, inadequate renal function or inability to tolerate volume expansion (e.g., renal insufficiency and congestive heart failure), or serum lithium level above 4.0 mEq/L in acute poisoning or above 2.5 mEq/L in chronic poisoning.
- Lithium has numerous drug interactions that may lead to adverse effects, including increased risk for lithium toxicity, increased lithium toxic effects, neuroleptic malignant syndrome, and serotonin syndrome.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Baldessarini RJ, Tondo L: Suicide risk and treatments for patients with bipolar disorder. *JAMA* 2003; 290:1157.
2. Bronstein AC, et al: 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS). *Clin Toxicol (Phila)* 2010; 48:979.
3. Offerman SR, Alsop JA, Lee J, Holmes JF: Hospitalized lithium overdose cases reported to the California Poison Control System. *Clin Toxicol (Phila)* 2010; 48:443.
4. Berridge MJ, Downes CP, Hanley MR: Neural and developmental actions of lithium: A unifying hypothesis. *Cell* 1989; 59:411.
5. Quiroz JA, Gould TD, Manji HK: Molecular effects of lithium. *Mol Interv* 2004; 4:259.
6. Rapoport SI, Bosetti F: Do lithium and anticonvulsants target the brain arachidonic acid cascade in bipolar disorder? *Arch Gen Psychiatry* 2002; 59:592.
7. Adityanjee A, Munshi KR, Thampy A: The syndrome of irreversible lithium-effectuated neurotoxicity. *Clin Neuropharmacol* 2005; 28:38.
8. Linakis JG, et al: Administration of activated charcoal or sodium polystyrene sulfonate (Kayexalate) as a gastric decontamination for lithium intoxication: An animal model. *Pharmacol Toxicol* 1989; 65:387.
9. Smith SW, Ling LJ, Halstenson CE: Whole-bowel irrigation as a treatment for acute lithium overdose. *Ann Emerg Med* 1991; 20:536.
10. Roberge RJ, Martin TG, Schneider SM: Use of sodium polystyrene sulfonate in a lithium overdose. *Ann Emerg Med* 1993; 22:1911.
11. Linakis JG, et al: Sodium polystyrene sulfonate treatment for lithium toxicity: Effects on serum potassium concentrations. *Acad Emerg Med* 1996; 3:333.
12. Linakis JG, Savitt DL, Trainor BJ, Young JE, Lacouture PG: Potassium repletion fails to interfere with reduction of serum lithium by sodium polystyrene sulfonate in mice. *Acad Emerg Med* 2001; 8:956.
13. Jaeger A, Sauder P, Kopferschmitt JK, Tritsch L, Flesch F: When should dialysis be performed in lithium poisoning? A kinetic study in 14 cases of lithium poisoning. *J Toxicol Clin Toxicol* 1993; 31:429.
14. Swartz CM, Jones P: Hyperlithemia correction and persistent delirium. *J Clin Pharmacol* 1994; 34:865.
15. Swartz DM, Dolinar LJ: Encephalopathy associated with rapid decrease of high levels of lithium. *Ann Clin Psychiatry* 1995; 7:207.
16. Bailey B, McGuigan M: Comparison of patients hemodialyzed for lithium poisoning and those for whom dialysis was recommended by PCC but not done: What lesson can we learn? *Clin Nephrol* 2000; 5:388.
17. Beckman U, Oakley PW, Dawson AH, Byth PL: Efficacy of continuous venovenous hemodialysis in the treatment of severe lithium toxicity. *J Toxicol Clin Toxicol* 2001; 39:393.

www.ketabpezeshki.com 66485457-66963820

Chapter 161

Antipsychotics

Mary A. Wittler and Eric J. Lavonas

PERSPECTIVE

The first antipsychotic, chlorpromazine, was used for the treatment of psychosis in France in 1951 and in the United States in 1954. Antipsychotic use has expanded significantly since then. The historic term *neuroleptic,* used with antipsychotic medication, is no longer appropriate because newer agents cause less sedation. The term *antipsychotic* is now preferred. In 2009, U.S. poison control centers reported more than 4700 exposures to phenothiazines and 43,000 exposures to atypical antipsychotics, resulting in 0 and 8 deaths, respectively.[1]

PRINCIPLES OF DISEASE

Antipsychotic medications are used to treat agitation and psychosis caused by schizophrenia, mania, acute idiopathic psychosis, substance-induced psychosis, and dementia. The antipsychotic medications are divided into three broad categories on the basis of their receptor profiles, clinical effects, and adverse effects (Table 161-1). All antipsychotic medications effectively treat the *positive symptoms* of psychotic disorders; they reduce hallucinations, control agitation, and aid in restructuring of disordered thinking. In general, the low-potency first-generation antipsychotics (FGAs) are the most sedating. Movement disorders, including extrapyramidal symptoms (EPS) and tardive dyskinesia (TD), are significant problems with both low-potency and high-potency FGAs. In addition to producing less sedation and fewer movement disorders, the atypical or second-generation antipsychotics (SGAs) assist with the *negative symptoms* of psychotic disorders, such as flat affect, avolition, social withdrawal, and impoverished thought and speech.[2] Although neuroleptic malignant syndrome (NMS) occurs with all agents, it occurs least with SGAs.

Anatomy and Physiology

Antipsychotic drugs block dopamine receptors in several areas of the brain, including the cerebral cortex, basal ganglia, limbic system, hypothalamus, and chemoreceptor trigger zone. All antipsychotic agents reduce the positive symptoms of schizophrenia by blocking the dopamine D_2 receptor subtype in the mesolimbic region of the brain. However, blockade of D_2 receptors in the nigrostriatal brain region produces undesired EPS. In addition, blockade of D_2 receptors in the mesocortical brain region impairs cognition and worsens the negative symptoms of schizophrenia. SGAs block both D_2 and serotonin 5-HT_{2A} receptors. Because these agents have lower affinity for dopamine receptor antagonism and more selective binding of D_2 receptors in the mesolimbic versus nigrostriatal areas of the brain, SGAs should have a lower rate of EPS and TD. The serotonin receptor antagonism is thought to reduce EPS effects and to improve the negative symptoms of schizophrenia.[3,4] However, studies have found no significant difference in reported rates of EPS and TD between perphenazine (a FGA) and several SGAs.[5,6] Antipsychotic medications also block other receptor types (see Table 161-1).

Some antipsychotic medications have additional clinical uses. The antiemetic effect of prochlorperazine, promethazine, and droperidol is from blockade of dopamine receptors in the chemoreceptor trigger zone of the medulla. Hydroxyzine controls itching by blocking histamine (H_1) receptors. Prochlorperazine and droperidol abort migraine headaches by preventing dopamine-mediated meningeal artery vasodilation. Chlorpromazine can treat severe hiccups, and haloperidol is the drug of choice for certain movement disorders, including Tourette's syndrome and Huntington's chorea.

Pathophysiology

EPS can be immediate or delayed after initiation of drug therapy. The acute EPS include dystonia, akathisia, and parkinsonism, which are caused by blockade of nigrostriatal D_2 receptors and reduced by blockade of muscarinic receptors. The propensity for antipsychotics to produce EPS is inversely proportional to the agents' muscarinic receptor antagonism.[4] The delayed-onset syndromes, including TD and tardive dystonia, develop after prolonged use of antipsychotic medications and are thought to occur from chronic dopamine receptor blockade in the nigrostriatal area leading to D_2 receptor upregulation and hypersensitivity to dopamine.[7-9] The pathophysiologic mechanism of NMS, an idiosyncratic reaction to antipsychotic medication, is unknown but thought to be neuroregulatory dysfunction secondary to D_2 receptor blockade in the nigrostriatum and hypothalamus, leading to rigidity and hyperthermia, respectively.[10] NMS is not associated with ryanodine receptor (RYR) gene mutations, which are associated with malignant hyperthermia.

Antipsychotic medications produce cardiovascular side effects, most commonly orthostatic hypotension with reflexive tachycardia due to alpha-adrenergic blockade. Many agents cause conduction delays, predominantly QT prolongation, resulting in prolonged repolarization and potentially torsades de pointes (TdP).[11] The degree of prolongation varies between antipsychotic agents, increasing with dose and with concomitant use of other drugs that prolong the QT interval.[12,13] The phenothiazines, particularly thioridazine and mesoridazine, have the greatest risk of cardiac toxicity. QT prolongation has also been reported with the butyrophenones haloperidol and droperidol.[12,14] The atypical antipsychotics produce less cardiotoxicity than the traditional agents do, although most can cause repolarization abnormalities in therapeutic doses and overdose.[12,15,16] Ultimately, a correlation

www.ketabpezeshki.com 66485457-66963820

Table 161-1 Selected Antipsychotic Agents Approved or Nearing Approval for Use in the United States

MEDICATION	RECEPTORS BLOCKED	CLINICAL EFFECTS	ADVERSE EFFECTS
Low Potency (First-Generation Antipsychotics)			
Chlorpromazine Chlorprothixene Fluphenazine Hydroxyzine Mesoridazine Molindone Perphenazine Prochlorperazine Promethazine Thioridazine	Dopamine D_2 (moderate affinity in mesolimbic and nigrostriatal areas) Acetylcholine muscarinic (generally strong affinity) Histamine H_1 (strong affinity) Alpha-adrenergic (moderate affinity) Dopamine D_1, D_3, D_4, D_5 (variable affinity)	Control positive symptoms of psychotic disorders: Hallucinations Delusions Agitation Disordered thoughts	Extrapyramidal syndromes (common) Tardive dyskinesia (common) Sedation (common) Orthostatic hypotension (common) Anticholinergic symptoms (common): Dry mouth Blurred vision Impaired sweating Constipation Weight gain Urinary retention Angle-closure glaucoma
High Potency (First-Generation Antipsychotics)			
Droperidol Haloperidol Loxapine Pimozide Thiothixene Trifluoperazine	Dopamine D_2 (strong affinity in mesolimbic and nigrostriatal areas) Acetylcholine muscarinic, histamine H_1, alpha-adrenergic (weak affinity) Dopamine D_1, D_3, D_4, D_5 (variable affinity)	Control positive symptoms of psychotic disorders	Extrapyramidal syndromes (common) Tardive dyskinesia (common) Sedation, orthostatic hypotension, and anticholinergic symptoms (uncommon in usual clinical doses)
Atypical (Second-Generation Antipsychotics)			
Aripiprazole Asenapine Clozapine Iloperidone Olanzapine Paliperidone Quetiapine Risperidone Ziprasidone	Serotonin 5-HT_{2A} (strong) Dopamine D_2 (mild to moderate affinity, selective for mesolimbic areas) Dopamine D_1, D_3, D_4, D_5 (variable affinity)	Control positive symptoms of psychotic disorders Control negative symptoms of psychotic disorders: Social withdrawal Flattened affect Decreased activity Paucity of speech Pseudodementia	Extrapyramidal syndromes and tardive dyskinesia (uncommon) Endocrine effects Prolactin elevation

between QT prolongation and dysrhythmias or TdP has not been established,[3] but antipsychotics are associated with an increased risk of sudden death, particularly with heart disease and in elderly patients.[17,18] However, psychotic disorders themselves are associated with an increased risk of sudden death.

Clozapine produces agranulocytosis in 1 or 2% of treated patients; however, this has been reduced to 0.4% after strict adherence to labeling requirements.[19] Although the mechanism of agranulocytosis is unknown, research supports an immunogenic cause and direct cytotoxic effect on human bone marrow mesenchymal stromal cells.[20] Seizure rarely occurs with antipsychotic drugs, but clozapine has the highest seizure incidence. Drug dosing and the patient's seizure risk profile influence seizure susceptibility.[21] FGAs and SGAs have been associated with weight gain, glycemic dysregulation, and dyslipidemia. The cause is not fully understood but partly blamed on the pharmacodynamic profile of these agents.[22]

CLINICAL FEATURES

Acute Overdose

In overdose, antipsychotic medications produce signs and symptoms that are exaggerations of the clinical effects. Most patients will have symptoms within a few hours. Central nervous system (CNS) depression is universally present, ranging from mild sedation and confusion to coma and loss of brainstem reflexes. Airway reflexes can be impaired. Respiratory depression can occur after a massive overdose with profound CNS depression. Pupils can be of any size. Mild orthostatic hypotension is a common finding from alpha-adrenergic blockade. Overdose with low-potency FGAs can cause an anticholinergic delirium. EPS have been reported with the FGAs and SGAs.

Atypical antipsychotic overdose is similar to that of traditional antipsychotics. Overdoses are characterized by CNS depression and tachycardia.[23-30] Miosis may be present, potentially mimicking opioid toxicity.[31] Extremity twitching is common. With the exception of clozapine, seizures rarely occur in overdose. Acute EPS have been reported, especially for risperidone overdose.[32]

Acute Extrapyramidal Syndromes

Acute dystonia is manifested as intermittent, involuntary motor tics or spasms of antagonistic muscle groups that most often involve the facial, neck, back, or limb muscles. This results in trismus, facial grimacing, dysarthria, tongue and lip distortion, torticollis, or oculogyric crisis. Dystonic reactions usually develop within the first several doses of treatment or after a large increase in dosage.[33] *Laryngeal dystonia* is a rare but life-threatening form of dystonia that is manifested as stridor, difficulty in breathing, or choking sensation.[5,34] Increased risk of death due to choking has been documented in schizophrenia patients.[35]

Akathisia is a subjective feeling of restlessness associated with objective motor restlessness, including repetitive foot shuffling, truncal rocking, or pacing. The subjective distress may precipitate aggressive behavior.[5,36] Akathisia usually develops within the first few days of treatment, but 40% of patients given 10 mg of intravenous prochlorperazine developed akathisia within 1 hour.[37]

A *parkinsonian syndrome* of bradykinesia, masked facies, shuffling gait, muscle rigidity, and resting tremor frequently develops during the first month of treatment; 90% of cases occur within 3 months of treatment. *Perioral tremor* (rabbit syndrome), in which

www.ketabpezeshki.com 66485457-66963820

the lip and nose movements resemble those of a rabbit, can also develop after prolonged therapy.[5]

Tardive Dyskinesia

TD is a chronic movement disorder induced by prolonged use of antipsychotic medication. Typical signs of TD include quick, involuntary movements of the face (blinking, grimaces, tongue movements, and chewing), extremities, or trunk. Twenty percent of patients treated with long-term traditional antipsychotics are affected. TD is difficult to treat and is frequently permanent. Anticholinergic agents may worsen TD; reduction of the antipsychotic dose or a change to an alternative agent should be considered.[5,38] TD improves in some patients switched to clozapine; amantadine improved symptoms compared with placebo in a small study.[39,40]

Respiratory dyskinesia, a variant of TD, is characterized by orofacial dyskinesia, dyspnea, dysphonia, and respiratory alkalosis. This chronic disorder often goes undiagnosed and can cause repeated bouts of aspiration pneumonia.

Neuroleptic Malignant Syndrome

NMS is a serious idiosyncratic drug reaction that typically develops during the first month of therapy but has occurred during stable drug regimens. Risk factors include rapid drug loading, high dosage, high-potency antipsychotics, parenteral formulations, dehydration, preceding psychomotor agitation, and previous episodes of NMS.[41,42] Other medications may contribute to NMS, including lithium, which inhibits dopamine secretion, as can withdrawal from dopaminergic agents used to treat Parkinson's disease.[5,10,43] The incidence of NMS in patients treated with antipsychotics is approximately 0.02%.[41] Atypical antipsychotic agents, including clozapine, risperidone, olanzapine, quetiapine, ziprasidone, amisulpride, and aripiprazole, have been associated with NMS.[44]

Table 161-2 lists the diagnostic criteria for NMS. Other features of NMS may include sialorrhea, dysarthria, dysphagia, metabolic acidosis, liver function elevations, sodium imbalance, dehydration, elevations in serum catecholamines, coagulopathy, generalized slowing on the electroencephalogram, pulmonary embolism, and renal failure.[42] Atypical presentations may lack full diagnostic criteria for NMS.[44,45]

Most patients have the cardinal features of altered mental status, muscle rigidity, hyperthermia, and autonomic nervous system instability during several hours to days. However, the signs of NMS may develop gradually and in any order. Agitation, often mistaken for worsening psychosis, may occur first. Physicians should consider discontinuation of antipsychotic drugs in a patient who has one or more of the major manifestations of NMS. Most episodes resolve within 2 weeks after cessation of the offending medication, but some cases last several months.

Table 161-2 Diagnostic Criteria and Clinical Features of Neuroleptic Malignant Syndrome

CRITERIA AND FEATURES	PREVALENCE
A. Development of severe muscle rigidity and elevated temperature associated with the use of a neuroleptic/antipsychotic medication	Rigidity: 97% Fever: 98%
B. Two (or more) of the following are present:	
Diaphoresis	98%
Dysphagia	
Tremor	
Incontinence	
Change in level of consciousness ranging from confusion to coma	97%
Mutism	
Tachycardia	88%
Elevated or labile blood pressure	61%
Leukocytosis	98%
Laboratory evidence of muscle injury (e.g., elevated creatine kinase)	95%
C. Symptoms in criteria A and B are not caused by another substance (e.g., phencyclidine), a neurologic or other general medical condition (e.g., viral encephalitis), or another mental disorder (e.g., mood disorder with catatonic features).	

Modified from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text rev. Washington, DC, American Psychiatric Association, 2000. Prevalence data from Caroff SN, Mann SC: Neuroleptic malignant syndrome. Med Clin North Am 77:185, 1993.

Cardiovascular Toxicity and Dysrhythmias

The most common cardiac effect is sinus tachycardia with a normal QRS duration. If QRS prolongation is present, another drug effect should be suspected. QT prolongation occurs during therapeutic dosing of many antipsychotic agents. Therapeutic doses of thioridazine, followed by ziprasidone, prolong the QT interval more than risperidone, olanzapine, quetiapine, or haloperidol does.[15,16] QT prolongation associated with TdP is a well-described adverse effect of thioridazine, mesoridazine, droperidol, sertindole, and haloperidol.[12] Among FGAs, thioridazine carries the greatest risk of cardiotoxicity. Among SGA overdoses, whereas ziprasidone carries the greatest risk of QTc prolongation,[46,47] TdP has been reported with amisulpride overdose.[30] QT prolongation should be considered a "class effect" of all antipsychotic medications.

Agranulocytosis

Clozapine produces agranulocytosis; 75% of occurrences develop within the first 18 weeks after initiation of therapy, peaking at 3 months.[19] The concomitant use of other bone marrow–suppressing agents (e.g., carbamazepine) should be avoided. Clozapine administration must be halted if the total white blood cell count falls below 3000 cells/mL or if the absolute neutrophil count is less than 1500 cells/mL. Agranulocytosis has not been reported after an acute overdose. Olanzapine, whose chemical structure is similar to that of clozapine, has also been associated with neutropenia and agranulocytosis, but all patients recovered after discontinuation of olanzapine.[48]

Seizures

Antipsychotic medications can lower the seizure threshold and induce epileptiform electroencephalographic abnormalities in many asymptomatic patients. However, antipsychotic-induced seizures are rare except for clozapine, which causes a dose-related increase in risk of seizures (approximately 5% at high doses). Antipsychotics can be prescribed for patients with known seizure disorder.[20,21,49]

DIFFERENTIAL CONSIDERATIONS

Differential considerations include a broad list of agents and clinical conditions that produce altered mental status, orthostatic hypotension, anticholinergic syndrome, seizure, QT prolongation, or TdP. Although the signs of NMS are similar, serotonin syndrome is more likely to have clonus, heatstroke is evident from the circumstances, and the causes of these conditions are quite different (Table 161-3). Malignant hyperthermia should be considered in patients receiving inhalational anesthetics or succinylcholine.

www.ketabpezeshki.com 66485457-66963820

Table 161-3 Differential Diagnosis of Neuroleptic Malignant Syndrome

DISEASE*	PATHOLOGIC MECHANISM	DIFFERENTIATING FACTOR	TIME COURSE	TREATMENT
Neuroleptic malignant syndrome	Impaired thermoregulation in hypothalamus and basal ganglia due to relative lack of dopamine activity	Antipsychotic medication use, muscle rigidity (diagnostic criteria in Table 161-2)	Gradual, progresses during several days	Stop offending medication Hydration Active cooling Intravenous benzodiazepines to relax muscles and control agitation Neuromuscular blockade (nondepolarizing agents) Controversial: Bromocriptine or amantadine Dantrolene
Serotonin syndrome	Excess serotonin and dopamine levels in central nervous system	Medications (usually a combination) that increase serotonin levels (e.g., SSRIs, MAOIs, dextromethorphan, lithium, meperidine, tramadol, tryptophan); muscle rigidity	Usually rapid after introduction of new medication or increase in dose; can be gradual	Stop offending medication Hydration Active cooling Cyproheptadine
Heatstroke	Environmental heat stress	Environmental exposure history; muscle rigidity rare	Rapid or gradual	Hydration Active cooling
Malignant hyperthermia	Genetic instability of sarcoplasmic reticulum, causing massive calcium release after administration of triggering medication	Occurs after administration of inhalational anesthetic or succinylcholine; muscle rigidity	Sudden, provoked by administration of anesthetic	Stop anesthetic Hydration Active cooling Dantrolene

MAOIs, monoamine oxidase inhibitors; *SSRIs,* selective serotonin reuptake inhibitors.
*Other clinical entities to consider in the diagnosis of these conditions include Addison's syndrome, central nervous system infection, delirium tremens, hypocalcemia, hypoglycemia, hyponatremia, intracranial hemorrhage, lethal catatonia, poisoning (e.g., amphetamines, anticholinergics, cocaine, nicotine, salicylates, sympathomimetics, strychnine, theophylline), sedative-hypnotic drug withdrawal, sepsis, status epilepticus (including nonconvulsive status), tetanus, thalamic infarct, thyroid storm, and psychotic agitation.

DIAGNOSTIC STRATEGIES

Blood levels are neither readily available nor helpful. As with any patient who presents with altered mental status, vital signs, blood glucose concentration, and pulse oximetry are indicated.

An electrocardiogram should be obtained in patients with significant antipsychotic overdose and in symptomatic patients taking thioridazine, mesoridazine, droperidol, or sertindole. Patients receiving high-dose intravenous haloperidol or droperidol for sedation may need rhythm monitoring, and if QT prolongation is present, serum potassium, calcium, and magnesium levels should be measured.

Patients who have NMS, parkinsonism with marked muscle rigidity, or prolonged seizures are at risk for rhabdomyolysis and should have serum creatine kinase, renal function, and urine myoglobin measured. Patients taking clozapine or olanzapine who present with infection or fever should be checked for leukopenia. Olanzapine and clozapine have been associated with new-onset diabetes with ketoacidosis.[3]

Other testing, such as brain computed tomography, lumbar puncture, serum acetaminophen level, and electrolyte measurements, may be helpful in some cases but are not indicated when the context and presentation support antipsychotic toxicity as the cause.

MANAGEMENT

Acute Overdose

Treatment is supportive; there is no specific antidote. Endotracheal intubation may be required to prevent aspiration or, less often, to support respiration. Hypotension is generally mild and responds to intravenous crystalloids. An alpha-adrenergic pressor such as norepinephrine may be used if needed. If sedation and miosis suggest opioid intoxication, a trial of naloxone is warranted. Physostigmine and flumazenil are not indicated and may precipitate seizures.

Activated charcoal has no proven benefit and may increase the morbidity of the overdose if it is administered to a patient with altered mental status at risk for aspiration.

Acute Extrapyramidal Syndromes

Dystonia will usually respond within 30 minutes to diphenhydramine 25 to 50 mg intravenously, intramuscularly, or orally or benztropine 1 to 2 mg intramuscularly or orally. Benzodiazepines may also be effective. If relief is not achieved, an alternative diagnosis should be sought. Akathisia is treated similarly or with a lipophilic beta-adrenergic blocker (e.g., propranolol). Treatment of parkinsonism syndrome may include anticholinergic agents. Patients with EPS who respond to diphenhydramine or benztropine should continue therapy for at least 48 hours to prevent recurrence.[5,50] In addition, patients should be referred to their treating physician, who may reduce the antipsychotic dose or change to an alternative agent as necessary. Benztropine, diphenhydramine, and the older antipsychotic medications cause anticholinergic effects, so combination therapy may worsen dry mouth, blurred vision, and urinary retention.

QT Prolongation and Torsades de Pointes

Correction of hypokalemia, hypomagnesemia, and hypocalcemia shortens the QT interval. Treatment of TdP includes intravenous magnesium sulfate, overdrive pacing, and possibly isoproterenol.

www.ketabpezeshki.com 66485457-66963820

Antiarrhythmic drugs that prolong the QT interval should be avoided.

Neuroleptic Malignant Syndrome

Treatment of NMS consists of supportive care and discontinuation of the offending medication. Agitation, psychomotor hyperactivity, and muscle rigidity should be treated with liberal doses of intravenous benzodiazepines. Lorazepam can be administered intravenously, 1 or 2 mg every 3 minutes, until muscle rigidity improves. Refractory cases or cases at risk for aspiration can be managed with rapid sequence intubation and neuromuscular blockade with a nondepolarizing agent (e.g., rocuronium and vecuronium). Hyperthermia should be managed with intravenous fluids and active external cooling with mist and fans. If rhabdomyolysis is present, intravenous hydration and urinary alkalinization are used to prevent renal damage.

Bromocriptine and amantadine have been suggested for treatment of NMS but do not consistently show a benefit.[43,51] Bromocriptine is administered orally or by nasogastric tube, beginning with 5 mg every 8 hours and titrated to a maximum of 20 mg per dose. The dose of amantadine for NMS is 200 mg orally every 12 hours. Response to therapy requires at least 24 hours. Dantrolene, which inhibits the release of calcium from the sarcoplasmic reticulum, has no proven benefit.[51] Because the muscle rigidity of NMS is thought to be from dopamine blockade in the CNS rather than a muscle abnormality, dantrolene offers no advantage over benzodiazepines and neuromuscular blockade.

DISPOSITION

Patients with NMS and overdose patients with hypotension, coma, TdP, or airway compromise should be admitted, usually to a critical care unit. Patients with a prolonged QT interval (QTc > 460 milliseconds) or symptomatic ingestions of thioridazine or mesoridazine should have at least 12 hours of cardiac monitoring. Patients with minimal signs of toxicity should be observed in the emergency department for a minimum of 4 hours from the time of ingestion, with hospitalization for persistent or worsening signs and symptoms. Criteria for hospital discharge include return to normal mental status and resolution of any vital sign, metabolic, and electrocardiographic abnormalities. Psychiatric consultation may be necessary to assess the risk of suicide.

KEY CONCEPTS

- Extrapyramidal movement disorders are a common complication of antipsychotic medications and are treated with benztropine, diphenhydramine, and benzodiazepines.
- The most common finding in antipsychotic overdose is central nervous system depression. Treatment centers on supportive care, airway control, and cardiac monitoring.
- QT prolongation and torsades de pointes are potential complications of many antipsychotic medications in overdose and can occur with therapeutic doses of some agents.
- The neuroleptic malignant syndrome is characterized by altered mental status, hyperthermia, muscle rigidity, and autonomic instability. Supportive care includes airway management, benzodiazepines, neuromuscular blockade, and active cooling.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Bronstein AC, et al: 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS). *Clin Toxicol (Phila)* 2010; 48:979.
2. Oliveira IR, Juruena MF: Treatment of psychosis: 30 years of progress. *J Clin Pharm Ther* 2006; 31:523.
3. Reilly TH, Kirk MA: Atypical antipsychotics and newer antidepressants. *Emerg Med Clin North Am* 2007; 25:477.
4. Horacek J, et al: Mechanism of action of atypical antipsychotic drugs and the neurobiology of schizophrenia. *CNS Drugs* 2006; 20:389.
5. Caroff SN, et al: Movement disorders induced by antipsychotic drugs: Implications of the CATIE schizophrenia trial. *Neurol Clin* 2011; 29:127.
6. Miller DD, et al: Extrapyramidal side-effects of antipsychotics in a randomized trial. *Br J Psychiatry* 2008; 193:279.
7. Casey D: Tardive dyskinesia: Pathophysiology and animal model. *J Clin Psychiatry* 2000; 61:5.
8. Farver D: Neuroleptic malignant syndrome induced by atypical antipsychotics. *Expert Opin Drug Saf* 2003; 2:21.
9. Sachdev P: Early extrapyramidal side-effects as risk factors for later tardive dyskinesia: A prospective study. *Aust N Z J Psychiatry* 2004; 38:445.
10. Bhanushali M, Tuite P: The evaluation and management of patients with neuroleptic malignant syndrome. *Neurol Clin North Am* 2004; 22:389.
11. Pacher P, Kecskemeti V: Cardiovascular side effects of new antidepressants and antipsychotics: New drugs, old concerns? *Curr Pharm Des* 2004; 10:2463.
12. Haddad PM, Anderson IM: Antipsychotic-related QTc prolongation, torsades de pointes and sudden death. *Drugs* 2002; 62:1649.
13. Reilly JG, et al: QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet* 2000; 355:1824.
14. Salih ISM, et al: Comparison of the effects of thioridazine and mesoridazine on the QT interval in healthy adults after single oral doses. *Clin Pharm Ther* 2007; 82:548.
15. *FDA Briefing Document for Zeldox Capsules (Ziprasidone)*. New York: Pfizer; 2000:78.
16. Harrigan EP, et al: A randomized evaluation of the effects of six antipsychotic agents on QTc, in the absence and presence of metabolic inhibition. *J Clin Psychopharmacol* 2004; 24:62.
17. Wang PS, et al: Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med* 2005; 353:2335.
18. Ray WA, et al: Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med* 2009; 360:225.
19. Honigfeld G, et al: Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. *J Clin Psychiatry* 1998; 59:3.
20. Oja S, Korhonen M, Andersson, LC: Clozapine is cytotoxic to primary cultures of human bone marrow mesenchymal stromal cells. *J Clin Psychopharmacol* 2010; 30:461.
21. Pisani F, et al: Effects of psychotropic drugs on seizure threshold. *Drug Saf* 2002; 25:91.
22. Monteleone P, Martiadis V, Maj M: Management of schizophrenia with obesity, metabolic, and endocrinological disorders. *Psychiatr Clin North Am* 2009; 32:775.
23. Ngo A, Ciranni M, Olson K: Acute quetiapine overdose in adults: A 5-year retrospective case series. *Ann Emerg Med* 2008; 52:541.
24. Kramer I, et al: Minimal dose for severe poisoning and influencing factors in acute human clozapine intoxication: A 13-year retrospective study. *Clin Neuropharmacol* 2010; 33:230.
25. Forrester MB: Pattern of ziprasidone exposures reported to Texas poison centers, 2001-2005. *Hum Exp Toxicol* 2008; 27:355.
26. Isbister GK, Duffull SB: Quetiapine overdose: Predicting intubation, duration of ventilation, cardiac monitoring and the effect of activated charcoal. *Int Clin Psychopharmacol* 2009; 24:174.
27. Young MC, et al: Risk assessment of isolated aripiprazole exposures and toxicities: A retrospective study. *Clin Toxicol (Phila)* 2009; 47:580.
28. Ciranni MA, Kearney TE, Olson KR: Comparing acute toxicity of first- and second- generation antipsychotic drugs: A 10-year, retrospective cohort study. *J Clin Psychiatry* 2009; 70:122.
29. Melhem S, et al: Prolonged toxicity in a 2-year-old after accidental ingestion of aripiprazole. *Pediatr Emerg Care* 2009; 25:105.
30. Isbister GK, et al: Amusulpride overdose is frequently associated with QT prolongation and torsades de pointes. *J Clin Psychopharmacol* 2010; 30:391.
31. O'Malley G: Olanzapine overdose mimicking opioid intoxication. *Ann Emerg Med* 1999; 34:279.
32. Page CB, Calver LA, Isbister GK: Risperidone overdose causes extrapyramidal effects but not cardiac toxicity. *J Clin Psychopharmacol* 2010; 30:387.
33. Sachdev P: Neuroleptic-induced movement disorders: An overview. *Psychiatr Clin North Am* 2005; 28:255.
34. Christodoulou C, Kalaitzi C: Antipsychotic drug–induced acute laryngeal dystonia: Two case reports and a mini review. *J Psychopharmacol* 2005; 19:307.
35. Ruschena D, et al: Choking deaths: The role of antipsychotic medication. *Br J Psychiatry* 2003; 183:446.
36. Kane JM, et al: Akathisia: An updated review focusing on second-generation antipsychotics. *J Clin Psychiatry* 2009; 70: 627.
37. Drotts D, Vinson D: Prochlorperazine induces akathisia in emergency patients. *Ann Emerg Med* 1999; 34:469.
38. Hubert F, Friedman J: Classification and treatment of tardive syndromes. *Neurologist* 2003; 9:16.
39. Tarsy D, Baldessarini RJ, Tarazi FI: Effects of newer antipsychotics on extrapyramidal function. *CNS Drugs* 2002; 16:23.
40. Pappa S, et al: Effects of amantadine on tardive dyskinesia: A randomized, double-blind, placebo-controlled study. *Clin Neuropharmacol* 2010; 33:271.
41. Strawn J, Keck P, Caroff S: Neuroleptic malignant syndrome. *Am J Psychiatry* 2007; 164:6.
42. Caroff S, Mann S: Neuroleptic malignant syndrome. *Med Clin North Am* 1993; 77:185.
43. Rosebush P, Stewart T: A prospective analysis of 24 episodes of neuroleptic malignant syndrome. *Am J Psychiatry* 1989; 146:717.
44. Trollor JN, Chen X, Sachdev PS: Neuroleptic malignant syndrome associated with atypical antipsychotic drugs. *CNS Drugs* 2009; 23:477.
45. Margetic B, Margetic B: Neuroleptic malignant syndrome and its controversies. *Pharmacoepidemiol Drug Saf* 2010; 19:429.
46. Buton S, et al: Ziprasidone overdose. *Am J Psychiatry* 2000; 157:835.
47. Bryant S: A case series of ziprasidone overdoses. *Vet Hum Toxicol* 2003; 45:81.
48. Tolosa-Vilella C, et al: Olanzapine-induced agranulocytosis: A case report and review of the literature. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; 26:411.
49. Alper K, et al: Seizure incidence in psychopharmacological clinical trials: An analysis of Food and Drug Administration summary basis of approval reports. *Biol Psychiatry* 2006; 62:345.
50. Miller C, Fleischhacker W: Managing antipsychotic-induced acute and chronic akathisia. *Drug Saf* 2000; 22:73.
51. Reulbach U, et al: Managing an effective treatment for neuroleptic malignant syndrome. *Crit Care* 2007; 11:R4.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 162

OPIOIDS

Christina Hantsch Bardsley

PERSPECTIVE

Opioid is a term that applies to all natural, synthetic, and semisynthetic agents with morphine-like actions. It is more inclusive than the term *opiate,* which refers only to natural agents. Both terms are derived from *opium,* the Greek word for juice in reference to poppy juice. Poppy juice contains more than 20 distinct natural alkaloids with morphine-like activity. The nonspecific term *narcotic* refers to any agent that induces sleep and should not be used. *Opioid* is more precise and is the correct medical term for the agents that act on opiate receptors in the body. Finally, the term *endorphin* applies to any of the endogenous opioid peptides, including endomorphins, dynorphins, enkephalins, and nociceptin.[1]

Pharmacologic actions of opioids involve many organ systems, including the central nervous system (CNS), cardiovascular system, pulmonary system, and gastrointestinal system, and cause characteristic clinical effects. Sedation and analgesia are the most common therapeutic goals of opioid medications, which are available alone or in combination with other agents (e.g., acetaminophen and salicylates) for these purposes. In addition, opioids and combination preparations are used therapeutically for their antitussive and antidiarrheal effects.

The *World Drug Report 2010* of the United Nations Office on Drugs and Crime estimates that between 155 and 250 million people (3.5 to 5.7% of the population aged 15 to 64 years) used illicit substances at least once in 2008. Globally, cannabis, amphetamine-type stimulant, and cocaine users outnumber opiate (heroin/opium) users, but opiates are associated with more harm with use. Annual prevalence of opiate (heroin/opium) use in the United States is estimated at 0.58% of the population aged 15 to 64 years. Mortality rate for dependent opiate users is between 6 and 20 times that expected for those in the general population of the same age and gender.[2]

In addition, nonmedicinal use of prescription opioids, in adults and teens, is an extensive and growing problem in the United States. According to the Centers for Disease Control and Prevention (CDC), in 2010, enough opioid analgesics were sold to medicate every American adult with a typical dose of 5 mg of hydrocodone every 4 hours for 1 month.[3] Fatal poisonings involving opioid analgesics more than tripled from 4000 to 13,800 from 1999 to 2006, including a multistate epidemic of nonpharmaceutical fentanyl-related overdoses that resulted in more than 1000 deaths from April 2006 to March 2007.[4] This trend continues to rise, and in 2010 there were more than 15,000 opioid analgesic–related fatalities reported to the CDC.

PRINCIPLES OF DISEASE

Anatomy and Physiology

Although opioids have been used for more than 5000 years, opiate binding to brain membrane receptors was not shown until the 1970s, and the first opioid receptor gene was not isolated until 1992. Subsequent molecular characterization of the endogenous opioid system, including peptides and receptors, has improved the understanding of opioid physiologic roles.[5]

The three established opioid receptors, mu/MOP (*OPRM1* gene), kappa/KOP (*OPRK1* gene), and delta/DOP (*OPRD1* gene), are transmembrane, G protein–coupled receptors distributed throughout the CNS, concentrated in areas associated with nociception as well as in areas of euphoria and respiratory control. Systemically, opioid receptors are localized in sensory nerve endings, the gastrointestinal tract, cardiovascular endothelial cells, and immune cells.[5,6] Whereas opioid receptor ligand binding has demonstrated variable pharmacologic effects, whether it is through specific opioid receptor subtypes or receptor gene splice variants, receptor dimerization, or biased ligand agonism is unclear.[7] Genetic variations in opioid receptors and in metabolic pathways account for some of the interindividual differences in response to both endogenous and exogenous opioids. Several polymorphisms of *OPRM1* have been identified, including A118G polymorphism, present in up to 30% of individuals of European descent and 50% of Asian descent,[8] which is associated with increased dosage requirements for pain control. Whereas it might also result in lower relative clinical toxicity after overdose, this has not been studied. Polymorphisms of several cytochrome P_{450} enzymes, including CYP2D6 (tramadol, codeine), CYP3A5 (fentanyl), and CYP2B6 (methadone), have been linked to variability in response to several opioids.[9]

Pathophysiology and Pharmacology

Toxicity

Opioids include therapeutic agents and illicit substances. Toxicity occurs as a result of intentional overdose, intentional abuse, or adverse effect of therapeutic use. Although different opioids have receptor preferences in therapeutic or low doses, this specificity is lost at higher doses.

Opioids are well absorbed after gastrointestinal (oral and rectal) or parenteral administration but also through nasal, buccal, pulmonary, and transdermal routes, depending on the lipid solubility

www.ketabpezeshki.com 66485457-66963820

of the specific opioid.[1] Heroin is usually abused through intravenous and subcutaneous routes, but it is also absorbed after nasal administration because it is lipid soluble. In general, opioid toxicity is less pronounced but more prolonged with ingestion than with parenteral administration.[1] Absorption of opioids after ingestion occurs in the small intestine and with therapeutic doses is complete within 1 or 2 hours. However, because of delayed gastric emptying, absorption and clinical effects of toxicity may be prolonged after overdose.

Most opioids have a large volume of distribution. Clinical effects depend on lipid solubility, which affects the rate at which opioids and their metabolites cross the blood-brain barrier. All opioids undergo hepatic metabolism and renal elimination, and variations in hepatic and renal function are important because metabolite activity may contribute to clinical effects and toxicity.[1]

The pharmacokinetics of the specific agent determine the clinical course of opioid toxicity. Heroin peaks in the serum within 1 minute of intravenous injection, 3 to 5 minutes of intranasal administration, and 10 minutes of subcutaneous injection. Heroin's lipophilic nature allows rapid transport across the blood-brain barrier into the CNS. In the CNS and blood, heroin is rapidly hydrolyzed to 6-monoacetylmorphine and then morphine, which is less lipid soluble. In the liver, morphine undergoes conjugation with glucuronic acid to form more water-soluble compounds that are excreted by the kidneys.[1] Morphine and heroin are not metabolized by cytochrome P450 enzymes and are not directly affected by P_{450} polymorphisms.

Withdrawal

Because the half-life of heroin is 30 minutes and the half-life of methadone is 15 to 40 hours, withdrawal symptoms occur 4 to 6 hours after discontinuation of heroin and 24 to 48 hours after discontinuation of methadone.[10,11] Duration of symptoms is 7 to 10 days and 2 weeks, respectively. The degree of physical dependence that has developed is also important. With chronic opioid exposure, cellular adaptation results in upregulation of cyclic adenosine monophosphate (cAMP). When the exposure is discontinued or an antagonist is administered, the result is a temporary elevation of cAMP levels and increased sympathetic activity above a normal baseline.

CLINICAL FEATURES

Toxicity

The toxidrome of opioid toxicity is CNS depression, respiratory depression, and miosis. Other potential findings are associated with toxicity from any opioid, but some symptoms are unique to a specific agent or route of exposure.

Neurologic

Direct CNS depression is well recognized, but hypoxia from CNS and respiratory depression also causes additional neurologic complications, such as seizures. Excitatory effects may also occur with opioid toxicity. Hypertonicity, myoclonus, and seizures have been reported with overdose of the synthetic opioids meperidine and propoxyphene. Meperidine-related seizures are probably caused by accumulation of normeperidine, especially after multiple or large doses or in patients with hepatic or renal insufficiency. Dysphoria and acute psychosis may occur with an agonist-antagonist opioid.

Parkinsonian symptoms in injection drug abusers have been attributed to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a side product during synthesis of a meperidine analogue in street laboratories. MPTP metabolite accumulates in CNS cell mitochondria and is associated with focal lesions in the substantia nigra and a syndrome clinically indistinguishable from idiopathic parkinsonism. The syndrome is irreversible in some patients.[12]

Spongiform leukoencephalopathy is associated with "chasing the dragon," a practice of inhaling heroin heated typically on aluminum foil. Patients have psychomotor retardation, dysarthria, ataxia, tremor, and other neurologic abnormalities.[13] This syndrome is thought to be related to a combination of mitochondrial injury and hypoxia from the heroin or, more likely, the method of preparation. One report also associates heroin-induced movement disturbance with basal ganglia lesions.[14]

Serotonin syndrome is a clinical triad of mental status changes, autonomic instability, and neuromuscular changes (see Chapter 151) and may be fatal. Most cases involve an interaction between a serotonergic agent and a second agent, usually a selective serotonin reuptake inhibitor or a monoamine oxidase inhibitor. Meperidine, dextromethorphan, methadone, and tramadol inhibit serotonin reuptake and are associated with serotonin syndrome, as are some opiate analogues without known serotonin reuptake effects, such as oxycodone and buprenorphine.[15]

Respiratory

By suppressing the sensitivity of the medullary respiratory center to hypercapnia, opioids decrease respiratory rate and tidal volume in a dose-dependent manner.[1] Although it initially remains intact, the hypoxic drive is overridden in severe poisoning or when antagonistic stimuli (e.g., pain) are blocked. Overdose of an agonist-antagonist agent produces less significant respiratory depression, presumably because of mu receptor antagonism (Table 162-1).

Table 162-1 Select Opioid Doses and Associated Respiratory Depression

DRUG	ORAL DOSE (mg)*	INTRAMUSCULAR DOSE (mg)*	TIME TO ONSET OF RESPIRATORY DEPRESSION†
Codeine	200	120	Fast
Dextromethorphan	700	—	Fast
Dihydrocodeine	150	60	Fast
Diphenoxylate	300	—	Slow (or even more delayed)
Fentanyl	—	0.125	Very fast
Heroin	15	3	Fast
Hydrocodone	100	—	Fast
Hydromorphone	6	1.5	Fast
Levorphanol	1	2	Fast
Meperidine	250	100	Fast
Methadone	20	10	Slow (or even more delayed)
Morphine	70	10	Fast
Oxycodone	30	10	Fast
Oxymorphone	6	1	Fast
Paregoric	175	—	Fast
Propoxyphene	600	—	Fast

*Equivalent to 10 mg of intramuscular morphine.
†Varies with the drug and route of administration. In addition, the effects of a dose in any particular patient depend on multiple factors, including age, weight, and comorbid conditions. After intramuscular administration, *very fast* means 5 to 30 minutes, *fast* means 15 to 60 minutes, and *slow* means 1 to 4 hours. After oral administration, these time definitions are approximately doubled.

www.ketabpezeshki.com 66485457-66963820

Central sleep apnea occurs with long-term opioid use and also with acute increased opioid use from baseline. Continuous positive airway pressure is usually ineffective for treatment of sleep apnea in these patients.[16]

Bronchospasm is rare with heroin use in both asthmatic and nonasthmatic patients after inhalational exposure and rarely after other routes. When it occurs, the bronchospasm is often severe, prolonged, and refractory to beta-agonist therapy, and it may require mechanical ventilation for several days. It is unclear whether the heroin, an adulterant, or a combination triggers the bronchospasm and whether the response is histamine mediated or from direct irritation.[17]

Acute lung injury occurs with therapeutic opioid use but is much more common after overdose.[18] The capillary leak is likely to be from hypoxia rather than a direct drug effect.

Ophthalmologic

In opiate overdoses, stimulation of mu receptors in the Edinger-Westphal nuclei of the third nerve usually results in miosis. Miosis is usually not seen with meperidine, propoxyphene, or diphenoxylate-atropine (Lomotil) overdose. Toxicity from agonist-antagonists (e.g., pentazocine) or multiple agents may not produce miosis.

Otologic

Sensorineural hearing loss has been reported with acute and chronic use of some opioids, including heroin, methadone, and hydrocodone, especially in combination with acetaminophen. Genetic polymorphism producing altered metabolism, direct cochlear effects, and comorbidities have been suggested as causative factors.[19,20]

Cardiovascular

Opioids cause mild hypotension and relative bradycardia. Hypotension is from histamine release and can be blocked by antihistamines (H_1 antagonists). The hypotension is typically orthostatic and resolves with supine positioning. In recent years, there are increasing reports of cardiovascular toxicity associated with certain opioids. Propoxyphene and especially norpropoxyphene, its cardioactive metabolite, are associated with sodium channel blockade, similar to type IA antidysrhythmic agents, and produce widening of the QRS complex.[21] In November 2010, because of dose-dependent PR interval prolongation, QRS widening, and QT prolongation, manufacturers voluntarily withdrew all proprietary and generic products containing propoxyphene from the United States market in response to a request from the Food and Drug Administration.[22] Levomethadyl, a three-dose per week opioid replacement for management of dependence, was discontinued in 2003 because of blockade of hERG potassium channels, resulting in QTc prolongation. Methadone also blocks this potassium channel and is associated with QTc prolongation, especially with other predisposing factors,[23] at higher doses, or with CYP2B6 polymorphism (resulting in delayed inactivation of methadone).

Gastrointestinal

Nausea and vomiting are common with therapeutic opioid use and overdose. Mechanisms include opioid-induced delayed gastric emptying, direct stimulation of the chemoreceptor trigger zone, and vestibular stimulation. Antihistamines and dopamine antagonists (e.g., chlorpromazine) may be effective in treatment.

Decreased gastrointestinal motility is common with therapeutic use and overdose of opioids. Severe cases may develop ileus.[1] Increased biliary tract pressures and choledochoduodenal sphincter spasm occur with therapeutic dosing of many opioids, including morphine, meperidine, and codeine. Spasm is not always reproducible within the same patient but seems related to individual susceptibility more than to a specific agent. Presenting clinical symptoms mimic biliary colic and may respond to naloxone or glucagon.[24]

Urologic

Opioids can cause urinary retention from urethral sphincter spasm and decreased detrusor tone. Alpha-adrenergic antagonists may reverse this effect. Glomerulosclerosis and renal amyloidosis are seen in end-stage "heroin nephropathy" of chronic opioid addicts.[25]

Dermatologic

Pruritus, flushing, and urticaria occur with certain opioids that release histamine (e.g., morphine) and do not represent a true allergy. Pruritus and erythema are often localized to the area of injection (e.g., along the vein through which the morphine was administered). Symptoms are typically easily controlled with antihistamines. Although all opioids have the potential to stimulate mast cell degranulation and histamine release, some (e.g., fentanyl) release only clinically negligible amounts of histamine and have good hemodynamic stability profiles.

Metabolic

Hypoglycemia occurs after opioid overdose, but the mechanism is unclear. Coingestants, especially ethanol, may contribute to this finding. Hypothermia is reported, but the mechanism is unclear. Hyperthermia should prompt a search for infectious complications, particularly in injection drug users, and for coingestants (e.g., cocaine and other stimulants) or adulterants (e.g., tripelennamine and scopolamine).[26]

Withdrawal

Opioid withdrawal occurs in tolerant individuals when opioid use is discontinued or an antagonist is administered. Increased sympathetic discharge and adrenergic hyperactivity are responsible for the clinical symptoms and signs. In contrast to the typical toxidrome of opioid toxicity (CNS and respiratory depression and miosis), withdrawal is associated with the opposite symptoms of CNS excitation, tachypnea, and mydriasis. Pulse and blood pressure are also increased. Although opioid withdrawal can be uncomfortable, it is not life-threatening.[10,11]

Neurologic manifestations are prominent in opioid withdrawal. Restlessness, agitation, and anxiety are virtually universal, and rare seizures may occur. Cognition and mental status are unaffected. Dysphoria and drug craving may be severe and prolonged.

Nausea, vomiting, diarrhea, and abdominal cramps can be significant and lead to dehydration and electrolyte depletion. Other symptoms may also include diffuse myalgias and insomnia. Signs include piloerection, yawning, lacrimation, rhinorrhea, and diaphoresis but are frequently absent.

DIAGNOSTIC STRATEGIES

The diagnosis of opioid intoxication is usually based on history and physical examination. Other than hypoglycemia, specific laboratory abnormalities are not seen. Carbon dioxide and oxygen saturation monitoring is helpful for identification of respiratory depression and hypoxia. When the patient has hypoxemia and pulmonary rales, a chest radiograph can evaluate for acute lung injury. A 12-lead electrocardiogram can confirm a suspected dys-

www.ketabpezeshki.com 66485457-66963820

rhythmia or evaluate for QRS widening or QT prolongation if propoxyphene or methadone overdose is suspected. An abdominal radiograph may identify packets of opioids or other illicit substances in a body packer (see Chapter 147 and Chapter 186). With ingestion of an unknown opioid preparation, acetaminophen and salicylate concentrations should be checked because many prescription opioids are available in combination products. Likewise, many illicit opioid users are exposed to additional drugs and contaminants.

Opiates are detected on most qualitative antibody-based enzymatic immunoassay urine toxicology screens. Semisynthetic and synthetic opioids, such as fentanyl and its derivatives, are often missed on typical urine screens unless they are specifically included or the assay cross-reacts. A urine test result is positive for days after last use, depending on the half-life. Poppy seed ingestion leads to a positive opiate screen for morphine and codeine; however, detection of 6-monoacetylmorphine, a specific metabolite of heroin, can confirm heroin use.[27]

As with opioid toxicity, no diagnostic test exists for opioid withdrawal.

DIFFERENTIAL CONSIDERATIONS

The diagnosis of opioid intoxication is usually based on history and physical examination, although patients with other intoxications or nontoxicologic conditions may have a similar presentation. Other drugs that should be considered are clonidine (or a related drug), tramadol, valproic acid, γ-hydroxybutyrate, and sedative-hypnotic agents. The differential diagnosis encompasses all causes of depressed mental status, but the coexistence of miosis and respiratory depression greatly narrows the possibilities.

Opioid withdrawal is usually a straightforward diagnosis, and the patient typically reveals it as the chief complaint. Simultaneous intoxication with or withdrawal from other classes of agents, especially CNS depressants and stimulants such as cocaine in a "speedball," is common.

MANAGEMENT

Attention to the airway, oxygenation, and ventilation, including airway protection and ventilatory support, is of primary and vital importance.

Gastrointestinal Decontamination

Gastrointestinal decontamination is not routinely recommended, and there is no convincing evidence that it provides any benefit. Despite this, whole-bowel irrigation has been used to hasten passage of drug packets from body packers, body stuffers, or patients with ingestions involving opioid combination products or multidrug ingestions. Although it is unnecessary because of an effective opioid antidote and of no demonstrated benefit, a single early dose of activated charcoal (1 g/kg in children and 50-100 g in adults) may be considered in rare circumstances after consultation with a poison center or toxicologist.[28]

Antidote with Opioid Antagonist

Naloxone, a pure opioid antagonist with a rapid onset of action, is the most useful antidote. It is ineffective after oral administration secondary to the first-pass effect, but intravenous, subcutaneous, intramuscular, inhalational, and endotracheal routes can be used. Naloxone competitively binds opioid receptors and can reverse all the receptor-mediated actions of opioids. Naloxone is indicated for patients with opioid intoxication who have significant CNS or respiratory depression. The initial intravenous dose is 0.4 to 2 mg for adults and children, but 10 mg (total initial dose) may be required to obtain a clinical response for synthetic opioids.

Naloxone can precipitate acute withdrawal in chronic opioid users. In this population, naloxone should be started at 0.04 to 0.2 mg and then slowly titrated. The duration of action of naloxone is 1 or 2 hours. Consequently, either repeated doses or a continuous infusion may be required, starting at two thirds of the effective initial dose, given per hour.[1]

Naloxone has an excellent safety profile. Acute lung injury, hypertension, and dysrhythmia have been rarely associated with use of naloxone after general anesthesia and in patients with underlying cardiac or pulmonary disease.[29] Whether naloxone is the cause of these complications is unproven. Idiosyncratic reactions and sympathetic discharge with precipitation of acute withdrawal have been proposed as explanations. The risk may be greater in those with ongoing hypoventilation before naloxone administration. Complete clinical recovery in response to naloxone is strongly suggestive of opioid overdose. Naloxone has been given to overdoses with valproic acid, clonidine, tramadol, and captopril and ethanol intoxication because of a presentation similar to opioid intoxication. These have been reported to improve to lesser degrees and inconsistently with naloxone. The mechanism of these responses to naloxone is not established. Some of these drugs may have activity at opioid receptors.[29]

Nalmefene is an opioid antagonist with a long half-life (8-11 hours) and duration of clinical effect. Intravenous nalmefene has a rapid onset of action in reversal of opioid-induced CNS and respiratory depression. Alternative administration routes are oral, subcutaneous, and intramuscular. The initial intravenous dose is 0.5 to 1.5 mg (the pediatric dose is not established). Higher doses have been used but are associated with increased risk of adverse effects.[30,31] When a clinical response has been achieved with nalmefene, repeated doses or continuous infusions are generally not required; however, the duration of induced withdrawal symptoms may be longer with nalmefene. Naloxone remains the preferred antidote in patients at risk for withdrawal or other adverse effects and in patients with anticipated short duration of opioid toxicity.

Supportive Care

Patients with acute lung injury may require oxygen and positive-pressure modalities, such as bi-level positive airway pressure, continuous positive airway pressure, or mechanical ventilation with positive end-expiratory pressure. Circulatory support usually does not require more than a crystalloid infusion. Seizures associated with opioid toxicity resolve with correction of hypoxia, correction of hypoglycemia, or administration of benzodiazepines. Most opioids have a large volume of distribution and cannot be cleared by dialysis. There are no clinically effective techniques for enhanced elimination of opioids.

Withdrawal

Opioid withdrawal is not life-threatening, but supportive and symptomatic care can decrease the distress and avoid the associated complications. When withdrawal is produced by administration of naloxone, the symptoms are of short duration.[10,11] Other patients with withdrawal can receive clonidine or symptomatic treatment (antiemetics, antidiarrheals, benzodiazepines) to alleviate symptoms in the emergency department (ED). In addition, fluid and electrolyte replacement is important for patients with dehydration from gastrointestinal symptoms.

Methadone, a long-acting opioid, provides opioid replacement to treat or to prevent withdrawal in chronic heroin users admitted for other medical conditions but should not be used for patients in the ED with uncomplicated acute withdrawal. The onset of

www.ketabpezeshki.com 66485457-66963820

action of an initial dose of methadone of either 20 mg orally or 10 mg intramuscularly is 30 to 60 minutes. This initial dose typically controls significant symptoms.[10] Some symptoms, particularly drug craving, may be ongoing and require a subsequent dose after several hours. Maintenance methadone therapy requires doses every 24 hours or may be tapered daily. In October 2002, the Food and Drug Administration approved a buprenorphine monotherapy product (Subutex) as well as a buprenorphine-naloxone combination product (Suboxone) for treatment of opioid addiction. In contrast to methadone, these products may be prescribed by physicians outside of traditional opioid treatment programs, but prescribing physicians must have a specific Drug Enforcement Administration waiver per the Drug Addiction Treatment Act of 2000.[32]

Clonidine, a central alpha$_2$-agonist, is used for treatment of opioid withdrawal without opioid replacement.[10] Clonidine controls symptoms by suppressing sympathetic hyperactivity. It may also shorten the duration of withdrawal. The initial dose is 0.1 mg orally. Repeated doses may be given every 30 to 60 minutes; relatively large total doses may be required. As with opioid replacement, clonidine therapy is titrated to individual clinical response. Hypotension may limit the treatment but is not common in the setting of opioid withdrawal treatment. Patches for transdermal administration of clonidine are available, but onset of action is delayed 24 hours. Oral doses still must be given initially.

Buspirone is an azapirone compound used to treat ethanol and nicotine addiction. Studies suggest that it may also be an option to treat opioid addicts by decreasing serotonergic neurotransmission in withdrawal, but further investigation is needed before ED use.[33]

DISPOSITION

Toxicity

Patients with opioid toxicity are often treated successfully in the ED, sometimes in conjunction with the ED observation unit. Patients who receive naloxone should be observed for 2 hours to assess the extent of resedation, hypoxia, and pulmonary complications.[34] Full reversal of opioid toxicity may produce an awake patient who is uncooperative with the observation duration. If these patients are discharged against medical advice, they should demonstrate decision-making capacity as well as a full understanding of the risks of return of severe toxicity and development of complications, including apnea. Asymptomatic patients can be observed in the ED until 4 hours after an ingestion, at which time they can be discharged with appropriate psychiatric evaluation or drug abuse counseling. However, patients who have ingested an opioid with a longer half-life, active metabolite, or modified-release preparation, as well as patients with multiple drug ingestions involving an opioid, may require longer observation periods.

Asymptomatic patients who have a known or possible ingestion of diphenoxylate-atropine (Lomotil) should be observed in a monitored unit; this includes small children who may have ingested only a single tablet (2.5 mg of diphenoxylate and 0.025 mg of atropine). The metabolite of diphenoxylate, difenoxin, has a longer half-life and is five times more active than diphenoxylate, and it may cause delayed and prolonged toxicity. Delayed absorption, caused by each component of Lomotil and enterohepatic recirculation, may contribute as well.[35]

Patients with a known or potential ingestion of packets of illicit opioid drugs, body packers and body stuffers, remain asymptomatic until one or more of the packets leak. Minimum necessary observation duration for these patients if they are asymptomatic is not clear. Body packers are typically admitted until the packets are passed; body stuffers may be discharged after 6 hours.[36]

Withdrawal

Patients with opioid withdrawal may be managed as outpatients. Clonidine may alleviate some of the symptoms of withdrawal but has a high incidence of postural hypotension. Patients with refractory complications (e.g., vomiting, dehydration, and electrolyte abnormalities) and patients with an uncertain diagnosis may require hospitalization. Some patients may need to be detoxified before entering chemical treatment programs. Substance abuse counseling and establishment of outpatient program referral should be completed before discharge.

KEY CONCEPTS

- Diagnosis of opioid intoxication is based on history, physical examination, and response to naloxone.
- The opioid toxidrome includes three prominent findings—CNS depression, respiratory depression, and miosis—but these may not be present in every patient.
- Airway protection and management, ventilation, and early administration of naloxone are crucial to management of patients with opioid toxicity.
- The duration of action of many opioids, especially after overdose, is significantly longer than that of naloxone. Patients responsive to naloxone should be observed for recurrence of opioid toxicity after the effect of naloxone has resolved.
- Opioid withdrawal syndrome does not include altered cognition. Patients with known or suspected opioid withdrawal who also have altered cognition should be evaluated for another cause of the altered cognition.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Yakesh T, Wallace MS: *Opioids, analgesia, and pain management*. In: Brunton LL, Chabner BA, Knollmann BC, eds: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 12th ed. New York: McGraw-Hill; 2011:481.
2. United Nations Office on Drugs and Crime: *World Drug Report 2010* (United Nations Publication, Sales No. E.10.XI.13). Available at www.unodc.org.
3. Centers for Disease Control and Prevention: Vital signs: Overdoses of prescription opioid pain relievers—United States, 1999-2008. *MMWR Morb Mortal Wkly Rep* 2011; 60:1487-1492.
4. Warner M, Chen LH, Makuc DM: *Increase in Fatal Poisonings Involving Opioid Analgesics in the United States, 1999-2006. NCHS Data Brief, No 22*. Hyattsville, Md: National Center for Health Statistics; 2009.
5. Kieffer BL, Evans CJ: Opioid receptors: From binding sites to visible molecules in vivo. *Neuropharmacology* 2009; 56(S1):205.
6. Dhawan BN, et al: International Union of Pharmacology XII classification of opioid receptors. *Pharmacol Rev* 1996; 48:567.
7. Dietis N, Rowbotham DJ, Lambert DG: Opioid receptor subtypes: Fact or artifact? *Br J Anaesth* 2011; 107:8.
8. Mague SD, Blendy JA: OPRM1 SNP (A118G): Involvement in disease development, treatment response and animal models. *Drug Alcohol Depend* 2010; 108:172.
9. Argoff CE: Clinical implications of opioid pharmacogenetics. *Clin J Pain* 2010; 26:S16.
10. Olmedo R, Hoffman RS: Withdrawal syndromes. *Emerg Med Clin North Am* 2000; 18:273.
11. Jenkins DH: Substance abuse and withdrawal in the intensive care unit. *Surg Clin North Am* 2000; 80:1033.
12. Ballard PA, Tetrud JW, Langston JW: Permanent human parkinsonism due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP): Seven cases. *Neurology* 1985; 35:949.
13. Chang WC: MRI features of spongiform leukoencephalopathy following heroin inhalation. *Neurology* 2006; 67:504.
14. Mätzler W, Nägele T, Gasser T, Krüger R: Acute parkinsonism with corresponding lesions in the basal ganglia after heroin abuse. *Neurology* 2007; 68:414.
15. Isenberg D, Wong SC, Curtis JA: Serotonin syndrome triggered by a single dose of suboxone. *Am J Emerg Med* 2008; 26:840.e.3.
16. Mogri M, Khan MI, Grant BJ, Mador MJ: Central sleep apnea induced by acute ingestion of opioids. *Chest* 2008; 133:1484.
17. Cygan J, Trunsky M, Corbridge T: Inhaled heroin–induced status asthmaticus: Five cases and a review of the literature. *Chest* 2000; 117:272.
18. Soto J, Sacristan JA, Alsar MJ: Pulmonary oedema due to fentanyl. *Anaesthesia* 1992; 47:913.
19. Yorgason JG, Kalinec GM, Luxford WM, Warren FM, Kalinec F: Acetaminophen ototoxicity after acetaminophen/hydrocodone abuse: Evidence from two parallel in vitro mouse models. *Otolaryngol Head Neck Surg* 2010; 142:814.
20. Shaw KA, Babu KM, Hack JB: Methadone, another cause of opioid-associated hearing loss: A case report. *J Emerg Med* 2011; 41:635.
21. Stork CM, et al: Propoxyphene-induced wide QRS complex dysrhythmia responsive to sodium bicarbonate: A case report. *J Toxicol Clin Toxicol* 1995; 33:179.
22. FDA Drug Safety Communication: FDA Recommends Against the Continued Use of Propoxyphene. Available at www.fda.gov/drugs/drugsafety/ucm234338.htm.
23. Hanon S, Seewald RM, Yang F, Schweitzer P, Rosman J: Ventricular arrhythmias in patients treated with methadone for opioid dependence. *J Interv Card Electrophysiol* 2010; 28:19.
24. Bird KJ: Narcotic-induced choledochoduodenal sphincter spasm reversed by naloxone. *Anaesthesia* 1986; 41:1120.
25. Dubrow A, et al: The changing spectrum of heroin-associated nephropathy. *Am J Kidney Dis* 1985; 5:36.
26. Perrone J, Shaw L, DeRoos F: Laboratory confirmation of scopolamine co-intoxication in patients using tainted heroin. *J Toxicol Clin Toxicol* 1999; 37:491.
27. Tenore PL: Advanced urine toxicology testing. *J Addict Dis* 2010; 29:436.
28. Von Westphal V, Jacobsen P: Time limits for gastrointestinal decontamination in poisoning. *Ugeskr Laeger* 2009; 171:718.
29. Chamberlain JM, Klein BL: A comprehensive review of naloxone for the emergency physician. *Ann Emerg Med* 1994; 12:650.
30. Kaplan JL, et al: Double-blind randomized study of nalmefene and naloxone in emergency department patients with suspected narcotic overdose. *Ann Emerg Med* 1999; 34:42.
31. Chumpa A: Nalmefene hydrochloride. *Pediatr Emerg Care* 1999; 15:141.
32. U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration: Buprenorphine. Available at www.buprenorphine.samhsa.gov.
33. Van den Brink W, Haasen C: Evidence-based treatment of opioid-dependent patients. *Can J Psychiatry* 2006; 51:635.
34. Etherington J, et al: Is early discharge after naloxone reversal of presumed opioid overdose? *CJEM* 2000; 2:157.
35. McCarron MM, Challoner KR, Thompson GA: Diphenoxylate-atropine (Lomotil) overdose in children: An update. *Pediatrics* 1991; 87:694.
36. Moreira M, Buchanan J, Heard K: Validation of a 6-hour observation period for cocaine body stuffers. *Am J Emerg Med* 2011; 29:299.

www.ketabpezeshki.com 66485457-66963820

Chapter 163

Pesticides

James W. Rhee

PERSPECTIVE

Pesticides, a generic term used to refer to all pest-killing agents, include numerous chemicals intended for use as insecticides, herbicides, rodenticides, fungicides, and fumigants. Many of these chemicals are general protoplasmic poisons affecting a wide range of organisms, including humans. These chemicals can be organized in general classes with associated characteristic clinical pictures that are important to recognize because patients with acute (and occasionally chronic) exposures to these agents come to the emergency department. In addition, other pesticides with particularly unique mechanisms of toxic effects are described.

ORGANOPHOSPHATE AND CARBAMATE INSECTICIDES

The first organophosphate insecticide, triethyl pyrophosphate, was synthesized in 1859 but did not replace nicotine as a pesticide until World War II. After World War II, these compounds were used as chemical warfare agents, as organophosphorus and carbamate insecticides, and as medicinal agents. With concern about the long half-life of the organochlorine dichlorodiphenyltrichloroethane (DDT), causing it to accumulate in the environment, the organophosphate insecticides became the most common pesticides for home and industrial use. Since the increased awareness of terrorism in the 1990s, nerve agents have gained prominence as weapons of mass destruction.[1]

Principles of Disease

Organophosphorus insecticides are highly lipid soluble and are readily absorbed through dermal, gastrointestinal, and respiratory routes. This lipid solubility results in the buildup of organophosphorus compounds in body fat, and toxic systemic levels often occur from repeated low-level exposures. The parent compound and its metabolites are acetylcholinesterase inhibitors, and because many parent organophosphorus compounds are less potent than their metabolites (e.g., parathion to paraoxon), delayed onset of clinical toxicity can occur.

Organophosphorus pesticides work by persistently inhibiting the enzyme acetylcholinesterase, the enzymatic deactivator of the ubiquitous neurotransmitter acetylcholine. Because of the global penetration of organophosphorus compounds, inhibition occurs at tissue sites (true acetylcholinesterase and represented by erythrocyte or red blood cell [RBC] cholinesterase) and in plasma (circulating pseudocholinesterase).[2] Inhibition of cholinesterase results in the accumulation and subsequent prolonged effect of acetylcholine at a variety of neurotransmitter receptors, including sympathetic and parasympathetic ganglionic nicotinic sites, postganglionic cholinergic sympathetic and parasympathetic muscarinic sites, skeletal muscle nicotinic sites, and central nervous system sites (Fig. 163-1).

Clinical Features

Signs and Symptoms

The accumulation of acetylcholine results in the classic SLUDGE cholinergic syndrome, manifested by hyperactivity of cholinergic responses at the receptor sites indicated previously. The clinical syndrome of muscarinic acetylcholinesterase inhibition (Table 163-1) causes postganglionic acetylcholine-induced hollow end-organ general hypersecretion, resulting in clinical findings that include miotic pupils, lacrimation, rhinorrhea, sialorrhea, bronchorrhea, vomiting, diarrhea, and urinary incontinence. Bradycardia is a classic sign of the cholinergic syndrome, but the increased release of norepinephrine from postganglionic sympathetic neurons precipitated by excess cholinergic activity at sympathetic ganglia may result in normal or even tachycardic heart rates (nicotinic effect). Sympathetic hyperactivity can cause diffuse diaphoresis, although this response is mediated by cholinergic receptors at preganglionic (nicotinic) and postganglionic (muscarinic) sites. The most lethal components of acetylcholinesterase inhibition occur in the brain and neuromuscular junction. A combination of sympathetic stimulation, involvement of the *N*-methyl-D-aspartate (NMDA) receptor, and enhanced acetylcholine concentrations can induce seizures.[3] At the neuromuscular junction, excess acetylcholine causes hyperstimulation of the muscles with secondary paralysis, and when the diaphragm is affected, cholinesterase poisoning leads to respiratory arrest.[4]

Although the classic clinical picture of acute organophosphorus poisoning is impressive, toxicity from gradual, cumulative exposure may be much more subtle. These patients commonly exhibit vague confusion or other central nervous system complaints; mild visual disturbances; or chronic abdominal cramping, nausea, and diarrhea.

Complications

Seizures, pulmonary hypersecretion (bronchorrhea), and bronchoconstriction are prominent mechanisms of early morbidity and mortality in cases of poisoning from acetylcholinesterase inhibitors. Bronchorrhea is often incorrectly called noncardiogenic pulmonary edema because the origin of the excessive pulmonary fluids is airway secretions, not transudation of fluid across the alveolar-capillary membrane. The obstruction of upper and lower airways, the potential intrusion of these bronchial secretions

www.ketabpezeshki.com 66485457-66963820

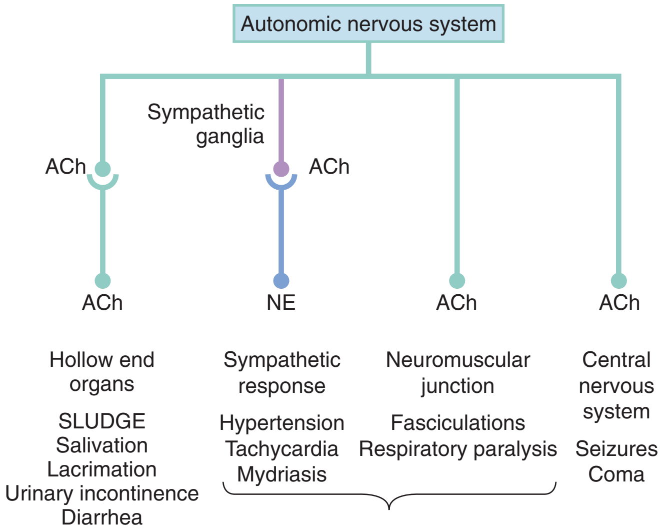


Figure 163-1. The autonomic nervous system comprises the sympathetic and parasympathetic nervous systems. The sympathetic nervous system is also known as the thoracolumbar outflow; the cell body lies in the spinal cord, and the first synapse occurs in the sympathetic ganglia. The neurotransmitter in this first synapse is acetylcholine (*ACh*, preganglionic), and the neurotransmitter in the postganglionic neuron with the target organ is norepinephrine (*NE*). In the parasympathetic nervous system (craniosacral outflow), nerves from the medulla and sacrum use ACh as the neurotransmitter in preganglionic and postganglionic target organs. The autonomic nervous system is divided further into the muscarinic and nicotinic receptors; atropine can block the muscarinic receptors but not the nicotinic receptors. The neuromuscular junction uses ACh as the effector neurotransmitter. In the brain, ACh is just one of several active neurotransmitters.

Table 163-1 SLUDGE Symptoms or DUMBELS

Salivation	**D**iarrhea/**D**iaphoresis
Lacrimation	**U**rination
Urinary incontinence	**M**iosis
Defecation	**B**radycardia/**B**ronchorrhea/**B**ronchospasm
Gastrointestinal cramps	**E**mesis
Emesis	**L**acrimation **S**alivation

into alveolar sacs, and bronchoconstriction produce hypoxia, which is the primary concern in the initial stages of poisoning.

Nicotinic hyperstimulation of skeletal muscle leads to significant morbidity and mortality associated with acetylcholinesterase inhibitor toxicity. Signs of skeletal muscle hyperactivity include involuntary twitches, fasciculations, and hyperactive reflexes. Muscle hyperactivity eventually progresses to muscle fatigue and paralysis, including the respiratory musculature and particularly the diaphragm.[4] Respiratory insufficiency may be delayed and result in death if it is not anticipated and corrected by mechanical or pharmacologic means.

Acetylcholinesterase inhibitors produce direct toxic effects on the central nervous system, leading to neurologic signs of confusion, combativeness, seizures, and coma. Status epilepticus may occur in severely poisoned patients. Structural central nervous system damage may occur if seizures are not terminated rapidly.[5]

A unique effect of organophosphorus insecticides results from "aging," the irreversible conformational change that occurs when the organophosphorus agent is bound to the cholinesterase enzyme for a prolonged time, causing clinical effects to persist for a prolonged time. On average, some aging for commercial organophosphorus agents will occur by 48 hours but may take longer. Once the enzyme has aged, an oxime antidote cannot regenerate the cholinesterase.

Diagnostic Strategies

Any patient with a clinically apparent cholinergic syndrome should be treated empirically without waiting for laboratory confirmation of decreased cholinesterase activity. Known or suspected exposure to cholinesterase inhibitors can be evaluated by ordering of plasma and erythrocyte (RBC) cholinesterase levels. However, these levels will not be readily available in most clinical settings. The patient's signs and symptoms should guide the management in the emergent time frame.

After acute exposures, the plasma cholinesterase levels decrease first, followed by decreases in RBC cholinesterase levels. The RBC cholinesterase level correlates best with activity at the nerve terminal.[2] Patients with chronic exposures may have a normal plasma cholinesterase level but have reduced RBC cholinesterase activity, which will confirm the poisoning. The true reflection of depressed cholinesterase activity is found in the RBC activity, and even a mild acute exposure may result in severe clinical poisoning. The RBC cholinesterase level recovers at a rate of 1% per day in untreated patients and takes approximately 6 to 12 weeks to normalize, whereas plasma cholinesterase levels may recover in 4 to 6 weeks. Other laboratory studies should focus on the evaluation of pulmonary, cardiovascular, and renal function and fluid and electrolyte balance. Patients presenting with no acidosis or only a metabolic acidosis on the arterial blood gas analysis have mortality lower than that of patients with a respiratory or mixed acidosis.[6]

Differential Diagnosis

Few toxins or other clinical conditions produce the same constellation of symptoms as acetylcholinesterase inhibitors. A species of mushroom, *Amanita muscaria,* historically has been mentioned in the differential diagnosis, but it actually contains alkaloids that usually produce an anticholinergic (antimuscarinic) syndrome. Conditions that induce excessive vagal responses (e.g., inferior wall myocardial infarction) may also produce some signs suggesting acetylcholinesterase inhibition, but other symptoms should make the primary cause apparent.

Management

Treatment is directed toward four goals: (1) decontamination, (2) supportive care, (3) reversal of acetylcholine excess at muscarinic sites, and (4) reversal of toxin binding at active sites on the cholinesterase molecule.

Decontamination should start in the out-of-hospital phase to prevent further absorption and subsequent toxicity and to protect care providers. Because dermal exposure is most likely, removal and destruction of clothing and thorough flushing of exposed skin may limit absorption and subsequent toxicity. Alternatively, dermal decontamination can be done with dry agents, such as military resins, flour, sand, or bentonite. Caregivers are at risk for contamination from splashes or handling of contaminated clothing. Treating personnel may be rotated to limit their exposure to the organophosphates.[4] Caregivers should use universal precautions, including eye shields, protective clothing, and nitrile or butyl rubber gloves. In the case of ingestion, gastrointestinal decontamination procedures are of questionable benefit because of the rapid absorption of these compounds. Profuse vomiting

www.ketabpezeshki.com 66485457-66963820

and diarrhea are seen early in ingestion and may limit[7] or negate any beneficial effect of additional gastrointestinal decontamination.[8,9] The administration of activated charcoal after ingestion has no proven benefit in these poisonings.[10]

Equipment, but not skin, may be washed with a 5% hypochlorite solution to inactivate the cholinesterase inhibitor.

Because death is due to airway and respiratory failure, supportive care should be directed primarily toward airway management and include suctioning of secretions and vomitus, oxygenation, and, when necessary, ventilatory support. Succinylcholine can be used for intubation but may have an extremely prolonged duration (up to 3 to 7 hours) as it is metabolized by acetylcholinesterase, which is inhibited in this setting.[2] It is preferable to use a competitive neuromuscular blocking agent, such as rocuronium, for rapid sequence intubation in these patients, but increased dosing may be necessary. Although some authors have advocated the use of beta-blockers to control tachycardia, this may increase cardiovascular instability and worsen bronchospasm.[8,11] Most cardiovascular effects from organophosphates rarely require specific therapy.

The definitive treatment of acetylcholinesterase inhibition starts with atropine. A competitive inhibitor of acetylcholine at muscarinic receptor sites, atropine reverses the clinical effects of cholinergic excess at parasympathetic end-organs and sweat glands. Large doses of atropine may be required.[12] Data suggest that the more rapid the atropinization, the faster control is obtained.[8,9] Suggested dosing is 1 or 2 mg of atropine (0.02-0.05 mg/kg) intravenously, with doubling of each subsequent dose every 5 minutes until there is control of mucous membrane hypersecretion and the airway clears.[4,8,9,13] If intravenous access is not immediately available, atropine may be administered intramuscularly. Patients may require 200 to 500 mg of atropine intravenously during the first hour, followed by prolonged continuous infusions of 5 to 100 mg/hr to maintain adequate secretion control.[13] Tachycardia and mydriasis may occur at these doses, but they are not indications to stop atropine administration. The endpoint of atropinization is drying of respiratory secretions, easing of respiration, and mean arterial pressure greater than 60 mm Hg.[13] Animal evidence suggests that early rapid atropinization may limit seizure propagation and, in conjunction with diazepam, prevent status epilepticus.[5] Atropine is not active at nicotinic sites and does not reverse the skeletal muscle effects (e.g., muscle fatigue and respiratory failure).[2,9] Other anticholinergic medications, such as diphenhydramine or ophthalmic agents, may have benefit if atropine is scarce or unavailable; however, optimal intravenous dosing is not known.[14]

The second part of acetylcholinesterase inhibition treatment is the use of an oxime, such as pralidoxime (2-PAM, Protopam) or obidoxime (Toxogonin), to regenerate the organophosphate-acetylcholinesterase complex and to restore cholinesterase activity at muscarinic and nicotinic sites.[2,4,9,15] There are several dosing regimens; the most common dose of pralidoxime is 1 or 2 g intravenously (pediatric dose, 25-50 mg/kg); additional doses may be given on the basis of clinical response. The medication may be given in a bolus of 1 or 2 g intravenously during 30 to 60 minutes every 4 to 8 hours or 500 mg/hr (pediatric dose, 10-25 mg/kg/hr).[15,16] The World Health Organization recommends an initial dose of 30 mg/kg, followed by 8 mg/kg/hr continued for at least 24 hours or, if an infusion cannot be used, 30 mg/kg every 4 hours.[17] The infusion may be continued for several days with no adverse effects attributable to the pralidoxime; however, rapid administration can lead to hypertension, vomiting, and a transient reversible neuromuscular blockade.[18] The ideal dose of pralidoxime should be determined by monitoring of the clinical condition of the patient and serial cholinesterase levels; the patient may require higher doses of oxime than are recommended here. The World Health Organization–recommended infusion dose of obidoxime is 4 mg/kg, followed by 0.5 mg/kg/hr; alternatively, intermittent intravenous doses of 4 mg/kg, then 2 mg/kg, every 4 hours are given.[17] Pralidoxime and obidoxime can be administered by intramuscular injection. Indications for oxime therapy include respiratory depression or apnea, fasciculations, seizures, arrhythmias, cardiovascular instability, and use of large amounts of atropine. Oxime therapy can be used whenever the patient requires more than a limited amount of atropine (2-4 mg) to completely reverse the signs and symptoms of intoxication or in any patient who requires repeated doses of atropine. Oxime therapy and atropine are synergistic.

In the past, pralidoxime was used only within the first 24 hours because of aging of the organophosphate-acetylcholinesterase complex, but not all organophosphates behave in a similar manner. Dimethyl and diethyl phosphoryl insecticides react differently at variable rates with acetylcholinesterase and oxime therapy. Many organophosphates are highly lipid soluble and slowly leach out of fat stores for up to 6 weeks, resulting in newly formed complexes with excellent clinical reversal of the cholinesterase inhibition by pralidoxime and by measurements of cholinesterase activity. Pralidoxime can also combine with unbound organophosphates and prevent their subsequent binding to nerve terminals. Even with optimal treatment, seriously intoxicated patients may require long-term supportive care, including ventilator support.[4,16]

Several studies have looked at the efficacy of pralidoxime.[19,20] The results have been mixed and may be due to the variability among different organophosphates. Until this variability is further elucidated, pralidoxime administration in patients with organophosphate toxicity is still recommended.

In conjunction with atropine and the oxime pralidoxime, patients with agitation, seizures, and coma should be treated with adequate doses of a benzodiazepine after the airway has been secured.[4,5,21] Although diazepam is most studied, any parenteral benzodiazepine may be used. The military has classically used diazepam autoinjectors for intramuscular injection, but midazolam is the best intramuscular agent, with lorazepam as an alternative.

Sarin, soman, tabun, and VX are nerve agents that might be used in a terrorist attack. These agents have important differences from the common household or commercial organophosphorus insecticides. These agents tend to age very quickly; tabun (GA) ages in 14 hours, sarin (GB) in 5 hours, soman (GD) in 5 or 6 minutes, and VX in 48 hours. Because of this rapid aging, reversal of nerve agent poisoning with pralidoxime is time sensitive. VX is an oily but highly toxic agent with low volatility. It does not readily vaporize, and because it has a low risk of inhalation, exposure is predominantly transcutaneous. The other agents can be mostly dispersed into the air by explosion or vaporization, resulting in inhalation exposure. These agents do not require the extremely large doses of atropine but do require pralidoxime.[22-24]

New therapies for treatment of organophosphorus poisoning, including the use of *N*-acetylcysteine and exogenous acetylcholinesterase, show promise in research studies.[25,26] When they are added to anticholinergics, NMDA receptor antagonists may decrease organophosphorus compound–induced seizures.[27]

Disposition

Because of the prolonged effects of acetylcholinesterase inhibition, most patients with significant exposures require hospital admission. On occasion, a person with chronic exposure, depressed cholinesterase levels, and mild visual or gastrointestinal symptoms may be observed on an outpatient basis; however, some patients, particularly those exposed to fenthion, initially present with signs and symptoms of mild exposure and progress to severe, life-threatening toxicity over time.[28] If plasma cholinesterase levels are

www.ketabpezeshki.com 66485457-66963820

available, they may be useful for treatment and disposition decisions. Asymptomatic or minimally symptomatic patients with normal or minimally depressed levels may be discharged after 4 to 6 hours with close outpatient follow-up to ensure that progressive toxicity does not occur. Patients who arrive with known severely depressed levels (usually associated with significant symptoms) require admission and close monitoring, usually in a high-intensity care unit. Patients may have rebound toxicity several days after apparently satisfactory response to initial treatment. Rebound toxicity may occur for many reasons, including persistent release of organophosphates from lipid stores.

A secondary syndrome, the intermediate syndrome (IMS), occurs 24 to 96 hours after exposure and consists of proximal muscle weakness specifically of the respiratory muscles. It is believed to be an abnormality at the neuromuscular junction. Patients with IMS present with respiratory failure several days after the acute cholinergic symptoms have resolved and may require several weeks of ventilatory support. It is theorized that this may be a result of inadequate initial oxime treatment or premature discontinuation of oxime therapy.[4,29] Oximes may be beneficial for IMS; however, this is controversial.[30]

Finally, organophosphorus delayed neuropathy has been reported as a different entity. It affects an axonal enzyme, neurotoxic esterase, with a peripheral sensorimotor neuropathy 7 to 21 days after exposure.[4]

CARBAMATE INSECTICIDES

Carbamate insecticides are another class of acetylcholinesterase inhibitors and are differentiated from the organophosphorus compounds by their relatively short duration of toxic effects. Carbamates inhibit acetylcholinesterase for minutes to 48 hours, and the carbamate-cholinesterase binding is reversible. Although the clinical picture of acute carbamate poisoning may be identical to that of organophosphate poisoning, the toxic effects are limited in duration, and patients may require only decontamination, supportive care, and treatment with adequate doses of atropine. Although the duration is limited, patients may become just as ill and require assisted ventilation and seizure therapy. The use of pralidoxime is controversial in carbamate poisoning; an animal study suggests that pralidoxime administration may produce greater toxicity in cases of carbaryl (Sevin) poisoning.[31] Nevertheless, if doubt exists as to whether a severe poisoning is due to a carbamate or organophosphate, pralidoxime should be administered.

CHLORINATED HYDROCARBON INSECTICIDES

DDT, the prototype of chlorinated hydrocarbon insecticides (sometimes referred to as organochlorine insecticides), was first used extensively during World War II for control of typhus and malaria and widely used in the United States as a general insecticide after the war. Because of the effectiveness of DDT, many other chlorinated hydrocarbon insecticides were developed and used extensively in agricultural, commercial, and residential pest control. Although these insecticides were effective, their widespread use, long half-life, and persistence had negative ecologic repercussions. Many of these insecticides have been targeted as persistent organic pollutants by international agencies, leading to their restricted use.[32]

Although chlorinated hydrocarbon insecticides are no longer used in the United States for agricultural use, γ-hexachlorobenzene, better known as lindane (Kwell), is still used as a topical medicinal agent for the treatment of head lice and scabies. As a result, lindane is probably the most common cause of toxicity from an organochlorine compound in the United States. Given its toxicity, lindane is no longer a first-line agent for the treatment of scabies.[33] In 2001, California issued a ban on the use and sale of lindane, and other states are considering a ban on lindane.[32]

Principles of Disease

Chlorinated hydrocarbon pesticides are highly lipid soluble. They are readily absorbed through dermal, respiratory, and gastrointestinal routes. Dermal and gastrointestinal exposures account for most clinical poisonings, including inappropriate external use of lindane or other compounds and the occasional accidental oral administration of lindane. Because they are so lipid soluble, these compounds are stored in fatty tissues, and repeated small exposures result in accumulation and eventual clinical toxicity.

Chlorinated hydrocarbon insecticides primarily affect axonal membranes, resulting in neuronal irritability and excitation. Toxicity occurs in central and peripheral neurons. Some of the organochlorines can inhibit the chloride channel of γ-aminobutyric acid (GABA) receptors, leading to decreased inhibition of the central nervous system. Chlorinated hydrocarbons induce hepatic microsomal enzymes and produce hepatic tumors in some animals. This potential carcinogenicity is the basis for human health concerns, but it is only theoretic. Chlorinated hydrocarbon insecticides, including chlorinated hydrocarbon solvents, may sensitize the myocardium to circulating catecholamines and increase susceptibility to ventricular dysrhythmias, such as tachycardia and fibrillation.

Clinical Features

Signs and Symptoms

The primary clinical picture of acute or cumulative toxicity from chlorinated hydrocarbon pesticides is related to their neurotoxicity. Premonitory peripheral signs and symptoms, such as tremor or paresthesias, may be absent, and the first sign of toxicity may be seizure activity.[34] Additional signs include confusion, combativeness, and muscle twitching. Untreated, continued muscle activity can lead to hyperthermia, metabolic acidosis, and rhabdomyolysis with secondary acute tubular necrosis. Because many of these agents are halogenated, ventricular dysrhythmias may occur from catecholamine sensitization and direct myocardial toxic effects. Immediate hepatotoxicity is unlikely without secondary hyperthermia or other metabolic complications. Long-term exposure may result in neuropsychiatric symptoms.[35] Diagnosis may be difficult in chlorinated hydrocarbon pesticide exposure because the patient may be unable to provide a history. Nonhospital personnel are often in the best position to obtain information on pesticide availability and the situation surrounding the exposure. Another clue is the solvent odor and oily feel of the hydrocarbon solvent containing the highly lipid-soluble chlorinated hydrocarbon pesticides.

Diagnostic Strategies

Diagnosis should be confirmed by history or by investigation at the site of the exposure to establish the offending agent with certainty. No specific tests are readily available to confirm the diagnosis of chlorinated hydrocarbon pesticide poisoning. Some reference laboratories can measure fat and plasma levels, but results are difficult to interpret and seldom available during the acute phase of toxicity. Ancillary laboratory and other studies should be based on the clinical condition, complications, and consideration of alternative diagnoses on an individual basis.

www.ketabpezeshki.com 66485457-66963820

Differential Considerations

The differential diagnosis includes virtually every condition that produces seizures. The specific diagnosis depends on obtaining the history of significant acute or chronic chlorinated hydrocarbon pesticide exposure.

Management and Disposition

Skin decontamination with soap and water may reduce toxicity in acute dermal exposure. High lipid solubility results in rapid absorption, and gastrointestinal decontamination is not of benefit. Elimination of some chlorinated hydrocarbon insecticides can be increased, and repeated doses of cholestyramine (4 g orally every 8 hours) given during a mass exposure of chlordecone (a chlorinated hydrocarbon insecticide) enhanced the fecal elimination of this compound.[35-37]

The primary objective is seizure control, best accomplished with short-acting benzodiazepines or barbiturates. Recurrent seizures or status epilepticus may require high-dose barbiturates and paralyzing agents (e.g., pancuronium or vecuronium) to prevent secondary morbidity from continuous motor activity in prolonged seizures. The seizure activity is usually self-limited, lasting only 1 or 2 days even in severe cases.[34,36,38]

Continuous cardiac monitoring during the acute phase is indicated because of the potential for myocardial sensitization. Ventricular dysrhythmias are most likely to occur during seizure activity because of the high circulating catecholamine levels and other metabolic abnormalities present during seizures. Dysrhythmias should be treated with beta-adrenergic antagonists, such as propranolol, metoprolol, or esmolol, to reduce the effect of catecholamines on the myocardium.

Additional treatment should focus on the complications of prolonged seizure activity, such as rapid external cooling measures for hyperthermia. Metabolic acidosis is almost always transient and resolves spontaneously without treatment. Rhabdomyolysis and myoglobinuria should be anticipated. Because of their high lipid solubility, chlorinated hydrocarbon pesticides are distributed largely in tissues and are not amenable to hemoperfusion or dialysis.

Patients who have acute or cumulative chlorinated hydrocarbon pesticide toxicity require hospitalization until their seizures are controlled, complications have resolved, and they have returned to their neurologic baselines, usually within 1 or 2 days. Severe complications, such as renal failure from rhabdomyolysis, may prolong the clinical course.

SUBSTITUTED PHENOLS

The substituted phenols include dinitrophenol (DNP), pentachlorophenol, and dinitrocresol. These compounds have been used since the 1930s as insecticides, termiticides, herbicides, and wood preservatives. They are currently used in agricultural, commercial, and residential applications, including over-the-counter preparations for home gardeners. Substituted phenols such as DNP are abused as weight reduction agents and occasionally in illegitimate weight reduction operations.[39]

Principles of Disease

Substituted phenols are readily absorbed through the skin and gastrointestinal tract, and aerosols may be absorbed through the respiratory tract. There is some potential for cumulative toxicity with repeated exposures, but much less than with the organophosphorus and chlorinated hydrocarbon pesticides.

Substituted phenols produce their toxicity by uncoupling cellular oxidative phosphorylation; this leads to inefficient production of high-energy phosphate substrates and increased cellular use of oxygen, glucose, and water, with subsequent excess heat production. These compounds are commonly used during the summer when the external heat predisposes users to increased toxicity.[40] In addition, nitro-substituted phenols may produce methemoglobinemia.

Clinical Features

Patients with substituted phenol toxicity present hypermetabolic and hyperthermic, tachycardic, tachypneic, and profusely diaphoretic. They may also have a relative hypovolemia from excessive insensible fluid losses through sweating and metabolic consumption. Loss of energy production in the brain results in neurologic changes ranging from confusion to seizures and coma. Renal and hepatic injury is common, as is rhabdomyolysis with myoglobinuria. Because phenols are corrosive, patients with dermal exposures often have irritation or chemical burns, and some substituted phenols, such as DNP, produce a characteristic yellow staining of the skin or mucous membranes at the site of absorption. This same staining can be found throughout the internal organs at autopsy.

Cataracts are a complication of long-term exposure. This condition was common in patients who used substituted phenols as part of a weight reduction regimen and was partially responsible for the banning of this substance. The cataracts regress spontaneously after exposure is discontinued.

Diagnostic Strategies

Laboratory evaluation of patients with substituted phenol toxicity is aimed at identification of deficiency of aerobic metabolic substrates, including oxygen, glucose, and water. A complete blood count may reveal hemoconcentration and a nonspecific leukocytosis. Electrolyte abnormalities depend on the duration and severity of symptoms, environmental factors, and complications or underlying disease states. Arterial blood gas measurements show varying degrees of acidosis, depending on the extent of anaerobic metabolic activity due to oxidative phosphorylation uncoupling and associated tissue hypoperfusion from dehydration. Serum enzyme determinations document the extent of hepatic, renal, and skeletal muscle injury. The presence of phenolic compounds in the urine of a patient with this clinical picture strongly suggests substituted phenol pesticides as the cause.

Differential Considerations

Acute toxicity from substituted phenol poisoning is difficult to distinguish from environmental heat-related emergencies or toxicity from sympathomimetics or salicylates. Continued evidence of hypermetabolic activity and metabolic acidosis after routine cooling measures, rehydration, and other supportive care should suggest toxin-induced states. Persistent hyperthermia and acidosis in a weight lifter should trigger concern for DNP abuse. The presence of yellow staining virtually clinches the diagnosis.

Management and Disposition

Initial treatment is directed toward control of body temperature; treatment of acidosis; protection of the kidneys, brain, and liver from hyperthermic damage; and provision of the basic substrates for excessive metabolic activity—oxygen, glucose, and water. If the chemical exposure is known or recognized, early skin decontamination is important. Therapy should be directed toward prevention or minimization of the associated complications discussed previously.

www.ketabpezeshki.com 66485457-66963820

Patients with mild toxicity can usually be stabilized after a few hours and discharged from the emergency department. Patients with significant organ system injury or prolonged or recurrent seizures, significant alteration of consciousness, and rhabdomyolysis require admission, usually to the intensive care unit.

CHLOROPHENOXY COMPOUNDS

The chlorophenoxy pesticides were developed in the early 1940s and hailed as a selective herbicide particularly effective against broadleaf weeds. This class of herbicide developed a special notoriety during the Vietnam War as Agent Orange, a defoliant used in aerial spraying, consisting of a mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Unfortunately, 2,4,5-T is almost always contaminated with isomers of tetrachlorodibenzodioxin. This concern for dioxin exposure has led to the extensive medical investigations of Vietnam veterans and severe restrictions on the production and use of 2,4,5-T.[41] Because of the relative safety and broadleaf selectivity of 2,4-D, however, most home gardeners have at least one chlorophenoxy compound on a shelf in their garage, and some old cans may contain 2,4,5-T or a mixture of both compounds.

Principles of Disease

Chlorophenoxy compounds may be absorbed through the skin, gastrointestinal tract, and respiratory tract, but almost all significant poisonings are a result of accidental or intentional ingestion. The lipid solubility of these compounds is low, and excretion is fairly rapid, so cumulative toxicity from repeated exposures does not occur.[42]

Although skeletal muscle is the target organ for chlorophenoxy herbicides, the exact mechanism is unknown. Depending on severity, muscle abnormalities may range from generalized muscle weakness to acute rhabdomyolysis. Higher doses may also uncouple oxidative phosphorylation and cause a hypermetabolic state similar to that seen with the substituted phenols.

Clinical Features

Similar to most organic pesticides in an organic solvent, the chlorophenoxy herbicides may produce mild, nonspecific dermal and gastrointestinal irritation with nausea, vomiting, and gastrointestinal distress. Large exposures are likely to cause systemic symptoms ranging from diffuse myotonia and muscle fasciculations progressing to rhabdomyolysis, hyperthermia, and a hypermetabolic state with metabolic acidosis.[43]

Diagnostic Strategies

There are no specific tests for the detection of the chlorophenoxy compounds. Laboratory evaluation should be aimed at evaluation of skeletal muscle injury and its complications. Severely poisoned patients require generalized organ system evaluation, including hepatic and renal function, because of the effects of rhabdomyolysis and hyperthermia.

Differential Considerations

Differential diagnostic possibilities include other causes of acute myopathy. The manifestation of chlorophenoxy compound toxicity is extremely rare, however, and without a definite history or strong suspicion of exposure, other explanations for acute myopathy should be pursued.

Management and Disposition

Treatment consists of initial skin decontamination and basic supportive care. Serious toxic effects develop within 4 to 6 hours after ingestion, and treatment can be directed toward the specific problems of muscle weakness, airway and ventilatory support, and rhabdomyolysis. Treatment of hyperthermia and acidosis has been discussed previously.

Asymptomatic or minimally symptomatic patients may be discharged after 4 to 6 hours of observation. Patients with muscle effects should be admitted for close observation and monitoring of respiratory effort.

BIPYRIDYL COMPOUNDS

The bipyridyl (also called dipyridyl) compounds paraquat and diquat were first investigated in the late 1950s and early 1960s. They are extremely effective contact herbicides that are rapidly inactivated by the surrounding soil in the event of overspray. Paraquat is activated when it is exposed to sunlight, which led to its use as the herbicide of choice during aerial spraying of marijuana by the U.S. and Mexican governments. After spraying, however, growers simply would harvest the crops before the plants were exposed to enough sunlight to damage them, resulting in an apparently healthy harvest but one contaminated with paraquat. The burning of marijuana pyrolyzes paraquat into a nontoxic form, a fact that was lost in the warning messages dispensed by the government at that time.[44]

Principles of Disease

Of the two bipyridyl compounds in use, paraquat is the most significant in terms of number of cases and toxic effects. Paraquat use is tightly regulated in the United States but is widespread throughout the world. Diquat is less regulated in the United States and is included in some formulations of herbicides sold for residential use. Paraquat is absorbed through the skin, gastrointestinal tract, and respiratory tract. Almost all fatal exposures have resulted from the ingestion of paraquat, although a few case reports have involved extensive skin contamination. Toxicity has occurred, but no fatal cases have been reported from inhalation of paraquat vapor or aerosols. Diquat is poorly absorbed through intact skin, and most cases of toxicity result from ingestion.[45]

Paraquat's toxic effect is from the production of superoxides created during cyclic oxidation-reduction reactions of the compound in tissues. Lipid peroxidation of cellular membranes seems to be one significant pathway of cellular injury.[46,47]

Paraquat selectively concentrates in the lungs because of an amine uptake mechanism in alveolar cells. In addition, high concentrations of oxygen significantly increase the extent of paraquat-induced injury so that the lungs are the major target organs. The pathophysiologic lesions include direct injury to the alveolar-capillary membrane followed by surfactant loss, adult respiratory distress syndrome, progressive pulmonary fibrosis, and respiratory failure. Paraquat damages other major organ systems by the same cellular membrane effects, including the liver, kidneys, heart, and central nervous system. Diquat has similar effects, with most of its toxicity concentrated in the kidneys rather than in lung tissue.[45]

Clinical Features

Signs and Symptoms

Both agents are extremely corrosive and cause nausea, vomiting, and severe chemical burns of the oropharynx soon after ingestion.

www.ketabpezeshki.com 66485457-66963820

Patients who ingest concentrated paraquat frequently die of esophageal perforation and mediastinitis before development of the characteristic progressive pulmonary injury. Patients with dermal paraquat exposures show significant skin irritation, and ocular exposures may produce severe corneal burns.

The paraquat-induced pulmonary injury usually progresses during 1 to 3 weeks, although the clinical course varies considerably with severity of poisoning, involvement of other organ systems, and underlying medical problems. This is not a factor in the emergency department, and the delayed pulmonary injury is not discussed here. Diquat usually spares the lungs but produces similar toxicity in all other organ systems.[45]

Diagnostic Strategies

Paraquat is measurable in the blood. As long as the time of acute exposure is known, the level serves as an accurate prognostic marker. The assay is not readily available in the United States, and by the time the results are obtained, nothing can be done to change the eventual outcome. There is a qualitative bedside test that uses the reduction of paraquat or diquat in alkalinized urine by sodium dithionite, but the reagent frequently is not available.[43] Studies should evaluate caustic gastrointestinal injury and pulmonary and renal damage.

Differential Considerations

A person with acute paraquat or diquat ingestion is likely to present with an acute corrosive injury; the differential diagnosis should encompass all corrosive agents. Successful therapeutic intervention for paraquat toxicity is extremely time dependent, and patient outcome depends on the history. Any patient who has evidence of pulmonary or other organ injury from paraquat exposure is probably already beyond recovery.

Management and Disposition

There are no studies comparing various treatment strategies, but the key to successful treatment of an acute paraquat exposure probably depends on early decontamination measures to limit absorption. There are no effective treatments once clinical effects are seen. Thorough skin cleansing is obvious and straightforward in dermal exposures. Careful gastric lavage and administration of activated charcoal may be lifesaving and should be undertaken in consultation with a poison center or a medical toxicologist. These treatments may be hazardous in the context of a corrosive ingestion. Early endoscopy and surgical intervention may be necessary if there is evidence of esophageal perforation and mediastinitis. Although fuller's earth and bentonite are recommended as adsorbents in paraquat ingestions, activated charcoal is much more readily available in the United States and has equal if not greater efficacy.

Oxygen treatment can theoretically exacerbate paraquat toxicity by the production of superoxides. Therefore, oxygen should be used only as minimally necessary in these cases.

Although it is controversial, many experts recommend rapid initiation of charcoal hemoperfusion to rapidly lower plasma paraquat levels and to limit pulmonary and other organ system uptake of paraquat. Many also recommend serial and combined hemoperfusion and hemodialysis, particularly during the first 24 hours after exposure.

Cyclophosphamides in combination with corticosteroids have also been investigated as a means to attenuate paraquat toxicity.[48,49] Whereas the results have been mixed, this therapy has been recommended by some experts in the setting of significant paraquat toxicity.

There are other suggested treatment adjuncts, such as *N*-acetylcysteine, nitric oxide, deferoxamine, and cytoprotective agents such as amifostine, but no single therapy has proved consistently successful.[50]

Patients with any significant dermal paraquat exposure and all patients with ingested paraquat require hospitalization and consideration of enhanced elimination therapy. These patients should be observed and treated expectantly until paraquat levels, if available, are reported to be nonexistent or nontoxic.

PYRETHRINS AND PYRETHROIDS

Pyrethrins are naturally occurring insecticides of the yellow *Chrysanthemum cinerariifolium* and *Tanacetum cinerariifolium* and are among the oldest known insecticides, first used in the 1800s. Extracts of the dried flowers contain the active compound pyrethrum, which contains six naturally occurring pyrethrins. In addition, numerous synthetic derivatives, pyrethroids, have been produced and have greater chemical stability than the natural pyrethrins. Type II pyrethroids contain a cyano substituent and are among the more toxic formulations of this class. These present a potential danger to humans, but type II pyrethroids are generally less toxic than many of the other classes already discussed and are being used more commonly.

Principles of Disease

Because pyrethrins and pyrethroids are most commonly aerosolized, inhalation is the most likely route of exposure. The patient may not be aware of an exposure because pyrethrin and pyrethroid aerosols are used frequently as automated insect sprays in public areas, such as in airplanes. In these situations, concentrations rarely reach levels likely to produce symptoms in any but the most sensitized patient. Occasional ingestions have been reported, and significant toxicity is possible by this route. Systemic absorption through the dermal route is unlikely, but topical effects are possible. Most pyrethrins and pyrethroids are rapidly metabolized and deactivated in human exposure, so cumulative toxicity is not a problem. Piperonyl butoxide, which is added as an insect "knock-down" agent, may increase the toxicity of the pyrethrum derivatives.

Pyrethrins and pyrethroids have a variety of effects in humans and other mammals.[51,52] Clinically, the naturally occurring pyrethrins can cause sensitization and allergic phenomena, but this does not occur with the synthetic pyrethroids. Both classes are associated with sodium channel blockade, slowing the rate of activation of the sodium channel and extending the time during which the channel is open. In addition, both classes affect GABA receptors, inhibiting chloride channel function. Less significant effects include potentiation of nicotinic cholinergic neurotransmission, enhancement of norepinephrine release, and inhibition of calcium adenosine triphosphatase interference with sodium-calcium exchange across membranes.[51,52]

Clinical Features

Effects are very rare. Allergic manifestations, including potentially life-threatening events, may occur after acute inhalation or dermal exposure. Inhalation exposure often occurs with the use of a pyrethrin-based aerosol in an enclosed, poorly ventilated space. Local effects include lacrimation, rhinitis, rhinorrhea, sneezing, throat irritation, and pharyngeal and laryngeal edema. Lower respiratory effects include cough, shortness of breath, chest pain, and wheezing. Rashes are consistent with a contact or allergic dermatitis, and photosensitivity may contribute to the dermatologic picture. There is potential for allergic cross-reactivity in patients who are allergic to ragweed.

www.ketabpezeshki.com 66485457-66963820

Sodium channel–mediated and GABA-mediated chloride channel effects mediate neurologic signs and symptoms. Facial paresthesias have been reported, and seizures occur with massive ingestions.[51,52] Nonspecific symptoms, such as headache, fatigue, dizziness, and weakness, are also reported.

Diagnostic Strategies

No laboratory tests are available to measure pyrethrins or pyrethroids in a clinical setting.

Differential Considerations

The differential diagnosis of the signs and symptoms of pyrethrin or pyrethroid toxicity includes the usual causes of bronchospasm and seizures and other acute neurologic complications.

Management and Disposition

Decontamination, including removal from a contaminated environment or washing, should be the first step. Definitive treatment is supportive and directed at the respiratory and neurologic complications.

Disposition of a patient with exposure to pyrethrins depends on the severity of the underlying complications. If discharge from the emergency department is anticipated, the patient should be counseled with regard to the possibility of recurrent allergic phenomena on reexposure.

GLYPHOSATE

Glyphosate was introduced as a broad-spectrum nonselective herbicide in 1971. It is the isopropyl ammonium salt of a non–cholinesterase-inhibiting organophosphate herbicide. It is sold mixed with the surfactant polyoxyethylene amine (POEA). Because it is effective on broadleaf weeds and does not undergo photodecomposition, it is popular in the home market, known as Roundup. Newer formulations of residential-use herbicides may contain glyphosate in conjunction with diquat.

Principles of Disease

Glyphosate is poorly absorbed through the skin so that most exposures result from ingestion. The concentrated solution is extremely irritating, and patients may vomit with subsequent aspiration. The concentrated solution is provided as 41% glyphosate in 15% POEA. The directions state that it should be diluted to a 1% glyphosate solution.

Glyphosate is toxic to plants by inhibition of the enzyme 5-enolpyruvylshikimate-3-phosphate synthase in the shikimic acid metabolic pathway. After application of glyphosate on the leaves, it is transported to the roots, where the enzyme is active. Humans lack this enzyme and do not have enzyme-related toxicity. Reported toxicity is believed to result largely from the surfactant POEA and may reflect the direct corrosive effect from the amine salt, or it may uncouple oxidative phosphorylation.[53]

Clinical Features

Most ingestions of the dilute solution cause only minimal symptoms, including gastrointestinal distress. Patients ingesting large volumes of dilute solutions or moderate volumes of concentrated solutions complain of sore throat, nausea, abdominal pain, and fever. They may have vomiting, diarrhea, respiratory distress, noncardiogenic pulmonary edema, dysrhythmias, shock, coma, and renal failure. Acidosis reflects poor tissue perfusion and cardiovascular compromise.[53] Negative prognostic indicators include shock, acidosis, and persistent hyperkalemia.[53]

Diagnostic Strategies

The critical element in diagnosis is history of ingestion. Laboratory analysis may demonstrate an anion gap metabolic acidosis, hypoxemia, and hyperkalemia. Elevated transaminases may occur in 30% of ill patients, and signs of renal failure may develop in persistent shock states. The electrocardiogram may show ventricular dysrhythmias and secondary signs of hypoxemia.[53]

Differential Diagnosis

The differential diagnosis includes most corrosive ingestions and causes of shock. The findings of hyperkalemia and metabolic acidosis may suggest hydrofluoric acid ingestions. A normal ionized calcium level may help rule out hydrofluoric acid exposure. Any cause of aspiration should also be considered. The history is the most useful factor in the differential diagnosis.

Management and Disposition

Treatment is supportive. The patient may require positive-pressure ventilation to overcome the noncardiogenic pulmonary edema. POEA may also be a direct cardiac depressant; inotropic agents can be useful. Hyperkalemia should be treated in the usual manner with fluids, medications to shift potassium into the cell (e.g., bicarbonate, calcium, and beta-adrenergic agonists), and Kayexalate. If there is an indication of significant corrosive ingestion, early endoscopy with placement of stent, high-dose steroids, and laparotomy may be considered.

Asymptomatic patients with small ingestions of dilute substances may be observed for 6 hours and discharged. Patients with complaints consistent with corrosive ingestions should be admitted and have a gastrointestinal evaluation. Patients with pulmonary complaints require admission and intensive supportive care.

DEET

N,*N*-Diethyl-*m*-toluamide or *N*,*N*-diethyl-3-methylbenzamide (DEET) is not a pesticide but an insect repellent. It is the most widely used chemical insect repellent in the United States. DEET was developed by scientists at the U.S. Department of Agriculture in 1946, patented by the U.S. Army soon thereafter, and released to the general public in 1957.[54] With the prevalence of Lyme disease and other concerning arthropod-borne diseases, the use of DEET has greatly increased. Formulations containing DEET range from 5 to 100%. The U.S. Army routinely used 75% solutions until 1987 but now uses a 35% time-release, polymer-based formulation. The American Academy of Pediatrics recommends 30% as the maximum concentration for use in infants and children and does not recommend use of DEET in infants younger than 2 months.[55]

Principles of Disease

DEET is lipophilic and can be absorbed through the skin. Skin absorption and toxicity increase with repeated applications, increased ambient temperatures, sweating, and abraded, thin skin. Ingestion may lead to toxicity.[56] DEET primarily affects the central nervous system. Its mechanism of action is unknown. It may sensitize the skin and cause allergic reactions.

www.ketabpezeshki.com 66485457-66963820

Clinical Features

Prolonged skin contact may lead to contact dermatitis, and prolonged contact with high concentrations has led to skin blisters. Patients who have ingested DEET or have repeated skin applications in a hot enclosed environment that enhances absorption have developed liver function test abnormalities and neurologic findings, including encephalopathy, seizures, movement disorders, and coma.[56] Most exposures to DEET result in no or minimal toxicity and should not preclude its use in susceptible populations in which significant arthropod-borne diseases are prevalent.[57]

Diagnostic Strategies

Exposure history is central to the diagnosis. Although DEET can be detected in urine, most laboratories are not able to do this testing during the acute toxicity phase. An electroencephalogram may be useful in a patient with coma or encephalopathy and seizures.

Differential Diagnosis

The differential diagnosis includes conditions that may cause encephalopathy, seizures, and movement disorders. Such conditions include drug intoxication, infectious causes, drug interactions, and structural defects.

Management and Disposition

Treatment is supportive. If DEET exposure is suspected, the skin should be thoroughly decontaminated. Oils or lipophilic agents should be avoided because they enhance skin absorption. After DEET ingestion, milk products and oil-containing foods should be avoided until the gastrointestinal tract has eliminated the offending agent. Seizures should be treated with benzodiazepines.

Asymptomatic patients who have ingested DEET-containing repellents should be observed for 4 to 6 hours. Patients who have neurologic symptoms should be admitted and observed.

KEY CONCEPTS

- All patients exposed to cholinesterase inhibitors should have skin decontamination. Health care personnel need to be protected during this process.
- Morbidity in cholinesterase inhibitor exposure results from early airway compromise secondary to copious secretions, status epilepticus, and late respiratory failure.
- Cholinesterase inhibitor exposure may include bradycardia or tachycardia, hypertension or hypotension, and miosis or mydriasis.
- The clinical endpoint for atropine administration is drying of airway secretions.
- Pralidoxime should be given to all organophosphorus-poisoned patients who require atropine regardless of time since exposure.
- With chlorinated hydrocarbon exposures, skin decontamination with protection of personnel is indicated.
- In chlorinated hydrocarbon exposures, supportive care, temperature control, and seizure control are important and catecholamine administration is avoided.
- Rapid cooling and glucose are the two most important therapies in substituted phenol toxicity.
- Diagnosis of chlorophenoxy compound toxicity depends on a history of accidental or deliberate ingestion.
- Rapid gastrointestinal decontamination is indicated in paraquat and diquat ingestions despite the corrosive injury.
- The predominant form of pyrethrin and pyrethroid toxicity is allergic.
- Small ingestions of dilute glyphosate solutions are gastrointestinal irritants. Large or concentrated ingestions may cause acidosis, hyperkalemia, and noncardiogenic pulmonary edema.
- DEET should not be applied over abraded or raw skin.
- DEET applications to children should be restricted to 30% solutions, should not be used under occlusive clothing, and should be washed off completely between applications.

ACKNOWLEDGMENT

I would like to thank Cynthia K. Aaron for her contributions as a previous author to this chapter.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. The Persian Gulf experience and health. NIH Technology Assessment Workshop Panel. *JAMA* 1994; 272:391.
2. Sener EB, Ustun E, Kocamanoglu S, Tur A: Prolonged apnea following succinylcholine administration in undiagnosed acute organophosphate poisoning. *Acta Anaesthesiol Scand* 2002; 46:1046-1048.
3. Johnson PS, Michaelis EK: Characterization of organophosphate interactions at *N*-methyl-D-aspartate receptors in brain synaptic membranes. *Mol Pharmacol* 1992; 41:750.
4. Johnson MK, et al: Evaluation of antidotes for poisoning by organophosphorus pesticides. *Emerg Med* 2000; 12:22.
5. Shih TM, Duniho SM, McDonough JH: Control of nerve agent–induced seizures is critical for neuroprotection and survival. *Toxicol Appl Pharmacol* 2003; 188:69.
6. Liu JH, et al: Acid-base interpretation can be the predictor of outcome among patients with acute organophosphate poisoning before hospitalization. *Am J Emerg Med* 2008; 26:24.
7. Petroianu G, Ruefer R: Poisoning with organophosphorus compounds. *Emerg Med (Fremantle)* 2001; 13:258.
8. Eddleston M, Roberts D, Buckley N: Management of severe organophosphorus pesticide poisoning. *Crit Care* 2002; 6:259.
9. Eddleston M, Singh S, Buckley N: Acute organophosphorus poisoning. *Clin Evid* 2003; 9:1542.
10. Eddleston M, et al: Multiple-dose activated charcoal in acute self poisoning: A randomised controlled trial. *Lancet* 2008; 371:579.
11. Sungur M, Guven M: Intensive care management of organophosphate insecticide poisoning. *Crit Care* 2001; 5:211.
12. Golsousidis H, Kokkas V: Use of 19 590 mg of atropine during 24 days of treatment, after a case of unusually severe parathion poisoning. *Hum Toxicol* 1985; 4:339.
13. Eddleston M, et al: Speed of initial atropinisation in significant organophosphorus pesticide poisoning: A systematic comparison of recommended regimens. *J Toxicol Clin Toxicol* 2004; 42:865.
14. Bryant SM, et al: Pretreating rats with parenteral ophthalmic antimuscarinic agents decreases mortality from lethal organophosphate poisoning. *Acad Emerg Med* 2007; 14:370.
15. Eddleston M, et al: Oximes in acute organophosphorus pesticide poisoning: A systematic review of clinical trials. *QJM* 2002; 95:275.
16. Worek F, et al: Reappraisal of indications and limitations of oxime therapy in organophosphate poisoning. *Hum Exp Toxicol* 1997; 16:466.
17. Feldman RJ, Szajewski J: *Cholingeric Syndrome*. IPIC INTOX Databank. Available at http://www.intox.org/databank/documents/treat/treate/trt15_e.htm. Accessed July 15, 2008.
18. Medicis JJ, et al: Pharmacokinetics following a loading plus a continuous infusion of pralidoxime compared with the traditional short infusion regimen in human volunteers. *J Toxicol Clin Toxicol* 1996; 34:289.
19. Eddleston M, et al: Differences between organophosphorus insecticides in human self poisoning: A prospective cohort study. *Lancet* 2005; 366:1422.
20. Eddleston M, et al: Pralidoxime in acute organophosphorus insecticide poisoning—a randomised controlled trial. *PLoS Med* 2009; 6:e1000104.
21. Shih T, McDonough JH Jr, Koplovitz I: Anticonvulsants for soman-induced seizure activity. *J Biomed Sci* 1999; 6:86.
22. Sidell FR, Borak J: Chemical warfare agents: II. Nerve agents. *Ann Emerg Med* 1992; 21:865.
23. Markenson D, Redlener I: Pediatric terrorism preparedness national guidelines and recommendations: Findings of an evidenced-based consensus process. *Biosecur Bioterror* 2004; 2:301.
24. Rotenberg JS, Newmark J: Nerve agent attacks on children: Diagnosis and management. *Pediatrics* 2003; 112:648.
25. Evron T, et al: Plant-derived human acetylcholinesterase-R provides protection from lethal organophosphate poisoning and its chronic aftermath. *FASEB J* 2007; 21:2961.
26. Yurumez Y, et al: Beneficial effect of *N*-acetylcysteine against organophosphate toxicity in mice. *Biol Pharm Bull* 2007; 30:490.
27. Dekundy A, et al: NMDA antagonists exert distinct effects in experimental organophosphate or carbamate poisoning in mice. *Toxicol Appl Pharmacol* 2007; 219:114.
28. Davies JO, Eddleston M, Buckley NA: Predicting outcome in acute organophosphorus poisoning with a poison severity score or the Glasgow coma scale. *QJM* 2008; 101:371.
29. Senanayake N, Sanmuganathan PS: Extrapyramidal manifestations complicating organophosphorus insecticide poisoning. *Hum Exp Toxicol* 1995; 14:600.
30. Karalliedde L, Baker D, Marrs TC: Organophosphate-induced intermediate syndrome: Aetiology and relationships with myopathy. *Toxicol Rev* 2006; 25:1.
31. Kurtz PH: Pralidoxime in the treatment of carbamate intoxication. *Am J Emerg Med* 1990; 8:68.
32. Humphreys EH, et al: Outcomes of the California ban on pharmaceutical lindane: Clinical and ecologic impacts. *Environ Health Perspect* 2008; 116:297.
33. Karr CJ, Solomon GM, Brock-Utne AC: Health effects of common home, lawn, and garden pesticides. *Pediatr Clin North Am* 2007; 54:63.
34. Jaeger U, et al: Acute oral poisoning with lindane-solvent mixtures. *Vet Hum Toxicol* 1984; 26:11.
35. Kilburn KH: Chlordane as a neurotoxin in humans. *South Med J* 1997; 90:299.
36. Aks SE, et al: Acute accidental lindane ingestion in toddlers. *Ann Emerg Med* 1995; 26:647.
37. Cohn WJ, et al: Treatment of chlordecone (Kepone) toxicity with cholestyramine: Results of a controlled clinical trial. *N Engl J Med* 1978; 298:243.
38. Cable GG, Doherty S: Acute carbamate and organochlorine toxicity causing convulsions in an agricultural pilot: A case report. *Aviat Space Environ Med* 1999; 70:68.
39. Miranda EJ, et al: Two deaths attributed to the use of 2,4-dinitrophenol. *J Anal Toxicol* 2006; 30:219.
40. Jorens PG, Schepens PJ: Human pentachlorophenol poisoning. *Hum Exp Toxicol* 1993; 12:479.
41. Kahn PC, et al: Dioxins and dibenzofurans in blood and adipose tissue of Agent Orange–exposed Vietnam veterans and matched controls. *JAMA* 1988; 259:1661.
42. Reifenrath WG, Hawkins GS, Kurtz MS: Percutaneous penetration and skin retention of topically applied compounds: An in vitro–in vivo study. *J Pharm Sci* 1991; 80:526.
43. Bradberry SM, et al: Mechanisms of toxicity, clinical features, and management of acute chlorophenoxy herbicide poisoning: A review. *J Toxicol Clin Toxicol* 2000; 38:111.
44. Landrigan PJ, et al: Paraquat and marijuana: Epidemiologic risk assessment. *Am J Public Health* 1983; 73:784.
45. Jones GM, Vale JA: Mechanisms of toxicity, clinical features, and management of diquat poisoning: A review. *J Toxicol Clin Toxicol* 2000; 38:123.
46. Wilks MF, et al: Improvement in survival after paraquat ingestion following introduction of a new formulation in Sri Lanka. *PLoS Med* 2008; 5:e49.
47. Fukushima T, et al: Mechanism of cytotoxicity of paraquat: I. NADH oxidation and paraquat radical formation via complex I. *Exp Toxicol Pathol* 1993; 45:345.
48. Lin JL, et al: A prospective clinical trial of pulse therapy with glucocorticoid and cyclophosphamide in moderate to severe paraquat-poisoned patients. *Am J Respir Crit Care Med* 1999; 159:357.
49. Perriens JH, et al: High-dose cyclophosphamide and dexamethasone in paraquat poisoning: A prospective study. *Hum Exp Toxicol* 1992; 11:129.
50. Wills BK, et al: The effect of amifostine, a cytoprotective agent, on paraquat toxicity in mice. *J Med Toxicol* 2007; 3:1.
51. Ray DE, Forshaw PJ: Pyrethroid insecticides: Poisoning syndromes, synergies, and therapy. *J Toxicol Clin Toxicol* 2000; 38:95.
52. Soderlund DM, et al: Mechanisms of pyrethroid neurotoxicity: Implications for cumulative risk assessment. *Toxicology* 2002; 171:3.
53. Lee HL, et al: Clinical presentations and prognostic factors of a glyphosate-surfactant herbicide intoxication: A review of 131 cases. *Acad Emerg Med* 2000; 7:906.
54. Fradin MS: Mosquitoes and mosquito repellents: A clinician's guide. *Ann Intern Med* 1998; 128:931.
55. American Academy of Pediatrics Committee on Environmental Health: Follow safety precautions when using DEET on children. *AAP News* 2003; 22:99.
56. Tenenbein M: Severe toxic reactions and death following the ingestion of diethyltoluamide-containing insect repellents. *JAMA* 1987; 258:1509.
57. Koren G, Matsui D, Bailey B: DEET-based insect repellents: Safety implications for children and pregnant and lactating women. *CMAJ* 2003; 169:209.

www.ketabpezeshki.com 66485457-66963820

Chapter 164

Plants, Mushrooms, and Herbal Medications

Richard D. Shih

PERSPECTIVE

Botanicals such as plants, herbal products, and mushrooms have a long-standing and important place in medical history. Their use as therapeutic agents has been documented in the earliest of medical writings. The extraction of alkaloids from the opium poppy in the 1800s was a forerunner of modern pharmacology. The general public increasingly is using herbal products for medicinal purposes. Despite the tremendous growth in popularity of herbal products, data on herbal efficacy and toxicity are limited. This chapter focuses not on the medicinal use of natural products but rather on the toxicology related to their exposure or utility.

Epidemiology

Although plants, mushrooms, and herbal products are derived naturally, they have different but predictable exposure patterns and epidemiology. Ingestions fall into three common exposure patterns.

Unintentional Childhood Exposure

Unintentional childhood exposure occurs most commonly with plants. Approximately 5% of all poison center calls involve plants. Of these, about 80% involve children younger than 5 years. Most of these cases involve household plants with a limited amount of plant material or toxin ingested, resulting in little or no toxicity.[1,2]

Misidentification of Botanical

Natural plant and mushroom gathering for personal food ingestion is a popular activity. Mistakes while foraging commonly occur, with the potential for serious toxicity and death. In contrast to unintentional childhood exposures, foraging accidents by adults usually involve the eating of plants or mushrooms and are associated with a much larger toxin burden because a larger quantity of the botanical is ingested. Another type of botanical misidentification occurs with herbal products when plants used for herbal manufacture are misidentified by the manufacturer and incorrectly packaged and marketed.

Plants as Drugs of Abuse

Many plants, mushrooms, and herbals are used and abused for their mind-altering potential. These include hallucinogenic mushrooms, peyote, kava kava, and anticholinergic plants such as jimsonweed.[3,4]

BOTANICAL IDENTIFICATION

Identification of the botanical in question is most useful, but most patients and medical professionals do not have enough knowledge of botany or plant identification. The name of the plant or mushroom is often confusing because the scientific name is not typically known, and common names often overlap. Most emergency department personnel cannot identify common plants, such as mistletoe, holly berries, philodendron, and others. Several resources may be helpful, including plant atlases, CD-ROM plant databases, a local botanical expert, botanical garden personnel, or a poison center. Alternatively, a digital photograph of the plant or mushroom in question can be quickly e-mailed to a local expert to aid in identification.[5] With herbal products, the product name or herbal plant may be known. Because of the limited Food and Drug Administration (FDA) regulation, however, the purported herb might have been harvested from the wrong plant or contaminated with other toxic material.

Plants

Among more than 60,000 plant exposures reported to U.S. poison centers annually, most plant exposures occur in children (younger than 5 years) and involve household plants. Hospitalization for plant poisoning is rare, and fatalities occur in less than one in 10,000 exposures. Of thousands of different plant species, only a few are dangerously toxic.[1,2,6] Following is a more detailed discussion of specific plants focusing on plants that are most poisonous or most commonly implicated in human exposures.[1,6]

Abrus precatorius

Abrus precatorius (Fig. 164-1), known by several different common names (jequirity pea, rosary pea, prayer bean, Seminole bean, Indian bean, and crab's eye), contains the toxin abrin, which affects protein synthesis, leading to cell death. The toxin is found in highest concentration in the seeds, which are used in jewelry or decoration. Because of their attractiveness, the seeds are often ingested by children. The hard, shiny coat causes most seeds to pass through the gastrointestinal tract without being digested. If the seeds are chewed or do not pass through the bowel rapidly and become digested, abrin is released, causing nausea, vomiting, and abdominal pain, which can be severe, and fluid and electrolyte balance is disturbed.[7-11] Systemic absorption of the toxin is limited because the protein is enzymatically digested in the gastrointestinal tract. Rare parenteral exposure of small amounts is associated with severe toxicity and possible death. Treatment is supportive, with attention to fluid rehydration and electrolytes. Symptomatic

www.ketabpezeshki.com 66485457-66963820

Figure 164-1. *Abrus precatorius* (jequirity pea or rosary pea). (Courtesy Steven Setzer.)

patients should be given activated charcoal to absorb leaking abrin, and whole-bowel irrigation has not been studied but may help in moving numerous seeds more rapidly through the gastrointestinal tract.

Brassaia

The *Brassaia* is a popular indoor plant known as schefflera, umbrella tree, Australian umbrella tree, dwarf schefflera, rubber tree, and starleaf. This plant contains calcium oxalate crystals, which can cause mouth pain, but most ingestions cause mild or no symptoms.

Capsicum annum

Capsicum annum includes many types of peppers (e.g., chili pepper, red pepper, bell pepper) and contains the active toxin capsaicin. This alkaloid releases and depletes selected nerve terminals of substance P, causing a severe local inflammatory response manifested by swelling, fluid exudation, and pain, which resolves rapidly as capsaicin depletes substance P. Capsaicin is not absorbed well through intact skin, but rarely symptoms can occur with prolonged and intense exposure.[12] Ingestions often cause gastrointestinal symptoms, depending on the amount of toxin exposure. Most capsaicin exposures are from a pepper spray product, causing chemical conjunctivitis. Keratitis can occur and is assessed with fluorescein. Treatment consists of local irrigation and analgesics. Despite their often dramatic appearance, cases resolve rapidly during several hours without sequelae.[13-15] Use of topical antacids may be effective for dermal exposures. Inhalation of capsaicin-containing powders is less common but can cause severe pulmonary exudation, potential acute respiratory distress syndrome, and death.[16] Treatment is supportive, but extracorporeal membrane oxygenation has been used in children who have acute respiratory distress syndrome.

Figure 164-2. *Cicuta maculata* (water hemlock). (Courtesy Steven Setzer.)

Cicuta maculata

Cicuta maculata (Fig. 164-2), commonly known as water hemlock, contains the potent neurotoxin cicutoxin.[17] Deaths from water hemlock are among the most commonly reported plant fatalities in the United States. Water hemlock has small white flowers at the ends of umbrella-like stems. They resemble *Daucus carota* (Queen Anne's lace) and *Heracleum lanatum* (cow parsnip). The mistaking of water hemlock for one of these edible plants is a common cause of exposure.[18] Ingestion of any part of the plant can lead to nausea, vomiting, and abdominal cramping. Severe toxicity is manifested by seizures occurring within the first hour, which often are intractable and are a common cause of death. The toxic mechanism may be due to γ-aminobutyric acid (GABA) receptor antagonism. The ingestion is highly toxic and may be fatal. Seizures are common and are initially treated with benzodiazepines (i.e., lorazepam, 1-2 mg intravenously). If response is poor, treatment is as described for status epilepticus in Chapter 102. Because of the severe toxicity and lack of effective antidote, activated charcoal may be useful. Consultation with a regional poison center may be useful in individual cases.

Conium maculatum

Conium maculatum (Fig. 164-3), or poison hemlock, was purported to be used in the execution of Socrates. It is mistaken for several edible plants, such as *Daucus carota* (Queen Anne's lace), *Foeniculum vulgare* (sweet fennel), and *Heracleum lanatum* (cow parsnip).[19] Poison hemlock contains the toxin coniine, which is similar to nicotine in structure and toxicity. The clinical picture and management resemble those of tobacco poisoning (see section on *Nicotiana tabacum*).[20,21]

Datura stramonium

Datura stramonium (jimsonweed) (Fig. 164-4) is one of numerous plants with alkaloids that have anticholinergic effects (see Chapter 150). The fruit is spiny and when opened contains 50 to 100 black seeds. All parts (including the seeds) contain the toxins atropine, hyoscyamine, and scopolamine, which are potent anticholinergic agents.[22,23] One hundred seeds approximate 6 mg of atropine.

www.ketabpezeshki.com 66485457-66963820

Figure 164-3. *Conium maculatum* (poison hemlock). (Courtesy Steven Setzer.)

Figure 164-4. *Datura stramonium* (jimsonweed). (Courtesy Steven Setzer.)

Exposures are most commonly a result of abuse for hallucinogenic effects, usually by smoking of dried leaves or ingestion of the seeds.[24-26] The clinical picture is that of the anticholinergic toxidrome.[27,28] The symptoms can last for several days if the overdose is due to ingestion of seeds. It is unclear if activated charcoal and gastric emptying measures are effective at decreasing the course of toxicity and are not routinely recommended. Consultation with a regional poison center may be useful in individual cases.[24] Treatment is as for anticholinergic poisoning[29,30] (see Chapter 150).

Dieffenbachia

Dieffenbachia (Fig. 164-5) has more than 30 different common names, including dumb cane, mother-in-law's tongue, dumb plant, and tuft root. Some of these names refer to the inability to talk that can occur after biting into parts of this plant. Typically, the mucous membranes of the mouth are affected immediately with severe pain, swelling, and the sensation of biting into glass. Most cases are limited to the mucous membranes of the oropharynx, but rare cases of airway compromise have been reported.[31] The local effects are due to calcium oxalate crystals, packaged into bundles called raphides, that are found in cellular structures called idioblasts.[32] These idioblasts also contain proteolytic enzymes that are ejected out of the idioblasts with the oxalate crystals when

Figure 164-5. *Dieffenbachia*. (Courtesy Steven Setzer.)

plant parts are chewed.[33,34] Because of the immediate pain, further exposure typically is limited. Treatment is aimed at pain relief and local supportive measures, typified by feeding of ice cream to a symptomatic infant. Analgesics such as nonsteroidal anti-inflammatory drugs or opioids may be needed for pain.

Epipremnum aureum

Epipremnum aureum is a common household plant also known as pothos ivy, devil's ivy, hunter's robe, and golden pothos. Toxicity is due to calcium oxalate crystals,[6] the same toxin found in the *Dieffenbachia*, and the toxicity and treatment are similar.

Eucalyptus

Eucalyptus plants have common names, such as the silver dollar, lemon-scented gum, cider gum, and blue gum. These plants are not toxic but are implicated in frequent plant exposures.[35] The plants are used, however, to produce concentrated (approximately 70%) eucalyptus oil. Ingestion of small amounts (1-3 mL) has been reported to cause severe toxicity.[36] The predominant symptoms are neurologic, including mental status alteration, headache, ataxia, and seizures. Treatment of severe toxicity is symptomatic supportive, except for seizures, which are treated as described in Chapter 102.

Euphorbia pulcherrima

Euphorbia pulcherrima (poinsettia) is a popular ornamental plant that is frequently implicated in plant exposures. It has a false reputation for being extremely poisonous. Ingestions are benign or cause minimal toxicity. However, contact dermatitis is relatively common with skin exposure and can be treated with steroids or antihistamines. Further discussion is found in Chapter 120.

Ilex

Ilex (holly) contains more than 400 different species and is frequently implicated in plant exposures. The plant's red and black berries are attractive to children and contain numerous toxins that are potent gastrointestinal irritants. Symptoms include nausea, vomiting, abdominal cramping, and diarrhea. Treatment is supportive and may require intravenous fluids and antiemetics.

www.ketabpezeshki.com 66485457-66963820

Figure 164-6. *Nerium oleander*. (Courtesy of Steven Setzer.)

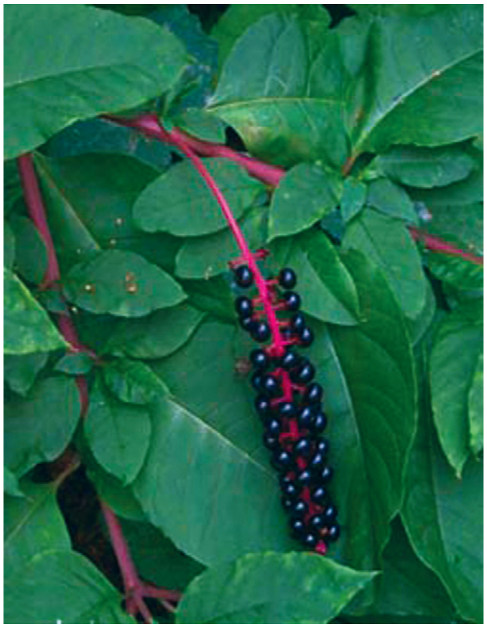


Figure 164-7. *Phytolacca americana* (pokeweed). (Courtesy Steven Setzer.)

Nerium oleander

Nerium oleander (Fig. 164-6), or oleander, is one of many plants that contain toxic cardiac glycosides[37,38] structurally similar to digoxin. Ingestion of several leaves is unlikely to cause serious symptoms.[39,40] Large exposures from suicide attempts or misidentification of plants used for teas or herbal products can lead to severe toxicity or death. The cardiac glycosides are potent sodium-potassium–adenosine triphosphatase inhibitors, and the symptoms they cause are similar to those of digoxin poisoning (see Chapter 152). Measurement of an abnormal digoxin level is only qualitative proof of exposure because the serum digoxin test can falsely measure nondigoxin cardiac glycosides. Conversely, a normal digoxin measurement does not rule out exposure because the level of cardiac glycoside cross-reactivity varies. Treatment of dysrhythmias and hypotension includes multidose activated charcoal (50 g every 6 hours for 3 days) and digoxin-specific Fab antibodies (see Chapter 152).[39-44] However, larger doses of Fab fragments generally are needed than for comparable digoxin poisonings. The initial empirical dose of digoxin-specific Fab fragments is 10 vials. If response to therapy is poor, repeated administration of an additional 10 vials is recommended.

Nicotiana tabacum

Nicotiana tabacum is widely grown in the southeastern United States as a source for cigarette and cigar tobacco. Several *Nicotiana* species contain nicotine as their major toxin, which activates and subsequently blocks acetylcholine receptors in the central nervous system (CNS) and peripheral autonomic nervous system. Most exposures are the ingestion of cigarettes or cigars by young children. Dermal exposure to workers harvesting plants and ingestion of wild plants mistaken for edible plants also have led to poisoning.[45,46]

The ingestion of one or two cigarettes has the potential to cause moderate poisoning in children, but most children ingesting cigarettes do not manifest toxicity. Patients without nausea and vomiting do not seem to progress to more severe toxicity.[47] Dermal exposure in tobacco workers has been called green tobacco sickness.[48] Nicotine is absorbed through the skin and occurs most severely when the skin or plant is wet. Exposure can be avoided by wearing of proper protective equipment.

Symptoms begin shortly after absorption. Nausea, vomiting, salivation, lacrimation, diarrhea, hypertension, tachycardia, diaphoresis, agitation, and fasciculation are seen initially. More severe toxicity is manifested by seizures, respiratory depression (muscle weakness), and hyperthermia.[49] Activated charcoal may be useful to limit absorption. Other treatments are supportive in nature because no specific antidote for nicotine is available. If seizures occur, initial treatment is with a benzodiazepine (i.e., lorazepam, 1-2 mg intravenously). If response is poor, treatment is as described for status epilepticus in Chapter 102. If severe salivation and lacrimation occur, atropine in 1-mg doses may be repeated until symptoms improve.

Phytolacca americana

Found in the eastern United States, *Phytolacca americana* (Fig. 164-7) is commonly known as pokeweed, poke, pokeberry, inkberry, scoke, American cancer, garget, phytolacca, and pigeonberry. Although the plant is poisonous, it can be detoxified by boiling it in water twice before use in salads or other recipes. Toxicity is seen when the plant is inadequately detoxified or raw parts of the plant are eaten.[50] Symptoms begin shortly after ingestion and include severe nausea, vomiting, abdominal cramping, and diarrhea. Treatment is supportive.

Pyracantha

Pyracantha, commonly known as the firethorn, has small red, orange, or yellow fruit attractive to and commonly ingested by children. The plant is not toxic, but the thorny parts can penetrate skin deeply and may be difficult to remove.

Rhododendron

Rhododendron includes more than 1000 species of azaleas and rhododendrons, including mountain laurel, dwarf laurel, rose bay, western Labrador tea, and Japanese pieris. Numerous structurally related toxins (diterpene polyalcohols) have been identified from these plants, including grayanotoxin, rhodojaponin, asebotoxin, and others.[51-53] These toxins bind to sodium channels and increase

www.ketabpezeshki.com 66485457-66963820

Figure 164-8. *Taxus* (yew). (Courtesy Steven Setzer.)

permeability (sodium channel openers), causing cardiovascular (e.g., bradycardia and hypotension) and gastrointestinal (e.g., nausea, vomiting, and abdominal pain) effects. Although ingestion of a few leaves is unlikely to cause symptoms, larger exposures can cause severe toxicity. In addition, these plant toxins can be concentrated in honey, so large honey ingestions, "mad honey," can also lead to toxicity.[52,54] However, no deaths have been reported. Treatment is supportive; atropine and cardiac pacing are used for bradycardia. For ventricular dysrhythmias, sodium channel–blocking agents, such as quinidine and procainamide, are used. However, limited efficacy data are available for these therapies. If response is poor, treatment with standard advanced cardiovascular life support (ACLS) protocol is warranted.

Spathiphyllum

Spathiphyllum includes the peace lily, Mauna Loa, white anthurium, and snowflower. These plants contain calcium oxalates and have toxicity and treatment similar to those of *Dieffenbachia*.

Taxus

Taxus (yew trees) (Fig. 164-8) have a hard seed surrounded by a fleshy red cup (the aril). The aril portion is not poisonous, and the seed has a hard coat that limits toxin release in the gastrointestinal tract so that most ingestions are nontoxic. If the seed is chewed or leaves are ingested, cardiac (e.g., bradycardia and hypotension) and gastrointestinal (e.g., nausea, vomiting, and abdominal pain) symptoms may occur. Deaths from this plant have been reported, usually in the setting of a suicide and secondary to cardiac manifestations. Bradycardia is treated with atropine. Wide-complex tachydysrhythmias are not responsive to sodium bicarbonate and should be treated per standard ACLS guidelines.[55,56]

HERBAL MEDICINES

Herbal products have gained an extraordinary amount of popularity in the past several decades. Although the highest use is among immigrants and patients with difficult-to-treat diseases, such as advanced cancer and acquired immunodeficiency syndrome (AIDS), these products are used by approximately 30% of the general population.[57-59] Consumers often perceive herbals as more "natural" and thus "safer" and "harmless" despite many examples of toxicity associated with their use. This is coupled with medical practitioners' having limited knowledge about herbal medications. In addition, herbals are widely marketed as safe and effective, especially on the Internet.[60] One study of pregnant patients documented 45% herbal medicine use during some point of the pregnancy.[61] Emergency department patients are also frequent users of herbal products.[62-64]

Herbal products are classified as dietary supplements and are not regulated as medications, even though they are used for their medicinal value.[58,64,65] Regulation of dietary supplements is limited. Safety, quality, and efficacy for medicines are the responsibility of manufacturers. For herbal products used as dietary supplements, of which there are thousands to hundreds of thousands of potential products, the burden of proving efficacy and safety lies with the FDA.[65-68]

Studies looking at the efficacy of herbal products are limited, with few randomized, controlled studies. The National Institutes of Health sponsored several high-profile randomized placebo-controlled studies assessing the efficacy of several well-known herbals: St. John's wort for depression, hawthorne extract for congestive heart failure, echinacea for the common cold, glucosamine–chondroitin sulfate for arthritis of the knee, saw palmetto for benign prostatic hypertrophy, and ginko biloba for dementia onset. Unfortunately, none of these trials has shown the herbal treatment to be effective.[69-74] In addition, herbal manufacturers are not required to conduct efficacy studies. Studies evaluating side effects, drug interactions, and toxicity are even less available.

Most herbal products have some direct pharmacologic action. The potency of these agents is usually limited, however. As a result, toxicity and side effects from the direct actions of herbal products are relatively uncommon.[69-76]

The lack of manufacturing quality control accounts for most toxicologic problems associated with their use. Four major types of toxicologic problems are associated with herbal product use: the misidentification of an herbal plant and toxicity resulting from a substituted plant, contamination with nonherbal toxic material, direct toxicity or overdose of the herbal product (Table 164-1), and drug-herbal interaction (Table 164-2).[77]

Misidentification of Herbal Plants

Incorrect plant identification and subsequent use in the production of herbal products have occurred on numerous occasions, leading to epidemic exposures with tragic outcomes. The following examples illustrate this problem.

Herbal Slimming Regimen, 1992

During the early 1990s, the Chinese herb *Stephania tetrandra* was used for weight loss in Belgium. More than 100 cases of renal failure and many cases of urethral dysplasia resulted from toxicity of this herbal regimen. It was discovered that *Aristolochia fangchi,* which contains the nephrotoxin aristolochic acid, was mistakenly used instead of *S. tetrandra*.[78-81]

Paraguay Tea, 1994

The South American herbal tea Paraguay tea is made from *Ilex paraguariensis,* used for urinary tract infections, cardiac insufficiency, and "lack of stamina." In 1994, several individuals had anticholinergic poisoning from Paraguay tea after the manufacturer had purchased and mistakenly used other plant materials containing the belladonna alkaloids atropine, scopolamine, and hyoscyamine directly from farmers before packaging.[82]

Digitalis lanata, 1997

An herbal dietary supplement used for "internal cleansing" contained 14 herbal ingredients. Two patients had complete heart

www.ketabpezeshki.com 66485457-66963820

Table 164-1 Common Herbal Medications and Adverse Effects

HERBAL NAME	BOTANICAL NAME	USES	ADVERSE EFFECT
Bee pollen	*Apis mellifera*	General tonic	Allergic reactions
Betel nut	*Areca catechu*	Stimulant	Bronchospasm
Blue cohosh	*Caulophyllum thalictroides*	Menstrual cramps	Nicotinic effects
Boron		Astringent, wounds	Dermatitis, GI, hepatic, renal, CNS
Buckthorn	*Rhamnus frangula*	Laxative	Diarrhea
Cantharidin	*Cantharis*	Aphrodisiac	GI, dermatitis, renal
Cat's claw	*Uncaria tomentosa*	AIDS, cancer, arthritis	None reported
Chamomile	*Matricaria chamomilla*	Fever, cough, colds, wounds	Allergic reactions
Chaparral	*Larrea tridentata*	Cancer, aging, general tonic	Hepatotoxicity
Comfrey	*Symphytum officinale*	Contusions and sprains	Hepatotoxicity
Compound Q	*Trichosanthes kirilowii*	AIDS	Pulmonary, CNS
Dandelion	*Taraxacum officinale*	Diuretic, appetite stimulant	None reported
Dong quai	*Angelica polymorpha*	Blood purifier, increase circulation	Anticoagulation, dermatitis
Echinacea	*Echinacea purpurea*	Common cold	Fever, nausea and vomiting
Ephedra	*Ephedra* spp.	Stimulant, asthma	Hypertension, tachycardia, CNS, MI
Fennel	*Foeniculum vulgare*	GI illnesses, cough	Allergic reactions
Fenugreek	*Trigonella foenumgraecum*	Expectorant, anti-inflammatory	None reported
Feverfew	*Tanacetum parthenium*	Migraines, antipyretic	Post-feverfew syndrome, rebound migraine
Garlic	*Allium sativum*	Infection, CAD, hypertension	Dermatitis, GI
Germander	*Teucrium chamaedrys*	Gout, fever, dietary aid	Hepatotoxicity
Ginger	*Zingiber officinale*	Motion sickness, GI illness	None reported
Ginkgo	*Ginkgo biloba*	General tonic, depression, anxiety, memory	GI effects, bleeding effects, drug interactions
Ginseng	*Panax ginseng*	General tonic, depression, stress, anxiety, fatigue	Ginseng abuse syndrome
Glucosamine		Arthritis	None reported
Goldenseal	*Hydrastis canadensis*	Cutaneous wounds	GI, CNS, and pulmonary effects in overdose
Gordolobo yerba	*Senecio longiloba*	URI, fever	Budd-Chiari syndrome
Henbane	*Hyoscyamus niger*	Sedative, GI discomfort	Anticholinergic toxicity
Jimsonweed	*Datura stramonium*	Asthma	Anticholinergic toxicity
Juniper	*Juniperus communis*	UTI, kidney stones, appetite	Renal toxicity
Kava kava	*Piper methysticum*	Sedative, aphrodisiac	Euphoria, CNS
Kumbucha		Cancer, memory loss	None reported
Larkspur	*Delphinium consolida*	Diuretic, sedative	Lethargy, muscle paralysis
Licorice	*Glycyrrhiza glabra*	Cough, GI illnesses	Hypokalemia, drug interactions
Ma huang	*Ephedra sinica*	General tonic, common cold	Sympathomimetic
Mate	*Ilex paraguayensis*	Stimulant	None reported
Milk thistle	*Silybum marinum*	General tonic, GI disorders	None reported
Mistletoe	*Viscum album*	GI illness, cancer, HIV infection	GI, bradycardia, CNS
Nutmeg	*Myristica fragrans*	Aphrodisiac, hallucinogen	CNS, GI
Parsley	*Petroselinum crispum*	UTI, kidney stones	Contact dermatitis
Pennyroyal	*Mentha pulegium*	Abortifacient, GI illnesses	Hepatotoxicity
Rose hips	*Rosa canina*	URI, vitamin C	None reported
Rue	*Ruta graveolens*	Menstrual disorders	Contact dermatitis, GI and CNS effects in overdose
Sage	*Salvia officinalis*	Antiseptic, wounds	Absinthism
St. John's Wort	*Hypericum perforatum*	Depression, anxiety	Drug interactions
Sassafras	*Sassafras albidum*	GI stimulant	Liver, carcinogen
Saw palmetto	*Serenoa repens*	Benign prostatic hypertrophy	GI effects

Continued

www.ketabpezeshki.com 66485457-66963820

Table 164-1 Common Herbal Medications and Adverse Effects—cont'd

HERBAL NAME	BOTANICAL NAME	USES	ADVERSE EFFECT
Scullcap	*Scutellaria lateriflora*	Nervous disorders, bitter tonic	Hepatotoxicity
Shepherd's purse	*Capsella bursa pastoris*	Hypertension, CHF, headaches, menstrual disorders	None reported
Siberian ginseng	*Eleutherococcus senticosus*	General tonic	None reported
Soy	*Glycine max*	Menopause, CAD	Carcinogen
Tonka bean	*Dipteryx odorata*	Whooping cough	Anticoagulant effect
T'u-san-chi	*Gynura segetum*	Stimulant tea	Budd-Chiari syndrome
Valerian	*Valeriana officinalis*	Sleep, anxiety, general tonic	Hepatotoxicity
Woodruff	*Galium odorata*	Diuretic, anxiety, menstrual disorders	Anticoagulant effect, CNS effects, hepatotoxicity
Wormwood	*Artemisia cina*	Worm infection, anxiety	Seizures, CNS effects
Yarrow	*Achillea millefolium*	Poor appetite, GI illnesses	Allergic reactions
Yew	*Taxus baccata*	GI illness, cancer	Dizziness, bradycardia
Yohimbine	*Pausinystalia yohimbe*	Sexual disorders, aphrodisiac	Hypertension, agitation, CNS effects

CAD, coronary artery disease; *CHF,* congestive heart failure; *CNS,* central nervous system; *GI,* gastrointestinal; *MI,* myocardial infarction; *URI,* upper respiratory infection; *UTI,* urinary tract infection.

Table 164-2 Common Herbal-Drug Interactions

HERBAL	DRUG	TYPE OF INTERACTION
Betel nut	Fluphenazine Prednisone and salbutamol	Extrapyramidal effects Bronchospasm
Boldo	Warfarin	Increased INR
Chili pepper	ACE inhibitors Theophylline	Cough Increased drug absorption
Curbicin	Warfarin	Increased INR
D-400	Oral hypoglycemics	Increased drug concentration and decreased serum glucose
Danshen	Warfarin	Increased INR
Devil's claw	Warfarin	Increased INR
Dong quai	Warfarin	Increased INR
Fenugreek	Warfarin	Increased INR
Garlic	Warfarin	Increased INR
Ginkgo	Aspirin Blood thinners Thiazide diuretics Warfarin	Increased platelet inhibition Bleeding side effects Hypertension Increased INR
Ginseng	Warfarin Ethanol	Decreased INR Increased ethanol clearance
Green tea	Warfarin	Decreased INR
Guar gum	Many drugs Digoxin	Decreased absorption of drug Decreased drug concentration
Karela	Chlorpropamide	Decreased serum glucose
Licorice	Oral contraceptives Prednisolone Antihypertensives	Hypertension, edema, hypokalemia Alteration of pharmacokinetics Hypokalemia
Lycium	Warfarin	Increased INR
Ma huang	Guanethidine MAO inhibitors	Sympathomimetic effects Sympathomimetic effects
Mango	Warfarin	Increased INR
Oat bran	Lovastatin	Decreased drug concentration
Papaya	Warfarin	Increased INR

www.ketabpezeshki.com 66485457-66963820

Table 164-2 Common Herbal-Drug Interactions—cont'd

HERBAL	DRUG	TYPE OF INTERACTION
PC-SPES	Warfarin	Increased INR
Pectin	Lovastatin	Decreased drug concentration
Psyllium	Lithium	Decreased drug concentration
St. John's wort	Selective serotonin reuptake inhibitors Theophylline Digoxin Cyclosporine Indinavir Irinotecan Nevirapine Oral contraceptives Simvastatin Warfarin	Serotonin syndrome Decreased drug concentration Decreased drug concentration Decreased drug concentration Decreased drug concentration Decreased drug concentration Decreased drug concentration Decreased drug concentration Decreased drug concentration Decreased INR
Siberian ginseng	Digoxin	Increased digoxin levels
Soy	Warfarin	Decreased INR
Tamarind	Aspirin	Increased drug absorption
Wheat bran	Digoxin	Decreased drug concentration
Yohimbine	Tricyclic antidepressants	Hypertension

ACE, angiotensin-converting enzyme; *INR,* international normalized ratio; *MAO,* monoamine oxidase.

block because one of the herbal ingredients, plantain, contained *Digitalis lanata* (a cardiac glycoside–containing plant).[83]

Dandelion Salad, 2004

Dandelion is a commonly ingested herb used as an appetite stimulant and diuretic. Many users grow and harvest their own plants. A 53-year-old woman who had ingested some home-grown dandelion had persistent nausea, vomiting, and bradycardia with a heart rate between 30 and 40 beats/minute. Her bradycardia persisted for several days and had associated syncope. Her diagnosis was unclear until it was discovered that she had mistakenly harvested and ingested foxglove instead of dandelion.[84]

Contamination with Nonherbal Toxic Material

Contamination with nonherbal toxic material as a mechanism of herbal toxicity may be due to contamination of the products at the time of manufacture or consumer fraud. Because of the limited FDA regulation of herbal manufacturers, one of the major risks of herbal use is the use of a product contaminated with a toxic substance. A study of Asian herbal patent medications sold in California found that 32% of these products were contaminated with heavy metals or undeclared pharmaceuticals.[85]

Lead, mercury, arsenic, cadmium, aluminum, tin, zinc, and copper have been found in herbal products.[86-89] The most common undeclared pharmaceuticals include ephedrine, chlorpheniramine, methyltestosterone, and phenacetin.[90] Metal shavings have been added to herbal preparations to increase selling price when the herbals are sold by weight. Some herbal products use the metal as an active ingredient with a purported medicinal benefit (e.g., lead in azarcon or mercury in cinnabar). Other cases involve contamination with the metals during the manufacturing process.[89-91] Consumer fraud in the herbal industry has been well documented on numerous occasions. Typically, an FDA-controlled pharmaceutical product is mixed in with an herbal product, or the label did not list the pharmaceutical agent.

Chuifong toukuwan, an herbal preparation, was associated with several cases of agranulocytosis. Analysis revealed that it contained phenylbutazone, indomethacin, and aminopyrine.[92] Gan mao tong, an herbal product found to contain phenylbutazone, caused aplastic anemia.[93] An undefined herbal preparation that was used "to avoid taking other medicine" was found to contain triamcinolone. A patient using the product for more than 1 year had several manifestations of steroid excess: thoracic compression fractures, proximal muscle weakness, and osteoporosis.[94] Tung shueh, an herbal product that was found to contain mefenamic acid and diazepam, caused gastrointestinal bleeding and acute interstitial nephritis.[95] Another herbal product was found to contain mefenamic acid, which caused acute renal failure necessitating hemodialysis. Dr. Tong Shap Yee's asthma pills were found to contain theophylline.[96] Leng Pui Kee herbal cough remedy was found to contain bromhexine.[96]

Direct Toxicity of Herbals and Herbal-Drug Interactions

Some herbal preparations can cause allergic reactions ranging from contact dermatitis to anaphylactic shock (Box 164-1).[97,98] Other herbal products are associated with uncommon idiosyncratic reactions, particularly hepatic toxicity (see Table 164-1).[99-104] Herbal products are often taken in overdose. Not controlled by a prescription system, herbal medicines are seen as natural and safe so that "if one is good, then two or three is better." Direct toxicity is often due to this overuse. Herbs associated with specific toxicities and side effects are listed in Table 164-1.[89,96,98,105-107]

Concurrent herbal and pharmaceutical use is common and can cause drug interactions. Of U.S. adults, 18% who take prescription medications also use an herbal or mineral supplement, and 60% who use alternative therapies are unlikely to report this to their physicians.[108] Individuals often do not consider that herbs can potentially interact with conventional medicines, and serious drug reactions associated with an herbal product are less likely to be reported than are reactions that occur with a conventional medicine. Common herbal-drug interactions are listed in Table 164-2.[109,110]

www.ketabpezeshki.com 66485457-66963820

Box 164-1 Herbals Associated with Allergic Reactions

Agnus castus	Gravel root
Angelica	Guaiacum
Aniseed	Holy thistle
Apricot	Hops
Aristochol	Hydrangea
Arnica	Hydrocotyle
Artichoke	*Inula helenium*
Asafetida	Jasmine
Balxum of Peru	Juniper
Bee pollen	Kava
Bee venom	Lady's slipper
Black cumin oil	Lavender
Boneset	Mai-Men-Dong-Tang
Camphor	Meadowsweet
Capsaicin	Motherwort
Cassia	Paprika
Cedar wood oil	Parsley
Celery	Peppermint oil
Chamomile	Pilewort
Chrysanthemum	Plantain
Cinnamon	Pulsatilla
Cowslip	Rosemary
Curcumin	Rosewood
Dandelion	Royal jelly
Echinacea	Rue
Elecampane	Slippery elm
Euphorbia	Tansy
Fennel	Tea tree oil
Feverfew	Tung seed
French marigold	Wild carrot
Fucus	Yarrow
Garlic	Ylang-ylang
Gingko	

Table 164-3 Mushroom Groups

GROUP/TOXIN	REPRESENTATIVE EXAMPLE	CLINICAL EFFECTS
Early Onset of Symptoms		
Coprine	*Coprinus atramentarius*	Disulfiram reaction with alcohol
GI toxin	Many species	Nausea, vomiting, diarrhea, abdominal pain
Ibotenic acid and muscimol	*Amanita muscaria*	Diverse CNS effects, including hallucinations, seizures, delirium, coma, agitation
Muscarine	*Clitocybe dealbata*	Peripheral cholinergic toxidrome
Psilocybin	*Psilocybe cubensis*	CNS effects, including hallucinations and euphoria
Late Onset of Symptoms		
Cyclopeptides	*Amanita phalloides*	GI effects followed by hepatotoxicity
Gyromitrin	*Gyromitra esculenta*	GI effects followed by seizures
Orellanine	*Cortinarius orellanus*	GI effects followed by renal toxicity
Allenic norleucine	*Amanita smithiana*	GI effects followed by renal toxicity

CNS, central nervous system; *GI,* gastrointestinal.

MUSHROOMS

U.S. poison center data estimate that five exposures take place for every 100,000 population per year. These exposures occur in three types of situations: ingestion of wild mushrooms by young children playing outdoors (which usually results in a small exposure), mistaken selection of poisonous mushrooms while foraging for edible wild mushrooms intended for a meal (which leads to a larger toxin exposure and most of the severe cases of mushroom poisoning, including deaths), and abuse of certain mushrooms for their mind-altering potential.[3,4] Mushrooms of abuse typically involve a young population that often abuses other drugs. Most of these cases do not come to medical attention and often involve other substances added to the mushrooms. Despite the potential for severe toxicity and death, most exposures are relatively benign.[2,111,112] Approximately 5% result in moderate poisoning, with only a few deaths reported per year.

Management of Mushroom Exposure

The prognosis depends on the specific species. Identification of the mushroom is the most helpful factor in deciding on a treatment plan. Techniques for mushroom identification are described in most mycology and toxicology textbooks. Local mycologists or a poison center may be helpful. If a specimen is available, it can be stored in a paper bag at room temperature for delivery. Alternatively, a digital picture can be taken and e-mailed.[5] Vomitus can be collected because mushroom parts may be recovered. Despite these measures, the species is unknown in more than 90% of ingestions. Because *Amanita* species are responsible for most deaths, a clinical strategy or algorithm for differential diagnosis and management is most often used to identify the highest risk ingestions.

Mushroom Groups

Ten general groupings have been found to be useful for clinical management (Table 164-3). These groups can be classified into mushrooms with early onset of symptoms (0-4 hours after ingestion), late onset of symptoms (<6 hours after ingestion), or no symptoms (edible). Mushrooms with serious toxicity and potential for death have late onset of symptoms. Particular attention should be paid to the timing of initial symptoms.[113-115] Mushroom species often grow together, and foragers frequently pick and eat more than one species of mushroom so that the onset of early symptoms does not preclude the diagnosis of a more serious poisoning.

Early Onset of Symptoms

Gastrointestinal symptoms of nausea, vomiting, diarrhea, and abdominal cramps are common among many of the mushroom groupings (see Table 164-3). These symptoms are most predominant, however, in the gastrointestinal toxin group. This group contains numerous diverse mushrooms, many with unknown toxins. They cause symptoms rapidly (0.5-3 hours) after ingestion, and symptoms typically last 24 hours. Treatment is supportive, with good outcome expected.

CNS effects are associated with two groups of mushrooms, ibotenic acid–muscimol and psilocybin.[113,114] Psilocybin is structurally related to serotonin and lysergic acid diethylamide (LSD). Similar to LSD, hallucinations and CNS effects are prominent. This mushroom is most often used as a drug of abuse and is often obtained from Internet sources.[3,4,116] Ibotenic acid and muscimol are toxins that are structurally related to glutamic acid and GABA.

www.ketabpezeshki.com 66485457-66963820

Glutamic acid is an excitatory neurotransmitter, whereas GABA is an inhibitory one. Lethargy, hallucinations, seizures, or severe agitation begins within 1 to 2 hours after ingestion. Treatment of seizures and supportive care produce a good outcome.

The cholinergic toxidrome is associated with muscarine-containing mushrooms. Muscarine is structurally related to acetylcholine. Because of muscarine's quaternary structure, it does not cross the blood-brain barrier. Symptoms include salivation, lacrimation, urination, defecation, gastroenteritis, and emesis (SLUDGE). Atropine can be used for severe symptoms. Pralidoxime is not indicated because acetylcholinesterase inhibition is not involved.[117]

The final mushroom group causes early onset of symptoms only with simultaneous ingestion of ethanol.[118] These coprine-containing mushrooms cause a disulfiram-like reaction by blocking acetaldehyde dehydrogenase. The symptoms include flushing, nausea, vomiting, and headache. The onset of this reaction associated with ethanol can occur 30 minutes to several days after mushroom ingestion. Treatment is supportive and similar to that of disulfiram reactions from other causes.

Late Onset of Symptoms

Four groups of mushrooms cause late onset of symptoms (>6 hours after ingestion): cyclopeptide, gyromitrin, orelline/orellanine, and allenic norleucine. The orelline/orellanine-containing mushrooms are infrequently found in the United States, and there have not been any reported cases of toxicity in North America. The allenic norleucine–containing mushrooms have involved the *Amanita smithiana* mushroom located in the Pacific Northwest. Only a few cases (<20 total cases) have been reported and have typically involved individuals foraging from that area of the United States for the edible matsutake or pine mushroom (*Tricholoma magnivelare*). The main toxicity is delayed-onset renal failure. Gastrointestinal symptoms are frequently present and may be manifested early after ingestion. These symptoms typically subside, and patients present with renal symptoms 3 to 4 days after ingestion.[119] The cyclopeptide group is responsible for most mushroom-related deaths in the United States.

The cyclopeptide mushrooms contain many species, of which *Amanita phalloides* is the most well known.[120] Several cyclopeptide toxins have been identified (e.g., amatoxins, virotoxins, phallotoxins) that are thought to be responsible for toxicity.[121,122] Initial manifestations, such as severe nausea, vomiting, diarrhea, and abdominal cramping, begin 6 to 24 hours after ingestion. Hydration and supportive care often lead to initial relief of symptoms and a relatively quiescent period. Hepatic toxicity followed by other end-organ involvement may ensue in the next several days to weeks. Progressive elevation of hepatic transaminases, jaundice, and hepatic encephalopathy can lead to death.[121]

Many cases are misdiagnosed as gastroenteritis. Numerous noninvasive therapies have been suggested, including silibinin, silybin, thioctic acid, activated charcoal, high-dose penicillin, dexamethasone, vitamin C, cytochrome *c*, cimetidine, *N*-acetylcysteine, kutkin, and aucubin.[122,123] None of these therapies has been rigorously tested in human-controlled studies. Multidose administration of activated charcoal seems to be reasonable because of its ability to bind the toxins and its availability and relative safety; however, its effectiveness is unclear.

Numerous invasive therapies also have been proposed for use in cyclopeptide poisoning, including forced diuresis, hemodialysis, hemoperfusion, hemofiltration, plasmapheresis, and hepatic transplantation.[124-127] Similar to the noninvasive modalities, it is not clear if any of these therapies are effective. There have been several reports of successful transplantation in severe cases of poisoning[124-127]; however, it is uncertain what criteria should be used for selection of candidates.[127-130] Patients with severe hepatic signs and symptoms should be considered for transfer to a transplant center.

Gyromitrin-containing mushrooms commonly are mistaken for edible mushrooms as they look like *Morchella* species (morel) mushrooms.[131] The metabolites of this toxin cause GABA neurotransmitter depletion similar to isoniazid toxicity, leading to excitatory CNS effects, such as headaches, agitation, and seizures. Effects also include nausea, vomiting, and possible hepatotoxicity. The onset of symptoms is at least 6 hours after ingestion. Because of its similarity to isoniazid toxicity, pyridoxine has been proposed as an antidote. It is unclear how effective this antidote is, but it is useful for gyromitrin-induced CNS effects because of its availability and safety profile.

Orelline/orellanine-containing mushrooms (*Cortinarius* genus) have been found in North America. There have been no reports of toxicity associated with cases in the United States, however, with most reported cases in Europe. Symptoms begin 1 to 2 days after ingestion, with nausea, vomiting, abdominal pain, and headache. Renal toxicity is manifested days to weeks after these initial symptoms and can progress to chronic renal failure.[132,133]

Disposition

Initial management is aimed at ruling out of mushroom groups associated with early onset of symptoms. If the patient remains asymptomatic after a 3-hour period of observation, the patient should be discharged with instructions to return if any symptoms are manifested during the next 72 hours.

KEY CONCEPTS

- Plant exposures occur commonly in children and most commonly involve household plants. Most exposures cause little or no toxicity.
- Plants and mushrooms are often ingested for their mind-altering properties.
- Misidentification of plants and herbal products is a common cause of plant-induced and herbal product–induced toxicity.
- Natural plant and mushroom gathering for personal ingestion is a popular activity. Mistakes while foraging occur commonly, with the potential for serious toxicity and numerous fatalities.
- Herbal medicines increasingly are being used by the general public. Limited information is available about the efficacy and toxicity of these products.
- In the assessment of a patient exposed to a mushroom, the timing of initial symptoms and the assessment for associated symptoms constitute the most important data needed to make a differential diagnosis.
- A patient who has eaten or been exposed to a wild mushroom may have another medical condition actually responsible for the symptoms.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Krenzelok EP, Mrvos R: Friends and foes in the plant world: A profile of plant ingestions and fatalities. *Clin Toxicol (Phila)* 2011; 49:142.
2. Bronstein AC, et al: 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 27th Annual Report. *Clin Toxicol (Phila)* 2010; 48:979.
3. Rimsza ME, Moses KS: Substance abuse on the college campus. *Pediatr Clin North Am* 2005; 52:307.
4. Richardson WH 3rd, Slone CM, Michels JE: Herbal drugs of abuse: An emerging problem. *Emerg Med Clin North Am* 2007; 25:435-457.
5. Fishbein CV, et al: Digital imaging: A promising tool for mushroom identification. *Acad Emerg Med* 2003; 10:808.
6. Froberg B, Ibrahim D, Furbee RB: Plant poisoning. *Emerg Med Clin North Am* 2007; 25:375.
7. Bradberry S: Ricin and abrin. *Medicine (Baltimore)* 2007; 35:576.
8. Griffiths GD, Phillips GJ, Holley J: Inhalation toxicology of ricin preparations: Animal models, prophylactic and therapeutic approaches to protection. *Inhal Toxicol* 2007; 19:873.
9. Sahoo R, Hamide A, Amalnath AS, Narayana BS: Acute demyelinating encephalitis due to *Abrus precatorius* poisoning—complete recovery after steroid therapy. *Clin Toxicol (Phila)* 2008; 46:1071.
10. Subrahmanyan D, Mathew J, Raj M: An unusual manifestation of *Abrus precatorius* poisoning: A report of two cases. *Clin Toxicol (Phila)* 2008; 46:173.
11. Jang DH, Hoffman RS, Nelson LS: Attempted suicide, by mail order: *Abrus precatorius. J Med Toxicol* 2010; 6:427.
12. Vogl TP: Treatment of Hunan hand. *N Engl J Med* 1982; 306:178.
13. Miller JJ, Skolnick J: Inhalation injury after capsaicin exposure. *J Ky Med Assoc* 2006; 104:103.
14. Forrester MB, Stanley SK: The epidemiology of pepper spray exposures reported in Texas in 1998-2002. *Vet Hum Toxicol* 2003; 45:327.
15. Kim-Katz SY, et al: Topical antacid therapy for capsaicin-induced dermal pain: A poison center telephone-directed study. *Am J Emerg Med* 2010; 28:596.
16. Snyman T, Stewart MJ, Steenkamp V: A fatal case of pepper poisoning. *Forensic Sci Int* 2001; 124:43.
17. Schep LJ, Slaughter RJ, Becket G, Beasley DM: Poisoning due to water hemlock. *Clin Toxicol (Phila)* 2009; 47:270.
18. Heath KB: A fatal case of apparent water hemlock poisoning. *Vet Hum Toxicol* 2001; 43:35.
19. Colombo ML, et al: Hemlock poisoning due to plant misidentification. *J Pharm Sci Res* 2009; 1:43.
20. Vetter J: Poison hemlock (*Conium maculatum* L). *Food Chem Toxicol* 2004; 42:1373.
21. West PL, Horowitz BZ, Montanaro MT, Lindsay JN: Poison hemlock–induced respiratory failure in a toddler. *Pediatr Emerg Care* 2009; 25:761.
22. Diker D, Markovitz D, Rothman M, Sendovski U: Coma as a presenting sign of *Datura stramonium* seed tea poisoning. *Eur J Intern Med* 2007; 18:336.
23. Andreola B, Piovan A, Da Dalt L, Filippini R, Cappelletti E: Unilateral mydriasis due to Angel's trumpet. *Clin Toxicol (Phila)* 2008; 46:329.
24. Salen P, et al: Effect of physostigmine and gastric lavage in a *Datura stramonium*–induced anticholinergic poisoning epidemic. *Am J Emerg Med* 2003; 21:316.
25. Honey BL, Hagemann TM, Lobb KM, McGoodwin L: Jimson weed abuse in an Oklahoma teen. *J Okla State Med Assoc* 2009; 102:351.
26. Forrester MB: Jimsonweed (*Datura stramonium*) exposures in Texas 1998-2004. *J Toxicol Environ Health* 2006; 69:1757.
27. Krenzelok EP: Aspects of *Datura* poisoning and treatment. *Clin Toxicol (Phila)* 2010; 48:104.
28. Stellpflug SJ, Harris CR: What signs and symptoms would be expected after ingestion of this plant? *J Med Toxicol* 2009; 5:90.
29. Krenzelok EP: *Datura* poisoning and the use of physostigmine. *Clin Toxicol (Phila)* 2010; 48:575.
30. Rasimas JJ, Donovan JW: Management of *Datura* poisoning. *Clin Toxicol (Phila)* 2010; 48:575.
31. Cumpston KL, et al: Acute airway compromise after brief exposure to a *Dieffenbachia* plant. *J Emerg Med* 2003; 25:391.
32. Watson JT, et al: Outbreak of food-borne illness associated with plant material containing raphides. *Clin Toxicol (Phila)* 2005; 43:17.
33. Lin TJ, et al: Common toxidromes of plant poisonings in Taiwan. *Clin Toxicol (Phila)* 2009; 47:161.
34. Dip EC, Pereira NA, Melo PA: Tongue angioedema in vivo: Antagonist response of anti-inflammatory drugs. *Clin Toxicol (Phila)* 2011; 49:153.
35. Krenzelok EP, Mrvos R, Jacobsen TD: Contrary to the literature, vomiting is not a common manifestation associated with plant exposures. *Vet Hum Toxicol* 2002; 44:298.
36. De Vincenzi M, Silano M, De Vincenzi A, et al: Constituents of aromatic plants: Eucalyptol. *Fitoterapia* 2002; 73:269.
37. Maffè S, et al: Digitalis must be banished from the table: A rare case of acute accidental *Digitalis* intoxication of a whole family. *J Cardiovasc Med (Hagerstown)* 2009; 10:727.
38. Oerther SE: Plant poisonings: Common plants that contain cardiac glycosides. *J Emerg Nurs* 2011; 37:102.
39. Eddleston M, et al: Anti-digoxin Fab fragment in cardiotoxicity induced by ingestion of yellow oleander: A randomized controlled trial. *Lancet* 2000; 355:967.
40. de Silva HA, et al: Multiple-dose activated charcoal for treatment of yellow oleander poisoning: A single-blind, randomised, placebo-controlled trial. *Lancet* 2003; 361:1935.
41. Eddleston M, et al: Multiple-dose activated charcoal in acute self-poisoning: A randomised controlled trial. *Lancet* 2008; 371:583.
42. Eyer P, Eyer F: Is this the epitaph for multiple-dose activated charcoal? *Lancet* 2008; 371:538.
43. de Silva HA, Pathmeswaran A, Lalloo DG, de Silva HJ, Aronson JK: Multiple-dose activated charcoal in yellow oleander poisoning. *Lancet* 2008; 371:2171.
44. Eddleston M, Juszczak E, Buckley N: Multiple-dose activated charcoal in yellow oleander poisoning—authors' reply. *Lancet* 2008; 371:2171.
45. Rao P, et al: Hispanic farmworker interpretations of green tobacco sickness. *J Rural Health* 2002; 18:503.
46. Schep LJ, Slaughter RJ, Beasley DM: Nicotinic plant poisoning. *Clin Toxicol (Phila)* 2009; 47:771.
47. Ingestion of cigarettes and cigarette butts by children—Rhode Island, January 1994–July 1996. *JAMA* 1997; 277:785.
48. McKnight RH, Spiller HA: Green tobacco sickness in children and adolescents. *Public Health Rep* 2005; 120:602.
49. Furer V, Hersch M, Silvetzki N, Breuer GS, Zevin S: *Nicotiana glauca* (tree tobacco) intoxication—two cases in one family. *J Med Toxicol* 2011; 7:47.
50. Hamilton RJ, et al: Mobitz type I heart block after pokeweed ingestion. *Vet Hum Toxicol* 1995; 37:66.
51. Choi SH, Lee SW, Hong YS, Lim SI: Grayanotoxin poisoning from flower of *Rhododendron mucronulatum* in humans. *Bull Environ Contam Toxicol* 2007; 78:11.
52. Koca I, Koca AF: Poisoning by mad honey: A brief review. *Food Chem Toxicol* 2007; 45:1315.
53. Gunduz A, Turedi S, Russell RM, Ayaz FA: Clinical review of grayanotoxin/mad honey poisoning past and present. *Clin Toxicol (Phila)* 2008; 46:437-442.
54. Okuyan E, Uslu A, Levent MO: Cardiac effects of "mad honey": A case series. *Clin Toxicol (Phila)* 2010; 48:528.
55. Jones R, et al: Yew tree poisoning: A near-fatal lesson from history. *Clin Med* 2011; 11:173.
56. Pierog JE, Kane B, Kane K, Donovan JW: Management of isolated yew berry toxicity with sodium bicarbonate: A case report in treatment efficacy. *J Med Toxicol* 2009; 5:84.
57. Kaufman DW, et al: Recent patterns of medication use in the ambulatory adult population of the United States: The Sloan survey. *JAMA* 2002; 287:337.
58. Tovar RT: Clinical approach to clinical herbal toxicity. *Semin Diagn Pathol* 2009; 26:28.
59. Kelly JP, et al: Recent trends in use of herbal and other natural products. *Arch Intern Med* 2005; 165:281.
60. Morris CA, Avorn J: Internet marketing of herbal products. *JAMA* 2003; 290:1505.
61. Glover DD, et al: Prescription, over-the-counter, and herbal medicine use in a rural, obstetric population. *Am J Obstet Gynecol* 2003; 188:1039.
62. Hung OL, et al: Herbal preparation use among urban emergency department patients. *Acad Emerg Med* 1997; 4:209.
63. Noonan K, Arensman RM, Hoover JD: Herbal medication use in the pediatric surgical patient. *J Pediatr Surg* 2004; 39:500.
64. Kinariwala N: Tighter regulation needed for dietary supplements in USA. *Lancet* 2003; 361:1566.
65. American College of Medical Toxicology position statement: Dietary supplements (Update) 2009. *J Med Toxicol* 2009; 5:99.
66. De Smet PA: Drug therapy: Herbal remedies. *N Engl J Med* 2002; 347:2046.
67. Marcus DM, Grollman AP: Botanical medicines—the need for new regulations. *N Engl J Med* 2002; 347:2073.
68. Cohen PA: American roulette—contaminated dietary supplements. *N Engl J Med* 2009; 361:1523.
69. Hypericum Depression Trial Study Group: Effect of *Hypericum perforatum* (St John's wort) in major depressive disorder: A randomized controlled trial. *JAMA* 2002; 287:1807.

www.ketabpezeshki.com 66485457-66963820

70. Zick SM, Vautaw BM, Gillespie B, Aaronson KD: Hawthorn Extract Randomized Blinded Chronic Heart Failure (HERB CHF) Trial. *Eur J Heart Fail* 2009; 11:990.
71. Turner RB, et al: An evaluation of *Echinacea angustifolia* in experimental rhinovirus infections. *N Engl J Med* 2005; 353:341.
72. Clegg DO, et al: Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006; 354:795.
73. Bent S, et al: Saw palmetto for benign prostatic hyperplasia. *N Engl J Med* 2006; 354:557.
74. Dodge HH, Zitzelberger T, Oken BS, Howieson D, Kaye J: A randomized placebo-controlled trial of *Ginkgo biloba* for the prevention of cognitive decline. *Neurology* 2008; 70:1809.
75. Chen S, Vieira A: A meta-analysis of medicinal plants to assess the evidence for toxicity. *Interdiscip Toxicol* 2010; 3:82.
76. Zuzak TJ, Rauber-Luthy C, Simoes-Wust AP: Accidental intakes of remedies from complementary and alternative medicine in children—analysis of data from the Swiss Toxicological Information Centre. *Eur J Pediatr* 2010; 169:681.
77. Tovar RT, Petzel RM: Herbal toxicity. *Dis Mon* 2009; 55:592.
78. Vanherweghem JL, et al: Rapidly progressive interstitial renal fibrosis in young women: Association with slimming regimen including Chinese herbs. *Lancet* 1993; 341:387.
79. Pitt JI: Chinese herbal medicines, aristolochic acid and Balkan endemic nephropathy. *Occup Environ Med* 2011; 68:237.
80. Vivekanand JHA: Herbal medicines and chronic kidney disease. *Nephrology* 2010; 15:10.
81. Lai MN, et al: Risks of kidney failure associated with consumption of herbal products containing Mu Tong or Fangchi: A population-based case-control study. *Am J Kidney Dis* 2010; 55:507.
82. Meggs WJ, et al: Anticholinergic poisoning associated with an herbal tea—New York City, 1994. *MMWR Morb Mortal Wkly Rep* 1995; 44:193.
83. Slifman NR, et al: Brief report: Contamination of botanical dietary supplements by *Digitalis lanata*. *N Engl J Med* 1998; 339:806.
84. Newman LS, Feinberg MW, LeWine HE: A bitter tale. *N Engl J Med* 2004; 351:594.
85. Ko RJ: Adulterants in Asian patent medicine. *N Engl J Med* 1998; 339:847.
86. Gasser U, Klier B, Kühn AV, Steinhoff B: Current findings on the heavy metal content in herbal drugs. *Pharmeur Sci Notes* 2009; 1:37.
87. Giampreti A, Bonetti C, Lonati D, Manzo L, Locatelli CA: A young Indian male with abdominal pain. *Clin Toxicol (Phila)* 2011; 49:191.
88. Lu YF, et al: Realgar, cinnabar and An-Gong-Niu-Huang Wan are much less chronically nephrotoxic than common arsenicals and mercurials. *Exp Biol Med (Maywood)* 2011; 236:233.
89. Raviraja A, et al: Three cases of lead toxicity associated with consumption of Ayurvedic medicines. *Indian J Clin Biochem* 2010; 25:326.
90. Saper RB, et al: Heavy metal content of Ayurvedic herbal medicine products. *JAMA* 2004; 292:2868.
91. Lewis AS: Organic versus inorganic arsenic in herbal kelp supplements. *Environ Health Perspect* 2007; 115:A575.
92. Ries CA, Sahud MA: Agranulocytosis caused by Chinese herbal medicines. *JAMA* 1975; 231:352.
93. Nelson L, Shih R, Hoffman R: Aplastic anemia induced by an adulterated herbal preparation. *J Toxicol Clin Toxicol* 1995; 33:467.
94. Capobianco DJ, et al: Proximal-muscle weakness induced by herbs. *N Engl J Med* 1993; 329:1430.
95. Diamond J, Pallone PL: Acute interstitial nephritis following use of Tung Shueh pills. *Am J Kidney Dis* 1994; 24:219.
96. Chan TY, Critchley JA: Usage and adverse effects of Chinese herbal medicines. *Hum Exp Toxicol* 1996; 15:5.
97. Wong HCG: Allergic reactions associated with Chinese herbal medicine. *Allergy Asthma* 2000; 13:13.
98. Ernst E: Adverse effects of herbal drugs in dermatology. *Br J Dermatol* 2000; 143:923.
99. Seeff LB: Herbal hepatotoxicity. *Clin Liver Dis* 2007; 11:577.
100. Poon WT, et al: Hepatitis induced by *Teucrium viscidum*. *Clin Toxicol (Phila)* 2008; 46:819.
101. Cheung WI, et al: Liver injury associated with the use of *Fructus Psoraleae* (Bol-gol-zhee or Bu-gu-zhi) and its related proprietary medicine. *Clin Toxicol (Phila)* 2009; 47:683.
102. Nin Chau T, et al: Causality assessment of herb-induced liver injury using multidisciplinary approach and Roussel Uclaf Causality Assessment Method (RUCAM). *Clin Toxicol (Phila)* 2011; 49:34.
103. Stadlbauer V, Weiss S, Payer F, Stauber RE: Herbal does not at all mean innocuous: The sixth case of hepatotoxicity associated with *Morinda citrifolia* (Noni). *Am J Gastroenterol* 2008; 103:2406-2407.
104. Schoepfer AM, et al: Herbal does not mean innocuous: Ten cases of severe hepatotoxicity associated with dietary supplements from Herbalife products. *J Hepatol* 2007; 47:521.
105. Richardson WN, Henderson L: The safety of kava: A regulatory perspective. *Br J Clin Pharmacol* 2007; 64:418.
106. Haller CA, Benowitz NL: Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 2000; 343:1833.
107. Palmer ME, et al: Adverse events associated with dietary supplements: An observational study. *Lancet* 2003; 361:1566.
108. Eisenberg DM, et al: Trends in alternative medicine use in the United States, 1990-97. *JAMA* 1998; 280:1569.
109. Izzo AA, et al: Cardiovascular pharmacotherapy and herbal medicines: The risk of drug interaction. *Int J Cardiol* 2005; 98:1.
110. Izzo AA: Herb-drug interactions: An overview of the clinical evidence. *Fundam Clin Pharmacol* 2005; 19:1.
111. Mrvos R, Swanson-Biearman B, Krenzelok EP: Backyard mushroom ingestions: No gastrointestinal decontamination—no effect. *J Emerg Med* 2007; 33:381.
112. Cassidy N, Duggan E, Tracey JA: Mushroom poisoning in Ireland: The collaboration between the National Poisons Information Centre and expert mycologists. *Clin Toxicol (Phila)* 2011; 49:171.
113. Diaz JH: Evolving global epidemiology, syndromic classification, general management, and prevention of unknown mushroom poisonings. *Crit Care Med* 2005; 33:419.
114. Diaz JH: Syndromic diagnosis and management of confirmed mushroom poisonings. *Crit Care Med* 2005; 33:427.
115. Barbee GA, et al: Analysis of mushroom exposures in Texas requiring hospitalization, 2005-2006. *J Med Toxicol* 2009; 5:59.
116. McClintock RL, Watts DJ, Melanson S: Unrecognized magic mushroom abuse in a 28-year-old man. *Am J Emerg Med* 2008; 26:972.e3.
117. Lurie Y, et al: Mushroom poisoning from species of genus *Inocybe* (fiber head mushroom): A case series with exact species identification. *Clin Toxicol (Phila)* 2009; 47:562.
118. Haberl B, Pfab R, Berndt S, Greifenhagen C, Zilker T: Case series: Alcohol intolerance with Coprine-like syndrome after consumption of the mushroom *Lepiota aspera*. *Clin Toxicol (Phila)* 2011; 49:113.
119. West PL, Lindgren J, Horowitz Z: *Amanita smithiana* mushroom ingestion: A case of delayed renal failure and literature review. *J Med Toxicol* 2009; 5:32.
120. French LK, Hendrickson RG, Horowitz BZ: *Amanita phalloides* poisoning. *Clin Toxicol (Phila)* 2011; 49:128.
121. Giannini L, et al: Amatoxin poisoning: A 15-year retrospective analysis and follow-up evaluation of 105 patients. *Clin Toxicol (Phila)* 2007; 45:539.
122. Ganzert M, Felgenhauer N, Schuster T, et al: Amanita poisoning—comparison of silibinin with a combination of silibinin and penicillin. *Dtsch Med Wochenschr* 2008; 133:2261.
123. Tong TC, et al: Comparative treatment of alpha-amanitin poisoning with *N*-acetylcysteine, benzylpenicillin, cimetidine, thioctic acid, and silybin in a murine model. *Ann Emerg Med* 2007; 50:282.
124. Karakayali H, et al: Pediatric liver transplantation for acute liver failure. *Transplant Proc* 2007; 39:1157.
125. Yildiz BD, Abbasoglu O, Saglam A, Sökmensüer C: Urgent liver transplantation for *Amanita phalloides* poisoning. *Pediatr Transplant* 2008; 12:105.
126. Mottram AR, Lazio MP, Bryant SM: *Lepiota subincarnata* induced fulminant hepatic failure presenting with pancreatitis. *J Med Toxicol* 2010; 6:155.
127. Deutsch M, Koskinas J, Kountouras D, Archimandritis AJ: *Amanita phalloides* poisoning: Reassessment of prognostic factors and indications for emergency liver transplantation. *J Hepatol* 2007; 47:728.
128. Escudie L, et al: *Amanita phalloides* poisoning: Reassessment of prognostic factors and indications for emergency liver transplantation. *J Hepatol* 2007; 46:466.
129. Durand F, Francoz C, Escudié L: Reply to "Reassessment of predictors of fatal outcome in amatoxin poisoning: Some critical comments." *J Hepatol* 2007; 47:425.
130. Ganzert M, Felgenhauer N, Zilker T: Indication of liver transplantation following amatoxin intoxication. *J Hepatol* 2005; 42:202.
131. Leathem AM, Dorran TJ: Poisoning due to raw *Gyromitra esculenta* (false morels) west of the Rockies. *Can J Emerg Med* 2007; 9:127.
132. Frank H, et al: Acute renal failure by ingestion of *Cortinarius* species confounded with psychoactive mushrooms: A case series and literature survey. *Clin Nephrol* 2009; 71:557.
133. Wynckel A, Talmud D: Renal failure induced by *Cortinarius* poisoning. *Pediatr Nephrol* 2011; 26:489.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 165

SEDATIVE HYPNOTICS

Leon Gussow and Andrea Carlson

BARBITURATES

Perspective

Barbiturates are discussed in do-it-yourself suicide manuals and were implicated in the high-profile deaths of Marilyn Monroe, Jimi Hendrix, Abbie Hoffman, and Margaux Hemingway as well as in the mass suicide of 39 members of the Heaven's Gate cult in 1997. Although barbiturates are still useful for seizure disorders, they rarely are prescribed as sedatives, with the availability of safer alternatives, such as benzodiazepines. Mortality from barbiturate poisoning declined from approximately 1500 deaths per year in the 1950s to only two fatalities in 2009.[1]

Barbiturates are addictive, producing physical dependence and a withdrawal syndrome that can be life-threatening. Whereas tolerance to the mood-altering effects of barbiturates develops rapidly with repeated use, tolerance to the lethal effects develops more slowly, and the risk of severe toxicity increases with continued use.

Principles of Disease

Barbiturates depress the activity of all excitable cells, especially those in the central nervous system (CNS), by enhancing the activity of γ-aminobutyric acid (GABA), the major central inhibitor. In acute overdose, barbiturates decrease neural transmission in autonomic ganglia, the myocardium, and the gastrointestinal tract and also inhibit the response to acetylcholine at the neuromuscular junction.

The $GABA_A$ receptor is a protein complex found on postsynaptic membranes in the CNS. Structurally, it consists of several distinct receptor sites surrounding a chloride ion (Cl^-) channel (Fig. 165-1). GABA opens the chloride channel. The resulting flow of Cl^- into the cell increases the negative resting potential, hyperpolarizing and stabilizing the membrane. There are separate receptor sites for barbiturates and for benzodiazepines and a third site that binds GABA, ethanol, and meprobamate. Although barbiturates and ethanol can directly increase Cl^- conductance, benzodiazepines require the presence of GABA to affect Cl^- flow, which may account for the relative safety of benzodiazepines in comparison with barbiturates.

Barbiturates produce dose-related depressive effects ranging from mild sedation to coma and fatal respiratory arrest. In the early stages of intoxication, some patients experience euphoria. Barbiturates have no analgesic effect and can paradoxically increase the reaction to pain at low doses.

Barbiturates act directly on the medulla to produce respiratory depression. In therapeutic doses, this respiratory depression mimics that of normal sleep. Starting with doses approximately three times therapeutic, the neurogenic, chemical, and hypoxic respiratory drives are progressively suppressed. Because airway reflexes are not inhibited until general anesthesia is achieved, laryngospasm can occur at low doses.

Therapeutic oral doses of barbiturates produce only mild decreases in pulse and blood pressure, similar to sleep. With toxic doses, more significant hypotension occurs from direct depression of the myocardium along with pooling of blood in a dilated venous system. Peripheral vascular resistance is usually normal or increased, but barbiturates interfere with autonomic reflexes, which then do not adequately compensate for the myocardial depression and decreased venous return. Barbiturates can precipitate severe hypotension in patients whose compensatory reflexes are already maximally stimulated, such as those with heart failure or hypovolemic shock. Barbiturates also decrease cerebral blood flow and intracerebral pressure. Although hypnotic doses of barbiturates do not affect gastric emptying, higher doses can decrease gastrointestinal smooth muscle tone and peristaltic contractions and delay gastric emptying.

Barbiturates are classified according to their onset and duration of action (Box 165-1): ultra-short acting (onset immediate after intravenous dose, duration minutes), short acting (onset 10-15 minutes after oral dose, duration 6-8 hours), intermediate acting (onset 45-60 minutes, duration 10-12 hours), and long acting (onset 1 hour, duration 10-12 hours). Only long-acting preparations have anticonvulsant effects in doses that do not cause sedation. Short- and intermediate-acting preparations are almost completely metabolized to inactive metabolites in the liver, whereas 25% of a phenobarbital (long-acting) dose is excreted unchanged through the kidney. Because phenobarbital is a weak acid (pK_a 7.2), alkalinization of the urine will increase the amount of drug present in ionized form, minimizing tubular reabsorption and increasing drug clearance. Short- and intermediate-acting barbiturates are not significantly affected by pH changes in this range.

Barbiturates cross the placenta, with fetal levels approaching those of the mother. They are also excreted in low concentration in breast milk. Use during pregnancy is associated with birth defects (category D).

Clinical Features

Mild barbiturate toxicity mimics ethanol intoxication. It is manifested with drowsiness, slurred speech, ataxia, unsteady gait, nystagmus, emotional lability, and impaired cognition.

In severe acute intoxication, CNS depression progresses from stupor to deep coma and respiratory arrest. Although pupils are usually normal or small and reactive, concomitant hypoxia can cause pupils to be fixed and dilated. Corneal and gag reflexes may

www.ketabpezeshki.com 66485457-66963820

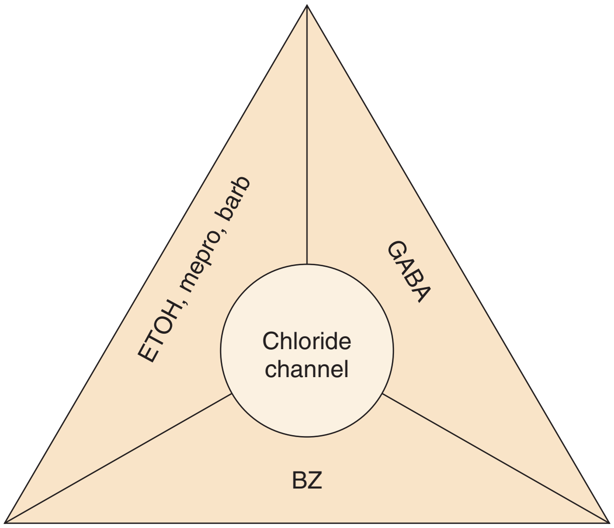


Figure 165-1. The γ-aminobutyric acid (GABA) receptor complex. *BZ,* benzodiazepine binding site; *GABA,* GABA binding site; *ETOH, mepro, barb,* binding sites for ethanol, meprobamate, and barbiturates, respectively.

Box 165-1 Barbiturates

Ultrashort Acting
Methohexital (Brevital)
Thiopental (Pentothal)

Short and Intermediate Acting
Pentobarbital (Nembutal)
Secobarbital (Seconal)
Amobarbital (Amytal)
Aprobarbital (Alurate)
Butabarbital (Butisol)
Butalbital (Fiorinal)

Long Acting
Phenobarbital (Solfoton, Luminal)
Mephobarbital (Mebaral)

be diminished or absent, muscle tone flaccid, and deep tendon reflexes diminished or absent. Flexor (decorticate) and extensor (decerebrate) posturing can occur in patients comatose from barbiturate intoxication. These neurologic signs are variable and do not always correlate with severity of intoxication or depth of coma. A fluctuating level of consciousness is commonly seen. High barbiturate levels depress gastrointestinal motility, delaying drug absorption. As the drug is metabolized and blood levels drop, peristalsis and drug absorption may increase, causing drug levels to rise.

The life threat in severe barbiturate toxicity is respiratory depression. Because respirations can be rapid but shallow, the degree of hypoventilation may not be apparent on clinical examination, and pulse oximetry or capnography may be needed to detect the ventilation compromise.

Hypotension is common in patients with severe intoxication, along with a normal or increased heart rate. Barbiturate overdose is associated with noncardiogenic pulmonary edema. Altered pulmonary capillary permeability can be caused by hypoperfusion, hypoxia, or a direct effect of the drug. Pneumonia may be delayed.

Barbiturate withdrawal syndrome includes tremors, hallucinations, seizures, and delirium (similar to the delirium tremens of ethanol withdrawal). However, severe withdrawal occurs only after dependence on short- or intermediate-acting barbiturates (e.g., pentobarbital, secobarbital, amobarbital, or butalbital). Because these drugs are not commonly used, this syndrome is now very rare.

Diagnostic Strategies

The therapeutic level of phenobarbital is 15 to 40 μg/mL (65-172 μmol/L). A serum level greater than 50 μg/mL can be associated with coma, especially in a patient who is not a chronic user. Levels greater than 80 μg/mL are potentially fatal. Serial phenobarbital levels can monitor effectiveness of treatment. Other than phenobarbital, barbiturates have high volumes of distribution, so serum levels do not accurately reflect CNS concentrations or correlate with clinical severity. A positive urine screen establishes only exposure to a barbiturate but does not prove that the drug is present in toxic amounts and should not be relied on to explain decreased mental status.

Chest radiographs can detect noncardiogenic pulmonary edema or pneumonia. Computed tomography of the head may be helpful in comatose patients with evidence of trauma, focal neurologic signs, papilledema, or uncertain diagnosis to detect other causes of stupor and coma.

Because the electroencephalogram may be silent as a result of barbiturate overdose, no patient should be declared "brain dead" if barbiturates are present at therapeutic levels or higher.

Management

Because barbiturates have no specific antidote, the key to management of these patients is supportive care, particularly with respect to the cardiovascular and respiratory systems. Severely intoxicated patients are unable to protect their airway and have decreased ventilatory drive. Supplemental oxygen may suffice for patients with mild to moderate overdose, but intubation is often required. Long-term induced paralysis is rarely necessary, and additional sedation usually is unnecessary for mechanical ventilation. Careful fluid replacement should maintain a systolic blood pressure above 90 mm Hg and adequate urine output. Patients should be monitored for fluid overload and pulmonary edema. Active warming should be initiated if the rectal temperature is below 30° C.

Gastrointestinal Decontamination and Enhanced Elimination

Gastric emptying by lavage is not indicated. For large overdoses, there is evidence that clearance of phenobarbital is markedly increased with multidose activated charcoal (MDAC).[2] One dosage for MDAC is 25 g every 2 hours in an adult; the pediatric dose is 0.5 g/kg every 2 hours. If vomiting occurs, a smaller dose or antiemetics should be used. MDAC can also be administered slowly through a nasogastric tube. Contraindications to MDAC include an unprotected airway and gastrointestinal obstruction or perforation. Decreased peristalsis can result in constipation with MDAC and is a relative contraindication to MDAC.[2] Although MDAC may shorten the duration of the intoxication, there is no evidence for improved outcome over supportive care, and supportive care without administration of activated charcoal is also an acceptable approach.

Although alkalinization of the urine with sodium bicarbonate has been recommended in the past, a nonrandomized study suggested that MDAC alone is most effective at increasing the drug's clearance.[3] The authors of that study hypothesize that alkalinization may interfere with the ability of the drug to diffuse across intestinal mucosa from the blood into the gut. A recent

www.ketabpezeshki.com 66485457-66963820

comprehensive review concluded that there is no role for urine alkalinization in acute barbiturate poisoning.[4]

Hemodialysis is rarely needed but may increase clearance of phenobarbital in the presence of renal or cardiac failure, acid-base or electrolyte abnormalities, unstable cardiorespiratory status, or inadequate response to less invasive measures. Because phenobarbital is 40 to 60% protein bound, hemoperfusion was advocated over hemodialysis; however, newer high-efficiency dialyzers using high blood flow rates provide drug clearance greater than that achieved by hemoperfusion.[5] Unfortunately, there are insufficient data to determine the true risk-benefit ratio of hemodialysis in acute barbiturate overdose.[4]

Disposition

An asymptomatic patient who arrives in the emergency department (ED) after ingesting barbiturates should be observed for 6 hours after ingestion for mental status changes, slurred speech, ataxia, hypotension, and respiratory depression. Symptoms generally occur within 1 hour of ingestion. Patients who remain asymptomatic and have no significant complicating coingestants or medical problems can be discharged or referred for psychiatric care. Patients who are still symptomatic after 6 hours should be admitted for observation and supportive care.

BENZODIAZEPINES

Perspective

Before 1950, treatment options for anxiety were limited. Whereas meprobamate, first synthesized in 1950, ultimately proved no safer than the barbiturates, its commercial success inspired the development of other nonbarbiturate anxiolytics. With chlordiazepoxide in 1960 and diazepam in 1963, benzodiazepines emerged as the principal agents for the treatment of anxiety. Cardiac effects and fatalities from pure benzodiazepine overdose are rare, and respiratory depression is less than with barbiturates. In addition, drug-drug interactions involving benzodiazepines are uncommon.

Benzodiazepines remain among the most widely prescribed class of drugs (Table 165-1) and are the most common prescription drugs used in suicide attempts. Fortunately, most benzodiazepine overdoses follow a relatively benign clinical course. Children make up 10% of benzodiazepine overdose cases.

Principles of Disease

Benzodiazepines produce sedative, hypnotic, anxiolytic, and anticonvulsant effects by enhancing the inhibitory actions of GABA. Binding of a benzodiazepine to a specific benzodiazepine receptor potentiates GABA effects on the chloride channel at the $GABA_A$ receptor, increasing intracellular flux of chloride ions and hyperpolarizing the cell. The net effect is a diminished ability of the nerve cell to initiate an action potential, inhibiting neural transmission.

Three unique benzodiazepine receptors exist, distributed variably throughout the central and peripheral nervous systems. Classic benzodiazepines are nonselective, producing a broad range of clinical effects. Newer benzodiazepines interact selectively with a single receptor subtype to achieve a desired result, such as sedation, while minimizing unwanted effects.

Pharmacokinetics

Benzodiazepines are rapidly absorbed orally. Intramuscular use of chlordiazepoxide and diazepam is limited by erratic absorption, but lorazepam and midazolam are predictably absorbed after intramuscular injection. After absorption, benzodiazepines distribute readily and rapidly penetrate the blood-brain barrier. In plasma, benzodiazepines are highly protein bound.[6]

All benzodiazepines are metabolized in the liver. Oxazepam, temazepam, and lorazepam are directly conjugated to an inactive, water-soluble glucuronide metabolite that is excreted by the kidney. Other benzodiazepines must first be converted by the hepatic cytochrome P_{450} system. Chlordiazepoxide, diazepam, flurazepam, and clorazepate are metabolized to active derivatives that are then slowly conjugated and excreted. The long elimination half-lives of these intermediates can cause accumulation in the body with repeated dosing. Triazolam, alprazolam, and midazolam are converted to hydroxylated intermediates that are active, but because they are so rapidly conjugated and excreted, they do not contribute significantly to the drug's overall effect.[6]

Table 165-1 Benzodiazepines

NAME	USUAL DOSE	ORAL PEAK (hr)	HALF-LIFE (hr)	PARENT METABOLITE ACTIVITY
Alprazolam (Xanax)	0.25-0.5 mg	1-2	6-27	Inactive
Chlordiazepoxide(Librium)	5-25 mg	0.5-4	5-30	Active
Clonazepam (Klonopin)	0.25-0.5 mg	1-2	18-50	Inactive
Clorazepate (Tranxene)	7.5-15 mg	1-2	1-3	Active
Diazepam (Valium)	2-10 mg	0.5-1	20-50	Active
Estazolam (ProSom)	1-2 mg	2	8-28	Inactive
Flurazepam (Dalmane)	15-30 mg	0.5-1	2-3	Active
Halazepam (Paxipam)	20-40 mg	1-3	14	Active
Lorazepam (Ativan)	0.5-2 mg	2-4	10-20	Inactive
Midazolam (Versed)	0.025-0.1 mg/kg	1-2	1.5-3	Active
Oxazepam (Serax)	10-30 mg	2-4	5-20	Inactive
Quazepam (Doral)	7.5-15 mg	2	39-41	Active
Temazepam (Restoril)	7.5-30 mg	1-2	3-19	Inactive
Triazolam (Halcion)	0.125-0.25 mg	1-2	1.5-5.5	Inactive

www.ketabpezeshki.com 66485457-66963820

Cytochrome P_{450} processes may be significantly impaired in elderly patients or those with liver disease, leading to prolonged elimination of some benzodiazepines. Coingestion of drugs that also undergo cytochrome P_{450} metabolism (e.g., cimetidine, ethanol) also prolongs the half-lives of these benzodiazepines, but the clinical significance of these interactions is unclear.[7]

Clinical Features

CNS depression is common in patients with benzodiazepine poisoning and ranges from mild drowsiness to coma. Respiratory depression is due mainly to upper airway obstruction and increased upper airway resistance from loss of muscle tone rather than central apnea. Significant respiratory depression is rare but can be seen with large oral overdoses or during intravenous conscious sedation, particularly when the benzodiazepine is combined with an opioid such as fentanyl.[7] Hypotension is uncommon. Other potential complications include aspiration pneumonia and pressure necrosis of skin and muscles.

Most children have symptoms within 4 hours of benzodiazepine ingestion. Ataxia is the most common sign of toxicity, occurring in 90% of patients. Respiratory depression occurs in less than 10% of pediatric cases, and hypotension has not been reported.

Prolonged or high-dose infusions of certain benzodiazepine preparations have been associated with the development of lactic acidosis. Metabolism of the propylene glycol diluent in diazepam and lorazepam intravenous solutions by alcohol dehydrogenase produces lactate, which can accumulate and cause acidosis severe enough to require intervention. Patients with renal or hepatic insufficiency are at increased risk for this complication.[8]

Diagnostic Strategies

Any patient with altered mental status should have a blood glucose level rapidly determined. Qualitative immunoassays for benzodiazepines in urine are available but do not aid management decisions. Most of these tests detect only benzodiazepines that are metabolized to oxazepam glucuronide; therefore, clonazepam, lorazepam, midazolam, and alprazolam are not detected on many urine drug screens.[9] Serum drug concentrations are not routinely available and do not correlate with clinical severity. A lack of alcohol odor or a negative breathalyzer or blood ethanol test result suggests benzodiazepine or another sedative as a possible cause.

The benzodiazepine antagonist flumazenil should not be routinely administered to patients with coma of unknown origin or suspected benzodiazepine overdose, either for diagnostic or for therapeutic purposes.[10] Any possibility of concomitant tricyclic overdose contraindicates flumazenil use.

Differential Considerations

Benzodiazepine overdose is usually suspected or diagnosed because of the clinical presentation. Many patients are arousable and can provide supporting information. Atypical or focal findings suggest the presence of other conditions. Profound coma or cardiopulmonary instability is rare with pure benzodiazepine overdose and should prompt the search for a coingestant. Nontoxicologic causes of CNS depression should also be considered.

Management

General

Initial stabilization, including endotracheal intubation, should not be delayed by the administration of an antidote. Most benzodiazepine overdoses can be managed expectantly. Activated charcoal is generally not beneficial in overdose.[11] MDAC, hemodialysis, and whole-bowel irrigation are not effective in benzodiazepine overdose.

Box 165-2 Use of Flumazenil

Indications
- Isolated benzodiazepine overdose in nonhabituated user (e.g., accidental pediatric exposure)
- Reversal of conscious sedation

Absolute Contraindications
- Suspected coingestant that lowers seizure threshold (e.g., tricyclic antidepressants, cocaine, lithium, methylxanthines, isoniazid, propoxyphene, monoamine oxidase inhibitors, bupropion, diphenhydramine, carbamazepine, cyclosporine, chloral hydrate)
- Patient taking benzodiazepine for control of a potentially life-threatening condition (e.g., seizures)
- Concurrent sedative-hypnotic withdrawal
- Seizure activity or myoclonus
- Hypersensitivity to flumazenil or benzodiazepines
- Patient with neuromuscular blockade

Relative Contraindications
- Chronic benzodiazepine use, not taken for control of life-threatening condition
- Known seizure disorder not treated with benzodiazepines
- Head injury
- Panic attacks
- Chronic alcoholism

Antidote

Flumazenil, a nonspecific competitive antagonist of the benzodiazepine receptor, can reverse benzodiazepine-induced sedation after general anesthesia, procedural sedation, and confirmed benzodiazepine overdose, but it is not recommended for the routine reversal of sedative overdose in the ED. Although theoretic benefits of flumazenil use include cost savings and avoidance of procedures and tests such as endotracheal intubation and lumbar puncture, several studies have not been able to demonstrate an actual benefit.[12] Seizures and cardiac dysrhythmias can occur after flumazenil administration, and fatalities have been reported. Flumazenil use can precipitate acute withdrawal in patients who are dependent on benzodiazepines. Similarly, this antidote is hazardous when it is given to patients who have coingested seizure-causing drugs (such as cocaine or a tricyclic antidepressant) because of loss of the benzodiazepine's protective anticonvulsant properties. Coingestants that cause dysrhythmias, such as carbamazepine and chloral hydrate, may increase the likelihood of cardiac effects. Other risk factors are summarized in Box 165-2. One study found that 12% of patients receiving flumazenil after known pure or mixed benzodiazepine overdose actually had a contraindication to its use.[13]

The initial adult dose of flumazenil is 0.2 mg given intravenously during 30 seconds. A second dose of 0.2 mg may be given, followed by 0.2-mg doses at 1-minute intervals to a total of 1 mg. In children, the initial dose is 0.01 mg/kg (up to 0.2 mg). Because the duration of action of flumazenil is short (0.7-1.3 hours), resedation occurs in up to 65% of patients and requires either redosing or continuous infusion (0.25-1.0 mg/hr).

In summary, benzodiazepine overdose requires primarily supportive care (including, in some cases, intubation). Flumazenil may precipitate seizures or acute withdrawal and should be used only in highly selected cases, such as small children with accidental poisoning or for accidental overdose of benzodiazepines during procedural sedation. When flumazenil is used, careful monitoring

www.ketabpezeshki.com 66485457-66963820

Box 165-3 Benzodiazepine Withdrawal Symptoms

Nonspecific
Anxiety, depression, insomnia, tremor, tachycardia, sweating

Severe (rare)
Visual hallucinations, delirium, seizures

is necessary because of the risk for recurrent respiratory depression or resedation. Use of flumazenil has not consistently altered outcome, complication rate, number of costly procedures performed, or duration of hospital stay in ED patients.[13]

Disposition

Patients remaining asymptomatic after 4 to 6 hours of ED observation may be medically cleared. For cases of deliberate overdose, appropriate psychiatric consultation should be obtained.

Benzodiazepine Withdrawal Syndrome

Abrupt discontinuation of a benzodiazepine in a chronic user results in a characteristic constellation of symptoms similar to ethanol withdrawal (Box 165-3). Risk for withdrawal is a function of both the dose of benzodiazepine and the duration of its use. Continuous treatment for more than 4 months is generally required before a patient is at risk for withdrawal. With abrupt discontinuation of a benzodiazepine, the most severe withdrawal symptoms are expected within several days to a week.[14] Use of flumazenil can precipitate immediate withdrawal symptoms. Treatment of withdrawal consists of restarting of benzodiazepines.

FLUNITRAZEPAM

Flunitrazepam (Rohypnol) has been used in Europe, Asia, and Latin America for insomnia and preoperative sedation since 1975. Although it has never been manufactured or sold in the United States, flunitrazepam has been suggested in many "date rape" incidents. Flunitrazepam has been an active agent in the illicit drug market, where it is used to alter the effects of other drugs, including heroin and cocaine.[15]

Flunitrazepam has 10 times more affinity than diazepam for certain benzodiazepine receptors. CNS depression occurs within 30 minutes. The drug is most frequently ingested with alcohol, producing additional disinhibition and amnesia. Despite marked CNS depression, patients can usually be aroused with noxious stimuli. The half-life of the drug is 16 to 35 hours, but coma can be prolonged for up to 48 hours.[15] Flunitrazepam is easily obtained outside the United States. The drug is not detected on routine urine drug screens, but if it is needed as evidence, urine should be refrigerated or frozen and the local or state police crime laboratory contacted to arrange specific testing. Metabolites of flunitrazepam are detected in the urine up to 72 hours after exposure.

BUSPIRONE

Buspirone (BuSpar) has been used for generalized anxiety since 1986. Unlike benzodiazepines, buspirone does not have any effect on GABA but is a partial serotonin (5-HT_{1A}) agonist. To a lesser extent, it also antagonizes dopamine (D_2) receptors. Buspirone has no hypnotic, anticonvulsant, or muscle relaxant effects.

Buspirone has several advantages over benzodiazepines. The drug causes minimal CNS depression, even in combination with ethanol. Dosage adjustment is not needed for elderly patients. A withdrawal state after discontinuation has not been reported. Only one case of isolated buspirone overdose has been published. That patient was lethargic and had a tonic-clonic seizure but recovered fully.[16]

ZOLPIDEM AND ZALEPLON

Zolpidem (Ambien) and zaleplon (Sonata) differ in structure from both the benzodiazepines and buspirone, and neither is detected on a benzodiazepine toxicology screen. They act selectively at a specific benzodiazepine receptor, producing sedation without many of the side effects seen with benzodiazepines. They have modest anxiolytic, muscle relaxant, and anticonvulsant properties. Significant drug interactions are rare. Compared with zolpidem, zaleplon causes less memory loss and sedation at therapeutic doses and is more rapidly eliminated.[17] Transient visual disturbances, transient global amnesia, and hallucinations can occur in patients with normal levels of consciousness with both zolpidem and zaleplon.[17-19] Abuse of zolpidem is limited by vomiting, which may occur after a supratherapeutic dose. Both zolpidem and zaleplon are rapidly eliminated and lack active metabolites.[20] In 2005, a controlled-release formulation of zolpidem (Ambien CR) became available. The dual-layered tablet releases an immediate dose of zolpidem, followed by a slow, extended release from the inner layer to maintain plasma zolpidem concentrations. Clinical experience thus far suggests that overdoses with the controlled-release formulation mirror those of the immediate-release preparation, with only small differences in the likelihood of drowsiness, hallucinations, and ataxia.[21]

Patients with zolpidem overdose do well with supportive care alone. Fatalities from isolated zolpidem overdose are rare. All published cases have involved individuals found dead at home and have been associated with coingestants, particularly other sedative-hypnotics or antipsychotics.[22] Drowsiness is by far the most common symptom. Coma and respiratory failure are rare, despite overdoses of up to 40 times the normal dose, although intubation may be required, particularly if there are coingestants. Zolpidem overdose in children follows a similarly benign course. Drowsiness, ataxia, and hallucinations generally resolve within 10 hours.[23]

Overdose information for zaleplon is limited. In one case series, patients had CNS depression and mild hypotension. Arousal was temporally associated with flumazenil use in one patient.[24] The only published fatality involved a mixed drug overdose including unknown quantities of zaleplon and butalbital, with postmortem serum zaleplon concentration 40 times greater than therapeutic.[25] Adverse effects with therapeutic use include headache, anterograde amnesia, and transient visual hallucinations.[20] The blue-green discoloration of gastric contents, mouth, and urine after zaleplon overdose is attributed to the indigo carmine dye present in zaleplon's capsule shell.[26]

ESZOPICLONE

Eszopiclone (Lunesta) has been marketed in the United States since 2005 for treatment of insomnia. It is the *S*-isomer of racemic zopiclone, which has been used for decades outside the United States. Eszopiclone has a structure unrelated to that of benzodiazepines, barbiturates, zolpidem, and zaleplon.[27-30]

The mechanism of eszopiclone's action is not completely described but may involve a specific $GABA_A$ receptor close to or coupled with the benzodiazepine receptor.[27-29] Eszopiclone is rapidly absorbed, with a peak serum level at 1 hour and a half-life of 6 hours. It is metabolized in the liver to minimally active metabolites. The usual bedtime dose is 3 mg. It is recommended that elderly patients and those with hepatic insufficiency be treated with a lower (1 mg) dose.

www.ketabpezeshki.com 66485457-66963820

Adverse effects with therapeutic use of eszopiclone include drowsiness, dizziness, dry mouth, unpleasant taste, nausea, and vomiting. Auditory and visual hallucinations have been reported.[31] Experience with eszopiclone overdose is limited. The key to treatment is good supportive care. CNS depression may be prolonged and pronounced in elderly patients.[32] A retrospective case review described 525 eszopiclone ingestions, but 259 of these patients had also ingested other drugs or chemicals.[28] The ingestions involved eszopiclone doses up to 210 mg and had mild to moderate symptoms at most. Two deaths occurred, both involving significant coingestants. A single case report described a 52-year-old man who had coronary vasospasm and a ventricular fibrillation arrest after ingestion of 45 to 60 mg of eszopiclone.[30] However, the arrest occurred approximately 20 hours after ingestion, and it is unclear what role, if any, eszopiclone played in causing the arrest.

CHLORAL HYDRATE

Perspective

Chloral hydrate has a low therapeutic ratio and can produce significant, potentially fatal toxicity. Whereas chloral hydrate use is rare today, it is still occasionally prescribed as a sedative in the elderly and for sedation in children undergoing medical procedures. The hypnotic oral adult dose is 0.5 to 1.0 g. The toxic oral dose in adults is approximately 10 g and may be as little as 1.5 g in a child.[33]

The toxic effects of chloral hydrate include CNS depression, gastrointestinal irritation, cardiovascular instability, hepatitis, and proteinuria.[34,35] The primary active metabolite of chloral hydrate, trichloroethanol, has a barbiturate-like effect on $GABA_A$ receptors and is responsible for most of the CNS depression seen with significant overdose.

Chloral hydrate is rapidly absorbed from the gastrointestinal tract and almost immediately metabolized to trichloroethanol by the enzyme alcohol dehydrogenase. Onset of action is 20 to 30 minutes.[36] Trichloroethanol is long acting, and its half-life can be significantly prolonged after overdose as metabolic pathways become saturated.

Chloral hydrate and ethanol in combination (the "Mickey Finn") potentiate each other's action to produce rapid loss of consciousness. Chloral hydrate increases the half-life of ethanol by competitively inhibiting the enzyme alcohol dehydrogenase, and the metabolism of ethanol generates NADH, a cofactor for the conversion of chloral hydrate to trichloroethanol.

Clinical Features

Chloral hydrate toxicity causes CNS and respiratory depression, gastrointestinal irritation, cardiovascular instability, and dysrhythmias.[34,35] The combination of deep coma and cardiac dysrhythmia without hypoxia is characteristic of severe cases.

Mild chloral hydrate toxicity can mimic ethanol or barbiturate overdose, with drowsiness, ataxia, and lethargy. A pear-like odor to the patient's breath or gastric contents may suggest the diagnosis. More severe toxicity includes miosis, muscle flaccidity, diminished deep tendon reflexes, hypoventilation, hypotension, and hypothermia.[33] Chloral hydrate is corrosive and causes nausea, vomiting, esophagitis, hemorrhagic gastritis, and, more rarely, gastrointestinal perforation or necrosis.[33] Transient hepatic or renal dysfunction can also occur.

Dysrhythmias from chloral hydrate toxicity can be fatal. Chloral hydrate decreases myocardial contractility, shortens the cardiac refractory period, and increases the sensitivity of myocardium to catecholamines. Dysrhythmias include atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, multifocal premature ventricular contractions, torsades de pointes, ventricular fibrillation, and asystole.[36] Hypotension results from inhibition of central neurovascular regulatory centers and impaired myocardial contractility.

Management

The key to management is support of cardiorespiratory function. Intubation may be required for airway protection or to support ventilation and oxygenation. Avoid naloxone or flumazenil, which may precipitate ventricular dysrhythmias.[33] Because chloral hydrate, like other chlorinated hydrocarbons, sensitizes myocardium to catecholamines, epinephrine and norepinephrine should also be avoided. Standard antidysrhythmic agents, such as lidocaine, do not appear effective against chloral hydrate–induced cardiac ectopy. The treatment of choice is a beta-blocker.[37] Intravenous propranolol can be given in adult doses of 0.5 mg until ectopy is suppressed, followed by an infusion of 1 to 2 mg/hr, titrated to a heart rate of 80 to 100 beats/minute. A short-acting agent such as esmolol can also be used. Torsades de pointes should be treated with intravenous magnesium or overdrive pacing. Type I antidysrhythmic agents such as quinidine should be avoided. Unstable patients not responding to conservative therapy can be treated with hemoperfusion or hemodialysis.[33]

OVER-THE-COUNTER SLEEP AIDS

Perspective

Over-the-counter (OTC) sleep aids currently available in the United States contain either diphenhydramine or doxylamine. Many preparations also contain acetaminophen or aspirin, added to achieve nighttime pain relief. The availability and frequent use of these agents may explain why overdose is so common.

Principles of Disease

Diphenhydramine and doxylamine are antihistamines that also have hypnotic, anticholinergic, and weak local anesthetic properties. They act as competitive antagonists of H_1 histamine receptors and cause sedation by inhibiting the actions of acetylcholine on muscarinic receptors in the CNS.

The pharmacokinetic profiles of diphenhydramine and doxylamine are similar. Both are rapidly absorbed, with peak plasma levels occurring at 1 to 2 hours after administration. In the systemic circulation, they are highly protein bound, with large volumes of distribution. Extensive metabolism occurs in the liver by the cytochrome P_{450} system. The elimination half-life is 4 hours for diphenhydramine and 9 hours for doxylamine.

Clinical Features

Impaired consciousness is the most frequent finding with diphenhydramine overdose. Somnolence, psychotic behavior, and agitation are common. Seizures can occur. Anticholinergic effects may be apparent, as noted in Chapter 150. Cardiovascular effects include sodium-channel blockade and wide-complex tachycardia.[38] Apart from a lower incidence of psychosis, doxylamine has toxicity similar to that of diphenhydramine. Seizures and rhabdomyolysis may occur with severe toxicity. Serious cardiotoxicity is rare. Doxylamine toxicity has been reported to cause false-positive results on some immunoassay-based drug screens for methadone and phencyclidine.[39]

Diagnostic Strategies

Some comprehensive urine drug immunoassays will detect diphenhydramine. Quantitative serum levels of diphenhydramine

www.ketabpezeshki.com 66485457-66963820

Box 165-4 γ-Hydroxybutyrate Street Names

GHB	Liquid ecstasy
Grievous bodily harm	Liquid G
GBH	Somatomax
Georgia home boy	Soap
Gib	Salty water
Natural sleep-500	Scoop
Gamma-OH	Sodium oxybate
Gamma hydrate	Easy lay
Liquid X	Cherry menth
Organic quaalude	Fantasy
Liquid E	G-Riffick

Box 165-5 γ-Butyrolactone Street Names

Blue Nitro	Nitro
Blue Nitro Vitality	NRG3
Enliven	Remforce
Fire Water	RenewTrient
Gamma G	Revitalize Plus
GH Revitalizer	Revivarant
GHRE (growth hormone release extract)	SomatoPro
	Verve 5.0

or doxylamine are neither routinely available nor clinically useful. Serum acetaminophen and salicylate concentrations should be measured in patients with OTC sleep aid overdoses because many preparations contain both a hypnotic and an analgesic. Measurement of serum creatine kinase and urinary myoglobin may help detect myoglobinuria.

Management

Management of mild to moderate toxicity from OTC sleep aid overdose is generally supportive. Specific details of anticholinergic toxicity are discussed in Chapter 150.

Disposition

Patients with minor sedation or anticholinergic effects that are resolving or who remain asymptomatic after a 4-hour observation period can be medically cleared. If the ingestion was a suicide attempt or gesture, psychiatric evaluation is indicated. Other patients require inpatient observation in a monitored setting.

γ-HYDROXYBUTYRATE

Perspective

Originally synthesized in the 1960s as an anesthetic, γ-hydroxybutyrate (GHB) was later discovered to be a naturally occurring metabolite of GABA. Since 1970, GHB has been used to treat narcolepsy, alcohol addiction, and opiate withdrawal.[40]

A 1977 report that GHB may enhance effects of steroids and increase release of growth hormone resulted in marketing of the agent as a "natural" aid for increasing muscle mass. Numerous reports of adverse effects followed. In 1989, the U.S. Food and Drug Administration (FDA) called for a voluntary withdrawal of the drug from store shelves. Its sale and manufacture were banned in 1990; however, illicit use of GHB increased, along with its precursors γ-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) (Box 165-4).[41] The Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000 made GHB a schedule I controlled substance. In 2005, GHB was approved by the FDA for the treatment of narcolepsy under the trade name Xyrem (sodium oxybate, 0.5 mg/mL) as a schedule III drug.

GHB remains a popular drug of abuse.[42] Some individuals take GHB for its purported muscle-building and fat-burning actions, others for its psychoactive effects. The drug's euphoria-producing properties make it popular at "raves" (large, crowded youth parties with energetic dancing to rhythmic music for many hours).[43] Self-treatment of insomnia with GHB has been reported and can cause dependence.[44] CNS depression, amnesia, and disinhibition caused by mixing of GHB with ethanol make this combination a potential agent in "date rape" situations.[45,46] A recent review of 226 GHB-associated deaths revealed that calls for medical assistance were often delayed or absent because of the false belief that victims need only "sleep off" their intoxications. Death occurs most often in the prehospital setting, both directly and by increasing the risk for fatal accidents. In this series, GHB was the sole intoxicant in 35% of deaths, underlining the lethal potential of the drug and its congeners.[47]

Chemical precursors to GHB are also commonly abused. GBL is rapidly converted to GHB by plasma lactonases. 1,4-BD is metabolized to γ-hydroxybutyraldehyde by the enzyme alcohol dehydrogenase and then to GHB by aldehyde dehydrogenase.[48,49]

Principles of Disease

GHB binds to specific GHB receptors and at high concentrations to $GABA_B$ receptors.[50] The complex interaction between these two receptors may explain the sometimes paradoxical manifestations of GHB toxicity of somnolence alternating with agitation. Through its action on the $GABA_B$ receptor, GHB decreases release of dopamine.[51,52]

As underground laboratories often synthesize liquid GHB by mixing and heating butyrolactone and sodium hydroxide, careless preparation can result in residual unreacted base, causing significant caustic injury when the liquid is ingested.[41]

GHB is lipophilic and rapidly absorbed. Onset of symptoms occurs within 15 to 30 minutes, and peak plasma levels are reached within 20 to 60 minutes. Unlike GABA, GHB readily crosses the blood-brain barrier. The half-life of GHB is 27 minutes but may increase at high doses.

GBL is an industrial solvent that is rapidly absorbed after ingestion and metabolized within minutes to GHB by peripheral and hepatic lactonases.[41] Before conversion to GHB, GBL itself is inactive and has no sedating effects.[40] It produces a clinical syndrome similar to that of GHB ingestion, but its effects are greater and more prolonged. In fact, after ingestion, GBL is more efficient at delivery of GHB to the CNS than GHB itself is.[53] GBL is available under a number of street names (Box 165-5).

1,4-BD is converted after ingestion to GHB by the enzyme alcohol dehydrogenase.[49] Like GBL, it is used as an industrial solvent. Unlike GBL, 1,4-BD itself has sedative-hypnotic effects. Clinical findings are similar to those of GHB. When 1,4-BD and ethanol are ingested together, ethanol acts as a competitive inhibitor of alcohol dehydrogenase, so the toxic effects of 1,4-BD are delayed and prolonged, and the risk of death is increased.[49] 1,4-BD is available under a number of street names (Box 165-6).

In 2007, a children's toy marketed under the names Aqua Dots and Bindeez Beads was contaminated when 1,4-BD was substituted for a more expensive industrial solvent during the manufacturing process. The toy consisted of tiny brightly colored spheres that were readily ingested by toddlers, causing decreased levels of consciousness, coma, or apparent seizures.[54]

www.ketabpezeshki.com 66485457-66963820

Box 165-6 1,4-Butanediol Street Names

Blue Raine	Revitalize Plus
Dream On	Serenity
Fubar	SomatoPro
Inner G	Thunder nectar
Pine needle extract	Weight belt cleaner
Pine needle oil	Zen
ReJuv@Nite	

Clinical Features

Diagnosis of GHB intoxication is based on the history and clinical course. Rapid recovery from coma, or periods of agitation alternating with periods of decreased level of consciousness, is characteristic. Hypothermia may occur.[43] In the presence of coma, bradycardia with or without hypotension may be seen and can respond to stimulation alone.[43] Miosis with or without nystagmus may be seen. Emesis occurs in 50% of cases.[43] Apparent seizure activity may actually represent random myoclonic movements of the face and extremities. Severity is dependent on the dose and the concurrent use of alcohol or other psychoactive drugs.[44]

Diagnostic Strategies

GHB is not detected on urine toxicology screens. If laboratory confirmation is required, specimens must be collected early and sent for gas chromatography–mass spectroscopy. The drug may be detected in urine up to 12 hours after ingestion.[55]

Poisoning with other sedative-hypnotics can produce a similar clinical picture. Unique to GHB, however, is the relatively rapid resolution of symptoms. In the absence of a coingestant such as ethanol, most patients will awaken within 3 to 4 hours. Nearly all patients recover fully within 8 hours. Prolonged coma should prompt a search for another cause. Cardiac effects and refractory seizures are rare and suggest the presence of other agents.

Management

Because of the high incidence of emesis with GHB overdose, intubation for airway protection should be seriously considered in patients with significant CNS depression. Bradycardia unresponsive to stimulation can be treated with atropine. Treatment of isolated GHB ingestion is supportive. Although some authors suggest physostigmine to reverse GHB-induced coma, the efficacy and safety of this intervention have not been demonstrated, and physostigmine is not indicated or recommended.[48,56,57]

Withdrawal

Patients who suddenly stop GHB or its precursors after chronic, frequent use can experience a severe and potentially life-threatening withdrawal syndrome.[50,58,59] Because of the short half-life of GHB, symptoms of withdrawal begin within several hours of the last dose. The typical patient will have been using these products for weeks or years, every 1 to 3 hours around-the-clock, to avoid withdrawal symptoms.

Mild withdrawal is manifested with anxiety, tremor, and insomnia. This can progress to confusion, delirium, overt psychosis, paranoid ideation, hallucinations (visual, aural, or tactile), and autonomic instability. Diagnosis relies on a history of symptoms beginning after abrupt cessation of use of these products. The differential diagnosis includes withdrawal from other sedatives or hypnotics, delirium tremens, sympathomimetic toxicity, serotonin syndrome, neuroleptic malignant syndrome, CNS infection, and thyroid storm.

Initial treatment begins with high-dose benzodiazepines. However, GHB withdrawal may involve depleted levels of GABA.[58] Because the effect of benzodiazepines requires the presence of GABA, they may not be effective in control of GHB withdrawal. Barbiturates, such as pentobarbital, which do not need GABA to be effective, are often required in cases of severe intoxication.[60]

These patients often require intensive care admission for aggressive sedation and to monitor fluctuating vital signs. Rhabdomyolysis and severe hyperthermia should be ruled out. Deaths have been reported, sometimes many days after presentation and after apparent improvement.[58]

Disposition

Because of GHB's short half-life, symptoms often resolve while the patient is still in the ED. The patient generally regains consciousness spontaneously. No delayed toxicity is expected. Patients should be counseled about the seriousness of GHB intoxication.[47]

KEY CONCEPTS

- Barbiturate intoxication is rare and most patients recover with observation and meticulous supportive care. Most will not require hemodialysis.
- A urine toxicology screen positive for barbiturates does not prove that the drug caused the patient's clinical condition . Serum barbiturate levels confirm the diagnosis but do not correlate with depth of coma or clinical outcome.
- Flumazenil is not needed in most benzodiazepine overdoses. Because it can precipitate seizures, it should not be used in patients who are regular benzodiazepine users. If flumazenil is used, patients should be monitored closely for recurrent respiratory depression and for resedation.
- Chloral hydrate–induced dysrhythmia should be treated with a beta-blocker.
- Endotracheal intubation to protect against emesis and respiratory depression should be strongly considered for patients with GHB overdose and significant CNS depression.
- Withdrawal from GHB or its precursors can be manifested with anxiety, tremor, and insomnia but can progress to a severe syndrome characterized by delirium and autonomic instability. Management of this syndrome often requires high-dose benzodiazepines or barbiturates.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Bronstein AC, et al: 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 27th Annual Report. *Clin Toxicol (Phila)* 2010; 48:979.
2. American Academy of Clinical Toxicology; European Association of Poison Centres and Clinical Toxicologists: Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. *J Toxicol Clin Toxicol* 1999; 37:731.
3. Ebid AI, et al: Pharmacokinetics of phenobarbital during certain enhanced elimination modalities to evaluate their clinical efficacy in management of drug overdose. *Ther Drug Monit* 2001; 23:209.
4. Roberts DM, et al: Enhanced elimination in acute barbiturate poisoning—a systematic review. *Clin Toxicol (Phila)* 2011; 49:2.
5. Palmer BF: Effectiveness of hemodialysis in the extracorporeal therapy of phenobarbital overdose. *Am J Kidney Dis* 2000; 36:640.
6. Chouinard G, et al: Metabolism of anxiolytics and hypnotics: Benzodiazepines, buspirone, zopiclone, and zolpidem. *Cell Mol Neurobiol* 1999; 19:533.
7. Tanaka E: Clinically significant pharmacokinetic drug interactions with benzodiazepines. *J Clin Pharm Ther* 1999; 24:347.
8. Zosel A, et al: Severe lactic acidosis after an iatrogenic propylene glycol overdose. *Pharmacotherapy* 2010; 30:219.
9. Perry HE, Shannon MW: Diagnosis and management of opioid- and benzodiazepine-induced comatose overdose in children. *Curr Opin Pediatr* 1996; 8:243.
10. Goldfrank LG: Flumazenil: A pharmacologic antidote with limited medical toxicology utility, or … an antidote in search of an overdose. *Acad Emerg Med* 1997; 4:935.
11. American Academy of Clinical Toxicology; European Association of Poison Centres and Clinical Toxicologists: Position statement: Single-dose activated charcoal. *J Toxicol Clin Toxicol* 1997; 35:721.
12. Seger DL: Flumazenil—treatment or toxin? *J Toxicol Clin Toxicol* 2004; 42:209.
13. Mathieu-Nolf M, et al: Flumazenil use in an emergency department: A survey. *J Toxicol Clin Toxicol* 2001; 39:15.
14. Molle HJ: Effectiveness and safety of benzodiazepines. *J Clin Psychopharmacol* 1999; 19:2.
15. Waltzman ML: Flunitrazepam: A review of "roofies." *Pediatr Emerg Care* 1999; 15:59.
16. Catalano G, et al: Seizures associated with buspirone overdose: Case report and literature review. *Clin Neuropharmacol* 1998; 21:347.
17. Drover DR: Comparative pharmacokinetics and pharmacodynamics of short-acting hypnosedatives: Zaleplon, zolpidem and zopiclone. *Clin Pharmacokinet* 2004; 43:227.
18. Tsai MJ, et al: A novel clinical pattern of visual hallucinations after zolpidem use. *J Toxicol Clin Toxicol* 2003; 41:869.
19. Tsai MY, et al: Transient global amnesia–like episode due to mistaken intake of zolpidem: Drug safety concern in the elderly. *J Patient Saf* 2009; 5:32.
20. Weitzel KW, et al: Zaleplon: A pyrazolopyrimidine sedative-hypnotic agent for the treatment of insomnia. *Clin Ther* 2000; 22:1254.
21. Forrester MB: Immediate- and controlled-release zolpidem ingestions reported to Texas poison centers. *Hum Exp Toxicol* 2009; 28:505.
22. Gock SB, et al: Acute zolpidem overdose: Report of two cases. *J Anal Toxicol* 1999; 23:559.
23. Kurta D, et al: Zolpidem (Ambien): A pediatric case series. *J Toxicol Clin Toxicol* 1997; 35:453.
24. Hojer J, et al: Zaleplon-induced coma and bluish-green urine: Possible antidotal effect by flumazenil. *J Toxicol Clin Toxicol* 2002; 40:571.
25. Moore KA, et al: Mixed drug intoxication involving zaleplon ("Sonata"). *Forensic Sci Int* 2003; 134:120.
26. Louis CJ, et al: A case of zaleplon overdose. *Clin Toxicol (Phila)* 2008; 46:782.
27. Eszopiclone. *Drugs* 2005; 6:111.
28. Forrester MB: Eszopiclone ingestions reported to Texas poison control centers, 2005-2006. *Hum Exp Toxicol* 2007; 26:795.
29. Halas CJ: Eszopiclone. *Am J Health Syst Pharm* 2006; 63:41.
30. Miller AH, et al: Lunesta overdose: ST-elevation coronary vasospasm, troponemia, and ventricular fibrillation arrest. *Am J Emerg Med* 2006; 24:741.
31. Duggal HS: New-onset transient hallucinations possibly due to eszopiclone: A case study. *Prim Care Companion J Clin Psychiatry* 2007; 9:468.
32. Lovett B, et al: Case report: Prolonged coma after eszopiclone overdose. *Am J Emerg Med* 2007; 25:735.e5-735.e6.
33. Stracciolini A: Chloral hydrate. *Clin Toxicol Rev* 1998; 21:1.
34. Laurent Y, et al: Electrocardiographic changes with segmental akinesia after chloral hydrate overdose. *J Emerg Med* 2006; 30:179.
35. Lin YC, et al: Severe esophageal burn following chloral hydrate overdose in an infant. *J Formos Med Assoc* 2006; 105:235.
36. Sing K, et al: Chloral hydrate toxicity from oral and intravenous administration. *J Toxicol Clin Toxicol* 1996; 34:101.
37. Zahedi A, et al: Successful treatment of chloral hydrate cardiac toxicity with propranolol. *Am J Emerg Med* 1999; 17:490.
38. Jang DH, et al: Status epilepticus and wide-complex tachycardia secondary to diphenhydramine overdose. *Clin Toxicol (Phila)* 2010; 48:945.
39. Syed H, et al: Doxylamine toxicity: seizure, rhabdomyolysis and false positive urine drug screen for methadone. *BMJ Case Rep* 2009; March 17. doi:10.1136/bcr.09.2008.0879.
40. Wong CG, et al: γ-Hydroxybutyric acid: Neurobiology and toxicology of a recreational drug. *Toxicol Rev* 2004; 23:3.
41. Palmer RB: γ-Butyrolactone and 1,4-butanediol: Abused analogues of γ-hydroxybutyrate. *Toxicol Rev* 2004; 23:21.
42. Miro O, et al: Trends in illicit drug emergencies: The emerging role of gamma-hydroxybutyrate. *J Toxicol Clin Toxicol* 2002; 40:129.
43. Chin RL, et al: Clinical course of gamma-hydroxybutyrate overdose. *Ann Emerg Med* 1998; 31:716.
44. Galloway GP, et al: Gamma-hydroxybutyrate: An emerging drug of abuse that causes physical dependence. *Addiction* 1997; 92:89.
45. Liechti ME: Clinical features of gamma-hydroxybutyrate and gamma-butyrolactone toxicity and concomitant drug and alcohol use. *Drug Alcohol Depend* 2006; 81:323.
46. Thai D, et al: Gamma-hydroxybutyrate and ethanol effects and interactions in humans. *J Clin Psychopharmacol* 2006; 26:524.
47. Zvosec DL, et al: Case series of 226 γ-hydroxybutyrate-associated deaths: Lethal toxicity and trauma. *Am J Emerg Med* 2011; 29:319.
48. Mason PE, Kerns WP: Gamma hydroxybutyric acid (GHB) intoxication. *Acad Emerg Med* 2002; 9:730.
49. Zvosek DL, et al: Adverse events, including death, associated with the use of 1,4-butanediol. *N Engl J Med* 2001; 344:87.
50. Wong C, et al: From the street to the brain: Neurobiology of the recreational drug γ-hydroxybutyric acid. *Trends Pharmacol Sci* 2004; 25:29.
51. Zvosek DL, et al: Agitation is common in γ-hydroxybutyrate toxicity. *Am J Emerg Med* 2005; 23:316.
52. Gable RS: Acute toxic effects of club drugs. *J Psychoactive Drugs* 2004; 36:303.
53. Graeme KA: New drugs of abuse. *Emerg Med Clin North Am* 2000; 18:626.
54. Gunja N, et al: γ-Hydroxybutyrate poisoning from toy beads. *Med J Aust* 2008; 188:54.
55. Smith KM, et al: Club drugs: Methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and γ-hydroxybutyrate. *Am J Health Syst Pharm* 2002; 59:1067.
56. Traub SJ, et al: Physostigmine as a treatment for gamma-hydroxybutyrate toxicity: A review. *J Toxicol Clin Toxicol* 2002; 40:781.
57. Zvosec DL, et al: Physostigmine for gamma-hydroxybutyrate coma: Inefficacy, adverse events, and review. *Clin Toxicol (Phila)* 2007; 45:281.
58. Dyer J, et al: Gamma-hydroxybutyrate withdrawal syndrome. *Ann Emerg Med* 2001; 37:147.
59. Schneir AB, et al: A case of withdrawal from the GHB precursors gamma-butyrolactone and 1,4-butanediol. *J Emerg Med* 2001; 21:31.
60. Sivilotti ML, et al: Pentobarbital for severe gamma-butyrolactone withdrawal. *Ann Emerg Med* 2001; 38:660.

www.ketabpezeshki.com 66485457-66963820

Section One
THE PEDIATRIC PATIENT

Chapter 166
General Approach to the Pediatric Patient

Genevieve Santillanes

PERSPECTIVE

Emergency medicine providers should be comfortable assessing and treating pediatric patients from the newly born through adolescence. Of the 124 million annual U.S. emergency visits, 23 million are for children younger than 15 years.[1] Twenty percent of children have at least one emergency department visit per year.[2] The age group with the highest emergency department use per capita is infants, with 85.5 visits per 100 infants.[1] Although some hospitals have separate pediatric emergency departments, most pediatric patients are seen in general emergency departments. Several recent surveys found that more than 80% of pediatric patients are seen in general emergency departments.[3,4] Therefore, all emergency providers need to be prepared to provide definitive treatment for many pediatric illnesses and injuries and to provide initial stabilization and treatment to critically ill and injured pediatric patients.

An understanding of the anatomic, physiologic, developmental, and behavioral differences between pediatric and adult patients is critical to appropriate treatment of many pediatric emergencies. In addition to these differences, caring for the pediatric patient also involves the parents or other caregivers. This chapter reviews these differences and describes approaches to evaluation and treatment of pediatric patients.

DISTINGUISHING PRINCIPLES OF DISEASE

Pathophysiology

Different patterns of illness and injury are seen in children because of their unique physiologic and anatomic characteristics. Illness and injury patterns not only differ between pediatric and adult patients but also vary in children of different ages. Understanding and anticipating these differences will help the emergency provider in evaluating and treating patients of all ages. Besides the obvious cognitive and behavioral development seen as children grow, temperature regulation, airway anatomy and physiology, cardiovascular physiology, immune function, and the musculoskeletal system all change with age. Furthermore, pediatric patients may present to the emergency department with previously undiagnosed congenital anomalies. Drug dosing and choice of medications depend on size and other physiologic considerations.

In most patients, the first step in assessment is a review of vital signs. Normal ranges for vital signs vary significantly by age. Early recognition of abnormal vital signs will help the emergency provider detect physiologic decompensation in its earliest stages. Normal vital signs by age are listed in Table 166-1. Abnormal vital signs should be repeated, and persistently abnormal vital signs should not be ignored.

Temperature Regulation

Infants and young children have a large surface area–to–mass ratio and lose more heat to the environment than adolescents and adults. Maintenance of a stable body temperature can be a significant metabolic demand in young infants, especially those stressed by injury or illness. Every effort should be made to maintain a neutral thermal environment. Patients can be exposed briefly for interventions and examinations but should be covered as soon as possible to avoid excessive heat loss. Critically ill young infants should be placed under radiant warmers. Overhead warming lights can be useful for older infants and children requiring prolonged exposure for resuscitation and procedures.

Airway

The pediatric airway differs in a number of ways from an adult airway.[5] Numerous characteristics of the pediatric airway predispose to obstruction. Infants and young children have relatively large tongues, which may lead to airway obstruction during seizures or periods of altered mental status. Use of nasopharyngeal airways can be helpful in bypassing obstruction due to a relatively large tongue. The small airways of children are more easily obstructed with secretions. In addition, young infants preferentially breathe through their noses and can have significant respiratory distress from nasal secretions. For these reasons, airway suctioning can dramatically diminish an infant's work of breathing. Infants and young children also have large occiputs, causing neck flexion and potential airway obstruction in the supine position. A shoulder roll can be used to properly position young patients; it may significantly decrease respiratory distress and improve intubating conditions (Fig. 166-1).

Cardiovascular

Healthy children have compensatory mechanisms that can support blood pressure even when cardiac output is decreasing. Children have the ability to increase their heart rate and peripherally vasoconstrict to shunt blood centrally. Hypotension is a late finding of shock in previously healthy children, and intervention should occur before the onset of hypotension. The earliest sign of cardiovascular compromise in most patients is tachycardia. Unfortunately, tachycardia is nonspecific and may be due to fever, pain, or anxiety. Repeated assessment of the heart rate can be helpful. Unexplained tachycardia in a calm or sleeping child is concerning.

www.ketabpezeshki.com 66485457-66963820

The quality of the pulse is also helpful in assessing patients. A thready pulse associated with tachycardia should be considered to be shock until it is proved otherwise. Bradycardia in ill children is especially ominous and may signal impending cardiac arrest.

Musculoskeletal

Growing children have musculoskeletal injury patterns different from those of adults. The weakest part of a growing child's bone is the physis, or growth plate, leading to a propensity to fracture. Physeal injuries should be considered in children even with normal radiographs. Treatment of fractures in children takes future growth potential into consideration. Certain physeal injuries can lead to long-term growth disturbance if not treated appropriately. At the same time, growing children have more potential for bone remodeling and greater degrees of angulation can be accepted for certain fractures. Ligaments are strong relative to the immature bone, so children have an increased propensity to fracture bones rather than to sprain ligaments.

Immunologic

Young infants are at increased risk of serious bacterial infections because of their immature immune system. Febrile infants younger than 1 month are an especially high-risk group and have an approximately 10% rate of serious bacterial infection.[6] For this reason, the evaluation of infants with fever differs from the evaluation of older children and adults, and the workup varies by the age and vaccination status of the infant.

Table 166-1 Normal Pediatric Vital Signs

AGE (yr)	RESPIRATORY RATE (breaths/min)	HEART RATE (beats/min)
<1	30-60	100-160
1-2	24-40	90-150
2-5	22-34	80-140
6-12	18-30	70-120
>12	12-16	60-100
Lower Limits of Systolic Blood Pressure*		
0-28 days: 60 mm Hg		
1-12 months: 70 mm Hg		
1-10 years: 70 mm Hg + (2 × age in years)		

From Dieckmann R, Brownstein D, Gausche-Hill M (eds): Pediatric Education for Prehospital Professionals. Sudbury, Mass, Jones & Bartlett, 2000, pp 43-45.
*From American Heart Association Emergency Cardiovascular Care (ECC) Guidelines, 2000.

Pharmacologic

Pediatric patients are particularly prone to medication errors for multiple reasons, including the fact that medications for children are calculated using weight-based dosing with attention to the adult maximum medication dose.[7] Most calculation-based dosing errors occur in pediatric patients.[7] Suggested safeguards include pharmacy review of medication orders, computerized order entry and use of templated order forms, resuscitation calculators, and length-based resuscitation tapes. One easily remedied potential error is the inadvertent calculation of a drug dose on the basis of weight in pounds, not kilograms, leading to a more than twofold overdose. For this reason, emergency department scales should be programmed to report weight in kilograms, not pounds, and weight in pounds should not be written in the medical chart.

In addition to potential dosing errors, certain frequently used medications should not be given to young children. For example, ceftriaxone is not recommended in the first month of life because it may cause bilirubin encephalopathy. Use of pediatric-specific drug references can help providers avoid medication errors.

Developmental

Assessment of pediatric patients requires some understanding of normal developmental milestones. Table 166-2 lists basic developmental milestones in the first 2 years of life. There will be variation in the rate at which children develop. Therefore, the parent's report of the child's developmental history and normal behavior is extremely important.

Young Infants

Infants younger than 2 months are especially challenging to assess because they have limited behavioral cues. They may not make eye contact or have a social smile. Normal behavior includes sleeping, crying, quiet alert time, feeding, and stooling. A change in any of these activities may indicate serious disease. Increased sleeping or crying or decreased interest in feeding may be the early sign of serious disease and should be investigated.

Infants (<12 months of age)

By 2 months of age, infants develop a social smile and track objects held near their faces. Lack of interaction with the parents is

Figure 166-1. Infant with neck in flexed position and after placement of a shoulder roll. (From Santillanes G, Gausche-Hill M: Pediatric airway management. Emerg Med Clin North Am 26:961-975, 2008.)

www.ketabpezeshki.com 66485457-66963820

Table 166-2 Developmental Milestones in Children Younger Than 2 Years

AGE	GROSS MOTOR	VISUAL-MOTOR AND PROBLEM SOLVING	LANGUAGE, SOCIAL, AND ADAPTIVE
1 mo	Raises head slightly from prone position, makes crawling movements	Birth: visually fixes 1 mo: has tight grasp, follows to midline	Alerts to sound Regards face
2 mo	Holds head in midline, lifts chest off table	No longer clenches fist tightly, follows object past midline	Smiles socially (after being stroked or talked to) Recognizes parent
3 mo	Supports on forearms in prone position, holds head up steadily	Holds hands open at rest, follows in circular fashion, responds to visual threat	Coos (produces long vowel sounds in musical fashion) Reaches for familiar people or objects, anticipates feeding
4 mo	Rolls front to back, supports on wrists and shifts weight	Reaches with arms in unison, brings hands to environment midline	Laughs, orients to voice Enjoys looking around
5 mo	Rolls back to front, sits supported	Transfers objects	Says "ah-goo," orients to bell (localizes laterally)
6 mo	Sits unsupported, puts feet in mouth in supine position	Unilateral reach, uses raking grasp	Babbles Recognizes strangers
7 mo	Creeps	7-8 mo: inspects objects 7-9 mo: finger-feeds	Orients to bell (localizes indirectly)
8 mo	Comes to sit, crawls		"Dada" indiscriminately
9 mo	Pivots when sitting, pulls to stand, cruises	Uses pincer grasp, probes with forefinger, gestures, waves bye-bye, holds bottle, throws objects	"Mama" indiscriminately, understands "no" Starts to explore environment, plays gesture games (e.g., patty cake) 10 mo: "Dada" and "Mama" discriminately, orients to bell (directly) 11 mo: 1 word other than "Dada" and "Mama," follows 1-step command with gesture
12 mo	Walks alone	Uses mature pincer grasp, releases voluntarily, marks paper with pencil	Uses 2 words other than "Dada" and "Mama," immature jargoning (runs several unintelligible words together) Imitates actions, comes when called, cooperates with dressing 13 mo: uses 3 words 14 mo: follows 1-step command without gesture
15 mo	Creeps up stairs, walks backward	Scribbles in imitation, builds tower of 2 blocks in imitation	Uses 4-6 words 15-18 mo: uses spoon, uses cup independently 17 mo: uses 7-20 words, points to 5 body parts, uses mature jargoning (includes intelligible words in jargoning)
18 mo	Runs, throws objects from standing without falling	Scribbles spontaneously, builds tower of 3 blocks, plays in company of other children	Uses 2-word combinations Copies parent in tasks (sweeping, dusting), turns 2-3 pages at a time 19 mo: knows 8 body parts
21 mo	Squats in play, goes up stairs	Builds tower of 5 blocks	Uses 50 words, 2-word sentences Asks to have food and to go to toilet
24 mo	Walks up and down steps without help	Imitates stroke with pencil, builds tower of 7 blocks, turns pages 1 at a time, removes shoes and pants	Uses pronouns (I, you, me appropriately), follows 2-step commands Parallel play

Modified from Gunn KL, Nechyba C (eds): The Harriet Lane Handbook, 16th ed. St Louis, CV Mosby, 2003.

concerning. After 6 months, infants may develop significant stranger anxiety, which can make the physical examination challenging. Whenever possible, examination of the infant in the parent's lap will lead to less anxiety of the patient and may facilitate the physical examination. Brightly colored toys or toys with lights or sounds serve to distract the infant and may be useful in keeping the patient calm.

Toddlers (1- to 2-year-olds)

Toddlers have limited expressive language skills but will be aware of and react to parental anxiety. A toddler may be able to participate in the history in a limited way, such as pointing to the location of pain. Toddlers vary in their response to physical examination. Some toddlers are fearful and unable to cooperate, whereas others are curious and cooperate more easily with the examination. When the patient is stable, it can be helpful to begin the encounter standing or sitting at a distance from the child while taking the history. Speaking in a soothing voice and distracting the child with toys or other interesting objects can facilitate the examination.

Preschoolers (3- to 5-year-olds)

Preschool-age children have increasing language skills. Like toddlers, their receptive language skills exceed their expressive language skills, and they often understand more than is realized. Preschoolers should be included in the conversation when possible. Providers should be cautious about talking to parents about procedures or diagnoses in front of the preschool child even if the child seems not to be paying attention or not to understand. Like

www.ketabpezeshki.com 66485457-66963820

toddlers, preschool children vary greatly in their cooperation with the physical examination. Providing limited options, such as sitting with the parent or on the gurney or choosing which ear should be examined first, may improve cooperation. Distraction with questions or stories can facilitate the physical examination. Simple, concrete explanations of procedures are appropriate immediately before and during the procedure. Preschool children may perceive illness or painful procedures as punishment for their actions, making simple explanations of what is occurring and why even more important.

School-Age Children

At least some questions during the history should be directed at the school-age child. Some older school-age children will be able to provide much of the history themselves. School-age children are often cooperative with the examination but may regress when they are frightened or in pain. School-age children become increasingly modest, and attempts should be made to provide privacy.

School-age children may attempt to negotiate or stall when painful or unpleasant examinations or procedures are planned. Honest and firm but reassuring explanations of what will happen are important. Appropriate concrete explanations include the sequence of events and what physical sensations the patient will experience. Preparation for procedures will give children some sense of control. Timing the explanation shortly before the procedure may decrease anxiety. School-age children may perseverate and become extremely anxious if there is a long delay between the explanation and the procedure.

Adolescents

Adolescents increasingly want independence from their parents but may regress in times of stress. Adolescents will be able to provide much if not all of the history. However, it is important to elicit the concerns of both the adolescent and the parent and to ensure that both understand the diagnosis and plan. The adolescent should be given a chance to speak to the provider without the parent in the room. Any sensitive questions, such as drug use and sexual activity, should be asked privately. Adolescents can generally be examined in a manner similar to adults. They are often extremely modest, and attempts should be made to preserve privacy with private rooms when possible and exposure of only the body part being examined. Adolescents may want the parent present during the physical examination or may prefer that the parent stay outside of the room.

Evaluation

Triage

Triage serves to identify patients requiring immediate care, to prioritize patients waiting to be seen, and to ensure that patients are treated in the most appropriate area of the emergency department. Pediatric-specific triage systems are important to avoid overtriage and undertriage of children. Application of adult-specific vital signs to children may lead to inappropriate triage level classification. In addition, signs and symptoms of serious illness may be subtle in infants and very young children.

Triage systems with pediatric modifications include the Emergency Severity Index, the pediatric Canadian Triage and Acuity Scale, the Manchester Triage System, and the Australasian Triage Scale.[8] All of these systems are five-level triage systems. In five-level triage systems, level 1 patients require immediate intervention. Level 2 patients are emergent and should be seen within 10 to 15 minutes. Level 3 patients are considered urgent and should be seen within 30 to 60 minutes, depending on the triage system. Level 4 and level 5 are thought to be stable patients. The Emergency Severity Index classifies patients by acuity and number of resources expected to be required.[9] A flowchart specific to pediatric patients with fever has been added. In the Canadian Triage and Acuity Scale, specific criteria for various presenting complaints are used to assign triage levels.[10] The pediatric modification includes pediatric-specific presenting complaints and determination of acuity by use of pediatric-specific vital signs. The Manchester Triage System contains flowcharts based on presenting complaint, with some pediatric-specific flowcharts.[11] The Australasian Triage Scale is mostly a general triage scale but has several pediatric-specific criteria.[12]

No triage system is clearly demonstrated to be superior, and data on reliability and validity are limited for all triage systems. The Emergency Severity Index, the Manchester Triage System, and the pediatric Canadian Triage and Acuity Scale have been demonstrated to be valid in pediatric patients.[8,13,14] Reliability is good for the Manchester Triage System and moderate for the Emergency Severity Index and pediatric Canadian Triage and Acuity Scale.[8,14] The Australasian Triage Scale appears to have lower reliability than the other triage systems.[8]

Box 166-1 Focused SAMPLE History

Signs and symptoms
Allergies
Medications
Past medical problems
Last food or liquid
Events leading to injury or illness

Modified from Dieckmann R, Brownstein D, Gausche-Hill M (eds): Pediatric Education for Prehospital Professionals. Sudbury, Mass, Jones & Bartlett, 2000, p 51.

History

In critically ill or injured patients, the SAMPLE history can be used as a way to quickly obtain a focused history (Box 166-1). The SAMPLE history reminds providers to ask for Signs and symptoms, Allergies, Medications, Past medical history, Last meal, and Events surrounding the illness or injury.

A more detailed history will be guided by the patient's complaint. In infants and very young children, the entire history will be obtained from the parent. Although the parent's concerns should be seriously considered, the history provided by the parent may be unreliable in cases of abuse and neglect. Furthermore, in cases of injury, the event may not have been witnessed, and details may not be available. In preverbal children, symptoms will be inferred by the parent on the basis of the child's behavior. Parents are often very perceptive and may notice subtle changes that are not immediately obvious to the provider performing a relatively brief assessment. Therefore, parental report of symptoms should not be disregarded.

Additional questions may be indicated in children of different ages. In neonates, pregnancy and birth history are important. In infants and toddlers, urine output, quantified in number of wet diapers, can be helpful in determining the hydration status. This can be especially helpful in breast-feeding newborns, whose intake is difficult to quantify. Vaccination status is important in infants and children presenting with symptoms such as fever and rash. Drug and alcohol use as well as sexual history become important in adolescents who have increased risk-taking behaviors.

www.ketabpezeshki.com 66485457-66963820

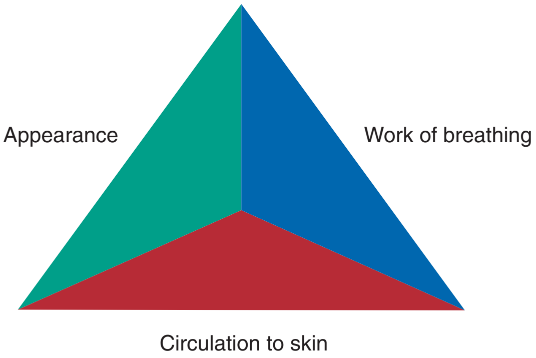


Figure 166-2. Pediatric assessment triangle.

Table 166-3 Pediatric Assessment Triangle Findings

APPEARANCE	WORK OF BREATHING	CIRCULATION TO THE SKIN
Tone	Abnormal sounds: stridor, grunting, snoring, wheezing	Pallor
Irritable, interactive	Abnormal positioning: sniffing, tripoding, refusal to lie down	Mottling
Consolable	Retractions	Cyanosis
Look/gaze	Head bobbing	Petechiae
Speech/cry	Nasal flaring	

Modified from Dieckmann R, Brownstein D, Gausche-Hill M (eds): Pediatric Education for Prehospital Professionals. Sudbury, Mass, Jones & Bartlett, 2000, pp 36-40.

Pediatric Assessment Triangle

Rapid recognition of the critically ill child or the child at risk for rapid decompensation is a critical skill for the emergency medicine provider. One tool that has been developed to assist providers in quickly assessing children is the pediatric assessment triangle (PAT) (Fig. 166-2).[15,16] It is an orderly approach that helps clinicians formulate an initial impression of the overall status of the child from the door of the examination room. The three components of the PAT are appearance, work of breathing, and circulation. On the basis of the initial PAT, the clinician is able to rapidly distinguish the “sick” from “well” child. Table 166-3 summarizes the findings that may be noted on each of the three arms of the triangle, and Table 166-4 summarizes the interpretation of the triangle.

Appearance. Observation of the child from a distance allows the provider to assess the patient’s overall status without upsetting the child. The mnemonic TICLS (tone, interactiveness, consolability, look/gaze, and speech/cry) summarizes the components of the assessment of overall appearance. Observation of the infant or child interacting with his or her parents gives many clues about the child’s overall status. An infant with a vacant or glazed look can be distinguished from an alert infant who attends to environmental stimuli. An infant who is awake but lying motionless on a gurney is much more concerning than an active infant moving all extremities. Irritability is an early sign of inadequate brain perfusion. This may be followed by lethargy and then coma as the poor perfusion continues.

The quality of the cry is another helpful clue. A persistently high-pitched or irritable cry is concerning for central nervous system disease, such as meningitis. A normal overall appearance suggests that oxygenation, ventilation, and perfusion are adequate.

Figure 166-3. Intercostal retractions in a child with respiratory distress.

Table 166-4 Interpretation of the Pediatric Assessment Triangle

PHYSIOLOGIC STATE	APPEARANCE	WORK OF BREATHING	CIRCULATION TO THE SKIN
Respiratory distress	Normal	Abnormal	Normal
Respiratory failure	Abnormal	Abnormal	Normal-abnormal
Compensated shock	Normal	Normal	Abnormal
Decompensated shock	Abnormal	Normal-abnormal	Abnormal
Brain injury or dysfunction	Abnormal	Normal	Normal
Cardiopulmonary failure	Abnormal	Abnormal	Abnormal

Modified from Dieckmann R, Brownstein D, Gausche-Hill M (eds): Pediatric Education for Prehospital Professionals. Sudbury, Mass, Jones & Bartlett, 2000, pp 30-57.

Work of Breathing. The work of breathing should be observed initially from a distance because it is difficult to adequately assess work of breathing in a crying child. The position of the child can be a clue to the level of respiratory distress. Infants and children with respiratory distress may assume the sniffing position in an attempt to decrease their work of breathing. Tripoding is an ominous sign of severe respiratory distress.

The quality of the voice or cry may be a clue to airway and respiratory disease or compromise. For instance, children with croup have hoarse voices, and children with peritonsillar abscesses have muffled or “hot potato” voices. Abnormal breath sounds may be audible without a stethoscope. Stridor, audible wheezing, grunting, and snoring respirations can all be clues to respiratory compromise.

For adequate assessment for the presence of retractions and abdominal breathing, the infant or young child will ideally be observed without a shirt. Retractions may be seen in the suprasternal, supraclavicular, intercostal, and subcostal areas and are indicative of increased work of breathing (Fig. 166-3). Nasal

www.ketabpezeshki.com 66485457-66963820

Figure 166-4. Nasal flaring in a child with respiratory distress from lower airway obstruction.

flaring is an attempt to decrease airway resistance and is a sign of severe respiratory distress (Fig. 166-4). Head bobbing occurs when infants use neck muscles to assist respiration and is another sign of severe respiratory distress. Seesaw breathing, an ineffective breathing pattern in which the abdomen moves outward and the chest moves inward during inspiration, is a sign of impending respiratory failure. As the child tires and nears complete respiratory failure, the respiratory rate can fall and the work of breathing may be diminished.

Abnormal respiratory patterns may also be a clue to nonrespiratory illness. Effortless tachypnea may be a sign of shock. A rapid respiratory rate may be a physiologic attempt to correct for metabolic acidosis with respiratory alkalosis. Neurologic disorders may also lead to abnormal respiratory patterns.

Circulation. Visual inspection of the skin can provide clues to the overall cardiovascular status. Early compensated shock is characterized by peripheral vasoconstriction and shunting of blood to the brain and other vital organs. At this stage, pallor may be appreciated. If the shock state is not corrected, the patient may become mottled (Fig. 166-5A). Mottling is a random pattern of vasoconstriction and vasodilation in adjacent areas of the skin. This may be confused with cutis marmorata, a lacy pattern on the skin caused by vascular instability (Fig. 166-5B). Cutis marmorata is a normal finding in young infants in cool environments. In contrast to infants with mottling, infants with cutis marmorata will be otherwise well appearing, and the skin findings will diminish or disappear if the infant is bundled or placed in a warm environment. Cyanosis may be present normally in children with congenital heart disease, but if cyanosis is a new finding for the patient, it is indicative of respiratory failure or decompensated shock.

Length-Based Resuscitation Tape

An accurate weight is often not available for critically ill children. Use of a color-coded length-based resuscitation tape gives an estimate of the child's weight. Each color on the tape corresponds to a weight range corresponding to ideal body weight for length. Medication doses and appropriate equipment are listed on the tape for each weight range. Use of the length-based resuscitation tape avoids the need for error-prone calculations in the high-stress setting of a pediatric resuscitation. In addition, pediatric resuscitation equipment organized by weight ranges minimizes the need to search for appropriately sized equipment.

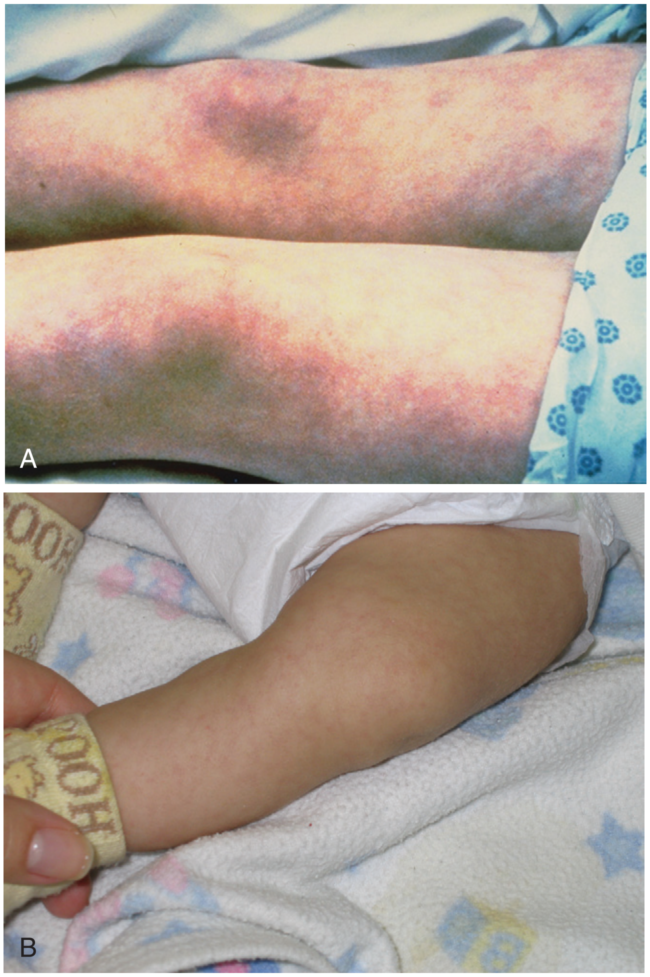


Figure 166-5. Infant with skin mottling (A) and cutis marmorata (B).

Physical Examination

The Glasgow Coma Scale is a useful way to objectively document the mental status examination and serves as an easy way to communicate the mental status to other providers. The pediatric modification for the Glasgow Coma Scale is shown in Table 166-5. A less comprehensive way to communicate the mental status is AVPU, or Alert, responsive to Verbal commands, responsive to Painful stimuli, or Unresponsive.

As in adults, the physical examination in critically ill or injured children will focus initially on airway, breathing, and circulation with correction of abnormalities in these systems before a complete physical examination is performed. In less critically ill infants and young children, auscultation of the heart and lungs should be performed before proceeding to frightening or uncomfortable parts of the examination. In general, the ears and oropharynx should be examined last because many children will cry, making the remainder of the physical examination difficult. Parents can hold frightened young children for ear examinations by holding the child in the lap with one arm around the head and one arm around the child's body and arms (Fig. 166-6). This allows the child to be held by the parent during an unpleasant part of the examination while having the head and arms adequately restrained to allow visualization of the tympanic membranes and avoidance of injury. When necessary, external examination of the vagina in young girls can be facilitated by having them sit in a frog-leg position in the parent's lap.

www.ketabpezeshki.com 66485457-66963820

Table 166-5 Glasgow Coma Scale Modified for Preverbal Pediatric Patients*

Eye Opening	
Spontaneous	4
To Speech	3
To Pain	2
None	1
Best Verbal Response	
Coos, babbles	5
Irritable, cries	4
Cries to pain	3
Moans to pain	2
None	1
Best Motor Response	
Normal spontaneous movement	6
Withdraws to touch	5
Withdraws to pain	4
Abnormal flexion	3
Abnormal extension	2
None	1

Modified from James HE: Neurologic evaluation and support in the child with an acute brain insult. Pediatric Ann 15:16-22, 1986.
*Total score key: severe, <9; moderate, 9-13; mild, 14-15.

Figure 166-6. Toddler being held for otoscopic examination of the ears.

Table 166-6 Top Five Emergency Department Diagnoses by Age in California

INFANTS YOUNGER THAN 1 YEAR	CHILDREN 1-17 YEARS
Acute upper respiratory infection	Acute upper respiratory infection
Fever	Otitis media
Otitis media	Open wounds of head
Unspecified viral and chlamydial infections	Contusions
Pneumonia	Upper extremity fractures

Modified from McConville S, Lee H: Emergency department care in California. Who uses it and why? California Counts Population Trends and Profiles 10:1-23, 2008.

Table 166-7 Top 10 Reasons for Pediatric Hospitalization (Excluding Neonatal and Maternity Care)

PRINCIPLE DIAGNOSIS	PERCENTAGE OF PEDIATRIC HOSPITAL STAYS
Pneumonia	7.8
Asthma	7.4
Acute bronchitis	6.7
Fluid and electrolyte disorders	4.3
Appendicitis	3.7
Affective disorders (primarily depression)	3.6
Epilepsy, convulsions	2.8
Urinary tract infections	2.3
Intestinal infections	2.3
Noninfectious gastroenteritis	2.1

Modified from Owens PL, Thompson J, Elixhauser A, Ryan K: Care of Children and Adolescents in U.S. Hospitals. HCUP Fact Book No. 4. AHRQ Publication No. 04-0004. Rockville, Md, Agency for Healthcare Research and Quality, 2003. Available at www.ahrq.gov/data/hcup/factbl4/. Accessed April 2011.

SPECIFIC DISORDERS

Fortunately, most pediatric visits to the emergency department are for minor illnesses and injuries, but emergency medicine providers needs to be prepared to care for critically ill and injured children as well. The most common reasons for infants and children to be seen in emergency departments are respiratory illness, fever, and injury.[17] Table 166-6 lists the most common emergency department diagnoses for infants and children in California, and Table 166-7 lists the most common reasons for hospitalization of pediatric patients in the United States. Causes of serious illness and injury vary by age. Respiratory illnesses are the most common causes of infant hospitalization after the immediate neonatal period.[18] Asthma and appendicitis are the most common reasons for hospitalization of school-age children, and affective disorders are the most common cause of adolescent hospitalizations.

This section focuses on complaints specific to the pediatric population and complaints in which the differential and approach vary significantly from those in adult populations.

Children with Special Health Care Needs

The assessment of children with chronic illnesses and other special health care needs is especially challenging. Parents or other daily caregivers can provide helpful information on baseline behavior and mental status, and the caregiver's input should be sought.

www.ketabpezeshki.com 66485457-66963820

However, relying on the parent's knowledge and recollection of detailed medical information can be a problem, especially during times of high stress. Parents may forget medication names or concentrations. One solution is the use of an Emergency Information Form (EIF) for children with special health care needs.[19] The form summarizes chronic medical conditions, medications, medical devices, and other critical information and is available at www.aap.org/advocacy/blankform.pdf. When they are accessible, these forms can quickly provide critical information to the emergency department provider, assisting in the early management and stabilization of the child until more detailed records are accessed or the specialist is contacted. Emergency departments can request that specialists affiliated with their hospitals provide EIFs for complex patients to facilitate rapid and appropriate emergency treatment.

Neonatal Intensive Care Unit Graduate

Ex-premature infants have unique health care needs and may be especially challenging to evaluate. Development is often delayed. It may be appropriate to consider gestational rather than chronologic age in assessing development. The parent's report of change in tone, activity, and level of alertness should be taken seriously. Neonatal intensive care unit graduates are at increased risk for complications from respiratory infections and may have impaired immunity compared with term infants of the same chronologic age. Infants born significantly prematurely are at risk for chronic lung disease and may be receiving supplemental home oxygen, inhaled corticosteroids, bronchodilators, and diuretics. There may be some degree of tachypnea or increased work of breathing at baseline. Again, parental report of baseline respiratory status is helpful in decision-making.

Many high-risk infants receive respiratory syncytial virus (RSV) immunoglobulin monthly during peak season. During RSV season, the parents of ex-premature infants with fever, cough, rhinorrhea, or respiratory distress should be queried about timing of the last RSV immunoglobulin injection.

Altered Mental Status

Although many of the possible causes of altered mental status are the same in adults and children, a few considerations in the differential are unique to pediatrics. A mnemonic for causes of altered mental status in children is AEIOUTIPS (Box 166-2). The postictal state, central nervous system infection, and ingestions cause altered mental status in both adults and children. However, child abuse, intussusception, and inborn errors of metabolism are pediatric-specific causes of altered mental status that should also be considered.

Box 166-2 Differential Diagnosis for Altered Mental Status in Children

A	Alcohol (adolescents), ammonia (inborn errors), abuse
E	Electrolytes, encephalopathy
I	Infection
O	Oxygen, overdose
U	Uremia
T	Trauma, tumor
I	Insulin (hypoglycemia), intussusception, inborn errors of metabolism
P	Psychiatric, poisoning
S	Seizure, shock, shunt malfunction, subarachnoid hemorrhage

Modified from Fuchs S, Gausche-Hill M, Yamamoto L (eds): APLS: The Pediatric Emergency Medicine Resource, 4th ed. Sudbury, Mass, Jones & Bartlett, 2003.

Seizures

Although the initial basic management of seizures does not differ between children and adults, infantile seizures can be subtle. Seizure activity may be manifested by lip smacking, bicycling of the legs, or apnea. The possibility of a seizure should be considered for any infant with stereotyped repetitive movements. In addition, causes such as hyponatremia secondary to inappropriate formula dilution, inborn errors of metabolism, and pyridoxine deficiency are considerations in young infants presenting with seizures.

Febrile seizures are another diagnosis unique to pediatrics. Simple febrile seizures are brief generalized seizures occurring no more often than once in a 24-hour period in children between the ages of 6 months and 5 years. Simple febrile seizures require no specific treatment and in an otherwise well-appearing, vaccinated child do not by themselves necessitate further workup.[20]

Trauma

Pediatric patients with blunt trauma have injury patterns different from those of adults. Children have relatively large heads in relation to their bodies, predisposing them to head trauma. They also have relatively elastic cervical spines and can have spinal cord injuries without radiologic evidence of injury. Therefore, any history of paresthesias, weakness, or other neurologic symptoms necessitates further investigation even if symptoms have resolved by the time of emergency department evaluation. Traumatic aortic injuries are less common in children than in adults.[21] In children with tension pneumothorax, the mediastinum is more mobile, resulting rapidly in an obstructive form of shock. Children have less intraperitoneal fat than adults do, and their solid abdominal organs are relatively large compared with the abdominal cavity, predisposing to splenic and liver lacerations. The kidneys lack perirenal fat and are relatively mobile, predisposing to renal trauma. The bladder is an abdominal organ and is less protected by the pelvis in young children.

Child Abuse

Nonaccidental trauma should be a consideration for all patients presenting with injuries or with certain otherwise unexplained medical complaints, such as altered mental status and apparent life-threatening events. Many children with abusive injuries are not diagnosed as being the victims of abuse at initial health care encounters, leaving them at risk for more serious injuries and death.[22,23] Historical clues to nonaccidental trauma include a mechanism inconsistent with the injury and a history inconsistent with the developmental level of the child (Box 166-3). Physical examination clues to abuse include bruises in young infants and bruises on certain areas of the body, such as the ear and trunk[24] (Box 166-4). Fractures in children younger than 18 months without a significant witnessed trauma mechanism are especially concerning.[25]

THE PEDIATRIC-READY EMERGENCY DEPARTMENT

Preparation to care for infants and children of all ages requires not only emergency department staff training but also pediatric medication formulations, intravenous fluids, and equipment and supplies in sizes appropriate for the premature neonate to the large adolescent. The American College of Emergency Physicians, the American Academy of Pediatrics, and the Emergency Nurses Association developed joint guidelines for care of children in the emergency department.[26,27] The guidelines include recommendations on necessary personnel, protocols, medications, equipment, and

www.ketabpezeshki.com 66485457-66963820

Box 166-3 Historical Features Concerning for Child Abuse

History lacking in details
Inconsistency—details change with repeated questioning
History inconsistent with child's developmental status
Reported mechanism inconsistent with injury

Box 166-4 Physical Examination and Radiologic Findings Concerning for Abuse

Bruising in young infants
Patterned bruises or burns
Bruises on the ears, trunk, inner thighs, neck, or groin
Posterior rib fractures
Classic metaphyseal fractures
Any fracture in a nonambulatory child
Fractures in different stages of healing

supplies. Surveys have found that emergency departments frequently lack items recommended in the guidelines.[3,28] One strong recommendation in the guidelines is the appointment of physician and nurse coordinators of pediatric emergency care.[26,27]

Pediatric emergency preparedness requires a plan for continuing care of critically ill and injured children. Small community hospitals often do not have pediatric intensive care units or access to pediatric subspecialists. Therefore, a plan for transfer of patients whose needs exceed available resources is critical. Potential receiving hospitals and a mechanism of transporting critically ill pediatric patients should be identified.

The Pediatric-Friendly Emergency Department

One topic that has received increasing attention in recent years is pain and anxiety management in pediatric patients. Procedural pain is frequently undertreated in infants.[29,30] Appropriate use of sedation, anesthesia, analgesia, and nonpharmacologic methods of pain management can increase the patient's cooperation and increase visit satisfaction for the child and parent. Children have significant anxiety and fear surrounding medical procedures, leading to additional challenges in successful performance of procedures. In addition to reducing pain and anxiety in the acute visit, adequate pain control is likely to have long-term benefits. Multiple studies have demonstrated that inadequate pain control can have long-term deleterious consequences, leading to increased pain perception with future painful procedures.[31]

A variety of options are available to minimize pain associated with drawing of blood and starting of intravenous lines, including vapocoolants, topical anesthetics, and needle-free jet injection of anesthetics.[32] Topical anesthetics can also decrease the pain of anesthetic injection before lumbar puncture and other procedures. Topical application of a lidocaine, epinephrine, and tetracaine mixture has been shown to have comparable efficacy to injected anesthesia for facial and scalp lacerations.[33] Oral sucrose seems to decrease procedural pain in neonates.[34] Nonpharmacologic distraction techniques such as bubbles, songs, books, videos, and videogames can be used to decrease anxiety.[31] In children, the use of anxiolytic medications or procedural sedation may be appropriate for procedures that could be accomplished with local anesthesia in more mature patients.

Another shift in recent years is increased support for family presence during invasive procedures and resuscitations.[35-37] Children are stressed when they are separated from parents, and one benefit of family presence is that parents are able to reassure and calm the child.[38] Studies have shown that family presence also decreases anxiety levels in family members.[39] Presence during unsuccessful cardiopulmonary resuscitation is perceived by families as beneficial in the grieving process.[40] Studies have shown that with well-implemented policies, family presence does not interfere with resuscitation.[41]

Families present during resuscitations should have a family support person assigned who can explain procedures and answer questions. A social worker, chaplain, or nurse could fulfill this role. Ideally, families are briefed on what to expect before entering the resuscitation room. Guidelines have been developed to assist emergency department providers in implementing family presence protocols at their institutions.[38]

KEY CONCEPTS

- Patterns of illness and injury vary by age, and a number of anatomic and physiologic characteristics affect presentation and management of pediatric emergencies.
- A basic understanding of normal development will aid the emergency provider in assessment of the pediatric patient.
- The pediatric assessment triangle (PAT) can be used as a tool for rapid evaluation of the patient's overall status.
- Simple airway maneuvers may dramatically improve respiratory status.
- Maintenance of a neutral thermal environment is necessary in critically ill infants.
- Child abuse should be considered when injuries are inconsistent with history, when details of the history change, or with certain injury patterns.
- Guidelines from the American College of Emergency Physicians, the American Academy of Pediatrics, and the Emergency Nurses Association outline recommended pediatric equipment, supplies, and training for emergency departments.
- Family presence may be appropriate for pediatric procedures and resuscitations.
- A variety of pharmacologic and nonpharmacologic techniques are available to decrease procedural pain and anxiety.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, Division of Data Services: *National Hospital Ambulatory Medical Care Survey: 2008 Emergency Department Summary Tables*. Available at www.cdc.gov/nchs/data/ahcd/nhamcs_emergency/nhamcsed2008.pdf. Accessed April 2011.
2. Garcia TC, Bernstein AB, Bush MA: *Emergency Department Visitors and Visits: Who Used the Emergency Room in 2007? NCHS Data Brief, No 38*. Huntsville, Md: National Center for Health Statistics; 2010.
3. Gausche-Hill M, Schmitz C, Lewis RJ: Pediatric preparedness of US emergency departments: A 2003 survey. *Pediatrics* 2007; 120:1229-1237.
4. Niska R, Bhuiya F, Xu J: National hospital ambulatory medical care survey: 2007 emergency department summary. *Natl Health Stat Report* 2010; 26:1-31.
5. Santillanes G, Gausche-Hill M: Pediatric airway management. *Emerg Med Clin North Am* 2008; 26:961-975.
6. Huppler AR, Eickhoff JC, Wald ER: Performance of low-risk criteria in the evaluation of young infants with fever. *Pediatrics* 2010; 125:228-233.
7. Kozer E, Berkovitch M, Koren G: Medication errors in children. *Pediatr Clin North Am* 2006; 53:1155-1168.
8. van Veen M, Moll HA: Reliability and validity of triage systems in pediatric emergency care. *Scand J Trauma Resusc Emerg Med* 2009; 17:38.
9. Gilboy N, Tanabe T, Travers D, Rosenau AM: *Emergency Severity Index (ESI): A Triage Tool for Emergency Department Care, Version 4. Implementation Handbook 2012 Edition. AHRQ Publication No. 12-0014*. Rockville, Md: Agency for Healthcare Research and Quality; November 2011. Available at www.ahrq.gov/research/esi/esihandbk.pdf.
10. Murray M, Bullard M, Grafstein E: Revisions to the Canadian Emergency Department Triage and Acuity Scale implementation guidelines. *CJEM* 2004; 6:421-427.
11. Mackway-Jones K, Marsden J, Windle J: *Emergency Triage, Manchester Triage Group*, 2nd ed. Oxford: Blackwell Publishing; 2006.
12. Australian Government, Department of Health and Ageing: *Emergency Triage Education Kit. Commonwealth of Australia; 2009*. Available at www.health.gov.au/internet/main/publishing.nsf/Content/5E3156CFFF0A34B1CA2573D0007BB905/$File/Triage%20Education%20Kit.pdf.
13. Durani Y, Brecher D, Walmsley D, Attia MW, Loiselle JM: The emergency severity index version 4: Reliability in pediatric patients. *Pediatr Emerg Care* 2009; 25:751-753.
14. Travers DA, Waller AE, Katznelson J, Agans R: Reliability and validity of the emergency severity index for pediatric triage. *Acad Emerg Med* 2009; 16:843-849.
15. Dieckmann R, Brownstein D, Gausche-Hill M: *Pediatric Education for Prehospital Professionals*. Sudbury, Mass: Jones & Bartlett; 2000.
16. Dieckmann RA, Brownstein D, Gausche-Hill M: The pediatric assessment triangle: A novel approach for the rapid evaluation of children. *Pediatr Emerg Care* 2010; 26:312-315.
17. McConville S, Lee H: Emergency department care in California? Who uses it and why? *California Counts Population Trends and Profiles* 2008; 10:1-23.
18. Owens PL, Thompson J, Elixhauser A, Ryan K: *Care of Children and Adolescents in U.S. Hospitals. HCUP Fact Book No. 4. AHRQ Publication No. 04-0004*. Rockville, Md: Agency for Healthcare Research and Quality; 2003. Available at www.ahrq.gov/data/hcup/factbl4/. Accessed April 2011.
19. American Academy of Pediatrics, Committee on Pediatric Emergency Medicine and Council on Clinical Information Technology, American College of Emergency Physicians, Pediatric Emergency Medicine Committee: Policy statement—emergency information forms and emergency preparedness for children with special health care needs. *Pediatrics* 2010; 125:829-837.
20. Subcommittee on Febrile Seizures, American Academy of Pediatrics: Neurodiagnostic evaluation of the child with a simple febrile seizure. *Pediatrics* 2011; 127:389-394.
21. Anderson SA, Day M, Chen MK, Huber T: Traumatic aortic injuries in the pediatric population. *J Pediatr Surg* 2008; 43:1077-1081.
22. Ravichandiran N, et al: Delayed identification of pediatric abuse-related fractures. *Pediatrics* 2010; 125:60-66.
23. Trokel M, Waddimba A, Griffith J, Sege R: Variation in the diagnosis of child abuse in severely injured infants. *Pediatrics* 2006; 117:722-728.
24. Pierce MC, Kaczor K, Aldridge S, O'Flynn J, Lorenz DJ: Bruising characteristics discriminating physical child abuse from accidental trauma. *Pediatrics* 2010; 125:67-74.
25. Kemp A, et al: Patterns of skeletal fractures in child abuse: Systematic review. *BMJ* 2008; 337:a1518.
26. American Academy of Pediatrics Committee on Pediatric Emergency Medicine, American College of Emergency Physicians Pediatric Committee, Emergency Nurses Association Pediatric Committee: Joint policy statement—guidelines for care of children in the emergency department. *Ann Emerg Med* 2009; 54:543-552.
27. American Academy of Pediatrics Committee on Pediatric Emergency Medicine, American College of Emergency Physicians Pediatric Committee, Emergency Nurses Association Pediatric Committee: Joint policy statement—guidelines for care of children in the emergency department. *Pediatrics* 2009; 124:1233-1243.
28. Middleton KR, Burt CW: Availability of pediatric services and equipment in emergency departments: United States, 2002-2003. *Adv Data* 2006; 367:1-16.
29. Hoyle JD Jr, Rogers AJ, Reischman DE, Powell EC, et al: Pain intervention for infant lumbar puncture in the emergency department: Physician practice and beliefs. *Acad Emerg Med* 2011; 18:140-144.
30. Fein D, Avner JR, Khine H: Pattern of pain management during lumbar puncture in children. *Pediatr Emerg Care* 2010; 26:357-360.
31. Khan KI, Wiesman SJ: Nonpharmacologic pain management strategies in the pediatric emergency department. *Clin Pediatr Emerg Med* 2007; 8:240-247.
32. Young KD: What's new in topical anesthesia? *Clin Pediatr Emerg Med* 2007; 8:232-239.
33. Ferguson C, Loryman B, Body R: Best evidence topic report. Topical anaesthetic versus lidocaine infiltration to allow closure of skin wounds in children. *Emerg Med J* 2005; 22:507-509.
34. Stevens B, Yamada J, Ohlsson A: Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev* 2010; 1:CD001069.
35. Henderson DP, Knapp JF: Report of the national consensus conference of family presence during pediatric cardiopulmonary resuscitation and procedures. *Pediatr Emerg Care* 2005; 21:878-891.
36. O'Malley P, Brown K, Mace SE; American Academy of Pediatrics, Committee on Pediatric Emergency Medicine; American College of Emergency Physicians, Pediatric Emergency Medicine Committee: Patient- and family-centered care and the role of the emergency physician providing care to a child in the emergency department. *Pediatrics* 2006; 118:2242-2244.
37. Dingeman RS, Mitchell EA, Meyer EC, Curley MA: Parent presence during complex invasive procedures and cardiopulmonary resuscitation: A systematic review of the literature. *Pediatrics* 2007; 120:842-854.
38. Farah MM, Thomas CA, Shaw KN: Evidence-based guidelines for family presence in the resuscitation room. A step-by-step approach. *Pediatr Emerg Care* 2007; 23:587-591.
39. Nishisaki A, Diekema DS: Mind the gap and narrowing it: Family presence during pediatric resuscitation and invasive procedures. *Resuscitation* 2011; 82:655-656. doi10.1016/j.resuscitation.2011.03.028.
40. Tinsley C, Hill JB, Shah J, Zimmerman G: Experience of families during cardiopulmonary resuscitation in a pediatric intensive care unit. *Pediatrics* 2008; 122:e799-e804.
41. Dudley NC, et al: The effect of family presence on the efficiency of pediatric trauma resuscitations. *Ann Emerg Med* 2009; 53:777-784.

www.ketabpezeshki.com 66485457-66963820

Chapter 167

Pediatric Fever

Nathan W. Mick

Fever is the most common chief complaint of pediatric patients presenting to the emergency department (ED), accounting for up to 20% of ED visits. Most cases of fever are viral in origin, are benign in course, and resolve spontaneously. Fever tends to be of a higher clinical importance in younger children as they are immunologically immature and incompletely vaccinated. Management of children presenting to the ED varies dramatically by the age of the child, with the following common, albeit arbitrary, divisions: 0 to 28 days, 1 to 2 months, 2 to 3 months, 3 to 6 months, 6 to 36 months, and 3 years to adulthood.[1] These divisions reflect differing immunologic and vaccination milestones as well as the spectrum of age-specific pathogens.

PERSPECTIVE

Definitions and Epidemiology

Fever is defined as any elevation in body temperature equal to or above 38.0° C and typically is the result of infection. The most reliable method to measure temperature is with a rectal thermometer, particularly in high-risk groups, such as infants 0 to 3 months of age, as axillary, oral, and tympanic thermometers are unreliable in this age group. The rectal route should not be used in patients who are potentially immunocompromised (e.g., children with fever who are receiving cytotoxic chemotherapy) because of the risk of mucosal damage, bacteremia, or transmission of infection. The cutoff for a clinically significant fever (i.e., one that triggers a laboratory evaluation) varies with the age and immunologic status of the child. A rectal temperature of 38.0° C is generally considered to be a clinically significant fever in an infant younger than 3 months, necessitating a thorough laboratory workup, whereas a toddler with a temperature of 39.5° C and an upper respiratory infection may not need any workup beyond a thorough history and physical examination. Fever is to be distinguished from hyperthermia, which is an elevation in the body's temperature "set point." Causes of hyperthermia include heatstroke, salicylate ingestion, malignant hyperthermia as a complication of inhalational anesthetics, and elevation in temperature secondary to hypothalamic central nervous system (CNS) damage.

The cause of fever varies with the age of the child (Table 167-1). The majority of pediatric fever is due to infections, and most infections are attributable to a viral source. Upper respiratory infections, viral gastroenteritis, croup, bronchiolitis, stomatitis, roseola, infectious mononucleosis, and varicella are all known causes of fever. Most viral illnesses are benign and self-limited, but infection with herpes simplex virus (HSV) or respiratory syncytial virus (RSV), particularly in the first month of life, can lead to significant morbidity and mortality.

Bacterial disease is also an important cause of fever in children. Serious bacterial illness (SBI) is typically defined as the presence of pathogenic bacteria in a previously sterile site and includes urinary tract infection (UTI), bacteremia, meningitis, osteomyelitis, bacterial gastroenteritis, bacterial pneumonia, cellulitis, and septic arthritis. Studies have found the risk of SBI in febrile infants younger than 3 months with a temperature above 38.0° C to be between 6 and 10%; children younger than 28 days have the highest incidence.[2] Pathogens change during early infancy, with vertical transmission of organisms such as group B streptococcus, *Listeria monocytogenes,* and HSV being more common in neonates. By 1 to 2 months of age, organisms such as *Streptococcus pneumoniae, Neisseria meningitidis,* and urinary pathogens (*Escherichia coli* or *Enterococcus*) become more common. In all children younger than 3 months, the urinary tract is the most common site of infection, followed by bacteremia and meningitis. UTIs are more common in white girls compared with other races and are of higher prevalence in patients in whom no source for infection is found and who have higher temperatures (i.e., >39.0° C).[3]

Children younger than 3 months may present with an apparent viral syndrome and still harbor serious bacterial illness. Levine and colleagues studied 1248 infants younger than 60 days who had temperatures above 38.0° C. Of these children, 22% were positive for RSV. Although, overall, children with documented RSV had a lower incidence of concomitant SBI than did those without RSV (12.5 vs. 7%), there was no significant difference in rates of SBI in children younger than 28 days (14.2% in RSV-negative neonates vs. 10.1% in RSV-positive infants). Most of the bacterial infections were UTIs.[4] Older children 3 to 36 months of age with recognizable viral syndromes (e.g., croup, bronchiolitis, varicella, stomatitis) have a very low incidence of bacteremia. Greenes and co-workers found that among 1347 patients with temperature above 39.0° C who had a recognizable viral syndrome, the risk of bacteremia was 0.2%.[5]

Occult bacteremia describes the presence of pathogenic bacteria in the bloodstream of a well-appearing febrile child in the absence of a focus of infection; it was first described as a clinical entity in the 1970s.[6] The term typically refers to children 3 to 36 months of age who are highly febrile (>39.0° C) but appear well. Before the adoption of the conjugate vaccines against *Haemophilus influenzae* type b and *S. pneumoniae,* the incidence of bacteremia in this population was approximately 5%.[7,8] Vaccination has proved remarkably effective, nearly eradicating *H. influenzae* type b as a significant pathogen and greatly reducing the burden of pneumococcal disease (Fig. 167-1).[9-11] Currently, the rate of occult bacteremia is below 1%, with pathogens such as *N. meningitidis* becoming proportionally more prevalent. Continued surveillance is ongoing to ensure that there is not a rise in invasive disease

www.ketabpezeshki.com 66485457-66963820

Table 167-1 Etiology of Fever in Children

AGE	BACTERIAL CAUSES	VIRAL CAUSES	OTHER
0-28 days	Group B streptococcus *Listeria monocytogenes* *Escherichia coli* *Chlamydia trachomatis* *Neisseria gonorrhoeae*	Herpes simplex virus Varicella Enteroviruses Respiratory syncytial virus Influenza	Bundling Environmental
1-3 months	*Haemophilus influenzae* *Streptococcus pneumoniae* *Neisseria meningitidis* *Escherichia coli*	Varicella Enteroviruses Respiratory syncytial virus Influenza	Bundling Environmental
3-36 months	*Streptococcus pneumoniae* *Neisseria meningitidis* *Escherichia coli*	Varicella Enteroviruses Respiratory syncytial virus Influenza Mononucleosis Roseola Adenovirus Norwalk virus Coxsackievirus	Leukemia Lymphoma Neuroblastoma Wilms' tumor
3 years to adulthood	*Streptococcus pneumoniae* *Neisseria meningitidis* *Escherichia coli* Group A streptococcus	Varicella Enteroviruses Respiratory syncytial virus Influenza Mononucleosis Roseola Adenovirus Norwalk virus	Leukemia Lymphoma Neuroblastoma Wilms' tumor Juvenile rheumatoid arthritis

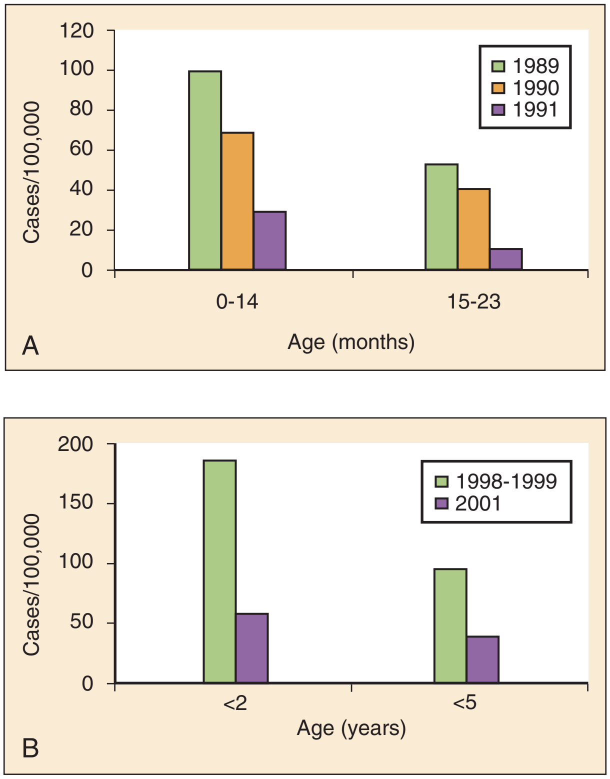


Figure 167-1. Decline in incidence of occult bacteremia after the introduction of the conjugate vaccine against *Haemophilus influenzae* (**A**) and *Streptococcus pneumoniae* (**B**).

caused by nonvaccine serotypes. Urinary pathogens, occurring in 2% of febrile children younger than 5 years, continue to be an important source of bacterial illness in infants and children. Rates are highest in boys younger than 6 months (2.7%) and girls younger than 12 months (6-8%).[12,13]

Bacterial illness in school-age children and adolescents includes focal infections, such as streptococcal pharyngitis, cellulitis, and pneumonia as well as bacteremia and meningitis. *N. meningitidis* has a bimodal distribution, with the highest incidence in children younger than 12 months (9.2/100,000 population). A second peak occurs during adolescence, when the rate of illness is 1.2/100,000 population, with a significant proportion of cases occurring in college students who reside in a dormitory setting (3.2/100,000 population).[14]

Although it is much less common than in viral or bacterial infection, fever can also be a presenting sign of autoimmune diseases, such as juvenile rheumatoid arthritis or Kawasaki disease. CNS lesions such as brain tumors also can infrequently be manifested with fever.

DISTINGUISHING PRINCIPLES OF DISEASE

Pathophysiology

The body's ability to fight infection varies with age. Maternal antibodies confer some protection after birth, but the infant's immune system is initially inadequate, particularly T-cell function and the ability to mount an immunoglobulin G response to infection. The immature neonatal immune system as well as exposure to certain pathogens during the birthing process (e.g., group B streptococcus, *Chlamydia trachomatis, Neisseria gonorrhoeae*) places the newborn at particular risk for SBI. Young infants are also at risk for disseminated infection as they are unable to mount

www.ketabpezeshki.com 66485457-66963820

the immune response needed to prevent a localized infection from spreading. Thus a simple cellulitis, mastitis, omphalitis, or, rarely, gonococcal eye disease can lead to sepsis or focal seeding of the CNS, making aggressive evaluation and treatment of such infections crucial. Immune function improves during the first 2 to 3 months of life, but the risk of SBI does not diminish appreciably until the primary series of vaccinations against *H. influenzae* type b and pneumococcus is completed (6 months of age).

History

In dealing with a febrile child, history taking should focus on the length of illness, presence of localizing symptoms, and any pertinent past medical history. In infants younger than 28 days, birth history, particularly the presence of potentially transmittable maternal infection (HSV or group B streptococcus), is critically important. Immunization status, sick contacts, use of antipyretics before evaluation, and prior use of antibiotics are also important historical items. Defervescence after acetaminophen administration has not been shown to reliably exclude bacteremia in children of any age.[15] Prior antibiotic use may mask the classic findings in diseases such as meningitis. Cough and congestion may suggest pneumonia or viral upper respiratory infection, whereas a harsh, barking, or seal-like cough is often a predominant complaint in viral laryngotracheitis (croup). Parents may report vomiting and diarrhea as a component of gastroenteritis or the presence of sore throat and lymphadenopathy with viral or streptococcal pharyngitis. Decreased oral intake or decreased urine output is frequently a complaint in gastroenteritis, but it may also be seen in patients with stomatitis as the painful aphthous ulcerations in the mouth make fluid intake difficult. Any history of lethargy, irritability, or altered mental status can be elicited with severe dehydration but raises the specter of meningitis or encephalitis. A rash occurs in many viral illnesses, such as roseola, but it also may be seen in life-threatening conditions, such as meningococcemia, Rocky Mountain spotted fever, and toxic shock syndrome. Complaints of headache and neck pain (meningitis or encephalitis) or ear pain (otitis media) are also important historical points.

Physical Examination

The physical examination of the febrile child should begin with a complete set of vital signs, including pulse oximetry. Hypoxia or significant respiratory distress manifested by tachypnea, grunting respirations, nasal flaring, or retractions may accompany sepsis or pulmonary infection. Stridor can be seen with croup but also with retropharyngeal abscess, epiglottitis, or bacterial tracheitis. Signs of shock, such as hypotension and poor peripheral perfusion, should be noted. Children typically mount a tachycardic response to fever, and hypotension is often a late and dire finding. Tachycardia is often due to the fever itself, but tachycardia out of proportion to the degree of fever is often seen in other conditions, such as early shock, myopericarditis, and dehydration. Greenes and colleagues found that in infants younger than 12 months, heart rate increases linearly by 9.6 beats/minute with each 1°C increase in body temperature; however, caution must be exercised in attributing tachycardia to fever alone.[16] Once oxygenation, ventilation, and perfusion have been assessed and deemed adequate, the physical examination should focus on a thorough search for focal infection. In young infants, particularly those younger than 3 months, and in children who lack immunocompetence, fever may be the only presenting sign of serious illness, including meningitis. The physical examination in this age group is sufficiently insensitive to exclude SBI, and clinicians should not be falsely reassured by a normal physical examination in small children.

Ancillary Testing

Numerous laboratory and radiographic studies can be used to evaluate the febrile child. In general, testing should be directed at identification of the source of infection or evaluation for complications. Several guidelines exist for the evaluation of febrile children, although there is marked variation in adherence to these guidelines. Pantell and associates found that office-based practitioners followed published guidelines only 42% of the time in the evaluation of febrile children.[17] Clinicians with less experience and those based in the hospital tend to order more tests compared with more experienced clinicians and those practicing in an office setting.

White Blood Cell Count

An elevated white blood cell (WBC) count (>15,000/mm^3) can be an indicator of bacteremia but is also present in many viral illnesses. Leukopenia (<5000/mm^3) can also be a sign of SBI or early sepsis. Pneumococcal infection is classically associated with leukocytosis, whereas infection with *N. meningitidis* and *H. influenzae* may be present even with normal WBC counts. Lee and colleagues found that the rate of pneumococcal bacteremia increased from 0.5% in highly febrile children (>39.0°C) with a WBC count between 10,000 and 15,000/mm^3 to 3.5% if the WBC count was 15,000 to 20,000/mm^3 and up to 18% with a WBC count above 30,000/mm^3.[18]

The WBC differential has also been used to risk stratify febrile children in various models; an increase in polymorphonuclear leukocytes and immature band forms increases the risk of bacterial disease. A rise in polymorphonuclear leukocytes is also seen early in some viral infections. An absolute neutrophil count (ANC) above 10,000/mm^3 suggests increased risk of pneumococcal bacteremia in febrile children (0.8% for children with an ANC below 10,000/mm^3 vs. 8% for children with an ANC above 10,000/mm^3).[19]

Blood Culture

A blood culture is a useful diagnostic test when bacteremia is suspected. In infants and children, blood should be obtained after sterile preparation of the skin, which includes an alcohol preparation and swabbing of the skin with povidone-iodine solution, which is then allowed to dry. Many centers obtain blood for culture during intravenous catheter placement after sterile preparation of the skin has been performed. This technique has the advantage of eliminating a second venipuncture solely to obtain blood for culture, although the rates of contamination with this technique have been shown to be higher in children (9.1 vs. 2.8%).[20] The risks of contamination should be weighed against the ability to obtain blood through a separate venipuncture. The yield of a single blood culture in infants and small children is actually good. The routine sending of more than one sample is generally not needed, and bacteremia is often accurately detected even if only 0.5 to 1 mL of blood is obtained. The advent of automated blood culture systems led to the identification of true pathogens more quickly than by traditional methods, often within 24 hours. Pathogens isolated in the first 24 hours are more likely to be true pathogens than are bacteria isolated after 24 hours.[21]

Urinalysis and Urine Culture

UTIs are common causes of bacterial illness in febrile children. Accurate documentation of UTI is imperative both to diagnose the cause of a fever and to identify those infants who need follow-up radiographic imaging (typically voiding cystourethrography, renal ultrasonography, or both) to exclude anatomic

www.ketabpezeshki.com 66485457-66963820

abnormalities that will predispose them to further infection. The only reliable method to obtain urine in a non–toilet-trained child is bladder catheterization or suprapubic aspiration. Bag collection of urine is notoriously unreliable; up to 85% of cultures from bag specimens will be falsely positive (defined as a culture growing a single organism with $>10^5$ colony-forming units [CFU]/mL or a mix of two or more organisms), which then places these children at risk for unneeded, potentially painful, and expensive follow-up diagnostic testing and antibiotics. A clean catch urine specimen is appropriate for older toilet-trained children.

UTI is defined as the combination of bacteriuria and pyuria. Bacteriuria in the absence of WBCs on microscopic examination represents asymptomatic bacteriuria. Urine is typically analyzed with a dipstick, followed by microscopic analysis of a centrifuged specimen of urine. Hoberman and colleagues described the test characteristics of an "enhanced" urinalysis, which is examination with a hemocytometer of an unspun specimen of urine for pyuria (defined as >10 WBCs per high-power field) or the presence of any bacteria per high-power field in Gram's stain of unspun urine. They reported a negative predictive value of 99.8%, perhaps making urine culture unneeded if pyuria and bacteriuria are absent by use of the enhanced urinalysis method.[22] Many centers are not using this enhanced method. Because dipstick and microscopic analysis have lower sensitivities, most experts recommend sending urine for culture in high-risk groups (febrile girls <24 months of age, uncircumcised boys <12 months of age, and circumcised boys <6 months of age).

A positive urine culture is defined as the growth of more than 10,000 CFU/mL of a uropathogen from urine obtained from a catheterized or suprapubic sample. In older children, in whom urine is typically obtained from a clean catch specimen, a higher threshold of more than 100,000 CFU/mL is typically used.

Lumbar Puncture

A sample of cerebrospinal fluid (CSF) should be obtained from any child with signs and symptoms of meningitis. Fluid should be obtained with the smallest pencil-point or noncutting spinal needle possible (typically a 22-gauge spinal needle) and sent for cell counts, manual differential, Gram's staining, culture, and measurement of CSF protein and glucose concentrations. Meningoencephalitis due to HSV is a potential cause of fever, particularly in children, and if it is suspected, sending of CSF for HSV polymerase chain reaction testing is indicated. The CSF in bacterial meningitis typically contains more than 1000 WBCs/mL, although there is considerable overlap in the CSF profile of bacterial and viral meningitis, making a determination of viral or aseptic meningitis difficult on the basis of CSF parameters such as cell count, protein, and glucose; thus CSF culture of a pathogenic bacterium is the "gold standard." A prediction rule has been developed and validated to differentiate bacterial from aseptic meningitis.[23] Children who lack all of the following criteria have a low risk (0.1%) of bacterial meningitis: positive CSF Gram's stain, CSF ANC of at least 1000 cells/mL, CSF protein concentration of at least 80 mg/dL, peripheral blood ANC of at least 10,000 cells/mL, and history of seizure before or at the time of presentation. This may obviate the need for empirical antibiotic therapy and hospital admission in some children who are at low risk for bacterial meningitis.

Contraindications to lumbar puncture include cellulitis over the proposed site of puncture, cardiopulmonary instability, bleeding diathesis or platelet count below 50,000/μL, focal neurologic deficits, and signs of increased intracranial pressure, including papilledema. In these patients, lumbar puncture should be deferred until the child is stable, and blood should be obtained for culture while the child is treated empirically, recognizing that up to 50% of children with meningitis will not have bacteremia.[24]

CSF contaminated by blood, or a traumatic lumbar puncture, can make interpretation of cell counts and differentials difficult. In these cases, fluid should be obtained for Gram's stain and culture and the child treated presumptively for meningitis until culture data are available. Nigrovic and co-workers have shown that risk factors for a traumatic lumbar puncture include operator experience, excessive patient movement during the procedure, advancement of the needle with the stylet in place, and lack of local anesthesia.[25]

Stool Studies

Stool studies are indicated in patients in whom bacterial gastroenteritis may be a cause of fever. A stool guaiac test for blood as well as Gram's stain for WBCs should be performed. Presence of more than 5 WBCs per high-power field in the stool of a febrile child should trigger a culture of stool for *Salmonella, Shigella, Campylobacter,* enterotoxigenic *Escherichia coli,* and *Yersinia* species. Patients with sickle cell disease are at particular risk for focal complications such as osteomyelitis from *Salmonella* infection.

Chest Radiography

Chest radiographs may be useful in the workup of the febrile child and are indicated when hypoxemia, respiratory distress, tachypnea, or focal findings on lung examination are present. Children younger than 6 months may present with tachypnea as the sole finding of bacterial pneumonia. Truly occult pneumonia can also occur, particularly in the highly febrile child (>39.0°C) without apparent source of fever. Bachur and associates found that 26% of children with temperature above 39.0°C and WBC counts higher than 20,000 had radiographic evidence of pneumonia.[26] Of note, this study was done in the era before the conjugate pneumococcal vaccine.

Rapid Viral Antigen Testing

Many clinical laboratories have the ability to perform rapid viral antigen testing for such common pediatric viral illnesses as influenza A and B and RSV. The presence of a viral "source" for the fever in an ill child may obviate the need for expensive, painful, and lengthy diagnostic workups for bacterial processes. Bonner and colleagues evaluated the impact of physician knowledge of the presence of a positive rapid influenza assay result.[27] The investigators studied 391 patients aged 2 months to 21 years who presented with classic signs and symptoms of influenza. Of these patients, more than half had positive rapid assays for influenza, and the investigators noted that significantly fewer laboratory and radiographic studies were ordered if the treating clinician was aware of these results. There were also fewer antibiotics prescribed. A large multicenter trial of febrile infants 60 days of age or younger revealed a decreased risk (2.5 vs. 11.7%) if the infant was influenza positive.[28]

RSV is also a frequent cause of fever in children. As previously noted, RSV decreases but does not completely eliminate the risk of SBI in children. This is especially true of UTI in infants younger than 28 days.

SPECIFIC DISORDERS

General Approach to the Febrile Infant and Child

The initial approach to any child with a febrile illness is a rapid assessment for evidence of cardiopulmonary compromise or shock. Significant respiratory distress, hypoxemia unresponsive to

www.ketabpezeshki.com 66485457-66963820

supplemental oxygen, or altered mental status may necessitate intubation by rapid sequence induction and mechanical ventilation. Evidence of shock (poor perfusion, hypotension, altered mentation) should be aggressively treated with fluid resuscitation. An intravenous or intraosseous line should be placed, and the initial resuscitative fluid should be 20 mL/kg of isotonic crystalloid. This should be repeated to a total of 60 mL/kg if signs of hypovolemia persist, after which vasopressor therapy (dopamine 1-20 µg/kg/min or norepinephrine 0.1-3 µg/kg/min titrated to blood pressure) should be considered.

Every effort should be made to obtain appropriate specimens for culture (blood and urine), even in the critically ill child, before antibiotic administration. Lumbar puncture may be deferred in the critically ill child until stabilization occurs. Empirical antibiotic therapy should be directed at the most likely causative organisms based on age. Sterilization of the CSF occurs quickly once antibiotic administration has been initiated: within 15 minutes to 2 hours in patients with meningococcal meningitis and within 4 to 10 hours in patients with pneumococcal meningitis.[29]

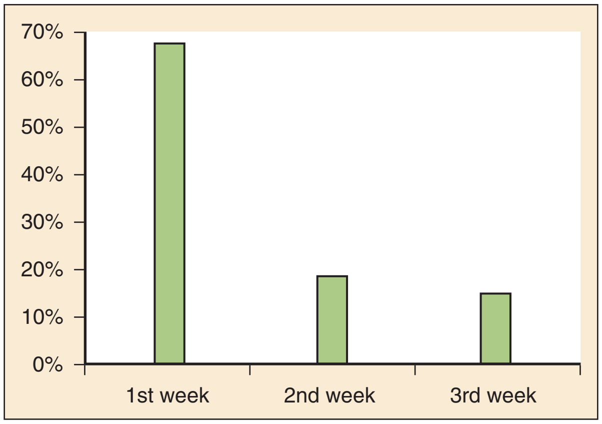


Figure 167-2. Age at presentation for neonatal herpes simplex virus infection.

Serious Bacterial Illness

Infants 0 to 28 Days of Age

Children presenting with temperature above 38.0°C who are younger than 28 days are at particularly high risk for bacterial illness, with rates as high as 12% quoted in the literature.[30,31] Often, fever is the only manifestation of potentially life-threatening disease, and other signs and symptoms may be exceedingly subtle. This has led to an aggressive approach to diagnostic testing, empirical antibiotic therapy, and hospitalization in this age group, even if the child appears well.

Children in this age group often present with nonspecific complaints, such as irritability, lethargy, poor feeding, and grunting. Besides fever, other signs of serious illness include a bulging fontanel, mottled extremities, petechiae, and tachypnea. Bacterial pathogens in this age group include group B streptococcus, *L. monocytogenes, N. meningitidis, S. pneumoniae,* and *E. coli*. Viral pathogens, including RSV and HSV, are also important considerations. Neonatal HSV infection in particular carries a high degree of morbidity and mortality and should be considered in any febrile neonate with a maternal history of genital herpes, who appears ill, who presents with fever and seizure, who has cutaneous vesicles on physical examination, or who has evidence of transaminitis or coagulopathy. HSV meningoencephalitis should also be considered in patients with fever and CSF pleocytosis but a negative CSF Gram's stain. The risk period for HSV disease tends to be between 2 and 12 days of age (Fig. 167-2). Other noninfectious causes of a septic-appearing neonate include the acute salt-wasting crisis associated with congenital adrenal hyperplasia and undiagnosed duct-dependent congenital heart disease.

Because of the high risk of bacterial pathogens and the difficulty in clinical assessment of children younger than 28 days, these patients require an aggressive diagnostic evaluation, including a complete septic workup. This consists of a complete blood count (CBC) with differential, blood culture, urinalysis and urine culture, and lumbar puncture. Lumbar puncture is indicated even in the presence of a UTI because of the risk of concomitant meningitis.[32] All children in this age group should be admitted to the hospital with empirical antibiotics until culture data become available. Appropriate parenteral antibiotic regimens include ampicillin (100 mg/kg/24 hr divided every 6 hours) plus either gentamicin (5 mg/kg/24 hr divided every 8 to 12 hours) or cefotaxime (150 mg/kg/24 hr divided every 8 hours). Ceftriaxone should be avoided in infants younger than 28 days because of a theoretic risk of inducing acute bilirubin encephalopathy as ceftriaxone causes bilirubin to be displaced from its protein binding sites. Empirical acyclovir should be added if risk factors for HSV disease exist (60 mg/kg/24 hr, divided every 8 hours).

Infants 29 to 90 Days of Age

Although there is a relative consensus as to the evaluation and management of febrile infants younger than 28 days, there is debate about the appropriate workup for the slightly older febrile infants. Ill-appearing children of any age should have a complete sepsis evaluation performed and be admitted to the hospital with empirical antibiotic therapy. Appropriate antibiotic therapy for high-risk children includes coverage of neonatal pathogens such as *L. monocytogenes* and group B streptococci as well as coverage against *H. influenzae, N. meningitidis,* and *S. pneumoniae*. Ampicillin, 50 to 100 mg/kg every 6 hours, plus cefotaxime, 50 mg/kg every 8 hours parenterally, is one alternative. Vancomycin, 40 to 60 mg/kg intravenously (IV) every 6 to 8 hours, should be considered if *S. pneumoniae* resistant to penicillins and cephalosporins is suspected.

Various strategies (herein referred to as the Rochester, Philadelphia, and Boston criteria) for the evaluation of well-appearing children have been reported, compared, and retested in the literature.[33-35] Each strategy has unique features, including the definition of fever (38.0°C vs. 38.2°C), the study population (0-3 months of age, 1-2 months of age, and 1-3 months of age), the clinical and laboratory variables studied, and the disposition (hospitalization with or without antibiotics or outpatient treatment with or without antibiotics). Each strategy seeks to identify a set of low-risk criteria that, if met, will allow less aggressive treatment or the withholding of empirical antibiotic therapy. The three main strategies are highlighted in Table 167-2. Baraff synthesized the recommendations of the Rochester, Philadelphia, and Boston criteria into an algorithm for the management of the previously healthy febrile infant 29 to 90 days of age (Fig. 167-3).[36] To be low risk, the child had to have been previously healthy with an uncomplicated nursery stay, to be nontoxic clinically, and to have no focal source of bacterial infection. Low-risk laboratory criteria in this schema included a normal WBC count (between 5000 and 15,000 WBCs/mm^3), fewer than 1500 bands/mm^3, normal urinalysis (negative Gram's stain and <5 WBCs per high-power field), and negative CSF Gram's stain and cell counts (<8 WBCs/mm^3), if obtained. When diarrhea was present, fewer than 5 WBCs per high-power field was the threshold for low risk.

Once the child is deemed to be at low risk by these criteria, two options are available to the clinician on the basis of the Philadelphia and Boston criteria. The first management strategy calls for a CBC, blood culture, urinalysis, and urine culture. Once these

www.ketabpezeshki.com 66485457-66963820

Table 167-2 Summary of Major Strategies for the Management of Febrile Infants Younger than 3 Months

	PHILADELPHIA	ROCHESTER	BOSTON
Age	29-60 days	<60 days	28-89 days
Temperature	>38.2° C	>38.0° C	>38.0° C
Examination	Well, no focus	Well, no focus	Well, no focus
Laboratory values (define low risk)	WBCs > 15,000/mm^3 Band/neutrophil ratio < 0.2 UA < 10 WBCs/hpf (negative Gram's stain) CSF < 8 WBCs/hpf (negative Gram's stain) Chest radiograph normal, stool negative (if obtained)	WBCs 5000-15,000/mm^3 Absolute band count < 1500 UA < 10 WBCs/hpf Stool < 5 WBCs/hpf (if obtained)	WBCs < 20,000/mm^3 UA < 10 WBCs/hpf CSF < 10 WBCs/hpf Chest radiograph normal (if obtained)
High risk	Admission + IV antibiotics	Admission + IV antibiotics	Admission + IV antibiotics
Low risk	Home, no antibiotics	Home, no antibiotics	Home, empirical antibiotics
Performance	Sensitivity 98% (92-100%) Specificity 42% (38-46%) PPV 14% (11-17%) NPV 99.7% (98-100%)	Sensitivity 92% (83-97%) Specificity 50% (47-53%) PPV 12% (10-16%) NPV 98.9% (97-100%)	Sensitivity not available Specificity not available PPV not available NPV 94.6%

CSF, cerebrospinal fluid; *IV,* intravenous; *NPV,* negative predictive value; *PPV,* positive predictive value; *UA,* urinalysis; *WBCs/hpf,* white blood cells per high-power field.

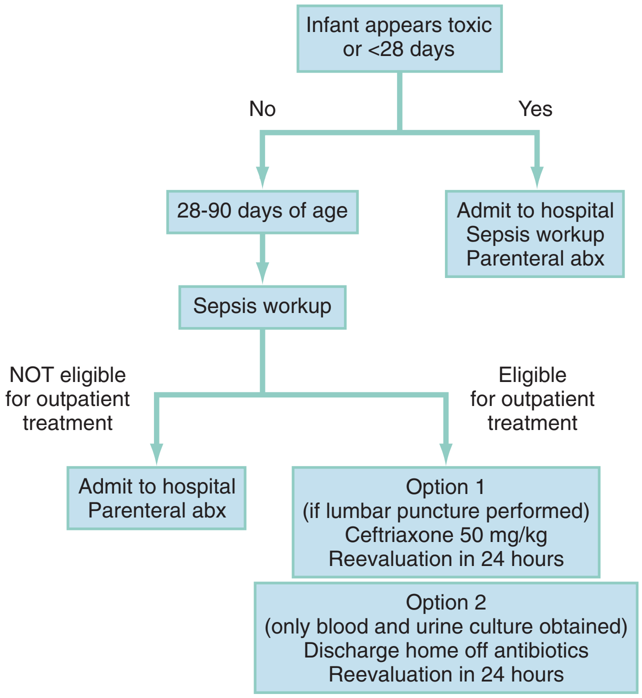


Figure 167-3. Algorithm for the management of febrile infants younger than 3 months. *abx,* antibiotics.

studies have been obtained and the results are normal, the child may be discharged with close outpatient follow-up. The second option, based on the Boston criteria, calls for a complete sepsis evaluation, including lumbar puncture, followed by empirical treatment with ceftriaxone (50 mg/kg IV or intramuscularly [IM]) and reevaluation within 24 hours. The important difference between these two strategies is that empirical antibiotics should not be administered unless a complete sepsis evaluation is performed, including a lumbar puncture. Otherwise, if a lumbar puncture is not initially performed and the child returns for reevaluation and a lumbar puncture is subsequently performed with the finding of CSF pleocytosis, pretreatment with antibiotics makes interpretation of culture results difficult. Thus a child with a possible viral process may be subjected to inpatient admission and 14 days of parenteral antibiotic therapy.

Infants 3 to 36 Months of Age

Fever in children 3 to 36 months of age is incredibly common; most cases represent self-limited viral illnesses. Common causes of fever in this age group include viral upper respiratory infections, croup, bronchiolitis, stomatitis (typically caused by HSV or Coxsackievirus), gastroenteritis, roseola, and fifth disease (parvovirus B19 infection). Focal infections, such as pyelonephritis, periorbital cellulitis, bacterial pharyngitis (group A streptococcus), septic arthritis, retropharyngeal abscess, meningitis, and bacterial pneumonia, also become common in this age group. Typically, these focal infections are apparent on the basis of history and physical examination findings, and diagnostic testing and treatment should be directed accordingly.

The history in this age group should focus on the duration of illness, associated symptoms that may focus the evaluation, immunization history (particularly vaccination for *H. influenzae* type B and pneumococcus), and sick contacts. A thorough physical examination is essential to rule out serious focal infection, such as meningitis. Young children may demonstrate inconsolable irritability or lethargy as the sole manifestation of meningitis; furthermore, classic meningeal signs, such as nuchal rigidity, are seen in less than 27% of infants (0-6 months) with bacterial meningitis.[37]

Prior research has focused on assessment of children in this age group for the presence of occult bacteremia. It was found that a small percentage of highly febrile children (>39.0° C) 3 to 36 months of age were bacteremic.[36,38-41] These children were noted to be highly febrile but lacked any localizing signs of infection. No historical or physical examination findings were sufficiently sensitive or specific to identify cases of occult bacteremia, making universal diagnostic testing necessary.[42-44] A typical workup included a CBC and blood culture, and empirical antibiotic therapy was prescribed for children with WBC counts above 15,000/mm^3. Empirical antibiotics were justified on the basis of studies that revealed treatment with antibiotics prevented focal sequelae of bacteremia such as meningitis and shortened the duration of fever.[45-47] Before the advent of almost universal immunization against *S. pneumoniae,* the rate of occult bacteremia was approximately 3%, and although pneumococcal bacteremia resolves

www.ketabpezeshki.com 66485457-66963820

without therapy up to 75% of the time, a small proportion of children have sepsis or focal infections such as meningitis. Pneumococcal meningitis has a high degree of morbidity and mortality, including permanent neurologic disability, hearing loss, and death.[48,49] Since the advent of Prevnar (conjugate pneumococcal vaccine), the number of invasive pneumococcal infections caused by vaccine-serogroup isolates among eight U.S. children's hospitals has decreased more than 75% among children younger than 24 months. Because of the decline in invasive pneumococcal disease brought on by vaccination, the cost-effectiveness of mandatory blood testing has been called into question.[50,51] Lee and colleagues evaluated the cost-effectiveness of various management strategies: no workup, relying on clinical judgment, blood culture, blood culture plus empirical antibiotics, WBC count plus blood culture and empirical antibiotics, and WBC count plus selective blood culture for WBC counts above 15,000 and empirical antibiotics. They found that at rates of pneumococcal bacteremia greater than 1.5%, obtaining a WBC count plus selective blood culture and empirical antibiotics were the most cost-effective approach. At rates of pneumococcal bacteremia less than 0.5%, strategies that used empirical testing and treatment were no longer cost-effective. They concluded that at lower rates of bacteremia, clinical judgment is more useful in selecting out high-risk populations who might benefit from selective testing and treatment.[52]

Although the incidence of pneumococcal bacteremia has declined in infants 3 to 36 months of age because of the aggressive campaign to vaccinate, infants 3 to 6 months of age have not yet completed the primary series of immunizations against *S. pneumoniae* and to a lesser extent *H. influenzae*. Thus, highly febrile infants (>39.0° C) without an apparent source on examination should be considered at risk for occult bacteremia and consideration given to obtaining a WBC count and blood culture as a screen. Empirical antibiotic therapy should be reserved for infants with WBC counts above 15,000/mm^3 or those with an ANC ≥10,000/mm^3. Although the conjugate pneumococcal vaccine contains antigens from the seven most common serotypes that cause invasive disease, there are approximately 90 serotypes that are capable of infecting humans. Continued bacterial surveillance is necessary to ensure that other serotypes do not rise in incidence to fill the void left by vaccination. No clinical prediction algorithm correctly identifies all patients with meningococcal disease.[53] Additional signs and symptoms that may suggest meningococcemia are purpuric rash, bandemia, limb pain, and exposure to a person with the disease. An appropriate flow diagram for the workup of febrile infants 3 to 36 months of age is presented in Figure 167-4.

Children Aged 3 Years to Adulthood

The incidence of occult bacteremia decreases after 3 years of age. Focal infections such as streptococcal pharyngitis, septic arthritis, pneumonia, peritonsillar abscess (most often in adolescents), and cellulitis become more common. Viral pathogens are also common, such as infectious mononucleosis. Infection with atypical pathogens, such as *Mycoplasma pneumoniae,* should also be considered in children presenting with pneumonia. Skin infections secondary to community-acquired methicillin-resistant *Staphylococcus aureus* (CMRSA) are also becoming more common. CMRSA occurs in all age groups but has clustered among such children as wrestlers (associated with contaminated wrestling mats) and football players (infected equipment).[54,55] This diagnosis should be considered in all children who present with pyogenic skin infection and skin abscesses. Appropriate therapy includes incision and drainage of the abscess cavity. Antibiotic therapy in addition to incision and drainage for simple abscesses has not been shown to hasten resolution of the infection but should be considered for patients with large abscesses (>5 cm), with cellulitis, or with

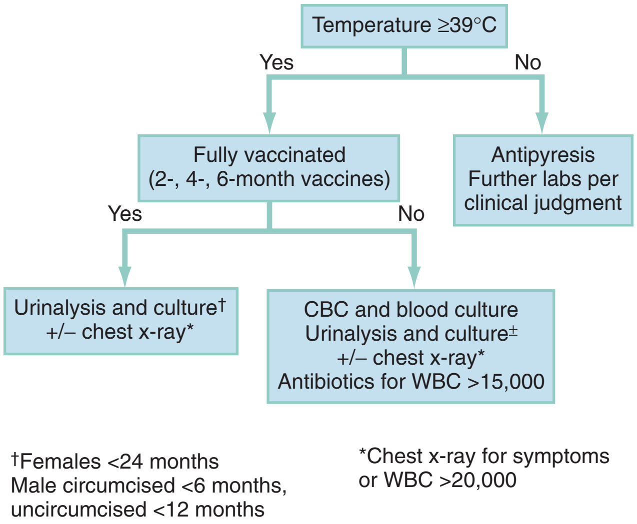


Figure 167-4. Algorithm for the management of febrile infants 3 to 36 months of age. *CBC,* complete blood count; *WBC,* white blood cell count.

fever.[56] The antibiotics used are dependent on local resistance patterns but could include trimethoprim-sulfamethoxazole or clindamycin.

There is also a second peak in incidence of meningococcal disease in adolescent children with an attack rate of 1.2 infections per 100,000 population. As opposed to infants, adolescents with meningococcal infection are more likely to present with meningococcemia (40 vs. 20%) and shock (69 vs. 27%) and to have a fatal outcome (22.5 vs. 4.6%). Meningococcal disease typically is manifested with one of three clinical syndromes: meningitis, bacteremia, or a combination of the two. College students residing in dormitories are at particular risk for infection, with attack rates of 3.2/100,000 population.[57] The history in cases of meningococcal infection is often one of rapidly progressive fever, headache, and stiff neck. Shock, altered mental status or frank coma, petechiae or purpura, seizures, and myalgias are also seen. Some of the first signs of meningococcal infection include leg pain, cold hands and feet, and abnormal skin mottling.[58] Children exposed to a patient with meningococcemia, particularly those with close contact with nasopharyngeal secretions, and who have any of the presenting signs should receive a full septic workup, admission to the hospital, and empirical treatment with antibiotics until results of blood and CSF cultures are known. Appropriate initial therapy for children suspected of having meningococcal infection is ceftriaxone 100 mg/kg IV.

In January 2005, the Food and Drug Administration approved the quadrivalent meningococcal conjugate vaccine (Menactra) for use in adolescents. This vaccine is a polysaccharide-protein conjugate directed against the four serotypes that cause most cases of invasive meningococcal disease in humans. The Advisory Committee on Immunization Practices recommends vaccination of adolescents at their 11- or 12-year-old well-child checkup, and the American Academy of Pediatrics (AAP) has also advised that all college freshmen living in dormitories be vaccinated. Use of the vaccine is associated with a 67% decrease in invasive disease and a 66% decrease in carriage rates.[59]

Febrile Seizures

Febrile seizures are a common cause of convulsions in children younger than 5 years. They are defined as a seizure accompanied by fever without the presence of CNS infection. They typically occur in infants and children aged 6 months to 5 years. It is

www.ketabpezeshki.com 66485457-66963820

thought that the at-risk period is the rapid rise or defervescence of a fever, rather than the absolute height of the fever. Many parents worry about the subsequent risk of epilepsy after a febrile seizure, although studies have borne out that the risk is only slightly increased. The risk of epilepsy in the general population is thought to be 0.5 to 1%, whereas the risk in a patient who has had a febrile seizure is 1 to 2%. Although they are generally benign in course, febrile seizures can sometimes be the presenting complaint of infants and children with CNS infection such as meningitis. Febrile seizures are classified as either simple or complex. Simple febrile seizures are brief (<15 minutes), single, and nonfocal or generalized tonic-clonic. Complex febrile seizures are prolonged, recurrent (more than one within 24 hours), or typically focal.

Differentiation of a benign febrile seizure from one that heralds CNS infection can be difficult. The AAP has published consensus guidelines for the evaluation and management of febrile seizures.[60] Laboratory and radiographic evaluation should be directed at finding the source of the fever, not driven by the seizure itself. The AAP suggests that a lumbar puncture be performed in any child with signs of meningeal irritation after the first febrile seizure and be considered in children who are incompletely immunized or have received prior antibiotic therapy. Routine referral for neuroimaging or electroencephalography is not indicated.[61] There is also no role for antiepileptic therapy after a single febrile seizure. Two retrospective studies have shown that the incidence of meningitis after the simple or complex febrile seizures is exceedingly low and that infants with meningitis will demonstrate signs of sepsis or meningitis after the seizure, making empirical lumbar puncture based solely on a febrile seizure unnecessary.[62,63]

Parents should be warned that 33% of children who have a febrile seizure will have another one and that 75% of these will occur within a year. The younger a child is at the age of the first seizure, the more likely it is that a second one will occur. Children who seize at lower temperatures are also at higher risk for recurrence (35% at 38.5°C vs. 13% at 40°C).

Fever and Petechiae

The presence of a petechial rash in the setting of a febrile illness is classically associated with meningococcal infection. In fact, Baker and colleagues found that the incidence of meningococcal infection was 7 to 11% in patients hospitalized with fever and petechiae.[64] The rate of bacteremia of any cause was found to be much lower (1.9%) in an ED population. The differential diagnosis of fever and petechiae also includes disseminated intravascular coagulation, Rocky Mountain spotted fever, pneumococcal bacteremia, *Streptococcus pyogenes* infection, various viral infections, idiopathic thrombocytopenic purpura, Henoch-Schönlein purpura, and leukemia. Petechiae can also be caused mechanically from a tourniquet, retching, or violent coughing. Petechiae due to vomiting or coughing are typically confined to the skin above the nipple line, but petechiae caused by SBI can have any distribution.

Because of the risk of serious illness in children with fever and petechiae, blood should be obtained for CBC and culture. In cases associated with pharyngitis, testing for group A streptococcus infection is indicated. Mandl and colleagues performed a prospective cohort study of 411 patients presenting to a pediatric ED with temperature higher than 38.0°C and petechiae in the hope of identifying clinical and laboratory criteria that would provide a means to screen for bacteremia.[65] They found that an abnormal WBC count (<5000 WBCs/mm^3 and >15,000 WBCs/mm^3) or abnormal coagulation studies were predictive but not diagnostic of invasive bacteremia. Also, well-appearing children with normal WBC and coagulation studies were exceedingly unlikely to have invasive bacteremia. In their study, only two well-appearing children had bacteremia (*S. pneumoniae*), and this study was done in the pre-Prevnar era. Empirical antibiotic therapy (ceftriaxone 50 mg/kg IV or IM) should be considered in all children presenting with fever and petechiae, even if an outpatient disposition is anticipated.

Kawasaki Disease (Mucocutaneous Lymph Node Syndrome)

Kawasaki disease (KD) is one of the most common vasculitides in childhood and should be considered in any infant or child with prolonged fever.[66] A more complete discussion of KD can be found in Chapter 171. Accurate diagnosis is important because the main complication of KD is the development of coronary artery aneurysms. Some patients will present with "incomplete KD," which occurs when not all diagnostic criteria are met. Despite the lack of classic findings, these children are still at risk for coronary complications. Laboratory abnormalities found in cases of KD include leukocytosis, thrombocytosis (platelet counts as high as 1,000,000/mm^3), and evidence of systemic inflammation with elevation in the erythrocyte sedimentation rate and C-reactive protein level.

Children with suspected KD should be hospitalized and receive therapy with intravenous immune globulin (2 g/kg infused during 10-12 hours) and aspirin (initial dose 80-100 mg/kg daily divided every 6 hours).[67] Pediatric cardiology consultation for echocardiography is also indicated.

Toxic Shock Syndrome

Toxic shock syndrome (TSS) refers to the toxin-mediated clinical syndrome that occurs with infection with *Staphylococcus aureus,* although a similar illness is caused by infection with group A streptococcus. The toxin implicated in TSS is an exotoxin termed TSS toxin 1. The syndrome is classically associated with tampon use by menstruating women, although cases also occur in males and prepubertal girls and also result from other sources of infection with *S. aureus*.[68-70]

Clinical manifestations of TSS include fever (>38.9°C), hypotension, diffuse erythroderma, and multisystem involvement. Patients may present with vomiting or diarrhea, severe myalgias, oropharyngeal hyperemia, or altered mental status. Laboratory abnormalities are common and include elevated creatine kinase, elevated blood urea nitrogen or creatinine, transaminitis, and thrombocytopenia. The Centers for Disease Control and Prevention (CDC) has developed a set of findings for case definition (Box 167-1).

Treatment of TSS involves aggressive fluid resuscitation as these patients typically have immense requirements and antistaphylococcal antibiotic therapy with clindamycin (25-40 mg/kg per day in three divided doses) and vancomycin (40 mg/kg per day IV in four divided doses).

Fever and Underlying Chronic Medical Illness

Oncology Patients

Children with cancer, particularly those undergoing treatment with cytotoxic chemotherapy, are at particular risk for sepsis and bacterial infection.[71] These life-threatening infections are most common during periods of profound neutropenia. Neutropenia is defined as an ANC of less than 500/mL or an ANC of less than 1000/mL that is falling. Children with cancer also frequently have indwelling catheters, predisposing them to surgical line infections.

www.ketabpezeshki.com 66485457-66963820

Box 167-1 CDC Case Definition for Toxic Shock Syndrome

Fever: temperature >38.9°C (102.0°F)
Hypotension: systolic blood pressure 90 mm Hg for adults or less than fifth percentile by age for children <16 years; orthostatic drop in diastolic blood pressure by 15 mm Hg
Orthostatic syncope or dizziness
Diffuse erythroderma
Desquamation: 1-2 weeks after onset of illness, particularly involving palms and soles
Multisystem involvement (3 or more of the following organ systems)
- Gastrointestinal: vomiting or diarrhea at onset of illness
- Muscular: severe myalgia or creatine kinase elevation >2 times the normal upper limit
- Mucous membranes: vaginal, oropharyngeal, or conjunctival hyperemia
- Renal: blood urea nitrogen or serum creatinine >2 times the normal upper limit, or pyuria (>5 white blood cells/high-power field)
- Hepatic: bilirubin or transaminases >2 times the normal upper limit
- Hematologic: platelets <100,000/L
- Central nervous system: disorientation or alterations in consciousness without focal neurologic signs in the absence of fever and hypotension

Negative results on the following tests, if obtained
- Blood, throat, or cerebrospinal fluid cultures for another pathogen (blood cultures may be positive for *Staphylococcus aureus*)
- Serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles

Criteria for a probable case include a patient with temperature >38.9°C, hypotension, diffuse erythroderma, desquamation (unless the patient dies before desquamation can occur), and involvement of at least three organ systems. A probable case is a patient who is missing one of the characteristics of the confirmed case definition.

Causative organisms include both gram-positive and gram-negative bacteria. Staphylococci and streptococci as well as *Pseudomonas* are frequent pathogens. Often, patients with focal infection may not present with classic signs because of their leukopenia. Focal infections specific to cancer patients include stomatitis and typhlitis, which is a necrotizing enterocolitis of the terminal ileum and cecum.

Children presenting with fever and possible neutropenia require prompt evaluation. Blood should be obtained for a CBC and manual differential as well as culture. If a central line infection is suspected, a separate culture specimen from the line should be obtained. Once appropriate laboratory studies are obtained, empirical antibiotic therapy should be initiated without waiting for the laboratory results. Appropriate monotherapy antibiotic regimens include cefepime, 50 mg/kg IV every 8 hours, and ceftazidime, 50 mg/kg IV every 8 hours. Vancomycin, 40 to 60 mg/kg every 6 to 8 hours, should be added for antistaphylococcal coverage in children with suspected central line infections or skin and soft tissue infections. Children with fever and neutropenia are rarely if ever treated as outpatients; if so, ceftriaxone 50 mg/kg IV every 24 hours is given, and close follow-up is essential.

Acquired Immunodeficiency Patients

Children with the acquired immunodeficiency syndrome (AIDS) are at risk for bacterial infection due to a whole host of different organisms, some common, some uncommon. Infections specific to AIDS include cryptococcosis and infection with *Mycobacterium tuberculosis, Mycobacterium avium-intracellulare,* and *Pneumocystis jiroveci (carinii)*. Viral infections, such as cytomegalovirus and Epstein-Barr virus infections, are also common.

Laboratory evaluation should be directed by the history and physical examination. Early initiation of broad-spectrum antibiotic therapy is warranted.

Sickle Cell Disease

Febrile children with sickle cell disease are at particular risk for overwhelming infection.[72] In fact, infection is the most common cause of sickle cell–related death, occurring in up to 40% of patients with sickle cell disease who die. Recurrent episodes of splenic infarction lead to functional asplenia early in life. Thus these patients are at particular risk for infection with encapsulated organisms, including *S. pneumoniae* and *H. influenzae*. Because of this risk of bacterial disease, it is recommended that all children with sickle cell disease be completely immunized. Prophylaxis with penicillin is recommended in children younger than 5 years, after which it can be safely discontinued in children who have not had a prior severe pneumococcal infection or surgical splenectomy.[73] The dose of penicillin is 125 mg orally twice daily until 3 years of age (at about 14 kg) and 250 mg orally twice daily after 3 years of age.[74]

High-risk criteria for bacterial infection include toxic appearance, temperature higher than 40°C, abnormal WBC count (<5000 or >30,000 WBCs/mm^3), and noncompliance with penicillin prophylaxis. Sickle cell patients are at particular risk for *Salmonella* osteomyelitis. All patients presenting with fever and sickle cell disease should have a blood specimen drawn for CBC, reticulocyte count, and culture. A reticulocyte count is important as many infections (e.g., parvovirus B19) can induce life-threatening aplastic crisis. Infection also predisposes children with sickle cell disease to acute chest syndrome.[75] Common causes of infection include *Chlamydia pneumoniae, Mycoplasma,* RSV, *S. aureus,* and *S. pneumoniae*. Further laboratory and radiographic evaluation should be directed by the presenting history and physical examination findings.

High-risk patients should be admitted for further evaluation and antibiotic therapy. Low-risk patients may be treated with a single dose of intravenous or intramuscular antibiotics, typically ceftriaxone 50 mg/kg, and discharged to close outpatient follow-up. All patients should be reevaluated within 24 hours or sooner if the clinical condition deteriorates.

Osteomyelitis typically is manifested with fever and bone pain. As patients with sickle cell disease may have frequent bone pain due to vaso-occlusive crisis, the diagnosis often can be difficult. All patients should have a blood specimen drawn for CBC with differential, erythrocyte sedimentation rate, and culture; a radionuclide bone scan or magnetic resonance imaging may help localize the infection. If *Salmonella* infection is suspected, a stool sample should be sent for culture.

Congenital Heart Disease

Children with congenital heart disease are at high risk for cardiovascular complications in the setting of febrile illness. Often, relatively minor viral illness can produce significant changes in cardiac function or make it difficult for children to be compliant with their oral medications. Children with congenital heart disease are also at risk for infective endocarditis. Infective endocarditis is heralded by fever and possibly a changing or worsening cardiac murmur. The modified Duke criteria for the diagnosis of endocarditis are presented in Box 167-2.[76]

Endocarditis is typically caused by *S. aureus,* viridans streptococci, *Streptococcus bovis,* enterococci, or infection with organisms from the HACEK group (*Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella* species,

www.ketabpezeshki.com 66485457-66963820

Box 167-2 Modified Duke Criteria for the Diagnosis of Infective Endocarditis

Major Criteria

Blood cultures positive for IE
- Typical microorganism for IE from two separate blood cultures
  - Viridians streptococci
  - *Streptococcus bovis,* including nutritional variant strains
  - HACEK group: *Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella* species, and *Kingella kingae*
  - *Staphylococcus aureus*
  - Community-acquired enterococci, in the absence of a primary focus; *or*
- Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from blood samples drawn more than 12 hours apart; *or*
- All of three or a majority of four or more separate blood cultures, with first and last samples drawn at least 1 hour apart
- Single blood culture positive for *Coxiella burnetii* or antiphase I immunoglobulin G antibody titer >1:800

Evidence of endocardial involvement

Echocardiogram positive for IE
- TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE (paravalvular abscess); TTE as first test in other patients
- Definition of positive echocardiogram
  - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; *or*
  - Abscess; *or*
  - New partial dehiscence of prosthetic valve

New valvular regurgitation (increase in or change in preexisting murmur not sufficient)

Minor Criteria*

Predisposition: predisposing heart condition or injection drug use

Fever: 38.0° C (100.4° F)

Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway's lesions

Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor

Microbiologic evidence: positive blood culture but not meeting major criterion (excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organism consistent with IE

IE, infective endocarditis; *TEE,* transesophageal echocardiography; *TTE,* transthoracic echocardiography.

*Echocardiographic minor criteria eliminated.

and *Kingella kingae*). Children with suspected endocarditis should have blood culture specimens drawn and be admitted to the hospital for treatment and echocardiography. The American Heart Association recommends that initial antibiotic therapy be with ceftriaxone, 100 mg/kg IV or IM every 24 hours, or vancomycin, 40 mg/kg IV every 24 hours. Therapy is typically continued at least 4 weeks. Ceftriaxone can be combined with gentamicin, 3 mg/kg IV divided every 8 hours, if a shorter treatment duration (2 weeks) is desired.[77] See Chapter 171 for a more complete discussion.

Ventriculoperitoneal Shunts

Children presenting with fever in the setting of ventriculoperitoneal shunts are at risk for shunt infection. If shunt infection is suspected, neurosurgical consultation should be obtained and a sample of CSF obtained. This is typically accomplished by sterile aspiration of fluid from the shunt reservoir. *S. aureus* and *Staphylococcus epidermidis* are the usual causative organisms. If altered mental status is present, a computed tomography scan should be obtained to assess ventricular size. Children with suspected shunt infection are typically managed as inpatients, and antibiotics should begin as soon as possible.

KEY CONCEPTS

- Fever is the most common complaint among pediatric patients presenting to the ED, although rates of bacterial illness are lower since the advent of universal vaccination for *H. influenzae* type b and *S. pneumoniae*.
- Infants younger than 3 months are at higher risk for bacterial illness with fever because of their immature immune systems and incomplete vaccination status, making aggressive workup of these children important.
- The most common cause of serious bacterial illness in children continues to be UTIs, and the only reliable method to obtain urine in a non–toilet-trained infant is bladder catheterization or suprapubic aspiration.
- RSV is a common viral cause of fever and respiratory distress in infants, although the presence of RSV does not lower the risk of concomitant serious bacterial illness in children younger than 28 days.
- Children presenting with fever and petechiae are at risk for infection with meningococcus; blood should be obtained for CBC and culture, and children should be treated with empirical parenteral antibiotics.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. McCarthy PL, et al: Fever without apparent source on clinical examination, infectious diseases, and lower respiratory infections in children. *Curr Opin Pediatr* 1998; 10:101.
2. Slater M, Krug SE: Evaluation of the infant with fever without source: An evidence based approach. *Emerg Med Clin North Am* 1999; 17:97.
3. Shaw KN, et al: Prevalence of urinary tract infection in febrile young children in the emergency department. *Pediatrics* 1998; 102:e16.
4. Levine DA, et al: Risk of serious bacterial infection in young febrile infants with respiratory syncytial virus infections. *Pediatrics* 2004; 113:1728.
5. Greenes DS, Harper MB: Low risk of bacteremia in febrile children with recognizable viral syndromes. *Pediatr Infect Dis J* 1999; 18:258.
6. McGowan JE Jr, et al: Bacteremia in febrile children seen in a "walk-in" pediatric clinic. *N Engl J Med* 1973; 288:1309.
7. Anderson AB, et al: *Haemophilus influenzae* type b unsuspected bacteremia. *Pediatr Emerg Care* 1987; 3:82.
8. Harper MB, Fleisher GR: Occult bacteremia in the 3-month-old to 3-year-old age group. *Pediatr Ann* 1993; 22:484.
9. Obonyo CO, Lau J: Efficacy of *Haemophilus influenzae* type b vaccination of children: A meta-analysis. *Eur J Clin Microbiol Infect Dis* 2006; 25:90.
10. Whitney CG, et al: Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med* 2003; 348:1737.
11. Kaplan SL, et al: Decrease of invasive pneumococcal infections among 8 children's hospitals in the United States after the introduction of the 7-valent pneumococcal conjugate vaccine. *Pediatrics* 2004; 113:443.
12. American Academy of Pediatrics: Practice parameter: The diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. Committee on Quality Improvement, Subcommittee on Urinary Tract Infection. *Pediatrics* 1999; 103:843.
13. Hoberman A, Walk ER: Urinary tract infections in young febrile infants. *Pediatr Infect Dis J* 1997; 16:11.
14. Bilukha OO, et al: Prevention and control of meningococcal disease: Recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep* 2005; 54:1.
15. Baker RC, et al: Severity of disease correlated with fever reduction in febrile infants. *Pediatrics* 1989; 83:1016.
16. Hanna CM, Greenes D: How much tachycardia in infants can be attributed to fever? *Ann Emerg Med* 2004; 43:699.
17. Pantell RH, et al: Management and outcomes of care of fever in early infancy. *JAMA* 2004; 291:1203.
18. Lee GM, Fleisher GR, Harper MB: Management of febrile children in the age of the conjugate pneumococcal vaccine: A cost-effectiveness analysis. *Pediatrics* 2001; 108:835.
19. Kuppermann N, Fleisher GR, Jaffe DM: Predictors of occult pneumococcal bacteremia in young febrile children. *Ann Emerg Med* 1998; 31:679.
20. Strand CL, Wajsbort RR, Sturmann K: Effect of iodophor vs iodine tincture skin preparation on blood culture contamination rate. *JAMA* 1993; 269:1004.
21. Kaplan RL, et al: Time to detection of positive cultures in 28- to 90-day-old febrile infants. *Pediatrics* 2000; 106:E74.
22. Hoberman A, et al: Enhanced urinalysis as a screening test for urinary tract infection. *Pediatrics* 1993; 91:1196.
23. Nigrovic LE, et al: Clinical prediction rule for identifying children with cerebrospinal fluid pleocytosis at very low risk of bacterial meningitis. *JAMA* 2007; 297:52.
24. Talan DA, Hoffman JR, Yoshikawa TT, Overturf GD: Role of empiric parenteral antibiotics prior to lumbar puncture in suspected bacterial meningitis: State of the art. *Rev Infect Dis* 1988; 10:365.
25. Nigrovic LE, Kuppermann N, Neuman MI: Risk factors for traumatic or unsuccessful lumbar punctures in children. *Ann Emerg Med* 2007; 49:762.
26. Bachur R, Perry H, Harper MB: Occult pneumonias: Empiric chest radiographs in febrile children with leukocytosis. *Ann Emerg Med* 1999; 33:166.
27. Bonner AB, et al: Impact of the rapid diagnosis of influenza on physician decision-making and patient management in the pediatric emergency department. *Pediatrics* 2003; 112:363.
28. Krief WI, et al: Influenza virus infection and the risk of serious bacterial infections in young febrile infants. *Pediatrics* 2009; 124:30.
29. Kanegaye JT, Soliemanzadeh P, Bradley JS: Lumbar puncture in pediatric bacterial meningitis: Defining the time interval for recovery of cerebral spinal fluid pathogen after parenteral antibiotic pretreatment. *Pediatrics* 2001; 108:1169.
30. Kadish HA, et al: Applying outpatient protocols in febrile infants 1-28 days of age: Can the threshold be lowered? *Clin Pediatr* 2000; 39:81.
31. Baker MD, Bell LM: Unpredictability of serious bacterial illness in febrile infants from birth to 1 month of age. *Arch Pediatr Adolesc Med* 1999; 153:508.
32. Bachur R, Caputo GL: Bacteremia and meningitis among infants with urinary tract infections. *Pediatr Emerg Care* 1995; 11:280.
33. Baker MD, et al: Outpatient management without antibiotics of fever in selected infants. *N Engl J Med* 1993; 329:1437.
34. Baskin MN, O'Rourke EJ, Fleisher GR: Outpatient treatment of febrile infants 28 to 89 days of age with intramuscular administration of ceftriaxone. *J Pediatr* 1992; 120:22.
35. Jaskiewicz JA, et al: Febrile infants at low risk for serious bacterial infection: An appraisal of the Rochester criteria and implications for management. Febrile Infant Collaborative Study Group. *Pediatrics* 1994; 94:390.
36. Baraff LJ: Management of fever without source in infants and children. *Ann Emerg Med* 2000; 36:602.
37. Walsh-Kelly C, et al: Clinical predictors of bacterial versus aseptic meningitis in childhood. *Ann Emerg Med* 1992; 21:910.
38. McCarthy PL, et al: Fever without apparent source on clinical examination, infectious diseases, and lower respiratory infections in children. *Curr Opin Pediatr* 1998; 10:101.
39. McGowan JE Jr, et al: Bacteremia in febrile children seen in a "walk-in" pediatric clinic. *N Engl J Med* 1973; 288:1309.
40. Anderson AB, et al: *Haemophilus influenzae* type b unsuspected bacteremia. *Pediatr Emerg Care* 1987; 3:82.
41. Harper MB, Fleisher GR: Occult bacteremia in the 3-month-old to 3-year-old age group. *Pediatr Ann* 1993; 22:484.
42. Teach SJ, Fleisher GR: Duration of fever and its relationship to bacteremia in febrile outpatients three to 36 months old. The Occult Bacteremia Study Group. *Pediatr Emerg Care* 1997; 13:317.
43. Kuppermann N, Fleisher GR, Jaffe DM: Predictors of occult pneumococcal bacteremia in young febrile children. *Ann Emerg Med* 1998; 31:679.
44. Isaacman DJ, et al: Predictors of bacteremia in febrile children 3 to 36 months of age. *Pediatrics* 2000; 106:977.
45. Jaffe DM, et al: Antibiotic administration to treat possible occult bacteremia in febrile children. *N Engl J Med* 1987; 317:1175.
46. Fleisher GR, et al: Intramuscular versus oral antibiotic therapy for the prevention of meningitis and other bacterial sequelae in young, febrile children at risk for occult bacteremia. *J Pediatr* 1994; 124:504.
47. Baraff LJ, Oslund S, Prathe M: Effect of antibiotic therapy and etiologic microorganism on the risk of bacterial meningitis in children with occult bacteremia. *Pediatrics* 1993; 92:140.
48. Arditi M, et al: Three-year multicenter surveillance of pneumococcal meningitis in children: Clinical characteristics, and outcome related to penicillin susceptibility and dexamethasone use. *Pediatrics* 1998; 102:1087.
49. Pikis A, et al: Long-term sequelae of pneumococcal meningitis in children. *Clin Pediatr* 1996; 35:72.
50. Nigrovic LE, Malley R: Evaluation of the febrile child 3 to 36 months old in the era of pneumococcal conjugate vaccine: Focus on occult bacteremia. *Clin Pediatr Emerg Med* 2004; 5:13.
51. Kuppermann N: The evaluation of young febrile children for occult bacteremia: Time to reevaluate our approach. *Arch Pediatr Adolesc Med* 2002; 156:855.
52. Lee GM, Fleisher GR, Harper MB: Management of febrile children in the age of the conjugate pneumococcal vaccine: A cost-effectiveness analysis. *Pediatrics* 2001; 108:835.
53. Kuppermann N, Malley R, Inkelis SH, Fleisher GR: Clinical and hematologic features do not reliably identify children with unsuspected meningococcal disease. *Pediatrics* 1999; 103:E20.
54. Begier EM, et al: A high-morbidity outbreak of methicillin-resistant *Staphylococcus aureus* among players on a college football team, facilitated by cosmetic body shaving and turf burns. *Clin Infect Dis* 2004; 39:1446.
55. Centers for Disease Control and Prevention: Methicillin-resistant *Staphylococcus aureus* infections among competitive sports participants—Colorado, Indiana, Pennsylvania, and Los Angeles County, 2000-2003. *MMWR Morb Mortal Wkly Rep* 2003; 52:793.
56. Lee MC, et al: Management and outcome of children with skin and soft tissue abscesses caused by community-acquired methicillin-resistant *Staphylococcus aureus*. *Pediatr Infect Dis* 2004; 23:123.
57. Kaplan SL, et al: Multicenter surveillance of invasive meningococcal infections in children. *Pediatrics* 2006; 118:e979.
58. Thompson MJ, et al: Clinical recognition of meningococcal disease in children and adolescents. *Lancet* 2006; 367:397.

www.ketabpezeshki.com 66485457-66963820

59. Ramsay ME, et al: Herd immunity from meningococcal serogroup C conjugate vaccination in England. *BMJ* 2003; 326:365.
60. American Academy of Pediatrics Subcommittee on Febrile Seizures. Febrile seizures: Guideline for the neurodiagnostic evaluation of the child with a simple febrile seizure. *Pediatrics* 2011; 127:389.
61. Sharma S, et al: The role of emergent neuroimaging in children with new-onset afebrile seizures. *Pediatrics* 2003; 111:1.
62. Kimia A, et al: Utility of lumbar puncture for first simple febrile seizure among children 6 to 18 months of age. *Pediatrics* 2007; 123:6.
63. Kimia A, et al: Yield of lumbar puncture among children who present with their first complex febrile seizure. *Pediatrics* 2010; 126:62.
64. Baker RC, et al: Fever and petechiae in children. *Pediatrics* 1989; 84:1051.
65. Mandl KD, et al: Incidence of bacteremia in infants and children with fever and petechiae. *J Pediatr* 1997; 131:398.
66. Holman RC, et al: Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. *Pediatrics* 2003; 112:495.
67. Oates-Whitehead RM, et al: Intravenous immunoglobulin for the treatment of Kawasaki disease in children. *Cochrane Database Syst Rev* 2003; 4:CD004000.
68. Reingold AL, et al: Toxic shock syndrome surveillance in the United States, 1980 to 1981. *Ann Intern Med* 1982; 96:875.
69. Centers for Disease Control and Prevention: Update: Toxic-shock syndrome—United States. *MMWR Morb Mortal Wkly Rep* 1983; 32:398.
70. Osterholm MT, et al: Toxic shock syndrome: Relation to catamenial products, personal health and hygiene, and sexual practices. *Ann Intern Med* 1982; 96:954.
71. Auletta JJ, O'Riordan MA, Nieder ML: Infections in children with cancer: A continued need for the comprehensive physical examination. *J Pediatr Hematol Oncol* 1999; 21:501.
72. Wilimas JA, et al: A randomized study of outpatient treatment with ceftriaxone for selected febrile children with sickle cell disease. *N Engl J Med* 1993; 329:472.
73. Falletta JM, et al: Discontinuing penicillin prophylaxis in children with sickle cell anemia: Prophylactic Penicillin Study II. *J Pediatr* 1995; 127:685.
74. Redding-Lallinger R, Knoll C: Sickle cell disease—pathophysiology and treatment. *Curr Probl Pediatr Adolesc Health Care* 2006; 36:346.
75. Vichinsky EP, Neumayr LD, Earles AN, Williams R: Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *N Engl J Med* 2000; 342:1855.
76. Li JS, et al: Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000; 30:633.
77. Baddour LM, et al: Infective endocarditis: Diagnosis, antimicrobial therapy, and management of complications: A statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association—executive summary: Endorsed by the Infectious Diseases Society of America. *Circulation* 2005; 11:3167.

www.ketabpezeshki.com 66485457-66963820

Chapter 168

Pediatric Respiratory Emergencies: Upper Airway Obstruction and Infections

Jeffrey Cukor and Mariann Manno

PERSPECTIVE

Respiratory distress from upper airway obstruction is an unusual but potentially catastrophic emergency in young children. It may be caused by a number of different processes, including an acute infectious process, a congenital anomaly, and a foreign body in the airway or esophagus. A working knowledge of the diseases of the upper airway is of critical importance in pediatric emergency medicine. Classification of airway disease can be based on the anatomic location, the patient's age, and whether it is congenital or acquired. Treatment is based on the underlying pathologic process and the urgency of the symptoms. The starting point for any classification is an appreciation of the unique aspects of pediatric airway anatomy.

DISTINGUISHING PRINCIPLES OF DISEASE

A number of differences between the adult and pediatric airway are important in airway management (Fig. 168-1). An infant's tongue is disproportionately large in relation to the mouth and protrudes back into the posterior of the pharynx. In the setting of hypotonia, posterior displacement of the tongue is the most common cause of functional upper airway obstruction. The infant larynx is more anterior and higher in the neck relative to the cervical spine (at C3-4) compared with an adult larynx (C4-5). The anterior aspect of the vocal cords is tipped inferiorly. The narrowest site of the infant airway is at the cricoid ring rather than the cords as in an adult. A child's epiglottis is relatively larger, longer, and omega shaped. It extends vertically beyond the opening of the cords, thus making a complete view of the airway difficult. The caliber of all airway structures is small; on average, newborn tracheal length is 57 mm and laryngeal diameter is 4 mm. All cartilaginous supporting structures are soft, pliable, and prone to collapse. Finally, a prominent occiput causes passive flexion of the head and neck on the cervical spine. In aggregate, these anatomic features of the pediatric airway predispose infants and young children to functional upper airway obstruction and make airway intervention technically challenging.

The type and size of equipment required for management of the pediatric airway are derived from this unique anatomy. A face mask should be sized so that the top and bottom rims fit on the bridge of the nose (below the eye) and in the cleft of the chin. A straight (Miller) blade is generally used for endotracheal intubation in infants and young children because the tip of the straight blade lifts the epiglottis up and out of the line of vision of the airway. Endotracheal tube size is a function of the patient's size. For children older than 1 year, endotracheal tube size (internal diameter in millimeters) can be estimated by the formula (age in years/4) + 4; for uncuffed tubes, a half size smaller than calculated should be used, except for 3.0-mm tubes. Alternatively, endotracheal tube size can also be estimated by use of a length-based measuring system, such as the Broselow-Luten tape. Recent evidence suggests that cuffed endotracheal tubes may be used safely in children of all ages. Cuffed endotracheal tubes allow the delivery of high pressures during ventilation without the air leak associated with uncuffed tubes and without increased complications, such as subglottic stenosis.[1]

There is a broad spectrum of clinical presentations in children with upper airway disease. It is important to consider the following general concepts:

- Acute infections of the upper airway range from relatively mild distress and self-limited signs and symptoms to the abrupt onset of a rapidly progressive airway obstruction.
- Undiagnosed congenital anomalies of the airway and surrounding structures may be manifested as chronic or progressive stridor or simply difficulty in feeding. An infant with a congenital airway anomaly in whom an acute airway infection develops is at higher risk for decompensation and respiratory failure.
- Upper airway obstruction from a foreign body in the airway or esophagus can cause partial or complete airway obstruction and may require urgent advanced airway management skills.

STRIDOR

Stridor is the classic sound associated with upper airway obstruction.[2-4] It is derived from the Latin *stridulus,* meaning harsh or grating. Stridor is caused by partial airway obstruction and the resultant turbulent airflow through some portion of the airway from the nose to the trachea. It is not a diagnosis in itself but an important sign that must be investigated in the symptomatic patient. Stridor should be described in its timing within the respiratory cycle (inspiratory, expiratory, biphasic) and by its quality (coarse or high pitched) (Table 168-1).

The upper airway can be artificially divided into four regions: the nose and pharynx, the supraglottic structures, the glottis and immediate subglottic area, and the intrathoracic trachea (Fig. 168-2). The characteristics of stridor differ by its cause and its precise origin in the airway.

Stridor from the nose or pharynx, such as from a peritonsillar abscess, tends to have a sonorous, gurgling, and coarse quality. The voice may be altered and have a muffled or "hot potato" quality to it. In contrast, conditions involving the supraglottic and immediate subglottic trachea, as with croup and laryngomalacia, usually have a higher pitched inspiratory stridor sound. The stridor is created by the forced narrowing of the extrathoracic airway

www.ketabpezeshki.com 66485457-66963820

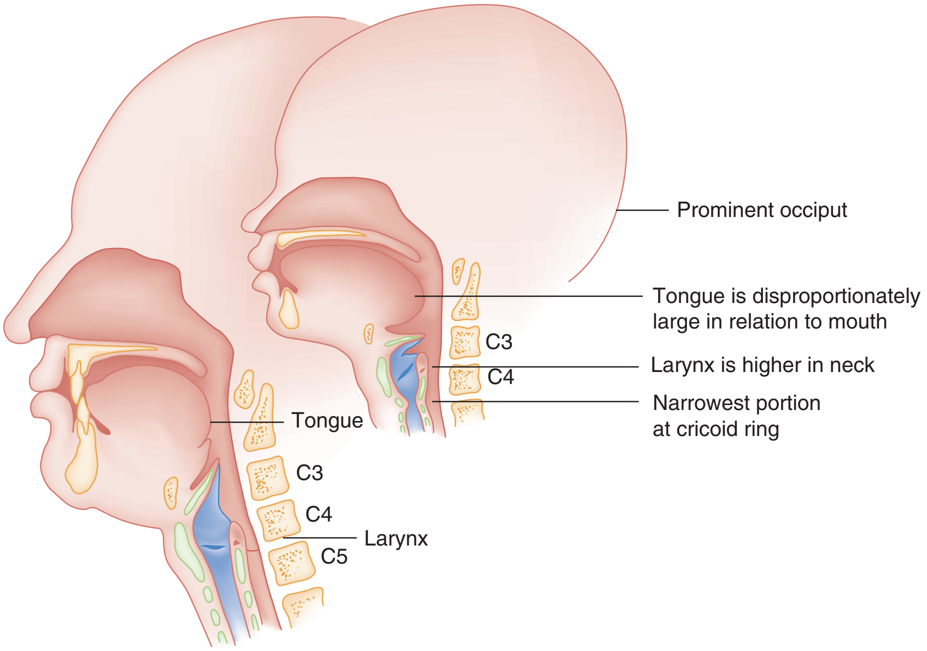


Figure 168-1. Comparison of adult and pediatric airways. (From Finucane BT: Principles of Airway Management. Philadelphia, FA Davis, 1988.)

Table 168-1 Causes of Stridor: Anatomic Location, Sound, and Etiology

FEATURES	SUPRAGLOTTIC	GLOTTIC	SUBGLOTTIC TRACHEA
Sound	Sonorous Gurgling Coarse Expiratory stridor	Biphasic stridor	High-pitched stridor Inspiratory stridor
Structures	Nose Pharynx Epiglottis	Larynx Vocal cords	Subglottic trachea
Congenital	Micrognathia Pierre Robin syndrome Treacher Collins syndrome Macroglossia Down syndrome Storage diseases Choanal atresia Lingual thyroid Thyroglossal cyst	Laryngomalacia Vocal cord paralysis Laryngeal web Laryngocele	Subglottic stenosis Tracheomalacia Tracheal stenosis Vascular ring Hemangioma cyst
Acquired	Adenopathy Tonsillar hypertrophy Foreign body Pharyngeal abscess Epiglottitis	Papillomas Foreign body	Croup Bacterial tracheitis Subglottic stenosis Foreign body

structures as the atmospheric pressure inside the airway becomes slightly lower than outside the airway. In these cases the voice may sound hoarse or weak.

Biphasic stridor is heard with inspiration and expiration and usually suggests a fixed lesion that does not change with respiration. Examples of conditions resulting in biphasic stridor are laryngeal webs and vocal cord paralysis. Stridor from the lower part of the trachea is usually expiratory. Bacterial tracheitis and foreign bodies are examples.

OVERVIEW OF THE EVALUATION AND MANAGEMENT OF A CHILD WITH AN UPPER AIRWAY OBSTRUCTION

Evaluation of a child with signs of airway obstruction begins with careful observation of the child both at rest and during activity (crying, feeding), noting the work of breathing, respiratory rate, alertness, and color. In most cases, observation and a

www.ketabpezeshki.com 66485457-66963820

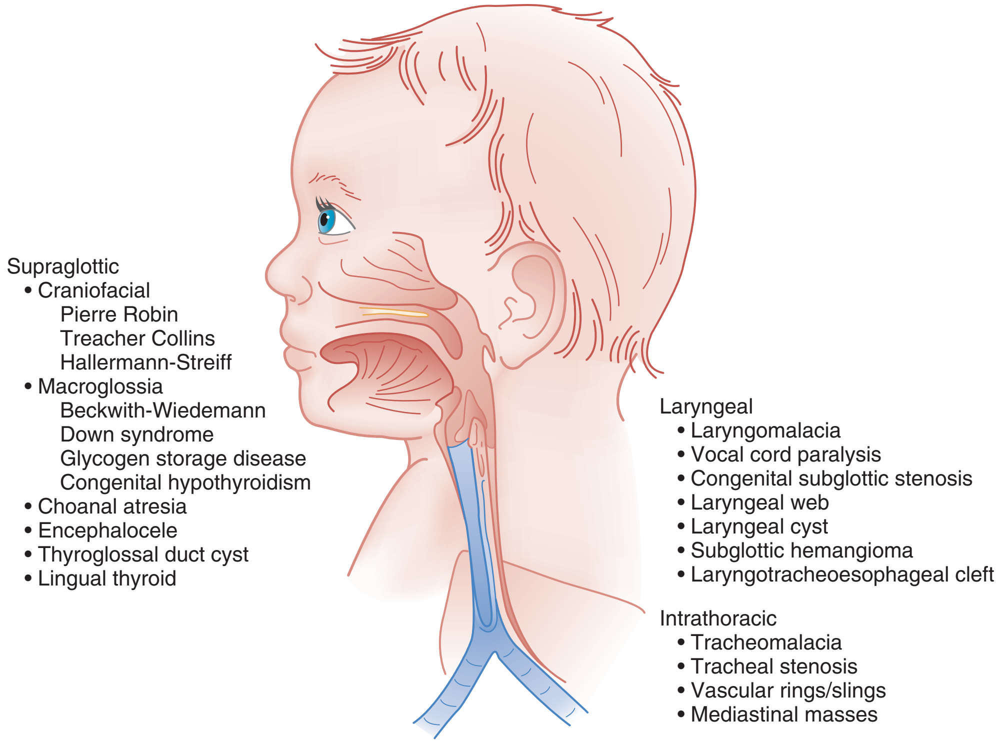


Figure 168-2. Regions and associated diseases of the pediatric upper airway. (From Simon NP, Simon N: Evaluation and management of stridor in the newborn. Clin Pediatr [Phila] 30:211, 1991.)

carefully obtained history will provide clues to the correct diagnosis. Important items to elucidate in the history include the following:

- Onset and duration (acute vs. chronic)
- Associated symptoms (respiratory distress, fever, toxicity, drooling, cyanosis)
- Progression with age (number of bouts and severity of "croup" with increasing age)
- Exacerbating factors (supine vs. prone position, upper respiratory infection [URI], crying)
- Feeding pattern (dysphagia, feeding abnormalities)
- Prior airway procedures (intubation in the neonatal period)
- Choking episode (foreign body aspiration)
- Baseline noises, quality of cry and voice (to help in location of obstructive lesion)

The initial physical examination should assess vital signs (respiratory rate, heart rate, oxygen saturation) and mechanics of breathing (retractions, flaring, grunting) to determine the severity of distress. Respiratory failure is identified by the presence of extreme distress, hypoventilation or hyperventilation, altered mental status, dusky skin color, cyanosis, or hypotonia. The character and timing of stridor, if it is present, as well as the symmetry and quality of breath sounds are also important observations.

Definitive airway management always takes precedence over laboratory and radiographic tests in a patient with an acute airway emergency. In a stable patient with an uncertain diagnosis, an individualized diagnostic evaluation is undertaken.

Radiographs of the soft tissues of the neck may be helpful and should include both lateral and anteroposterior views. These views assess the adenoid and tonsillar size, the contour of the epiglottis, the thickness of the retropharyngeal soft tissue space, the vallecula, the aryepiglottic folds, and the tracheal air column (Fig. 168-3).[5,6] Optimally, the child's head should be positioned in extension and the film taken during inspiration. Views of the chest may be helpful to assess the heart size, the trachea and bronchi, the location of the aortic arch, and the presence of other pulmonary pathologic processes.

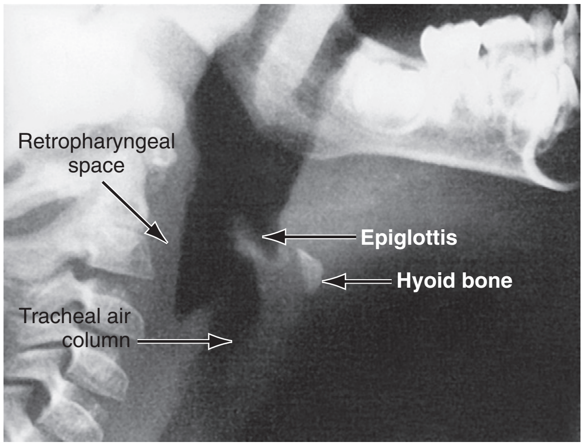


Figure 168-3. Normal appearance of upper airway structures on a lateral neck radiographic study. Note the hyoid bone, epiglottis, retropharyngeal space, and tracheal air column.

Additional studies may be indicated in specific settings. Bedside fiberoptic nasopharyngoscopy can be performed without general anesthesia and allows visualization and assessment of the supraglottic structures and the vocal cords. The nasopharyngoscope may also be used to aid with a fiberoptic-assisted intubation. Esophagography can help define lesions compressing the airway and trachea; computed tomography (CT), magnetic resonance imaging (MRI), and bronchoscopy also may have roles in evaluating the upper airway and should be considered on an individual basis.

www.ketabpezeshki.com 66485457-66963820

SPECIFIC DISORDERS

Supraglottic Airway Diseases

Perspective

The supraglottic portion of the airway includes the nose, pharynx, epiglottis, and surrounding structures. Disease of the nose and pharynx is commonly associated with noisy, congested breathing and respiratory distress. Congenital lesions involving these structures may cause mild symptoms at baseline but dramatic distress when there is a superimposed infectious process. Congenital lesions with which the emergency physician should be familiar include choanal atresia, macroglossia, micrognathia, thyroglossal duct cyst, and lingular thyroid. Important acquired causes of supraglottic disease include nasal foreign body, nasal polyps, hypertrophic tonsils and adenoids, epiglottitis, retropharyngeal abscess, peritonsillar abscess, pharyngitis, mononucleosis, and upper airway foreign body. The most common ones are discussed in the following sections.

Congenital Lesions

Choanal atresia, the most common congenital anomaly of the nose, is caused by persistence of the bucconasal membrane or a bony septum in the posterior naris. Infants are "obligate nose breathers" because they breathe nasally when the mouth is closed at rest and to maintain breathing while feeding. In infants, the posterior aspect of the soft palate extends downward and contacts the tip of the epiglottis. Bilateral choanal atresia is a life-threatening emergency that is identified shortly after birth. Infants with bilateral choanal atresia become acutely distressed and cyanotic at birth and are managed with an oral airway that opens the mouth to allow a passage for breathing. Surgical correction of the obstructing membrane is required. Unilateral choanal atresia may go undetected in the nursery and become apparent only when the normal, patent naris is obstructed by swelling or secretions, most frequently from URI.

Macroglossia, an abnormally large tongue that protrudes posteriorly into the hypopharynx, is associated with a number of conditions, including Down syndrome, glycogen storage disease, and congenital hypothyroidism. The increased secretions and swelling often associated with a URI exacerbate the underlying obstruction, and stridor or labored breath sounds are heard.

With *micrognathia,* an abnormally small mandible posteriorly displaces the normal-sized tongue. This is associated with syndromes such as Pierre Robin and Treacher Collins. Signs of obstruction often worsen when the patient is supine.

Infectious Etiologies

Retropharyngeal Abscess

Perspective. A retropharyngeal abscess is a potentially life-threatening airway emergency resulting from infection of the retropharyngeal soft tissue space. The retropharyngeal space is a potential space between the posterior pharyngeal wall and the prevertebral fascia that extends from the base of the skull to the level of T2. It is rich in lymph tissue that drains the nose, pharynx, sinuses, and ears. An abscess may result from direct trauma from a fall with an object in the mouth like a toothbrush, suppuration of lymph nodes, contiguous spread of infection, or hematogenous seeding.[7] Approximately 50% of pediatric cases occur in children 6 to 12 months of age. Almost all of the pediatric cases occur before 3 years of age, and 96% of all diagnosed pediatric retropharyngeal abscesses are seen before 6 years of age.[8] These infections are commonly polymicrobial, with *Streptococcus* and anaerobes the most commonly isolated organisms.[9] Recent case reports highlight the emerging role of methicillin-resistant *Staphylococcus aureus* in these infections.[10]

Clinical Features. The variable presentation of a retropharyngeal abscess can make it a challenging diagnosis in young children.[11-14] Common signs and symptoms include fever, sore throat, neck stiffness or nuchal rigidity, torticollis, trismus, neck swelling, drooling, stridor, and muffled voice. In a prospective study of 17 patients with retropharyngeal abscess, stridor and airway obstruction were observed in approximately half (56%) of the patients.[15] This common finding of acute airway obstruction is a function of the high position of the larynx in the neck. Such anatomy places the airway proximate to and easily compressed by the bulging retropharyngeal mass. In patients with airway compression, the clinical appearance can resemble epiglottitis. Reluctance to extend the neck and an unwillingness to look side to side is often seen with retropharyngeal abscess and may help differentiate it from other supraglottic infections.[16] With less obvious signs of airway obstruction, patients can exhibit a mixture of symptoms (fever, neck stiffness, generalized toxicity) that may also suggest meningitis or sepsis. Other serious complications of retropharyngeal abscess include aspiration pneumonia, mediastinitis, and empyema.

Diagnostic Strategies. Careful evaluation of airway patency takes precedence in management of a child with a presumed retropharyngeal abscess. Examination of the pharynx may reveal bulging of the posterior pharyngeal wall. A soft tissue lateral view of the neck may be helpful to establish the diagnosis; in the normal patient, the width of the retropharyngeal space should not exceed the diameter of the adjacent vertebral body (Fig. 168-4). In general, soft tissue width should not be larger than 7 mm at C2 or exceed 14 mm at C6. The majority of patients (in some studies 88-100%) will demonstrate retropharyngeal thickening on the lateral neck radiograph.[8,17,18] An air-fluid level is more commonly seen with perforations and anaerobic infections. Redundant soft tissue of the retropharyngeal space complicates interpretation of lateral neck films in young infants with a retropharyngeal abscess. Artifactual widening of a normal retropharyngeal space is commonly seen when the radiograph is taken with the head and neck in flexion or during exhalation (or both). CT may be beneficial in delineating the size and extent of an abscess and determining possible impingement on airway structures. Before the patient is

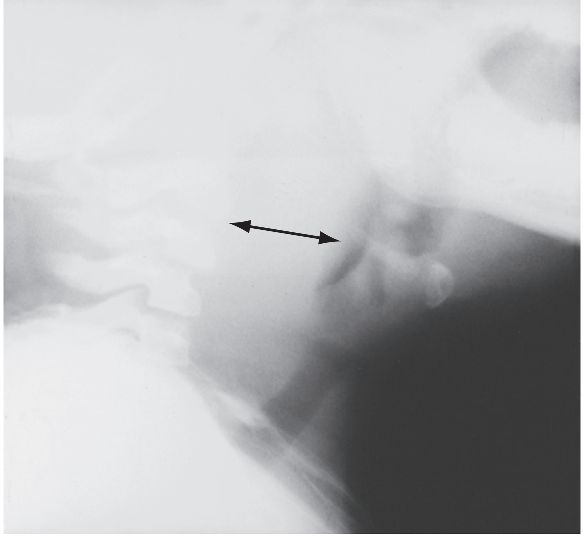


Figure 168-4. Retropharyngeal abscess. Note the widened retropharyngeal soft tissue space.

www.ketabpezeshki.com 66485457-66963820

placed in the CT scanner, the ability to tolerate being supine should be tested, and staff and airway equipment should be immediately available.

Management. The size of the abscess, the degree of airway obstruction, and the overall toxicity of the patient dictate management. The need for intubation or surgical drainage is determined on an individual basis, and these patients generally benefit from involvement of an ear, nose, and throat (ENT) specialist. Intubation can be complicated by distorted anatomy and can lead to abscess rupture.[19] Not all retropharyngeal abscesses require surgical drainage as many will respond to intravenous antibiotics. A study by Craig and Schunk showed a resolution rate with antibiotics of 37%.[20] Clindamycin is a common appropriate first choice for antibiotic therapy.

Peritonsillar Abscess. Peritonsillar abscess more commonly occurs in older children and teenagers. Although it can cause drooling and a muffled, hot potato voice, severe respiratory distress is less common. Peritonsillar abscess is associated with trismus, bulging or asymmetry of the tonsils, and deviation of the uvula away from the abscess side. Throat pain also may radiate to the ear.[7] Treatment involves antibiotics and either incision and drainage or, more commonly, needle aspiration. Posterior pharynx ultrasonography or CT scanning can confirm the diagnosis and help guide treatment. Any drainage effort must take great care to avoid puncture of the proximate carotid artery or aspiration of drained material by the patient.

Mononucleosis. Infectious mononucleosis, caused by the Epstein-Barr virus, can lead to mucosal edema and an exudative pharyngitis. Uncommonly, massive tonsillar enlargement can occur and create upper airway distress. In addition to airway management and general supportive care, some studies have shown benefit of steroids and racemic epinephrine in reducing tonsillar edema.[21,22]

Ludwig's Angina. Ludwig's angina is a rapidly progressive infection and inflammatory process of the sublingual, submandibular, and submaxillary spaces. Elevation of the tongue above the lower teeth and tenderness in the sublingual space are hallmark signs along with trismus and odynophagia. It can create a functional upper airway obstruction or respiratory distress through significant swelling and direct airway compression. CT is useful to confirm the diagnosis and extent of infection; treatment involves antibiotics, airway support, and admission for close monitoring. ENT and anesthesia consultants can help in planning and support if an emergent airway is required.

Epiglottitis

Perspective. Although it is still a feared pediatric emergency, acute epiglottitis has declined markedly in incidence since widespread administration of *Haemophilus influenzae* type b vaccine.[23-25] First licensed in 1985 for children 24 months old, the vaccine became available for immunization of infants 2 months of age in 1990.

Principles of Disease. Epiglottitis is an invasive bacterial disease that causes inflammation and edema of the epiglottis, aryepiglottic folds, arytenoids, and surrounding supraglottic tissues. As these structures become inflamed and distended, they protrude downward and over the glottic opening. Uncommon in the first year of life, epiglottitis was historically caused by *H. influenzae* type b in children 3 to 7 years of age and occurred year-round. This traditional profile has changed.[26-28] In a survey of patients with epiglottitis since 1990, the average patient is older (80 vs. 35 months) with varying microbiology. *H. influenzae* type b is seen in a small minority of patients, and organisms such as group A beta-hemolytic streptococcus, *S. aureus*, and *Streptococcus pneumoniae* are more common.[29] Noninfectious causes are rare and include thermal injury from swallowing of hot liquids.[30,31]

Clinical Features. Epiglottitis is classically acute in onset. It is marked by high fever, intense sore throat, toxicity, and rapid progression. In one study, 85% of children with epiglottitis were symptomatic for less than 24 hours before seeking medical care.[32] Children with epiglottitis appear anxious and maintain a "sniffing" or "tripod" position with the jaw jutting forward and the neck extended to maximize airway patency. As symptoms worsen, cough and phonation are usually absent. Drooling is prominent because of an inability to swallow.[33] Singer and McCabe showed that in children younger than 24 months, toxicity, altered mental status, dyspnea, stridor, retractions, and fever are common initial symptoms.[34] Losek and co-workers reported a series of 236 patients in which 7 patients (3%) died. In addition, the correct diagnosis of epiglottitis was not made in 11 of 58 children younger than 2 years (19%) and in 49 of 178 children between 2 and 18 years old (28%). Incorrect diagnoses in patients who died of epiglottitis included croup, summer virus, and pharyngitis. Croup was the most commonly assigned misdiagnosis and more often made in the setting of very young children or those in whom drooling and difficulty in swallowing were not prominent.[32] The older patient is less likely to show dramatic signs of upper airway obstruction compared with the younger child because the diameter of the airway is larger and thus takes a greater degree of swelling to produce symptoms. Epiglottitis caused by bacteria other than *H. influenzae* tends to have a slower onset and is less likely to cause airway compromise. A majority of patients with *H. influenzae* epiglottitis were also found to have bacteremia (50-75%).[35]

Diagnostic Strategies. Direct examination or manipulation of the pharynx should be avoided in cases in which epiglottitis is strongly suspected. A lateral neck radiograph can be helpful to confirm the diagnosis and should be evaluated for an enlarged epiglottis ("thumbprint sign"; Fig. 168-5), thickened aryepiglottic folds, lack of air in the vallecula, and dilated hypopharynx. Careful observation of a child with suspected epiglottitis is essential, and clinicians skilled in airway management should accompany the patient at all times. Laboratory tests, intravenous fluids and antibiotics, and blood and epiglottis cultures are all important considerations once the airway has been secured.

Management. The clinical features of classic epiglottitis are usually sufficiently characteristic that diagnostic tests are not

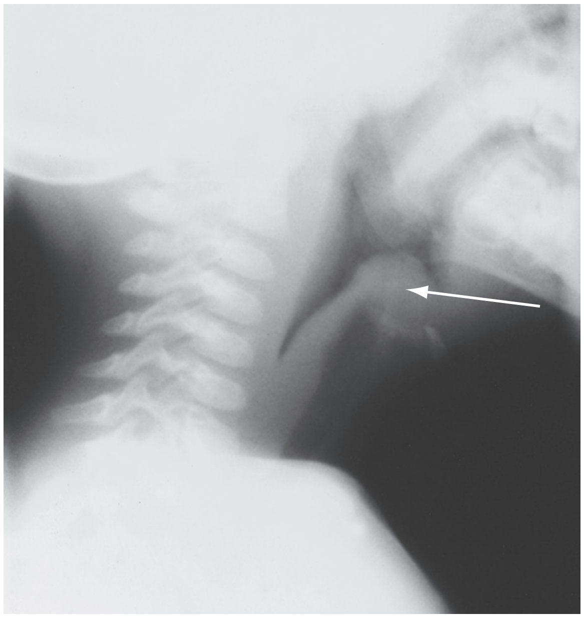


Figure 168-5. Epiglottitis. Note the "thumbprint sign" of the epiglottis and thickened aryepiglottic folds.

www.ketabpezeshki.com 66485457-66963820

necessary and should be avoided so as not to agitate the patient. The importance of securing the airway takes precedence over diagnostic evaluation. A "stable" patient who is maintaining a patent airway and adequate oxygenation should not be moved or repositioned for examination, laboratory tests, or radiography. Such patients should be carefully transported to a setting where definitive airway management can be achieved in a controlled fashion, generally the operating room. If diagnostic studies are needed, constant and close observation is vital.

Careful decision-making is essential when a child with epiglottitis or suspected epiglottitis requires transport. A survey of pediatric intensive care and emergency physicians reported that half recommended intubation before inter-hospital transport in all cases. The remainder individualized the recommendation for intubation before transport in part on the basis of the referring physician's perceived ability to intubate the child.[36]

Unstable patients with respiratory failure require assisted ventilation. Bag-valve-mask ventilation should be attempted first and, if it is successful, continued until intubation can be performed by the emergency physician or anesthesiologist. If neither bag-valve-mask ventilation nor intubation is successful, more aggressive techniques, such as needle cricothyroidotomy or tracheostomy, may be indicated. Regardless of the approach to securing the airway, it is prudent for the emergency physician to rapidly consult other experts in airway management, such as an anesthesiologist (fiberoptic intubation), ENT specialist, or general surgeon (surgical approaches), so that a plan of approach can be made and morbidity reduced. Once they are intubated, patients generally remain so for 3 to 5 days of antibiotic therapy to allow adequate decrease in epiglottic size and surrounding tissue edema. A second- or third-generation cephalosporin is appropriate.

Other Noninfectious Supraglottic Disease

Trauma and Burns. Thermal injury from facial burns and inhaled smoke or steam and trauma to the face and neck can create physical findings similar to infectious epiglottitis. Rapidly progressive stridor, drooling, an unwillingness to lie flat, and a swollen, inflamed epiglottis may occur. Some studies show a mortality around 20% in children with burn injuries when airway burns are also present. Toddlers are particularly prone to inhalation of hot liquids as they more independently eat and drink without initially being attentive to temperature. Aspiration of hot liquids is the most common cause of airway burns in infants and young children.[37] The initial physical examination of the oropharynx may be relatively normal. Elective securing of the airway is suggested when laryngeal edema is suspected as progression of symptoms and edema may occur during the hours immediately after the injury.[16] Bronchodilators may help with bronchospasm; steroids are controversial and not routinely recommended for use.

Allergic Reaction. Acute allergic reactions may cause supraglottic edema with respiratory distress and stridor. Food is the most common precipitant in infants and children, with higher mortality noted in peanut allergies and in children with atopy or asthma. Anaphylaxis with respiratory compromise should immediately be treated with intramuscular (more rapid onset) injection of epinephrine 1:1000 solution at 0.01 mg/kg up to 0.3 mg. Intravenous epinephrine 1:10,000 can be considered for patients in shock with severe allergic reactions. Rapid administration of antihistamines, oxygen, nebulized bronchodilators, and steroids should follow. Early intubation may be needed. Repeated doses of epinephrine may be needed, and the use of racemic epinephrine may also be considered. All discharged patients should have injectable epinephrine (EpiPen 0.3 mg epinephrine); a referral to an allergist and a MedicAlert bracelet are recommended. An EpiPen Jr contains a dose of 0.15 mg of epinephrine and should be prescribed for children weighing less than 30 kg.

Diseases of the Larynx

The larynx and vocal cords compose an important region in the airway that is often associated with airway disease causing obstruction. Many of these obstructing conditions are congenital lesions, including laryngomalacia, laryngeal web, and vocal cord paralysis. Acquired lesions include laryngeal papillomas.

Congenital Lesions

Laryngomalacia, the most common cause of chronic stridor in infants,[38,39] is a result of incomplete development of the supporting cartilage of the larynx. With inspiration, the long, floppy epiglottis, arytenoids, and aryepiglottic folds are drawn into the larynx and create a partial obstruction (Fig. 168-6). Baseline inspiratory stridor begins several weeks after birth and worsens with

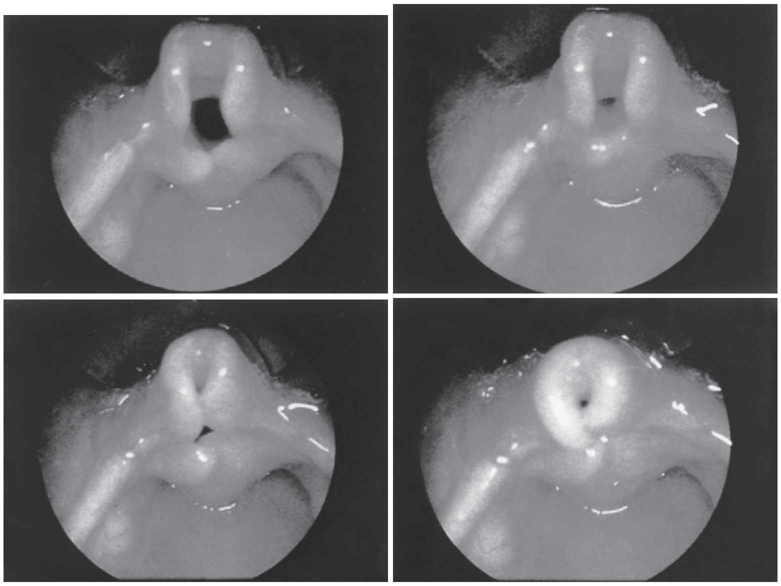


Figure 168-6. Laryngomalacia. Note the progressive obstruction with inspiration as the epiglottis and surrounding structures collapse into the glottic opening.

www.ketabpezeshki.com 66485457-66963820

Figure 168-7. Large laryngeal web.

supine positioning and increased respiratory effort (crying, URI). Laryngomalacia is rarely associated with significant respiratory distress, feeding difficulties, or failure to thrive. Most patients experience complete resolution of symptoms by 2 years of age. However, Richter and Thompson described late-onset laryngomalacia in a series of 17 older children who presented with feeding disorders (mean age, 3.3 years), sleep disorders (mean age, 6.3 years), and exercise-induced stridor (mean age, 15 years).[40] Fiberoptic bronchoscopy is used to confirm the diagnosis and to identify the existence of coexisting or synchronous anomalies (such as subglottic stenosis and tracheomalacia).

Vocal cord paralysis is the second most common cause of chronic stridor in infants. Bilateral vocal cord paralysis results in severe respiratory distress and stridor and is often associated with serious central nervous system abnormalities, such as Arnold-Chiari malformation. Unilateral vocal cord paralysis is most commonly left sided and related to traction on the left recurrent laryngeal nerve at birth or compression from mediastinal structures. Infants with unilateral vocal cord paralysis have a hoarse, weak cry. Stridor often worsens with distress and improves with positioning of the affected side down.

A *laryngeal web* results from failure of complete canalization of the airway.[41] Most webs lie between the cords and appear as a partial anterior fusion (Fig. 168-7). The spectrum of symptoms reflects the size of the web. Small webs may cause a hoarse, weak cry and mild stridor. Larger, more complete webs are associated with aphonia and severe respiratory distress.

Laryngeal Papillomas

Laryngeal papillomas arise from the laryngeal epithelium and may result from perinatal or postnatal exposure to human papillomavirus. When papillomas are acquired in the prenatal period, hoarseness, abnormal cry, and inspiratory stridor commonly occur by 3 to 4 years of age. Symptoms can progress to severe respiratory distress as the lesions enlarge and obstruct the larynx. Ultrasonography has been described as a useful adjunct in the diagnosis and management of patients with airway papillomas.[42]

Subglottic Tracheal Diseases

The subglottic trachea is the origin of the high-pitched inspiratory sound commonly associated with upper airway obstruction. The subglottic space is the narrowest part of the airway in children younger than 8 years and is completely surrounded by the cricoid ring. Such anatomy predisposes this part of the airway to obstruction. Subglottic narrowing or stenosis can result from a congenital anomaly, inflammation from infection, and trauma associated with prolonged intubation.

Congenital Lesions

Congenital laryngotracheal ("subglottic") stenosis is a result of a congenital defect in canalization of the subglottic trachea. Deformity of the cricoid ring is usually seen. Infants with severe stenosis have stridor at birth. Milder lesions may be asymptomatic until additional obstruction from infection or inflammation occurs. Subglottic stenosis is also an acquired condition that occurs after prolonged intubation or blunt trauma to the neck.

A *subglottic hemangioma* is a less common cause of stridor and subglottic airway obstruction in infants. The infant is usually asymptomatic at birth, but stridor (which may be biphasic) and cough develop within the first few weeks to months of life. Symptoms generally peak at 6 months as a result of rapid growth of the infant and the hemangioma during the first months of life. Respiratory symptoms worsen with crying and agitation. Cutaneous hemangiomas are seen in approximately half of cases. Hemangiomas of the airway may be seen on plain film as an asymmetrical lesion along the tracheal air column.

Viral Croup

Principles of Disease. Croup (laryngotracheobronchitis) is the most common cause of upper airway distress and obstruction in childhood. It occurs most commonly in late fall, early winter, and spring, with a peak incidence at 2 years (range, 6 months to 6 years) of age. Rarely, viral croup is seen in older, healthy children. Parainfluenza virus type 1 accounts for about half of cases; parainfluenza virus types 2 and 3, respiratory syncytial virus, influenza A and B viruses, and rhinovirus are responsible for the remainder.[43] Croup is caused by inflammation, exudate, and edema of the loosely adherent mucosal and submucosal tissues of the subglottic space. The inflamed mucosa expands into the airway lumen because the cricoid cartilage forms a complete cartilaginous (nonexpanding) ring in this part of the trachea.

The actual incidence of croup is unknown. Most children will have an uncomplicated course, and many cases are managed without medical intervention. Only a small percentage of those who receive urgent care require hospitalization. Croup is recurrent in a small number of patients. A subset of children with croup have involvement of the lower airway and exhibit bronchoconstriction, lower airway edema, and atelectasis.

Clinical Features. Croup is most often diagnosed clinically. Children with typical croup have a constellation of symptoms, including a barky cough, hoarse voice, and high-pitched, inspiratory stridor. These findings usually follow a several-day prodrome of mild fever and URI symptoms.

Scoring systems have been developed for assessment of croup and include an evaluation of worsening stridor, retractions, cyanosis, heart rate, and respiratory rate. Although a formal croup score is often not assigned in many clinical settings, the determination of mild, moderate, or severe croup should be based on careful evaluation of these five signs as well as mental status and air movement. Mild croup is characterized by an intermittent barky cough, stridor with agitation but not at rest, mild tachypnea, and tachycardia. A child with mild croup is minimally distressed and well hydrated and has normal mental status. Moderate croup is characterized by audible stridor at rest, worsening stridor with agitation, barky cough, and increased work of breathing (retractions, tachypnea, tachycardia). A patient with moderate croup may be fussy but is alert, interactive, and comforted by parents. Hypoxia is atypical in mild or moderate croup. When hypoxia is seen, it may signify concomitant lower respiratory disease, another disease process, or severe croup.

www.ketabpezeshki.com 66485457-66963820

Laboratory tests are nondiagnostic. Radiographic studies of the neck are useful when the diagnosis is in doubt, but they do not change management. The classic finding in croup is a tapered narrowing of the normal shouldered appearance of the subglottic trachea such that it has the appearance of a pencil or steeple.

Management. Glucocorticoids are the mainstay of treatment of croup, resulting in reduced symptoms, reduced need for aerosolized epinephrine, fewer readmissions to the emergency department (ED), and shorter hospital stays.[44,45] Evidence for the use of routine steroids in croup was Geelhoed and Macdonald's comparison of the experience at Princess Margaret Hospital for Children before and after steroids became mandatory in the treatment of croup in patients in the intensive care unit (ICU).[46] Before 1989, less than 5% of ICU patients received steroids. At that time, an average of 11% were intubated yearly, and the total ICU days were 129 (yearly average). Beginning in 1989, every child admitted to the ICU received 0.6 mg/kg dexamethasone intramuscularly. The intubation rate declined to 1% (yearly average), and total ICU days dropped to 21 (yearly average).

The role of oral, parenteral, and inhaled steroids in the treatment of croup has been well documented.[44] Geelhoed and Macdonald demonstrated that oral dexamethasone in doses as small as 0.15 mg/kg is as effective as higher doses in decreasing the duration of symptoms and hospitalization.[47] Steroids in patients with mild croup have also been shown to improve symptoms and to reduce the need for return to medical care.[48] More recently, a Cochrane review of 38 randomized controlled trials (4299 patients) found treatment of croup with glucocorticoids to be associated with the following outcomes: shorter length of stay in the ED, fewer return visits, and decreased use of epinephrine.[49]

Budesonide is an inhaled steroid with potent topical anti-inflammatory properties. A single dose (2 mg) of nebulized budesonide was shown to shorten ED length of stay, to decrease the rate of hospitalization, and to cause a more rapid improvement in symptoms in children with mild to moderate croup evaluated in the ED.[45] Inhaled budesonide (2 mg per dose) was shown to be as effective as oral dexamethasone (0.6 mg/kg) in decreasing the duration of hospital stay, improving clinical symptoms, and decreasing the ongoing requirement for aerosolized epinephrine.

Aerosolized epinephrine, either racemic epinephrine (containing D and L isomers) or L-epinephrine, acts on alpha-adrenergic receptors in the subglottic mucosa.[50] Through vasoconstriction, epinephrine reverses edema and relieves acute symptoms in a subset of patients. It is a temporizing measure with a quick onset of action (within 10 minutes) and duration of effect between 1 and 2 hours. Racemic epinephrine has traditionally been preferred to L-epinephrine because the racemic mixture has been associated with fewer cardiovascular side effects. However, the L form of epinephrine is the active isomer and has the same degree of safety and efficacy as racemic epinephrine[51]; either form may be used. The "rebound" phenomenon of epinephrine is defined as recurrence or worsening of the patient's pretreatment symptoms when aerosolized epinephrine wears off. This rebound is rarely clinically significant if steroids are given early in management.[52]

It has been demonstrated that many patients with moderate croup who are treated with steroids and epinephrine can be safely discharged from the ED after treatment.[53] A retrospective study evaluating the policy of discharging selected patients after treatment with racemic epinephrine yielded favorable results. Of 50 patients discharged after the administration of epinephrine, none was subsequently hospitalized and only one required retreatment within 48 hours as an outpatient. Importantly, 92% were discharged on a regimen of steroids. The investigators recommend that children with moderate croup who have received aerosolized epinephrine can be safely discharged (1) after 2 hours of observation after administration of epinephrine, (2) if they are free of stridor and retractions, and (3) if they have access to follow-up care. They also recommend administration of steroids in these patients.[54] The decision to discharge after administration of aerosolized epinephrine should also be based on the patient's symptoms, such as dehydration, preexisting airway disease, and other congenital anomalies.

Box 168-1 Croup: Indications for Admission

- Severe respiratory distress or failure
- Unusual symptoms (hypoxia, hyperpyrexia)
- Dehydration
- Persistence of stridor at rest after aerosolized epinephrine and steroids
- Persistence of tachycardia, tachypnea
- Complex past medical history (prematurity, pulmonary, cardiac disease)

Cool mist has been advocated as a useful therapy for croup symptoms but has not been demonstrated to improve outcomes. It is hypothesized to act by moistening thickened secretions, thereby making them easier to mobilize out of the airway. A meta-analysis by Moore and Little of three randomized controlled trials (135 patients) reported that administration of humidified air to children with mild to moderate croup did not improve croup scores. They concluded that there is insufficient evidence to support the routine use of this intervention.[55]

A small percentage of patients with croup require admission. The decision to admit a child with moderate croup is based on a number of factors: severity of symptoms at initial evaluation, persistence of respiratory distress, stridor at rest, oxygenation, response to treatment, hydration, history suggesting airway disease or recurrent croup, young age (<6 months), high fever, and parental reliability (Box 168-1).

Severe croup is rare and associated with signs of impending airway obstruction and respiratory failure: fatigue, hypoxia, hypercapnia, abnormal mental status, extreme respiratory distress, and stridor. Since the advent of steroid administration, only an estimated 1 to 2% of patients with croup require intubation. An endotracheal tube at least a half size smaller than expected for the child's size is often necessary. If the endotracheal tube that can be passed is too small to allow adequate ventilation, tracheostomy may be required.

Spasmodic Croup

Spasmodic croup is a somewhat indistinct clinical entity with many features that overlap those of viral croup. It is characterized by the sudden onset of severe stridor and a barky cough without a viral prodrome. It may be recurrent and has been associated with allergy and gastroesophageal reflux. Previous parainfluenza infection has been postulated as a predisposing condition for a hypersensitivity reaction on later exposure to the virus. There is little in the literature to delineate the difference between spasmodic croup and viral croup.

Diseases of the Trachea

Obstruction of the trachea distal to the subglottic space can be a result of both congenital and acquired lesions.

Congenital Lesions

Tracheomalacia results from abnormally soft, undeveloped supporting cartilage of the tracheal rings. Primary or congenital tracheomalacia is seen in otherwise healthy term newborns as well as in infants with conditions such as Down syndrome and DiGeorge

www.ketabpezeshki.com 66485457-66963820

syndrome. Healthy infants with isolated disease have a good prognosis because symptoms improve as the cartilage strengthens with growth. Secondary disease is associated with extrinsic compression of the trachea (vascular rings, tumor, nodes, cysts).[56] This diagnosis should be suspected in patients with a history of stridor that increases during the first few weeks of life and worsens with agitation, supine positioning, and infection. Plain radiographs are usually nondiagnostic, but dynamic studies, such as fluoroscopy, may be helpful.

Tracheal stenosis is a congenital anomaly that results from complete tracheal rings. Infants have persistent stridor and respiratory distress. Because the tracheal diameter is "fixed," symptoms worsen with agitation and age.

A *vascular ring* is an anomaly of the aortic arch and related vessels in which a ring of vessels encircles the trachea, esophagus, or both. Examples of "vascular rings" include a double aortic arch, right-sided aortic arch with a persistent left ligament, aberrant right subclavian artery, and pulmonary sling (anomalous origin of the left pulmonary artery, which can cause tracheal compression). These conditions are rare and are often manifested in infancy with a variety of symptoms related to breathing and feeding. However, the nonspecific nature of the infant's symptoms and the low prevalence of these lesions often result in an initial incorrect diagnosis of croup or URI. In a retrospective review of 38 patients, the diagnosis was made in the first year of life in 87%. Stridor (50%), wheezing (53%), and dyspnea (45%) were the most common initial symptoms, followed by cough (34%), recurrent URI (32%), and dysphagia (32%). Sixty-three percent of these patients had associated cardiovascular anomalies.[57]

This diagnosis should be considered in any infant with persistent, unexplained respiratory and feeding problems. A chest radiograph revealing an abnormal (right-sided) aortic arch may suggest the diagnosis in the ED. Definitive diagnosis requires further investigation. Traditionally, barium esophagography has been considered to be the single most important diagnostic procedure in patients with complete vascular rings (Fig. 168-8). The need for additional studies, such as CT, MRI, angiography, or bronchoscopy, should be individualized. Importantly, the common association of congenital cardiac anomalies is a consideration in the workup of these patients.

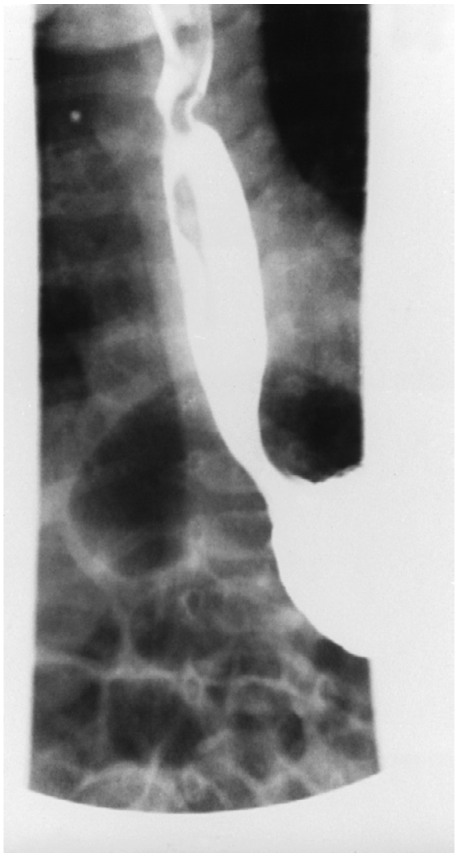


Figure 168-8. Barium esophagogram. Note the indentation of the esophagus caused by an encircling vascular ring.

Bacterial Tracheitis

Principles of Disease. Bacterial tracheitis (membranous croup, bacterial croup, pseudomembranous croup) is a relatively rare but serious cause of stridor and airway obstruction in children. The epidemiology of upper airway infections has changed since widespread immunization for *H. influenzae* and use of steroids for croup. This has increased the relative frequency of bacterial tracheitis as a cause of respiratory failure from upper airway infection. A recent series of 35 pediatric ICU admissions for life-threatening airway infections reported that 17 were for bacterial tracheitis, 16 for viral croup, and 2 for epiglottitis.[58] Bacterial tracheitis generally affects younger children, with a peak incidence at approximately 3 to 4 years of age. However, it is also reported in patients well beyond this age group, thus making it a diagnosis seen in adolescence and young adulthood as well.

The pathogenesis of bacterial tracheitis is severe inflammation of the tracheal epithelium and the production of thick mucopurulent secretions. The lining of the trachea forms a loosely adherent membrane that sloughs into the lumen. Traditionally, *S. aureus* has been the organism primarily responsible for bacterial tracheitis. More recently, the microbiology of bacterial tracheitis has been better defined. In a review of bacterial tracheitis in 14 children, Brook reported that aerobic bacteria (43%), anaerobic bacteria (20%), and mixed anaerobic and aerobic flora (36%) were cultured. The predominant organisms recovered in tracheal secretions were *S. aureus* (5), *H. influenzae* type b (4), *Moraxella catarrhalis* (2), *Peptostreptococcus* species (4), *Prevotella* and *Porphyromonas* (4), and *Fusobacterium* species (2).[59] Others have reported *S. pneumoniae*, alpha-hemolytic and group A streptococci, and *Candida albicans*.

Clinical Features. The clinical features of bacterial tracheitis overlap the symptoms of both croup and epiglottitis (Table 168-2). Patients experience a viral prodrome of fever, barky cough, and stridor. These symptoms typically intensify. The child appears toxic, and signs of airway obstruction and respiratory failure may develop acutely. Differentiation of bacterial tracheitis from severe croup or epiglottitis on clinical grounds alone can be difficult. In one report of 16 patients with bacterial tracheitis, an initial diagnosis of croup was made in 7 and acute epiglottitis in 2.[60] Features that suggest bacterial tracheitis include a viral prodrome followed by acute decompensation, symptoms atypical for croup (high fever, cyanosis, and severe distress), poor response to usual treatment of croup (steroids and aerosolized epinephrine), and both inspiratory and expiratory stridor.

Diagnostic Strategies. Evaluation of a toxic-appearing child with bacterial tracheitis should be conducted expeditiously. Laboratory tests are nondiagnostic. The white blood cell count is normal or slightly elevated. Blood cultures are usually negative. Lateral and anteroposterior views of the neck and chest may be helpful. Findings on plain radiographs include subglottic narrowing, a ragged edge of the usually smooth tracheal air column, and a hazy density within the tracheal lumen. The epiglottis and supraglottic structures appear normal. In addition, the chest radiograph may reveal coexisting pneumonia. Bronchoscopy is both diagnostic and therapeutic and should be performed on an emergency basis. This procedure should allow visualization of the supraglottic structures and larynx, exclusion of other disease, suctioning

www.ketabpezeshki.com 66485457-66963820

Table 168-2 Comparison of Croup, Epiglottitis, and Bacterial Tracheitis

	CROUP	EPIGLOTTITIS	BACTERIAL TRACHEITIS
Peak age	6 months to 3 years	5-7 years, but can be seen throughout childhood	3-5 years, but seen throughout childhood
Pathologic features	Subglottic inflammation, edema	Inflammation and edema of the epiglottis, aryepiglottic folds	Bacterial superinfection with inflammation of the tracheal mucosa, copious mucopurulent secretions obstructing the trachea
Organisms	Parainfluenza virus, RSV, adenovirus	Group A beta-hemolytic streptococcus, *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae*	*Staphylococcus aureus* or mixed flora
Clinical features	Onset follows URI prodrome consisting of croupy cough, hoarse voice, low-grade fever, inspiratory stridor	Rapid progression of high fever, toxicity, drooling, stridor	Several-day prodrome of crouplike illness progressing to toxicity, inspiratory and expiratory stridor, marked distress
Laboratory and radiographic findings	Steeple sign on PA view of the neck, or normal	Thumbprint sign on lateral aspect of the neck, thickened aryepiglottic folds, loss of air in the vallecula	Normal upper airway structures, shaggy tracheal air column
Management	Steroids uncommon, aerosolized epinephrine	Intubation, antibiotics	Intubation common, antibiotics rare, intubation

PA, posteroanterior; *RSV,* respiratory syncytial virus; *URI,* upper respiratory infection.

of tracheal secretions and debris, and establishment of an artificial airway.

Management. In relatively few cases, severe distress requires immediate intubation and suctioning in the ED. Airway management in the setting of the operating room is preferred. These patients require hospital admission, intensive care, supplemental oxygen, fluid resuscitation, and broad-spectrum antibiotics.

Endotracheal intubation is required in the majority of patients.[58,61] The duration of intubation in patients with bacterial tracheitis is reported to be 4 or 5 days, as opposed to 48 hours for croup and 54 hours for epiglottitis.[60] Complications that have been reported in association with bacterial tracheitis include toxic shock syndrome, septic shock, renal failure, postintubation pulmonary edema, acute respiratory distress syndrome, and need for reintubation.[61]

Aeroesophageal Foreign Bodies

Airway Foreign Body

Perspective. Asphyxia from airway obstruction by an airway or esophageal foreign body is a common cause of death in children. Characteristics of patients admitted with an airway or esophageal foreign body obstructing the airway include male gender (59%), young age (mean of 3.5 years), food (42%) and nonfood (58%) objects, and hospital mortality of 3.4%.[62] Round foods (e.g., grapes, raisins, peanuts, and hot dogs) are especially common. Conformable objects are the most difficult to manage and remove, and balloons, including those made from examination gloves found in physicians' offices, are the objects most likely to result in death.

In general, objects that pass through the subglottic space will lodge in a bronchus, usually the right mainstem bronchus, or in a more terminal part of the airway. Large objects that lodge in the upper airway and trachea tend to cause obvious and dramatic signs of upper airway obstruction: dyspnea, drooling, stridor, and cyanosis. They also carry the worst prognosis.

Clinical Features. An upper airway foreign body can cause partial or complete obstruction. A patient who is adequately oxygenated and is moving air should be initially allowed to maintain a preferred position, to continue coughing to clear the obstruction, and to breathe spontaneously.

Clinical signs of complete obstruction include poor air exchange, ineffective cough, severe distress, and cyanosis. The response to complete obstruction will be determined by the setting and available equipment. Outside a setting in which laryngoscopy and airway equipment is available, relief of a complete obstruction should follow the American Heart Association age-specific guidelines for obstruction by a foreign body.[63,64]

Diagnostic Strategies. In a child with an aspirated foreign body in the upper airway, there is often no time nor is it prudent to obtain diagnostic imaging. In a stable patient, a portable lateral neck radiograph and a chest radiograph may be obtained as long as the patient is allowed to maintain a position of comfort.

Management. Basic life support maneuvers for removal of a foreign body in children vary by age of the child. Choking infants younger than 1 year should receive a series of five back blows delivered between the shoulder blades, followed by five chest thrusts. Chest thrusts should be performed in a manner similar to chest compressions; the thumb encircling technique is preferred in infants. The infant's head should be held below the trunk. Abdominal thrusts should not be performed in infants because of the possibility of injury to abdominal organs. Blind finger sweeps are not performed in infants or children because this maneuver may push the object further into the airway.

In children older than 1 year, the Heimlich maneuver is used in children who are conscious and chest compressions in children who are unconscious. When performing the Heimlich maneuver, the rescuer places the fist of one hand in the other hand and against the abdomen of the victim. Five thrusts are delivered between the waist and rib cage. The rescuer's hands should not be placed on the xiphoid. This maneuver is performed in the standing position in a conscious victim. An unconscious child should be placed supine with the rescuer kneeling astride the victim. In the hospital setting, the airway should be open with a jaw thrust and the patient assessed for respirations. If there is no chest rise, assisted ventilation with a bag-mask device (manual resuscitator) is indicated. If there is still no chest rise, laryngoscopy should be performed to visualize and to remove the foreign body with pediatric Magill forceps. If the foreign body cannot be seen in the pharynx or larynx, it may be located in the esophagus, where it could be pushing on the soft cartilage of the trachea and causing the obstruction. In this case, basic life support maneuvers may dislodge the foreign body into the mouth, where it can be removed.

www.ketabpezeshki.com 66485457-66963820

If it appears within the subglottic space or trachea and cannot be removed, basic life support maneuvers may dislodge it into the oropharynx, or an attempt to push it into a mainstem bronchus with an endotracheal tube may allow ventilation of the other lung but may result in irreversible airway obstruction. Recruiting of additional expertise in the form of an ENT specialist, anesthesiologist, or general surgeon may be valuable.

Needle cricothyrotomy is a technique that can be used to access the airway in an obstructed patient who cannot be intubated or bag-mask ventilated. A large intravenous catheter (14-18 gauge) is passed through the midline of the inferior edge of the cricothyroid membrane. When air is aspirated, the plastic catheter is advanced and connected to the adapter of a 3-0 endotracheal tube and then connected to a manual resuscitator. Needle cricothyrotomy kits are also commercially available. Jet ventilation devices or the use of wall oxygen flow may allow greater ventilation than is possible with a self-inflating manual resuscitator.[62,65] This is generally considered a temporizing measure that allows oxygenation until another airway can be established.

KEY CONCEPTS

Retropharyngeal Abscess

- A potentially life-threatening emergency in young children with signs of upper airway obstruction or meningismus, a retropharyngeal abscess is often related to oral trauma.
- Retropharyngeal abscess is most frequently caused by *Staphylococcus aureus,* group A streptococci, and anaerobes.

Epiglottitis

- In the post–*H. influenzae* type b vaccine era, the typical profile of epiglottitis has changed to include older patients. Group A streptococcus causes the majority of infections; *H. influenzae* type b is the infectious agent in a minority of cases.
- The clinical features of epiglottitis are usually sufficiently characteristic that diagnostic tests are not necessary for the diagnosis.

Croup

- Viral croup is the most common infection of the upper airway in young children and is often mild.
- The mainstays of management of moderate to severe croup are vaporized epinephrine and glucocorticoids. These patients can be discharged from the ED after a post-treatment observation period of several hours if they remain free of stridor and distress and have access to follow-up care.

Bacterial Tracheitis

- The clinical features of bacterial tracheitis represent a progression from a viral URI to acute toxicity and marked respiratory distress. *S. aureus* is the most common cause of this infection.
- Bronchoscopy is both diagnostic and therapeutic and should be performed on an emergency basis.

Airway Foreign Body

- Children with an airway foreign body are managed with basic followed by advanced life support procedures for removal of the foreign body.
- Emergency cricothyroidotomy is reserved for obstructed patients who cannot be intubated or ventilated.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Newth CJ, Rachman B, Patel N, Hammer J: The use of cuffed versus uncuffed endotracheal tubes in pediatric intensive care. *J Pediatr* 2004; 144:333-337.
2. Leung AK, Cho H: Diagnosis of stridor in children. *Am Fam Physician* 1999; 60:2289-2296.
3. Simon NP: Evaluation and management of stridor in the newborn. *Clin Pediatr (Phila)* 1991; 30:211-216.
4. Tunkel DE, Zalzal GH: Stridor in infants and children: Ambulatory evaluation and operative diagnosis. *Clin Pediatr (Phila)* 1992; 31:48-55.
5. Walner DL, Ouanounou S, Donnelly LF, Cotton RT: Utility of radiographs in the evaluation of pediatric upper airway obstruction. *Ann Otol Rhinol Laryngol* 1999; 108:378-383.
6. Goodman TR, McHugh K: The role of radiology in the evaluation of stridor. *Arch Dis Child* 1999; 81:456-459.
7. Luqman Z, Khan MA, Nazir Z: Penetrating pharyngeal injuries in children: Trivial trauma leading to devastating complications. *Pediatr Surg Int* 2005; 21:432-435.
8. Coulthard M, Isaacs D: Retropharyngeal abscess. *Arch Dis Child* 1991; 66:1227-1230.
9. Abdel-Haq NM, Harahsheh A, Asmar BL: Retropharyngeal abscess in children: The emerging role of group A beta hemolytic streptococcus. *South Med J* 2006; 99:927-931.
10. Fleisch AF, Nolan S, Gerber J, Coffin SE: Methicillin-resistant *Staphylococcus aureus* as a cause of extensive retropharyngeal abscess in two infants. *Pediatr Infect Dis J* 2007; 26:1161-1163.
11. Coulthard M, Isaacs D: Neonatal retropharyngeal abscess. *Pediatr Infect Dis J* 1991; 10:547-549.
12. Gaglani MJ, Edwards MS: Clinical indicators of childhood retropharyngeal abscess. *Am J Emerg Med* 1995; 13:333-336.
13. Goldenberg D, Golz A, Joachims HZ: Retropharyngeal abscess: A clinical review. *J Laryngol Otol* 1997; 111:546-550.
14. Harries PG: Retropharyngeal abscess and acute torticollis. *J Laryngol Otol* 1997; 111:1183-1185.
15. Morrison JE Jr, Pashley NR: Retropharyngeal abscesses in children: A 10-year review. *Pediatr Emerg Care* 1988; 4:9-11.
16. D'Agostino J: Pediatric airway nightmares. *Emerg Med Clin North Am* 2010; 28:119-126.
17. Yeoh LH, Singh SD, Rogers JH: Retropharyngeal abscesses in a children's hospital. *J Laryngol Otol* 1985; 99:555-566.
18. Broughton RA: Nonsurgical management of deep neck infections in children. *Pediatr Infect Dis J* 1992; 11:14-18.
19. Shah S, Sharieff GQ: Pediatric respiratory infections. *Emerg Med Clin North Am* 2007; 25:961-979, vi.
20. Craig FW, Schunk JE: Retropharyngeal abscess in children: Clinical presentation, utility of imaging, and current management. *Pediatrics* 2003; 111:1394-1398.
21. Tynell E, et al: Acyclovir and prednisolone treatment of acute infectious mononucleosis: A multicenter, double-blind, placebo-controlled study. *J Infect Dis* 1996; 174:324-331.
22. Brandfonbrener A, Epstein A, Wu S, Phair J: Corticosteroid therapy in Epstein-Barr virus infection. Effect on lymphocyte class, subset, and response to early antigen. *Arch Intern Med* 1986; 146:337-339.
23. Adams WG, et al: Decline of childhood *Haemophilus influenzae* type b (Hib) disease in the Hib vaccine era. *JAMA* 1993; 269:221-226.
24. Broadhurst LE, Erickson RL, Kelley PW: Decreases in invasive *Haemophilus influenzae* diseases in US Army children, 1984 through 1991. *JAMA* 1993; 269:227-231.
25. Murphy TV, et al: Declining incidence of *Haemophilus influenzae* type b disease since introduction of vaccination. *JAMA* 1993; 269:246-248.
26. Balsam D, Sorrano D, Barax C: *Candida* epiglottitis presenting as stridor in a child with HIV infection. *Pediatr Radiol* 1992; 22:235-236.
27. Bogger-Goren S: Acute epiglottitis caused by herpes simplex virus. *Pediatr Infect Dis J* 1987; 6:1133-1134.
28. Narasimhan N, van Stralen DW, Perkin RM: Acute supraglottitis caused by varicella. *Pediatr Infect Dis J* 1993; 12:619-620.
29. Gorelick MH, Baker MD: Epiglottitis in children, 1979 through 1992. Effects of *Haemophilus influenzae* type b immunization. *Arch Pediatr Adolesc Med* 1994; 148:47-50.
30. Harjacek M, Kornberg AE, Yates EW, Montgomery P: Thermal epiglottitis after swallowing hot tea. *Pediatr Emerg Care* 1992; 8:342-344.
31. Kulick RM, Selbst SM, Baker MD, Woodward GA: Thermal epiglottitis after swallowing hot beverages. *Pediatrics* 1988; 81:441-444.
32. Losek JD, Dewitz-Zink BA, Melzer-Lange M, Havens PL: Epiglottitis: Comparison of signs and symptoms in children less than 2 years old and older. *Ann Emerg Med* 1990; 19:55-58.
33. Mauro RD, Poole SR, Lockhart CH: Differentiation of epiglottitis from laryngotracheitis in the child with stridor. *Am J Dis Child* 1988; 142:679-682.
34. Singer JI, McCabe JB: Epiglottitis at the extremes of age. *Am J Emerg Med* 1988; 6:228-231.
35. Wynder SG, Lampe RM, Shoemaker ME: Uvulitis and *Hemophilus influenzae* b bacteremia. *Pediatr Emerg Care* 1986; 2:23-25.
36. Waisman Y, et al: Management of children with epiglottitis during transport: Analysis of a survey. *Pediatr Emerg Care* 1993; 9:191-194.
37. Rosen D, Avishai-Eliner S, Borenstein A, Leviav A, Tabachnik E: Life-threatening laryngeal burns in toddlers following hot liquid aspiration. *Acta Paediatr* 2000; 89:1018-1020.
38. Lis G, Szczerbinski T, Cichocka-Jarosz E: Congenital stridor. *Pediatr Pulmonol* 1995; 20:220-224.
39. Nussbaum E, Maggi JC: Laryngomalacia in children. *Chest* 1990; 98:942-944.
40. Richter GT, Thompson DM: The surgical management of laryngomalacia. *Otolaryngol Clin North Am* 2008; 41:837-864, vii.
41. Cohen SR: Congenital glottic webs in children. A retrospective review of 51 patients. *Ann Otol Rhinol Laryngol Suppl* 1985; 121:2-16.
42. Bryson PC, Leight WD, Zdanski CJ, Drake AF, Rose AS: High-resolution ultrasound in the evaluation of pediatric recurrent respiratory papillomatosis. *Arch Otolaryngol Head Neck Surg* 2009; 135:250-253.
43. Marx A, Torok TJ, Holman RC, Clarke MJ, Anderson LJ: Pediatric hospitalizations for croup (laryngotracheobronchitis): Biennial increases associated with human parainfluenza virus 1 epidemics. *J Infect Dis* 1997; 176:1423-1427.
44. Geelhoed GC: Sixteen years of croup in a Western Australian teaching hospital: Effects of routine steroid treatment. *Ann Emerg Med* 1996; 28:621-626.
45. Klassen TP, Feldman ME, Watters LK, Sutcliffe T, Rowe PC: Nebulized budesonide for children with mild-to-moderate croup. *N Engl J Med* 1994; 331:285-289.
46. Geelhoed GC, Macdonald WB: Oral and inhaled steroids in croup: A randomized, placebo-controlled trial. *Pediatr Pulmonol* 1995; 20:355-361.
47. Geelhoed GC, Macdonald WB: Oral dexamethasone in the treatment of croup: 0.15 mg/kg versus 0.3 mg/kg versus 0.6 mg/kg. *Pediatr Pulmonol* 1995; 20:362-368.
48. Custer JR: A randomized trial of a single dose of oral dexamethasone for mild croup. *J Pediatr* 2005; 146:434-435.
49. Russell KF, Liang Y, O'Gorman K, Johnson DW, Klassen TP: Glucocorticoids for croup. *Cochrane Database Syst Rev* 2011; 1:CD001955.
50. Corneli HM, Bolte RG: Outpatient use of racemic epinephrine in croup. *Am Fam Physician* 1992; 46:683-684.
51. Waisman Y, et al: Prospective randomized double-blind study comparing L-epinephrine and racemic epinephrine aerosols in the treatment of laryngotracheitis (croup). *Pediatrics* 1992; 89:302-306.
52. Prendergast M, Jones JS, Hartman D: Racemic epinephrine in the treatment of laryngotracheitis: Can we identify children for outpatient therapy? *Am J Emerg Med* 1994; 12:613-616.
53. Kelley PB, Simon JE: Racemic epinephrine use in croup and disposition. *Am J Emerg Med* 1992; 10:181-183.
54. Ledwith CA, Shea LM, Mauro RD: Safety and efficacy of nebulized racemic epinephrine in conjunction with oral dexamethasone and mist in the outpatient treatment of croup. *Ann Emerg Med* 1995; 25:331-337.
55. Moore M, Little P: Humidified air inhalation for treating croup: A systematic review and meta-analysis. *Fam Pract* 2007; 24:295-301.
56. Doshi J, Krawiec ME: Clinical manifestations of airway malacia in young children. *J Allergy Clin Immunol* 2007; 120:1276-1278.
57. Bakker DA, Berger RM, Witsenburg M, Bogers AJ: Vascular rings: A rare cause of common respiratory symptoms. *Acta Paediatr* 1999; 88:947-952.
58. Hopkins A, Lahiri T, Salerno R, Heath B: Changing epidemiology of life-threatening upper airway infections: The reemergence of bacterial tracheitis. *Pediatrics* 2006; 118:1418-1421.
59. Brook I: Aerobic and anaerobic microbiology of bacterial tracheitis in children. *Pediatr Emerg Care* 1997; 13:16-18.
60. Damm M, Eckel HE, Jungehulsing M, Roth B: Management of acute inflammatory childhood stridor. *Otolaryngol Head Neck Surg* 1999; 121:633-638.

www.ketabpezeshki.com 66485457-66963820

61. Tebruegge M, et al: Bacterial tracheitis: A multi-centre perspective. *Scand J Infect Dis* 2009; 41:548-557.
62. Shah RK, Patel A, Lander L, Choi SS: Management of foreign bodies obstructing the airway in children. *Arch Otolaryngol Head Neck Surg* 2010; 136:373-379.
63. Berg MD, et al: Part 13: Pediatric basic life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122:S862-S875.
64. Kleinman ME, et al: Part 14: Pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122:S876-S908.
65. Marr JK, Yamamoto LG: Gas flow rates through transtracheal ventilation catheters. *Am J Emerg Med* 2004; 22:264-266.

www.ketabpezeshki.com 66485457-66963820

Chapter 169

Pediatric Respiratory Emergencies: Lower Airway Obstruction

Richard J. Scarfone and Jeffrey A. Seiden

ASTHMA

Perspective

Introduction and Epidemiology

Asthma, the most prevalent chronic disease of childhood, affects almost 7 million children in the United States.[1] In the past 25 years, childhood asthma prevalence rates have more than doubled.[1] The public health burden posed by this disease, as assessed by emergency department (ED) visits, hospitalizations, and deaths, remains at a historically high level. About 3% of all ED visits among children are for asthma, which accounts for 750,000 such visits annually.[1] Similarly, about 3% of all hospitalizations for children are due to asthma, totaling about 200,000 per year.[1] In addition, there are astonishing racial disparities among children with this condition. Compared with white children, black children have a 60% higher prevalence rate, a 260% higher ED visit rate, a 250% higher hospitalization rate, and a 500% higher death rate due to asthma.[1]

Thus asthma is one of the few chronic diseases of childhood for which there have been increases in prevalence, morbidity, and mortality in recent decades. These trends are occurring despite unprecedented investments in terms of money, preclinical and clinical research, and national focus. The reasons for these trends are no doubt multifactorial and are beyond the scope of this discussion. This portion of the chapter focuses on the recognition, evaluation, and clinical management of children in the ED with acute asthma.

Distinguishing Principles of Disease

Anatomy and Physiology

Asthma, a lower airway disease marked by bronchoconstriction, mucosal edema, and pulmonary secretions, may lead to respiratory failure if it is not treated in a timely or effective manner. Important anatomic and physiologic differences exist between children and adults that may hasten the development of respiratory failure, mandating that clinicians quickly recognize and take appropriate measures to reverse respiratory distress.

An upper respiratory infection (URI) associated with copious rhinorrhea, a common trigger of an asthma exacerbation, may significantly increase airway resistance. Further, a small decrease in the internal diameter of the upper airway causes a greater increase in resistance for the young child compared with the adult. In fact, just 1 mm of edema can decrease the cross-sectional area of the infant's airway by 75%.

Regarding the thorax, the young child has a compliant chest wall and horizontally located ribs. These factors limit use of the thorax to increase tidal volume; instead, ventilation is dependent on diaphragmatic movement. However, abdominal distention as might occur with crying or swallowing of air will impede diaphragmatic breathing. With the inability to significantly increase tidal volume, minute ventilation becomes rate dependent, quickly leading to fatigue.

An infant younger than 12 months has an oxygen consumption index that is double that of an adult because of a higher rate of metabolism. Increased airway resistance and chest wall compliance necessitate more rapid breathing and increased energy expenditure. Increased work of breathing may account for as much as 15% of total oxygen consumption, at a time when oxygenation is poor. As a result, the child will have hypoxemia rapidly in response to respiratory disease. The child with significant respiratory distress and inadequate oxygenation may become bradycardic, leading to cardiopulmonary arrest within minutes if appropriate interventions are not undertaken.

Clinical Features

Clinical Evaluation

All acutely wheezing children arriving for ED care should be attached to a cardiorespiratory monitor and have oxygen saturation determined by pulse oximetry. If it is needed, supplemental oxygen should be provided. After this, the clinician may begin the clinical assessment.

History

In evaluating the child with acute wheezing, the treating physician should obtain a concise history, perform a brief and focused physical examination, determine the initial degree of illness, and initiate appropriate therapy. After therapy has begun, a more comprehensive history and physical examination can be conducted. The initial history should include questions about the child's age, duration and severity of symptoms, possible choking episode (foreign body aspiration), and recent medication use. The parents should be able to relate how the severity of this attack compares with that of previous exacerbations. A history of difficulty in sleeping, eating, or speaking as a result of this attack suggests a moderate to severe exacerbation. The names, doses, and frequency of administration of asthma medications recently received should be noted. A child who has been receiving aggressive therapy with short-acting $beta_2$-agonists (SABAs) just before ED arrival may not

www.ketabpezeshki.com 66485457-66963820

respond favorably to that same therapy in the ED. Any comorbidities should be identified early in the clinical course.

A more comprehensive history should include questions about asthma triggers, such as URIs, cigarette smoke, allergies, or exercise. Inquiries about fever and hydration status should be part of a complete review of systems. A past medical history of frequent asthma exacerbations, ED visits for asthma, or hospitalizations to either the general ward or the intensive care unit would raise the concern for poorly controlled asthma. The impact that asthma has on the child's life may be gauged by the monthly frequency of daytime or nighttime symptoms, such as cough, wheezing, shortness of breath, or chest tightness, as well as missed days of school or restricted activity. Persistent asthma has been defined as having at least 3 days per week of symptoms or use of SABA or awakening at night with asthma symptoms several nights per month.[2] Conversely, some will consider any child treated for an asthma exacerbation in the ED to have persistent asthma. A child who meets criteria for persistent asthma should be receiving daily anti-inflammatory therapy, and those older than 5 years should be monitoring symptoms with a peak flow meter.[2] If the child is wheezing for the first time, inquiries about other possible causes of wheezing (see Differential Considerations) should be made. Family and social histories should focus on asthma, cystic fibrosis, or atopic disease and the adequacy of support systems at home.

Physical Examination

In the initial focused physical examination of the wheezing child, vital signs should be obtained and the level of consciousness assessed. A child who is anxious, restless, or lethargic may be hypoxemic. No single asthma score has been universally adopted to assess degree of illness or treatment responses.[3,4] Most asthma scores include key clinical factors, such as respiratory rate, degree of wheezing, inspiratory to expiratory ratio, use of accessory muscles, and oxygen saturation in room air.[4] Such scores can assist in the assessment of the pretreatment degree of illness at ED triage and in tracking of the child's response to therapy.

For a child with severe disease, wheezing may be audible without a stethoscope, or no wheezing may be detected if aeration is extremely poor. Asymmetrical wheezing suggests pneumonia, pneumothorax, or the presence of a foreign body. Palpation of the chest and neck may reveal subcutaneous air associated with a pneumomediastinum or pneumothorax. After this initial assessment, the remainder of the physical examination may be performed. The most anxiety-provoking aspects of the examination, such as otoscopy, should be delayed until after treatment is well under way.

Diagnostic Strategies

Pulse Oximetry and Arterial Blood Gas Analysis

Adjunctive studies, such as arterial oxygen saturation measured by pulse oximetry, may assist in determining the initial degree of illness.[5] Pulse oximetry is noninvasive and inexpensive, and it provides objective data about the degree of illness of a wheezing child. The oxygen saturation of any child with respiratory distress should be determined soon after ED arrival, and supplemental oxygen should be provided if the oxygen saturation is 92% or less.

With the widespread use of pulse oximetry, physicians rarely need to obtain an arterial blood gas (ABG) analysis, especially if the sole purpose is to determine the partial pressure of oxygen. The acquisition of an ABG analysis should be reserved for the child with severe disease to measure the extent of respiratory acidosis and hypercapnia. The timing of this test is important. For a severely ill child requiring admission to the intensive care unit, it may be helpful to obtain this test after ED therapy has been initiated when a clinical plateau has been reached. ABG results can then be used as a baseline that may be compared with subsequent results during the hospitalization. An apparently normal partial pressure of carbon dioxide ($Paco_2$) or pH may actually reflect severe disease. For example, a "normal" $Paco_2$ of 40 mm Hg in a child with extreme tachypnea and retractions suggests impaired ventilation and impending respiratory failure.

Peak Expiratory Flow Rate

Measurement of the peak expiratory flow rate (PEFR) is a means of obtaining an objective assessment of exacerbation severity, but it has limited utility in the evaluation of acutely ill children. Young children, in particular, may be unable to properly comply with this testing, and in one study just two thirds of children older than 5 years were able to complete PEFR testing during an asthma exacerbation.[3] Ideally, the PEFR should be determined with the child standing and the best of three attempts recorded. Therefore, moderately to severely ill or younger children may not be able to cooperate with this assessment.

Chest Radiographs

URIs marked by low-grade fever and coughing are common triggers of asthma exacerbations. These signs overlap with those found among children with pneumonia, making it difficult to determine the necessity of obtaining a chest radiograph in the evaluation of an acutely wheezing child. No set of predictors has been found that can accurately identify children likely to have abnormalities on chest radiography.[6] Hyperinflation, interstitial markings, and atelectasis are common radiographic findings that may be seen in a wheezing child, but these should not result in initiation of antibiotic therapy or other changes in management. More serious conditions associated with asthma, such as pneumonia, pneumomediastinum, and pneumothoraces, are much less common. Rarely is an unsuspected diagnosis made on the basis of a chest radiograph in an acutely wheezing child, even if the child has never wheezed before.[7]

It should not be a routine practice to obtain chest radiographs for all wheezing children, even those who are wheezing for the first time or those who are being hospitalized.[7] Chest radiographs should be considered for those with focal chest findings, fever, extreme distress, subcutaneous emphysema, or a history of choking. Reassessment after treatment to evaluate for the resolution of focal findings may further decrease the need to obtain a chest radiograph. This selective approach will be more cost-effective and lessen unnecessary radiation exposure and overuse of antibiotics. On the other hand, clinicians may have a lower threshold to obtain chest radiographs for infants with first-time wheezing because of a slightly greater likelihood of uncovering an anatomic abnormality.

Differential Considerations

Although most children with wheezing have asthma, other conditions should be considered. A differential diagnosis for childhood asthma is listed in Table 169-1. Of these conditions, bronchiolitis, laryngotracheobronchitis (croup), pneumonia, and gastroesophageal reflux are those that clinicians will encounter most often. Bronchiolitis is the one disease that is most commonly confused with asthma. Although the viruses associated with bronchiolitis infect children of all ages, clinical bronchiolitis marked by wheezing is seen almost exclusively in those younger than 12 months. Patients with bronchiolitis typically present between November and March. There is much clinical overlap between asthma and bronchiolitis, and the two cannot be distinguished by physical

www.ketabpezeshki.com 66485457-66963820

Table 169-1 Differential Diagnosis of Asthma

CONDITION	DISTINGUISHING CHARACTERISTICS
Infections	
Bronchiolitis	Infant, preceding upper respiratory infection, seasonal, no history of atopy, no family history of asthma
Laryngotracheobronchitis (croup)	Inspiratory stridor, barky cough, fever, response to humidified air
Pneumonia	Focal wheezing, rhonchi, rales, grunting, fever
Tuberculosis	Diffuse adenopathy, weight loss, prolonged fever
Bronchiolitis obliterans	Prolonged cough or chest pain, inhalational exposure to toxin
Anatomic or Congenital	
Gastroesophageal reflux	Frequent emesis, weight loss, aspiration
Cystic fibrosis	Diarrhea, weight loss, chronic cough, salty sweat
Congestive heart failure	Rales, murmur, gallop, hepatosplenomegaly, cardiomegaly or pulmonary vascular congestion on chest radiograph
Tracheoesophageal fistula	Choking, coughing, cyanosis with feeds
Mediastinal mass	Chest pain, mediastinal density on chest radiograph
Vascular ring	Stridor, cyanosis, apnea, high-pitched brassy cough, dysphagia
Acquired	
Foreign body aspiration	History of choking, toddler, asymmetrical pulmonary examination, unilateral hyperinflation on chest radiograph
Anaphylaxis	Abrupt onset, urticarial rash, angioedema, history of allergies

examination findings alone. A complete discussion of bronchiolitis is included later in this chapter.

Croup may have a viral or allergic etiology and affects children from infancy through early school age. The hallmark of the disease is inflammation of the upper airway, resulting in a harsh, barky cough and inspiratory stridor. Symptoms are often worse at night. Asthma will not be manifested with stridor alone, but a subset of children with croup may present with both stridor and wheezing and may be misdiagnosed with asthma.

Children with pneumonia may sometimes present with a component of wheezing, although respiratory rales and rhonchi are the usual auscultative findings. Infants and young children may also have high fever, cough, grunting, nasal flaring, or retractions, whereas more classic asymmetrical pulmonary findings are more easily detected in older children.

In addition to asthma, gastroesophageal reflux can account for recurrent wheezing in infants. In these children, poor lower esophageal sphincter function results in regurgitation and aspiration of gastric contents, leading to reflex bronchospasm. Young infants with recurrent wheezing, frequent "spitting up" of feeds, or failure to thrive should be referred for a diagnostic workup.

Management

For purposes of patient management, it is best to stratify children by degree of illness on the basis of the initial clinical assessment (Fig. 169-1). This will help ensure the timely initiation of an appropriately aggressive approach for sicker children while minimizing adverse effects from unnecessary therapy among those with milder exacerbations. Of course, during the ED stay, the illness severity may change, making frequent examinations to assess response to therapy essential.

Mild Exacerbation

A mild exacerbation is characterized by alertness, slight tachypnea, expiratory wheezing only, mildly prolonged expiratory phase, minimal accessory muscle use, and oxygen saturation of greater than 95%. Children who are able to provide a PEFR should have a value greater than 70% of personal best. Patients with a mild exacerbation, especially those who were not receiving any asthma therapy before the ED visit, will usually require SABA therapy only. The Expert Panel of the National Heart, Lung, and Blood Institute (NHLBI) recommends that patients receive therapy every 20 minutes in the first hour of care.[2] Children with mild exacerbations often improve promptly with just one or two SABA treatments. Many of these patients are managed without systemic corticosteroids. However, systemic corticosteroids may be given to those who are already undergoing a course of treatment with them before ED arrival or to those who do not respond promptly to SABA therapy (see later section on moderate exacerbation).

Because of its rapid onset of action, relatively long duration of action, and good safety profile, racemic albuterol has become the SABA of choice for treatment of children with acute asthma. Options for mode of delivery include small-volume nebulizers (NEBs) and the metered-dose inhaler with a spacer (MDI-S), and studies have assessed the use of levalbuterol in this setting.

Nebulizers versus Metered-Dose Inhalers with Spacers. There is considerable debate about the optimal method for delivery of SABAs to children with acute asthma. About three fourths of pediatric emergency medicine physicians report using NEBs to administer SABAs, regardless of illness severity.[8] NEBs provide a passive means of receiving aerosolized medication. Precise coordination between respiration and aerosol delivery is not needed, and medications such as anticholinergics as well as humidified oxygen may be delivered concurrently with the SABA. However, delivery is inefficient, with only about 10% of the drug in the reservoir delivered to the small airways.[9,10] In addition, administration takes about 10 minutes, increasing respiratory therapy time and costs, and an external power source is needed, limiting portability.

On the other hand, spacers used with MDIs provide a reservoir of medication that is available to be inhaled. Therefore, precise coordination between actuation and inhalation is not needed, and there is no need for breath-holding. Drug deposition in the oropharynx and systemic absorption are reduced with the use of a spacer.[11] The decreased administration time associated with MDI-S use may result in reduced costs.[12-14] A recent cost analysis determined that the use of MDIs with spacers in place of NEBs to treat children with mild to moderate asthma exacerbations in the ED could yield significant cost savings.[15] The portability of the MDI-S allows older children to use it during the school day. Face mask–equipped spacers are available for children too young to use the spacer's mouthpiece, although mouthpieces are preferable for older children to decrease nasal filtering of drug, which may reduce lung deposition. After each actuation, children should take five to eight breaths to completely empty the spacer.

These NEB disadvantages along with the development and widespread use of spacers have led investigators to assess the role of MDI-S for delivery of SABAs in the ED. Numerous clinical trials and meta-analyses have consistently demonstrated that delivery by MDI-S is at least as effective as delivery by NEBs.[11,16-23] Among children 1 to 4 years old, MDI-S use was associated with a greater

www.ketabpezeshki.com 66485457-66963820

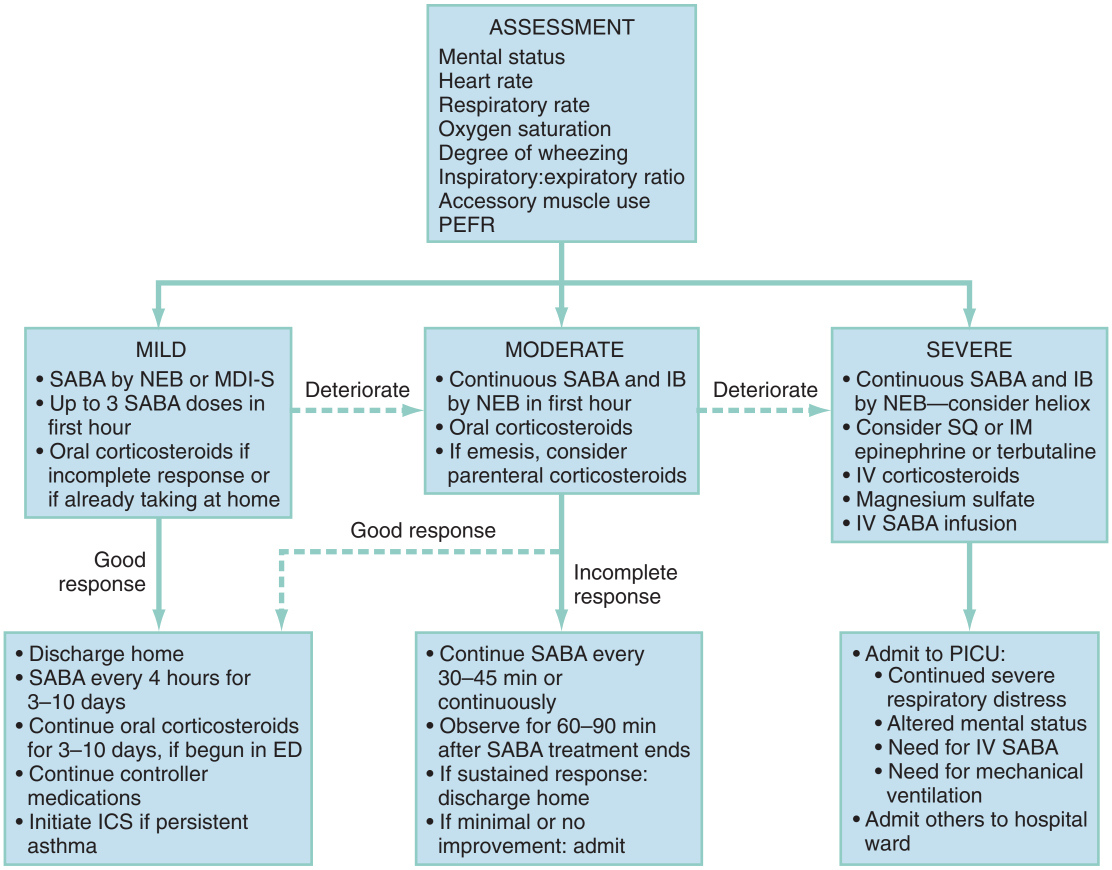


Figure 169-1. Emergency department management of acute asthma. *ED,* emergency department; *IB,* ipratropium bromide; *ICS,* inhaled corticosteroids; *MDI-S,* metered dose inhaler with spacer; *NEB,* nebulizer; *PEFR,* peak expiratory flow rate; *PICU,* pediatric intensive care unit; *SABA,* short-acting beta$_2$-agonist.

reduction in wheezing and a lower hospitalization rate.[14] One systematic review evaluated trials in which a total of 2066 children with acute asthma were randomized to receive SABAs by one of these two methods.[17] Those children treated with MDI-S had shorter ED length of stay and a reduced hospitalization rate that was not statistically significant. The American College of Chest Physicians and American College of Asthma, Allergy, and Immunology concluded that both the NEB and MDI-S are appropriate for the delivery of SABA in the ED.[24] Thus, compared with NEBs, MDI-S administration has been shown to be equally effective for children of all ages,[14,16] with a wide range of illness severity and by multiple outcome measures.

Typically, when racemic albuterol is administered by intermittent nebulization, a dose of 0.15 mg/kg is placed in the reservoir of a NEB. This dose is well established as one that is both effective and safe.[25,26] Optimal dosing for albuterol administered by MDI-S is not as well defined. A review assessed 10 randomized controlled trials comparing MDI-S with NEBs for delivery of SABAs to children with acute asthma.[11] In some studies, up to seven times more drug was placed in the NEB reservoir compared with that released by MDI-S, yet outcomes were similar. This reflects the inefficiency inherent with NEB delivery, with much drug being lost to the environment. Multiple puffs of SABAs delivered by MDI-S seem to be well tolerated, even by young children.[14,16] In one trial, children 1 to 4 years old treated with six puffs of albuterol by MDI-S had less tachycardia than did those treated with 2.5 mg of albuterol by NEB.[14] The 2007 NHLBI guidelines state that "equivalent bronchodilation can be achieved either by high doses (4-12 puffs) of a SABA by MDI with a valved holding chamber … or by nebulizer"; they suggest a dose of four to eight puffs.[2] Table 169-2 provides recommended SABA doses stratified by the patient's weight.

Racemic Albuterol versus Levalbuterol. Another consideration in the use of SABAs is the potential role of levalbuterol. Racemic albuterol is an equal mix of the active *R*-albuterol and the inactive *S*-albuterol. *R*-Albuterol produces bronchodilation as well as side effects such as tachycardia and tremors. *S*-Albuterol was long thought to be inert. However, there is some evidence that *S*-albuterol may increase reactivity to histamine, have proinflammatory effects, and exhibit "characteristics of a typical contractile agent."[27-33] Further, there seems to be preferential retention of *S*-albuterol in the lungs of healthy volunteers[34-36]; this may account for diminished effectiveness with frequent dosing. Levalbuterol is pure *R*-albuterol without the *S* component. In theory, levalbuterol should be more effective than racemic albuterol at half the dose because there are no competing harmful effects from the *S*-isomer.

Studies assessing the use of levalbuterol for treatment of children with acute asthma have not consistently demonstrated this theoretic advantage. In the first of these clinical trials, levalbuterol (1.25 mg) was compared with racemic albuterol (2.5 mg) in the ED treatment of more than 500 children with acute asthma.[37] The use of levalbuterol was associated with a decreased need for hospitalization. However, the baseline hospitalization rate in this study was high even though patients with all degrees of illness severity were enrolled. Subsequently, three other randomized trials comparing the ED use of the two drugs have failed to find a levalbuterol benefit.[38-40] These three studies analyzed children with a wide range of illness severities and baseline hospitalization rates and used various outcome measures, such as asthma scores, pulmonary function test results, and hospitalization rates. Racemic

www.ketabpezeshki.com 66485457-66963820

Table 169-2 Recommended Doses of Medications for Acute Asthma

Albuterol	0.15 mg/kg/dose (0.03 mL/kg/dose, max. 1.0 mL)	
	≤10 kg	2.5 mg (0.5 mL)
	11-19 kg	3.75 mg (0.75 mL)
	≥20 kg	5 mg (1.0 mL)
Continuous albuterol	1.0 mg/kg/hr by nebulization (max. 20 mg/hr)	
	≤10 kg	10 mg/hr (2 mL/hr)
	10-20 kg	15 mg/hr (3 mL/hr)
	≥0 kg	20 mg/hr (4 mL/hr)
Albuterol by metered-dose inhaler	Dose is not well established	
	≤10 kg	2-4 puffs
	11-19 kg	4-6 puffs
	≥20 kg	6-8 puffs
Levalbuterol	Half the recommended albuterol doses	
Ipratropium bromide	≤20 kg	250 µg/dose
	>20 kg	500 µg/dose
L-Epinephrine (1:1000) or terbutaline (1.0 mg/mL)	0.01 mL/kg/dose SC or IM (max. 0.4 mL) May be repeated every 10-15 minutes	
IV terbutaline	10 µg/kg bolus during 10 minutes, then 0.1-0.3 µg/kg/min infusion Every 30 minutes, may increase infusion by 0.3 µg/kg/min to a maximum of 5 µg/kg/min	
Prednisone	2 mg/kg (max. 60 mg), in emergency department 1 mg/kg/dose twice daily (max. 30 mg/dose), home therapy	
Dexamethasone	0.6 mg/kg PO, 2 doses 24 hours apart	
IV methylprednisolone	1-2 mg/kg (max. 125 mg)	
IV magnesium sulfate	50-75 mg/kg during 20 minutes (max. 2.5 g)	

albuterol was demonstrated to be as effective as levalbuterol under each of these circumstances.

Similarly, a clinical trial failed to demonstrate a benefit with the use of continuously nebulized levalbuterol.[41] Children who failed to respond to ED treatment and required hospitalization were randomized to receive either continuously nebulized levalbuterol or albuterol. There were no differences in the two groups with respect to time that continuous therapy was needed or time to discharge home. The acquisition cost of levalbuterol is more than 10 times greater than that of racemic albuterol.[40] Until there are more compelling data to demonstrate conclusively that the additional costs of levalbuterol are offset by the need for fewer nebulizations, decreased length of ED or hospital stay, or decreased need for hospitalization, racemic albuterol should remain the drug of choice for children with acute asthma exacerbations.

Disposition. Most children with a mild exacerbation will be able to be discharged home. Those sustaining clinical improvement 60 minutes after the most recent SABA treatment may be discharged. SABAs should be continued for the next 3 to 10 days. If systemic corticosteroid therapy was administered in the ED, it should also be continued for 3 to 10 days; 2 mg/kg/day of oral prednisone is recommended. Children should continue all other asthma controller medications, including inhaled corticosteroids (ICS).

For those who are not already receiving ICS, it is unclear if prescribing them at ED discharge leads to improved short-term outcomes. Among adult asthmatics discharged from the ED after acute asthma exacerbations, the addition of inhaled flunisolide did not lead to improved outcomes.[42] Of note, though, compliance with the inhaled medication was low, and many patients were lost

Table 169-3 Short-Acting Beta$_2$-Agonists in Acute Asthma

	MILD	MODERATE	SEVERE
Delivery method	Intermittent NEB or MDI-S	Continuous by NEB for 1 hour, then reassess	Consider subcutaneous or intramuscular therapy Continuous by NEB
Comments	Most patients will need 1-2 treatments Allows MDI-S teaching No IB needed	Not superior to MDI-S Easier to adhere to NHLBI guidelines for the first hour of therapy Concurrent IB therapy is more easily delivered	Better outcomes in severe asthma

IB, ipratropium bromide; *MDI-S*, metered dose inhaler with spacer; *NEB*, nebulizer; *NHLBI*, National Heart, Lung, and Blood Institute.

to follow-up. On the other hand, adults randomized to inhaled budesonide after ED discharge had a marked decrease in relapse rates, frequency of SABA use, and asthma symptoms.[43] A review concluded that there is "insufficient evidence that ICS therapy provides additional benefit" when it is added to systemic corticosteroids at ED discharge.[44] Pediatric emergency medicine physicians rarely prescribe ICS at ED discharge, even to children who have persistent asthma.[45]

Rather than prescribing ICS to prevent ED relapse, emergency physicians should consider longer term goals for those with persistent disease. National guidelines state that ICS are the medications of choice when long-term controller therapy is initiated for children with persistent asthma.[2] These drugs are safe and well tolerated at recommended doses. Longitudinal studies show that daily use of ICS may decrease growth velocity, but these changes are small and reversible.[46,47] Therefore, emergency physicians should identify children who, during the preceding month, have had frequent asthma symptoms, nighttime awakenings, and the need for frequent use of SABAs for asthma control. As stated by national asthma guidelines, initiation of ICS therapy at ED discharge "should be considered" for these patients.[2] Those already taking low doses of daily ICS may benefit from an increase in dosing. Initiation or increase of ICS would be in addition to the 3- to 10-day course of systemic corticosteroids after ED discharge.

In addition to prescribing medications, emergency physicians should also provide asthma education at discharge. Some EDs provide standardized information to families with a video or DVD while they undergo ED therapy. This education should include a description of how to identify and to avoid asthma triggers, a written asthma action plan explaining proper steps to take in response to an asthma flare, a review of discharge medications, and instruction on proper MDI-S use. Also, follow-up asthma care within 1 to 4 weeks should be arranged.

Summary. For children with mild asthma exacerbations, racemic albuterol should be administered every 20 minutes, as needed (see Fig. 169-1). Most children will respond promptly to therapy and be well enough to be discharged home after one or two treatments. Systemic corticosteroids may be considered for those who exhibit a suboptimal response to SABAs (see later section on moderate exacerbation). NEBs and MDI-S are each reasonable options for delivery of SABAs intermittently. Table 169-2 lists recommended doses for SABAs and other asthma medications in the ED, and Table 169-3 provides a recommended strategy for SABA administration. Rather than base the method of delivery on the issue of

www.ketabpezeshki.com 66485457-66963820

efficacy, clinicians should assess other factors. Determination of the number of treatments a child is likely to need, the anticipated cooperation with a given delivery method, the need to deliver concurrent medications, and costs will help guide decision-making.

Moderate Exacerbation

Children who are alert but very tachypneic and have wheezing throughout expiration, an inspiratory-expiratory ratio of 1 : 2, and significant use of accessory muscles are experiencing a moderate asthma exacerbation. Typically, the oxygen saturation will be 92 to 95% and the PEFR will be 41 to 70% of the personal best. As with children experiencing milder attacks, the cornerstone of therapy is aggressive SABA therapy. In addition, other medications such as ipratropium bromide (IB) and corticosteroids should be added, and consideration should be given to delivery of SABAs continuously.

Anticholinergics. Stimulation of airway cholinergic receptors results in reflex bronchoconstriction, which may be blocked with the use of anticholinergic agents such as IB. This medication is available as an MDI and as a solution for nebulization that may be mixed directly with racemic albuterol. The MDI formulation should not be given to patients with allergy to peanut or soy because it contains soya lecithin; this is not a concern with the solution for nebulization.

Studies have shown that use of SABAs with IB is more effective than SABAs alone.[47,48] In a randomized, double-blind clinical trial, three doses of IB administered concurrently with the first three SABA treatments were shown to be superior to just one dose of IB.[49] In another study, more than 400 children were randomized to receive racemic albuterol and prednisone alone or that therapy plus IB.[48] Those judged to be moderately ill did not experience an IB benefit. However, among those with an initial PEFR less than 50% predicted, the use of IB resulted in a significantly lower hospitalization rate. A systematic review and meta-analysis compared the use of SABAs plus anticholinergics with SABAs alone among children older than 18 months.[50] In the 16 trials assessed, combination therapy was associated with significantly lower hospitalization rates and improvements in asthma scores and pulmonary function test results. These investigators concluded that multiple doses of IB added to SABAs should be standard treatment of children with moderate to severe asthma exacerbations.

Clinical benefits after IB use may be delayed for up to 60 minutes.[49] However, it is inexpensive, and because less than 1% is absorbed systemically, it is virtually free of adverse effects.[50] IB should be administered to children with moderate to severe exacerbations. Three doses may be mixed with racemic albuterol and delivered concurrently and continuously by NEB in the first hour of care (see Table 169-3). This means of administration, although not superior to delivery by MDI-S, will help ensure compliance with the goal of the equivalent of three albuterol treatments in the first hour of care.[2] Alternatively, four to eight puffs of IB may be given every 20 minutes in the first hour of care,[2] but these children will also need to receive a substantial number of puffs of SABAs, and as clinicians care for other patients, there may be delays in receiving appropriately aggressive therapy. In summary, sicker patients require three albuterol treatments soon after ED arrival. Continuous delivery by NEB during 1 hour may be preferred to intermittent MDI-S, not for superior efficacy but to help ensure timely medication delivery.

Systemic Corticosteroids. There are compelling data to show that the prompt use of corticosteroids can decrease the need for hospitalization and that they should be used routinely for patients with moderate disease.[4,51-56] Clinicians must decide the optimal agent and route of administration.

Oral versus Parenteral. Two early clinical trials established the efficacy of parenterally administered corticosteroids in the ED. Compared with those treated with placebo, adults treated with intravenous methylprednisolone had a lower hospitalization rate,[51] as did children treated with intramuscular methylprednisolone.[52] Scarfone and colleagues were the first to demonstrate the efficacy of orally administered corticosteroids in this setting.[4] Children treated with frequent SABAs and oral prednisone had a reduced need for hospitalization compared with those treated with SABA therapy alone. Further, a meta-analysis determined that compared with placebo, oral corticosteroids were effective in reducing the need for hospitalization among children with acute asthma exacerbations.[55]

There have been few clinical trials directly comparing oral and parenteral therapy. In one small study, there were no differences in any outcome measures for children in the ED with moderate to severe asthma who were treated with equal doses of either intravenous or oral methylprednisolone.[57] The most recent NHLBI guidelines recommend oral administration of corticosteroids because this is less invasive and the benefits seem to be equivalent to those of parenteral therapy.[58,59] Further, oral corticosteroid therapy is inexpensive, the drugs are rapidly and completely absorbed, and this mode of administration provides the potential for out-of-hospital administration either at home or in a physician's office.

Prednisone versus Dexamethasone. As with SABAs, clinicians have a choice in the specific corticosteroid to be used. Oral prednisone has been the drug of choice in this setting. Significant clinical benefits begin 2 hours after administration, are most pronounced among the sickest children, and result in a decreased need for hospitalization.[4] Dexamethasone phosphate may be given orally or parenterally and has a substantially longer (36-72 hours) half-life than prednisone (18-36 hours).[60] Investigators treated children in the ED with either 0.6 mg/kg of dexamethasone or 2 mg/kg of prednisone in a randomized fashion.[60] Those in the dexamethasone group were provided one additional dose to take the following day, whereas those in the prednisone group were given a prescription for an additional 4 days of prednisone. There were no differences in hospitalization or relapse rates or symptom persistence. Significantly fewer dexamethasone patients vomited the study drug in the ED and reported noncompliance with it after ED discharge. Of note is that Orapred, a more palatable form of oral prednisone, was not used in this study.

These data suggest that either dexamethasone or prednisone may be used in the treatment of moderately ill children with acute asthma. Given that clinical benefits from corticosteroids are delayed and that all moderately ill children will require corticosteroids whether or not they require hospitalization, they should be administered as soon as possible after ED arrival in an attempt to hasten clinical improvement and perhaps to prevent the need for hospitalization.[53,56] Because SABAs are administered by inhalation and corticosteroids may be given orally, most children with a moderate asthma exacerbation can be managed without the insertion of an intravenous line. This avoids unnecessary pain and anxiety as well as the delays in drug administration associated with intravenous line insertion. Intramuscular therapy is a reasonable option for children who vomit orally administered corticosteroids yet do not require an intravenous line for other reasons.

Inhaled Corticosteroids. The use of ICS for the ED treatment of acute asthma is an area of ongoing research. In three clinical trials, ICS were compared with oral prednisone in the ED setting.[61-63] Scarfone and colleagues treated children with either nebulized dexamethasone or oral prednisone.[61] The two groups had similar rates of hospitalization, although there was a trend toward greater rate of improvement among the dexamethasone-treated children. A potential limitation to the widespread use of nebulized dexamethasone is that it contains sodium bisulfite, a

www.ketabpezeshki.com 66485457-66963820

preservative that may induce wheezing among allergic individuals. Budesonide, an ICS that has a high topical activity and low systemic absorption, is effective in the treatment of children with croup.[64] Investigators from India found three nebulized doses of budesonide to be superior to one dose of prednisone in the treatment of acute asthma.[62] In another trial, fluticasone-treated children with asthma were more likely to be hospitalized and experienced a significantly smaller degree of improvement compared with those treated with prednisone.[63] Finally, investigators determined that children with asthma treated in the ED with inhaled triamcinolone had lower hospitalization rates and relapse rates compared with those treated with either prednisone or intravenous corticosteroids.[65]

Rather than replacing systemic corticosteroids, other investigators have assessed whether the addition of ICS to systemic therapy results in clinical benefits; however, few such studies have been performed in children, and few have assessed the need for hospitalization.[66-68] Thus the niche for ICS in the ED treatment of acute asthma is still being defined. Additional areas for further investigation include determination of the optimal agent, the proper dose, and the appropriate mode of delivery and defining of the population of patients most likely to benefit from this therapy. At this time, there is no proven role for the routine use of ICS in the ED setting. Because of its greater bioavailability and proven benefits, moderately ill children should receive systemic corticosteroid therapy.

Intermittent versus Continuous Therapy. Children requiring very frequent intermittently nebulized albuterol may benefit from receiving albuterol continuously instead. In one clinical trial among asthmatic children, patients were randomized to receive the same total dose of albuterol nebulized either intermittently or continuously during 2 hours.[69] Those in the continuous group had a greater mean improvement in their asthma scores and significantly less respiratory therapy time, although there were no differences in mean PEFR or admission rates. A systematic review found that those treated with continuously nebulized SABAs had lower rates of hospitalization, greater improvements in pulmonary function test results, and similar rates of adverse events compared with those treated intermittently.[70]

Perhaps the greatest advantage of continuous over intermittent therapy is one of a practical nature: it allows greater compliance with the goal of delivering the equivalent of three intermittent albuterol treatments in the first hour of care.[2] In addition, this method will result in less respiratory therapy time and costs; it has been shown to be safe,[71,72] and it may benefit the sickest patients the most.[73,74] On the other hand, young children may not tolerate a face mask for prolonged periods.

Many clinicians find it helpful to determine the total of racemic albuterol that would be delivered if three treatments were to be given intermittently during an hour, place that total dose in the NEB reservoir, and administer it continuously during an hour. Alternatively, a dose range may be used on the basis of the child's weight (see Table 169-2).

Summary. A suggested approach to the management of children with moderately acute asthma is as follows. Supplemental oxygen should be provided if the initial oxygen saturation is 92% or less in room air. Albuterol and IB should be administered continuously by nebulization for 1 hour (see Fig. 169-1). This will ensure that an appropriate amount of each is delivered in the first hour of ED care. As soon as possible after ED arrival, a single dose of either oral prednisone or dexamethasone should be given. Intramuscular dexamethasone is an option for children who vomit the initial oral corticosteroid dose within 15 minutes of its administration or who vomit repeated doses.

After 1 hour of therapy, a clinical reassessment should be made; evaluation at this time is better than the initial assessment at predicting the need for hospitalization.[75] At this point, patients can generally be grouped into one of three categories: markedly improved, not improved or worse, or slightly improved. Children who are markedly improved may be observed without SABAs to ensure that there is no clinical deterioration. It is wise to delay a disposition decision until at least 60 minutes after the most recent SABA treatment so that a clinical relapse may be noted. In making the disposition decision, the clinician should determine the patient's physical examination findings and also consider the frequency of prior hospitalizations and ED visits and issues such as compliance and support systems. The medications and education to be provided at ED discharge are the same as outlined for those with a mild exacerbation.

Children who remain moderately ill after the first hour should continue to be treated aggressively with SABAs, either continuously or with frequent administration of intermittent therapy. If, after 2 hours, subjective and objective measures reveal that the degree of respiratory distress is unchanged or worse, hospitalization is warranted. On the other hand, there will be a subset of patients who demonstrate some degree of clinical improvement at the 2-hour assessment but are not yet well enough to be sent home. One study showed that among prednisone-treated children who would have been hospitalized after 2 hours of ED therapy, less than half were actually hospitalized when aggressive SABA therapy was continued for an additional 2 hours, and none returned to the ED within 48 hours of discharge.[4] Presumably, the onset of prednisone's effects allowed these children to avoid hospitalization. Therefore, the continuing treatment of such children with SABAs for a total of 3 to 4 hours, perhaps in an ED observation area, would be expected to avoid the need for many hospitalizations.

Severe Exacerbation

A severe exacerbation is characterized by restlessness or lethargy, extreme tachypnea and tachycardia, wheezing that is audible without a stethoscope, inspiratory-expiratory ratio exceeding 1:2, significant use of accessory muscles, and oxygen saturation less than 92%. Some older children with a severe exacerbation may have bradypnea because of a prolonged expiratory phase, and wheezing may not be audible if aeration is markedly decreased. The PEFR will typically be less than 40% predicted, although most children will be too ill to use the peak flow meter.

Figure 169-1 provides an outline for the approach to management of severely ill children. They should be attached to a cardiorespiratory monitor and blood pressure cuff with continuous monitoring of oxygen saturation by pulse oximeter. As with the moderately ill child, supplemental oxygen and continuously nebulized albuterol and IB should be provided soon after arrival. To achieve an oxygen saturation of 92% or greater, it may be necessary to use a non-rebreathing face mask. Severely ill children may be too sick to tolerate oral medications and will likely need an intravenous catheter for other indications. Therefore, an intravenous line should be established as soon as possible and a dose of methylprednisolone given.

Subcutaneous or Intramuscular Therapy. For children with very poor inspiratory flow, nebulized SABAs may not be effectively delivered to the smallest airways. Short inspiratory time, prolonged expiration, and low inspiratory pressures will impair delivery of inhaled medications. Here, subcutaneous or intramuscular terbutaline or epinephrine should be used, especially if an intravenous line is yet to be established. Terbutaline may be preferable because it is a more selective agent with fewer side effects, such as tremors, vomiting, or palpitations. Very ill anxious young children who are uncooperative with the inhalation treatments may also benefit from this therapy. There are no data to suggest that one mode of administration is superior to the other, although intramuscular therapy is recommended for children

www.ketabpezeshki.com 66485457-66963820

with bronchospasm due to anaphylaxis.[76] Subcutaneous or intramuscular therapy may be repeated every 10 to 15 minutes, as needed.

Magnesium Sulfate. There is accumulating evidence that magnesium sulfate may benefit adults and children with severe asthma. Meta-analyses determined that use of magnesium resulted in improved outcomes for both adults[77] and children.[78] In two separate trials, children with a suboptimal response to initial SABA therapy who were randomized to receive magnesium had significantly greater improvements in pulmonary function compared with those treated with placebo.[79,80] In contrast, Scarfone and colleagues conducted a randomized, controlled trial assessing the use of 75 mg/kg of magnesium in asthmatic children.[81] They sought to determine if magnesium was efficacious as a component of *initial* therapy for children with moderate to severe exacerbation, without waiting to judge response to early albuterol therapy. No magnesium benefits were found for this population.

Magnesium is inexpensive and has minimal adverse effects.[82] The most common adverse effect is hypotension; this may be avoided by infusion of the dose during 20 minutes. The most recent NHLBI guidelines recommend the consideration of magnesium for select patients; this represents a key difference from prior reports. At this point, existing literature indicates that magnesium should be considered for moderately ill patients who have a suboptimal response to SABAs, IB, and corticosteroids as well as for all severely ill children.

Intravenous Short-Acting Beta$_2$-Agonists. The NHLBI guidelines conclude that there are insufficient data to make recommendations for the use of intravenous SABAs.[2] Similarly, a systematic review of randomized, controlled trials failed to support this practice.[83] However, of the 15 studies included, just three were performed in children and just three assessed the combination of intravenous and inhaled SABAs compared with inhaled SABAs alone.[84] Rather than definitively demonstrating lack of efficacy, these data highlight the need for more and larger clinical trials.

Potential adverse effects from the use of intravenous SABAs are substantial and include dysrhythmias, hypertension, and hypokalemia. Because of the concern for toxicities, there is no role for initiation of therapy with intravenous SABAs, even for severely ill children. However, for those who are poorly responsive to the interventions outlined before, with impending respiratory failure, the risk-benefit ratio shifts toward their use.

Heliox. Heliox is a low-density mixture (often in a 70 : 30 ratio) of helium and oxygen that results in less turbulent flow through narrowed airways. Theoretically, its use is associated with decreased work of breathing, less respiratory muscle fatigue, and lower likelihood of ventilatory failure. In one trial, children with acute severe asthma treated with heliox had a significantly greater decrease in pulsus paradoxus and dyspnea index, and increase in PEFR, compared with others. A more recent study compared the use of heliox versus oxygen alone to deliver continuously nebulized SABAs.[85] At 240 minutes, children in the heliox group had greater improvement as assessed by decreased asthma scores and need for hospitalization. However, after reviewing 10 clinical trials assessing the use of heliox, investigators concluded that there is insufficient evidence to support the use of heliox for all patients with asthma,[86] although it may be considered for severely ill children who are not responding to more conventional therapy.[2]

Mechanical Ventilation. When making decisions about the need for mechanical ventilation of the severely ill patient, one should assess the entire clinical picture, including duration of wheezing, illness severity, response to therapy, and ABG results. Making this decision on the basis of the ABG results alone should be discouraged. For example, the child with a pH of 7.10 and a $Paco_2$ of 55 who shows marked improvement with intravenous SABA therapy may not require ventilatory assistance, yet the child with a pH of 7.18 and a $Paco_2$ of 50 who appears fatigued and is not responding to therapy probably does. Ketamine is a bronchodilator and is the drug of choice for sedation and analgesia of the asthmatic child who requires intubation.

With mechanical ventilation, air trapping with resultant pneumothorax is a major concern. *Permissive hypercapnia* is a term used to describe a strategy of minimizing tidal volumes and respiratory rate to minimize peak pressures. Enough expiratory time must be allowed for air exit from the lungs.

There are many potential therapies that are not recommended for the treatment of acutely ill asthmatic children. These include methylxanthines such as aminophylline, routine use of antibiotics in the absence of known bacterial infection, aggressive hydration, chest physiotherapy, mucolytics, sedation, and noninvasive ventilation.[2]

Summary

Asthma is one of the few diseases in which there have been increases in prevalence, morbidity, and mortality in the past two decades. More than ever, emergency physicians need to be vigilant in the recognition and treatment of children with acute asthma. In all cases, appropriate doses of albuterol should be given promptly, and early use of multidose IB and corticosteroids is indicated for those who are moderately or severely ill. Aggressive use of subcutaneous or intramuscular terbutaline, continuously nebulized albuterol, and magnesium is warranted for those who are severely ill; intravenous SABAs are reserved for those not responding to therapy.

BRONCHIOLITIS

Perspective

Background

Bronchiolitis is an acute infectious disease that results in inflammation of the small airways in children younger than 2 years. This process is manifested clinically as wheezing and increased work of breathing along with the typical signs and symptoms of a URI. Nearly all children are affected by the viruses that cause bronchiolitis at least once during their first 2 years of life, but it is more common for infants younger than 12 months to have clinical bronchiolitis.

Epidemiology

Bronchiolitis is a seasonal disease, with most cases occurring between November and April in temperate climates. It accounts for approximately 3% of all ED visits in the United States.[87] Overall, approximately 19 to 27% of children presenting to an ED with bronchiolitis are admitted for inpatient management.[87,88] This disease accounts for more than 20% of acute care hospitalizations for children younger than 1 year, and the total cost for all bronchiolitis-related hospitalizations is more than $500 million per year.[89] Hospitalization rates vary according to many factors, and these rates have increased dramatically during the past two decades. In the United States, Hispanic children and those of Alaskan or American Indian descent are more likely to be admitted to the hospital after presenting with bronchiolitis.[88,90] Boys and younger infants are also more likely to need admission.[91] Other factors that seem to be associated with hospitalization are poverty, household crowding, exposure to environmental tobacco smoke, and daycare attendance.[92] Clearly, underlying chronic medical conditions, such as congenital heart disease and chronic lung disease, lead to a more severe course in patients with this disease.

Bronchiolitis is rarely fatal, with an average mortality rate of 2.0 per 100,000 live births in the United States. Low birth weight

www.ketabpezeshki.com 66485457-66963820

(<2500 g), low 5-minute Apgar score, high birth order, and young maternal age are associated with an increased risk of death.[93,94] Breast-feeding, on the other hand, appears to be associated with a less severe clinical course.[95]

Distinguishing Principles of Disease

Etiology

Many viruses are implicated as the underlying cause of bronchiolitis. Respiratory syncytial virus (RSV), the most common agent identified in children diagnosed with this disease, is estimated to cause up to 70% of cases in previously healthy children.[96] Other viruses commonly isolated are parainfluenza, human metapneumovirus, influenza, adenovirus, bocavirus, and rhinovirus.[96-101]

Pathophysiology

Most respiratory viruses that cause bronchiolitis in children are transmitted from one host to another by fomites spread from hand to nose or by droplets produced by sneezing or coughing of respiratory secretions. Shedding of the virus often begins before the onset of significant clinical symptoms and can continue for 2 to 3 weeks in an immunocompetent infant. The typical incubation period is 2 to 8 days from the time of initial contact.[102]

In an infected patient, viral replication often begins in the epithelial cells of the upper airway before spreading to the mucosal surfaces of the lower respiratory tract. The infected epithelial cells are generally destroyed by lysis or apoptosis, which results in the desquamation of these cells and release of host inflammatory mediators.[103] Affected lungs demonstrate epithelial cell necrosis, monocytic inflammation and edema of the peribronchial tissues, and mucus and fibrin plugging of the distal airways on histologic examination. These findings translate into the clinical findings of wheezing and lower airway obstruction in an infant with bronchiolitis. Younger infants, whose distal airways are of smaller caliber and whose immune systems lack active immunity to most respiratory viruses, are prone to more severe clinical symptoms.[92] Severe lower airway obstruction leads to air trapping and atelectasis, resulting in mismatched ventilation and perfusion and hypoxemia. In addition, younger infants are at increased risk for fatigue, leading to hypercarbia and respiratory failure.

Clinical Features

Patient History

Typically, infants with bronchiolitis are younger than 12 months and present during the winter months. The first symptoms are generally those of a URI, such as nasal congestion and copious rhinorrhea. This is followed within a few days by development of a tight cough, often associated with difficulty in feeding. Some parents will report audible wheezing as well. A history of fever is common but not universal; one study reported fever in approximately one third of patients admitted with bronchiolitis.[104] Very young infants may present with a history of apnea, and this may precede the onset of typical symptoms of respiratory infection. It is essential to ascertain information about the infant's hydration status, including the amount and frequency of oral intake, urine output, vomiting, and diarrhea.

A child's past medical history is important as well. Specifically, comorbidities such as congenital heart disease, chronic lung disease, and prematurity can have a significant impact on the clinical course of bronchiolitis. A past history or family history of wheezing or atopy may make the diagnosis of asthma more likely, particularly in the older infant. Other elements of the patient history that may be helpful are whether the child attends daycare and if there are household contacts with respiratory symptoms.

Physical Examination

As in any pediatric patient, an assessment of vital signs and general appearance is crucial to the evaluation of an infant with bronchiolitis. Common vital sign abnormalities include fever, tachycardia, tachypnea, and hypoxia. Pulse oximetry is noninvasive and inexpensive, and it provides objective data about the degree of illness of a wheezing child. The oxygen saturation (Sao_2) of any moderately or severely ill infant should be obtained soon after ED arrival as an adjunct to the physical examination. With the use of pulse oximetry, an ABG analysis is generally unnecessary to assess a patient's oxygenation. Thus the acquisition of an ABG analysis should be reserved for those with severe disease and impending respiratory failure to measure the extent of hypercarbia and respiratory acidosis. Irritability or lethargy may be present, especially in those infants with more severe disease. Nasal flaring and retractions are visible signs of respiratory distress that may be present. Lung auscultation often reveals decreased air movement, rales, rhonchi, wheezing, and increased ratio of expiratory to inspiratory times. Using these physical examination findings, the clinician may stratify patients into mild, moderate, and severe categories of disease (Table 169-4).

The combination of poor feeding and increased insensible fluid losses often has an impact on an affected infant's hydration status. A careful assessment of the anterior fontanel, mucous membranes, and skin turgor can assist in determination of whether an infant is dehydrated.

Complications

Clinicians caring for children with bronchiolitis need to understand the typical course of the disease, both for their ability to accurately diagnose and manage these patients and to advise

Table 169-4 Suggested Bronchiolitis Assessment Tool

	MILD	MODERATE	SEVERE
Feeding	Normal	Less	Poor
Sao_2 in room air	≥95%	92-94%	<92%
Respiratory rate (breaths/min)	<60	60-70	>70
Retractions	None or minimal	Intercostal	Substernal
Accessory muscle use	None	None	Neck or abdominal
Wheeze	None or minimal	Moderate expiratory	Severe inspiratory-expiratory, audible without stethoscope
Air exchange	Good, equal breath sounds	Localized, decreased breath sounds	Multiple areas of decreased breath sounds

www.ketabpezeshki.com 66485457-66963820

parents about the recovery phase. The worst phase of the illness that may necessitate hospitalization generally occurs in the first few days, and median length of hospital stay has been reported to be between 2 and 3 days.[105,106] However, the entire course of illness can last much longer, with a median duration of 12 days.[107] Coughing and noisy breathing, in particular, can last for more than 4 weeks.

Bacterial acute otitis media is the most common condition associated with bronchiolitis, with a prevalence of up to 60%. The bacterial pathogens are similar to those recovered in other children with acute otitis media; thus it should be treated according to standard recommendations. Other concurrent bacterial infections are rare. In one study of more than 2000 children hospitalized with RSV bronchiolitis, approximately 1% also had a urinary tract infection (UTI).[108] Pathologic bacteremia and meningitis were not found in any of these patients. Similar rates of UTI without bacteremia are found in febrile children with clinical bronchiolitis, with or without documented RSV infection.[109] Infants younger than 8 weeks with fever and bronchiolitis present a unique dilemma for emergency physicians. The rate of serious bacterial infections (SBIs), defined as UTI, bacteremia, bacterial meningitis, or bacterial enteritis, among all febrile infants younger than 8 weeks is reported to be up to 12%. However, in infants with documented RSV infection or clinical bronchiolitis at the time of ED presentation, the rate of SBI is substantially lower.[110,111] In a large, prospective, multicenter study, Levine and colleagues reported that 7% of febrile infants younger than 61 days who were RSV positive had a concurrent SBI, compared with 12.5% of those who were RSV negative. Of the patients with SBIs, most (82%) had a UTI. Bacteremia was rare and occurred only in infants younger than 1 month. None of the RSV-positive infants had bacterial meningitis. As a result, most would advocate performance of a workup for UTI in febrile infants between 1 and 2 months of age who are known to be RSV positive or have clinical bronchiolitis. Additional testing to obtain culture specimens of cerebrospinal fluid and blood may be done selectively. Similarly, these infants may not require empirical antibiotic therapy for presumed SBIs. On the other hand, in the first month of life, all febrile infants should undergo testing for evaluation for SBIs and be empirically treated with antibiotics regardless of RSV status.

Apnea is commonly reported in young infants with bronchiolitis, especially those who are admitted for inpatient management. Eight percent of admitted patients have a history of apnea, and nearly 3% will have apnea during the hospital stay.[112,113] Risk factors for development of in-hospital apnea include age younger than 1 month in full-term infants, postconceptional age younger than 48 weeks in preterm infants, and history of apnea before admission. The absence of all of these risk factors has a high negative predictive value for the development of in-hospital apnea.[113]

The long-term outcomes after bronchiolitis have also been examined extensively. It is clear that those who experience the disease in infancy have a higher prevalence of lower respiratory diseases, including asthma, in adolescence and adulthood.[114-117] Whether there is a causal relationship remains undetermined.

Differential Considerations

Asthma is the condition that has the most clinical overlap with bronchiolitis. Physical examination findings alone cannot distinguish the two. Younger age, presentation during winter months, antecedent URI symptoms, and absence of prior or family history of atopic disease and wheezing suggest bronchiolitis as the cause of wheezing in an individual patient. Some infants will have clinical features consistent with both conditions. For example, a 12-month-old may present in July with a URI and wheezing for the first time. For this child, a clinician may choose to initiate therapy for acute asthma. A complete discussion of other conditions that should be differentiated from bronchiolitis is included earlier in this chapter and in Table 169-1.

Diagnostic Strategies

Bronchiolitis should be diagnosed primarily on the basis of history and physical examination findings. Viral diagnostic testing can be performed on nasopharyngeal secretions by enzyme-linked immunosorbent assays, indirect fluorescent antibody detection, polymerase chain reaction, or viral culture. In general, this is not warranted for those patients for whom outpatient management is sufficient. However, identification of a viral respiratory pathogen can be useful in certain situations. For example, if test results can be obtained rapidly, identification of a viral etiology may eliminate the need for further laboratory evaluation for infants who present with fever. In addition, having a specific viral diagnosis can allow the appropriate cohorting of patients admitted for inpatient management, thus decreasing nosocomial transmission among patients and staff. Providers should exercise contact and droplet precautions until the causative viral agent is identified.

There is tremendous variability in the use of diagnostic imaging; in one series, a chest radiograph was obtained for more than 70% of infants hospitalized with bronchiolitis.[118] In children with clinical findings that are typical for bronchiolitis, however, radiographic imaging is rarely necessary. Hyperinflation, atelectasis, and peribronchial cuffing are the findings most commonly associated with this disease. In ambulatory patients with acute lower respiratory infections, obtaining of a chest radiograph does not affect clinical outcome,[119] and this practice has been associated with increased use of unnecessary antibiotics.[118] Further, the likelihood of a chest radiograph's revealing findings inconsistent with the clinical diagnosis of bronchiolitis is less than 1%.[120] Diagnostic imaging may be helpful in patients with severe distress, significant hypoxia, or atypical presentation or clinical course. In summary, as recommended by the American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis, "clinicians should diagnose bronchiolitis and assess disease severity on the basis of history and physical examination. Clinicians should not routinely order laboratory and radiologic studies for diagnosis."[121]

Management

Therapy

Whereas the diagnosis of bronchiolitis is fairly straightforward, the management of children with the disease often presents clinicians with confusing and controversial dilemmas. The literature is often contradictory, making it difficult to reach a consensus. As a result, there exists wide practice variation in the management of bronchiolitis.[122-124] However, it is clear that a consistent, evidence-based approach to this disease can lead to more efficient and effective care.[113,125-128] Supportive care, such as providing hydration and supplemental oxygen, is the cornerstone of therapy for affected children.[121] A management strategy, stratified by the patient's initial degree of illness, is outlined in Figure 169-2.

SABAs are the treatment of choice for children with wheezing due to asthma. However, the evidence supporting their use in wheezing caused by bronchiolitis is less favorable than for asthma. In a meta-analysis of 22 clinical trials, a small short-term benefit in clinical score was observed for children with bronchiolitis treated with SABAs. This treatment had no significant effect on rates or duration of hospitalization. Although rare, adverse effects such as tachycardia, decreased oxygen saturation, flushing, and hyperactivity occurred more frequently in children treated with

www.ketabpezeshki.com 66485457-66963820

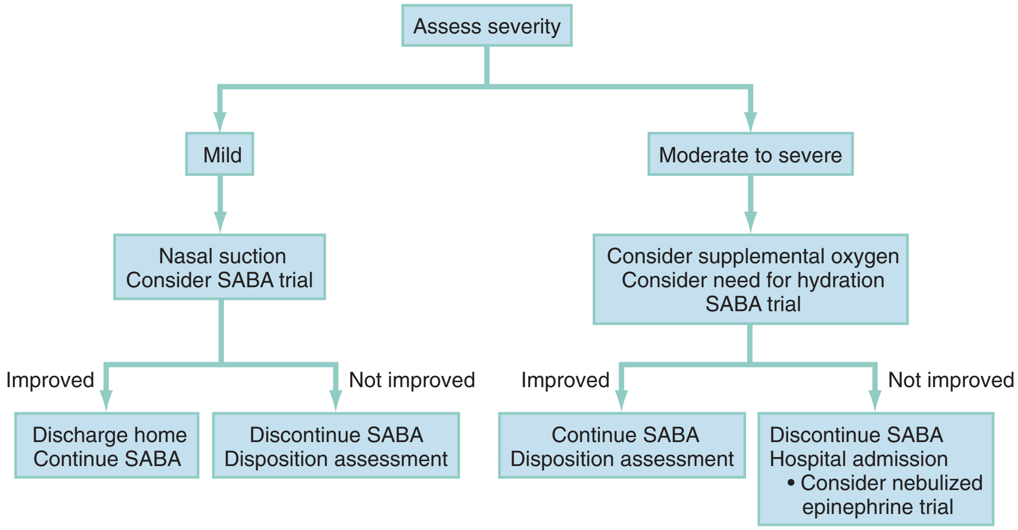


Figure 169-2. Emergency department management of bronchiolitis. *SABA,* short-acting beta$_2$-agonist.

SABAs.[129] Thus the American Academy of Pediatrics does not recommend the routine use of SABAs for bronchiolitis; instead, clinicians should consider a trial of such medications to determine if a patient has a positive clinical response.[121]

Similar controversy exists with respect to the utility of nebulized epinephrine in treatment of bronchiolitis. A meta-analysis of 14 studies concluded that there is not enough evidence to support the use of epinephrine for inpatients, but it does provide some clinical benefit over other bronchodilators and placebo for outpatients.[130] Treatment does not decrease the rate of hospitalization or the length of hospital stay for admitted patients.[131] One difficulty with the use of epinephrine in the ED is that it is not a treatment that can be continued at home. Thus nebulized epinephrine should be considered for children with moderate to severe distress in whom beta-agonist therapy was not effective and who will likely require hospitalization. As with SABAs, nebulized epinephrine should be continued only for those patients who demonstrate a clinical benefit.

Studies on the use of nebulized anticholinergic agents (e.g., ipratropium bromide) have not been conclusive. Whereas one study in the ED setting reported a decreased need for additional treatment of patients receiving an anticholinergic medication in addition to SABAs,[132] a similarly designed ED study found no benefit.[133] There is currently not sufficient evidence to recommend the use of anticholinergic agents for young children with wheezing and suspected bronchiolitis.[134]

Many of the symptoms of bronchiolitis are a result of increased and thickened respiratory secretions. A great deal of literature supports the use of nebulized hypertonic saline in the treatment of cystic fibrosis, in which clearance of thickened secretions is vital.[135] Although there is not yet enough literature to definitively recommend its use for bronchiolitis, one study suggested that nebulized hypertonic saline is a safe medication that reduces the length of stay for hospitalized children.[136] Thus far, studies have not demonstrated any clinically significant benefits associated with its use in ED patients.[137] Chest physiotherapy has also been examined as a means to clear respiratory secretions. A meta-analysis of three randomized, controlled trials revealed no improvement in clinical score, length of stay, or oxygen requirement after chest physiotherapy.[138]

Systemic corticosteroids are well established as being effective treatment of wheezing due to acute asthma. Despite reports that more than half of infants may be prescribed corticosteroids when they are diagnosed with bronchiolitis,[124] well-designed controlled trials have demonstrated no benefit for their use in terms of rate of admission, clinical score, or any other outcome.[121,139,140] Specifically, Corneli and colleagues conducted a double-blind, randomized trial comparing oral dexamethasone with placebo in 600 children with acute moderate to severe bronchiolitis. The investigators concluded that oral dexamethasone had no significant effect on the rate of hospitalization, respiratory status after 4 hours of observation, or later outcomes, such as length of inpatient stay, repeated medical visits, and adverse events. Another multicenter trial did, however, demonstrate a reduction in hospitalization rates in patients treated with the combination of oral dexamethasone and nebulized epinephrine.[141] Further research is needed to clarify the role of systemic corticosteroids in the treatment of bronchiolitis. ICS also provide no positive effect on clinical course.[142]

Whereas infants with severe bronchiolitis requiring intensive care and mechanical ventilation frequently have concurrent or secondary bacterial infections,[143] this is an uncommon complication for most children. Despite some reports that clarithromycin may hasten recovery in RSV bronchiolitis,[144] there is no evidence for the routine use of antibiotics for bronchiolitis, and they should be reserved for patients with true bacterial infections.[139,145]

Ribavirin is a specific antiviral agent directed toward treatment of RSV infections. Several smaller studies suggested a small benefit with respect to duration of mechanical ventilation and length of stay in patients with severe disease.[146] Its high cost and potential risks to caregivers, however, limit its role in routine management. Ribavirin may be indicated in selected cases of documented RSV bronchiolitis with severe respiratory compromise.[121]

Prophylaxis

Although emergency physicians generally do not have a role in the administration of preventive medications, they should be aware of the options available to their patients. Palivizumab (Synagis) consists of monoclonal antibodies against RSV. Whereas RSV-specific immune globulin is not effective in treatment of the acute disease process,[147] palivizumab is effective in reducing hospitalization rates for RSV in certain high-risk populations.[148-151] It is recommended for most children younger than 24 months with chronic lung disease, congenital heart disease, or prematurity and is administered as a monthly intramuscular injection during the high-prevalence months.[152]

www.ketabpezeshki.com 66485457-66963820

Disposition

An essential component in the evaluation and management of bronchiolitis in the ED is the ability to predict the severity of its clinical course. Because it is a dynamic disease, evaluations at a single point in time may not be sufficient to fully estimate its severity; thus serial examinations are necessary. A number of demographic and clinical features have been associated with a severe clinical course. These factors, which may mandate hospitalization, include age younger than 3 months, gestational age less than 34 weeks, ill appearance, hypoxemia ($Sao_2 < 95\%$), tachypnea (>70 breaths/min), and significant atelectasis on the chest radiograph (if it is obtained). Most of the literature, however, focuses on inpatients. In addition to younger age and prematurity, a history of hemodynamically significant congenital heart disease, chronic lung disease, and immunocompromised state have been associated with higher morbidity and mortality among inpatients.[121,153]

Ultimately, the emergency physician should assess more than just the child's degree of respiratory distress. Patients for whom the respiratory symptoms negatively affect their ability to feed and to maintain hydration warrant inpatient admission. Assessment of the family's ability to continue supportive measures at home and to seek further medical care if necessary is central to the disposition decision. In children for whom outpatient management is deemed appropriate, expedient follow-up (within 24 hours) with a primary care provider is essential. If SABA therapy provides a sustained clinical improvement in symptoms in the ED, it should be continued as part of home therapy. On the other hand, for the subset of infants who fail to respond to SABA therapy yet meet other criteria for discharge, outpatient treatment with SABAs is not warranted. As in all of pediatric medicine, anticipatory guidance must be provided. Parents should be instructed about the signs of worsening respiratory distress, including poor feeding, retractions, increased tachypnea, lethargy, and irritability; seeking of immediate medical care is warranted should these signs occur.

Summary

Bronchiolitis is a common respiratory disease in infancy that accounts for many ED visits and hospitalizations. It is primarily a clinical diagnosis based on key history and physical examination findings. Serious complications, such as apnea, are rare and mostly occur in very young infants or those with underlying medical conditions. Treatment is largely supportive, and the use of nebulized SABAs may be helpful for a subset of patients. Ultimately, ED clinicians must understand the dynamic and variable nature of bronchiolitis and be able to effectively predict the severity of its clinical course.

KEY CONCEPTS

- Almost all children treated in the ED for asthma will require systemic corticosteroids. However, children with mild exacerbations who respond promptly to a single SABA treatment may be managed without systemic corticosteroids.
- Albuterol delivered by MDI-S is as effective as that delivered by NEB for children in the ED with acute asthma. Therefore, the mode of delivery is largely chosen on the basis of cost and ability to adhere to the goal of three treatments within the first hour of care.
- To date, most studies have failed to demonstrate that levalbuterol leads to better ED outcomes compared with racemic albuterol. Racemic albuterol, at a substantially lower cost, should remain the drug of choice for children with acute asthma exacerbations.
- National guidelines recommend that emergency providers initiate controller therapy for children with persistent asthma at ED discharge.
- Bronchiolitis is a clinical diagnosis based on a history of prodromal URI symptoms in a young infant, followed by findings on physical examination of wheezing and increased work of breathing. The utility of diagnostic imaging and laboratory evaluation is limited, and these measures should not be used routinely.
- The management of infants with bronchiolitis focuses largely on supportive measures, and most patients can be managed as outpatients as long as the ability to tolerate oral hydration is not significantly compromised. Disposition from the ED depends on the assessment of multiple risk factors that may predict a more severe clinical course.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Akinbami L: The state of childhood asthma, United States, 1980-2005. *Adv Data* 2006; 381:1.
2. National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma—Summary Report 2007. *J Allergy Clin Immunol* 2007; 120(Suppl 1):94.
3. Gorelick MH, Stevens MW, Schultz TR, Scribano PV: Performance of a novel clinical score, the Pediatric Asthma Severity Score (PASS), in the evaluation of acute asthma. *Acad Emerg Med* 2004; 11:10.
4. Scarfone RJ, Fuchs SM, Nager AL, Shane SA: Controlled trial of oral prednisone in the emergency department treatment of children with acute asthma. *Pediatrics* 1993; 92:513.
5. Geelhoed GC, Landau LI, Le Souef PN: Evaluation of Sao_2 as a predictor of outcome in 280 children presenting with acute asthma. *Ann Emerg Med* 1994; 23:1236.
6. Walsh-Kelly CM, Kim MK, Hennes HM: Chest radiography in the initial episode of bronchospasm in children: Can clinical variables predict pathologic findings? *Ann Emerg Med* 1996; 28:391.
7. Gershel JC, et al: The usefulness of chest radiographs in first asthma attacks. *N Engl J Med* 1983; 309:336.
8. Tien I, Dorfman D, Kastner B, Bauchner H: Metered-dose inhaler: The emergency department orphan. *Arch Pediatr Adolesc Med* 2001; 155:1335.
9. Kacmarek RM: The interface between patient and aerosol generator. *Respir Care* 1991; 36:952.
10. Rubilar L, Castro-Rodriguez JA, Girardi G: Randomized trial of salbutamol via metered-dose inhaler with spacer versus nebulizer for acute wheezing in children less than 2 years of age. *Pediatr Pulmonol* 2000; 29:264.
11. Amirav I, Newhouse MT: Metered-dose inhaler accessory devices in acute asthma: Efficacy and comparison with nebulizers: A literature review. *Arch Pediatr Adolesc Med* 1997; 151:876.
12. Camargo C, Kennedy P: Assessing costs of aerosol therapy. *Respir Care* 2000; 45:756.
13. Dewar AL, Stewart A, Cogswell JJ, Connett GJ: A randomised controlled trial to assess the relative benefits of large volume spacers and nebulisers to treat acute asthma in hospital. *Arch Dis Child* 1999; 80:421.
14. Leversha AM, Campanella SG, Aickin RP, Asher MI: Costs and effectiveness of spacer versus nebulizer in young children with moderate and severe acute asthma. *J Pediatr* 2000; 136:497.
15. Doan Q, Shefrin A, Johnson D: Cost-effectiveness of metered-dose inhalers for asthma exacerbations in the pediatric emergency department. *Pediatrics* 2011; 127:e1105.
16. Castro-Rodriguez JA, Rodrigo GJ: Beta-agonists through metered-dose inhaler with valved holding chamber versus nebulizer for acute exacerbation of wheezing or asthma in children under 5 years of age: A systematic review with meta-analysis. *J Pediatr* 2004; 145:172.
17. Cates CJ, Crilly JA, Rowe BH: Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev* 2006; 2:CD000052.
18. Freelander M, Van Asperen PP: Nebuhaler versus nebuliser in children with acute asthma. *BMJ (Clin Res Ed)* 1984; 288:1873.
19. Lee N, et al: Comparison of efficacy and safety of albuterol administered by power-driven nebulizer (PDN) versus metered-dose inhaler (MDI) with Aerochamber and mask in young children with asthma. *J Allergy Clin Immunol* 1991; 87:307.
20. Parkin PC, et al: Randomised trial spacer vs nebuliser for acute asthma. *Arch Dis Child* 1995; 72:239.
21. Williams JR, Bothner JP, Swanton RD: Delivery of albuterol in a pediatric emergency department. *Pediatr Emerg Care* 1996; 12:263.
22. Ploin D, et al: High-dose albuterol by metered-dose inhaler plus a spacer device versus nebulization in preschool children with recurrent wheezing: A double-blind, randomized equivalence trial. *Pediatrics* 2000; 106(Pt 1):311.
23. Wildhaber JH, et al: Inhalation therapy in asthma: Nebulizer or pressurized metered-dose inhaler with holding chamber? In vivo comparison of lung deposition in children. *J Pediatr* 1999; 135:28.
24. Dolovich MB, et al: Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest* 2005; 127:335.
25. Schuh S, et al: High-versus low-dose, frequently administered, nebulized albuterol in children with severe, acute asthma. *Pediatrics* 1989; 83:513.
26. Schuh S, et al: Nebulized albuterol in acute childhood asthma: Comparison of two doses. *Pediatrics* 1990; 86:509.
27. Mazzoni L, Naef R, Chapman ID, Morley J: Hyperresponsiveness of the airways following exposure of guinea pigs to racemic mixtures and distomers of $beta_2$-selective sympathomimetics. *Pulm Pharmacol* 1994; 7:367.
28. Johansson F, Rydberg I, Aberg G, Andersson RG: Effects of albuterol enantiomers on in vitro bronchial reactivity. *Clin Rev Allergy Immunol* 1996; 14:57.
29. Templeton AG, et al: Effects of *S*-salbutamol on human isolated bronchus. *Pulm Pharmacol Ther* 1998; 11:1.
30. Volcheck GW, Gleich GJ, Kita H: Pro- and anti-inflammatory effects of beta adrenergic agonists on eosinophil response to IL-5. *J Allergy Clin Immunol* 1998; 101(Suppl):35.
31. Leff AR, et al: Effect of enantiomeric forms of albuterol on stimulated secretion of granular protein from human eosinophils. *Pulm Pharmacol Ther* 1997; 10:97.
32. Yamaguchi H, McCullough JR: *S*-Albuterol exacerbates calcium responses to carbachol in airway smooth muscle cells. *Clin Rev Allergy Immunol* 1996; 14:47.
33. Mitra S, et al: (*S*)-Albuterol increases intracellular free calcium by muscarinic receptor activation and a phospholipase C–dependent mechanism in airway smooth muscle. *Mol Pharmacol* 1998; 53:347.
34. Dhand R, et al: Preferential pulmonary retention of (*S*)-albuterol after inhalation of racemic albuterol. *Am J Respir Crit Care Med* 1999; 160:1136.
35. Lipworth BJ, Clark DJ, Koch P, Arbeeny C: Pharmacokinetics and extrapulmonary β_2 adrenoceptor activity of nebulised racemic salbutamol and its *R* and *S* isomers in healthy volunteers. *Thorax* 1997; 52:849.
36. Cockcroft DW, Swystun VA: Effect of single doses of *S*-salbutamol, *R*-salbutamol, racemic salbutamol, and placebo on the airway response to methacholine. *Thorax* 1997; 52:845.
37. Carl JC, Myers TR, Kirchner HL, Kercsmar CM: Comparison of racemic albuterol and levalbuterol for treatment of acute asthma. *J Pediatr* 2003; 143:731.
38. Qureshi F, et al: Clinical efficacy of racemic albuterol versus levalbuterol for the treatment of acute pediatric asthma. *Ann Emerg Med* 2005; 46:29.
39. Hardasmalani MD, DeBari V, Bithoney WG, Gold N: Levalbuterol versus racemic albuterol in the treatment of acute exacerbation of asthma in children. *Pediatr Emerg Care* 2005; 21:415.
40. Ralston ME, et al: Comparison of levalbuterol and racemic albuterol combined with ipratropium bromide in acute pediatric asthma: A randomized controlled trial. *J Emerg Med* 2005; 29:29.
41. Andrews T, et al: High-dose continuous nebulized levalbuterol for pediatric status asthmaticus: A randomized trial. *J Pediatr* 2009; 155:205.
42. Brenner BE, Chavda KK, Camargo CA Jr: Randomized trial of inhaled flunisolide versus placebo among asthmatic patients discharged from the emergency department. *Ann Emerg Med* 2000; 36:417.
43. Rowe BH, et al: Inhaled budesonide in addition to oral corticosteroids to prevent asthma relapse following discharge from the emergency department: A randomized controlled trial. *JAMA* 1999; 281:2119.
44. Edmonds ML, et al: Inhaled steroids in acute asthma following emergency department discharge. *Cochrane Database Syst Rev* 2000; 3:CD002316.
45. Scarfone RJ, Zorc JJ, Angsuco CJ: Emergency physicians' prescribing of asthma controller medications. *Pediatrics* 2006; 117:821.
46. Guilbert TW, et al: Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006; 354:1985.
47. Childhood Asthma Management Program Research Group: Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000; 343:1054.
48. Qureshi F, Pestian J, Davis P, Zaritsky A: Effect of nebulized ipratropium on the hospitalization rates of children with asthma. *N Engl J Med* 1998; 339:1030.
49. Schuh S, et al: Efficacy of frequent nebulized ipratropium bromide added to frequent high-dose albuterol therapy in severe childhood asthma. *J Pediatr* 1995; 126:639.
50. Rodrigo GJ, Castro-Rodriguez JA: Anticholinergics in the treatment of children and adults with acute asthma: A systematic review with meta-analysis. *Thorax* 2005; 60:740.
51. Littenberg B, Gluck EH: A controlled trial of methylprednisolone in the emergency treatment of acute asthma. *N Engl J Med* 1986; 314:150.
52. Tal A, Levy N, Bearman JE: Methylprednisolone therapy for acute asthma in infants and toddlers: A controlled clinical trial. *Pediatrics* 1990; 86:350.

www.ketabpezeshki.com 66485457-66963820

53. Rachelefsky G: Treating exacerbations of asthma in children: The role of systemic corticosteroids. *Pediatrics* 2003; 112:382.
54. Rowe BH, et al: Corticosteroid therapy for acute asthma. *Respir Med* 2004; 98:275.
55. Rowe BH, et al: Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane Database Syst Rev* 2001; 1:CD002178.
56. Scarfone RJ, Friedlaender E: Corticosteroids in acute asthma: Past, present, and future. *Pediatr Emerg Care* 2003; 19:355.
57. Barnett PL, Caputo GL, Baskin M, Kuppermann N: Intravenous versus oral corticosteroids in the management of acute asthma in children. *Ann Emerg Med* 1997; 29:212.
58. Harrison BD, et al: Need for intravenous hydrocortisone in addition to oral prednisolone in patients admitted to hospital with severe asthma without ventilatory failure. *Lancet* 1986; 1:181.
59. Ratto D, et al: Are intravenous corticosteroids required in status asthmaticus? *JAMA* 1988; 260:527.
60. Qureshi F, Zaritsky A, Poirier MP: Comparative efficacy of oral dexamethasone versus oral prednisone in acute pediatric asthma. *J Pediatr* 2001; 139:20.
61. Scarfone RJ, et al: Nebulized dexamethasone versus oral prednisone in the emergency treatment of asthmatic children. *Ann Emerg Med* 1995; 26:480.
62. Devidayal SS, Singhi S, Kumar L, Jayshree M: Efficacy of nebulized budesonide compared to oral prednisolone in acute bronchial asthma. *Acta Paediatr* 1999; 88:835.
63. Schuh S, et al: A comparison of inhaled fluticasone and oral prednisone for children with severe acute asthma. *N Engl J Med* 2000; 343:689.
64. Klassen TP, et al: The efficacy of nebulized budesonide in dexamethasone-treated outpatients with croup. *Pediatrics* 1996; 97:463.
65. Macias CG, Felner EI, Gan V: Inhaled corticosteroids may be superior to systemic corticosteroids in children with moderate-to-severe acute asthma. *Pediatr Asthma Allergy Immunol* 2003; 16:121.
66. Edmonds ML, Camargo CA Jr, Pollack CV Jr, Rowe BH: The effectiveness of inhaled corticosteroids in the emergency department treatment of acute asthma: A meta-analysis. *Ann Emerg Med* 2002; 40:145.
67. Edmonds ML, Camargo CA Jr, Pollack CV Jr, Rowe BH: Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. *Cochrane Database Syst Rev* 2003; 3:CD002308.
68. Rodrigo GJ: Rapid effects of inhaled corticosteroids in acute asthma: An evidence-based evaluation. *Chest* 2006; 130:1301.
69. Khine H, Fuchs SM, Saville AL: Continuous vs intermittent nebulized albuterol for emergency management of asthma. *Acad Emerg Med* 1996; 3:1019.
70. Camargo CA Jr, Spooner CH, Rowe BH: Continuous versus intermittent beta-agonists in the treatment of acute asthma. *Cochrane Database Syst Rev* 2003; 4:CD001115.
71. Papo MC, Frank J, Thompson AE: A prospective, randomized study of continuous versus intermittent nebulized albuterol for severe status asthmaticus in children. *Crit Care Med* 1993; 21:1479.
72. Katz RW, et al: Safety of continuous nebulized albuterol for bronchospasm in infants and children. *Pediatrics* 1993; 92:666.
73. Rudnitsky GS, et al: Comparison of intermittent and continuously nebulized albuterol for treatment of asthma in an urban emergency department. *Ann Emerg Med* 1993; 22:1842.
74. Lin RY, et al: Continuous versus intermittent albuterol nebulization in the treatment of acute asthma. *Ann Emerg Med* 1993; 22:1847.
75. Kelly AM, Kerr D, Powell C: Is severity assessment after one hour of treatment better for predicting the need for admission in acute asthma? *Respir Med* 2004; 98:777.
76. Stevenson MD, Ruddy RM: *Asthma and allergic emergencies*. In: Fleisher GR, Ludwig S, eds: *Textbook of Pediatric Emergency Medicine*, 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2006:1067.
77. Rowe BH, et al: Intravenous magnesium sulfate treatment for acute asthma in the emergency department: A systematic review of the literature. *Ann Emerg Med* 2000; 36:181.
78. Cheuk DK, Chau TC, Lee SL: A meta-analysis on intravenous magnesium sulphate for treating acute asthma. *Arch Dis Child* 2005; 90:74.
79. Ciarallo L, Sauer AH, Shannon MW: Intravenous magnesium therapy for moderate to severe pediatric asthma: Results of a randomized, placebo-controlled trial. *J Pediatr* 1996; 129:809.
80. Ciarallo L, Brousseau D, Reinert S: Higher-dose intravenous magnesium therapy for children with moderate to severe acute asthma. *Arch Pediatr Adolesc Med* 2000; 154:979.
81. Scarfone RJ, et al: A randomized trial of magnesium in the emergency department treatment of children with asthma. *Ann Emerg Med* 2000; 36:572.
82. Scarfone RJ: Use of magnesium sulfate in the treatment of children with acute asthma. *Clin Pediatr Emerg Med* 1999; 1:6.
83. Travers A, et al: Intravenous beta$_2$-agonists for acute asthma in the emergency department. *Cochrane Database Syst Rev* 2001; 2:CD002988.
84. Browne GJ, Penna AS, Phung X, Soo M: Randomised trial of intravenous salbutamol in early management of acute severe asthma in children. *Lancet* 1997; 349:301.
85. Kim IK, et al: Helium/oxygen-driven albuterol nebulization in the treatment of children with moderate to severe asthma exacerbations: A randomized, controlled trial. *Pediatrics* 2005; 116:1127.
86. Rodrigo G, Pollack C, Rodrigo C, Rowe BH: Heliox for nonintubated acute asthma patients. *Cochrane Database Syst Rev* 2006; 4:CD002884.
87. Mansbach JM, Emond JA, Camargo CA Jr: Bronchiolitis in US emergency departments 1992 to 2000: Epidemiology and practice variation. *Pediatr Emerg Care* 2005; 21:242.
88. Johnson DW, et al: Differences in admission rates of children with bronchiolitis by pediatric and general emergency departments. *Pediatrics* 2002; 110:e49.
89. Pelletier AJ, Mansbach JM, Camargo CA Jr: Direct medical costs of bronchiolitis hospitalizations in the United States. *Pediatrics* 2006; 118:2418.
90. Liu LL, et al: Asthma and bronchiolitis hospitalizations among American Indian children. *Arch Pediatr Adolesc Med* 2000; 154:991.
91. Shay DK, et al: Bronchiolitis-associated hospitalizations among US children, 1980-1996. *JAMA* 1999; 282:1440.
92. Coffin SE: Bronchiolitis: In-patient focus. *Pediatr Clin North Am* 2005; 52:1047.
93. Shay DK, et al: Bronchiolitis-associated mortality and estimates of respiratory syncytial virus–associated deaths among US children, 1979-1997. *J Infect Dis* 2001; 183:16.
94. Holman RC, et al: Risk factors for bronchiolitis-associated deaths among infants in the United States. *Pediatr Infect Dis J* 2003; 22:483.
95. Chatzimichael A, et al: The role of breastfeeding and passive smoking on the development of severe bronchiolitis in infants. *Minerva Pediatr* 2007; 59:199.
96. Henrickson KJ, Hoover S, Kehl KS, Hua W: National disease burden of respiratory viruses detected in children by polymerase chain reaction. *Pediatr Infect Dis J* 2004; 23(Suppl):11.
97. Williams JV, et al: Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. *N Engl J Med* 2004; 350:443.
98. Smyth RL, Openshaw PJ: Bronchiolitis. *Lancet* 2006; 368:312.
99. Korppi M, et al: Rhinovirus-associated wheezing in infancy: Comparison with respiratory syncytial virus bronchiolitis. *Pediatr Infect Dis J* 2004; 23:995.
100. van den Hoogen BG, et al: A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nat Med* 2001; 7:719.
101. van den Hoogen BG, et al: Prevalence and clinical symptoms of human metapneumovirus infection in hospitalized patients. *J Infect Dis* 2003; 188:1571.
102. Black CP: Systematic review of the biology and medical management of respiratory syncytial virus infection. *Respir Care* 2003; 48:209.
103. Dakhama A, Lee YM, Gelfand EW: Virus-induced airway dysfunction: Pathogenesis and biomechanisms. *Pediatr Infect Dis J* 2005; 24(Suppl):159.
104. El-Radhi AS, Barry W, Patel S: Association of fever and severe clinical course in bronchiolitis. *Arch Dis Child* 1999; 81:231.
105. Klassen TP, et al: Dexamethasone in salbutamol-treated inpatients with acute bronchiolitis: A randomized, controlled trial. *J Pediatr* 1997; 130:191.
106. Richter H, Seddon P: Early nebulized budesonide in the treatment of bronchiolitis and the prevention of postbronchiolitic wheezing. *J Pediatr* 1998; 132:849.
107. Swingler GH, Hussey GD, Zwarenstein M: Duration of illness in ambulatory children diagnosed with bronchiolitis. *Arch Pediatr Adolesc Med* 2000; 154:997.
108. Purcell K, Fergie J: Concurrent serious bacterial infections in 2396 infants and children hospitalized with respiratory syncytial virus lower respiratory tract infections. *Arch Pediatr Adolesc Med* 2002; 156:322.
109. Kuppermann N, et al: Risks for bacteremia and urinary tract infections in young febrile children with bronchiolitis. *Arch Pediatr Adolesc Med* 1997; 151:1207.

www.ketabpezeshki.com 66485457-66963820

110. Levine DA, et al: Risk of serious bacterial infection in young febrile infants with respiratory syncytial virus infections. *Pediatrics* 2004; 113:1728.
111. Titus MO, Wright SW: Prevalence of serious bacterial infections in febrile infants with respiratory syncytial virus infection. *Pediatrics* 2003; 112:282.
112. Willwerth BM, Harper MB, Greenes DS: Identifying hospitalized infants who have bronchiolitis and are at high risk for apnea. *Ann Emerg Med* 2006; 48:441.
113. Vogel AM, et al: Variations in bronchiolitis management between five New Zealand hospitals: Can we do better? *J Paediatr Child Health* 2003; 39:40.
114. Gomez R, Colas C, Sebastian A, Arribas J: Respiratory repercussions in adults with a history of infantile bronchiolitis. *Ann Allergy Asthma Immunol* 2004; 93:447.
115. Hyvarinen M, Piippo-Savolainen E, Korhonen K, Korppi M: Teenage asthma after severe infantile bronchiolitis or pneumonia. *Acta Paediatr* 2005; 94:1378.
116. Sznajder M, et al: Respiratory development of 5- to 6-year-old children experiencing a first bronchiolitis episode before age one. *Eur Ann Allergy Clin Immunol* 2005; 37:392.
117. Piippo-Savolainen E, Korppi M, Korhonen K, Remes S: Adult asthma after non–respiratory syncytial virus bronchiolitis in infancy: Subgroup analysis of the 20-year prospective follow-up study. *Pediatr Int* 2007; 49:190.
118. Christakis DA, et al: Variation in inpatient diagnostic testing and management of bronchiolitis. *Pediatrics* 2005; 115:878.
119. Swingler GH, Hussey GD, Zwarenstein M: Randomised controlled trial of clinical outcome after chest radiograph in ambulatory acute lower-respiratory infection in children. *Lancet* 1998; 351:404.
120. Schuh S, et al: Evaluation of the utility of radiography in acute bronchiolitis. *J Pediatr* 2007; 150:429.
121. American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis: Diagnosis and management of bronchiolitis. *Pediatrics* 2006; 118:1774.
122. Plint AC, et al: Practice variation among pediatric emergency departments in the treatment of bronchiolitis. *Acad Emerg Med* 2004; 11:353.
123. Brand PL, Vaessen-Verberne AA: Differences in management of bronchiolitis between hospitals in The Netherlands. Dutch Paediatric Respiratory Society. *Eur J Pediatr* 2000; 159:343.
124. Willson DF, et al: Effect of practice variation on resource utilization in infants hospitalized for viral lower respiratory illness. *Pediatrics* 2001; 108:851.
125. Perlstein PH, et al: Evaluation of an evidence-based guideline for bronchiolitis. *Pediatrics* 1999; 104:1334.
126. Perlstein PH, et al: Sustaining the implementation of an evidence-based guideline for bronchiolitis. *Arch Pediatr Adolesc Med* 2000; 154:1001.
127. Kotagal UR, et al: Impact of a bronchiolitis guideline: A multisite demonstration project. *Chest* 2002; 121:1789.
128. Todd J, Bertoch D, Dolan S: Use of a large national database for comparative evaluation of the effect of a bronchiolitis/viral pneumonia clinical care guideline on patient outcome and resource utilization. *Arch Pediatr Adolesc Med* 2002; 156:1086.
129. Gadomski AM, Bhasale AL: Bronchodilators for bronchiolitis. *Cochrane Database Syst Rev* 2006; 3:CD001266.
130. Hartling L, et al: Epinephrine for bronchiolitis. *Cochrane Database Syst Rev* 2004; 1:CD003123.
131. Wainwright C, et al: A multicenter, randomized, double-blind, controlled trial of nebulized epinephrine in infants with acute bronchiolitis. *N Engl J Med* 2003; 349:27.
132. Naspitz CK, Sole D: Treatment of acute wheezing and dyspnea attacks in children under 2 years old: Inhalation of fenoterol plus ipratropium bromide versus fenoterol. *J Asthma* 1992; 29:253.
133. Schuh S, et al: Efficacy of adding nebulized ipratropium bromide to nebulized albuterol therapy in acute bronchiolitis. *Pediatrics* 1992; 90:920.
134. Everard ML, et al: Anticholinergic drugs for wheeze in children under the age of two years. *Cochrane Database Syst Rev* 2005; 3:CD001279.
135. Elkins MR, et al: A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med* 2006; 354:229.
136. Kuzik BA, et al: Nebulized hypertonic saline in the treatment of viral bronchiolitis in infants. *J Pediatr* 2007; 151:266.
137. Grewal S, et al: A randomized trial of nebulized 3% hypertonic saline with epinephrine in the treatment of acute bronchiolitis in the emergency department. *Arch Pediatr Adolesc Med* 2009; 163:1007.
138. Perrotta C, Ortiz Z, Roque M: Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. *Cochrane Database Syst Rev* 2007; 1:CD004873.
139. Corneli HM, et al: A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *N Engl J Med* 2007; 357:331.
140. Patel H, Platt R, Lozano JM, Wang EE: Glucocorticoids for acute viral bronchiolitis in infants and young children. *Cochrane Database Syst Rev* 2004; 3:CD004878.
141. Plint AC, et al: Epinephrine and dexamethasone in children with bronchiolitis. *N Engl J Med* 2009; 360:2079.
142. Blom D, et al: Inhaled corticosteroids during acute bronchiolitis in the prevention of post-bronchiolitic wheezing. *Cochrane Database Syst Rev* 2007; 1:CD004881.
143. Thorburn K, et al: High incidence of pulmonary bacterial co-infection in children with severe respiratory syncytial virus (RSV) bronchiolitis. *Thorax* 2006; 61:611.
144. Tahan F, Ozcan A, Koc N: Clarithromycin in the treatment of RSV bronchiolitis: A double-blind, randomised, placebo-controlled trial. *Eur Respir J* 2007; 29:91.
145. Spurling GK, Fonseka K, Doust J, Del Mar C: Antibiotics for bronchiolitis in children. *Cochrane Database Syst Rev* 2007; 1:CD005189.
146. Ventre K, Randolph AG: Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. *Cochrane Database Syst Rev* 2007; 1:CD000181.
147. Fuller H, Del Mar C: Immunoglobulin treatment for respiratory syncytial virus infection. *Cochrane Database Syst Rev* 2006; 4:CD004883.
148. Feltes TF, et al: Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *J Pediatr* 2003; 143:532.
149. IMpact–RSV Study Group: Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* 1998; 102(Pt 1):531.
150. Parnes C, et al: Palivizumab prophylaxis of respiratory syncytial virus disease in 2000-2001: Results from the Palivizumab Outcomes Registry. *Pediatr Pulmonol* 2003; 35:484.
151. Romero JR: Palivizumab prophylaxis of respiratory syncytial virus disease from 1998 to 2002: Results from four years of palivizumab usage. *Pediatr Infect Dis J* 2003; 22(Suppl):46.
152. American Academy of Pediatrics: *Respiratory syncytial virus*. In: Pickering LK, Baker CJ, Long SS, McMillan JA, eds: *Red Book: 2006 Report of the Committee on Infectious Diseases*, 27th ed. Elk Grove, Ill: American Academy of Pediatrics; 2006:560-566.
153. Purcell K, Fergie J: Driscoll Children's Hospital respiratory syncytial virus database: Risk factors, treatment and hospital course in 3308 infants and young children, 1991 to 2002. *Pediatr Infect Dis J* 2004; 23:418.

www.ketabpezeshki.com 66485457-66963820

Chapter 170

Pediatric Respiratory Emergencies: Disease of the Lungs

David M. Stocker

PNEUMONIA

Perspective

Background

Acute infections of the respiratory tract are among the most common infections in children and one of the most common reasons for a visit to the emergency department. Although most of these infections involve the upper respiratory tract, physicians caring for children in the emergency department frequently encounter lower respiratory infections, most notably bronchiolitis and pneumonia. Bronchiolitis is primarily seen in children younger than 2 years and is defined as wheezing and congestion due to a viral or bacterial lung infection. Pneumonia is an inflammation of the lung tissue and is most often due to an infection but occasionally may follow a noninfectious insult. Although the diagnosis of pneumonia may be suggested by clinical signs and symptoms, pneumonia is diagnosed by an abnormal chest radiograph showing pulmonary infiltrates. The clinical picture of pneumonia is highly variable and may range from a mild illness to life-threatening disease. Given the wide variety of agents that can cause pneumonia and the limitations of diagnostic testing, determination of a precise etiologic diagnosis may be difficult. Clinical, laboratory, and radiographic findings sometimes suggest a specific organism, but the definitive etiology often remains unknown.

Epidemiology

Infection rates for pneumonia in children vary inversely with age, averaging 40 per 1000 in preschool-age children and decreasing gradually to 7 per 1000 in 12- to 15-year-olds, with a male predominance of 2:1. Three fourths of all deaths from pneumonia result from bacterial infections.

The causative organisms also vary with the age of the child. Because the organism is not definitively identified in most pneumonia cases, it is difficult to determine the true incidence of the specific etiologic agents.[1] Overall, it has been estimated that viral agents cause 60 to 90% of pneumonias.[2] Viral agents are more common in younger children. Bacteria predominate in neonates but are a less frequent causative agent in toddlers and older children. Outside of the neonatal period, the incidence of bacterial agents is stable throughout different age groups.[2] Mixed viral and bacterial infections or concomitant bacterial infections may occur in one third of pneumonias.[2,3] *Chlamydia trachomatis* is a unique cause of pneumonia in infants 3 to 19 weeks old. *Bordetella pertussis* classically occurs in children younger than 1 year but also occurs in older children and adolescents.[4,5] *Mycoplasma pneumoniae* is one of the most common causes of pneumonia among children older than 5 years and may play a role in younger children.[6,7] *Chlamydia pneumoniae* is more often seen in children older than 5 years but also may cause infection in younger children.[7,8]

Among bacteria, group B streptococci and gram-negative bacilli predominate in neonates. *Ureaplasma urealyticum* and *Listeria monocytogenes* may cause illness in infants younger than 3 months.[1] *Streptococcus pneumoniae* is the leading bacterial cause of pneumonia in all age groups beyond the newborn period; *Haemophilus influenzae* and *Staphylococcus aureus* are less common etiologic agents, most often seen in the first years of life. The incidence of *H. influenzae* type b disease has decreased by 90% since the onset of immunization of infants and young children.[9] The heptavalent pneumococcal conjugate vaccine Prevnar (Lederle Laboratories/Wyeth-Ayerst Pharmaceuticals, Wayne, N.J.) was licensed by the U.S. Food and Drug Administration in 2000 and is recommended as a primary series at 2, 4, and 6 months of age, with a fourth booster dose given at 12 to 15 months of age. Clinical trials suggested 85% protection against serotype-specific cases of bacteremic pneumonia.[10] Studies have also shown a decrease in carriage rates of the serotypes included in the daycare setting.[11] Pneumococcal polysaccharide vaccines have been recommended for children older than 2 years at high risk for pneumococcal disease since 1985, but they are not immunogenic in younger patients. Pneumococcal vaccine has also been shown to provide some protection against viral pneumonia. One study found a 31% reduction in the incidence of pneumonia associated with seven respiratory viruses in hospitalized children. This may be because viral pneumonia in hospitalized children is often associated with concurrent pneumococcal infection.[12] Other, less common bacterial agents include group A streptococci, *Neisseria meningitidis,* and anaerobic bacteria, the last being particularly common in the setting of aspiration pneumonia. Unusual causes of pneumonia include *Pseudomonas aeruginosa, Legionella pneumophila, Pneumocystis jiroveci,* and rickettsial infections. The incidence of *Mycobacterium tuberculosis* is increasing in the United States, particularly in urban and low-income areas and among nonwhite racial or ethnic groups. Infants and adolescents are at highest risk in the United States.

Respiratory syncytial virus (RSV) and parainfluenza are the most frequent viral agents in infants younger than 1 year. Viruses that may be responsible for neonatal pneumonia include rubella, cytomegalovirus (CMV), and herpes simplex virus. Other viral agents include influenza, adenovirus, rhinovirus, enterovirus, measles, varicella, and Epstein-Barr virus. The immunocompromised host is susceptible to all these causes of pneumonia and mixed and opportunistic infections, including bacterial, viral (CMV, varicella), protozoan (*P. jiroveci*), and fungal disease.

www.ketabpezeshki.com 66485457-66963820

Principles of Disease

Pathophysiology

The lung is protected from infection by a variety of local and systemic immune mechanisms. Passively acquired maternal antibodies are important in protection against *S. pneumoniae* and *H. influenzae* infections during the first few months of life. Children with altered protective mechanisms are at increased risk for development of pneumonia; this includes children with congenital anatomic abnormalities (cleft palate, tracheoesophageal fistulas, pulmonary sequestration, congenital cystic adenomatoid malformation), immune deficiencies, neurologic alterations that predispose to aspiration (coma, seizures, cerebral palsy, general anesthesia), and alterations in quality of secreted mucus (cystic fibrosis [CF]).

Bacterial pneumonia and mycoplasmal infections are transmitted most often person to person by droplet aspiration. Asymptomatic upper airway colonization often occurs in children and may spread infection to other children.[13] Less commonly, bacterial pneumonia also may result from hematogenous spread from a distant focus or during primary bacteremia. Viral agents that cause pneumonia proliferate in the upper respiratory tract and spread contiguously to involve the lower respiratory tract. Viruses such as varicella, CMV, herpes simplex, Epstein-Barr, measles, and rubella also may infect the lung through hematogenous spread.

Clinical Features

Symptoms and Signs

History. Clinical symptoms and signs of pneumonia in pediatric patients vary with the age of the patient, specific pathogen, and severity of the disease. Infants younger than 3 months generally have respiratory symptoms, such as tachypnea, cough, retractions, and grunting, but may show only nonlocalizing symptoms, such as isolated fever or hypothermia, vomiting, poor feeding, irritability, and lethargy. Toddlers with *S. pneumoniae* infection may have nonspecific symptoms, such as high fever and lethargy, without respiratory symptoms. In general, with increasing age, signs and symptoms in children become more specific and are manifestations of generalized infection, lower respiratory tract disease, and associated extrapulmonary disease, although pneumonia in any child may have only a few or subtle manifestations. General symptoms related to the infection include fever and chills, headache, rigors, and malaise. Symptoms of lower respiratory tract disease may include cough and wheezing. Pleural irritation may cause chest, abdominal, or neck pain or result in neck stiffness. Vomiting or poor oral intake can be seen with pneumonia of any cause and may imply more severe disease or dehydration.

Other important points that should be elicited in the history include birth and immunization history (particularly pneumococcal and *H. influenzae* type b vaccination), sickle cell status, history of previous pneumonia or frequent infections, and presence of underlying chronic disease. Children with known respiratory (e.g., bronchopulmonary dysplasia or CF) or cardiac disease tend to have more severe courses of illness; children with primary or acquired immune deficiencies are also prone to more severe and fulminant disease from common, uncommon, and opportunistic pathogens.

Physical Examination. Physical examination of a child with suspected pneumonia should begin by noting the general appearance and breathing pattern. Vital signs, including oxygen saturation, also should be evaluated on arrival. Important findings include toxicity, level of alertness and interaction, color, and state of hydration and perfusion. Fever most often is present with bacterial pneumonia but may be low grade or absent in neonates and patients with nonbacterial disease. Cardiovascular parameters may indicate dehydration or, rarely, shock. Tachypnea, although not universal, is the most sensitive indicator of pneumonia and may be the only manifestation in a young child.[14] The World Health Organization has published guidelines for the clinical diagnosis of pneumonia in developing countries and cites tachypnea and retractions as indicators of lower respiratory disease. Tachypnea is defined by the World Health Organization as a respiratory rate of more than 50 breaths/minute in infants younger than 1 year and more than 40 breaths/minute in children older than 1 year.[15] Other manifestations of lower airway disease may include cough, wheezing, nasal flaring, retractions, grunting, and use of accessory muscles. The characteristics of the cough may aid in the diagnosis; a staccato and paroxysmal cough in an infant may indicate pneumonia caused by *C. trachomatis* or *B. pertussis*. A hacking quality is often present with *Mycoplasma* infection. Auscultatory examination of an older child may reveal rales, wheezing, and diminished breath sounds, often with dullness to percussion and associated decreased fremitus. Although these findings may be present, the clinical findings are much less consistent in a younger child; rales may be masked by poor inspiratory effort or noisy upper airway sounds.

Pleural irritation may cause abdominal tenderness or meningismus, and pulmonary hyperinflation may cause downward displacement of the liver and spleen. Extrapulmonary findings may include rhinorrhea, pharyngitis, stridor, or exanthems with viral infections; conjunctivitis with chlamydial disease; pharyngitis and exanthems with mycoplasmal pneumonia; or extrapulmonary infections, such as soft tissue abscesses, otitis media, sinusitis, meningitis, and pericarditis, with bacterial pathogens.

Specific Disorders

Bacterial Pneumonia

Perspective. *S. pneumoniae* is one of the most frequently seen bacterial agents causing pneumonia in children.[12] Whereas any child can acquire *S. pneumoniae*, children at increased risk for development of infection from *S. pneumoniae* are children with immune deficiency, chronic renal disease, or functional or anatomic asplenia and Native Americans.[10] *S. aureus* pneumonia, although less common, tends to cause a more severe pneumonia; more than 70% of all cases occur in the first year of life.[16] Children with foreign body aspiration, immunosuppression, or skin infections may be at increased risk for *S. aureus* pneumonia. Progression of the disease is rapid, and empyema (90%), pneumatocele (50%), pneumothorax (25%), and bacteremia are common complications (Fig. 170-1). In contrast to classically described methicillin-resistant *S. aureus*, which is typically broadly resistant and nosocomially acquired, this agent is resistant to fewer antibiotics.[17]

Before widespread immunization, *H. influenzae* was the second most common bacterial cause of pneumonia. However, its incidence has decreased by 90% since the onset of effective immunization, and it is rarely seen presently.[9] *H. influenzae* previously was considered a disease of younger children, but most cases now occur in older children.[18] Although it is often clinically indistinguishable from *S. pneumoniae* pneumonia, *H. influenzae* pneumonia has a higher incidence of associated pleural effusions (25-75%) and bacteremia (75-95%).[19]

Although it is still uncommon, the incidence of group A streptococcal pneumonia may have increased since the 1980s. One study reported an increase in the incidence from 0.16 per 100,000 in 1992 to 0.35 per 100,000 in 1999 in Canada, whereas another study suggested stable rates since the 1980s.[19,20] Group A streptococcal pneumonia may occur sporadically and may be a complication of varicella.[19] It is typically a severe illness with abrupt onset,

www.ketabpezeshki.com 66485457-66963820

Figure 170-1. Radiograph shows staphylococcal pneumonia with empyema and abscess on right. (Courtesy Brianna Enriquez, MD, and Marianne Gausche-Hill, MD.)

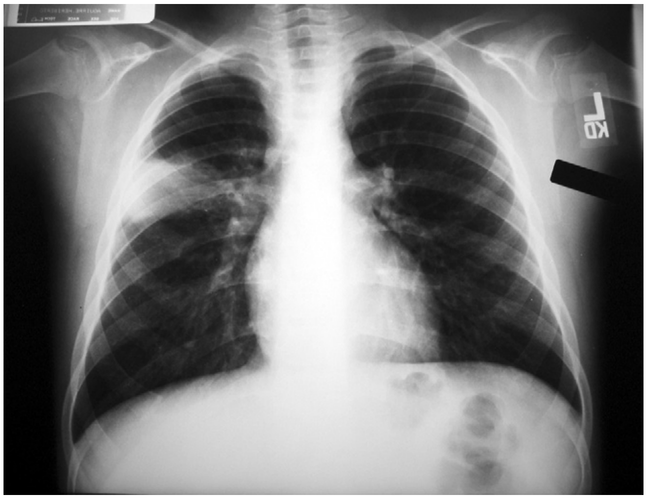


Figure 170-2. Radiograph shows pneumococcal pneumonia with infiltrate in right upper lobe. (Courtesy Marianne Gausche-Hill, MD.)

rapid progression to toxicity, and high fatality rate (30-60% fatality rate reported in a study of all ages).[19]

Clinical Features. Bacterial pneumonia beyond the neonatal period generally has a sudden onset, and fever is almost universal (temperature often above 39° C). Patients may or may not have a cough and often appear relatively toxic with tachypnea disproportionate to the fever. Confined rales or wheezes and localized decreased or tubular breath sounds commonly occur in older children, although the physical examination in a younger child may be completely unrevealing.

Diagnostic Considerations. Patients with pneumococcal infections often have a preceding dramatic presentation with high white blood cell (WBC) counts with associated pleural effusion and bacteremia in 10 to 30% of children.[21] Radiographic findings may show an alveolar infiltrate in a patchy or consolidated lobar (Fig. 170-2) or subsegmental distribution, although patients with bacterial pneumonia may have an interstitial infiltrate.[22] Bilateral involvement, pleural effusion, pneumatocele, and pneumothorax may occur with more severe disease. Although the WBC count may be normal with bacterial pneumonia, leukocytosis often occurs, sometimes exceeding 20,000/mm^3. Uncomplicated bacterial pneumonia often has a rapid response to institution of appropriate antibiotics; a stagnant or worsening clinical picture should prompt further investigation.

Management. Of particular concern is the emergence of resistance to penicillin and cephalosporins. At this time, it seems that the outcome of otherwise healthy children with pneumonia secondary to resistant pneumococcus may not differ significantly from the outcome of children with pneumonia secondary to penicillin-sensitive pneumococcus.[23] Pneumonia caused by *S. pneumoniae* may be complicated by empyema, pleural effusion, lung abscess, or necrotizing pneumonia. Since the 1990s, there seems to have been an increase in the incidence of such complications; one study noted an increase from 22.6% in 1994 to 53% in 1999 in children hospitalized with pneumococcal pneumonia.[56] It does not seem that this increased incidence is related to intermediate resistant organisms. It is unclear if highly resistant organisms play a role.[56] High-dose amoxicillin is recommended for initial outpatient treatment of suspected pneumococcal pneumonia in children younger than 4 years; a standard dose may be used in older children who are immunocompetent (Table 170-1). Children who appear well can be treated with oral antibiotics. In some cases, a dose of intravenous antibiotics followed by an oral prescription may be beneficial. One study reported decreased admission rates for children with *S. pneumoniae* given an initial intravenous dose of antibiotics followed by oral antibiotics.[56]

Viral Pneumonia

Viral pneumonia occurs more commonly in the winter and generally has a gradual onset during several days, often with associated cough, congestion, and low-grade fever. Tachypnea may be the only physical finding; however, retractions, rales, and wheezing are common, with grunting, cyanosis, lethargy, dehydration, and apnea apparent in more severely affected children. The diagnosis of viral pneumonia is often made clinically. A chest radiograph is usually not needed for diagnosis of a child with viral pneumonia who presents during the winter months with fever, cough, congestion, and wheezing. Rapid antigen testing is often used in the diagnosis of RSV infection or influenza A and B, but it is not highly sensitive. However, for cohorting of similar patients in the hospital or when the use of antivirals is being considered, definitive diagnosis may be helpful. Other viral agents may be diagnosed with culture of nasopharyngeal secretions. Although in the past the use of viral cultures was limited by the time required to grow viruses, improved culture techniques may yield results within 2 days and prove useful if a cause needs to be established.

The WBC count is variable but tends to be less than 15,000/mm^3 with lymphocyte predominance. Radiographic findings typically include hyperinflation and peribronchial thickening with diffuse increase in interstitial findings. Patchy areas of consolidation may be present, representing lobular atelectasis or alveolar pneumonia. Although lobar consolidation and small pleural effusions may occur in viral pneumonia, these findings are more consistent with a bacterial cause.

Most viral pneumonias resolve without specific therapy. Because of the likelihood of bacterial superinfection and the difficulty in differentiating between bacterial and viral pneumonia, antibiotics should be considered in a more severely ill child. Potential complications include dehydration, local progression of the disease, bronchiolitis obliterans, and apnea (most commonly in the first 3 months of life).[25]

www.ketabpezeshki.com 66485457-66963820

Table 170-1 Antibiotics for Treatment of Pediatric Pneumonia

AGE GROUP	AGENTS	OUTPATIENT TREATMENT	INPATIENT TREATMENT
0-12 weeks	Group B streptococcus Gram-negative bacilli (*Listeria monocytogenes*)		Ampicillin + cefotaxime *or* Ceftriaxone*
	Bordetella pertussis or *Chlamydia trachomatis*	Erythromycin estolate	Erythromycin estolate
12 weeks to preschool age	*Streptococcus pneumoniae* (*Haemophilus influenzae, Staphylococcus aureus,* group A streptococcus, *Neisseria meningitidis*)	Amoxicillin *or* Amoxicillin–clavulanic acid *or* Cefuroxime axetil *or* Azithromycin *or* Clarithromycin	Cefuroxime *or* Cefotaxime *or* Ceftriaxone *or* Clindamycin
	Mycoplasma pneumoniae or *Chlamydia pneumoniae*	Add erythromycin *or* Azithromycin *or* Clarithromycin	Add erythromycin (IV or PO) *or* Azithromycin (IV or PO) *or* Clarithromycin (PO)
	MRSA or critically ill		Add vancomycin
School age to adolescent	*Mycoplasma pneumoniae* or *Chlamydia pneumoniae*	Erythromycin *or* Azithromycin *or* Clarithromycin *or* Tetracycline (>8 years) or fluoroquinolone (>16 years)	Cefuroxime *or* Cefotaxime *or* Ceftriaxone *or* Clindamycin *and* Macrolide
	MRSA or critically ill		Add vancomycin

* Ceftriaxone is contraindicated in infants younger than 1 month.
MRSA, methicillin-resistant *Staphylococcus aureus.*

Mycoplasmal Pneumonia

Mycoplasmal pneumonia accounts for 10 to 20% of all pneumonias and has traditionally been thought to occur most commonly in 5- to 18-year-olds. It is now clear that it also may play a significant role in younger children but is still rare in infants younger than 1 year.[25] The onset is classically gradual and insidious, but some patients also may present with abrupt onset of symptoms similar to its bacterial counterpart.[4] Prodromal symptoms include fever, headache, and malaise, followed several days later by a nonproductive, hacking cough. Patients also may present with pertussis-like illness. Other symptoms of infection may include hoarseness, sore throat, and chest pain; coryza is unusual. Children with mycoplasmal pneumonia generally appear nontoxic. Patients may have rales; wheezing occurs less often. Pharyngitis, cervical lymphadenopathy, conjunctivitis, and otitis media may occur occasionally. Bullous myringitis, although rare, is believed to be indicative of *Mycoplasma*.[25] Rash is present in 10% of patients and may be urticarial, erythema multiforme, maculopapular, or vesicular.[26] The course may be complicated by pneumatocele, pleural effusion, pneumothorax, or bronchiectasis. *Mycoplasma,* typically thought to be a benign and self-limited infection, has been shown to play a significant role in exacerbation of asthma and may cause chronic pulmonary structural abnormalities.[4]

Physical findings generally are less impressive than the radiographic picture; involvement is usually unilateral and in the lower lobes. The radiographic findings are wide ranging, however, and may show lobar consolidation, scattered segmental infiltrates, or interstitial disease. Pleural effusions may occur but are uncommon. The WBC count is usually normal; the erythrocyte sedimentation rate tends to be elevated.

Laboratory diagnosis is problematic. Although it has been used in the past, bedside cold agglutination testing is a poor indication of infection, especially in patients younger than 12 years, and is rarely used today.[25] Infection often is diagnosed clinically and treated empirically. Diagnosis may be confirmed with acute and convalescent antibody titers; however, patients may take 4 to 6 weeks to seroconvert, and some patients may fail to mount an immune response.[4,26] Culture is not routinely available; polymerase chain reaction diagnosis at this time is available only from research laboratories.[4] Complications are varied but unusual and include hemolytic anemia, myopericarditis, neurologic disease (meningoencephalitis, Guillain-Barré syndrome, transverse myelitis, cranial neuropathy), rhabdomyolysis, arthritis, and rash.

Chlamydial Pneumonia

C. trachomatis is a common sexually transmitted organism causing cervical infection in 2 to 30% of pregnant women.[8] It can be transmitted from the genital tract of infected mothers to their newborn infants, resulting in conjunctivitis in 22 to 44% and pneumonia in 5 to 20%.[8] An infant with pneumonia caused by *C. trachomatis* presents at 3 to 19 weeks of age after colonization with the organism at birth. The illness usually begins with nasal congestion followed by cough. In half of the cases, conjunctivitis precedes the onset of respiratory symptoms. The infant is often afebrile and alert but tachypneic, with a repetitive staccato cough that may interfere with feeding or sleeping. It can resemble the paroxysms of pertussis and occasionally precipitates episodes of alarming respiratory distress. Mild retractions and diffuse inspiratory crepitant rales are noted on chest examination; expiratory wheezing is usually absent or minimal. Middle ear abnormalities are present in half of the cases.

The radiograph usually shows hyperinflation with bilateral and symmetrical diffuse interstitial infiltrates (Fig. 170-3). The total WBC count is usually normal but often with an eosinophilia of

www.ketabpezeshki.com 66485457-66963820

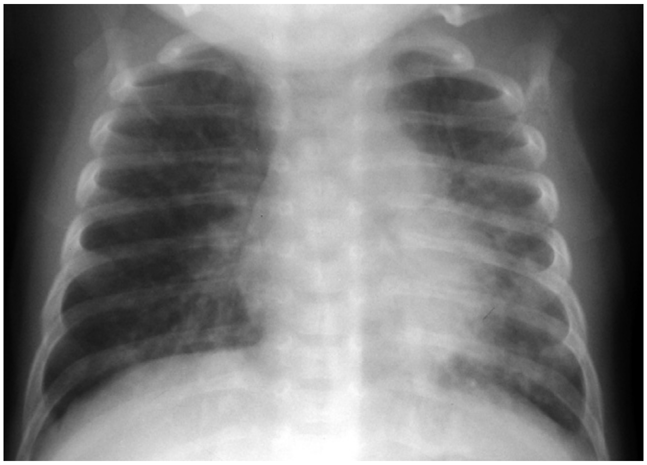


Figure 170-3. Radiograph shows chlamydial pneumonia in an infant. Note the symmetrical interstitial infiltrates. (Courtesy Michael Diament, MD.)

more than 400/mm^3.[8] Definitive diagnosis is made by isolation of the organism in the tissue culture specimen; diagnostic tests based on polymerase chain reaction are more sensitive than fluorescent antibody stain or tissue culture but may not be as specific. Although it is often a mild illness, chlamydial pneumonia may be complicated by apnea and hypoxemia. Treatment with erythromycin may shorten the course; however, the disease tends to be protracted, with cough and tachypnea often requiring weeks to clear despite the administration of antibiotics.

C. pneumoniae is a species of *Chlamydia* that is antigenically, genetically, and morphologically distinct from other *Chlamydia* species. *C. pneumoniae* infection is readily transmitted from person to person. *C. pneumoniae* may play a role in respiratory tract infections in infants and young children and may cause mild illness or asymptomatic infection in children and adults. Like *Mycoplasma, C. pneumoniae* may play a much greater role in pediatric pneumonia than was previously thought. It also commonly may be present as a mixed bacterial infection.[4] *C. pneumoniae* has been reported to cause sore throat, fever, headache, pertussis-like cough, pneumonia, and influenza-like illness.[27] Outbreaks have been reported in schools, daycare centers, military camps, adolescents, and families.[28] Infection with *C. pneumoniae* can trigger acute episodes of wheezing in children with asthma.

Pertussis

Pertussis, or whooping cough, is a respiratory tract infection seen most commonly in infants younger than 6 months (38% of cases are in children younger than 6 months, and 71% of cases are in children younger than 5 years). The incidence of pertussis increased in the 1980s and 1990s, especially in adolescents and adults, despite high immunization rates.[28]

The disease is characterized by three clinical stages: catarrhal stage, paroxysmal stage, and convalescent stage.[12] In infants, the disease begins with mild upper respiratory tract symptoms and cough; this catarrhal stage usually lasts 1 to 2 weeks. The disease progresses to severe paroxysms of a staccato cough, followed by post-tussive emesis, and may be accompanied by periods of cyanosis and apnea in infants younger than 6 months.[6] Classic whoop is rare, occurring in only 6% of patients, and is generally seen in children older than 2 to 3 years. Fever is often absent, and the examination findings are remarkably normal between paroxysms. The paroxysmal stage lasts 2 to 4 weeks and is followed by a convalescent stage, during which symptoms gradually wane. The duration of the illness in more complicated cases may be 6 to 10 weeks.[6]

Immunization is only 80% effective in providing immunity after three doses. Pertussis still must be considered in an immunized infant, although the illness may be mild.[12] The WBC count *is usually elevated, exceeding 15,000/mm^3 and occasionally 40,000/mm^3, with a marked* lymphocytosis, although this finding may not be present in infants younger than 3 to 6 months. The chest radiograph may show a "shaggy" right-sided heart border or have clear lung fields. The organism is most easily recovered in the catarrhal or early paroxysmal stages and is rarely found after the fourth week of illness.[12] *B. pertussis* can be cultured from nasopharyngeal secretions. Cultures may be negative during the first week or after the fourth week of illness in immunized patients or patients treated with antibiotics.[12] Direct fluorescent antibody staining may be used, but this test has low specificity and variable sensitivity.[12] Diagnosis made by direct fluorescent antibody should be confirmed by culture.

Polymerase chain reaction is overall more sensitive and specific. Pertussis is a particularly severe disease in the first year of life; complications are common and include apneic episodes, seizures, secondary bacterial pneumonia, encephalopathy, and death. Pertussis has been increasing in incidence among immunized children and young adults who have waning immunity.[5] Adults are believed to be a significant source for the disease within the community. The illness in these patients does not follow the classic stages as described here. These patients have a mild but prolonged course. A dry cough is the predominant symptom, often lasting 3 weeks or more. Because of the risk of apnea, all children younger than 6 months with presumed pertussis should be observed in the hospital for monitoring and supportive care and should be treated with erythromycin. Other macrolides and trimethoprim-sulfamethoxazole are possible alternatives.[12] Antimicrobials have no effect on the disease progression after the paroxysmal stage is established but may be beneficial because they limit the spread of organisms. Vaccination of health care workers and the adult population in general with Tdap has been shown to decrease rates of pertussis in infants.[8]

Aspiration Pneumonia

Aspiration pneumonia may be due to mechanical, chemical, or bacterial causes. Bacterial aspiration occurs in children with anatomic abnormalities and central nervous system disturbances that impair normal swallowing or protective airway reflexes. Pulmonary damage results from chemical (e.g., stomach acid) and bacterial (gastrointestinal and upper respiratory organisms) insults. Within several hours of the aspiration, the child may have the onset of cough, tachypnea, and fever. Physical examination commonly reveals rales and wheezing with cyanosis as the disease progresses. Radiographic findings include localized (right middle lobe, right lower lobe) and diffuse infiltrates, which are often bilateral.

Pneumonia in an Immunocompromised Host

Children with chronic disease and congenital, acquired, and iatrogenic immune deficiencies are susceptible to the aforementioned respiratory pathogens and to a multitude of opportunistic organisms, including *P. jiroveci,* CMV, and fungi. Presenting symptoms may be similar to those in normal hosts; however, the course tends to be more rapid, severe, and fulminant. Rigorous attempts to identify a pathogen are warranted, and patients should be hospitalized for this investigation and to await the results of cultures for monitoring, supportive therapy, and treatment with intravenous antibiotics active against a broad spectrum of organisms. If the patient fails to improve after initial

www.ketabpezeshki.com 66485457-66963820

therapy, it is necessary to obtain tissue for diagnosis of potentially treatable organisms.

Diagnostic Strategies

Not every child thought to have pneumonia requires laboratory or radiographic evaluation. A well-appearing child with cough and rales may be diagnosed clinically and treated with antibiotics as an outpatient. A child who appears ill or in whom the diagnosis is unclear requires further evaluation. Young children with high fever and leukocytosis may have an occult pneumonia. A chest radiograph should be considered in these patients even in the absence of respiratory findings.[29]

Laboratory Studies

Any child with pneumonia is at risk for hypoxemia and should have pulse oximetry to determine oxygen saturation. An arterial blood gas study is not needed in most patients but may be considered in a child with severe respiratory distress; it may be useful in following the effectiveness of respiratory status or ventilation. Serum electrolytes, blood urea nitrogen, and creatinine are useful in assessing the degree of dehydration and guiding fluid management when clinically relevant.

Further laboratory studies are obtained only as warranted to help identify the disease process and potential complications. The leukocyte count may be useful in differentiating causes of pneumonia; peripheral WBC counts greater than 15,000/mm^3, with predominance of mature and immature granulocytes, suggest bacterial infection; pneumococcal pneumonia typically produces the highest WBC counts.[30] Marked leukocytosis and toxic granulation of WBCs also may help identify a child at risk for bacteremia and its potential complications. Normal to elevated WBC counts with lymphocytosis may be seen in viral infections, and eosinophilia suggests chlamydial disease. Increased WBC counts with extreme lymphocytosis typically are associated with pertussis, but this hematologic finding may be absent in infants younger than 6 months. Blood cultures may grow pathogens in only 1 to 10% of cases of bacterial pneumonia. Unfortunately, the contamination rate at most hospitals for cultures is in this range as well. In a well-appearing child with an uncomplicated pneumonia, blood culture is unlikely to be helpful.[1,31] When a blood culture is positive, however, it identifies the specific pathogen, and blood culture should be considered in an ill patient in whom hospitalization with bacterial pneumonia is likely. Sputum cultures may be useful in adolescents but are technically difficult and not useful in younger children.[32,33]

Patients with pleural effusions should have lateral decubitus radiographs to assess effusion size and loculation. Computed tomography scan is useful to provide greater detail of effusions and lung abnormalities in critically ill children with complicated pneumonia.[34] Routine computed tomography to establish the diagnosis is not recommended. Patients with significant effusions should have thoracentesis for diagnostic and therapeutic purposes. Although parapneumonic effusions are most suggestive of bacterial infection, they also occur with mycoplasmal and occasionally with viral infections.[35] The fluid should be sent for Gram's stain and culture (anaerobic and aerobic bacterial), cell count and differential, total protein level, pH, and glucose concentration. Interpretation of pleural fluid in children follows adult guidelines (see Chapters 76 and 77). Cultures for rare pathogens may be considered if initial assessment is not diagnostic. Bronchoscopy with bronchoalveolar lavage may be useful in a severely ill child.

Nasopharyngeal viral cultures, antigen detection for specific viral or bacterial agents, and serum antibodies for specific agents may be helpful in determining certain etiologic agents. Although most pediatric patients with tuberculosis do not have pulmonary symptoms, skin testing for tuberculosis should be considered for patients with lobar pneumonia, pulmonary effusions, or hilar adenopathy, especially in immunocompromised children or children who have recently immigrated from less developed countries. Acid-fast bacilli often may be shown on an early morning gastric aspirate.[36] Sputum specimens generally are not helpful in a child younger than 8 years because of contamination by organisms of the upper respiratory tract.

Bacterial cultures of upper respiratory secretions are of no value and usually grow either normal flora or organisms that reflect only colonization. Although transtracheal sampling and direct aspiration from the lung may permit a more precise diagnosis, the invasiveness of these tests limits their usefulness. Evaluation of potential additional infectious foci should be guided clinically with particular attention to the meninges, pericardium, epiglottis, soft tissue, and joints to identify the offending pathogen and to delineate the disease process fully.

Radiology

A chest radiograph may be obtained to confirm or to rule out an infiltrate. Rarely, a dehydrated child with pneumonia may have a normal study, and once the child is rehydrated, the infiltrate becomes readily apparent. The radiograph also may provide clues to the underlying disease process. Although great variability exists, bacterial pathogens classically produce alveolar infiltrates in a lobar distribution but may produce diffuse interstitial infiltrates.[37] Viral and chlamydial infections tend to appear as diffuse interstitial infiltrates, commonly with hyperinflation and atelectasis. Chest radiographs also identify multilobar disease, pleural effusions, pneumatoceles, and pneumothorax (Fig. 170-4). Hilar adenopathy may indicate tuberculosis or malignant neoplasm.

Children without comorbid conditions, who are without fever, unilateral wheezing, or tachypnea, are unlikely to have pneumonia and a chest radiograph is unnecessary. Further, a Cochrane review demonstrated that for non–ill-appearing children with fewer than 14 days of symptoms and clinical signs of pneumonia, chest radiography does not reduce subsequent hospitalization rates or duration of symptoms.[38,39] Routine chest radiography is not beneficial in these ambulatory children older than 2 months with acute lower respiratory infections.[39]

Differential Considerations

The major conditions to be differentiated in children with pneumonia include bacterial pneumonias amenable to conventional

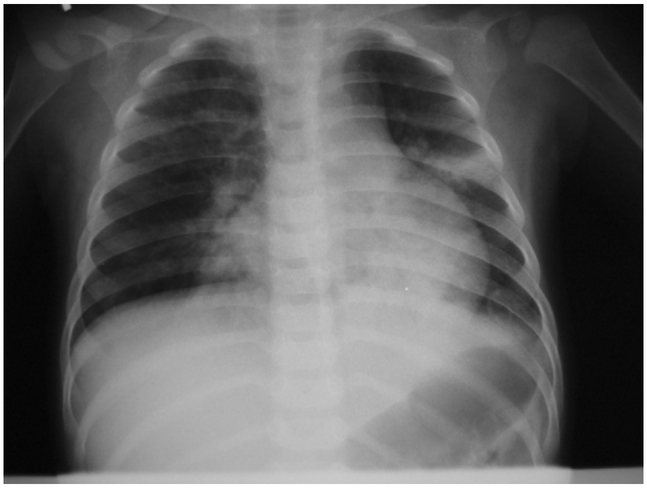


Figure 170-4. Radiograph shows multilobar pneumonia in a child with respiratory distress. (Courtesy Marianne Gausche-Hill, MD.)

www.ketabpezeshki.com 66485457-66963820

antibiotics, viral disease, other unusual infectious causes (mycobacterial, protozoal, fungal), and noninfectious pathologic conditions (Box 170-1). Certain features help differentiate the common infectious causes (Table 170-2). As detailed previously, each disease entity has certain classic historical, clinical, and laboratory findings. At the extremes of presentation, these diseases can be distinguished easily; however, the broad spectrum of illness for each process may make accurate diagnosis in an individual patient difficult. No specific feature reliably differentiates patients with bacterial infection from children with nonbacterial pneumonia. Because of limitations of reliably detecting bacterial pneumonia by culture technique, one should strongly consider a bacterial cause in a child with a temperature higher than 39° C, clinical toxicity, lobar infiltrate, or pleural effusions. Although it is often difficult to make a precise etiologic diagnosis, consideration of host factors, epidemiology, and the clinical picture with judicious use of laboratory tests generally points the clinician toward the likely diagnosis and allows effective patient management.

Complications

Several complications of pneumonia result from local and systemic effects of the infection. Pleural effusions or empyemas accumulate most often with bacterial pathogens (notably *S. pneumoniae, H. influenzae,* and *S. aureus*) but are occasionally associated with mycoplasmal, viral, and tuberculous pneumonia. An increase in the occurrence of such complications seemed to have occurred in the 1990s for reasons unknown.[40] Similarly, lung abscess, pneumatocele, and pneumothorax are local complications primarily seen with bacterial disease, particularly with *S. aureus*. Extensive pulmonary involvement of any cause may lead occasionally to hypoxia

Box 170-1 Noninfectious Causes That May Present as Pneumonia

- Radiologic technique
  - Inadequate inspiration
  - Breast shadow
  - Thymus
  - Uneven grid on film
  - Underpenetrated film
- Primary pulmonary
  - Asthma
  - Bronchiectasis
  - Atelectasis
  - Bronchopulmonary dysplasia
  - Cystic fibrosis
  - Pulmonary sequestration
  - Congenital cystic adenomatoid malformation
  - α_1-Antitrypsin deficiency
- Aspiration
  - Foreign body
  - Chemical
  - Recurrent caused by anatomic or physiologic disorders
- Primary cardiac
  - Congenital heart disease
  - Congestive heart failure
- Pulmonary infarction
  - Sickle cell vaso-occlusive crisis
  - Pulmonary embolism
- Collagen vascular disorders
- Acute respiratory distress syndrome
- Pleural effusion
- Neoplasm

From Boyer KM: Nonbacterial pneumonia. In Feigin RD, Cherry JD (eds): Textbook of Pediatric Infectious Diseases, 4th ed. Philadelphia, WB Saunders, 1998, pp 260-273.

Table 170-2 Pneumonia Syndromes

	BACTERIAL	VIRAL	CHLAMYDIAL	MYCOPLASMAL
Historical				
Age	Any	Any	4-16 weeks	5-18 years
Fever	High (>39° C)	Low grade	Usually none	Low
Onset	Abrupt, often after upper respiratory infection	Gradual	Gradual	Gradual
Cough	Productive	Nonproductive	Staccato	Hacking
Associated symptoms	Chest pain Focal infarct	Myalgias Rash Sore throat Coryza	Conjunctivitis	Headache Sore throat Rash
Physical	Toxic appearance			
Lungs	Confined rales	Diffuse rales Wheeze Stridor	Diffuse rales Rare wheeze	Unilateral rales
Chest radiograph				
Infiltrate	Lobar or segmental	Interstitial	Diffuse Interstitial	Lobar or diffuse
Pleural effusion	Occasional	Rare	None	Rare
Other	Pneumatocele Abscess	Hyperinflation Atelectasis	Hyperinflation	
Laboratory	Increased WBC granulocytosis	Normal or increased WBC count Lymphocytosis	Normal WBC count Eosinophilia	Normal WBC count
Pathogens (common)	*Streptococcus pneumoniae* *Haemophilus influenzae* *Staphylococcus aureus* <2 months: Group B streptococcus Gram-negative enterics *Listeria monocytogenes*	RSV Parainfluenza Influenza Adenovirus Enterovirus	*Chlamydia trachomatis*	*Mycoplasma pneumoniae*

RSV, respiratory syncytial virus; *WBC,* white blood cell.

www.ketabpezeshki.com 66485457-66963820

and progressive respiratory failure with multiple organ failure. Apnea without other symptoms is seen most often in viral, chlamydial, and pertussis infections in infants younger than 3 months. The most common systemic complication of pneumonia is dehydration, which is a result of decreased intake from malaise and excessive respiratory effort and increased losses of fluid caused by vomiting, fever, and tachypnea. Another systemic complication of bacterial disease is the development of additional infectious foci resulting from bacteremia (e.g., meningitis, epiglottitis, pericarditis, septic arthritis, and soft tissue infections). Viral and bacterial pneumonias are rarely associated with meningitis, encephalitis, arthritis, rhabdomyolysis, and hemolytic anemia.

Management and Disposition

Infants Younger Than 2 Months

Treatment of pneumonia in a pediatric patient consists of appropriate antimicrobial use and supportive therapy (see Table 170-1). Because of the difficulty in identifying an etiologic agent, antibiotic choice is generally empirical. The three most important factors in directing management are the patient's age, likely pathogen, and degree of illness. An infant younger than 2 months with pneumonia should usually be admitted to the hospital. This age group is immunologically immature, and signs of sepsis may be subtle. Blood, urine, and cerebrospinal fluid cultures generally are indicated before initiation of antibiotics. Ampicillin plus an aminoglycoside or ampicillin and a third-generation cephalosporin would be appropriate initial antibiotic choices for an infant younger than 1 month (although ceftriaxone is contraindicated in infants younger than 1 month).

Infants 2 to 3 Months of Age

In an infant 2 to 3 months old, blood and urine cultures are appropriate. The decision to perform a lumbar puncture depends on clinical suspicion of central nervous system infection. Ampicillin and a third-generation cephalosporin are reasonable for an infant 1 to 3 months old. If *C. trachomatis* or *B. pertussis* is suspected, the infant also should be treated with erythromycin after appropriate diagnostic samples have been obtained; other macrolides or sulfonamides (trimethoprim-sulfamethoxazole) may be an alternative in older infants and children.[12] Supportive therapy in this age group consists of fever control and intravenous hydration. A trial of inhaled beta-agonists or racemic epinephrine may be indicated if the patient is wheezing or in significant respiratory distress; supplemental oxygen and respiratory support should be provided as needed. All infants should be monitored with continuous pulse oximetry because apnea and respiratory failure may be precipitous.

Infants and Children Older Than 3 Months

In an older child, pneumonia should be categorized into likely bacterial, viral, or mycoplasmal disease, if possible. Because no single pathognomonic test exists to differentiate bacterial from viral infection, the physician should base the presumptive etiologic diagnosis on clinical, radiographic, and laboratory findings. Although the categorization is not always clear, a toxic child with high fever, lobar consolidation, and leukocytosis is likely to have a bacterial process, whereas a child with a disease of gradual onset, low-grade fever, and interstitial infiltrate with air trapping is more likely to have a viral process.

If a viral agent is suspected and the child is not ill, antibiotics should be withheld. Uncomplicated bacterial pneumonia in immunocompetent children is safe to treat as an outpatient disease. A well-appearing infant or preschool-age child with isolated pneumonia may be treated with oral antibiotics on an outpatient basis. In an infant beyond the neonatal period or a preschool-age child, amoxicillin and amoxicillin–clavulanic acid are considered appropriate first-line agents. Cefuroxime axetil or high-dose amoxicillin (80-100 mg/kg/day) may be used when resistant *S. pneumoniae* is suspected. Azithromycin is considered an appropriate first-line oral agent in this age group by some researchers.[1,33] One study of the treatment of pediatric community-acquired pneumonia showed no difference in clinical cure rate when azithromycin, erythromycin estolate, and amoxicillin–clavulanic acid were compared.[41] A macrolide is the first-line antibiotic choice in a school-age child or adolescent, in whom *M. pneumoniae* and *C. pneumoniae* are more common. Every child with bacterial pneumonia treated as an outpatient should be reevaluated within 24 to 48 hours. Patients who are not afebrile, clinically improved, and well hydrated should be evaluated at this time for possible admission to the hospital for parenteral antibiotic therapy. For patients in whom signs of bacteremia are present, a single dose of intramuscular ceftriaxone followed by outpatient oral therapy is recommended. In these cases, close follow-up monitoring is crucial.

For a patient who is admitted to the hospital, intravenous therapy with cefuroxime, cefotaxime, or ceftriaxone is appropriate. Addition of a macrolide should be considered if *M. pneumoniae* is a possible etiologic agent. Vancomycin should be added if methicillin-resistant *S. aureus* is suspected.[13,23] If an organism has been identified, an antibiotic with a more specific spectrum might be indicated.

Since the 1980s, *S. pneumoniae* has been developing increasing resistance to penicillin and other antibiotics; in general, this has not been clinically relevant because higher doses overcome the relative resistance. Clinical outcomes with intermediate resistance levels seem to be unchanged.[42] These patients still respond to penicillin and the cephalosporins at higher doses. If the patient does not respond clinically after a trial of these agents or if the patient is critically ill, use of vancomycin with or without rifampin is recommended.[43]

Supportive therapy includes hydration and fever control with antipyretics. Appropriate laboratory testing should be performed to attempt identification of more virulent pathogens. The child should be examined for development of an additional infectious focus, and a repeated radiograph may be considered to determine spread or development of a pleural effusion.

Indications for hospitalization at the time of diagnosis include toxic appearance, vomiting or dehydration, respiratory compromise (distress, hypoxia, or inadequate ventilation), multilobar disease, pleural effusions, impaired immune function, and unstable social environments. Strong consideration should be given to hospitalization of children younger than 6 months because they are prone to complications of bacterial pneumonia more than older children are. Supportive therapy for the inpatient should include maintenance of fluid and electrolyte balance and fever control, supplemental oxygen, inhaled bronchodilators, ventilatory assistance, and pleural fluid drainage as indicated. Parenteral antibiotic therapy should be administered until clinical improvement occurs. Other factors that influence duration of parenteral antibiotic treatment include the age of the patient, specific pathogen, presence of bacteremia, and any additional infectious foci.

A trial of bronchodilators may be worthwhile (aerosolized $beta_2$-adrenergic agent) even in the absence of wheezing and should be considered in a patient with respiratory distress. Although this treatment is not always successful, if the child responds with diminished wheezing, improved aeration, or reduced work of breathing, one may continue with nebulized bronchodilators.

www.ketabpezeshki.com 66485457-66963820

Children with neurologic or anatomic abnormalities who aspirate oral or gastric contents are susceptible to pneumonia predominantly from anaerobes. Penicillin and clindamycin are appropriate first-line antibiotic choices. In seriously ill patients or patients not responding to the first-line treatments, agents such as chloramphenicol, metronidazole, and cefoxitin may be more useful. Nosocomial infections should be treated with antibiotics also active against aerobes and gram-negative bacilli. Children with significant aspiration should be admitted to the hospital, and supportive therapy should include hydration, supplemental oxygen, oropharyngeal suctioning, and intubation of the trachea if airway reflexes are impaired or respiratory failure is manifested.

Long-term management of a child with pneumonia should include a clinical reevaluation 2 to 3 weeks after diagnosis. If the child had a prompt response to therapy and is entirely well at follow-up evaluation with a normal physical examination, a repeated radiograph is unnecessary.[44] If the child has undergone a complicated disease course (e.g., pleural effusion), has residual symptoms, or manifests any abnormality on examination or if the illness is not the child's first episode of pneumonia, a chest radiograph should be obtained to ensure complete resolution of the disease. The follow-up radiograph should be performed 6 to 8 weeks after diagnosis.

In management of a child with pneumonia, it is essential to consider the age and clinical presentation of the child in delineating specific etiologic agents. Common pathogens may be treated as an outpatient disease in nontoxic patients; infants and children who exhibit some respiratory compromise may require parenteral antibiotics, support, and hospitalization. During the past several years, the patterns of etiologic organisms have been changing. The spectrum of antimicrobial sensitivities also has changed, particularly with the emergence of penicillin-resistant *S. pneumoniae*. Repeated chest radiographs are indicated in children who fail to respond to a course of treatment; immunocompetent patients who respond to therapy may be observed clinically, and a repeated chest radiograph is not necessary to document cure.

OTHER RESPIRATORY EMERGENCIES

Cystic Fibrosis

Perspective

CF is an autosomal recessive disease caused by a mutation in the CF transmembrane conductance regulator (*CTFR*) gene. In whites, approximately 1 in 25 is a carrier, and the disease has an incidence of 1 in 2500 births.[44] The disease also is present (in decreasing incidence) in Hispanics, Native Americans, African Americans, and Asians. Progressive lung disease and infection account for most of the morbidity and nearly all of the mortality in CF. Defects in chloride transport across the airway epithelium result in reduced ciliary clearance of thickened mucus, decreased antimicrobial effect of the airway surface, increased bacterial adherence, and innate secretion of inflammatory cytokines. All of these factors result in a unique sensitivity to bacterial infection of the airway.[45,46]

Diagnostic Strategies

Chest radiographic findings of CF include emphysema, peribronchial thickening, bronchiectasis, and focal infiltration, which may be linear or nodular in nature (Fig. 170-5). Crucial to the effective treatment of pulmonary infections in CF patients is the identification of pathogens involved, usually through sputum culture. Early childhood pneumonias in patients with CF are predominantly caused by *S. aureus* and *H. influenzae*.

Management

With the emergence of methicillin-resistant *S. aureus*, careful attention should be paid to antibiotic coverage. Patients receiving antistaphylococcal prophylaxis may be at increased risk for pseudomonal infections.[44] There is emerging evidence that CF patients

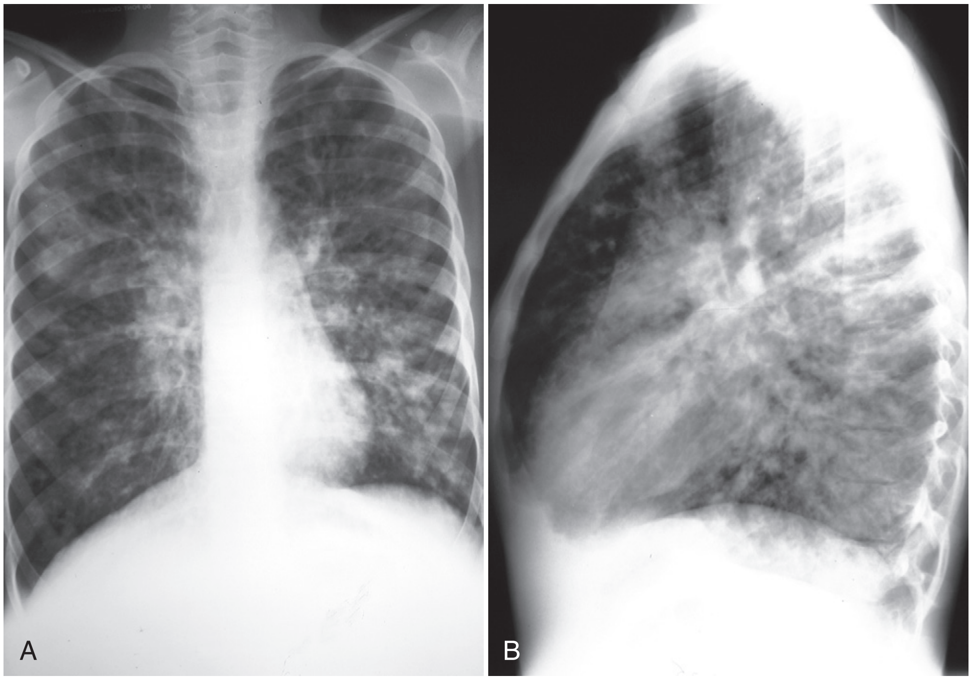


Figure 170-5. Posteroanterior (A) and lateral (B) radiographs of a teenager with cystic fibrosis. Note emphysema and nodular infiltrates. (Courtesy Michael Diament, MD.)

www.ketabpezeshki.com 66485457-66963820

also are at increased risk for hospitalization with nonbacterial pathogens.[47]

By 18 years of age, 80% of patients are colonized with *P. aeruginosa*. When colonization is established, it is generally considered permanent.[48] Acute infective exacerbations generally are managed by oral and intravenous antimicrobial drugs, typically a penicillin (e.g., ticarcillin or piperacillin) or ceftazidime combined with an aminoglycoside for purposes of synergy.[5] If a patient's previous sputum culture result is available, care should be taken to ensure coverage of the last known bacterial pathogens. Resistant strains may benefit from imipenem or meropenem. Patients routinely are hospitalized for 10 to 14 days for the course of therapy.[44]

Burkholderia cepacia, a significant pathogen in CF patients, has been associated with an accelerated decline in clinical status and increased mortality. In general, antimicrobial coverage is similar to that for *Pseudomonas*. Resistance is common, however, and the existence of differing colonization and resistance patterns of patients with CF necessitates respiratory isolation from other susceptible individuals.[49]

Clearance of thick mucoid secretions is vital for treatment. Patients may respond favorably to bronchodilator therapy and to mucolytics, such as inhaled *N*-acetylcysteine, in the acute setting.[50] Chest physiotherapy often is provided by a high-frequency oscillator device. A flutter valve or a positive expiratory pressure mask also may be of assistance for improved mucoid clearance. Short-term control of inflammation may be obtained by inhaled corticosteroids.[51]

Chronic Lung Disease

Chronic lung disease (CLD) of infancy, also called bronchopulmonary dysplasia, is extremely common in premature infants and affects 40% of children with a birth weight of less than 1000 g.[52] The severity of disease is related to several factors, including degree of prematurity, use of peripartum steroids, damage incurred by ventilation in the neonatal period, and nutritional status. Infants with CLD have greatly increased rates of hospitalization because of respiratory illness in the first year of life, approaching 65% in infants born weighing less than 1000 g.[53]

Immunizations are vital to the prevention of pneumonia in patients with CLD. All infants 6 to 23 months old should receive the influenza vaccine during the appropriate season. The heptavalent pneumococcal vaccine and *H. influenzae* type b vaccine are especially vital for prevention of bacterial pneumonia.[54] In addition, monthly prophylaxis against RSV is administered to carefully selected patients with the monoclonal immunoglobulin palivizumab, which reduces the incidence of RSV disease and risk of subsequent hospitalization.[12,55]

Patients with CLD have increased airway resistance, decreased lung compliance, and obstructive lung disease. Pneumonia in patients with CLD may be complicated by a reactive airway component. If complicated by pneumonia, radiographs show marked hyperinflation and infiltrates (Fig. 170-6). Inhaled bronchodilators may be efficacious, although these medications may worsen air exchange in patients with concomitant airway malacia. Hypoxia and hypercarbia are common, despite an increased respiratory effort. Patients with severe CLD may be receiving long-term diuretic therapy to improve lung mechanics; care should be taken not to confuse pneumonia with cor pulmonale, which is especially prevalent in younger infants with chronic supplemental oxygen requirements.[52]

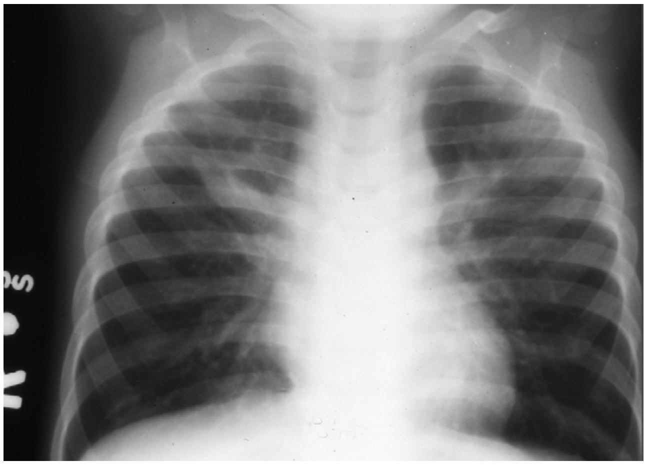


Figure 170-6. Radiograph of a child with bronchopulmonary dysplasia shows findings of chronic lung disease and hyperinflation. (Courtesy Michael Diament, MD.)

KEY CONCEPTS

- It may be difficult to determine the etiologic agent of pneumonia by clinical presentation, radiographic findings, or laboratory studies. Mixed infections occur commonly.
- Infants and younger children with pneumonia may have subtle or nonspecific signs and symptoms on presentation.
- Pertussis should be considered in a young infant with a lower respiratory tract infection, staccato cough, or episodes of cyanosis.
- *M. pneumoniae* and *C. pneumoniae* may play a role in pneumonia in a younger child.
- In patients with CF, defects in chloride transport across the airway epithelium result in reduced ciliary clearance of thickened mucus, which results in increased likelihood for pneumonia, especially that caused by *P. aeruginosa*.
- CF may respond favorably to bronchodilator therapy and to mucolytics, such as inhaled *N*-acetylcysteine.
- Patients with CLD have increased airway resistance, decreased lung compliance, and obstructive lung disease; reactive airway disease and pneumonia are common in these patients.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Pelton SI, Hammerschlag MR: Overcoming current obstacles in the management of bacterial community-acquired pneumonia in ambulatory children. *Clin Pediatr (Phila)* 2005; 44:1.
2. Juven T, et al: Etiology of community acquired pneumonia in 254 hospitalized children. *Pediatr Infect Dis J* 2000; 10:293.
3. Korppi M: Community-acquired pneumonia in children: Issues in optimizing antibacterial treatment. *Paediatr Drugs* 2003; 12:821.
4. Yaari E, et al: Clinical manifestations of *Bordetella pertussis* infection in immunized children and young adults. *Chest* 1999; 115:1254.
5. Mink CA, et al: Outbreak of pertussis in a fully immunized adolescent and adult population. *Arch Pediatr Adolesc Med* 1994; 148:153.
6. Principi N, Esposito S: Emerging role of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in paediatric respiratory-tract infections. *Lancet Infect Dis* 2001; 1:334.
7. Principi N, et al: Role of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in children with community-acquired lower respiratory tract infections. *Clin Infect Dis* 2001; 32:1281.
8. Centers for Disease Control and Prevention: Preventing tetanus, diphtheria, and pertussis among adults: Use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine. *MMWR Recomm Rep* 2006; 55:17.
9. Hinman AR, Orenstein WA, Schuchat A; Centers for Disease Control and Prevention: Vaccine-preventable diseases, immunizations, and MMWR—1961-2011. *MMWR Surveill Summ* 2011; 60(Suppl 4):49-57.
10. Overturf GD; American Academy of Pediatrics Committee on Infectious Disease: Technical report: Prevention of pneumococcal infections, including the use of pneumococcal conjugate and polysaccharide vaccines and antibiotic prophylaxis. *Pediatrics* 2000; 106:367.
11. Dagan R, et al: Effect of a noncovalent conjugate vaccine on carriage of antibiotic-resistant *Streptococcus pneumoniae* in day-care centers. *Pediatr Infect Dis* 2003; 22:532.
12. Madhi SA, Klugman KP; The Vaccine Trialist Group: A role for *Streptococcus pneumoniae* in virus-associated pneumonia. *Nat Med* 2004; 10:811-813.
13. Bradley JS, et al, Pediatric Infectious Diseases Society and the Infectious Diseases Society of America: The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2011; 53:e25-e76.
14. Mani CS, Murray DL: *Acute pneumonia and its complications*. In: Long SS, Pickering LK, Prober CG, eds: *Principles and Practice of Pediatric Infectious Diseases*, 3rd ed. New York: Churchill Livingstone; 2008.
15. The WHO Young Infants Study Group: Serious infections in young infants in developing countries: Rationale for a multicenter study. *Pediatr Infect Dis J* 1999; 18(Suppl):4.
16. Jain A, Ben-Ami T, Daum RS: Staphylococcal infections in children: Part 2. *Pediatr Rev* 1999; 20:219.
17. Marcinak J, Frank A: Treatment of community-acquired methicillin-resistant *Staphylococcus aureus* in children. *Curr Opin Infect Dis* 2003; 16:265.
18. Melville CAS, Flaurenson JF, Augrow JA: Invasive disease due to *Haemophilus influenzae* infection [letter]. *BMJ* 1994; 309:58.
19. Muller M, et al: Clinical and epidemiologic features of group A streptococcal pneumonia in Ontario, Canada. *Arch Intern Med* 2003; 163:467.
20. O'Brien K, Beall B, Barrett N: Epidemiology of invasive group A streptococcus disease in the United States, 1995-1999. *Clin Infect Dis* 2002; 35:268.
21. Todd JK: *Pneumonia*. In: Behrman RE, ed: *Nelson Textbook of Pediatrics*, 16th ed. Philadelphia: WB Saunders; 2000:1432.
22. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H: Epidemiology and etiology of childhood pneumonia. *Bull World Health Organ* 2008; 86:408.
23. Gomez-Barreto D, et al: Clinical outcome of invasive infections in children caused by highly penicillin-resistant *Streptococcus pneumoniae* compared with infections caused by penicillin-susceptible strains. *Arch Med Res* 2000; 31:592.
24. Reference deleted in proofs.
25. Cimolai N: *Mycoplasma pneumoniae* respiratory infection. *Pediatr Rev* 1998; 19:327.
26. Waris ME, et al: Diagnosis of *Mycoplasma pneumoniae* pneumonia in children. *J Clin Biol* 1998; 36:3155.
27. Hagiwara K, et al: An epidemic of pertussis-like illness caused by *Chlamydia pneumoniae*. *Pediatr Infect Dis J* 1999; 18:271.
28. Vitek C, et al: Increase in deaths from pertussis among young infants in the United States in the 1990's. *Pediatr Infect Dis J* 2003; 22:628.
29. Bachur R, Perry H, Harper MB: Occult pneumonias: Empiric chest radiographs in febrile children with leukocytosis. *Ann Emerg Med* 1999; 33:166.
30. Lin CJ, et al: Radiographic, clinical, and prognostic features of complicated and uncomplicated community-acquired lobar pneumonia in children. *J Microbiol Immunol Infect* 2006; 39:489.
31. Shah SS, et al: Blood cultures in the emergency department evaluation of childhood pneumonia. *Pediatr Infect Dis J* 2011; 30:6.
32. Bradley J: Management of community-acquired pediatric pneumonia in an era of increasing antibiotic resistance and conjugate vaccines. *Pediatr Infect Dis J* 2002; 21:592.
33. McCracken G: Diagnosis and management of pneumonia in children. *Pediatr Infect Dis J* 2000; 19:924.
34. Hodina M, et al: Imaging of cavitary necrosis in complicated childhood pneumonia. *Eur Radiol* 2002; 12:391.
35. Givan DC, Eigen H: Disease of the pleura: Common pleural effusions in children. *Clin Chest Med* 1998; 19:363.
36. Starke JR: Pediatric tuberculosis: Time for a new approach. *Tuberculosis* 2003; 83:208.
37. Virkki R, et al: Differentiation of bacterial and viral pneumonia in children. *Thorax* 2002; 57:438.
38. Swingler GH, Hussey GD, Zwarenstein M: Randomised controlled trial of clinical outcome after chest radiograph in ambulatory acute lower-respiratory infection in children. *Lancet* 1998; 351:404.
39. Swingler GH, Zwarenstein M: Chest radiograph in acute respiratory infections. *Cochrane Database Syst Rev* 2008; 1:CD001268.
40. Byington C, et al: An epidemiological investigation of a sustained high rate of pediatric parapneumonic empyema: Risk factors and microbiological associations. *Clin Infect Dis* 2002; 34:434-440.
41. Wubbel L, et al: Etiology and treatment of community-acquired pneumonia in ambulatory children. *Pediatr Infect Dis J* 1998; 18:98.
42. Kaplan S, et al: Outcome of invasive infections outside the central nervous system caused by *Streptococcus pneumoniae* isolates nonsusceptible to ceftriaxone in children treated with beta-lactam antibiotics. *Pediatr Infect Dis J* 2001; 20:392.
43. American Academy of Pediatrics Committee on Infectious Diseases: Therapy for children with invasive pneumococcal infections. *Pediatrics* 1997; 99:289.
44. Brennan AL, Geddes DM: Cystic fibrosis. *Curr Opin Infect Dis* 2002; 15:175.
45. Conese M, Assael BM: Bacterial infections and inflammation in the lungs of cystic fibrosis patients. *Pediatr Infect Dis J* 2001; 20:207.
46. Hanutcu R, Woo MS: Advanced cystic fibrosis lung disease in children. *Curr Opin Pulm Med* 2001; 7:448.
47. Meissner HC: Selected populations at increased risk from respiratory syncytial virus infection. *Pediatr Infect Dis J* 2003; 22(Suppl):40.
48. Rajan S, Saiman L: Pulmonary infections in patients with cystic fibrosis. *Semin Respir Infect* 2002; 17:47.
49. Garau J, Gomez L: *Pseudomonas aeruginosa* pneumonia. *Curr Opin Infect Dis* 2003; 16:135.
50. Ramsey BW: Management of pulmonary disease in patients with cystic fibrosis. *N Engl J Med* 1996; 335:179.
51. van der Schans C, et al: *Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis (Cochrane Review)*. In: *The Cochrane Library, Issue 1*. Chichester, UK: John Wiley & Sons; 2004.
52. Marshall DD: Primary care follow-up of the neonatal intensive care unit graduate. *Clin Fam Pract* 2003; 5:243.
53. Davis PG, et al: Evaluating "old" definitions for the "new" bronchopulmonary dysplasia. *J Pediatr* 2002; 140:555.
54. Saari TN; American Academy of Pediatrics Committee on Infectious Diseases: Immunization of preterm and low birth weight infants. *Pediatrics* 2003; 112:193.
55. Welliver RC: Review of epidemiology and clinical risk factors for severe respiratory syncytial virus (RSV) infection. *J Pediatr* 2003; 143(Suppl):112.
56. Chumpa A, Bachur RG, Harper MB: Bacteremia-associated pneumococcal pneumonia and the benefit of initial parenteral antimicrobial therapy. *Pedia Inf Disease J* 1999; 18:12.

www.ketabpezeshki.com 66485457-66963820

Chapter 171

Cardiac Disorders

Timothy Horeczko and Alson S. Inaba

PERSPECTIVE

Pediatric cardiac disease traditionally has been divided into congenital and acquired disorders, with a further subdivision of the congenital heart disorders into cyanotic and acyanotic lesions. From a purely clinical standpoint, however, children with cardiac disorders present to the emergency department in one of two scenarios. In the first scenario, the child has signs and symptoms that may represent an exacerbation or complication of an already known underlying cardiac disorder. In cases with a known underlying cardiac disorder, early consultation with the child's cardiologist along with comparisons of the child's previous and most recent diagnostic cardiac studies, such as chest radiographs, electrocardiograms (ECGs), and echocardiograms, would also be extremely useful in the evaluation and management phases.

The second scenario represents more of a challenge to the emergency physician: the child with an undiagnosed congenital or acquired cardiac disorder who presents to the emergency department with nonspecific or concerning signs and symptoms (Box 171-1). This chapter focuses on some of the more common and life-threatening cardiac disorders in infants and children who present to the emergency department, with an emphasis on rapid evaluation, stabilization, and management of these disorders.

PRINCIPLES OF DISEASE

Fetal and Neonatal Circulation

Some of the key features of the fetal circulation that differ from the circulation of a child are the ductus venosus, the ductus arteriosus, and a patent foramen ovale. During fetal development, blood is oxygenated by the placenta, flows to the fetus through the umbilical vein, bypasses the fetal liver through the ductus venosus, and returns to the fetal heart through the inferior vena cava. Blood returning from the inferior vena cava then enters the right atrium and is preferentially shunted across to the left atrium through the patent foramen ovale (Fig. 171-1). The blood in the left atrium is then pumped from the left ventricle to the aorta. The oxygenated blood ejected through the ascending aorta is preferentially directed to the fetal coronary and cerebral circulations.

Deoxygenated blood that returns to the right atrium through the superior vena cava crosses the tricuspid valve and is pumped into the fetal pulmonary artery through the right ventricle. Because the fetal pulmonary vascular resistance (PVR) is higher than the fetal systemic vascular resistance (SVR), this deoxygenated blood bypasses the nonoxygenated fetal lungs through the patent ductus arteriosus (see Fig. 171-1). This poorly oxygenated blood enters the aorta through the patent ductus arteriosus and then mixes with the well-oxygenated blood in the descending aorta. The mixed blood in the descending aorta then returns to the placenta for oxygenation through the two umbilical arteries.

Once the infant is delivered and the umbilical cord is cut, expansion and aeration of the lungs cause a decrease in PVR, with a concomitant increase in pulmonary blood flow. Increased oxygenation causes a physiologic closure of the umbilical arteries, umbilical vein, ductus venosus, and ductus arteriosus. An increase in the pulmonary blood flow to the infant's left atrium also promotes closure of the foramen ovale. Complete anatomic closure of the foramen ovale does not occur until about 3 months of age. Although the ductus arteriosus functionally closes at about 10 to 15 hours of life, complete anatomic closure does not occur until about 2 to 3 weeks of life.

In the absence of any congenital cardiac defects, these transitional circulatory changes pose no physiologic problems to the infant. However, closure of the ductus arteriosus can pose life-threatening complications in neonates with specific congenital cardiac defects that are dependent on the patency of the ductus arteriosus for survival.

Pathophysiology of Cardiovascular Compensatory Responses

There are two fundamental and clinically useful physiologic formulas to keep in mind during the clinical assessment and management of cardiac disorders:

$$\text{Cardiac output} = \text{stroke volume} \times \text{heart rate}$$

$$\text{Blood pressure} = \text{cardiac output} \times \text{SVR}$$

The young myocardium is inefficient and unable to increase its contractility in response to demand.[1] When more cardiac output is needed, infants and children respond with an increase in heart rate. Therefore, bradycardia in infants and young children is an ominous sign that connotes a severely compromised cardiac output. Children develop the adult capacity to increase their stroke volume to improve overall cardiac output by 8 to 10 years of age.[2]

On the basis of the first physiologic formula, as stroke volume decreases, a compensatory increase in the heart rate will be necessary to preserve a normal cardiac output. A decrease in stroke volume can be produced by a weak "pump," decreased volume in the circulation, or both. The most common cause of decreased stroke volume in children is hypovolemia due to dehydration. Other causes of decreased stroke volume in children may be implicated (Box 171-2). Thus tachycardia is the first compensatory cardiovascular response when the stroke volume is decreased. If tachycardia alone is not enough to maintain a normal cardiac

www.ketabpezeshki.com 66485457-66963820

Box 171-1 Common Presenting Signs and Symptoms of Cardiac Disorders in Infants and Children

General
Fussiness
Lethargy
Poor feeding (with or without associated diaphoresis)
Poor growth

Respiratory
Respiratory distress
Wheezing
Apnea

Cardiovascular
Tachycardia
Shock
Paleness
Mottling
Cyanosis
Palpitations
Chest pain
Syncope
Various dysrhythmias

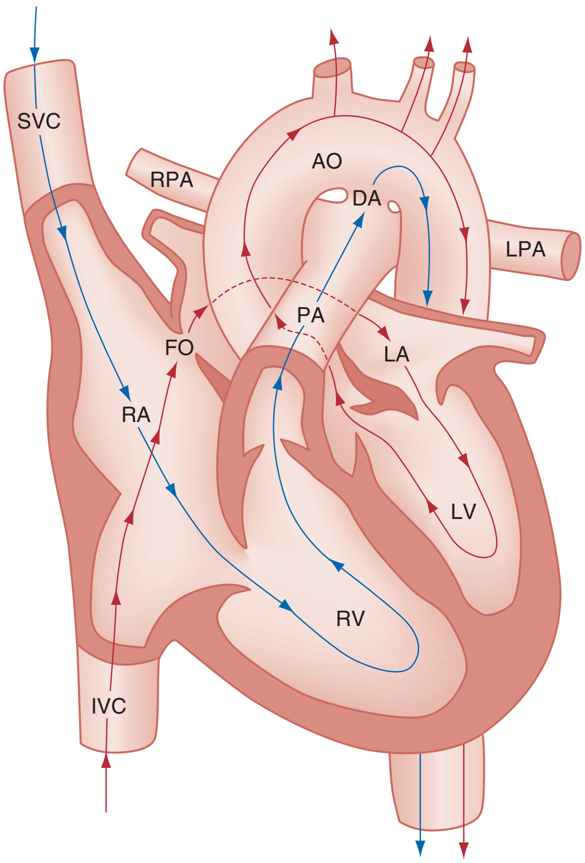


Figure 171-1. Normal intracardiac fetal circulation: physiologic shunting through the patent foramen ovale (*FO*) and the patent ductus arteriosus (*DA*). Oxygenated blood from the placenta *(red arrows)* reaches the right atrium (*RA*) through the inferior vena cava (*IVC*). This well-oxygenated blood is preferentially shunted from the RA across to the left atrium (*LA*) through the FO and is then ejected out the left ventricle (*LV*) to the ascending aorta (*AO*). Deoxygenated blood *(blue arrows)* returning from the superior vena cava (*SVC*) preferentially travels from the RA into the right ventricle (*RV*) and then out through the main pulmonary artery (*PA*). Because of the high pulmonary vascular resistance in the fetal lungs, this deoxygenated blood bypasses lungs and enters the descending aorta through the DA. Thus the areas of the fetal body that are perfused by arteries proximal to the DA receive well-oxygenated blood, whereas those areas of the body that are perfused by arteries distal to the DA receive blood with a mixed oxygenation. *LPA,* left pulmonary artery; *RPA,* right pulmonary artery.

output, the next compensatory physiologic mechanism to preserve perfusion is an increase in the SVR. This increase in SVR is exhibited as an increase in the diastolic blood pressure, which in turn accounts for a narrowed pulse pressure. The clinical examination findings of the extremities of a child with an increased SVR

Box 171-2 Causes of Decreased Stroke Volume in Infants and Children

Hypovolemia (most commonly secondary to dehydration)
Congestive heart failure (acquired or secondary to underlying congenital cardiac defects)
Myocarditis
Hypertrophic cardiomyopathy with decreased diastolic filling
Dilated cardiomyopathy with decreased systolic ejection
Pericarditis or pericardial effusion with cardiac tamponade
Tachydysrhythmias with decreased diastolic filling times

include pallor, mottling, cool skin, delayed capillary refill time (>2 seconds), and weak or thready distal pulses.

Pathophysiology of Cyanosis

Perspective

Cyanosis is a clinical sign caused by the presence of deoxygenated blood in the capillary beds, most readily observed in the mucous membranes, conjunctiva, nail beds, and skin. The presence of cyanosis usually means that there are at least 4 to 5 g/dL of deoxyhemoglobin in the blood, which correlates with an oxygen saturation of about 80 to 85%.[3] Central cyanosis results from a decrease in pulmonary ventilation and oxygenation, a decrease in pulmonary perfusion, the shunting of deoxygenated blood directly into the systemic circulation, or the presence of abnormal hemoglobin. Cyanosis in the neonate can be due to a variety of cardiac, pulmonary, or hematologic causes. Cardiac causes of cyanosis include congenital lesions with right-to-left shunts and cardiac lesions with decreased or increased pulmonary blood flow. Common pulmonary causes of cyanosis include bronchiolitis, pneumonia, and pulmonary edema. Methemoglobinemia can be one of the hematologic causes of cyanosis.

Clinical Features of Cyanosis

The region of the body that is cyanotic can provide important clinical clues to the cause of the cyanosis. Central cyanosis involves the lips, tongue, and mucous membranes, whereas peripheral cyanosis (acrocyanosis) involves the hands and feet. Acrocyanosis is a common phenomenon in neonates caused by cold stress and peripheral vasoconstriction. Central cyanosis reflects a pathologic origin and is an ominous sign. Infants with cyanosis secondary to a congenital heart defect may not exhibit as much respiratory distress compared with the infant with cyanosis due to a pulmonary cause. Thus a cardiac cause of central cyanosis may be more likely than a purely pulmonary cause in the child who appears “comfortably blue.” Another important clinical clue to the cause of central cyanosis is that cyanosis of cardiac origin usually worsens with crying, whereas cyanosis due to a pulmonary cause may improve when the infant cries.[4] Cyanotic congenital heart defects with right-to-left shunting will demonstrate a minimal improvement with supplemental oxygen, whereas cyanosis of a purely pulmonary origin typically exhibits a significant improvement with supplemental oxygen (Table 171-1).

CLINICAL FEATURES AND DIAGNOSTIC STRATEGIES: THE CARDIAC EVALUATION

The key elements that should be elicited in the history of a child with a known underlying cardiac disorder are listed in Box 171-3. Early consultation with the child’s cardiologist or cardiac surgeon is extremely useful.

www.ketabpezeshki.com 66485457-66963820

Table 171-1 Clinical Clues to Help Distinguish between Cardiac and Pulmonary Causes of Central Cyanosis

	CARDIAC ETIOLOGY	PULMONARY ETIOLOGY
Respiratory status	May be "comfortably blue"	Respiratory distress
Response to crying	Worsening cyanosis	Improved cyanosis
Response to oxygen	Minimal or no improvement	Improvement with oxygen

Cyanosis due to severe pulmonary disease (e.g., severe pneumonia, tension pneumothorax, acute chest syndrome of sickle cell disease) may not show significant improvement with supplemental oxygen, but these children will also typically exhibit severe respiratory distress along with clinical cyanosis.

Box 171-3 Key Elements to Elicit in the History of a Child with a Known Cardiac Disorder

Cardiac Diagnosis
Congenital or acquired disorder?
Any episodes of previous decompensation? (If so, are the current signs and symptoms similar to or different from those previous episodes?)

Oxygen Issues
Currently receiving home oxygen supplementation (continuous or only during feedings and sleep)?
Baseline oxygen saturation (room air or while receiving home oxygen)?
Any recent need for increasing the amount of supplemental oxygen?

Medications
Names and dosages of all current medications (cardiac and noncardiac medications)?
Were any of these cardiac medications stopped recently (by the cardiologist or parental noncompliance)?
Any recent increases in the cardiac medications (reasons for the increase, previous dosage versus the current dosage, and the date this dosage was increased)?
Any new cardiac medications added recently and the reason for these additions?
Recent digoxin level if the patient is receiving daily digoxin therapy?

Results of Most Recent Studies (Chest Radiograph, Electrocardiogram, Echocardiogram, and Cardiac Catheterization)
When were the last studies performed, and what were the results?
Why were those studies performed (routine follow-up studies or obtained because of decompensation from baseline, or a planned evaluation for an upcoming surgical procedure)?

Surgical Procedures
Previous procedures and complications?
Any future planned procedures?

In addition to a well-focused history and physical examination, a chest radiograph and an ECG should be obtained for any child with a known or suspected cardiac disorder. Other useful ancillary studies include an arterial blood gas analysis, hemoglobin and hematocrit levels, digoxin levels in those patients receiving daily digoxin, serum electrolyte values in those patients receiving daily diuretic therapy, and the 100% oxygen (hyperoxia) challenge.

History

The presence of certain maternal medical conditions has been associated with a higher incidence of cardiac disorders. For example, congenital heart blocks have been associated with maternal systemic lupus erythematosus and other collagen vascular disorders; infants of diabetic mothers have a higher incidence of cardiomyopathy.

Infants with an underlying congenital heart disorder may exhibit diaphoresis during feeds and poor weight gain secondary to congestive heart failure (CHF). The cause of the infant's hypoxia—cardiac or pulmonary—may be ascertained by the age at onset and the events surrounding a change in color. For example, an infant who sweats during feeding may exhibit a splanchnic steal from anomalous coronary arteries, causing transient ischemia, pain, color change, and diaphoresis that resolve after eating.[1] A child with an undiagnosed congenital heart defect may take longer to feed, frequently pausing to catch his or her breath, with subsequent poor weight gain and gradually increased work of breathing due to having CHF and pulmonary edema. Respiratory tract infections are common during childhood and may cause an acute deterioration in a child with an underlying cardiac disorder. In turn, children with congenital heart disease (CHD) with large left-to-right shunts and increased pulmonary blood flow tend to have a higher incidence of lower respiratory tract infections. Acute respiratory distress in these patients may be from a combination of pulmonary and cardiac factors (e.g., CHF).

Chest Pain

The majority of pediatric chest pain cases are noncardiac in origin and benign in nature. Common causes include musculoskeletal or chest wall pain, costochondritis, asthma exacerbations, pneumonia, pleurisy, gastritis, and gastroesophageal reflux. An often underdiagnosed cause of acute chest pain in the child or adolescent is referred to as the precordial catch syndrome (also known as Texidor's twinge). The pain is sharp, nonradiating, and located in the left periapical area of the chest wall; it occurs suddenly and is often exacerbated during inspiration but is not associated with dyspnea.[5] Patients may report that the pain took their breath away or that they were afraid to move; it typically resolves within a few minutes and is not associated with dysrhythmias or other sequelae. The pathophysiologic mechanism of precordial catch syndrome is unknown; the pain may originate from the parietal pleura or costal cartilage.[5] If an ECG and a chest radiograph are performed, findings are normal in these patients. The pain is fleeting but may recur at any time and at any age; giving the patient's symptoms a name emphasizes certainty in and familiarity with the diagnosis and reassures family members concerned about a cardiac etiology of their child's chest pain.[6]

Chest pain or syncope on exertion may be due to an underlying cardiac condition and deserves a more thorough investigation, especially if there is a positive family history of sudden unexplained death in young adulthood. Myocardial involvement secondary to drug abuse (e.g., cocaine, amphetamines, crystal methamphetamine) should be considered a potential cause in any adolescent patient who presents with chest discomfort or pain. Pulmonary embolism is a possible cause of chest pain, especially in pregnant adolescent girls or those who are taking oral contraceptive agents. The rare though life-threatening condition of aortic dissection should be considered as a cause of chest pain in a patient with physical examination stigmata that are suggestive of a collagen vascular disorder, such as Marfan syndrome. Patients with a known congenital heart defect or an acquired cardiac disorder (e.g., Kawasaki disease, acute rheumatic heart disease, myocarditis, pericarditis, cardiomyopathy) who present with chest pain also deserve a more thorough diagnostic evaluation,

www.ketabpezeshki.com 66485457-66963820

Table 171-2 Pediatric Vital Signs and Pertinent Formulas for Estimation of Blood Pressure

Simplified Pediatric Vital Signs[7]		
AGE GROUP	HEART RATE (beats/min)	RESPIRATORY RATE (breaths/min)
Newborn to 1 year	140	40
1-4 years	120	30
4-12 years	100	20
>12 years	80	15
Formulas to Calculate the Estimated Normal Blood Pressures in Children ≥1 Year of Age		
Estimated systolic blood pressure (SBP): [age in years × 2] + 90 mm Hg		
Estimated diastolic blood pressure: ⅔ × [estimated SBP]		
Minimum Acceptable Systolic Blood Pressure for Age		
Newborn to 1 month	60 mm Hg	
1 month to 1 year	70 mm Hg	
1-10 years	[Age in years × 2] + 70 mm Hg	
>10 years	90 mm Hg	

including serial cardiac biomarkers and ECGs to rule out myocardial infarction.

Physical Examination

General Appearance and Pulses

All four extremities should be palpated for the presence and quality of pulses. The brachial and femoral pulses are the easiest to feel in infants. Bounding pulses are typically present in infants with a patent ductus arteriosus. Coarctation of the aorta should be suspected in any child with strong or unequal pulses in the upper extremities and weak pulses in the lower extremities. The pulse may be weak and thready in all extremities in a child who presents with CHF and shock.

Vital Signs and Blood Pressures

A mild resting tachypnea or tachycardia may be the only clinical clue to an underlying cardiovascular disorder. Age-related variables in heart rates, respiratory rates, and blood pressures can be a source of frustration and confusion to those clinicians who do not manage pediatric patients on a routine basis. Although there are numerous tables of pediatric vital signs with variations based on sleep or awake states, one can easily recall a rough estimate of the normal pediatric heart rates and respiratory rates by a simplified table of pediatric vital signs (Table 171-2).[7] The methods to calculate the normal expected blood pressures and hypotensive blood pressures are also listed in Table 171-2.[8]

An accurate blood pressure reading is accomplished by use of a cuff that covers two thirds of the upper arm or thigh. A cuff that is too narrow will overestimate the patient's true blood pressure, and a cuff that is too large will underestimate the true blood pressure. Any child with a suspected cardiac disorder should have blood pressures measured in both arms. If the blood pressure in the left arm is significantly lower than the blood pressure in the right arm, a coarctation of the aorta proximal to the origin of the left subclavian artery should be suspected. Blood pressures should be measured in the thighs in any child with a suspected aortic coarctation or documented hypertensive blood pressures in the upper extremities. The mere presence of femoral pulses does not rule out clinically the possibility of a coarctation of the aorta. Even with an appropriately sized cuff, the blood pressures in the thighs can be 10 to 20 mm Hg higher than the blood pressures in the upper extremities because of the lack of well-designed blood pressure cuffs for the legs. Therefore, if the measured blood pressure in the lower extremities is lower than the blood pressure in the upper extremities, coarctation of the aorta should be suspected. Pulse oximetry readings that are lower in the legs than in the upper extremities are also suggestive of either a coarctation of the aorta or a right-to-left-shunt across a patent ductus arteriosus.[9]

Box 171-4 A Pathologic Etiology of a Heart Murmur Should Be Suspected with Any of the Following Criteria

- Diastolic murmurs
- Systolic murmurs that are louder than a grade 3/6, continuous, or associated with a thrill
- Murmurs that are associated with abnormal heart sounds (clicks, rubs, or gallop rhythms)
- Presence of cyanosis or respiratory distress
- Bounding pulses or weak pulses
- Abnormalities on the electrocardiogram
- An abnormal cardiac silhouette, abnormal pulmonary vascularity, or cardiomegaly on the chest radiograph

Cardiac Auscultation

The intensity and degree of splitting of the S_2 heart sound (which reflects closure of the pulmonic and aortic valves) are extremely important in a pediatric cardiologic evaluation. In normal children, both components (aortic closure and pulmonic closure) of S_2 should be heard along the left upper sternal border (the pulmonic area). A widely split and fixed S_2 suggests a physiologic problem resulting from either a constant volume overload to the right side of the heart (e.g., atrial septal defect) or a pressure overload to the right side of the heart (e.g., pulmonic stenosis). The classic congenital heart defect that is associated with a widely split and fixed S_2 is the atrial septal defect. The intensity of the S_2 component may be louder than normal in the child with pulmonary hypertension.

The third heart sound (S_3), which is best heard along the lower left sternal border or the apex, can be a normal finding in children and young adults. S_3 is produced by a rapid filling of the ventricles and is heard during early diastole, just after the S_2 sound. A loud S_3, however, is pathologic and due to dilated ventricles from volume overload (e.g., CHF and large ventricular septal defects). The fourth heart sound (S_4) occurs late in diastole, just before the S_1 sound. The finding of an S_4 is due to a decrease in compliance of a stiff, hypertrophic ventricle, best heard at the apex with the patient in the left lateral decubitus position.

Cardiac murmurs are produced by turbulent blood flow through the heart. The presence of a cardiac murmur may not be associated with an underlying cardiac defect, however. The location, intensity, quality, timing, and radiation of the murmur determine whether the murmur is suggestive of an underlying cardiac pathologic condition. Although systolic murmurs can be present without any underlying anatomic abnormalities, diastolic murmurs are always considered pathologic in nature. Some of the other criteria that would suggest an underlying anatomic cardiac abnormality are listed in Box 171-4. Murmurs may be difficult to appreciate in the noisy emergency department setting and given the degree of tachycardia that is often present even in normal infants. However, the location of the murmur may be a valuable clinical tool in determining the underlying anatomic origin of the murmur (Box 171-5).

www.ketabpezeshki.com 66485457-66963820

Box 171-5 Auscultation Locations of Common Systolic Murmurs in Children

Left Upper Sternal Border (Pulmonic Area)
Pulmonic valvular stenosis
Atrial septal defects (due to an increased pulmonic flow)
Innocent pulmonic ejection murmur
Neonate pulmonic flow murmur
Patent ductus arteriosus (a continuous, "machinery" sounding murmur)

Left Lower Sternal Border
Innocent vibratory Still's murmur
Ventricular septal defects
Endocardial cushion defects
Tetralogy of Fallot
Hypertrophic cardiomyopathy

Apex
Innocent vibratory Still's murmur
Mitral regurgitation
Aortic stenosis
Hypertrophic cardiomyopathy

Right Upper Sternal Border (Aortic Area)
Aortic stenosis
Coarctation of the aorta

Murmurs without any underlying anatomic abnormalities or hemodynamic significance are termed innocent or functional murmurs. All innocent murmurs are associated with normal ECGs and normal chest radiographs. Two of the most common innocent murmurs encountered in the pediatric population are the neonatal pulmonic flow murmur (also known as the peripheral pulmonic stenosis murmur) and Still's murmur. The pulmonic flow murmur of the neonate is due to the relatively thin walls and angulation of the right and left pulmonary arteries at birth. This systolic murmur is best heard at the left upper sternal border with radiation throughout the entire chest, axilla, and back. It usually disappears by 3 to 6 months of age. Persistence of a systolic murmur in the pulmonic area beyond this period should raise the possibility of a pathologic pulmonary arterial stenosis.

Another common innocent murmur in children is Still's murmur, which is a systolic murmur that typically occurs in children between 2 and 6 years of age. This systolic murmur is best heard along the left midsternal border. The distinctive quality of this murmur has been described as being vibratory, musical, and twanging and results from turbulent flow. The distinct quality of this murmur helps distinguish Still's murmur from a ventricular septal defect murmur, which has a harsher quality. The intensity of Still's murmur can be increased with fever, excitement, exercise, or anemia.

Hyperoxia Test

The hyperoxia test is an important bedside diagnostic tool to help differentiate between cardiac and pulmonary causes of central cyanosis. This test consists of assessment of the rise in arterial oxygenation with the administration of 100% oxygen. An arterial blood gas is measured on room air (if tolerated) and repeated after several minutes on high-flow oxygen (100% oxygen); the two blood gas analyses are then compared. When the child is breathing high-flow oxygen, an arterial oxygen partial pressure (Pao_2) of more than 250 mm Hg virtually excludes hypoxia due to CHD—a "passed" hyperoxia test.[10] An arterial oxygen reading of less than 100 mm Hg (in a child without obvious pulmonary disease) is consistent with a right-to-left shunt and is highly predictive of CHD—a "failed" hyperoxia test.[10] Values between 100 and 250 mm Hg may indicate lesions with intracardiac mixing. Pulse oximetry is not an appropriate substitute for an arterial blood gas analysis; it is not sensitive enough to determine "pass or fail" of the test because a child breathing high-flow oxygen and registering 100% on pulse oximetry may actually have a Pao_2 anywhere between 80 and 680 mm Hg.[1] Prolonged administration of 100% oxygen may cause some theoretic problems, such as closure of the ductus arteriosus in those infants with critical left-sided heart obstructions or pulmonary vasodilation (which would potentially worsen pulmonary vascular congestion).[3] However, oxygen should not be withheld initially in critically ill infants; continuous reassessment is crucial in the evaluation and management of children with suspected CHD.[1]

Arterial Blood Gas Analysis

Patients with CHF exacerbation can exhibit respiratory acidosis (low pH and high $Paco_2$) in addition to a low Pao_2. In contrast, children with compensated cyanotic congenital heart defects may have a normal pH despite a (chronically) low Pao_2. Patients with congenital heart defects who are not experiencing respiratory failure are unlikely to exhibit elevation in $Paco_2$. Any cardiac condition that results in inadequate tissue perfusion (i.e., any of the acyanotic congenital heart defects that are manifested in CHF) will exhibit a metabolic acidosis with or without respiratory compensation.

Hemoglobin and Hematocrit Levels and Serum Electrolyte Values

The hemoglobin and hematocrit levels may reveal a compensatory physiologic elevation (i.e., polycythemia) in children with cyanotic congenital heart defects. Any concurrent medical illness or blood loss that produces an acute anemia could potentially precipitate an acute deterioration by compromising the oxygen-carrying capacity in these children with an underlying congenital heart defect. Hemoglobin and hematocrit levels are also helpful in evaluating whether a child's pallor is due to CHF or anemia. Serum electrolyte values may be helpful in the evaluation of children with acute dysrhythmias or suspected metabolic acidosis and those children who are receiving chronic diuretic therapy.

Chest Radiography

Three features of the chest radiograph (Fig. 171-2) that deserve special attention are the cardiac size (cardiothoracic ratio), the cardiac shape (silhouette), and the degree of pulmonary vascular markings. The easiest method to determine the heart size in children is to determine the cardiothoracic ratio, which is obtained by comparing the largest transverse diameter of the cardiac shadow on the posteroanterior view of the chest radiograph with the widest internal diameter (measured from the inside rib margin to the widest point above the costophrenic angles) of the chest. The films should be obtained during maximal inspiration whenever possible.

The normal cardiothoracic ratio in children is approximately 50%. The cardiothoracic ratio is not very accurate in newborns and small infants, in whom a good inspiratory view is rarely obtained.[11] A cardiac silhouette that is larger than normal may be due to a shunt lesion, cardiomegaly, or pericardial effusion.[11] An enlarged heart shadow on a chest radiograph more reliably reflects a problem with volume overload rather than pressure overload. Problems with pressure overload are better represented on the ECG.

The cardiac size can be falsely increased in infants by the presence of the thymus, which can be seen in the mediastinum on the chest radiograph from birth until about 5 years of age. The thymic borders are typically wavy in appearance and sometimes can be

www.ketabpezeshki.com 66485457-66963820

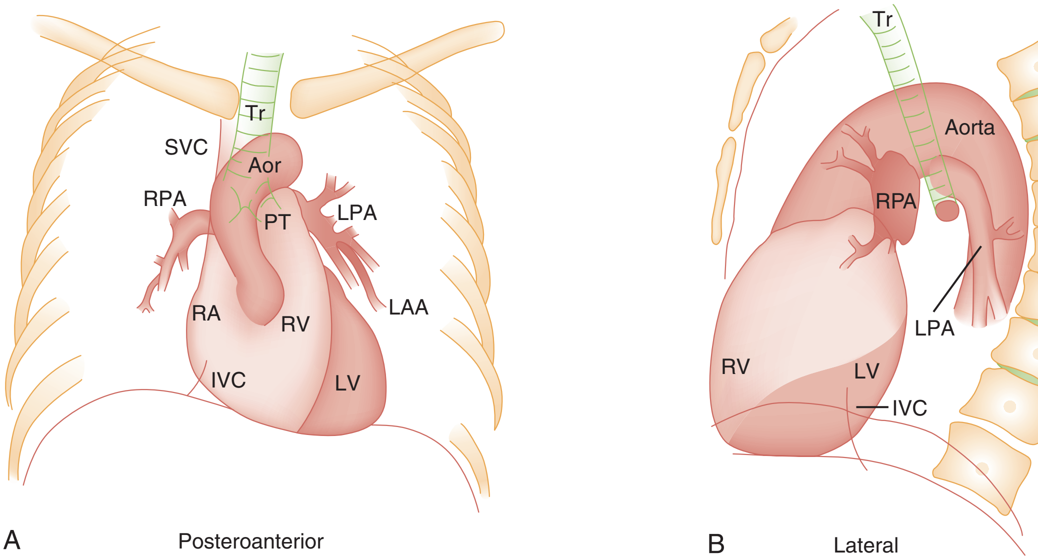


Figure 171-2. Diagrammatic representations of the anatomy of the chest radiograph. **A,** Normal heart in a young man, posteroanterior projection. *Aor,* aorta; *IVC,* inferior vena cava; *LAA,* left atrial appendage; *LPA,* left pulmonary artery; *LV,* left ventricle; *PT,* pulmonary trunk; *RA,* right atrium; *RPA,* right pulmonary artery; *RV,* right ventricle; *SVC,* superior vena cava; *Tr,* trachea. **B,** Right lateral projection of a normal heart in a young man. *IVC,* inferior vena cava; *LPA,* left pulmonary artery; *LV,* left ventricle; *RPA,* right pulmonary artery; *RV,* right ventricle; *Tr,* trachea.

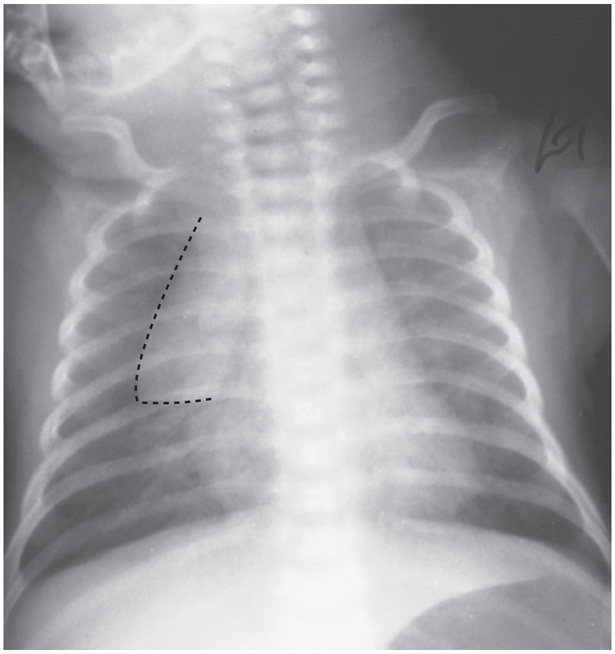


Figure 171-3. Thymic shadow demonstrating the "sail sign" along the right cardiac border (*dotted line*).

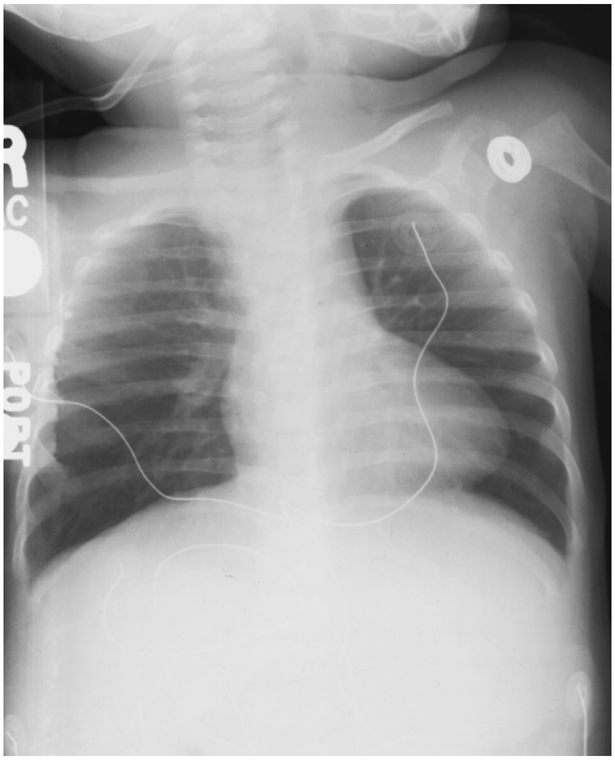


Figure 171-4. The classic boot-shaped heart of tetralogy of Fallot.

seen as the classic "sail sign" along the superior right border of the heart (Fig. 171-3). The thymic shadow may not be visible radiographically in infants during times of physiologic stress but should reappear when the infant recovers.

The three classic cardiac silhouettes seen in patients with congenital heart defects are the boot-shaped heart of tetralogy of Fallot (Fig. 171-4), the egg-on-a-string silhouette of transposition of the great vessels, and the snowman-shaped or figure-of-eight heart of total anomalous pulmonary venous return.

The degree of pulmonary vascular markings is one of the key factors to consider in working through the differential diagnosis of congenital heart defects. Increased pulmonary vascularity is present when the pulmonary arteries appear enlarged and are visible in the lateral third of the lung fields or the lung apices. Another marker of increased pulmonary vascularity is when the diameter of the right pulmonary artery in the right hilum on the posteroanterior view of the chest is wider than the internal diameter of the trachea. The differential diagnosis of a cyanotic infant with decreased vascular markings includes tetralogy of Fallot, pulmonary atresia, and tricuspid atresia. The cyanotic infant with increased vascular markings may have transposition of the great

www.ketabpezeshki.com 66485457-66963820

Table 171-3 Normal Electrocardiographic Values (PR, QRS, QTc, and QRS Axes) in Infants and Children[8]

AGE	PR INTERVAL Average (upper limit)	QRS DURATION Average (upper limit)
0-1 month	0.10 (0.12)	0.05 (0.07)
1 month to 1 year	0.10 (0.14)	0.05 (0.07)
1-3 years	0.11 (0.15)	0.06 (0.07)
3-8 years	0.13 (0.17)	0.07 (0.08)
8-12 years	0.15 (0.18)	0.07 (0.09)
12-16 years	0.15 (0.19)	0.07 (0.10)
Adult	0.16 (0.21)	0.08 (0.10)

The QTc interval should not exceed:
0.45 second in infants < 6 months old
0.44 second in children and adolescents

NORMAL QRS AXES IN INFANTS AND CHILDREN

Age	Mean Degrees (Range)
1 week to 1 month	+110 (+30 to +180)
1-3 months	+70 (+10 to +125)
3 months to 3 years	+60 (+10 to +110)
>3 years	+60 (+20 to +120)
Adults	+50 (−30 to +105)

NORMAL T WAVE AXIS IN INFANTS AND CHILDREN

Age	Leads V_1 and V_2	Lead AVF	Leads I, V_5, and V_6
Birth to 1 day	+/–	+	+/–
1-4 days	+/–	+	+
4 days to adolescent	–	–	+
Adolescent to adult	+	+	+

+, upright T wave; –, inverted T wave.

vessels, total anomalous pulmonary venous return, or truncus arteriosus. Increased vascular markings in an acyanotic infant are suggestive of an endocardial cushion defect, ventricular septal defect, atrial septal defect, or patent ductus arteriosus.

In a normal left-sided aortic arch, the aorta descends to the left of the midline and displaces the tracheal air shadow slightly toward the right of midline above the level of the carina. In contrast to this, the tracheal air shadow may be midline or deviated toward the left in the presence of a right-sided aortic arch.[3] It is important to note this finding because a right-sided aortic arch is found in up to 25% of the children with tetralogy of Fallot.[9] Rib notching secondary to increased collateral blood flow along the intercostal vessels can sometimes be appreciated between the fourth and eighth ribs in older children with undiagnosed coarctation of the aorta but is rarely visualized in children with coarctation of the aorta who are younger than 5 years.[11]

Electrocardiography

The electrocardiographic findings in infants and children can sometimes be problematic because various components of the ECGs change according to the child's age (Table 171-3).[8] At birth, the muscle mass of the right ventricle is greater than that of the left ventricle; this is demonstrated by right axis deviation on the neonatal ECG. By the end of the first month of life, the left ventricle assumes dominance. By 6 months of age, the left ventricular to right ventricular mass ratio is 2:1, which then reaches the adult ratio of 2.5:1 by adolescence. The durations of the PR interval, QRS complex, and QT intervals increase with age.

Left axis deviation is present when the QRS axis is less than the lower limit of normal for the child's age; it occurs with left ventricular hypertrophy and left bundle branch block. Right axis deviation is present when the QRS axis is greater than the upper limit of normal for the child's age; it occurs with right ventricular hypertrophy and right bundle branch block. A "superior" QRS axis (0 to −180 degrees with an S wave in aVF greater than the R wave) may be suggestive of an endocardial cushion defect or tricuspid atresia.

Some of the more common indications to obtain an ECG in a pediatric patient include chest pain, dyspnea, syncope, palpitations, and suspected dysrhythmias. Another indication to obtain an ECG is in those children with known cardiac disorders who present with signs and symptoms that could reflect an acute decompensation of their underlying disorder. A rare but potentially fatal congenital cardiac abnormality that will demonstrate electrocardiographic abnormalities (i.e., ischemic changes) is the condition of the anomalous origin of the left coronary artery. These infants have a history of poor feeding, irritability, and failure to thrive, then suddenly present with cardiogenic shock secondary to myocardial ischemia.

Biochemical Markers

As in adults, cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are highly sensitive and specific in children for myocardial damage.[11] Reference values are slightly higher for neonates younger than 3 months; normal and indeterminate values will depend on the bioassay used.[11] The indications for troponin testing in children include suspected cardiac ischemia (of any etiology), myocarditis, and myocardial dysfunction in sepsis syndrome.[11,12] Several studies have evaluated the use of plasma B-type natriuretic peptide (BNP) levels in the assessment and management of CHF in adults.[13] Studies of BNP levels in children have demonstrated a similar correlation of elevated levels in children with CHF, and these also correlated with the clinical symptoms of heart failure and the ejection fraction as measured by echocardiography.[14] The clinician is urged to refer to the particular range of age-specific values from the laboratory kit used at his or her institution.

SPECIFIC DISORDERS

Congenital Heart Disease

Perspective

The incidence of CHD in the United States has remained fairly constant at approximately 1%, or 8 to 10 cases per 1000 live births. This equates to approximately 32,000 infants born each year with some form of CHD[15] (Table 171-4). Although a large percentage of CHD is now detected with prenatal ultrasonograms, one study also recommended routine pulse oximeter readings in all newborns before discharge from the nursery as an additional inexpensive screening tool for CHD.[16]

Clinical Features

The age, severity of symptoms, and time of presentation of a child with CHD vary by the specific defect, complexity and severity of the defect, and timing of the normal physiologic changes that occur as the fetal circulation transitions to that of a neonate (Table 171-5). The more severe or complex CHD lesions may not be clinically apparent immediately after birth. However, as the ductus arteriosus begins to close in the first several weeks of life, cardiac defects with obstructive lesions of the pulmonary or systemic

www.ketabpezeshki.com 66485457-66963820

Table 171-4 Incidence of Specific Congenital Heart Defects (CHDs)

DEFECT	PERCENTAGE OF CHD
Acyanotic CHDs	
Ventricular septal defect	20-25
Atrial septal defect	5-10
Patent ductus arteriosus	5-10
Coarctation of the aorta	8
Pulmonic stenosis	5-8
Aortic stenosis	5
Cyanotic CHDs	
Tetralogy of Fallot	10
Transposition of the great arteries	5
Tricuspid atresia	1-2
Total anomalous pulmonary venous return	1
Truncus arteriosus	<1
Pulmonary atresia	<1
Ebstein's anomaly	<1
Hypoplastic left heart syndrome	<1
Hypoplastic right heart syndrome	<1

Table 171-5 Symptomatic Presentation of Congenital Heart Defects (CHDs) and Time of Presentation

DEFECT	TIME OF PRESENTATION
CHDs That Present with Cyanosis	
Transposition of the great arteries	Birth to 2 weeks
Total anomalous pulmonary venous return	Birth to 2 weeks
Tricuspid atresia	Birth to 2 weeks
Ebstein's anomaly of the tricuspid valve	Birth to 2 weeks
Truncus arteriosus	Birth to 2 weeks
Pulmonary atresia	Birth to 2 weeks
Hypoplastic right heart syndrome	Birth to 2 weeks
Hypoplastic left heart syndrome	Birth to 2 weeks
Tetralogy of Fallot	Birth to 12 weeks
CHDs That Present with Shock	
Coarctation of the aorta	From first week on
Aortic stenosis	From first week on
CHDs That Present with Congestive Heart Failure	
Ventricular septal defects	From 4 weeks on
Patent ductus arteriosus	From 4 weeks on

circulations will be unmasked, and these infants will present clinically with acute cyanosis, shock, or both. Even the harsh systolic murmur of a large, isolated ventricular septal defect may not be heard until about the fourth to sixth week of life when the left-to-right shunt across the ventricular septal defect increases because of the decrease in the PVR. In general, the more severe the anatomic defect is (i.e., lack of pulmonary blood flow or lack of systemic blood flow), the earlier in life these conditions will be manifested with cyanosis and shock.

Box 171-6 Clinical Clues to Aid in the Diagnosis of Congenital Heart Disease (CHD)

Presence or Absence of Central or Peripheral Cyanosis?

Central cyanosis with minimal respiratory distress ("comfortably blue") is suggestive of CHD more than of a purely pulmonary etiology.

Abnormalities in Cardiac Auscultation?

Murmurs: systolic versus diastolic, location, and radiation
Quality of S_1, S_2, and the presence of any clicks or gallops

Change in the Degree of Central Cyanosis with Crying?

Worsening of cyanosis with crying suggests a cardiac rather than a purely pulmonary etiology.

Response of PaO_2 to the Hyperoxia Challenge (Administering 100% Oxygen)?

Purely pulmonary causes of cyanosis: PaO_2 should rise to levels above 250 mm Hg
Cyanotic CHD associated with an increased pulmonary blood flow: PaO_2 may occasionally reach as high as 150 mm Hg
Cyanotic CHD associated with a decreased pulmonary blood flow: PaO_2 will not rise above 100 mm Hg

Chest Radiograph Abnormalities?

Cardiac size and shape (one of the three classic cardiac silhouettes)?
- Boot-shaped heart: tetralogy of Fallot
- Egg-on-a-string silhouette: transposition of the great vessels
- Snowman-shaped or figure-of-eight heart: total anomalous pulmonary venous return

Degree of Pulmonary Blood Flow?

Increased (acyanotic): atrial septal defect, Eisenmenger's syndrome, ventricular septal defect, patent ductus arteriosus, endocardial cushion defects
Increased (cyanotic): transposition of the great arteries, total anomalous pulmonary venous return, hypoplastic left heart syndrome, truncus arteriosus
Decreased or normal (acyanotic): pulmonic stenosis, aortic stenosis, coarctation of the aorta
Decreased (cyanotic): tetralogy of Fallot, severe pulmonic stenosis, Ebstein's anomaly, tricuspid atresia, pulmonary atresia, hypoplastic right heart syndrome

Electrocardiographic Abnormalities?

Evidence of chamber enlargement: right ventricular hypertrophy, left ventricular hypertrophy, biventricular hypertrophy, right atrial hypertrophy, or left atrial hypertrophy
An abnormal superior QRS axis is suggestive of endocardial cushion defect or tricuspid atresia.

Although CHD has been subdivided traditionally into cyanotic and acyanotic conditions, not all CHD lesions will fit neatly into a single category; some of the more complex defects have mixed pathophysiologic effects. The exact anatomic diagnosis of a CHD is dependent on echocardiography or cardiac catheterization; establishment of the exact anatomic diagnosis seldom is possible in the emergency department setting.

Diagnostic Strategies

The emergency physician must rely on several key elements of the clinical examination in addition to findings on the chest radiograph and ECG to narrow the diagnostic possibilities. For example, with use of the data in Box 171-6, the presence of cyanosis, a grade 3/6 systolic ejection murmur best heard at the midleft sternal border, a boot-shaped heart, and a decreased pulmonary blood flow on the chest radiograph with evidence of right ventricular

www.ketabpezeshki.com 66485457-66963820

Box 171-7 Duct-Dependent Cardiac Lesions in the Neonate

Congenital heart diseases that require a patent ductus arteriosus to preserve blood flow from the aorta to the pulmonary circulation
- Tetralogy of Fallot
- Tricuspid atresia
- Pulmonary atresia
- Hypoplastic right heart syndrome
- Transposition of the great vessels

Congenital heart diseases that require a patent ductus arteriosus to preserve blood flow from the main pulmonary artery to the systemic circulation
- Severe coarctation of the aorta
- Severe aortic stenosis
- Hypoplastic left heart syndrome

Box 171-8 Prostaglandin E_1 (PGE_1) Infusion Preparation for Duct-Dependent Congenital Heart Disease

Infusion rate 0.05-0.1 µg/kg/min

Available PGE_1 solution: 500 µg/mL (Alprostadil)—always follow manufacturer's directions.

Add one ampule (500 µg) PGE_1 to 250 mL of D_5W. This yields 2 µg/mL. To achieve 0.1 µg/kg/min, infuse at 0.05 mL/kg/min or 3 mL/kg/hr.

The above concentration of 2 µg/mL may be run as follows:

2-kg infant	0.1 mL/min or 6 mL/hr to achieve 0.1 µg/kg/min of PGE_1
2.5-kg infant	0.125 mL/min or 7.5 mL/hr to achieve 0.1 µg/kg/min of PGE_1
3-kg infant	0.15 mL/min or 9 mL/hr to achieve 0.1 µg/kg/min of PGE_1
3.5-kg infant	0.175 mL/min or 10.5 mL/hr to achieve 0.1 µg/kg/min of PGE_1
4-kg infant	0.2 mL/min or 12 mL/hr to achieve 0.1 µg/kg/min of PGE_1
4.5-kg infant	0.225 mL/min or 13.5 mL/hour to achieve 0.1 µg/kg/min of PGE_1
5-kg infant	0.25 mL/min or 15 mL/hour to achieve 0.1 µg/kg/min of PGE_1

From Siegfried BH, Henderson TO: Cardiology. In Gunn VL, Nechyba C (eds): The Harriet Lane Handbook: A Manual for Pediatric House Officers, 16th ed. Philadelphia, Mosby, 2002, p 123.

hypertrophy on the ECG suggest tetralogy of Fallot. Only a brief discussion of some of the more common CHDs is presented in this chapter.

Management

The majority of children who present to the emergency department with shock due to dehydration and hypovolemia are typically given intravenous fluids in boluses of 20 mL/kg. However, if a child with a suspected CHD presents to the emergency department in possible cardiogenic shock, one should consider use of smaller boluses of 10 mL/kg to prevent an iatrogenic complication of fluid overload. Frequent reassessment should be performed and the child's response after each bolus of 10 mL/kg monitored to determine whether additional fluid boluses or inotropic agents are necessary.

One unique pharmacologic intervention that can be lifesaving in infants involves the use of prostaglandin E_1 (PGE_1) to maintain the patency of the ductus arteriosus. CHD that is manifested within the first 2 to 3 weeks of life with a sudden onset of cyanosis or cardiovascular collapse is typically due to duct-dependent cardiac lesions (Box 171-7).[4]

Closure of the ductus arteriosus in patients with these specific cardiac lesions causes life-threatening situations by either an interruption of blood flow to the lungs, producing cyanosis (i.e., tricuspid atresia), or a disruption of blood flow to the systemic circulation, producing shock (i.e., hypoplastic left heart syndrome).[4] Box 171-8 details one suggested method to prepare this potentially lifesaving PGE_1 infusion. The PGE_1 infusion is typically started at 0.05 to 0.1 µg/kg/min (the method of preparation described in Box 171-8). A known adverse reaction to a PGE_1 infusion is apnea; one should perform endotracheal intubation on these infants before the initiation of the PGE_1 infusion. Not only will intubation provide a secure airway, but controlled ventilation will also help decrease the infant's work of breathing, shunting much needed cardiac output and metabolic demands from the overtaxed respiratory apparatus. Other adverse reactions to a PGE_1 infusion include fever, seizures, bradycardia, hypotension, flushing, and decreased platelet aggregation.

Acyanotic Congenital Heart Defect

Acyanotic CHD can be further subdivided (Fig. 171-5) into obstructive lesions (i.e., pulmonic stenosis, aortic stenosis, and coarctation of the aorta) and lesions characterized by left-to-right shunts with an associated increase in pulmonary blood flow (i.e., ventricular septal defects, atrial septal defects, patent ductus arteriosus, and endocardial cushion defects). These acyanotic lesions

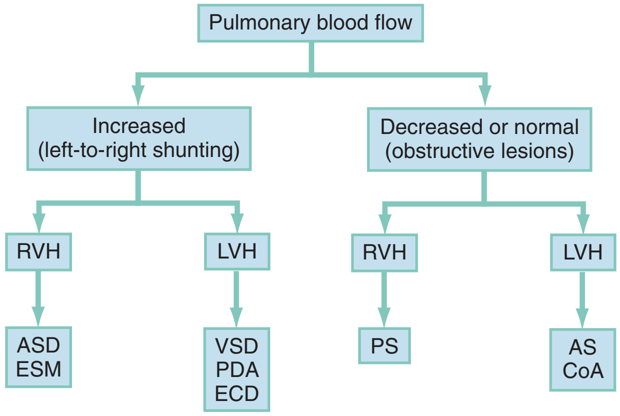


Figure 171-5. Clinical clues to diagnosis of acyanotic congenital heart defects. *AS,* aortic stenosis; *ASD,* atrial septal defect; *CoA,* coarctation of the aorta; *ECD,* endocardial cushion defect; *ESM,* Eisenmenger's syndrome; *LVH,* left ventricular hypertrophy; *PDA,* patent ductus arteriosus; *PS,* pulmonic stenosis; *RVH,* right ventricular hypertrophy; *VSD,* ventricular septal defect.

usually are manifested within the first 6 months of life with symptoms of CHF; however, atrial septal defects can remain asymptomatic until adulthood.

Ventricular Septal Defect

Perspective. Ventricular septal defects are the most common congenital cardiac defects and account for 20 to 25% of all cases of CHD. Spontaneous closure occurs in 30 to 40% of all ventricular septal defects overall and in 50 to 70% of smaller ventricular septal defects.[17]

Clinical Features. The degree of symptoms is dependent on the size of the ventricular septal defect and the degree of PVR. Most ventricular septal defects are clinically asymptomatic (minimal or no left-to-right shunting) immediately after birth because of the high PVR. When the PVR decreases to the normal levels at 6 to 8 weeks after birth, left-to-right shunting can then occur, and the

www.ketabpezeshki.com 66485457-66963820

typical systolic murmur of a ventricular septal defect will then be appreciated. Small ventricular septal defects may remain completely asymptomatic throughout childhood. Approximately 10% of the infants with large ventricular septal defects will eventually have signs and symptoms of CHF (e.g., poor feeding and poor growth) by 2 to 3 months of age because of the increased pulmonary blood flow. Older children with ventricular septal defects may exhibit signs of decreased exercise tolerance and recurrent pulmonary infections. If moderate to large ventricular septal defects are not surgically corrected, irreversible changes in the pulmonary vasculature may begin to occur as early as 6 to 12 months of age, which will result in an elevation of the PVR and pulmonary hypertension. This in turn can lead to a reversal of the shunt direction across the ventricular septal defect to now become a right-to-left shunt, Eisenmenger's syndrome, with resultant cyanosis.

Diagnostic Strategies. The chest radiograph in children with small ventricular septal defects may be entirely normal, but cardiomegaly with increased pulmonary vascular markings is usually present with untreated moderate to large ventricular septal defects. The ECG of moderate-sized ventricular septal defects typically reveals left ventricular hypertrophy, but biventricular hypertrophy may be present in ventricular septal defects with large left-to-right shunting.

Management. All ventricular septal defects, regardless of the size of the defect, are at risk for bacterial endocarditis because of the high velocity of turbulent blood flow through them.

Traditional closure of ventricular septal defects required open heart surgery. Today, however, a transcatheter closure technique that avoids the inherent risks and complications of open heart surgery and cardiopulmonary bypass has supplanted traditional methods.[18-20]

Atrial Septal Defect

Perspective. Atrial septal defects account for 5 to 10% of all cases of CHD. The majority of infants and children with atrial septal defects remain clinically asymptomatic until adulthood. Spontaneous closure has been reported in up to 40% of the cases within the first 5 years of life.[17]

Clinical Features. Large atrial septal defects or those associated with comorbid conditions, such as bronchopulmonary dysplasia, can be manifested with symptoms of CHF and pulmonary overcirculation (e.g., dyspnea with feedings, poor weight gain, and frequent lower respiratory tract infections).[3] The majority of atrial septal defects are discovered when a suspicious murmur is detected on a routine physical examination. A widely split and fixed S_2 is a characteristic finding of atrial septal defects.

Diagnostic Strategies. The chest radiograph of children with atrial septal defects will reveal varying degrees of cardiomegaly, right atrial and right ventricular enlargement, and a prominent main pulmonary artery segment and increased pulmonary vascular markings. The ECG will reveal varying degrees of right axis deviation and right ventricular hypertrophy. All patients with unrepaired atrial septal defects will have symptoms if pulmonary hypertension ensues. Patients with large atrial septal defects that are not detected and repaired are at risk for development of Eisenmenger's syndrome. Unlike ventricular septal defects, uncomplicated atrial septal defects are not associated with high risk of bacterial endocarditis because of the lower turbulence and velocity of blood flow through the atrial septal defects.

Management. The traditional closure of atrial septal defects, like that of ventricular septal defects, required open heart surgery to place a patch over the septal defect. Newer therapies involving closures with septal occluder devices placed by the transcatheter approach have been described.[21,22] Antiplatelet therapy during the 6-month period after placement of the device is typically given and is safe and effective in preventing thrombus formation on the surface of the septal occluder device.

Eisenmenger's Syndrome. Eisenmenger's syndrome can occur in any large left-to-right shunt defect that is not surgically corrected. When large ventricular septal defects and atrial septal defects are not surgically corrected, irreversible changes can occur in the pulmonary arterioles, leading to pulmonary vascular obstruction and pulmonary hypertension. As the degree of pulmonary hypertension increases, the PVR may then begin to exceed the SVR. This causes right-sided pressures to exceed those on the left, causing right-to-left shunting. The reversal in the direction of shunt flow produces cyanosis. Other clinical features of patients who have Eisenmenger's syndrome include chest pain, dyspnea on exertion, and hemoptysis.[23]

Coarctation of the Aorta

Perspective. Coarctation of the aorta accounts for approximately 8% of all CHD, and up to 50% of patients with coarctation of the aorta also have an associated bicuspid aortic valve.[24] The area of coarctation can occur proximal to the insertion of the ductus arteriosus (preductal type) or distal to the insertion of the ductus arteriosus (postductal type). The majority of cases (89%) are of the postductal type.[24]

Clinical Features. The severity of the symptoms and the age at time of presentation are dependent on the location of the coarctation, the degree of narrowing, and the presence of any other associated cardiac defects. Infants with the rarer, preductal type of coarctation of the aorta may also exhibit differential cyanosis if the ductus arteriosus remains open.[25] The upper half of the body is perfused with well-oxygenated blood supplied by the left ventricle and the ascending aorta. However, the lower half of the body will appear cyanotic, as it is largely perfused by right-to-left shunting of deoxygenated blood from the patent ductus arteriosus into the descending aorta. Infants with the preductal type of coarctation of the aorta will present with signs of circulatory failure and shock when the ductus arteriosus begins to close. The astute clinician may find a "brachial-femoral delay" by palpating both pulses simultaneously.[26]

Most of the asymptomatic cases of the more common postductal coarctation of the aorta are diagnosed as a result of a cardiology referral for a systolic murmur or a hypertension workup, but infants with severe postductal coarctation of the aorta can also present during the first few weeks of life with signs of circulatory failure and shock. If a child is discovered to have hypertension on a routine physical examination, it is necessary to obtain blood pressure measurements in the lower extremities to assess the possibility of coarctation of the aorta. A systolic blood pressure in the right arm that is 15 to 20 mm Hg higher than that in the legs is sufficient evidence to suspect coarctation of the aorta because the systolic blood pressure in the legs is normally higher than that in the arms.[25] If the systolic pressure in the right arm is higher than that in the left arm, the area of coarctation is probably preductal and located proximal to the origin of the left subclavian artery. In general, diastolic blood pressures are similar in the upper and lower extremities.

Diagnostic Strategies. The chest radiograph will most often reveal a normal-sized cardiac silhouette and normal pulmonary vascular markings, but notching along the lower borders of the posterior fourth to eighth ribs due to the pressure of the dilated collateral vessels may be exhibited in children older than 5 years. The absence of rib notching, however, does not rule out the possibility of coarctation of the aorta. The ECG typically reveals a left axis and left ventricular hypertrophy. Suspected cases of coarctation of the aorta should be imaged with transthoracic echocardiography or cardiac magnetic resonance imaging to confirm and to define the coarctation[26]; in stable patients, this can be done on an outpatient basis.

Management. Definitive surgical repair of coarctation of the aorta involves resection of the narrowed section of the aorta with an end-to-end anastomosis. Complications of undiagnosed

www.ketabpezeshki.com 66485457-66963820

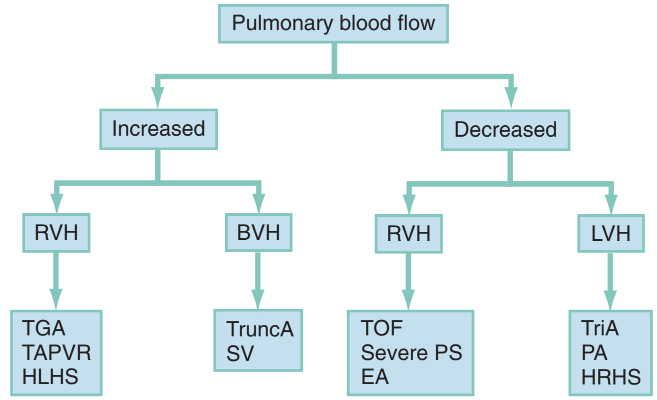


Figure 171-6. Clinical clues to diagnosis of cyanotic congenital heart defects. *BVH,* biventricular hypertrophy; *EA,* Ebstein's anomaly; *HLHS,* hypoplastic left heart syndrome; *HRHS,* hypoplastic right heart syndrome; *LVH,* left ventricular hypertrophy; *PA,* pulmonary atresia; *PS,* pulmonary stenosis; *RVH,* right ventricular hypertrophy; *SV,* single ventricle; *TAPVR,* total anomalous pulmonary venous return; *TGA,* transposition of the great arteries; *TOF,* tetralogy of Fallot; *TriA,* tricuspid atresia; *TruncA,* truncus arteriosus.

cases are related to the resultant hypertension and can include heart failure, hypertensive encephalopathy, and intracranial hemorrhages.

Cyanotic Congenital Heart Diseases

Cyanotic CHDs are a result of either decreased pulmonary blood flow to the lungs or right-to-left shunting of desaturated blood directly into the systemic circulation. They can be further subdivided into those conditions with an increased pulmonary blood flow and those lesions with decreased pulmonary blood flow (Fig. 171-6). The classic cyanotic CHD can be remembered by the five *t*'s: truncus arteriosus, transposition of the great vessels, tricuspid atresia, tetralogy of Fallot, and total anomalous pulmonary venous return. Other forms of cyanotic CHD include Ebstein's anomaly, pulmonary atresia, severe pulmonary stenosis, hypoplastic left heart syndrome, and hypoplastic right heart syndrome. Many of these cyanotic heart lesions are routinely detected either on prenatal ultrasonographic examinations or in the nursery; only tetralogy of Fallot is covered in this section.

Tetralogy of Fallot

Perspective. Tetralogy of Fallot accounts for approximately 10% of all cases of CHD and is the most common cause of cyanotic CHD beyond infancy. Tetralogy of Fallot is often associated with other cardiac defects, such as right-sided aortic arch (25% of patients), atrial septal defect (10% of patients), and anomalous origin of the left coronary artery.[27] Tetralogy of Fallot arises from a single embryologic defect in which the subpulmonic conus fails to expand, resulting in the four abnormalities (Fig. 171-7): (1) right ventricular outflow tract obstruction; (2) large, unrestrictive, malaligned ventricular septal defect; (3) over-riding aorta that receives blood flow from both ventricles; and (4) right ventricular hypertrophy secondary to the high pressure load placed on the right ventricle by the right ventricular outflow tract obstruction. These anatomic defects collectively result in decreased pulmonary blood flow and varying degrees of right-to-left shunting of deoxygenated blood across the ventricular septal defect.

Clinical Features. The degree of cyanosis and the age at presentation are directly dependent on the degree of right ventricular outflow tract obstruction. Infants with tetralogy of Fallot typically have worsening of their cyanosis during crying and feeding. Older children with tetralogy of Fallot may have cyanotic exacerbations during periods of physical exertion. Infants who have milder

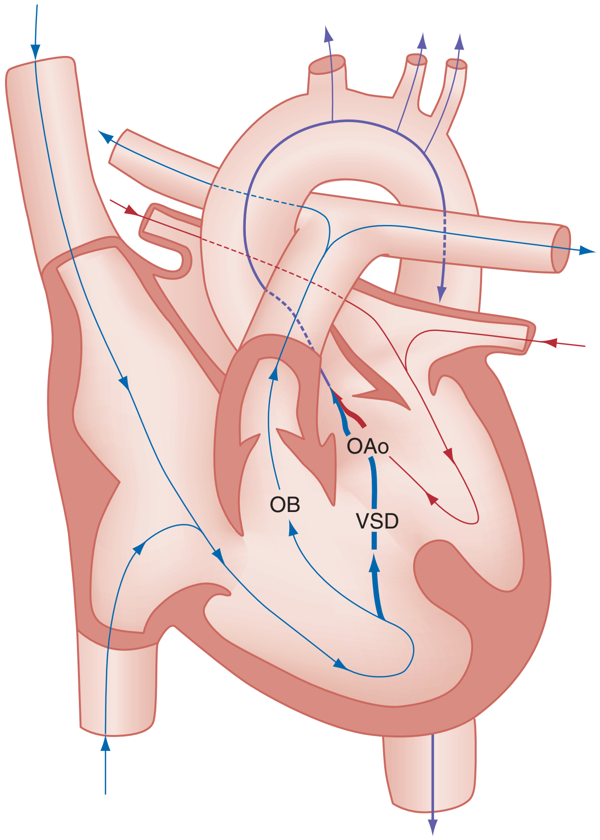


Figure 171-7. Diagrammatic representation of the right-to-left shunting that occurs in tetralogy of Fallot. Some of the deoxygenated blood (*thick blue arrow*) in the right ventricle is shunted across the ventricular septal defect (*VSD*) into the left ventricle. This deoxygenated blood mixes with the well-oxygenated blood from the lungs (*red arrow*). The blood that is ejected out through the overriding aorta (*OAo*) therefore contains blood of mixed oxygenation (*purple arrows*). The amount of deoxygenated blood that is shunted through the VSD (*thick blue arrow*) is dependent on a combination of factors, including the severity of right ventricular outflow tract obstruction (*OB*), the size of the VSD, and the degree of systemic vascular resistance. When the systemic vascular resistance falls (as occurs during a tet spell), more deoxygenated blood from the right ventricle will be shunted across the VSD into the systemic circulation, which results in hypoxia, metabolic acidosis, and worsening cyanosis.

forms of right ventricular outflow tract obstruction may be acyanotic and are sometimes referred to as having a "pink" tetralogy of Fallot. However, the majority of the cases of tetralogy of Fallot exhibit some degree of cyanosis. Infants with severe right ventricular outflow tract obstruction exhibit profound cyanosis within the first few days of life and may even require a PGE_1 infusion to preserve pulmonary blood flow by left-to-right shunting from the aorta into the main pulmonary artery through the patent ductus arteriosus.

The physical examination can reveal varying degrees of cyanosis and a systolic ejection murmur along the left sternal border. Chronic hypoxemia results in a compensatory polycythemia and varying degrees of clubbing of the fingers and toes.

Diagnostic Strategies. The chest radiograph of a patient with cyanotic tetralogy of Fallot (see Fig. 171-4) reveals decreased pulmonary vascular markings and a boot-shaped heart (secondary to a concave main pulmonary artery segment along the superior aspect of the left border of the heart). The heart size in tetralogy of Fallot is normal, and a right-sided aortic arch may be seen in 25% of the cases. The ECG of cyanotic tetralogy of Fallot reveals

www.ketabpezeshki.com 66485457-66963820

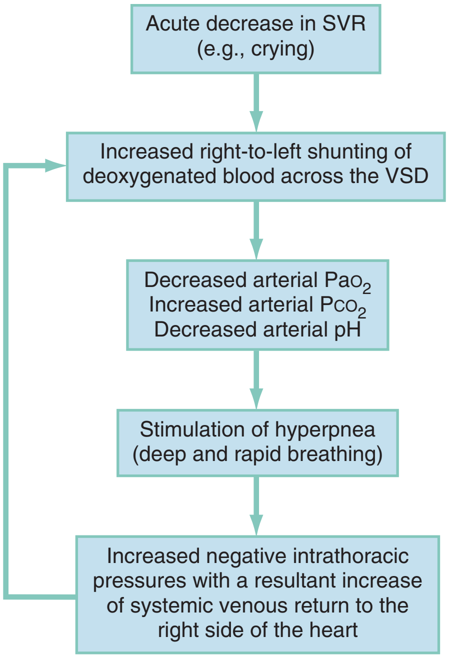


Figure 171-8. Pathophysiologic mechanisms of a hypoxic (tet) spell. *SVR,* systemic vascular resistance; *VSD,* ventricular septal defect.

right ventricular hypertrophy and a right axis deviation. Children with pink tetralogy of Fallot may not initially exhibit any degree of right ventricular hypertrophy, but these acyanotic forms of tetralogy of Fallot gradually develop the cyanotic form by 1 to 3 years of age.

A potentially life-threatening complication of tetralogy of Fallot that can be seen in a patient who presents to the emergency department is the so-called tet spell, which has also been referred to as the hypercyanotic spell or the hypoxic spell. Although these hypoxic spells can occur in children with other forms of CHD, they are most commonly seen in infants and children with tetralogy of Fallot and hence the term *tet spells*. These episodes occur most commonly in infants, with a peak incidence between 2 and 4 months of age.[27]

Any event that suddenly lowers the SVR, such as crying or defecation, will produce a large right-to-left shunt across the ventricular septal defect, beginning the vicious circle of a hypoxic spell. Acute hypovolemia and tachycardia can also precipitate tet spells. The large right-to-left shunt through the ventricular septal defect bypasses the lungs, which then causes a decrease in the Pao_2, an increase in the Pco_2, and a fall in the arterial pH. These metabolic changes then stimulate the respiratory centers in the brain to produce hyperpnea (deep and rapid respirations), which increases the negative intrathoracic pressure during inspiration, causing an increase in the systemic venous blood return to the right side of the heart. This increased volume of blood in the right ventricle is then shunted through the ventricular septal defect by the combination of the existing right ventricular tract outflow obstruction and the acute decrease in the SVR. This in turn further decreases the arterial oxygen saturation, perpetuating the hypoxic spell (Fig. 171-8).

These hypoxic spells are characterized clinically by periods of hyperpnea, uncontrollable crying, and worsening cyanosis. Limpness, seizures, cerebrovascular accidents, and even death have been reported with more severe tet spells. During a tet spell, the intensity of the murmur decreases because of less blood flow through the right ventricular tract obstruction and more blood being shunted from the right ventricle to the left ventricle through the ventricular septal defect.

Box 171-9 Management of Tetralogy of Fallot Hypoxic Spells

Place the infant in the knee-to-chest position to increase the systemic vascular resistance, which decreases the right-to-left shunt across the ventricular septal defect.
Provide supplemental oxygen (limited value by itself).
Morphine: 0.1-0.2 mg/kg IV or IM
Fentanyl: 1 µg/kg/dose IV or IM as an alternative to morphine
Sodium bicarbonate: 1 mEq/kg IV
Consider ketamine: 1-2 mg/kg IV or IM
Consider propranolol[8]: 0.01-0.2 mg/kg IV
Consider phenylephrine[8]: 0.01-0.02 mg/kg IV

Management. The overall treatment goals for tet spells (Box 171-9) are to increase the SVR, to abolish the hyperpnea, and to correct the metabolic acidosis. Although supplemental oxygen should be provided, this alone will not reverse a tet spell because there is a decrease in the amount of pulmonary blood flow and an increase in the amount of right-to-left shunting across the ventricular septal defect. The infant should be picked up and placed in a knee-to-chest position. Older children can be placed in the squatting position. Both maneuvers are believed to increase the SVR and to decrease the amount of systemic venous blood return to the right side of the heart. Morphine (0.1-0.2 mg/kg) has been traditionally given intramuscularly to calm the child, to decrease catecholamine surge, and to decrease the respiratory rate. A theoretic adverse effect of morphine, however, is that it can cause systemic vasodilation (further decreasing the SVR) by endogenous histamine release.[28] Although there are no current studies evaluating the use of other medications that may also suppress the respiratory centers, fentanyl and midazolam may be used for the same effect without the potential risk of endogenous histamine release. Ketamine (1-2 mg/kg intravenously or 3-5 mg/kg intramuscularly) has also been suggested for its sedative effect as well as for its effect on increasing the SVR.[25] Sodium bicarbonate (1 mEq/kg intravenously) can be given to correct clinically suspected or documented (pH < 7.4) metabolic acidosis and to reduce the respiratory center—stimulating effects of acidosis. Most infants respond to these measures and exhibit an improvement in their oxygenation and a decrease in their degree of cyanosis. Infants whose condition does not improve with these measures may require a vasopressor such as phenylephrine to increase the SVR and thereby to decrease the degree of right-to-left shunting across the ventricular septal defect. An intravenous fluid bolus may also be considered to increase the volume of blood flow through the pulmonary artery. Propranolol has also been used as an adjunct to break the cycle of a tet spell. Although the exact pharmacophysiologic mechanisms by which propranolol accomplishes this is uncertain, it is thought to increase the SVR and perhaps to promote an increase in the pulmonary blood flow by reducing spasms of the right ventricular outflow tract obstruction.

Palliative surgical procedures to increase the amount of blood flow temporarily to the pulmonary arteries are performed in infants with severe cyanotic tetralogy of Fallot. The most commonly performed procedure is the modified Blalock-Taussig shunt, in which an anastomosis is created between the subclavian artery and the ipsilateral pulmonary artery. Definitive surgical repair of tetralogy of Fallot consists of closing the ventricular septal defect and opening the right ventricular outflow tract obstruction by resection of the infundibular tissue. The mortality rate is 5 to 10% within the first 2 years after definitive surgical repair in uncomplicated tetralogy of Fallot cases. Complications that can occur after definitive surgical repair include complete heart block, ventricular dysrhythmias, and right bundle branch block (secondary to the right ventriculotomy). Bacterial

www.ketabpezeshki.com 66485457-66963820

endocarditis prophylaxis is still recommended after the definitive surgical repair of tetralogy of Fallot.

Postoperative Complications of Congenital Heart Defects

A variety of postoperative complications can be seen in patients who present to the emergency department weeks to months after cardiac surgery. The types of complications that could occur in each case depend on the original underlying cardiac defect and the surgical procedure that was used to correct that defect. Some of the complications that may be seen in the emergency department include thrombosis of a shunt-conduit with decreased flow, increased shunt-conduit flow with resultant CHF, atrial and ventricular dysrhythmias, heart blocks, myocardial ischemia, and endocarditis. The size of the cardiac silhouette and the degree of pulmonary blood flow visualized on the chest radiograph may provide valuable clues as to whether there is an increased or decreased blood flow through a surgical conduit that was created to provide an improvement in blood flow to the pulmonary system.[29] Comparison of the child's other postoperative chest radiographs can help determine whether there has been a change in the heart size and pulmonary vascularity.

The postpericardiotomy syndrome is an inflammatory pericarditis that can occur 1 to 6 weeks after any surgical procedure that involved a pericardiotomy. This immunologic phenomenon is believed to occur as a sequela of blood in the pericardial sac. This syndrome is characterized by fever, chest pain, and pericardial effusion. A pericardial friction rub may be heard, depending on the amount of fluid that accumulates in the pericardial sac. The chest radiograph may reveal an enlarged cardiac silhouette, and the echocardiogram will confirm the diagnosis. Pericardiocentesis is rarely required but may be necessary if the amount of pericardial effusion is significant enough to cause a pericardial tamponade. The majority of cases will resolve within 2 to 3 weeks with bed rest and nonsteroidal anti-inflammatory medication.

Many of these postoperative complications, including the postpericardiotomy syndrome, can be avoided in children who undergo closure of patent ductus arteriosus, atrial septal defects, and ventricular septal defects by the transcatheter placement of various occluder devices.

Respiratory Syncytial Virus Infections in Infants and Children with Congenital Heart Defects

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections in infants and children worldwide, with the majority of children being infected at least once by 2 years of age. Reinfection occurs commonly throughout life.[29] RSV lower respiratory tract infections account for more than 125,000 pediatric admissions annually in the United States, with a fatality rate of 6.3 deaths per 100,000 patients up to 4 years of age (Box 171-10).[30,31] Children with CHD who have RSV infections tend to have a higher rate of intensive care unit admissions and require mechanical ventilation more frequently than those children who do not have CHD. Children with CHD who require hospitalization for RSV infection have a fatality rate that is two to six times greater than that of children without CHD.[30,31] RSV is responsible for a mortality rate of 40% in infants with CHD and up to 70% in infants with CHD and associated pulmonary hypertension.

Two products can be used to prevent RSV infections. Both of these preparations require monthly administration before the onset of the peak RSV season, which typically runs from November through March in most of the United States. The two currently available preparations are palivizumab (Synagis, a humanized monoclonal antibody) and RSV immune globulin (RespiGam).[32] The use of palivizumab in the prevention of RSV infections in high-risk infants and children has largely replaced RSV immune globulin because palivizumab can be given intramuscularly, requires a 100-fold lesser volume, and has a 50-fold smaller protein load than RSV immune globulin.[33]

In 1998 the Food and Drug Administration gave approval for the use of palivizumab in prevention of RSV lower respiratory tract infections in selected infants and children who were deemed to have a higher risk of severe infections. During the 4-year period from 1998 to 2002, several multicenter studies involving more than 24,000 subjects (including data from the Palivizumab Outcomes Registry) have demonstrated the efficacy of palivizumab in preventing hospitalizations of high-risk infants and children.[34] During this same 4-year period, another multicenter study involving six countries demonstrated a 45% relative reduction in hospitalization of 1287 high-risk children younger than 2 years with CHD who were given monthly intramuscular injections of palivizumab during a 5-month period.[33] This study also demonstrated a significant reduction in the total number of hospital days, supplemental oxygen requirement, total number of days in the intensive care unit, and total number of days requiring intubation in the group that received the monthly palivizumab intramuscular injections. On the basis of these results, the Food and Drug Administration in September 2003 gave approval for the use of palivizumab in infants and children with hemodynamically significant CHD (Box 171-11). The American Academy of Pediatrics emphasizes that prophylaxis with palivizumab should be initiated before the onset of the RSV season. RSV can persist on environmental surfaces for several hours; the best method to prevent the spread of RSV-contaminated secretions within the emergency department setting is meticulous handwashing and wearing of a mask in caring for children with a documented or suspected RSV infection.

Box 171-10 Conditions Associated with an Increased Risk of Severe or Fatal Respiratory Syncytial Virus Infections

- Cyanotic or complex congenital heart defects
- Pulmonary hypertension
- Prematurity (especially those infants with bronchopulmonary dysplasia or chronic lung disease)
- Immunodeficiency states

Box 171-11 Recommendations for Palivizumab Administration in Children with Congenital Heart Disease (CHD)

- CHD conditions that would benefit from palivizumab administration (15 mg/kg intramuscularly every 30 days during the respiratory syncytial virus season only)
  - Cyanotic or complex CHD
  - Congenital heart failure requiring medications
  - Moderate to severe pulmonary hypertension
- Children with hemodynamically insignificant CHD who do not require palivizumab administration
  - Secundum atrial septal defect
  - Small ventricular septal defect
  - Pulmonic stenosis
  - Uncomplicated aortic stenosis
  - Mild coarctation of the aorta
  - Patent ductus arteriosus

www.ketabpezeshki.com 66485457-66963820

Congestive Heart Failure

Perspective

CHF is defined as a clinical syndrome in which the cardiac output is unable to meet the hemodynamic and metabolic demands of the body. Although there is a wide array of causes of CHF, the primary cause in infants and children is CHD, which results in volume or pressure overload. Other causes of CHF include the anomalous left coronary artery in infants, myocarditis, endocarditis, rheumatic heart disease, pericardial effusions, anemia, cardiomyopathies, systemic hypertension, hypothyroidism, electrolyte imbalances, endocrine disorders, cardiac toxins, and dysrhythmias that compromise cardiac output.

CHF can result from a derangement in any of the four primary determinants of normal cardiac function: (1) excessive preload (e.g., large left-to-right shunts and severe chronic anemia); (2) decreased cardiac contractility (e.g., myocarditis); (3) excessive afterload (i.e., left-sided obstructive lesions); and (4) rhythm abnormalities that compromise cardiac output or stroke volume (e.g., paroxysmal supraventricular tachycardia and severe forms of heart block). The treatment of CHF depends on which of these four primary determinants of normal cardiac function are compromised. For example, inotropic agents and diuretics may be required in a child with volume overload and decreased cardiac contractility, whereas vasodilatory agents may be required in a child with CHF due to an increased afterload.

Clinical Features

Although the clinical manifestations of CHF depend on the exact pathophysiologic cause of the CHF, common presenting signs and symptoms include tachycardia, gallop rhythm (especially an S_3), tachypnea with rales, hepatomegaly, peripheral edema, and decreased peripheral perfusion of the extremities. Wheezing and a chronic cough may also be the presenting symptoms of CHF.

Diagnostic Strategies

The chest radiograph typically reveals an enlargement of the cardiac silhouette and varying degrees of pulmonary congestion. An echocardiogram will be able to assess the ejection fraction as well as to identify underlying anatomic defects. Plasma BNP has been reported to be helpful in differentiating cardiac from pulmonary causes of dyspnea in children.[35] Other diagnostic studies to consider are case specific and depend on the suspected cause of the child's CHF.

Management

Acute stabilization of any child who presents with CHF includes administration of supplemental oxygen and agents to augment cardiac contractility and to improve cardiac output. Children who present in severe respiratory distress secondary to pulmonary edema may require intubation to support oxygenation and ventilation. Children with respiratory distress due to pulmonary congestion may also benefit from elevation of the head and upper torso. Continuous positive airway pressure or biphasic positive airway pressure ventilation may be useful initially to avert the need for endotracheal intubation. Plasma BNP levels have been used also to monitor the response to treatment regimens in patients with CHF.[14]

Diuretics and inotropic agents are the mainstay for treatment of the majority of children with CHF. Furosemide (Lasix) in a dose of 1 mg/kg is the most common loop diuretic used to increase renal perfusion and to improve urine output. With the proper use of furosemide and digoxin (Table 171-6), most children with CHF will demonstrate a favorable response. The narrow therapeutic index of digoxin requires that levels be monitored closely to prevent iatrogenic digoxin toxicity, which could cause a worsening of the preexisting CHF.

Table 171-6 Digoxin Dosing for Infants and Children with Congestive Heart Failure[8]

AGE	TOTAL DIGITALIZING DOSE (ORAL)*	DAILY MAINTENANCE DOSE (ORAL)
Premature	20 µg/kg/24 hr	5 µg/kg/day
Full term	30 µg/kg/24 hr	8-10 µg/kg/day
<2 years	40-50 µg/kg/24 hr	10-12 µg/kg/day
2-10 years	30-40 µg/kg/24 hr	8-10 g/kg/day
>10 years	0.75-1.25 mg/24 hr	0.125-0.25 mg/day

*The intravenous dose of digoxin is equal to 75% of the oral dose (except in children older than 10 years, in whom the intravenous dose is the same as the oral dose).
The total daily digitalizing dose (TDD) is given as follows: ½ of the TDD given initially, followed by ¼ of the TDD given every 8-12 hours × 2 doses after the initial dose.
The daily maintenance dose is divided into a twice-daily dosing regimen (except in children older than 10 years, in whom the maintenance dose can be given as a single daily dosing regimen).
Intravenous digoxin is supplied as 100 µg/mL and 250 µg/mL solutions.
Oral digoxin suspension is supplied as a 50 µg/mL elixir.
Therapeutic range: 0.8-2.0 µg/L.
A lower dosing regimen may be required in those patients with renal failure because digoxin is excreted by the kidneys.

Other inotropic agents that are used for the treatment of CHF in infants and children are dopamine, dobutamine, and epinephrine (Table 171-7). Standardized drips have been established and have replaced the dated "rule of six."[36] Dopamine is an endogenous catecholamine with complex cardiovascular effects. Dopamine can increase renal blood flow in low doses (2-5 µg/kg/min) and will increase the cardiac contractility and heart rate in moderate doses (5-10 µg/kg/min). Dopamine stimulates cardiac beta$_1$-adrenergic receptors both directly and indirectly through the release of endogenous norepinephrine stored in the cardiac sympathetic nerves. Because of this, some of the inotropic effects of dopamine may be reduced in those patients with decreased endogenous myocardial norepinephrine stores (i.e., patients with chronic CHF and neonates). At higher doses (10-20 µg/kg/min), dopamine will also increase the SVR, but excessive vasoconstriction may compromise end-organ perfusion at infusion rates of more than 20 µg/kg/min. If additional inotropic effects are required, the addition of either dobutamine or epinephrine infusions may be preferable to an increase in the dopamine infusion to more than 20 µg/kg/min. The major toxicities of dopamine are tachycardia, vasoconstriction, and ventricular ectopy.

Dobutamine is a synthetic catecholamine with more selective cardiac inotropic effects and some beta$_2$-adrenergic vasodilatory effects. It is not a vasopressor, but it could be a good adjunct in the treatment of low cardiac output states that are secondary to poor myocardial function. Dobutamine may have an advantage over dopamine in that it has fewer arrhythmogenic effects than dopamine and may also have a more direct effect on the enhancement of coronary blood flow. The main toxicities of dobutamine are tachycardia, ventricular ectopy, and hypotension.

Epinephrine is a potent inotrope and chronotrope and also increases the SVR. Epinephrine is useful in scenarios in which poor cardiac output is also associated with diminished systemic vascular tone. Toxicities associated with epinephrine include tachydysrhythmias, severe hypertension, hyperglycemia, lactic acidosis, and hypokalemia.

Amrinone and milrinone are newer inotropic agents that also have peripheral vasodilatory effects. These agents have been used to improve cardiac index in septic shock and to prevent

www.ketabpezeshki.com 66485457-66963820

Table 171-7 Inotropic and Load-Altering Agents Used in the Treatment of Congestive Heart Failure

	INOTROPE	CHRONOTROPE	VASCULAR EFFECTS	INFUSION RANGES
Dobutamine	+	+/–	Vasodilator	2-20 μg/kg/min
Dopamine	+	+	Pressor	2-20 μg/kg/min
Epinephrine	+	+	Pressor	0.1-1.0 μg/kg/min
Milrinone	+	No	Vasodilator	0.5-2 mg/kg bolus during 5 minutes, followed by 5-10 μg/kg/min
Nitroprusside	No	No	Potent vasodilator	0.5-10 μg/kg/min

low cardiac output states for children with CHD. Side effects of these medications include profound hypotension, dysrhythmias, hypersensitivity reactions, fever, hepatotoxicity, and thrombocytopenia.

Another vasodilating medication that has been used for arterial and venous dilatory effects is nitroprusside. Nitroprusside has potent vasodilatory effects on both the systemic and pulmonary circulatory systems. This medication has a prompt onset of action and a short duration of action. Nitroprusside should be used cautiously in patients with either hepatic or renal impairment or both to avoid cyanide toxicity (severe metabolic acidosis and coma) or thiocyanate toxicity (irritability, seizures, abdominal pain, and vomiting).

Box 171-12 Conditions Associated with a High Risk for Development of Dysrhythmias

- Congenital heart defects (uncorrected defects and postoperative complications)
- Congenital complete heart blocks (e.g., maternal systemic lupus erythematosus)
- Myocarditis
- Rheumatic heart disease
- Kawasaki disease with involvement of the coronary arteries
- Cardiomyopathy
- Prolonged QT syndrome
- Aberrant atrioventricular conduction pathways (e.g., Wolff-Parkinson-White syndrome)
- Electrolyte abnormalities (e.g., potassium, calcium, and magnesium disturbances)
- Commotio cordis
- Profound hypothermia
- Hypoxia

Pediatric Dysrhythmias

Perspective

Dysrhythmias are not as common in children as they are in adults. The most common cause of cardiopulmonary arrest in infants and children is the untreated progression of respiratory failure or shock rather than a primary cardiac dysrhythmia.[37] Accordingly, the most common arrest rhythm that will confront the emergency physician will be asystole or bradycardia rather than ventricular fibrillation or ventricular tachycardia. When confronted with a child with a primary cardiac dysrhythmia, the physician must identify and treat the underlying cause quickly and systematically. The conditions in children who are at risk for development of dysrhythmias are listed in Box 171-12. Various medications, drugs, and toxins can also precipitate dysrhythmias in children. Even those medications that are used to treat underlying cardiac problems, such as digoxin, amiodarone, and procainamide, can themselves precipitate dysrhythmias. Drugs of abuse (e.g., cocaine and crystal methamphetamine, among others) and overdose of prescription medications (e.g., cyclic antidepressants) should be considered in the evaluation of any previously healthy adolescent patient who presents with an acute dysrhythmia.

Pediatric dysrhythmias can be divided into three broad categories of rhythms by their effect on the child's pulse: *slow* (sinus bradycardia and heart blocks), *fast* (supraventricular tachycardia or ventricular tachycardia with a pulse), or *absent* (ventricular tachycardia without a pulse, ventricular fibrillation, pulseless electrical activity, or asystole).[38] The most common dysrhythmia in children is supraventricular tachycardia, which occurs most commonly in infants and young children. Although supraventricular tachycardia can spontaneously occur in infants without any underlying structural cardiac defects, ventricular tachycardias typically are due to an underlying myocardial abnormality.

Clinical Features

Rhythm disturbances in infants can be manifested with symptoms such as fussiness, lethargy, poor feeding, pallor, respiratory distress, or cardiogenic shock. Older children present with chest pain, palpitations, difficulty in breathing, or syncope. The type and degree of severity of the presenting signs and symptoms must be taken into account in the evaluation and management of the specific dysrhythmia in each case.

Management

Not every child who exhibits a rhythm disturbance requires emergency intervention. Emergency treatment and stabilization of any dysrhythmia depend on two key clinical questions: (1) Does the child have a pulse? and (2) If a pulse is present, is it slow or fast, and is the child hemodynamically stable or unstable? Children who have a pulse with good perfusion parameters (i.e., an alert child with strong distal pulses, warm extremities, and brisk capillary refill times) do not require emergency intervention unless they exhibit a rhythm that has the potential to rapidly degenerate into a more serious condition. Children who exhibit electrocardiographic evidence of conduction abnormalities (e.g., Mobitz type II second-degree heart blocks, complete heart blocks, prolonged QT intervals, or aberrant conduction such as the Wolff-Parkinson-White syndrome) may also warrant more emergency treatment.

A summary of the treatment algorithms for pediatric dysrhythmias and the most commonly used medications in treatment of these dysrhythmias are listed in Box 171-13. Although some medications can be used to treat only atrial tachycardias (e.g., the use of adenosine for supraventricular tachycardia) or ventricular tachycardias (e.g., the use of lidocaine for ventricular tachycardia), amiodarone and procainamide can be used for a wide array of both atrial and ventricular dysrhythmias, including supraventricular tachycardia and ventricular tachycardia.[38-40]

www.ketabpezeshki.com 66485457-66963820

Box 171-13 Summary of Pediatric Dysrhythmia Treatment Options and Defibrillation, Cardioversion, and Medication in Resuscitation

Simplified Summary of Dysrhythmia Treatment Options

Asystole and Pulseless Electrical Activity

Cardiopulmonary resuscitation (CPR) and endotracheal intubation
Epinephrine
Consider and manage treatable causes (6 *h*'s and 5 *t*'s mnemonic).

Ventricular Fibrillation (VF) and Pulseless Ventricular Tachycardia (VT)

Each defibrillation is followed immediately by 2 minutes of uninterrupted CPR. Start at 2 joules/kg; then increase dose to 4 joules/kg and up to maximum of 10 joules/kg (or maximum adult dose for defibrillator) for all subsequent attempts.
Epinephrine is administered with the second defibrillation at 4 joules/kg (repeat epinephrine every 3-5 minutes, followed by defibrillation).
Antidysrhythmic agents are administered with the third defibrillation at 4-10 joules/kg (up to maximum adult dose for the defibrillator): amiodarone or lidocaine (if amiodarone is not available) or magnesium (for suspected hypomagnesemia or torsades de pointes).

SIMPLIFIED VF/PULSELESS VT ALGORITHM
Start CPR → Rhythm check (confirms VF or pulseless VT) → Defibrillation → 2 minutes of uninterrupted CPR (plus medications as indicated above)

VT (with a Pulse)

Unstable:
- Immediate cardioversion (start at 0.5-1 joule/kg, then 2 joules/kg)

Stable:
- Amiodarone or lidocaine or procainamide (note: avoid concurrent use of amiodarone and procainamide)

Supraventricular Tachycardia

Unstable:
- If intravenous access is immediately available, administer adenosine while preparing for cardioversion; otherwise perform immediate cardioversion if intravenous access is not available or if the patient is hemodynamically very unstable.

Stable:
- Vagal maneuvers (ice water slurry to the face, Valsalva maneuver, blowing on an occluded straw or blowing on the tip of a syringe in an attempt to blow the plunger out)
- Adenosine if vagal maneuvers fail

Bradycardia (Hypoxia Is the Most Common Cause)

Unstable:
- Ensure adequate oxygenation and ventilation.
- Epinephrine
- Atropine (if increased vagal tone or cholinergic toxicity is suspected)
- Cardiac pacing

Stable:
- No emergent treatment is required.

Defibrillation, Cardioversion, and Medications in Resuscitation

Cardioversion

Start at 0.5-1 joule/kg; then the dose may be doubled up to 2 joules/kg.

Defibrillation

Start at 2 joules/kg; then increase dose to 4 joules/kg and up to maximum of 10 joules/kg (or maximum adult dose for defibrillator) for all subsequent attempts.

Adenosine

Start at 0.1 mg/kg (maximum, 6 mg); then may be repeated at 0.2 mg/kg × 2 doses (maximum, 12 mg/dose).

Epinephrine

Standard dose = 0.01 mg/kg (equals 0.1 mL/kg of the 1:10,000 solution) intravenously (IV) or intraosseously (IO)
Endotracheal tube (tracheal dose) = 0.1 mg/kg (equals 0.1 mL/kg of the 1:1,000 solution)
Neonatal doses: use the 1:10,000 solution as 0.01 mg/kg IV, IO, or through the umbilical venous catheter; if no access is immediately available IV, IO, or by umbilical catheter, use 0.1 mg/kg of the 1:1000 solution through the endotracheal tube.

Atropine

0.02 mg/kg with minimum of 0.1 mg/dose to avoid paradoxical bradycardia. Maximum single dose is 0.5 mg in a child or 1 mg in an adolescent, with an overall dosage total maximum of 1 mg in a child or 2 mg in an adolescent.

Amiodarone

5 mg/kg intravenous bolus for ventricular fibrillation or slowly during 20-60 minutes for stable ventricular tachycardia to avoid the hypotensive effects of amiodarone
Amiodarone can be used to treat a wide array of both atrial and ventricular dysrhythmias in children because of its ability to slow conduction both through the atrioventricular node and within the ventricles.
Avoid concurrent use of other medications (e.g., procainamide) that can also prolong the QT interval.

Procainamide

15 mg/kg IV slowly during 30-60 minutes
Procainamide can be used to treat a wide array of both atrial and ventricular dysrhythmias in children because of its ability to slow conduction both through the atrioventricular node and within the ventricles.
Avoid concurrent use of other medications (e.g., amiodarone) that can also prolong the QT interval.

Lidocaine

1 mg/kg IV
Lidocaine does not cause QT prolongation like amiodarone and procainamide.

Magnesium

25-50 mg/kg (maximum of 2 g) intravenous bolus for VF or pulseless VT (if hypomagnesemia or torsades de pointes is suspected)

6 h's, 5 t's

Hypovolemia, hypoxia, hydrogen ion (acidosis), hypokalemia/hyperkalemia, hypoglycemia, and hypothermia
Toxins, tamponade, tension pneumothorax, thrombosis, and trauma

From Kleinman ME, et al: Part 14: Pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 122(Suppl 3):S876-S908, 2010; and Perlman JM, et al; on behalf of the Neonatal Resuscitation Chapter Collaborators: Part 11: Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation 122(Suppl 2):S516-S538, 2010.

www.ketabpezeshki.com 66485457-66963820

Bradydysrhythmias

Sinus Bradycardia. Bradycardia is defined as a heart rate that is slower than the lower limit of normal for a child's age. According to the current definition by the American Heart Association (AHA) guidelines in Pediatric Advanced Life Support (PALS), clinically significant bradycardia in children is a heart rate slower than 60 beats/minute that is associated with poor systemic perfusion.[38] Bradycardia is poorly tolerated in infants and children because they are not physiologically capable of increasing their stroke volume to maintain an adequate cardiac output in the face of significant bradycardia.

The most common cause of symptomatic bradycardia in infants and children is hypoxia. Therefore, the first step in the management of symptomatic bradycardia in children is to ensure adequate oxygenation and ventilation before automatically reaching for medications or pacing. Epinephrine is the first-line medication for treatment of symptomatic bradycardia in children that is not responsive to appropriate oxygenation and ventilation. This is in contrast to the treatment of bradycardia in adults, in which atropine is considered to be the first-line medication. If additional doses of intravenous or intraosseous epinephrine are required to treat symptomatic bradycardia, the dose should remain at standard dosing (0.01 mg/kg). Atropine will have no effect on the denervated heart (e.g., after cardiac transplantation). If vascular access is not available, both epinephrine and atropine can be administered through the tracheal tube, although the intravenous route is preferred.

Other causes of bradycardia include hypothermia, increased intracranial pressure, heart blocks (congenital and acquired), denervated heart status after cardiac surgery, hypothyroidism, sick sinus syndrome, and various medications and toxins (e.g., digoxin, beta-blockers, calcium channel blockers, and cholinergic agents). One should consider emergency pacing for Mobitz type II second-degree atrioventricular block, complete third-degree heart block, or sick sinus syndrome.

Athletic adolescent patients may have resting baseline heart rates slower than 60 beats/minute and do not require emergency treatment if they are completely asymptomatic.

Tachydysrhythmias

Supraventricular Tachycardia

Perspective. Supraventricular tachycardia is the most common symptomatic dysrhythmia in infants and children.[37] In children younger than 12 years, the most common cause of supraventricular tachycardia is a reentry mechanism due to an accessory atrioventricular pathway.[41] No cardiac abnormalities are found in approximately half of the cases, and the Wolff-Parkinson-White syndrome is present in only 10 to 20%.[42] The QRS complex is narrow (<0.08 second) in up to 90% of the cases of pediatric supraventricular tachycardia.[43] The type of supraventricular tachycardia that occurs most commonly in infants and children involves a reentrant mechanism that uses an accessory pathway and the atrioventricular node. The *orthodromic* reentry phenomenon involves the normal antegrade conduction from the atria to the ventricles down the atrioventricular node with retrograde conduction back from the ventricles to the atria by the accessory pathway. Orthodromic conduction will produce a narrow–QRS complex supraventricular tachycardia. The less common reentry mechanism is the *antidromic* form in which conduction from the atria to the ventricles first goes antegrade down the accessory pathway then retrograde back to the atria by the atrioventricular node. Antidromic conduction will produce a wide–QRS complex supraventricular tachycardia. Supraventricular tachycardia in a child with a preexisting bundle branch block can also result in a wide-complex supraventricular tachycardia. The ECG in Figure 171-9 reveals a case of a wide-complex supraventricular

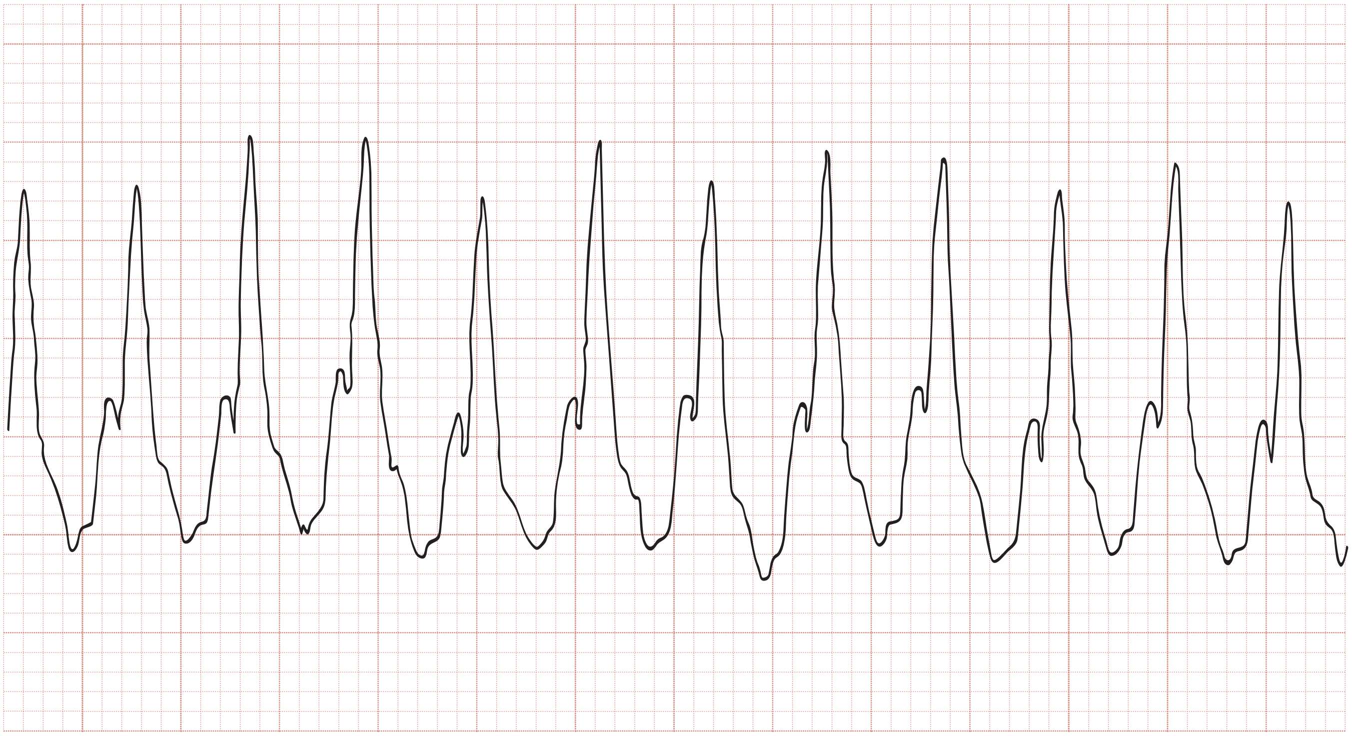


Figure 171-9. An example of an electrocardiogram showing a wide-complex supraventricular tachycardia at a rate of approximately 270 beats/minute in an infant with Ebstein's anomaly of the tricuspid valve. This infant was in supraventricular tachycardia for approximately 2 days and presented with an acute exacerbation of her congestive heart failure, as evidenced by the cardiomegaly on the chest radiograph (see Fig. 171-10). Note that the cardiothoracic ratio in this infant is approximately 70%.

www.ketabpezeshki.com 66485457-66963820

tachycardia in a child with Ebstein's anomaly of the tricuspid valve who also presented with CHF (Fig. 171-10).

Clinical Features and Diagnostic Strategies. The width of the QRS interval in patients with pediatric supraventricular tachycardia is most commonly narrow complex, with heart rates in infants usually higher than 220 beats/minute (Fig. 171-11). It is sometimes difficult to distinguish between sinus tachycardia and supraventricular tachycardia (Table 171-8).

Infants with supraventricular tachycardia typically present with nonspecific symptoms, such as fussiness and difficulty in feeding. Although healthy infants can generally tolerate supraventricular tachycardia with heart rates approaching 300 beats/minute, supraventricular tachycardia may begin to produce signs of CHF and shock if it is left untreated. Older children with supraventricular tachycardia commonly present with palpitations, difficulty in breathing, and chest discomfort.

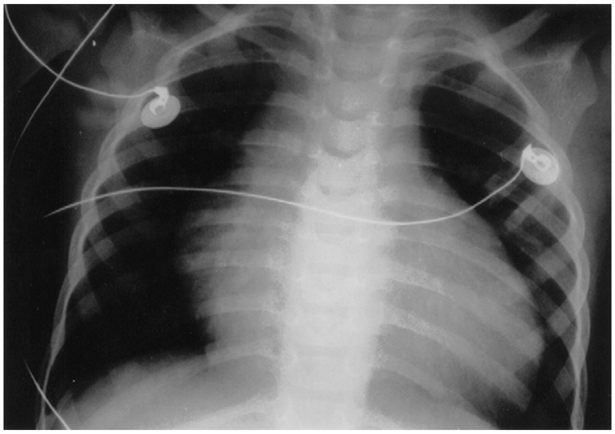


Figure 171-10. Chest radiograph of same infant as in Figure 171-9.

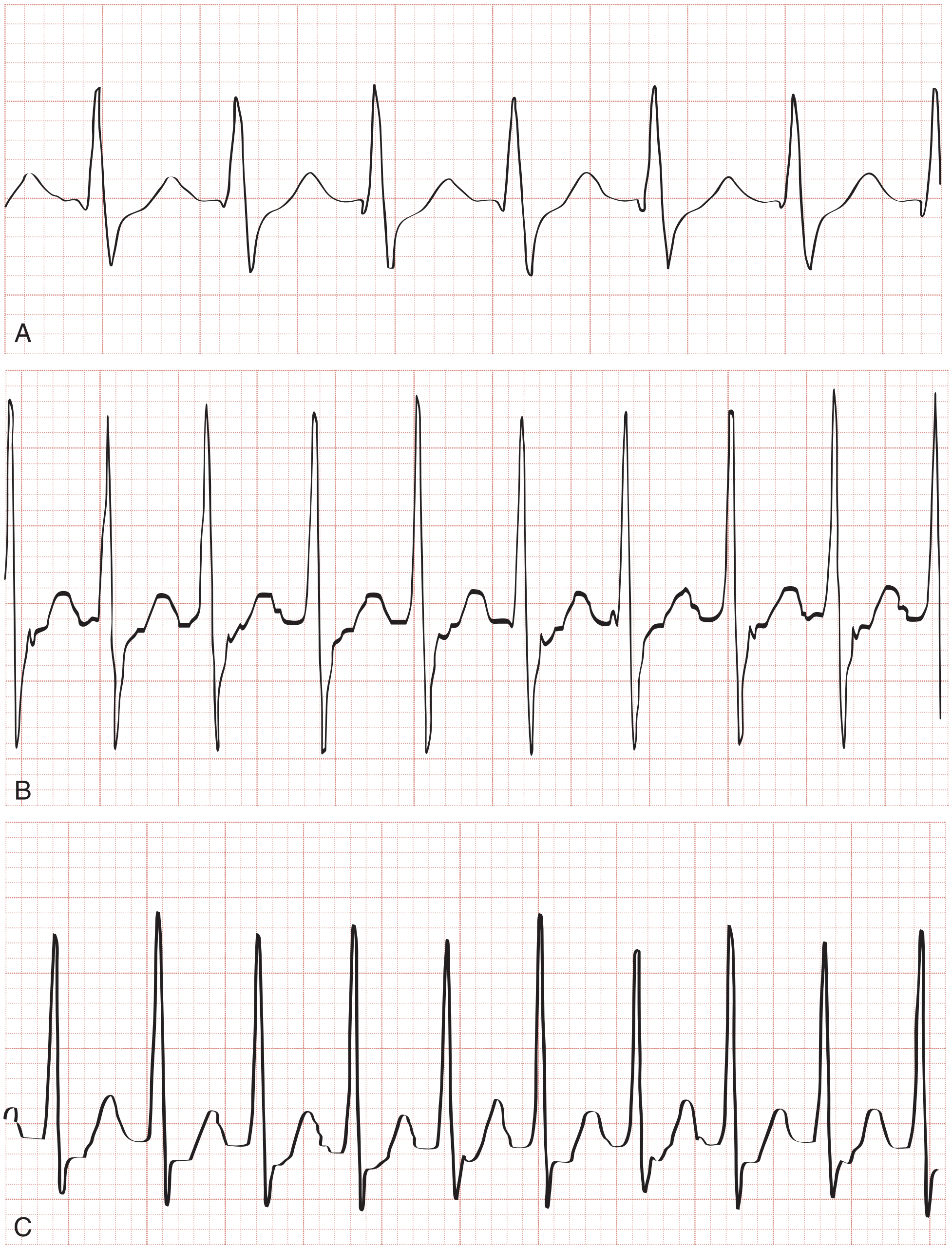


Figure 171-11. Three electrocardiographic examples of classic narrow-complex supraventricular tachycardia in children. The heart rate is approximately 240 beats/minute in the first two examples (**A** and **B**) and approximately 270 beats/minute in the third example (**C**).

www.ketabpezeshki.com 66485457-66963820

Management. Management of supraventricular tachycardia depends on the hemodynamic stability of the child. If the child with supraventricular tachycardia is hemodynamically unstable and intravenous access in not available, immediate cardioversion starting at 0.5 to 1 joule/kg is indicated. If the child does not convert with this initial cardioversion attempt, the energy dose can be doubled up to 2 joules/kg on subsequent attempts. If the child is hemodynamically stable, vagal maneuvers or adenosine, or both, can be attempted initially before cardioversion, depending on the individual case scenario. Regardless of the method selected to convert the supraventricular tachycardia, a continuous rhythm strip should be run to document the response to each conversion attempt. Vagal maneuvers (e.g., a bag containing a slurry of crushed ice and water to the face, blowing on an occluded straw, or blowing on the tip of a syringe) can be attempted before adenosine administration only in the child with hemodynamically stable supraventricular tachycardia. Application of ice to the face has been demonstrated to be a fairly effective method of converting supraventricular tachycardia in infants and children.[44,45] One method to perform this maneuver is to fill a plastic bag or surgical glove with a slurry of crushed ice and water, which is then placed over the infant's forehead, eyes, and bridge of the nose for 10 to 15 seconds. Care must be taken not to occlude the nose or mouth with the bag of ice water. External ocular pressure should be avoided; it can be dangerous in children because excessive pressure can lead to a ruptured globe. Carotid massage is less effective and is not recommended as a vagal maneuver in infants or children.[38]

The initial dose of adenosine in children is 0.1 mg/kg with a maximum initial dose of 6 mg. If this initial dose of adenosine fails to convert the supraventricular tachycardia, the dose is then doubled to 0.2 mg/kg with a maximum of 12 mg/dose. This 0.2 mg/kg dose of adenosine can be attempted once more during the third adenosine dose. Elective cardioversion or esophageal overdrive pacing under conscious sedation may be required in children who fail to convert with adenosine. Asystole and various dysrhythmias, including adenosine-induced wide-complex tachycardia (secondary to an occult accessory conduction pathway), are complications of adenosine administration (Fig. 171-12). The use of verapamil to convert supraventricular tachycardia in infants and younger children should be avoided because of the potential of profound hypotension and cardiovascular collapse when this medication is administered in this age group.[38]

Table 171-8 Clinical and Electrocardiographic Features to Differentiate Sinus Tachycardia from Supraventricular Tachycardia in Children[38]

	SINUS TACHYCARDIA	SUPRAVENTRICULAR TACHYCARDIA
Precipitating events	Dehydration, fever, pain	No precipitating event
P waves on electrocardiogram	Present	Absent
Heart rate varies with activity	Yes	No
Beat-to-beat variability	Yes	Constant R-R intervals
Heart rate in infants (beats/minute)	Usually <220	Usually >220
Heart rate in children (beats/minute)	Usually <180	Usually >180

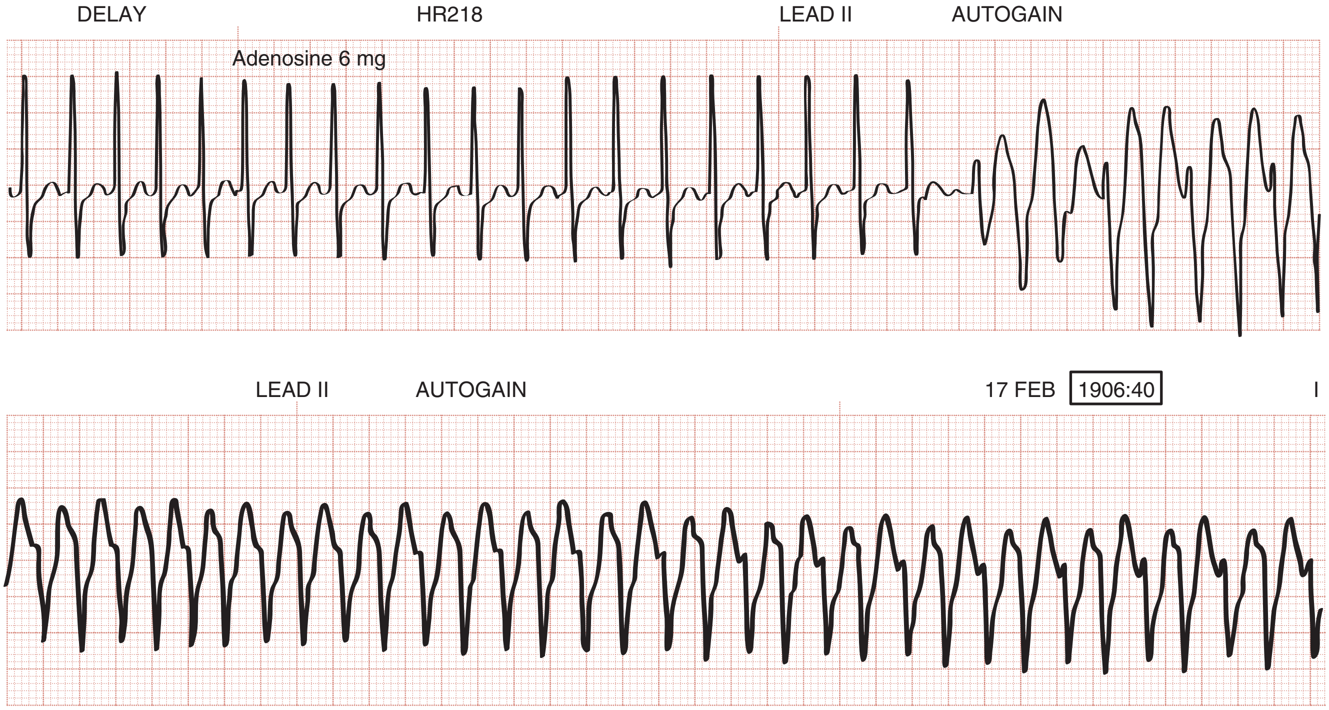


Figure 171-12. An example of adenosine-induced wide-complex tachycardia. A dose of 6 mg of adenosine was administered to this previously healthy 15-year-old girl who presented with a 6-hour history of palpitations. She had no previous cardiac problems except for intermittent palpitations in the past that always resolved spontaneously without any medical interventions. Once adenosine blocked the conduction through the atrioventricular node, a wide-complex tachycardia appeared on the electrocardiogram, which was probably due to antegrade conduction through an accessory pathway. During the 30 seconds of this wide-complex tachycardia, the patient remained alert with excellent perfusion parameters. This wide-complex tachycardia then spontaneously converted to normal sinus rhythm. Although the patient's postconversion electrocardiogram did not reveal an accessory pathway, Holter monitoring 1 month later detected the classic electrocardiographic findings of Wolff-Parkinson-White syndrome.

www.ketabpezeshki.com 66485457-66963820

Once the patient has been converted to sinus rhythm, a 12-lead ECG should be obtained to assess for the possibility of Wolff-Parkinson-White syndrome or any other underlying conduction abnormalities that may have predisposed the child to development of the supraventricular tachycardia.

Atrial Flutter and Atrial Fibrillation. Both atrial flutter and atrial fibrillation are rare in children and are usually associated with underlying heart conditions (i.e., CHD, status post–open heart surgical procedures that involved the atria, myocarditis, and digoxin toxicity). Hemodynamic stability of these two dysrhythmias depends on the rate of the ventricular response. Cardioversion is the treatment of choice for children who present with hemodynamically unstable atrial flutter or atrial fibrillation. The initial treatment priority in patients with hemodynamically stable atrial flutter and atrial fibrillation is first to slow down the rate of the ventricular response with medications such as digoxin, beta-blockers, or diltiazem. Once the ventricular rate is controlled, the rhythm can then be converted and suppressed with amiodarone, procainamide, or elective cardioversion. If the patient who presents with atrial flutter or atrial fibrillation is known to have an underlying Wolff-Parkinson-White syndrome, the four medications that should be avoided are the A-B-C-D medications (adenosine, beta-blockers, calcium channel blockers, and digoxin) because all of these medications preferentially block conduction down the atrioventricular node, leaving the accessory pathway open to conduct the atrial tachycardia to the ventricles at a potentially lethal rate.[45,46] Under these circumstances, amiodarone, procainamide, or cardioversion would be the safer alternative. Consultation with the cardiologist and initiation of anticoagulation should also be considered to prevent a thromboembolic complication before conversion of either of these atrial dysrhythmias in the hemodynamically stable patient believed to have the rhythm disorder 48 to 72 hours before presentation.

Ventricular Tachycardia. Ventricular tachycardia is not a common dysrhythmia in children. The majority of children with ventricular tachycardia have an underlying condition, such as post–cardiac surgery status, myocarditis, prolonged QT syndrome, drug or toxin exposures (e.g., cyclic antidepressants), or electrolyte abnormalities. The treatment of ventricular tachycardia will depend on whether a pulse is present and on the hemodynamic status of the patient (Box 171-14). Torsades de pointes is a unique type of polymorphic ventricular tachycardia characterized by QRS complexes that change in polarity and amplitude. Prolonged QT syndrome, underlying congenital cardiac defects, hypomagnesemia, and various medications (e.g., cyclic antidepressants) have been identified as known causes of torsades de pointes. The treatment of choice is intravenous magnesium. Class IA (i.e., procainamide) and class III (i.e., amiodarone) antidysrhythmic agents are contraindicated in the treatment of torsades de pointes because these two antidysrhythmic agents are capable of prolonging the QT interval, which could then precipitate the degeneration of the torsades de pointes into a more lethal rhythm.

Box 171-14 Clinical Conditions in Which Bacterial Endocarditis Should Be Suspected in a Child with an Underlying Anatomic Cardiac Defect

- Fever of unknown etiology
- A change in the quality of the preexisting heart murmur or the presence of a new heart murmur
- Development of a neurologic deficit (secondary to central nervous system emboli)
- New-onset microscopic hematuria
- Splenomegaly
- Petechiae
- Splinter hemorrhages involving the conjunctiva, nail beds, palms, or soles
- Myalgias

Pulseless Rhythms

Ventricular Fibrillation and Pulseless Ventricular Tachycardia. Ventricular fibrillation and pulseless ventricular tachycardia account for approximately 9 to 10% of out-of-hospital cardiac arrest cases in which a terminal rhythm was recorded.[47,48] The survival rate for out-of-hospital ventricular fibrillation and pulseless ventricular tachycardia can be as high as 30%, whereas the survival rate from asystolic cardiac arrest is less than 1%.[35] In a study of in-hospital cardiac arrests, a shockable rhythm was present during some point of the resuscitation in 25% of the children.[49] The survival rate of children who initially exhibited shockable rhythms was higher than that of those children who presented with nonshockable rhythms. However, the survival rates in those children who later had a shockable rhythm at some time during their resuscitation were not as favorable.[49-51] Ventricular fibrillation should also be suspected as the arrest rhythm in cases of commotio cordis or in cases of sudden cardiac arrest. Current arrhythmia detection algorithms for automated external defibrillators (AEDs) appear to have a high sensitivity and specificity for detection of shockable rhythms in children. Cardiopulmonary resuscitation (CPR) and the early use of AEDs by first responders in the field are encouraged; AEDs may be used in the hospital setting if more advanced equipment and staff are not readily available.[52] The use of AEDs is now acceptable in all age ranges, including infants and children. Pediatric pads (attenuating pads) should be used whenever possible for children 1 year to 8 years old (or less than 25 kg).[53-56] In infants younger than 1 year, manual defibrillation is preferred.[52] If a manual defibrillator is unavailable or its use is delayed, an AED with a pediatric attenuator may be used; if neither is available, an AED without a dose attenuator may be used.[52]

The treatment algorithm and medication dosages for ventricular fibrillation and pulseless ventricular tachycardia are listed in Box 171-13. On the basis of the 2010 PALS guidelines, ventricular fibrillation and pulseless ventricular tachycardia are treated with a single defibrillation, followed immediately by 2 minutes of uninterrupted CPR.[44] Although a single shock with a biphasic defibrillator has a high likelihood of terminating ventricular fibrillation, the resulting rhythm is typically a nonperfusing rhythm, which therefore requires CPR to maintain perfusion to the heart and brain until normal cardiac contractility can resume.[44,56] Epinephrine is given with the second defibrillation, and antiarrhythmic agents are added to the treatment algorithm with the third defibrillation. Although biphasic defibrillators can convert ventricular fibrillation at lower dosages than with the previous monophasic defibrillators in adults, until more data are gathered on biphasic defibrillation dosages in children, the current AHA recommendation for pediatric defibrillation with biphasic defibrillators remains the same as that with monophasic defibrillators (i.e., starting at 2 joules/kg, followed by 4 joules/kg). The 2010 PALS guidelines recommend escalating doses for subsequent shocks, up to 10 joules/kg or the maximum adult dose delivered from the defibrillator.

Asystole and Pulseless Electrical Activity. Asystole is the most common rhythm found in cases of out-of-hospital cardiac arrest in children and is associated with a less than 1% chance of survival.[57-62] The treatment algorithm and medication dosages for asystole and pulseless electrical activity are listed in Box 171-13. Pulseless electrical activity can be a slow or fast rhythm and have a narrow or wide QRS complex. The use of high-dose epinephrine is no longer recommended.[44,52]

The key to survival from any pulseless electrical activity rhythm is to rapidly identify and to correct the underlying cause. The causes of pulseless electrical activity can be remembered by the six *h*'s and five *t*'s: hypovolemia, hypoxia, hydrogen ion (acidosis),

www.ketabpezeshki.com 66485457-66963820

hypokalemia/hyperkalemia, hypoglycemia, hypothermia, toxins, tamponade, tension pneumothorax, thrombosis, and trauma.[38,44] The most common cause of pulseless electrical activity in children is profound hypovolemia. Therefore, an intravenous fluid bolus should always be considered as a therapeutic option during the treatment of pulseless electrical activity.

Special Resuscitation Situations in Children

Children with single-ventricle physiology (e.g., hypoplastic left heart syndrome, double-outlet right ventricle physiology, among others) after a palliative shunting procedure should be given standard resuscitation care.[52] Heparin may be used in the pre-arrest or arrest of infants with a systemic–to–pulmonary artery shunt or right ventricle–to–pulmonary artery shunt to halt thrombus propagation in this low circulatory flow state.[52] A target oxyhemoglobin saturation (Spo_2) of approximately 80% is preferred in these children. End-tidal carbon dioxide readings after resuscitation may lag behind because of varying pulmonary blood flow changes that do not necessarily reflect cardiac output. The goal is to provide adequate preload with judicious fluids to balance systemic and pulmonary blood flow.[52] If it is available, extracorporeal membrane oxygenation may be considered in these patients.[52,53]

Children with a history of pulmonary hypertension should also receive standard PALS care. Preload should be optimized with isotonic saline boluses. Inhaled nitric oxide in the intensive care unit may be given to reduce PVR.[52,54] Intravenous prostacyclin is also used to decrease PVR and may be an option in the emergency department. Early contact with the child's cardiologist and cardiothoracic surgeon is instrumental in the postresuscitative care of children with CHD.

Bacterial Endocarditis

Perspective

Bacterial endocarditis involves an infection of the endothelial surfaces of the heart with a propensity for the valves. The incidence of bacterial endocarditis in children may be increasing slightly because of the many advances in surgical technology that are now allowing many children with very complex congenital heart lesions to survive. Children with indwelling intravenous lines with or without underlying CHD are also at risk for development of bacterial endocarditis. Although bacterial endocarditis most commonly occurs in children with an underlying CHD or an acquired cardiac lesion (e.g., acute rheumatic valvular heart disease), it can also occur in patients with no underlying anatomic defects of the valves or endocardium.[63]

Factors that predispose children with underlying anatomic cardiac defects to bacterial endocarditis include dental procedures and other surgical procedures involving the respiratory, gastrointestinal, or genitourinary tracts. Those cardiac lesions with a more turbulent blood flow or a higher flow velocity are more prone to development of bacterial endocarditis secondary to a greater risk of endothelial surface damage, which then increases the risk of platelet deposition and vegetation formation. Cardiac lesions that carry this higher risk include ventricular septal defects, aortic valvular stenosis, tetralogy of Fallot, single-ventricle states, prosthetic valves, and postoperative systemic-to-pulmonary shunts. Isolated secundum atrial septal defects carry a much lower risk for bacterial endocarditis because the shunt flow through the atrial septal defect is typically of a much lower velocity.

Clinical Features and Diagnostic Strategies

The early clinical manifestations of bacterial endocarditis may be nonspecific. The child may simply present with only fever and tachycardia. However, bacterial endocarditis should be suspected in any child with an anatomic cardiac defect who presents with an unexplained fever. This diagnosis should always be considered in any child with a known CHD or an acquired cardiac lesion who presents with any of the conditions listed in Box 171-14. A new heart murmur is present in less than 50% of the bacterial endocarditis cases.[64] The largest study of pediatric infective endocarditis to date[65] found common presenting signs to be fever (99%), petechiae (21%), changing murmur (21%), dental caries (14%), and hepatosplenomegaly (14%); less common signs were CHF (9%), splinter hemorrhages (5%), Roth's spots (5%), and Osler's nodes (4%).

Box 171-15 Cardiac Conditions for Which Endocarditis Prophylaxis Is Reasonable

- Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
- Previous infective endocarditis
- Congenital heart disease (CHD)*
  - Unrepaired cyanotic CHD, including palliative shunts and conduits
  - Completely repaired congenital heart defect with prosthetic material or device during the first 6 months after the procedure†
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or device (which inhibit endothelialization)
- Cardiac transplantation recipients who have cardiac valvulopathy

From American Heart Association: Prevention of infective endocarditis. Guidelines from the American Heart Association. Circulation 116:1736, 2007.
*Except for those conditions above, antibiotic prophylaxis is no longer recommended for any other form of CHD.
†Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.

In addition to vigilance for the diagnosis of infective endocarditis, especially in children with CHD, the emergency physician should be aware of the indications for prophylaxis. In 2007 the AHA in conjunction with the American Academy of Pediatrics and the Infectious Diseases Society of America published revised guidelines for the prevention of infective endocarditis.[66] The changes simplify and greatly narrow the recommendations to provide prophylaxis for only the higher risk patients and procedures (Box 171-15). For those children for whom prophylaxis is recommended, the indications are (1) all dental procedures and (2) any manipulation or perforation of the gingival or oral mucosa.[66] Antibiotic prophylaxis for infective endocarditis is no longer recommended for gastrointestinal and genitourinary procedures (Box 171-16). The committee found that it is still reasonable to give prophylaxis for procedures on the respiratory tract, infected skin, or musculoskeletal tissue only for high-risk patients (Table 171-9).[66]

Diagnostic studies for a child with suspected bacterial endocarditis include a complete blood cell count, C-reactive protein (CRP) assessment, measurement of erythrocyte sedimentation rate (ESR), three blood cultures,[67] chest radiography, and electrocardiography. Cultures from scrapings of cutaneous emboli can also aid in the diagnosis. Although the definitive diagnostic study is the echocardiogram, it is only 80% sensitive in detecting the nidus of infection on the endocardium or valves.[68] *Streptococcus viridans* and *Staphylococcus aureus* are the two most common offending organisms recovered from the blood cultures of children with bacterial endocarditis. Studies have shown that in children with CHD, 60% of the cases caused by staphylococcal species are methicillin resistant and associated with increased risk of mortality.[69]

www.ketabpezeshki.com 66485457-66963820

Box 171-16 Procedures for Which Endocarditis Prophylaxis Is Recommended

All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa*
Consider prophylaxis for incisional procedures on the respiratory tract, infected skin, or musculoskeletal tissue only for high-risk patients

From American Heart Association: Prevention of infective endocarditis. Guidelines from the American Heart Association. Circulation 116:1736, 2007.
*The following procedures do not need prophylaxis: routine anesthetic injections through noninfected tissue, dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, and bleeding from trauma to the lips or oral mucosa.

Table 171-9 Regimens for Prophylaxis of Infective Endocarditis

		SINGLE DOSE 30-60 MINUTES BEFORE PROCEDURE	
SITUATION	AGENT	Adults	Children
Oral	Amoxicillin	2 g PO	50 mg/kg PO
Unable to take oral medications	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin	2 g PO	50 mg/kg PO
	or Clindamycin	600 mg PO	20 mg/kg PO
	or Azithromycin or clarithromycin	500 mg PO	15 mg/kg PO
Allergic to penicillins or ampicillin—unable to take oral medications	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
	or Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

Modified from American Heart Association: Prevention of infective endocarditis. Guidelines from the American Heart Association. Circulation 116:1736, 2007.

Management

Antibiotics should be started immediately after blood culture samples have been obtained. Although the choice of intravenous antibiotics depends on the suspected source of seeding and the child's immune status, a common recommended regimen includes an aminoglycoside plus a penicillinase-resistant penicillin such as oxacillin. If methicillin-resistant staphylococci are suspected, vancomycin should also be included in the initial empirical antibiotic regimen.[70]

A surge of antibiotic resistance to the three major causes of bacterial endocarditis—streptococci, staphylococci, and enterococci—has increased the mortality rate of bacterial endocarditis, now at 25 to 40%.[71] Complications of bacterial endocarditis include systemic septic emboli, pulmonary emboli, central nervous system emboli with resultant neurologic deficits, dysrhythmias, CHF, myocarditis, myocardial abscesses, and valvular obstruction and destruction. Despite appropriate antibiotic treatment, surgical intervention to remove septic vegetations or valve replacement is sometimes necessary.

Myocarditis

Perspective

Myocarditis is an inflammatory condition of the myocardium with various infectious and noninfectious origins. In the United States, the most common cause is viral; Coxsackievirus B and enteroviruses account for the majority of cases. Other viral causes include echoviruses, influenza A and B viruses, adenovirus, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, and hepatitis B virus. Bacterial causes include *Corynebacterium diphtheriae, Streptococcus pyogenes, S. aureus, Mycoplasma pneumoniae, Borrelia burgdorferi*, and meningococcus. Noninfectious causes include Kawasaki disease, acute rheumatic fever (ARF), collagen vascular disorders (e.g., systemic lupus erythematosus), toxins (e.g., cocaine and doxorubicin), endocrine disorders (e.g., hyperthyroidism), and drug-induced hypersensitivity (e.g., penicillins, sulfonamides, phenytoin, carbamazepine).

Clinical Features

Myocarditis usually has a gradual onset with preceding upper respiratory tract infection symptoms. The presenting signs and symptoms of a child with myocarditis depend on the cause of the myocarditis, the age of the patient, and the degree of myocardial inflammation. The key to diagnosis of myocarditis in infants and children is to include it in the differential diagnosis of a child with symptoms disparate from the presentation. In mild cases, the only sign of myocarditis may be tachycardia. Tachycardia that is disproportionate to the degree of fever should alert the clinician to the possibility of myocarditis.[72] Other presenting signs and symptoms include fever, myalgias, fatigue, tachypnea, wheezing, abdominal pain, and chest pain. More severe cases of myocarditis can even have signs and symptoms of acute CHF and various dysrhythmias. The physical examination may reveal a new murmur, a gallop rhythm, or a pericardial friction rub with muffled heart tones (if the myocarditis is also accompanied by pericarditis and subsequent pericardial effusion). In general, these are sick children with vague symptoms.

Diagnostic Strategies and Management

The evaluation and management of the child with myocarditis depend on the suspected cause and the presenting signs and symptoms. Blood cultures and viral titers should be considered in infectious and postinfectious cases. Appropriate antibiotics should be initiated immediately in cases with suspected bacterial origin. The chest radiograph may be normal in very mild cases, but cardiomegaly will be evident in more advanced cases. The electrocardiographic findings are usually nonspecific and can include low-voltage, nonspecific ST segment abnormalities, T wave inversions, atrioventricular blocks, and various other dysrhythmias. Creatine kinase-MB, cTnT, cTnI, CRP, and ESR may be elevated.

The echocardiogram is an essential component of the workup of any child with suspected myocarditis. The echocardiogram will not only be useful to assess the degree of left ventricular function, but it will also be able to detect associated pericardial effusion that may accompany the myocarditis. Although an endomyocardial biopsy is rarely required, it is the definitive method to confirm the diagnosis and origin of myocarditis. If the endomyocardial biopsy is performed, it will typically demonstrate a myocardial inflammation with lymphocytic and monocytic infiltrates. The goal of treatment is to maintain adequate cardiac output and to control any associated dysrhythmias. Children who present in CHF may require inotropic support and diuretics. Digoxin and the various pressors must be used very cautiously in children with

www.ketabpezeshki.com 66485457-66963820

myocarditis because the inflamed myocardium is sensitive to the dysrhythmogenesis of these medications. The use of beta-blockers is contraindicated,[72] and the routine use of immunosuppressive agents remains controversial.[73] Although the majority of children with acute viral myocarditis make a full recovery, a few patients will progress to dilated cardiomyopathy, which is characterized by dilated ventricles and impaired systolic contractility.

Pericarditis

Perspective

Pericarditis is an inflammatory process within the pericardial sac that may not be associated with a pericardial effusion. In the majority of cases, pericarditis in children is self-limited and follows a benign clinical course. In children, there are normally about 10 to 15 mL of fluid within the pericardial sac. A sudden increase or a large amount of fluid within this pericardial sac can cause a tamponade-induced decrease in stroke volume, which will cause a diminished cardiac output and hypotension.

Although the most common causes of pericarditis include bacterial and viral infections, other causes are ARF, systemic lupus erythematosus, uremia, postpericardiotomy syndrome, leukemia, lymphoma, and tuberculosis. Approximately 30% of pericarditis cases are due to bacteria such as pneumococcus, *S. aureus,* meningococcus, and *Haemophilus influenzae*.[2] Approximately 30% of the purulent bacterial pericarditis cases occur in children younger than 6 years.[28] Viral causes are common, but a specific viral pathogen is recovered in only 20 to 30% of the cases.[28] Common viral causes include Coxsackieviruses, echoviruses, adenovirus, Epstein-Barr virus, and influenza viruses.

Clinical Features

The presenting signs and symptoms of pericarditis depend on the cause of the pericarditis as well as on the amount of fluid that has accumulated within the pericardial sac. Chest pain that varies with position is a common complaint with pericarditis. The chest pain that is classically associated with pericarditis is exacerbated with inspiration and the supine position but relieved when the patient sits up or leans forward. Tachycardia is also a common finding in patients with pericarditis and may be the only clue to the diagnosis. Other physical examination findings that have been associated with pericarditis include fatigue, tachypnea, neck vein distention, pulsus paradoxus, hepatomegaly, lower extremity edema, and thready distal pulses if heart failure is present. The cardiac auscultatory findings in a patient with pericarditis can include a harsh-sounding friction rub or diminished or muffled heart tones, if there is a significant amount of fluid within the pericardial sac. The pericardial friction rub, if present, is best heard when the patient sits up or leans forward. This friction rub of pericarditis can be distinguished from a pleural friction rub by having the patient hold his or her breath during auscultation. The friction rub of pericarditis will remain present during breath-holding; the pleural friction rub will no longer be heard while the patient holds the breath.

The chest radiograph in a child with pericarditis may not reveal an enlarged cardiac silhouette, depending on the amount of fluid that has accumulated within the pericardial sac. If there is a large collection of fluid within the pericardial sac, the heart shadow on the chest radiograph will resemble a "water bottle" silhouette. Approximately 50% of pericarditis cases also have an associated pleural effusion.[2]

The classic electrocardiographic findings of pericarditis include diffuse ST segment elevation and diffuse T wave inversions in all leads. The classic electrocardiographic changes associated with pericarditis evolve through four phases (Fig. 171-13). During the initial phase, there is diffuse ST segment elevation in all leads secondary to subepicardial inflammation; PR segment depression may also be seen. During the second phase, the previously elevated ST segments begin to return to isoelectric baseline, and the T wave amplitudes begin to decrease with flattening of the T waves. During the third phase, although the ST segments are now back to isoelectric baseline, the T waves are now inverted. The fourth and final phase demonstrates complete resolution of the ST segment and T wave abnormalities. Diminished electrocardiographic voltages in all leads can also occur if there is a significant amount of fluid accumulated within the pericardial sac.

The diagnostic procedure of choice in any patient with suspected pericarditis is the echocardiogram; this study will confirm both the presence and the amount of accumulated fluid within the pericardial sac. Although echocardiography cannot accurately quantify the exact amount of fluid that has accumulated within the pericardial space, the presence of an anterior and posterior fluid collection is suggestive of a large collection.

Management

The management of a child with pericarditis depends on both the suspected cause and the amount of fluid that has accumulated within the pericardial space. These children require admission for observation and analgesia with nonsteroidal anti-inflammatory drugs. Certainly those patients with fever, respiratory distress, or signs of CHF should be admitted and an echocardiogram performed emergently. An emergency pericardiocentesis will be required in those patients who have signs of acute cardiac tamponade. Any fluid that is aspirated from the pericardial space should be sent for routine cell counts, Gram's stain, and cultures. Anti-inflammatory agents and appropriate antibiotics should also be initiated on the basis of the suspected cause. Steroids are reserved for refractory cases that are not responsive to these agents and would be considered only after an infectious etiology is ruled out.[74]

Kawasaki Disease

Perspective

Kawasaki disease, originally described as mucocutaneous lymph node syndrome by Dr. Tomisaku Kawasaki in 1967, has emerged as a significant cause of acquired cardiac disease in children in the United States. An estimated 3000 to 5000 cases of Kawasaki disease are diagnosed annually in the United States. Up to 20% of untreated children have some degree of coronary artery abnormalities.[75] This febrile, exanthematous, multisystem vasculitis is seen most commonly in children younger than 5 years with a male-to-female ratio of 1.5:1. The incidence is higher in Asian children and in certain geographic locations, such as Hawaii. Although the exact cause of this vasculitis of small and medium-sized vessels remains unknown, early clinical recognition and initiation of high-dose aspirin and intravenous immune globulin (IVIG) therapies have improved the morbidity and mortality rates of Kawasaki disease in children.

Clinical Features

The key to prevention of the coronary artery complications of Kawasaki disease is first to recognize the clinical signs and symptoms of this disease. In addition to fever, the physical examination of a child with Kawasaki disease may reveal the typical findings as listed in Box 171-17 and illustrated in Figure 171-14. The classic features of Kawasaki disease may be manifested simultaneously or in series of days; a careful history and physical examination may elucidate the need for further testing. In addition, very young

www.ketabpezeshki.com 66485457-66963820

Figure 171-13. The classic electrocardiographic progression of a patient with pericarditis. First phase: diffuse ST segment elevation. Second phase: ST segments back to isoelectric, but decreased T wave amplitude. Third phase: T wave inversion. Fourth phase: complete resolution. Notice that the first three phases of the electrocardiographic abnormalities of pericarditis in this patient are evident during the first 2 weeks of his illness. A follow-up electrocardiogram obtained 5 months later reveals a complete resolution of all the previous electrocardiographic abnormalities.

Box 171-17 Diagnostic Criteria for Kawasaki Disease

- Fever ≥5 days
- At least four of the five following physical examination findings:
  - Bilateral, nonexudative bulbar conjunctival injection (bilateral scleral injection with perilimbic sparing)
  - Oropharyngeal mucous membrane changes (pharyngeal erythema, red and cracked lips, and a strawberry tongue)
  - Cervical lymphadenopathy (with at least one node > 1.5 cm in diameter)
  - Peripheral extremity changes (diffuse erythema and swelling of the hands and feet during the acute phase or periungual desquamation during the convalescent phase of the illness). This diffuse palmar erythema seen in Kawasaki disease is in contrast to the discrete macular lesions of various viral illnesses (e.g., measles) that can sometimes be seen on the palms and soles.
  - A polymorphous generalized rash (nonvesicular and nonbullous). There is no specific rash that is pathognomonic for Kawasaki disease.

In a child with ≥4 criteria, the diagnosis may be made on day 4 of the fever.[71]

children may not have a classic presentation and require further investigation. All children with suspected Kawasaki disease, with either classic or incomplete features, should undergo echocardiography for detection of the presence and degree of coronary aneurysm.[76]

Incomplete Kawasaki Disease.

The classic presentation of Kawasaki disease is a clinical diagnosis of four or more of the five criteria in a child who is febrile 5 days or more. However, these strict criteria may miss a substantial number of children who present with incomplete Kawasaki disease. Any child may have an incomplete presentation, but this is mostly seen in infants younger than 6 months.[76]

The AHA's Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease has published consensus guidelines on the approach to incomplete Kawasaki disease.[71] The more inclusive criteria recommend that in a child who is febrile 5 days or more, the presence of two or three criteria should prompt further testing. A CRP of 3 mg/dL or more or an ESR of 40 mm/hr or more or both necessitate further laboratory investigations, such as those listed in Box 171-18. All of these children will also need

www.ketabpezeshki.com 66485457-66963820

Figure 171-14. Classic physical examination findings of Kawasaki disease. Note the bilateral nonexudative scleral injections (A) with perilimbic sparing (the thin margin of white sclera around the cornea), red and cracked lips with a strawberry tongue (B), diffuse palmar erythema (C), red soles (D), and polymorphous exanthem (E). The diffuse palmar erythema of Kawasaki disease (C) is distinct from the palmar findings seen in other viral illnesses, such as the discrete macular lesions on the palms in this child with measles (F).

echocardiography to assess for coronary aneurysm, and the recommendation is to treat empirically those whose supplementary laboratory values (see Box 171-18) are positive for systemic inflammation while echocardiographic confirmation is awaited.[76]

Children with a CRP of less than 3 mg/dL and an ESR of less than 40 mm/hr may be observed daily and reassessed. The committee also added a stipulation that the infant 6 months or younger with fever of 7 days or more should also undergo supplemental laboratory testing and, if any signs of systemic inflammation are found, should have an echocardiogram. This underscores the current limits of diagnosis of Kawasaki disease as well as the obligation to prevent the disastrous sequelae of aneurysmal development.

Differential Considerations

Measles can mimic Kawasaki disease but is rare in vaccinated children (i.e., a febrile illness with red eyes, a rash, and erythema of the oropharynx). The measles rash classically begins on the head and face and progresses caudally. The rash of Kawasaki

www.ketabpezeshki.com 66485457-66963820

Box 171-18 Supplemental Laboratory Criteria for Kawasaki Disease

Albumin ≤3 g/dL
Anemia for age
Platelet count of ≥450,000/mm^3
White blood cell (WBC) count ≥15,000 mm^3
Elevation of alanine aminotransferase
Sterile pyuria of ≥10 WBCs per high-power field

From Newburger JW, et al: Diagnosis, treatment, and long-term management of Kawasaki disease: A statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 110:2747, 2004.

disease typically begins on the trunk and then spreads to the face and extremities. In contrast, Kawasaki disease can exhibit a polymorphous rash that is nonbullous and nonvesicular.

The palmar lesions of measles are discrete macular lesions (Fig. 171-14F), whereas the palmar finding in children with Kawasaki disease is diffuse erythema, which may later lead to desquamation (Fig. 171-14C).

Streptococcal disease, including pharyngitis and scarlet fever, can be confused with Kawasaki disease, but conjunctivitis and swelling of the hands and feet are unusual for streptococcal disease. Other infectious or autoimmune causes that may mimic Kawasaki disease include Rocky Mountain spotted fever, leptospirosis, Stevens-Johnson syndrome, and juvenile rheumatoid arthritis.[76]

There are many imitators of Kawasaki disease. Conversely, this systemic vasculitis can affect any organ system and thus mislead the clinician in diagnosis. For example, Kawasaki disease can be manifested with nausea, vomiting, and abdominal pain in a febrile child, which may be mistaken for a surgical abdomen. In addition, a febrile, irritable child with Kawasaki disease may exhibit a cerebrospinal fluid pleocytosis and be misdiagnosed with viral meningitis. For this reason, Kawasaki disease should be included in the differential diagnosis of any child with several days of fever, rash, and nonpurulent conjunctivitis to avoid the pitfall of early diagnostic closure.

Clinical Course

Kawasaki disease is postulated to be caused by an infectious agent that enters the respiratory tract and initiates an oligoclonal immunoglobulin A response, which activates lymphocytes, cytokines, and proteinases that weaken vessel walls and predispose the entire circulation to aneurysms.[77] The main reason to recognize this disease entity in children is to initiate prompt therapies to prevent the cardiac complications of Kawasaki disease, which occur in two phases. Approximately 25% of patients have mild diffuse myocardial inflammation. This occurs during the acute febrile period and is characterized by tachycardia, a gallop rhythm, and nonspecific ST-T wave changes. Up to 5% of the children also exhibit some degree of CHF during this acute phase of their illness. This carditis usually resolves when the fever resolves. Pericardial effusions also occur in up to 20 to 40% of cases. Mild mitral and aortic regurgitation is also seen in 1 to 2% of untreated cases on echocardiographic examinations. This phase of the disease is mild and self-resolving. Therapy during this phase of the illness is primarily supportive.

The second phase of the disease involves coronary artery dilation, which usually peaks 2 to 4 weeks from the onset of the illness and is seen in 15 to 25% of the untreated patients with Kawasaki disease.[78] Without the appropriate treatment, 15 to 20% of children with Kawasaki disease go on to have coronary aneurysms within 1 to 3 weeks from the onset of their illness.[2] These coronary aneurysms can then lead to myocardial infarction, thrombosis, rupture, and a variety of ischemia-induced dysrhythmias. Significant risk factors for coronary aneurysmal formation include male gender, age younger than 1 year or older than 8 years, prolonged febrile period longer than 10 to 14 days, early myocarditis, anemia (hemoglobin <10 g/dL), white blood cell count greater than 30,000, increased band count, elevated ESR, elevated CRP level, low serum albumin levels, aneurysms involving other arteries (renal, axillary, or iliac), and giant coronary aneurysms (>8 mm in diameter). Death from Kawasaki disease is primarily due to myocardial infarction secondary to coronary artery occlusion. Giant coronary artery aneurysmal rupture is rare. Although most of the fatalities of Kawasaki disease occur within 6 weeks from the onset of the illness, sudden death can also occur many years after the illness. Prompt recognition and treatment have decreased this mortality rate from 2% to less than 0.01%.[75]

Management

The main goal of treatment during the acute febrile phase of Kawasaki disease is to provide supportive care and to decrease the inflammation of the myocardium and coronary arteries. The two major components of treatment include IVIG infusion and high-dose aspirin therapy, which together have an additive effect. This combination of IVIG and high-dose aspirin, when it is initiated within 10 days from the onset of the illness, can substantially decrease the progression to coronary artery dilation and aneurysm formation compared with aspirin therapy alone and results in a more rapid resolution of fever and the other indicators of acute inflammation.[76] However, despite prompt treatment with IVIG and high-dose aspirin, 2 to 4% of the children still have coronary artery abnormalities.[76]

The current IVIG regimen involves an infusion of 2 g/kg during 10 to 12 hours. Side effects of IVIG include hypotension, nausea, vomiting, headache, and seizures. Close cardiac monitoring during the IVIG infusion is recommended. The 5 to 10% of children who receive IVIG and experience a persistent or recurrent fever after the initial dose of IVIG may be given a second infusion at the same dose. Approximately two thirds of those children who fail to respond to the initial dose of IVIG will improve with the second infusion.

Aspirin is initiated at 80 to 100 mg/kg/day orally divided into an every-6-hour dosing regimen until the child is afebrile for 48 to 72 hours (or longer). This dose is then decreased to 3 to 5 mg/kg orally each day until the laboratory study results return to normal, which typically occurs 6 to 8 weeks after the onset of the disease. Aspirin therapy is continued beyond this period only in those children in whom coronary artery abnormalities are present. Ibuprofen can antagonize the antiplatelet effects of aspirin and should be avoided during treatment.[76]

The use of corticosteroids as primary treatment has not been well established. A multicenter, randomized, double-blind study to determine the efficacy of the addition of methylprednisolone to initial conventional therapy showed no difference in clinical outcome, including dimensions of coronary artery aneurysms, length of hospital stay, and rate of re-treatment with IVIG.[79] The current recommendations include corticosteroids for refractory cases of Kawasaki disease, in which high-dose aspirin is continued, a second dose of IVIG is administered, and corticosteroids are added to decrease the risk of coronary artery aneurysm.[76,80] Other complications, such as coronary aneurysmal thrombosis, likewise have limited data to guide management. Therapeutic options include streptokinase, tissue-type plasminogen activator, and interventional cardiac catheterization.[76]

The follow-up of children with Kawasaki disease depends on the degree and presence of carditis and coronary artery abnormalities detected on the initial echocardiogram. Other imaging modalities used to follow aneurysmal parameters include

www.ketabpezeshki.com 66485457-66963820

electron-beam computed tomography, coronary magnetic resonance angiography, and multislice spiral computed tomography.[76] Those children with more severe cardiac abnormalities require close follow-up by a cardiologist who is experienced in managing the cardiac complications of Kawasaki disease. Overall, prompt diagnosis and appropriate therapies can prevent coronary aneurysm formation in up to 95% of the cases as well as result in rapid symptomatic improvement in up to 90% of the cases.[81]

Acute Rheumatic Fever

Perspective

ARF is the result of a delayed immune reaction to a group A streptococcal infection. ARF is one of the most common causes of acquired heart disease in children. In the United States, ARF most commonly occurs in children 5 to 15 years of age and has an attack rate of 0.3% in children with an untreated streptococcal infection. Although this disease affects multiple organ systems, carditis is the most serious complication.

Clinical Features and Diagnostic Considerations

The diagnosis of ARF is based on the Jones criteria (Box 171-19). In addition to the Jones criteria, there must also be evidence of an antecedent streptococcal infection, which can be documented by a positive throat culture, a positive rapid streptococcal antigen test finding, or an elevated antistreptolysin O (ASO) titer. The ASO titer begins to rise 1 to 3 weeks after streptococcal infection, peaks at 3 to 5 weeks, and reliably falls to baseline after 6 months.[82] The streptozyme test is not as reliable and therefore should not be used as a definitive test for evidence of an antecedent group A streptococcal infection.[83] The diagnosis of ARF is made in a patient with a documented antecedent streptococcal infection who exhibits either two major criteria or one major plus two minor criteria. The most common presenting major criterion is the migratory polyarthritis, which commonly involves the larger joints of the extremities as well as the smaller tarsal joints in the foot and the smaller carpal joints in the hand. The carditis of ARF most commonly involves valvulitis of the mitral and aortic valves, which clinically is manifested as occult mitral or aortic insufficiency. The murmur of mitral insufficiency is characterized as a holosystolic murmur best heard over the apex with radiation to the axilla. The murmur of aortic insufficiency is characterized as a diastolic murmur that is best heard over the base of the heart. Innocent murmurs that are normally exacerbated with fever can be mistaken for the murmurs of mitral or aortic insufficiency. The other cardiac manifestations of ARF include CHF, pericarditis, and various degrees of heart block. The two dermatologic major criteria (erythema marginatum and subcutaneous nodules) and chorea occur less commonly than the migratory polyarthritis and carditis. Chorea may occur as the only manifestation of ARF. If arthritis is used as a major component, arthralgia cannot be used as a minor component to make the diagnosis. Likewise, if carditis is used as a major component, a prolonged PR interval cannot be used as a minor component.[83]

In addition to the ECG, CRP level, ESR, and documentation of an antecedent streptococcal infection, the diagnostic workup of ARF should also include a chest radiograph as well as an echocardiogram to evaluate the degree of cardiac involvement.

Box 171-19 Jones Criteria for the Diagnosis of Acute Rheumatic Fever

The diagnosis of acute rheumatic fever is based on the documentation of an antecedent streptococcal infection and either two major criteria or one major criterion plus two minor criteria.

Major Criteria
- Carditis
- Migratory polyarthritis
- Erythema marginatum
- Subcutaneous nodules
- Chorea

Minor Criteria
- Clinical findings
  - Fever
  - Arthralgia
- Laboratory findings
  - Elevated C-reactive protein or erythrocyte sedimentation rate
  - Prolonged PR interval
- Supporting evidence of an antecedent group A streptococcal infection with either
  - A positive throat culture or rapid streptococcal antigen test result
  - An elevated antistreptolysin O titer

Differential Considerations

The differential diagnosis of ARF includes myocarditis, bacterial endocarditis, Lyme disease, systemic lupus erythematosus, juvenile rheumatoid arthritis, serum sickness, and septic arthritis.

Management

The acute management of ARF should first focus on stabilization and treatment of any of the symptomatic cardiac manifestations of the illness, such as CHF or tamponade due to a pericardial effusion. Additional goals in ARF management include appropriate antibiotic therapy to eradicate the streptococcal infection, bed rest, and anti-inflammatory agents for the arthritis. Steroids should be used in the treatment of carditis only under direction of a cardiologist. Another important aspect in the management of ARF is the prevention of recurrent attacks through the prophylactic use of penicillin, which can be given as monthly injections of 1.2 million units of benzathine penicillin G. Alternative prophylactic regimens include oral penicillin administered twice daily and, for penicillin-allergic patients, twice daily oral erythromycin. This prophylaxis with penicillin or erythromycin is required until 18 years of age at the minimum but can be continued for life, depending on the degree of cardiac involvement and the risk for recurrence.

Cardiac Causes of Sudden Death in Young Athletes

Perspective

In a large registry study of 1866 sudden deaths in young athletes, 1048 (56%) were found to be due to cardiovascular disease, and 416 (22%) were due to direct blunt trauma.[84] The most common cardiovascular cause of sudden death in the athlete is hypertrophic cardiomyopathy, which accounts for up to 36% of the cardiovascular-related cases (Box 171-20).[70]

Specific Disorders

Congenital Coronary Artery Anomalies. An additional 24% of the cases of sudden death are due to various anomalies of the coronary arteries.[85] Congenital coronary artery anomalies are difficult to detect from a clinical standpoint, but 37% of those individuals who died of congenital coronary artery anomalies exhibited previous symptoms of exercise-induced syncope or chest pain.[86] The

www.ketabpezeshki.com 66485457-66963820

Box 171-20 Cardiovascular Causes of Sudden Death in Young Athletes

Hypertrophic cardiomyopathy
Various congenital coronary artery anomalies
Prolonged QT interval syndrome
Various preexcitation syndromes (e.g., Wolff-Parkinson-White syndrome)
Commotio cordis
Aortic rupture secondary to Marfan syndrome
Idiopathic dilated cardiomyopathy
Myocarditis
Coronary artery disease secondary to Kawasaki disease
Aortic stenosis
Mitral valve prolapse

exact pathophysiologic mechanism of sudden death in individuals with congenital coronary anomalies is unknown. Although there are a variety of congenital coronary artery anomalies, the most common potentially lethal lesion is the anomalous left coronary artery, in which the left main and right coronary arteries both arise from the right sinus of Valsalva. Individuals with this particular anomaly have a 46% incidence of sudden death, with more than 85% of the known cases of sudden death occurring during exercise.[84] Congenital coronary artery hypoplasia is another uncommon cause of exercise-induced sudden death. Any athlete with exertional syncope or chest pain should be evaluated by a cardiologist for the possibility of a congenital coronary artery anomaly. If an anomaly is detected and surgically corrected, the athlete may resume full activity and participation in competitive sports.

Marfan Syndrome. Individuals with Marfan syndrome should be evaluated for potential cardiac abnormalities before being allowed to participate in competitive sports. Clinical manifestations of the disease include tall and slender habitus, striae atrophicae of the skin (multiple stretch marks on skin), disproportionately long extremities compared with the trunk, scoliosis, pectus excavatum or carinatum, and dislocated lenses of the eye. Approximately 50% of patients with Marfan syndrome have cardiac manifestations, such as mitral valve prolapse or aortic dilation. The most serious cardiac complication of Marfan syndrome is the progressive dilation of the aorta with the potential risk of aortic rupture, which most commonly involves the descending portion of the aorta. Therefore, patients with Marfan syndrome should be prohibited from participation in contact sports. Those individuals who are known to have aortic dilation should also be prohibited from participation in any competitive sports regardless of the degree of contact involved.[85] All patients with Marfan syndrome with or without cardiac involvement on their initial evaluation should be observed by a cardiologist with serial imaging studies of the aorta by echocardiography, magnetic resonance imaging, or computed tomography.

Hypertrophic Cardiomyopathy

Perspective. Although the nonobstructive form of hypertrophic cardiomyopathy is an uncommon cardiac malformation that occurs in only 0.2% of the general population, it is the single most common cardiac cause of sudden death in the young athlete.[87-89] Hypertrophic cardiomyopathy is a familial disease that is inherited in an autosomal dominant fashion with variable penetrance. The hypertrophy of the left ventricle in this condition is idiopathic in nature and not due to chronic pressure overload conditions, such as systemic hypertension or aortic stenosis. The systolic left ventricular contractile function is vigorous but the thickened muscle of the left ventricle is stiff, resulting in impaired ventricular relaxation and high diastolic filling pressures.[90]

Sudden death in previously asymptomatic individuals with hypertrophic cardiomyopathy occurs during moderate or severe physical exertion. The proposed pathophysiologic mechanism of sudden death during exertion in these individuals is thought to be a transient decrease of blood flow out through the aorta or dysrhythmia secondary to the hypertrophied ventricular myocardium.

Clinical Features. Some individuals with hypertrophic cardiomyopathy have experienced previous "warning" episodes of chest pain, dyspnea, syncope, or palpitations during vigorous activities. A family history of sudden unexplained death in young adults should also alert the clinician to the possibility of hypertrophic cardiomyopathy. The majority of young athletes who die of this condition have the nonobstructive form of hypertrophic cardiomyopathy, and the classic loud systolic ejection murmur that is present with the obstructive form may not be heard during the routine pre-sports physical examination.[91]

If a systolic murmur along the lower left sternal border is heard on the routine screening physical examination of a young athlete, a Valsalva maneuver may help differentiate the murmur of aortic stenosis from the systolic murmur associated with the obstructive form of hypertrophic cardiomyopathy. During the Valsalva maneuver, the venous blood return to the heart is decreased, which in turn transiently reduces the left ventricular size. The transient reduction in the size of the left ventricle will increase the degree of obstruction and thus cause an increase in the intensity of the systolic murmur heard with the obstructive form of hypertrophic cardiomyopathy. In contrast to this, the systolic murmur of aortic stenosis will decrease in intensity during a Valsalva maneuver because of the transient reduction of blood flow through the stenotic aortic valve.

Current recommendations for pre-sports screening include a detailed family and personal history of known or suspected heart disease, physical examination, and 12-lead ECG. If any suspicion remains, further workup (e.g., echocardiography, Holter monitoring, other imaging studies) and referral to a cardiologist are indicated.[91]

Diagnostic Studies. The electrocardiographic findings in individuals with hypertrophic cardiomyopathy typically reveal various degrees of left ventricular hypertrophy and left atrial enlargement. Other electrocardiographic findings include prominent Q waves in the inferolateral leads and diffuse T wave inversions. The most accurate study for the diagnosis of hypertrophic cardiomyopathy is the echocardiogram, which will demonstrate various degrees of left ventricular hypertrophy most commonly involving the ventricular septum in up to 90% of the cases.[90] Those patients who have echocardiographic evidence of hypertrophic cardiomyopathy should be observed with serial echocardiographic examinations to monitor progression of the condition.

Management. Although beta-blockers have been used in patients with hypertrophic cardiomyopathy, they have not been shown to prevent sudden death in these patients. The use of digoxin is contraindicated in patients with hypertrophic cardiomyopathy because its positive inotropic effect may worsen the left ventricular outflow obstruction. Sudden death in these patients with hypertrophic cardiomyopathy is thought to be due to exertion-induced ventricular fibrillation or pulseless ventricular tachycardia. Therefore, the current recommendation is that all individuals who are diagnosed with hypertrophic cardiomyopathy as well as those individuals with an equivocal diagnosis of hypertrophic cardiomyopathy should not participate in vigorous activities and competitive sports.

Prolonged QT Syndrome

Perspective. In 1957, Jervell and Lange-Nielsen first described the association of recurrent syncope, sudden death, and long QT interval in a series of deaf patients. Later, in 1963, Romano reported a similar association of symptoms with long QT intervals in patients with normal hearing. Both the Jervell–Lange-Nielsen and the Romano-Ward syndromes are inherited disorders with

www.ketabpezeshki.com 66485457-66963820

variable penetrance, characterized by a prolonged QT interval that has been associated with sudden death. The corrected QT interval (QTc) in normal individuals should not exceed 0.44 second in children or 0.42 second in adolescents. Individuals with QTc intervals longer than 0.55 second have a higher risk of sudden death. Prolongation of the QT interval predisposes the individual to ventricular tachycardia, torsades de pointes, and ventricular fibrillation, which is often initiated by a premature ventricular contraction occurring during the prolonged repolarization phase. In addition to the inherited syndromes of prolonged QT intervals, other causes of prolonged QT intervals include hypocalcemia, hypokalemia, hypomagnesemia, myocarditis, and medications (e.g., procainamide, erythromycin, cyclic antidepressants, phenothiazines, quinidine, organophosphates).

Clinical Features. Symptoms in the young athlete that are suggestive of QT prolongation include exercise-induced palpitations, chest pains, syncope, dizziness, and atypical seizures. The young athlete who has any of these symptoms should be evaluated by a cardiologist, especially if the family history is positive for sudden unexplained death, cardiac problems, syncope, or deafness. Any young athlete who has been diagnosed with a prolonged QT syndrome should be prohibited from participation in competitive sports and vigorous activities. The growing popularity and presence of AEDs in public places and at sporting events can potentially save the lives of those athletes who suddenly collapse because of an underlying prolonged QT syndrome–induced nonperfusing ventricular dysrhythmia.

Management. Treatment of a prolonged QT interval depends on the cause. Correction of any underlying metabolic disorder and discontinuation of a medication that induced the prolongation of the QT interval are the easiest therapies to implement. Magnesium sulfate is the drug of choice in the treatment of torsades de pointes. Antidysrhythmic agents that also can prolong the QT interval, such as procainamide and amiodarone, should be avoided. Therefore, the safest medication to use in a patient with prolonged QT interval–induced ventricular tachycardia or fibrillation is lidocaine. Beta-blockers have been used to prevent sudden ventricular dysrhythmias in those patients with the familial forms of QT prolongation. Adjunctive treatment in these selected patients also includes the insertion of pacemakers or internal defibrillators.

Commotio Cordis. The phenomenon of commotio cordis occurs when an object such as a baseball strikes the chest and produces sudden death. This phenomenon most commonly occurs in children between 5 and 15 years of age with no known predisposing cardiac conditions.[85,92] Although commotio cordis most commonly occurs in baseball, it has also been reported to occur in ice hockey, lacrosse, softball, and fist fights.[78] In a few cases in which the cardiac rhythm was documented after the blunt trauma to the chest, the most common rhythm documented was ventricular fibrillation.[93] The majority of patients who sustain commotio cordis do not survive, especially if they are not rapidly treated with defibrillation. If an AED is not immediately available and the patient is completely unresponsive with no pulse after sustaining a direct blow to the chest, some practitioners have proposed that performance of chest thumps during CPR may be of some benefit under this particular circumstance.

KEY CONCEPTS

- The possibility of a congenital heart defect should be considered in an infant who presents with central cyanosis that does not respond to 100% supplemental oxygen (hyperoxia challenge).
- Neonates with duct-dependent cardiac lesions typically present within the first 2 to 3 weeks of life with either acute cyanosis or shock. Initiation of a PGE_1 infusion (0.05-0.1 µg/kg/min) will be lifesaving in these neonates.
- Treatment of a hypoxic tet spell first includes the placement of an infant in the knee-to-chest position or of an older child in a squatting position to increase SVR and the provision of supplemental oxygen. Sedative agents can be used to decrease hyperpnea. Various medications can be used as adjunctive treatment to increase the SVR and thereby decrease the degree of right-to-left shunting across the ventricular septal defect.
- Prompt recognition of the clinical findings and symptoms of Kawasaki disease along with the rapid initiation of high-dose aspirin and IVIG infusion can prevent the formation of coronary aneurysms.
- Acute bacterial endocarditis should always be considered in a child with a known congenital heart defect or an acquired cardiac defect who presents with fever of unknown origin, acute neurologic deficits, new-onset microscopic hematuria, myalgias, splenomegaly, petechiae, or other signs of systemic embolization.
- Oxygen, diuretics (furosemide), and inotropic agents (digoxin) are the mainstays for treatment of infants and children who present with CHF.
- If vagal maneuvers fail to convert stable paroxysmal supraventricular tachycardia in children, rapid adenosine administration (0.1 mg/kg for the first dose, followed by 0.2 mg/kg on repeated doses) is the treatment of choice. Verapamil should be avoided in children younger than 1 year because of its profound hypotensive effects.
- One should consider the use of lidocaine instead of amiodarone in cases of ventricular fibrillation or ventricular tachycardia due to medications (e.g., cyclic antidepressants) or toxins that prolong the QT interval.
- Young athletes with a positive family history of sudden unexplained death or exertion-induced symptoms such as chest pain, dyspnea, palpitations, and syncope should be evaluated by a cardiologist before their resumption of vigorous activity.
- The increased presence of AEDs in public places and at sporting events can potentially save the lives of more young athletes who suddenly collapse secondary to hypertrophic cardiomyopathy, prolonged QT syndromes, and commotio cordis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Horeczko T, Young KD: *Congenital heart disease*. In: Strange GR, Ahrens WR, Schaftermeyer RW, Wiebe RA, eds: *Pediatric Emergency Medicine: A Comprehensive Study Guide*, 3rd ed. New York: McGraw-Hill; 2009.
2. Fitzmaurice L, Gerardi MJ: *Cardiovascular system*. In: Gausche-Hill M, Fuch S, Yamamoto L, eds: *APLS: The Pediatric Emergency Medicine Resource*, 4th ed. Sudbury, Mass: Jones & Bartlett; 2004:106.
3. Woolridge DP, Love JC: Congenital heart disease in the pediatric emergency department. Part I: Pathophysiology and clinical characteristics. *Pediatr Emerg Med Rep* 2002; 7:69.
4. Sharieff GQ, McCollough M: The nightmare neonate: Life-threatening events in the first month of life. *Emerg Med Pract* 2003; 5:1.
5. Miller AJ, Texidor TA: Precordial catch, a neglected syndrome of precordial pain. *JAMA* 1955; 159:1364-1365.
6. Gumbiner CH: Precordial catch syndrome. *South Med J* 2003; 96:38-41.
7. Inaba AS: A simple way to remember pediatric vital signs. *Contemp Pediatr* 2002; 19:16.
8. Siegfried BH, Henderson TO: *Cardiology*. In: Gunn VL, Nechyba C, eds: *The Harriet Lane Handbook: A Manual for Pediatric House Officers*, 16th ed. Philadelphia: Mosby; 2002:123.
9. Park MK: *Physical examination*. In: Park MK, ed: *Pediatric Cardiology for Practitioners*, 4th ed. St. Louis: Mosby; 2002:10.
10. Cloherty JP, et al: *Manual of Neonatal Care*, 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2004:407.
11. Adamcova M: Troponins in children and neonates. *Acta Pædiatr* 2003; 92:1373-1375.
12. Fenton KE, Sable CA, Bell MJ, Patel KM, Berger JT: Increases in serum levels of troponin I are associated with cardiac dysfunction and disease severity in pediatric patients with septic shock. *Pediatr Crit Care Med* 2004; 5:533-538.
13. Maisel A: B-type natriuretic peptide in the diagnosis and management of congestive heart failure. *Cardiol Clin* 2001; 19:557.
14. Mir TS, et al: Plasma concentrations of N-terminal pro–brain natriuretic peptide in control children from the neonatal to adolescent period and in children with congestive heart failure. *Pediatrics* 2002; 110:e76.
15. Hoffman JI: The incidence of congenital heart disease. *J Am Coll Cardiol* 2002; 39:12.
16. Koppel RI, et al: Effectiveness of pulse oxymetry screening for congenital heart disease in asymptomatic newborns. *Pediatrics* 2003; 111:451.
17. Park MK: *Left-to-right shunt lesions*. In: Park MK, ed: *Pediatric Cardiology for Practitioners*, 4th ed. St. Louis: Mosby; 2002:129.
18. Thanopoulos BD, et al: Transcatheter closure of perimembranous ventricular septal defects with the Amplatzer asymmetric ventricular septal defect occluder: Preliminary experience in children. *Heart* 2003; 89:918.
19. Chessa M, et al: Transcatheter closure of congenital and acquired muscular ventricular septal defects using the Amplatzer device. *J Invasive Cardiol* 2002; 14:322.
20. Arora R, et al: Transcatheter closure of congenital ventricular septal defects: Experience with various devices. *J Interv Cardiol* 2003; 16:83.
21. Brandt RR: Transcatheter closure of atrial septal defect and patent foramen ovale in adult patients using the Amplatzer occlusion device: No evidence for thrombus deposition with antiplatelet agents. *J Am Soc Echocardiogr* 2002; 15:1094.
22. Wilkinson JL: Interventional pediatric cardiology: Device closures. *Indian J Pediatr* 2000; 67(Suppl):30.
23. Niwa K, et al: Eisenmenger syndrome in adults: Ventricular septal defects, truncus arteriosus, univentricular heart. *J Am Coll Cardiol* 1999; 34:223.
24. Park MK: *Obstructive lesions*. In: Park MK, ed: *Pediatric Cardiology for Practitioners*, 4th ed. St. Louis: Mosby; 2002:155.
25. Chen YB, Liberthson RR, Freed MD: *Congenital heart disease*. In: Lilly L, ed: *Pathophysiology of Heart Disease: A Collaborative Project of Medical Students and Faculty*, 3rd ed. Baltimore: Lippincott Williams & Wilkins; 2003:347.
26. Warnes CA, et al: ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Adults With Congenital Heart Disease). *Circulation* 2008; 118:2395-2451.
27. Park MK: *Cyanotic congenital heart defects*. In: Park MK, ed: *Pediatric Cardiology for Practitioners*, 4th ed. St. Louis: Mosby; 2002:174.
28. Gewitz MH, Vetter V: *Cardiac emergencies*. In: Fleisher GR, Ludwig S, eds: *Textbook of Pediatric Emergency Medicine*, 4th ed. Baltimore: Lippincott Williams & Wilkins; 2000:659.
29. Woods WA, Schutte DA, McCulloch MA: Care of children who have had surgery for congenital heart disease. *Am J Emerg Med* 2003; 21:318.
30. Shay DK, et al: Bronchiolitis-associated hospitalizations among US children. *JAMA* 1999; 282:1140.
31. Shay DK, et al: Bronchiolitis-associated mortality and estimates of respiratory syncytial virus–associated deaths among US children. *J Infect Dis* 2001; 183:16.
32. American Academy of Pediatrics: *Respiratory syncytial virus*. In: Pickering LK, et al, eds: *Red Book: 2003 Report of the Committee on Infectious Diseases*, 26th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2003:523.
33. Feltes TF, et al: Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *J Pediatr* 2003; 143:523.
34. Romero JR: Palivizumab prophylaxis of respiratory syncytial virus disease from 1998 to 2002: Results from four years of palivizumab usage. *Pediatr Infect Dis J* 2003; 22(Suppl):46.
35. Koulouri S, et al: Utility of B-type natriuretic peptide in differentiating congestive heart failure from lung disease in pediatric patients with respiratory distress. *Pediatr Cardiol* 2004; 25:341.
36. Vaidya VU, et al: A computerized program for changing the rule of six to standardized drips. *Pediatr Crit Care Med* 2005; 6:109.
37. Young KD, Seidel JS: Pediatric cardiopulmonary resuscitation: A collective review. *Ann Emerg Med* 1999; 33:195.
38. Hazinski MF, et al: *Rhythm disturbances*. In: Ralston M, ed: *PALS Provider Manual*. Dallas, Texas: American Heart Association; 2002:185.
39. Naccarelli GV, et al: Amiodarone: Clinical trials. *Curr Opin Cardiol* 2000; 15:64.
40. Saul JP, et al: Intravenous Amiodarone Pediatric Investigators: Intravenous amiodarone for incessant tachyarrhythmias in children: A randomized, double-blind, antiarrhythmic drug trial. *Circulation* 2005; 112:3470-3477.
41. O'Connor M, McDaniel N, Brady WJ: The pediatric electrocardiogram, part II: Dysrhythmias. *Am J Emerg Med* 2008; 26:348-358.
42. Park MK: *Cardiac arrhythmias*. In: Park MK, ed: *Pediatric Cardiology for Practitioners*, 4th ed. St. Louis: Mosby; 2002:333.
43. Manole MD, Saladino RA: Emergency department management of the pediatric patient with supraventricular tachycardia. *Pediatr Emerg Care* 2007; 23:176-185.
44. Ralston M, et al: *Recognition and management of cardiac arrest*. In: Ralston M, ed: *PALS Provider Manual*. Dallas, Texas: American Heart Association; 2006:153.
45. Schlechte EA, Boramanand N, Funk M: Supraventricular tachycardia in the pediatric primary care setting: Age-related presentation, diagnosis, and management. *J Pediatr Health Care* 2008; 22:289-299.
46. Cummins RO: *Stable tachycardias*. In: Cummins RO, ed: *ACLS Provider Manual*. Dallas, Texas: American Heart Association; 2001:167.
47. Donoghue AJ, et al: Out-of-hospital pediatric cardiac arrest: An epidemiologic review and assessment of current knowledge. *Ann Emerg Med* 2005; 46:512-522.
48. Young KY, Gausche-Hill M, McClung CD, Lewis RJ: A prospective, population-based study of the epidemiology and outcome of out-of-hospital pediatric cardiopulmonary arrest. *Pediatrics* 2004; 114:157.
49. Nadkami VM, et al: First documented rhythm and clinical outcome from in-hospital cardiac arrest among children and adults. *JAMA* 2006; 295:50.
50. Smith BT, et al: Ventricular fibrillation in pediatric cardiac arrest. *Acad Emerg Med* 2006; 13:525.
51. Samson RA, et al: Outcomes of in-hospital ventricular fibrillation in children. *N Engl J Med* 2006; 354:2328.
52. Kleinman ME, et al: Part 14: Pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122(Suppl 3):S876-S908.
53. Alsoufi B, et al: Survival outcomes after rescue extracorporeal cardiopulmonary resuscitation in pediatric patients with refractory cardiac arrest. *J Thorac Cardiovasc Surg* 2007; 134:952-959.
54. Morris K, Beghetti M, Petros A, Adatia I, Bohn D: Comparison of hyperventilation and inhaled nitric oxide for pulmonary hypertension after repair of congenital heart disease. *Crit Care Med* 2000; 28:2974-2978.
55. Samson RA, Berg RA, Bingham R: Use of automated external defibrillators for children: An update (an advisory statement from the Pediatric Advanced Life Support Task Force, International Liaison Committee on Resuscitation). *Circulation* 2003; 107:3250.
56. Jun K, ed: AEDs and children: Evidence for safe use now sufficient. *Currents* 2003; 14:11.

www.ketabpezeshki.com 66485457-66963820

57. American Academy of Pediatrics Committee on Pediatric Emergency Medicine; American Academy of Pediatrics Section on Cardiology and Cardiac Surgery; Markenson D: Ventricular fibrillation and the use of automated external defibrillators in children. *Pediatrics* 2007; 120:1159.
58. Markenson D, et al: Ventricular fibrillation and the use of automated external defibrillators in children. *Pediatrics* 2006; 120:e1368.
59. Berg M, et al: Post-shock chest compression delays with automatic external defibrillator usage. *Resuscitation* 2005; 64:287.
60. Hickey RW, Zuckerbraun NS: Pediatric cardiopulmonary arrest: Current concept and future directions. *Pediatr Emerg Med Rep* 2003; 8:1.
61. Kochanek PM, et al: Cerebral resuscitation after traumatic brain injury and cardiopulmonary arrest in infants and children in the new millennium. *Pediatr Clin North Am* 2001; 48:661.
62. Sirbaugh PE, et al: A prospective, population-based study of the demographics, epidemiology, management, and outcome of out-of-hospital pediatric cardiopulmonary arrest. *Ann Emerg Med* 1999; 33:174.
63. Ferrieri P, et al: From the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the American Heart Association Council on Cardiovascular Disease in the Young: Unique features of infective endocarditis in childhood. *Circulation* 2002; 105:2115-2126.
64. Brook MM: Pediatric bacterial endocarditis treatment and prophylaxis. *Pediatr Clin North Am* 1999; 46:275.
65. Martin JM, Neches WH, Wald ER: Infective endocarditis: 35 years of experience at a children's hospital. *Clin Infect Dis* 1997; 24:669-675.
66. American Heart Association: Prevention of infective endocarditis. Guidelines from the American Heart Association. *Circulation* 2007; 116:1736.
67. Lee A, Mirrett S, Reller LB, Weinstein MP: Detection of blood stream infections in adults: How many blood cultures are needed? *J Clin Microbiol* 2007; 45:3546.
68. Ferrieri P, et al: Unique features of infective carditis in childhood. *Pediatrics* 2002; 109:931.
69. Yoshinaga M, et al: Risk factors for in-hospital mortality during infective endocarditis in patients with congenital heart disease. *Am J Cardiol* 2008; 101:114.
70. American Academy of Pediatrics: *Antimicrobial prophylaxis*. In: Pickering LK, et al, eds: *Red Book: 2003 Report of the Committee on Infectious Diseases*, 26th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2003:782.
71. Baddour LM, et al: Infective endocarditis: Diagnosis, antimicrobial therapy, and management of complications: A statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: Endorsed by the Infectious Diseases Society of America. *Circulation* 2005; 111:e394-e434.
72. Freedman SB, et al: Pediatric myocarditis: emergency department clinical findings and diagnostic evaluation. *Pediatrics* 2007; 120:1278.
73. Hia CP, Yip WC, Tai BC, Quek SC: Immunosuppressive therapy in acute myocarditis: An 18 year systematic review. *Arch Dis Child* 2004; 89:580-584.
74. Imazio M, et al: Treatment of refractory recurrent pericarditis. *J Cardiovasc Med* 2007; 8:748.
75. American Academy of Pediatrics: *Kawasaki syndrome*. In: Pickering LK, et al, eds: *Red Book: 2003 Report of the Committee on Infectious Diseases*, 26th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2003:392.
76. Newburger JW, et al: Diagnosis, treatment, and long-term management of Kawasaki disease: A statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 2004; 110:2747.
77. Falcini F: Kawasaki disease. *Curr Opin Rheumatol* 2006; 18:33.
78. Hsieh KS, et al: Treatment of acute Kawasaki disease: Aspirin's role in the febrile stage revisited. *Pediatrics* 2004; 114:e689-e693.
79. Newburger JW, et al: Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. *N Engl J Med* 2007; 356:663.
80. Wooditch A, Aronoff S: Effect of initial corticosteroid therapy on coronary artery aneurysm formation in Kawasaki disease: A meta-analysis of 862 children. *Pediatrics* 2005; 116:989.
81. Sundel RP: *Rheumatologic emergencies*. In: Fleisher GR, Ludwig S, eds: *Textbook of Pediatric Emergency Medicine*, 4th ed. Baltimore: Lippincott Williams & Wilkins; 2000:1191.
82. Rantz LA, Randall E, Rantz HH: Antistreptolysin O; a study of this antibody in health and in hemolytic streptococcal respiratory disease in man. *Am J Med* 1948; 5:3.
83. Park MK: *Rheumatic fever*. In: Park MK, ed: *Pediatric Cardiology for Practitioners*, 4th ed. St. Louis: Mosby; 2002:304.
84. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO: Sudden deaths in young competitive athletes: Analysis of 1866 deaths in the United States, 1980-2006. *Circulation* 2009; 119:1085-1092.
85. Washington RL: Most sudden deaths in adolescent athletes caused by cardiac conditions. *Pediatr Ann* 2003; 32:751.
86. Basso C, et al: Clinical profile of congenital coronary artery anomalies with origin from the wrong aortic sinus leading to sudden death in young competitive athletes. *J Am Coll Cardiol* 2000; 35:1493.
87. Eckart RE, Jones SO, Shry EA, Garrett PD, Scoville SL: Sudden death associated with anomalous coronary origin and obstructive coronary disease in the young. *Cardiol Rev* 2006; 14:161-163.
88. Basavarajaiah S, et al: Prevalence of hypertrophic cardiomyopathy in highly trained athletes: Relevance to pre-participation screening. *J Am Coll Cardiol* 2008; 51:1033-1039.
89. Bar-Cohen Y, Silka MJ: Sudden cardiac death in pediatrics. *Curr Opin Pediatr* 2008; 20:517-521.
90. Chen YB, Dec GW, Lilly LS: *The cardiomyopathies*. In: Lilly L, ed: *Pathophysiology of Heart Disease: A Collaborative Project of Medical Students and Faculty*, 3rd ed. Baltimore: Lippincott Williams & Wilkins; 2003:237.
91. Corrado D, et al: Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: Proposal for a common European protocol. Consensus Statement of the Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. *Eur Heart J* 2005; 26:516-524.
92. Maron BJ, Gohman TE, Kyle SB, Estes NA, Link MS: Clinical profile and spectrum of commotio cordis. *JAMA* 2002; 287:1142-1146.
93. Geddes LA, Roeder RA: Evolution of our knowledge of sudden death due to commotio cordis. *Am J Emerg Med* 2005; 23:67-75.

www.ketabpezeshki.com 66485457-66963820

Chapter 172

Gastrointestinal Disorders

Mark A. Hostetler

PERSPECTIVE

Gastrointestinal disorders affecting the pediatric population vary significantly with the age of the child. Consideration of age as well as of signs and symptoms has an important role in distinguishing cause. Infants, for example, may have disorders such as necrotizing enterocolitis (NEC), hypertrophic pyloric stenosis, or intussusception, whereas older children are more likely to present with appendicitis, pancreatitis, or biliary tract disease.

DISTINGUISHING PRINCIPLES OF DISEASE

Pediatric gastrointestinal disorders can be divided into different groups on the basis of their unique pathophysiologic mechanisms and reasons for development. Several disorders occur as a normal variant of development (neonatal jaundice, gastroesophageal reflux, hypertrophic pyloric stenosis), congenital malformations (malrotation, Meckel's diverticulum), or genetic abnormalities (Hirschsprung's disease). Idiopathic causes include NEC, intussusception, Henoch-Schönlein purpura (HSP), and inflammatory bowel disease (IBD).

SPECIFIC DISORDERS

Neonatal Jaundice

Perspective

Many infants become jaundiced during the newborn period, most often as a result of a benign, self-limited process. *Physiologic jaundice of the newborn,* the most common cause of neonatal jaundice, occurs in approximately 60% of normal newborns during the first week of life. *Breast milk jaundice* is the second most common cause of jaundice in the newborn period.

Principles of Disease

Bilirubin is formed by the breakdown of heme-containing proteins, primarily hemoglobin. Heme protoporphyrin is sequentially degraded into biliverdin and unconjugated bilirubin. Unconjugated bilirubin binds to albumin in the blood and is carried to the liver, where it is conjugated by glucuronyl transferase and excreted into bile. Jaundice may be caused by increased amounts of either unconjugated or conjugated bilirubin and becomes clinically apparent when the total bilirubin level reaches approximately 5 mg/dL. Conjugated hyperbilirubinemia occurs when the direct-reacting portion exceeds 2 mg/dL or is greater than 20% of the total.

The exact pathogenetic mechanism of breast milk jaundice is uncertain. Breast milk jaundice may be hormonally mediated or related to intestinal excretion and resorption of bile. Other causes of jaundice vary significantly, depending on the percentage conjugation and the age of the infant (Tables 172-1 and 172-2). Although jaundice in adults usually is the direct result of primary liver disease, infantile jaundice has a variety of extrahepatic causes—genetic, metabolic, infectious, and obstructive. The list of diagnostic possibilities in neonatal jaundice is extensive and requires careful consideration because the morbidity and mortality rates for many of these entities are high.

Clinical Features

Physiologic jaundice of the newborn is the most common cause of neonatal jaundice and occurs in normal newborns during the first week of life. Affected infants are born with normal bilirubin levels that gradually increase to a peak level of 6 mg/dL on the third day of life and then decline to normal within 2 weeks. Breast milk jaundice is the next most common cause of hyperbilirubinemia in newborns. Affected infants exhibit the same gradual increase seen with physiologic jaundice. Levels continue to increase, however, and reach a higher peak level at 10 days to 3 weeks of life. Elevated levels may persist for 3 to 10 weeks and then gradually subside.

Toxic levels of bilirubin (more than 20 mg/dL and dependent on age) may be associated with neurotoxicity, encephalopathy, and the development of kernicterus. Kernicterus is characterized by yellow staining in areas of the brain, including the basal ganglia. Clinical manifestations begin with poor feeding and lethargy and may progress to muscle rigidity, opisthotonos, seizures, and death. Survivors may have residual problems with coordination and hearing and learning disabilities.[1] The cornerstones of therapy are phototherapy and exchange transfusion.

Diagnostic Strategies

Although physiologic jaundice of the newborn and breast milk jaundice are most common, it is important to identify truly pathologic causes of jaundice. Initial testing requires determination of fractionated levels of total and direct bilirubin. Box 172-1 lists indications for workup in infants presenting with hyperbilirubinemia. Conjugated (direct) hyperbilirubinemia is always pathologic. In such cases, a minimal workup should include a complete blood count (CBC) with peripheral smear and a Coombs test for immune-mediated major blood group incompatibility. Ill-appearing infants also require finger-stick blood glucose measurement, electrolyte panel, urine assay for reducing substances, and

www.ketabpezeshki.com 66485457-66963820

Table 172-1 Differential Considerations for Hyperbilirubinemia in Infants

ETIOLOGIC CATEGORY	UNCONJUGATED (INDIRECT)	CONJUGATED (DIRECT)
Benign, physiologic	Physiologic jaundice of the newborn Breast milk jaundice	
Hemolysis	ABO incompatibility Physiologic breakdown of birth trauma hematoma (cephalhematoma) Intraventricular or intracranial hemorrhage Spherocytosis, elliptocytosis Sickle cell anemia Thalassemia Glucose-6-phosphate dehydrogenase deficiency Pyruvate kinase deficiency	
Infectious	TORCHS infections Urinary tract infection Sepsis	TORCHS infections Urinary tract infection Gram-negative sepsis Listeriosis Tuberculosis Hepatitis B Varicella Coxsackievirus infection Echovirus infection HIV infection
Obstructive	Meconium ileus Hirschsprung's disease Duodenal atresia Pyloric stenosis	Biliary atresia Choledochal cyst Bile duct strictures Inspissated bile syndrome Neonatal hepatitis Alagille syndrome Byler's disease Congenital hepatic fibrosis
Metabolic or genetic	Galactosemia Congenital hypothyroidism Crigler-Najjar syndrome Gilbert's syndrome	Galactosemia Tyrosinemia Glycogen storage disease type IV Niemann-Pick disease Wolman's disease Gaucher's disease Cholesterol ester storage disease α_1-Antitrypsin deficiency Cystic fibrosis Dubin-Johnson syndrome Neonatal hypopituitarism Zellweger's syndrome Donohue syndrome (leprechaunism) Rotor syndrome
Miscellaneous		Drugs and toxins Parenteral nutrition

CMV, cytomegalovirus; *HIV,* human immunodeficiency virus; *TORCHS,* toxoplasmosis, other infections, rubella, CMV, herpes, syphilis.

Table 172-2 Differential Considerations for Hyperbilirubinemia in Older Children

ETIOLOGIC CATEGORY	UNCONJUGATED (INDIRECT)	CONJUGATED (DIRECT)
Obstructive		Gallstones Tumor Choledochal cyst Bile duct stricture
Infectious		Hepatitis Sepsis Urinary tract infection
Genetic	Sickle cell Thalassemia Spherocytosis, elliptocytosis Glucose-6-phosphate dehydrogenase deficiency Pyruvate kinase deficiency Crigler-Najjar syndrome Gilbert's syndrome	Dubin-Johnson syndrome Rotor syndrome Wilson's disease Cystic fibrosis α_1-Antitrypsin deficiency Glycogen storage disease
Other	Drug-induced hemolytic anemia Autoimmune hemolytic anemia Microangiopathic hemolytic anemia Hypersplenism	Cirrhosis Sclerosing cholangitis Cholestatic jaundice of pregnancy Drugs and toxins (acetaminophen, estrogens)

Box 172-1 Indications for Workup in Jaundiced Infants

Jaundice appearing within 24 hours of birth
Elevated direct (conjugated) bilirubin level
Rapidly rising total serum bilirubin unexplained by history or physical examination
Total serum bilirubin approaching exchange level or not responding to phototherapy
Jaundice persisting beyond 3 weeks of age
Sick-appearing infant

serum ammonia determination to rule out inborn errors of metabolism.[2]

Differential Considerations

Birth history should be obtained to elicit any history of trauma because large, resolving hematomas can result in jaundice. Family history should focus on identification of siblings or other relatives with a history of jaundice or genetic or metabolic disorders and any unexplained infant deaths. Tables 172-1 and 172-2 present full lists of differential considerations for jaundiced infants and children, respectively.

Infants with direct hyperbilirubinemia represent a special subset of patients. All infants with direct hyperbilirubinemia require hospital admission and evaluation for the cause of the jaundice based on history and presenting signs and symptoms. This evaluation may include any or all of the following: sepsis workup, TORCHS (toxoplasmosis, other infections, rubella, cytomegalovirus, herpes, syphilis) titers, basic metabolic studies, α_1-antitrypsin, sweat test for cystic fibrosis, ultrasound studies, radioisotope (hepatobiliary iminodiacetic acid [HIDA] or diisopropyl iminodiacetic acid [DISIDA]) scan, and liver biopsy. In children, hemolytic anemia, infection, and drugs are the most common causes of jaundice. The history should focus on travel, exposures, medications, and associated signs and symptoms, such as fever, malaise, and weight loss. Gentle palpation of the liver is

www.ketabpezeshki.com 66485457-66963820

useful to estimate size, firmness, and tenderness and to distinguish hepatomegaly from liver inflammation.

Management

Treatment of infants with hyperbilirubinemia centers on the prevention of kernicterus. Guidelines for use of phototherapy and exchange transfusion have been recommended by the American Academy of Pediatrics[3] (Fig. 172-1). Feeding should be continued to the extent possible because oral intake stimulates enterohepatic circulation and decreases bilirubin levels. Unless the infant is severely jaundiced, breast-feeding can be continued and supplemented with formula as needed. Infants who are premature or who have significant comorbidities require treatment at lower levels. Phototherapy often is now readily available on an outpatient basis.

Disposition

In general, infants with bilirubin levels greater than 18 to 20 mg/dL require hospital admission and phototherapy. All infants with direct hyperbilirubinemia require admission and workup.

Hypertrophic Pyloric Stenosis

Perspective

Hypertrophic pyloric stenosis is the most common cause of infantile gastrointestinal obstruction beyond the first month of life. This condition occurs in 1 of every 250 live births.[4] Boys are affected at four times the rate of girls. Hypertrophic pyloric stenosis tends to run in families; however, the exact pattern of inheritance is unclear. The incidence rate is 1 in 14 if the father is affected; the rate is even higher if the mother is affected.[4] Whites are affected more often than African Americans, and the disease is rare in Asian Americans.

Principles of Disease

Infants are born with a normal pylorus that undergoes hypertrophy only as time progresses. The exact etiology is unknown. As the pylorus continues to hypertrophy, there is progressive gastric outlet obstruction. As vomiting continues, the infant loses hydrogen and chloride ions through emesis of gastric juices. As this metabolic derangement worsens, the kidney attempts to retain

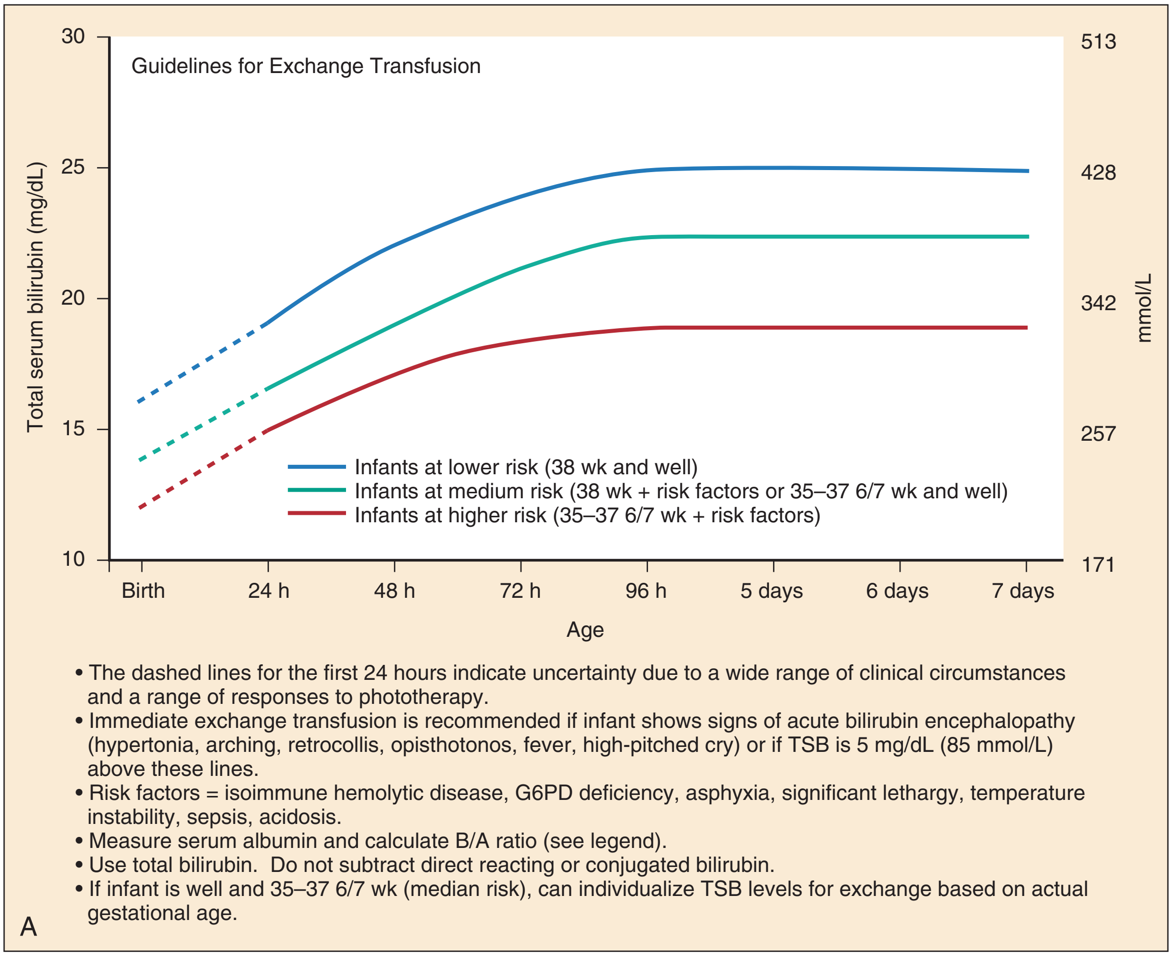


Figure 172-1. A, Guidelines for exchange transfusion in infants 35 weeks or more of gestation. Note that these suggested levels represent a consensus but are based on limited evidence, and the levels shown are approximations. During birth hospitalization, exchange transfusion is recommended if the total serum bilirubin (TSB) rises to these levels despite intensive phototherapy. For rehospitalized infants, if the TSB level is above the exchange level, repeat TSB measurement every 2 to 3 hours and consider exchange if the TSB remains above the levels indicated after intensive phototherapy for 6 hours. *B/A,* bilirubin/albumin; *G6PD,* glucose-6-phosphate dehydrogenase.

www.ketabpezeshki.com 66485457-66963820

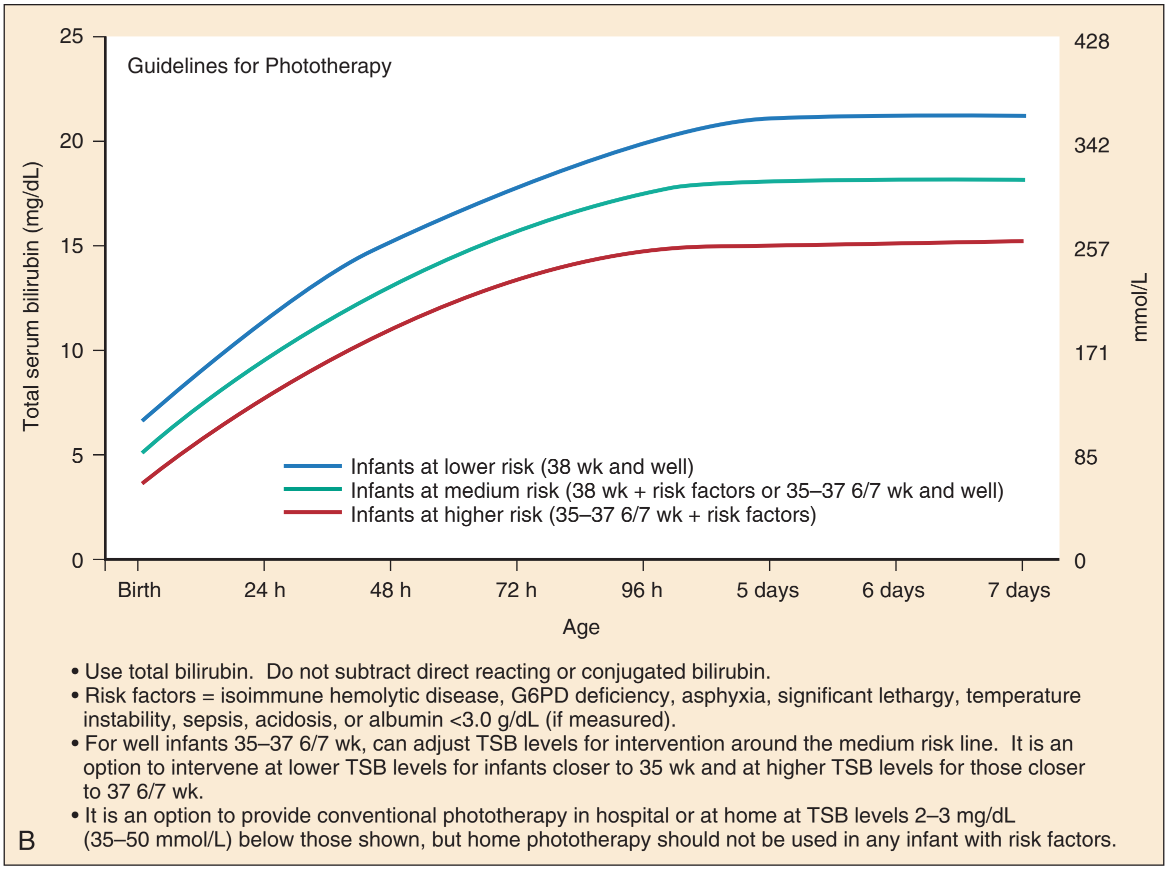


Figure 172-1, cont'd. B, Guidelines for phototherapy in hospitalized infants 35 weeks or more of gestation. Note that these guidelines are based on limited evidence, and the levels shown are approximations. The guidelines refer to intensive phototherapy, which should be used when the TSB exceeds the line indicated for each category. Infants are designated "higher risk" because of the potential negative effects of the conditions listed on albumin binding of bilirubin, the blood-brain barrier, and the susceptibility of the brain cells to damage by bilirubin. (From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 114:305, 2004.)

hydrogen ions in exchange for potassium, resulting in a hypochloremic, hypokalemic metabolic alkalosis.

Clinical Features

Infants classically present at 2 to 6 weeks old with gradually progressive emesis that becomes projectile and remains nonbilious. Infants remain vigorous with a ravenous appetite. They rapidly finish an entire feeding, only to regurgitate the entire volume in a projectile fashion. In the later stages of the disease, children may exhibit visible waves of abdominal peristalsis in response to intense contractions against an obstruction. Children in the later stages of disease may exhibit marasmus (protein-calorie malnutrition) as a result of impaired nutrient absorption.

Diagnostic Strategies

Children may have a palpable pylorus, commonly referred to as an olive in the right epigastrium, on abdominal examination. Placement of a nasogastric tube and emptying the stomach or placement of the infant in the prone position often facilitates palpation. Hypertrophic pyloric stenosis may be confirmed by ultrasonography or upper gastrointestinal series. Ultrasonography is the diagnostic modality of choice because it is simple, readily available, and without serious complications such as aspiration. With both modalities, reported accuracy is greater than 95%. Ultrasound examination reveals a thickened pylorus, which is diagnostic.[5] A characteristic "string sign," reflecting passage of contrast material through the narrowed pyloric sphincter, can be seen in the upper gastrointestinal tract. In advanced stages with complete obstruction at the pylorus, plain films may reveal an enlarged body of the stomach and pylorus (Fig. 172-2).

Differential Considerations

Etiologic possibilities vary by whether the course of vomiting has been sudden in onset, gradually progressive, or chronic. The frequency and volume of emesis may have important implications about the severity of disease and the potential risk for dehydration or electrolyte disturbance. In infants, other major considerations in the differential diagnosis include gastroesophageal reflux and malrotation. The age of the child and the timing of vomiting provide important clues to the etiology. Reflux classically begins early in life, usually shortly after birth, and remains relatively constant. With pyloric stenosis, vomiting does not begin until 2 to 3 weeks of age and then becomes increasingly severe and projectile; the emesis is rarely if ever bilious. In neonates, bilious vomiting requires diagnostic evaluation to rule out the possibility of malrotation with volvulus.[6] The imaging modality of choice for pyloric stenosis is ultrasonography.

Many causes of vomiting do not have a true gastrointestinal origin, including sepsis, increased intracranial pressure, middle ear disturbances, urinary tract infections, inborn errors of metabolism, pain, medications, and drug intoxications. Differential considerations for vomiting in children vary by age (Table 172-3).

www.ketabpezeshki.com 66485457-66963820

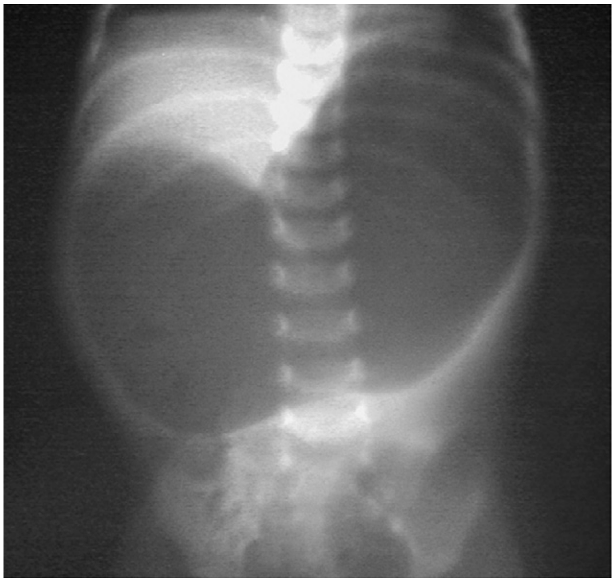


Figure 172-2. Plain radiograph of the abdomen revealing enlargement of the body and pyloric portions of the stomach; this is seen in advanced stages of hypertrophic pyloric stenosis. (Courtesy Mark A. Hostetler, MD.)

Management

Treatment consists of fluid and electrolyte replacement and surgical consultation. Fluid resuscitation should begin with a bolus of 20 mL/kg of normal saline, followed by additional boluses as necessary to treat signs of shock. When the patient is stable and shows no signs of shock, 5% dextrose and half-normal saline at 1.5 to 2 times maintenance may be administered. Potassium supplementation is often necessary. Hypertrophic pyloric stenosis is a chronic, progressive disease, not an acute ischemic process. Confirmatory radiographic diagnosis with ultrasonography may be done on a semiurgent basis as the patient's condition warrants. Pediatric surgical consultation is recommended although usually not emergent. The definitive corrective surgical procedure is the Ramstedt pyloromyotomy, which has an excellent track record of safety.[7] More recently, laparoscopic pyloromyotomy has gained increasing acceptance as being safe and effective.[8] Associated mortality is rare.

Disposition

Most children probably are best managed with hospital admission for rehydration and correction of electrolyte abnormalities. Imaging and surgical consultation are obtained on a semielective basis.

Table 172-3 Differential Considerations for Vomiting by Age

ETIOLOGIC CATEGORY	INFANCY	CHILDHOOD	ADOLESCENCE
Mechanical	Gastroesophageal reflux Malrotation with midgut volvulus Pyloric stenosis Meckel's diverticulum Intussusception Bowel obstruction Incarcerated hernia Tracheoesophageal fistula	Constipation Incarcerated hernia Meckel's diverticulum Bowel obstruction	Constipation Incarcerated hernia
Inflammatory or infectious	Necrotizing enterocolitis Gastroenteritis Sepsis Henoch-Schönlein purpura Meningitis Pneumonia Otitis media	Gastritis or gastroenteritis Otitis media Appendicitis Pancreatitis Henoch-Schönlein purpura Biliary tract disease	Gastroenteritis Appendicitis Pancreatitis Gastritis Biliary tract disease
Genitourinary	Urinary tract infection	Urinary tract infection	Urinary tract infection Pregnancy Testicular or ovarian torsion
Central nervous system	Hydrocephalus Intracranial hemorrhage Intracranial tumor	Migraine headache Hydrocephalus Intracranial hemorrhage Intracranial tumor Reye syndrome	Migraine headache Hydrocephalus Intracranial hemorrhage Intracranial tumor Glaucoma
Metabolic	Diabetic ketoacidosis Congenital adrenal hyperplasia Urea cycle defects Organic acidurias Amino acidopathies Fatty acid oxidation disorders	Diabetic ketoacidosis Urea cycle defects Fatty acid oxidation disorders	Diabetic ketoacidosis
Other or atypical	Occult trauma (abuse) Toxic ingestions Munchausen syndrome by proxy	Sickle cell Toxic ingestions Occult trauma (abuse) Munchausen syndrome by proxy	Sickle cell Toxic ingestions Occult trauma (abuse) Munchausen syndrome or Munchausen syndrome by proxy

www.ketabpezeshki.com 66485457-66963820

Malrotation with Midgut Volvulus

Perspective

Malrotation occurs in 1 in 500 live births and has a male predominance by at least 2:1.[9] Among infants with malrotation, volvulus eventually will develop in approximately 75%, and 75% of these infants present within the first month of life. Overall, 90% of patients present within the first year of life, although cases of adult midgut volvulus have been reported.[9] Bilious emesis is the hallmark presentation and is seen in more than 75% of cases.[6,9,10] Malrotation with volvulus carries a mortality rate of 3 to 15%.[9]

Principles of Disease

During embryologic development, the gastrointestinal tract rotates around the superior mesenteric artery. As it completes the rotation, the duodenum forms a C-loop and is fixed to the retroperitoneum in the left upper quadrant at the ligament of Treitz. The cecum becomes similarly fixed in the right lower quadrant. The duodenum and cecum normally come to lie widely separated and loosely connected by a broad-based mesentery. They are fixed firmly in position by peritoneal attachments called Ladd's bands. In cases of malrotation, the duodenum and the cecum do not rotate completely but end up close to each other, suspended in the midgut region by their vascular attachment containing the superior mesenteric artery. This unusually close proximity of the intervening mesentery results in a short stalk of mesentery that easily twists on itself, resulting in obstruction of the distal duodenum and compression of the superior mesenteric artery. Vascular compression results in ischemia of the bowel and, if it is not rapidly reversed, necrosis of the bowel wall in 1 to 2 hours.[9,11] Twisting of the pedicle also results in various degrees of obstruction secondary to Ladd's bands that are malpositioned and straddling the duodenum.

Bilious emesis is the hallmark presentation and is a result of severe obstruction. Any pigmented staining of the vomitus suggests the presence of bile. When bile is initially produced, it is bright yellow and turns green only with time and oxidative exposures. Differential coloring of bile-stained emesis, yellow versus green, is not predictive of surgical condition.

Clinical Features

Infants classically present with sudden-onset bilious emesis and abdominal distention.[12] The obstruction may be relatively high, however; consequently, a distended abdomen may not always be present. Infants usually appear quite ill and may present in shock.[13,14] Infants also may present with a history of intermittent, relatively mild episodes of emesis that suddenly become more intense. Although bilious emesis in a neonate suggests the possibility of acute obstruction and volvulus, presenting manifestations in children may be nonspecific, such as abdominal distention or an ill appearance.[12,13]

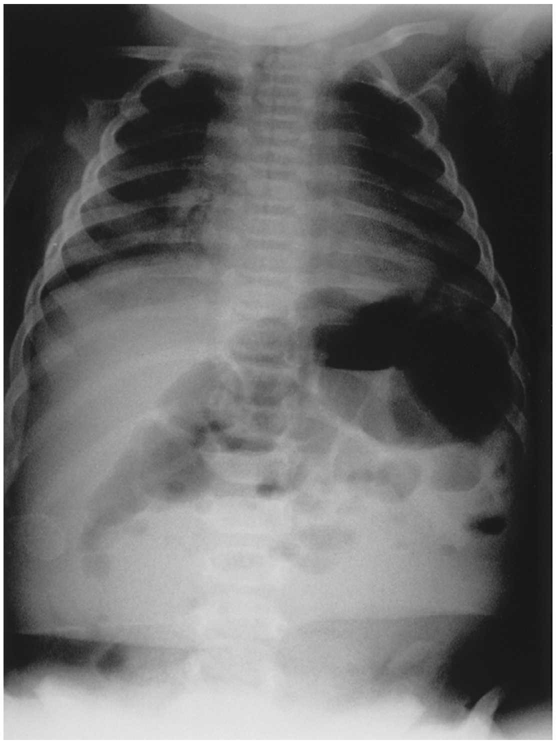


Figure 172-3. Upright abdominal radiograph obtained in an infant with bilious vomiting illustrates dilated loops of small bowel and a paucity of bowel gas distally, consistent with proximal obstruction secondary to malrotation with midgut volvulus. (Courtesy Mark A. Hostetler, MD.)

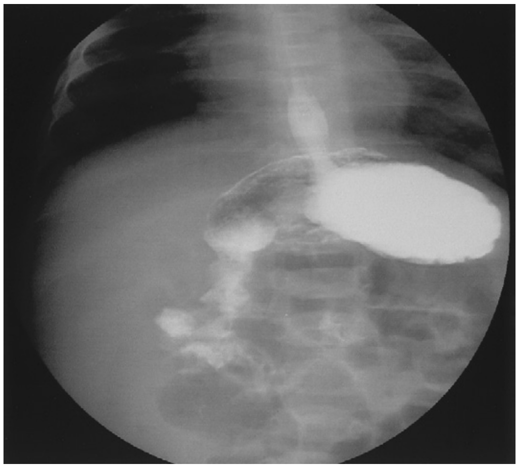


Figure 172-4. Upper gastrointestinal film, obtained in the same infant as in Figure 172-3, reveals abnormal positioning of the duodenal C-loop to the right of the spinal column, consistent with malrotation. (Courtesy Mark A. Hostetler, MD.)

Diagnostic Strategies

Diagnostic strategies may include a plain film of the abdomen, an upper gastrointestinal series, or a computed tomography (CT) scan of the abdomen. The imaging modality of choice is an upper gastrointestinal series with small bowel follow-through. Findings on plain abdominal films may include air-fluid levels suggesting obstruction, dilated loops overlying the liver, and a paucity of small bowel gas distally[11] (Fig. 172-3). In addition, a "double-bubble sign" may be present. The classic double bubble represents a dilated stomach and obstructed proximal duodenum and is seen with duodenal atresia and malrotation with midgut volvulus. Duodenal atresia is limited to the newborn nursery and is manifested within 24 hours of life. Malrotation with midgut volvulus typically is manifested with bilious vomiting within the first month of life. The modified double-bubble sign seen with hypertrophic pyloric stenosis represents a dilated body of the stomach and pylorus and is associated with nonbilious emesis.

The diagnostic procedure of choice to determine midgut volvulus is the upper gastrointestinal series, which reveals abnormal position of the duodenal C-loop (Fig. 172-4) and small bowel with a characteristic corkscrew appearance (Fig. 172-5).[11] It is very low

www.ketabpezeshki.com 66485457-66963820

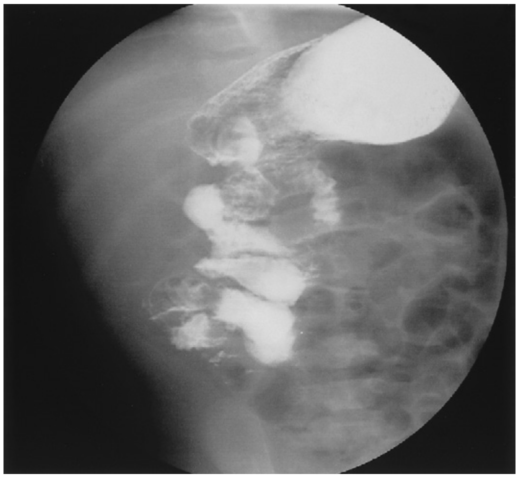


Figure 172-5. Another spot film from the upper gastrointestinal series obtained in the infant in Figure 172-3. This radiograph shows the characteristic corkscrew appearance seen on small bowel follow-through in patients with malrotation. (Courtesy Mark A. Hostetler, MD.)

risk, but an experienced technician or a radiologist is required to perform the test. An ultrasound scan may be obtained because of abdominal pain and may reveal abnormal positioning of the duodenal C-loop and superior mesenteric artery; a "whirlpool sign" is described with the spiraled mesentery causing an echogenic twisting pattern. The place of ultrasonography in the evaluation of children with midgut volvulus has yet to be determined.[10,15] CT is usually not recommended as it carries the risk of additional radiation without benefit of improved diagnostic ability over upper gastrointestinal series.

Differential Considerations

Vomiting in childhood is common and occurs across a wide spectrum of illnesses (see Table 172-3). Causes vary by the age of the child and whether the course of vomiting has been sudden in onset, gradually progressive, or chronic. Gastroesophageal reflux classically begins early in life, usually shortly after birth, and remains relatively constant. With pyloric stenosis, vomiting does not begin until the age of 2 to 3 weeks and then becomes increasingly severe, projectile, and nonbilious. Acute obstruction causes sudden-onset vomiting, which may be bilious. In a neonate, bilious vomiting requires diagnostic evaluation to rule out the possibility of malrotation with volvulus.[12,13] NEC is another consideration but most often is manifested within the first weeks of life. Neonates with NEC may present with obstructive signs and symptoms, including bilious emesis and abdominal distention. Whereas malrotation usually is associated with a paucity of small bowel air on plain films, NEC is characterized radiographically by diffusely dilated loops of small bowel. In addition, the presence of pneumatosis intestinalis is diagnostic of NEC but is not a feature of malrotation.

Management

Infants with bilious emesis of sudden onset who appear ill or have a distended abdomen require emergency consultation with a pediatric surgeon.[16] Intravenous access should be obtained and laboratory studies performed for CBC, electrolyte values, and liver function. Repeated fluid boluses of normal saline, 20 mL/kg, are necessary until adequate circulation has been obtained. A fingerstick sample for blood glucose determination and specimens for blood and urine cultures should be obtained. A nasogastric or orogastric tube should be placed. After consultation with a pediatric surgeon, an upper gastrointestinal series may be needed emergently. Ill-appearing infants require broad-spectrum, triple-antibiotic coverage with ampicillin, gentamicin, and either clindamycin or metronidazole. Time is of the essence in the evaluation and operative management of these patients. Rapid pediatric surgical consultation should be obtained in any neonate or infant with bilious vomiting even before diagnostic studies have been performed, especially for infants who appear ill. In contrast to hypertrophic pyloric stenosis, in which surgery does not need to be immediate, operative intervention must be rapid to save the bowel from necrosis.

Disposition

Patients thought to have malrotation require definitive imaging and an immediate surgical evaluation. If the diagnosis is confirmed or equivocal, hospital admission and surgical management are required.

Necrotizing Enterocolitis

Perspective

NEC, the most common gastrointestinal emergency in neonates, affects 2000 to 4000 infants in the United States every year.[17] NEC also is the most common cause of intestinal perforation during the newborn period.[17] Because most affected infants are premature and acquire the condition in the neonatal intensive care unit, NEC usually is not considered a disease of the emergency department (ED). Many of these infants may be discharged relatively early, however, because they are "feeding and growing" and come to treatment in the first month of life. Ten percent of infants with NEC are full-term babies.[18] Development of NEC is related closely to gestational age. In infants born at 24 to 28 weeks of gestation, NEC develops within 2 to 3 weeks of life[19]; in those born at 29 to 32 weeks of gestation, it is seen within 1 to 3 weeks of life. Among more mature or full-term infants, NEC tends to develop in the first week of life.[17] Complications in children who survive NEC may include strictures (in 10-20% of cases), fistulas, and short gut syndrome.

Principles of Disease

The exact pathophysiologic mechanism of NEC is unclear but seems to be multifactorial. Proposed risk factors include prematurity, aggressive enteral feedings, birth-related hypoxic-ischemic insults, and infectious causes. Prematurity is the most common and universally accepted risk factor; 90% of all affected infants are premature at birth.[18,19] Rapid advancement of feedings also has been associated with increased rates of NEC.[20] Infection has been implicated as an important causative mechanism.[21] Evidence suggests that hypoxic-ischemic insults are not an independent risk factor for the development of NEC.[18] The primary pathologic event may be inflammation or injury to the intestinal wall, which begins in the mucosa and then extends transmurally. The distal ileum and proximal colon are more commonly affected, and the involvement may be continuous or patchy.[22]

Clinical Features

Infants with NEC present with feeding intolerance and emesis. Emesis may be either nonbilious or bilious. On occasion, individual loops of bowel become distended with air and are palpable on abdominal examination. In the more severe stages of the disease, infants may appear extremely ill, with hematemesis, hematochezia, and shock. NEC commonly is placed into one of

www.ketabpezeshki.com 66485457-66963820

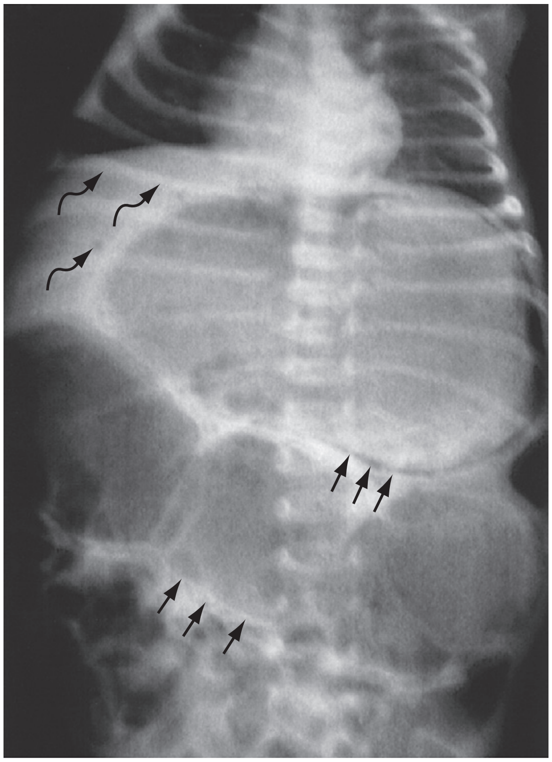


Figure 172-6. Plain radiograph obtained in an infant with necrotizing enterocolitis. Straight arrows indicate air within the wall of the small bowel and gastric mucosa (pneumatosis intestinalis and gastralis). Curved arrows indicate air in the biliary tree (portal venous gas). (Courtesy Mark A. Hostetler, MD.)

three clinical stages on the basis of criteria developed by Bell.[23] Stage I represents early or suspected NEC based on feeding intolerance, vomiting, or ileus. Stage II represents definite NEC as proved by abdominal radiographs showing intestinal dilation and pneumatosis intestinalis. Stage III represents advanced disease and is associated with perforation. Infants in this stage are acutely ill, with marked abdominal distention, metabolic acidosis, disseminated intravascular coagulation, and shock.

Diagnostic Strategies

Dilated loops of bowel are a common but nonspecific finding in stage I. Another early and more specific radiographic sign is the loss of a normal symmetrical gas pattern and replacement with an asymmetrical pattern of bowel gas, with a variable degree of dilation. Intramural air (pneumatosis intestinalis) is specific for NEC and is present in stage II[23] (Fig. 172-6). Pneumatosis is present in 75% of patients with NEC.[18] Air also may be seen within the biliary tract (portal vein gas) or occasionally in the gastric wall (pneumatosis gastralis; see Fig. 172-6). Portal vein gas is present in 10 to 30% of cases.[18] Ultrasonography and barium enema, which have been described as adjunctive diagnostic imaging modalities in patients with suspected NEC, are rarely helpful in the ED. No individual laboratory features are diagnostic or specific for NEC.

Differential Considerations

Etiologic possibilities vary according to whether the emesis is bilious and the course of vomiting has been sudden in onset, gradually progressive, or chronic (see Table 172-3). Gastroesophageal reflux classically begins early in life, usually shortly after birth, and remains relatively constant in character. Pyloric stenosis—related vomiting does not begin until 2 to 3 weeks of age and then becomes increasingly severe and projectile. In neonates, bilious vomiting requires careful consideration to rule out the possibility of malrotation with volvulus. As noted previously, with malrotation, a paucity of small bowel air usually is noted on plain films, whereas with NEC, diffusely dilated loops of small bowel typically are seen. In addition, the presence of pneumatosis is diagnostic of NEC but is not a radiographic feature of malrotation.

Management

Patients thought to have NEC should receive nothing by mouth (i.e., NPO [*nil per os*] status), with placement of either an orogastric or a nasogastric tube for decompression of the stomach and small bowel. These patients frequently appear quite ill and may have periods of apnea or significant respiratory distress. The airway should be secured as indicated. Intravenous access should be established and routine laboratory studies performed to include CBC, electrolyte panel, type and screen, and coagulation studies (prothrombin time [PT] and partial thromboplastin time [PTT]). A bedside blood glucose value should be obtained. Cultures of the blood and urine also are indicated. Careful attention should be given to management of fluids and electrolytes because considerable third spacing of fluids may occur in these patients. Repeated fluid boluses at 20 mL/kg of normal saline should be administered until adequate circulation is obtained. These boluses may be augmented with dopamine or epinephrine drips as necessary for patients in refractory shock when euvolemia has been achieved. Fluids should be continued with 5% dextrose in water and half-normal saline at a minimum of 1.5 to 2 times maintenance. Infants with NEC require broad-spectrum, triple-antibiotic coverage with ampicillin, gentamicin, and either clindamycin or metronidazole. Emergent consultation should be obtained from a pediatric surgeon. Patients with evidence of perforation, peritonitis, or gangrenous bowel require surgical intervention. Only one half to three quarters of patients with perforation have free air detectable on radiographs.[23]

Disposition

Children thought to have NEC require admission to an intensive care unit (either pediatric or neonatal) and pediatric surgical consultation.

Gastroesophageal Reflux

Perspective

Gastroesophageal reflux, one of the most common causes of vomiting during infancy, refers to the regurgitation of stomach contents into the esophagus.

Principles of Disease

Gastroesophageal reflux occurs as a result of an incompetent lower esophageal sphincter. Chronic reflux of gastric contents into the esophagus may result in esophagitis, aspiration, and failure to thrive if it is severe.

Clinical Features

Clinical manifestations occur along a wide spectrum of disease, ranging from occasional episodes of spitting up to severe, persistent vomiting and failure to thrive. Gastroesophageal reflux generally responds to conservative measures and resolves with age. It

www.ketabpezeshki.com 66485457-66963820

usually begins shortly after birth and resolves by the age of 1 year. The disorder may be associated with stereotypical opisthotonic movements, collectively referred to as Sandifer's syndrome. Affected children exhibit extension and stiffening of the arms and legs and extension of the neck, often accompanied by a shrill or guttural cry. It may be associated with a brief period of apnea and pallor as formula is refluxed into the esophagus. Sandifer's syndrome most commonly occurs shortly after feeding and usually is not associated with cyanosis.

Diagnostic Strategies

In the ED, the diagnosis of gastroesophageal reflux typically is made on the basis of a careful history and physical examination. However, for ill patients in whom the diagnosis is uncertain, other diagnostic studies are available with gastroenterology consultation, such as esophageal pH probes to check for reflux of acid, barium swallow, and direct visualization by endoscopy.

Differential Considerations

Children with gastroesophageal reflux exhibit nonbilious emesis that begins shortly after birth and is relatively constant over time. Typically, no sudden starting or ending point, as would be suggested by an acute obstruction, can be identified. Vomiting usually is neither gradually progressive nor projectile, as seen with pyloric stenosis. Most children with gastroesophageal reflux of milder severity continue to gain weight.

Management

Most infants respond to conservative measures, such as smaller feedings, frequent "burpings," thickening of formula with cereal, and semiupright position for 45 minutes to 1 hour after feeding. Pharmacologic regimens are reserved for more severe cases. Weight loss is an important historical feature and necessitates pediatric gastroenterology referral for evaluation. Children exhibiting failure to thrive or esophagitis often are prescribed ranitidine and metoclopramide. Ranitidine, a histamine blocker, reduces gastric acid secretion. Metoclopramide increases lower esophageal tone, reduces pyloric sphincter tone, and increases gastric motility. Patients not responding to medical management occasionally require surgical intervention with a Nissen fundoplication, which involves wrapping of a portion of the stomach around the esophagus to prevent the reflux.

Disposition

Most children can be discharged home safely with conservative measures. Children who exhibit failure to thrive should be referred to a pediatrician or pediatric gastroenterologist for consideration of pharmacologic management. Children with dehydration and children in whom other diagnoses have yet to be excluded may benefit from hospital admission and further evaluation.

Intussusception

Perspective

Intussusception is the most common cause of intestinal obstruction in children younger than 2 years and occurs most commonly in infants 5 to 12 months of age.[11,23] An estimated incidence of 1 per 2000 children younger than 15 years, with a male predominance, has been reported.[23] Siblings of affected children have a relative risk 15 to 20 times higher than that in the general population. The mortality rate for untreated intussusception is high.

Principles of Disease

The exact etiology of intussusception is unclear, but the most prevalent theory relates to a lead point that causes telescoping of one segment of intestine into another.[23] As the process continues and intensifies, edema develops and obstructs venous return, resulting in ischemia of the bowel wall. As ischemia of the bowel wall continues, peritoneal irritation ensues, and perforation may occur.

In younger children, lead points are most often the result of enlarged Peyer's patches secondary to a recent viral infection. In children older than 5 years, an underlying lesion is found in more than 75% of cases; lesions include HSP vasculitis, Meckel's diverticulum, lymphoma, polyps, postsurgical scars, celiac disease, and cystic fibrosis.[23-27] Intussusception may occur at any point along the gastrointestinal tract. Ileocolic intussusceptions are most common. Ileoileal intussusception may occur in children with HSP.

Clinical Features

The classic triad of clinical findings in intussusception consists of abdominal pain, vomiting, and bloody stools. All three features are present in less than one third of patients, however. Three quarters of patients with intussusception have two of these findings, and 13% have either none or only one.[27] In a typical presentation, the child experiences cyclic episodes of severe abdominal pain. The pain typically lasts 10 to 15 minutes and has a periodicity of 15 to 30 minutes. During the painful episodes, the child is inconsolable, often described as drawing the legs up to the abdomen and screaming in pain. The clinical presentation occasionally does not include more typical evidence of pain; instead, the child presents with profound lethargy. Vomiting and diarrhea may be associated features. Blood may be present in either the stool or the emesis. Diarrhea containing mucus and blood constitutes the classic "currant jelly" stool most often associated with intussusception, although in actuality this finding is relatively infrequent. Children often have had a recent viral illness. Palpation of the abdomen may reveal a sausage-like mass in the right upper quadrant representing the actual intussusceptus and an empty space in the right lower quadrant representing the movement of the cecum out of its normal position. This combination of findings is called Dance's sign and is considered pathognomonic for intussusception. Its occurrence is relatively uncommon, however. Intussusception usually is not associated with a high fever; however, low-grade fevers may occur.

Diagnostic Strategies

Initial screening films should be obtained, with a minimum of two views of the abdomen. Attention should be focused on visualization of the entire colon and in particular the cecum. Films also should be examined for evidence of a soft tissue mass or mass effect, obstruction, target sign (representing air in the intussusceptum as it telescopes into adjacent bowel), meniscus sign (representing air compressed like a meniscus from invaginating bowel), and free air (Fig. 172-7). Normal findings on radiographs of the abdomen revealing complete visualization of the entire colon, including the cecum, make intussusception unlikely; however, indeterminate or nonspecific findings on films in which the entire colon cannot be visualized do not rule out intussusception and require additional imaging. Ultrasonography is the least invasive and most commonly used modality to visualize intussusception and is highly accurate.[28] Ileocolic intussusceptions are most common and are easily detected by ultrasonography, even in inexperienced hands.[29] The goal of the ultrasound examination is to visualize the ileocecal junction, which should be in the

www.ketabpezeshki.com 66485457-66963820

Figure 172-7. Plain radiograph obtained in a child with crampy abdominal pain and vomiting, later confirmed to have intussusception. Findings include a poorly defined soft tissue density in the right upper quadrant, obscuration of the liver edge, and focally dilated loops of small bowel, consistent with an acute obstructive process (intussusception). (Courtesy Mark A. Hostetler, MD.)

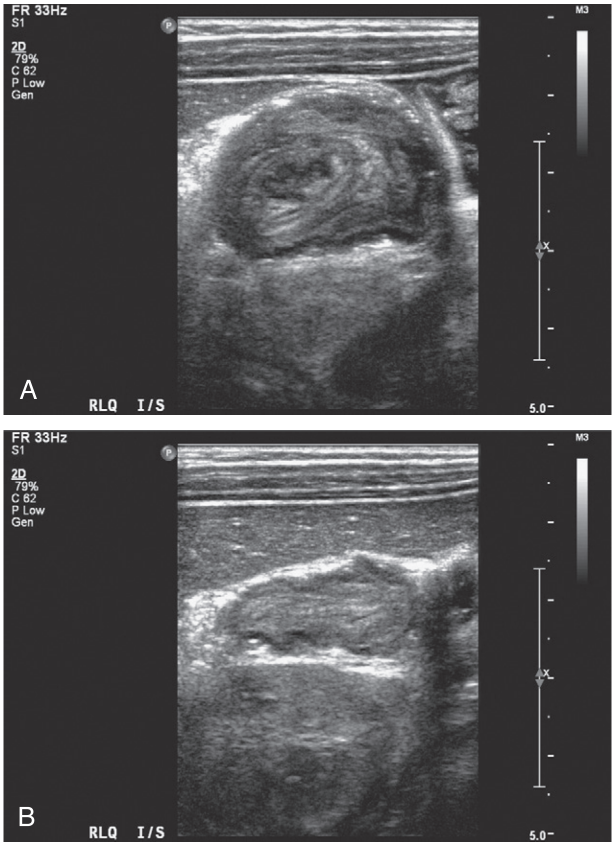


Figure 172-8. Abdominal ultrasound examination in a child with colicky abdominal pain and vomiting, later confirmed to have intussusception. On the transverse view (**A**), findings include a complex mass with a multilayered or rolled appearance. In the long view (**B**), the ileum can be seen protruding up into the cecum, forming the intussuscipiens-intussusceptum complex. (Courtesy Mark A. Hostetler, MD.)

right lower quadrant but may be translocated into the right middle to upper quadrant. On the ultrasound scan, the intussusception appears on the transverse view as a multilayered or wrapped complex mass and on the longitudinal view as a tube within a tube as the ileum projects up into the cecum (Fig. 172-8). Because of the readily identifiable anatomic location and the absence of ionizing radiation, this is usually the diagnostic imaging modality of choice. Contrast enemas may be both diagnostic and therapeutic and, with a high index of suspicion (i.e., children with the triad of paroxysms of pain, vomiting, and blood in stool), may be done as first-line therapy. The enema will reveal a sharp cutoff at the point where the intussusceptum meets the contrast material (Fig. 172-9). Air-contrast enemas are equally efficacious, have success rates averaging more than 60%, and are preferred to barium contrast studies by some physicians.[28-31] Either type of enema requires readily available backup by a pediatric surgeon in the event of failure of the bowel to reduce or perforation. Before any radiologic studies are performed, intravenous access should be established, and the patient should receive at least one bolus of 20 mL/kg of normal saline along with appropriate parenteral pain relief.

Figure 172-9. Contrast enema image obtained in a child with intussusception shows a sharp cutoff where the contrast material meets the intussusceptum and the acute obstruction. (Courtesy Mark A. Hostetler, MD.)

Differential Considerations

Differential considerations for abdominal pain in children by age are listed in Table 172-4. Slow, progressive onset of pain is more likely to be associated with appendicitis, constipation, or pancreatitis. Children with peritoneal irritation invariably lie still, often on the side with the knees bent, and refrain from all extraneous movement. Sudden onset of severe pain is associated most often with acute obstruction or vascular occlusion, as seen with intussusception, volvulus, or torsion of the testicle or ovary. Children with intussusception have severe colicky pain and often rock back and forth, frequently moaning or crying. Children with ischemic pain exhibit symptoms out of proportion to the findings on examination. They may appear diaphoretic, clammy, or pale and complain of excruciating abdominal pain although exhibiting only mild tenderness to palpation and no localizing findings.

www.ketabpezeshki.com 66485457-66963820

Table 172-4 Differential Considerations for Abdominal Pain by Age

ETIOLOGIC CATEGORY	INFANCY	CHILDHOOD	ADOLESCENCE
Mechanical	Malrotation with midgut volvulus Intussusception Incarcerated hernia Meckel's diverticulum Hirschsprung's disease	Constipation Incarcerated hernia Meckel's diverticulum Bowel obstruction	Constipation Incarcerated hernia Meckel's diverticulum Bowel obstruction
Inflammatory or infectious	Necrotizing enterocolitis	Gastroenteritis Appendicitis Henoch-Schönlein purpura Pancreatitis Gastritis Biliary tract disease	Gastroenteritis Appendicitis Henoch-Schönlein purpura Pancreatitis Gastritis Biliary tract disease
Genitourinary	Urinary tract infection	Urinary tract infection	Urinary tract infection Nephroureterolithiasis Pregnancy, ectopic Pelvic inflammatory disease Testicular or ovarian torsion
Other or atypical	Colic Occult trauma (abuse) Toxic ingestions Munchausen syndrome by proxy	Pneumonia Diabetic ketoacidosis Sickle cell Toxic ingestions Occult trauma (abuse) Munchausen syndrome by proxy	Pneumonia Diabetic ketoacidosis Sickle cell Toxic ingestions Occult trauma (abuse) Munchausen syndrome or Munchausen syndrome by proxy

Management

Patients require intravenous access and screening CBC and electrolyte values. Intravenous fluids are given in boluses of 20 mL/kg of normal saline until adequate vascular volume is achieved. Children should be maintained on NPO status. Nasogastric tube decompression may be necessary if there is evidence of significant gaseous distention. Prompt surgical consultation is required. Ill-appearing or febrile children require broad-spectrum, triple-antibiotic coverage with ampicillin, gentamicin, and either clindamycin or metronidazole. Diagnostic and therapeutic interventions depend on location and resources available. Patients may undergo an initial ultrasound examination, or if history and plain film findings suggest intussusception, the patient may go straight to either air or hydrostatic barium enema. Surgical intervention is required if the reduction is unsuccessful or if perforation occurs. The overall success rate for air-contrast enema or barium enema approaches 90%. Intussusception may recur in 7 to 10% of radiologic reductions and in 2 to 5% of surgical reductions, usually within 24 hours. Admission for observation usually is recommended for all patients after reduction.[30]

Disposition

Children with suspected intussusception require definitive imaging with ultrasonography. Children with documented intussusception require reduction with either enema or surgery. Hospital admission is recommended for all patients after reduction.

Hirschsprung's Disease

Perspective

Hirschsprung's disease accounts for approximately 20% of cases of partial intestinal obstruction in early infancy. Hirschsprung's disease occurs at a rate of 1 in 5000 live births and is four to five times more common in boys. It usually is sporadic in occurrence but may be associated with Down syndrome or a variety of other anomalies of the gastrointestinal, genitourinary, or central nervous system.[32]

Principles of Disease

Hirschsprung's disease represents congenital aganglionosis of the colon and is characterized by an absence of ganglion cells in the myenteric plexus of the distal colon.[32] The anus is invariably involved, with aganglionic bowel usually extending proximally 4 to 25 cm. Absence of colonic ganglion cells interferes with that segment's ability to relax, creating a functional obstruction. Stool accumulates proximal to the level of obstruction and produces dilation of the colon, the so-called megacolon.

Clinical Features

Neonates with Hirschsprung's disease often present in the nursery with failure to pass meconium. Infants brought to the ED may have a history of constipation and obstipation. Vomiting, irritability, and abdominal distention may be features. Symptoms and signs may be subtle and include a history of chronic constipation and poor weight gain or failure to thrive. Hirschsprung's disease usually is diagnosed in infancy; however, a spectrum of disease is recognized, and presentation may be later in life. Children who appear ill with fever should be evaluated for enterocolitis and toxic megacolon. Enterocolitis is characterized by abdominal distention, bloody stools, fever, and elevated white blood cell count.

Diagnostic Strategies

Plain films of the abdomen may reveal evidence of fecal impaction with proximal obstruction, air-fluid levels, and dilated colon. A barium enema revealing a narrowed aganglionic segment with proximal dilation is highly suggestive of Hirschsprung's disease.[32,33] The diagnosis is confirmed by biopsy or manometry.

Differential Considerations

Constipation is one of the most common causes of abdominal pain and vomiting in children.[33,34] Children in the process of "potty training" occasionally become pathologic in their ability to delay defecation. Pathologic causes of constipation are

www.ketabpezeshki.com 66485457-66963820

uncommon. In addition to Hirschsprung's disease, considerations include cystic fibrosis, infantile botulism, and hypothyroidism. An acquired variant of the disease also may occur in which other factors produce similar dilated colonic findings, resulting in acquired megacolon. Risk factors include anal fissures, fecal impaction, toilet training issues, and neuromuscular dysfunction secondary to neurologic disease, drugs, or metabolic causes.

The exact definition of constipation is elusive because it varies with age and diet. Infants during the first few months of life may have stool frequencies that range from one per feeding to one every other day, with breast-fed infants having more frequent stools than formula-fed infants. Frequency continues to decrease with age such that stools may average two or three per day during the first year of life and one or two per day from 1 to 5 years of age. Defecation occurs as a combination of physiologic, behavioral, and psychological factors. Relaxation of the external sphincter required for defecation is under voluntary control, whereas relaxation of the internal sphincter is involuntary. Children with a history of unpleasant or painful experiences associated with defecation may contract the external sphincter voluntarily in an effort to delay defecation for as long as possible. Accumulation of stool over time causes the rectum to dilate and decrease its propulsive activity, resulting in an increasing capacity for stool and chronic constipation. Acute episodes may be the result of dietary changes, travel, lack of normal exercise, or stress.

Management

Initial management is focused on ensuring adequate fluid and electrolyte status. Abdominal films should be obtained. With evidence of acute obstruction, seen as marked dilation, decompression may be necessary. Decompression usually can be accomplished easily with a rectal tube. Children who appear ill with fever should be evaluated for enterocolitis and toxic megacolon. Enterocolitis is characterized by abdominal distention, bloody stools, fever, and an elevated white blood cell count. Patients with enterocolitis require broad-spectrum, triple-antibiotic coverage with ampicillin, gentamicin, and either clindamycin or metronidazole. Urgent consultation should be made with a pediatric surgeon. Definitive therapy is surgical, with resection of the aganglionic segments. Acquired megacolon is managed by decompressing the colon and addressing the underlying problems.

Management of constipation requires three considerations: cleanout, maintenance, and behavior modification. Acute constipation is easier to manage because fewer functional problems are involved. The acute management of constipation usually is relatively easy and requires primarily the cleaning out of stool. Most experts recommend an approach that includes stool softeners or laxatives from above and suppositories or enemas from below. In milder cases, only the administration of enemas is necessary to soften feces and to stimulate defecation. Tap water, Castile soap, and oil enemas are generally equally efficacious. Maintenance includes keeping the stool soft for as long as necessary with use of stool softeners or laxatives. Dietary modifications include increasing fiber and water in the diet and avoiding foods that may be constipating. Management of chronic constipation is more difficult and usually requires a multidisciplinary approach with attention to behavior modification. Children with an underlying pathologic process, such as cystic fibrosis, may benefit from more intense measures, such as administration of large volumes of polyethylene glycol (GoLYTELY).

Disposition

Unless children appear ill, most can be managed safely on an outpatient basis.

Meckel's Diverticulum

Perspective

Meckel's diverticulum is the most common congenital malformation of the small intestine and follows the rule of 2's: The diverticulum is 2 cm wide and 2 cm long and usually located within 2 feet of the ileocecal valve. Moreover, the condition occurs in 2% of the population, and only 2% of affected patients ever become symptomatic.[35] Half of all patients with the condition become symptomatic by the age of 2 years, and most present by the age of 20 years.[35]

Principles of Disease

Diverticula are remnants of the omphalomesenteric duct and contain bowel wall, with 60% containing heterotopic tissue.[36] This tissue most commonly involves gastric mucosa, but other types include pancreatic, duodenal, and endometrial tissue.[34-36] Bleeding occurs when acid secretion from ectopic gastric mucosa causes ulceration and erosion.

Clinical Features

Patients are classically boys younger than 5 years who present with massive, painless rectal bleeding of acute onset; however, it can occur at any age. Some children may have some complaints of abdominal cramping. In older children, the presentation may be similar to appendicitis. The blood often is described as brick red. Complications may include intussusception, obstruction, perforation, and peritonitis.

Diagnostic Strategies

A technetium scan, also known as Meckel's scan, is the diagnostic modality of choice and has an accuracy of 90% when ectopic gastric mucosa is present.[37] Administration of pentagastrin, cimetidine, or glucagon may increase the sensitivity of the test.[38] CT scan of the abdomen may be obtained to look for signs of obstruction or if the diagnosis is unclear. Definitive diagnosis is confirmed by laparoscopy or laparotomy.

Differential Considerations

Gastrointestinal bleeding is uncommon in childhood. The first step in evaluation of a child with suspected gastrointestinal bleeding is to determine whether the substance is actually blood. Children commonly eat or drink substances containing dyes that lead to factitious changes in the stool's color. A simple Hemoccult test of the stool or Gastroccult test of the emesis can document the presence of hemoglobin. False-positive results may occur with red meat and iodine. Patients consuming products with bismuth (Pepto-Bismol), iron, and spinach may have black stools falsely appearing melanotic; the Hemoccult test result is negative.

After it has been determined that the substance is blood, the second step is to determine its origin. The location of bleeding often is difficult to determine but may be theorized on the basis of the appearance of the blood. Hematemesis implies bleeding proximal to the ligament of Treitz. Blood exposed to gastric acids for any time develops the classic coffee-grounds appearance. Bright red upper gastrointestinal bleeding implies either more proximal bleeding, such as from varices or esophagitis, or brisk gastric or duodenal bleeding. Bleeding that originates beyond the ligament of Treitz but proximal to the ileocecal valve results in melena. Hematochezia, with a visibly red to maroon appearance of the blood, implies bleeding from the descending colon. Distal lesions, such as fissures or hemorrhoids, can result in bright red

www.ketabpezeshki.com 66485457-66963820

Table 172-5 Differential Considerations in Gastrointestinal Bleeding by Pediatric Age Group

ETIOLOGIC CATEGORY	INFANCY	CHILDHOOD	ADOLESCENCE
Factitious	Swallowed maternal blood Dyes in foods and beverages Vaginal origin Urinary origin	Dyes in foods and beverages Swallowed nasopharyngeal blood Vaginal origin Urinary origin	Dyes in foods and beverages Swallowed nasopharyngeal blood Vaginal origin Urinary origin
Upper gastrointestinal tract	Necrotizing enterocolitis Intussusception Gastroenteritis Gastritis	Esophagitis Gastroenteritis Gastritis Peptic ulcer disease	Esophagitis Gastroenteritis Gastritis Peptic ulcer disease
Lower gastrointestinal tract	Necrotizing enterocolitis Intussusception Gastroenteritis Milk allergy Vascular malformation	Gastroenteritis Intussusception Meckel's diverticulum Inflammatory bowel disease Vascular malformation Henoch-Schönlein purpura Hemolytic-uremic syndrome Colitis	Gastroenteritis Intussusception Meckel's diverticulum Inflammatory bowel disease Vascular malformation Henoch-Schönlein purpura Hemolytic-uremic syndrome Polyps Colitis
Rectal	Rectal fissure	Rectal fissure	Rectal fissure Hemorrhoids Trauma
Other or atypical	Bleeding dyscrasia Occult trauma (abuse) Toxic ingestions Munchausen syndrome by proxy	Bleeding dyscrasia Toxic ingestions Occult trauma (abuse) Munchausen syndrome by proxy	Bleeding dyscrasia Toxic ingestions Occult trauma (abuse) Munchausen syndrome or Munchausen syndrome by proxy

blood. Barium contrast studies of the upper and lower gastrointestinal tract sometimes are helpful; however, nuclear medicine scans (Meckel's scan) are the procedure of choice for detection of Meckel's diverticulum. Endoscopic examination has the highest rate of determining the location of bleeding; however, the diagnosis often is confirmed first on Meckel's scan.

In neonates, the most common etiologic category of gastrointestinal bleeding is idiopathic. Careful examination of the rectum should be performed because the most identifiable cause of bleeding is a fissure or excoriation of the perirectal area. In young neonates, an Apt test may be performed to determine if the blood is maternal or fetal: 1% sodium hydroxide is added to the bloody stool. Fetal hemoglobin resists oxidation and remains pinkish red, whereas maternal hemoglobin changes to dark brown.

Another common cause of gastrointestinal bleeding in infancy is milk protein allergy. Affected children typically are younger than 6 months with a history of sudden-onset mucoid, blood-streaked stools. Children otherwise appear well. Although the causative allergy most commonly is to milk protein, gastrointestinal bleeding may occur with consumption of any protein and has been described in relation to soybean-based products. Children with persistent perianal excoriations and fissures refractory to standard emollients may be infected with group A streptococci and may benefit from treatment with an oral penicillin. Table 172-5 lists the differential considerations for gastrointestinal bleeding in children by age.

Management

Management of gastrointestinal bleeding begins by assessment of circulatory status and ensuring that it is adequate. Screening laboratory studies should include CBC, coagulation studies (PT and PTT), and type and screen. Two radiographic views of the abdomen should be obtained in patients in whom obstruction or perforation is suspected. A technetium scan is the imaging modality of choice to evaluate for Meckel's diverticulum. Consultation with a pediatric surgeon should be obtained.

Disposition

Children with suspected Meckel's diverticulum should undergo Meckel's scan. Children with minor bleeding and normal findings on screening laboratory studies may be observed closely on an outpatient basis. Children with more active bleeding should be hospitalized for care by either a pediatric surgeon or a pediatric gastroenterologist.

Henoch-Schönlein Purpura

Perspective

HSP, also known as anaphylactoid purpura, is a systemic vasculitis commonly associated with abdominal pain and rash. It is most common in children 4 to 11 years of age but also may occur in adults. HSP occurs most commonly in the spring after a viral upper respiratory infection. It also has been associated with insect stings and certain drugs.[39]

Principles of Disease

HSP is a hypersensitivity vasculitis with immune complex deposition with immunoglobulin A, mainly affecting the arterioles and capillaries. Although it is most well known for its characteristic petechial to purpuric rash, HSP is a systemic vasculitis and may affect any blood vessel. Less common manifestations are seen in cases in which the disease is more severe or widespread.

Clinical Features

Symptoms include abdominal pain, nausea, vomiting, and diarrhea. Patients most often are diagnosed clinically on the basis of the classic rash, abdominal pain, microscopic hematuria, and arthralgias. The classic rash is palpable purpura located on the buttocks and lower extremities (Fig. 172-10). Up to 70% of patients with HSP have gastrointestinal complaints. Microscopic

www.ketabpezeshki.com 66485457-66963820

Figure 172-10. Henoch-Schönlein purpura in a 7-year-old child. Note typical red-purple rash on the lower extremities. (Courtesy Marianne Gausche-Hill, MD.)

hematuria occurs in 50%.[40] Intussusception may occur and may be atypical in that ileoileal intussusception is more common than the ileocolic intussusception that normally occurs. The syndrome often is relapsing and remitting for several weeks and may be associated with arthralgias. Neurologic involvement also may be a feature of HSP, although this manifestation is uncommon in children.[41]

Diagnostic Strategies

Patients most often are diagnosed clinically on the basis of the classic rash, abdominal pain, microscopic hematuria, and mild arthralgias. Screening studies should include a CBC with differential and platelet counts, urinalysis, blood culture, and sedimentation rate determination. Children with worrisome abdominal pain require CT to rule out ileoileal intussusception.

Differential Considerations

The most important entity in the differential diagnosis for this type of rash is meningococcemia, in which the patient has a fever and looks very ill. It is essential to rule out meningococcemia because the condition is life-threatening and requires an entirely different approach to management involving hospitalization, fluid resuscitation, and intravenous antibiotics. The classic triad of palpable purpura, abdominal pain, and hematuria in an otherwise well-appearing child virtually ensures the diagnosis. Erythema nodosum occasionally is confused with the rash of HSP; however, the rash of erythema nodosum is described most often as subcutaneous purplish red nodules with the appearance of a bruise on the extensor surfaces of the distal extremities. Erythema nodosum usually involves only the shins but in more severe cases also may involve the forearms, hands, and feet.

Management

Most children with HSP can be managed with close follow-up and require no treatment other than symptomatic support. Severe or intermittent abdominal pain in children with HSP is suggestive of intussusception; imaging to investigate this possibility should be done with ultrasonography, followed by CT scan if the ultrasound study is normal because ileoileal intussusception may occur and is not detected easily by ultrasonography. Management with steroids is controversial. Corticosteroids, at a dose of 1 mg/kg/day (maximum, 60 mg), are reserved for patients with illness on the more severe end of the spectrum, with abdominal pain, hematuria, or arthralgias.

Disposition

Indications for hospital admission include uncertain diagnosis to exclude the possibility of meningococcemia, severe abdominal pain, and vomiting. Most patients can be managed safely with close outpatient follow-up.

Inflammatory Bowel Disease

Perspective

The two major entities included within the category of IBD are Crohn's disease and ulcerative colitis. Approximately 20% of patients present before the age of 20 years.[42] Most patients do not experience symptoms until adolescence, although childhood presentations have been described. IBD is rare in children younger than 1 year.[43]

Principles of Disease

Ulcerative colitis is an inflammatory disease primarily involving the mucosa and submucosa of the rectum and distal colon. *Crohn's disease* is a transmural inflammatory disease that may involve any portion of the intestinal tract. The most common area of involvement in cases with single-segment disease is distal ileum; however, multiple segments in different areas may be involved. Chronic inflammation may result in the formation of abscess, fistula, or stricture.

Clinical Features

Although patients experiencing complications frequently present to the ED, the diagnosis is rarely made in this setting. More commonly, children with known disease present in the midst of a flare, usually with bloody diarrhea and abdominal pain. Extraintestinal manifestations also occur and include fever, anemia, oral ulcerations, erythema nodosum, pyoderma gangrenosum, uveitis, liver dysfunction, and failure to thrive.[43] Some of these manifestations may occur even before the child has experienced any gastrointestinal symptoms. The most feared complication is toxic megacolon, which classically is manifested with abdominal pain, fever, and bloody diarrhea and is associated most often with ulcerative colitis.

Diagnostic Strategies

Flares of IBD are diagnosed by the increased frequency of diarrheal or bloody stools and abdominal pain. Patients who appear ill require plain films of the abdomen to rule out toxic megacolon. Patients with toxic megacolon usually have a fever, appear volume depleted, and demonstrate significant abdominal tenderness to palpation. X-ray films reveal dilation of the transverse colon to more than 6 to 7 cm in diameter. Free air also should be looked for because perforation may occur. Screening laboratory studies should include a CBC with differential and platelet counts, type and screen, coagulation studies (PT and PTT), and electrolyte panel.

www.ketabpezeshki.com 66485457-66963820

Differential Considerations

There are a wide number of differential considerations for abdominal pain and gastrointestinal bleeding (see Tables 172-4 and 172-5). Gastroenteritis is the most common consideration in this clinical scenario. Children experiencing their first episode of IBD are much more likely to be misdiagnosed with an acute gastroenteritis. Children outside the usual age at presentation also are more likely to be misdiagnosed with gastroenteritis. Children with recurrent symptoms or a family history of IBD should be referred to a pediatric gastroenterologist for further evaluation.

Management

Initiation of corticosteroid therapy in conjunction with a gastroenterologist constitutes the mainstay for treatment of acute exacerbations. Prednisone at a dose of 1 mg/kg/day (maximum, 60 mg/day) usually is recommended and should be provided in consultation with a pediatric gastrointestinal specialist. Other agents commonly used include sulfasalazine, azathioprine, and a host of other immunosuppressive agents. Management in the ED begins with attention to volume status and resuscitation with boluses of 20 mL/kg of normal saline until the volume status is adequate. Patients with suspected toxic megacolon require intravenous broad-spectrum, triple-antibiotic therapy (with ampicillin, gentamicin, and metronidazole) and immediate surgical consultation.

Disposition

Indications for admission include children who are dehydrated and toxic or ill appearing and those patients for whom the diagnosis is uncertain. Children with ongoing diarrhea productive of bloody stools usually benefit from intravenous fluids until the flare has been controlled. Children with evidence of toxic megacolon require surgical consultation and admission.

Gastrointestinal Foreign Bodies

Perspective

Most gastrointestinal foreign bodies occur in toddlers, who experience life by first putting objects in their mouths. Children younger than 3 years are particularly at risk because of the combination of inappropriate mouthing of objects and a general lack of coordination in swallowing. Although food is the most common esophageal foreign body in adults, coins are most common in children.[44,45] Children with mental retardation swallow a variety of objects. Adolescents occasionally swallow objects in an attempt at suicide. Rectal foreign bodies are uncommon in the pediatric age group.

Principles of Disease

Most swallowed foreign bodies pass without difficulty. Foreign bodies may become lodged in any of three areas of normal physiologic narrowing: upper esophageal sphincter (cricopharyngeus muscle)—thoracic inlet (C6-T1), aortic arch—tracheal bifurcation (T4-6), and lower esophageal sphincter—diaphragmatic hiatus (T10-11). In general, 80 to 90% of objects that have made it into the stomach are passed without difficulty.[46]

Clinical Features

The classic clinical presentation is that of a child who is seen from across the room putting coins in his or her mouth. Children frequently gag and sputter as they attempt to swallow the object. Aspirated objects generally produce persistent coughing, wheezing, or increased work of breathing. Objects that have been swallowed may result in the child's remaining asymptomatic or may produce symptoms ranging from persistent gagging to drooling, continuous dry heaves, or wheezing. Larger foreign bodies may compress the airway and cause significant respiratory distress. Rapidly progressive symptoms of dysphagia, pain, respiratory distress, or fever raise the possibility of a perforation. Perforation is uncommon, even with sharp objects such as straight pins. The ileocecal valve is the most common site for perforation, which occurs in less than 1% of patients.[46] Button batteries warrant special mention. Button batteries in the esophagus should be removed in as rapid a manner as possible because erosions and mediastinitis ultimately may occur. Button batteries in the stomach usually pass without difficulty and do not require removal unless they fail to pass the pylorus within 24 to 48 hours of ingestion.[47] The National Capital Poison Center in Washington, DC, operates a 24/7 website (http://www.poison.org/battery/) and hotline (202-625-3333) for battery ingestion cases. On occasion, objects pass into the stomach that are too large to pass through the pylorus; this is uncommon and is heralded by persistent vomiting. Long-present unrecognized foreign bodies may result in erosion, perforation, infection, stricture, or fistula formation.[48]

Diagnostic Strategies

Plain radiography is the most common method of visualizing location and is used to verify positioning past the lower esophageal sphincter into the stomach. Patients who are symptomatic after foreign body ingestion require imaging to determine location. On occasion, patients who are asymptomatic also have objects remaining in the esophagus.[49] Radiographs should include anteroposterior and lateral views of the chest, neck, and abdomen (Fig. 172-11). The lateral view helps delineate soft tissues in the hypopharynx and evaluate for swelling, particularly if the foreign body is either unknown or of a nonradiopaque material. A single view of the neck, chest, and upper abdomen often can be obtained easily in the pediatric patient. Unless the patient becomes symptomatic, repeated films are otherwise never necessary. Asking parents to sieve the stool typically is unproductive, and even sharp objects such as pins and razor blades usually pass through the gastrointestinal tract without incident. Patients presenting with a history of button battery ingestion represent the exception in that they require repeated films to document passage beyond the pylorus. Rather than using standard radiography, some institutions have noted success with intradepartment fluoroscopy or hand-held metal detectors.[49-51] Contrast studies may be helpful to delineate nonradiopaque foreign bodies or to evaluate for perforations.

Differential Considerations

Not all foreign bodies are radiopaque and visible with standard radiography. Patients who remain symptomatic require further contrast-enhanced imaging or direct visualization.

Management

If the object has made it into the stomach, usually it will pass without incident, and no further treatment is necessary. If the foreign body is in the esophagus, most experts recommend removal within 24 hours to decrease the risk of aspiration and esophageal erosion. The preferred method by which to remove esophageal foreign bodies is controversial and varies by institution. Options include fluoroscopic Foley catheter removal, bougie advancement into the stomach, endoscopic removal in the ED, and removal by rigid bronchoscopy under general anesthesia in the

www.ketabpezeshki.com 66485457-66963820

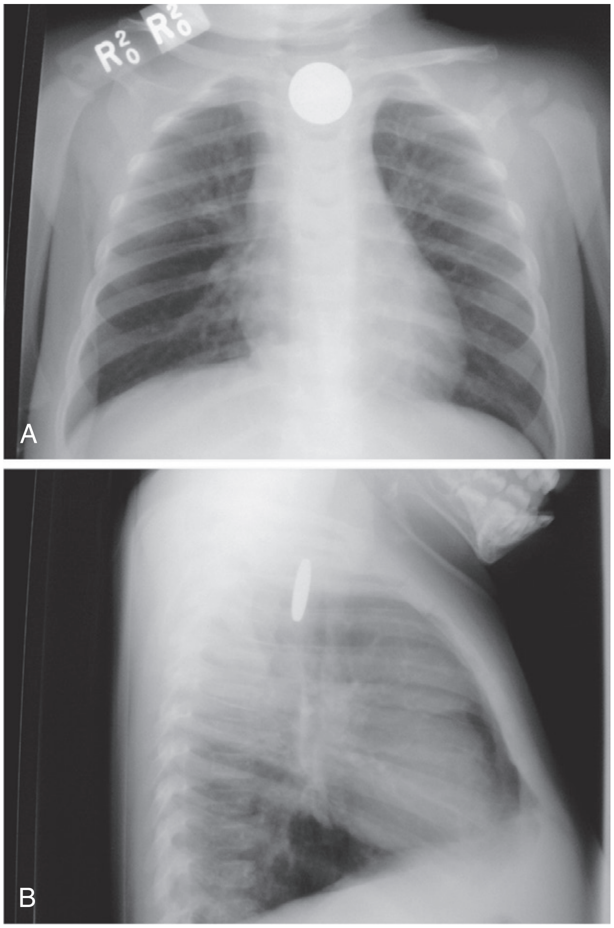


Figure 172-11. Plain radiographs obtained in a child with an esophageal coin foreign body. Posteroanterior (**A**) and lateral (**B**) views show the expected orientation for a coin lodged in the esophagus. (Courtesy Mark A. Hostetler, MD.)

operating room. Foley catheter removal and bougienage do not require sedation in cooperative patients, but young children invariably require sedation in the operating room. Children should be positioned on the side to decrease the risk of aspiration. With the last two methods, the technique involves actually holding onto the foreign body, which—at least theoretically—decreases the chance of inadvertent aspiration. They also have the additional benefit of directly visualizing the integrity of the mucosa and evaluating for perforation. Gastric foreign bodies generally do not require removal. Indications for surgical removal of gastric foreign bodies include objects that are more than 2 cm in width, objects that are more than 5 cm in length, and objects that are sharp (pins, razor blades).

Disposition

Esophageal foreign bodies require removal as described previously. After foreign bodies have made it into the stomach, most pass without difficulty, and no further follow-up is necessary. Button batteries constitute the exception and necessitate follow-up films to document passage beyond the pylorus.

Pancreatitis

Perspective

Pancreatitis is uncommon in childhood, especially in children younger than 10 years. Pancreatitis has an incidence of approximately 1 case in 50,000 in children and carries a mortality rate of 14%.[52,53] In adults, pancreatitis is associated most commonly with alcohol and biliary tract disease. In children, a fairly equal association of approximately 10 to 20% each has been documented for trauma, infection, structural disease, systemic disease, and drugs or toxins.[53] Mumps is the most common viral cause of pancreatitis and accounts for 10 to 15% of all cases.[53] Idiopathic causes account for 30% of cases. Biliary obstruction should be considered in the adolescent.

Principles of Disease

Whether the result of trauma, obstruction, or inflammation, a series of events occurs, resulting in inflammation, edema, and autodigestion of pancreatic tissue by pancreatic enzymes. In severe cases, the inflammatory process may progress to necrosis and hemorrhage, resulting in necrotizing or hemorrhagic pancreatitis. Further complications include the formation of abscesses, pseudocysts, and fistulas.

Clinical Features

Patients classically present with complaints of severe epigastric pain that radiates to the back. Pain is gradually progressive and constant and often is associated with nausea and vomiting. Pain classically is described as being worse with eating. Significant abdominal tenderness usually can be elicited in the epigastric area, accompanied by voluntary guarding and hypoactive bowel sounds. The abdomen may be slightly distended. Patients with biliary colic and gallstone pancreatitis have variable presentations from classic right upper quadrant pain associated with nausea and vomiting to intermittent epigastric pain and jaundice.

Diagnostic Strategies

Screening laboratory studies reveal elevations in serum lipase. Evidence of liver inflammation and elevated bilirubin and alkaline phosphatase may be seen in patients with biliary obstruction. Plain films of the abdomen may be indicated to investigate the possibility of free air or obstruction. An ileus pattern is common, often with a sentinel loop of dilated small bowel noted in the left upper quadrant. An ultrasound study or CT scan may be helpful to evaluate anatomy for congenital malformations or biliary tract disease and to evaluate for pseudocyst or abscess formation. In patients with pseudocysts, hemorrhagic pancreatitis may develop that may become life-threatening. For patients with respiratory distress, a chest film can be helpful to evaluate for a coexistent pleural effusion caused by the pancreatitis.

Differential Considerations

Slow, progressive onset of pain is more likely to be associated with appendicitis, constipation, or pancreatitis. Children with peritoneal irritation invariably lie still, often on the side with knees bent, and refrain from all extraneous movement. Sudden onset of severe pain is associated most often with acute obstruction or vascular occlusion as seen with intussusception, volvulus, or torsion. Differential considerations for abdominal pain in children by age are listed in Table 172-4; differential considerations for the causes of pancreatitis are listed in Table 172-6.

Management

Management begins with attention to volume status and correction of electrolyte abnormalities if present. A bedside finger-stick blood glucose value should be obtained. Adequate pain relief with parenteral narcotics should be provided. The patient should be

www.ketabpezeshki.com 66485457-66963820

Table 172-6 Differential Considerations for Pancreatitis in Children

ETIOLOGIC CATEGORY	SPECIFIC DISORDERS
Trauma	Handlebar injury
Infectious	*Viral*: mumps, influenza A, Epstein-Barr virus infection, cytomegalovirus infection, hepatitis A and B, rubella, rubeola *Bacterial*: salmonellosis, leptospirosis
Structural	Choledochal cyst, duplication cyst, anomalous bile duct, duodenal stenosis Pancreas divisum Tumor Cholelithiasis
Systemic, genetic	Cystic fibrosis Glycogen storage disease Familial hyperlipidemias α_1-Antitrypsin deficiency Sickle cell disease
Systemic, acquired	Systemic lupus erythematosus Kawasaki disease Hemolytic-uremic syndrome Henoch-Schönlein purpura Crohn's disease Reye syndrome Diabetes mellitus
Drugs or toxins	Steroids, oral contraceptives Valproic acid Sulfasalazine, azathioprine Rifampin, pentamidine, metronidazole, tetracycline Thiazides, ethacrynic acid, furosemide Alcohol, L-asparaginase
Idiopathic	No definitive cause found

maintained on NPO status and given adequate fluids. Intravenous fluids are given in boluses of 20 mL/kg of normal saline until adequate vascular volume is achieved and then are followed by 5% dextrose in water and half-normal saline at 1.5 times maintenance. Antiemetics are indicated to help control nausea and vomiting. A nasogastric tube usually is not necessary or helpful unless an ileus or persistent vomiting is present. Steroids and antibiotics are not indicated.

Disposition

Most children with pancreatitis require hospitalization unless they have known or recurrent disease for which an outpatient regimen providing adequate analgesia and hydration is available.

Appendicitis

Perspective

Appendicitis is the most common surgical condition involving the abdomen and the most common nontraumatic surgical emergency in children.[11] Approximately 200,000 appendectomies are performed every year, and appendicitis develops in approximately 1 of every 15 people in the general population sometime during their lifetime.[11,23,54] The peak age of incidence of appendicitis is between 9 and 12 years, and it is uncommon in children younger than 5 years.[11,23,54]

Acute appendicitis has an overall mortality rate of less than 1%. For unruptured appendicitis, the mortality rate is 0.1%; the mortality rate increases to approximately 3% for ruptured appendicitis. In children, the rate of appendiceal perforation before surgery varies, ranging from 17 to 40%, and is inversely related to age, with higher rates of perforation occurring in younger age groups. In children younger than 2 years, perforation will have occurred in 90% by the time of surgery.

Principles of Disease

The appendix is a blind pouch that may become obstructed. After it is obstructed, a vicious circle is established, with increasing edema, vasocongestion, inflammation, ischemia, infarction, necrosis, and perforation. In adults, a thicker appendiceal wall protects against perforation, and a well-developed omentum aids in walling off the infection to prevent its diffuse spread. Children have neither, so rupture tends to occur earlier and diffuse peritonitis develops more readily.

Clinical Features

Patients classically present with a constellation of symptoms that includes abdominal pain, nausea, vomiting, fever, and anorexia. All of these symptoms are gradually progressive during 4 to 24 hours. Abdominal pain usually is described as vague, crampy, and periumbilical on origination, which then becomes more severe, constant, and localized to the right lower quadrant. Fever usually develops later, sometimes not until after the patient already has presented to the ED. Nausea and vomiting are progressive and most often are associated with anorexia. Patients occasionally may have a multiphasic course to their illness, which begins with the classic abdominal pain, with progression of symptoms until they suddenly resolve, followed several days later by development of fever, chills, and abdominal pain. This course represents acute appendicitis with spontaneous rupture and formation of an abscess.

Physical examination may reveal several classic findings. In patients with inflammation surrounding the appendix, peritoneal findings that localize to the right lower quadrant are typical. Pain occurs with movement, so the patient prefers to lie still. Patients are unable to jump up and down and complain that even rocking the bed or tapping their heels causes pain. The abdomen usually is quiet, with an absence of bowel sounds. Rebound tenderness can be elicited in the right lower quadrant. Rovsing's sign also may be present and consists of severe pain in the right lower quadrant occurring when the examiner presses in the left lower quadrant and rapidly releases the examining hand. Other findings associated with appendicitis include the psoas and obturator signs. The psoas sign is pain elicited by having the patient, in lateral decubitus position, hyperextend the right thigh at the hip, thereby stretching the psoas muscle, which overlies the inflamed appendix. The obturator sign similarly is pain elicited by having the patient internally rotate the flexed right thigh against resistance. These signs are not frequently present but when present increase significantly the likelihood of appendicitis.

Diagnostic Strategies

Appendicitis may be diagnosed on the basis of history and physical findings alone. Patients with the appropriate constellation of findings consistent with appendicitis may not require any testing and can proceed directly to the operating room for either laparoscopic or open exploration. Patients in whom the diagnosis is suspected usually require some diagnostic workup. Screening studies should include a CBC with differential, urinalysis, and pregnancy test. An estimated 96% of patients with appendicitis have either an elevated white blood cell count greater than 10,000/μL or a left-shifted differential with more than 75% neutrophils.[55] Although an elevated white blood cell count supports the diagnosis, it is not specific for appendicitis. The appendix is close to the ureters, so

www.ketabpezeshki.com 66485457-66963820

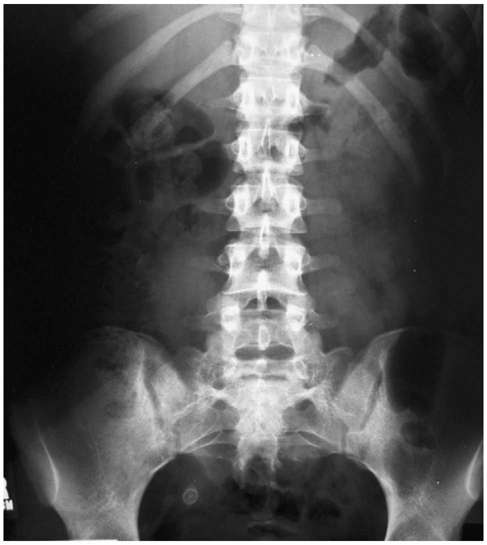


Figure 172-12. Fecalith in a child with appendicitis. (Courtesy Marianne Gausche-Hill, MD.)

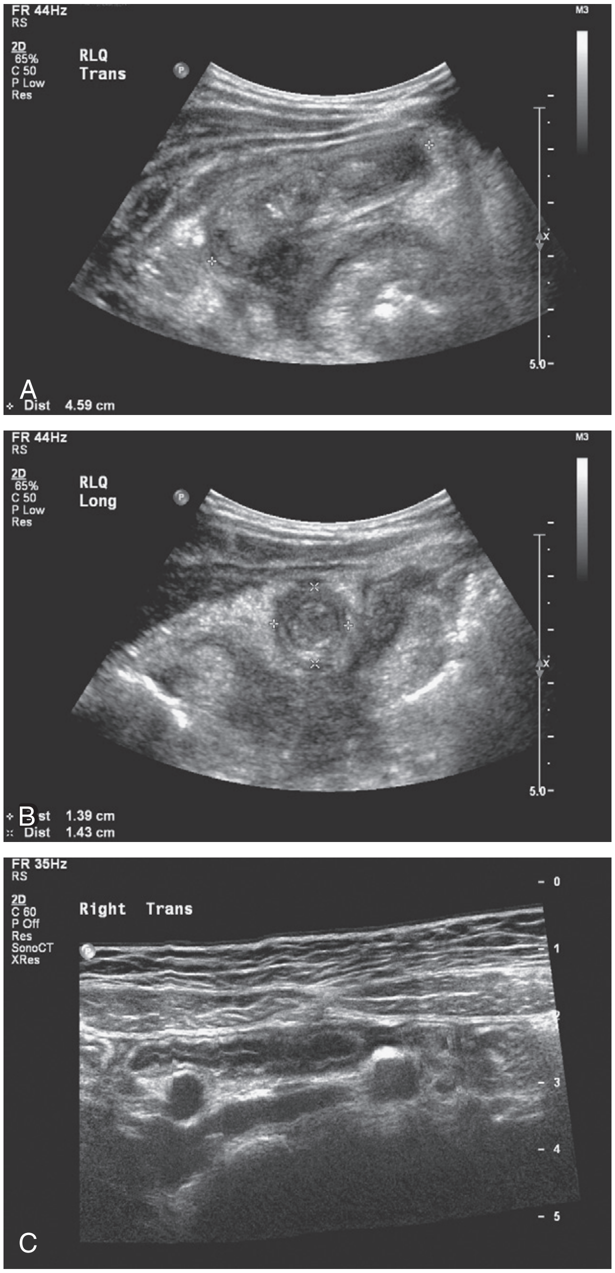


Figure 172-13. Ultrasound images obtained in children with appendicitis. Findings include an enlarged, noncompressible tubelike structure in the longitudinal view with an appendicolith (**A**), an enlarged, noncompressible structure seen in cross section (**B**), and, in another patient, an enlarged, poorly compressible structure with a moderate amount of free fluid consistent with acute perforation (**C**). (Courtesy Mark A. Hostetler, MD.)

appendicitis may induce some degree of sterile pyuria. Inflammatory changes related to appendicitis generally result in fewer than 5 to 10 white and red blood cells per high-power field and an absence of bacteria. Findings in excess of these amounts suggest a urinary tract etiology (e.g., infection, stone, mass, trauma). Consideration also may be given to a rapid streptococcal test in patients with a red or sore throat as streptococcal pharyngitis may present with abdominal pain.

Diagnostic imaging options include plain films of the abdomen, ultrasonography, and limited CT scan of the appendix. Plain films help rule out free air or obstruction and occasionally show an appendiceal fecalith, also called an appendicolith (Fig. 172-12). Although the presence of an appendicolith is essentially pathognomonic for acute appendicitis, it is present in only 10% of cases.[54] Ultrasound findings consistent with appendicitis include an enlarged, noncompressible appendix that is painful during scanning (Fig. 172-13A and B). A fecalith may be evident inside an enlarged and inflamed appendix, the so-called target sign.[56] Appendiceal ultrasound studies have a sensitivity, specificity, and overall accuracy of 90 to 95%.[56-59] Ultrasound imaging is particularly useful to evaluate for abscesses and fluid collections; however, a great deal of operator and reader variability is characteristic (Fig. 172-13C). Ultrasonography does not involve exposure to ionizing radiation. Use of an ultrasound examination as an initial screen for appendicitis, in which only patients with normal or equivocal scans were required to undergo CT, resulted in a sensitivity of 96% and a negative predictive value of 98%.[60,61]

Limited CT of the appendix is the most recent technology to have emerged in terms of imaging.[62-66] Limited CT scans of the appendix have sensitivity and specificity rates of 95 to 100%.[63-66] The ready availability of appendiceal CT has been shown to reduce the negative laparotomy rate from 20% to 7%; the highest accuracy is reported with use of new focused appendiceal CT techniques with rectal administration of contrast material.[66] For patients with relatively low probability of appendicitis, CT may offer a cost-effective screening tool, particularly compared with inpatient admission and observation.[62] Imaging of the pelvis and the right lower quadrant (with either CT or ultrasonography) not only establishes the diagnosis of appendicitis but also aids in identifying the two most common considerations in the differential diagnosis: IBD and mesenteric adenitis.[64-66] An important point is that CT scanning involves exposure to a significant amount of ionizing radiation, which places children at increased risk for future malignant neoplasms.[67] Beginning in the past decade, the number of CT scans has increased dramatically (nearly 700%), and appendicitis is believed to be the single primary reason accounting for its surge in use.[67] In weighing all of the risks and benefits, sequential imaging with ultrasonography followed by CT scan is likely to be the best choice.

Differential Considerations

Mesenteric adenitis is the most common condition associated with the signs and symptoms of appendicitis. It often is associated with significant diffuse tenderness and may localize in the right middle to lower quadrant. Children often lack fever, however, and

www.ketabpezeshki.com 66485457-66963820

do not have true peritoneal signs. Mesenteric adenitis usually follows a viral illness and results from nonspecific inflammation of mesenteric lymph nodes. It is perhaps even more common than appendicitis. Differential considerations for abdominal pain by age are listed in Table 172-4. Other considerations include nonaccidental trauma (abuse), malingering, and Munchausen syndrome.[67] Girls of reproductive age merit consideration of a gynecologic origin and require a pregnancy test and pelvic examination; the possibility of ovarian torsion, particularly if the pain seems to be severe and out of proportion to physical examination findings, should not be overlooked. Boys require an external genital examination to rule out the possibility of testicular torsion. Cryptorchidism in the face of acute abdominal pain should raise suspicion for testicular torsion.

Management

In patients with suspected appendicitis, NPO status should be maintained and an intravenous line established. Most patients have vomiting and anorexia and benefit from at least one fluid bolus of 20 mL/kg of normal saline and then administration of 1.5 to 2 times maintenance fluids with dextrose 5% in water and half-normal saline and administration of antiemetics. Screening studies should be initiated, and appropriate consultation with a surgeon is indicated. Ongoing pain should be addressed adequately. Intravenous narcotics are safe and effective and should not alter the diagnostic accuracy of the physical examination. Patients with high fever, suspected perforation, or unusual delay to surgery require coverage with intravenous broad-spectrum antibiotics, which should be initiated in the ED after consultation with the surgeon.[68,69] A reasonable regimen for antibiotic therapy consists of ampicillin, gentamicin, and either metronidazole or clindamycin. Nasogastric tubes are reserved for patients with persistent nausea or vomiting related to abdominal distention or ileus.

Disposition

Children with appendicitis as documented by physical examination or diagnostic imaging are hospitalized for appendectomy. Patients with nonspecific symptoms and signs who do not undergo definitive diagnostic study can be hospitalized and observed for a period of 12 to 24 hours or, with adequate family and social support, discharged home with careful instructions to return for re-examination.

Biliary Tract Disease

Perspective

Biliary tract disease is uncommon in childhood and has causes distinct from those of disease in adults. In children, gallstones are associated with hemolytic disease, cystic fibrosis, total parenteral nutrition, sepsis, and dehydration.[70,71] Ceftriaxone also has been associated with sludging and biliary disease, particularly in neonates. Acute acalculous cholecystitis has been associated with Rocky Mountain spotted fever and a variety of bacterial infections, including those due to *Salmonella* and *Shigella* organisms. Hydrops of the gallbladder (i.e., fluid distention of the gallbladder from chronic cystic duct inflammation or obstruction) is associated with viral upper respiratory or gastrointestinal infections, Kawasaki disease, streptococcal pharyngitis, mesenteric adenitis, nephrotic syndrome, and leptospirosis.

Principles of Disease

Gallstones are classified as either cholesterol or pigment stones. Pigment stones occur in childhood, whereas cholesterol stones usually do not begin appearing until adolescence. Pigment stones result from the excess breakdown of red blood cells and are seen most commonly in hemolytic anemia, such as from sickle cell disease and spherocytosis. Gallstones occurring in infants usually are associated with abdominal surgery, sepsis, NEC, or administration of total parenteral nutrition.[71] In young children, gallstones most commonly develop as a result of their hemolytic disease. Adolescents form gallstones in association with oral contraceptives, pregnancy, obesity, or underlying hemolytic disease. In acute acalculous cholecystitis, the ultrasound scan will reveal evidence of gallbladder inflammation in the absence of calculi. Hydrops of the gallbladder is an acute noninflammatory, noninfectious process that results in a markedly enlarged gallbladder without evidence of calculi.

Clinical Features

Similar to adult patients, pediatric patients usually present with right upper quadrant pain that radiates through to the back and may be associated with fever, nausea, and vomiting. Jaundice occurs in one third of patients.[71,72]

Diagnostic Strategies

Biliary tract disease usually is associated with elevations in liver enzymes and bilirubin; however, absence of elevations does not exclude the diagnosis. Accordingly, right upper quadrant ultrasound imaging should be undertaken in cases in which gallbladder disease is suspected. Elevations in alkaline phosphatase suggest cholestasis. Elevated white blood cell counts are nonspecific but if associated with fever may represent an acute infectious process (e.g., ascending cholangitis). Ultrasonography is the imaging modality of choice. It can reproduce pain on scanning (sonographic Murphy's sign) and determine the presence of gallstones, amount of dilation of the gallbladder and bile ducts, gallbladder wall thickness, presence of pericystic fluid consistent with the diagnosis, and anatomic configuration of the biliary and pancreatic collecting system. When ultrasound findings are equivocal or normal in the face of strong clinical evidence, the "gold standard" modality for biliary tract imaging is still considered to be cholescintigraphy (DISIDA scanning); rarely, percutaneous cholecystocholangiography is necessary.[71] Although only 15% of gallstones in adults are calcified and visible on plain radiographs of the abdomen, 50% of stones are visible in children.[72,73]

Differential Considerations

Biliary tract disease is uncommon in children and requires consideration of underlying or coexistent disease. Differential considerations for abdominal pain by age are listed in Table 172-4.

Management

Management of biliary tract disease begins with attention to fluid and electrolyte status. Adequate pain control should be provided, usually with a parenteral opioid. Asymptomatic patients with incidental findings of gallstones require no further therapy in the ED and may be referred to a surgeon for outpatient care. Patients who are afebrile usually can be managed safely on an outpatient basis with adequate pain control. Febrile patients require hospital admission and intravenous antibiotics. A reasonable regimen for empirical antibiotic coverage consists of ampicillin and gentamicin plus either clindamycin or metronidazole.

Several management options have been used in the treatment of children with cholecystitis: medical management with ursodeoxycholic acid to dissolve the stone, expectant management, and

www.ketabpezeshki.com 66485457-66963820

surgical management.[74] Laparoscopic cholecystectomy is considered safe and effective in children.[75]

Disposition

Indications for hospital admission include pain control, hydration, fever, and need for operation.

KEY CONCEPTS

- Physiologic jaundice of the newborn and breast milk jaundice are the most common causes of jaundice in the neonatal period.
- Direct hyperbilirubinemia in infants is always pathologic and requires a detailed workup.
- Hypertrophic pyloric stenosis is manifested with gradually progressive nonbilious emesis that becomes projectile.
- Hypochloremic, hypokalemic metabolic alkalosis is the classic electrolyte abnormality for children with hypertrophic pyloric stenosis.
- Bilious vomiting in the neonate should initiate a diagnostic evaluation for possible malrotation and volvulus.
- In infants with bilious emesis, a toxic appearance, a distended abdomen, or an acute obstructed pattern on abdominal radiographs constitutes a true surgical emergency.
- Necrotizing enterocolitis occurs more commonly in premature infants, but 10% of affected infants are full term.
- Gastroesophageal reflux usually responds to conservative measures (positioning, thickening of formula, smaller and more frequent feedings).
- The classic clinical triad in intussusception consists of abdominal pain, vomiting, and heme-positive stools; however, the triad occurs in less than one third of patients.
- Children with intussusception may present without pain and with lethargy alone.
- Hirschsprung's disease is a common cause of constipation in the neonate and usually is manifested by delayed passage of meconium.
- Meckel's diverticulum classically is manifested in children younger than 5 years with painless brick-red rectal bleeding.
- More than 90% of gastrointestinal foreign bodies pass without difficulty.
- Causes of pancreatitis in children include viruses, trauma, drugs, and toxins.
- Imaging strategies for children with suspected appendicitis that include initial ultrasound examination followed by CT scan of the abdomen have been shown to reduce costs and negative laparotomy rates.
- Cholelithiasis is diagnosed with right upper quadrant ultrasound imaging; management strategies include medical and surgical approaches.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Bhutani VK, Donn SM, Johnson LH: Risk management of severe neonatal hyperbilirubinemia to prevent kernicterus. *Clin Perinatol* 2005; 32:125-139.
2. Hostetler MA, et al: Hypoketotic hypoglycemic coma in a 21-month-old child. *Ann Emerg Med* 1999; 34:394.
3. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2004; 114:297.
4. Chung E: Infantile hypertrophic pyloric stenosis: Genes and environment. *Arch Dis Child* 2008; 93:1003-1004.
5. Vasavada P: Ultrasound evaluation of acute abdominal emergencies in infants and children. *Radiol Clin North Am* 2004; 42:445.
6. Malhotra A, Lakkundi A, Carse E: Bilious vomiting in the newborn: 6 years data from a Level III Centre. *J Paediatr Child Health* 2010; 46:259-261.
7. Hall NJ, et al: Recovery after open versus laparoscopic pyloromyotomy for pyloric stenosis: A double-blind multicentre randomised controlled trial. *Lancet* 2009; 373:390-398.
8. Leclair MD, et al: Laparoscopic pyloromyotomy for hypertrophic pyloric stenosis: A prospective, randomized controlled trial. *J Pediatr Surg* 2007; 42:692-698.
9. Applegate KE: Evidence-based diagnosis of malrotation and volvulus. *Pediatr Radiol* 2009; 39(Suppl 2):S161-S163.
10. Nehra D, Goldstein AM: Intestinal malrotation: Varied clinical presentation from infancy through adulthood. *Surgery* 2011; 149:386-393.
11. Durkin ET, Lund DP, Shaaban AF, Schurr MJ, Weber SM: Age-related differences in diagnosis and morbidity of intestinal malrotation. *J Am Coll Surg* 2008; 206:658-663.
12. McCollough M, Sharieff GQ: Abdominal surgical emergencies in infants and young children. *Emerg Med Clin North Am* 2003; 21:909-935.
13. Cohen HL, Greene E: The vomiting neonate or young infant. *Ultrasound Clin* 2010; 5:97-112.
14. Messineo A, et al: Clinical factors affecting mortality in children with malrotation of the intestine. *J Pediatr Surg* 1992; 27:1343.
15. Applegate KE: *Imaging of clinically suspected malrotation in children*. In: Santiago Medina L, Applegate KE, Blackmore CC, eds: *Evidence-Based Imaging in Pediatrics*. New York: Springer; 2010:435-445.
16. Spigland N, Brandt ML, Yarbeck S: Malrotation presenting beyond the neonatal period. *J Pediatr Surg* 1990; 25:1139.
17. Maheshwari A, Corbin LL, Schelonka RL: Neonatal necrotizing enterocolitis. *Res Rep Neonatol* 2011; 1:39-53.
18. Thompson AM, Bizzarro MJ: Necrotizing enterocolitis in newborns: Pathogenesis, prevention and management. *Drugs* 2008; 68:1227-1238.
19. Lin PW, Nasr TR, Stoll BJ: Necrotizing enterocolitis: Recent scientific advances in pathophysiology and prevention. *Semin Perinatol* 2008; 32:70-82.
20. Härtel C, et al: Does the enteral feeding advancement affect short-term outcomes in very low birth weight infants? *J Pediatr Gastroenterol Nutr* 2009; 48:464-470.
21. Turcios-Ruiz RM, et al: Outbreak of necrotizing enterocolitis caused by norovirus in a neonatal intensive care unit. *J Pediatr* 2008; 153:339-344.
22. Neu J, Walker WA: Necrotizing enterocolitis. *N Engl J Med* 2011; 364:255-264.
23. Lehnert T, Sorge I, Till H, Rolle U: Intussusception in children—clinical presentation, diagnosis and management. *Int J Colorectal Dis* 2009; 24:1187-1192.
24. Applegate KE: Intussusception in children: Evidence-based diagnosis and treatment. *Pediatr Radiol* 2009; 39(Suppl 2):S140-S143.
25. Weihmiller SN, Buonomo C, Bachur R: Risk stratification of children being evaluated for intussusception. *Pediatrics* 2011; 127:e296-e303.
26. Ebert EC: Gastrointestinal manifestations of Henoch-Schönlein purpura. *Dig Dis Sci* 2008; 53:2011-2019.
27. Robb A, Lander A: Intussusception in infants and young children. *Surgery* 2008; 26:291-293.
28. Saverino BP, Lava C, Lowe LH, Rivard D: Radiographic findings in the diagnosis of pediatric ileocolic intussusception: Comparison to a control population. *Pediatr Emerg Care* 2010; 26:281-284.
29. Applegate KE: *Intussusception in children: Diagnostic imagining and treatment*. In: Santiago Medina L, Applegate KE, Blackmore CC, eds: *Evidence-Based Imaging in Pediatrics*. New York: Springer; 2010:459-473.
30. Bucher BT, Hall BL, Warner BW, Keller MS: Intussusception in children: Cost-effectiveness of ultrasound vs diagnostic contrast enema. *J Pediatr Surg* 2011; 46:1099-1105.
31. Kaiser AD, Applegate KE, Ladd AP: Current success in the treatment of intussusception in children. *Surgery* 2007; 142:469-475.
32. Amiel J, et al; Hirschsprung Disease Consortium: Hirschsprung disease, associated syndromes and genetics: A review. *J Med Genet* 2008; 45:1-14.
33. de Lorijn F, Kremer LC, Reitsma JB, Benninga MA: Diagnostic tests in Hirschsprung disease: A systematic review. *J Pediatr Gastroenterol Nutr* 2006; 42:496-505.
34. Bardisa-Ezcurra L, Ullman R, Gordon J; Guideline Development Group: Diagnosis and management of idiopathic childhood constipation: Summary of NICE guidance. *BMJ* 2010; 340:c2585.
35. Park JJ, Wolff BG, Tollefson MK, Walsh EE, Larson DR: Meckel diverticulum: The Mayo Clinic experience with 1476 patients (1950-2002). *Ann Surg* 2005; 241:529-533.
36. Sagar J, Kumar V, Shah DK: Meckel's diverticulum: A systematic review [erratum in *J R Soc Med* 2007; 100:69]. *J R Soc Med* 2006; 99:501-505.
37. Thurley PD, et al: Radiological features of Meckel's diverticulum and its complications. *Clin Radiol* 2009; 64:109-118.
38. Rerksuppaphol S, Hutson JM, Oliver MR: Ranitidine-enhanced ^{99m}technetium pertechnetate imaging in children improves the sensitivity of identifying heterotopic gastric mucosa in Meckel's diverticulum. *Pediatr Surg Int* 2004; 20:323.
39. Trapani S, et al: Henoch-Schönlein purpura in childhood: Epidemiological and clinical analysis of 150 cases over a 5-year period and review of literature. *Semin Arthritis Rheum* 2005; 35:143.
40. Flynn JT, et al: Treatment of Henoch-Schönlein purpura glomerulonephritis in children with high-dose corticosteroids plus oral cyclophosphamide. *Am J Nephrol* 2001; 21:128.
41. Peru H, et al: Henoch-Schönlein purpura in childhood: Clinical analysis of 254 cases over a 3-year period. *Clin Rheumatol* 2008; 27:1087.
42. Baumgart DC, Sandborn WJ: Inflammatory bowel disease: Clinical aspects and established and evolving therapies. *Lancet* 2007; 369:1641-1657.
43. Mamula P, et al: Inflammatory bowel disease in children 5 years of age or younger. *Am J Gastroenterol* 2002; 97:2005.
44. Digoy GP: Diagnosis and management of upper aerodigestive tract foreign bodies. *Otolaryngol Clin North Am* 2008; 41:485-496.
45. Weissberg D, Refaely Y: Foreign bodies in the esophagus. *Ann Thorac Surg* 2007; 84:1854-1857.
46. Kay M, Wyllie R: Pediatric foreign bodies and their management. *Curr Gastroenterol Rep* 2005; 7:212-218.
47. Litovitz T, Whitaker N, Clark L, White NC, Marsolek M: Emerging battery-ingestion hazard: Clinical implications. *Pediatrics* 2010; 125:1168-1177.
48. Little DC, et al: Esophageal foreign bodies in the pediatric population: Our first 500 cases. *J Pediatr Surg* 2006; 41:914-918.
49. Waltzman ML: Management of esophageal coins. *Curr Opin Pediatr* 2006; 18:571-574.
50. Chung S, Forte V, Campisi P: A review of pediatric foreign body ingestion and management. *Clin Pediatr Emerg Med* 2010; 11:225-230.
51. Muntz H: *Foreign body management*. In: Mitchell RB, Pereira KD, eds. *Pediatric Otolaryngology for the Clinician*. New York: Humana Press; 2009:215-222.
52. Lowe ME, Greer JB: Pancreatitis in children and adolescents. *Curr Gastroenterol Rep* 2008; 10:128.
53. Lautz TB, Chin AC, Radhakrishnan J: Acute pancreatitis in children: Spectrum of disease and predictors of severity. *J Pediatr Surg* 2011; 46:1144-1149.
54. Kwok M, Kim M, Gorelick M: Evidenced-based approach to diagnosis of appendicitis in children. *Pediatr Emerg Care* 2004; 20:690.
55. Kessler N, et al: Appendicitis: Evaluation of sensitivity, specificity, and predictive values of US, Doppler US, and laboratory findings. *Radiology* 2004; 230:472.
56. Doria AS: Optimizing the role of imaging in appendicitis. *Pediatr Radiol* 2009; 39(Suppl 2):S144-S148.
57. Neufeld D, et al: Management of acute appendicitis: An imaging strategy in children. *Pediatr Surg Int* 2010; 26:167-171.
58. Kamat S, Garcia Pena BM, Blackmore C, Santiago Medina L: *US versus CT: Evidence-based medicine and cost-effectiveness in imaging acute appendicitis in children*. In: Keyzer C, Gevenois PA, eds: *Imaging of Acute Appendicitis in Adults and Children*. Berlin: Springer; 2012:177-182.
59. Puig S, Staudenherz A, Felder-Puig R, Paya K: Imaging of appendicitis in children and adolescents: Useful or useless? A comparison of imaging techniques and a critical review of the current literature. *Semin Roentgenol* 2008; 43:22-28.
60. Adibe OO, et al: An evidence-based clinical protocol for diagnosis of acute appendicitis decreased the use of computed tomography in children. *J Pediatr Surg* 2011; 46:192-196.
61. Rosendahl K, Aukland SM, Fosse K: Imaging strategies in children with suspected appendicitis. *Eur Radiol* 2004; 14(Suppl 4):L138.

www.ketabpezeshki.com 66485457-66963820

62. Garcia-Pena BM, et al: Effect of computed tomography on patient management and costs in children with suspected appendicitis. *Pediatrics* 1999; 104:440.
63. Rao PM, Rhea JT, Novelline RA: CT diagnosis of mesenteric adenitis. *Radiology* 1997; 202:145.
64. Rao PM, et al: Effect of computed tomography of the appendix on the treatment of patients and use of hospital resources. *N Engl J Med* 1998; 338:141.
65. Rao PM, et al: The computed tomography appearance of recurrent and chronic appendicitis. *Am J Emerg Med* 1998; 16:26.
66. Rao PM, et al: Introduction of appendiceal CT: Impact on negative appendectomy and appendiceal perforation rates. *Ann Surg* 1999; 229:344.
67. Shah NB, Platt SL: ALARA: Is there a cause for alarm? Reducing radiation risks from computed tomography scanning in children. *Curr Opin Pediatr* 2008; 20:243.
68. Marin JR, Alpern ER: Abdominal pain in children. *Emerg Med Clin North Am* 2011; 29:401-428.
69. Tiwari MM, Reynoso JF, Tsang AW, Oleynikov D: Comparison of outcomes of laparoscopic and open appendectomy in management of uncomplicated and complicated appendicitis. *Ann Surg* 2011; 254:927-932.
70. Wesdorp I, et al: Clinical presentations and predisposing factors of cholelithiasis and sludge in children. *J Pediatr Gastroenterol Nutr* 2000; 31:411-417.
71. Wesdorp I, et al: Clinical presentations and predisposing factors of cholelithiasis and sludge in children. *J Pediatr Gastroenterol Nutr* 2000; 31:411.
72. Punia RP, Garg S, Bisht B, Dalal U, Mohan H: Clinico-pathological spectrum of gallbladder disease in children. *Acta Paediatr* 2010; 99:1561-1564.
73. Takiff H, Fonkalsrud EW: Gallbladder disease in childhood. *Am J Dis Child* 1984; 138:565.
74. Della Corte C, et al: Management of cholelithiasis in Italian children: A national multicenter study. *World J Gastroenterol* 2008; 14:1383.
75. St Peter SD, et al: Laparoscopic cholecystectomy in the pediatric population. *J Laparoendosc Adv Surg Tech A* 2008; 18:127.

www.ketabpezeshki.com 66485457-66963820

Chapter 173

Infectious Diarrheal Disease and Dehydration

Patricia Padlipsky

ACUTE INFECTIOUS DIARRHEA

Perspective

Acute diarrhea is defined as the abrupt onset of abnormally high fluid content in the stool with increased volume or frequency or both. Episodes of diarrhea are classically categorized into acute or chronic on the basis of their duration. As supported by the World Health Organization, acute diarrhea is defined as an episode that has an acute onset and lasts no longer than 14 days; chronic or persistent diarrhea is defined as an episode that lasts longer than 14 days. This classification is important not only from the standpoint of epidemiologic studies but also from a practical standpoint because protracted diarrhea often has different causes, poses unique problems in management, and has a prognosis different from that of acute diarrhea. Acute infectious diarrhea can occur with or without vomiting. When it occurs with vomiting, it is often referred to as acute gastroenteritis. Children are at a higher risk than adults for complications from acute diarrhea with or without vomiting because of their smaller physical size, low physiologic reserve, higher metabolism, and immature immune system. Some of these complications include hypoglycemia, electrolyte abnormalities, metabolic acidosis, dehydration, and shock.

The prevalence of acute gastroenteritis in children has not changed much during the past four decades, but the mortality has declined sharply.[1] Although dehydration is the most common complication of acute infectious diarrhea, one of the most important reasons for the decline in mortality has been the increasing international support for the use of oral rehydration solutions (ORSs) as the treatment of choice for acute diarrhea. However, in emergency departments (EDs) across the nation, intravenous therapy is still routinely used for treatment of volume depletion due to infectious diarrhea. A few reasons that EDs still routinely use intravenous therapy instead of oral rehydration are the misconceptions that intravenous therapy is more effective, that it takes less time, and that it poses little risk. However, some potential serious complications have emerged as a result of overuse of parenteral rehydration. These include local complications from intravenous infiltrations (hematoma, thrombosis, phlebitis, postinfusion phlebitis, thrombophlebitis, infiltration, local infection, extravasation, and vasospasm) and systemic complications from overly aggressive replacement of volume deficits leading to central nervous system sequelae and pulmonary edema. In many situations, diarrhea-related volume depletion can be treated by enteral replacement by oral intake or delivered by nasogastric or orogastric tubes.

Epidemiology

In 2008, of the estimated 8.795 million deaths in children younger than 5 years worldwide, infectious diseases caused 5.970 million (68%) of these deaths. The largest percentages were due to pneumonia, diarrhea, and malaria (in decreasing order). Diarrhea was responsible for 15% or 1.336 million of these deaths.[2] Regional differences in resources, epidemiology, underlying general health status of the population, and availability of safe food and water affect the actual disease burden. In the United States, acute gastroenteritis historically accounts for approximately 10% of hospital admissions of children younger than 5 years, estimated at 220,000 admissions per year; 300 to 400 deaths per year are caused by diarrhea, most occurring in the first year of life.[2,3] In the United States, acute gastroenteritis is responsible for 3.7 million physician visits, 135,000 to 220,000 pediatric admissions (approximately 10% of total hospitalization for children younger than 5 years), and 150 to 300 deaths among children younger than 5 years.[3-5] Costs to society are significant, with approximately one billion dollars in total costs attributed to rotavirus alone.[6,7] The incidence of diarrhea in children younger than 3 years has been estimated to be 1.3 to 2.3 episodes per child per year; rates in children attending daycare centers are higher.

Pediatric death due to diarrhea is related to severe dehydration and associated complications. Improvements in recognition and treatment of dehydration have prevented many deaths in the United States. Risks factors for death from diarrhea include age younger than 1 year; birth weight less than 2500 g; African American, Hispanic American, or American Indian ethnicity; immunocompromise; and illness during winter months.[3,4]

In the United States, viruses are responsible for most cases of acute infectious diarrhea. Rotavirus, norovirus, astrovirus, and enteric adenovirus have been recognized as the most common agents responsible for viral diarrhea in children. Bacteria cause approximately 7 to 10% of cases of acute infectious diarrhea. The most common bacteria are *Escherichia coli, Campylobacter* species, *Salmonella* species, *Shigella* species, and *Yersinia enterocolitica*. *Clostridium difficile* is also seen as a cause of infectious diarrhea, especially in patients who have recently taken antibiotics and hospitalized patients. Parasitic causes of infectious diarrhea are uncommon in the immunocompetent patient, but they can occur. The most common parasitic organisms are *Cryptosporidium, Giardia,* and *Entamoeba histolytica*.[8-11] Infectious diarrhea in children is most often contracted through the fecal-oral route and through poor food-handling practices. Daycare centers remain a main source of cases, with infection spread by diaper handling, fecal-oral transmission, and sharing of toys. Causative agents may

www.ketabpezeshki.com 66485457-66963820

be endemic, epidemic with food- and water-borne outbreaks, or sporadic. For most agents, a large inoculum is required to transmit the illness. The exceptions are *Campylobacter, Giardia,* and *Shigella,* for which 10 to 200 organisms are sufficient to cause disease. Some groups are at higher risk for acquiring infectious diarrhea and suffer greater clinical consequences. Among these are premature infants, young infants (<3 months), and patients who are immunosuppressed or malnourished or who have a chronic disease. Recent hospitalization, treatment with broad-spectrum antibiotics, and travel to developing countries are additional risk factors.

Principles of Disease

Pathophysiology

The gastrointestinal tract normally takes in, secretes, and absorbs large quantity of fluids. Up to 9 L of fluid from diet and endogenous secretions enter the proximal bowel each day in the adult. In children, a proportionately larger volume of fluid per body weight is ingested and secreted to maintain homeostasis (e.g., 125 mL/kg per 24 hours in adults versus 220 mL/kg per 24 hours in newborns). Ninety percent of the fluid is absorbed in the small bowel and the remainder in the large bowel. Water follows osmotic gradients created by the transport of electrolytes, sugars, and amino acids into the bloodstream. Both active transport– and passive transport–facilitated mechanisms are in place. Glucose and certain amino acids are absorbed by active carrier-mediated transport and coupled to sodium absorption. This concept of cotransporter is important in understanding the role of the combination of dextrose and sodium in enteral rehydration.

Infectious agents cause diarrhea by adherence, mucosal invasion, enterotoxin production, or cytotoxin production or a combination thereof. Infectious diarrhea occurs when this balance is disrupted, either as a result of increased secretion from the gastrointestinal tract or because of decreased absorption of fluids. Although this distinction is useful conceptually, cases of infectious diarrhea often occur through both mechanisms.

Definitions. *Secretory diarrhea* is the result of increased intestinal secretion caused by a variety of mechanisms. In the case of *Vibrio cholerae,* an enterotoxin causes an increase in cyclic adenosine monophosphate (cAMP) in the endothelial cell, resulting in increased chloride and bicarbonate secretion. Clinically, secretory diarrhea is often characterized by the absence of expected reduction in stool volume with fasting, a stool pH above 6, and the absence of reducing substances in the stool. Other bacteria that produce enterotoxins include *Salmonella, Shigella, E. coli,* and *C. difficile.*

Osmotic diarrhea is caused by the presence of poorly absorbed solutes in the colon as a result of altered bacterial gut flora, damage to the mucosal absorptive surface, or ingestion of substances. These substances alter the normal mechanisms of fluid transport by creating an osmotic gradient across the bowel lumen. This results in movement of water and electrolytes into the luminal fluid. Typical acute viral gastroenteritis, caused by rotavirus or norovirus, produces injury to the small bowel epithelium with consequent disruption of microvilli. This disruption decreases the absorptive area and prevents normal fluid, electrolyte, and nutrient absorption. The illness is compounded when the colon is unable to cope with the large fluid volume. Diagnostic clues to an osmotic etiology are diarrhea that decreases or stops with fasting, a stool pH below 5, and the presence of reducing substances in the stool.

Dysentery is defined as diarrhea associated with blood and mucus in the stool. The presence of dysentery often implies that the infection has compromised the bowel wall. Acute inflammation, caused by enteroinvasive organisms such as *Salmonella, Shigella,* and *Campylobacter,* leads to infiltration of the gastrointestinal tract by neutrophils, which in turn release a host of enzymes and factors causing both increased secretion and decreased absorption by the intestinal tract. Although blood loss may be clinically appreciable, it is usually less significant than the fluid and electrolyte losses. Systemic infection should be suspected if the patient appears ill or has fever and chills or if an elevated count or a left shift is seen on a white blood cell count.

Before the diagnosis of acute infectious diarrhea is established, other potentially life-threatening illnesses that can be manifested with diarrhea with or without vomiting should be excluded. This can usually be accomplished with a thorough history and physical examination (Tables 173-1 and 173-2).

Table 173-1 Common Causes of Vomiting in Children

ETIOLOGIC CATEGORY	CLINICAL SYNDROMES
Central nervous system	Infections, space-occupying lesion
Gastrointestinal	Obstruction, peritonitis, hepatitis, liver failure, appendicitis, pyloric stenosis, midgut volvulus, intussusception, inborn errors of metabolism
Drug	Ingestion, overdose, drug effect
Endocrine	Addisonian crisis, diabetic ketoacidosis, congenital adrenal hyperplasia
Renal	Urinary tract infection, pyelonephritis, renal failure, renal tubular acidosis
Cardiac	Congestive heart failure of any cause
Infection	Pneumonia, acute otitis media, sinusitis, sepsis
Other	Psychogenic, respiratory insufficiency

Table 173-2 Common Causes of Diarrhea in Children

ETIOLOGIC CATEGORY	CLINICAL SYNDROMES
Gastrointestinal	Malabsorption (e.g., milk intolerance, excessive fruit juice), intussusception, inflammatory bowel disease, irritable bowel syndrome, short gut syndrome
Drug	Ingestion, overdose, drug effect
Endocrine	Thyrotoxicosis, addisonian crisis, diabetic enteropathy, congenital adrenal hyperplasia
Renal	Urinary tract infection, pyelonephritis
Infection	Pneumonia, acute otitis media, sinusitis, sepsis
Other	Parental anxiety, chronic nonspecific diarrhea

Physiologic Factors

Several physiologic factors predispose pediatric patients to more severe complications from vomiting and diarrhea. Children have larger extracellular fluid compartments compared with adults. As a result, children can lose proportionately more fluids through their gastrointestinal tracts. The turnover of fluids and solute in infants and young children can be as much as three times that of adults. This rapid turnover of fluids is the result of higher metabolic rates, increased body surface area to mass index, and higher body water contents (water constitutes approximately 70% of body weight in infants, 65% in children, and 60% in adults). Children also have limited stores of metabolic substrates such as fat and glycogen, limited ability to access fluids and the lack of

www.ketabpezeshki.com 66485457-66963820

intake when not feeling well, and kidneys that do not conserve water as well as adult kidneys. These factors make children more susceptible to large fluctuations in fluid, electrolytes, and nutrients.

Extracellular fluid loss in acute diarrhea may lead to significant intravascular volume depletion, which in turn may lead to primary metabolic acidosis with varying degrees of respiratory compensation. The metabolic acidosis usually results from the loss of bicarbonate (HCO_3^-) in diarrheal fluid but also may be caused by renal tubular acidosis, excessive lactate production from poor tissue perfusion, and therapeutic interventions (e.g., salicylates). One effect of metabolic acidosis is an increase in minute ventilation. On clinical examination, these children are hyperpneic, with deep and labored breathing, even when they are at rest. Patients with metabolic acidosis from diarrhea require restoration of intravascular volume to allow delivery of nutrient substrate and elimination of byproducts of cellular metabolism rather than rapid correction of the acid-base disorder with buffer. Restoration of intravascular volume often corrects what appears to be respiratory distress in the child who is severely volume depleted.

Etiology

A variety of viruses, bacteria, and protozoa can cause acute infectious diarrhea in children (Table 173-3). In developed countries such as the United States, viral causes predominate. In countries in which access to clean water and food supply is limited, bacterial agents contribute the major portion of the morbidity and mortality associated with infectious diarrhea.

Viruses

In the United States and Europe, the majority of cases of diarrhea with or without vomiting are caused by viral diseases that peak in the winter. The most common of these is rotavirus, which is the most common cause of infectious diarrhea worldwide. Other typical causes of acute infectious diarrhea include adenovirus serotypes 40 and 41, noroviruses, astrovirus, and adenovirus.

Rotavirus is the leading cause of diarrhea worldwide among children younger than 5 years.[12] In the United States, rotavirus is responsible for 410,000 office visits, 205,000 to 272,000 ED visits, and 55,000 to 77,000 hospitalizations each year. This virus is endemic and accounts for nearly one third of the cases in children with diarrhea. The number of cases of rotavirus infection peaks in the winter and spring. Rotavirus causes acute illness with vomiting and diarrhea that may or may not be associated with fever. The diarrhea is watery, and the volume may be large enough to result in significant and rapid intravascular volume depletion. Rotavirus also may cause symptoms of an upper respiratory tract infection. Most infections are transmitted person to person through the fecal-oral route. There is also evidence that it may be transmitted through respiratory secretions as airborne droplets. The incubation period is 1 to 3 days. Postinfection excretion may be prolonged up to 21 days after the onset of symptoms in the immunocompetent patient.[13]

Rotavirus selectively destroys the villus tip cells in the small intestine, leading to malabsorption and diarrhea. A proliferative response occurs, producing an abundance of incompletely differentiated cells in the gut mucosa. In the healthy host, repair of the epithelium and differentiation of the immature brush border take approximately 3 to 5 days and occur without specific intervention. In the chronically ill or malnourished child, the infection may lead to complications beyond the usual brush border injury. Failure to repair the epithelium leads to the vicious circle of malnutrition and progressive epithelial injury.[13]

Diagnosis is made by demonstration of antigens in stool specimens by enzyme immunoassay. Modern assays have up to 97% sensitivity and 97% specificity for rotavirus antigens in human stool. The test can be performed on undiluted stool without special preparation. Results are usually available within 24 hours.[13]

An effective vaccine was available for a short time (1998-1999) until it was noted to be associated with increased risk of intussusception, usually occurring 3 to 20 days after administration. This vaccine was subsequently withdrawn from the U.S. market.[14] Until recently, only two orally administered live virus vaccines were licensed for use among infants in the United States. RotaTeq vaccine was licensed in 2006 as a three-dose series, and in 2008 Rotarix, a live oral human attenuated vaccine, was licensed as a two-dose series for infants. The American Academy of Pediatrics does not express a preference for either vaccine. To date, no association with intussusception has been reported.[15,16] Preliminary surveillance data from the Centers for Disease Control and Prevention (CDC) have noted a 64% decrease among rotavirus-positive test results in the first year after vaccine release.[17] Recently, a new vaccine was introduced, the RV1 vaccine; studies in Brazil and Mexico show the risk of intussusception after RV1 vaccine to be 1 in 51,000 to 68,000. The authors concluded that this increased risk results in an annual excess of 96 hospitalizations and that this risk is outweighed by the benefit of the vaccine, which prevented 80,000 admissions and 1300 deaths.[17]

Noroviruses (previously known as Norwalk-like viruses) are the second most common cause of childhood acute infectious diarrhea. Norovirus accounts for approximately 12% of severe gastroenteritis among children younger than 5 years. In the United States, norovirus is responsible for more than 235,000 clinic visits, 91,000 ED visits, and 23,000 hospitalizations for children younger than 5 years.[18,19] Infection can occur year-round and in any age group but is most common during the colder months of the year. This virus causes the abrupt onset of watery diarrhea with or without vomiting. It is often accompanied by abdominal cramps and nausea. It is a self-limited disease, lasting 2 or 3 days. This virus can be transmitted person to person by the fecal-oral route as well as through contaminated food and water sources. In the United States, norovirus accounts for more than 90% of community outbreaks associated with viral gastroenteritis, which occur in all age groups. Common-source outbreaks in long-term care

Table 173-3 Common Causes of Infectious Diarrhea

Viruses (70-80% of infectious diarrhea in developed countries)
Rotavirus
Noroviruses
Astrovirus
Adenovirus
Hepatitis A
Bacteria (10-20% of infectious diarrhea; responsible for more cases of severe diarrhea)
Salmonella species
Shigella species
Campylobacter jejuni
Yersinia enterocolitica
Escherichia coli
Enterotoxigenic
Enteroinvasive
Enterohemorrhagic (*E. coli* O157:H7)
Clostridium perfringens
Clostridium difficile
Staphylococcus aureus
Vibrio cholerae
Vibrio parahaemolyticus
Parasites (<10%)
Cryptosporidium
Giardia
Entamoeba histolytica

www.ketabpezeshki.com 66485457-66963820

facilities contribute significantly to morbidity and mortality among the residents. In addition, these agents most commonly are associated with outbreaks of acute gastroenteritis on cruise ships and in schools and hospitals. The incubation period is 12 to 48 hours, and the excretion of the virus lasts 5 to 7 days after the onset of symptoms in approximately 50% of infected people. In about 25% the excretion of the virus can be up to 3 weeks, and asymptomatic excretion can be longer in the immunocompromised.[20]

Astrovirus infections occur mostly in children younger than 4 years; cases peak in the late winter and early spring in the United States. The illness is characterized by diarrhea of short duration (a few days) accompanied by vomiting, fever, and occasionally abdominal pain. The incubation period is 1 to 4 days and transmission is person to person by the fecal-oral route. Viral shedding may begin a day before symptoms start and can continue for several days after cessation of diarrhea. However, asymptomatic shedding has been seen to last up to several weeks after the symptoms of the illness have resolved in healthy children There are no commercial tests for diagnosis in the United States, but enzyme immunoassays are available in many other countries. There are a few different tests available in some research and reference laboratories; the reverse transcription–polymerase chain reaction assay is the most sensitive.[21]

Adenovirus is well known for causing infections of the respiratory tract along with pharyngitis, otitis media, and pharyngoconjunctival fever. Enteric adenovirus serotypes cause gastroenteritis. These strains are transmitted through the fecal-oral route. Enteric disease occurs throughout the year and affects children younger than 4 years more commonly. The incubation period is 3 to 10 days. It is most contagious during the first few days of the acute illness, but asymptomatic shedding of the virus for months is not uncommon.[22]

The mainstay for treatment of viral enteritis is supportive care. Rehydration with ORS or intravenous fluids is recommended (see section on dehydration).

Bacteria

The common bacterial organisms causing acute diarrhea in the United States are *Salmonella* species, *Shigella* species, *Campylobacter jejuni, Yersinia enterocolitica,* and enterotoxigenic, enteroinvasive, and enterohemorrhagic strains of *E. coli*. Other, less common bacterial causes include *Clostridium perfringens, Clostridium difficile, Staphylococcus aureus, Vibrio cholerae,* and *Vibrio parahaemolyticus,* each accounting for less than 1% of cases of acute infectious diarrhea in children.

Salmonella infections usually are divided into those caused by nontyphoidal *Salmonella* and *Salmonella typhi* (typhoid fever). Nontyphoidal *Salmonella* account for more than 98% of the cases in the United States. Infection can result in an asymptomatic carrier state, acute gastroenteritis, bacteremia, and a disseminated abscess syndrome. It is thought that salmonellae invade the mucosa of the distal small intestine as well as the colon and produce a cholera-like enterotoxin and a cytotoxin. It is an illness marked by diarrhea, abdominal cramps, nausea, and fever; it may be manifested as dysentery or a cholera-like illness. Acute gastroenteritis occurs at any age but is most common in the first 4 years of life. Sustained or intermittent bacteremia can occur, and focal infections are seen in up to 10% of patients with *Salmonella* bacteremia. Animal reservoirs include poultry, livestock, and reptiles, which may be kept as pets by young children. Transmission is usually through foods such as poultry, beef, eggs, and dairy products. Other modes of transmission include ingestion of contaminated water and contact with infected reptiles, amphibians, and possibly rodents. The incubation period for gastroenteritis is 12 to 36 hours (range, 6-72 hours). Invasive disease and mortality are higher for infants and those with immunosuppressive conditions, hemoglobinopathies (e.g., sickle cell disease), malignant neoplasms, and human immunodeficiency virus (HIV) infection.[23]

Although it is uncommon, *Salmonella* serotype *typhi* can cause a bacteremic illness often referred to as enteric or typhoid fever. *S. typhi* is found only in humans, and infection implies direct contact with an infected person or with an item contaminated by a carrier. It is uncommon in the United States (approximately 400 cases per year) but is endemic in many countries. Consequently, typhoid fever infections in people in the United States usually are acquired during international travel. There is a gradual onset of symptoms that include fever, headache, malaise, anorexia, lethargy, abdominal pain, and tenderness. Patients may have hepatosplenomegaly, rose spots, and a change in mental status. It may appear as a nonspecific febrile illness in young children, in whom sustained or intermittent bacteremia may occur. Constipation is often seen early in the course of the disease, but diarrhea does occur in children.[23]

Treatment of nontyphoidal *Salmonella* infection is usually supportive. Antibiotics given to patients with nontyphoidal *Salmonella* infections have been found not only to be ineffective in shortening the duration of symptoms but also to prolong the carrier state. Therefore, antibiotics are generally not recommended for asymptomatic cases or for uncomplicated cases. Antibiotic treatment is indicated in infants younger than 3 months or those with complications (such as failure to improve within 5 to 7 days; bacteremia; focal infection in the central nervous system, bone, joint, kidney, or pericardium; and immunosuppressive conditions, hemoglobinopathies, malignant neoplasms, HIV infection, or chronic gastrointestinal disease). If treatment is necessary, ampicillin, amoxicillin, or trimethoprim-sulfamethoxazole usually is effective. Because of changing resistance patterns, susceptibility testing should be performed on all isolates. In areas where resistance to these antibiotics is common, ceftriaxone, cefotaxime, azithromycin, and fluoroquinolones are usually effective (fluoroquinolones are not recommended in people younger than 18 years) (Table 173-4).

For children with *S. typhi* infection, antibiotics are recommended. Multidrug-resistant isolates of *S. typhi* are common, often requiring empirical treatment with an antibiotic such as an expanded-spectrum cephalosporin, azithromycin, or fluoroquinolone. Relapse of enteric fever occurs in up to 15% of patients and requires re-treatment. Treatment failures have occurred in people treated with cephalosporins, aminoglycosides, and furazolidone despite in vitro testing indicating susceptibility.[23]

Shigella species consist of four antigenic groups of 40 serotypes. Among *Shigella* isolates reported in industrialized nations, including the United States, approximately 86% are *Shigella sonnei,* 12% are *Shigella flexneri,* 3% are *Shigella boydii,* and less than 1% are *Shigella dysenteriae*.[24]

S. sonnei is the most common cause of dysentery (diarrhea with significant blood, pus, and mucus) in the United States. Shigellosis usually begins as an enterotoxin-like secretory diarrhea with watery stools and fever that may progress to bacillary dysentery with or without systemic manifestations. Clinical illness varies from mild to severe, with some patients exhibiting abdominal cramps and tenderness. Shigellosis rarely infects infants younger than 3 months and is most common between 2 and 3 years of age. Symptoms usually are self-limited and resolve within 72 hours. Extraintestinal symptoms and signs are relatively common in children with *Shigella* infection and may include hallucinations, confusion, and seizures. Reactive arthritis can occur weeks after the infection. Rare complications of *Shigella* infection include bacteremia, hemolytic-uremic syndrome (HUS), and encephalopathy (Ekiri syndrome). Ingestion of as little as 10 to 200 organisms is all that is needed for infection to occur. Transmission occurs through the fecal-oral route, contact with contaminated objects, ingestion of contaminated food or water, and sexual contact.

www.ketabpezeshki.com 66485457-66963820

Table 173-4 Diarrheal Pathogens in Children and Specific Therapy

	SPECIFIC THERAPY BEYOND SUPPORTIVE CARE	COMMENTS
Bacteria		
Campylobacter jejuni	Oral: Azithromycin 10 mg/kg/day for 3 days *or* Erythromycin 30-50 mg/kg/day divided q8h for 5 days	Illness is usually self-limited. Treatment can shorten duration of illness and excretion of organism and prevent relapse.
Clostridium difficile	Oral or IV: Metronidazole 30 mg/kg/day divided q6h for at least 10 days (max. dose 2 g/day) *or* Oral: Vancomycin 40 mg/kg/day divided q6h for at least 10 days (max. dose 2 g/day)	Stop the offending agent. Up to 25% will have relapse after adequate treatment but usually will respond to a second course of the same medicine. Do not give antimotility agents.
E. coli—STEC	No antibiotic treatment; may increase risk of HUS	Antibiotics have shown no benefit and HUS may occur.
E. coli—ETEC (traveler's diarrhea)	Oral: Azithromycin 10 mg/kg/day for 5 days *or* Fluoroquinolones (>17 years) Oral ciprofloxacin 500 mg q12h for 1-2 days Oral norfloxacin 400 mg q12h for 3 days *or* Oral rifaximin (>12 years) 200 mg q8h for 3 days	As effective as ciprofloxacin.
Salmonella species, nontyphoidal	No antibiotics for asymptomatic or uncomplicated disease If antibiotics are given and susceptibility is known IV or oral: Ampicillin 200 mg/kg/day divided q6h Oral: TMP-SMZ, 10 mg TMP/kg/day divided q12h Susceptibility not known or areas of high resistance IV or IM: Ceftriaxone 100 mg/kg/day qd or divided q12h *or* Oral or IV: Azithromycin 10 mg/kg/day *or* Oral: Ciprofloxacin (>17 years) 500 mg/kg/day divided q12h Localized invasive disease: empirical therapy until susceptibility is known, then can change to oral IV: Cefotaxime 150-200 mg/kg/day divided q4-6h (max. 12 g/day) IV: Ceftriaxone 100 mg/kg/day qd or divided q12h	Antibiotics do not shorten duration of diarrheal disease. Antibiotics can prolong duration of fecal excretion. Antibiotics are recommended for infants. Treatment is initiated in children <3 months and with complications: chronic gastrointestinal disease, invasive disease (central nervous system, joint, bone, pericardium involvement), prolonged illness, bacteremia, malignant neoplasms, hemoglobinopathies, immunosuppression. Localized invasive disease: treat for total of 4 weeks (6 weeks if meningitis). Bacteremia: treat for total of 10-14 days. Drug of choice, route of administration, and duration of therapy are based on susceptibility of organisms, site of infection, host, and clinical response.
Salmonella species, typhoid	Start with IV medications; may change to oral when susceptibility is known and clinical improvement is seen Ceftriaxone 100 mg/kg/day qd or divided q12h *or* Cefotaxime 200 mg/kg/day divided q4-6h (max. 12 g/day) *or* Fluoroquinolone (>17 years or benefits outweigh risks) Ciprofloxacin 20 mg/kg/day divided q12h	Multidrug resistance is common. 10- to 14-day treatment is usually needed. Check susceptibilities.
Shigella species	IV for proven or suspected shigellosis or not able to take orals, immunosuppression, or bacteremia Ceftriaxone 50 mg/kg/dose for 5 days *or* Ciprofloxacin (>17 years or ceftriaxone contraindicated) 20 mg/kg/day divided q12h or azithromycin 10 mg/kg/day for 3 days Oral treatment (check local resistant patterns) First line: Azithromycin 12 mg/kg/day for first day, then 6 mg/kg/day for days 2-5 *or* Fluoroquinolone (>17 years or deemed necessary) Ciprofloxacin 20 mg/kg/day divided q12h for 5 days Norfloxacin 10-15 mg/kg/day for 5 days TMP-SMZ 10 mg TMP/kg/day divided q12h for 5 days *or* Ampicillin 100 mg/kg/day divided q6h for 5 days	Disease is usually self-limited, but treatment decreases diarrhea and eradicates organisms from stool. If there is no bacteremia or immunodeficiency and the child is afebrile after 2 days, two doses of ceftriaxone only may be given. Use TMP-SMZ and ampicillin only if isolated strain is susceptible because of high resistance.
Vibrio parahaemolyticus	Supportive treatment only; self-limited	
Vibrio cholerae	Oral doxycycline single dose *or* Oral tetracycline for 3 days	Antibiotics for moderately to severely ill Tetracycline is not recommended for children <8 years unless benefits outweigh risk of staining developing teeth.

www.ketabpezeshki.com 66485457-66963820

Table 173-4 Diarrheal Pathogens in Children and Specific Therapy—cont'd

	SPECIFIC THERAPY BEYOND SUPPORTIVE CARE	COMMENTS
Yersinia enterocolitica	Antibiotics for bacteremia, extraintestinal disease, immunocompromised host Oral: TMP-SMZ, 10 mg TMP/kg/day divided q12h *or* Oral or IV: Fluoroquinolone (>17 years or deemed necessary) Ciprofloxacin 20 mg/kg/day divided q12h Norfloxacin 10-15 mg/kg/day *or* IV: Ceftriaxone 50-100 mg/kg/day divided qd or q12h *or* Cefotaxime 150-200 mg/day divided q4-6h (max. 12 g/day)	Antibiotics do decrease duration of fecal excretion. Antibiotics do not decrease length of diarrhea. Isolates are usually resistant to first-generation cephalosporins and most penicillins but respond well to most aminoglycosides. Tetracycline or doxycycline (>8 years) can also be used for treatment. Extraintestinal disease: treat for 4 weeks.
Protozoa		
Cryptosporidium	Nitazoxanide for children at least 1 year of age 1-3 years: 100 mg divided q12h for 3 days 4-11 years: 200 mg divided q12h for 3 days 12 years and older: 500 mg q12h for 3 days	
Entamoeba histolytica	Asymptomatic cyst excretors Drug of choice: Iodoquinol 30-40 mg/kg/day (max. 2 g) PO divided q8h for 7 days *or* Paromomycin 25-35 mg/kg/day PO divided q8h for 7 days	
	Mild to severe intestinal disease and extraintestinal disease First line: Metronidazole 35-50 mg/kg/day divided q8h for 7-10 days *or* Tinidazole (>3 yr) 50 mg/kg/day (max. 2 g) PO daily for 3 days	For severe disease, tinidazole should be used for 5 days instead of 3 days.
	followed by luminal amebicide Iodoquinol 30-40 mg/kd/day (max. 2 g) PO divided q8h for 20 days *or* Paromomycin 25-35 mg/kg/day PO divided q8h for 7 days	Iodoquinol and paromomycin should be taken with meals.
Giardia	Metronidazole 15 mg/kg/day PO divided q8h for 5-7 days (max. 250 mg q8h) *or* Tinidazole 50 mg/kg single dose for children >3 years (max. single 2-g dose)	

Data from Pickering LK, Baker CJ, Long SS (eds): Red Book: 2009 Report of the Committee on Infectious Diseases, 28th ed. Elk Grove Village, Ill, American Academy of Pediatrics, 2009; and Custer JW, Rau RE (eds): The Harriet Lane Handbook: A Manual for Pediatric House Officers, 18th ed. Philadelphia, Mosby–Year Book, 2009.
ETEC, enterotoxigenic *E. coli*; *HUS,* hemolytic-uremic syndrome; *STEC,* Shiga-toxin producing *E. coli*. *TMP-SMZ,* trimethoprim-sulfamethoxazole.

Children 5 years and younger in daycare settings, their caregivers, and other people living in crowded conditions are at increased risk for infection. Travel to developing countries with inadequate sanitation also increases the traveler's risk for infection. Houseflies may also be vectors through transport of infected feces. The incubation period varies from 1 to 7 days. With or without antibiotics, the carrier state usually lasts about 1 week from the onset of symptoms; chronic carrier state is rare. Antibiotics are reserved for patients with prolonged symptoms, dysentery, or underlying immune compromise.[25] For this high-risk population of patients, if *Shigella* is suspected (patient with contact with a person with *Shigella* or a known regional outbreak), it is recommended that empirical treatment be started while culture and susceptibility results are awaited. According to the CDC surveillance data from 2000 to 2009, approximately 40 to 60% of isolates were resistant to ampicillin, approximately 30% were resistant to trimethoprim-sulfamethoxazole, and less than 1% were resistant to ceftriaxone and ciprofloxacin.[24] Therefore, parenteral ceftriaxone or an oral fluoroquinolone (such as ciprofloxacin or ofloxacin) could be used for 5 days in adult patients who are seriously ill. For less ill adult patients, an oral fluoroquinolone is recommended. In children, parenteral ceftriaxone for seriously ill children or oral azithromycin for less ill children is recommended. Therapy is usually recommended for 5 days. A 2-day course of ceftriaxone may be used if there is a good clinical response and no extraintestinal infection[25] (see Table 173-4).

Campylobacter species cause a significant proportion of diarrheal disease worldwide, with 2.4 million cases yearly in the United States. According to data from the CDC, there has been a 30% decline in the incidence of infection since 1996.[26] Children younger than 5 years have the highest rate of infection. It takes as few as 500 *Campylobacter* organisms to cause infection in exposed people. The organism is found in the gastrointestinal tracts and feces of fowl, farm animals, and pets. Of the five types, *C. jejuni* and *C. coli* are the most common. Illness consists of abdominal cramps, diarrhea, chills, fever, and *Shigella*-like dysentery. The clinical presentation may be similar to acute appendicitis or intussusception. Invasion of the mucosa with toxin production has been described. A 1- to 7-day incubation period is normal, and the illness usually lasts less than a week. However, approximately 20% will have a relapse or a prolonged or severe illness. Severe or prolonged disease can mimic inflammatory bowel disease. *Campylobacter* organisms are transmitted by ingestion of contaminated food (improperly cooked poultry and unpasteurized milk)

www.ketabpezeshki.com 66485457-66963820

or untreated water. Fecal-oral spread can occur, especially among very young children with diarrhea. There have been outbreaks in childcare centers, but this is rare. There has also been spread by neonates born to infected mothers that has resulted in outbreaks in nurseries. Excretion typically lasts 2 to 3 weeks without treatment. Diagnosis is made by darkfield microscopy. Oral azithromycin or erythromycin shortens the course of the illness and excretion of organisms and prevents relapse when given early (see Table 173-4). Treatment will usually eradicate the organism from the stool within 2 to 3 days. However, most children will recover without treatment.[27]

Y. enterocolitica is a relatively uncommon cause of simple self-limited diarrhea and vomiting in the United States. According to the CDC, the mean annual incidence is 0.3 per 100,000 people. However, for children younger than 5 years, the incidence is 1.9 per 100,000.[26] Infection usually is manifested with fevers and diarrhea, which may be watery, contain mucus or blood, or both. As many as 6% of older children and adults may present with an appendicitis-like illness with right lower quadrant tenderness, usually as a result of reactive mesenteric adenitis.[28] Infections usually result from eating undercooked pork or drinking unpasteurized milk. Symptoms may be prolonged, lasting 14 days or more. There have been no clinical benefits of antimicrobial therapy in the immunocompetent host with enterocolitis or mesenteric adenitis. Antibiotics are indicated for the immunocompromised with enterocolitis and in cases of septicemia and extraintestinal infections. First-line treatment of *Y. enterocolitica* infection is trimethoprim-sulfamethoxazole and aminoglycosides. Other effective antibiotics include cefotaxime, fluoroquinolones (patients 18 years or older), tetracycline, and doxycycline (patients 8 years of age or older). Isolates are often resistant to first-generation cephalosporins and most penicillins (see Table 173-4).[29]

C. difficile causes a spectrum of illnesses ranging from asymptomatic to watery diarrhea to pseudomembranous colitis. Patients usually present with diarrhea, abdominal cramps, and fever. Other common features include abdominal tenderness to palpation and dysenteric stools. Complications can include toxic megacolon and intestinal perforation. Severe disease is more common in neutropenic patients with leukemia, in infants with Hirschsprung's disease, and in patients with inflammatory bowel disease. *C. difficile* gastroenteritis most often occurs in hospitalized patients, with onset during hospitalization or within 60 days after antibiotic therapy. The organism is transmitted by fecal-oral contamination. Asymptomatic infants can be colonized with the organism; intestinal colonization in healthy neonates and young infants can be as high as 50% but usually is less than 5% in children older than 2 years. The disease is thought to be brought on by the change in the gut flora as a result of antibiotic administration. Incubation time is unknown. Pseudomembranes and friable rectal mucosa are characteristic. *C. difficile* toxin in the stool is diagnostic. In many institutions the fecal enzyme immunoassay is used for detection of toxins A and B. The results of this test are often available within hours. The sensitivity of this test is approximately 75%. Toxigenic stool culture is the most sensitive test but takes 2 to 3 days for results. Stopping the offending agent and adding therapy with oral or intravenous metronidazole or oral vancomycin for 10 days are indicated (see Table 173-4). Up to 25% of patients experience a relapse after discontinuation of therapy, but the infection usually responds to a second course with the same agent. Drugs that decrease intestinal motility should not be given.[30]

Ingested *C. perfringens* organisms produce an enterotoxin during sporulation in the gut that causes fluid collection in ileal loops and diarrhea. The result is a short-lived (usually 24 hours) illness characterized by watery diarrhea, moderate to severe abdominal cramps, and midepigastric pain. Vomiting and fever are uncommon. Food source contamination, often from catered food services (raw meat and poultry, gravies, and dried or precooked foods), is the usual source of outbreaks. The illness cannot be transferred from person to person by the fecal-oral route. The incubation time is 6 to 24 hours. The finding of high spore counts in the stool can make the diagnosis. No specific treatment is required.[31]

S. aureus produces the "typical" food poisoning from ingestion of preformed enterotoxin, usually from contaminated food. Onset of symptoms is within minutes to hours of exposure. The illness is short-lived (1-2 days) and self-limited. Abrupt and sometimes violent onset of severe nausea, vomiting, abdominal cramps, and diarrhea without fever is typical. However, low-grade fever or mild hypothermia may occur. Recovery of large numbers of bacteria or enterotoxin from stool or vomitus supports the diagnosis. Treatment is supportive. No antibiotics are indicated as the disease is self-limited.[32]

V. cholerae is an Asian-African organism that also is seen in South America. Most cases occur in travelers returning from endemic areas. A unique strain is endemic to the Gulf Coast of the United States. The disease is acquired through ingestion of contaminated water and food, such as undercooked shellfish and raw vegetables. Because a large inoculum is required, person-to-person transmission does not occur. Diarrhea is caused by a heat-labile enterotoxin that increases cAMP through adenylate cyclase, resulting in inhibition of sodium reabsorption with chloride and fluid secretion into the gut. The illness is characterized by the painless production of large amounts of watery diarrhea without abdominal cramps or fever. Dehydration, hypokalemia, metabolic acidosis, and occasionally hypovolemic shock can occur within 4 to 12 hours if fluid losses are not replaced. Antibiotic treatment should be considered for patients with moderate to severe disease—oral doxycycline as a single dose or tetracycline for 3 days in severe cholera infection. Although it is not recommended in children younger than 8 years, the benefits may outweigh the risk of staining developing teeth. It has been shown that one course of doxycycline is unlikely to cause significant tooth discoloration. Susceptibility testing is recommended because of changing resistance patterns.[33]

V. parahaemolyticus is commonly found in seawater, shellfish, and fish. Illness is most commonly associated with ingestion of contaminated raw or undercooked seafood. Diarrhea, abdominal cramps, and nausea are common, whereas vomiting, headache, fever, and chills are less common. The disease usually is self-limited and does not require treatment with antimicrobials.[33]

E. coli is part of the normal flora in the lower gastrointestinal tract. Several types within this species are recognized to cause disease. Transmission of most diarrhea caused by *E. coli* is from food or water contaminated with human or animal feces or from infected symptomatic people or carriers. *E. coli* is identified by distinct groups of either somatic or flagellar antigens that determine virulence properties. The enterotoxigenic *E. coli* (ETEC) strain produces heat-stable and heat-labile enterotoxins that affect the small intestine and cause a secretory diarrhea. It is common in infants in developing countries and in travelers of all ages. It is uncommon as a cause of diarrhea in the United States. The enteroinvasive *E. coli* (EIEC) strain is closely related antigenically and biochemically to *Shigella* species and can cause a similar dysenteric illness. It invades the large bowel epithelial cells, producing enterotoxins and colonic epithelial cell death. It can cause bloody or nonbloody diarrhea and fever in all ages. The enteropathogenic *E. coli* (EPEC) strain is responsible for sporadic and endemic diarrhea. The diarrhea is usually watery and can be severe. The illness occurs predominantly in children younger than 2 years and mainly in developing countries. It can become chronic and cause growth retardation. This form does not produce toxins. The enteroaggregative *E. coli* (EAEC) strain causes watery diarrhea in people of all ages in developing and developed countries. It has been associated with a prolonged course. The enterohemorrhagic *E. coli*

www.ketabpezeshki.com 66485457-66963820

(EHEC) strain, also known as Shiga toxin–producing *E. coli* (STEC), produces bloody diarrhea without fever; *E. coli* O157:H7 is the prototype and most virulent of the EHEC. Outbreaks have been linked to ground beef, exposure to animals in public settings (petting zoos), contaminated apple cider, raw fruits and vegetables, and ingestion of water in recreational areas. The infectious dose is low, and person-to-person transmission is common during outbreaks.[34] HUS is a serious sequel of EHEC infection.[35]

HUS consists of the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency. It typically develops in the second week of illness, often after the diarrhea has resolved. Patients often present with pallor, weakness, irritability, and oliguria or anuria. HUS occurs in up to 20% of children with *E. coli* O157:H7.[36] Approximately 50% of patients who have HUS will require dialysis, and 3 to 5% die. Patients with hemorrhagic colitis should be aggressively hydrated, admitted, and monitored closely (including complete blood cell count with smear and blood urea nitrogen [BUN] and creatinine concentrations) to detect changes suggestive of HUS. If patients have no laboratory evidence of hemolysis, thrombocytopenia, or nephropathy 3 days after resolution of diarrhea, their risk for development of HUS is low.[35]

Controversy exists about the indications for antibiotic treatment of *E. coli* diarrhea. Early data indicated that antimicrobials offer no substantial benefit and may increase the risk for development of HUS.[37] In addition, in vitro studies have shown that subinhibitory antibiotic concentrations can increase toxin production.[38] However, a subsequent meta-analysis failed to confirm the association between the use of antibiotics and the increased risk for HUS.[39] In the absence of conclusive evidence, empirical antibiotics should not be administered because of the potential risk of HUS. For severe watery diarrhea in a traveler to a developing country, azithromycin or a fluoroquinolone may be considered in an older child (>18 years).[34]

Protozoa

Protozoa can also cause diarrhea in children but are responsible for less than 1% of all cases of acute infectious diarrhea. The most common protozoa causing diarrhea are *Cryptosporidium, Giardia intestinalis,* and *Entamoeba histolytica*.

Cryptosporidium hominis is the most common of the *Cryptosporidium* species to infect humans. Children present with frequent, nonbloody, watery diarrhea. Other symptoms may include abdominal cramps, fatigue, fever, vomiting, anorexia, and weight loss. *Cryptosporidium* has been found in mammals, birds, and reptiles.[40] Outbreaks have been associated with contaminated municipal water and exposure to contaminated swimming pools. In children, the incidence is greatest during the summer and early fall. Person-to-person spread can occur and can cause outbreaks in daycare centers. In the immunocompetent child, the illness is self-limited, lasting 1 to 20 days. In the immunocompromised patient, chronic, severe diarrhea can develop and result in malnutrition, dehydration, and death. Treatment is usually supportive. However, the U.S. Food and Drug Administration has approved a 3-day course of nitazoxanide oral suspension for the treatment of immunocompetent children older than 1 year. In patients who are immunocompromised, oral administration of intravenous immune globulin is recommended.[41]

Infection with *Giardia* is limited to the small intestine and biliary tract. Children can present with intermittent watery diarrhea with abdominal pain, or they can experience protracted, intermittent, often debilitating disease characterized by foul-smelling stools with flatulence, abdominal distention, and anorexia. The disease can become chronic and can lead to weight loss, failure to thrive, and anemia. Asymptomatic infection is common. Humans are the main reservoir, although it has been found in the stool of dogs, cats, beavers, and other animals.[42] These animals can contaminate water with stool containing cysts that are infectious for humans. People contract the disease by hand-to-mouth transfer of cysts from stool of an infected person or by ingestion of fecally contaminated water or food. Epidemics from person-to-person transmission occur in childcare centers and in institutions for people with developmental delays. Duration of cyst excretion can last for months. The disease can be spread for as long as the infected person excretes cysts. Identification of trophozoites or cysts in stool specimens, duodenal fluid, or small bowel tissues by direct microscopic examination by staining methods, enzyme immunoassay, or polymerase chain reaction makes the diagnosis. An examination of a single direct smear of stool has a sensitivity of 75% and specificity of 95%. The sensitivity increases in diarrheal stools because they have a higher concentration of organisms. Looking at three or more specimens collected every other day can also increase sensitivity. Treatment includes correction of dehydration and electrolyte abnormalities and antibiotics. Tinidazole, metronidazole, and nitazoxanide are the drugs of choice (see Table 173-4). If therapy fails, a course can be repeated with the same drug. Relapse is common in the immunocompromised host, who often requires prolonged treatment. Treatment of asymptomatic carriers is not recommended except in households with hypogammaglobulinemia or cystic fibrosis.[43]

E. histolytica can be found worldwide but is more prevalent in the lower socioeconomic population and in developing countries, where the prevalence of amebic infection may be as high as 50% in some communities. Immigrants from areas with endemic infection, institutionalized people, and men who have sex with other men are at increased risk for infection. People with intestinal amebiasis often have 1 to 3 weeks of increasingly severe diarrhea progressing to grossly bloody dysenteric stools with lower abdominal pain and tenesmus. Weight loss is common, but fever occurs in less than half of the patients. Symptoms can become chronic and may mimic inflammatory bowel disease. Complications include fulminant colitis, toxic megacolon, and ulceration of the colon and perianal area, rarely with perforation. Complications are more common in patients treated inappropriately with corticosteroids or antimotility drugs. *E. histolytica* is transmitted through amebic cysts by the fecal-oral route. Ingested cysts are unaffected by gastric acid. Infected persons who are untreated can excrete cysts for years. Transmission has also been associated with contaminated food and water. Sexual transmission may also occur. Identification of trophozoites or cysts in stool specimens secures the diagnosis. Examination of serial specimens is often necessary. Enzyme immunoassay test kits are also available for routine serodiagnosis of amebiasis. Treatment of asymptomatic cyst excreters is to provide them with a luminal amebicide such as iodoquinol, paromomycin, or diloxanide (see Table 173-4). Patients with mild to moderate or severe intestinal symptoms or extraintestinal disease (liver abscess) should be treated with metronidazole or tinidazole, followed by a course of luminal amebicide. Follow-up stool examination is recommended after completion of therapy because complete eradication of intestinal infection is difficult. Asymptomatic household members with stools positive for *E. histolytica* should also be treated.[44]

Unusual Organisms in Immunosuppressed Patients

Acute infectious diarrhea in the chronically ill and immunosuppressed patient is often caused by the organisms discussed previously. However, several unusual organisms can cause diarrhea in this population of patients. In patients with acquired immunodeficiency syndrome, these infections may be acute, chronic, or recurrent and difficult to treat. Unusual organisms may include *Mycobacterium avium* and cytomegalovirus. Because of frequent antibiotic exposure, infections caused by *C. difficile,*

www.ketabpezeshki.com 66485457-66963820

Box 173-1 Indications for Medical Evaluation of Children with Acute Diarrhea

Young age (e.g., <6 months or weight <8 kg)
History of premature birth, chronic medical conditions, or concurrent illness
Fever to ≥38° C for infants <3 months or ≥39° C for children 3-36 months
Visible blood in stool
High output, including frequent and substantial volumes of diarrhea
Persistent vomiting
Caregiver's report of signs consistent with dehydration (e.g., sunken eyes or decreased tears, dry mucous membranes, or decreased urine output
Change in mental status (e.g., irritability, apathy, or lethargy)
Suboptimal response to oral rehydration therapy already administered or inability of the caregiver to administer oral rehydration therapy

Modified from King CK, et al: Managing acute gastroenteritis among children: Oral rehydration, maintenance, and nutritional therapy. MMWR Recomm Rep 52:1, 2003.

Candida albicans, and *Pseudomonas aeruginosa* are more common in immunosuppressed patients.

Clinical Features

Diagnostic Findings

Although acute diarrhea in children often results in self-limited mild disease, it can cause significant fluid and electrolyte abnormalities that can have serious consequences. Indications for medical evaluation of children with diarrhea have been proposed (Box 173-1). Serious illnesses may be overlooked on cursory examination. The principal goals of the ED evaluation are to identify and to correct fluid, electrolyte, acid-base, and nutrient deficits that may result from vomiting, diarrhea, or decreased oral intake and to determine which children would benefit from prolonged management.

The history should include specific information about the order of presentation, duration, severity, and quantity (if applicable) for each symptom. The clinician should solicit the presence or absence of fever, nausea, vomiting, hematemesis, abdominal pain, diarrhea, and hematochezia. It is often difficult to quantify the volume of diarrhea from the history. Helping the parent describe the stool relative to usual bowel habits may provide valuable information. The consistency and content of stools are important. The relationship of symptoms to eating and drinking should be established. It is helpful to know whether other persons in the household have a similar illness and whether previous episodes have occurred. A history of travel to endemic or epidemic areas and exposure to household pets (especially turtles or reptiles) may provide important information. Quantity and time of recent oral intake and information about recent pre-illness weight can be helpful. Information about orthostatic symptoms and the patient's activity level is desirable. The past medical history should identify any chronic conditions, history of recent illnesses, rotavirus vaccination, and current medication use.

The physical examination should include close scrutiny of the vital signs while keeping in mind that clinical signs are often insensitive and nonspecific for dehydration.[45] For example, tachycardia is sensitive but nonspecific because there are many other causes of tachycardia, such as fever and anxiety. On the other hand, hypotension is specific but insensitive because children usually will maintain adequate blood pressure until severe intravascular depletion occurs. The evaluation of the child should begin with looking at the child from across the room in a position of comfort, noting the patient's overall appearance, responsiveness, activity, and work of breathing. A head-to-toe physical examination of the patient then should be performed, focusing on signs of dehydration (sunken eyes, dry mucous membranes, absence of tears, poor skin turgor, delayed capillary refill time). A general assessment of the abdomen and lungs should always be done to help rule out other pathologic processes. Clinicians often overestimate the extent of dehydration (see Table 173-5 for degree of dehydration). Clinical signs are usually not present until a child has lost at least 5% of his or her body weight. The three most useful signs in determining dehydration of more than 5% are prolonged capillary refill time, abnormal skin turgor, and abnormal respiratory pattern.[45] Older children and adults may manifest symptoms at a lesser degree of volume depletion because of relatively smaller total body water and extracellular fluid volume.

Table 173-5 Clinical Assessment of Degree of Dehydration

Older child	Mild (<3%) (30 mL/kg)	Moderate (6%) (60 mL/kg)	Severe (9%) (90 mL/kg)
Infant	Mild (<5%) (50 mL/kg)	Moderate (10%) (100 mL/kg)	Severe (15%) (150 mL/kg)
Signs and Symptoms			
Dry mucous membrane	±	+	+
Reduced skin turgor (pinch retraction)	–	±	+
Depressed anterior fontanel	–	+	+
Mental status	Alert	Irritable	Lethargic
Sunken eyeballs	–	+	+
Hyperpnea	–	±	+
Hypotension (orthostatic)	–	±	+
Increased pulse	–	+	+
Capillary refill	<2 sec	>2 sec	>2 sec
Laboratory			
Urine			
Volume	Small	Oliguria	Oliguria or anuria
Specific gravity*	≥1.020†	≥1.030	≥1.035
Blood			
BUN	WNL†	Elevated	Very high
pH (arterial)	7.40-7.30	7.30-7.10	>7.10

From Barkin RM, Rosen P: Emergency Pediatrics, 5th ed. St Louis, Mosby, 1999.
BUN, blood urea nitrogen; *WNL,* within normal limits.
*Specific gravity can provide evidence that confirms the physical assessment.
†Not usually indicated in mild or moderate dehydration.
+, present; –, absent; ± variable.

Complications

The complications of acute diarrheal illness are reflected primarily in abnormalities of fluid, electrolytes, and acid-base status and in the systemic involvement from the infection. Systemic involvement (depending on the cause of the acute diarrheal illness) may include bacteremia, osteomyelitis, polyarthritis, and HUS. Hypoglycemia and metabolic acidosis are common in younger children

www.ketabpezeshki.com 66485457-66963820

yet are manifested with nonspecific signs and symptoms. To inexperienced eyes, children may appear to compensate well, only to sometimes undergo rapid decompensation. With severe illness or illness superimposed on underlying chronic conditions, children may arrive at the ED in extremis. Children may present with weakness, lethargy, respiratory distress, shock, anuria, cardiac dysrhythmia, seizure, or coma. It is vital to recognize early signs of shock, such as persistent tachycardia, hyperpnea, irritability, and lethargy, and to restore intravascular volume before decompensation.

Diagnostic Strategies

Children who present with mild disease often require no diagnostic testing. In children assessed to have significant dehydration from acute diarrhea with or without vomiting, serum electrolyte levels and glucose concentration should be assessed. The usefulness of laboratory testing to estimate hydration status has been evaluated in multiple studies. In general, these studies concluded that laboratory tests are helpful only when results are markedly abnormal, and none alone is considered definitive for dehydration.[45-48]

Although stool culture is not indicated in most cases of uncomplicated acute gastroenteritis, stool samples should be obtained for culture if specific therapy, hospitalization, or infection control measures may be indicated. Stool cultures should also be considered in patients with systemic involvement or underlying chronic medical complications or if the illness involves dysenteric (stool with mucus, blood, or both) features. In many hospital laboratories, a routine stool culture does not include testing for *E. coli* O157:H7.[49] However, according to the CDC in 2009, all stools submitted for testing from patients with acute community-acquired diarrhea (i.e., for detection of the enteric pathogens *Salmonella, Shigella,* and *Campylobacter*) should be cultured for O157 on selective and differential agar. These stools should also be simultaneously assayed for non-O157 STEC with a test that detects the Shiga toxins or the genes encoding these toxins.[50] Therefore, for patients with suspected *E. coli* O157 infection (dysentery, diarrhea with tenesmus), one should specify to the laboratory as this culture is not routinely performed.

In immunosuppressed patients and infants younger than 3 months or children with possible bacteremia, a complete blood count, stool studies, and blood and other cultures are indicated. The stool studies of primary utility in the ED evaluation are microscopic analysis for leukocytes and occult blood to differentiate dysentery from acute gastroenteritis. Testing for fecal leukocytes is a useful initial test because it may support a diagnosis of invasive disease. This test should be considered in a febrile child with diarrhea and in a child with mucus or blood in the stool. If the test result is negative for fecal leukocytes, stool culture may not be necessary. However, if the test result is positive, stool culture is indicated. The presence of fecal leukocytes (more than five per high-power field), blood, or both indicates that the offending organism has crossed the mucosal barrier and that the risk of invasiveness has increased. Many children with acute diarrhea caused by *Salmonella* or *Shigella* organisms will have fecal leukocytes in the stool. Fecal leukocytes are also found in patients with *Campylobacter* organisms, *Y. enterocolitica,* invasive *E. coli,* and *V. parahaemolyticus*. Other studies, such as stool electrolytes, fecal fat, culture, ova, and parasites, are of greater interest and may be of help in follow-up management by the child's primary care physician.

Stool culture, enzyme-linked immunoassay for rotavirus, and other tests are indicated in patients who have not responded in the expected manner or in whom the illness is of prolonged duration (more than 2 weeks) or has dysenteric features. Additional studies also are indicated if it is necessary to identify a cause for a community outbreak. Urinalysis can provide an indication of hydration, urinary tract infection, hepatitis, and potential renal injury.

Differential Considerations

Vomiting in children is a common sign with an exhaustive list of causes. In addition to other usual causes of nausea, children may vomit in response to pain, anxiety, or fear. Some general and life-threatening causes of vomiting are presented in Table 173-1. Diarrhea also is a common reason for parents to bring their children to the ED. Most often, diarrhea is associated with other features of acute gastroenteritis, but it may be the sole presenting complaint. Table 173-2 presents a brief list of causes of diarrhea in children. An important point is that although most children with diarrhea or vomiting, or both, have a relatively benign cause of their illness, other, more sinister diagnoses should be considered and ruled out. This can often be done by careful history and physical examination.

There are some surgical diagnoses to consider in the child with diarrhea, vomiting, abdominal pain, or some combination. Appendicitis is the most common surgical condition in children and adolescents. The signs and symptoms are notoriously variable. The presence of vomiting and diarrhea does not necessarily rule out the diagnosis of appendicitis, especially when the child has abdominal pain. Intussusception is another diagnosis to consider in a young child with vomiting and abdominal pain, with or without bloody stool. The passage of currant jelly stool is often a late sign. Bilious vomiting in a child should raise concern for intestinal obstruction, such as from midgut volvulus. Enterocolitis can be the presenting manifestation as well as a subsequent serious complication of Hirschsprung's disease. HUS is a rare but potentially fatal complication of enterocolitis caused by *E. coli* O157:H7 and *Shigella*.

Management

See also the next section on dehydration.

In addition to resuscitation of children in shock, the priorities in ED management of children with diarrhea are to consider and to rule out other potential causes of diarrhea other than infectious diarrhea; to assess for and treat underlying deficits and potential complications; to determine which patients require prolonged treatment or hospitalization; and, when necessary, to arrive at a microbiologic diagnosis. Table 173-4 lists the common infectious agents of diarrhea and the indicated treatment.

Antibiotics are not needed in viral gastroenteritis or in most cases of uncomplicated bacterial gastroenteritis. Cases that may require antimicrobial therapy are those with increased potential to develop complications. This population includes those with septicemia, immunosuppression, or chronic diseases; premature babies (<1 year), neonates, and young infants; and those with articular or valve prostheses. Antibiotics are also recommended for *Giardia, Cryptosporidium,* and amebic dysentery. The child with bloody diarrhea is at higher risk for complications, including sepsis and other systemic diseases; therefore, the threshold for admission of such children to the hospital for close observation is lower. Stool cultures are indicated in the setting of acute bloody diarrhea and are helpful to guide therapy. In the majority of cases, empirical antimicrobial agents should not be administered while culture results are awaited because antimicrobial therapy might not be indicated even when culture results are positive.[51]

Antidiarrheal compounds that impair gastrointestinal motility, such as loperamide (Imodium), diphenoxylate, and atropine (Lomotil), have no role in the treatment of acute infectious diarrhea in young children. They have been shown to prolong and to

www.ketabpezeshki.com 66485457-66963820

exacerbate disease. They also have been shown to cause lethargy, paralytic ileus, toxic megacolon, central nervous system depression, coma, and even death.

There is evidence to support the use of probiotics, especially *Lactobacillus* GG (LGG), in acute infectious diarrhea in otherwise healthy infants and young children. In a randomized, double-blind, placebo-controlled trial by Szymanski and colleauges,[52] administration of LGG significantly shortened the duration of rotavirus diarrhea by a mean of 40 hours, but the duration of diarrhea of other causes was not affected. Results of other studies and a Cochrane review have indicated that probiotics reduce the number of diarrheal stools and the duration of diarrhea by approximately 1 day. These studies also reported that LGG is the most effective at doses greater than 10^{10} colony-forming units. It also appears that probiotics are more effective if they are given early in the course of the disease.[52-56] Used alongside rehydration therapy, probiotics appear to be safe and have clear beneficial effects in shortening the duration of and reducing stool frequency in acute infectious diarrhea. However, studies do not agree on the type of probiotic or dosing at this time.

Zinc deficiency is common in developing countries and occurs in most parts of Latin America, Africa, the Middle East, and south Asia. During the past 10 to 15 years, studies have shown that zinc supplementation given to children living in developing countries has decreased the duration and severity of diarrhea illness. The majority of zinc trials were conducted in countries at high risk for zinc deficiency, but those conducted at medium risk showed similar effect on duration and severity. On the basis of these findings, the World Health Organization endorses zinc supplementation for children with acute diarrhea (<6 months 10 mg/day, >6 months 20 mg/day for 10 to 14 days),[57] despite the lack of data from studies in developed countries. Currently, Children's Hospital in Boston is recruiting patients for a study on the effects of oral zinc in children with acute diarrhea in the United States.

Disposition

Most cases of childhood diarrhea can be managed on an outpatient basis by continuing routine formula or diet specific for age. Supplemental maintenance electrolyte solutions may be given. If home oral rehydration therapy is ordered, feeding should resume with an age-appropriate diet as soon as vomiting subsides. Routine fasting for diarrhea illnesses is not recommended. Before discharge from the ED, careful and specific instruction about the signs and symptoms of expected improvement or complications should be given to the parents or caregiver (Box 173-2). Instructions should address proper hygiene and handwashing techniques to prevent others from contracting the illness. Monitoring of handwashing in daycare facilities has been shown to reduce bacterial contamination in children. Follow-up by the patient's primary care physician should be timely and should address concerns of worsening of the condition and complications that may have developed. Hospitalization should be considered in children at high risk for complications: children younger than 1 year, very-low-birth-weight infants, children with chronic medical problems, children with electrolyte abnormalities who require intravenous repletion, children with severe dehydration, and children with dysentery. Hospitalization may also be warranted in cases of protracted vomiting, diarrhea with losses in excess of fluid administration, worsening clinical status despite therapy, presence of an underlying condition that would complicate therapy, or suspected systemic involvement. Very-low-birth-weight infants, because of low physiologic reserve and immature immune system, are at the highest risk for complications of acute gastroenteritis in the first year of life.

Box 173-2 Parent Instruction Sheet for Children with Vomiting and Diarrhea

Give clear liquids, as much as the child wants.
- Children younger than 2 years should be given a maintenance electrolyte solution, such as Pedialyte or Infalyte.
- Children older than 2 years may be given other clear fluids, such as decarbonated sodas, Gatorade, or clear soups.

If your child is vomiting, give clear liquids (as above) in small frequent volumes initially and advancing to normal volumes for the child's age as tolerated. It may be necessary to use teaspoons, cups, syringes, or ladles to administer the small volume. Fluid can be administered beginning 5 to 10 minutes after an episode of vomiting and should be continued despite the persistence of vomiting.

The child's diet may be advanced as soon as the vomiting has stopped and the child can tolerate fluids without vomiting. It is reasonable to wait 2 hours after the last episode of vomiting to resume feeding.
- Formula- or breast-feeding infants should be given their regular formula or returned to the breast.
- Older children should be given bland, starch-containing foods, protein, and vegetables in small quantities first and advancing to larger quantities and more complex items as the child's appetite returns.

The child may return to a regular diet as soon as the appetite returns and foods are desired.

Many foods may worsen diarrhea; pectin-containing foods, such as applesauce and other fruits and fruit juices, and foods high in fat and sugar are not recommended until the diarrhea resolves.

If cow's milk appears to cause the diarrhea to increase, reduce the amount of cow's milk products in the diet until the diarrhea has lessened significantly.

Call your child's physician or return to the emergency department if any of the following occurs:
- The diarrhea or vomiting worsens in frequency or amount.
- The vomiting lasts for more than 24 hours.
- The stool or vomitus contains blood or the vomit becomes persistently green.
- The child has decreased urine output (not as many wet diapers), does not produce tears when crying, or becomes less active or difficult to arouse.

DEHYDRATION

Clinical Features

Dehydration, or decrease in total body water, can be caused by a variety of mechanisms. Broadly speaking, however, mechanisms of dehydration represent three general categories: *decreased intake,* such as with stomatitis; *increased output,* such as with diarrhea and diabetes; and *increased insensible losses,* such as with fever. The severity of dehydration usually is measured as the acute weight (presumably fluid) loss as a percentage of pre-illness total body weight. Dehydration of more than 5% is considered significant and often can be identified by history and physical examination (see Table 173-5). Because pre-illness weights generally are not available or reliably reported, the clinician will need to rely on historical information, physical examination findings, and laboratory test results in assessing the severity of dehydration. Parental reports of history and observation are of significant value, with good sensitivity in detecting dehydration.[58] In a child who is dehydrated, initial physical examination may reveal an activity level lower than expected for age. The child may appear weak or lethargic. If the fontanel is still open, it may be sunken. The eyes appear sunken and the mucous membranes are dry (if the child has recently had something to drink, the mucous membranes may falsely appear moist). Tachycardia and hyperpnea may be present.

www.ketabpezeshki.com 66485457-66963820

Table 173-6 Types of Dehydration Reflected by Serum Sodium Concentration

PHYSICAL SIGN	DEHYDRATION TYPE BY SERUM SODIUM LEVEL		
	Isotonic: 130-150 mEq/L	Hypotonic: <130 mEq/L	Hypertonic >150 mEq/L
Skin			
Turgor	Poor	Very poor	Fair
Feel	Dry	Clammy	Thick, doughy
Mucous membranes	Dry	Dry	Parched
Sunken eyeballs	++	+	++
Depressed anterior fontanel	++	+	++
Mental status	Lethargic	Coma, seizure	Irritable, seizure
Increased pulse rate	++++	++	++
Decreased blood pressure	++++	+++	++

From Barkin RM, Rosen P: Emergency Pediatrics, 5th ed. St Louis, Mosby, 1999.
+, ++, +++, relative prominence of finding.

Table 173-7 Differential Diagnosis of Volume Depletion

FLUID LOSS CATEGORY	POTENTIAL ETIOLOGIC DISORDERS OR CONDITIONS
Renal	Diuretics, renal tubular acidosis, renal failure, urinary tract obstruction, diabetes insipidus, diabetes mellitus, hypothyroidism, adrenal insufficiency, renal trauma, salt-wasting nephritis
Extrarenal	Third spacing (pancreatitis, peritonitis, sepsis), skin loss (burns, cystic fibrosis), lung loss, congestive heart failure, liver failure, hemorrhage

Box 173-3 Principles of Appropriate Treatment of Children with Diarrhea and Dehydration

Oral rehydration solutions should be used for rehydration.
Oral rehydration should be performed as rapidly as possible.
Unrestricted diet is recommended as soon as dehydration is corrected.
For breast-fed infants, nursing should be continued.
For formula-fed infants, diluted formula is not recommended. Special formula is not necessary.
Additional oral rehydration solution should be administered for ongoing diarrheal losses.

Modified from King CK, et al: Managing acute gastroenteritis among children: Oral rehydration, maintenance, and nutritional therapy. MMWR Recomm Rep 52:1, 2003.

The skin over the trunk should be examined for tenting (suggesting hyponatremia) or a doughy texture (suggesting hypernatremia). It is important to keep in mind that clinical signs and symptoms of dehydration are variable and often subtle. The three most useful signs to determine dehydration of more than 5% are prolonged capillary refill time, abnormal skin turgor, and abnormal respiratory pattern.[45]

Laboratory tests may be helpful in assessing children for etiology, severity, and complications of dehydration. A serum electrolyte panel and BUN, serum creatinine, and blood glucose determinations are the tests most commonly ordered.[59] Sodium concentration is important in identifying isonatremic, hyponatremic, and hypernatremic states for appropriate choice of therapy (Table 173-6). A low serum HCO_3^- level may indicate loss of HCO_3^- in the stool or may reflect poor tissue perfusion. Newer noninvasive techniques for detection of dehydration have been described, such as ultrasound assessment of inferior vena cava diameter[60] and measurement of exhaled carbon dioxide as a marker for acidosis.[61] Children with dysentery should have BUN and serum creatinine concentrations measured and stool culture specimens sent and examined for *E. coli* O157:H7 to identify potential cases of HUS. Serum glucose level is important because hypoglycemia is common in young children with viral gastroenteritis, and this test may help identify children with previously undiagnosed fatty acid oxidation disorders or other inborn errors of metabolism.

Differential Considerations

Most commonly, dehydration in children results from diarrhea and vomiting caused by infectious gastroenteritis. Table 173-7 lists some other causes of dehydration that should be considered when the gastrointestinal tract is not primarily involved.

Fluid and Electrolyte Management

Oral Rehydration Therapy

Oral rehydration therapy (ORT) is a safe and effective treatment of infants and children with mild to moderate dehydration.[62-65] ORT may be instituted even if the patient continues to vomit or has diarrhea. Children with severe dehydration, shock, lethargy, acute abdomen, suspected intestinal obstruction, sodium derangement, or significant underlying illness should be identified by means of a thorough history and physical examination and laboratory tests and be excluded from ORT. Some of these principles are illustrated in Box 173-3.

The ORT period in the ED may span 4 to 8 hours and provide an opportunity to educate the family in skills of evaluating and treating childhood diarrhea. A number of ORSs have been shown to be effective. The main ingredients are water, glucose, sodium chloride, and bicarbonate in various concentrations (Table 173-8). In most situations, rehydration can be accomplished without the risk of causing hyponatremia or hypernatremia.

In infants and children with minimal dehydration, treatment should be directed at maintaining hydration and nutrition with an age-appropriate diet. Fluid intake should be increased, or ORS can be administered to cover maintenance and to replace losses. Losses can be replaced at 10 mL/kg for each stool and 2 mL/kg for each emesis. Diet should not be restricted.[62]

Children with mild to moderate dehydration should have their estimated fluid deficit replaced. The volume of ORS is calculated in the following manner:

1. Estimate the degree of volume depletion as mild or moderate with information from the history, clinical signs, and physical examination findings (see Table 173-1).
2. Calculate the desired volume of ORS as 30 to 50 mL/kg for mild (3-5%) and 60 to 80 mL/kg for moderate (6-9%) volume depletion.
3. Administer 25% of the volume of ORS to be replaced each hour for the first 4 hours.
4. Continue to replace ongoing losses as described above.
5. Monitor progress hourly and re-evaluate frequently.

This technique requires that the ED have the facilities and personnel to observe and to monitor the patient for an extended time

www.ketabpezeshki.com 66485457-66963820

Table 173-8 Common Oral Hydrating Solutions

SOLUTION	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	HCO_3^-/CITRATE (mEq/L)	GLUCOSE* (g/dL)	mOsm/L
Rehydration						
Rehydralyte	75	20	65	30	2.5	270
WHO solution	90	20	80	10	2.0	310
Maintenance						
Lytren	50	25	45	30	2.0	
Pedialyte	45	20	35	30	2.5	270
Infalyte	50	25	45	34	1.9	200
Clear Liquids						
Gatorade	20	3			2.1	
Cola	3	0.1-0.9		7-13	10.0	
Ginger ale	4	0.2			9.0	

From Barkin RM, Rosen P: Emergency Pediatrics, 5th ed. St Louis, Mosby, 1999.
*May be long-chain oligosaccharide subject to hydrolysis.

to determine the success or failure of ORT. The parent or other caregiver can be taught to administer ORT. Nursing personnel also should instruct the parent in observation skills, methods of administration of the fluid, and types of fluid that are considered appropriate for children with vomiting and diarrhea. During the monitoring period, a child who is unable to tolerate intake of the prescribed volume of fluid at the expected rate should receive intravenous fluids. It is important to determine whether the failure is the result of the child's inability to ingest the fluid, excessive fluid loss through vomiting or diarrhea, or poor technique or motivation on the parent's part. It usually is possible to maintain the fluid administration rate in children who continue to vomit by administering small volumes frequently. This may require, for instance, use of a spoon or syringe to slowly drip the fluid by hand. Some success has been obtained with the use of nasogastric tubes.[66]

The patient is reassessed at the end of the first few hours. If the clinical examination indicates adequate volume repletion, the child may be discharged home with further specific instructions for parents about maintenance fluid requirements with ORS. If, on the other hand, the child still exhibits mild or moderate volume depletion on clinical examination but no deterioration in status has occurred, the child is reevaluated as if from the beginning, and another 2- to 4-hour trial is attempted. If the child is unable to ingest the appropriate volume to keep up with ongoing losses or if volume repletion is not achieved at the end of 8 hours, intravenous therapy and admission should be initiated.

In the last several years, ondansetron has become a useful adjunct in the treatment of acute gastroenteritis in the pediatric ED. Ondansetron, a selective 5-hydroxytryptamine type 3 receptor antagonist, acts at chemoreceptors in the peripheral and central nervous system to alleviate nausea, which has been shown in numerous well-designed studies in children to reduce episodes of vomiting in the pediatric ED, to reduce the need for intravenous fluid rehydration, and to improve oral intake in the pediatric ED.[67-71]

Intravenous Therapy

Some dehydrated children brought to the ED may not qualify for ORT, and others may fail to improve with ORT. These patients include those with shock, severe dehydration, increasing deficit or clinical deterioration during ORT, intractable vomiting, hypoglycemia, or electrolyte derangements.

Patients are evaluated in accordance with their immediate (emergency phase, phase I), short-term (repletion phase, phase II), and long-term (early refeeding phase, phase III) needs.[72] During the *emergency* phase, the aim of fluid resuscitation is to restore circulatory volume. This fluid needs to be administered rapidly to prevent imminent serious morbidity or death. During the *repletion* phase, fluid and electrolyte derangements are reversed, and ongoing losses are replaced. This phase lasts 24 hours. In the *early refeeding* phase, long-term needs are addressed in the next few days, during which the body recovers fluid, electrolyte, and nutritional homeostasis. Immediate and short-term therapies are initiated in the ED, with subsequent phases carried out in the inpatient setting or at home as managed by the primary care physician. In clinical practice, this algorithm represents a continuum of care and not three distinct, separate phases. Monitoring of serum electrolyte, BUN, and blood glucose concentrations is indicated for patients receiving intravenous fluid therapy.

Emergency Resuscitation Phase.[72] Rapid reexpansion of the intravascular space is the goal of immediate resuscitation and can be achieved with an isotonic crystalloid solution. Administration of 20 mL/kg of 0.9% saline (or other appropriate isotonic crystalloid solution) intravenously at a rapid rate should result in reversal of signs of shock within 5 to 15 minutes. In critical situations, intraosseous routes should be used if venous access is not immediately available. Subcutaneous administration may be considered in resource-limited areas of the world as an alternative for rehydration when oral rehydration is not successful. Patients should be reevaluated periodically, and those with excessive deficits should receive repeated boluses of 20 mL/kg until clinical improvement occurs. Signs of recovery include normalization of blood pressure measurements, improvement of mental status, improvement of tachycardia and capillary refill time, and production of urine. Volume requirements greater than 60 mL/kg without signs of improvement warrant investigation for other conditions, such as septic shock, hemorrhage, capillary leak with third-space fluid sequestration, congestive heart failure, and toxic shock.

A rapid determination of serum glucose is important. Children require glucose as an energy substrate and often have marginal stores available in illnesses. If the serum glucose concentration is low (<50 mg/dL), dextrose 0.25 to 0.5 g/kg should be rapidly administered intravenously or intraosseously. For neonates, a D10 solution is used, and approximately 4 mL/kg is given. For children 1 month of age to approximately 8 years or 25 kg, 2 mL/kg of D25

www.ketabpezeshki.com 66485457-66963820

is given. In children older than 2 years, 1 mL/kg of D50 can be used. Glucose levels should be monitored (every 30 to 60 minutes until stable) to ensure improvement and to identify ongoing needs. Repeated episodes of hypoglycemia should raise concern for sepsis, fatty acid oxidation defects, and other inborn errors of metabolism.

Repletion Phase.[72] After immediate resuscitation, appropriate fluid therapy for the patient should be determined. Some patients may return to ORT after initial resuscitation. Calculations should take into account the fluids already administered and maintenance fluid (Table 173-9), and they should also accommodate changes in the patient's clinical status. To allow accurate planning of the type and amount of fluid to be administered, volume replacement should proceed from the serum sodium level: hypernatremia (>150 mEq/L), hyponatremia (<130 mEq/L), or isonatremia (130-150 mEq/L).

Isonatremic Volume Depletion.[72] Isonatremic volume depletion is the most common form of volume depletion and results from relatively equal losses of sodium and water. No change in body fluid tonicity or redistribution of fluid between the extracellular and intracellular fluid spaces occurs. This results in loss of fluid from the extracellular space and therefore intravascular volume depletion. Gastrointestinal fluid loss with or without decreased intake or increased urine loss is the most common cause. Repletion fluids are outlined for a sample patient in Box 173-4. In general, with use of 5% dextrose in 0.45% sodium chloride, half of the deficit fluids is given during the first 8 hours of repletion along with maintenance fluids. Potassium may be added to maintenance fluids once urine output is established and serum potassium levels are within a normal range. Continued losses (emesis, diarrhea) should also be replaced.

Table 173-9 Maintenance Fluid and Electrolytes

BODY WEIGHT	WATER mL/kg/day	WATER mL/kg/hr	ELECTROLYTES mEq/100 mL H_2O
First 10 kg	100	4	Na^+ 3
Second 10 kg	50	2	Cl^- 2
Each additional kg	20	1	K^+ 2

Modified from Custer JW, Rau RE (eds): The Harriet Lane Handbook: A Manual for Pediatric House Officers, 18th ed. Philadelphia, Mosby–Year Book, 2009.

Box 173-4 Sample Calculation of Fluid and Electrolyte Requirements in a Patient with Isonatremic Volume Depletion

Isonatremic Volume Depletion: Management of Moderate to Severe Deficits

Initial Findings

Pre-illness weight: 10 kg (a 1-year-old)
Degree of volume depletion: moderate (10%)
Body weight on admission: 9 kg
Electrolytes: Na^+ 135 mEq/L, K^+ 5 mEq/L, Cl^- 115 mEq/L, HCO_3^- 12 mEq/L

Summary of Fluid Requirements

	H_2O (mL)	Na^+ (mEq)	K^+ (mEq)
Maintenance	1000 (100 mL/kg)	30 (3 mEq/kg)	20 (2 mEq/kg)
Deficit (100 mL/kg)*			
ECF (60%)	600	84 (140 mEq × 0.6)	
ICF (40%)	400		30 (150 mEq × 0.4 × 50% correction)
TOTAL	1000 mL	84 mEq	30 mEq
Resuscitation fluids	200 mL	28 mEq	
Net deficit	800 mL	56 mEq	30 mEq

Na^+ extracellular fluid (ECF) concentration = 140 mEq/L.
K^+ intracellular fluid (ICF) concentration = 150 mEq/L.

Fluid Schedule

Phase	Calculation	Fluids Administered
I (0-½ hr)	20 mL/kg	200 mL 0.9% NS or LR during 20-30 minutes
II (½-9 hr)	½ net deficit: 400 mL D_5W with 28 mEq NaCl and 15 mEq KCl ⅓ maintenance: 333 mL D_5W with 10 mEq NaCl and 7 mEq KCl TOTAL: 733 mL with 38 mEq NaCl and 22 mEq KCl	733 mL (~90 mL/hr) of D_5W/0.45% NS with 22 mEq KCl (~30 mEq/L) (this approximation facilitates care)
III (9-25 hr)	½ deficit ⅔ maintenance	1067 mL (~67 mL/hr) of D_5W/0.45% NS with 28 mEq KCl (~26 mEq/L) (this approximation facilitates care)

Notes

1. Fluid resuscitation is crucial during phase I. If initial response is poor, additional infusions are warranted. In general, the initial emergency fluid bolus should be included as part of the deficit replacement.
2. Blood glucose concentration should be assessed early, especially in children with prolonged vomiting, diarrhea, or inadequate intake. Early glucose infusion may be warranted.
3. In the face of acidosis, serum potassium concentration does not reflect total body deficit.
4. Adjust for fever (add 10% for each 1° C above 37° C), stool loss (5 mL/kg), or vomiting (volume for volume).

Modified from Barkin RM, Rosen P (eds): Emergency Pediatrics, 5th ed. St Louis, Mosby, 1999; and Custer JW, Rau RE (eds): The Harriet Lane Handbook: A Manual for Pediatric House Officers, 18th ed. Philadelphia, Mosby–Year Book, 2009.
*Deficit = % dehydration × weight (kg) × 1000 mL/kg.
D_5W, 5% dextrose in water; *NS,* normal saline; *LR,* lactated Ringer's solution.

www.ketabpezeshki.com 66485457-66963820

Box 173-5 Sample Calculation of Fluid and Electrolyte Requirements in a Patient with Hyponatremic Volume Depletion

Hypotonic Volume Depletion: Management of Moderate to Severe Deficits

Initial Findings

Pre-illness weight: 10 kg (a 1-year-old)
Degree of volume depletion: moderate (10%)
Body weight on admission: 9 kg
Electrolytes: Na^+ 110 mEq/L, K^+ 5 mEq/L, Cl^- 90 mEq/L, HCO_3^- 12 mEq/L

Summary of Fluid Requirements

	H_2O (mL)	Na^+ (mEq)	K^+ (mEq)
Maintenance	1000 (100 mL/kg)	30 (3 mEq/kg)	20 (2 mEq/kg)
Deficit (100 mL/kg)			
ECF (60%)	600	84 (140 mEq × 0.6)	
ICF (40%)	400		30 (150 mEq × 0.4 × 50% correction)
Sodium deficit*		125	
TOTAL	1000 mL	209 mEq	30 mEq
Resuscitation fluids	200 mL	28 mEq	
Net deficit	800 mL	181 mEq	30 mEq

Fluid Schedule

	Fluids	
Phase	**Calculation**	**Administered**
I (0-½ hr)	20 mL/kg	200 mL 0.9% NS or LR during 20-30 minutes
II (½- 9 hr)	½ net deficit: 400 mL D_5W with 90 mEq NaCl and 15 mEq KCl ⅓ maintenance: 333 mL D_5W with 10 mEq NaCl and 7 mEq KCl TOTAL: 733 mL with 100 mEq NaCl and 22 mEq KCl	733 mL (~90 mL/hr) of D_5W/0.9% NS with 22 mEq KCl (~30 mEq/L) (this approximation facilitates care)
III (9-25 hr)	½ deficit ⅔ maintenance	1067 mL (~67 mL/hr) of D_5W/0.9% NS with 28 mEq KCl (~26 mEq/L) (this approximation facilitates care)

*Sodium Deficit Calculation

A. Na^+ required to correct to 135 mEq/L = 135 mEq/L – 110 mEq/L (observed Na^+) = 25 mEq/L
B. Total body water (TBW) (L/kg) = 0.6 L/kg (pre-illness TBW) – 0.1 L/kg (water loss) = 0.5 L/kg
C. Pre-illness weight = 10 kg
Sodium deficit = A × B × C = 25 mEq/L × 0.5 L/kg × 10 kg = 125 mEq

Notes

1. Fluid resuscitation is crucial during phase I. If initial response is poor, additional infusions are warranted. In general, the initial emergency fluid bolus should be included as part of the deficit replacement.
2. In the face of severe hyponatremia with decreased total body water in symptomatic patients, hypertonic 3% saline must be given to raise the serum sodium level to 125 mEq/L. A 3% saline solution contains approximately 0.5 mEq/mL of Na^+. Patients may be given 3% saline 4 mL/kg intravenously during 10 minutes and the response monitored. Once seizures have stopped, half of the deficit may be corrected during the next 8 hours as outlined in the fluid schedule.
3. If excess water load is the cause, furosemide (Lasix) 1 mg/kg/dose intravenously may be used. During the subsequent diuresis, urinary sodium, potassium, and chloride should be measured and replaced milliequivalent for milliequivalent with 3% saline and supplemental potassium chloride.
4. Blood glucose concentration should be assessed early, especially in children with prolonged vomiting, diarrhea, or inadequate intake. Early glucose infusion may be warranted.
5. In the face of acidosis, serum potassium concentration does not reflect total body deficit.
6. Adjust for fever (add 10% for each 1° C above 37° C), stool loss (5 mL/kg), or vomiting (volume for volume).

Modified from Barkin RM, Rosen P (eds): Emergency Pediatrics, 5th ed. St Louis, Mosby, 1999; and Custer JW, Rau RE (eds): The Harriet Lane Handbook: A Manual for Pediatric House Officers, 18th ed. Philadelphia, Mosby–Year Book, 2009.
D_5W, 5% dextrose in water; *ECF,* extracellular fluid; *ICF,* intracellular fluid; *NS,* normal saline; *LR,* lactated Ringer's solution.

Note that the sample patient is mildly acidemic ($HCO_3^- >$ 12 mEq/L) and that restoration of intravascular volume results in improved tissue perfusion and correction of the metabolic acidosis. These calculations account for water and electrolyte requirements (maintenance and deficit) and demonstrate that use of a standard fluid preparation (0.9%, 0.45%, or 0.2% saline) permits close approximation of calculated requirements and facilitates treatment by relying on readily stocked supplies.

Hyponatremic Volume Depletion.[72] Hyponatremic volume depletion is a result of loss of relatively more sodium than water, resulting in extracellular water shift into the intracellular fluid space to maintain equal osmolarity. This results in a significant decrease in intravascular volume and hemodynamic compromise. This type of volume depletion usually is caused by gastrointestinal fluid loss that has been replaced with hypotonic fluid. Specific signs and symptoms of hyponatremia are largely neurologic, ranging in severity from malaise and irritability to seizures and coma.

Appropriate management of hyponatremic dehydration for a sample patient is described in Box 173-5. If the serum sodium concentration is 120 to 130 mEq/L, 5% dextrose in 0.9% saline is administered, with half of the daily fluid requirement given in the first 8 hours and the remainder during the succeeding 16 hours. Monitoring of serum electrolyte values, BUN level, weight, and intake and output is recommended. Rapid correction of hyponatremia can be associated with central pontine myelinolysis. Close

www.ketabpezeshki.com 66485457-66963820

monitoring of serum sodium concentration is indicated, and the amount of sodium in the fluid is adjusted to maintain a slow correction. The target rate of rise of sodium is 2 to 4 mEq/L every 4 hours or 10 to 20 mEq/L in 24 hours.[72] Potassium chloride, 20 mEq/L, is added to the intravenous fluids after renal function is assessed and urine output has been established. If the serum sodium concentration is less than 120 mEq/dL, the patient may exhibit seizures, hyperexcitability, or other neurologic symptoms. In such cases, 3% saline (sodium chloride 0.5 mEq/mL) should be administered as a bolus dose of 4 mL/kg. This dose will raise the serum sodium concentration by 3 to 4 mEq/L.

Hyponatremic dehydration should be differentiated from another common cause of hyponatremia, the syndrome of inappropriate antidiuretic hormone secretion (SIADH). In this syndrome, caused by a variety of conditions, the kidneys inappropriately excrete sodium and retain water, resulting in low serum sodium and high urinary sodium concentrations. Initial treatment is with fluid restriction.

Hypernatremic Volume Depletion.[72] Hypernatremic volume depletion (serum sodium level >150 mEq/L) arises with loss of relatively more water than sodium. It can occur if inappropriate types of fluids are given, if the fluid or formula is mixed incorrectly, or if fever or hyperventilation complicates the illness. This is the least common type of volume depletion because of a generally lower content of sodium in most modern infant fluids and formulas. Intracellular water shifts to the extracellular fluid space to maintain osmolar balance; therefore, intravascular volume is relatively preserved. Signs and symptoms specific to hypernatremia are doughy skin and altered central nervous system function (manifested as irritability, seizures, or high-pitched cry). Care should be taken not to administer hypotonic fluid at too fast a rate because water will equilibrate across the cerebral blood-brain barrier almost immediately (long before the sodium concentration is corrected), creating increased intracranial pressure. The most important goal is to reestablish intravascular volume and return serum sodium levels toward normal gradually (48-72 hours). After adequate volume expansion, rehydration fluids should be initiated with 5% dextrose in 0.2% to 0.45% sodium chloride at a slow rate during 48 to 72 hours. Serum sodium levels should be assessed every 4 hours. The goal is to reduce the serum sodium level at a rate of 0.5 to 1 mEq/L per hour.[73] If the sodium level has decreased by less than 0.5 mEq/L per hour, sodium content of the rehydration fluid is decreased. This will allow a slow controlled correction of the hypernatremia. Box 173-6 provides guidelines for the calculation of fluids and electrolytes for a sample case. Close monitoring of neurologic status and serum electrolyte levels is important during the period of rehydration. It is imperative to remember to replace ongoing losses.

Hospital-Acquired Hyponatremia. One of the complications that can develop during intravenous rehydration in children is acute hyponatremia. In children, this rare disturbance can lead to significant neurologic morbidity, including seizures, coma, and brain herniation or even death. For acute hyponatremia to occur, two conditions have to be met: (1) an exogenous source of free water must be available, and (2) secretion of antidiuretic hormone must occur. Many experts therefore recommend use of isotonic saline rather than hypotonic saline as the replacement intravenous fluid of choice in hospitalized children.[74,75] This practice is not universally accepted.[76] In any case, vigilance in monitoring of the neurologic status of children undergoing intravenous rehydration is essential.

Box 173-6 Hypertonic Dehydration

A 2-week-old infant presents to the emergency department with a history of 1 day of poor breast milk intake. Weight yesterday at a well-baby visit was 4 kg; today the child weighs 3.4 kg. Laboratory study findings include serum Na^+ 155 mEq/L, K^+ 4.5 mEq/L, and HCO_3^- 13 mEq/L.

Maintenance Therapy

100 mL/day for first 10 kg = 400 mL
Na^+ requirements = 3 mEq/kg × 4 kg = 12 mEq
K^+ requirements = 2 mEq/kg × 4 kg = 8 mEq

Total Fluid Deficit: 4.0 – 3.4 = 0.6 L

Free water deficits = observed Na^+ – ideal Na^+ (145 mEq/L) × 4 mL/kg × wt (kg) = (155 – 145) × 4 mL/kg × 4 kg = 160 mL

Na^+ Deficit

The illness is less than 3 days in duration. Therefore, the fluid lost is 75% from the ECF and 25% of the ICF. The primary sodium reservoir is the ECF.

$$\begin{aligned} Na^+ \text{ loss} &= (\text{ECF } Na^+ \text{ concentration}) \\ &\quad \times (75\% \text{ of solute fluid deficit*}) \\ &= (140\ \text{mEq/L}) \times (0.75 \times 0.440\ \text{L}) \\ &= 46\ \text{mEq} \end{aligned}$$

NOTE: Solute containing deficit:
Total fluid deficit – free water deficit = 600 mL – 160 mL = 440 mL

K^+ Deficit (Primary Potassium Reservoir is ICF)

$$\begin{aligned} K^+ \text{ loss} &= (\text{ICF } K^+ \text{ concentration}) \\ &\quad \times (25\% \text{ of solute fluid deficit}) \\ &= (150\ \text{mEq/L}) \times (0.25) \times 0.440\ \text{L} \\ &= 16\ \text{mEq} \end{aligned}$$

48-Hour Requirements = Maintenance + Deficits

Total deficits:
Fluid (mL) = (400 × 2) mL + 160 mL (free) + 440 mL (solute) = 1400 mL
Sodium (mEq) = 24 + 46 = 70 mEq
Potassium (mEq) = 16 + 16 = 32 mEq

Fluid Schedule

The fluid is administered in a stepwise fashion during 48 hours. Half of the deficit is given in the first 24 hours; then the remainder is given during the next 24 hours.

First Day Fluids = Maintenance + ½ Deficits

First day fluids = (400 mL + 12 mEq Na^+ + 8 mEq K^+) + ½(600 mL + 46 mEq Na^+ + 16 mEq K^+)
First day fluids = 700 mL D_5W + 35 mEq Na^+ + 16 mEq K^+

In practice (and after the calculations are done), the usual fluid that is required to rehydrate the child with hypertonic dehydration is either D_5W/0.2% NS or D_5W/0.45% NS because it would appear that the *rate* rather than the type of fluid is most important. The volume of free water needed to lower a serum sodium concentration above 145 mEq/L is approximately 4 mL/kg of free water for each 1 mEq/L during 48 hours. Studies demonstrate that D_5W, D_5W/0.2% NS, and D_5W/0.45% NS are acceptable if the fluid is infused at a conservative rate, correcting deficits during 48 hours.

Modified from Barkin R, et al: Pediatric Emergency Medicine, 2nd ed. St Louis, Mosby, 1997.
D_5W, 5% dextrose in water; *ECF*, extracellular fluid; *ICF*, intracellular fluid; *NS*, normal saline.
*Calculated as (600 mL fluid deficit – 160 mL free water deficit).

www.ketabpezeshki.com 66485457-66963820

KEY CONCEPTS

Identification of Pathogen

- Stool studies are not indicated in most uncomplicated cases of acute gastroenteritis. Exceptions are those cases in which specific treatment, specific prophylaxis, or health precautions are required or in which the patient has systemic involvement or underlying medical complications or the illness involves dysenteric features.

Fecal Leukocytes

- Testing for fecal leukocytes is a useful initial test because it may support a diagnosis of invasive disease. This test should be considered in a febrile child with diarrhea and in a child with mucus or blood in the stool. If the test result is negative, stool culture may not be necessary. If the test result is positive, stool culture is indicated. The presence of fecal leukocytes (more than five per high-power field), blood, or both indicates that the offending organism has crossed the mucosal barrier and that the risk of invasiveness has increased. Nearly 90% of patients with acute diarrhea caused by *Salmonella* or *Shigella* organisms will have fecal leukocytes in the stool.

Oral Rehydration

- Most patients with mild to moderate dehydration can be treated with ORT. With ORT, resumption of feeding with age-appropriate diet should begin as soon as vomiting subsides. Routine fasting with infectious diarrhea is not recommended.

Dehydration Assessment

- The degree of volume depletion is estimated by information from the history, clinical signs, and physical examination findings. The desired volume of oral rehydration solution (ORS) is calculated as 30 to 50 mL/kg for mild and 60 to 80 mL/kg for moderate volume depletion; then 25% of the volume of ORS is to be replaced every hour (100% during 4 hours).

Severe Dehydration

- In severe dehydration, 20 mL/kg of 0.9% saline (or other appropriate isotonic crystalloid solution) given intravenously at a rapid rate should result in reversal of signs of shock within 5 to 15 minutes. Repeated boluses of 20 mL/kg are indicated until clinical improvement occurs, but volume requirements greater than 60 mL/kg without signs of improvement suggest other conditions, such as septic shock, hemorrhage, capillary leak with third-space fluid sequestration, and heart failure.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Kosek M, Bern C, Guerrant RL: The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. *Bull World Health Organ* 2003; 81:197.
2. Black R, et al: Global, regional, and national causes of child mortality in 2008: A systematic analysis. *Lancet* 2010; 375:1969.
3. Glass RI, Lew JF, Gangarosa RE, LeBaron CW, Ho MS: Estimates of morbidity and mortality rates for diarrheal disease in American children. *J Pediatr* 1991; 118:527.
4. Fischer TK, et al: Hospitalization and deaths from diarrhea and rotavirus among children <5 years of age in the United States, 1993 through 2003. *J Infect Dis* 2007; 195:1117.
5. Maleck MA, et al: Diarrhea- and rotavirus-associated hospitalizations among children less than 5 years of age: United States 1997 through 2000. *Pediatrics* 2006; 117:1187.
6. Widdowson MA, et al: Cost-effectiveness and potential impact of rotavirus vaccination in the United States. *Pediatrics* 2007; 119:684.
7. Lee BP, et al: Nonmedical costs associated with rotavirus disease requiring hospitalization. *Pediatr Infect Dis J* 2005; 24:984.
8. Klein EJ, et al: Diarrhea etiology in a Children's Hospital Emergency Department: A prospective cohort study. *Clin Infect Dis* 2006; 43:807.
9. Lyman WH, et al: Prospective study of etiologic agents of acute gastroenteritis outbreaks in childcare centers. *J Pediatr* 2009; 154:253.
10. Vernacchio L, et al: Diarrhea in American infants and young children in community setting—incidence, clinical presentation, and microbiology. *Pediatr Infect Dis J* 2006; 25:2.
11. Denno DM, et al: Etiology of diarrhea in pediatric outpatient settings. *Pediatr Infect Dis J* 2005; 24:142.
12. Widdowson MA, Bresee JS, Gentsch JR, Glass RI: Rotavirus disease and its prevention. *Curr Opin Gastroenterol* 2005; 21:26.
13. American Academy of Pediatrics: *Rotavirus infections*. In: Pickering LK, ed: *Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009:576-579.
14. Dennehy PH: Rotavirus vaccines: An update. *Curr Opin Pediatr* 2005; 17:88.
15. Cortese MM, Parashar UD: Prevention of rotavirus gastroenteritis among infants and children: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2009; 58:1.
16. Centers for Disease Control and Prevention: Prevention of rotavirus gastroenteritis among infants and children. Recommendation of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2009; 58:1.
17. Patel MM, et al: Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. *N Engl J Med* 2011; 364:2283.
18. Patel MM, et al: Systematic literature review of role of norovirus in sporadic gastroenteritis. *Emerg Infect Dis* 2008; 14:1224.
19. Glass RI, Parashar UD, Estes MK: Norovirus gastroenteritis. *N Engl J Med* 2009; 361:1776.
20. American Academy of Pediatrics: *Human calicivirus infections (norovirus and sapovirus)*. In: Pickering LK, ed: *Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009:241-242.
21. American Academy of Pediatrics: *Astrovirus infections*. In: Pickering LK, ed: *Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009:225.
22. American Academy of Pediatrics: *Adenovirus infections*. In: Pickering LK, ed: *Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009; 204-206.
23. American Academy of Pediatrics: *Salmonella infections*. In: Pickering LK, ed: *Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009:584-589.
24. Centers for Disease Control and Prevention: *National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS): Human Isolates Final Report, 2009*. Atlanta, Ga: U.S. Department of Health and Human Services, CDC; 2010.
25. American Academy of Pediatrics: *Shigella infections*. In: Pickering LK, ed: *Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009:593.
26. Centers for Disease Control and Prevention: Vital signs: Incidence and trends of infection with pathogens transmitted commonly through food—Foodborne Diseases Active Surveillance Network, 10 U.S. sites, 1996-2010. *MMWR Morb Mortal Wkly Rep* 2011; 60:749.
27. American Academy of Pediatrics: *Campylobacter infections*. In: Pickering LK, ed: *Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009:243-245.
28. Perdikogianni C, et al: *Yersinia enterocolitica* infection mimicking surgical conditions. *Pediatr Surg Int* 2006; 22:589.
29. American Academy of Pediatrics: *Yersinia enterocolitica and Yersinia pseudotuberculosis infections*. In: Pickering LK, ed: *Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009:733-735.
30. American Academy of Pediatrics: *Clostridium difficile*. In: Pickering LK, ed: *Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009:263-265.
31. American Academy of Pediatrics: *Clostridium perfringens food poisoning*. In: Pickering LK, ed: *Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009:265-266.
32. American Academy of Pediatrics: *Staphylococcal food poisoning*. In: Pickering LK, ed: *Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009:600-601.
33. American Academy of Pediatrics: *Vibrio infections*. In: Pickering LK, ed: *Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009:727.
34. American Academy of Pediatrics: *Escherichia coli diarrhea*. In: Pickering LK, ed: *Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009:294.
35. Ochoa TJ, Cleary TG: Epidemiology and spectrum of disease of *Escherichia coli* O157. *Curr Opin Infect Dis* 2003; 16:259.
36. Nataro JP: *Escherichia coli*. In: Long S, Pickering LK, Prober CG, eds: *Principles and Practice of Pediatric Infectious Disease*, 3rd ed. Orlando, Fla: Churchill Livingstone; 2008.
37. Wong CS, et al: The risk of the hemolytic-uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. *N Engl J Med* 2000; 342:1930.
38. Schering J, Andreoli SP, Zimmerhackl LB: Treatment and outcome of Shiga-toxin–associated hemolytic uremic syndrome (HUS). *Pediatr Nephrol* 2008; 23:1749.
39. Safdar N, Said A, Gangnon R, Maki D: Risk of hemolytic uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 enteritis. *JAMA* 2002; 288:996.
40. Centers for Disease Control and Prevention: Cryptosporidiosis surveillance—United States, 2003-2005. *MMWR Surveil Summ* 2007; 56:1-10.
41. American Academy of Pediatrics: *Cryptosporidiosis*. In: Pickering LK, ed: *Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009:272.
42. Hlavsa MC, Watson JC, Beach MJ: Giardiasis surveillance—United States, 1998-2002. *MMWR Surveill Summ* 2005; 54:9-16.
43. American Academy of Pediatrics: *Giardia intestinalis infections (giardiasis)*. In: Pickering LK, ed: *Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009:303.
44. American Academy of Pediatrics: *Amebiasis*. In: Pickering LK, ed: *Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009:206.
45. Steiner MJ, DeWalt DA, Byerley JS: Is this child dehydrated? *JAMA* 2004; 291:2746.
46. Gorelick MH, Shaw KN, Murphy KO: Validity and reliability of clinical signs in the diagnosis of dehydration in children. *Pediatrics* 1997; 99:E6.
47. Duggan C, et al: How valid are the clinical signs of dehydration in infants? *J Pediatr Gastroenterol Nutr* 1996; 22:56.
48. Emond S: Dehydration in infants and young children. *Ann Emerg Med* 2009; 53:395.
49. Voetsch AC, et al: *Stool specimen practices in clinical laboratories, FoodNet sites, 1995-2000*. In: *International Conference on Emerging Infectious Diseases*. Atlanta, Ga: Centers for Disease Control and Prevention; 2002:94.
50. Gould LH, et al: Recommendations for diagnosis of Shiga toxin–producing *Escherichia coli* infections by clinical laboratories. *MMWR Recomm Rep* 2009; 58:1.
51. King CK, Glass R, Bresee JS, Duggan C; Centers for Disease Control and Prevention: Managing acute gastroenteritis among children: Oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep* 2003; 52:9.

www.ketabpezeshki.com 66485457-66963820

52. Szymaski H, et al: Treatment of acute infectious diarrhoea in infants and children with a mixture of three *Lactobacillus rhamnosus* strains: A randomized, double-blind, placebo-controlled trial. *Aliment Pharmacol Ther* 2006; 23:247-253.
53. Szajewska H, Mrukowicz JZ: Probiotics in the treatment and prevention of acute infectious diarrhea in infants and children: A systematic review of published randomized, double-blind, placebo-controlled trials. *J Pediatr Gastroenterol Nutr* 2001; 33(Suppl 2):S17-S25.
54. Van Niel CW, Feudtner C, Garrison MM, Christakis DA: *Lactobacillus* therapy for acute infectious diarrhea in children: A meta-analysis. *Pediatrics* 2002; 109:678.
55. Huang JS, Bousvaros A, Lee JW, Diaz A, Davidson EJ: Efficacy of probiotic use in acute diarrhea in children: A meta-analysis. *Dig Dis Sci* 2002; 47:2625.
56. Allen SJ, Okoko B, Martinez E, Gregorio G, Dans LF: Probiotics for treating infectious diarrhoea. *Cochrane Database Syst Rev* 2010; 11:CD003048.
57. WHO/UNICEF Joint Statement: *Clinical Management of Acute Diarrhoea*. Geneva: The United Nations Children's Fund/World Health Organization; 2004.
58. Porter SC, Fleisher GR, Kohane IS, Mandl KD: The value of parental report for diagnosis and management of dehydration in the emergency department. *Ann Emerg Med* 2003; 41:196.
59. Wathen JE, MacKenzie T, Bothner JP: Usefulness of the serum electrolyte panel in the management of pediatric dehydration treated with intravenously administered fluids. *Pediatrics* 2004; 114:1227.
60. Chen L, Kim Y, Santucci KA: Use of ultrasound measurement of the inferior vena cava diameter as an objective tool in the assessment of children with clinical dehydration. *Acad Emerg Med* 2007; 14:841.
61. Nagler J, Wright R, Krauss B: End-tidal carbon dioxide as a measure of acidosis among children with gastroenteritis. *Pediatrics* 2006; 118:260.
62. King CK, et al: Managing acute gastroenteritis among children: Oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep* 2003; 52:1.
63. Fonseca BK, Holdgate A, Craig JC: Enteral vs intravenous rehydration therapy for children with gastroenteritis: A meta-analysis of randomized controlled trials. *Arch Pediatr Adolesc Med* 2004; 158:483.
64. Hartling L, et al: Oral versus intravenous rehydration for treating dehydration due to gastroenteritis in children. *Cochrane Database Syst Rev* 2006; 3:CD004390.
65. Spandorfer PR, Alessandrini EA, Joffe MD, Localio R, Shaw KN: Oral versus intravenous rehydration of moderately dehydrated children: A randomized, controlled trial. *Pediatrics* 2005; 115:295.
66. Nager AL, Wang VJ: Comparison of nasogastric and intravenous methods of rehydration in pediatric patients with acute dehydrations. *Pediatrics* 2002; 109:566.
67. Freedman SB, Adler M, Seshadri R, Powell EC: Oral ondansetron for gastroenteritis in a pediatric emergency department. *N Engl J Med* 2006; 354:1698.
68. Ramsook C, Sahagun-Carreon I, Kozinetz CA, Moro-Sutherland D: A randomized clinical trial comparing oral ondansetron with placebo in children with vomiting from acute gastroenteritis. *Ann Emerg Med* 2002; 39:397.
69. Alhashimi D, Al-Hashimi H, Fedorowicz Z: Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents. *Cochrane Database Syst Rev* 2009; 2:CD005506.
70. Roslund G, Hepps TS, McQuillen KK: The role of oral ondansetron in children with vomiting as a result of acute gastritis/gastroenteritis who have failed oral rehydration therapy: A randomized controlled trial. *Ann Emerg Med* 2008; 52:22.
71. Stork CM, Brown KM, Reilly TH, Secreti L, Brown LH: Emergency department treatment of viral gastritis using intravenous ondansetron or dexamethasone in children. *Acad Emerg Med* 2006; 13:1027.
72. Custer JW, Rau RE, eds: *The Harriet Lane Handbook: A Manual for Pediatric House Officers*, 18th ed. Philadelphia: Mosby–Year Book; 2009.
73. Androgue HJ, Madias NE: Hypernatremia. *N Engl J Med* 2000; 342:1493.
74. Hoorn EJ, et al: Acute hyponatremia related to intravenous fluid administration in hospitalized children: An observational study. *Pediatrics* 2004; 113:1279.
75. Moritz ML, Ayus JC: Prevention of hospital-acquired hyponatremia: A case for using isotonic saline. *Pediatrics* 2003; 111:227.
76. Holliday MA, et al: Acute hospital-induced hyponatremia in children: A physiologic approach. *J Pediatr* 2004; 145:584.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 174

Genitourinary and Renal Tract Disorders

Maureen McCollough and Ghazala Q. Sharieff

PERSPECTIVE

This chapter discusses some of the more common causes of scrotal, testicular, and penile pain in children that precipitate a visit to the emergency department (ED). Also discussed are other renal or genitourinary tract disorders in this age group for which emergent treatment may be sought, including acute renal failure, urinary tract infections, and hypertension.

SPECIFIC DISORDERS

Penile Disorders

Priapism

Principles of Disease. Priapism is the engorgement of the dorsal corpora cavernosa, resulting in dorsal penile erection and ventral penile flaccidity. The more common low-flow priapism is secondary to decreased venous outflow and is characterized by prolonged painful erection. Sickle cell disease and leukemia are responsible for the majority of cases in children. Immunosuppressive disorders, anticoagulation, and intracavernosal injection of agents such as papaverine, phentolamine, and prostaglandin E_1 also can result in priapism. Other drugs, such as phenothiazines, sedative-hypnotics, selective serotonin reuptake inhibitors, antihypertensives, anticoagulants, and drugs of abuse (e.g., cocaine, alcohol, marijuana), may be causal. Priapism complications include penile fibrosis, urinary retention, and impotence.

High-flow priapism usually is painless and typically is associated with penile arterial laceration and excessive inflow of arterial blood or spinal trauma resulting in corporal engorgement. With prolonged engorgement of the corpora cavernosa, the resultant stagnation and hypoxia of the blood lead to the development of thrombosis and ischemia.

Clinical Features. Priapism is a clinical diagnosis and can be distinguished from other causes of erection by careful history and complete physical examination. The history should include past medical history with attention to previous treatment of anemia, leukemia, sickle cell disease, or drug abuse and current history of trauma or symptoms of immunosuppressive disease. Although priapism is a clinical diagnosis, laboratory studies may assist in isolation of the cause of the condition. A complete blood count (CBC), urinalysis, and coagulation studies may be useful in some cases. Diagnostic studies of penile blood flow may be indicated in cases for which the cause is unclear. Studies that the urologist may request include magnetic resonance imaging, color Doppler cavernosography, and technetium Tc-99m penile scanning. Angiography is helpful in localization of the arterial bleeding site in high-flow priapism.

Differential Considerations. The differential diagnosis for priapism in children differs from that in adults. In adults, penile erection from sexual arousal, urethral foreign bodies, Peyronie's disease, spinal cord injury, and penile implants may occur, but these etiologic factors are rare in children. Anticoagulation, drugs of abuse, medications, trauma (including spinal trauma), Kawasaki disease, leukemia, and sickle cell disease are associated with priapism in children.

Management and Disposition. Management centers on hydration, pain control, relief of urinary obstruction, and treatment of any other underlying conditions. Local anesthesia by a dorsal nerve block with 1% lidocaine without epinephrine may be beneficial. In patients with sickle cell disease, treatment with oxygen, hydration at 1.5 times maintenance volume, and analgesics should be initiated. Low-flow priapism may respond to sitz baths or hot compresses because the heat increases blood flow, thereby potentially relieving the obstruction. Oral terbutaline (adult dose 5-10 mg, followed by another 5-10 mg 15 minutes later) produces resolution in about one third of patients. If no resolution occurs within 30 minutes of treatment, aspiration and irrigation therapy is required.

Cavernosal aspiration plus irrigation has been effective in patients with low-flow priapism. This procedure should be performed within the first few hours of symptom onset and rarely is beneficial after 48 hours. Vasoactive substances such as phentolamine and phenylephrine may be used for irrigation therapy; however, these are best administered with urologic consultation. Parenteral vasodilators, such as methylene blue, hydralazine, and terbutaline, also have been tried with variable success, and therefore the treating urologist can help ascertain the best treatment approach.[1-4]

Exchange transfusion for patients with priapism and sickle cell disease previously has been recommended; however, this treatment may not offer any advantage over conventional therapy and has been associated with serious neurologic sequelae, as in the so-called ASPEN syndrome (*a*ssociation of *s*ickle cell disease, *p*riapism, *e*xchange transfusion, and *n*eurologic events).[2,3] Patients with leukemia may respond with detumescence after chemotherapy is begun.

High-flow priapism can be effectively addressed by arterial embolization. Studies have shown success with the use of autologous blood clot embolization.[4]

If nonsurgical approaches are unsuccessful, referral to a urologist for a corpus cavernosum–glans shunt procedure may be necessary. Ultrasound-guided compression of the perineal arteriocavernous fistula has been successful.[5] Interventions should be initiated within 12 hours of symptom onset to avoid long-term dysfunction and irreversible infarction.[6] Patients with persistent priapism or underlying disorders, such as leukemia or sickle cell

www.ketabpezeshki.com 66485457-66963820

disease, may require hospitalization. Pediatric urologic consultation should be arranged as soon as possible. If the priapism has been treated successfully, the patient may be discharged home after some period of observation with urologic specialist follow-up.

Phimosis

Principles of Disease. Phimosis is a pathologic condition of the uncircumcised penis in which constriction of the foreskin prevents retraction of the prepuce from the glans. It can result in pain, hematuria, glans ischemia, infarction, and urinary outlet obstruction. Most cases are physiologic, representing normal development, and do not require intervention. Only 4% of newborn boys have a fully retractable foreskin. This percentage increases with age: 25% of 6-month-old, 50% of 1-year-old, 80% of 2-year-old, and 90% of 4-year-old boys have fully retractable foreskins.[7] Phimosis also may result from trauma, infections, chemical irritation, poor hygiene, and congenital abnormality or be a complication of circumcision.

Clinical Features. Phimosis is a clinical diagnosis. History may reveal that the foreskin is unretractable, along with narrowing or diversion of the urinary stream and bulging out of the foreskin with urination. Pain and hematuria may be accompanying features.

Management and Disposition. Because the ability to retract the foreskin fully is age related, parents should be advised not to retract the prepuce forcefully. Gentle retraction with good hygiene should be stressed. If signs of urinary outlet obstruction are present, dilation of the prepuce or the urethral meatus or both can be performed by gentle use of forceps. With vascular compromise of the glans, a dorsal split procedure, circumcision, preputial plasty, or balloon dilation may be necessary.[8,9] Topical steroid treatment (with betamethasone valerate 0.6% cream) for 6 weeks has been 87% effective in reducing inflammation and treating phimosis.[10-12] In patients with severe stenosis, obstructive uropathy can result. In such rare cases, blood urea nitrogen (BUN) and serum creatinine levels should be obtained, and a renal ultrasound examination should be performed if signs of obstructive renal failure are present. Patients who are able to urinate and have no evidence of severe infection or ischemia can be discharged from the ED with outpatient urologic follow-up.

Figure 174-1. Paraphimosis in a 4-year-old uncircumcised boy. (Courtesy Marianne Gausche-Hill, MD.)

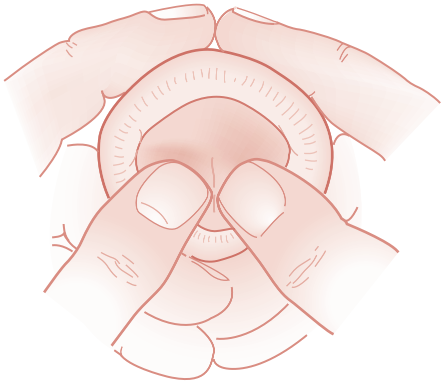


Figure 174-2. Paraphimosis reduction. (Courtesy P. P. Kelalis.)

Paraphimosis

Principles of Disease. Paraphimosis is another pathologic condition of the uncircumcised penis in which the proximal foreskin cannot be returned to its anatomic position covering the glans penis, resulting in distal venous congestion with the potential for dire consequences. Paraphimosis can be caused by infection, masturbation, trauma, or hair or clothing tourniquets. Iatrogenic causes include failure to reduce the foreskin after a medical examination. Paraphimosis constitutes a true urologic emergency and can result in arterial compression, penile necrosis, and gangrene.

Clinical Features. The patient typically is anxious, and the history often reveals that the parents or the patient retracted the foreskin and then could not replace the foreskin over the glans (Fig. 174-1). The history should include verification that the patient is uncircumcised because hair tourniquet syndrome in a circumcised patient may mimic paraphimosis. Physical examination reveals a flaccid proximal penis with erythema and engorgement distal to the obstruction. The foreskin is retracted, and cellulitis may be present. The diagnosis of paraphimosis is based on clinical findings, but if a penile foreign body is a concern, radiographs can be obtained after relief of the vascular occlusion.

Management and Disposition. Pain can be controlled either parenterally or by a local dorsal penile nerve block. Procedural sedation also may be necessary. Placement of a finger of a rubber glove filled with ice water over the glans and foreskin can reduce the edema. Circumferential compression of the penis starting at the glans also can reduce the edema. Compression may need to be held for several minutes to achieve adequate reduction of edema. Manual reduction may be necessary, with application of gentle, steady pressure on the glans with both thumbs while the shaft is pulled straight (Fig. 174-2). Another method is to puncture the edematous foreskin with an 18- or 21-gauge needle.[13,14] The puncture may be followed by squeezing of the glans penis to further facilitate fluid drainage. Dorsal band traction has been performed in some cases with Adson forceps applied directly to the band formed by the retracted foreskin and application of traction and countertraction to loosen the constriction. If all such attempts fail, urologic consultation proceeding to circumcision or a dorsal slit procedure may be necessary. Patients can be discharged home after reduction if they are able to void spontaneously and urologic follow-up care can be arranged. Any evidence of cellulitis or necrosis warrants hospital admission, intravenous antibiotics, and urologic consultation.

Balanoposthitis

Principles of Disease. Balanoposthitis, an inflammation that involves the glans and the foreskin, occurs in up to 6% of

www.ketabpezeshki.com 66485457-66963820

Figure 174-3. Balanoposthitis in an 8-month-old boy caused by candidal infection. (Courtesy Marianne Gausche-Hill, MD.)

uncircumcised males.[15] Balanitis involves the glans penis only. The primary cause of balanoposthitis is infection; however, chemical irritation, trauma, fixed drug rash, and contact dermatitis also can be contributory. Infectious organisms are gram negative and gram positive, including group A beta-hemolytic streptococci and rarely *Neisseria gonorrhoeae* and *Chlamydia*.[16] Recurrent episodes of *Candida albicans* balanoposthitis should raise suspicion for diabetes mellitus.

Clinical Features. Physical examination reveals penile erythema, edema, and possibly a discharge (Fig. 174-3). Systemic symptoms and signs such as fever, vomiting, and diarrhea are unusual. Diagnosis is clinical and treatment is based on clinical findings; however, if symptoms are severe, the offending organism can be identified by culture of any discharge.

Management and Disposition. Management includes emphasis on adequate hygiene with sitz baths to reduce inflammation. Painful micturition can be addressed by having the child urinate while in a bath of warm water. In patients with cellulitis, antibiotic treatment with agents effective against *Staphylococcus aureus* and *Streptococcus pyogenes* is recommended. Seven days of a first-generation cephalosporin is an appropriate regimen. If group A beta-hemolytic streptococci are identified, a streptococcus-specific antibiotic is required.[17] Severe inflammation may be treated with 0.5% hydrocortisone cream applied sparingly to the area. Candidal infections should be treated topically with antifungals. A blood glucose determination should be considered in patients presenting with recurrent candidal balanoposthitis. Patients with a toxic appearance or those who exhibit evidence of cellulitis or constricting phimosis with uropathy should be hospitalized for appropriate management. Circumcision may be required for patients with recurrent disease.

Complications of Circumcision

Principles of Disease. Although there remains societal controversy about circumcision, it is usually advocated for prevention of phimosis, paraphimosis, recurrent balanoposthitis, urinary tract infections, and penile cancer. Any of three techniques can be used: application of a Plastibell or Gomco clamp, excision, or dorsal slit procedure. The choice of procedure depends on the preference of the operator. The most common complication of these procedures is hemorrhage, which usually is minor and can be controlled by direct pressure, silver nitrate application, or suture placement. Significant bleeding may be a sign of a blood dyscrasia. Localized, systemic, or urinary tract infection also can occur.

Management and Disposition. Postoperative pain usually resolves within 12 to 24 hours. Occlusive dressings can contribute to urinary retention and edema and should be removed. Stenosis of the now exposed urethral meatus may result from prolonged exposure to the ammonia in urine. Application of a Plastibell that is too small also can lead to meatal stenosis in 8 to 31% of cases.[18] Signs and symptoms include pain with urination, bloody discharge resulting from an inflamed meatus, high-velocity stream, and the need to sit while voiding. Postcircumcision phimosis may result if excess foreskin remains. If the constriction is severe and urinary outlet obstruction occurs, dilation of the stenosis can be performed with a hemostat. Surgical revision usually is necessary.[19]

Skin bridges are small fibrotic bands that attach the glans to the penile shaft and may form after circumcision. Inclusion cysts result from smegma retained in the wound or from epidermis involution along the circumcision site. Skin bridges and inclusion cysts are treated by surgical resection. These complications may be prevented by proper hygiene and application of an antimicrobial ointment to the circumcision site for 7 to 10 days after the procedure.

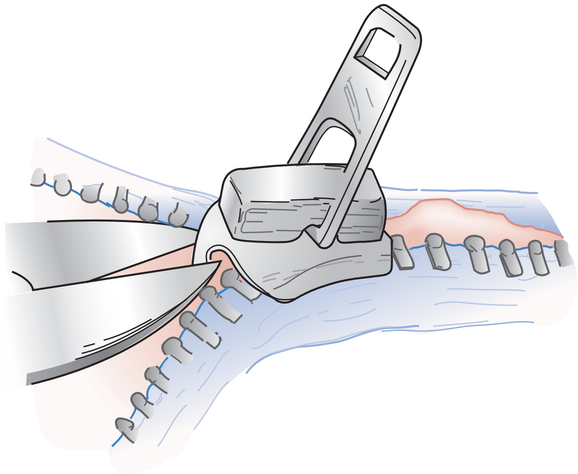


Figure 174-4. Release of zipper entrapment by cutting of the median bar. (From Snyder HM 3rd, et al: Genitourinary trauma. In Fleisher GR, Ludwig S [eds]: Textbook of Pediatric Emergency Medicine, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2000.)

Penile Entrapment and Tourniquet Injuries

Penile rings, string, wire, and human hair tourniquets can result in penile venous and arterial occlusion. The patient presents with swelling of the glans, wherein the offending agent may be difficult to visualize because of edema of the coronal sulcus. In addition to the vascular supply, the dorsal penile nerve supply can be occluded. The foreign body can be cut with small surgical scissors. Hair tourniquets have also been successfully removed with Nair. Once the foreign body is removed, urethral obstruction can be evaluated by means of retrograde urethrography, and Doppler ultrasonography can be performed to assess penile arterial blood flow. Once it is identified, the constriction is relieved, and the patient should not be discharged until spontaneous voiding is ensured. Urologic consultation may be necessary emergently if penile arterial flow is disrupted and the constricting object cannot be removed rapidly or signs of necrosis are present.

Zipper entrapment of the foreskin also can occur in children, typically those between 2 and 6 years of age. The zipper can be removed with bone or metal cutters or a mini-hacksaw to cut the median bar of the zipper[20,21] (Fig. 174-4). The zipper falls apart, and the foreskin is freed. Although local anesthesia is not necessary, the patient may be anxious and require sedation before its

www.ketabpezeshki.com 66485457-66963820

Figure 174-5. Epididymitis in a 5-year-old boy; note mild swelling and erythema on the left. (Courtesy Marianne Gausche-Hill, MD.)

removal. Success has been reported with soaking of the penis in mineral oil before zipper removal.[22] Additional methods to release the foreskin under the zipper mechanism include cutting of the zipper below the entrapment and pulling the two halves of the zipper apart; cutting of the zipper teeth above and below the entrapment and, with pliers, squeezing the median bar to allow more room to disengage the trapped prepuce; and insertion of a flat screwdriver between the faceplates of the zipper mechanism to pry open the faceplates and allow the prepuce to be released.[23-25] Parents should be instructed to encourage their children to wear underwear to decrease the risk of entrapment.

Scrotal Masses and Swelling

Epididymitis

Principles of Disease. Epididymitis is inflammation of the epididymis, which is located along the posterior aspect of the testicle. The most common cause is infectious, and the etiology varies by age. Adolescents should be evaluated for possible sexually transmitted diseases, such as *N. gonorrhoeae* and *Chlamydia trachomatis*. Patients may have a history of previous urinary tract infections, anatomic abnormalities, or previous genitourinary instrumentation. Urinary tract infections leading to epididymitis typically are caused by viruses or bacterial agents, such as *Escherichia coli, Klebsiella pneumoniae, Proteus,* or *Pseudomonas aeruginosa*.

Clinical Features. Patients present with a painful, edematous scrotum and tenderness at the epididymis (Fig. 174-5). A urethral discharge may be present, particularly when the condition is secondary to a sexually transmitted disease. Systemic signs and symptoms, such as nausea, vomiting, fever, and lower abdominal, scrotal, or testicular pain, also may be present. Infants and young children may present with fever without other symptoms. Accordingly, in the ED evaluation of all children with fever or other systemic symptoms or signs, a complete examination should include a genitourinary examination.

As the edema increases, obliteration of the sulcus between the testis and epididymis occurs, making differentiation from testicular torsion extremely difficult. Relief of pain with scrotal elevation (Prehn's sign) is unreliable.

Diagnostic Strategies. Urinalysis and urine culture should be part of the ED evaluation for all infants and children younger than 2 years. In children 2 years of age or older, urine culture may be performed only if the urinalysis results indicate urinary tract infection. Lack of pyuria does not rule out epididymitis because up to 50% of patients may have normal results on such studies. CBC may show leukocytosis, although this finding is nonspecific. Any urethral discharge should be cultured and sent for Gram's stain and tests for *N. gonorrhoeae* and *C. trachomatis*. Color Doppler ultrasonography is not necessarily performed in all children with suspected epididymitis. However, if there is doubt about the diagnosis, it is the preferred diagnostic study because it does not require placement of an intravenous line and is more readily available at all hours of the day. If color flow Doppler ultrasonography or radionuclide scintigraphy is performed, it will reveal a normal testis and preserved or increased vascular flow toward the side of the inflamed epididymis.[26,27]

Management and Disposition. Scrotal elevation, placement of ice packs on the swollen area as tolerated, and nonsteroidal anti-inflammatory or narcotic medications are useful to control pain and inflammation. If urethral discharge is present, the adolescent patient should be treated presumptively for both *N. gonorrhoeae* and *C. trachomatis*. The treatment for sexually acquired epididymitis in children 9 years of age or older consists of ceftriaxone 250 mg intramuscularly, followed by doxycycline 100 mg orally twice a day or tetracycline 500 mg orally four times a day. A single 1-g dose of azithromycin may also be used to increase compliance. Patients younger than 9 years should be treated with erythromycin 50 mg/kg orally per day, divided four times a day. The course of treatment typically ranges from 7 to 14 days, depending on the antibiotic regimen. In children, non–sexually acquired epididymitis without evidence of urinary tract infection may be managed expectantly with analgesics for pain.[28] Infants with or without positive findings on urinalysis and young children with positive urinalysis findings may be treated with trimethoprim twice a day or cephalexin three times a day if a bacterial urinary tract infection is suspected. Other antibiotic options include oral erythromycin, clarithromycin, and azithromycin for patients who do not respond to other therapies because *Mycoplasma genitalium* and *Ureaplasma urealyticum* may cause a more chronic form of epididymitis. Infants and children with epididymitis may be discharged for follow-up by their primary care physician, and urine cultures should be checked to determine definitively if urinary tract infection is present. Patients with systemic symptoms and toxicity should be admitted for intravenous antibiotic therapy with either ceftriaxone or cefotaxime. Children need close urologic follow-up to rule out any contributing anatomic abnormalities and to ensure that the antibiotic chosen treats the infecting organism.

Orchitis

Orchitis is a result of a bacterial or viral testicular infection leading to diffuse edema, pain, and discoloration of the scrotum. The most common pathogen is paramyxovirus, which can be the causative agent in up to 38% of postpubertal males with mumps-associated orchitis. Other etiologic agents include *E. coli, K. pneumoniae, P. aeruginosa, Staphylococcus* or *Streptococcus* species, Epstein-Barr virus, Coxsackievirus, arbovirus, enterovirus, *Brucella,* granulomatous disease, and filariae.

During the course of mumps, orchitis usually develops after the first week and is manifested with tenderness and edema of the testis with discoloration of the scrotum. Bilateral cases are relatively rare, occurring in 2 to 5% of affected patients. If epididymitis coexists, a urethral discharge also may be present. Bacterial orchitis can result in scrotal abscess formation. Because orchitis typically is unilateral, fertility usually is maintained.

Doppler ultrasound imaging may be necessary to distinguish orchitis from testicular torsion. For patients with a clearly viral origin such as mumps, treatment is aimed at pain control (scrotal elevation, nonsteroidal anti-inflammatory agents, and possibly narcotics). When the diagnosis is unclear or when concurrent epididymitis is present, empirical treatment includes oral antibiotics with predominantly gram-negative organism coverage. Hospital admission is warranted for patients who have a toxic appearance or exhibit evidence of a scrotal or testicular abscess or in whom

www.ketabpezeshki.com 66485457-66963820

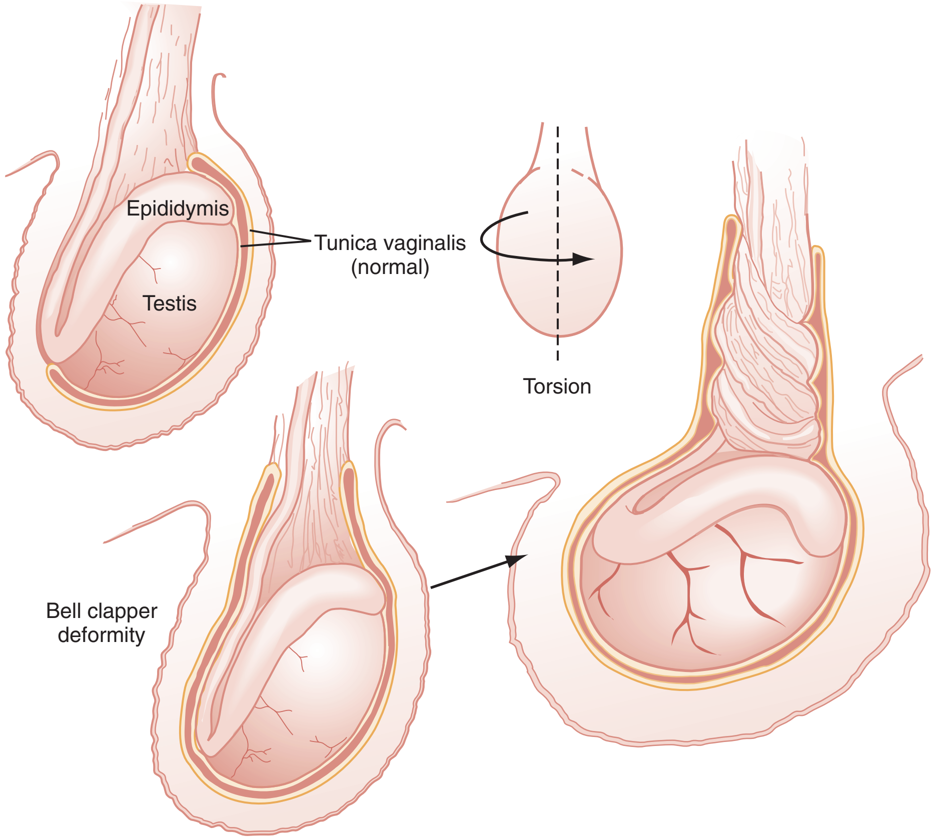


Figure 174-6. Anatomy of testicular torsion. (From Snyder HM 3rd, et al: Pain—scrotal. In Fleisher GR, Ludwig S [eds]: Textbook of Pediatric Emergency Medicine, 4th ed. Philadelphia, Lippincott Williams & Wilkins, 2000.)

outpatient management has failed. Urologic follow-up should be arranged.

Testicular Torsion

Principles of Disease. Torsion of the spermatic cord is a common cause of an acutely painful scrotum. Delay in diagnosis and treatment can result in loss of spermatogenesis and, in severe cases, necrotic, gangrenous testes. Testicular salvage rates are time dependent; the success rate is 96% if detorsion is performed less than 4 hours from symptom onset, decreasing to less than 10% if there is more than a 24-hour delay to treatment.[29] The overall incidence of testicular torsion is 1 in 4000, with a peak incidence at age 13 years. Testicular torsion has been reported in all age groups, from the developing fetus to the elderly, but is most common in adolescence.

The testis enters the scrotum through the inguinal canal after descent from the abdomen. The peritoneum invaginates through the canal and partially covers the testis and epididymis, forming the tunica vaginalis. Typically, the tunica vaginalis attaches to the posterior wall of the hemiscrotum and superior pole of the testis to achieve testicular fixation. If the tunica completely covers the testis and attaches higher up on the spermatic cord (bell clapper deformity), proper testicular fixation does not occur, and there is a predisposition to torsion (Fig. 174-6). In intravaginal torsion, the testicle may rotate within the tunica vaginalis, thereby constricting the arterial blood flow. Extravaginal torsion is seen most commonly in neonates who are premature and also can occur antenatally.

Clinical Features. Patients present with acute scrotal pain and swelling, an elevated testicle, and, typically, absence of the cremasteric reflex.[30] This reflex can be demonstrated by lightly stroking the skin of the inner thigh downward from the hip toward the knee. This causes the cremaster muscle on the ipsilateral side to contract rapidly and results in elevation of the testicle. Although in one series the cremasteric reflex was absent in 100% of patients with torsion and in only 14% of patients with epididymitis, the presence of the cremasteric reflex does not preclude testicular torsion. Abnormal epididymal and testicular position also may be noted, with left-sided torsions slightly more common than right. Nausea, vomiting, and a low-grade fever also may be seen. In the patient with an undescended testicle who presents with abdominal pain, torsion should be a consideration.[31]

Diagnostic Strategies. Unless an alternative diagnosis is absolutely secure (e.g., epididymitis), the patient should be evaluated for testicular torsion. Alternatively, with a relatively confident clinical diagnosis of torsion, diagnostic testing should not delay appropriate management. Results of a urinalysis are rarely helpful as pyuria can be seen in cases of testicular torsion and epididymitis. The widely preferred diagnostic study for the prospect of torsion is color flow Doppler ultrasonography. This technique has a sensitivity of 79 to 86%, with a specificity of almost 100%, for detection of testicular torsion. Scintigraphy has a sensitivity ranging from 79 to 100% and a specificity of 89 to 100%.[27,32,33] Magnetic resonance imaging has been evaluated as another diagnostic modality, with a sensitivity in one study of 93% and specificity of 100%.[34] In cases of indeterminate ultrasound findings, the urology consultant should be notified for disposition decisions; in addition, scintigraphy may be performed as resources allow. When clinical suspicion is strong, surgical exploration should not be delayed for diagnostic studies, especially in patients in whom duration of symptoms is less than 12 hours.

Management. If the patient presents within 12 hours of symptom onset, immediate surgical exploration is indicated,

www.ketabpezeshki.com 66485457-66963820

predicated on clinical findings or confirmatory clinical studies.[35] Detorsion of the affected testicle is performed, followed by an elective orchiopexy of the contralateral side to avoid recurrence. Approximately 40% of patients have a bell clapper deformity of the contralateral testicle. Manual detorsion also may be performed by rotation of the testicle in an "open book" fashion as viewed from below, from medial to lateral, until detorsion is complete.[36] Because the procedure is painful, sedation and pain relief should be considered before this intervention. Manual detorsion should be attempted only if there is a delay in getting a urologist to come in for operative detorsion and the patient has had continuous pain for less than 24 hours or if, in the judgment of the emergency physician, the time zone of opportunity to salvage the testis has not passed.

Torsion of the Testicular Appendage

The appendix testis is a remnant of the müllerian duct. The appendix testis is involved in 92% of the cases of testicular appendage torsion, and the appendix epididymis is involved in the remaining cases. The average age at occurrence is 10 years. Patients typically present with moderate pain of sudden onset that is localized to the involved hemiscrotum. The pathognomonic "blue dot" sign, a small area with a bluish hue less than 3 mm across located in the upper lateral portion of the hemiscrotum, is present in less than 25% of cases and represents the cyanotic appendage below the scrotal wall. If any doubt exists about the diagnosis, a nuclear radioisotope scan or color Doppler ultrasound study should be performed. Color Doppler ultrasonography reveals normal or increased flow to the affected testicle. Conservative therapy with analgesics and scrotal support are usually all that is indicated; the involved appendage undergoes autoamputation within 1 week, accompanied by resolution of symptoms.

Varicocele

A varicocele is a collection of venous varicosities of the spermatic veins in the scrotum caused by incomplete drainage of the pampiniform plexus. Incidence rates of 14 to 16% in adolescent males have been reported,[37] but varicoceles are rare in children younger than 10 years.[38] Left-sided varicoceles account for 85 to 95% of cases; however, bilateral varicoceles may be present in up to 22% of patients.[39] Intra-abdominal disease should be suspected in cases of right-sided varicocele because these usually are caused by inferior vena cava thrombosis or compression of this vessel by tumors.[40] The acute presentation of a left-sided varicocele should raise suspicion for renal cell carcinoma with obstruction of the left renal vein.

The dilated venous collection may be tender on physical examination. It can be palpated superior and posterior to the testis and usually is more pronounced with the patient in the upright position. Therefore, the patient should be examined in both the standing and supine positions. Patients in whom scrotal swelling persists in the supine position should be evaluated with a computed tomography (CT) scan of the abdomen, with oral and intravenous contrast administration for conditions obstructing the renal vein. Varicoceles have been described as a "bag of worms" both in appearance and on palpation. Surgical correction may be required if the patient becomes symptomatic or has bilateral varicoceles.[41]

Idiopathic Scrotal Edema

Idiopathic scrotal edema is painless erythema and induration of the scrotum; 77% of cases occur before the age of 10 years. Two thirds of cases are unilateral, and no specific causes have been identified. The condition is characterized by the development of painless erythema and induration of the scrotum, which may be pruritic. There is minimal tenderness on physical examination, but the edema and erythema may extend to the phallus, groin, and abdomen. Examination of the testes and epididymis reveals no palpable masses. Systemic signs and symptoms are rare. Patients can be discharged home with outpatient follow-up after an acute pathologic process has been ruled out. Most cases resolve spontaneously within a few days and do not require any specific treatment. Recurrence rates of up to 21% have been described.

Hydrocele

A hydrocele is a collection of fluid that accumulates in the tunica vaginalis. Communicating hydroceles result when the upper processus vaginalis fails to be obliterated, leaving an open tract between the peritoneum and the scrotum. The tract is closed in noncommunicating hydroceles. Most hydroceles are right sided. They may be present at birth, but they usually are painless and worsen with crying or exertion. Hydroceles often resolve spontaneously by the age of 18 months. Examination with transillumination reveals enlargement of the scrotum. Color flow Doppler ultrasonography or radionuclide scintigraphy may be necessary to determine the cause of the hydrocele and to exclude an acute pathologic process in patients with acute symptoms of pain; otherwise, asymptomatic patients can be discharged home with urologic follow-up. Patients with a hydrocele that has persisted for more than 1 year or who are older than 18 months should undergo ultrasonography to ensure that the hydrocele is not a reactive hydrocele caused by testicular tumor or inflammation.

Inguinal Hernia

Principles of Disease. Inguinal (direct and indirect) hernias are more common in males, with bimodal peaks before 1 year of age and then again after the age of 40 years. An indirect inguinal hernia occurs when the processus vaginalis is not obliterated in infancy and abdominal contents invaginate through this patent sac. Entrapment of mesentery, bowel, intraperitoneal organs, and the hernial sac can occur and is more common with small hernias. If the contents of the hernia can be returned to their anatomic position, the hernia is reducible; if the contents remain entrapped, it is incarcerated or irreducible. Hernias that remain incarcerated can undergo strangulation, with resultant necrosis of bowel or mesentery.

Clinical Features. Patients with incarcerated hernias may present with pain, edema extending to the scrotum, nausea, vomiting, and low-grade fever. Physical examination may reveal bowel sounds in the scrotal sac. If the inguinal mass can be palpated separately from the testes, it is possible to diagnose an inguinal hernia on clinical grounds alone. Rarely, the incarcerated and strangulated hernia can be manifested as a tense blue mass in the scrotum.

Management and Disposition. The patient should be placed in the Trendelenburg position with an ice pack applied to the groin to reduce swelling; sedation may be necessary before reduction. Slow, gentle pressure should be applied to reduce the hernia. If the pressure technique is not successful in reducing the hernia, the opposite technique can be tried: the hernia mass can be "pulled" to straighten out the entrapped contents, thereby allowing them to slip back into the abdomen.

If the hernia cannot be reduced or strangulation is suspected (as indicated by fever, overlying cellulitis, or signs of peritonitis), the patient should receive fluid resuscitation, broad-spectrum parenteral antibiotics, and an emergent surgical consultation.[42]

Patients who are found to have a hernia on routine examination or who have had the hernia reduced and are without symptoms suggestive of incarceration or strangulation should be referred for surgical repair.

www.ketabpezeshki.com 66485457-66963820

Carcinoma

Principles of Disease. Testicular and scrotal cancer represents approximately 1% of solid tumors in children. An increased incidence of testicular cancer, in both the undescended testicle and the contralateral descended testicle, has been noted in patients with cryptorchidism. Tumor types include teratomas, embryonal carcinomas, yolk sac tumors, choriocarcinomas, Leydig cell tumors, and Sertoli cell tumors. Lymphoma and leukemia can metastasize to the testicle as well.

Patients typically present with a painless unilateral mass palpated separately from the testis or may describe a feeling of fullness, tugging, or increased weight of the scrotum and testicular enlargement. A reactive hydrocele may be present in 7 to 25% of patients and can lead to a delay in diagnosis. Physical examination reveals a firm mass, smooth or nodular, that cannot be transilluminated. A complete physical examination looking for lymphadenopathy, petechiae, abdominal mass, hepatosplenomegaly, or gynecomastia should be performed.

Diagnostic Strategies. Diagnostic evaluation includes a CBC, urinalysis, urine human chorionic gonadotropin (produced by germ cell tumors) assay, and ultrasonography of the testis.

Management and Disposition. ED management includes prompt referral for urologic and oncologic consultation. Admission to the hospital to facilitate the evaluation may be necessary.

Urinary Tract Infections

Perspective

Sequelae of untreated urinary tract infections may include sepsis and renal scarring, and accurate and early diagnosis is important. At the same time, avoidance of unnecessary evaluation and treatment of children at lower risk for these infections is cost-effective and minimizes the chance for iatrogenic harm. Diagnosis of urinary tract infections in infants and young children can be challenging because the clinical signs often are nonspecific, and it can be difficult to obtain useful urine specimens.

Principles of Disease

The risk for development of urinary tract infections before the age of 12 years is approximately 3% for girls and 1% for boys. Neonatal boys are more susceptible than girls to urinary tract infections, but beyond that period, infections in females prevail. Girls younger than 2 years and uncircumcised boys younger than 6 to 12 months also are especially at risk.[43]

Approximately 5% of children younger than 2 years with a temperature above 39° C and presenting without a source for the fever have an occult urinary tract infection.[44] Urinary tract infections are also significant in the very young infant, with up to 9% prevalence in one study of febrile infants younger than 60 days.[45,46] Fever duration also appears to correlate with the prevalence of urinary tract infections. Two days of fever was more likely than one day to be associated with a urinary tract infection.[44] Other risk factors for female infants include white race, age younger than 12 months, temperature above 39° C, and no other identifiable source for the fever.[44] Risk factors for male infants include nonblack race, similar temperature, and no other identifiable source for the fever.[44] Moreover, up to 4% with a significant fever and an associated upper respiratory tract infection or acute otitis media also may have a urinary tract infection.[47] By comparison, the background prevalence of asymptomatic bacteriuria is estimated to be 1 to 2% in all children.[48]

On the basis of renal nuclear scans, it is estimated that 75% of children younger than 5 years with a febrile urinary tract infection have pyelonephritis.[45] Vesicoureteral reflux from the bladder into the ureter is a common cause of the pyelonephritis and renal scarring. Urinary tract infection in infants younger than 3 months is associated with bacteremia in up to 50% of cases; in children older than 3 months, the risk drops to 5%. Renal scarring can occur in 27 to 64% of children after pyelonephritis and may lead to renal failure and a risk for hypertension later in life.[45]

E. coli is the predominant cause of urinary tract infections in children; *Klebsiella* species are more likely to be the etiologic agents in newborn children. *Enterobacter, Proteus, Morganella, Serratia,* and *Salmonella* species also are important pathogens.[49] Organisms such as *Lactobacillus,* coagulase-negative staphylococcus, and *Corynebacterium* are not considered clinically relevant pathogens in otherwise healthy children.[44] In neonates and young infants, bacteremia is considered the route of infection to the urinary tract. In older children, infection in the lower tract often is the source of upper tract infection. A common cause of urinary tract infections in toilet-trained girls is believed to be improper wiping after urination. Young girls should be taught to wipe from anterior to posterior (front to back) after urination.

Clinical Features

Infants and Children Younger than 2 Years. Signs and symptoms usually are nonspecific and include decreased oral intake, lethargy, jaundice, fever, vomiting, abdominal pain, and irritability. Young children may not be able to verbalize when urination is painful. It is assumed that a urinary tract infection in this age group represents upper tract disease and would therefore arise with more systemic symptoms and signs.

Children Older than 2 Years. Urinary tract infection in children older than 2 years can be either an isolated cystitis or upper tract disease with symptoms and signs of a more systemic nature. Cystitis usually is associated with local symptoms (i.e., suprapubic tenderness and dysuria). Clinical manifestations of pyelonephritis may include fever, costovertebral angle tenderness to palpation, abdominal pain, vomiting, and ill appearance. New-onset bedwetting also may be a sign of a urinary tract infection.

Diagnostic Strategies

Various techniques can be used for collection of urine samples from children. Because of the difficulty in cleaning the perineal area, the bag collection method is associated with an increased risk of contamination by periurethral flora; false-positive results range from 12 to 83%.[45] Because urethral catheterization is almost always successful, suprapubic aspiration to obtain a urine sample is rarely needed.[48,49] A suprapubic bladder aspiration may be used for young infants because the expanded bladder is located more intra-abdominally. Bladder aspiration is considered more invasive and is more painful than the urethral catheterization method.[44] Chances of a full bladder and successful aspiration improve if 45 to 60 minutes have elapsed since the last diaper change. Ultrasonographic guidance has been advocated to enhance the probability of obtaining urine by the suprapubic and catheterization methods. Nursing staff can be trained to use this enhanced method of urinary collection.[50,51]

Urethral catheterization is relatively simple and poses little risk, although it may be more difficult in uncircumcised boys or in young infants. There is a slight risk of both trauma to the urethra and introduction of bacteria into the urinary tract with this technique. A 5-F feeding tube can be used in young infants. Young male infants sometimes spontaneously urinate when the urethral meatus is cleansed; a midstream clean-catch urine specimen may then be obtained.

For a clean-catch urine sample from a toilet-trained child, the parent can clean the child's urogenital area with soap and water before urination. Children can be instructed to sit backward on

www.ketabpezeshki.com 66485457-66963820

the toilet to urinate, allowing better access to obtain the urine specimen. A urine sample with more than 10 white blood cells (WBCs) per high-power field and a large number of epithelial cells should be considered contaminated, and either an improved clean-catch method or catheterization should be tried. Females with a vaginal discharge, regardless of age, should be catheterized.

In children younger than 2 years, a urinalysis alone is not considered adequate to rule out urinary tract infections. As many as 10 to 50% of patients with urinary tract infection can have false-negative results on urinalysis.[52,53] Nitrite and leukocyte esterase urinalysis markers have the highest combined sensitivity and specificity for detection of infection. If both markers are positive, the false-positive rate is less than 4%. The urine dipstick alone appears to work less well in young infants.[45,55] Gram's stain of the urine has a sensitivity of 93%.[45,55] New guidelines have redefined urinary tract infections in children. To establish the diagnosis of urinary tract infection in children, the clinician should require both of the following: (1) urinalysis results suggesting infection (pyuria, bacteriuria, or both) and (2) the presence of at least 50,000 colony-forming units (CFU) per milliliter of a uropathogen cultured from a urine specimen.[44] Old guidelines of 100,000 CFU/mL were based on studies of adult women and are considered no longer applicable to children.

Renal function tests are rarely abnormal but should be performed in children with hypertension, proteinuria, or signs of dehydration. In general, blood cultures are not indicated in a majority of well-appearing children with urinary tract infection. The true-positive rate for blood culture in the presence of a urinary tract infection in older infants and young children is low, and the organism identified is invariably the same as the organism in the urine culture.[56]

Differential Considerations

Underlying renal disease or urinary tract abnormality should be considered in a child presenting with hypertension, hematuria, or difficulty with urination; it should be suspected in children with elevated BUN or creatinine concentration, electrolyte abnormalities, or acidosis on laboratory examination. CT of the abdomen may be necessary to delineate the extent of urinary tract abnormalities.

Several other causes of dysuria in children are recognized (Box 174-1). Irritants such as bubble bath and soaps may cause local irritation and dysuria. A retained foreign body in the vagina or penis (such as toilet paper) can cause irritation or bacterial growth with associated dysuria and vaginal discharge. Pinworms in the genitourinary area can cause itching and scratching. Balanitis in uncircumcised boys also can cause dysuria and pyuria.

Accidental injuries to the genital area can cause abrasions or lacerations and subsequent dysuria. Sexual or physical abuse should be considered in any young child with a history of multiple urinary tract infections.

Box 174-1 Etiology of Dysuria in Children

Infection
- Urinary tract infection, including cystitis and pyelonephritis
- Vaginitis resulting from *Gardnerella, Trichomonas, Candida,* or sexually transmitted organisms
- Pinworms
- Balanitis

Irritation
- Bubble bath, new soaps, or douches
- Vaginal foreign body, such as retained toilet paper

Trauma
- Sexual or physical abuse
- Straddle injury (unintentional)
- Self-stimulation or masturbation

Other
- Labial adhesions
- Renal stones or hypercalciuria

Management

Children who are considered "ill appearing" or "toxic" or who are unable to take oral medications should be treated with parenteral antibiotics until clinical improvement, generally 24 to 48 hours, and they are able to retain oral medications and fluids. If compliance is in question, parenteral antibiotics should also be considered.

Infants Younger than 2 Months. Young infants with urinary tract infections are at risk for associated sepsis. The age at which a urinary tract infection warrants hospital admission has decreased dramatically. Infants younger than 2 months are still considered to be at high risk for the development of sepsis and should therefore be admitted to the hospital for intravenous antibiotic therapy (e.g., with gentamicin and ampicillin). One study, however, showed low adverse events in young infants (29-60 days of age) diagnosed with a urinary tract infection who appeared well in the ED and did not have a high-risk past medical history.[57-59]

Children 2 Months to 2 Years. Although inpatient treatment of children with suspected pyelonephritis has traditionally been recommended, studies now show that well-appearing children without signs of toxicity may be managed as outpatients.[60] A meta-analysis of data from both adult and pediatric studies found no significant evidence suggesting that oral antibiotic therapy is less effective than parenteral or initial parenteral therapy for treatment of severe urinary tract infection.[61] Choices of oral antibiotics include a cephalosporin, amoxicillin with clavulanic acid, and trimethoprim-sulfamethoxazole.[44] Antibiotics that are excreted in the urine but do not reach sufficient levels in the bloodstream, such as nitrofurantoin, should not be used.[44] Community antimicrobial resistance patterns are important to consider in deciding on an appropriate antimicrobial. Rates of *E. coli* resistance to trimethoprim-sulfamethoxazole can be as high as 20 to 30% in some communities.[62] The first dose of a parenteral antibiotic and a double dose of an oral antibiotic appear to be equivalent. Because urinary tract infections in this age group are considered to be upper tract disease processes, a longer course of antimicrobials is indicated (e.g., 7 to 14 days). Although a review of studies found no difference in the frequency of positive urine cultures between short-course therapy (2 to 4 days) and longer course therapy (7 to 14 days), most of these studies mixed children younger than 2 years with older children, including adolescents. Thus the recommendation for short-course therapy in children younger than 2 years is not supported at this time.[44,63] Follow-up in 2 to 3 days is essential to evaluate the culture and sensitivity results and to assess clinical status. Older recommendations required both ultrasonography and voiding cystourethrography to be performed on all infants with first-time urinary tract infections. Newer recommendations focus only on a renal and bladder ultrasound examination looking for evidence of renal scarring or anatomic abnormalities that require further evaluation. For children who clinically improve quickly, this ultrasound examination can be done at a later time on an outpatient basis.[44]

Children Older than 2 Years. In older children with simple cystitis, a short 3-day course of antibiotics, such as trimethoprim-sulfamethoxazole or amoxicillin-clavulanate, is adequate. Shorter courses result in higher failure rates and are not indicated. In older children with pyelonephritis, a longer course of antibiotics (generally 7-14 days) is recommended.[44] In the adult population, a study

www.ketabpezeshki.com 66485457-66963820

showed that a 7-day course of a fluoroquinolone is as effective as a 14-day course of trimethoprim-sulfamethoxazole.[64] In children, fluoroquinolones are still contraindicated because of the concern for their effect on skeletal development.[65]

Disposition

Children with signs of toxicity, urinary obstruction, or inability to take oral medications should be hospitalized for intravenous antibiotic therapy.[66] On discharge, parents should be instructed to return if the child is unable to take the oral medication or if the symptoms worsen. The child may remain febrile for 48 hours despite adequate antimicrobial therapy. The child's clinical status should be checked in 48 to 72 hours, either in person or by telephone. At follow-up, the urine culture results should be checked to ensure appropriate antimicrobial therapy.[67]

Hematuria

Perspective

Hematuria is common in the pediatric population. Hematuria, defined as the presence of red blood cells (RBCs) on examination of two successive urine samples, has a prevalence rate of 1 to 2% in children 6 to 15 years of age.[68] Microscopic hematuria is defined as the presence of more than 5 RBCs/mm^3 and is detected by chemical reagent strips and microscopic urinalysis. Persistent hematuria is defined as positive results on three urinalyses during a 2- to 3-week period.[68] Macroscopic or gross hematuria is presence of blood in the urine visible to the naked eye and may be associated with clots.

Box 174-2 Etiology of Hematuria in Children

Extrarenal
Trauma
Meatal stenosis or posterior urethral valves
Exercise
Menstruation or rectal bleeding
Foreign bodies
Cystitis, urethritis, or epididymitis

Intrarenal
Pyelonephritis
Renal or bladder stones or tumors
Poststreptococcal or idiopathic glomerulonephritis
Acute interstitial nephritis
Acute tubular necrosis
Basement membrane glomerular disease
Renal vein or artery thrombosis
Recurrent familial hematuria
Polycystic kidney disease

Systemic
Henoch-Schönlein purpura
Systemic lupus erythematosus
Hemolytic-uremic syndrome
Infectious mononucleosis
Sickle cell disease or other hemoglobinopathies
Bacterial endocarditis or artificial cardiac valves
Bleeding disorders, warfarin, or aspirin
Medications such as amitriptyline or chlorpromazine, radiocontrast dyes
Munchausen syndrome or factitious

Principles of Disease

Hematuria results from the entry of RBCs into the urinary tract. Inflammation, infection, trauma, or anatomic abnormalities can occur anywhere from the glomerulus to the urethra. The endothelium and basement membrane of the glomerulus usually are impervious to large proteins such as RBCs and hemoglobin, but myoglobin may pass freely. Damage to the glomerulus, however, may allow RBCs and hemoglobin to pass into the collecting system.

Urine with lysed RBCs tests positive for hemoglobin and negative for RBCs and may be pink. Urine containing myoglobin from muscle breakdown tests positive for hemoglobin and negative for RBCs. Evaluation of creatine kinase and fractionated bilirubin levels and hematocrit often can help differentiate hemoglobinuria from myoglobinuria. Not all red urine contains blood. Certain drugs or foods, such as phenothiazines, ibuprofen, beets, and blueberries, can cause reddish urine. In neonates, urate crystals can cause red-tinged urine in the diaper. *Serratia marcescens,* a fecal pathogen, can cause a red pigmentation when left in the diaper. Bleeding from the vagina or rectum can sometimes be mistaken for blood in the urine.

Clinical Features

The history and physical examination should focus on signs of infection, trauma, or bleeding disorders. Signs of renal disease (e.g., hypertension), edema, rales, and cardiac murmurs are important findings. An examination of the genitalia may reveal inflammation or bleeding.

Differential Considerations

The etiology of hematuria comprises a diverse group of disorders and conditions (Box 174-2). Presence of RBCs in the urine as a result of trauma is discussed elsewhere.

Extrarenal causes of hematuria include urethral valves and meatal stenosis. Extensive exercise can also cause hematuria or myoglobinuria as a result of both direct renal trauma and ischemic injury.

Intrarenal disorders include pyelonephritis, renal or bladder tumors, poststreptococcal acute glomerulonephritis, and basement membrane disease of the glomerulus.

Systemic illnesses that cause hematuria, such as Henoch-Schönlein purpura and hemolytic-uremic syndrome (HUS), are discussed later in this chapter. Other systemic causes of hematuria include bleeding disorders, aspirin, and anticoagulants.

Diagnostic Strategies

A urinalysis that shows more than 5 RBCs per high-power field indicates hematuria. The presence of WBCs or leukocyte esterase should be noted. RBC casts in the urine or significant proteinuria demonstrates a glomerular origin for the hematuria. If glomerular disease is suspected, a throat culture, antibody test for streptococcus, complement studies, erythrocyte sedimentation rate determination, antinuclear antibody assay, or hepatitis B serology tests should be considered. If the patient has signs of hypertension, edema, or proteinuria, laboratory tests for electrolytes, total protein, and albumin should be ordered.[69]

If the cause of the hematuria is still unclear, follow-up with the patient's pediatrician for a 24-hour urine collection for creatinine and protein is important. Because hypercalciuria is common in children, urine and plasma calcium levels should also be measured as they will give a better indication of the cause of the hypercalciuria.

Because younger pediatric patients have predominantly renal stones rather than ureteral stones, ultrasonography can be used as the first-line imaging modality for the diagnosis of renal stones in institutions with dedicated pediatric ultrasonographers. Should the ultrasound study be normal in a patient when renal stones are

www.ketabpezeshki.com 66485457-66963820

still a concern, a non–contrast-enhanced helical CT scan can then be ordered.

Management

Management of the child with hematuria depends on the underlying cause. The management of the child with renal stones and renal tumors is discussed later in the chapter.

Disposition

The disposition of a child with hematuria depends on the underlying cause. Simple cystitis or pyelonephritis can be treated in the ED with follow-up by the child's primary care physician. A child diagnosed with a renal tumor or stone should be referred to a nephrologist or urologist. Children with acute renal failure, especially those with signs of fluid overload or hyperkalemia, need to be hospitalized for appropriate management. For children with no known cause of the hematuria but who appear well in the ED, follow-up with their own pediatrician in the next 1 to 2 weeks is important. Persistent hematuria with no known cause should be followed up by a nephrologist for further evaluation.

Renal Stones

Perspective

Renal stones result from a complex process of crystallization involving growth inhibitors and promoters and changes in urine pH and flow. Congenital abnormalities, trauma, or infection also can be an inciting cause. An increased risk for hypercalciuria and the formation of renal stones often is inherited.

Principles of Disease

Renal stones are uncommon in children, with approximately 1 case diagnosed for every 1000 pediatric hospital admissions.[70] Calcium-containing stones are responsible for approximately 60% of all cases, followed by struvite, uric acid, and cystine stones.[70] Struvite stones are composed of ammonium, magnesium, and phosphate and are potentiated by urea-splitting organisms such as *Proteus, Pseudomonas,* and *Klebsiella*. Renal stones are three to four times more common in white children than in nonwhite children. Family history also seems to play a role in the formation of kidney stones.[71] In younger pediatric patients, renal stones predominate over ureteral stones.[72]

Clinical Features

The signs and symptoms of renal stones in older children typically include colicky flank pain, vomiting, and hematuria. Younger children with renal stones also can present with less specific complaints, such as nontender abdominal pain, vomiting, or malaise. In a study from the United Kingdom, 17% of pediatric patients with renal stones were found to present with hematuria only, without flank or abdominal pain.[71] In the initial evaluation of children with possible renal stones, the history should ascertain potentially relevant factors, including previous urinary tract infections (especially those caused by organisms such as *Proteus* species), family history of renal stones, and diet (including excessive vitamin use) and fluid intake. Toxins introduced into the human food supply have also been associated with the development of renal stones as was seen in China with melamine-contaminated powdered infant formula.[73]

Obstruction of the collecting system can sometimes lead to infection, papillary necrosis, or decrease in renal function. Fever in the presence of a renal stone should be taken as an indicator of upper tract infection.

Diagnostic Strategies

In children thought to have renal stones, the urine should be checked for hematuria and evidence of infection, such as positive leukocyte esterase or nitrites, leukocytes, and bacteria. The urine also should be strained and any crystals sent for analysis. Other laboratory tests to consider are CBC, electrolyte panel, and determination of BUN, creatinine, uric acid, total protein, and albumin levels. Ninety percent of renal calculi are visible on a plain abdominal radiograph, although stool can sometimes obscure the view. Other types of calcifications appearing on plain abdominal radiographs are gallstones, phleboliths, vessel or lymph node calcifications, and calcified malignant neoplasms. Plain films of the abdomen have no additional value over CT scan of the abdomen and should not be obtained in lieu of the CT scan or other imaging.

Non–contrast-enhanced helical CT is the current study of choice for the identification of renal and ureteral stones. It has exceptional sensitivity and specificity for detection of calculi as small as 1 mm and can identify associated processes, such as obstruction, hydroureter, hydrocalyx, and renal abscess. In addition, it is superior to intravenous pyelography in determining alternative diagnoses, such as abdominal tumor. In children, however, the risk of ionizing radiation with CT scanning pushes clinicians to look for alternative forms of imaging. Because renal stones predominate over ureteral stones in younger pediatric patients, ultrasonography is a viable alternative for imaging in this population. In one study, sensitivity of ultrasonography was 90% for renal stones and 38% for ureteral stones.[72] Ultrasonography for renal stones in pediatric patients will be of highest utility in institutions with a large pediatric patient volume and dedicated pediatric ultrasonographers. The use of CT scanning in smaller institutions or after a normal ultrasound study in a patient in whom renal stones are still a concern is a reasonable approach.

Differential Considerations

The differential diagnosis for colicky flank or abdominal pain in the pediatric patient generates a long list of possibilities. Gastroenteritis and constipation are more common than kidney stones as causes of colicky abdominal pain in young children. Intussusception most commonly occurs in children younger than 2 years and can be manifested with intermittent abdominal pain. In adolescents, biliary colic and intermittent gonadal torsion also must be considered.

Management

Initial pain management should include a narcotic analgesic in conjunction with a longer-acting nonsteroidal anti-inflammatory drug (NSAID). The analgesic effect of NSAIDs is directly related to the inhibition of prostaglandin-mediated contraction of the ureter and is characteristic of all NSAIDS (e.g., ibuprofen, naproxen, ketorolac). Patients with signs of volume depletion or with a history of fever, vomiting, or poor fluid intake should be adequately hydrated to improve urine flow and to prevent urinary stasis, which may contribute to stone formation. Excessive fluid administration to increase urine flow has not been proved effective, however, to enhance movement of the stone down the urinary tract. Although tamsulosin, an alpha-blocker, has been shown to be effective in adults to increase the passage of kidney stones, there are no significant studies in children to support the practice. One review of hospitalizations of children for renal stones found, however, that the use of tamsulosin had increased in the hospitals

www.ketabpezeshki.com 66485457-66963820

surveyed from less than 1% to more than 8% in pediatric patients during the years surveyed.[74]

After culture specimens have been obtained, children with infected urinary tracts with stones should be treated with antibiotics; hospitalization generally will be required. Children with larger renal stones may undergo shockwave lithotripsy as a therapeutic modality. In some centers, ureteroscopy also may be a management option for larger stones.[75]

Children with normal renal function and adequate pain control, without signs of toxicity or renal infection, can be safely discharged home with good follow-up. Several studies have shown that stones 5 mm or smaller appear to pass safely in pediatric patients.[76] Follow-up with a nephrologist or urologist may include parathyroid hormone assay, analysis of fasting urine samples for calcium-to-creatinine ratio, or 24-hour urine collection for determination of calcium, magnesium, phosphorus, uric acid, oxalate, cystine, protein, and creatinine levels.[70,77]

Renal Tumors

Perspective

Abdominal masses in children are not uncommon, and in infants most are benign renal tumors or cysts.[78]

Principles of Disease

Renal tumors in children can range from the benign cystic nephroma to the more aggressive malignant rhabdoid tumor. The prognosis will depend on the type and staging of the renal tumor.

Clinical Features

The most frequent presentation for a child with a renal tumor is that of an abdominal mass found by the parent while bathing or dressing the child. Hematuria or pain is a less common presenting manifestation than in the adult population.

Diagnostic Strategies

Because a significant number of abdominal masses are the result of renal cysts, renal ultrasonography is the imaging study of choice. Ultrasonography can define the mass in question and is not associated with exposure to ionizing radiation. Laboratory tests should include CBC, platelet count, BUN and serum creatinine concentrations, urinalysis, and urine catecholamine levels. Urinary catecholamines are increased in 95% of patients with neuroblastoma but are normal in those with Wilms' tumor. Any solid masses found on ultrasonography will be better defined by CT of the abdomen. If the mass appears malignant, a CT scan of the chest is indicated to look for pulmonary metastases.[79]

Differential Considerations

Considerations in the differential diagnosis for a renal mass include cystic lesions, such as those of polycystic kidney disease, and severe hydronephrosis resulting from obstruction or severe reflux. Solid masses include Wilms' tumor, renal cell carcinoma, mesoblastic nephromas, and cystic nephromas.

Management and Disposition

Management depends on the function of the urinary tract. Because the renal mass typically involves only one kidney, renal function usually is maintained.

A preliminary diagnosis of the cause of the mass should be obtained before discharge of the child from the ED. Well-appearing children with normal renal function for whom close follow-up can be ensured may be managed on an outpatient basis. Because of the potential seriousness of a renal tumor, hospital admission should be considered for all children. Consultations with a nephrologist, urologist, and hematologist-oncologist can be coordinated during the admission process.

Proteinuria

Perspective

The normal glomerulus is relatively impervious to albumin, a high-molecular-weight protein. Low-molecular-weight proteins, however, pass through the glomeruli and are reabsorbed in the proximal tubule. Proteinuria can result from either increased passage through the glomeruli or decreased reabsorption by the tubules. In most cases, proteinuria is benign and asymptomatic. If the amount of protein lost is significant, such as in nephrotic syndrome, the resultant hypoalbuminemia (albumin less than 2 g/dL and protein less than 4 g/dL) may cause ascites and generalized edema.

Principles of Disease

Proteinuria is a common finding in children. Trace to mild proteinuria (1+ to 2+) can be seen in up to 85% of children and adolescents screened, especially during the summer months.[80,81]

Clinical Features

Clinical features seen in a proteinuric child depend on the cause of the proteinuria. Recent pharyngitis, presence of hematuria, changes in weight or urine output, or family history of proteinuria should be investigated. Abnormal findings may include hypertension, edema, ascites, or palpable kidneys in infants. A butterfly rash of systemic lupus or the purpuric rash of Henoch-Schönlein purpura may be evident.

Differential Diagnosis

Causes of proteinuria can be divided into glomerular and tubular. Glomerular causes include nephrotic syndrome, glomerulonephritis, and post-transplantation rejection. Transient causes of altered glomerular function include exercise, fever, and seizures. Tubular causes of proteinuria include heavy metal poisoning, urinary tract infections, and diabetes; an asymptomatic tubular proteinuria also has been described.[80,81] False-positive results on urinary dipstick testing for proteinuria can be obtained when the urine is alkaline or when it contains mucus, blood, vaginal secretions, semen, or a significant number of inflammatory cells.

Orthostatic proteinuria is a benign condition characterized by the presence of protein in the urine collected with the patient in an upright position but not in samples collected from a supine child. Proteinuria that is persistent or associated with hematuria or other signs of renal disease usually is a sign of a more serious condition.

Diagnostic Strategies

Mild proteinuria (2+ or less; equivalent to 100 mg/dL or less) requires no further investigation unless there are signs of infection. Moderate proteinuria (3+ or more; equivalent to 300 mg/dL or more) necessitates additional evaluation with laboratory tests for serum total protein and albumin, serum electrolyte, BUN, and serum creatinine levels and urine culture. The child should be referred to a nephrologist, who can initiate a 24-hour urine collection for protein. The urine protein-to-creatinine ratio (urine

www.ketabpezeshki.com 66485457-66963820

Pr/Cr, expressed in mg/dL) in a random urine sample, however, correlates strongly with the protein levels found in a 24-hour urine collection.[80] Urine Pr/Cr of less than 0.2 mg/dL is considered normal for children older than 2 years and for adults. Children 6 months to 2 years of age normally have a ratio of less than 0.5 mg/dL. A urine Pr/Cr of more than 3.0 mg/dL is consistent with nephrotic syndrome.

Antistreptolysin O (ASO) titer can be measured to identify a previous streptococcal infection as the cause of the proteinuria. In young children, renal ultrasonography detects polycystic disease or anatomic abnormalities. Referral to the child's primary care physician or a pediatric nephrologist for follow-up and renal biopsy is indicated. Renal biopsy may be indicated in patients with increased creatinine levels, low complement levels, or hematuria.[82]

Management

The approach to management for a child found to have proteinuria depends on the underlying cause. Management of children with proteinuria involves assessment for signs of urinary infection, pharyngeal infection, and renal function. Other evaluation for poststreptococcal glomerulonephritis and nephrotic syndrome can take place on an outpatient basis unless the patient shows signs of systemic disease, hypertension, or renal failure.

Disposition

A child with significant edema and ascites from the loss of albumin needs to be hospitalized. Children with significant hypertension resulting from glomerulonephritis or with marked impairment of renal function also need to be hospitalized. Well-appearing children for whom good follow-up can be ensured can be discharged home.

Poststreptococcal Glomerulonephritis

Perspective

Poststreptococcal glomerulonephritis (PSGN) is one of the sequelae of streptococcal pharyngitis and, less commonly, infections of the skin. Treatment of streptococcal pharyngitis with antibiotics has not been shown definitively to decrease the incidence of PSGN, as opposed to acute rheumatic fever, another sequela of streptococcal pharyngitis. PSGN remains more of a cause of morbidity and mortality in developing countries and among impoverished populations.[83]

Principles of Disease

PSGN is not well understood but probably results from deposition of circulating immune complexes in the kidney.[84] This results in decreased glomerular filtration, allowing proteins to flow freely into the urine.

Clinical Features

PSGN most commonly occurs in children 3 to 7 years of age, usually with a history of pharyngitis with fever 2 weeks before the onset of glomerulonephritis. Symptoms can be localized to the urinary tract, manifested as hematuria or flank pain, or may be less specific, such as lethargy or generalized edema. Some children may present with more significant clinical signs, such as pulmonary edema, cardiac arrhythmias, or significant hypertension. Renal failure is found in 2% of these patients.[85,86] In one study, delay in diagnosis of PSGN was associated with a negative infection history and absence of gross hematuria.[87]

Diagnostic Strategies

Urinalysis shows significant blood and protein, with RBC casts in 60% of cases. Pyuria with granular or hyaline casts also may be found.

The ASO titer and immunoglobulin G levels are elevated in PSGN. Total complement levels, especially C3, are decreased in most patients during the first 2 weeks of the illness. The complement levels should return to normal within 3 to 4 weeks. The BUN concentration is elevated; hyponatremia and hyperkalemia also may be present.[86]

Differential Considerations

Considerations in the differential diagnosis include the entities previously mentioned regarding proteinuria, including nephrotic syndrome and urinary tract infection.

Management and Disposition

Management includes restriction of fluid and salt intake and sometimes use of diuretics. A child with significant hypertension, congestive heart failure, or uremia requires hospitalization for inpatient management. Significant hypertension should be treated as outlined in the section on hypertension.

Children with mild symptoms in whom good follow-up can be ensured can be managed on an outpatient basis.

Nephrotic Syndrome

Perspective

Nephrotic syndrome is characterized by hypoproteinemia, proteinuria, and edema. Primary nephrotic syndrome applies to diseases limited to the kidney; renal biopsy is used to stratify patients and to determine therapeutic and prognostic decisions. Secondary nephrotic syndrome results from systemic illnesses such as PSGN.

Principles of Disease

From 2 to 7 cases of nephrotic syndrome per 100,000 children are discovered each year.[82] Boys are affected twice as often as girls are, but the distribution equalizes by adulthood. Primary nephrotic syndrome occurs more commonly in children younger than 5 years, and secondary nephrotic syndrome occurs more often in older children. Ninety percent of affected children have the primary disease; 85% have minimal change nephrotic syndrome, 10% focal sclerosis, and 5% mesangial proliferation (referring to the thin membrane-supporting capillaries surrounding the tubule of nephrons).

The etiology of primary nephrotic syndrome is thought to be idiopathic, but various theories involving bacterial or viral infections, allergic reactions (pollens, poison ivy), or drug ingestions (heroin, mercury) have been investigated.[82]

Clinical Features

Characteristics of nephrotic syndrome include edema, hypoalbuminemia, proteinuria, and hyperlipidemia. The onset of edema may be insidious, beginning with periorbital edema. As weight increases, pants and shoes may not fit. The edema progresses, but the child usually does not appear ill unless pulmonary edema or ascites is present. Other features may include anorexia, nausea, and vomiting secondary to edema of the intestine. Hypertension, hematuria, or oliguria may be present. Acute renal failure is rare in primary nephrotic syndrome.

www.ketabpezeshki.com 66485457-66963820

Nephrotic children also are at risk for thrombosis, with a reported rate of thromboembolic complications of 2%.[88] Renal veins are particularly vulnerable to thrombosis, as characterized by flank pain, hematuria, and worsening renal function. Nephrotic children should not undergo punctures to deep vessels because of this risk of thrombosis.

Children with nephrotic syndrome taking corticosteroids also are at greater risk for side effects of corticosteroid use even at dosages as low as 1 mg/kg per 48 hours.[89] Acute mood changes, from depression to mania, are associated with use of steroids. Irritability, excessive crying, and sleeping difficulties can result.

Because of steroid therapy and decreased levels of immunoglobulins, nephrotic children are at risk for bacterial infections, such as from *E. coli* and *Streptococcus pneumoniae*.

Diagnostic Strategies

Proteinuria in nephrotic syndrome is defined as excretion of more than 3.5 g of protein per 1.73 m^2 per 24 hours or more than 50 mg/kg per 24 hours. This corresponds to 3+ or 4+ on the dipstick reading. Specific gravity may be high because of the proteinuria. Microscopic hematuria also may be present. Total serum protein usually is low at 4.5 to 5.5 g/dL, and serum albumin is less than 2 g/dL.

Hyperlipidemia may occur because of the increased serum cholesterol. Hyponatremia may be present, but other electrolytes usually are normal. If an elevated cholesterol level is present, the lowered sodium level may be a combination of true hyponatremia and pseudohyponatremia. BUN and creatinine concentrations usually also are normal, and hemoglobin and hematocrit levels may be elevated because of hemoconcentration.

Chest radiographs sometimes show pleural effusions or pulmonary edema. The heart appears normal or small because of hypovolemia. An abdominal radiograph may reveal ascites, and ultrasonography may show a renal abnormality.

Renal biopsy is important for diagnostic and therapeutic decisions and should be performed in older children or in patients with evidence of hematuria, elevated BUN, or persistent hypertension or in whom the renal dysfunction fails to respond to steroids.

Differential Considerations

Other renal diseases that cause edema include glomerulonephritis and renal failure. A vasculitis or acute thrombosis of the renal vessels also must be considered. Gastrointestinal disorders that produce hypoproteinemia include cirrhosis, cystic fibrosis, and protein-losing enteritides.

Management

Despite the edema, children with signs of hypovolemia or shock need to be resuscitated with crystalloid. Hypertension may result from the intrinsic disease; prompt recognition and treatment of this condition are important.

After consultation with a pediatric nephrologist, patients between 12 months and 5 years of age with no gross hematuria and no large loss of protein or complement can be treated with corticosteroids. After the initial evaluation is completed, including a tuberculin test, prednisone at 2 mg/kg per 24 hours orally, divided two or three times a day, can be initiated. Relapses or steroid resistance may necessitate a second course of steroids.[82]

Diuretics such as furosemide, 1 to 2 mg/kg per 24 hours orally or intravenously in divided doses, may be necessary if respiratory distress or significant ascites is present. Salt restriction may be required. Fluid intake should be restricted only if edema is present despite salt restriction or if the child exhibits hyponatremia because of an impaired ability to excrete excess water.

The relatively immunocompromised status of nephrotic children increases the risk of infection. A fever or signs of peritonitis must be investigated thoroughly. A paracentesis should be performed and fluid sent for cell and differential counts, Gram's stain, and culture. Hospital admission and empirical antibiotic therapy with agents with activity against *S. pneumoniae* and *E. coli* are appropriate.[82]

Disposition

Hospitalization should be considered for newly diagnosed patients for initial evaluation, treatment, and education of both the child and the parents. Patients with signs of shock or respiratory distress should be admitted to the hospital after initial stabilization. Other patients with suspected bacterial infections, peritonitis, edema refractory to therapy, or evidence of renal insufficiency also should be hospitalized.

Acute Renal Failure

Perspective

Acute renal failure results from impaired glomerular filtration rate. Blood pressure, acid-base balance, removal of nitrogen waste, and fluid management may be affected. The incidence of acute renal failure is unknown, but large children's hospitals may see 30 to 50 new cases each year.

Principles of Disease

Acute renal failure can be divided into three categories: prerenal, which involves decreased renal perfusion; renal (intrarenal), which is caused by parenchymal damage; and postrenal, which involves obstruction of the urinary tract (Box 174-3).

Causes of prerenal failure include hypovolemia resulting from a variety of factors (e.g., dehydration, burns, hemorrhage), shock (e.g., sepsis, anaphylaxis), and congestive heart failure (e.g., decreased cardiac output). Obstruction of the renal artery or thrombosis of the renal vein also can cause acute renal failure.

Intrarenal causes involve damage to the nephron. Glomerular damage most commonly results from PSGN. Systemic lupus erythematosus, HUS, and sepsis with hypoperfusion are systemic causes of renal failure. Tubular damage can result from heavy metal poisonings or hemoglobin-myoglobin in the tubules from a crush injury, burn, or hemolytic crisis. Cases of acute renal failure in dehydrated children after NSAID use have been reported.[90]

Postrenal failure resulting from an obstruction in the urinary tract may be caused by infection, tumor, renal stones, or posterior urethral valves. Bilateral obstruction of the kidneys usually is necessary for renal failure to occur.

Clinical Features

A child with acute renal failure accumulates nitrogen wastes shown by an increase in BUN and serum creatinine levels. A decrease in urine output is sometimes seen. A urinary output of 1 mL/kg per hour usually is considered adequate, but the output may be lower if the patient is dehydrated. Nephrotoxic agents such as certain aminoglycosides can actually increase the urinary output because of renal tubular damage, but BUN and serum creatinine levels are still elevated.

Acute renal failure can result in life-threatening complications that must be recognized and treated promptly. These include severe hyperkalemia, pulmonary edema or fluid overload,

www.ketabpezeshki.com 66485457-66963820

Box 174-3 Etiology of Acute Renal Failure in Children

Prerenal
Decreased intravascular volume or dehydration
- Burns or hemorrhage
- Third spacing
- Sepsis

Decreased cardiac output
- Cardiac shock

Decreased renal artery blood flow

Intrarenal
Glomerular disease
- Poststreptococcal and other glomerulonephritis
- Pyelonephritis

Systemic causes
- Hemolytic-uremic syndrome
- Henoch-Schönlein purpura or other vasculitides
- Systemic lupus erythematosus
- Sepsis or other causes of prolonged decreased perfusion

Toxins
- Heavy metal poisonings, such as lead and gold
- Myoglobin or hemoglobin deposits
- Antibiotics such as aminoglycosides
- Anticonvulsants such as phenytoin
- Radiocontrast dyes

Postrenal
Obstructive lesions
- Nephrolithiasis or tumor
- Posturethral valves
- Intra-abdominal tumor obstructing urinary flow
- Infection

Renal vein thrombosis

hypertensive encephalopathy, septic shock from renal obstruction and infection, and seizures from metabolic abnormalities or encephalopathy.[91]

Diagnostic Strategies

Preliminary laboratory tests should include CBC; determination of electrolyte, calcium, phosphorus, BUN, and serum creatinine levels; and urinalysis with microscopy and culture. Diagnostic studies such as ASO titer (for acute PSGN), C3 complement (for lupus), total serum albumin, cholesterol, and albumin-to-globulin ratio (for nephrotic syndrome and cirrhosis) may be obtained. RBC casts in the urine indicate glomerulonephritis. WBC casts indicate infection as an etiologic disorder, whereas hyaline casts suggest dehydration or acute tubular necrosis.[92]

Ultrasonography is the imaging modality of choice for the preliminary evaluation of obstructive causes of renal failure. Non–contrast-enhanced CT urography also can readily identify the site of obstruction and avoids the use of nephrotoxic radiocontrast material. Voiding cystourethrography shows extrinsic pressure on the bladder by posterior urethral valves.

Differential Considerations

Significant dehydration can result in temporary decreased urine output. Renal markers are typically increased, with BUN rising more than creatinine. After hydration and repletion of intravascular volume, urine output should improve and the elevated BUN and creatinine concentrations should resolve. Processes that can result in retention of fluids with associated renal failure include liver disease and decreased cardiac output.

Management

The initial management of a child with acute renal failure depends on the clinical evaluation. If hypovolemia resulting from dehydration or blood loss is thought to be the cause of the renal failure, immediate rehydration is necessary. A bolus of 20 mL/kg of crystalloid should be given to prevent possible progression to acute tubular necrosis. If no urinary response is obtained after two boluses of crystalloid, diuretics may be useful in the euvolemic patient. Furosemide, 1 mg/kg per dose every 2 to 6 hours intravenously, may be tried if there is no evidence of obstruction. Bumetanide, 0.015 to 0.1 mg/kg per dose every 6 to 24 hours intravenously (maximum of 10 mg per 24 hours), can be useful if furosemide has no effect. Mannitol, 0.75 g/kg per dose every 6 hours intravenously, also may be helpful but because of the resultant increased urine flow is contraindicated if there is evidence of obstruction.

If the child is considered euvolemic and has no urine output despite diuretic therapy, renal-dose dopamine should be initiated (2 to 5 µg/kg per minute). Consultation with a nephrologist should be obtained.[91]

If hypertension with encephalopathy develops, a controlled 10 to 20% reduction in blood pressure should be achieved by use of nitroprusside or other intravenous blood pressure agents. Oral medications, such as nifedipine and captopril, are useful but are associated with the risk of a precipitous drop in blood pressure. Overaggressive reduction in blood pressure can result in hypoperfusion of central target organs, such as the brain, heart, and kidneys, that have become accustomed to higher perfusion pressures. Further discussion of hypertensive emergencies and treatment can be found in Chapter 84.

Hyperkalemia can result in cardiac dysrhythmias. Potassium levels higher than 6.5 mEq/L may cause changes on the electrocardiogram such as peaked T waves and, if significant, widened QRS complexes. Hyperkalemia with resultant electrocardiographic changes, such as loss of the p wave or widened QRS complex, should be treated with calcium gluconate, 10% solution, 0.5 mL/kg per dose given intravenously over 5 minutes (maximum dose, 20 mL [2 g]). Calcium alters the action potentials of the cardiac cells, thereby decreasing the risk of arrhythmias. The calcium dose may be repeated in 5 minutes.

Sodium bicarbonate, 1 to 2 mEq/kg per dose intravenously every 4 hours, also can be administered. The resultant alkalosis helps move the potassium intracellularly by exchanging H^+ for K^+. Continued therapy with sodium bicarbonate should be administered in conjunction with pediatric nephrology services because of the risk of increasing volume load with repetitive dosages of sodium. Potassium-binding agents such as sodium polystyrene sulfonate (Kayexalate) are administered orally or rectally and exchange Na^+ for K^+ in a 1:1 ratio.

Glucose (50% dextrose in water for ≥3 years old and 25% dextrose in water for ≤2 years old), 0.5 to 1 g/kg, should be given along with regular insulin (1 unit for every 4 g of glucose administered). The insulin temporarily shifts the potassium intracellularly.

Nebulized albuterol also can be used to shift potassium temporarily into the cells and lowers serum potassium by 1 to 1.5 mEq/L during 30 minutes.[93] Severe cases and those associated with renal failure should be immediately referred to a pediatric nephrologist for emergent dialysis.[91]

Acute renal failure may lead to seizures caused by either hypertensive encephalopathy or a metabolic derangement, most commonly hyponatremia resulting from dilution of the sodium by free water. Intractable hyponatremic seizures may rarely necessitate the use of hypertonic saline (3% sodium chloride). Each 1 mL/kg of 3% sodium chloride increases the serum sodium by approximately 1 mEq/L. A child with hyponatremic symptoms, such as seizures, will often improve after receiving 3 to 5 mL/kg of 3% sodium

www.ketabpezeshki.com 66485457-66963820

chloride. Once the seizures have ceased, sodium correction should then continue more slowly to avoid central pontine myelinolysis. Recommendations are to correct the sodium no faster than 10 to 12 mEq/L in the first 24 hours and not more than 18 mEq/L in the first 48 hours.

Normal saline (0.9%) is relatively hypertonic compared with serum and therefore also may be helpful in correcting the hyponatremia. Water restriction along with the administration of saline usually is only a temporary treatment because many of these hyponatremic patients ultimately require dialysis.

Sodium bicarbonate will correct a persistent metabolic acidosis and maintain pH 7.1 or higher and a serum bicarbonate level of 15 mEq/L. The base deficit can determine the amount of bicarbonate needed:

$$\text{Base deficit} = [0.6 \times (\text{body weight in kg}) \times (\text{desired bicarbonate level} - \text{observed level})] \div 2$$

Half the replacement is given in the first 3 hours, with the remainder given during the next 24 hours.

Hemodialysis or peritoneal dialysis may be indicated for refractory fluid overload associated with hypertension, congestive heart failure, pulmonary edema, severe hyperkalemia, hyponatremia or hypernatremia, metabolic acidosis, myoglobinuria resulting from burn or crush injuries, or HUS with hemoglobinuria or encephalopathy.[91]

Disposition

All children with acute renal failure should be admitted to the hospital. Any child with signs of congestive heart failure, pulmonary edema, significant hyperkalemia, or acidosis should be admitted to a monitored bed.

Hypertension

Perspective

Hypertension is defined as a systolic or diastolic blood pressure higher than 2 SDs above the mean for the age and sex of the patient (Table 174-1). This diagnosis requires three or more accurate blood pressure measurements during the course of several weeks. A correct cuff size should be chosen (i.e., the air bladder should cover 80 to 100% of the circumference and two thirds of the length of the upper arm).[85] It is recommended that all children receive yearly blood pressure measurements starting at the age of 3 years.[85] A child who is in pain or agitated may have falsely elevated blood pressure readings.

Principles of Disease

Hypertension occurs throughout childhood in both boys and girls. It probably occurs more often in African American children than in white children, just as in the adult population. Predisposing factors include obesity, physical inactivity, and a strong family history. Metabolic syndrome, a combination of insulin resistance, hypertension, and hyperlipidemia, may affect up to 50% of overweight adolescents.[94]

Just as in adulthood, primary or essential hypertension is unrelated to a second systemic disease. Children diagnosed with primary hypertension are more likely to become adults with hypertension. Secondary hypertension results from endocrinologic, cardiac, neurologic, or other factors, such as exposure to certain drugs or poisons (Box 174-4). In children with significant hypertension, the underlying cause usually is renal (as in glomerulonephritis) or renovascular.

Table 174-1 Blood Pressure Limits in Children

	BLOOD PRESSURE: UPPER LIMIT	
AGE	Systolic	Diastolic
0-2 years	110 mm Hg	65 mm Hg
3-6 years	120 mm Hg	70 mm Hg
7-10 years	130 mm Hg	75 mm Hg
11-15 years	140 mm Hg	80 mm Hg

From Daniels SR: Consultation with the specialist. The diagnosis of hypertension in children: An update. Pediatr Rev 18:131, 1997.

Box 174-4 Etiology of Hypertension in Children

Primary
Essential hypertension

Secondary
Renal
Glomerulonephritis
Henoch-Schönlein purpura
Pyelonephritis
Obstruction or reflux
Polycystic kidney disease
Diabetic nephropathy
Trauma
Renal transplant or hemodialysis
Tuberous sclerosis
Systemic lupus nephritis

Endocrine
Pheochromocytoma
Cushing's syndrome
Congenital adrenal hyperplasia
Corticosteroid treatment
Hyperthyroidism
Neuroblastoma
Ovarian tumor

Cardiac
Congestive heart failure
Coarctation of the aorta

Vascular
Hemolytic-uremic syndrome
Kawasaki syndrome
Renal artery thrombosis or stenosis

Neurologic
Central nervous system tumor or infection
Central nervous system trauma or abuse
Increased intracranial pressure
Guillain-Barré syndrome

Neoplastic
Neuroblastoma
Wilms' tumor
Pheochromocytoma
Adrenal carcinoma

Drugs
Corticosteroids
Cocaine
Sympathomimetics
Oral contraceptives
Phencyclidine
Beta-blocker or clonidine withdrawal
Lead, mercury

Others
Iatrogenic fluid overload
Volume overload from end-stage renal disease

www.ketabpezeshki.com 66485457-66963820

Clinical Features

There are a variety of clinical presentations of hypertension in children. First, asymptomatic or mildly symptomatic hypertension may show up in routine vital signs measured in children evaluated in the ED for unrelated illnesses. When asked, these children may complain of headaches, abdominal pain, irritability, or nosebleeds. Personality changes and difficulties in school are sometimes noted.

Hypertension in young children may also be manifested as severe elevations in systolic or diastolic blood pressures (younger than 10 years: systolic blood pressure 160 mm Hg or higher, diastolic blood pressure 105 mm Hg or higher; older than 10 years: systolic blood pressure 170 mm Hg or higher, diastolic blood pressure 110 mm Hg or higher) but without signs of end-organ damage. These cases are also important to recognize as close follow-up with a primary care physician will be important.

In children experiencing a hypertensive emergency, clinical signs of end-organ damage will be present. A severe elevation in blood pressure is associated with acute neurologic changes or encephalopathy, pulmonary edema, myocardial ischemia, or proteinuria. The electrocardiogram may show signs of ischemia or ventricular hypertrophy. Chest radiography may reveal cardiomegaly or pulmonary edema. Hypertensive emergencies require prompt recognition and treatment. However, overaggressive treatment of long-standing hypertension can produce relative hypotension, leading to worsening neurologic deficit.

Hypertensive encephalopathy symptoms include headache, vomiting, altered mental status, visual disturbances (including blurry vision and diplopia), and seizures or stroke. Papilledema, decreased retinal venous pulsations, and cranial nerve palsies may be found on examination. The diagnosis is confirmed when the symptoms and signs subside rapidly after the blood pressure is lowered. Headache alone, without any other associated symptoms or signs, generally is not considered to represent a hypertensive emergency.

Diagnostic Strategies

In addition to a thorough history and physical examination, laboratory and radiologic studies performed in the ED often can determine both the cause of the hypertension and whether a hypertensive emergency exists (Box 174-5).

Box 174-5 Diagnostic Evaluation in Hypertensive Emergencies* in Children

History of medications or drugs, or family history of cardiovascular disorders
Symptoms of severe headache or chest pain
Physical examination focused on acute neurologic changes, funduscopic abnormalities, pulmonary edema
Urinalysis for significant protein
Chest radiograph for cardiomegaly or congestive heart failure
Electrocardiogram for ventricular hypertrophy

Primary or Secondary Cause?
Laboratory and Radiologic Tests to Consider

Urinalysis and urine culture
Urine catecholamine assay
Complete blood count with platelet count
Blood smear
Sodium, potassium, chloride, carbon dioxide, calcium, phosphorus, magnesium, uric acid measurement
Blood urea nitrogen and creatinine determinations
Serum C3 complement assay, antistreptolysin O titer, antinuclear antibody assay
Plasma renin level
Computed tomography urography or intravenous pyelography
Voiding cystourethrography
Renal ultrasound scan
Renal arteriography

*Evidence of end-organ damage.

Differential Considerations

Any situation that causes undue agitation or pain in a child can cause a transient rise in blood pressure. Therefore, the diagnosis of hypertension in a pediatric patient should be based only on carefully measured blood pressures in a nonagitated child during several weeks. Secondary hypertension is more likely in symptomatic younger children, especially those without a strong family history.

Other disorders with presentations similar to that of hypertensive encephalopathy include meningitis, brain tumor, intracerebral hemorrhage, stroke, and uremia. These conditions, however, generally produce only a mild increase in the systolic blood pressure[95]; CT or lumbar puncture also can help identify these other disorders.

Management

The management of hypertensive emergencies also is discussed in Chapter 84. When a child with severe hypertension is seen in the ED, questions should focus on a history of hypertension, urinary tract infections, hematuria, edema, or umbilical artery catheterization. A history of joint pain or swelling, palpitations, weight loss, flushing of the skin, or drug ingestion or a family history is important to ascertain.

A physical examination emphasizing the central nervous system and cardiopulmonary system is indicated. Examination of the fundus may reveal papilledema or hemorrhages. Signs of congestive heart failure or a difference in the upper and lower extremity blood pressures should be noted. Coarctation of the aorta may be manifested with a difference in either blood pressure or palpable pulse between the upper and lower extremities. A renal cause of the hypertension may be revealed by the presence of peripheral edema or palpable kidneys. An abdominal or flank bruit suggests renovascular hypertension. Initial laboratory tests should include a CBC, electrolyte values, BUN and creatinine concentrations, urinalysis, urine culture, chest radiograph, and electrocardiogram.

A child in whom clinical findings are consistent with a hypertensive emergency (e.g., acute end-organ damage as found by physical examination, laboratory, or radiologic results) should have intravenous access and be monitored with continuous blood pressure readings; an arterial catheter is preferable. The goal of therapy is to reduce the mean arterial blood pressure by 10 to 20% during several minutes to hours, depending on the nature of the emergency. Headache and vomiting require blood pressure control during several hours, whereas intracranial bleeding or herniation requires reduction in several minutes. Beta-blockers are contraindicated in patients with decreased cardiac output and clinical signs of congestive heart failure. Oral nifedipine is contraindicated in patients with signs of end-organ damage, such as intracerebral bleeding, because of the inability to control the amount of blood pressure reduction. For avoidance of overaggressive treatment and resultant relative hypotension, medications that can be controlled by intravenous infusions are preferred (Table 174-2).

Severe hypertension without evidence of end-organ damage, as stated earlier, is also important to recognize. Antihypertensives should be started or restarted for these patients to prevent end-organ sequelae. Angiotensin-converting enzyme inhibitors or calcium channel blockers are useful as first-line agents and usually are well tolerated. The child may be observed for a few hours after

www.ketabpezeshki.com 66485457-66963820

Table 174-2 Medications Used in Hypertensive Emergencies

MEDICATION	DOSE	TIME TO REPEAT DOSE	DURATION OF EFFECT	SIDE EFFECTS
Nitroprusside	0.3-0.5 μg/kg/min IV (max. 10 μg/kg/min)	30-60 minutes	During infusion	Headache, abdominal pain, chest pain, gastrointestinal upset, seizures, thiocyanate and cyanide toxicity*
Hydralazine†	0.1-0.2 mg/kg IV (max. 20 mg) slowly during 15 minutes	10-20 minutes	4-12 hours	Tachycardia, skin flushing, headache, vomiting, diarrhea, hypotension
Labetalol‡§	May bolus 0.2-1 mg/kg IV (max. 20 mg), then 0.4-1 mg/kg/hr IV (max. 3 mg/kg/hr)	10 minutes	6 hours, but variable	Gastrointestinal upset, headache, sedation
Esmolol‖¶**	Load 100-500 μg/kg IV during 1-2 minutes, then maintenance 25-100 μg/kg/min	10 minutes	During infusion	Similar to labetalol
Phentolamine	0.1 mg/kg/dose IV (max. 5 mg)	30 minutes	30-60 minutes	Tachycardia, abdominal pain

*Avoid in pregnancy.
†Use with caution in renal patients.
‡Avoid in asthma, pulmonary edema, and heart block.
§Avoid in second and third trimesters of pregnancy.
‖With inadequate response, readminister loading dose or increase maintenance dose by 25-50 μg/kg/min every 5-10 minutes.
¶Usual maintenance range: 50-500 μg/kg/min.
**Morphine may increase esmolol levels.
Note: Diazoxide is no longer recommended because of the associated potential for an acute drop in blood pressure.

administration of the medication for evaluation of effectiveness or complications. With no evidence of acute end-organ damage, the child can be safely discharged home, assuming that good follow-up can be ensured.

Children with mildly elevated blood pressures (5 to 10 mm Hg above normal) unrelated to the ED visit require repeated blood pressure measurements before treatment of hypertension is begun. If the blood pressure is moderately elevated and the patient is asymptomatic, appropriate management consists of discharge home for outpatient workup of the hypertension and follow-up with the patient's primary care physician for monitoring of blood pressure values. Thiazide diuretics or beta-blockers may be started at low doses.

Disposition

A child with evidence of a hypertensive emergency (i.e., acute end-organ damage) must be hospitalized for evaluation and care in a monitored bed. A child with significantly elevated blood pressure but without evidence of end-organ damage can be discharged home if good follow-up can be ensured.

Henoch-Schönlein Purpura

Perspective

Henoch-Schönlein purpura is an immunoglobulin A–mediated systemic vasculitis involving the small blood vessels supplying the skin, gastrointestinal tract, and joints.[96] The peak incidence is between 4 and 7 years of age, with an overall occurrence rate of 13.5 episodes per 100,000 children annually.

Principles of Disease

Immune complex deposition results in a systemic vasculitis, with up to 33% of patients experiencing recurrences.[97] Approximately 50% of affected children have a history of previous upper respiratory tract infection, and as many as 75% have group A beta-hemolytic streptococci cultured from the oropharynx. Other theorized predisposing factors include exposure to cold weather, certain foods, drugs, and insect bites. Varicella-zoster virus, *Mycoplasma* species, parvovirus, *Campylobacter enteritidis,* parvovirus B19, and Epstein-Barr virus also have been implicated.

Clinical Features

The hallmark of Henoch-Schönlein purpura is a palpable, purpuric, or petechial rash most prominent on the lower extremities, starting at the lateral malleoli and extending to the buttocks. The cutaneous manifestations are the initial presenting complaint in 50% of patients. Arthralgia or arthritis occurs commonly[98] and usually involves the knee and ankle joints. Gastrointestinal manifestations are present in up to 65% of patients, with the most common symptom being dull periumbilical pain resulting from bleeding into the intestinal wall.[98] The abdominal pain typically occurs concurrently with or immediately after onset of the rash; however, in up to 25 to 50% of patients, abdominal pain or arthritis can be the initial complaint.[98,99] A self-limited glomerulonephritis manifested by hematuria develops in 25 to 50% of children. This condition progresses to chronic renal insufficiency in less than 1% of these patients. Children presenting with acute renal failure, nephrotic syndrome, or hypertension are more likely to have unfavorable outcomes, such as chronic renal failure.[92] Testicular involvement occurs in up to 35% of patients; they may present with severe scrotal edema that resembles acute testicular torsion.

Diagnostic Strategies

There are no specific tests to confirm the diagnosis of Henoch-Schönlein purpura, and recognition of the disorder can be difficult if the classic rash is absent at the time of presentation. Screening tests such as urinalysis, BUN and serum creatinine determinations, CBC, and coagulation studies may be needed to rule out other pathologic conditions. Ultrasound findings in patients with abdominal pain typically include evidence of intraluminal hematomas and duodenal wall thickening.[100] Intussusception also may complicate the disease.

Differential Considerations

Considerations in the differential diagnosis include meningococcemia, Rocky Mountain spotted fever, intussusception, trauma,

www.ketabpezeshki.com 66485457-66963820

appendicitis, thrombotic thrombocytopenic purpura, juvenile rheumatoid arthritis, bacterial endocarditis, systemic lupus erythematosus, kidney stones, and primary renal disease.

Management

Treatment of Henoch-Schönlein purpura remains controversial because most cases resolve spontaneously and do not require therapy. NSAIDs can be used to treat joint pain, but close attention must be paid to renal function. Corticosteroids have been used to treat severe renal or gastrointestinal involvement. A meta-analysis of data on the use of steroids for Henoch-Schönlein purpura found these agents to be effective in reducing the time to resolution of abdominal pain and to reduce the odds for development of persistent renal disease.[101] Prednisone or methylprednisolone pulse therapy has shown some benefit, but an acute surgical process should be excluded before initiation of steroids.[100] Therapy for patients with severe renal involvement also includes intravenous immune globulin, although promising results also have been seen in patients with severe abdominal pain.[102] Other treatment options for patients with severe Henoch-Schönlein purpura–related nephropathy include early treatment with oral immunosuppressants[103] and possibly the use of methylprednisolone and urokinase pulse therapy.[104] A nephrologist should be consulted for appropriate management of patients with renal involvement, and good follow-up must be ensured.

Disposition

Patients with only the skin manifestations of Henoch-Schönlein purpura usually can be discharged home with symptomatic therapy for the joint pain and malaise. An NSAID or acetaminophen usually is sufficient, but close follow-up should be ensured. Patients with abdominal pain or renal involvement should be admitted for further evaluation and treatment.

Hemolytic-Uremic Syndrome

Perspective

HUS continues to be one of the most common causes of acute renal failure in children.[105] It most commonly affects infants and children, with a mean age at presentation of 3 years, but is rare after 5 years of age. There is no sex predilection, and outbreaks can be sporadic or epidemic, especially when the disorder is related to the most common offending agent, verotoxin produced by *E. coli* serotype O157:H7. Transmission is through person-to-person contact and also exposure to contaminated food, such as unpasteurized dairy products or beef.[106] Other causes of HUS include *Shigella* organisms, *S. pneumoniae, Aeromonas,* human immunodeficiency virus, and drugs; hereditary, familial, and idiopathic forms are recognized as well.

Principles of Disease

Renal compromise is the result of injury to the renal vascular endothelium induced by viral or bacterial agents or the toxins released. Microangiopathic hemolytic anemia then results from injury to the RBCs by fibrin strands along the narrowed blood vessels. Platelets, complement, and fibrin also are deposited in the glomerular lumen, leading to a decrease in glomerular filtration rate and renal failure.

Clinical Features

Patients with HUS present with watery diarrhea, crampy abdominal pain, and occasionally fever. From 2 to 3 days after onset of symptoms, patients experience increased abdominal pain with bloody stools, the latter developing in up to 89% of patients by day 5.[107] Other pathologic features may include toxic megacolon, ischemic colitis, intussusception, perforation, or delayed colonic stricture. After the prodromal gastroenteritis, patients experience sudden onset of hemolytic anemia, thrombocytopenia, and acute renal insufficiency, with possible progression to renal failure. In a meta-analysis published in 2003, death or end-stage renal disease occurred in 12% of cases of diarrhea-associated HUS, and 25% of survivors demonstrated long-term renal sequelae.[108] Pancreatic insufficiency resulting in insulin-dependent diabetes mellitus also has been reported. There are reports of HUS occurring in association with urinary tract infection as well.[109]

Central nervous system irritability may develop and may result in seizures in 40% of patients. Hypertension occurs in up to 50% of patients and may contribute to the development of encephalopathy. HUS recurrences have been associated with a 30% mortality rate.

Diagnostic Strategies

Leukocyte counts and C-reactive protein levels were found to be significantly higher in patients with toxin-producing *E. coli* O157:H7.[106] The peripheral blood smear shows microangiopathic changes such as teardrop cells, helmet cells, microspherocytes, and burr cells. WBC counts may be elevated, and the platelet count may be less than 50,000/µL. The hemoglobin can be as low as 5 g/dL as a result of the rapid hemolysis that occurs.

Differential Considerations

Considerations in the differential diagnosis of HUS include thrombocytopenic thrombotic purpura, ulcerative colitis, intussusception, and other causes of acquired hemolytic anemia.

Management

Supportive therapy and early peritoneal dialysis account for the reduction in current mortality rates to less than 5%. Patients should be rehydrated; however, it is important not to overload these children with fluids. Hyperkalemia is common and should be treated with sodium bicarbonate, calcium gluconate or chloride, dextrose and insulin, and sodium polystyrene sulfonate (Kayexalate). Patients with severe hyperkalemia, hyperphosphatemia, or severe metabolic acidosis require dialysis.

Packed RBCs (5 mL/kg during 4 hours) typically are administered if the hemoglobin falls below 6 g/dL. Platelet transfusions are required only for life-threatening bleeding or before an invasive procedure. Hypertension is responsive to calcium channel blockers, labetalol, captopril, or nitroprusside in refractory cases. Seizures typically respond to benzodiazepines and phenytoin; however, if they are secondary to hyponatremia, treatment with 3% saline (4 mL/kg) may be indicated. Treatment of the colitis itself also is supportive only because antimotility agents may lead to toxic megacolon. To date, no randomized trials have been conducted to show the effectiveness of antibiotics for the prevention of the development of HUS. Accordingly, because antibiotics may enhance the release of verotoxin from the bacteria, antibiotics should be avoided.[110] Hyperglycemia, ketonemia, and acidosis secondary to pancreatic islet cell necrosis are managed with insulin therapy.

Idiopathic HUS may be treated with plasmapheresis, especially if neurologic involvement is present. If this therapeutic measure is unsuccessful, renal transplantation may be required. Unfortunately, idiopathic HUS also can recur in the transplanted kidney.

www.ketabpezeshki.com 66485457-66963820

Disposition

Patients with HUS require hospital admission, and consultation with a pediatric nephrologist and a urologist should be arranged. Early dialysis and supportive therapy result in return to baseline renal function in up to 90% of patients with acute renal failure.

KEY CONCEPTS

Priapism

- In low-flow priapism, cavernosal aspiration plus irrigation has been effective when it is performed within the first 48 hours, and preferably within a few hours, of symptom onset. Phentolamine, phenylephrine, ephedrine, or 1 : 1,000,000 epinephrine often is added to the irrigation solution used in performing corporal aspiration.

Phimosis and Paraphimosis

- Steroid cream is first-line therapy for phimosis. In paraphimosis involving vascular compromise of the glans penis, a dorsal slit procedure may be necessary.

Testicular Torsion

- Delay in diagnosis and treatment can result in loss of spermatogenesis and, in severe cases, a necrotic, gangrenous testis. Testicular salvage rates are time dependent, with a 96% success rate if detorsion is performed less than 4 hours after symptom onset; with more than a 24-hour delay in time to treatment, the success rate decreases to less than 10%.

Varicoceles

- Left-sided varicoceles account for 85 to 95% of the cases. Intra-abdominal disease should be suspected in cases of right-sided varicoceles because these usually are caused by inferior vena cava thrombosis or compression of this vessel by tumors.

Urinary Tract Infections

- In children younger than 2 years, a urinalysis alone is inadequate to rule out urinary tract infections because this study yields false-negative results in as many as 10 to 50% of patients.

Hematuria

- Hematuria is common in children with causes as simple as a urinary tract infection to more complicated conditions, such as glomerulonephritis or Henoch-Schönlein purpura.

Renal Failure

- Renal failure thought to be secondary to dehydration should be corrected immediately with a bolus of normal saline, with repeated laboratory studies showing an improvement in renal function.

Hypertension

- Other significant clinical conditions, such as meningitis, brain tumor, intracerebral hemorrhage, stroke, and uremia, may be manifested similar to a hypertensive emergency; these conditions, however, in general have only mildly elevated blood pressure.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Roberts JR, Price C, Mazzeo T: Intracavernous epinephrine: A minimally invasive treatment for priapism in the emergency department. *J Emerg Med* 2009; 36:285-289.
2. Siegel JF, Rich MA, Brock WA: Association of sickle cell disease, priapism, exchange transfusion, and neurological events: ASPEN syndrome. *J Urol* 1993; 150:1480.
3. Merritt AL, Haiman C, Henderson SO: Myth: Blood transfusion is effective for sickle cell anemia–associated priapism. *CJEM* 2006; 8:119.
4. Cantasdemir M, Gulsen F, Solak S, Numan F: Posttraumatic high-flow priapism in children treated with autologous blood clot embolization: Long-term results and review of the literature. *Pediatr Radiol* 2011; 41:627-632.
5. Volgger H, Pfefferkorn S, Hobisch A: Posttraumatic high-flow priapism in children: Noninvasive treatment by color Doppler ultrasound–guided perineal compression. *Urology* 2007; 70:590.e3.
6. Huang YC, Harraz AM, Shindel AW, Lue TF: Evaluation and management of priapism: 2009 update. *Nat Rev Urol* 2009; 6:262-271.
7. Van Howe R: Cost-effective treatment of phimosis. *Pediatrics* 1998; 102:E43.
8. Wein AJ, Kavoussi LR, Campbell MF: *Campbell-Walsh Urology*, 10th ed. Philadelphia: WB Saunders; 2012.
9. Lerman SE, Liao JC: Neonatal circumcision. *Pediatr Clin North Am* 2001; 48:1539-1557.
10. Palmer LS, Palmer JS: The efficacy of topical betamethasone for treating phimosis: A comparison of two treatment regimens. *Urology* 2008; 72:68-71.
11. Ashfield JE, et al: Treatment of phimosis with topical steroids in 194 children. *J Urol* 2003; 169:1106.
12. Esposito C, et al: Topical steroid application versus circumcision in pediatric patients with phimosis: A prospective randomized placebo controlled clinical trial. *World J Urol* 2008; 26:187.
13. Kumar V, Javle P: Modified puncture technique for reduction of paraphimosis. *Ann R Coll Surg Engl* 2001; 3:126.
14. Turner CD, Kim HL, Cromie WJ: Dorsal band traction for reduction of paraphimosis. *Urology* 1999; 54:917.
15. American Academy of Pediatrics: Circumcision policy statement. *Pediatrics* 1999; 103:686-693.
16. Orden B, et al: Balanitis caused by group A beta-hemolytic streptococci. *Pediatr Infect Dis J* 1996; 15:920.
17. Chacko MR, Staat MA, Woods CR: *Genital infections in childhood and adolescence*. In: Feigin RD, Cherry JD, Demmler GJ, Kaplan SL, eds: *Textbook of Pediatric Infectious Diseases*, 5th ed. Philadelphia: WB Saunders; 2004:562-604.
18. Van Howe RS: Neonatal circumcision and penile inflammation in young boys. *Clin Pediatr (Phila)* 2007; 46:329-333.
19. Langer J, Coplen D: Circumcision and pediatric disorders of the penis. *Pediatr Clin North Am* 1998; 45:801.
20. Inoue N, Crook SC, Yamamoto LG: Comparing 2 methods of emergent zipper release. *Am J Emerg Med* 2005; 23:480-482.
21. Strait RT: A novel method for removal of penile zipper entrapment. *Pediatr Emerg Care* 1999; 15:412.
22. Kanegaye J: Penile zipper injury: A simple and less threatening approach using mineral oil. *Pediatr Emerg Care* 1993; 9:90.
23. Mishra SC: Safe and painless manipulation of penile zipper entrapment. *Indian Pediatr* 2006; 43:252.
24. Mellick L: Wire cutters and penis skin entrapped by zipper sliders. *Pediatr Emerg Care* 2011; 27:451-452.
25. Raveenthiran V: Releasing of zipper-entrapped foreskin: A novel nonsurgical technique. *Pediatr Emerg Care* 2007; 23:463.
26. Munden MM, Trautwein LM: Scrotal pathology in pediatrics with sonographic imaging. *Curr Probl Diagn Radiol* 2000; 29:185-205.
27. Nussbaum Blask AR, et al: Color Doppler sonography and scintigraphy of the testis: A prospective, comparative analysis in children with acute scrotal pain. *Pediatr Emerg Care* 2002; 18:67-71.
28. Santillanes G, Gausche-Hill M, Lewis RJ: Are antibiotics necessary for pediatric epididymitis? *Pediatr Emerg Care* 2011; 27:174-178.
29. Mushtaq I, Fung M, Glasson MJ: Retrospective review of paediatric patients with acute scrotum. *ANZ J Surg* 2003; 73:55-58.
30. Ciftci AO, Senocak ME, Tanyel FC, Büyükpamukçu N: Clinical predictors for differential diagnosis of acute scrotum. *Eur J Pediatr Surg* 2004; 14:333-338.
31. Moore CP, Marr JK, Huang CJ: Cryptorchid testicular torsion. *Pediatr Emerg Care* 2011; 27:121-123.
32. Baker LA, et al: An analysis of clinical outcomes using color Doppler testicular ultrasound for testicular torsion. *Pediatrics* 2000; 105:604.
33. Dogra V, Bhatt S: Acute painful scrotum. *Radiol Clin North Am* 2004; 42:349-363.
34. Terai A, et al: Dynamic contrast-enhanced subtraction magnetic resonance imaging in diagnostics of testicular torsion. *Urology* 2006; 67:1278.
35. Granados EA, Caicado P, Garat JM: Testicular torsion after 12 hours. III. *Arch Esp Urol* 1998; 51:978.
36. Garel L, et al: Preoperative manual detorsion of the spermatic cord with Doppler ultrasound monitoring in patients with intravaginal acute testicular torsion. *Pediatr Radiol* 2000; 30:41-44.
37. Bong GW, Koo HP: The adolescent varicocele: To treat or not to treat. *Urol Clin North Am* 2004; 31:509-515, ix.
38. Kass EJ: The adolescent varicocele: Treatment and outcome. *Curr Urol Rep* 2002; 3:100-106.
39. Gatti JM, Murphy JP: Acute testicular disorders. *Pediatr Rev* 2008; 29:235-241.
40. Bomalaski A, Mills J, Argueso L: Iliac vein compression syndrome: An unusual cause of varicocele. *J Vasc Surg* 1993; 18:1065.
41. Riccabona M, et al: Optimizing the operative treatment of boys with varicocele: Sequential comparison of 4 techniques. *J Urol* 2003; 169:666-668.
42. Zamakhshary M, To T, Guan J, Langer JC: Risk of incarceration of inguinal hernia among infants and young children awaiting elective surgery. *CMAJ* 2008; 179:1001-1005.
43. Gorelick MH, Shaw KN: Clinical decision rule to identify febrile young girls at risk for urinary tract infection. *Arch Pediatr Adolesc Med* 2000; 154:386.
44. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management: Urinary tract infection: Clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics* 2011; 128:595.
45. Zorc JJ, et al; Multicenter RSV-SBI Study Group of the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics: Clinical and demographic factors associated with urinary tract infection in young febrile infants. *Pediatrics* 2005; 116:644.
46. Shaikh N, Morone NE, Lopez J: Does this child have a urinary tract infection? *JAMA* 2008; 298:2895.
47. Jakobsson B, Esbjorner E, Hansson S: Minimum incidence and diagnostic rate of first urinary tract infection. *Pediatrics* 1999; 104:222.
48. American Academy of Pediatrics, Committee on Quality Improvement, Subcommittee on Urinary Tract Infection: Practice parameter: The diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. *Pediatrics* 1999; 103:843.
49. Rushton H: Urinary tract infections in children—epidemiology, evaluation and management. *Pediatr Clin North Am* 1997; 44:1133.
50. Munir V, Barnett P, South M: Does the use of volumetric bladder ultrasound improve the success rate of suprapubic aspiration of urine? *Pediatr Emerg Care* 2002; 18:346.
51. Baumann BM, et al: Volumetric bladder ultrasound performed by trained nurses increases catheterization success in pediatric patients. *Am J Emerg Med* 2008; 26:18.
52. Doley A, Nelligan M: Is a negative dipstick urinalysis good enough to exclude urinary tract infection in pediatric emergency department patients? *Emerg Med* 2003; 15:77.
53. Bachur R, Harper MB: Reliability of the urinalysis for predicting urinary tract infections in young febrile children. *Arch Pediatr Adolesc Med* 2001; 155:60.
54. Mori R, et al: Diagnostic performance of urine dipstick testing in children with suspected UTI: A systematic review of relationship with age and comparison with microscopy. *Acta Paediatr* 2010; 99:581.
55. Zorc JJ, Kiddoo DA, Shaw KN: Diagnosis and management of pediatric urinary tract infections. *Clin Microbiol Rev* 2005; 18:417.
56. Pitetti RD, Choi S: Utility of blood cultures in febrile children with UTI. *Am J Emerg Med* 2002; 20:271.
57. Crain EF, Gershel JC: Urinary tract infections in febrile infants younger than 8 weeks of age. *Pediatrics* 1990; 83:363.
58. Ishimine P: *The approach to the infant with fever*. In: Sharieff G, McCollough M, eds: *Infant and Neonatal Emergencies*. New York: Cambridge University Press; 2008.
59. Schnadower D, et al: Febrile infants with urinary tract infections at very low risk for adverse events and bacteremia. *Pediatrics* 2010; 126:1074.
60. Hoberman A, et al: Oral versus intravenous therapy for urinary tract infections in young febrile children. *Pediatrics* 1999; 104:79.
61. Pohl A: Modes of administration of antibiotics for symptomatic severe urinary tract infection. *Cochrane Database Syst Rev* 2007; 4:CD003237.

www.ketabpezeshki.com 66485457-66963820

62. McLoughlin TG, Joseph MM: Antibiotic resistance patterns of uropathogens in pediatric emergency department patients. *Acad Emerg Med* 2003; 10:347.
63. Michael M, et al: Short compared with standard duration of antibiotic treatment for urinary tract infection: A systematic review of randomized controlled trials. *Arch Dis Child* 2002; 87:118.
64. Talan DA, Stamm EW, Hooton TM: Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women. *JAMA* 2000; 283:1583.
65. Bradley JS, Jackson MA; Committee on Infectious Diseases, American Academy of Pediatrics: The use of systemic and topical fluoroquinolones. *Pediatrics* 2011; 128:e1034.
66. Nelson DS, Gurr MB, Schunk JE: Management of febrile children with urinary tract infections. *Am J Emerg Med* 1998; 16:643.
67. Nairn SJ, Sugarman JM: Adequacy of follow-up in children diagnosed with urinary tract infections in a pediatric emergency department. *Pediatr Emerg Care* 1995; 11:156.
68. Feld LG, et al: Hematuria—an integrated medical and surgical approach. *Pediatr Clin North Am* 1997; 44:1191.
69. Feld LG, Meyers KE, Kaplan BS: Limited evaluation for microscopic hematuria in pediatrics. *Pediatrics* 1998; 102:965.
70. Demirkesen O, et al: Extracorporeal shockwave lithotripsy in the pediatric population. *J Endourol* 1999; 13:147.
71. Coward RJM, et al: Epidemiology of pediatric renal stone disease in the UK. *Arch Dis Child* 2003; 88:962.
72. Palmer JS, Donaher ER, O'Riordan MA, Dell KM: Diagnosis of pediatric urolithiasis: Role of ultrasound and computerized tomography. *J Urol* 2005; 174:1413.
73. Panfeng S, et al: Management of pediatric urolithiasis induced by melamine-contaminated powdered formula (report of 619 cases). *Urology* 2011; 78:411-416.
74. Bush NC, et al: Hospitalizations for pediatric stone disease in United States, 2002-2007. *J Urol* 2010; 183:1151.
75. Smaldone MC, et al: Is ureteroscopy first line treatment for pediatric stone disease? *J Urol* 2007; 178:2128.
76. Pietrow PK, Pope JC, Adams MC, Shyr Y, Brock JW 3rd: Clinical outcomes of pediatric stone disease. *J Urol* 2002; 167:670.
77. Slavkovic A, et al: Extracorporeal shock wave lithotripsy for cystine urolithiasis in children: Outcome and complications. *Int Urol Nephrol* 2002-2003; 34:457.
78. Pinto E, Guignard JP: Renal masses in the neonate. *Biol Neonate* 1995; 68:175.
79. Schamberger RC: Pediatric renal tumors. *Semin Surg Oncol* 1999; 16:105.
80. Maxson WT: Benign proteinuria of childhood and adolescence: A survey. *Clin Pediatr* 1963; 2:662.
81. Loghman-Adham M: Evaluating proteinuria in children. *Am Fam Physician* 1998; 58:1145.
82. Mahan JD, Turman MA, Mentser MI: Evaluation of hematuria, proteinuria, and hypertension in adolescents. *Pediatr Clin North Am* 1997; 44:1573.
83. Ahn S, Inguli E: Acute poststreptococcal glomerulonephritis: An update. *Curr Opin Pediatr* 2008; 20:157.
84. Matsell DG, Wyatt RJ, Gaber LW: Terminal complement complexes in acute poststreptococcal glomerulonephritis. *Pediatr Nephrol* 1994; 8:671.
85. Daniels SR: Consultation with the specialist: The diagnosis of hypertension in children: An update. *Pediatr Rev* 1997; 18:131.
86. Simckes AM, Spitzer A: Poststreptococcal acute glomerulonephritis. *Pediatr Rev* 1995; 16:278.
87. Pais P, Kump T, Greenbaum L: Delay in diagnosis of poststreptococcal glomerulonephritis. *J Pediatr* 2008; 153:560.
88. Louis CU, Morgenstern BZ, Butani L: Thrombotic complications in childhood-onset idiopathic membranous nephropathy. *Pediatr Nephrol* 2003; 18:1298.
89. Soliday E, Grey S, Lande MB: Behavioral effects of corticosteroids in steroid-sensitive nephritic syndrome. *Pediatrics* 1999; 104:104.
90. Ulinski T, et al: Acute renal failure after treatment with non-steroidal anti-inflammatory drugs. *Eur J Pediatr* 2004; 163:148.
91. Belsha CW, Kohaut EC, Warady BA: Dialytic management of childhood acute renal failure: A survey of North American pediatric nephrologists. *Pediatr Nephrol* 1995; 9:361.
92. Stewart CL, Barnett R: Acute renal failure in infants, children and adults. *Crit Care Clin* 1997; 13:575.
93. Kemper MJ, Harps E, Muller-Wiefel DE: Hyperkalemia: Therapeutic options in acute and chronic renal failure. *Clin Nephrol* 1996; 46:67.
94. Nathan BM, Moran A: Metabolic complications of obesity in childhood and adolescence: More than just diabetes. *Curr Opin Endocrinol Diabetes Obes* 2008; 15:21.
95. Proulx F, et al: Convulsions and hypertension in children: Differentiating cause from effect. *Crit Care Med* 1993; 21:1541.
96. McCarthy HJ, Tizard EJ: Clinical practice: Diagnosis and management of Henoch-Schönlein purpura. *Eur J Pediatr* 2010; 169:643-650.
97. Chang WL, Yang YH, Wang LC, Lin YT, Chiang BL: Renal manifestations in Henoch-Schönlein purpura: A 10-year clinical study. *Pediatr Nephrol* 2005; 20:1269-1272.
98. Gonzalez LM, Janniger CK, Schwartz RA: Pediatric Henoch-Schönlein purpura. *Int J Dermatol* 2009; 48:1157.
99. Sharieff G, Francis K, Kupperman N: Atypical presentation of Henoch-Schönlein purpura in two children. *Am J Emerg Med* 1997; 15:375.
100. Wang L, et al: Successful treatment of mesenteric vasculitis caused by Henoch-Schönlein purpura with methylprednisolone pulse therapy. *Clin Rheumatol* 2003; 22:140.
101. Weiss PF, et al: Effects of corticosteroids on Henoch-Schönlein purpura: A systematic review. *Pediatrics* 2007; 120:1079.
102. Tullus K, Marks SD: Vasculitis in children and adolescents: Clinical presentation, etiopathogenesis, and treatment. *Paediatr Drugs* 2009; 11:375.
103. Tanaka H, et al: Early treatment with oral immunosuppressants in severe proteinuric purpura nephritis. *Pediatr Nephrol* 2003; 18:347.
104. Kawasaki Y, et al: Efficacy of methylprednisolone and urokinase pulse therapy for severe Henoch-Schönlein nephritis. *Pediatrics* 2003; 111:785.
105. Flynn J: Causes, management approaches, and outcome of acute renal failure in children. *Curr Opin Pediatr* 1998; 10:184.
106. Kawamura N, Yamazaki T, Tamai H: Risk factors for the development of *Escherichia coli* O157:H7 associated with hemolytic uremic syndrome. *Pediatr Int* 1999; 41:218.
107. Cohen MB: *Escherichia coli* O157:H7 infection: A frequent cause of bloody diarrhea and the hemolytic-uremic syndrome. *Adv Pediatr* 1996; 43:171.
108. Garg AX, et al: Long term renal prognosis of diarrhea-associated hemolytic uremic syndrome. *JAMA* 2003; 290:1360.
109. Tarr P, et al: Hemolytic-uremic syndrome in a six-year-old girl after a urinary tract infection with Shiga toxin–producing *Escherichia coli* O103:H2. *N Engl J Med* 1996; 335:635.
110. Iijima K, Kamioka I, Nozu K: Management of diarrhea-associated hemolytic uremic syndrome in children. *Clin Exp Nephrol* 2008; 12:16.

www.ketabpezeshki.com 66485457-66963820

Chapter 175

Neurologic Disorders

David H. Rubin, Dina Halpern Kornblau, Edward E. Conway, Jr., and Stuart M. Caplen

PERSPECTIVE

Many acute neurologic manifestations of disease that precipitate a visit to the emergency department (ED), such as seizure, vertigo, ataxia, and headache, appear in both adults and children. However, associated signs and symptoms and diagnostic considerations in children are unique and markedly different from those in the adult population. Moreover, bacterial meningitis, once a predominantly pediatric disease, is now mainly a disease of adults; yet it remains imperative to recognize subtle signs and symptoms of this lethal disease in infants and young children.

ACUTE BACTERIAL MENINGITIS

Perspective

Despite advances in medical care, acute bacterial meningitis (ABM) remains a potentially life-threatening emergency. Nationwide mortality rates for treated cases are 20 to 30% in neonates and adults and 2% in infants and children.[1] With the recommendation in 1991 that all infants, starting at 2 months of age, receive the conjugated vaccine against *Haemophilus influenzae* type b, the incidence of bacterial meningitis caused by this organism has been reduced in children by more than 99%. However, recent data show that the highest incidence is still found in children younger than 2 months.[1,2] Even with the best care, 10 to 30% of all survivors of bacterial meningitis of all types demonstrate persistent, functionally important disabilities.[3,4] These include hearing deficits, seizures, learning and behavioral problems, and cognitive impairments.

Neonates

Group B streptococci account for more than three quarters of the cases of neonatal meningitis; *Escherichia coli* (and other coliforms), *Listeria monocytogenes, Streptococcus pneumoniae, Neisseria meningitidis,* and *H. influenzae* are responsible for another one fourth of cases.[2] The incidence of early-onset group B streptococcal disease has declined as a result of intrapartum prophylaxis. However, late-onset disease (after 7 days of life) has not. *Staphylococcus epidermidis*, *Staphylococcus aureus*, *S. pneumoniae*, *N. meningitidis*, group D streptococci, *Ureaplasma urealyticum*, *H. influenzae* type b, and nontypable strains are less common pathogens in neonatal infection. *L. monocytogenes* rarely is the agent of meningitis in neonates but is important because of its prevalence within some immigrant groups, its association with unpasteurized dairy products, and its resistance to cephalosporins.[5]

Infants and Children

Beyond the neonatal period, in the United States, *S. pneumoniae, N. meningitidis,* and *H. influenzae* account for 90% of the documented cases of ABM.[2] Unusual pathogens include *Salmonella* species, *Campylobacter* species, *L. monocytogenes*, group G streptococci, *Francisella tularensis,* group B beta-hemolytic streptococci, and several anaerobic organisms.[1,2] Recent advances involving the heptavalent pneumococcal conjugate vaccine (PCV7), recommended for all children younger than 2 years, have dramatically reduced the number of cases of bacterial meningitis caused by invasive pneumococcal disease.[6] It is anticipated that the newly released 13-valent pneumococcal conjugate vaccine (PCV13) will have an even greater impact on the reduction of invasive pneumococcal disease.[7]

Principles of Disease

Host factors influence the degree of susceptibility to meningitis. Newborn infants younger than 1 month, particularly those born prematurely, are at greatest risk for ABM owing to their immunologic immaturity. Other groups predisposed to ABM include males, Native Americans, African Americans, malnourished persons, indigent urban dwellers, daycare center attendants, patients with compromised immune status (from sickle hemoglobinopathies, acquired immunodeficiency syndrome [AIDS], asplenia, renal disease, hepatic disease, diabetes mellitus, or dysgammaglobulinemia), and those undergoing immunosuppressive treatment, including corticosteroid therapy.

Bacterial meningitis is thought to result from infection of the respiratory tract, development of bacteremia, invasion of the meninges, and inflammation of the meninges and brain.[5] Invasion of the meninges by bacterial pathogens is facilitated by mechanical disturbances. These include recent neurosurgical procedures, such as ventriculoperitoneal shunt placement and lumbar puncture, and skull fracture with a persistent cerebrospinal fluid (CSF) leak. Congenital or developmental central nervous system (CNS) abnormalities also predispose affected patients to bacterial seeding of the CNS. These include intracranial cysts and epidermoid or dermoid tumors, often with an associated congenital dermal sinus track.

For ABM to occur, organisms must gain entrance into the subarachnoid space. On rare occasions, this occurs as a direct extension from a contiguous focus, such as sinusitis, mastoiditis, or otitis media. In a majority of cases, the bacterial organism gains access to the bloodstream and hematogenously seeds through inflamed capillaries within the choroid plexus. Most cases of ABM follow a progression of events. After exposure and nasopharyngeal

www.ketabpezeshki.com 66485457-66963820

colonization, invasion of the blood occurs. The organism can be recovered from the bloodstream in up to 90% of patients with CSF culture–proven bacterial meningitis.

If bacteria gain entrance into the subarachnoid space, they replicate. Microbial traversal of the blood-brain barrier occurs by microbial interactions with host receptors. Each organism may gain entry in a specific manner. For example, *E. coli* penetration into the brain involves binding to and invasion of the human brain microvascular endothelial cells, which are part of the blood-brain barrier.[8] Host inflammatory mediators and cytokines, including interleukin-1, tumor necrosis factor, and platelet-activating factor, may also be produced and secreted by CNS macrophages and endothelial cells. As a result of an inflammatory response, vascular and parenchymatous cerebral changes occur. These include vasculitis, microthrombus formation, occlusion of venous sinuses, reduced blood flow, increased permeability of the blood-brain barrier, increased intracranial pressure (ICP), diffuse cerebral edema, and intracerebral hemorrhage. Changes involved in microbial invasion of the blood-brain barrier may be different from those involved in the release of inflammatory mediators and cytokines in response to meningitis-causing pathogens.[8]

Clinical Features

In three fourths of children ultimately diagnosed with ABM, the clinical presentation is subacute, evolving during 2 to 5 days. At onset, affected children typically exhibit a variety of symptoms and signs, such as fever, malaise, decreased interest in surroundings, irritability, alteration in sleeping pattern, anorexia, nausea, vomiting, or diarrhea. These findings are nonspecific, seen with equal frequency in children who are suffering from trivial and self-limited illnesses.[8,9] If the patient is examined early in the course, physical signs may be subtle or lacking.

Children with this insidious presentation have a better prognosis than that of patients with ABM who present with a rapid progression of signs and symptoms. In one fourth of children with ABM, an acute illness with manifestations such as vomiting, fever, and lethargy develops in less than 24 hours. In such patients, the diagnosis is rarely missed.[10] Those with fulminant illness exhibit a higher risk for death as well as immediate and long-term complications.

The cutaneous expression of ABM may be a helpful finding suggestive of specific organisms. Petechial and purpuric eruptions may suggest meningococcemia but also can be seen in cases of pneumococcal disease and *H. influenzae* meningitis. Herpes simplex virus (HSV) infection in the neonate is suggested by blisters or erosions in or around the eye or mouth or on the skin.

Neonatal Period (Up to the Age of 1 Month)

The clinical findings with ABM in the neonate are nonspecific and may include altered vital signs, behavioral changes, neurologic aberrations, dermatologic lesions, and gastrointestinal manifestations (Table 175-1). In the first 30 days of life, patients who present to an ED with a temperature of 38° C (100.4° F) or higher are found to have serious bacterial illness (SBI) and ABM in 4 to 15% and 1 to 2% of cases, respectively.[11] The absence of fever does not eliminate the possibility of SBI because more than half of neonates with meningitis are afebrile or exhibit hypothermia. Other vital sign changes include tachycardia, bradycardia, tachypnea, and apnea. Apnea with cessation of breathing for longer than 20 seconds may signify either seizure activity or a nonspecific medullary respiratory center dysfunction.

Neonates have a limited behavioral repertoire. Within that range, even subtle changes in behavioral patterns can reflect early meningeal involvement. Restlessness, listlessness, increased or decreased sleeping time, and irritability may be clues. Irritability

Table 175-1 Clinical Findings with Bacterial Meningitis

FEATURE	NEWBORN	INFANT AND CHILD
General	Apnea Tachypnea Hypothermia Hyperthermia Bradycardia	Fever Shaking chills Myalgia Neck ache, backache Tachycardia
Behavioral	Restlessness Paradoxical irritability Lethargy	Malaise Irritability Lethargy
Neurologic	High-pitched cry Nystagmus Vacant stare Seizure Opisthotonos Altered tone Nuchal rigidity Bulging fontanel	Altered mentation Focal neurologic signs Hearing deficit Seizure Gait disturbance Photophobia Nuchal rigidity Kernig's and Brudzinski's signs
Dermatologic	Cyanosis Petechiae Purpura Delayed capillary refill Livedo reticularis	Cyanosis Petechiae Purpura Delayed capillary refill
Gastrointestinal	Altered feeding Diarrhea Vomiting Abdominal distention Jaundice	Anorexia Nausea Vomiting

in a neonate without meningeal invasion generally is alleviated by human contact. Increased irritability with cuddling should suggest the diagnosis of ABM. The neurologic manifestation of ABM in the neonate may be a high-pitched cry, incessant cry, absent cry, or moan. A vacant stare, hypertonicity, trembling chin, or bicycling motion of the extremities suggests a seizure. Focal or generalized tonic-clonic activity, although possible, is less commonly seen. Nuchal rigidity occurs in less than 25% of cases of neonatal ABM. A bulging fontanel and diastasis of the sutures, both hallmarks of an increased ICP, are present in approximately 15% of the cases of neonatal ABM.

Rashes are infrequent manifestations of neonatal meningitis.[12] One clue may be generalized pallor accompanied by indistinctly outlined truncal patches of blue discoloration (livedo reticularis). Difficulty in feeding and unusual stooling patterns are nonspecific gastrointestinal features. Nonprojectile vomiting may appear in the course of meningitis, becoming projectile only after ICP has increased. Increased stool volume, irritability during defecation, abdominal distention, hepatomegaly, and jaundice can develop with meningitis.

One Month to 12 Months

In young infants (younger than 3 months), symptoms of SBI are similar to those in the neonate, but as the infant grows older, the social repertoire and motor capability expand, allowing greater opportunity for assessment on physical examination of alteration in behavior or signs and symptoms of bacterial meningitis. Nuchal rigidity, although not commonly present, is highly predictive of ABM in this age group. The absence of nuchal rigidity does not preclude the possibility of CNS infection; however, other signs often are present, such as poor tone, decreased interactiveness, inconsolability, alteration in gaze and focus, and weak cry.

www.ketabpezeshki.com 66485457-66963820

One Year to 5 Years

The cardinal features in this age group are fever, headache, vomiting, and stiff neck. Obtundation and lethargy also are common findings with meningitis but are nonspecific. After the first year of life, neck stiffness with difficulty in flexing the neck is reliably seen during the acute phase of meningitis. A patient rarely may exhibit torticollis.[13] The clinician can attempt to elicit nuchal rigidity by forced flexion of the neck with the child in the supine position. However, this method is less reliable than attempting neck flexion with the child seated with both legs outstretched. Both of these maneuvers involve passive motion that many children voluntarily resist. More reliable methods that have fewer false-negative and false-positive results involve active neck motion on the part of the child. In a toddler, a distracting object can be used to attract eye contact, and the active range of neck motion can be determined. In addition, the neck stiffness that accompanies ABM may be displayed in both the prone and supine positions when the child's shoulders are placed at the edge of the examining table and minimal support of the occiput or forehead is provided manually. Presence of Kernig's sign (flexion of the hip 90 degrees with subsequent pain on extension of the leg) and Brudzinski's sign (involuntary flexion of the hips and knees after passive flexion of the neck performed with the patient supine) is less reliable. Kernig's and Brudzinski's signs are seen in approximately 27% and 51%, respectively, of children 1 to 5 years of age with ABM.[14]

Older than 5 Years

Headache, fever, stiff neck, and alteration of sensorium are common presenting signs and symptoms in children older than 5 years, as they are in the adult patient with ABM.

Diagnostic Strategies

Lumbar Puncture

Indications

Lumbar puncture is indicated in any child in whom bacterial meningitis is suspected (Box 175-1). Patients to be considered candidates for this procedure are those with classic signs and symptoms, such as fever, stiff neck, and photophobia, but in infants and children, classic signs often are absent. In a study by Walsh-Kelly and colleagues, nuchal rigidity was present in only 27% of infants younger than 6 months with bacterial meningitis. By 12 months of age, 71% showed nuchal rigidity; this rate rose to more than 95% by 19 months of age.[15] Therefore, the decision to perform a lumbar puncture in children with suspected meningitis should be based primarily on the constellation of presenting signs and symptoms.

Nuchal Signs. A lumbar puncture should be performed in ill children who exhibit nuchal rigidity or Kernig's sign or Brudzinski's sign and who have suspected meningitis. These three signs of meningeal irritation can also be seen in non-ABM, such as subarachnoid hemorrhage and trauma.

Suspected Sepsis in Young Infants. A bacterial infection is the most likely etiologic disorder in any infant younger than 3 months who is ill.[11] Current practice advocates that the possibility of severe bacterial infection be pursued with an ill young infant. No distinguishing features differentiate sepsis from meningitis in this age group. Because 50% of neonates with acute meningitis are bacteremic at the time of the initial evaluation, and because an intracranial infection subsequently develops in 25% of bacteremic neonates, blood cultures and lumbar puncture should be undertaken concomitantly.[16,17] In infants older than 1 month but younger than 3 months, history and physical examination, even if augmented with selective laboratory investigations (excluding lumbar puncture), may fail to identify those infants with SBI. A lumbar puncture should be undertaken unless there is a contraindication as part of the sepsis evaluation in this age group.[8,18,19]

Toxic Appearance. A lumbar puncture also should be considered in any child with toxic appearance. Such observations include a blunted response to social overtures, poor perfusion, altered motor tone, and abnormal cry. Febrile pediatric patients of all ages with a toxic appearance have an increased incidence of severe bacterial infections, including ABM.[8]

When obvious clues to the source of an apparent infectious process exist and an initial lumbar puncture yields normal findings in the face of increasing severity of illness, additional information can be obtained by repeating the lumbar puncture. The CSF composition may change from normal cellularity to marked pleocytosis within as little as 30 minutes.[20] Thus later reexamination of the CSF may be invaluable in establishing the nature of an occult intracranial infection.

Febrile Illness after Intimate Contact. All children who have prolonged and close physical involvement with persons found to have a serious bacteremic illness require prompt medical evaluation. In particular, a strong indication for lumbar puncture is the development of fever after intimate contact with high-risk patients with meningococcal disease (higher risk: household contacts, children younger than 2 years, history of direct exposure to secretions from index case or having slept in same dwelling 7 days before onset of illness, and passengers seated next to an index case on a flight longer than 8 hours) or *Haemophilus* disease (higher risk: household with at least one contact younger than 4 years who is either unimmunized or poorly immunized, a child younger than 12 months who has not received the primary series of immunizations, an immunocompromised child of any age regardless of *H. influenzae* type b immunization status, and a child who attends daycare where two or more cases have been seen in a 60-day period). Even in the absence of pleocytosis, the emergency physician should consider admission and antibiotic treatment when a child has been exposed to meningococcemia and is symptomatic (e.g., fever, headache) as absence of meningitis is a poor prognosis in this disease.

Febrile Seizures. Children 6 months to 5 years of age who have experienced a simple febrile seizure and who appear well (alert, active, playful) are extremely unlikely to have meningitis. In general, patients who exhibit complex features of the febrile seizure are at increased risk for meningitis. Lumbar puncture should be *considered* in patients who have characteristics that increase their risk for ABM or who show signs and symptoms of ABM. The historical features are age between 6 and 12 months; exposure to another child with meningitis or serious bacterial infection; deficiency in *H. influenzae* or *S. pneumoniae* immunizations, or immunization status cannot be determined; and pretreatment with antibiotics. Children with febrile seizures who exhibit any clinical sign associated with increased risk for intracranial infection, including lethargy, decreased motor tone, doll's eye sign,

Box 175-1 Indications for Lumbar Puncture in Suspected Acute Bacterial Meningitis

- Signs and symptoms of meningitis or toxic appearance
- Suspected neonatal sepsis
- Febrile infant younger than 2 months
- Suspected sepsis in an abnormal host
- *Consider* lumbar puncture in suspected acute bacterial meningitis
  - Febrile illness after intimate contact with person with meningitis or serious bacterial infection
  - Fever and seizure
  - Fever and petechiae

www.ketabpezeshki.com 66485457-66963820

inability to fix and follow, decreased response to painful stimuli, nuchal rigidity, full fontanel, petechiae, and poor skin perfusion, should undergo lumbar puncture.[21]

Fever and Petechiae. Trivial to life-threatening infectious disease can cause fever and petechiae. No current optimal strategy has emerged for evaluation of febrile children with petechial eruptions. Well-appearing febrile children with localized petechiae, especially above the nipple line and with no purpura, are unlikely to have invasive bacterial disease. Patients at highest risk for invasive bacterial disease are more likely to appear ill or to have generalized petechiae and purpura or signs of meningeal irritation.[22] In the high-risk group, unless it is contraindicated by coagulopathy, lumbar puncture should be performed to exclude concurrent meningitis.[23]

Sepsis Suspected in an Abnormal Host. Immunocompromised pediatric patients are at risk for the development of both opportunistic infections and invasive illness from pathogens common to all children. Immunologically incompetent children may not exhibit the typical manifestations of intracranial infections, including nuchal rigidity. However, meningitis should be suspected in an immune-impaired child who experiences only a change in mental status. CSF parameters in these patients are less sensitive indicators of the presence of bacterial meningitis compared with normal host response to a bacterial invasion of the meninges. A lumbar puncture nonetheless should be performed in the process of excluding meningitis in a compromised host.

Penetration of Dura. Fracture through the paranasal sinuses or anterior or middle cranial fossa and penetrating nasal injury or instrumentation may lead to dural tears. Such defects constitute a potential portal of entry for microorganisms into the CNS. Evidence of CNS infection generally is seen within 2 weeks of the initial injury, but clinical manifestations may be delayed for years. Persistent CSF otorrhea or rhinorrhea may be encountered but is not a clinical prerequisite for post-traumatic meningitis. When patients with a recent or remote history significant for craniofacial trauma develop any constellation of symptoms suggestive of meningitis, lumbar puncture should be performed after a computed tomography (CT) scan.

Acute Hearing Loss. Hearing loss has been identified in up to one third of patients with ABM. Hearing impairment may be identified in the acute phase or become apparent only in the post-meningitic period. Of significance, hearing loss may precede the onset of systemic complaints and herald the appearance of meningitis. This is especially true for patients with an inner ear fistula or basilar skull fracture. Acute hearing loss should be an indication for lumbar puncture in patients with traumatic injury, which may have directly inoculated organisms into the labyrinth or basilar subarachnoid space, and in patients who have symptoms suggestive of meningitis.

Contraindications

Most children with ABM exhibit some mental status changes, but rapid onset and progression to deep coma (Glasgow Coma Scale score of less than 8) usually reflect increased ICP, and lumbar puncture is contraindicated.[24] Herniation of the temporal lobes through the tentorium or herniation of the cerebellar tonsils through the foramen magnum rarely occurs in patients with meningitis and increased ICP. Focal neurologic signs suggestive of an abscess are further contraindications to lumbar puncture in children.

Positioning and Precautions

When it is not contraindicated, emergency lumbar puncture with CSF examination should be performed to confirm a presumptive diagnosis of ABM. Patients with suspected bacterial meningitis traditionally were placed in the lateral decubitus position with the spine flexed and the knees drawn upward toward the chest, with shoulders and back perpendicular to the table. Studies with ultrasonography have called this positioning into question and reveal that the interspinous space is greatest in the sitting position with the hips flexed, and neck flexion did not result in increase in the interspinous space.[25] These data reveal that forward head flexion may not be necessary. Opening pressure should be obtained if possible with the patient in the lateral decubitus position. In circumstances in which opening pressure measurement cannot be obtained, an alternative position is sitting with the thighs flexed toward the abdomen.

In the stable monitored patient, the potential for complications is sufficiently low that sampling of the CSF should be routine. Prevention of post–lumbar puncture cephalgia is enhanced by use of smaller gauge needles, restriction of the sample fluid volume to 3 mL, and reinsertion of the stylet before removal of the needle. The small risk of introducing bacterial skin flora is reduced with proper aseptic technique. Causing meningitis by performance of a lumbar puncture in the course of a bacteremic illness is a theoretic concern but does not occur. The information obtained from the lumbar puncture outweighs this hypothetical risk.

Standard Cerebrospinal Fluid Interpretation

A standard CSF examination includes bacterial culture and Gram's stain from tube 1, protein and glucose assessment from tube 2, and blood cell count from tube 3. If there is not an adequate amount of CSF collected, the most important is the specimen sent for culture and Gram's stain. In cases of culture-proven bacterial meningitis, up to 6% of patients have normal glucose and protein levels, few white blood cells, and negative result on Gram's staining. Patients who have received antibiotics before their first lumbar puncture merit special mention. Although the CSF can be sterilized after the administration of antibiotics in the ED, especially in cases of pneumococcal and meningococcal disease, the CSF profile often is unaffected for more than 12 to 24 hours after therapy.[6]

Glucose. The CSF glucose concentration should be interpreted in relation to a concomitant serum glucose value. The normal steady-state ratio of CSF glucose to serum glucose is approximately 0.6. Hypoglycorrhachia, defined as a ratio below 0.4, is characteristically found in cases of ABM with common pathogens and with *Mycobacterium tuberculosis*. Hypoglycorrhachia also may be associated with viral meningitis, although CSF glucose concentration in such cases typically is normal.

Protein. The normal CSF protein range is 55 to 80 mg/dL in newborns (65-150 mg/dL in preterm babies) and 5 to 40 mg/dL in children. Normal to modest elevations in protein concentration occur in the course of viral meningitis. Higher levels of protein are encountered with ABM. After a traumatic lumbar puncture, each 800 to 1000 red blood cells elevate the protein level by 1 mg/dL.

Cellularity. A representative cellularity profile is presented in Table 175-2. Unfortunately, these numbers have been largely derived from healthy or nonsystemically ill children.[26] The standard "panic values" that have been quoted often are more than 2 SDs above the mean or are figures that are seen in only 5 to 10% of studied populations. Cellularity that exceeds these typical threshold values can be seen with conditions that indirectly influence the CNS; however, such cases should be considered to represent possible ABM and treated accordingly. These conditions include generalized seizure, shigellosis, and parameningeal foci of infections such as otitis media, sinusitis, and mastoiditis. Patients with suspected sepsis or with foci of infection distant from the CNS, such as pneumonia, also may have increased cellularity. Classically in ABM, the total CSF white blood cell count ranges from 1000 to 20,000/mm^3. A white blood cell count higher than 2000/mm^3 is present in more than one third of cases of ABM. Significant

www.ketabpezeshki.com 66485457-66963820

Table 175-2 Reported Values for Cerebrospinal Fluid Cellularity

AGE	TOTAL WHITE BLOOD CELLS/µL Mean	Range	Threshold Exceeded
Preterm	7	0-44	>9
Term newborn	8	0-32	>22
0-4 weeks	11	0-50	>35
4-8 weeks	7	0-50	>10
>8 weeks	2	0-8	>6

pleocytosis also can accompany aseptic meningitis in as many as 95% of cases.[27]

Of note, the practice of "correcting" for white blood cells in bloody CSF samples may have little scientific support. Underestimation of the white blood cell count may occur in the setting of culture-positive meningitis. Furthermore, consideration should be given to other illnesses, such as HSV encephalitis, in which an increased number of red blood cells may be seen in the CSF.[5]

In the first month of life, up to 60% of the cells in the normal CSF are polymorphonuclear leukocytes (i.e., neutrophils [PMNs]). Beyond 1 month in the normal state, not more than 3 PMNs/mm^3 should be seen. Shortly after invasion of the meninges, white blood cells can be sampled from the lumbar space. Traditional teaching suggests that a rise in PMNs is characteristic of ABM. However, PMNs and bands may be present in patients with viral meningitis as well.

Gram's Stain. The probability of visualizing bacteria with Gram's staining depends on the number of bacterial organisms present at the time of sampling.[8] One fourth of the smears yield positive results with 10^3 or more colony-forming units (CFUs) per milliliter; 60% of the smears show positive results with 10^3 to 10^5 CFUs/mL, and 97% show positive results with 10^6 CFUs/mL. A positive result on Gram's staining necessitates immediate antibiotic therapy, even in the absence of increased white blood cells and protein levels or decreased glucose level in the CSF.

Other Cerebrospinal Fluid Tests

Antigen Detection. Commercial antigen detection kits are available for the common pathogens causing ABM. Microbial antigens in CSF are detected by coagglutination, latex agglutination, countercurrent immunoelectrophoresis, enzyme-linked immunosorbent assay, and centrifugation-augmented solid-phase immunoassay. Because antigens remain measurable after antibiotic treatment, antigen detection proves to be most effective in cases of partially treated meningitis or in patients in whom the CSF Gram's stain and culture results are negative and ABM is strongly suspected. In any meningitic state, either untreated or pretreated, the CSF antigen detection kits (commercially available to detect multiple organisms in one packaged product) are most sensitive when more than 500 white blood cells are present in the CSF. The antigens typically are present at high levels in the CSF for several days, even after parenteral antibiotics have been initiated. A positive CSF assay result provides reliable bacteriologic diagnosis. A negative antigen test result cannot exclude the diagnosis of ABM.

Cytokines. Assayed concentrations of C-reactive protein, various interleukins, tumor necrosis factor, and prostaglandins are elevated with ABM. These assays require sophisticated techniques and expensive equipment and take several hours to complete. For these reasons, the assays are of little utility in the ED setting.

Polymerase Chain Reaction Testing. Polymerase chain reaction (PCR) is useful in the identification of pathogens in those patients previously treated with antibiotics or in resource-poor settings. It has been shown to have a higher detection rate compared with other tests.[8]

Other Laboratory Testing Instruments

The performance of other diagnostic tests in addition to CSF analysis should be guided by the clinical situation. Blood cultures are of proven value in the patient with ABM. A pretreatment blood culture will identify the organism recovered from the CSF in 86 to 92% of cases. Culture of specimens from body surfaces and orifices (e.g., nose and throat) is not helpful in identifying the causative pathogen. Positive results on culture from urine, stool, and pleural space samples substantiate systemic bacterial disease but do not ensure the presence of an intracranial infection with the same organism.

Determination of serum electrolyte levels and serum glucose concentration may be helpful because changes in body water content and electrolytes may be a feature of ABM. The serum sodium level may be below 135 mEq/L in more than half of the patients at the time of presentation. The blood glucose level should be estimated rapidly with a glucose oxidase tape because hypoglycemia secondary to poor intake, vomiting, and metabolic derangements is a common complication. The estimated value should be confirmed with a serum sample submitted for electrolyte determinations.

No hematologic profiles can consistently identify pediatric patients with ABM; nevertheless, a complete blood count is (CBC) warranted because the total white blood cell count and platelet counts may aid prognostic risk assessment. Either thrombocytopenia or neutropenia at admission may be an ominous feature.

At the time of establishment of the diagnosis of ABM in a moderately ill patient, arterial blood gas determination can be performed in selected cases as indicated by apparent hypoventilation or hypoxia or presence of signs of metabolic acidosis.

Gram's stain smear of a petechial or purpuric lesion may reveal an offending organism causing systemic invasion. Serum C-reactive protein assay, erythrocyte sedimentation rate determination, and measurements of the various cytokines can be used to support the diagnosis of systemic bacterial infection. These tests yield nonspecific findings, however, and cannot be used to include or to exclude a diagnosis of ABM. Elevated pretreatment values may be tracked to determine the most effective duration of therapy for ABM.

A urine specimen should be submitted for analysis. If the patient is pretreated with antibiotic agents, urine microbial antigen detection should be performed. Urine antigen detection may be positive in up to 87% of pretreated cases of ABM. A midstream clean-catch voided specimen or urine acquired by catheterization should be submitted. Urine from a bag specimen that is potentially contaminated by fecal material may yield false-positive results from cross-reactivity with *E. coli* organisms.

Radiology

CT of the head should be performed when the clinical findings suggest subdural empyema, cavernous sinus thrombosis, lateral sinus thrombosis, cerebral hemorrhage, brain tumor, brain abscess, or parameningeal focus of infection. CT of the head without contrast enhancement should be performed on an emergency basis when the patient exhibits signs and symptoms of elevated ICP. Concern for raised ICP is warranted if the patient has cranial nerve palsy, absence of retinal venous pulsations, altered pupillary responses, papilledema, focal seizure, hemiparesis, ataxia, obtundation, persistent vomiting, decorticate or decerebrate posturing, or bradycardia unassociated with hypoxemia. A decision to image the head or other body parts (such as the chest) must not delay

www.ketabpezeshki.com 66485457-66963820

Box 175-2 Differential Diagnosis of Acute Bacterial Meningitis

Infectious
Septicemia
Rickettsemia
Encephalitis
Subdural empyema
Spinal epidural abscess
Intracranial epidural abscess
Viral meningitis
Fungal meningitis
Tuberculous meningitis
Myocarditis
Shigellosis

Traumatic
Shaken baby syndrome
Closed head injury

Metabolic
Hypoglycemia
Ketoacidosis
Hyponatremia
Hypernatremia
Uremia
Urea cycle defect

Miscellaneous
Intussusception
Intoxication
Toxic exposure
Seizure disorder
Brain tumor
Arteriovenous malformation
Ruptured dermoid cyst

antibiotic administration for patients with ABM. If patients with a ventriculoperitoneal shunt demonstrate fever or signs of increased ICP, they also should undergo CT before tapping of the shunt for CSF.

Differential Considerations

Any of the manifestations of ABM can be expressed in a single patient. The most common presentation involves a combination of thermal instability, altered behavior, blunted mental status, and neck stiffness. The differential diagnosis for this constellation comprises infectious, metabolic, traumatic, and miscellaneous conditions (Box 175-2).

Many conditions cause a child to appear ill. Any infectious agent can cause clinical illness in children, particularly in the first months of life. Infants with infectious disease exhibit altered affect, including significant changes in mental status, strongly suggesting an intracranial pathologic process. Beyond infancy, children may exhibit a toxic appearance with any focal infection or with extensions from a primary focus leading to systemic invasion.[10] In addition to infection, a change in mental status may be noted with endocrinopathy, hypoglycemia, electrolyte imbalance, metabolic disease, uremia, seizure, unintentional trauma, abusive head injury, intussusception, or exposure to toxins.

Nuchal rigidity provokes strong consideration of ABM. However, neck stiffness associated with altered mentation or neurologic deficit can occur with spontaneous intracranial hemorrhage, hemorrhage into brain tumor, epidural abscess, or brain abscess. Other causes of stiff neck include retropharyngeal abscess, peritonsillar abscess, and torticollis.

Viral Meningitis

In the first few years of life, the signs and symptoms of bacterial and viral meningitis can be indistinguishable.[28] Beyond 1 year of age, a majority of children with viral meningitis have a relatively mild illness compared with children with ABM. Fever and retroorbital or frontal headache are frequent symptoms of both diseases. Gastrointestinal disturbances, such as anorexia, nausea, and diarrhea, are more common with viral meningitis. Generalized myalgia also may be a feature, and patients often complain of neck ache or neck stiffness. However, reduction in active neck flexion is uncommon.

Modest elevation of PMNs in CSF specimens coupled with normal glucose level, normal to slightly elevated protein concentration, and negative result on Gram's staining is anticipated with viral meningitis. These laboratory findings can confirm a clinical suspicion of viral meningitis. However, atypical features, such as hypoglycorrhachia and significant pleocytosis, can be found in 20% of encounters. This blurs the distinction between the two states and may alter management. Decision rules have been proposed to distinguish viral from bacterial meningitis, but their usefulness in clinical practice may be limited if they cannot identify every case of ABM. Nigrovic and colleagues, however, demonstrated a low risk (0.1%) for bacterial meningitis in children who lack the following criteria: positive result of CSF Gram's stain, CSF absolute neutrophil count of at least 1000 cells/μL, CSF protein concentration of at least 80 mg/dL, peripheral blood absolute neutrophil count of at least 10,000 cells/μL, and history of seizure before or at the time of presentation.[27]

Management

Management priorities for ABM include airway protection, oxygenation, and volume resuscitation with monitored preservation of organ function. If the capillary refill time is delayed more than 2 seconds or the patient is hypotensive, the patient should be treated for shock. A bolus infusion of 20 mL/kg of normal saline or lactated Ringer's solution should be provided while an indwelling urinary catheter is inserted. Up to 40 mL/kg should be provided as bolus infusions. If vital signs fail to stabilize after an infusion of 40 mL/kg of crystalloid solution and a urine flow of 0.5 mL/kg per hour or more cannot be maintained, vasopressors should be given. In the patient without shock, an hourly infusion rate should be established that provides normal maintenance fluids. Fluid restriction, previously advocated, may be deleterious to the patient's survival and neurologic recovery.

Beyond support of cardiopulmonary and hemodynamic status, initial management of ABM includes prevention of hypoglycemia, control of seizures, and administration of agents to maintain cerebral blood flow.

Antibiotic Therapy

Intuitively, it makes biologic sense to advocate expeditious antibiotic administration for the patient thought to have ABM. In reality, no studies have shown that a duration of any given time frame arbitrarily chosen to constitute an "excessive delay" affects morbidity or mortality; however, most experts agree that antibiotics should be administered within 1 to 2 hours of presentation in patients with suspected ABM. The timing of antibiotic administration in a patient with a CNS syndrome compatible with ABM should be driven by the specifics of the clinical scenario. A conservative approach for children with suspected ABM consists of treatment with empirical antibiotics and hospitalization for observation. Other strategies include stratification of patients into low- and high-risk categories as a basis for appropriate management (i.e., to restrict hospitalization and antibiotic therapy to children with suspected bacterial meningitis).

A major consideration in the choice of antibiotics is the emergence of antimicrobial-resistant organisms, including *S. pneumoniae* resistant to second- and third-generation cephalosporins and gram-negative bacilli resistant to many β-lactam drugs. Thus empirical treatment in areas where there are resistant strains of *S. pneumoniae* needs to include vancomycin.[8] The four clinical categories of patients and their management are as follows.

Nontoxic, low risk: In a non-pretreated patient with no evidence of systemic toxicity in whom the clinical picture is suggestive of viral meningitis, if the CSF indices confirm a clinical suspicion of viral meningitis (negative result on Gram's stain, few white blood cells in the CSF, and normal CSF protein and glucose levels), antibiotics can be withheld in consultation with the patient's primary care physician or a neurologist. Another rarely considered option is to discharge the patient

www.ketabpezeshki.com 66485457-66963820

and to schedule repeated lumbar puncture within 12 hours after antibiotic therapy. These strategies are not without risk because it often is difficult to distinguish viral meningitis from other infections, such as Rocky Mountain spotted fever and ABM. If biochemical parameters or cytologic assessment findings resemble those in ABM, it is appropriate to begin empirical antibiotic therapy and to hospitalize the patient for observation.

Nontoxic, high risk: A patient with no evidence of toxicity but with high-risk historical factors (such as pretreatment with antibiotics, exposure to an invasive organism [*H. influenzae* or *N. meningitidis*], or age younger than 1 year) prompting increased concern for ABM requires blood culture and lumbar puncture for CSF analysis. If the spinal fluid is cloudy, antibiotic therapy should begin immediately rather than being withheld pending complete CSF analysis. In symptomatic patients exposed to a person with meningococcemia, appropriate management consists of a full range of cultures, empirical antibiotic therapy, and hospitalization for observation until the results of all cultures are known because the absence of meningitis does not rule out the presence of meningococcal disease.

Critical, stable: For the patient with classic signs of ABM who has a protected airway, adequate ventilation, normal perfusion, and no evidence of coagulopathy and is assessed as being in critical but stable condition, a blood culture with phlebotomy and a second culture with placement of an intravenous catheter, urinalysis and culture, blood chemistries, and CBC are recommended, after which a lumbar puncture is performed. Antibiotics should be administered immediately after lumbar puncture and before the results of the CSF or other studies become available from the laboratory.

Critical, unstable: A patient with a CNS syndrome, abnormal vital signs for age, unprotected airway, ongoing seizure activity, focal neurologic deficit, or coagulopathy is considered to be in critical and unstable condition. In these patients, the clear risk of an adverse outcome (i.e., respiratory failure) as a result of diagnostic lumbar puncture is magnified, especially if the procedure is carried out before the patient is stabilized. Although the cause and effect relationship is controversial, patients with clinical signs of increased ICP may experience fatal cerebral herniation (even if CT findings are normal) after a lumbar puncture.[24] Two blood culture samples and blood and urine specimens for antigen detection should be obtained. Antibiotics should be administered and the lumbar puncture deferred.

ED antimicrobial treatment decisions are empirically based. The choice of agents should be based on knowledge of the prevalent organisms responsible for intracranial infections and the regional patterns of their antimicrobial susceptibility. The initial regimen chosen for treatment should be broad enough to provide coverage for the various pathogens typical for the age group being treated (Table 175-3).[8]

In the newborn, no single antibiotic has bactericidal activity against all of the possible organisms commonly encountered. The most widely used combination therapy consists of ampicillin with an aminoglycoside or ampicillin plus cefotaxime, which is equally effective. For infants older than 1 month and younger than 3 months, in the absence of any evidence for presence of unusual organisms, conventional therapy is ampicillin and a third-generation cephalosporin. Beyond the age of 3 months, monotherapy with a third-generation cephalosporin provides adequate coverage, except in cases involving resistant strains of *S. pneumoniae*. When gram-positive cocci are identified on the CSF Gram's stain, the combination of a broad-spectrum cephalosporin (e.g., cefotaxime, ceftriaxone) and vancomycin is now routinely recommended.[8]

Table 175-3 Empirical Antibiotics for Treatment of Acute Bacterial Meningitis

	FIRST INTRAVENOUS DOSE	
AGE	**Antibiotic**	**mg/kg**
0-4 weeks	Ampicillin	50-100
	plus	
	Gentamicin	2.5
	or	
	Cefotaxime	50
4 weeks-3 months	Ampicillin	100
	plus	
	Cefotaxime	75
	or	
	Ceftriaxone	50
	or	
	Vancomycin	15
3 months-21 years	Cefotaxime	75
	or	
	Ceftriaxone	50
	plus	
	Vancomycin	15

Steroid Therapy

The role of dexamethasone therapy for ABM has long been the focus of clinical interest. Consensus opinion suggests that for infants beyond 8 weeks of age, dexamethasone may mitigate some neurologic sequelae.[1]

Use of dexamethasone is not without risk. The most commonly reported deleterious effect of dexamethasone is gastrointestinal bleeding. The anti-inflammatory effects of dexamethasone have led to a false sense of clinical improvement, overshadowing the failure of the chosen antibiotic to eradicate an invasive organism. Reduced penetration of vancomycin with dexamethasone therapy has been demonstrated.[29] As a potentially universal distribution of cephalosporin-resistant and penicillin-resistant *S. pneumoniae* approaches, reducing the penetrating effect of vancomycin may cause undue harm. In summary, it is best to adhere to the latest recommendations of the American Academy of Pediatrics (AAP) and to limit the use of dexamethasone to the presumptive treatment of pneumococcal meningitis in infants who are older than 6 weeks after consideration of potential benefits and risks. The AAP recommendation is that dexamethasone may also be beneficial for infants and children with *H. influenzae* meningitis to decrease the risk of neurologic sequelae, including hearing loss, if it is given before or concurrently with the first dose of an antimicrobial agent.[8,30]

For optimal management, close observation is suggested for the patient with newly diagnosed and treated ABM. Vital signs, systemic perfusion, and level of consciousness can rapidly change. Complications from the disease state, such as shock and seizure, or from interventions, such as anaphylaxis and post–lumbar puncture herniation of cerebral contents, can be addressed only if the patient undergoes continuous monitoring.

Acyclovir

The issue of empirical treatment of a neonate or young infant (younger than 3 months) with acyclovir is controversial because identification of infected infants is challenging. Acyclovir should be administered in an ill or febrile infant with a history of maternal HSV infection, presence of vesicles on the skin, seizure, or focal neurologic signs. Use of acyclovir also should be considered in atypical presentations of sepsis or meningitis.[5] The dose of acyclovir is 20 mg/kg intravenously every 8 hours for 21 days in

www.ketabpezeshki.com 66485457-66963820

full-term immunocompetent infants (<35 weeks postconceptual age: 40 mg/kg/day divided q12hr IV for 14-21 days and ≥35 weeks postconceptual age: 60 mg/kg/day divided q8hr IV for 14-21 days). The dose for immunocompromised infants is 750 to 1500 mg/m^2/24 hours divided every 8 hours for 7 to 14 days. PCR assay for HSV should be performed in these cases. Treatment may be initiated on the basis of the criteria outlined earlier before results of PCR tests.

Disposition

A child newly diagnosed with ABM is best managed by experienced physicians and nurses who are capable of addressing critical care needs. The best resource is a hospital that can provide pediatric intensive care. If transfer of the patient to another hospital is necessitated by the lack of appropriate inpatient pediatric care, the composition, expertise, and equipment of the interfacility transport team are important. Strong consideration should be given to the administration of empirical antibiotics. Accordingly, the relevant logistics are best worked out in advance of the actual patient encounter.

SEIZURES

Perspective

A seizure is defined as a paroxysmal event characterized by a change in behavior of the patient; it is caused by abnormal and excessive activity of a group of cortical neurons. The clinical manifestation of the seizure depends on the location and extent of brain involved. Seizures are classified as either provoked or unprovoked. *Provoked* seizures are caused by a broad array of disturbances, including fever, metabolic disarray, and trauma. *Unprovoked* seizures have no clear immedate precedent. *Epilepsy* is commonly defined as the occurrence of two or more *unprovoked* seizures.

Seizure disorders are the most common neurologic disorders of childhood; 4 to 10% of children suffer at least one seizure in the first 16 years of life. Etiology, clinical appearance, and electroencephalographic patterns differ from children to adults.

Principles of Disease

Pathophysiology

The young (<5 years), immature nervous system is remarkably susceptible to seizures. Early in development, excitatory activity predominates and inhibitory systems are undeveloped.[32] This is known as the period of vulnerability. A paucity of synaptic connections and alterations in the synthesis of neurotransmitters also may play a role.

Seizures and Brain Damage

It is well known that children with epilepsy are at a significant risk for cognitive impairment and behavioral abnormalities. It is difficult to distinguish the relative contributions of the effect of the seizures from the underlying CNS disease and from the effect of anticonvulsants. A single prolonged seizure (>30 minutes) has been shown to damage the brain, particularly the temporal lobes and hippocampus.[33] In addition, a growing body of evidence points to the lasting effect of repetitive, brief seizures in early childhood.[34]

Clinical Features

Classification of Seizure Type

Seizures are classified into two main types: partial (consciousness is maintained) and generalized (consciousness is lost) (Box 175-3). There are two types of partial, or focal, seizures: complex and simple. In *complex partial* seizures, the patient experiences a change in level of awareness and may exhibit bizarre behaviors, including staring, lip smacking, wandering, or picking at clothing. In *simple partial* seizures, the patient experiences no change in mentation.

Box 175-3 Classification of Seizures

Generalized seizures
- Tonic-clonic (in any combination)
- Absence
  - Typical
  - Atypical
  - Absence with special features
  - Myoclonic absence
  - Eyelid myoclonia
- Myoclonic
  - Myoclonic
  - Myoclonic atonic
  - Myoclonic tonic
- Clonic
- Tonic
- Atonic

Focal seizures
- Without impairment of consciousness or awareness (simple partial seizures)
- With impairment of consciousness or awareness (complex partial seizures)

Unknown
- Epileptic spasms

From Berg AT, et al: Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 54:676, 2010.

Generalized seizures may be *convulsive* or *nonconvulsive*. A convulsive seizure may start focally and secondarily generalize. The most common type of generalized nonconvulsive seizure is an absence seizure. Absence seizures are marked by a brief arrest of consciousness and movement typically lasting 5 to 30 seconds; no postictal drowsiness occurs. In children, it may be difficult to differentiate a brief complex partial seizure, in which a child may stare and not respond, from an absence seizure.

Classification of Epilepsy: Epileptic Syndromes

An epileptic syndrome is characterized by a triad of age at onset, seizure type, and electroencephalographic findings. Identification of the epileptic syndrome provides information on prognosis and informs management decisions. Several of the more common epileptic syndromes of infancy and childhood are reviewed (Box 175-4).

Infantile Spasms

Infantile spasms are manifested during the first year of life with rapid flexor or extensor spasms that appear in clusters. The electroencephalogram (EEG) shows *hypsarrhythmia*, an abnormal pattern characterized by high-voltage slow waves and disorganized spike activity.

Approximately two thirds of children with infantile spasms have an underlying CNS disorder, such as a congenital brain malformation or tuberous sclerosis. The outcome is poor; only half will attain remission of seizures, and the large majority will be mentally retarded. Treatment is notoriously difficult. In the United States, a course of ACTH has traditionally been the treatment of choice; prednisolone treatment is being used with increasing frequency.[35] Vigabatrin was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of infantile spasms and is particularly useful in the setting of tuberous sclerosis.

www.ketabpezeshki.com 66485457-66963820

Box 175-4 Classification of Epileptic Syndromes

Neonatal Period
Benign familial neonatal epilepsy
Early myoclonic encephalopathy

Infancy
Epilepsy of infancy with migrating focal seizures
West syndrome (infantile spasms)
Myoclonic epilepsy in infancy
Benign infantile epilepsy
Benign familial infantile epilepsy
Myoclonic encephalopathy in nonprogressive disorders

Childhood
Febrile seizures plus (can start in infancy)
Epilepsy with myoclonic atonic (previously astatic) seizures
Benign epilepsy with centrotemporal spikes
Autosomal dominant nocturnal frontal lobe epilepsy
Late-onset childhood occipital epilepsy (Gastaut type)
Lennox-Gastaut syndrome
Epileptic encephalopathy with continuous spike-and-wave during sleep
Childhood absence epilepsy

Adolescence-Adult
Juvenile absence epilepsy
Juvenile myoclonic epilepsy
Epilepsy with generalized tonic-clonic seizures alone
Progressive myoclonus epilepsies
Autosomal dominant epilepsy with auditory features
Other familial temporal lobe epilepsies

Less Specific Age Relationship
Familial focal epilepsy with variable foci (childhood to adult)
Reflex epilepsies

Distinctive Constellations
Mesial temporal lobe epilepsy with hippocampal sclerosis
Rasmussen syndrome
Gelastic seizures with hypothalamic hamartoma
Hemiconvulsion-hemiplegia-epilepsy

Epilepsies Attributed to and Organized by Structural-Metabolic Causes
Malformations of cortical development (e.g., hemimegalencephaly, heterotopias)
Neurocutaneous syndromes (e.g., tuberous sclerosis complex, Sturge-Weber)
Tumor
Infection
Trauma
Angioma
Perinatal insults
Stroke
Other

Epilepsies of Unknown Cause
Benign neonatal seizures
Febrile seizures

Modified from Berg AT, et al: Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 54:676, 2010.

Childhood and Juvenile Absence Epilepsy

Childhood and juvenile absence epilepsy begins between 4 and 12 years of age and is characterized by frequent absence seizures; generalized convulsive seizures occur in up to 50% of the patients. The diagnosis is frequently missed for prolonged periods; the parent or physician may assume the child is daydreaming or purposely not responding. Bursts of spike-and-wave activity at 3/second on the EEG during an absence spell are indicative of this syndrome. Hyperventilation can trigger absence seiziures and can be used to diagnose absence epilepsy. Treatment is with ethosuximide; if convulsions also occur, valproic acid or lamotrigine are used instead.[36] The prognosis is excellent, and the majority of children outgrow this disorder by 16 years of age.

Benign Epilepsy with Centrotemporal Spikes

This epilepsy syndrome typically begins between 3 and 13 years of age. The seizures occur most commonly during sleep and involve the facial muscles; secondary generalization frequently occurs. The typical electroencephalographic pattern is one of central temporal (rolandic) spikes, particularly during sleep. The prognosis is excellent; the seizures typically cease by 16 years of age. Considerable controversy exists as to whether anticonvulsant treatment of a patient with brief, infrequent seizures is warranted.[37]

Lennox-Gastaut Syndrome

Developmental disability, multiple seizure types and a "slow" spike and wave pattern on EEG in a young child (2-5 years) are the characteristics of Lennox Gastaut Syndrome. Infantile spasms commonly evolves into Lennnox Gastaut. Valproic acid, lamotrigine, topiramate, felbamate, and rufinamide have shown promise for the treatment of Lennox-Gastaut syndrome,[38] but treatment is notoriously difficult.

Febrile Seizures

A febrile seizure is defined as a seizure occurring in the presence of fever without CNS infection or other cause. A *simple* febrile seizure is generalized, lasts less than 15 minutes, and occurs in a neurologically and developmentally normal child between 6 months and 6 years of age.[39] Simple febrile seizures typically occur early in the course of the febrile illness. Temperature does not need to be markedly elevated; almost half the children with a febrile seizure have a documented temperature below 39° C. *Complex* febrile seizures are diagnosed when multiple seizures occur during the same illness, the seizures are prolonged (longer than 15 minutes), or the seizures have a focal component.

Febrile seizures are common, occurring in 2 to 5% of children. Thirty percent of children with a simple febrile seizure will have a recurrence; of these, half will have a third event.[40] The younger the age at onset, the higher the likelihood of recurrence. Children with simple febrile seizures have a 2 to 3% chance for development of epilepsy (compared with a 1% rate of epilepsy in the general population). Those with complex febrile seizures have a significantly higher risk. Treatment with long-term anticonvulsants does not affect the later risk of epilepsy.[41]

Rectal diazepam (Diastat) is safe and effective for the termination of prolonged or repetitive febrile seizures and should be available for home use in the child with recurrent, prolonged febrile seizures.[42] Long-term anticonvulsant use is rarely warranted.[39] The use of antipyretics, such as acetaminophen and ibuprofen, does not decrease the likelihood of recurrence.[43] Reassurance and education are the mainstays of management (see the section on management of febrile seizure and the discussion about lumbar puncture).

Neonatal Seizures

The frequency of seizures is higher in the first month of life than at any other time in childhood. Neonatal seizures may be subtle; apnea, sustained eye deviation, chewing, or limb bicycling movements may be the only apparent signs. There is a high incidence of subclinical electrographic seizures.[44] Focal clonic movements are often associated with an underlying structural lesion.

Although there are many causes of neonatal seizures, a relatively few account for a majority of cases. These include hypoxic-ischemic encephalopathy, intracranial infection, congenital brain malformation, cerebrovascular events, and metabolic

www.ketabpezeshki.com 66485457-66963820

disturbances, particularly hypoglycemia and hypocalcemia (Box 175-5). Although inborn errors of metabolism are rare, early treatment can be lifesaving.

Neonatal seizures may predispose to the development of cognitive and behavioral difficulties and to an increased risk of epilepsy later in life, although the prognosis ultimately depends on the etiology of the seizure.[44]

Status Epilepticus

Convulsive status epilepticus is a true neurologic emergency; it is associated with high morbidity and mortality rates that increase with duration of the seizure activity. Status epilepticus is defined as greater than 30 minutes of either continuous seizure activity or repeated brief seizures without full recovery of consciousness between seizures. In clinical practice, any seizure lasting more than 5 minutes warrants intervention.[45] Although the diagnosis of convulsive status epilepticus usually is obvious, the duration of the seizures often is underestimated because the intensity of the jerking tends to diminish with time. The importance of careful observation cannot be overstated.

Status epilepticus occurs significantly more frequently in children than in adults, particularly in those younger than 1 year.[46] Febrile illness is by far the most common precipitant of status epilepticus in children. Medication change, toxic ingestion, idiopathic epilepsy, metabolic derangements, and congenital abnormalities are the next most common. Although morbidity and mortality rates are significantly lower than in adults, they are still significant at 30% and 4%, respectively.

Nonconvulsive status epilepticus is marked by an altered mental status. Patients may demonstrate confusion, unresponsiveness, abnormal motor movements, twitches, lip smacking, or automatisms. An EEG can confirm the diagnosis and should be obtained if nonconvulsive status is suspected.

Box 175-5 Etiology of Neonatal Seizures

Hypoxic-ischemic encephalopathy
Central nervous system infection
Intracranial hemorrhage
Cerebral infarction
Chromosomal abnormalities
Congenital brain abnormalities
Metabolic disturbances
- Hypoglycemia
- Hypocalcemia
- Hypomagnesemia
- Pyridoxine dependency
- Inborn errors of metabolism

Drug withdrawal or intoxication

Etiology of Seizures and Differential Considerations

Differential Diagnosis

The first task of the ED evaluation is to determine whether the event in question was truly a seizure. Box 175-6 lists disorders that may be mistaken for seizures.

Syncope is one of the more common disorders mistaken for a seizure. Syncope is characterized by a sudden loss of consciousness and motor tone caused by a transient global cerebral hypoperfusion. Just before the event, the patient will often complain of lightheadedness and blurry vision and may appear pale and sweaty. Postictal confusion does not occur, but trembling and stiffening are common. Vasovagal syncope is common in otherwise healthy children and does not warrant further workup unless it is recurrent. On the other hand, cardiogenic syncope, such as prolonged QTc syndrome, is potentially fatal. Syncope should be considered if there is no post ictal period or tonic or clonic activity, if the event occurred during exercise or if palpitations were present.

Breath-holding spells occur in 4 to 5% of children, primarily between the ages of 6 and 18 months. They are triggered by pain or emotional upset. The child becomes pale or cyanotic and may lose consciousness. If so, the child is typically limp, but a brief period of clonic movements or opisthotonos may occur. The average attack lasts approximately 40 seconds.[47]

Migraines may mimic seizures, particularly when they are accompanied by an aura, motor dysfunction, clouding of consciousness, or vomiting.

Disorders of sleep are distinguished by excessive daytime sleepiness or by disordered nighttime sleep. In *narcolepsy,* daytime sleep attacks, sleep paralysis, hypnagogic hallucinations (vivid hallucinations while falling asleep), and cataplexy (sudden loss of motor tone) occur. Cataplexy may be mistaken for atonic or absence seizures. *Nocturnal enuresis* may raise concern for an unwitnessed nighttime seizure associated with incontinence. In *night terrors* (pavor nocturnus), the child wakens suddenly, crying, inconsolable, and unresponsive; the event concludes with the child's returning to sleep. *Sleepwalking (somnambulism)* and *sleeptalking (somniloquy)* are common among school-age children.

Movement disorders may mimic seizures. *Tics* are rapid, repetitive, brief involuntary movements that occur intermittently and in flurries. Those most commonly seen are eye blinking and head shaking. Patients do not lose consciousness. *Shudder attacks* are uncommon but easily mistaken for seizures. The movement is that of the chill experienced when cold water runs down the back. *Paroxysmal choreoathetosis* is an abnormal motor movement that may be spontaneous or triggered by the child's movement.

Behavioral or psychiatric disturbances can produce behaviors that may appear epileptic. *Panic attacks* may be mistaken for

Box 175-6 Episodic Disorders That May Mimic Seizures

Newborns
Jitteriness
Benign neonatal sleep myoclonus
Nonepileptic apnea
Opisthotonos
Normal movement

Non-Newborn
Breath-holding spells
Rigors or chills
Gastroesophageal reflux (Sandifer's syndrome)
Migraine
Benign paroxysmal vertigo of childhood
Syncope
Neurovascular event
Sleep disorders
- Sleep myoclonus
- Narcolepsy
- Nightmares, night terrors, somnambulism

Movement disorders
- Tics or stereotypies
- Infantile shuddering attacks
- Paroxysmal choreoathetosis or dystonia

Psychological
- Psychogenic seizures
- Panic attack

www.ketabpezeshki.com 66485457-66963820

Box 175-7 Etiology of Acute and Remote Symptomatic Seizures

Febrile seizures
Infectious processes
- Meningitis
- Encephalitis
- Brain abscess
- *Shigella* infection
- Neurocysticercosis

Traumatic lesions
- Cerebral contusion
- Hemorrhage: subdural, epidural, subarachnoid, intraparenchymal
- Impact seizure

Toxic conditions
- Drug intoxication (see Box 175-8)
- Drug withdrawal

Metabolic disturbances
- Hypoglycemia
- Hyponatremia
- Hypernatremia
- Hypomagnesemia
- Hypophosphatemia
- Hepatic or renal disorder
- Hyperosmolar states
- Inborn errors of metabolism (e.g., aminoacidurias, organic acidurias, mitochondrial diseases)
- Pyridoxine dependency syndrome

Neoplastic disease
Vascular disorders
- Arteriovenous malformation
- Subarachnoid hemorrhage
- Intraparenchymal hemorrhage
- Cerebral venous thrombosis
- Ischemic infarct
- Hypertensive encephalopathy

Neurocutaneous disorder
- Neurofibromatosis
- Tuberous sclerosis
- Sturge-Weber syndrome

Neurodegenerative disorder
Miscellaneous
- Eclampsia
- Dialysis
- After immunization
- Hypoxia
- Hypoxic-ischemic encephalopathy
- Ventriculoperitoneal shunt malfunction
- Cerebral dysgenesis
- Cerebral palsy
- Intrauterine infection (e.g., TORCH)
- Primary epilepsy

TORCH, toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex.

complex partial seizures. The patient has a sudden sensation of intense fear accompanied by shortness of breath, dizziness, palpitations, sweating, choking, chest discomfort, and fear of dying. *Psychogenic seizures* are involuntary events that mimic seizures. Many children with psychogenic seizures also have epileptic seizures. Prolonged electroencephalographic monitoring may be necessary to differentiate an epileptic seizure from a psychogenic seizure.

Infants with gastrointestinal reflux may exhibit *Sandifer's syndrome,* characterized by episodes of abnormal posturing, arching of the back, and torticollis.

Etiology of Seizures in Children

After the diagnosis of seizure is made, the seizure type and the etiology should be determined. Seizures can be divided into three main etiologic categories: acute symptomatic, remote symptomatic, and idiopathic seizures (Box 175-7).

Acute symptomatic seizures are provoked by an acute event. Febrile seizures are the most common cause of acute symptomatic seizures in children. Remote symptomatic seizures are due to an earlier, or remote, CNS lesion. Examples include cerebral palsy, congenital brain malformation, and any other chronic brain injury. Idiopathic seizures have no definable cause.

Acute Symptomatic Seizures

Fever is the most common cause of acute symptomatic seizures in children. Meningitis should always be considered in any patient with seizures and fever. The section below on febrile seizures further discusses this important issue. In general, a child whose mental status is normal both before and after the seizure is unlikely to have meningitis.

Inborn errors of metabolism or metabolic disease is a common cause of seizures in children. Hypoglycemia (blood glucose concentration of less than 60 mg/dL in adults and less than 40 mg/dL in children), hyponatremia (serum sodium concentration of less than 125 mEq/L), and hypernatremia (serum sodium concentration of more than 150 mEq/L) are associated with seizures. Dehydration is the most common cause of hypernatremia.

Hypocalcemia and hypomagnesemia may lead to muscle spasms, paresthesias, hyperactive reflexes, weakness, tetany, as well as seizures. Hypocalcemic seizures are a common cause of neonatal seizures.

Post-traumatic seizures occur in as many as 15% of children after head injury. *Impact seizures,* occurring within 1 hour of a head trauma, are not associated with significant injury or with the later development of epilepsy; however, it may be difficult to distinguish these from seizures associated with intracranial injury, and a CT scan of the head without contrast enhancement is indicated. *Early post-traumatic seizures* (occurring within the first week of injury) may arise from cerebral edema or intracranial hemorrhage, laceration, or contusion. Phenytoin is effective in preventing early post-traumatic seizures but does not influence the development of epilepsy.[48]

Brain tumors cause a wide variety of symptoms, depending on their location and the type of tumor. Infratentorial tumors, the most common location in the pediatric population, do not typically cause seizures.

Seizure may be the presenting sign of stroke. Congenital heart disease, sickle cell anemia, and homocystinuria are major risk factors for ischemic stroke in children. Vascular malformations, such as arteriovenous malformations, may cause hemorrhagic stroke.

Numerous drugs are known to cause seizures. Cyclic antidepressants, cocaine and other stimulants, antihistamines, and isoniazid are the most common agents of drug-induced seizures. Drugs that may be associated with seizures are summarized in Box 175-8. Seizures also may occur during drug withdrawal, usually within 48 hours of drug cessation. Drug withdrawal in the neonate is a significant issue. Withdrawal of benzodiazepines and barbiturates leads to an abstinence syndrome similar to ethanol withdrawal.

Reflex seizures are precipitated by a specific, identifiable stimulus. For example, flashing lights on television or video games may induce seizures in photosensitive children.[49]

Remote Symptomatic Seizures

Causes of remote symptomatic seizures include congenital brain malformations, neurocutaneous disorders, cerebral palsy and neurodegenerative disease.

Diagnostic Strategies

The initial diagnostic evaluation is directed toward determination of whether the event was indeed a seizure and, if so, identification of a specific underlying cause. If the patient arrives in the ED actively convulsing, the first priority is to stop the seizure.

www.ketabpezeshki.com 66485457-66963820

Box 175-8 Drugs That May Cause Seizures

Anesthetic and Analgesic Agents
Etomidate
Enflurane
Ketamine
Lidocaine
Methohexital
Narcotics

Antibiotics
Penicillin
β-Lactams
Isoniazid
Metronidazole

Anticholinergics

Anticholinesterases
Organophosphates
Physostigmine

Anticonvulsants
Carbamazepine
Phenytoin

Antidepressants
Tricyclic antidepressants
Selective serotonin reuptake inhibitors
Bupropion
Monoamine oxidase inhibitors

Antidysrhythmics
Mexiletine
Tocainide
Procainamide

Antihistamine
Diphenhydramine

Antipsychotics
Phenothiazines
Butyrophenones

Antitumor Agents
Busulfan
Chlorambucil
Cyclosporine
Cytosine arabinoside
Methotrexate

Beta-Blockers
Sympathomimetics
- Cocaine
- Amphetamines
- Phenylpropanolamine
- Methylphenidate

Bronchial Agents
Theophylline
Aminophylline

Other Agents
Baclofen
Camphor
Carbon monoxide
Cyanide
Radiocontrast agents
Ethanol
Flumazenil
Hypoglycemic agents
Hyperbaric oxygen therapy
Lead
Lithium
Nicotine

A complete history is key to establishment of the diagnosis of a seizure or epilepsy. Effort should be made to obtain a description from an eyewitness as well as an account from the patient. The history should include the following.

Events leading up to the attack: What was the patient doing at the time? Did the patient become confused or complain of dizziness, a bad smell, flashing lights, or anything else?

The event itself: Did the patient get stiff or limp? Did the patient shake? Was there a loss of consciousness? Did the eyes or head turn in one direction? Was there incontinence? Having the observer demonstrate the movements can be helpful.

Events directly after the attack: Was the patient lethargic or confused and for how long? Did the patient remember the event? The occurrence of postictal confusion, headache, or fatigue can help differentiate a seizure from a nonepileptic event.

Possible precipitants of seizures: Has there been recent fever, illness, rash, head trauma, drug use, or medication or supplement use?

Risk factors for epilepsy: Is there a past history of meningitis, head injury, febrile seizures, congenital anomalies, or developmental delay? a family history of epilepsy? presence of unusual color or number of birthmarks?

Previous history of abnormal movements, staring spells, or myoclonus: It is not uncommon for a patient with a first generalized tonic-clonic seizure to have underlying, undiagnosed absence epilepsy.

Box 175-9 Summary Approach to the Child with a Seizure

- Determine if the event was truly a seizure.
- Determine seizure type.
- Identify precipitating factors (e.g., hypoglycemia, hypocalcemia, electrolyte imbalance, low anticonvulsant levels, fever, trauma, central nervous system infection, toxin) and treat accordingly.
- Determine if anticonvulsant therapy is appropriate at this time.

In a patient with known epilepsy who has a breakthrough seizure, determine the dosage of anticonvulsant, whether any doses were missed, whether any new medications or supplements were started, any precipitants (fever, illness, trauma, etc.) present, and the baseline frequency of seizures.

The general physical examination should concentrate on signs of systemic disease that can cause seizure. Particular attention should be paid to evidence of meningitis, trauma, drug use, dehydration, hypertension, and heart disease. Skin lesions, such as café au lait spots or hypopigmented nevi, may point to a neurocutaneous disorder. An abnormal head circumference may point to hydrocephalus or abnormal brain growth.

A careful neurologic examination should assess for signs of increased ICP and focal neurologic deficits.

Management

The management of four categories of seizures—febrile seizures, afebrile seizures, neonatal seizures, and status epilepticus—is described next. Box 175-9 provides an overview of the approach to a child with a seizure.

Febrile Seizures

In general, a child with fever between 6 months and 5 years of age who presents after a brief seizure (<15 minutes) with a normal neurologic examination can be assumed to have had a simple febrile seizure.[39] Blood and urine testing may be required as part of the work up for the fever, but is not required for work up of a febrile seizure. According to the newer AAP recommendations, lumbar puncture is not necessary in children older than 12 to 18 months in whom the clinical findings are not suggestive of meningitis. Lumbar puncture should be considered in children between 6 and 12 months of age whose vaccination status for *H. influenzae* type b or *S. pneumoniae* is incomplete and in children who have been pretreated with antibiotics.[21] Lumbar puncture should be strongly considered in children younger than 6 to 12 months because signs of meningitis can be subtle in this age group. Electroencephalography and neuroimaging generally are not required.

Afebrile Seizures

Laboratory Studies. Laboratory tests generally include determinations of calcium, glucose, urea, electrolytes, and magnesium.[50] The results of such studies are rarely abnormal in the child who is neurologically normal after a brief seizure.[51] If drug exposure is a possibility, toxicology screen is sent. Anticonvulsant levels are measured if applicable.

A lumbar puncture is mandated in the patient with an abnormal mental status or other signs of meningitis, regardless of whether fever is present. If the concern for meningitis is low in a postictal patient, it is acceptable to observe the patient over the next 2 to 3 hours, and if the patient returns to baseline, a lumbar

www.ketabpezeshki.com 66485457-66963820

puncture can be avoided. A prolonged seizure can cause a mild elevation of white blood cells in the CSF, presumably from a transient disruption of the blood-brain barrier. CSF should be sent for cell counts, protein and glucose concentrations, culture, and PCR for HSV.

Radiography and Other Imaging. Consensus is lacking in regard to the need for neuroimaging in children who arrive in the ED after a first seizure. Emergent imaging should be performed in a patient with new focal deficits, persistent altered mental status, recent trauma, persistent headache, or partial-onset seizures.[52] Because a generalized convulsion may have begun as a focal onset seizure, it is crucial to obtain a careful history from both an eyewitness and the patient. Children with generalized unprovoked seizures and normal examination findings do not necessarily require acute imaging. At follow-up evaluation, further evidence, such as a focal abnormality on the EEG, may indicate a need for neuroimaging, which can be done at that time. Children with a history of epilepsy do not need neuroimaging unless there is a change in clinical status.

If imaging is indicated in the acute period, either CT or magnetic resonance imaging (MRI) may be used. Although MRI provides superior anatomic detail, sedation is commonly needed in the pediatric patient, thus masking assessment of the patient's mental status. Therefore, CT, which provides rapid imaging and is highly sensitive for detection of acute blood and fractures, is often the imaging study of choice in the child with a seizure.

Special Procedures. The EEG is the most important laboratory test for evaluation of the patient with an unprovoked seizure. It rarely needs to be performed in the acute situation unless nonconvulsive status epilepticus is suspected. The EEG helps determine the seizure type, specific epilepsy syndrome, and risk for recurrence.[51] Transient postictal slowing may occur for several days after a seizure.

Sleep deprivation, hyperventilation, and photic stimulation are techniques that can enhance the sensitivity of the EEG. Ideally, all EEGs should be recorded while the patient is awake, drowsy, and asleep.

Treatment of Specific Causes of Acute Seizures. Hypoglycemia in children older than 2 months is treated with an intravenous bolus of 10% dextrose, 2.5 mL/kg. Neonates are treated with 2 mL/kg of 10% dextrose solution. Severe symptomatic hyponatremia may be treated with the intravenous administration of 3% saline (2 mL/kg infused during 30 minutes) to raise the serum sodium level by 3 to 7 mEq/L. The remainder of the correction should occur slowly during the next 24 hours. Hypernatremia is corrected slowly during 48 hours. Hypocalcemia is treated with 10% calcium gluconate, 100 mg/kg intravenously; the patient should be on a cardiac monitor during the infusion. Toxic ingestions are treated based on the specific toxin involved. One specific example is the treatment of isoniazid poisoning with pyridoxine. The dose of pyridoxine is 1 g IV for every gram of INH ingested. When the quantity of INH ingested is unknown, 5 g IV may be administered to an adult and 70 mg/kg (maximum 5 g) to a child.

Empirical treatment with antibiotics is ordered if meningitis is a possibility. (see Table 175-3). The patient with altered mental status and focal seizures is treated additionally for herpes encephalitis with acyclovir, 20 mg/kg per dose (10 mg/kg per dose in children older than 12 years) every 8 hours. In patients with acute significant brain injury, such as depressed skull fracture or intracerebral hematoma, anticonvulsant treatment reduces the incidence of early seizure, and should be given. Although there is no consensus on the ideal drug, phenytoin is most commonly used as it does not cause significant sedation and is conveniently loaded intravenously. The optimal duration of therapy is not clear and depends in part upon the severity of injury.

Box 175-10 Diagnostic Assessment of Neonatal Seizures

Blood Testing
Blood glucose
Calcium
Magnesium
Electrolytes
Ammonia
Lactate
pH
Complete blood count

Urine Testing
Urinalysis
Toxicology screen
Reducing substances, organic acids

Lumbar Puncture and Cerebrospinal Fluid Examination
Cells
Protein and glucose
Cultures
Herpes virus polymerase chain reaction assay
Lactate
Amino acids

Neuroimaging
Head ultrasound examination
Head computed tomography
Brain magnetic resonance imaging

Neonatal Seizures

The common underlying causes of neonatal seizures differ from those in older children and adults (see Box 175-5). The diagnostic assessment of neonatal seizures is detailed in Box 175-10. It includes metabolic testing, CSF analysis, and neuroimaging. Glucose, calcium, magnesium, and electrolyte levels and CBC are determined immediately. If findings are normal, lactic acid, ammonia, and pH determinations should be considered. As clinical assessment for meningitis is not reliable in young infants, lumbar puncture is performed and fluid sent for cells, protein and glucose determinations, culture, and herpes PCR assay. Head CT or MRI should be obtained. In the unstable neonate, a head ultrasound scan may be performed at the bedside to rule out a neurosurgical emergency, until more definitive imaging can be obtained.

Empirical antibiotic therapy should be started in affected infants (see previous section on meningitis). Acyclovir (20 mg/kg per dose every 8 hours) is initiated if herpes encephalitis is a clinical concern (red cells in CSF, continued seizures with no other clear etiology). Hypoglycemia is corrected with 2 mL/kg of 10% dextrose solution intravenously.

Hypocalcemia is treated with either 10% calcium gluconate (1 mL/kg over 5 to 10 minutes with monitoring of the heart rate and infusion site) or calcium chloride (0.2 mL/kg). Hypomagnesemia, which may be associated with hypocalcemia, is treated with a 0.25 mL/kg dose of 50% solution magnesium sulfate injected intramuscularly.

Phenobarbital is typically the drug of choice for neonatal seizures. A loading dose of 20 mg/kg is given; additional doses of 5 to 10 mg/kg may be given if necessary. If seizures continue, fosphenytoin 20 PE/kg may be loaded. Lorazepam 0.1 mg/kg intravenously may be useful but is associated with hypotension and respiratory depression. Refractory seizures may be treated with midazolam infusion.[34] Continuous electroencephalographic recording is necessary at this point. If seizures are refractory to medical treatment, empirical treatment with pyridoxine, 100 mg

www.ketabpezeshki.com 66485457-66963820

Management

Impending/Established Status

Out-of-hospital or No IV Access Available
Buccal midazolam (0.2 mg/kg), intranasal midazolam (0.2 mg/kg) or rectal diazepam (0.3 mg/kg).

Emergency Room
Lorazepam 0.1 mg/kg IV (max 5 mg) over 1 min
Allow 5 minutes to determine whether seizure terminates.

Give oxygen. Stabilize airway, respiration, and hemodynamics. Obtain IV access. Check bedside glucose. Begin ECG monitoring. Avoid hyperthermia, hypoglycemia, and hyperglycemia.

If hypoglycemic, administer bolus of 2 ml/kg 50% glucose. Consider thiamine 100 mg IV first.

Repeat benzodiazepine administration if patient has not received 2 doses of benzodiazepines. (Be sure to consider pre-hospital dosing).

Administer 2nd anticonvulsant:
Fosphenytoin 25-30 mg PE/kg IV at 3 mg PE/kg/min (max 150 mg PE/min) (PE = phenytoin equivalents)
Phenytoin 25-30 mg/kg IV at 1 mg/kg/min (max 50 mg/min)

If < 2 years, consider pyridoxine 100 mg IV push.

Testing to be considered:
Bedside Glucose, Basic Metabolic Panel, Magnesium, Phosphate, Complete Blood Count, Liver Function Panel, Coagulation Tests, Anticonvulsant Levels, Toxicology, Cultures, Head CT.

Draw phenytoin level (~10 min after infusion completed)

Refractory Status

If seizure continues 10 minutes after fosphenytoin/phenytoin infusion then patient has refractory SE regardless of time elapsed.

Administer 3rd anticonvulsant:
Levetiracetam 40 mg/kg IV at 5 mg/kg/min.
Consider in patients with hemodynamic instability or possible metabolic/liver disease. OR
Valproate Sodium 40 mg/kg at 5 mg/kg/min.
Contraindicated if liver disease, thrombocytopenia, or possible metabolic disease. OR
Phenobarbital 30 mg/kg IV at 2 mg/kg/min (max rate 60 mg/min).
May cause respiratory depression and hypotension.

If seizure continues 5 minutes after 3rd anticonvulsant, then consider administration of different third-line anticonvulsant, or proceed directly to pharmacologic coma initiation.

Admit to PICU. Prepare to secure airway, mechanically ventilate, obtain central venous access and continuous hemodynamic monitoring through arterial line.

Once clinical seizure terminates may need EEG monitoring to assess for non-convulsive seizures.

Initiate coma with midazolam 0.2 mg/kg bolus (max 10 mg) over 2 min and then initiate infusion at 0.1 mg/kg/hr. If clinical seizures persist 5 min after initial midazolam bolus then administer additional midazolam bolus of 0.2 mg/kg bolus. Continue infusion. If clinical seizures persist after another 5 minutes, then administer another midazolam bolus of 0.2 mg/kg and increase infusion to 0.2 mg/kg/hr. Repeat as needed.

If seizure persist at maximum midazolam (generally 2-3 mg/kg/hr) or midazolam infusion is not tolerated, then consider transition to pentobarbital (3-5 mg/kg bolus followed by maintenance infusion of 0.3-3 mg/kg/hr, up to 10 mg/kg/hr).

Other options include: Isoflurane or Propofol.

Consider addition of topiramate, valproic acid, levetiracetam, or ketamine.

Malignant Status

Continue pharmacologic coma for 24 hours after last seizure with EEG goal of burst-suppression.

Continue initial medications and check levels:

Ensure an additional anticonvulsant is administered to provide coverage during weaning coma.

Reduce midazolam by 0.05 mg/kg/hr every 3 hours with frequent EEG review. If no clinical or electrographic seizures then wean until off.

Continue EEG for at least 24 hours after end of infusion to evaluate for recurrent electrographic seizures.

If clinical or subclinical seizures occur then re-institute coma with midazolam for 24 hours. Start midazolam at infusion rate that achieved burst suppression (approximately 50/50) and increase according to suggested midazolam titration algorithm.

Add additional anticonvulsants (topiramate, levetiracetam, ketamine, high dose phenobarbital).

Additional imaging (3 Tesla MRI, consider Magnetoencephalography) and surgical evaluation.

Airway, Breathing, Hemodynamics, Temperature, Glucose Levels

EEG Monitoring

Figure 175-1. Management of status epilepticus in children. *CT,* computed tomography; *ECG,* electrocardiography; *EEG,* electroencephalography; *MRI,* magnetic resonance imaging; *PICU,* pediatric intensive care unit; *SE,* status epilepticus. (Modified from Abend NS, Gutierrez-Colina AM, Dlugos DJ: Medical treatment of pediatric status epilepticus. Semin Pediatr Neurol 17:169, 2010. Used with permission.)

www.ketabpezeshki.com 66485457-66963820

intravenously, is indicated. This will abort seizures in the rare child with pyridoxine dependency syndrome.

Status Epilepticus

Status epilepticus is a true medical emergency. Position the patient to maximize ventilation and to prevent aspiration. The cervical spine must be protected if trauma cannot be ruled out. Oxygen is administered by nasal cannula or face mask. A large suction catheter should be available to suction secretions. In the younger patient, the tongue may obstruct the airway; a nasopharyngeal airway will keep the tongue forward and improve respiratory status.

If there is evidence of increased ICP, the airway is compromised, or respiratory failure occurs, the patient should be intubated. Do not paralyze unless absolutely necessary because this will mask signs of seizure activity. Short-acting neuromuscular blockers, such as succinylcholine and vecuronium, should be used if needed.

Monitor heart rate, blood pressure, respiratory rate, and pulse oximetry and treat hyperthermia with antipyretics and cooling blankets. Place an intravenous line and send blood samples for electrolyte values, glucose concentration (including rapid blood glucose test), calcium and magnesium levels, renal function tests, liver function tests, antiepileptic levels (if indicated), and CBC. Urine should be sent for toxicology.[53]

Correct any metabolic abnormalities (see previous section on afebrile seizures). If necessary, an intraosseous line may be used.

Begin anticonvulsant treatment as quickly as possible. Figure 175-1 presents a protocol for treatment of status epilepticus in a child.[54] Benzodiazepines, particularly lorazepam and diazepam, are the initial drugs used in the treatment of status epilepticus. They diffuse quickly into the CNS, rapidly terminating seizure activity 70% of the time. The recommended pediatric intravenous dosage for lorazepam is 0.1 mg/kg (maximum 4 mg) over 1 minute. Hypotension, respiratory depression, and impaired consciousness may occur.

Rectal diazepam may be used if intravenous access cannot be obtained. The dosage is 0.5 mg/kg (maximum 20 mg). If Diastat, a rectal preparation of diazepam, is not available, the intravenous preparation may be instilled through a lubricated feeding tube inserted 4 to 6 cm into the rectum. Buccal and intranasal midazolam preparations at a dosage of 0.2 mg/kg are also effective.[55]

If the seizure continues, give a second dose of benzodiazepine. If the seizure continues, load fosphenytoin (use phenytoin, if fosphenytoin is not available); patients who already are receiving phenytoin should receive phenobarbital 20 mg/kg instead.

Fosphenytoin is a water-soluble phosphate ester of phenytoin that is rapidly converted in plasma to phenytoin. Unlike phenytoin, fosphenytoin can be administered intramuscularly, can be administered with common intravenous solutions, and is substantially less cardiotoxic and less sclerosing to the vasculature. In addition, it can be given three times more rapidly than phenytoin. Fosphenytoin produces plasma concentrations similar to those achieved for phenytoin in the same time.

The standard loading dosage of fosphenytoin is 20 PE (phenytoin equivalents)/kg at 3 PE/kg per minute (maximum of 150 PE/min). The loading dose of phenytoin is 20 mg/kg at a rate of 1 mg/kg per minute (maximum of 50 mg/min). Monitor cardiovascular status, including blood pressure and electrocardiogram, with either medication. If hypotension results, decrease the rate of infusion.

If the seizure continues, a third drug is loaded. The most commonly used drug is phenobarbital, at a loading dose of 20 mg/kg at a rate of 2 mg/kg per minute (maximum dose of 60 mg/min).

Because phenobarbital can cause apnea, depressed consciousness, and hypotension, all of which are more pronounced in the presence of benzodiazepines. Other options for the third medication have begun to take precedence. These include valproate sodium and levetiracetam. Valproate sodium is loaded at a dose of 40 mg/kg at 5 mg/kg/min. It is contraindicated in the presence of liver disease, thrombocytopenia, or possible metabolic disease. Levetiracetam is loaded at 40 mg/kg at 5 mg/kg/min.

If the seizure continues, either a different third-line medication is used or, pharmacologic coma is induced. Concurrent electroencephalographic monitoring is helpful at this point. If the patient has not yet been intubated, do so now.

Midazolam is a safe and effective benzodiazepine used to treat status epilepticus that is refractory to conventional agents. A bolus of 0.2 mg/kg over 2 minutes is followed by infusion of 0.1 mg/kg per hour.[56] The dose is increased every 15 minutes as necessary to a maximum of 3 mg/kg per hour. Tachyphylaxis may occur, necessitating high doses.

If midazolam is not well tolerated or seizures persist, pentobarbital may be administered with an initial bolus of 5 mg/kg IV followed by a continuous infusion of 0.5 to 5.0 mg/kg per hour. Severe hypotension, cardiovascular toxicity, and postinfusion weakness are common complications of pentobarbital coma.

Propofol also has been shown to be highly effective in the treatment of refractory status. An initial intravenous bolus of 1 to 2 mg/kg is followed by infusion of 2 to 10 mg/kg per hour.[57] Propofol is contraindicated in children on the ketogenic diet.

Nonconvulsive status epilepticus is more difficult to recognize and often requires electroencephalography for diagnosis. Treatment is with benzodiazepines or intravenous valproic acid.[58]

Once the seizure has been effectively terminated, neuroimaging and lumbar puncture are indicated.

Disposition

Hospitalization is unnecessary for most patients after a first brief unprovoked seizure as long as the neurologic examination is normal and follow-up evaluation is possible. Electroencephalography and imaging studies can be performed on an outpatient basis.

Children with simple febrile seizures can almost always be sent home. Warden and Hauser and their colleagues outlined advice to be given to families in the ED[59,60] (Box 175-11).

For the child who had a prolonged febrile seizure or cluster of seizures, a prescription for rectal diazepam (Diastat AcuDial, 0.5 mg/kg per rectum rounded up to the nearest 2.5 mg; maximum of 10 mg in young children and 20 mg in older children) can be prescribed for outpatient use after consultation with the child's neurologist or primary care physician. Instruct parents to give Diastat *only* if a seizure continues beyond 5 minutes and to then call emergency medical services for transportation to the ED for further evaluation.

Children who have had a prolonged seizure or who are not back to their baseline within a few hours should be admitted to the hospital. Hospitalization is also recommended if adequate follow-up evaluation cannot be arranged or in the case of extreme parental anxiety.

Initiating Anticonvulsant Therapy

The decision to start anticonvulsant prophylaxis must balance the risk for recurrence of seizure against the potential complications associated with long-term medication use.

Side effects of medication are common and include sedation, dizziness, blurred vision, ataxia, gastrointestinal disturbances, and cognitive and behavioral changes. Idiosyncratic reactions include hepatotoxicity, agranulocytosis, aplastic anemia, rash, Stevens-Johnson syndrome, and serum sickness.

Two thirds of children with a first unprovoked seizure never experience a recurrence.[60] The risk for recurrence is increased with

www.ketabpezeshki.com 66485457-66963820

Box 175-11 Advice to Parents about Simple Febrile Seizures

- Febrile seizures occur in 2 to 5% of all children between the ages of 6 months and 5 years.
- These seizures may appear frightening to observers but generally are harmless.
- Simple febrile seizures often occur in the first 24 hours of the febrile illness and occur only once. If the seizure recurs, your child should be reevaluated.
- A febrile seizure may be manifested by body stiffening, twitching of the face or arms and legs, eye rolling, jerking of the arms and legs, staring, or loss of consciousness.
- Febrile seizures generally last less than a minute but can last up to 15 minutes.
- Your child may appear not to be breathing and the skin color may become darker; if so, call 911 or emergency personnel and lay the child on the floor on his or her back. Do *not* place your fingers in the child's mouth.
- Febrile seizures do not cause brain damage or paralysis.
- A child who has febrile seizures has only a slightly increased risk for development of a seizure disorder compared with a child who never had a febrile seizure.
- Febrile seizures tend to run in families.
- Febrile seizures can recur with subsequent febrile illnesses. Medicines generally are not given to prevent simple febrile seizures.
- Use of medicines such as acetaminophen or ibuprofen for fevers has not been shown to prevent febrile seizures.

Modified from Warden CR, et al: Evaluation and management of febrile seizures in the out-of-hospital and emergency department settings. Ann Emerg Med 41:2, 2003.

the presence of neuroimaging or electroencephalographic abnormalities, developmental delay, family history of epilepsy, remote symptomatic seizure, occurrence of the first seizure during sleep, or Todd's paralysis. If none of these risk factors is present, the 5-year recurrence risk is only 21%.

There is no evidence that early treatment with anticonvulsant medications after a single seizure alters the later risk of epilepsy,[61] nor is there evidence to show that a single self-limited seizure causes neurologic sequelae.

Balancing this information, anticonvulsants generally are started only after a second unprovoked seizure and, if possible, only after consultation with the patient's primary care provider or a neurologist.

Patients with acute symptomatic seizures associated with a risk factor for recurrence, such as cerebral hemorrhage, meningitis, or contusion, should be treated in house with prophylactic anticonvulsants, such as phenytoin or fosphenytoin. When the patient is stable, the decision to continue or to discontinue treatment is made.

The choice of medication is dictated by the seizure type and syndrome and the side effect profile of the agent. Drug levels must be monitored with the older anticonvulsants, but most of the newer anticonvulsants do not necessitate monitoring.

Of the older medications, phenytoin, phenobarbital, valproic acid, and carbamazepine are all excellent medications for treatment of generalized and partial seizures. However, phenytoin is a poor long-term choice in children because of the development over time of hirsutism, gum hyperplasia, and facial coarsening. Phenobarbital is rarely used in children older than 2 years because of the high rate of hyperactivity, sleep disturbances, and lowered intelligence quotient (IQ). Because of its consistent absorption and excellent safety profile, phenobarbital is frequently used in infants. Of the older medications, carbamazepine is the first choice for the management of partial epilepsy. It should be noted that carbamazepine, as well as phenytoin, can worsen absence and myoclonic seizures. Valproic acid is a first-line treatment for primary generalized epilepsy and is particularly useful for myoclonic and absence seizures. Because valproic acid has a relatively high incidence of hepatotoxicity, particularly in children younger than 2 years, as well as significant teratogenicity, newer anticonvulsants are often used first. Ethosuximide is the drug of choice for absence seizures; it is not effective for convulsive seizures.

In the past 20 years, several new anticonvulsants have been approved by the FDA. These include gabapentin, felbamate, lamotrigine, topiramate, zonisamide, oxcarbazepine, levetiracetam, vigabatrin, lacosamide, rufinamide, and clobazam. Their role in the management of pediatric epilepsy is becoming increasingly important. Table 175-4 provides a summary of the commonly used anticonvulsants in children.

HEADACHES IN CHILDREN

Perspective

Headache is an extremely common problem in children and adolescents. Even though a majority of patients have benign causes of headaches, which usually can be diagnosed by a careful history and physical examination, neuroimaging with CT or MRI or both may be necessary in selected cases. Proper diagnosis, treatment, and close monitoring of these patients are extremely important to ensure that no serious cause of the headache has been overlooked.

Studies of schoolchildren have indicated that 40% of children will experience a headache by 7 years and 75% will experience a headache by 15 years of age and that migraine (one of the most common causes of headache in childhood) occurs in 1% of children by 7 years and 5% of children by 15 years of age. Studies in the United States have found that the highest incidence (246 episodes per 100,000 person-years) of migraine headache is in boys 10 to 14 years of age.

Principles of Disease

Several pathophysiologic theories have emerged to explain the mechanisms of headache. However, there is still ongoing debate as to whether the vascular component of migraines or neurogenic inflammation is the sole basis for the clinical expression of headache. The *vascular theory* proposes that headaches are produced by dilation of intracranial or extracranial arteries. The change in vessel diameter triggers the auras before and the pain during a headache; the dilation may be relieved by vasoconstrictive drugs, such as ergots. The *neuronal theory* proposes that headaches are due to a primary dysfunction of the brain; a wave of spreading neuronal depression is accompanied by decreased cerebral blood flow. Serotonin (5-hydroxytryptamine [5-HT]) may be a key mediator in this cascade of events. Serotonin agonists have been shown to relieve migraine pain. The *trigeminovascular theory* is an integrated hypothesis that combines elements of both theories. The trigeminal nerve makes synaptic connections with cerebral blood vessels, and the headache is an expression of the nerve–blood vessel interaction. Another theory that combines elements of the vascular and neuronal theories suggests that an initial electrical phenomenon beginning in the cerebrum initiates a cascade of events that affects the vasculature, with the release of biochemical substances leading to neurogenic inflammation.[63,64]

Clinical Features

Headaches can be classified into five temporal patterns: acute, acute recurrent, chronic progressive, chronic nonprogressive, and mixed. An *acute* headache is new in onset and different from previous headaches; it can herald a broad range of conditions

www.ketabpezeshki.com 66485457-66963820

Table 175-4 Summary of Commonly Used Anticonvulsants in Children

DRUG	SEIZURE TYPE	AVERAGE DAILY MAINTENANCE (mg/kg/day)	THERAPEUTIC LEVEL (µg/mL)	DOSE-RELATED SIDE EFFECTS*	IDIOSYNCRATIC EFFECTS
Carbamazepine (Tegretol, Carbatrol)	Partial, GTC	10-20 Start 5-10	6-12	Ataxia, nystagmus, vertigo, occasionally increased seizures	SIADH, aplastic anemia, hepatotoxicity, Stevens-Johnson syndrome (highest risk in Asian patients)
Diazepam (Diastat)	Clusters	0.5 mg/kg rectally prn	Not routinely measured	Respiratory depression	
Ethosuximide (Zarontin)	Absence	15-30 Start 5-10	40-100	Nausea, gastrointestinal distress	Aplastic anemia, Stevens-Johnson syndrome
Phenobarbital	Partial, GTC	3-6	15-40	Hyperactivity, decreased IQ	Angioedema, serum sickness
Phenytoin (Dilantin)	Partial, GTC	4-7	10-20	Ataxia, nystagmus, vertigo, hirsutism, gum hyperplasia	Stevens-Johnson syndrome, aplastic anemia
Valproic acid (Depakene, Depakote)	Absence, myoclonic, atonic, GTC	15-40 Start 10-15	40-120	Thrombocytopenia, weight gain, tremor, platelet dysfunction	Hepatotoxicity, pancreatitis, aplastic anemia, Stevens-Johnson syndrome
Lamotrigine	Partial, GTC, absence, Lennox-Gastaut syndrome	5-15 (1-5 if taking valproic acid)	Not routinely measured	Dizziness, diplopia, ataxia	Stevens-Johnson syndrome (especially if used with valproic acid)
Levetiracetam (Keppra)	Partial, GTC, myoclonic	20-40 Start 10	Not routinely measured	Agitation, somnolence	
Topiramate (Topamax)	Partial, GTC, myoclonic, Lennox-Gastaut syndrome	5-9 Start 1-3	Not routinely measured	Kidney stones, weight loss, psychomotor slowing	Hepatotoxicity, glaucoma, hyperthermia

Modified from Flomin O, Nield L, Kamat D: Seizure medications: A review for the primary care pediatrician. Clin Pediatr 44:383, 2005; and Bourgeois BF: Broader is better: The ranks of broad-spectrum antiepileptic drugs are growing. Neurology 69:1734, 2007.
GTC, generalized tonic-clonic; *SIADH,* syndrome of inappropriate secretion of antidiuretic hormone.
*Not including sedation and dizziness.

ranging from a viral illness to a subarachnoid hemorrhage. *Acute recurrent* headaches can be expressed as periodic events separated by pain-free intervals. *Chronic progressive* headaches occur during weeks to months. They can signify serious medical disorders, such as brain tumors or arteriovenous malformations. *Chronic nonprogressive* headaches usually occur for years and are classified as primary headaches (as opposed to secondary symptomatic headaches). *Mixed* headaches are acute recurrent headaches (migraine) superimposed on a pattern of daily chronic nonprogressive headaches.[63,65]

The primary goal of the ED evaluation is to differentiate symptomatic headaches from primary headaches, such as migraine or tension headaches. The history is critical in investigating children's complaints of headache and is the most important component of the evaluation to determine the correct diagnosis. Both the patient and family members should be asked about specific factors related to the headache. Rothner has created a patient questionnaire to generate a "headache database" from which clinicians can formulate a diagnosis, which is presented in Box 175-12.[65]

In addition to the important questions in Box 175-12, the clinician must focus on a detailed history of the neurologic system to identify any related symptoms (e.g., lethargy, ataxia, seizures, weakness, visual disturbances) and a general review of other organ systems. Warning signs of symptomatic headaches include recent onset, occurrence with straining or athletic endeavors, association with neurologic symptoms, change in headache pattern, nocturnal awakening, and bilateral occipital headaches. Additional information related to the past medical history (e.g., history of recent head

Box 175-12 Patient Questionnaire to Generate Headache Database

- Do you have more than one type of headache?
- How did the headache begin?
- Was there associated trauma or infection?
- How long has the headache been present?
- Are the symptoms worsening or staying the same?
- How often do the symptoms occur and how often do they last?
- Do the headaches occur at any special time or circumstance?
- Are the headaches preceded by warning signs?
- Where does it hurt?
- What is the quality of the pain? Is there pounding or a sharp sensation?
- Do you have any associated symptoms during the headache? abdominal pain? Is there any nausea or vomiting?
- Do you stop what you are doing during the headache?
- Do you have any other medical problems?
- Are you taking other medications?
- Are there activities that make the headache worse?
- Does any medication make the headache better?
- Does anyone in your family have headaches?
- What do you think is causing your headache?

Data from Lewis DW, Rothner DA: Headache in children and adolescents. In Johnson RT, Griffin JW, McArthur JC (eds): Current Therapy in Neurological Diseases, 6th ed. Philadelphia, Mosby, 2002.

www.ketabpezeshki.com 66485457-66963820

trauma, neurologic or psychiatric disorders, hospital admissions, medications) also is important to obtain.

The physical examination, including vital signs, should be performed in a careful manner with particular attention to those findings unique to children. Height, weight, and head circumference should be compared with standard percentiles and the child's previous growth history; a change in the rate or direction of growth may indicate an intracerebral mass or hydrocephalus. Blood pressure also should be carefully measured, with use of age-appropriate cuff size and percentiles for age. The child's head also should be auscultated for bruits associated with arteriovenous malformations, and a skin examination should be performed to look for stigmata of neurocutaneous disorders, such as neurofibromatosis. The neurologic examination should begin with assessment of the child's mental status, language, and level of consciousness. It also should include assessment of cranial nerves; gait analysis; cerebellar, sensory, and motor function testing; and evaluation of deep tendon reflexes. The ophthalmologic examination should include pupillary reactivity, visual acuity, extraocular movements, and funduscopy. Observation of interactions between the patient and family members also may provide clues to potential family problems, depression, or anxiety.

Differential Considerations and Headache Syndromes

The list of differential considerations for headache is extensive (Box 175-13).[66]

Acute Headache

The acute headache is a common problem in children and adolescents and accompanies many infectious processes. In the absence of other signs of CNS involvement (such as nuchal rigidity or alteration in level of consciousness), headaches in febrile children usually do not constitute evidence of CNS infection. In fact, nonspecific viral illnesses represent a majority of diagnoses in children presenting to the ED with an acute headache.

The most common cause of subarachnoid hemorrhage in young adults is a ruptured cerebral aneurysm. In younger children, rupture of an arteriovenous malformation that is near the subarachnoid space may cause subarachnoid and intraparenchymal hemorrhage. A common site of bleeding is the anterior cerebral artery with resulting pressure on the third cranial nerve. Varying degrees of ptosis, lateral deviation of the eye, and pupillary dilation may be seen with this type of aneurysm.

Box 175-13 Differential Diagnosis of Headache

Aneurysm, arteriovenous malformation
Congenital malformation (e.g., Dandy-Walker syndrome)
Hydrocephalus
Hematoma: subdural, epidural (acute), intraparenchymal
Hypertension
Infectious: viral illness, abscess, meningitis, encephalitis
Metabolic
Neoplasm
Pseudotumor cerebri
Subarachnoid hemorrhage; berry aneurysm rupture
Toxic (medication, cocaine abuse, analgesia rebound)
Trauma

Data from May A, Goadsby PJ: The trigeminovascular system in humans: Pathophysiologic implications for primary headache syndromes of the neural influences on the cerebral circulation. J Cerebr Blood Flow Metab 19:115, 1999.

If subarachnoid hemorrhage is suspected, CT of the head (non–contrast enhanced) should be performed as soon as possible. If the CT scan does not show subarachnoid blood, a lumbar puncture should be performed because head CT findings are normal 5 to 10% of the time, especially if only a small amount of bleeding has occurred. The first and last samples taken in the lumbar puncture are examined for cells to eliminate the possibility of a "traumatic tap" (in which the number of red blood cells would be expected to decrease by the last tube) and the presence or absence of xanthochromia.

Localized acute headaches commonly are due to sinusitis, otitis media, dental disorders, or traumatic head injury. Dental disorders usually are accompanied by pain localized to the teeth, gums, or jaw. Temporomandibular joint dysfunction usually is associated with unilateral pain in the ear, jaw, or mouth. Headache associated with trauma must always be carefully investigated for the possibility of subdural or epidural hematomas, fractures, and leptomeningeal cyst (a "growing" skull fracture in a child 3 years of age or younger with a history of recent trauma). Ophthalmologic problems, such as astigmatism, refractory errors, eye strain, and squint, also are occasionally responsible for headaches in children.

Chronic Progressive Headache

The chronic progressive headache category is composed of disorders that cause progressively severe headaches in children. The development of increased ICP, which can be caused by brain tumors, pseudotumor cerebri, hydrocephalus, brain abscess, or intracranial bleeding, is a major problem in this category. Headache that awakens the child or is present on first awakening is a classic symptom of increased ICP. Impaired venous outflow in the supine position leads to excess fluid (blood, CSF, or edema) inside the skull, leading to increased pressure. Nocturnal or morning emesis also may suggest increased ICP. The physical examination may show symptoms or signs of increased ICP (papilledema, brisk reflexes, cranial nerve deficits, upturning toes in response to stimulation of the sole of the foot, decreased level of consciousness) as well as focal symptoms related to the location of the lesion (e.g., hemiparesis, ataxia, visual field deficits).

Headaches may be the first symptom of a brain tumor and as such occur with increasing frequency with age. In a study by Flores and colleagues, 18% of 0- to 5-year-olds, 52% of 6- to 10-year-olds, and 68% of 11- to 20-year-olds who had brain tumors presented with headaches. Only 38% of primary brain tumors were diagnosed within the first month after the onset of symptoms. More than 50% of these patients had at least three associated symptoms or signs, such as nausea, vomiting, visual effects, problems with walking, weakness, changes in personality or school performance, or speech changes. The most common neurologic findings were papilledema, abnormal eye movements, ataxia, abnormal tendon reflexes, and abnormalities on the visual examination.[67]

Clinical findings with pseudotumor cerebri (idiopathic intracranial hypertension) are secondary to the increased ICP and include papilledema, sixth cranial nerve palsy, and visual field obstruction. This condition is more common in females and in younger children is associated with obesity; presence of otitis media or head trauma; use of vitamin A, steroids, birth control pills, or tetracycline; presence of menstrual irregularities or diseases that produce obstruction of the CSF pathways; and obstruction of the major venous sinuses. By definition, neuroimaging findings are normal. The lumbar puncture usually demonstrates elevated pressure, often higher than 20 cm H_2O, and normal CSF protein and glucose levels. Neuroimaging should precede lumbar puncture when increased ICP is suspected from mass or injury. Treatment can include diuretics and repeated lumbar puncture for

www.ketabpezeshki.com 66485457-66963820

removal of CSF.[68] Hydrocephalus may be related to a previous episode of meningitis, subarachnoid hemorrhage, or head injury or may be congenital.

Brain abscess can result from meningitis, head trauma, chronic otitis media and sinusitis, or septic embolization in children with congenital heart disease. Focal neurologic signs as well as fever and headache also may be present, but the patient may look surprisingly well. CT of the head without contrast enhancement is not sufficiently sensitive when an abscess is considered in the differential; CT with and without contrast enhancement or MRI is indicated. CSF findings (performed only after neuroimaging) usually include a mild leukocytosis (10-200 leukocytes/mm^3), slightly elevated protein level, and normal glucose level. The CSF smear and culture usually do not reveal any organisms.

A subdural hematoma is associated with head trauma. Symptoms include those associated with increased ICP; seizures and other focal neurologic deficits also may be present. The diagnosis is confirmed by neuroimaging. Postconcussive headaches are common. These headaches can be severe and associated with dizziness and vomiting. Chronic progressive headache also can be a symptom of systemic diseases, such as hypertension, collagen vascular disease, hypothyroidism, Lyme disease, mononucleosis, or inborn errors of metabolism.

Migraine Headache

The diagnosis of migraine is based on symptoms of recurrent headaches separated by pain-free intervals. A revised classification of migraine syndromes has been produced for pediatric migraine (Box 175-14).[69]

Migraine headaches are classified primarily into migraine with and without an aura. *Migraine without an aura,* also known as *common migraine,* is the most frequent type of pediatric and adolescent migraine and includes the following criteria: more than five attacks that last 1 to 48 hours (untreated), accompanied by either nausea and/or vomiting or photophobia and/or phonophobia, and including a minimum of two of the following criteria: unilateral location, pulsing quality, moderate to severe intensity, and aggravated by routine physical activities.

Migraine with an aura, previously known as *classic migraine,* is diagnosed when at least two attacks fulfilling the diagnosis of migraine occur accompanied by a variety of sensory warning symptoms, such as flickering lights, loss of vision, and tingling or numbness. The symptoms develop during 5 minutes or more and completely resolve within 60 minutes.[69,70]

Hemiplegic migraine is characterized by the sudden onset of hemiparesis or loss along with headache in the contralateral hemisphere. This type of migraine is seen more frequently in children than in adults. Even though symptoms usually last for hours or days, affected persons rarely are left with permanent deficits. *Ophthalmoplegic migraine* is characterized by severe unilateral eye pain and headache, followed by ipsilateral third nerve palsy of variable degree. Rarely, the fourth or sixth cranial nerve, rather than the third nerve, may be affected. *Basilar artery migraine,* also common in children, is manifested with a combination of visual symptoms (e.g., transient bilateral blindness, blurred vision) and visual hallucinations, vertigo, ataxia, loss of consciousness, and drop attacks. An *acute confusional state* consists of a change in personality, orientation, or behavior. The *Alice in Wonderland syndrome* includes perceptions of distortion in body images and shapes. Objects appear either much larger (macropsia) or smaller (micropsia) before, during, or after a headache.

Migraine variants are not uncommon and can be misdiagnosed. *Abdominal migraine* is characterized by recurrent abdominal pain, nausea, vomiting, and recurrent headaches. Benign paroxysmal vertigo is manifested as the sudden onset of vertigo, pallor, and nystagmus. *Paroxysmal torticollis* is defined as recurrent episodes of head tilt associated with headache, nausea, and vomiting. Of note, this is a diagnosis of exclusion. A child with a head tilt, vomiting, and headache should first be evaluated for a posterior fossa lesion. *Ocular migraine* is characterized by transient monocular visual blurring to blindness with bright flashes of light.

Epilepsy and migraine headache are distinct clinical syndromes, yet they share several characteristics, such as aura, vertigo, nausea, pallor, loss of consciousness, drowsy postictal state, confusion, and transient focal neurologic deficits. The incidence of seizures is higher in patients with migraine than in the general population. The differentiation of these two clinical entities may be difficult in certain cases. Headache as the sole manifestation of a seizure is uncommon; however, headaches frequently may follow tonic, tonic-clonic, and brief complex partial seizures. Bilateral frontal throbbing headaches also may follow episodes of status epilepticus. Further neurologic evaluation, including electroencephalography, may occasionally be necessary to try to distinguish between these two syndromes.

Box 175-14 1998 Revised Criteria for Pediatric Migraine without an Aura

A. Five or more attacks fulfilling features B through D.
B. Headache attack lasting 1-48 hours (*adults:* 2-72 hours)
C. Headache has at least two of the following features:
   1. Either bilateral or unilateral (frontal-temporal) location (*adults*: unilateral)
   2. Pulsating quality
   3. Moderate to severe intensity
   4. Aggravated by routine physical activities
D. At least one of the following accompanies headache:
   1. Nausea and/or vomiting
   2. Photophobia and/or phonophobia (*adults:* both photophobia and phonophobia)

Chronic Nonprogressive Headache

Chronic nonprogressive headache commonly is seen in the adolescent population. Included in this category of headache are muscle contraction headache, depressive equivalents, and conversion headaches. The International Headache Society classification of headaches refers to these types of headaches as *tension headaches*. This type of headache includes the following symptoms: bilateral or unilateral; nonthrobbing, pressing, or bandlike tightness of mild to moderate intensity; and the absence of nausea, vomiting, and aura. These headaches are further classified as either episodic (10 to fewer than 15 episodes/month lasting 30 minutes to 7 days) or chronic (more than 15 episodes/month for more than 6 months).

Cluster Headache

Cluster headache is a distinctive headache syndrome more commonly seen in male patients. The syndrome rarely is seen in those younger than 10 years. Cluster headache is characterized by one to several attacks recurring each 24 hours, during several weeks to months, with headache-free periods between the cluster headaches. The headache-free periods may last months to years. The pain is throbbing, severe, and unilateral; occurs over the same orbitotemporal region; and is associated with ipsilateral scleral injection, lacrimation, nasal stuffiness, and, less often, partial Horner's syndrome (enophthalmos, ptosis, miosis, and anhidrosis, unilateral affecting sympathetic innervation of the eye). The pain

www.ketabpezeshki.com 66485457-66963820

lasts 30 minutes to several hours and can occur at any time of day or night.

Diagnostic Strategies

The diagnosis of a specific headache syndrome usually is determined by the history and physical examination. The primary goal of the ED evaluation is to eliminate the possibility of an intracranial lesion or serious extracranial pathologic condition. Skull radiography and electroencephalography are of limited value in this setting for the routine evaluation of children with chronic headaches.

Radiology

CT of the head and cranial MRI are both excellent studies to evaluate patients with headaches but are often not needed emergently.[71] In general, MRI provides superior anatomic detail compared with a CT scan. MRI is particularly useful in the detection of abnormalities in the sella turcica, posterior fossa, and cervicomedullary junction. MRI also is better at detection of arteriovenous malformations and low-grade tumors. However, a patient cannot be closely monitored during the MRI study, and MRI is not always available in the ED. CT scan is superior to MRI in the detection of acute blood and skull fractures. Therefore, CT is usually the modality of choice in the ED if neuroimaging is required. However, most patients presenting with headache do not require neuroimaging. Indications for the use of neuroimaging are presented in Box 175-15.[68]

Laboratory and Special Procedures

Lumbar puncture occasionally is helpful in the evaluation of patients with headache. If the possibility of a mass lesion is a concern (as suggested by history of early-morning headaches and vomiting or focal neurologic findings on physical examination), radiologic imaging should precede the lumbar puncture. The lumbar puncture is a necessary procedure to determine the presence of an infectious process, subarachnoid hemorrhage, or idiopathic intracranial hypertension.

Box 175-15 Indications for Radiologic Imaging in Patients with Headache

Strongly Indicated If
- Abnormal neurologic examination findings
- Signs and symptoms of elevated intracranial pressure
- Meningeal signs plus focal neurologic findings or altered mental status
- Progressive or new neurologic signs
- Significant head trauma
- Severe nocturnal headaches that awaken the patient from sleep or are present on awakening
- Severe (characterized by patient as "worst headache of my life") headaches of increasing frequency and duration
- Presence of ventriculoperitoneal shunt
- Chronic progressive headache

Consider If
- Headache or vomiting on awakening
- Unvarying location of headache, especially occipital
- Persistent headache plus no family history of migraine
- Neurocutaneous syndrome
- Age younger than 3 years (limited verbal skills)

Data from Qureshi F, Lewis D: Managing headache in the pediatric emergency department. Clin Pediatr Emerg Med 4:159, 2003.

In a patient with suspected chronic progressive headaches, the headaches may be a symptom of a systemic disease. Laboratory tests that may be considered include CBC; urinalysis; erythrocyte sedimentation rate determination; antinuclear antibody assay; liver function studies; thyroid function studies; serum lipid assay and determination of serum magnesium, lactate, and pyruvate concentrations; and Lyme disease titer.

Management

Treatment of primary childhood headaches requires attention to initial pharmacologic management as well as reassurance, removal of potential triggering factors, and initiation of a behavioral management program.[64,70,72,73,75,76] Nonmedical interventions may have some impact and should be strongly considered. These include avoidance of triggers, placement of the child in a darkened room with minimal or no extraneous noise, avoidance of hypoglycemia by feeding during a migraine, avoidance of caffeinated beverage (except for possible use as a migraine medication during an acute migraine), application of a cool compress on the forehead, use of a gentle fan, and breathing exercises and relaxation techniques.[64] A headache diary is important to help the patient identify potential triggers and the effects of medications. Common triggers include reduction in sleep, perimenstrual stress, missed meals, and foods (such as chocolate, processed meats, alcohol, hard cheeses, red wine, monosodium glutamate, yeast extracts, nuts, figs, aspartame, and sauerkraut). Children with primary headaches are not hospitalized for care unless the diagnosis is uncertain and a serious cause of secondary headache is being considered.

Migraine

Treatment of migraine headache includes analgesics, vasoconstrictors, sedatives, triptans, antiemetics, anti-inflammatory agents, and other modalities.[64,72,73,75,76] The patient should be placed in a quiet and safe environment. Simple analgesics and rest are the first line of treatment for patients with migraine as well as nonmigraine headache. Medications include acetaminophen (pediatric: oral or rectal, 10-15 mg/kg/dose po/pr q4-6h, maximum dosage 90 mg/kg/24 hours; adolescent: 325-650 mg/dose, maximum dosage, 4 g/24 hours) and the nonsteroidal anti-inflammatory drugs (aspirin, 10-15 mg/kg/dose, 650-1000 mg for patients 12 years of age and older, maximum dosage 4 g/24 hours; ibuprofen 5-10 mg/kg/dose q6-8h; or 400 mg/dose for those 12 years of age and older, maximum daily dose of 1200 mg per day; or naproxen 2.5-5.0 mg/kg/ dose q8-12h, 250-300 mg for those 12 years of age and older to a maximum daily dosage of 1000 mg/24 hours). Some children respond well to small doses of caffeine.

For severe migraine episodes, more potent analgesics may be needed. These include ketorolac tromethamine (Toradol), a nonsteroidal anti-inflammatory that can be used parenterally in children who are vomiting (0.5 mg/kg intravenously or intramuscularly every 6 hours, to a maximum dose of 30 mg); codeine (0.5 to 1.0 mg/kg per dose every 4 to 6 hours orally, to a maximum dose of 60 mg); and oxycodone (0.05 to 0.15 mg/kg orally per dose every 4 to 6 hours, to a maximum dose of 5 mg every 6 hours). Combination medications, such as Fiorinal (butalbital, aspirin, and caffeine), Fioricet (butalbital, acetaminophen, and caffeine), and Midrin (isometheptene, acetaminophen, dichloralphenazone) also are effective. The dose is 1 or 2 capsules in children older than 12 years. Caution should be used in prescribing these medications. In addition to producing an analgesic effect, these medications may produce alterations of emotional state, sedation, and psychological dependence.

Vasoconstrictor drugs are used less commonly in the adolescent population than in the adult population. Antiemetic agents,

www.ketabpezeshki.com 66485457-66963820

although not as well studied in the pediatric as in the adult population, also may be considered. This group of dopamine receptor antagonists includes metoclopramide (in children older than 14 years: 10 mg intravenously × 1; children younger than 14 years: 0.1 to 0.2 mg/kg per dose intravenously), promethazine (in children: 0.25 to 0.5 mg/kg per dose intramuscularly or rectally every 4 to 6 hours as needed; in adults: 12.5 to 25 mg every 4 to 6 hours as needed), and prochlorperazine (in children weighing more than 10 kg or older than 2 years: 0.4 mg/kg per 24 hours orally or rectally, divided three to four times per day, or 0.1 to 0.15 mg/kg per dose intramuscularly, three to four times per day). Dystonic reactions with antiemetics are more common in children, so these agents should be used with caution in this population. Brousseau, in one of the few pediatric randomized clinical trials examining the efficacy of prochlorperazine compared with ketorolac for the treatment of acute migraine, found that by 60 minutes, a greater reduction in headache pain was obtained in the prochlorperazine group, even though 30% of patients in each group experienced some recurrence of headache symptoms.[77] In older patients who may be treated for nausea without sedation, ondansetron (a serotonin receptor antagonist) can be considered (0.15 mg/kg per dose intravenously or 4 to 8 mg/day orally).

Sumatriptan is a selective 5-HT_1 receptor agonist that can mediate cerebral vasoconstriction and block inflammatory response; it can be administered orally, intranasally, or subcutaneously. A review of medication trials of triptans in children with migraine highlighted the important finding that randomized clinical trials found no difference in outcome between the control and the experimental groups.[72] However, nasal sumatriptan (5 to 20 mg, repeated in 2 hours, to a maximum daily dose of 40 mg) has been shown to be effective in the adolescent population, along with oral preparations of 25 to 50 mg (repeated in 2 hours, to a maximum daily dose of 200 mg).[73] Sumatriptan should be avoided in persons with cardiac disorders or hypertension and in patients who have received an ergot alkaloid in the preceding 24 hours. Other newer 5-HT1 agents, such as zolmitriptan (Zomig) at doses of 2.5 mg intranasally and 5 mg orally compare favorably with sumatriptan. In a recent randomized clinical trial, the onset of significant pain relief was seen at 15 minutes asfter treatment with 5 mg of zolmitriptan nasal spray and at 1 hour produced a higher headache response rate compared with placebo (58.1% vs 43.3%).[74] Cluster headaches, which are brief and may not respond to oral therapy, can be treated with inhalation of oxygen at 4 to 5 L/minute, the ergot alkaloid Cafergot, or sumatriptan.[65] The most recently released triptan is a combination of sumatriptan and naproxen sodium (Treximet). It is approved for the treatment of migraine in adults only, although there is a recently completed adolescent clinical trial that could result in its approval.[64]

The use of pharmacologic agents for prophylaxis in children with migraine headache requires careful observation and follow-up evaluation by the child's primary care physician. The indications for use of these medications include more than two or three headaches per week and interference with lifestyle, particularly missed schooldays or inability to participate in social activities. In keeping with or perhaps reflecting the high spontaneous remission rate of childhood migraine, the placebo effect of many medications is high. Controlled studies are extremely limited. Medications that have been used include propranolol (initiated slowly at a dose of 2 to 4 mg/kg per day, divided three times a day; contraindicated in asthma patients), amitriptyline (initiated at a dose of 25 mg at bedtime for adolescents; baseline electrocardiogram is recommended), calcium channel blockers, anticonvulsants (particularly valproic acid), cyproheptadine, and naproxen sodium. Cyproheptadine, valproic acid, and naproxen are available in liquid form, which is a valuable feature in the pediatric population. Methysergide should be avoided in children owing to serious side effects, including retroperitoneal fibrosis. Amitriptyline may be useful for adolescents with a diagnosis of migraine and muscle contraction headaches and in depressed children with headaches.

PEDIATRIC ATAXIA

Perspective

Ataxia comes from the Greek word *ataktos,* meaning "lacking order," and describes a pathologic abnormality of organization or modulation of movement.[78]

Pathophysiology

Ataxia can be caused by congenital abnormalities or can be acquired. Congenital ataxia is associated with CNS abnormalities. Acquired ataxia can be acute, episodic, or chronic. The chronic ataxias are usually caused by inherited metabolic or genetic disorders. Most commonly, ataxia is caused by cerebellar dysfunction. Lesions in the corticospinal tract or dorsal columns of the spinal cord may also be causative.

Clinical Features

Most children with ataxia are seen in the first few days after onset, usually because of a refusal to walk, unsteadiness of arm movements, or sudden development of a wide-based "drunken" gait. The history should identify any recent infection, injury, inadvertent drug ingestion, or other family members with the same problem. Mental status usually is normal in cases of postinfectious ataxia. If it is abnormal, the possibility of ingestion, acute disseminated encephalomyelitis, or stroke should be considered. Nystagmus is common if the cerebellum is affected. Papilledema or cranial nerve palsies suggest hydrocephalus or a central nervous system lesion.[79]

Differential Considerations

In children, 40% of ataxia cases are caused by acute cerebellar ataxia (Box 175-16). Boys are more commonly affected, with the highest incidence at the ages of 2 to 4 years. Seventy percent of patients have a history of recent illness with multiple causative

Box 175-16 Etiology of Childhood Ataxia

- Acute cerebellar ataxia
- Acute postinfectious demyelinating encephalomyelitis
- Brainstem encephalitis
- Drug ingestion
- Guillain-Barré syndrome
- Metabolic disorders
  - Aminoacidopathies
  - Mitochondrial disorders
  - Organic acidopathies
  - Urea cycle disorders
- Migraine headaches
- Multiple sclerosis
- Neoplasm
- Opsoclonus-myoclonus syndrome
- Recurrent and chronic genetic ataxias
- Seizures
- Stroke
- Vertebral artery dissection

Modified from Ryan M, Engle E: Acute ataxia in childhood. J Child Neurol 18:309, 2003.

www.ketabpezeshki.com 66485457-66963820

agents, but varicella virus is the most common, with up to 26% of cases associated with varicella. Coxsackievirus and echovirus are other etiologic agents. The disease is thought to be due to an autoimmune phenomenon leading to cerebellar demyelination. Symptoms and signs are maximal at onset, with the extremities more seriously affected than the trunk, and range from unsteadiness and wide-based gait to complete inability to walk. Mental status is normal, and nystagmus is common. Fever and seizures are uncommon outcomes.[79]

Acute postinfectious demyelinating encephalomyelitis can also cause ataxia and occurs in the recovery phase of a viral illness or vaccination. It is distinguished from acute cerebellar ataxia by alteration in consciousness and multifocal neurologic deficits as well as by fever and the frequent occurrence of seizures. Brainstem encephalitis can involve the cerebellum, causing ataxia in association with focal neurologic abnormalities and respiratory irregularities. Etiologic agents include Epstein-Barr virus, *L. monocytogenes,* and enteroviruses.[78,79]

Up to 32% of cases of acute childhood ataxia are due to drug toxicity, most commonly from ingestion of anticonvulsants, benzodiazepines, alcohol, or antihistamines and less commonly from exposure to organic chemicals or heavy metals. The ataxia usually is accompanied by lethargy, confusion, and inappropriate speech or behavior. Nystagmus may be present as well.

Approximately 45 to 60% of all childhood brain tumors arise in the brainstem or cerebellum and can be manifested with slowly progressive ataxia. Acute decompensation can occur with the development of hydrocephalus or hemorrhage into the lesion.

Head injuries with cerebellar contusion or hemorrhage can cause ataxia. In patients with neck injuries, ataxia can be caused by vertebral artery dissection. Posterior circulation strokes are rare in children but should be considered after neck trauma with possible vertebral artery dissection as a cause of the ataxia.

The opsoclonus-myoclonus syndrome consists of ataxia, rapid chaotic multidirectional eye movements, and myoclonic jerks of the extremities, head, trunk, and face. Most commonly, this is seen as a presenting manifestation of neuroblastoma or ganglioneuroblastoma in which the ataxia is thought to be due to a paraneoplastic autoimmune phenomenon involving cross-reactivity of tumor and cerebellar antigens. Spontaneous vertebral artery dissections also have been reported in children without a known history of trauma.[78]

Ataxia can be seen in patients with basilar migraine and can be associated with vertigo, hemiparesis, cranial nerve dysfunction, nausea, vomiting, or headache.[78]

Loss of sensory input to the cerebellum can cause a sensory ataxia. Clinical manifestations will include a Romberg sign, decreased deep tendon reflexes, and impaired proprioception and vibration sense. Fifteen percent of patients with Guillain-Barré syndrome have sensory ataxia. In the Miller Fisher variant of Guillain-Barré syndrome, the triad of ataxia, areflexia, and ophthalmoplegia of vertical gaze is characteristic.[78]

Transient ataxia can be present in the ictal or postictal phase of seizures. Inborn errors of metabolism also can be manifested with ataxia, which can develop acutely or be intermittent, depending on dietary intake or the presence of other illness. Such disorders should be considered when ataxia is accompanied by lethargy, encephalopathy, vomiting, diarrhea, or unusual body odor. Defects in urea acid cycle enzymes called aminoacidurias as well as defects in pyruvate and lactate metabolism can cause such signs and symptoms. Other inherited disorders, such as Niemann-Pick, Tay-Sachs, and Wilson's diseases, also can cause ataxia. Repeated attacks of ataxia also can be the presenting manifestation of multiple sclerosis.

A discussion of all of the genetic disorders that can cause ataxia is too vast to be included here, but the two most common genetic disorders are Friedreich's ataxia and ataxia-telangiectasia.

Friedreich's ataxia is a disorder of autosomal recessive inheritance characterized by progressive gait and limb disturbance. It is caused by mutation in the gene encoding a mitochondrial protein, frataxin, that results in loss of gene function. Affected patients demonstrate dysarthria, lower limb areflexia, proprioceptive sensory loss, and high-arched feet (pes cavus). Most patients are unable to walk by the age of 30 years. Death is most commonly due to cardiomyopathy, causing intractable congestive heart failure, and respiratory compromise from severe kyphoscoliosis.[78]

Ataxia-telangiectasia is a disorder of recessive inheritance caused by gene mutation manifested as a truncal ataxia in infancy that leaves most patients wheelchair bound by the age of 12 years. Oculocutaneous telangiectasias usually appear by the age of 3 to 5 years. These patients also demonstrate dysarthria, nystagmus, dystonic posturing, myoclonic jerks, and accelerated aging. They have deficient immunoglobulin A and decreased immunoglobulin E and M levels. They suffer from frequent sinus and pulmonary infections and have a 50- to 100-fold risk for development of leukemia and lymphoma. The mean age at death from this disorder is 20 years.[80]

Diagnosis

The key to making the diagnosis is to take a complete history and to perform a thorough physical examination. In particular, testing of cerebellar function can be accomplished by assessment of the child for dysmetria and dysdiadochokinesia.[81] Urine and serum toxicologic studies are the laboratory tests most likely to prove diagnostic. CT and MRI findings usually are normal in patients with postinfectious ataxia, but demyelination, tumor, hydrocephalus, or traumatic injuries may be identified. CSF analysis may show mild pleocytosis or lymphocytosis in acute postinfectious ataxia; findings are normal in most other cases. Electroencephalography is recommended for patients with altered consciousness and fluctuating clinical signs. A pattern of epileptiform discharges or slowing is seen in 66% of children with acute cerebellar ataxia. Electroencephalography also can diagnose nonconvulsive or convulsive seizures. The electroencephalographic pattern is normal in the opsoclonus-myoclonus syndrome. Electromyography may be helpful if sensory ataxia is suspected and may help diagnose Guillain-Barré syndrome. Urinary catecholamines can be assayed for diagnosis of neuroblastoma. Testing for newborn errors of metabolism includes a CBC; liver function tests; measurement of blood ammonia, lactate, pyruvate, and ketone levels; and determination of acid-base status. Other tests include plasma and urinary amino acid assays, urine organic acid assay, determination of serum biotinidase level, and CSF lactate assays. Genetic or other specialized testing also may be required. In the absence of developmental delay or positive family histories, however, these investigations for inborn errors of metabolism are unlikely to be helpful.[81]

Management

Children with ataxia usually require hospital admission for a complete evaluation. Consultation with a pediatric neurologist should be sought for patients in whom the cause of the ataxia is not evident on the ED evaluation.

Most children with acute cerebellar ataxia recover completely. Improvement is seen within a week and complete recovery in 3 months for 50% of children. Sixty-six percent to 90% recover completely. Some children exhibit persistent gait disturbances, ataxia, and delayed speech development. Evidence is lacking for improved outcomes with immunosuppressive therapies. Recovery is slower from acute postinfectious demyelinating encephalopathy. Corticosteroids may hasten recovery. Relapse can occur in up to

www.ketabpezeshki.com 66485457-66963820

10% of children. Most children recover fully, but some are left with significant permanent sequelae. Brainstem encephalitis should be treated with broad-spectrum antibiotics effective against *L. monocytogenes;* acyclovir should be included to provide coverage for varicella and other viruses until an organism is discovered. Patients with Guillain-Barré syndrome will need to be hospitalized and may require intravenous immune globulin and plasmapheresis to reduce circulating antibodies.

PEDIATRIC VERTIGO

Perspective

Vertigo is defined as an illusion of movement, a sensation that the external world is revolving around an individual (objective vertigo) or that the affected person is revolving in space (subjective vertigo). Vertigo is well recognized to occur in the pediatric age group and has many potential causes.

Pathophysiology

Disease processes that affect the balance of the vestibular, visual, and proprioceptive systems can cause vertigo by impairing the neural activity of the vestibular nucleus. Diseases of the ear, the eighth cranial nerve, the neck, the brainstem, or, rarely, the eye can lead to vertiginous symptoms. Vertigo is characterized as *central* or *peripheral,* depending on whether the cause is in the CNS.

Clinical Features

Vertigo often is manifested with dizziness. There may be a history of sudden falls, grasping for support, or unwillingness to move. Review of symptoms should include those related to the ear, such as otalgia, hearing loss, and tinnitus. Other important historical features that should be asked about include headache, loss of consciousness, head trauma or barotrauma, and family history of migraine and seizure disorders.

Diagnostic Strategies

For determination of the cause of vertigo, patients can be divided into those who have hearing loss and those who have normal hearing. In the group with hearing loss, further characterization of the loss as conductive or sensorineural in character and identification of the presence of trauma, and whether the causative disorder involves the CNS or the peripheral nervous system from the labyrinth or eighth cranial nerve, will help in diagnosis (Fig. 175-2).

Differential Considerations

Although vertigo is not as common in the pediatric age group as in adults, it has many potential causes (Box 175-17).[82] It usually is helpful to separate those conditions that cause vertigo into those with and those without associated hearing loss.

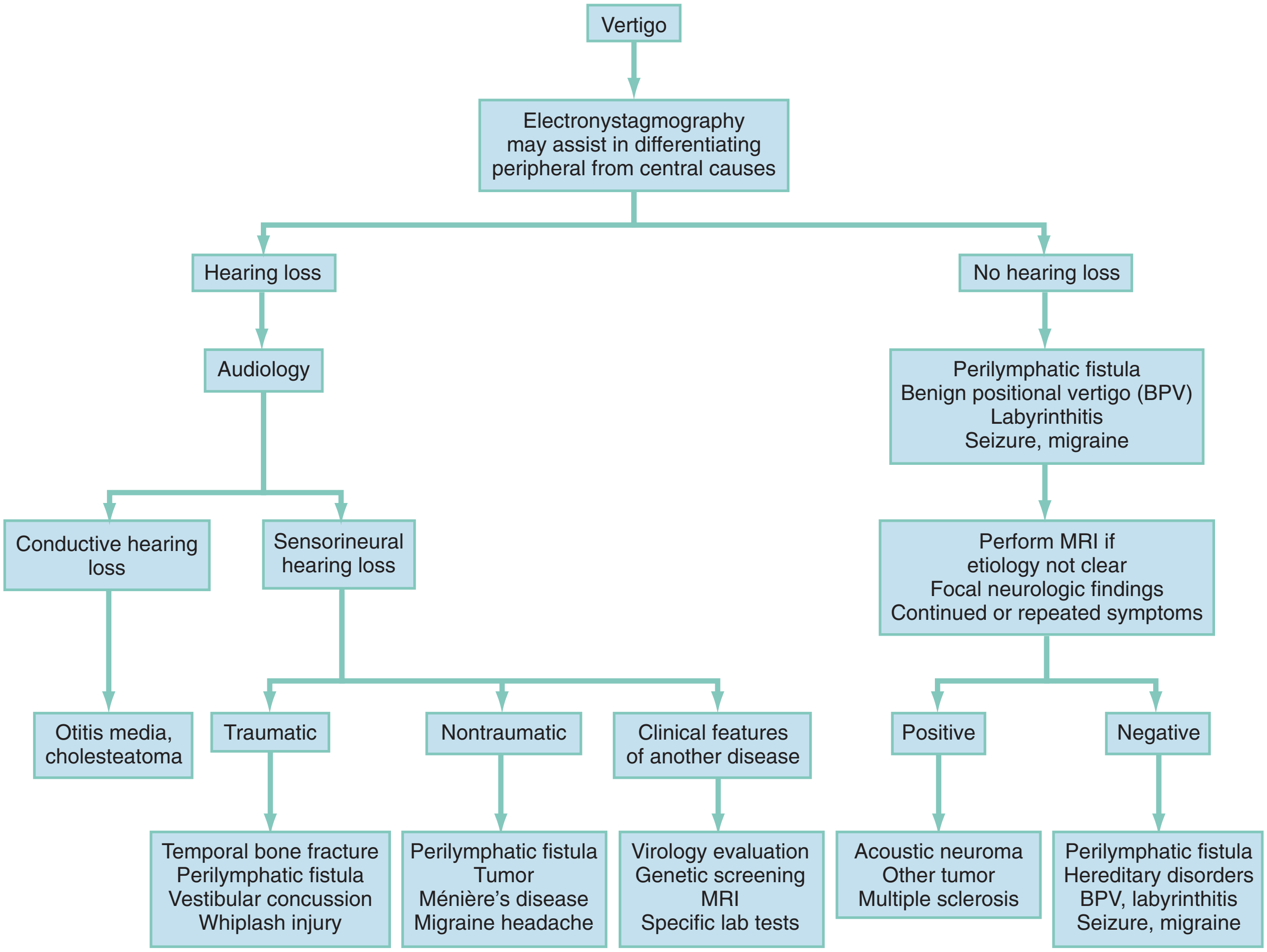


Figure 175-2. Vertigo evaluation. *MRI,* magnetic resonance imaging. (Modified from Rudolph C, Rudolph A [eds]: Rudolph's Pediatrics, 21st ed. New York, McGraw-Hill, 2003, pp 1246-1247.)

www.ketabpezeshki.com 66485457-66963820

Box 175-17 Etiology of Pediatric Vertigo

Central Vertigo
Atrioventricular malformations
Brain abscess
Chiari malformations
Demyelinating disorders
Encephalitis
Meningitis
Migraine headaches
Neoplasm
Seizures
Trauma

Peripheral Vertigo
Alport syndrome
Benign paroxysmal torticollis
Benign paroxysmal vertigo of childhood
Benign positional vertigo
Cholesteatoma
Diabetes mellitus
Labyrinthine dysplasia or aplasia
Labyrinthine concussion
Labyrinthitis
Lyme disease
Otitis media, suppurative and serous
Ototoxins
Ocular disorders
Pendred syndrome
Perilymphatic fistula
Stenosis of the internal auditory canal
Syphilitic inner ear disease
Thyroid disease
Trauma
Usher syndrome
Vestibular neuronitis
Waardenburg syndrome (genetic disorder associated with deafness, wide-spaced eyes)

Modified from Rudolph C, Rudolph A (eds): Rudolph's Pediatrics, 21st ed. New York, McGraw-Hill, 2003, p 1248.

Box 175-18 Causes of Vertigo with and without Hearing Loss

Hearing Loss
Conductive
Otitis media with effusion
Chronic suppurative otitis media or cholesteatoma should be considered

Sensorineural
Perilymphatic fistula
Tumor
Ménière's disease
Migraine headache
Genetic syndromes
Temporal bone fracture
Vestibular concussion

No Hearing Loss
Acute Vertigo
Perilymphatic fistula
Benign positional vertigo
Seizure
Labyrinthitis

Recurrent or Chronic Vertigo
Acoustic neuroma
Multiple sclerosis

Benign paroxysmal vertigo of childhood is defined by the repeated occurrence of vertiginous episodes lasting seconds to minutes, with occasional vomiting. This entity usually remits spontaneously within months to years. The most frequent cause of benign paroxysmal vertigo of childhood is a migraine headache,[80] with vertigo occurring as the aura of an episode.

Patients with basilar artery migraines also present with vertigo; hemiparesis; ataxia; palsies of the third, sixth, or seventh cranial nerve; drop attacks; and blindness in various combinations followed by migraine headache. Children with benign paroxysmal vertigo of childhood or basilar migraines usually have a family history of migraine headaches.

Benign positional vertigo is rare in children, and the earliest age at which it has been reported is 11 years. It is believed to be due to an otolith that has moved out of its normal position in the utricle and can occur spontaneously as well as after trauma.

Ménière's disease, a syndrome with a combination of vertigo, fluctuating hearing loss, and tinnitus, is responsible for 1.5 to 4% of cases of pediatric vertigo.[83,84]

Vestibular neuronitis is manifested with vertigo without hearing loss. A viral infection is thought to be the cause. Sixty percent of patients have a preceding cold. It is manifested with severe vertigo that resolves in a few days, after which the child will have vertigo only with rapid head movements, which persists for weeks or months until central compensation occurs.[85]

Labyrinthitis is an inflammatory process involving the inner ear membranous labyrinth. It is manifested with vertigo, hearing loss, and tinnitus. Viruses such as cytomegalovirus, rubella virus, and rubeola virus are etiologic agents. Bacterial labyrinthitis also can occur, usually in association with meningitis. Lyme disease and syphilis may cause vertigo if the inner ear is affected.[86] Neurofibromatosis can be manifested with vertigo if it involves the superior vestibular nerve; café au lait spots should be looked for. Other genetic syndromes also are associated with vertigo (see Box 175-17).[86]

Ototoxic drugs, such as aminoglycosides and chemotherapeutic drugs, can be a cause of vertigo, usually in association with hearing loss (Box 175-18). Cerebellar and brainstem lesions on occasion also are manifested with vertigo. Cranial nerve deficits associated with vertigo may indicate a lesion or tumor.[85,86]

Multiple sclerosis can have vertigo as one of the symptoms, and vertigo is the presenting symptom in 5 to 12% of cases. Endocrine disorders, such as thyroid disease and diabetes mellitus, have rarely been reported to cause vertigo.

In post-traumatic vertigo, disturbances of cochlear and vestibular functions are the most common etiology of late-onset vertigo from head injury in children. If labyrinthine damage is caused by trauma (labyrinthine concussion), vertigo, gait unsteadiness, and swaying toward the affected side are present along with nausea and vomiting. Symptoms and signs subside during a period of 4 to 6 weeks. Signs of vestibular dysfunction may be present many years after the injury. Positional nystagmus with the quick component toward the uninvolved side usually is present. Vestibular concussions can cause vertigo without hearing loss after a blow to the parietal-occipital or temporal-parietal region. It normally is continuous for several days, followed by improvement, but it may recur intermittently with certain head positions. Displacement of an otolith is thought to be responsible.[87]

Temporal bone fracture (especially transverse) may cause vertigo by injury to the eighth cranial nerve or the otic capsule; it also may cause sensorineural hearing loss.[87] Whiplash injuries to the neck also can cause vertigo; up to 50% of patients experience hearing loss or tinnitus. Post-traumatic migraine and seizures also can cause vertigo and occur in 5 to 7% of patients with closed head injuries.[88]

Perilymphatic fistula is manifested with sensorineural hearing loss of sudden onset. It frequently is associated with congenital

www.ketabpezeshki.com 66485457-66963820

cranial deformities and congenital abnormalities of the ear. However, barotrauma (flying, extreme coughing, retching, or straining) or direct trauma also can be a cause. There is leakage of fluid from the oval or round window into the middle ear. Having the patient perform a Valsalva maneuver may precipitate vertigo. Hennebert's sign, which consists of nystagmus and vertigo after negative pressure is induced in the ear by a pneumatic otoscope, may be a feature.[85] Treatment usually consists of surgical repair.

Ocular disorders, such as convergence insufficiency, strabismus, and amblyopia, have been reported to cause a sensation of vertigo. Treatment of these disorders will eliminate the vertigo in children.[87]

Diagnostic Strategies

For most patients, the final diagnosis for the cause of the vertigo may not be able to be made in the ED. A complete physical examination, including otologic and neurologic evaluation, is important. Looking for nystagmus and cerebellar testing are especially critical. Having the child hop as well as stand from a seated position on the floor with eyes open and closed may reveal vestibular dysfunction. Looking for physical signs of other disease processes, such as café au lait spots in neurofibromatosis, may aid in diagnosis. If a Valsalva maneuver or the Hennebert maneuver initiates vertigo, the cause probably is a perilymphatic fistula.

Vertical nystagmus is usually from a central cause. Nystagmus from peripheral causes tends to be extinguished or to diminish after rapidly repeated stimulation, whereas central nystagmus does not. Helpful laboratory tests in the vertiginous patient include glucose and electrolyte assessment, thyroid function tests, and viral titers or serologic studies (e.g., for Lyme disease or syphilis), as the physical examination dictates.[86] The Hallpike-Dix positioning maneuver may help diagnose benign positional vertigo.[85] A CT or MRI scan is indicated only in cases of central vertigo.

Management

Management of the vertiginous patient depends on the underlying cause, which may not be evident in the ED.[89] For acute symptomatic relief, vestibular suppressants such as meclizine and diazepam may be helpful. Otoliths causing inappropriate stimulation may be restored to their proper place by Epley's maneuver.[82] Vestibular rehabilitation exercises that encourage patients to move the head while viewing a stimulus may assist in vestibular adaptation and reduce symptoms. Follow-up, including examination, testing, and treatment by a neurologist or an otolaryngologist for vertiginous patients, is recommended.[90] Highly symptomatic children may need to be admitted to the hospital.

SYNCOPE

Perspective

Syncope is defined as a sudden, reversible, typically brief loss of consciousness and muscle tone (between 20 and 60 seconds) with spontaneous and complete recovery after a brief duration. Presyncope is defined as having a sensation of passing out but remaining conscious with a transient loss of postural tone. The exact incidence of syncopal episodes is not known, but 15 to 25% of children and adolescents experience one episode by young adulthood.[91] The peak incidence occurs between 15 and 19 years of age, and females are affected more frequently than males. The presentation of these events can be frightening to the patient and those who witness them. Gordon and co-workers found that in a group of pediatric patients presenting to the ED, a mean of six diagnostic tests were performed per patient, 40% of these patients were admitted to the hospital, and total charges averaged $3000 per patient, yet significant pathologic conditions were found in less than 10% of the patients.[92]

Principles of Disease

The causes of syncope can be divided into autonomic, cardiac, and noncardiac. The most common cause of syncope is reflex syncope (also called autonomic, vasovagal, neurocardiogenic, or vasodepressor syncope or fainting). Venous pooling and decreased preload associated with prolonged standing normally are compensated by reflex tachycardia and increased sympathetic tone. However, patients with vasopressor syncope who are prone to syncope demonstrate a cardioinhibitory response causing bradycardia or a vasodepressor response causing hypotension or, most commonly, a combination of both. Patients with cardiac syncope have decreased cerebral blood flow resulting from poor cardiac filling or contractility, elevated afterload, or cardiac arrhythmias.

Clinical Features

Patients can experience syncope during intercurrent illnesses, with mild dehydration, during menstruation, or after vigorous exertion. In those with situational syncope, typical triggers may include emotion, pain, hyperventilation, shower, cough, swallowing, urination, or defecation. Before the event, they may experience dizziness, lightheadedness, weakness, nausea, chest discomfort, palpitations, blurred vision, headache, tremulousness, and anxiety. After the event, loss of consciousness is brief (usually for less than 20 seconds), and the patient is described as ashen appearing, with sweating and coolness of the extremities.[93] Other examples of conditions associated with neurally mediated syncope are postural orthostatic tachycardia syndrome, chronic fatigue syndrome, and pandysautonomia.[94] Patients with postural orthostatic tachycardia syndrome and pandysautonomia experience orthostatic palpitations rather than straightforward syncope, do not appear healthy between events, and complain of fatigue and exercise intolerance. Patients with pandysautonomia also exhibit thermoregulatory impairment, sweating, and bowel dysfunction. Although cardiac causes of syncope are rare, they can be life-threatening and should be suspected when the episode occurred during exercise or physical activity. Noncardiac causes include seizures. Helpful features to differentiate seizures from syncope include the following: seizures usually occur in a supine rather than in an upright position; convulsions occur before rather than after the loss of consciousness; and warm, flushed, or cyanotic-appearing skin, rather than pale and sweaty skin, is characteristic.

Diagnosis

Evaluation of the patient begins by obtaining a description of the event, previous episodes, and past personal and family history. A detailed description of the event and particular note of any presyncopal symptoms or signs, such as sweating, nausea, pallor, visual changes, or onset with a rapid change in position, can suggest vasovagal syncope. A thorough physical examination including a detailed neurologic examination is essential. A baseline electrocardiogram should be obtained to rule out structural heart disease or an arrhythmia. If the history, physical examination, and electrocardiogram are typical for a neurally mediated event, further testing is not usually required. Additional testing is warranted with family history of sudden death, early infarction, or arrhythmia; previous personal history of fatigue with a known arrhythmia or heart defect; syncope preceded by chest pain or palpitations; occurrence of syncope during exercise; occurrence of syncope without a prodrome; recurrent syncope (more than two or three episodes); and a syncopal event with neurologic sequelae.[95]

www.ketabpezeshki.com 66485457-66963820

Differential Considerations

Cardiac causes of syncope may be life-threatening. Such disorders include underlying structural abnormalities of the heart, such as cardiomyopathies (hypertrophic, dilated, and restrictive), postoperative congenital heart anatomic changes (Mustard, Fontan), congenital coronary artery abnormalities, myocarditis, aortic and subaortic stenosis, and pulmonary hypertension. Other cardiac abnormalities include those classified as electrical disorders, such as prolonged QT syndrome, Wolff-Parkinson-White syndrome, atrioventricular block, idiopathic ventricular fibrillation, and Brugada syndrome. Patients with an underlying cardiac abnormality merit further investigation, which may include 24- to 48-hour Holter monitoring, echocardiography, or exercise stress testing. Tilt-table testing can be used after diseases such as myocarditis, hypertrophic cardiomyopathy, and long QT syndrome have been ruled out because such testing in this subgroup can have fatal consequences.

Common noncardiac causes of syncope include neurologic disorders (seizures, migraines, tumor, and vertigo), breath-holding spells, electrolyte abnormalities (hypoglycemia), hyperventilation (hypocapnia), endocrinopathies, toxins (carbon monoxide), and drugs of abuse.

Management and Disposition

Syncope is a common pediatric problem and usually has a benign, neurally mediated cause. Patients with a potential serious cause, such as a cardiac or neurologic condition, should be treated and admitted.[95] Certain groups of patients may have an increased risk for cardiac syncope and should eventually be referred to a pediatric cardiologist for evaluation. These include athletes, patients with eating disorders or chronic fatigue, persons who use illicit substances, and survivors of congenital heart disease. Athletes with suspected hypertrophic cardiomyopathy, aortic stenosis, or other potentially critical cardiac conditions should be restricted from exercise until they are evaluated by a cardiologist.[91]

The approach to management of patients with neurocardiogenic syncope is primarily one of education, involving avoidance of potential triggering events (hot, crowded environments; volume depletion) and recognition of the early signs and symptoms to allow timely maneuvers to abort the syncopal episode (e.g., assumption of a supine position, ingestion of fluids, leg crossing). The patient and the family should be reassured that these events are not life-threatening. A simple approach is to encourage liberal fluid intake and to increase dietary salt intake. In a subgroup of patients with recurrent syncope or recurrent dizziness, however, a trial of an appropriate medication may be warranted. No large pediatric randomized studies have been conducted to investigate this application of such medications, which include beta-blockers, fludrocortisone, selective serotonin reuptake inhibitors, and alpha-agonists.[96]

KEY CONCEPTS

- Signs and symptoms of bacterial meningitis vary by age and can include nonspecific manifestations, such as irritability and lethargy, in infants and young children.
- A careful and detailed history is instrumental in determining whether an event was a seizure. If the event was a seizure, the history should delineate what type of seizure occurred (partial or generalized) and whether the clinical event fits into a known epilepsy syndrome.
- Status epilepticus constitutes a neurologic emergency that carries high morbidity and mortality rates. Usual initial treatment is with lorazepam followed by fosphenytoin or phenytoin.
- For patients experiencing a febrile seizure, ED management should include a review with family members of appropriate first aid, use of antipyretics, recurrence risk and risk for epilepsy, and follow-up care with the child's primary care physician.
- The possibility of acute symptomatic, or provoked, seizures should be considered, particularly because many of the causes of such seizures are treatable.
- A majority of headaches in children have benign causes that usually can be diagnosed by a careful history and physical examination.
- Radiologic evaluation by CT or MRI, or both, may be necessary to rule out secondary causes of headache, such as intracranial hemorrhage, subarachnoid hemorrhage, brain abscess, and brain tumor.
- A toxicology screen is the test with the highest diagnostic yield for acute-onset ataxia in children. The most common cause of benign positional vertigo in children is a migraine headache. The etiology of vertigo with hearing loss is significantly different from that of vertigo with no hearing loss.
- Most children with ataxia require hospitalization for evaluation and diagnosis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Saez-Lorens X, McCracken GH: Bacterial meningitis in children. *Lancet* 2003; 361:2139.
2. Thigpen MC, et al: Bacterial meningitis in the United States 1998-2007. *N Engl J Med* 2011; 364:2016.
3. Kaplan SL: Clinical manifestations, diagnosis, and prognostic factors of bacterial meningitis. *Infect Dis Clin North Am* 1999; 13:579.
4. Grimwood K, et al: Adverse outcomes of bacterial meningitis in school-age survivors. *Pediatrics* 1995; 95:646.
5. Peters ML: Suspected meningitis in the emergency department: Diagnosis and management. *Clin Pediatr Emerg Med* 2003; 4:186.
6. Peters TR, Poehling KA: Invasive pneumococcal disease: The target is moving. *JAMA* 2007; 297:1825.
7. Bryant KA, et al: Safety and immunogenicity of a 13 valent pneumococcal conjugate vaccine. *Pediatrics* 2010; 125:866.
8. Kim KS: Acute bacterial meningitis in infants and children. *Lancet Infect Dis* 2010; 10:32.
9. Bundy DG: Several clinical signs and symptoms are associated with the likelihood of bacterial meningitis in children; the most reliable diagnostic combination is uncertain. *Evid Based Med* 2011; 16:89.
10. Bonadio WA: Assessing patient clinical appearance in the evaluation of the febrile child. *Am J Emerg Med* 1995; 13:321.
11. Baker MD, Bell LM: Unpredictability of serious bacterial infection in febrile infants from birth to one month of age. *Arch Pediatr Adolesc Med* 1999; 153:508.
12. Arango CA, Rathore MH: Neonatal meningococcal meningitis: Case reports and review of literature. *Pediatr Infect Dis J* 1996; 15:1134.
13. McIntosh D, et al: Torticollis and bacterial meningitis. *Pediatr Infect Dis J* 1993; 12:160.
14. Amarilyo G, et al: Diagnostic accuracy of clinical symptoms and signs in children with meningitis. *Pediatr Emerg Care* 2011; 27:196-199.
15. Walsh-Kelly C, et al: Clinical predictors of bacterial versus aseptic meningitis in childhood. *Ann Emerg Med* 1992; 21:910.
16. Kellogg JA, et al: Frequency of low level bacteremia in infants from birth to 2 months of age. *Pediatr Infect Dis J* 1997; 16:381.
17. Schelonka RL, et al: Volume of blood required to detect common neonatal pathogens. *J Pediatr* 1996; 129:275.
18. Baker MD, Avner JR, Bell LM: Failure of infant observation scales in detecting serious illness in febrile, 4- to 8-week-old infants. *Pediatrics* 1990; 85:1040.
19. Jaskiewicz JA, et al: Febrile infants at low risk for serious bacterial infection: An appraisal of the Rochester criteria and implications for management. *Pediatrics* 1994; 94:390.
20. Korones DN, Shapiro ED: Occult pneumococcal bacteremia: What happens to the child who appears well at reevaluation? *Pediatr Infect Dis J* 1994; 13:382.
21. Subcommittee on Febrile Seizures, American Academy of Pediatrics: Neurodiagnostic evaluation of the child with a simple febrile seizure. *Pediatrics* 2011; 127:389.
22. Mandl KD, Stack KM, Fleisher GR: Incidence of bacteremia in infants and children with fever and petechiae. *J Pediatr* 1997; 131:398.
23. Cnota JF, Barton LL, Rhee KH: Purpura fulminans associated with *Streptococcus pneumoniae* infection in a child. *Pediatr Emerg Care* 1999; 15:187.
24. Shetty AK, et al: Fatal cerebral herniation after lumbar puncture in a patient with normal CT scan. *Pediatrics* 1999; 103:1284.
25. Abo A, et al: Positioning for lumbar puncture in children evaluated by bedside ultrasound. *Pediatr Emerg Care* 2010; 125:5:e1149-e1153.
26. Bonadio WA: The cerebrospinal fluid: Physiologic aspects and alterations associated with bacterial meningitis. *Pediatr Infect Dis J* 1992; 11:423.
27. Nigrovic LE, et al: Clinical prediction rule for identifying children with cerebrospinal fluid pleocytosis at very low risk of bacterial meningitis. *JAMA* 2007; 52:297.
28. Rorabaugh ML, et al: Aseptic meningitis in infants younger than 2 years of age: Acute illness and neurologic complications. *Pediatrics* 1993; 92:206.
29. Chandy JC: Treatment failure with the use of a third-generation cephalosporin for penicillin-resistant pneumococcal meningitis: Case report and review. *Clin Infect Dis* 1994; 18:188.
30. American Academy of Pediatrics: *Pneumoccocal infections*. In: *Red Book: 2009 Report of the Committee on Infectious Diseases*, 39th ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2009:524.
31. Friedman MJ, Sharieff GQ: Seizures in children. *Pediatr Clin North Am* 2006; 53:257.
32. Volpe JV: *Neonatal seizures*. In: Volpe JV, ed: *Neurology of the Newborn*, 3rd ed. Philadelphia: WB Saunders; 1995.
33. Homes GL: Do seizures cause brain damage? *Epilepsia* 1991; 32:514.
34. Levene M: The clinical conundrum of neonatal seizures. *Arch Dis Child Fetal Neonatal Ed* 2002; 86:F75.
35. Mackay M, Weiss S, Snead OC 3rd: Treatment of infantile spasms: An evidence-based approach. *Int Rev Neurobiol* 2002; 49:157.
36. Glauser TA, et al: Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *N Engl J Med* 2010; 362:790-799.
37. Peters JM, Camfield CS, Camfield PR: Population study of benign rolandic epilepsy: Is treatment needed? *Neurology* 2001; 59:476.
38. Hancock E, Cross H: Treatment of Lennox-Gastaut syndrome. *Cochrane Database Syst Rev* 2003; 3:CD003277.
39. Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures, American Academy of Pediatrics: Febrile seizures: Clinical practice guideline for the long-term management of the child with simple febrile seizures. *Pediatrics* 2011; 127:389-394.
40. Sadleir LG, Scheffer IE: Febrile seizures. *BMJ* 2007; 334:307.
41. Shinnar S, Glauser TA: Febrile seizures. *J Child Neurol* 2002; 17S:S44.
42. Dreifuss FE, et al: A comparison of rectal diazepam gel and placebo for acute repetitive seizures. *N Engl J Med* 1998; 338:1869.
43. Warden CR, et al: Evaluation and management of febrile seizures in the out-of-hospital and emergency department settings. *Ann Emerg Med* 2003; 41:215.
44. Booth D, Evans DJ: Anticonvulsants for neonates with seizures. *Cochrane Database Syst Rev* 2004; 4:CD004218.
45. Appleton RC, Martland TP, Scott R, Whitehouse W: The treatment of convulsive status epilepticus in children. The Status Epilepticus Working Party. *Arch Dis Child* 2000; 83:415.
46. Riviello JJ Jr, et al; American Academy of Neurology Subcommittee, Practice Committee of the Child Neurology Society: Practice parameter: Diagnostic assessment of the child with status epilepticus (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2006; 67:1542.
47. Dimario FJ: Breath-holding spells in childhood. *Am J Dis Child* 1992; 146:125.
48. The Brain Trauma Foundation, the American Association of Neurological Surgeons, the Joint Section on Neurotrauma and Critical Care: Role of antiseizure prophylaxis following head injury. *J Neurotrauma* 2001; 17:549.
49. Ritaccio AL: Reflex seizures. *Neurol Clin* 1994; 12:57.
50. Scott RC, Kirkham FJ: Clinical update: Childhood convulsive status epilepticus. *Lancet* 2007; 370:724.
51. Hirtz D, et al: Practice parameter: Treatment of the child with a first unprovoked seizure: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2003; 60:166-175.
52. Hirtz D, et al: Practice parameter: Evaluating a first nonfebrile seizure in children: Report of the Quality Standards Subcommittee of the American Academy of Neurology, the Child Neurology Society, and the American Epilepsy Society. *Neurology* 2000; 55:616-623.
53. Scott RC, Kirkham FJ: Clinical update: Childhood convulsive status epilepticus. *Lancet* 2007; 370:724.
54. Abend ND, Gutierrez-Colina AM, Dlugos DJ: Medical treatment of pediatric status epilepticus. *Semin Pediatr Neurol* 2010; 17:169.
55. Wolfe TR, Macfarlane TC: Intranasal midazolam therapy for pediatric status epilepticus. *Am J Emerg Med* 2006; 24:343.
56. Lowenstein DH, Alldredge BK: Status epilepticus. *N Engl J Med* 1998; 338:970.
57. Stecker MM, et al: Treatment of refractory status epilepticus with propofol: Clinical and pharmacokinetic findings. *Epilepsia* 1998; 39:18.
58. Aldenkamp A, Vigevano F, Arzimanoglou A, Covanis A: Role of valproate across the ages: Treatment of epilepsy in children. *Acta Neurol Scand Suppl* 2006; 184:1.
59. Warden CR, et al: Evaluation and management of febrile seizures in the out-of-hospital and emergency department settings. *Ann Emerg Med* 2003; 41:215.
60. Hauser WA, et al: Risk of recurrent seizures after two unprovoked seizures. *N Engl J Med* 1998; 338:429.
61. Musicco M, Beghi E, Solari A: Treatment of first tonic-clonic seizure does not improve the prognosis of epilepsy. First Seizure Trial Group (FIRST Group). *Neurology* 1997; 49:991.
62. Reference deleted in proofs.
63. May A, Goadsby PJ: The trigeminovascular system in humans: Pathophysiologic implications for primary headache syndromes of the neural influences on the cerebral circulation. *J Cerebr Blood Flow Metab* 1999; 19:115.
64. Lewis KS: Pediatric headache. *Semin Pediatr Neurol* 2010; 17:224.

www.ketabpezeshki.com 66485457-66963820

65. Lewis DW, Rothner DA: *Headache in children and adolescents*. In: Johnson RT, Griffin JW, McArthur JC, eds: *Current Therapy in Neurological Diseases*, 6th ed. Philadelphia: Mosby; 2002.
66. Rothner DA: *Headaches*. In: Swaiman KF, Ashwal S, eds: *Pediatric Neurology: Principles and Practice*, 3rd ed. St. Louis: Mosby; 1999:747-758.
67. Flores LE, et al: Delay in the diagnosis of pediatric brain tumors. *Am J Dis Child* 1986; 140:684.
68. Qureshi F, Lewis D: Managing headache in the pediatric emergency department. *Clin Pediatr Emerg Med* 2003; 4:159.
69. Headache Classification Committee of the International Headache Society: The International Classification of Headache Disorders. *Cephalgia* 2004; 24(Suppl 1):1.
70. Hershey AD, et al: Headaches. *Curr Opin Pediatr* 2007; 19:663.
71. Lewis DW, et al: Practice parameter: Evaluation of children and adolescents with recurrent headache. *Neurology* 2002; 59:490.
72. Lewis D, et al: Practice parameter: Pharmacologic treatment of migraine headache in children. Report of the American Academy of Neurology Quality Standards Committee and Practice Committee of the Child Neurology Society. *Neurology* 2004; 63:2215.
73. Walker DM, Teach SJ: Emergency department treatment of primary headaches in children and adolescents. *Curr Opin Pediatr* 2008; 20:248.
74. Lewis DW, et al: Efficacy of zolmitriptan nasal spray in adolescent migraine. *Pediatrics* 2007; 120:390.
75. Richer LP, et al: Treatment of children with migraine in emergency departments: National practice variation study. *Pediatrics* 2010; 126:e150.
76. Winner P, et al: A randomized, double blind, placebo controlled study of sumatriptan nasal spray in the acute treatment of acute migraine in adolescents. *Pediatrics* 2000; 106:989.
77. Brousseau DC, et al: Treatment of pediatric migraine headaches: A randomized double blind trial of prochlorperazine versus ketorolac. *Ann Emerg Med* 2004; 43:256.
78. Ryan M, Engle E: Acute ataxia in childhood. *J Child Neurol* 2003; 18:309.
79. Adams C, et al: Autoantibodies in childhood post-varicella acute cerebellar ataxia. *Can J Neurol Sci* 2000; 27:316.
80. Paulson H, Ammache Z: Ataxia and hereditary disorders. *Neurol Clin* 2001; 19:759.
81. Avery M, First L, eds: *Pediatric Medicine*, 2nd ed. Baltimore: Williams & Wilkins; 1993:785-787.
82. Rudolph C, Rudolph A, eds: *Rudolph's Pediatrics*, 21st ed. New York: McGraw-Hill; 2003:1246-1247.
83. Weisleder P, Fife TD: Dizziness and headache: A common association in children and adolescents. *J Child Neurol* 2001; 16:727.
84. Balkany TJ, Finkel RS: The dizzy child. *Ear Hearing* 1986; 7:138.
85. Tusa R, et al: Dizziness in childhood. *J Child Neurol* 1994; 9:261.
86. Papp J, Dorsey S: A preschool age child with first-time seizure and ataxia. *J Emerg Med* 2009; 36:30. Epub 2007 Jul 20.
87. Meyerhoff W, et al: Ménière's disease in children. *Laryngoscope* 1978; 88:1504.
88. Akagi H, et al: Ménière's disease in children. *J Pediatr Otorhinolaryngol* 2001; 6:259.
89. Eviatar L: Dizziness in children. *Otolaryngol Clin North Am* 1994; 27:557.
90. Anoh-Tanon MJ, et al: Vertigo is an underestimated symptom of ocular disorders: Dizzy children do not always need an MRI. *Pediatr Neurol* 2000; 23:49.
91. Fischer J, Cho C: Pediatric syncope: Cases from the emergency department. *Emerg Med Clin North Am* 2010; 28:501.
92. Gordon TA, et al: A retrospective analysis of the cost effective workup of syncope in children. *Cleve Clin J Med* 1987; 54:391-394.
93. Driscoll DJ, Jacobsen SJ, Porter CJ, Wollan PC: Syncope in children and adolescents. *J Am Coll Cardiol* 1997; 29:1039.
94. DiVasta A, Alexander M: Fainting freshmen and sinking sophomores: Cardiovascular issues of the adolescent. *Curr Opin Pediatr* 2004; 16:350.
95. Ouyang H, Quinn J: Diagnosis and evaluation of syncope in the emergency department. *Emerg Med Clin North Am* 2010; 28:471.
96. Johnsrude CL: Current approach to pediatric syncope. *Pediatr Cardiol* 2000; 21:522.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 176

MUSCULOSKELETAL DISORDERS

Kemedy K. McQuillen

PERSPECTIVE

Each year there are more than 11 million pediatric injury-related emergency department (ED) visits, 14.3% of which are due to fractures and dislocations.[1]

As a result of the physiologic and anatomic differences between children and adults, pediatric patients are susceptible to problems that do not affect the adult population. An understanding of these differences helps the emergency physician appropriately diagnose and treat musculoskeletal complaints in children. This chapter reviews the general principles and physiology of the pediatric musculoskeletal system, highlights the more common pediatric fractures, and describes musculoskeletal problems specific to the pediatric population.

PRINCIPLES OF DISEASE

Anatomy and Physiology

Several factors distinguish the pediatric musculoskeletal system from that of the adult. The most striking difference is the presence of a physis or growth plate. The physis is made up of proliferating cartilage cells between the metaphysis and epiphysis. Because it is composed of cartilage, the growth plate is the weakest part of the bone and is more likely to separate before the adjacent tendon or ligament tears. Accordingly, sprains are less frequent in the pediatric population than in the adult population, and physeal injuries are common.

Another factor that influences pediatric musculoskeletal injuries is the presence of a thick, physiologically active periosteum that is easily stripped from the bony cortex. When injuries occur, the periosteum often is torn on the convex side (i.e., the reverse aspect of a bone subjected to a deforming force) while remaining intact on the concave side (the aspect directly incurring the force of injury). In any case, the periosteum acts as a tether to reduce the amount of fracture displacement and, when it remains intact, aids in fracture reduction. The great bone-forming potential of the periosteum also facilitates the healing process; callus formation is vigorous, and nonunion almost never occurs.

Growing bone is more porous, more pliable, and less dense than adult bone. These characteristics result in less strength, thus making children more susceptible to fractures. However, although it takes less force to cause deformation, pediatric bone is more likely to buckle when it is compressed or to bow when it is bent. Finally, because the bones are still growing, the potential for remodeling is greater with metaphyseal fractures. Growth can compensate for postreduction imperfections in both apposition and alignment, with deformities occurring in the plane of motion having the greatest potential for remodeling.

Fracture Patterns

As with fractures in adults, description of pediatric fractures includes the bone location (diaphysis, metaphysis, physis, or epiphysis), configuration, relationship of fracture fragments to one another (angulation and displacement), and relationship of fracture fragments to adjacent tissue (open or closed). The inherent differences between pediatric and adult bone result in fracture configurations that are not found in the adult population. Pediatric fractures can be classified as follows:

- Plastic deformation: Bone is bowed with no obvious cortical disruption.
- Torus fracture (buckle fracture): Buckling of bone without cortical disruption tends to occur because of compression failure of the bone at the metaphyseal-diaphyseal junction (Fig. 176-1). These fractures may be immobilized with a splint or cast or, if they involve the distal end of the radius, a Velcro wrist splint[2] or backslab.[3] The splint or backslab can be removed by the family or primary care provider in 3 to 4 weeks, thereby obviating the need for orthopedic follow-up. Children treated with removable splints also had less pain, improved function, and fewer unscheduled ED visits because of problems with the cast.[4] Buckle fractures also may be treated with a soft cast[5,6] or a plaster splint.[7]
- Greenstick fracture: Bone and one cortex are disrupted; the periosteum on the fracture's compression side remains intact (Fig. 176-2). Some authors recommend immobilization of minimally angulated (<15 degrees) distal radius greenstick fractures with splints[8]; others contend that casting is necessary because of continued fracture displacement during the first 2 weeks of healing.[9]
- Complete fracture: The fracture propagates completely through the bone; included are transverse (Fig. 176-3), spiral (Fig. 176-4), oblique, and comminuted (Fig. 176-5) fractures.

The relatively weak cartilaginous physis in growing bone makes physeal injury common in the skeletally immature. Although injuries to the physis can occur at any age, they are more common during rapid skeletal growth. The Salter-Harris classification system is the most frequently used tool to describe physeal injuries. This classification system is based on the extent of involvement of the physis, epiphysis, and joint (Table 176-1). Types I and II Salter-Harris injuries (Figs. 176-6 and 176-7) do not involve the germinal layer of the growth plate; therefore, the risk for growth arrest is small. In general, the higher the Salter-Harris classification (Salter-Harris types III to V), the greater the damage to the growth plate and the greater the likelihood of growth arrest or limb-length abnormalities (Figs. 176-8 to 176-10). Type II fractures are the most common Salter-Harris injury and account for approximately three fourths of all growth plate injuries.

www.ketabpezeshki.com 66485457-66963820

Figure 176-1. Buckle fracture of the distal end of the radius. Treatment consists of immobilization for 3 to 6 weeks.

Figure 176-2. Greenstick fracture of the radius. This fracture may need to be completed for an anatomic reduction to be achieved.

Figure 176-3. Transverse fractures of the radius and ulna.

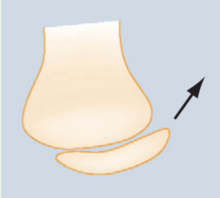
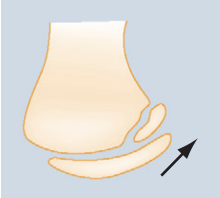
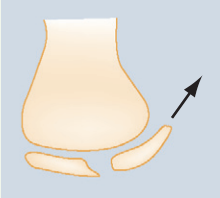
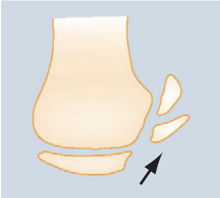
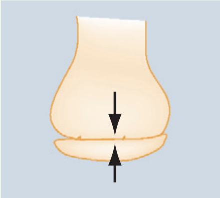
Figure 176-4. Spiral fracture of the femur.

www.ketabpezeshki.com 66485457-66963820

Figure 176-5. Comminuted fractures of the tibia and fibula.

Figure 176-6. Salter-Harris type I fracture of the fibula. The only finding on examination was point tenderness over the distal end of the fibula. Radiographic findings include soft tissue swelling over the growth plate and minimal physeal widening.

Table 176-1 Salter-Harris Fracture Classification

Type I	Fracture extends through the physis (see Fig. 176-6)	
Type II	Fracture extends from the physis into the metaphysis (away from the joint space) (see Fig. 176-7)	
Type III	Fracture extends from the physis into the epiphysis (toward the joint space) (see Fig. 176-8)	
Type IV	Fracture extends from the physis into the metaphysis and epiphysis (see Fig. 176-9)	
Type V	Crush injury of the physis (see Fig. 176-10)	

SPECIFIC DISORDERS

Clavicle Fracture

The clavicle is one of the most frequently broken bones in children. The physis of the clavicle does not close until the age of 23 to 25 years and is at risk for injury until that time. Midshaft fractures account for approximately 85% of all clavicle fractures; distal and proximal fractures account for approximately 10% and 5%, respectively. The usual mechanism of injury is a fall on the shoulder or, less commonly, direct trauma to the bone itself. The child typically supports the affected side with the other hand and tilts the head toward the side of the fracture. Physical examination reveals point tenderness at the fracture site, with or without an obvious bone deformity. With a minimally displaced fracture, shoulder motion may be tolerated. Otherwise, range of motion of the shoulder is limited by pain. Although complications are rare, the proximity of the clavicle to the great vessels and brachial plexus calls for a thorough neurovascular evaluation; severe posterior sternoclavicular displacement can cause injury to the trachea, esophagus, and subclavian vessels; lateral clavicular displacement can result in injury to the brachial plexus. Middle third fractures have been associated with neurovascular bundle injuries, pulmonary injury, and pneumothorax.

An anteroposterior (AP) radiograph of the clavicle (Fig. 176-11) confirms the diagnosis. If clinical suspicion is high and the AP view does not reveal a fracture, a 30-degree cephalic view can be helpful. Specialized imaging studies are rarely needed, although

www.ketabpezeshki.com 66485457-66963820

Figure 176-7. Salter-Harris type II fracture of the radius. The triangular piece of the metaphysis is referred to as the Thurston-Holland segment.

Figure 176-8. Salter-Harris type III fracture of the middle phalanx.

Figure 176-9. Salter-Harris type IV fracture of the proximal phalanx.

Figure 176-10. Salter-Harris type V fracture of the distal end of the radius. The crush injury has obliterated the physis.

www.ketabpezeshki.com 66485457-66963820

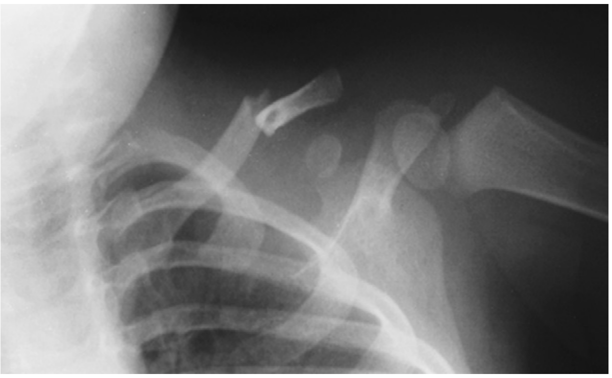


Figure 176-11. Fracture of the middle third of the clavicle.

computed tomography (CT) and duplex ultrasonography may be considered with proximal, posteriorly displaced fractures or dislocations to evaluate for the aforementioned complications.[10]

Clavicle fractures usually do not require anatomic reduction for healing or function; therefore, treatment is typically directed at maintenance of comfort with splinting, ice, and analgesics. Figure-of-eight splinting helps bring the clavicle out to length, relieves muscle spasm, and minimizes motion at the fracture site. Immobilization with the figure-of-eight splint, previously the treatment of choice, has fallen out of favor because of the risk for brachial plexus palsy with long-term use. Alternatively, a sling with or without a swath can be used to provide comfort by supporting the upper extremity and relieving the suspensory forces usually maintained by the clavicle. Most clavicle fractures heal without any problems, except for the development of bony callus at the fracture site; the younger the patient, the greater the potential for remodeling of this deformity. As the fracture stabilizes and the comfort level improves, range-of-motion exercises can be started, with gradual progression in intensity. Younger children generally require shorter periods of immobilization (2-4 weeks) than those used in adolescents and adults (4-8 weeks). Rehabilitation includes early range of motion and strengthening of the rotator cuff. Patients may return to contact sports when there is no tenderness at the fracture site or pain with range of motion and they have achieved normal strength.

Although surgical intervention is uncommon with clavicle fractures, immediate orthopedic consultation should be obtained for fractures that are open or associated with neurovascular compromise or for fractures that are associated with more than 100% displacement of the fracture fragment with severe skin tenting. In addition, distal clavicular fractures in general and middle clavicular fractures that are severely comminuted or displaced more than 20 mm may also require surgical management, and these patients should be seen by an orthopedic surgeon within 72 hours. High-level athletes should also be referred to an orthopedist for surgical evaluation as surgical repair may expedite their return to sports.

Clavicle fractures also can occur during childbirth and represent more than 90% of obstetric fractures. They occur equally in boys and in girls and on the right and on the left sides. Displaced clavicle fractures are identified by crepitus, edema, lack of movement of the affected extremity, asymmetrical bone contour, and crying with passive motion in the immediate period after delivery. Nondisplaced asymptomatic fractures may not be noticed until 10 days of age, when the bony callus becomes apparent. The diagnosis is made by radiographs of the chest, clavicle, and upper extremity; these radiographs help differentiate clavicle fractures from traumatic separation of the proximal humeral epiphysis, humeral shaft fractures, and dislocations of the shoulder, all of which may be manifested with similar findings. In addition, the presence of a clavicle fracture warrants further investigation for accompanying brachial plexus injury.

Table 176-2 Gartland Classification of Extension-Type Supracondylar Fractures

Type I	Nondisplaced fracture
Type II	Displaced fracture with intact posterior cortex
Type III	Displaced fracture with no cortical contact A: Posteromedial rotation of the distal fragment B: Posterolateral rotation of the distal fragment

Modified from Gartland JJ: Management of supracondylar fractures of the humerus in children. Surg Gynecol Obstet 109:145, 1959.

Supracondylar Fractures of the Humerus

Supracondylar fracture is the most common elbow fracture in the pediatric population. Most such fractures are sustained in children younger than 8 years. Until that age, the tensile strength of the ligaments and joint capsule is greater than that of the bone itself; the weaker bone therefore yields to the stronger ligament complex around the joint.

Supracondylar fractures are classified as flexion or extension according to mechanism of injury. The extension type of fracture constitutes 95% of all supracondylar fractures and typically results from a hyperextension injury to the elbow incurred in a fall onto the outstretched arm. In this injury, the olecranon is forcefully driven into the olecranon fossa, and the forces are concentrated in the supracondylar area. This mechanism results in failure of the anterior cortex and displacement of the distal fragment posteriorly. With extension-type supracondylar fractures, the degree of displacement and continuity of the cortex are further defined by the Gartland classification[11] (Table 176-2). In the less common flexion type of supracondylar fracture, the elbow is flexed when it hits the ground, and energy is transferred from the posterior aspect of the proximal end of the ulna to the distal end of the humerus. This mechanism results in a supracondylar fracture with anterior displacement of the distal fragment and failure of the cortex posteriorly.

Children with supracondylar humerus fractures may present with anything from mild swelling and elbow pain to a grossly displaced humerus. Gentle palpation is useful to determine the site of injury; however, manipulation should be avoided because movement may cause further neurovascular damage. Children with extension-type supracondylar fractures hold the affected arm in extension with an S-shaped configuration of the elbow and exhibit a prominence at the olecranon. Children with flexion-type supracondylar fractures hold the arm in flexion and exhibit an empty space where the olecranon should be. In all cases it is important to carefully assess distal neurovascular status. Motor and sensory function should be evaluated by assessment of the radial, ulnar, and median nerves (Table 176-3). Two-point discrimination on the fingers provides a sensitive means of assessing sensory status: an abnormal value (>5 mm) indicates a deficit. Vascular assessment should include evaluation of radial and brachial pulses and capillary refill of the hand. Patients with displaced fractures should have ongoing assessment for the development of compartment syndrome of the forearm. With pain on flexion or extension of the fingers, forearm swelling, tenseness or tenderness, or pain that is disproportionate to the injury, compartment pressures should be measured immediately. Unrecognized ischemic injury can result in Volkmann's ischemic contracture, which is characterized by fixed elbow flexion, forearm pronation, wrist flexion, metacarpophalangeal joint extension, and interphalangeal flexion.

www.ketabpezeshki.com 66485457-66963820

Table 176-3 Neurologic Examination of the Distal Upper Extremity

	EXAMINATION COMPONENT	
NERVE	Motor	Sensory
Radial	Wrist extension	Thumb and first finger web space
Ulnar	Wrist flexion and adduction	Little finger
Median	Wrist flexion and abduction Thumb opposition	Thumb, index, and middle fingers Radial aspect of palm of hand
Anterior interosseous	Distal phalanx flexion (thumb and first finger)	None

Table 176-4 Sequence of Ossification around the Elbow: CRITOE

OSSIFICATION CENTER	AGE AT APPEARANCE	AGE AT CLOSURE
Capitellum	6-12 months	14 years
Radial head	4-5 years	16 years
Medial (Internal) epicondyle	5-7 years	15 years
Trochlea	8-10 years	14 years
Olecranon	8-9 years	14 years
Lateral (External) epicondyle	9-13 years	16 years

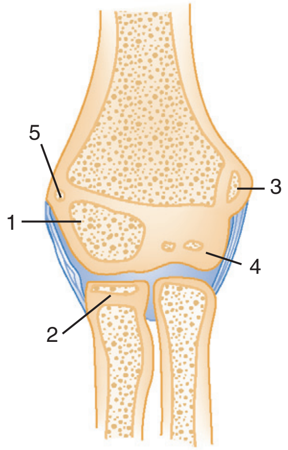


Figure 176-12. Ossification centers of the elbow: *1,* capitellum; *2,* radial head; *3,* medial epicondyle; *4,* trochlea; *5,* lateral epicondyle. (From Connolly JF: DePalma's Management of Fractures and Dislocations. Philadelphia, WB Saunders, 1981.)

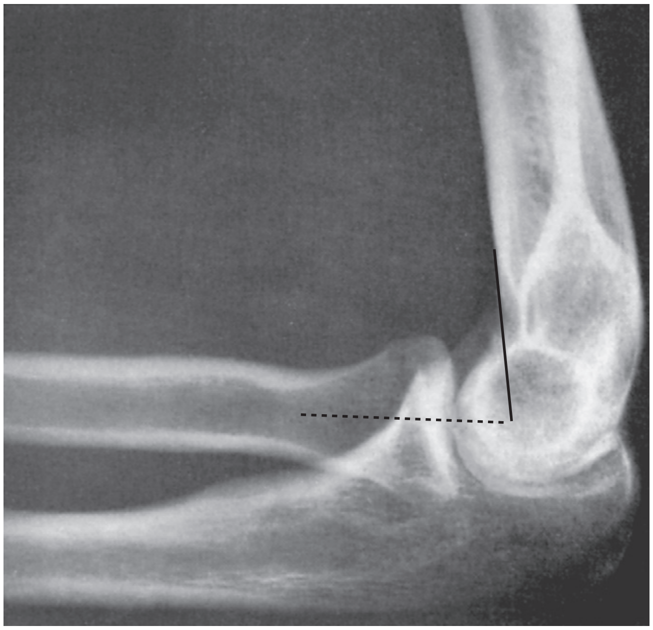


Figure 176-13. Lateral radiograph demonstrating the bone relationships in a normal elbow. The anterior humeral line (*solid*) and proximal radial line (*dashed*) bisect the capitellum. (From Weissman BN, Sledge CB: Orthopedic Radiology. Philadelphia, WB Saunders, 1986.)

Radiographic evaluation of any elbow injury should include an AP view of the extended elbow and a lateral view of the flexed elbow. If these views do not show a fracture but clinical suspicion is high, oblique views are helpful. Even with proper radiographs, diagnosis of a pediatric elbow fracture can be difficult. The elbow is largely cartilaginous during early childhood, and the six secondary centers of ossification around the elbow can camouflage or be mistaken for fractures (Fig. 176-12). These ossification centers can be remembered by the mnemonic CRITOE: capitellum, radius, internal (medial) epicondyle, trochlea, olecranon, and external (lateral) epicondyle. The approximate ages at which these sites ossify may be estimated at 1, 3, 5, 7, 9, and 11 years, respectively (Table 176-4).

Bone relationships are helpful in evaluation of a radiograph for a supracondylar fracture (Fig. 176-13). A true lateral view should demonstrate a figure-of-eight appearance of the distal humerus with bisection of the capitellum by the anterior humeral line. If the capitellum falls posterior to this line, an extension-type supracondylar fracture is likely. In all views, the proximal end of the radius and radial neck should point to the capitellum. Baumann's angle also is helpful in diagnosis of subtle supracondylar fractures[12] (Fig. 176-14). This angle is formed by a line drawn to follow the growth plate of the capitellum transected with a line that runs perpendicular to the axis of the humerus. The angle should be approximately 75 to 80 degrees. Baumann's angle should be the same in both elbows, and differences between elbows can be used

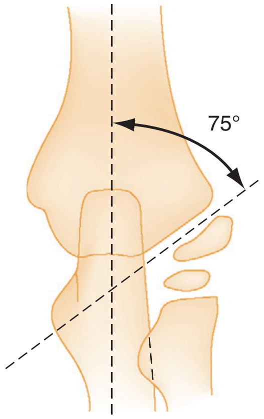


Figure 176-14. Baumann's angle in a normal elbow on an anteroposterior radiograph. (From Worlock P: Supracondylar fractures of the humerus: Assessment of cubitus varus by the Baumann angle. J Bone Joint Surg Br 68:755, 1986.)

www.ketabpezeshki.com 66485457-66963820

Figure 176-15. Lateral radiograph of a supracondylar fracture with an anterior fat pad "sail sign" and a posterior fat pad.

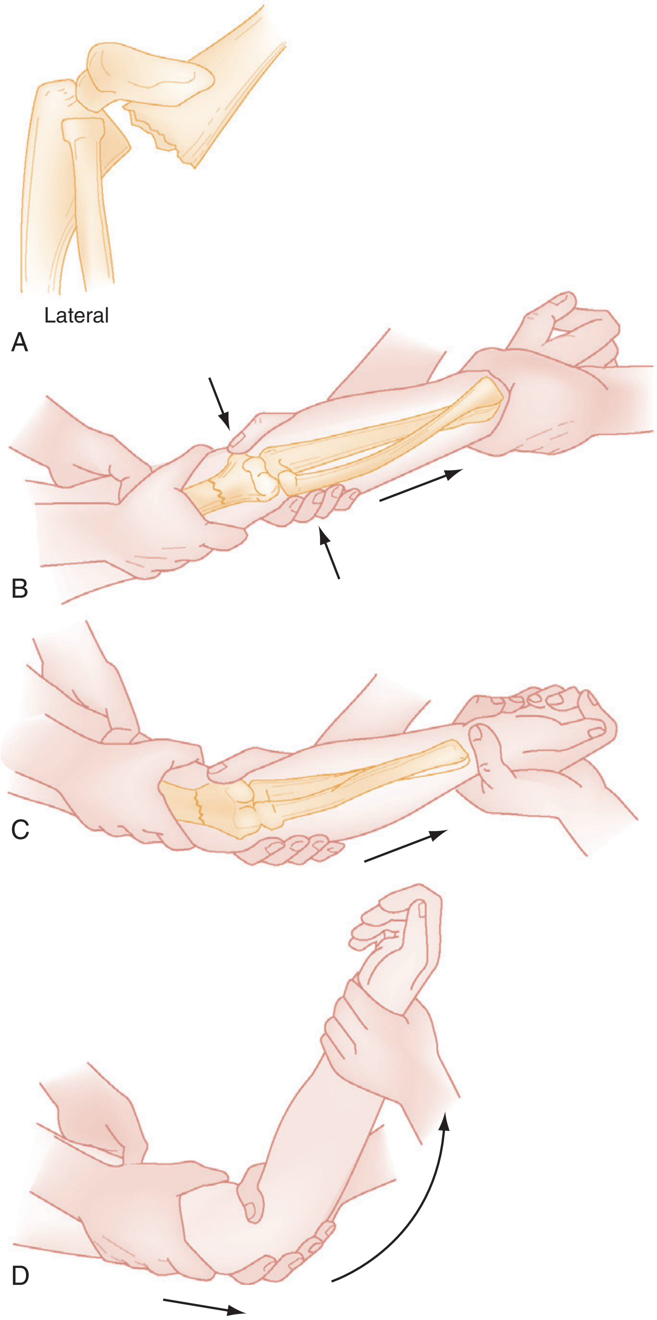


Figure 176-16. Steps in reduction of a displaced supracondylar fracture, seen in **A**. **B,** The assistant fixes the arm of the patient while the physician grasps the patient's wrist and applies steady traction in line with the long axis of the arm while keeping the forearm in the neutral, thumb-up position. **C,** If the distal fragment is displaced laterally, it is pushed inward with the physician's other hand. If it is displaced medially, it is pushed outward. Throughout manipulation, traction is maintained. **D,** After length is restored and the medial and lateral displacement is corrected, the physician's thumb is placed over the anterior surface of the proximal fragment with the fingers behind the olecranon, and the elbow is gently flexed. The arm is then immobilized with the forearm pronated; laterally displaced fractures are immobilized with the forearm supinated. (From Geiderman JM, Magnusson AR: Humerus and elbow. In Rosen P, Barkin R [eds]: Emergency Medicine: Concepts and Clinical Practice, 4th ed. St Louis, CV Mosby, 1998.)

to detect subtle supracondylar fractures. In children younger than 3 years, difficult-to-distinguish bone landmarks limit the utility of Baumann's angle. Postreduction alterations in Baumann's angle reliably predict the final carrying angle.[13]

Fat pads also provide a means for detection of occult supracondylar fractures. A lateral radiograph with the elbow flexed at 90 degrees may show an anterior fat pad protruding from the coronoid fossa. This finding is normal unless the pad is bulging or in the shape of a ship's sail. This "sail sign" may indicate fluid in the joint, although alone it may not be a reliable predictor of a fracture. The posterior fat pad, however, sits snugly within the olecranon fossa and should never be seen unless there is a fracture around the elbow. In this case, blood pushes the fat pad laterally, thereby making it visible on a lateral radiograph of the elbow. Accordingly, visualization of a posterior fat pad suggests the presence of an occult fracture around the elbow. The presence of a posterior fat pad without an obvious fracture warrants oblique views of the elbow (Fig. 176-15), splinting, and follow-up.

Plain radiographs usually are sufficient for diagnosis of supracondylar fractures. However, if the diagnosis remains in question after AP, lateral, and oblique radiographs are obtained, ultrasound imaging may be useful in infants,[14] and magnetic resonance imaging (MRI) may be useful in older children.[15]

ED treatment of supracondylar humeral fractures is determined by displacement and neurovascular status. A pale, pulseless cold hand mandates emergency consultation with an orthopedic surgeon. If an orthopedic surgeon is unavailable and the vascular supply has not been restored, reduction should be attempted (Fig. 176-16). If necessary, reduction can be performed by a single operator. With the patient supine, the shoulder held in 90 degrees of forward flexion, and the elbow slightly flexed, both hands are placed on the arm proximal to the fracture, and both thumbs are placed on the posterior aspect of the fracture fragment. Then, while the thumbs are directed distally, the fragment is lifted onto the distal metaphysis. The return of blood supply is marked by the hand's becoming warm and pink. If perfusion does not improve, another reduction may be attempted, with care taken to not entrap the brachial artery and median nerve. Multiple attempts at reduction increase the likelihood of neurovascular injury and swelling; therefore, no more than two reductions should be attempted. If perfusion is not reestablished, the child requires urgent operative

www.ketabpezeshki.com 66485457-66963820

intervention. A supracondylar fracture with a pulseless hand that is warm and pink does not need to be reduced immediately and should be splinted as it lies so that vascular status is not further compromised. The elbow should be splinted in relative extension because too much flexion in conjunction with swelling may obstruct the brachial artery and contribute to limb ischemia.

Gartland type I fractures can be splinted in the ED with the arm maintained in 90 degrees of flexion and neutral rotation. Hospital admission is not required, but these children do require urgent follow-up with an orthopedic surgeon. Gartland type III fractures require immediate orthopedic consultation and should be treated by either closed reduction and percutaneous pinning or open reduction and internal fixation in the operating room. Treatment of a partly displaced type II fracture is controversial. Some surgeons reduce and pin it in the operating room, whereas others perform closed reduction and keep the arm immobilized in a cast. Treatment of displaced supracondylar fractures by closed reduction and casting is associated with higher complication rates than is treatment by closed reduction and pinning; therefore, most such fractures are treated with pinning and casting for 3 to 4 weeks.

The primary complications of supracondylar fractures are related to neurovascular injury. Type III fractures are at greatest risk, with neurovascular compromise occurring in as many as 49% of patients.[16] Neurovascular compromise, however, can occur with any displaced fracture. The median nerve is involved in half of the cases and is associated with posterolateral displacement. The radial nerve is involved in almost one third of patients and is associated with posteromedial displacement. Brachial artery injuries, including arterial entrapment, laceration, intimal tears, thrombosis, and compression from compartment syndrome, occur in approximately 40% of patients and are found with either type of displacement. Fortunately, the brachial artery has many branches around the elbow, and flow to the forearm and hand can be maintained even when the brachial artery is injured.

Despite the frequency of neurovascular deficits immediately after the injury, most nerve palsies are caused by stretching or contusion and resolve spontaneously. The typical course for nerve injuries is complete resolution. Although motor function usually returns within 12 weeks, sensory function may not return for 6 months or longer.[17] If clinical or electromyographic evidence of nerve recovery is lacking after 5 months, exploration and neurolysis are indicated.[18] Volkmann's ischemic contracture (contracture deformity of the fingers, hand, and wrist) and permanent limb disability are the end result of untreated vascular injury. This complication is extremely rare and easily prevented by close observation and evaluation for the development of compartment syndrome. A few supracondylar fractures heal with a "gunstock" deformity; however, the combination of varus, hyperextension, and medial rotation of the limb is not a functional problem and, except in severe cases, requires no treatment. Severe cases can be corrected by humeral osteotomy.

Monteggia's Fracture-Dislocation

Monteggia's fracture-dislocations are characterized by a fracture of the proximal third of the ulna plus dislocation of the radial head. The radiographic evidence can be subtle, with only a minor greenstick fracture or bowing of the ulna. Isolated ulna fractures are rare in children; therefore, with all such fractures, AP and lateral radiographs of the elbow should be obtained to rule out dislocation of the radial head. The radial head should align with the capitellum on all radiographs of the elbow; if it does not, a Monteggia injury should be suspected (Fig. 176-17).

An orthopedic surgeon should be consulted promptly for closed reduction of the radial head dislocation and repair of the ulna fracture. Complications include permanent radial head dislocation, valgus deformity of the arm, loss of pronation, and late radial nerve palsy.

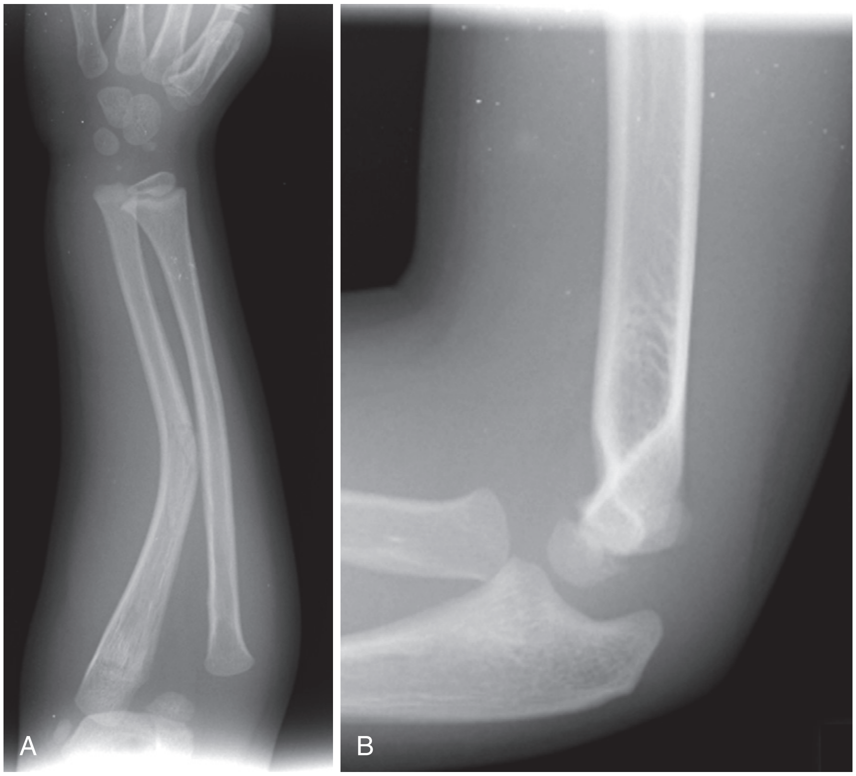


Figure 176-17. A, Anteroposterior view of elbow revealing a distal ulna fracture with radial head dislocation; the radial head should align with the capitellum in all views. B, Lateral view of the elbow demonstrating poor alignment of the radial head with the capitellum consistent with Monteggia's fracture-dislocation. (Images courtesy Dr. Michael Diament, Pediatric Radiology, Harbor-UCLA Medical Center, Torrance, Calif.)

www.ketabpezeshki.com 66485457-66963820

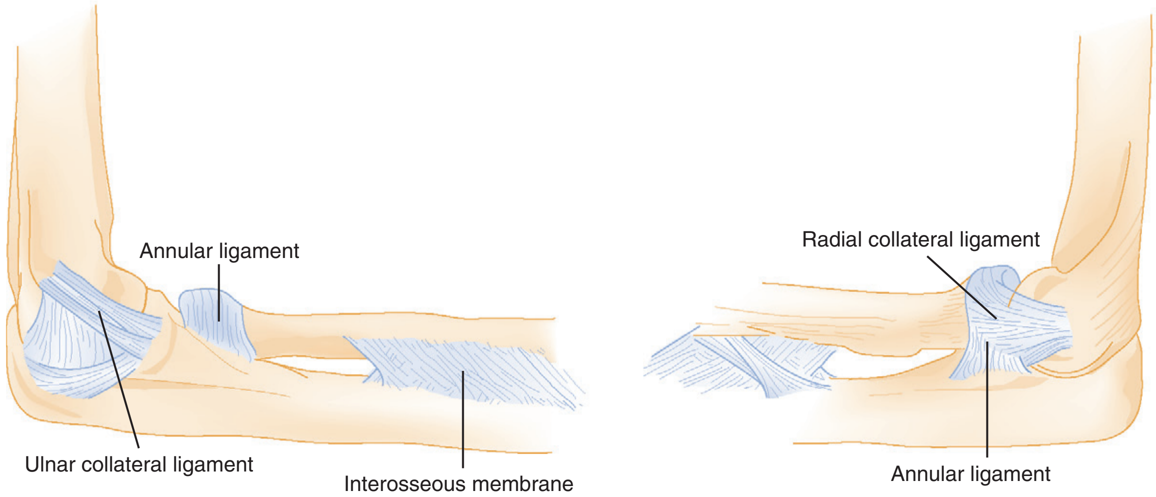


Figure 176-18. Nursemaid's elbow. In a nursemaid's elbow injury, as an axial force is applied, the annular ligament around the radial head is dislodged. The ligament is then partially dislocated into the radiocapitellar joint when the arm is released. (From Simon R, Koenigsknecht S: Emergency Orthopedics: The Extremities, 2nd ed. Norwalk, Conn, Appleton & Lange, 1987.)

Nursemaid's Elbow

In one study, radial head subluxation, or nursemaid's elbow, was the most common upper extremity injury in children younger than 6 years presenting to a pediatric ED.[19] It typically occurs when axial traction is placed on an extended and pronated arm, as when the child is pulled up or swung by the arms. It also may occur when the child falls onto the outstretched arm, sustains minor direct trauma to the elbow, or simply twists the arm. In infants, radial head subluxation can occur when an extended arm is caught beneath the infant's body while being rolled over. In pathoanatomic terms, subluxation occurs when the annular ligament becomes loosened from the head of the radius and slips into the radiocapitellar joint, where it becomes entrapped (Fig. 176-18).

Nursemaid's elbow occurs in children a few months to 5 years of age and has a peak incidence between 2 and 3 years of age.[20] It has been reported in children younger than 6 months[20] and has been seen in children as old as 9 years. This injury has a slight predilection for girls.

The history often includes an event involving a mechanism consistent with the injury followed by acute onset of arm pain that may or may not be localized to the elbow. The affected arm is held against the body, with the elbow slightly flexed and the arm pronated. Physical examination is significant for lack of swelling, erythema, ecchymosis, or deformity. Examination may reveal mild tenderness to palpation of the radial head. Pain is elicited with supination, pronation, and elbow flexion.

The diagnosis of nursemaid's elbow is made clinically, and radiographs are not necessary. If, however, significant point tenderness, swelling, or ecchymosis is present or if the history suggests another injury, such as a supracondylar fracture, radiographs should be obtained. Although it is not commonly used as a diagnostic procedure, ultrasound imaging may demonstrate a widened space between the radial head and the capitellum.[21]

Radial head subluxation is an orthopedic injury that is easily reduced without sequelae. Classically, the affected elbow is gripped with the clinician's thumb over the radial head, and with the other hand, the clinician flexes and supinates the patient's arm. As the radial head relocates, the clinician feels it click or "clunk" under the thumb. Hyperpronation of the forearm also is effective in reducing radial head subluxation. As is done in the flexion-supination maneuver, the child's affected elbow is held with the clinician's thumb over the radial head, but then flexion-supination is replaced with hyperpronation of the forearm. Success rates range from 80[20] to 92%[22] with supination and from 93[23] to 98%[24] with pronation. Pronation also may be less painful to the patient[24,25] and is the reduction method of choice.[24] After successful reduction, the child typically uses the arm normally within 10 minutes. This may be delayed in younger children and when the injury occurred more than 4 to 6 hours before reduction. Neither splinting nor orthopedic referral is required after a successful reduction.

Failure to reduce the subluxation of nursemaid's elbow may result from improper reduction technique; swelling of the annular ligament as a result of edema, hemorrhage, or hematoma; or disruption of the annular ligament. Persistence of the subluxation also is more likely if reduction is attempted 12 hours or longer after the injury.

If two attempts at reduction fail to restore normal use of the arm, alternative diagnoses should be entertained. Because of the similarity in clinical findings, children also should be assessed for fractures of the clavicle and elbow. If no other pathologic process is found and the child is still not using the arm, a posterior splint should be applied with the elbow kept at 90 degrees and the forearm in supination. Follow-up evaluation with an orthopedic surgeon should be arranged for the next day.

Parents should be cautioned to avoid traction on the forearm and elbow because recurrence rates of radial head subluxation range from 5 to 39%, depending on the referral population studied.[20,22,24] With recurrent subluxations, immobilization in a posterior splint with the elbow maintained at 90 degrees and the forearm supinated may be warranted. The need for open reduction or repair of the annular ligament is exceedingly rare.

Toddler's Fracture

Toddler's fractures are oblique nondisplaced fractures caused by low-energy torsional forces applied to the porous bone of infants and young children. Previously, it referred only to tibial fractures in children between 9 and 36 months of age, but the term is now applied more loosely. The mechanism of injury can be as mild as the child's twisting on the leg while walking or a fall from an insignificant height. In some instances, the mechanism of injury may be unknown. The child will exhibit a limp or may refuse to walk on the affected leg. Some children will revert to crawling and can crawl without pain. Examination may show mild swelling of the leg and point tenderness. Gentle twisting of the lower part of the leg may elicit pain.

www.ketabpezeshki.com 66485457-66963820

Figure 176-19. Toddler's fracture.

AP and lateral radiographs may reveal a spiral or oblique fracture extending downward and medially through the distal third of the tibia (Fig. 176-19). An internal oblique radiograph is helpful if evidence of fracture is absent on the AP or lateral view. If findings on all views are normal, consideration should be given to fractures elsewhere in the limb. If no fracture is apparent, the child should be splinted for comfort and radiographs repeated in 10 days, at which time periosteal new bone or sclerosis of the fracture edges will make the fracture visible. If findings on these radiographs are normal and the child is still limping, further evaluation should be undertaken to rule out osteomyelitis and malignant neoplasm. Bone scans often are helpful in the assessment of a limping toddler and are more sensitive than plain radiographs for detection of fractures. Ultrasonography is also emerging as an imaging option in the detection of occult fractures in toddlers as well as in older children.[26] Treatment of a toddler's fracture consists of a below-knee walking cast for approximately 3 weeks.

The presence of a spiral fracture without an appropriate history may raise concern for nonaccidental trauma (i.e., child physical abuse). Midshaft fractures, which are more common in abused children, and tibial fractures in nonambulating children as well as other unexplained or frequent injuries should prompt further evaluation.

Skeletal Aspects of Nonaccidental Trauma

Perspective

Fractures are the second most common manifestation of child physical abuse, second only to soft tissue injury, and are present in up to 70% of physically abused children. Fractures associated with child abuse occur in the very young, 50% in children younger than 12 months[27] and 94% in children younger than 3 years.[28] With child abuse, a timely and accurate diagnosis is imperative because children who are returned to an abusive home face a 35% chance of repeated abuse and a 10% chance of death; more than 20% of children who were diagnosed with a fracture from nonaccidental trauma had at least one previous physician visit at which abuse was missed.[29]

No fracture is pathognomonic for abuse, but certain fracture patterns are more worrisome than others. Any fracture in a child younger than 1 year, fractures at different stages of healing, and bilateral or multiple fractures indicate a need for thorough assessment for nonaccidental trauma (see Chapter 66). Injuries that are especially concerning include complex skull fractures, rib fractures, metaphyseal fractures, and vertebral fractures or subluxations. Midshaft humeral and scapular fractures are nearly always associated with abuse, as are approximately 70% of femoral fractures in children younger than 1 year.

Specific Disorders and Injuries

Diaphyseal Fractures

Although multiple fractures at different stages of healing are strongly suggestive of child abuse, the most common manifestation is an isolated diaphyseal fracture, which occurs four times as often as classic metaphyseal fractures. The humerus, femur, and tibia are the most frequently fractured long bones; the radius and ulna are the most infrequently fractured. With the exception of supracondylar fractures, all fractures of the midshaft of the humerus in children younger than 3 years are strongly suggestive of abuse.

Metaphyseal Fractures

Although less common than diaphyseal fractures, metaphyseal fractures are more specific for child abuse. Metaphyseal fractures most commonly affect the tibia, femur, and proximal end of the humerus. Corner fractures and bucket-handle fractures, which are probably the same fracture viewed in two different projections, result from violent shaking or forceful pulling or twisting of an infant's limb. The diagnosis is made by careful evaluation of high-quality plain radiographs. The tight adherence of the periosteum at the metaphysis precludes an active periosteal response, making these fractures difficult to diagnose even in the healing stages. In addition, after healing, these fractures may not be visible because of rapid bone remodeling. Bone scans, although sometimes helpful, are difficult to interpret because of the normally increased radionuclide uptake in the metaphyseal area.

Rib Fractures

Rib fractures are present in 5 to 27% of cases of child abuse; 90% of such fractures occur in children younger than 2 years. The young pediatric rib cage is compliant, and considerable force is required to break a rib. Accordingly, rib fractures are seldom seen in unintentional injury and are almost never seen after cardiopulmonary resuscitation.[30] When present, postresuscitation rib fractures are anterior and also may be multiple.[30] In a child younger than 3 years, the positive predictive value of a rib fracture as an indicator of intentional trauma approaches 100%.[31]

With nonaccidental trauma, posterior rib fractures are most common and result from maximal mechanical stress as the rib is levered over the transverse process of the vertebral body when infants are grasped and shaken. The ribs fail mechanically at the head or neck. Abuse-related rib fractures tend to be multiple and symmetrical and may be difficult to diagnose acutely on standard radiographs. Repeated radiographic examination at 7 to 10 days after the injury is advised if findings on the initial films are normal but the level of clinical suspicion is high. Radiographic findings include callus formation or widening of the rib neck as a result of apposition of new bone subperiosteally. Bone scans can be helpful in detection of fractures in the acute setting.

Skull Fractures

Skull fractures are the second most frequent injury in abuse and occur more commonly in abuse cases than from unintentional trauma.[26] Eighty percent occur in infants younger than 1 year, and

www.ketabpezeshki.com 66485457-66963820

although complex skull fractures are more suspicious for abuse, linear skull fractures are the most common type. Standard skull radiographs may not be adequate for diagnosis and are reported to miss more than 25% of head injuries. Children who meet high-risk criteria (the presence of rib fractures, multiple fractures or facial injury, or age younger than 6 months) should undergo CT or MRI for assessment of occult head injury.[32]

Periosteal New Bone Formation

Periosteal new bone formation, which is one of the most common findings in cases of abuse, reflects separation of the periosteum from the bone and may be the only manifestation of orthopedic trauma related to child abuse. It may be present with or without a fracture. It results from shaking, from acceleration-deceleration forces applied to an unsupported limb, or from forceful gripping.

Diagnostic Strategies: Radiology. Conventional skeletal radiography is the screening examination of choice in cases of suspected physical abuse. Unsuspected fractures are found in 22% of physically abused children and are more common in the very young. A complete skeletal survey is recommended for all physically abused children younger than 3 years and for all infants younger than 1 year with evidence of abuse or neglect. Complete skeletal surveys are rarely indicated in children older than 5 years; in children between 3 and 5 years of age, the need for a skeletal survey is determined on a case-by-case basis. Although standard practice has been to obtain skeletal surveys in infants with skull fractures without intracranial injury or suspicious clinical findings, their routine use has come into question as they have been found to find additional fractures in only 1.4% of patients.[33]

A skeletal survey consists of an AP view of the extremities (including the hands and feet), frontal and lateral views of the thoracolumbar spine (including the ribs), and an AP and lateral skull series. In cases in which abuse is strongly suspected but radiographic findings are normal, bone scanning serves as an adjunct and is complementary to the skeletal survey in detection of injury. It is sensitive for detection of subtle rib, spine, and diaphyseal trauma, especially in the acute setting, but because the radiographic abnormalities can persist for years, it is not reliable in determination of the age of the fracture.

Differential Considerations. Although most cases of intentional injury are easily diagnosed with a thorough history and physical examination, certain conditions can be confused with child abuse. Metaphyseal cupping and spurring and periosteal new bone formation are two normal variants that radiographically are almost identical to the findings in cases of child abuse. These features are seen in more than 40% of normal infants. They appear between 2 and 3 months of age and may persist until 8 months of age. These findings can be differentiated from child abuse by subtle radiographic clues: normal-variant infantile metaphyseal spurs are in continuity with normal bone and cortex, and physiologic periostitis is bilateral, confined to the diaphysis, and smooth and lamellar in appearance. Physiologic periostitis also tends to be more obvious on the medial aspect of the bone and most commonly involves the femur, although it also is seen in the humerus and tibia. Radiographic differentiation between normal variants and trauma-related injury is extremely difficult, and the clinical findings must be taken into account.

Osteogenesis imperfecta (OI), a heritable disorder of connective tissue, is an alternative cause of multiple fractures with minimal trauma. In the United States, the estimated incidence is 1 in 20,000 persons. This estimate includes cases in children in whom the condition is diagnosed within 1 year of birth but does not include milder forms of the disease that are not diagnosed until later in life. Accordingly, the true incidence of OI may be significantly higher. Most types of OI have been linked to mutations in type I collagen genes that interfere with either the synthesis or the construction of collagen subunits. Clinical features include bone fragility, ligament laxity, defective dentinogenesis, short stature, scoliosis, middle ear deafness, blue sclera and tympanic membranes, and misshapen skull. On radiographs, the bones are diffusely osteopenic, with thin cortices and attenuated trabecular patterns. The long bones have narrow diaphyses, and bowing and fractures are common (Fig. 176-20).

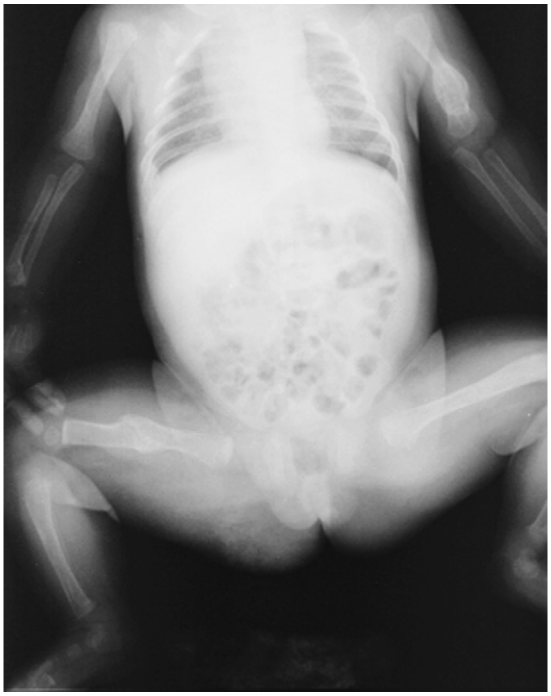


Figure 176-20. Radiograph obtained in a child with osteogenesis imperfecta. Note the narrow diaphyses, osteopenia, and multiple fractures.

Patients with OI present with a wide range of conditions from intrauterine demise to occurrence of multiple fractures in an infant to almost complete absence of symptoms in an adult. The diagnosis of OI is made on the basis of the history, physical examination, and radiographic findings. Confirmation is by skin biopsy and culture of dermal fibroblasts for evaluation of type I collagen. However, because the molecular basis for the entire spectrum of disease has not been established, up to 10% of cases of OI would be missed with skin biopsy alone. ED management of children with OI includes appropriate orthopedic referral for fractures and primary care referral for hearing evaluation.

In addition to musculoskeletal complaints, children with OI are predisposed to abdominal pain and neurologic abnormalities. The abdominal pain is thought to be related to the trefoil-shaped pelvis and acetabular protrusion associated with OI. These structural abnormalities narrow the pelvic outlet, resulting in partial rectosigmoid obstruction and subsequent constipation or obstipation. Neurologic abnormalities associated with OI result from basilar impression. Basilar impression, or elevation of the floor of the posterior cranial fossa, is reported to occur in 25% of patients with OI.[34] The signs of basilar impression (nystagmus, facial spasm, nerve paresis, pyramidal signs, and papilledema) may predate the symptoms (headache, neuralgia, imbalance, weakness, and incontinence). The most serious outcomes with basilar impression include brainstem compression, respiratory arrest, and sudden death. Any neurologic changes in a patient with OI mandate neurosurgical evaluation.

Several metabolic abnormalities can be associated with frequent fractures and radiographic abnormalities. Rickets, which results

www.ketabpezeshki.com 66485457-66963820

from vitamin D or calcium deficiency or hyperparathyroidism, can be manifested by diffuse osteopenia, fraying of the metaphysis, fractures, periosteal new bone formation, widening of the physis, and well-defined transverse stress fractures in the shafts of long bones. The diagnosis can be confirmed with laboratory testing. Menkes' kinky hair syndrome, a rare disorder of X-linked recessive inheritance involving inadequate copper absorption, is characterized by wormian (intersutural) skull bones, osteopenia, and metaphyseal fractures and spurring. Affected children have sparse, kinky hair with abnormal dentition and exhibit developmental delay. Serum levels of copper and ceruloplasmin are low and confirm the diagnosis. Hypervitaminosis A, although a rare cause of fractures, results in a thick periosteal reaction of tubular bones, most frequently the ulna and metatarsals, and widening of the cranial sutures. The epiphyses and metaphyses are normal. The diagnosis is based on the history and vitamin A levels.

Congenital syphilis also can mimic nonaccidental trauma. Skeletal findings in congenital syphilis frequently are diffuse and symmetrical and involve the long bones, skull, and small bones of the hands and feet. Radiographic findings include osteolytic defects, periosteal reaction, and metaphyseal lucencies parallel to the physis. The diagnosis is confirmed by serologic testing.

Developmental Dysplasia of the Hip

Perspective

Developmental dysplasia of the hip (DDH), formerly known as congenital dislocation of the hip, is abnormal formation of the hip joint that occurs between organogenesis and fetal maturity.[35] It encompasses a spectrum of disease ranging from "subluxatable" ("loose") hips to frank dislocation of the hips.

In white neonates, the incidence of dysplasia is 1%, and the incidence of dislocated hips is 0.1%. DDH is more common in Native American populations and less common in African American, Korean, and Chinese populations. An apparent familial predilection for the development of DDH has been reported; one British study noted that more than 20% of children who required treatment for DDH had a positive family history.[35] DDH is more common in girls and most frequently is unilateral (80%). With unilateral involvement, a predilection for the left side is characteristic. Associated birth factors include oligohydramnios, breech presentation, torticollis, talipes equinovarus, metatarsus adductus, and first-born status.[36] Postnatally, swaddling of infants with their hips and knees in extension predisposes to dislocation.

Principles of Disease

The etiology of DDH is not entirely clear. Three theories have been postulated: mechanical issues related to fetal position and environment, primary acetabular dysplasia, and ligamentous laxity that is enhanced by maternal relaxin hormone. Each theory has merit, and a combination of factors that contribute to the development of DDH is most likely.

Clinical Features

DDH may be diagnosed at birth, or despite frequent and appropriate physical examinations, it may not be discovered until later in life. In one study, 6% of children with documented DDH had normal findings on physical examination at birth.[35] Conversely, in more than 50% of infants found to have unstable hips at birth, spontaneous stabilization occurs within 3.5 days.[37]

The clinical manifestations of and physical examination findings with DDH are as diverse as the disease itself. This variability is due to differences in the severity of the dysplasia and the progressive changes that occur over time. Up to 4 to 6 months of age, the diagnosis of DDH is based on physical examination findings of leg length, skinfold, and range-of-motion asymmetry and abnormal findings on the Barlow provocative test and the Ortolani reduction maneuver. Skinfold asymmetry (Fig. 176-21) can be noted in the groin, below the buttock, and along the thighs. Although skinfold asymmetry is not specific for DDH, being present in approximately 30% of infants with normal hips, it is sensitive, and the diagnosis of DDH is unlikely in infants with normal skinfold symmetry. Range of hip motion also is helpful in diagnosis of DDH; any asymmetry in hip flexion, abduction, and external rotation should prompt further investigation. Although the general physical examination can be helpful in assessment of hip stability, the physical diagnostic cornerstones for diagnosis of DDH in young infants are the Ortolani reduction maneuver and the Barlow provocative test. The Ortolani reduction maneuver is performed in an attempt to reduce a dislocated hip into normal position, and the Barlow provocative test detects a subluxatable or dislocatable hip (Box 176-1). Abnormal findings are the presence of a clunk with the Ortolani test and any abnormal movement between the femoral head and the acetabulum with the Barlow maneuver.

After approximately 4 to 6 months of age, soft tissue contractures develop, the Ortolani and Barlow tests yield less information in detection of unstable hips, and range-of-motion abnormalities become more apparent. Parents may notice limited or asymmetrical leg movements or difficulty with diapering. Findings on examination include limited abduction (Fig. 176-22), relative shortening of the ipsilateral femur (Galeazzi's sign; Fig. 176-23), and skinfold asymmetry. In children with bilateral DDH, the diagnosis is even more difficult beyond the first few months of life because of the absence of asymmetry. After the development of contractures, physical findings in bilateral DDH include widening of the

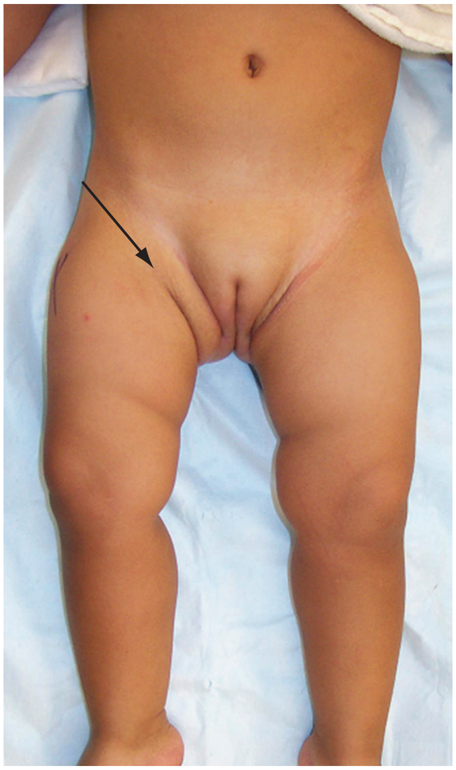


Figure 176-21. A 21-month-old child with right hip dislocation. Note the asymmetrical skinfolds in the upper thigh *(arrow)*. (From Storer SK, Skaggs DL: Developmental dysplasia of the hip. Am Fam Physician 74:1310, 2006.)

www.ketabpezeshki.com 66485457-66963820

Box 176-1 Ortolani and Barlow Maneuvers

Ortolani (Reduction) Maneuver
1. Stabilize the pelvis with one hand.
2. With the other hand, slightly abduct the infant's hip.
3. With the index and long fingers over the greater trochanter, pull up the thigh to gently reduce the hip.

Barlow (Provocative) Test
1. Stabilize the pelvis with one hand.
2. Place the thumb on the inner aspect of the thigh near the lesser trochanter.
3. Adduct the hip.
4. Exert downward pressure on the thigh with the thumb and push it into the table.

Figure 176-22. A 3-year-old child with a left hip dislocation. Note the limited abduction. (From Storer SK, Skaggs DL: Developmental dysplasia of the hip. Am Fam Physician 74:1310, 2006.)

Figure 176-23. Galeazzi's sign in a 7-month-old girl with left hip dislocation. Apparent inequality of femur length is manifested as asymmetry in the level of the patient's knees. (From Storer SK, Skaggs DL: Developmental dysplasia of the hip. Am Fam Physician 74:1310, 2006.)

perineum, abduction of less than 60 degrees, and the appearance of abnormally short thigh segments.

With the onset of walking, gait asymmetry or asymmetrical in-toeing or out-toeing is a clue to the presence of DDH. Adduction and flexion contractures, Galeazzi's sign, hyperlordosis, and waddling gait are common features. Clinical observation of the appropriate maneuver reveals Trendelenburg's sign: while standing, the patient lifts one leg up at a time, and because the gluteal muscles are weakened on the affected side, the pelvis drops to the opposite side. With bilateral DDH, children have a wide-based waddling gait.

Diagnostic Strategies

Radiographs of infant hips are extremely difficult to interpret and may provide a false sense of security if the findings seem normal. Before the child is 3 to 6 months old, at which time the femoral head ossifies, an abnormal relationship between the upper end of the femur and the acetabulum may not be apparent. In addition, in infants with unstable but nondislocated hips, radiographs will show the hip in position, so its instability goes undetected. Before femoral head ossification, a better diagnostic test is ultrasonography.[38] Because a large percentage of infants will have abnormal ultrasound findings in the first week of life, with many of these abnormalities resolving within a few weeks,[35] it is best to delay ultrasound imaging in children with nondislocated but possibly unstable hips until 4 to 6 weeks of age. Children with dislocated hips require immediate ultrasound examination. Plain radiographs are useful after the age of approximately 6 months. A standard AP radiographic view of the pelvis with both legs extended in neutral abduction is then sufficient for diagnosis. Radiographic findings may include displacement of Shenton's line (a curvilinear line defined by the medial border of the femoral neck and the superior border of the obturator foramen) and a widened acetabular angle; angles greater than 30 degrees are abnormal, and those greater than 40 degrees indicate dislocation (Fig. 176-24).

Management

Treatment of DDH is most successful when it is begun early, and delay in detection can be associated with a significantly worse outcome. Patients with untreated abnormalities of the hips that persist beyond the newborn period are at risk for osteoarthritis, pain, abnormal gait, leg-length discrepancy, and decreased agility. For this reason, all children who are seen in the ED should have their hips examined until they are able to walk. Neonates who have a dislocated hip at birth should be referred to a pediatric orthopedist immediately. When a newborn has a loose but nondislocated hip, referral can be made within 2 weeks. Children with loose hips who are seen after the newborn period should be referred to a pediatric orthopedic surgeon immediately.

The essential basic goal of treatment is concentric reduction of the hip. After concentric reduction, stability should be obtained so that when the leg is allowed to move, it does not subluxate or dislocate. This position is maintained until all of the dysplastic features of the bone and cartilage have resolved. The two most important complications are failure to achieve these goals and aseptic necrosis of the femoral head.

In the first 6 months of life, use of the Pavlik harness is the mainstay of treatment. It is a dynamic splint that allows movement while preventing hip extension or adduction. Other treatment options include application of the Craig and von Rosen splints.[39] If these modalities are unsuccessful, application of a hip spica cast usually is the next choice. Beyond 6 months of age, use of a hip spica cast or fixed orthosis is required. Surgical release of contracted muscles may be necessary in older infants and children, and open surgical reduction is required if complete closed reduction is not achieved. Femoral or pelvic osteotomy (or both) may be necessary to reduce and to stabilize dislocated hips in children older than 18 months.[40] Beyond the age of 4 years in bilateral cases and 8 years in unilateral cases, reduction should not be attempted. The risk of aseptic necrosis and the potential for a poor result are too high.[36]

www.ketabpezeshki.com 66485457-66963820

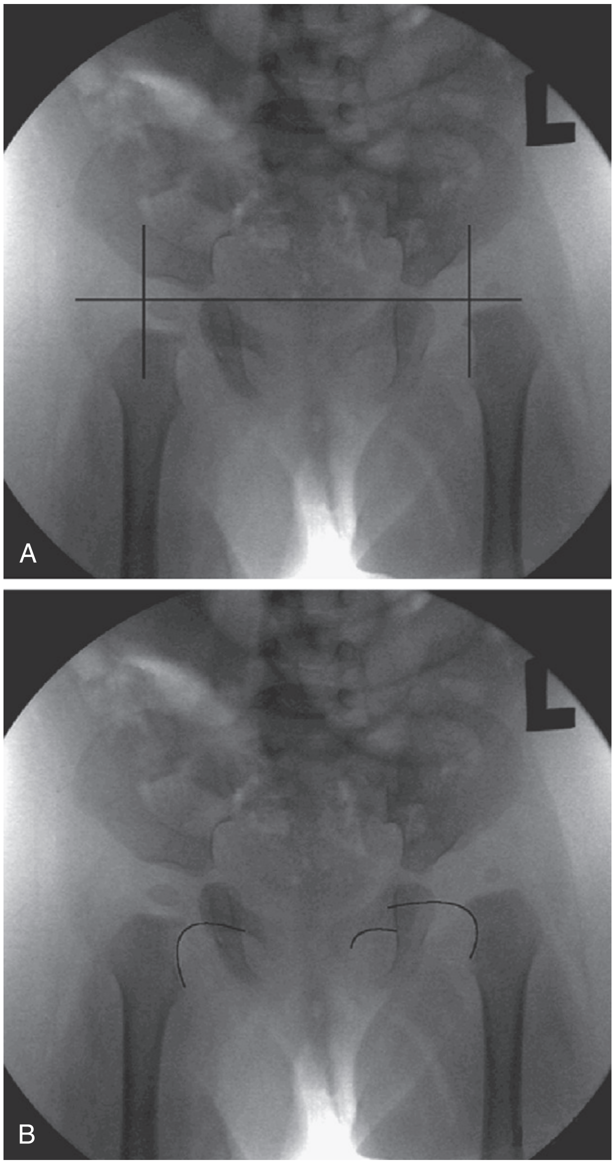


Figure 176-24. Anteroposterior radiographs obtained in a 7-month-old girl with developmental dysplasia of the left hip. **A,** The horizontal line is Hilgenreiner's line; the vertical lines are Perkin's lines. Note that the femoral head on the right (normal) side lies in the inferomedial quadrant formed by those lines. The left hip is dislocated; its femoral head lies in the superolateral quadrant. **B,** Shenton's line is disrupted on the left (dislocated) hip. (From Storer SK, Skaggs DL: Developmental dysplasia of the hip. Am Fam Physician 74:1310, 2006.)

Hip Pain in Children

Perspective

Hip pain in children is an extensive topic with myriad causes (Box 176-2). The extensive differential diagnosis precludes an in-depth review of the topic in this chapter, but an overview of some of the more common causes of hip pain in children is presented next.

Specific Disorders and Injuries

Transient Synovitis

Transient synovitis is the most common cause of hip pain in childhood.[41] It is a self-limited condition caused by a nonpyogenic inflammatory response of the synovium. Although it has been reported in children as young as 3 months and occasionally occurs in adults,[42] its peak incidence is between 3 and 6 years of age. Transient synovitis of the hip affects boys more commonly than girls and has a slight predilection for the right side. Less than 5% of cases are bilateral. Approximately half of the patients are seen acutely, usually within the first 3 days of the onset of symptoms, whereas the other half have a more insidious course, with symptoms occurring for weeks to months before medical evaluation.[43] Although transient synovitis most commonly affects the hip, it also can affect the knee.

The etiology of transient synovitis is unknown. Current theories imply an association with active or recent infection, trauma, or allergic hypersensitivity. At least half of the children with transient synovitis have or recently have had an upper respiratory illness.[44] One study demonstrated a fourfold rise in viral titers in 45% of patients and elevated serum interferon levels, consistent with a concurrent viral infection, in 43% of patients with transient synovitis.[45] Trauma commonly is associated with transient synovitis, but no clear relationship has been demonstrated. Similarly, a causal association with an allergic reaction to an infectious agent has been suggested but not proved.

It is estimated that transient synovitis of the hip may occur in up to 3% of children. Hip or groin pain is the most common initial finding, but referred pain to the medial aspect of the thigh or knee is found in 10 to 30% of patients. Affected patients either walk with a limp or, with severe pain, refuse to walk at all. The leg is held in flexion with slight abduction and external rotation. On examination, passive movement usually is pain free; however, pain and a slightly decreased range of motion may be noted with extreme internal rotation or abduction. Although most children with transient synovitis tend to otherwise be well, some will have a low-grade fever and malaise.

The diagnosis of transient synovitis is one of exclusion and relies on the history and physical examination in combination with limited laboratory testing and AP and frog-leg lateral radiographs of the pelvis. Laboratory tests are used to help distinguish children with transient synovitis from those with septic arthritis. In transient synovitis, laboratory values may be normal or may reveal mild elevations in the white blood cell count and erythrocyte sedimentation rate (ESR), both consistent with a nonspecific inflammatory process. Multiple studies have attempted to define criteria to help differentiate transient synovitis from septic arthritis. Clinical decision rules have included the presence or absence of fever, the ability to bear weight, white blood cell counts, the inflammatory markers ESR and C-reactive protein (CRP), side-to-side differences in the width of the joint space on radiographs, and previous visits to a health care provider for related symptoms. Kocher and colleagues found four independent multivariant predictors of septic arthritis: fever, inability to bear weight, ESR of

Box 176-2 Causes of Hip Pain in Children

Trauma
Hip or pelvis fractures
Overuse injuries

Infection
Septic arthritis
Osteomyelitis
Myositis
Lyme disease

Inflammation
Transient synovitis
Juvenile rheumatoid arthritis
Rheumatic fever

Neoplasm
Leukemia
Osteogenic or Ewing's sarcoma
Metastatic disease

Hematologic Disorders
Hemophilia
Sickle cell anemia

Miscellaneous
Legg-Calvé-Perthes disease
Slipped capital femoral epiphysis

www.ketabpezeshki.com 66485457-66963820

40 mm/hr or higher, and serum white blood cell count higher than 12,000 cells/μL. Patients with three of the four predictors had a 93% chance of having septic arthritis, and those with all four had a 99% likelihood.[46] A subsequent study to validate these findings showed that patients with none of the predictors had a 2% probability of septic arthritis; with one of four predictors, a 9.5% probability; with two of four predictors, a 35% probability; with three of four predictors, a 73% probability; and with all four predictors, a 93% probability of septic arthritis.[47] When this algorithm was tested at another institution, however, the presence of all four Kocher criteria predicted septic arthritis only 59% of the time.[48] In general, in children with transient synovitis and septic arthritis, the overlap of laboratory values and historical features is too great to provide a foolproof diagnostic algorithm.

Although radiographs of the hip and pelvis tend to be normal in appearance with transient synovitis, they are helpful to exclude other diseases. Radiographic findings consistent with transient synovitis include medial joint space widening, accentuated pericapsular shadow, and Waldenström's sign, which is lateral displacement of the femoral epiphysis with surface flattening secondary to effusion. However, these findings also are apparent in Legg-Calvé-Perthes disease and, if present, mandate close follow-up or further investigation with MRI. If joint aspiration is necessary to clarify the diagnosis, ultrasonography can be used to guide hip joint aspiration. Effusions are present in 60 to 70% of cases of transient synovitis; however, they also are present with septic arthritis, osteomyelitis, acute slipped capital femoral epiphysis (SCFE), Legg-Calvé-Perthes disease, rheumatoid and infectious arthritis, malignant disease, and osteoid osteoma. Accordingly, the presence of an effusion on ultrasonography cannot be used to distinguish transient synovitis from other causes of hip pain.[49] Nuclear scintigraphy in patients with transient synovitis is helpful in differentiation of transient synovitis from osteomyelitis (with or without septic arthritis), Legg-Calvé-Perthes disease, and SCFE. Scintigraphy may demonstrate differential uptake in the capital femoral epiphysis, with decreased uptake early in the course of the disease and increased uptake later on. The early changes also are seen with very early Legg-Calvé-Perthes disease and suggest that some children with transient synovitis experience ischemia of the capital femoral epiphyses. This ischemia may be caused by an intracapsular effusion that tamponades vessels along the femoral neck. These ischemic findings have not yet been shown to have clinical significance.

Most cases of transient synovitis can be managed at home with close follow-up by the child's primary care provider. In general, these children have a mild limp, and treatment with nonsteroidal anti-inflammatory medication often results in clinical improvement with relief of symptoms. A complete blood count and determination of ESR should be performed, and radiographs should be obtained. Patients with severe symptoms, fever, and elevated ESR should be evaluated for septic arthritis. If there is any doubt about the diagnosis, immediate orthopedic consultation is necessary.

Treatment of transient synovitis is twofold: (1) rest of the affected joint achieved with non-weightbearing or, in cases associated with extreme pain, bed rest and (2) reduction of the inflammatory process with anti-inflammatory medications. Temperatures should be monitored closely, and any fever should be reported to the physician. Children are allowed a gradual return to activity as the pain subsides, and full unrestricted activity is permitted when the hip is completely pain free with no evidence of a limp. Although many children with transient synovitis have an effusion, therapeutic aspiration of the joint is not routinely performed, and there is no strong evidence that aspiration shortens the clinical course or prevents osteonecrosis. Repeated examination is recommended for all children within 12 to 24 hours and then again after 10 to 14 days if the symptoms have not resolved.

The prognosis for children with transient synovitis is excellent. Up to 75% of patients have complete resolution of pain within 2 weeks and 88% within 4 weeks. The remainder may have less intense but persistent pain for up to 8 weeks. Relapse is possible, although infrequent, and usually occurs within 6 months. In general, long-term sequelae of transient synovitis are infrequent; these may include asymptomatic coxa magna (enlargement and deformity of the femoral head and neck caused by hypertrophy of cartilage secondary to inflammation) and mild degenerative cystic changes of the femoral neck. These changes persist for years and may be accompanied by radiographic degenerative change, but they do not tend to cause long-term functional disability. In addition, a small number (2%) of cases of transient synovitis follow a clinical and radiographic course consistent with Legg-Calvé-Perthes disease. Whether this is due to ischemia of the capital femoral epiphyses during the early stages of synovitis or reflects an initial misdiagnosis is unclear. It is recommended that children with persistent symptoms undergo ultrasonography to evaluate for the presence of an effusion. Persistent joint effusion beyond 4 to 6 weeks may be associated with the subsequent development of Legg-Calvé-Perthes disease.[50] Some experts recommend routine 6-month follow-up radiographs for all children with transient synovitis,[43] whereas others reserve radiographs for children who remain symptomatic.[51]

Acute Septic Arthritis

Septic arthritis refers to microbial invasion and infection of the joint space. Bacterial pathogens are common in patients with acute septic arthritis, whereas fungal and mycobacterial pathogens tend to be associated with a more indolent septic arthritis. Acute septic arthritis occurs in all age groups but is more common in children; 70% of cases occur in children younger than 4 years, and the peak incidence is between 6 and 24 months. Boys are affected twice as frequently as girls. Predisposing factors include preceding viral infection, trauma, immunodeficiency, hemoglobinopathy, hemophilia with recurrent hemarthroses, diabetes, injection drug abuse, rheumatoid arthritis, and intra-articular injections or operations. In 75% of cases of septic arthritis, the pathologic process involves the joints of the lower extremity, with the knee being most commonly and the hip second most commonly involved. Other affected joints, in order of involvement, include the ankle, elbow, shoulder, and wrist. More than 90% of the cases are monarticular.

Hematogenous seeding, local spread, or traumatic or surgical infection may cause septic arthritis. In children, it most commonly results from hematogenous spread as bacteria pass into the synovial space through the highly vascular synovial membrane. The synovial membrane lacks a limiting basement membrane, which facilitates bacterial translocation. The bacteria then bind to bone and cartilage, initiating an inflammatory response that breaks down the joint by two mechanisms: directly through the effects of proteolytic enzymes and indirectly through pressure necrosis caused by accumulation of purulent synovial fluid.

Contiguous spread of infection from osteomyelitis to the joint space occurs in approximately 10% of cases and is more common in newborns and young infants. In these children, blood vessels cross the physis, thereby connecting the metaphysis and epiphysis and allowing bacteria direct access into the joint space. In addition, the joint capsules of the hip and shoulder overlie the bony metaphyses of the femur and humerus, facilitating direct extension of osteomyelitis into these joint spaces.

The most common bacterial causes of septic arthritis are listed in Table 176-5. Overall, *Staphylococcus aureus* is the most common cause of septic arthritis and infection in children; community-acquired methicillin-resistant *S. aureus* (MRSA) accounts for up to 65% of *S. aureus* infections.[52] In neonates, group B streptococci and gram-negative organisms are common causes. In addition to

www.ketabpezeshki.com 66485457-66963820

the organisms listed in Table 176-5, additional causative organisms include *Neisseria gonorrhoeae* in neonates and sexually active adolescents, *Pseudomonas aeruginosa* and *Candida* species in injection drug abusers, *Salmonella* species in children with sickle cell disease, and gram-negative bacteria in immunosuppressed children. *Kingella kingae,* a fastidious gram-negative coccobacillus that colonizes the respiratory and oropharyngeal tracts in children, has been implicated as a common cause of osteoarticular infections in young children. *K. kingae* was found to be the causative agent in up to 50% of osteoarticular infections.[53,54] In previously well children, more than 95% of *K. kingae* infections are diagnosed between 6 months and 4 years of age; it may also cause infections in older children with underlying medical conditions.[55] Fortunately, *K. kingae* is susceptible to a wide array of antibiotics that are given empirically to young children for septic arthritis.

The clinical picture of septic arthritis varies with age. Infants tend to have fever, failure to feed, lethargy, pseudoparalysis of the extremity, and pain with being handled. In one study, however, neonates (younger than 1 month) were found to have less fever and fewer systemic signs of illness than in older infants, thus making the diagnosis even more difficult. Most older children have systemic signs and symptoms of fever, malaise, poor appetite, and irritability as well as localized symptoms of pain and refusal to move the affected joint or, if the lower part of the body is involved, limp or refusal to walk. With septic arthritis, the onset of symptoms is more acute than with osteomyelitis. Physical examination reveals local erythema, warmth, and swelling. If the hip is affected, it often is held in flexion, abduction, and external rotation. Range of motion is decreased because of pain and muscle spasm, and passive joint movement is painful. In infants, joint dislocation may be observed.

Table 176-5 Septic Arthritis Pathogens and Treatment

AGE	ORGANISM	TREATMENT
Birth to 2 months	Group B streptococci *Staphylococcus aureus* Gram-negative rods *Neisseria gonorrhoeae*	Nafcillin, 50 mg/kg, and cefotaxime, 50-75 mg/kg
2 months to 5 years	*Staphylococcus aureus* *Streptococcus pneumoniae* *Streptococcus pyogenes* *Kingella kingae* *Haemophilus influenzae*	Nafcillin, 50 mg/kg, and ceftriaxone, 50 mg/kg (consider vancomycin, 10 mg/kg)
5 years to 12 years	*Staphylococcus aureus* *Streptococcus pyogenes*	Nafcillin, 50 mg/kg, and ceftriaxone, 50 mg/kg (consider vancomycin, 10 mg/kg)
>12 years	*Staphylococcus aureus* *Neisseria gonorrhoeae*	Nafcillin, 50 mg/kg, and ceftriaxone, 50 mg/kg (consider vancomycin, 10 mg/kg)

Laboratory studies helpful in diagnosis of septic arthritis include a white blood cell count, ESR, CRP assay, blood cultures, and evaluation of joint fluid. Use of the white blood cell count and ESR is discussed in the section on transient synovitis. The ESR rises 24 hours or more after the onset of signs and symptoms of infection, so it may not be helpful during the first day of illness. The CRP level may be a better monitor than the ESR for septic arthritis. The CRP assay is a simpler test that requires only a fingerstick sample of blood. The CRP level rises more quickly than the ESR, typically is elevated at the time of the initial evaluation, and with appropriate therapy will normalize within a week; by contrast, the ESR will not normalize for more than a month.[56] In patients with septic arthritis, the peripheral white blood cell count, ESR, and CRP level generally are elevated, although white blood cell counts and acute-phase reactants may be normal, especially with *K. kingae* infection.[55,57]

Blood cultures should be included in the evaluation of a child with suspected septic arthritis. Culture results are positive in 20 to 50% of cases.[56] When culture results are positive, they not only help direct antibiotic treatment but also provide an organism for serum bactericidal testing as the child progresses to oral antibiotics.

If *N. gonorrhoeae* infection is suspected, special media are required for cultures of joint fluid, blood, pharynx, skin lesions, cervix, urethra, vagina, and rectum. Urine, urethral, cervical, and vaginal specimens also can be obtained for nucleic amplification testing.

If the patient has signs or symptoms of pharyngitis, a throat swab should be sent for culture of *Streptococcus pyogenes*. Antibody titers to antistreptolysin O and anti-DNase B also may help in establishment of a causative organism.

Evaluation of synovial fluid is the standard modality for diagnosis of septic arthritis. If septic arthritis is being considered, joint aspiration should be performed without delay and the sample sent for Gram's stain, aerobic and anaerobic cultures, cell count with differential count, and glucose determination. The synovial fluid in patients with septic arthritis tends to be turbid or grossly purulent, with a white blood cell count higher than 40,000 cells/μL and a predominance of polymorphonuclear cells (Table 176-6). Synovial glucose concentration may be low (synovial fluid glucose/blood glucose ratio of less than 0.5) and protein and lactate levels elevated. Because of the intrinsic immunoglobulins in the synovial fluid, results on culture of the fluid will be positive in only half of the children in whom the clinical picture is consistent with septic arthritis. Joint fluid should be inoculated directly into blood culture bottles to enhance identification of fastidious organisms such as *K. kingae*.[52,57] Culture specimens may need to be incubated for a week or longer.[54]

In septic arthritis of the hip, plain radiographs may be normal in appearance or, in the presence of a large joint effusion, may

Table 176-6 Synovial Fluid Findings in Different Types of Arthritis

CONDITION	CHARACTER	WBC COUNT (cells/μL)	PMNs (%)	OTHER
Normal	Clear; yellow	<200	<10	
Juvenile rheumatoid arthritis	Turbid	250-50,000	50-70	50% with decreased complement
Reactive arthritis	Cloudy to turbid; may be clear	1000-150,000	50-70	Increased complement
Lyme arthritis	Turbid	500-100,000	>50	
Septic arthritis	Turbid; white-gray	10,000-250,000	>75	Low glucose High lactate

PMNs, polymorphonuclear leukocytes (neutrophils); *WBC,* white blood cell.

www.ketabpezeshki.com 66485457-66963820

show periarticular soft tissue swelling, widening of the joint space, obliteration or displacement of the gluteal lines, and asymmetrical fullness of the iliopsoas and obturator soft tissue planes. Late in the course of infection, subchondral bone erosions and narrowing of the joint space are seen. Ultrasonography is much more sensitive than plain radiography for detection of hip effusion and provides direct visualization of the fluid and needle during joint aspiration. Scintigraphy also may be useful in diagnosis of septic arthritis; during the "blood pool" or delayed images of the joint, symmetrical uptake in periarticular tissue on both sides of the joint is seen. Scintigraphy is diagnostic of septic arthritis earlier than other imaging techniques are and is a useful adjunct in identification of associated osteomyelitis or avascular necrosis of the femoral head. CT can confirm the presence of an effusion but does not differentiate septic from nonseptic arthritis. Changes in signal intensity and femoral epiphysis perfusion seen on MRI may provide diagnostic clues in attempting to differentiate septic arthritis from transient synovitis.[58,59]

Septic arthritis requires immediate hospital admission, antibiotics, and surgical intervention. Surgical options range from needle aspiration to open surgical drainage, but no randomized, controlled trials have compared these two treatment approaches. Some experts recommend surgical drainage in all infants and young children with septic arthritis because needle aspiration has been shown to be inferior in this population.[60] Indications for surgical drainage in children with septic arthritis include involvement of the hip joint, presence of large amounts of pus or debris in the joint, loculated fluid, recurrence of joint fluid after four or five aspirations, and lack of clinical improvement within 3 days of the initiation of appropriate therapy.[61-64] In joints other than the hip, the need for surgical drainage is determined on a case-by-case basis.

Empirical antibiotic therapy for septic arthritis is directed against the most likely organisms as dictated by the patient's age and comorbid conditions (see Table 176-5). Treatment may then be changed after culture and sensitivity results are known. If a pathogen is not isolated but the patient is improving, initial antibiotic therapy is continued. If a pathogen is not identified and the patient is not improving, reaspiration of the joint or the possibility of a noninfectious process should be considered. To maximize culture results, antibiotics should not be given until a specimen of joint fluid is obtained. Initial treatment should be parenteral to ensure adequate serum antibiotic concentrations. In neonates, the entire course of antibiotics should be administered parenterally. Patients older than 1 month can be transitioned to oral antibiotics after they have been afebrile for 48 to 72 hours and have improved signs and symptoms of infection, a white blood cell count that has normalized, and decreasing inflammatory markers (CRP and ESR). In general, doses two to three times those used for mild infections are sufficient. Response to therapy is measured by clinical improvement and assays for acute-phase reactants (CRP and ESR).

The mortality rate associated with septic arthritis has fallen to less than 1%, but the morbidity remains significant. Sequelae include leg-length discrepancy, persistent pain, limited range of motion and ambulation, and ischemic necrosis of the femoral head. Predictors of a poor outcome include infection of the hip or shoulder, adjacent osteomyelitis, delay of 4 days or more before antibiotic and surgical intervention, and prolonged time to sterilization of synovial fluid.

Legg-Calvé-Perthes Disease

Idiopathic avascular necrosis of the proximal femoral epiphysis, also known as Legg-Calvé-Perthes disease, is named after the men who independently described it in the early 1900s. It usually occurs between the ages of 3 and 12 years, with the peak incidence between the ages of 5 and 7 years. Legg-Calvé-Perthes disease has been reported in teenagers as well as in children as young as 2 years. Boys are affected three to five times more frequently than girls, and the disease is familial approximately 10% of the time. The disorder is bilateral in up to 20% of cases. Trauma often is related to the onset of symptoms, but a direct relationship between the two has not been clearly established. Thrombophilia also may be associated with Legg-Calvé-Perthes disease; however, studies are conflicting.

Despite extensive research, the etiology of Legg-Calvé-Perthes disease remains unclear. Ponseti and colleagues[65] suggested that the disease is a local manifestation of a transient generalized disorder of epiphyseal cartilage. Their histologic studies showed thickening and disorganization of the growth plate, which could block penetration of the blood vessels and render the femoral epiphysis avascular. Other etiologic theories involve abnormalities in the vascular anastomotic network around the femoral epiphysis, increased blood viscosity leading to infarction, and abnormalities in growth hormone.

On clinical examination, children with Legg-Calvé-Perthes disease initially exhibit a limp of insidious and stuttering onset. Associated pain, when present, usually is related to activity and relieved by rest. The pain tends to be localized to the groin or referred to the anteromedial aspect of the thigh or knee region. Symptoms and limp severity usually are worse at the end of the day. On examination, children have limited hip motion, particularly abduction and internal rotation. Early in the course of disease, the limited abduction is secondary to synovitis and muscle spasm. As the disease progresses, limitation of motion is due to deformity of the femoral head, and with time, the limited abduction may become permanent. Children with Legg-Calvé-Perthes disease demonstrate Trendelenburg's sign (see the earlier section on developmental dysplasia of the hip) accompanied by thigh, calf, and buttock atrophy related to disuse. With advanced disease and femoral head collapse, limb-length discrepancy may be noted.

The role of laboratory evaluation in the diagnosis of Legg-Calvé-Perthes disease is limited to ruling out of other causes of hip pain (e.g., septic arthritis) when the diagnosis is in question or evaluation for hormonal, metabolic, or genetic causes in patients with bilateral hip involvement.

Legg-Calvé-Perthes disease is diagnosed and staged by plain radiographs obtained in the AP and frog-leg lateral views. This radiographic survey shows the extent of epiphyseal involvement and the stage of the disease and also provides prognostic information. Radiographic "head at risk" signs that are associated with poor results include a radiolucent V-shaped defect in the lateral epiphysis and adjacent metaphysis (Gage's sign), speckled calcification lateral to the capital epiphysis, diffuse metaphyseal reaction (metaphyseal cysts), lateral capital femoral epiphysis subluxation, and horizontal physis. These prognostic signs help guide treatment. In early Legg-Calvé-Perthes disease, radionuclide bone scanning may be diagnostic before the development of abnormalities on plain film. Bone scintigraphy also has been shown to provide accurate information concerning the extent of the necrotic process as well as the degree of vascularization and hence the stage of the disease. Scintigraphy, however, was not able to predict disease outcome.[66] Compared with plain radiography and bone scanning, MRI gives earlier and more reliable information about the extent of necrosis of the femoral head. MRI also is better than scintigraphy at showing revascularization. Despite the usefulness of MRI in early Legg-Calvé-Perthes disease, its role in healed Legg-Calvé-Perthes disease is limited because it provides no additional information about the configuration and structure of the femoral head beyond that from plain radiography.[66] Arthrography is useful in delineation of flattening of the femoral head, demonstration of the hinge abduction phenomenon with abduction of the leg, and, in conjunction with plain films or CT, diagnosis of osteochondritis dissecans after Legg-Calvé-Perthes disease.

www.ketabpezeshki.com 66485457-66963820

Figure 176-25. Crescent sign (subchondral lucent zone) in early Legg-Calvé-Perthes disease. (Courtesy Marianne Gausche-Hill, MD.)

There are four radiographic classification stages of Legg-Calvé-Perthes disease: initial, fragmentation, reossification, and healed. Radiographic findings in the initial stage include a femoral head that appears smaller than the opposite unaffected femoral head, widening of the medial joint space, subchondral lucent zone (subchondral collapse, the so-called crescent sign; Fig. 176-25), irregular physeal plate, and blurry and radiolucent metaphysis. In the fragmentation phase, the repair aspects of the disease become more prominent. The epiphysis begins to fragment, and areas of increased radiolucency appear as new bone forms as well as areas of increased radiodensity. During the reossification stage, the repair process continues as normal bone density returns, radiodensities replace radiolucencies, and alterations in the shape of the femoral head and neck become apparent. The healed stage is the final radiographic stage of Legg-Calvé-Perthes disease, and radiographs of the proximal third of the femur obtained during this stage of the illness will demonstrate any residual deformities.

Multiple prognostic classification systems of Legg-Calvé-Perthes disease have been devised. In general, a poor prognosis is associated with a greater degree of deformity of the femoral head and acetabulum at maturity, disease onset in children 6 to 8 years of age or older, female gender, and prolonged duration of disease.

When the diagnosis of Legg-Calvé-Perthes disease is suspected, orthopedic consultation is recommended. Goals in the treatment of Legg-Calvé-Perthes disease are to improve range of motion, to prevent deformity, to limit growth disturbance, and to prevent degenerative joint disease. Treatment is not indicated in all affected children, but when it is indicated, it should be started in the initial or fragmentation phase of the disease. Treatment is recommended for patients who have a poor prognosis on the basis of clinical and radiographic findings. The cornerstone for treatment of Legg-Calvé-Perthes disease is referred to as containment: the femoral head is contained within the acetabulum to equalize pressure on the head and to subject it to the molding action of the acetabulum to maintain the spherical nature of the femoral head. Containment can be achieved through nonoperative or operative methods, and optimal treatment is determined on a case-by-case basis.

Residual deformities resulting from Legg-Calvé-Perthes disease follow four patterns: coxa magna (enlargement and deformation of the head of the femur), premature physeal arrest, irregular head formation, and osteochondritis dissecans. Despite these deformities, most patients with childhood hip disease are capable of bone remodeling with subsequent improvement in femoral head deformities. During their early years, regardless of radiographic appearance, patients with Legg-Calvé-Perthes disease tend to do well.[67] A majority (70-90%) of patients are active and pain free and have good range of motion 20 to 40 years after the onset of symptoms. Only patients with flattened irregular femoral heads at the time of primary healing or premature physeal closure experienced clinical deterioration and increasing pain.[68] Later in life, function becomes markedly reduced, and degenerative joint disease develops in a majority of patients by their 50s and 60s.[67] With noncontainment treatment, however, the outcome is not as good. Yrjonen found that at an average of 35 years of follow-up, 48% of patients had evidence of degenerative joint disease and 17% either had undergone total hip arthroplasty or had clinical symptoms that warranted total hip arthroplasty.[69]

Slipped Capital Femoral Epiphysis

SCFE refers to posterior and inferior slippage of the proximal femoral epiphysis on the metaphysis. The femoral head sits securely in the acetabulum, whereas the epiphysis separates from the femoral neck through the growth plate. The average annual incidence of SCFE ranges from 0.2 (in Japan)[70] to 10.8 (in the United States) per 100,000 children; boys are affected almost twice as frequently as girls are.[71] The peak incidence is during the adolescent growth spurt: boys between 12 and 16 years of age (mean age, 13.5 years) and girls between 10 and 14 years of age (mean age, 11.5 years). The age at diagnosis decreases with increasing obesity. A majority of children with SCFE have delayed skeletal maturation, with bone age being as much as 20 months behind chronologic age. African American and Hispanic children are affected more frequently than white children are. The literature reports SCFE to be bilateral in up to 80% of cases, although 30 to 40% of these cases are asymptomatic and discovered only on screening radiographs. In unilateral cases, the left hip is affected twice as often as the right.

SCFE is associated with endocrine disorders (hypothyroidism, panhypopituitarism, hypogonadism, and growth hormone administration), renal osteodystrophy, and radiation therapy. Most cases of SCFE, however, are idiopathic and associated with obesity. The etiology of idiopathic SCFE is unknown. It is likely to be multifactorial and related to biomechanical factors such as obesity and physeal architecture as well as hormonal factors that weaken physeal strength. Obesity results in increased shear forces across a more vertically and posteriorly oriented growth plate that has been weakened by architectural irregularities and hormonal changes of puberty. The consequence is slippage of the epiphysis inferiorly and posteriorly in the direction of the weight-bearing force.

The traditional classification of SCFE was based on the duration of symptoms, with acute slippage defined as symptom duration of less than 3 weeks, chronic slippage defined as symptoms for 3 weeks or longer, and acute-on-chronic slippage defined as symptom duration of more than 3 weeks with a recent sudden exacerbation. This classification has been replaced by one based on stability: in stable SCFE, ambulation is possible (with or without crutches), whereas in unstable SCFE, ambulation is not possible (with or without crutches).[72] This classification system is preferred to the traditional classification because it does not rely on patient or parent recall for duration of symptoms and provides information about prognosis.

The signs and symptoms of SCFE vary with its stability. Children with stable SCFE have symptoms of intermittent limp and pain of several weeks to months in duration. Stable SCFE is found in approximately 95% of all cases.[72] The pain of SCFE may be localized to the hip but more commonly is poorly localized to the thigh, groin, or knee. Atypical manifestations of SCFE include weakness and easy fatigability of the affected limb and limping on exertion. With continued slippage, internal rotation, flexion, and abduction are lost, and parents and children may note progressive external rotation and shortening of the involved lower extremity with subsequent difficulty in daily activities, such as tying shoes. On examination, children initially have a slight loss of internal rotation and experience pain only at the extremes of motion. Their

www.ketabpezeshki.com 66485457-66963820

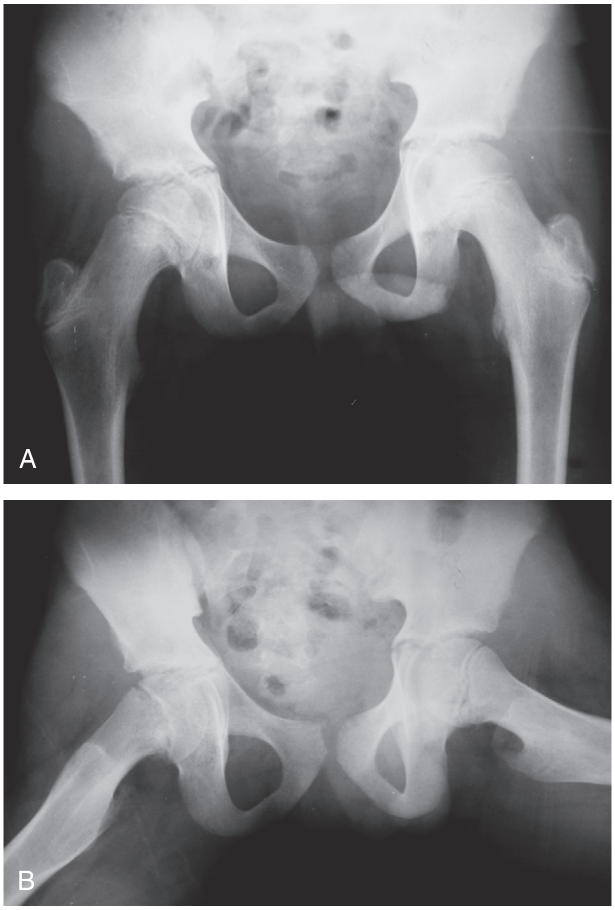


Figure 176-26. A, Anteroposterior radiograph of the pelvis with a unilateral slipped capital femoral epiphysis; note widening of the physis on the right compared with the left. B, Early inferior and posterior slippage is evident on the lateral view. (A and B courtesy Marianne Gausche-Hill, MD.)

gait is antalgic, and muscle atrophy is minimal. As the slip becomes more severe, the gait becomes more antalgic, internal rotation is lost, abduction and flexion of the hip increase, thigh and gluteal muscle atrophy is more pronounced, and leg-length discrepancy develops. A frequently seen sign associated with SCFE can be elicited during passive flexion of the affected hip: as flexion is increased from an extended position, the thigh abducts and externally rotates.

Unstable SCFE in children typically initially comes to attention after a sports-related injury or a fall with a twisting injury. These children experience acute onset of extreme pain and, on examination, hold the hip in flexion, external rotation, and abduction. The children resist any type of movement of the affected leg, and if unstable SCFE is suspected, no passive movement should be attempted for fear of further displacement of the epiphysis.

The diagnosis of SCFE is made with AP and lateral radiographs of both hips. With stable slippage, AP and frog-leg lateral pelvic radiographs should be obtained. When an unstable slip or a minimal slip is suspected, a cross-table radiograph replaces the frog-leg lateral view. Early in the course of SCFE, the initial slippage is posterior, so the AP view is normal in appearance or shows widening of the physis; the slip is better seen on the lateral projection (Fig. 176-26). Early findings on lateral radiographs include a minimal posterior step-off at the anterior physeal plate and widening of the growth plate. On AP radiographs, signs of slippage include Klein's line and the blanch sign of Steele. Klein's line is a line drawn along the superior margin of the femoral neck. With a normal hip, the line intersects with or falls within the epiphysis, whereas in a hip with a slipped epiphysis, the line does not come in contact with the epiphysis. The blanch sign of Steele is a crescent-shaped area of increased density in the proximal portion of the femoral neck that is created by superimposition of the posteriorly displaced epiphysis on the femoral neck. The femoral metaphysis of the affected hip also appears to be more laterally displaced from the medial wall of the acetabulum. As the slip continues, the epiphysis continues to be displaced inferiorly and posteriorly relative to the metaphysis. Over time, remodeling smoothes away the superior and anterior portions of the femoral neck, and in an attempt to buttress the slippage, callus is formed at the inferior and posterior portions of the femoral neck. Acute, unstable slips in children without previous symptoms will not be associated with evidence of bone healing or remodeling.

Ultrasonography has been used in the diagnosis of SCFE but offers little if any information beyond that provided by conventional radiography. CT and MRI can be used to confirm and to quantitate epiphyseal displacement in patients who have symptoms but no radiographic findings suggestive of SCFE.

Slip severity is described in either of two ways. The simplest classification describes the amount of displacement of the femoral head on the femoral neck. In mild SCFE, the amount of displacement is less than one third; moderate SCFE has displacement between one third and one half; and severe SCFE is marked by displacement of the femoral head by more than half the width of the femoral neck. A more accurate description of the magnitude of slippage is obtained by measurement of the epiphyseal-shaft angle of Southwick. On a frog-leg lateral radiograph of the pelvis, a line is drawn between the anterior and posterior tips of the epiphysis at the physeal plate level. A second line is then drawn perpendicular to the epiphyseal line. Next, a line is drawn along the midshaft of the femur. The epiphyseal-shaft angle is formed by the intersection of the perpendicular and the femoral shaft lines. The magnitude of slip displacement is the angle of the involved hip minus the angle of the normal hip. If involvement is bilateral, 12 degrees is used as the control angle. Mild SCFE involves displacement of less than 30 degrees, a moderate slip is between 30 and 50 degrees, and severe displacement is more than 50 degrees.[73]

When SCFE is diagnosed in the ED, non-weightbearing status is assigned immediately, and the child is provided with either crutches or a wheelchair; an urgent orthopedic consultation should be obtained. For a stable slip, definitive treatment is best performed within a few days; however, hospital admission is prudent. With an unstable slip, some orthopedic surgeons recommend immediate fixation.

The goals of treatment are to prevent further slippage and to achieve physeal stability, to avoid complications, and to maintain adequate hip function. A stable slip can be fixed with internal fixation (pinning), bone graft epiphyseodesis, corrective osteotomy, or spica cast immobilization. Most orthopedic surgeons recommend internal fixation with a single central screw. Failure of this repair is rare, and with new techniques that avoid opening of the hip joint, it has become a procedure associated with minimal blood loss and wound complications and minimal need for hospitalization and rehabilitation. Postoperatively, non-weightbearing or touch-toe weightbearing for 4 to 6 weeks is followed by a gradual return to normal activity. Running and contact sports may be resumed once the physis is closed. With unstable SCFE, controversy has arisen about the timing of the surgery, the optimal number of fixative devices that should be used, whether reduction should be performed, and whether preliminary traction and bed rest should be used before surgery. Treatment is dependent on the degree of slippage and the preference and experience of the orthopedic surgeon.

The two most worrisome short-term complications of SCFE are avascular necrosis and chondrolysis; the risk for either process

www.ketabpezeshki.com 66485457-66963820

increases with the severity of the initial slippage.[74] Avascular necrosis has been reported to occur in 10 to 15% of children with SCFE. The risk is higher with unstable SCFE,[75,76] greater degrees of slippage, and multiple attempts at reduction.[76] In children with stable slips treated by single-screw internal fixation without reduction, reported rates of avascular necrosis are as low as 0 to 5%.[77]

Chondrolysis occurs in approximately 5% of patients with SCFE, with an increased incidence in children with greater degrees of slippage. Chondrolysis may develop before and as a result of treatment. It should be suspected when pain and loss of motion are disproportionate to the severity of the slip. On radiographs, loss of articular cartilage may be seen. When SCFE is treated by spica cast immobilization, the rate of chondrolysis is reported to range from 19 to 67%.[78,79] Approximately 50% of cases of chondrolysis will resolve during the course of several years; however, in other cases, it may progress to such severe pain and contractures that hip arthrodesis is needed.

Other complications of SCFE include nonunion, premature closure of the epiphyseal plate, and degenerative changes. Degenerative hip arthritis develops gradually during decades and has an earlier onset with more severe degrees of slippage.

Apophyseal Injuries

Perspective and Principles of Disease

The apophysis is a cartilaginous structure that serves as a site for insertion of tendons on the growing bone. It has its own growth plate that has a slower rate of growth than the nearby epiphyseal plate. Apophysitis is unique to patients with skeletal immaturity and involves inflammation of this actively growing bone prominence that is under great tensile stress. Common apophyseal injuries include medial epicondylitis, Osgood-Schlatter syndrome, and Sever's disease.

Apophysitis may be secondary to a single episode of macrotrauma or may follow repetitive microtrauma to the secondary center of ossification, which causes multiple tiny avulsion fractures. This scenario sets up an inflammatory cycle that is perpetuated by continued activity and trauma to the apophysis.

Growth also contributes to the development of apophysitis. As the musculoskeletal system goes through a growth spurt, muscle development lags behind bone development. This difference in development leads to a muscle-tendon imbalance manifested as tight and inflexible muscle groups in which excessive stress is placed on the apophyseal centers at which these muscles insert.

The true incidence of apophysitis is unknown. One study found an incidence of 18% in a population of 1000 patients seen at an urban general pediatric clinic during a 4.5-month period.[80] Another study, which looked at patient visits to a sports medicine clinic, found an incidence of 31%.[81] Children between 8 and 15 years of age most frequently are affected, with involvement of different apophyseal centers affected at different ages.

Specific Disorders and Injuries

Osgood-Schlatter Syndrome

In 1903, Osgood and Schlatter independently reported traumatically induced apophyseal injury to the tibial tubercle in adolescents.[82] This entity, now known as Osgood-Schlatter syndrome, is the most common of the apophyseal disorders.[83] It is found most commonly in boys between 10 and 15 years of age and in girls between 8 and 13 years of age and frequently is bilateral. Boys are affected more often than girls are, although this trend is changing as more girls are becoming increasingly involved in competitive sports. Bilateral involvement is found in 20 to 30% of patients.

Clinically, patients with Osgood-Schlatter syndrome have tenderness, pain, and swelling at the site of insertion of the patellar tendon on the tibial tubercle. The tibial tubercle may be prominent and the quadriceps tight. Pain is worsened with activities (such as running and jumping) that cause the quadriceps to contract, thereby stressing the tubercle. Extension of the knee against resistance causes pain, but resisted straight-leg raises are painless. Osgood-Schlatter syndrome is a clinical diagnosis, and radiographs generally are not indicated. If radiographs are obtained, however, lateral views of the tibial tubercle may appear normal or may show an enlarged, fragmented, and irregular tibial tuberosity with or without an overlying bony ossicle. These findings are nonspecific, however, and are not diagnostic on their own. Ultrasonography, which has been proposed as a diagnostic tool by some experts, may reveal pretibial swelling, fragmentation of the ossification center, insertional thickening of the patellar tendon, or excessive fluid collection in the infrapatellar bursa.[84]

Treatment of Osgood-Schlatter syndrome is conservative and symptomatic. Initially, the pain can be effectively managed with ice and modification of activity, with or without nonsteroidal anti-inflammatory medications. The use of a patellar strap may help relieve symptoms. After the acute inflammatory process has resolved, treatment focuses on strengthening and stretching of the quadriceps muscles. Mild pain during activity is not an absolute contraindication to participation; however, with more severe symptoms, the risk of avulsion of the tibial tubercle should be weighed against the benefits of competing. In rare instances, conservative therapy is insufficient, and a 2- to 3-week trial of crutches is required. Steroid injections have been used in the past but are not currently recommended owing to the associated risk of patellar tendon rupture. Complete recovery without residual pain or weakness is the rule. Recovery usually occurs within weeks but in some cases may not be complete until the underlying growth plate is closed. However, if the patient reaches skeletal maturity and is still symptomatic, consideration should be given to surgical removal of the tibial tubercle or the bony ossicle overlying the tibial tubercle (or both).

Sever's Disease

Sever's disease is an apophysitis of the calcaneus due to traction by the gastrocnemius-soleus complex. It initially was described in 1912[85] and commonly is manifested as posterior heel pain in an 8- to 13-year-old athlete. It is bilateral in 60% of cases. As with other apophyseal injuries, pain is exacerbated by activity. Sever's disease can be associated with growth or tight heel cords or other biomechanical abnormalities. Impact sports, especially those that involve running, and sports in which cleats are worn frequently are implicated in the development of Sever's disease.

Patients have pain at the insertion site of the Achilles tendon and plantar fascia on the calcaneus. Tenderness is elicited when the calcaneus is squeezed bilaterally. Dorsiflexion of the ankle is restricted by tight heel cords. Radiographs may be normal in appearance or may show partial fragmentation and increased density of the calcaneal apophysis, although these findings also can be seen in normal feet.

As in Osgood-Schlatter syndrome, treatment of Sever's disease is conservative and symptomatic. Treatment consists of ice, massage, stretching of the plantar fascia and involved muscles (gastrocnemius-soleus complex and ankle invertors and evertors), nonsteroidal anti-inflammatory drugs, and addition of shock-absorbing shoe inserts. Heel cups also have been found to be helpful, but they should be accompanied by stretching to avoid exacerbation of the calf muscle contracture. Patients in whom conservative management fails have been found to have bone bruising and edema in the calcaneal metaphysis and apophysis, suggesting that calcaneal stress fractures may be the cause of persistent heel pain. Modification of activity and a trial of crutches for 3 to 4 weeks may be necessary.[86] Plantar fasciitis can cause heel pain as well, but patients will experience tenderness along the

www.ketabpezeshki.com 66485457-66963820

plantar fascia, especially at the attachment of the fascia to the calcaneus. Treatment involves the use of anti-inflammatory agents, rest, and relaxation of the plantar fascia with heel support pads.

Little League Elbow

Little League elbow is a term used to describe a group of injuries of the elbow, including apophysitis, medial epicondylitis, and osteochondritis dissecans of the radial head and capitellum. The injury involves an overuse phenomenon resulting in inflammation at the site where the forearm flexor muscles originate. As its name suggests, it commonly affects baseball pitchers in children's leagues and is associated with overhead arm motion. It also is seen in other skeletally immature overhand athletes, including tennis players. Little League elbow is caused by the excessive forces placed on the medial side of the elbow during the late cocking and acceleration phases of throwing.

Patients tend to be preadolescents in whom pain on the medial aspect of the elbow is associated with diminished throwing effectiveness and decreased throwing distance. Examination reveals localized tenderness and swelling over the medial epicondyle and pain with resisted flexion of the wrist. There may be a slight flexion contracture. Radiographs may be normal in appearance or may show fragmentation, sclerosis, and widening of the medial epicondylar apophysis. Treatment consists of a regimen of ice, nonsteroidal anti-inflammatory drugs, and modification of activity. Throwing is restricted until the symptoms have resolved. After resolution of the pain, the patient can begin a program of muscle stretching and strengthening, with a gradual return to throwing. Recovery usually takes 4 to 6 weeks. If pain returns during resumption of pitching, rest should be reinstituted. Patients with persistent pain, locking or decreased range of motion of the joint, or lateral elbow pain should be evaluated for avulsion fractures, loose bodies, and osteochondritis dissecans.

To minimize the risk of medial epicondylitis in children's league pitchers, the American Academy of Pediatrics recommends limiting the number of pitches to 200 per week or 90 pitches per outing[87]; however, the USA Baseball Medical and Safety Advisory Committee recommends lower pitch counts: 75 to 125 pitches per week or 50 to 75 pitches per outing, depending on age.[88] Preseason conditioning, use of proper pitching mechanics, and gradual increases in the amount and intensity of throwing are other preventive measures.

Apophysitis of the Hip

Apophyseal injuries of the hip involve sites around the hip where major abdominal and hip muscles either originate or insert: the anterior superior iliac spine, the anterior inferior iliac spine, the iliac crests, and the ischial tuberosities. Dancers and distance runners most commonly are affected. Patients with apophysitis of the hip experience dull pain near the hip that is related to activity. Treatment includes strengthening and stretching of the abdominal and hip muscles and restriction of activity.

Avulsion Fractures

Apophysitis tends to have an insidious onset; therefore, any patient with sudden onset of apophyseal pain after an acute traumatic event should be evaluated for an avulsion fracture of the apophysis or the adjacent bone. Such fractures occur when the muscle attachments to the apophyses are pulled off during strong active contractions against resistance, such as with a single powerful throw. Examination will reveal localized tenderness and swelling. The diagnosis usually is readily apparent on plain films (Fig. 176-27); however, bone scan and ultrasonography may play a role when the diagnosis is in question. Ultrasonography is advantageous because it involves no radiation exposure, it can detect a fracture before the development of an ossification center, and it provides a dynamic examination. Findings consistent with an avulsion fracture include a hypoechogenic zone, increased distance to the apophysis, dislocation of the apophysis, and mobility of the apophysis on dynamic examination.[89] Treatment of an avulsion fracture is based on the degree of separation. If the displacement is minimal (less than 2 cm with a hip avulsion and less than 5 mm with avulsion of the medial epicondyle[90]), immobilization for 4 to 6 weeks with subsequent slow resumption of activities usually is sufficient. With widely separated avulsion fractures, some experts recommend open reduction and fixation.[90]

Figure 176-27. Avulsion of the inferior iliac spine in a child with hip pain after kicking a soccer ball. (Courtesy Marianne Gausche-Hill, MD.)

KEY CONCEPTS

- Knowledge of the pediatric musculoskeletal system is imperative for appropriate evaluation and treatment of the skeletally immature patient.
- Child abuse should be suspected in children younger than 3 years with nonsupracondylar humerus fractures, femur fractures, rib fractures, and complex skull fractures.
- Children with displaced supracondylar fractures are at significant risk for neurovascular injury and should have frequent evaluations to assess for compartment syndrome.
- All children who are not yet walking should have a thorough hip evaluation on any visit to the ED.
- All patients with a gait disturbance need a thorough physical examination and directed laboratory and radiographic evaluation.
- Septic arthritis constitutes a medical and surgical emergency that mandates immediate orthopedic consultation.
- Examination of the hip is warranted in all patients with knee pain.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Simon TD, Bublitz C, Hambidge SJ: External causes of pediatric injury–related emergency department visits in the United States. *Acad Emerg Med* 2004; 11:1042.
2. Davidson JS, et al: Simple treatment for torus fractures of the distal radius. *J Bone Joint Surg Br* 2001; 83:1173.
3. Solan MC, Rees R, Daly K: Current management of torus fractures of the distal radius. *Injury* 2002; 33:503.
4. Firmin F, Crouch R: Splinting versus casting of "torus" fractures to the distal radius in the paediatric patient presenting at the emergency department (ED): A literature review. *Int Emerg Nurs* 2009; 17:173.
5. West S, et al: Buckle fractures of the distal radius are safely treated in a soft bandage: A randomized prospective trial of bandage versus plaster cast. *J Pediatr Orthop* 2005; 25:322.
6. Khan KS, et al: A randomized trial of "soft cast" for distal radius buckle fractures in children. *Acta Orthop Belg* 2007; 73:594.
7. Plint AC, et al: A randomized, controlled trial of removable splinting versus casting for wrist buckle fractures in children. *Pediatrics* 2006; 117:691.
8. Boutis K, et al: Cast versus splint in children with minimally angulated fractures of the distal radius: A randomized controlled trial. *CMAJ* 2010; 182:1507.
9. Randsborg P, Sivertsen EA: Distal radius fractures in children: Substantial difference in stability between buckle and greenstick fractures. *Acta Orthop* 2009; 80:585.
10. Hanby CK, Pasque CB, Sullivan JA: Medial clavicle physis fracture with posterior displacement and vascular compromise: The value of three-dimensional computed tomography and duplex ultrasound. *Orthopedics* 2003; 26:81.
11. Gartland JJ: Management of supracondylar fractures of the humerus in children. *Surg Gynecol Obstet* 1959; 109:145.
12. Williamson D, et al: Normal characteristics of the Baumann angle: An aid in the assessment of supracondylar fractures. *J Pediatr Orthop* 1992; 12:633.
13. Worlock P: Supracondylar fractures of the humerus: Assessment of cubitus varus by the Baumann angle. *J Bone Joint Surg Br* 1986; 68:755.
14. Davidson RS, et al: Ultrasonographic evaluation of the elbow in infants and young children after suspected trauma. *J Bone Joint Surg Am* 1994; 76:1804.
15. Beltran J, et al: Pediatric elbow fractures: MRI evaluation. *Skeletal Radiol* 1994; 23:277.
16. Campbell CC, et al: Neurovascular complications resulting from supracondylar humerus fractures. *J Pediatr Orthop* 1995; 15:47.
17. Dormans JP, Squillante R, Sharf H: Acute neurovascular complications with supracondylar humerus fractures in children. *J Hand Surg Am* 1995; 20:1.
18. Culp RW, et al: Neural injuries associated with supracondylar fractures of the humerus in children. *J Bone Joint Surg Am* 1990; 72:1211.
19. Schutzman SA, Teach S: Upper extremity impairment in young children. *Ann Emerg Med* 1995; 26:474.
20. Schunk JE: Radial head subluxation: Epidemiology and treatment of 87 episodes. *Ann Emerg Med* 1990; 19:1019.
21. Kosuwon W, et al: Ultrasonography of pulled elbow. *J Bone Joint Surg Br* 1993; 75:421.
22. Quan L, Marcuse EK: The epidemiology and treatment of radial head subluxation. *Am J Dis Child* 1985; 139:1194.
23. McDonald J, Whitelaw C, Goldsmith LJ: Radial head subluxation: Comparing two methods of reduction. *Acad Emerg Med* 1999; 6:715.
24. Macias CG, Bothrer J, Wiebe R: A comparison of supination/flexion to hyperpronation in the reduction of radial head subluxation. *Pediatrics* 1998; 102:e10.
25. Green DA, et al: Randomized comparison of pain perception during radial head subluxation reduction using supination-flexion or forced pronation. *Pediatr Emerg Care* 2006; 22:235.
26. Cho K, Lee S, Lee Y, Suh K: Ultrasound diagnosis of either an occult or missed fracture of an extremity in pediatric-aged children. *Korean J Radiol* 2010; 11:84.
27. Leonidas J: Skeletal trauma in the child abuse syndrome. *Pediatr Ann* 1983; 12:875.
28. Herndon WA: Child abuse in a military population. *J Pediatr Orthop* 1983; 3:73.
29. Ravichandiran N, et al: Delayed identification of pediatric abuse-related fractures. *Pediatrics* 2010; 125:60.
30. Maguire S, et al: Does cardiopulmonary resuscitation cause rib fractures in children? A systematic review. *Child Abuse Negl* 2006; 30:739.
31. Barsness KA, et al: The positive predictive value of rib fractures as an indicator of nonaccidental trauma in children. *J Trauma* 2003; 54:1107.
32. Rubin DM, et al: Occult head injury in high-risk abused children. *Pediatrics* 2003; 111:1382.
33. Wood JN, Christian CW, Adams CM, Rubin DM: Skeletal surveys in infants with isolated skull fractures. *Pediatrics* 2009; 123:e247.
34. Sillence DO: Craniocervical abnormalities in osteogenesis imperfecta: Genetic and molecular correlation. *Pediatr Radiol* 1994; 24:427.
35. Marks DS, Clegg J, al-Chalabi AN: Routine ultrasound screening for neonatal hip instability: Can it abolish late-presenting congenital dislocation of the hip? *J Bone Joint Surg Br* 1994; 76:534.
36. Novaceck TF: Developmental dysplasia of the hip. *Pediatr Clin North Am* 1996; 43:829.
37. Barlow TC: Early diagnosis and treatment of congenital dislocation of the hip. *J Bone Joint Surg Br* 1962; 44:292.
38. Boal DK, Schwenkter EP: The infant hip: Assessment with real-time ultrasound. *Radiology* 1985; 157:667.
39. Wilkinson AG: The efficacy of the Pavlik harness, the Craig splint and the von Rosen splint in the management of neonatal dysplasia of the hip: A comparative study. *J Bone Joint Surg Br* 2002; 84:716.
40. Storer SK, Skaggs DL: Developmental dysplasia of the hip. *Am Fam Physician* 2006; 74:1310.
41. MacEwen GD, Dehse R: The limping child. *Pediatr Rev* 1991; 12:268.
42. Nyska M, et al: Benign synovitis of the hip in adults. *Br J Rheumatol* 1993; 32:820.
43. Haueisen DC, Weiner DS, Weiner SD: The characterization of "transient synovitis of the hip" in children. *J Pediatr Orthop* 1986; 6:11.
44. Koop S, Quanbeck D: Three common causes of childhood hip pain. *Pediatr Clin North Am* 1996; 43:1053.
45. Tolat V, et al: Evidence for viral aetiology of transient synovitis of the hip. *J Bone Joint Surg Br* 1993; 75:973.
46. Kocher M, Zurakowski D, Kasser J: Differentiating between septic arthritis and transient synovitis of the hip in children: An evidence-based clinical prediction algorithm. *J Bone Joint Surg Am* 1999; 81:1662.
47. Kocher M, et al: Validation of a clinical prediction rule for differentiation between septic arthritis and transient synovitis of the hip in children. *J Bone Joint Surg Am* 2004; 86:1629.
48. Luhmann S, et al: Differentiation between septic arthritis and transient synovitis of the hip in children with clinical prediction algorithms. *J Bone Joint Surg Am* 2004; 86:956.
49. Zamzam MM: The role of ultrasound in differentiating septic arthritis from transient synovitis of the hip in children. *J Pediatr Orthop B* 2006; 15:418.
50. Eggl H: Ultrasonography in the diagnosis of transient synovitis of the hip and Legg-Calvé-Perthes disease. *J Pediatr Orthop B* 1999; 8:177.
51. Hart JJ: Transient synovitis of the hip in children. *Am Fam Physician* 1996; 54:1587.
52. Harik NS, Smeltzer MS: Management of acute hematogenous osteomyelitis in children. *Expert Rev Anti Infect Ther* 2010; 8:175.
53. Chometon S, et al: Specific real-time polymerase chain reaction places *Kingella kingae* as the most common cause of osteoarticular infections in young children. *Pediatr Infect Dis J* 2007; 25:377.
54. Osteomyelitis/septic arthritis caused by *Kingella kingae* among day care attendees—Minnesota, 2003. *MMWR Morb Mortal Wkly Rep* 2004; 53:241.
55. Yagupsky P, Porsch E, St. Geme JW: *Kingella kingae:* An emerging pathogen in young children. *Pediatrics* 2011; 127:557.
56. Kallio MJT, et al: Serum C-reactive protein, erythrocyte sedimentation rate and white blood cell count in septic arthritis of children. *Pediatr Infect Dis J* 1997; 16:411.
57. Gutierrez K: Bone and joint infections in children. *Pediatr Clin North Am* 2005; 52:779-794.
58. Kwack KS, et al: Septic arthritis versus transient synovitis of the hip: Gadolinium-enhanced MRI finding of decreased perfusion at the femoral epiphysis. *AJR Am J Roentgenol* 2007; 189:437.
59. Yang WJ, et al: MR imaging of transient synovitis: Differentiation from septic arthritis. *Pediatr Radiol* 2006; 36:1154.
60. Brower AC: Septic arthritis. *Radiol Clin North Am* 1996; 34:193.
61. Syriopoulou V, Smith A: *Osteomyelitis and septic arthritis.* In: Feigin R, Cherry J, eds: *Musculoskeletal Infections: Textbook of Pediatric Infectious Disease*, 3rd ed. Philadelphia: WB Saunders; 1992.
62. Dunkle LM: Toward optimum management of serious focal infections: The model of suppurative arthritis. *Pediatr Infect Dis J* 1989; 8:195.
63. Green NE, Edward K: Bone and joint infections in children. *Orthop Clin North Am* 1987; 18:555.
64. Nade S: Acute septic arthritis in infancy and childhood. *J Bone Joint Surg Am* 1983; 65:234.
65. Ponseti IV, et al: Legg-Calvé-Perthes disease: Histochemical and ultrastructural observations of the epiphyseal cartilage and physis. *J Bone Joint Surg Am* 1983; 65:797.

www.ketabpezeshki.com 66485457-66963820

66. Kaniklides C: Diagnostic radiology in Legg-Calvé-Perthes disease. *Acta Radiol* 1996; 406:1.
67. Weinstein SL: *Legg-Calvé-Perthes syndrome*. In: Morrisey RT, Weinstein SL, eds: *Lovell & Winter's Pediatric Orthopedics*, 4th ed. Philadelphia: Lippincott-Raven; 1996.
68. Weinstein SL: *Legg-Calvé-Perthes disease: Results of long-term follow up*. In: Fitzgerald RH Jr, ed: *The Hip: Proceedings of the Thirteenth Open Scientific Meetings of the Hip Society*. St. Louis: CV Mosby; 1985.
69. Yrjonen T: Prognosis in Perthes' disease after non-containment treatment: 106 hips followed for 28-47 years. *Acta Orthop Scand* 1992; 63:523.
70. Aronsson DD, Loder RT, Breur GJ, Weinstein SL: Slipped capital femoral epiphysis: Current concepts. *J Am Acad Orthop Surg* 2006; 14:666.
71. Lehmann CL, Arons RR, Loder RT, Vitale MG: The epidemiology of slipped capital femoral epiphysis: An update. *J Pediatr Orthop* 2006; 26:286.
72. Loder RT: Controversies in slipped capital femoral epiphysis. *Orthop Clin North Am* 2006; 37:211.
73. Green DW, et al: A modification of Klein's Line to improve sensitivity of the anterior-posterior radiograph in slipped capital femoral epiphysis. *J Pediatr Orthop* 2009; 29:449-453.
74. Rattey T, Piehl F, Wright JG: Acute slipped capital femoral epiphysis: Review of the outcomes and rate of avascular necrosis. *J Bone Joint Surg Am* 1996; 78:398.
75. Kennedy JG, et al: Osteonecrosis of the femoral head associated with slipped capital femoral epiphysis. *J Pediatr Orthop* 2001; 21:189.
76. Tokmakova KP, Stanton RP, Mason DE: Factors influencing the development of osteonecrosis in patients treated for slipped capital femoral epiphysis. *J Bone Joint Surg Am* 2003; 85:798-801.
77. Ward WT, et al: Fixation with a single screw for slipped capital femoral epiphysis. *J Bone Joint Surg Am* 1992; 74:799.
78. Carney BT, Weinstein SL, Noble J: Long term follow up of slipped capital femoral epiphysis. *J Bone Joint Surg Am* 1991; 73:667.
79. Meier MC, Meyer LC, Ferguson RL: Treatment of slipped capital femoral epiphysis with a spica cast. *J Bone Joint Surg Am* 1992; 74:1522.
80. de Inocencio J: Musculoskeletal pain in primary care pediatric care: Analysis of 1000 consecutive general pediatric clinic visits. *Pediatrics* 1998; 102:e63.
81. Micheli LJ, Fehlandt AF Jr: Overuse injuries to tendons and apophyses in children and adolescents. *Clin Sports Med* 1992; 11:713.
82. Osgood RB: Lesions of the tibial tubercle occurring during adolescence. *Boston Med J* 1903; 148:114.
83. Peck DM: Apophyseal injuries in the young athlete. *Am Fam Physician* 1995; 51:1891.
84. Blankstein A, et al: Ultrasonography as a diagnostic modality in Osgood-Schlatter disease: A clinical study and review of the literature. *Arch Orthop Trauma Surg* 2001; 121:536.
85. Sever JW: Apophysitis of the os calcis. *N Y Med J* 1912; 95:1025.
86. Ogden JA, Ganey TM, Hill JD, Jaakkola JI: Sever's injury: A stress fracture of the immature calcaneal metaphysis. *J Pediatr Orthop* 2004; 24:488.
87. Committee on Sports Medicine and Fitness, American Academy of Pediatrics: Risk of injury from baseball and softball in children. *Pediatrics* 2001; 107:782.
88. USA Baseball Medical and Safety Advisory Committee: *Position Statement on Youth Baseball Pitching Injury: 2004*. Available at www.usabaseball.com/ot/usab-med-safety-list.html. Accessed February 2008.
89. Lazovic D, et al: Ultrasound for the diagnosis of apophyseal injuries. *Knee Surg Sports Traumatol Arthrosc* 1996; 3:234.
90. Bennet JB, Tullos HS: *Ligamentous and articular injuries in the athlete*. In: Morrey BF, ed: *The Elbow and Its Disorders*. Philadelphia: WB Saunders; 1985.

www.ketabpezeshki.com 66485457-66963820

Section Two
THE PREGNANT PATIENT

Chapter 177
General Approach to the Pregnant Patient

Laurie J. Morrison, Alina Toma, and Sara H. Gray

PERSPECTIVE

Remarkable trends in the epidemiology of fertility have emerged that may have an impact on the demographic and diagnostic profile of patients encountered in today's emergency department (ED). The birth rates and fertility rates for all races and the mean age at menarche in both the United States and Canada have fallen during the past decade. The age-specific fertility rate has declined in women younger than 30 years, and the rate of multiple births is rising.

The 2008 report from the U.S. National Center for Health Statistics noted that the birth rate for women younger than 25 years, the principal childbearing age, had fallen from 43% in 1990 to 34.4% in 2009.[1] The overall birth rate for teens aged 15 to 19 years dropped from 15% in 1990 to 10% in 2009,[1] which resulted in a historic low of 66.7 pregnancies per 1000 women.[2] Nearly half of all pregnancies in the United States occur among unmarried women, and this number is rising, increasing from 2.7 million in 1990 to 2.8 million in 2004, whereas rates among married women continue to fall, from 4.1 million in 1990 to 3.5 million in 2004 (newer data do not exist at the time of publication). Pregnancy outcomes in the United States vary across the black, Hispanic, and white populations. The rate of pregnancies resulting in live births is highest in Hispanic women (98%) compared with non-Hispanic whites (69%) and non-Hispanic blacks (50%), whereas the rate of pregnancy resulting in abortion is highest in non-Hispanic blacks (37%) compared with non-Hispanic whites (12%) and Hispanic women (19%).[1] The median age at menarche for adolescent American girls fell from 15.5 years in 1900 to 12.3 years in 2000[3] (Fig. 177-1).

From 1980 to 2008, the number of twin births in the United States rose more than 100% (from 68,339 to 138,660), and triplet and higher order births rose just less than 400% (from 1377 to 6268 births).[2] At the same time, differences in twin birth rates between non-Hispanic white and non-Hispanic black mothers disappeared. Non-Hispanic white women were more than twice as likely as non-Hispanic black or Hispanic women to have a triplet birth.[2]

Maternal mortality related to complications of pregnancy and childbirth in the United States has slowly been declining during the past several years from 2960 maternal deaths in 1950 to 548 deaths in 2007.[4] The highest number of deaths is attributed to women older than 35 years, with 32 deaths per 100,000 live births, which is four times the rate for women 29 years of age and younger.[2] The most common causes of death are pulmonary embolism, diseases of the circulatory system, and postpartum hemorrhage.[5]

Rates of elective cesarean deliveries in industrialized countries are continuing to rise secondary to a common perception of safety and potential benefits of elective low-risk cesarean delivery compared with vaginal delivery. In Canada, the rate of planned cesarean deliveries has increased to 26% in 2003 compared with 5% in 1969.[4] A retrospective cohort study, which evaluated more than 2.3 million healthy pregnant patients, demonstrated a composite severe morbidity of 27 per 1000 deliveries for planned cesarean delivery for breech presentation versus 9 per 1000 deliveries for planned vaginal delivery for any reason, respectively.[4] Furthermore, although the study showed an increased risk of maternal cardiac arrest of 2% in the planned cesarean delivery group and 0.4% in the vaginal delivery group, the difference in the rate of in-hospital maternal death was nonsignificant ($P = .87$). Decisions about planned cesarean sections for other than conventional indications require a discussion of the risks and benefits of this intervention.

Statistical data concerning pregnant patient demographics and frequency of use of the ED and the diagnostic profile are incomplete because most observational data sets group perinatal and pregnancy as "other medical diagnosis," which accounts for less than 2% of visits to the ED in the United States and Canada[5]; however, persons between the ages of 18 and 44 years account for approximately 22% of all ED visits, so the risk of an unknown pregnancy complicating the diagnosis may be higher than anticipated.[6] A study of random pregnancy tests performed on female trauma patients revealed that 2% were pregnant.[7,8] Even when the chance of pregnancy was remote, female patients seeking treatment in the ED had a pregnancy rate of at least 10%.[7]

Maternal cardiac arrest is rare, although recent data from the Confidential Enquiries into Maternal and Child Health data set show a maternal cardiac arrest frequency that is on the rise with a current rate of 1:20,000 pregnancies, up from the previous rate of 1:30,000.[9]

Pregnant patients may present with symptoms and signs related to an undiagnosed, normal pregnancy (abdominal discomfort, nausea, urinary frequency, breast swelling and tenderness, fatigue, or near-syncope), symptoms and signs related to complications of pregnancy (see Chapter 178), or clinical manifestations of chronic medical illnesses that may be exacerbated by pregnancy (see Chapter 179). This chapter covers the following aspects of a normal pregnancy: common initial signs and symptoms, diagnostic tests, and considerations for treatment and referral.

Definitions

Gravidity refers to the number of pregnancies that the patient has had. This number includes all normal and abnormal pregnancies, including the current one.

Parity is the total number of times that the patient has given birth, regardless of outcome. Multiple births are counted

www.ketabpezeshki.com 66485457-66963820

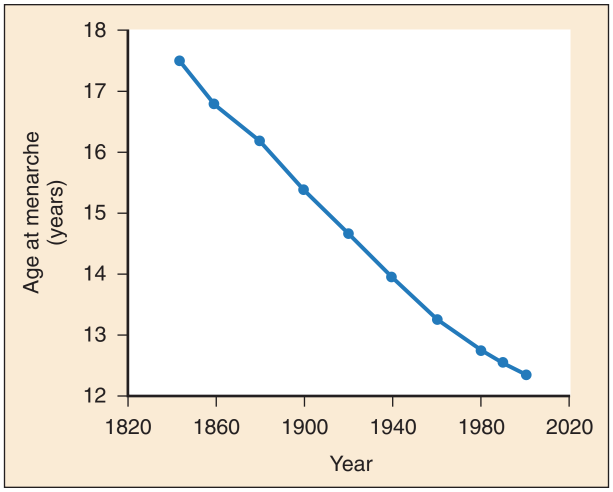


Figure 177-1. Age at menarche among European girls during the past 150 years. (Modified from Tanner JM: Growth at Adolescence. Oxford, Blackwell, 1962; Cunningham FG, et al: Williams Obstetrics, 19th ed. Norwalk, Conn, Appleton & Lange, 1993; and MacDonald PC, et al: Recurrent secretion of progesterone in large amounts: An endocrine/metabolic disorder unique to young women? Endocr Rev 12:372, 1991.)

individually for the purpose of calculating parity. *Grand multiparity* refers to a woman who has had five or more births. Parity can be divided into four distinct categories; they usually are written on the chart parenthetically, adjacent to the parity level, and separated by hyphens. The four categories are identified by the letters T-P-A-L and refer to numbers of term infants, preterm infants, abortions, and children currently living (e.g., G10 P9 [6-1-2-7]).

Gestational age refers to the number of completed weeks of pregnancy from the last menstrual period. A *term infant* is a child born between 38 and 42 completed weeks of gestation, a *preterm infant* is born before 38 completed weeks of gestation, and a *postterm infant* is born any time after 42 weeks of gestation. The conceptus is considered an *embryo* from conception until after the eighth week, when it is termed a *fetus*. An *abortus* is a fetus or embryo removed or expelled from the uterus during the first half of gestation (20 weeks or earlier) and that weighs less than 500 g or measures less than 25 cm. *Premature* labor occurs before 37 weeks of gestation, and *postmature* labor occurs beyond 42 or 43 weeks of gestation.

CLINICAL FEATURES

History

It is prudent practice to suspect pregnancy in all female patients of childbearing age presenting to the ED. Cyclic ovulation occurs on average for 38 years. Of a possible 10,000 ovarian follicles, 500 achieve ovulation. Thus there are 500 opportunities for pregnancy which likely can be achieved by sexual intercourse on any one of 1500 days. Physicians of all specialties must be constantly vigilant and sensitive to the possibility that women of reproductive age may be pregnant irrespective of their presenting complaint.

The reliability of the sexual and menstrual history has been notably poor. Ramoska and colleagues reported that 11.5% of women with abdominal pain or vaginal bleeding had positive pregnancy test results, in contrast to their perception that there was "no chance" they were pregnant.[7] Missed diagnosis of pregnancy in adolescents was associated with failure to document a sexual or menstrual history. Adolescents rarely mentioned the possibility of pregnancy at triage (10% of those found to be pregnant), and 10% of those with a positive pregnancy test result denied being sexually active.[10] Interestingly, pregnancy rates in adolescents continue to rise in the United States, with estimates of 42.5 per 1000 women of this age group, and have increased 5% from 2005-2007 data.[1] Thus one should have a high index of suspicion of pregnancy in adolescents who present with symptoms of pregnancy, which include cessation of menses, anorexia, nausea, easy fatigability, urinary frequency, breast swelling and tenderness, and perception of fetal movement or "quickening" (beginning at 16 to 20 weeks).

Cessation of menses becomes suggestive of pregnancy at 10 days or longer after the time that menstruation is expected. Intermittent, spontaneous vaginal bleeding or vaginal discharge is common during the first half of pregnancy, particularly in multiparous women. Most women without cervical lesions experience bleeding on or before the 40th day of pregnancy. This bleeding has been interpreted by some investigators to be physiologic in origin and a result of implantation.[11] Nevertheless, any patient presenting with vaginal bleeding during pregnancy should be considered to be at risk for a pathologic cause of the bleeding.

It is possible to calculate the estimated date of delivery in a regularly menstruating woman who has 28-day cycles and can give a reliable history. Franz K. Nägele, a German obstetrician in the 18th century, developed Nägele's rule, which is still the current standard: add 7 days to the date of the first day of the last menstrual period and subtract 3 months. Currently, with the increasing use of smart phones, hand-held devices, and the Internet, literally hundreds of calculators are available to clinicians to aid in the estimation of delivery date. In the absence of reliable recall of the first day of the last menstrual period, first-trimester ultrasonography may estimate the date of delivery. Ultrasonography dating is most accurate if it is done between 10 and 12 weeks.[12]

Physical Examination

During the last half of pregnancy, the physical examination should be done with the patient in the left lateral recumbent position to avoid precipitation of the supine hypotension syndrome.

Vital signs in a pregnant patient are essentially the same as those in a nonpregnant patient. The only changes are seen in the heart rate and blood pressure. The resting heart rate increases approximately 10 to 15 beats/minute, and blood pressure demonstrates a mean arterial decrease of 6 to 10 mm Hg, which reaches a nadir in mid–second trimester and slowly increases to the patient's nonpregnant value by term. Blood pressure in the brachial artery is highest in the sitting position, lowest when lying in the left lateral position, and intermediate in the supine position, except in pregnant women who have supine hypotension syndrome. Pathologic hypertension of pregnancy is defined as a sustained rise of 30 mm Hg systolic or 15 mm Hg diastolic above baseline values on at least two occasions, 6 hours or more apart. A study demonstrated a steady increase in prevalence of hypertension in pregnant women from 67 per 1000 pregnant patients in 1998 to 83 per 1000 patients in 2006. The highest risk cohort is women older than 35 years, with a reported rate of 89 per 1000 patients.[13] The authors concluded that hypertension and related illnesses are major risk factors for severe obstetric morbidity. Furthermore, as more women have children later in life, in addition to the increasing prevalence of obesity, the number of patients with hypertension-related illness due to pregnancy will most likely continue to rise.[13]

Fetal heart activity should be included as the fifth vital sign in the evaluation of a pregnant patient. It can be auscultated with a stethoscope at 17 weeks of gestation on average and by 19 weeks in nearly all pregnancies in nonobese women. With the use of Doppler ultrasonography, fetal cardiac activity can be detected as early as 8 weeks; however, it is more commonly heard by 10 weeks.

www.ketabpezeshki.com 66485457-66963820

With improved transvaginal ultrasonography technology, it has been possible to detect fetal cardiac activity in embryos as small as 6 mm.[14]

Auscultation of the pregnant abdomen reveals numerous findings that may be confusing. In addition to fetal heart sounds, it may be possible to identify sounds of fetal movement, the maternal pulse, maternal bowel sounds, and the fundic and uterine souffle. The fundic or umbilical cord souffle is created by blood rushing through the umbilical arteries. The resultant whistling sound is timed with the fetal pulse and is present in 15% of pregnancies. The uterine souffle is a soft blowing sound timed with the maternal pulse, usually heard in the lower portion of the uterus. It is a function of blood flow through the dilated uterine vessels and can be heard in pregnancy and in women with uterine myomas or large tumors of the ovaries.

Breast tenderness and fullness are common manifestations of pregnancy that can be appreciated on gentle physical examination. Objective breast changes include darkening of the areolae, greater prominence of the glands of Montgomery around the nipple, engorgement of the breasts with tiny bluish venules, and presence of colostrum at the nipple with gentle massage of the breasts. This milky material may persist for months or even years, especially if the patient continues to breast-feed.

Increased skin pigmentation (melasma gravidarum) and abdominal striae occur not only in pregnancy but also in women who ingest estrogen-progestin contraceptives.

Braxton-Hicks contractions are painless contractions that begin in early pregnancy and occur spontaneously and irregularly throughout the pregnancy. They also occur in patients with hematometra and those with uterine myomas. These contractions are not reliable for the diagnosis of pregnancy; however, they do not occur in ectopic pregnancy.

Uterine enlargement can be felt in nonobese women. At 6 to 8 weeks, the uterus is approximately the size of an orange. At 12 weeks, the top of the fundus should be at the level of the symphysis pubis; at 16 to 20 weeks, at the level of the umbilicus; and at 36 to 38 weeks, at the level of the xiphoid process of the sternum. Thereafter, the fetus descends into the pelvis, and fundal height may decrease accordingly.

Hegar's sign, which is softening of the lower uterine segment caused by hyperemia, can be appreciated during an internal pelvic examination at approximately 6 to 8 weeks of pregnancy. In some cases the softening is sufficient to allow the examiner to easily distinguish the cervix from the fundus on palpation. It can be found in other conditions, but it is not as easily detected as it is in pregnancy (Fig. 177-2).

The vaginal mucosa becomes hyperemic during pregnancy and with any other condition that causes congestion of the pelvic organs. In response, the color of the mucosa of the vaginal walls changes from pink to blue to violet and can be visualized at the vaginal introitus (Chadwick's sign).[15]

At midpregnancy the fetus can be detected by ballottement or palpated through the maternal abdominal wall in a nonobese patient. The fetus floats in a large volume of amniotic fluid. Thus, with ballottement, pressure exerted on the uterus causes the fetus to sink and then to rebound to its original position. Palpation of the outline of the fetal body becomes easier near the end of pregnancy; however, subserosal myomas can simulate the fetal head and small parts, or both.[10]

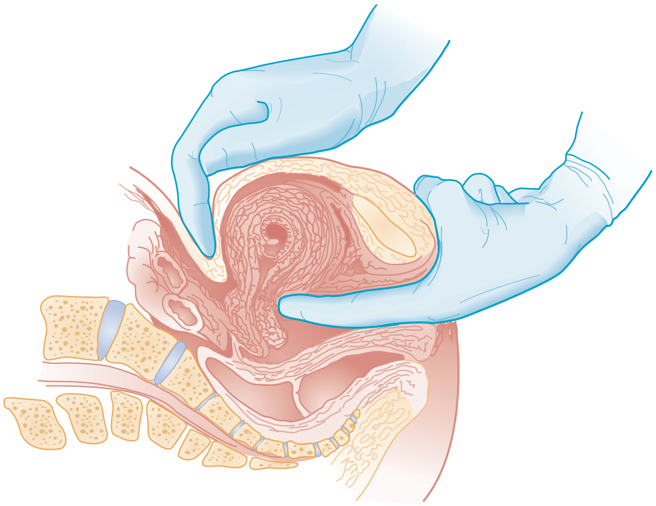


Figure 177-2. Hegar's sign. The softness and compressibility of the lower uterine segment can be so extreme that the fundus and cervix may even feel like separate organs. (Modified from Willson JR, et al: Obstetrics and Gynecology, 5th ed. St Louis, CV Mosby, 1975.)

DIAGNOSTIC STRATEGIES

Laboratory Tests

Determination of the urine or serum level of human chorionic gonadotropin (hCG) is important in clinical management. Applications include diagnosis and monitoring of pregnancy and diagnosis and evaluation of the course of neoplastic trophoblastic disease or response to treatment (i.e., hydatidiform choriocarcinoma, gonadal teratoma, a carcinoma with ectopic secretion of hCG).

The hCG assays are referenced to standard hCG preparations. Thus the reference standard should always be noted in comparison of results. One nanogram of hCG equals 9.3 mIU of the international reference standard provided by the World Health Organization (used in this chapter) and equals 5.0 mIU of the second international standard.

Biologic assays for hCG are now only of historical interest. Since the 1960s, all hCG assays have been immunoassays. Enzyme-linked immunosorbent assay (ELISA) for hCG is the state-of-the-art pregnancy test. It offers greater user convenience and has a sensitivity for levels of hCG between 25 and 50 mIU/mL.

The pregnancy test has undergone a number of refinements over the years. Antibodies are selected that act against the purified beta subunit of hCG, and this modification has resulted in improved sensitivity for low levels of hCG in the presence of luteinizing hormone. The development of monoclonal antibodies has improved specificity for the purified beta subunit of hCG.

The fundamental process of ELISA involves an antibody adherent to a solid-faced support (usually plastic) that binds to a region of the hCG molecule. A second antibody chemically linked to an enzyme (e.g., alkaline phosphatase) binds to another side of the trapped hCG molecule. The hCG molecule is sandwiched between the two antibodies. Excess enzyme-linked antibody is washed away, and a color developer is added and becomes blue when it comes in contact with the enzyme (Fig. 177-3). The antibodies can be polyclonal or monoclonal. Many variations exist with respect to the solid-faced support and the method of developing the color reaction.

In 1988 the first one-step pregnancy test became available. It was developed and patented by Unipath and sold as Clearblue One Step. This test uses monoclonal antibodies specific for the beta subunit of hCG. It includes a unique built-in control that shows a blue line when the test is complete and performed correctly.[16] This test appeals to consumers because it is rapid (requiring less than 5 minutes), requires no manipulation by the user, offers hygienic sample handling, provides clear and easy-to-read results, and has a sensitivity level of hCG between 25 and 50 mIU/mL. This level of sensitivity means that more than 95% of pregnancies

www.ketabpezeshki.com 66485457-66963820

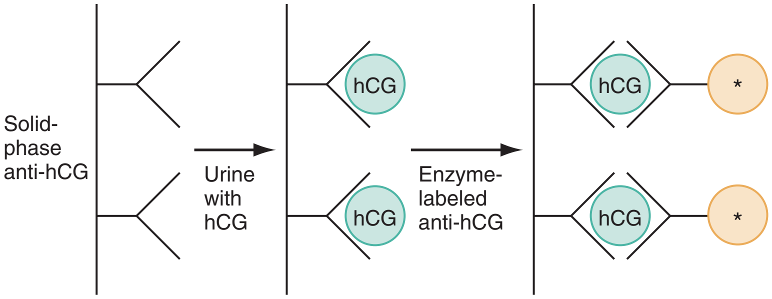


Figure 177-3. The principle of enzyme immunoassay (also sometimes known as sandwich or immunometric assay). *hCG,* human chorionic gonadotropin. (Modified from Chard T: Pregnancy tests: A review. Hum Reprod 7:701, 1992.)

within 3 days after missed menses will be detected by a home pregnancy device.[17] For detection to occur on the day of missed menses, a lower sensitivity level of 12.5 mIU/mL is required. A study in 2001 compared routine urinary hCG point-of-care qualitative tests performed by nurses in the ED with laboratory tests and found the former to be equally accurate and much faster, shaving 35 minutes off wait times for results.[18]

A well-designed ELISA applied to urine is not affected by drugs or a concurrent physiologic state. The only exception is patients taking exogenous hCG for induction of ovulation.[19]

Normal hCG levels in men and premenopausal women range from 0.02 to 0.8 mIU/mL. Postmenopausal women may have higher levels.[20] The blastocyst begins to secrete hCG 7 days after fertilization.[21] Thus the hCG released can be detected as early as 6 to 8 days after conception.[22]

The initial doubling time is fast and has been attributed to the actual process of implantation. This is followed by a slower rate of doubling as trophoblast hCG and maternal circulatory hCG levels equilibrate[22] (Fig. 177-4). Levels of hCG peak at 7 to 10 weeks of pregnancy, with a mean value of 50,000 mIU/mL and a range of 20,000 to 200,000 mIU/mL.[21]

The test results for hCG become positive in 98% of patients 7 days after implantation, which coincides with the time of the expected period. When a test with a sensitivity of 25 to 50 mIU/mL is used, a negative result 1 week from the expected time of the missed period essentially guarantees that a woman is not pregnant.[19]

False-positive results can be attributed to postmenopausal status, abortion in the first trimester, exogenous hCG for induction of ovulation, or hCG-secreting tumor. Levels of hCG may take as long as 60 days to return to zero after an abortion.[23] Failure to decline during 60 days and persistent elevation of hCG beyond 60 days after abortion may indicate an incomplete abortion, a twin pregnancy with only one fetus removed, or an ectopic pregnancy.[1]

The hCG assay continues to be the standard for the diagnosis of pregnancy. Routine clinical detection of pregnancy by ultrasonography is not possible until at least 5 weeks' gestation, when the hCG level is 1000 mIU/mL or more.[24-26]

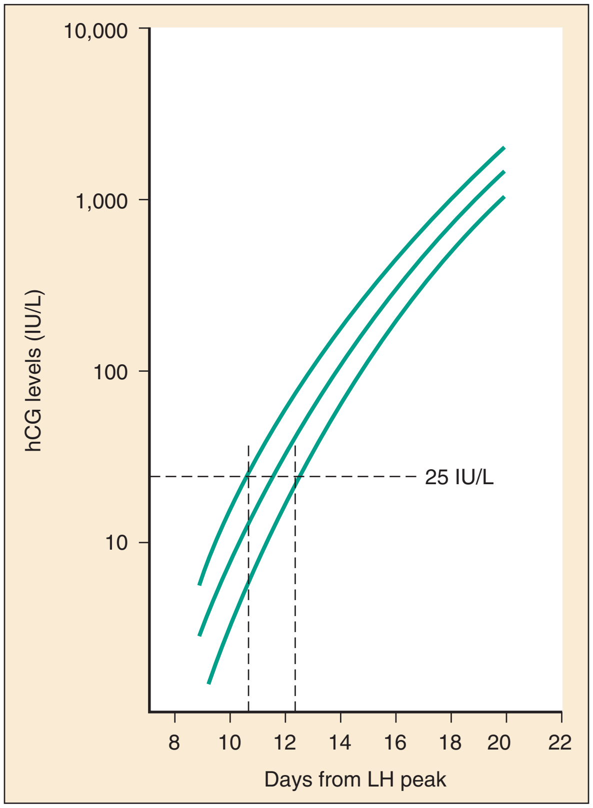


Figure 177-4. Levels of circulating human chorionic gonadotropin (*hCG*) in early pregnancy, showing that an assay with a sensitivity level of 25 mIU/mL would yield a positive result in some subjects between 10 and 11 days after the peak in luteinizing hormone (*LH*) and in most subjects at 12 to 13 days after the peak. (Modified from Chard T: Pregnancy tests: A review. Hum Reprod 7:701, 1992.)

Radiology

Ultrasonography

Ultrasonography is reliable for the diagnosis of intrauterine pregnancy during the first trimester. Systematic reviews demonstrate that ultrasonography scans performed in the ED have a sensitivity of 90% and specificity of 98% in the detection of an intrauterine pregnancy.[27] In addition to diagnosis, it also locates the embryo and assesses gestational age and viability. Transabdominal sonography is more commonly used; however, transvaginal sonography may be necessary during the first trimester if transabdominal sonography is not diagnostic.

Sonography during the second trimester is used to survey fetal anatomy. The anatomic survey includes the cerebral ventricles, four-chamber view of the heart, spine, stomach, urinary bladder, umbilical cord insertion on the abdominal wall, and kidneys.[28]

Much debate exists about whether ultrasonography should be performed as part of routine prenatal screening in all pregnancies. The American College of Obstetricians and Gynecologists (ACOG) recommends that all physicians discuss the benefits and limitations of ultrasonography with patients and come to a decision together about the screening examination.[28] Although prenatal screening is still an object of contention, the ACOG states that there is good evidence for the safety and accuracy of

www.ketabpezeshki.com 66485457-66963820

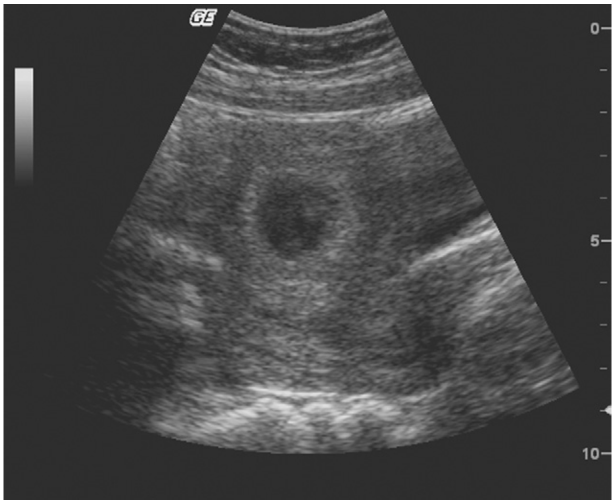


Figure 177-5. Transabdominal ultrasonography image showing a gestational sac with no fetal pole or yolk sac. (Courtesy Andrew A. Common, MD.)

ultrasonography examination to determine gestational age, major fetal anomalies, fetal number, viability, and placental location and recommends the test if these areas are in question.[28] First-trimester ultrasonography, in conjunction with biochemical parameters, is an integral part of first-trimester genetic screening for aneuploidy and is usually performed at 11 to 13 weeks of age.

Transabdominal Sonography. At 6 weeks the gestational sac can be visualized by transabdominal sonography (Fig. 177-5). This sonographic finding disappears after the 11th week of gestation. Presence of the gestational sac is confirmed when two central uterine echoes are visualized within the hypertrophied endometrium. This diagnostic echo is called the double ring sign. The gestational sac is eccentrically positioned within an asymmetrically thickened decidua. A healthy pregnancy can be determined by correlating the size of the sac with gestational age and quantitative hCG values. At 8 weeks the fetal pole and fetal heart activity can be visualized reliably with transabdominal ultrasonography in a normal pregnancy. Diagnosis of an intrauterine pregnancy with ultrasonography can be made with the following findings: yolk sac or fetal pole visualized inside myometrium, bladder-uterine juxtaposition confirmed, and myometrial mantle of 5 mm[29] (Fig. 177-6). Diagnosis of a live intrauterine pregnancy also requires visualization of intrauterine fetal heart activity.

Transvaginal Sonography. Transvaginal sonography affords greater resolution than transabdominal sonography and does not require a full bladder. Transvaginal ultrasonography examination can identify an intrauterine gestational yolk sac at 4 to 5 weeks' gestation. Fetal heart motion can be detected with transvaginal ultrasonography evaluation at 6 weeks' gestation.

An intrauterine pregnancy can be diagnosed by sonographic findings in the following order of appearance: the double ring sign, the double gestational sac, the intrauterine fetal pole, and intrauterine fetal heart activity (see Fig. 177-6).

Magnetic Resonance Imaging

No significant side effects have been documented to date with the magnetic field and radio waves used in magnetic resonance imaging (MRI). Gadolinium is the most common intravenous contrast agent, and allergic reactions with this agent are rare. Currently, the ACOG recommends that nonionizing imaging procedures like MRI and ultrasonography be used preferentially, when appropriate, and they are not known to be associated with adverse fetal effects.[30]

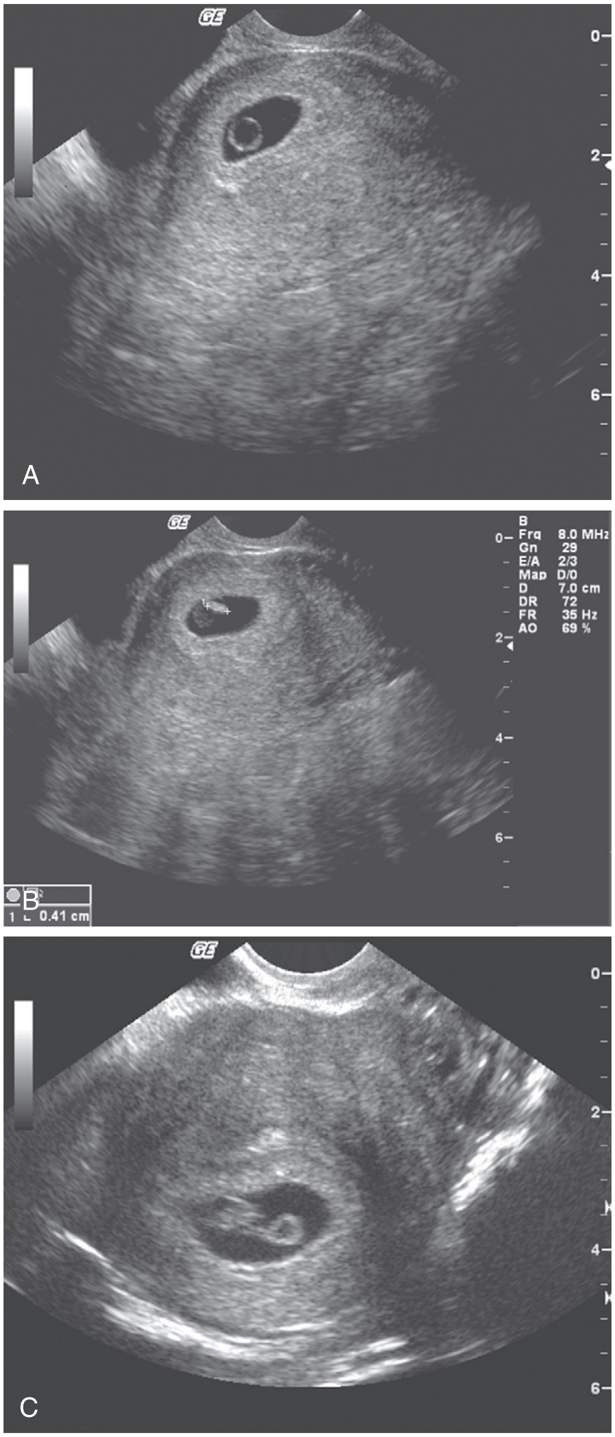


Figure 177-6. Transvaginal ultrasonography images. **A,** Yolk sac. **B,** Fetal pole. **C,** Fetal pole, vitelline duct, and yolk sac. (Courtesy Andrew A. Common, MD, and Derek Muradali, MD.)

Plain Radiographic Fetal Identification

The fetus can be reliably recognized by plain radiography after 16 weeks' gestation. Fetal foci of ossification can be identified as early as 14 weeks.

Diagnostic Imaging Considerations in Pregnant Patients

The decision to perform imaging investigations in a pregnant patient must take into consideration the risk to the developing

www.ketabpezeshki.com 66485457-66963820

fetus from radiation exposure and the inherent risks with such investigations for the mother, balanced with the risk to the mother and fetus associated with missing the diagnosis because of reluctance to use available diagnostic imaging techniques. The potential for adverse outcomes with intrauterine fetal exposure to the radiation used in radiography is minimal.[31] Case-control studies report a slight but statistically significant increase in the relative risk for childhood cancer.[32] Radiation is a dose-dependent teratogen.[33] The fetal central nervous system is most vulnerable to the teratogenic effects of radiation at 8 to 15 weeks after conception. The fetal dose of radiation is estimated from the ovarian or uterine dose. Pregnant women exposed to less than 50 mGy have pregnancy outcomes similar to those of control subjects.[34] A study of childhood cancers in the offspring of female radiologists revealed a cancer frequency of 0.16% in children exposed to 10 mGy of radiation in utero. In comparison, the frequency of cancer is 0.07% among children who were not exposed to radiation in utero.

Table 177-1 summarizes the estimated fetal radiation exposure associated with the more common diagnostic imaging modalities. Radiation exposure depends on the equipment and technique, and estimates listed may not be generalizable to every radiology department.

A thoughtful, common-sense approach to the differential diagnosis will provide a sound basis for imaging investigations that will undoubtedly be in the best interests of the mother and the fetus. It is important not to defer investigations that are medically necessary, so long as the anticipated fetal doses are less than 50 mGy.[35]

Table 177-1 Fetal Radiation Exposure with Various Imaging Modalities

PROCEDURE	ESTIMATED FETAL RADIATION EXPOSURE (μGy)
Chest plain film with an abdominal shield	10*
Chest CT with an abdominal shield	100*
Abdomen plain film	2400*
Abdomen CT: with and without contrast agent	20,000 and 10,000*
Cardiac catheterization: with and without pelvic fluoroscopy	13,000 and 1000*
Head CT	100*
Unilateral venography without an abdominal shield	3050
Limited venography with an abdominal shield	500
Pulmonary angiography via femoral access	4050
Pulmonary angiography via brachial access with an abdominal shield	500
Perfusion lung scan using ^{99m}Tc-MAA	
3 mCi	180
1-2 mCi	60-120
Ventilation lung scan using	
^{133}Xe	30-200
^{99m}Tc-DTPA	70-350
^{99m}Tc-SC	10-50
Ventilation-perfusion scan	500

Modified from Ginsberg JS, et al: Thrombotic complications in the obstetric patient. In Coleman RW, et al (eds): Hemostasis and Thrombosis: Basic Principles and Clinical Practice, 3rd ed. Philadelphia, JB Lippincott, 1994.
CT, computed tomography; *DTPA,* diethylenetriaminepentaacetic acid; *MAA,* microaggregated albumin; *SC,* sulfur colloid.
*Data from Duke University and Duke Medicine Radiation Safety Division: Fetal radiation dose estimates. Available at www.safety.duke.edu/radsafety/fdose/fdxray.asp. Accessed March 12, 2011.

DIFFERENTIAL CONSIDERATIONS

Considerations in the differential diagnosis with early pregnancy include myomas, hematometra, adenomyosis, and extrauterine mass or masses. Patients with these diagnoses, excluding hematometra (a blood collection or retention in the uterus), typically have persistent regular menses. The enlarged uterus in these nonpregnant conditions generally is firmer and less elastic and boggy than it is in pregnancy.

Spurious pregnancy is imaginary pregnancy or pseudocyesis (false phantom). It usually occurs in women nearing menopause or in women who have an overwhelming desire for pregnancy. The associated increase in abdominal girth generally is attributable to fat deposition, fluid accumulation, or intestinal gas. The menses may become unpredictable with respect to timing, duration, and amount of flow. This condition can be associated with changes in the breasts, including enlargement, galactorrhea, and increased areolar pigmentation. Patients may have morning sickness of psychogenic origin. The associated use of phenothiazines may cause amenorrhea, hyperprolactinemia, breast enlargement, and galactorrhea. Women with this condition may perceive fetal movements. Most commonly these movements can be attributed to muscle contractions of the abdominal wall and normal gastrointestinal peristalsis.

The diagnosis is confirmed by the presence of a small uterus and a negative pregnancy test result. The challenge in this condition is to convince the affected woman of the lack of pregnancy and to address the underlying reason for the delusion.

SPECIFIC DISORDERS

Perspective

In general, a pregnant patient should be treated and assessed in the same way as all other patients are. However, the normal physiologic changes of pregnancy may mask or unmask underlying medical conditions. Thus it is important to ascertain whether the presenting complaint is due to the pregnancy, an unrelated problem that is affected by the pregnancy, or a problem that affects the pregnancy.[36] In addition, consideration should be given to the increased medical risks of pregnancy (e.g., deep venous thrombosis) and risk to the fetus associated with diagnostic imaging or surgical interventions.

Headache

The most common headache during pregnancy is a muscle contraction headache.[37] The patient usually has had a history of headaches before the pregnancy. The headaches begin on waking and increase in intensity during the day. The headache is described as a broad band, squeezing or constricting in quality, and localized to the vertex. The paracervical muscles are taut, and palpation usually reproduces or exacerbates the pain. During pregnancy these headaches are worsened by postural changes and psychosocial stress. Commonly used abortive medications for migraines in pregnancy include acetaminophen (e.g., Tylenol), aspirin, opioids, triptans, antiemetics, and caffeine.[37] From 18 to 86% of classic migraine sufferers experience remission from attacks during pregnancy, particularly women with menstrual migraines.[37,38] Therefore, any headache in a pregnant patient requires investigation, except a typical headache in a patient with a known primary headache disorder.[37,39]

www.ketabpezeshki.com 66485457-66963820

Brain tumors enlarge during pregnancy and shrink temporarily postpartum.[40] Most brain tumors become symptomatic during the second half of pregnancy, and they account for 10% of maternal deaths during pregnancy. Both pituitary gland and prolactin-secreting adenomas swell during pregnancy. Headache usually develops during the first trimester and precedes visual changes by approximately 1 month.[40] On occasion, central venous thrombosis may occur during pregnancy and mimic eclampsia. The lack of proteinuria and hypertension points to central venous thrombosis.[37] Central venous thrombosis is an unusual cause of postpartum headache that is associated with a mortality rate of 40%.[37]

Pseudotumor cerebri is benign intracranial hypertension in the absence of a mass lesion and hydrocephalus. Symptoms and signs often include headache and papilledema. Other associated findings include decreased visual acuity, loss of color vision, defects in visual fields, and horizontal diplopia caused by abducens nerve palsy. Pseudotumor cerebri associated with pregnancy usually occurs in obese women and begins during the third to fifth months of pregnancy. Symptoms resolve spontaneously after 1 to 3 months.[41]

Spontaneous subarachnoid hemorrhage accounts for 10% of maternal deaths. Reviews of the risk for subarachnoid hemorrhage in pregnant versus nonpregnant patients have been conflicting. The absolute risk has been estimated to be 1 in 2000 to 10,000. In a majority of cases, the intracranial bleeding is attributable to rupture of an arteriovenous malformation or a ruptured intracranial aneurysm. The overall risk for rupture of an arteriovenous malformation is identical in pregnant and nonpregnant patients without previous bleeding.[42] Arteriovenous malformations usually bleed during the second trimester and during labor. Berry aneurysms typically bleed during the third trimester, and the incidence of bleeding increases as the pregnancy advances.

Nearly one third of cases of subarachnoid hemorrhage are a result of bleeding disorders, bacterial endocarditis, metastatic tumor, and sickle cell disease. Cerebral hemorrhage is the most common cause of death in toxemia. It occurs in 60% of patients who die after becoming eclamptic.

New-onset headache or a change in the usual pattern of headache pain during pregnancy or the postpartum period warrants a closer look. A thorough history and a detailed physical examination with emphasis on visual field and funduscopic examination can, in most cases, exclude the aforementioned serious disorders.

Chest Pain

The diagnosis of cardiac disease is complicated by the fact that the signs and symptoms of a normal pregnancy are suggestive of heart disease. Pregnancy is associated with easy fatigability, dyspnea, orthopnea, palpitations, syncope, peripheral edema, chest discomfort, and reflux. Triggers for further cardiac evaluation include progressive orthopnea, dyspnea severe enough to limit activity, paroxysmal nocturnal dyspnea, syncope during or immediately after exertion, hemoptysis, and chest pain in an ischemic distribution at rest or associated with exertion, anxiety, or anger.

Cardiovascular findings are altered in normal pregnancy. Peripheral edema is present in 80% of pregnant women. A third heart sound and systolic murmurs are common. Diastolic murmurs and systolic murmurs of grade higher than 2/6 warrant investigation. Other worrisome signs include cyanosis, clubbing, pulmonary rales, distended neck veins throughout the cardiac cycle associated with hepatomegaly and peripheral edema, persistent split S_2, and criteria of pulmonary hypertension (left parasternal lift and a loud P_2).

The pregnant patient is predisposed to thromboembolic disease as a result of increased venous pressure, decreased distal venous flow, and significant venous stasis from compression of the pelvic veins and inferior vena cava by the enlarging uterus. Other predisposing factors may include the use of oral contraceptives before conception and the propensity for stasis secondary to lack of activity in the workplace and at home as the pregnancy progresses. The annual incidence of thromboembolism is five times higher in postpartum women than in pregnant women.[43] The incidence of deep venous thrombosis is three times higher than that of pulmonary embolism; however, the incidence of deep venous thrombosis during pregnancy has remained constant during the last 30 years, whereas that of pulmonary embolism during pregnancy doubled.[43] This increased risk for pulmonary embolism in pregnancy should prompt thorough evaluation of pregnant patients who present with pleuritic chest pain, syncope, acute right-sided heart failure, or more subtle signs, such as unexplained fever, dyspnea, or tachycardia.

Abdominal Pain

Displacement of the abdominal contents by the expanding uterus during pregnancy causes abdominal discomfort that may be associated with nausea, vomiting, gastroesophageal reflux, delayed gastric emptying, bowel irregularity, urinary frequency, and back and buttock pain. These findings may complicate the clinical assessment of a pregnant woman with abdominal pain. Delay in diagnosis or failure to diagnose and to treat underlying pathologic conditions may result in maternal and fetal morbidity and death.

Obstetric causes of abdominal pain early in pregnancy include vascular congestion of the pelvic tissues, round ligament tension, ectopic pregnancy, and threatened abortion. With increasing rates of infertility and use of fertility-enhancing drugs, there has been a corresponding increased incidence of women with ovarian hyperstimulation syndrome (OHSS). OHSS is an iatrogenic syndrome characterized by ovarian enlargement (from multiple ovarian cysts) and fluid shifts to the extravascular space, causing ascites, hypovolemia, and electrolyte abnormalities. Studies have suggested that in vitro fertilization treatments have been associated with up to 33% of mild forms of OHSS and 3 to 8% of severe cases.[44] Severe forms of OHSS require urgent diagnosis and treatment to mitigate the high risk of associated thromboembolic events, respiratory failure, and renal failure.

Later in pregnancy, considerations in the obstetric differential diagnosis should include Braxton-Hicks contractions, toxemia, premature labor, abruptio placentae, and rupture of the uterus. Nonobstetric causes include all diagnoses seen in a nonpregnant patient (e.g., cholecystitis, pyelonephritis, renal colic, ovarian torsion, salpingitis, corpus luteum cyst rupture or torsion, degeneration of a uterine myoma). Common surgical diseases that may complicate pregnancy include appendicitis, gallbladder disease, and intestinal obstruction.

Appendicitis is the most common surgical emergency in pregnancy.[45,46] The incidence ranges from 0.06 to 0.1%, or 1 in 1500 deliveries. Although the incidence is relatively close to that of nonpregnant patients, the perforation rate is higher during pregnancy.[46-48] The state of pregnancy results in delays in diagnosis of appendicitis that contribute significantly to maternal and fetal morbidity and mortality.[48] The perinatal mortality rate for women with nonperforated appendicitis is 4.8%. It rises, however, to 27.8% in those experiencing perforation at the time of surgery. The perforation rate is as high as 30% during the third trimester.[48]

The diagnosis of appendicitis is more difficult during the latter half of pregnancy, but it is challenging even in early pregnancy. Anorexia, nausea, and vomiting are symptomatic of appendicitis and may be misinterpreted as hyperemesis of pregnancy. As the uterus enlarges, the appendix moves upward and outward toward

www.ketabpezeshki.com 66485457-66963820

the right. As the appendix moves higher, the omentum is unable to surround the appendix and to contain the infection if rupture occurs. Thus appendiceal rupture in pregnant women results in generalized peritonitis. However, even though there is a change in the relative position of the appendix during pregnancy, the most common symptom of appendicitis is right lower quadrant pain that occurs close to McBurney's point in the majority of women regardless of the stage of pregnancy.[44,49,50] A retrospective review comparing MRI findings with surgical confirmation of disease suggested that MRI is useful for triage of pregnant patients with acute abdominal and pelvic pain.[50] When it is available, MRI should be considered in this setting of nonconclusive findings on ultrasonography, particularly during the first trimester of pregnancy, because of the higher levels of radiation exposure associated with computed tomography of the abdomen.

Musculoskeletal Pain

Hand symptoms are common during pregnancy. The median nerve is at risk for compression distally within the carpal tunnel. Approximately 25% of pregnant women complain of hand symptoms compatible with median nerve compression, but only 2.3% are actually found to have carpal tunnel syndrome.[51] Symptoms of carpal tunnel syndrome include the classic triad of burning pain, numbness, and tingling in the thenar area or median nerve distribution. The patient often is awakened from sleep with the onset of symptoms. In 80% of cases, the symptoms are bilateral. Tapping over the median nerve at the wrist (Tinel's sign) or hyperflexing the wrist (Phalen's test) reproduces the symptoms and is diagnostic. Because the symptoms usually resolve during the postpartum period, only supportive treatment is required. A sleep splint applied with the hand in slight flexion resolves the symptoms in 80% of patients.[51]

Postural changes in the cervical spine, the shoulder girdle, and the lumbar spine result in pregnancy-related posterior pelvic pain and low back pain. Lordosis is exaggerated and becomes progressively more symptomatic during pregnancy. Low back pain usually is localized to the lumbar region just above the sacroiliac joint, worsened by forward flexion at the waist, and results in decreased range of motion and tenderness to palpation of the erector spinae muscles. The pain may radiate to one or both of the legs. The nature of the referred pain lacks the radicular quality of diskogenic pain and does not extend beyond the knee. Patients should avoid wearing high-heeled shoes because this will increase the lumbar lordosis with exacerbation of the pain. Swimming and conditioning exercises are recommended. Pregnancy-related posterior pelvic pain is hypothesized to occur because of asymmetrical sacroiliac joint laxity. It is important to distinguish this from low back pain because the treatments are different. Pregnancy-related pelvic pain is a stabbing pain in the buttocks, distal and lateral to the L5-S1 area, which may or may not radiate to the posterior thigh or knee, with a normal range of motion at hips and spine. The *posterior pelvic pain provocation test* has a positive predictive value of 0.91 for pregnancy-related pelvic pain. The test is performed with the patient in the supine position with the hips and knees bent at 90 degrees. The examiner applies pressure with one hand at the knee along the long axis of the femur from anterior to posterior while using the other hand to stabilize the pelvis at the contralateral anterior iliac spine. A positive test result is gluteal pain on the side of femoral pressure.[52]

Meralgia paresthetica is a painful dysesthesia along the lateral aspect of the thigh caused by entrapment of the purely sensory lateral femoral cutaneous nerve as it passes beneath the inguinal ligament. This condition develops during the third trimester in obese pregnant women or in pregnant women with excessive and rapid weight gain. It resolves during the postpartum period without treatment.

Trauma

The ACOG reports that 1 in every 12 pregnancies is complicated by physical trauma.[53] Trauma is the leading cause of maternal death secondary to nonobstetric etiologic conditions or disorders.[54] One study suggested that fetal mortality after trauma is significantly associated with higher injury severity score (of 28 or higher), lower final hemoglobin level, higher number of transfusions, longer hospital stay, and higher incidence of disseminated intravascular coagulation.[55] A retrospective institutional review during 5 years demonstrated that older maternal age, first-trimester presentation, elevated serum lactate level, and high injury severity score were associated with poor fetal outcome.[56] Other studies have not demonstrated a correlation between injury severity scores and maternal and fetal morbidity, although the authors advocated enhanced clinical vigilance for the unexpected in caring for obstetric trauma victims (see Chapter 37).[57]

Maternal Cardiac Arrest

Maternal cardiac arrest affects 1 in every 20,000 pregnancies, with an estimated survival rate of 6.9%.[58] A number of anatomic and physiologic changes in pregnancy contribute to cardiac arrest; the most common causes are trauma, hemorrhage, embolism, eclampsia, cardiac disease, and acute coronary syndrome.[59] When a health care provider first approaches a maternal cardiac arrest, important initial measures include activation of the maternal cardiac arrest and neonatal resuscitation teams, placement of the patient supine, and initiation of chest compressions per normal basic life support algorithms.[9,59] When the maternal arrest team arrives, a member of the group should perform a manual displacement of the uterus to the left. Performance of this maneuver will help remove the gravid uterus from the inferior vena cava, thereby relieving some aortocaval compression.[9,59] Other modifications to the nonpregnant cardiac arrest are starting of intravenous lines above the diaphragm, early assessment of hypovolemia and appropriate fluid resuscitation, and termination of any magnesium intravenous therapy. While active resuscitative measures are in progress, the obstetric and neonatal teams should prepare for an emergent cesarean section if there is no return of spontaneous circulation within 4 minutes of the onset of the maternal cardiac arrest; the goal is to perform the delivery of the child at 5 minutes if maternal circulation is not restored.[9,59]

Domestic Violence

Up to 35% of all ED visits by women are due to injuries or illnesses related to domestic violence. Domestic violence is conservatively estimated to occur in 10 to 20% of North American spousal relationships. Estimates of abuse during pregnancy vary widely, ranging from 1% up to 37%. The wide variation in estimates is attributable to different study designs, definitions of abuse, and sample population demographics.[60-66] Moreover, it generally is accepted that violence in the home is under-reported and the prevalence is higher than studies estimate.

A survey taken between 2004 and 2007 of 134,955 pregnant women in the United States showed that the prevalence of violence during pregnancy is approximately 3.6%.[66] Risk factors for violence during pregnancy include a recent divorce or separation (15.6%), a partner who expresses that he did not want the pregnancy (14.6%), and being close with someone who has a substance abuse or drinking problem (12.7%).[66] Other significant demographic variables associated with abuse and pregnancy can be classified under the major headings of social instability, unhealthy lifestyle, and physical health problems.[67] Abused pregnant women are more commonly of lower educational levels, unmarried, unemployed, eating an unhealthy diet, abusing drugs

www.ketabpezeshki.com 66485457-66963820

and alcohol, and experiencing an unplanned pregnancy; they may also delay seeking of prenatal care.[67-69] Evidence of physical abuse is more common in the facial area in a nonpregnant patient, whereas blunt abdominal trauma is the most common injury type in a pregnant patient.[67,70] Blunt abdominal trauma can result in miscarriage, abruptio placentae, fetal loss, premature labor, fetal fractures, low birth weight, and premature delivery. Other common injury sites in abused pregnant patients are the breasts and genitals.

Abused pregnant women often suffer from low self-esteem, despair, anxiety, fear, withdrawal, post-traumatic stress disorder, passivity, learned helplessness, and depression and have high rates of attempted suicide.[67,71] Abused pregnant women may have vague physical symptoms, including headache, fatigue, insomnia, choking sensations, gastrointestinal complaints, pelvic pain, and backache. These symptoms may be manifestations of a deep depression or of a conversion reaction related to the adversity of the home environment.

Abused pregnant women do not believe that they have control over the health of their fetus. They hold a strong belief that chance is the major determinant in fetal outcome. This perception and the associated behavior (e.g., cigarette smoking, alcohol and drug abuse) are unlikely to change unless abused women leave their abusive situation. Only then will they be able to improve their sense of power and self-esteem and to make changes in their behavior that are in the best interest of the fetus.[67] Identification and appropriate referral are paramount in the management of an abused pregnant patient. Most abused patients will not volunteer information about domestic violence unless they are specifically asked. Cross-sectional survey data obtained from interviews with 261 pregnant women in 1991 suggest that 33.3% of women will report abuse when asked. They are more likely to disclose such information to another woman or medical personnel of either sex who are sympathetic and offer protection, support, and access to help.[71] Fear that an abused woman will be offended by direct questioning is unfounded.[67] It is important to include direct queries about abuse or risk of abuse in taking a history from a patient in the absence of her partner. Direct questioning may take the form of the following:

How do you and your partner resolve disagreements?

Have you been hit or hurt by anyone in the last year?[67]

Are you concerned for your safety or the safety of your children?

Many women come to the ED with similar problems and are victims of violence. Could this be what happened to you today?[71]

If a pregnant patient is found to be at high risk and living in dangerous circumstances, it is prudent to arrange for immediate shelter or hospital admission. All patients identified as victims of abuse should be referred to social services, community support groups, and, if appropriate, substance abuse programs. Referral for psychiatric and high-risk obstetric consultations may be indicated as well.

MANAGEMENT

Perspective

The assessment and care of pregnant patients require specialized equipment and access to specific ancillary tests. Basic equipment for the management of all obstetric and gynecologic emergencies includes a variety of specula, a Doppler ultrasonographic device for fetal heart readings, and ultrasonography with a transabdominal probe. The specula should be available in at least four blade widths: extra narrow at 16 mm (e.g., Miltex Pederson), narrow at 22 mm (e.g., Miltex Pederson), regular at 25 mm (e.g., Pederson), and wide at 35 mm (e.g., Graves). Speculum blades are available in three lengths: small at 7.7 cm, medium at 10.2 cm, and large at 17.8 cm. The medium-length Pederson speculum provides adequate exposure for most women. Virginal or postmenopausal women may require a narrow or extra-narrow speculum with a 10.2-cm-long blade. Pelvic examination of obese patients or patients in whom the vaginal walls are loose and redundant may necessitate the use of a Graves speculum.

Appropriate diagnostic imaging (transabdominal and transvaginal sonography as well as color Doppler ultrasonography or impedance plethysmography) and laboratory testing (both quantitative and qualitative hCG testing) should be available at all times. Access to MRI should be available by prior arrangement if equipment is not on site. If ready access to a high-risk obstetric unit is not available, prearranged agreements for transport to specialized centers for high-risk obstetric patients and neonates should be in place.

Health Promotion and Disease and Injury Prevention in Pregnancy

After complications of pregnancy and comorbid conditions have been excluded, pregnant patients should initially be counseled, appropriately referred, and encouraged to participate in regular prenatal care. The proportion of American women beginning prenatal care during the first trimester has consistently increased since the early 1990s, with a rate of 84% reported in 2004.[1] Although the time for prenatal counseling is limited in the ED, such counseling can have a positive impact on both fetal and maternal health. The following discussion is not inclusive of all prenatal issues; however, it does outline some of the most commonly identified risks and patient concerns along with the appropriate advice that should be given.

Use of Seat Belts, Helmets, and Air Bags

The use of three-point seat belt restraints should be emphasized. There is no evidence that these restraints will increase the chance of fetal injury. The proper use of seat belts is a good predictor of a favorable maternal and fetal outcome in the case of vehicular trauma.[72] The lap belt should be snugly and comfortably placed low across the maternal pelvis, below the uterine corpus and fundus and across the thighs, with the shoulder belt positioned between the breasts and no excessive slack allowed anywhere in the belt.[73] The National Highway Traffic Safety Administration does not consider pregnancy to be an indication for the deactivation of air bags and recommends the combined use of seat belts and air bags.[74] All patients should be encouraged to wear helmets when riding a bicycle or a motorcycle, whether voluntarily or in compliance with the law; these modes of transportation are ill-advised during pregnancy and certainly inappropriate during the third trimester.

Safe infant feeding should be reinforced. It is inappropriate and unsafe to breast-feed in a moving vehicle. Similarly, it is unsafe to remove the child from the restraining device to bottle-feed while in a moving vehicle.

Sexual Intercourse during Pregnancy

Sexual intercourse is considered harmless for a normal pregnant female. Most texts recommend abstinence during the last 4 weeks of pregnancy or when abortion or preterm labor is threatened.

Safety of Douching during Pregnancy

Guidelines should be adhered to for the proper use of douches during pregnancy. Hand-held bulb syringes are prohibited because of the risk of air embolism. The height of the douche bag should

www.ketabpezeshki.com 66485457-66963820

be limited to 2 feet or less above the level of the hips to prevent high fluid pressure. The nozzle should not be inserted more than 8 cm into the vagina.

Travel Restrictions during Pregnancy

Current ACOG guidelines suggest that occasional travel is generally safe for pregnant patients in the absence of maternal or obstetric complications (i.e., preeclampsia, intrauterine growth restriction).[75] Most airlines allow women with normal pregnancies to travel up to 35 or 37 weeks. It should be emphasized to the pregnant traveler that she should walk about at least every 2 hours to minimize the risk for thromboembolism. Other concerns, such as noise, vibration, and cosmic radiation, are a negligible risk for the occasional pregnant air traveler.[75] However, pregnant airline employees or frequent flyers should consult a physician during pregnancy because of their increased exposure to these potential risks.

Immunization during Pregnancy

The Advisory Committee on Immunization Practices posts guidelines for immunization during pregnancy on the website of the Centers for Disease Control and Prevention (CDC). Immunization of pregnant women should be guided by risk-versus-benefit logic. Relative indications for vaccination follow three guiding principles: (1) the risk of exposure is high, (2) the infection could cause harm to the mother or infant, and (3) the vaccine is unlikely to cause harm. Live virus vaccines generally are contraindicated during pregnancy because of the theoretic risk of transmission of the virus to the fetus. If a pregnant patient has received a live virus vaccine in the 3 months before the pregnancy, she should be referred for counseling on the potential risks to the fetus.[76] The annual influenza vaccination is recommended by the CDC for pregnant patients as there is increased risk of acquiring the illness while pregnant and higher morbidity and mortality rates due to influenza.[77] Comprehensive and specific guidelines for each vaccine are updated and posted on the CDC website (www.cdc.gov/vaccines/pubs/ACIP-list.htm).

Importance of Regular Appropriate Exercise

Suitable regular exercise should be encouraged during pregnancy because it helps prevent venous stasis and thromboembolic disease, maintain regular bowel movements, improve posture and perineal muscle strength, and regulate weight gain. Sedentary lifestyles and work activities that are performed predominantly in the sitting position should be discouraged. The ACOG recommends that healthy pregnant women without medical or obstetric complications adhere to the standard of exercise for nonpregnant patients recommended by the CDC and the American College of Sports Medicine. The standard aimed at improving health and well-being includes an accumulation of 30 minutes or more of moderate activity daily. Pregnant patients with comorbid conditions require exercise also and should engage in regular exercise with close medical supervision.

Patients should be encouraged to strengthen the abdominal muscles; to stretch the lower part of the back; to balance pectoralis muscle strength with that of the trapezius, rhomboids, and latissimus dorsi; to strengthen the cervical spine flexors; and to perform regular pelvic tilt exercises in all positions to correct the postural imbalance of pregnancy, to relieve discomfort, and to reduce the frequency of stress incontinence. Women with previous exercise regimens should be encouraged to continue these throughout their pregnancy and may even include high-impact activities such as jogging in the absence of medical or obstetric complications. Moderate exercise should be performed on most if not all days of the week, with special attention paid to adequate hydration and nutrition. Women starting an exercise regimen during pregnancy should generally wait until the second trimester and subsequently follow a graduated prescription for the amount and intensity of exercise throughout the remainder of their pregnancy.[78] Aggressive abdominal exercises are discouraged after 12 weeks of gestation because they may exacerbate the development of diastasis recti. Moderate regular abdominal strengthening exercises will minimize the lordosis of pregnancy.

Diet, Vitamin Supplementation, and Weight Gain Recommendations

It is not recommended that pregnant patients take routine multivitamin supplementation; however, iron supplements may be recommended, especially during the latter half of pregnancy. It also is recommended that 1 mg of folic acid be taken daily, beginning 1 month before conception and continuing throughout the first trimester to reduce the risk for neural tube defects.

Obesity is an increasingly common concern that is complicating pregnancies worldwide. Estimates of obesity in pregnant women in the United States range from 18 to 38%.[79] Obesity has been shown to complicate pregnancy by increasing rates of gestational diabetes, pregnancy-induced hypertension, preeclampsia, and venous thromboembolism.[79]

The ACOG recommends an average weight gain for pregnant women of between 10 and 12 kg.[80] The normal physiologic changes of pregnancy account for approximately 9 kg. The remainder is maternal fat storage.[81] The Institute of Medicine makes weight gain recommendations according to prepregnancy weight: underweight women (13-18 kg), normal-weight women (11-16 kg), overweight women (7-11 kg), and obese women (5-9 kg).[82]

Appropriate Management of Pregnant Patients with Substance Abuse Problems

The risks of smoking, illicit drug use, and excessive alcohol consumption during pregnancy are widely known to the lay public; however, despite warnings, some pregnant women continue to smoke and imbibe excessively. Cigarette smoking during pregnancy has declined steadily since 1989, to 18% in 2002-2003 and 16% in 2007-2008.[83] Nonetheless, tobacco use by pregnant mothers aged 18 to 25 years continues to be high, with a reported rate of 22% in 2008. The U.S. Department of Health and Human Services Substance Abuse and Mental Health Services Administration concluded from its National Household Survey on Drug Abuse (2007-2008 database) that among women 15 to 44 years of age who were currently pregnant, 5% used one or more illicit drugs in the past month, 4.5% engaged in "binge" alcohol use, and slightly less than 20% were past-month cigarette smokers. *Binge drinking* was defined as drinking five or more drinks on the same day at least once during the previous 30 days. In comparison with a nonpregnant cohort, women who abuse substances reported curtailing their use during pregnancy and resuming use postpartum. Substance abuse during pregnancy was more frequent in unmarried women without a high-school education. The prevalence decreased as the amount of adult education increased. The prevalence of drug abuse during the last month of pregnancy showed no difference between Hispanic and white pregnant women. Drug abuse during pregnancy was significantly more common among black than among Hispanic patients.[83]

www.ketabpezeshki.com 66485457-66963820

KEY CONCEPTS

- Female patients of childbearing age should be assumed to be pregnant; 11.5% of women with abdominal pain or vaginal bleeding have a positive result on pregnancy testing even when they have stated that there is "no chance" they are pregnant.
- Accurate vital signs are best obtained with pregnant patients in the left lateral decubitus position and should include measurement of the fetal heart rate, if it is obtainable.
- ELISA is the state-of-the-art urine pregnancy test. It offers excellent user convenience and has a sensitivity for levels of hCG between 25 and 50 mIU/mL.
- The decision to perform diagnostic imaging investigations in a pregnant patient must take into consideration the risk to the developing fetus from radiation exposure, the inherent risk of such investigations for the mother, and the risk to the mother and the fetus associated with missing the diagnosis because of reluctance to use available imaging techniques.
- In general, a pregnant patient should be treated and assessed in the same way as all other patients are. However, the normal physiologic changes of pregnancy may mask or unmask underlying medical conditions.
- The ED encounter is an opportunity to reinforce or to provide primary education and advice on health promotion and disease and injury prevention in pregnancy.

ACKNOWLEDGMENT

The authors would like to acknowledge with permission granted that Michael J. Romano contributed to the formatting, updating of the literature, and first draft of the revisions for this version of the chapter. None of the authors has any financial conflicts of interest pertaining to the subject addressed in this chapter.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Ventura SJ, Abma JC, Mosher WD, Henshaw SK: Estimated pregnancy rates by outcome for the United States, 1990-2004. *Natl Vital Stat Rep* 2008; 56:1-25, 28.
2. Martin JA, et al: Births: Final data for 2009. *Natl Vital Stat Rep* 2011; 60:1-70.
3. Chumlea WC, et al: Age at menarche and racial comparisons in US girls. *Pediatrics* 2003; 111:110.
4. Xu JQ, et al: Deaths: Final report for 2007. *National Vital Statistics Reports* 2010; 58:19.
5. Clark SL, et al: Maternal death in the 21st century: causes, prevention, and relationship to cesarean delivery. *Am J Obstet Gynecol* 2008; 199:36.e1-36.e5.
6. *Health, United States, 2010: With Special Feature on Death and Dying*. Hyattsville, Md: National Center for Health Statistics; 2011.
7. Ramoska EA, Sacchetti AD, Nepp M: Reliability of patient history in determining the possibility of pregnancy. *Ann Emerg Med* 1989; 18:48-50.
8. Lippman S, et al: Detection of unknown early pregnancy: A matter of safety. *Postgrad Med* 1988; 83:129.
9. Vanden Hoek TL, et al: Part 12: Cardiac arrest in special situations: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122(Suppl 3):S829-S861.
10. Causey AL, Seago K, Wahl NG, Voelker CL: Pregnant adolescents in the emergency department: Diagnosed and not diagnosed. *Am J Emerg Med* 1997; 15:125-129.
11. Speert H, Guttmacher AF: Frequency and significance of bleeding in early pregnancy. *JAMA* 1954; 155:712-715.
12. Verburg BO, et al: New charts for ultrasound dating of pregnancy and assessment of fetal growth: Longitudinal data from a population-based cohort study. *Ultrasound Obstet Gynecol* 2008; 31:388-396.
13. Kuklina EV, Ayala C, Callaghan WM: Hypertensive disorders and severe obstetric morbidity in the United States. *Obstet Gynecol* 2009; 113:1299-1306.
14. Ramsey E, Shilitto J: How early can fetal heart pulsations be detected reliably using modern ultrasound equipment? *Ultrasound* 2008; 16:193-195.
15. Chadwick JR: Value of the bluish coloration of the vaginal entrance as a sign of pregnancy. *Trans Am Gynecol Soc* 1986; 11:399.
16. Storring PL, Gaines-Das RE, Bangham DR: International Reference Preparation of Human Chorionic Gonadotrophin for Immunoassay: Potency estimates in various bioassay and protein binding assay systems; and International Reference Preparations of the alpha and beta subunits of human chorionic gonadotrophin for immunoassay. *J Endocrinol* 1980; 84:295-310.
17. Cole LA, Khanlian SA, Sutton JM, Davies S, Rayburn WF: Accuracy of home pregnancy tests at the time of missed menses. *Am J Obstet Gynecol* 2004; 190:100-105.
18. Lazarenko GC, Dobson C, Enokson R, Brant R: Accuracy and speed of urine pregnancy tests done in the emergency department: A prospective study. *CJEM* 2001; 3:292-295.
19. Chard T: Pregnancy tests: A review. *Hum Reprod* 1992; 7:701-710.
20. Lee CL, Iles RK, Shepherd JH, Hudson CN, Chard T: The purification and development of a radioimmunoassay for beta-core fragment of human chorionic gonadotrophin in urine: Application as a marker of gynaecological cancer in premenopausal and postmenopausal women. *J Endocrinol* 1991; 130:481-489.
21. Hay DL, Lopata A: Chorionic gonadotropin secretion by human embryos in vitro. *J Clin Endocrinol Metab* 1988; 67:1322-1324.
22. Lenton EA, et al: Normal and abnormal implantation in spontaneous in-vivo and in-vitro human pregnancies. *J Reprod Fertil* 1991; 92:555-565.
23. Steier JA, Bergsjo P, Myking OL: Human chorionic gonadotropin in maternal plasma after induced abortion, spontaneous abortion, and removed ectopic pregnancy. *Obstet Gynecol* 1984; 64:391-394.
24. Daya S, Woods S, Ward S, Lappalainen R, Caco C: Early pregnancy assessment with transvaginal ultrasound scanning. *CMAJ* 1991; 144:441-446.
25. Daya S, Woods S, Ward S, Lappalainen R, Caco C: Transvaginal ultrasound scanning in early pregnancy and correlation with human chorionic gonadotropin levels. *J Clin Ultrasound* 1991; 19:139-142.
26. Fossum GT, Davajan V, Kletzky OA: Early detection of pregnancy with transvaginal ultrasound. *Fertil Steril* 1988; 49:788-791.
27. McRae A, Murray H, Edmonds M: Diagnostic accuracy and clinical utility of emergency department targeted ultrasonography in the evaluation of first-trimester pelvic pain and bleeding: A systematic review. *CJEM* 2009; 11:355-364.
28. ACOG Practice Bulletin No. 101: Ultrasonography in pregnancy. *Obstet Gynecol* 2009; 113(Pt 1):451-461.
29. Canadian Emergency Ultrasound Society: *Recommended Standards*. Available at www.ceus.ca/002-standards/002-00.standards.htm. Accessed March 22, 2011.
30. ACOG Committee on Obstetric Practice: ACOG Committee Opinion. Number 299, September 2004 (replaces No. 158, September 1995). Guidelines for diagnostic imaging during pregnancy. *Obstet Gynecol* 2004; 104:647-651.
31. McCollough CH, et al: Radiation exposure and pregnancy: When should we be concerned? *Radiographics* 2007; 27:909-917; discussion 917-918.
32. Ginsberg JS, Hirsh J, Rainbow AJ, Coates G: Risks to the fetus of radiologic procedures used in the diagnosis of maternal venous thromboembolic disease. *Thromb Haemost* 1989; 61:189-196.
33. Ratnapalan S, Bona N, Koren G: Ionizing radiation during pregnancy. *Can Fam Physician* 2003; 49:873-874.
34. Bentur Y: *Ionizing and nonionizing radiation in pregnancy*. In: Koren G, ed: *Maternal-Fetal Toxicology. A Clinician's Guide*. New York: Marcel Dekker; 2001.
35. Duke University and Duke Medicine Radiation Safety Division: *Fetal Radiation Dose Estimates*. Available at www.safety.duke.edu/radsafety/fdose/fdxray.asp. Accessed March 11, 2011.
36. Patient Safety Authority, Commonwealth of Pennsylvania: Triage of the obstetrics patient in the emergency department: Is there only one patient? *Pa Patient Saf Adv* 2008; 5:96.
37. Menon R, Bushnell CD: Headache and pregnancy. *Neurologist* 2008; 14:108-119.
38. Marcus DA: Managing headache during pregnancy and lactation. *Expert Rev Neurother* 2008; 8:385-395.
39. Von Wald T, Walling AD: Headache during pregnancy. *Obstet Gynecol Surv* 2002; 57:179-185.
40. Bickerstaff ER, Small JM, Guest IA: The relapsing course of certain meningiomas in relation to pregnancy and menstruation. *J Neurochem* 1958; 21:89-91.
41. Digre KB, Varner MW, Corbett JJ: Pseudotumor cerebri and pregnancy. *Neurology* 1984; 34:721-729.
42. Grosset DG, Ebrahim S, Bone I, Warlow C: Stroke in pregnancy and the puerperium: What magnitude of risk? *J Neurol Neurosurg Psychiatry* 1995; 58:129-131.
43. Heit JA, et al: Trends in the incidence of venous thromboembolism during pregnancy or postpartum: A 30-year population-based study. *Ann Intern Med* 2005; 143:697-706.
44. Delvigne A, Rozenberg S: Systematic review of data concerning etiopathology of ovarian hyperstimulation syndrome. *Int J Fertil Womens Med* 2002; 47:211-226.
45. Andersson RE, Lambe M: Incidence of appendicitis during pregnancy. *Int J Epidemiol* 2001; 30:1281-1285.
46. Andersen B, Nielsen TF: Appendicitis in pregnancy: Diagnosis, management and complications. *Acta Obstet Gynecol Scand* 1999; 78:758-762.
47. Bickell NA, Aufses AH Jr, Rojas M, Bodian C: How time affects the risk of rupture in appendicitis. *J Am Coll Surg* 2006; 202:401-406.
48. Tamir IL, Bongard FS, Klein SR: Acute appendicitis in the pregnant patient. *Am J Surg* 1990; 160:571-575; discussion 575-576.
49. Mourad J, Elliott JP, Erickson L, Lisboa L: Appendicitis in pregnancy: New information that contradicts long-held clinical beliefs. *Am J Obstet Gynecol* 2000; 182:1027-1029.
50. Oto A, et al: MR imaging in the triage of pregnant patients with acute abdominal and pelvic pain. *Abdom Imaging* 2009; 34:243-250.
51. Ekman-Ordeberg G, Salgeback S, Ordeberg G: Carpal tunnel syndrome in pregnancy. A prospective study. *Acta Obstet Gynecol Scand* 1987; 66:233-235.
52. Ostgaard HC, Zetherstrom G, Roos-Hansson E: The posterior pelvic pain provocation test in pregnant women. *Eur Spine J* 1994; 3:258-260.
53. American College of Obstetricians and Gynecologists: Trauma during pregnancy, ACOG Technical Bulletin 161—November 1991. *Int J Gynaecol Obstet* 1993; 40:165-170.
54. Moise KJ Jr, Belfort MA: Damage control for the obstetric patient. *Surg Clin North Am* 1997; 77:835-852.
55. Ali J, Yeo A, Gana TJ, McLellan BA: Predictors of fetal mortality in pregnant trauma patients. *J Trauma* 1997; 42:782-785.
56. Aboutanos SZ, et al: Predictors of fetal outcome in pregnant trauma patients: A five-year institutional review. *Am Surg* 2007; 73:824-827.

www.ketabpezeshki.com 66485457-66963820

57. Schiff MA, Holt VL, Daling JR: Maternal and infant outcomes after injury during pregnancy in Washington State from 1989 to 1997. *J Trauma* 2002; 53:939-945.
58. Lewis G, ed: *Saving Mothers' Lives: Reviewing Maternal Deaths to Make Motherhood Safer—2003-2005*. The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. London: CEMACH; 2007.
59. Jeejeebhoy FM, et al: Management of cardiac arrest in pregnancy: A systematic review. *Resuscitation* 2011; 82:801-809.
60. Committee on Wife Assault: *Reports on Wife Assault*. Toronto: Ontario Medical Association; 1991.
61. Centers for Disease Control (CDC): Family and other intimate assaults—Atlanta, 1984. *MMWR Morb Mortal Wkly Rep* 1990; 39:525-529.
62. Bland R, Orn H: Family violence and psychiatric disorder. *Can J Psychiatry* 1986; 31:129-137.
63. Bain JE: Wife assault: Physicians cannot ignore it. *CMAJ* 1991; 144:283-284.
64. Flitcraft AH: Violence, values, and gender. *JAMA* 1992; 267: 3194-3195.
65. Lent B: Wife abuse in pregnancy: The role of the physician. *Perinatal Outreach Program of Southwestern Ontario Newsletter* 1991; 9:1.
66. Shah PS, Shah J: Maternal exposure to domestic violence and pregnancy and birth outcomes: A systematic review and meta-analyses. *J Womens Health (Larchmt)* 2010; 19:2017-2031.
67. Stewart DE, Cecutti A: Physical abuse in pregnancy. *CMAJ* 1993; 149:1257-1263.
68. Gee V: *Perinatal Statistics in Western Australia. Ninth Annual Report of the Western Australian Midwives' Notification System*. Perth: Health Services Statistics and Epidemiology Branch, Health Department of Western Australia; 1991.
69. Sampselle CM, Petersen BA, Murtland TL, Oakley DJ: Prevalence of abuse among pregnant women choosing certified nurse-midwife or physician providers. *J Nurse Midwifery* 1992; 37:269-273.
70. Webster J, Sweett S, Stolz TA: Domestic violence in pregnancy. A prevalence study. *Med J Aust* 1994; 161:466-470.
71. Jaffe P, et al: Emotional and physical health problems of battered women. *Can J Psych* 1986; 31:625.
72. Pearlman MD, et al: A comprehensive program to improve safety for pregnant women and fetuses in motor vehicle crashes: A preliminary report. *Am J Obstet Gynecol* 2000; 182:1554-1564.
73. Van Hook JW: Trauma in pregnancy. *Clin Obstet Gynecol* 2002; 45:414-424.
74. *Final Report: National Conference on Medical Indications for Air Bag Disconnection.* George Washington University Medical Center, 1997. Available at www.nhtsa.gov/airbags/air%20bag%20conference%20final%20report.doc.
75. ACOG Committee on Obstetric Practice: ACOG Committee Opinion No. 443: Air travel during pregnancy. *Obstet Gynecol* 2009; 114:954-955.
76. Atkinson WL, et al: General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). *MMWR Recomm Rep* 2002; 51:1-35.
77. Fiore AE, et al: Prevention and control of influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep* 2010; 59:1-62.
78. Davies GA, Wolfe LA, Mottola MF, MacKinnon C: Joint SOGC/CSEP Clinical Practice Guideline: Exercise in pregnancy and the postpartum period. *J Obstet Gynaecol Can* 2003; 25:516-522.
79. Guelinckx I, Devlieger R, Beckers K, Vansant G: Maternal obesity: Pregnancy complications, gestational weight gain and nutrition. *Obes Rev* 2008; 9:140-150.
80. American College of Obstetricians and Gynecologists, Committee on Professional Standards: *Standards for Obstetric-Gynecologic Services*, 7th ed. Washington, DC: American College of Obstetricians and Gynecologists; 1989.
81. Hytten F: *Weight gain in pregnancy*. In: Hytten F, Chamberlain G, eds: *Clinical Physiology in Obstetrics*. Oxford: Blackwell Scientific; 1991.
82. Institute of Medicine and National Research Council: *Weight Gain During Pregnancy: Reexamining the Guidelines*. Washington DC: The National Academies Press; 2009.
83. Substance Abuse and Mental Health Services Administration: *Results from the 2008 National Survey on Drug Use and Health: National Findings*. Rockville, Md: Office of Applied Studies; 2009. Available at http://oas.samhsa.gov/nsduh/2k8nsduh/2k8Results.cfm. Accessed December 5, 2011.

www.ketabpezeshki.com 66485457-66963820

Chapter 178

Acute Complications of Pregnancy

Debra E. Houry and Bisan A. Salhi

PERSPECTIVE

Acute complications of pregnancy can appear in all trimesters and pose challenges in diagnosis and management for the emergency physician. Life-threatening disorders, such as ectopic pregnancy in early pregnancy, pregnancy-induced hypertension in mid to late pregnancy, and abruptio placentae in late pregnancy, are relatively common. Clinicians must consider the signs and symptoms, stage of pregnancy, and hemodynamic stability of the patient in developing diagnostic and treatment strategies.

PROBLEMS IN EARLY PREGNANCY

Miscarriage

Perspective

Miscarriage, the most common serious complication of pregnancy, is defined as the spontaneous termination of pregnancy before 20 weeks of gestation. Fetal demise after 20 weeks of gestation or when the fetus is more than 500 g is considered premature birth. Loss of early pregnancy, defined as detection of human chorionic gonadotropin (hCG) within 6 weeks of the last normal menstrual period, occurs in approximately 20 to 30% of pregnancies.[1-3] Embryonic and fetal loss after implantation occurs in up to one third of detectable pregnancies. The risk of miscarriage rises with increasing maternal age (fivefold increase in those older than 40 years compared with those 25 to 29 years), increasing paternal age, alcohol use, increased parity, history of prior miscarriage, poorly controlled diabetes mellitus and thyroid disease, low pre-pregnancy body mass index, maternal stress, and history of vaginal bleeding.[4-6] Approximately 80% of miscarriages occur during the first trimester; the rest occur before 20 weeks of gestation.

Threatened or actual miscarriage is a common presentation of patients in the emergency department (ED). Approximately one fourth of clinically pregnant patients experience some bleeding. It is estimated that up to 50% of all women who have bleeding during early pregnancy miscarry, although the risk is probably higher in the ED population.[7,8] Patients who have a viable fetus visualized on ultrasound examination have a much lower risk of miscarriage (3-6%), although vaginal bleeding is a high-risk indicator, even when a viable fetus is present.[9] Those with a history of bleeding who do not miscarry may have otherwise normal pregnancies, although they have an approximately twofold increased risk of premature birth and low-birth-weight infants.[10]

Principles of Disease

Pathophysiology. The majority of miscarriages are due to either uterine malformations or chromosomal abnormalities, which account for the majority of miscarriages that occur within 10 weeks of gestation.[6] In some cases the ovum never develops (anembryonic gestation). In the majority of early miscarriages, fetal death precedes clinical miscarriage, often by several weeks. Although clinical symptoms of miscarriages are most common between 8 and 12 weeks of gestation, sonographic evidence in most cases demonstrates death before 8 weeks; if fetal viability can be demonstrated by heart activity and a normal sonogram, the subsequent risk of fetal loss decreases significantly.

Maternal factors that increase the risk of miscarriage include congenital anatomic defects, uterine scarring, leiomyomas, and cervical incompetence. Other conditions associated with increased miscarriage rates include toxins (e.g., alcohol, tobacco, and cocaine), autoimmune factors, endocrine disorders, including luteal phase defects, and occasional maternal infections.[2-5]

Terminology. Miscarriage can be broadly categorized into three categories. The first is a *threatened miscarriage,* in which the patient presents with vaginal bleeding but is found to have a closed internal cervical os. The risk of miscarriage in this population is estimated at 35 to 50%, depending on the patient's risk factors and severity of symptoms.[11] If the internal cervical os is open, the miscarriage is considered *inevitable.* If products of conception are present at the cervical os or in the vaginal canal, the miscarriage is termed *incomplete,* the second classification of miscarriage. The third classification is a *completed* miscarriage, which occurs when the uterus has expelled all fetal and placental material, the cervix is closed, and the uterus is contracted. Establishment of the diagnosis of completed miscarriage is difficult in the ED. A gestational sac should be visualized for diagnosis because the cervix may close after an episode of heavy bleeding and clot passage without or after only partial expulsion of the products of conception. Unless an intact gestation is passed and recognized, completed miscarriage should be diagnosed only after dilation and curettage (D&C) with pathologic confirmation of gestational products, demonstration by sonography of an empty uterus with a prior known intrauterine pregnancy (IUP), or reversion to a "negative" pregnancy test result. This may take up to several weeks after the initial presentation.

Missed abortion is a relatively obsolete term referring to clinical failure of uterine growth over time. The terms *anembryonic gestation* (when no fetus is seen), *first-* or *second-trimester fetal death* (failure to see fetal heart activity in a fetus with at least a 5-mm crown-rump length), and *delayed miscarriage* are more appropriate.

www.ketabpezeshki.com 66485457-66963820

Clinical Features

Patient history should include the estimated length of the gestation; time since last menstrual period; symptoms of pregnancy (including evolution or loss of pregnancy symptoms); degree of bleeding; duration of bleeding; presence of cramps, pain, or fever; and attempts by the patient to induce miscarriage. Whereas the history is important, it is not helpful in the classification of the type of miscarriage. In addition, the severity of symptoms does not correlate well with the risk of miscarriage, although cramping and passage of clots are thought more likely to occur as the miscarriage becomes inevitable.

The assessment of the patient who experiences first-trimester vaginal bleeding includes a careful abdominal examination to evaluate for tenderness or peritoneal irritation from a potential ectopic pregnancy as well as to determine uterine size (the uterus should not be palpable abdominally). Pelvic examination should be performed to evaluate whether the cervix is closed or open, to look for clots or the products of conception, and to determine the degree of vaginal bleeding as well as uterine size and tenderness. The cervix should be gently probed with a ring forceps (not a cotton-tipped applicator) to determine whether the internal os (1.5 cm deep to the external os) is open or closed. This is unnecessary in the patient who has a clearly open os or visible products of conception but can be safely performed during the first trimester as long as the forceps are used gently and do not penetrate the cervix more than 2 or 3 cm. In the patient with second-trimester bleeding, probing should not be done because the uterus is more vascular and the organized placenta may overlie the cervical os. Parous women normally have an open or lax external os, a finding of no significance. The adnexa may be enlarged, often unilaterally, either because the corpus luteum is cystic or because the pregnancy is ectopic. Significant adnexal or uterine tenderness should always raise the possibility of an ectopic pregnancy. Much less commonly, pelvic infection can cause uterine and adnexal tenderness during early pregnancy.

Any tissue that is passed should be suspended in saline or tap water (or viewed under low-power microscopy) to differentiate sloughing endometrium and organized clot from chorionic villi, which form fronds and appear feathery in the saline suspension. Except in the rare instance of heterotopic pregnancy (combined intrauterine and ectopic pregnancies), this reliably excludes ectopic pregnancy. Passage of tissue called the *decidual cast* in ectopic pregnancy can easily be confused with intrauterine miscarriage if the physician does not confirm the absence of chorionic villi in the tissue.[12]

Diagnostic Strategies

A hemoglobin level is useful to provide a baseline measurement and to evaluate the degree of blood loss in women whose bleeding persists. In addition, an Rh type should be obtained. Ultrasonography is the primary means of evaluating the health of the fetus as well as its location (Table 178-1). Because historical and clinical estimations of gestational age are often inaccurate, ultrasonography is useful to provide an accurate measure of fetal age and viability (Box 178-1).

In the stable patient with threatened miscarriage, expectant management may be sufficient to determine when intervention is needed as long as ectopic pregnancy has been excluded. Serial quantitative hCG levels are used to assess the health of the fetus if sonographic findings are indeterminate or if the gestational age is less than 6 or 7 weeks. The sonographic "discriminatory zone" is defined as the quantitative hCG level at which a normally developing IUP should reliably be seen. This is considered to be 6500 mIU/mL for transabdominal ultrasonography and 1000 to 2000 mIU/mL for transvaginal ultrasonography.[13] Ultrasonography can be performed or repeated when hCG levels rise to 1500 to 3000 mIU/mL. If hCG levels are flat or decline or if sonographic criteria for fetal demise are demonstrated (see Box 178-1), the patient should be referred to an obstetrician for follow-up to ensure miscarriage completion and to rule out subsequent complications.

Table 178-1 Landmarks for Gestational Age and β-hCG Level by Transvaginal Ultrasonography

FINDING	WEEKS FROM LMP	β-hCG (mIU/mL)
Gestational sac (25 mm)	5	1000
Discriminatory zone	5-6	1000-2000
Yolk sac	6	2500
Upper discriminatory zone	6-7	3000
Fetal pole	7	5000
Fetal heart motion	6-7	7000

Modified from Ramsey E, Shilitto J: How early can fetal heart pulsations be detected reliably using modern ultrasound equipment? Ultrasound 16:193-195, 2008.
β-hCG, beta subunit of human chorionic gonadotropin; *LMP,* last menstrual period.

Box 178-1 Sonographic Criteria for Abnormal Pregnancy with Transvaginal Ultrasonography

No gestational sac at β-hCG level of 3000 mIU/mL
No yolk sac with gestational sac of 13 mm (or at 32 days since last menstrual period)
5-mm crown-rump length with no fetal heart tones
No fetus with gestational sac of 25 mm mean diameter
No fetal heart tones after 10-12 weeks' gestational age

Adapted from Dart RG: Role of pelvic ultrasonography in evaluation of symptomatic first-trimester pregnancy. Ann Emerg Med 33:310. 1999.
β-hCG, beta subunit of human chorionic gonadotropin.

Differential Considerations

Ectopic pregnancy can masquerade as a threatened miscarriage in the early stages of pregnancy and should always be considered in the differential diagnosis. Even in the patient with painless vaginal bleeding, the diagnosis of ectopic pregnancy must be considered.[12] Thus early ultrasonography is imperative to locate the pregnancy in the patient who has bleeding or pain.

Other diagnoses should also be considered. A small amount of bleeding occurs at the time of implantation of the blastocyst into the endometrium and occasionally at the time of the first missed menses. Molar pregnancy is also characterized by vaginal bleeding, usually during the late first trimester or the second trimester. This condition can be identified by ultrasonography. Cervical and vaginal lesions can also cause local bleeding and can usually be seen on vaginal inspection.

Management

After assessment of hemodynamic status and management of blood loss, a patient with a threatened miscarriage requires very little specific medical treatment. Anti-D immune globulin should be administered if the patient is Rh negative (unless the father is also known to be Rh negative). A 50-μg dose is used during the first trimester and a full 300-μg dose after the first trimester.[14] Once ectopic pregnancy has been excluded, ultrasonography can be scheduled more routinely at a later time in the patient without significant pain as long as the patient is aware that the potential for ectopic pregnancy exists until it is excluded by identification

www.ketabpezeshki.com 66485457-66963820

of an IUP. In the patient who is planning pregnancy termination, prompt referral should be encouraged and chorionic villi confirmed at the time of uterine evacuation.

Unless an IUP is diagnosed, the patient with threatened miscarriage should be given careful instructions on discharge to return if she has signs of hemodynamic instability, significant pain, or other symptoms that might indicate ectopic pregnancy (so-called ectopic precautions). In conjunction with gynecologic colleagues, an ED protocol is useful to determine when follow-up sonographic evaluation and serial hCG measurements should be obtained as ultrasonography can be an inaccurate diagnostic tool if the hCG level is significantly low, if vaginal bleeding is significant, or if ultrasonographic findings do not include a fetal pole or yolk sac.[15]

Although 50% or more of women with threatened miscarriage who are seen in the ED ultimately miscarry, treatment to "prevent" miscarriage is not useful as most fetuses can be shown to be nonviable 1 to 2 weeks before symptoms occur. In most cases, spontaneous miscarriage is the body's natural method of expelling an abnormal or undeveloped (blighted) pregnancy. Thus a major goal of early management should be patient education and support. Patients should be advised that moderate daily activities do not affect the pregnancy. Tampons, intercourse, and other activities that might induce uterine infection should be avoided as long as the patient is bleeding, and she should return immediately for fever, abdominal pain, or a significant increase in bleeding. Cramping from a known IUP can be safely treated with oral synthetic narcotics, if needed. If the patient passes tissue, it should be brought to a provider to be examined for products of conception because differentiation of fetal parts or villi from decidual slough or casts is difficult.

Patient counseling is paramount with threatened miscarriage.[16,17] Determination of fetal viability can be helpful in either reassuring the mother or preparing her for probable fetal loss. Miscarriages are associated with a significant grieving process, which is frequently more difficult because early pregnancy is unannounced and early fetal death is not publicly recognized. Because many women consider that small falls, injuries, or stress during the first trimester can precipitate miscarriage, patients should be reassured that they have done nothing to cause miscarriage. It is important to make them aware that miscarriage is common, grieving is normal, and counseling may be beneficial.[18,19] A follow-up appointment should be scheduled after miscarriage to support the patient in resolving such issues.

Treatment of the patient with incomplete miscarriage includes expectant management, medical management with misoprostol, or surgical evacuation.[18,20] When the miscarriage is incomplete, the uterus may be unable to contract adequately to limit bleeding from the implantation site. Bleeding may be brisk, and gentle removal of fetal tissue from the cervical os with ring forceps during the pelvic examination often slows bleeding considerably.

Management of patients with presumed completed miscarriage is more complicated. If the patient brings tissue with her, this should be sent to the pathology department for evaluation. Unless an intact gestational sac or fetus is visualized, it is rarely clear clinically whether miscarriage is "complete." Studies have shown that in women with a history consistent with miscarriage who have minimal remaining intrauterine tissue as determined by ultrasonography, expectant management is safe, but only if ectopic pregnancy can be excluded.[20] If endometrial tissue is not seen with ultrasonography, bleeding is mild, and gestational age is less than 8 weeks, curettage is frequently unnecessary and the patient can be safely observed by a gynecologist for serial hormonal assays. Up to 80% of women with first-trimester miscarriage complete the miscarriage without intervention.[21] However, the need for later visits and procedures may be decreased by uterine curettage, particularly if the fetal pole or a gestational sac is visible on the sonogram at the time of evaluation.[20] Medical management with misoprostol instead of D&C is also an option and has a success rate of up to 96%.[18,22,23] The patient should be instructed to return if uncontrolled bleeding, severe pain or cramping, fever, or tissue passage occurs. Follow-up is recommended in 1 or 2 weeks to ensure that the miscarriage is complete.

After miscarriage, the patient should be advised that fetal loss, even during the first trimester, can cause significant psychological stress.[16] Follow-up in 1 or 2 weeks with a gynecologist should be provided. Some physicians prescribe antibiotics after D&C (usually doxycycline or metronidazole), particularly in populations of patients at high risk for genital tract infections. Ergonovine or methylergonovine (0.2 mg orally twice daily) can be used to stimulate uterine involution. The patient should be advised to return if signs of infection (fever or uterine tenderness) occur, if bleeding resumes, or if further tissue is passed.

Ectopic Pregnancy

Perspective

Ectopic pregnancy, or pregnancy implanted outside the uterus, is an increasingly frequent problem that poses a major health risk to women during the childbearing years. It is the third leading cause of maternal death, responsible for 6% of maternal mortality.[24] The incidence of ectopic pregnancy has risen steadily during several decades and now accounts for approximately 2% of all pregnancies. Although the incidence of ectopic pregnancy is highest in women aged 25 to 34 years, the rate is highest among older women and women belonging to minority groups. Simultaneous intrauterine and extrauterine gestations (heterotopic pregnancy) have historically been rare, occurring in approximately 1 in 4000 pregnancies; more recently, women who have undergone assisted reproduction techniques with embryo transfer have demonstrated a risk of one of the pregnancies being ectopic of 4% or greater. The incidence of ectopic pregnancy among women presenting to the ED with vaginal bleeding or pain in the first trimester is consistently approximately 10% in several series.[25,26]

Principles of Disease

Implantation of the fertilized ovum occurs approximately 8 or 9 days after ovulation. Risk factors for an abnormal site of implantation include prior tubal infection (50% of cases), anatomic abnormalities of the fallopian tubes, and abnormal endometrium (host factors). These result in failure of the embryo to implant in the endometrium. The risk of ectopic pregnancy increases approximately threefold after a patient has had pelvic inflammatory disease (PID). In recent studies, one fourth of patients with ectopic pregnancies have had tubal surgery, including tubal sterilization or removal of ectopic pregnancy.[27] If the patient is currently using an intrauterine device, increased risk can occur from complicating PID or from failure of the intrauterine device to prevent pregnancy while preventing endometrial implantation. All forms of contraception except the intrauterine device and tubal sterilization decrease the incidence of ectopic pregnancy. After an ectopic pregnancy, the risk of a subsequent ectopic pregnancy was 22% in one series of women trying to conceive again (Box 178-2).[28]

When abnormal implantation occurs in the fallopian tubes, on the ovaries, or in the cervix, the pregnancy usually grows at a less than normal rate, which can result in abnormally low or declining hCG production. Blood leaks intermittently through the tubal wall or out the fimbrial ends, with spillage into the peritoneal cavity. Bleeding and other symptoms are usually intermittent. Three outcomes are possible: spontaneous involution of the pregnancy, tubal abortion into the peritoneal cavity or vagina, or rupture of the pregnancy with internal or vaginal bleeding.

www.ketabpezeshki.com 66485457-66963820

Box 178-2 Risk Factors for Ectopic Pregnancy

Tubal surgery (for tubal sterilization or ectopic pregnancy)
Pelvic inflammatory disease
Smoking
Advanced age
Prior spontaneous abortion
Medically induced abortion
History of infertility
Intrauterine device

Modified from Bouyer J, et al: Risk factors for ectopic pregnancy: A comprehensive analysis based on a large case-control, population-based study in France. Am J Epidemiol 157:185, 2003.

Implantation in the uterine horn (cornual pregnancy) is particularly dangerous because the growing embryo can use the myometrial blood supply to grow larger (10-14 weeks of gestation) before rupture occurs.

Clinical Features

The classic clinical picture of ectopic pregnancy is a history of delayed menses, followed by abdominal pain and vaginal bleeding in a patient with known risk factors. Unfortunately, this history is neither sensitive nor specific. Risk factors for ectopic pregnancy are absent in almost half of patients. Fifteen percent to 20% of patients with symptomatic ectopic pregnancy have not missed a menstrual period, and occasionally the patient has no history of vaginal bleeding. Abdominal pain is most commonly severe, peritoneal in nature, and constant. Shoulder pain implies free fluid in the peritoneal cavity and is suggestive of an ectopic pregnancy with significant hemorrhage. The pain of ectopic pregnancy can also be crampy, intermittent, or even absent.[12,29]

The physical examination findings in ectopic pregnancy are likewise variable. Vaginal bleeding, uterine or adnexal tenderness, or both in the patient with a positive pregnancy test result should trigger consideration of ectopic pregnancy. Tachycardia is not always present, even with significant hemoperitoneum; hemoglobin level is usually normal, and hypotension may be seen.[29] The presence of peritoneal signs, cervical motion tenderness, or lateral or bilateral abdominal or pelvic tenderness indicates increased likelihood of an ectopic pregnancy. If significant peritoneal irritation is present, pain can preclude accurate bimanual examination. Adnexal masses are felt in only 10 to 20% of patients with ectopic pregnancy.[12,29] Vaginal bleeding is often mild. Heavy bleeding with clots or tissue usually suggests a threatened or incomplete miscarriage, although the patient with an ectopic pregnancy who has decreasing hormonal levels may experience endometrial sloughing, which can be mistaken for passage of fetal tissue. Passed tissue should be examined, as with cases of miscarriage, in tap water or saline (or under low-power microscopy). Unless fetal parts or chorionic villi are seen, ectopic pregnancy should not be excluded in the patient with bleeding or passage of "tissue."

Diagnostic Strategies

Because both the history and the physical examination of the patient with ectopic pregnancy are insensitive and nonspecific, ancillary studies are essential to locate the pregnancy in any patient who has abdominal pain or vaginal bleeding and a positive pregnancy test result. Technologic advances have allowed accurate detection or exclusion of ectopic pregnancy in the assessment of the woman with first-trimester vaginal bleeding or pelvic pain. Ultrasonography and hormonal assays are the most commonly used ancillary tests. Laparoscopy may be the most efficient diagnostic tool in some instances.

Box 178-3 Sonographic Findings in the Patient with Suspected Ectopic Pregnancy

Diagnostic of Intrauterine Pregnancy
"Double" gestational sac
Intrauterine fetal pole or yolk sac
Intrauterine fetal heart activity

Diagnostic of Ectopic Gestation
Pregnancy in fallopian tube (Fig. 178-1)
Ectopic fetal heart activity (Fig. 178-2)
Ectopic fetal pole

Suggestive of Ectopic Gestation
Moderate or large cul-de-sac fluid without intrauterine pregnancy
Adnexal mass without intrauterine pregnancy*

Indeterminate
Empty uterus (Fig. 178-3)
Nonspecific fluid collections (Fig. 178-4)
Echogenic material
Abnormal sac (Fig. 178-5)
Single gestational sac

Modified from Dart RG: Role of pelvic ultrasonography in evaluation of symptomatic first-trimester pregnancy. Ann Emerg Med 33:310, 1999.
*Complex mass is the most suggestive of ectopic pregnancy, but a cyst can also be seen with ectopic pregnancy.

Figure 178-1. Pregnancy in the fallopian tube, diagnostic of an ectopic pregnancy. (Courtesy Mary Ann Edens, MD.)

Ultrasonography. Ultrasonography is the primary method used to locate early gestation, to establish gestational age, and to assess fetal viability. Transabdominal ultrasonography is most useful for identification of IUPs with fetal heart activity and exclusion of ectopic pregnancy (except in patients at high risk for heterotopic pregnancy because of infertility procedures).[13] Transvaginal ultrasonography is more sensitive, recognizes IUP earlier than transabdominal ultrasonography does, and is diagnostic in up to 80% of stable patients presenting in the first trimester.[30]

Sonographic findings in the patient with suspected ectopic pregnancy are listed in Box 178-3 and illustrated in Figures 178-1 to 178-5. In general, an indeterminate ultrasound study usually does not result in a diagnosis of normal pregnancy; one series of more than 1000 pelvic ultrasound examinations reported that 53% of indeterminate ultrasound studies resulted in a diagnosis of embryonic demise, 15% were ectopic pregnancies, and only 29% had an IUP.[31] However, correlation of sonographic results with quantitative hCG measurements can add to the predictive value.[32] With hCG levels of less than 1000 mIU/mL, the risk of

www.ketabpezeshki.com 66485457-66963820

Figure 178-2. Fetal heart movements detected by ultrasonography in the fallopian tube, diagnostic of an ectopic pregnancy. (Courtesy Mary Ann Edens, MD.)

Figure 178-4. Ultrasonography showing fluid around the fallopian tube. (Courtesy Mary Ann Edens, MD.)

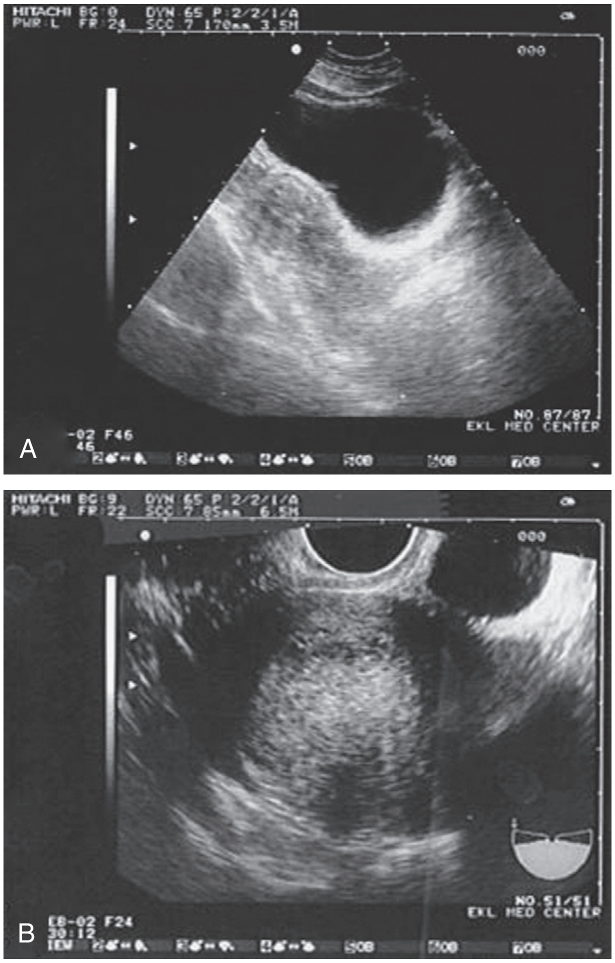


Figure 178-3. Ultrasonography showing an empty uterus, indeterminate for diagnosis of an ectopic pregnancy. (Courtesy Mary Ann Edens, MD.)

Figure 178-5. Ultrasonography showing a gestational pseudosac. (Courtesy Mary Ann Edens, MD.)

ectopic pregnancy increases fourfold; ultrasonography is still diagnostic in a significant minority of patients (one third of patients with ectopic pregnancy), although the accuracy of sonographic findings may decrease.[31] Normal pregnancy is unlikely if no gestational sac is seen by transvaginal ultrasonography with an hCG level higher than 1000 to 2000 mIU/mL, depending on the institution's discriminatory zone, but the differential diagnosis includes both miscarriage and ectopic pregnancy. Unfortunately, levels of approximately 1500 mIU/mL develop in only approximately half of patients with ectopic pregnancies (see Table 178-1).[8,13]

Indeterminate sonograms, which demonstrate neither an IUP nor extrauterine findings suggestive of ectopic pregnancy, occur in approximately 20% of ED evaluations of women with first-trimester bleeding or pain. Ectopic pregnancy is more likely among this subgroup with indeterminate sonograms if the hCG level is less than 1000 mIU/mL and when the uterus is empty. Endometrial debris and fluid in the uterus do not exclude ectopic pregnancy.[33]

Use of bedside ultrasonography in the ED for the diagnosis of IUP and the exclusion of ectopic pregnancy has shown good sensitivity and negative predictive value in ruling out ectopic pregnancy, but it requires significant operator training.[34-38] In addition to operator-based limitations, it is also limited by device availability and quality within the ED.

Hormonal Assays. The quantitative hCG levels have two primary uses: serial levels can be used in the stable patient who can be observed as an outpatient, and a single level can be correlated with sonographic results for improved interpretation. Serum hCG

www.ketabpezeshki.com 66485457-66963820

levels normally double every 1.8 to 3 days for the first 6 or 7 weeks of pregnancy, beginning 8 or 9 days after ovulation. An initial quantitative level can be measured at the time of the ED visit, particularly if the sonogram is indeterminate or the gestational age is estimated as less than 6 weeks. A repeated level should be measured 48 to 72 hours later. Levels that fall or rise slowly are associated with abnormal pregnancy, either intrauterine or ectopic. Twenty-one percent of women with an ectopic pregnancy in one series had an initial rise in hCG at a rate consistent with an IUP.[36]

Single quantitative hCG levels can also be useful in conjunction with ultrasonography; normal IUPs should be visible transvaginally at 1000 to 2000 mIU/mL hCG or higher (see Table 178-1). A benign course for ectopic pregnancy cannot be assumed with low hCG levels; ruptured ectopic pregnancies requiring surgery have been reported with very low or absent levels of hCG.[39]

Serum progesterone levels have been studied as an additional or alternative marker to determine which patients need further evaluation and follow-up for possible ectopic pregnancy. Progesterone rises earlier than hCG in normal pregnancy and plateaus with levels higher than 20 ng/mL, so measurement of serial levels over time is not necessary. Levels below 5 ng/mL exclude viable IUP (with rare exceptions) and could be useful when hCG levels are low, ultrasonography is indeterminate, and the clinician is considering D&C or laparoscopy. The ability of a progesterone level to differentiate ectopic pregnancy from a failed IUP is limited, however, and it is not a standard tool for ED evaluation.

Other Ancillary Studies. Dilation and evacuation can be used in patients without a viable IUP or ectopic pregnancy on ultrasonography to differentiate intrauterine miscarriage from ectopic pregnancy. Identification of chorionic villi in endometrial samples is seen in approximately 70% of patients and excludes ectopic pregnancy (except in infertility patients). Identification of chorionic villi can be made even in 50% of women with an empty uterus on ultrasonography and limits the need for laparoscopy to exclude ectopic pregnancy in this population.[40]

Although it is invasive, laparoscopy is extremely accurate as a diagnostic (and therapeutic) procedure for possible ectopic pregnancy. It is the diagnostic treatment of choice in the unstable first-trimester patient with frank peritoneal signs and is also indicated in patients with significant peritoneal fluid or an ectopic gestation in the pelvic cavity. Medical alternatives for management of ectopic pregnancy have resulted in decreased indications in stable patients.[32,41]

Differential Considerations

The spectrum of clinical presentations in ectopic pregnancy is wide, so the differential diagnosis includes essentially all first-trimester complications. Threatened miscarriage, the most common alternative diagnosis, can be recognized by sonographic evidence of an IUP, either healthy or failed. Hypovolemia may be seen, particularly in incomplete miscarriage, but hypotension without significant vaginal hemorrhage is highly suggestive of ectopic pregnancy. Identification of fetal parts or chorionic villi in tissue expelled or obtained during D&C is useful to confirm a complication of IUP, although this is not sufficient to exclude ectopic pregnancy in the patient who has received infertility treatment and has an increased risk of heterotopic gestation.

A ruptured corpus luteum cyst should also be considered in the patient who has first-trimester bleeding associated with peritoneal pain or irritation. The corpus luteum normally supports the pregnancy during the first 7 or 8 weeks. Rupture causes pelvic pain and peritoneal irritation. Ultrasonography is helpful if it reveals an IUP (except in patients with in vitro fertilization). During early gestation, when ultrasonography is nondiagnostic, free fluid is usually visible by ultrasonography, and serial observation may be required (see Fig. 178-4). If the patient is unstable (especially if an IUP cannot be identified by ultrasonography), laparoscopy or, rarely, laparotomy may be required to differentiate between the two conditions.

Management

Classically, approximately 20% of women with ectopic pregnancies manifest signs and symptoms warranting immediate intervention.[41] This includes patients with significant hypovolemia, large amounts of peritoneal fluid, or an open cervical os. For patients with significant signs of hypovolemia, rapid volume resuscitation should be instituted with intravenous fluids and blood products as necessary, and a baseline hemoglobin level and type and crossmatch should be obtained. A D&C or evacuation procedure with examination of endometrial contents for products of conception can be performed urgently in the unstable patient with an open cervical os.

If the patient remains unstable, immediate surgery is warranted. Laparoscopy may be indicated for patients who stabilize with treatment or for those who are hemodynamically stable but exhibit significant peritoneal signs. One study reported that identification of free fluid in Morison's pouch on bedside ultrasonography predicted the need for operative intervention in the majority of cases in patients with suspected ectopic pregnancies.[26] All patients with ectopic pregnancy who are Rh negative should be given Rh immune globulin 50 μg intramuscularly, unless the father is known to be Rh negative.

The majority of patients who seek treatment for bleeding or pain during the first trimester of pregnancy are stable. In such patients, the goal should be to exclude ectopic pregnancy in a timely manner. In the patient with significant pain by history or examination or significant risk factors for ectopic pregnancy, ultrasonography should be performed before discharge. If the results are indeterminate, a quantitative hCG level may be helpful in determining the patient's risk for ectopic pregnancy.

In low-risk patients with only minor symptoms or bleeding, ectopic pregnancy is still a possibility. Two general outpatient approaches can be considered. In most institutions, ultrasonography is the initial screening tool (Fig. 178-6). If an IUP is not seen, quantitative hCG levels help stratify patients by risk. In all cases, if the patient is discharged, careful instructions are given for symptoms that would require her earlier return (ectopic precautions).

An alternative strategy uses hCG levels first. However, waiting times for the serum assay can increase ED length of stay. In addition, ultrasonography is usually diagnostic of IUP or ectopic pregnancy, even if the hCG level is less than 1000 mIU/mL.[29,30] In most hands, the initial sonogram provides more rapid and accurate information.

A significant minority of patients have indeterminate sonographic results and hCG levels below 1000 mIU/mL. When the hCG levels never rise to the discriminatory zone, the differential diagnosis includes intrauterine fetal demise and ectopic pregnancy. Early D&C with identification of products of conception can be useful in the patient with nonrising hCG levels to detect chorionic villi and to confirm a failed IUP or to strongly suggest ectopic pregnancy.[40] Alternatively, hCG levels can be followed until they reach zero, particularly if initial levels are low.

Although laparotomy may be required for patients who have ectopic pregnancies, an increasing number of surgeries are being performed through the laparoscope. Salpingostomy is preferred to salpingectomy if the patient is stable and the procedure is technically feasible. Overall, the advent of transvaginal ultrasonography has resulted in a decreased number of surgeries and a trend toward nonoperative management.[42]

Medical management has become standard in many areas for the stable patient with minimal symptoms and is cost-effective

www.ketabpezeshki.com 66485457-66963820

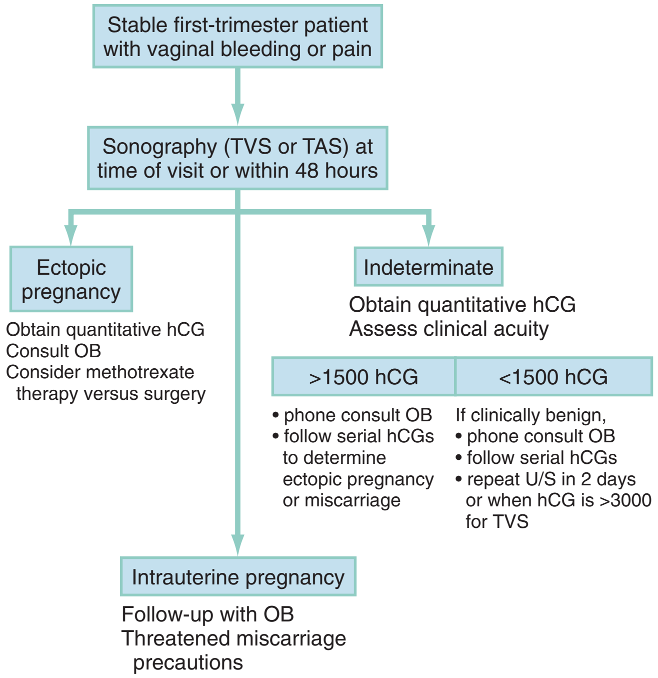


Figure 178-6. Management of vaginal bleeding or pain in the stable first-trimester pregnant patient. *hCG,* human chorionic gonadotropin; *OB,* obstetrics specialist; *TAS,* transabdominal sonography; *TVS,* transvaginal sonography; *U/S,* ultrasonography.

when subsequent fertility is being considered.[41] Methotrexate is the drug most commonly used to treat early ectopic pregnancy. It causes destruction of rapidly dividing fetal cells and involution of the pregnancy. Medical treatment is most often used for patients who are hemodynamically stable with a tubal mass smaller than 3.5 cm in diameter, no fetal cardiac activity, and no sonographic evidence of rupture. Although there is no agreed on cutoff for single-dose methotrexate, a systematic review found that patients with an hCG level above 5000 mIU/mL had an increased failure rate.[43] Medical therapies are associated with an 85 to 93% success rate, with no significant difference between single- and multiple-dose protocols.[44] Pelvic pain is common (60%) in patients receiving methotrexate, even when it is used successfully.[45] Indications of methotrexate failure and need for rescue surgery include decreasing hemoglobin levels, significant pelvic fluid, and unstable vital signs. All patients receiving methotrexate require close follow-up until the hCG level reaches zero, which may take 2 or 3 months.

Molar Pregnancy

Molar pregnancy, also known as gestational trophoblastic disease, comprises a spectrum of diseases characterized by disordered proliferation of chorionic villi. In the absence of fetal tissue, the pregnancy is termed a *complete hydatidiform mole*. More rarely, if fetal tissue is present and trophoblastic hyperplasia is focal, it is called an *incomplete mole*. In approximately 19% of molar pregnancies, neoplastic gestational disease develops, with persistence of molar tissue after the pregnancy has been evacuated.[46,47] Metastatic disease can develop, requiring chemotherapy and intensive oncologic management.

Early molar pregnancy is usually not clinically apparent. The most well described risk factor for development of a molar pregnancy is extremes of maternal age.[48] Many patients present with abdominal pain, nausea and vomiting, or vaginal bleeding, and it may be difficult to differentiate these patients from those with threatened miscarriage or ectopic pregnancy by historical features alone.[49] Patients sometimes seek treatment for apparent persistent hyperemesis gravidarum from high circulating levels of hCG, bleeding or intermittent bloody discharge, or respiratory distress; failure to hear fetal heart tones during the second trimester is the usual initial clue to diagnosis.[50,51] If molar pregnancy spontaneously aborts, it is usually in the second trimester (before 20 weeks), and the patient or physician may note passage of grape-like hydatid vesicles. Uterine size is larger than expected by date (by more than 4 weeks) in approximately 30 to 40% of patients. Theca lutein cysts may be present on the ovaries as a result of excessive hormonal stimulation, and torsion of affected ovaries can be seen.[50,51]

The diagnosis of hydatidiform mole is based on the characteristic sonographic appearance of hydropic vesicles within the uterus, described as a "snowstorm" appearance (Fig. 178-7). Alternatively, cystic changes are seen in partial molar pregnancies. In some cases, partial molar pregnancy is detected only on pathologic examination of abortion specimens.[52] Complications of molar pregnancy include preeclampsia or eclampsia (which can develop before 24 weeks of gestation), pulmonary embolization of trophoblastic cells, hyperemesis gravidarum, and significant uterine bleeding, either acute or chronic. Ultrasonography usually provides the diagnosis of complete molar pregnancy, either in the second-trimester patient who has "threatened miscarriage" or during sonographic assessment for fetal well-being and size. However, ultrasonography is only 58% sensitive, and diagnosis of partial mole is made in 17% of cases.[52] Up to two thirds of molar pregnancies are diagnosed by pathologic specimens after miscarriage.[52]

COMPLICATIONS OF LATE PREGNANCY

Vaginal Bleeding in Later Pregnancy

Perspective

Bleeding during the second half of pregnancy occurs in approximately 4% of pregnancies. Only 20% of miscarriages occur after the first trimester, and the most important differential diagnoses after 12 to 14 weeks of gestation are abruptio placentae and placenta previa. The cause is often not determined, although occult marginal placental separations (which can be recognized only by placental inspection at delivery) are held to be a common source of bleeding from above the cervix. Other causes of late vaginal bleeding include early labor, various cervical and vaginal lesions, lower genital tract infections, and hemorrhoids.

Bleeding during the second trimester before the fetus is potentially viable (14-24 weeks) is not benign. One third of fetuses are ultimately lost when maternal bleeding occurs. Management is supportive and expectant because fetal rescue is impossible at this level of fetal immaturity. In the third trimester, vaginal bleeding is still associated with significant morbidity in approximately one third of women, but the treatment includes consideration of urgent delivery.[53]

Abruptio Placentae

Principles of Disease. Abruptio placentae, or separation of the placenta from the uterine wall, is believed to account for approximately 30% of episodes of bleeding during the second half of pregnancy. In addition, small subclinical or marginal separations may go undetected until the placenta is examined at delivery and probably account for many of the other self-limited episodes of bleeding for which no diagnosis is made. In cases of nontraumatic abruptio placentae, apparently spontaneous hemorrhage into the

www.ketabpezeshki.com 66485457-66963820

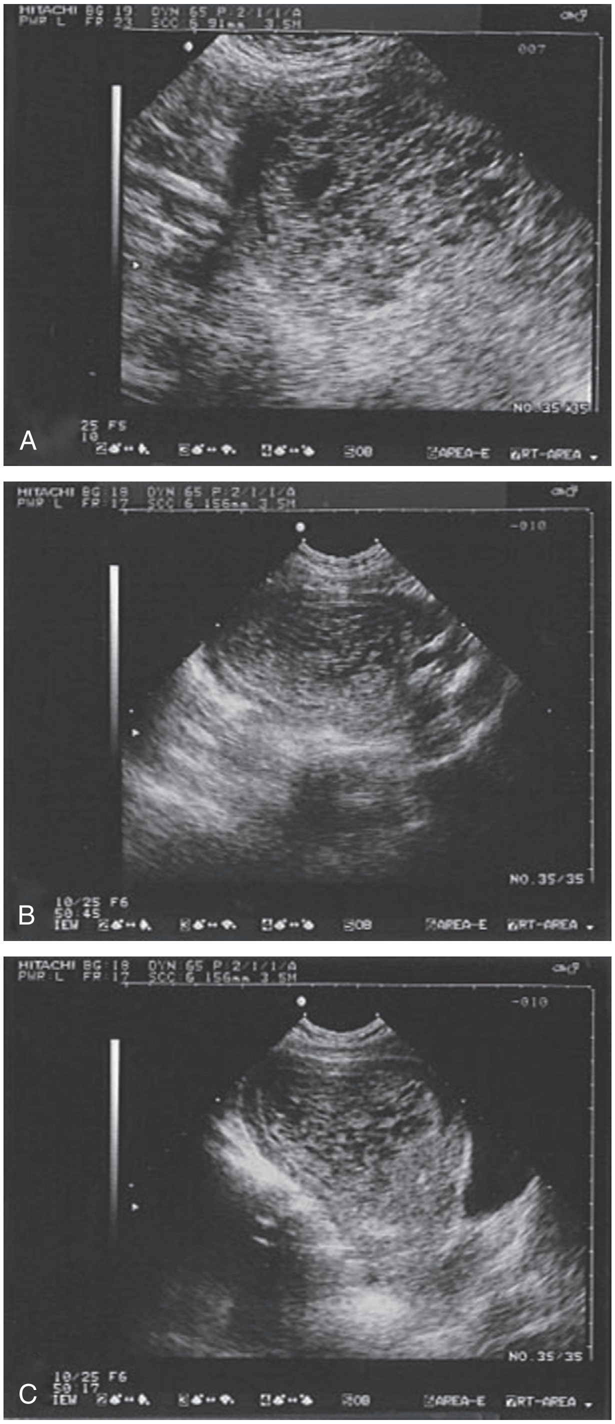


Figure 178-7. Ultrasonography showing molar pregnancy. (Courtesy Mary Ann Edens, MD.)

decidua basalis occurs, causing separation and compression of the adjacent placenta. Small amounts of bleeding may be asymptomatic and remain undetected until delivery. In other instances, the hematoma expands and extends the dissection; bleeding may be concealed or may be clinically apparent if dissection occurs along the uterine wall and through the cervix. Placental separation can be acute or an indolent problem throughout late pregnancy.

Abruptio placentae is most clearly associated with maternal hypertension and preeclampsia; it is also more common with increasing maternal age and parity, history of smoking, thrombophilia, prior miscarriage, prior abruptio placentae, and cocaine use.[53,54] Placental separation can also be associated with blunt trauma to the abdomen. In such instances, the cause appears to be shearing of a nonelastic placenta from the easily distorted elastic uterine wall at the time of traumatic impact. Women who reported physical violence during pregnancy were twice as likely as women who did not report violence to have an abruption.[55]

Clinical Features. Vaginal bleeding occurs in 70% of patients with abruptio placentae.[55] Blood is characteristically dark and the amount is often insignificant, although the mother may have hemodynamic evidence of significant blood loss. Uterine tenderness or pain is seen in approximately two thirds of women; uterine irritability or contractions are seen in one third. With significant placental separation, fetal distress occurs and the maternal coagulation cascade may be triggered, causing disseminated intravascular coagulation.[53]

There is a wide spectrum of severity of symptoms and risk in placental separation. Up to 20% of women will have no pain or vaginal bleeding.[54] Assessment is generally based on clinical features, coagulation parameters, and signs of fetal distress. Slight vaginal bleeding, little or no uterine irritability, absence of signs of fetal distress, and normal coagulation characterize mild abruption. As the separation becomes more extensive, it is associated with more vaginal bleeding (or hidden maternal blood loss), increased uterine irritability with or without tetanic contractions, declining fibrinogen levels, and evidence of fetal distress and maternal tachycardia. In cases of severe abruptio placentae (15% of cases), the uterus is tetanically contracted and very painful, maternal hypotension results from visible or concealed uterine blood loss, fibrinogen levels are less than 150 mg/dL, and fetal death can occur. Ultrasonography is insensitive in the diagnosis of abruptio placentae, often because the echogenicity of fresh blood is so similar to that of the placenta. Symptomatic or even fetus-threatening abruption can occur in the presence of a normal sonogram.[53]

Fetal distress and death occur in approximately 15% of patients with abruptio placentae by interruption of placental blood and oxygen flow. Risk of fetal death increases in proportion to both the percentage of placental surface involved and the rapidity of separation. Fetal distress may result from the loss of placental blood flow, associated maternal hemorrhage (into the uterine cavity or externally), increased uterine tone, or resultant disseminated intravascular coagulation. Maternal death can result, usually from coagulopathy or exsanguination. Fetomaternal transfusion occurs in a significant minority of patients. Placental separation also predisposes the mother to amniotic fluid embolism.

Differential Considerations. The main alternative diagnosis in the woman with late-pregnancy bleeding is placenta previa, which is usually associated with painless, bright red bleeding and must be excluded with ultrasonography. Lower genital tract or rectal lesions and bloody show (blood-tinged cervical mucous plug) are also considerations.

In the patient with abdominal pain but no vaginal bleeding, abruptio placentae with concealed hemorrhage must be distinguished from other causes of abdominal pain in later pregnancy: complications of preeclampsia, pyelonephritis, various liver diseases, gallbladder disease, appendicitis, and ovarian torsion. Uterine irritability caused by abruptio placentae can also be confused with early labor; in one series, almost one fourth of patients were misdiagnosed as having premature labor until fetal distress occurred. If the patient has acute catastrophic hypotension, amniotic fluid embolus (with or without abruptio placentae) and uterine rupture must be considered.[53]

Placenta Previa

Principles of Disease. Placenta previa, or implantation of the placenta over the cervical os, is the other major cause of bleeding episodes during the second half of pregnancy. The risk of placenta

www.ketabpezeshki.com 66485457-66963820

previa is increased with maternal age, multiparity, cesarean section, and preterm labor.[56] Bleeding occurs when marginal placental vessels implanted in the lower uterine segment are torn, either as the lower uterine wall elongates or with cervical dilation near the time of delivery. Early bleeding episodes tend to be self-limited unless separation of the placental margin is aggravated by iatrogenic cervical probing or onset of labor.

Clinical Features. Painless, fresh vaginal bleeding is the most common symptom of placenta previa. In approximately 20% of cases, some degree of uterine irritability is present, but this is usually minor. Vaginal examination usually reveals bright blood from the cervical os. Digital or instrumental probing of the cervix should never be done during the second half of pregnancy because it can precipitate severe hemorrhage in the patient with an asymptomatic or minimally symptomatic placenta previa. In the ED, speculum examination of the vagina and cervix should be performed only in those settings in which obstetric consultation is not readily available. It should be limited to an atraumatic partial speculum insertion to identify whether the bleeding is coming from the cervical os (and a presumed placenta previa), hemorrhoids, or a vaginal lesion that might not require urgent management.

Most cases of placenta previa identified during the midtrimester resolve by the time of delivery as the lower uterine segment elongates and the placenta no longer overlaps the cervical os. Central or total previa (which occurs in approximately 20% of cases) can, however, cause severe hemorrhage, with risk of exsanguination for the fetus and mother.

Diagnostic Strategies. Ultrasonography is the diagnostic procedure of choice for localization of the placenta and diagnosis of placenta previa. Accuracy is excellent; visualization of the placenta as well as of the internal cervical os is required. The bladder should be emptied before examination for suspected placenta previa to avoid overdiagnosis of placenta previa. Transvaginal ultrasonography is safe and even more accurate for visualization of the relationships between the placenta and the internal os.[57]

Management

Patients who experience vaginal bleeding during late pregnancy should have immediate obstetric consultation and arrangements for safe transfer to an appropriate obstetric facility. Initial management consists of maternal stabilization, with establishment of two large-bore intravenous lines and fluid resuscitation, as well as continuous fetal monitoring if it is available. A baseline hemoglobin level should be obtained, and blood should be sent for type and crossmatch; baseline coagulation studies including platelet count, prothrombin time, and partial thromboplastin time should be performed; and fibrinogen level and the presence of fibrin split products should be determined. The normal fibrinogen level in pregnancy is 400 to 450 mg/dL; values below 300 mg/dL indicate significant consumption of coagulation factors.

Blood loss requiring transfusion can occur in patients with placenta previa or abruptio placentae. Fresh frozen plasma or fresh whole blood may be needed because of the coagulopathy associated with significant abruptio placentae. Fetomaternal hemorrhage can occur with abruption. If the Rh-negative patient has not yet received her routine Rh immune globulin prophylaxis at 28 weeks, 300 µg of Rh immune globulin should be administered within 72 hours (unless the father is known to be Rh negative).[58] Transfer to the obstetric unit should be expedited if the patient is stable, or it should be done after initiation of resuscitation if she is unstable. If transfer to another hospital is required, a high-risk transfer team should be used if bleeding is significant or if the fetus is in distress. Although the bleeding source may not be identified or may be relatively benign, assessment is best accomplished by obstetricians who are accustomed to evaluation of late-pregnancy complications and who can perform emergent cesarean section if it is needed.

In the obstetrics unit, fetal monitoring is continued. Ultrasonography is used primarily to locate the placenta and to diagnose placenta previa; it may not be reliable in confirming the diagnosis of abruptio placentae. On occasion, subplacental hemorrhages of abruptio placentae can be seen and changes in size of the collection can be monitored. If evidence of placenta previa is absent or equivocal, vaginal examination is performed in the delivery suite, where emergency cesarean section can be performed if uncontrolled bleeding is encountered.

Patients who have significant abruptio placentae may require early delivery (either vaginal or surgical, depending on fetal status). If placenta previa is diagnosed or if abruptio placentae is considered mild, the patient is admitted for close monitoring. The goal is to support the patient, ideally until fetal maturity is demonstrated and a successful delivery can be accomplished.

Pregnancy-Induced Hypertension (Preeclampsia and Eclampsia)

Perspective

Hypertension is observed in approximately 6 to 8% of pregnancies and is generally divided into several categories.[59] *Gestational hypertension* occurs during pregnancy, resolves during the postpartum period, and is recognized by a new blood pressure reading of 140/90 mm Hg or higher. *Preeclampsia* is gestational hypertension with proteinuria (>300 mg/24 hr), and *eclampsia* is the occurrence of seizures in the patient with signs of preeclampsia. Progression of preeclampsia to eclampsia is unpredictable and can occur rapidly. *Pregnancy-aggravated hypertension* is chronic hypertension with superimposed preeclampsia or eclampsia. *Chronic or coincidental hypertension* is present before pregnancy or persists more than 6 weeks postpartum.[59]

Approximately 2 to 7% of pregnancies are complicated by pregnancy-induced hypertension. The incidence of actual eclampsia has progressively declined, but it is still one of the major causes of maternal mortality. The risk of pregnancy-induced hypertension is greatest in women younger than 20 years; primigravidas; those with twin or molar pregnancies; those with hypercholesterolemia, pregestational diabetes, or obesity; and those with a family history of pregnancy-induced hypertension.[60]

Principles of Disease

Gestational hypertension/preeclampsia is a vasospastic disease of unknown cause unique to pregnant women. Vasospasm, ischemia, and thrombosis associated with preeclamptic changes cause injury to maternal organs, placental infarction and abruption, and fetal death from hypoxia and prematurity. The cause of eclampsia is not known, but recent research has centered on vascular responsiveness to endogenous vasopressors in the preeclamptic woman. Vascular responsiveness is normally depressed during pregnancy, which is a high-output, low-resistance state. Gestational hypertension is characterized by an even greater elevation in cardiac output, followed by an abnormally high peripheral resistance as clinical manifestations of the disease develop. In patients with preeclampsia, the cardiac output eventually drops as peripheral resistance rises.[61] The cause of these changes is not known, but endothelial dysfunction is purported to release vasoactive mediators and to result in vasoconstriction.[62] Antiplatelet agents during pregnancy have been reported to reduce the risk of development of preeclampsia, supporting the premise of an imbalance between levels of thromboxane and prostacyclin in preeclampsia.[63]

The vasospastic effects of gestational hypertension/preeclampsia are protean. Intravascular volume is lower than in normal

www.ketabpezeshki.com 66485457-66963820

pregnancy, central venous pressures are normal, and capillary wedge pressures are variable. Liver effects are believed to be due to hepatocellular necrosis and edema resulting from vasospasm. Renal injury causes proteinuria and may result in decreased glomerular filtration. Microangiopathic hemolysis may result from vasospasm, causing thrombocytopenia. Central nervous system effects include microvascular thrombosis and hemorrhage as well as focal edema and hyperemia.[60]

Clinical Features

Signs and Symptoms. The patient with gestational hypertension has mild systolic or diastolic blood pressure elevation, no proteinuria, and no evidence of organ damage. Mental status assessment, testing of reflexes, abdominal examination, liver function studies, and coagulation studies should yield normal results. Preeclampsia is associated with kidney changes and, in severe cases, other end-organ symptoms. Edema is often difficult to assess because pregnancy is normally associated with excess extracellular fluid and dependent edema, and it is no longer used as a criterion for preeclampsia. Proteinuria (300 mg/24 hr) is variable at any given time and may not be detectable in a random urine specimen.[59]

In cases of severe preeclampsia, diastolic blood pressure can exceed 110 mm Hg, proteinuria is more severe, and there is evidence of vasospastic effects in various end organs. Central nervous system effects commonly include headache or visual disturbances. Thrombocytopenia may be present, liver function test findings may be elevated, and the liver is often tender. Renal dysfunction may be indicated by oliguria and elevated creatinine levels in addition to proteinuria.

Complications. The HELLP syndrome, a particularly severe form of preeclampsia that develops in 5 to 10% of women who have preeclamptic symptoms, is characterized by *h*emolysis, *e*levated *l*iver enzymes, and *l*ow *p*latelet count (100,000/mL). Prothrombin time, partial thromboplastin time, and fibrinogen level are normal, and blood studies reveal microangiopathic hemolytic anemia. Other complications of preeclampsia include spontaneous hepatic and splenic hemorrhage and abruptio placentae.

The most dangerous complication is eclampsia, which is the occurrence of seizures or coma in the setting of signs and symptoms of preeclampsia. Warning signs for development of frank eclampsia include headache, nausea and vomiting, and visual disturbances.[64] Elevated total leukocyte count, creatinine, and aspartate aminotransferase are also predictive of increased morbidity for the patient with severe preeclampsia.[65] Particularly in early eclampsia before 32 weeks of gestation, seizures may develop abruptly and hypertension may not be associated with edema or proteinuria.[66] In postpartum women who have eclampsia, more than half (55%) are not previously diagnosed with preeclampsia, and patients may present with headache, vision changes, elevated blood pressure, or seizure up to 4 weeks after delivery.[67] After 48 hours postpartum and without predelivery signs of preeclampsia, other diagnoses, such as intracranial hemorrhage, should be considered. Maternal complications of eclampsia include permanent central nervous system damage from recurrent seizures or intracranial bleeding, renal insufficiency, and death.

The maternal mortality rate from eclampsia has been reduced with modern management and is currently less than 1%. Perinatal mortality has also decreased, although it remains 4 to 8%.[60] Causes of neonatal death include placental infarcts, intrauterine growth retardation, and abruptio placentae. In addition, fetal hypoxia from maternal seizures and the complications of premature delivery contribute significantly to fetal mortality and morbidity.

Diagnostic Strategies

The patient who has severe preeclampsia should have an intravenous line and fetal monitoring initiated in a quiet but closely observed area. Blood testing should include complete blood cell count, renal function studies, liver function tests, platelet count, and coagulation profile. A baseline magnesium level should also be obtained. In the patient with actual seizures, serum glucose concentration should be tested. If a history of preeclampsia is not obtained or the symptoms are refractory to magnesium sulfate therapy, a computed tomography (CT) scan of the head should be performed to exclude cerebral venous thrombosis or an intracranial bleed, either of which can occur in pregnancy (with or without pregnancy-induced hypertension) and may require specific treatment. CT scan abnormalities can be seen in half of patients with eclampsia. Patchy hemorrhage and microinfarcts of the cortex are characteristic and may be due to loss of cerebral autoregulation in patients with severe pregnancy-related hypertension. Diffuse cerebral edema can also be seen.[68]

Differential Considerations

Peripheral edema is common in normal pregnancy, and it may be difficult to differentiate normal edema from that of early preeclampsia. Differentiation of gestational hypertension from preexistent hypertension is often impossible if no record of normal blood pressure is available. Seizures during pregnancy may be due to epilepsy as well as other intracranial catastrophes, such as thrombosis or hemorrhage.

Management

In the patient who has mild preeclampsia, appropriate management includes documentation of blood pressure and reflexes, weight, and testing to ensure normal end-organ function. Accurate determination of gestational age by ultrasonography is needed to allow optimal management if symptoms progress. Limitation of physical activities (including bed rest) is the only demonstrated means of reducing blood pressure and allowing the pregnancy to be sustained longer. Definitive treatment is delivery of the fetus, although expectant management is standard in women at less than 34 weeks of gestation. Arrangement for close follow-up is important for patients who are not hospitalized.

Hospitalization is usually required for patients with sustained hypertension above 140/90 mm Hg and signs of severe preeclampsia. Baseline laboratory studies to identify end-organ effects in the liver, kidney, and hematologic systems should be obtained. Both diuresis and antihypertensive therapy have been remarkably unsuccessful in improving fetal outcome or prolonging pregnancy. Admission does, however, allow the obstetrician to accurately assess fetal age and well-being, maternal organ function, and the effect of bed rest on blood pressure before the optimal timing of delivery is decided.[59]

Fulminant or severe preeclampsia, with marked blood pressure elevation (160/110 mm Hg) associated with epigastric or liver tenderness, visual disturbance, or severe headache, is managed in the same way as eclampsia (Box 178-4). The goal is prevention of seizures and permanent damage to maternal organs. Magnesium sulfate is given for seizure prophylaxis.

Seizures and coma are the hallmarks of eclampsia, the ultimate consequence of preeclampsia. As in all seizure patients, hypoglycemia, drug overdose, and other causes of seizures should be excluded with appropriate tests. Eclamptic seizures are controlled in almost all patients by adequate doses of magnesium sulfate, although the mechanism of action remains elusive. Magnesium has little antihypertensive effect but is the most effective anticonvulsant, preventing recurrent seizures while maintaining uterine

www.ketabpezeshki.com 66485457-66963820

Box 178-4 Management of Eclampsia and Severe Preeclampsia

Control seizures with magnesium sulfate.
Control hypertension after seizure control if diastolic blood pressure >105 mm Hg.
Obtain initial laboratory studies to assess organ injury:
- Complete blood count and platelet count
- Liver function tests
- Blood urea nitrogen, creatinine

Monitor urine output: maintain at <25 mL/hr.
Limit intravenous fluid administration unless significant losses occur.
Avoid diuretics and hyperosmotic agents.
Perform a computed tomography scan of head if consciousness is decreased or seizures persist, lateralizing signs are present, or there are other concerns.
Initiate steps to delivery.

Modified from Pritchard J, et al: The Parkland Memorial Hospital protocol for treatment of eclampsia: Evaluation of 245 cases. Am J Obstet Gynecol 161:261, 1989.

and fetal blood flow. The goals of magnesium sulfate therapy are to terminate ongoing seizures and to prevent further seizures. An intravenous loading dose of 6 g magnesium, followed by 2 g/hr intravenously, is recommended. Magnesium administration should be accompanied by clinical observation for loss of reflexes (which occurs at approximately 10 mg/dL) or respiratory depression (which occurs at levels of 12 mg/dL, although actual serum magnesium levels are rarely monitored). The infusion should be stopped if signs of hypermagnesemia are seen; such patients may require assisted ventilation. Calcium gluconate, 1 g given slowly into a secure vein, will reverse the adverse effects of hypermagnesemia.[60]

Despite ongoing controversy, the familiarity with magnesium sulfate and its physiologic advantages to the fetus, wide margin of safety, and high success rate in controlling seizures make it the first-line drug in patients with eclampsia. A Cochrane review found that magnesium sulfate is more effective than other anticonvulsants and diazepam for prophylaxis against or treatment of eclamptic seizures, more than halving the risk.[69] If seizures persist after the recommended doses of magnesium sulfate have been administered, further therapy should be given in conjunction with obstetric consultation, and a careful search for other causes of seizures (e.g., hypoglycemia and intracranial bleed) should be instituted.

Although magnesium sulfate is not a direct antihypertensive, the hypertension associated with eclampsia is often controlled adequately by stopping of the seizures. Rapid lowering of blood pressure can result in uterine hypoperfusion, so specific antihypertensive treatment is initiated only if the diastolic blood pressure remains above 105 mm Hg after control of seizures. Many patients do not require specific antihypertensive treatment after treatment with magnesium sulfate. The antihypertensive used most often by obstetricians is hydralazine. The dose is 5 mg intravenously, with repeated doses of 5 to 10 mg intravenously every 20 minutes as needed to keep the diastolic blood pressure below 105 mm Hg. Nimodipine and labetalol have also been reported to be safe and effective, although they are less widely used.[70] Other antihypertensive agents are not well studied in this population because there are specific risks to uncontrolled lowering of blood pressure and loss of uteroplacental blood flow.

Although total body water in the eclamptic patient is excessive, intravascular volume is contracted and the eclamptic patient is sensitive to further volume changes. Hypovolemia results in decreased uterine perfusion. Thus diuretics and hyperosmotic agents should be avoided in patients with eclampsia. Although intravascular volume expansion in the face of volume contraction, increased systemic resistance, and vasospasm would seem reasonable, invasive monitoring has demonstrated that vasospasm is not reversed with intravenous fluid administration. Rather, excessive intravenous fluids increase extravascular fluid stores that are difficult to mobilize postpartum, resulting in a higher incidence of pulmonary edema in patients treated aggressively with fluid therapy. Invasive pulmonary artery pressure monitoring may be required for accurate fluid management in the eclamptic patient.

Amniotic Fluid Embolus

Perspective

Amniotic fluid embolus is the release of amniotic fluid into the maternal circulation during intense uterine contractions or uterine manipulation or at areas of placental separation from the uterine decidua basalis (abruptio placentae), triggering a rapidly fatal anaphylactoid-type maternal response. Although amniotic fluid embolus most commonly occurs during labor, in which circumstance the maternal mortality rate is 25% or higher, it can also occur after induced abortions and miscarriages and spontaneously during the second and third trimesters. Amniotic fluid embolus can also occur after amniocentesis or in association with abruptio placentae after abdominal trauma. Although it is a rare syndrome, amniotic fluid embolus is responsible for 13 to 30% of maternal deaths and is the second leading cause of direct maternal death.[71]

Clinical Features

Amniotic fluid embolus should be suspected during the second or third trimester of pregnancy, particularly in the setting of uterine manipulation or contraction, when a patient experiences sudden hypotension, hypoxia, and coagulopathy. The embolization of amniotic fluid and the particulate matter suspended in it triggers a profound immunologic response when it enters the maternal circulation. The list of proposed mediators is extensive and includes histamine, endothelin, and leukotrienes.[71] In survivors, disseminated intravascular coagulation, acute respiratory distress syndrome, and left ventricular dysfunction develop. An initial seizure is seen in approximately 20% of patients. Bleeding diathesis may be the initial sign in some women, and disseminated intravascular coagulation occurs in approximately 50%.

Diagnostic Strategies

When amniotic fluid embolus is suggested, a complete blood cell count, coagulation studies, arterial blood gas analysis, and chest radiograph should be obtained. Urine output should be monitored after urinary catheter placement. The diagnosis is usually made with certainty only at autopsy, with the finding of fetal hairs, squamous cells, and debris in the maternal circulation. Because squamous epithelial cells can be seen normally in the maternal pulmonary circulation, the typical clinical syndrome is also required for diagnosis.[71]

Differential Considerations

Catastrophic pulmonary embolus, drug-induced anaphylaxis, and septic shock must be considered in the differential diagnosis. Seizure occurs in patients with eclampsia, but hypertension rather than cardiovascular collapse should be observed in that condition. Coagulopathy may be seen in patients with preeclampsia (HELLP

www.ketabpezeshki.com 66485457-66963820

syndrome), abruptio placentae, or other chronic coagulopathies seen in the nonpregnant patient.

Management

Amniotic fluid embolus is uncommon, so treatment is mainly anecdotal and based on animal studies. The most helpful modalities appear to be high-flow oxygen, support of ventilation and oxygenation with intubation, aggressive fluid resuscitation, inotropic cardiovascular support, and anticipation and management of consumptive coagulopathy. Adequate management usually requires invasive hemodynamic monitoring in an intensive care unit.

Rh (Anti-D) Immunization in Pregnancy

Rh immunization occurs when an Rh-negative woman is exposed to Rh-positive fetal blood. Small numbers of fetal cells enter the maternal circulation spontaneously throughout pregnancy, but the maternal immune system is triggered only by significant loads of fetal cells, which can occur during the third trimester and at delivery. Sensitization occurs in up to 15% of Rh-negative women carrying Rh-positive fetuses. To prevent this, anti-D immune globulin (RhoGAM) is routinely administered to Rh-negative mothers (if the father is Rh positive or his status is unknown) at approximately the 28th week of gestation to protect the mother from spontaneous sensitization, which occurs during the third trimester. Transplacental hemorrhage can also occur during uterine manipulation, threatened miscarriage (even without fetal loss), spontaneous miscarriage, surgery for ectopic pregnancy, and amniocentesis, although the risk is not clear. Anti-D immune globulin should be administered when these events occur. A dose of 50 μg can be used if the patient is at less than 12 weeks of gestation, although many pharmacies carry only the 300-μg dose, which can also be given. After 12 weeks, a 300-μg dose should be given. The half-life of immune globulin is 24 days, and it needs to be administered within 72 hours of a sensitization event to prevent antibody development.[14]

The Kleihauer-Betke test of maternal blood has been used to detect fetal cells in the maternal circulation. Unfortunately, the test is difficult to perform, not immediately available in most emergency laboratories, and only sensitive enough to detect 5 mL of fetal cells in the maternal circulation. Because only 0.1 mL of fetal cells is required to sensitize the mother, routine immune globulin administration has been recommended in situations likely to result in sensitization. Patients with third-trimester bleeding are not at increased risk of sensitization compared with patients with normal pregnancy; RhoGAM should be administered only if the patient did not receive her prophylactic dose at 28 weeks.[58] In instances of significant blunt trauma to the uterus, the Kleihauer-Betke test should be ordered to detect the rare large fetal transfusions that may require specific fetal blood therapy or administration of additional immune globulin to the mother. The standard dose (300 μg) is sufficient to prevent maternal immunization for fetal transfusions of up to 15 mL of red blood cells or 30 mL of whole blood.[14]

MEDICAL AND SURGICAL PROBLEMS IN THE PREGNANT PATIENT

Perspective

Clinicians should be aware of a variety of illnesses, both related and unrelated to pregnancy, that may have altered symptoms, risk, and treatment in the pregnant patient (Tables 178-2 and 178-3).

Table 178-2 Differential Diagnosis of Abdominal Pain in Pregnancy

DIAGNOSIS	GESTATIONAL AGE	COMMENTS
Gynecologic		
Miscarriage	<20 weeks, 80% <12 weeks	Ultrasonography to confirm location
Septic abortion	<20 weeks	Fever, uterine tenderness
Ectopic pregnancy	<14 weeks	Must always be considered in first trimester until intrauterine pregnancy confirmed
Corpus luteum cyst	<12 weeks	Sudden focal peritoneal pain; no fever
Ovarian torsion	Especially <24 weeks	Ischemic pain
Pelvic inflammatory disease	<12 weeks	Very rare
Chorioamnionitis	>16 weeks	Tender uterus, fever; amniocentesis reveals white blood cells
Abruptio placentae	>16 weeks	Focal uterine tenderness, fetal distress, variable bleeding
Preeclampsia	>20 weeks	Hypertension, proteinuria, edema, right upper quadrant pain
Nongynecologic		
Appendicitis	Throughout	Guarding may be less prominent; location changes
Cholecystitis	Throughout	Confirm with ultrasonography
Hepatitis	Throughout	Confirm with liver function tests
Pyelonephritis	Throughout	Flank pain, fever, positive catheterized urinalysis

Abdominal Pain

Appendicitis

Perspective. Appendicitis is the most common surgical emergency in pregnant patients. The incidence of appendicitis in pregnant patients is the same as that in nonpregnant patients, but delays in diagnosis contribute to an increased rate of perforation, which results in significant fetal mortality and maternal morbidity.[72,73] During the first half of pregnancy, diagnostic findings are usually similar to those in the nonpregnant woman, but the clinical picture becomes less classic during the second half of pregnancy.

Principles of Disease. Traditionally, the appendix was thought to be displaced counterclockwise out of the right lower quadrant after the third month of gestation, with its ultimate location deep in the right upper quadrant, superior to the iliac crest (Fig. 178-8). However, one study found that in only 23% of pregnant patients does the location change from the right lower quadrant, even in the third trimester.[74] Displacement of the abdominal wall away from the abdominal viscera can result in difficulty in palpation of organs and loss of signs of parietal peritoneal irritation. The physiologic increase in white blood cell count and erythrocyte sedimentation rate in pregnancy should also be considered in the evaluation of the patient with possible appendicitis because these may confuse the overall clinical picture.

www.ketabpezeshki.com 66485457-66963820

Table 178-3 Differential Diagnosis of Common Symptoms in Pregnancy

DIAGNOSIS	GESTATIONAL AGE	COMMENTS
Vaginal Bleeding		
Miscarriage	<20 weeks	Usually no fetal heart activity at 8 weeks; decreasing hCG level
Ectopic pregnancy	<14 weeks	Evaluate with ultrasonography
Molar pregnancy	12-24 weeks	No fetal heart tones, characteristic sonogram
Cervical lesions	Throughout	Perineal and vaginal inspection
Vaginitis, cervicitis	Throughout	White blood cells on wet mount, with culture
Placenta previa	>16 weeks	Ultrasonography to localize placenta
Abruptio placentae	>16 weeks	Ultrasonography to exclude previa; fetal distress, tenderness
Seizure		
Eclampsia	>24 weeks	Blood pressure >140/90 mm Hg; usually history of PIH, edema, proteinuria
Amniotic fluid embolus	>12 weeks	Hypotension, respiratory distress, DIC
Epilepsy	Throughout	History; lack of PIH findings
Dyspnea		
Pulmonary embolus	Especially 6 weeks prepartum and postpartum	Usual diagnostic studies
Dyspnea of pregnancy	>24 weeks	Exclude other causes
Pulmonary infection	Throughout	Examination; radiography
Amniotic fluid embolus	>12 weeks	Uterine manipulation, bleeding diathesis, hypotension
Jaundice		
Cholestasis of pregnancy	>24 weeks	Well patient; itching and jaundice
Hepatitis	Throughout	Abnormal liver function test results
Acute fatty liver	>24 weeks	Rapid liver failure; coma, seizures, hypoglycemia
Bleeding Diathesis		
Eclampsia	>24 weeks	Blood pressure >140/90 mm Hg; proteinuria, edema, HELLP syndrome
Amniotic fluid embolus	>12 weeks	Respiratory distress, cardiovascular collapse
Abruptio placentae	>20 weeks	Uterine tenderness; vaginal bleeding; fetal distress

DIC, disseminated intravascular coagulation; *hCG,* human chorionic gonadotropin; *HELLP,* hemolysis, elevated liver enzymes, low platelets; *PIH,* pregnancy-induced hypertension.

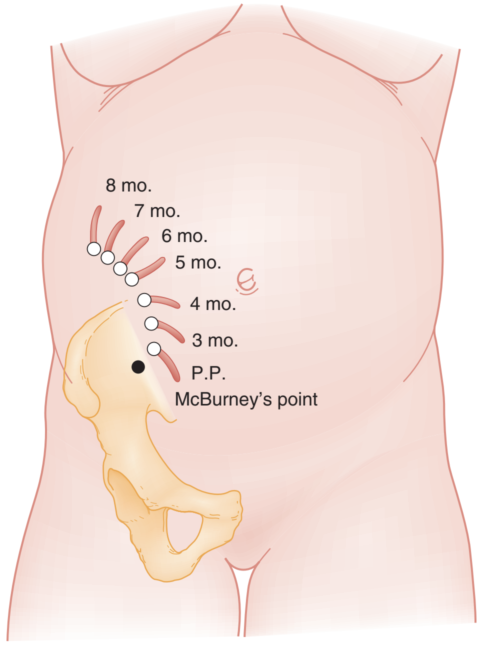


Figure 178-8. Locations of the appendix during succeeding months of pregnancy. In planning an operation, it is better to make the abdominal incision over the point of maximal tenderness unless there is great disparity between that point and the theoretic location of the appendix. *P.P.,* postpartum. (From Gabbe SG, et al [eds]: Obstetrics: Normal and Problem Pregnancies. New York, Churchill Livingstone, 2007. Redrawn from Baer JL, Reis RA, Arens RA: Appendicitis in pregnancy. JAMA 98:1359, 1932.)

Clinical Features. The gastrointestinal symptoms of appendicitis, such as anorexia, nausea, and vomiting, mimic those of pregnancy, particularly during the first trimester, making such symptoms relatively nonspecific. Right-sided abdominal pain is the most constant finding, although this is less reliable later in pregnancy. Peritoneal signs are likewise most common during the first trimester. Lack of fever, leukocytosis, or tachycardia has been reported.[74,75] The cause of these differences in clinical findings in pregnant patients with appendicitis may be a blunted inflammatory response from elevated maternal levels of pregnancy-related steroids. Pyuria without bacteriuria is seen in up to 58% of patients.[76]

Because of confounding factors, the misdiagnosis rate for appendicitis is 30 to 35% overall in pregnancy, with a 40 to 50% rate of removal of normal appendix during the third trimester.[74,76] In contrast to the relative safety of performing an exploratory laparotomy or laparoscopy during pregnancy, the risk of fetal loss and maternal morbidity from failure to diagnose appendicitis and perforation is considerable, so clinical vigilance is required even in the absence of classic signs. In later pregnancy, when peritoneal signs are often absent and the uterus obscures normal physical findings, diagnosis is frequently delayed, and the perforation rate may approach 25%.

Differential Considerations. Pyelonephritis, cholecystitis, nephrolithiasis, and pregnancy-related diseases such as ectopic pregnancy, broad ligament pain, corpus luteum cyst leakage, and ovarian torsion should be considered in the patient who has right-sided abdominal pain. Pyelonephritis is the most common condition that is confused with appendicitis. During its migration, the appendix takes up a position very near the kidney, resulting in a high incidence of pyuria and flank pain (see Fig. 178-8). In cases of appendicitis, unless there is coincident urinary tract infection, the urine is free of bacteria, a feature distinguishing it from

www.ketabpezeshki.com 66485457-66963820

pyelonephritis. Salpingitis, another common misdiagnosis, is very rare in pregnancy, although it can occur before 12 weeks of gestation.

Diagnostic Strategies. Leukocytosis is common in pregnant patients with appendicitis, although it is rarely high enough to distinguish it from the physiologic leukocytosis of pregnancy. Pyuria in a catheterized urine specimen suggests pyelonephritis, but it is also seen in 20% of patients with appendicitis.[74] Bacteriuria is uncommon. Ultrasonography, with graded-compression techniques, may reveal a noncompressible tubular structure in the right lower quadrant consistent with appendicitis. Studies regarding the diagnostic utility of ultrasonography in the diagnosis of appendicitis are limited but suggest that it has a high positive predictive value but a low negative predictive value.[76,77] Butala and colleagues recommend abdominal ultrasonography as the first imaging modality for patients, and if it is inconclusive, CT is the next imaging modality.[78] When it is available, magnetic resonance imaging (MRI) is also useful in evaluation of pregnant patients with suspected appendicitis (see Chapter 93). Otherwise, laparoscopy or laparotomy is the diagnostic procedure of choice in the pregnant patient thought to have appendicitis. Early exploration is to be encouraged even more in pregnant than in nonpregnant patients because of the variability of clinical signs and the increased fetal risk if diagnosis is delayed.

Management. The pregnant patient with suspected appendicitis should be admitted to the hospital after appropriate consultation with surgeons and obstetricians. Ultrasonography, MRI, or CT scan should be considered diagnostic options. The patient should be kept on nothing by mouth (NPO) status, with intravenous fluid hydration to maintain intravascular volume. Although prompt surgery is required if the diagnosis is clear, in unclear cases a period of inpatient observation may allow clarification of signs and symptoms.

Gallbladder Disease

Perspective. Cholelithiasis is present in approximately 5% of pregnant women and is the second most common nonobstetric surgical condition in pregnant patients. The natural history of asymptomatic cholelithiasis is believed to be similar to that in nonpregnant women, with less than half of patients with gallstones developing symptoms.[79]

Principles of Disease. Changes in gallbladder kinetics are believed to be due to high pregnancy-related steroid levels. Progesterone decreases smooth muscle tone and induces gallbladder hypomotility and cholestasis, causing an increased risk of stone formation. In addition, pregnancy induces changes in bile composition and increased cholesterol secretion, thus increasing the incidence of cholesterol stone formation.[80]

Clinical Features. The signs and symptoms of acute cholecystitis during pregnancy are the same as those in nonpregnant women. Epigastric or right upper quadrant pain and tenderness and nausea predominate. Leukocytosis must be interpreted carefully because of the increased white blood cell count seen normally in pregnancy. Likewise, a slightly elevated amylase level can be normal during pregnancy, and alkaline phosphatase, which is produced by the placenta, may be twice the nonpregnant level. A history of self-limited pain episodes associated with food intake is useful in suggesting the diagnosis.

Diagnostic Strategies. Ultrasonography is a reliable means of recognizing stones within the gallbladder, although it may not differentiate symptomatic from asymptomatic stones. In the patient with right upper quadrant pain, simultaneous sonographic evaluation of the liver is useful but technically difficult, particularly during the third trimester, when subcapsular liver hematomas and other intrinsic hepatocellular disease can occur but the liver may be obscured under the ribs.

Differential Considerations. Pyelonephritis should be considered in the patient with right upper quadrant pain with or without fever. During the third trimester, appendicitis can also be associated with right upper quadrant pain. Hepatitis and fatty liver infiltration occur in pregnancy; liver distention and inflammation associated with pregnancy-induced hypertension can also cause right upper quadrant pain. In addition, spontaneous intrahepatic bleeding can occur in late pregnancy, mimicking cholecystitis. Because of the potential for other serious diseases, diagnostic studies should always be performed to verify a clinical diagnosis of symptomatic cholelithiasis and cholecystitis in pregnancy.

Management. The patient who has fever, leukocytosis, prolonged pain, or evidence of cholecystitis should be made NPO and given intravenous fluid hydration, adequate pain control, and broad-spectrum antibiotics. These patients must be admitted for inpatient management. Some patients can be managed medically for prolonged or complicated cholecystitis. Patients with obstructive jaundice, gallstone pancreatitis, or sepsis or patients who fail to respond to conservative management should have surgery. Discharge should be considered only in patients with uncomplicated and sonographically proven cholelithiasis who do not meet admission criteria after consultation with an obstetrician. Pregnant patients with symptomatic cholelithiasis have a high rate of symptomatic relapse and increased severity of disease with each relapse.[81] Early follow-up should be arranged and the patient should be given careful instructions to return if she experiences fever, vomiting, or persistent pain. In one study, patients who were observed during pregnancy had a higher rate of pregnancy-related complications (36%) in contrast to much lower rates of complications in those who had laparoscopic cholecystectomy.[82]

Liver Disorders

Perspective. Pregnancy is associated with several unique liver abnormalities in addition to more usual hepatic diseases. Clinicians should recognize the various symptoms of liver disease during pregnancy as well as the hepatic diseases unique to pregnant women. Liver metabolism increases during pregnancy, but hepatic blood flow is unchanged, and little change occurs in liver function. Bilirubin, transaminase, and lactate dehydrogenase levels and prothrombin times are unchanged from the nonpregnant state. Albumin levels decrease secondary to an increase in maternal circulating plasma volume. Alkaline phosphatase levels may be up to double the nonpregnant values, and amylase levels may also be slightly elevated.[83,84]

Hepatitis

Hepatitis is the most common cause of liver disease in pregnancy, accounting for 40% of cases of jaundice in pregnancy. Management and treatment are supportive and unchanged from those for nonpregnant patients. Hepatitis E, however, has been reported to have a more aggressive course in pregnancy.[84] Maintenance of adequate nutrition is a priority. Vertical transmission of hepatitis B can occur if the disease is not recognized. Prophylaxis should be administered to the newborn.

Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy is a disorder of the third trimester that can result in hepatic failure, complicated labor, and fetal mortality. The disease is rare, occurring most often in primiparous patients and patients with twin gestations.

Principles of Disease. The cause of acute fatty liver of pregnancy is unknown, although studies suggest that a deficiency in the fetus's fatty acid metabolism leads to an accumulation of hepatotoxic metabolites in the maternal circulation.[84-87] On microscopic examination, fatty infiltration of the hepatocytes with edema and vacuolization can be seen, but there is no necrosis or

www.ketabpezeshki.com 66485457-66963820

inflammation. Liver function returns to normal after delivery if the patient can be supported through the acute phase. Although up to 50% of patients have signs of preeclampsia, the two are not clearly related.[87] The diagnosis must be differentiated from viral hepatitis and HELLP syndrome, which have similar disease presentations and laboratory findings but, again, are not clearly related.[84,85]

Clinical Features. Nausea and vomiting associated with malaise or jaundice during the third trimester should trigger consideration of a diagnosis of acute fatty liver.[88] The right upper quadrant or epigastrium is usually tender. The disease may progress to coagulopathy, jaundice, seizures, disseminated intravascular coagulation, and hepatic encephalopathy. The diagnosis is often delayed secondary to the multiple differential considerations.

Diagnostic Strategies. Typically, leukocytosis is present, the platelet count and fibrinogen level are low, prothrombin time and partial thromboplastin time are elevated, and fibrin split products are present. In a series of 11 patients, raised transaminase and serum bilirubin concentrations were found in all patients, hypoglycemia was found in 18%, and hypoproteinemia was found in 46%.[88] In contrast to Reye's syndrome, the serum ammonia level is only mildly elevated. Hyperuricemia is usually present. Bilirubin is elevated late in the course of the disease. The CT scan and the sonogram may be normal, so liver biopsy is used to make the definitive diagnosis.

Differential Considerations. Liver tenderness and coagulopathy most often suggest preeclampsia during the third trimester. Jaundice and increases in aminotransferase level are distinguishing features because they are unusual in cases of liver disease associated with pregnancy-induced hypertension. Similarly, rapid progression of hepatic failure, hypoglycemia, and coagulopathy is unlikely in cases of preeclampsia. The patient with viral hepatitis is likely to have more marked elevations in transaminase levels. Drug-induced hepatic failure should be excluded by history and toxicologic screen for acetaminophen or other toxins if appropriate. Cholecystitis may be distinguished by ultrasound examination, but it may also be characterized by right upper quadrant pain; it is not associated with coagulopathy or progressive liver failure.

Management. The patient with acute fatty liver of pregnancy requires immediate stabilization if she is experiencing seizure or coma. Hypoglycemia may occur, which should be rapidly corrected with dextrose. Coagulation parameters should be assessed. Fluid resuscitation and replacement of clotting factors may be required, and the patient should be admitted to an obstetric service capable of managing this serious disease. The diagnosis is usually made with liver biopsy if the disease has not progressed to severe coagulopathy. Rapid delivery is usually advisable when the diagnosis has been established. Fresh frozen plasma, platelet transfusions, and glucose may be needed to sustain the patient until delivery can be accomplished.

Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy, also termed idiopathic jaundice of pregnancy, icterus gravidarum, or pruritus gravidarum, is a rare syndrome that occurs during the third trimester of pregnancy. It is the second most common cause of jaundice in pregnancy, after hepatitis. On histologic examination, the disease is characterized by cholestasis and dilated canaliculi in the biliary tree. The liver is normal. It is more common with increasing maternal age, with multiple gestations, and in the winter months.[84]

Clinical Features. Generalized pruritus and mild jaundice are the hallmarks of intrahepatic cholestasis of pregnancy. Only 20% of patients present with this combination, however, and 80% present with pruritus alone. The pruritus usually begins in the palms and soles and ascends to the trunk. Although insomnia and fatigue occasionally accompany the pruritus, the patient appears nontoxic, without fever, vomiting, diarrhea, or significant malaise. The bilirubin level is rarely above 5 mg/dL, the alkaline phosphatase level can be elevated sevenfold to tenfold, and transaminase levels are in the normal range. Resolution occurs when the woman delivers. Although maternal outcome is favorable, women with intrahepatic cholestasis of pregnancy are at increased risk for preterm delivery, meconium passage, and intrauterine fetal demise.[84,89]

Differential Considerations and Management. Exclusion of more serious entities, such as viral hepatitis, acute fatty liver, drug-induced cholestasis, and complicated cholecystitis, is required. Outpatient management is appropriate, provided the diagnosis is clear and the patient has close obstetric follow-up. Some authors advocate aggressive fetal surveillance and delivery after fetal lung maturity to improve fetal outcome.[84] Symptomatic treatment with antihistamines, ursodeoxycholic acid, bile salts, guar gum, benzodiazepines, and other medications has been tried with variable success.[90]

Hyperemesis Gravidarum

Nausea and vomiting are common in pregnancy, particularly from 6 to 20 weeks of gestation. Hyperemesis gravidarum is defined as nausea and vomiting that cause starvation metabolism, weight loss, dehydration, and prolonged ketonemia and ketonuria. It occurs in a small minority of pregnant patients. The cause of hyperemesis gravidarum is not clear; associations have been made with increasing estradiol and hCG levels as well as with maternal cytokines.[91,92] Several studies have suggested an increased infection rate with *Helicobacter pylori* in patients with hyperemesis gravidarum, and Mansour showed that a nonteratogenic regimen for *H. pylori* treatment resulted in decreased vomiting in hyperemesis patients.[93] Initial management involves rehydration with intravenous fluids, antiemetics, and demonstration of ability to take oral hydration. Patients may require enteral nutrition. Most standard antiemetics are in Food and Drug Administration category C and are used successfully to treat hyperemesis gravidarum.[94] A short course of oral prednisolone has been reported to be therapeutic for intractable hyperemesis.[95,96] Oral vitamin B_6 has also been reported to be helpful.[97] Bilirubin and alkaline phosphatase levels can be mildly elevated but should return to normal after delivery. Hyperemesis may be complicated by liver disease and abnormal liver function test results, which are expected to resolve with supportive treatment.[97]

Thromboembolic Disease in Pregnancy

Principles of Disease

Thromboembolic disease accounts for almost 20% of obstetric mortality, making it the leading cause of death in pregnancy.[24] Pregnancy is a hypercoagulable state, with increased coagulation factors and stasis as pregnancy progresses and significant vascular trauma at the time of delivery. The risk of venous thrombosis increases during pregnancy to five or six times that of nonpregnant women. Although the risk is increased throughout pregnancy, it is highest during the puerperium. Risk factors include smoking, obesity, age older than 35 years, hypercoagulable state, varicose veins, and prior superficial venous thrombosis. Women who deliver prematurely or have postpartum hemorrhage are also at higher risk.[98-101]

Clinical Features

As in nonpregnant patients, clinical signs of pain, tenderness, and swelling are poor predictors of deep venous thrombosis (DVT) in pregnancy. The clinical diagnosis of pulmonary embolus (PE) is

www.ketabpezeshki.com 66485457-66963820

likewise difficult. Although tachypnea, tachycardia, dyspnea, and pleuritic pain are commonly associated with PE, the symptoms are nonspecific and may be associated with such diverse diseases as hepatic inflammation, pyelonephritis, and diaphragmatic impingement from a normal gravid uterus.

Diagnostic Strategies

Arterial blood gas analysis may not be very helpful in the diagnosis of PE. The alveolar-arterial oxygen gradient is a poor screening test for PE in pregnancy and postpartum, with a sensitivity of 77% and specificity of 20%.[102] A chest radiograph (shielding the pelvis and uterus) should be obtained to exclude other disease processes that may mimic a PE. The diaphragm is normally symmetrically elevated during late pregnancy.

Because of its widespread availability, Doppler ultrasonography has superseded noninvasive impedance plethysmography as the first-line test for the diagnosis of DVT. Both tests, however, are useful in the diagnosis of DVT of the femoral or popliteal veins in pregnancy, and these studies provide the least risk to the patient. An abnormal flow study finding is sufficient reason to treat the pregnant patient in most cases. However, normal leg study results can be seen with isolated iliac vein disease, which is common in pregnancy and requires imaging with MRI or CT for diagnosis. If thromboembolic disease is suspected, serial indirect Doppler testing or CT may be required.[103] The risk of anticoagulation usually outweighs the risk of definitive studies when the diagnosis is equivocal.

Currently, studies do not support D-dimer tests in pregnancy to exclude the diagnosis of PE as this test may lack sufficient sensitivity in pregnant patients.[104] Thus imaging is recommended, usually lung scintigraphy or CT. Lung scintigraphy and CT angiography have comparable performances for PE diagnosis during pregnancy, although CT angiography delivers higher maternal radiation dose.[105] Pulmonary angiography may be required if the diagnosis of PE is unclear after less invasive studies have been performed.

Management

Warfarin (Coumadin) is contraindicated during pregnancy because of its teratogenic effects and high risk of abortions and fetal hemorrhage. Heparinoids are used to treat thromboembolic disease during pregnancy. Unfractionated heparin carries a poorly understood risk of fetal osteoporosis, thrombocytopenia, prematurity, or miscarriage. In general, acute anticoagulation with intravenous heparin is followed by subcutaneous heparin twice daily, usually continued for 3 to 6 months postpartum in patients who have DVT or PE during pregnancy. Patients receiving this treatment require laboratory testing every 1 or 2 weeks, and the efficacy of anticoagulation may be variable in pregnancy. Low-molecular-weight heparin is considered safe in pregnancy and offers several advantages over unfractionated heparin: decreased bleeding risk, reliable pharmacokinetics, decreased risk of heparin-induced thrombocytopenia, fixed dosages, less frequent dosing, and decreased risk of osteoporosis and thrombocytopenia.[106-108] In patients with a history of DVT or PE, prophylaxis for subsequent gestations is usually recommended.[109-111]

Genitourinary Infections

Urinary Tract Infection

Principles of Disease. Asymptomatic bacteriuria in pregnancy predisposes the patient to development of symptomatic lower and upper tract genitourinary infections, resulting in the U.S. Preventive Services Task Force recommendation to screen for asymptomatic bacteriuria with urine culture in pregnant women at 12 to 16 weeks' gestation or at the first prenatal visit, if later (Grade A recommendation).[112] Uterine pressure exerted on the bladder and ureters, poor emptying of the bladder with voiding, and progesterone-induced smooth muscle relaxation that inhibits ureteral peristalsis appear to contribute to increased risk of infection during pregnancy.

Prenatal screening of patients with asymptomatic bacteriuria in early pregnancy identifies approximately 95% of individuals at risk for subsequent bacteriuria during the pregnancy. Because up to 30% of women who have asymptomatic bacteriuria will have pyelonephritis if they are untreated, treatment of bacteriuria is cost-effective and important.[113]

Clinical Features and Diagnostic Strategies. The pregnant patient who presents with lower urinary tract symptoms (e.g., dysuria, frequency, and urgency) or upper tract symptoms (e.g., fever, malaise, or back pain) should have a pelvic examination and evaluation of an uncontaminated urine specimen (preferably catheterized). There is a predominance of right-sided symptoms during pregnancy, probably the result of increased mechanical forces on the right ureter, but left-sided flank pain or bilateral symptoms may be caused by pyelonephritis. Rarely, urinalysis may yield normal results or cultures may produce negative findings, either because of failure to report lower colony counts or because of complete obstruction of the involved ureter.

The major risk of asymptomatic and lower urinary tract infection is spread to the renal parenchyma. Acute pyelonephritis carries considerable morbidity in pregnancy, including maternal sepsis, permanent renal injury, and premature labor.[113] The risk of prematurity can be minimized by effective treatment and continued monitoring for recurrence. The development of premature labor in the woman who has pyelonephritis is ominous and can be prevented only by aggressive recognition and treatment earlier in pregnancy.

Differential Considerations. Vaginitis, herpes genitalis, chlamydial infection of the urethra, and ovarian torsion can masquerade as urinary tract symptoms. A history of external dysuria (burning at the perineum with urination) suggests herpes or vaginitis. A pelvic examination should be performed to obtain cervical culture specimens and to identify perineal or vaginal causes of dysuria. Appendicitis, cholecystitis, pancreatitis, and liver diseases in pregnancy must be considered in the differential diagnosis of upper urinary tract infection. Back pain may also be a sign of premature labor. Careful evaluation of an uncontaminated catheterized urine specimen is essential to the correct diagnosis.

Management. Patients with asymptomatic bacteriuria or lower urinary tract signs and symptoms should be treated with 7 to 10 days of an antibiotic that is active against usual urinary pathogens and is safe in pregnancy. The most common choices are a cephalosporin, a nitrofurantoin, or a sulfonamide (except during the third trimester). Clinicians should consider factors such as cost, local availability, and side effects in the selection of the best treatment option.[114]

Patients with fever, back pain, and evidence of acute pyelonephritis in pregnancy are usually admitted for intravenous antibiotic administration, although outpatient parenteral therapy can be effective and safe in selected patients.[115] In such cases, aggressive intravenous hydration, obstetric consultation, and urine cultures should be initiated. At least one parenteral dose of antibiotics should be given, with antibiotic coverage guided by known organism susceptibilities in a given hospital. Because the resistance of *Escherichia coli* to ampicillin is considerable in most regions, a cephalosporin is the usual intravenous medication administered. Cultures must be performed to ensure that the original choice of antibiotic was correct, and the patient must have a repeated culture and be observed closely after treatment.

www.ketabpezeshki.com 66485457-66963820

Vaginitis

Bacterial Vaginosis

Bacterial vaginosis (formally known as *Gardnerella* vaginitis or *Haemophilus vaginalis* vaginitis) is an overgrowth of multiple endogenous vaginal bacteria, in some cases producing excessive discharge and vaginal malodor. Prevalence rates for bacterial vaginosis in pregnancy are estimated at 15 to 20%. Bacterial vaginosis is associated with an increased risk of chorioamnionitis, subclinical PID, premature rupture of membranes, fetal prematurity, and postpartum endometritis after vaginal delivery. However, treatment of bacterial vaginosis is directed toward symptomatic relief for the patient and does not necessarily improve fetal outcomes. Management includes a 7-day course of metronidazole or a 7-day course of clindamycin. Intravaginal treatment is not recommended in pregnant patients.[116]

Candida albicans Vaginitis

The incidence of vulvovaginal candidiasis is increased during pregnancy by high levels of estrogen and other steroids. Oral azoles are contraindicated in pregnancy because of an association with adverse fetal outcomes.[117] Treatment with vaginal azoles for 7 days during pregnancy is considered safe, with an estimated 85 to 100% cure rate.[116] Recurrent disease may require a vaginal culture to confirm diagnosis and to identify unusual candidal species (e.g., *Candida glabrata*) that may be resistant to conventional treatment. Longer treatment or treatment of a potential *Candida* reservoir in the patient's partner may also be required. However, there is no association of *Candida* colonization with adverse pregnancy outcomes, and treatment is for relief of symptoms only.[118]

Trichomonas Vaginitis

Trichomoniasis is a sexually transmitted vaginitis caused by a protozoan parasite, *Trichomonas vaginalis*. Of patients who have trichomoniasis, 50% are asymptomatic. Symptoms include vaginal itching, malodorous discharge, and vaginal irritation. Diagnosis is made by direct visualization or protozoans on wet mount. The recommended treatment is metronidazole, a one-time dose of 2 g, for symptomatic patients only.[116] Although trichomoniasis has been associated with increased prematurity, treatment with metronidazole has not been shown to improve fetal outcomes, so clinicians should counsel patients and consider deferment of treatment in asymptomatic pregnant women until after 37 weeks' gestation.[119]

Sexually Transmitted Diseases in Pregnancy

Sexually transmitted diseases are treated in pregnant patients according to the latest Centers for Disease Control and Prevention guidelines. In general, the tetracyclines and quinolones are contraindicated in pregnant patients. Treatment of genital tract infections may be important in both preventing preterm labor and decreasing transmission to the infant.

Chlamydia trachomatis Infection

Chlamydia trachomatis infection is the most common sexually transmitted disease, both in the United States and worldwide. Its prevalence is currently three to five times that of *Neisseria gonorrhoeae* infection. Clinical diagnosis is difficult during pregnancy because cervical mucus is usually cloudy and contains white blood cells, but urine sampling can be done and is equivalent to endocervical sampling in pregnancy infections.[120] Routine chlamydia screening during pregnancy is important to prevent complications of preterm labor and postpartum endometritis, both of which are more common in patients who have chlamydial cervical infections.[119] Chlamydial infections of infants born to infected mothers include conjunctivitis and pneumonitis. Treatment during pregnancy or breast-feeding is azithromycin (single 1-g dose), which improves compliance and decreases gastrointestinal side effects; a 7-day course of amoxicillin is an acceptable alternative.[116]

Herpes Simplex Infection

Herpes simplex virus infections pose a significant risk in pregnancy to both the mother and the newborn. Women who have genital herpes during the third trimester have a 30 to 50% increased risk of transmission compared with women with herpes simplex virus infection in the first trimester (1%). The virus can be transmitted prenatally through transplacental infection or ascending vaginal infection and by vaginal delivery, particularly when herpetic lesions are present. Infections in the neonate often are disseminated or involve the central nervous system, causing significant morbidity and mortality. In the ED, culture of new suspected herpetic lesions of the cervix, vagina, or perineum identifies patients at risk for perinatal complications. Although the risk of oral acyclovir and valacyclovir use in pregnancy is not well known, it is recommended for first-episode genital herpes. Suppressive therapy can reduce the need for cesarean section in women whose first clinical episode of genital herpes simplex occurred during pregnancy but may not eliminate the need for cesarean section in women with recurrent herpes simplex.[121,122] Treatment should be undertaken with obstetric consultation and careful patient monitoring.

Neisseria gonorrhoeae Infection

Gonococcal infection of the cervix occurs during pregnancy in 1% of women. Symptoms are similar to those in nonpregnant women. Salpingitis is rare but may develop during the first trimester from upper genital extension of cervical infection. Some practitioners believe that the incidence of the disseminated infection is increased in pregnant patients because of elevated progesterone levels and increased vascularity in the area of the cervix. Gonococcal arthritis is the most common manifestation of gonococcal dissemination. Diagnosis and treatment of gonococcal infections are unchanged by pregnancy, and treatment includes cephalosporins or azithromycin.[116] Treatment of possible coexistent chlamydial infection is recommended for pregnant and nonpregnant women. The major complications of third-trimester gonococcal infection are neonatal gonococcal ophthalmia and sepsis.[116,119]

Upper Genital Tract Infection

Pelvic Inflammatory Disease

PID is very rare in pregnancy and does not occur after the first trimester. Differential diagnosis includes ectopic pregnancy, septic abortion, and appendicitis, all of which are more common. In the patient with suspected infection, smears or cultures for chlamydia and gonorrhea should be performed. Given the risk of endometrial infection in pregnancy and the need to consider other diagnoses, pregnant patients who have suspected PID require hospitalization and intravenous antibiotics.[116]

Chorioamnionitis

Chorioamnionitis is the infection or inflammation of the placenta and fetal membranes. After 16 weeks of pregnancy, the chorioamniotic membranes adhere to the cervical os and may become infected. The risk is increased in women with preterm labor. Chorioamnionitis is diagnosed by the findings of fever, maternal and fetal tachycardia, and uterine tenderness in a patient past 16 weeks of pregnancy.[123] Leukocytosis can be suggestive of chorioamnionitis but is not diagnostic. Patients should have blood specimens drawn for culture. Vaginal and cervical culture specimens for group B streptococci, *E. coli,* chlamydia, and gonorrhea should also be obtained. Urgent obstetric consultation should be obtained,

www.ketabpezeshki.com 66485457-66963820

and hospitalization for intravenous administration of antibiotics is required. Patients are usually treated with intravenous ampicillin and gentamicin. In addition, a study reported that antenatal steroids may reduce adverse neonatal outcome after preterm birth associated with chorioamnionitis.[124]

KEY CONCEPTS

- There are several types of miscarriages (incomplete, complete, inevitable, and threatened) that must be differentiated because management priorities for these patients differ.
- The history and the physical examination of the patient with ectopic pregnancy are insensitive and nonspecific; therefore pelvic ultrasonography and serum hCG levels are used to evaluate patients deemed to be at risk.
- The major conditions associated with vaginal bleeding in the second half of pregnancy include abruptio placentae and placenta previa. Patient history, physical examination, and results of ultrasonography can be used to distinguish these conditions.
- Appendicitis is the most common surgical emergency in pregnancy, and the clinical presentation of these patients may not be classic, leading to a misdiagnosis rate of 30 to 35% in pregnant patients.
- The treatment of eclampsia includes magnesium sulfate for seizures, reduction of blood pressure, and delivery of the fetus.

ACKNOWLEDGMENT

We thank Dr. Jean Abbott for her work on prior editions of this chapter.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Wang X, et al: Conception, early pregnancy loss, and time to clinical pregnancy. *Fertil Steril* 2003; 79:577.
2. Garcia-Enguidanos A, et al: Risk factors in miscarriage. *Eur J Obstet Gynecol* 2002; 102:111.
3. Ellish NJ, et al: A prospective study of early pregnancy loss. *Hum Reprod* 1996; 11:406-412.
4. Maconochie N, et al: Risk factor for first trimester miscarriage: Results from a UK-population based case-control study. *Br J Obstet Gynaecol* 2007; 114:170.
5. Ablovich M, et al: Overt and subclinical hypothyroidism complicating pregnancy. *Thyroid* 2001; 12:63-68.
6. Sierra S, Stephenson M: Genetics of recurrent pregnancy loss. *Semin Reprod Med* 2006; 24:17-24.
7. Mallin M, et al: Prospective outcomes of pregnant ED patients with documented fetal cardiac activity on ultrasound. *Am J Emerg Med* 2012; 30:472-475.
8. Kohn MA, et al: Beta-human chorionic gonadotropin levels and the likelihood of ectopic pregnancy in emergency department patients with abdominal pain or vaginal bleeding. *Acad Emerg Med* 2003; 10:119.
9. Juliano M, Dabulis S, Heffner A: Characteristics of women with fetal loss in symptomatic first-trimester pregnancies with documented fetal cardiac activity. *Ann Emerg Med* 2008; 52:143-147.
10. Johns J, et al: Threatened miscarriage as a predictor of obstetric outcome. *Obstet Gynecol* 2006; 107:845.
11. Hessert MJ, Juliano M: Fetal loss in symptomatic first-trimester pregnancy with documented yolk sac intrauterine pregnancy. *Am J Emerg Med* 2012; 30:399-404.
12. Abbott JT, et al: Ectopic pregnancy: Ten common pitfalls in diagnosis. *Am J Emerg Med* 1990; 8:515.
13. Dart RG: Role of pelvic ultrasound in evaluation of symptomatic first trimester pregnancy. *Ann Emerg Med* 1999; 33:310.
14. Bowman J: Rh-immunoglobulin: Rh prophylaxis. *Best Pract Res Clin Haematol* 2006; 19:27.
15. Barnhart KT, et al: Clinical factors affecting the accuracy of ultrasonography in symptomatic first-trimester pregnancy. *Obstet Gynecol* 2011; 117:299-306.
16. Lok IH, Neugebauer R: Psychological morbidity following miscarriage. *Best Pract Res Clin Obstet Gynaecol* 2007; 332:1235-1240.
17. Wallace RR, Goodman S, Freedman LR, Dalton VK, Harris LH: Counseling women with early pregnancy failure: Utilizing evidence, preserving preference. *Patient Educ Couns* 2010; 81:454-461.
18. Neilson JP, Gyte GM, Hickey M, Vazquez JC, Dou L: Medical treatments for incomplete miscarriage (less than 24 weeks). *Cochrane Database Syst Rev* 2010; 1:CD007223.
19. Nikcevic AV, et al: The influence of medical and psychological interventions on women's distress after miscarriage. *J Psychosom Res* 2007; 63:283.
20. Sur SD, Raine-Fenning NJ: The management of miscarriage. *Best Pract Res Clin Obstet Gynaecol* 2009; 23:479-491.
21. Luise C, et al: Outcome of expectant management of spontaneous first trimester miscarriage. *Br Med J* 2003; 324:873.
22. Graziosi GC, Mol BW, Ankum WM, Bruinse HW: Management of early pregnancy loss. *Int J Gynaecol Obstet* 2004; 86:337-346.
23. Zhang J, et al: A comparison of medical management with misoprostol and surgical management for early pregnancy failure. *N Engl J Med* 2005; 353:761.
24. Chang J: Pregnancy-related mortality surveillance—United States, 1991-1999. *MMWR Surveill Summ* 2003; 52:1.
25. Kohn MA, et al: Beta-human chorionic gonadotropin levels and the likelihood of ectopic pregnancy in emergency department patients with abdominal pain or vaginal bleeding. *Acad Emerg Med* 2003; 10:119-126.
26. Moore C, Todd W, O'Brien E, Lin H: Free fluid in Morison's pouch on bedside ultrasound predicts need for operative intervention in suspected ectopic pregnancy. *Acad Emerg Med* 2007; 14:755-758.
27. Bouyer J, et al: Risk factors for ectopic pregnancy: A comprehensive analysis based on a large case-control, population-based study in France. *Am J Epidemiol* 2003; 157:185.
28. Bouyer J, et al: Sites of ectopic pregnancy: A 10 year population-based study of 1800 cases. *Hum Reprod* 2002; 17:3224.
29. Kaplan BC, et al: Ectopic pregnancy: Prospective study with improved diagnostic accuracy. *Ann Emerg Med* 1996; 28:10.
30. Tayal VS, et al: Outcome of patients with an indeterminate emergency department first-trimester pelvic ultrasound to rule out ectopic pregnancy. *Acad Emerg Med* 2004; 11:912.
31. Condous G, et al: Diagnostic accuracy of varying discriminatory zones for the prediction of ectopic pregnancy in women with a pregnancy of unknown location. *Ultrasound Obstet Gynecol* 2005; 7:770.
32. Kirk E, et al: Ectopic pregnancy: Using the hCG ratio to select women for expectant or medical management. *Acta Obstet Gynecol Scand* 2011; 90:264-272.
33. Dart RG: Sub-classification of indeterminate pelvic ultrasonography: Prospective evaluation of the risk of ectopic pregnancy. *Ann Emerg Med* 2002; 39:382.
34. Stein JC, et al: Evaluation of ectopic pregnancy with bedside ultrasound by emergency physicians: A meta-analysis. *Ann Emerg Med* 2010; 56:674-683.
35. Wang R, et al: Use of a β-hCG discriminatory zone with bedside pelvic ultrasonography. *Ann Emerg Med* 2011; 58:12-20.
36. Silva C, et al: Human chorionic gonadotropin profile for women with ectopic pregnancy. *Obstet Gynecol* 2006; 107:605.
37. McRae A, Murray H, Edmonds M: Diagnostic accuracy and clinical utility of emergency department targeted ultrasonography in the evaluation of first-trimester pelvic pain and bleeding: A systematic review. *CJEM* 2009; 11:355-364.
38. Jang TB, Ruggeri W, Dyne P, Kaji AH: Learning curve for emergency physicians using emergency bedside sonography for symptomatic first-trimester pregnancy. *J Ultrasound Med* 2010; 29:1423-1428.
39. Kalinski MA, et al: Hemorrhagic shock from a ruptured ectopic pregnancy in a patient with a negative urine pregnancy test result. *Ann Emerg Med* 2002; 40:102.
40. Dart R, et al: Utility of a dilatation and evacuation procedure in patients with symptoms suggestive of ectopic pregnancy and indeterminate transvaginal ultrasonography. *Acad Emerg Med* 1999; 6:1024.
41. Seror V, et al: Care pathways for ectopic pregnancy: A population-based cost-effectiveness analysis. *Fertil Steril* 2007; 87:737.
42. Atri M, et al: Effect of transvaginal sonography on the use of invasive procedures for evaluating patients with a clinical diagnosis of ectopic pregnancy. *J Clin Ultrasound* 2003; 31:1.
43. Menon S, et al: Establishing a human chorionic gonadotropin cutoff to guide methotrexate treatment of ectopic pregnancy: A systematic review. *Fertil Steril* 2007; 87:481.
44. Alleyassin A, et al: Comparison of success rates in the medical management of ectopic pregnancy with single-dose and multiple-dose administration of methotrexate: A prospective, randomized clinical trial. *Fertil Steril* 2006; 85:1661.
45. Potter M, et al: Predictors of success with methotrexate treatment of tubal ectopic pregnancy at Grady Memorial Hospital. *Am J Obstet Gynecol* 2003; 188:1192.
46. Horn L, et al: Clinicopathologic characteristics and subsequent pregnancy outcome in 139 complete hydatidiform moles. *Eur J Obstet Gynecol Reprod Biol* 2006; 128:10.
47. Lurain JR: Gestational trophoblastic disease I: Epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. *Am J Obstet Gynecol* 2010; 203:531-539.
48. Garner EI, Goldstein DP, Feltmate CM, Berkowitz RS: Gestational trophoblastic disease. *Clin Obstet Gynecol* 2007; 50:112-122.
49. Murphy R, et al: Characteristics of ED patients who present with molar pregnancy. *South Med J* 2008; 101:797.
50. Niemann I, Petersen LK, Hansen ES, Sunde L: Differences in current clinical features of diploid and triploid hydatidiform mole. *BJOG* 2007; 114:1273-1277.
51. Soper JT, Mutch DG, Schink JC: American College of Obstetricians and Gynecologists: Diagnosis and treatment of gestational trophoblastic disease: ACOG Practice Bulletin No. 53. *Gynecol Oncol* 2004; 93:575-585.
52. Sebire NJ, et al: The diagnostic implications of routine ultrasound examination on histologically confirmed early molar pregnancies. *Ultrasound Obstet Gynecol* 2001; 18:662.
53. Cunningham G, et al, eds: *Obstetrical hemorrhage*. In: *Williams Obstetrics*, 21st ed. New York: McGraw-Hill; 2001:619-670.
54. Tikkanen M, et al: Clinical presentation and risk factors of placental abruption. *Acta Obstet Gynecol Scand* 2006; 85:700.
55. Rachana C, et al: Prevalence and complications of physical violence during pregnancy. *Eur J Obstet Gynecol* 2002; 103:26.
56. Matsuda Y, et al: Comparison of risk factors for placental abruption and placenta previa: Case-cohort study. *J Obstet Gynaecol Res* 2011; 37:538-546.
57. Mustafa SA, et al: Transvaginal ultrasonography in predicting placenta previa at delivery: A longitudinal study. *Ultrasound Obstet Gynecol* 2002; 20:356.

www.ketabpezeshki.com 66485457-66963820

58. Balderston KD, et al: Is the incidence of fetal-to-maternal hemorrhage increased in patients with third-trimester bleeding? *Am J Obstet Gynecol* 2003; 188:1615.
59. Sibai BM: Diagnosis and management of gestational hypertension and preeclampsia. *Obstet Gynecol* 2003; 102:181.
60. Steegers PA: Pre-eclampsia. *Lancet* 2010; 376:631.
61. Bosio PM, et al: Maternal central hemodynamics in hypertensive disorders of pregnancy. *Obstet Gynecol* 1999; 94:978.
62. Baumwell S, et al: Pre-eclampsia: Clinical manifestations and molecular mechanisms. *Nephron Clin Pract* 2007; 106:c72.
63. Askie LM, et al: Antiplatelet agents for prevention of pre-eclampsia: A meta-analysis of individual patient data. *Lancet* 2007; 369:1791.
64. Cavkaytar S, et al: Are clinical symptoms more predictive than laboratory parameters for adverse maternal outcome in HELLP syndrome? *Acta Obstet Gynecol Scand* 2007; 86:648.
65. von Dadelszen P, et al: The prediction of adverse maternal outcomes in preeclampsia. *J Obstet Gynaecol Can* 2004; 26:871.
66. Mattar F, et al: Eclampsia: Risk factors for maternal morbidity. *Am J Obstet Gynecol* 2000; 182:307.
67. Yancey LM: Postpartum preeclampsia: Emergency department presentation and management. *J Emerg Med* 2011; 40:380.
68. Zeeman GG: Cerebral infarction in eclampsia. *Am J Obstet Gynecol* 2004; 190:714.
69. Duley L, et al: Magnesium sulfate and other anticonvulsants for women with pre-eclampsia. *Cochrane Database Syst Rev* 2010; 10:CD000025.
70. Belfort MA, et al: Comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. *N Engl J Med* 2003; 348:304.
71. Conde-Agudelo A, et al: Amniotic fluid embolism: An evidence-based review. *Am J Obstet Gynecol* 2009; 201:445.
72. Pastore PA, et al: Appendicitis in pregnancy. *J Am Board Fam Med* 2006; 19:621.
73. Hodjati H, et al: Location of the appendix in the gravid patient: A re-evaluation of the established concept. *Int J Gynecol Obstet* 2003; 81:245.
74. Mourad J, et al: Appendicitis in pregnancy: New information that contradicts long-held clinical beliefs. *Am J Obstet Gynecol* 2000; 185:259.
75. Ueberrueck T, et al: Ninety-four appendectomies for suspected acute appendicitis in pregnancy. *World J Surg* 2004; 28:508.
76. Yilmaz HG, et al: Acute appendicitis in pregnancy: Risk factors associated with principal outcomes: A case control study. *Int J Surg* 2007; 5:192.
77. Williams R: Ultrasound scanning in the diagnosis of appendicitis in pregnancy. *Emerg Med J* 2007; 24:359.
78. Butala P, et al: Surgical management of acute right lower-quadrant pain in pregnancy: A prospective cohort study. *J Am Coll Surg* 2010; 211:490.
79. Indar AA, et al: Acute cholecystitis. *BMJ* 2002; 325:639.
80. Mendez-Sanchez N, et al: Pregnancy and gallbladder disease. *Ann Hepatol* 2006; 101:2263.
81. Lu EJ, et al: Medical versus surgical management of biliary tract disease in pregnancy. *Am J Surg* 2004; 188:755.
82. Dupar R, et al: Is there a benefit to delaying cholecystectomy for symptomatic gallbladder disease during pregnancy? *Surg Endosc* 2010; 24:108.
83. Angel Garcia AL: Effect of pregnancy on pre-existing liver disease: Physiological changes during pregnancy. *Ann Hepatol* 2006; 5:184.
84. Guntupalli SR, et al: Hepatic disease and pregnancy: An overview of diagnosis and management. *Crit Care Med* 2005; 33:S332.
85. Mjahed K, et al: Acute fatty liver of pregnancy. *Arch Gynecol Obstet* 2006; 274:349.
86. Fesenmeier MF, et al: Acute fatty liver of pregnancy in 3 tertiary care centers. *Am J Obstet Gynecol* 2005; 192:1416.
87. Ibdah JA: Acute fatty liver of pregnancy: An update on pathogenesis and clinical implications. *World J Gastroenterol* 2006; 12:7397.
88. Wei Q, et al: Clinical diagnosis and treatment of acute fatty liver of pregnancy: A literature review and 11 new cases. *J Obstet Gynaecol Res* 2010; 36:751.
89. Mullally BA, et al: Intrahepatic cholestasis of pregnancy. *Obstet Gynecol Surg* 2001; 57:47.
90. Burrows RF, et al: Interventions for treating cholestasis in pregnancy. *Cochrane Database Syst Rev* 2001; 4:CD000493.
91. Lagiou P, et al: Nausea and vomiting in pregnancy in relation to prolactin, estrogens, and progesterone. *Obstet Gynecol* 2003; 101:639.
92. Kaplan PB: Maternal serum cytokine levels in women with hyperemesis gravidarum in the first trimester of pregnancy. *Fertil Steril* 2003; 79:498.
93. Mansour GM, Nashaat EH: Role of *Helicobacter pylori* in the pathogenesis of hyperemesis gravidarum. *Arch Gynecol Obstet* 2011; 284:843-847.
94. Quinlan JD, et al: Nausea and vomiting of pregnancy. *Am Fam Physician* 2003; 68:121.
95. Nelson-Piercy C, et al: Randomised, double-blind, placebo-controlled trial of corticosteroids for the treatment of hyperemesis gravidarum. *Br J Obstet Gynecol* 2001; 108:9.
96. Bondok RS, et al: Pulsed steroid therapy is an effective treatment for intractable hyperemesis gravidarum. *Crit Care Med* 2006; 34:2781.
97. Vitoratos N, et al: Severe liver injury due to hyperemesis gravidarum. *J Obstet Gynaecol* 2006; 26:172.
98. Danilenko-Dixon DR, et al: Risk factors for deep vein thrombosis and pulmonary embolism during pregnancy or post partum. *Am J Obstet Gynecol* 2001; 184:104.
99. Lockwood CJ: Pregnancy-associated changes in the hemostatic system. *Clin Obstet Gynecol* 2006; 49:836.
100. Stone SE, et al: Pulmonary embolism during and after pregnancy. *Crit Care Med* 2005; 33:S294.
101. Romero A, et al: Risk of venous thromboembolic disease in women: A qualitative systematic review. *Eur J Obstet Gynecol Reprod Biol* 2005; 121:8.
102. Deutsch AB, et al: Assessment of the alveolar-arterial oxygen gradient as a screening test for pulmonary embolism in pregnancy. *Am J Obstet Gynecol* 2010; 203:373.
103. Scarsbrook AF, et al: Diagnosis of suspected venous thromboembolic disease in pregnancy. *Clin Radiol* 2006; 61:1.
104. Sivandarajah S: Towards evidence-based emergency medicine: Best BETs from the Manchester Royal Infirmary. BET 4: Current evidence does not support the use of a negative D-dimer to rule out suspected pulmonary embolism in pregnancy. *Emerg Med J* 2011; 28:245.
105. Revel MP, et al: Pulmonary embolism during pregnancy: Diagnosis with lung scintigraphy or CT angiography? *Radiology* 2011; 258:590.
106. Jacobsen AF, et al: Low molecular weight heparin (dalteparin) for the treatment of venous thromboembolism in pregnancy. *Br J Obstet Gynecol* 2003; 110:139.
107. Greer I, et al: Low molecular weight heparin in pregnancy: Current issues. *Br J Haematol* 2005; 128:593.
108. Greer I, et al: Low molecular weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: A systematic review of safety and efficacy. *Blood* 2005; 106:401.
109. Marks PW: Management of thromboembolism in pregnancy. *Semin Perinatol* 2007; 31:227.
110. Zotz RB, et al: Prediction, prevention, and treatment of venous thromboembolic disease in pregnancy. *Semin Thromb Hemost* 2003; 29:143.
111. James AH, et al: Thromboembolism in pregnancy: Recurrence and its prevention. *Semin Perinatol* 2007; 31:167.
112. U.S. Preventive Services Task Force: Screening for asymptomatic bacteriuria in adults: U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med* 2008; 149:43.
113. Smaill F, et al: Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev* 4:CD00490, 2007.
114. Guinto VT, et al: Different antibiotic regimens for treating asymptomatic bacteriuria in pregnancy. *Cochrane Database Syst Rev* 2010; 8:CD007855.
115. Vazquez JC, et al: Treatments for symptomatic urinary tract infections during pregnancy. *Cochrane Database Syst Rev* 2011; 19:CD002256.
116. Workowski KA, et al: Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep* 2010; 59:1.
117. Lopez-Rangel E, Van Allen MI: Prenatal exposure to fluconazole: An identifiable dysmorphic phenotype. *Birth Defects Res A Clin Mol Teratol* 2005; 73:919.
118. Cotch MF, et al: Epidemiology and outcomes associated with moderate to heavy *Candida* colonization during pregnancy. Vaginal Infections and Prematurity Study Group. *Am J Obstet Gynecol* 1998; 178:374.
119. Majeroni BA, et al: Screening and treatment for sexually transmitted infections in pregnancy. *Am Fam Physician* 2007; 76:265.
120. Roberts SW, et al: Urine screening for *Chlamydia trachomatis* during pregnancy. *Obstet Gynecol* 2011; 117:883.
121. Gardella C, et al: Managing genital herpes infections in pregnancy. *Cleve Clin J Med* 2007; 74:217.
122. Baker DA: Consequences of herpes simplex virus in pregnancy and their prevention. *Curr Opin Infect Dis* 2007; 20:73.
123. Tita AT, et al: Diagnosis and management of clinical chorioamnionitis. *Clin Perinatol* 2010; 37:339.
124. Been JV, et al: Antenatal steroids and neonatal outcome after chorioamnionitis: A meta-analysis. *BJOG* 2011; 118:113.

www.ketabpezeshki.com 66485457-66963820

Chapter 179

Chronic Medical Illness during Pregnancy

Kirsten K. Calder

PRINCIPLES OF DISEASE

The physiologic changes that occur in pregnancy may exceed the patient's underlying compensatory mechanisms, resulting in initial symptom onset or rapid decompensation of medical illness during pregnancy. Certain chronic medical conditions also pose a serious threat to the mother's health or result in a poor fetal outcome. Finally, some medical illnesses result in a difficult delivery or the need for special resuscitation measures in the neonate.

The incidence of pregnancy in chronically ill patients is increasing because of improved survival of patients with diseases such as diabetes, epilepsy, renal failure, and various cancers. Also, the demographics of pregnancy are changing in that maternal age at the time of first pregnancy is increasing. Advances in assisted reproduction, including in vitro fertilization and oocyte donation, have made it possible for older women—including those who are postmenopausal—to become pregnant. Older pregnant women experience an increased rate of antepartum and intrapartum complications and are more likely to have comorbid conditions such as cardiovascular disease.

SPECIFIC DISORDERS

Asthma

Asthma is the most common pulmonary problem in pregnancy; it affects up to 8% of gestations, and the prevalence appears to be increasing.[1] The overall effect of pregnancy on asthma seems to be that one third of patients will experience a worsening of the disease, one third will experience improvement, and the other third will remain unchanged.[2] The exact effect of asthma on the fetus is likely to depend on the severity of disease and how well it is managed during pregnancy. Studies show that pregnant asthmatics have good perinatal outcomes in the setting of well-controlled symptoms.[3-6] On the other hand, women with asthma exacerbations during pregnancy are at increased risk for complications, including congenital malformations and preterm delivery[7-9] (see Table 179-1).

Several changes in respiratory physiology during normal pregnancy affect the management of asthma in this context; both the tidal volume and the minute ventilation rise, increasing up to 50% by term. This increase in minute ventilation, or "hyperventilation of pregnancy," lowers the resting P_{CO_2} by an average of 8 to 10 mm Hg to a P_{CO_2} of 32 mm Hg. In response to chronic hyperventilation, there is a compensatory increase in the renal excretion of bicarbonate, with serum levels averaging 19 mEq/mL (19 mmol/L). The net result is a slight respiratory alkalosis, with a serum pH ranging from 7.40 to 7.45. It is important to keep these "normal" values in mind in gauging the severity of an asthma exacerbation in the pregnant patient. Acute asthma exacerbations pose a significant maternal and fetal risk, and the pregnant patient should be managed as aggressively as the nonpregnant patient.[10]

The inhaled beta-agonist agents are generally considered safe in pregnancy (Tables 179-1 and 179-2). As in the nonpregnant patient, inhaled short-acting beta-agonists are first-line agents for acute asthma exacerbations.[3,10] Long-acting agonists (in conjunction with inhaled corticosteroids) are also recommended for maintenance use in patients with moderate or severe disease.[3,10] Selective agonists are preferred because nonselective agents such as epinephrine theoretically decrease uteroplacental blood flow through beta-mediated effects. In addition, although they are safe from a teratogenic perspective, beta-agonists are tocolytics and will usually halt active labor.

Corticosteroids remain the core component for maintenance treatment of asthma in the pregnant patient. In fact, current data support the safety of inhaled corticosteroids,[11] and their chronic use is recommended in all asthmatic patients except those with mild intermittent disease.[3,10] Use of systemic corticosteroids is sometimes necessary on a chronic basis in patients with severe persistent asthma and as a short burst in patients with exacerbations that exhibit inadequate or poor response to initial beta-agonist therapy.

The methylxanthine theophylline has been shown to be safe in pregnancy at therapeutic doses and is an acceptable alternative medication for maintenance therapy for patients with moderate to severe disease.[3,10] There are limited data for cromolyn sodium, but this agent is considered class B (presumed safety) during pregnancy, and its use as an alternative agent is acceptable.[10] Likewise, the leukotriene receptor antagonists (montelukast and zafirlukast) have not been widely investigated. However, an initial small study in pregnant women did not find a significant increase in adverse outcomes, and these medications are also considered class B in pregnancy.[12] Magnesium sulfate has received a good deal of attention in the acute treatment of refractory asthma exacerbations because it has a wide safety profile and potent bronchodilator properties. Although large doses of magnesium have been used for the treatment of eclampsia, at this time there are insufficient data to support routine use of magnesium in this population of patients.

Perhaps the most important tenet of treatment is that if the mother is hypoxic, the fetus is hypoxic as well. In addition, the fetus is more sensitive to hypoxia; thus normal maternal oxygen saturation does not preclude fetal distress. Supplemental oxygen should be administered to all pregnant patients with an acute asthma exacerbation, and assessment of fetal well-being is indicated for viable pregnancies.[3]

www.ketabpezeshki.com 66485457-66963820

Table 179-1 Gestational Effects and Treatment of Medical Illnesses during Pregnancy

MEDICAL ILLNESS	GESTATIONAL CONCERNS	TREATMENT
Asthma	*Fetal:* IUGR, PTD, hypoxia, meconium-stained amniotic fluid, fetal loss *Maternal:* preeclampsia, gestational hypertension, gestational diabetes, hyperemesis gravidarum, need for labor induction	Good prenatal outcomes are seen in well-controlled asthma. Treatment of acute exacerbations is the same as for the nonpregnant patient. Fetal monitoring for exacerbations during the third trimester is recommended even in the absence of maternal hypoxia. Maintenance therapy also is unchanged with the following precautions: Corticosteroids: inhaled agents are preferred, but the oral route may be necessary with severe, persistent disease; patients receiving long-term steroids require "stress dose" hydrocortisone during labor and delivery. Methylxanthines: safe but debatable benefit; use only in refractory disease; reduced clearance during pregnancy may result in maternal toxicity and fetal tachycardia. Leukotriene receptor antagonists: avoid zileuton.
Acute coronary syndrome	*Fetal:* perinatal death, PTD *Maternal:* uterine hemorrhage and abruption (related to use of antiplatelet, antithrombotic, and fibrinolytic agents)	Standard medical therapy is the same as for the nonpregnant patient, although antiplatelet, antithrombotic, and fibrinolytic agents are best avoided when delivery is imminent. Avoid maternal hypotension when nitrates are used; they may result in fetal distress. Avoid beta-blockers in the first trimester (teratogenic). Coordinate definitive care (fibrinolytics vs. percutaneous coronary intervention) with cardiologist.
Valvular heart disease	*Fetal:* perinatal death, PTD *Maternal:* heart failure, thromboembolism, death	Appropriate antithrombotic therapy is indicated for patients with prosthetic valves and atrial fibrillation (see text). Mitral stenosis: diuresis and beta-blockade; avoid volume depletion when diuretics are used; valvuloplasty or open cardiac surgery for severe symptomatic disease; consider early pregnancy termination in women with severe stenosis. Mitral and aortic regurgitation: diuresis in patients with pulmonary congestion; surgical therapy for acute regurgitant lesions. Aortic stenosis: avoid hypotension and the supine hypotensive syndrome; vigorous fluid replacement during delivery; valvuloplasty or open cardiac surgery for severe symptomatic disease; consider early pregnancy termination with severe symptoms despite therapy.
Hypertension	*Fetal:* perinatal death, IUGR, PTD *Maternal:* progression of target end-organ damage, superimposed preeclampsia, abruption, cardiac decompensation	The majority of perinatal complications occur in patients with preeclampsia or secondary causes of hypertension; outcomes are usually good with mild essential hypertension. Fetal cyanide poisoning might develop after several hours of sodium nitroprusside. Avoid prolonged infusions and use as agent of last resort. The most commonly used agents include methyldopa (preferred agent), labetalol, and hydralazine. Avoid beta-blockers in the first trimester as they may cause fetal growth restriction and may also decrease placental blood flow. Avoid angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.
Iron deficiency anemia	*Fetal:* low birth weight, PTD, low fetal iron stores, fetal loss (with severe anemia) *Maternal:* preeclampsia, high-output heart failure (rare); effects on maternal mortality unclear	Oral iron supplementation is indicated to improve maternal iron stores. Several over-the-counter preparations are available. There is a delay from onset of therapy to increase in serum hemoglobin. Parenteral iron replacement is safe and effective although rarely required. Transfusion is rarely required but is a consideration for fetal well-being in mothers with severe anemia.
Sickle cell anemia	*Fetal:* fetal loss, IUGR, PTD, and premature rupture of membranes *Maternal:* ↑ need for cesarean section, preeclampsia, infection, heart failure, pulmonary infarction, ↑ incidence of painful crises; maternal mortality low with treatment; false-positive Apt and Kleihauer-Betke test results secondary to persistent hemoglobin F	Management of pain crises and infections is the same as for the nonpregnant patient, with rest, hydration, narcotic analgesia, supplemental oxygen, and antibiotics as indicated. Narcotic analgesics should not be withheld, but the need for neonatal respiratory support should be anticipated if delivery is imminent. Prophylactic transfusion is not indicated. Fetal monitoring and assessment of fetal well-being are indicated for viable pregnancies. Chronic maintenance care includes pneumococcal vaccination and supplemental folate. Hydroxyurea has been discouraged during pregnancy, but few adverse fetal effects have been reported in humans.

Continued

www.ketabpezeshki.com 66485457-66963820

Table 179-1 Gestational Effects and Treatment of Medical Illnesses during Pregnancy—cont'd

MEDICAL ILLNESS	GESTATIONAL CONCERNS	TREATMENT
Epilepsy	*Fetal:* various congenital malformations associated with AEMs, fetal hypoxia and bradycardia, fetal loss *Maternal:* variable changes in seizure frequency; alterations in AEM levels; increased seizure frequency secondary to voluntary medication noncompliance; abruption, anemia, hyperemesis gravidarum, preeclampsia, possible need for labor induction and cesarean section, premature rupture of membranes	Management of status epilepticus is the same as for the nonpregnant patient. Maintenance therapy should be coordinated by the patient's neurologist (or primary care practitioner) and obstetrician. In general, a single AEM given at the lowest effective dose is recommended. In general, patients with pregravid seizure control with AEM monotherapy may continue their current regimen. There is limited experience with newer AEMs, but these are likely to have a more favorable side effect profile. Folate supplementation (at least 0.4 mg/day) is indicated for patients taking older AEMs. Consider administration of oral vitamin K to the mother during the last month of pregnancy and parenteral vitamin K to the newborn.
Myasthenia gravis	*Fetal:* transient neonatal myasthenia syndrome *Maternal:* variable changes in disease severity; arrest of labor; disease exacerbation in the postpartum period	Management is the same as for the nonpregnant patient. Ventilatory support is the most important aspect of therapy. Note that patients with myasthenia gravis are relatively resistant to depolarizing paralytic agents; higher doses may be required. Pyridostigmine therapy can be continued; intravenous therapy is recommended during labor. Patients receiving maintenance corticosteroids require "stress dose" hydrocortisone during labor and delivery. Plasmapheresis is safe during pregnancy.
Diabetes mellitus: insulin dependent (IDDM), non–insulin dependent (NIDDM), and gestational (GDM)	*Fetal:* congenital malformations; macrosomia; IUGR; fetal loss; neonatal hypoglycemia, jaundice, hypomagnesemia, and hypocalcemia *Maternal:* preeclampsia, "brittle" diabetes, ↑ need for cesarean section; mothers with GDM have increased risk for development of postpartum diabetes	Every attempt should be made to maintain maternal serum glucose concentration of 100 mg/dL. Note that insulin requirements decrease during the immediate postpartum period, and the mother may not need insulin for 24-48 hours after delivery. Insulin therapy, with either intermittent dosing or continuous subcutaneous infusion, is standard care for patients with both IDDM and NIDDM. Management of diabetic ketoacidosis is the same as for the nonpregnant patient with the addition of an assessment of fetal well-being and continuous fetal heart monitoring; blood glucose concentration may be normal or only slightly elevated. GDM is often manageable with diet alone, but insulin therapy may be required when the fasting plasma glucose level remains >105 mg/dL. New data suggest that glyburide may be acceptable, but avoid hypoglycemia.
Hyperthyroidism	*Fetal:* PTD, low birth weight, fetal thyroid dysfunction, fetal loss *Maternal:* preeclampsia, heart failure	Management of thyroid storm is the same as for the nonpregnant patient and includes a search for the underlying precipitant. Therapy for hyperthyroidism in the absence of thyroid storm: Reversal of sympathetic effects: propranolol in standard doses is useful until thyroid hormone synthesis has been blocked by thioamides. Thioamides: both propylthiouracil (PTU) and methimazole at the lowest effective dose are acceptable; PTU is preferred. Surgical therapy: thyroidectomy is useful in refractory cases. Other: avoid iodide if possible; hydrocortisone decreases peripheral conversion of T_4 to the more active T_3 and can be used during pregnancy. Radioactive iodine is absolutely contraindicated.
Hypothyroidism	*Fetal:* congenital malformations, low birth weight, fetal loss, fetal thyroid dysfunction, and goiter *Maternal:* preeclampsia, abruption, postpartum hemorrhage, ↑ need for cesarean section	Maintenance therapy includes levothyroxine 0.15 mg/day. Appropriate treatment prevents adverse obstetric and fetal outcomes. Myxedema coma is rare, but when present, treatment is the same as for the nonpregnant patient.
Tuberculosis	*Fetal:* fetal loss, low birth weight, PTD; fetal and neonatal tuberculosis *Maternal:* preeclampsia; potential for delayed diagnosis and treatment out of concern for the fetus	Positive response to purified protein derivative (PPD)/normal chest radiograph: 6- to 9-month course of isoniazid (starting after the first trimester) for patients with recent conversion (<2 years); patients who have been PPD positive > 2 years may defer treatment until after delivery but should still be offered a course of isoniazid because it is safe in pregnancy. Active tuberculosis: 9-month course (starting immediately) of isoniazid plus rifampin or ethambutol (all three agents in combination recommended by the American Thoracic Society). Multidrug-resistant tuberculosis warrants aggressive therapy without regard to potential teratogenicity. Pyridoxine is indicated for all patients receiving isoniazid.

www.ketabpezeshki.com 66485457-66963820

Table 179-1 Gestational Effects and Treatment of Medical Illnesses during Pregnancy—cont'd

MEDICAL ILLNESS	GESTATIONAL CONCERNS	TREATMENT
HIV/AIDS	*Fetal:* HIV infection, PTD, fetal loss; neonatal drug withdrawal if the mother uses injection drugs *Maternal:* postpartum endometritis, uterine bleeding (in the setting of thrombocytopenia)	Antiretroviral therapy: Highly active antiretroviral therapy (HAART) should be offered to all pregnant patients with HIV infection and viral load > 1000 copies/mL. The HAART regimen should include zidovudine (AZT) to prevent vertical transmission of the virus. There are specific HAART drug-related concerns during pregnancy; decisions about therapy are best made by appropriate specialists. AZT monotherapy is not recommended except in those patients with a low viral load who do not wish to take HAART. In these cases, AZT is appropriate to reduce disease transmission. Cesarean section is recommended with viral load > 1000 copies/mL. Opportunistic infections require standard therapies despite the potential fetal effects.
Syphilis	*Fetal:* congenital syphilis, fetal loss, PTD, IUGR, nonimmune hydrops	Primary, secondary, early latent (<1 year): benzathine penicillin G, 2.4 million units IM × one dose Late latent (>1 year or unknown duration): benzathine penicillin G, 2.4 million units IM weekly × three doses Neurosyphilis: aqueous penicillin G, 2-4 million units IV q4h × 10-14 days, or procaine penicillin G, 2.4 million units IM, and probenecid, 500 mg PO q6h × 10-14 days

AEM, antiepileptic medicine; *IUGR,* intrauterine growth restriction; *PTD,* preterm delivery.

Table 179-2 Drugs Used in the Treatment of Acute Asthma Exacerbations during Pregnancy

PHARMACOLOGIC CLASS	EXAMPLES	DOSAGE	COMMENTS
Inhaled beta-agonists	Albuterol Levalbuterol	2.5-5 mg every 20 minutes 1.25-2.5 mg every 20 minutes	Inhaled beta-agonists first-line therapy May also be administered by metered-dose inhaler Up to three doses in first hour; continuous use in severe exacerbations
Injectable beta-agonists	Epinephrine Terbutaline	0.3-0.5 mg SC (1:1000 or 1 mg/mL) every 20 minutes 0.25 mg SC (1 mg/mL) every 20 minutes	No proven benefit over inhaled dosing Up to three doses in first hour
Systemic corticosteroids	Prednisone Prednisolone Methylprednisolone	Dosage applies to all preparations Initial inpatient therapy: variable dosing; need at least 120-180 mg/day Outpatient burst therapy: 40-60 mg/day for 3-10 days	No benefit of intravenous dosing over oral except in patients with impending respiratory failure who cannot take oral medications
Inhaled anticholinergics	Ipratropium bromide	0.5 mg every 20 minutes	Not first-line therapy; should be used with beta-agonists Consider for use in patients with severe exacerbations
Smooth muscle relaxants	Magnesium sulfate		Limited data on its use for asthma in pregnancy

Modified from National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program Asthma and Pregnancy Working Group: NAEPP Expert Panel Report. Managing asthma during pregnancy: Recommendations for pharmacologic treatment—2004 update. J Allergy Clin Immunol 115:34, 2005.

Hypertension

Chronic Hypertension and Hypertensive Emergencies

Chronic hypertension is defined as elevated blood pressure that is present before the onset of pregnancy or that begins before the 20th week of gestation. It affects up to 7% of pregnancies and represents a significant source of maternal and fetal mortality and morbidity (see Table 179-1).[13,14] The emergency physician may be required to provide therapy for hypertensive emergencies in patients with chronic hypertension and to differentiate between the various hypertensive disorders of pregnancy (Table 179-3).[13-15]

In the treatment of chronic hypertension in pregnancy, the physician should try to balance the goal of reducing maternal blood pressure with the requirements to maintain cardiac output and to minimize adverse effects for both mother and fetus.[13,14,16,17] Precipitous and marked decreases in blood pressure may significantly diminish uteroplacental blood flow. Treatment of patients with mild to moderate disease does not have an appreciable effect on perinatal outcomes, nor does it reduce the incidence of superimposed preeclampsia. In addition, these patients are likely to have a decrease in blood pressure without pharmacologic agents because of normal physiologic changes that occur in pregnancy, and they are often successfully managed without medications.[13,14,17] On the contrary, patients with more severe hypertension, patients with evidence of end-organ damage, and patients taking more than one pregestational antihypertensive medication probably need maintenance medical therapy (see Table 179-1).[13,17] Lifestyle modification is a potential mode of therapy, but it is unclear whether strict dietary and weight restrictions are appropriate in the gravid patient.[18]

www.ketabpezeshki.com 66485457-66963820

Table 179-3 Hypertensive Disorders of Pregnancy

	CHRONIC HYPERTENSION	GESTATIONAL HYPERTENSION	PREECLAMPSIA	CHRONIC HYPERTENSION WITH SUPERIMPOSED PREECLAMPSIA
Definition	Hypertension* that antedates pregnancy	Hypertension diagnosed after 20 weeks of gestation in the absence of proteinuria or other evidence of preeclampsia	Hypertension that begins after 20 weeks of gestation in association with new-onset proteinuria (>300 mg/24 hr)	Hypertension that antedates pregnancy in association with new-onset proteinuria
	Hypertension diagnosed before 20 weeks of gestation			Sudden increase in proteinuria in a woman with chronic hypertension* and proteinuria before 20 weeks of gestation Hypertension that antedates pregnancy in association with sudden increase in blood pressure
	Comment: rarely, preeclampsia presents before 20 weeks of gestation	*Comment:* may progress to preeclampsia; may also represent previously undiagnosed hypertension		Hypertension that antedates pregnancy in association with decreased platelets or elevated liver transaminases

Modified from Roberts JM, et al: Summary of the NHLBI Working Group on Research on Hypertension During Pregnancy. Hypertension 41:437, 2003; and the National Institutes of Health: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, Md, U.S. Department of Health and Human Services.
*Defined as blood pressure > 140 mm Hg systolic or > 90 mm Hg diastolic.

Decisions about maintenance therapy are most appropriately made by the patient's primary care practitioner in conjunction with her obstetrician. However, the emergency physician may be called on to make treatment decisions for patients with severely elevated blood pressure and for patients with superimposed eclampsia. Methyldopa remains the preferred maintenance agent, but nearly all of the major classes of antihypertensive agents are acceptable in the pregnant patient, with the exception of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. Diuretics are considered second-line agents because of concerns about plasma volume constriction (see Table 179-1).[13,14,15,17] Hydralazine and labetalol are the agents most commonly used for hypertensive emergencies associated with eclampsia and are also appropriate for such emergencies in the patient with chronic hypertension. Sodium nitroprusside can cause fetal cyanide toxicity after several hours of infusion and is considered a second-line agent (Table 179-4).[13,17]

Patients with chronic hypertension are more likely to have preeclampsia, a situation that results in increased morbidity and mortality compared with either process in isolation. Coexistence of the two disorders should be suspected in the following situations: (1) new onset of proteinuria after 20 weeks of gestation in a patient with known hypertension and (2) pregnant patients with hypertension and proteinuria before 20 weeks of gestation who have thrombocytopenia, increased transaminase levels, or an acute increase in proteinuria or blood pressure (see Table 179-3).[18]

Table 179-4 Antihypertensive Agents for Hypertensive Emergencies

ANTIHYPERTENSIVE AGENT	DOSE	COMMENT
Hydralazine	5 mg IV, then 10 mg IV every 20-30 minutes until target blood pressure is achieved	Consider another agent if inadequate response despite administration of 25 mg
Labetalol	20 mg IV; subsequent dosing with 40 mg, then two doses of 80 mg every 10 minutes until target blood pressure is achieved	Consider another agent if inadequate response despite administration of 220 mg Standard contraindications apply
Sodium nitroprusside	Infusion rates vary; start at 0.25 µg/kg/min	Use only if other agents are not effective; fetal cyanide toxicity is possible after several hours

From the National Institutes of Health: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, Md, U.S. Department of Health and Human Services; August 2004. NIH Publication No. 04-5230.

Pulmonary Hypertension

The cardiovascular changes associated with pregnancy and delivery are poorly tolerated in patients with pulmonary hypertension. Data for pregnancy in women with pulmonary hypertension are generally limited to case series, but maternal mortality rates have classically been reported to range from 30 to 56%, depending on the underlying cause (primary pulmonary hypertension, secondary vascular pulmonary hypertension, or Eisenmenger's syndrome). Recent case series suggest that a lower mortality rate is possible in the setting of aggressive monitoring and care, including use of prostacyclin analogues and phosphodiesterase inhibitors.[19,20] Unfortunately, however, a recent literature review shows that mortality remains unacceptably high (17-33%).[21]

The primary goals in treatment of the pregnant patient with pulmonary hypertension are to ensure high right ventricular filling pressures by maintenance of adequate volume status and to obtain early consultation with obstetrics and cardiology services. Pregnancy is not recommended in women with pulmonary hypertension, and those with early gestations should be referred for elective pregnancy termination.

Cardiac Disorders

Acute Coronary Syndromes

Coronary artery disease is rare in pregnant women; a population-based study noted a diagnosis of acute myocardial infarction

www.ketabpezeshki.com 66485457-66963820

(AMI) in up to 6.2 per 100,000 deliveries.[22] Prior mortality rates were reported to be approximately 20%, but more recent studies reveal rates ranging from 5 to 11%.[22-24] Normal physiologic changes of pregnancy, such as increased cardiac output and reduced oxygen-carrying capacity secondary to physiologic anemia, have the potential to exceed the threshold for angina if a fixed coronary artery stenosis is present. Certain conditions are also associated with an increased risk of pregnancy-related AMI, including advanced maternal age, thrombophilia, hypertensive disorders, anemia, diabetes mellitus, and tobacco use.[22,23] A review found that comorbid conditions such as tobacco use and diabetes are relatively common in gravid patients with AMI.[24] AMI can occur anytime during the gestational period but peaks during the last trimester and peripartum period.[22,23] Because increases in cardiac output peak during labor and delivery, maternal mortality from AMI is higher in the intrapartum period than during the antepartum or postpartum period.[23,24]

There are a number of potential causes of AMI in pregnant women. Despite their relatively young age, a review found that only 13% of gravidas with AMI have normal coronary arteries.[24] Other pathophysiologic mechanisms besides atherosclerosis that cause AMI in the pregnant patient include coronary artery dissection, vasospasm, and coronary artery thrombosis in otherwise normal vessels. The relative significance of these lesions varies according to the gestational period. Atherosclerotic disease causes the majority of AMIs in the antepartum period, whereas coronary artery dissection is the most common causative lesion during the intrapartum and postpartum stages.[24] Pulmonary embolus, reflux esophagitis, biliary colic, and aortic dissection are all more common than myocardial ischemia during pregnancy and need to be considered in the differential diagnosis. Unfortunately, some women continue to use illicit drugs during their pregnancy, and it is important to consider cocaine use in the pregnant patient presenting with chest pain.

The diagnosis of acute coronary syndrome is similar to that in nonpregnant patients with certain exceptions. Electrocardiographic changes sometimes occur in normal pregnancies and delivery. These include T wave flattening and T wave inversion (mainly in lead III) and nonspecific ST changes during pregnancy as well as ST depression during labor induction for cesarean section.[24] As a result, additional evaluation may be necessary. Echocardiography is useful in correlation of suspicious electrocardiographic findings with wall motion abnormalities. The enzymatic diagnosis of myocardial infarction is unchanged except during and immediately after delivery, when troponin is preferred to creatine kinase, which rises above baseline during this time. Angiography is appropriate in high-risk patients with acute coronary syndrome but is generally avoided in low-risk and stable gravidas.[24] There have been reported cases of dissection resulting from percutaneous intervention during pregnancy.[24] Radionuclide studies carry a lower radiation risk than does angiography but are also generally avoided in stable and low-risk patients.

Treatment of AMI during pregnancy is similar in most respects to treatment of the nonpregnant patient. Survival of the mother is the primary concern, and therapy to improve maternal outcome should not be withheld. Standard treatment includes antiplatelet agents, nitroglycerin, beta-blockers, and antithrombotic agents. However, there are potential adverse effects of such therapy on the mother and fetus (see Table 179-1), and emergent consultation with a cardiologist is recommended. Regarding antiplatelet agents, aspirin remains the first-line agent. There is limited experience with clopidogrel and eptifibatide, but both have been used successfully and are considered safe from a teratogenic standpoint. Heparin has long been considered the antithrombotic agent of choice in pregnant patients, but newer low-molecular-weight agents, specifically dalteparin and enoxaparin, appear to be efficacious and safe and are deemed appropriate for use.[25] Heparin is preferable for patients in the late third trimester because there is a more predictable response to protamine sulfate should labor begin.

Experience with thrombolytic therapy in pregnancy is extremely limited; most experience has occurred in the setting of stroke, prosthetic valve thrombosis, and massive pulmonary embolism.[26,27] The majority of pregnant patients receiving tissue plasminogen activator have had favorable maternal and fetal outcomes, but most were being treated for indications other than AMI.[26] Reported adverse effects have included maternal hemorrhage, maternal death, placental abruption, preterm delivery, fetal death, and fetal intracranial hemorrhage, although the causal relationship in many of these cases is unclear because neither tissue plasminogen activator nor streptokinase crosses the placenta. Because thrombolytic therapy precludes major surgery and epidural anesthesia in the hours to days immediately after administration, the emergency physician must carefully consider whether to use these agents in pregnant women who are close to term, especially if the need for cesarean delivery is anticipated. In addition, the use of thrombolytics in coronary artery dissection is not advised. Because of the lack of data and potential risks of fibrinolytics in gravidas, emergent percutaneous intervention is the treatment of choice for definitive management of AMI.[24,28]

In the setting of peripartum AMI, labor should be conducted with continuous monitoring of both the mother's hemodynamic status and fetal well-being. There are benefits and risks of both vaginal and operative delivery. Cesarean section avoids prolonged exertion by the mother but subjects the patient to general anesthesia if use of antithrombotic agents precludes epidural catheter placement. In addition, surgical delivery places the patient at risk for typical postoperative complications, such as infection, hemorrhage, and thromboembolism. Therefore, assisted vaginal delivery is preferred unless there is an obstetric reason for cesarean section.[24] Resolution of angina may occur during the postpartum period as physiologic demands lessen, but its occurrence during pregnancy merits a complete cardiac evaluation for acute coronary syndrome.

Valvular Heart Disease

Maternal valvular heart disease can be congenital or acquired and is one of the leading causes of nonobstetric death. Acquired valvular disease is mainly the result of rheumatic fever and endocarditis. In the United States, most cases of significant congenital heart disease are identified and corrected surgically before puberty. The ability of patients to tolerate pregnancy without significant adverse effects depends on the type and severity of the lesion. Mild to moderate lesions (New York Heart Association classes I and II) are often associated with good outcomes. On the other hand, mitral stenosis (beyond class I), advanced aortic stenosis, aortic and mitral lesions associated with moderate to severe ventricular dysfunction or pulmonary hypertension, and mechanical prosthetic valves requiring anticoagulation can result in significant maternal mortality and require directed therapy (see Table 179-1).[29]

Mitral Stenosis

Mitral stenosis is the most commonly encountered valvular lesion in pregnancy and is also the most important lesion to detect in early pregnancy because maternal mortality is not insignificant.[30] The increased resting heart rate and stroke volume in normal pregnancy increase the pressure gradient across the mitral valve. The result is high left atrial pressures, pulmonary vascular congestion, and the symptoms and physical findings typical of left ventricular failure. Patients may also develop atrial dysrhythmias that have the potential to decrease cardiac output and worsen

www.ketabpezeshki.com 66485457-66963820

symptoms.[30] The likelihood of maternal symptoms and worsening of cardiovascular status is directly related to the severity of disease. Pregnancy in women with mild mitral stenosis is generally well tolerated.[30]

In patients with symptomatic mitral stenosis, treatment is aimed at reduction of the plasma volume and slowing of the heart rate (see Table 179-1). Surgical intervention is indicated in patients with refractory symptoms despite optimal medical management and in patients with pulmonary hypertension. The preferred procedure is percutaneous balloon valvotomy, which is associated with good maternal and fetal outcomes when it is performed in experienced centers.[28-30]

Aortic and Mitral Regurgitation

In most cases, chronic regurgitant lesions are well tolerated during pregnancy and may even improve as the reduced systemic vascular resistance of pregnancy allows more forward and less regurgitant flow. In addition, this effect is aided by the increase in heart rate and shortened diastole that occur in pregnancy.[28-30] When necessary, medical therapy consists of diuresis, digoxin, and vasodilators. Patients with acute mitral regurgitation due to ruptured chordae do not fare as well and may require surgical therapy.[28-30]

Aortic Stenosis

Symptomatic aortic stenosis during pregnancy usually occurs in the setting of a congenital bicuspid valve.[28,29] Patients with mild to moderate aortic stenosis tend to have uncomplicated pregnancies,[30,31] and conservative management is often possible. Severely symptomatic patients may need percutaneous valvotomy in an experienced institution, although this procedure is risky for both the mother and the fetus.[28,29]

Prosthetic Heart Valves

Anticoagulation for the pregnant patient with a prosthetic heart valve is complicated. Warfarin is considered to be contraindicated during weeks 6 through 12 of gestation, although the risk of embryopathy is likely to be low when the dose is less than 5 mg/day.[28,29] In addition, because warfarin crosses the placenta, there is a risk of fetal bleeding. If warfarin is used after the first trimester, it should be replaced by a heparin compound several weeks before anticipated delivery.[29,32] Neither unfractionated heparin (UFH) nor low-molecular-weight heparin (LMWH) crosses the placenta or is teratogenic, but there are problems with their use in pregnancy. The response to UFH is more unpredictable in the pregnant patient, and aggressive dosing with frequent monitoring of the activated partial thromboplastin time is indicated.[32] LMWH is an acceptable alternative to UFH in pregnant patients with thromboembolic disease, but there are still only limited data on its use in the gravida with a mechanical valve.[29] In addition, there is an increased incidence of valve thrombosis in the setting of inadequate dosing and monitoring of anticoagulation.[32] If the practitioner elects to use LWMHs, frequent monitoring of anti-Xa levels is recommended with the goal of achieving a level of approximately 1.0 unit/mL 4 hours after injection.[29,32] In addition, intravenous UFH is substituted for LMWH 24 hours before delivery in anticipation of epidural or spinal anesthesia.[32]

Hematologic Disorders

Anemia

By far the most common medical complication of pregnancy is anemia. The physiologic adaptations to pregnancy include expansion of plasma volume in excess of the increase in red blood cell (RBC) mass. This results in the dilutional, physiologic anemia of pregnancy, with nadir hemoglobin occurring near the beginning of the third trimester. Any type of anemia can complicate pregnancy, but the three types most commonly involved are iron deficiency, folate deficiency, and sickle cell hemoglobinopathy.

Iron Deficiency Anemia

Iron deficiency anemia is common, occurring in approximately 20 to 25% of pregnancies in industrialized countries.[33] Apart from chronically low or marginal iron stores in many women, diversion of maternal iron to the fetus for development of its own RBCs and iron stores and increased maternal demand for iron exacerbate the deficiency during pregnancy. Pregnant patients are also subject to other causes of iron deficiency anemia, such as malnutrition, chronic underlying disease, and blood loss from the gastrointestinal or genitourinary tracts.

Anemia in pregnancy is defined by the World Health Organization as a hemoglobin concentration of less than 11 g/dL (110 g/L). Because of physiologic dilution, this level may be slightly lower after the 25th week of gestation. The risks of adverse pregnancy outcomes (see Table 179-1) have been noted to be related to the severity of the anemia. This generally is manifested as a proportionate increase in the risk of preterm delivery and low-birth-weight babies for women with mild to moderate anemia.[33-35] Severe anemia (<6 to 7 g/dL or 60 to 70 g/L), especially occurring early in pregnancy, is associated with even higher rates of preterm delivery and low birth weights as well as increased fetal mortality, abnormal fetal oxygenation, premature rupture of membranes, gestational hypertension, and reduced volume of amniotic fluid.[36,37]

It is currently recommended that all pregnant patients be screened for iron deficiency anemia.[36] The diagnosis is most accurately made in the very early stages of pregnancy because serum ferritin, the most sensitive and specific (and preferred) test, is affected by the dilutional effect of increased plasma volume occurring later in pregnancy. After the first trimester, other blood tests performed in combination may be necessary. The use of RBC indices is not a reliable screening tool because microcytosis and hypochromia are not reliably present in pregnant patients. Other supporting laboratory evidence includes low plasma iron levels, increased free erythrocyte protoporphyrin, and elevated total iron-binding capacity.

Iron supplementation with non–enteric-coated preparations is recommended to increase maternal iron stores (see Table 179-1) in women with iron deficiency,[36] even though it remains unclear whether such therapy improves perinatal outcomes.[38] Patients with an uncomplicated physiologic anemia who are not iron deficient can be expected to have good obstetric outcomes without therapy and do not require treatment. The use of prophylactic supplementation in women with normal hemoglobin levels (>11 g/dL or 110 g/L) and normal iron stores (ferritin > 20 mg/dL or 20 μg/L) to prevent anemia in late pregnancy remains controversial. One randomized controlled trial found that iron supplements for such women before 28 weeks of gestation did not reduce the prevalence of preterm delivery or development of anemia later in pregnancy but did result in a decreased incidence of low-birth-weight infants.[39] Another trial noted no effect on iron status but found that the incidence of both preterm delivery and low birth weight was reduced in women receiving prophylactic iron.[40] On the other hand, a more recent randomized controlled trial found that nonanemic women receiving oral iron supplementation were more likely to have infants small for gestational age as well as hypertension during gestation.[41] Other investigators have noted that pregnant patients with hemoglobin values typically considered "normal" in the nongravid patient have an increase in adverse outcomes, and the practitioner should consider that gravid patients with hemoglobin values of 13 to 15 g/dL (130 to 150 g/L) have inadequate expansion of their plasma volume.[42]

www.ketabpezeshki.com 66485457-66963820

Folate Deficiency Anemia

Folate deficiency is one of a number of causes of megaloblastic anemia, a condition characterized by abnormal DNA synthesis and ineffective RBC production. The incidence of folate deficiency in pregnancy is low in developed countries but remains higher in other populations. The risk for development of folate deficiency is increased in patients with multiple gestations, short interpregnancy intervals, preexisting malnutrition, hyperemesis gravidarum, malabsorption syndromes, alcoholism, and diets lacking green leafy vegetables and animal protein.[36,43] Use of certain antiepileptic medications also places women at increased risk for deficiency.

Iron deficiency and folate deficiency anemias often coexist, making the peripheral blood smear difficult to interpret. Measurement of serum and RBC folate levels is indicated in cases of suspected folate deficiency, but both have limitations. Serum folate is noted to exhibit a rapid response to folate intake, and low levels may normalize within days after a folate-rich meal. Serum folate is also affected by the hemodilution of pregnancy. RBC folate levels are more static and are indicative of folate status several months before analysis. RBC folate levels may be misleading in more acute cases and are affected as well by the increase in RBC production that occurs in pregnancy.

As is the case for iron deficiency, effects on the fetus depend on the degree of anemia; the most significant complications are neural tube defects (NTDs). Folate supplementation reduces the risk of NTDs,[44,45] and oral folate supplementation with 0.4 mg daily is routinely recommended for all women during pregnancy and before conception as the requirement for this micronutrient increases during gestation.[36] The American College of Obstetricians and Gynecologists recommends 1.0 mg for those women who have a known pregnancy-related deficiency of folate.[36] Women at higher risk for NTDs (e.g., NTDs in prior pregnancy) are advised to take much higher doses of folate at 4 mg daily under the close supervision of their obstetrician.[46]

Sickle Cell Anemia

Sickle cell disease (SCD) is one of the major sources of maternal and fetal complications in the United States. The details of the pathophysiologic mechanism and genetics of SCD are discussed in Chapter 121, but it is useful to review the most common phenotypes that affect pregnancy. The sickle gene can be homozygous (hemoglobin SS or SCD), and this form of the disease is responsible for most pregnancy complications. The sickle gene can also be heterozygous with normal hemoglobin A (sickle cell trait or hemoglobin SA), in which case symptoms are rare except under extreme environmental conditions. The hemoglobin S can also be heterozygous with a large number of abnormal hemoglobins, such as hemoglobin C, several variants of thalassemia, and other rare hemoglobin variants, and each variant has its own complication profile. Of these, the most relevant in terms of pregnancy complications is hemoglobin SC.

Patients with SCD are subject to many chronic medical problems secondary to a variety of pathophysiologic mechanisms, including sickling of RBCs, anemia, immunosuppression caused by autosplenectomy, and repeated transfusion. Median life expectancy is in the fifth decade for both sexes affected by SCD, and female fertility is generally unaffected, so it is likely that the emergency physician will encounter pregnant patients with the disease. Maternal complications are common in patients with SCD and include preterm labor, eclampsia, premature rupture of membranes, maternal infections, more frequent pain crises, thrombosis, and increased need for cesarean delivery.[47-52] Despite these complications, the maternal mortality rate is less than 1% with current treatment.[48,49,51,52]

SCD also results in adverse effects on the fetus (see Table 179-1).[47] Placental infarction and insufficiency are common, and the incidence of small-for-gestational-age and low-birth-weight infants is significantly increased in SCD pregnancies compared with normal controls.[48-51,53] The reported perinatal mortality rate varies but is low in the setting of appropriate maternal and neonatal care.[49,50,52]

Management of SCD during pregnancy is similar to that of the nonpregnant patient (see Table 179-1). Folate supplementation is standard even in the nonpregnant state because of the increased turnover of RBCs, and the recommended daily dose of folate increases to 4 mg daily during pregnancy.[47] The use of supplemental iron and transfusion is controversial because of the potential for iron overload. The need for therapy is best determined by the appropriate specialists after a complete analysis of relevant hematologic parameters. Transfusion or exchange transfusion is generally reserved for patients with symptomatic anemia, cardiopulmonary instability, acute chest syndrome, intrapartum hemorrhage, and preeclampsia and possibly for patients with increasingly frequent pain crises. It is also used preoperatively for anticipated blood loss in patients undergoing cesarean section.[49] In general, the goal with transfusion or exchange transfusion is to lower the percentage of hemoglobin S to 40% and to achieve hemoglobin values of approximately 10 g/dL (110 g/L).[47] Hydroxyurea is not recommended for use in pregnancy because of potential teratogenicity.[47]

Neurologic Disorders

Epilepsy

Epilepsy is the most common neurologic complication of pregnancy but remains relatively rare, affecting less than 1% of all gestations. Epilepsy refers to a broad spectrum of seizure disorders that range from relatively benign and infrequent seizures to a disabling condition with daily, poorly controlled generalized convulsions; therefore, care is individualized. Management of epilepsy during pregnancy entails balancing the risk of increased frequency and duration of seizures to both the mother and the fetus against the teratogenic risks of antiepileptic medications (AEMs).

The effect of pregnancy on epilepsy is variable. Most (50-76%) epileptic patients experience no change in their seizure frequency, whereas approximately 15% experience more frequent seizures.[54-56] A decrease in plasma drug concentrations is expected with certain AEMs, such as phenytoin, lamotrigine, oxcarbazepine, and levetiracetam.[54] This results from a number of potential pregnancy-related physiologic changes, including increased plasma volume, decreased protein binding, and increased renal clearance. In addition, some patients engage in voluntary noncompliance with medications to avoid teratogenic effects on the fetus.

Although gravid patients with epilepsy may be at increased risk for cesarean section, postpartum hemorrhage, and other adverse outcomes (see Table 179-1),[57] the primary complication in these pregnancies is congenital malformations.[56] Of primary concern is the risk for NTDs, facial clefts, and cardiac anomalies with the older generation agents: valproate, carbamazepine, and phenytoin. There is a twofold or threefold increase in the incidence of serious congenital malformations in offspring of epileptic mothers taking these agents. The risk is greatest with valproate and is also increased with AEM polypharmacy.[55,56,58,59] Of all the older agents, carbamazepine appears to be the safest for use as monotherapy.[55,56,58] Controversy exists as to whether infants of epileptic patients not taking AEMs have an increased incidence of congenital malformations compared with the general population. Studies comparing these infants with infants born to mothers without epilepsy noted a similar incidence of malformations.[58] Data are limited, but preliminary results suggest that the rate of congenital malformations with the newer agents lamotrigine and levetiracetam is similar to

www.ketabpezeshki.com 66485457-66963820

that in the general population, and these agents are being used with increased frequency in gravid patients.[59-62]

Care should be provided by specialists in high-risk obstetrics and neurology disciplines. However, emergency physicians may be forced to confront this problem in several clinical scenarios: the pregnant patient with a first-time seizure or status epilepticus and the patient with epilepsy who is found to be pregnant.

New-Onset Seizure

Pregnant patients may seek treatment for idiopathic new-onset seizures; however, drug toxicity or withdrawal, head injury, meningitis, stroke, and eclampsia should be considered possible causes. The most important of these is eclampsia. Patients in the immediate postictal phase often have hypertension resulting from increased sympathetic neural activity, and even those with normal pregnancies may have mild edema of the lower extremities. Consequently, urinalysis is indicated to search for proteinuria, which may be the only differentiating factor in the initial assessment of these patients. After a period of observation, elevated blood pressure in the noneclamptic patient will likely revert to normal. If the patient remains hypertensive or has other signs of eclampsia, magnesium sulfate and other agents are indicated to prevent further seizures and to control blood pressure. In patients who do not have signs of eclampsia, investigation of the cause of the seizure should proceed as with the nonpregnant patient.

Status Epilepticus

Any potential cause of seizure, including eclampsia, may result in status epilepticus. Despite this, status epilepticus in pregnancy is relatively rare, and limited data are available about its occurrence and therapy. Observations from the European Epilepsy Pregnancy Registry note that status epilepticus may occur at any time during gestation and even at delivery. It may also occur in patients who have been seizure free throughout their pregnancy, and no specific risk factors for its occurrence have been identified.[54] Older reports noted a high fetal and maternal mortality, but recent data support a much lower complication rate.[54]

The risk of untreated status epilepticus to both the mother and the fetus clearly outweighs the potential for adverse teratogenic effects, and standard resuscitative measures as well as drug therapy are indicated. Continuous fetal monitoring should be instituted as soon as possible and the mother positioned in the left lateral decubitus position to avoid the supine hypotensive syndrome.

Pregnant Epileptic Patient

Patients with epilepsy coming to the emergency department for unrelated reasons may be found to be pregnant. Although no immediate change in their therapeutic regimen needs to be made, these patients should be advised of the potential risk of AEMs in pregnancy and be referred to appropriate specialists. Unintentional pregnancy is seen even in patients taking oral contraceptives because AEMs can cause increased clearance of these medications, thereby reducing their efficacy.

There are significant obstetric complications related to prolonged seizure activity, and long-term treatment with an AEM for most patients with seizures is warranted (see Table 179-1). Patients who have nonconvulsive seizure disorders or who are seizure free for a sufficient period before conception are candidates for nonpharmacologic observation, but this decision should be deferred to the patient's primary physician or neurologist. Because phenytoin, carbamazepine, valproate, and possibly other AEMs interfere with folate metabolism, oral supplementation with at least 0.4 mg/day is recommended for all women of childbearing age taking these drugs as it may have some efficacy in preventing malformations associated with these agents.[63] Enzyme-inducing AEMs such as carbamazepine, phenytoin, and phenobarbital have been reported to cause neonatal vitamin K deficiency and hemorrhagic complications. However, results from a prospective study of 667 neonates in 662 women taking enzyme-inducing AEMs (none of whom received antenatal vitamin K) indicate that the actual risk of hemorrhage is low and without significant relationship to AEM use.[64] The American Academy of Neurology and the American Epilepsy Society note that there is inadequate evidence to determine a definitive relationship between AEM use and neonatal hemorrhage.[63]

Multiple Sclerosis

Multiple sclerosis (MS) affects approximately 400,000 Americans and is twice as common in women as in men. The peak age at onset is 20 to 35 years, which overlaps peak childbearing years. The disease is characterized by intermittent episodes of central nervous system demyelination with consequent neurologic impairment that follows a relapsing-remitting course. Progressive neurologic deficits and permanent disability develop in certain patients.

The impact of pregnancy on the course of MS has been closely studied in various cohorts of women, and a pattern has emerged. As in other autoimmune diseases, the frequency and severity of exacerbations of MS improve because of the immunosuppressant effects of pregnancy. This effect is most pronounced in the third trimester. During the 3 months after delivery, the rate of relapse increases and then returns to the pre-pregnancy baseline.[65] The risk of postpartum relapse is increased in those women with relapses during the pre-pregnancy year and during pregnancy. Relapses are also more likely in MS patients with higher disability at the time of pregnancy onset. On the other hand, it does not seem that postpartum relapses are related to the duration of disease or the total number of relapses before conception.[65] In addition, pregnancy does not appear to have any significant long-term adverse effects on disease progression.[65] In fact, pregnancies occurring after onset of MS may confer a protective effect in regard to disease course.[66]

MS patients with disease exacerbation are often treated with immunomodulators such as intravenous immune globulin (IVIG), corticosteroids, and interferon beta. Although concerns exist about the use of interferon during pregnancy, small studies in gravid patients have shown that use of IVIG during pregnancy and the postpartum period is safe and may decrease the relapse rate.[67-69] Likewise, the use of intermittent steroids in the postpartum period may decrease the likelihood of disease relapse.[70]

Maternal relapse rate is unaffected by epidural anesthesia,[65] and decisions about anesthesia should be based solely on obstetric considerations. Labor may be complicated by fatigue and uncoordinated voluntary motor activity in pushing, and MS patients may be more likely to require assisted vaginal delivery.[71] These pregnancies may also be at increased risk for preterm delivery and small-for-gestational-age infants.[72] In general, however, pregnancies in the setting of MS have outcomes similar to those in unaffected patients.[71]

Spinal Cord Injuries

Because spinal cord injury (SCI) occurs mainly in young people and usually does not impair fertility, there is a relatively large population of paraplegic and quadriplegic patients who become pregnant. Although many of these pregnancies are uneventful, these patients are at risk for certain complications.

The increased coagulability of pregnancy combined with chronic immobilization results in an increased incidence of thromboembolic disease.[73] The incidence of urinary tract infection is also markedly increased as a result of neurogenic changes and the need for catheterization.[73] Infections are even more likely during pregnancy[74] and may progress to pyelonephritis, with the

www.ketabpezeshki.com 66485457-66963820

subsequent increased risk of fetal loss, prematurity, and maternal sepsis.

A unique problem in the patient with SCI is the detection of the onset of labor, which may be painless and precipitous. Patients with spinal cord lesions below T10 to T12 have an intact uterine nerve supply and will experience labor pains; however, with lesions above T10, labor may be imperceptible or experienced as only mild abdominal discomfort.[73] In addition, up to 85% of patients with high lesions (above T5 to T6) experience potentially life-threatening autonomic dysreflexia.[75] This is manifested as severe paroxysmal hypertension, headache, tachycardia, diaphoresis, piloerection, mydriasis, and nasal congestion. Because the response is not specific to labor and may be precipitated by distention of bowel or bladder, other causes may need to be pursued as well. Pregnant patients with SCI who have these symptoms should be assessed for cervical dilation and have uterine contractions monitored. Emergency department treatment is directed at restoration of normal blood pressure with standard agents. Definitive therapy is with regional anesthesia. Both spinal anesthesia and epidural anesthesia obliterate and prevent this response and should be used as soon as possible during labor for all women with SCI.[75] Because of the difficulty in detecting labor, pregnant patients with SCI are sometimes admitted for observation near term.

Myasthenia Gravis

Myasthenia gravis is a rare disorder in which autoimmune destruction of the postsynaptic cholinergic receptor results in profound muscle fatigability. Treatment with cholinesterase inhibitors can supply additional acetylcholine to achieve virtually normal muscle contractility but should be titrated to avoid precipitation of a cholinergic crisis. Adjustments in medication dosing are frequently required to preserve this balance.

The effect of pregnancy and the postpartum state on myasthenia gravis is unpredictable in the individual patient, but overall approximately 25 to 40% of patients experience exacerbation of disease, with the remainder having improvement or no change in disease severity.[76-78] Several important pregnancy complications are associated with myasthenia gravis. Because of weight gain, anemia, and other physiologic adjustments of pregnancy that may result in fatigue, the distinction between normal pregnancy symptoms and myasthenia may be difficult. Most deliveries are accomplished vaginally without complication in adequately treated patients; assisted and surgical delivery in these women is indicated mainly for obstetric reasons rather than for specific myasthenia-related care.[76,77,79]

Up to 30% of neonates born to mothers with myasthenia gravis have a transient neonatal myasthenic syndrome through placental transport of acetylcholine receptor antibodies.[77] The risk of neonatal myasthenia gravis is decreased in those infants born to mothers who have undergone thymectomy.[77,80] Onset of neonatal myasthenia is typically within the first hours of life but may be delayed by a period of days. Manifestations include poor feeding and suck, diminished reflexes, hypotonia, and respiratory failure. As in adults, the symptoms respond to cholinesterase inhibitors, but treatment should be done in an intensive care unit setting. The duration of the syndrome depends on its severity; severely affected infants sometimes require therapy for several months.[77]

Fortunately, myasthenic crises during pregnancy are rare.[77,78] When exacerbations do occur, treatment is no different from treatment of nonpregnant patients (see Table 179-1). Assessment of pulse oximetry, forced vital capacity, and arterial blood gas parameters will guide respiratory therapy. For patients presenting with weakness, an edrophonium (Tensilon) challenge test to distinguish myasthenic from cholinergic crisis is appropriate after initiation of appropriate ventilatory support. Standard medical treatment is continued during labor and delivery to maximize motor strength. Epidural anesthesia is also recommended to reduce pain and fatigue. Sedatives and other agents that increase fatigue are best avoided during this time. The physician should be aware that 30% of patients experience an exacerbation during the postpartum period as the protective immunosuppressant effect of pregnancy dissipates.[77] In addition, puerperal infections place the patient at risk for disease exacerbation and warrant aggressive therapy.[77]

Renal Disorders

Several alterations in renal hemodynamics occur during pregnancy. Both the glomerular filtration rate and effective renal plasma flow increase by 30 to 50% compared with the nonpregnant state. Because no substantial alterations are present in the production of creatinine or urea nitrogen, levels of these solutes decrease from low normal nonpregnant values of 0.7 and 12.0 mg/dL (53.38 μmol/L and 4.28 mmol/L) to 0.5 and 9.0 mg/dL (38.13 μmol/L and 3.21 mmol/L), respectively. Thus blood urea nitrogen and creatinine levels considered normal in nonpregnant women (creatinine 0.8 mg/dL or 61 μmol/L and blood urea nitrogen 12 mg/dL or 4.28 mmol/L) indicate underlying renal impairment and warrant further investigation.

The primary factors that determine how renal disease affects pregnancy outcome are the degree of underlying dysfunction and the presence of associated hypertensive disorders. In general, patients with mild insufficiency (creatinine $<$ 1.4 mg/dL or 106.76 μmol/L) and no hypertension can expect good pregnancy outcomes and preserved renal function. On the other hand, patients with moderate to severe renal dysfunction have a much higher risk of further decline in renal function as well as adverse obstetric outcomes, including preeclampsia, placental abruption, fetal loss, preterm delivery, low birth weight, polyhydramnios, and increased need for cesarean section and neonatal intensive care.[81-87] Worsening of underlying renal function is more likely in patients with decreased glomerular filtration rate who also have associated proteinuria or hypertension.[84] Because worsening renal function is manifested by hypertension and proteinuria, differentiation from preeclampsia can be difficult. In this setting, it is best to treat the patient for presumed preeclampsia with the caveat that magnesium administration be performed judiciously on the basis of serum magnesium levels.

Pregnant women with chronic renal failure require aggressive and timely management to optimize their chances for a successful gestation without causing further deterioration in renal function. Baseline renal function studies are done early in pregnancy and then reassessed every 4 to 6 weeks. Evidence of renal function deterioration or the development or exacerbation of hypertension warrants admission for specialized inpatient care. Hemodialysis is indicated for creatinine levels above 3.5 to 5 mg/dL (266.91 to 381.3 μmol/L). Pregnancy in women who are already dialysis dependent has been associated with poor outcomes, and pregnancy has previously been discouraged in this population of patients. However, studies including small numbers of women have noted live birth rates approaching 60 to 85% when mothers receive specialized prenatal care.[82,85,86] Such care includes correction of anemia, appropriate antihypertensive therapy, and more aggressive dialysis with more frequent or prolonged sessions.[81,86,88]

Metabolic and Endocrine Disorders

Diabetes

Three types of diabetes are involved in pregnancy: type 1, or insulin-dependent diabetes mellitus (IDDM); type 2, or non–insulin-dependent diabetes mellitus (NIDDM); and gestational diabetes mellitus (GDM). Although NIDDM is sometimes considered a more benign form of disease, the risk of malformations is

www.ketabpezeshki.com 66485457-66963820

the same for both NIDDM and IDDM.[89] Maternal and fetal complications relate to inadequate glycemic control as well as to the presence of vascular complications or severe renal insufficiency more than to the type of diabetes. All pregnant patients with diabetes are considered "brittle" and require regular follow-up by appropriate specialists. In addition, all patients, including those with GDM, should perform routine self-monitoring of glucose concentration.

Maternal Complications

The physiology of glucose regulation during pregnancy is complex. During the first half of gestation, some patients have an increased sensitivity to insulin,[90] although this is not a universal finding and the change in insulin requirements in early pregnancy may be variable. In addition, hormonal changes of pregnancy combined with emesis, increased use of glucose by the placenta and fetus, and decreased hepatic glucose production predispose the gravid diabetic to more rapid onset of hypoglycemia. During later gestation, there is progressive insulin resistance that peaks during the third trimester and then falls again during labor and the immediate postpartum period. Obesity and underlying insulin resistance in NIDDM may exacerbate hyperglycemia during pregnancy.[91] Pregnancy also predisposes to ketosis, and this effect is exacerbated in the setting of emesis. Specific adverse pregnancy-related outcomes are more common and include stillbirth, preeclampsia, preterm delivery, and the requirement for cesarean delivery.[92-94]

The effects of pregnancy on underlying diabetes vary by the organ system. The data are limited, but pregnancy is not advised for diabetic patients with significant coronary artery disease because of the cardiovascular demands of pregnancy and the high mortality of AMI during pregnancy.[92] Patients with diabetic nephropathy are at increased risk for preeclampsia and the subsequent requirement for preterm delivery.[91,92] The renal effects of pregnancy depend on the severity of underlying disease. Patients with mild to moderate renal dysfunction do not seem to experience permanent disease progression. On the other hand, women with more severe renal dysfunction are at increased risk for progression of their nephropathy.[91,92] Retinopathy may worsen acutely during pregnancy, especially in patients with high hemoglobin A_{1c} (HbA_{1c}) levels, hypertension, nephropathy, and active nonproliferative or proliferative retinopathy.[91,95] Laser therapy of preexisting retinopathy is recommended before conception as well as in pregnant patients with severe disease.[91,92,95] Autonomic neuropathy does not accelerate during pregnancy, with the exception of a possible increase in symptomatic severity of gastroparesis,[91] and the combination of hyperemesis gravidarum and gastroparesis often causes problems. Frequent vomiting results in dehydration and inadequate intake of nutrients that can cause hypoglycemic episodes if the insulin dosage is not adjusted accordingly.

Diabetic ketoacidosis (DKA) occurs in up to 9% of diabetic patients during pregnancy and may be the initial presentation of diabetes. DKA is most commonly seen in patients with IDDM but also complicates pregnancies in women with NIDDM and GDM.[91,92,96] Common precipitating events include the typical factors seen in nonpregnant patients, such as insulin noncompliance and infection. Other pregnancy-specific factors are increased insulin resistance, hyperemesis, use of beta-mimetic medications for tocolysis, and use of corticosteroids to hasten fetal lung maturity. The serum pH may be deceptively normal in a pregnant patient with DKA because the initial pH tends to be higher in pregnancy as a result of physiologic hyperventilation. In addition, serum glucose concentration may be normal or only moderately elevated, and screening for DKA is indicated in gravid diabetics with vomiting or with persistent hyperglycemia.[91,96] Maternal mortality is rare in appropriately treated DKA. Fetal mortality rates are relatively high, ranging from 10 to 35%.[92]

Fetal Complications

Diabetes has many deleterious effects on the fetus (see Table 179-1). The rate of congenital malformations in patients with prepregnancy diabetes is increased threefold or fourfold compared with the nondiabetic population, with anomalies being more likely in pregnancies with poor glycemic control.[91,92,97-99] Glucose crosses the placenta, and prolonged fetal exposure to maternal hyperglycemia induces fetal pancreatic hyperplasia and high insulin production. Elevated insulin levels in turn promote fetal growth, resulting in macrosomia and the need for cesarean section. Conversely, preeclampsia and placental infarction secondary to vascular disease may result in impaired fetal development and stillbirth.[94] After delivery, continued high insulin secretion in the absence of a maternal glucose supply results in a significant rate of neonatal hypoglycemia. Because these infants are more likely to be preterm, hyperbilirubinemia and respiratory problems are also more frequent.[92,93]

Management

Treatment of NIDDM and IDDM requires individualized and carefully adjusted insulin administration with the goal of maintaining strict glycemic control while avoiding hypoglycemia. Several studies suggest that sulfonylureas and metformin are safe and effective in pregnancies complicated by GDM,[100,101] but experts recommend that NIDDM patients taking oral agents be transitioned to insulin during pregnancy.[91,92,102] Ideally, HbA_{1c} values should not be higher than 6%[91,92] (see Table 179-1). Frequent self-monitoring is recommended, and these patients should also have frequent office visits with their practitioner throughout the duration of pregnancy. It is preferable to achieve glycemic control as manifested by a normal or nearly normal HbA_{1c} level before conception to minimize the risks of congenital malformations and other complications.[91,93,97,98] Treatment of DKA does not differ from treatment given in the nonpregnant state except that fetal viability and well-being should be assessed.

The timing and mode of delivery depend on whether obstetric or maternal complications exist. In the absence of suspected problems, vaginal delivery at term is recommended. Elective delivery is indicated in the setting of poor metabolic control, significant diabetic complications, and fetal macrosomia with suspected birth weight greater than 4500 g.[92] Delivery is timed to avoid fetal growth into the macrosomic range while allowing sufficient fetal lung maturity. If corticosteroids are administered, close glucose monitoring is required because insulin requirements are likely to increase. Pregnancy progression beyond term is not recommended.

Gestational Diabetes

GDM is defined as glucose intolerance that begins (or is first detected) during pregnancy. As the incidences of both NIDDM and IDDM have increased, so has that of gestational disease.[103] It is important to detect and to address glycemic disorders because maternal glucose intolerance increases the likelihood of adverse perinatal outcomes, such as fetal macrosomia and maternal hypertensive disorders, even at glycemic levels that are considered below the threshold for diagnosis of diabetes.[104-107] GDM is also a risk factor for the subsequent development of nongestational diabetes; an increased risk is seen with obesity, higher HbA_{1c} values in pregnancy, advanced age at time of GDM diagnosis, lower beta cell function, and need for insulin dosing in late pregnancy.[108-111] It is recommended that all postpartum patients with GDM be educated about diet and exercise and undergo routine postnatal screening at repeated intervals long term.[108,109,112]

The exact protocol to follow for the diagnosis of GDM and preexisting, undiagnosed diabetes mellitus is controversial. It is recommended that pregnant patients undergo screening at

www.ketabpezeshki.com 66485457-66963820

the beginning of prenatal care in an effort to identify those patients who are at risk for GDM and pregestational diabetes mellitus to minimize adverse pregnancy outcome and progression of diabetic complications.[105] However, it remains unclear whether universal laboratory testing at the first prenatal visit (as opposed to clinical screening) is cost-effective or if this type of screening should be applied only to those populations with a high prevalence of diabetes.[105] The International Association of the Diabetes and Pregnancy Study Groups recommends laboratory screening of all women (if prevalence of disease is high in the population being tested) or only high-risk women at the first prenatal visit with subsequent testing at 24 to 28 weeks' gestation for all women unless they have already been diagnosed with a glycemic disorder.[105] The American Diabetes Association advocates selective laboratory assessment as soon as possible in gestation for patients at high risk for GDM. This group includes patients older than 25 years; certain high-risk ethnic groups; and patients with obesity, known first-degree relatives with diabetes, personal history of diabetes or glucose intolerance, and personal history of poor pregnancy outcome.[109] Average-risk women and those high-risk women not diagnosed with GDM early in pregnancy then undergo laboratory screening at 24 to 28 weeks' gestation.[111] On the other hand, the American College of Obstetricians and Gynecologists recommends universal laboratory screening.[108]

The majority of patients with GDM achieve metabolic control with dietary therapy. Traditionally, insulin administration is indicated if dietary control is unsuccessful[108,109] (see Table 179-1). Standard practice has been to avoid oral medications because of concerns for placental transfer. However, glyburide has minimal transfer, and studies comparing insulin with glyburide in GDM found that glyburide provided similar glycemic control without an increase in adverse pregnancy outcomes.[110,113,114] A summary from the Fifth International Workshop-Conference on GDM noted that glyburide may be considered in patients with GDM as long as care is taken to prevent maternal hypoglycemia.[115] Similarly, initial investigations of metformin in the setting of GDM have not noted any increase in perinatal complications, although some patients taking these agents have required supplemental insulin.[101,116] At this time, however, further study is recommended before its widespread use.[115] There are limited data for other oral medications.

Thyroid Disorders

The peak incidence of thyroid disease is in women of childbearing age. Both hypoactivity and hyperactivity lead to obstetric complications and warrant specific therapy. As with other organ systems, there are physiologic changes in thyroid function that occur in normal pregnancies. Human chorionic gonadotropin (hCG) is structurally similar to thyroid-stimulating hormone (TSH) and stimulates the thyroid gland. As a result, women with normal pregnancies may experience a temporary suppression in TSH production and slightly lower TSH levels during the first trimester, which mirrors the high circulating hCG levels seen at this gestational period. This hCG-mediated effect may lead to a transient hyperthyroidism if hormone levels are markedly increased. Estrogen also increases the amount of thyroid hormone–binding proteins, which ultimately leads to an increase in the amount of total T_4 and T_3 even though free hormone levels remain normal.

During the first trimester, the fetus is entirely dependent on placental transfer of maternal thyroid hormone. After 10 to 12 weeks of gestation, the fetus makes its own thyroid hormone but still requires placental transport of iodine and adequate maternal intake of this element (250 μg/day).

Hyperthyroidism

The most common cause of hyperthyroidism is Graves' disease, in which autoimmune thyroid-stimulating immunoglobulin results in increased production and release of thyroid hormone. Because the symptoms of hyperthyroidism resemble the physiologic changes expected during pregnancy in many respects, the diagnosis may not be immediately evident. Patients with Graves' disease have disease-specific findings including a diffusely enlarged, soft, mildly tender thyroid gland, exophthalmos, and dermopathy. Other symptoms, such as dyspnea, heat intolerance, hyperemesis, tachycardia, palpitations, systolic flow murmurs, increased appetite, and fatigue, are common to both conditions, making clinical diagnosis difficult. In cases of suspected hyperthyroidism, thyroid function studies and antibody assays are indicated and will confirm the presence of disease.

There are several obstetric concerns for both the mother and the fetus in the setting of untreated clinical hyperthyroidism (see Table 179-1).[117] Thyroid storm is the most serious manifestation of the disease. It may be precipitated by stressors such as infection and delivery, and it is manifested with fever, dysrhythmias, myocardial dysfunction, mental status changes, and circulatory collapse. In addition to the more general complications stemming from thyroid hormone excess, Graves' disease places the fetus at risk for autoimmune-mediated thyroid dysfunction through placental transfer of maternal thyroid-stimulating immunoglobulins. Up to 17% of neonates of mothers with Graves' disease and positive thyroid-stimulating immunoglobulin values have transient hyperthyroidism lasting 3 to 12 weeks. The condition gradually clears as maternal antibodies are metabolized.[118] Manifestations are potentially severe and include irritability, tachycardia, goiter, cardiomegaly, congestive heart failure, premature craniosynostosis, low birth weight, and failure to thrive.[119] These infants also have an increased mortality rate, so routine thyroid assessment is indicated in all infants born to mothers with autoimmune thyroid disease.[120]

The mainstay of treatment of hyperthyroidism (see Table 179-1) consists of antithyroid drugs. Propylthiouracil is preferred to methimazole because of an increased potential for adverse congenital drug effects from methimazole.[120,121] However, both medications cross the placenta and can stimulate the fetal thyroid, so maternal thyroid function should be assessed periodically during pregnancy with the goal of keeping free thyroxine in the high-normal range.[120] Most patients respond to pharmacologic manipulation, although thyroidectomy may be considered in severe cases in which patients cannot tolerate antithyroid medication or in the setting of medication failure.[120] Use of iodine-131 radionuclide to ablate the maternal thyroid is contraindicated because it will also destroy the fetal thyroid gland.

Additional therapy with beta-blockade to mitigate the hemodynamic effects of sympathetic stimulation may be required in certain cases pending adequate disease control with antithyroid medications. In the nonpregnant patient, iodides may be used to transiently block the release of stored T_4 from the thyroid gland and to inhibit organification of iodide. However, the fetal thyroid is extremely sensitive to iodide, which may result in neonatal goiter and hypothyroidism. Therefore, iodide is considered class D in pregnancy, and its use should be reserved for severe cases with duration of therapy limited to a period of days. As with other autoimmune conditions, transient improvement of Graves' disease during pregnancy is common, with rebound and clinical deterioration occurring in a majority of patients after delivery.[122]

Postpartum Thyroiditis

Postpartum thyroiditis is a relatively common condition that develops in approximately 4 to 8% of parturients within 9 months of delivery.[117,123,124] The risk for development of postpartum

www.ketabpezeshki.com 66485457-66963820

thyroiditis is increased in patients with diabetes as well as in patients who have thyroid peroxidase antibodies.[120] Patients experience transient hyperthyroidism, transient hypothyroidism, or transient hyperactivity followed by transient hypoactivity. Symptoms are typical for the type of impairment. The need for medication seems to be confined to those patients with postpartum hypothyroidism[123]; thyroid replacement is recommended for patients who are symptomatic or who have a markedly elevated TSH. Hypothyroid patients trying to conceive another pregnancy should be treated as well.[120] On occasion, patients with transient hyperthyroidism require a short course of beta-blockers, but antithyroid drugs are not helpful because the pathophysiologic process relates to release of preformed thyroid rather than to excess thyroid hormone production. Approximately 30% of patients with postpartum thyroiditis develop permanent thyroid failure, and this percentage is increased to 50% or more in patients with postpartum hypoactivity.[124,125]

Hypothyroidism

The most common cause of hypothyroidism is Hashimoto's thyroiditis. Overt hypothyroidism is often associated with infertility, so most cases seen during pregnancy are less severe or subclinical forms or occur in patients already undergoing levothyroxine therapy for known disease. Undiagnosed subclinical hypothyroidism may be manifested during pregnancy as physiologic adjustments result in a greater requirement for thyroid hormone production. In addition, iodine deficiency may be exacerbated by pregnancy because renal losses of iodine increase as the glomerular filtration rate increases and as the fetus diverts iodine for its own thyroid hormone synthesis. When signs and symptoms do occur, they are identical to those in the nonpregnant state. Myxedema coma is extremely rare but should be considered along with other causes of coma in a pregnant patient.

As with hyperthyroidism, there is an increased incidence of adverse maternal and fetal effects in women with clinical hypothyroidism (see Table 179-1).[117,126] The majority of patients who are already undergoing treatment for hypothyroidism will require an increased dosage of levothyroxine during pregnancy, and close monitoring of thyroid function is recommended as soon as possible after conception.[120,127,128] Treatment of newly diagnosed patients consists of prompt initiation of thyroid hormone replacement with the goal being to achieve a normal TSH level.[117,120]

Approximately 3 to 5% of women of childbearing age have subclinical hypothyroidism,[129] as defined by an elevated TSH level and a normal T_4 level.[130] It has been noted that clinical and subclinical hypothyroidism result in adverse perinatal outcomes and adverse neurologic outcomes for affected infants.[120,130] One study also found an increased risk of placental abruption and preterm delivery in subclinical hypothyroidism, and the authors suggested that premature birth may have a direct impact on cognitive outcome in affected infants.[131] Conversely, another more recent analysis found no increase in adverse outcomes in subclinical hypothyroidism.[132]

The issue of whether to provide routine prenatal screening for hypothyroidism remains controversial. At present, both the American College of Obstetricians and Gynecologists and the Endocrine Society note that there is insufficient evidence to confirm that diagnosis and treatment of subclinical disease significantly improve perinatal neurologic outcomes.[120,130] These organizations state that screening should include symptomatic patients and those at risk for disease (prior thyroid diagnoses or other endocrine or autoimmune problems).[120,130] On the other hand, other sources recommend assessment of TSH levels in all women before conception or as soon as possible after becoming pregnant because targeted screening may miss up to one third of affected women.[133,134]

Congenital hypothyroidism, associated with severe mental retardation, occurs in approximately 4 in 10,000 births in the United States.[135] It is most often the result of sporadic fetal thyroid dysgenesis or ectopy rather than maternal thyroid dysfunction.[136] Diagnosis is often difficult because clinical signs and symptoms may be masked by maternal thyroid hormone. Congenital hypothyroidism is successfully treated with hormone replacement begun in the first days of life, and screening for congenital hypothyroidism is routinely performed in most developed countries.

Systemic Infections

Tuberculosis

Acquisition and presentation of tuberculosis are unchanged during pregnancy. However, the effect of tuberculosis on pregnancy is unclear. Some studies reveal an increase in gestational complications[137-139] (see Table 179-1), but these outcomes are likely to be significantly influenced by the site of disease and specifics of treatment. In addition, conclusions are limited by the fact that these studies are often small or performed retrospectively. Other small studies found no significant increase in gestational complications in 32 and 111 pregnant patients with properly treated tuberculosis.[140,141] Complications are more likely in patients with inadequate or delayed treatment, delayed diagnosis, and extrapulmonary (extranodal) tuberculosis.[137,138] Neonatal tuberculosis acquired by exposure to undiagnosed and untreated active disease places infants at significant risk for acquiring tuberculosis during the first year of life, with significant mortality. In addition, congenital tuberculosis is possible after the fetus becomes infected through the placenta or aspiration of infected amniotic fluid. The latter is rare if the mother has received appropriate therapy.

Current recommendations are to administer a tuberculin skin test early in pregnancy to all patients at high risk for disease and to obtain a chest radiograph if the purified protein derivative (PPD) skin test response is positive or if the patient's signs and symptoms suggest tuberculosis. Universal screening should be considered in urban areas with a high prevalence of disease. Definitive treatment is indicated in all pregnant patients with confirmed tuberculosis as well as in those high-risk women with suspected disease (see Table 179-1).[142] Isoniazid, ethambutol, and rifampin in their usual doses have not been shown to be teratogenic to human fetuses and are acceptable during pregnancy and breastfeeding.[143] On the other hand, streptomycin causes fetal ototoxicity, and little is known about the safety of other second-line agents during pregnancy. These less commonly used agents should be avoided except in the case of multidrug-resistant disease (MDR-TB). One retrospective study of 38 gravidas with MDR-TB found no significant increase in perinatal complications, and even patients with drug-resistant disease can be considered for continuation of pregnancy.[144]

HIV Infection and AIDS

Human immunodeficiency virus (HIV) infection is one of the leading health problems in pregnancy. In 2008, 25% of reported cases of HIV infection and acquired immunodeficiency syndrome (AIDS) in the United States were in women, with a significant percentage being in women of childbearing age.[145] Estimates of the seroprevalence of HIV infection in pregnant women vary on a regional basis. In the United States, the overall prevalence and number of perinatally infected infants are low but also vary according to the population, with increased rates seen in the southern states and in the black and Hispanic populations.[145,146]

The mechanism of vertical transmission is multifactorial. The majority of cases are thought to occur during delivery through exposure to maternal blood and secretions; other infants are likely

www.ketabpezeshki.com 66485457-66963820

to be infected in utero or through breast-feeding. Various factors influence the rate of transmission. The most important is maternal viral load, although infection can occur even with low maternal viral load.[147-149] Other contributing factors for transmission include vaginal infections, injection drug use, premature delivery, low birth weight, and prolonged rupture of membranes.[147,149-151] Vertical transmission of HIV in the United States and other developed countries has declined significantly since its peak in the early 1990s because of the implementation of a number of interventions, including routine voluntary testing, antiretroviral therapy (ART), use of elective cesarean section, and avoidance of breast-feeding.[152] However, vertical transmission remains a concern in women without adequate prenatal care as well as a global concern. It is estimated that perinatal infection occurs in approximately 20% of deliveries if the mother is untreated, whereas the previously mentioned interventions reduce this rate to less than 1 or 2%.[149,150,152-154] Because of this beneficial effect, it is recommended that all pregnant women undergo screening during their routine prenatal evaluation, with repeated screening in the third trimester for women engaging in high-risk behavior or those who have concurrent sexually transmitted diseases (STDs). Rapid HIV screening is recommended for women in labor whose HIV status is unknown.[147,155,156]

Treatment of the pregnant patient with HIV infection includes appropriate ART as well as standard therapy for opportunistic infections (see Table 179-1).[147,157] There are limited data on specific therapy for opportunistic infections during pregnancy, but the practitioner should take into account the fact that medication clearance may be affected by various pregnancy-related changes, including increased renal clearance, dilutional anemia, and fetal metabolism of medications.[157] Periodic ultrasonographic assessments of fetal growth are indicated if required medications have an unknown safety profile in pregnancy.

Optimal therapy to prevent vertical transmission includes three stages: antepartum administration of highly active antiretroviral therapy (HAART), intrapartum intravenous zidovudine dosing, and treatment of the infant with 4 to 6 weeks of zidovudine.[147,158] The specific ART regimen to follow depends on a number of variables. In patients who are already taking ART with good disease control (viral load < 1000 copies/mL) at the time or pregnancy diagnosis, the current medication regimen should be continued with the exception of efavirenz, which should be discontinued.[147] Women who have never received ART are started on a standard multidrug HARRT regimen that avoids use of efavirenz in the first trimester. Delayed initiation of HAART until the second trimester may be considered in women if the only goal of therapy is to prevent mother-to-child transmission (maternal viral load < 1000 copies/mL).[147,158] In HIV-infected mothers without prenatal care, intrapartum ART followed by postexposure zidovudine treatment of the infant reduces the likelihood of infection but is less effective than the recommended three-stage regimen.[147] Elective cesarean section is recommended in mothers with a viral load greater than 1000 copies/mL.[147] It is reasonable to present cesarean delivery as an option for patients with lower viral loads, although the benefit for these lower risk mothers in uncertain,[147,159] and the risk of mother-to-child transmission by vaginal delivery is very low when mothers have received effective HAART.[148,160]

Whereas breast-feeding is associated with mother-to-child transmission of HIV infection and is not recommended in urban areas with access to formula preparations, it remains the preferred mode of feeding in resource-poor areas where formula use is not possible. Studies have shown that continued infant prophylaxis with ART is effective in reducing mother-to-child transmission through breast-feeding, with the absolute risk of transmission being very low.[161,162] Exclusive breast-feeding has also been shown to confer a mortality benefit and to reduce the risk of acquired infections,[163,164] and the World Health Organization now encourages exclusive breast-feeding in women when adequate and safe formula-feeding is not possible.[165] Ideally, breast-feeding mothers should be maintained with ART. If ART is not available, breast-feeding is preferable when replacement nutrition is not an option.[165]

Even in the setting of ART, commonly used serologic tests to detect antibodies for HIV yield positive results in virtually all neonates born to HIV-positive mothers because of placental transfer of maternal antibodies. These antibodies may be present for up to 18 months and are not necessarily indicative of infection. The preferred means of diagnosis of perinatal HIV infection is by use of assays to detect viral RNA or DNA. Infants are considered noninfected if there have been two negative viral assays after 1 month of age, with one of the assays being done after 4 months of age, or with negative results of two antibody tests done on separate occasions after 6 months of age. In addition, there should be no clinical or other laboratory findings to suggest infection.[166] Clinical assessment for possible HIV infection is also warranted. Infants with AIDS typically present with recurrent bacterial infections, *Pneumocystis* pneumonia, encephalopathy, extrapulmonary tuberculosis, and generalized wasting. Recent analysis reveals that HAART therapy in infants and children is extremely effective in reducing HIV-related morbidity and mortality.[167]

The effects of pregnancy in women with symptomatic HIV infection include an increased incidence of infant mortality, prematurity, stillbirth, and low birth weight and also gestational diabetes.[164,168,169] Seropositive mothers who undergo cesarean delivery generally have an uncomplicated postoperative course, although some studies note a slightly increased risk of postpartum endometritis and other maternal infections, with the highest rate of infection seen in women who have low $CD4^+$ cell counts.[170-172] It is also important to consider the effect of ART on pregnancy outcomes. It is recommended that efavirenz be avoided in the first trimester of pregnancy because of potential teratogenicity and fetal anomalies.[147,173-175] Overall, however, most antiretroviral medications are considered safe in this regard. Several large studies have noted no increase in adverse outcomes in women taking ART, with the possible exception of preterm delivery, although this remains a matter of controversy.[176-178]

The effect of pregnancy is unclear. An observational cohort study in which a majority of women were using HAART found that pregnancy had no impact on the rate of disease progression.[179] Additional studies are necessary for definitive conclusions to be drawn.

Syphilis

The incidence of primary and secondary syphilis among reproductive-age women in the United States increased during 2004 through 2008, with a current rate of 1.5 cases per 100,000 women.[180] Unfortunately, the incidence of congenital syphilis has shown a similar increase from 2005 to 2008, with a current rate of 8.2 per 100,000 live births.[181] Of all the congenital syphilis cases for 2008, half were born to black mothers and an additional 30% to Hispanic mothers, highlighting the need for better screening in these high-risk populations.[181]

Syphilis causes numerous gestational complications (see Table 179-1), but its most significant sequela is congenital syphilis. This syndrome is characterized by clinical abnormalities such as hepatosplenomegaly, osteochondritis, jaundice, rash, lymphadenopathy, rhinitis, Hutchinson's teeth, and anemia. Infant mortality for cases occurring in 2008 was 6.5%.[181] Screening for all pregnant patients is indicated at the first prenatal visit and again in the early third trimester and at delivery for high-risk patients[156] because vertical transmission rates can be reduced significantly with appropriate penicillin therapy.[156,182] Either the Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR) test

www.ketabpezeshki.com 66485457-66963820

can be used to detect nontreponemal antibody. Pregnancy may cause false-positive results for nontreponemal studies, so confirmation with specific treponemal tests is indicated for a positive VDRL or RPR study. Patients with latent syphilis and those whose titers fail to respond to therapy should undergo cerebrospinal fluid analysis to screen for tertiary syphilis. In addition, fetal ultrasonography before the 20th week of gestation is indicated to assess for abnormalities consistent with congenital syphilis.[156]

Treatment is identical to that given to nonpregnant patients with use of benzathine penicillin G appropriate for the disease stage[156] (see Table 179-1). Penicillin-allergic patients are sometimes treated with macrolides.[182] However, it is preferable that these patients undergo skin testing and desensitization if the skin test result is positive because alternative therapy is not reliably effective in preventing congenital syphilis.[156,183,184] Treatment failures are rare with appropriately administered penicillin but do occur. Failures leading to congenital syphilis are more likely in mothers with secondary syphilis, high VDRL or RPR levels, and an interval from treatment to delivery of less than 30 days.[156,182,184,185]

Hepatitis

Hepatitis B

The prevalence of hepatitis B virus (HBV) infection among pregnant women varies by the population studied, with the highest rates seen in Asians and women of African descent.[186,187] The rate of vertical transmission depends on the acuity of maternal infection and when it occurs during the gestation. Perinatal transmission is approximately 10 to 20% in women seropositive for HBsAg alone but approaches 90% in mothers who are seropositive for HBsAg and HBeAg, and it is also more likely if the mother has acute infection during the third trimester.[188] Of infants who have HBV infection, up to 90% become chronic carriers as adults and are at risk for complications such as cirrhosis and hepatocellular carcinoma.[188]

Routine screening for HBV during early pregnancy is recommended because treatment with hepatitis B immune globulin and hepatitis B vaccine is effective in reducing the rate of vertical transmission.[156,188-190] Repeated testing is indicated at the time of delivery for women at high risk for infection.[156] Although these therapies are effective in reducing neonatal infection, treatment failures do occur in the setting of maternal seropositivity for HBeAg and high viral loads of HBV DNA.[191,192] Studies suggest that lamivudine given in late pregnancy to these high-risk gravidas reduces viral transmission when it is given in conjunction with HBV vaccine and immune globulin.[193,194] Vaccination against HBV is currently recommended for all infants in the United States. The treatment schedule and the need for additional therapy with immune globulin vary according to maternal seropositivity. Infants of HBsAg-positive mothers should receive hepatitis B immune globulin and the first dose of vaccine within 12 hours of birth. Two additional doses of vaccine are administered at a later date.[188,195] Pregnancy is not a contraindication to either therapy. All HBsAg-negative gravidas at risk for HBV infection or other STDs or who are seeking STD treatment should receive the vaccine.[156] Pregnant patients who are exposed to HBV should receive both hepatitis B immune globulin and vaccine.

Hepatitis C

As with HBV, the prevalence of hepatitis C virus (HCV) infection among pregnant women varies by the population, ranging from less than 1% to approximately 4%. Vertical transmission is rare in mothers with anti-HCV antibodies and no circulating HCV RNA. However, perinatal transmission is significantly increased by the presence of HCV viremia, occurring in approximately 4 to 6% of cases.[196] The transmission rate is even higher in the setting of coinfection with HIV.[197,198] Unfortunately, cesarean delivery has not been shown to prevent HCV transmission.[156,188,197] No available vaccine or immune globulin exists to prevent hepatitis C, and routine prenatal screening is not indicated.[156]

Inflammatory Disorders

Rheumatic diseases or collagen vascular diseases are characterized by sterile inflammation in multiple anatomic sites. The most common rheumatic diseases encountered in pregnancy are systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Gravid patients with collagen vascular disease may have preexisting cardiovascular or renal compromise and may not tolerate the increased intravascular volume and other physiologic changes that occur during pregnancy. The following discussion focuses on SLE, which is the rheumatic disease responsible for the majority of gestational complications. Most of the treatment guidelines for SLE are relevant to other rheumatologic disorders as well.

Systemic Lupus Erythematosus

SLE primarily affects women of reproductive age, and fertility is usually unaffected. The disease course during pregnancy varies, but studies indicate that acute flares occur in less than one third of patients in clinical remission at the time of conception.[199-201] Disease activity tends to involve the skin and musculoskeletal system, although renal involvement is not uncommon, especially in those patients with active lupus nephritis.[202-204] The gestational effects of SLE also depend on the underlying severity of disease. Patients with active disease, especially lupus nephritis, have a higher incidence of disease flares and pregnancy complications,[199,201,203-205] and it is best for women to achieve good disease control before pregnancy. Many patients have acceptable outcomes, but lupus pregnancies are associated with an increased maternal mortality as well as an increased rate of other complications, including preeclampsia, preterm delivery, thrombocytopenia, anemia, intrauterine growth retardation, fetal loss, and need for cesarean section.[199,205-207] Other comorbid conditions that adversely affect pregnancy, such as diabetes and thrombophilia, are also seen more commonly in SLE patients.[207] The risk of preeclampsia is especially increased in patients with active lupus nephritis.[201,203] As with other renal disease, increasing proteinuria warrants a careful evaluation to distinguish between lupus glomerulonephritis and preeclampsia. The presence of abnormal urine sediment, increasing titers of anti-DNA antibody, and decreasing levels of C3 and C4 suggest lupus nephritis.

Numerous other organ systems in addition to the kidneys are involved in SLE, and differentiation from pregnancy-related changes may be difficult. Mild thrombocytopenia occurs in normal pregnancies and is also common in patients with SLE, although the severity and clinical significance vary from patient to patient. Anemia is a frequent complication of lupus and magnifies the normal dilutional anemia of pregnancy. Various musculoskeletal and cutaneous symptoms associated with pregnancy, such as arthralgias and facial and palmar erythema, can also resemble active SLE. In addition, preexisting lupus rashes become more erythematous because of the increased cutaneous blood flow during pregnancy. Neurologic disease in SLE may be manifested as psychosis, seizures, chorea, or peripheral neuropathy. The incidence of these complications is low during pregnancy, although the occurrence of seizures in late pregnancy in patients with coexistent hypertension and renal insufficiency may pose a diagnostic dilemma between the neurologic effects of SLE and eclampsia.

www.ketabpezeshki.com 66485457-66963820

Other Rheumatologic Diseases

RA is characterized by chronic, destructive, symmetrical joint inflammation. Less common manifestations include the development of subcutaneous nodules, neuropathy, pleuropericarditis, and vasculitis. Systemic symptoms, including weight loss, lymphadenopathy, and fatigue, are common. Because the median age at onset is later with RA, this disorder is seen less frequently than SLE in the pregnant population.[208] Disease improvement has classically been estimated to occur in approximately two thirds of patients with RA. However, a prospective study noted disease improvement in about half of pregnant patients, with almost 40% of patients experiencing a subsequent exacerbation after delivery.[209]

Patients with RA tend to have good pregnancy outcomes in the setting of well-controlled disease. Those women with active disease are more likely to have small-for-gestational-age infants,[210] possibly as a result of underlying vasculopathy and associated effects on the placenta.[210]

Treatment

The rheumatologic diseases are similar with respect to the therapeutic approach. Corticosteroids form the basis of treatment for most disease complications and exacerbations. These drugs may result in a minimally increased risk of cleft deformities (data are inconclusive) but have not been found to have any other significant teratogenic effects and are considered relatively safe to use for disease control in pregnant patients.[211,212] Steroid use during pregnancy does have a dose-related effect on intrauterine growth retardation and predisposes the patient to GDM and hypertension, so close monitoring is advised.

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are also a mainstay of therapy in many patients with rheumatic diseases and may be used in pregnancy. There are potential adverse effects of aspirin and NSAIDs on gestation, including miscarriage when they are taken early in pregnancy, premature closure of the fetal ductus arteriosus, increased maternal hemorrhage, and prolongation of gestation and labor when they are taken later in pregnancy. There are also conflicting data about an increased risk for gastroschisis, cleft defects, and cardiac defects with NSAID use.[213-217] If a true association exists, the risk for these anomalies remains extremely small in absolute terms. Use of these agents after 32 weeks of gestation should be avoided to minimize the risks of maternal and fetal hemorrhage and premature ductus closure.

Acute flares often require institution of cytotoxic drugs. Cyclophosphamide and methotrexate are contraindicated during the first trimester and should be used only in extreme circumstances because of their teratogenicity and abortifacient properties. Azathioprine has a much more favorable safety profile, and it is the cytotoxic agent of choice during pregnancy. Although the drug and its metabolites cross the placenta, it does not appear to have any major teratogenic effects.[218,219] There is an association between azathioprine use and preterm delivery and low birth weight, but it is likely that these adverse outcomes are also related to the underlying disease.[219,220] Cyclosporine also seems to lack teratogenicity and is an acceptable alternative to azathioprine.[221]

The antimalarial agents chloroquine and hydroxychloroquine are also useful in the treatment of SLE and RA and have been found to be safe during pregnancy. Gravis patients using antimalarials have a decrease in lupus activity, and as a result, these agents may allow a decrease in corticosteroid dosage.[222,223] In addition, patients who have been maintained with hydroxychloroquine before conception experience an increased rate of disease flares when the agent is discontinued.[222]

There are limited numbers of pregnant patients using the newer anti–tumor necrosis factor medications, such as infliximab and etanercept. A review of the Food and Drug Association database noted an increase in congenital malformations with anti–tumor necrosis factor agents.[224] However, other data suggest that these agents have an acceptable risk profile and that they may be continued in pregnancy.[225,226] Because the safety of these medications remains uncertain, their use should be reserved for patients with severe disease who are not adequately treated by other more established medications.[225]

KEY CONCEPTS

- The physiologic demands of pregnancy may cause previously occult medical conditions to become apparent and known problems to rapidly deteriorate.
- The physiologic adjustments of pregnancy alter the normal ranges for certain laboratory values. The adjusted values need to be considered in interpretation of results.
- The possibility of pregnancy should be considered in the differential diagnosis of certain conditions, including new-onset seizures or status epilepticus (eclampsia), glucose intolerance (GDM), persistent vomiting (hyperemesis gravidarum), and thyroid disorders.
- The immunosuppressive effects of pregnancy may cause temporary improvement in inflammatory and autoimmune conditions. This beneficial effect is lost in the postpartum period, resulting in exacerbations of asthma, thyroid disorders, and myasthenia gravis. Medication requirements can change drastically during pregnancy and the postpartum period.
- Certain medical conditions in the mother result in neonatal complications requiring special resuscitative measures.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Kwon HL, et al: Asthma prevalence among pregnant and childbearing-aged women in the United States: Estimates from national health surveys. *Ann Epidemiol* 2003; 13:317.
2. Schatz M, et al: Asthma morbidity during pregnancy can be predicted by severity classification. *J Allergy Clin Immunol* 2003; 112:283.
3. Dombrowski MP, Schatz M; ACOG Committee on Practice Bulletins–Obstetrics: ACOG practice bulletin: Clinical management guidelines for obstetrician-gynecologists number 90, February 2008: Asthma in pregnancy. *Obstet Gynecol* 2008; 111:457.
4. Bracken MB, et al: Asthma symptoms, severity, and drug therapy: A prospective study of effects on 2205 pregnancies. *Obstet Gynecol* 2003; 102:739.
5. Dombrowski MP, et al: Asthma during pregnancy. *Obstet Gynecol* 2004; 103:5.
6. Tata LJ, et al: A comprehensive analysis of adverse obstetric and pediatric complications in women with asthma. *Am J Respir Crit Care Med* 2007; 175:991.
7. Bakhireva LN, et al: Asthma control during pregnancy and the risk of preterm delivery or impaired fetal growth. *Ann Allergy Asthma Immunol* 2008; 101:137.
8. Blais L, Forget A: Asthma exacerbations during the first trimester of pregnancy and the risk of congenital malformations among asthmatic women. *J Allergy Clin Immunol* 2008; 121:1379.
9. Enriquez R, et al: Effect of maternal asthma and asthma control on pregnancy and perinatal outcomes. *J Allergy Clin Immunol* 2007; 120:625.
10. National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program Asthma and Pregnancy Working Group: NAEPP Expert Panel Report. Managing asthma during pregnancy: Recommendations for pharmacologic treatment—2004 update. *J Allergy Clin Immunol* 2005; 115:34.
11. Blais L, et al: High doses of inhaled corticosteroids during the first trimester of pregnancy and congenital malformations. *J Allergy Clin Immunol* 2009; 124:1229.
12. Bakhireva LN, et al: Safety of leukotriene receptor antagonists in pregnancy. *J Allergy Clin Immunol* 2007; 119:618.
13. Lindheimer M, et al: ASH Position Paper: Hypertension in pregnancy. *J Clin Hypertens* 2009; 11:214.
14. Podymow T, August P: Update on the use of antihypertensive drugs in pregnancy. *Hypertension* 2008; 51:960.
15. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 2000; 183:S1.
16. Abalos E, et al: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2007; 24:CD002252.
17. National Institutes of Health: *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*. Bethesda, Md: U.S. Department of Health and Human Services; August 2004. NIH Publication No. 04-5230.
18. Roberts JM, et al: Summary of the NHLBI Working Group on Research on Hypertension During Pregnancy. *Hypertension* 2003; 41:437.
19. Goland S, et al: Favorable outcome of pregnancy with an elective use of epoprostenol and sildenafil in women with severe pulmonary hypertension. *Cardiology* 2010; 115:205.
20. Kiely DG, et al: Improved survival in pregnancy and pulmonary hypertension using a multiprofessional approach. *BJOG* 2010; 117:565.
21. Bédard E, et al: Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? *Eur Heart J* 2009; 30:256.
22. James AH, et al: Acute myocardial infarction in pregnancy: A United States population-based study. *Circulation* 2006; 113:1564.
23. Ladner HE, et al: Acute myocardial infarction in pregnancy and the puerperium: A population-based study. *Obstet Gynecol* 2005; 105:480.
24. Roth A, Elkayam U: Acute myocardial infarction associated with pregnancy. *J Am Coll Cardiol* 2008; 52:171.
25. American College of Obstetricians and Gynecologists: ACOG Committee Opinion No. 276: Safety of Lovenox in pregnancy. *Obstet Gynecol* 2002; 100:845.
26. Leonhardt G, et al: Thrombolytic therapy in pregnancy. *J Thromb Thrombolysis* 2006; 21:271.
27. Te Raa GD, et al: Treatment options in massive pulmonary embolism during pregnancy: A case-report and review of literature. *Thromb Res* 2009; 124:1.
28. Task Force on the Management of Cardiovascular Diseases During Pregnancy of the European Society of Cardiology: Expert consensus document on management of cardiovascular diseases during pregnancy. *Eur Heart J* 2003; 24:761.
29. Bonow RO, et al; American College of Cardiology/American Heart Association Task Force: 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2008; 118:e523.
30. Elkayam U, Bitar F: Valvular heart disease and pregnancy: Part I: Native valves. *J Am Coll Cardiol* 2005; 46:223.
31. Yap SC, et al. Risk of complications during pregnancy in women with congenital aortic stenosis. *Int J Cardiol* 2008; 126:240.
32. Elkayam U, Bitar F: Valvular heart disease and pregnancy: Part II: Prosthetic valves. *J Am Coll Cardiol* 2005; 46:403.
33. Ren A, et al: Low first-trimester hemoglobin and low birth weight, preterm birth and small for gestational age newborns. *Int J Gynaecol Obstet* 2007; 98:124.
34. Kidanto HL, et al: Risks for preterm delivery and low birth weight are independently increased by severity of maternal anaemia. *S Afr Med J* 2009; 99:98.
35. Ronnenberg AG, et al: Preconception hemoglobin and ferritin concentrations are associated with pregnancy outcome in a prospective cohort of Chinese women. *J Nutr* 2004; 134:2586.
36. American College of Obstetricians and Gynecologists: ACOG Practice Bulletin No. 95: Anemia in pregnancy. *Obstet Gynecol* 2008; 112:201.
37. Rohilla M, et al: Severe anemia in pregnancy: A tertiary hospital experience from northern India. *J Obstet Gynaecol* 2010; 30:694.
38. Peña-Rosas JP, Viteri FE: Effects and safety of preventive oral iron or iron + folic acid supplementation for women during pregnancy. *Cochrane Database Syst Rev* 2009; 7:CD004736.
39. Cogswell ME, et al: Iron supplementation during pregnancy, anemia, and birth weight: A randomized controlled trial. *Am J Clin Nutr* 2003; 78:773.
40. Siega-Riz AM, et al: The effects of prophylactic iron given in prenatal supplements on iron status and birth outcomes: A randomized controlled trial. *Am J Obstet Gynecol* 2006; 194:512.
41. Ziaei S, et al: A randomized placebo-controlled trial to determine the effect of iron supplementation on pregnancy outcome in pregnant women with haemoglobin > or = 13.2 g/dl. *BJOG* 2007; 114:684.
42. Von Tempelhoff GF, et al: Mean maternal second-trimester hemoglobin concentration and outcome of pregnancy: A population-based study. *Clin Appl Thromb Hemost* 2008; 14:19.
43. Van Eijsden M, et al: Association between short interpregnancy intervals and term birth weight: The role of folate depletion. *Am J Clin Nutr* 2008; 88:147.
44. Berry RJ, et al: Prevention of neural-tube defects with folic acid in China. China-U.S. Collaborative Project for Neural Tube Defect Prevention. *N Engl J Med* 1999; 341:1485.
45. De-Regil LM, et al: Effects and safety of preconceptual folate supplementation for preventing birth defects. *Cochrane Database Syst Rev* 2010; 6:CD007950.
46. American College of Obstetricians and Gynecologists: *Nutrition in Pregnancy*. Available at www.acog.org/publications/patient_education/bp001.cfm. Accessed March 25, 2011.
47. ACOG Committee on Obstetrics: ACOG Practice Bulletin No. 78: Hemoglobinopathies in pregnancy. *Obstet Gynecol* 2007; 109:229.
48. Al Jama FE, et al: Pregnancy outcome in patients with homozygous sickle cell disease in a university hospital, Eastern Saudi Arabia. *Arch Gynecol Obstet* 2009; 280:793.
49. Ngô C, et al: Pregnancy in sickle cell disease: Maternal and fetal outcomes in a population receiving prophylactic partial exchange transfusions. *Eur J Obstet Gynecol Reprod Biol* 2010; 152:138.
50. Sun PM, et al: Sickle cell disease in pregnancy: Twenty years of experience at Grady Memorial Hospital, Atlanta, Georgia. *Am J Obstet Gynecol* 2001; 184:1127.
51. Villers MS, et al: Morbidity associated with sickle cell disease in pregnancy. *Am J Obstet Gynecol* 2008; 199:125.
52. Yu CK, et al: Outcome of pregnancy in sickle cell disease patients attending a combined obstetric and haematology clinic. *J Obstet Gynaecol* 2009; 29:512.
53. Serjeant GR, et al: Outcome of pregnancy in homozygous sickle cell disease. *Obstet Gynecol* 2004; 103:1278.
54. The EURAP Study Group: Seizure control and treatment in pregnancy: Observations from the EURAP Epilepsy Pregnancy Registry. *Neurology* 2006; 66:354.
55. Eroglu E, et al: Pregnancy and teratogenicity of antiepileptic drugs. *Acta Neurol Belg* 2008; 108:53.

www.ketabpezeshki.com 66485457-66963820

56. Mawer G, et al: Pregnancy with epilepsy: Obstetric and neonatal outcome of a controlled study. *Seizure* 2010; 19:112.
57. Borthen I, et al: Delivery outcome of women with epilepsy: A population-based cohort study. *BJOG* 2010; 117:1537.
58. Morrow J, et al: Malformation risks of antiepileptic drugs in pregnancy: A prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2006; 77:193.
59. Vajda FJ, et al: Foetal malformations and seizure control: 52 months data of the Australian Pregnancy Registry. *Eur J Neurol* 2006; 13:645.
60. Cunnington M, et al: Effect of dose on the frequency of major birth defects following fetal exposure to lamotrigine monotherapy in an international observational study. *Epilepsia* 2007; 48:1207.
61. Hunt S, et al: Levetiracetam in pregnancy: Preliminary experience from the UK Epilepsy and Pregnancy Register. *Neurology* 2006; 67:1876.
62. Longo B, et al: Levetiracetam use in pregnancy. *Ann Pharmacother* 2009; 43:1692.
63. Harden CL, et al: Management issues for women with epilepsy—focus on pregnancy (an evidence-based review): III. Vitamin K, folic acid, blood levels, and breast-feeding: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia* 2009; 50:1247.
64. Kaaja E, et al: Enzyme-inducing antiepileptic drugs in pregnancy and the risk of bleeding in the neonate. *Neurology* 2002; 58:549.
65. Vukusic S, et al: Pregnancy and multiple sclerosis (the PRIMS study): Clinical predictors of post-partum relapse. *Brain* 2004; 127:1353.
66. D'hooghe MB, et al: Long-term effects of childbirth in MS. *J Neurol Neurosurg Psychiatry* 2010; 81:38.
67. Achiron A, et al: Effect of intravenous immunoglobulin treatment on pregnancy and postpartum-related relapses in multiple sclerosis. *J Neurol* 2004; 251:1133.
68. Haas J, Hommes OR: A dose comparison study of IVIG in postpartum relapsing-remitting multiple sclerosis. *Mult Scler* 2007; 13:900.
69. Hellwig K, et al: Immunomodulation and postpartum relapses in patients with multiple sclerosis. *Ther Adv Neurol Disord* 2009; 2:7.
70. De Seze J, et al: Intravenous corticosteroids in the postpartum period for reduction of acute exacerbations in multiple sclerosis. *Mult Scler* 2004; 10:596.
71. Jalkanen A, et al: Pregnancy outcome in women with multiple sclerosis: Results from a prospective nationwide study in Finland. *Mult Scler* 2010; 16:950.
72. Chen YH, et al: Does multiple sclerosis increase risk of adverse pregnancy outcomes? A population-based study. *Mult Scler* 2009; 15:606.
73. Ghidini A, et al: Pregnancy and women with spinal cord injuries. *Acta Obstet Gynecol Scand* 2008; 87:1006.
74. Skowronski E, Hartman K: Obstetric management following traumatic tetraplegia: Case series and literature review. *Aust N Z J Obstet Gynaecol* 2008; 48:485.
75. American College of Obstetricians and Gynecologists: ACOG Committee Opinion: Number 275, September 2002. Obstetric management of patients with spinal cord injuries. *Obstet Gynecol* 2002; 100:625.
76. Almeida C, et al: Myasthenia gravis and pregnancy: Anaesthetic management—a series of cases. *Eur J Anaesthesiol* 2010; 27:985.
77. Djelmis J, et al: Myasthenia gravis in pregnancy: Report on 69 cases. *Eur J Obstet Gynecol* 2002; 104:21.
78. Téllez-Zenteno JF, et al: Myasthenia gravis and pregnancy: Clinical implications and neonatal outcome. *BMC Musculoskelet Disord* 2004; 5:42.
79. Wen JC, et al: No increased risk of adverse pregnancy outcomes for women with myasthenia gravis: A nationwide population-based study. *Eur J Neurol* 2009; 16:889.
80. Hoff JM, et al: Myasthenia gravis in pregnancy and birth: Identifying risk factors, optimising care. *Eur J Neurol* 2007; 14:38.
81. Bahadi A, et al: Pregnancy during hemodialysis: A single center experience. *Saudi J Kidney Dis Transpl* 2010; 21:646.
82. Chou CY, et al: Pregnancy in patients on chronic dialysis: A single center experience and combined analysis of reported results. *Eur J Obstet Gynceol Reprod Biol* 2008; 136:165.
83. Fischer MJ, et al: Kidney disease is an independent risk factor for adverse fetal and maternal outcomes in pregnancy. *Am J Kidney Dis* 2004; 43:415.
84. Imbasciati E, et al: Pregnancy in CKD stages 3 to 5: Fetal and maternal outcomes. *Am J Kidney Dis* 2007; 49:753.
85. Luders C, et al: Obstetric outcome in pregnant women on long-term dialysis: Case series. *Am J Kidney Dis* 2010; 56:77.
86. Piccoli GB, et al: Pregnancy in dialysis patients: Is the evidence strong enough to lead us to change our counseling policy? *Clin J Am Soc Nephrol* 2010; 5:62.
87. Piccoli GB, et al: Pregnancy and chronic kidney disease: A challenge in all CKD stages. *Clin J Am Soc Nephrol* 2010; 5:844.
88. Tan LK, et al: Obstetric outcomes in women with end-stage renal failure requiring dialysis. *Int J Gynaecol Obstet* 2006; 94:17.
89. Balsells M, et al: Maternal and fetal outcome in women with type 2 versus type 1 diabetes mellitus: A systematic review and metaanalysis. *J Clin Endocrinol Metab* 2009; 94:4284.
90. Garcia-Patterson A, et al: Insulin requirements throughout pregnancy in women with type 1 diabetes mellitus: Three changes of direction. *Diabetologia* 2010; 53:446.
91. Kitzmiller JL, et al: Managing preexisting diabetes for pregnancy: Summary of evidence and consensus recommendations for care. *Diabetes Care* 2008; 31:1060.
92. American College of Obstetricians and Gynecologists: ACOG Practice Bulletin: Pregestational diabetes mellitus. Number 60, March 2005. *Obstet Gynecol* 2005; 105:675.
93. Gonzalez-Quintero VH, et al: The impact of glycemic control on neonatal outcome in singleton pregnancies complicated by gestational diabetes. *Diabetes Care* 2007; 30:467.
94. Persson M, et al: Obstetric and perinatal outcomes in type 1 diabetic pregnancies: A large, population-based study. *Diabetes Care* 2009; 32:2005.
95. Rahman W, et al: Progression of retinopathy during pregnancy in type I diabetes mellitus. *Clin Experiment Ophthalmol* 2007; 35:231.
96. Guo RX, et al: Diabetic ketoacidosis in pregnancy tends to occur at lower blood glucose levels: Case-control study and a case report of euglycemic diabetic ketoacidosis in pregnancy. *J Obstet Gynaecol Res* 2008; 34:324.
97. American Diabetes Association: Standards of medical care in diabetes—2007. *Diabetes Care* 2007; 30(Suppl 1):S4.
98. Jensen DM, et al: Peri-conceptional A1C and risk of serious adverse pregnancy outcome in 933 women with type 1 diabetes. *Diabetes Care* 2009; 32:1046.
99. Lapolla A, et al: A multicenter Italian study on pregnancy outcome in women with diabetes. *Nutr Metab Cardiovasc Dis* 2008; 18:291.
100. Dhulkotia JS, et al: Oral hypoglycemic agents vs insulin in management of gestational diabetes: A systematic review and metaanalysis. *Am J Obstet Gynecol* 2010; 203:457.
101. Rowan JA, et al: Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med* 2008; 358:2003.
102. Ekpebegh CO, et al: A 10-year retrospective analysis of pregnancy outcome in pregestational type 2 diabetes: Comparison of insulin and oral glucose-lowering agents. *Diabet Med* 2007; 24:253.
103. Getahun D, et al: Gestational diabetes in the United States: Temporal trends 1989 through 2004. *Am J Obstet Gynecol* 2008; 198:525.
104. Metzger BE, et al; HAPO Study Cooperative Research Group: Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008; 358:1991.
105. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, et al: International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010; 33:676.
106. Ferrara A, et al: Pregnancy plasma glucose levels exceeding the American Diabetes Association thresholds, but below the National Diabetes Data Group thresholds for gestational diabetes mellitus, are related to the risk of neonatal macrosomia, hypoglycemia, and hyperbilirubinaemia. *Diabetologia* 2007; 50:298.
107. Landon MB, et al: A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med* 2009; 364:1339.
108. American College of Obstetricians and Gynecologists: ACOG Practice Bulletin: Gestational diabetes. Number 30, September 2001. *Obstet Gynecol* 2001; 98:525.
109. American Diabetes Association: Gestational diabetes mellitus. *Diabetes Care* 2003; 26:S103.
110. Ekelund M, et al: Prediction of postpartum diabetes in women with gestational diabetes mellitus. *Diabetologia* 2010; 53:452.
111. Kim SH, et al: Nutritional risk factors of early development of postpartum prediabetes and diabetes in women with gestational diabetes mellitus. *Nutrition* 2011; 27:782.
112. Committee on Obstetric Practice: ACOG Committee Opinion No. 435: Postpartum screening for abnormal glucose tolerance in women who had gestational diabetes. *Obstet Gynecol* 2009; 113:1419

www.ketabpezeshki.com 66485457-66963820

113. Moretti ME, et al: Safety of glyburide for gestational diabetes: A meta-analysis of pregnancy outcomes. *Ann Pharmacother* 2008; 42:483.
114. Nicholson W, et al: Benefits and risks of oral diabetes agents compared with insulin in women with gestational diabetes. *Obstet Gynecol* 2009; 113:193.
115. Metzger BE, et al: Summary and recommendations of the Fifth International Workshop-Conference on gestational diabetes mellitus. *Diabetes Care* 2007; 30:S251.
116. Moore LE, et al: Metformin compared with glyburide in gestational diabetes: A randomized controlled trial. *Obstet Gynecol* 2010; 115:55.
117. American College of Obstetricians and Gynecologists: ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists. Number 37, August 2002. Thyroid disease in pregnancy. *Obstet Gynecol* 2002; 100:387.
118. Rosenfeld H, et al: Pregnancy outcome, thyroid dysfunction and fetal goiter after in utero exposure to propylthiouracil: A controlled study. *Br J Clin Pharmacol* 2009; 68:609.
119. Peleg D, et al: The relationship between maternal serum thyroid-stimulating immunoglobulin and fetal and neonatal thyrotoxicosis. *Obstet Gynecol* 2002; 99:1040.
120. Abalovich M, et al: Clinical practice guideline: Management of thyroid dysfunction during pregnancy and postpartum: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2007; 92:S1.
121. Clementi M, et al: Treatment of hyperthyroidism in pregnancy and birth defects. *J Clin Endocrinol Metab* 2010; 95:E337.
122. Rotondi M, et al: The effect of pregnancy on subsequent relapse from Graves' disease after a successful course of antithyroid drug therapy. *J Clin Endocrinol Metab* 2008; 93:3985.
123. Lucas A, et al: Postpartum thyroiditis: Long term follow-up. *Thyroid* 2005; 15:1177.
124. Stagnaro-Green A, et al: High rate of persistent hypothyroidism in a large-scale prospective study of postpartum thyroiditis in southern Italy. *J Clin Endocrinol Metab* 2011 ;96:652.
125. Azizi F: The occurrence of permanent thyroid failure in patients with subclinical postpartum thyroiditis. *Eur J Endocrinol* 2005; 153:367.
126. Sahu MT, et al: Overt and subclinical thyroid dysfunction among Indian pregnant women and its effect on maternal and fetal outcome. *Arch Gynecol Obstet* 2010; 281:215.
127. Alexander EK, et al: Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med* 2004; 351:241.
128. Hallengren B, et al: Pregnant women on thyroxine substitution are often dysregulated in early pregnancy. *Thyroid* 2009; 19:391.
129. Aoki Y, et al: Serum TSH and total T_4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999-2002). *Thyroid* 2007; 17:1211.
130. Committee on Patient Safety and Quality Improvement; Committee on Professional Liability: ACOG Committee Opinion No. 381: Subclinical hypothyroidism in pregnancy. *Obstet Gynecol* 2007; 110:959.
131. Casey BM, et al: Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol* 2005; 105:239.
132. Cleary-Goldman J, et al: Maternal thyroid dysfunction and pregnancy outcome. *Obstet Gynecol* 2008; 112:85.
133. Gharib H, et al: Consensus statement: Subclinical thyroid dysfunction: A joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. *J Clin Endocrinol Metab* 2005; 90:581.
134. Vaidya B, et al: Detection of thyroid dysfunction in early pregnancy: Universal screening or targeted high-risk case finding? *J Clin Endocrinol Metab* 2007; 92:203.
135. Hinton CF, et al: Trends in incidence rates of congenital hypothyroidism related to select demographic factors: Data from the United States, California, Massachusetts, New York, and Texas. *Pediatrics* 2010; 125:S37.
136. Dias VM, et al: Congenital hypothyroidism etiology. *J Pediatr Endocrinol Metab* 2010; 23:815.
137. Jana N, et al: Perinatal outcome in pregnancies complicated by pulmonary tuberculosis. *Int J Gynaecol Obstet* 1994; 44:119.
138. Jana N, et al: Obstetrical outcomes among women with extrapulmonary tuberculosis. *N Engl J Med* 1999; 341:645.
139. Lin HC, et al: Increased risk of low birthweight and small for gestational age infants among women with tuberculosis. *BJOG* 2010; 117:585.
140. Kothari A, et al: Tuberculosis and pregnancy—results of a study in a high prevalence area in London. *Eur J Obstet Gynecol Repod Biol* 2006; 126:48.
141. Tripathy SN, Tripathy SN: Tuberculosis and pregnancy. *Int J Obstet Gynecol* 2003; 80:247.
142. American Thoracic Society; CDC; Infectious Diseases Society of America: Treatment of tuberculosis. *MMWR Recomm Rep* 2003; 52(RR-11).
143. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. *Am J Respir Crit Care Med* 2003; 167:603.
144. Palacios E, et al: Drug-resistant tuberculosis and pregnancy: Treatment outcomes of 38 cases in Lima, Peru. *Clin Infect Dis* 2009; 48:1413.
145. Centers for Disease Control and Prevention: *HIV/AIDS Surveillance Report*, 2008; vol. 20. Available at www.cdc.gov/hiv/surveillance/resources/reports/2008report/pdf/2008SurveillanceReport.pdf. Accessed February 23, 2011.
146. Centers for Disease Control and Prevention: Racial/ethnic disparities among children with diagnoses of perinatal HIV infection—34 states, 2007-2007. *MMWR Morb Mortal Wkly Rep* 2010; 59:97.
147. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission: *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1–Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*, May 24, 2010. Available at http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf. Accessed February 22, 2011.
148. Townsend CL, et al: Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS* 2008; 22:973.
149. Warszawski J, et al: Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. *AIDS* 2008; 22:289.
150. Garcia-Tejedor A, et al: Influence of highly active antiretroviral treatment (HAART) on risk factors for vertical HIV transmission. *Acta Obstet Gynecol Scand* 2009; 88:882.
151. Peters VB, et al: Trends in perinatal HIV prevention in New York City, 1994-2003. *Am J Public Health* 2008; 98:1857.
152. Centers for Disease Control and Prevention: Achievements in public health: Reduction in perinatal transmission of HIV infection, 1985-2005. *MMWR Morb Mortal Wkly Rep* 2006; 55:592.
153. Shapiro RL, et al: Antiretroviral regimens in pregnancy and breast-feeding in Botswana. *N Engl J Med* 2010; 362:2282.
154. Townsend CL, et al: Trends in management and outcome of pregnancies in HIV-infected women in the UK and Ireland, 1990-2006. *BJOG* 2008; 115:1078.
155. American College of Obstetricians and Gynecologists: ACOG Committee Opinion No. 418: Prenatal and perinatal human immunodeficiency virus testing: expanded recommendations. *Obstet Gynecol* 2008; 112:739.
156. Workowski KA, Berman S; Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep* 2010; 59:1.
157. Kaplan JE, et al: Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep* 2009; 58:1.
158. World Health Organization: *Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants, 2010 version*. Available at http://whqlibdoc.who.int/publications/2010/9789241599818_eng.pdf. Accessed March 29, 2011.
159. Boer K, et al: Mode of delivery in HIV-infected pregnant women and prevention of mother-to-child transmission: Changing practices in Western Europe. *HIV Med* 2010; 11:368.
160. Boer K, et al: The AmRo study: Pregnancy outcome in HIV-1–infected women under effective highly active antiretroviral therapy and a policy of vaginal delivery. *BJOG* 2007; 114:148.
161. Kesho Bora Study Group: Eighteen-month follow-up of HIV-1–infected mothers and their children enrolled in the Kesho Bora Study Group. *J Acquir Immune Defic Syndr* 2010; 54:533.
162. Kesho Bora Study Group: Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV (Kesho Bora study): A randomized controlled trial. *Lancet Infect Dis* 2011; 11:171.
163. Coovadia HM, et al: Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: An intervention cohort study. *Lancet* 2007; 369:1107.

www.ketabpezeshki.com 66485457-66963820

164. Kurewa EN, et al: Effect of maternal HIV status on infant mortality: Evidence from 9-month follow-up of mothers and their infants in Zimbabwe. *J Perinatol* 2010; 30:88.
165. World Health Organization: *Guidelines on HIV and Infant Feeding*, 2010. Available at http://whqlibdoc.who.int/publications/2010/9789241599535_eng.pdf. Accessed February 22, 2011.
166. Schneider E, et al; Centers for Disease Control and Prevention: Revised surveillance: Infection among adults, adolescents, and children aged < 18 months and for HIV infection and AIDS among children aged 18 month to < 13 years—United States, 2008. *MMWR Recomm Rep* 2008; 57:1.
167. Mahdavi S, et al: Treatment and disease progression in a birth cohort of vertically-infected children in Ukraine. *BMC Pediatr* 2010; 10:85.
168. Aebi-Popp K, et al: Pregnancy and delivery outcomes of HIV infected women in Switzerland. *J Perinat Med* 2010; 38:353.
169. Martí C, et al: Obstetric and perinatal complications in HIV-infected women. Analysis of a cohort of 167 pregnancies between 1997 and 2003. *Acta Obstet Gynecol Scand* 2007; 86:409.
170. Cavasin H, et al: Postoperative infectious morbidities of cesarean delivery in human immunodeficiency virus–infected women. *Infect Dis Obstet Gynecol* 2009; 2009:827405.
171. Louis J, et al: Perioperative morbidity and mortality among human immunodeficiency virus infected women undergoing cesarean delivery. *Obstet Gynecol* 2007; 110:385.
172. Maiques V, et al: Perioperative cesarean delivery morbidity among HIV-infected women under highly active antiretroviral treatment: A case-control study. *Eur J Obstet Gynecol Reprod Biol* 2010; 153:27.
173. Brogly SB, et al: Birth defects among children born to human immunodeficiency virus–infected women: Pediatric AIDS clinical trials protocols 219 and 219C. *Pediatr Infect Dis J* 2010; 29:721.
174. Joao EC, et al: Maternal antiretroviral use during pregnancy and infant congenital anomalies: The NISDI perinatal study. *J Acquir Immune Defic Syndr* 2010; 53:176.
175. Watts DH, et al: Birth defects among a cohort of infants born to HIV-infected women on antiretroviral medication. *J Perinat Med* 2011; 39:163.
176. Briand N, et al: No relation between in-utero exposure to HAART and intrauterine growth retardation. *AIDS* 2009; 23:1235.
177. Townsend C, et al: Antiretroviral therapy and preterm delivery—a pooled analysis of data from the United States and Europe. *BJOG* 2010; 117:1399.
178. Patel K, et al: Prenatal protease inhibitor use and risk of preterm birth among HIV-infected women initiating antiretroviral drugs during pregnancy. *J Infect Dis* 2010; 201:1035.
179. Tai JH, et al: Pregnancy and HIV disease progression during the era of highly active antiretroviral therapy. *J Infect Dis* 2007; 196:1044.
180. Centers for Disease Control and Prevention: *Sexually Transmitted Disease Surveillance*, 2008. Available at www.cdc.gov/std/stats08/main.htm. Accessed March 1, 2011.
181. Centers for Disease Control and Prevention: Congenital syphilis—United States, 2003-2008. *MMWR Morb Mortal Wkly Rep* 2010; 59:413.
182. Cheng JQ, et al: Syphilis screening and intervention in 500,000 pregnant women in Shenzhen, the People's Republic of China. *Sex Transm Infect* 2007; 83:347.
183. Zhou P, et al: Occurrence of congenital syphilis after maternal treatment with azithromycin during pregnancy. *Sex Transm Dis* 2007; 34:472.
184. Sheffield JS, et al: Congenital syphilis after maternal treatment for syphilis during pregnancy. *Am J Obstet Gynecol* 2002; 186:569.
185. Zhu L, et al: Maternal and congenital syphilis in Shanghai, China, 2002 to 2006. *Int J Infect Dis* 2010; 14(Suppl 3):e45.
186. Lobstein S, et al: Prevalence of hepatitis B among pregnant women and its impact on pregnancy and newborn complications at a tertiary hospital in the eastern part of Germany. *Digestion* 2011; 83:76.
187. Salleras L, et al: Seroepidemiology of hepatitis B virus infection in pregnant women in Catalonia (Spain). *J Clin Virol* 2009; 44:329.
188. American College of Obstetricians and Gynecologists: ACOG Practice Bulletin No. 86: Viral hepatitis in pregnancy. *Obstet Gynecol* 2007; 110:941.
189. Lee C, et al: Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: Systematic review and meta-analysis. *BMJ* 2006; 332:328.
190. Shi Z, et al: Hepatitis B immunoglobulin injection in pregnancy to interrupt hepatitis B virus mother-to-child transmission—a meta-analysis. *Int J Infect Dis* 2010; 14:e622.
191. Song YM, et al: Factors associated with immunoprophylaxis failure against vertical transmission of hepatitis B virus. *Eur J Pediatr* 2007; 166:813.
192. Wiseman E, et al: Perinatal transmission of hepatitis B virus: An Australian experience. *Med J Aust* 2009; 190:489.
193. Shi Z, et al: Lamivudine in late pregnancy to interrupt in utero transmission of hepatitis B virus: A systematic review and meta-analysis. *Obstet Gynecol* 2010; 116:147.
194. Xu WM, et al: Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: A multicentre, randomized, double-blind, placebo-controlled study. *J Viral Hepat* 2009; 16:94.
195. National Center for Immunization and Respiratory Diseases: General Recommendations on Immunization—Recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep* 2011; 60:1.
196. McMenamin MB, et al: Obstetric management of hepatitis C–positive mothers: Analysis of vertical transmission in 559 mother-infant pairs. *Am J Obstet Gynecol* 2008; 199:315.
197. Marine-Barjoan E, et al: HCV/HIV co-infection, HCV viral load and mode of delivery: Risk factors for mother-to-child transmission of hepatitis C virus? *AIDS* 2007; 21:1811.
198. Polis CB, et al: Impact of maternal HIV coinfection on the vertical transmission of hepatitis C virus: A meta-analysis. *Clin Infect Dis* 2007; 44:1123.
199. Al Arfaj AS, et al: Pregnancy outcome in 396 pregnancies in patients with SLE in Saudi Arabia. *Lupus* 2010; 19:1665.
200. Carvalheiras G, et al: Pregnancy and systemic lupus erythematosus: Review of clinical features and outcome of 51 pregnancies at a single institution. *Clin Rev Allergy Immunol* 2010; 38:302.
201. Smyth A, et al: A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin J Am Soc Nephrol* 2010; 5:2060.
202. Ambrósio P, et al: Lupus and pregnancy—15 years of experience in a tertiary center. *Clin Rev Allergy Immunol* 2010; 38:77.
203. Gladman DD, et al: The effect of lupus nephritis on pregnancy outcome and fetal and maternal complications. *J Rheumatol* 2010; 37:754.
204. Imbasciati E, et al: Pregnancy in women with pre-existing lupus nephritis: Predictors of fetal and maternal outcome. *Nephrol Dial Transplant* 2009; 24:519.
205. Wagner SJ, et al: Maternal and fetal outcomes in pregnant patients with active lupus nephritis. *Lupus* 2009; 18:342.
206. Chen CY, et al: Increased risk of adverse pregnancy outcomes for hospitalisation of women with lupus during pregnancy: A nationwide population-based study. *Clin Exp Rheumatol* 2010; 28:49.
207. Clowse MEB, et al: A national study of the complications of lupus in pregnancy. *Am J Obstet Gynecol* 2008; 199:127.
208. Chakravarty EF, et al: Obstetric hospitalizations in the United States for women with systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Rheum* 2006; 54:899.
209. De Man YA, et al: Disease activity of rheumatoid arthritis during pregnancy: Results from a nationwide prospective study. *Arthritis Rheum* 2008; 59:1241.
210. De Man YA, et al: Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: Results of a national prospective study. *Arthritis Rheum* 2009; 60:3196.
211. Park-Wyllie L, et al: Birth defects after maternal exposure to corticosteroids: Prospective cohort study and meta-analysis of epidemiological studies. *Teratology* 2000; 62:385.
212. Pradat P, et al: First trimester exposure to corticosteroids and oral clefts. *Birth Defects Res A Clin Mol Teratol* 2003; 67:968.
213. Cassina M, et al: First trimester diclofenac exposure and pregnancy outcome. *Reprod Toxicol* 2010; 30:401.
214. da Silva DP, et al: Dipyrone use during pregnancy and adverse perinatal events. *Arch Gynecol Obstet* 2009; 279:293.
215. Ericson A, Källén BA: Non-steroidal anti-inflammatory drugs in early pregnancy. *Reprod Toxicol* 2001; 15:371.
216. Kallen BA, Otterblad OP: Maternal drug use in early pregnancy and infant cardiovascular defect. *Reprod Toxicol* 2003; 17:255.
217. Nielsen GL, et al: Risk of adverse birth outcome and miscarriage in pregnant users of nonsteroidal anti-inflammatory drugs: Population based observational study and case-control study. *BMJ* 2001; 322:266.
218. Goldstein LH, et al: Pregnancy outcome of women exposed to azathioprine during pregnancy. *Birth Defects Res A Clin Mol Teratol* 2007; 79:696.

www.ketabpezeshki.com 66485457-66963820

219. Langagergaard V, et al: Birth outcome in women treated with azathioprine or mercaptopurine during pregnancy: A Danish nationwide cohort study. *Aliment Pharmacol Ther* 2007; 25:73.
220. Cleary BJ, et al: Early pregnancy azathioprine use and pregnancy outcomes. *Birth Defects Res A Clin Mol Teratol* 2009; 85:647.
221. Bar Oz B, et al: Pregnancy outcome after cyclosporine therapy during pregnancy: A meta-analysis. *Transplantation* 2001; 27:1051.
222. Clowse ME, et al: Hydroxychloroquine in lupus pregnancy. *Arthritis Rheum* 2006; 54:3640.
223. Ruiz-Irastorza G, et al: Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: A systematic review. *Ann Rheum Dis* 2010; 69:20.
224. Carter JD, et al: A safety assessment of tumor necrosis factor antagonists during pregnancy: A review of the Food and Drug Administration database. *J Rheumatol* 2009; 36:635.
225. Clowse MEB: The use of anti-TNFα medications for rheumatologic disease in pregnancy. *Int J Womens Health* 2010; 2:199.
226. Schnitzler F, et al: Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy. *Inflamm Bowel Dis* 2011; 17:1846.

www.ketabpezeshki.com 66485457-66963820

Chapter 180

Drug Therapy in Pregnancy

Rania Habal

PERSPECTIVE

Major birth defects affect 3 to 5% of all live births.[1] Most are of unknown etiology, but 1 to 3% of these are thought to be due to pharmaceutical or environmental agents.[1,2] A *teratogen* is any chemical, pharmacologic, environmental, or mechanical agent that can cause deviant or disruptive development of the conceptus.[1,2] Included in this definition are functional impairment, growth restriction, and congenital malformations.[2] These may range from subtle neurobehavioral effects to devastating physiologic effects and physical deformities, including fetal death.[1-3] Why one pregnancy would be affected and not another remains to be elucidated. Highly teratogenic medications seem to be few in number, estimated at well below 50 agents (Box 180-1).[3,4]

The process of establishing teratogenicity is tedious and often flawed. Animal research, although valuable in determining risk initially, is not always applicable to humans,[1,2,5] and controlled prospective human studies are generally not performed for ethical reasons. As a result, much of our current knowledge on teratogenicity has been derived from case reports, case-control studies, or cohort studies, which are inherently weak in establishing a causal relationship.[1,2,5,6] These reports are often complicated by a multitude of confounding factors, making the determination of a causal link between a specific exposure and malformations difficult. The genetic background of the fetus, timing and duration of the exposure, environmental factors, multiple exposures, nutritional deficits, maternal illness, and illicit drug use all contribute to the outcome of pregnancy.[1,2,5,6] Large population studies are needed to understand the connection between the outcome of a pregnancy and an associated in utero exposure.[6] Finally, as in the case of diethylstilbestrol, teratogenicity may not be apparent for years after birth.

Classification of Teratogenic Risk

To aid physicians in determining the teratogenic potential of a particular medication, the U.S. Food and Drug Administration (FDA) assigns one of five letters, A, B, C, D, and X, to the drug, depending on the strength of evidence for its safety or teratogenicity (Box 180-2). This classification system has been criticized as overly simplistic and perhaps inaccurate.[1,2,5-7] Many clinicians believe that the classification system conveys the incorrect impression that there is a gradation of reproductive risk from exposure across categories (i.e., that risk increases from A to B to C to D to X) and that the drugs within a given category present similar reproductive risks.[7] Yet more than 90% of newly introduced drugs in the United States are assigned to class C, an undetermined teratogenic risk.[8] The FDA has acknowledged these problems, and in 2008 it proposed new rules for drug labeling during pregnancy. The proposed rules recommend giving a narrative description of the risks and the likelihood of developmental abnormalities and are awaiting the final stages of clearance.[9] Currently, a number of clinical teratology resources that assign risk are available online. These include TERIS, REPROTOX, and Micromedex REPRORISK (Shepard's *Catalog of Teratogenic Agents*).

PRINCIPLES OF DISEASE

Drugs may affect the fetus through a variety of mechanisms. Some alter the availability of substrates, such as vitamins, glucose, oxygen, and amino acids, needed for normal nutrition and growth.[1-3] Others directly affect cellular growth and differentiation. The age at which fetal exposure occurs is crucial in determining its impact on the pregnancy. The fetus is most vulnerable to toxic insults during the time of organogenesis (days 21-56 of fetal life).[1-3] Exposure during this period may result in major anatomic defects. Exposure after the period of organogenesis may affect the growth and development of the fetus.[1-3] Functional development of the central nervous system (CNS) is affected when it is exposed to a CNS teratogen during the 10th to 17th weeks of pregnancy.[1-3]

Drug Transfer across the Placenta

Drug transfer across the placenta occurs most commonly by simple passive diffusion or by protein transport.[1-3,10] A thin layer of trophoblastic cells is all that separates maternal from fetal circulation.[1-3,10] The degree to which a drug gains access to fetal circulation depends on molecular size, ionic state, lipid solubility, and extent of protein binding. Drugs with a molecular mass of less than 5 kDa readily diffuse.[1-3,10] Anionic forms diffuse through the lipid layer more readily than ionized forms.[1-3,10] Free drug diffuses more readily than a drug that is bound to plasma proteins.[1-3,10] Because fetal pH is slightly more alkalotic than maternal pH, weak organic acids (e.g., salicylate) may become ion trapped in the fetal circulation, increasing fetal exposure.[1-3,10]

Drug Transfer during Lactation

For the most part, drugs and substances that are ingested or injected by the mother diffuse passively into milk and then back into the maternal circulation for excretion.[11] The amount of drug diffusing into milk depends on many factors. Lipid-soluble and nonionic substances diffuse more readily, and highly protein bound substances diffuse less readily.[11] Whether a substance is concentrated in maternal milk or not, the neonate generally is able to detoxify it with no adverse effects, and only a few drugs pose a serious danger to a breast-feeding infant.[11-13] The interruption of

www.ketabpezeshki.com 66485457-66963820

Box 180-1 Drugs and Agents Considered Human Teratogens and Developmental Toxins

- Alkylating agents (e.g., busulfan, chlorambucil, cyclophosphamide)
- Aminopterin and methotrexate*
- Amiodarone
- Aminoglycosides (streptomycin and others)
- Androgens*
- Angiotensin-converting enzyme inhibitors*
- Carbamazepine
- Carbon monoxide
- Chlorobiphenyls*
- Cocaine*
- Corticosteroids
- Coumarin derivatives*
- Danazol
- Diethylstilbestrol*
- Ergotamine
- Ethanol (in large doses)*
- Fluconazole (in high doses)
- Iodine
- Ionizing radiation*
- Isotretinoin (systemic)*
- Lead*
- Lithium*
- Methimazole
- Methylene blue
- Methylmercury*
- Misoprostol
- Nonsteroidal anti-inflammatory agents
- Paramethadione, trimethadione*
- Phenytoin*
- Polychlorinated biphenyls*
- Progestins
- Quinine
- Statins
- Tetracycline*
- Thalidomide *
- Tobacco
- Trimethadione*
- Valproic acid*

Modified from Shepard TH: Catalog of Teratogenic Agents, 14th ed. Baltimore, Johns Hopkins University Press, 2010; and Fine JS: Reproductive and perinatal principles. In: Goldfrank LR, et al (eds): Goldfrank's Toxicologic Emergencies, 9th ed. New York, McGraw-Hill, 2011, 423-445.
*Teratogen.

Box 180-2 Food and Drug Administration Classification: Teratogenic Risk of Drugs

- Class A: Controlled studies have shown no risk. Adequate well-controlled studies in pregnant women have failed to show risk to fetus.
- Class B: No evidence exists of risk for humans. Animal studies show risk or are negative, but no human studies have been done.
- Class C: Use may engender risk for fetus. Human studies are lacking, and animal studies may be positive or lacking. Potential for benefit may outweigh potential for harm.
- Class D: Positive evidence of risk is based on studies or postmarketing data. Potential for benefit may outweigh potential for harm.
- Class X: Drugs are contraindicated in pregnancy on the basis of human or animal studies or postmarketing reports that indicate benefit is clearly outweighed by risk.

breast-feeding should not be advocated except in rare situations of known drug toxicity to the infant and in all cases of maternal critical illness.[11,12] Table 180-1 summarizes the compatibility of medications and their effects in pregnancy and lactation.

DRUG THERAPY DURING PREGNANCY

In general, the health of the fetus is directly related to the health of the mother. Physicians should not withhold lifesaving medications from pregnant patients because of a reported risk to the fetus and should resuscitate pregnant patients according to advanced life support guidelines. Physicians may also prescribe any agent that presents maternal benefits outweighing the risks to the fetus. Included in this category are therapeutic medications for asthma, arrhythmias, status epilepticus, life-threatening overdoses, and human immunodeficiency virus (HIV) infection. When prescribing drugs to pregnant and lactating women, physicians must weigh the benefits of treatment against the inherent risks of treatment or disease, consider the pharmacokinetics of the drug during pregnancy and lactation, choose the drug with the lowest known toxicity, and use the lowest effective dose.

Analgesic Agents

Acetaminophen

Acetaminophen (paracetamol) is widely used during pregnancy and has not been associated with congenital malformations.[13-15] In fact, in a population-based case-control study, acetaminophen was associated with a decreased risk of certain craniofacial malformations when it was used for febrile illnesses in the first trimester.[13,15] Acetaminophen is safe during lactation because only a small amount is excreted into breast milk, and the amount involved is tolerated by the neonate's sulfhydration pathway.[11-13] However, in overdose situations, there may be an increase in the incidence of spontaneous abortion and fetal demise, especially when antidote treatment with *N*-acetylcysteine is delayed.[13,16]

Aspirin

Early studies linked aspirin to an increased risk of perinatal and neonatal bleeding, increased risk of postmaturity, prolonged labor, low birth weight, neonatal hypoglycemia, neonatal metabolic acidosis, and neonatal death.[13,14] However, a number of meta-analyses in humans failed to demonstrate a teratogenic effect of aspirin,[13,14,17,18] and in the Perinatal Antiplatelet Review of International Studies (PARIS) Collaboration, low doses of aspirin were actually found to be beneficial and to reduce the risk of preeclampsia, premature birth, and adverse perinatal outcomes.[19] There was a trend, however, toward a slightly increased incidence of gastroschisis (a defect in the abdominal wall through which abdominal contents protrude) with use of nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin in the first trimester.[13,18-20] Aspirin is excreted into breast milk, and because of its association with Reye's syndrome, its use is therefore discouraged in breast-feeding.[11-13]

Nonsteroidal Anti-Inflammatory Drugs

Prostaglandin synthesis inhibitors such as NSAIDs have been shown to block blastocyst implantation and may therefore inhibit conception.[20] Their use in the first trimester has been linked to an increased risk of spontaneous abortions and a slight increase in cardiac septal defects, oral clefts, and gastroschisis.[13,14,20-22] When they are used in the third trimester, NSAIDs inhibit labor and have been used as tocolytic agents for premature labor.[13,14,21] When they are used in the latter part of pregnancy, NSAIDs have been linked to a number of negative effects on the neonate, most notably premature closure of the ductus arteriosus, leading to neonatal pulmonary hypertension and death.[13,14,21,23] An increased incidence of fetal periventricular hemorrhages, fetal nephrotoxicity, oligohydramnios, and neonatal gastrointestinal hemorrhage has also been reported.[13,14,21,23] Their use in the latter part of pregnancy is therefore discouraged. NSAIDs in general appear to be safe during lactation.[12,13]

Opiate Analgesics

In general, short-term, episodic use of opiates such as oxycodone, hydrocodone, morphine, and fentanyl appears to be safe in pregnancy.[13,14] Their use near term, however, may result in severe respiratory depression of the neonate.[13,14] In addition, prescribing of narcotics for long periods can lead to fetal addiction, low birth

Text continued on p. 2322

www.ketabpezeshki.com 66485457-66963820

Table 180-1 Summary of Medication Safety in Pregnancy and Lactation

MEDICATION	PREGNANCY	LACTATION
Analgesic Agents		
Acetaminophen or paracetamol	Safe (B)	Compatible
Nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs)	Discouraged (D) in third trimester because of premature closure of ductus arteriosus	Compatible
Salicylate	Traditionally discouraged (D); may be safe in low doses	Discouraged because of risk of Reye's syndrome
Opiates: Most opiates are considered safe for short-term use, but all are reclassified in category D if they are used for prolonged periods or if they are used in high doses at term (because of respiratory depression in the newborn). Do not use opiates combined with aspirin or NSAIDs. Use of opiates during breast-feeding may result in sedation and respiratory depression of the newborn, especially if high doses are used for prolonged periods. These infants may require close observation		
Codeine	Safe (C) for short-term use, but not at term (D)	Discouraged if longer than 2 days
Fentanyl	Safe (C) for short-term use, but not at term (D)	Compatible
Hydrocodone	Safe (C) for short-term use, but not at term (D)	Probably compatible
Hydromorphone	Safe (C) for short-term use, but not at term (D)	Probably compatible
Meperidine	Safe (C) for short-term use, but not at term (D)	Discouraged
Methadone	Safe (C) for short-term use, but not at term (D)	Compatible
Morphine	Safe (C) for short-term use, but not at term (D)	Compatible
Oxycodone	Safe (C) for short-term use, but not at term (D)	Probably compatible
Anesthetics, Sedative-Hypnotics, and Neuromuscular Blockers		
Etomidate	Safety unknown (C)	Insufficient data; probably compatible after 12 hours
Ketamine	Probably safe (B); risk with high doses close to delivery	Insufficient data; probably compatible after 12 hours
Lorazepam	Probably safe for short periods; unsafe for chronic use (D)	Insufficient data; potential toxicity
Midazolam	Probably safe for short periods; unsafe for chronic use (D)	Insufficient data; potential toxicity
Propofol	Insufficient data; potential neonatal depression (B)	Insufficient data; probably compatible after 12 hours
Neuromuscular blockers: Breast-feeding is not appropriate in critically ill, paralyzed patients.		
Rocuronium	Potential risk around delivery (C)	Safety unknown
Succinylcholine	Potential risk around delivery (C)	Safety unknown
Vecuronium	Potential risk around delivery (C)	Safety unknown
Anticoagulants and Thrombolytics		
Heparin	Safe (B)	Compatible
Low-molecular-weight heparin	Safe (B)	Compatible
Warfarin	Contraindicated (X)	Compatible
Thrombolytics: Potential benefits of drug treatment outweigh potential risks to pregnancy outcome. Breast-feeding is not appropriate in the critically ill.		
Alteplase	Safety unknown (C)	Safety unknown
Reteplase	Safety unknown (C)	Safety unknown
Streptokinase	Safety unknown (C)	Safety unknown
Tenecteplase	Safety unknown (C)	Safety unknown
Urokinase	Safety unknown (C)	Safety unknown
Antidotes: Potential benefits of drug treatment outweigh potential risks to pregnancy outcome. Breast-feeding is not appropriate in the critically ill and the poisoned patient.		
Deferoxamine antidote: iron toxicity	Safety unknown (C)	No data; probably compatible
Digoxin immune Fab antidote: digitalis	Safety unknown (C)	No data; probably compatible
Dimercaprol antidote: heavy metals	Safety unknown (C); teratogenic in animals	No data; probably compatible
Flumazenil antidote: benzodiazepines	Safety unknown (C); safe in animals	No data; probably compatible
Fomepizole antidote: toxic alcohols	Safety unknown (C)	Safety unknown
Hydroxycobalamin antidote: cyanide	Safe (B)	Compatible
Methylene blue antidote: methemoglobinemia	Known human risk (C)	Discouraged
N-Acetylcysteine antidote: acetaminophen overdose	Safe (B)	Compatible
Naloxone antidote: narcotics	Safety unknown (C); may precipitate fetal withdrawal	Safety unknown
Physostigmine antidote: anticholinergics	Safety unknown (C)	Safety unknown

www.ketabpezeshki.com 66485457-66963820

Table 180-1 Summary of Medication Safety in Pregnancy and Lactation—cont'd

MEDICATION	PREGNANCY	LACTATION
Pralidoxime antidote: organophosphates	Safety unknown (C)	Safety unknown
Pyridoxine antidote: isoniazid overdose	Safe (B)	Compatible
Succimer antidote: lead poisoning	Safety unknown (C); teratogenic in animals	Safety unknown
Antimicrobials: Use of antibiotics near term may interfere with culture results in neonates.		
Aminoglycosides	Discouraged (D)	Compatible
Cephalosporins		
First generation: cephalexin, cefazolin, cefadroxil	Safe (B)	Compatible
Second generation: cefuroxime, cefaclor, cefoxitin, cefprozil	Safe (B)	Compatible
Third generation: cefdinir, cefotaxime, ceftazidime, ceftriaxone, cefpodoxime, ceftizoxime	Safe (B)	Probably compatible
Chloramphenicol	Probably safe until term (C); contraindicated at term (gray baby syndrome)	Discouraged (gray baby syndrome)
Clindamycin	Relatively safe (B)	Compatible, but caution advised (diarrhea and bloody stools in nursing infant)
Linezolid	Safety unknown (C) Known animal risk	Safety unknown
Macrolides		
Azithromycin	Safe (B)	Compatible
Clarithromycin	Probably safe (C); evidence is inconclusive	Probably compatible; evidence is inconclusive
Erythromycin: Do not use estolate salt.	Safe (B)	Compatible
Metronidazole	Contraindicated in first trimester, safe in second and third trimesters (B)	Discouraged
Nitrofurantoin	Safe (B), except in third trimester (hemolytic anemia in newborn)	Probably compatible
Penicillins		
First generation: penicillin G, benzathine penicillin, Bicillin, penicillin VK	Safe (B)	Compatible
Second generation: oxacillin, dicloxacillin, nafcillin	Safe (B)	Compatible
Third generation: ampicillin, ampicillin-sulbactam, amoxicillin, amoxicillin-clavulanate	Safe (B)	Compatible
Fourth generation: ticarcillin, ticarcillin-clavulanate, piperacillin, piperacillin-tazobactam, carbenicillin	Safe (B)	Probably compatible
Quinolones have been linked to abnormalities in cartilage and bone, but recent data are contradictory. Their use is discouraged during pregnancy and lactation.		
First generation: nalidixic acid	Use is discouraged (C)	Use is discouraged
Second generation:		
ciprofloxacin	Use is discouraged (C)	Compatible
norfloxacin, ofloxacin	Use is discouraged (C)	Safety unknown
Third generation: levofloxacin	Use is discouraged (C)	Safety unknown
Fourth generation: gatifloxacin, moxifloxacin	Use is discouraged (C)	Safety unknown
Sulfonamides	Use is discouraged near term (C) (kernicterus in newborn); contraindicated throughout pregnancy if combined with trimethoprim	Probably compatible, except in premature infants or infants with G6PD deficiency or hyperbilirubinemia
Tetracyclines have been linked to abnormalities in teeth and bone; their use in pregnancy is discouraged.		
Tetracycline	Contraindicated (D)	Compatible
Doxycycline	Contraindicated (D)	Discouraged
Vancomycin	Probably safe (C); insufficient data	Safety unknown
Antifungals		
Clotrimazole	Relatively safe (C)	Safety unknown
Fluconazole	Contraindicated (D)	Probably compatible
Ketoconazole	Insufficient data (C)	Safety unknown
Nystatin	Relatively safe (C)	Safety unknown
Terbinafine	Probably safe (B)	Safety unknown
Antituberculous medications in general present a maternal benefit that is much greater than the fetal or embryonic risk and may be prescribed during any stage of pregnancy when indicated.		
Isoniazid	Relatively safe (C)	Probably compatible
Rifampin	Relatively safe (C)	Probably compatible
Ethambutol	Relatively safe (C)	Probably compatible

Continued

www.ketabpezeshki.com 66485457-66963820

Table 180-1 Summary of Medication Safety in Pregnancy and Lactation—cont'd

MEDICATION	PREGNANCY	LACTATION
Antiviral Agents		
Antiherpetic medications		
Acyclovir	Relatively safe (B)	Compatible
Famciclovir	Safety unknown (B)	Discouraged
Valacyclovir	Relatively safe (B)	Compatible
Anti-influenza agents: Potential benefits of drug treatment may outweigh potential risks to pregnancy outcome.		
Amantadine	Possible risk (C)	Safety unknown
Oseltamivir	Insufficient data; minor risks in rats (C)	Safety unknown
Neurologic Medications		
Anticonvulsants: Use of highly teratogenic anticonvulsants is contraindicated unless convulsions are refractory. Monotherapy is recommended. Newer anticonvulsants appear to be safer, although data and experience remain limited.		
Carbamazepine	Known teratogen (D)	Probably compatible
Lamotrigine	Safety unknown (C)	Safety unknown
Levetiracetam	Data limited (C)	Safety unknown
Phenobarbital	Discouraged (D)	Discouraged
Phenytoin	Known teratogen (D)	Compatible
Topiramate	Data limited (C)	Safety unknown
Valproic acid	Known teratogen (D)	Probably compatible
Cardiac Medications		
Antiarrhythmics: In cases of refractory arrhythmias, the benefits to the mother may outweigh risks to the fetus or embryo. Critically ill patients are not expected to breast-feed.		
Adenosine	Safe (C)	Compatible
Amiodarone	Discouraged (D)	Discouraged
Digoxin	Safe (C); caution in third trimester (oxytocic)	Compatible
Flecainide	Safety unknown (C)	Probably compatible
Ibutilide	Safety unknown (C); teratogenic in animals	Discouraged
Lidocaine	Safe (B)	Probably compatible
Procainamide	Not teratogenic, but associated with lupus-like reaction (C)	Compatible
Quinidine	Safe (C)	Compatible
Sotalol	Probably safe (B)	Probably compatible
Antihypertensives: Angiotensin antagonists and angiotensin-converting enzyme inhibitors have been associated with fetal renal agenesis, oligohydramnios, and stillbirths. They are contraindicated in pregnancy.		
Angiotensin-converting enzyme inhibitors	Discouraged (D)	Variable safety
Angiotensin II receptor antagonists	Discouraged (D)	Safety unknown
Beta-blockers: Beta-blockers have been associated with growth restriction and small-for-gestational-age babies. Caution is advised when they are prescribed in the first trimester or for prolonged periods. At term, some have been associated with neonatal bradycardia, hypoglycemia, and respiratory depression.		
Atenolol	Caution is advised (D)	Potential toxicity
Esmolol	Caution is advised (C)	Safety unknown
Labetalol	Probably safe (C)	Probably compatible
Metoprolol	Caution is advised (D)	Potential toxicity
Propranolol	Caution is advised (C)	Probably compatible
Calcium channel blockers: Data are conflicting. Teratogenic effects in animals have not been found in humans. Evidence remains insufficient, but observational studies are leaning toward their safety in pregnancy.		
Amlodipine	Safety unknown (C)	Safety unknown
Diltiazem	Insufficient evidence (C) but has been used safely	Probably compatible
Nicardipine	Caution is advised (C)	Safety unknown
Nifedipine	Insufficient evidence (C) but has been used safely; sublingual form is contraindicated	Probably compatible
Verapamil	Insufficient evidence (C) but has been used safely	Probably compatible
Diuretics: Caution for dehydration and electrolyte abnormalities.		
Furosemide	Caution is advised (C)	Caution is advised
Hydrochlorothiazide	Caution is advised (C); contraindicated in gestational hypertension	Caution is advised
Nitrates		
Nitroglycerin	Probably safe (C)	Probably compatible
Nitroprusside	Caution is advised (C)	Potential toxicity
Others		
Clonidine	Caution is advised (C)	Safety unknown
Hydralazine	Safe (C)	Compatible
Methyldopa	Safe (B)	Compatible

www.ketabpezeshki.com 66485457-66963820

Table 180-1 Summary of Medication Safety in Pregnancy and Lactation—cont'd

MEDICATION	PREGNANCY	LACTATION
Endocrine Medications		
Medications used in the treatment of diabetes		
Insulin	Safe (B)	Compatible
Sulfonylurea: Data on sulfonylureas in pregnancy are limited. They are considered acceptable alternatives to insulin in areas where insulin use is not feasible. Hypoglycemia may occur in nursing infants. Nursing infants should be monitored		
Glipizide	Insufficient evidence (C); fetotoxicity in animals	Caution is advised
Glyburide	Insufficient evidence (C)	Caution is advised
Metformin	Insufficient evidence (C)	Caution is advised
Thyroid medications		
Levothyroxine	Safe (B)	Compatible
Propylthiouracil	Insufficient data (D)	Compatible
Methimazole	Discouraged; fetotoxicity reported	Compatible
Gastrointestinal Medications		
Antacids		
H_2 blockers		
Famotidine	Low risk (B)	Probably compatible
Ranitidine	Safe (B)	Probably compatible
Nizatidine	Low risk (B)	Probably compatible
Cimetidine	Safe (B)	Compatible
Proton pump inhibitors		
Omeprazole	Low risk (C)	Safety unknown
Esomeprazole	Low risk (B)	Safety unknown
Lansoprazole	Low risk (B)	Safety unknown
Pantoprazole	Low risk (B)	Safety unknown
Antiemetics		
Dopamine antagonists		
Metoclopramide	Safe (B)	Potential toxicity
Prochlorperazine	Safe (C)	Potential toxicity
Promethazine	Safe (C)	Discouraged
5-HT_3 antagonists: generally safe		
Dolasetron	Low risk (B)	Probably compatible
Granisetron	Low risk (B)	Probably compatible
Ondansetron	Safe (B)	Probably compatible
Respiratory Medications		
Medications used in the treatment of asthma, allergies, and upper respiratory infection: For asthmatic patients, maternal benefits outweigh risks to fetus or embryo.		
Anticholinergic agents		
Ipratropium	Safe (B)	Safety unknown
Beta-adrenergics considered safe for short-term use		
Albuterol	Safe (C)	Probably compatible
Epinephrine	Potential risk (C)	Potential toxicity
Terbutaline	Potential risk (B); recent label change by FDA	Probably compatible
Corticosteroids safe for short-term use: Human data suggest an increased risk of orofacial clefts.		
Methylprednisolone	Safe for short-term use (C)	Compatible
Prednisolone	Safe for short-term use (C)	Compatible
Prednisone	Safe for short-term use (C)	Compatible
Antihistamines		
Chlorpheniramine	Safe (C)	Discouraged
Diphenhydramine	Safe (B)	Discouraged
Hydroxyzine	Safety unknown (C)	Discouraged
Meclizine	Safe (B)	Probably compatible
Cetirizine	Probably safe (B)	Safety unknown
Fexofenadine	Safety unknown (C)	Compatible
Loratadine	Probably safe (B)	Compatible
Decongestants		
Pseudoephedrine	Discouraged (C)	Probably compatible

G6PD, glucose-6-phosphate dehydrogenase.

www.ketabpezeshki.com 66485457-66963820

weight, and neonatal abstinence syndrome.[13,14,24] Neonatal abstinence syndrome is characterized by CNS hyperirritability and autonomic nervous system dysfunction and a higher mortality in the offspring.[24]

The short-term use of opiates during lactation appears to be safe, but nursing infants should be closely monitored for respiratory depression.[12,13] A case report of the death of a nursing infant whose mother was taking codeine for pain[13,25] and a review of complications of codeine use in nursing mothers prompted the FDA to issue an advisory for codeine use in lactation.

Anesthetics, Sedative-Hypnotics, and Neuromuscular Blockers

General anesthetics, sedative-hypnotics, and neuromuscular blockers are indicated for rapid sequence intubation (RSI). Some anesthetics and sedative-hypnotics are also used for procedural sedation. Most of the data regarding the use of these agents during pregnancy have been obtained from animal studies and from retrospective human data. None of the agents has been consistently associated with congenital malformations.[26-28]

Anesthetics

Etomidate. Etomidate is an ultra-short-acting hypnotic agent that is commonly used for procedural sedation or RSI. It has not been linked to congenital defects in animals even when high doses were used.[13,14,26,27] Similarly, it is not associated with an increase in congenital anomalies in humans.[13,14,26,27] However, newborns of mothers undergoing cesarean section with etomidate were found to have significant reductions in serum cortisol concentrations 1 hour after delivery.[13,14,27,28] The significance of this effect remains unclear. Because etomidate is excreted in milk in very small amounts and decreases rapidly, it is most likely compatible with breast-feeding.[13,14,28]

Ketamine. Ketamine is a rapidly acting dissociative anesthetic that is commonly used in pediatric procedural sedation and may be used in RSI. It is frequently used in obstetrics and has not been associated with fetal developmental malformations.[13,14,26,27] Ketamine has a dose-dependent oxytocic effect and in high doses (>2 mg/kg) has been associated with uterine tetany.[13,14,26,27] It may also result in increased maternal blood pressure and heart rate and an increased neonatal muscle tone.[13,14] Neonatal depression has also been reported.[13,14] Whereas there are no published data on the effects of maternal ketamine use on the nursing infant, the amount of ketamine in the mother's plasma should be undetectable after 12 hours, and the American Academy of Pediatrics (AAP) considers it compatible with breast-feeding when it is used after this time.[12-14]

Midazolam. Midazolam is a short-acting benzodiazepine commonly used in procedural sedation or RSI. It has not been linked to congenital defects in most laboratory animals even when high doses are used.[13,14,26-28] In humans, there are no data available on its use in the first and second trimesters of pregnancy, but benzodiazepines do not appear to result in malformations in human observational studies.[13,14,26-28] When it is used at term, midazolam has been associated with neonatal respiratory depression and decreased muscle tone.[13,14,26-28] The AAP considers midazolam use during lactation of concern because there are few data addressing the issue.[12] However, in a number of studies, the concentration of midazolam in breast milk was found to be negligible 8 hours after maternal ingestion.[13,14,29]

Propofol. Propofol is a rapidly acting sedative anesthetic that is commonly used in RSI and procedural sedation. No data are available regarding its use in the first and second trimesters of pregnancy in humans, but it does not result in malformations in animal studies.[13,14,26,27] Its use at term also appears to be safe, although high doses have been linked to neonatal respiratory and CNS depression.[13,14,26-28] Propofol is thought to be compatible with breast-feeding because only negligible amounts are found in breast milk 24 hours after its use.[13,14,26-29]

Thiopental. Thiopental is an ultra-short-acting barbiturate that may be used during RSI or for status epilepticus. It has not been linked to congenital defects in laboratory animals even when high doses are used.[13,14,26-28] Similarly, it has not been associated with an increase in congenital anomalies in humans.[13,14,26-28] Thiopental is excreted in milk in concentrations that are too low to be pharmacologically significant and is considered compatible with breast-feeding.[12-14]

Neuromuscular Blockers

Nondepolarizing Neuromuscular Blocking Agents. Nondepolarizing neuromuscular blocking agents, such as rocuronium and vecuronium, are used in RSI. The effects of these agents on organogenesis in humans are not known, but these agents are not thought to pose a significant teratogenic risk because very little of the maternal dose crosses the placenta.[13,14,26-28] Furthermore, according to the manufacturers, there was no increase in congenital anomalies noted when small laboratory animals were injected with rocuronium daily.[13,14,26-28] Because of their chemical properties, very little of either drug is excreted in milk.[13,14,26-28] Women are not expected to breast-feed while taking neuromuscular blockers.

Depolarizing Neuromuscular Blocking Agents. Succinylcholine is a depolarizing neuromuscular blocking agent used in RSI for its rapid onset of action and short duration of paralysis. It has not been associated with congenital defects, although there is limited experience with its use in early pregnancy in humans.[13,14,26-28] In addition, it does not appear to have any effects on the newborn, except in rare cases of neonates with pseudocholinesterase deficiency.[13,14,26-28] As occurs in adults with the same condition, newborns with cholinesterase deficiency exhibit prolonged respiratory depression and paralysis.[13,14,26-28] Succinylcholine in lactation has not been studied; however, it is probably safe because it is hydrolyzed quickly.[13,14]

Sedative-Hypnotics

Benzodiazepines. Benzodiazepines are commonly used for the sedation of the acutely agitated patient, in the treatment of acute seizures and alcohol withdrawal, and as a sedative during RSI. The short-term use of benzodiazepines during pregnancy appears to be safe. Case reports have linked their use during the first trimester of pregnancy to increased risk of oral clefts,[10,13,14] but in an observational study based on the Swedish medical birth registry, no such association was found.[13,14,30] Neonates exposed to benzodiazepines may exhibit signs of toxicity, including apnea, cyanosis, unresponsiveness, hypotonia, poor feeding, and withdrawal symptoms characterized by irritability and tremulousness.[10,13,14] Because of the reported risk of apnea, it is recommended that neonates exposed to benzodiazepines through breast-feeding be monitored closely.[10,12-14]

Anticoagulants and Thrombolytics

Warfarin

Warfarin (Coumadin) is a known human teratogen and affects 4 to 5% of exposed fetuses. The risk from exposure is greatest during 6 to 9 weeks of gestation and seems to be dose dependent.[14,15,31] The fetal warfarin syndrome is associated with multiple abnormalities, such as hypoplasia of the nasal bones, midline dysplasia including agenesis of the corpus callosum, optic atrophy

www.ketabpezeshki.com 66485457-66963820

and blindness, mental retardation, seizures, and stippling of the bones with scoliosis and shortening of limbs.[10,14,15,31,32] Because warfarin is so highly protein bound, only a little is secreted into milk, and use by breast-feeding mothers is acceptable.[12-14,31] Caution should be used in breast-feeding of premature infants because they may be at increased risk for intraventricular hemorrhage.[13,31]

Heparin

Unfractionated heparin is a highly charged heterogeneous molecule with a molecular mass between 5 and 35 kDa.[13] It does not cross the placenta and does not present a direct risk to the fetus.[13,14] Early reports on the use of heparin for the prevention or treatment of venous thromboembolism during pregnancy noted an increased risk of prematurity, stillbirth, and fetal hemorrhage.[14] However, these risks were recently attributed to the underlying maternal condition rather than to heparin.[14,15,31,33] When anticoagulation during pregnancy is required, heparin is considered the agent of choice.[13,14,33] Its use is sometimes associated with maternal osteopenia and immune-mediated thrombocytopenia and maternal hemorrhage at delivery.[13,14,31,33] Patients need to be carefully monitored for these adverse effects. Because of its high molecular weight, heparin is not excreted in breast milk and is compatible with breast-feeding, but critically ill patients are not expected to breast-feed.[12-14,31]

Low-molecular-weight heparin may be used during pregnancy and in the postnatal period for therapeutic or prophylactic anticoagulation.[14,15,31,33] All currently available low-molecular-weight heparin products have been used safely during pregnancy.[14,15,31,33] Data are limited, however, because of their relatively recent introduction.

Thrombolytic Agents

Alteplase, reteplase, urokinase, and streptokinase have been used successfully in pregnant women in cases of life-threatening pulmonary embolus[34] or myocardial infarction. Experience with these agents during pregnancy, however, remains limited. To date, no teratogenic effects have been reported in humans, but intrapartum maternal hemorrhage has been reported with alteplase and urokinase.[14,15,31] Most thrombolytics are thought to be compatible with breast-feeding because of their short half-life.[13,14]

Antidotes

N-Acetylcysteine

N-Acetylcysteine is a mucolytic agent that has been used successfully and without untoward effects in pregnant women who have overdosed on acetaminophen.[13-16,35] No teratogenic effects have been reported, and pregnant patients who overdose on acetaminophen should be treated in the same manner as nonpregnant patients are.[13-16,35] Although there are no reports of *N*-acetylcysteine use during lactation, it is most likely safe because it has been used in neonates without untoward effects.[13,14,35]

Deferoxamine

Deferoxamine is indicated for iron toxicity occurring from iron overdose or from multiple transfusions in thalassemia patients. It has been associated with developmental effects on ossification in some animal species.[13,14,35,36] Experience in humans is limited, but it does not appear to affect the fetus.[13,14,35,36] The effects of deferoxamine on the nursing infant are not known, but it is probably compatible.[13,14]

Digoxin Immune Fragment

Digoxin immune fragment (Fab) therapy is indicated for life-threatening digitalis overdose and is being studied for treatment of preeclampsia.[13,14,35] There are very few case reports of the use of digoxin immune Fab during pregnancy, and a conclusion on its effects on the offspring cannot be made.[13,14] Thus in cases of life-threatening digitalis overdose with arrhythmias, the benefits of treatment of the mother outweigh the risk to the fetus. Digoxin immune Fab is not likely to be excreted in large amounts in milk, and it is probably safe for use during lactation.[12-14]

Dimercaprol

Dimercaprol or British antilewisite is a chelating agent that is used as an antidote for acute mercury, lead, arsenic, and gold poisoning.[13,14,35,37] It has also been used in Wilson's disease.[13,14] It is teratogenic in mice and has been associated with increased mortality, growth restriction, cleft facial features, cerebral herniation, and abnormal digits, but experience in humans is limited.[13,14,35,37] In general, in cases of heavy metal poisoning, the maternal benefits of treatment will outweigh the potential risks to the unborn fetus. Breast-feeding is contraindicated in patients poisoned by heavy metals.[13,14]

Flumazenil

Flumazenil is a benzodiazepine antagonist. No teratogenic effects have been reported in animals, and data on humans are limited.[13,14,35] Its use in pregnancy and lactation depends on the potential maternal benefit compared with possible risks to the fetus and nursing infant. Because it has a short half-life, breast-feeding may resume after a few hours.[13,14]

Fomepizole

Fomepizole is a competitive inhibitor of alcohol dehydrogenase indicated in cases of methanol and ethylene glycol poisoning. Its use during pregnancy has not been studied in animals or humans. Its safety during pregnancy is not known.[13,14,35] In cases of toxic alcohol poisoning, the benefits of treatment of the mother outweigh the possible risks to the fetus or nursing infant. Use of ethyl alcohol in these situations may be considered.[13,14] Breast-feeding is not expected to continue during acute toxic alcohol poisoning.

Hydroxycobalamin

Hydroxycobalamin is a vitamin B_{12} derivative that is indicated in the treatment of cyanide toxicity. The effects of hydroxycobalamin on human pregnancy have not been studied, but benefits of its use in cyanide poisoning outweigh any risk to the fetus. Studies in animals do not reveal an association with any developmental abnormality.[13,14] Breast-feeding is not expected to continue during cyanide poisoning, but hydroxycobalamin, like its related compounds, is considered compatible with breast-feeding.[12-14]

Methylene Blue

Methylene blue is used in the treatment of methemoglobinemia. In the past, it was injected into the amniotic sac to identify twins and to detect rupture of the membranes, but these practices were associated with hemolytic disease in the newborn, hyperbilirubinemia, and deep blue staining of the newborn.[13,14,35,38] Methylene blue in pregnancy has also been associated with an increased incidence of intestinal obstruction and atresia in the newborn.[13,14,35,38] Breast-feeding is not expected to continue during acute severe

www.ketabpezeshki.com 66485457-66963820

methemoglobinemia, but the effects of methylene blue on the nursing infant are expected to be minimal.[13,14]

Naloxone

Naloxone, used to reverse severe respiratory depression in opiate overdose, readily crosses the placenta. Although it has not been associated with reproductive abnormalities,[13,14,35] its use during pregnancy results in increased fetal wakefulness, increased fetal movement, and increased heart rate, effects attributable to antagonism of fetal endorphins.[13,14,35] In addition, its use in opiate-addicted mothers may precipitate withdrawal in both mother and term fetus.[13,14,39] It is compatible with breast-feeding.[12-14]

Physostigmine

Physostigmine is an anticholinesterase agent indicated in cases of severe anticholinergic poisoning associated with delirium. Experience with the medication during pregnancy is limited, and its effects on the developing fetus are unknown.[13,14,35] Use of physostigmine at term was associated with only mild decreases of Apgar scores at 1 and 5 minutes.[13,14,40] Breast-feeding is not expected to continue during anticholinergic poisoning, but physostigmine is thought to be probably compatible with breast-feeding.[13,14]

Pralidoxime

Pralidoxime is indicated for organophosphate/cholinergic poisoning because it is able to reactivate cholinesterase. Experience with pralidoxime in pregnancy is limited, and its effects on fetal development are not known.[13,14,35,40] In cases of organophosphate poisoning, the benefits to the mother generally outweigh the possible risk to the fetus. Breast-feeding is not expected to continue during cholinergic poisoning.

Pyridoxine

Pyridoxine is a vitamin required for good maternal health and good fetal development. It is indicated in isoniazid poisoning and in gyromitrin mushroom poisoning. Its use has been advocated by some for nausea and vomiting of pregnancy, gestational hypertension, and diabetes.[13,14] It has not been associated with any adverse developmental effects, and it is safe in lactation.[13,14]

Succimer

Succimer is a heavy metal chelator that is indicated in lead poisoning. It has also been used in arsenic, mercury, and cadmium poisoning. It has been linked to congenital defects in animal models, possibly because of its negative effects on zinc and copper metabolism.[13,14,35] Experience with the use of succimer in human pregnancy is limited to case reports, which did not shed any light on its teratogenicity in humans.[13,14,35,37,41] There are no reports of succimer use during lactation, but breast-feeding is contraindicated in heavy metal poisoning.[13,14]

Antimicrobial Agents

Infections in the pregnant woman have the potential to adversely affect pregnancy outcome as well as fetal development. When they occur in the first trimester, they are a common cause of spontaneous abortion, and when they occur in the second or third trimester, they are the most common cause of preterm labor and delivery. Antimicrobial agents also may adversely affect the pregnancy. Aminoglycosides, for example, may be nephrotoxic and ototoxic in both the mother and her offspring,[13,14,41,42] tetracyclines may result in dental staining of the developing fetus,[13,14,41,42] and lincosamides may be skeletotoxic.[13,14] The penicillins, cephalosporins, and macrolide antibiotics remain the drugs of choice for infections during pregnancy.[41,42] Other classes of antibiotics are prescribed only if these have failed to control the infection or in cases of severe maternal intolerance to these drugs.[13,14,41,42] The choice of antimicrobial therapy will depend on the age of the pregnancy, severity of infection, and maternal tolerance for the drug used. Many drugs also are secreted into breast milk. Potential problems for the neonate include direct effects on the neonate, changes in bowel flora, diarrhea, and potential interference with culture results.[12-14]

Antibiotics

Aminoglycosides. The association of aminoglycosides such as gentamicin, streptomycin, tobramycin, and neomycin with nephrotoxicity and ototoxicity is well known in the literature and in practice.[13,14,41,42] Aminoglycosides, however, do not appear to have any structural teratogenic effect in humans,[43] but kanamycin and streptomycin have been reported to cause ototoxicity in the mother and her offspring.[13,14] There are no reports definitively linking in utero exposure to gentamicin, streptomycin, tobramycin, and neomycin to either ototoxicity or nephrotoxicity.[13,14] Aminoglycosides are secreted in small amounts in breast milk and are poorly absorbed from the gastrointestinal tract.[12-14] They are probably compatible with breast-feeding.[12-14]

Cephalosporins. The first- to fourth-generation cephalosporins appear to be safe for use during pregnancy, although there are no controlled studies examining their safety.* Some cephalosporins are excreted into breast milk and may interfere with culture results in the workup of neonatal sepsis.[13]

Chloramphenicol. Chloramphenicol is a broad-spectrum antibiotic with excellent blood-brain barrier penetration. It remains the drug of choice for meningitis in many developing countries, but it has been associated with bone marrow suppression and aplastic anemia,[13,14,42] which may be fatal. Outside of these complications, its use during pregnancy appears to have no effects on the developing fetus.[13,14,31] However, when it is used at term, chloramphenicol has been associated with cardiovascular collapse in the neonate (the "gray baby" syndrome),[13,14,31,41,42] prompting its contraindication at term. The safety of chloramphenicol during breast-feeding is unknown; however, because of its potential for bone marrow depression and its association with gray baby syndrome, it is not recommended for use during lactation.[12-14]

Clindamycin. Clindamycin has not been associated with birth defects in humans, and animal studies have failed to link clindamycin to congenital abnormalities in the offspring.[13,31,41,42] The AAP considers clindamycin to be compatible with breast-feeding.[12-14] However, this recommendation is not echoed by other agencies because of its rare association with bloody diarrhea in the nursing infant.[13,14]

Fluoroquinolones. Fluoroquinolones have been linked to numerous toxic effects on bone and cartilage growth in animal models and are discouraged from use during pregnancy, particularly during the first trimester.† A number of observational studies, however, have failed to demonstrate such a toxic effect on the human fetus.[13,14,31] Furthermore, a recent meta-analysis did not reveal any increase in the rates of spontaneous abortions, birth defects, prematurity, or low birth weight in women exposed to fluoroquinolones in the first trimester.[44] The AAP considers ciprofloxacin to be compatible with breast-feeding because breast-fed infant plasma levels are low.[12-14] Data are inconsistent for other quinolones, and they are best avoided in lactation.

Linezolid. Linezolid is effective in the treatment of methicillin-resistant *Staphylococcus aureus* infection. It has been linked to

*References 11, 13, 14, 31, 41, 42.
†References 10, 13, 14, 31, 41, 42.

www.ketabpezeshki.com 66485457-66963820

embryonic death, decreased weight, and abnormalities in cartilage and ossification in animal studies,[13,14] but there is no information about its effects in humans. Its use in pregnant women should be limited to cases in which the maternal benefits outweigh possible risks to the fetus.[13,14] Linezolid is excreted into breast milk, but the amount that reaches the nursing infant appears to be small, and it is likely to be compatible with breast-feeding.[13,14]

Macrolides. Erythromycin, azithromycin, and clarithromycin are considered to be safe for use in pregnancy and compatible with breast-feeding, although there are no well-controlled studies examining their effects on the fetus.[13,14,31,41,42] Some reports have linked erythromycin to pyloric stenosis, but the studies were not controlled.[13,14,31,41,42] The estolate salt of erythromycin has also been associated with the development of hepatotoxicity in pregnant women and should be avoided during pregnancy.[13,14,31] Clarithromycin has been associated with an increased risk of fetal and embryonic death as well as with congenital malformations in animal species.[13,14] To date, however, this has not been shown in humans. For example, in a prospective controlled multicenter observational study comparing the outcomes of pregnancies exposed to new macrolides (including clarithromycin) with matched controls, no difference in the types or patterns of malformations between the groups was found.[13,14,45] Azithromycin is poorly concentrated in breast milk and may be the preferred agent in lactating mothers.[12-14]

Metronidazole. Metronidazole is indicated for the treatment of anaerobic infections, amebiasis, *Clostridium difficile* infection, and bacterial vaginoses. It is mutagenic and carcinogenic in mice and rats.[13,14] In humans, a number of studies failed to demonstrate a clear association between metronidazole use and congenital malformations when it was used in the first trimester of pregnancy.[13,14,35,46] Metronidazole has also been frequently used during the second and third trimesters to treat bacterial vaginosis with no untoward effects.[13,14] However, because of its effects in mice, many physicians avoid prescribing it at all during pregnancy.[13] Use of metronidazole during lactation is discouraged because of its potential mutagenic and carcinogenic effects in rats and its slow elimination from infants.[12-14]

Nitrofurantoin. Nitrofurantoin is commonly used for the treatment of uncomplicated urinary tract infections and has traditionally been considered safe for use throughout pregnancy except near term. However, a population-based multicenter case-control study linked its use in the first trimester to a number of congenital abnormalities, including anencephaly, microcephaly, hypoplastic left heart, atrial septal defects, and craniofacial clefts.[42] Its use near term has been associated with hemolytic anemia in the newborn.[13,14,31,47]

Penicillins. The first- to fourth-generation penicillins and their derivatives (including procaine, benzathine, clavulanate, sulbactam, and tazobactam) are considered safe for use in pregnancy, as is oral probenecid.[13,14,31,41,42] Penicillins are considered safe during breast-feeding, but their use may interfere with culture results if workup is required for a neonatal fever.[12,13]

Sulfonamides. Sulfonamides are used in the treatment of uncomplicated urinary tract infections and are indicated in the treatment of *Pneumocystis jiroveci* (formerly known as *Pneumocystic carinii*) pneumonia. They are also effective against methicillin-resistant *S. aureus*. Sulfamethoxazole is commonly combined with trimethoprim, presumably to improve antimicrobial efficacy. Both are folic acid synthesis inhibitors and have traditionally been contraindicated in pregnancy because of an increased risk of neural tube defects[13,14,31] and other congenital abnormalities, such as cleft palate.[13,14,31,41,42] A number of observational studies have demonstrated an increased risk of cardiovascular and urinary tract malformations in the offspring of women treated with trimethoprim-sulfamethoxazole in the first trimester.[42,48] Sulfonamides are contraindicated near term because of their association with kernicterus.[13,14,41,42] They compete with bilirubin for protein-binding sites, leaving large amounts of free bilirubin to diffuse freely into the brain. This results in bilirubin deposition in the infant's brain, causing kernicterus. To date, however, this complication has not been reported in neonates, presumably because free bilirubin is effectively cleared by the placental circulation.[13,14] In contradistinction, kernicterus has occurred in newborns exposed to sulfonamides after birth.[13,14] Sulfonamides are excreted into breast milk in low concentrations and are generally tolerated by a healthy neonate.[12-14] They should be avoided, however, in ill or premature infants and in infants with hyperbilirubinemia or glucose-6-phosphate dehydrogenase deficiency.[12-14]

Tetracyclines. Tetracyclines are effective in a number of infections, including infections with atypical bacteria, *Yersinia pestis* infection, and anthrax. Both tetracycline and doxycycline readily cross the placenta.[13,14,31] Tetracycline, but not doxycycline, has been associated with the development of fatal fatty liver in pregnant women.[13,14,31] Tetracycline also chelates calcium, causing abnormalities in bone growth and staining of decidual teeth.[13,14,31,41,42] It has also been associated with fetal genitourinary anomalies, inguinal hernias, and limb abnormalities.[13,14,31,41,42] Tetracycline should therefore be avoided during pregnancy. Doxycycline, on the other hand, does not bind to calcium and is associated less with stained teeth than is tetracycline.[13,14,31] In addition, it does not appear to cause an increase in any type of congenital malformation.[13,14,31] Despite these findings, doxycycline is not recommended in pregnancy.[13,14,31,42]

Because tetracycline binds to breast milk calcium, only a small amount reaches the nursing infant, and it may be used for short periods (<10 days) during breast-feeding.[13,14,31] Doxycycline does not bind to breast milk calcium and is present in greater quantities in breast milk.[12-14] This could theoretically increase its side effects in the newborn. Its use in nursing infants is best avoided.[12-14,31]

Vancomycin. Vancomycin is effective against methicillin-resistant *S. aureus* and *C. difficile*. It has not been linked to birth defects in animals or in humans.[13,14,31,49] Reports of auditory abnormalities and renal insufficiency in neonates of mothers treated with vancomycin are believed to be false positives because these abnormalities were resolved on retesting.[13,14] Vancomycin is excreted into milk but not well absorbed by the gastrointestinal tract.[12-14,31] Its effects on the nursing infant have not been studied.[12-14,31]

Antifungal Medications

Nystatin has a long safety profile during pregnancy and lactation. It is poorly absorbed from skin, mucous membranes, and the gastrointestinal tract, and it is considered the antifungal agent of first choice for treatment of mucocutaneous fungal infections.[13,14,31] Clotrimazole, miconazole, and ketoconazole seem to be safe during pregnancy and lactation as they have not been associated with major birth defects.[13,14,31] However, a minor increase in the incidence of hypoplastic left ventricle was reported in one case-control study.[13,14,31,50] In addition, ketoconazole is teratogenic in rats.[13,14,31,50] For these reasons, clotrimazole, miconazole, and ketoconazole are considered second-line treatment of fungal infections in pregnancy.[13,14,31,50] Fluconazole is teratogenic in high doses (>400 mg/day) and has been associated with an increased incidence of craniofacial and cardiovascular defects in offspring and multiple abnormalities of the skeleton and cartilage.[13,14,31,50] These anomalies were not noted when lower doses were used or with single-dose (150 mg) therapy for vaginal candidiasis.[13,14,31,50]

Ketoconazole, fluconazole, and itraconazole are excreted into breast milk.[12-14] On the basis of the safe use of ketoconazole in

www.ketabpezeshki.com 66485457-66963820

neonates and the lack of negative reports, it is considered compatible with breast-feeding.[12-14]

Antituberculous Agents

Untreated tuberculosis places the mother and fetus at greater risk than does the use of antituberculous medications. Isoniazid, ethambutol, and rifampin cross the placenta,[13,14,31] and in a review of antituberculous treatment during pregnancy, no association was found between these medications and major congenital malformations.[13,14,51] Rifampin has been associated with hemorrhagic disease of the newborn.[13,14,51] Despite this adverse effect, it maintains its first-line quality in the treatment of tuberculosis.[13,14,51] All three antituberculous medications are considered compatible with breast-feeding.[12,13,51]

Antiviral Agents

Antiherpetic Drugs. Acyclovir is a purine analogue commonly used in the treatment of herpesvirus infections. Valacyclovir is rapidly metabolized to L-valine and acyclovir, the active metabolite.[13,14] In humans, acyclovir readily crosses the placenta and reaches higher concentrations in fetal circulation than in maternal circulation.[13,14] Neither acyclovir nor valacyclovir has been associated with congenital malformations or adverse effects on the offspring.[13,14,52] Intravenous acyclovir is the drug of choice for life-threatening maternal herpes simplex virus infections,[13,14,53] such as disseminated disease, herpes encephalitis, and varicella pneumonia, which carries a maternal mortality of 44% if it is untreated.[13,14,53] For non–life-threatening genital herpes infection in pregnant women, either acyclovir or valacyclovir may be used.[13,53,54] Experience with famciclovir is limited and it is therefore not recommended for use in pregnancy.[13,14,52] Acyclovir is concentrated in milk, in which levels may be higher than in plasma.[12-14] Because there are no reported adverse outcomes in infants of mothers taking acyclovir or in infants treated with acyclovir for disseminated herpes, it is considered safe during breast-feeding.[12-14]

Anti-Influenza Drugs. Influenza in pregnancy carries a high risk of morbidity and mortality. During the 2009-2010 H1N1 pandemic, 6% of confirmed H1N1 deaths in the United States occurred in pregnant women.[55] Antiviral therapy with either M2 ion channel inhibitors, such as amantadine and rimantadine, or neuraminidase inhibitors, such as oseltamivir and zanamivir, is associated with improved maternal and pregnancy outcomes.[13,14,56,57] Whereas amantadine had been linked to various malformations including cardiac defects in humans and is considered teratogenic and embryotoxic in rats,[13,14] a cohort study found that neither class of anti-influenza drugs was associated with an increase in malformations or stillbirths.[13,57] There was, however, an increase in the incidence of necrotizing colitis in premature newborns exposed to either of these classes of drugs.[13,14] Oseltamivir appears safe in lactation.[13,14]

Anti-HIV Drugs. Anti-HIV drugs may be indicated immediately after a needle-stick injury or sexual contact with an infected individual. No specific pattern of birth defects has been described with the use of these drugs,[13,14] but there are a number of unanswered questions relating to the drugs' mutagenesis and carcinogenesis and their long-term effects on the liver, heart, and reproductive system.[13,14]

Animal and human data suggest that didanosine, lamivudine, stavudine, zidovudine, and zalcitabine present a small risk of structural malformations and mitochondrial dysfunction in the developing fetus,[13,14] but no specific pattern of birth defects has been described with protease inhibitors, such as ritonavir and nelfinavir.[13,14] Despite potential risks, it is thought that the benefit from treatment of HIV infection far outweighs the risk of these drugs, and treatment should not be withheld. In addition, zidovudine has been shown to significantly reduce vertical and perinatal transmission of HIV from the mother to the fetus.[13,14,53,58] Because of the risk of postnatal HIV transmission through milk, the Centers for Disease Control and Prevention advises against breast-feeding by HIV-positive mothers.[53]

Cardiovascular Agents

Antidysrhythmics

Atrial and ventricular arrhythmias are common during pregnancy. Most are benign; however, malignant degeneration occasionally occurs.[59-62] All unstable tachycardias should be treated with electrical cardioversion and according to advanced cardiac life support guidelines.[59-62] Stable patients may be treated medically, but the choice of drugs needs to be modified to protect the patient as well as the fetus from the drug's harmful effects.[59-62]

Adenosine. Adenosine is a naturally occurring compound that is metabolized quickly in the body. It has been used safely throughout pregnancy and is the drug of choice for termination of maternal supraventricular tachycardia.[13,14,59-62] Adenosine has also been used safely in termination of incessant tachycardia in the fetus.[13,14,59-62] Adenosine is safe in lactation.[12-14]

Amiodarone. Amiodarone is a class D agent. It contains large amounts of iodine and has been associated with congenital goiter and transient neonatal hyperthyroidism and hypothyroidism.[13,14,59-63] In addition, amiodarone has been linked to many congenital abnormalities, including growth restriction, structural cardiac abnormalities, corneal deposits, and developmental delay.[13,14,59-63] It should be used only in refractory cases of supraventricular or ventricular tachycardias in the mother and incessant tachycardias in the fetus.[13,14,59-63] Because of its high iodine content, its excretion into milk, and its long elimination half-life, amiodarone should not be used in nursing mothers.[12-14,31]

Digoxin and Quinidine. Digoxin and quinidine are considered safe for use during pregnancy and lactation.* Neither has been linked to congenital defects in humans or animals, and they are first-line agents for the treatment of significant maternal dysrhythmias.* They have also been successfully used in fetal tachycardia.* Overdoses of these drugs, on the other hand, have led to premature labor, spontaneous abortions, and, in the case of digoxin, fetal death.[13,14] During lactation, digoxin appears compatible with breast-feeding; there is very little information about quinidine's use in breast-feeding.[12-14]

Lidocaine. Lidocaine is a weak base. It rapidly crosses the placenta and becomes ion trapped in the fetus.[13,14] There is no evidence of a link between use of lidocaine in the first trimester and any fetal developmental malformations.[13,14,31,59-61] However, high doses used near term are associated with neonatal CNS depression, apnea, hypotonia, seizures, and bradycardia.[13,14,59-61] Lidocaine is considered compatible with breast-feeding.[12-14]

Procainamide. Procainamide has been successfully and safely used in the treatment of stable wide-complex tachydysrhythmias during pregnancy.[59-62] It has not been associated with fetal developmental abnormalities and appears well tolerated when it is used for short durations.[13,14,59-62] It has been associated with a high incidence of maternal antinuclear antibodies and the occurrence of a lupus-like reaction in humans.[13,14,31] During lactation, both procainamide and its metabolite, *N*-acetylprocainamide, have been found in breast milk,[13,14] and although the AAP considers its short-term use compatible with breast-feeding,[12] other authorities do not recommend it.[13,14]

Flecainide. Flecainide is a class IC antiarrhythmic agent that is structurally related to procainamide.[13,14] It has been used safely to

*References 13, 14, 31, 59, 60, 62.

www.ketabpezeshki.com 66485457-66963820

terminate maternal and fetal tachycardia,* but it has been associated with fetal hyperbilirubinemia, hepatotoxicity, and loss of fetal heart rate variability.* Flecainide has also been found to be teratogenic in some animal species, resulting in cardiac and musculoskeletal abnormalities.* Flecainide is found in breast milk, but apparently in concentrations that are not toxic to infants.[12-14] The AAP considers flecainide compatible with breast-feeding despite limited experience.[12,13]

Ibutilide. Ibutilide is a class III antiarrhythmic used to terminate atrial fibrillation and flutter. There are only a few case reports of its successful and safe use during the latter part of pregnancy in humans.* In animals, however, ibutilide was found to be teratogenic and caused cardiac septal defects as well as skeletal dysgenesis in rats,[13,14] especially when high doses were given. Ibutilide should be reserved for refractory cases in which the benefits of therapy outweigh any fetal risk.[13,14]

Sotalol. Sotalol has been used in pregnant women to successfully and safely treat atrial arrhythmias as well as hypertension.[59-62] It has also been successfully used to terminate fetal atrial tachycardias.[59-62,64] It does not appear to have teratogenic effects in animals.[13,14] Some of the negative effects of sotalol include bradycardia in the newborn, persisting for 24 hours.[13,14] Sotalol is concentrated in milk but does not appear to result in bradycardia or hypotension in the nursing infant, and according to the AAP it is compatible with breast-feeding.[12-14]

Antihypertensives

Hypertension complicates 12% of pregnancies and is most commonly seen in the third trimester.[65] It accounts for 16% of maternal deaths in the United States.[65] Labetalol is the agent of choice for hypertensive emergencies in pregnancy.[66-68]

Angiotensin-Converting Enzyme (ACE) Inhibitors. ACE inhibitors are classified as category D drugs and are contraindicated for use during pregnancy.[13,14,69] Furthermore, ACE inhibitors are embryocidal in animals and increase the rate of stillbirths in some animal species.[13,14] In humans, the most significant adverse fetal effects occur when they are used in the second and third trimesters.[13,14,66-69] These include oligohydramnios, anuria, renal agenesis resulting in death, increased risk of stillbirth, intrauterine growth restriction, fetal skull abnormalities, pulmonary hypoplasia, respiratory distress syndrome, and fetal and neonatal hypotension.[13,14,66-69] Captopril and enalapril are considered compatible with breast-feeding.[12-14,68]

Angiotensin II Receptor Antagonists. Angiotensin II receptor antagonists should be avoided during pregnancy because their use has been reported to result in fetal abnormalities similar to the abnormalities seen with ACE inhibitors, including renal agenesis, neonatal anuria, oligohydramnios, intrauterine growth restriction, persistent patent ductus arteriosus, abnormal ossification, and death.[13,14,66-69] Their safety in lactation is unknown.

Beta-Blockers. Beta-blockers have become a first-line treatment of hypertension in pregnancy.[70,71] They have not been associated with fetal malformations and appear to be safe when they are used for short periods.† Adverse fetal effects include intrauterine growth restriction and a low placental weight.† Beta-blockers lacking intrinsic sympathomimetic activity, such as acebutolol, atenolol, nadolol, and propranolol, are more likely to be associated with these adverse effects.† When beta-blockers are given near term, they have been associated with persistent beta blockade in the newborn.† Nonselective beta-blockers, such as propranolol, also have resulted in neonatal hypoglycemia, respiratory depression, and hyperbilirubinemia in the newborn.* These adverse effects are less common when a cardioselective beta-blocker, such as atenolol or metoprolol, is used.* Esmolol, a short-acting beta-blocker commonly used to terminate maternal supraventricular dysrhythmias and hypertension during surgery, has been associated with fetal bradycardia, neonatal bradycardia and hypotonia, and fetal distress requiring emergent cesarean section.* Beta-blockers have variable effects on the nursing infant, and close monitoring of the infant for adverse effects is recommended.[12-14,68]

Calcium Channel Blockers. Calcium channel blockers have been used for the treatment of hypertension and the termination of supraventricular rhythm disturbances during pregnancy.† Intravenous verapamil has also been used to terminate fetal tachycardia,† and intravenous nicardipine has been used for severe preeclampsia.† In addition, some calcium channel blockers, such as nifedipine and diltiazem, have been used as tocolytic agents.[13,14,31] In laboratory animals, use of calcium channel blockers in the first trimester was associated with a dose-dependent increase in embryonic mortality and skeletal abnormalities.[13,14,31] To date, however, these abnormalities have not been seen in humans, although data remain limited.[13,14,66-68] A prospective multicenter observational study of 299 patients exposed to calcium channel blockers in the first trimester did not reveal an increase in congenital malformations compared with controls.[71] Some complications of calcium channel blocker use during pregnancy include maternal hypotension, tachycardia, and fetal distress,† especially pronounced when sublingual nifedipine or intravenous nicardipine is used.[13,14] The AAP considers these drugs compatible with breast-feeding.[12,13,31]

Clonidine has been safely used in the treatment of severe hypertension throughout pregnancy, but experience during the first trimester remains limited.[13,14,66-68] It does not appear to be teratogenic in laboratory animals and does not increase fetal mortality.[13,14] Transient neonatal hypertension has been reported in neonates.[4,14,66-68] Its effects on breast-feeding neonates are unknown, but it is considered to be compatible with breast-feeding.[12-14,68]

Hydralazine is a direct vasodilator that has a rapid onset of action. Its use, however, has been associated with higher rates of maternal hypotension, placental abruption, and neonatal distress compared with labetalol.‡ It is therefore no longer recommended as a first-line agent in the treatment of severe acute hypertension in pregnancy. It may still be used as a second-line agent.[66-68,73] Hydralazine is considered compatible with breast-feeding.[12-14,68]

Methyldopa has been safely used to treat chronic hypertension throughout pregnancy, and most reviews have not linked it to any teratogenic effects on the offspring or adverse effects on the pregnancy.[13,14,31,66-68] Many clinicians continue to prescribe it as first-line therapy for hypertension during pregnancy. Methyldopa is compatible with breast-feeding.[12-14,68]

Diuretics. Diuretics are no longer used for gestational hypertension or preeclampsia because, in general, affected patients tend to be hypovolemic.[13,66-68]

Loop diuretics such as furosemide are indicated in the treatment of pulmonary edema due to congestive heart failure. In laboratory animals, furosemide has been linked to renal and skeletal abnormalities when it is used in pregnancy.[13,14] These effects have not been seen in humans, but a slightly increased risk of hypospadias has been reported.[13,14] Furosemide is secreted into breast milk but is considered compatible with breast-feeding.[12-14]

Thiazide diuretics have been associated with hypoglycemia and electrolyte abnormalities in neonates when they are given near term and an increase in meconium staining and perinatal

---

*References 13, 14, 31, 59-62.
†References 13, 14, 66-68, 70.

*References 13, 14, 66-68, 70.
†References 13, 14, 66-68, 71, 72.
‡References 13, 14, 31, 66-68, 73.

www.ketabpezeshki.com 66485457-66963820

mortality.[13,14] Moreover, thiazide diuretics may have a direct effect on smooth muscle and inhibit labor.[13,14] In general, these agents are excreted in low quantities into breast milk and are considered safe during breast-feeding.[12-14]

Nitrates. Nitroglycerin has not been shown to cause fetal harm in animal studies.[13,14,31] Limited reports in humans do not show any major effects on the fetus or neonate.[13,14,31] Nitroglycerin is rarely used during pregnancy, but it appears to be a safe, effective, rapidly acting and short-acting agent.* It appears to be effective in relieving intrapartum fetal distress related to uterine hyperactivity.[76] Nitroprusside for the treatment of hypertensive emergencies in pregnancy has the same advantages and disadvantages as in nonpregnant patients. During prolonged administration of high doses, nitroprusside may result in cyanide toxicity and severe acidosis.[13,14,74,75] It readily crosses the placenta, and fetal levels of cyanide can increase as high as twice maternal levels.[13,14,74,75] Standard doses do not seem to subject the fetus to major risk of toxicity,[13,14] but with the availability of safer alternatives, notably labetalol, nitroprusside is considered a last-resort agent.† No data are available on its use during lactation, but breast-feeding is not expected to continue during critical illness.

Vasopressors

Vasopressors are indicated in shock states only after intravascular volume has been restored. Whereas they are effective in restoration of intravascular resistance and blood pressure, all have the potential to increase uterine vascular resistance, resulting in a proportional decrease in placental blood flow.[74,75,77,78] Each of the vasopressors has its indications, its benefits, and its inherent risks. At this time, on the basis of its safety profile, phenylephrine appears to be the vasopressor of choice in the treatment of vascular collapse during pregnancy.[74,75,77,78]

Dobutamine. Dobutamine is an inotrope used in the setting of cardiac dysfunction and sepsis.[74,75] It has not been associated with any negative reproductive effects in laboratory animals or in humans.[13,14]

Dopamine. Dopamine has a dose-dependent effect on dopaminergic, alpha, and beta receptors and has been used in maternal shock, including spinal shock due to spinal anesthesia.[13,14,74,75] Low-dose dopamine has been successfully used to improve cardiac and urine output in patients with preeclampsia and oliguria,[74,75] but this has not been shown to improve mortality or renal function.[79] No significant fetal side effects have been directly linked to its use in animal studies, even though it has been shown to decrease uterine vascular flow.[13,14] Its safety during breast-feeding has not been studied, but breast-feeding is not expected to continue during critical illness.[12,13]

Epinephrine. Epinephrine is the preferred agent for the treatment of anaphylaxis and is commonly used in status asthmaticus. It has also been used to treat shock from any cause during pregnancy.[13,74,75] However, it has been associated with anoxic injury to the fetus, intracranial hemorrhage, and increased incidence of inguinal hernias.[13,14,74,75] Safety during breast-feeding has not been studied.[12,13]

Norepinephrine. Norepinephrine use during pregnancy has been associated with the occurrence of vascular and skeletal abnormalities in rodents and a significant decrease in placental blood flow and fetal oxygenation.[13,14] It has also been associated with increased incidence of cerebral hemorrhage.[13,14,74,75] Its safety during breast-feeding has not been studied,[13] but breast-feeding is not expected to continue during critical illness.[12,13]

Ephedrine and Phenylephrine. Ephedrine and phenylephrine are both effective in the treatment of shock from any cause in pregnancy.[74,75,77] Compared with phenylephrine, ephedrine was associated with higher heart rates, more maternal gastric upset, and greater incidence of fetal acidosis.[13,14,74,75,77] Ephedrine is no longer the agent of choice in shock during pregnancy as it has been replaced by phenylephrine.[77]

Endocrine Agents

Diabetes Medications

Diabetes mellitus is associated with a number of congenital malformations involving multiple organ systems.[13,14,78] It is also associated with a significant increase in perinatal morbidity.[13,14,78] Glycemic control in pregnancy is therefore important and should be accomplished in a controlled manner as hypoglycemia is also associated with adverse pregnancy outcomes.[13,14,78]

Insulin. Insulin is a large peptide that does not cross the blood-placenta barrier. It is considered to be the drug of choice in the United States for diabetes mellitus types 1 and 2 in pregnancy.[13,78]

Sulfonylureas. Sulfonylureas are regarded as possibly teratogenic and less effective than insulin in the control of gestational diabetes.* They have also been associated with neonatal hypoglycemia with use at term.* In reality, outside the perinatal period, there is little information about their use during pregnancy, and in a randomized study, glyburide proved to be as effective and safe as insulin during pregnancy.[80] Glyburide and glipizide are highly protein bound and are not likely to pass into breast milk; nursing infants should nevertheless be monitored.[12,13,78]

Metformin. Metformin has been associated with serious adverse effects in adults, including life-threatening metabolic acidosis and hepatotoxicity.[13,14,78] It has not been associated with fetal malformations in animals,[13,14,31,78] and there were no major birth defects in women taking metformin for polycystic ovary disease in a 2004 report.[13,81] In addition, metformin does not appear to result in neonatal hypoglycemia, a complication commonly seen with the use of sulfonylureas at term.[13,14,78,81] In the developing world, where the administration of insulin may be problematic, metformin is a good alternative to insulin for type 2 diabetes mellitus when diet alone is not effective.[13,81] Whereas metformin is considered compatible with breast-feeding by the AAP,[12] it should be used with caution in lactating mothers because of its potential for serious effects in adults and its excretion into milk.[13]

Thyroid Medications

Maternal hyperthyroidism is associated with an increased risk of spontaneous abortion, preterm labor, placental abruption, and maternal congestive heart failure. Effects of the disease on the offspring include intrauterine growth restriction, intrauterine fetal death, and neonatal goiter.[13]

Propylthiouracil (PTU). PTU, the drug of choice during pregnancy, prevents the synthesis of thyroid hormone and prevents the peripheral conversion of T_4 to T_3.[13,31] Complications of treatment include transient goiter and hypothyroidism of the newborn.[13,82] There does not appear to be an increase in the risk of congenital defects with PTU.[13,14,31,82] Other drugs used to control hyperthyroidism in pregnancy include methimazole and carbimazole, both of which have been associated with abnormal development of the skin, albeit inconsistently.[13,14,31,82] PTU is excreted into breast milk in insignificant amounts and is considered compatible with breast-feeding.[12,13]

*References 13, 14, 31, 74, 75.
†References 13, 14, 66-68, 74, 75.

*References 13, 14, 31, 78, 80.

www.ketabpezeshki.com 66485457-66963820

Iodides. Iodides are reserved for thyrotoxic patients. These agents are readily taken up by the fetal thyroid gland, resulting in prolonged fetal hypothyroidism and goiter.[13,14]

Levothyroxine. Hypothyroidism in pregnancy may result in an increased risk for spontaneous abortion, intrauterine growth restriction, placental abruption, and fetal demise and has been associated with severe neurologic impairment of the offspring.[13,14] Levothyroxine, a synthetic formulation of naturally occurring T_4, has not been associated with any negative effects on the offspring and is the treatment of choice for hypothyroidism in pregnant women.[13,14,31] It is compatible with breast-feeding.[12,13]

Gastrointestinal Agents

Antacids

H_2 Receptor Antagonists. Antacids are commonly prescribed throughout pregnancy. None of the H_2 receptor antagonists has been linked to congenital malformation, and they all appear to be safe for the nursing infant.[13,14] There is one report in the literature, however, linking in utero gastric suppression to an increased incidence of asthma during childhood.[13,14,83]

Proton Pump Inhibitors. Despite the limited size of most studies on proton pump inhibitor use in pregnancy, a meta-analysis found no association with an increased risk for major congenital birth defects, spontaneous abortions, or preterm delivery.[84] Proton pump inhibitors, such as esomeprazole, lansoprazole, pantoprazole, and rabeprazole, are accepted for use during pregnancy.[13,14] There are reports, however, of an increased incidence of gastrointestinal, hepatic, and thyroid cancers in rats and mice.[13,14] There are no human data studying the effect of proton pump inhibitors on nursing infants.[12,13]

Antiemetic Medications

Phenothiazines. Phenothiazines, such as metoclopramide, prochlorperazine, and promethazine, are dopamine antagonists commonly used in the treatment of nausea and vomiting during pregnancy. Although there are reports of increased risk of cardiac defects,[13,14] these reports did not consider other factors, such as the mother's health, when the drug was reviewed. The bulk of evidence does not support a link to congenital abnormalities.[13,14,85] These agents are excreted in milk. The AAP cautions against their use in nursing mothers as they may cause sedation and other untoward effects.[12,13]

Serotonin 5-HT$_3$ Receptor Antagonists. Dolasetron, granisetron, and ondansetron have not been linked to any fetal malformations,[13,14,85] although experience with the newer agents remains limited.[13,14,85] The AAP considers these agents compatible with breast-feeding.[12,13]

Neurologic Agents

Anticonvulsants

Anticonvulsants are known teratogens, and 30% of neonates exposed to commonly used anticonvulsants exhibit congenital anomalies.* The risks for birth defects increase with the duration of exposure and with the number of agents used.[86,87] Valproate is associated with the most frequent serious adverse effects on the pregnancy and fetus (20.3% incidence of serious adverse outcomes) compared with phenytoin, carbamazepine, and lamotrigine (10.7%, 8.2%, and 1.0%, respectively).[13,86,87] Despite the risks, most practitioners believe that it is important to control seizures during pregnancy. Generalized seizures during pregnancy are associated with an increased risk of spontaneous abortion, hypoxic injury to the fetus, and impaired neuropsychological functioning.[13,31]

*References 13, 14, 31, 86, 87.

Monotherapy is the most appropriate option and is recommended at the lowest effective anticonvulsant dose.[13,31,86,87] Dividing of the daily dose to decrease peak plasma levels may be considered. Adjustment of the dosage upward is often required to maintain adequate seizure control.[13,31,86,87]

Classic Anticonvulsants. The classic anticonvulsants are considered class D agents and are teratogenic.* Carbamazepine has been linked to an increased risk of craniofacial defects, neural tube defects, and developmental delay.* Phenobarbital has been associated with a slightly increased risk of congenital heart disease and cleft lip or palate.* In addition, its chronic use during pregnancy has been associated with neonatal withdrawal.* Phenytoin use during pregnancy has been associated with the fetal hydantoin syndrome, which affects 5 to 10% of pregnancies.* This syndrome is characterized by varying degrees of ossification abnormalities of the extremities and digits, craniofacial abnormalities including cleft lip and palate, impaired growth, delayed neurologic development, and multiple cardiovascular anomalies.* Valproic acid is associated with multiple facial anomalies, neural tube defects, strabismus, and congenital heart defects.*

Carbamazepine, phenobarbital, and phenytoin have also been associated with hemorrhagic disease of the newborn, presumably because they competitively inhibit placental transport of vitamin K.[13,14,31]

Carbamazepine, phenytoin, and valproic acid are secreted into breast milk in low quantities and are considered compatible with breast-feeding.[11-14] Phenobarbital, on the other hand, has been associated with neonatal sedation and toxicity and is not advised during breast-feeding.[11-14]

Newer Anticonvulsants. Newer anticonvulsants, such as lamotrigine, levetiracetam, and topiramate, have been associated with a slightly increased incidence of major birth defects, such as oral clefts, skeletal abnormalities, and hypospadias.[13,14,86,87] The incidence of these birth defects increases significantly when these substances are combined with other anticonvulsants, such as valproic acid.[13,31,86,87] These findings, however, were not seen in two studies comparing the newer anticonvulsants.[88,89] In the lamotrigine pregnancy registry,[88] a study conducted by the manufacturer of lamotrigine, and in an observational study from Denmark,[89] first-trimester exposure to lamotrigine, oxcarbazepine, topiramate, gabapentin, or levetiracetam was not associated with an increased risk of major birth defects.

These agents also appeared to be well tolerated by the nursing infant, except for topiramate, which caused excess sedation.[13,31]

Migraine Medications

Ergot Alkaloids. Ergotamine and dihydroergotamine are commonly used in the treatment of migraines. Whereas neither has been associated with teratogenic effects, they are contraindicated in pregnancy because of their oxytocic effects[13,14] and their effects on uterine blood flow.[13,14] In a number of animals, these alkaloids have been associated with intrauterine growth restriction, probably because of reductions in uteroplacental blood flow.[13,14] They are also contraindicated during breast-feeding because of possible ergot poisoning of the nursing infant manifested by convulsions and gastrointestinal symptoms.[12-14]

Triptans. The triptans are selective serotonin agonists that are effective in the treatment of vascular headaches, including migraines and cluster headaches. They have been found to be

*References 13, 14, 31, 86, 87.

www.ketabpezeshki.com 66485457-66963820

teratogenic in a number of animal species,[13,14] but recent data in humans appear to favor their safety during pregnancy.[90] Sumatriptan is excreted into milk, but oral bioavailability appears to be low, and very little reaches the nursing infant.[13,14] It is considered compatible with breast-feeding, especially if the milk is discarded for 8 hours after the last dose.[12,13]

Respiratory Agents

Antihistamines

Antihistamines including chlorpheniramine, diphenhydramine, doxylamine, hydroxyzine, and meclizine have been safely used in the treatment of allergic reactions during pregnancy and as antiemetics in the treatment of nausea and vomiting during pregnancy.[13,14,31] This has been further confirmed in recent meta-analyses involving more than 200,000 patients.[91,92] First-generation antihistamines are not recommended during breast-feeding because they are thought to inhibit lactation.[12-14] In addition, serious adverse CNS effects, including seizures, have been reported to develop in neonates receiving antihistamines, especially when they are premature.[12,13]

The newer generation antihistamines, such as cetirizine and loratadine, also appear safe during pregnancy.[13,14,92,93] They may be acceptable alternatives for severe allergies if the first-generation antihistamines are not tolerated.[13,14,92,93] These drugs are excreted into human milk, but in the case of loratadine, very small amounts reach the neonate.[13,14] The AAP classifies these drugs as compatible with breast-feeding.[12,13]

Asthma Medications

Pregnant women with asthma are at risk for neonatal death, preterm birth, low-birth-weight infants, preeclampsia, and small-for-gestational-age infants.[94] Asthmatic mothers may also have a higher rate of chorioamnionitis, hypertensive disorders of pregnancy, cesarean section, and prolonged hospital stay compared with control mothers.[94] Better asthma control has been associated with an improved outcome.[94]

Beta-adrenergic medications such as albuterol, metaproterenol, and terbutaline are commonly used in the treatment of asthma. Beta-adrenergic agents have also been used during the last trimester to treat premature labor.[13,14] Albuterol is the most commonly prescribed and is the treatment of choice in asthma.* It appears safe even when it is used long term.[13,14,92,94] None of the beta-adrenergic medications has been linked to fetal or congenital malformations, but some have been associated with significant cardiovascular and metabolic effects, which are transient and generally well tolerated by the fetus.* Transient hyperglycemia followed by insulin secretion may also occur, resulting in neonatal hypoglycemia, especially in diabetic patients.* Terbutaline, when it is used intravenously or orally in pregnant women, may result in significant maternal and fetal arrhythmias.[13,14] Maternal pulmonary edema and death have been reported.[13,14] The FDA has recommended a label change to add a warning against its use in preterm labor because safer beta$_2$-agonists and tocolytic agents are available.[95] Long-acting beta-agonists also appear to be safe during pregnancy.[13,14,92,94] Albuterol is compatible with breast-feeding.[12-14]

Ipratropium has not been found to be teratogenic in numerous animal models,[13,14,92,94] but there are few data regarding its safety in human pregnancy.[13,14] It is considered compatible with breast-feeding.[12,13]

*References 13, 14, 31, 92, 94.

Cromolyn sodium has not been associated with any significant risk of birth defects or negative perinatal outcomes.[13,14] It is considered compatible with breast-feeding.[12,13]

Corticosteroids

Corticosteroids are commonly used during pregnancy for the treatment of various disorders, including autoimmune diseases and asthma. Inhaled corticosteroids are the main therapy for the prevention of asthma exacerbations during pregnancy. Oral corticosteroids are the mainstay of therapy for acute exacerbations of asthma. Although they are not considered human teratogens, there may be a slightly increased incidence of orofacial clefts when oral steroids are used during the first trimester.* Furthermore, their use in the third trimester has been linked to an increased incidence of preterm delivery, low birth weight, preeclampsia, and cataracts in the newborn.† Other authors have also raised concerns about the development of congenital adrenal hyperplasia in newborns.[13,14] Prednisone is considered safe during breast-feeding.[12,13]

Data on the use of leukotriene antagonists in pregnancy are limited. One study did not find an association with congenital abnormalities, but there was a slight increase in intrauterine growth restriction. However, these results should be interpreted with caution because of the small sample size of the study.[13,14,98] Zileuton is mutagenic in animal studies and should be avoided during pregnancy and lactation.[13,14,98]

Decongestants

Decongestants with strong vasoconstrictive properties, such as phenylpropanolamine and pseudoephedrine, cause placental vasoconstriction and are not recommended during pregnancy.[13,14] There are limited data suggesting that their use in the first trimester may result in an increased incidence of abnormalities typically associated with placental vascular disruption, such as gastroschisis and intestinal atresia.[13,14] The risk, however, appears to be low. Pseudoephedrine is excreted in milk in small quantities, limiting the nursing infant's exposure.[13,14] The AAP classifies pseudoephedrine compatible with breast-feeding.[12,13]

KEY CONCEPTS

- Chemically induced birth defects are believed to be responsible for approximately 1 to 3% of anomalous births.
- The age of the fetus is crucial in determination of the impact of any given exposure. During the time of organogenesis (days 21-56 of fetal life) when major body organs are formed, exposure to a teratogen may result in major anatomic defects.
- Certain medications, such as anticonvulsants, warfarin derivatives, NSAIDs, sulfonamides, fluoroquinolones, ACE inhibitors, and oral hypoglycemic agents, are known teratogens or cause potential toxic effects in the newborn and should be avoided, if possible, during pregnancy.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

*References 13, 14, 92, 94, 96, 97.
†References 13, 14, 31, 92, 94.

www.ketabpezeshki.com 66485457-66963820

References

1. Schardein JL: *Principles of teratogenesis applicable to drug and chemical exposure*. In: Schardein JL, ed. *Chemically Induced Birth Defects*. New York: Dekker; 2000:1-65.
2. O'Rahilly RR, Muller F: *Teratology and prenatal diagnosis*. In: O'Rahilly RR, Muller F, eds. *Human Embryology and Teratology*, 3rd ed. New York: John Wiley; 2001:115-133.
3. Shepard TH: *Catalog of Teratogenic Agents*, 13th ed. Baltimore: Johns Hopkins University Press; 2010.
4. Fine JS: *Reproductive and perinatal principles*. In: Goldfrank LR, et al, eds. *Goldfrank's Toxicologic Emergencies*, 9th ed. New York: McGraw-Hill; 2011:423-445.
5. Buhimschi CS, Weiner CP: Medications in pregnancy and lactation: Part 1. Teratology. *Obstet Gynecol* 2009; 113:166-188.
6. Mitchell AA: Systematic identification of drugs that cause birth defects—a new opportunity. *N Engl J Med* 2003; 349:2556.
7. Doering PL, Boothby LA, Cheok M: Review of pregnancy labeling of prescription drugs: Is the current system adequate to inform of risks? *Am J Obstet Gynecol* 2002; 187:333.
8. Lo WY, Friedman JM: Teratogenicity of recently introduced medications in human pregnancy. *Obstet Gynecol* 2002; 100:465.
9. Proposed rule: Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. *Fed Regist* 2008; 73:30831.
10. Ostrea EM, Mantaring JB, Silvestre MA: Drugs that affect the fetus and newborn infant via the placenta or breast milk. *Pediatr Clin North Am* 2004; 51:539-579.
11. Ito S: Drug therapy for breast-feeding women. *N Engl J Med* 2000; 343:118-126.
12. American Academy of Pediatrics Committee on Drugs: The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108:776.
13. Briggs GG, et al: *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*, 9th ed. Baltimore: Lippincott Williams & Wilkins; 2011.
14. *REPROTOX: An information system on environmental hazards to reproduction and development*. Washington, DC: The Reproductive Toxicology Center, Columbia Hospital for Women Medical Center. Available at www.REPROTOX.org.
15. Feldkamp ML: Acetaminophen use in pregnancy and risk of birth defects: Findings from the National Birth Defects Prevention Study. *Obstet Gynecol* 2010; 115:109-115.
16. Wilkes JM: Acetaminophen overdose in pregnancy. *South Med J* 2005; 98:1118-1122.
17. Sørensen HT: Aspirin in early pregnancy is not associated with an increased risk of congenital anomalies—meta-analysis. *Evid Based Obstet Gynecol* 2003; 5:103.
18. Kozer E, et al: Aspirin consumption during the first trimester of pregnancy and congenital anomalies: A meta-analysis. *Am J Obstet Gynecol* 2002; 187:1523.
19. Askie LM, et al: PARIS Collaborative Group: Antiplatelet agents for prevention of pre-eclampsia: A meta-analysis of individual patient data. *Lancet* 2007; 369:1791.
20. Østensen M, et al: Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res Ther* 2006, 8:209.
21. Nielsen GL, Sørensen HT, Larsen H, Pedersen L: Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: Population-based observational study and case-control study. *BMJ* 2001; 322:266.
22. Ofori B, et al: Risk of congenital anomalies in pregnant users of non-steroidal anti-inflammatory drugs: A nested case control study. *Birth Defects Res B Dev Reprod Toxicol* 2006; 77:268.
23. Koren G, et al: NSAIDS during third trimester and the risk of prenatal closure of the ductus arteriosus: A meta-analysis. *Ann Pharmacother* 2006; 40:824-829.
24. Jones HE, et al: Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 2010; 363:2320-2331.
25. Koren G, et al: Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 2006; 368:704.
26. Cheek TG, Baird E: Anesthesia for the nonobstetric surgery: Maternal and fetal considerations. *Clin Obstet Gynecol* 2009; 52:535-545.
27. Kuczkowski KM: Laparoscopic procedures during pregnancy and the risks of anesthesia: What does an obstetrician need to know? *Arch Gynecol Obstet* 2007; 276:201-209.
28. Kuczkowski KM: The safety of anesthetics in pregnant women. *Expert Opinion Drug Saf* 2006; 5:251-264.
29. Nitsun M, et al: Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. *Clin Pharmacol Ther* 2006; 79:549-557.
30. Wikner BN, et al: Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: Neonatal outcome and congenital malformations. *Pharmacoepidemiol Drug Saf* 2007; 16:1203-1210.
31. Buhimschi CS, Weiner CP: Medications in pregnancy and lactation: Part 2. Drugs with minimal or unknown human teratogenic effect. *Obstet Gynecol* 2009; 113(Pt 1):417-432.
32. Chan KY, Gilbert-Barness E, Tiller G: Warfarin embryopathy. *Pediatr Pathol Mol Med* 2003; 22:277.
33. Santoro R, et al: Efficacy and safety of the long-term administration of low-molecular-weight heparins in pregnancy. *Blood Coagul Fibrinolysis* 2009; 20:240-243.
34. Ahearn GS, et al: Massive pulmonary embolism during pregnancy successfully treated with recombinant tissue plasminogen activator: A case report and review of treatment options. *Arch Intern Med* 2002; 162:1221-1227.
35. Bailey B: Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; 67:133-140.
36. Nassar AH, et al: Pregnancy in patients with beta thalassemia intermedia: Outcome of mothers and newborns. *Am J Hematol* 2006; 81:499-502.
37. Weizsaecker K: Lead toxicity during pregnancy. *Primary Care Update OB/GYNS* 2003; 10:304-309.
38. Albert M, Lessin MS, Gilchrist BS: Methylene blue: A dangerous dye. *J Pediatr Surg* 2003; 38:1244-1245.
39. Guinsburg R, Wyckoff M: Naloxone during neonatal resuscitation: Acknowledging the unknown. *Clin Perinatol* 2006; 33:121-132.
40. Adhikari K, Ghosh A, Alauddin MD, Moitra A, Datta AK: Organophosphate poisoning in pregnancy. *J Obstet Gynaecol* 2011; 31:290-292.
41. Mylonas I: Antibiotic chemotherapy during pregnancy and lactation period: Aspects for consideration. *Arch Gynecol Obstet* 2011; 283:7-18.
42. Crider CS, et al: Antibacterial medication use in pregnancy and risk of birth defects. *Arch Pediatr Adolesc Med* 2009; 163:978-985.
43. Czeizel AE, Rockenbauer M, Olsen J, Sørensen HT: A teratological study of aminoglycoside antibiotic treatment during pregnancy. *Scand J Infect Dis* 2000; 32:309-313.
44. Bar-Oz B, et al: The safety of fluoroquinolones: A meta-analysis. *Eur J Obstet Gynecol Reprod Biol* 2009; 142:75-78.
45. Bar-Oz B, et al: Pregnancy outcome after gestational exposure to the new macrolides: A prospective multicenter observational study. *Eur J Obstet Gynecol Reprod Biol* 2008; 141:31-34.
46. Diav-Citrin O, Shechtman S, Gotteiner T, Arnon J, Ornoy A: Pregnancy outcome after gestational exposure to metronidazole : A prospective controlled cohort study. *Teratology* 2001; 63:186-192.
47. Bruel H, et al: Hemolytic anemia in a newborn after treatment with nitrofurantoin at the end of pregnancy. *Arch Pediatr* 2000; 7:745-747.
48. Czeizel AE, et al: The teratogenic risk of trimethoprim-sulfonamides: A population based case-control study. *Reprod Toxicol* 2001; 15:637-646.
49. Czeizel AE, et al: A teratologic study of aminoglycoside antibiotic treatment during pregnancy. *Scand J Infect Dis* 2000; 32:309-313.
50. Carter C, et al: Antifungals and the risk of selected birth defects. *Am J Obstet Gynecol* 2008;19:191.
51. Czeizel AE, et al: A population-based case-control study of the safety of oral anti-tuberculosis drug treatment during pregnancy. *Int J Tuberc Lung Dis* 2001; 5:564-568.
52. Pasternak B, Hviid A: Use of acyclovir, valacyclovir and famciclovir in the first trimester of pregnancy and the risk of birth defects. *JAMA* 2010; 304:905-906.
53. Workowski KA, Berman S: Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep* 2010; 59:1-112.
54. ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists. No. 82 June 2007. Management of herpes in pregnancy. *Obstet Gynecol* 2007; 109:1489-1498.
55. Centers for Disease Control and Prevention: *Pregnant women and novel influenza A (H1N1) virus: Considerations for clinicians*, June 30, 2009.
56. Greer LG, et al: Maternal and neonatal outcomes after antepartum treatment of influenza with antiviral medications. *Obstet Gynecol* 2010; 115:711-716.
57. Tanaka T, et al: Safety of neuraminidase inhibitors against novel influenza A (H1N1) in pregnancy and breast feeding women. *CMAJ* 2009; 181:55-58.
58. Ahmad N: The vertical transmission of human immunodeficiency virus type 1: Molecular and biological properties of the virus. *Crit Rev Clin Lab Sci* 2005; 42:1-34.
59. Trappe HJ: Emergency therapy of maternal and fetal arrhythmias during pregnancy. *J Emerg Trauma Shock* 2010; 3:153-159.

www.ketabpezeshki.com 66485457-66963820

60. Newstead-Angel J, Gibson PS: Cardiac drug use in pregnancy: Safety, effectiveness and obstetric implications. *Expert Rev Cardiovasc Ther* 2009; 7:1569-1580.
61. Burkart TA, Conti JB: Cardiac arrhythmias during pregnancy. *Curr Treat Options Cardiovasc Med* 2010; 12:457-471.
62. Ghosh N, et al: The acute treatment of maternal supraventricular tachycardias during pregnancy: A review of the literature. *J Obstet Gynaecol Can* 2011; 33:17-23.
63. Strasburger JF, et al: Amiodarone therapy for drug-refractory fetal tachycardia. *Circulation* 2004;109:375-379.
64. Oudjik MA, et al: Treatment of fetal tachycardia with sotalol: Transplacental pharmacokinetics and pharmacodynamics. *J Am Coll Cardiol* 2003; 42:765.
65. Chang J, et al: Pregnancy-related mortality surveillance—United States, 1991-1999. *MMWR Surveill Summ* 2003; 52:1-8.
66. Duley L, Henderson-Smart DJ, Meher S: Drugs for treatment of very high blood pressure during pregnancy. *Cochrane Database Syst Rev* 2006; 3:CD001449.
67. Podymow T, August P: Update on the use of antihypertensive drugs in pregnancy. *Hypertension* 2008; 51:960-969.
68. Ghanem FA, Movahed A: Use of antihypertensive drugs during pregnancy and lactation. *Cardiovasc Ther* 2008; 26:38-49.
69. Cooper WO, et al: Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med* 2006; 354:2443-2451.
70. Magee LA, et al: Risks and benefits of beta-receptor blockers for pregnancy induced hypertension: Overview of the randomized trials. *Eur J Obstet Gynecol Reprod Biol* 2000; 88:15.
71. Weber-Schoendorfer C, et al: The safety of calcium channel blockers during pregnancy: A prospective, multicenter, observational study. *Reprod Toxicol* 2008; 26:24-30.
72. Khan K, et al: Safety concerns for the use of calcium channel blockers in pregnancy for the treatment of spontaneous preterm labour and hypertension: A systematic review and meta-regression analysis. *J Matern Fetal Neonatal Med* 2010; 23:1030-1038.
73. Magee LA, Cham C, Waterman EJ, Ohlsson A, von Dadelszen P: Hydralazine for treatment of severe hypertension in pregnancy: Meta-analysis. *BMJ* 2003; 327:955-960.
74. Miller MA, Bourjeily G: *Managing the critically ill pregnant patient*, Apr 15, 2009. Available at www.chestnet.org/accp.
75. Munnur U, Bandi V, Guntupalli KK: Management principles of the critically ill obstetric patient. *Clin Chest Med* 2011; 32:53-60.
76. Thurlow JA, Kinsella SM: Intrauterine resuscitation: Active management of fetal distress. *Int J Obstet Anesthes* 2002; 11:105-116.
77. Reidy J, Douglas J: Vasopressors in obstetrics. *Anesthesiol Clin* 2008; 26:75-88.
78. Young J, Aresh A: Diabetic medications in pregnancy. *Curr Diabetes Rev* 2009; 5:252-258.
79. Friedrich JA, et al: Meta-analysis: Low dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med* 2005; 142:510-524.
80. Langer L, et al: A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med* 2000; 343:1134.
81. Glueck CJ, et al: Metformin, pre-eclampsia and pregnancy outcomes in women with polycystic ovary syndrome. *Diabet Med* 2004; 21:829-836.
82. Diav-Citrin O, Ornoy A: Teratogen update: Antithyroid drugs. Methimazole, carbimazole and propylthiouracil. *Teratology* 2002; 65:38-44.
83. Yen EH, et al: Acid blocking therapy during pregnancy increases the odds for childhood asthma. *J Allergy Clin Immunol* 2008; 121:794.
84. Gill SK, et al: The safety of proton pump inhibitors (PPIs) in pregnancy: A meta-analysis. *Am J Gastroenterol* 2009; 104:1541-1545.
85. Magee LA, Mazzotta P, Koren G: Evidence-based view of safety and effectiveness of pharmacologic therapy for nausea and vomiting of pregnancy (NVP). *Am J Obstet Gynecol* 2002; 186:5.
86. Holmes LB, et al: The teratogenicity of anticonvulsant drugs. *N Engl J Med* 2001; 344:1132.
87. Meador KJ; NEAD Study Group: In utero antiepileptic drug exposure: Fetal death and malformations. *Neurology* 2006; 67:407.
88. *The Lamotrigine Pregnancy Registry: Final report. 1 September 1992 through 31 March 2010*. Wilmington, NC: GlaxoSmithKline; July 2010.
89. Molgaard-Nielsen D, Hviid A: Newer-generation antiepileptic drugs and the risk of major birth defects. *JAMA* 2011; 305:1996-2002.
90. Evans EW, Lorber KC: Use of 5-HT_1 agonists in pregnancy. *Ann Pharmacother* 2008; 42:543-549.
91. Seto A, Einarson T, Koren G: Pregnancy outcome following first trimester exposure to antihistamines: Meta-analysis. *Am J Perinatol* 1997; 14:119-123.
92. Kallen B: Use of antihistamine drugs in early pregnancy and delivery outcome. *J Matern Fetal Neonatal Med* 2000; 11:146.
93. Tan KS, Thompson NC: Asthma in pregnancy. *Am J Med* 2000; 109:727.
94. Chambers C: The safety of asthma and allergy medication during pregnancy. *Immunol Allergy Clin North Am* 2006; 26:13.
95. U.S. Food and Drug Administration: *Terbutaline: Label change—warnings against use for treatment of preterm labor*, 2011. Available at www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm243843.htm. Accessed February 17, 2011.
96. Blais L, et al: High doses of inhaled corticosteroids during the first trimester of pregnancy and congenital malformations. *J Allergy Immunol* 2009; 124:1229-1234.
97. Hviid A, Molgaard-Nielsen D: Corticosteroid use during pregnancy and risk of orofacial clefts. *CMAJ* 2011; 183:796-804.
98. Bakhireva LN, et al: Safety of leukotriene receptor antagonists in pregnancy. *J Allergy Clin Immunol* 2007; 119:618.

www.ketabpezeshki.com 66485457-66963820

Chapter 181

Labor and Delivery and Their Complications

Shoma Desai and Sean O. Henderson

PERSPECTIVE

Emergency department (ED) births are rare. In most cases, patients in labor are triaged directly to the obstetric suite for urgent management, maintaining a continuum of care with their primary providers. Because some births are precipitous and obstetric resources may not be immediately available, the emergency physician must possess the basic skills for intrapartum management of both normal and abnormal deliveries. In addition, a general knowledge of postpartum care is required in case of the occasional out-of-hospital delivery.[1,2]

Limitations of the Emergency Department

The ED is a suboptimal location for the management of a complicated delivery. The obstetric suite has experienced personnel and appropriate resources, including tocodynamometry, fetal scalp electrodes, intrauterine pressure monitors, vacuum extractors, and forceps. Also, the obstetrician usually has prenatal care information for each patient that helps optimize maternal and fetal outcomes. Such information includes accurate gestational dates, presence of multiple gestations, estimated fetal weights, detailed maternal pelvimetry, placental anatomy, amniocentesis results, maternal blood type and Rh factor, and prior documented obstetric complications. This information allows the obstetrician to anticipate complications of labor and delivery. It is difficult if not impossible to obtain these data in the ED while preparing for imminent delivery. Finally, in certain situations, cesarean section is the best way to ensure successful delivery. This surgical option is not available in the ED except in dire perimortem circumstances.

Epidemiology of Emergency Delivery

In 2004 the perinatal mortality rate in the United States was 6.2 per 1000 live births and fetal deaths (<20 weeks of gestation).[3] Delivery complications and mortalities do occur with greater frequency in the ED, where the perinatal mortality rate is approximately 8 to 10%.[4] There are multiple causes of the "high-risk" ED delivery profile. The ED is often selected by an obstetric population with unexpected complications. Antepartum hemorrhage, premature rupture of membranes (PROM), eclampsia, premature labor, abruptio placentae, precipitous delivery, malpresentation, and umbilical cord emergencies are overrepresented in the ED population.[4]

Psychosocial factors further skew the epidemiology of ED deliveries. Women who present with precipitous deliveries often have had little or no prenatal care.[5] Pregnant women who have drug or alcohol problems or are victims of domestic violence represent a disproportionate number of patients who deliver in the ED. Women who are unaware or in denial of their pregnancies or immigrants without access to other medical care also present to the ED when labor begins.[6-8]

Patient Transfer Considerations

Because of the high risk associated with ED delivery, patients should be transported to a facility that has obstetric and neonatal resources whenever possible. The management of a premature infant may require highly specialized intensive care that is unavailable at many community hospitals. The desire to transfer a woman with an impending high-risk delivery to such a facility should be tempered, however, by clinical and medicolegal judgment.[9,10]

Medicolegal Considerations

Transfer, with resultant en route delivery, can be disastrous for the mother and fetus. Such a transfer also violates federal law. The Consolidated Omnibus Reconciliation Budget Act (COBRA) of 1989 was based on an "inappropriate" obstetric transfer.[11] Federal law has identified labor as a condition unsuitable for transfer because of its unstable nature. Although the intent of this legislation is to protect women from medical abandonment because of financial reasons, COBRA runs the risk of forcing emergency physicians to occasionally perform difficult high-risk deliveries that might have better outcomes with transfer.[12]

Nursery Requirements

For many ED deliveries, labor will have progressed to a point at which tocolysis is contraindicated and delivery is imminent. In general, this is when the mother feels the urge to push or the head is crowning. Whenever possible, a neonatologist or pediatrician should attend high-risk preterm (<36 weeks of gestation) deliveries, and preparations for neonatal resuscitation and high-level nursery care should be initiated (Box 181-1).

NORMAL DELIVERY

Although the epidemiology and high complication rate associated with ED births demand caution, most are normal deliveries. Knowledge of normal labor and delivery mechanics aids safe vaginal delivery and facilitates the identification of complications.

Whenever a woman in the third trimester of pregnancy seeks treatment in the ED, the possibility that she is in labor must be considered. A wide array of nonspecific symptoms may herald the onset of labor. Abdominal pain, back pain, cramping, nausea,

www.ketabpezeshki.com 66485457-66963820

vomiting, urinary urgency, stress incontinence, and anxiety can be symptoms of labor. After 24 weeks' gestation, any medical assessment should include the mother and the fetus because fetal viability becomes established near that time. In addition, given the generally high-risk nature of this population of patients and the abundance of body fluids that the health care provider and newborn are exposed to during delivery, serologic testing for infectious disease may be warranted. With the development of rapid bedside testing technology, human immunodeficiency virus (HIV) infection and hepatitis screening before delivery is indicated in a significant group of patients presenting with active labor.

Distinguishing False from True Labor

Braxton Hicks contractions, or false labor, must be differentiated from true labor. During the third trimester, the uterus develops into a contractile organ. After 30 weeks of gestation, the previously small and uncoordinated contractions of the uterus become more synchronous and may be perceived by the mother. Braxton Hicks contractions do not escalate in frequency or duration, in contrast to the contractions of true labor. By definition, this muscle activity is associated with minimal or no cervical dilation or effacement. Examination should also reveal intact membranes. Care not to rupture the membranes is important to avoid inducing labor prematurely. If the diagnosis remains in doubt, external electrical monitoring of uterine activity can rule out true labor. Any discomfort associated with false labor is usually relieved with mild analgesia, ambulation, or change in activity.

Unlike false labor, true labor is characterized by cyclic uterine contractions of increasing frequency, duration, and strength, culminating in delivery of the fetus and placenta. In contrast to Braxton Hicks contractions, true labor causes cervical dilation to begin, marking the first stage of labor.

Box 181-1 Levels of Nursery Care

Level 1 Nurseries
These nurseries care for infants presumed healthy. In such units, screening and surveillance are primary responsibilities. Rooming-in units are encouraged, with emphasis on support of breast-feeding and assessment of parenting skills.

Level 2 Nurseries
These nurseries care for infants >30 weeks' gestation and >1200 g who require special attention short of circulatory or ventilator support and major surgical procedures. A high percentage of the patients in such nurseries have had obstetric complications (e.g., birth trauma, fetal distress, and obstetric anesthesia).

Level 3 Nurseries
These nurseries are staffed and equipped to care for all newborn infants who are critically ill, regardless of the level of support required. They are regional institutions serving as referral centers for other nurseries and for this reason are often linked with transport services.

Perinatal Centers
A perinatal center provides services to high-risk mothers and to infants requiring level 3 nursery care. Ample data show a higher neonatal survival rate for high-risk pregnancies cared for in such centers.

Bloody Show

Early in pregnancy, the cervix becomes increasingly vascular and develops edema, giving the cervix a boggy texture. The vascularity of the cervix also increases, giving rise to Chadwick's sign (a blue-violet coloration). At the onset of labor, the cervical mucus plug is expelled, resulting in what is called a bloody show. The bleeding associated with the process is slight, and usually only a few dark red spots are noticed. The dark color is due to its venous origin, and it is admixed with the mucous components of the cervical plug. The significance of a bloody show is that it is a fairly reliable indicator of the onset of true labor, specifically stage 1. Bloody show is not a contraindication to vaginal examination for determination of cervical effacement and dilation. If bleeding continues or is of a larger volume, more serious causes should be suspected, such as placenta previa and placental abruption, which are contraindications for a vaginal examination.

Stages of Labor

First Stage of Labor

The first stage of labor is the cervical stage, ending with a completely dilated, fully effaced cervix. It is divided into a latent phase, with slow cervical dilation, and an active phase, with more rapid dilation. The active phase begins once the cervix is dilated 3 cm.[13] In multiparous women, the active phase can progress rapidly into stage 2 of labor (delivery of the fetus). Most women who deliver in the ED arrive while in the active phase of stage 1 or early stage 2 labor (Fig. 181-1).[4]

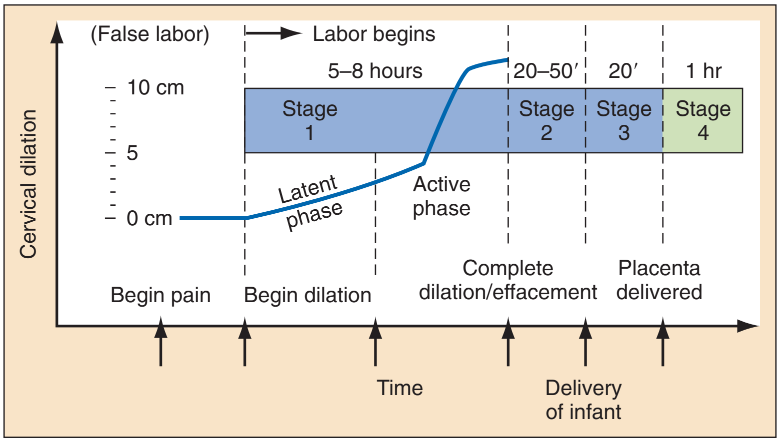


Figure 181-1. Stages of labor and delivery. Stage 1, cervical stage; stage 2, fetal expulsion; stage 3, placental expulsion (20 minutes); stage 4, uterine contraction (1 hour post partum).

www.ketabpezeshki.com 66485457-66963820

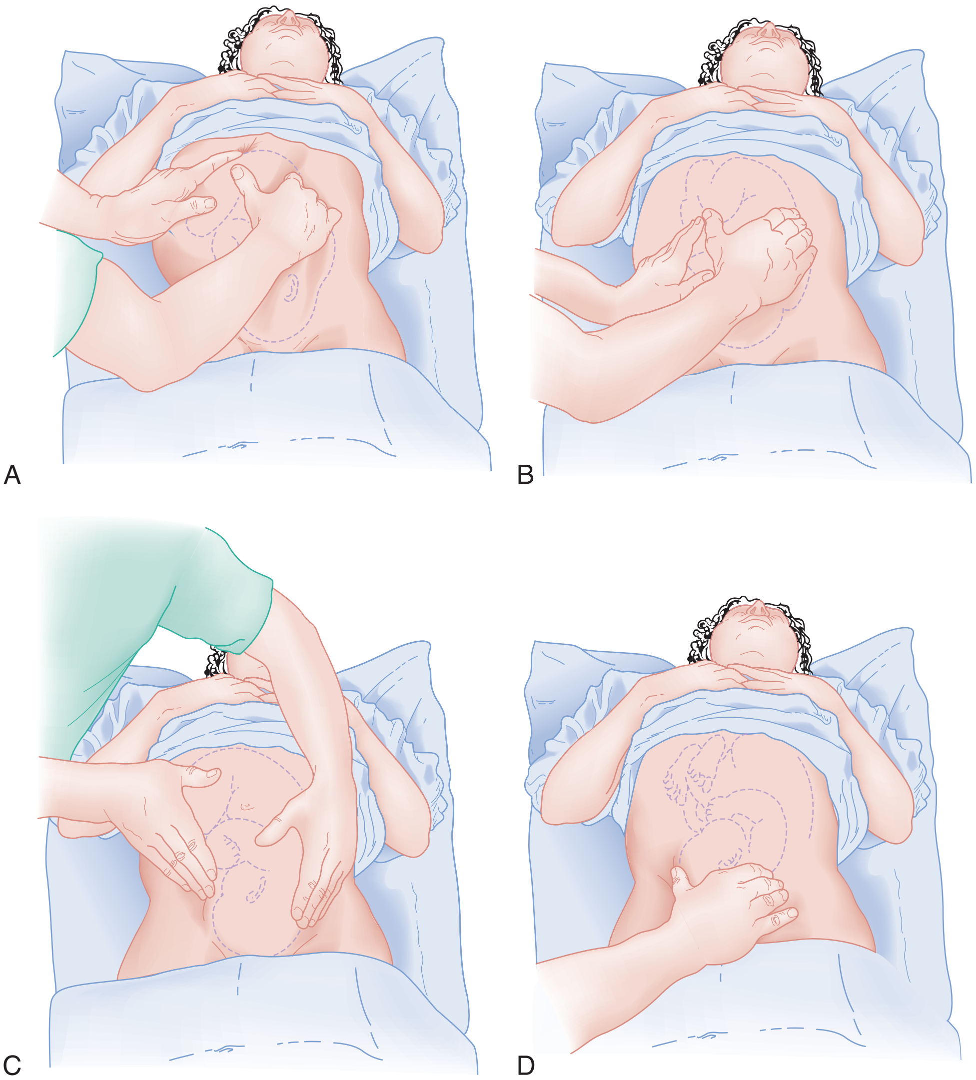


Figure 181-2. Leopold's maneuvers. **A,** The first Leopold maneuver reveals what fetal part occupies the fundus. **B,** The second Leopold maneuver reveals the position of the fetal back. **C,** The third Leopold maneuver reveals what fetal part lies over the pelvic inlet. **D,** The fourth Leopold maneuver reveals the position of the cephalic prominence. (Modified from Willson JR, et al: Obstetrics and Gynecology, 9th ed. St. Louis, Mosby, 1991.)

The duration of the first stage of labor averages 8 hours in nulliparous women and 5 hours in multiparous women. During this time, frequent assessment of fetal well-being is important. For low-risk pregnancies, fetal heart tones should be auscultated approximately every 15 minutes. For higher risk pregnancies, continuous external electrical monitoring may help identify fetal distress, allowing appropriate intervention.[14]

Abdominal examination with Leopold's maneuvers may confirm the lie of the fetus (Fig. 181-2). After labor has begun, particularly during the active phase of stage 1, Leopold's maneuvers are difficult to use. The firm contractions of the uterus prevent the identification of fetal "small parts." Other modalities of assessing the lie, such as ultrasonography, may be necessary if presentation remains in question.[15]

Maternal examination also provides a rough guide to gestational age. At 20 weeks' gestation, the uterine fundus reaches the umbilicus. Approximately 1 cm of fundal height is added per week of gestation until 36 weeks. At that time, the fundal height decreases as the fetus "drops" into the pelvis (Fig. 181-3). These estimates help establish gestational age rapidly.

The accurate determination of the stage of labor depends on examination of the cervix. A sterile approach with use of sterile gloves, a sterile speculum, and povidone-iodine (Betadine) solution is indicated to prevent ascending infection, such as chorioamnionitis. On pelvic examination, the clinician should determine the following:

Effacement refers to the thickness of the cervix. A paper-thin cervix is 100% effaced.

Dilation indicates the diameter of the cervical opening in centimeters. Complete, or maximum, dilation is 10 cm.

Position describes the relationship of the fetal presenting part to the birth canal. The most common position of the head is occiput anterior.

Station indicates the relationship of the presenting fetal part to the maternal ischial spines (Fig. 181-4).

Presentation specifies the anatomic part of the fetus leading through the birth canal.

In 95% of all labors, the presenting part is the occiput, or vertex. On digital examination, a smooth surface with 360 degrees of firm bony contours and palpable suture lines is noted. Palpation of the suture lines and the fontanels where they join allows the examiner to determine the direction the fetus is facing. Three sutures radiate from the posterior fontanel, and four radiate from the anterior fontanel (Fig. 181-5). The lateral margins are examined carefully

www.ketabpezeshki.com 66485457-66963820

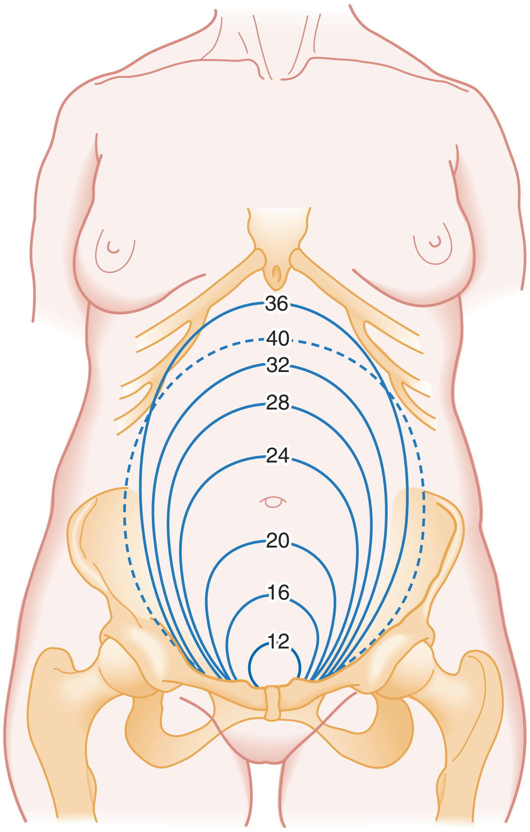


Figure 181-3. Height of fundus by weeks of normal gestation with a single fetus. Dotted line indicates height after lightening. (Modified from Barkaukas V, et al: Health and Physical Assessment. St. Louis: Mosby; 1994.)

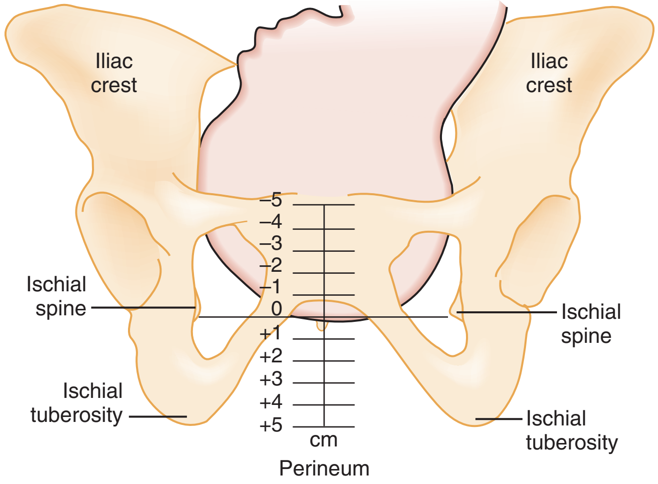


Figure 181-4. Fetal stations. The level of the ischial spines is considered 0 station. The silhouette of the infant's head is shown approaching station +1. (Courtesy Ross Laboratories, Columbus, Ohio.)

for fingers or facial parts that indicate compound or brow presentations.

When the clinician suspects rupture of membranes, a sterile speculum examination is performed. This may reveal pooling of amniotic fluid. Two tests to confirm the presence of amniotic fluid include a fernlike pattern when the fluid is allowed to dry on a microscope slide and the use of Nitrazine paper, which should turn blue, indicating an alkaline amniotic fluid ($pH > 6$). Although vaginal blood, cervical mucus, semen, and infection can interfere

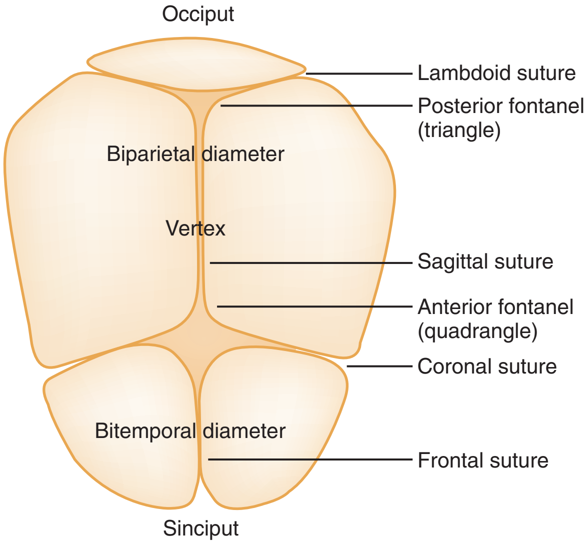


Figure 181-5. Bone landmarks of the fetal skull. (Modified from Willson JR, et al: Obstetrics and Gynecology, 9th ed. St. Louis, Mosby, 1991.)

with results, sensitivities of both Nitrazine paper and ferning in detection of amniotic fluid are nearly 90%.[16]

Of note, if vaginal bleeding is evident, both digital and speculum examination of the pelvis should be deferred until an ultrasound study can be obtained to rule out placenta previa.

Second Stage of Labor

The second stage of labor is characterized by a fully dilated cervix and accompanied by the urge to bear down and push with each uterine contraction. The fetal station is advanced to +3, with crowning of the presenting part as expulsion begins. Stage 2 uterine contractions may last 1 or 2 minutes and recur after a resting phase of less than 1 minute. The median duration of this stage is 50 minutes in nulliparous women and 20 minutes in multiparous women. More rapid progression through stage 2 should be anticipated for low-birth-weight premature infants. A prolonged second stage of labor is defined as more than 3 hours in nulliparous women if regional anesthesia is administered, more than 2 hours in nulliparous women without anesthesia or in multiparous women with regional anesthesia, and more than 1 hour in multiparous women without regional anesthesia.[17] Prolonged second stage of labor is associated with an increase in maternal complications, including postpartum hemorrhage, infection, and severe vaginal lacerations.[18]

Antenatal Fetal Assessment

The assessment of a woman in the third trimester includes an assessment of fetal well-being. After 24 weeks' gestation, the fetal condition affects clinical decision-making. During labor and delivery, the identification of fetal distress and appropriate intervention can reduce fetal morbidity and mortality.

There are currently three methods of assessing a fetus in utero. Clinical monitoring, electrical monitoring, and ultrasonography all have a role in the assessment of the fetus. External electrical monitoring and ultrasonography merit consideration for use in the care of women laboring in the ED. The machinery for both technologies is portable and easy to use and can provide real-time information helpful for diagnosis of fetal distress and assistance with intrapartum decision-making.

Electronic Fetal Monitoring. Intrapartum fetal assessment by electronic fetal monitoring is most useful during stage 1 of labor.

www.ketabpezeshki.com 66485457-66963820

Electronic fetal monitoring confirms true labor and may help diagnose fetal distress. Tracings of fetal heart rate and uterine activity provide information that in combination with clinical data can presage fetal distress due to hypoxia and provide a window for intervention.

Uterine activity is measured transabdominally by a pressure transducer, creating a recording of the contraction frequency. Because the measurements are indirect, the strength of the contractions correlates poorly with the tracing. The tracings are position and placement sensitive. Documentation of organized cyclic uterine contractions confirms the onset of labor and rules out Braxton Hicks contractions that are too disorganized to be registered in this manner. Premature onset of labor can also be diagnosed. Finally, this type of external electrical monitoring may be used to determine the efficacy of administered tocolytic agents.

Fetal heart rate tracings have several components that can be assessed: baseline heart rate, variability, accelerations, decelerations, and diagnostic patterns. Baseline heart rate, by definition, is the average fetal heart rate during a 10-minute period (in the absence of a uterine contraction) and is the most important aspect of fetal heart rate monitoring. Fetal bradycardia is defined as a baseline rate of less than 110 beats per minute; fetal tachycardia is defined as a baseline rate of more than 160 beats per minute.[19]

Variability can be instantaneous (beat to beat) or long term during intervals of 1 minute or more. Both types of variability are indicators of fetal well-being. Accelerations of heart rate are an important component of long-term variability. Accelerations occur during fetal movement and reflect an alert, mobile fetus. Brief periods of umbilical cord compression also can cause accelerations by decreasing the venous return and reflexively generating fetal tachycardia. Meanwhile, decreased variability may indicate fetal acidemia and hypoxemia or may be a side effect of a wide array of drugs. Analgesics, sedative-hypnotics, phenothiazines, and alcohol have been reported to cause decreased variability.

Decelerations in fetal heart rate are more complicated, and their interpretation should be integrated with the clinical situation. There are three types of deceleration: variable, early, and late (Fig. 181-6). These terms refer to the timing of the deceleration relative to the uterine contraction.

Variable and early decelerations are common. Present on more than 50% of all tracings, these heart rate changes can represent physiologic reflexes associated with head compression in the birth canal or intermittent cord compression. Variable decelerations that are persistent and repetitive usually indicate repeated episodes of umbilical cord compression. The resultant hypoxia and acidosis may cause fetal distress. Attempts to shift maternal and fetal weight off the umbilical cord by changing position are indicated. If these variable decelerations continue, the situation calls for efforts to hasten the delivery or, if obstetric backup becomes available, to perform an emergency cesarean section.

Late decelerations are more serious and most often indicate uteroplacental insufficiency. The tracing contours are generally smooth, with the heart rate nadir occurring well after maximal uterine contraction (typically 30 seconds or more afterward).[19] The lag, slope, and magnitude of late decelerations correlate with increasing fetal hypoxia. Late decelerations are particularly ominous in association with poor variability, nonreactivity, and baseline bradycardia. When these findings are present, immediate obstetric consultation for delivery to prevent further hypoxia is indicated. The need for newborn resuscitation should be anticipated and preparation for critical care established for these deliveries. Overall, 30% of infants with late decelerations have good outcomes. The remaining 70% have suboptimal outcomes related to either the underlying pathologic condition or hypoxia.

Finally, the clinician should be aware of the significance of sinusoidal tracings. Tracings of this type have low baseline heart rates and little beat-to-beat variability. The sinusoidal tracing is an ominous finding that is often premorbid. The differential diagnosis includes erythroblastosis fetalis, placental abruption, fetal hemorrhage (trauma), and amnionitis.

Ultrasonography. Ultrasonographic techniques have wide application in obstetric care. In the third trimester or during labor, ultrasonography can provide crucial information pertaining to impending delivery. When a technician and radiologist are available, the gestational age, biophysical profile, and amniotic fluid index as well as a survey of fetal and placental anatomy may be discerned (Table 181-1). The parameters of immediate interest in the ED are fetal viability (specifically in utero gestation and fetal heart rate), lie, and presentation. Ultrasonography may also reveal multiple gestations, allowing preparation and early communication with other specialists (from obstetrics, neonatology, and anesthesia). In 1991 the American College of Obstetricians and Gynecologists (ACOG) published recommendations regarding the indications for ultrasonography in the third trimester (Box 181-2). A 2- to 5-MHz transducer is appropriate for all bedside transabdominal sonographic assessments. Transvaginal ultrasonography is relatively contraindicated in the peripartum period, particularly in the cases of PROM and placenta previa.[20]

Delivery

As stage 2 of labor progresses, preparation for delivery should be under way. A radiant warmer should be available and heated. Neonatal resuscitation adjuncts, such as a towel, scissors, umbilical clamps, bulb suction, airway management equipment (oxygen, bag-mask device with appropriate-sized masks, and endotracheal intubation and suctioning equipment for meconium), and equipment to achieve vascular access, should be available. Most deliveries require only basic equipment to cut and clamp the umbilical cord, to suction the mouth and nose, and to dry and stimulate the infant. A nurse should be at the bedside to coach and to provide reassurance to the mother.

The mother is placed in the dorsal lithotomy position and prepared for delivery. The Sims position, or left lateral position with knees drawn toward the mother's chest and back to the physician, is also an acceptable position for delivery. The vulva and perineum are cleared and gently scrubbed with sterile water or saline, directing all mucoid debris and feces away from the introitus. A repeated sterile examination to assess labor progression and to confirm presentation may be performed. Firm digital stretching of the perineum, particularly posteriorly, may prevent tears and lacerations later in delivery.

Controlled, coordinated expulsion with coaching to sustain each push aids with crowning and delivery of the head. When the fetus is crowning, care is exercised to have the delivery occur in a slow, controlled manner. Precipitous delivery is more likely to cause maternal injuries, such as perineal, rectal, urethral, labial, vaginal, and uterine lacerations, and fetal injuries.[21]

The most vulnerable moment is when the fetal head begins to stretch and distend the perineum. Instructing the mother to pant and not push slows the passage of the head and the shoulders as indicated. Calm communication between the physician and the mother is the best way to maintain control of the delivery. With a controlled delivery, routine performance of an episiotomy is not recommended.

One described technique to potentially decrease the rate of maternal injury is the modified Ritgen maneuver.[22] In the modified Ritgen maneuver, a towel-draped, gloved hand is used to stretch the perineum and gently exert pressure on the chin of the fetus. The second hand puts pressure on the occiput superiorly, guiding the head into slight extension. When the head is at the perineum, this slight extension of the head promotes delivery by positioning the head so that its smallest diameter passes through the pelvic outlet and perineum.

www.ketabpezeshki.com 66485457-66963820

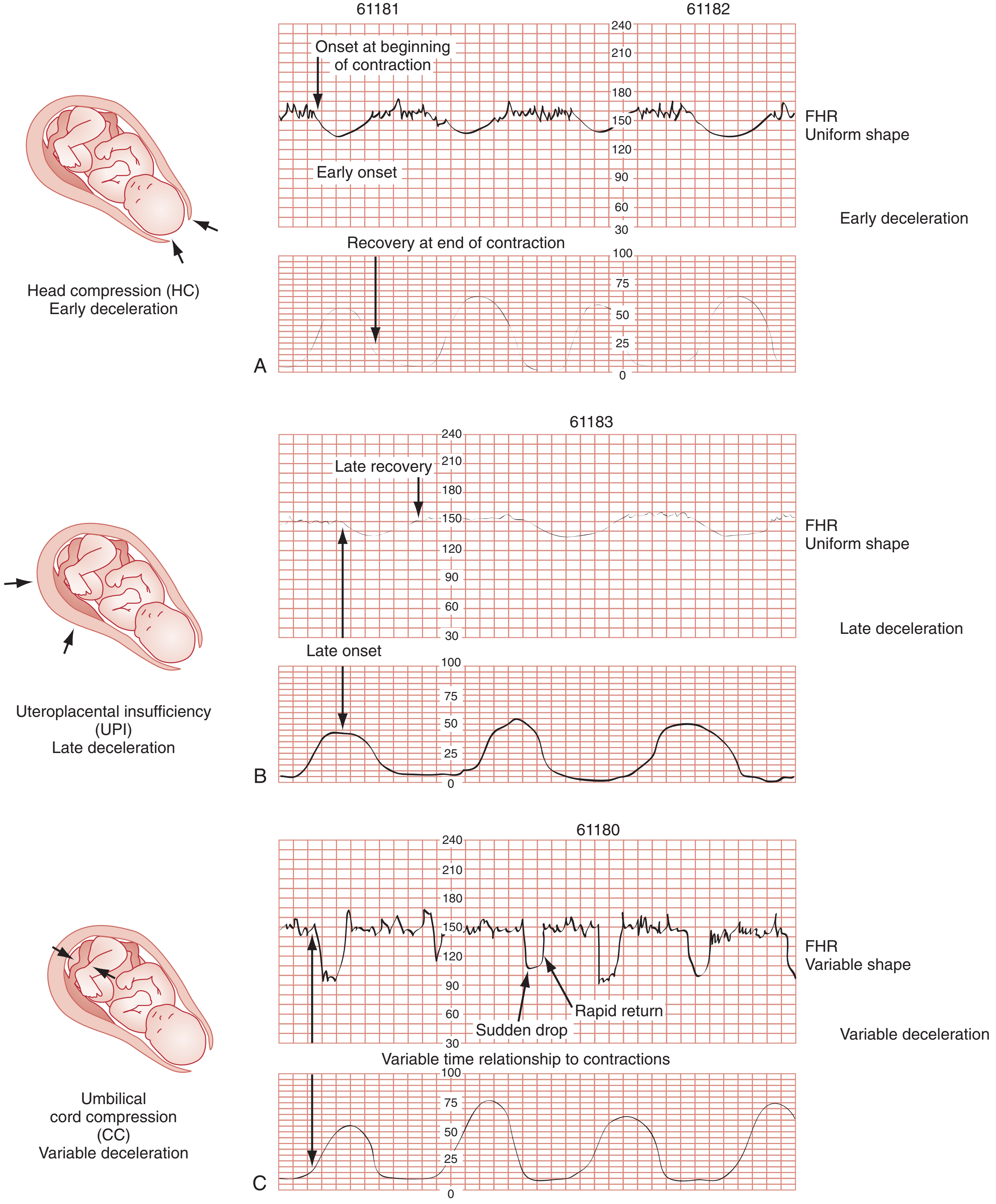


Figure 181-6. Deceleration patterns of the fetal heart rate (FHR). **A,** Early deceleration caused by head compression. **B,** Late deceleration caused by uteroplacental insufficiency. **C,** Variable deceleration caused by cord compression. (Modified from Lowdermilk DL, et al: Maternity and Women's Health Care, 6th ed. St. Louis, Mosby, 1997.)

www.ketabpezeshki.com 66485457-66963820

Table 181-1 Biophysical Profile: 30 Minutes of Ultrasonographic Observation

ELEMENT ASSESSED	NORMAL SCORE = 2	ABNORMAL SCORE = 0
Fetal heart rate reactivity	2 accelerations >15 beats/minute for >15 seconds	<2 accelerations
Amniotic fluid index	1 pocket >1 cm in orthogonal planes	No large pockets
Fetal muscle tone	1 episode of active flexion-extension with full return to flexed posture	<1 episode or slow, incomplete actions
Body movements	3 discrete moves	≤2
Breathing motions	1 episode of fetal breathing of at least 60 seconds in duration during 30 minutes of observation	No breathing activity *or* The absence of 1 episode of fetal breathing of at least 60 seconds in duration during 30 minutes of observation

Box 181-2 Third-Trimester Ultrasonography: Possible Indications

Determine number of fetuses
Establish fetal presentation
Identify fetal heart motion
Locate placenta
Measure amniotic fluid
Determine gestational age
Survey fetal anatomy
Diagnose cord prolapse
Diagnose cause of third-trimester bleeding
Rule out placental abruption

After the head is delivered, the physician allows the head to rotate toward the maternal thigh and clears the fetal face and airway. Coordination with the mother is important to prevent uncontrolled fetal expulsion.

Next, the shoulders, usually anterior shoulder first, clear the perineum. The shoulders often deliver spontaneously, with little effort by the physician. First, gentle downward traction on the head promotes delivery of the anterior shoulder. A subsequent upward motion pulls the posterior shoulder through the pelvic outlet, minimizing maternal trauma. If delay occurs in delivery of the shoulders, the potential for shoulder dystocia should be considered.

As the infant clears the perineum, attention focuses on the umbilical cord. The infant should be kept low or at the level of the perineum to promote blood flow into the infant from the placenta. The cord is clamped and cut. Clamps should be placed 4 or 5 cm apart, with the proximal clamp 10 cm from the infant's abdomen. An adequate umbilical stump is important for venous access if the child requires resuscitation. Suctioning of the nose and mouth at this time may reduce secretions that can cause increased airway resistance.

The infant is now clear of the mother and can be wrapped in towels and moved to the warmer. Gentle drying with a towel and suctioning usually provide adequate respiratory stimulation. If not, flicking the soles of the feet and rubbing the back are other modalities. Apgar scores at 1, 5, and 10 minutes after birth should be documented.

Episiotomy. Previously, the need for episiotomy in normal deliveries was an area of controversy. The original potential benefit of episiotomy included the substitution of a straight surgical incision for a ragged, uncontrolled traumatic laceration. Theoretically, the surgical approach decreased the incidence of severe rectovaginal tears. This rationale led to widespread routine episiotomy, with a medial incision used in the United States and a mediolateral incision used in the Commonwealth countries.

Recent literature has shown that both types of incisions increase maternal morbidity, and they are no longer recommended for uncomplicated deliveries. Women receiving episiotomies have been shown to have a higher incidence of perineal trauma and maternal blood loss during delivery and more pelvic pain, sexual dysfunction, and urinary incontinence in the postpartum period.[23]

Episiotomy should be performed only for specific indications, such as shoulder dystocia or breech delivery. When the decision is made to use an episiotomy, the procedure should be done before excessive stretching of the perineal muscles occurs but near the time of delivery to avoid excessive bleeding. Common practice is to cut the episiotomy when the head is visible during a contraction and the introitus opens to a diameter of 3 or 4 cm. Most authors currently recommend a mediolateral incision to avoid perineal tears and rectal involvement; this is particularly true for a complicated delivery in which lacerations extending the surgical incision are likely (Fig. 181-7).

Table 181-2 summarizes some of the adjuncts used in normal labor and delivery, with recommendations for their use in the high-risk setting of an ED delivery.

Third Stage of Labor

The third stage of labor involves the delivery of the placenta and is a time of observation of the patient with frequent checks of the tone and height of the uterine fundus. Signs of placental separation include the following:

The uterus becomes firmer and rises.
The umbilical cord lengthens 5 to 10 cm.
There is a sudden gush of blood.[24]

These signs usually occur within 5 to 10 minutes of the delivery of the infant but may extend to 30 minutes. The risk of postpartum hemorrhage increases beyond 18 minutes and is in fact up to six times more likely after 30 minutes.[25] Although the placenta may be delivered expectantly, active management reduces the length of the third stage of labor and thereby decreases the risk of postpartum hemorrhage. Active management includes the administration of uterotonics, gentle traction of the clamped umbilical cord with mild pressure applied above the symphysis pubis, and uterine massage after delivery.[26] Be aware that any attempt to deliver the placenta before it separates is contraindicated.

Examination of the placenta and umbilical cord is an essential part of the delivery process. Abnormalities of the cord should be noted at this time. Also, a segment of the umbilical cord should be kept available as a source of cord blood.

Normally a three-vessel structure, the umbilical cord is filled with a connective tissue known as Wharton's jelly and is approximately 50 to 60 cm long and 12 mm in diameter. Normal architecture places the two umbilical arteries on either side of the single umbilical vein. A two-vessel cord (one umbilical artery) occurs in 1 of 500 deliveries, is more common in African Americans, and is a result of aplasia or atrophy. Approximately 30% of two-vessel cord infants have congenital defects. An association also exists between fetal structural anomalies and placental vascular occlusion or thrombosis.[27]

The placenta should also be examined for abnormalities. Clots adherent to the uterine aspect may indicate placental abruption. Accessory lobes (succenturiate placenta if completely separate) and abnormal cord insertion are common abnormalities. The umbilical cord and placenta routinely should be held for pathologic review.[28] The discovery of an incomplete placenta or

www.ketabpezeshki.com 66485457-66963820

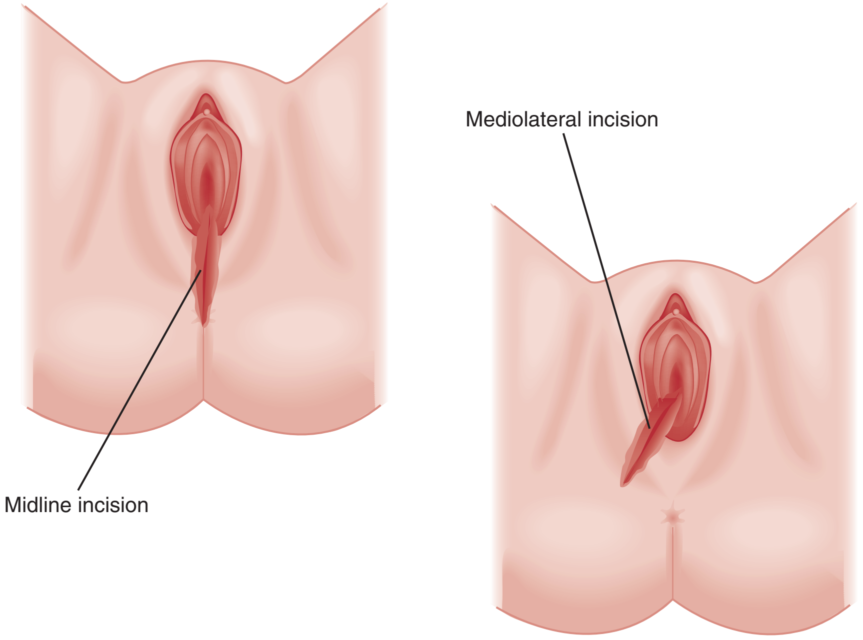


Figure 181-7. A mediolateral episiotomy incision is preferred to a strictly midline incision. (Redrawn from www.aurorahealthcare.org/healthgate/images/exh44028a_ma.jpg.)

Table 181-2 Risk-Benefit Analysis of Routine Adjuncts to Normal Labor and Delivery

PRACTICE OR PROCEDURE	RISK	BENEFIT	UTILITY IN THE EMERGENCY DEPARTMENT
Nothing by mouth status and intravenous hydration	Fluid overload, osmolar and acid-base disturbances	Venous access, decreased risk of aspiration	Yes
Enemas	Time-consuming	Reduced pain caused by constipation	Minimal or none
Pubic shaving	Infections and irritation	None	None
Nitrous oxide analgesia	Incomplete pain control	Self-administered, minimal fetal side effects, noninvasive	Yes
Narcotic analgesia	Neonatal depression	Excellent pain control	As needed
Regional anesthesia	Technically difficult, incomplete pain control	Excellent pain control when technically successful (paracervical or pudendal block)	Variable (operator dependent)
Electronic fetal monitoring	Increased incidence of surgical intervention	Early diagnosis of fetal distress	Variable (operator dependent)
Ultrasonography	None	Rapid augmentation of database	Yes (operator dependent)
Amniotomy	Augmented labor, prolapsed umbilical cord	None	No
Episiotomy	Poor maternal outcomes	None for uncomplicated delivery	No
Ritgen maneuver	None	Decreased birth trauma	Yes

membranes should alert the emergency physician to the possibility of postpartum complications and should be documented.

Fourth Stage of Labor

The fourth stage of labor refers to the first hour after delivery of the placenta and is a critical period because postpartum hemorrhage is most likely to occur during this time. Thus careful examination and repair of any vaginal lacerations should be performed. The cervix and vaginal fornices are visually inspected to avoid missing deep lacerations as a result of delivery.

At this point, oxytocin is infused to promote contraction of the uterus and to control hemorrhage. The uterus is evaluated frequently for tone and massaged transabdominally if any sign of relaxation exists. Oxytocin should not be given before delivery of the placenta because this may result in the trapping of placental fragments or may hinder the delivery of an undetected twin.

SPECIFIC DISORDERS

Third-Trimester Complications Associated with Delivery

Obstetric problems in the third trimester often result in the initiation of labor. Premature labor, PROM, and third-trimester bleeding are relatively common complications. The fundamental

www.ketabpezeshki.com 66485457-66963820

Box 181-3 Factors Linked to Preterm Labor

Demographic and Psychosocial
Extremes of age (>40 years, teenagers)
Lower socioeconomic status
Tobacco use
Cocaine abuse
Prolonged standing (occupation)
Psychosocial stressors

Reproductive and Gynecologic
Prior preterm delivery
Diethylstilbestrol exposure
Multiple gestations
Anatomic endometrial cavity anomalies
Cervical incompetence
Low pregnancy weight gain
First-trimester vaginal bleeding
Placental abruption or previa

Surgical
Prior reproductive organ surgery
Prior paraendometrial surgery other than genitourinary (appendectomy)

Infectious
Urinary tract infections
Nonuterine infections
Genital tract infections (bacterial vaginosis)

Box 181-4 Commonly Used Tocolytic Agents

Magnesium sulfate
- 4-6 g IV bolus over 20 minutes
- 2-4 g/hr IV infusion

Terbutaline
- 5-10 mg PO q4-6h
- 0.25 mg SC q20min
- 10-80 μg/min IV

Ritodrine*
- 10 mg PO q2-4h
- 10 mg IM q3-8h
- 0.05-0.35 mg/min IV infusion

Isoxsuprine
- 20 mg PO q6h
- 0.2-0.5 mg/min IV infusion

*Ritodrine has been discontinued in the United States.

question to be addressed in these settings is whether the fetus would fare better in utero or delivered.

Premature Labor

Perspective. Premature or preterm labor and fetal immaturity are the leading causes of neonatal mortality. Preterm labor is defined as uterine contractions with cervical changes before 37 weeks of gestation. Women with premature labor are a heterogeneous group. Many underlying conditions result in preterm labor, which accounts for 9.6% of all pregnancies but 70% of all perinatal mortality.[29] Factors linked to this problem include substance abuse, history of preterm delivery, multiple gestations, placental anomalies, infections, and lifestyle or psychosocial stressors[30] (Box 181-3). The unexpected nature of premature labor often results in an ED visit. When delivery is not imminent, the patient can be moved to the obstetrics unit for further care.

Clinical Features. The diagnosis of preterm labor requires the identification of uterine activity and cervical changes before 37 weeks of gestation. Early maternal signs and symptoms include an increase or change in vaginal discharge, pain resulting from uterine contractions (sometimes perceived as low back pain), pelvic pressure, vaginal bleeding (usually bloody show), and fluid leak.

Diagnostic Strategies. If uterine contractions and cervical changes are present and the estimated fetal weight on ultrasonography is less than 2500 g, the diagnosis of premature labor is likely. The differentiation of false labor (Braxton Hicks contractions) from true labor is best done by electrical monitoring. Ultrasonography may aid in the diagnosis because fetal breathing movements make the diagnosis of false labor unlikely. The initial evaluation of a woman with possible preterm labor includes urinalysis, complete blood count, and pelvic ultrasonography. If delivery is not imminent, these studies can be performed in the ED or obstetrics area, whichever would provide the best monitoring. When possible, these patients should be transferred to a perinatal center with an associated intensive care unit.

Management. A viable fetus and healthy mother are indications for medical management directed toward the prolongation of gestation. Preterm labor should not be postponed with medical management in the cases of fetal compromise, major congenital anomalies, intrauterine infection, placental abruption, eclampsia, significant cervical dilation, or, most important, PROM.[31]

The treatment of preterm labor involves multiple modalities. Tocolytics and fetal maturation therapy combined with bed rest and hydration are used in the hope of prolonging pregnancy (Box 181-4). These patients optimally should be transferred to an appropriate center before delivery whenever possible because medical management fails in more than 25% of preterm patients in whom it is attempted.[32]

Tocolysis

The two classically used tocolytics are magnesium sulfate and beta-mimetic drugs. Other medications that have been shown to be effective include prostaglandin synthetase inhibitors (nonsteroidal anti-inflammatory drugs [NSAIDs]) and calcium channel blockers.[33] When they are indicated and in coordination with an obstetric consultant, tocolytics initiated in the ED may arrest premature labor, preventing imminent delivery in 75 to 80% of patients for 48 to 72 hours.[29]

Magnesium Sulfate

Magnesium sulfate competitively inhibits calcium uptake into smooth muscle and allows relaxation. The efficacy of magnesium sulfate as a tocolytic agent has not been clearly established.[34] Women treated with magnesium require monitoring. Magnesium produces respiratory and neurologic depression at elevated levels, exacerbated by renal insufficiency. Pulmonary edema and cardiac dysrhythmias have also been reported.[29] These effects can be reversed rapidly by the administration of calcium-containing solutions (i.e., 1 g of 10% calcium gluconate solution) (Table 181-3).

Beta-Mimetics

Beta-mimetics (ritodrine and terbutaline) cause smooth muscle relaxation by activating enzymes that bind calcium to the sarcoplasmic reticulum. This effect is mediated by $beta_2$ receptors that increase cyclic adenosine monophosphate concentrations in the myometrium. The beta-mimetic is titrated to effect because the dosage needed to eliminate uterine activity varies. In one meta-analysis, beta-mimetics and magnesium sulfate had similar efficacy in elimination of contractions.[33]

Despite evidence that beta-mimetics are effective tocolytics, their side effect profile is somewhat prohibitive for their selection

www.ketabpezeshki.com 66485457-66963820

Table 181-3 Drug and Labor Interactions

DRUG	EFFECT ON LABOR
Barbiturates	Can stop labor in anesthetic doses
Alcohol	Decreases oxytocin release, smooth muscle relaxant
Cocaine	Increased prematurity, placental infarction
Caffeine or aminophylline	Increased duration of labor
Narcotics	Increased latent phase, slow dilation (minimal effect once in active labor)
Atropine, scopolamine	Lower uterine segment relaxation, decreased frequency of contractions
Halothane	Strong inhibition of labor
IV nitroglycerin	Profound uterine relaxation

Box 181-5 Contraindications to Tocolysis

Absolute
Acute vaginal bleeding
Fetal distress (not tachycardia alone)
Lethal fetal anomaly
Chorioamnionitis
Preeclampsia or eclampsia
Sepsis
Disseminated intravascular coagulopathy

Relative
Chronic hypertension
Cardiopulmonary disease
Stable placenta previa
Cervical dilation >5 cm
Placental abruption

over other options. Maternal pulmonary edema, myocardial ischemia, and cardiac dysrhythmia are the main adverse effects of high-dose beta-mimetics. Pulmonary edema is more likely to occur in mothers with preexisting cardiac disease, multiple gestation, and maternal infection. Pulmonary edema is caused by high-output failure and tends to occur when there is sustained maternal tachycardia of more than 120 beats/minute. Beta-mimetics should be gradually titrated according to uterine activity and maternal heart rate.[30]

Other beta-mimetic side effects include gluconeogenesis and glycogenolysis, which can be a problem for diabetic mothers. Surveillance of the urine for glucose and ketones is recommended. Fetal heart stimulation can result in both fetal dysrhythmia and cardiac hypertrophy. Also, some studies have shown an association between beta-mimetics and an increased incidence of fetal intraventricular hemorrhage.[35]

NSAIDs

The prostaglandin synthetase inhibitors, specifically indomethacin and sulindac, have been shown to be as effective as magnesium and the beta-mimetics in multiple trials. However, in the fetus, pulmonary hypertension, ductus arteriosus constriction, renal insufficiency, necrotizing enterocolitis, and intraventricular hemorrhage have been reported with NSAID use. Potential maternal side effects include a prolonged bleeding time and renal insufficiency.[33,36]

Calcium Channel Blockers

Calcium channel blockers have also been used as tocolytics with success, reducing muscle contractility by their effect on transmembrane calcium influx. Nifedipine or nicardipine may be given.[37] Equal in efficacy to ritodrine and magnesium sulfate, calcium channel blockers have been shown to have relatively good maternal and fetal side effect profiles.[30]

Aggressive titratable tocolytics are best for the initial 24 to 48 hours of preterm labor. After uterine contractions have been stopped, the patient can usually be maintained with oral agents, although the benefits of maintenance tocolysis, studied to date primarily with beta-mimetics and magnesium, have yet to be shown.[33] It is important to review the contraindications to tocolytics before initiation of these therapies (Box 181-5). Any patient receiving tocolytics should be externally monitored (electrically) for signs of fetal distress.

Premature Rupture of Membranes

Clinical Features. PROM, also known as amniorrhexis, is defined as rupture of the amniotic and chorionic membranes before the onset of labor. It affects 3% of all gestations.[38] During pregnancy, the chorionic and amniotic membranes protect the fetus from infection and provide an environment that allows fetal growth and movement. The amniotic fluid is constantly exchanged by fetal swallowing and urination and umbilical cord transfer. The fetal airway also contains a secreted fluid that allows fetal breathing movements, promoting fetal respiratory development. This fluid is produced at 5 mL/kg/hr at term gestation and is resorbed rapidly by the pulmonary lymphatics, blood vessels, and upper airway at birth.

The word *premature* in PROM refers to rupture before labor, not to fetal prematurity. In 8% of PROM cases, the fetus is at or near term, and PROM may result in normal labor. When PROM occurs before 37 weeks, it is called preterm PROM and is associated with significant fetal morbidity and mortality. PROM is the inciting event in one third of all preterm deliveries.[39]

After the membranes rupture, the period from latency to the onset of labor varies. Longer latent periods are common earlier in pregnancy, and the latency shortens as gestational age increases. At term, labor is a desirable result of PROM, but with fetal immaturity labor is a problem because delivery would result in fetal complications, such as hyaline membrane disease.

Diagnostic Strategies. The diagnosis of PROM usually can be established by history and physical examination. The patient usually describes a spontaneous gush of watery fluid followed by a mild persistent seepage. In most cases, the patient suggests the diagnosis and usually is correct. Urinary incontinence or excess vaginal or cervical secretions are occasionally confused with PROM.

Examination of women with potential PROM is performed under sterile conditions to prevent ascending infection. Direct digital examination of the cervix is avoided. The incidence of infection has been shown to be proportional to the number of examinations. The identification of amniotic fluid was previously discussed. Table 181-4 summarizes the bedside testing modalities available to confirm the diagnosis of PROM. Visualization of the cervix for prolapsed cord or abnormal fetal presentation (prolapse of a small part) is performed during the evaluation for effacement and dilation. Culture specimens for group B streptococci, *Chlamydia trachomatis,* and *Neisseria gonorrhoeae* should be obtained.[39]

Management. When the diagnosis of PROM is established, management depends on several factors: the gestational age and fetal maturity, the presence of active labor, the presence or absence of infection, the presence of placental abruption, and the degree of fetal well-being or distress.[39] Fetal heart rate monitoring, obstetric consultation, and admission are indicated.

www.ketabpezeshki.com 66485457-66963820

Table 181-4 Bedside Testing for Premature Rupture of Membranes

METHOD	RESULT
Nitrazine	Amniotic fluid (pH >6.5) will turn nitrazine paper blue; normal vaginal secretions (pH <5.5) will leave nitrazine paper yellow
Ferning	Amniotic fluid crystallizes
Smear combustion	Amniotic fluid, when flamed, turns white and crystallizes Vaginal secretions caramelize and turn brown

Gestational age may be well known by menstrual history and previous ultrasonographic scans. In the absence of such data, immediate ultrasonography provides an estimated gestational age quickly. Fetal maturity is a more complex determination. Beyond 36 weeks of gestation, fetal pulmonary maturity is likely. If the gestational age is less than 36 weeks, testing of the amniotic fluid for the lecithin-to-sphingomyelin ratio or for phosphatidylglycerol can establish maturity. Fluid pooling in the posterior vaginal vault can be used for this purpose.

In the immature fetus (24-31 weeks of gestation), administration of corticosteroids can accelerate pulmonary maturation and, some studies suggest, also decrease rates of intraventricular hemorrhage and necrotizing enterocolitis.[40] The benefit of this strategy has been shown with preterm PROM; however, this therapy is less well documented for PROM. In PROM, treatment with steroids seems to decrease the incidence and severity of hyaline membrane disease but may increase the risk of maternal infectious complications. Rupture of the membranes also stimulates fetal lung maturation, making it more difficult to establish a treatment benefit in PROM compared with preterm PROM. Therefore, patients with PROM between 31 and 33 weeks' gestation are usually managed expectantly (unless fetal pulmonary maturity can be confirmed); those at or beyond 34 weeks of gestation are generally delivered.[40] When gestational age is less than 26 weeks, the latent interval to delivery is often 1 week. Tocolytics seem an obvious choice, but their use is controversial. When tocolytics are used, the goal is to temporize, allowing time for both corticosteroid and antibiotic therapy to take effect. These treatment decisions should be coordinated with the receiving obstetrician.

All patients with PROM should be assessed for intra-amniotic infection. Infectious complications should be diagnosed and treated before the mother has overt clinical signs of infection. Preterm PROM is usually treated with intravenous ampicillin (or amoxicillin) and erythromycin.[40] Of note, amoxicillin–clavulanic acid has been found to increase the risk of necrotizing enterocolitis in several studies and is therefore not recommended.[39,40] Treatment of term PROM is indicated when the patient is group B streptococcus positive or has not been tested. The signs and symptoms of chorioamnionitis are late manifestations of advanced infection and are discussed next.

Chorioamnionitis

Chorioamnionitis occurs when vaginal or cervical bacteria ascend into the uterus, instigating an inflammation of the chorion and amnion layers of the amniotic sac.[41] It occurs in 1 to 10% of all pregnancies, and risk factors include prolonged labor, PROM, excessive vaginal examinations, and recent amniocentesis. Box 181-6 summarizes the findings and evaluation of chorioamnionitis. Chorioamnionitis may result in prolonged first- and second-stage labor and decreased responsiveness to oxytocin. Early, aggressive treatment, even before evidence of infection occurs, decreases neonatal morbidity and delays delivery, allowing fetal maturation.[42,43]

Box 181-6 Chorioamnionitis Evaluation

Fluid in Vaginal Vault
Phosphatidylglycerol

Cervical Cultures
Escherichia coli and other gram-negative bacteria
Neisseria gonorrhoeae

Vaginal Cultures
Chlamydia spp.
Mycoplasma hominis
Group B streptococci
Ureaplasma urealyticum

Amniocentesis Studies
Gram's stain (group B streptococci)
Culture
Glucose
Lecithin-to-sphingomyelin ratio

Maternal Signs and Symptoms
Premature rupture of membranes
Uterine tenderness
Fever
Tachycardia (maternal or fetal)
Malodorous vaginal discharge
Leukocytosis

Fetal Signs and Symptoms
Decreased activity
Abnormal biophysical profile (ultrasonographic examination)
Fetal tachycardia
Decreased variability of fetal heart rate

Vertical Transmission of Human Immunodeficiency Virus

Emergency deliveries may involve women who are known to be HIV positive in addition to women who are infected but have never been tested. The latter group generally includes pregnant women with little or no prenatal care who are at risk for precipitous delivery. In 2000, between 280 and 370 infants were born in the United States with HIV infection. Of these, 29% were born to mothers undiagnosed with HIV infection before delivery.[44] Transmission may occur in the antepartum, intrapartum, or postpartum (breast-feeding) period. Because intrapartum transmission accounts for up to 75% of vertically transmitted HIV infections, antiretroviral therapy on presentation, even while labor progresses, can decrease vertical HIV transmission.[45] Potential mechanisms of transmission include microtransfusion during contractions, absorption of virus through the mucous membranes, and even invasion through the epithelium. Risk factors for transmission include high viral loads, prolonged rupture of membranes, maternal drug use, vaginal delivery, and breast-feeding (see Table 181-4).[46,47]

In November 2002, the Food and Drug Administration approved the OraQuick Rapid HIV-1 Antibody Test (OraSure Technologies, Bethlehem, Pa).[48] Point-of-care testing for HIV with a median turnaround time of 45 minutes realistically allows the clinician to initiate intrapartum and neonatal antiretroviral therapy when the test result is positive. Serologic confirmation is recommended, but emergent interventions can proceed on the basis of the bedside result.[49] Since 1994, it has been known that immediate treatment during labor can significantly decrease vertical transmission to the newborn.[50]

A positive HIV test result in some cases may allow a change in the method of delivery. Cesarean section decreases the rate of HIV transmission compared with vaginal delivery methods. In a 1999

www.ketabpezeshki.com 66485457-66963820

meta-analysis from the United States and Europe, vertical HIV transmission was decreased by cesarean section with an odds ratio of 0.43 (95% confidence interval, 0.33-0.56). The protective effect of surgical delivery over other delivery methods persisted even when the data were stratified for receipt of antiretroviral therapy.[51] This finding was tempered by an increase in maternal morbidity and mortality in HIV-positive women undergoing cesarean section because of an increased incidence of endometritis, maternal sepsis, pneumonia, and transfusion.[52] Taking into account the risks and benefits, current ACOG and Department of Health and Human Services panel guidelines recommend elective cesarean section for all HIV-infected women with viral loads of more than 1000 copies/mL at 38 weeks of gestation.[53]

Ideally, decisions about the mode of delivery and the need for antiretroviral therapy can be made before the rupture of membranes. The risk of transmission increases after that time and continues to increase as the fetus traverses the birth canal.[53] When antiretroviral therapy and elective cesarean section are used, the likelihood of vertical transmission is reduced by 87% compared with that for women receiving neither intervention.[51]

This relatively new diagnostic and therapeutic burden placed on the emergency physician faced with an imminent delivery is challenging. Data indicate that antiretroviral treatment and the mode of delivery make labor a true emergency for an HIV-positive patient. In addition, pregnant women with advanced HIV disease have a higher incidence of premature births, postpartum endometritis, and perinatal mortality.[47] Currently, the main obstacle to this type of care is the availability of point-of-care HIV testing. Since the late 1990s, the results supporting this approach have become increasingly robust and seem to justify the efforts.[54,55]

Complicated Delivery

Perspective

Complicated deliveries, involving dystocia, malpresentation, and multiple gestations, are potentially life-threatening emergencies. The emergency physician cannot "solve" these obstetric problems with cesarean section and will therefore face the prospect of an extremely high risk vaginal delivery. As expected, these abnormal deliveries increase the risk of fetal and maternal complications. Aggressive attempts to obtain obstetric, neonatal, and anesthesia support are warranted. If the delivery proceeds in the ED, preparations for maternal and neonatal resuscitation should be made rapidly.

Principles of Disease

Knowledge of abnormal labor and its anatomy and physiology is important for the clinician facing a complicated delivery. Intrapartum management skills will enable the physician to proceed with delivery in an efficient, capable manner.

Dystocia and Malpresentation. Dystocia, or abnormal labor progression, accounts for one third of all cesarean sections and half of primary cesarean sections. Because rapid surgical resolution is unavailable to the emergency physician, intrapartum management skills are important.

Dystocia can be divided into three etiologic categories. Labor fails to progress when there are problems related to the pelvic architecture (the passage), when there are fetal size or presentation problems (the passenger), and when uterine expulsive forces are inadequate. Although it is useful to consider these causes independently, dystocia is usually caused by a combination of factors. Presentation problems are particularly important because they become apparent during stage 2 of labor and require immediate action.

Table 181-5 Relative Incidence of Malpresentations

MALPRESENTATION	INCIDENCE
Breech presentation	1/25 live births
Shoulder dystocia	1/300 live births
Face presentation	1/550 live births
Brow presentation	1/1400 live births

In order of increasing incidence, brow, face, shoulder, and breech presentations are the most common malpresentations (Table 181-5). True fetopelvic disproportion is much less common. Cesarean section is indicated when labor arrest or cord prolapse coexists with these presentations.[56]

Breech Delivery

Perspective. Breech is the most common malpresentation, occurring in just less than 4% of all deliveries.[57] Three types of breech presentation exist: frank, incomplete, and complete (Fig. 181-8; Box 181-7). The main mechanical problem with breech presentations is that the buttocks and legs do not provide a sufficient wedge, hindering cervical accommodation of the relatively larger head. In addition, because the presenting part does not completely occlude the cervical opening, umbilical cord prolapse may occur.

The terminology for breech deliveries is complicated. By convention, the presentation (frank, incomplete, and complete) is followed by the relationship of the fetus to the birth canal, with the fetal sacrum as a reference point. The mode of delivery also has specific terminology. *Spontaneous breech delivery* refers to vaginal delivery without manual aid, almost always of a small premature infant. *Assisted breech delivery* and *partial breech extraction* are terms that apply when delivery is manually assisted after the umbilicus clears the perineum. The head may be delivered by intrapartum maneuvers or forceps. Complete breech extraction consists of the application of traction to the lower extremities or groin before delivery of the buttocks. This approach is never indicated for a singleton breech because it increases the chances of head entrapment. Confusion arises because the word *complete,* as used here, describes the mode of delivery, not the presentation.

Correlated with this abnormal presentation are several factors: prematurity, multiparity, fetal abnormalities, prior breech presentation, polyhydramnios, and uterine abnormalities.[57]

Overall, one third of breech fetal deaths are believed to be preventable. Asphyxia is often due to umbilical cord prolapse or entrapment of the head. Fetal head and neck trauma can occur if inappropriate delivery techniques are used. Scheduled cesarean section for these patients reduces the potential for ED presentation. However, emergency physicians should be prepared for vaginal delivery of breech presentations in the event of premature or unforeseen labor in the absence of immediate surgical services.[58]

Diagnostic Strategies. Before labor, Leopold's maneuvers facilitate the diagnosis of breech presentation. In the case of breech presentation, Leopold's first maneuver identifies a firm, round mass (the head) in the fundus of the uterus. The third maneuver reveals the softer breech at the pelvic inlet. For the emergency physician, active labor restricts the use of Leopold's maneuvers; thus vaginal examination is required.

The differentiation of a vertex presentation from a breech by tactile vaginal examination is not always simple. Any time a fontanel is not identified on examination, a breech presentation should be suspected. During the vaginal examination, it is helpful to remember that the face and the skull have a complete circle of bone, whereas the anus is flanked by bone on only two sides.

www.ketabpezeshki.com 66485457-66963820

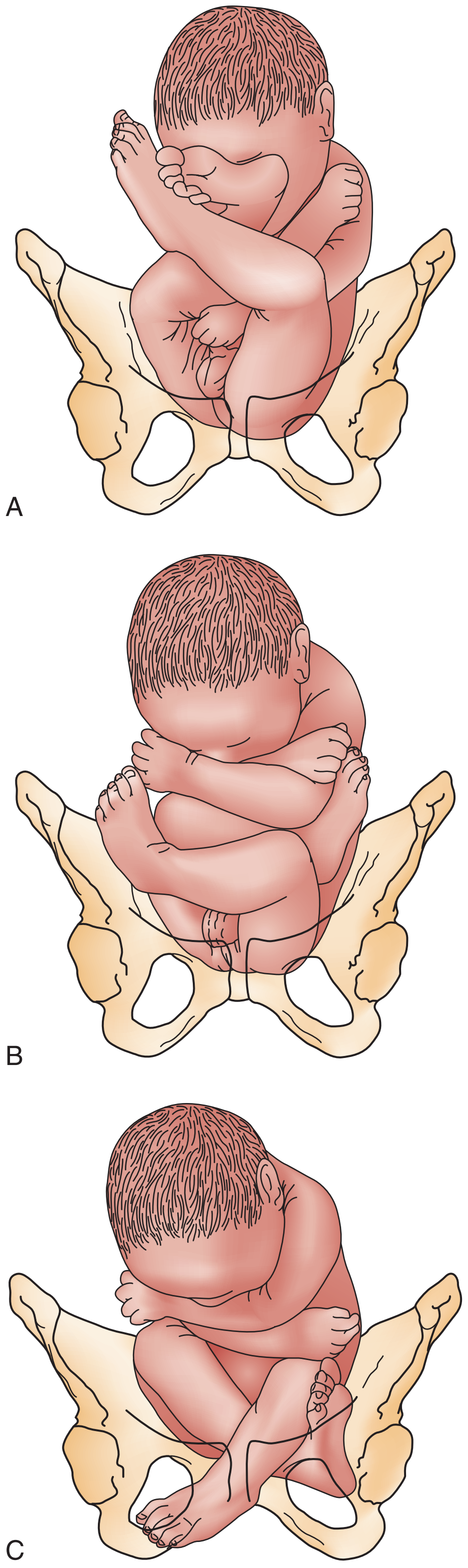


Figure 181-8. Breech presentations. **A,** Frank breech presentation. **B,** Complete breech presentation. **C,** Incomplete breech presentation. (Modified from Cunningham FG, et al: Williams Obstetrics, 19th ed. Norwalk, Conn, Appleton & Lange, 1993.)

If time allows, ultrasound examination is indicated to obtain information on the type of breech presentation, gestational age and fetal weight, and position of the fetal arms and neck.[59] If the fetus has a hyperextended neck, vaginal delivery is associated with a 70% incidence of spinal cord injuries. If possible, labor should be delayed to allow cesarean section.[60] Likewise, if the arms are over the head, they increase the dystocia when the head enters the birth canal. If ultrasound examination reveals anencephaly or massive hydrocephaly, vaginal breech delivery should be allowed to continue because cesarean section is undesirable.

Box 181-7 Breech Presentations

Frank Breech
60-65% of all breech presentations
Hips flexed, knees extended
Buttocks act as good dilating wedge
Incidence of cord prolapse approximately 0.5%

Complete Breech
Least common, occurs in approximately 5% of all breech presentations
Hips and knees flexed
Buttocks act as good dilating wedge
Incidence of cord prolapse is 5-6%

Incomplete Breech
25-35% of all breech presentations
Incomplete hip flexion, single or double footling
Poor wedge
Increased incidence of prolapsed cord (15-18%)

Box 181-8 Vaginal Breech Delivery

Actions to Do as Able
Monitor fetal heart rate.
Obtain a focused history.
Diagnose a breech lie.
Determine cervical dilation and station.
Obtain an ultrasound or plain radiographic study.
Evaluate for prolapsed cord if there is spontaneous rupture of membranes.
Perform an episiotomy.
Flex knees and sweep out legs.
Pull out a 10- to 15-cm loop of cord (room to work) after the umbilicus clears the perineum.
Use the bony pelvis as a means of holding the infant.
Keep face and abdomen away from the symphysis and use rotation to deliver the more accessible arm.
Perform the Mauriceau maneuver.

Actions to Avoid
Inappropriate transfer with delivery en route
Misdiagnosis of cervical dilation
Iatrogenic rupture of membranes (cord prolapse)
Moving of patients or leaving them unmonitored
Traction on the fetus during delivery
Grasping of the fetus by the waist, causing abdominal organ injury
Arm entrapment over head
Neck hyperextension

Management. Premature infants in the breech position often deliver spontaneously without difficulty. As the infant comes to term, dystocia becomes increasingly common. With commitment to a vaginal delivery, knowledge of breech dystocia mechanics may allow atraumatic delivery. The key goals are to maximize the size of the passage and to minimize the dystocia of the after-coming head. Box 181-8 summarizes the actions associated with successful vaginal breech delivery.

The Mauriceau maneuver is the use of the fetal oral aperture to flex the fetal neck and draw in the chin. Because fetal neck extension is associated with cord injuries and worsening dystocia, this

www.ketabpezeshki.com 66485457-66963820

maneuver is useful to ensure a successful vaginal delivery. This maneuver should be attempted only once the fetal elbows and chin have entered the pelvic inlet to avoid inducing the Moro reflex (in which fetal head flexion results in the arms being suddenly extended).[59] While the Mauriceau maneuver is used, the fetal pelvis should be supported to avoid abdominal injuries. Generous episiotomy may even be necessary to facilitate the Mauriceau maneuver in a full-term infant. If the after-coming head cannot be delivered quickly, the chances of good fetal outcome are poor. For term infants, labor arrest, asphyxia, or brachial plexus injuries are potential complications of vaginal breech deliveries.

Shoulder Dystocia

Perspective. Shoulder dystocia is the second most common malpresentation, occurring in 0.6 to 1.4% of all vaginal vertex deliveries.[61] In contrast to a breech presentation, which may be diagnosed in the antepartum period, shoulder dystocia develops in the intrapartum period. Maternal and fetal factors are associated with shoulder dystocia. Maternal factors include diabetes, obesity, and precipitous or protracted labor; fetal factors include macrosomia, postmaturity, and erythroblastosis fetalis. The combination of prenatal data, estimated fetal weight, and fetal biometry cannot reliably identify most deliveries complicated by shoulder dystocia. The fact that shoulder dystocia responds well to a variety of intrapartum maneuvers means that delivery skill is an important determinant of fetal outcome.

The consequences of shoulder dystocia can be devastating. As with breech presentation, infant complications are more common and severe than maternal complications. Traumatic brachial plexus injuries, clavicular fractures, and hypoxic brain injury are all well-documented complications.[61] Maternal complications are related to traumatic delivery and include vaginal, perineal, and anal sphincter tears as well as urinary incontinence.[62]

Diagnostic Strategies

Shoulder dystocia is diagnosed clinically by the inability to deliver either shoulder. The fetal head may appear to retract toward the maternal perineum. This finding is known as the "turtle sign." Traction on the head extends and abducts the shoulders, increasing the bisacromial diameter and worsening the dystocia. Figure 181-9 shows the normal and abnormal relationship of the shoulders to the birth canal and illustrates why the bisacromial diameter is an important element of fetal biometry.

Normally, the shoulders negotiate the maternal pelvis in sequential fashion, anterior shoulder first. With shoulder dystocia, both shoulders attempt to clear the maternal pelvis simultaneously. In addition to the turtle sign, examination often reveals that the fetal shoulders are on a vertical axis (rather than oblique). These findings in combination with an arrested delivery confirm the diagnosis of shoulder dystocia.[63]

Management. When shoulder dystocia becomes evident, knowledge of intrapartum delivery maneuvers can be lifesaving. Successful vaginal delivery is most likely when a directed sequential approach to each maneuver is used. Rapid resolution of shoulder dystocia is important to avoid fetal asphyxia and resultant central nervous system injury. Obstetric and neonatology assistance may improve the outcome, and aggressive attempts to obtain help in these areas are warranted.

Initial attempts to resolve shoulder dystocia involve increasing the anteroposterior diameter of the passage. An episiotomy may be used for fetal maneuvering by allowing access to the posterior shoulder. Anteriorly, draining the bladder with a Foley catheter can generate room.

The most important first step is to use McRoberts' maneuver (Fig. 181-10). Maternal leg flexion to a knee-chest position may disengage the anterior shoulder, allowing rapid vaginal delivery to follow. This maneuver "walks" the pubic symphysis over the anterior shoulder and flattens the sacrum, helping the fetus pass through the birth canal one shoulder at a time. This method, although requiring very little effort, is successful in 40% of shoulder dystocia cases when it is used alone.[64]

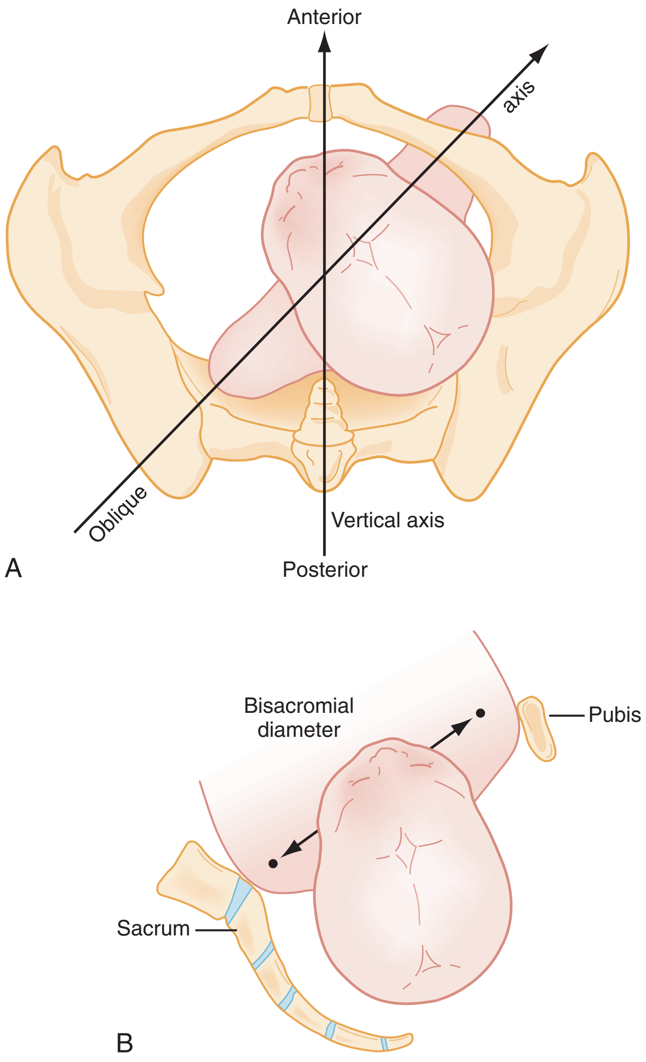


Figure 181-9. **A,** Normal delivery. As the fetal head rotates, the shoulders assume an oblique position and enter the pelvis one at a time. **B,** Shoulder dystocia. Both shoulders attempt to clear the pelvis simultaneously, forcing the bisacromial diameter into the opening.

If McRoberts' maneuver does not free the anterior shoulder, suprapubic pressure may accomplish the goal. Pressure may slip the anterior shoulder beneath the pubis or cause the posterior shoulder to retreat into the hollow of the sacrum. Digital pressure on the posterior shoulder (through the episiotomy) may help facilitate posterior shoulder retreat.

Use of these intrapartum maneuvers resolves most cases of shoulder dystocia. However, if delivery is still impossible, more drastic interventions are warranted. It may be possible to decrease the bisacromial diameter by pushing the most accessible shoulder toward the fetal chest, termed Rubin's maneuver (Fig. 181-11). Often, both shoulders assume the same attitude, decreasing the bisacromial diameter and allowing delivery. Attempts to manipulate the shoulders for Rubin's maneuver may be transabdominal, through the introitus (anterior shoulder), or through the episiotomy (posterior shoulder).

If the shoulders remain undeliverable, the next step is to use Wood's corkscrew maneuver. In this process, the impacted shoulders are released through rotation of the fetus 180 degrees. Fetal rotation is achieved by pushing the most accessible shoulder in

www.ketabpezeshki.com 66485457-66963820

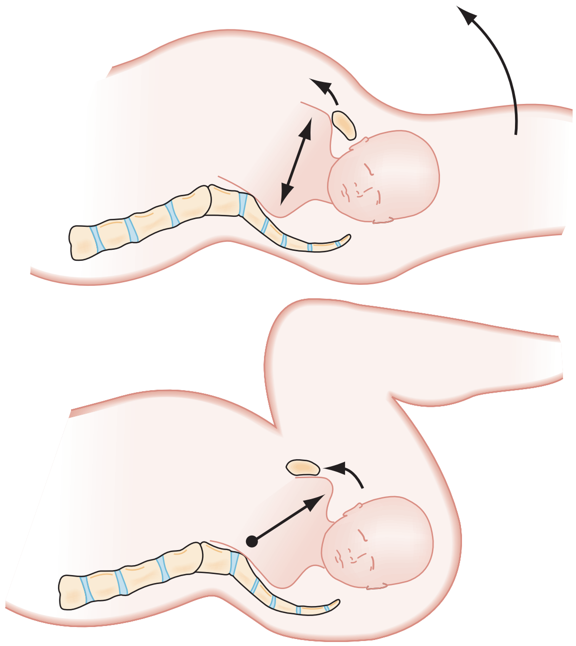


Figure 181-10. McRoberts' maneuver. *Top,* Bisacromial diameter pinned behind pubic symphysis. *Bottom,* Removing the maternal legs from the stirrups and putting the knees up to the chest fulcrum the pubic symphysis over the impacted anterior shoulder.

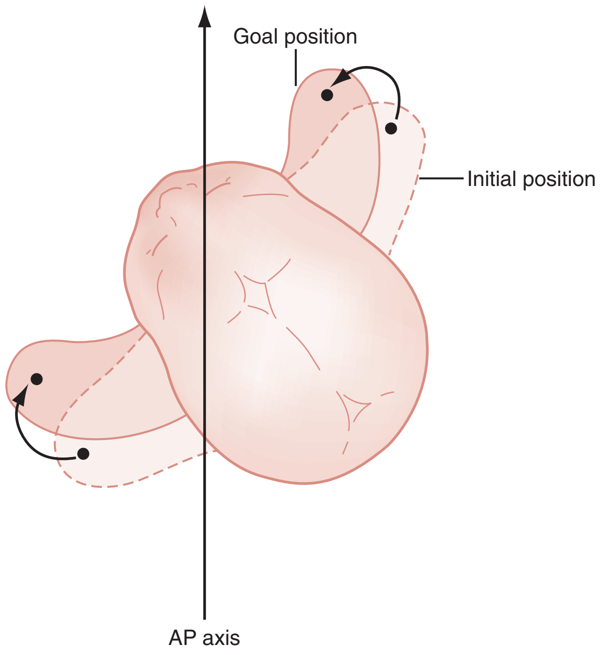


Figure 181-11. Rubin's maneuver decreases the bisacromial diameter. *AP,* anteroposterior.

toward the chest.[65] The fetal axilla can be snared with a digit, or a hand can be slid in along the fetal spine to sweep the hips and generate rotation. Wood's corkscrew maneuver is difficult to perform but should be attempted before reaching for an arm. A slightly oblique anteroposterior position for the shoulders provides the largest passage through the pelvic outlet.

At this juncture, if the fetus remains trapped and several attempts have failed to yield delivery, consideration of delivery of an arm is appropriate. A hand is introduced along the posterior aspect of the posterior shoulder. This would be a tight fit,

Box 181-9 HELPER Mnemonic for Shoulder Dystocia

Help
  Obstetrics, neonatology, anesthesia
Episiotomy
  Generous, possibly even episioproctotomy
Legs flexed
  McRoberts' maneuver
Pressure
  Suprapubic pressure, shoulder pressure
Enter vagina
  Rubin's maneuver or Wood's maneuver
Remove posterior arm
  Splint, sweep, grasp, and pull to extension

requiring tactile identification of fetal anatomy. The posterior arm is swept across the chest, bringing the fetal hand up to the chin. Attempts to splint the humerus may prevent fractures and brachial plexus injuries. The fetal hand is grasped and pulled out of the birth canal across the face, delivering the posterior shoulder. The mnemonic HELPER (Box 181-9) has been proposed to help keep these steps organized and to facilitate a sequential approach. These steps successfully deliver almost all cases of shoulder dystocia.

Face, Brow, and Compound Presentations. Face and brow presentations yield a larger engaging aspect of the fetal head and predispose to labor arrest. Although these abnormal presentations can be diagnosed with ultrasonography or Leopold's maneuvers, most are discovered during labor by vaginal examination. Approximately half are discovered during the second stage of labor.

The engaging diameter of the head in vertex position is approximately 0.8 cm less than a face presentation and 1.5 cm less than a brow presentation. Face presentations are described with the chin as a reference point (e.g., mentum anterior). Face presentation is managed expectantly. The obstetric adage "if a face presentation is progressing, leave it alone" arises from the fact that mentum anterior presentations usually deliver vaginally and mentum transverse presentations frequently rotate to become mentum anterior. Brow presentations, occurring when the fetal head is partially flexed, also spontaneously convert to vertex or face presentations in more than 50% of cases.[57]

A persistent mentum posterior face and brow presentation cannot be delivered vaginally if the fetus is full term. The resultant labor arrest requires symphysiotomy or cesarean section. Prolongation of the second stage is the most common outcome of both of these malpresentations at term. For the emergency physician, this prolonged second stage may provide a window during which obstetric help may arrive.

Compound presentations are those in which an extremity enters the birth canal with the head or breech. Small and premature fetuses generally proceed to vaginal delivery without incident.

Labor arrest and umbilical cord prolapse are accepted indications for cesarean section in the setting of face, brow, and compound presentations. Manipulation of a compound presentation, including attempts to reduce the hand or arm, increases the rate of cord prolapse. Therefore, manipulation attempts are contraindicated. Cord prolapse rates are 10 to 20% even without manipulation. Close monitoring and careful examination are indicated.

Multiple Gestations

Perspective. Although twin gestations accounted for less than 1% of all deliveries historically, there has been a recent increase in the frequency of twin and triplet or higher births (65 and 500%, respectively) because of the increasing use of infertility treatments.[66] In 2003 twin deliveries accounted for 31.5 per 1000 live births. Because multiple gestation deliveries have a higher

www.ketabpezeshki.com 66485457-66963820

incidence of preterm labor and low birth weights, both maternal and fetal complication rates are correspondingly increased.[67]

Diagnostic Strategies

Most women with multiple gestations have the situation identified well before the third trimester. In patients who have had little or no prenatal care, bedside ultrasonography allows rapid diagnosis and early preparation. The stages of labor for twins and other multiple gestations are similar to the stages for a singleton. Nulliparous women experience longer labors than multiparous women, with an overall labor duration that is similar to that of singleton pregnancies. Of importance to the emergency physician is a relatively short latent phase of labor, with rapid progression to the active phase. The active phase is usually longer, however. The prolongation of the active phase is due to overdistention of the uterus plus malpresentation and may allow time for obstetric assistance to arrive.

Vertex twin A and vertex twin B occur in approximately 40% of deliveries. In the remaining 60%, one or both of the twins has a malpresentation, usually twin B.[68] Delivery problems with twin B cause most of the preventable perinatal mortality of twin gestation.[69]

Management. The presentation of the twins is an important determinant for the safety of vaginal delivery. Twins who are vertex-vertex, the most common presentation, can be delivered vaginally barring any other obstetric complication. If twin B is nonvertex, some obstetricians recommend cesarean section to prevent delivery-related complications for twin B. External cephalic version may also be attempted to convert twin B to a cephalic, longitudinal lie and then proceed to vaginal delivery. Breech extraction is a third, more difficult, option. The general consensus is that if twin A is nonvertex, cesarean section is the preferred route. In such cases, efforts should be made to delay delivery until an operative approach can be used. Proceeding vaginally can result in interlocking of twins, associated with a high mortality.[70]

The interval between the delivery of twin A and twin B is variable. Although in most cases twin B delivers in minutes, prolonged interdelivery times with good fetal outcomes have been reported. When twin B does not follow rapidly, in utero assessment is important to document fetal well-being. If fetal heart tracings are reassuring, the delivery of twin B (especially nonvertex) should not be hastened. Repeated ultrasonographic evaluation may be used to confirm twin B's presentation and well-being during the interdelivery period.

After every ED delivery, particularly deliveries that are precipitous or that occur in the out-of-hospital setting, the mother should be examined for the possibility of twins. Ongoing labor may be confused with postpartum cramping, only to have twin B and all of the potential complications surprise the clinician. This situation is particularly relevant for women with inadequate prenatal care and low-birth-weight infants.

Umbilical Cord–Related Emergencies

Perspective

Umbilical cord–related complications can occur in normal and abnormal deliveries. Immediate intervention is required to prevent fetal morbidity and mortality. The spectrum of cord-related emergencies includes prolapsed cord, nuchal loops of the umbilical cord, body coils, cord knots, and entangled cords in monoamniotic twins. Cord length is believed to be proportional to fetal activity in utero during the first and second trimesters. Excess cord length increases the potential for umbilical cord complications of all types. Because the umbilical cord supplies the fetus with all of its oxygen, interruption of cord circulation before establishment of fetal respiration is a life-threatening emergency. Fetal asphyxia caused by cord circulation compromise is potentially preventable with appropriate delivery interventions.

Table 181-6 Conditions Associated with Umbilical Cord Prolapse

PRESENTATION	INCIDENCE (%)
Vertex	0.14
Breech	2.5-3.0
Frank breech	0.4
Complete breech	5
Incomplete breech	10
Shoulder	5-10
Compound	10-20
Face or brow	Rare

Umbilical Cord Prolapse

Clinical Features. Umbilical cord prolapse occurs when the umbilical cord precedes the fetal presenting part or the presenting part does not fill the birth canal completely. Most instances of cord prolapse are unexpected and develop during the second stage of labor.

Cord prolapse has a variable rate of association with different fetal presentations. Compound, shoulder, and breech presentations yield gaps and a relatively poor dilating wedge. Table 181-6 summarizes the rates of umbilical cord prolapse with various fetal presentations. Overall, malpresentations account for 50% of cord prolapse cases; therefore, prolapse may be the first indication of a malpresentation.[71] The reported incidence of cord prolapse ranges from 0.1 to 0.6% of all deliveries, and associated perinatal mortality is estimated to be just below 10%.[72,73]

Diagnostic Strategies. Umbilical cord prolapse may be overt or occult, requiring a pelvic examination to reveal the umbilical cord lying beside the presenting part. The diagnosis also may be made with Doppler ultrasonography. In most cases, the diagnosis is obvious, and the cord is encountered at the perineum or introitus.

Management. Whenever a prolapsed cord occurs with a viable infant, cesarean section is the delivery method of choice. If surgical delivery is available, maneuvers to preserve umbilical circulation should be instituted immediately. The mother should be placed in the knee-chest position with the bed in the Trendelenburg position as the presenting part is manually elevated off the umbilical cord. It is crucial that the mother be instructed to refrain from pushing to avoid further compression of the cord. Placement of a Foley catheter and instillation of 500 to 750 mL of saline into the bladder may help lift the fetus off the cord, particularly in the first stage of labor.[73]

Preparation for an emergency ("crash") cesarean section should be under way. The time from prolapse to surgical intervention is an important factor in fetal outcome. Perinatal mortality rates are significantly higher for out-of-hospital cases (approximately 40%) versus those within a monitored setting (approximately 3%), and outcomes correlate with time from diagnosis to delivery.[73] This finding has implications for the availability of obstetric and surgical backup for the ED.

If surgical delivery cannot be done in a timely fashion, funic reduction (manual replacement of the cord into the uterus) and rapid vaginal delivery may be the only options available. The same maneuvers to decrease cord compression are used, and the umbilical cord is pushed gently, in a retrograde fashion, above

www.ketabpezeshki.com 66485457-66963820

the presenting part. Manipulation and cord trauma is kept to a minimum because the resultant vasospasm can cause fetal hypoxia. After funic reduction, the development of umbilical cord body coils or nuchal loops is common and should be anticipated.[74]

Subsequent to delivery, the physician should be prepared for resuscitation of a distressed newborn. If one is available, a neonatologist should attend the delivery.

Cord Entanglement

The umbilical cord can also become entangled with itself, spontaneously knotting. Umbilical cord knots are related to intrauterine movements early in pregnancy. Approximately 4 or 5% of stillbirths are found to have knots that are believed to have caused fetal demise. Despite this association, cord knots can persist without problems as long as perfusion is maintained.

Loose umbilical cord knots pulled tight at delivery may cause fetal distress. As with cord prolapse, this situation must be resolved quickly to prevent fetal asphyxia. Rapid delivery with avoidance of further cord traction optimizes fetal outcome. No specific interventions exist to deal with this problem.

Long umbilical cords are associated with true knots as well as with entanglements and prolapse. Because the fetal limbs are short and flexed in most presentations, they are rarely involved. Loops around the neck and body do occur, however. Umbilical cord loops can be single or multiple, and there are reports of six nuchal loops. Risk factors for excessive cord length include increasing parity and fetal weight. Although generally benign, they may result in fetal complications, such as nonreassuring fetal status (fetal distress) and respiratory distress.[75]

During delivery, loose nuchal cords should be reduced at the perineum. Loose body coils usually disentangle spontaneously. The reduction process may be aided by slipping them over the extremities or forward over the head. On occasion, loops are tight enough to impede delivery and cannot be reduced. The solution is to cut the clamped cord and deliver the infant rapidly. The high frequency of nuchal loops (one in five births) means that the emergency physician should expect to encounter this problem.

Maternal Complications of Labor and Delivery

Perspective

Maternal complications of labor and delivery include postpartum hemorrhage, uterine inversion and rupture, amniotic fluid embolism, infections, and more. Many of these problems can be managed nonsurgically. When they are severe, however, these complications threaten the reproductive future and the life of the mother and may require emergent surgical intervention.

Postpartum Hemorrhage

Clinical Features. Postpartum hemorrhage is the most common complication of labor and delivery. Defined as hemorrhage of more than 500 mL after vaginal delivery, it affects 5 to 10% of all deliveries and accounts for up to 25% of obstetric deaths.[76] Postpartum hemorrhage is divided into primary and secondary categories. The primary category includes blood loss that occurs within the first 24 hours; the secondary category is hemorrhage 24 hours to 6 weeks after delivery. The clinical picture is as expected with any type of hemorrhage, although because of maternal adaptations during pregnancy, the patient may not show signs of shock until more than 1500 mL of volume is lost.[77]

Differential Considerations. The differential diagnosis of primary postpartum hemorrhage includes uterine atony, genital tract trauma, retained placental tissue, and coagulopathies, or the four *t*'s: tone, trauma, tissue, and thrombin.

Uterine Atony

The most common cause of serious immediate postpartum hemorrhage is laxity of the uterus after delivery. It accounts for 75 to 90% of postpartum hemorrhage cases.[78] Postpartum bleeding from the placental implantation site normally is limited by contraction of the myometrium, constricting the spiral arteries. If the uterus does not contract, ongoing hemorrhage will occur. Predisposing factors include overdistention of the uterus (multiple gestations, fetal macrosomia, and polyhydramnios), prolonged labor, chorioamnionitis, use of tocolytics, and general anesthesia with halogenated compounds. Despite the myriad causes, uterine atony is a diagnosis of exclusion. Physical examination to rule out obstetric trauma and retained products of conception ought to be done before the diagnosis is reached. On examination, the uterus is palpable as a soft, boggy mass.

After other causes have been excluded, therapy to augment myometrial contraction is instituted to prevent further hemorrhage. Two-handed uterine massage may stimulate uterine contraction. One hand exerts pressure transabdominally while the other supports the uterus through the introitus. Uterotonics in conjunction with massage usually provide enough stimuli to control bleeding. Blood is typed, crossmatched, and available for resuscitation should these measures fail.

Maternal Birth Trauma

Maternal birth trauma is the second most common cause of postpartum hemorrhage, accounting for 20% of the cases. Uncontrolled delivery, macrosomia, episiotomy, nulliparity, maternal coagulopathy, operative delivery, prolonged second stage of labor, preeclampsia, and malpresentation may result in maternal birth-related trauma.[79] Although genitourinary structures are most commonly involved, any part of the birth canal–associated anatomy may be injured, with resultant postpartum hemorrhage. Tears and lacerations may involve the perineum, rectum, cervix, vagina, vulva, and urethra. Blood vessels beneath the vulvar or vaginal epithelium can also be injured without frank hemorrhage, resulting in the formation of large, contained hematomas. These hematomas may go unrecognized for hours, gradually enlarging and possibly resulting in hemorrhagic shock. This type of hemorrhage should be suspected whenever there is evidence of ongoing blood loss and no identifiable obstetric site of bleeding (a firm uterus and negative examination findings for lacerations). Delayed postpartum hemorrhage at these sites can also occur and is often a diagnostic challenge. Physical examination may reveal uterine displacement (lateral or cephalad), and confirmation by radiologic means may be used in stable patients. Management, decided in conjunction with specialists, may be expectant, involve vascular embolization, or require surgical intervention, depending on the severity of clinical presentation.[79]

Vaginal tears, especially posteriorly over the ischial spines, are diagnosed early by postpartum exploration rather than hours later when the mother is hemorrhaging. The vulva, including periurethral structures, should be examined. Although minor tears may be left, any laceration involving subcutaneous tissue is repaired with absorbable suture.

The most common sites of tears are within the vaginal, perineal, and rectal structures. Tears are classified as first, second, third, and fourth degree. First-degree tears involve the perineal skin and vaginal mucous membranes without involvement of the underlying fascia and muscle. Second-degree tears extend through the skin into the fascia and muscles of the perineal body but not into the rectal sphincter. Third-degree tears involve the skin, mucous membranes, perineal body, and anal sphincter. Fourth-degree tears extend through all layers, including the rectal mucosa. These

www.ketabpezeshki.com 66485457-66963820

lacerations are also associated with tears in the region of the urethra.

The repair of these tears and the repair of episiotomies are virtually identical. Commonly, repair of the episiotomy is delayed until the placenta is delivered, which allows an uninterrupted approach to potentially complicated repairs. The goal of these repairs is to restore anatomy and to provide hemostasis with a minimum of suturing. Third-degree and fourth-degree tears should be repaired by the obstetrician in an operating room.

Retained Products of Conception

Approximately 10% of postpartum hemorrhage cases are due to retained placental tissue. Normally, the plane of cleavage between the zona basalis and the zona spongiosa results in clean separation of the placenta from the uterus. When this occurs, the placental tissue delivers as a single unit, without evidence of fragmentation. On occasion, accessory placental tissue exists as succenturiate placenta, but this also should cleave normally and deliver spontaneously.

Any placental defect or evidence of accessory placental tissue may signify a retained cotyledon (part of the embryo). Retained fragments prevent myometrial constriction and result in hemorrhage. Inappropriate traction on the placenta during stage 3 of labor can result in tears with retained products of conception, which may cause immediate and delayed postpartum hemorrhage. Ultrasonography may be used in the diagnosis of retained placenta; an empty or fluid-filled uterus provides a high negative predictive value, and an expanded endometrium or solid echogenic mass within the uterus provides evidence of retention.[80,81]

Treatment requires removal of the remnant placental tissue. Digital uterine exploration with blunt dissection of the fragments from the myometrium allows myometrial contraction. Normal placental tissue cleaves away easily, allowing removal. Abnormally adherent tissue is not freed by this mechanism.

Placenta accreta, placenta increta, and placenta percreta describe various degrees of abnormal placental attachment to the uterus. Placental villi may invade the myometrium at the site of implantation, firmly rooting the placenta and obliterating the normal cleavage plane. Thus abnormal attachment results in retained products of conception and postpartum hemorrhage. When the placenta adheres to the myometrium without the intervening decidua basalis, it is termed *placenta accreta*. In *placenta increta,* the villi extend into the myometrium. In *placenta percreta,* the placenta penetrates the full thickness of the myometrium.[82]

The current incidence of placenta accreta is approximately 3 per 1000 deliveries, a relative increase from past decades. Associated risk factors include multiparity, prior cesarean sections, placenta previa, previous curettage, and uterine anomalies.[83]

Coagulopathies

A speedy search for the refractory cause of hemorrhage is warranted because coagulopathies may complicate obstetric hemorrhage. Disseminated intravascular coagulation (DIC) can occur as a consequence of placental abruption, eclampsia, amniotic fluid embolism, postpartum infections, and dilution of clotting factors caused by aggressive volume resuscitation. Also, retained products of conception and dead fetal tissue contain excess thromboplastin, which can initiate DIC. All women with severe postpartum hemorrhage should be evaluated for DIC. As with DIC from nonobstetric causes, clinical signs of bleeding are associated with hypofibrinogenemia, thrombocytopenia, and elevated levels of fibrin split products and D-dimer.[84]

Appropriate management entails hemodynamic support as well as correction of coagulopathies. In fact, investigations have reported the successful use of recombinant factor VIIa for severe cases of postpartum hemorrhage.[85]

Management

Uterine Exploration and Removal of the Placenta

In the face of ongoing hemorrhage and retained products of conception, attempts to remove the placenta manually are indicated. The procedure entails risk of infection, perforation, and increased hemorrhage but may be the most expeditious way to control bleeding. Before beginning, the patient is placed on a monitor, good vascular access is established, and blood products are available. Also, a Foley catheter may be placed to reduce bladder distention and to monitor urinary output.[86] The umbilical cord is traced through the cervical os to the placenta, allowing the identification of a placental margin. The placental membranes are digitally perforated, and the placenta is gradually divided from the myometrium. The palmar surface of the hand is directed toward the placenta, with care taken to avoid uterine perforation. After removal of the placenta, the uterus is explored for retained cotyledons. Removal of any more fragments still present requires curettage of the uterine cavity by an obstetrician. Placenta accreta, placenta percreta, and placenta increta may be diagnosed in this way because these are not digitally dissectible.

Once it is emptied, the uterus is stimulated to contract. Uterine massage, oxytocin, and prostaglandins may be used. Prophylactic antibiotic administration at the time of manual placenta extraction is somewhat debated in the literature. If it is used, a single dose of metronidazole and either ampicillin or cefazolin may be given.[86]

Uterine Packing

Uterine packing to decrease postpartum hemorrhage was widely used previously but now is uncommon. For the emergency physician, this technique may be used to create tamponade, preventing further blood loss. The procedure has limited morbidity and is straightforward. The physician introduces 15 to 20 yards of 4-inch gauze with a ring forceps and packs it into the uterus by a layering technique. A special "uterine packer" is available to help direct gauze high into the uterus but is not necessary. Another option is to place a Foley catheter or Sengstaken-Blakemore tube into the uterus and to instill the balloon with saline.[86]

Opponents of packing point out that an atonic uterus may accommodate a large volume of packing and blood without effective tamponade. Packing may also increase the risk of postpartum infection even when prophylactic antibiotics are given. As with all uterine manipulation and instrumentation, some risk of perforation also exists. Because pelvic embolization and hysterectomy sometimes are not immediately available to the emergency physician, the importance of uterine packing as a temporizing measure is increased.[87]

Pelvic Vessel Embolization

Pelvic bleeding post partum can be difficult to control. Hysterectomy as a solution results in infertility and brings with it all the complications of general anesthesia and major surgery. Radiographic embolization of the bleeding vessels by an interventional radiologist is another option. The procedure does not require an anesthesiologist, operating room, or obstetrician and may be more readily available on an emergent basis. Reported success rates of embolization in control of postpartum hemorrhage range from 95 to 100%.[86]

A catheter is placed in the aorta and fluoroscopically guided to the bleeding sites that are imaged by radiopaque dye. The vessels are embolized with absorbable gelatin sponges placed through the catheter. Common sites of bleeding include the uterine artery, pudendal artery, and hypogastric artery. Because only the smallest involved branches are embolized and recanalization usually occurs, future reproductive capability is generally preserved.[88]

www.ketabpezeshki.com 66485457-66963820

Uterotonic Agents

Although they are commonly applied on delivery of the placenta, uterotonic agents also have special application in the case of postpartum hemorrhage. Uterotonics, such as oxytocin, ergot alkaloids, and prostaglandins, control bleeding by inducing myometrial contraction. Oxytocin is considered to be first-line treatment, given either intramuscularly or intravenously. Ergot alkaloids, such as methylergonovine and ergotamine, may induce hypertension and are therefore contraindicated in patients with preeclampsia or other comorbid conditions. Finally, prostaglandins may also be used (e.g., misoprostol), although they have shown no clear advantage over oxytocin or ergot alkaloids in published reports.[86]

Hysterectomy

Most postpartum hemorrhages are controllable with uterotonics and massage or uterine exploration for products of conception. Rarely, hemorrhage continues despite the interventions outlined. Life-threatening obstetric bleeding may require emergency hysterectomy. The desire to preserve the patient's reproductive capabilities should not be given priority if her life is in jeopardy.[89]

Uterine Inversion

Perspective. Uterine inversion is an uncommon but serious complication of delivery that occurs during stage 4 of labor. The resultant postpartum hemorrhage can be severe and life-threatening, accounting for a maternal mortality rate of up to 15%. Uterine inversion is relatively rare, complicating 1 in 2000 deliveries.[90] It is classified by duration as well as by degree of inversion. Risk factors include excessive fundal pressure during delivery, forceful traction on the umbilical cord (especially in conjunction with a fundal placenta), placenta accreta, maternal congenital abnormalities of the uterus, use of magnesium sulfate in the antepartum period, and primiparity.[90,91]

Clinical Features. Clinically, the patient notes the sudden onset of severe abdominal pain. Abdominal examination reveals tenderness and an absence of the uterine corpus, which is potentially visualized at the cervical os or bulging from the introitus. Profuse bleeding leading to hemodynamic instability can also occur. Ultrasound examination may assist in the diagnosis. Once uterine inversion is identified, the appropriate mobilization of resources should begin simultaneously with efforts to re-establish the correct anatomic position of the uterus.

Management. As with other causes of postpartum hemorrhage, initial management involves aggressive fluid resuscitation.

The highest likelihood for successful repositioning of the inverted uterus is immediately after inversion occurs. If the placenta is still adherent, it should not be removed until after repositioning. Removal of the placenta while the uterus is inverted is associated with excessive blood loss. The initial attempt to reposition the uterus should be to push the fundus upward through the introitus. Digital pressure should be directed toward the mother's umbilicus along the long axis of the uterus. Contraction of the cervical uterine segments can create a muscular ring, preventing repositioning. Therefore, all uterotonic agents should be withheld immediately on diagnosis of uterine inversion.

If initial attempts fail and a cervical ring develops, pharmacologic attempts to relax the uterus are indicated. Sedation and tocolytics can be used to facilitate uterine replacement. Terbutaline and magnesium sulfate have been used successfully to relax cervical rings. When the uterus has been repositioned, the muscle relaxants should be halted, and oxytocin and prostaglandin therapy should be initiated. Firm manual pressure through the introitus should be maintained until uterine contraction begins, the cervical ring contracts, and the uterus can no longer invert. If all these measures fail and surgical backup becomes available, halogenated anesthetics may be used to induce relaxation of the cervical rings with or without an attempt at surgical repair.[90] Once the uterine inversion is resolved, an assessment must be made to screen for uterine perforation, adherent placenta, and vaginal lacerations.[79]

Uterine Rupture

Perspective. Criticism of the high rate of cesarean delivery in the United States has led to an advocacy of vaginal birth after cesarean (VBAC). Prior cesarean section is no longer an automatic indication for repeated cesarean delivery. The high success rate and relative safety of VBAC are countered partly by the risk of uterine rupture. Dehiscence of a surgical scar occurs in 0.6% of VBAC deliveries.[92] As more women have VBAC, emergency physicians can expect to encounter uterine rupture, which is associated with high morbidity and mortality rates.

Clinical Features. Uterine rupture is an unpredictable event occurring late in pregnancy or as stage 1 of labor transitions to the active phase. It is defined as a full-thickness uterine wall perforation. The severity of rupture ranges from simple scar dehiscence to complete fetal extrusion. It may be spontaneous, but it is most often linked with previous uterine surgery.[93] Other risk factors for uterine rupture include congenital uterine abnormalities, trauma, and medications used for labor induction and abortions.[79] As the degree of fetal expulsion through the rupture increases, the fetal mortality rate increases as well. Minimal fetal extrusion results in a perinatal mortality rate of less than 1%, whereas complete extrusion results in a 10 to 20% mortality rate. Maternal death is rare, but significant hemorrhage is common, complicating one third of cases. Maternal genitourinary injury may also occur in association with uterine rupture.

Diagnostic Strategies and Difficulties. The diagnosis of uterine rupture may be difficult because pain is not always present. In fact, clinical presentation of uterine rupture ranges from nonreassuring fetal heart rate patterns to frank maternal hemorrhagic shock.[79] Intrapartum vaginal bleeding may signal the problem, but its absence by no means precludes rupture. Prolonged fetal heart rate deceleration, indicating fetal distress, is the most reliable sign of fetal extrusion.[80] Emergency ultrasonography may reveal a protruding amniotic sac, hemoperitoneum, or the site of myometrial rupture; however, good sensitivity data are lacking.[93]

Management. If uterine rupture is suspected, delivery should be hastened to limit fetal hypoxia. Emergency cesarean section is the best method to speed delivery and to repair the injury. The ACOG guidelines for uterine rupture identify a 30-minute window of opportunity that maximizes fetal outcome.[94] At surgery, the maternal condition dictates whether uterine repair or hysterectomy is indicated. In the absence of opportunity for emergency laparotomy, appropriate interventions remain speculative. Uterotonic agents may exacerbate the rupture and are contraindicated.

Amniotic Fluid Embolism

Amniotic fluid embolism is a rare and catastrophic complication of labor and delivery. The incidence rate is 6.0 and 14.8 per 100,000 in primigravid and multiparous deliveries, respectively.[95] Although the mechanism is not well understood, it is thought to involve the spread of amniotic fluid through the maternal vasculature, activating either a complement or anaphylactic cascade. Cesarean delivery, forceps- or vacuum-assisted delivery, uterine rupture, eclampsia, placenta previa, and placental abruption have been found to have a significant association with amniotic fluid embolism. Patients will demonstrate moderate to severe pulmonary hypertension, right ventricular failure, and, in severe cases, left ventricular failure. The diagnosis is clinically evident during labor, during delivery, or within 48 hours of delivery. It is characterized

www.ketabpezeshki.com 66485457-66963820

by the sudden onset of dyspnea, hypoxia, altered mental status, seizure, hemorrhage (from coagulopathy), fetal compromise, or cardiovascular collapse. DIC occurs in approximately 50%, and both maternal and fetal mortality rates are high. Treatment is generally supportive and may include assisted ventilation, central hemodynamic monitoring, vasopressors or inotropes, and blood products.[96-99]

Postpartum Endometritis

Perspective. Puerperal infections affect 5% of all vaginal deliveries and 10% of all cesarean sections. Operative delivery, prolonged rupture of membranes, lack of prenatal care, prolonged stage 2 labor, use of intrauterine monitoring, and frequent vaginal examinations have been linked to these ascending gynecologic infections.[100] It is estimated that sepsis results in up to 15% of maternal deaths worldwide.[101] Causative organisms for these infections include gram-positive cocci and gram-negative coliforms. Less commonly, *Chlamydia* and *Mycoplasma* species have been implicated.

Clinical Features. Endometritis is the most common puerperal infection, usually developing on the second or third day post partum. Typically, the lochia has a foul odor and the white blood cell count is elevated. Fever and abdominal pain indicate greater severity of infection, often warranting inpatient care and intravenous antibiotics. A coexistent surgical wound infection is often present. A search for retained products of conception is indicated, particularly if bleeding is ongoing.

Management. Treatment is empirical and directed at gram-positive, gram-negative, and anaerobic organisms. A combination of clindamycin and an aminoglycoside is recommended. Another commonly used antibiotic regimen is a second- or third-generation cephalosporin plus metronidazole.[102] Most patients with postpartum endometritis require admission.

Peripartum Cardiomyopathy

Perspective. For unclear reasons, the peripartum period is associated with the relatively sudden onset of cardiomyopathy in healthy women without evidence of prior cardiac disease. Estimates indicate that peripartum cardiomyopathy (PPCM) occurs in 1 of 4000 pregnancies; reported risk factors include advanced maternal age, preeclampsia, gestational hypertension, multiparity, and African American race.[103] Proposed causes include viral, immunologic, hormonal, toxic, and genetic factors, but no specific cause is found in most cases. Reported mortality rates for PPCM range from 0 to 19%.[104]

Clinical Features. Symptom onset varies, as does the severity of the cardiomyopathy. Onset is usually days to weeks after delivery, and symptoms range from mild fatigue to acute pulmonary edema. PPCM is often unrecognized in its milder form, leading to the consensus that the condition may be more prevalent than reported. Dyspnea on exertion, orthopnea, and fatigue may be easily misinterpreted as normal in a mildly anemic woman who is breast-feeding a new infant at home. The clinician should not dismiss these symptoms because severe congestive heart failure, thromboembolism, and dysrhythmias may ensue.

Management. Treatment with diuretics, vasodilators, and oxygen relieves the symptoms in many cases. Angiotensin-converting enzyme inhibitors are contraindicated if PPCM occurs during the last month of pregnancy (owing to teratogenicity) but should be considered a mainstay of treatment post partum. Amlodipine (a dihydropyridine calcium channel blocker) may also have a role in the treatment of PPCM.[105,106]

Cardiac function returns to normal in half of patients with PPCM during the following 6 months. Others have residual left ventricular dysfunction, although the overall survival rate at 5 years is 94%.[107] The presence of cardiomyopathy after one pregnancy does not predict recurrence during subsequent pregnancies.[108] Most obstetricians recommend against future pregnancies, however, especially if some residual cardiac function impairment exists. If such a pregnancy cannot be avoided, it should be considered high risk and observed closely.

Postpartum Depression

Perspective. Postpartum depression is likely to be underdiagnosed, but it is estimated that it affects 10 to 15% of mothers. Although in many cases it is self-limited, the condition has been recognized as having important consequences for the mother, infant, and family. Risk factors for postpartum depression include previously diagnosed depression and neuroticism, inadequate spousal support, adverse socioeconomic factors, recent life stressors, and emergency delivery.[109]

Clinical Features. Postpartum depression patients present with symptoms not unlike those of other major depressive disorders. These symptoms include depressed mood, anhedonia, loss of appetite, insomnia, fatigue, decreased concentration, feelings of guilt and worthlessness, and suicidal ideation.[110] Most women with postpartum depression do not have vegetative signs or symptoms. Symptoms peak at 10 to 12 weeks post partum, although some cases are diagnosed up to 1 year post partum.[111]

When postpartum depression is unrecognized, these women are at high risk for suicide and may come to the ED with overdoses or other manifestations of a suicidal attempt.

Management. Early identification and referral are the key components of therapy. Dismissal of postpartum fatigue as normal, without consideration of the diagnosis of postpartum depression, can be disastrous. Not only does this condition contribute to marital discord, maternal risk for suicide, and even infanticide, but studies have shown that children of depressed mothers have an increased incidence of delayed cognitive, psychological, neurologic, and motor development.[112] Therefore, sensitivity to the possibility of postpartum depression is crucial to successful treatment.

KEY CONCEPTS

- ED deliveries should be considered high risk. Antepartum hemorrhage, PROM, eclampsia, premature labor, precipitous delivery, malpresentation, and umbilical cord emergencies are overrepresented in emergency deliveries.
- Women in labor who present to the ED are generally best cared for in the obstetric suite. Women with the urge to push or with the head of the infant crowning are at imminent risk of delivery, which should take place in the ED. The transfer of a woman with an impending high-risk delivery to a perinatal center ought to be tempered by clinical and medicolegal judgment.
- Most ED deliveries require only basic equipment to cut and clamp the umbilical cord and to dry and suction the infant. However, the ED should have the equipment and staff available to care for a newborn requiring further resuscitation.
- Maternal complications of labor and delivery include obstetric trauma, postpartum hemorrhage, uterine inversion and rupture, amniotic fluid embolism, coagulation disorders, and infections. Many of these problems can initially be managed nonsurgically in the ED.
- Deliveries complicated by dystocia, malpresentation, or multiple gestations are life-threatening emergencies. The clinician should develop strategies to treat each of these potential complications of delivery.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Pons PT: Prehospital considerations in the pregnant patient. *Emerg Med Clin North Am* 1994; 12:1.
2. Moscovitz HC, et al: Care and outcome of out-of-hospital deliveries. *Acad Emerg Med* 2000; 7:757.
3. MacDorman MF, Munson ML, Kirmeyer S: Fetal and perinatal mortality, United States, 2004. *Natl Vital Stat Rep* 2007; 56:1.
4. Brunette DD: Prehospital and emergency department delivery: A review of eight years experience. *Ann Emerg Med* 1989; 18:1116.
5. Elixhauser A, et al: Health care for children and youth in the United States: 2001 annual report on access, utilization, quality, and expenditures. *Ambul Pediatr* 2002; 2:419.
6. Chasnoff JJ, et al: Cocaine use in pregnancy. *N Engl J Med* 1985; 313:666.
7. Verenson A, et al: Perinatal morbidity associated with violence experienced by pregnant women. *Am J Obstet Gynecol* 1994; 170:1760.
8. Abbott J, et al: Domestic violence against women: Incidence and prevalence in an emergency department population. *JAMA* 1995; 273:1763.
9. Katz VL, Hansen AR: Complications in the emergency transport of pregnant women. *South Med J* 1990; 83:7.
10. Ayres RJ Jr: Legal considerations in prehospital care. *Emerg Med Clin North Am* 1993; 11:853.
11. Strobos J: Tightening the screw: Statutory and legal supervision of interhospital patient transfers. *Ann Emerg Med* 1991; 20:302.
12. Lee NG: Update on EMTALA. *Am J Nurs* 2000; 100:57.
13. Albers L: The evidence for physiologic management of the active phase of the first stage of labor. *J Midwifery Womens Health* 2007; 52:207.
14. ACOG Committee on Practice Bulletins: ACOG Practice Bulletin. No. 62: Intrapartum fetal heart rate monitoring. *Obstet Gynecol* 2005; 105(Pt 1):1161.
15. Trott A: Diagnostic modalities in gynecologic and obstetric emergencies. *Emerg Med Clin North Am* 1987; 5:405.
16. Medina TM, Hill DA: Preterm premature rupture of membranes: Diagnosis and management. *Am Fam Physician* 2006; 73:659.
17. American College of Obstetrics and Gynecology Committee on Practice Bulletins–Obstetrics: ACOG Practice Bulletin Number 49, December 2003: Dystocia and augmentation of labor. *Obstet Gynecol* 2003; 102:1445.
18. Altman MR, Lydon-Rochelle MT: Prolonged second stage of labor and risk of maternal and perinatal outcomes: A systematic review. *Birth* 2006; 33:315.
19. Stout MJ, Cahill AG: Electronic fetal monitoring: Past, present, and future. *Clin Perinatol* 2011; 38:127.
20. Vintzileos AM, et al: Use of ultrasound in the labor and delivery. *J Matern Fetal Neonatal Med* 2010; 23:269.
21. Shiono P, et al: Midline episiotomies: More harm than good? *Obstet Gynecol* 1990; 75:765.
22. Jonsson ER, et al: Modified Ritgen's maneuver for anal sphincter injury at delivery: A randomized control trial. *Obstet Gynecol* 2008; 112:212.
23. Webb DA, Culhane J: Hospital variation in episiotomy use and the risk of perineal trauma during childbirth. *Birth* 2002; 29:132.
24. Norwitz ER, Robinson JN, Repke JT: *Labor and delivery*. In: Gabbe SG, Niebyl JR, Simpson JL, eds. *Obstetrics: Normal and Problem Pregnancies*. New York: Churchill Livingstone; 2003:353-390.
25. Magann EF, et al: The length of the third stage of labor and the risk of postpartum hemorrhage. *Obstet Gynecol* 2005; 105:290.
26. Bair ME, Williams J: Management of the third stage of labor. *J Midwifery Womens Health* 2007; 52:412.
27. Macpherson T: Fact and fancy: What can we really tell from the placenta? *Arch Pathol Lab Med* 1991; 115:672.
28. Salatia CM, Vintzilcos AM: Why all placentas should be examined by a pathologist in 1990. *Am J Obstet Gynecol* 1990; 163:1282.
29. Katz VL, Farmer RM: Controversies in tocolytic therapy. *Clin Obstet Gynecol* 1999; 42:801.
30. Goldenberg RL: The management of preterm labor. *Obstet Gynecol* 2002; 100:1020.
31. ACOG Committee on Practice Bulletins; American College of Obstetricians and Gynecologists: ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologist. Number 43, May 2003. Management of preterm labor. *Obstet Gynecol* 2003; 101(Pt 1):1039.
32. Canadian Preterm Labor Investigators Group: Treatment of preterm labor with the β-adrenergic agonist ritodrine. *N Engl J Med* 1992; 327:308.
33. Rodts-Palenik S, Morrison JC: Tocolysis: An update for the practitioner. *Obstet Gynecol Surv* 2002; 57:S9.
34. Crowther CA, et al: Magnesium sulfate for preventing preterm birth in threatened preterm labour. *Cochrane Database Syst Rev* 2002; 4:CD001060.
35. Pryde PG, et al: Risk-benefit effects of tocolytic therapy. *Expert Opin Drug Saf* 2004; 3:639.
36. Sawdy RJ, Lye S, Fisk NM, Bennett PR: A double-blind randomized study of fetal side effects during and after the short-term maternal administration of indomethacin, sulindac, and nimesulide for the treatment of preterm labor. *Am J Obstet Gynecol* 2003; 188:1046.
37. Conde-Agudelo A, et al: Nifedipine in the management of preterm labor: A systemic review and metaanalysis. *Am J Obstet Gynecol* 2011; 204:134.e1.
38. Wenstrom KD, et al: Premature rupture of membranes. *Obstet Gynecol Clin North Am* 1992; 19:241.
39. ACOG Committee on Practice Bulletins–Obstetrics: ACOG Practice Bulletin No. 80: Premature rupture of membranes. Clinical management guidelines for obstetrician-gynecologists. *Obstet Gynecol* 2007; 109:1007.
40. Yudin MH, et al: Antibiotic therapy in preterm premature rupture of the membranes. *J Obstet Gynaecol Can* 2009; 31:863.
41. Curran CA: Perianesthesia care following obstetric emergencies at risk for multisystem organ dysfunction. *J Perianesth Nurs* 2005; 20:185.
42. Gorgas DL: Infections related to pregnancy. *Emerg Med Clin North Am* 2008; 26:345.
43. Kenyon S, Boulvain M, Neilson J: Antibiotics for preterm rupture of membranes. *Cochrane Database Syst Rev* 2003; 2:CD001058.
44. Office of Inspector General: Reducing Obstetrician Barriers to Offering HIV Testing. Washington, DC: Department of Health and Human Services; 2002. OEI-05-01-00260.
45. Kotler DP: Human immunodeficiency virus and pregnancy. *Gastroenterol Clin North Am* 2003; 32:437.
46. McGowan JP, Shah SS: Prevention of perinatal HIV transmission during pregnancy. *J Antimicrob Chemother* 2000; 46:657.
47. Minkoff H: Human immunodeficiency virus infection in pregnancy. *Am Coll Obstet Gynecol* 2003; 101:797.
48. Centers for Disease Control and Prevention: Approval of a new rapid test for HIV antibody. *MMWR Morb Mortal Wkly Rep* 2002; 51:1051.
49. Centers for Disease Control and Prevention: Rapid point-of-care testing for HIV-1 during labor and delivery—Chicago, Illinois, 2002. *MMWR Morb Mortal Wkly Rep* 2003; 52:866.
50. Mofenson LM; Centers for Disease Control and Prevention, U.S. Public Health Service Task Force: U.S. Public Health Service Task Force recommendations for use of antiretroviral drugs in pregnant HIV-1–infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. *MMWR Recomm Rep* 2002; 51:1.
51. International Perinatal HIV Group: The mode of delivery and the risk of vertical transmission of HIV-1—a meta-analysis of 15 prospective cohort studies. *N Engl J Med* 1999; 340:977.
52. Louis J, Landon MB, Gersnoviez RJ: Perioperative morbidity and mortality among human immunodeficiency virus infected women undergoing cesarean delivery. *Obstet Gynecol* 2007; 110:385.
53. Legardy-Williams JK, et al: Prevention of mother-to-child transmission of HIV-1: The role of caesarean delivery. *Clin Perinatol* 2010; 37:777.
54. Moodley D, et al: A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum transmission of HIV-1. *J Infect Dis* 2003; 187:725.
55. Simonds RJ, et al: Impact of zidovudine use on risk and risk factors for perinatal transmission of HIV. *AIDS* 1998; 12:301.
56. Stallard TC, Burns B: Emergency delivery and perimortem C-section. *Emerg Med Clin North Am* 2003; 21:679.
57. Stitely ML, Gherman RB: Labor with abnormal presentation and position. *Obstet Gynecol Clin North Am* 2005; 32:165.
58. Mukhopadhyay S, Arulkumaran S: Breech delivery. *Best Pract Res Clin Obstet Gynaecol* 2002; 16:31.
59. Kotaska A, et al: Vaginal delivery of breech presentation. *J Obstet Gynaecol Can* 2009; 31:557.
60. Seffah JD, Armah JO: Antenatal ultrasonography for breech delivery. *Int J Gynaecol Obstet* 2000; 68:7.
61. Jevitt CM: Shoulder dystocia: Etiology, common risk factors, and management. *J Midwifery Womens Health* 2005; 50:485.
62. Mazouni C, et al: Maternal morbidity associated with obstetrical maneuvers in shoulder dystocia. *Eur J Obstet Gynecol Reprod Biol* 2006; 129:15.
63. Stallard TC, Burns B: Emergency delivery and perimortem C-section. *Emerg Med Clin North Am* 2003; 21:679.
64. Gurewitsch ED: Optimizing shoulder dystocia management to prevent birth injury. *Clin Obstet Gynecol* 2007; 50:592.

www.ketabpezeshki.com 66485457-66963820

65. Benrubi GI: *Handbook of Obstetric and Gynecologic Emergencies*. Philadelphia: Lippincott Williams & Wilkins; 2005.
66. American College of Obstetrics and Gynecologists; Society for Maternal-Fetal Medicine; ACOG Joint Editorial Committee: ACOG Practice Bulletin #56: Multiple gestation: complicated twin, triplet, and high-order multifetal pregnancy. *Obstet Gynecol* 2004; 104:869.
67. Carroll MA, Yeomans ER: Vaginal delivery of twins. *Clin Obstet Gynecol* 2006; 49:154.
68. Apfelbaum JD, Colwell CB, Roe EJ: Precipitous breech delivery of twins. *Prehosp Emerg Care* 2000; 4:78.
69. Adams DM, Chervenak FA: Intrapartum management of twin gestation. *Clin Obstet Gynecol* 1990; 33:52.
70. Carroll MA, Yeomans ER: Vaginal delivery of twins. *Clin Obstet Gynecol* 2006; 49:154.
71. Barnett WM: Umbilical cord prolapse: A true obstetrical emergency. *J Emerg Med* 1989; 7:149.
72. Kinugasa M, et al: Antepartum detection of cord presentation by transvaginal ultrasonography for term breech presentation: Potential prediction and prevention of cord prolapse. *J Obstet Gynaecol* 2007; 33:612.
73. Lin MG: Umbilical cord prolapse. *Obstet Gynecol Surv* 2006; 61:269.
74. Barrett JM: Funic reduction for the management of umbilical cord prolapse. *Am J Obstet Gynecol* 1991; 165:654.
75. Baergen RN, et al: Morbidity, mortality, and placental pathology in excessively long umbilical cords: Retrospective study. *Pediatr Dev Pathol* 2001; 4:144.
76. Higgins S: Obstetric haemorrhage. *Emerg Med* 2003; 15:227.
77. Curran C: Intrapartum emergencies. *J Obstet Gynecol Nurs* 2003; 32:802.
78. Dildy GA: Postpartum hemorrhage: New management options. *Clin Obstet Gynecol* 2002; 45:330.
79. Mirza FG, Gaddipati S: Obstetric emergencies. *Semin Perinatol* 2009; 33:97.
80. Lazebnik N, Lazebnik RS: The role of ultrasound in pregnancy-related emergencies. *Radiol Clin North Am* 2004; 42:315.
81. Shen O, Rabinowitz R, Eisenberg VH, Samuelhoff A: Transabdominal sonography before uterine exploration as a predictor of retained placental fragments. *J Ultrasound Med* 2003; 22:561.
82. Zahn CM, Yoemans ER: Postpartum hemorrhage, placenta accreta, uterine inversion, and puerperal hematomas. *Clin Obstet Gynecol* 1990; 33:422.
83. Belfort MA; Publications Committee, Society for Maternal-Fetal Medicine: Placenta accreta. *Am J Obstet Gynecol* 2010; 203:430.
84. Gerbasi FR, et al: Increased intravascular coagulation associated with pregnancy. *Obstet Gynecol* 1990; 75:385.
85. Hamaekers AE, et al: Successful use of recombinant factor VIIa for treatment of severe postpartum hemorrhage. *Am J Crit Care* 2006; 15:399.
86. Rajan PV, Wing DA: Postpartum hemorrhage: Evidence-based medical interventions for prevention and treatment. *Clin Obstet Gynecol* 2010; 53:165.
87. Goldrath MH: Uterine tamponade for the control of acute uterine bleeding. *Am J Obstet Gynecol* 1983; 147:869.
88. Vegas G, Illescas T, Munoz M, Perez-Pinar A: Selective pelvic arterial embolization in the management of obstetric hemorrhage. *Eur J Obstet Gynecol Reprod Biol* 2006; 127:68.
89. Stanco LM, et al: Emergency peripartum hysterectomy and associated risk factors. *Am J Obstet Gynecol* 1993; 168:879.
90. Hostetler DR, Bosworth, MF: Uterine inversion: A life-threatening obstetric emergency. *J Am Board Fam Pract* 2000; 13:120.
91. Lago JD: Presentation of acute uterine inversion in the emergency department. *Am J Emerg Med* 1991; 9:239.
92. Chauhan SP, et al: Maternal and perinatal complications with uterine rupture in 142,075 patients who attempted vaginal birth after cesarean delivery: A review of the literature. *Am J Obstet Gynecol* 2003; 189:408.
93. Kaakaji Y, Nghiem HV, Nodell C, Winter TC: Sonography of obstetrics and gynecologic emergencies. *AJR Am J Roentgenol* 2000; 174:641.
94. ACOG practice bulletin. Vaginal birth after previous cesarean delivery. Number 5, July 1999. *Int J Gynaecol Obstet* 1999; 66:197.
95. Kramer MS, et al: Amniotic-fluid embolism and medical induction of labor: A retrospective, population-based cohort study. *Lancet* 2006; 368:1444.
96. Davies S: Amniotic fluid embolism and isolated DIC. *Can J Anaesth* 2000; 47:481.
97. Green BT, Umana E: Amniotic fluid embolism. *South Med J* 2000; 93:721.
98. Stafford I, Sheffield J: Amniotic fluid embolism. *Obstet Gynecol Clin North Am* 2007; 34:545.
99. Conde-Agudelo A, Romero R: Amniotic fluid embolism: An evidence-based review. *Am J Obstet Gynecol* 2009; 201:445.
100. Faro S: Postpartum endometritis. *Clin Perinatol* 2005; 32:803.
101. Van Dillen J, et al: Maternal sepsis: Epidemiology, etiology and outcome. *Curr Opin Infect Dis* 2010; 23:249.
102. Maharaj D: Puerperal pyrexia: A review. Part II. *Obstet Gynecol Surv* 2007; 62:400.
103. Ramaraj R, Sorrell V: Peripartum cardiomyopathy: Causes, diagnosis, and treatment. *Cleve Clin J Med* 2009; 76:289.
104. Elkayam U: Clinical characteristics of peripartum cardiomyopathy in the United States: Diagnosis, prognosis, and management. *J Am Coll Cardiol* 2011; 58:659.
105. Pearson GD, et al: Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and the Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. *JAMA* 2000; 283:1183.
106. Packer M, et al; PRAISE Study Group: Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med* 1996; 335:1107.
107. Felker GM, et al: Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2000; 342:1077.
108. Witlin AG, et al: Peripartum cardiomyopathy: An ominous diagnosis. *Am J Obstet Gynecol* 1997; 176:182.
109. Koo V, Lynch J, Cooper S: Risk of postnatal depression after emergency delivery. *J Obstet Gynecol* 2003; 29:246.
110. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Association; 2000.
111. Steinberg SI, Bellavance F: Characteristics and treatment of women with antenatal and postpartum depression. *Int J Psychiatry Med* 1999; 29:209.
112. Gjerdingen DK, Yawn BP: Postpartum depression screening: Importance, methods, barriers, and recommendations for practice. *J Am Board Fam Med* 2007; 20:280.

www.ketabpezeshki.com 66485457-66963820

Section Three
THE GERIATRIC PATIENT

CHAPTER 182
The Elder Patient

Diane M. Birnbaumer

There are no diseases of the aged, but simply diseases among the aged.

Leonard Larson, 1960

PERSPECTIVE

The population of the United States is aging, with the proportion of people older than 65 years increasing at twice the rate of younger people. In 2010, 13% of the population was older than 65 years, and by 2045 one in five people are expected to be older than that age.[1] In 2008 the first baby boomer turned 62 years old, and as of January 2011 this so-called silver tsunami began to qualify for Medicare.

These changing demographics affect the practice of emergency medicine. In 2008 elders accounted for 46% of the 123 million emergency department (ED) visits, and ED visits in this age group are increasing by one third every 10 years.[2] Elders presenting to the ED are more likely to arrive by ambulance, to have a more emergent condition than younger patients, and to require longer evaluations.[3] One third of these patients are admitted, many to the intensive care unit.[4] As the number of ED visits by elders continues to climb, the health care impact will be enormous.

PRINCIPLES OF DISEASE

Physiologic Changes of Aging

Physiologic changes of aging affect virtually every organ system and have many effects on the health and functional status of elders (Table 182-1). Heart disease is the leading cause of hospitalization and death.[5] Increased peripheral vascular resistance with aging leads to an increased risk of hypertension. Decreased inotropic and chronotropic cardiac functioning compromises the patient's ability to respond to physiologic stressors. Atherosclerosis is common and contributes not only to the rate of heart disease but also to the risk of vascular conditions (e.g., stroke, mesenteric ischemia, peripheral vascular disease, aortic dissection, and abdominal aortic aneurysm).

Because of several changes that occur with aging, elders are at higher risk for infections. Prostate disease in men and incomplete bladder emptying in women with pelvic floor abnormalities predispose to urinary tract infections. Microaspiration increases the risk of pneumonia, and fragile, aging skin prone to injury and breakdown increases the risk of infections of the skin and soft tissues. *Immunosenescence* of cell-mediated immunity predisposes patients to reactivation of latent diseases (e.g., tuberculosis) and may be associated with increased susceptibility to neoplasms. Cancer is the second most common cause of hospitalization and death in older patients.[5]

Fractures are the fifth leading cause of hospitalization, reflecting the high rate of osteoporosis, particularly in women.[4] Arthritis is the most prevalent outpatient disease in elders because of the wear on cartilaginous joints, particularly of the knees, hips, and hands.[4] Arthritis greatly affects quality of life, and these patients report fair or poor health approximately three times more often than patients without arthritis do.

Although the physiology of aging often affects a patient's functional status, laboratory values are usually within the normal range. Abnormal laboratory values in elders should be evaluated as abnormal findings and should not be attributed to "normal effects of aging."

Pharmacologic Considerations

Polypharmacy, drug interactions, and misuse and abuse of medications in elders are crucial health care issues. Elders currently consume more than 30% of the prescription drugs in the United States, and this figure is projected to increase to 50% by 2020. More than 40% of elders use five or more drugs weekly, and more than 10% use ten or more.[6,7]

Although multiple medications may be necessary to treat the medical problems that occur with aging, significant adverse health effects may result. Underlying medical problems, multiple physicians, changing pharmacokinetics of aging, and treatment of side effects of one medication with another drug are all contributory. Twelve percent to 30% of admitted elders have adverse drug reactions or interactions as a primary or major contributing factor to their admission, and 25% of these drug reactions or interactions are serious or life-threatening.[6,7]

Pharmacokinetics may change with age. Altered gastrointestinal motility and blood flow, decreased lean body mass, increased proportion of adipose tissue, decreased creatinine clearance, and decreased hepatic blood flow may alter the absorption, distribution, and clearance of medications. Despite these changes, the bioavailability of most medications is not significantly altered in elders. Medication interactions and side effects pose significant problems, however, particularly because many elders take multiple medications. Emergency physicians may unwittingly contribute to this problem by adding a new medication at discharge that may have an adverse drug interaction with a patient's preexisting medications. In addition, the altered pharmacokinetics in elders necessitates caution when medications are administered in the ED, particularly sedative-hypnotics and narcotics. For these agents, a good rule of thumb is "start low and go slow."

Several medications frequently used in the outpatient elder population are considered to be "potentially inappropriate medications." This list includes but is not limited to narcotic analgesics, nonsteroidal anti-inflammatory agents, sedative-hypnotics,

www.ketabpezeshki.com 66485457-66963820

Table 182-1 Physiologic Changes of Aging and Potential Effects

PHYSIOLOGIC CHANGE	POTENTIAL EFFECT
Nervous System	
Decreased efficiency of blood-brain barrier	Increased risk of meningitis Potential for exaggerated medication responses
Decreased response to changes in temperature	Impaired thermoregulation
Alteration of autonomic system function	Variations in blood pressure; risk of orthostatic hypotension Reduced erectile function Urinary incontinence
Alterations in neurotransmitters	Slowing of complex mental functioning
Skin and Mucosa	
Atrophy of all skin layers	Decreased insulation Increased risk of skin injury Increased risk of infection
Sweat glands decreased in number or activity	Potential for hyperthermia
Musculoskeletal System	
Progressive bone loss	Increased risk of fractures
Atrophy of fibrocartilaginous and synovial tissues	Joint instability and pain Impaired balance and mobility
Decrease in lean body mass	Alteration in pharmacokinetics
Increase in proportion of adipose tissue	Alteration in pharmacokinetics
Immune System	
Decrease in cell-mediated immunity	Increased susceptibility to neoplasms Tendency to reactivate latent diseases
Decreased antibody titers	Increased risk of infection
Cardiovascular System	
Decreased inotropic response	Less efficient response to myocardial wall stress
Decreased chronotropic response	Decreased maximal heart rate
Increased peripheral vascular resistance	Increased blood pressure
Decreased ventricular filling	Changes in organ perfusion
Pulmonary System	
Decreased vital capacity	
Decreased lung and airway compliance	Increased airway resistance
Decreased chemoreceptor response to hypercapnia or hypoxemia	Potential for rapid decompensation
Decreased ventilatory drive	Decreased Pao_2 and increased $Paco_2$
Decreased diffusion capacity	Decreased Pao_2
Hepatic Function	
Decrease in hepatic cell mass	Reduced ability to regenerate
Decrease in hepatic blood flow	Alteration in pharmacokinetics
Alterations in microsomal enzyme activity	Alteration in pharmacokinetics
Renal System	
Decrease in renal cell mass	Decreased drug elimination
Thickening of basement membrane	Decreased drug elimination
Reduced hydroxylation of vitamin D	Risk of hypocalcemia, osteoporosis
Decrease in total body water	Alteration in pharmacokinetics
Decreased thirst response	Risk of dehydration and electrolyte abnormalities
Decreased renal vasopressin response	Risk of dehydration and electrolyte abnormalities
Gastrointestinal System	
Decrease in gastric mucosa	Increased risk of gastric ulcer
Decrease in bicarbonate secretion	Increased risk of gastric ulcer
Decrease in blood flow to gastrointestinal system	Increased risk of perforation
Decreased epithelial cell regeneration	Longer healing times

www.ketabpezeshki.com 66485457-66963820

muscle relaxants, and antihistamines.[8-10] These agents are generally not recommended for use in this population of patients and should be used sparingly.

The medications most often implicated in adverse reactions in elders in the ambulatory setting are cardiovascular medications, followed by diuretics, nonopioid analgesics, hypoglycemics, and anticoagulants.[11,12] Caution should be used in prescribing any of these classes as they can contribute to morbidity and mortality in this age group.

The various analgesic medications used in the elderly can cause a wide range of adverse reactions and interactions. Narcotics and sedative-hypnotic agents can decrease cognition and increase the risk of falls and accidents. Nonsteroidal anti-inflammatory drugs (NSAIDs) may have serious and potentially lethal side effects. The toxicity of NSAIDs includes azotemia, worsened hypertension, and congestive heart failure as a result of sodium retention. Gastrointestinal toxicity ranges from bleeding to perforation.[13] The data support use of extreme caution in prescribing NSAIDs. These complications can be seen in patients taking widely available over-the-counter formulations of these drugs. The significant increase in cardiovascular risk with the use of cyclooxygenase 2 inhibitors has led to a dramatic decrease in the use of these agents.

Because of these concerns, pain management in the elderly can pose a challenge. Although a “first, do no harm” philosophy is laudable, treatment of pain is one of the most important remedies physicians have to offer. Three major considerations influence the choice of medication for elderly patients. First, chronic pain (e.g., arthritis pain) may require treatment different from that of an acute painful condition (e.g., wrist fracture). Second, the patient’s underlying medical problems, social situation, and baseline functional status need to be considered.[14] Third, starting with low doses, then titrating upward to effect, is the safest strategy.

Overall, acetaminophen has the highest safety profile in elders and often is the drug of choice for chronic painful conditions (e.g., degenerative joint disease). Although inadvertent excessive dosing can occur, acetaminophen is safe and should be considered first-line management for chronic pain and acute conditions causing mild to moderate pain.

NSAIDs effectively ease pain, but these agents have a ceiling analgesic effect. Increasing the dose increases the risk of side effects without increasing the analgesic benefit. These agents in low doses should be used as second-line agents after acetaminophen in chronic or acute painful conditions.

Narcotics may be necessary for acutely painful conditions and chronic conditions refractory to acetaminophen or NSAIDs. The common side effect of constipation can be a problem, and older patients need to be instructed to exercise regularly, to eat high-fiber foods or supplements, and to remain well hydrated. Because these agents may decrease cognition, start with low doses and titrate upward as needed, and patients and their families should be told of the increased risk of falls associated with these agents.

Psychosocial Issues

The possibility of drug dependence and ethanol abuse should be considered in the treatment of elders. These patients often present with mental status or gastrointestinal complaints or after falls or other trauma. Ethanol dependence is a factor in elders who present in the ED, and dependence on prescription drugs, particularly sedative-hypnotics, is also more prevalent than suspected.[15,16] The routine outpatient use of sedative-hypnotics should be avoided and duration limited; dependence on these drugs may cause decreased cognition, and withdrawal from these agents can be life-threatening.

Psychiatric disease in elders often is manifested in atypical fashion. Depression, a common problem, may be manifested as agitation, anxiety, and somatic complaints in addition to the typical depressive symptoms.[17,18] Depression often follows chronic illness, loss of physical mobility, diminished cognitive function, bereavement from the death of a spouse or long-time friend, and financial pressures, all of which are common features of old age. Social isolation and loss of independence produce a sense of helplessness and hopelessness that may result in suicidal ideation or action. Certain types of depression, such as “late-life delusional depression” and involutional depression, occur exclusively in old age. In addition, depression may be caused by medication side effects or reversible physiologic conditions (e.g., thyroid disease and malnutrition). Elders often respond to pharmacologic treatment of depression but are prone to the development of adverse effects from antidepressants; selective serotonin reuptake inhibitors seem to be safer. A phenomenon known as *sundown syndrome* occurs in elderly demented patients, who become highly agitated and disoriented after dark when visual sensory input is diminished and the environment becomes unfamiliar.

EVALUATION AND CLINICAL FEATURES

The evaluation of elders is often difficult. Elders living independently have an average of three medical problems, which increases up to ten for those living in care facilities. Underlying illnesses complicate the evaluation. Use of ancillary services can be increased by 50% in elders, most likely because of vague or atypical presentations and complicated medical backgrounds.

History

Obtaining a medical history from an elder can require meticulous and painstaking work. Cognitive and physical deficits should be recognized, and physicians often need to be creative and thorough to obtain adequate information.

Cognitive deficits may compromise an elder’s recall and result in an inaccurate medical history. Enlistment of family members, consultation with the patient’s primary care physician, and review of past medical records may be necessary. Particular attention should be paid to past medical and surgical problems and to the patient’s current medications, including over-the-counter and herbal preparations.

Physical deficits also may impede the history-taking process. Sequelae from previous strokes (e.g., aphasia) are usually obvious. Hearing impairment affects communication and can lead to potentially dangerous misunderstandings. Elders tend to lose high-frequency hearing earlier than other ranges, so physicians should lower the pitch of their voice and speak loudly while ensuring the patient’s privacy. Hearing loss can be embarrassing for the patient; thus the physician should address the issue with sensitivity to allow adequate communication while maintaining the patient’s dignity.

Physical Examination

Because of the physiologic changes that occur with aging, the physical examination may be misleadingly benign in an elder, despite the presence of a potentially lethal illness. In addition, medications may alter the response of elders to physiologic stressors. Antihypertensives, particularly beta-blockers, may alter the patient’s ability to mount tachycardia in response to hypovolemia or sepsis or may predispose the patient to hypotension.

Of elders with a serious infection, 30% present with a blunted or absent fever response.[19] The temperature measurement should be accurate. As an oral temperature may be spuriously low, a rectal temperature should be measured when the presence of fever is uncertain in a patient with a possible infection. When fever is present, elders are much more likely to have a serious (nonviral)

www.ketabpezeshki.com 66485457-66963820

infection than are younger patients.[20] Of febrile elders presenting to an ED, 89% have an infectious disease.[20] Approximately one third are respiratory tract infections, one fifth are urinary tract infections, and nearly one fifth are bacteremia or sepsis.[20] Fever in an elder should be taken seriously, with appropriate ancillary testing and a low threshold for admission. Also, a lack of fever does not exclude infection.

DIAGNOSTIC STRATEGIES

Because of the difficulty in obtaining accurate histories and the often poor sensitivity of physical findings in elders with significant underlying disease, more diagnostic tests are generally obtained for these patients than for their younger counterparts who present with similar complaints. This increased use of resources is appropriate because the accuracy and timeliness of diagnosis are critical in elders, who suffer greater morbidity and mortality with delays in definitive treatment.

SPECIFIC DISORDERS

Myocardial Infarction

The incidence of atypical presentation of acute myocardial infarction (AMI) increases with age.[21-23] In patients older than 85 years, atypical presentation of myocardial infarction may be anticipated, and a lack of chest pain may be the rule. Only 2 to 6% of elders with AMI, however, have an asymptomatic presentation.[21] A painless myocardial infarction is more common with increasing age and occurs more often in women than in men.[21-23] Sudden onset of dyspnea may be the only presenting complaint in elders with myocardial infarction. Other presenting complaints include syncope, influenza-like symptoms, nausea, vomiting, confusion, and generalized weakness.[22,23] As the prognosis for AMI in elders who present atypically is the same as that for elders who present typically, these atypical presentations are not more benign.

Infections

Elders are prone to infectious diseases more than younger patients are, with both greater morbidity and higher mortality. Common infections occur regularly, but aging causes this population to be more susceptible to unusual organisms. Although immunosenescence is a contributory factor, predisposing illnesses and institutionalization are more significant causes of this increased risk. Hospitalization increases the risk of nosocomial infection. Instrumentation and catheterization are also significant risk factors for acquisition of infectious diseases.

Evaluation of infections may be difficult because up to nearly half of elders with proven bacterial infections do not have a fever at presentation.[24] In addition, the sensitivity of an elevated white blood cell count and bandemia is poor, approximately 44% and 32%, respectively.[24]

Several infections, particularly pneumonia, urinary tract infections, and sepsis, occur more often in elders. Pneumonia is one of the ten leading causes of hospitalization and death.[5] The elderly are more prone because of decreased vital capacity, decreased lung and airway compliance, less ventilatory drive, and poor ciliary function. Combined with decreased cough response and increased esophageal reflux with microaspiration, pneumonia is the leading cause of hospitalization due to infection in elders. Pneumococcus is still a common cause, but gram-negative organisms are also common, as are mixed infections. Reactivation of tuberculosis also should be considered in this age group.

Urinary tract infections are common in elders. The incidence of bacteriuria is 20% in men older than 70 years and 20% in women 65 to 70 years of age, increasing to 23% and 50%, respectively, in men and women older than 80 years.[25] Laxity of the pelvic floor and urinary incontinence are significant risk factors in women, whereas prostate enlargement is a significant risk factor in men. The incidence of urinary tract infections increases dramatically in patients with chronic indwelling catheters.

Table 182-2 Differential Diagnoses of Abdominal Pain in Elderly Patients

DISORDER	INCIDENCE (%)
Cholecystitis, biliary colic	12-41
Nonspecific abdominal pain	9.6-23
Appendicitis	2.5-15.2
Obstruction	7.3-14
Hernia	4-9.6
Perforation	2.3-7
Pancreatitis	2-7.3
Diverticular disease	3.4-7

Abdominal Pain

Abdominal pain is arguably the most difficult presenting complaint to evaluate in elderly patients. Despite this, most patients have a specific diagnosis made in the ED. Two thirds of elders with abdominal pain are admitted, and nearly one fifth go directly to the operating room.

The differential diagnosis (Table 182-2) of abdominal pain in the elderly differs significantly from that in younger patients, particularly in regard to the number of serious and potentially life-threatening causes. The pathologic condition in more than 60% is surgical in nature, a rate nearly double that of younger patients. There is a tenfold higher risk of mortality compared with younger patients.[26]

Because of the physiologic changes of aging, even life-threatening causes of abdominal pain may be manifested with few or no alarming findings. Elders may complain of vague abdominal pain despite the occurrence of a catastrophic process. The complication rates of typically benign processes in younger patients are dramatically higher in older patients. With aging, the abdominal musculature decreases, and patients are less able to manifest guarding and rebound. In addition, the omentum shrinks and is less able to contain intra-abdominal processes. Atherosclerotic disease, with its resultant decrease in blood flow, causes increased perforation rates in diseases such as cholecystitis and appendicitis. This increased rate of vascular disease also contributes to higher rates of vascular causes of abdominal pain, such as mesenteric ischemia and leaking or ruptured abdominal aortic aneurysms.[27] The high prevalence of gallstones in elders leads to an increased risk of cholecystitis.

Because of the vague presentation and high rate of serious disease, evaluation of an elderly patient with abdominal pain often requires an extensive battery of laboratory and radiographic tests.[28] Elders with potentially catastrophic intra-abdominal processes may not present with a fever or an elevated white blood cell count.[26] As a result, ancillary diagnostic ultrasonography, computed tomography, radionuclide studies, and, occasionally, angiography may be vital. Because many elders with abdominal pain have a serious disease, consider admission and close observation when symptoms persist and the diagnosis remains unclear. If the patient is not admitted, a period of ED observation or re-evaluation within 12 hours is prudent.

www.ketabpezeshki.com 66485457-66963820

Major Trauma

Major trauma in elders (see Chapter 39) is relatively uncommon, constituting 8 to 15% of cases in major trauma databases. Elder trauma patients, however, experience higher mortality and poorer functional recovery for a given trauma score.[29-32] For virtually any trauma in elderly patients, the circumstances leading to the injury need to be determined and the circumstances questioned. Trauma in the elderly may be due to potentially serious or life-threatening medical causes, such as syncope, hypovolemia due to dehydration or bleeding, cardiac or cerebrovascular disease, or medications.[29] Motor vehicle crashes, particularly involving a single vehicle, may result from transient loss of consciousness due to dysrhythmias, syncope, medication side effects, transient ischemic attacks, strokes, or myocardial infarctions.[31] These serious medical problems require simultaneous diagnosis and treatment in the setting of trauma and may be as important as or more important than the traumatic injuries.

The presence of comorbid illness and the limited physiologic reserve in the cardiopulmonary and renal systems often complicate the trauma resuscitation in this age group. More aggressive ventilatory support and early use of invasive hemodynamic monitoring are indicated to guide volume resuscitation. Shock is poorly tolerated in elders because hemodynamic compensation is limited, and end-organ failure occurs earlier.

Certain injuries are more common and severe in elders. A subdural hematoma may occur after relatively trivial head trauma, and chronic subdural hematoma may be manifested as progressive dementia with only subtle neurologic findings. Increasing ankylosis of the spine, osteoarthritis, and decreased bone density as a result of osteoporosis render the geriatric cervical spine more susceptible to fracture. The elderly have more severe pulmonary contusions and a higher incidence of rib fractures and resultant complications (e.g., atelectasis and pneumonia) from preexisting pulmonary disease and a brittle thoracic wall. Skeletal fractures are more common, and lacerations and avulsions of atrophic skin are more difficult to repair and more prone to infection. This thin skin is also prone to decubitus breakdown in patients who are immobile, even for short periods, such as during spinal immobilization on an unpadded backboard.

PREVENTIVE CARE

Immunizations

Pneumonia, influenza, accidents, and adverse medical events are among the top seven causes of death in elders.[5] These conditions account for 15% of admissions and are potentially preventable. Annually, 36,000 adults die of complications from influenza and pneumococcal infections, and most of these deaths occur in elders. Immunization would reduce the incidence of clinical and serologic influenza by half in this population of patients. The Centers for Disease Control and Prevention (CDC) has a goal of an 80% immunization rate for patients in high-risk groups, including elders. The actual vaccination rate falls significantly below this goal. In patients 65 years old, 66% and 62% were vaccinated for influenza and pneumococcal disease, respectively, with the lowest rates among multiracial ethnic groups and people of lower socioeconomic means.[33] As a result, the CDC recommends that potential vaccination sites be extended to include walk-in clinics and EDs. Elders who have not been hospitalized or have not seen their primary care physician in the previous 3 years average at least one visit to an ED, and many are willing to be vaccinated there.

Despite this information, controversy exists about vaccination of elders in the ED. Emergency physicians can be reluctant to give vaccinations, citing time constraints and their concern about delivering primary care. Considering the low threshold in the ED for administration of the tetanus vaccine, it seems feasible that influenza and pneumococcal vaccination programs could be relatively easy and effective in the ED.

Falls

In combination with vaccinations, education about accident prevention in the home could have a considerable impact on the overall morbidity and mortality in elders. Falls and adverse medical events are the seventh leading cause of death in elders.[5] Whereas a primary care or social service provider may be a more appropriate source of information on fall prevention, the ED may be an additional resource to provide educational services to elders on a case-by-case basis, particularly in reference to any specific incident that prompted the need for emergency care. The leading cause of falls in elders is related to the use of pharmacologic agents, often prescription drugs.[30] Reviewing the patient's medications, searching for agents that might cause decreased cognition or dehydration, and addressing the need for these agents with the patient and the primary care provider could significantly decrease the risk for falls. In addition, informing the patient's primary care provider that the patient has fallen may facilitate education by the primary physician.

KEY CONCEPTS

- Polypharmacy and side effects of prescription and nonprescription drugs often occur in elders and should be considered in their evaluation.
- Physiologic changes that occur with aging make the clinical evaluation of elders difficult. Because of the difficulty in obtaining accurate histories and the often poor sensitivity of physical findings in elders with significant underlying disease, more diagnostic tests are generally obtained for these patients than for their younger counterparts who present with similar complaints.
- The immunosenescence that accompanies aging may blunt the fever response to infection and cause a less elevated white blood cell count.
- Myocardial infarction frequently presents atypically in elders as dyspnea, syncope, weakness, confusion, or abdominal complaints, often in the absence of accompanying chest pain.
- Abdominal pain in elders is often caused by surgical conditions that may require extensive evaluation in the ED, including radiographic studies.
- Elderly trauma patients have a higher morbidity and mortality than their younger counterparts because of exacerbation of underlying medical problems.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. U.S. Census Bureau: *Age and Sex Composition: 2010*, issued May 2011. Available at http://2010.census.gov/news/releases/operations/cb11-cn147.html.
2. Centers for Disease Control and Prevention, National Center for Health Statistics: *National Health Interview Survey*. Available at www.cdc.gov/nchs/data/databriefs/db38_tables.pdf.
3. Aminzadeh F, Dalziel WB: Older adults in the emergency department: A systematic review of patterns of use, adverse outcomes, and effectiveness of interventions. *Ann Emerg Med* 2002; 39:238.
4. National Hospital Ambulatory Care Survey: *2008 Emergency department summary tables*. Available at www.cdc.gov/nchs/data/ahcd/nhamcs_emergency/nhamcsed2008.pdf.
5. Heron M: Deaths: Leading causes for 2006. *Nat Vital Stat Rep* 2010; 58:1. Available at www.cdc.gov/nchs/data/nvsr/nvsr58/nvsr58_14.pdf.
6. Budnitz DS, et al: Medication use leading to emergency department visits for adverse drug event in older adults. *Ann Intern Med* 2007; 147:755.
7. Caterino JM, Emond JA, Camargo CA Jr: Inappropriate medication administration to the acutely ill elderly: A nationwide emergency department study, 1992-2000. *J Am Geriatr Soc* 2004; 52:1847.
8. McDonnell PJ, Jacobs MR: Hospital admissions resulting from preventable adverse drug reactions. *Ann Pharmacother* 2002; 36:1331.
9. Chin MH, et al: Appropriateness of medication selection for older persons in an urban academic emergency department. *Acad Emerg Med* 1999; 6:1232.
10. Gaddis GM, Holt TR, Woods M: Drug interactions in at-risk emergency department patients. *Acad Emerg Med* 2002; 9:1162.
11. Gurwitz JH, et al: Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA* 2003; 239:1107.
12. Hustey FM, Wallis N, Miller J: Inappropriate prescribing in an older ED population. *Am J Emerg Med* 2007; 25:804.
13. Buffum M, Buffum C: Nonsteroidal anti-inflammatory drugs in the elderly. *Pain Manag Nurs* 2000; 1:40.
14. Culberson JW, Ziska M: Prescription drug misuse/abuse in the elderly. *Geriatrics* 2008; 63:22.
15. Onen SH, et al: Alcohol abuse and dependence in elderly emergency department patients. *Arch Gerontol Geriatr* 2005; 41:191.
16. Blazer DB, Wu LT: The epidemiology of substance use and disorders among middle aged and elderly community adults: National Survey on Drug Use and Health. *Am J Geriatr Psychiatry* 2009; 17:237.
17. Piechniczek-Buczek J: Psychiatric emergencies in the elderly population. *Emerg Med Clin North Am* 2006; 24:467.
18. Borja B, Borja CS, Gade S: Psychiatric emergencies in the geriatric population. *Clin Geriatr Med* 2007; 23:391.
19. Norman DC: Fever in the elderly. *Clin Infect Dis* 2000; 31:148.
20. Lee CC, et al: Comparison of clinical manifestations and outcome of community-acquired bloodstream infections among the oldest old, elderly, and adult patients. *Medicine (Baltimore)* 2007; 86:138.
21. Rich MW: Epidemiology, clinical features, and prognosis of acute myocardial infarction in the elderly. *Am J Geriatr Cardiol* 2006; 15:7.
22. Alexander KP, et al; American Heart Association Council on Clinical Cardiology; Society of Geriatric Cardiology: Acute coronary care in the elderly, part I: Non–ST-segment-elevation acute coronary syndromes: A scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: In collaboration with the Society of Geriatric Cardiology. *Circulation* 2007; 115:2549.
23. Alexander KP, et al; American Heart Association Council on Clinical Cardiology; Society of Geriatric Cardiology: Acute coronary care in the elderly, part II: ST-segment-elevation myocardial infarction: A scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: In collaboration with the Society of Geriatric Cardiology. *Circulation* 2007; 115:2570.
24. Marco CA, et al: Fever in geriatric emergency patients: Clinical features associated with serious illness. *Ann Emerg Med* 1995; 26:18.
25. Juthani-Mehta MA: Symptomatic bacteriuria and urinary tract infection in older adults. *Clin Geriatr Med* 2007; 23:585.
26. Lewis LM, et al: Etiology and clinical course of abdominal pain in senior patients: A prospective, multicenter study. *J Gerontol A Biol Sci Med Sci* 2005; 60:1071.
27. Kim AY, Ha HK: Evaluation of suspected mesenteric ischemia: Efficacy of radiologic studies. *Radiol Clin North Am* 2003; 41:327.
28. Hustey FM, et al: The use of abdominal computed tomography in older ED patients with acute abdominal pain. *Am J Emerg Med* 2005; 23:259.
29. Aschkenasy MT, Rothenhaus TC: Trauma and falls in the elderly. *Emerg Med Clin North Am* 2006; 24:413.
30. Soriano TA, DeCherrie LV, Thomas DC: Falls in the community-dwelling older adult: A review for primary-care providers. *Clin Interv Aging* 2007; 2:545.
31. Cook LJ, et al: Motor vehicle crash characteristics and medical outcomes among older drivers in Utah, 1992-1995. *Ann Emerg Med* 2000; 35:585.
32. Rathlev NK, et al: Intracranial pathology in elders with blunt head trauma. *Acad Emerg Med* 2006; 13:302.
33. Centers for Disease Control and Prevention: Public health and aging: Influenza vaccination coverage among adults aged > or = 50 years and pneumococcal vaccination coverage among adults aged > or = 65 years—United States, 2002. *MMWR Morb Mortal Wkly Rep* 2003; 52:987.

www.ketabpezeshki.com 66485457-66963820

Section Four

THE PATIENT WITH COMPROMISED IMMUNE FUNCTION

CHAPTER 183

The Immunocompromised Patient

Michael J. Burns

PERSPECTIVE

As increased numbers of immunocompromised persons present to the emergency department (ED), it is essential that emergency physicians possess the knowledge and skills to recognize and to treat infectious complications of cancer, organ transplantation, diabetes, renal failure, cirrhosis, asplenism, human immunodeficiency virus (HIV) infection, and other immunosuppressive conditions. These include infectious complications of immunosuppressive and immunomodulating medications used for a wide variety of disorders.

Compared with individuals with an intact immune system, infections in immunocompromised patients are more common, progressive, and severe, and they are caused by a wider variety of microorganisms. Immunocompromised persons who present with acute infections may appear deceptively benign initially, their symptoms and signs often mimicking noninfectious complications, only to deteriorate rapidly if they are not aggressively treated. Many interrelated factors cause patients to become immunocompromised and predispose them to the development of infections with potentially pathogenic microorganisms. These include disruption of the body's protective surfaces, such as skin and mucosal barriers (oral and respiratory mucosa and intestinal and genitourinary surfaces); disorders that directly impair the function of the body's immune system (e.g., lymphoma, asplenism, and myeloma); drugs and irradiation that suppress or alter immune function; alterations in body substances (hyperglycemia) or solid organ function (kidney and liver failure); and malnutrition, aging, and exposure to antimicrobial agents that inhibit the normal protective resident bacterial flora.[1]

PRINCIPLES OF DISEASE

The body's defense mechanisms consist of surface barriers, such as skin, enzymes, and mucus, as well as innate (natural) and acquired (adaptive) responses. Innate responses occur to the same extent regardless of how often the body encounters the infectious agent, whereas acquired responses improve on repeated exposure.[2] Innate immunity is activated immediately on exposure to an infecting agent, rapidly controlling replication and allowing the requisite 3 to 5 days for the adaptive component to clone sufficient T and B cells to respond more specifically.[3-5]

Non–Microbe-Specific Immunity

Physical Barriers

The first line of defense against microorganisms consists of physical barriers. These include intact skin, gastrointestinal and respiratory mucosa, cilia, biofilm, gastric acid, antibacterial substances in pancreatic and biliary secretions, antimicrobial peptides and proteins on skin and mucous membranes, and resident microflora.[6]

In the respiratory tract, mucociliary transport and the cough reflex remove particulate matter and microbes, but this mechanism is impaired with smoking and ineffective cough. Mechanical ventilation or tracheostomy introduces large numbers of microbes that often overwhelm natural clearance.[7]

Gastric acid and pancreatic enzymes have antibacterial properties that prevent overgrowth in the upper gastrointestinal tract. Normal peristalsis and mucosal shedding help maintain normal gut flora. Alterations in these factors increase susceptibility to infection. Broad-spectrum antibiotics alter normal flora, permitting overgrowth of pathogens such as *Candida* species, multiantibiotic-resistant bacteria, and *Clostridium difficile*.

Initial Inflammatory Response and Innate Immunity

The first response to microbial invasion, the initial inflammatory response (formerly called the acute-phase response), acts to promote phagocytosis and microbial killing and to activate the immune system.[8] Sentry cells detect pathogens, immediately triggering inflammation. This innate immune response is not dependent on prior exposure to the pathogen. The initial inflammatory response factors, mainly produced in the liver, activate many cell types to synthesize and to release cytokines, chemokines, and "trigger molecules" that kill the invading organism.[3]

This response delivers humoral and cellular immune components to sites of inflammation and initiates antibody responses. Cytokines, platelet-activating factor, and hormone-like proteins, including interferons, are secreted from various immune cells and play important roles in mediation of this response.[9] These cytokines result in migration and adhesion of polymorphonuclear leukocytes and monocytes to sites of bacterial invasion. These cells release granules of substances that mediate vasodilation and increased vascular permeability, leading to edema, warmth, and redness, but also allow both phagocytic cells and humoral components to be concentrated at the site of infection.

A family of distinct transmembrane proteins, called Toll-like receptors, are found on many cell types, including macrophages, neutrophils, dendritic cells, mucosal epithelial cells, and endothelial cells. They recognize molecular patterns associated with microorganisms even in the absence of prior exposure, alert the host to the presence of the infectious agent and rapidly initiate a cascade of processes to activate innate immune responses, and help bridge innate and adaptive immune responses.[3,6]

www.ketabpezeshki.com 66485457-66963820

Reticuloendothelial System

The reticuloendothelial system, composed of tissue macrophages and their blood-borne counterparts, monocytes, removes particulate matter, including microbes, from the lymph and blood. The tissue component is concentrated in the lymph nodes, spleen, liver, marrow, and lung and has particular affinity for encapsulated bacteria such as pneumococci, meningococci, and *Haemophilus influenzae*. The vital importance of this non–microbe-specific system is demonstrated by the overwhelming sepsis from encapsulated organisms in patients with asplenia.

Adaptive (Microbe-Specific) Immunity

Humoral Immunity

Antibodies. Antibodies are produced by B lymphocytes, and each B cell produces a single microbe-specific antibody type. Stimulation by an antigen (or microbe) causes proliferation of this particular B cell so that large quantities of a specific circulating antibody can be produced. Furthermore, B cells are active in presenting antigens to T lymphocytes, which promotes cell-mediated immunity.

Immunoglobulins. IgM is the first immunoglobulin to appear in response to a new antigen. Although it has less affinity at binding antigens than IgG does, IgM provides some recognition of antigens and begins B-cell proliferation before the subsequent development of IgG.[10] IgM is detectable earlier in serum than IgG and serves as a marker for a patient's early response to acute infection.

Secretory IgA is the predominant immunoglobulin present in gastrointestinal fluids, nasal and oral secretions, tears, and other mucous fluids. IgA inhibits cell adherence of viral, bacterial, and protozoan pathogens and therefore prevents invasion by organisms through the respiratory or gastrointestinal tract.[10]

IgE, which is expressed in high concentration on the surface of mast cells and basophils, is responsible for immediate-type hypersensitivity responses. Mast cells and IgE are important in defense against helminthic pathogens.

IgG, which accounts for 75% of the total immunoglobulin mass, is widely distributed in tissues. It crosses the placenta and provides fetal immunity during the first 6 months of life. Congenital or acquired deficiencies of IgG lead to infection with encapsulated organisms because the predominant subtype (IgG2) has affinity for the dense polysaccharides of bacterial cell capsules, such as those of *Streptococcus pneumoniae* and *H. influenzae*.

Complement. The complement cascade, consisting of a complex interaction of 30 proteins, is another crucial component of humoral response. Complement is important in producing inflammation and leukocytosis and in recruiting leukocytes to sites of infection by production of chemoattractants. Complement also neutralizes viruses, enhances opsonization of bacteria, and produces bacterial cell wall and membrane lysis.

Both IgG and IgM, when they are in contact with an antigen, activate the classical pathway, whereas molecules with repeating chemical structures (e.g., bacterial cell walls and capsules) activate the cascade through the alternative pathway. Components of C3, the merging point of the classical and alternative paths, provide opsonization and modulate the response of lymphocytes (cell-mediated immunity). Opsonization is important in defense against infection with *S. pneumoniae, Streptococcus pyogenes, H. influenzae*, and *Staphylococcus aureus*. The terminal leg of the cascade, C5 through C9, forms the membrane attack complex, which inserts into cell walls and membranes and leads to cell death.

Individuals with inherited complement deficiencies are predisposed to frequent and recurrent infections with *S. pneumoniae, H. influenzae,* and especially *Neisseria meningitidis* and *Neisseria gonorrhoeae*.[11] The risk of meningococcal infection is increased several thousand-fold and most often develops in people deficient in C3 and in late complement components (C5-C8). Paradoxically, the disease is usually milder with complement deficiency, and mortality is likewise reduced fivefold to tenfold.[12] This suggests that the host response may be, in part, responsible for the severity of disease in normal individuals and is attenuated in complement deficiency. People with meningococcemia should be tested for inherited complement deficiencies because they may benefit from immunization.

Acquired deficiencies of complement function may develop in people with rheumatologic diseases, especially systemic lupus erythematosus (SLE). Approximately 40% of patients with SLE have an inhibitor of C5a-derived chemotaxis in their serum that results in enhanced susceptibility to infection.[13]

Cell-Mediated Immunity

Cell-mediated immunity (CMI) generally includes immune responses that are mediated by T lymphocytes, natural killer (NK) cells, and mononuclear phagocytes. CMI is vitally important in the control of infections caused by microbes that survive and replicate intracellularly, including most viruses and some bacterial (obligate and facultative intracellular types), fungal, and protozoan pathogens.

Only 5% of lymphocytes are in circulating blood. Most mature and are active in the marrow, thymus, spleen, and lymph nodes. The last two sites expose T cells to circulating antigen from invading microbes.[6] Specialized antigen-presenting cells in the lymphoid system sequester antigen and antigen-antibody complexes and present them to T cells. This process involves internalization and processing of the antigen, followed by formation of peptides that bind to a cell surface molecule called the major histocompatibility complex (MHC). Only with this specific presentation can a T lymphocyte become activated against a particular antigen.

Two major types of T lymphocytes are CD4 (helper cell) and CD8 (suppressor cell), corresponding to type II and type I of MHC, respectively. CD4 lymphocytes provide help for other cells in the immune system, including enhanced B-cell antibody production and production of cytokines. CD8 lymphocytes are generally cytotoxic and mediate the eradication of virally infected target cells and certain tumors. A decline in the number of CD4 cells, with predominance of CD8 cells, is responsible for the increased susceptibility to infection in patients with acquired immunodeficiency syndrome (AIDS).[6] Despite the cytotoxicity of CD8 cells, immunity is reduced without adequate numbers of CD4 cells.

Patients with defects in CMI are at increased risk for disseminated infection with intracellular bacteria, such as *Mycobacterium tuberculosis, Listeria monocytogenes,* and *Salmonella* species. The DNA viral infections, such as cytomegalovirus, herpes simplex, and varicella-zoster, also affect these patients more severely, as do fungal infections with *Candida, Cryptococcus, Mucor, Aspergillus,* and *Pneumocystis*. Finally, some protozoa are pathogenic without intact CMI, as infections with *Toxoplasma gondii* demonstrate.[14,15] Some infections are seen only below a certain CD4 cell count. *Pneumocystis* pneumonia is seen almost exclusively in patients with counts below 200 cells/mL (2×10^5 cells/L), whereas almost all patients with toxoplasmosis or cryptococcal meningitis have counts below 100 cells/mL (1×10^5 cells/L).

NK cells, closely related to lymphocytes but neither B nor T cells, are important in the innate immune response and are found in high concentrations in blood and spleen.[3,6] NK cells recognize infected cells and respond by directly killing these cells, and they secrete cytokines that activate macrophages to destroy phagocytosed microbes. These cells are important in defense against

www.ketabpezeshki.com 66485457-66963820

intracellular microbes, particularly viruses and intracellular bacteria such as *L. monocytogenes*.

Granulocytic Phagocytes

Granulocytic phagocytes are the cellular effectors of microbe killing, engulfing them and enzymatically lysing their cell membranes or walls. Two major types are polymorphonuclear leukocytes (also called neutrophils) and macrophages (the tissue version of circulating monocytes). Macrophages have surface receptors that recognize nonvertebrate carbohydrates such as mannose, which form the cell wall of some microorganisms. Hence, they can identify and attack "invaders" rather than "self."

Two other types of granulocytes, eosinophils and basophils, are less involved in the ingestion of organisms.[16] Eosinophils mediate the destruction of certain parasitic helminths through release of toxic proteins. Normally only 3% of total granulocytes, this cell type can reach 20% during times of high parasite load. Basophils (rare in circulation) and their tissue counterparts, mast cells, have high affinity for IgE. On exposure to antigens, they release granules with histamine, prostaglandins, and leukotrienes, which affect the allergic-inflammatory response with increased vascular permeability, bronchospasm, and vasodilation.[2]

Neutrophils constitute 90% of circulating granulocytes and spend only 6 to 8 hours of their average 4-day life in circulation (the remainder in tissues). Effective antibacterial activity depends on the ability of neutrophils to travel to sites of infection, a process known as chemotaxis. The locomotion of neutrophils along vascular endothelium is facilitated by adherence to cell surface proteins whose production is enhanced in the initial inflammatory response.[16]

Half of all neutrophils that leave the bone marrow circulate in the plasma. The other half become marginated, adhering to endothelium, primarily in the lungs, liver, and spleen. During periods of stress or with endogenous or exogenous catecholamines or corticosteroids, these neutrophils demarginate and enter the circulation. As long as the patient is not neutropenic, demargination causes an increased peripheral neutrophil count composed of mature cells, whereas with infection, an increased proportion of immature (band) forms is typically seen.

Neutrophils (and macrophages in tissue) bind to and ingest bacteria, a process called phagocytosis. This process is enhanced by proteins called opsonins that bind to bacterial surfaces. C-reactive protein, one of the initial inflammatory response proteins, fulfills this function for certain bacteria, including *S. pneumoniae*. IgG and complement protein C3b also opsonize bacteria, again illustrating the interdependence of the immune system. Actual killing takes place within granulocytes when cytoplasmic granules enzymatically produce potent oxidants. Granulocytes further control bacterial proliferation at the site of infection by elaborating lactoferrin, which locally binds free iron necessary for bacterial replication.

In addition to phagocytosis, macrophages (located in the spleen, alveoli, liver, and lymph nodes) modulate the immune response by presenting antigens to lymphocytes and releasing cytokines and complement components. Activation of macrophages to ingest bacteria depends on interaction with interferon-γ, a cytokine manufactured by T cells.[6] Thus the once clear demarcation between cellular and humoral immunity is breaking down as more is understood about the interdependent immune system.

SPECIFIC IMMUNOCOMPROMISED STATES

Solid Organ Transplants

See Chapter 184.

Cancer

Patients with cancer frequently have multiple immune defects, such as neutropenia and impaired function of T and B cells, induced by cancer chemotherapy or by the disease process itself, which predisposes them to infection. Other factors leading to infection are defects in physical barriers (skin and mucous membranes), including cytotoxic effects of chemotherapy on cells lining the gastrointestinal tract. In addition, splenic dysfunction or splenectomy, use of long-term intravascular catheters, frequent use of complex invasive diagnostic and therapeutic procedures, toxic effects of radiation therapy, and frequent colonization with antimicrobial-resistant pathogens are predisposing factors. Cancer treatments (e.g., allogeneic bone marrow and autologous stem cell transplantation, platelet transfusion, granulocyte colony-stimulating factor, and implanted central venous catheters) increase survival during episodes of profound immunosuppression, allowing patients to receive more intense cytotoxic cancer chemotherapy regimens. This results in long survival of patients with neoplastic diseases that were formerly rapidly fatal. Despite many advances in supportive care, infections continue to result in serious morbidity and mortality. Furthermore, increasing resistance to antimicrobials is occurring among common pathogens along with the emergence of new opportunistic pathogens. Infection is much more common in patients with acute leukemia and lymphoma (75% of patients) and multiple myeloma (50% of patients) than in those with solid tumors.[17] Factors predisposing to infection in immunocompromised patients are listed in Box 183-1.

Neutropenia

Principles of Disease. Neutropenia is defined as a neutrophil count of less than 500 cells/mL (5×10^5 cells/L), including band forms, or less than 1000 cells/mL (1×10^6 cells/L) and expected to fall to less than 500 cells/mL.[18,19] It usually results from cytotoxic chemotherapy or radiation therapy or the disease process, especially in hematologic malignant neoplasms. In addition, cancer chemotherapeutic agents and radiation therapy can cause functional defects in granulocytes. The risk of febrile neutropenia and mortality is higher in the first one or two cycles of multicycle cytotoxic chemotherapy regimens.[20]

The incidence and severity of infection in cancer patients with neutropenia are inversely proportional to the absolute neutrophil count and directly proportional to the duration of neutropenia. Although the incidence begins to rise as the neutrophil count falls below 500 cells/mL (5×10^5 cells/L), most severe infections and almost all bacteremias occur when the neutrophil count is less than 100 cells/mL.[21] Fever in the neutropenic patient is defined as a single temperature of 38.3° C (101° F) or higher or a temperature of 38.0° C (100.4° F) or higher during 1 or 2 hours.[19] In neutropenic patients, the temperature should be measured orally or tympanically, not rectally. Although fever can be suppressed or lessened by immunosuppressive agents such as corticosteroids and nonsteroidal anti-inflammatory drugs, most cancer patients with infection manifest fever despite the use of these agents.[22] Also, although it is uncommon, immunocompromised patients can have serious local or systemic infections without fever. This is manifested by unexplained tachypnea or tachycardia, mental status changes, metabolic acidosis, increased volume requirements, rapid changes in serum glucose or sodium concentration, or acute abdominal pain. Because the onset of life-threatening infections can be rapid in cancer patients with severe neutropenia or a history of splenectomy, urgent evaluation and initiation of antimicrobial therapy are essential. A prospective multicenter observational study of febrile neutropenic cancer patients in EDs in France found that critically ill patients were poorly recognized and undertreated,

www.ketabpezeshki.com 66485457-66963820

Box 183-1 The Immunocompromised Patient: Factors Predisposing to Infection and the Most Common Pathogens

Neutropenia

Bacteria

Gram-negative bacilli
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Enterobacter* sp.
- *Serratia* sp.
- *Citrobacter* sp.
- *Proteus* sp.
- *Acinetobacter* sp.
- *Stenotrophomonas maltophilia*

Gram-positive cocci
- *Staphylococcus epidermidis*
- *Staphylococcus aureus* including methicillin-resistant strains
- Viridans streptococci
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*
- Less common: *Enterococcus* sp., including vancomycin-resistant strains

Gram-positive rods
- *Corynebacterium* sp.
- Less common: *Bacillus* sp.

Fungi

Candida sp.
Aspergillus sp.
Less common: *Mucor* sp., *Rhizopus* sp., *Trichosporon beigelii*, *Fusarium* sp., *Pseudallescheria boydii*

Cellular Immune Dysfunction

Bacteria

Listeria monocytogenes
Salmonella sp.
Mycobacterium tuberculosis
Mycobacterium avium-intracellulare
Legionella sp.
Nocardia sp.

Fungi

Cryptococcus neoformans
Histoplasma capsulatum
Coccidioides immitis
Candida sp.
Aspergillus sp.
Pneumocystis jiroveci (formerly *carinii*)

Viruses

Herpes simplex
Varicella zoster
Cytomegalovirus
Epstein-Barr
Less common: Measles, adenovirus

Parasites

Toxoplasma gondii
Cryptosporidium sp.
Strongyloides stercoralis

Humoral Immune Dysfunction (Antibody Deficiency)

Bacteria

Streptococcus pneumoniae
Haemophilus influenzae
Neisseria meningitidis
Staphylococcus aureus

Splenectomy or Functional Asplenia

Bacteria

Streptococcus pneumoniae
Haemophilus influenzae
Neisseria meningitidis
Capnocytophaga canimorsus
Bordetella holmesii

Parasites

Babesia sp.

Complement Deficiency

Bacteria

Neisseria meningitidis
Streptococcus pneumoniae
Haemophilus influenzae

low-risk patients were overtreated, and compliance with established guidelines was low.[23]

The most common sites of infection in neutropenic patients are the lung (25%); mouth and pharynx (25%); gastrointestinal tract (15%); skin, soft tissue, and intravascular catheters (15%); perineum and anorectal area (10%); urinary tract (5%); and nose and sinuses (5%).[24] Pneumonia and anorectal infection are more likely to be associated with bacteremia. Bacteremia may occur without an obvious source despite intensive investigation. Historically, the most important bacteria are three gram-negative bacilli—*Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*—and four gram-positive cocci—*Staphylococcus epidermidis*, viridans group streptococci, *Enterococcus* species, and *S. aureus*. Many centers that treat large numbers of cancer patients note a decrease in these gram-negative bacilli and an increase in infections caused by others, such as *Enterobacter*, *Citrobacter*, and *Serratia* species, which are capable of rapidly developing resistance to cephalosporins and extended-spectrum penicillins. Anaerobes are uncommon but may be important in certain mixed infections (e.g., mouth, abdominal, and perianal).

During the past 25 years, infection with gram-positive organisms (e.g., coagulase-negative staphylococci, *S. aureus*, viridans streptococci, and *Enterococcus* species) has increased, and this is now the leading cause of bacterial infection (50-70% at some centers) in febrile neutropenic cancer patients in the United States, Canada, and western Europe. Gram-negative organisms still predominate in developing countries.[25,26] With the exception of viridans streptococci, most of these gram-positive organisms do not produce immediately life-threatening infections compared with the rapid lethality of many gram-negative infections. Life-threatening bloodstream infections caused by viridans streptococci (especially *Streptococcus mitis*) are common in many cancer centers and often respond poorly to penicillins and cephalosporins. Risk factors for serious viridans streptococcal infections include aggressive cytoreduction therapy for acute leukemia or allogeneic bone marrow transplantation (especially after high-dose cytosine arabinoside treatment), profound neutropenia, and severe oral mucositis. Other factors include prophylactic use of trimethoprim-sulfamethoxazole or fluoroquinolones, use of antacids or H_2 receptor antagonists, and childhood.[27,28]

Aspergillus and *Candida* species are the most common fungi producing infection in cancer patients with fever and neutropenia.[24,29,30] Infection is most likely to develop in neutropenic patients treated with broad-spectrum antimicrobials and in those whose fever persists for more than 7 days. *Aspergillus* species usually produce necrotizing infections in the lung or sinuses. Pulmonary aspergillosis often is manifested with pleuritic pain, hemoptysis, and localized wheezing. The chest radiograph demonstrates

www.ketabpezeshki.com 66485457-66963820

pleural effusion or focal infiltrates. Computed tomography (CT) is more sensitive in detection of pulmonary infiltrates compatible with aspergillosis, and it may demonstrate a distinct halo of low attenuation surrounding a pulmonary infiltrate. This pattern is highly suggestive of invasive aspergillosis, although mucormycosis and other disorders may mimic the halo. Invasive aspergillosis originating in the paranasal sinuses may extend to the surrounding bone and brain. Often, an initial red-purple lesion on the nasal turbinate or palate turns pale and then black as vascular invasion produces infarction of the mucosa and bone. The black eschar on the nose or palate is easily misdiagnosed as dried blood. Patients presenting with head or facial pain or swelling, or proptosis, should be rapidly evaluated for invasive aspergillosis and mucormycosis. *Candida* species produce infections of the skin, oral cavity, and esophagus as well as fungemia. The sudden onset of generalized rash consisting of pink-purple, nontender subcutaneous nodules is characteristic of candidemia.

Less common fungi producing infection in these patients include *Mucor* and *Rhizopus* species (necrotizing pneumonia and sinusitis), *Trichosporon* species (pneumonia and fungemia), and *Pseudallescheria boydii* (soft tissue infection). Other than *Candida* species, these fungi are rarely found in blood cultures. Specific diagnosis requires biopsy.

Clinical Features. Certain clinical findings are characteristic of specific pathogens (Table 183-1). Noninfectious causes of fever also need to be considered, such as drug toxicity, drug allergy, transfusion reactions, and pulmonary emboli.[17] Fever is frequently the only sign of infection because these patients are unable to mount a full inflammatory response at a site of infection.[24] Usual symptoms and signs of infection may not be present, especially when the neutrophil count is less than 100 cells/mL (1×10^5 cells/L). When pneumonia develops, purulent sputum may be absent, and the initial chest radiograph may not show an infiltrate. Pyuria may be absent in the presence of urinary tract infection. Areas of cellulitis may have diminished or absent induration and redness and no purulent drainage. Tenderness may be the only finding in perineal and anal infections. The neutropenic patient with a documented infectious cause of fever may be difficult to distinguish from the patient with fever not caused by infection. The performance of a procedure before the onset of fever, presence of chills, "toxic appearance," and lack of localized findings do not help determine whether the patient is bacteremic.[31] Only 20% of febrile neutropenic patients have a clinical focus of infection identified at presentation, and only 30% of patients have positive blood cultures.

Table 183-1 Characteristic Clinical Findings in Neutropenia That May Be Associated with Infection with Specific Pathogens

CHARACTERISTIC CLINICAL FINDINGS	SUSPECT PATHOGENS
Ulcerative lesions in the mouth	Viridans streptococci, herpes simplex, *Candida*, anaerobes
Necrotizing skin lesions	*Pseudomonas aeruginosa, Aeromonas hydrophila, Aspergillus, Mucor*
Nontender subcutaneous nodules	*Nocardia, Cryptococcus*
Nontender pink skin papules	*Candida*
Black eschar of nose or palate	*Aspergillus, Mucor*
Generalized macular red rash	Viridans streptococci
Right lower quadrant abdominal pain, tenderness, distention, bloody diarrhea	Typhlitis (neutropenic enterocolitis) caused by *Pseudomonas aeruginosa, Escherichia coli, Clostridium septicum*
Perineal pain and tenderness without inflammation or abscess	Gram-negative bacilli, anaerobes
Redness or pain at vascular catheter sites	Coagulase-negative staphylococci, *Corynebacterium, Bacillus* species

Mucositis involving the mouth and other mucous membranes is a painful and debilitating condition that commonly occurs in cancer patients receiving intense chemotherapy. It is a frequent prelude to viridans streptococcal bacteremia, which can produce sudden onset of acute respiratory distress syndrome, a toxic shock–like syndrome, rash, and pneumonia.

Diagnostic Strategies. The evaluation of the cancer patient with fever and neutropenia should include a meticulous search for subtle symptoms and signs of inflammation at common sites: oral cavity and pharynx, lower esophagus, lung, skin, perineum including anus, bone marrow aspiration sites, vascular catheter sites, and tissue around the nails.[21] In nearly two thirds of patients, the initial evaluation does not identify a focus of infection.[22] Two sets of blood culture specimens should be obtained. If the patient has a central venous catheter, culture specimens of blood should be obtained from each lumen of a multilumen catheter and from at least one peripheral site.[19] Specimens for culture should also be obtained from any site of inflammation, including inflamed or draining catheter exit sites. Patients with severe mucositis should have herpes simplex cultures performed if they are not receiving antiherpes prophylaxis, and they should have a smear for *Candida* pseudohyphae. Complete blood count, electrolyte values, transaminase levels, blood urea nitrogen concentration, and creatinine concentration should be determined to plan management and to monitor the occurrence of drug toxicity.

Urine culture should be performed if symptoms or signs of a urinary tract infection are present, if a urinary catheter is in place, or if the urinalysis is abnormal. Examination of the cerebrospinal fluid is not recommended as a routine procedure unless subtle symptoms or signs of meningitis are present.

A chest radiograph should be obtained in patients with respiratory symptoms and signs.[19] If the chest radiograph is normal or inconclusive but there is still suspicion for pneumonia, high-resolution CT or thin-section multislice CT scanning of the chest without contrast enhancement should be obtained because pneumonia is often detected by chest CT in febrile neutropenic patients with normal findings on the chest radiograph.[32] CT evaluation of the sinuses should be performed if facial pain or swelling is present. In patients with abdominal pain and tenderness, CT scanning of the abdomen is useful for diagnosis of neutropenic enterocolitis ("typhlitis"), a necrotizing infection of the bowel wall that usually affects the cecum. This is more commonly seen in acute leukemia and is not generally treated surgically. Ultrasonography over a subcutaneous tunneled catheter track and its vein of insertion may reveal the presence of an abscess or infected thrombus.[33]

In patients with diarrhea, stool testing for *C. difficile* toxin as well as culture for routine bacterial pathogens should be obtained. *C. difficile* colitis occasionally produces abdominal pain in the absence of diarrhea. *Cryptosporidium parvum,* a protozoan, may cause profuse, watery diarrhea and is detected by acid-fast staining or immunofluorescence testing of stool.

Management of Febrile Neutropenia

Antibiotic Therapy. Broad-spectrum antimicrobial therapy should be initiated promptly in the febrile neutropenic patient if the neutrophil count is less than 500 cells/mL (5×10^5 cells/L) or if the neutrophil count is 500 to 1000 cells/mL (5 to 10×10^5 cells/L) and expected to drop.[19,34] Moreover, even afebrile neutropenic patients who have symptoms and signs (e.g., abdominal pain and tenderness) compatible with an infection should be treated empirically (Table 183-2).

Use of a single antimicrobial agent is preferred in most patients because there is no conclusive evidence of a benefit from multiple drugs.[19,35,36] Factors that should be considered in choosing an antimicrobial agent include renal and hepatic function, drug allergies,

www.ketabpezeshki.com 66485457-66963820

Table 183-2 Selected Antimicrobial Agents Useful in the Immunocompromised Patient

DRUG	DOSAGE: Adult	DOSAGE: Child (age > 28 days)	PRECAUTIONS AND COMMENTS
Aminoglycosides			
Gentamicin	2 mg/kg loading dose, then 5 mg/kg/day IV q8-12h, *or* 5-7 mg/kg IV once daily	Same as adult	Decrease maintenance dose in elderly or with renal dysfunction.
Tobramycin	Same as gentamicin	Same as adult	
Amikacin	10 mg/kg/day loading dose, then 15 mg/kg/day IV q12h or once daily	Same as adult	
Extended-Spectrum Penicillins and β-Lactamase Inhibitors			
Piperacillin-tazobactam	4.5 g IV q6h	240-400 mg/kg/day IV q6h	For *Pseudomonas aeruginosa*, administer with aminoglycoside.
Cephalosporins			
Ceftazidime Cefepime	1-2 g IV q6-8h 1-2 g IV q8h	150 mg/kg/day IV q8h 150 mg/kg/day IV q8h	Both are active against *P. aeruginosa,* but cefepime is more active than ceftazidime against gram-positive organisms and some resistant gram-negative bacilli.
Carbapenems			
Imipenem-cilastatin	0.5-1 g IV q6h	60-100 mg/kg/day IV q6h	Adjust dose in elderly or with renal dysfunction.
Meropenem	0.5-1 g IV q8h	60-120 mg/kg/day IV qh8	Seizures are associated with imipenem. May be cross-allergenic with penicillin Broad-spectrum activity against gram-positive and gram-negative organisms, including *P. aeruginosa* and anaerobes
Other			
Aztreonam	1-2 g IV q8h	120 mg/kg/day IV q6h	Active against gram-negative bacilli including *P. aeruginosa* Not active against gram-positive organisms Safe in penicillin-allergic patient
Vancomycin	15 mg/kg IV q12h	40 mg/kg/day IV q6-12h	Infuse during 2 hours (flushing, hypotension with rapid infusion).
Amphotericin B	0.5-1.5 mg/kg/day IV once daily	Same as adult	Refer to infectious disease or pharmacology text.
Acyclovir			Infuse during 1 hour.
Herpes simplex, mucocutaneous*	5 mg/kg IV q8h *or* 400 mg PO three times a day	250 mg/m^2 IV q8h *or* 15 mg/kg/day PO q4h	
Herpes zoster			
Not severe†	800 mg PO five times a day	20 mg/kg PO four times a day	
Severe	10 mg/kg IV q8h	500 mg/m^2 IV q8h	Elderly: 7.5 mg/kg IV q8h
Primary varicella	10 mg/kg IV q8h	500 mg/m^2 IV q8h	

*Alternative for herpes simplex: famciclovir 250 mg three times a day, or valacyclovir 1 g two times a day PO.
†Alternative for herpes zoster: famciclovir 500 mg three times a day, or valacyclovir 1 g three times a day PO q8-12h.

suspected site of infection or organism, and cost. Antimicrobial resistance varies widely, and in the absence of a written hospital-specific protocol, immediate consultation with an oncologist or an infectious diseases specialist may be of great assistance.

Monotherapy with intravenous cefepime, ceftazidime, imipenem, meropenem, or piperacillin-tazobactam is preferred, with an aminoglycoside (gentamicin, tobramycin, or amikacin) added for the more seriously ill patient.[19,24,37,38] Monotherapy, without an aminoglycoside, may be advantageous in the patient with mild to moderate renal dysfunction or for patients receiving nephrotoxic agents, such as cisplatin, cyclosporine, or amphotericin B. Ceftazidime-resistant gram-negative bacilli are common pathogens at some centers. In addition, ceftazidime is the least active against gram-positive organisms, compared with cefepime, cefotaxime, or ceftriaxone. Cefepime, a broad-spectrum cephalosporin with excellent activity against both gram-positive and gram-negative organisms, including *P. aeruginosa,* is preferred at many centers. The carbapenems imipenem and meropenem provide excellent activity against gram-negative organisms (including *P. aeruginosa*), gram-positive organisms, and anaerobic bacteria. None of the antimicrobial agents previously listed is active against vancomycin-resistant *Enterococcus* species or methicillin-resistant staphylococci.

For patients who are allergic to β-lactam antibiotics (e.g., penicillins, cephalosporins, imipenem, and meropenem), coverage of gram-negative bacilli, including *P. aeruginosa,* can be provided by aztreonam. Because aztreonam is not active against gram-positive or anaerobic bacteria, it should be combined with an antimicrobial such as vancomycin. If anaerobes are suspected (i.e., oral, abdominal, or perianal infection) in the β-lactam–allergic patient or in the patient receiving cephalosporin monotherapy, an anti-anaerobic drug such as clindamycin or metronidazole should be

www.ketabpezeshki.com 66485457-66963820

administered. Empirical treatment with intravenous fluoroquinolones is not recommended in the febrile neutropenic cancer patient because of frequent prophylactic use of these agents in the cancer patient, risk for rapid emergence of resistance in gram-negative bacilli, and predisposition to *C. difficile* infection.[19,39,40]

When a focus of infection is identified, empirical therapy should cover the most likely pathogens causing infections at the site. For example, patients with pneumonia may need coverage for *Legionella* (fluoroquinolone, azithromycin, doxycycline, or erythromycin), *Pneumocystis* (trimethoprim-sulfamethoxazole), or fungi (amphotericin B) in addition to standard antibacterial coverage. Agents effective against anaerobes (clindamycin, metronidazole, imipenem, meropenem, and piperacillin-tazobactam) should be considered for patients with perianal or oral infection and those with abdominal pain, who may have appendicitis, diverticulitis, or typhlitis (neutropenic enterocolitis). Acyclovir should be considered for patients with ulcerative or vesicular lesions who may have herpes simplex or varicella-zoster virus infections. Ganciclovir may be required for treatment of cytomegalovirus infection, which is rare in febrile neutropenic cancer patients. Foscarnet may be needed for acyclovir-resistant herpes simplex or ganciclovir-resistant cytomegalovirus infections. In patients with severe mucositis and febrile neutropenia, a carbapenem or extended-spectrum penicillin is preferred for empirical treatment rather than a higher generation cephalosporin because of superior efficacy against viridans streptococci.

Routine empirical use of vancomycin for the febrile neutropenic cancer patient is not recommended because of concern about the development of vancomycin-resistant organisms.[19,27,41,42] Randomized clinical trials show no survival advantage when vancomycin is in the initial therapy for all neutropenic patients, even those with indwelling catheters. Because most infections with gram-positive bacteria are indolent, vancomycin therapy can be safely delayed for 24 to 48 hours in most patients until a vancomycin-requiring gram-positive infection is identified.[43]

Indications for initial empirical vancomycin therapy include serious catheter-related infections, known colonization with penicillin-resistant pneumococci or methicillin-resistant *S. aureus,* and positive blood culture for gram-positive organisms before final identification and susceptibility testing. Other indications include shock; severe mucositis; prior fluoroquinolone prophylaxis; and institutions in which methicillin-resistant *S. aureus,* vancomycin-susceptible enterococci, and *S. mitis* are frequent pathogens.

Patients previously colonized or infected with methicillin-resistant *S. aureus,* vancomycin-resistant enterococci, extended-spectrum β-lactamase–producing gram-negative bacteria, and carbapenemase-producing organisms may require modifications to initial empirical therapy.[19]

Amphotericin B (and its lipid formulations) is the drug of choice for treatment of invasive fungal infections in patients with neutropenia.[19,41,44] Up to one third of febrile neutropenic patients not responding to 1 week of antibiotics have systemic fungal infections, usually *Candida* or *Aspergillus*. Antifungal agents, such as caspofungin, voriconazole, or posaconazole, may be indicated in selected cases. Empirical use of fluconazole is not recommended because of lack of activity against *Aspergillus* and some *Candida* species.

Cell Stimulation Therapy

For prevention and treatment of neutropenia, some centers routinely use human recombinant hematopoietic or colony-stimulating growth factors (granulocyte colony-stimulating factor: filgrastim, pegfilgrastim; granulocyte-macrophage colony-stimulating factor: sargramostim) to stimulate the proliferation and maturation of bone marrow progenitor cells and to increase the number and function of these committed cell populations. Although they are safe and well tolerated, they are very expensive. Treatment with these agents after chemotherapy may shorten the hospital stay and the duration of fever, but no good evidence exists that they prolong survival or affect the frequency of severe infections. Many authorities recommend that use of these agents should be limited to high-risk neutropenic patients, such as elders and those with severe sepsis, multiorgan failure, or recurrent febrile neutropenia.[19,45,46]

Risk Assessment for the Patient with Febrile Neutropenia, Including the Concept of Brief Observation and Early Discharge of the Low-Risk Patient

Febrile neutropenic cancer patients can be classified into high-risk and low-risk groups.[19,47-49] Factors associated with high-risk patients include the following: status as inpatient when fever and neutropenia develop; presence of comorbid medical conditions; uncontrolled cancer; acute leukemia; hemodynamically unstable; evidence of organ failure; presence of pneumonia, severe soft tissue infection, infection of a central line, abdominal pain, or neurologic or mental status abnormalities; and neutropenia expected to last more than 10 days. These patients should be treated in the hospital with intravenous antibiotics.

Low-risk patients generally have an excellent outcome with therapy and are clinically stable outpatients with solid tumors, lymphomas, or chronic leukemia who lack any of the high-risk factors noted previously and who are not receiving fluoroquinolone prophylaxis. Low-risk patients with fever and neutropenia may be treated in the hospital with oral antibiotics, such as ciprofloxacin plus amoxicillin-clavulanate (or ciprofloxacin plus clindamycin in penicillin-allergic patients).[47-49] Furthermore, oral antibiotic therapy with early discharge is safe and effective in carefully selected low-risk patients.[19,49-52] Hospitalization exposes low-risk patients to potential iatrogenic complications and antimicrobial-resistant nosocomial pathogens, and early discharge followed by outpatient treatment allows an improved quality of life.

Low-risk patients may be hospitalized initially, stabilized during 12 to 48 hours, and then discharged to continue parenteral or oral antibiotics. Some authorities recommend a period of observation less than 12 hours, which may allow discharge from the ED, an observation unit, or physician's office.[49] The patient should be observed for at least 2 hours after administration of the first dose of antibiotics and discharged only after consultation with the patient's oncologist. Patients sent home need adequate instructions, family support, and easy access to a hospital in case of emergency.[49-57] The 2011 clinical practice guidelines of the Infectious Diseases Society of America and the National Comprehensive Cancer Network support outpatient or short-stay oral antibiotic therapy in carefully selected low-risk patients with neutropenic fever.[19,49]

Non-Neutropenic Conditions in the Cancer Patient

The Solid Cancer Patient without Neutropenia. Most solid cancer patients who have fever and infection are not neutropenic. Infections often occur after surgical procedures and may include wound infection, deep abscess, or perforated viscus. Infections may be associated with central venous or urinary catheters, stents, and prosthetic devices. In addition, solid tumor patients with large tumor lesions may have obstructive infections (of bronchus, bile duct, or ureter). The spectrum of microorganisms includes a wide variety of indigenous organisms (bacterial, fungal, and viral) as well as nosocomial multiantibiotic-resistant pathogens.

Prompt initiation of antimicrobial therapy in the febrile non-neutropenic solid cancer patient is not always indicated. Rapid surgical intervention may be more important than

www.ketabpezeshki.com 66485457-66963820

the urgent initiation of empirical antibiotics. In febrile non-neutropenic cancer patients who are not ill-appearing and have no identified focus of infection, it may be appropriate to obtain culture specimens and to observe the patient. After consultation with an oncologist, some patients can be discharged home with close follow-up. Indications for urgent antibiotics include signs of sepsis, mental status changes, lactic acidosis, shock, abdominal pain, history of splenectomy, and identification of a focal site of infection.[58,59]

Impaired Cell-Mediated Immunity. The T-cell defects resulting from impaired CMI in cancer patients usually result from cancer chemotherapy or corticosteroid treatment. The cancer impairs CMI in patients with Hodgkin's disease, non-Hodgkin's lymphoma, and hairy cell leukemia.

Bacterial Infections. *Listeria monocytogenes* is one of the more common bacterial organisms infecting cancer patients with impaired CMI.[60-63] *Listeria* infection is also seen in patients with organ transplants, diabetes, cirrhosis, and AIDS and in those receiving high-dose corticosteroids. No early characteristics distinguish *Listeria* infection from bacteremias caused by other organisms. Meningitis, which may be accompanied by cerebritis or brain abscess, is the most common focus of infection and may be manifested with personality changes or focal neurologic signs.[64] Cerebrospinal fluid examination frequently does not reveal the organism on Gram's stain, but protein is elevated and pleocytosis is present. Treatment should be with ampicillin and gentamicin. Trimethoprim-sulfamethoxazole is the alternative drug for patients with penicillin allergy. Vancomycin is not effective in treatment of *Listeria* infections even when in vitro susceptibility is shown. Cephalosporins, such as ceftriaxone and cefotaxime, are not active against *Listeria*.

Infections caused by *Salmonella* species are common in patients with impaired CMI and usually are manifested with fever with or without enteritis.[65] Bacteremia can result in infection of bones, joints, central nervous system, and endovascular devices. Multidrug-resistant *Salmonella* species are increasing. Treatment usually includes a third-generation cephalosporin or a fluoroquinolone because many isolates are resistant to ampicillin and trimethoprim-sulfamethoxazole.[66]

Patients with solid tumors, lymphoma, and leukemia (especially hairy cell leukemia) are at increased risk for pneumonia from *Legionella* species, with the highest risk in cancer patients receiving high-dose corticosteroids.[67,68] Non-*pneumophila* species of *Legionella* (e.g., *Legionella micdadei* and *Legionella bozemanii*) are particularly common in these patients.[69] Clinical and radiographic manifestations of *Legionella* infection in the immunocompromised patient often differ from those in the immunocompetent host. For example, pleuritic chest pain may be a prominent symptom in the immunocompromised patient and may mimic pulmonary embolism. These patients can have fever without any other symptoms of pneumonia despite the presence of radiographic pulmonary infiltrates. In addition, the chest radiograph may reveal an expanding pulmonary nodule or cavitation of a nodule or infiltrate rather than the usual lower lobe alveolar filling defects. Hyponatremia (serum sodium <130 mEq/L [mmol/L]) is particularly common. Although gastrointestinal and neurologic symptoms and elevated serum transaminase levels are common in patients with *Legionella* infections, these are not more common in patients with *Legionella* than in those with other causes of pneumonia. The treatment of choice for immunocompromised patients with *Legionella* infection is a fluoroquinolone or azithromycin (alternatively, doxycycline or erythromycin, each combined with rifampin).

Nocardiosis is an uncommon but often severe bacterial infection caused by a weakly acid-fast gram-positive branching filamentous rod. It occurs in cancer patients, in those receiving high-dose corticosteroids, and in others with defective CMI.[70,71] Subacute pneumonia with nodular infiltrates is the most common manifestation, but *Nocardia* may also produce cellulitis, subcutaneous abscesses, meningitis, and brain abscess. Diagnosis requires biopsy, tissue stains, and culture. Treatment is with sulfonamides often combined with other agents.

Mycobacterial Infections. Tuberculosis and other mycobacterial diseases may produce severe disease in those with defective CMI and be manifested as fever of undetermined origin, pneumonia, lymphadenopathy, or skin lesions.[72,73] It is easily mistaken for signs caused by the patient's underlying disease or treatment. Disseminated nontuberculous mycobacterial infections are more common in patients with hairy cell leukemia or chronic myelogenous leukemia.

Fungal Infections. Infections with *Cryptococcus neoformans* and *Cryptococcus gattii* occur in patients with Hodgkin's and non-Hodgkin's lymphoma, chronic myelogenous leukemia, and chronic lymphocytic leukemia, especially those taking high-dose corticosteroids.[74] Patients with HIV infection, solid organ transplants, diabetes, renal insufficiency, and cirrhosis are also at risk, as are patients receiving prolonged high-dose corticosteroids for connective tissue diseases. Meningitis is the most common manifestation, often with the insidious onset of low-grade fever and subacute (and often intermittent) headache. Many other organ systems can become infected, including the lung, skin, bones, and joints. Diagnosis is made by measurement of cryptococcal antigen (*not antibody*) in serum and cerebrospinal fluid and by fungal cultures and tissue biopsy.[75]

Impaired CMI may result in reactivation of *Histoplasma capsulatum* and *Coccidioides immitis* with resultant disseminated disease. Infections with *Candida* species are also common in cancer patients with defective CMI, but disseminated disease is less likely than in patients with neutropenia. Invasive aspergillosis may develop in cancer patients receiving high-dose corticosteroids but not as commonly as in those with organ transplants or prolonged neutropenia. *Pneumocystis jiroveci* (formerly *carinii*) pneumonia is most common in patients with AIDS, leukemia, and lymphoma and in patients with solid tumors taking high doses of corticosteroids.

Parasitic Infections. Reactivation of central nervous system infection with the protozoan *T. gondii* occurs most often in cancer patients with lymphoma and leukemia as well as in HIV infection. *Strongyloides stercoralis,* an intestinal nematode, is the only helminthic organism producing severe infection in patients with deficient CMI, almost exclusively in those receiving high-dose corticosteroids.[76,77] Larvae of the parasite disseminate from intestine to the lung and other organs, including the central nervous system and skin. Wheezing, cough, dyspnea, hemoptysis, and rash are common symptoms. Chest radiographs may show focal or diffuse infiltrates. Dissemination is often accompanied by bacterial infection, usually caused by enteric gram-negative bacilli carried by the parasites from the intestinal tract. Diagnosis includes examination of sputum and stool for parasites. Treatment of choice is ivermectin; thiabendazole is a less effective alternative.

Viral Infections. The most common viruses producing serious infections in cancer patients with defective CMI are varicella-zoster, herpes simplex, and cytomegalovirus.[78] Visceral dissemination is common in primary varicella in nonimmune immunocompromised children and adults. When a nonimmune immunocompromised child or adult is exposed to varicella, varicella-zoster immune globulin (VariZIG, approved by the Food and Drug Administration in the United States for this indication) can be given within 96 hours of exposure to ameliorate the disease.[79] Herpes zoster infection is common in cancer patients, particularly those with Hodgkin's and non-Hodgkin's lymphoma and leukemia. Disease usually remains localized to the primary dermatome, but dissemination occurs in approximately 11% of patients. Dissemination is usually limited to the skin, but visceral

www.ketabpezeshki.com 66485457-66963820

involvement (lung and liver) occasionally occurs. Skin lesions in primary varicella or zoster often become hemorrhagic in these patients.

Reactivation of herpes simplex virus is common, resulting in severe mucocutaneous infection in oral or genital areas. Spread may occur to the esophagus, lungs, or other organs. Herpetic lesions in cancer patients tend to be larger and deeper than those in the immunocompetent patient. Acyclovir given intravenously is the treatment of choice for varicella-zoster and herpes simplex infections in immunocompromised patients, but some authorities recommend oral famciclovir or valacyclovir for stable patients.

Cytomegalovirus infection may occur in cancer patients treated with corticosteroids. Measles virus, although uncommon, may produce severe infection with defective CMI. Fever, rash, pneumonia, and encephalitis are common manifestations. Immune serum globulin may be given after exposure to ameliorate disease. Common community respiratory viruses, such as respiratory syncytial virus, influenza, and adenovirus, may produce severe or fatal pneumonia.[80]

Humoral Immune (B-Cell) Defects. Hypogammaglobulinemia is common in patients with chronic lymphocytic leukemia and myeloma. Low immunoglobulin levels predispose to infections with encapsulated bacteria, such as *S. pneumoniae, H. influenzae,* and *N. meningitidis*.[81-84] Pneumonia is the most common manifestation, but sepsis, otitis media, cellulitis, and urinary tract infection may occur. After receiving cytotoxic agents and corticosteroids for treatment, these patients become susceptible to infections associated with impaired CMI as well as bacterial infections caused by *S. aureus* and gram-negative bacilli. Regular infusions of intravenous immune globulin may decrease the incidence of infection but do not prolong survival. Patients should receive pneumococcal vaccine, but many do not respond.

Disruption of Natural Barriers. Disruption of natural anatomic barriers (e.g., mucous membranes and skin) by ulcerating tumors, chemotherapy, radiation therapy, diagnostic and therapeutic procedures, and catheters can lead to infection by gram-positive and gram-negative organisms, including anaerobes.[85] Oral mucositis, a debilitating and intensely painful condition associated with radiation therapy and high-dose chemotherapy, frequently results in serious local and systemic infections, including life-threatening sepsis with viridans streptococci.[86,87] Cancers may cause partial or total obstruction of body lumens and cavities. Stenosis of a lumen may result from radiation therapy. Bronchial obstruction by tumor can lead to pneumonia. Obstruction of the urinary tract may result in infection. Gastrointestinal tract obstruction can lead to perforation and peritonitis.

Opportunistic Infections Mimicking Neoplasm. Infectious agents can produce laboratory, radiologic, or physical findings that resemble those caused by the spread of tumor. For example, mass lesions in the brain caused by *Nocardia* or *Toxoplasma* can be mistaken for cancer metastases. *Aspergillus, Mucor, Rhizopus,* and related fungi invade blood vessel walls and produce thrombosis, which may result in Budd-Chiari syndrome (hepatic vein obstruction), nephrotic syndrome, or oculomotor palsy that may be misattributed to the spread of tumor. Renal vein thrombosis can be caused by infection with gram-negative bacilli. *Candida* fungus balls may develop in one or both ureters, producing a picture of postrenal obstructive uropathy. *Histoplasma, Pneumocystis, Legionella, Aspergillus, Nocardia,* and other organisms can produce pulmonary nodules and be mistaken for pulmonary metastases.

Pulmonary Infections in the Immunocompromised Patient. In neutropenic cancer patients, pneumonia is commonly caused by gram-negative bacilli early in neutropenia and by fungal organisms such as *Aspergillus* late. In those with impaired CMI, cytomegalovirus, *Pneumocystis, Legionella, Nocardia,* mycobacteria, and fungal organisms predominate. Pneumococcal pneumonia is most common in patients with impaired humoral immunity. Patients with primary lung cancer or with pulmonary metastases from other cancers develop postobstructive pneumonia, lung abscess, and empyema related to *S. aureus,* gram-negative bacilli, and anaerobes. Mimics of pneumonia in the immunocompromised host include pulmonary emboli and infarction, congestive heart failure, metastatic or primary carcinoma, lymphangitic spread of carcinoma, alveolar hemorrhage, leukoagglutinin reactions, and radiation- and drug-induced pneumonitis.[88] An acute presentation of "pneumonia" suggests bacterial pneumonia, pulmonary emboli, congestive heart failure, or pulmonary hemorrhage. Subacute presentation suggests a fungal, nocardial, mycobacterial, or viral etiology (Table 183-3).[89,90]

Table 183-3 Pulmonary Infiltrates in the Immunocompromised Patient: Common Patterns of Disease and Differential Diagnosis

DIFFUSE BILATERAL INFILTRATES	FOCAL OR PATCHY INFILTRATES
Viruses	Bacterial pneumonias, including *Legionella*
Cytomegalovirus	Fungi
Respiratory syncytial virus	Invasive pulmonary aspergillosis
Influenza, parainfluenza	Zygomycosis (mucormycosis)
Adenovirus	*Fusarium*
Varicella	*Pseudallescheria*
Pneumocystis jiroveci	Tuberculosis
Fluid overload and pulmonary edema	Nontuberculous mycobacteria
Acute lung injury due to transfusion of blood products	Nocardiosis
Radiation damage	Pulmonary embolus
Chemotherapy-induced toxicity	
Acute respiratory distress syndrome due to viridans streptococcal bacteremia	
Bronchiolitis obliterans	
Pulmonary hemorrhage	
Progression of disease (lymphangitic spread of carcinoma, leukemic infiltrates)	

Diabetes

Diabetic patients have increased susceptibility to infection because of defects in immune function, excess substrate for fungal and bacterial growth, vascular insufficiency related to microangiopathy and atherosclerosis, and sensory neuropathy that leads to wound neglect.[91-93]

Neutrophil and monocyte-macrophage functions are impaired in diabetic patients, including adherence to bacteria, chemotaxis, phagocytosis, and intracellular killing. These defects are exacerbated by hyperglycemia and improved by tight glucose control. Although decreased lymphocyte proliferative responses to phytohemagglutinin and certain pathogens are described, cellular immunity appears normal or only minimally affected by diabetes. Humoral immunity is normal in diabetics.[94,95]

Infections seen with increased frequency in diabetic patients include rhinocerebral zygomycosis (formerly mucormycosis) caused by *Rhizopus* and *Mucor* species; malignant (or necrotizing) otitis externa caused by *P. aeruginosa*; pneumonia caused by *S. aureus* and gram-negative bacilli; tuberculosis, emphysematous cholecystitis, and urinary tract infections including emphysematous cystitis and pyelonephritis; polymicrobial necrotizing fasciitis involving the perineum (Fournier's gangrene) and lower extremities; and psoas abscess, spinal epidural abscess, and foot infections with osteomyelitis. Diabetics are not more likely to have pneumococcal pneumonia but are more likely to become bacteremic and to have a higher mortality rate.

www.ketabpezeshki.com 66485457-66963820

Alcoholism and Cirrhosis

Alcohol consumption predisposes to infection through direct suppression of the immune system, alterations in blood flow, depression of mental status, and delay in seeking medical care.[96]

With alcoholic cirrhosis, there is deficient hepatic clearance and killing of bacteria by reticuloendothelial cells as well as splenic hypofunction.[97] Complement deficiency occurs because the liver is the primary site of C3 synthesis. Neutrophils show impaired recruitment to infective sites and defective chemotaxis and phagocytosis.[98,99] Cellular immune deficiency occurs and is exacerbated by malnutrition. Bactericidal activity of IgM antibody against gram-negative pathogens such as *E. coli* and *H. influenzae* is decreased.

Acute ethanol intoxication is associated with granulocytopenia and diminished leukocyte mobilization that is reversible with abstinence. Ethanol intoxication interferes with most respiratory tract defense mechanisms, resulting in alterations of normal flora, impaired mechanical and cellular clearance because of a suppressed cough reflex, decreased ciliary motility, and resultant aspiration. These effects are often compounded by malnutrition, cigarette smoking, and chronic lung disease. Alcoholics exhibit an increased incidence of oropharyngeal colonization by gram-negative bacteria (35-59% of ambulatory alcoholic patients) compared with control subjects (14-18%). Alcoholics are also more likely to aspirate because of loss of reflex glottic closure associated with acute intoxication, withdrawal seizures, and encephalopathy.

Common infections include spontaneous bacteremia and sepsis caused by *E. coli, K. pneumoniae, Salmonella,* streptococci, *Vibrio vulnificus,* and *Aeromonas*; spontaneous bacterial peritonitis, usually caused by *E. coli, K. pneumoniae, S. pneumoniae,* or enterococci; pneumonia related to pneumococci, gram-negative bacilli (*E. coli, K. pneumoniae,* and *H. influenzae*), and anaerobes; tuberculosis; meningitis caused by *S. pneumoniae* and *L. monocytogenes*; and skin and soft tissue infections with *S. aureus,* streptococci, and gram-negative bacilli. Nasopharyngeal and cutaneous diphtheria also occurs.[100]

Renal Failure

Infections cause up to 20% of all deaths among patients with chronic renal failure and are the second most common cause of mortality after coronary artery disease.[101,102] Disruption of cutaneous barriers at vascular access sites and peritoneal dialysis catheter sites and numerous immune system defects are responsible for the increased incidence of infection. Uremic pruritus with excoriation, epidermal and sweat gland atrophy, dryness, and vesicular eruptions also compromise the cutaneous barrier. Reduced renal clearance of unknown toxins, nutritional deficiencies, and administration of immunosuppressive medications lead to aberrant immune regulation early in the course of renal failure.

Chronic kidney failure leads to a state of generalized immune hyporesponsiveness. Neutrophils show reduced mobility, chemotaxis, adherence, phagocytosis, and intracellular bactericidal activity, and leukopenia is commonly present. CMI is severely impaired, with decreased activation and proliferation of T lymphocytes and reduced NK cell activity, which cannot be reversed by hemodialysis. Furthermore, humoral immunity is adversely affected, resulting in deficient production of certain IgG subclass antibodies. Poor response to vaccines is common but can be improved by reinforced vaccination schedules, increased vaccine dosage, and adjunct immunomodulators.[103]

Additional predisposing factors to infection in uremic patients include low serum albumin, iron overload, increased intracellular calcium, circulating low-molecular-weight uremic toxins, metabolic acidosis, circulating inhibitors to chemotactic factors, decreased production of endogenous pyrogens, and invasive vascular procedures for dialysis access. The annual mortality rate from sepsis in dialysis patients is increased 100 to 300 times.[104]

Skin and soft tissue infections, especially those caused by *S. aureus,* are particularly severe in diabetics and in those with peripheral vascular disease or peripheral neuropathy. Vascular access site infections are usually caused by *S. aureus* but occasionally by gram-negative bacilli and enterococci. Patients using central venous catheters for dialysis have much higher rates of sepsis compared with fistulas or grafts. Bacteremia may lead to hematogenous osteomyelitis, usually involving the ribs or thoracic vertebrae, as well as endocarditis, meningitis, epidural abscess, and septic arthritis. Although the incidence of pneumonia is not increased overall in renal failure, it is often more severe, and there is an increased incidence of *Legionella* pneumonia. Tuberculosis and fungal infections caused by *Candida* species, *Cryptococcus, Histoplasma,* and *Coccidioides* occur with increased frequency. In addition, *C. difficile* colitis occurs more frequently and is more severe in patients with chronic renal failure. Infections of the urinary tract are more prevalent, with urinary bladder catheterization the most frequent predisposing factor. There is a poor correlation between the presence of pyuria and urinary tract infection in these patients. *Candida* infection of the urinary tract may develop in patients with chronic renal failure treated with broad-spectrum antibiotics.

Up to two thirds of patients receiving chronic ambulatory peritoneal dialysis have peritonitis in their first year, and one third may be forced to discontinue dialysis because of recurrent infections. *S. aureus* and *S. epidermidis* predominate, followed by streptococci, gram-negative bacilli, and *Candida* species. Fortunately, peritoneal dialysis patients have much lower rates of sepsis than those on hemodialysis do.

Splenectomy, Hyposplenia, and Functional Asplenia

The spleen is the most important organ in the reticuloendothelial system and the primary site for IgM synthesis, the first early immune response of the body. Opsonin production in the spleen facilitates phagocytosis of bacteria by intracellular macrophages. Patients without a spleen also have decreased production of neutrophils, NK cells, and immunomodulating cytokines.[105,106]

The spleen is the principal site of clearance of *S. pneumoniae* from the blood. Splenectomy or functional asplenia predisposes to overwhelming pneumococcal infection and fulminant infection with other encapsulated organisms (*H. influenzae, N. meningitidis,* and *Capnocytophaga canimorsus* after dog bites) and gram-negative bacilli (*E. coli* and *P. aeruginosa*). Asplenic people who become infected with *Babesia microti,* a malaria-like protozoan transmitted by tick bite in the United States, develop severe and often fatal hemolysis. Human granulocytic anaplasmosis (formerly ehrlichiosis), another tick-borne infection, is severe and sometimes fatal in asplenic patients. In addition, the gram-negative coccobacillus *Bordetella holmesii* produces a non–life-threatening acute febrile illness with bacteremia in patients with asplenia. Pneumococcal sepsis represents 50 to 90% of cases. Most healthy adults who die after fulminating pneumococcal sepsis have had a splenectomy or have a congenitally small or abnormal spleen.[107-110]

Overwhelming postsplenectomy sepsis is rare, and the true incidence is unknown because of a lack of prospective studies.[111] The risk is greater in children than in adults, and children younger than 2 years are at greatest risk. The risk is highest in the first few years after splenectomy but persists throughout life into old age. People undergoing splenectomy for a hematologic disorder or lymphoma are at much higher risk for overwhelming postsplenectomy infection than are those undergoing splenectomy for

www.ketabpezeshki.com 66485457-66963820

trauma. This is probably because of the occurrence of splenic implants (splenosis) or accessory spleens in traumatized patients. Patients with functional asplenia from sickle cell anemia or thalassemia major are at high risk for overwhelming bacterial infections as well.

Functional hyposplenism occurs in a variety of conditions besides sickle cell disease, including sickle cell–hemoglobin C disease, ulcerative colitis, celiac disease, sarcoidosis, amyloidosis, rheumatoid arthritis, and SLE. The presence of anatomic or functional hyposplenism may be recognized by the finding of Howell-Jolly bodies in red blood cells on a peripheral blood smear.

When overwhelming postsplenectomy infection occurs, often no obvious source of infection is found. Prodromal symptoms, such as fever, rigors, malaise, myalgias, headache, vomiting, and diarrhea, may be present for 1 or 2 days.[112] Patients seen at this time may be misdiagnosed as having a viral illness, gastroenteritis, or food poisoning. Abrupt deterioration then occurs during hours, with rapid progression to septic shock with disseminated intravascular coagulation, purpura, and multiorgan dysfunction. The mortality rate is high (50-70%), with younger children having the highest mortality rate. In addition, meningitis without overwhelming infection or shock is a common presentation of pneumococcal infection in asplenic patients.[113] When fever develops in a person at risk for this disorder, treatment with an antimicrobial agent effective against *S. pneumoniae* should be initiated without delay. After blood culture is performed, the patient should receive ceftriaxone or cefotaxime, with addition of vancomycin in areas where penicillin resistance is prevalent. Clindamycin, levofloxacin, and moxifloxacin are alternatives for patients with serious penicillin allergy.

Use of pneumococcal vaccine in patients at risk is especially important now that antimicrobial-resistant *S. pneumoniae* is prevalent.[114] Asplenic people should be immunized against pneumococcus, *H. influenzae* type b, *N. meningitidis,* and influenza virus. People with functional hyposplenism related to serious underlying diseases often respond poorly to pneumococcal vaccine. Children should receive prophylaxis with oral penicillin or amoxicillin up to the age of 5 years and for at least 1 or 2 years after splenectomy, provided they have not had an invasive pneumococcal infection and have received pneumococcal immunizations. Long-term antimicrobial prophylaxis is generally not recommended in adults. These patients should have standby oral antibiotics at home (amoxicillin-clavulanate, levofloxacin, or moxifloxacin) with instructions to self-administer at the first sign of infection, and they should be provided with information and a medical alert bracelet. Fatal pneumococcal infection has occurred in patients immunized with pneumococcal vaccine who were also taking penicillin. An ED-based pneumococcal vaccine program, if it is implemented, could reduce mortality in high-risk patients while remaining cost-effective.[115,116]

IMMUNOSUPPRESSIVE THERAPY

Corticosteroids

High doses of corticosteroids alter the distribution and function of neutrophils, monocytes, and lymphocytes.[117] Corticosteroids suppress inflammation and enhance susceptibility to infection by impairing the mobilization and function of neutrophils and mononuclear cells at sites of primary lodgment of microorganisms in tissues. Corticosteroids inhibit neutrophil adherence to endothelium, decrease chemotaxis of neutrophils and monocytes, and inhibit phagocytosis and intracellular killing of microorganisms. Corticosteroids also severely impair CMI, probably a result of inhibition of the migration of lymphocytes to the site of antigen challenge, inhibition of lymphokine production, and consequent inhibition of lymphocyte proliferation. They also inhibit both classical and alternative pathways of complement activation. The hyperglycemia that occurs with corticosteroid use also contributes significantly to infection risk. Moreover, patients receiving high-dose corticosteroids have infection risks related to anatomic abnormalities of the underlying disease, treatment with other immunosuppressive agents, cancer chemotherapeutic agents, radiation therapy, and implantation of foreign bodies.[118-120]

Acute administration of corticosteroids produces marked alterations in circulating leukocyte numbers. Basophils, eosinophils, and monocytes decrease, whereas neutrophils are increased. These changes occur within 4 to 6 hours and abate by 24 to 48 hours after a single steroid dose. There is a redistribution of lymphocytes, predominantly T cells, out of the circulation, resulting in lymphocytopenia. Acute or chronic corticosteroid therapy has little effect on serum immunoglobulin levels.

The most common infections occurring in patients receiving high-dose corticosteroids are those caused by pyogenic bacteria (*S. aureus,* streptococci, and gram-negative bacilli). Despite the profound depression of CMI that occurs in patients taking corticosteroids, these patients generally have few infections commonly recognized as associated with defective CMI. The most common are tuberculosis and severe or disseminated infections caused by varicella-zoster and herpes simplex viruses. Patients receiving moderate doses of corticosteroids for asthma and other disorders are at increased risk for lethal primary varicella infection.[121] Other infections seen with corticosteroid use include those caused by *Listeria, Salmonella, Legionella, Nocardia, Candida, Aspergillus, Cryptococcus, Histoplasma, Coccidioides, Pneumocystis, Toxoplasma, Cryptosporidium,* and *Strongyloides*. Patients with neurologic diseases have much higher rates of infectious complications than do patients with intestinal, hepatic, or renal disease. The infectious complications related to corticosteroid use increase with doses of prednisone equivalents of more than 20 mg/day in adults, with total doses of more than 700 mg, and with treatment longer than 30 days. The risk of adrenal suppression can be decreased by use of prednisone doses less than 7.5 mg/day, administration of doses early in the day, avoidance of split doses, and use of alternate-day dosing.

Corticosteroids decrease leukocyte accumulation at inflammatory sites, and the whole cascade of responses leading to local manifestations of infection is slowed. These effects result in late presentation of serious infections. The ability of parietal cavities to localize sepsis is reduced. In addition, prolonged administration of corticosteroids results in delayed wound healing. For example, skin sutures should be left in place 50 to 100% longer than in normal patients. Short-term treatment has little effect on wound healing.[122]

The diagnosis of peritonitis resulting from perforation of colonic diverticula, appendicitis, peptic ulcer, or another primary intra-abdominal condition is particularly difficult.[123] These patients have abdominal discomfort, but they may have few abdominal findings and need rapid and aggressive investigation for life-threatening abdominal disease. CT scan of the abdomen and pelvis and surgical consultation may be needed emergently in these patients. Broad-spectrum antimicrobials to cover for gram-negative enteric bacilli and anaerobes should be administered without delay.

Other complications unrelated to the effects on the immune system include iatrogenic Cushing's syndrome, peptic ulcer disease, benign intracranial hypertension (pseudotumor cerebri), glaucoma, posterior subcapsular cataract, pancreatitis, avascular necrosis of bone (especially the femoral and humoral heads), psychosis, poor wound healing, hyperglycemia, diabetic ketoacidosis,

www.ketabpezeshki.com 66485457-66963820

hyperosmolar nonketotic diabetic coma, myopathy, and osteoporosis, resulting in vertebral compression fractures and other spontaneous fractures. In addition, adrenocortical insufficiency may occur on withdrawal of therapy.

Other Immunosuppressive Medications

Commonly used immunosuppressives include cyclosporine, tacrolimus, sirolimus, mycophenolate, azathioprine, methotrexate, and cyclophosphamide. They treat a wide variety of conditions, including rheumatoid arthritis, psoriasis, nephrotic syndrome, and inflammatory bowel disease, and they are used in the prevention and treatment of organ transplant rejection.[124] These drugs depress immune function, especially CMI. In addition, they have a narrow therapeutic window, wide-ranging toxic side effects, and many significant drug-drug and drug-food interactions. Patients may present for evaluation of symptoms caused by an adverse drug reaction or an infection. Before altering current medications, the physician needs to check carefully for drug interactions. For a more detailed discussion of the toxic effects of these agents, refer to Chapter 184.

Immunomodulating agents are available for treatment of a variety of immune-mediated inflammatory diseases, including rheumatoid arthritis, psoriasis and psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel disease. Some of these drugs include inhibitors of tumor necrosis factor alpha (infliximab, adalimumab, certolizumab, golimumab, etanercept), inhibitors of interleukins (tocilizumab, anakinra), inhibitor of pyrimidine synthesis (leflunomide), and inhibitor of T-cell activation (abatacept). These agents, particularly the tumor necrosis factor inhibitors, are associated with increased susceptibility to infection, particularly disseminated infection with various intracellular pathogens. Reactivation of latent infection with *Mycobacterium tuberculosis,* nontuberculous mycobacterial infection, histoplasmosis, and coccidioidomycosis is frequently disseminated and extrapulmonary at presentation. Additional infections seen at increased frequency include cryptococcosis, listeriosis, legionellosis, salmonellosis, aspergillosis, candidiasis, and pneumocytosis. The clinician should be alert to unusual manifestations of infection in patients taking these agents as misdiagnosis and delayed diagnosis increase mortality.[125-127] These drugs may also cause impaired wound healing, so skin sutures should be left in place for a longer time than is usual.[128]

KEY CONCEPTS

- Fever in the neutropenic patient is defined as a single temperature of 38.3° C (101° F) or higher or a temperature of 38.0° C (100.4° F) or higher during 1 or 2 hours. In neutropenic patients, the temperature should be measured orally or tympanically, not rectally.
- Fever in cancer patients with chemotherapy-induced neutropenia indicates infection until it is proved otherwise, most often caused by gram-positive (especially coagulase-negative staphylococci, *S. aureus,* viridans streptococci) and gram-negative (especially *E. coli, K. pneumoniae, P. aeruginosa*) bacteria but also occasionally by fungi (especially *Candida, Aspergillus*).
- Rapid diagnosis and early initiation of therapy are essential in preventing serious morbidity and mortality in immunocompromised patients, who often have subtle or unusual presentations and are difficult to diagnose. Early use of broad-spectrum antibiotics is indicated after appropriate cultures of all potential sites of infection, including intravascular catheters.
- Invasive aspergillosis originating in the paranasal sinuses may extend to the surrounding bone and brain. Often, an initial red-purple lesion on the nasal turbinate or palate turns pale and then black as vascular invasion produces infarction of the mucosa and bone. The black eschar on the nose or palate is easily misdiagnosed as dried blood.
- Patients with functional or surgical asplenia are at high risk for overwhelming sepsis from encapsulated bacteria, especially pneumococci, which may easily be misdiagnosed early in the course as a viral illness or food poisoning.
- Some infections are seen only below a certain CD4 cell count. *Pneumocystis* pneumonia is seen almost exclusively in patients with counts below 200 cells/mL (2×10^5 cells/L), whereas almost all patients with toxoplasmosis or cryptococcal meningitis have counts below 100 cells/mL (1×10^5 cells/L).
- If the chest radiograph is normal or inconclusive but there is still suspicion for pneumonia, high-resolution CT or thin-section multislice CT scanning of the chest without contrast enhancement should be obtained because pneumonia is often detected by chest CT in febrile neutropenic patients with normal findings on the chest radiograph.
- High doses of corticosteroids cause profound dysfunction of neutrophils and mononuclear cells and impair cell-mediated immunity, resulting in a marked increase in infections caused by pyogenic bacteria, varicella-zoster and herpes simplex viruses, tuberculosis, and a wide variety of other bacteria, fungi, and parasites.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Donnelly JP, et al: *Infections in immunocompromised hosts: General principles*. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia: Elsevier/Churchill Livingstone; 2010:3781-3791.
2. Delves PJ, Roitt IM: The immune system: First of two parts. *N Engl J Med* 2000; 343:37.
3. Kaufmann S, Rouse B, Sacks D, eds: *The Immune Response to Infection*. Washington, DC: American Society of Microbiology Press; 2011.
4. Zabriskie JB: *Essential Clinical Immunology*. New York: Cambridge University Press; 2009.
5. Medzhitov R, Janeway C Jr: Innate immunity. *N Engl J Med* 2000; 343:338.
6. Abbas AK, Lichtman AH, Pillai S, eds: *Cellular and Molecular Immunology*, 6th ed. Philadelphia: Saunders; 2007.
7. Newhouse M, Sanchis J, Biennenstock J: Lung defense mechanisms. *N Engl J Med* 1976; 295:990.
8. Dieffenback CW, et al: *Innate (general or nonspecific) host defense mechanisms*. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia: Elsevier/Churchill Livingstone; 2010:37-47.
9. Delves PJ, Roitt IM: The immune system: Second of two parts. *N Engl J Med* 2000; 343:108.
10. Birdsall HH: *Antibodies*. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia: Elsevier/Churchill Livingstone; 2010:59-75.
11. Figueroa JE, Densen P: Infectious diseases associated with complement deficiencies. *Clin Microbiol Rev* 1991; 4:359.
12. Ross SC, Densen P: Complement deficiency states and infection: Epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency. *Medicine (Baltimore)* 1984; 63:243.
13. Perez HD, Lipton M, Goldstein IM: A specific inhibitor of complement (C5a)–derived chemotactic activity in serum from patients with systemic lupus erythematosus. *J Clin Invest* 1978; 78:29.
14. Klastersky J: Infections in cancer patients with suppressed cellular immunity. *Recent Results Cancer Res* 1993; 132:147.
15. Francis P, Walsh TJ: Current approaches to the management of fungal infections in cancer patients. *Oncology* 1992; 6:81.
16. Nauseef WM, Clark RA: *Granulocytic phagocytes*. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia: Elsevier/Churchill Livingstone; 2010:99-127.
17. Rolston KVI, Bodey GP: *Infections in patients with cancer*. In: Hong WI, et al, eds. *Holland-Frei Cancer Medicine*, 8th ed. Shelton, Conn: People's Medical Publishing House; 2010.
18. Alexander SW, Pizzo PA: Current considerations in the management of fever and neutropenia. *Curr Clin Top Infect Dis* 1999; 19:160.
19. Freifeld AG, et al: Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2011; 52:e56.
20. Crawford J, Dale DC, Lyman GH: Chemotherapy-induced neutropenia: Risks, consequences, and new directions for its management. *Cancer* 2004; 100:228.
21. Schimpff SC, Scott DA, Wade JC: Infections in cancer patients: Some controversial issues. *Support Care Cancer* 1994; 2:94.
22. Pizzo PA: Fever in immunocompromised patients. *N Engl J Med* 1999; 341:893.
23. Andre S, et al: Febrile neutropenia in French emergency departments: Results of a prospective multicentre survey. *Crit Care* 2010; 14:R68.
24. Giamarellou H, Antoniadou A: Infectious complications of febrile leukopenia. *Infect Dis Clin North Am* 2001; 15:457.
25. Zinner SH: Changing epidemiology of infections in patients with neutropenia and cancer: Emphasis on gram-positive and resistant bacteria. *Clin Infect Dis* 1999; 29:490.
26. Wisplinghoff H, Seifert H, Wenzel RP, Edmond MB: Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. *Clin Infect Dis* 2003; 36:1103.
27. Haslam DB: Managing the child with fever and neutropenia in an era of increasing microbial resistance. *J Pediatr* 2002; 140:5.
28. Tunkel AR, Sepkowitz KA: Infections caused by viridans streptococci in patients with neutropenia. *Clin Infect Dis* 2002; 34:1524.
29. Patterson TF, et al: Invasive aspergillosis: Disease spectrum, treatment practices, and outcomes. *Medicine (Baltimore)* 2000; 79:250.
30. Walsh TJ, et al: Treatment of aspergillosis: Clinical practice guideline of the Infectious Diseases Society of America. *Clin Infect Dis* 2008; 46:327.
31. Pizzo PA, Robichaud KJ, Wesley R, Commers JR: Fever in the pediatric and young adult patient with cancer: A prospective study of 1001 episodes. *Medicine (Baltimore)* 1982; 61:153.
32. Heussel CP, Kauczor HU, Ullmann AJ: Pneumonia in neutropenic patients. *Eur Radiol* 2004; 14:256.
33. Lordick F, et al: Ultrasound screening for internal jugular vein thrombosis aids the detection of central venous catheter–related infections in patients with haemato-oncological diseases: A prospective observational study. *Br J Haematol* 2003; 120:1073.
34. Lin MY, et al: Delay of active antimicrobial therapy and mortality among patients with bacteremia: Impact of severe neutropenia. *Antimicrob Agents Chemother* 2008; 52:3188.
35. Furno P, Bucaneve G, Del Favero A: Monotherapy or aminoglycoside-containing combinations for empirical antibiotic treatment of febrile neutropenic patients: A meta-analysis. *Lancet Infect Dis* 2002; 2:231.
36. Paul M, Soares-Weiser K, Leibovici L: Beta lactam monotherapy versus beta lactam–aminoglycoside therapy for fever with neutropenia: Systematic review and meta-analysis. *BMJ* 2003; 326:1111.
37. Raad II, et al: Treatment of febrile neutropenic patients with cancer who require hospitalization: A prospective randomized study comparing imipenem and cefepime. *Cancer* 2003; 98:1039.
38. Drugs for bacterial infections. *Treat Guidel Med Lett* 2010; 8:43.
39. Gafter-Gvili A, et al: Meta-analysis: Antibiotic prophylaxis reduces mortality in neutropenic patients. *Ann Intern Med* 2005; 142:979.
40. Leibovici L, et al: Antibiotic prophylaxis in neutropenic patients. *Cancer* 2006; 107:1743.
41. Viscoli C, Castagnola E: *Prophylaxis and empirical therapy of infection in cancer patients*. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia: Elsevier/Churchill Livingstone; 2010:3793-3807.
42. Recommendations for preventing the spread of vancomycin resistance. Recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR Recomm Rep* 1995; 44:1.
43. Paul M, et al: Additional anti–gram-positive treatment for febrile neutropenia. *Cochrane Database Syst Rev* 2005; 3:CD003914 (updated 2010).
44. Gotzsche PC, Johansen HK: Routine versus selective antifungal administration for control of fungal infections in patients with cancer. *Cochrane Database Syst Rev* 2002; 2:CD000026.
45. Kuderer NM, Dale DC, Crawford J, Lyman GH: Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: A systematic review. *J Clin Oncol* 2007; 25:3158.
46. Sung L, et al: Meta-analysis: Effect of prophylactic hematopoietic colony-stimulating factors on mortality and outcomes of infection. *Ann Intern Med* 2007; 147:400.
47. Koh A, Pizzo PA: Empirical oral antibiotic therapy for low risk febrile cancer patients with neutropenia. *Cancer Invest* 2002; 20:420.
48. Kamana M, Escalante C, Mullen CA: Bacterial infections in low-risk, febrile neutropenic patients: Over a decade of experience at a comprehensive cancer center. *Cancer* 2005; 104:422.
49. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: *Prevention and Treatment of Cancer-Related Infections, version 1*. 2011. Available at NCCN.org. Accessed July 15, 2011.
50. Freifeld A, et al: A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. *N Engl J Med* 1999; 341:305.
51. Kern WV, et al: Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. *N Engl J Med* 1999; 341:312.
52. Innes HE, et al: Oral antibiotics with early hospital discharge compared with inpatient intravenous antibiotics for low-risk febrile neutropenia in patients with cancer: A prospective randomized controlled single centre study. *Br J Cancer* 2003; 89:43.
53. Cherif H, et al: The feasibility of early hospital discharge with oral antimicrobial therapy in low risk patients with febrile neutropenia following chemotherapy for hematologic malignancies. *Haematologica* 2006; 91:215.
54. Klastersky J, et al: Outpatient oral antibiotics for febrile neutropenic cancer patients using a score predictive for complications. *J Clin Oncol* 2006; 24:4129.
55. Vidal L, et al: Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients. *Cochrane Database Syst Rev* 2004; 4:CD003992.
56. Mullen CA: Ciprofloxacin in treatment of fever and neutropenia in pediatric cancer patients. *Pediatr Infect Dis J* 2003; 22:1138.

www.ketabpezeshki.com 66485457-66963820

57. Uzun O, Anaissie EJ: Outpatient therapy for febrile neutropenia: Who, when, and how? *J Antimicrob Chemother* 1999; 43:317.
58. Gea-Banacloche J, Segal BH: *Infections in the cancer patient*. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*, 9th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011:2262-2299.
59. Rolston KVI, Rubenstein EB: *Neutropenia and sepsis in cancer patients*. In: Shaw AD, et al, eds. *Acute Care of the Cancer Patient*. Boca Raton, Fla: Taylor & Francis; 2005:539-566.
60. Gellin BG, Broome CV: Listeriosis. *JAMA* 1989; 261:1313.
61. Khardori N, et al: Spectrum and outcome of microbiologically documented *Listeria monocytogenes* infection in cancer patients. *Cancer* 1989; 64:1968.
62. Lorber B: Listeriosis. *Clin Infect Dis* 1997; 24:1.
63. Safdar A, Armstrong D: Listeriosis in patients at a comprehensive cancer center. *Clin Infect Dis* 2003; 37:359.
64. Pruitt A: Nervous system infections in patients with cancer. *Neurol Clin North Am* 2003; 21:193.
65. Cohen JI, Bartlett JA, Corey GR: Extraintestinal manifestations of *Salmonella* infections. *Medicine (Baltimore)* 1987; 66:349.
66. Pegues DA, Miller SI: *Salmonella species, including Salmonella typhi*. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia: Elsevier/Churchill Livingstone; 2010:2887-2903.
67. Edelstein PH: Legionnaires' disease. *Clin Infect Dis* 1993; 16:741.
68. Stout JE, Yu VL: Legionellosis. *N Engl J Med* 1997; 337:682.
69. Fang GD, Yu VL, Vickers RM: Disease due to the Legionellaceae (other than *Legionella pneumophila*): Historical, microbiological, clinical and epidemiological review. *Medicine (Baltimore)* 1989; 68:116.
70. Berkey P, Bodey GP: Nocardial infection in patients with neoplastic disease. *Rev Infect Dis* 1989; 11:407.
71. Lerner PI: Nocardiosis. *Clin Infect Dis* 1996; 22:891.
72. Kaplan MH, Armstrong D, Rosen P: Tuberculosis complicating neoplastic disease: A review of 201 cases. *Cancer* 1974; 33:850.
73. Akiyama H, Maruyama T, Uetake T: Systemic infection due to atypical mycobacteria in patients with chronic myelogenous leukemia. *Rev Infect Dis* 1991; 13:815.
74. Kaplan MH, Rosen P, Armstrong D: Cryptococcosis in a cancer hospital: Clinical and pathological correlates in forty-six patients. *Cancer* 1977; 39:2265.
75. Chayakulkeeree M, Perfect JR: Cryptococcosis. *Infect Dis Clin North Am* 2006; 20:507.
76. Siddiqui AA, Berk SL: Diagnosis of *Strongyloides stercoralis* infection. *Clin Infect Dis* 2001; 33:1040.
77. Keiser PB, Nutman TB: *Strongyloides stercoralis* infection in the immunocompromised population. *Clin Microbiol Rev* 2004; 17:208.
78. Wade JC: Viral infections in patients with hematological malignancies. *Hematology Am Soc Hematol Educ Program* 2006; 368.
79. VariZIG for prophylaxis after exposure to varicella. *Med Lett Drugs Ther* 2006; 48:69.
80. Whimbey E, Englund JA, Couch RB: Community respiratory virus infections in immunocompromised patients with cancer. *Am J Med* 1997; 102:10.
81. Blade J, Rosinol L: Complications of multiple myeloma. *Hematol Oncol Clin North Am* 2007; 21:1231.
82. Wadhwa PD, Morrison VA: Infectious complications of chronic lymphocytic leukemia. *Semin Oncol* 2006; 33:240.
83. Morrison VA: Infectious complications of chronic lymphocytic leukemia: Pathogenesis, spectrum of infection, preventive approaches. *Best Pract Res Clin Haematol* 2010; 23:145.
84. Nucci M, Anaissie E: Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. *Clin Infect Dis* 2009; 49:1211.
85. Glauser M: Alterations of host defenses: The key to the multifaceted spectrum of infections in immunocompromised patients. *Recent Results Cancer Res* 1991; 121:321.
86. Wilkes JD: Prevention and treatment of oral mucositis following cancer chemotherapy. *Semin Oncol* 1998; 25:538.
87. Epstein JB: Mucositis in the cancer patient and immunocompromised host. *Infect Dis Clin North Am* 2007; 21:503.
88. Shorr AF, Susla GM, O'Grady NP: Pulmonary infiltrates in the non–HIV-infected immunocompromised patient. Etiologies, diagnostic strategies, and outcomes. *Chest* 2004; 125:260.
89. Cunha B: Pneumonias in the compromised host. *Infect Dis Clin North Am* 2001; 15:591.
90. Rolston KV: The spectrum of pulmonary infections in cancer patients. *Curr Opin Oncol* 2001; 13:218.
91. Geerlings SE, Hoepelman AI: Immune dysfunction in patients with diabetes mellitus. *FEMS Immunol Med Microbiol* 1999; 26:259.
92. Calvet HM, Yoshikawa TT: Infections in diabetes. *Infect Dis Clin North Am* 2001; 15:407.
93. Delamaire M, et al: Impaired leucocyte functions in diabetic patients. *Diabet Med* 1997; 14:29.
94. Gupta S, et al: Infections in diabetes mellitus and hyperglycemia. *Infect Dis Clin North Am* 2007; 21:617.
95. Peleg AY, et al: Common infections in diabetes: Pathogenesis, management and relationship to glycaemic control. *Diabetes Metab Res Rev* 2007; 23:3.
96. MacGregor RR, Louria DB: Alcohol and infection. *Curr Clin Top Infect Dis* 1997; 17:291.
97. Szabo G, Mandrekar P: A recent perspective on alcohol, immunity, and host defense. *Alcohol Clin Exp Res* 2009; 33:220.
98. Engelich G, Wright DG, Hartshorn KL: Acquired disorders of phagocyte function complicating medical and surgical illnesses. *Clin Infect Dis* 2001; 33:2040.
99. Christou L, Pappas G, Falagas ME: Bacterial infection–related morbidity and mortality in cirrhosis. *Am J Gastroenterol* 2007; 102:1510.
100. Johnson DH, Cunha BA: Infections in cirrhosis. *Infect Dis Clin North Am* 2001; 15:363.
101. Minnaganti VR, Cunha BA: Infections associated with uremia and dialysis. *Infect Dis Clin North Am* 2001; 15:385.
102. Bloembergen WE, Port FK: Epidemiological perspectives on infections in chronic dialysis patients. *Adv Ren Replace Ther* 1996; 3:201.
103. Johnson DW, Fleming SJ: The use of vaccines in renal failure. *Clin Pharmacokinet* 1992; 22:434.
104. Foley RN: Infections in patients with chronic kidney disease. *Infect Dis Clin North Am* 2007; 21:659.
105. Sumaraju V, Smith LG, Smith SM: Infectious complications in asplenic hosts. *Infect Dis Clin North Am* 2001; 15:551.
106. William BM, Corazza GR: Hyposplenism: A comprehensive review. Part I: Basic concepts and causes. *Hematology* 2007; 12:1.
107. Brigden ML: Detection, education and management of the asplenic or hyposplenic patient. *Am Fam Physician* 2001; 63:499.
108. Davidson RN, Wall RA: Prevention and management of infections in patients without a spleen. *Clin Microbiol Infect* 2001; 7:657.
109. Lutwick LI: Life threatening infections in the asplenic or hyposplenic individual. *Curr Clin Top Infect Dis* 2002; 22:78.
110. Shepard CW, et al: *Bordetella holmesii* bacteremia: A newly recognized clinical entity among asplenic patients. *Clin Infect Dis* 2004; 38:799.
111. Price VE, Blanchette VS, Ford-Jones EL: The prevention and management of infections in children with asplenia or hyposplenia. *Infect Dis Clin North Am* 2007; 21:697.
112. Lutwick LI: *Infections in asplenic patients*. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia: Elsevier/Churchill Livingstone; 2010:3865-3873.
113. Schutze GE, et al: Invasive pneumococcal infections in children with asplenia. *Pediatr Infect Dis J* 2002; 21:278.
114. William BM, et al: Hyposplenism: A comprehensive review. Part II: Clinical manifestations, diagnosis, and management. *Hematology* 2007; 12:89.
115. Stack SJ, Martin DR, Plouffe JF: An emergency department–based pneumococcal vaccination program could save money and lives. *Ann Emerg Med* 1999; 33:299.
116. Rimple D, et al: An emergency department–based vaccination program: Overcoming the barriers for adults at high risk for vaccine-preventable diseases. *Acad Emerg Med* 2006; 13:922.
117. Fareau GG, Vassilopoulou-Sellin R: Hypercortisolemia and infection. *Infect Dis Clin North Am* 2007; 21:639.
118. Stuck AE, Minder CE, Frey FJ: Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis* 1989; 11:954.
119. Lionakis MS, Kontoyiannis D: Glucocorticoids and invasive fungal infections. *Lancet* 2003; 362:1828.
120. Klein NC, Go H, Cunha BA: Infections associated with steroid use. *Infect Dis Clin North Am* 2001; 15:423.
121. Dowell SF, Bresee JS: Severe varicella associated with steroid use. *Pediatrics* 1993; 92:223.
122. Nohr C: *Host defenses*. In: Meakins JL, ed. *Surgical Infections: Diagnosis and Treatment*. New York: Scientific American; 1994:21-28.
123. Nathans A, et al: *Peritonitis and other intra-abdominal infections*. In: Howard RJ, Simmons RL, eds. *Surgical Infectious Diseases*, 3rd ed. Norwalk, Conn: Appleton & Lange; 1995:959-1009.

www.ketabpezeshki.com 66485457-66963820

124. Smith JM, Nemeth TL, McDonald RA: Current immunosuppressive agents: Efficacy, side effects, and utilization. *Pediatr Clin North Am* 2003; 50:1283.
125. Bongartz T, et al: Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies. *JAMA* 2006; 295:2275.
126. Raychaudhuri SP, et al: Incidence and nature of infectious disease in patients treated with anti-TNF agents. *Autoimmun Rev* 2009; 9:67.
127. Koo S, Marty FM, Baden LR: Infectious complications associated with immunomodulating biologic agents. *Infect Dis Clin North Am* 2010; 24:285.
128. Busti AJ, et al: Effects of perioperative anti-inflammatory and immunomodulating therapy on surgical wound healing. *Pharmacotherapy* 2005; 25:1566.

www.ketabpezeshki.com 66485457-66963820

Section Five
THE PATIENT WITH AN ORGAN TRANSPLANT

Chapter 184
The Solid Organ Transplant Patient

Matthew T. Keadey

PERSPECTIVE

The successful rehabilitation of patients with end-stage renal, pulmonary, hepatic, and cardiac failure through organ transplantation is one of the great achievements of modern biomedical science. Because 1-year survival rates for all solid organ transplants exceed 80% and many patients survive much longer, increasing numbers of transplant patients with complications are being seen in the emergency department (ED). Although organ transplant patients tend to seek care at their transplant center, many live a great distance from their facility and may require care at their local ED.

PRINCIPLES OF DISEASE

Transplanted organs are devoid of their native innervations and thus pain is an unreliable sign of underlying disease. Transplanted organs also have surgical anastomoses to a variety of structures, including vessels, bronchi, ureters, intestines, and even the bladder. Furthermore, the normal inflammatory and immunologic responses to infection and malignant disease are impaired. Subtle symptoms and signs may be the harbingers of serious complications, and each complaint merits careful investigation. Even in the most advanced stages of severe disease, patients may have few specific complaints and physical findings. The baseline physiologic capacity of the allograft will aid in interpretation of chief complaints in the context of possible organ failure. Small changes in allograft function may be a harbinger of an episode of rejection.

Transplant organ complications can generally be classified into one of four categories: anatomy, infection, rejection, and drug toxicity. Each category should be considered in the differential diagnosis for any transplant patient presenting to the ED. Often, the exact etiology is not determined until the patient is admitted to the hospital. In addition, time since transplantation must be considered in the evaluation. Time can help the clinician focus his or her investigative efforts and tailor treatment regimens.

Anatomy

Anatomic complications of solid organ transplants can be categorized into three groups: vascular, nonvascular anastomosis, and complications related to surgery. These are often manifested early in the post-transplantation course, but delayed presentations can occur.

Vascular complications can include both arterial and venous structures. Acute thrombosis of arteries may lead to fulminant organ failure. This is especially true in liver transplant recipients, in whom the hepatic artery is the sole source of blood flow for the biliary system. An ultrasound examination with color flow Doppler study is often performed immediately after liver transplantation to ensure arterial patency and flow. Arterial stenosis may also develop later in the course, with its effects typically determined by the degree of blood flow restriction. Pseudoaneurysms may develop and quickly lead to hemorrhagic shock if they rupture.

Nonvascular organ anastomoses may include bile ducts, bronchi, and ureters. Complications related to these structures include leaks and obstructions that often lead to acute graft dysfunction. Early identification is vital to salvage of the graft. Leaks are often manifested with pain and may lead to abscess formation. Conservative therapy may include antibiotics and percutaneous drainage. Refractory or severe cases may require surgical intervention. Obstructions may be due to scar tissue, migration of stents, or stone development. If the obstruction is not treated, graft dysfunction may lead to infections such as cholangitis and pyelonephritis. Bronchial leaks may cause a pneumothorax or pneumomediastinum. Prolonged leaks may lead to abscess formation in the thorax, requiring antibiotics and surgical drainage.

Complications related to the surgery are directly associated with the procedure but not specific to the transplanted organ. These may include problems related to technique that lead to hematoma or lymphocyte formation. Fever in the acute postoperative period must be evaluated for complications specific to the transplanted organ as well as for other common causes of postoperative fever.

Infection

Lifelong immunosuppression is generally necessary for all recipients of solid organ transplants, and infection is the primary cause of mortality after transplantation. Two thirds of transplant patients have at least one significant infection, most commonly nosocomial during the surgical recovery period or, subsequently, community acquired (Box 184-1).[1,2]

Signs of infection in this population of patients are often blunted by an impaired inflammatory response. Minor complaints or the chief complaint of a fever in an afebrile patient may herald a severe infection. Aggressive management usually translates into increased patient survival and graft function.[1]

Primary sources of infection in transplant recipients include pretransplantation, community acquired, transmission from organ donor, and nosocomial. Transplant patients should be vaccinated, but live viral antigens should be avoided. Close family members should not be given live vaccines because of the risk of transmission. The timing of infection can be separated into three periods: first month after transplantation, between 1 and 6 months after transplantation, and more than 6 months after transplantation. These distinctions help predict the etiologic agents of the infection.

www.ketabpezeshki.com 66485457-66963820

Box 184-1 Infectious Pathogens in Transplant Patients

Exposure before Transplantation
Tuberculosis
Histoplasmosis
Coccidioidomycosis
Blastomycosis
Strongyloides stercoralis
Hepatitis B and C
Human immunodeficiency virus
Cytomegalovirus
Epstein-Barr virus
Varicella-zoster virus
Herpes simplex virus

Community-Acquired Exposure after Transplantation
Influenza
Primary varicella
Salmonellosis
Tuberculosis and fungal infections (see above)
Legionellosis
Nocardiosis
Cryptococcosis
Cytomegalovirus
Epstein-Barr virus

Nosocomial Exposure
Aspergillosis
Legionellosis
Pseudomonas aeruginosa and other gram-negative bacilli

Modified from Gorbach S (ed): Infectious Diseases. Philadelphia, WB Saunders, 1992.

First Month after Transplantation

Infections occurring in the first month after transplantation are likely to be related to the transplant procedure, stents, catheters, and intubation. In addition, the typical causes of postoperative fever should always be considered. Hospital-acquired pathogens are prominent, and management is similar for any immunosuppressed patient recently discharged.[2]

1 to 6 Months after Transplantation

Infections occurring 1 to 6 months after transplantation are divided into two general types: immunomodulating viral infections and opportunistic infections. Immunomodulating viruses include cytomegalovirus (CMV), hepatitis B and C viruses, BK polyomavirus, human herpesvirus 6, and Epstein-Barr virus (EBV). Opportunistic pathogens include *Pneumocystis*, *Listeria*, and fungal species.

CMV is the most important and prevalent immunomodulating virus 1 to 6 months after transplantation.[1] CMV infection may produce disease in multiple systems, but pneumonitis is particularly common and may be manifested insidiously. CMV infection may be primary or due to reactivation from latent viral particles found in lymphocytes. Typically, signs of CMV infection occur at a median of 40 days after transplantation. Survival from CMV infection is improving because of aggressive use of bronchoscopy that leads to earlier diagnosis and treatment with ganciclovir and CMV-specific immune globulin. Prophylaxis with ganciclovir reduces CMV incidence and death due to infection, but routine use of ganciclovir is associated with a number of potential side effects.[3] Because the risk of CMV infection is greatest during antilymphocyte therapy, some transplant centers administer ganciclovir only selectively during the treatment period, although CMV infection is still often fatal.[4,5]

Active CMV infection can trigger or exacerbate organ rejection. CMV is linked to a particular form of glomerulopathy in renal allograft recipients as well as acute hepatic dysfunction and the disappearing bile duct syndrome of chronic hepatic allograft dysfunction.[6,7] Furthermore, both acute cardiac dysfunction and accelerated coronary artery atherosclerosis of chronic heart transplant rejection are linked to CMV.[8,9]

EBV infection causes clinical effects similar to those of CMV infection. EBV contributes to immunosuppression and can cause a mononucleosis-like syndrome associated with lymphadenopathy, weakness, and low-grade fevers. Because CMV and EBV often coexist, both seem to trigger graft rejection. EBV is also implicated in B-cell lymphoproliferative syndrome, which is histologically similar to polymorphic B-cell lymphoma.[10]

6 Months after Transplantation

Six months after organ transplantation, patients with functioning solid organ allografts receiving immunosuppression therapy can be categorized into three groups relative to infection susceptibility: healthy transplant, chronic viral infection, and chronic rejection.

Healthy Transplant. Healthy transplant patients have no chronic immunomodulating viral infections and a functioning allograft; they are maintained with low doses of immunosuppressant medications. They have a mildly increased susceptibility to normal community-acquired infections, such as influenza, urinary tract infection, and pneumococcal pneumonia.

Chronic Viral Infection. Progressive disease may develop as a result of the combination of viral immunomodulating infections and long-term immunosuppression. Progressive liver disease due to recurrent or acquired viral hepatitis as well as hepatocellular carcinoma may occur. B-cell lymphoproliferative disorder associated with EBV infection may also develop.[1,2]

Primary varicella infection may lead to rapid dissemination with pneumonia, pancreatitis, hepatitis, encephalitis, and disseminated intravascular coagulation. Patients who are varicella-zoster virus (VZV) seronegative need high doses of intravenous varicella-zoster immune globulin after any exposure, preferably before the development of the rash. Therapy can be lifesaving if it is administered early before dissemination occurs.[1,2]

Reactivation of latent VZV infection, manifested as cutaneous herpes zoster, affects at least 10% of solid organ transplant recipients. Fortunately, reactivation of VZV is usually confined to a single dermatome and does not disseminate. Intravenous acyclovir therapy accelerates healing but does not change the incidence of painful neuralgia. Facial zoster involving the cornea and disseminated infections in more than one dermatome are indications for admission.[1] In patients who have never contracted VZV, many patients are immunized before transplantation.

Herpes simplex virus (HSV) reactivation is common after solid organ transplantation and can be manifested as oral or anogenital lesions, more often ulcers than vesicles. Some transplant centers prescribe oral acyclovir for 3 to 6 months after transplantation, whereas others choose to treat HSV immediately at the first sign of recurrence.[11]

Chronic Rejection. Patients with chronic rejection require ongoing aggressive immunosuppressive treatment to protect the allograft. These patients are at the highest risk for life-threatening opportunistic infections with fungi (e.g., *Candida, Cryptococcus, Coccidioides, Blastomyces,* and *Histoplasma*), bacteria (e.g., *Listeria* and *Nocardia*), and parasites (e.g., *Pneumocystis, Toxoplasma,* and *Strongyloides*).

Fungal infections are distinct to geographic regions and typically are manifested with subacute respiratory complaints associated with fever and focal, disseminated, or miliary infiltrates on the chest radiograph.[1] Invasive candidiasis and aspergillosis can also develop in the chronically immunosuppressed group. Primary

www.ketabpezeshki.com 66485457-66963820

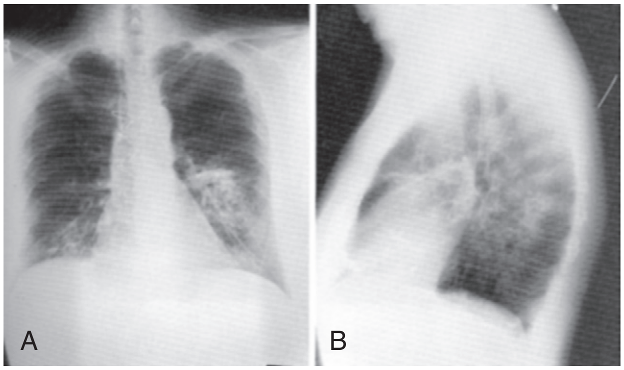


Figure 184-1. A and B, Bilateral perihilar and lower lobe alveolar infiltrates in a cardiac transplant recipient from *Pneumocystis jiroveci*. (From Tewari S, Maurer J: Pulmonary considerations of organ transplantation. In: Ginnes LG, Cosimi AB, Morris PJ [eds]: Transplantation. Malden, Mass, Blackwell Science, 1999, 617.)

infections in the lungs, gastrointestinal tract, or nasal sinuses lead to fungemia and contamination of intravenous lines and wounds. Treatment is with antifungal agents such as amphotericin B or agents such as micafungin (Mycamine).

Diverticulitis is the principal bacterial gastrointestinal infection observed in transplant patients with chronic rejection. Inflammation is suppressed with chronic steroid therapy, which leads to an increased incidence of perforation before diagnosis. Patients complain of an insidious onset of pain, change in bowel habits, and sometimes fever, but they typically lack peritoneal signs. Transplant patients are also susceptible to mucosal invasion with salmonellae (nontyphoidal) and *Listeria*. Infection with both organisms can be manifested as acute diarrheal syndromes that progress to bacteremia or meningitis.[1,2]

Pulmonary infection with *Nocardia asteroides* may occur in transplant patients. Primary infection is subacute, with cough, fever, pleurisy, purulent sputum, and subsequent metastatic infection of the brain and skin. Seizures or subcutaneous nodules may be the presenting complaint with a primary *Nocardia* infection.

Pneumocystis jiroveci (carinii) pneumonia is often found in combination with CMV infection because CMV inhibits alveolar macrophage function (Fig. 184-1). Fortunately, its incidence is reduced with prophylactic low-dose trimethoprim-sulfamethoxazole. Without prophylaxis, infection may develop 1 to 6 months after transplantation and is manifested subacutely with fever, nonproductive cough, progressive dyspnea, and an interstitial infiltrate on the chest radiograph. Differentiation from CMV pneumonia is impossible without bronchoscopic confirmation. Treatment of *Pneumocystis* pneumonia includes intravenous trimethoprim-sulfamethoxazole and steroids, depending on the degree of hypoxia.

Disseminated toxoplasmosis is a particular concern in heart transplant patients. Toxoplasmosis can lay dormant in the tissues, especially the heart, and be reactivated during immunosuppression, resulting in myocarditis, brain abscesses, or diffuse encephalitis. Typically, treatment of toxoplasmosis is a combination of intravenous sulfadiazine and pyrimethamine.

Strongyloides stercoralis, an intestinal nematode that normally causes minimal symptoms, can become an invasive pathogen during immunosuppression. A *hyperinfection syndrome* can develop, causing a necrotizing hemorrhagic enterocolitis and hemorrhagic pneumonia. Disseminated strongyloidiasis occurs when the larvae migrate from the gastrointestinal tract. Dissemination and hyperinfection can lead to gram-negative bacteremia and meningitis secondary to impairment of the blood-gut barrier.

Figure 184-2. A 22-year-old man with a kidney transplant who presented with fever and a cough was diagnosed with reactivated tuberculosis by sputum analysis.

Mycobacterial disease can be manifested as opportunistic reactivation or a primary infection. Even disseminated disease can be clinically silent, with invasion of the bowel, skin, and gastrointestinal tract. Pulmonary disease can be absent, miliary, or cavitary (Fig. 184-2). Treatment is difficult because typical agents can cause graft dysfunction.[1,2]

Rejection

The course of rejection may vary, but each individual typically has a lifelong course of a waxing and waning immune response to the allograft, mandating ongoing surveillance of allograft function. Differentiation of infection and rejection is often difficult in the ED. Determination is often made only after biopsy of the transplanted organ or positive culture results are identified.

Rejection typically occurs in three phases: hyperacute, acute, and chronic. *Hyperacute rejection* is rare with careful donor-recipient matching. It typically occurs in the immediate perioperative period. *Acute rejection* occurs within the first months after transplantation. The patient presents with constitutional symptoms and signs of transplant organ insufficiency. Expeditious laboratory assessment, including possible allograft biopsy, can confirm the diagnosis of rejection, and an appropriate adjustment can be made in the immunosuppressant regimen. If immunosuppression is stopped, acute rejection may occur at any time. *Chronic rejection* has a time course of years and results in the gradual failure of the transplanted organ over time.[12]

Drug Toxicity of Immunosuppression

Pharmacology of Immunosuppression

Immunosuppressive therapy requires correctly timed drug combinations to establish a delicate balance between immunosuppression, rejection, and susceptibility to infection. Multiple agents are standard. Regimens are typically transplant center specific, but most include a calcineurin inhibitor, an antimetabolite, and varying dosages of steroids. Recognition of the side effects,

www.ketabpezeshki.com 66485457-66963820

toxicities, and potential drug interactions of immunosuppressant medications is an important component in the care of any transplant patient.

A new term, *operational tolerance,* reflects long-term acceptance of transplanted organs without indefinite immunosuppression.[13] Allogeneic bone marrow transplantation from the solid organ donor may facilitate operational tolerance. Successful bone marrow transplantation may revolutionize the treatment of solid organ rejection and immunosuppressive therapy.

Accommodation, an acquired resistance of an organ to immune-mediated damage, has been recognized for more than 20 years. Initially, it was identified in blood group–incompatible kidney transplants that survived and functioned normally in recipients with high titers of anti–blood group antibodies directed against antigens in the grafts. Variable sublethal graft injury induces accommodation, and that may be a dynamic condition, eventuating into tolerance on the one hand and chronic graft injury on the other.[14]

Because of the toxicities of current immunosuppression medications, improvement in long-term transplantation outcomes may depend on new agents with novel mechanisms of action, devoid of the toxicities.[15] Inhibitors of pathways in B-cell and plasma cell activation, including belimumab and atacicept, combat the humoral immune response. Biologic agents for maintenance immunosuppression include monoclonal antibodies and fusion receptor proteins that target molecular pathways and enzymes.

Calcineurin Inhibitors

Cyclosporine. A variety of immunosuppression strategies are being tested, but the mainstay of transplant immunosuppression is cyclosporine.[16,17] Cyclosporine inhibits both cellular and humoral immunity by binding to cyclophilins, which block cytokine transcription and production, thereby inhibiting lymphocyte signal transduction. The result is a potent immunosuppression of helper-inducer T cells, without affecting the suppressor T-cell subset.[16,18] The helper-inducer T cells enhance antibody recognition and production by B cells.

Cyclosporine exhibits dose-related nephrotoxicity, which is additive to other nephrotoxic drugs typically used after transplantation, such as amphotericin B, aminoglycosides, and high-dose trimethoprim-sulfamethoxazole. Cyclosporine causes renal tubular injury and direct renal artery vasospasm in a dose-dependent manner, leading to systemic hypertension in many recipients.[16] Hypertension should be treated aggressively with standard regimens to preserve renal function and to prevent atherosclerosis. Cyclosporine may also aggravate hyperlipidemia, leading to atherosclerosis.[19] Therefore, monitoring of cyclosporine levels and renal function is routine.

Cyclosporine also causes hyperuricemia and gout in transplant patients. The nephrotoxic effects of cyclosporine complicate the management of gouty attacks in renal transplant patients.[20] Traditionally, nonsteroidals are the mainstay of gout therapy, but their use is limited in transplant patients receiving cyclosporine because of a potential synergistic nephrotoxic effect.

Cyclosporine levels are altered by many common post-transplantation medications (Table 184-1). Drugs that inhibit cytochrome P_{450} metabolism, such as erythromycin and ketoconazole, produce elevated cyclosporine levels and enhanced toxicity.[21] Treatment with rifampin can increase cyclosporine metabolism, which triggers episodes of organ rejection. Cyclosporine can also cause hepatotoxicity, hyperkalemia, hirsutism, tremor, and gingival hyperplasia.[16]

Table 184-1 Drug Interactions with Cyclosporine

AGENT	PHARMACOKINETIC ACTION	EFFECT
Carbamazepine Nafcillin Phenobarbital Phenytoin Rifampin	Induce cytochrome P_{450} enzymes	Decreased half-life and immunosuppressive effect
Colchicine Diltiazem Fluconazole Fluoroquinolones Ketoconazole Macrolide antibiotics Oral contraceptives Verapamil	Inhibit cytochrome P_{450} enzymes	Increased half-life and potential drug toxicity or immunosuppression
Aminoglycosides Amphotericin B Cimetidine Nonsteroidals Sulfur	Interact at a glomerular or tubular level	Increased nephrotoxicity

Tacrolimus

Tacrolimus is a macrolide compound that binds to lymphocyte proteins and inhibits cytokine synthesis. Because of an improved side effect profile and more effective immunosuppression, tacrolimus is used as either primary or rescue therapy for allograft rejection and is effective for rejection in all types of solid organ transplants.[22-24]

Like cyclosporine, tacrolimus causes nephrotoxicity as well as neurotoxicity. In combination with steroids, tacrolimus can lead to hyperglycemia and eventual secondary diabetes. Tacrolimus can also cause anorexia, diarrhea, dyspepsia, and nausea. Macrolide antibiotics should not be prescribed to patients receiving tacrolimus because of potential toxic levels.[22]

Antimetabolites

Azathioprine. Azathioprine is an antimetabolite derivative of 6-mercaptopurine. Long an important component of immunosuppressive therapy in solid organ transplants, azathioprine inhibits both deoxyribonucleic acid and ribonucleic acid synthesis, resulting in a suppression of lymphocyte proliferation. It is typically used in combination with other agents.[25] Since the introduction of the calcineurin inhibitor class, the use of azathioprine has been reduced because of cyclosporine's improved side effect profile.

Azathioprine is a bone marrow toxin, and patients exhibit dose-related neutropenia. The drug is given at the minimum effective dose to maintain a peripheral white blood cell count of 4000 to 6000 cells/mL. Azathioprine may also cause hepatic dysfunction and other gastrointestinal disturbances.[25]

Mycophenolate Mofetil. Mycophenolate mofetil (MMF) prevents and suppresses organ rejection after solid organ transplantation.[26,27] MMF is an antimetabolite with more potent and selective inhibition of lymphocyte proliferation. It reduces the incidence of acute rejection but with no significant change in the long-term survival of transplant recipients or their allografts.[18,25]

MMF has the advantage of a low side effect profile and should be used concomitantly with cyclosporine and corticosteroids when the patient can tolerate oral medication. The mostly mild effects resulting from its gastrointestinal and hematologic toxicity include abdominal pain, nausea, diarrhea, gastroenteritis, leukopenia, and thrombocytopenia. Because magnesium and aluminum antacids interfere with the absorption of MMF, care should be exercised in treatment of the gastrointestinal symptoms.[27]

Corticosteroids. Corticosteroids have been used for immunosuppression since the 1960s. Glucocorticoids have a wide range of effects on the immune system, specifically the T lymphocytes. Because of the significant long-term toxic effects associated with chronic glucocorticoid administration, every effort is made to

www.ketabpezeshki.com 66485457-66963820

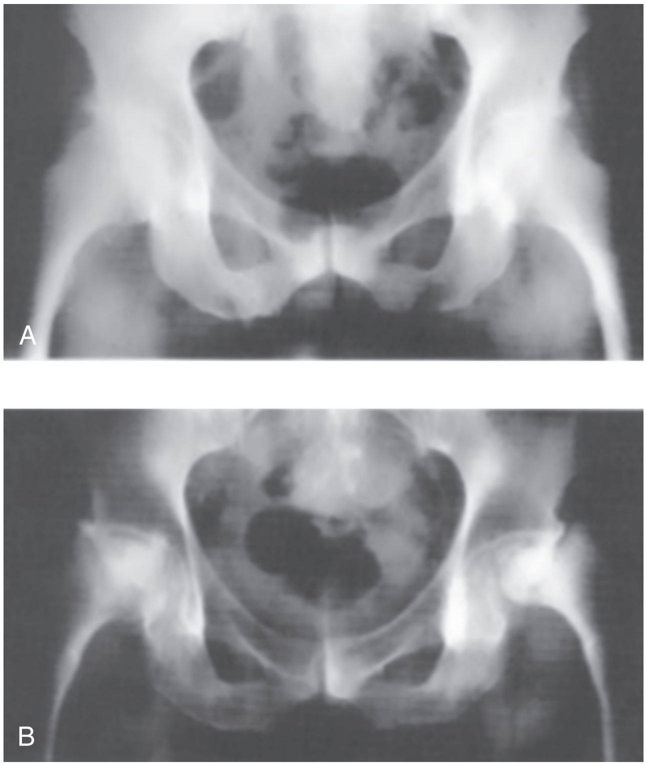


Figure 184-3. Radiographic appearance of a 24-year-old renal transplant patient with early (**A**) and late (**B**) findings consistent with avascular necrosis from chronic steroid use. (From Walker RG: Steroids and transplantation. In: Ginnes LG, Cosimi AB, Morris PJ [eds]: Transplantation. Malden, Mass, Blackwell Science, 1999, 121.)

minimize glucocorticoid use. *Combination therapy,* in which two or more immunosuppressants are administered simultaneously, decreases the reliance on long-term, high-dose glucocorticoid administration for allograft survival.[26]

Long-term corticosteroid therapy causes osteoporosis, cataracts, gastrointestinal bleeding, glucose intolerance, skeletal myopathy, bone disease, and adrenal suppression (Fig. 184-3).[28] Acute administration may lead to glucose and electrolyte abnormalities as well as altered mental status. Acute withdrawal or severe illness may lead to an addisonian crisis.

Antilymphocyte Monoclonal Antibody Preparations. OKT3 and antithymocyte globulin are used in short courses to reverse allograft rejection.[26,29] OKT3 is a mouse-derived monoclonal antibody to T cells. Chills, fever, hypotension, and headache often occur. Pulmonary edema may also develop in overhydrated, oliguric patients. OKT3 is effective in more than 90% of first rejections in most organs.[18]

OKT3 toxicity is common because of T-cell activation and lymphokine release caused by these agents. Patients receiving these agents are at increased risk of infection with opportunistic pathogens, particularly CMV. An increased risk of lymphoproliferative disease also exists.[26,29]

SPECIFIC DISORDERS

Clinical Features

The pertinent clinical features of organ transplant complications are extensive. Allograft rejection symptoms are usually vague and nonspecific. Complications of the organ often result in localized symptoms and dysfunction of the allograft. The clinical features of infectious complications depend on the nature of the pathogenic organism, location of the infection, and level of immunosuppression. The resuscitation of a traumatized transplant patient should focus on standard injury patterns.[30] Every complaint and finding in the organ transplant recipient should be examined in the most suspicious light to avoid missing catastrophic illness.

Diagnostic Strategies

Transplant patients should undergo liberalized laboratory and radiographic evaluation to rule out myriad infectious causes, to assess allograft function, and to survey for signs of drug toxicity. Laboratory assessments should include organ-specific measures of function and a careful search for evidence of infection. When infection is suspected, appropriate culture specimens and serologic studies should be obtained. Radiologic interventions focus on sources of infection and the relevant anatomy of the patient's allograft.

MANAGEMENT

Heart Transplant

General Approach

Human heart transplantation was first performed in 1967. Currently, more than 3000 procedures are done annually in the United States. The 5-year survival rates for adults and children are 72% and 80%, respectively.[31] Typically, the recipient heart is removed and replaced by the donor heart (orthotopic transplant), but the recipient heart is occasionally left in place with the donor heart anastomosed to the native vessels (heterotopic transplant) (Fig. 184-4).

Patients are usually discharged from the hospital within 2 or 3 weeks. In the Stanford experience, 37% of heart transplant patients made at least one ED visit in the ensuing 3 years (range, one to six visits). The most common complaints are fever (37%) and shortness of breath (13%). Sixty percent of these patients are admitted, compared with an overall ED admission rate of 15%. The most common ED diagnoses are sepsis (18%), rejection (11%), and pneumonia (8%).[19]

Treatment of the traumatized transplanted heart should not differ from that of native hearts. Baseline tachycardia is expected because of denervation of the vagus nerve. Despite the absence of a pericardium, scarring and adhesions may result in clinical tamponade with pericardial fluid or blood. Blind pericardiocentesis should not be attempted.[30]

Infection and rejection are the leading causes of mortality in the first year. Any heart transplant patient presenting to the ED with congestive heart failure (CHF), fever (temperature above 38.0°C), shortness of breath, hypoxia, hypotension, poorly controlled hypertension, syncope, or new dysrhythmia should be admitted. Chest pain is rarely related to cardiac ischemia because the denervated heart is incapable of producing angina.[32] Accelerated atherosclerosis of the graft vessels is the hallmark of chronic rejection. Ischemia is manifested as CHF, ventricular dysrhythmias, hypotension, syncope, or sudden death.[33,34] CMV infections also appear to be a risk factor for accelerated atherosclerosis.[9,21,35]

Drug Toxicity

Lifelong immunosuppression is required; most centers use a three-drug regimen of cyclosporine, prednisone, and azathioprine. Each drug has potential for toxicity, and the combination of cyclosporine and prednisone aggravates hyperlipidemia in many patients.[19,36] Rarely, cyclosporine toxicity can result in a

www.ketabpezeshki.com 66485457-66963820

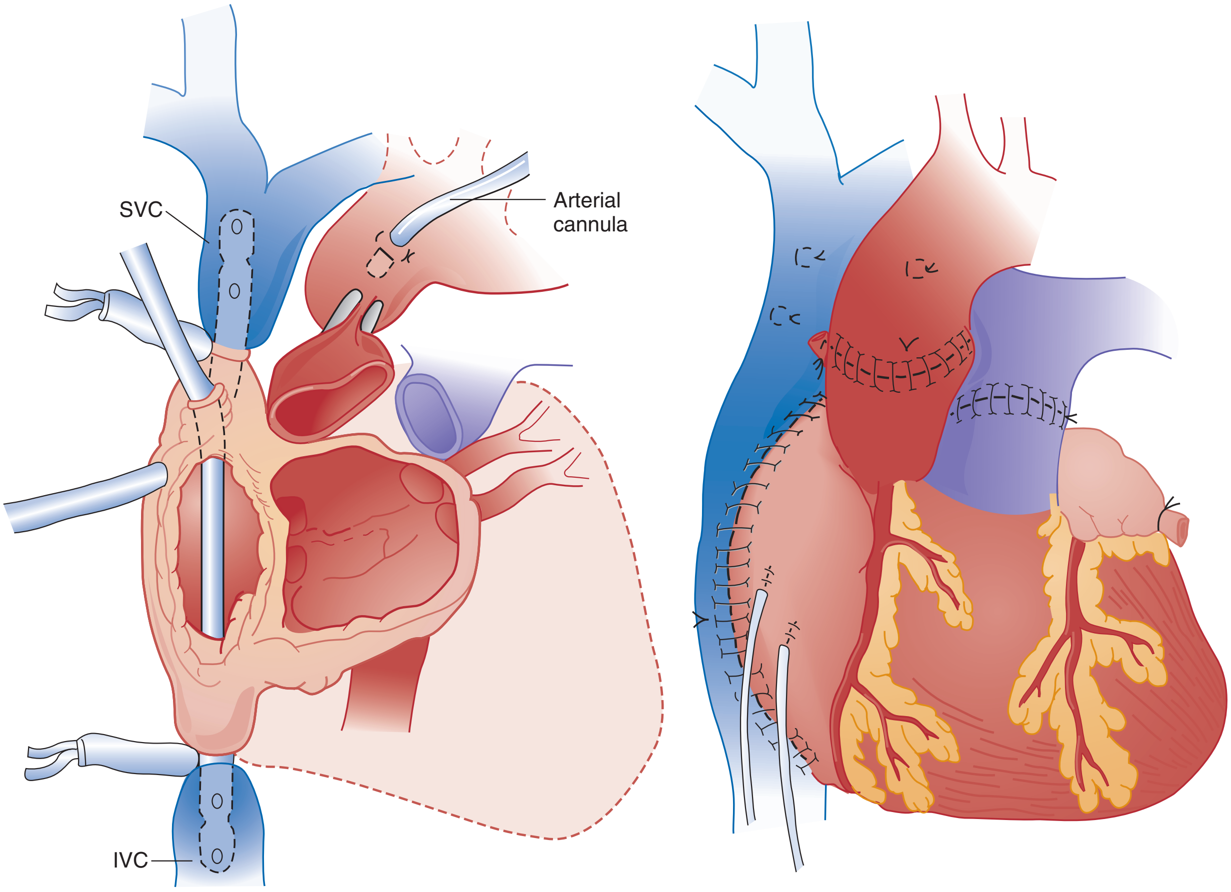


Figure 184-4. **A** and **B,** Typical anastomoses of an orthotopic heart transplant. *IVC,* inferior vena cava; *SVC,* superior vena cava. (From Hunt SA, Schroeder JS, Berry GJ: Cardiac transplantation, mechanical ventricular support, and endomyocardial biopsy. In: Furster VL, et al [eds]: Hurst's The Heart. New York, McGraw-Hill, 2001, 729-730.)

neurotoxic syndrome of seizures, confusion, cortical blindness, and quadriplegia, progressing to coma if it is left untreated.[37-39]

Rejection

Of patients who have acute rejection, 75 to 85% do so within the first 3 months. Manifestations may be subtle when cyclosporine is included in the immunosuppressive regimen. Previously, rejection was obvious, with decreased QRS voltage, a new S_3 heart sound, new-onset CHF, or dysrhythmias. These features are now present only during episodes of severe rejection, and the diagnosis often requires endomyocardial biopsy showing lymphocyte infiltration or myocyte necrosis.[1,19] Because most episodes of early or mild rejection are asymptomatic, frequent biopsies are performed to monitor the success of the immunosuppressive regimen throughout the transplant patient's lifetime.[40,41]

Acute rejection is treated with increased doses of corticosteroids (methylprednisolone, 500-1000 mg/day) and cyclosporine or with OKT3 or antithymocyte globulin. Immunosuppression is continued lifelong, with endomyocardial biopsies at least every 3 to 6 months.[41,42]

Without parasympathetic tone, the transplanted heart maintains a rate of 100 to 110 beats/minute. The electrocardiogram typically demonstrates two P waves. One wave is from the native sinus node in the posterior right atrium, which is often left in place. The second P wave is from the donor sinoatrial node, which should conduct to the ventricles as usual with a normal PR interval. In the rare heterotopic heart transplant, bizarre electrocardiographic recordings may be seen that do not conform to normal standards (Fig. 184-5).

The transplanted heart rate can increase with exercise or stress through the effects of endogenous catecholamines, up to 70% maximum for age. Exogenous pressor agents are effective in the transplanted heart. Upregulation of beta-adrenergic receptors appears to occur in the graft, with a slightly enhanced response to norepinephrine and isoproterenol.[37,42-44] Typical antihypertensive agents can be used as in the nontransplant patient. Atropine is ineffective because of vagal denervation.

Infection

The most vulnerable period for infection is the first 3 months, when immunosuppression is maximal. One quarter of deaths after transplantation result from infection. Although one third of patients will have a major infection develop in the first year after transplantation, life-threatening infection after 1 year is rare.[1,21]

In the first month, nosocomial infection predominates, with the usual gram-positive and gram-negative bacteria. After the first 3 months, patients experience an overall 20% per year rate of infection. The most common skin infection is herpes zoster, which is treated with high-dose acyclovir. Nausea, vomiting, or diarrhea should prompt a search for CMV by culture and serologic testing.[2,19,40]

All heart transplant patients with fever should be aggressively evaluated unless a minor source of infection, such as an upper

www.ketabpezeshki.com 66485457-66963820

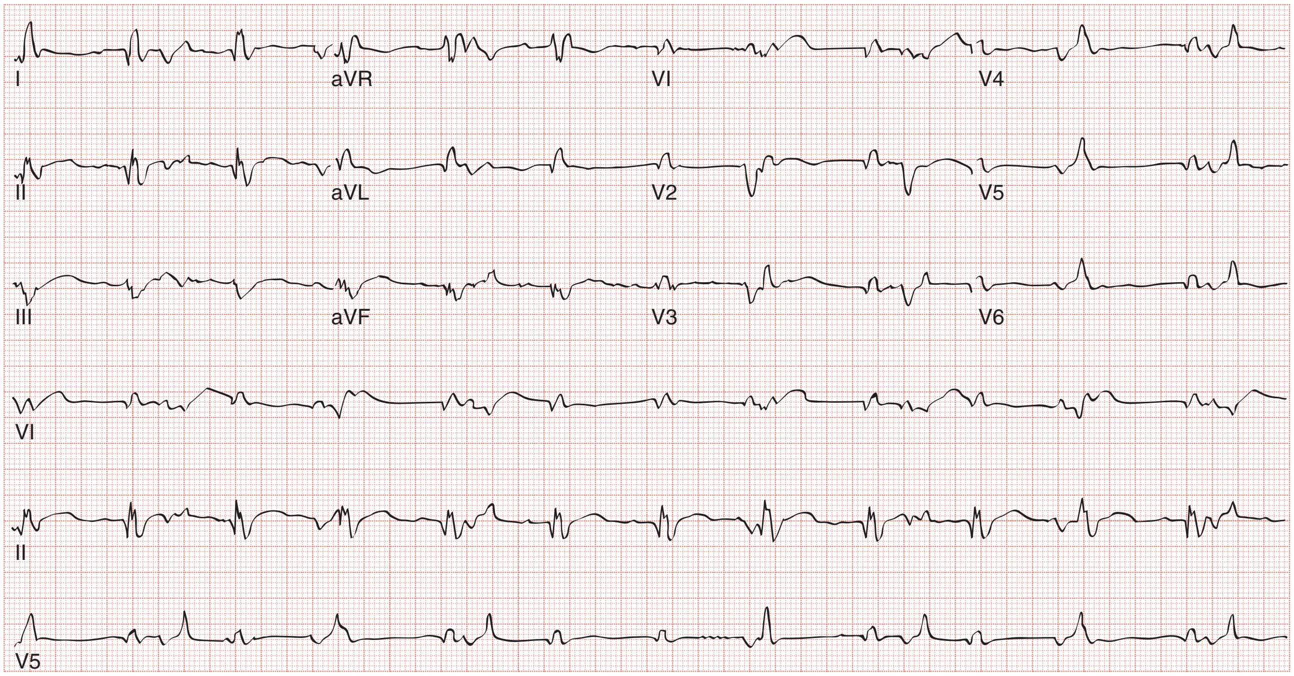


Figure 184-5. A 68-year-old man status post–heterotopic heart transplantation; native heart rate of 55 beats/minute and donor heart rate of 75 beats/minute.

respiratory infection, is obvious. The diagnostic workup in the ED can include blood and urine cultures, computed tomography (CT) scan, lumbar puncture, and bronchoscopy. In addition, complete blood count, glucose concentration, serum chemistries, blood urea nitrogen and creatinine concentrations, chest radiography, and electrocardiography are recommended. In one series of 131 ED visits by such patients, 23 patients were admitted with a diagnosis of "rule out sepsis," and an infecting organism was identified in 12 (52%).[19,37,41]

Any new headache with or without visual changes may be the first symptom of meningitis or brain abscess, and a CT scan of the head and a lumbar puncture should be obtained. Fever, lethargy, headache, altered mental status, and seizures are presenting signs of *Listeria* infection, cryptococcal meningitis, *Toxoplasma gondii* infection, or brain abscesses from *Nocardia* or *Aspergillus*. A more definitive diagnosis can often be made through biopsy or drainage. Aseptic meningitis may also occur in 10 to 14% of patients treated with OKT3 approximately 6 to 10 days after therapy but may be difficult to differentiate from other causes by cerebrospinal fluid analysis alone.[1,21]

Because of the attendant risk of endocarditis, antibiotic prophylaxis should be provided for invasive procedures likely to cause bacteremia. VZV immune globulin is recommended as soon as possible when seronegative patients are exposed to chickenpox or herpes zoster.[2,19]

Liver Transplant

Liver transplants have 1- and 3-year survival rates of 86% and 76%, respectively.[31] Complications are common, and loss of function of the graft organ is rapidly life-threatening.

Anatomic Considerations

The typical liver transplant is connected to its host through five anastomoses (Fig. 184-6). The vessels are connected first, allowing organ reperfusion. The biliary system is then reconstructed and often stented with a T tube to prevent stenosis. In the early post-transplantation period, T tubes may be replaced if restenosis develops. The most common vascular complication is hepatic artery thrombosis, which most commonly occurs in the early post-transplantation period. Severe graft dysfunction is invariable, and mortality approaches 75%.[45]

Rejection

Liver transplant rejection is the norm despite immunosuppressive therapy. Rejection often begins 1 or 2 weeks after surgery, with fever, right upper quadrant pain, and elevated bilirubin and transaminase levels. Leukocytosis may occur but is nonspecific. Related conditions that simulate graft rejection are mechanical biliary obstruction, primary nonfunctioning graft, ischemia from thrombosis of vascular anastomoses, viral infections, drug toxicity, and recurrent primary disease.[46-49]

As soon as transplant rejection is suspected, hospitalization and treatment with high-dose methylprednisolone should begin. If steroids fail, OKT3 monoclonal antibodies are used in addition to polyclonal antilymphocyte globulin.[46]

Infection

After the first postoperative month, viral (CMV and HSV), fungal (*Aspergillus, Candida,* and *Cryptococcus*), protozoan (*Pneumocystis* and *Toxoplasma*), and unusual bacterial (*Nocardia, Legionella,* and *Listeria*) infections occur. In addition, ascending cholangitis due to colonization of biliary stents with staphylococcal species, enterococci, and gram-negative organisms is common. Subsequent injury to the graft during biopsy or cholangiography can also cause cholangitis or liver abscess.

Kidney (Renal) Transplant

With survival rates of 96% at 1 year and 91% at 3 years, kidney transplants are the most successful of the solid organs.[31] Kidney transplantation provides better long-term survival than dialysis does. The best survival is in patients who receive transplants

www.ketabpezeshki.com 66485457-66963820

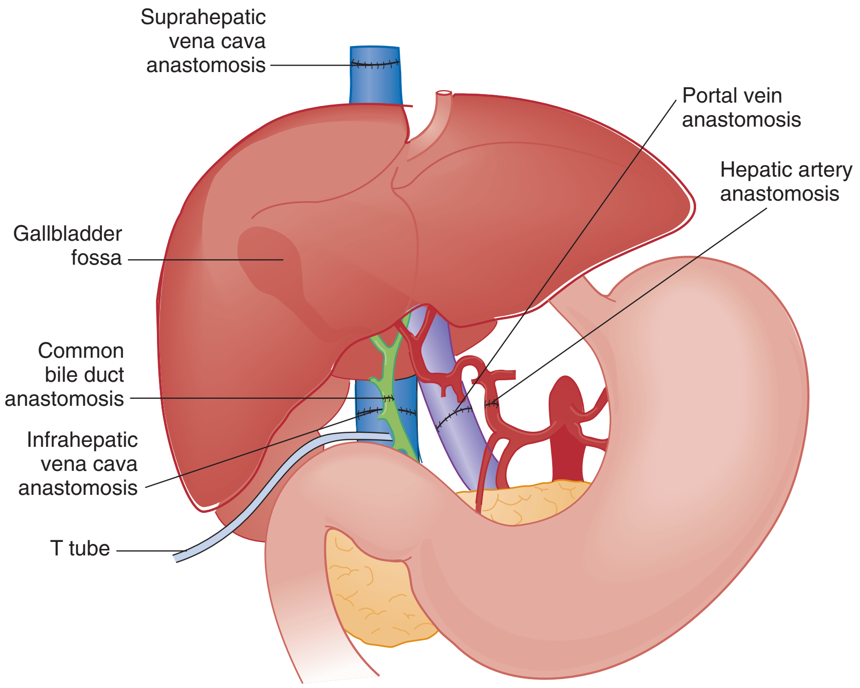


Figure 184-6. Typical anastomoses of an orthotopic liver transplant. (From Powelson JA, Cosimi AB: Liver transplantation. In: Ginnes LG, Cosimi AB, Morris PJ [eds]: Transplantation. Malden, Mass, Blackwell Science, 1999, 352.)

before they need dialysis, otherwise known as preemptive transplantation.[50] Eventually many kidney transplant patients may avoid the sequelae of end-stage kidney disease and many of the complications of dialysis. Parenthetically, traumatic injury of the transplanted kidney is rare, despite its location in the retroperitoneal area of the anterior pelvis, where it may be at risk from direct blows and seat belt injuries.[30]

Infection

The classic example of bacterial infection in transplanted organs is pyelonephritis in renal allografts, which often occurs in the first month after surgery during high-dose immunosuppression. During this period, an increased risk of sepsis exists. Gram-positive organisms associated with wound infections and gram-negative organisms are the predominant causes. Pyelonephritis occurs in 35% of patients during the first 4 months, but the incidence can be reduced by prophylactic antibiotics. All transplant patients who have pyelonephritis are admitted for aggressive antibacterial therapy.[51,52]

Hepatitis C virus (HCV) infection is the most common cause of hepatitis in renal transplant patients. It may be transferred to the recipient by blood transfusion or through the donor organ because pretransplantation antibody testing is a poor predictor of latent HCV infection. Liver disease develops in approximately 50% of seropositive patients, occurring approximately 4 months after transplantation. Most patients have chronic hepatitis with an increased susceptibility to sepsis and spontaneous bacterial peritonitis. Pretransplantation screening is the only avenue of prevention.[1,52]

Rejection

Early kidney transplant rejection is mediated through T lymphocytes against antigen donor tissues, including cytotoxic CD8 and CD4 cells. In addition, B lymphocytes, natural killer cells, and macrophages infiltrate the foreign tissues. The B lymphocytes manufacture specific antibodies, which results in microvascular lesions that impair perfusion.

Chronic transplant rejection occurs after several years of adequate function and is a result of nephrosclerosis. This process involves proliferation of the vascular intima of renal vessels with marked decrease in the lumen size. Systemic hypertension ensues as the graft fails from ischemia, with resultant tubular and glomerular atrophy.

With cadaveric kidney transplants, histocompatibility differences are almost universal and routinely require long-term immunosuppressive therapy. This is accomplished with a combination of azathioprine, prednisone, and cyclosporine. On diagnosis of acute rejection, high-dose intravenous methylprednisolone (500-1000 mg) is begun daily and continued for 3 days. After 6 to 12 months, many patients need only lower doses of prednisone (10-20 mg/day) to maintain immunosuppression.[51,52]

Clinically, renal graft rejection is manifested with fever, swelling and tenderness over the allograft, and decreased urine output. A subtle rise in serum creatinine concentration should prompt great concern. Renal ultrasound examination with color flow Doppler study should be performed to rule out obstruction, abscess, vascular thrombosis, and perirenal collections of blood, pus, or lymph.[52] Early consultation with the nephrologist is prudent.

Lung Transplant

Reasonably compelling data document the beneficial impact of lung transplantation on functional status, hemodynamics, and quality of life, but the data are less compelling to prove a survival benefit.[53] The lung may be transplanted alone or in combination with the heart, with 1-year survival rates of 76% and 56%, respectively.[31] Lung transplants are typically done unilaterally, except for cystic fibrosis. Unequal lung sounds are to be expected. There is no published experience with lung injury after transplantation. Comparison of chest radiographs with preinjury studies is critical in the evaluation of trauma. Chest tube place-

www.ketabpezeshki.com 66485457-66963820

ment on the transplanted side may be difficult because of adhesions and loculations.[30]

Rejection

Although lung transplantation is still rare, it is increasing in frequency; more than 800 are performed annually in the United States.[31] Most patients have early rejection, and 25 to 40% have chronic rejection. An episode of acute rejection can occur as early as a few days after transplantation or as late as several years. Clinically, the patient presents with cough, dyspnea, and fever. Rales and rhonchi are heard, with deterioration in oxygenation and pulmonary function. Early rejection is often accompanied by infiltrates on the chest radiograph. When rejection occurs more than a month after transplantation, 75% of radiographs are normal or unchanged. The diagnosis of rejection is made by transbronchial biopsy showing lymphocytic infiltration.[21,54-56]

Suspected episodes of acute rejection are treated with high-dose methylprednisolone (500-1000 mg/day). This is successful in reversing most episodes, but OKT3 can be used in refractory cases.[55]

Chronic lung transplant rejection is a leading cause of late morbidity and mortality. Antecedent acute rejection and CMV pneumonia are risk factors. On pathologic examination, vascular sclerosis and progressive limitation to airflow occur from obliterative bronchiolitis. Rejection can occur several years after transplantation, but the mean time to onset is 8 to 12 months. Clinically, this rejection mimics an upper respiratory infection or bronchitis. If dyspnea is a component of the presenting complaint, a search for transplant rejection should be initiated.[55,57]

Chronic rejection is treated with high-dose methylprednisolone (500-1000 mg/day). Antilymphocyte antibodies are used as well, but relapse of the rejection episode is common.

Infection

Transplanted lungs are highly susceptible to pneumonia because they can be colonized by bacteria during the ventilator stage of the brain-dead donor. After transplantation, diminished mucociliary clearance, decreased cough reflex due to denervation, and defective function of alveolar macrophages are present. The most common infections are caused by gram-negative bacteria such as *Pseudomonas* and by *Staphylococcus aureus*. Antibiotic therapy should be aggressively directed toward any pathogenic bacteria cultured from the tracheobronchial tree. Community-acquired pneumonia should be considered as well. *Pneumocystis* pneumonia is uncommon because of routine prophylaxis with trimethoprim-sulfamethoxazole.[1,55]

CMV pneumonia is the most common opportunistic pulmonary infection after lung transplantation. Patients are at highest risk between 3 weeks and 4 months. Clinically, CMV infection closely resembles transplant rejection. Tissue biopsy and viral culture are required to differentiate the two entities. Treatment with ganciclovir is effective and is often required long term (>12 months). Colonization by *Candida* is common, but invasive disease with *Aspergillus* and *Candida* provides the most significant fungal threat to the transplanted lung. When these species are invasive, they can cause bronchiolitis obliterans syndrome by inflammation and obstruction of the bronchioles.[58] Reactivation of tuberculosis is rare.[55,56]

Pancreas Transplant

The pancreas may be transplanted singly or in combination with a kidney. This is typically secondary to diabetes. Isolated pancreatic transplants have a high complication rate, with 1-year graft survival rates as low as 72%. Because the exocrine functions of the allograft pancreas are usually drained into the bladder, genitourinary complaints are also common. Duodenocystostomy fistulas may form in the early post-transplantation period. The clinical findings are abdominal pain, tenderness, hyperamylasemia, leukocytosis, and elevated serum creatinine. Other types of pancreatic transplant complications include urinary tract infections, hematuria, reflux pancreatitis, rejection, and pancreatic graft thrombosis.[59-61]

Anatomic considerations are important when these patients suffer major trauma because pancreas transplants are placed in the pelvis overlying the iliac vessels.[30] Exocrine secretions are drained into the bladder for excretion, and patients have a chronic non–anion gap acidosis through loss of bicarbonate into the bladder. This should not be confused with lactic acidosis. These trauma patients should not require exogenous insulin unless the graft is injured. Positive amylase on peritoneal lavage (CT is recommended if the patient is stable) can result from either native organ or graft trauma or from a ruptured bladder. CT scanning should be done with rectal administration of contrast material, in addition to intravenous and oral agents, to better define the native and transplanted pelvic organs.[30]

Islet cell transplantation is under investigation as a treatment of diabetes mellitus and has entered the mainstream of therapy. Although the procedural complication rate is significantly less compared with a whole pancreas transplant, islet transplantation requires several donors for adequate islet cell mass to achieve insulin independence. In addition, there is an increased attrition of islet graft function that occurs during the first few years compared with whole pancreas transplantation. As a result, these factors have made whole pancreas transplantation the most commonly performed type of beta cell replacement therapy.[62]

PSYCHOLOGICAL ASPECTS OF ORGAN TRANSPLANTATION

The psychological issues that surface while an individual is under consideration for an organ transplant or after transplantation affect many patients. Organ transplantation is no longer considered experimental, and it is a common therapeutic option for end-stage organ failure. Strong emotions naturally occur and should be acknowledged in donors, recipients, and transplanters.

Transplant programs widely use psychosocial selection criteria. In general, the cardiac programs have the most stringent criteria. The side effects of lifelong immune suppression or steroid withdrawal can include anxiety, depression, and insomnia. On the other hand, successful transplantation often improves psychological well-being. Transplant social workers can provide awareness of and access to the social network that should surround each transplant recipient. Long-term compliance with all aspects of treatment will minimize graft rejection.[63]

DISPOSITION

Patients with solid organ transplants presenting to the ED have a much higher than average rate of hospitalization.[31,49] The insidious nature of the diseases affecting this immunosuppressed population necessitates a thorough structured approach to evaluation. If organ rejection, infection, or drug toxicity is suspected, local transplantation specialists should be consulted. Physicians without significant transplant experience should contact the patient's transplant center to obtain consultation and to coordinate follow-up care. Patients who are discharged require careful instructions and close follow-up.

The continuing shortfall of organs for transplantation has increased the use of donation after cardiac death (DCD). Some patients with catastrophic injuries in the ED might have potential for controlled DCD. Identification of potential donors after

www.ketabpezeshki.com 66485457-66963820

cardiac death in the ED with appropriate use of critical care for selected patients may contribute to a reduction in the shortfall of organs for transplantation.[64] Although this area remains controversial, most states require that the local organ procurement network be contacted for any recently deceased patient.

KEY CONCEPTS

- The possibility of organ rejection, infection, or drug toxicity should be considered in all organ transplant patients who present to the ED despite subtle presentations.
- A patient's inability to take oral immunosuppressants for even a single day should be considered an emergency condition.
- When prescribing care in the ED, the physician should be careful to avoid drug interactions and toxicity.
- Infections that occur 1 to 6 months after transplantation are generally immunomodulating viral infections, such as with CMV, or opportunistic infections.
- Close family members of transplant patients should not receive live viral antigen vaccines because of the risk of transmission.
- Differentiation of infection and rejection is often difficult in the ED. Determination is often made only after biopsy of the transplanted organ or positive culture results are identified.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Dummer JS, Ho M: *Infections in solid organ transplant recipients*. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 6th ed. Philadelphia: Churchill Livingstone; 2005:3501-3510.
2. Rubin RH, Fishman JA: *Infection in the organ transplant recipient*. In: Ginns LC, Cosimi AB, Morris PJ, eds. *Transplantation*. Malden, Mass: Blackwell Science; 1999:747-770.
3. Hodson EM, et al: Antiviral medications to prevent cytomegalovirus disease and early death in recipients of solid organ transplants: A systemic review of randomized controlled trials. *Lancet* 2005; 365:2105.
4. Sweny P: Infection in solid organ transplantation. *Curr Opin Infect Dis* 1993; 6:412.
5. Sweny P, Burroughs AK: Infections in solid organ transplantation. *Curr Opin Infect Dis* 1994; 7:436.
6. Richardson WP, et al: Glomerulopathy associated with cytomegalovirus viremia in renal allografts. *N Engl J Med* 1981; 305:57.
7. O'Grady JG, et al: Cytomegalovirus infection and donor/recipient HLA antigens: Interdependent cofactors in pathogenesis of vanishing bile duct syndrome after liver transplantation. *Lancet* 1988; 2:302.
8. Rubin RH: The indirect effects of cytomegalovirus infection on the outcome of organ transplantation. *JAMA* 1989; 261:3607.
9. Grattan MT, et al: Cytomegalovirus infection is associated with cardiac allograft rejection and atherosclerosis. *JAMA* 1989; 261:3561.
10. Benkerron M, Durandy A, Fischer A: Therapy for transplant-related lymphoproliferative disease. *Hematol Oncol Clin North Am* 1993; 7:467.
11. Pettersson E, et al: Prophylactic oral acyclovir after renal transplantation. *Transplantation* 1985; 39:279.
12. Dallman MJ: *Immunobiology of graft rejection*. In: Ginns LC, Cosimi AB, Morris PJ, eds. *Transplantation*. Malden, Mass: Blackwell Science; 1999:23-36.
13. Bishop GA, et al: Approaching the promise of operational tolerance in clinical transplantation. *Transplantation* 2011; 91:1065-1074.
14. Lynch RJ, Platt JL: Accommodation in renal transplantation: Unanswered questions. *Curr Opin Organ Transplant* 2010; 15:481-485.
15. Webber A, Hirose R, Vincenti F: Novel strategies in immunosuppression: Issues in perspective. *Transplantation* 2011; 91:1057-1064.
16. Keown PA: *Molecular and clinical therapeutics of cyclosporine in transplantation*. In: Ginns LC, Cosimi AB, Morris PJ, eds. *Transplantation*. Malden, Mass: Blackwell Science; 1999:101-113.
17. Harlan DM, Kirk AD: The future of organ and tissue transplantation: Can T-cell costimulatory pathway modifiers revolutionize the prevention of graft rejection? *JAMA* 1999; 282:1076.
18. Halloran PF: Immunosuppressive agents in clinical trials in transplantation. *Am J Med Sci* 1997; 313:283.
19. Sternbach GL, et al: Emergency department presentation and care of heart and heart/lung transplant recipients. *Ann Emerg Med* 1992; 21:1140.
20. Edwards NL: *Gout: Clinical features*. In: Klippel JH, ed. *Primer on the Rheumatic Diseases*, 13th ed. Atlanta: Arthritis Foundation; 2001:241-250.
21. Petri WA: Infections in heart transplant recipients. *Clin Infect Dis* 1994; 18:141.
22. Klintmalm GB: *Tacrolimus*. In: Ginns LC, Cosimi AB, Morris PJ, eds. *Transplantation*. Malden, Mass: Blackwell Science; 1999:127-136.
23. Starzl TE, Fung JJ: *Tacrolimus: Commentary*. In: Ginns LC, Cosimi AB, Morris PJ, eds. *Transplantation*. Malden, Mass: Blackwell Science; 1999.
24. Fung J, et al: Immunosuppression in liver transplantation: Beyond calcineurin inhibitors. *Liver Transplant* 2005; 11:267.
25. Calne RY: *Azathioprine*. In: Ginns LC, Cosimi AB, Morris PJ, eds. *Transplantation*. Malden, Mass: Blackwell Science; 1999.
26. Bungardner GL, Roberts JP: New immunosuppressive agents. *Gastroenterol Clin North Am* 1993; 22:421-429.
27. Rayhill SC, Sollinger HW: *Mycophenolate mofetil: Experimental and clinical experience*. In: Ginns LC, Cosimi AB, Morris PJ, eds. *Transplantation*. Malden, Mass: Blackwell Science; 1999:147-162.
28. Walker RG: *Steroids and transplantation*. In: Ginns LC, Cosimi AB, Morris PJ, eds. *Transplantation*. Malden, Mass: Blackwell Science; 1999:115-123.
29. Parlevliet KJ, Schellekens PT: Monoclonal antibodies in renal transplantation: A review. *Transplant Int* 1992; 5:234.
30. Barone GW, et al: Trauma management in solid organ transplant recipients. *J Emerg Med* 1997; 15:169.
31. International Society for Heart and Lung Transplantation/United Network for Organ Sharing: *International Heart and Lung Transplant Registry*. Available at http://ishlt.org/registries. Accessed December 1, 2007.
32. Gao SZ, et al: Acute myocardial infarction in cardiac-transplant recipients. *Am J Cardiol* 1989; 64:1093.
33. Hosenpud JD: Coronary artery disease after heart transplantation and its relation to cytomegalovirus. *Am Heart J* 1999; 138:S469.
34. Weis M, von Scheidt W: Cardiac allograft vasculopathy: A review. *Circulation* 1997; 96:2069.
35. Wagoner LE: Management of the cardiac transplant recipient: Roles of the transplant cardiologist and primary care physician. *Am J Med Sci* 1997; 314:173.
36. Hunt SA, Schroeder JS: Managing patients after cardiac transplantation. *Hosp Pract* 1989; 24:83.
37. Cooper DK, et al: Does central nervous system toxicity occur in transplant patients with hypocholesterolemia receiving cyclosporine? *J Heart Transplant* 1989; 8:221.
38. Rubin AM: Transient cortical blindness and occipital seizures with cyclosporine toxicity. *Transplantation* 1989; 47:572.
39. Velu T, Debusscher L, Stryckmans PA: Cyclosporine-associated fatal convulsions. *Lancet* 1985; 1:219.
40. Dec GW: *Cardiac transplantation*. In: Ginns LC, Cosimi AB, Morris PJ, eds. *Transplantation*. Malden, Mass: Blackwell Science; 1999:438-474.
41. Taylor AJ, Bergin JD: Cardiac transplantation for the cardiologist not trained in transplantation. *Am Heart J* 1995; 129:578.
42. McCarthy PM: *Cardiac transplantation*. In: Libby P, Bonow RO, Mann DL, Zipes DP, eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 8th ed. Philadelphia: WB Saunders; 2007:665-683.
43. Borow KM, et al: Cardiac and peripheral vascular responses to adrenoceptor stimulation and blockage after cardiac transplantation. *J Am Coll Cardiol* 1989; 14:1229.
44. Yusuf S, et al: Increased sensitivity of the denervated transplanted human heart to isoprenaline both before and after beta-adrenergic blockade. *Circulation* 1987; 75:696.
45. Washington K: Update on post–liver transplantation infections, malignancies, and surgical complications. *Adv Anat Pathol* 2005; 12:221.
46. Powelson JA, Cosimi AB: *Liver transplantation*. In: Ginns LC, Cosimi AB, Morris PJ, eds. *Transplantation*. Malden, Mass: Blackwell Science; 1999:324-374.
47. Jain A, et al: Immunosuppressive therapy. *Surg Clin North Am* 1999; 79:59.
48. Munoz SJ, et al: Long-term care of the liver transplant recipient. *Clin Liver Dis* 2000; 4:691.
49. Savitsky EA, Uner AB, Votey SR: Evaluation of orthotopic liver transplant recipients presenting to the emergency department. *Ann Emerg Med* 1998; 31:507.
50. Davis CL: Preemptive transplantation and the transplant first initiative. *Curr Opin Nephrol Hypertens* 2010; 19:592-597.
51. Peddi VR, First MR: Primary care of patients with renal transplants. *Med Clin North Am* 1997; 81:767.
52. Morris PJ: *Renal transplantation*. In: Ginns LC, Cosimi AB, Morris PJ, eds. *Transplantation*. Malden, Mass: Blackwell Science; 1999:285-312.
53. Kotloff RM: Does lung transplantation confer a survival benefit? *Curr Opin Organ Transplant* 2009; 14:499-503.
54. Glover FL, et al: The past, present, and future of lung transplantation. *Am J Surg* 1997; 173:523.
55. Ginns LC, Wain JC: *Lung transplantation*. In: Ginns LC, Cosimi AB, Morris PJ, eds. *Transplantation*. Malden, Mass: Blackwell Science; 1999:490-551.
56. Midthun DE, et al: Medical management and complications in the lung transplant recipient. *Mayo Clin Proc* 1997; 72:175.
57. Scott JP, et al: Posttransplantation physiologic features of the lung and obliterative bronchiolitis. *Mayo Clin Proc* 1997; 72:170.
58. Lease ED, Zaas DW: Update on infectious complications following lung transplantation. *Curr Opin Pulm Med* 2011; 17:206-209.
59. Hickey DP, et al: Urological complications of pancreatic transplantation. *J Urol* 1997; 157:2042.
60. Stegall MD, et al: Pancreas transplantation for the prevention of diabetic nephropathy. *Mayo Clin Proc* 2000; 75:49.
61. Auchincloss H, Shaffer D: *Pancreas transplantation*. In: Ginns LC, Cosimi AB, Morris PJ, eds. *Transplantation*. Malden, Mass: Blackwell Science; 1999:395-422.
62. Berney T, Johnson PR: Donor pancreata: Evolving approaches to organ allocation for whole pancreas versus islet transplantation. *Transplantation* 2010; 90:238-243.
63. Craven J, Rodin GM, eds: *Psychiatric Aspects of Organ Transplantation*. New York: Oxford University Press; 1993.
64. Blackstock M, McKeown DW, Ray DC: Controlled organ donation after cardiac death: Potential donors in the emergency department. *Transplantation* 2010; 89:1149-1153.

www.ketabpezeshki.com 66485457-66963820

Section Six

THE ALCOHOLIC AND SUBSTANCE ABUSE PATIENT

Chapter 185

Alcohol-Related Disease

John T. Finnell

PERSPECTIVE

As eloquently stated by Paracelsus in the 16th century, "all substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy."

Epidemiology

The disastrous effects and widespread incidence of alcoholism are well known to the emergency physician. Almost all societies that consume alcohol show related health and social problems.[1] Motor vehicle collisions, drowning, suicides, homicides, divorce, violent crime, child abuse, unemployment, and disruption of the family are often either directly or indirectly associated with excessive alcohol consumption. The tragic effects of alcohol not only affect the individual drinker but also have far-reaching implications for the family, community, and workplace. In the United States, an estimated 7.6 million visits to the emergency department (ED) a year are related to alcohol, accounting for 7.9% of all ED visits.[2] Table 185-1 lists the causes of death related to alcohol abuse.

Alcohol is the most common recreational drug taken by Americans, and per capita consumption is increasing. An estimated 18 million alcoholics live in the United States; with more than 85,000 alcohol-related deaths each year, resulting in 2.3 million years of potential life lost,[3] alcohol is the third leading cause of preventable death in the United States.[4] Alcoholism permeates all levels of society and is a preventable cause of morbidity and mortality, with a cost to the nation estimated to be greater than $185 billion annually.[5]

The alcohol-use disorders consist of alcohol dependence, alcohol abuse, and dependence or harmful use. These disorders are common in all developed countries and are more prevalent in men than in women, with lower but still substantial rates in developing countries. However, most people with alcohol-use disorders are difficult to identify because they are likely to have jobs and families and to present with general complaints, such as malaise, insomnia, anxiety, sadness, or a range of medical problems.

Diagnosis

Alcohol dependence is associated with major physiologic consequences and life impairment. Dependence can be identified as repetitive problems, affecting three or more areas of life, and about 80% of people who are diagnosed with dependence at any point still have alcohol-related problems when they are assessed a year or more later.[6] Dependence criteria are reliable across different ages, sexes, and most cultural groups. Alcohol abuse is defined by the *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (DSM-IV), as one or more problems with functioning in a 12-month period in a person without dependence: failure in obligations; alcohol use in hazardous situations; recurrent legal problems; or continued use despite social or interpersonal problems.[7]

Alcohol Screening Questionnaires

Detection of risky drinking behaviors can be through clinical history or the administration of short alcohol screening tools in the ED setting, such as the Alcohol Use Disorders Identification Test (AUDIT), Fast Alcohol Screening Test (FAST), and CAGE questionnaires. The objectives of these screening tools vary; the AUDIT and FAST are focused on detection of recent hazardous or harmful alcohol consumption and associated problems, whereas the CAGE is designed to detect lifetime alcohol dependence.

The AUDIT-C Screening Questionnaire

1. How often do you have a drink containing alcohol?
   Never (0 points), monthly or less (1 point), two to four times a month (2 points), two or three times a week (3 points), four or more times a week (4 points)
2. How many drinks containing alcohol do you have on a typical day when you are drinking?
   1 or 2 (0 points), 3 or 4 (1 point), 5 or 6 (2 points), 7 to 9 (3 points), 10 or more (4 points)
3. How often do you have six or more drinks on one occasion?
   Never (0 points), less than monthly (1 point), monthly (2 points), weekly (3 points), daily or almost daily (4 points)

Scoring: The sum of scores for the three questions results in an AUDIT-C score of 0 to 12 points.

The AUDIT-C screening thresholds are ≥4 points for men (sensitivity 86%, specificity 89%) and ≥3 points for women (sensitivity 73%, specificity 91%).

A positive answer to the question Have you ever had a drinking problem? plus evidence of alcohol consumption in the previous 24 hours provides greater than 90% sensitivity and specificity as a screening tool for identification of alcoholism.

Blood tests can be useful if the history is in doubt and can also help patients recognize that alcohol has adversely affected their health. One such marker is γ-glutamyltransferase, an enzyme important in amino acid transport. Results of at least 35 units/L indicate the probability of heavy drinking. A second test is for carbohydrate-deficient transferrin, which measures a change in the structure of a proportion of transferrin that is likely to occur with heavy drinking during a long period; a result of 20 units/L or more indicates heavy drinking. Tests of liver function that measure aspartate transaminase (AST) and alanine transaminase (ALT) can identify heavy drinking and alcohol-use disorders with

www.ketabpezeshki.com 66485457-66963820

sensitivities of 25 to 45% and specificities as high as 90%. A ratio of AST to ALT higher than 2, especially if concentrations of these enzymes do not exceed 400 units/L, suggests alcoholic hepatitis. Although many newer biomarkers are not yet available, these newer markers (acetaldehyde adducts) rely on protein modifications by acetaldehyde and play an important role in the pathogenesis of tissue damage in alcoholics (Tables 185-2 and 185-3).

Pathophysiology

Causes and Origins

About 40 to 60% of the risk of alcohol-use disorders is explained by genes and the rest through gene-environment associations. The environment includes the availability of alcohol, attitudes toward drinking and drunkenness, peer pressures, levels of stress and related coping strategies, models of drinking, and laws and regulatory frameworks.

First, variations (polymorphisms) in genes for enzymes that metabolize alcohol are generally associated with a lower risk of alcohol-use disorders because they increase sensitivity to alcohol. At least one variant of aldehyde dehydrogenase (the *ALDH2*2* allele) produces an aversive response to alcohol. Second, gene forms associated with impulsivity, disinhibition, and sensation seeking contribute to vulnerability to both drug-use and alcohol-use disorders, perhaps through impaired judgment and difficulty in learning from mistakes that could reduce control of alcohol intake. Relevant polymorphisms include variations in receptors for γ-aminobutyric acid (e.g., *GABRA2*), acetylcholine (e.g., *CHRM2*), and dopamine (e.g., *DRD2*). Third, people who have low responsiveness (or low sensitivity) to alcohol are more likely to drink more on each occasion to obtain the desired effect, which increases their risk of alcohol-use disorders but not of other drug-related disorders. Additional genetic mechanisms might regulate dopamine-reward systems.

Table 185-1 Causes of Death Related to Alcohol Abuse

1	Mouth and oropharynx cancer
2	Alcohol use disorders
3	Ischemic heart disease
4	Liver cirrhosis
5	Road traffic accidents
6	Poisonings
7	Falls
8	Intentional injuries

Modified from Miranda-Mendez A, Lugo-Baruqui A, Armendariz-Borunda J: Molecular basis and current treatment for alcoholic liver disease. Int J Environ Res Public Health 7:1872-1888, 2010.

Definition and Natural History

A precise definition of alcoholism is difficult. A proposed definition encompassing the features of alcoholism is "a primary chronic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations." The disease is often progressive and fatal. It is characterized by impaired control over drinking, preoccupation with and use of alcohol despite adverse consequences, and distortions in thinking, most notably denial. Each of these symptoms may be periodic or continuous.[8] Alcoholism is present when drinking adversely affects an individual's physical health, ability to function in society, or interpersonal relationships.

Hazardous or "at-risk" drinking is defined by the National Institute on Alcohol Abuse and Alcoholism as the following:

Table 185-2 Current Biomarkers in Alcoholism

MARKER	ABBREVIATION	HALF-LIFE/ELIMINATION RATE	CLINICAL CHARACTERISTICS
Blood ethanol	EtOH	1 g/1 h/10 kg	Levels exceeding 1.5% without evidence of intoxication or 3% at any time indicate ethanol tolerance typically found in alcohol abusers and alcohol-dependent patients. Suitable for emergency clinics
γ-Glutamyltransferase	GGT	2-3 weeks	A sensitive and inexpensive marker Age dependent Specificity decreased by obesity, diabetes, nonalcoholic liver diseases, pancreatitis, hyperlipidemia, cardiac insufficiency, severe trauma, medications (barbiturates, drugs for epilepsy, anticoagulants), nephrotic syndrome, renal rejection
Mean corpuscular volume of erythrocytes	MCV	2-4 months	More sensitive in women Specificity decreased by vitamin B_{12} or folic acid deficiency, liver diseases, hematologic diseases, hypothyroidism, reticulocytosis, smoking
Carbohydrate-deficient transferrin (desialotransferrin)	CDT	2-3 weeks	Most specific of the currently available methods Specificity decreased by genetic variants of transferrin on rare occasions
GGT-CDT combination	GGT-CDT (γ-CDT)	2-3 weeks	A mathematically formulated combination that is easy to manage in hospital laboratories Improves sensitivity without a loss of specificity Good correlation with the amount of recent ethanol intake Suitable for routine use
Aminotransferases	AST, ALT	2-3 weeks	AST/ALT ratio above 2 suggests alcoholic etiology in liver disease patients

From Niemelä O: Biomarkers in alcoholism. Clin Chim Acta 377:39-49, 2007.

www.ketabpezeshki.com 66485457-66963820

Table 185-3 Emerging Biomarkers in Alcoholism

MARKER	ABBREVIATION	HALF-LIFE/ELIMINATION RATE	CLINICAL CHARACTERISTICS
Acetaldehyde adducts	AA	Depends on carrier protein	Present in circulation and tissues of alcoholics Antigen for autoimmune responses Anti-adduct IgAs specific for alcohol abusers
5-Hydroxytryptophol	5-HTOL	14-15 hours	Measurements from urine Sensitive indicator of relapses 5-HTOL ratio to 5-hydroxyindole-3-acetic acid improves specificity
Ethyl glucuronide	EtG	3-5 days	Measurements from urine
Phosphatidylethanol	PEth	2 weeks	A specific metabolite of ethanol Sensitive to sample storage
Sialic acid	SA	2-5 weeks	Sensitive for alcohol abuse but lacks specificity May help differentiate between alcohol abuse and secondary effects of liver disease

From Niemelä O: Biomarkers in alcoholism. Clin Chim Acta 377:39-49, 2007.

Men: more than 14 drinks per week or more than 4 drinks per occasion
Women: more than 7 drinks per week or more than 3 drinks per occasion
Age older than 65 years: more than 7 drinks per week or more than 1 drink per occasion

Harmful drinkers present with negative consequences related to alcohol.

The natural history of alcoholism is variable, and it may appear in any patient despite age or social status. The age at onset of alcoholism continues to decrease. Up to 6% of high school seniors drink daily, and it is not unusual to see children younger than 16 years who have already graduated from an alcohol detoxification program.[9] Many individuals also begin drinking heavily after the age of 60 years.

The DSM-IV has two categories for substance disorders that include alcohol abuse: (1) substance abuse and (2) substance dependence.[7] The chronic *substance abuse* of alcohol eventually leads to *acquired tolerance,* a condition in which larger and larger doses of alcohol are required for the same effect.

PRINCIPLES OF DISEASE: METABOLISM OF ALCOHOL

Ethanol is rapidly absorbed from the stomach and small intestine. It is distributed uniformly to all organ systems, including the placenta. Although 2 to 10% of alcohol is excreted through the lungs, urine, and sweat, the majority is metabolized to acetaldehyde, primarily by alcohol dehydrogenase (ADH). The oxidation of alcohol is a complex process involving three enzyme systems, all contained in the hepatocyte. The class I ADH isoenzymes, ADH1A, ADH1B, and ADH1C, oxidize ethanol, but ADH1B and ADH1C have polymorphic properties with distinct kinetic properties. Acetaldehyde is then quickly converted to carbon dioxide and water, primarily through aldehyde dehydrogenase (ALDH). The common forms of ADH decrease the alcohol concentration in blood by about 4.5 mmol/L ethanol per hour (the equivalent of about one drink per hour).

$$\text{Ethanol} \xrightarrow[\text{NAD}\rightarrow\text{NADH}]{\text{Alcohol hydrogenase}}$$
$$\text{Acetaldehyde} \xrightarrow[\text{NAD}\rightarrow\text{NADH}]{\text{Alcohol dehydrogenase}}$$
$$\text{Acetyl coenzyme A} \xrightarrow[\text{Cycle}]{\text{Citric acid}} CO_2 + H_2O$$

At least two variations of ADH genes (*ADH1B*2* and *ADH1C*1*) produce a slightly more rapid breakdown of alcohol and therefore potentially faster production of acetaldehyde, which is rapidly metabolized by *ALDH2*. However, about 40% of Asian people (Japanese, Chinese, and Koreans) have an inactive *ALDH2* mutation that results in much higher acetaldehyde levels after drinking than normal. About 10% of people who are homozygous for this gene form cannot drink alcohol without becoming sick and have almost no risk of alcohol-use disorders, whereas those who are heterozygous have a relatively low rate of alcohol-use disorders.

An alternative pathway, the microsomal ethanol-oxidizing system (MEOS), is induced by chronic alcohol exposure. The primary component of the MEOS is the molecule cytochrome P_{450}, which exists in several variants. The variant most important for alcohol metabolism is cytochrome P_{450} 2E1 (CYP2E1). Many effects of alcoholism are produced by the toxic byproducts (hydrogen, acetaldehyde), the acceleration of metabolism of other drugs, and activation of hepatotoxic compounds by these metabolic pathways.

Although the liver is the major site of ethanol metabolism, other tissues contribute to its metabolism. ADH is found in the gastric mucosa, but the gastric metabolism of alcohol is decreased in women and those of Asian descent. This increased bioavailability of ethanol or decreased first-pass metabolism may explain the greater vulnerability of women to acute and chronic complications of alcohol.

Alcohol elimination has two phase curves. The alcohol elimination rate approximates zero-order kinetics (constant rate) for lower ethanol levels and first-order kinetics (amount of drug removed over time is proportional to the concentration of the drug) for higher levels, especially in chronic alcoholics; most likely, through induction of the MEOS pathway, the elimination rate is increased at higher blood levels.

The absorption and elimination rates of alcohol vary by individual and depend on many factors: diet, gender, body weight and habitus, speed of consumption, gastric motility, presence of food in the stomach, smoking history, age, whether the person is a chronic alcohol consumer with enzyme induction and high-activity MEOS, advanced cirrhosis, presence of ascites, and state of nourishment.[10] There is enormous variation among patients in the rate of disappearance of ethanol from the blood, ranging from 9 to 36 mg/dL per hour in published data. Although the clearance rate may be as high as 36 mg/dL per hour in some chronic drinkers, 20 mg/dL per hour is a reasonable rate to assume in a typical intoxicated ED patient. This holds true for adults, adolescents, and children.[11]

Physiologic effects vary directly with the blood alcohol level (Table 185-4). Diminished fine motor control and impaired judgment appear with alcohol concentrations as low as 20 mg/dL

www.ketabpezeshki.com 66485457-66963820

Table 185-4 Physiologic Effects and Blood Alcohol Levels

BLOOD ALCOHOL CONCENTRATION (mg/dL)	EFFECTS*
20-50	Diminished fine motor control
50-100	Impaired judgment; impaired coordination
100-150	Difficulty with gait and balance
150-250	Lethargy; difficulty sitting upright without assistance
300	Coma in the novice drinker
400	Respiratory depression

*These effects are for the occasional drinker. Chronic drinkers can function at much higher alcohol concentrations because of tolerance. On the other hand, patients may become comatose with low levels of alcohol in mixed alcohol-drug overdose.

(0.02 mg%), but wide individual variability exists. Chronic alcoholics can exhibit impressive tolerance. The blood alcohol concentration of a person cannot be accurately determined without quantitative testing. More than 50% of the adult population is obviously intoxicated with a level of 150 mg/dL (0.15 mg%). As the ethanol level rises, the patient's level of consciousness declines, eventually ending in coma. Death is caused by aspiration or respiratory depression.

Alcohol through passive diffusion will be present anywhere there is water in the body. Hence, expired breath alcohol or saliva can be used to obtain a reliable approximation of blood alcohol concentration in a cooperative patient. This value can be used as a rapid screen for alcohol intoxication.[12,13]

DIFFERENTIAL CONSIDERATIONS

Acute alcohol intoxication is a diagnosis of exclusion. Before it is assumed that a patient's behavior is caused only by alcohol, other conditions should be considered. Hypoglycemia, hypoxia, carbon dioxide narcosis, mixed alcohol-drug overdose, ethylene glycol poisoning, isopropanol or methanol poisoning, hepatic encephalopathy, psychosis, severe vertigo, postictal state, and psychomotor seizures can be manifested in a manner similar to ethanol intoxication. The possibility of occult head trauma and the presence of associated metabolic disorders should be considered after alcohol intoxication has been established. Shock from gastrointestinal bleeding or sepsis, hypothermia, hyperthermia, and hepatic encephalopathy are all possible. These potentially catastrophic diagnoses are usually detected by a thorough history and physical examination, a blood alcohol level (as coma is rare in chronically intoxicated patients with blood alcohol levels below 200 mg/dL), and close observation (an intoxicated patient's level of consciousness should constantly improve over time). Adequate history from paramedics and family, repeated physical examinations by the same clinician, and diagnostic adjuncts can help resolve this dilemma.

MANAGEMENT

Comatose or stuporous patients need to have airway and ventilation evaluated and managed with endotracheal intubation as necessary. Thiamine (100 mg intravenously [IV]) to prevent or to treat Wernicke-Korsakoff syndrome, glucose (dextrose, 25 to 50 g IV) for hypoglycemia, and naloxone (0.8 mg IV) for possible opioid ingestion should be considered in comatose patients. As magnesium is a necessary cofactor for thiamine metabolism, consider magnesium 2 g IV. When possible, hypoglycemia should be documented before the empirical administration of glucose. With the airway maintained and respirations supported, the patient's liver eventually metabolizes the alcohol, and most patients recover.

Glucose (dextrose, 25 g IV) produces a dramatic response in alcohol-induced hypoglycemic patients. Unlike hypoglycemia of other causes, alcohol-induced hypoglycemia may be unresponsive to glucagon because of depleted liver glycogen stores. Although Wernicke's encephalopathy is a medical emergency, alcohol-induced hypoglycemia is a much more common condition with serious and permanent morbidity if it is left untreated. Therefore, thiamine can be given in a timely fashion, but glucose therapy should not be delayed.[14]

Intoxicated patients require evaluation and treatment in the ED regardless of their obstreperousness. Inappropriate discharge and failure to diagnose are two common areas of liability in treatment of the alcohol-dependent patient. The theoretic liability for detention by reasonable restraint is less than the potential liability for injury sustained by the alcohol-dependent patient or an innocent bystander after premature discharge. Discharge can be considered when a patient is clinically sober and able to dress, walk, and function independently as judged and well documented by the treating clinician. Under ideal circumstances, another concerned, sober adult is available and willing to take responsibility for and remain with the patient for the next 24 to 48 hours.

ALCOHOL WITHDRAWAL SYNDROME

Principles of Disease

The neurophysiology of alcohol withdrawal is complex and not fully understood. Chronic alcohol consumption has a depressant effect on the central nervous system (CNS). The hallmark of alcohol withdrawal is CNS excitation with increased cerebrospinal fluid, plasma, and urinary catecholamine levels. Chronic alcohol consumption affects central adrenergic alpha receptors, glutamate, central adrenergic beta receptors, the inhibitory neurotransmitter γ-aminobutyric acid (GABA), and dopamine turnover.[15]

Differential Considerations

Alcohol withdrawal syndrome can initially be confused with acute schizophrenia, encephalitis, drug-induced psychosis, thyrotoxicosis, anticholinergic poisoning, and withdrawal from other drugs of the sedative-hypnotic type. It may be difficult to differentiate between alcohol withdrawal and alcohol-induced hypoglycemia.

Signs of alcohol withdrawal usually begin 6 to 24 hours after a decrease in the patient's usual intake of alcohol. If patients manifest withdrawal 3 to 4 days or more after their last drink, drugs with a longer half-life should be considered. The barbiturate and benzodiazepine withdrawal syndromes usually progress more slowly, with a higher frequency of seizures later (7 days versus 2 days), and status epilepticus is more common than with alcohol withdrawal.

Clinical Features

Isbell's classic study in 1955 confirmed the relationship between alcohol and the withdrawal syndrome.[16] He documented that the severity of signs and symptoms depends on both the dose and the duration of ethanol consumption. The withdrawal syndrome may occur any time after the blood alcohol level starts to fall. Therefore, only a reduction, not the abrupt cessation, of ethanol intake may result in withdrawal.

Minor alcohol withdrawal occurs as early as 6 hours and usually peaks at 24 to 36 hours after cessation of or significant decrease in alcohol intake. It is characterized by mild autonomic hyperactivity: nausea, anorexia, coarse tremor, tachycardia, hypertension,

www.ketabpezeshki.com 66485457-66963820

hyper-reflexia, sleep disturbances (e.g., insomnia, vivid dreams), and anxiety.[17]

Major alcohol withdrawal occurs after more than 24 hours and usually peaks at 50 hours but occasionally takes up to 5 days to be manifested after the decline or termination of drinking. The syndrome is characterized by pronounced anxiety, insomnia, irritability, tremor, anorexia, tachycardia, hyper-reflexia, hypertension, fever, decreased seizure threshold, auditory and more commonly visual hallucinations, and finally delirium.[18]

Delirium tremens is a life-threatening manifestation of alcohol withdrawal and consists of gross tremor, frightening visual hallucinations, profound confusion, agitation, and a hyperadrenergic syndrome characterized by temperature above 101° F, blood pressure higher than 140/90 mm Hg, and tachycardia. It seldom appears before the third post-abstinence day. Only 5% of patients hospitalized for alcohol withdrawal have delirium tremens.

Management

Family, friends, bystanders, or paramedics often give more reliable historical data than the patient does. Accurate vital signs are essential. This may require a rectal temperature. Hyperthermia, hypothermia, tachypnea, or tachycardia may suggest serious disorders that often accompany the alcohol-dependent patient. These disorders should be considered during this first assessment.

A rapid, thorough examination should be performed with attention to the level of consciousness, signs of hepatic failure, or coagulopathy. Signs of trauma are sought, such as subcutaneous emphysema, ecchymosis, subconjunctival hemorrhage, hemotympanum, or Battle's sign, and palpation is done for occult injuries. The neurologic examination should search for focal findings, including central facial nerve palsy, hemiparesis, and asymmetry of pupillary response.

The alcohol withdrawal syndrome should be promptly recognized and treated to provide relief from anxiety and hallucinations; to halt progression to major withdrawal and withdrawal seizures; to allow detection of a treatable primary psychiatric illness; to prepare the patient for long-term alcohol abstinence with the lowest risk of new drug dependence; and to calm the patient and allow adequate examination for the detection of medical illnesses that typically accompany alcoholism, such as gastritis, dehydration, pancreatitis, pneumonia, electrolyte disorders, and hepatitis.

In combination with appropriate chemical sedation, detention by reasonable restraint may be an option to prevent potential injury that patients may inflict on themselves or the hospital staff. These appropriate measures need to be instituted, and decision-challenged patients should not be permitted to sign an "against medical advice" form and be discharged.

Patients suffering from alcohol withdrawal should receive pharmacologic intervention along with supportive care. The ideal drug for alcohol withdrawal would have a rapid onset, wide margin of safety, metabolism not dependent on liver function, and limited abuse potential. Although no one drug class fits all these requirements, benzodiazepines are clearly the mainstay of treatment.

Benzodiazepines. The benzodiazepines have superior anticonvulsant activity, have the least respiratory and cardiac depressive effect of all the CNS depressants, and can be given parenterally in the uncooperative patient. By interacting with receptors linked to the GABA-associated chloride ion channel, benzodiazepines substitute for the withdrawal of the GABA-potentiating effect of alcohol and abate withdrawal signs and symptoms.[19] Numerous benzodiazepines have been studied, but there is no evidence of clear superiority of any one benzodiazepine.

Lorazepam has good bioavailability with oral, intramuscular, and intravenous routes. It is rapidly and completely absorbed from intramuscular sites in agitated patients with no intravenous access. Lorazepam's half-life is intermediate (7-14 hours), and it reaches a steady state in 36 to 48 hours without active metabolites. Excessive sedation, confusion, and ataxia are potential complications of all benzodiazepines with prolonged half-lives. Lorazepam is metabolized (conjugated) in the liver, yielding inactive products. Although the half-life of lorazepam increases in patients with cirrhosis or liver failure, it is much less than the increase with chlordiazepoxide. Lorazepam's elimination is only minimally altered in patients with renal failure and in the elderly. Lorazepam may be given intravenously in a dose of 1 to 4 mg, depending on the severity of the withdrawal. Dosing can be repeated at 5- to 15-minute intervals for patients in severe withdrawal. Although it is not ideal, an intramuscular dose of 1 to 4 mg can be used every 30 to 60 minutes until the patient is calm and then every hour as needed for light somnolence. The oral schedule for moderate withdrawal is 6 mg/day in three divided doses, tapering the amount by 1 to 2 mg/day during 4 to 6 days.

As one dosing regimen, diazepam, 5 mg IV every 5 to 10 minutes (2.5 mg/min), can be given in major withdrawal until the patient is calm. The dose can be repeated in 5 to 10 minutes. If the second dose of 5 mg is not working, consider 10 mg for the third and fourth doses every 5 to 10 minutes. If this is not effective, consider 20 mg for the fifth and subsequent dose until adequate sedation is obtained.[20,21]

Butyrophenones. Haloperidol, a dopamine antagonist, can be considered in patients with major alcohol withdrawal or delirium tremens not responding to intravenous benzodiazepines. Haloperidol has little effect on myocardial function or respiratory drive, and its safety and efficacy by the intravenous, intramuscular, or oral route in the ED have been established. Haloperidol has no anticonvulsant properties; however, extrapyramidal effects may be seen. Caution should be used in patients who may be susceptible to a prolonged QTc. Droperidol has effects similar to those of haloperidol. Despite the 2001 Food and Drug Administration black box warning for QTc prolongation and torsades de pointes after droperidol use, droperidol remains a safe and effective treatment for agitated patients.[22]

Emergency Department and Outpatient Approaches

Outpatient treatment consists of lorazepam, 1 to 2 mg three times a day in a tapering dose for 3 to 6 days; chlordiazepoxide, 25 to 100 mg three times a day, in a tapering dose for 3 to 6 days; or diazepam, 30 mg once a day tapered during 5 days, depending on the severity of symptoms. Adequate diet, abstinence, and participation in a rehabilitation program in the community are also desirable. Any patient requiring 300 mg of chlordiazepoxide or 60 mg of diazepam per day to control withdrawal should be considered for admission. Patients with major alcohol withdrawal (disorientation, hallucinations, diaphoresis, or fever) are admitted.

Adjunctive Therapy

Patients being treated for major alcohol withdrawal may be given thiamine (100 mg IV) and magnesium (2 g IV). Although magnesium sulfate does not decrease the severity of withdrawal symptoms, the incidence of delirium, or seizures, it carries no significant risk (with adequate renal function).

If volume depletion is present, it can be corrected with normal saline. Reversal of electrolyte and metabolic disorders (hypomagnesemia, hypophosphatemia, hypokalemia, and acidosis) benefits the patient, but it does not abate the withdrawal syndrome.

ALCOHOL-RELATED SEIZURES

Among the many medical problems related to alcohol abuse, the differential diagnosis and management of seizures remain among

www.ketabpezeshki.com 66485457-66963820

Box 185-1 Differential Diagnosis of Alcohol-Related Seizures

Withdrawal (alcohol or drugs)
Exacerbation of idiopathic or post-traumatic seizures
Acute intoxication (amphetamines, anticholinergics, cocaine, isoniazid, organophosphates, phenothiazines, tricyclic antidepressants, salicylates, lithium)
Metabolic (hypoglycemia, hyponatremia, hypernatremia, hypocalcemia, hepatic failure)
Infectious (meningitis, encephalitis, brain abscess)
Trauma (intracranial hemorrhage)
Cerebrovascular accident
Sleep deprivation
Noncompliance with anticonvulsants

the most challenging and controversial (Box 185-1). Patients presenting to the ED with seizures should be questioned about alcohol intake. Of seizure patients presenting to an ED, 20 to 40% will have their seizures related to alcohol use or abuse.[23] Alcohol is a causative factor in 11 to 24% of patients with status epilepticus.[24,25] In states where alcohol sales are restricted on Sundays, EDs see a spike in alcohol-related seizures on Mondays.[26]

The primary consideration in the initial care of seizure patients who use alcohol is the recognition of treatable, life-threatening causes. These causes include but are not limited to CNS infection, metabolic disorders, and intracranial hemorrhage. Alcohol may act in one of several ways to produce seizures in patients with or without underlying foci: by its partial or absolute withdrawal after a period of chronic intake, by an acute alcohol-related metabolic disorder (e.g., hypoglycemia, hyponatremia), by creation of a situation leading to cerebral trauma, by precipitation of seizures in patients with idiopathic or post-traumatic epilepsy, or by lowering of the seizure threshold in patients with prior existing intracerebral disease states. Moreover, alcoholics are more susceptible to other disorders associated with seizures, including neurosyphilis, acquired immunodeficiency syndrome (AIDS), brain abscess, and meningitis.[27-29]

Alcohol Withdrawal Seizures

Descriptions of alcohol withdrawal seizures are based on data collected by Victor and Brausch.[30] Seizures occurred 6 to 48 hours after the cessation of drinking. Ninety percent had one to six generalized tonic-clonic seizures. Sixty percent experienced multiple seizures within a 6-hour period. However, seizure recurrence can be reduced to 3% with lorazepam administration after the initial seizure.[31] The incidence of partial seizures, common with post-traumatic epilepsy, is increased in alcohol withdrawal. The term *alcohol withdrawal seizure* is reserved for seizures with the characteristics described by Victor and Brausch.[30] The term *alcohol-related seizure* is used to refer to all seizures in the aggregate associated with alcohol use, including this subset of alcohol withdrawal seizure.

Patients Presenting with Normal Findings on Neurologic Examination

New-Onset Alcohol-Related Seizures

Patients with new-onset alcohol-related seizure should be thoroughly evaluated. This includes alcoholics who claim to have had seizures but for whom no documentation or an appropriate work-up is available. Metabolic disorders, toxic ingestion, infection, and structural abnormalities should be considered. Laboratory and radiographic testing to include electrolyte values and blood urea nitrogen, creatinine, glucose, and anticonvulsant levels and brain computed tomography (CT) scan may be necessary. Of 259 patients presenting with their first alcohol-related seizure, clinical management was changed in 3.9% on the basis of head CT results.[32]

If the initial physical examination findings, imaging studies, and laboratory test results are within normal limits, patients who remain seizure free and symptom free with no sign of withdrawal after 4 to 6 hours of observation may be discharged. It may be unclear whether the patient has had a pure alcohol withdrawal seizure or a new-onset seizure disorder in the setting of alcohol ingestion. Long-term treatment with antiepileptic drugs is not useful in unprovoked new-onset seizures that have resolved or when a clear relation to alcohol consumption can be identified.

Optimal outpatient treatment includes follow-up and referral to a detoxification or rehabilitation program. Ideally, the help of a concerned family member or friend who is not a drinking partner and can remain with the patient for at least 1 or 2 days is helpful.

Seizures in the Alert Patient with a History of Seizures during Prior Withdrawal

The risk of seizure increases significantly in alcoholic patients with manifestations of alcohol withdrawal who relate a history of alcohol withdrawal seizure.[33,34] Detoxification with benzodiazepines reduces alcohol withdrawal seizure and should be initiated early because most seizures occur within the first 24 hours after alcohol withdrawal. An initial dose of 2 mg of lorazepam or 5 mg of diazepam can be given intravenously. These doses frequently need to be repeated.[35] The patient should be observed for 4 to 6 hours before discharge is considered. The prescription of benzodiazepines or antiepileptic drugs on discharge carries its own hazards. Benzodiazepines (other than a short 3- to 6-day tapering dose for withdrawal) may increase the potential risk of addiction. In a noncompliant patient, antiepileptic drugs, such as phenytoin, may paradoxically increase the number of seizures. The poorly compliant alcoholic patient may do better without outpatient anticonvulsants for a concurrent seizure disorder.[33] The ideal disposition is referral to a detoxification or rehabilitation unit.

Patients with an Abnormal Neurologic Presentation

New-Onset Partial Seizures

Partial seizures account for 24 to 51% of alcohol-related seizures.[36] Conversely, studies have shown that 17 to 21% of patients with partial alcohol-related seizure have structural lesions: hematomas, tumors, vascular abnormalities, or stroke.[37] These primary causes of partial alcohol-related seizure, such as prior head trauma, may be easily missed in the history taking. As a result, an emergent CT scan is indicated to evaluate new-onset partial seizures. The patient with a history of a focal alcohol-related seizure who has been previously evaluated does not require an emergency CT scan, provided a return to baseline occurs promptly. A patient presenting with a focal alcohol-related seizure with subsequent normal neuroimaging findings can be managed with supportive care, observation for 4 to 6 hours, and a benzodiazepine for withdrawal signs or symptoms. Appropriate follow-up should be arranged.

Obtundation

The obtunded or stuporous alcohol-dependent patient with a history of seizure activity poses a diagnostic challenge. The patient's decreased level of consciousness may be the result of a postictal state, occult head trauma, unrecognized metabolic

www.ketabpezeshki.com 66485457-66963820

disorder, or other poisoning. The first diagnostic task is quickly to determine the possibility of hypoglycemia (diagnosed and reversed at the bedside in minutes) and to evaluate for other metabolic and toxic causes of altered mental status. Patients with an acute alteration in mental status should undergo a head CT scan if they are not demonstrating expected and obvious improvement.

Patients Taking Phenytoin-Anticonvulsant

Phenytoin has no significant benefit over placebo in prevention of recurrence of uncomplicated (e.g., no old subdural) alcohol withdrawal seizure. Considering the risks of phenytoin and no demonstrated benefit in the setting of alcohol withdrawal seizure, it is not indicated for the treatment of alcohol withdrawal seizure. The sudden withdrawal of phenytoin may potentiate the convulsive effects of alcohol withdrawal.[23,38]

A patient currently taking antiepileptic drugs for an antecedent seizure disorder who presents with a seizure while intoxicated falls into a different category. Such an episode could be an isolated event in a usually compliant patient without a history of chronic alcohol abuse. In this patient, a seizure in the setting of a subtherapeutic antiepileptic drug level may represent the consequences of noncompliance with antiepileptic medication or sleep deprivation versus alcohol withdrawal seizure.[33]

OTHER CLINICAL FEATURES AND MANAGEMENT

Cardiovascular Effects

Acute and chronic ethanol consumption can affect the mechanical function of the heart, produce dysrhythmias, and exacerbate coronary artery disease (CAD). It may alter myocardial function by direct toxic effects, by associated hypertension, or indirectly by altering specific electrolytes. Acute intoxication can decrease cardiac output in both alcoholic and nonalcoholic patients with preexisting cardiac disease.[38]

Studies have linked moderate alcohol consumption (two to four drinks per day in men and one or two in women) to a protective effect from CAD. Low to moderate alcohol consumption decreases platelet aggregation, raises plasma levels of endogenous tissue plasminogen activator,[39] and lowers insulin resistance. Experimental data suggest that alcohol may have antioxidant properties, produce effects on smooth muscles through interactions with nitric oxide, and alter plasma total homocysteine levels.[40,41] The red versus white wine hypothesis rests on human studies showing short-term cardiovascular benefits achieved by de-alcoholized red but not white wine and many studies on isolated tissues or organs assessing the effects of polyphenols in red wine, especially resveratrol. Therefore, red wine potentially has beneficial effects beyond alcohol content.[42]

Studies suggest that moderate alcohol consumption, through a reduced risk of CAD, may also protect individuals from congestive heart failure (Box 185-2).[43] All of these beneficial effects are lost in heavy drinkers, in whom chronic alcoholism is associated with hypertension and congestive cardiomyopathy.

Up to one third of chronic alcoholic patients have left ventricular dysfunction demonstrated by radionuclide ventriculography, usually coexisting with skeletal muscle disease. Those who stop using alcohol may have an improved ejection fraction during the course of 3 years.[44] Although the primary functional abnormality of alcoholic cardiomyopathy was thought to be a depression in systolic function, it is now appreciated that an impairment in diastolic function is present in one third of alcoholics who have a normal systolic function; in many, systolic dysfunction and diastolic dysfunction coexist. Excess alcohol consumption affects not only the cardiomyocytes but striated skeletal muscle as well. Women appear to be more sensitive than men to the toxic effects of alcohol on striated muscle and are at greater risk for cardiomyopathy and myopathy as well as for skeletal myopathy for any given lifetime amount of alcohol.[44]

Heavy alcohol consumption has a detrimental effect on those with preexisting CAD. It can reduce exercise tolerance, induce coronary vasoconstriction, and raise heart rate and blood pressure.[45] Additive cardiovascular effects of ethanol and nicotine contribute to dysrhythmias and sudden death in patients with CAD. In one study, nearly half the patients with alcohol withdrawal had prolongation of the QT interval. Prolonged QT can precipitate a dysrhythmia, resulting in sudden death.[46] There is an increased incidence of sudden death among heavy drinkers regardless of concomitant CAD or smoking.

Supraventricular (usually atrial fibrillation) and ventricular (usually transitory ventricular tachycardia) dysrhythmias, labeled "holiday heart," have been documented in alcoholic patients who have been drinking heavily. One study reported that alcohol contributes to or causes new-onset atrial fibrillation in approximately two thirds of patients younger than 65 years. Tachydysrhythmias as a result of episodic drinking commonly revert to sinus rhythm with abstinence and do not require immediate intervention if the patient is hemodynamically stable.

Alcohol also affects cardiac function indirectly by lowering potassium and magnesium levels. Data from the Framingham Heart Study indicate that patients with lower levels of potassium and magnesium have higher rates of dysrhythmias.[47]

Pulmonary Effects

Alcohol reduces the mobilization of alveolar macrophages and their bactericidal capacity. Their impairment is greatest in alcoholics with hepatic cirrhosis. In alcoholic patients, the lungs are more vulnerable to oxidative stress and injury. There is evidence that chronic alcohol consumption decreases the level of glutathione, promoting inflammation and remodeling of the lung tissue.[48] These effects, along with aspiration, decreased airway sensitivity, concomitant smoking, and malnutrition, probably account for the increased incidence of pneumonia, particularly lobar pneumonia, among alcoholic patients.[49] Alcohol abuse is also associated with an increased likelihood of intensive care unit admission and a longer hospital length of stay than for non-alcoholic patients with community-acquired pneumonia.[50]

At least 80% of alcoholics are smokers, making it difficult to distinguish between alcohol-induced and tobacco-induced injury to the lungs. The high prevalence of respiratory disease in alcoholics is largely caused by smoking. Patients with sepsis and chronic alcohol abuse are at least twice as likely to require mechanical ventilation and have a twofold to fourfold risk for development of the acute respiratory distress syndrome.[50]

Alcohol induces bronchospasm in some asthmatics and increases ventricular ectopy and sleep apnea in patients with chronic obstructive pulmonary disease. Alcoholic patients with hepatic cirrhosis can have hypoxemia as a result of precapillary shunting in their lungs. Hyperventilation and respiratory alkalosis are also seen with hepatic cirrhosis. One or two drinks per day has been found to decrease the risk of pulmonary embolus and deep venous thrombosis in elderly patients.[51]

Gastrointestinal and Hepatic Effects

Esophagus and Stomach

Alcoholic patients have a higher incidence of esophagitis, gastric cancer, and esophageal carcinoma than that in the general population. Acute alcohol ingestion also decreases lower esophageal sphincter pressure, delays gastric emptying, and disrupts the

www.ketabpezeshki.com 66485457-66963820

Box 185-2 Risks and Benefits of Light, Moderate, and Heavy Drinking

Light-Moderate Drinking

Risks		Benefits	
Established	Heavy drinking	Probable	Decreased risk of coronary heart disease
Unresolved	Breast cancer		Decreased risk of ischemic stroke
	Fetal damage		Decreased risk of gallstones
Unlikely	Bowel cancer	Possible	Decreased risk of diabetes
	Hemorrhagic stroke		Decreased risk of peripheral vascular disease
	High blood pressure		

Heavy Drinking

Risks		Benefits
Noncardiovascular	Liver cirrhosis	None
	Pancreatitis	
	Certain cancers	
	Accidents	
	Homicides	
	Suicides	
	Fetal damage	
	Degenerative central nervous system disorders	
Cardiovascular	High blood pressure	
	Arrhythmia	
	Hemorrhagic stroke	
	Cardiomyopathy	

Modified from Klatsky A: Drink to your health? Sci Am 288:74, 2003. Copyright © Scientific American, Inc.

normal gastric mucosal barrier. Alcohol consumption, because of its inherent toxicity, has been shown to eliminate infection of the gastric mucosa by *Helicobacter pylori*.[52] Vomiting is common among drinkers. Forceful or persistent emesis can lead to a Mallory-Weiss tear or Boerhaave's syndrome.

Gastrointestinal Bleeding

Alcohol is closely associated with gastrointestinal bleeding. Causes and contributing factors include Mallory-Weiss tears, esophagitis, esophageal varices, acute and chronic gastritis, thrombocytopenia, portal hypertensive gastropathy, qualitative and quantitative platelet disorders, and prolonged clotting times. Alcohol may exacerbate gastric mucosal damage when it is combined with non-steroidal anti-inflammatory drugs (NSAIDs), but ethanol itself is not a risk factor for peptic ulcer disease. An inverse relationship exists between consumption of alcohol, particularly wine, and active *H. pylori* infection. Peptic ulcer disease is the most common cause of bleeding in alcoholic patients with upper gastrointestinal hemorrhage as well as in those who do not drink.[53]

Liver

Hepatic damage has been recognized for centuries as the hallmark of chronic alcohol abuse. Obesity potentiates the severity of alcohol-induced liver damage.[54] The activation of the immune system with the production of cytokines such as tumor necrosis factor alpha is one of the earliest events in many types of liver injury.[55] This cascade stimulates Kupffer cells and the production of other cytokines that together enlist inflammatory cells, kill hepatocytes, and initiate healing through fibrogenesis. There is no single test that can be used to diagnose alcoholic liver disease reliably. However, the ratio of AST to ALT higher than 2 suggests that alcohol is the cause of liver injury.[56] Alcoholic liver disease is the most common liver disorder in the Western world and along with hepatitis C is a leading cause of liver transplantation.[57]

The earliest, mildest, and most common liver change in alcoholism is the accumulation of macrovesicular fat in the hepatocytes, predominantly involving triglycerides. Alcoholic fatty liver is usually asymptomatic, associated with mild elevations of AST and ALT. It is detected by the finding of hepatomegaly on physical examination or abnormalities on ultrasonography or CT but is confirmed by liver biopsy. Fatty liver is a reversible disorder if the patient can refrain from drinking.[58]

Alcoholic Hepatitis

Alcoholic hepatitis is more serious than fatty infiltration and develops in up to 35% of heavy drinkers.[59] These individuals usually have right upper quadrant pain, tender enlarged liver, fever, jaundice, leukocytosis, and altered liver function test results. AST levels are usually less than 400 IU/L, and ALT levels are typically less than half the AST level. Alcoholic hepatitis has a range of clinical manifestations, from mildly symptomatic hepatomegaly to fulminant hepatic failure. The severity of the disease can be estimated in the ED by a prolonged prothrombin time/international normalized ratio (INR)[60] or with the use of discriminant factor.[61] The ABIC (age, bilirubin, INR, creatinine) score and the Model for End-stage Liver Disease (MELD) are also helpful in predicting mortality in these patients.[59,62]

Evaluation of symptomatic patients includes complete blood count, electrolyte values, blood urea nitrogen and creatinine concentrations, glucose concentration, prothrombin time/INR, liver function tests, and urinalysis. If the patient has an abnormal prothrombin time/INR and is actively bleeding, fresh frozen plasma should be started in the ED. Steroids are indicated in severe cases (encephalopathy, coagulopathy).[63] Steroids are relatively contraindicated in patients with gastrointestinal bleeding or concurrent infection. In those for whom steroid treatment is contraindicated, pentoxifylline has been shown to be beneficial.[64] Up to 80% of patients with alcoholic hepatitis who continue to drink eventually have cirrhosis.

www.ketabpezeshki.com 66485457-66963820

Alcoholic Cirrhosis

Cirrhosis is the disruption of the normal architecture of the liver by scarring and regenerating nodules of parenchyma. Alcoholism is the most common cause of cirrhosis in the United States and is responsible for approximately 50% of all cirrhotic deaths. Alcoholic cirrhosis usually requires 10 to 15 years of chronic drinking, often punctuated by one or more episodes of acute alcoholic hepatitis. The clinical outcome is determined by the development of complications of portal hypertension and by hepatic dysfunction. It is unknown why hepatic damage develops in some alcoholic patients and not in others exposed to identical amounts of alcohol. The disorder was originally described as "nutritional cirrhosis," but it has been shown that alcohol, independent of malnutrition, produces the liver damage. Alteration of the normal hepatic architecture by fibrosis and nodule formation may eventually lead to portal hypertension. Portal hypertension may be complicated by ascites and esophageal varices. Although cirrhosis is irreversible, its progression may be halted with abstinence.

Hepatitis C antibodies are found in one third to one half of alcoholics with alcoholic liver disease, presumably from similar risk factors. Patients with alcoholic liver disease and hepatitis C have histologically more severe disease, shorter survival, and tenfold increased rates of cirrhosis and liver cancer.[65]

No specific medical therapy exists for alcoholic liver disease other than abstinence, proper diet, and management of the subsequent hepatic decompensation (i.e., ascites and encephalopathy). A decrease in the amount of alcohol consumed during 1 year is associated with a 60% decrease in mortality.[66]

Pancreatitis and Malabsorption

The association of ethanol with both acute and chronic pancreatitis is well established, but the exact pathogenesis is unclear. Hypotheses include reflux of duodenal contents and bile into the pancreatic duct, obstruction by a plug of pancreatic juice rich in proteins, and direct toxic effect of ethanol.

The diagnosis of alcoholic pancreatitis can be difficult because asymptomatic alcoholics may have an elevated amylase level. Conversely, up to 30% of patients with acute alcoholic pancreatitis have an amylase value within normal limits. Serum lipase rises after amylase, remains elevated longer, and is a more reliable indicator of alcoholic pancreatitis, especially when it is more than three times normal.[67] Alcohol is the leading cause of chronic pancreatitis.

Diarrhea and impaired intestinal absorption are common problems of the chronic alcoholic. Alcohol increases small intestine transit time and decreases brush border enzyme activity. Thiamine, vitamin B_{12}, amino acids, folic acid, and glucose have impaired absorption in alcoholics. Dietary deficiencies in folic acid and protein, pancreatic insufficiency, abnormal biliary secretion, and direct toxic effects of ethanol on the gastrointestinal tract contribute to malabsorption. Abstinence and adequate nutrition reverse the diarrhea and much of the malabsorption.[58]

Neurologic Effects

Neuropathy

A symmetrical sensorimotor polyneuropathy is common with chronic alcohol abuse, usually in the lower extremities. It is thought to be a combination of nutritional deficiency with thiamine or B_{12} deficit and a direct neurotoxic effect of alcohol. Burning pain and paresthesia are common complaints. Findings on physical examination include loss of light touch, decreased pinprick sensation, and reduced lower extremity deep tendon reflexes. Distal muscle weakness is a late finding. The neuropathy may lead to nonhealing ulcers on the feet. Treatment of alcoholic neuropathy is abstinence, adequate diet, and thiamine. Complete recovery is rare.

"Saturday night palsy" or "honeymooner's syndrome" is a wrist drop caused by radial nerve compression. The patient usually has spent the night with the arm drooped over the back of a chair, bench, or a companion, compressing the radial nerve against the humerus and producing a neurapraxia. Loss of function due to radial nerve neurapraxia usually returns after a few weeks to months.

Wernicke-Korsakoff Syndrome

Although they are similar pathologically and caused by thiamine deficiency, Wernicke and Korsakoff syndromes are clinically distinct. Wernicke's encephalopathy, a medical emergency with a mortality rate of 10 to 20%, remains a clinical diagnosis and is often unrecognized. Contemporary criteria require two of these signs: dietary deficiencies, oculomotor abnormalities (nystagmus is most common), cerebellar dysfunction, and either an altered mental state or mild memory impairment.[68] Mental abnormalities include lethargy, inattentiveness, abulia, and impaired memory, progressing without treatment to coma.

Genetic and environmental factors may play a part in the pathogenesis of this disorder. A thiamine-dependent enzyme, transketolase, is deficient or less active in some patients who have Wernicke-Korsakoff syndrome. This may explain why the disorder develops in only a few alcoholics. Persons with transketolase deficiency are asymptomatic until they are stressed by thiamine deficiency. Protracted vomiting, inadequate diet, and malabsorption contribute to thiamine deficiency in the alcoholic.[69]

Korsakoff's psychosis or amnesic state, also called alcohol-induced persisting amnestic disorder, is a disorder with recent memory impairment, inability to learn new information or to recall previously learned information, apathy, and confabulation. Although it is common, confabulation is not essential for the diagnosis. Whereas 80% of patients with acute Wernicke's encephalopathy have Korsakoff's syndrome, age older than 40 years and many years of heavy alcohol use are additional risk factors.[70]

Treatment of Wernicke-Korsakoff syndrome consists of abstinence, adequate diet, and thiamine. The ophthalmoplegia and nystagmus usually have a good response to thiamine within hours to days. The ataxia and mental changes may take days to weeks to improve and usually have a poorer prognosis. Less than 25% of patients show any real recovery, 50% show some recovery, and the remainder show no response despite adequate thiamine replacement. Because magnesium is a cofactor for this enzyme system, serum levels should be corrected. Patients with Wernicke's syndrome require admission and aggressive thiamine and magnesium repletion.

Movement Disorders

Alcohol withdrawal is associated with tremor, ataxia, and myoclonus. Acute alcohol consumption ameliorates essential tremor and myoclonus. Persistent tremor is occasionally seen in chronic alcoholism. This alcoholic tremor may persist up to 1 year after abstinence. Although the pathophysiologic mechanism is poorly understood, studies have confirmed that essential tremor and alcoholic tremor are distinct entities.[71]

Alcoholic Cerebellar Degeneration

Characterized by ataxia of the extremities, cerebellar ataxia of alcoholism results in a wide-based stance and uncoordinated gait. Lower extremity involvement predominates, although the arms may rarely be involved. Pathologic changes consist of degeneration

www.ketabpezeshki.com 66485457-66963820

of elements in the cerebellum, especially the Purkinje cells. The diagnosis is based on history, physical examination, and magnetic resonance imaging or CT (which shows severe cerebellar atrophy). Treatment consists of abstinence, adequate nutrition, and thiamine.[72]

Dementia

Some studies suggest that ethanol may offer direct neuroprotection to the brain, bearing on the apparent risk reduction of dementia in selected drinkers.[73] Once again, a J-shaped curve emerges, with moderate intake reducing the risk of cognitive impairment and heavy drinking increasing it.[74] Whereas small amounts of ethanol probably protect against dementia and Alzheimer's disease but not against vascular dementia or cognitive decline, these conclusions are controversial.[75]

Infections

Experimental and clinical data support the conclusion that alcohol is a potent immunomodulatory agent. Chronic alcohol abuse (≥8 drinks/day) leads to immunosuppression.[76] Animal and human studies have implicated acute and chronic ethanol ingestion in causing decreased serum bactericidal activity, impaired mononuclear phagocyte function, diminished cell-mediated immune functions, reduced delayed hypersensitivity reaction, and defective polymorphonuclear neutrophils. Neutropenia may be found in up to 8% of hospitalized alcoholics.[77]

Alcohol ingestion prevents the normal delivery (chemotaxis) of polymorphonuclear neutrophils to sites of bacterial infection. Chronic alcohol exposure depresses the development and expression of cell-mediated immunity. This depression may contribute to the high incidence of tuberculosis and head, neck, and upper gastrointestinal cancers in alcoholics. Alcohol's suppression of macrophage function reduces the reticuloendothelial system's ability to clear particles. This may contribute to spontaneous bacteremia, spontaneous bacterial peritonitis, and pneumonia. Primary antibody response to new antigens is also depressed. Malnutrition and liver failure also contribute to an immunocompromised state in the alcoholic.

The most common infection in alcoholism is pneumonia. Associated risk factors for pneumonia in alcoholics include smoking, decreased ciliary function, decreased surfactant production, depressed cough reflex, malnutrition, and poor oral hygiene. Although alcoholic patients may contract a variety of bacterial pneumonias, *Streptococcus pneumoniae* is still the most common organism. Periods of alcoholic stupor with incomplete glottic closure and subsequent aspiration can lead to aspiration pneumonia or lung abscess. *Klebsiella pneumoniae,* classically associated with alcoholism, is currently more common in patients with cytotoxic chemotherapy, hematologic malignant disease, and transplantation than in the chronic alcoholic. In addition, these infections now tend to be nosocomial rather than community acquired.[77]

Chronic alcoholism is also associated with a threefold increase of tuberculosis.[78] Alcoholism itself does not seem to influence the long-term relapse rates in tuberculous patients if they have closely supervised therapy of adequate duration. Homeless alcoholic patients are an important reservoir of tuberculosis in the United States.

Spontaneous bacterial peritonitis occurs in cirrhotic patients with ascites and has a high mortality rate (50-90%). A common presentation consists of fever, abdominal pain, and leukocytosis. *Escherichia coli, K. pneumoniae,* and *S. pneumoniae* are the most common bacteria cultured from the ascitic fluid. Patients with new ascites and fever should have a diagnostic paracentesis as part of their evaluation.

Hepatitis C appears to be related to concomitant injection drug use rather than the direct effect of alcohol abuse. Alcoholism is associated with a high prevalence of unsafe sexual behavior and human immunodeficiency virus (HIV) seropositivity,[79] with greater immunologic changes in HIV-1–positive patients who also consume alcohol.[80]

Fever in the chronic alcoholic may result from a vast array of causes. The most common infection remains pneumonia. Occult urinary tract infections are more common than expected. The most common noninfectious causes of fever are alcohol withdrawal and alcoholic hepatitis. A leukocytosis is associated with both, often making the differentiation from infection difficult. Both infectious and noninfectious causes may coexist, and there may be multiple sources of infection. Most febrile alcoholics without an identifiable source are best served by hospitalization.

Endocrine Effects

Alcohol dependence adversely affects many endocrine systems. Both peripheral thyroid hormone dysfunction and central hypothalamic-pituitary-thyroid axis deregulation are seen.[81] Male hypogonadism and feminism are seen in chronic male alcoholics. Alcohol's effects on both the testes and the hypothalamus decrease testosterone production in men.[82] Alcohol may cause impotence by CNS sedation, secondary depression, or decreased testosterone production. Decreased testosterone, increased estrogen (in patients with liver disease), and increased prolactin can lead to decreased libido, feminization, and gynecomastia in male alcoholics and to abnormalities in lactation and menstruation in women. In female alcoholics, increased levels of testosterone and estrogen are found. Estrogen replacement therapy may increase hormonal levels threefold and thus increase the risk of cholelithiasis and breast cancer.[83]

Metabolic Effects

Carbohydrates

Alcohol-induced hypoglycemia occurs in 1 to 4% of intoxicated ED patients. It is more frequently seen in chronic alcoholics.[84] Coma, seizures, hemiparesis, and a variety of other neurologic signs have been described in patients presenting with alcohol-induced hypoglycemia. Starvation, depletion of liver glycogen stores, decreased plasma cortisol levels, impaired release of growth hormone, and inhibition of gluconeogenesis contribute to this phenomenon.

Hyperglycemia and diabetes may be found in chronic alcoholism. Alcohol abuse can lead to chronic pancreatitis, resulting in underproduction of insulin by the damaged pancreatic cells. Alcohol also impairs peripheral glucose utilization, causing a relative insulin resistance (similar to type 2 diabetes). In diabetic patients, alcohol can induce hypoglycemia and also mask the signs of hypoglycemia. This is more prominent in the fasting state.[85]

Lipids

A reversible hypertriglyceridemia occurs in many chronic alcoholics. Ethanol increases hepatic synthesis of triglycerides. Abstention is necessary to reduce elevated triglyceride levels. Except for its relationship to fatty infiltration of the liver, the clinical significance of this hyperlipidemia is unknown.[86]

Electrolytes

Ethanol has numerous effects on electrolytes and mineral metabolism as summarized in Table 185-5. Hyponatremia and hypokalemia are common in active drinkers. Vomiting, diarrhea, magnesium

www.ketabpezeshki.com 66485457-66963820

Table 185-5 Effect of Ethanol on Mineral Metabolism

MINERAL	CAUSE OF DEPLETION	ADDITIONAL EFFECT OF COMPARTMENT SHIFTS	CONSEQUENCES
Magnesium	Alcohol Diarrhea Poor intake Phosphate depletion Hyperaldosteronism	↓ Hyperventilation ↓ Free fatty acids	Pseudohypoparathyroidism Myopathy Potassium depletion Phosphate depletion Electrocardiographic abnormalities Seizures
Phosphorus	Poor intake Diarrhea Metabolic alkalosis Hypomagnesemia	↓ Metabolic alkalosis ↓ Respiratory alkalosis ↓ Glucose (refeeding) ↑ Hypoparathyroidism (secondary to hypomagnesemia) ↑ Rhabdomyolysis	Rhabdomyolysis Platelet dysfunction White blood cell dysfunction Central nervous system dysfunction Cardiac failure Renal tubular acidosis
Calcium	Poor intake Steatorrhea Hypovitaminosis K	↓ Hypoparathyroidism (secondary to hypomagnesemia) ↓ Rhabdomyolysis ↓ Hypovitaminosis D ↓ Hyperphosphatemia ↓ Pancreatitis ↓ Hypoalbuminemia ↑ Recovery from rhabdomyolysis	Tetany Seizures
Potassium	Poor intake Metabolic alkalosis Hyperaldosteronism Diarrhea	↓ Glucose (refeeding) ↓ Hyperventilation ↑ Rhabdomyolysis	Weakness Paralysis Myopathy Sudden death

From Kaysen G, Noth R: The effects of alcohol on blood pressure and electrolytes. Med Clin North Am 1984; 68:239.
↓ out of plasma; ↑ into plasma.

depletion, malnutrition, and metabolic alkalosis contribute to these abnormalities.

Alcoholism is the most common cause of severe magnesium deficiency in adult outpatients. Thirty percent of alcoholics are magnesium deficient as a result of malabsorption, malnutrition, diarrhea, vomiting, and increased urinary losses. Oral magnesium supplementation in chronic alcoholics improves liver function test findings, electrolyte balance, and muscle strength.[87] Multivitamin preparations may be considered for chronic malnutrition. Although their clinical benefit is not proved, they carry no significant risk or cost.

Hypocalcemia is common in alcoholic patients with magnesium depletion. The mechanism is related to diminished parathyroid hormone secretion, decreased tissue responsiveness to parathyroid hormone, decreased vitamin D metabolism, and decreased calcium release from bone independent of parathyroid hormone. Correction of magnesium depletion is necessary to restore calcium to normal levels. Hypoalbuminemia, pancreatitis, or vitamin D deficiency also contributes to low serum calcium or low total body stores of calcium in alcoholic patients.[88]

Hypophosphatemia is found in 30 to 50% of hospitalized patients with alcoholism. Phosphorus depletion results from malnutrition, vomiting, respiratory alkalosis, diarrhea, enhanced release of calcitonin, phosphate-binding antacids, and urinary loss (related to vitamin D deficiency and secondary hyperparathyroidism). Hypophosphatemic patients often have low magnesium levels.[89] Rehydration, carbohydrate repletion, and parenteral alimentation further exacerbate phosphorus depletion. Glucose bolus and infusion have been shown to produce a significant fall in serum inorganic phosphate levels. Severe hypophosphatemia (<1 mg/dL) has been associated with acute respiratory failure; myocardial depression; dysfunction of erythrocytes, leukocytes, and platelets; CNS irritability; and rhabdomyolysis.

Although chronic alcoholics requiring admission often have potassium, magnesium, and phosphate depletion, empirical treatment with potassium and phosphate is discouraged. Serum levels and renal function should be determined. Unintended hyperkalemia and hyperphosphatemia can produce significant morbidity, and phosphate infusion exacerbates hypocalcemia if it is present. Because most magnesium is intracellular, a normal serum magnesium level does not rule out decreased total body magnesium stores. If the serum level is normal, total body levels may still be low. As long as renal function is adequate, empirical magnesium treatment can be considered. Abstinence and a proper diet resolve electrolyte and nutritional deficiencies in the ambulatory alcoholic patient who is healthy enough to be treated as an outpatient.

Alcoholic Ketoacidosis

Alcoholic ketoacidosis most frequently occurs in severe chronic alcoholics who have had a recent binge followed 1 to 3 days later by protracted vomiting, decreased food intake, dehydration, and abstinence. Nausea, vomiting, and abdominal pain are common presenting complaints.[90] These patients have tachypnea, dehydration, ketonuria, and little or no glucosuria. Serum glucose levels are usually less than 200 mg/dL. Normal blood pH may be found despite ketonemia because of coexisting respiratory alkalosis and metabolic alkalosis.

The exact mechanism responsible for the increase in ketone bodies is unclear. Acute starvation superimposed on chronic malnutrition as well as release of an alcohol-induced block in ketogenesis allowing marked ketosis may explain the disorder. An increased ratio of reduced (NADH) to unreduced nicotinamide adenine dinucleotide (NAD) in the alcoholic predisposes to the accumulation of β-hydroxybutyrate and the inhibition of gluconeogenesis, which may underlie the common occurrence of hypoglycemia in alcoholic ketoacidosis.

The alcoholic patient with metabolic acidosis presents an interesting dilemma because most of these patients have an

www.ketabpezeshki.com 66485457-66963820

increased anion gap acidosis. Glucosuria may suggest diabetes; crystalluria can be seen in ethylene glycol poisoning; low specific gravity, proteinuria, and casts can be seen in renal failure; leukocytes and bacteria are present with urosepsis; and significant ketones in an otherwise normal urine may indicate starvation or alcoholic ketosis. Elevated levels or a very high osmolal gap (>25 mOsm/kg) is specific (88%) for methanol or ethylene glycol ingestion.[91]

Treatment of alcoholic ketosis consists of normal saline, glucose, thiamine, and correction of hypokalemia. This can be accomplished with 5% dextrose in normal saline and either 30 mEq of potassium chloride or 30 mEq of oral potassium. Bicarbonate is seldom necessary but may be considered in the rare patient with a pH below 7.1. If no serious complicating illness is present, the ketosis is reversed in 12 to 24 hours with this treatment.

Hematologic Effects

The alcoholic presents with myriad hematologic abnormalities. The direct toxic effect of ethanol and its metabolites, secondary nutritional deficiency, and hepatic disease, individually or in combination, affect red blood cells, white blood cells, platelets, hemostasis, and the immune system.[92] Macrocytosis is the most common hematologic manifestation of the chronic alcoholic. It may be caused by folate deficiency, reticulocytosis (the younger reticulocytes are larger), liver disease (producing an abnormal lipid coating of the red blood cell membrane), or vitamin B_{12} deficiency. The most common condition is idiopathic macrocytosis of alcoholism.

Anemia

Several mechanisms cause anemia, which is common in the alcoholic. Megaloblastic anemia resulting from folate deficiency is the most common anemia in alcoholics. The mean corpuscular volume (MCV) is typically increased but may be normal when iron deficiency coexists. Malnutrition, inability of the cirrhotic liver to store folate, excessive urinary loss, and malabsorption decrease folate stores. Alcohol accelerates the development of megaloblastic anemia in individuals with depleted folate (MCV > 100 fL) stores by an unknown mechanism.

Iron deficiency anemia is common and usually a result of blood loss from the gastrointestinal tract. With iron deficiency anemia, the serum iron is decreased, the total serum iron-binding capacity is elevated, and serum ferritin is decreased. Alcoholics frequently have chronic inflammatory diseases, such as endocarditis, tuberculosis, empyema, lung abscess, malignant disease, and hepatic disease. These chronic inflammatory illnesses can produce the anemia of chronic disease, a mild microcytic or normocytic anemia in which the serum iron is low, but in contrast to iron deficiency, the total serum iron-binding capacity is low or low-normal, and serum ferritin is increased.

Ethanol also has a direct toxic effect on erythropoiesis. Bone marrow biopsies reveal vacuolization of erythroid precursors, resulting in decreased reticulocytosis and a reversible sideroblastic anemia. Sideroblastic anemia, usually in the presence of malnutrition with pyridoxine deficiency and folate deficiency, occurs in 25 to 30% of anemic alcoholics.

Leukocyte Abnormalities

Leukopenia is common in the alcoholic patient and has several possible causes. Sepsis, folate deficiency, and hypersplenism all lead to a decreased white blood cell count. Alcohol has a direct toxic effect on white blood cell production in the bone marrow. Granulocyte mobilization (chemotaxis) and adherence are also impaired, resulting in a decreased inflammatory response.

Platelet Disorders

Thrombocytopenia can occur with folate deficiency, sepsis, disseminated intravascular coagulation, or splenic sequestration. The direct toxic effects of alcohol decrease measured survival time and impair production of platelets in the bone marrow, but marrow toxicity will rarely reduce the platelet count below 30,000. Qualitative platelet function is also impaired. Binge drinking is associated with a reactive thrombocytosis potentially responsible for acute stroke and sudden death.[93]

Hemostasis

Alcoholic patients have a bleeding diathesis for many reasons, including thrombocytopenia, qualitative platelet disorders, deficient production of hepatic clotting factors, gastrointestinal variceal formation, and vitamin K deficiency. A complete blood count, peripheral smear, platelet count, reticulocyte count, thrombin time, prothrombin time/INR, and partial thromboplastin time help evaluate episodes of significant bleeding. Bleeding associated with coagulation abnormalities may require fresh frozen plasma for immediate correction of coagulation factor depletion; vitamin K (10 mg IV) takes 6 to 10 hours to reverse the vitamin K–dependent factors II, VII, IX, and X. Because of poor diet and impaired hepatobiliary function, alcoholics may have insufficient vitamin K storage and benefit from vitamin K delivery. However, alcoholic patients with profound liver failure are unable to produce the precoagulation factors II, VII, IX, X, and IV, so vitamin K therapy is futile. Platelet transfusions should be started in the ED for adult patients with active bleeding when the platelet count is less than 50,000/mm^3.

Oncologic Effects

Worldwide, 389,000 annual cases of cancer representing 3.6% of all cancers are alcohol related.[94,95] Although alcohol itself is not carcinogenic, its metabolite, acetaldehyde, is emerging as an important contributor, being able to form stable DNA adducts, to trigger mutations in tumor suppressors and oncogenes, and to interfere with DNA repair. Smoking certainly has an additional role as a cause of neoplasia and is difficult to isolate in these studies.

Chronic alcohol use is associated with an increased incidence of upper alimentary and respiratory tract cancers with a clear dose-response relationship. Specifically, alcohol increases the risk of cancer of the mouth, pharynx, larynx, lung, esophagus, liver, and pancreas.[96] Chronic hepatitis B infection may sensitize the liver to alcohol, producing hepatocellular carcinoma. Women who drink two to five drinks per day have a relative risk of 1.41 for invasive breast cancer compared with nondrinkers.[97] There is also a significant increase in endometrial cancer risk among postmenopausal women who consume more than two alcoholic drinks/day.[98] Moderate alcohol consumption leads to an increased risk of colorectal and prostate cancer.[99]

Hypothermia

Acute alcohol ingestion is one of the most common precipitating factors for accidental hypothermia and occurs in 33 to 73% of patients presenting with a core temperature below 35° C.[100] Alcohol exacerbates hypothermia of other causes with depressed hypothalamic thermoregulation, peripheral vasodilation producing heat loss, CNS depression, sepsis, inability to shiver, hypoglycemia, and increased risk of environmental exposure. Hypothermia may be the presentation of Wernicke's syndrome, possibly caused by lesions of the posterior hypothalamus, hypoglycemia, or sepsis. Intoxicated patients may have slower rewarming rates.

www.ketabpezeshki.com 66485457-66963820

Psychiatric Effects

Forty-five percent of alcohol-dependent adults are diagnosed with one or more additional psychiatric conditions during their lifetime. Of alcoholic men admitted to a psychiatric ward, approximately 40% have another psychiatric disorder unrelated to substance abuse, in particular, antisocial personality disorder, schizophrenia, mood disorders, and anxiety disorders.

Depression and antisocial personality are the two most common psychiatric disorders that correlate with alcoholism, with a prevalence of 30 to 60% in most studies. Chronic alcohol use can produce an imbalance in the serotoninergic system. This imbalance may lead to increased anxiety, aggression, and depression. Interestingly, aggressive behavior is more strongly linked to depression than to alcohol dependence.[101] Secondary depression may be caused by alcoholism, or the primary affective disorder may be present with secondary alcoholism. Mild depressive symptoms are also common in alcohol withdrawal. Antisocial individuals are at high risk for alcoholism and drug dependence, although an unstable, unhappy childhood environment appears to be more important than alcohol to the development of sociopathy. Alcohol increases the lifetime risk of suicide, with 17% of all alcoholics eventually dying by suicide.[102,103] Alcoholism, major depression, and antisocial personality all predispose to suicide, and interaction among the three is particularly dangerous, but the acute risk on any day is difficult to assess.

An alcoholic patient who presents with an apparent psychiatric disorder poses a diagnostic dilemma. Does the patient have a primary affective disorder with secondary alcoholism, or is the patient manifesting anxiety or depressive behavior because of alcoholism? In general, alcoholic patients with psychiatric disorders are best treated with medications that are specific for their psychiatric condition.[104] Many alcoholics with mild depression have spontaneous resolution of symptoms with abstinence. Nevertheless, depression meeting DSM-IV criteria is best treated with antidepressants.[105,106] If abstinence can be achieved, underlying psychiatric disorders are more easily diagnosed and treated.

ALCOHOL-DRUG INTERACTIONS

Alcohol is associated with a vast number of drug interactions (Table 185-6). These may occur through several mechanisms: altered absorption; enhanced metabolism and activated toxic metabolites through the hepatic CYP2E1 pathway; additive or synergistic effects; disulfiram-ethanol–like reactions; and congeners, compounds found in alcoholic beverages. In general, chronic alcoholism is associated with an increased rate of drug clearance as a result of enhanced metabolism and enzyme induction (cytochrome P_{450} system). Conversely, acute alcohol intoxication reduces clearance for other drugs, increasing their serum concentration because of competition for a shared detoxification pathway.[107]

Table 185-6 Effects and Mechanisms of Alcohol-Drug Interactions

CLINICAL EFFECT	MECHANISM	DRUGS INVOLVED	COMMENTS
Increased blood alcohol levels	Inhibition of gastric ADH	Cimetidine Ranitidine Aspirin	Debatable role
Increased blood alcohol levels	Increased rate of gastric emptying	Cisapride Erythromycin	
Liver damage	Increased hepatotoxicity (chronic or "heavy" alcohol use) Decreased metabolism of drug (acute alcohol use)	Acetaminophen Isoniazid Phenylbutazone Narcotics Barbiturates Benzodiazepines Warfarin	"Heavy" drinkers can experience severe consequences even with therapeutic doses. "Binge" drinkers may have toxicity from standard doses.
May require higher dosages	Induction of enzymes	Benzodiazepines Phenytoin Propranolol Warfarin	Chronic alcoholics
Increased bleeding time		Aspirin NSAIDs	
Sedation		Antihistamines	
Psychomotor impairment	Disulfiram-like reactions	Barbiturates Benzodiazepines Narcotics Tricyclic antidepressants Oral hypoglycemics Antibiotics: metronidazole, sulfonamides, griseofulvin, cefoperazone Nitroglycerin	
Hypoglycemia		Long-acting oral hypoglycemics	
Hypotension		Aldomet Hydralazine Nitroglycerin	

Data from Fraser AG: Pharmacokinetic interactions between alcohol and other drugs. Clin Pharmacokinet 1997; 33:79; and Adams WL: Interactions between alcohol and other drugs. Int J Addict 30:1903, 1995.

ADH, alcohol dehydrogenase; *NSAIDs*, nonsteroidal anti-inflammatory drugs.

www.ketabpezeshki.com 66485457-66963820

Enhanced Metabolism and Toxic Metabolites

Most alcohol is metabolized by ADH. A small percentage of alcohol is metabolized by the MEOS–cytochrome P_{450} system, which is also responsible for the metabolism of many drugs. The MEOS metabolic pathway is enhanced in chronic alcoholics, which is associated with the acceleration of the degradation of these other drugs. For example, the half-lives of warfarin, phenytoin, and isoniazid are 50% shorter in abstaining alcoholics than in nondrinkers. Barbiturates, diazepam, propranolol, and rifampin may have increased rates of clearance and shorter half-lives when they are taken by chronic alcoholics. This effect can persist for days to weeks after the cessation of drinking.[58,108]

Acetaminophen is the most widely used analgesic in the United States and is often recommended to alcoholic patients instead of NSAIDs to prevent gastritis. Chronic alcohol ingestion may enhance acetaminophen hepatotoxicity by accelerating the biotransformation to a toxic metabolite on the basis of a few case reports of severe or lethal acetaminophen toxicity in alcoholics taking therapeutic doses. Increased vulnerability seems to occur immediately after cessation of drinking. A synergistic effect apparently occurs with alcohol, fasting, and acetaminophen use in combination with depleted glutathione stores. A prospective observational study suggested that acute ethanol intake may be associated with a lower risk of hepatotoxicity after acetaminophen overdose.[109] Greatly elevated AST levels (3000-48,000 in one series), increased ALT levels, and greatly elevated prothrombin/INR times help distinguish acetaminophen hepatotoxicity from alcoholic hepatitis.[107]

Additive or Synergistic Effects

Alcohol has long been known to have additive or even synergistic effects with several drugs. Acute intoxication decreases the rate of drug metabolism, which is at least partially explained by competition for the same enzymatic process in the liver. For example, ethanol has additive sedative effects when it is taken with first-generation antihistamines, barbiturates, cyclic antidepressants, benzodiazepines, phenothiazines, propoxyphene, propofol, and narcotics. Alcohol may also increase the activity of methyldopa and nitroglycerin. Alcohol can increase tetracycline levels by 30%. Selective serotonin reuptake inhibitors do not appear to affect alcohol kinetics or psychomotor performance.

When cocaine and ethanol are taken concomitantly, the unique metabolite, cocaethylene, is a neurologically active compound that is significantly more toxic than cocaine to the heart, liver, and brain and more addicting and more lethal than cocaine alone. Cocaethylene produces a higher incidence of confusion, lower mean Glasgow Coma Scale (GCS) scores, and a higher incidence of violent trauma and more often requires endotracheal intubation.[110] Hemodynamically, these patients demonstrate an elevated heart rate (1.5-5 times normal) and blood pressure higher than with either drug alone. Sudden death is increased 18- to 25-fold above that associated with use of cocaine alone. Plasma levels of cocaine in this combined group were higher than in those who used cocaine alone.[111]

Ethanol increases aspirin-induced prolongation of bleeding time and reduces the metabolism of warfarin, leading to increased anticoagulant effects. There is an increased risk of upper gastrointestinal bleeding when alcohol is combined with NSAIDs. This may be the most dangerous additive or synergistic effect of alcohol.[112]

Disulfiram and Similar Reactions

Most patients pretreated with disulfiram (Antabuse) who then consume even small amounts of alcohol experience an extremely unpleasant reaction. These patients have a hypersensitivity to ethanol and experience a direct response within 15 minutes and lasting 30 minutes to several hours. The reaction consists of skin flushing on the head that spreads to the trunk along with nausea, vomiting, headache, chest and abdominal discomfort, diaphoresis, vertigo, palpitations, and confusion. A severe reaction may produce hypotension, seizures, and dysrhythmias. Disulfiram-ethanol reaction is thought to occur by the accumulation of acetaldehyde secondary to inhibition of the aldehyde dehydrogenase enzyme, which may be deficient in many Asians, or another unknown toxic factor. This incapacitating reaction has been used to discourage chronic alcohol ingestion.

A similar but milder disulfiram-ethanol–like reaction has been described when alcohol combines with several different drugs. The reaction may occur days to weeks after the last dose of medication. Four cephalosporins (cefamandole, cefoperazone, cefotetan, moxalactam), metronidazole, chloramphenicol, griseofulvin, nitrofurantoin, sulfonamides, all sulfonylureas, and chloral hydrate have produced this reaction in combination with alcohol. Life-threatening toxic reactions between griseofulvin and small amounts of alcohol have been reported.[113] Treatment for disulfiram reaction is usually just observation, an antiemetic for symptoms and intravenous fluids, and rarely dopamine for severe hypotension.

Oral Hypoglycemics

Profound hypoglycemia can occur when alcohol and oral hypoglycemic agents are combined. Patients taking metformin may have an increased risk for development of lactic acidosis when it is combined with heavy drinking. A disulfiram-ethanol–like reaction has been described with many hypoglycemic agents.[108]

ADOLESCENT PATIENT

Although a significant percentage of children drink alcohol, there are as yet few established screening instruments for this population. The usual age at first drinking, independently of the family, is about 15 years (although this varies across cultural groups) and has not changed much in decades.[6] The period of heaviest drinking is usually between 18 and 22 years of age and also does not differ between those with future alcohol-use disorders and the general population. More than 60% of teenagers, even those without alcohol-use disorders, have experienced drunkenness by the age of 18 years, and about 30% have given up events such as school or work to drink or have driven while intoxicated.

Alcohol is often associated with the three leading causes of death among youth: unintentional injury, homicide, and suicide.[114] Adolescent drinking is associated with many negative consequences including suicide, carrying weapons, driving under the influence and resultant fatalities, unsafe or increased sexual activity, sexual assault, and date rape. Seventy-eight percent of high school students have tried alcohol, and 30% admit to binge drinking at least once a month.[115] Binge drinking, typically defined as drinking more than five drinks on an occasion, accounts for 90% of the alcohol consumed by 12- to 17-year-old youths.[114]

The age at drinking onset may be an indicator for increased risk of alcohol-related injury. Adolescents who began drinking regularly before the age of 14 years are at least three times more likely to be diagnosed with alcohol dependence than are those who began drinking at the age of 21 years. In addition, adolescents who began drinking before the age of 21 years were significantly more likely, during their lives, to be injured while under the influence of alcohol.[116]

www.ketabpezeshki.com 66485457-66963820

ELDERLY PATIENT

Unhealthy drinking is found in up to 15% of elderly (older than 65 years) ED patients.[117] Fifty percent of older people drink alcohol, and 2 to 4% meet criteria for alcohol abuse or dependence. Common screening tests (e.g., CAGE) tend to be less sensitive in this age group. Alcohol may exacerbate underlying disease by masking anginal chest pain, worsening hypertension, and inducing dysrhythmias.[118] However, elderly persons consuming low to moderate levels of alcohol may have a decreased risk for development of dementia and heart failure.[119] More than 90% of people aged 65 years or older use more than one prescribed medication.[120] Aging alters gastrointestinal absorption, lowers volume of distribution, diminishes homeostatic responses, and reduces renal and hepatic function.[108] Elderly persons also demonstrate increased end-organ sensitivity, particularly involving the CNS, with concomitant drug use increasing their risk for alcohol and drug interactions.

A protective effect on cognitive functioning has been shown with moderate alcohol consumption, particularly in women.[121] Moderate consumption is associated with a 38% reduced risk of dementia.[122] Still, elderly patients are more likely to have neuropsychiatric complications of alcoholism: sleep problems, anxiety, depression, and dementia. Alcohol is involved in one third of suicides in elderly persons. Older subjects also perform less well than younger subjects on tests of perception and attention at all blood alcohol levels. This may result in an increased risk of fractures from falling and osteoporosis. However, recent evidence suggests that compared with abstinence, consumption of up to one drink per day is associated with a decreased risk of osteoporotic hip fracture and a beneficial effect of moderate alcohol consumption on bone density.[123]

PREGNANCY

Many scientific reports confirm alcohol's teratogenic effects. According to the National Institute on Drug Abuse, almost 19% of all children born in the United States have been exposed to alcohol during gestation.[124] Pregnant women who report use of any alcohol, binge drinking, or frequent drinking are more likely to be older than 30 years, employed, and unmarried.[125]

Fetal alcohol syndrome is characterized by a triad of CNS defects, including mild to moderate mental retardation; dysmorphology, involving mostly facial structures; and growth deficiencies, usually consisting of short stature and microcephaly.[126] Fetal alcohol syndrome is now considered the most common identifiable source of mental retardation. Children exposed to prenatal alcohol exhibit increased activity levels, cognitive and attention deficits, perseverative behavior, and language and motor problems, which persist into adulthood.[127]

Ethanol rapidly diffuses across the placenta and is distributed to all fetal tissue with a predilection for gray matter. Although infants of mothers who drink heavily have the poorest outcome, children of mothers who consume only two or three alcoholic drinks a day also display abnormalities. Even in the absence of growth retardation or congenital abnormalities, children born to women who consume excessive alcohol during pregnancy appear to be at increased risk for attention deficit disorders. These findings are referred to as fetal alcohol effects.

Whereas there is no known safe amount of consumption during pregnancy, in a cohort study of more than 5000 patients observed for 14 years, an average of less than one drink per day in early or late pregnancy showed no measurable impact on a child's learning or cognitive functioning. Adverse outcomes in this study were associated with an average of more than one drink per day, binge drinking, and consumption of alcohol later in pregnancy.[128] The American Academy of Pediatrics recommends abstinence from alcohol for women who are pregnant or who are planning a pregnancy.[129]

TRAUMA

The single greatest contributor to alcohol-related mortality in the United States is unintentional injury, accounting for approximately 26,000 deaths per year.[130] The importance of alcohol misuse as a precursor to serious injury is widely accepted enough that since 2006 the American College of Surgeons Committee on Trauma requires screening for problem drinking for designation as a level I or level II trauma center. In addition, level I trauma centers must provide an intervention for problem drinkers identified. Alcohol and trauma are inextricably linked. Independently, the tragic effects of each are numerous; in combination, they are staggering. Injury is the leading cause of death between the ages of 1 and 44 years, accounting for more than 50 million injuries per year. In the United States, alcohol is the major risk factor for virtually all categories of intentional and unintentional injury. Besides increasing the frequency and severity of injury, alcohol significantly complicates the management of the trauma victim.[131] Alcohol intoxication often complicates the initial assessment of injury severity, resulting in an increased need for invasive diagnostic and therapeutic procedures (e.g., intubation, CT scan, intracranial pressure monitoring).[132]

Alcohol may diminish the patient's capacity to respond to hemorrhagic shock by altering hemodynamic effects and acid-base balance. Volume depletion as a result of the diuretic effect of alcohol or vomiting can impair the reserve of the intoxicated trauma patient. Peripheral vasodilation caused by alcohol may contribute to hypotension and hypothermia. Although these effects may be minimal, they underscore the need for early and adequate fluid resuscitation in these patients. Intoxicated patients with severe non-neurologic trauma may have lower blood pressures and carbon dioxide levels (indicative of a compensatory hyperventilation) on hospital arrival compared with sober patients. More important, a poorly understood cardiac depressant effect also increases the depth of shock and volume requirements for resuscitation. Alcohol-induced skin vasodilation may be accompanied by an increase in skeletal muscle, mesenteric, and renal bed constriction and left ventricular stroke work. Thus the overall effect on systemic vascular resistance and blood pressure may be balanced.[133]

Intoxication renders the signs and symptoms of intra-abdominal and retroperitoneal injury less reliable than usual. If the risk of an intra-abdominal injury exists, further evaluation (e.g., ultrasonography, CT) should be considered.

Alcohol intoxication predisposes to abdominal wall laxity and thus less protection from blunt trauma.[133] These patients are also likely to have full stomachs, increasing the risk of gastric injury after trauma and predisposing to vomiting and aspiration, especially during airway management. The fatty liver changes of alcoholism can result in hepatomegaly. Portal hypertension in alcoholics may produce splenomegaly. These organs can become more vulnerable to the effects of trauma because of their enlarged size, protrusion beneath the protection of the ribs, and increased intracapsular pressure.

Alcohol intoxication contributes to CNS injury in many ways. It is associated with aggressive behavior, impaired reflexes and coordination, and inappropriate avoidance responses. A higher degree of trauma to the spinal cord and much worse neurologic and functional recovery occur in patients who are intoxicated during trauma compared with sober patients.[134]

www.ketabpezeshki.com 66485457-66963820

Experimental evidence suggests that alcohol acts synergistically with mechanical injury of the spinal cord to amplify the trauma response by increasing edema formation within the contused tissue.[135]

No consensus exists on the indications for an emergency CT scan in patients with “minor head injury” (loss of consciousness, post-traumatic amnesia, GCS score of 14 to 15, normal findings on neurologic examination). One disturbing prospective study found that the GCS score and 1 hour of observation were unable to predict abnormal head CT scans in intoxicated patients with minor head trauma. Patients with signs of head trauma and focal or generalized seizures need an urgent CT scan. CT scans of the head should be performed for any patient with deteriorating mental status, focal neurologic findings, new-onset seizures even without obvious signs of history of trauma, failure to improve over time, or mental status changes out of proportion to the degree of intoxication.[136]

The good news is that during the past 20 years, there has been a decline in the number of alcohol-related fatalities. Five states (Hawaii, Illinois, Indiana, Pennsylvania, and Utah) have enacted mandatory hospital and provider reporting laws.[137]

ADMISSION GUIDELINES AND DISPOSITION

Most alcoholics suffer from a combination of medical, psychiatric, and social problems. Hospitalization is often necessary to diagnose and to treat these multiple problems. Moreover, with alcoholics who are no longer able to care for themselves, hospitalization is often dictated for this reason alone. Unfortunately, many managed care and Medicaid plans limit or do not cover inpatient detoxification. In choosing medical versus psychiatric admission, a medical illness usually takes priority. Optimal outpatient therapy for chronic alcoholics includes concerned family or friends to ensure that the patients take their medications properly, keep follow-up appointments, abstain from alcohol, and maintain an adequate diet. Alcoholic patients who undergo outpatient treatment need close supervision; therefore, a follow-up clinic appointment within 24 to 48 hours should be considered.

Acute Intoxication

Acute intoxication alone seldom requires admission. However, combined alcohol-drug overdose or associated medical, psychiatric, or social problems may require hospitalization. Acute alcohol intoxication is a diagnosis of exclusion reached after adequate observation to ensure that the altered mental status resolves.

Alcohol levels that may be tolerated by an adult can be lethal in children. It is prudent to admit children with acute intoxication unless close psychosocial follow-up can be ensured. Children presenting with hypoglycemia or medical complications should be admitted. Child abuse or neglect should be considered.

Alcohol Withdrawal

Patients with signs of major withdrawal (fever, hallucinations, confusion, extreme agitation) require admission. Patients with mild alcohol withdrawal can be observed in the ED. After 4 to 6 hours of observation and treatment, the alert, oriented patient whose vital signs, physical examination findings, and results of appropriate laboratory analysis are within normal limits may be released with appropriate medications and aftercare instructions. Nevertheless, the patient requires treatment for the underlying disease of alcoholism and should be advised or referred accordingly.

Seizures

Patients experiencing their first alcohol-related seizure may be admitted. Admission allows initiation of drug therapy, diagnostic evaluation, and continued monitoring of the patient’s status. However, the alcoholic patient with a first-time alcohol-related seizure may be discharged to a suitable social situation when the patient’s alcohol withdrawal is mild and controlled either by supportive care or with low-dose benzodiazepines; the diagnostic workup, including a head CT scan, is unremarkable; the patient has had fewer than two seizures; and the patient has been observed to be alert and oriented, with normal vital signs, physical examination findings, and laboratory study results, during the 6 hours since the last seizure, and appropriate outpatient follow-up can be ensured.

Patients with a documented history of alcohol-related seizure can be discharged if they have had no more than two alcohol-related seizures during a 6-hour period with a lucid interval between seizures and are observed to be seizure free and at baseline mental and physical status for at least 6 hours after their last alcohol-related seizure. Three to five brief, self-limited seizures may occur with alcohol withdrawal seizure. Nevertheless, admission for patients with two or more seizures is advised because of the potential for deterioration to status epilepticus. This is especially appropriate in the malnourished, immunocompromised, homeless, or noncompliant alcoholic patient.

Patients with partial seizures or focal neurologic findings on physical examination require admission unless these findings are previously documented. Patients with seizures associated with head trauma or with mixed alcohol-drug withdrawal are admitted. Status epilepticus or recurrent seizures during ED observation indicate a lack of seizure control also requiring hospitalization.

Psychiatric and Social Problems

Alcoholic patients requiring admission with acute intoxication, alcohol-related seizure, alcohol withdrawal, or medical or surgical disorders are usually best managed in acute care units rather than by a general psychiatric service. Some psychiatric and social conditions in the alcoholic can be better handled on a general psychiatric unit: psychosis, exacerbation of schizophrenia, depression with suicidal tendencies, any patient who is a danger to self or others, or alcoholic hallucinosis with an otherwise clear sensorium.

Patients who are no longer able to care for themselves may also require admission. Although these patients’ ultimate destination is a rehabilitation center or a board-and-care program, hospitalization may be necessary to rule out medical or psychiatric illness and to treat impending withdrawal symptoms. Patients who wish to stop drinking are usually admitted to a detoxification unit for treatment of impending withdrawal. Data and interest are increasing for outpatient drug therapy in alcohol dependence. The U.S. Food and Drug Administration has approved disulfiram, naltrexone, acamprosate, and topiramate for treatment of alcohol dependence.[104] There is growing evidence that patients with alcohol dependence who carry a particular variant of an opioid receptor gene are more likely to respond to naltrexone, raising the possibility that genetic tests may one day guide medication selection.[138] Naltrexone, ondansetron, acamprosate, and acamprosate plus naltrexone have had mixed results facilitating abstinence.[139,140] The role of medications in combination with behavioral therapy is actively investigated.[141,142]

Several other medications are under active study and are sometimes prescribed for alcoholism treatment on an unapproved or off-label basis. Baclofen, because of its anticraving action and

www.ketabpezeshki.com 66485457-66963820

safety, could have an important role for treatment of alcohol-dependent patients with advanced liver disease.[143] Gabapentin is used as monotherapy or as an add-on pharmacotherapy in outpatient settings in the control of alcohol consumption and craving and in helping patients achieve abstinence.[144] Ondansetron may show benefit in early-onset but not in late-onset alcoholics.[145]

Brief intervention has reduced alcohol consumption in some well-designed ED studies but not in others.[146,147] Alcohol dependence and a positive screen for alcohol-related injuries are decreased after screening and brief intervention.[148] Internet-based interventions show promise for reducing alcohol consumption, especially among those meeting criteria for hazardous or harmful drinking.[149] Telephone contact after the ED visit may be another effective tool to screen injured patients for hazardous drinking and to offer brief intervention while avoiding interruptions to patient flow.[150] Referral and brief intervention are warranted.[151] Most communities have either an Alcoholics Anonymous (AA) chapter or a treatment center for anyone who desires help with alcohol. In smaller communities, clergy or social workers can usually arrange rehabilitation.

Alcohol kills—it kills the alcoholic and it kills unintended victims by the acts of inebriated persons. Whereas medical, psychological, or social problems bring the alcoholic to the ED, the underlying problem is alcoholism and the ultimate goal is abstinence. This disease surely progresses if alcoholism is not first recognized and the patient is never given the opportunity to participate in a rehabilitation program.[152] The emergency physician can intervene on behalf of the patient and the public.

KEY CONCEPTS

- Moderate alcohol consumption is defined as one or two drinks per day for men and one drink for women.
- Benzodiazepines are the main treatment of alcohol withdrawal and alcohol withdrawal seizures.
- Inappropriate alcohol consumption or alcohol dependence should be considered in patients in almost any clinical situation, including trauma, potential drug-alcohol reactions, pneumonia, cardiomyopathy, new-onset atrial fibrillation, hepatitis, gastrointestinal bleeding, pancreatitis, altered mental status, depression, suicide, magnesium deficiency, and anemia.
- Minor alcohol withdrawal occurs as early as 6 hours and usually peaks at 24 to 36 hours after the cessation of or significant decrease in alcohol intake.
- Major alcohol withdrawal occurs after 24 hours and usually peaks at 50 hours (but occasionally takes up to 5 days) after the decrease or termination of drinking.
- Delirium tremens is the extreme end of the alcohol withdrawal spectrum and consists of gross tremor, profound confusion, fever, incontinence, and frightening visual hallucinations.
- Not all alcohol-related seizures are alcohol withdrawal seizures.
- Brief intervention in the emergency department can decrease drinking and its long-term consequences

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Rehm J, et al: Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* 2009; 373:2223-2233.
2. Miner JR, Gaetz A, Biros MH: The association of a decreased level of awareness and blood alcohol concentration with both agitation and sedation in intoxicated patients in the ED. *Am J Emerg Med* 2007; 25:743-748.
3. Bernstein SL: The clinical impact of health behaviors on emergency department visits. *Acad Emerg Med* 2009; 16:1054-1059.
4. *Seventh Special Report to the U.S. Congress on Alcohol and Health from the Secretary of Health and Human Services*. Rockville, Md: National Institute on Alcohol Abuse and Alcoholism, Department of Health and Human Services; 1990.
5. Pitzele HZ, Tolia VM: Twenty per hour: Altered mental state due to ethanol abuse and withdrawal. *Emerg Med Clin North Am* 2010; 28:683-705.
6. Schuckit MA: Alcohol-use disorders. *Lancet* 2009; 373:492-501.
7. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Association; 1994.
8. Morse RM, Flavin DK: The definition of alcoholism. The Joint Committee of the National Council on Alcoholism and Drug Dependence and the American Society of Addiction Medicine to Study the Definition and Criteria for the Diagnosis of Alcoholism. *JAMA* 1992; 268:1012-1014.
9. Werner MJ, Adger H Jr: Early identification, screening, and brief intervention for adolescent alcohol use. *Arch Pediatr Adolesc Med* 1995; 149:1241-1248.
10. Jones AW: Disappearance rate of ethanol from the blood of human subjects: Implications in forensic toxicology. *J Forensic Sci* 1993; 38:104-118.
11. Brennan DF, Betzelos S, Reed R, Falk JL: Ethanol elimination rates in an ED population. *Am J Emerg Med* 1995; 13:276-280.
12. Christopher TA, Zeccardi JA: Evaluation of the Q.E.D. Saliva Alcohol Test: A new, rapid, accurate device for measuring ethanol in saliva. *Ann Emerg Med* 1992; 21:1135-1137.
13. Degutis LC, Rabinovici R, Sabbaj A, Mascia R, D'Onofrio G: The saliva strip test is an accurate method to determine blood alcohol concentration in trauma patients. *Acad Emerg Med* 2004; 11:885-887.
14. Krishel S, SaFranek D, Clark RF: Intravenous vitamins for alcoholics in the emergency department: A review. *J Emerg Med* 1998; 16:419-424.
15. McKeon A, Frye MA, Delanty N: The alcohol withdrawal syndrome. *J Neurol Neurosurg Psychiatry* 2008; 79:854-862.
16. Isbell H, Fraser HF, Wikler A, Belleville RE, Eisenman AJ: An experimental study of the etiology of rum fits and delirium tremens. *Q J Stud Alcohol* 1955; 16:1-33.
17. Turner RC, Lichstein PR, Peden JG Jr, Busher JT, Waivers LE: Alcohol withdrawal syndromes: A review of pathophysiology, clinical presentation, and treatment. *J Gen Intern Med* 1989; 4:432-444.
18. Berk W, Todd K: Relationship of abstinence to the presentation and peak intensity of signs and alcohol withdrawal. *Ann Emerg Med* 1993; 22:339.
19. Mayo-Smith MF: Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. *JAMA* 1997; 278:144-151.
20. Daeppen JB, et al: Symptom-triggered vs fixed-schedule doses of benzodiazepine for alcohol withdrawal: A randomized treatment trial. *Arch Intern Med* 2002; 162:1117-1121.
21. Mayo-Smith MF, et al: Management of alcohol withdrawal delirium. An evidence-based practice guideline. *Arch Intern Med* 2004; 164:1405-1412.
22. Shale JH, Shale CM, Mastin WD: A review of the safety and efficacy of droperidol for the rapid sedation of severely agitated and violent patients. *J Clin Psychiatry* 2003; 64:500-505.
23. Rathlev NK, et al: The lack of efficacy of phenytoin in the prevention of recurrent alcohol-related seizures. *Ann Emerg Med* 1994; 23:513-518.
24. Alldredge BK, Lowenstein DH: Status epilepticus related to alcohol abuse. *Epilepsia* 1993; 34:1033-1037.
25. Lowenstein DH, Alldredge BK: Status epilepticus at an urban public hospital in the 1980s. *Neurology* 1993; 43(Pt 1):483-488.
26. Rathlev NK, et al: Etiology and weekly occurrence of alcohol-related seizures. *Acad Emerg Med* 2002; 9:824-828.
27. Brust JC: Acute neurologic complications of drug and alcohol abuse. *Neurol Clin* 1998; 16:503-519.
28. Lacy JR, Filley CM, Earnest MP, Graff-Radford NR: Brain infarction and hemorrhage in young and middle-aged adults. *West J Med* 1984; 141:329-334.
29. Ng SK, Hauser WA, Brust JC, Susser M: Alcohol consumption and withdrawal in new-onset seizures. *N Engl J Med* 1988; 319:666-673.
30. Victor M, Brausch C: The role of abstinence in the genesis of alcoholic epilepsy. *Epilepsia* 1967; 8:1-20.
31. D'Onofrio G, Rathlev NK, Ulrich AS, Fish SS, Freedland ES: Lorazepam for the prevention of recurrent seizures related to alcohol. *N Engl J Med* 1999; 340:915-919.
32. Smith BJ: Treatment of status epilepticus. *Neurol Clin* 2001; 19:347-369.
33. Hillbom ME, Hjelm-Jager M: Should alcohol withdrawal seizures be treated with anti-epileptic drugs? *Acta Neurol Scand* 1984; 69:39-42.
34. Marx J, Berner J, Bar-Or D, Gorayeb M: Prophylaxis of alcohol withdrawal seizures: A prospective study [abstract]. *Ann Emerg Med* 1986; 15:637.
35. Kahan M, Borgundvaag B, Borsoi D, Edwards C, Ladhani N: Treatment variability and outcome differences in the emergency department management of alcohol withdrawal. *CJEM* 2005; 7:87-92.
36. Brathen G, Brodtkorb E, Helde G, Sand T, Bovim G: The diversity of seizures related to alcohol use. A study of consecutive patients. *Eur J Neurol* 1999; 6:697-703.
37. Earnest MP, et al: Intracranial lesions shown by CT scans in 259 cases of first alcohol-related seizures. *Neurology* 1988; 38:1561-1565.
38. Segel L: Alcohol and the heart. *Med Clin North Am* 1984; 68:147.
39. Ridker PM, Vaughan DE, Stampfer MJ, Glynn RJ, Hennekens CH: Association of moderate alcohol consumption and plasma concentration of endogenous tissue-type plasminogen activator. *JAMA* 1994; 272:929-933.
40. Agarwal DP: Cardioprotective effects of light-moderate consumption of alcohol: A review of putative mechanisms. *Alcohol Alcohol* 2002; 37:409-415.
41. Fagrell B, et al: The effects of light to moderate drinking on cardiovascular diseases. *J Intern Med* 1999; 246:331-340.
42. Opie LH, Lecour S: The red wine hypothesis: From concepts to protective signalling molecules. *Eur Heart J* 2007; 28:1683-1693.
43. Walsh CR, et al: Alcohol consumption and risk for congestive heart failure in the Framingham Heart Study. *Ann Intern Med* 2002; 136:181-191.
44. Kloner RA, Rezkalla SH: To drink or not to drink? That is the question. *Circulation* 2007; 116:1306-1317.
45. Mukamal KJ, Maclure M, Muller JE, Sherwood JB, Mittleman MA: Prior alcohol consumption and mortality following acute myocardial infarction. *JAMA* 2001; 285:1965-1970.
46. Otero-Anton E, et al: Prolongation of the QTc interval during alcohol withdrawal syndrome. *Acta Cardiol* 1997; 52:285-294.
47. Tsuji H, Venditti FJ Jr, Evans JC, Larson MG, Levy D: The associations of levels of serum potassium and magnesium with ventricular premature complexes (the Framingham Heart Study). *Am J Cardiol* 1994; 74:232-235.
48. Thakur L, et al: Alcohol consumption and development of acute respiratory distress syndrome: A population-based study. *Int J Environ Res Public Health* 2009; 6:2426-2435.
49. Thomsen JL: Diseases of the airways and lungs in forensic autopsy material of alcoholics. *Med Sci Law* 1997; 37:23-26.
50. de Wit M, Best AM, Gennings C, Burnham EL, Moss M: Alcohol use disorders increase the risk for mechanical ventilation in medical patients. *Alcohol Clin Exp Res* 2007; 31:1224-1230.
51. Pahor M, et al: Alcohol consumption and risk of deep venous thrombosis and pulmonary embolism in older persons. *J Am Geriatr Soc* 1996; 44:1030-1037.
52. Gao L, Weck MN, Stegmaier C, Rothenbacher D, Brenner H: Alcohol consumption, serum gamma-glutamyltransferase, and *Helicobacter pylori* infection in a population-based study among 9733 older adults. *Ann Epidemiol* 2010; 20:122-128.
53. Brenner H, Rothenbacher D, Bode G, Adler G: Inverse graded relation between alcohol consumption and active infection with *Helicobacter pylori*. *Am J Epidemiol* 1999; 149:571-576.
54. Alatalo PI, et al: Effect of moderate alcohol consumption on liver enzymes increases with increasing body mass index. *Am J Clin Nutr* 2008; 88:1097-1103.
55. Nguyen-Khac E, Houchi H, Daoust M, Dupas JL, Naassila M: The −308 TNFα gene polymorphism in severe acute alcoholic hepatitis: Identification of a new susceptibility marker. *Alcohol Clin Exp Res* 2008; 32:822-828.
56. Diehl AM: Liver disease in alcohol abusers: Clinical perspective. *Alcohol* 2002; 27:7-11.

www.ketabpezeshki.com 66485457-66963820

57. Breitkopf K, et al: Current experimental perspectives on the clinical progression of alcoholic liver disease. *Alcohol Clin Exp Res* 2009; 33:1647-1655.
58. Lieber CS: Hepatic and other medical disorders of alcoholism: From pathogenesis to treatment. *J Stud Alcohol* 1998; 59:9-25.
59. Dominguez M, et al: A new scoring system for prognostic stratification of patients with alcoholic hepatitis. *Am J Gastroenterol* 2008; 103:2747-2756.
60. Alcoholic liver disease: The ACG's recommendations. *J Crit Illn* 1999; 14(264).
61. Maddrey WC, et al: Corticosteroid therapy of alcoholic hepatitis. *Gastroenterology* 1978; 75:193-199.
62. Dunn W, et al: MELD accurately predicts mortality in patients with alcoholic hepatitis. *Hepatology* 2005; 41:353-358.
63. Mathurin P, et al: Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): Individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. *J Hepatol* 2002; 36:480-487.
64. Akriviadis E, et al: Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: A double-blind, placebo-controlled trial. *Gastroenterology* 2000; 119:1637-1648.
65. Khan KN, Yatsuhashi H: Effect of alcohol consumption on the progression of hepatitis C virus infection and risk of hepatocellular carcinoma in Japanese patients. *Alcohol Alcohol* 2000; 35:286-295.
66. Sigal SH, Lieber CS: Treating the most severe manifestations of alcoholic liver disease. *J Crit Illn* 1996; 11(155).
67. Gumaste V, Dave P, Sereny G: Serum lipase: A better test to diagnose acute alcoholic pancreatitis. *Am J Med* 1992; 92:239-242.
68. Harper C: The neuropathology of alcohol-specific brain damage, or does alcohol damage the brain? *J Neuropathol Exp Neurol* 1998; 57:101-110.
69. Reuler JB, Girard DE, Cooney TG: Current concepts. Wernicke's encephalopathy. *N Engl J Med* 1985; 312:1035-1039.
70. Donnino MW, Vega J, Miller J, Walsh M: Myths and misconceptions of Wernicke's encephalopathy: What every emergency physician should know. *Ann Emerg Med* 2007; 50:715-721.
71. Cardoso F, Jankovic J: Movement disorders. *Neurol Clin* 1993; 11:625-638.
72. Charness ME, Simon RP, Greenberg DA: Ethanol and the nervous system. *N Engl J Med* 1989; 321:442-454.
73. Brust JC: Ethanol and cognition: Indirect effects, neurotoxicity and neuroprotection: A review. *Int J Environ Res Public Health* 2010; 7:1540-1557.
74. Peters R, Peters J, Warner J, Beckett N, Bulpitt C: Alcohol, dementia and cognitive decline in the elderly: A systematic review. *Age Ageing* 2008; 37:505-512.
75. Lobo E, et al: Is there an association between low-to-moderate alcohol consumption and risk of cognitive decline? *Am J Epidemiol* 2010; 172:708-716.
76. Goral J, Karavitis J, Kovacs EJ: Exposure-dependent effects of ethanol on the innate immune system. *Alcohol* 2008; 42:237-247.
77. Cook RT: Alcohol abuse, alcoholism, and damage to the immune system—a review. *Alcohol Clin Exp Res* 1998; 22:1927-1942.
78. Lonnroth K, Williams BG, Stadlin S, Jaramillo E, Dye C: Alcohol use as a risk factor for tuberculosis—a systematic review. *BMC Public Health* 2008; 8:289.
79. Avins AL, et al: HIV infection and risk behaviors among heterosexuals in alcohol treatment programs. *JAMA* 1994; 271:515-518.
80. Szabo G: Consequences of alcohol consumption on host defence. *Alcohol Alcohol* 1999; 34:830-841.
81. Ozsoy S, Esel E, Izgi HB, Sofuoglu S: Thyroid function in early and late alcohol withdrawal: Relationship with aggression, family history, and onset age of alcoholism. *Alcohol Alcohol* 2006; 41:515-521.
82. Noth RH, Walter RM Jr: The effects of alcohol on the endocrine system. *Med Clin North Am* 1984; 68:133-146.
83. Ginsburg ES, et al: Effects of alcohol ingestion on estrogens in postmenopausal women. *JAMA* 1996; 276:1747-1751.
84. Sucov A, Woolard RH: Ethanol-associated hypoglycemia is uncommon. *Acad Emerg Med* 1995; 2:185-189.
85. Bell DS: Alcohol and the NIDDM patient. *Diabetes Care* 1996; 19:509-513.
86. Baraona E, Lieber CS: Alcohol and lipids. *Recent Dev Alcohol* 1998; 14:97-134.
87. Gullestad L, et al: Oral magnesium supplementation improves metabolic variables and muscle strength in alcoholics. *Alcohol Clin Exp Res* 1992; 16:986-990.
88. Vamvakas S, Teschner M, Bahner U, Heidland A: Alcohol abuse: Potential role in electrolyte disturbances and kidney diseases. *Clin Nephrol* 1998; 49:205-213.
89. Elisaf MS, Siamopoulos KC: Mechanisms of hypophosphataemia in alcoholic patients. *Int J Clin Pract* 1997; 51:501-503.
90. Fulop M: Alcoholic ketoacidosis. *Endocrinol Metab Clin North Am* 1993; 22:209-219.
91. Almaghamsi AM, Yeung CK: Osmolal gap in alcoholic ketoacidosis. *Clin Nephrol* 1997; 48:52-53.
92. Lindenbaum J: Hematologic complications of alcohol abuse. *Semin Liver Dis* 1987; 7:169-181.
93. Renaud SC, Ruf JC: Effects of alcohol on platelet functions. *Clin Chim Acta* 1996; 246:77-89.
94. Toriola AT, Kurl S, Dyba T, Laukkanen JA, Kauhanen J: The impact of alcohol consumption on the risk of cancer among men: A 20-year follow-up study from Finland. *Eur J Cancer* 2010; 46:1488-1492.
95. Watters JL, Park Y, Hollenbeck A, Schatzkin A, Albanes D: Alcoholic beverages and prostate cancer in a prospective US cohort study. *Am J Epidemiol* 2010; 172:773-780.
96. Thygesen LC, et al: Cancer incidence among patients with alcohol use disorders—long-term follow-up. *Alcohol Alcohol* 2009; 44:387-391.
97. Dumitrescu RG, Shields PG: The etiology of alcohol-induced breast cancer. *Alcohol* 2005; 35:213-225.
98. Setiawan VW, et al: Alcohol consumption and endometrial cancer risk: The multiethnic cohort. *Int J Cancer* 2008; 122:634-638.
99. Sesso HD, Paffenbarger RS Jr, Lee IM: Alcohol consumption and risk of prostate cancer: The Harvard Alumni Health Study. *Int J Epidemiol* 2001; 30:749-755.
100. Kortelainen ML: Drugs and alcohol in hypothermia and hyperthermia related deaths: A retrospective study. *J Forensic Sci* 1987; 32:1704-1712.
101. Bacaner N, Kinney TA, Biros M, Bochert S, Casuto N: The relationship among depressive and alcoholic symptoms and aggressive behavior in adult male emergency department patients. *Acad Emerg Med* 2002; 9:120-129.
102. Bourgeois JA, Nelson JL, Slack MB, Ingram M: Comorbid affective disorders and personality traits in alcohol abuse inpatients at an Air Force Medical Center. *Mil Med* 1999; 164:103-106.
103. O'Connor PG, Schottenfeld RS: Patients with alcohol problems. *N Engl J Med* 1998; 338:592-602.
104. Swift RM: Drug therapy for alcohol dependence. *N Engl J Med* 1999; 340:1482-1490.
105. Mason BJ, Kocsis JH, Ritvo EC, Cutler RB: A double-blind, placebo-controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. *JAMA* 1996; 275:761-767.
106. Nunes EV, Levin FR: Treatment of depression in patients with alcohol or other drug dependence: A meta-analysis. *JAMA* 2004; 291:1887-1896.
107. Wootton FT, Lee WM: Acetaminophen hepatotoxicity in the alcoholic. *South Med J* 1990; 83:1047-1049.
108. Fraser AG: Pharmacokinetic interactions between alcohol and other drugs. *Clin Pharmacokinet* 1997; 33:79-90.
109. Waring WS, Stephen AF, Malkowska AM, Robinson OD: Acute ethanol coingestion confers a lower risk of hepatotoxicity after deliberate acetaminophen overdose. *Acad Emerg Med* 2008; 15:54-58.
110. Andrews P: Cocaethylene toxicity. *J Addict Dis* 1997; 16:75-84.
111. Vanek VW, et al: Concurrent use of cocaine and alcohol by patients treated in the emergency department. *Ann Emerg Med* 1996; 28:508-514.
112. Henry D, Dobson A, Turner C: Variability in the risk of major gastrointestinal complications from nonaspirin nonsteroidal anti-inflammatory drugs. *Gastroenterology* 1993; 105:1078-1088.
113. Fett DL, Vukov LF: An unusual case of severe griseofulvin-alcohol interaction. *Ann Emerg Med* 1994; 24:95-97.
114. Miller JW, Naimi TS, Brewer RD, Jones SE: Binge drinking and associated health risk behaviors among high school students. *Pediatrics* 2007; 119:76-85.
115. Foster SE, Vaughan RD, Foster WH, Califano JA Jr: Alcohol consumption and expenditures for underage drinking and adult excessive drinking. *JAMA* 2003; 289:989-995.
116. Hingson RW, Heeren T, Jamanka A, Howland J: Age of drinking onset and unintentional injury involvement after drinking. *JAMA* 2000; 284:1527-1533.
117. Merrick EL, et al: Unhealthy drinking patterns in older adults: Prevalence and associated characteristics. *J Am Geriatr Soc* 2008; 56:214-223.
118. Adams WL: Potential for adverse drug-alcohol interactions among retirement community residents. *J Am Geriatr Soc* 1995; 43:1021-1025.

www.ketabpezeshki.com 66485457-66963820

119. Ruitenberg A, et al: Alcohol consumption and risk of dementia: The Rotterdam Study. *Lancet* 2002; 359:281-286.
120. Moore AA, Whiteman EJ, Ward KT: Risks of combined alcohol/medication use in older adults. *Am J Geriatr Pharmacother* 2007; 5:64-74.
121. McGuire LC, Ajani UA, Ford ES: Cognitive functioning in late life: The impact of moderate alcohol consumption. *Ann Epidemiol* 2007; 17:93-99.
122. Peters R, Peters J, Warner J, Beckett N, Bulpitt C: Alcohol, dementia and cognitive decline in the elderly: A systematic review. *Age Ageing* 2008; 37:505-512.
123. Berg KM, et al: Association between alcohol consumption and both osteoporotic fracture and bone density. *Am J Med* 2008; 121:406-418.
124. Young NK: Effects of alcohol and other drugs on children. *J Psychoactive Drugs* 1997; 29:23-42.
125. Centers for Disease Control and Prevention: Alcohol use among women of childbearing age—United States, 1991-1999. *JAMA* 2002; 287:2069-2071.
126. Gottlieb LD, Horwitz RI, Kraus ML, Segal SR, Viscoli CM: Randomized controlled trial in alcohol relapse prevention: Role of atenolol, alcohol craving, and treatment adherence. *J Subst Abuse Trea* 1994; 11:253-258.
127. O'Connor MJ, et al: Psychiatric illness in a clinical sample of children with prenatal alcohol exposure. *Am J Drug Alcohol Abuse* 2002; 28:743-754.
128. O'Callaghan FV, O'Callaghan M, Najman JM, Williams GM, Bor W: Prenatal alcohol exposure and attention, learning and intellectual ability at 14 years: A prospective longitudinal study. *Early Hum Dev* 2007; 83:115-123.
129. American Academy of Pediatrics Committee on Substance Abuse and Committee on Children with Disabilities: Fetal alcohol syndrome and fetal alcohol effects. *Pediatrics* 1993; 91:1004-1006.
130. Shults RA, Elder RW, Hungerford DW, Strife BJ, Ryan GW: Emergency department visits for alcohol-related unintentional traumatic injuries, United States, 2001. *J Safety Res* 2009; 40:329-331.
131. Kitchens JM: Does this patient have an alcohol problem? *JAMA* 1994; 272:1782-1787.
132. Jurkovich GJ, et al: Effects of alcohol intoxication on the initial assessment of trauma patients. *Ann Emerg Med* 1992; 21:704-708.
133. Marx J: Alcohol and trauma. *Emerg Med Clin North Am* 1990; 8:929-938.
134. Kiwerski J, Krasuski M, Wozniak E: Sequelae of injuries of thoracic vertebrae with spinal cord trauma in persons under the influence of alcohol [in Polish]. *Pol Tyg Lek* 1989; 44:910-912.
135. Brodner RA, Van Gilder JC, Collins WF Jr: Experimental spinal cord trauma: Potentiation by alcohol. *J Trauma* 1981; 21:124-129.
136. Stein SC, O'Malley KF, Ross SE: Is routine computed tomography scanning too expensive for mild head injury? *Ann Emerg Med* 1991; 20:1286-1289.
137. McManus J, Magaret ND, Hedges JR, Rayner NB, Rice M: A survey of Oregon emergency physicians to assess mandatory reporting knowledge and reporting patterns regarding intoxicated drivers in the state of Oregon. *Acad Emerg Med* 2005; 12:896-899.
138. Anton RF, et al: An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence. *Arch Gen Psychiatry* 2008; 65:135-144.
139. Kenna GA, McGeary JE, Swift RM: Pharmacotherapy, pharmacogenomics, and the future of alcohol dependence treatment, part 2. *Am J Health Syst Pharm* 2004; 61:2380-2388.
140. Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA: Naltrexone in the treatment of alcohol dependence. *N Engl J Med* 2001; 345:1734-1739.
141. Anton RF, et al: Combined pharmacotherapies and behavioral interventions for alcohol dependence: The COMBINE study: A randomized controlled trial. *JAMA* 2006; 295:2003-2017.
142. Bazargan-Hejazi S, et al: Evaluation of a brief intervention in an inner-city emergency department. *Ann Emerg Med* 2005; 46:67-76.
143. Addolorato G, et al: Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: Randomised, double-blind controlled study. *Lancet* 2007; 370:1915-1922.
144. Furieri FA, Nakamura-Palacios EA: Gabapentin reduces alcohol consumption and craving: A randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2007; 68:1691-1700.
145. Myrick H, et al: Effect of naltrexone and ondansetron on alcohol cue-induced activation of the ventral striatum in alcohol-dependent people. *Arch Gen Psychiatry* 2008; 65:466-475.
146. Ahmed M: Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. Is emergency department based brief intervention worthwhile in adults presenting with alcohol related events? *Emerg Med J* 2007; 24:785-788.
147. Daeppen JB, et al: Brief alcohol intervention and alcohol assessment do not influence alcohol use in injured patients treated in the emergency department: A randomized controlled clinical trial. *Addiction* 2007; 102:1224-1233.
148. Field CA, Caetano R: The effectiveness of brief intervention among injured patients with alcohol dependence: Who benefits from brief interventions? *Drug Alcohol Depend* 2010; 111:13-20.
149. Cunningham JA, Wild TC, Cordingley J, Van Mierlo T, Humphreys K: Twelve-month follow-up results from a randomized controlled trial of a brief personalized feedback intervention for problem drinkers. *Alcohol Alcohol* 2010; 45:258-262.
150. Diguiseppi C, Goss C, Xu S, Magid D, Graham A: Telephone screening for hazardous drinking among injured patients seen in acute care clinics: Feasibility study. *Alcohol Alcohol* 2006; 41:438-445.
151. Crawford MJ, et al: Screening and referral for brief intervention of alcohol-misusing patients in an emergency department: A pragmatic randomised controlled trial. *Lancet* 2004; 364:1334-1339.
152. Davidson P, Koziol-McLain J, Harrison L, Timken D, Lowenstein SR: Intoxicated ED patients: A 5-year follow-up of morbidity and mortality. *Ann Emerg Med* 1997; 30:593-597.

www.ketabpezeshki.com 66485457-66963820

Chapter 186

Substance Abuse

Alicia B. Minns and Richard F. Clark

PERSPECTIVE

The use and abuse of psychoactive substances are not unique to our country or century. People used hallucinogenic plants to achieve altered states of consciousness in prehistoric times, and psychoactive substances have been used in all eras and cultures. As Osler remarked, "The desire to take medicine is, perhaps, the great feature which distinguishes man from other animals."[1] The human cost of substance abuse is high, and deaths secondary to the use of psychoactive substances are common. In the United States, illicit drug use results in thousands of deaths each year (Box 186-1).[2]

A major barrier to appropriate recognition and treatment of substance abuse is the lack of a precise definition. The American Psychiatric Association defines it as a maladaptive pattern of drug use associated with some manifest harm to the user or others.[3] Physicians have a difficult time recognizing such abuse when up to 44% of emergency department (ED) patients report underlying chronic pain syndromes.[4] Chronic pain may not manifest the typical overt sympathetic changes or physical findings of acute pain.[5] Therefore, emergency physicians constantly walk a tightrope between undertreating legitimate pain and inappropriately rewarding substance abusers with controlled medications.

EPIDEMIOLOGY

A variety of stereotypes come to mind in compiling the profile of a substance abuser. These stereotypes pose dangerous traps for the clinician. Physicians are likely to ignore the possibility of drug intoxication in the well-dressed businessman or in those at the extremes of age. Yet children may ingest psychoactive substances they find in homes where drugs are used.

Abuse of prescription and over-the-counter (OTC) drugs by adolescents is on the rise. According to the 2005 Partnership for a Drug-Free America's 18th annual self-administered study of 7300 teenagers in grades 7 to 12, one in five (19%, or 4.5 million) report abusing prescription medications and one in ten (10%, or 2.4 million) report abusing cough medications to "get high." This use is on par with or higher than the abuse of illegal drugs such as ecstasy and cocaine.[6] Dextromethorphan abuse has become epidemic in the last decade. Increasing numbers of teens are ingesting dextromethorphan-containing OTC products such as Coricidin HBP Cough & Cold tablets,[7] known on the streets as triple C, red devils, red C, red box, or skittles. Other dextromethorphan compounds include cough medicines, such as NyQuil and Robitussin DM, that provide the sought-after high known as the robo-buzz. Adolescents may also abuse medication used to treat obsessive-compulsive disorder and attention-deficit/hyperactivity disorder. Methylphenidate and related compounds have been a particular concern. Tablets can be abused orally, or they can be crushed and the powder injected or snorted. Despite its abuse potential, experts disagree about the extent to which methylphenidate is diverted from therapeutic use to abuse in preteens and adolescents.[8] In addition, some parents deliberately give psychoactive substances to their children to calm or to abuse them.

The emergence of "legal highs" has become a concerning trend. Numerous synthetic and naturally derived psychoactive substances are easy to obtain from Internet websites, "head shops," and local suppliers. One such example is known as bath salts. These products are available in small quantities, with packaging that usually includes the disclaimer "not for consumption" to avoid regulation.[9] Bath salts contain synthetic cathinones, which are pharmacologically similar to methamphetamine and MDMA (ecstasy) and produce similar clinical effects.[10] A variety of adverse effects have been reported from cathinone derivatives, including tachycardia, hypertension, agitation, hyponatremia, hallucinations, paranoia, and suicide.[9-11] The legal status of bath salts is rapidly changing. The U.S. Department of Justice Drug Enforcement Administration has temporarily placed three of the synthetic stimulants under Schedule I of the Controlled Substances Act; however, numerous other synthetic cathinones have been found in these products.[9]

The elderly also abuse substances, and geriatric patients may suffer new-onset psychosis as a result of sympathomimetic abuse or drug withdrawal. Drug use is frequent among pregnant women, resulting in both maternal and fetal morbidity. A study of an inner-city population reported that 19% of women had a positive urine toxicology screen for at least one of seven substances at the time of admission for delivery.[12] Manifestations of abuse may be acute, as in abruptio placentae or premature birth, or insidious, producing growth restriction and birth defects. Drug problems are more prevalent among the disadvantaged minority and lower socioeconomic groups. As a result, these groups are disproportionately affected by drug-related problems, such as incarceration, acquired immunodeficiency syndrome, and tuberculosis.

The Drug Alert Warning Network (DAWN) collects data from hospital EDs and medical examiners that include drug-related visits or deaths. The data consist of patients who abuse illegal drugs or use legal substances for a nonmedical purpose. According to DAWN, the drugs of misuse or abuse most commonly involved in deaths are cocaine, opioids, antidepressants, benzodiazepines, stimulants, and club drugs.[13]

For 2005, DAWN estimated that 816,696 ED visits involved an illicit drug; cocaine was involved in 448,481, marijuana in 242,200, heroin in 164,572, and stimulants (including amphetamines and methamphetamine) in 138,950 ED visits. Other illicit drugs (phencyclidine [PCP], ecstasy, and γ-hydroxybutyric acid [GHB]) were much less frequent.[14] Despite efforts to control nonmedical

www.ketabpezeshki.com 66485457-66963820

Box 186-1 Complications of Illicit Drug Use

Infectious	**Pulmonary**
Hepatitis	Chronic lung disease
Pneumonia	Pulmonary hypertension
Skin abscess	Pulmonary edema
Brain abscess	Eosinophilic pneumonia
Endocarditis	Pneumonitis
HIV infection	Barotrauma (pneumomediastinum)
Osteomyelitis	Pulmonary fibrosis
Botulism	Emphysema
Gangrene	
Cardiovascular	**Psychosocial**
Cardiomyopathy	Unemployment
Aortic dissection	Inadequately treated depression
Myocardial infarction	Conduct disorders
Dysrhythmias	Hallucinations
Pseudoaneurysms	Suicide
Arteritis	Homicide
Hypertension	
Neurologic	**Miscellaneous**
Stroke	Dental caries and periodontal disease
Drug-induced parkinsonism	Rhabdomyolysis
Dystonia	Thrombophlebitis
Vasculitis	Tattooing
Intracerebral hemorrhage	Placental abruption
Cerebral atrophy	Congenital malformations
Radiculopathy	
Leukoencephalopathy	

use of prescription drugs in the United States, the estimated number of ED visits for nonmedical use of opioid analgesics increased 111% during 2004-2008 (from 144,600 to 305,900 visits) and increased 29% during 2007-2008. The highest numbers of these ED visits were recorded for oxycodone, hydrocodone, and methadone, all of which showed statistically significant increases during the 5-year period. The estimated number of ED visits involving nonmedical use of benzodiazepines increased 89% during 2004-2008 (from 143,500 to 271,700 visits) and 24% during 2007-2008. In 2008, the number of ED visits involving nonmedical use of prescription or OTC drugs matched the number of ED visits involving illicit drugs.[15]

Illicit drug use generates significant costs to the health care system. In 2001, the hospital and ambulatory care costs of illicit drug use as a whole were an estimated $1.34 billion. The cost for illicit drug–related skin and soft tissue infections alone was estimated to be more than $193 million.[16] More recently in 2008, the cost of hospital days stemming from drug overdoses without alcohol involvement was estimated to be $737 million.[17]

PHARMACOLOGY

Knowledge of drug interactions assists in the diagnosis and care of substance abuse victims. A careful medication history for all legal and illegal drugs, including ethanol, may pinpoint the source of an adverse reaction. For example, a variety of agents can increase the effects of cocaine. The coingestion of ethanol and cocaine results in an active metabolite, cocaethylene, that also enhances and magnifies cocaine's effects. Serotonin syndrome, manifested by muscle rigidity, hyperthermia, diarrhea, and seizures, may result when sympathomimetic drugs are taken concurrently with selective serotonin reuptake inhibitors such as fluoxetine. Amphetamines elevate serotonin either directly or by reversible inhibition of monoamine oxidase. In fact, a selective serotonin reuptake inhibitor can result in flashbacks in prior amphetamine

Figure 186-1. Freon abuser. (Copyright Stephen A. Colucciello.)

users. Monoamine oxidase inhibitors can provoke hypertensive crisis in patients taking sympathomimetics. Interactions between medications commonly prescribed for patients with human immunodeficiency virus (HIV) infection and recreational drugs may be associated with serious clinical consequences because protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) can inhibit or induce the cytochrome P_{450} system, which could result in either drug accumulation or toxicity or withdrawal reactions.[18] For example, patients maintained with methadone who are subsequently treated with NNRTIs are at risk for development of methadone withdrawal by NNRTI-mediated enzyme induction.[18]

Household products and medications also have abuse potential. For example, dextromethorphan in common cough medications is converted into a substance (dextrorphan) similar to ketamine and PCP, which causes dissociative effects by antagonizing the *N*-methyl-D-aspartate (NMDA) receptor. Recreational users describe mild hallucinations and an "out-of-body" state.[19] Some common chemicals in the home and workplace have an intoxicating effect that may be unexpected. Solvents, paint, lacquers, glues, aerosols, refrigerants, and other propellants (Fig. 186-1) are readily accessible for abuse among children and teens. Inhaled hydrocarbons, such as toluene, are rapidly absorbed and easily pass through the lipophilic blood-brain barrier to give an inexpensive high.

Illicit drug laboratories have poor quality control, and many drugs are combined or "cut" with other substances to increase profits. Up to 50% of street samples lack the alleged drug. Some additives, such as local anesthetics or sugars, may be innocuous, but others, such as strychnine, may be lethal. Levamisole, a widely available anthelmintic agent, is now a common cocaine adulterant and can result in life-threatening agranulocytosis, leukoencephalopathy, and cutaneous vasculitides.[20] Other drugs, such as PCP, are misleadingly sold as a different drug, such as lysergic acid diethylamide (LSD). During the 1990s, many doses of purported ecstasy (MDMA) actually contained amphetamine drug mixtures or even simple caffeine or ephedrine.[21,22] Drug combinations and unanticipated additives or substitutions may produce a clinical picture discordant with what the patient claims to have taken.

"Look-alike" drugs may also have toxic effects. Teens in particular may take look-alike or "knock-off" drugs that look like a desired product, such as Ritalin or Coricidin, in the hope of getting high, when in reality they may suffer unanticipated effects from an unrelated medication sold by an unscrupulous dealer. Teenagers can present with dystonias after unsuspectingly taking haloperidol instead of diazepam (each can have a "letter" inscribed in the middle of the pill).

www.ketabpezeshki.com 66485457-66963820

CLINICAL FINDINGS

History

A drug history should be obtained from patients reporting drug reactions, acute anxiety or other psychiatric problems, and acute cardiopulmonary or neurologic symptoms. This information should include use of legal and illegal substances, prescription and OTC medications, vitamins, herbals, tonics, and potions. When it is appropriate, the physician should specifically ask if the patient is suicidal. A physician who is neutral and nonjudgmental in approach is more likely to obtain accurate information.

Parents should be asked what they believe their son or daughter took and when. The "street name" may be unfamiliar to the emergency physician; there are numerous websites available for reference information, such as www.whitehousedrugpolicy.gov/pdf/street_terms.pdf.[23] Regardless, there is no guarantee that the purported ingestant is pure or unadulterated; therefore, a careful examination may provide the most reliable clues about the exposure. Prehospital personnel, family members, and friends may be able to offer additional information. Patients who are brought from the scene of a club, "rave," or circuit party with altered mental status may be under the influence of a club drug such as MDMA (ecstasy), GHB, flunitrazepam (Rohypnol), or ketamine. Other club drugs, such as Verve and Jolt, contain γ-butyrolactone (GBL) and are sold on the Internet as precursor molecules to GHB. These dangerous drugs are especially appealing to teens.[24]

The RAFFT questionnaire may be useful in detection of substance abuse in adolescents. Each yes response receives a score of 1, and each no response receives a score of 0. The scores for the five questions are added together, and a RAFFT total score of 3 or more indicates that an individual needs further assessment[25]:

Relax: Do you drink/use drugs to relax, feel better about yourself, or fit in?
Alone: Do you ever drink/use drugs while you are by yourself, alone?
Friends: Do any of your closest friends drink/use drugs?
Family: Does a close family member have a problem with alcohol or drugs?
Trouble: Have you ever gotten into trouble from drinking or using drugs?

Injection drug abusers often have infectious complications, such as septic pulmonary emboli, skin or brain abscesses, endocarditis, and HIV-related disease. Wound botulism can also be a complication of injection drug use.

Physical Examination

Documentation of vital signs is essential. Temperatures are frequently neglected in violent or agitated patients, and external skin temperature can be misleading. Because rapid mouth breathing, dry mucous membranes, and agitation may produce unreliable oral temperatures, a rectal temperature can confirm suspected alterations in temperature. Patients should be undressed and completely examined, with particular attention paid to the skin, pupils, and mental status, and evaluated for signs of trauma. Needle marks and track marks may be found in unusual areas, such as the supraclavicular space.

Physical examination includes evaluation for specific toxic syndromes. The presence of diaphoresis, mydriasis, tachycardia, hypertension, abnormal mental status, and urinary retention suggests sympathomimetic toxicity. In comparison, the anticholinergic (antimuscarinic) syndrome has these same features with the exception of dry skin and mouth Also, patients with antimuscarinic delirium tend to be less violent and paranoid than those with sympathomimetic toxicity. The mental status evaluation should address both the level of consciousness and appropriateness of affect. Specific physical findings, such as dental disease, skin abscesses, cardiac murmur, or focal neurologic abnormalities such as tremor or ataxia, can assist in identification of chronic drug abuse. Dental disease, with extensive caries, has traditionally been attributed to methamphetamine use, but it is common with other forms of chemical dependency.[26] The skin provides important clues to substance abuse, such as residue of chemicals or drugs on the hand or face or track marks from injection drug use.

DIFFERENTIAL DIAGNOSIS

It is unreliable to assume that abnormal behavior or altered mental status in the unkempt young patient is due to drug intoxication. Many serious illnesses can be manifested as an overdose, including sepsis, meningitis, encephalitis, head trauma, unintentional poisoning (e.g., carbon monoxide), hypothermia, heatstroke, intracranial hemorrhage, complex seizures, and drug withdrawal. Hypoglycemia and other metabolic and endocrine derangements are important considerations. Similarly, drug intoxication should be considered in the differential diagnosis of altered mental status or abnormal vital signs regardless of age. Although patients with decompensated psychiatric disease can present similarly to those with drug intoxication, the hallucinations from psychiatric disease are usually auditory in nature, whereas hallucinations from drug intoxication or withdrawal tend to be visual hallucinations. Otherwise, the behavior and agitation associated with drug abuse can be similar to those of decompensated psychiatric disease.

COMPLICATIONS

Illicit drugs produce a wide variety of complications involving all major organ systems. Neurologic complications are especially prominent. Up to 10% of strokes are secondary to drug abuse.[27] Cerebral infarction, cerebral and cerebellar hemorrhage, and subarachnoid bleeding are often secondary to use of cocaine and amphetamines and, occasionally, PCP or heroin.[28] Single generalized tonic-clonic seizures are common with substance abuse, and status epilepticus can occur. Although sympathomimetics such as cocaine and amphetamines are responsible for the majority of seizures, heroin, tricyclic antidepressants, and PCP are high risk. Withdrawal from benzodiazepines and alcohol can also result in seizures, including status epilepticus.

The dangers of substance abuse extend far beyond the toxic effects of a particular drug. Associated hazards include HIV infection, not only secondary to injection but also from the promiscuous lifestyle associated with the drug culture. The prevalence of HIV infection in injection drug users is approximately 12 to 17%.[29]

Recent declines in the incidence of HIV infection among injection drug abusers are encouraging, but resurgences have been associated with needle sharing and inadequate methadone treatment.[30] Accompanying this phenomenon is a decrease in hepatitis B and hepatitis C among injection drug users in some U.S. cities. This is probably due to increases in preventive measures, such as needle-exchange programs, condom use, and vaccination for hepatitis B.[31] Almost 20% of cocaine abusers have a positive tuberculosis skin test result. Sexually transmitted disease is common, especially in the sex-for-drugs culture of crack cocaine. Syphilis, in particular, is endemic among crack abusers.

The lungs are target organs for impurities in intravenous drugs, and pyrogens become trapped in this massive filter. This can produce "cotton fever," characterized by high fever, tachycardia, and tachypnea 10 to 20 minutes after injection.[32] This self-limited illness contrasts with the long-term restrictive and obstructive lung diseases with the prolonged intravenous abuse of methylphenidate. Right-sided endocarditis is a frequent sequela of chronic injection drug abuse, and the nonspecific influenza-like symptoms that accompany this disease can mislead the clinician. In addition

www.ketabpezeshki.com 66485457-66963820

to endocarditis and HIV infection, injection drug abusers have septic pulmonary emboli, cellulitis, botulism, tetanus, and other infectious complications. They may have unusual sites of osteomyelitis or septic arthritis involving the spine or sternoclavicular or sacroiliac joints.

Psychiatric complications of substance abuse are frequent and include anxiety, depression, suicidal ideation, mood swings, paranoia, and panic attacks. Paranoia and depression and associated suicide attempts are common among stimulant abusers, and hallucinations of parasites under the skin (formication) are frequent in those addicted to amphetamine derivatives and cocaine. Sympathomimetics are strongly associated with aggressive behavior and street crime. Traumatic injuries are endemic among substance abusers and arise from both assault and motor vehicle collisions. Psychedelic drugs, such as LSD and PCP, can prompt extreme behavioral changes that can in turn lead to traumatic injuries. On occasion, trauma can be occult, and the unwary physician may overlook a stab wound in a patient whose clinical picture is predominantly drug-induced agitation.

DIAGNOSTIC ADJUNCTS

All patients with acute alterations in mental status in whom hypoglycemia is possible require either a finger-stick glucose test or the empirical administration of 50% dextrose solution. Patients who are unstable or with altered mental status may need evaluation of electrolytes, blood urea nitrogen, and creatinine. The electrocardiogram will occasionally diagnose a myocardial infarction in patients with drug-related chest pain as well as changes specific to certain drugs and medications, such as prolongation of the QRS or QTc interval. A complete blood cell count is of little value, except to follow serial hemoglobin values if occult trauma or hemolysis is suspected. Arterial blood gas analysis may be useful in assessment of acid-base status as well as in measurement of oxygenation and ventilation. Rhabdomyolysis, most often seen with psychostimulant abuse or prolonged periods in the same body position after abuse of sedatives (e.g., barbiturates), is best detected by measurement of serum creatine kinase or myoglobin.[33] Rhabdomyolysis is usually defined as creatine kinase levels more than five times the upper limit of normal, but absolute levels may not correlate with renal dysfunction. Dipstick urinalysis may screen positive for hemoglobin without accompanying red blood cells but is insensitive for this condition.

The use of qualitative toxicology screens is less important than the patient's history and clinical status. Although unsuspected drugs may be detected on a urine toxicology screen, this knowledge rarely affects acute management of the patient.[34,35] Quantitative levels of suspected substances, such as acetaminophen, acetylsalicylic acid, lithium, and certain anticonvulsants, may be valuable in certain circumstances. A new generation of rapid bedside "drug of abuse" urine toxicology screens may provide timely information, but their use requires further study.[36] There are some special circumstances in which rapid qualitative urine toxicology screening may have some utility. For example, positive urine screens for sympathomimetics can occasionally be found in children presenting with bizarre or abnormal behavior or new-onset convulsions if they have been exposed to these substances in the home environment where they are being used or manufactured. These findings in older children may also assist parents in assessing changing behavior or school performance in some situations.

MANAGEMENT

Agitation

Few antidotes exist for psychoactive drug intoxication, and with a few notable exceptions, treatment is supportive. Violent or agitated patients require rapid sedation. Benzodiazepines such as lorazepam (Ativan) can best sedate patients with sympathomimetic symptoms, whether they are due to drug intoxication or withdrawal. For other patients, intramuscular or intravenous butyrophenones, such as haloperidol (Haldol) and droperidol (Inapsine), are rapidly effective and generally safe. Droperidol has a box warning from the Food and Drug Administration (FDA) for QT prolongation and potentially torsades de pointes. However, in September 2007, the FDA added a warning that "torsades de pointes and QT prolongation have been observed in patients receiving haloperidol, especially when the drug is administered intravenously or in higher doses than recommended. Haloperidol is not approved for intravenous use."[37] Most reported cases of butyrophenone-induced dysrhythmias have been in individuals receiving large doses for prolonged periods, such as hours to days, or in elderly populations (older than 60 years). These medications lack the respiratory depression potentially caused by other agents and may be beneficial in some cases when sedation is required. For these reasons, the butyrophenones remain safe and effective agents for treatment of drug-induced agitation. In cases of cocaine or methamphetamine toxicity, in which hyperthermia or convulsions have occurred or can occur, benzodiazepines may be preferred. Phenothiazines, such as chlorpromazine, are not generally recommended in the drug-intoxicated patient because of their strong anticholinergic effects and potential to produce hypotension and lower the seizure threshold.

Body Packers and Stuffers

The body *stuffer* swallows loosely packaged drugs, or the raw drug itself, in an attempt to conceal contraband during arrest. The body *packer* (a "mule") delivers professionally packaged drugs in his or her intestinal tract, usually on a flight from another country. In many cases, these packets can be visualized radiographically.[38]

There is considerable debate about the best approach to these patients. Some sources recommend activated charcoal for body stuffers and whole-bowel irrigation for body packers, but others adopt a less aggressive approach.[39,40] In severe cases of body packing in which packet rupture occurs, surgical removal may be considered. In asymptomatic cases, the patient's right to refuse care usually supersedes local laws for forcible removal of such evidence, but patients who are significantly confused from drug effects (or comatose) are incapable of refusing lifesaving interventions.

Referral

After acute medical issues have been managed, substance abusers should be asked whether they would like help in overcoming their addiction. Studies show that intervention may be most successful for abusers of heroin, nonprescribed methadone, and benzodiazepines. Users of crack cocaine appear to be more resistant to treatment.[41] Offering symptomatic relief from withdrawal with short courses of medications including antiemetics, antidiarrheals, and benzodiazepines, when indicated, may improve the patient's ability to sustain sobriety.

Drug Seeker

As the front line in medical care, EDs are frequently confronted by patients with drug-seeking behavior, typically for pain medication or benzodiazepines. Although only 1% of ED patients have a formally recorded diagnosis of substance abuse, as many as 27% of ED patients are actually in need of substance abuse treatment.[42] This drug-seeking behavior is described as a compulsion for seeking and taking drugs after prolonged use of a certain drug.[43] Although health care providers should not facilitate drug-seeking

www.ketabpezeshki.com 66485457-66963820

behavior, inadequate pain management is internationally considered unethical.[44] Drug diversion has also become an increasing problem. The street value of prescription opioids such as oxycodone is greater than that of marijuana and heroin.[45]

Emergency physicians need to judiciously provide pain medication to avoid long-term problems from undertreatment of genuine acute pain. However, an overly liberal approach can contribute to addictive behavior. It is difficult for the individual health care provider to screen effectively for drug seeking or abuse on just a single encounter. Self-admission would be the easiest screen, but 90% of patients who abuse opioids deny it.[42] Although it is not sensitive, a prior history of drug or alcohol abuse may identify patients at risk for abuse of opioids, the most commonly abused agents of the prescription drug seeker.[46] Repeated visits for the same complaint, rapid dose escalation, unusual and multiple allergies, and demands for specific agents (often in specific milligram amounts) are all warning signs of potential drug seeking.[47] Unfortunately, there is no reliable finding that can consistently identify drug seeking while not penalizing those in true need of analgesics.

In response to this problem, both individual hospitals and some states are starting to track patients who habitually receive opioid prescriptions.[48] The effectiveness of such programs is not known. Some locales have had success with pain guidelines that restrict the use of opioids to proven conditions, with electronic flagging of habitual visitors who present for medical care.[47] Such approaches may work if they are done in conjunction with referral to chronic pain clinics or detoxification centers. A multifaceted approach that combined counseling, denial of narcotic prescriptions in the ED, and referral to a single pharmacy resulted in a 72% decrease in ED visits by frequent users.[49] Restriction or removal of meperidine from EDs can decrease visits from substance-abusing patients.[50]

Beyond facility-wide policies, individual physicians and other health care providers can attenuate drug-seeking behaviors. In addition, the conservative use of long-acting opioids, such as specialized forms of oral morphine, may decrease the reinforcement of drug-seeking behavior while providing compassionate pain alleviation.[51] Finally, pain contracts or explaining to the patient that opioids or other controlled substances are not appropriate may be helpful, but only if other physicians in the group or community agree on such a strategy for a particular patient.[45]

KEY CONCEPTS

- Substance abuse can affect people from all socioeconomic groups and all ages.
- For the majority of patients with toxin-induced violent behavior, intramuscular butyrophenones such as haloperidol (Haldol) are safe and rapidly effective sedating agents. With suspected sympathomimetic (e.g., cocaine and amphetamines) intoxication, benzodiazepines such as lorazepam (Ativan) should be used.
- Presentation to an ED with a complication of substance abuse may be a "teaching moment." Substance abusers should be offered drug treatment services.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Osler W: Recent advances in medicine. *Science* 1891; 17:170.
2. Mokdad AH, Marks JS, Stroup DF, Gerberding JL: Actual causes of death in the United States, 2000 [erratum appears in *JAMA* 2005; 293:293]. *JAMA* 2004; 291:1238.
3. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Association; 1994.
4. Todd KH, et al: Pain and pain-related functional interference among discharged emergency department patients. *Ann Emerg Med* 2004; 44:S86.
5. Todd KH: Chronic pain and aberrant drug-related behavior in the emergency department. *J Law Med Ethics* 2005; 33:761.
6. Levine DA: "Pharming": The abuse of prescription and over-the-counter drugs in teens. *Curr Opin Pediatr* 2007; 19:270-274.
7. Banerji S, Anderson IB: Abuse of Coricidin HBP cough and cold tablets: Episodes recorded by a poison center. *Am J Health Syst Pharm* 2001; 58:1811.
8. Klein-Schwartz W: Abuse and toxicity of methylphenidate. *Curr Opin Pediatr* 2002; 14:219.
9. Fass J, Fass AD, Garcia AS: Synthetic cathinones (bath salts): Legal status and patterns of abuse. *Ann Pharmacother* 2012; 46:436-441.
10. Prosser JM, Nelson LS: The toxicology of bath salts: A review of synthetic cathinones. *J Med Toxicol* 2012; 8:33-42.
11. Rosenbaum CD, Carreiro SP, Babu KM: Here today, gone tomorrow … and back again? A review of herbal marijuana alternatives (K2, Spice), synthetic cathinones (bath salts), kratom, *Salvia divinorum,* methoxetamine, and piperazines. *J Med Toxicol* 2012; 8:15-32.
12. Azadi A, Dildy GA: Universal screening for substance abuse at the time of parturition. *Am J Obstet Gynecol* 2008; 198:e30-e32.
13. U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Office of Applied Studies: *Drug Abuse Warning Network, 2009: Area Profiles of Drug-Related Mortality*. Rockville, Md: U.S. Department of Health and Human Services; 2011.
14. U.S. Department of Health and Human Services: *Drug Abuse Warning Network, 2005: National Estimates of Drug-Related Emergency Department Visits*. Rockville, Md: U.S. Department of Health and Human Services; 2008.
15. Centers for Disease Control and Prevention: Emergency department visits involving nonmedical use of selected prescription drugs—United States, 2004-2008. *MMWR Morb Mortal Wkly Rep* 2010; 59:705-709.
16. Takahashi TA, Maciejewski ML, Bradley K: US hospitalizations and costs for illicit drug users with soft tissue infections. *J Behav Health Serv Res* 2010; 37:508-518.
17. White AM, Hingson RW, Pan IJ, Yi HY: Hospitalizations for alcohol and drug overdoses in young adults ages 18-24 in the United States, 1999-2008: Results from the Nationwide Inpatient Sample. *J Stud Alcohol Drugs* 2011; 72:774-786.
18. Antoniou T, Tseng AL: Interactions between recreational drugs and antiretroviral agents. *Ann Pharmacother* 2002; 36:1598.
19. Schwartz RH: Adolescent abuse of dextromethorphan. *Clin Pediatr* 2005; 44:565-568.
20. Buchanan JA, Heard K, Burbach C, Wilson ML, Dart R: Prevalence of levamisole in urine toxicology screens positive for cocaine in an inner-city hospital. *JAMA* 2011; 205:1657-1658.
21. Parrott AC: Is ecstasy MDMA? A review of the proportion of ecstasy tablets containing MDMA, their dosage levels, and the changing perceptions of purity. *Psychopharmacology* 2004; 173:234.
22. Tanner-Smith EE: Pharmacological content of tablets sold as "ecstasy": Results from an online testing service [erratum appears in *Drug Alcohol Depend* 2008; 93:190]. *Drug Alcohol Depend* 2006; 83:247.
23. Executive Office of the President, Office of National Drug Control Policy, Drug Policy Information Clearinghouse: *Street Terms: Drugs and the Drug Trade*. Rockville, Md: Executive Office of the President; 2008.
24. Winickoff JP, Houck CS, Rothman EL, Bauchner H: Verve and jolt: Deadly new Internet drugs. *Pediatrics* 2000; 106:829.
25. Bastiaens L, Francis G, Lewis K: The RAFFT as a screening tool for adolescent substance use disorders. *Am J Addict* 2000; 9:10.
26. Cretzmeyer M, Walker J, Hall JA, Arndt S: Methamphetamine use and dental disease: Results of a pilot study. *J Dent Child* 2007; 74:85.
27. Sloan MA, Kittner SJ, Rigamonti D, Price TR: Occurrence of stroke associated with use/abuse of drugs. *Neurology* 1991; 41:1358.
28. Westover AN, McBride S, Haley RW: Stroke in young adults who abuse amphetamines or cocaine: A population-based study of hospitalized patients. *Arch Gen Psychiatry* 2007; 64:495.
29. Des Jarlais DC, et al: Convergence of HIV seroprevalence among injecting and non-injecting drug users in New York City. *AIDS* 2007; 21:231-235.
30. Mehta SH, et al: HIV incidence among injection drug users in Baltimore, Maryland (1988-2004). *J Acquir Immune Defic Syndr* 2006; 43:368.
31. Burt RD, et al: Trends in hepatitis B virus, hepatitis C virus, and human immunodeficiency virus prevalence, risk behaviors, and preventive measures among Seattle injection drug users aged 18-30 years, 1994-2004. *J Urban Health* 2007; 84:436.
32. Harrison DW, Walls RM: "Cotton fever": A benign febrile syndrome in intravenous drug abusers. *J Emerg Med* 1990; 8:135.
33. Melli G, Chaudhry V, Cornblath DR: Rhabdomyolysis: An evaluation of 475 hospitalized patients. *Medicine (Baltimore)* 2005; 84:377.
34. Brett AS: Implications of discordance between clinical impression and toxicology analysis in drug overdose. *Arch Intern Med* 1988; 148:437.
35. Mahoney JD, et al: Quantitative serum toxic screening in the management of suspected drug overdose. *Am J Emerg Med* 1990; 8:16.
36. Peace MR, Tarnai LD, Poklis A: Performance evaluation of four on-site drug-testing devices for detection of drugs of abuse in urine. *J Anal Toxicol* 2000; 24:589.
37. U.S. Food and Drug Administration: *FDA Alert: Information for Healthcare Professionals: Haloperidol*. Rockville, Md: U.S. Food and Drug Administration; 2007.
38. Traub SJ, Hoffman RS, Nelson LS: Body packing—the internal concealment of illicit drugs. *N Engl J Med* 2003; 349:2519.
39. Tarabar AF, et al: Failed whole bowel irrigation in heroin body packer: Late endoscopic removal of the packages. *Clin Toxicol* 2005; 43:519.
40. de Prost N, et al: Prognosis of cocaine body-packers. *Intensive Care Med* 2005; 31:955.
41. Gossop M, Marsden J, Stewart D, Kidd T: The National Treatment Outcome Research Study (NTORS): 4-5 year follow-up results. *Addiction* 2003; 98:291.
42. Rockett IR, Putnam SL, Jia H, Smith GS: Assessing substance abuse treatment need: A statewide hospital emergency department study. *Ann Emerg Med* 2003; 41:802.
43. Vanderschuren LJ, Everitt BJ: Behavioral and neural mechanisms of compulsive drug seeking. *Eur J Pharmacol* 2005; 526:77.
44. Brennan F, Carr DB, Cousins M: Pain management: A fundamental human right. *Anesth Analg* 2007; 105:205.
45. Hansen GR: The drug-seeking patient in the emergency room. *Emerg Med Clin North Am* 2005; 23:349-365.
46. Robinson RC, et al: Screening for problematic prescription opioid use. *Clin J Pain* 2001; 17:220.
47. Hawkins SC, et al: Emergency management of chronic pain and drug-seeking behavior: An alternate perspective. *J Emerg Med* 2008; 34:125.
48. Millard WB: Grounding frequent flyers, not abandoning them: Drug seekers in the ED. *Ann Emerg Med* 2007; 49:481.
49. Pope D, Fernandes CMB, Bouthillette F, Etherington J: Frequent users of the emergency department: A program to improve care and reduce visits. *Can Med Assoc J* 2002; 162:1017.
50. Kaye KI, et al: Pethidine in emergency departments: Promoting evidence-based prescribing. *Med J Austr* 2005; 183:129.
51. Murphy TM: Chronic opioids for chronic low back pain—solution or problem? *J Am Board Fam Pract* 1996; 9:225.

www.ketabpezeshki.com 66485457-66963820

Section Seven

THE DEVELOPMENTALLY OR PHYSICALLY DISABLED PATIENT

Chapter 187

Evaluation of the Developmentally or Physically Disabled Patient

Terry A. Adirim and Elizabeth D. Rosenman

PERSPECTIVE

Children and adolescents who are developmentally or physically disabled, have chronic illnesses, or are technology dependent for mobility or survival have special health care needs. The following definition of children with special health care needs (CSHCN) has become widely accepted within the pediatric community:

> *Children with special health care needs are those who have or are at increased risk for a chronic physical, developmental, behavioral, or emotional condition and who also require health and related services of a type or amount beyond that required by children generally.*[1]

The prevalence and characteristics of the CSHCN community depend on the definition used. With use of the federal definition derived by the Maternal and Child Health Bureau of 1998, a study analyzing data from 2006 to 2008 found that approximately one in six children in the United States experienced a special health care need.[2] There is a higher prevalence among older children, boys, and non-Hispanic white and black children, and after adjustment for demographic factors, families in poverty are more likely to have CSHCN.

Advances in medical science and technology have been instrumental in allowing children with complex medical problems to survive beyond the neonatal period. Moreover, family-centered care has been the goal for the care of these children, and as a result, many are living at home instead of in institutions.[3] CSHCN are frequent users of the emergency medical system. Emergency medical services are typically activated during the time of a crisis. This crisis may occur because of equipment failure or panic by the caregiver who is fatigued or new to caring for the child with special needs. However, a survey of 100 families with CSHCN conducted at a tertiary care urban pediatric center demonstrated that although 97% of the families had sought emergency care in the past, only 23% of the caregivers had ever called 911 before, and 93% had driven their child to the hospital during an emergency.[4] Families may transport their children either to the nearest community hospital or to their "home" institution, which is likely to be a tertiary care center. Most emergency medical service jurisdictions transport to the nearest "appropriate" medical facility.

Children (and youth) with special health care needs are usually cared for by adults who have been trained to manage their child's daily care. In general, families are knowledgeable about their child's medical conditions and technologic needs. Families may have detailed medical plans that specify such things as the size of tubes, how often to change tubes, dosages of medications, and ventilator settings. One example of a program that provides information to medical care providers is the Emergency Preparedness for Children with Special Health Care Needs program of the American Academy of Pediatrics and the American College of Emergency Physicians.[5] This emergency notification program's purpose is to communicate specific information to medical caregivers about the conditions and medications of a child or adolescent with special needs. An emergency information form is completed by the child's primary care physician or family and is carried with the child. Although most caregivers are adept at handling many of their children's emergencies, caregivers seek help for a variety of reasons, including the need for respite, equipment malfunction, an overwhelming medical problem, or help with transport to the child's home hospital.

In contrast to the pediatric population, there is no universally recognized definition for adults with special health care needs. The Institute of Medicine (IOM) has used several different definitions for disability, including an "inability or limitation in performing socially defined activity and roles expected of individuals within a social and physical environment."[6] The number of adults who meet this broad definition is difficult to calculate. Current estimates indicate that as many as 50 million U.S. residents have some type of disability.[7] Estimates come from various national surveys that vary in their definitions, questions, and target populations. Even more importantly, of 18 different national surveys reviewed by the IOM Committee on Disability in America, only four include institutionalized individuals.[7] Given the large number of surveillance groups, the IOM has recommended adoption of the World Health Organization's International Classification of Functioning, Disability and Health, which is currently being used in many countries as a standardized assessment tool for both individuals and populations.

Regardless of the definition used, patients with disabilities will have a wide spectrum of health care needs. Many individuals with mild disabilities are able to manage their medical needs independently or with minimal assistance from a primary health care provider, whereas others require frequent and even continuous interactions with the health care system. An individual's needs will probably change over time as well. Many of the childhood conditions that are associated with special health care needs, such as cerebral palsy, will persist into adulthood. The relative incidence of traumatic injury is highest among adolescents and young adults, making traumatic brain and spinal cord injuries a significant contributor to both physical and cognitive disability. In the aging population, vascular disease becomes more common, including cerebrovascular accidents and amputations secondary to peripheral vascular disease and diabetes. Finally, dementia, movement disorders, and general deconditioning are prevalent among the elderly population.

www.ketabpezeshki.com 66485457-66963820

DISTINGUISHING PRINCIPLES OF DISEASE

General Issues for Children and Youth with Special Health Care Needs

CSHCN differ from other children in a variety of ways. Some CSHCN may be neurologically impaired and therefore have intellectual disabilities. Their physical growth may be limited, resulting in stature smaller than that of other children of the same age. As a result, medical personnel cannot rely on age- and weight-based norms and should either ask caregivers for this information or use length-based tapes to estimate weight, to calculate drug dosages, and to determine fluid management. Children and adolescents with chronic health conditions may have vital signs that differ from those expected for children without chronic conditions of the same age.[4] For example, baseline vital signs are altered in children with cardiac conditions or who are on mechanical ventilators. A child with an unrepaired complex congenital heart defect may have a baseline pulse oximetry reading in the low 80s. Some children with lung diseases may have respiratory rates higher than expected, yet these higher respiratory rates are considered their baseline.[4] Also, some children may have sensorineural deficits, such as blindness and deafness, that may make history taking and physical assessment challenging. Medical care providers need to be cognizant of these differences.

Care should be taken when children with physical or cognitive disabilities are treated and moved as they may become frightened easily with quick motions and unfamiliar sights and sounds. Use of a calming tone while speaking at a developmental level the child can comprehend can decrease anxiety and most likely increase cooperation. Allowing parents to be at the bedside is vital for all children but most especially for these children. Moving of children with musculoskeletal disorders can best be accomplished with slow, deliberate motions so as not to frighten the child. The child's caregivers are the best resource in determining the most appropriate methods for communicating with or moving a child with special needs.

General Issues for Adults with Special Health Care Needs

Adults who have suffered a neurologic insult, whether it is congenital, traumatic, or medical, may have communication limitations ranging from mild to severe. A wealth of information may be provided by contacting the nursing facility from which a patient was transferred or calling a family member at home. Equally important is identification of any special communication devices, such as a Passy-Muir (speaking) valve or a writing board, that will facilitate the history-taking process and empower the patient.

Weakness, paralysis, pain, and spasticity can contribute to impaired mobility and make the physical examination challenging. Patients may be reluctant or unable to get out of their wheelchair or to get undressed. This can be a time-consuming and frustrating process in a busy emergency department (ED). Enlistment of help from ancillary staff can expedite this process and ensure the patient's safety.

Patients with special health care needs often have indwelling catheters and implanted devices. It is important to ask about these as complications are not infrequent. Catheters can fall out or become clogged, and implanted devices can malfunction or migrate. Furthermore, anywhere there is a foreign body, there is increased risk of infection.

For all patients and especially those with impaired communication, limited mobility, or indwelling or implanted devices, it is crucial to perform a meticulous physical examination. A patient with a fever and cloudy urine may also have a rectal abscess or erythema around a dialysis catheter that could easily be overlooked if a thorough physical examination is not routinely performed.

SPECIFIC DISORDERS

Airway and Pulmonary Conditions

Tracheomalacia

Tracheomalacia is a condition of abnormally weak tracheal walls due to the loss of supporting cartilage and structural integrity. This frequently causes collapse of the trachea on inspiration. Tracheal collapse is most prominent during times of increased airflow, such as when the infant is coughing, crying, or feeding or has an upper respiratory infection.

There are three causes of tracheomalacia: congenital or intrinsic tracheal anomaly (occurring within the trachea), which may be associated with a tracheoesophageal fistula (a patent connection between the trachea and esophagus); extrinsic defects (occurring outside the trachea), such as abnormal development of the vasculature around the trachea that may create a ring, which places pressure on the trachea and interferes with airflow; and acquired malacia, which occurs in children with prolonged intubation or chronic tracheal infections.[8]

Medical management for tracheomalacia consists of symptomatic treatment. A child may experience respiratory compromise with simple viral infections. Racemic epinephrine may decrease swelling of the upper airway under these circumstances. It is prudent to observe these children in the hospital until they are no longer compromised. For children with severe tracheomalacia, a stent or rigid piece of cartilage may be surgically placed in the collapsed area of the trachea to establish permanent patency. Infants with vascular rings have varying degrees of tracheal compromise. Treatment of constricting vessels consists of surgical division and reattachment to surrounding structures to release the pressure on the trachea. In rare instances, tracheostomies are placed to provide a patent airway until the child's airway grows and strengthens. Fortunately, most infants with tracheomalacia require no specific treatment, and over time the airway grows and the condition improves.

Regardless of the underlying cause, infants and children with tracheomalacia who are in respiratory distress present with similar signs and symptoms. These include cough, prolonged expiratory phase, stridor, accessory muscle use, and hypoxia.

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD), a chronic lung disease occurring in infants, is characterized by poor lung compliance and chronic exacerbations. BPD is a worldwide problem, with 5000 to 10,000 new cases reported each year. BPD, cystic fibrosis, and asthma are the three most common chronic lung diseases in infants.[9]

BPD develops primarily in low-birth-weight infants who have respiratory distress syndrome. Babies born before 32 weeks' gestation may not have enough surfactant to keep their alveoli open.[10] However, BPD development is not limited to survivors of respiratory distress syndrome. BPD may result from alveolar damage caused by other lung diseases, exposure to prolonged high oxygen concentrations, use of mechanical ventilation after birth because of conditions such as neonatal pulmonary hypertension and pneumonia or other infections, or trauma to the lungs.[10]

A combination of fewer air sacs and a lack of surfactant can result in abnormally stiff lungs. This increases the work of breathing for affected infants, who can quickly become fatigued. Respiratory infections can also worsen the inflammatory response in the

www.ketabpezeshki.com 66485457-66963820

lungs, leading to more fluid in the lungs and bronchospasm. Signs and symptoms of BPD can vary in severity by the infant's lung maturity. They may include tachypnea, retractions, paradoxical respirations, abnormal posturing, and wheezing.

BPD causes the most difficulties during the first year of life, which is when most deaths from this disorder occur. The most common long-term lung complication of BPD is asthma, which occurs in approximately half of patients. Other less common complications include apnea during infancy, gastroesophageal reflux, pulmonary hypertension, high blood pressure, pulmonary edema, aspiration, subglottic stenosis, and tracheomalacia. Infants who have BPD are at risk for frequent hospitalizations because of their borderline respiratory reserve, hyperactive airway, and increased susceptibility to respiratory infection.

Treatment of BPD involves symptomatic relief. Home management may include oxygen, bronchodilators, corticosteroids, diuretics, antibiotics, and, in rare cases, ventilator support through a tracheostomy.

Apnea

Apnea in infants and young children is defined as a cessation in breathing for more than 20 seconds or associated with a change in color, limpness, altered mental status, or bradycardia. Apnea occurs more frequently in infants born prematurely and generally reflects immature neurologic and respiratory control mechanisms.[11] These pauses in respiration may be due to central apnea, which is the result of an absence of a neurologic signal to the respiratory muscles. Underlying causes include encephalitis, brainstem infarction or tumor, neuromuscular disorders such as muscular dystrophy, and thoracic restrictive disorders such as kyphoscoliosis. These children are discharged home from the hospital on an apnea monitor. Apnea monitor alarms often result in ED visits. The apnea monitor should be transported with the child to the hospital. Most monitors contain a computer chip that records information that can be downloaded into a computer at the child's regular hospital (home hospital) to determine the origin of the monitor alarms (high or low heart rate, apnea, or artifact).

The most common type of childhood apnea is obstructive apnea, which is caused by an occlusion in the upper airway at the oropharyngeal level or by gastroesophageal reflux disease. Gastroesophageal reflux disease occurs when the lower esophageal sphincter opens, causing stomach contents to pass into the esophagus during or after a meal. Younger children tend to outgrow this condition. Those who continue to be symptomatic can experience complications such as a chronic cough, recurrent pneumonia, difficulty in swallowing, recurrent vomiting, and weight loss. Symptoms can often be controlled with positioning, diet, medications, and, in rare circumstances, surgery.

Mixed apnea is central apnea that is followed by an obstructive apnea event. Obstructive sleep apnea may be managed by providing oxygen during sleep or through continuous positive airway pressure (CPAP), which may be delivered through a nose mask or tracheostomy. Central apnea is managed with supplemental oxygen and CPAP but also responds to medications that stimulate the respiratory system or mechanical ventilation.

Apnea in adults is most frequently related to obstructive sleep apnea. This can be due to altered oropharyngeal anatomy but is most commonly secondary to obesity. Decreased muscle tone during sleep leads to obstruction of the pharynx and hypopharynx with redundant tissue. Central sleep apnea is also seen in patients with heart failure. Regardless of etiology, sleep apnea can result in mild to severe sleep disturbances leading to daytime somnolence and irritability. It is also associated with significant morbidity and mortality, including heart failure, acute coronary syndrome, cerebrovascular accidents, and death.[12-15] Like pediatric obstructive apnea, obstructive sleep apnea in adults is treated with noninvasive positive-pressure ventilation, such as CPAP, during sleep.

Chronic Respiratory Failure in Adults

A wide range of disorders can lead to chronic respiratory failure in adults. These can be divided into three broad categories: intrinsic lung disease, central nervous system disease, and neuromuscular disorders. One of the most common causes of lung disease and chronic respiratory failure in adults is chronic obstructive pulmonary disease (COPD), which is usually due to long-term tobacco exposure. A patient with mild COPD may be managed with inhaled bronchodilators and anticholinergics. With disease progression, patients may require supplemental oxygen at home and may have substantial disability secondary to exertional dyspnea. In the evaluation of a patient with COPD, it is important to ask about home oxygen requirements and baseline oxygen saturation.

Patients with COPD may present in respiratory distress secondary to an exacerbation of their underlying disease. COPD is an obstructive process; people with severe disease will often have elevated carbon dioxide levels at baseline (carbon dioxide retainers), and respiratory drive is often dependent on arterial oxygen concentrations rather than on carbon dioxide concentrations. Attempting to correct oxygen saturation to 100% can decrease the patient's inherent respiratory drive and result in further carbon dioxide retention and altered mental status secondary to hypercarbia (carbon dioxide narcosis). Other common reasons for ED visits include bronchitis and pneumonia. Finally, patients may run out of their oxygen or have an equipment malfunction. A social worker, if available, can assist in coordinating replacement of supplies and ensuring that the patient has a reliable source for home oxygen.

Other less common causes of lung disease include bronchiectasis, sarcoidosis, fibrosis, α_1-antitrypsin deficiency, and pulmonary hypertension. These all have specific management issues, and it is helpful to involve the patient's pulmonologist whenever possible. Individuals with chronic lung disease, regardless of the etiology, may have significant functional limitations related to dyspnea and deconditioning. In an otherwise well-appearing patient, ambulation can reveal hypoxia and dyspnea that may be missed on initial evaluation.

Central nervous system disorders can result in respiratory failure secondary to impaired or absent neurologic control or respiratory muscle weakness or paralysis. The initiation and coordination of respiratory effort is complex and involves multiple areas within the brainstem. Brainstem lesions can result in central apnea or asynchronous respiratory efforts and generally require tracheostomy and mechanical ventilation. The diaphragm is innervated by C3-5 and the intercostal muscles are innervated by T1-7, so cervical and thoracic cord lesions can result in respiratory muscle weakness. The severity of weakness depends on the level and nature of the lesion, with higher and more complete lesions causing more severe impairment. Examples of spinal cord lesions include traumatic cord injuries; compressive lesions, such as spinal cord hematomas and abscesses; and intrinsic cord disease, such as transverse myelitis.

Myasthenia gravis is a neuromuscular disorder that can cause respiratory insufficiency and failure. Myasthenia gravis is an autoimmune process that attacks the postsynaptic acetylcholine receptors at the neuromuscular junction. It most commonly affects the bulbar muscles but can also result in generalized weakness.[16] Other neuromuscular disorders that can affect the respiratory muscles include muscular dystrophy, multiple sclerosis, and amyotrophic lateral sclerosis. In any patient with respiratory muscle weakness secondary to a neuromuscular disease, pulmonary function tests are an important component of the assessment. One test that can

www.ketabpezeshki.com 66485457-66963820

rapidly be obtained in the ED is a negative inspiratory force or maximal inspiratory pressure. A value of less than 20 cm H_2O is the generally accepted cutoff for severe impairment and can help determine which patients need ventilatory support. This test is usually performed by a respiratory therapist with use of a pressure gauge connected to a disposable mouthpiece.

Finally, there are a few conditions that do not fall into any of the prior categories but that can cause respiratory insufficiency and hypoventilatory respiratory failure by restricted chest wall expansion. Examples are severe scleroderma and morbid obesity.

For all causes of chronic respiratory insufficiency, affected individuals will fatigue more rapidly when they are faced with any new pulmonary insult and may rapidly progress to respiratory failure. Any of these disease processes may require tracheostomy and mechanical ventilation because of either baseline respiratory insufficiency or the frequency of exacerbations leading to respiratory failure.

Tracheostomy Tubes

Tracheostomy tubes are placed to facilitate mechanical ventilation, to provide a bypass of the upper airway, or to keep the airways clear of secretions. The more common conditions for which tracheostomy tubes are placed include tracheal stenosis, tracheomalacia, certain craniofacial anomalies, BPD, muscular dystrophy, spinal cord injury or disease, traumatic or anoxic brain injury, and cerebrovascular accidents.[8]

Because the tubes are available from several manufacturers, their sizing and markings vary. Common brands are Shiley, Bivona, Hollinger, Portex, and Bardeen. Typically, the sizes are marked on the packaging and on the flange, or wings, of each tube. They range in size from 00 for newborns to 7.0 for older adolescents and adults. The inner and outer diameter ranges are provided so that comparisons between brands can be made. They range from 2.5 mm for infants to 10.0 mm for adolescents and adults. This information is helpful for emergency personnel in replacing a tracheostomy tube or in choosing an endotracheal tube for oral intubation or use through a stoma. The inner diameter of a tracheostomy tube should be used to choose the endotracheal tube size for insertion through a stoma. Tracheostomy tubes also come in various lengths. Neonatal tubes are shorter than pediatric tubes, although the inner diameters may be the same.[8]

There are several types of tracheostomy tubes and attachments: single-cannula tubes (Fig. 187-1), double-cannula tubes (Fig. 187-2), cuffed tubes (Fig. 187-3), and fenestrated tubes (Fig. 187-4).[8] Neonates, infants, and young children use single-cannula tracheostomy tubes. A double-cannula tube can be used in older children and adults. It contains an outer tube that stays in the stoma and an inner tube that is removable for cleaning and pulmonary toilet. Tracheostomy tubes for older children and adults have an inflatable cuff to keep the tube in place and to prevent air leaks. Fenestrated tubes have a hole in the cephalic portion of the tube that redirects air into the upper airway to allow the individual to speak and to breathe through the nose and mouth. This is facilitated by a decannulation plug that is attached to the opening of the tube.

Attachments to the tracheostomy tube may include a tracheostomy nose, a tracheostomy collar, and a speaker valve. A tracheostomy nose is placed over the external opening of the tracheostomy tube of a nonmechanically ventilated person to provide air filtration and humidification. Likewise, a tracheostomy collar is used to provide humidified air or supplemental oxygen to the nonmechanically ventilated patient. A speaker valve is an attachment that redirects airflow through the upper airway to facilitate speech.

Individuals with tracheostomy tubes seek emergency care for four primary reasons: exacerbation of the underlying pulmonary disease, blockage of the tube by a mucous plug, equipment failure, and dislodgement of the tracheostomy tube. Signs and symptoms of respiratory distress include nasal flaring, retractions, increased respiratory rate, decreased breath sounds, decreased oxygen saturation, cyanosis, wheezing, rales, and increased secretions.

Sudden onset of respiratory distress may suggest a mucous plug or equipment failure rather than a pulmonary infection, which is usually heralded by a more progressive deterioration of respiratory status and fever. Airway assessment should include inspection of the tracheostomy tube for patency.

In a patient experiencing an exacerbation of pulmonary disease, infection and reactive airway disease are the most likely possibilities. Acute treatment of wheezing includes administration of a

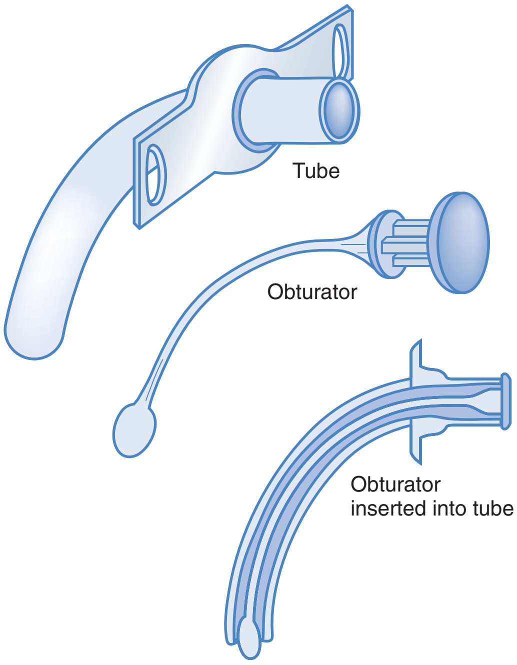


Figure 187-1. Single-cannula tracheostomy tube. (Modified from Susan Gilbert in Teaching Resource for Instructors in Prehospital Pediatrics [TRIPP]; www.cpem.org.)

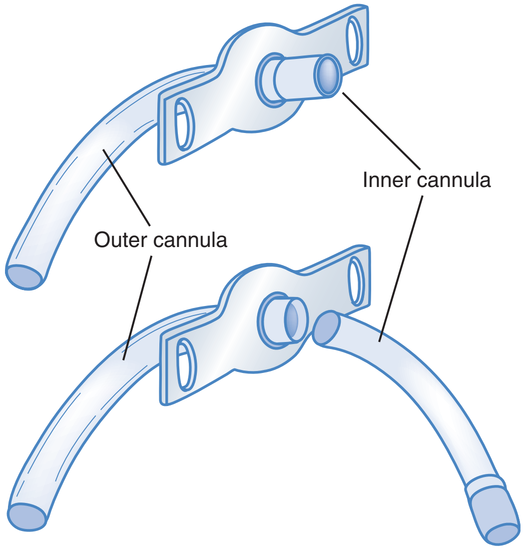


Figure 187-2. Double-cannula tracheostomy tube. (Modified from Susan Gilbert in Teaching Resource for Instructors in Prehospital Pediatrics [TRIPP]; www.cpem.org.)

www.ketabpezeshki.com 66485457-66963820

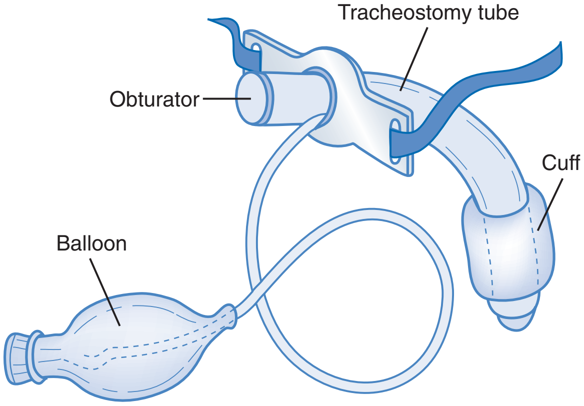


Figure 187-3. Cuffed tracheostomy tube. (Modified from Susan Gilbert in Teaching Resource for Instructors in Prehospital Pediatrics [TRIPP]; www.cpem.org.)

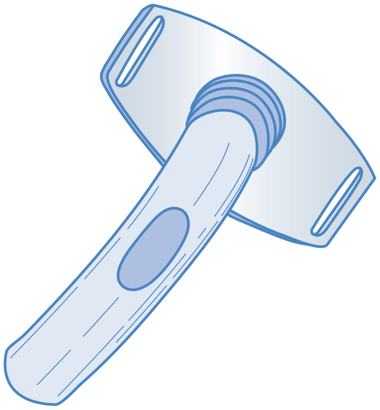


Figure 187-4. Fenestrated tracheostomy tube. (Modified from Susan Gilbert in Teaching Resource for Instructors in Prehospital Pediatrics [TRIPP]; www.cpem.org.)

bronchodilator by nebulizer through the tracheostomy or in-line with the ventilator if the patient is mechanically ventilated. In a patient presenting with a fever or an increase in secretions, infection should be considered. Chest radiography should be obtained. Tracheostomy cultures are controversial given high rates of bacterial colonization of tracheostomy tubes. Early antibiotic coverage is indicated if pneumonia is suspected. The need for hospitalization is determined by a combination of factors including age, medical history, severity of illness, and diagnosis.

For sudden onset of respiratory distress, suctioning of the tracheostomy tube may be helpful. Approximately 2 to 3 mL of normal saline should be instilled before suctioning. If suctioning two or three times does not relieve the obstruction or respiratory distress, the medical provider should change the tracheostomy tube because there may be a thick mucous plug obstructing airflow through the tube. An endotracheal tube can be used as a substitute if the appropriate size of a tracheostomy tube is not available. For patients cared for at home, the parents or caregivers often have spare equipment in their "go" bags that can be used (for troubleshooting, see Tables 187-1 and 187-2).

Home Mechanical Ventilation

Many individuals with tracheostomy tubes are also mechanically ventilated. Indications for mechanical ventilation include severe lung disease and abnormal respiratory drive either from central causes or secondary to weakness or paralysis. Some people are dependent on ventilators continuously; some depend on ventilators while they are asleep, others for part of the day.[11]

There are two types of ventilators: pressure-cycled ventilators and volume ventilators. Pressure-cycled ventilators tend to be used in infants. They are set to deliver a given pressure with each breath. Volume ventilators give a tidal volume with each breath. There are two common modes of ventilations: intermittent mandatory ventilation and controlled mechanical ventilation. Intermittent mandatory ventilation mode delivers a mechanical breath between the patient's own respirations to ensure that the patient achieves a certain number of breaths per minute. In this mode, the ventilator can synchronize its breaths with the patient's breaths. On the other hand, with controlled mechanical ventilation, the ventilator is set to deliver a certain number of breaths per minute whether or not the patient can breathe without assistance. Some ventilators have an assist-control mode in which the ventilator gives a breath at the same time the patient takes a breath to augment the patient's effort.[8]

There are five types of home ventilator alarms: low pressure/apnea, low power, high pressure, setting error, and power switchover. The causes of a low-pressure alarm include a loose or disconnected circuit, a leak in the circuit, and a leak around the tracheostomy site. The low-power alarm indicates that the internal battery is near completion and the ventilator will need to be plugged into an electrical outlet. A high-pressure alarm indicates that there is an obstructed circuit or increased airway pressures. Increased airway pressure can result from any type of lung disease, including bronchospasm, pneumothorax, infection, and pulmonary edema. A setting-error alarm indicates that the setting has been improperly adjusted. Under these circumstances, the patient should be manually ventilated until the ventilator can be set properly. The power-switchover alarm sounds whenever the ventilator switches from AC power to battery power. When this happens, check to ensure that the battery is powering the unit before pressing the "alarm silent" button.[8]

Possible causes of respiratory distress in a ventilator-dependent individual include airway obstruction (e.g., obstructed tracheostomy tube), obstruction or leak in the ventilator tubing, problems with the oxygen supply, equipment failure involving the ventilator, and a medical condition. If a ventilator-dependent patient is found to be in respiratory distress and the cause is not easily determined, the patient should be taken off the ventilator promptly and ventilated with a manual resuscitator (bag-mask ventilation device). Manual ventilation of the patient can help determine if the equipment has failed or a medical condition is responsible.

Neurologic Conditions

Cerebral Palsy

Cerebral palsy (CP) is the leading cause of childhood disability,[17] and population studies have shown that more than 80% of children with CP will survive into adulthood.[18] CP is a group of disorders affecting the development of movement attributed to nonprogressive disturbances that occur in the developing fetal or infant brain. The motor disorders are often accompanied by one or more of the following: disturbances of sensation, cognition, communication, perception, or behavior or a seizure disorder.[19] Premature birth is the most common associated historical factor, and prenatal maternal infection and multiple pregnancies have also been associated with CP.[17]

CP is classified on the basis of the type of movement disorder and the area of the body involved: spastic, athetoid, ataxic, or mixed and hemiplegia, diplegia, or quadriplegia. The most common form, spasticity, is defined as a velocity-dependent resistance to stretch. When the extremities of an individual with the spastic form of CP are stretched beyond their range of motion,

www.ketabpezeshki.com 66485457-66963820

Table 187-1 Medical Devices: Common Problems and Solutions

DEVICE	PROBLEM	ACTION
Tracheostomy	Obstruction	Attempt assisted ventilation with high-concentration oxygen. Attempt to suction. Change tracheostomy tube. Ventilate through stoma.
	Dislodged	Replace tracheostomy. Provide assisted ventilation with high-concentration oxygen through the stoma.
	Unable to reinsert	Attempt to place a tracheostomy tube one size smaller. If attempt fails, attempt to place a similar size endotracheal tube. If attempt fails, provide assisted ventilation through stoma or through the child's mouth while blocking the stoma.
Home ventilator	Respiratory distress	Ask parents to check whether ventilator is functioning properly. Assist in adjustment of ventilator. Assess tracheostomy for obstruction. Remove patient from ventilator and provide assisted ventilation.
Pacemaker	Failure	Assess heart rate and perfusion. Treat for shock. Follow appropriate PALS guidelines.
Central intravenous catheter	Dislodged or damaged	Apply direct pressure to stop bleeding. Clamp or tie exposed catheter to prevent further blood loss. Assess and treat patient for hemothorax and shock.
	Air embolism	Clamp the line. Place patient on left side with head down. Administer high-flow oxygen.
Central venous catheter site	Signs of infection at the site	Treat as a potentially serious infection.
Oral or nasal feeding catheter	Dislodged	Remove catheter. Have patient seek medical attention for tube reinsertion.
Surgically placed feeding catheter	Dislodged	Cover open stoma with gauze.
	Abdominal distention or obstruction	Unclamp tube. Decompress stomach (aspirate air or fluids).
CSF shunt	Failure or obstruction	Treat ABCs. Keep head elevated. Give anticonvulsants for seizure activity. Follow appropriate PALS guidelines for arrhythmias.

Modified from Adirim T, Smith E: Special Children's Outreach and Prehospital Education. Sudbury, Mass, Jones and Bartlett, 2006.
ABCs, airway, breathing, and circulation; *CSF,* cerebrospinal fluid; *PALS,* pediatric advanced life support.

the muscles contract and increase resistance. Clonus and persistent primitive reflexes are characteristic. Because CP is a movement disorder, gross motor skills are delayed. There is a lack of coordination and differential strength and tone in the musculature of the individual. Treatment is focused on management of spasticity. Some of the treatments include daily range-of-motion exercises, casting, and splinting. Some people may take oral medications (baclofen, diazepam, and clonidine) to improve muscle spasticity or to decrease the drooling that is evident in 10% of children with CP, caused by poor oromotor control combined with decreased sensation and poor head control.[18]

Some individuals with CP are now treated with baclofen pumps inserted directly into the thecal sac surrounding the spinal cord. Baclofen is directly infused into this space by a small pump through continuous infusion. Baclofen acts by binding to receptors in the spinal cord, thereby inhibiting spinal reflexes. Complications include overdose when the pump is filled incorrectly or programming is inaccurate. Overdose can lead to respiratory depression and death. Some less serious side effects of the medication are drowsiness, dizziness, hypotension, headache, and nausea. The physician presented with a comatose patient with CP on a baclofen pump must maintain the patient's airway, breathing, and circulation until the pump is urgently stopped with a specialized device. If this device is not readily available, emptying of the reservoir with a 22-gauge needle is an alternative treatment. This can be done by locating the pump in the abdominal wall and inserting the needle in the center of it. Another complication is medication withdrawal due to pump failure, which is usually the result of tube obstruction or faulty pump programming. Symptoms of withdrawal include increased spasticity, tachycardia, blood pressure changes, severe hyperthermia, and rhabdomyolosis.[19,20]

Intellectual Disability

Intellectual disability, previously known as mental retardation, is commonly found in both children and adults. Approximately 30 to 50% of individuals with CP have significant intellectual disabilities. Most have milder cognitive deficits and learning disabilities, and some individuals with CP have normal intelligence. Other causes of intellectual disability include prenatal and perinatal exposures, traumatic or anoxic brain injuries, and genetic syndromes. The term *developmental delay* is often used interchangeably with mental retardation and intellectual disability. Mental retardation has a specific definition, however. Mental retardation is a fixed disability characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills.[21] Developmental delay is a failure to achieve age-appropriate milestones; these children have the potential to "catch up" and eventually to progress normally with their growth and development. In all situations, it is important to assess the developmental level of the patient as well as associated problems, such as hearing or visual impairment.

www.ketabpezeshki.com 66485457-66963820

Table 187-2 Troubleshooting Gastrostomy Tubes and Buttons

PROBLEM	POSSIBLE CAUSATION	ACTIONS
Nausea, vomiting, cramping, or diarrhea	Too rapid feeding Feeding too cold Spoiled formula or a change in formula	Increase feeding time. Ensure that feeding is at room temperature.
Leakage of stomach contents	Mechanical Broken or sticking valve Malpositioned tube wedged into the gastric mucosa Balloon not inflated properly Organic Increased volume of feeding (too much gas or formula) Constipation Ileus Pneumonia (from coughing), seizures	Place insertion obturator, decompression tube, or 8- to 10-Fr suction catheter into shaft of button so it moves the flex valve. The anti-reflux valve makes a popping sound when it moves back into closed position. Ensure that the balloon is fully inflated. Check stomach residual; readjust method of feedings as appropriate. Evaluate for other organic causes and treat accordingly.
Blockage of button	Feeding or medications too thick or remain in shaft too long	Flush button with 5-10 mL of tap water after use. Use thin solutions with well-crushed medications. Use insertion obturator or 8- to 10-Fr suction catheter to gently try to push the plug through.
Accidental removal of button	Vigorous pulling on the button Spontaneous deflation of the gastrostomy balloon	Insert gastrostomy tube to keep stoma open. As a last resort, a Foley catheter with an anti-migration device may be inserted into the stoma. The tube must be securely taped in place. Immediately transport to tertiary hospital for button replacement. Button length may be too long.
Stoma site irritation Maceration due to moisture Gastric acid burn from leakage of gastric contents Purulent mucus	Regular cleaning not effective Incomplete drying Feeding spillage with incomplete cleaning Leakage of gastric contents from or around tube Excessive granulation tissue	Button length may be too short. Do not use occlusive dressing, gauze, tape, or creams. Rotate button 360 degrees once a day. Clean site daily with soap and water. Clean site with ⅓-strength hydrogen peroxide if it is irritated. Consider use of a skin barrier cream and H_2 blocker for gastric burns.
Balloon leaks or ruptures	Silicone balloons generally last about 3 months; however, life of balloon may vary	Replace gastrostomy button.

From Adirim TA, Smith E, Singh T: Special Children's Outreach and Prehospital Education. Sudbury, Mass, Jones and Bartlett, 2006.

Autism and Other Neurodevelopmental Disorders

The 2007 National Survey of Child Health estimates that there are 673,000 children in the United States with autism spectrum disorders, and data from the 2006 Autism and Developmental Disabilities Monitoring Network estimate the prevalence of autism to be 1% of all children in the United States.[22,23] Autism spectrum disorders are a group of neurodevelopmental disorders characterized by impaired development in socialization, communication, and behavior. These disorders include autism, Asperger's syndrome, and pervasive developmental disorder, not otherwise specified. Studies have shown that these children have a high level of functional limitations and poor health status, an accompanying high level of health care use and unmet health needs, and increased parenting stress and family burden.[24-26] In fact, a Pennsylvania Autism Needs Assessment from September 2011 reported that both the untreated or undertreated symptoms of autism and co-occurring disorders can result in unwanted outcomes, including police contact, ED visits, and inpatient psychiatric hospital care, and that the incidence of these outcomes increases markedly with age from less than 5% of children to more than 10% for ED visits to almost 25% for police contacts in adults with autism. The most common reasons for emergency and inpatient hospital-based care are aggression and defiant behaviors, followed by self-injury, anxiety, and depression.

More than 40% of children and adolescents with autism and other neurodevelopmental disorders have multiple conditions. For children with autism, more than 95% have a co-occurring developmental disorder, such as attention deficit disorder, attention-deficit/hyperactivity disorder, learning disabilities, mental retardation, stuttering, and other developmental delays.[24] Also, children with autism have a higher incidence of seizure disorders. Therefore, children with autism are more likely to be taking prescription medications and to access health care services at higher rates than normal children do.

Working with these children, adolescents, and adults in the ED presents a number of challenges because of their impaired communication skills, intellectual disability, and co-occurring psychiatric conditions. Determine the patient's level of cognitive function and tolerance for new places and people by talking to the caretaker. Engage the family in the care of the patient to lessen the patient's anxiety. Avoid forcing the patient to submit to an examination or to undergo a diagnostic procedure. Speak softly and reassuringly and speak directly to the patient. With the family, ascertain the cause of the patient's distress because uncontrolled behaviors could be due to a medical condition or a response to pain.

Strategies typically used to treat aggression and other behavioral disorders are often less effective in people with autism. Consultation with specialists with knowledge of the care of people with autism is recommended (e.g., specialists at regional tertiary care centers). Children with autism spectrum disorders with aggressive behaviors not controlled by behavioral therapy are increasingly being treated with atypical antipsychotic agents, such

www.ketabpezeshki.com 66485457-66963820

as risperidone.[27] Management of uncontrolled behavior may necessitate medication, especially to protect patients from harming themselves or others.

Seizures

Seizure disorders affect approximately 10% of children who are disabled, compared with only 0.5% of healthy children. The frequency of seizure disorders in adults is more difficult to estimate as adults have less consistent health care and are more likely than children to have seizures secondary to other medical or toxicologic issues. In a 2004 nationwide survey, 2.9% of participants reported a diagnosis of epilepsy or seizure disorder.[21] Patients with seizure activity often have normal intelligence, and their seizures can be well controlled by anticonvulsant medication.[28] With age comes an increasing frequency of secondary seizure syndromes, such as post-traumatic seizures, adverse reactions to medications, and seizures related to structural lesions such as masses, or encephalomalacia. In someone receiving antiepileptic therapy with stable symptoms, a "breakthrough" seizure may occur as a result of toxic or subtherapeutic blood levels of seizure medication. This may occur for a variety of reasons. These include but are not limited to poor absorption of the medication secondary to a gastrointestinal illness, missing of one or more doses of anticonvulsant medication, medication dosages not being appropriately adjusted for a patient's growth or weight gain, and lowered seizure threshold from an illness or accidental multidosing of a patient's medication (Table 187-3). For patients with multiple abnormalities, seizure activity is generally more severe and is more difficult to control with anticonvulsant medications.

Table 187-3 Antiseizure Medications, Their Side Effects, and Examples of Drugs Interfering with Serum Concentration

BRAND NAME (GENERIC NAME)	POSSIBLE SIDE EFFECTS	DRUGS INCREASING SERUM CONCENTRATION	DRUGS DECREASING SERUM CONCENTRATION
Ativan (lorazepam)	Drowsiness, sleepiness, fatigue, poor coordination, unsteadiness, behavior changes		Carbamazepine, phenobarbital, phenytoin, primidone
Banzel (rufinamide)	Drowsiness, attention difficulty, headache, fatigue, loss of appetite, vomiting, dizziness, irritability, itchiness, stomach pain		
Carbatrol (extended-release carbamazepine)	Dizziness, drowsiness, blurred or double vision, nausea, rashes, abnormal blood counts (rare)	Felbamate, valproic acid Fluoxetine, trazodone Clarithromycin, erythromycin, fluconazole, isoniazid, ketoconazole, metronidazole Cimetidine, danazol, diltiazem, risperidone, verapamil	May reduce the efficacy of oral contraceptives
Depakene (valproate)	Upset stomach, altered bleeding time, liver toxicity, hair loss, weight gain, tremor	Felbamate, sertraline, isoniazid, cimetidine	
Depakote (divalproex sodium)	Upset stomach, altered bleeding time, liver toxicity, hair loss, weight gain, tremor		
Depakote ER (extended-release divalproex sodium)	Hair loss, upset stomach, tremor, altered bleeding time, liver toxicity, weight gain, headaches, drowsiness, dizziness, blurred or double vision, twitching		
Diamox (acetazolamide)	Appetite loss, frequent urination, drowsiness, confusion, extremity numbness, kidney stones		
Diastat AcuDial (diazepam rectal gel)	Drowsiness, sleepiness, fatigue, poor coordination, unsteadiness, behavior changes		
Dilantin (phenytoin)	Clumsiness, insomnia, motor twitching, nausea, rash, gum overgrowth, hairiness, thickening of features	Felbamate, oxcarbazepine, sulthiame, valproic acid Fluoxetine, fluvoxamine, imipramine, sertraline, trazodone, viloxazine Chloramphenicol, fluorouracil, tamoxifen, tegafur, UFT Allopurinol, amiodarone, cimetidine, diltiazem, omeprazole, tacrolimus	May reduce the efficacy of oral contraceptives
Felbatol (felbamate)	Anorexia, vomiting, insomnia, nausea, headache, liver and blood toxicity		May reduce the efficacy of oral contraceptives
Gabitril (tiagabine)	Tremor, dizziness, nervousness, difficulty concentrating, sleepiness, weakness		
H.P. Acthar gel (ACTH [adrenocorticotropic hormone])	Insomnia, increased appetite, weight gain, irritability, fluid retention		

Continued

www.ketabpezeshki.com 66485457-66963820

Table 187-3 Antiseizure Medications, Their Side Effects, and Examples of Drugs Interfering with Serum Concentration—cont'd

BRAND NAME (GENERIC NAME)	POSSIBLE SIDE EFFECTS	DRUGS INCREASING SERUM CONCENTRATION	DRUGS DECREASING SERUM CONCENTRATION
Keppra (levetiracetam)	Sleepiness, fatigue, poor coordination, loss of strength, dizziness		
Klonopin (clonazepam)	Drowsiness, sleepiness, fatigue, poor coordination, unsteadiness, behavior changes		
Lamictal (lamotrigine)	Dizziness, headache, blurred vision, clumsiness, sleepiness, nausea, rash	Valproic acid, sertraline	May reduce the efficacy of oral contraceptives
Lyrica (pregabalin)	Weight gain, blurred or double vision, dry mouth, difficulty concentrating, dizziness, swelling of hands and feet, sleepiness, drowsiness		
Mysoline (primidone)	Clumsiness, dizziness, appetite loss, fatigue, drowsiness, hyperirritability, insomnia, depression, hyperactivity (children)		May reduce the efficacy of oral contraceptives
Neurontin (gabapentin)	Sleepiness, dizziness, clumsiness, fatigue, twitching		
Phenobarbital (phenobarbital)	Drowsiness, irritability, hyperactivity (children), behavioral problems, difficulty concentrating, depression	Felbamate, phenytoin, sulthiame, valproic acid, chloramphenicol	May reduce the efficacy of oral contraceptives
Sabril (vigabatrin)	Vision loss, abnormal magnetic resonance imaging scans, anemia, sleepiness, numbness of extremities, weight gain, swelling, hyperactivity		
Tegretol (carbamazepine)	Dizziness, drowsiness, blurred or double vision, nausea, rashes, abnormal blood counts (rare)		May reduce the efficacy of oral contraceptives
Tegretol XR (extended-release carbamazepine)	Dizziness, drowsiness, blurred or double vision, nausea, rashes, abnormal blood counts (rare)		May reduce the efficacy of oral contraceptives
Topamax (topiramate)	Confusion, sleepiness, dizziness, clumsiness, difficulty thinking or talking, tingling sensation of the skin, nausea, decreased appetite		May reduce the efficacy of oral contraceptives
Tranxene (clorazepate)	Drowsiness, sleepiness, fatigue, poor coordination, unsteadiness, behavior change		
Trileptal (oxcarbazepine)	Difficulty concentrating, sleepiness, fatigue, dizziness, double vision, nausea, unsteadiness, rash		May reduce the efficacy of oral contraceptives
Zarontin (ethosuximide)	Appetite loss, nausea, drowsiness, headache, dizziness, fatigue, rash, abnormal blood counts (rare)	Isoniazid	
Zonegran (zonisamide)	Sleepiness, dizziness, loss of appetite, headache, nausea, irritability, difficulty concentrating, unsteadiness, fever, kidney stones, rash (should not be used in individuals allergic to sulfa drugs)		

Modified from the Epilepsy Foundation, Western/Central Pennsylvania: Anti-seizure medication and their side effects. Available at www.efwp.org/programs/side_effects.shtml. Accessed November 25, 2011; and Perucca E: Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol 61:246-255, 2006.

Individuals with structural brain abnormalities are more likely to experience status epilepticus. Status epilepticus is a condition of generalized convulsions in adults and older children (older than 5 years) for 5 minutes continuously or two or more discrete seizures without full recovery of consciousness.[28-30] Treatment initially includes benzodiazepines, which are often effective; if two doses of a benzodiazepine are not effective, subsequent doses are not likely to work, and phenytoin (Dilantin) or fosphenytoin (Cerebyx) is considered the next line of medication.[28] It is important to rapidly assess for and to treat underlying conditions that may have triggered the seizure or make it refractory to standard therapies, even in patients with known seizure disorders. This includes testing for hypoglycemia and electrolyte abnormalities, such as hyponatremia, as well as a focused history and physical examination looking for signs of trauma, infection, or changes in home medications. (For complete discussions of the management of adult and childhood seizures, see Chapters 102 and 175, respectively.) Intractable epilepsy affects approximately 20 to 30% of

www.ketabpezeshki.com 66485457-66963820

patients with seizures. Newer antiepileptic drugs and surgical procedures decrease seizure frequency in a significant number of patients. Even among this group, up to 10% continue to have disabling seizures. For these patients, the vagal nerve stimulator (VNS) provides hope for better seizure control.[31]

The VNS is an implantable device that looks like a pacemaker. It is implanted by a neurosurgeon just under the skin in the chest. In the small number of children who have had the VNS placed, most have had a reduction in seizure frequency of 50%.[31] How the VNS works on the brain is not known. The VNS is programmed by the neurologist with a programming wand and a laptop computer to provide baseline intermittent stimulation of the left vagus nerve. Although the VNS system delivers stimulation automatically in regular pulses all the time, a special magnet can be used to deliver extra electronic stimulation in between cycles. The patient or caregiver activates the device by placing the hand-held magnet over the device implanted in the chest.[32] Patients who can sense that they are about to experience a seizure can activate the VNS themselves by passing the magnet over the device. Out-of-hospital providers who encounter a seizing patient with the VNS should assist the caregiver with its activation or seek advice from medical control. Individuals with VNS devices should otherwise be treated like other seizing patients, with careful attention to airway, breathing, and circulation. The special magnet can also be used to stop the stimulation by holding the magnet over the device. While the magnet is held directly over the generator, the switch inside the generator remains closed and stimulation is not delivered. When the magnet is removed, the switch opens and the device is able to deliver stimulation.[33,34] Sometimes the patient may want to shut the stimulation off. Some reasons for this include when the patient is eating if the stimulation causes problems with swallowing, when the patient plans to speak or to sing in public as the stimulation can change one's voice, and if the stimulation causes discomfort.[33]

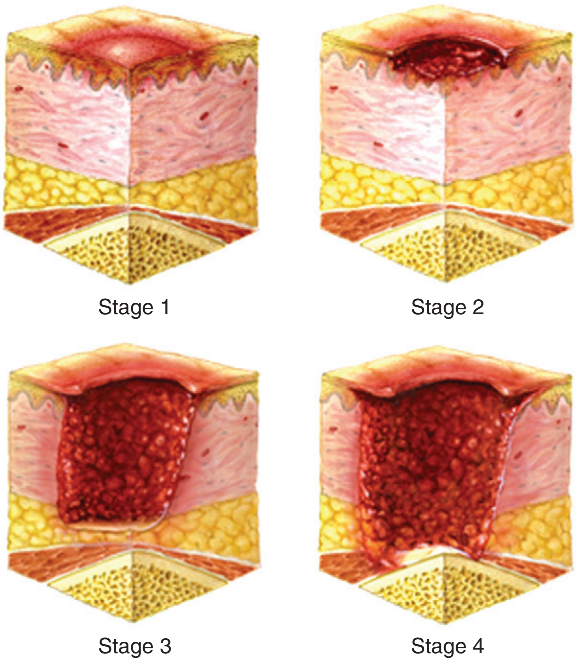


Figure 187-5. Staging of pressure ulcers. (Used with permission of the National Pressure Ulcer Advisory Panel.)

Myelomeningocele and Hydrocephalus

Myelomeningocele (or spina bifida) refers to a congenital gap in the vertebral arches. The most common types of spina bifida are spina bifida occulta, the milder form, and spina bifida associated with malformation of the spine and attachment of the sac, a condition known as myelomeningocele. The rate of spina bifida in the United States has decreased markedly since the introduction of folic acid to the diets of women of childbearing age.

Clinical presentation depends on the level of the defect. The condition results in partial or complete paralysis and loss of sensory function (not always symmetrical). In addition, the child may present with loss of bladder or bowel control, cognitive impairments, visual deficits, and seizure disorders. Bladder and bowel dysfunction is common among children with spina bifida. In such cases, there is incomplete emptying of the bladder, predisposing the child to urinary tract infections. Management of such cases requires emptying of the bladder by urinary catheterization several times a day. Hydrocephalus associated with Chiari malformation (displacement of the brainstem and part of the cerebellum downward through the skull) occurs in more than 68% of children with spina bifida.[34] Because of frequent exposure to latex products early in life, children with spina bifida should be assumed to be allergic to latex.[35,36]

Spinal Cord Disease

Spinal cord disease is a broad topic that includes traumatic injuries, damage from compressive lesions such as hematomas and abscesses, and a host of medical disorders. Some of the medical conditions include transverse myelitis, cord infarction, and multiple sclerosis. This can result in partial or complete deficits below the level of the lesion that may be unilateral or bilateral, depending on the location of the lesion. In addition to weakness, mobility may be limited by spasticity and contractures. In some situations, such as traumatic injuries, patients may know the exact level of their injury. Other diseases, such as multiple sclerosis, often have patchy and fluctuating symptoms. Regardless of the situation, it is important ask patients about their baseline level of motor and sensory function. Sensory deficits can occur internally as well as externally, so symptoms like abdominal pain and dysuria may be absent and the physical examination findings may be falsely reassuring.

Impaired sensation and strength place individuals with spinal cord disease at increased risk for pressure ulcers. The sacral region is the most commonly recognized site, although any region overlying a bone prominence is at risk for tissue injury. Examples include the occiput, elbows, heels, and posterior aspect of the pinna in the supine patient. Other risk factors for pressure ulcers include age, diabetes, chronic steroid use, tobacco exposure, and malnutrition. Pressure ulcers are categorized as stage 1 to stage 4 (Fig. 187-5). Stage 1 describes the often subtle color, temperature, and tactile changes that occur before actual ulceration. Stage 2 ulcers are shallow, with involvement limited to the epidermis and dermis. Stage 3 lesions penetrate into the subcutaneous fat, and stage 4 lesions penetrate through the deep fascia and may involve underlying muscle and bone. Prevention and early recognition are paramount as severe lesions can be refractory and often require prolonged treatment and surgical intervention. Preventive measures include frequent position changes, padded support devices, daily skin examinations, meticulous hygiene, and avoidance of temperature extremes. In some situations, hospitalization may be necessary for care of extensive wounds or treatment of superimposed infection, which may lead to bacteremia and sepsis. In one prospective cohort, pressure sores accounted for nearly 18% of hospitalizations in patients with spinal cord injury.[37] In the case of infection, blood and wound culture specimens should be obtained and antibiotics should be initiated with specific concern for skin flora.

Autonomic dysreflexia is another common problem in individuals with spinal cord injuries at or above T6. Autonomic

www.ketabpezeshki.com 66485457-66963820

dysreflexia results from inappropriate sympathetic stimulation in response to a noxious stimulus below the level of the cord lesion. The sympathetic surge leads to a subsequent parasympathetic response above the level of the lesion. Signs and symptoms include elevated blood pressure, headache, diaphoresis and flushing cephalad to the lesion, chills, anxiety, dyspnea, and palpitations. The most common cause of autonomic dysreflexia is bladder distention. Additional causes are urinary tract infections, kidney stones, bowel impaction, intra-abdominal infections, skin lesions, sexual activity, pregnancy, sexually transmitted diseases, orthopedic injuries, and deep venous thrombosis. Initial management includes rapid screening for some of the more common causes and blood pressure monitoring. Any constricting item should be removed, including clothes, watchbands, urinary catheter straps, and compression stockings. The bladder should be drained either by placing a new catheter or by flushing or replacing an existing catheter. Urine should be sent for microscopy and culture. Persistent symptoms should prompt the provider to search for other sources of infection, bowel impaction, and musculoskeletal injuries. Blood pressure should be monitored frequently in patients with severe symptoms, and short-acting antihypertensive therapy should be initiated while the patient is undergoing further evaluation. Correction of the underlying problem usually results in resolution of the presenting signs and symptoms, including elevated blood pressure. Patients may require hospitalization for treatment of the underlying cause or for persistent symptoms, regardless of cause. Complications may result from elevated blood pressures and can include ischemic events and intracranial bleeds.

Indwelling Catheters

Ventriculoperitoneal Shunts

Ventriculoperitoneal (VP) shunts are catheters that are inserted into the ventricles within the brain and then threaded under the skin from the skull to the peritoneum, where excess cerebrospinal fluid (CSF) is drained (Fig. 187-6). Less commonly the shunt may drain into the pleural space (ventriculopleural shunt) or right atrium (ventriculoatrial shunt). Hydrocephalus occurs with an obstruction somewhere in the CSF circulation system. If the obstruction is beyond the lateral ventricles, they enlarge with CSF, increasing intracranial pressure. Hydrocephalus can be seen in formerly premature infants who sustained an intracranial hemorrhage during the neonatal period and in adults with a traumatic or spontaneous subarachnoid or intraventricular hemorrhage. Both children and adults can have hydrocephalus secondary to brain tumors or other mass lesions causing obstruction of normal CSF flow. Finally, children with spina bifida (myelomeningocele) often have hydrocephalus if they have an Arnold-Chiari malformation that obstructs CSF flow.

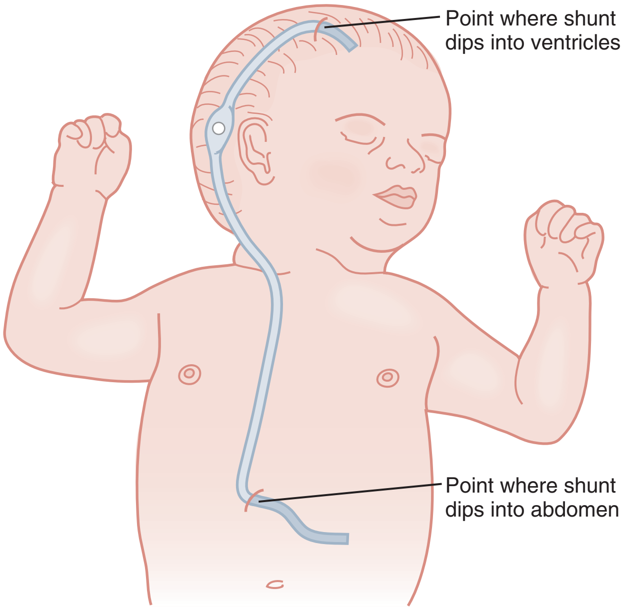


Figure 187-6. Ventriculoperitoneal shunt. (Modified from Susan Gilbert in Teaching Resource for Instructors in Prehospital Pediatrics [TRIPP]; www.cpem.org.)

A person with a VP shunt can rarely have an infection of the shunt track during the first 3 months postoperatively. Symptoms include fever, ill appearance, erythema or tenderness over the shunt site or tubing, abdominal pain and tenderness, vomiting, and altered mental status. Infection can also occur outside of the immediate postoperative setting in patients with bacteremia or primary central nervous system infections leading to seeding of the shunt. A VP shunt infection should be considered in anyone presenting with a fever; if a shunt infection is suggested clinically, CSF should be drawn from the shunt, preferably by a neurosurgeon, and sent for cell count and culture. Broad-spectrum antibiotics should be administered pending cell count and culture results; likely organisms include *Staphylococcus epidermidis, Staphylococcus aureus,* and rarely *Haemophilus influenzae*. Neurosurgeons should manage all shunt infections.[38,39]

Peritonitis is another complication of VP shunts. The tip of the shunt empties into the peritoneal cavity and as a foreign body can serve as a nidus for infection. Signs and symptoms include fever, vomiting, abdominal pain and tenderness, and abdominal distention. Management is similar to that for VP shunt infections and should include diagnostic laboratory work, broad-spectrum antibiotics, and consultation with the neurosurgeon.

The more common complication of a VP shunt is shunt obstruction or malfunction. This can occur with an increase in protein in the CSF that causes a blockage in the tubing or as a result of a mechanical disruption in the shunt tubing. This can cause a buildup of CSF in the ventricles and an increase in intracranial pressure. Signs and symptoms include headache, nausea, vomiting, irritability, altered mental status, ataxia, and change in vital signs. A bulging fontanel may also be seen in infants. Initial management should include elevation of the patient's head and management of the patient's airway, breathing, and circulation. Stable patients should have head computed tomography performed, and a neurosurgeon should be consulted as soon as possible. The definitive treatment is surgical shunt revision.[40]

Gastrostomy Tubes

Gastrostomy tubes are placed in individuals who need long-term nutritional supplementation or cannot take food by mouth. Many conditions necessitate placement of an artificial feeding tube, including severe developmental delay, coma, short bowel syndrome, swallowing difficulties and aspiration burns to the mouth and esophagus, failure to thrive, dysphagia secondary to neurologic disorders, oropharyngeal and esophageal malignant neoplasms, and chronic diseases that affect nutrition (e.g., cystic fibrosis).[41]

Gastrostomy tubes are surgically or endoscopically placed feeding catheters. These tubes include gastrostomy tubes (G tubes), jejunostomy tubes (J tubes), and percutaneous endoscopic gastrostomy tubes (PEGs or buttons). Gastric feeding is generally preferred, but a J tube may be more appropriate for patients with gastroesophageal reflux disease, delayed or impaired gastric emptying, aspiration, or pancreatitis. The tube is placed in the stomach and then passed through the junction between the stomach and jejunum, bypassing the stomach. PEGs are placed by gastroenterologists and surgeons.[42]

www.ketabpezeshki.com 66485457-66963820

There are three potential gastrostomy tube emergencies. The tube can leak gastric contents, become obstructed, or come completely out. When a patient presents with any of these problems, assessment of hydration status is important, especially in anyone who is dependent on the feeding tube for hydration and nutrition. One should inquire about prescribed medications and whether any doses were missed.[43]

If there is leaking around the catheter, management focuses on delineating and fixing the cause of the leak. Possible causes of leakage include balloon deflation, coughing, constipation, bowel obstruction, stoma dilation, and seizure. Addressing the cause may solve the problem; otherwise, consultation with the subspecialty service that manages the tube may be necessary (Table 187-4).

Sometimes a patient's G tube becomes clogged with medication or food. Obstructed tubes can be cleared with either Coca-Cola or a proteolytic enzyme solution; otherwise, they need to be replaced.[8]

G tubes that have fallen completely out of the patient need to be replaced as soon as possible so that the stoma does not constrict and make replacement difficult. Gastrostomy-jejunostomy tube placement is more challenging and is usually done under fluoroscopy by a radiologist familiar with this procedure.[42] For G tube replacement, the physician should ask when the tube was first inserted. Maturation of a tube site generally occurs within a few weeks but may be prolonged in certain populations. For tubes that are less than 3 months old, consultation with the person or service that performed the procedure is necessary because the track may not yet be fully formed and insertion by a practitioner not adept at replacement of these tubes may create a false track.

When the reinsertion procedure is performed, a similar size gastrostomy tube should be used. Families often have an extra tube with them. When a G tube is not available, a Foley catheter can be used to temporarily keep the stoma open until definitive placement can occur.[11]

Once the G tube is replaced, tube placement can be confirmed by instillation of a small amount of diatrizoate meglumine (Gastrografin) dye into the tube (15-30 mL) and obtaining two

Table 187-4 Potential Central Line Emergencies and Physician Management or Considerations

External catheter dislodgement	Apply direct pressure to the skin site. Clamp line near the exit site. Place a peripheral intravenous line to continue necessary fluids and medications. Obtain a chest radiograph to locate distal end of catheter. Consider a dye study to determine location of catheter tip. Obtain surgical consultation.
Complete catheter dislodgement	Apply direct pressure to the skin site. Place a peripheral intravenous line to continue necessary fluids and medications. Obtain surgical consultation to determine disposition.
Damaged catheter	Clamp catheter proximal to the break with a hemostat wrapped in gauze. Estimate blood loss. Observe for symptoms of air embolus. If a peripherally inserted central venous catheter line is in place, remove it. For other partially implanted lines, repair catheter if more than 2 inches of the line exit the skin.
Bleeding at catheter entry site	Apply direct pressure to the entry site. Estimate blood loss. Place a peripheral intravenous line to continue necessary fluids and medications. Obtain a chest radiograph to locate distal end of catheter. Consider a dye study to determine location of catheter tip. Obtain surgical consultation.
Internal bleeding	Apply direct pressure to the site. Observe for symptoms of hemopneumothorax. Place a peripheral intravenous line to continue necessary fluids and medications. Obtain a chest radiograph to locate distal end of catheter. Consider a dye study to determine location of catheter tip. Obtain surgical consultation.
Catheter occlusion	For problems with the withdrawal of blood, try placing the child in various positions (e.g., arms high, lying supine). Attempt to gently aspirate the clot with a 10-mL syringe half filled with normal saline placed directly onto the male Luer lock of the catheter. Consider use of a fibrinolytic agent.
Dislodgement of blood clot	Never force fluids through the catheter! Pulmonary embolism may result. Observe for tachycardia, tachypnea, hypoxemia, and chest pain. Immediately stop infusion of fluids. Clamp catheter.
Air embolus	Observe for *sudden* changes: tachypnea, chest pain, shortness of breath, or loss of consciousness. Clamp system, place child on left side in a head-down position, and give oxygen.
Fever	Consider the patient bacteremic or septicemic until it is proven otherwise. Sepsis can quickly develop in immunosuppressed children. Evaluate for source of infection. Begin broad-spectrum antibiotics. Admit to the hospital for antibiotic therapy.
Reactions from home nutrient or medication infusions	Immediately stop infusion of medications and begin infusion of normal saline. Treat signs of allergic reaction with diphenhydramine, steroids, and subcutaneous injections of 1 : 1000 epinephrine if symptoms are severe.

From Adirim TA, Smith E, Singh T: Special Children's Outreach and Prehospital Education. Sudbury, Mass, Jones and Bartlett, 2006.

www.ketabpezeshki.com 66485457-66963820

radiographic views (anteroposterior and cross-table lateral) to observe the tube and dye in the stomach. Confirmation of replacement of the G tube is indicated when the track is relatively new (placed within 1 month of the ED visit), when the tube is difficult to replace, or when there is any doubt that the tube is in the stomach. Patients should not be discharged home without a definitive G tube placement.

Central Venous Catheters

Central venous catheters, or central lines, are used in individuals who require frequent venous access for delivery of medications, blood products, or nutrition directly into a central vein. Common uses include chemotherapy, long-term antibiotic administration, and parenteral nutrition. Another common use is dialysis in patients with end-stage renal disease.

There are three types of catheters. Peripherally inserted central venous catheters are long catheters inserted into the cephalic vein through the antecubital fossa. The catheter is advanced into the subclavian vein. These tubes are used for temporary venous access, such as antibiotic therapy, and can be placed by nonsurgeons.

Centrally inserted central venous catheters include single- and multiple-lumen catheters and can be tunneled or nontunneled. Common insertion sites are the jugular, subclavian, and cephalic veins. Nontunneled catheters are used for temporary access and are generally limited to inpatient use. Tunneled catheters, however, are frequently used in the outpatient setting. These include the Broviac, Hickman, and Groshong catheters. These are generally placed by surgeons or radiologists. In addition to medication administration and blood draws, these catheters are frequently used in dialysis-dependent patients. They are sometimes used temporarily while waiting for more definitive access, such as a maturing arteriovenous fistula, but may also be considered permanent access for those patients with prior arteriovenous fistula complications or failures. Implanted vascular access ports (Port-A-Cath, PAS Port, and Med-A-Ports) are also common. The insertion sites and method are the same as for the tunneled central venous catheters. The distal end of the catheter consists of a reservoir that is covered with a self-healing rubber septum. This reservoir rests subcutaneously, and a special needle is needed to access this line. The advantages of the implanted vascular ports are that they need to be flushed with heparin only once a month and after each access, as opposed to daily heparin flushes, and they are hidden and so may be more acceptable to older children, for whom body image is more of an issue. They have also been shown to have lower infection rates than catheters with external ports.[44]

Complications from central venous catheters include catheter damage, catheter dislodgement, air embolus, catheter occlusion, and fever. Catheters that are damaged should be clamped proximal to the break with a hemostat. With catheters that are dislodged, the practitioner should apply direct pressure at the entry site to stop or to prevent bleeding. This is a potential life-threatening emergency. The patient should be brought to a facility that can repair or replace the catheter. Air emboli in the tubing can cause sudden onset of respiratory distress, chest pain, and altered mental status. If an embolus is suggested, the patient should be placed on his or her left side, in Trendelenburg's position, and given oxygen. Catheter occlusion may occur secondary to thrombosis. Flushing of the line with a thrombolytic is often effective in re-establishing catheter patency. Many hospitals have a nursing protocol for this procedure, which can be obtained from the pharmacy. Peripheral intravenous line placement should be considered any time a catheter is not functioning properly.

Fever is a common problem in individuals with central lines, and the central line should be considered a potential source of infection. The line is a foreign body that can act as a direct conduit for microorganisms, "which is particularly dangerous for immunocompromised patients who are at increased risk for sepsis. Treatment should include obtaining blood cultures, a complete blood count, and administration of broad-spectrum antibiotics until culture results are known. Immunocompromised patients should be admitted to the hospital for intravenous antibiotics pending blood culture results. Patients with purulence at the catheter site should also be admitted as they will likely need removal and replacement of their lines after temporary access is established. In borderline cases, consultation with the primary care physician or specialist can aid in making disposition decisions.

Bladder Catheters

Individuals with neurogenic bladder secondary to spinal cord or brainstem disease may use a variety of different approaches to bladder management. These approaches include pharmaceutical agents, intermittent catheterization, and chronic indwelling catheters. Spontaneous voiding and intermittent catheterization are associated with a lower rate of urinary tract infections; however, a chronic indwelling catheter may be necessary, depending on the location of the spinal cord lesion and the individual's level of function. Indwelling catheters may also be used in patients with altered genitourinary anatomy secondary to traumatic or postsurgical changes. Catheters may be either urethral or suprapubic in placement. Suprapubic catheters are often preferred by patients and may be associated with lower rates of infection.[45-47] Regardless of site, indwelling urinary catheters are subject to bacterial colonization. Pyuria and bacteriuria are common findings, and patients are often asymptomatic. Whereas *Escherichia coli* is still the most common pathogen, patients with spinal cord disease have higher rates of *Pseudomonas, Proteus,* and *Serratia* colonization than in the general population.[47] Candiduria is also a common finding in asymptomatic patients with long-term catheterization.[48] Determination of when to initiate antimicrobial therapy is controversial. The National Institute on Disability and Rehabilitation Research defines significant bacteriuria as $\geq 10^4$ CFU/mL for clean-void specimens, whereas any degree of bacterial growth is considered significant in patients with indwelling catheters.[49] Despite these sensitive definitions, this consensus report recommends against treatment of asymptomatic bacteriuria unless a urease-producing organism is isolated.[49] This recommendation is based on the association between urea-producing organisms, such as *Proteus,* and bladder stone formation. If a patient is febrile without another obvious source, critically ill, or symptomatic with abdominal or flank pain, vomiting, chills, or rigors, it is appropriate to treat a presumed urinary tract infection. When possible, the catheter should be replaced or temporarily removed before urine is sent for microscopy and culture. In immunocompetent patients who have minor or vague symptoms and who have appropriate follow-up care, it may be appropriate to wait for culture results before antibiotics are started.

Other catheter-related emergencies include dislodgement and obstruction. A clogged catheter should be flushed, and if it is still obstructed, it may need to be replaced. Likewise, if a catheter has been partially dislodged, the catheter balloon should be fully deflated and the catheter removed. Depending on the duration of bladder outflow obstruction and the degree of bladder distention, secondary sequelae, such as postobstructive diuresis and autonomic dysreflexia, should be considered.

www.ketabpezeshki.com 66485457-66963820

KEY CONCEPTS

- Children and adults with special health care needs are usually brought to the ED by parents and caregivers who often know their child's or family member's issues well. They may have information cards or notebooks describing conditions and equipment and listing medications, or the patient may be wearing medical jewelry.
- CSHCN may be physically smaller than children of the same chronologic age, may have vital signs outside the range of normal for age, and may be developmentally delayed.
- Most CSHCN suffer the same typical diseases as their normal counterparts do. Treatment of CSHCN should begin with assessment of the child followed by assessment of medical equipment. When in doubt about the best course of action, maintain the child's airway, breathing, and circulation while seeking consultation from the child's pediatrician or surgeon.
- A common cause of respiratory distress for adults and children with tracheostomy tubes is obstruction from hardened secretions. Immediate instillation of normal saline and suctioning may relieve the obstruction. If suctioning does not relieve the obstruction or respiratory distress, the tracheostomy tube should be changed because there may be a thick mucous plug obstructing airflow through the tube. An endotracheal tube can be used as a substitute if the appropriate size of a tracheostomy tube is not available.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. McPherson M, Arango P, Fox H, et al: A new definition of children with special health care needs. *Pediatrics* 1998; 102:137.
2. Boyle CA, et al: Trends in the prevalence of developmental disabilities in US children, 1997-2008. *Pediatrics* 2011; 127:1034-1042.
3. Turchi RM, Berhane Z: Care coordination for CSHCH: Associations with family-provider relations and family/child outcomes. *Pediatrics* 2009; 124(Suppl 4):S428-S434.
4. Singh T, Adirim TA: Vital sign ranges for children with special health care needs [abstract]. *Pediatr Res* 2004; 49.
5. American Academy of Pediatrics, Committee on Pediatric Emergency Medicine: Policy statement—emergency information forms and emergency preparedness for children with special health care needs. *Pediatrics* 2010; 125:829-837.
6. Pope AM, Tarkiv AR, eds; Committee on a National Agenda for the Prevention of Disabilities, Institute of Medicine: *Disability in America: Toward a National Agenda for Prevention*. Washington, DC: National Academy Press; 1991.
7. Field MJ, Jette AM, eds; Committee on Disability in America, Institute of Medicine: *The Future of Disability in America*. Washington, DC: National Academy Press; 2007.
8. Adirim TA, Smith E, Singh T: *Special Children's Outreach and Prehospital Education*. Sudbury, Mass: Jones and Bartlett; 2006.
9. National Heart, Lung, and Blood Institute, National Institutes of Health: *Bronchopulmonary dysplasia*. Available at www.nhlbi.nih.gov/health/dci/Diseases/Bpd/Bpd_WhatIs.html. Accessed July 14, 2011.
10. Stanley FJ: Cerebral palsy trends: Implications for perinatal care. *Acta Obstet Gynecol Scand* 2004; 73:5.
11. Adirim TA: *Children with special health care needs: The technology dependent child*. In: Cooper A, et al, eds. *APLS: The Pediatric Emergency Resource*, 4th ed. Sudbury, Mass: Jones and Bartlett; 2006.
12. Yaggi HK, et al: Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med* 2005; 353:2034-2041.
13. Marshall NS, et al: Sleep apnea as an independent risk factor for all-cause mortality: The Busselton Health Study. *Sleep* 2008; 31:1079-1085.
14. Young JS, et al: Sleep in hospitalized medical patients, part 1: Factors affecting sleep. *J Hosp Med* 2008; 3:473-482.
15. Gottlieb DJ, et al: Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: The Sleep Heart Health Study. *Circulation* 2010; 122:352-360.
16. National Center for Biotechnology Information, U.S. National Library of Medicine: *Myasthenia gravis*. Available at www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001731. Accessed July 14, 2011.
17. Bax M, et al: Proposed definition and classification of cerebral palsy. *Dev Med Child Neurol* 2005; 47:571.
18. Green LB, Hurvitz EA: Cerebral palsy. *Phys Med Rehabil Clin North Am* 2007; 18:859.
19. Hutton JL, Cooke T: Life expectancy in children with cerebral palsy. *BMJ* 1994; 309:431-435.
20. Shirley K, Kothare S, Piatt J, Adirim TA: Baclofen overdose by intrathecal pump. *Pediatr Emerg Care* 2006; 22:258.
21. American Association of Intellectual and Developmental Disabilities: *FAQ on intellectual disability*. Available at www.aaidd.org/content_104.cfm. Accessed July 14, 2011.
22. Centers for Disease Control and Prevention: Prevalence of autism spectrum disorders—Autism and developmental disabilities monitoring network, United States, 2006. *MMWR Surveill Summ* 2009; 58:1. Available at www.cdc.gov/mmwr/preview/mmwrhtml/ss5810a1.htm. Accessed November 25, 2011.
23. Kogan MD, et al: Prevalence of parent reported diagnosis of autism spectrum disorder among children in the US, 2007. *Pediatrics* 2009; 124:1395-1403. Available at www.pediatrics.org/cgi/doi/10.1542/peds.2009-1522.
24. Boulet SL, Boyle CA, Schieve LA: Health care use and health and functional impact of developmental disabilities among US children. *Arch Pediatr Adolesc Med* 2009;163:19-26.
25. Kogan MD, et al: A national profile of the health care experiences and family impact of autism spectrum disorder among children in the United States, 2005-2006. *Pediatrics* 2008; 122:e1149-e1158. Available at www.pediatrics.org/cgi/content/full/122/6/e1149.
26. Schieve LA, Blumberg SJ, Rice C, Visser SN, Boyle C: The relationship between autism and parenting stress. *Pediatrics* 2007; 119(Suppl 1):S114-S121.
27. McCracken JT, et al: Risperidone in children with autism and serious behavioral problems. *N Engl J Med* 2002; 347:314-321.
28. Weinstein SL, Gaillard WD: *Epilepsy*. In: Batshaw M, ed. *Children with Disabilities*, 6th ed. Baltimore, Md: Paul H. Brookes; 2007:439-460.
29. Lowenstein DH, Bleck T, Macdonald RL: It's time to revise the definition of status epilepticus. *Epilepsia* 1999; 40:120.
30. Abend NS, Dlugos DJ: Treatment of refractory status epilepticus: Literature review and a proposed protocol. *Pediatr Neurol* 2008; 38:377-390.
31. Pellock JM: Overview: Definitions and classifications of seizure emergencies. *J Child Neurol* 2007; 22(Suppl):9S.
32. McLachlan RS: Vagus nerve stimulation for intractable epilepsy: A review. *J Clin Neurophysiol* 2007; 14:358.
33. Al-Otaibi FA, Hamani C, Lozano AM: Neuromodulation in epilepsy. *Neurosurgery* 2011; 69:957-979.
34. Epilepsy Foundation: *Treatment options: Vagus nerve stimulation*. Available at www.epilepsyfoundation.org/about/treatment/vns/. Accessed July 14, 2011.
35. Stevenson KL: Chiari Type II malformation: Past, present, and future. *Neurosurg Focus* 2004; 16:5.
36. Paker N, Soy D: Reasons for rehospitalization in patients with spinal cord injury: 5 years' experience. *Int J Rehabil Res* 2006; 29:71-76.
37. Korinek AM, Fulla-Oller L: Morbidity of ventricular cerebrospinal fluid shunt surgery in adults: An 8-year study. *Neurosurgery* 2011; 68:985-994.
38. Bokhary MA, Kamal H: Ventriculo-peritoneal shunt infections in infants and children. *Libyan J Med* 2008; 3:20-22.
39. Khan AA, Jabbar A: Cerebrospinal shunt malfunction: Recognition and emergency management. *Br J Hosp Med (Lond)* 2007; 68:651-655.
40. Gottrand F, Sullivan PB: Gastrostomy tube feeding: When to start, what to feed and how to stop. *Eur J Clin Nutr* 2010; 64(Suppl 1):S17-S21.
41. Shah M, Klooster M: Frequency and methods of gastrojejunal tube replacement in children. *Curr Gastroenterol Rep* 2010; 12:223-227.
42. El-Matary W: Percutaneous endoscopic gastrostomy in children. *Can J Gastroenterol* 2008; 22:993-998.
43. Pinon M, Bezzio S: A prospective 7-year survey on central venous catheter–related complications at a single pediatric hospital. *Eur J Pediatr* 2009; 168:1505-1512.
44. Mitsui T, Minami K: Is suprapubic cystostomy an optimal urinary management in high quadriplegics? A comparative study of suprapubic cystostomy and clean intermittent catheterization. *Eur Urol* 2000; 38:434-438.
45. MacDiarmid SA, Arnold EP: Management of spinal cord injured patients by indwelling suprapubic catheterization. *J Urol* 1995; 154(Pt 1): 492-494.
46. Esclarín De Ruz A, García Leoni E: Epidemiology and risk factors for urinary tract infection in patients with spinal cord injury. *J Urol* 2000; 164:1285-1289.
47. Newman E, Price M: External catheters: Hazards and benefits of their use by men with spinal cord lesions. *Arch Phys Med Rehabil* 1985; 66:310-313.
48. Goetz LL, Howard M: Occurrence of candiduria in a population of chronically catheterized patients with spinal cord injury. *Spinal Cord* 2010; 48:51-54.
49. National Institute on Disability and Rehabilitation Research Consensus Statement: The prevention and management of urinary tract infections among people with spinal cord injuries. January 27-29, 1992. *J Am Paraplegia Soc* 1992; 15:194-204.

www.ketabpezeshki.com 66485457-66963820

Chapter 188

The Combative Patient

Jason D. Heiner and Gregory P. Moore

PERSPECTIVE

Background

Combative patients are among the most difficult patients emergency physicians encounter. Often brought in against their will, they are agitated, confrontational, and nearly impossible to examine, and they may physically harm themselves or others. The emergency physician should seek to control the patient and the situation, diagnose and treat reversible causes of violence, and protect the patient and staff from harm.

Epidemiology

Violence is referred to as our nation's shameful epidemic. Injury is the leading cause of death in persons younger than 44 years, and homicide is the second leading cause of death in persons aged 15 to 24 years.[1,2] Rates of firearm violence and death from firearms are higher in the United States than in any other industrialized country.[3-5] For each death there are an estimated 19 additional injuries requiring hospitalization.[6] The high lifetime cost of treating gunshot injuries and associated disabilities is a public health issue as a large proportion of the expense is covered by U.S. taxpayers.[7-9]

The emergency department (ED) is a volatile environment because of high stress, illness, prolonged waiting times, and frequent lack of communication. The 24-hour open door policy, availability of potential hostages, and widespread accessibility of drugs and weapons compound the potential for violent behavior. Among hospital workers, the majority of assaults occur in the ED, psychiatric ward, waiting rooms, and geriatric units.[10] In a survey of 242 emergency care workers in five Midwestern hospitals, the majority reported being verbally threatened, and 51% of physicians and 67% of nurses reported being physically assaulted at least once in the past 6 months.[11] Another survey of attending physicians (n = 171) in Michigan EDs reported that 75% experienced a verbal assault and 28% a physical assault in the past 12 months; 82% were occasionally fearful of workplace violence.[12] An additional survey of 263 emergency medicine residents and attending physicians found that 78% of participants experienced a violent workplace act in the prior year and that workplace violence is experienced equally by men and women.[13] An ED census of at least 50,000 patients annually or an average waiting time of at least 2 hours is significantly associated with an increased incidence of violence.[14,15] The risk of workplace assault in the ED, however, exists across hospitals of all sizes and reflects the rate of violence in the community.[16] Despite these obvious risks, health care providers are typically not trained in the identification and management of combative patients.[13]

Patients armed with lethal weapons pose a serious threat to ED staff. The carriage of weapons in the ED population is estimated at approximately 4 to 8%.[17,18] One large urban hospital ED with a metal detector reported confiscation of an average of 5.4 weapons a day.[19] At this center, 27% of major trauma patients seen in the ED during a 14-year period were initially armed with lethal weapons (84% knives and 16% guns). The potential risk posed by concealed weapons also exists in pediatric EDs.[20] Unfortunately, prediction of weapons carriage in any particular patient is impossible.[21] Therefore, it is prudent to assume that all violent patients are armed until it is proved otherwise, especially those presenting with major trauma.

Identification of potentially violent patients is difficult; male gender, prior history of violence, and drug or ethanol abuse are the only positive predictors.[22-26] Ethnicity, diagnosis, age, marital status, and education are not reliable identifiers. A study conducted in an outpatient psychiatric setting found that the incidence of violent behavior occurring after psychiatric evaluation does not vary with the experience of the psychiatrist.[23] Actuarial prediction of patient violence in a 6-month period by use of criteria such as age, drug use, and prior history of violence is substantially more accurate than prediction of future violence by evaluating attending psychiatrists.[27] The prediction, prevention, and control of violent outbursts in the ED are difficult. Appreciation of the potential for violence, preparedness, and proper use of verbal techniques and physical or chemical restraints assist the patient while preventing injury.

PRINCIPLES OF DISEASE

Pathophysiology

The pathogenesis of violent behavior is conjectural. Potential causes include environmental, historical, interpersonal, biochemical, genetic, hormonal, neurotransmitter, and substance abuse disorders.[28-30] Psychiatric illness is also a risk factor, with schizophrenia (paranoid and nonparanoid), personality disorders, mania, and psychotic depression most frequently associated with violence.[26,29,31-33] Delusional schizophrenic patients become violent, believing that others are attempting to harm them. They may also have auditory hallucinations commanding harm to others. Antisocial and borderline personality disorder patients typically do not feel remorse for their violent actions. The patient with acute mania is unpredictably dangerous because of emotional lability, a situation in which pleasantness can quickly turn

Disclaimer: The views expressed herein are solely those of the authors and do not represent the official views of the Department of Defense or Army Medical Department.

www.ketabpezeshki.com 66485457-66963820

to aggression. Substance abuse disorders are consistently associated with violent behavior in both psychiatric and nonpsychiatric populations.[25,26,34-36] Biologically, the serotonin system controls aggression and inhibition, with diminished serotonergic function possibly disinhibiting aggression against self and others.[37-43] Generalized brain dysfunction may predispose patients to violence by disruption of the regulation of aggression, particularly in the prefrontal and temporal cortex.[28,42-44] Cerebral imaging documents both functional and structural impairments in violent criminals and antisocial patients.[42-46] Genetic and hormonal influences are also implicated in the neurobiology of aggression.[28,38,47]

MANAGEMENT

Risk Assessment

Evaluation of the combative patient begins with risk assessment and attention to safety measures. Violence often erupts after a period of mounting tension. The astute practitioner may identify verbal and nonverbal cues and subsequently have the opportunity to defuse the situation.[33,48-50] In a typical scenario, the patient first becomes angry, then resists authority, and finally becomes confrontational and violent. When physicians have a "gut feeling" that a dangerous situation may be developing, they should take appropriate precautions.[49,50] Violent behavior may also erupt without warning, especially in patients with an organic brain syndrome, so clinicians should not feel overly confident in their ability to sense impending danger.

An obviously angry ED patient should be considered potentially violent. Provocative behavior, angry demeanor, pacing, loud or pressured speech, tense posture, gripping arm rails intensely, frequently changing body position, pounding walls or throwing things, and clenched fists are all symptoms and signs of impending violence. To prevent escalation, the patient should be removed from contact with other belligerent accomplices as well as from other provocative patients. A quiet area with a window or direct observation is optimal. Because increased waiting times correlate positively with violent behavior, consider evaluating the potentially violent patient expeditiously to prevent escalation of aggression.[10,14,15] Often, the perception of preferential treatment will defuse the patient's anger.

All patients should be screened for weapons before the interview. The use of metal detection is ideal before ED entry. Patients brought to the ED by ambulance may bypass routine security booths and metal detectors.[51] The practice of undressing patients and placing them in a gown is useful both as a nonconfrontational search for weapons and for easy identification in the event of the patient's escape from the ED. Although screening and searching of patients for weapons may appear to be a violation of privacy, routine disarming of all ED patients results in an increased feeling of safety for both patients and staff.[18,52]

The ideal setting for the patient interview should emphasize privacy but not isolation.[31,50] Some EDs have seclusion rooms specifically designed for interview of potentially dangerous patients.[53] Security should be nearby and the door left open to facilitate both intervention and escape for the provider. The patient and interviewer may be seated roughly equidistant from the door, or the interviewer may sit between the patient and the door. Blocking of the door, however, poses a risk of harm to the clinician if the patient feels the urge to escape. Two exits should ideally be available, and doors should swing outward. The clinician should have unrestricted access to the door and never sit behind a desk. The room should not contain heavy or potentially dangerous objects that may be thrown. There ideally should be a mechanism to alert others of danger, such as a panic button or a code word or phrase that summons security (e.g., "I need Dr. Armstrong in here."). For personal protection, earrings, necklaces, and neckties should be removed. Personal accessories that may be used against the caregiver, such as a stethoscope or scissors, should be removed. The physician should be aware of any objects within the room or on the patient's body, such as pens, watches, or belts, that may be used as weapons.[48-50]

Verbal Management Techniques

The patient should be made as comfortable as possible, and the interviewer should adopt an honest and straightforward manner. In some cases, an agitated patient may be aware of the impulse control problem and welcome limit setting by the clinician (e.g., "I can help you with your problem, but I cannot allow you to continue threatening me or the ED staff."). The interviewer should act as an advocate for the patient. Offering a soft chair or something to eat or drink (not a hot liquid, which may be used as a weapon) may help establish trust. A significant percentage of patients relax at this point because offering food or drink appeals to their most basic human needs and builds trust. The interviewer should adopt a nonconfrontational demeanor and be an attentive and receptive listener without conveying weakness or vulnerability. The interviewer should respond verbally in a calm and soothing tone of voice. It is also important to stand at least an arm's length away and to avoid prolonged direct eye contact, approaching the patient from behind, or sudden movements.[48-50]

A key mistake in interviewing a potentially violent patient is failing to address the issue of violence directly.[23,48,49] The patient should be asked relevant questions about suicidal or homicidal ideations or plans, possession of weapons, history of violent behavior, and current use of intoxicants. Acknowledgment of the obvious (e.g., "You look angry.") may help the patient to begin sharing emotions. If the patient becomes more agitated, it is important to speak in a conciliatory manner and to offer supportive statements, such as "You obviously have a lot of will power and are good at controlling yourself," to help defuse the situation. If this is not successful, a respectful offer of medication or restraints to the patient if another health care provider is close by may prevent further escalation.

Counterproductive approaches to the combative patient include argumentation, machismo, and condescension.[48,49] These inappropriate strategies challenge patients to "prove themselves." An open threat to call security personnel also invites aggression. The clinician should be aware of her or his own reactions to the patient and avoid transference of anger. The deception of a patient (e.g., "I am sure you will be out of here in no time.") only invites violent consequences once the lie is uncovered. The unsuspecting nurse or colleague who follows the interviewer may be victimized. It is especially important not to deny or downplay threatening behavior. If verbal techniques are unsuccessful and escalation of violence occurs, the physician should leave the room and summon help.

Physical Restraints

Physical restraint should be considered when verbal techniques prove unsuccessful. The use of restraints can be humane and effective in facilitating diagnosis and treatment of the patient while preventing injury to the patient or medical staff.[48,54,55] The liability one incurs for restraining a patient against his or her will is negligible compared with the potential liability for allowing a patient to lose control and cause physical harm.[50]

Indications for emergency seclusion and restraint include the prevention of imminent harm to the patient, others, or the immediate environment and as part of an ongoing behavior treatment program.[48-50,56,57] Seclusion or restraint may be contraindicated because of the patient's clinical or medical condition. Seclusion should not be used in an unstable patient who requires close

www.ketabpezeshki.com 66485457-66963820

monitoring and should be avoided when the patient is suicidal, self-abusive, or self-mutilating or has had an intentional ingestion of drugs or poisons.[33,57] Restraints should not be applied for convenience or as a punitive response for disruptive behavior. If one is available, a colleague should document agreement with the application of restraints, mentioning the specific indications (e.g., "I restrained Mr. Smith because he told me he was going to beat me up and then took a swing at me." is preferable to "I restrained Mr. Smith because he was violent.").

The implementation of restraints should be systematic, and an ED protocol should be in place. This protocol begins when the examiner leaves the room after verbal techniques are unsuccessful. It may be helpful to consider the application of restraints as a procedure analogous to running an advanced cardiac life support code.[49] The restraint team ideally consists of at least five people, including a team leader. The leader, whether a physician, nurse, or security officer, will be the only person giving orders and should be the person with the most experience in implementing restraints. Before entering the room, the leader outlines the restraint protocol and warns of anticipated danger (e.g., the presence of objects that may be used as weapons). All team members should remove personal objects that the patient could use against them. If the patient is female, at least one member of the restraint team should be female to potentially mitigate allegations of sexual assault.

The team enters the room in force and displays a professional rather than threatening attitude. Many violent individuals calm down at this point as a large show of force protects their ego (e.g., "I would have fought back but there were too many against me."). The leader speaks to the patient in a calm and organized manner, explaining why restraints are needed and what the course of events will be (e.g., "You require a medical and psychiatric examination as well as treatment."). The patient is instructed to cooperate and to lie down to have restraints applied. Some patients are relieved at the protection to self and others afforded by restraints when they feel themselves losing control. Even if the patient suddenly appears less dangerous, however, once the decision to restrain is made, do not negotiate.

If physical force becomes necessary, one team member restrains a preassigned extremity by controlling the major joint (knee or elbow). The team leader controls the head. If the patient is armed, two mattresses can be used to charge and immobilize or sandwich the patient. Restraints are applied securely to each extremity and tied to the solid frame of the bed (not side rails, as later repositioning of side rails also repositions the patient's extremity). Leather is the optimal type of restraint because it is a physically stronger material and less constricting than typical soft restraints. For this reason, gauze should not be used. Soft restraints may help restrict extremity use in the semicooperative patient but are likely to be less effective in the truly violent patient who is continuing to struggle and attempt escape. If chest restraints are used, it is vital that adequate chest expansion for ventilation is ensured. The application of a soft Philadelphia collar to the patient's neck minimizes head banging and biting. Whenever possible, the treating physician should not actively participate in restraint application to preserve the physician-patient relationship. The restraining of patients on their sides helps prevent aspiration, although restraint supine with the head elevated is more comfortable and allows a more thorough medical examination while providing some protection against aspiration.[33,58] Once the patient is immobilized, announcing "the crisis is over" will have a calming effect on the restraint team and the patient.

After restraints are successfully applied, the patient should be monitored frequently and positions changed to prevent neurovascular sequelae such as circulatory obstruction, paresthesias, and rhabdomyolysis associated with continued combativeness. A standardized form should be completed for physically restrained patients. Documentation includes the specific indication for restraint and, ideally, colleagues' agreement that restraints are necessary.

Sudden, unexpected deaths occur in restrained patients.[59-64] Although healthy volunteers, when restrained and undergoing physical exertion, do not appear to experience clinically significant positional asphyxia,[65-67] the combative ED patient often suffers from other conditions that may predispose to increased morbidity. Patients who are cocaine or stimulant intoxicated or restrained in the prone position appear to be uniquely at risk.[59-64] Increased sympathetic tone and altered pain sensation allow exertion beyond normal physiologic limits in these patients. Sympathetic-induced vasoconstriction may impede clearance of metabolic waste products. Alteration of respiratory mechanics in an acidemic patient resulting from the position of restraint can be a contributing factor by impairment of respiratory compensation. As a general guideline, the prone restraint position should be avoided when possible and chemical sedation used when a patient continues to struggle against physical restraints.

The Joint Commission on Accreditation of Health Care Organizations has guidelines governing the use of restraint and seclusion for behavioral health patients. Educational materials and specific details about seclusion and restraint are available at www.jointcommission.org/. Several general essential elements to be provided in a restraint situation include the following:

Hospital policies and procedures guide appropriate and safe use of restraint.

The implementation of restraint or seclusion is limited to emergencies where imminent risk of harm exists to the patient or others.

Staff is trained and competent to apply restraint safely.

Staff is trained to minimize the use of restraint.

Patients in restraint are timely and regularly monitored.

Time-limited orders for restraint use are provided by licensed practitioners.

Medical records document that the use of restraint or seclusion is consistent with organizational policy.

Chemical Restraints

Chemical restraints should be considered alone or in conjunction with physical restraint in the management of an agitated or violent patient in the ED. A struggling patient who is physically restrained may have an increased risk of morbidity and mortality and may benefit from the calming effect of these medications. Chemical restraints subdue patients who may otherwise harm themselves or others and facilitates their medical evaluation and treatment. Clinical and administrative guidelines for their use are similar to those for the use of physical restraints. The use of medication to calm a patient may obscure the mental status examination and clinical diagnosis. This should be weighed, however, against the increased risk that both the patient and staff may face if such medication is withheld.

Several pharmaceutical agents can quickly achieve safe behavioral control, or "rapid tranquilization," of such a patient without oversedation. The ideal agent should be effective, safe and well tolerated, rapid in onset, titratable, and available through multiple routes of administration. In the ED, benzodiazepines and antipsychotics (also known as neuroleptics) are commonly used either alone or in combination for rapid tranquilization. The intramuscular route is often advantageous in the uncooperative and dangerous patient refusing an oral medication or an intravenous catheter. A chemical restraint should ideally be taken voluntarily by a patient as the offer of voluntary administration may restore some feeling of control and ease escalating agitation.[49,68-70] As with physical restraints, it is imperative that these patients be evaluated regularly for changes in their clinical status.

www.ketabpezeshki.com 66485457-66963820

Benzodiazepines, particularly lorazepam (Ativan) and midazolam (Versed), are often used in the ED for rapid tranquilization of an agitated or violent patient. Benzodiazepines enhance the activity of the major inhibitory neurotransmitter γ-aminobutyric acid to cause anxiolytic, anticonvulsant, and sedative effects. These agents are particularly preferred for the management of agitation caused by ethanol or sedative-hypnotic drug withdrawal as well as cocaine and sympathomimetic drug ingestions.[48,54] Although they are generally well tolerated, side effects of benzodiazepines include excessive sedation, ataxia, confusion, nausea, and respiratory depression, which may be amplified in the presence of concurrent alcohol and other depressant use.

Lorazepam is frequently preferred to other benzodiazepines because of its rapid onset of action, short half-life, route of elimination with no active metabolites, and effectiveness by oral, intramuscular (IM), or intravenous (IV) route of administration.[48,54,71] Recommended initial oral, IM, or IV doses of lorazepam range from 0.5 to 4 mg. Typical doses for chemical restraint in the ED begin at 1- to 2-mg increments intramuscularly or intravenously with upward titration as needed.[68,71] The onset of action after administration of lorazepam is generally 5 to 20 minutes if it is given intravenously or 15 to 30 minutes if it is given intramuscularly, with a duration of action of 6 to 8 hours.[54,68,72]

Midazolam is also an effective benzodiazepine for achievement of mild sedation and has a more rapid onset of action and a shorter duration of clinical effects than lorazepam. The intramuscular route is used widely to calm the agitated patient with a typical initial dose of 5 mg IM.[48,54] When it is administered intramuscularly, the medication usually takes effect in about 15 minutes with a mean duration of 2 hours.[48,54,73] In a comparison of midazolam 5 mg IM to lorazepam 2 mg IM and to the antipsychotic haloperidol 5 mg IM to sedate violent and agitated patients, all three showed similar efficacy, but midazolam demonstrated a more rapid onset of action and shorter duration of activity than the other two medications.[74] The choice of midazolam versus lorazepam should be determined by the duration of sedation desired.

Antipsychotic medications also play a prominent role in the chemical restraint of the violent ED patient. These medications include the older "typical" (or "classic") antipsychotics and the newer "atypical" antipsychotics. The precise mechanisms of action are unclear, but typical antipsychotics strongly block brain dopamine receptors, whereas the atypical antipsychotics less strongly and more specifically antagonize dopamine as well as serotonin receptors.[48,75] Both classes of antipsychotics have variable effects on other receptors, such as the adrenergic, cholinergic, and histaminic receptors.[75] The typical antipsychotics can be categorized in terms of their "potency," a description referring to the relative dosing of the medication and generally predictive of its side effect profile. The incidence of sedation, hypotension, and anticholinergic side effects is higher with the low-potency antipsychotics, whereas the incidence of extrapyramidal symptoms is greatest with the high-potency antipsychotics. Low-potency antipsychotics include chlorpromazine (Thorazine) and thioridazine (Mellaril), medium-potency antipsychotics include loxapine (Loxitane) and molindone (Moban), and high-potency antipsychotics include haloperidol (Haldol) and droperidol (Inapsine).

Of the older typical antipsychotics, the butyrophenones haloperidol and droperidol have been widely used in the emergency setting. Haloperidol is the most frequently administered antipsychotic to control the agitated patient in the ED.[48,69,70,76] It is available in oral, intramuscular, and intravenous preparations, although the commonly used intravenous route of administration is not approved by the Food and Drug Administration (FDA). Haloperidol is generally given in 2.5- to 10-mg IM doses (often 5 mg IM for the average adult), with half doses administered to the elderly and with repeated dosing every 20 to 60 minutes as needed.[48,54,71,77-79] Effects are usually seen by 30 minutes by the intramuscular route; the average patient requires fewer than three doses for the desired clinical effect.[54,71,79]

Droperidol has been commonly used at doses of 5 to 10 mg IM and 2.5 to 5 mg IV in a manner similar to haloperidol to control the agitated or combative patient.[48,80-83] Compared with haloperidol, droperidol appears to more rapidly reduce agitation at equal intramuscular dosing; it has a shorter duration of effect, more sedation, a larger incidence of orthostatic hypotension, and a lesser incidence of extrapyramidal symptoms.[78,81,84] Compared with midazolam 10 mg IM, droperidol 10 mg IM has an equally rapid onset of action and requires fewer additional doses for sedation.[85] The clinical use of droperidol decreased markedly after it was given a controversial black box warning in 2001 by the FDA for concern of QTc prolongation and torsades de pointes.[86-89]

Haloperidol is also associated with QTc prolongation and torsades de pointes.[90-93] It is prudent to use caution when these medications are administered to patients with other identified risk factors for or the known presence of existing QTc prolongation. In 2007 an FDA alert recommended electrocardiographic monitoring of patients receiving haloperidol intravenously to further minimize this risk.[94] If it is possible to obtain an electrocardiogram or to place the patient on a cardiac monitor before the administration of haloperidol, that should be done. If this is precluded by poor cooperation of the patient, it should be accomplished as soon as possible once the patient becomes more cooperative.

Common side effects of haloperidol and droperidol are sedation, orthostatic hypotension, and extrapyramidal symptoms. Extrapyramidal symptoms are thought to be due to mesolimbic dopamine receptor blockade, not dose related, and may occur immediately or days after medication administration.[78] Patients can have akathisia (extreme restlessness) and uncoordinated involuntary movements known as dystonia, including of the muscles of the mouth (buccolingual), neck (torticollis), back (opisthotonos), eyes (oculogyric crisis), and trunk (abdominopelvic). Treatment includes diphenhydramine 25 to 50 mg IV or IM or benztropine 1 to 2 mg IV or IM acutely and extended for 3 days to minimize symptom recurrence. Both haloperidol and droperidol have minimal anticholinergic properties and are often coadministered with diphenhydramine or benztropine, so they should not be used to control agitation in a patient with known anticholinergic intoxication. The use of these medications in the sympathomimetic-intoxicated patient is concerning because some antipsychotics may lower the seizure threshold. Seizure activity after administration of haloperidol or droperidol, however, appears to be a rare event, and in the animal model haloperidol is protective against seizures in cocaine intoxication and reduces mortality in amphetamine intoxication.[83,95,96]

Neuroleptic malignant syndrome is a rare and potentially lethal idiosyncratic reaction estimated to occur in 0.01 to 0.02% of patients receiving antipsychotic medications.[97] Characteristic symptoms include autonomic instability, hyperthermia, lead-pipe muscle rigidity, and altered mental status. If neuroleptic malignant syndrome occurs, further antipsychotics should be withheld and supportive treatment initiated. The role for any specific pharmacotherapy is uncertain.[97]

Chemical restraint with newer atypical antipsychotics is safe and effective in the treatment of agitated and violent patients, although their role in the treatment of the ED patient is still evolving.[71,78,98] Compared with the typical antipsychotics such as haloperidol, these medications appear to provide more tranquilization than sedation, have increased efficacy on both positive and negative symptoms in the outpatient, and have fewer extrapyramidal side effects.[71,78,99,100] Their use in the ED is facilitated by intramuscular and oral dissolving tablet formulations that may assist in a smoother transition to oral dosing in those patients requiring ongoing antipsychotic therapy.[78,101-103] Atypical antipsychotics

www.ketabpezeshki.com 66485457-66963820

such as olanzapine, ziprasidone, and aripiprazole are proving useful in the ED. Although the clinical significance is uncertain, all of these atypical antipsychotics carry a black box warning associating their use with an increased risk of death in elderly patients with dementia-related psychosis.

Olanzapine (Zyprexa) is readily available in intramuscular, oral, and oral dissolving tablet formulations and has a distinct calming effect in clinical practice.[104] It has FDA-approved indications for the treatment of agitation associated with bipolar I mania and schizophrenia. Intramuscular olanzapine has an onset of action of 15 to 45 minutes after the initial administration.[54] The intramuscular form is typically administered as an initial dose of 2.5 to 10 mg with one or two subsequent doses every 2 to 4 hours for a total maximum dose of 30 mg.[105,106] Although it is generally well tolerated, side effects include sedation, mild hypotension, and anticholinergic properties that can exacerbate existing anticholinergic intoxication. Olanzapine has minimal QTc-prolonging effects and a lesser occurrence of acute dystonia and akathisia compared with haloperidol.[107-109] Compared with lorazepam 2 mg IM, olanzapine 10 mg IM demonstrates more rapid effectiveness in reducing acute agitation in patients with bipolar mania.[110] In the acutely agitated schizophrenic patient, olanzapine IM at doses of 5 mg, 7.5 mg, and 10 mg is more rapidly effective than haloperidol 7.5 mg IM.[108,109] In acute dementia-related agitation, olanzapine IM at doses of 2.5 mg and 5 mg is well tolerated and as effective as lorazepam 1 mg IM.[111]

Ziprasidone (Geodon) is FDA approved for treatment of the agitated schizophrenic and bipolar manic patient, and IM doses of 10 to 20 mg are effective in reducing acute agitation in patients with underlying psychotic disorders.[112,113] By the intramuscular route, typical dosing is 10 mg every 2 hours or 20 mg every 4 hours (not to exceed 40 mg/day) with an onset of action of 15 to 30 minutes.[69,76] Ziprasidone is generally well tolerated, although side effects such as somnolence, dizziness, and headache are not uncommon.[112,114] Ziprasidone has more QTc-prolonging effects than olanzapine, haloperidol, or risperidone and is associated with torsades in polydrug exposures.[71,115-117] This QTc-prolonging effect may be clinically insignificant in most patients, but the use of ziprasidone is not recommended in those patients with significant risk for or known QTc prolongation.[102,118-120] An observational study of ziprasidone IM in a psychiatric ED reported rapid clinical efficacy and decreased total time in restraints compared with historical controls who had received various doses of medications including haloperidol and lorazepam.[121] A randomized double-blind trial comparing IM ziprasidone 20 mg, droperidol 5 mg, and midazolam 5 mg to treat undifferentiated agitation in the ED reported a relative delay of sedation onset with ziprasidone and a more frequent need for rescue medication to achieve sedation with midazolam-treated patients.[122]

Aripiprazole (Abilify) has FDA-approved indications for the treatment of agitation associated with the schizophrenia or bipolar disorders. Recommended doses for the acutely agitated emergency patient are 5.25 to 15 mg IM (often 9.75 mg) every 2 hours as needed (to a maximum daily dose of 30 mg).[123] Compared with haloperidol IM (6.5 or 7.5 mg) in the agitated schizophrenic patient, aripiprazole 9.75 mg IM is equivalent and well tolerated without oversedation and with a lower risk of extrapyramidal symptoms.[124-126] In the treatment of the agitated bipolar patient, aripiprazole IM (9.75 and 15 mg) has comparable efficacy to lorazepam 2 mg IM and a low risk of oversedation with the 9.75-mg dose.[127]

Benzodiazepines and typical antipsychotics are commonly used in combination to chemically restrain the agitated or violent patient. Lorazepam 2 mg and haloperidol 5 mg given together are more rapidly sedating than either medication alone, have fewer adverse effects such as extrapyramidal symptoms when combined, and are compatible within the same syringe for up to 16 hours.[70,128,129] This combination, given intramuscularly or intravenously and repeated every 30 minutes as needed, is often recommended to treat the combative patient with undifferentiated agitation and no contraindications to either of these medications.[70,71,76,78,102,130] Half doses should be administered to otherwise appropriate elder patients.

Assault and Hostage Situations

Unfortunately, physical assault may occur despite appropriate precautions and interventions. When it happens, maintain a sideward posture, keeping the arms ready for self-protection. If you are faced with a punch or a kick, deflect with an arm or a leg. If choking is attempted, tuck the chin in to protect the airway and carotids. If bitten, do not pull away but rather push toward the mouth and hold the nares shut to entice opening of the mouth. If threatened with a weapon, try to appear calm and comply with demands.[50] Adopt a nonthreatening posture and avoid sudden movements. Do not attempt to reach for the weapon. Avoid argument, despair, or whining. Attempt to establish a human connection with the hostage taker.[31,131] Offering to administer aid to other ill or injured hostages allows a hostage to appear less expendable. Do not bargain or make promises, and do not lie, as the consequences could be disastrous. Reassure the hostage taker that someone authorized to hear the complaint or demand should arrive promptly.[131] If a weapon is put down, do not reach for it but rather attempt to verbally resolve the crisis while awaiting the arrival of security personnel. Legal authorities can be called on to provide a professional hostage negotiator if one is needed.

Each hospital should have a plan of action for cases of extreme violence. The plan should include prevention and safety measures, a means for rapid notification of security and police personnel, evacuation plans, medical treatment, and crisis intervention.[50,131,132] A novel approach uses a violence management team trained in the preceding techniques to provide a mechanism for dealing with aggressive patients and protecting the staff.[133]

CLINICAL FEATURES

History and Physical Examination

Once combative patients are controlled, they need to be evaluated for organic causes of their agitated behavior. Separation of functional from organic disease is a challenging task complicated by the fact that many patients with psychiatric disorders suffer from organic medical disorders that may worsen their symptoms. Patients who exhibit violent behavior that is caused or exacerbated by an organic problem may rapidly deteriorate if the medical issues are not addressed in a timely fashion. A focused history and physical examination assist the physician in differentiating functional from organic illness.

Several historical features distinguish functional (psychiatric) from organic (medical) illness. Patients older than 40 years who have a new onset of psychiatric symptoms are more likely to have an organic cause.[134,135] Also, elders are at higher risk for organic delirium from medical illness or adverse medication reactions. Patients with a history of drug or ethanol abuse may exhibit violent behavior as a manifestation of an intoxication or withdrawal syndrome. The acute onset of agitated behavior as well as behavior that waxes and wanes over time suggests an organic origin. Most psychiatric patients are alert and oriented and have a past psychiatric history. Table 188-1 lists clues to distinguish functional from organic causes of violent behavior.

The history should include psychiatric, medical, family, and social information, including suicidal ideation, medication use, and any recent changes to prescribed medications. Family and friends can often provide valuable details as the agitated patient

www.ketabpezeshki.com 66485457-66963820

may be unreliable. When they are available, they should be interviewed independently from the patient. Medical records may detail medical and psychiatric history as well as prior history of violence. Drug and ethanol use is an important part of the history as substance abuse is highly correlated with violent behavior.

The patient should be asked for permission to perform a thorough physical examination to search for an organic cause of violent behavior and to uncover any resulting injury. Restraint of the patient may be necessary to accomplish even the most rudimentary physical examination. The importance of obtaining routine vital signs including temperature and performing a thorough mental status and neurologic examination cannot be overemphasized. Patients with persistently abnormal vital signs, a clouding of consciousness, or focal neurologic findings are more likely to suffer from organic disease and require further diagnostic evaluation. A careful examination should focus on the patient's general appearance (e.g., hygiene, nourishment, tremors) and vital signs, evidence of trauma or needle tracks, characteristic odors, neurologic and mental status, and signs of a possible toxidrome (Table 188-2).[136]

DIAGNOSTIC STRATEGIES

Although some authors advocate a standardized panel of laboratory and radiographic studies for patients with psychiatric symptoms, most recommend tailoring of diagnostic studies on the basis of clinical findings.[130,134,137-141]

A rapid blood glucose determination and pulse oximetry should be obtained for all combative patients. Patients younger than 40 years with a prior psychiatric history, normal physical examination findings including vital signs, calm demeanor, normal orientation, and no physical complaints are likely to require no further diagnostic testing.[139] Additional studies that may be useful in selected patients include serum electrolyte values, blood and urine toxicology screening, serum ethanol level, thyroid function panel, cranial imaging, and electroencephalography.[29,32,50,134] A lumbar puncture may be performed if a central nervous system infection is suggested. Specific medication levels may be determined when toxic levels would affect therapy. An electrocardiogram may be useful in elders and in the setting of a suggested intentional ingestion. Patients who may have intentionally ingested a toxic substance should also have aspirin and acetaminophen level measurements as these potentially fatal ingestions may be difficult to diagnose clinically.

An additional consideration in the diagnostic workup is the concern of the psychiatrist who will ultimately evaluate the patient. Although serum ethanol and toxicology screening may not significantly influence a patient's ED treatment, the psychiatrist may use them to assess the degree to which ethanol or drug use contributes to the patient's behavioral issues.[134,142-144] Ideally, an agreement on a diagnostic strategy should be reached between the psychiatrist and emergency physician before referral. Unnecessary diagnostic testing prolongs ED length of stay and delays definitive psychiatric care.

Table 188-1 Distinguishing Organic from Functional Causes of Violent Behavior

CLINICAL FEATURE	ORGANIC: Delirium	ORGANIC: Dementia	FUNCTIONAL
Onset	Acute	Gradual	Gradual
Age at onset	Any	>50 years	<40 years
Alertness	Altered	Normal	Normal or hyperalert
Orientation	Impaired	Normal	Normal
Hallucinations	Common; can be visual, auditory, or tactile	None	Auditory in schizophrenia, otherwise uncommon
Symptom picture	Fluctuating	Stable	Stable
Abnormal vital signs	Common	Uncommon	Uncommon
Psychiatric history	No	No	Yes

DIFFERENTIAL CONSIDERATIONS

Violent behavior often occurs in association with head trauma, hypoxia, hypoglycemia, electrolyte imbalance, infections (particularly herpes encephalitis), drug intoxication or withdrawal or adverse reaction, and metabolic and endocrine derangements.[31,50] Uncommon organic causes include seizures (e.g., temporal lobe, limbic), tumors (particularly those in the limbic system), limbic encephalitis, multiple sclerosis, porphyria, Wilson's disease, Huntington's disease, sleep disorders, hyperparathyroidism, and vitamin and mineral deficiencies (e.g., folate, vitamin B_{12}, niacin, and vitamin B_6).[145] In the ED setting, drug or ethanol intoxication and withdrawal are the most common diagnoses in combative patients.[33,58] The mnemonic FIND ME (*f*unctional, *i*nfectious, *n*eurologic, *d*rugs, *m*etabolic, *e*ndocrine) helps organize a diagnostic search for the cause of violence (Box 188-1).

Medical Clearance

The emergency physician often provides "medical clearance" for the psychiatric or combative patient, although medical clearance is a misnomer and the patient is not "cleared" of all possible

Table 188-2 Vital Signs and Toxic Syndromes

TOXIN	BP	P	RR	T	PUPIL SIZE	SKIN	EXAMPLE
Sympathomimetic	↑	↑	↑	↑	↑	Wet	Cocaine
Anticholinergic	↑/↓	↑	↑/↓	↑	↑	Dry	Diphenhydramine
Cholinergic	↑/↓	↑/↓	—	—	↓	Wet	Pesticides
Opiates	↓	↓	↓	↓	↓	—	Morphine
Sedatives	↓	↓	↓	↓	↑/↓	—	Lorazepam
Withdrawal (ethanol, sedative-hypnotics)	↑	↑	↑	↑	↑	Wet	Benzodiazepine withdrawal

Modified from Olshaker JS, Browne B, Jerrard DA, Prendergast H, Stair TO: Medical clearance and screening of psychiatric patients in the emergency department. Ann Emerg Med 4:124, 1997.
BP, blood pressure; *P*, pulse; *RR*, respiratory rate; *T*, temperature; ↑, increased; ↓, decreased; —, no change.

www.ketabpezeshki.com 66485457-66963820

Box 188-1 Problems Associated with Violence

Psychiatric
Schizophrenia
Paranoid ideation
Catatonic excitement
Mania
Personality disorders
- Borderline
- Antisocial
- Delusional depression
- Post-traumatic stress disorder
- Decompensating obsessive-compulsive disorders

Homosexual panic

Situational Frustration
Mutual hostility
Miscommunication
Fear of dependence or rejection
Fear of illness
Guilt about disease process

Antisocial Behavior
Violence with no associated medical or psychiatric explanation (these patients may be managed by the police or security)

Organic
Diseases
Delirium
Dementia
Trauma
Central nervous system infection
Seizure
Neoplasm
Cerebrovascular accident
Vascular malformation
Hypoglycemia
Hypoxia
Acquired immunodeficiency syndrome (AIDS)
Electrolyte abnormality
Hypothermia or hyperthermia
Anemia
Vitamin deficiency
Endocrine disorder

Drugs
Unanticipated reaction to prescribed medication (especially sedatives in brain-injured or elderly patients)
Alcohol (intoxication and withdrawal)
Amphetamines
Cocaine
Sedative-hypnotics (intoxication or withdrawal)
Phencyclidine (PCP)
Lysergic acid diethylamide (LSD)
Anticholinergics
Aromatic hydrocarbons (e.g., glue, paint, gasoline)
Steroids

medical conditions on completion of the ED evaluation.[137,146] In addition, there is no standard process for the provision of what may be more accurately termed a focused medical assessment.[130]

The incidence of organic disease in patients presenting with psychiatric complaints ranges from 24 to 80%.[134,147,148] The more relevant issue for the emergency physician is to detect medical problems that are contributing to the patient's violent behavior. Misattribution of aberrant organic behavior in a patient with known psychiatric disease is a common cause of litigation.[149] Most psychiatrists rely on the emergency physician's medical assessment of the patient. Low-risk patients with functional illness can be rapidly referred for psychiatric evaluation once they are calm and cooperative with a therapeutic psychiatric interview. Patients at higher risk for an acute organic illness require further diagnostic studies.

Once the medical screening evaluation is completed, the findings should be communicated to the consulting psychiatrist. The medical record should reflect that the evaluation shows no evidence that an acute medical condition is contributing to the patient's behavior. If the cause of the patient's violent behavior is drug or ethanol intoxication, the patient should be observed until a therapeutic interview can be conducted by the psychiatrist. Alternatively, the patient may be transported to a facility where observation can occur until the effects of the intoxicants have abated.

Preparing the Emergency Department to Prevent Violence

The risk of violence in the ED should be minimized in a cost-effective manner without creating a hostile or negative environment. The prevention of violence is best accomplished by development of a system that includes ongoing staff education, adequate personnel, and a well-designed physical structure.

Security Personnel

A well-trained and responsive security force is a key element of any hospital security system. Such personnel are expensive, and their expertise is often sacrificed quickly during budget curtailments, so decisions about the type and number of guards are often made on an economic basis. The use of guns by hospital security personnel is controversial, as is allowing other armed law enforcement officers into the ED. Other devices, such as the Taser, stun gun, and mace, are suggested as less lethal alternatives to guns.

Patient Searches

Searching of patients for weapons as they enter the ED is permissible when it is performed in a nondiscriminatory manner.[131] Warning signs should be prominently displayed, perhaps reading "For the safety of patients and staff, individuals entering the ED may be screened for weapons." Almost all patients and families will cooperate with searches and may actually feel safer as a result.[52] Clear written policies about searches and disposal of contraband should be distributed to the staff and closely followed.

Alarm Systems

The goal of any alarm system is to obtain rapid appropriate response with a minimum of false alarms. A tiered alarm system is usually best. Panic buttons in each room activate a central buzzer in the department. Several designated ED personnel respond initially and then judge the level of response needed. Every ED should have at least one telephone with a direct line to police or security in case additional personnel are deemed necessary. A verbal code (e.g., "Dr. Armstrong to room 9") is also a useful adjunct.[50]

Limited Access to the Emergency Department

Control of flow into the ED can be an effective method of preventing violent acts. High-risk departments should limit access to one or two entrances, especially during the evening hours. Bulletproof glass barriers and buzzer access systems are useful as well.

Use of a Designated Room

The American College of Emergency Physicians recommends that most EDs contain at least one secure examination room with

www.ketabpezeshki.com 66485457-66963820

shatterproof ceiling lights, solid ceiling, heavy indestructible chairs, well-secured restraint bed, two doors that can be locked from the outside, and emergency distress button that can be activated unobtrusively.[131] If it is desired, this room can be set up for video monitoring by security or ED staff. One large urban county hospital with a high incidence of violent behavior in the ED is equipped with a large security force, metal detectors, bulletproof Plexiglas triage area, keypad security entry, controlled entryway into the ED, and metal bars to prohibit cars from driving into the department.[19] This hospital reported no occurrence of weapons-related violence or injury in the ED after these measures were implemented.

Prevention

The concepts of primary, secondary, and tertiary prevention of violence can be applied to the ED environment.[14] Primary prevention refers to trying to control those factors that encourage the development of frustration and aggression. Long waiting times are associated with development of violent behavior. Attempts to shorten waiting times and to make the waiting room environment as pleasant as possible may diminish previolent aggression. The presence of surveillance cameras and a visible security force also act as deterrents.

Secondary prevention of violence involves response to previolent agitation and aggression. Successful intervention involves the recognition of risk and implementation of de-escalation techniques. Staff should be trained to recognize previolent individuals who should be seen in a timely manner. The aura of preferential treatment often defuses the situation.[133] Training of staff in techniques for management of violence leads to increased staff confidence and comfort while decreasing the rate of aggressive incidents.[150,151]

Tertiary prevention refers to limitation of the actual act of violence itself once it has occurred. Physical and chemical restraints are used, and security and police intervention are often needed. Protocols for dealing with the violent patient are important to minimize risks to the patient and staff. Enhanced security measures may be indicated in an ED with substantial risk for violence.

Violence is increasingly a major public health issue, with increased focus on improving surveillance and universal preventive measures to target large populations.[152-154] Physicians are increasingly aware of their role in reducing violence, and the ED is uniquely positioned to have an impact on at-risk populations. Proposed agendas for violence prevention for emergency medicine include improvements in medical education, research, and clinical practice as well as involvement with public education and advocacy.[155,156] Resources, particularly those aimed at youth violence intervention and prevention in the medical setting, are available to assist health care providers in the ED.[154]

KEY CONCEPTS

- ED staff should be trained to recognize potentially violent individuals and to intervene with de-escalation techniques.
- The ED should have a written plan of action to deal with violence that integrates the activities of ED staff, hospital administration, security, and local authorities.
- The emergency physician should be familiar with the use of physical and chemical restraints.
- The possibility of an organic (medical) cause of aggressive behavior should be considered in all violent patients, even those with known psychiatric disease.
- ED leadership should be proactive in attempting to create an environment that is safe and supportive for both patients and staff.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Vyrostek SB, Annest JL, Ryan GW: Surveillance for fatal and nonfatal injuries—United States, 2001. *MMWR Surveill Summ* 2004; 53:1.
2. Karch DL, Dahlberg LL, Patel N: Surveillance for violent deaths—National Violent Death Reporting System, 16 States, 2007. *MMWR Surveill Summ* 2010; 59:1.
3. Weiner J, et al: Reducing firearm violence: A research agenda. *Inj Prev* 2007; 13:80.
4. Reiss AJ, Roth JA: *Understanding and Preventing Violence*. Washington, DC: National Academy Press; 1993.
5. Krug EG, Powell KE, Dahlberg LL: Firearm related deaths in the United States and 35 other high and upper middle income countries. *Int J Epidemiol* 1998; 27:214.
6. Adams PF, Benson V: Current estimates from the National Health Interview Survey. *Vital Health Stat* 1991; 10:184.
7. Coben JH, Steiner CA: Hospitalization for firearm-related injuries in the United States, 1997. *Am J Prev Med* 2003; 24:1.
8. Cook PJ, Lawrence BA, Ludwig J, Miller TR: The medical costs of gunshot injuries in the United States. *JAMA* 1999; 282:447.
9. DiScala C, Sege R: Outcomes in children and young adults who are hospitalized for firearms-related injuries. *Pediatrics* 2004; 113:1306.
10. National Institute for Occupational Safety and Health (NIOSH): *Violence: Occupational Hazards in Hospitals, DHHS (NIOSH) Publication No. 2002-101*, 2002. Available at www.cdc.gov/niosh. Accessed 2011.
11. Gates DM, Ross CS, McQueen L: Violence against emergency department workers. *J Emerg Med* 2006; 31:331.
12. Kowalenko T, Walters BL, Khare RK, Compton S: Workplace violence: A survey of emergency physicians in the state of Michigan. *Ann Emerg Med* 2005; 46:142.
13. Behnam M, Tillotson RD, Davis SM, Hobbs GR: Violence in the emergency department: A national survey of emergency medicine residents and attending physicians. *J Emerg Med* 2011; 40:565.
14. Lavoie FW, Carter GL, Danzl DF, Berg RL: Emergency department violence in United States teaching hospitals. *Ann Emerg Med* 1988; 17:1227.
15. McAneney CM, Shaw KN: Violence in the pediatric emergency department. *Ann Emerg Med* 1994; 23:1248.
16. Blando JD, et al: Emergency department security programs, community crime, and employee assaults. *J Emerg Med* 2012; 42:329.
17. McNeil DE, Binder RL: Patients who bring weapons to the psychiatric emergency room. *J Clin Psychiatry* 1987; 48:230.
18. McCulloch LE, McNiel DE, Binder RL, Hatcher C: Effects of a weapon screening procedure in a psychiatric emergency room. *Hosp Community Psychiatry* 1986; 37:837.
19. Ordog GJ, Wasserberger J, Ordog C, Ackroyd G, Atluri S: Weapons carriage among major trauma victims in the emergency department. *Acad Emerg Med* 1995; 2:109.
20. Simon HK, Khan NS, Delgado CA: Weapons detection at two urban hospitals. *Pediatr Emerg Care* 2003; 19:248.
21. Anderson AA, Ghali AY, Bansil RK: Weapon carrying among patients in a psychiatric emergency room. *Hosp Community Psychiatry* 1989; 40:845.
22. Cherry D, Annest JL, Mercy JA, Kresnow M, Pollock DA: Trends in fatal and nonfatal firearm-related injury rates in the United States, 1985-1995. *Ann Emerg Med* 1998; 32:51.
23. Dubin WR, Wilson SJ, Mercer C: Assaults against psychiatrists in outpatient settings. *J Clin Psychiatry* 1988; 49:339.
24. Beech DJ, Mercadel R: Correlation of alcohol intoxication with life-threatening assaults. *J Natl Med Assoc* 1998; 90:761.
25. Scott KD, Sachafer J, Greenfield TK: The role of alcohol in physical assault perpetration and victimization. *J Stud Alcohol* 1999; 60:528.
26. Citrome L, Volavka J: Violent patients in the emergency setting. *Psychiatr Clin North Am* 1999; 22:789.
27. Gardner W, Lidz CW, Mulvey EP, Shaw EC: Clinical versus actuarial predictions of violence of patients with mental illnesses. *J Consult Clin Psychol* 1996; 64:602.
28. Miczek KA, et al: Neurobiology of escalated aggression and violence. *J Neurosci* 2007; 27:11803.
29. Tardiff K: *Diagnosis and management of violent patients*. In: Michels R, Cavenar JD, Cooper AM, et al, eds. Psychiatry, vol 3. Philadelphia: Lippincott-Raven; 1997:1-17.
30. Volavka J: The neurobiology of violence: An update. *J Neuropsychiatry Clin Neurosci* 1999; 11:307.
31. Tardiff K: The current state of psychiatry in the treatment of violent patients. *Arch Gen Psychiatry* 1992; 49:293.
32. Tardiff K: Unusual diagnoses among violent patients. *Psychiatr Clin North Am* 1998; 21:567.
33. Dubin WR, Weiss KJ: *Emergency psychiatry*. In: Michels R, Cavenar JD, Cooper AM, et al, eds. Psychiatry, vol 2. Philadelphia: Lippincott-Raven; 1997:1-15.
34. Fazel S, Långström N, Hjern A, Grann M, Lichtenstein P: Schizophrenia, substance abuse, and violent crime. *JAMA* 2009; 301:2016.
35. Arboleda-Florez J: Mental illness and violence: An epidemiological appraisal of the evidence. *Can J Psychiatry* 1998; 43:989.
36. Eronen M, Angermeyer NC, Schulze B: The psychiatric epidemiology of violent behaviour. *Soc Psychiatry Psychiatr Epidemiol* 1998; 33(Suppl 1):S13.
37. Caramaschi D, de Boer SF, de Vries H, Koolhaas JM: Development of violence in mice through repeated victory along with changes in prefrontal cortex neurochemistry. *Behav Brain Res* 2008; 189:263.
38. Popova NK: From gene to aggressive behavior: The role of brain serotonin. *Neurosci Behav Physiol* 2008; 38:471.
39. Mann JJ, Currier D: A review of prospective studies of biologic predictors of suicidal behavior in mood disorders. *Arch Suicide Res* 2007; 11:3.
40. Coccaro EF, Lee R, Kavoussi RJ: Aggression, suicidality, and intermittent explosive disorder: Serotonergic correlates in personality disorder and healthy control subjects. *Neuropsychopharmacology* 2010; 35:435.
41. Jokinen J, Nordström AL, Nordström P: Cholesterol, CSF 5-HIAA, violence and intent in suicidal men. *Psychiatry Res* 2010; 178:217.
42. Meyer JH, et al: Serotonin$_{2A}$ receptor binding potential in people with aggressive and violent behaviour. *J Psychiatry Neurosci* 2008; 33:499.
43. Seo D, Patrick CJ, Kennealy PJ: Role of serotonin and dopamine system interactions in the neurobiology of impulsive aggression and its comorbidity with other clinical disorders. *Aggress Violent Behav* 2008; 13:383.
44. Damasio AR, Tranel D, Damasio H: Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. *Behav Brain Res* 1990; 41:81.
45. Muller JL, Sommer M, Dohnel K, et al: Disturbed prefrontal and temporal brain function during emotion and cognition interaction in criminal psychopathy. *Behav Sci Law* 2008; 26:131.
46. Yang Y, Glenn AL, Raine A: Brain abnormalities in antisocial individuals: Implications for the law. *Behav Sci Law* 2008; 26:65.
47. Siever LJ: Neurobiology of aggression and violence. *Am J Psychiatry* 2008; 165:429.
48. Rossi J, Swan MC, Isaacs ED: The violent or agitated patient. *Emerg Med Clin North Am* 2010; 28:235.
49. Petit JR: Management of the acutely violent patient. *Psychiatr Clin North Am* 2005; 28:701.
50. Rice MM, Moore GP: Management of the violent patient: Therapeutic and legal considerations. *Emerg Med Clin North Am* 1991; 9:13.
51. Rankins RC, Hendey GW: Effect of a security system on violent incidents and hidden weapons in the emergency department. *Ann Emerg Med* 1999; 33:676.
52. Mattox EA, Wright SW, Bracikowski AC: Metal detectors in the pediatric emergency department: Patron attitudes and national prevalence. *Pediatr Emerg Care* 2000; 16:163.
53. Downey LV, Zun LS, Gonzales SJ: Frequency of alternative to restraints and seclusion and uses of agitation reduction techniques in the emergency department. *Gen Hosp Psychiatry* 2007; 29:470.
54. Coburn VA, Mycyk MB: Physical and chemical restraints. *Emerg Med Clin North Am* 2009; 27:655.
55. Zun LS: A prospective study of the complication rate of use of patient restraint in the emergency department. *J Emerg Med* 2003; 24:119.
56. Masters KJ, et al: Summary of the practice parameter for the prevention and management of aggressive behavior in child and adolescent psychiatric institutions with special reference to seclusion and restraint. *J Am Acad Child Adolesc Psychiatry* 2001; 40:1356.
57. Baron DA, Dubin WR, Ning Autumn: *Other psychiatric emergencies*. In: Sadock BJ, Sadock VA, Ruiz P, eds. *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*, 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:2737-2738.
58. Lavoie FW: Consent, involuntary treatment, and the use of force in an urban emergency department. *Ann Emerg Med* 1992; 21:25.
59. Otahbachi M, Cevik C, Bagdure S, Nugent K: Excited delirium, restraints, and unexpected death: A review of pathogenesis. *Am J Forensic Med Pathol* 2010; 31:107.
60. Grant JR, et al: Death in custody: A historical analysis. *J Forensic Sci* 2007; 52:1177.

www.ketabpezeshki.com 66485457-66963820

61. Stratton SJ, Rogers C, Brickett K, Gruzinski G: Factors associated with sudden death of individuals requiring restraint for excited delirium. *Am J Emerg Med* 2001; 19:187.
62. Hick JL, Smith SW, Lynch MT: Metabolic acidosis in restraint-associated cardiac arrest: A case series. *Acad Emerg Med* 1999; 6:239.
63. Reay DT, Fligner CL, Stilwell AD, Arnold J: Positional asphyxia during law enforcement transport. *Am J Forensic Med Pathol* 1992; 13:90.
64. Pollanen MS, Chaisson DA, Cairns JT, Young GJ: Unexpected death related to restraint for excited delirium: A retrospective study of deaths in police custody and in the community. *CMAJ* 1998; 158:1603.
65. Michalewicz BA, et al: Ventilatory and metabolic demands during aggressive physical restraint in healthy adults. *J Forensic Sci* 2007; 52:171.
66. Chan TC, Neuman T, Clausen J, Eisele J, Vilke GM: Weight force during prone restraint and respiratory function. *Am J Forensic Med Pathol* 2004; 25:185.
67. Chan TC, Vilke GM, Neuman T, Clausen JL: Restraint position and positional asphyxia. *Ann Emerg Med* 1997; 30:578.
68. Adimando AJ, Poncin YB, Baum CR: Pharmacological management of the agitated pediatric patient. *Pediatr Emerg Care* 2010; 26:856.
69. Zimbroff DL: Pharmacological control of acute agitation: Focus on intramuscular preparations. *CNS Drugs* 2008; 22:199.
70. Yildiz A, Sachs GS, Turgay A: Pharmacological management of agitation in emergency settings. *Emerg Med J* 2003; 20:339.
71. Battaglia J: Pharmacological management of acute agitation. *Drugs* 2005; 65:1207.
72. Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds: *Lexi-Comp's Drug Information Handbook 2010-2011: A Comprehensive Resource for All Clinicians and Healthcare Professionals*, 19th ed. Hudson, Ohio: Lexi-Comp; 2010:929-931.
73. Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds: *Lexi-Comp's Drug Information Handbook 2010-2011: A Comprehensive Resource for All Clinicians and Healthcare Professionals*, 19th ed. Hudson, Ohio: Lexi-Comp; 2010:1014-1016.
74. Nobay F, Simon BC, Levitt MA, Dresden GM: A prospective, double-blind, randomized trial of midazolam versus haloperidol versus lorazepam in the chemical restraint of violent and severely agitated patients. *Acad Emerg Med* 2004; 11:744.
75. Horacek J, et al: Mechanism of action of atypical antipsychotic drugs and the neurobiology of schizophrenia. *CNS Drugs* 2006; 20:389.
76. Foley S: Short-term pharmaceutical management of the violent/aggressive patient in the emergency department. *J Emerg Nurs* 2010; 36:504.
77. Richards JR, Derlet R, Dundan D: Chemical restraint for the agitated patient in the emergency department: Lorazepam versus droperidol. *J Emerg Med* 1998; 16:567.
78. Currier GW, Trenton A: Pharmacological treatment of psychotic agitation [comment]. *CNS Drugs* 2002; 16:219.
79. Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds: *Lexi-Comp's Drug Information Handbook 2010-2011: A Comprehensive Resource for All Clinicians and Healthcare Professionals*, 19th ed. Hudson, Ohio: Lexi-Comp; 2010:731-732.
80. Dubin WR, Feld JA: Rapid tranquilization of the violent patient. *Am J Emerg Med* 1989; 7:313.
81. Thomas HJ, Schwartz E, Petrilli R: Droperidol versus haloperidol for chemical restraint of agitated and combative patients. *Ann Emerg Med* 1992; 21:407.
82. Rosen CL, et al: The efficacy of intravenous droperidol in the prehospital setting. *J Emerg Med* 1996; 15:13.
83. Chase PB, Biros MH: A retrospective review of the use and safety of droperidol in a large, high-risk, inner-city emergency department patient population. *Acad Emerg Med* 2002; 9:1402.
84. Resnick M, Burton BT: Droperidol vs. haloperidol in the initial management of acutely agitated patients. *J Clin Psychiatry* 1984; 45:298.
85. Isbister GK, et al: Randomized controlled trial of intramuscular droperidol versus midazolam for violence and acute behavioral disturbance: The DORM study. *Ann Emerg Med* 2010; 56:392.
86. U.S. Food and Drug Administration: *Medical Product Safety Information, 2001 Safety Alerts: Inapsine (droperidol)*. Available at www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm172364.htm. Accessed 2011.
87. Kao LW, Kirk MA, Evers SJ, Rosenfeld SH: Droperidol, QT prolongation, and sudden death: What is the evidence? *Ann Emerg Med* 2003; 41:546.
88. McCormick CG: FDA alert: Current FDA report on droperidol status and basis for the "black box" warning. *Am Soc Anesthesiol News* 2002; 66:19.
89. Shale JH, Shale CM, Mastin WD: A review of the safety and efficacy of droperidol for the rapid sedation of severely agitated and violent patients. *J Clin Psychiatry* 2003; 64:500.
90. Lawrence KR, Nasraway SA: Conduction disturbances associated with administration of butyrophenone antipsychotics in the critically ill: A review of the literature. *Pharmacotherapy* 1997; 17:531.
91. Wilt JL, Minnema AM, Johnson RF, Rosenblum AM: Torsade de pointes associated with the use of intravenous haloperidol. *Ann Intern Med* 1993; 119:391.
92. Tisdale JE, Rasty S, Padhi ID, Sharma ND, Rosman H: The effect of intravenous haloperidol on QT interval dispersion in critically ill patients: Comparison with QT interval prolongation for assessment of risk of torsades de pointes. *J Clin Pharmacol* 2001; 41:1310.
93. Sharma ND, Rosman HS, Padhi ID, Tisdale JE: Torsades de pointes associated with intravenous haloperidol in critically ill patients. *Am J Cardiol* 1998; 81:238.
94. U.S. Food and Drug Administration: *FDA Alert: Haloperidol. Information for Health Care Providers*. Available at www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm085203.htm. Accessed 2011.
95. Branney SW, Colwell CB, Aschbrenner JK, Pons PT: Safety of droperidol for sedating out-of-control ED patients. *Acad Emerg Med* 1996; 3:527.
96. Derlet RW, Albertson TE, Rice P: The effect of haloperidol in cocaine and amphetamine intoxication. *J Emerg Med* 1989; 7:633.
97. Seitz DP, Gill SS: Neuroleptic malignant syndrome complicating antipsychotic treatment of delirium or agitation in medical and surgical patients: Case reports and a review of the literature. *Psychosomatics* 2009; 50:8.
98. Currier GW, et al: Safety of medications used to treat acute agitation. *J Emerg Med* 2004; 27:S19.
99. Rund DA, Ewing JD, Mitzel K, Votolato N: The use of intramuscular benzodiazepines and antipsychotic agents in the treatment of acute agitation or violence in the emergency department. *J Emerg Med* 2006; 31:317.
100. Currier GW: Atypical antipsychotic medications in the psychiatric emergency service. *J Clin Psychiatry* 2000; 61:21.
101. Currier GW, et al: Novel therapies for treating acute agitation. *J Emerg Med* 2004; 27:S13.
102. Bellnier TJ: Continuum of care: Stabilizing the acutely agitated patient. *Am J Health Syst Pharm* 2002; 59:S12.
103. Currier GW, Medori R: Orally versus intramuscularly administered antipsychotic drugs in psychiatric emergencies. *J Psychiatr Pract* 2006; 12:30.
104. Battaglia J, Lindborg SR, Alaka K, Meehan K, Wright P: Calming versus sedative effects of intramuscular olanzapine in agitated patients. *Am J Emerg Med* 2003; 21:192.
105. Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds: *Lexi-Comp's Drug Information Handbook 2010-2011: A Comprehensive Resource for All Clinicians and Healthcare Professionals*, 19th ed. Hudson, Ohio: Lexi-Comp; 2010:1119-1121.
106. Wagstaff AJ, Easton J, Scott LJ: Intramuscular olanzapine: A review of its use in the management of acute agitation. *CNS Drugs* 2005; 19:147.
107. Lindborg SR, Beasley CM, Alaka K, Taylor CC: Effects of intramuscular olanzapine vs. haloperidol and placebo on QTc intervals in acutely agitated patients. *Psychiatry Res* 2003; 119:113.
108. Breier A, et al: A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia [comment]. *Arch Gen Psychiatry* 2002; 59:441.
109. Wright P, et al: Double-blind, placebo-controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation in schizophrenia. *Am J Psychiatry* 2001; 158:1149.
110. Meehan K, et al: A double-blind, randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania. *J Clin Psychopharmacol* 2001; 21:389.
111. Meehan KM, et al: Comparison of rapidly acting intramuscular olanzapine, lorazepam, and placebo: A double-blind, randomized study in acutely agitated patients with dementia. *Neuropsychopharmacology* 2002; 26:494.
112. Daniel DG, Potkin SG, Reeves KR, Swift RH, Harrigan EP: Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: A double-blind, randomized trial. *Psychopharmacology (Berl)* 2001; 155:128.

www.ketabpezeshki.com 66485457-66963820

113. Lesem MD, Zajecka JM, Swift RH, Reeves KR, Harrigan EP: Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients. *J Clin Psychiatry* 2001; 62:12.
114. Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds: *Lexi-Comp's Drug Information Handbook 2010-2011: A Comprehensive Resource for All Clinicians and Healthcare Professionals*, 19th ed. Hudson, Ohio: Lexi-Comp; 2010:1643-1646.
115. Heinrich TW, Biblo LA, Schneider J: Torsades de pointes associated with ziprasidone. *Psychosomatics* 2006; 47:264.
116. Manini AF, Raspberry D, Hoffman RS, Nelson LS: QT prolongation and torsades de pointes following overdose of ziprasidone and amantadine. *J Med Toxicol* 2007; 3:178.
117. Klein-Schwartz W, Lofton AL, Benson BE, Spiller HA, Crouch BI: Prospective observational multi–poison center study of ziprasidone exposures. *Clin Toxicol (Phila)* 2007; 45:782.
118. Blair J, Scahill L, State M, Martin A: Electrocardiographic changes in children and adolescents treated with ziprasidone: A prospective study. *J Am Acad Child Adolesc Psychiatry* 2005; 44:73.
119. Miceli JJ, et al: Effects of oral ziprasidone and oral haloperidol on QTc interval in patients with schizophrenia or schizoaffective disorder. *Pharmacotherapy* 2010; 30:127.
120. Taylor D: Ziprasidone in the management of schizophrenia: The QT interval issue in context. *CNS Drugs* 2003; 17:423.
121. Preval H, Klotz SG, Southard R, Francis A: Rapid-acting IM ziprasidone in a psychiatric emergency service: A naturalistic study. *Gen Hosp Psychiatry* 2005; 27:140.
122. Martel M, Sterzinger A, Miner J, Clinton J, Biros M: Management of acute undifferentiated agitation in the emergency department: A randomized double-blind trial of droperidol, ziprasidone, and midazolam. *Acad Emerg Med* 2005; 12:1167.
123. Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds: *Lexi-Comp's Drug Information Handbook 2010-2011: A Comprehensive Resource for All Clinicians and Healthcare Professionals*, 19th ed. Hudson, Ohio: Lexi-Comp; 2010:131-134.
124. Andrezina R, et al: Intramuscular aripiprazole for the treatment of acute agitation in patients with schizophrenia or schizoaffective disorder: A double-blind, placebo-controlled comparison with intramuscular haloperidol. *Psychopharmacology (Berl)* 2006; 188:281.
125. Andrezina R, et al: Intramuscular aripiprazole or haloperidol and transition to oral therapy in patients with agitation associated with schizophrenia: Sub-analysis of a double-blind study. *Curr Med Res Opin* 2006; 22:2209.
126. Tran-Johnson TK, et al: Efficacy and safety of intramuscular aripiprazole in patients with acute agitation: A randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2007; 68:111.
127. Zimbroff DL, et al: Management of acute agitation in patients with bipolar disorder: Efficacy and safety of intramuscular aripiprazole. *J Clin Psychopharmacol* 2007; 27:171.
128. Battaglia J, et al: Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double blind, emergency department study. *Am J Emerg Med* 1997; 15:335.
129. Trissel L: *Handbook on Injectable Drugs*, 10th ed. Bethesda, Md: American Society of Health System Pharmacists; 1998.
130. Lukens TW, et al: Clinical policy: Critical issues in the diagnosis and management of the adult psychiatric patient in the emergency department. *Ann Emerg Med* 2006; 47:79.
131. *Emergency Department Violence: Prevention and Management*. Dallas: American College of Emergency Physicians; 1997.
132. Walsh-Kelly CM, Straid R: Impact of violence and the emergency department response to victims and perpetrator. *Pediatr Clin North Am* 1998; 45:449.
133. Brayley J, Lange R, Baggoley C, Bond M, Harvey P: The violence management team: An approach to aggressive behavior in a general hospital. *Med J Aust* 1994; 161:254.
134. Williams ER, Shepherd SM: Medical clearance of psychiatric patients. *Emerg Med Clin North Am* 2000; 18:185.
135. Reeves RR, Pendarvis EJ, Kimble R: Unrecognized medical emergencies admitted to psychiatric units. *Am J Emerg Med* 2000; 18:390.
136. Flomenbaum NE, Goldfrank LR, Hoffman RS, et al, eds: *Vital signs and toxic syndromes*. In: *Goldfrank's Toxicologic Emergencies*. New York: McGraw-Hill; 2006:37-41.
137. Henneman PL, Mendoza R, Lewis RJ: Prospective evaluation of emergency department medical clearance [comment]. *Ann Emerg Med* 1994; 24:672.
138. Herbert M: Assessment for medical clearance. *Ann Emerg Med* 1995; 25:852.
139. Korn CS, Currier GW, Henderson SO: "Medical clearance" of psychiatric patients without medical complaints in the emergency department. *J Emerg Med* 2000; 18:173.
140. Olshaker JS, Browne B, Jerrard DA, Prendergast H, Stair TO: Medical clearance and screening of psychiatric patients in the emergency department. *Acad Emerg Med* 1997; 4:124.
141. Janiak BD, Atteberry S: Medical clearance of the psychiatric patient in the emergency department. *J Emerg Med* 2010; [Epub ahead of print]
142. Allen MH, Currier GW: Medical assessment in the psychiatric emergency service. *New Dir Ment Health Serv* 1999 82:21.
143. Tenenbein M: Do you really need that emergency drug screen? *Clin Toxicol (Phila)* 2009; 47:286.
144. Fortu JM, et al: Psychiatric patients in the pediatric emergency department undergoing routine urine toxicology screens for medical clearance: Results and use. *Pediatr Emerg Care* 2009; 25:387.
145. Link BG, Andrews H, Cullen F: The violent and illegal behavior of mental patients reconsidered. *Am Sociol Rev* 1992; 57:275.
146. Dubin WR, Weiss KJ, Zeccardi JA: Organic brain syndrome: The psychiatric imposter. *JAMA* 1993; 249:60.
147. Tintinalli JE, Peacock FW, Wright MA: Emergency medical evaluation of psychiatric inpatients. *Ann Emerg Med* 1994; 23:859.
148. Hall RC, Gardner ER, Stickney SK, LeCann AF, Popkin MK: Physical illness manifesting as psychiatric disease: Analysis of a state hospital inpatient population. *Arch Gen Psychiatry* 1980; 37:989.
149. Estate of Reverend Ronel Huggins v Eastern Health Care. *Medical Malpractice: Verdicts, Settlements, and Experts* 2006; 22:24.
150. Nijman HK, Merckelbach HL, Allertz WF, Campo JM: Prevention of aggressive incidents on a closed psychiatric ward. *Psychiatr Serv* 1997; 48:694.
151. Fernandes CM, et al: The effect of an education program on violence in the emergency department. *Ann Emerg Med* 2002; 39:47.
152. Winett LB: Constructing violence as a public health problem. *Public Health Rep* 1998; 113:498.
153. Brener ND, Simon TR, Krug EG, Lowry R: Recent trends in violence-related behaviors among high school students in the United States. *JAMA* 1999; 282:440.
154. Cunningham R, et al: Before and after the trauma bay: The prevention of violent injury among youth. *Ann Emerg Med* 2009; 53:490.
155. Muelleman RL, et al: An emergency medicine approach to violence throughout the life cycle. *Acad Emerg Med* 1996; 3:708.
156. Houry D, et al: Violence prevention in the emergency department: Future research priorities. *Acad Emerg Med* 2009; 16:1089.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 189

THE DIFFICULT PATIENT

Robert J. Vissers

PERSPECTIVE

Certain patients consistently arouse negative reactions in health care providers. These negative reactions may be initiated by a patient's appearance, apparent attitude, interactive style, or presenting complaint. Difficult patients can rapidly disrupt the harmony and efficiency of an emergency department (ED). Such patients are referred to with a number of pejorative terms, such as *gomer, crock,* and other even less complimentary slang terms of disdain. They may receive suboptimal medical care, impede patient flow, and adversely influence the quality of care given to other patients, thus posing a medicolegal risk. Moreover, recurrent exposure to such patients, in the absence of a well-thought-out approach to dealing with them, may lead to escalating frustration for staff, promote unprofessional behaviors, and contribute to eventual burnout.

Historically, the medical literature has largely ignored the possibility of a physician's harboring negative feelings toward any type of patient. Anger, hatred, and frustration are traditionally considered feelings that physicians should disown in favor of humor, compassion, and integrity. Although these are admirable attributes, to deny the presence of negative reactions is unrealistic. Physicians are as human as the patients they serve. Not until Freud coined the term *countertransference* were the negative reactions that patients can arouse in physicians actually recognized for their potential effect on care and used as diagnostic tools.

Good interpersonal skills are essential to the maintenance of the patient-physician relationship.[1] Although some clinicians have more natural abilities in this area than others do, the myth that these skills are intuitive and cannot be taught is erroneous.[2] Teaching of communication and relationship-building skills is now a priority of most medical schools and many primary care specialties.[3] Guidelines for teaching and evaluating interpersonal skills within emergency medicine residency programs have been developed.[2,4,5] The Accreditation Council for Graduate Medical Education identifies professionalism and interpersonal communication skills as two of the six core competencies required in the curriculum of all U.S. residency programs, including emergency medicine, prompting greater interest in research and education in these areas. Although it remains a challenge to measure the effectiveness of these initiatives, innovative curricula on professionalism and communication are being implemented in emergency medicine residencies.[6-9]

DISTINGUISHING PRINCIPLES

Difficult patients are often referred to as problem patients, disruptive medical patients, unwanted patients, and, less diplomatically, hateful patients.[10] Patients with personality disorders are commonly included in this group because of their rigid, maladaptive personality traits. Difficult patients, however, do not necessarily have personality disorders and may fall into one of several other familiar patient categories (e.g., drug seekers, hostile patients, malingerers, and ED repeaters).

There is no universally agreed on definition of the difficult patient. The difficult patient is *one who interferes with the physician's ability to establish a normal patient-physician relationship.* This impaired patient-physician relationship is often but not necessarily associated with negative feelings toward the patient.

PATHOLOGY OF THE PATIENT-PHYSICIAN RELATIONSHIP

An understanding of the difficult patient-physician relationship is hampered by a tendency to view it as a consequence of some inherent problem with the patient. Physician characteristics and the ED environment also play a role.[11-13]

Physician Factors

Impaired communication is a common problem in all forms of interpersonal relations and is often exaggerated in the medical setting. Patient satisfaction is highly correlated with patients' beliefs that clinicians listen to them and understand their requests, coupled with the perceived professionalism of the physician.[14,15] Despite this, physicians continue to focus on their own medical agenda, which may differ from patients' concerns. When confronted with patients who have difficult social situations, physicians exacerbate the problem when they refuse to deviate from their own rigid medical model.

Physicians often have preconceived notions of how patients should behave when they are ill and tend to rapidly categorize them as either the acceptable "truly sick" patient type or the "burdensome, difficult" patient type. Patients placed within the former category are excused for their symptoms, but patients in the latter category are not. Patients may also be judged as difficult when cultural differences or language barriers interfere with the development of a mutual understanding between patient and physician.[13]

Physician failure to provide sufficient and interpretable information to patients about their diagnosis, treatment, and follow-up evaluation is another area of common communication breakdown. Studies show that in 20 minutes of patient-physician interaction, only 1 minute is reserved for educating patients about the illness.[16] Personal biases and prejudices also affect patient treatment.[11,12,17] The rapid formulation of an opinion based solely on appearance is a skill that physicians rely on to quickly form a "gestalt" about a patient. This is an essential skill for an emergency

www.ketabpezeshki.com 66485457-66963820

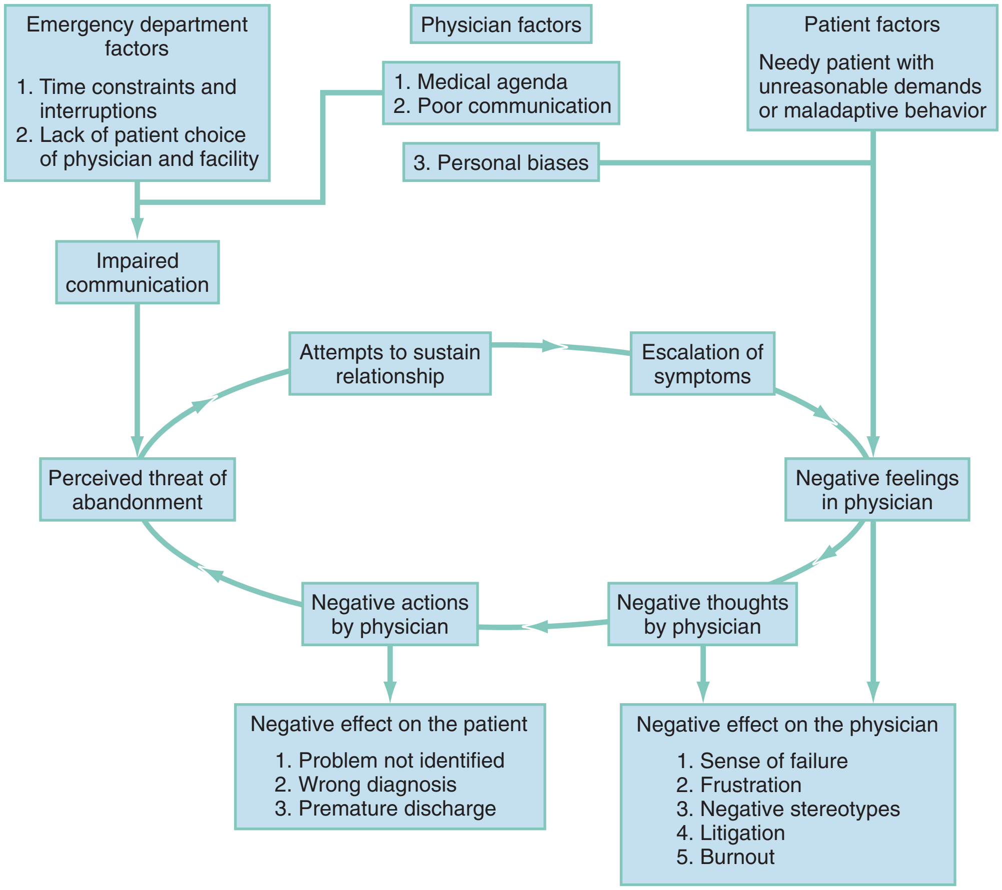


Figure 189-1. Cycle of the impaired patient-physician relationship.

physician. To assume that such preconceived notions are influential only in a positive way, however, is unrealistic.[18]

Emergency Department Factors

The ED is an environment plagued with distractions and frequent interruptions, rarely approaching the comforting atmosphere that many patients expect and deserve.[19,20] A sense of urgency and strict time constraints are often present. Patient assessments are sometimes conducted in suboptimal environments, such as hallways. The physician interaction is often perceived to be brief and punctuated by interruptions, which may imply to the patient that the physician does not care or that the evaluation is incomplete.[19-22] Patients may enter the encounter frustrated because of a lack of choice about their physicians or facilities and upset because of long waiting times, and physicians may enter the encounter biased by nursing comments or stressed by the prospect of losing control of the department while trying to deal with these particularly challenging patients.[13]

The Cycle of Impaired Patient-Physician Relationships

Difficult patients are often perceived by the physician to be making unreasonable demands (Fig. 189-1). Physicians react with negative feelings and may direct negative actions toward the patient. Patients are sensitive to these negative reactions, feel threatened with abandonment, and attempt to sustain the relationship by escalating symptoms. Physicians experience greater frustration at the maladaptive behavior of the patients, and so the cycle is perpetuated.

The consequences of this impaired relationship for the patient include failure to identify the real problems, missing of medical diagnoses, "another poor experience" with the medical establishment, and premature or inappropriate discharge.[23] The negative effect on the staff is manifested by frustration, a sense of failure and defeat, fear of litigation, and the development of unconstructive stereotypes and unrecognized prejudices, all of which may contribute to eventual professional burnout.

STRATEGIES FOR TREATMENT OF THE DIFFICULT PATIENT

This section discusses the treatment of difficult patients from three approaches: general strategies, dealing with negative reactions, and crisis intervention.

General Strategies

Box 189-1 lists several general strategies that are helpful in dealing with difficult patients.

Be Supportive

Being supportive is not always the natural response to difficult patients because of the negative feelings they arouse in the physician. Nevertheless, initiating the interaction with a clear and explicit demonstration of concern and empathy may be the single most powerful tool at one's disposal. Some physicians are concerned that seeming to be "soft" with a demanding or entitled patient may exacerbate the situation. To the contrary, expressing a respectful and empathetic concern for their problem effectively

www.ketabpezeshki.com 66485457-66963820

Box 189-1 General Strategies for Dealing with Difficult Patients

Be supportive.
Structure the interview.
Set limits.
Point out impasses.
Share your reactions.
Redirect the interview.
Take time out.
Use teamwork.
Understand the patient's agenda.

disarms many patients who are preparing for a long and arduous battle to be taken seriously. The possible news that there is no immediate solution available is more willingly received by patients who are convinced that they have been heard and believe the physician's desire to help is sincere.[24]

Connecting emotionally with the patient can take time. Initially addressing a smaller concern in a caring and respectful manner can build trust and create greater rapport and compliance. For example, a patient who seeks treatment for self-inflicted lacerations but who will not cooperate with a history aimed at assessment of suicidal risk is often more candid after the physician has rendered appropriate wound care in a nonjudgmental way.

Structure the Interview

Setting of self-imposed time limits for contact with difficult patients helps control the anxiety associated with falling behind in a busy ED. Flexibility in the structure of the assessment may be necessary. It is fair and appropriate to tell the patient of the need to excuse oneself to care for other patients. The fulfilled promise of returning to complete the next element of the assessment helps build trust and rapport.

Set Limits

It is helpful to share the ground rules of reasonable behavior with patients. For example, profane patients should be reminded that they are entitled to treatment but that their language may offend other patients. The physician may suggest that they censor their remarks or be escorted from the area.

Point Out Impasses

At times, patient expectations and physician limit setting produce an impasse. When this occurs, it may be necessary to agree to disagree. Some issues can be resolved by pointing out impasses and giving the patient a chance to help solve the problem. Impasses sometimes can be resolved if difficult issues are set aside and returned to later in the interview. This fundamental approach to negotiations is generally underused in the ED.

Share Your Reactions

Pointing out impasses may not be effective if a patient senses annoyance or frustration in the physician. It may be helpful at such times to share one's feelings explicitly with the patient while continuing treatment.

Redirect the Interview

Some patients love to talk about issues unrelated to the problem at hand. Pursuing trivial or chronic complaints should be avoided. Patients often require redirection to focus on issues that have some potential for resolution. Asking them to take a chronologic approach in discussing a specific concern may help keep them on track.

Take Time Out

Physicians occasionally feel unable to contain their frustration. One should feel comfortable retreating from the room and returning when both parties have regained their composure.

Use Teamwork

Individuals who intimidate or split the staff are much more easily treated from the outset with teamwork. This is especially important with violent patients requiring restraint when a show of strength in numbers may defuse potentially dangerous situations. A more subtle but equally important application of teamwork is in the treatment and discharge planning of patients with complex problems who require an especially well organized, multidisciplinary approach involving medical and support services in the community. On occasion, if it is available, the benefit of a "second opinion" from an emergency medicine colleague can help identify the difficult patient and allow the treating physician to regain clinical perspective.

Understand the Patient's Agenda

Sometimes physicians ask themselves, Why is this patient here?[1] It is often productive to ask the patient the same question in a nonjudgmental fashion. The patient may have an easily satisfied although unanticipated agenda. This may be as simple as needing a bus ticket to get home or reassurance that there is no immediate danger of dying of some minor disorder. When the patient's needs are not as easily met, a clear understanding of the purpose of the visit may allow the opportunity to set more realistic goals.[25]

Dealing with Negative Reactions

Although negative reactions make dealing with difficult patients an unpleasant experience, they can also provide valuable diagnostic information. Physicians should accept these reactions as understandable responses to a patient's unpleasant behavior and use them to their advantage.

Physicians typically have similar reactions to certain patient behaviors. The variations in these reactions depend on the individual physician's personality style, previous experiences, and unrecognized prejudices. Physicians should know their own reactions to specific behavioral patterns to use them as diagnostic aids.

Early recognition of these reactions may, in addition to their diagnostic value, allow the physician to analyze them as the first step in preventing failure in the therapeutic relationship.[11-13]

Negative Thoughts about the Patient

Negative thoughts about patients have the greatest potential to adversely affect patient care. Patients are often placed into such stereotyped categories as drug addict, malingerer, or crock. These labels may describe individual patients more or less accurately, but the potential exists for physicians to make inaccurate and potentially dangerous assumptions on the basis of the biases linked to these labels.

The process of assigning patients to epidemiologic categories is a normal part of clinical judgment. Certain categories are used to help define the likelihood of encountering diseases in particular populations of patients, thereby influencing decisions about investigation, treatment, and disposition. The danger in dealing with difficult patients is that this process can result in inaccurate assumptions about patients and compromise patient care.

www.ketabpezeshki.com 66485457-66963820

Inaccurate assumptions about patients based on prejudicial, stereotyped labels are called *cognitive distortions*.[12,26] The following case exemplifies the effect that cognitive distortions can have on clinical decision-making.

An injection drug user requests analgesia for severe neck pain after minor trauma. The physician labels the patient a drug seeker and assumes the complaints to be fictitious. After becoming aware of the physician's assumption, the patient becomes belligerent and aggressive. He is escorted from the ED by security. A few days later, he returns with quadriplegia resulting from a cervical epidural abscess.

The physician assumed that the patient was malingering because of past experience with injection drug users and did not consider other legitimate explanations for the patient's behavior. This phenomenon, known as all-or-none thinking, leads to the real disease being overlooked.

Negative Self-Perceptions

Self-directed negative thoughts by physicians often reflect a sense of inadequacy or despair. Some patients contribute to the problem by criticizing their care in ways that reinforce the physician's feelings of inadequacy. Unreasonable expectations of patients, coupled with their secret conviction that no one can really help, combined with the all too prevalent rescue fantasies of physicians create a potent recipe for physician frustration, which in the long term can contribute to eventual burnout.

Negative Behaviors

Physician behaviors can be the most obvious manifestations of negative feelings and thoughts. Examples include rudeness, sarcasm, and indifference toward patients. A patient may receive an incomplete clinical evaluation, and unnecessary ancillary tests may be performed as an attempt to compensate. Physical or chemical restraint use, administration of naloxone, or the performance of other procedures may be used inappropriately or punitively. Analgesics may be withheld or used sparingly. Faulty communication may result in misunderstood discharge instructions and poor compliance. Impaired patient-physician relationships may lead to a refusal of care, forcing treatment against patients' wishes or resulting in their leaving against medical advice.[27]

Although patients can suffer at the hands of physicians, the potential exists for the reverse to occur. Dissatisfied patients with incorrect diagnoses and poor follow-up instructions are prone to initiate successful malpractice suits against physicians. The physician may become the victim of patient violence.[28] Negative physician behaviors can also have an effect on the rest of the ED staff. Actions viewed by colleagues as inappropriate can compromise team morale and functioning. Physicians who are feeling angry, demoralized, and stressed may vent their frustrations on team members or consulting services, resulting in a further deterioration of the immediate situation and potential damage to long-term working relationships.

Strategies to Manage Negative Reactions

Six strategies are helpful in managing physicians' negative reactions toward patients.

Maintain Appropriate Emotional Distance

Physicians should avoid reciprocating hostile reactions offered by patients. This may be difficult to resist and is best accomplished by maintaining sufficient emotional distance to avoid taking the patient's behavior personally. This "detached concern" should be balanced with sufficient emotional investment to convey a sense of caring and empathy for the patient.[11,24]

Generate Alternatives to Negative Reactions

Instead of applying negative labels, physicians should attempt to view the patient as a victim of circumstance. Patients do not choose the social and genetic pool into which they are born. They do not choose to be abused children, to suffer from psychiatric disorders, or to experience many of the life events that lead to an ED visit. They are entitled to high-quality care, delivered with courtesy and empathy, despite their behavior.

Attempt to Understand the Patient's Behavior as a Symptom

The second step in managing negative reactions is to recognize that patients relate to the world in a particular way because of their condition, culture, and circumstances. The condition may include a variety of medical and psychiatric problems, intoxication, cognitive impairment, or personality disorders or traits. The behaviors that one finds so disturbing should be recognized as the symptoms resulting from these conditions. Cultural differences and social circumstances can result in behaviors that seem irrational or difficult if the underlying issues are not understood. In attempting to maintain a compassionate approach to a particularly troubled and troubling patient, it is sometimes helpful to imagine how difficult one would find it to *be* that patient.

Look for the Cognitive Distortion

Cognitive distortions are best identified by looking for evidence that patients or situations are being stereotyped. Physicians should be aware of the effects on clinical judgment that arbitrary inferences and all-or-none thinking have on interactions with patients.[29]

Find a Rational Response to Cognitive Distortions

The initial reaction to the elderly schizophrenic patient presenting with chest pain might be to discount the symptoms as delusional. Psychosis, however, is not protective against ischemic heart disease, and the principle of first considering the most potentially life-threatening diagnosis serves both the patient and physician well in the ED.

Place Negative Reactions in Perspective by Viewing Them in Context

The ED is a stressful work environment. An expectation exists that emergency physicians will deal with problems quickly and effectively. Patients who thwart physicians' attempts to perform accordingly may be identified as undesirable. Such patients are difficult to view objectively when one is feeling overwhelmed. The frustration resulting from dealing with such difficult situations may produce an exaggerated response to a patient's behavior. Recognizing this may help reduce the loss of objectivity that leads to problems with patient care.

Although dealing with negative reactions is not the panacea for dealing with difficult patients, it provides the foundation for restructuring of one's interactions with them in a way that will ultimately benefit the patient clinically and the physician emotionally.

Crisis Intervention

Some presenting complaints, such as "can't sleep," "nervous stomach," "anxiety," and "can't cope," are especially likely to

www.ketabpezeshki.com 66485457-66963820

produce a sense of frustration and dread among caregivers. Attempts to deal with such complaints directly often prove unfruitful, partly because the patient's seemingly exaggerated affect interferes with effective communication. These are, however, all signs of a patient presenting in crisis.[30]

Anatomy of a Crisis

A crisis occurs when a hazardous event is encountered and customary problem-solving strategies prove ineffective.[24] People experience crises of various intensities many times in their lives; common examples include the death of a loved one, the loss of a job, serious illness, and domestic violence. The usual response of an individual to such stress is to experience an inner tension that mobilizes coping skills. Different problem-solving behaviors are then tried on the basis of previous experience.

If an effective means of resolving the crisis is chosen, the person returns to a more organized state. If a resolution to the crisis is not easily found, a period of disorganization follows. During this time, the person experiences intense emotions, such as confusion, anxiety, fear, anger, and despair. It is during the state of emotionally charged disorganization that a person may seek help at the ED.

Patients in crisis will, by the nature of their complaints and behavior, fall into the category of "the difficult patient" whether or not they actually are a "difficult person." It is important to be able to apply certain techniques of crisis intervention in dealing with such patients.

Dealing with the Crisis

Recognizing the Crisis. The presenting complaint of a patient in crisis may be a description of an event, situation, emotion, or physical symptom that can be vague or specific (domestic violence, inability to cope, anxiety, unwell, headache). Patients who present with crisis-related symptoms are a heterogeneous group. At one end of the spectrum are patients who have chief complaints that describe some type of emotional suffering and who do not require a traditional "medical" workup. At the other extreme are patients who need to be reassured in absolute terms about the absence of serious disease before their anxiety is alleviated. Between these two extremes are patients who partially understand how their circumstances might be contributing to their suffering. They can accept the idea that "the effect of stress often produces these kinds of physical symptoms." Many patients, however, are justifiably unwilling to accept this explanation until they believe their medical complaint is adequately assessed. This usually requires no more than a careful history and physical examination followed by reassuring communication from the physician and the patient's perception that the complaint is taken seriously.

Some patients who are in severe crisis need to be taken through the steps of formal crisis intervention. The complex nature and considerable time required for this are often beyond the scope of practice of a busy emergency physician. The unfortunate increase in the length of stay for psychiatric patients in the ED, because of diminishing resources for these patients, may provide an opportunity for social workers, psychiatrists, or psychiatric nurse practitioners to use this technique. A recognition of the patient in crisis is critical to creating a functional patient-physician relationship, addressing the underlying illness, and beginning the process of intervention (Box 189-2).

Box 189-2 Five Basic Steps in Crisis Intervention

Recognizing the crisis
Gathering basic information
Understanding the development of the crisis
Reproducing the peak tension of the crisis
Finding the solution

Gathering Basic Information. The first step in crisis intervention, after recognition of the crisis, involves gathering general information about the patient's home environment, work situation, personal relationships, and social involvements. The purpose of basic information gathering is to place the patient and the crisis into context before exploring the crisis itself. This step is time-consuming and cannot be rushed, and it needs to be performed by providers other than the emergency physician.

Understanding the Development of the Crisis. A structured interview is performed to obtain information about the sequence of events leading up to the crisis and the nature of the crisis itself. The objective is to understand the situation while keeping the interview organized and directed so that the patient can describe events without being overwhelmed by the emotion attached to them.

Reproducing the Peak Tension of the Crisis. Once the crux of the crisis is identified, the care provider should proceed to help the patient express the intense emotions associated with the situation. Through empathetic, active listening, the person in crisis is allowed to experience the previously overwhelming emotions in a safe context. This places the care provider in a position of trust and sets the stage for problem solving.

Finding the Solution. In the final phase of crisis intervention, the physician reframes the circumstances in objective, realistic, and understandable terms for all those concerned to facilitate a solution to the problem. Possible solutions to the crisis are then suggested, with participation from the involved parties, and the best plan for resolution is implemented. It is important that this be a joint effort and that the patient have some ownership of the solution.[30]

SPECIFIC APPROACHES FOR DEALING WITH DIFFICULT PATIENTS: PUTTING IT ALL TOGETHER

The various management strategies described here can be consolidated to formulate a practical approach to dealing with difficult patients. The first step is the recognition of specific behavior types, rather than traditional diagnoses. These behavior types describe the most difficult patients seen in the ED. Patients displaying some but not all characteristics of a certain behavioral type may still be amenable to the management strategies for that type.

Behavioral Classification

Individuals with personality disorders frequently present as difficult patients. Although reliably establishing the diagnosis of a personality disorder during the typical brief ED encounter is difficult, an awareness of those personality disorders having a high prevalence in the ED helps ease communication with colleagues when the diagnosis has been previously established (Box 189-3).

An alternative to the traditional diagnostic categories for classification of difficult patients is based on four specific behavioral presentations and the negative reactions they produce.[23,31] To adapt this classification system, with more neutral terms, the behavioral categories are *dependent patients, entitled patients, intractable patients,* and *self-destructive patients*. Through recognition of the difficult patient's maladaptive behavior and identification of the physician's subsequent negative reactions, patients can be placed into one of these behavioral categories. The behavioral categories in turn suggest effective treatment strategies for each patient type (Table 189-1).

www.ketabpezeshki.com 66485457-66963820

Box 189-3 Commonly Encountered Personality Disorders

Borderline Personality Disorder

Pattern of instability of interpersonal relationships, self-image, and affect that is accompanied by marked impulsiveness beginning by early adulthood and present in a variety of contexts. It may be indicated by five or more of the following:

1. Frantic efforts to avoid real or imagined abandonment
2. A pattern of unstable and intense interpersonal relationships characterized by alternating extremes of idealization and devaluation
3. Identity disturbance: markedly and persistently unstable self-image or sense of self
4. Impulsiveness in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating)
5. Recurrent suicidal behavior, gestures, threats, or self-mutilating behavior
6. Affective instability caused by a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days)
7. Chronic feelings of emptiness
8. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights)
9. Transient, stress-related paranoid ideation or severe dissociative symptoms

Antisocial Personality Disorder

Pattern of disregard for and violation of the rights of others since the age of 15 years as indicated by three or more of the following:

1. Failure to conform to social norms with respect to lawful behaviors as indicated by repeatedly performing acts that are grounds for arrest
2. Deceitfulness, as indicated by repeated lying, use of aliases, or conning others for personal profit or pleasure
3. Impulsiveness or failure to plan ahead
4. Irritability and aggressiveness, as indicated by repeated physical fights or assaults
5. Reckless disregard for safety of self or others
6. Consistent irresponsibility, as indicated by repeated failure to sustain consistent work behavior or honor financial obligations
7. Lack of remorse, as indicated by being indifferent to or rationalizing having hurt, mistreated, or stolen from another

Dependent Personality Disorder

Pattern of pervasive and excessive need to be taken care of that leads to submissive and clinging behavior and fears of separation beginning by early adulthood. It may be indicated by five or more of the following:

1. Has difficulty making everyday decisions without an excessive amount of advice and reassurance from others
2. Needs others to assume responsibility for most major areas of his or her life
3. Has difficulty expressing disagreement with others because of fear of loss of support or approval
4. Has difficulty self-starting projects or doing things (because of a lack of self-confidence in judgment or abilities rather than a lack of motivation or energy)
5. Goes to excessive lengths to obtain nurturing and support from others, to the point of volunteering to do things that are unpleasant
6. Feels uncomfortable or helpless when alone because of exaggerated fears of being unable to care for self
7. Urgently seeks another relationship as a source of care and support when a close relationship ends
8. Is unrealistically preoccupied with fears of being abandoned

Paranoid Personality Disorder

Pattern of distrust and suspiciousness of others, such that their motives are interpreted as malevolent, beginning in early adulthood as indicated by four or more of the following:

1. Suspects, without sufficient basis, that others are being exploitive, harmful, or deceitful
2. Is preoccupied with unjustified doubts about the loyalty or trustworthiness of friends or associates
3. Is reluctant to confide in others because of unwarranted fear that the information will be used maliciously against him or her
4. Reads hidden demeaning or threatening meanings into benign remarks or events
5. Persistently bears grudges (i.e., is unforgiving of insults, injuries, or slights)
6. Perceives attacks on character or reputation that are not apparent to others and is quick to react angrily or to counterattack
7. Has recurrent suspicions, without justification, regarding the fidelity of spouse or sexual partner

Histrionic Personality Disorder

Pattern of excessive emotionality and attention seeking beginning by early adulthood as indicated by five or more of the following:

1. Is uncomfortable in situations in which the center of attention is someone else
2. Interaction with others is often characterized by inappropriate sexually seductive or provocative behavior
3. Displays rapidly shifting and shallow expression of emotions
4. Consistently uses physical appearance to draw attention to self
5. Has style of speech that is excessively impressionistic and lacking in detail
6. Shows self-dramatization, theatricality, and exaggerated expression of emotion
7. Is suggestible (i.e., easily influenced by others or circumstances)
8. Considers relationships to be more intimate than they actually are

Narcissistic Personality Disorder

Pattern of grandiosity, need for admiration, and lack of empathy beginning by early adulthood as indicated by five or more of the following:

1. Has a grandiose sense of self-importance (e.g., exaggerates achievements and talents, expects to be recognized as superior without commensurate achievements)
2. Is preoccupied with fantasies of unlimited success, power, brilliance, beauty, or ideal love
3. Believes self to be "special" and unique and can only be understood by, or should associate with, other special or high-status people (or institutions)
4. Requires excessive admiration
5. Has a sense of entitlement (i.e., unreasonable expectations of especially favorable treatment or automatic compliance with their expressed expectations)
6. Is interpersonally exploitive (i.e., takes advantage of others to achieve personal ends)
7. Lacks empathy, is unwilling to recognize or identify with the feelings and needs of others
8. Is often envious of others or believes that others are envious of him or her
9. Shows arrogant, haughty behaviors or attitudes

Modified from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC, American Psychiatric Association, 2000.

www.ketabpezeshki.com 66485457-66963820

Table 189-1 Management Strategies: Putting It All Together

BEHAVIORAL CLASSIFICATIONS	ASSOCIATED TRADITIONAL DIAGNOSTIC CATEGORIES	SUGGESTED MANAGEMENT STRATEGIES
Dependent Patients		
Excessive needs for attention, reassurance, analgesia	Personality disorders: dependent, histrionic, borderline	Try to view the patient's neediness as a symptom. Be supportive while setting limits on the patient's expectations.
Uses helplessness and seduction	Malingerers, chronic psychiatric patients	May need crisis intervention
Physician initially feels special, then drained and frustrated		Follow up with appropriate, consistent physician
Patient increases needs when ultimately rejected		
Entitled Patients		
Fear of loss of power causes entitled behavior	Personality disorders: paranoid, narcissistic	Be supportive of entitlement to good care while setting limits on unreasonable demands.
Uses intimidation, name dropping, hostility, and threats	Substance abusers	Allow patients to choose between reasonable treatment options.
Physician feels intimidated, angry, sometimes inadequate	VIPs	Avoid power struggles.
Potential for litigation		
Intractable Patients		
Excessive needs for attention met by having unsolvable problems with multiple visits, doctor shopping, poor compliance, and no hope for successful treatment	Personality disorders: antisocial, borderline Malingerers	Distinguish from other complicated patients, and manage appropriately.
Physician feels frustrated, angry, but fears "sharing" pessimism and missing significant illness		Beware of cognitive distortions that may obscure significant illness.
Cycle of "help me, but nothing helps"		Be supportive while setting reasonable expectations.
Self-Destructive Patients		
Disregard for own health and repeated visits for serious illness	Borderline personality disorder Substance abusers	Provide appropriate medical care.
Often overtly self-destructive, denying of illness	Chronically suicidal patients	Learn to deal with own negative and nihilistic reactions to patients.
Physician feels frustrated, helpless, angry, and guilty for wishing the patient success		Look for signs of depression and consider psychiatric referral as needed.

VIPs, very important persons.

Dependent Patients

Dependent patients see physicians as inexhaustible sources of compassion and understanding. Their initially reasonable requests rapidly escalate into repeated demands for reassurance, affection, analgesia, or other forms of attention. They are excessive in their gratitude; however, the more care they receive, the more their needs multiply. Initially, the physician may feel powerful and unique. Dependent patients give the message "You're the only doctor who cares," and the physician often believes it. As the demands escalate, the physician's patience diminishes and initial feelings of inflated self-esteem are replaced with feelings of frustration, exhaustion, and failure. This leads to a natural desire to discharge or refer these patients, along with their demands, to another unfortunate physician. The patient leaves feeling rejected and then begins the same vicious circle with the next physician. Patients with certain personality disorders (dependent, borderline, and histrionic), somatoform disorders, malingering, and chronic psychiatric disorders often fall into this behavior category.[32]

Dependent patients are best treated early in the relationship before the help-rejection cycle is fully established. Some of their earliest identifying features are the negative reactions they produce in physicians. The replacement of physicians' strong feelings of self-esteem by frustration and failure is a diagnostic clue to this type of patient. Although it is important to be supportive with such patients, it is imperative to set limits as tactfully and firmly as possible. Physicians should point out their own limited time and resources. Reasonable expectations for the patient should be established while giving assurances that one will try to help. After appropriate management, disposition should be arranged, and written discharge instructions with defined criteria for return visits to the ED should be provided. The need for follow-up visits with the appropriate primary care provider should be emphasized.

Dependent patients are especially likely to seek solutions to their problems at the ED in times of crisis. Looking for the underlying issues and structuring the interview along the lines of crisis intervention can assist in finding a satisfactory resolution to the patient's problem.

Entitled Patients

Very important persons (VIPs) are often well-informed, independent professionals who may be knowledgeable in medical matters. They spend their professional lives in a position of authority and control. The traits that make them successful in the workplace,

www.ketabpezeshki.com 66485457-66963820

however, can cause them to be demanding, fault-finding, and self-entitled patients.

Entitled patients also seem to have endless needs, but instead of helplessness or seduction, they use intimidation, hostility, and threats to attain their often unreasonable demands. Entitled patients fear being helpless and dependent on physicians. They use a shield of entitlement to protect themselves. An example is the lawyer who, in his refusal to accept his illness, roams from physician to physician demanding repeated tests and opinions while threatening to sue the previous physician who had tried to help him. Physicians experience the natural responses of disgust, anger, and antagonism when they are faced with such patients. There may be an urge to enter into a power struggle with the patient. The other common temptation is to accept the patient's terms at the price of compromising his or her care. On occasion, the physician may even experience shame at being unable to meet the patient's unrealistic demands. The maladaptive behaviors of entitled patients are commonly seen in people with paranoid and narcissistic personality disorders as well as in addicted patients and VIPs.[32]

Because the behavior of the entitled patient stems from insecurity, it is important to be supportive. While reassuring patients that they are entitled to good medical care, physicians must set limits that unreasonable demands will not be met. Prolonged debates with the patient about diagnostic and therapeutic options should be avoided. Recommendations about management options should be offered and patients left to exercise their autonomy in choosing their preferred course. At the same time, physicians must communicate their acceptance of the patients' rights to exercise this control and that their decision will not jeopardize subsequent access to appropriate care.

Intractable Patients

Intractable patients, like dependent and entitled patients, have insatiable needs for emotional support. They are, however, neither seductive nor dependent in their behaviors. They present the antithesis of entitlement; they believe nothing will help. Intractable patients desperately seek help despite the failure of all previous medical assistance. Their history is punctuated by multiple emergency visits and behaviors that are self-defeating, covert, and manipulative. These negative behaviors undermine treatment and antagonize physicians, creating feelings of anger, self-doubt, and frustration. Patients with borderline and antisocial personality disorders and malingerers often fall into this behavioral category.[32]

Malingerers are among the most difficult patients presenting to the ED. Malingering is the intentional production of false or grossly exaggerated physical or psychiatric symptoms, motivated by external incentives that are unrelated to illness. These patients may be seeking narcotics, shelter, or monetary compensation; may be attempting to avoid work or criminal prosecution; or may simply be lonely.

Malingering represents deceptive, manipulative behavior and is coded in the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV), as a "problem" rather than a mental disorder.[32] This contrived behavior should be distinguished from the psychiatric illness of somatoform disorders. Somatization is the involuntary production of symptoms without the patient's awareness. Unlike malingerers, somatizers are not motivated by any conscious desire for secondary gain.[33]

Repeaters are patients who frequent the ED excessively to the point that most staff know them by name. Although chronic schizophrenics often fall into this category, this behavior can occur in any patient with poor coping skills and maladaptive responses to psychosocial stressors. The easy accessibility of the ED often makes it the only support system immediately available to chronically decompensated patients. Despite the perception that "frequent flyers" are often inappropriate in their ED use, studies demonstrate that frequent users are in poor health and require medical attention more often than less frequent users.[34,35]

Geriatric patients with multiple medical problems and those abandoned in the ED by caretakers who are no longer willing or able to meet their needs are also patient types that deserve special attention. Although these patients have problems that are often difficult to solve, the patients themselves are not necessarily difficult people.

Intractable patients elicit strong negative reactions from physicians and are sometimes identified by the feelings of futility that they produce in their caregivers. Their multiple, vague complaints that defy diagnosis and successful treatment often cause them to be labeled crocks, along with dependent patients.

Intractable patients pose a particular risk of missed diagnosis or premature discharge. Physicians should avoid the temptation to overreact with cognitive distortions and dismiss the possibility of genuine illness in the patient. Intractable patients should be distinguished from other complicated patients, evaluated for conditions that require immediate intervention, and provided appropriate management and disposition. Alternatively, there may be a tendency to inappropriately launch into extensive investigations if the behavior type is not recognized. Collateral information from previous medical records and other caregivers is valuable in providing diagnostic guidance.

Because this type of behavior stems from a need for a relationship and fear of rejection, it is important for physicians to be supportive. The belief that showing empathy only encourages maladaptive behavior is generally untrue. To the contrary, an escalation of symptoms usually follows when these patients interpret a physician's lack of concern as rejection.

Nevertheless, limits should be set regarding patients' expectations. Physicians should use this strategy while acknowledging the difficulty of the patients' problems and sharing their deep concern, and perhaps even pessimism, about the outcome of the investigations and treatment. It is helpful to make statements such as, "You know, Mr. Jones, you obviously have a very difficult problem here. You've seen lots of doctors and had lots of tests and treatments that don't seem to be helping much. There is no way, given the limited resources available in the ED at 11 o'clock on a Friday night, that we are going to be able to get to the bottom of this. What I can do is examine you and do some tests to make sure that there is no new, serious problem going on tonight. Then you will be able to follow up with your regular doctor on Monday." In this way the physician can communicate both an interest in the patient and empathy for the patient's condition while setting limits on expectations. Both the physician and patient then understand the "contract" and have a way of terminating the encounter satisfactorily.[25]

Self-Destructive Patients

Self-destructive patients are particularly difficult to treat. Unlike intractable patients, they do not seek help. Rather, they are repeatedly brought to the ED because of their neglectful and self-destructive behaviors. Their ability to deny their problems is profound and sets up the maladaptive cycle of "nothing is wrong and nothing will help." Yet their behaviors often require repeated heroic efforts to save their lives. Their chronic self-destructive behaviors may temporarily meet their immediate needs of shelter and food and perhaps, paradoxically, some of the attention they outwardly reject. This lethal cycle usually leads to a premature death. The *substance abuser,* the *violent patient,* and the *suicidal patient* are included in this category of difficult patient.[10]

It is not surprising that ED staff respond to such patients negatively, feel frustrated and helpless, and may even secretly wish

www.ketabpezeshki.com 66485457-66963820

them success in their self-destructive efforts. These are among the most difficult patients to treat. In reality, physicians can do little apart from providing appropriate care for the multiple presentations characteristic of this type of patient. The greatest obstacle for physicians may be to come to terms with their own complacency about the survival or demise of such patients. The lack of real concern about whether they live or die, or worse, actually wishing that they would die, is repugnant and produces feelings of self-recrimination. Our inability to relate to the self-destructive decisions made by these individuals contributes to our complacency about their plight. Remembering our own human weaknesses or risk-taking behaviors and viewing their seemingly incomprehensible behavior as a difference in degree rather than in kind may help us to have more empathy for them.[11] Being supportive is important. Signs of depression in the patient may indicate the need for psychiatric referral. These patients should be screened for risk of suicide and, when appropriate, held for psychiatric evaluation after medical stabilization.

SUMMARY

Dealing with difficult patients is a common problem in the ED. The impaired patient-physician relationships associated with them have multiple negative implications for both patients and physicians. Their treatment may be optimized by use of the general principles discussed in this chapter, by dealing realistically with one's own negative reactions, and by use of techniques of crisis intervention when it is appropriate. These strategies are best applied within the context of a behavioral classification that avoids pejorative terms and stereotypes, labels that differentiate them from "worthier" patients.[11] Although this approach is not a panacea for dealing with difficult patients, the framework may help physicians render appropriate care while minimizing personal frustration, medicolegal exposure, and eventual physician burnout.

One of the great challenges of medical practice is to maintain humanity when caring for these difficult and highly vulnerable individuals. By focusing on their humanity, we have the best chance of preserving our own.[11] It is easy to care for patients who generate sympathy and noble to care for those who do not.[13]

In the end, the ability to accept distressing behavior as a symptom and to treat even the most irritating individuals with compassion and kindness may be the key to surviving them. When asked how he had avoided burnout after decades in emergency medicine, one well-known patriarch of the specialty simply responded, "You've got to love the patients."[36] This is a tall order, and not meant in the literal sense. But the degree to which we can show caring and empathy, even to the unlovable, may be the key to maintaining the quality of our care, our satisfaction with the specialty, and our long-term survival in practice.

KEY CONCEPTS

- Difficult patients may elicit negative reactions in caregivers, resulting in undesirable implications for both themselves and their caregivers.
- Management of the difficult patient can be optimized by understanding the multiple factors contributing to the impaired physician-patient relationship.
- Behavioral classifications should be used instead of pejorative stereotypes in characterizing difficult behaviors.
- General and specific strategies, including understanding of our own reactions, are helpful in dealing with the impaired physician-patient relationship.
- The ability to accept difficult behaviors as symptoms and to treat even the most difficult patient with kindness is central to providing good care while avoiding personal frustration, medicolegal repercussions, and physician burnout.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Rhodes KV, et al: Resuscitating the physician-patient relationship: Emergency department communication in an academic medical center. *Ann Emerg Med* 2004; 44:262.
2. Hobgood CD, Riviello RJ, Jourilles N, Hamilton G: Assessment of communication and interpersonal skills competencies. *Acad Emerg Med* 2002; 9:1257.
3. Yedidia MJ, et al: Effect of communications training on medical student performance. *JAMA* 2003; 290:1157.
4. Larkin GL, Binder L, Houry D, Adams J: Defining and evaluating professionalism: A core competency for graduate emergency medical education. *Acad Emerg Med* 2002; 9:1249.
5. Falvo T, McKniff S, Smolin G, Vega D, Amsterdam JT: The business of emergency medicine: A nonclinical curriculum proposal for emergency medicine residency programs. *Acad Emerg Med* 2009; 16:900.
6. Van Groenou AA, Bakes KM: Art, chaos, ethics and science (ACES): A doctoring curriculum for emergency medicine. *Ann Emerg Med* 2006; 48:532.
7. Gisondi MA, Smith-Coggins R, Harter PM, Soltysik RC, Yarnold PR: Assessment of resident professionalism using high fidelity simulation of ethical dilemmas. *Acad Emerg Med* 2004; 11:931.
8. Knopp R: The challenges of teaching professionalism. *Ann Emerg Med* 2006; 48:538.
9. Welch SJ, Slovis C, Jensen K, Chan T, Davidson SJ: Time for a rigorous performance improvement curriculum for emergency medicine residents. *Acad Emerg Med* 2006; 13:783.
10. *Disruptive medical patients*. In: Hyman SE, Tesar G, eds. *Manual of Psychiatric Emergencies*. Boston: Little, Brown; 1994.
11. Croskerry P: The affective imperative: Coming to terms with our emotions. *Acad Emerg Med* 2008; 14:184.
12. Croskerry P: Achieving quality in clinical decision making: Cognitive strategies and detection of bias. *Acad Emerg Med* 2002; 9:1184.
13. Adams J, Murray R: The general approach to the difficult patient. *Emerg Med Clin North Am* 1998; 16:689.
14. Brown AD, Sandoval GA, Levinton C, Blackstien-Hirsch P: Developing an efficient model to select emergency department satisfaction improvement strategies. *Ann Emerg Med* 2005; 46:3.
15. Taylor C, Benger JR: Patient satisfaction in emergency medicine. *Ann Emerg Med* 2004; 44:262.
16. Waitzkin H: Doctor-patient communication: Clinical implications of social scientific research. *JAMA* 1984; 252:1441.
17. Birdwell BD, Herbers JE, Kroenke K: Evaluating chest pain: The patient's presentation style alters the physician's diagnostic approach. *Arch Intern Med* 1993; 153:1991.
18. Croskerry P, Abbass A, Wu AW: How doctors feel: Affective issues in patients' safety. *Lancet* 2008; 372:1205.
19. Fairbanks RJ, Bisantz AM, Sunm M: Emergency department communication links and patterns. *Ann Emerg Med* 2007; 50:396.
20. Tijunelis MA, Fitzsullivan E, Henderson SO: Noise in the ED. *Am J Emerg Med* 2005; 23:332.
21. Murphy A: To sit or not to sit: A question of cultural performance. *Ann Emerg Med* 2008; 51:194.
22. Cramm KJ, Dowd MD: What are you waiting for? A study of resident physician–parent communication in a pediatric emergency department. *Ann Emerg Med* 2008; 51:361.
23. Strous RD, Ulman A, Kotler M: The hateful patient revisited: Relevance for 21st century medicine. *Eur J Intern Med* 2006; 17:387.
24. Lin C, Hsu MF, Chong C: Differences between emergency patients and their doctors in the perception of physician empathy: Implications for medical education. *Education for Health* 2008; 21:1. Available at www.educationforhealth.net.
25. Drossman DA: Psychological sound bites: Exercises in the patient-doctor relationship. *Am J Gastroenterol* 1997; 92:1418.
26. Croskerry P: The importance of cognitive errors in diagnosis and strategies to prevent them. *Acad Med* 2003; 78:1.
27. Simon JR: Refusal of care: The physician-patient relationship and decision-making capacity. *Ann Emerg Med* 2007; 50:456.
28. Kowalenko T, Walters BL, Khare RK, Compton S: Workplace violence: A survey of emergency physicians in the state of Michigan. *Ann Emerg Med* 2005; 46:142.
29. Croskerry P: Critical thinking and decision-making: Avoiding the perils of thin-slicing. *Ann Emerg Med* 2006; 48:720.
30. Kercher EE: Crisis intervention in the emergency department. *Emerg Med Clin North Am* 1991; 9:219.
31. Groves JE: Taking care of the hateful patient. *N Engl J Med* 1978; 296:883.
32. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Association; 2000.
33. Larkin GL, et al: Mental health and emergency medicine: A research agenda. *Acad Emerg Med* 2009; 16:1110.
34. Hunt KA, Weber EJ, Showstack AJ, Colby DC, Callaham ML: Characteristics of frequent users of emergency departments. *Ann Emerg Med* 2006; 48:1.
35. Bernstein SL: Frequent emergency department visitors: The end of inappropriateness. *Ann Emerg Med* 2006; 48:18.
36. Harrison DW: Emergency medicine as a martial art. *Ann Emerg Med* 1999; 17:115.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 190

Emergency Medical Services: Overview and Ground Transport

Thomas H. Blackwell

PERSPECTIVE

Development of Emergency Medical Services

Before the advent of civilian ambulance services, the sick and injured were transported by any means available, including passerby motorists, wagons, farm machinery, delivery carts, buses, and taxicabs. Figure 190-1 depicts the early Larrey ambulance used during the Napoleonic Wars, the Rucker wagon used during the American Civil War, and a modern ambulance used today. In 1865, the Commercial Hospital in Cincinnati established the first hospital-based ambulance service. Four years later, the first city service began at New York's Bellevue Hospital.[1]

In 1965, the President's Commission on Highway Safety recommended a National Accident Response Program to decrease death and injury from highway accidents.[2] Results from a second national survey by the National Academy of Sciences–National Research Council were used to draft a white paper entitled *Accidental Death and Disability: The Neglected Disease of Modern Society*.[3] Published in 1966, this document described the hazardous conditions of emergency care provision at all levels and outlined the necessary building blocks for future maturation of emergency medical services (EMS). These national efforts were the impetus for congressional legislation that directed the U.S. Department of Transportation (DOT)–National Highway Traffic Safety Administration (NHTSA) to develop a program for improving emergency medical care.

During the mid-1960s, out-of-hospital cardiac care included field defibrillation programs in Belfast, Northern Ireland, and cardiac arrest research in several U.S. cities.[4,5] In 1969, the first National Conference on EMS convened, resulting in the development of a curriculum, certification process, and national registry for the emergency medical technician–ambulance (EMT-A). By 1972, the U.S. Department of Labor recognized the EMT as an occupational specialty.[6] Interested physicians and nurses later provided advanced educational courses and practical experiences for the EMTs, and thus began the paramedic providers.[7,8]

Additional programs prompted Congressional passage of the EMS Systems Act of 1973 (P.L. 93-154), which authorized funding that dramatically improved the development of comprehensive regional EMS delivery systems. Efforts to improve pediatric emergency care occurred in 1984 when Congress adopted the Emergency Medical Services for Children (EMS-C) initiative through the Health Services, Preventive Health Services, and Home Community Based Services Act of 1984 (P.L. 98-555).[9] An Institute of Medicine (IOM) study, released in 1994, promoted the integration of EMS-C not just into existing EMS systems but into comprehensive systems of care provision, including injury prevention, primary and definitive care, and rehabilitation services.[10]

In 1996, the NHTSA published *Emergency Medical Services Agenda for the Future,* which broadly outlined the principles required for future EMS development.[11] All components of an EMS system, both operational and clinical, were identified and discussed. This document has been used by many individuals and organizations as valuable reference material for planning, administration, and forecasting of the future of EMS delivery. More than 40 years since publishing the 1966 white paper, the IOM released a report on the status of emergency care entitled *The Future of Emergency Care in United States Health System*. The report focused on three separate yet related topics: (1) emergency care: at the breaking point, (2) emergency medical services at the crossroads, and (3) emergency care for children: growing pains.[12-14]

A major focus included the need to strengthen the integration of EMS into the entire health care system because lack of such coordination often results in patients being diverted from overcrowded to inappropriate or distant facilities. The recommendation was to ensure that the delivery of emergency medical and trauma care is organized into a coordinated, regional system such that patients receive care at the most appropriate facility on the basis of their injury or illness. Additional recommendations targeting EMS improvement included national accreditation for paramedic educational programs, adoption of a national certification system for individual state licensure, and recognition of common levels of EMS certification across the United States.

The concern for inadequate funding for EMS systems operations and disaster response was also addressed. Recommendations included development by Congress of regionally funded, multiyear demonstration projects that encourage states to identify and to test strategies for creation of seamless systems of care, workforce strengthening, evidence-based practices, and disaster preparedness. It was further recommended that an advisory committee be created to work with the Centers for Medicare and Medicaid Services to improve reimbursement and policies related to reimbursement.

Finally, a small yet significant proportion of EMS transports involve the pediatric population; thus it is often difficult for prehospital providers to maintain the knowledge and skills necessary to care for critically ill or injured children. Many plans, including disaster preparedness, often neglect children. As such, the IOM report recommended several items, the most important of which is that the care of children be integrated into the overall EMS system and not separated from that of adults, with pediatric emergency care competencies being defined and training enhanced to maintain those competencies. Because it is difficult to ascertain whether systems have targeted the pediatric population, the IOM

www.ketabpezeshki.com 66485457-66963820

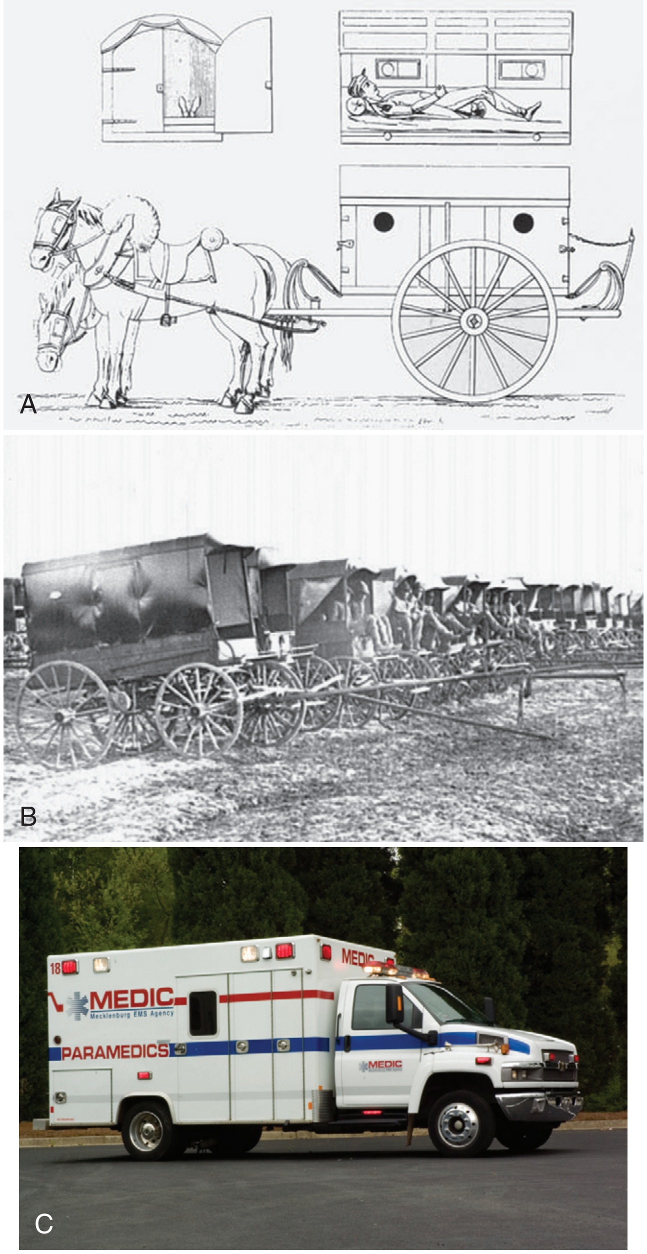


Figure 190-1. Larrey's flying ambulance (**A**), Letterman's Rucker wagon (**B**), and the modern ambulance used today (**C**). (**A** courtesy the National Library of Medicine, History of Medicine Division. **B** courtesy the Library of Congress, Prints and Photographs Division, LC-88171-2585 DLC. **C** courtesy Monroe Hicks, Mecklenburg EMS Agency, Charlotte, North Carolina.)

further recommended that a pediatric coordinator be included in all EMS systems to advocate for ensuring that equipment, medications, training, and protocols are appropriate for children.

Each of the three IOM reports supported the development by the federal government of national standards for emergency care performance indicators and evaluation and protocols for triage, treatment, and transport of patients. To accomplish this objective, a lead federal agency should be identified. Debate exists as to whether EMS at a national level should remain under the NHTSA or reside in other applicable agencies. Regardless, the parent organization should ensure that research is supported to improve the knowledge base and evidence for the practice of out-of-hospital medical care.

Emergency Medical Service Systems

Multiple EMS system designs exist, all predicated on the type of community served. Whereas this is a local decision, all states incorporate an administrative office that governs or oversees the provision of EMS activities. Typically the role is not to direct any individual service but to assist in planning, licensing services, and establishing or enforcing the scope and standards for practice. Other functions may include training, examining, certifying, and recertifying providers; record keeping; data collection; and auditing or investigating programs. A description of systems for the 200 most populous cities in the United States is periodically published in the *Journal of Emergency Medical Services.*[15] For simplicity, the following categorization of systems is used: private and public agencies; basic life support (BLS) and advanced life support (ALS) services; and single-tiered, multitiered, and first responder systems.

Private and Public Agencies

Where local government has not assumed primary responsibility for EMS services, communities may depend on private providers. Financial responsibility varies but usually depends on federal reimbursement (Medicare or Medicaid) and user fees. A local government subsidy may or may not supplement the operation. If multiple providers are serving one jurisdiction, calls may be allocated by rotation or specified zone coverage. Dispatching varies by the system but may be by the provider or by a central agency. Medical direction is often provided by a contracted physician or physician oversight board.

Hospital-based EMS systems are few in number and may be managed by a single hospital or hospital corporation. Not all hospital-based EMS programs are considered private, in that the hospital may be a division under local or state government or operating under a public authority. As in private models, financial responsibility is usually in the form of user fees, with or without additional subsidy. Dispatching may be provided by a local public safety agency that may also be responsible for police and fire communications. An emergency physician from a sponsor or base hospital typically provides medical direction for these systems.

A public utility model is a hybrid between private and public design that allows local government to contract with a private or public provider. The successful bidder for service becomes a contracted entity that agrees to provide the specified services (ALS, BLS, or both) to the catchment area and, depending on the arrangement, may bill the patient directly or receive uniform reimbursement. Depending on local structure and interagency agreement, dispatching may be performed by an existing public safety organization or by the parent company. Medical direction is usually a specified individual subject to contractual terms.

When government officials were faced with planning and establishment of EMS systems during the early maturation periods, many decided that the fire department was the logical choice to incorporate EMS. Fire stations were strategically located throughout the community, and personnel were already used to providing emergency response. Firefighters could be cross-trained as a firefighter-paramedic or dedicated to either fire or EMS function with the opportunity for transfer. Public EMS systems that were not incorporated into fire departments evolved into their own separate entity, referred to as a municipal third-service system. Such agencies are operated by local municipalities and are endorsed and supported by local government. Many cities have been successful in combining police, fire, and EMS under a global public safety agency, with all department heads or chiefs reporting to one manager or administrator. Financially, public EMS systems may be supported by a tax base, which may or may not be supplemented by user fees. Regardless of design, medical oversight for a

www.ketabpezeshki.com 66485457-66963820

municipal EMS system may be provided by a physician appointed and contracted by a local hospital, an advisory council, or a medical oversight board.

Basic Life Support and Advanced Life Support Service

BLS describes the provision of emergency care without the use of advanced therapeutic interventions. Skills include airway management (oral and nasal airways, bag-mask ventilation), cardiopulmonary resuscitation (CPR), hemorrhage control, fracture and spine immobilization, and childbirth assistance. Defibrillation with an automated external defibrillator (AED) is often included by many BLS systems. Services are provided by certified or medical first responders or emergency medical technicians (EMTs) certified at the basic level (EMT-B).

BLS systems may be associated with poor survival rates from out-of-hospital cardiac arrest, especially those not incorporating AED technology.[16] Alternatively, there is debate on the effectiveness of ALS for medical and traumatic emergencies.[17] Despite this evidence, few urban communities across the United States operate solely at the BLS level. Many rural and some suburban EMS services rely on volunteers who may not wish to become advanced-level providers. Because these services may have low call volumes, it becomes more difficult for personnel to maintain advanced skills and a proficient knowledge base. Also, such communities may not have access to medical supervision or hospital sponsorship for ALS care.[18]

Systems categorized as ALS offer a more comprehensive level of service by highly educated providers, usually certified at the intermediate or paramedic level (EMT-I or EMT-P, respectively) or equivalent levels, depending on individual state certifications. Provider skills include advanced airway interventions, intravenous line placement, medication administration, cardiac monitoring and manual defibrillation, and certain invasive procedures. Most EMS systems in urban cities operate at the ALS level of care.

The number of EMT-Ps in any jurisdiction has come under scrutiny, in that cities with more paramedics per capita tend to have lower survival rates.[19] Although this may seem implausible, one explanation might be that the number of patient encounters per paramedic decreases and the sharpness of skills degrades when that community is saturated with paramedics.

Single-Tiered, Multitiered, and First Responder Systems

In a single-tiered system, every response regardless of the call type receives the same level of personnel expertise and equipment allocation (all BLS or ALS). Multiple-tiered systems use a combination of ALS and BLS levels, depending on the nature of the call. Differences in cost and effectiveness between a mixed ALS-BLS service and an all-ALS service have been debated. A single-tiered ALS response may prove to be cost-effective in specific locales, ensures the capability of providing a consistent advanced level of care to all patients regardless of illness or injury severity, and obviates the potential for undertriage or overtriage by 9-1-1 telecommunicators. Alternatively, a multitiered system may meet the needs of individual communities or agency infrastructure. This design often meets with employee satisfaction and has the potential to preserve ALS resources for higher priority calls in that BLS transport of nonurgent patients allows ALS ambulances to be available for potential critical responses.

Regardless of single- or multiple-tier design, EMS systems usually include first responder services as part of their structure. The first responder, usually a police officer or firefighter, is the nontransport BLS or ALS provider who responds to the scene of an emergency to provide initial care before definitive medical care and transportation assets arrive. The first responder quickly assesses the situation and patients, determines whether additional resources are required, initiates patient care, and provides advance information to responding personnel.

The design of an EMS system is targeted toward providing quality patient care in the briefest time after unexpected injury or illness. A desirable and cost-effective design might include BLS nontransport first responders with short response times (average 2-4 minutes), having the capability of providing early defibrillation and airway support, coupled with ensuring ALS care and transport services.[20]

Levels of Provider and Scope of Practice

At the federal level, the NHTSA is responsible for development of the education standards and scope of practice for the different certification levels. The National EMS Education Agenda[21] and the National EMS Scope of Practice Model[22] now define the curriculum, education content, and core competencies for each level of provider. Individual state legislation is responsible for provider levels recognized, initial and continuing medical education requirements at each level, testing, and time intervals for course completion and recertification. The following sections outline the new suggested levels of provider and incorporated skills. Suggested hours of training are listed in Table 190-1.

Emergency Medical Responder

The emergency medical responder, formerly referred to as first responder, is typically the first to arrive on the scene of an incident. Initial scene and patient assessment along with limited lifesaving interventions is the primary function. Along with CPR and basic airway management skills, the emergency medical responder should be able to control hemorrhage and initiate spinal immobilization.

The four elements referred to as the chain of survival by the American Heart Association, which decrease mortality from out-of-hospital cardiac arrest, are early access to care, CPR, defibrillation, and advanced airway management and medications.[23] Because early defibrillation may improve the odds of survival of out-of-hospital cardiac arrest, the use of an AED should be a mandatory procedure for the emergency medical responder.[24]

Emergency Medical Technician

The EMT, formerly referred to as the EMT-Basic, is the minimum level required to staff a BLS ambulance and is commonly used for nonemergency and convalescent transport services. In addition to the skills of the first responder, the EMT is also involved with triage, more detailed patient assessment, and transportation. Like first responders, EMTs should have the capability of providing early defibrillation.

In 1995, the NHTSA released the revised EMT curriculum to include 46 lessons, each with cognitive, effective, and psychomotor objectives.[25] Many states expanded the course to include more skills, such as AED use, epinephrine autoinjections, albuterol administration by hand-held nebulizer or metered-dose inhaler, and use of adjunctive airway devices such as the extraglottic airway.

Advanced Emergency Medical Technician

The advanced emergency medical technician (AEMT), formerly referred to as the EMT-Intermediate, was established to allow a more comprehensive approach to care when paramedic services are unavailable or unobtainable. Many states recognize the AEMT certification, but others designate alternative but comparable

www.ketabpezeshki.com 66485457-66963820

Table 190-1 Emergency Medical Services Provider Level Training and Skills

PROVIDER LEVEL	DOT RECOMMENDED HOURS OF TRAINING	SKILL SET
Emergency medical responder	Initial: 48-60 didactic and laboratory hours	Initial scene and patient assessment and stabilization Basic airway skills CPR Control hemorrhage Spinal immobilization
EMT	Initial: 150-190 hours that include didactic, laboratory, clinical, and field experience	First responder skills plus: Triage and detailed patient assessment AED May assist in some systems: use of epinephrine autoinjectors for anaphylaxis; albuterol for wheezing
Advanced EMT	Initial: 150-250 hours that include didactic, laboratory, clinical, and field experience	EMT-Basic skills plus: Endotracheal intubation Manual defibrillation Intravenous line placement Limited pharmacologic treatments May assist in some systems: laryngeal mask airway
EMT-Paramedic	Initial: Typical range of 1000-1300 hours as suggested by the Commission on Accreditation of Allied Health Education Programs	EMT-Intermediate skills plus: Cardiac rhythm recognition Expanded pharmacologic treatments Needle decompression of a tension pneumothorax Needle or surgical cricothyrotomy Transthoracic cardiac pacing

AED, automated external defibrillator; *CPR,* cardiopulmonary resuscitation; *DOT,* Department of Transportation; *EMT,* emergency medical technician.

levels, depending on specific skills and procedures. This level is useful for rural systems because it provides some ALS care for less cost and educational time expended. The scope of practice for the AEMT varies across the United States. Most systems allow the AEMT to establish an intravenous line, to manually defibrillate, and to administer limited medications.

Emergency Medical Technician–Paramedic

The EMT-P is the most advanced provider. Paramedics have the capability to address most prehospital emergencies. The scope of practice includes a wide variety of therapeutics and procedures including cardiac rhythm recognition, expanded pharmacologic treatments, and advanced airway interventions. Other important invasive procedures include needle decompression of a tension pneumothorax, needle or surgical cricothyrotomy, and transthoracic cardiac pacing.

The initial training course for the EMT-P includes didactic, clinical, and field education. All course content focuses on technical and professional competencies. Additional modules are included that allow programs to incorporate an expanded scope of practice.[26] With the expansion of EMS technology and management career options, many paramedic educational programs have advanced from 1-year certificate curriculums to 2-year associate or 4-year baccalaureate degrees. The National EMS Education Standards document recommends that all paramedic education programs be accredited in the future by the Commission on Accreditation of Allied Health Education Programs.

Future

To complement many of the educational issues addressed in the EMS Agenda for the Future document and at the request of the National Association of State EMS Officials (NASEMSO), the NHTSA along with the Health Resources and Services Administration under the Department of Health and Human Services published the *Emergency Medical Services Education Agenda for the Future: A Systems Approach* in 2000.[27] This document sets forth the processes required to improve EMS education delivery similar to what is realized with other allied health care professions, provides a means of ensuring more instructor flexibility and EMS adaptation to community needs and resources, and moves toward standardization of all levels of certification across the United States. From this document, multiple activities have been completed and published, including the National EMS Core Content, a National EMS Scope of Practice Model of minimum competencies, and the 2009 National EMS Education Standards, which would ultimately replace the current National Standard Curricula for each level of provider. The NASEMSO has been collaborating with multiple EMS stakeholders and the federal partner organizations to assist states in implementing this agenda. The National Registry of Emergency Medical Technicians is in the process of revising their examination, with a new paramedic examination being finalized by January 2013. Future goals include the establishment of a national EMS certification program, consistent levels of provider that build off of each advancing level (emergency medical responder, emergency medical technician, advanced emergency medical technician, and paramedic), the requirement for educational programs to be nationally accredited, and the limitation of examinations only to those graduates who completed these accredited programs.

Material Resources

Before the mid-1960s, few if any regulations governed system design, operations, and equipment. As EMS development progressed, guidelines for emergency vehicle specifications were adopted by the DOT and equipment lists were proposed. Today, collaborative efforts from multiple professional medical colleges and organizations continue to publish documents that recommend design, equipment, and medications for ambulances.[28]

Medications

During the 1980s, many believed that prehospital drug administration was unjustified and simply delayed hospital transport.[29,30] Moreover, although there was a profound paucity of outcomes-based research into the use of various medications and practices

www.ketabpezeshki.com 66485457-66963820

in the prehospital environment, this has been improved in recent years.[31] There is significant evidence for early defibrillation and certain advanced cardiac life support medications, which are carried by most ALS services.[24,32] The wide variety of alternative medications is less uniform. This includes respiratory and anaphylaxis medications, preparations for altered mental status, analgesics, and antiemetics. Medications are traditionally administered in the field by the parenteral route, but the intranasal route is becoming popular for certain preparations. The beneficial aspects are that absorption is rapid with an onset of action similar to that of parenteral administration. Medications that are commonly administered intranasally are naloxone for narcotic overdose, midazolam for pediatric seizure, and fentanyl for pain control.[33,34]

Equipment

Basic ambulance equipment should include items necessary for emergency procedures (i.e., airway support, hemorrhage control, fracture and spine immobilization, childbirth), personal protection, patient movement, and basic rescue procedures. Additional patient care equipment is predicated on the level of provision outlined by the system design. Many ALS systems have adopted the equipment necessary for the acquisition of prehospital 12-lead electrocardiograms to provide earlier diagnosis of acute myocardial infarction. This information often guides destination protocols to deliver these patients directly to acute care facilities that incorporate 24-hour cardiac catheterization laboratories with staff to facilitate emergent percutaneous coronary interventions.

Ambulances

Three basic ambulance vehicle designs are recognized by the DOT: type I, type II, and type III. Both type I and type III ambulances incorporate a modular patient compartment mounted on a conventional truck and van chassis, respectively. The type II vehicle is a standard van. The larger medium-duty vehicle, mounted on a business-class chassis, has become popular in recent years. This configuration requires less periodic maintenance and offers extended service time. Each ambulance manufacturer promotes various interior cabinetry and all include sufficient lighting, outlets for 110-volt equipment, suction, oxygen systems, and external audible and visual warning devices. The six-pointed blue star, or Star of Life, surrounding the staff of Aesculapius is recognized worldwide as the standard symbol for EMS.[35]

Communications

Integral to out-of-hospital care systems, EMS communications involve multiple components, all interlinked to support expedient patient care. Effective communication systems include public information and education programs regarding general access to care, technology to ensure simplified access, means of call prioritization and management of available resources, protocols for providing emergency patient care instructions before EMS arrival, ability to communicate with allied agency and hospital personnel, educational opportunities for telecommunicators, and quality improvement processes.

Access

Since 1973, the 9-1-1 universal emergency access telephone number has been adopted by many communities throughout the United States. Basic 9-1-1 service simply connects a caller to a central communications center or public safety answering point (PSAP). Most primary PSAPs are under the domain of law enforcement. Although many of these handle all public service (police, fire, EMS) calls, many larger cities have secondary PSAPs for fire and EMS. Enhanced 9-1-1 provides additional information by immediately displaying the caller's telephone number and address.

Emergency Medical Dispatch

Dispatching encompasses multiple elements that assist patients in receiving expeditious medical care.[36] There are several recognized programs with varying sensitivities and specificities that assist call-takers in identifying a patient's acuity level on the basis of the caller's information.[37,38]

The emergency medical dispatcher (EMD) is responsible for ascertaining the primary medical condition and severity. Communication centers that model their dispatch response protocols on priority use a finite list of common chief complaints, each having associated predetermined questions. Answers to these questions ultimately dictate a predefined response mode. Depending on the response assigned and system configuration, an ambulance (BLS or ALS) and possibly a first responder resource is dispatched to respond in an emergency or nonemergency mode. When critical conditions are identified, the EMD may proceed to give specific prearrival instructions to assist the caller in providing critical interventions before EMS arrival. These include procedures such as opening and clearing an airway, performing CPR, controlling hemorrhage, and assisting with childbirth. Such assistance dramatically narrows the response time interval for receiving emergency medical care.

Systems Status Management

Depending on system size, population served, and resources available, systems status management has proved beneficial for many services. On the basis of historical data, high-performance or peak-demand periods of the day coupled to service areas or call location can be identified so that coverage plans or posting assignments may be instituted. Such mechanisms place ambulances at predetermined locations where potential calls are likely to occur. Response vehicles may be equipped with an automatic vehicle locator that functions as a telemetry unit or a global positioning satellite system that provides a site interface with the computer-aided dispatch system. This site information is helpful in the staging or redeployment of vehicles during periods of high call volume or when resources are limited.

Field Communications

At the scene or during transport, EMTs usually have the capability of communicating with hospital staff. A consultative patient report may be given to receive medication or intervention orders or simply for arrival notification. Additional information resources may include cardiac telemetry or transmission of a 12-lead electrocardiogram. EMS providers should also have the capability of communicating with all allied public safety agencies for mutual aid purposes, mass casualty situations, or disaster responses. If air medical services are available, EMS and fire personnel must have the capability of communicating with the helicopter pilot and crew members. Scene personnel must relay landing zone information and potential hazards to the pilot and should provide a preliminary patient report to the medical crew.

OVERSIGHT

Federal

Various federal agencies participate in the oversight of EMS development and refinement. Specifically, the lead agency in the federal government is the EMS Division of NHTSA under the DOT. In 2007, the National EMS Advisory Council was formed to provide

www.ketabpezeshki.com 66485457-66963820

advice and recommendations from consumers, advocates, and stakeholders regarding EMS to the NHTSA. Additional federal support comes from EMS-C under the Maternal and Child Health Bureau, Department of Health and Human Services. In an effort to better coordinate federal agencies involved with state, local, tribal, or regional EMS, Congress formed the Federal Interagency Committee on EMS in 2005. The purpose of this organization is to simplify the processes and efforts by which federal agencies support EMS by identifying state and local EMS needs and recommending the addition, expansion, or improvement of programs. Although it is not regulatory, the National Association of EMS Physicians is an international organization of physicians and prehospital professionals interested in promoting research, innovation, and excellence in prehospital care delivery.

State

Each state incorporates a governmental agency that oversees EMS. Duties typically include enforcement, regulation, and implementation of EMS rules adopted by the state and possibly a medical board, licensing services, and certifying providers. The NASEMSO assists in developing policy, providing insight, and ensuring leadership and resources for EMS development at the state, regional, and local levels.

Local

EMS Medical Director

An EMS medical director is a physician with specialized interest and knowledge of patient care activities unique to the out-of-hospital environment. Medical oversight must extend from the communications center through all components of field care. Typically, a contractual arrangement for services provides the physician with administrative authority to implement patient care protocols, to interact with all aspects of the system, and to remove a provider from practice if medical care or behavior is substandard. Published guidelines describing the activities and performance of an EMS medical director have been prepared by the American College of Emergency Physicians, National Association of EMS Physicians, NHTSA, and Health Resources and Services Administration.[39-41]

Medical direction consists of off-line (indirect) and on-line (direct) control. Off-line medical control includes protocol development, personnel education, prospective and retrospective patient care review, and other quality improvement processes. Direct medical control concerns real-time interaction between a physician or designee and the field provider.

Indirect Medical Control

Medical accountability for patient care activities is the basis for indirect medical control and functions either before a patient is encountered (prospective) or after hospital transport has occurred (retrospective). Patient care guidelines and protocol development for EMTs and EMDs, continuing medical education, medical-legal policies, and quality and performance improvement processes are important elements.

Perhaps the most important duty of the medical director is to develop patient care protocols. Protocols serve as pre-established practice guidelines that define the standard of care for most illnesses or injuries encountered in the out-of-hospital setting. Operational issues, such as hospital designation and destination policies, termination of resuscitation, and patient transport refusal, may be included. Depending on state regulations, protocols may include standing orders for particular clinical situations in which EMTs may perform certain procedures or administer medications for predefined patient conditions before communication with hospital personnel. Protocol development should be driven by system resources and patient needs and should include guidelines for triage and care of specific populations of patients, including trauma patients, newborns, and children.

Regardless of local communication protocols, out-of-hospital providers should always be able to discuss a case with a physician for clarification or guidance when clinical questions or controversial situations arise. Furthermore, hospital notification is important when critical patients are being transported.

Medical directors should be familiar with and actively involved in local or regional educational programs for initial and continuing education courses for all levels of EMT certification. Course curriculum development and administration, evaluation, and revision processes should be understood. Systems that incorporate their own educational programs allow modifications that reflect intrinsic needs of the system and the providers.

Field personnel and telecommunicators should be given regularly scheduled courses that improve competency in knowledge and skills. Instructional formats and resources to accomplish educational objectives may include didactic classroom lectures, skill laboratories, direct field observation, and distance learning models for self-paced opportunities. Standardized core content is important for maintenance of consistency and quality of care.

Once patient care protocols are developed and implemented, there must be mechanisms, such as retrospective patient care report review or direct field observation, for evaluation of individual and system performance and patient outcome. Deviations from specific protocols may reflect problems with individual EMTs, medical control personnel, or the protocol itself, each requiring education and re-evaluation. Deficiencies, both operational and clinical, should be identified for appropriate remediation to occur, which may be in the form of counseling, educational instruction, or revisions of system design or patient care protocols.[42] Competency, knowledge retention, and skill performance are measurable parameters. Time standards (e.g., out-of-chute time [time from ambulance notification to deployment], response time, and scene time) are equally important measures.[43-46]

Direct Medical Control

Direct medical control is the concurrent direction of EMTs providing patient care. This may be in the form of radio or telephone communications or by direct scene observation and may be considered centralized or decentralized. In a centralized system, a selected hospital is designated the lead facility (base station hospital, resource hospital, or sponsor hospital) and is responsible for providing all direct medical control orders and notification regardless of the receiving facility. In a decentralized system, each hospital functions as a base station, providing direction to EMTs transporting patients to its facility.

Personnel responsible for direct medical control must be knowledgeable about the entire EMS system, receiving facilities, protocols, medication formulary and equipment, administrative and operational issues, and medical-legal implications for certain presenting situations. Systems whose protocols include standing orders may require direct communication only for specific reasons. Thus, whereas these medical and administrative protocols may guide EMTs through most circumstances, medical control consultation may assist with medical-legal issues, situational problems at the scene, patient nontransport, or a multitude of potential ethical dilemmas that may be encountered. Nevertheless, direct medical control is usually invaluable for notification of a receiving facility for treatment room and staff preparation when critical or potentially critical patients are being transported.

Agencies and organizations involved in EMS development and oversight are listed in Table 190-2.

www.ketabpezeshki.com 66485457-66963820

Table 190-2 Emergency Medical Services Resource and Contact Information

RESOURCE	URL
Advocates for EMS	www.advocatesforems.org
American Ambulance Association	www.the-aaa.org
American College of Emergency Physicians	www.acep.org
Centers for Disease Control and Prevention	www.cdc.gov
Commission on Accreditation of Ambulance Services	www.caas.org
EMS Division, NHTSA	www.nhtsa.dot.gov/people/injury/ems
Maternal and Child Health Bureau, EMS-C	www.ems-c.org
National Association of EMS Educators	www.naemse.org
National Association of EMS Physicians	www.naemsp.org
National Association of EMTs	www.naemt.org
National Association of State EMS Officials	www.nasemso.org
National Registry of EMTs	www.nremt.org

EMS, emergency medical services; *EMT,* emergency medical technician; *NHTSA,* National Highway Traffic Safety Administration.

OUT-OF-HOSPITAL MEDICAL CARE AND CONTROVERSIES IN MANAGEMENT

Airway Support and Respiratory Emergencies

Interventions

Respiratory complaints account for a significant number of EMS responses. Basic measures to control and support a patient's airway include manual maneuvers (e.g., chin lift or jaw thrust), oral and nasopharyngeal devices, and bag-mask ventilation. At a more advanced level, interventions may include use of extraglottic-type airway devices (e.g., Combitube, laryngeal mask airway, or laryngeal tracheal airway), which have been shown to enable faster placement and to provide improved minute ventilation. Studies have shown that basic-level EMTs were able to successfully place laryngeal mask airways in simulated arrest models and also demonstrated an improved minute ventilation with these devices compared with bag-valve mask ventilations.[47,48] Similar studies have demonstrated that laryngeal mask airways are more successful than endotracheal intubation for paramedics because they provide a faster technique, require fewer attempts for successful insertion, and improve ventilation.[49]

Commonly used by air medical services, drug-assisted intubation (DAI) and rapid sequence intubation (RSI) procedures are well established in ground transport services, despite a lack of supporting evidence. Although many services routinely perform intubation, several studies have challenged the effectiveness of out-of-hospital intubation, particularly in view of an alarming incidence of esophageal intubation in some systems and poor outcomes with the use of RSI for head-injured patients.[50-53] One prospective, randomized study of pediatric out-of-hospital airway management concluded that in the urban setting, bag-mask ventilation may be superior to intubation in certain groups of patients.[54] Although controversy exists and the debate will continue, most would agree that to have a successful airway management program, the educational and quality management component must be meaningful and should be as comprehensive and compulsive as possible.[55] For programs using DAI or RSI procedures, the experiential component should include operating room time and simulator sessions. Ideally, training would also occur in an emergency department setting where patients requiring emergent intubation would potentially have the full complement of confounding variables (e.g., combative status, full stomachs, blood and vomit in the airway). Such training may be difficult or impossible to achieve, particularly ongoing maintenance of skills sessions, especially in rural communities. Unless EMS systems perform a large number of intubations, with at least several intubations per provider per year, use of an extraglottic device for tracheal intubation should be strongly considered.[56]

Traditionally used in the hospital, continuous positive airway pressure (CPAP) is intensifying in the out-of-hospital setting. The effectiveness of out-of-hospital use of CPAP has been demonstrated; however, patient outcome studies have been limited.[57,58] Out-of-hospital use would require strict protocols that outline such variables as indications and contraindications, clinical applications, mental status assessment, hemodynamic status, and mechanisms for transfer of the patient at the hospital.

Medications

Most advanced programs have adopted the use of clinically proven medications for bronchospasm, chronic obstructive pulmonary disease, and anaphylaxis, but no studies have demonstrated benefit to administration of these medications in the out-of-hospital environment. Whereas some studies might be considered unethical (e.g., an out-of-hospital study of epinephrine for anaphylaxis), others (e.g., out-of-hospital use of beta$_2$-agonists or steroids for asthma, or loop diuretics for pulmonary edema) could easily be performed, with the results far from certain. Pending further studies, most systems have adopted the position that these medications do not harm patients in the out-of-hospital setting, may be helpful, and may provide comfort and clinical improvement for most patients experiencing varying degrees of respiratory distress. The overhead for training and maintenance of knowledge related to these additional, probably unnecessary medications is rarely considered.

Cardiovascular Emergencies

Interventions

Early research demonstrated the effectiveness of early defibrillation for termination of ventricular fibrillation and improvement of survival rates from sudden cardiac death.[59] Advances in technology have improved such that defibrillators, traditionally used by paramedics, are now used by a variety of public safety responders and bystanders. Public access defibrillation programs are continuing to be implemented throughout the country, with devices being placed in high-volume, populous, and secluded areas such as airports and airplanes, casinos, churches, office buildings, and other locations identified as high risk for resuscitation.[60] The acquisition and transmission of out-of-hospital 12-lead electrocardiograms is becoming more prevalent as well. Although it is expensive to implement, several studies have revealed minimal delays in scene time while the electrocardiogram is obtained and a shorter time to intervention (thrombolytic administration or catheterization laboratory admission) by use of this technology.[61,62]

A factor now recognized to improve survival from cardiac arrest is uninterrupted or minimally interrupted chest compressions.

www.ketabpezeshki.com 66485457-66963820

Each interruption of compressions (e.g., while intubating, checking for pulses, analyzing rhythms) decreases coronary perfusion pressure, which in turn decreases cellular respiration.[63] This same tenant may be used for prearrival telephone CPR instructions in that more bystanders may be willing to perform continuous chest compressions if artificial ventilations were discarded.

Although the statistics for cardiac arrest survival across the United States are dismal, those who do survive may suffer some degree of hypoxic encephalopathy. Recent evidence suggests that with cooling of patients who achieve a spontaneous return of circulation after cardiac arrest, especially with ventricular fibrillation as the initial rhythm, higher survival rates and level of neurologic functioning are achieved.[64,65] The explanation may be due to several mechanisms, including a decrease in neuronal cell oxygen consumption, cell membrane protection, slowing of degradative reactions resulting from reperfusion, and limiting of acidosis.[66] International guidelines now call for the institution of hypothermia for patients who are resuscitated from cardiac arrest, and many out-of-hospital systems have implemented protocols that may include administration of chilled saline, sedation, or neuromuscular blockers in coordination with receiving hospital emergency departments.

Medications

Traditional cardiac medications recommended by advanced cardiac life support are used by most ALS systems. Recent investigations involving amiodarone as an out-of-hospital agent to terminate refractory ventricular fibrillation have resulted in higher survival rates to hospital arrival; however, improvement in survival to discharge is still not significant.[67] Whether amiodarone should replace lidocaine for out-of-hospital ventricular fibrillation requires further investigation, although many systems have already made this expensive change. The use of out-of-hospital fibrinolytic agents for acute ST elevation myocardial infarction has not gained wide acceptance and may be a useful intervention only for systems having prolonged transport times or if hospitals may not have catheterization or intervention facilities available. Future recommendation for out-of-hospital use of these agents remains speculative.

Traumatic Emergencies

Interventions

Interventions for specific medical emergencies, such as cardiac arrest (i.e., defibrillation, intubation, intravenous line, and medication administration), may be effectively performed while on the scene or before hospital transport. Alternatively, it is widely accepted that most interventions for traumatic injuries should be performed en route to the hospital, and all efforts should be extended to reduce on-scene time. Only two interventions should be considered for critical injuries, control of the airway to reverse hypoxemia and to prevent aspiration and stopping of uncontrolled hemorrhage. Although it is a routine part of prehospital trauma care, tracheal intubation is not known to be beneficial for severely injured patients.[68] There are many potential drawbacks to prehospital intubation for major trauma. To be successful, paramedics should rapidly place the endotracheal tube correctly, assess and confirm the placement, and secure the tube to prevent displacement. In addition, providing the correct minute and tidal volumes is equally important. Inadvertent hyperventilatory rates may impair cardiac output and cause further tissue damage. Patients sustaining blunt head injury pose special problems that should be expeditiously addressed and resolved. Intubation is but one means of providing ventilatory assistance and airway protection, but misadventure, complications, and improper postintubation care may negate these potential benefits. Attempting to intubate head-injured patients may result in dental or soft tissue damage in those patients with clenched teeth, and intracranial pressure may be exacerbated from an intact gag reflex or from subsequent regurgitation. Studies on the use of RSI in head-injured patients reveal that patients experience significant hypoxia and bradycardia during the procedure, and outcome is actually worse.[46] Thus the role of RSI in prehospital airway management in trauma patients is in question, just as it is for medical patients. The use of extraglottic airway devices may be a promising addition to prehospital airway management in trauma patients. Routine use of prehospital intubation is not recommended unless the system can ensure that its providers meet the standards previously outlined. Emergent hemorrhage control is also essential in reducing mortality in severe trauma. For internal bleeding, limiting of total prehospital time and transfer to definitive surgical care are paramount. Recent evidence on the battlefield has demonstrated the effectiveness of tourniquet application to extremity wounds. These devices may have application in the civilian setting, are quick and easy to apply, and do not result in the complications once thought to exist.[69]

The issue of intravenous fluid administration has gained controversy over the years. High-volume intravenous fluid for hemodynamic instability resulting from traumatic injury has traditionally been the accepted standard in most out-of-hospital care systems. Previous data, however, support a paradigm shift to restrictive or hypotensive resuscitation for penetrating truncal injuries. Restoration of hemodynamic stability with fluid resuscitation before definitive surgical hemostasis may lead to increased morbidity.[70] The use of prehospital intubation and high-volume crystalloid infusion bears unfortunate similarity to the widespread, unsupported adoption of the pneumatic antishock garment in the 70s and 80s. Despite lack of evidence of benefit and significant evidence of harm or potential harm, these practices are notoriously difficult to discontinue once adopted.

INTERFACILITY AND SPECIALIZED TRANSPORTS

Transportation between health care facilities may occur for several reasons, including patient preference, unavailable diagnostic or therapeutic resource availability at the transferring facility, and managed care requirements that patients be cared for in predesignated hospitals after stabilization. Hospital corporations engaged in networks or alliances that share resources and services depend on interhospital transport systems to convey patients to allied institutions for specialized tests or procedures. Likewise, critical patients admitted to less specialized facilities may need to be transferred to tertiary care or designated trauma centers. Whereas long-distance transports may be best accomplished by air medical services, regional or local transports should use ground systems. These may be provided by either local EMS resources or those owned and operated by the hospital.

Interfacility transfer of patients that is medically indicated must fall under a set of requirements referred to as the Emergency Medical Treatment and Active Labor Act.[71] Although the EMS system providing the transport plays a key role, these guidelines primarily involve particular information and obligations that must be satisfied by the transferring and receiving facilities before transfer. An unstable patient should not be transferred to another facility at the request of a managed care organization unless the transferring hospital is incapable of providing standard care and the receiving hospital does have the capability to manage the condition and foreseeable complications. Box 190-1 lists various requirements that should be completed before a patient is transferred to another facility.

www.ketabpezeshki.com 66485457-66963820

Box 190-1 EMTALA Requirements for Patient Transfers

Complete certification (risks and benefits) of transfer
Informed consent obtained from the patient or family
Appropriate transportation (equipment and personnel) arranged
Treatment and stabilization performed
Acceptance from receiving facility ensured
Appropriate patient care data sent (fax or with patient)

EMTALA, Emergency Medical Treatment and Active Labor Act.

Depending on the patient's condition, specialized transport services may function at the BLS or ALS level, providing emergency or nonemergency transportation. Patient transfers considered ALS may include interhospital (either emergency department or intensive care unit) neonatal or high-risk infant, critical cardiac, and trauma transports. Personnel configuration depends on system design and level of care provided. Many programs use a nurse-paramedic combination. Patients requiring specialized care may need the services of specifically trained individuals, such as respiratory therapists, neonatal nurses, or other specialized critical care personnel. The presence of a physician is not mandatory but may be useful in selected cases.

As with any EMS activity, all interfacility transports should be reviewed for appropriateness of transfer and medical care provided. In 1993, the Practice Management Committee of the American College of Emergency Physicians updated the 1990 policy statement on interfacility transfers.[72]

THE FUTURE

Providing quality, efficient, and responsible health care to the right patient, in the right setting, at the right time will be a laudable objective for any system, but there is a need for research to demonstrate which interventions are conducive to better patient outcome. As the call volumes increase, it is imperative that systems focus on those interventions, from both the training and health care delivery perspectives, that are known to be of benefit.

Acknowledgments

The author again wishes to express thanks to Joey, Alex, and Marty for their love and support.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Haller JS: The beginnings of urban ambulance service in the United States and England. *J Emerg Med* 1990; 8:743.
2. President's Commission on Highway Safety: *Health, Medical Care, and Transportation of the Injured*. Washington, DC: U.S. Government Printing Office; 1965.
3. Division of Medical Sciences, National Academy of Sciences–National Research Council: *Accidental Death and Disability: The Neglected Disease of Modern Society*. Washington, DC: National Academy of Sciences; 1966.
4. Pantridge JF, Geddes JS: A mobile intensive care unit in the management of myocardial infarction. *Lancet* 1967; 2:271.
5. Cobb LA, Alvarez H, Kopass MK: A rapid response system for out-of-hospital cardiac emergencies. *Med Clin North Am* 1976; 60:283.
6. U.S. Department of Transportation–National Highway Traffic Safety Administration: *Basic Training Program for Emergency Medical Technician–Ambulance*. Washington, DC: U.S. Department of Transportation; 1971.
7. Lewis RP, et al: Effectiveness of advanced paramedics in a mobile coronary care system. *JAMA* 1979; 241:1902.
8. Nagel EL, et al: Telemetry–medical command in coronary and other mobile emergency care systems. *JAMA* 1970; 214:332.
9. Law of the 98th Congress: *Health Services, Preventive Health Services, and Home Community Based Services Act of 1984, Public Law 98-555*. Washington, DC; 1984.
10. Institute of Medicine, National Academy of Sciences: *Emergency Medical Services for Children*. Washington, DC: National Academy of Sciences; 1993.
11. U.S. Department of Transportation–National Highway Traffic Safety Administration: *Emergency Medical Services Agenda for the Future*. Washington, DC: U.S. Department of Transportation; 1996.
12. Institute of Medicine, Committee of the Future of Emergency Care in the U.S. Health System: *Hospital-Based Emergency Care: At the Breaking Point*. Washington, DC: National Academy Press; 2006.
13. Institute of Medicine, Committee of the Future of Emergency Care in the U.S. Health System: *Emergency Medical Services at the Crossroads*. Washington, DC: National Academy Press; 2006.
14. Institute of Medicine, Committee of the Future of Emergency Care in the U.S. Health System: *Emergency Care for Children: Growing Pains*. Washington, DC: National Academy Press; 2006.
15. Williams DM, Ragone M: 2009 JEMS 200-city survey. Zeroing in on what matters. *JEMS* 2010; 35:38.
16. Nichol G, et al: Effectiveness of emergency medical services for victims of out-of-hospital cardiac arrest: A metaanalysis. *Ann Emerg Med* 1996; 27:700.
17. Bickell WH, et al: Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med* 1994; 331:1105.
18. Custalow CB, Armacost M, Honigman B: Unique curriculum for emergency medicine residents as medical directors for rural out-of-hospital agencies. *Acad Emerg Med* 2000; 7:6743.
19. Davis R: Many lives are lost across USA because emergency services fail. *USA Today* 2005; May 20. Available at www.usatoday.com/news/nation/ems-day1-cover.htm.
20. Nichol G, et al: Cost-effectiveness analysis of potential improvements to emergency medical services for victims of out-of-hospital cardiac arrest. *Ann Emerg Med* 1996; 27:711.
21. *National EMS Education Agenda*. Available at www.nasemso.org/EMSEducationImplementationPlanning/documents/FinalEducationAgenda.pdf.
22. *National EMS Scope of Practice Model*. Available at www.nasemso.org/EMSEducationImplementationPlanning/documents/EMS_Feb07_PMS314SOP.pdf.
23. Cummins RO, et al: Improving survival from sudden cardiac arrest: The "chain of survival." *Circulation* 1991; 83:1832.
24. Berdowski J, et al: Survival and health care costs until hospital discharge of patients treated with onsite, dispatched or without automated external defibrillator. *Resuscitation* 2010; 81:962.
25. U.S. Department of Transportation–National Highway Traffic Safety Administration: *Emergency Medical Technician–Basic: National Standard Curriculum*. Washington, DC: U.S. Department of Transportation; 1994.
26. U.S. Department of Transportation–National Highway Traffic Safety Administration: *Emergency Medical Technician–Paramedic: National Standard Curriculum*. Washington, DC: U.S. Department of Transportation; 1998.
27. U.S. Department of Transportation–National Highway Traffic Safety Administration: *Emergency Medical Services Education Agenda for the Future: A Systems Approach*. Washington, DC: U.S. Department of Transportation; 2000.
28. American College of Surgeons Committee on Trauma, American College of Emergency Physicians, National Association of EMS Physicians, Pediatric Equipment Guidelines Committee–Emergency Medical Services for Children (EMSC) Partnership for Children Stakeholder Group, American Academy of Pediatrics Position Paper: Equipment for Ambulances. *Prehosp Emerg Care* 2009; 13:364.
29. Smith JP, Bodai BI: The urban paramedic's scope of practice. *JAMA* 1989; 253:544.
30. Shuster M, Chong J: Pharmacologic intervention in prehospital care: A critical appraisal. *Ann Emerg Med* 1989; 18:192.
31. Millin MG, et al: Evolution of the literature identifying physicians' roles in leadership, clinical development, and practice of the subspecialty of emergency medical services. *Prehosp Disaster Med* 2011; 26:49.
32. Neumar CW, et al: Part 8: Adult Advanced Cardiovascular Life Support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122:S729-S767.
33. Barton ED, et al: Intranasal administration of naloxone by paramedics. *Prehosp Emerg Care* 2002; 6:54.
34. Lahat E, et al: Comparison of intranasal midazolam and intravenous diazepam for treating febrile seizures in children: Prospective randomized study. *BMJ* 2000; 321:83.
35. Department of Transportation–National Highway Traffic Safety Administration: *"Star of Life" Emergency Medical Care Symbol*. Washington, DC: U.S. Department of Transportation; 1979. Publication No. HS-803-721.
36. National Association of Emergency Medical Services Physicians Position Paper: Emergency medical dispatching. *Prehosp Disaster Med* 1989; 4:163.
37. Feldman MJ, et al: Comparison of the medical priority dispatch system to an out-of-hospital patient acuity score. *Acad Emerg Med* 2006; 13:954.
38. Hinchey P, et al: Low acuity EMS dispatch criteria can reliably identify patients without high-acuity illness or injury. *Prehosp Emerg Care* 2007; 11:42.
39. Alonso-Serra H, Blanton D, O'Connor RE: Position paper, National Association of EMS Physicians: Physician medical direction in EMS. *Prehosp Emerg Care* 1998; 2:153.
40. Polsky S, et al; American College of Emergency Physicians: Guidelines for medical direction of prehospital EMS. *Ann Emerg Med* 1993; 22:742.
41. U.S. Department of Transportation–National Highway Traffic Safety Administration, National Association of EMS Physicians, American College of Emergency Physicians, Health Resources and Services Administration–Maternal and Child Health Bureau: *Guide for Preparing Medical Directors*. Washington, DC: U.S. Department of Transportation; 2001.
42. Persse DE, Key CB, Baldwin JB: The effect of a quality improvement feedback loop on paramedic-initiated nontransport of elderly patients. *Prehosp Emerg Care* 2002; 6:31.
43. Blackwell TH, Kaufman JS: Response time effectiveness: Comparison of response time and survival in an urban emergency medical services system. *Acad Emerg Med* 2002; 9:288.
44. Pons PT, et al: Paramedic response time: Does it affect patient survival? *Acad Emerg Med* 2005; 12:594.
45. Blackwell TH, et al: Lack of association between prehospital response times and patient outcomes. *Prehosp Emerg Care* 2009; 13:444.
46. Newgard CD, et al; Resuscitation Outcomes Consortium Investigators: Emergency medical services intervals and survival in trauma: Assessment of the "golden hour" in a North American prospective cohort. *Ann Emerg Med* 2010; 55:235.
47. Kurola J, et al: Airway management in cardiac arrest—comparison of the laryngeal tube, tracheal intubation and bag-valve mask ventilation in emergency medical training. *Resuscitation* 2004; 61:149.
48. Guyette FX, et al: Feasibility of laryngeal mask airway use by prehospital personnel in simulated pediatric respiratory arrest. *Prehosp Emerg Care* 2007; 11:245.
49. Hoyle JD, et al: Comparative study of airway management techniques with restricted access to patient airway. *Prehosp Emerg Care* 2007; 11:330.
50. Mizelle HL, et al: Preventable morbidity and mortality from prehospital paralytic assisted intubation: Can we expect outcomes comparable to hospital-based practice? *Prehosp Emerg Care* 2002; 6:472.
51. Davis DP, et al: The effect of paramedic rapid sequence intubation on outcome in patients with severe traumatic brain injury. *J Trauma* 2003; 54:444.
52. Katz SH, Falk JL: Misplaced endotracheal tubes by paramedics in an urban emergency medical services system. *Ann Emerg Med* 2001; 37:62.

www.ketabpezeshki.com 66485457-66963820

53. Davis DP: Prehospital intubation of brain-injured patients. *Curr Opin Crit Care* 2008; 14:142.
54. Gausche M, et al: Effect of out-of-hospital pediatric endotracheal intubation on survival and neurological outcome: A controlled clinical trial. *JAMA* 2000; 283:783.
55. National Association of EMS Physicians Position Paper: Drug-assisted intubation in the prehospital setting. *Prehosp Emerg Care* 2006; 10:260.
56. Burton JH, et al: Endotracheal intubation in a rural EMS state: Procedure utilization and impact of skills maintenance guidelines. *Prehosp Emerg Care* 2003; 7:352.
57. Kallio T, Kuisma M, Alaspää A, Rosenberg PH: The use of prehospital CPAP treatment in presumed acute severe pulmonary edema. *Prehosp Emerg Care* 2003; 7:209.
58. Kosowsky J, et al: Prehospital use of CPAP for presumed pulmonary edema: A preliminary case series. *Prehosp Emerg Care* 2006; 5:190.
59. Eisenberg MS, et al: Cardiac arrest and resuscitation: A tale of 29 cities. *Ann Emerg Med* 1990; 19:179.
60. Folke F, et al: Location of cardiac arrest in a city center: Strategic placement of automated external defibrillators in public locations. *Circulation* 2009; 120:510.
61. Patel RJ, Vilke GM, Chan TC: The prehospital electrocardiogram. *J Emerg Med* 2001; 21:35.
62. Ferguson JD, et al: The prehospital 12-lead electrocardiogram: Impact on management of the out-of-hospital acute coronary syndrome patient. *Am J Emerg Med* 2003; 21:136.
63. Bobrow BJ, et al: Minimally interrupted cardiac resuscitation by emergency medical services for out-of-hospital cardiac arrest. *JAMA* 2008; 299:1158-1165.
64. Peberdy MA, et al: Part 9: Post Cardiac Arrest Care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010; 122:S768-S786.
65. Bernard SA, et al: Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; 346:557.
66. The Hypothermia After Cardiac Arrest Study Group: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002; 346:549.
67. Kudenchuk PJ, et al: Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med* 1999; 341:871.
68. Davis DP, et al: The relationship between out-of-hospital airway management and outcome among trauma patients with Glasgow Coma Scale Scores of 8 or less. *Prehosp Emerg Care* 2011; 15:184.
69. Kragh JF Jr, et al: Survival with emergency tourniquet use to stop bleeding in major limb trauma. *Ann Surg* 2009; 249:1.
70. Haul ER, et al: Prehospital intravenous fluid administration is associated with higher mortality in trauma patients: A National Trauma Data Bank analysis. *Ann Surg* 2011; 253:371.
71. Testa PA, Gang M: Triage, EMTALA, consultations, and prehospital medical control. *Emerg Med Clin North Am* 2009; 27:627.
72. American College of Emergency Physicians: Appropriate interhospital patient transfer. *Ann Emerg Med* 1993; 22:766.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 191

Air Medical Transport

Howard Rodenberg, Ira J. Blumen, and Stephen H. Thomas

PERSPECTIVE

The history of air medical transport (AMT) dates to before World War I, when the French evacuated soldiers from Serbia using airplanes as ambulances as early as 1915. The first recorded use of a U.S. military air ambulance was in 1918 when an airplane was converted to accommodate a litter patient in the rear cockpit. During World War II, more than 1.1 million sick and wounded soldiers were airlifted to the United States during the last 3 years of the war. The Korean War introduced the helicopter to AMT, and more than 20,000 battlefield medical evacuations were flown during the conflict. During the Vietnam War, Operation Dustoff transported nearly 1 million of the injured from the front lines to care.

The impact of AMT on the wounded soldier was clear. During World War II, the average time from injury to definitive care was 6 to 12 hours, with a mortality rate of 5.8%. In Korea, the time was 2 to 4 hours, with 2.4% mortality. In Vietnam, the time was 65 minutes, and mortality was less than 1%.[1] Encouraged by the military experience, civilian AMT in the United States was propelled by the 1969 start of the first hospital-sponsored, fixed-wing air medical program. The first civilian helicopter emergency medical services (HEMS) program in the United States was established in 1972.

AVIATION PHYSIOLOGY

A working knowledge of aviation physiology is vital to understanding of the effects of AMT on pilots, medical personnel, and patients.[2]

Boyle's Law

The cornerstone of aviation physiology is Boyle's law, which states that the volume of a unit of gas ("unit" defined as a specific number of molecules) is inversely proportional to the pressure on it. In concrete terms, Boyle's law means that as altitude increases and atmospheric pressure decreases, the molecules of gas grow apart, and the volume of the gas expands. With descent (increasing atmospheric pressure), the molecules are condensed, and gas volumes contract.

Physiologic difficulties from expansion and contraction of gases within the closed spaces of the body may occur with altitude change. Squeeze injuries from contraction of air and associated soft tissues within closed cavities occur on descent and are common causes of barotitis, barosinusitis, and toothache. Reverse squeeze injuries occur on ascent, as decreasing barometric pressure leads to an increased volume of the air trapped within the space, exerting pressure on structures. Ascent injuries can include conversion of a simple pneumothorax into a tension pneumothorax or rupture of a hollow viscus by expansion of intestinal gas. The operation of medical equipment containing closed air spaces, such as intravenous tubing and pumps, air splints, ventilators, and endotracheal tube and laryngeal airway cuffs, may also be affected by altitude.[3-7]

Boyle's law is predominantly responsible for the presence of hypoxia at altitude as there are fewer molecules of oxygen present per volume of inhaled gas at altitude. Similarly, dispersion of molecules of water vapor within a gas volume is seen at height, and "dry air" results.

Charles' Law

Charles' law follows from the volume effects of Boyle's law. It notes that as the volume of a unit of gas rises, the temperature of that volume falls. The molecular dispersion seen with increases in gas volume at altitude (Boyle's law) means there is less chance of molecular collision with resulting generation of heat. Charles' law explains why the ambient temperature decreases with increased altitude.

Dalton's Law

Dalton's law states that the total barometric pressure at any given altitude equals the sum of the partial pressures of gases in the mixture ($P_t = P_1 + P_2 + P_3 \ldots P_n$). Whereas oxygen still constitutes 21% of the atmospheric pressure at altitude, Boyle's law notes that each breath brings fewer oxygen molecules per breath to the lungs, and hypoxia results (Table 191-1). The clinical effect of Dalton's law is manifested as a decrease in arterial oxygen tension with increasing altitude.

Initial physiologic responses to hypoxia include tachypnea and tachycardia. With prolonged exposure, oxygen supply to the brain becomes insufficient to support cerebral metabolism. Progressive cerebral hypoxia causes headache, nausea, drowsiness, fatigue, unconsciousness, and death. Although the onset and severity of symptoms may vary with individuals, no one is exempt from the effects of hypoxia.

Henry's Law

Henry's law states that the mass of gas absorbed by a liquid is directly proportional to the partial pressure of the gas above the liquid. Henry's law has its most familiar applications in diving medicine, in which the increased pressure exerted on gases in the body at depth forces the gases into solution in the bloodstream. Rapid ascent from depth causes the gas to come out of solution within the bloodstream, resulting in decompression sickness.

www.ketabpezeshki.com 66485457-66963820

Table 191-1 Effects of Altitude on Oxygenation

ALTITUDE (ft)	BAROMETRIC PRESSURE (mm Hg)	Po_2 (mm Hg)	PAO_2 (mm Hg)	$Paco_2$ (mm Hg)	OXYGEN SATURATION (%)
Sea level	760	159.2	103.0	40	98
8,000	565	118.4	68.9	36	93
10,000	523	109.6	61.2	35	87
15,000	429	89.9	45.0	32	84
18,000	380	79.6	37.8	30.4	72
20,000	349	73.1	34.3	29.4	66
22,000	321	67.2	32.8	28.4	60

PAO_2, partial pressure of alveolar oxygen; $Paco_2$, partial pressure of arterial carbon dioxide.

Henry's law does not carry the same weight in aviation medicine because the degree of change in atmospheric pressure per unit of distance is considerably less than the degree of change in water. However, sudden decompression at altitude may result in dysbarism.

Additional Stresses of Flight

Other stresses of flight that can affect the patient or crew include temperature fluctuations, dehydration, noise, and vibration. Temperature changes may produce increases in metabolic rate and oxygen consumption. As noted, at altitude the moisture per volume of air falls. Fluid intake should be monitored carefully during transport, and all patients should receive humidified medical oxygen. Noise and vibration represent the most ubiquitous stresses encountered in AMT, and both may interfere with patient care or the function of medical equipment. Hearing protection should be worn at all times during aircraft operations by patient and crew. Exposures to environmental extremes may result in fatigue, motion sickness, disorientation, ear damage, and deterioration in task performance.

PRINCIPLES OF AIR MEDICAL TRANSPORT SYSTEMS

Administrative Structure

Air medical services may take several forms. Despite a tremendous growth of operations in the past 20 years, the most common type of HEMS program in the United States remains the hospital-sponsored operation transporting patients from outlying referral centers or accident scenes to tertiary care centers. A single hospital or a consortium of institutions may sponsor these flight programs. In 2011, there were more than 220 dedicated HEMS programs operating more than 750 dedicated aircraft throughout the nation.[8] Approximately 54% of the programs were hospital sponsored, and the balance were operated by privately owned or publicly traded companies. Whereas these for-profit companies represent 46% of the programs, they operate more than 61% of the dedicated helicopters in the United States.[8] Public service agencies may also sponsor air medical services or partner with private companies; vehicles used by these programs are often multifunctional aircraft that serve in medical, search and rescue, fire suppression, and law enforcement roles. The Military Assistance to Safety and Traffic (MAST) program operated by the U.S. Armed Forces provides additional HEMS resources to the community,[9] but in recent years their role for civilian support has been generally limited to Hawaii and Alaska.[9] Together, the public service and MAST helicopters add more than 120 additional aircraft available for patient transport.[8] There is no accurate accounting of the number of fixed-wing air ambulance companies or airplanes. Although some hospitals do sponsor fixed-wing AMT, it is more common for these programs to be private fee-for-service operations.

Types of Missions

Air medical missions may involve primary or secondary response. Primary responses ("scene flights") are responses in which the aircraft serves as the sole means of patient transport to a receiving facility. Aircraft involved in secondary responses—interfacility transport—move patients from outlying hospitals to facilities offering higher levels of care. AMT missions may also be classified according to the level of care provided. This may be critical care transport, specialty care transport, or advanced or basic life support.

Air Medical Aircraft

Although the ground ambulance remains the primary means of out-of-hospital and interfacility patient transport, the use of the air ambulance has grown significantly since the 1970s. No one aircraft is ideal for the needs of all air medical programs or patients.

Helicopters (Rotor-Wing Aircraft)

The helicopter offers several advantages over other transport vehicles. Traveling "as the crow flies" at speeds of 120 to 180 mph, helicopter transport time is often 75% less than that for an equivalent distance by ground. The service area of helicopter programs is generally up to 150 to 200 miles from its base of operations. Rotor-wing aircraft have the ability to avoid common traffic delays and ground obstacles and can fly into locations that may be inaccessible to other modes of travel. Helicopter landing zone requirements are a disadvantage compared with ground ambulances but offer an advantage over the airport requirements of airplanes.

Disadvantages to HEMS include noise, vibration, thermal variances, and other stressors on patients and crew exaggerated by rotor-wing flight. Weather considerations may significantly limit the availability of helicopter transport. In smaller aircraft, cramped spaces and weight limitations may limit the number of patients, transport personnel, or equipment that can be carried. This may sometimes compromise optimal patient care (Fig. 191-1).

Many helicopter programs permit flight only under visual flight rules. When the weather conditions (ceiling and visibility) fall below established program minimums, a program may decline to undertake a transport for safety reasons. However, an increasing

www.ketabpezeshki.com 66485457-66963820

Figure 191-1. Confined spaces within helicopters may make it more challenging to perform procedures. (Photograph courtesy Ira Blumen, MD.)

number of programs are equipping their helicopters and training their pilots for instrument flight rules (IFR) to allow safe travel in less favorable weather conditions. IFR flight may facilitate use of fixed locations, such as hospital helipads, but it does not facilitate travel to the scene of illness or injury.

Airplanes (Fixed-Wing Aircraft)

Although rotor-wing missions attract more media attention, fixed-wing flights constitute a significant portion of AMT operations. Fixed-wing aircraft provide increased range, greater speed, and often more patient, crew, and equipment capacity than do rotor-wing vehicles. The decreased cabin noise and turbulence creates fewer patient management problems, and pressurization combats the physiologic impact of altitude. Fixed-wing operations are limited to areas that have airports with runways of appropriate length or condition and refueling facilities. During fixed-wing transports, patient transfers require multiple vehicles to go from hospital to airport and back.

Various fixed-wing aircraft are available for medical transport. These range from unpressurized light planes with single- or twin-piston engines to pressurized turboprops and jets. The selection of the ideal aircraft depends on the nature of the air medical mission.

Air Medical Flight Crew

Air medical crew members represent the broad spectrum of health care providers. AMT services that provide critical care transport, advanced life support, or specialty care transport must staff the vehicle with a minimum of two medical personnel to provide direct patient care.[10,11] The majority of AMT programs in the United States provide critical care transport teams composed of one registered nurse and an additional crew member (paramedic, respiratory therapist, physician, or a second nurse); most common is the nurse-paramedic crew.[12] AMT crew configuration may also be mission dependent. A service may at times believe that it is appropriate to use a single medical crew member. For example, it may be appropriate while transporting a stable patient on a routine interfacility transport. Certain flight conditions and situations may also necessitate flying with a single crew member, including heat, humidity, altitude, distance, fuel on board, and weight of the patient.[12]

Flight nurses generally have extensive experience in intensive care units or emergency departments. They may be specialized within the transport team to care for adult, pediatric, or neonatal patients. Paramedics often make their greatest contribution in the transport of critical patients from the scene of illness or injury. Respiratory therapists bring expertise in airway and ventilator management and oxygen delivery systems. Flight physicians may be residents or attending physicians. Much of the early research in AMT crew composition focused on the need for the flight physician. Although this remains controversial, what seems clear is that the crew used by an AMT program must be explicitly tailored to the needs of the community and the patients it serves.

The AMT environment imposes unique considerations on the air medical flight crew that can influence their ability to provide patient care. Human factors work has shown that most medical care procedures are more difficult to perform in an AMT vehicle than in other ground-based settings.[13] Auscultation of the heart and lungs, palpation of pulses, performance of cardiopulmonary resuscitation, endotracheal intubation, radio communications while using a respirator or face mask, and recognition of visual alarms may all be impaired while aloft.[14-19] In addition, fatigue, motion sickness, exposure to engine exhausts, an erratic pattern of work activity, and the high risk involved in AMT operations may affect task performance significantly.[20-22] Seizures from photic stimuli associated with rotor motion ("flicker illness") has also been reported.[23] High-fidelity simulation of air medical missions can acquaint flight crew to the novel environment, but fiscal and personnel costs may be prohibitive.[24]

Medical Direction

All air medical services require the active involvement of a physician as medical director responsible for supervising, evaluating, and ensuring the quality of medical care provided by the AMT team.[25] Emergency physicians play a significant role, with nearly 50% of all air medical directors having a background in emergency medicine.[26] The medical director must have the final authority over all clinical aspects of the air medical service and should ensure that the flight crew have adequate training and qualifications to optimize patient care. Medical care policies and procedures should be established, including specific provisions for on-line and off-line medical control. The Air Medical Physician Association and the National Association of EMS Physicians have established guidelines for the medical director of an air medical service.[27,28]

Safety

Safety is the predominant concern of air medical operations, and ensuring safe flight is a fundamental part of every flight program.[29] Safety must also be an overriding consideration in weighing the risks and benefits of AMT. The role of aircraft pilots and mechanics is essential to the airworthiness of the vehicle, and medical personnel must also be proficient in both routine and emergency operations in and around the aircraft. Checklists may aid in safety practices but alone may not detect significant operational concerns.[30] Crew fatigue and other self-imposed stresses that could affect safety, such as the use of prescription or over-the-counter medications, tobacco, and alcohol, must be scrupulously avoided.

Weather requirements ("minimums") must be strictly enforced. On receipt of a flight request, the pilot must verify the weather conditions and the condition of the aircraft. To ensure impartiality, the pilot should not be told of the patient's condition or acuity. The pilot maintains the unquestioned right to decline a mission because of aircraft or weather considerations.

The practice of "helicopter shopping" has been a major factor in a number of fatal HEMS events. Helicopter shopping refers to

www.ketabpezeshki.com 66485457-66963820

Figure 191-2. Landing zone safety is paramount to delivery of patients to hospitals. (Photograph courtesy Dan Lemkin, MD.)

the practice of a requesting EMS agency or hospital calling numerous HEMS operators until one agrees to accept a flight without disclosure to the accepting HEMS operator that other programs have declined the flight because of bad weather or other safety concerns.[31,32] The practice has been so common that in 2006, the Federal Aviation Administration issued a letter to all state EMS directors describing helicopter shopping and requesting that they take action to prohibit this practice.[33]

Landing Zones

Helicopter landing zones are inherently dangerous places. The most obvious risk of injury is impact with rotor blades. This danger is heightened during ground operations because the blades dip lowest to the ground at the slower rotor speeds associated with engine start-up and shutdown. Injuries also may occur as a result of debris being propelled through the air by "rotor wash," increased noise levels and an inability to hear warnings, and slippery surfaces found on exposed landing sites.

Many hospitals have designated landing areas that are appropriately lit and secured (Fig. 191-2), with fixed coordinates and predesignated liftoff and approach patterns. However, most primary (scene) responses occur at unmarked sites. Ground personnel must be trained to designate and secure a safe landing zone for helicopter operations. AMT programs have an obligation to help train ground staff on proper landing zone setup and conduct (Boxes 191-1 and 191-2).

Helicopter flights direct to the scene of an accident pose unique risks to AMT from hazards near the landing zone. This risk is heightened at night. In response to this concern, out-of-hospital care providers and flight programs have found it beneficial and safer to use a hospital helipad for rendezvous. This practice raised concerns about Emergency Medical Treatment and Active Labor Act (EMTALA) responsibilities to provide a medical screening examination for these patients. In May 2004, the Centers for Medicare and Medicaid Services resolved this issue, noting that the use of a helipad on hospital property does not trigger EMTALA provisions as long as the helipad is being used only as a stopping place for EMS personnel to rendezvous with AMT, facilitating transport of a patient to the closest appropriate facility.[34]

Other adjuncts to landing zone safety and night operations in general are night vision goggles and terrain avoidance warning systems. A growing number of AMT programs are equipping their aircraft with these sophisticated technologies in an effort to enhance safety.

Box 191-1 Landing Zone Safety

Vehicles and personnel should be kept at least 100 ft from the landing zone.
Spectators should be kept at least 200 ft from the landing zone.
No smoking or running is permitted within 50 ft of the helicopter.
All items (e.g., intravenous lines, poles) should be kept below shoulder height.
The flight crew opens and closes aircraft doors.
The flight crew directs and supervises the loading and unloading of the patient and equipment.
Ground personnel should use eye and ear protection.
Approach the helicopter *only* when signaled to do so by the pilot or an onboard crew member.
Approach and depart the helicopter *only* forward of the rear cabin door and in a crouched position with your head down.
Never approach or depart from the rear of the helicopter.
Stay clear of the tail rotor; it is virtually invisible and extremely dangerous.
If the aircraft is parked on a slope, approach and depart on the downhill side (greatest clearance under the blades).
Keep the landing zone clear of (or hold on to) all loose articles (e.g., hats, scarves, sheets, pillows).
Protect patient from the dust and debris.
Follow the flight crew's instructions at all times.
In disaster situations and mass casualty incidents, victims, witnesses, and spectators may become hysterical or exhibit signs of an acute situational reaction. These individuals must be kept clear of the landing zone and helicopter *at all times.* Injured victims who exhibit this behavior should *not* be triaged for helicopter transport, or they should be transported *only* with adequate physical or chemical restraints in use.
If you do not know, ask.

Courtesy University of Chicago Aeromedical Network (UCAN), University of Chicago Medical Center and Illinois Association of Air and Critical Care Transport (IAACCT), 2011.

Integration of Air Medical Transport within Emergency Medical Service Systems

AMT should be an integral resource within a comprehensive EMS system. Integration begins with the establishment of geographic service areas. Service areas may be determined on the basis of program mission description, aircraft range and speed, placement of specialty centers and receiving facilities, and population densities. As a general rule, helicopters are generally less useful in urban settings because of the proximity of health care facilities and a lack of open and safe landing zones. Paramedics, emergency medical technicians, and other public safety personnel should be provided with guidelines specifying when AMT should be considered. These protocols are best developed by EMS medical directors in close collaboration with their air medical colleagues.

CLINICAL CONCEPTS AND PATIENT CARE

Although virtually all types of patients have been transported by air medical services, available data do not allow prospective, definitive identification of which patients will benefit from flight. Many questions about the triage of patients to air or ground transport, the efficacy of air medical care, and the precise effects of AMT on morbidity and mortality in medical and surgical conditions remain unanswered. There are volumes of studies indicating what patients *can* be cared for in the air medical environment and what skills and equipment *can* be used, and there are also many studies

www.ketabpezeshki.com 66485457-66963820

Box 191-2 Landing Zone (LZ) Requirements for Air Medical Transport

Landing Area

LZ should be as close as possible to the scene or hospital entrance, but not so close that it may interfere with ground operations or patient care.
LZ should be at least 100 × 100 ft.
LZ should be as flat and level as possible.
LZ *must* be clear of debris.

Hazards and Obstructions

Identify all potential hazards that may be on the ground or near the approach/departure path of LZ.
LZ should be clear of wires, poles, trees, buildings, vehicles, and spectators.
Road cones, ropes, tape, and barricades are *not* recommended for use near LZ.
Perimeter of LZ should be at least 50 ft away from potential obstructions and hazards.
LZ should be located *upwind* from any hazardous material incident.

Approach and Departure Path

Path should point into the wind and be free of obstruction to an altitude of 500 ft above the surface.
Path should *not* pass over command posts, treatment areas, or operationally congested areas on the ground.

Day Operations

Use radio communications and hand signals.
Stand with your back to the wind.

Night Operations

Use radio communications and lighting to designate LZ.
Spotlights should be directed at the top of possible hazards, *not* toward the approaching or departing aircraft.
Position a portable light, vehicle headlights, emergency vehicle flashing lights, flare, or chemical stick at each corner, with a fifth light upwind.
Nonessential lights should be turned off.

Light Sources

Lights *must* be clear of LZ.
If portable, lights *must* be well secured.
Never point lights toward an approaching or departing helicopter.

Wind Indicator

Indicator may be a wind sock, flag, flare, or smoke.
Indicator *must* be clear of LZ.
If portable, indicator *must* be well secured.

Courtesy University of Chicago Aeromedical Network (UCAN), University of Chicago Medical Center and Illinois Association of Air and Critical Care Transport (IAACCT), 2008.

demonstrating benefit to air transport. Unfortunately, there is a relative paucity of clinical investigation addressing potential solutions to the problems of triage and appropriate use. What does seem clear is that medical flight is generally associated with safe patient care and a low incidence of adverse effects.[35] In an effort to ensure that AMT resources are used wisely, the Air Medical Physician Association (AMPA) has established a detailed medical condition list for the appropriate use of AMT.[36] A more general approach to the need for AMT is illustrated in Box 191-3.

Trauma

Most trauma studies have addressed air medical use for scene response.[37] Methodological heterogeneity precludes formal meta-analysis of the AMT outcomes data. However, existing data support an estimate of 20 to 35% improvement is survival rates, or the saving of three to six lives (fewer for pediatric patients) per 100 air medical trauma flights.[38-46] As demonstrated by a large 2011 study assessing nearly 75,000 secondary HEMS transports, interfacility air transport of the more seriously injured patient (but not those with lesser severity) is also associated with improved outcomes.[47] Two studies also found improved outcomes with seriously injured patients transported by HEMS while also concluding that stable patients may be transported from outlying hospital to definitive care by ground with equal effect.[47,48] Noting that HEMS represents the *only* modality by which nearly 28% of U.S. residents have timely (within 1 hour) access to level I or level II trauma centers emphasizes the vital role of AMT in care of the injured patient.[49] Studies have also presented data that suggest lack of HEMS benefit for the trauma victim, but these studies represent a minority of works and are limited by confounding factors such as inclusion of transports to nontrauma centers.[50] Whereas caution should be exercised in definitive statements about the criteria for and the value of AMT, and such statements can be interpreted only in light of the overall local environment in which the transport system exists, the clear message from the literature is that HEMS functions best as a part of a comprehensive trauma system and not as an isolated entity.[51-53]

Work in HEMS casts doubt on the supposed logistical advantages of the helicopter itself.[54] Faster times to trauma centers are not required for the accrual of better outcomes. It is true that in some studies, subgroup analyses suggest improved trauma outcomes due to HEMS scene response for the more severely injured.[55] However, studies conducted in regions as disparate as California and The Netherlands demonstrate HEMS mortality benefit but find similar scene–to–trauma center times for ground and air transports.[45,56] It seems clear that for many patients, factors other than speed (such as the provision of advanced levels of care over that provided by ground personnel) are responsible for AMT's benefits.

In terms of specific populations of patients, some studies suggest that most trauma victims transported by air have non–life-threatening injuries.[57] Fortunately, the best large-scale population analysis, of more than 40,000 HEMS transports from the 2007 American College of Surgeons National Trauma Data Bank, clearly demonstrates that HEMS-transported patients are indeed of much higher acuity than ground-transported patients.[37] For example, the median Injury Severity Score of HEMS patients exceeded the commonly used "severe injury" cutoff of 15; HEMS patients also had a 43% rate of intensive care unit admission.[37] If we look more specifically within the trauma population, we find that data from Pennsylvania and California of head injury patients undergoing out-of-hospital intubation demonstrate HEMS-associated improvements in both morbidity and mortality.[58,59] A 2009 study from Italy confirmed the association between HEMS transport and improved head injury outcome as assessed by either mortality or functional endpoints.[60]

AMT is unlikely to improve outcome in those whose injuries are either trivial or grave. However, if the Injury Severity Score is collapsed into five ordinal categories, a significant association between helicopter transport and improved mortality is found in the middle three categories (survival odds ratios range from 2.1 to 2.6). Other work has also found that AMT shows benefit over ground transport only for those more seriously injured patients in both rural and urban environments.[61,62] In all these cases, it remains uncertain if improvements in outcome are related to the provision of improved on-scene care or the integration of HEMS into a comprehensive trauma system as opposed to the air transport itself. Fortunately, even the acknowledged imprecision of triage to HEMS does not preclude "real-world" identification of AMT-associated trauma outcomes benefit. In a 2010 population-based study in Canada, patients were entered into the study if HEMS services were requested, and outcomes were compared between those who actually underwent AMT and those who went

www.ketabpezeshki.com 66485457-66963820

Box 191-3 Criteria for Air Medical Transport (AMT)

Distance to the closest appropriate facility is too great for safe and timely transport by ground ambulance.
Patient's clinical condition requires that the time spent in transport be as short as possible.
Patient's condition is time critical, requiring specific or timely treatment not available at the referring hospital.
Potential for transport delay associated with ground transport is likely to worsen the patient's clinical condition.
Patient requires critical care life support during transport that was not available from the local ground ambulance service.
Patient is located in an area inaccessible to regular ground traffic, impeding ambulance egress or access.
Local ground units are not available for long-distance transport.
Use of local ground transport services would leave the local area without adequate EMS coverage.
For interfacility medical transport, the requesting physician based on his/her best medical judgment and information available at that time of transport determined the need for AMT.
For scene medical transport, the requesting authorized out-of-hospital provider based on applicable policy, his/her best medical judgment and information available at that time of transport determined the need for AMT.

Courtesy University of Chicago Aeromedical Network (UCAN), University of Chicago Medical Center, 2011. Based on Association of Air Medical Services: Position paper on the appropriate use of emergency air medical services. J Air Med Transp 9:29, 1990; and Determination of medical necessity for air and critical care medical transportation. Position statement of the Air Medical Physician Association. Revised April 13, 2002. In: Blumen IJ (ed): Principles and Direction in Air Medical Transport. Salt Lake City, Utah, Air Medical Physician Association, 2006.

by ground because of the unavailability of HEMS. The study identified a benefit of HEMS, compared with ground transport, of 5.61 more lives saved per 100 transports.[62]

Cardiac Disorders

The ability to study HEMS-related outcomes benefit in acute coronary syndrome is limited by the lack of validated scores that can be used to stratify risk and to predict outcome. Works have noted that helicopter transport extends the geographic referral base of primary angioplasty centers and that outcomes of patients flown from a distance for definitive care equal outcomes of patients presenting primarily to the referral center.[63] AMT systems have been shown to be able to safely transport complicated cardiovascular patients with conditions such as acute coronary syndrome, ST segment elevation myocardial infarction, and aortic aneurysm.[64-67]

Although HEMS could conceivably shorten door to percutaneous coronary intervention (PCI) time by transporting patients with ST segment elevation myocardial infarction rapidly from hospitals without PCI capability to a referral center, in many circumstances the patient will not have angioplasty of the infarct-related vessel performed within the recommended window and would be best served by receiving thrombolytic therapy at the initial hospital and then being transported in a less emergent fashion. AMT might therefore be better used for transport of critical cardiology patients who require emergent care, such as bypass surgery or balloon pump support, that is beyond the capability of the sending hospital.

Stroke

With the advent of time-critical therapy for ischemic stroke, HEMS has played an increasing role in the regionalization of acute neurologic care. Early studies demonstrating safety of transport of post-thrombolysis stroke patients have been complemented by case series illustrating the increasing use of helicopter interfacility transport for stroke.[68,69] Case reports and series have demonstrated the utility of air medical dispatch for primary (scene) transport of patients with strong suspicion of stroke.[70-72] In one region, ground EMS providers were able to identify stroke with accuracy, and helicopter-transported patients composed nearly 25% of the stroke center's thrombolytic volume. The use of strict triage definitions kept inappropriate calls for AMT to acceptably low levels while allowing a significant extension of the geography served by an individual stroke center.[71] Performance measurement programs can monitor the efficacy of the AMT service.[72]

Pregnancy

With appropriate triage, the speed of air transport of the high-risk pregnancy can counterbalance the risk of delivering an infant in an aircraft's confined space.[73,74] Case series demonstrate that high-risk obstetric patients transported by air from distant hospitals have outcomes as good as those of patients presenting primarily to an obstetric referral center.[73,75] Common reasons for obstetric transport include preterm labor and premature rupture of membranes.[76]

Neonates and Children

The use of AMT to extend the geographic reach of neonatal care centers is reported from many settings.[77,78] The most rigorous analysis suggests that long-distance AMT allows infants with medical complications born in remote areas to achieve outcomes equal to those of infants born in urban centers. Although neonates are vulnerable to physiologic deterioration, specialty team air transport is associated with no more derangement in oxygenation and ventilation than is transport by ground vehicle.[77] As in the case of trauma, the question remains if the advantage of AMT is related to the use of air transport or specialty services brought to the patient's side.

Many areas depend on AMT to deliver critically ill or injured children to regional pediatric centers. Although speed of transport may be an important consideration, as with neonates it seems the emphasis is often more on the transport *team* than on the *mode* of transport. Experienced pediatric transfer teams often bring a level of expertise unavailable to the pediatric patient in the outlying hospital and are noted to have fewer adverse events during transport than nonspecialty teams.[79-81] Appropriate training, experience, and competency are essential for those responsible for transport.[82] AMT has been shown to be safe for moving of even the most critical children requiring extracorporeal membrane oxygen support.[83]

EFFICACY AND COST-EFFECTIVENESS

Cost-benefit is an area of increasing focus for AMT. The crux of the problem lies in the inability to precisely identify in a prospective manner which patients will truly benefit from fixed-wing or rotor-wing flight. As a result, in many cases there is little if any guidance regarding when air medical dispatch is indicated.[84] With use of endorsed guidelines (such as those endorsed by the AMPA) for air medical dispatch, EMS regional authorities should collaborate to generate criteria best for their own systems, with constant refinement guided by rigorous use review.[85] Despite this ideal, however, in practice the lack of firm indications and guidelines means that AMT often acts more as a "taxi service" responding to the needs of referring physicians, hospitals, and EMS services

www.ketabpezeshki.com 66485457-66963820

rather than the actual needs of the patient. There is a strong economic argument to be made for maintaining this "looseness" of service, as flight revenues keep AMT services available for those truly in need.

Compared with the cost-benefit ratios of other medical interventions, AMT is well within the accepted range per quality-adjusted life-year saved.[86-88] One Scandinavian study concluded that the benefits of ambulance missions flown by helicopters exceed the costs by a factor of almost six.[89] Another group from the region estimated that HEMS contributes to the cost-effectiveness of primary PCI, and other investigators have demonstrated the favorable cost-effectiveness of helicopter stroke transports.[90,91] However, these results cannot be taken as definitive statements on a global basis, as any cost-benefit calculation is applicable only within the health care environment of the system under study.[92]

Cost-effectiveness determinations are not straightforward. It is difficult to calculate true cost-effectiveness for transports that are not likely to occur (as with high-risk obstetrics cases at risk of precipitous delivery)[73] or that would deliver patients outside critical time windows (as for stroke or cardiac transports) in the absence of AMT.[68,93] Cost-efficiency is also difficult to demonstrate when there are no comparison options (such as transport from coastal islands or locations without road access) or when integrated ground and air transport systems have already become established in ways that effectively prohibit head-to-head comparisons of risks and outcomes (as is true in most of the United States). If we accept that HEMS represents the only mechanism by which more than 80 million U.S. citizens have timely access to mortality-improving high-level trauma center care,[49] it is obvious that some form of air transport is a "must-have" for some EMS regions, and calculations of cost-efficiency fall away in favor of service provision.

Although transport by air is nearly always more expensive than that by ground, the costs of air medical flight should be viewed in contrast with the "real-life" alternative mode of transport. In many cases, and especially where time and distance are significant factors, the total fiscal and opportunity costs of AMT are arguably less expensive than the alternative.[94] Unfortunately, the work of assessing the cost-effectiveness of AMT is complicated by the extremely limited amount of information on the cost-effectiveness of ground-based modes of transport.[95] Experts assessing existing literature have concluded that although the available data do not enable rigorous meta-analysis, most investigations do demonstrate that appropriately used HEMS is cost-effective.

FUTURE OF AIR MEDICAL TRANSPORT

AMT works best and provides the most benefit to the patient when it is integral to and enhances an overall system of out-of-hospital care and interfacility transport and when systems are in place to educate requesting agencies and professionals about the appropriate use of available air and ground resources.

This work has noted that the major challenge within the AMT community is to determine not *whether* but rather *in whom* there is benefit to air medical flight. Currently, the major dilemma facing helicopter transport outcomes researchers is the identification of triage variables that can prospectively (i.e., at the time of transport vehicle selection) guide use of the air medical resource.[84,85,96] It also seems that over time, advances in ground-based EMS and the availability of critical care ground ambulances for interfacility transports are beginning to offset many of the assumed benefits of AMT. Nonetheless, the regionalization of specialty services, development of new therapies that are highly time sensitive, and inflexible geography mean that there will always be a role for AMT in emergency care.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Lindsay MB: *Trauma management: Issues for the air medical crew*. In: Blumen IJ, ed. *Principles and Direction in Air Medical Transport*. Salt Lake City, Utah: Air Medical Physician Association; 2006:386-398.
2. Blumen IJ, Callejas S: *Transport physiology*. In: Blumen IJ, ed. *Principles and Direction in Air Medical Transport*. Salt Lake City, Utah: Air Medical Physician Association; 2006:357-377.
3. Wilson GD, Sittig SE, Schears GJ: The laryngeal mask at altitude. *J Emerg Med* 2008; 34:171.
4. Rodriquez D Jr, et al: Effects of simulated altitude on ventilator performance. *J Trauma* 2009; 66:S172.
5. Miyashiro RM, Yamamoto LG: Endotracheal tube and laryngeal mask airway cuff pressures can exceed critical values during ascent to higher altitude. *Pediatr Emerg Care* 2011; 27:367-370.
6. Tollefsen WW, et al: Endotracheal tube cuff pressures in pediatric patients intubated before aeromedical transport. *Pediatr Emerg Care* 2010; 26:361-363.
7. Bassi M, Zuercher M, Erne JJ, Ummenhofer W: Endotracheal tube intracuff pressure during helicopter transport. *Ann Emerg Med* 2010; 56:89-93.e1.
8. Blumen IJ: *HEMS Accident Analysis—The State of the Union*. Presented at the Air Medical Transport Conference; St. Louis, Missouri; October 2011.
9. *Data compiled from the Atlas and Database of Air Medical Services. Center for Transportation Injury Research in alliance with the Association of Air Medical Services and the air medical industry, with support from the Federal Highway Administration and the National Highway Traffic Safety Administration*. Available at www.adamsairmed.org. Accessed October 2010.
10. Warren J, Fromm RE Jr, Orr RA, Rotello LC, Horst HM; American College of Critical Care Medicine: Guidelines for the inter- and intrahospital transport of critically ill patients. *Crit Care Med* 2004; 32:256-262.
11. Commission on Accreditation of Medical Transport Systems: *Accreditation Standards*, 8th ed. Anderson, SC: Commission on Accreditation of Medical Transport Systems; 2010. Available at www.camts.org/component/option,com_docman/task,cat_view/gid,17/Itemid,44/. Accessed May 15, 2011.
12. Stocking JC: *Crew configuration*. In: Blumen IJ, ed. *Principles and Direction in Air Medical Transport*. Salt Lake City, Utah: Air Medical Physician Association; 2006:36-42.
13. Myers KJ, Rodenberg H, Woodard D: Influence of the helicopter environment on patient care capabilities: Flight crew perceptions. *Air Med J* 1995; 14:21.
14. Blumen IJ, Thomas F, Williams D: *Transportation of the critically ill patient*. In: Hall J, ed. *Principles of Critical Care*, 3rd ed. New York: McGraw-Hill; 2005:79-91.
15. Bott S: *Patient care capabilities and limitations*. In: Blumen IJ, ed. *Principles and Direction in Air Medical Transport*. Salt Lake City, Utah: Air Medical Physician Association; 2006:30-35.
16. Driscoll K, Saia M, Thomas S: *Considerations in air medical transport of the critically ill patient*. In: Blumen IJ, ed. *Principles and Direction in Air Medical Transport*. Salt Lake City, Utah: Air Medical Physician Association; 2006:399-405.
17. Eljaik LF, Davidiff JB, Stubba W: *Biomedical equipment and technology in critical care transport*. In: Blumen IJ, ed. *Principles and Direction in Air Medical Transport*. Salt Lake City, Utah: Air Medical Physician Association; 2006:449-457.
18. Havel C, et al: Quality of closed chest compressions in ambulance vehicles, flying helicopters, and at the scene. *Resuscitation* 2007; 73:264.
19. Thomas F, et al: Does wearing a surgical facemask or N-95 respirator impair radio communication? *Air Med J* 2011; 30:97.
20. Braude D, Goldsmith, Weiss SJ: Assessing air medical crew real-time readiness to perform critical tasks. *Prehosp Emerg Care* 2011; 15:254.
21. Gregory KB, Winn W, Johnson K, Rosekind MR: Pilot fatigue survey: Exploring fatigue factors in air medical transport. *Air Med J* 2010; 29:309.
22. MacDonald RD, Thomas L, Rusk FC, Marques SD, McGuire D: Occupational health and safety assessment of exposure to jet fuel combustion products in air medical transport. *Prehosp Emerg Care* 2010; 14:202.
23. Cushman JT, Floccare DJ: Flicker illness: An under-recognized but preventable complication of helicopter transport. *Prehosp Emerg Care* 2007; 11:85.
24. Wright SW, et al: High fidelity medical simulation in the difficult environment of a helicopter: Feasibility, self-efficacy, and cost. *BMC Med Educ* 2006; 6:49.
25. Carrubba C: *Role of the medical director in air medical transport*. In: Blumen IJ, ed. *Principles and Direction in Air Medical Transport*. Salt Lake City, Utah: Air Medical Physician Association; 2006:113-119.
26. Rinnert KJ, Blumen IJ, Gabram SGA, Zanker M: A descriptive analysis of air medical directors in the United States. *Air Med J* 1999; 18:6.
27. *Medical direction and medical control of air medical services: Position statement of the Air Medical Physician Association. Revised April 13, 2002*. In: Blumen IJ, ed. *Principles and Direction in Air Medical Transport*. Salt Lake City, Utah: Air Medical Physician Association; 2006:727-728.
28. Thomas SH, Williams KA, Claypool D: Medical director for air medical transport programs: Position paper of the National Association of EMS Physicians. *Prehosp Emerg Care* 2002; 6:455.
29. Blumen IJ, Lees D: *Air medical safety: Your first priority*. In: Blumen IJ, ed. *Principles and Direction in Air Medical Transport*. Salt Lake City, Utah: Air Medical Physician Association; 2006:519-532.
30. Frakes MA, Van Voorhis S: Effectiveness of a challenge-and-respond checklist in ensuring safety behavior compliance by medical team members at a rotor-wing air medical program. *Air Med J* 2007; 26:248.
31. Alexander RJ; Indiana Association of Air Medical Services: *Helicopter shopping: What hospitals and first responders need to know*. Available at www.in.gov/dhs/files/helicopter_shopping.pdf. Accessed May 16, 2011.
32. Larrabee C; International Association of Flight Paramedics: *Position paper on helicopter shopping*, released September 2006. Available at www.flightparamedic.org/docs/HelicopterShopping.pdf. Accessed May 16, 2011.
33. Federal Aviation Administration: *FAA letter to state EMS Director on helicopter shopping*, August 2006. Available at http://data.memberclicks.com/site/nemsp/FAAStateLetter.pdf. Accessed May 16, 2011.
34. Department of Health and Human Services, Centers for Medicare & Medicaid Services: *Revised Emergency Medical Treatment and Labor Act (EMTALA) Interpretive Guidelines*. Baltimore, Md: Department of Health and Human Services; May 13, 2004. Available at www.cms.hhs.gov/SurveyCertificationGenInfo/downloads/SCLetter04-34.pdf. Accessed May 16, 2011.
35. Macdonald RD, Banks BA, Morrison M: Epidemiology of adverse events in air medical trnapsort. *Acad Emerg Med* 2008; 15:923.
36. Air Medical Physician Association: Medical condition list and appropriate use of air medical transport: Position statement of the Air Medical Physician Association. *Prehosp Emerg Care* 2002; 6:464.
37. Brown JB, et al: Helicopters and the civilian trauma system: National utilization patterns demonstrate improved outcomes after traumatic injury. *J Trauma* 2010; 69:1030-1034; discussion 1034-1036.
38. Schiller J, et al: Improvement of trauma-related mortality with implementation of helicopter transport [abstract]. *J Trauma* 2006; 61:1572.
39. Baxt W, Moody P, Cleveland H: Hospital-based rotorcraft aeromedical emergency care services and trauma mortality: A multicenter study. *Ann Emerg Med* 1985; 14:859-864.
40. Oppe S, DeCharro F: The effect of medical care by a helicopter trauma team on the probability of survival and the quality of life of hospitalized victims. *Accid Anal Prev* 2001; 33:129-138.
41. Mitchell AD, Tallon JM, Sealy B: Air versus ground transport of major trauma patients to a tertiary trauma center: A province-wide comparison using TRISS analysis. *Can J Surg* 2007; 50:129-133.
42. Thomas S, et al: Helicopter transport and blunt trauma outcome. *J Trauma* 2002; 52:136-145.
43. McVey J, Petrie D, Tallon J: Air versus ground transport of the trauma patient: A natural experiment [abstract]. *Prehosp Emerg Care* 2007; 11:128.
44. Davis D, et al: The impact of aeromedical response to patients with moderate to severe traumatic brain injury. *Ann Emerg Med* 2005; 46:115-122.
45. Frankema S, et al: Beneficial effect of helicopter emergency medical services on survival of severely injured patients. *Br J Surg* 2004; 91:1520-1526.
46. Ringburg AN, et al: Lives saved by helicopter emergency medical services: An overview of literature. *Air Med J* 2009; 28:298-302.
47. Brown JB, et al: Helicopters improve survival in seriously injured patients requiring interfacility transport for definitive care. *J Trauma* 2011; 70:310.
48. Svenson JE, O'Connor JE, Lindsay MB: Is air transport faster? A comparison of air versus ground transport times for interfacility transfers in a regional referral system. *Air Med J* 2006; 25:170.
49. Branas CC, et al: Access to trauma centers in the United States. *JAMA* 2005; 293:2626.

www.ketabpezeshki.com 66485457-66963820

50. Chappell VL, Mileski WJ, Wolf SE, Gore DC: Impact of discontinuing a hospital-based air ambulance service on trauma patient outcomes. *J Trauma* 2002; 52:486-491.
51. Stewart KE, Cowan LD, Thompson DM, Sacra JC: Factors at the scene of injury associated with air versus ground transport to definitive care in a state with a large rural population. *Prehosp Emerg Care* 2011; 15:193.
52. Karanicolas PJ, et al: The fastest route between two points is not always a straight line: An analysis of air and land transfer of non-penetrating trauma patients. *J Trauma* 2006; 61:396.
53. Butler DP, Anwar I, Willet K: Is it the H or the EMS in HEMS that has had an impact on trauma patient mortality? A systematic review of the evidence. *Emerg Med J* 2010; 27:692.
54. Ringburg AN, et al: Helicopter emergency medical services (HEMS): Impact on on-scene times. *J Trauma* 2007; 63:258-262.
55. Talving P, et al: Helicopter evacuation of trauma victims in Los Angeles: Does it improve survival? *World J Surg* 2009; 33:2469-2476.
56. Davis DP, et al: The impact of prehospital endotracheal intubation on outcome in moderate to severe traumatic brain injury. *J Trauma* 2005; 58:933.
57. Bledsoe BE, Wesley AK, Eckstein M, Dunn TM, O'Keefe MF: Helicopter scene transport of trauma patients with non life-threatening injuries: A meta-analysis. *J Trauma* 2006; 60:1257.
58. Wang H, et al: Out-of-hospital endotracheal intubation and outcome after traumatic brain injury. *Ann Emerg Med* 2004; 44:439.
59. Davis D, Stern J, Ochs M: A follow-up analysis of factors associated with head-injury mortality after paramedic rapid sequence intubation. *J Trauma* 2005; 59:486.
60. Berlot G, et al: Influence of prehospital treatment on the outcome of patients with severe blunt traumatic brain injury: A single-centre study. *Eur J Emerg Med* 2009; 16:312-317.
61. Talving P, et al: Helicopter evacuation of trauma victims in Los Angeles: Does it improve survival? *World J Surg* 2009; 33:2469.
62. McVey J, Petrie DA, Tallon JM: Air versus ground transport of the major trauma patient: A natural experiment. *Prehosp Emerg Care* 2010; 14:45.
63. Grines C, Westerhausen D, Grines L: A randomized trial of transfer for primary angioplasty versus on-site thrombolysis in patients with high-risk myocardial infarction (Air PAMI trial). *J Am Coll Cardiol* 2002; 39:1713.
64. Youngquist ST, McIntosh SE, Swanson ER, Barton ED: Air ambulance transport times and advanced cardiac life support interventions during the interfacility transfer of patients with acute ST-segment elevation myocardial infarction. *Prehosp Emerg Care* 2010; 14:292.
65. Trojanowski J, Macdonald RD: Safe transport of patients with acute coronary syndromes or cardiogenic shock by skilled air medical crews. *Prehosp Emerg Care* 2011; 15:240.
66. Shewakramani S, Thomas SH, Harrison TH, Gates JD: Air transport of patients with unstable aortic aneurysms directly into operating rooms. *Prehosp Emerg Care* 2007; 11:337.
67. Stewart AM, McNay R, Thomas R, Mitchell AR: Early aeromedical transfer after acute coronary syndromes. *Emerg Med J* 2011; 28:325.
68. Thomas SH, et al: The evolving role of helicopter emergency medical services in the transfer of stroke patients to specialized centers. *Prehosp Emerg Care* 2002; 6:210.
69. Konstantopoulos WM, et al: Helicopter emergency medical services and stroke care regionalization: Measuring performance in a maturing system. *Am J Emerg Med* 2007; 25:158.
70. Thomas SH, Schwamm LH, Lev MH: Case records of the Massachusetts General Hospital. Case 16-2006. A 72-year-old woman admitted to the emergency department because of a sudden change in mental status. *N Engl J Med* 2006; 354:2263.
71. Silliman S, et al: Use of a field-to-stroke-center helicopter transport program to extend thrombolytic therapy to rural residents. *Stroke* 2003; 34:729.
72. Konstantopoulos WM, et al: Helicopter emergency medical services and stroke care regionalization: Measuring performance in a maturing system. *Am J Emerg Med* 2007; 25:158.
73. Elliott J, O'Keeffe D, Freeman R: Helicopter transportation of patients with obstetric emergencies in an urban area. *Am J Obstet Gynecol* 1982; 143:157.
74. Ohara M, et al: Safety and usefulness of emergency maternal transport using helicopter. *J Obstet Gynaecol Res* 2008; 34:189.
75. van Hook J, Leicht T, van Hook C: Aeromedical transfer of preterm labor patients. *Tex Med* 1998; 94:88.
76. Jony L, Baskett TF: Emergency air transport of obstetric patients. *J Obstet Gynaecol Can* 2007; 29:406.
77. Hon K, Olsen H, Totapally B, Leung TF: Air versus ground transportation of artificially ventilated neonates: Comparative differences in selected cardiopulmonary parameters. *Pediatr Emerg Care* 2006; 22:107.
78. Berge S, Berg-Utby C, Skogvoll E: Helicopter transport of sick neonates: A 14-year population-based study. *Acta Anaesthesiol Scand* 2005; 49:999-1003.
79. Hanson JH, Orr RA: *The air medical transfer process of the critically ill or injured pediatric patient*. In: Blumen IJ, ed. *Principles and Direction in Air Medical Transport*. Salt Lake City, Utah: Air Medical Physician Association; 2006.
80. Coppola CP, Tyree M, Larry K, De Geronimo R: A 22-year experience in global transport extracorporeal membrane oxygenation. *J Pediatr Surg* 2008; 43:46.
81. Orr RA, et al: Pediatric specialty care teams are associated with improved outcomes. *Pediatrics* 2009; 124:40-48.
82. American Academy of Pediatrics, Section on Transport Medicine: *Guidelines for Air and Ground Transportation of Neonatal and Pediatric Patients*, 3rd ed. Elk Grove Village, Ill: American Academy of Pediatrics; 2007.
83. Cabrera AG, et al: Interhospital transport of children requiring extracorporeal membrane oxygenation support for cardiac dysfunction. *Congenit Heart Dis* 2011; 6:202-208.
84. Shatney C, Homan J, Sherck J, Ho CC: The utility of helicopter transport of trauma patients from the injury scene in an urban trauma system. *J Trauma* 2002; 53:817-822.
85. Thomson D, Thomas S: Guidelines for air medical dispatch: Position statement for National Association of EMS Physicians. *Prehosp Emerg Care* 2003; 7:265.
86. Kurola J, et al: Paramedic helicopter emergency service in rural Finland—do benefits justify the cost? *Acta Anaesthesiol Scand* 2002; 46:771.
87. Wood AJ: When increased therapeutic benefit comes at increased cost. *N Engl J Med* 2002; 346:1819.
88. Nicholl J, et al: *A Review of the Costs and Benefits of Helicopter Emergency Ambulance Services in England and Wales: Report to the Department of Health*. London: Department of Health; 2003.
89. Elvik R: Cost-benefit analysis of ambulance and rescue helicopters in Norway: Reflections on assigning a monetary value to saving a human life. *Appl Health Econ Health Policy* 2002; 1:55.
90. Selmer R, et al: Cost-effectiveness of primary percutaneous coronary intervention versus thrombolytic therapy for acute myocardial infarction. *Scand Cardiovasc J* 2005; 39:276.
91. Silbergleit R, et al: Cost-effectiveness of helicopter transport of stroke patients for thrombolysis. *Acad Emerg Med* 2003; 10:966.
92. Taylor CB, et al: A systemic review of the costs and benefits of helicopter emergency medical services. *Injury* 2010; 41:10.
93. Thomas S, et al: Prehospital EKG and early helicopter dispatch to expedite interfacility transfer for percutaneous coronary intervention. *Crit Pathways Cardiol* 2006; 5:155.
94. Hankins DG: Air medical transport of trauma patients. *Prehosp Emerg Care* 2006; 10:324-327.
95. Lerner EB, et al: Economic value of out-of-hospital emergency care: A structured literature review. *Ann Emerg Med* 2006; 47:515.
96. Thomas SH, Biddinger PD: Helicopter trauma transport: An overview of recent outcomes and triage literature. *Curr Opin Anesth* 2003; 16:153-158.

www.ketabpezeshki.com 66485457-66963820

Chapter 192

Tactical Emergency Medical Support and Urban Search and Rescue

Richard B. Schwartz and John G. McManus

TACTICAL EMERGENCY MEDICAL SUPPORT

Perspective

Law enforcement agencies in the 21st century face an increase in terrorist threats and new challenges, including organized opposing forces, military-type weapons, direct fire, hostage and barricade situations, and potential toxic hazards. As these threats have increased, so has the recognition of the need for integrated medical support of tactical operations.[1] Tactical emergency medical support (TEMS) is the specialty of emergency medical services (EMS) established to maintain safety, health, and welfare for combat medical units and special operations civilian law enforcement units, such as special weapons and tactics (SWAT) teams, hostage rescue teams, and special emergency rescue teams.[1] These specially trained teams are composed of highly trained and specially equipped personnel who are tasked with mitigating and responding to many different high-risk situations.[2-5] Events such as the World Trade Center bombings and hurricane Katrina have demonstrated the need for many nonhospital health care personnel to use some of these current military out-of-hospital medical strategies.

Tactical Medical History

The principles of TEMS have largely been developed through lessons learned from military conflicts. Civilian TEMS structure most closely emulates the medical support structure of military special operations units, such as Army Special Forces, Navy Seals, Army Rangers, and Air Force Pararescuemen. These small, unique tactical units frequently operate outside the normal realm of military operations remote from dedicated medical resources, often for long periods.

In the civilian setting, snipers, mass demonstrations, riots, and fire bombings gained notoriety as new forms of urban conflict in the United States during the late 1960s and early 1970s, which led to the formation of the first SWAT unit. In 1996, there were more than 5000 SWAT teams in the United States supporting local, state, and federal agencies. Essentially today, more than 90% of municipalities with a population greater than 50,000 have a SWAT team.[5] With the evolution of these specialized law enforcement tactical teams, the need for military-style EMS support began to emerge.

Because of the dangerous environment, SWAT team members are at high risk for injury, with a casualty rate of 33 injuries per 1000 officer missions. Suspects are injured at the rate of 18.9 injuries per 1000 officer missions, and bystanders are injured at the rate of 3.2 per 1000 officer missions. It was recognized that traditional EMS providers were not properly trained or equipped to enter these unique and sometimes remote austere environments to care for casualties. In fact, basic EMS training still emphasizes that personnel should wait until the "scene is safe" before rendering medical care to patients. Past incidents, such as shootings at Columbine High School in Littleton, Colorado, Ruby Ridge in Idaho, the University of Texas in Austin, and the Mormon Library in Salt Lake City, proved that sequestering of medical personnel far from the area of operations leads to delays in definitive trauma care, with potentially higher morbidity and mortality.[6] The tactical environment necessitates that the medical provider possess a unique training and skill subset to use a different set of field assessment and treatment priorities and strategies for monitoring and sustaining health maintenance. Provision of tactical medical care has now become an integral part of preplanning for federal, state, and local tactical teams in response from lessons learned.[1,2]

The principles of tactical combat casualty care (TCCC) have been refined and now applied on today's battlefield[7-10] as well as in most civilian TEMS teams.[1,11-13] TCCC is a set of guidelines that aim to prevent further casualties, to accomplish the tactical mission, to save the maximum number of lives, and to minimize morbidity of the injured. These guidelines are developed by the Committee on Tactical Combat Casualty Care, which falls under the U.S. Defense Health Board. The TCCC guidelines are based on treatment of the leading preventable causes of combat death, which include hemorrhage from a compressible site, tension pneumothorax, and airway compromise.[11-13] In the most recent TCCC guidelines, attention to hypothermia prevention, intravenous access, improved en route care, closed head injury, and pain management techniques are also addressed.[11] Whereas TCCC is widely accepted in the military combat setting and has largely been extrapolated to the civilian environment, there are some data that question the applicability of TCCC to the civilian environment.[12]

Goals of Tactical Emergency Medical Support

In the early years of development, TEMS focus was on care and evacuation of wounded. This role has now evolved to include more emphasis on mission planning, primary care, preventive medicine, and emergency care of illness and injury. Although the primary goal of TEMS is to enhance the law enforcement mission, the tactical medical role involves a continuum of care that includes maintenance of team health; reconnaissance of environmental and situational aspects of the mission; coordination of local emergency medical support; creation of evacuation plan and routes; and assessment of future medical needs of the team, perpetrators, bystanders, and possible hostages.[1,14] Implementation of

www.ketabpezeshki.com 66485457-66963820

Box 192-1 Goals of Tactical Emergency Medical Support

Enhance mission accomplishment
Prepare medical threat assessment
Monitor the medical effects of environmental conditions
Reduce death, injury and illness, and related effects among team members, innocents, and perpetrators
Reduce lost work time
Maintain good team morale
Maintain health of team and provide preventive medicine
Coordinate with surrounding agencies and hospitals
Decrease liability
Possess basic forensic knowledge and crime scene preservation

an effective tactical medical support program is directed at achievement of several important goals (Box 192-1).

Tactical Team Structure, Training, and Integrated Medical Support

SWAT team and combat TEMS structure and size vary throughout the United States according to location and purpose. The typical team is composed of assault teams, which make initial contact with suspects, and arrest teams, which support the assault team. There are also rescue teams, backup teams, and hostage and negotiation teams. A unit commander supervises the operation from a command post.[2]

The TEMS component of a tactical unit, like team structure, varies widely throughout the United States. Some SWAT teams use "standby" EMS personnel, whereas others have physician-only TEMS providers. Much like the military Special Forces, many civilian tactical law enforcement agencies are now integrating medical support into the tactical team to enhance mission success.[2]

Although it is not ideal, the minimal medical coverage at a tactical location should be the use of standby civilian EMS personnel in a predetermined location. The standby EMS personnel treat casualties that are brought to them but are unable to assist in medical preplanning or inner perimeter rescue. This minimal medical support for tactical missions may be inadequate for some missions, given the high degree of potential injury and delay in definitive care.

Law enforcement agencies using integrated medical support have varying medical qualifications. The use of an emergency medical technician for medical coverage has the advantage of availability and modest cost. Medical directors may be able to train basic providers with an enhanced skill set to provide appropriate medical care for tactical support. However, the increased skill set possessed by advanced nonhospital providers makes them favorable in a TEMS environment.[2,11] In a small number of jurisdictions, emergency physicians and residents provide medical oversight for TEMS units and are also deployed as medical operators in the tactical environment.[2,4] Although physician providers offer a broader scope of practice and do not require direct medical control, they usually have limited out-of-hospital experience and also require tactical training. In addition, as the law enforcement mission takes on additional roles overseas, there is a growing need for forward surgical teams similar to military forward surgical teams that can function in remote areas. The Georgia Health Sciences University has developed one such surgical resuscitation team that has been deployed in support of law enforcement operations (www.georgiahealth.edu/ems/COM/Tactical/).

Training Issues

The tactical environment is different from the traditional EMS environment. Traditional EMS doctrine taught personnel to ensure that the scene is "safe" before attempting to render care.[11] This principle is not possible in some tactical situations. Tactical training needs to take into account team tactics and movement; cover and concealment; equipment issues; nuclear, biologic, and chemical training; rappelling; weapons familiarity; and noise and light discipline training.[2] Also, routine training needs to be done in basic rescue tactics, tactical room entries, open area rescues and tactics, movement under fire, cover and concealment, officer down drills, and, in some systems, firearm training (Fig. 192-1). Furthermore, many teams are now training all team members in medical management for lifesaving interventions.

Figure 192-1. Special response team training for the extraction of an injured suspect. Note that the suspect is secured with handcuffs to ensure the safety of the team and bystanders. (Photograph by Richard Schwartz.)

In the military and operational environments, there is a significant increase in the number of penetrating traumatic injuries (e.g., gunshot, fragmentary, and blast propellant wounds).[13-15] Because of the increased complexity and number of combat casualties and the possibility that civilian TEMS providers may be exposed to such, additional training and knowledge of the TCCC guidelines are important for the operational and tactical medic. Although advanced trauma life support may be applicable to the emergency department management of trauma patients in both civilian and military hospitals, it was not created for combat or tactical out-of-hospital medicine.[11,16] The three goals of TCCC are to treat the casualty, to prevent additional casualties, and to complete the mission.[6] TCCC is divided into three distinct phases to provide the correct medical interventions at the correct time in the continuum of out-of-hospital care (Box 192-2).

www.ketabpezeshki.com 66485457-66963820

Box 192-2 Phases of Tactical Combat Care

Care under fire
Tactical field care
Casualty evacuation care

Care under Fire. In terms of medical delivery in the civilian tactical environment, the area is usually divided into three zones—cold, warm, and hot. These zones are based on tactical environment, threat level, and treatment options, which are based on a risk-benefit ratio relative to the medical provider and patient. The cold zone is a safe environment with no threat to injury. This zone is outside the inner perimeter, and regular EMS treatment principles usually apply. In the warm zone, threat is not considered immediate but still exists. Finally, the hot zone is characterized by possible direct exposure to hostile fire.

As such, *care under fire* refers to care being rendered in the hot zone. In this zone, the medic and casualty are under direct effective hostile fire. Care in this phase is limited but not nonexistent. When care may be rendered, airway management, the first medical priority in routine out-of-hospital medicine, is best deferred until the tactical field care phase because of difficulty in maintaining the airway during evacuation under direct fire. Also, cardiopulmonary resuscitation and cervical spine immobilization have little or no role in the treatment of penetrating injuries in this phase and are not a priority in the combat environment.[16-18] Recommended care is limited to mitigation of threat (i.e., suppressive fire), placement of the casualty in rescue position if possible, tourniquet use, and evacuation of the casualty to a safer "zone" or "phase" of care if possible.

Because uncontrolled extremity hemorrhage was the leading cause of preventable battlefield death, a large portion of research and training was directed toward hemorrhage control.[13,19] During the current conflict in Iraq and Afghanistan, newer tourniquets, hemostatic agents, and dressings and intravenous therapies have been developed, researched, and fielded by the military with unprecedented speed, reducing morbidity and mortality for compressible, extremity hemorrhage.[19] During the care under fire phase, extremity hemorrhage control is ideally gained through the use of tourniquets. Although shunned for many years, tourniquets have re-emerged as the standard of care in this environment because of low complication rates, ease of use, rapid application, and effectiveness in stopping blood loss.[6,19-24] Improvised tourniquets such as rubber surgical tubing are not recommended and should not be used unless commercial tourniquets are unavailable.[23] Several studies have found that tourniquet use on the current battlefield has not resulted in increased limb loss or permanent disability even among patients thought to have had tourniquets applied unnecessarily and has resulted in a reduction in mortality with application before onset of shock and in the prehospital environment.[6,19,21]

Many types of extremity tourniquets are presently available for both civilian and military use. Two tourniquets currently used on today's battlefield by the U.S. Army are the Combat Application Tourniquet (C-A-T) and the Special Operations Forces Tactical Tourniquet (SOFT-T).[19,24] On the basis of current literature, both the U.S. and the Israeli military, the International Committee of the Red Cross, and civilian agencies in the United States have embraced tourniquets as an initial hemorrhage control option during the care under fire phase as well as for uncontrolled extremity hemorrhage to achieve rapid control of bleeding.[11,21] The current TCCC recommendation is for liberal use of appropriate tourniquets for uncontrolled extremity hemorrhage in the tactical environment.

Tactical Field Care. The second phase of care, tactical field care, is medical treatment rendered in the warm zone. This phase consists of medical care that is delivered while the medic and casualty are still under threat of injury but not under direct, effective hostile fire. Simply by dragging a casualty 5 feet around the corner of a building could transition the medic from care under fire to tactical field care. Care in this phase focuses on several areas that have been shown to increase morbidity and mortality in tactical environments if they are not addressed.[17] Airway establishment and maintenance are first addressed in this phase of treatment. Next, breathing issues, such as tension pneumothorax and open pneumothorax (sucking chest wound), may need to be addressed in this phase of care. Circulatory issues, such as tourniquet replacement with direct pressure dressings or advanced hemostatic agents and fluid therapy, are then addressed. Intravenous or interosseous access needs to be established. Hypothermia prevention, adequate analgesia, prophylactic antibiotics, and appropriate use of cardiopulmonary resuscitation are also addressed in this phase.[13]

Advanced Hemostatic Agents. The ideal out-of-hospital hemostatic agent ideally would require little training; be nonperishable, durable, flexible, and inexpensive; adhere to the wound only; pose no direct risk of disease; not induce a tissue reaction; and effectively control hemorrhage from arterial, venous, and soft tissue bleeding. There is no single ideal advanced hemostatic agent that currently meets all of these criteria for either military or civilian use. However, many hemostatic agents have been used successfully for uncontrolled hemorrhage on today's battlefield and have contributed to reduced morbidity and mortality in penetrating combat trauma.[25-30]

Although many hemostatic agents are approved by the U.S. Food and Drug Administration (FDA) and have been used in both the civilian and military environments, the agent currently recommended by the Committee on Tactical Combat Casualty Care is Combat Gauze. Combat Gauze, a mineral-based dressing containing a kaolin coating, is thought to function by activation of clotting factors. More recent dressings with fine-mesh poly-rayon gauze and chitosan impregnation have been demonstrated to be at least as efficacious as Combat Gauze in a porcine model.[29]

Point Compression Devices and Trunk Tourniquets. The rapid development and fielding of tourniquets and hemostatic agents on today's battlefield have greatly reduced morbidity and mortality from previously uncontrolled hemorrhage, particularly from isolated extremity injuries. However, exsanguination-related mortality still exists. Anatomic areas that are not amenable to tourniquet application, referred to as junctional areas (i.e., neck, groin, axilla), have now become the focus of hemostatic research.[31] In fact, the current combat epidemiology reports that junctional injury and bleeding is now the most common "potentially survivable" combat injury. Because junctional injuries continue to be a challenge to hemorrhage control in the tactical setting, newer devices are being developed to control these injuries in the field setting to allow the casualty time to have surgical control in an operative setting.[30-32] One of the newer devices has been approved by the FDA for control of proximal femoral artery injuries, the Combat Ready Clamp (CRoC, Combat Medical Systems). This is a large C-clamp that is placed over the femoral vessels to provide direct compression. Another device under development is the abdominal aortic tourniquet, which is a pneumatic tourniquet that externally compresses and occludes the abdominal aorta at its bifurcation. This device has been shown to occlude the abdominal aorta in a pig model for up to 60 minutes without evidence of bowel ischemia or hyperkalemia and is pending FDA approval for the indication of hemorrhage control of proximal femoral and pelvic vascular injuries.[33]

Tension Pneumothorax. Another leading cause of potentially preventable battlefield death is tension pneumothorax, accounting for up to 3 or 4% of all fatal injuries.[14,34] McPherson and

www.ketabpezeshki.com 66485457-66963820

colleagues[34] studied radiologic and autopsy examinations of 978 fatalities from the Vietnam conflict; 15 of the casualties with identified tension pneumothorax lived long enough to be treated by a medic, but none underwent needle decompression and all of them died.

Although needle thoracostomy is a controversial procedure in the civilian trauma setting for adults, current TCCC guidelines recommend consideration of needle decompression in casualties with chest trauma and progressing respiratory distress.[17,34] The current recommendation is to use a 14-gauge or larger 3.25-inch needle. This recommendation is based on computed tomography evaluation of the chest wall, which indicted that a standard 2.0-inch needle would penetrate the pleural space in only 75% of causalities.[35]

Airway Management. Airway compromise is also a potentially preventable cause of battlefield death.[36] Historically, airway compromise is responsible for approximately 1% of fatal injuries on the battlefield and is due to facial or neck trauma causing obstruction. These data are consistent with a more recent review of fatal airway injuries from Operation Enduring Freedom and Operation Iraqi Freedom, which demonstrated an airway fatality rate of 1.8%, with 100% having penetrating injuries to the face or neck.[36]

Initially, in an unconscious patient with intact upper airway anatomy at risk for airway compromise, the recovery position and minimally invasive adjuncts, such as the nasopharyngeal airway and the oropharyngeal airway, are emphasized. However, given the high incidence of trauma as a cause of airway obstruction, the cricothyroidotomy is taught as the definitive airway management technique on the battlefield if simple maneuvers fail. Traditional methods providing ventilation, such as endotracheal intubation, the laryngeal mask airway, the Combitube, and the King laryngeal tube airway, may not be as feasible in tactical situations. The initial training requirements as well as maintenance issues for these skills for all military medics are simply not practical. Furthermore, use of white light required for laryngoscopy may draw enemy fire on the battlefield. Finally, on the basis of the best available data, many patients needing airway management are likely to have disrupted upper airway anatomy, for which these skills would not be successful and cricothyroidotomy would be indicated. A recent review of battlefield fatalities demonstrated a high failure rate of cricothyroidotomy (5/5) and raises the question of the most appropriate algorithm for airway management in the tactical setting.[36]

Intravenous Access and Fluid Resuscitation. The tactical environment often makes intravenous access difficult, and alternative techniques and routes may be needed to establish access.[17,37-39] Medics therefore are trained to obtain intraosseous access for fluid administration if intravenous access is not obtainable or timely. Several newer intraosseous devices are used in both civilian and combat tactical environments, including the EZ-IO, the Pyng FAST1 sternal intraosseous infusion device, and the Bone Injection Gun, with great success and little morbidity.[40,41]

The current recommendations for intravenous resuscitation on the battlefield focus only on those patients with signs of hemorrhagic shock. Because the majority of combat casualties present with non–life-threatening penetrating extremity injuries, the number of casualties actually requiring intravenous fluids in the field is few. In fact, fluids are encouraged to be taken orally if the casualty is conscious and can tolerate drinking.[17] If fluids are necessary, TCCC guidelines recommend an infusion of 500 mL of Hextend, followed by an additional 500 mL in 30 minutes if shock is still present.[17,31]

Hextend, a colloid, is the recommended fluid of choice over crystalloid solutions. Hextend remains in the intravascular space longer, requiring significantly less volume than crystalloids. These factors are critical when supplies must be carried in the medic's pack. Future battlefield resuscitation strategies may include hypertonic saline or combinations of hypertonic solutions and colloids. A growing scientific literature supports this "hypotensive resuscitation" strategy.[31,42,43]

Hypothermia Management. Hypothermia has been well recognized as an independent factor contributing to increased morbidity and mortality in trauma patients. Studies have shown hypothermia to be associated with increases in acidosis, coagulopathy, multiple organ failure, length of hospital stay, and mortality.[44,45] In the austere environment, prolonged out-of-hospital times, cold fluid administration, and environmental factors affect the patient's core temperature, as does bleeding that results in hypoperfusion, which alters the body's thermoregulation and results in hypothermia.

TCCC emphasizes prevention of hypothermia (<34°C) in patients with penetrating trauma. Prevention of heat loss should start as soon as possible after wounding. This is optimally accomplished in a layered manner. Several new devices are being tested and fielded in the combat out-of-hospital setting for hypothermia prevention to maintain casualty core temperature as well as to administer warmed fluids.[46]

Analgesia. The tactical environment exacerbates the typical challenges found in treatment of acute pain and has the additional obstacles of a lack of supplies and equipment, delayed or prolonged evacuation times and distances, devastating injuries, provider inexperience, and dangerous tactical situations.[47,48] Studies have shown an increase in the incidence of chronic pain and posttraumatic stress disorder (PTSD) with failure to recognize and to treat acute pain appropriately as well as a reduction in PTSD incidence when pain is adequately managed, particularly with early use of ketamine.[49,50]

Finally, other newer analgesic agents and routes of delivery are being used on the battlefield. Oral transmucosal fentanyl citrate has been found to relieve moderate to severe pain on the battlefield and is currently carried by many Special Forces medics.[51] Also, ketamine has been used successfully as an out-of-hospital analgesic in the civilian and combat setting.[52] Ketamine in subanesthetic doses is an almost ideal analgesic because of its profound pain relief, its role in prevention of opioid hyperanalgesia, and its large margin of safety.[53]

Triage and Advanced Vital Signs. It has been hypothesized that some trauma deaths may be preventable if the severity of blood loss can be recognized earlier during out-of-hospital medical care. It is obviously better to prevent hemodynamic compromise (i.e., shock) than to treat it once it has already begun to occur.

In an attempt to provide new possibilities for more efficient algorithms that may assist in determination of treatment and evacuation priorities for patients with unrecognized hypovolemia and early shock, new and more accurate noninvasive indicators of the underlying physiologic status in trauma patients who have initial normal systolic blood pressure and Glasgow Coma Scale scores have been investigated and implemented in current combat operations.[54,55] Some of these indicators of hypovolemia include derived physiologic variables (e.g., shock index, pulse pressure, and field trauma score)[55-57] and continuous "real-time" variables (e.g., electrocardiogram R wave amplitude and heart rate variability).[58,59] The National Association of EMS Physicians, with funding from the Centers for Disease Control and Prevention, has led an effort to standardize mass casualty triage. Through this project, a new triage system has been developed that uses the principles of TCCC. This system is called SALT (sort, assess, lifesaving interventions, and treatment or transport) and has been endorsed by multiple organizations, including the American College of Emergency Physicians.[60]

Combat Casualty Evacuation Care. Combat casualty evacuation care is the third phase of care. It is rendered to the casualty in the cold zone and while the casualty is evacuated to definitive medical

www.ketabpezeshki.com 66485457-66963820

Figure 192-2. Combat casualty evacuation care is usually provided by aeromedical transport or advanced life support ambulance in the civilian setting. (Photograph courtesy the *Augusta Chronicle* and Andrew Davis Tucker.)

care. Care now begins to closely approximate traditional civilian field medical care and includes advanced life support en route to the receiving facility, often a trauma center (Fig. 192-2).[11]

Intravenous Hemostatic Agents. In the future, optimal out-of-hospital hemorrhage control in the combat environment may also involve use of intravenous agents for replacement and coagulation principles. In selected combat nonhospital settings, tranexamic acid, hemoglobin substitutes, lyophilized plasma, freeze-dried blood, and component products are currently being developed or evaluated for appropriate use.[42,61] In this phase of care, on the basis of recent literature, the TCCC currently recommends that tranexamic acid be administered as 1 g in 100 mL of normal saline or lactated Ringer's solution as soon as possible, but not later than 3 hours after injury, if the casualty has major hemorrhage or is probably going to require a significant transfusion.[61,62]

TEMS Environment

Training

Practicing effective medical care in the tactical environment requires TEMS personnel to be well educated, trained, and equipped. Integrated "team" training allows the medical support members to understand their roles and to learn all aspects of tactical law enforcement operations and fundamentals on how to approach the tactical medical arena. TEMS competency-based guidelines have recently been published to guide the development of TEMS training curricula.[1] A project has been initiated by the Centers for Disease Control and Prevention to develop a nationally standardized curriculum for tactical medicine training. This project, using an expert panel and review of the scientific literature, refined the previously published outcome competencies and developed terminal and enabling training objectives to the competencies. The results of this project will be published as a national TEMS curriculum. In addition, training curricula have been established, such as the National Tactical Officers Association's Specialized Tactics for Operational Rescue and Medicine (STORM) for medics, operators, medical directors, and team commanders. These courses are based on the national TEMS curriculum and use the trainer methodology.

Equipment

The medical equipment selected and carried by TEMS providers varies and is based on usage, size, weight, budget, training, experience, and mission type. Use of conventional EMS medications and equipment with bright markings and color coding is often discouraged in the tactical environment to maintain concealment.

Remote Patient Assessment

Remote patient assessment is another function of TEMS. Medical personnel assess the injured person from a distance with use of binoculars, gun scopes, night vision goggles, cameras, and microwave radar motion detectors.

Hazardous Materials

Incidents involving clandestine drug laboratories and weapons of mass destruction are also considerations in a TEMS environment. Rapid decontamination must be taught and practiced by tactical teams because adequate decontamination is usually not available in the inner perimeter.[63]

Forensic Science

Basic knowledge of forensic science is important for recognition and preservation of evidentiary items. Documentation of wound and blood patterns should be done. All evidence should be collected appropriately and the chain of custody maintained.[64]

Medical Threat Assessment

Medical threat assessment (MTA) is an important part of medical planning and should be integrated into the tactical operation.[2] The MTA considers the potential medical threats that may confront the team during the tactical operations and develops the plan to mitigate and to respond to the threats. Once the MTA is complete, a plan is then developed on the basis of the medical intelligence to address each possible situation, with the realization that the plan may change as the mission evolves.

Preventive Medicine and Force Health Protection

The maintenance of the tactical team's health is an important aspect of a TEMS program. Poor health has been shown to directly correlate with poor job performance and mission failure.

Liability

Because special operations lend themselves to high litigation and possible disability, TEMS providers need to ensure that they have proper malpractice and disability coverage.[2,65]

URBAN SEARCH AND RESCUE

It was hard to breathe. The air was thick and choking. It looked as though black snow had fallen, covering everything.

It was as dark as a tunnel and the air was as thick as soup. Despite repeatedly scooping chunks of dust and debris from my mouth and nostrils, I inhaled and swallowed large quantities.

www.ketabpezeshki.com 66485457-66963820

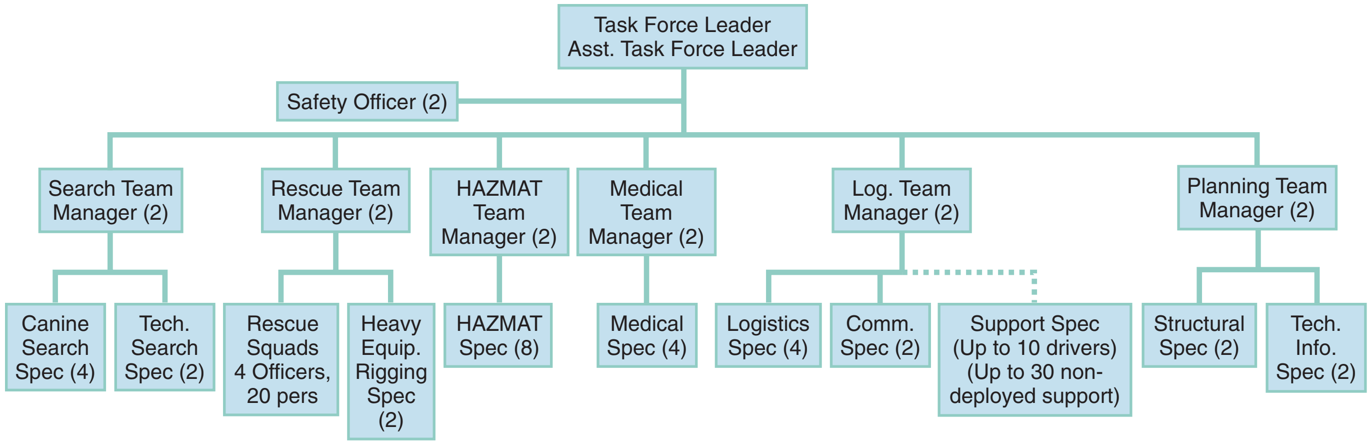


Figure 192-3. Structure of a FEMA US&R team.

It took an hour to wash off the layers of dust, which by now had become like a layer of concrete.

Drs. Kelly and Prezant, New York City Fire Department, during the September 11, 2001, terrorist attacks.

Perspective

Urban search and rescue (US&R) is the science of responding to, locating, reaching, medically treating, and safely extricating victims entrapped by collapsed structures. US&R is a "multihazard" discipline because it may be needed in a variety of emergencies and disasters, including wilderness mishaps, natural disasters such as the recent earthquakes in Haiti and Japan, and man-made disasters (e.g., terrorist attacks, building and structure collapse, hazardous materials spills).[65,66] Federal activation of US&R teams occurs when local and state resources have been overwhelmed and there has been a request from a state governor to the President for the activation of federal response assets. In addition, in catastrophic events, the activation of military assets may be required to assist in a support role of other local, state, and federal assets.[66,67] For responding resources to be effective, they should be highly trained, quickly deployable, mobile, and self-sufficient.

Components and Structure of an Urban Search and Rescue Team

The responding team must mobilize quickly to accomplish its objectives and should not place additional demands on the already stressed infrastructure. Figure 192-3 shows the organizational structure of a Federal Emergency Management Agency (FEMA) US&R team.[66] There are 28 FEMA US&R task forces throughout the continental United States that are trained and equipped to handle structural collapse. FEMA will deploy the three closest task forces within 6 hours of notification of an emergency. Each task force consists of two 31-person teams, four canines, and a comprehensive equipment cache. US&R task force members work in four areas of specialization: search, to find victims trapped after a disaster; rescue, which includes safely digging victims out of tons of collapsed concrete and metal; technical, made up of structural specialists who make rescues safe for the rescuers; and medical, which cares for the victims before and after a rescue.

An effective US&R team needs both properly trained personnel and appropriate equipment. The equipment cache should allow the task force to be totally self-sufficient for the first 72 hours and to be capable of 24-hour operation for 10 days.[65,67] The FEMA equipment cache is divided into five groups: rescue equipment, medical equipment, technical equipment, communications equipment, and logistics equipment. The medical equipment cache was designed to treat the unique medical needs of trapped victims as well as the medical needs of the team. The medical cache contains enough supplies to handle 10 critical cases, 15 moderate cases, and 25 minor cases. The cost of the entire cache is approximately $2 million.[66,67]

Coordination and cooperation with local resources and other teams are critical.[68] The US&R team is integrated into the Incident Command System at the disaster.

The search team is responsible for development and implementation of a plan to search the area for victims. The search team can be subdivided into two teams, a canine search team and a technical search team. The canine team uses specially trained dogs to locate trapped victims. The technical team uses specialized microphones, listening devices, cameras, and fiberoptic devices to locate victims in confined spaces. The search team is responsible for locating victims and identifying probable areas where victims may be found.

The rescue team is composed of rescue specialists. Once a victim or potential victim is located, the rescue team is responsible for breaching the area and creating a safe entrance to and exit from the victim's position.

The technical team is composed of various specialists, including structural specialists, hazardous materials specialists, heavy rigging and equipment specialists, technical information specialists, and communications specialists.[68] These specialists work collaboratively to ensure a safe and efficient operation.

The logistics team is responsible for all the equipment needs, including inventory, issuing, and record keeping.[68]

Finally, the medical component is composed of medical personnel who are responsible for the medical needs of both the task force personnel and the victims. Typically, the medical personnel are emergency physicians and paramedics.[68,69]

Medical Team Operations in Urban Search and Rescue

A number of unique considerations must be addressed for US&R. As with TEMS, team physicians must realize that they will be operating outside of their usual environment and that they are not in charge overall. Typically, the physician on the team works with the team leader and the managers of the other components. To do this efficiently, the physician should be familiar with the capabilities and training of all the members on the team and the Incident Command System. Cross-training of team members is ideal.[68-70]

www.ketabpezeshki.com 66485457-66963820

Box 192-3 Medical Intelligence Gathering before Deployment

- Type of disaster and predicted numbers and types of potential victims
- Capabilities of the team to deal with the medical aspects of the situation, including dealing with injured team members
- Local emergency department's level of functioning; trauma center status and location
- Local EMS resources
- Location of planned triage staging area
- Communications with local resources (e.g., EMS, police, emergency departments, fire and rescue)
- Weather, environment, or hazardous materials issues
- Availability of other resources (military, NDMS, DMAT)

DMAT, disaster medical assistance team; *EMS,* emergency medical services; *NDMS,* National Disaster Medical System.

Medical Team Tasks

Predeployment. The job of the medical team in the predeployment phase is to ensure that the entire team is fit and functional for deployment and that the medical equipment cache is organized and up-to-date.[69] The perceived medical threats in the deployed area must also be addressed (e.g., endemic disease, water contamination, insect threats, existing medical support). A family and communication support system should also be set up before the deployment.

Deployment. The medical team is responsible for much more than just treatment of the victims. Medical intelligence information needs to be collected and addressed (Box 192-3). A plan is required for transfer and transport of victims and for fatality management.

The medical action plan is critical for ensuring smooth operations and should be updated as conditions or knowledge changes.[66,68,69] The medical component of a US&R team needs to be able to provide care for its own team members, whose needs may exceed those of the victims. The medical team also needs to assess the adequacy of team members' rest and sleep and the psychological effects of the situation.[68,69] In addition, the US&R medical assets must be integrated with the overall medical response that is guided under Emergency Support Function #8, Public Health and Medical Services. This includes integration with existing medical resources, disaster medical assistance teams, TEMS resources, military resources, and public health. If there is a canine search component, the medical team should receive some sort of basic veterinary training before deployment.[68,69]

Confined Space Issues

A confined space is defined as any space with limited access and ventilation. The physician and medical team must be prepared to work in this setting during a deployment and should be aware of issues related to team and victim safety, air purification, and structural dynamics related to collapse or impending collapse.[68-70] Medical providers may be asked for input on ceasing of rescue operations based on the likelihood of finding survivors. Evidence from the 2010 Haitian earthquake indicates that this decision should be based on the individual characteristics of the event and should not rely on predefined time frames to determine ceasing of search and rescue operations.[71]

Specific Disorders in Urban Search and Rescue

US&R teams will typically be responding to the aftermath of earthquakes, collapsed structures, terrorist bombings, hurricanes, and other natural and man-made disasters.[68,71] Reviews of the literature have identified the types of medical problems and conditions that might be encountered.[65,66,69,70] Most of the medical conditions are those encountered in the emergency department and are handled similarly. The following clinical problems occur with much greater frequency in the US&R environment: crush syndrome, compartment syndrome, particulate inhalation, hazardous materials exposures, and blast injuries.[69] Since the terrorist attacks of September 11, 2001, there has also been an emphasis on preparing the US&R teams for the medical response to weapons of mass destruction.

Crush Injury and Crush Syndrome

Compartment syndrome is defined as crush injury caused by swelling of tissue inside the confining fibrous sheath of a muscle compartment, which can cause further destruction of the intracompartment muscle and nerves. Compartment syndrome is discussed in Chapter 49.

Crush syndrome is defined as the systemic manifestations caused by crushed muscle tissue. This typically occurs when blood flow is restored to the crushed tissue and the toxins are released systemically. It is estimated that 3 to 20% of earthquake victims and up to 40% of survivors of multistory building collapses will have crush syndrome.[72] Early hydration of the victim in the rubble before, during, and after extrication can lessen the renal effects of crush syndrome.

The amount of time required for crush syndrome to develop depends on both the amount of pressure and patient factors. It can occur within 1 hour if the pressure is severe, but it usually takes 4 to 6 hours to develop.

Pathophysiology of Crush Syndrome. The cause of muscle injury in crush injury is not fully understood and controversial. The intracellular contents of the cell include lactic acid, potassium, myoglobin, uric acid, enzymes, leukotrienes, thromboxane, phosphate, and others. There is also increased capillary permeability. This can lead to edema and third spacing of fluid.[72] These effects occur locally until the tissue is released and reperfused. This is why victims can be trapped for days with severe crush injury and appear stable when they are reached by rescuers only to deteriorate soon after being rescued. There are reports of patients going into cardiac arrest soon after rescue.[73,74] When the crushed area is released, there is a release of all the intracellular contents that have been building up locally into the systemic circulation, causing systemic symptoms. The major causes of early death due to crush syndrome are hypovolemia due to third spacing of fluid, dysrhythmias due to severe metabolic acidosis, and hyperkalemia. Delayed causes of death include renal failure, acute respiratory distress syndrome, sepsis, ischemic organ injury, disseminated intravascular coagulopathy, and electrolyte disturbances.[72,73]

Management of Crush Syndrome. Early aggressive therapy is essential for prevention of crush syndrome, and it should begin before extrication.[72-74] All victims who have an obvious crush injury or are immobilized for 4 hours or more should be considered to have crush injury. The severity of the crush syndrome may be related to the number of extremities with crush injury. In a Japanese study of earthquake victims, the incidence of acute renal failure due to crush syndrome was 50% for one involved extremity, 75% for two involved extremities, and 100% for three or more involved extremities. Once a victim is located, the medical component needs to be actively involved with the rescue process and begin treatment before extrication. Cardiovascular instability is commonly seen in crush syndrome. As extrication is being done, continuous cardiac monitoring is recommended. Adequate hydration is recommended along with the usual management of hyperkalemia (e.g., insulin or glucose, ion exchange resins, beta-agonists, and dialysis). The current guidelines taught in the FEMA medical

www.ketabpezeshki.com 66485457-66963820

Figure 192-4. Massive amounts of dust and contaminants can exacerbate existing medical conditions, such as asthma and chronic obstructive pulmonary disease, during US&R operations.

specialists course recommend intravenous calcium only for arrhythmias that do not respond to other measures or when there is a documented severe hypocalcemia.[69] It has been suggested that an average-size adult may require up to 12 L/day of fluids to sustain a forced diuresis of 8 L/day to prevent renal complications. Continued monitoring of the patient's vital signs, hydration status, and urine output should be done to guide fluid administration until more invasive monitoring is available.[70] Alkalinization of the urine to prevent renal failure has been recommended in crush syndrome but has not been subjected to proper study, and the effects of the alkalinization, if any, are impossible to separate from those of the volume fluid used. Rhabdomyolysis and its relationship to renal failure are discussed in Chapter 127.

Other Medical Problems in Urban Search and Rescue

Another unique medical problem in US&R is dust and airway contamination. During earthquakes and building collapses, a tremendous amount of dust is released into the air. During the first 48 hours of rescue efforts at the World Trade Center, 90% of the 10,116 New York City Fire Department rescue workers evaluated at the site reported an acute cough often accompanied by nasal congestion, chest tightness, or chest burning, but only three required hospitalization for respiratory symptoms (Fig. 192-4). A cough was eventually found in 1561 (29.1%) firefighters at baseline and 1186 (22.1%) at follow-up, including 559 with delayed onset.[75] The victim of a collapsed structure should be assumed to have some sort of dust contamination. Evaluate the airway for any evidence of burns or hazardous materials exposure. During the extrication process, monitor the patient's airway and be prepared for deterioration. If intubation is being considered, it is better to do it early before edema obstructs the airway, making the procedure more difficult. Medical management of the victim reached after prolonged entrapment is different from that in the typical trauma setting. The "scoop and run" approach of the trauma patient is not always appropriate or possible.

Chemical, explosive, and radiologic agents represent potential threats to the US&R team. Hazardous materials may be released from many sources, such as manufacturing plants or transportation vehicles. Explosion and fires from disrupted gas lines or other flammable and explosive gases and liquids present a significant hazard. Radiation is a danger that may threaten search and rescue operations as demonstrated by the Fukushima nuclear reactor radiation leak after the recent earthquake in Japan. US&R team members should work closely with hazardous materials response teams when responding to these threats.

Hypothermia may also be an issue for patients subjected to environmental conditions. Stabilization, extrication, and ongoing treatment should also be directed at the prevention or reversal of hypothermia, as discussed previously.

KEY CONCEPTS

- The hostile environment that is intrinsic to combat and urban SWAT team operations requires specialized training and planning for medical personnel.
- Determination of medical capability for the hot, warm, and cold zones of a conflict area requires evaluation of local characteristics, the nature of the threat, team safety, and community resources.
- US&R teams have many integrated components. Typically, the medical component is the smallest part of the team but has some of the greatest responsibilities.
- Medical problems, including crush syndrome, compartment syndrome, exacerbation of respiratory illness, and hypothermia, will be encountered in US&R.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Schwartz RB: Tactical medicine—competency-based guidelines. *Prehosp Emerg Care* 2011; 15:67-82.
2. Vayer JA, Schwartz RB: Developing a tactical emergency medical support program. *Topics Emerg Med* 2003; 25:282.
3. Heck JJ, Pierluisi G: Law enforcement special operations medical support. *Prehosp Emerg Care* 2001; 5:403.
4. Bozeman WP: Tactical EMS: An emerging opportunity in graduate medical education. *Prehosp Emerg Care* 2002; 6:322.
5. Heck JJ, Pierluisi G: Law enforcement special operations medical support: NAEMSP position paper. *Prehosp Emerg Care* 2001; 5:403.
6. Mabry RL, et al: United States Army Rangers in Somalia: An analysis of combat casualties on an urban battlefield. *J Trauma* 2000; 49:515.
7. Butler FK: Tactical medicine training for SEAL mission commanders. *Mil Med* 2001; 166:625.
8. Butler FK, Greydanus D, Holcomb J: *Combat Evaluation of TCCC Techniques and Equipment: 2005.* USAISR Report No. 2006-01, November 2006.
9. Butler FK, et al: Tactical combat casualty care 2007: Evolving concepts and battlefield experience. *Mil Med* 2007; 172(Suppl):1-19.
10. Holcomb JB, Stansbury LG, Champion HR, Wade C, Bellamy RF: Understanding combat casualty care statistics. *J Trauma* 2006; 60:397-401.
11. National Association of Emergency Medical Technicians: *PHTLS: Prehospital Trauma Life Support*, 7th ed. St. Louis: Mosby; 2011.
12. Sztajnkrycer MD: Tactical medical skill requirements for law enforcement officers: A 10-year analysis of line of duty deaths. *Prehosp Disaster Med* 2010; 25:346-352.
13. Mabry R, McManus JG: Prehospital advances in the management of severe penetrating trauma. *Crit Care Med* 2008; 36(Suppl):S258-S266.
14. Holcomb JB, et al: Causes of death in U.S. Special Operations Forces in the global war on terrorism: 2001-2004. *Ann Surg* 2007; 245:986.
15. Sebesta J: Special lessons learned from Iraq. *Surg Clin North Am* 2006; 86:711.
16. Butler FK, et al: Tactical management of urban warfare casualties in special operations. *Mil Med* 2000; 65:1.
17. McSwain N, ed. *Military Medicine. Prehospital Trauma Life Support*, 5th ed. St. Louis: Mosby; 2003.
18. Haut ER, et al: Spine immobilization in penetrating trauma: More harm than good? *J Trauma* 2010; 68:115-120; discussion 120-121.
19. Kragh F, et al: Practical use of emergency tourniquets to stop bleeding in major limb trauma. *J Trauma* 2008; 64(Suppl 2):S38-S50.
20. Mabry RL: Tourniquet use on the battlefield. *Mil Med* 2006; 171:352.
21. Kragh JF, et al: Survival with emergency tourniquet use to stop bleeding in major limb trauma. *Ann Surg* 2009; 249:1-7.
22. Welling D, et al: A balanced approach to tourniquet use: Lessons learned and relearned. *J Am Coll Surg* 2006; 203:106.
23. Walters TJ, Mabry RL: Issues related to the use of tourniquets on the battlefield. *Mil Med* 2005; 170:770.
24. Walters TJ, et al: An observational study to determine the effectiveness of self-applied tourniquets in human volunteers. *J Prehosp Care* 2005; 9:416.
25. Pusateri AE, et al: Advanced hemostatic dressing development program: Animal model selection criteria and results of a study of nine hemostatic dressings in a model of severe large venous hemorrhage and hepatic injury in swine. *J Trauma* 2003; 55:518.
26. Wedmore I, McManus J, Pusateri A, Holcomb J: A special report on the chitosan-based hemostatic dressing: Experience in current combat operations. *J Trauma* 2006; 60:655.
27. Kheirabadi BS, et al: Comparison of new hemostatic granules/powders with currently deployed hemostatic products in a lethal model of extremity arterial hemorrhage in swine. *J Trauma* 2009; 66:316-328.
28. Kheirabadi BS, et al: Determination of efficacy of new hemostatic dressings in a model of extremity arterial hemorrhage in swine. *J Trauma* 2009; 67:450-459.
29. Schwartz RB, et al: Comparison of two packable hemostatic gauze dressings in a porcine hemorrhage model. *Prehosp Emerg Care* 2011; 15:477-482.
30. Kheirabadi BS, et al: Clot-inducing minerals versus plasma protein dressing for topical treatment of external bleeding in the presence of coagulopathy. *J Trauma* 2010; 69:1062-1073.
31. Butler F: Fluid resuscitation in tactical combat casualty care: Brief history and current status. *J Trauma* 2011; 70:S11-S12.
32. Kheirabadi B: Evaluation of topical hemostatic agents for combat wound treatment. *US Army Med Dep J* 2011; Apr-June:25-37.
33. Greenfield EM, et al: *Efficacy and safety of a novel abdominal tourniquet device for the control of pelvic and lower extremity hemorrhage.* Paper presented at 16th World Congress for Disaster and Emergency Medicine; May 12-15, 2009; Victoria, BC, Canada. Available at Abstracts of Scientific and Invited Papers, R102, s35: http://pdm.medicine.wisc.edu/Volume_24/issue_2/16wcdem.pdf5. Accessed September 1, 2011.
34. McPherson JJ, Feigin DS, Bellamy RF: Prevalence of tension pneumothorax in fatally wounded combat casualties. *J Trauma* 2006; 60:573.
35. Givens ML, Ayotte K, Manifold C: Needle thoracostomy: Implications of computed tomography chest wall thickness. *Acad Emerg Med* 2004; 11:211-213.
36. Mabry RL, Edens JW, Pearse L, Kelly JF, Harke H: Fatal airway injuries during Operation Enduring Freedom and Operation Iraqi Freedom. *Prehosp Emerg Care* 2010; 14:272-277.
37. Miller DD, et al: Feasibility of sternal intraosseous access by emergency medical technician students. *Prehosp Emerg Care* 2005; 9:73.
38. Calkins MD, et al: Intraosseous infusion devices: A comparison for potential use in special operations. *J Trauma* 2000; 48:1068.
39. Dubrick MA, Holcomb JB: A review of intraosseous vascular access: Current status and military application. *Mil Med* 2000; 165:552.
40. Vojtko M, Hanfling D: The sternal IO and vascular access—any port in a storm. *Air Med J* 2003; 22:32-34.
41. Miller L, Morissette C: VidaPort—an advanced easy IO device. *Prehosp Emerg Care* 2004; 8:110-111.
42. McSwain NE, et al: State of the art of fluid resuscitation 2010: Prehospital and immediate transition to the hospital. *J Trauma* 2011; 70:S2-S10.
43. Dubick M: Current concepts in fluid resuscitation for prehospital care of combat casualties. *US Army Med Dep J* 2011; Apr-Jun:18-24.
44. Wade CE, Salinas J, Eastridge BJ, McManus JG, Holcomb JB: Admission hypo- or hyperthermia and survival after trauma in civilian and military environments. *Int J Emerg Med* 2011; 4:35.
45. Eastridge B, et al: Admission physiology criteria after injury on the battlefield predict medical resource utilization and patient mortality. *J Trauma* 2006; 61:820.
46. Allen PB: Preventing hypothermia: Comparison of current devices used by the US Army in an in vitro warmed fluid model. *J Trauma* 2010; 69(Suppl 1):S154-S161.
47. Black I, McManus JG: Pain management in current combat operations. *Prehosp Emerg Care* 2009; 13:223-227.
48. Wedmore IS, Johnson T, Czarnik J, Hendrix S: Pain management in the wilderness and operational setting. *Emerg Med Clin North Am* 2005; 23:585.
49. Otis JD, Keane TM, Kerns RD: An examination of the relationship between chronic pain and post-traumatic stress disorder. *J Rehabil Res Dev* 2003; 40:397.
50. McGhee LL: The correlation between ketamine and posttraumatic stress disorder in burned service members. *J Trauma* 2008; 64(Suppl):S195-S198; discussion S197-S198.
51. Kotwal RS, et al: A novel pain management strategy for combat casualty care. *Ann Emerg Med* 2004; 44:121.
52. Bredmose PP, Lockey DJ, Grier G, Watts B, Davies G: Pre-hospital use of ketamine for analgesia and procedural sedation. *Emerg Med J* 2009; 26:62-64.
53. Galinski M: Management of severe acute pain in emergency settings: Ketamine reduces morphine consumption. *Am J Emerg Med* 2007; 25:385-390.
54. Convertino VA, et al: Use of advanced machine-learning techniques for noninvasive monitoring of hemorrhage. *J Trauma* 2011; 71:S25-S32.
55. Ryan KL: Advanced technology development for remote triage applications in bleeding combat casualties. *J Trauma* 2011; 71:S61-S72.
56. Eastridge B, et al: Hypotension begins at 110 mm Hg: Redefining “hypotension” with data. *J Trauma* 2007; 63:291.
57. Holcomb JB, et al: Manual vital signs reliably predict need for life-saving interventions in trauma patients. *J Trauma* 2005; 59:821-828.
58. Cooke WH, et al: Heart period variability in trauma patients may predict mortality and allow remote triage. *Aviat Space Environ Med* 2006; 77:1107.
59. McManus J, et al: R-wave amplitude in lead II of an electrocardiograph correlates with central hypovolemia in human beings. *Acad Emerg Med* 2006; 13:1003.
60. Lerner EB, et al: Mass casualty triage: An evaluation of the data and development of a proposed national guideline. *Disaster Med Public Health Prep* 2008; 2(Suppl 1):S25-S34.
61. Cap AP: Tranexamic acid for trauma patients: A critical review of the literature. *J Trauma* 2011; 71(Suppl):S9-S14.
62. Roberts I, et al: CRASH-2 collaborators: The importance of early treatment with tranexamic acid in bleeding trauma patients: an

www.ketabpezeshki.com 66485457-66963820

exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 2011; 377:1096-1101, 1101.e1-2.
63. Heck JJ, Byers D: Chemical and biological agents: Implications for TEMS. *Tactical Edge* 2000; 19:52.
64. Carmona RH, Rasumoff D: Forensic aspects of tactical emergency medical support. *Tactical Edge* 1992; 10:54.
65. Heggie TW, Heggie TM: Search and rescue trends and the emergency medical service workload in Utah's National Parks. *Wilderness Environ Med* 2008; 19:164-171.
66. *Urban Search & Rescue*. Federal Emergency Management Agency (FEMA) online. Available at www.fema.gov/emergency/usr/index.shtm. Accessed December 19, 2011.
67. Cone D: Rescue from the rubble: Urban search and rescue. *Prehosp Emerg Care* 2000; 4:352.
68. U.S. Department of Homeland Security/Federal Emergency Management Agency (FEMA): *National Urban Search and Rescue (US&R) Response System Field Operations Guide*. Washington, DC: U.S. Department of Homeland Security/FEMA; 2003. Available at www.fema.gov/doc/emergency/usr/usrfog3.doc.
69. Federal Emergency Management Agency (FEMA): *US&R Response System Task Force Medical Team Training Manual*. Washington, DC: FEMA; 1997. Available at www.fema.gov.
70. Federal Emergency Management Agency (FEMA): *National Urban Search and Rescue Response System Task Force Equipment Cache List*, approved January 28, 2000. Available at www.fema.gov.
71. Macintyre AG, Barbera JA, Petinaux BP: Survival interval in earthquake entrapments: Research findings reinforced during the 2010 Haiti earthquake response. *Disaster Med Public Health Prep* 2011; 5:13-22.
72. Ashkenazi I, et al: Prehospital management of earthquake casualties buried under rubble. *Prehosp Disaster Med* 2005; 20:22-33.
73. Vandholder R, et al: Acute renal failure related to crush syndrome: Towards an era of seismo-nephrology? *Nephrol Dial Transplant* 2000; 15:1517.
74. Kazancioglu R, et al: The characteristics of infections in crush syndrome. *Clin Microbiol Infect* 2002; 8:202.
75. Niles JK, et al: Comorbid trends in World Trade Center cough syndrome and probable posttraumatic stress disorder in firefighters. *Chest* 2011; 140:1146-1154.

www.ketabpezeshki.com 66485457-66963820

Chapter 193

Disaster Preparedness

Carl H. Schultz and Kristi L. Koenig

PERSPECTIVE

Disasters occur in all areas of the world and cause harm to people, property, infrastructures, economies, and the environment. Harm to people includes death, injury, disease, malnutrition, and psychological stress. Recent catastrophes include earthquakes in Pakistan (2005) and Haiti (2010) (Fig. 193-1); devastating tsunamis in the Indian Ocean (2004) and Japan (2011); massive hurricanes in the southern United States (2005); severe flooding in Australia (2011); tornadoes in Arkansas, Tennessee, and Kentucky (2008); and unusual weather conditions producing record snowfalls in the United States and Europe (2011). Increasing population density in floodplains and in earthquake- and hurricane-prone areas and the effects of global warming point to the probability of future catastrophic disasters with large numbers of casualties.

Factors that indicate an increasing probability of mass casualty incidents include terrorist activity; increasing population density in floodplains, seismic zones, and areas susceptible to hurricanes; production and transportation of thousands of toxic and hazardous materials; risks associated with fixed-site nuclear and chemical facilities (illustrated by damage to the Fukushima nuclear power plants after the 2011 Japan earthquake and tsunami); the possibility of catastrophic fires and explosions; and global warming. As an example, the U.S. Geological Survey has identified volcanoes in the western United States and Alaska that are likely to erupt in the future, including Mt. Hood, Mt. Shasta, and the volcano underlying Mammoth Lakes in California. Because of the rising population density in these areas, hazards from volcanic activity are increasing. Ash from the 2010 Eyjafjallajökull eruption in Iceland grounded aircraft in Europe for weeks.

Given this probability and the increasing role of emergency medicine in disaster preparation, mitigation, response, and recovery, this chapter discusses disaster planning and operations with emphasis on the role of the emergency physician. The emergency physician has extensive responsibilities for community disaster preparedness and disaster medical services, including response to terrorism. In position and policy documents, the American College of Emergency Physicians outlines the scope of emergency medicine's involvement in preparedness and response to disasters and terrorism, stating that "emergency physicians should assume a primary role in the medical aspects of disaster planning, management, and patient care" and that "emergency department personnel will become the *first responders* to a covert biological attack."[1,2]

A committed emergency department alone is insufficient to provide hospitals with a successful disaster preparedness program. Institutional commitment by every hospital department and the administration is necessary to coordinate effectively with system-wide resources for disaster management. This is especially critical for creation of hospital surge capacity.[3-5] A partial listing of general disaster medicine resources can be found in Table 193-1.

Surge Capacity

The concept of surge capacity has emerged as a way to manage an event that produces a sudden influx of casualties with medical and health needs that exceed current hospital resources.[6] This can be due to either the volume or types of victims. The three basic components of the surge capacity system are commonly referred to as the three *s*'s of staff (hospital personnel), stuff (supplies and pharmaceuticals), and structure (physical location and management infrastructure). A complete discussion of surge capacity is beyond the scope of this chapter but has been published elsewhere.[7]

Within the context of surge capacity, new protocols are being developed that address allocation of resources when the medical and health needs of a population exceed current inventory. The issues involve creation of an equitable system for scarce resource allocation strategies, including assignment to an intensive care unit. Although no universally accepted approach currently exits, a system to optimize patient outcomes in a resource-constrained environment is clearly needed.

NATURE OF DISASTERS

Definitions

One of the challenges facing those responsible for disaster preparation is that no standard definition of *disaster* exists. Some events that have been routinely classified as disasters clearly are not. For example, many would consider a plane crash a disaster, yet it may not even approach overwhelming of the resources of the local responders. Because disaster medicine is multidisciplinary and depends on the integration of multiple levels of responders, the use of a common, precise terminology is essential.

In general terms, an event can be considered a disaster when it overwhelms response capabilities. These response capabilities can change in diverse environments or even in the same location at different times of the day or days of the week. For example, a multiple-vehicle collision with 6 critically injured patients and 12 patients with minor injuries could overwhelm both the emergency medical services system and the hospital in a small rural community. In an urban area with multiple hospitals that participate in a trauma system, however, this same event could be managed with routine resources. Thus it is the functional impact on the specific entity that is the key concept in determining whether a disaster exists.

www.ketabpezeshki.com 66485457-66963820

Figure 193-1. Large-scale catastrophes, such as this earthquake in Pakistan (2005), have the potential to cause much injury and psychological stress.

Table 193-1 List of Disaster Medicine Resources

ORGANIZATION	WEBSITE
The Joint Commission	www.jointcommission.org/
American College of Emergency Physicians	www.acep.org
Centers for Disease Control and Prevention, Emergency Preparedness and Response	www.bt.cdc.gov/training/
FEMA National Preparedness Directorate, National Training and Education	http://training.fema.gov/
National Response Framework	www.fema.gov/emergency/nrf/
Agency for Healthcare Research and Quality	http://archive.ahrq.gov/prep/
Koenig and Schultz's Disaster Medicine: Comprehensive Principles and Practices	Cambridge University Press www.cambridge.org

Classic Terminology

The words *internal* and *external* refer to a hospital setting to help distinguish whether an event has occurred within the hospital grounds (internal) or in the community (external). This concept distinguishes between preparing for casualties to arrive at the hospital and dealing with casualties or resource problems within the hospital. This geographic distinction between internal and external may be useful, but it has severe limitations. Many events can be both internal and external to the facility at the same time (e.g., major earthquake or hurricane). Furthermore, simply identifying the location of the event does not answer the critical question: How are response capabilities affected?

An etiologic descriptor for an event is another customary classification. It does not matter whether a disruption in the ability of the hospital to respond is caused by nature or by humankind. The key consideration is what actions are required to mitigate and then to rectify the situation. Although the terms *natural* and *man-made* are prevalent disaster descriptors, they generally do not add anything of value, and therefore some experts have advocated removing them from the disaster lexicon, particularly because the etiology of the event may be unclear in its initial aftermath.

Some definitions have been based on the number of casualties. As previously described, the absolute number of patients is much less important than whether their medical and health needs exceed the resources to care for them at a given point in time. Another historical scheme divides disasters into three levels. Level I denotes a situation in which local resources are adequate to care for casualties. For example, the 2002 collision between a freight train and commuter train in Orange County, California, was managed effectively by local responders. Level II means that regional mutual aid is required to respond to the event. This was the case at the Hyatt Regency Hotel in Kansas City in 1981 when two skywalks collapsed, killing 114 people and injuring hundreds. Level III incidents require state and federal aid. The attack on the World Trade Center in 2001 (Fig. 193-2) and hurricane Katrina in 2005 were such events, causing such massive destruction that federal disaster medical assistance teams were deployed to New York and Louisiana, respectively, to provide medical personnel and supplies.

Figure 193-2. The World Trade Center attack of 2001 overwhelmed local resources and necessitated state and federal help.

One model eliminates the word *disaster* and replaces it with the acronym for potential injury-creating event, *PICE*.[8-10] The PICE nomenclature is an attempt to resolve the issue regarding diverse meanings for *disaster*. This model is referenced in the Joint Commission standards and in publications from several countries. The PICE system is discussed here to help clarify important concepts in describing an event.

Potential Injury-Creating Event Nomenclature

The acronym PICE and its modifiers concisely describe the critical features of most types or degrees of disaster.[8-10] The same occurrence can have different effects at different points in time; thus, as an event evolves over time, its description may change.

Modifiers are chosen from a standardized group of prefixes along with a stage to indicate the need for outside medical assistance (Table 193-2). The first prefix (column A) describes the potential for additional casualties. The second prefix (column B) describes whether local resources are overwhelmed and, if so, whether they must simply be augmented (disruptive) or whether they must first be totally reconstituted (paralytic). The third prefix (column C) shows the extent of geographic involvement.[8-10] Column C refers strictly to the affected region and not to the

www.ketabpezeshki.com 66485457-66963820

Table 193-2 PICE Nomenclature

PREFIX					
A	B	C	PICE STAGE	PROJECTED NEED FOR OUTSIDE AID	STATUS OF OUTSIDE AID
Static	Controlled	Local	0	None	Inactive
Dynamic	Disruptive Paralytic	Regional National International	I II III	Small Moderate Large	Alert Standby Dispatch

PICE, potential injury-creating event.

Table 193-3 PICE Nomenclature Examples

World Trade Center attack, September 11, 2001	Dynamic, paralytic, local, PICE stage III
Los Angeles civil disturbance	Dynamic, paralytic, regional, PICE stage I
Northridge earthquake	Dynamic, disruptive, regional, PICE stage II
Oklahoma City bombing	Dynamic, disruptive, local, PICE stage I

PICE, potential injury-creating event.

Box 193-1 Six Critical Substrates for Hospital Operations

Physical plant
Personnel
Supplies and equipment
Communication
Transportation
Supervisory managerial support

Box 193-2 Examples of Paralytic PICE

Destructive	Nondestructive
Bomb explosion	Snowstorm
Earthquake	Employee strike
Fire	Power failure
Civil unrest	Water supply cutoff

location that sends assistance. Rather, the “stage” rating scale defines the likelihood that outside medical assistance will be needed either to augment or to completely reconstitute resources.[8] Stage 0 means that there is little or no chance. Stage I means that there is a small chance and requires placing outside medical help on alert. Stage II means that there is a moderate chance and outside help should be placed on standby. Stage III means local resources are clearly overwhelmed and require the dispatch of outside resources and commitment of personnel. For example, a multivehicle collision with a dozen injuries and several deaths in a large city would be a stage 0, whereas in a small rural town it might be a stage III (Table 193-3).

A PICE can be either static or dynamic. *Dynamic* implies an evolving situation in which it is too soon after the incident to determine the numbers and types of casualties and the impact on the hospital. Alternatively, a *static* situation results if 10 people are injured in an incident and little potential for further harm exists.[8-10]

In some situations, enhancement of routine operations is not sufficient or possible. A PICE can completely overwhelm the capability to mount a normal response so that a substitute plan for recovery must be used. Situations that require significant reconstitution of critical resources are termed *paralytic*.[8-10] Within the hospital, there are six critical elements necessary to provide a response (Box 193-1).[11] If one or more of these resources are compromised, they must be reconstituted or a substitute must be implemented. Such paralytic events can be either destructive or nondestructive (Box 193-2).[8]

Hazard Vulnerability Analysis

An important consideration in disaster planning is an awareness of the types of events for which the hospital or community is vulnerable. The classic example is the monumental risk from earthquakes in the central United States resulting from the combination of the New Madrid fault and the limited seismic safety requirements for buildings in that area. The planner must learn what types of support are available from outside agencies (e.g., hazardous materials decontamination from fire departments and information from poison control centers). Although awareness of such resources is critical, contingency plans must be available when such assistance is not accessible.

After performing a hazard vulnerability analysis (www.emsa.ca.gov/disaster/files/kaiser_model.xls), emergency planners should consider the most probable events and prepare for them. There should also be planning for events that are rare but catastrophic.[12] The major peacetime threat to life and limb in the United States is probably a large earthquake in a densely populated area or a terrorist attack. The disaster planner should proactively identify all such hazards and prepare contingency plans for each.

TRIAGE

The term *triage* derives from the French verb *trier,* meaning “to sort.” The concept of triage was used as far back as Napoleon’s time to assign priorities to treatment of the injured when resources were limited. Priority is given to the most salvageable patients with the most urgent conditions. The emergency department uses triage in the hospital setting on a daily basis, but the focus of such triage is changed under disaster conditions.[13,14] Standard emergency department triage is intended to identify the most seriously ill patients first and to ensure that they receive rapid care. The goal of disaster triage is slightly different, that is, “to do the most good for the most people.” In other words, there is a shift from focus on individual patients to focus on the entire affected population.[15] It can be difficult for physicians to realize that to achieve the goal of maximizing benefit to an entire population of patients, they may need to let some patients die with only comfort care. Under true disaster conditions, cardiopulmonary resuscitation should not be performed.[16]

Routine Multiple-Casualty Triage

To assist in understanding of triage techniques, it is useful to consider a routine out-of-hospital event with multiple casualties

www.ketabpezeshki.com 66485457-66963820

(e.g., a multivehicle collision). In such situations, rescue personnel often use a Simple Triage and Rapid Treatment (START) technique that depends on a quick assessment of respiration, perfusion, and mental status.[17] These three assessments can be remembered by the mnemonic RPM (respirations, perfusion, and mental status). Initially, all victims who are able to walk are asked to move away from the immediate incident area. These patients are classified as green, or "walking wounded," and are reassessed after the more immediately critical patients are triaged.

The Pediatric Triage Tape (PTT) and JumpSTART have been proposed for the triage of children. JumpSTART is a modification of the START triage protocol that includes an additional step of five rescue ventilations for children presenting apneic and modification of criteria for hypoventilation and tachypnea as well as for a decrease in mental status. The PTT uses criteria that change in proportion to increasing victim size. The parameters for a child 50 to 80 cm in length are illustrated in Figure 193-3. In a comparison of sensitivity and specificity between the PTT and JumpSTART in pediatric trauma patients, the PTT demonstrated superior outcomes.[18] Both START and the PTT appear to be useful tools, but only START has been evaluated in an actual disaster situation.[19-21]

As illustrated in Figure 193-4, a rescuer can assess each patient in seconds, quickly checking respiratory rate, pulse, and ability to follow commands (mental status), and divide the patients into the remaining three categories: red (immediate), yellow (delayed), and black (deceased). The only patient care interventions provided during this process are the opening of an obstructed airway and direct pressure on obvious external hemorrhage. At this point, patients are generally transported to a hospital for definitive care. Most often, patients arrive with a color-coded triage tag and are reassessed and retriaged by the hospital staff (Fig. 193-5). An outcomes-based evaluation of the performance of START triage in an actual disaster (2002 Placentia Linda train crash) demonstrated acceptable levels of undertriage (100% sensitivity

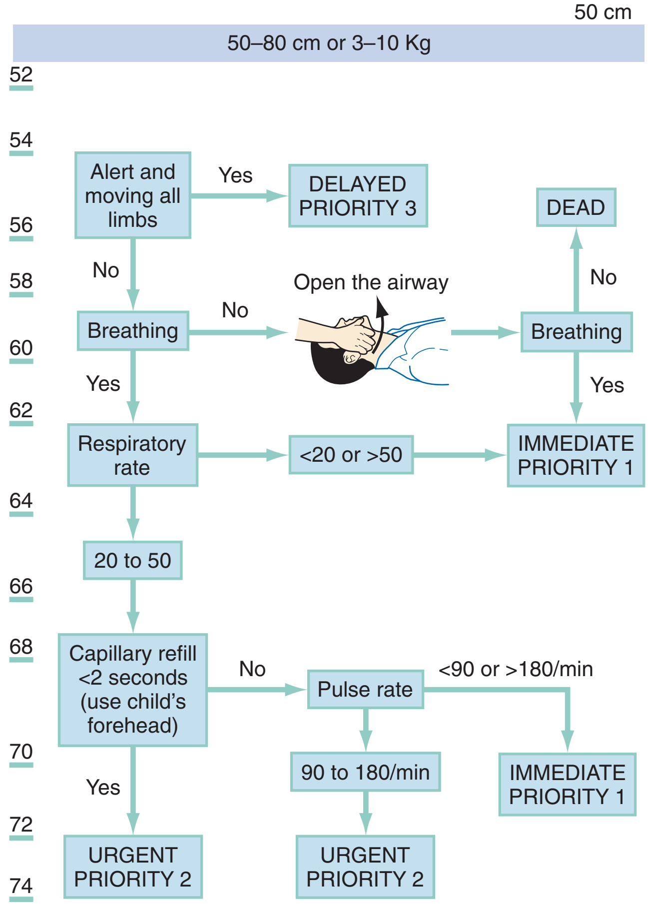


Figure 193-3. Pediatric Triage Tape algorithm for a child 50 to 80 cm in length.

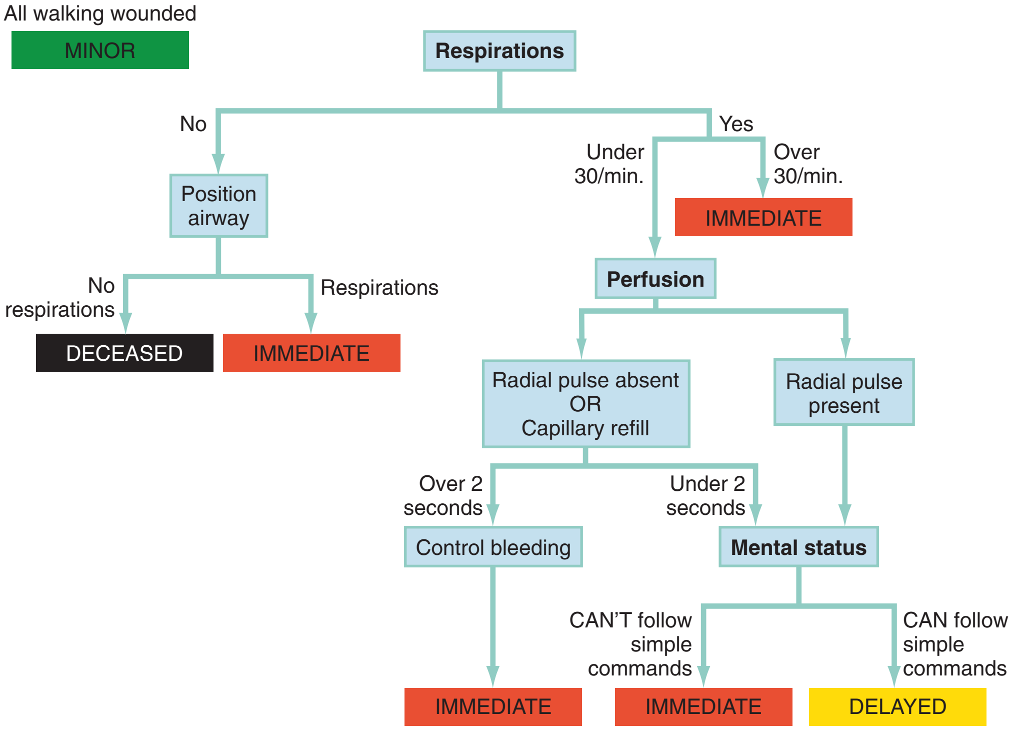


Figure 193-4. Simple Triage and Rapid Treatment (START). Victims who can walk are identified first and triaged into the "minor" category. Those remaining are triaged by the algorithm. (Modified from Triage—START and SAVE. In: Medical Disaster Response Training Course Syllabus. Dana Point, Calif, Medical Disaster Response, 1993.)

www.ketabpezeshki.com 66485457-66963820

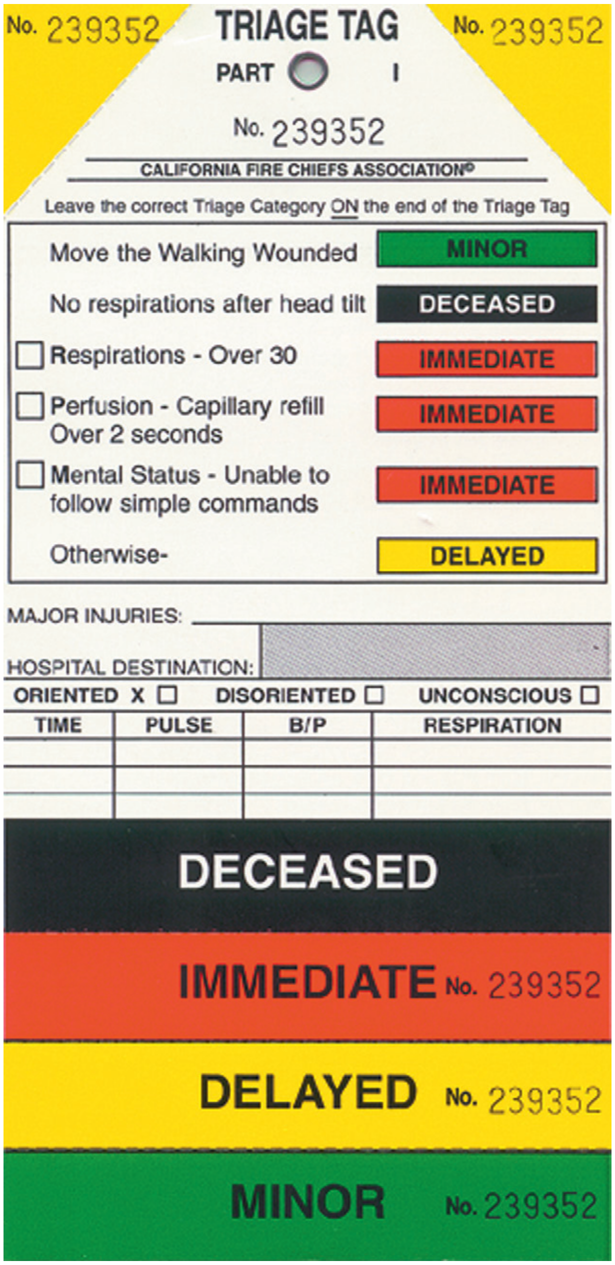


Figure 193-5. Triage tag to be used in multicasualty or disaster patient assessments.

of the red category and 90% specificity of the green category).[21] However, significant amounts of overtriage occurred. Use of START also appropriately prioritized the transport of victims, with patients triaged as red arriving at hospitals earlier than patients triaged as yellow or green.

Recently, a multidisciplinary group was formed to propose a potential national triage system for the United States. The result, derived by consensus of opinions, was referred to as SALT (sort, assess, lifesaving interventions, and treatment or transport).[22] It differs from START mainly in the assessment of respirations (relies on a qualitative evaluation of respiratory distress rather than a number), the requirement for performance of certain emergent interventions (chest decompression), and an unstructured estimate of survivability. The algorithm is more complicated than START, and no current data exist evaluating its sensitivity, specificity, or other performance characteristics in a disaster. As such, it is not currently possible to make recommendations for its use.

Catastrophic Casualty Management

Triage during a widespread, catastrophic disaster differs from triage performed in routine out-of-hospital and hospital settings. The number of victims is vastly increased, and medical resources are severely limited or even initially absent. Patients may remain on scene for an extended period and should be frequently reassessed. If hospitals remain accessible, patients tend to seek care at the closest one, a phenomenon known as convergence. Hospitals close to the disaster scene are overwhelmed, whereas hospitals located only a few miles away may receive few if any patients. More likely, the hospitals will be rendered nonfunctional. The triage process will then be decentralized, occurring at multiple sites, or compartments, simultaneously throughout the disaster zone. Rather than a single scene or localized disaster, this can be thought of as a compartmentalized disaster.

To address this situation, researchers developed the Secondary Assessment of Victim Endpoint (SAVE) system of triage.[23] The SAVE triage system is designed to identify patients who are most likely to benefit from care available under austere field conditions in a resource-poor environment. When it is combined with the START protocol, SAVE triage is useful for any scenario in which multiple patients experience a prolonged delay in accessing definitive care.

The SAVE methodology is designed for use by health care providers under two conditions: (1) for those working within the disaster zone that begin caring for patients immediately but may not be able to transport patients to a definitive care facility for days and (2) for those caring for patients within hospitals where demand for resources exceeds supply. This second situation can occur as hospitals attempt to increase surge capacity. It is immediate and dynamic rather than delayed and static. Although there are many elements in common with other triage systems, rapid transport to a functional medical center within the "golden hour" may not be possible.

The SAVE triage methodology divides patients into three categories: (1) those who will die regardless of how much care they receive, (2) those who will survive whether or not they receive care, and (3) those who will benefit significantly from austere field interventions. Only those patients expected to improve receive care beyond basic and comfort measures. With use of SAVE, patients are separated into these three categories so resources can be focused appropriately. The decision to place patients in a particular group is based on field outcome expectations derived from existing survival and morbidity statistics.[23] An example is a situation in which three victims require chest tubes (two victims require one tube each and one victim requires two tubes), but only two chest tubes are available. The SAVE principles guide providers to place their last two chest tubes into the two victims who need it rather than into the single victim requiring two tubes.

During the triage process, individuals who would most benefit from early transport should be marked as "first out," in case an evacuation opportunity occurs. These would be victims with medical problems readily treatable at a hospital or facility with equivalent capabilities but untreatable and fatal in the field. A patient requiring surgery for intra-abdominal hemorrhage is a common example.

Since nuclear, biologic, and chemical terrorism has become a threat, new triage systems are under development.[13,24] These systems attempt to incorporate the added threats from exposure and contamination into the triage process. One such method for biologic casualties triages many individuals to home observation rather than hospitalization to optimize resource use and to minimize the spread of the infectious agent.[24] In addition, responders must be protected from secondary contamination or exposure; therefore, part of the triage algorithm should include a risk assessment and determination of whether and what type of personal

www.ketabpezeshki.com 66485457-66963820

protective equipment should be donned before patients are assessed. A quick determination is critical to prevent patient deaths from traumatic injuries while awaiting medical care from responders concerned about their own health and safety. This is particularly true in a "combined event" scenario, such as an event involving a radiologic dispersion device. Also associated with terrorism incidents are large numbers of *psychogenic casualties,* those who believe they were exposed but actually were not and those at risk for post-traumatic stress disorder. The emergency plan should include a mechanism to assess and to sort these individuals so as not to overwhelm the emergency department and also provide mental health care. While performing triage, the emergency physician should also consider the effects of extremes of age, underlying disease, and multiple injuries when assessing the potential prognosis for a given patient. Fortunately, the treatment of many nontraumatic emergencies can be accomplished with field interventions that do not consume extensive resources. Therefore, patients with such illnesses should usually be triaged to the treatment area.

Vulnerable Triage Populations

Certain groups of patients, such as children, the elderly, and disabled persons, may have special needs that present challenges to routine triage. For example, if a person is too young to follow commands or is deaf, the individual would not be able to respond to a command to walk away from an incident site for reasons that may not indicate severe injury. Triage schemes should accommodate language and cultural barriers as well as physical and psychological limitations that result in social or medical vulnerabilities.

Special Triage Categories

To maximize personnel resources, disaster victims who would normally be triaged to the observation area can be triaged to the treatment area if they possess special skills valuable to the medical team (e.g., medical expertise and translation skills). By the increase in the number of functional team members, the effectiveness of the overall response will improve. The guiding principle supports the disaster triage goal of maximizing benefit to the most people.

CARE OF SPECIAL NEEDS POPULATIONS

Within the general population, groups of unique individuals exist that are at greater risk for injury, death, and property loss resulting from a disaster. These vulnerable populations include children, the elderly, racial and ethnic minorities, the disabled, those residing in institutions such as skilled nursing facilities, and the mentally ill. Challenges in the management of these populations with special needs during a disaster include lack of mobility, tracking of victim movement during evacuations and issues of reunification with responsible family members, inability to understand English or to comprehend instructions issued by local authorities, and poor access to transportation resources. A detailed discussion on the disaster management of these populations is beyond the scope of this chapter but available elsewhere.[25,26] Those responsible for disaster planning should ensure that policies and procedure are developed that address the unique needs of such groups.

OUT-OF-HOSPITAL RESPONSE

Emergency Medical Services System Protocols

To prepare adequately, hospitals must be familiar with and involved in the development of county or regional plans. For example, some emergency medical services systems use automatic systems such that each hospital may be expected to accept a fixed number of critically ill or injured and minor patients without previous notification.

Physicians working at hospitals should be familiar with community disaster management operations, including the function of the emergency operations center.[11] Mutual aid agreements with other hospitals or regions should be considered for situations in which current hospital capacity is exceeded or evacuation is necessary.

Incident Command System

Some form of an incident management system is now a standard component of emergency command and control throughout the United States. It provides a flexible management structure on which to organize a response.[27] The federal version, known as the National Incident Management System, is incorporated into the National Response Framework and provides strategic guidance on the U.S. government's involvement in disaster response. All states must use an incident management system, and it must be compliant with the National Incident Management System.[28] By standardizing an organizational structure and using common terminology, an incident command system provides a management configuration that is adaptable to events involving a multiagency or multijurisdictional response. At the most basic level, there are five functional elements in the organizational structure: incident command, operations, planning, logistics, and finance. The principles of an incident command system can also be applied to the hospital setting through implementation of a Hospital Incident Command System. With this type of organizational infrastructure and the flexibility to expand and to collapse functions as needed, an orderly and efficient response to any incident can be accomplished. Because hospitals cannot anticipate every contingency, a system such as the Hospital Incident Command System assists with planned improvisation. The Joint Commission (formerly known as the Joint Commission on Accreditation of Healthcare Organizations) standards require use of an incident management system in health care facilities.

Incident Command

The incident commander has overall management responsibility for the incident. Physicians should understand that they are not in charge at the scene of an out-of-hospital incident.[28] In general, nonhospital providers can manage the scene, and physicians should remain at the hospital to provide definitive care. When a physician is on scene, the best way to assist is to ask the incident commander where medical help is most needed.

The incident commander may choose to appoint a command staff to manage public information, safety, and interagency liaisons.[27] When an event involves multiple jurisdictions, a unified command is established that coordinates a common and consistent action plan to make the best use of available resources.

Operations Section

The operations section has a chief who is responsible for the management of all incident tactical activities.[27] This section can be expanded and subdivided into branches (e.g., law, fire, and medical) and divisions. Operations also manages the resources assigned to staging areas. Ambulances, personnel, and supplies should be staged outside the perimeter of the scene and directed in as needed rather than converging on the disaster site, potentially disrupting activities and blocking the exodus of patients. It is under the operations section that all medical triage and care is provided.

www.ketabpezeshki.com 66485457-66963820

Planning Section

The planning section collects, evaluates, and disseminates information about incident operations and the status of resources. This section also develops incident action plans and conducts planning meetings.[27]

Logistics Section

The logistics section's chief is responsible for providing facilities, services, and material in support of the incident. This includes procuring equipment and supplies, providing food and medical support, and meeting transportation needs.[27]

Finance Section

The finance section is responsible for maintaining records on personnel and equipment, providing payments to vendors for supplies and use of equipment, and determining the cost of various alternatives for strategic planning.

Organization of the Out-of-Hospital Disaster Scene

The disaster site is organized into several distinct areas. The command post is the nerve center of the operation and contains the incident commander and section chiefs. A staging area for incoming personnel and equipment should be established on the outer perimeter. If air evacuation is needed, a safe landing zone must be identified. A casualty collection point and morgue should be designated. In conjunction with an incident command system, this structure brings order to the response.

PLANNING AND HOSPITAL RESPONSE

Comprehensive Emergency Management

The comprehensive emergency management all-hazard approach to disaster preparedness has been a Joint Commission requirement since January 2001. Comprehensive emergency management consists of four phases: mitigation, preparedness, response, and recovery.[29,30] *Mitigation* involves taking actions to reduce the impact of identified hazards. Training, drills, and cataloging of resources are examples of *preparedness* activities. *Response* includes assessment of the situation and coordination of resources. Finally, *recovery* consists of a return to normal operations and debriefing to critique the response and to provide long-term psychological support to the victims and rescuers.

As required by the Joint Commission, a hospital's disaster or "emergency management" plan must address events that occur both inside (internal) and outside (external) the institution.[30] Because some incidents affect both internal and external operations, a hospital emergency management program should contain plans that address all circumstances.

Hospital Disaster Response Plan

A disaster event can disrupt daily, routine hospital functions. This can represent an infrastructure failure (e.g., loss of electric power and water) or a threat to the safety of patients and hospital personnel (e.g., labor dispute or approaching hurricane). Because the response varies from postponement of elective surgery to facility evacuation, every hospital department must participate in the planning process. At a minimum, the disaster plan should clearly delineate the circumstances in which the plan is activated; identify the command structure with defined lines of authority and responsibility; describe a response strategy for each anticipated incident; estimate an incident's impact on safety and hospital function, providing for evacuation if necessary; and list essential information, such as critical telephone numbers (e.g., elevators, key personnel, and pay telephones), community agencies (emergency medical services, police, and public health), and sources of vital supplies (water, oxygen, and drugs).[29]

After plan activation, the primary role of the emergency department is to assess and to treat individuals with illness or injury. In the absence of casualties, other hospital departments primarily manage disasters that disrupt hospital operations. Nevertheless, the medical director of the emergency department should continuously monitor the response process.

In the unlikely event that evacuation of the emergency department is necessary, evacuation routes and relocation destinations that have been planned in advance maximize safety and efficiency. When resources are plentiful, emergency department patients in critical condition are assigned the highest priority for evacuation and transport. Less ill patients receive a lower priority.[31] When resources are limited (e.g., in the event of a large-magnitude earthquake), the reverse strategy applies. The least critically ill patients receive the highest priority for evacuation.

Another scenario would be an event occurring in the community that results in a sudden influx of patients requiring emergency care at hospitals. This type of incident has no direct impact on hospital capacity or function. However, the need to rapidly increase surge capacity may require implementation of different patient management strategies (i.e., temporary creation of alternate care sites on hospital grounds). Participation in the planning and execution of the hospital disaster response is an important administrative responsibility.[16] Available data guiding development of disaster strategies are incomplete, but an effective disaster response can be created by reviewing the essential components of disaster plans and the previous experience of hospitals.[16,29,31,32] A member of the emergency department must have a leadership role in the planning and implementation of the disaster plans.

Basic Components of a Hospital Comprehensive Disaster Response Planning Process

Interdepartmental Planning Group

The interdepartmental planning group has the responsibility for hazard identification and disaster preparedness activities. The process of conducting a hazard vulnerability analysis is complex, but templates such as the one created by the Kaiser Foundation Health Plan may be informative.[33] Frequently referred to as the disaster or emergency preparedness committee, it is composed of representatives from all departments vital to the hospital's response, including administration, medical staff, nursing, safety, security, emergency department, and engineering. Additional input may occasionally be necessary from outside agencies (e.g., fire department, hospital suppliers of goods and services, and emergency medical services agency).

The committee should be structured to ensure that the plan is properly constructed, tested, and executed. Hospital resources must be provided to support the planning process and testing of the plan, and there must be a detailed educational program for all affected hospital staff.[30,34]

Resource Management

A full inventory of the hospital's resources is necessary. In addition to equipment, space, and personnel within the institution, potential support from outside the hospital must be sought. It is also necessary to develop contingency plans to compensate

www.ketabpezeshki.com 66485457-66963820

for lost resources (e.g., failure of hospital computers during a power outage or cyber attack). Augmentation of such resources is critical to the successful increase of the hospital's surge capacity.[4,5,35]

Strong relationships with community agencies (e.g., fire department and regional emergency medical services system) are important to ensure a coordinated disaster response. Hospitals located near companies using large amounts of hazardous materials are required by Title III of the Superfund Amendments and Reauthorization Act to participate in local emergency planning committees, sometimes termed LEPCs.[36]

Command Structure

An organized system establishing lines of authority and decision responsibility must be in place. This system should designate a command center where the disaster response can be coordinated and create a clear chain of command. This prevents confusion if certain individuals are missing, a common situation on nights and weekends or in cases of a community-wide disaster during which hospital personnel may become victims. The command center should contain sufficient equipment to support command and control functions, even if the center must be moved as a result of hospital damage. Implementation of the Hospital Incident Command System or similar management structure will support all such requirements.

Media

The media can be an important source of information but can also significantly disrupt the hospital's disaster response. Therefore, arrangements should be made in advance for a designated individual to coordinate all media interactions and for these briefings to occur in a designated location. Media coordinators should inform reporters of the time they will receive their next update so they do not intrude on response operations while trying to obtain information. A strong media liaison can facilitate dissemination of important information to the public, such as that no blood shortage exists so that individuals refrain from coming to the hospital to donate blood. In fact, crisis and emergency health risk communication is now an important part of managing the disaster response and can have a significant impact on the public's perception of events.[37] Individuals designated the media coordinator should be familiar with the basic principles of emergency health risk communication. Security should be involved in managing the media response to the hospital and in preventing media from interfering with triage and treatment of patients.

Communication

Communication systems are probably the most important but also most vulnerable component of a disaster plan.[16,31] Redundant systems are essential. Those responsible for mobilizing the emergency response require access to at least one other communication system besides the telephone (which is frequently one of the first systems compromised during a disaster). Two-way radios are often used, as are pay telephones, independent fax lines, and cellular phones. Another option is the use of satellite phones and wireless hand-held devices to transmit e-mail messages. Recent advances in communication technology exemplified by Facebook and Twitter show promise. Survivors of the 2011 Japan earthquake used these techniques to provide early information to the outside world on conditions within the disaster zone.[38] Runners are also useful for intrahospital communication if all else fails.

Personnel

The disaster plan must include a roster of all critical positions and personnel and establish a reliable method for their mobilization. Several individuals should be assigned to each position in case some personnel cannot be reached. A protocol for managing volunteers is also crucial. A large group of uncontrolled volunteers descending on a hospital ("convergent volunteerism") can be as disruptive as the disaster.[39]

Credentialing of volunteer health professionals in a timely manner so hospitals can use their services during a disaster remains a challenge. A federally supported program known as the Emergency System for Advance Registration of Volunteer Health Professionals (ESAR-VHP) is attempting to address this problem. It will provide a system for credentialing of volunteer health care providers in advance of a disaster so they will have emergency privileges should the need for their services arise.[40] There remain significant challenges with such a system, including whether sufficient numbers of providers will participate, how fast they can deploy, how well qualified they will be, and whether they will have competing obligations during a disaster. An alternative system that permits hospitals to recognize each other's credentialing process through a shared database shows promise. Not only will this alternative system facilitate participation by most health care providers, but it also permits hospitals to grant emergency privileges within minutes after a disaster.[40]

Patient Management

A systematic approach to patient management is necessary to maximize resources. This includes protocols for decontamination, triage, patient prioritization, evacuation, and control of patients' families. Alternative use of hospital facilities should be anticipated, such as the conversion of a parking lot into a clinic area for suturing of lacerations or a decontamination zone. Provisions for patient identification and treatment documentation are also important to facilitate federal and third-party reimbursement at the conclusion of the disaster.

Training Exercises

Disaster exercises are one of the more effective ways of familiarizing hospital staff with their responsibilities. All hospital departments should participate, and community agencies should be involved. The Joint Commission requires two drills a year; these should mimic incidents that are likely to occur. Methods to assess the effectiveness of these exercises as measures of overall hospital disaster preparedness are improving.[41]

REVIEW OF HOSPITAL AND COMMUNITY DISASTER RESPONSE EXPERIENCE

Disaster plan implementation is complex and difficult. Knowledge can be gained from review of previous disaster response experiences, resulting in improved implementation strategies. The following discussion highlights potential challenges.

Focal Disasters

Most disasters experienced by hospitals are focal in nature. Hospital function is typically unimpaired. The majority of problems encountered are related to a sudden increase in patient volume and acuity or arrival of patients with illnesses not usually treated at that facility (e.g., burns, radiation exposure, and severe acute respiratory syndrome).

www.ketabpezeshki.com 66485457-66963820

Hospitals frequently experience difficulty in effectively using and interfacing with community resources. Field triage should allocate patients rationally, and transfer agreements must be in place to facilitate interhospital movement of patients and evacuation of patients to alternate care sites.

Media access must be controlled. During the Loma Prieta earthquake in 1989, a news helicopter occupied a nearby community hospital's only landing zone, preventing the possibility of landing a medical helicopter.

Redundant communication systems must be in place. Typical backup systems to the telephone are radios and cellular phones, but the frequencies can be overloaded in both systems. Use of cellular phones for text communication may offer another solution. Two-way radios are reliable and should be part of the communications network. Satellite phones are also an option.

Catastrophic Disasters

In a large-scale disaster, paramedics may be unavailable to assist in patient transfers or hospital evacuations. Disaster medical assistance teams and urban search and rescue teams will deploy, but their time to arrival on scene may be variable. Each individual hospital may have to remain self-sufficient for 48 to 72 hours or longer.[42] Generator problems are frequent; they either fail altogether (as they did during the Loma Prieta earthquake) or supply insufficient power to meet emergency needs (as during the Northridge earthquake). Evacuation plans must not require elevators for this reason. Telephone service will cease as lines are disrupted or deliberately restricted by the phone company. Cellular phones may function within a local area, but failure is likely if more distant sites within the city are dialed. Hospital radios designated for disaster use should have the hardware secured to prevent earthquake damage.

Under catastrophic conditions, mobilization of personnel is more difficult. Because telephone communication is unreliable, at least one additional system to contact personnel at home should be in place. An alternative is to institute an automatic response system, in which personnel report to the hospital or another location when communications are impaired.

After earthquakes or explosions, immediate access to structural engineers is important. In the Northridge earthquake, eight hospitals in the Los Angeles area sustained enough damage to force evacuation of at least one patient. Four institutions completely evacuated their facilities in the first 24 hours, including two hospitals that met the most current structural earthquake standards. Further structural damage was subsequently identified, and two additional hospitals were forced to evacuate completely in the next 2 weeks. Ultimately, four of these hospitals were permanently closed and demolished.[31]

Hospitals are also vulnerable to hurricanes. In a study of hurricane Rita's (2005) impact on regional hospitals in Texas and Louisiana, seven hospitals were forced to evacuate patients.[32] Significant problems included prolonged loss of power, potable water, and staff. It was also difficult to obtain vehicles for transportation of patients to other facilities. Nonmedical vehicles were sometimes used to evacuate stable patients.

Catastrophic earthquakes can cause extensive casualties, including large numbers of patients with crush syndrome and lacerations. Up to 90% of victims with serious but survivable injuries are rescued by local responders and volunteer citizens in the first 24 to 48 hours. Therefore, special medical teams, such as disaster medical assistance teams and urban search and rescue teams, may not significantly affect survival from acute injuries if they arrive after more than 48 to 72 hours. If hospitals are not functional and no backup plan exists, immediate advanced medical care will not be available, and many people will die. Therefore, planners should include a backup system to provide medical care at alternate non-hospital care sites.

Need for Local Response

Currently, it is not possible for outside assistance to arrive in force during the crucial first 48 hours after the event. Therefore, an alternative source of immediate, sophisticated medical care is necessary. It appears this is best provided by local responders who can begin caring for patients soon after the event.[43] The Medical Disaster Response Project is the most advanced model of a local medical response to such a disaster. Developed by emergency physicians in southern California, the Medical Disaster Response Project has two components: (1) training of health care providers in the management of disaster victims under austere conditions and (2) placement of sophisticated medical supplies at designated sites within the community.[42] Under this plan, victims could receive rapid, advanced medical care from surviving volunteer health care providers even if hospitals were destroyed. The current Strategic National Stockpile is modeled after components of this plan. In addition, it was used as a major source document for the development of the Medical Reserve Corps.

Toxic Disasters (Hazardous Material)

Hospitals in the vicinity of major chemical industries, transportation corridors, or probable terrorist targets (e.g., major theme parks or nationally symbolic buildings) should be aware of potential hazards from incidents involving chemical and radioactive substances and be prepared to decontaminate large numbers of individuals exposed to these hazardous substances. Effective decontamination of victims and the need for safety measures on the part of rescue personnel to prevent secondary contamination are critical.[44] Decontamination equipment should be stored near the emergency department, and the staff must be trained in its use. This location must be known to personnel.[45] When such an emergency occurs, there is little time to search the hospital for the necessary supplies.

Ideally, patients contaminated with hazardous chemicals should first be brought to a designated decontamination area containing a warm-water shower with a container to hold drainage water. Victims should remove all clothing. Clothing and valuables are bagged, tagged, and stored. Contaminated patients must never be brought into regular patient care areas because of the danger of contaminating other patients, hospital staff, and equipment. In 1994, paramedics unsuspectingly transported a patient contaminated with a degradation product of dimethyl sulfoxide to an emergency department in Riverside, California. Before the presence of the hazardous material was detected, six health care workers were exposed, including an emergency physician. The emergency physician experienced a near-fatal exposure and required intubation and an extensive stay in the hospital's intensive care unit. Uncontrolled spread of the toxin resulted in evacuation and temporary closure of the emergency department.[46]

The emergency department must close off the air intake vents in rooms containing contaminated patients so toxic products do not enter the ventilation system and circulate to other areas of the hospital. Rescue personnel and hospital staff should be protected by gowns, gloves, and masks and, if necessary, supplied air respirators. The goals are to reduce the initial level of external contamination, to contain the contamination that remains, and to prevent further spread of these potentially dangerous substances to other patients and staff members (secondary contamination).

www.ketabpezeshki.com 66485457-66963820

CHEMICAL, BIOLOGIC, RADIOLOGIC, NUCLEAR, AND EXPLOSIVE TERRORISM

In addition to the familiar threat from hazardous materials, there is another challenge: a potential attack by terrorists using biologic, radiologic, or chemical weapons (see Chapter 194). Although somewhat similar to hazardous materials situations, management of patients exposed to weapons of mass destruction (WMD) requires additional knowledge and skills. Expertise in the management of patients attacked with unconventional weapons is important, but emergency physicians should also be familiar with treatment of blast injuries. High-explosive events, including suicide bombers, remain the most probable type of terrorism.

The most likely radiation source used by terrorists will probably not come from the detonation of a nuclear weapon. Instead, simple radiologic devices, such as those used by hospitals for radiation therapy, are believed to be the source of choice. They do not explode and give no warning of their presence. Terrorists can also dismantle such devices and incorporate the radioactive source into an explosive radiologic dispersion device ("dirty bomb"). Therefore, providers must recognize the presentation of patients suffering from radiation exposure to make the diagnosis. In addition to damage from radiation, these casualties may also suffer blast injuries. Initial treatment of such victims, if they are critically injured, should address stabilization of the blast injuries first before the radiation exposure is considered. Patients who are irradiated but not externally or internally contaminated pose no threat to emergency department personnel.

One of the greatest challenges with respect to WMD is the detection of biologic weapons. Patients exposed to biologic agents often initially present with vague symptoms associated with influenza-like illnesses. Decontamination is not a priority unless the exposure is immediate; standard precautions are generally sufficient.

Unlike radiologic or biologic weapons, chemical agents produce symptoms quickly. The challenge is decontamination and treatment. Approximately 80% of mass casualty decontaminations are performed at hospitals. Therefore, hospitals must be prepared to decontaminate patients outside the emergency department. Personal protective equipment is also essential for responders and hospital "first receivers" because of the risk of exposure during the decontamination process.[45,46]

DISASTER STRESS MANAGEMENT

Emergency health care providers experience high levels of stress when responding to the needs of disaster victims. If this excessive stress exceeds the capacity of normal coping mechanisms, it can potentially interfere with job performance and produce symptoms, including depression, sleep disturbances, increased use of alcohol and drugs, irritability, and anxiety. Post-traumatic stress disorder can result. In an attempt to reduce the psychological impact of these events on medical responders, various therapeutic techniques have been introduced throughout the years and are collectively known as critical incident stress management. This formal process of resolving emotional conflict using mental health professionals is now widely practiced.

In general, the longer the delay between exposure to the critical incident and subsequent psychological intervention, the smaller is the chance for a successful outcome. Therefore, the critical incident stress management process is designed for rapid implementation. During the incident, stress management staff or even a colleague can provide on-scene intervention. The goal is to assist the health care worker in regaining emotional control by facilitating communication of feelings and reactions through listening and support.

If a critical incident has profoundly affected participants and if symptoms are still present many hours later, urgent assistance is provided in the form of defusing. The critical incident defusing process is coordinated by mental health and peer support staff and focuses on information and venting of emotions. This process often takes place away from public view to protect confidentiality. If the psychological stress is severe, the process transitions to formal care provided by psychiatrists or psychologists.[47] Data from previous experiences suggest that such intervention can assist providers in maintaining job performance and satisfaction.

In addition to disaster health care providers, the victims themselves can suffer significant psychological trauma. Rapid identification of such individuals is a priority and can be facilitated by use of a recently developed psychological triage algorithm known as PsySTART. The tool itself has been previously validated and, in a recent trial, appears to assist health care workers in rapidly identifying patients who may benefit from acute psychological intervention.[48]

DISASTER MANAGEMENT AND RESPONSE ORGANIZATIONS WITHIN THE U.S. GOVERNMENT

Department of Homeland Security

The Department of Homeland Security (DHS), a cabinet-level department formed after the terrorist attacks of September 11, 2001, is the federal government's lead organization for emergency management activities in the United States. The Federal Emergency Management Agency (FEMA) was incorporated into DHS and retained its name. DHS has a coordinating responsibility for the entire spectrum of disasters irrespective of their size or etiology. DHS assists state and local organizations to mitigate, to prepare for, to respond to, and to recover from emergencies and is a source of funding for these endeavors. In 2003, the President directed that the DHS develop a National Incident Management System and a National Response Plan. Existing federal plans, including the National Response Plan, were then incorporated into the National Response Framework. The National Response Framework includes 15 Emergency Support Functions (ESFs.) Each has a primary (lead) federal agency and many supporting agencies. ESF #8 is entitled Public Health and Medical Services and is of key importance to the health care community. The primary agency is the Department of Health and Human Services (DHHS). Examples of functions within ESF #8 include coordination of health care personnel, supplies, pharmaceuticals, surveillance and reporting, and mass fatality management.

Urban Search and Rescue (ESF #9 of the National Response Framework)

When a building collapses because of an earthquake, terrorist bombing, structural failure, or other reason, various challenges confront rescue and medical personnel.[49] Some victims require field amputations to facilitate extrication,[49] and use of urban search and rescue teams and effective emergency medical care may improve the outcomes of such lifesaving efforts. This national system of multidisciplinary task forces is designed for rapid deployment to the sites of collapsed structures.[50] The medical team's responsibilities include caring for task force members, victims recovered by search and rescue activities, and the search team's dogs. There are also WMD urban search and rescue teams trained by FEMA to respond to nuclear, biologic, and chemical terrorist attacks.

www.ketabpezeshki.com 66485457-66963820

Department of Health and Human Services

On December 19, 2006, the President signed the Pandemic and All-Hazards Preparedness Act (S. 3678) into law and created a new position, the Assistant Secretary for Preparedness and Response (ASPR), within the DHHS. The office of the ASPR oversees the department's responsibilities for emergency preparedness and response activities, including the National Disaster Medical System (NDMS) and the Hospital Preparedness Cooperative Agreement Program, the coordination of the Medical Reserve Corps, the ESAR-VHP, the Strategic National Stockpile, and the Cities Readiness Initiative.

National Disaster Medical System

The NDMS is a federally coordinated initiative designed to augment the emergency medical response capability of the United States in the event of a catastrophic disaster. This system is a cooperative program of four agencies in the federal government: the Department of Defense, the DHHS, the DHS, and the Department of Veterans Affairs (VA). Although oversight of the NDMS has moved between federal departments, the DHHS currently has the lead for the NDMS. The NDMS provides an interstate medical mutual aid system linking the federal government, state and local agencies, and private sector institutions to address the medical needs of victims of catastrophic disasters. Its medical response element includes dozens of volunteer civilian disaster medical assistance teams that supplement the local medical infrastructure.

In a disaster, the NDMS is activated when state resources are overwhelmed and the governor makes a request for federal assistance. The disaster medical assistance teams must meet specific NDMS standards. Throughout the NDMS, emergency physicians are taking key roles in defining training standards, the deployment of clinical services, and the administration of field operations and in developing the concept of a civilian-federal disaster response capacity during national emergencies.

Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention (CDC), based in Atlanta, is a U.S. federal agency under the DHHS. Its major responsibilities include preparing for and responding to public health emergencies (e.g., disasters) and conducting investigations into the health effects and medical consequences of these events. The major aims of CDC researchers are to assess the risks of death and injury and to develop strategies to prevent or to mitigate the impact of future disasters. Other responsibilities of CDC staff in the area of emergency preparedness and response include rapid assessment of the health and medical needs of disaster victims in the immediate postdisaster period; development and maintenance of national systems for acute environmental hazard surveillance; and provision of epidemiologic, sanitary, laboratory, and other relevant scientific support services to agencies involved in disaster planning and response.

Metropolitan Medical Response System

Metropolitan Medical Strike Teams (MMSTs) are highly trained, readily deployable, and fully equipped groups of medical, fire, and rescue professionals. As a component of the larger Metropolitan Medical Response System (MMRS), they support other local personnel in treating the victims of a chemical, biologic, or nuclear attack. In 2008 the MMRS expanded to include 124 participating jurisdictions. Although composed of local personnel, MMSTs are under the direction of the DHS. Their goal is to enhance local planning and response capability. However, hospital and community planners must still create an independent response because MMSTs require 90 minutes or longer to deploy.[51] MMSTs are equipped with chemical agent monitoring devices, protective equipment, and pharmaceutical supplies.

Department of Veterans Affairs

The VA has not traditionally been regarded as a disaster response entity. However, one of the VA's four legally mandated missions is emergency management. A unique feature of the VA is that its facilities and personnel are situated nationwide, and these are used to support federal health and medical assistance to state and local governments during disasters. The VA has highly trained specialty personnel who can support disaster medical activities. In addition to the vast pool of human resources, the VA provides large amounts of the pharmaceuticals and expendable supplies for on-site disaster support. For example, the VA purchases the contents of the CDC's Strategic National Stockpile. VA support is coordinated through the DHS and DHHS, as the lead federal agency for health and medical response. In addition to the VA's role in the federal response to disasters, as the largest integrated health care system in the nation, it has a well-developed hospital emergency management program. The VA *Emergency Management Program Guidebook* is an open-source reference that provides up-to-date information on emergency management concepts and various templates for emergency operations plans and hazard vulnerability assessment tools for hospitals.[52]

Department of Defense

On April 17, 2002, Secretary of Defense Donald Rumsfeld announced the formation of the Northern Command, or NorthCom, to assume responsibility over all military forces that operate within the United States in response to external threats and in support of civil authorities. The stated purpose of NorthCom is to assist the Department of Defense to better deal with natural disasters, attacks on U.S. soil, or other civil difficulties. It will provide for a more coordinated military support to civil authorities, such as the Federal Bureau of Investigation (FBI), FEMA, and state and local governments. Another important asset at the state level is the National Guard. The governor has authority to activate the National Guard for its disaster response and recovery missions.

FUTURE DIRECTIONS

The field of disaster medicine has become a major subspecialty within emergency medicine, and standing committees and membership sections for disaster medicine are now organized within the American College of Emergency Physicians and the Society for Academic Emergency Medicine. There are also numerous national and international forums for the presentation of disaster medical research results. Since the American College of Emergency Physicians first defined a disaster medicine curriculum suitable for residencies and fellowships, a number of disaster medicine fellowships have been established in the United States and elsewhere.[53] Disaster medicine textbooks and journals are increasing. In the 21st century, disaster medicine will continue to develop as a professional activity and unique academic specialty.

www.ketabpezeshki.com 66485457-66963820

KEY CONCEPTS

- Comprehensive emergency management consists of four phases: mitigation, preparedness, response, and recovery.
- Mass casualty planning must account for the fact that traditional transport and communications systems will break down.
- Field personnel should be specifically trained in mass casualty triage and stabilization because austere field conditions change management strategies.
- All plans must protect caregivers and rescue personnel.
- Critical incident stress management may be highly desirable after an event and should be planned for in advance.
- Planners should establish and exercise a hospital-based incident management system.
- Disaster planning must include policies to address the needs of vulnerable populations, such as children, disabled, and the elderly.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Waeckerle JF, et al: Executive summary: Developing objectives, content, and competencies for the training of emergency medical technicians, emergency physicians, and emergency nurses to care for casualties resulting from nuclear, biological, or chemical (NBC) incidents. *Ann Emerg Med* 2001; 37:587.
2. American College of Emergency Physicians: *Clinical Policies: Disaster Medical Services*, October 2006. Available at www.acep.org/disaster. Accessed July 15, 2011.
3. Kaji AH, Koenig KL, Lewis RJ: Current hospital disaster preparedness. *JAMA* 2007; 298:2188.
4. Kaji A, Koenig KL, Bey T: Surge capacity for healthcare systems: A conceptual framework. *Acad Emerg Med* 2006; 13:1157.
5. Barbisch D, Koenig KL: Understanding surge capacity: Essential elements. *Acad Emerg Med* 2006; 13:1098.
6. California Department of Public Health: *Standards and Guidelines for Healthcare Surge During Emergencies*. Available at www.bepreparedcalifornia.ca.gov. Accessed April 22, 2011.
7. Barbisch D, Haik J, Tessone A, Hanfling D: *Surge capacity*. In: Koenig KL, Schultz CH, eds. *Koenig and Schultz's Disaster Medicine: Comprehensive Principles and Practices*. New York: Cambridge University Press; 2010.
8. Koenig KL, Dinerman N, Kuehl AE: Disaster nomenclature: A functional impact approach: The PICE system. *Acad Emerg Med* 1996; 3:723.
9. Nocera A: Australian major incident nomenclature: It may be a "disaster" but in an "emergency" it is just a mess. *Aust N Z J Surg* 2001; 71:162.
10. Burkle FM: Integrating international responses to complex emergencies, unconventional war, and terrorism. *Crit Care Med* 2005; 33:S7.
11. Auf der Heide E: *Resource management*. In: *Disaster Response: Principles of Preparation and Coordination*. St. Louis: Mosby; 1989. Available at http://orgmail2.coe-dmha.org/dr/DisasterResponse.nsf/section/31219255A624812F0A25691A00671909?opendocument&home=flash. Accessed April 22, 2011.
12. Department of Health and Human Services: *Medical Surge Capacity and Capability: A Management System for Integrating Medical and Health Resources During Large Scale Emergencies*. Washington, DC: Department of Health and Human Services; 2004.
13. Cone DC, Koenig KL: Mass casualty triage in the chemical, biological, radiological, or nuclear environment. *Eur J Emerg Med* 2003; 12:287.
14. Garner A, Lee A, Harrison K, Schultz CH: Comparative analysis of multiple-casualty incident triage algorithms. *Ann Emerg Med* 2001; 38:541.
15. Kahn CA, Lerner EB, Cone DC: *Triage*. In: Koenig KL, Schultz CH, eds. *Koenig and Schultz's Disaster Medicine: Comprehensive Principles and Practices*. New York: Cambridge University Press; 2010.
16. Waeckerle JF: Disaster planning and response. *N Engl J Med* 1991; 324:815.
17. Critical Illness and Trauma Foundation: *START: Simple Triage and Rapid Treatment*. Newport Beach, Calif: Critical Illness and Trauma Foundation, Newport Beach Fire Department; 2001. Available at www.citmt.org/start/default.htm. Accessed April 29, 2011.
18. Wallis LA, Carley S: Comparison of pediatric major incident primary triage tools. *Emerg Med J* 2006; 23:475-478.
19. Romig LE: *The JumpSTART Pediatric MCI Triage Tool*. Available at www.jumpstarttriage.com. Accessed April 29, 2011.
20. Sanddal TL, Loyacono T, Sanddal ND: Effect of JumpSTART training on immediate and short-term pediatric triage. *Pediatr Emerg Care* 2004; 20:749.
21. Kahn CA, Schultz CH, Miller KT, Anderson CL: Does START triage work? An outcomes assessment after a disaster. *Ann Emerg Med* 2009; 54:424-430.
22. Lerner EB, et al: Mass casualty triage: An evaluation of the data and development of a proposed national guideline. *Disaster Med Public Health Prep* 2008; 2(Suppl 1):S25-S34.
23. Benson M, Koenig KL, Schultz CH: Disaster triage: START then SAVE—a new method of dynamic triage for victims of a catastrophic earthquake. *Prehosp Disaster Med* 1996; 11:117.
24. Burkle FM: Population-based triage management in response to surge-capacity requirements during a large-scale bioevent disaster. *Acad Emerg Med* 2006; 13:1118.
25. Phillips BD: *Special needs populations*. In: Koenig KL, Schultz CH, eds. *Koenig and Schultz's Disaster Medicine: Comprehensive Principles and Practices*. New York: Cambridge University Press; 2010.
26. National Commission on Children and Disasters: *2010 Report to the President and Congress*. Rockville, Md: Agency for Healthcare Research and Quality; October 2010. AHRQ Publication No. 10-M037.
27. Emergency Management Institute: *IS-100.b: Introduction to Incident Command System, ICS-100*. Emmitsburg, Md: Emergency Management Institute, Federal Emergency Management Agency; 2010. Available at http://training.fema.gov/EMIWeb/IS/IS100b.asp. Accessed February 22, 2008.
28. U.S. Department of Homeland Security: *National Response Framework*. Washington, DC: Department of Homeland Security; 2008. Available at www.fema.gov/pdf/emergency/nrf/nrf-core.pdf. Accessed April 29, 2011.
29. Schultz CH, Mothershead JL, Field M: Bioterrorism preparedness I: The emergency department and hospital. *Emerg Med Clin North Am* 2002; 20:437.
30. Joint Commission: *Comprehensive Accreditation Manual for Hospitals*. Oak Brook Terrace, Ill: Joint Commission; 2007.
31. Schultz CH, Koenig KL, Lewis RJ: Implications of hospital evacuation after the Northridge, California, earthquake. *N Engl J Med* 2003; 348:1349.
32. Andress K, Downey E, Schultz CH: Implications of hospital evacuation after hurricane Rita [abstract]. *Acad Emerg Med* 2007; 14(Suppl 1):S190.
33. Hoyle JD: *Healthcare facility disaster management*. In: Koenig KL, Schultz CH, eds. *Koenig and Schultz's Disaster Medicine: Comprehensive Principles and Practices*. New York: Cambridge University Press; 2010.
34. California Emergency Medical Services Authority: *Hospital Incident Command System*. Sacramento, Calif: Emergency Medical Services Authority; 2006. Available at www.emsa.ca.gov/hics. Accessed April 14, 2011.
35. Schultz CH, Koenig KL: State of research in high-consequence hospital surge capacity. *Acad Emerg Med* 2006; 13:1153.
36. *Superfund Amendments and Reauthorization Act of 1986 (SARA), Title III, Section 305(a), Emergency Training; Homeland Security Act of 2002, Codified in 6 U.S. Code, Public Law 107-296*. Available at www.fema.gov/government/grant/sara.shtm. Accessed April 29, 2011.
37. Reynolds BS, Shenhar G: *Crisis and emergency risk communication*. In: Koenig KL, Schultz CH, eds. *Koenig and Schultz's Disaster Medicine: Comprehensive Principles and Practices*. New York: Cambridge University Press; 2010.
38. Keim ME, Noji E: Emergent use of social media: A new age of opportunity for disaster resilience. *Am J Disaster Med* 2011; 6:47-54.
39. Cone DC, Weir SD, Bogucki S: Convergent volunteerism. *Ann Emerg Med* 2003; 41:457.
40. Schultz CH, Stratton SJ: Improving hospital surge capacity: A new concept for emergency credentialing of volunteers. *Ann Emerg Med* 2007; 49:602.
41. Kaji AH, Langford V, Lewis RJ: Assessing hospital disaster preparedness: A comparison of an on-site survey, directly observed drill performance, and video analysis of teamwork. *Ann Emerg Med* 2008; 52:195-201.
42. Schultz CH, Koenig KL, Noji EK: A medical disaster response to reduce immediate mortality following an earthquake. *N Engl J Med* 1996; 334:438.
43. Kazzi AA, et al: Earthquake epidemiology: The 1994 Los Angeles earthquake emergency department experience at a community hospital. *Prehosp Disaster Med* 2000; 15:12.
44. Koenig KL, et al: Healthcare facility–based decontamination of victims exposed to chemical, biological, and radiological material. *Am J Emerg Med* 2008; 26:71.
45. Koenig KL, et al: Health care facilities' "war on terrorism": A deliberate process for recommending personal protective equipment. *Am J Emerg Med* 2007; 25:185.
46. Koenig KL: Strip and shower: The duck and cover for the 21st century. *Ann Emerg Med* 2003; 42:391.
47. Oster NS, Doyle CJ: *Critical incident stress*. In: Hogan DE, Burstein JL, eds. *Disaster Medicine*. Philadelphia: Lippincott Williams & Wilkins; 2007:30-37.
48. Schreiber M, et al: PsySTART Rapid Disaster Mental Health Triage System: Performance during a full scale terrorism exercise in Los Angeles County hospitals [abstract]. *Acad Emerg Med* 2011; 18:S26.
49. Schultz CH, Koenig KL: Preventing crush syndrome: Assisting with field amputation and fasciotomy. *J Emerg Med Services* 1997; 22:30.
50. Better OS, Stein JH: Early management of shock and prophylaxis of acute renal failure in traumatic rhabdomyolysis. *N Engl J Med* 1990; 322:825.
51. Institute of Medicine and National Research Council: *Chemical and Biological Terrorism: Research and Development to Improve Civilian Medical Response*. Washington, DC: National Academy Press; 1999.
52. U.S. Department of Veterans Affairs, Emergency Management Strategic Health Care Group: *2008 Emergency Management Program Guidebook*. Available at www1.va.gov/emshg/page.cfm?pg=114. Accessed February 24, 2008.
53. *European Master in Disaster Medicine*. Available at http://www.dismedmaster.com. Accessed April 29, 2011.

www.ketabpezeshki.com 66485457-66963820

Chapter 194

Weapons of Mass Destruction

Carl H. Schultz and Kristi L. Koenig

PERSPECTIVE

Besides managing the injuries and illnesses from common disasters such as earthquakes and airplane crashes, emergency physicians should also have competence in treating victims generated by terrorist attacks with nuclear, biologic, chemical, or high-energy explosive weapons. Conventional explosives remain the most common weapon used by terrorists; however, the risk from nuclear, biologic, and chemical agents may increase over time. The nomenclature for these weapons remains controversial. Some authors have proposed the use of *weapons of mass effect* or *weapons of mass disruption*. The military uses the acronym CBRNE, pronounced "see-burn-ee," referring to *c*hemical, *b*iologic, *r*adiologic, *n*uclear, and *e*xplosive. This chapter uses *weapons of mass destruction* (WMD) because of its wide acceptance.

The results of an attack with WMD, although admittedly of low probability, are potentially catastrophic. According to a World Health Organization estimate, 50 kg of anthrax spores aerosolized above a city of 5 million people would result in 100,000 deaths, with an additional 150,000 people seriously infected. The cost of managing 100,000 cases of anthrax exposure is estimated at between $6.4 and $26.2 billion.[1] Given these considerations, most authorities believe that preparedness for such threats is a priority.

Children are particularly vulnerable to these weapons. They breathe at a faster rate than adults do, increasing their relative exposure to aerosolized agents. Some chemicals, such as sarin, are heavier than air, so they tend to accumulate at the level where children are more likely to inhale them. Children have a greater surface area–to–volume ratio and their skin is thinner. This makes them more susceptible to agents that act on or through the skin. They have smaller fluid reserves and higher metabolic rates. Therefore, they are more vulnerable to dehydration from vomiting and diarrhea and suffer increased toxicity from a given exposure, such as to radioactive iodine (^{131}I).

The use of biologic and chemical agents dates to biblical times, although the threat from radiation and nuclear detonation is relatively new. Assyrians poisoned the wells of their enemies with rye ergot in the 6th century BC. The Mongols catapulted bodies infected with bubonic plague over the walls of Kaffa in the 14th century. The British Army gave American Indians blankets taken from individuals infected with smallpox during Pontiac's Rebellion in 1763. During World War I, the Germans effectively used chlorine and mustard agent against the advancing Allied armies. The Japanese killed hundreds to thousands of Chinese citizens with bubonic plague during World War II by spraying towns with fleas infected with *Yersinia pestis*. Saddam Hussein used a mustard agent against the Iranians during the Iran-Iraq War in the 1980s.

The use of WMD has been predominantly by the military during times of conflict. In recent history, however, the use of these agents has taken an ominous turn. Nonaffiliated groups have begun using WMD directed at civilians to achieve political ends. The Bhagwan cult sprayed salad bars in Oregon with *Salmonella* in an attempt to influence an election in 1984.[2] The Aum Shinrikyo used the nerve agent sarin in an unsuccessful 1994 assassination attempt on three judges in Matsumoto, Japan. This same group used sarin again in the 1995 Tokyo subway attack that killed 11 people.[3] The United States experienced multiple anthrax hoaxes during 1997 and 1998, motivated by personal or political agendas. Terrorists initiated an actual anthrax attack using the U.S. mail in 2001 that resulted in 11 deaths. No one has yet used radiologic or nuclear devices in a successful mass terrorist attack, but at least one attempt has occurred. In addition, several highly radioactive sources have been stolen from U.S. medical facilities, and a Russian dissident, Alexander Litvinenko, was assassinated with a radiologic agent (polonium-210) in 2006.

Many agents are potential candidates for weaponization, and some represent a substantial risk (Box 194-1). Management strategies for patients exposed to WMD are frequently similar to strategies for hazardous materials exposure. However, several features associated with WMD make these events unique (Box 194-2). Additional knowledge and skills are required in the evaluation and treatment of WMD victims. These plans represent only one small part of an overall comprehensive emergency management strategy for all hazards (see Chapter 193). Names of departments, bureaus, and agencies that can assist with planning and response to WMD events are listed in Table 194-1.

NUCLEAR AND RADIOLOGIC DEVICES

Terrorists selecting radiation as a means to inflict casualties are unlikely to use nuclear weapons. These devices are heavily guarded, difficult to move because of their size and weight, and easy to detect. Although Russia acknowledges that 50 to 100 of its 1-kiloton "suitcase" nuclear weapons are missing, the problems of purchasing, moving, and detonating these devices are formidable. Sabotage at nuclear power stations is possible, but given tight security, multiple safety systems, and thick concrete housings surrounding the reactors, the threat is probably low.

Instead, simple radiologic devices, such as those used by hospitals for radiation therapy, are thought to be the source of choice. These sources are plentiful. They do not detonate on their own and give no warning of their presence unless they are dispersed by a conventional explosive (radiologic dispersal device). Thefts of radiotherapy sources have occurred in the United States. Accidental dispersion from a stolen hospital therapy source in Brazil

www.ketabpezeshki.com 66485457-66963820

resulted in the screening of 112,000 people for contamination. A total of 249 people were found to be exposed, 4 of whom ultimately died.[2] Placement of such a device at an information kiosk in a crowded mall during a busy holiday shopping season would silently expose countless persons to significant radiation.

Ionizing radiation, regardless of its type, causes injury at the cellular level, usually by damaging DNA. Rapidly dividing cells are the most sensitive. Patients have symptoms within hours to days, depending on the dose. Common syndromes associated with radiation exposure include dermal burns, bone marrow failure, and gastrointestinal dysfunction (e.g., vomiting and gastrointestinal bleeding) (see Chapter 146). A U.S. Department of Homeland Security task force developed an expert consensus document on medical treatment of radiologic casualties, and the results were subsequently published in the peer-reviewed literature.[4]

A basic emergency department radiation protocol must address decontamination, triage, staff safety, personal protective equipment (PPE), and diagnostic procedures that emphasize radiation monitoring. Victims presenting to the emergency department will suffer from three types of exposure: irradiation, internal contamination, and external contamination. Irradiated victims have been exposed to a beam of radiation, similar to someone undergoing a chest x-ray examination. They are not radioactive and pose no threat to emergency department personnel.

Contaminated patients are more challenging, and early involvement of the radiation safety officer is critical. This individual evaluates the degree of the victim's contamination and monitors radioactivity levels throughout the decontamination process. Internally contaminated patients present a therapeutic challenge because they have radioactive material inside their bodies (e.g., lungs and gastrointestinal tract) or incorporated into their cells. They should be placed in an isolation room, where all secretions and body fluids can be collected. Various medications are available for administration to internally contaminated patients and can limit uptake or facilitate removal of certain radioactive elements. These medications include Radiogardase (Prussian blue) for cesium and thallium ingestions and diethylenetriaminepentaacetic acid (DTPA) for plutonium exposure. Health care providers can receive assistance by calling the Radiation Emergency Assistance Center/Training Site (REAC/TS; http://orise.orau.gov/reacts) at 865-576-3131 (emergency number: 865-576-1005).

Externally contaminated victims have radioactive material on their skin or clothing and are decontaminated by removal of clothing and washing with soap and water. Washing by protected personnel should continue until monitoring by the radiation safety officer demonstrates the absence of radioactivity. If wounds are present, they are decontaminated first. After the wounds are covered with a sterile, waterproof dressing, the remaining skin is washed. Hospitals must be prepared to decontaminate patients because historical data suggest that up to 80% of patients do not receive this intervention before arrival.[2] Decontamination before hospital entry is crucial because these individuals can expose caregivers to radiation and contaminate the entire hospital through the ventilation system. Removal of clothing and covering of the head with a surgical cap can reduce contamination by 80% to permit stabilization in the decontamination unit, but complete decontamination should occur before exposure of unprotected staff if the patient's medical condition permits.

Initial triage of radiation casualties is based on their overall pathologic condition, not on exposure.[5] Even patients who have received a lethal dose of radiation do not die immediately as a consequence of the ionizing exposure. Therefore, a patient in acute distress from a myocardial infarction or urosepsis would be triaged ahead of a radiation victim with stable vital signs, regardless of the dose received. If a radiation casualty also suffers a severe injury or illness, immediate intervention is required. Most of the immediate morbidity and mortality associated with a radiologic dispersion device is related to traumatic injuries from the explosion and not to radiation exposure.[4]

In addition to patient contamination, the radiation safety officer is responsible for monitoring of the exposure of hospital staff. All personnel involved in the care of contaminated patients

Box 194-1 Potential Agents of High Concern for Use as Weapons of Mass Destruction

Chemical
- Nerve agents
  - Sarin
  - Soman
  - Tabun
  - VX
- Mustard agent

Biologic
- Anthrax
- Plague
- Smallpox
- Botulism
- Viral hemorrhagic fever
- Tularemia

Radiologic
- Simple device
- Dispersal device

Box 194-2 Features of Weapons of Mass Destruction Threat

- Fear of unknown or unfamiliar
- Lack of training for hospital personnel
- Lack of equipment, including personal protective equipment and diagnostic aids
- Potential for mass casualties
- Psychological casualties
- Crime scene requiring evidence collection and interaction with law enforcement
- Potential for ongoing morbidity and mortality (dynamic situation)

Table 194-1 Resources and Contacts for Planning and Response to Events Involving Weapons of Mass Destruction

ORGANIZATION	WEBSITE	TELEPHONE
Radiation Emergency Assistance Center/Training Site (REAC/TS)	http://orise.orau.gov/reacts	Daytime: 865-576-3131 Emergency: 865-576-1005
State and local health departments	www.statepublichealth.org www.cdc.gov/other.htm#states	
Centers for Disease Control and Prevention (CDC)	www.bt.cdc.gov	800-CDC-INFO
Federal Bureau of Investigation (FBI)	www.fbi.gov	
Federal Emergency Management Agency (FEMA)	www.fema.gov	800-621-FEMA
U.S. Army Medical Research Institute of Chemical Defense	http://chemdef.apgea.army.mil	

www.ketabpezeshki.com 66485457-66963820

Table 194-2 Treatment with Potassium Iodide (KI) for Radioactive Iodine Exposure

SUBPOPULATION	PREDICTED EXPOSURE (cGy)	KI DOSE (mg)	NUMBER OF 130-mg TABLETS
Adults >40 years	>500	130	1
Adults 18-40 years	≥10	130	1
Pregnant and lactating women	≥5	130	1
Children 3-18 years	≥5	65	½
Children 1 month to 3 years	≥5	32	¼
Neonates, birth to 1 month	≥5	16	⅛

should wear dosimeters, which measure the amount of radiation received by the wearer. The safety officer tracks the amount of radiation received by each staff member and can remove a health care worker from the area if the exposure is too high. Radiation monitoring is complex, and the radiation safety officer should be involved as early as possible. Hospitals should consider conducting disaster drills that include casualties suffering radiation injuries.

Although many radioactive elements are candidates for use in a terrorist attack, ^{131}I and related isotopes deserve additional discussion because of heightened interest. ^{131}I is found only after a nuclear detonation or in reactor fuel rods. Although it is not impossible, the probability that terrorists could tap either of these sources is very small. The use of ^{131}I in a radiologic dispersal device is unlikely because of its short half-life (8 days). Even if such a device could be made, it is extremely unlikely that the radiologic dispersal device could disperse sufficient radioactive material to pose an immediate health hazard.[6] Given these facts, the probability that any significant exposure of the population (especially children) to ^{131}I will occur is equally small. The large number of childhood thyroid cancers that occurred after the accident at the Chernobyl nuclear power plant resulted, to a significant degree, from situations that will not occur in the United States. These include delayed reporting of a breach in the reactor containment vessel preventing timely evacuation of all exposed populations, failure to effectively quarantine contaminated milk and vegetables, and significant iodine deficiency in the exposed population.[7] The risk to children in communities surrounding the Fukushima nuclear power plant is also an issue that will require long-term monitoring. Nonetheless, concern about treatment to prevent thyroid cancer after potential exposure to ^{131}I remains. Current recommendations for treatment with potassium iodide, which blocks uptake of ^{131}I by the thyroid, are listed in Table 194-2. Caveats for use of this table include increasing the amount of potassium iodide for adolescents approaching 70 kg to the adult dose (130 mg) and monitoring thyroid-stimulating hormone and free T_4 levels in neonates when possible. Nonpregnant adults older than 40 years are unlikely to benefit from this intervention.

BIOLOGIC WEAPONS

By convention, biologic weapons are divided into three groups: bacteria, viruses, and toxins. A characteristic shared by these agents is their ability to be dispersed as an aerosol. Because this is the most effective means to expose a large population, aerosol dispersal is the most likely route that terrorists will use to deploy such weapons. Therefore, victims will have respiratory signs and symptoms. Dermal contact and ingestion are also potential pathways for exposure, and some agents are effective by these routes. People infected in the 2001 U.S. anthrax attack were inoculated through aerosol and dermal exposures. However, it is logistically more difficult to produce large casualty numbers by nonrespiratory portals of entry, so agents spread primarily by injection or through the gastrointestinal tract are less likely candidates for wide deployment. If the goal is to disrupt the economy or to spread fear among the population, then almost any type of release will suffice, whether or not people actually die.

Box 194-3 Signs Suggesting Biologic Weapon Deployment

Syndromes
Pulmonary symptoms, pneumonia
Rashes
Sepsis syndrome
Influenza symptoms

Epidemiology
Multiple, simultaneous events
Dead animals
Large numbers of patients with high toxicity and death rate

Patients exposed to biologic agents usually present with vague symptoms associated with an influenza-like illnesses. Unless a biologic attack is announced or suspected, the emergency department staff may not realize that they are treating victims. Indeed, it is not always possible to distinguish natural occurrences from engineered outbreaks of diseases. Examples of non-terrorist outbreaks of anthrax include cutaneous disease in intravenous heroin users in Europe and an outbreak of cutaneous anthrax in Bangladesh in 2010 with more than 400 cases. Because of the challenges in identifying the true etiology of acute events, personnel should be vigilant and at least consider the possibility, especially when warning signs are present (Box 194-3). For example, large numbers of patients suddenly presenting with "the flu" not during influenza season should cause concern. For these reasons, health surveillance will be paramount in identifying agents and potential sources. The emergency department should have a working relationship with local and state health departments as well as with local law enforcement and stay apprised of Centers for Disease Control and Prevention (CDC) and Department of Homeland Security guidelines.

Several infectious agents with potential for use as biologic weapons can spread in a hospital environment. Examples include Ebola and smallpox.[2,8] Hospitals need protocols for PPE and patient isolation to ensure a safe environment.[9-12] Fortunately, such protocols are similar to those applied to other infectious diseases (Box 194-4). Implementation of such precautions is credited with halting of the in-hospital spread of the Ebola virus in the 1995 Zaire outbreak. Decontamination is not a priority unless the exposure is immediate. Standard (universal) precautions are generally sufficient, and special suits (e.g., levels A, B, and C) are unnecessary.[13]

Whereas the CDC lists six Category A (high threat) agents (www.bt.cdc.gov/agent/agentlist-category.asp), this chapter

www.ketabpezeshki.com 66485457-66963820

Box 194-4 Recommendations for Prevention of In-Hospital Transmission of Contagious Agents

Isolate patient in single room with adjoining anteroom.
Have handwashing facilities and personal protective equipment available in anteroom.
Use negative air pressure if possible.
Use strict barrier precautions: personal protective equipment, gowns, gloves, HEPA filter respirators, shoe covers, protective eyewear.
Alert hospital departments that generate aerosols: laboratory (centrifuges), pathology (autopsies).

focuses on three biologic agents—anthrax, plague, and smallpox—that represent the greatest interest.[14]

Anthrax

Bacillus anthracis, a gram-positive spore-forming bacterium, is the causative agent of anthrax ("woolsorter's disease"). The spores are extremely hardy and can survive for years in the environment. The disease is caused by exposure to the spores, not the bacilli in their vegetative state. It is normally a disease of sheep, cattle, and horses and is rarely seen in developed countries because of animal and human vaccination programs. Disease in humans can occur when spores are inhaled, ingested, or inoculated into the skin. The spores germinate into bacilli inside macrophages. The bacteria then produce disease by releasing toxins (e.g., protective antigen, edema factor, and lethal factor) that cause edema and cell death.

Russia and the United States have developed anthrax into a biologic weapon. The effectiveness of this agent was clearly demonstrated by two events: an accidental release of spores from a biologic weapons facility in the former Soviet Union town of Sverdlovsk in 1979 and the intentional distribution of anthrax spores through the mail along the eastern seaboard of the United States in 2001. After the Sverdlovsk release, at least 66 people died downwind from the compound during the next several weeks, and animal cases of anthrax were reported 30 miles away.[15,16] The ability of non–state-sponsored terrorist groups to develop anthrax as a weapon is uncertain. The Japanese organization Aum Shinrikyo made several attempts to disperse anthrax throughout Tokyo without success.[1] The individual believed responsible for the U.S. anthrax attack was not a foreign national. This is consistent with the fact that the strain of anthrax used in the attack (Ames strain) was developed by the U.S. government.

Inhalational anthrax is the most lethal form of the disease and is caused by inhalation of spores into the lungs. The mortality rate was thought to exceed 90%. However, data from the 2001 anthrax exposure call this figure into question (5 deaths in 11 cases). Although the actual mortality rate is unknown, it is probably in the 50% range.[17,18] The minimum number of spores required to produce disease is unknown. The original number quoted in the literature, 10^4 spores, appears high given recent experience.[19] After phagocytosis by macrophages, the spores germinate and are transported to the tracheobronchial lymph nodes, where the bacteria multiply. During 2 to 10 days, patients have an influenza-like illness, with malaise, fever, and nonproductive cough. This initial phase can be delayed for more than 1 month in some patients. Within 24 to 48 hours, abrupt deterioration occurs, with overwhelming sepsis, shock, hemorrhagic mediastinitis, dyspnea, and stridor. A chest radiograph obtained at this time may show a widened mediastinum and hilar adenopathy, but typical radiographic findings are not dramatic and could be missed (Fig. 194-1). Computed tomography scanning of the chest is more sensitive and should be performed if the disease is suspected. Bloody pleural effusions can also occur, and examination of the lung fields

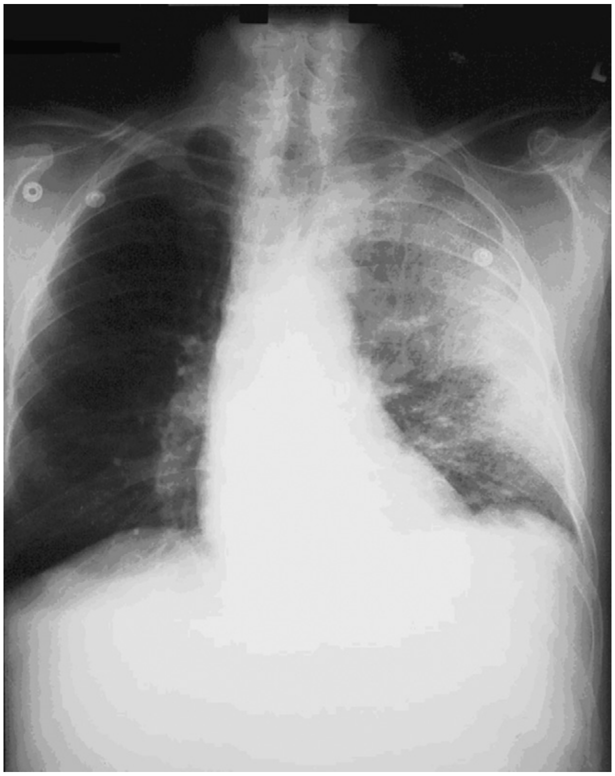


Figure 194-1. Chest radiograph of anthrax patient showing diffuse left lung consolidation consistent with pneumonia. There is no mediastinal widening. (Courtesy the U.S. Centers for Disease Control and Prevention.)

Figure 194-2. Chest computed tomography scan of an anthrax patient showing pulmonary consolidation and effusions. (Courtesy the U.S. Centers for Disease Control and Prevention.)

frequently reveals consolidation. This can easily be confused with pneumonia (Fig. 194-2). Death usually results within 3 days, and 50% of patients have hemorrhagic meningitis. Human-to-human transmission has not been reported with inhalational anthrax.

Initial diagnosis is generally made clinically on the basis of an influenza-like or septic illness; a suspicious chest radiograph or computed tomography scan demonstrating hilar adenopathy,

www.ketabpezeshki.com 66485457-66963820

Figure 194-3. Adult with cutaneous anthrax. (Courtesy the U.S. Centers for Disease Control and Prevention.)

infiltrates, or pleural effusions; and a reason to consider anthrax in the first place (e.g., current outbreak or warning from authorities). Several clinical algorithms exist that attempt to separate patients with influenza from those with anthrax.[20,21] Unfortunately, they are based on a handful of anthrax cases, and their usefulness remains in doubt.[18] Sputum culture, Gram's stain, and blood cultures are not helpful until late in the course of the disease. Tests to confirm the diagnosis of inhalational anthrax include the polymerase chain reaction for identification of anthrax markers in pleural fluid, serologic detection of immunoglobulin to protective antigen, and immunohistochemical testing of biopsy specimens.

In addition to inhalational anthrax, cutaneous anthrax can occur in any area where large numbers of spores are released, as was the case in the United States in 2001. This form of the disease occurs when spores are introduced into the skin, usually through open wounds or abrasions. The mortality rate is approximately 20% without treatment and 1% with treatment. Antibiotics do not affect the course of local disease but are used to prevent dissemination and death. After an incubation period of 1 to 5 days, a papule develops, progressing to form a large vesicle during the next several days. Severe edema occurs around the lesion and is associated with regional lymphadenitis. The lesions are not tender, and the patient may or may not be febrile (Fig. 194-3). After approximately 1 week, the lesion ruptures, forming a black eschar (thus the name *anthrax,* from the Greek word for "coal"). In the next 2 or 3 weeks, either the eschar sloughs off and the illness is over or the organism disseminates and the patient dies. As with inhalational anthrax, the diagnosis is predominantly clinical. Confirmation is established by culture of the lesion, punch biopsy, or serologic testing. A total of 11 cutaneous anthrax cases occurred in the United States after the 2001 attack.[22]

A few cases of gastrointestinal anthrax and oropharyngeal anthrax are also possible after a terrorist attack. These rare manifestations usually occur with the ingestion of insufficiently cooked, contaminated meat. The mortality rate is approximately 50%. After ingestion, the spores are transported to regional lymphatic tissue, where symptoms develop after a 2- to 5-day incubation period. Patients with oropharyngeal anthrax present with sore throat and neck swelling from cervical and submandibular lymphadenitis. The tonsils are also frequently involved, and symptoms are associated with fever and toxicity. Dysphagia and respiratory distress often follow. Gastrointestinal anthrax begins with nausea, vomiting, and fever associated with mesenteric lymphadenitis. Patients then experience severe abdominal pain, hematemesis, ascites, and bloody diarrhea and may present with an acute abdomen.

Box 194-5 Treatment of Anthrax

Cutaneous Anthrax *without* Toxicity

Adults

Ciprofloxacin, 500 mg PO bid
or
Doxycycline, 100 mg PO bid
or
Amoxicillin, 500 mg PO tid

Children

Ciprofloxacin, 20-30 mg/kg/day PO divided bid (max. 1 g)
or
Doxycycline, 4.4 mg/kg/day PO divided bid (max. 200 mg)
or
Amoxicillin, 20-40 mg/kg/day PO divided tid (max. 1500 mg)
All doses are given for 7-10 days.

Inhalational, Cutaneous, or Gastrointestinal Anthrax *with* Toxicity

Adults

Ciprofloxacin, 400 mg IV q12h
or
Doxycycline, 100 mg IV q12h
or
Penicillin G, 4 million units IV q4h

Children

Ciprofloxacin, 20 mg/kg/day IV divided q12h (max. 800 mg)
or
Doxycycline, 4.4 mg/kg/day IV divided q12h (max. 200 mg)
or
Penicillin G, 100,000-400,000 units/kg/day IV divided q4h (max. 24 million units)

All doses are given until toxicity resolves, then switch to oral form. Treat for 60 days or until the patient receives three doses of vaccine.

Postexposure Prophylaxis

The same drugs and dosage are prescribed as for cutaneous anthrax without toxicity. Treat for 60 days or until the patient receives three doses of vaccine.

Treatment

Traditional treatment of anthrax infection has been penicillin. However, weapons-grade anthrax is probably resistant to penicillin (although this was not the case with the U.S. attack). Current treatment recommendations reflect this fact (Box 194-5).[1,2] These consensus recommendations include fluoroquinolones and tetracycline for all children, regardless of age. Balancing the potential risks of such drugs against the consequences of infection by drug-resistant anthrax strains, the benefits justify the recommendations. Nontoxic victims with cutaneous anthrax can be treated as outpatients with oral ciprofloxacin or doxycycline for 7 to 10 days. Victims with inhalational, cutaneous, or gastrointestinal disease and toxicity require intravenous therapy with ciprofloxacin or doxycycline plus at least two other antibiotics (e.g., rifampin, clindamycin, imipenem, or an aminoglycoside). Patients can be switched to oral antibiotics when toxicity resolves. Other modalities that may be helpful include chest tube drainage of pleural effusions and possibly tracheal intubation and mechanical ventilation.[22] Surprisingly, the latter intervention did not improve mortality. All patients intubated after the U.S. anthrax attack died.[17,19]

Treatment must continue for 60 days or until the patient has received three doses of the anthrax vaccine, given on days 0, 14,

www.ketabpezeshki.com 66485457-66963820

and 28. The complete vaccine course requires 18 months. This treatment regimen is also recommended for children and pregnant women. If the anthrax strain proves susceptible, patients can be switched to intravenous penicillin or oral amoxicillin. In vitro studies suggest that ofloxacin or levofloxacin can be substituted for ciprofloxacin.[1]

For postexposure prophylaxis, oral ciprofloxacin (500 mg) or doxycycline (100 mg) twice a day is recommended. Amoxicillin can be substituted if sensitive strains are identified. Antibiotic prophylaxis must continue for 60 days or until patients have received at least three doses of the vaccine. The vaccine is approved by the U.S. Food and Drug Administration (FDA) for adults but not for children. A review by the Institute of Medicine found the vaccine both safe and effective for prophylaxis against inhalational anthrax.[23]

Plague

Plague has been a human pathogen since antiquity. Many regions of the world, including Asia and India, are currently witnessing the third pandemic of plague, and this affliction is endemic in the western half of the United States. Plague is caused by *Yersinia pestis,* a gram-negative bacillus. It is normally a disease of rodents that is transmitted to humans through the bite of an infected flea or by inhalation. Three forms of the disease exist: pneumonic, bubonic, and septicemic plague. The bacteria do not form spores and die rapidly in the environment. However, they are viable for days in dry sputum, flea feces, and human remains. Dogs are relatively resistant to infection, but cats are highly susceptible and could form a reservoir for maintaining the disease in a human population. Recovery is followed by temporary immunity.

Primary pneumonic plague results when bacilli are inhaled into the lungs. It has a mortality rate approaching 100% if it is not treated early. Pneumonic plague will be the most frequently encountered form of the disease because terrorists are likely to use aerosolization as the method of dispersal. After an incubation period of 2 or 3 days, victims have sudden onset of fever, chills, and an influenza-like illness. This is followed within 24 hours by a fulminant pneumonia associated with hemoptysis, systemic toxicity, respiratory failure, circulatory collapse, and death. The pneumonia is classically lobar, but any x-ray pattern is possible, including acute respiratory distress syndrome. Six percent to 10% of victims have plague meningitis. Coagulation abnormalities and hepatocellular injury occur. The coagulopathy is characterized by ecchymoses, disseminated intravascular coagulation, and acral gangrene (“black death”). The gangrene is caused by bacterial production of the coagulase enzyme in areas of the body where the temperature drops below 37°C. This causes blood to clot in fingers, toes, and the nose, with resultant infarction and gangrene. If the victims survive, long-term rehabilitation is required. Pneumonic plague is transmissible human to human.

Bubonic plague occurs when organisms are inoculated into the skin, usually from a flea bite. During the 2- or 3-day incubation period, the bacilli migrate to regional lymph nodes, where they multiply and cause inflammation and necrosis of lymphatic tissue, resulting in large, tender nodes, or buboes. Typically, buboes develop in the groin, axilla, or cervical region and are so painful that the patient will refrain from moving the affected area (Fig. 194-4). Individuals experience fever, chills, and weakness. In approximately 25% of patients, vesicles or ulcerations occur at the site of the flea bite. The buboes are usually nonfluctuant but rarely can suppurate. Organisms can be aspirated from the nodes for diagnosis, but incision and drainage are not recommended because the lymphadenitis resolves with antibiotic treatment, and practitioners could become infected if they are exposed during the procedure.

Figure 194-4. Child with bubonic plague demonstrating axillary bubo. (Courtesy Frederick M. Burkle, Jr., MD, MPH.)

During the next week or more, the bacteria disseminate in approximately 50% of patients with bubonic plague. These victims have septicemic plague or secondary pneumonic plague and die if they are untreated. Those with septicemic plague experience endotoxemia, shock, disseminated intravascular coagulation, and coma. If bacteremia does not occur, most victims recover. A small percentage of those infected by fleas have septicemic plague without detectable buboes. Direct human-to-human transmission does not occur with bubonic or septicemic plague. However, both of these conditions can lead to secondary pneumonic plague, which is communicable. Therefore, initial isolation (for the first 48 hours) is recommended for all patients with plague.

Differential Diagnosis

The preliminary diagnosis of plague is clinical. Few diseases other than plague cause fulminant gram-negative pneumonia associated with hemoptysis in previously healthy individuals. The same can be said for diseases that cause lymphadenopathy. Cat-scratch disease, tularemia, and staphylococcal or streptococcal infections are all in the differential diagnosis. However, the extremely tender nature of the lymphadenopathy and the toxicity of the patient strongly suggest plague. Once the disease is suspected, Gram's stain and culture of sputum, blood, cerebrospinal fluid, or lymph node aspirate are helpful. State health departments or the CDC can test specimens for the presence of the capsular antigen by direct fluorescent antibody staining. Polymerase chain reaction also holds promise. Unfortunately, all laboratory tests require several days to complete, so initial management decisions must be based on clinical findings.

Treatment

Antibiotic treatment is essentially identical for all three types of plague (Box 194-6).[24] The same caveats for the use of fluoroquinolones and tetracycline in children with anthrax apply to plague. In the case of pneumonic and septicemic plague, treatment should be started within 24 hours of symptoms for outcome to be improved. Antibiotics are given for a minimum of 10 days. As patients improve, oral antibiotics are substituted for intravenous therapy to complete the course. Respiratory isolation of patients with pneumonic plague is necessary for 4 days after beginning of antibiotics to guarantee sterilization of sputum. Patients with septicemic and bubonic plague require isolation for 48 hours. If they do not have pneumonia or draining lesions during this time, isolation can be discontinued. Nonseptic patients with mild bubonic plague can be treated at home with oral doxycycline or tetracycline for 10 days.

www.ketabpezeshki.com 66485457-66963820

Box 194-6 Treatment of Plague

Parenteral Therapy
Adults
Streptomycin,* 1 g IM bid
Gentamicin, 5-7 mg/kg once daily IM or IV
Doxycycline, 100 mg IV bid
Ciprofloxacin, 400 mg IV bid
Chloramphenicol, 25 mg/kg IV qid

Children
Streptomycin,* 15 mg/kg IM bid (max. 2 g/day)
Gentamicin, 2.5 mg/kg IM or IV tid
Doxycycline, 2.2 mg/kg IV bid (max. 200 mg/day)
Ciprofloxacin, 10 mg/kg IV bid (max. 800 mg/day)
Chloramphenicol, 25 mg/kg IV qid

Pregnant women
Same as above but exclude streptomycin and chloramphenicol

Oral Therapy
Adults
Doxycycline, 100 mg bid
Ciprofloxacin, 500 mg bid
Chloramphenicol, 25 mg/kg qid

Children
Doxycycline, 2.2 mg/kg bid (max. 200 mg/day)
Ciprofloxacin, 15 mg/kg bid (max. 1 g/day)
Chloramphenicol, 25 mg/kg qid

Pregnant women
Same as above but exclude chloramphenicol

*Although streptomycin is recommended as first-line treatment, it may not be readily available.

The mainstay of prophylaxis against plague remains oral antibiotics. A vaccine exists but has no value in an acute outbreak. It is effective only against bubonic disease and requires several months to impart immunity. The drugs for prophylaxis are tetracycline, doxycycline, ciprofloxacin, chloramphenicol, and possibly trimethoprim-sulfamethoxazole for children.

Smallpox

Smallpox was eradicated in 1980. The only known repositories of the variola virus, the etiologic agent of smallpox, are in the United States and Russia. However, Russia was successful in weaponizing the virus, which may have been sold or smuggled out of the country.[8] The effectiveness of Russia's weaponized strain was demonstrated in 1971 when an individual became infected while traveling on a ship 15 km downwind from a Soviet bioweapons test site (Vozrozhdeniye Island in the Aral Sea).[25] In addition, most of the world's population is no longer fully immune to infection because vaccination against smallpox ceased approximately 40 years ago in nonmilitary personnel. Given its high infectivity and lethality, this makes smallpox an excellent biologic weapon.

The variola virus is spread as an aerosol. It can survive for 24 hours, and possibly 48 hours, in the environment. The occurrence of smallpox in hospital employees whose only exposure was handling of laundry from infected people is testimony to its viability. Approximately 30% of exposed people become ill. One infected person has the potential to infect up to 20 other individuals. People are infectious from the time the rash first appears until the scabs fall off (1 or 2 weeks). Anyone exposed to smallpox should be quarantined and observed for 17 days to rule out infection.

The disease is manifested clinically in several forms. Variola major and variola minor represent 90% of the cases. Variola major is the classic form, a more severe illness with a mortality rate of 30%. Variola minor is a milder form, with less toxicity, fewer pox, and a mortality rate of 1%. Two other forms of the disease, hemorrhagic and malignant (or flat) smallpox, are seen in 10% of cases; the mortality rate is greater than 90%. Patients with hemorrhagic smallpox have symptoms earlier and become toxic quickly. Instead of pox, their rash is characterized by petechiae and hemorrhage. Death occurs in 5 or 6 days. Those with malignant smallpox have a similar course, but their rash is characterized by soft, flattened lesions that never progress to pustules. If they survive, the lesions resolve without forming scabs.

Figure 194-5. Man with smallpox. (From the U.S. Centers for Disease Control and Prevention Public Health Image Library.)

The infection begins when the virus is inhaled. After migrating to regional lymph nodes, the virus replicates for 3 or 4 days and then asymptomatically spreads to the spleen, bone marrow, other lymphoid tissue, and liver. A second viremia occurs 8 to 12 days later and is associated with fever, prostration, and headache. Mental status changes can occur. During this phase, which lasts 2 or 3 days, the virus localizes to the skin and pharyngeal mucosa. A maculopapular rash soon appears, which becomes vesicular and finally pustular. In contrast to chickenpox, the rash first appears on the face and forearms, later spreading to the legs and trunk. All the lesions in any one area of the body are the same age (Fig. 194-5). During the next 8 to 14 days, the pustules crust over and separate from the skin, leaving pitted scars.

A clinical algorithm developed by the CDC can assist in assessing the probability that an individual has smallpox. It relies on three major and five minor criteria. The major criteria are a febrile prodrome, classic smallpox lesions, and lesions in the same stage of development. The minor criteria are centrifugal distribution of pustules; first lesions on the oral mucosa, face, or forearms; toxic appearance; slow evolution of lesions; and pustules on the palms and soles. A patient with all three major criteria is at high risk and should be isolated and reported to public health authorities and law enforcement agencies immediately. Patients with the febrile prodrome and either four minor criteria or one other major criterion are at moderate risk. Consultation with infectious disease and dermatology specialists should be sought and tests ordered to confirm varicella. If smallpox cannot be ruled out after these interventions, the patient should be treated as high risk. If a patient does not have the febrile prodrome or has the prodrome but no other major criteria and has fewer than four minor criteria, the individual is at low risk for smallpox. These patients can be managed as clinically indicated.[26]

Differential Diagnosis

As with anthrax and plague, the initial diagnosis of smallpox is clinical. Other illnesses resembling smallpox include chickenpox,

www.ketabpezeshki.com 66485457-66963820

herpes simplex, and monkeypox. Unlike with variola, the rash associated with chickenpox (varicella) is seen first on the trunk and then spreads to the extremities and face. In addition, the pustules are in different stages of evolution in any one area of the body. If the first case seen is hemorrhagic or malignant smallpox, the diagnosis will probably be missed until more typical cases present. For confirmation of the diagnosis, vesicular fluid or scabs were traditionally sent for electron microscopic examination. Polymerase chain reaction techniques appear promising for rapid viral identification, with sensitivities and specificities in the 98% range.[27]

Treatment

No effective therapy exists for victims infected with smallpox who become symptomatic. However, potential antiviral agents, such as cidofovir, show promise. In mice exposed to a lethal cowpox challenge, administration of an oral lipid prodrug of cidofovir in modest doses once a day for 5 days produced 100% survival.[28] Vaccinia immune globulin (VIG) has no role in the treatment of active disease. Some practitioners suggest that most smallpox patients should be isolated at home or other nonhospital facilities because the virus spreads easily in a hospital environment and the disease is currently untreatable.[8]

The best strategy for containment of the disease is vaccination of the susceptible population. Vaccination of an immunocompetent individual within 3 days of exposure will prevent or significantly ameliorate illness. Vaccination up to 7 days after exposure may prevent death. Complications from vaccination with vaccinia virus occur and can be fatal. Groups at risk for these adverse consequences include pregnant women and people with eczema, human immunodeficiency virus infection, and immunosuppressive conditions (e.g., malignant disease, chronic steroid use, and hereditary immunodeficiencies). Given the seriousness of the disease, the current recommendation is to vaccinate these individuals if there is risk of exposure and simultaneously administer 0.3 mL/kg of VIG intramuscularly. For people who have complications from the vaccine (e.g., progressive vaccinia, ocular autoinoculation, and eczema vaccinatum), the dose of VIG is 0.6 mL/kg intramuscularly and is divided during 24 to 36 hours. Ribavirin can be administered but is considered experimental. VIG is not indicated for vaccinia-associated encephalitis.

The smallpox vaccine supply situation has improved dramatically in the United States. The CDC has 100 million doses of the traditional smallpox vaccine (Dryvax). These vials can be diluted 5 : 1 to produce a total of 500 million doses without any decrement in the vaccine's efficacy.[29] In 2004, a British company delivered an additional 209 million doses of a second-generation vaccine derived from the same vaccinia virus used in Dryvax but grown in cell cultures. In addition, work is commencing on production of an improved modified vaccinia Ankara vaccine. The virus used in the modified vaccinia Ankara vaccine is so attenuated that it does not replicate in a human host. This may make it safe for administration to immunocompromised individuals.

CHEMICAL WEAPONS

Unlike victims of biologic weapons, casualties exposed to chemical agents manifest symptoms quickly, from immediately to a few hours after chemical contact.[30] Therefore, surveillance and recognition are less problematic. The challenge is decontamination and treatment.

Terrorism with chemical weapons produces casualties similar to those seen in hazardous materials incidents, and medical management is comparable. However, the unique features of such events, including the volume of patients and the risk of hospital contamination, necessitate additional preparation. For example, the Tokyo subway attack with use of sarin in 1995 resulted in 11 deaths and more than 5000 patients converging on local emergency departments. Although the majority of these patients had subclinical exposure or psychological symptoms alone, the health care system was severely stressed. Secondary contamination by direct contact or vaporization occurred in ambulances and at the hospitals.[3]

Box 194-7 Emergency Department Preparedness for Chemical Weapons of Mass Destruction

- Community-based hospital planning
- Personnel trained in recognition, mass casualty triage, and treatment
- Decontamination facility with protocols (e.g., runoff water, warm water)
- Personal protective equipment readily accessible and compliant with regulations
- Rapid access to antidotes, cyanide kits, and anticonvulsants
- Hospital incident management system in place
- Knowledge of how to access experts quickly

Health care facilities should have protocols in place to deal with the eventuality of chemically contaminated patients (Box 194-7).[31,32] Current recommendations for levels of PPE and types of decontamination facilities necessary in a hospital setting have been advanced, but evidence-based recommendations remain inconclusive.[33,34] Collection of waste water from the decontamination process in a containment vessel is ideal but not required if this would impede necessary and appropriate actions to protect human life (www.epa.gov/oem/docs/chem/runoff.pdf).

The four basic classes of chemical agents are nerve, vesicant (blistering), blood, and pulmonary (choking). Although all have potential for use as weapons, the nerve agents and vesicants are thought to represent the greatest threat.

Nerve Agents (Sarin, Tabun, Soman, and VX)

Nerve agents are organophosphates. They inhibit the enzyme acetylcholinesterase, blocking the degradation of acetylcholine at the postsynaptic membrane. Acetylcholine accumulates, resulting in overstimulation of muscarinic and nicotinic receptors. Symptoms are receptor dependent. Stimulation of muscarinic receptors produces miosis, salivation, rhinorrhea, lacrimation, bronchorrhea, bronchospasm, vomiting, and defecation. The major life threat associated with this syndrome is ventilatory compromise from profound bronchorrhea and bronchoconstriction. Stimulation of nicotinic receptors produces muscle fasciculations, flaccid paralysis, tachycardia, and hypertension. Unlike with typical organophosphates, exposure to nerve agents has not been associated with urination. In addition, bradycardia is rare, and miosis does not respond to systemic therapy.[2]

Nerve agents also cause direct central nervous system toxicity that is manifested as seizures, coma, and apnea. In survivors, residual central nervous system effects are manifested as psychological changes that can last 4 to 6 weeks. These manifestations are caused by chemical effects, not stress.

A preliminary diagnosis of nerve agent exposure is based on clinical findings. Important features include muscle fasciculations and miosis, which are sufficient to justify treatment pending further evaluation. Diagnosis is confirmed by measurement of red blood cell cholinesterase levels. This test is not readily available, however, so treatment must begin before test results are known.

Terrorists are most likely to use the nerve agents sarin (designated GB) and VX. Sarin exists as a liquid at room temperature but represents primarily a vapor threat because of its high volatility. Symptoms occur within seconds after inhalation of vapor and

www.ketabpezeshki.com 66485457-66963820

Box 194-8 Type and Degree of Nerve Agent Exposure

Vapor Exposure (Sarin)
Mild: rhinorrhea and miosis
Moderate: mild symptoms plus increased secretions, wheezing or dyspnea, muscle weakness or fasciculations, or gastrointestinal effects
Severe: apnea, seizures, loss of consciousness, flaccid paralysis, or major involvement of two organ systems

Liquid Exposure (VX)
Mild: localized sweating and fasciculations where a drop touches the skin; no miosis; may be delayed for 18 hours
Moderate: gastrointestinal effects; miosis uncommon; may be delayed for 18 hours
Severe: apnea, seizures, loss of consciousness, flaccid paralysis, or major involvement of two organ systems; occurs in less than 30 minutes at or above LD_{50}

peak at 5 minutes. There are no delayed effects; patients remaining asymptomatic 1 hour after possible chemical contact have not received a clinically significant exposure. They can be sent home. VX is a thick liquid with low volatility. It represents a liquid threat only. In general, victims have symptoms after skin exposure. The median lethal dose (LD_{50}) for VX is 10 mg, a droplet slightly larger than a pinhead. Death from doses of this size occurs in less than 30 minutes. Delayed symptoms occur, so individuals must be observed for 18 hours before potential intoxication can be ruled out.

Decontamination of victims exposed to sarin vapor requires only removal of clothing. People contaminated with VX or liquid sarin should have their clothing removed and then must be decontaminated by use of showers. When the level of exposure or the involved agent is uncertain, full decontamination is prudent. Responders caring for patients in the presence of liquid sarin exposure may require level A or B protective suits.

Treatment

The treatment of nerve agent victims depends on the form (liquid or vapor) and level of exposure (mild, moderate, or severe) (Box 194-8). Three drugs are the mainstay of treatment: atropine for the muscarinic effects (improves ventilation), pralidoxime chloride (2-PAM) for the nicotinic effects (reverses paralysis), and diazepam for the prevention and treatment of seizures (Box 194-9). The dose of atropine is titrated to the drying of respiratory secretions and not to heart rate or pupil size. If diazepam is unavailable, other benzodiazepines can be used. 2-PAM is most effective if it is administered within 4 to 6 hours of sarin exposure. After this period, the drug's impact wanes because of "aging," defined as the permanent attachment of sarin to the acetylcholinesterase enzyme. Hypertension can occur during 2-PAM administration and is controlled by intravenous phentolamine, 5 mg for adults and 1 mg in repeated doses for children. Recently, investigators have published data that question the efficacy of oximes in the treatment of commercial insecticide exposure. In one study, the use of oximes did not improve clinically important outcomes.[35] Whether these results apply to nerve agents remains uncertain.

An autoinjector kit (Mark I) approved by the FDA consists of two cartridges, one containing atropine (2 mg) and the other 2-PAM (600 mg). Mark I kits are available as part of civilian pharmaceutical caches strategically located throughout the United States. A newer version with both drugs combined in a single autoinjector (Antidote Treatment Nerve Agent Auto-Injector referred to as DuoDote) will gradually replace the Mark I kits. An autoinjector containing 10 mg of diazepam is an additional option if intravenous access is not possible. Doses should be adjusted for pediatric and geriatric patients. Atropine autoinjectors are manufactured in three doses (2 mg, 1 mg, and 0.5 mg) for these groups. Use of the Mark I kits to treat children and the elderly can be problematic because of difficulty in adjusting the dose. An alternative solution is to inject the medication into a sterile vial. The drug can then be reaspirated in an appropriate amount for the patient's weight or age and administered.[36]

Box 194-9 Treatment of Nerve Agent Exposure* Vapor

Mild: *Observe for 1 hour,* then release; no treatment
Moderate:
- One or two Mark I kits IM *or*
- Atropine, 2-4 mg IV, may repeat every 5-10 minutes as needed; *and* 2-PAM, 1 g IV during 30 minutes, may repeat every hour as needed

Severe:
- Three Mark I kits IM and one diazepam autoinjector IM *or*
- Atropine, 6 mg IV, may repeat 2-mg boluses IV every 5-10 minutes; *and* 2-PAM, 1 g IV during 30 minutes, repeat every hour for total of 3 g; *and* diazepam, 5 mg IV, may repeat as needed

Liquid
Mild:
- One Mark I kit IM *or*
- Atropine, 2 mg IV, *and* 2-PAM, 1 g IV during 30 minutes

Moderate: Same as for vapor
Severe: Same as for vapor

Pediatric Doses
Atropine, 0.02 mg/kg IV
2-PAM, 20-40 mg/kg IV during 20-30 minutes
Diazepam, 0.2-0.3 mg/kg IV

*Give atropine before attempting intubation. Otherwise, airway resistance will inhibit ventilation. Continue atropine until secretions are dry (usually 20 mg). In hypoxic patients, IV atropine has been reported to cause ventricular fibrillation, so consider use of IM atropine.

Vesicants (Mustard)

Vesicants (blistering agents) are chemical warfare agents that induce blister formation on contact with skin. Terrorists could use several of these compounds, but mustard is considered the chemical of choice. Mustard is a liquid at room temperature but has both liquid and vapor toxicity. Injury from mustard exposure occurs in 1 or 2 minutes, but symptoms do not develop for 4 to 8 hours. The exact mechanism is unknown, but the agent damages DNA, causing eventual cell death. Mustard has both local and systemic toxicity. Local effects occur from direct exposure to the skin, eyes, and airway. Systemic effects result from the impact of absorbed mustard on the bone marrow. Treatment is supportive and includes decontamination (to prevent secondary contamination) and airway maintenance. Although no specific antidote for mustard is currently available, a topical iodine preparation shows promise. When it is applied within 1 hour after mustard exposure to the skin of guinea pigs, an iodine-tetraglycol solution reduced vesicle formation and signs of inflammation.[37] Application of the solution more than 1 hour after exposure was not effective in preventing symptoms.

Eye damage from mustard exposure varies from conjunctivitis to corneal ulcer and perforation; however, only 1% of patients have permanent eye damage. Severe pain is frequently associated with mustard injury and causes significant blepharospasm. Irrigation is beneficial if it is performed within minutes of exposure but ineffective once symptoms occur. Standard treatment includes

www.ketabpezeshki.com 66485457-66963820

mydriatics, topical antibiotics, oral analgesics, and petroleum jelly applied to the lids to prevent adhesions. Topical steroids are indicated only within the first 24 hours.

The hallmark of mustard injury is skin blisters resembling second-degree burns. Within 4 to 8 hours of exposure, erythema and burning occur, followed by vesicle and bulla formation. Most vapor injuries do not involve the entire dermis, so wounds will not require skin grafting. If liquid exposure occurs to skin, full-thickness burns may result. The patient should be decontaminated by removal of clothing and washing with water or a dilute bleach (1 : 10 hypochlorite) solution. More concentrated bleach solutions are contraindicated as they can cause skin damage. Decontamination immediately after exposure prevents further injury to the patient, but delayed decontamination is indicated to protect staff. Treatment is supportive and includes standard burn wound management, analgesia, and tetanus prophylaxis. An important exception is fluid resuscitation. Fluid losses from mustard injury are much less than those associated with thermal burns. Therefore, standard burn formulas for fluid administration do not apply, and caution should be used to avoid overhydration.

The degree of airway injury after mustard exposure is dose dependent. Mild exposure causes irritation of the nose, sinuses, and pharynx and can be treated with cool, humidified mist. Moderate exposure extends to the larynx and upper trachea and may require treatment with oxygen, continuous positive airway pressure, or even intubation. Severe exposure involves the lungs, producing hemorrhagic necrosis of the bronchioles. Pulmonary edema is rare. Intubation is usually required, and patients may benefit from positive end-expiratory pressure and in-line bronchodilators. Steroids are of questionable benefit, and antibiotics should be given only for established infection.

Systemic toxicity from mustard is caused by bone marrow suppression. Absorbed mustard kills stem cells, causing the white blood cell count to decline after 3 to 5 days. Survival is rare if the white blood cell count falls below 200, which generally occurs when more than 50% of the total body surface area is involved from exposure to liquid agent. Death after mustard exposure usually results from secondary infection.

Blood Agents (Cyanide)

Blood agents such as cyanide bind to cytochromes within mitochondria and inhibit cellular oxygen use. Low-dose exposures result in tachypnea, headache, dizziness, vomiting, and anxiety. Symptoms subside when the patient is removed from the source. At higher doses, the symptoms progress to seizures, respiratory arrest, and asystole within minutes of exposure.

Victims should be removed from the area, have their clothing discarded, and receive oxygen. If no improvement occurs, the cyanide antidote is given. This has traditionally been the sequential administration of amyl nitrate, sodium nitrite, and sodium thiosulfate. However, the FDA has approved intravenous hydroxocobalamin for treatment of cyanide exposure. The initial dose is 5 g and can be repeated if necessary.[38]

Pulmonary Agents (Phosgene and Chlorine)

Pulmonary or choking agents cause an inflammatory reaction when they come into direct contact with the eyes and upper airway. They can be life-threatening if inhaled. No specific antidote exists. Treatment is mainly supportive and consists of removal of the patient from the source, decontamination, airway maintenance, bronchodilator administration, and eye irrigation.

KEY CONCEPTS

- Emergency department preparedness for a radiation incident must address decontamination (an external freestanding decontamination unit is best), triage, staff safety, PPE, and diagnostic procedures that emphasize radiation monitoring. The emergency personnel should make sure that they know their radiation safety officer.
- Management of acute life-threatening conditions takes priority over radiation-associated issues.
- Aerosol dispersal is a likely route that terrorists may use to deploy biologic weapons, so victims will present primarily with respiratory complaints.
- In addition to "flulike" symptoms, anthrax typically causes mediastinal widening, pulmonary consolidation, and pleural effusions best seen on chest computed tomography scans.
- Smallpox can spread in a hospital environment; thus patients thought to have smallpox should be admitted to locations separated from the rest of the hospital.
- Decontamination is a key activity in the management of patients exposed to chemical agents, and hospitals should provide this intervention.
- Nerve agents are organophosphates, and patients exposed to these agents are treated with large doses of atropine (repeated frequently), pralidoxime, and benzodiazepines.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. DeAngelo G: Cost minimization and medical examinations: The case of anthrax. *J Homeland Security Emergency Management* 2008; 5:Article 30. DOI: 10.2202/1547-7355.1318.
2. Chemical and Biological Defense Command: *Domestic Preparedness Training Program: Hospital Provider Manual*. Edgewood Arsenal, Md: Chemical and Biological Defense Command; 1999.
3. Okumura T, et al: Report on 640 victims of the Tokyo subway sarin attack. *Ann Emerg Med* 1996; 28:129.
4. Koenig KL, et al: Medical treatment of radiologic casualties: Current concepts. *Ann Emerg Med* 2005; 45:643.
5. Hatchett RJ, Kaminiski JM, Goans RE: *Nuclear and radiologic events*. In: Koenig KL, Schultz CH, eds. *Koenig and Schultz's Disaster Medicine: Comprehensive Principles and Practices*. New York: Cambridge University Press; 2010.
6. Health Physics Society: *Guidance for Protective Actions Following a Radiological Terrorist Event. Position Statement of the Health Physics Society*. McLean, Va: Health Physics Society; 2004. Available at http://hps.org/documents/rddpags_ps019-s010.pdf. Accessed April 15, 2011.
7. Bennett B, Repacholi M, Carr Z, eds: *Health Effects of the Chernobyl Accident and Special Health Care Programmes: Report of the UN Chernobyl Forum Health Expert Group*. Geneva: World Health Organization; 2006. Available at www.who.int/ionizing_radiation/chernobyl/WHO%20Report%20on%20Chernobyl%20Health%20Effects%20July%2006.pdf. Accessed July 16, 2011.
8. Henderson DA, et al: Smallpox as a biological weapon: Medical and public health management. *JAMA* 1999; 281:2127.
9. Koenig KL, et al: Health care facilities' "war on terrorism": A deliberate process for recommending personal protective equipment. *Am J Emerg Med* 2007; 25:185.
10. Koenig KL, et al: Health care facility–based decontamination of victims exposed to chemical, biological, and radiological material. *Am J Emerg Med* 2008; 26:71.
11. Koenig KL, Kahn CA, Schultz CH: Medical strategies to handle mass casualties from the use of biological weapons. *Clin Lab Med* 2006; 26:313.
12. Shih F, Koenig KL: Improving surge capacity for biothreats: Experience from Taiwan. *Acad Emerg Med* 2006; 13:1114.
13. Schultz CH, Mothershead JL, Field M: Bioterrorism preparedness I: The emergency department and hospital. *Emerg Med Clin North Am* 2002; 20:437.
14. Darling R, Woods JB, Cieslak TJ: *Biological events*. In: Koenig KL, Schultz CH, eds. *Koenig and Schultz's Disaster Medicine: Comprehensive Principles and Practices*. New York: Cambridge University Press; 2010.
15. Purcell BK, Worsham PL, Friedlander AM: *Anthrax*. In: Lenhart MK, Lounesbury DE, Martin JM, eds. *Medical Aspects of Biological Warfare, Textbook of Military Medicine*. Washington, DC: Office of the Surgeon General, U.S. Army; 2007:69-90.
16. Dixon TC, et al: Anthrax. *N Engl J Med* 1999; 341:815.
17. Jernigan JA, et al: Bioterrorism-related inhalational anthrax: The first 10 cases reported in the United States. *Emerg Infect Dis* 2001; 7:933.
18. Schultz CH: Chinese curses, anthrax, and the risk of bioterrorism. *Ann Emerg Med* 2004; 43:329.
19. Centers for Disease Control and Prevention: Update: Investigation of bioterrorism-related inhalational anthrax—Connecticut, 2001. *MMWR Morb Mortal Wkly Rep* 2001; 50:1029.
20. Hupert N, Bearman GML, Mushlin AI, Callahan MA: Accuracy of screening for inhalational anthrax after a bioterrorist attack. *Ann Intern Med* 2003; 139:337.
21. Kuehnert MJ, et al: Clinical features that discriminate inhalational anthrax from other acute respiratory illnesses. *Clin Infect Dis* 2003; 36:328.
22. Bell DM, et al: Conference Summary: Clinical issues in the prophylaxis, diagnosis, and treatment of anthrax. *Emerg Infect Dis* 2002; 8:222.
23. Joellenbeck LM, et al: *The Anthrax Vaccine—Is it safe? Does it work?* Washington, DC: Committee to Assess the Safety and Efficacy of the Anthrax Vaccine, Institute of Medicine, National Academy Press; 2002.
24. Inglesby TV, et al: Plague as a biological weapon: Medical and public health management. *JAMA* 2000; 283:2281.
25. Tucker JB, Zilinskas RA: *The 1971 Smallpox Epidemic in Aralsk, Kazakhstan, and the Soviet Biological Warfare Program, Occasional Paper No. 9*. Monterey, Calif: Chemical and Biological Weapons Nonproliferation Project, Center for Nonproliferation Studies, Monterey Institute of International Studies; 2002.
26. Centers for Disease Control and Prevention: *Evaluating Patients for Smallpox: Acute, Generalized Vesicular or Pustular Rash Illness Protocol*. Available at http://emergency.cdc.gov/agent/smallpox/diagnosis/pdf/poxalgorithm11-14-07.pdf. Accessed July 16, 2011.
27. Aitichou M, Javorschi S, Ibrahim MS: Two-color multiplex assay for the identification of orthopox viruses with real-time LUX-PCR. *Mol Cell Probes* 2005; 19:323.
28. De Clercq E: Cidofovir in the therapy and short-term prophylaxis of poxvirus infections. *Trends Pharmacol Sci* 2002; 23:456.
29. Frey SE, et al: Clinical responses to undiluted and diluted smallpox vaccine. *N Engl J Med* 2002; 346:1265.
30. Urbanetti J: *Clinical aspects of large-scale chemical events*. In: Koenig KL, Schultz CH, eds. *Koenig and Schultz's Disaster Medicine: Comprehensive Principles and Practices*. New York: Cambridge University Press; 2010.
31. Macintyre AG, et al: Weapons of mass destruction events with contaminated casualties: Effective planning for health care facilities. *JAMA* 2000; 283:242.
32. Burgess JL, et al: Emergency department hazardous material protocol for contaminated patients. *Ann Emerg Med* 1999; 34:205.
33. Koenig KL, et al: Health care facilities' "war on terrorism": A deliberate process for recommending personal protective equipment. *Am J Emerg Med* 2007; 25:185-195.
34. Koenig KL, et al: Healthcare facility–based decontamination of victims exposed to chemical, biological, and radiological material. *Am J Emerg Med* 2008; 26:71-80.
35. Eddleston M, et al: Pralidoxime in acute organophosphorus insecticide poisoning—a randomised controlled trial. *PLoS Med* 2009; 6:e1000104. doi:10.1371/journal.pmed.1000104.
36. Henretig FM, Mechem C, Jew R: Potential use of autoinjector-packaged antidotes for treatment of pediatric nerve agent toxicity. *Ann Emerg Med* 2002; 40:405.
37. Wormser U, et al: Topical iodine preparation as therapy against sulfur mustard–induced skin lesions. *Toxicol Appl Pharmacol* 2000; 169:33.
38. Borron SW, et al: Prospective study of hydroxocobalamin for acute cyanide poisoning in smoke inhalation. *Ann Emerg Med* 2007; 49:794.

www.ketabpezeshki.com 66485457-66963820

Chapter 195

Observation Medicine and Clinical Decision Units

Malcolm Mahadevan and Louis Graff IV

PRINCIPLES OF OBSERVATION MEDICINE

Observation services are an extension of emergency department (ED) services specifically designed to address unmet patient needs. Observation services improve patient care by continuing the evaluation and management of selected ED patients who would otherwise require admission for acute care services. Approximately 80% of patients treated on observation services can be sent home without the need for hospitalization. The cost to evaluate and to treat these patients is half that incurred by admission.[1,2] In addition, the physician threshold for extended evaluation (traditionally provided with hospitalization) is lowered. Patients with atypical signs and symptoms are more fully evaluated to rule out serious conditions, such as acute myocardial infarction or acute appendicitis. Thus in addition to lower costs, there is also a simultaneous decrease in the inadvertent release home of patients with serious disease.[1]

An ED observation unit is a designated area to provide these short-term services for up to 24 hours. Names given to observation units vary and include *chest pain unit, clinical decision unit,* and *rapid diagnostic treatment unit*. An ED-based observation unit is not a holding unit. A holding unit stems from hospital overcrowding and is an area where patients admitted to the hospital are held passively until they can be transferred to an inpatient hospital bed.

Two categories of patients benefit from extension of the usual 2- to 4-hour ED visit to up to 24 hours. One group is selected patients with a critical diagnostic syndrome (Box 195-1). These are patients whose diagnoses are unclear after the initial ED evaluation and who will benefit from further evaluation during observation. They are either admitted if they are found to have a serious disease or released home. The second group is patients with selected emergency conditions (see Box 195-1). Those patients not successfully treated during the traditional ED treatment period benefit from further treatment in an observation unit.

OBSERVATIONAL APPROACH

The traditional ED encounter lasts less than 4 hours. The physician performs a history and physical examination and orders laboratory and radiologic tests. When the test results return, the physician either admits the patient to the hospital or discharges the patient home.

The observational approach adds a third option at the completion of the initial evaluation. The patient is treated and further tested for up to 24 hours. After the observation period, patients are then admitted to the hospital or discharged home.

Observation begins with the physician's writing of observation orders. The patient is transferred to the observation unit from the main ED. An observation unit chart is generated, and treatment and investigations are begun. The observation orders include the clinical impression, the reason for observation, the therapeutic evaluation plan, the expected outcome, the criteria and time frame for disposition, and the physician responsible for the patient's care and disposition. The responsible physician may be the emergency physician or the patient's private physician or a consultant.

Adequate staffing of the observation unit is crucial for the success of the program. The patient receives services for an average of 12 to 24 hours beyond the ED visit. The amount of nursing staff required is proportional to the type and intensity of treatment offered, the number of beds, whether the beds are monitored or nonmonitored, and the patient's acuity. The average staff is one registered nurse per four to six patients in monitored beds and one registered nurse per six to nine patients in nonmonitored beds.

Staff nursing skills should be broad based and include the ability to care for patients of all ages with a wide spectrum of conditions. Nurses should have the ability to provide critical care when it is needed and frequent assessments of patients under their care. Nurses should be able to provide prolonged patient and family interactions, including hygiene care, meals, and emotional support. These are all skills present in emergency nurses. When nonemergency nurses are recruited for the observation unit, they should be cross-trained, serving some shifts each month in the ED.

Additional physician staffing is also required for the observation unit. Management of ED patients in the observation unit for an additional 12 to 14 hours requires approximately a doubling of the physician service for a single patient.[3] Calculations of the physician staffing for the amount of additional services will be approximately one full-time equivalent for every 2000 patients observed per year. As with the nurses, physicians in the observation unit must have broad-based knowledge and experience in the management of a wide variety of disease processes. Emergency physicians possess the skill sets necessary for observation medicine. The emergency physician is ultimately responsible for the care of the patient and needs to provide clear leadership at all times.

Patients and staff involved in the observation process must be well informed about the goals and benefits provided by the extended service. Well-written, condition-specific observation protocols ensure a continuum of care, including the transfer of patient care at shift change. The services provided in an ED observation unit are equivalent to inpatient services, albeit at an accelerated pace.

www.ketabpezeshki.com 66485457-66963820

Box 195-1 Conditions Appropriate for Observation

Evaluation: Critical Diagnostic Syndromes
- Abdominal pain
- Chest pain
- Deep venous thrombosis
- Gastrointestinal bleeding
- Syncope
- Transient ischemic attack
- Trauma
  - Blunt abdominal
  - Blunt chest
  - Penetrating abdominal
  - Penetrating chest
  - Head injury

Treatment: Emergency Conditions
- Asthma
- Atrial fibrillation
- Congestive heart failure
- Dehydration
- Infections
  - Pneumonia
  - Pyelonephritis

Box 195-2 Observation Criteria for Abdominal Pain*

Exclusions (any criterion indicates too high risk for observation; the patient should be admitted)
- Severe dehydration
- Hemodynamic instability
- Sodium concentration < 120 mEq or > 155 mEq
- Concomitant acute severe medical condition (e.g., acute renal failure or sepsis)
- Acute peritonitis
- Probability of discharge within 24 hours < 80%
- High or moderate probability of serious, dangerous disease, such as acute appendicitis, small bowel obstruction, or bowel perforation

Inclusions (appropriate to refer to observation if at least one criterion is met)
- Inability to correct symptoms
- Inability to take fluids orally
- Possibility that patient has serious, dangerous cause of symptoms
- Inability to control pain with oral medication

*Note: These criteria are based on the authors' expert opinion.

Consultants must be available to the observation unit as they would be to any inpatient service. They provide therapeutic and management advice and assist in the serial examinations of patients as requested. The observation unit must identify needs, notify the consultant, assemble all the needed information, and carry out the consultant's recommendations within the shortest time frame possible.

Residents and medical students are included in the functioning of the observation unit because exposure to the observational approach is an integral part of their training program. Emergency residents specifically need training in this area of emergency medicine through clinical practice, lectures, and review of published literature. Residents from other specialties benefit from the exposure by having a better understanding of the role of observation medicine and its applicability in a select group of ED patients.

The amount and type of ancillary personnel needed in the observation unit depend on its size and the type of services offered in the unit. An observation unit that offers chest pain evaluation may require different ancillary personnel than one that does not. Personnel may be from outside the department or function full-time in the observation unit (e.g., respiratory therapists). They may also be personnel who have not traditionally been available to the ED, such as psychiatric nurses. Also crucial for proper functioning of the unit are adequate secretarial and clerical staff.

The structure of the observation unit will determine its clinical effectiveness and financial viability. Models for the structure of the observation unit are reviewed in the American College of Emergency Physicians textbook *Emergency Department Design.*[4] An observation unit that is properly designed and located adjacent to the ED will result in a 50% lowered cost compared with traditional hospital admission while providing equivalent or improved quality of patient care.

An emergency physician designated and empowered to manage the observation unit is critical for success. The complexity of patient care is multiplied when an ED adds observation services. The manager develops and implements clinical protocols for efficient quality patient care. The manager schedules and supervises the observation unit staff and leads the continuous quality improvement team monitoring the observation unit's functioning.

CLINICAL CONDITIONS

Evaluation of Critical Diagnostic Syndromes

Abdominal Pain

Traditional Approach. Abdominal pain is one of the most frequent complaints in the ED and accounts for 4 to 8% of all visits.[5] The typical ED evaluation of the patient with abdominal pain includes a thorough history and physical examination and the appropriate diagnostic tests. Within the short time frame of 2 to 4 hours, patients are given a provisional diagnosis and are either hospitalized or sent home.

Problem with Traditional Approach. The ED evaluation is inadequate for many patients, and in 40% of patients the origin of abdominal pain is never determined. Acute appendicitis is the most common abdominal surgical emergency and illustrates the inadequacies of the traditional approach. The diagnosis of acute appendicitis is missed in 20 to 30% of cases (false-negative decisions). In addition, 20 to 30% of patients taken to surgery for acute appendicitis are found to have no abnormality (false-positive decisions).[5] Whereas abdominal computed tomography (CT) imaging has been found to improve physician performance in identifying patients with acute appendicitis,[6-8] there is increasing concern for the amount of ionizing radiation exposure to patients from the increased use of CT.[9]

Observational Approach. With observation, the ED evaluation can be extended from 2 to 4 hours to up to 23 hours for selected patients (Box 195-2). After the initial history and physical examination of the patient, the physician estimates the probability that the patient has appendicitis by use of validated risk stratification tools, such as the Alvarado score. Those patients deemed to have a low probability of disease are ideal candidates for the observational approach.[10] Patients who are at greater risk of having their diagnosis missed, such as those who are immunocompromised, pregnant, or at the extremes of age, often benefit from observation. Elders in particular benefit from observation; surgical problems are often missed because of the atypical clinical findings that occur with older age.[11]

During the period of observation, the patient is usually kept fasted and hydrated intravenously. Serial abdominal examinations

www.ketabpezeshki.com 66485457-66963820

are repeated at 4-hour intervals, and laboratory tests such as complete blood count and C-reactive protein level are repeated as appropriate. Imaging and consultations are also arranged during this time frame. Patients without appendicitis will experience improvement of their pain and have had completion of diagnostic workup and exclusion of surgical disease.[12] Patients are hospitalized if they have no improvement, worsening of their clinical findings, or surgical disease diagnosed by testing. In patients who do have appendicitis, signs and symptoms will continue or worsen.[13]

Physician decision-making improves with observation, and false-positive surgeries can nearly be eliminated. Intensive observation with serial physical examinations at least every 8 hours rather than once per day has been found to reduce the false-positive rate from 20 to 5%.[13,14] The use of a period of observation can also help identify many patients whose diagnoses otherwise would be missed during the initial ED evaluation. Initially, many appendicitis patients have few clinical signs or symptoms of appendicitis on presentation, making diagnosis difficult.[12] Physicians delaying disposition decisions in questionable cases can avoid these false-negative decisions. Appendicitis patients have more signs and symptoms during short-term observation, whereas those without the disorder clear their signs and symptoms. Thus fewer patients have an unclear clinical picture after observation with fewer false-negative decisions.[15] Missing of the diagnosis at the initial evaluation delays surgery up to 72 hours and doubles complications (perforation, abscess).[11] Physicians who observe selected patients with low probability of disease rather than discharge them after their initial evaluation can avoid most of these missed diagnoses and the resulting complications.

Chest Pain

Traditional Approach. The ED evaluation of chest pain is composed of two assessments: (1) the probability that the patient has an acute myocardial infarction (AMI) or acute coronary ischemia (ACI) and (2) the risk of the patient's having a life-threatening event. These two factors determine the appropriate setting for further testing and monitoring. The probability of AMI is traditionally assessed in the ED with a directed history, physical examination, and electrocardiogram (ECG) and an initial measurement of cardiac biomarkers, such as creatine kinase MB fraction (CK-MB), cardiac troponin I or T, B-type natriuretic peptide (BNP), and myoglobin. Other markers, such as high-sensitivity C-reactive protein, myeloperoxidase, and D-dimer, are used less frequently.[1-5,7,8,16-23]

Patients with clear evidence of AMI on the ECG are potential candidates for immediate reperfusion therapy with either thrombolytics or emergency angioplasty. This subset is at high risk for life-threatening events and best managed in the coronary care setting with close monitoring. This approach has been shown to improve survival in patients with AMI.

Depending on the evaluating physician's threshold, chest pain patients without definite evidence of AMI at initial evaluation are generally admitted to the hospital to confirm or to exclude ("rule in" or "rule out") ACI or AMI. Patients who are judged to have low probability of ACI after the initial evaluation are released home for outpatient follow-up.

Problem with Traditional Approach. The poor performance of initial diagnostic testing makes the evaluation of chest pain highly dependent on clinical judgment. The initial ECG is diagnostic in only 50% of AMI patients,[24] and the initial CK-MB measurement has a sensitivity of only 35%.[25] Reliance on physician judgment and initial ED testing has resulted in as many as 2 to 5% of AMI patients being discharged home with inadvertent reassurance.[1,26] AMI patients not identified at the initial evaluation and released from the ED have up to a 25% risk of poor outcome.[1] Fear of inadvertently releasing AMI patients has led many emergency physicians to err on the side of admitting a large number of patients who do not have AMI or unstable angina. As a result of the increased sensitivity of a more liberal admission policy, two thirds of patients admitted for chest pain have a noncardiac cause of their symptoms.[1] Costs range in the billions of dollars for these negative evaluation hospitalizations.[4] Despite this liberal admission policy, missed AMI remains one of the leading causes of malpractice suits against emergency physicians.[27]

Box 195-3 Observation Criteria for Chest Pain*

Exclusions (any criterion indicates too high risk for observation; the patient should be admitted)
- Diagnostic electrocardiographic changes or positive cardiac biomarkers
- Moderate or high probability of serious, dangerous disease or risk of adverse event
- Continuing chest pain
- Unstable vital signs

Inclusions (appropriate to refer to observation if all criteria are met)
- Nontraumatic chest pain
- Low probability of serious, dangerous disease or risk of adverse event
- Stable vital signs

*Note: These criteria are based on the authors' expert opinion.

Observational Approach. The emergency physician can use the observation unit to extend the evaluation of selected patients with chest pain (Box 195-3). When it is used principally for such a purpose, the observation unit has been termed a chest pain unit. The chest pain unit has been successful in improving the sensitivity and specificity of the evaluation process.[28,29] Patients with low risk of AMI are transferred to the observation unit. Patients unsuitable for observation unit evaluation include those who have a high to moderate probability of acute myocardial ischemia, unstable vital signs, electrocardiographic findings of AMI, or persistent or recurring chest pain consistent with unstable angina.

The physician identifies patients with low probability for ACI by use of one or more risk stratification tools. Risk stratification based on classic risk factors alone has been shown to be a poor predictor of short-term outcome.[30] Risk stratification based on electrocardiographic findings is more reliable. The Brush ECG criteria classify as low risk those without ST segment elevation or depression, T wave inversion or strain, new (or presumed new) Q waves, left bundle branch block, or paced rhythm.[31] Another useful risk stratification tool is the Goldman protocol, which uses history, physical examination, and electrocardiographic findings to classify patients into high (>70%), moderate, or low (>7%) risk.[32] Another tool is the acute cardiac ischemia time-insensitive predictive instrument, which uses age and gender of the patient, presence or absence of chest pain, and electrocardiographic findings to assign a probability of acute ischemia.[33]

Patients admitted to the observation unit are first evaluated to rule out a myocardial infarction. They are serially tested with cardiac markers and ECGs. CK-MB estimation at 0, 3, and 6 hours after presentation has 100% sensitivity, 98% specificity, and 100% negative predictive value in the detection of AMI.[28,29] Other useful serum cardiac markers are the troponins (I and T) and myoglobin. Patients who present more than 24 hours after symptom onset have negative CK-MB and myoglobin testing findings, but troponin T or I remains positive for up to 6 days. Patients are monitored with continuous ECG monitors equipped with dysrhythmia alarms and memory storage capabilities. Continuous electrocardiographic ST segment monitoring can detect

www.ketabpezeshki.com 66485457-66963820

dynamic ST segment changes indicative of ischemia, which, when present, indicate an increased likelihood for an adverse cardiac event.[34] Continuous electrocardiographic monitoring also helps detect arrhythmias that may be associated with acute coronary syndrome.

After evaluation to exclude AMI, the patient is evaluated for possible acute coronary syndrome. This may be performed before release of the patient from the observation unit or at follow-up evaluation within 72 hours of discharge. The most common testing modality used is exercise stress testing.[35] Patients who obtain their target heart rate without electrocardiographic evidence of ischemia can be released home. They have an annual mortality rate of less than 1%.[35] The performance of exercise testing depends on the ability of the patient to exercise adequately, gender (women have higher false-positive rates), interpretability of the resting ECG, and availability of the test. Other testing modalities include stress echocardiography, technetium (^{99m}Tc) sestamibi scanning, and cardiac CT angiography.

Approximately one third of ED patients with chest pain are candidates for observation, with 80 to 85% released home after observation.[1] This reduces the hospitalization rate from 60 to 70% down to 40 to 50%.[1] The cost of evaluation with observation is half that of traditional evaluation with hospitalization.[1] The safety and cost-effectiveness of the observation approach have been confirmed in four randomized clinical trials.[36-39] Payers expect clinicians to be cost-effective and to use observation for evaluation of patients with chest pain when it is appropriate. The Centers for Medicaid and Medicare Services began audits in 2010 by Recovery Audit Contractors to deny payment for patients with low probability of AMI chest pain who were admitted to the hospital rather than evaluated in the lower cost outpatient observation unit. The use of observation units for chest pain evaluation is thus becoming the standard in U.S. hospitals.

Deep Venous Thrombosis

Traditional Approach. The primary objectives for the treatment of deep venous thrombosis (DVT) are to prevent pulmonary embolism, to reduce morbidity, and to prevent or to minimize the risk for development of postphlebitic syndrome. Patients with suspected DVT are usually hospitalized when diagnostic testing is unavailable in the ED or the diagnosis has been confirmed and further management is required. Traditionally, anticoagulation with unfractionated heparin has been administered by continuous intravenous infusion for 5 to 7 days while oral anticoagulation is instituted.[40] Meta-analyses of randomized trials of unfractionated heparin and low-molecular-weight heparin (LMWH) showed that they were similar, with a risk of recurrent DVT of 4%, a risk of pulmonary embolism of 2%, and a risk of major bleeding of 3%.[41,42] The anticoagulant response to this treatment varies markedly among patients, and therefore the dosage must be monitored by coagulation profiles.[43]

Problem with Traditional Approach. New modalities for investigation and treatment have made it possible to manage DVT on an outpatient basis with lower costs than with hospitalization. There are new, less invasive investigative tests and newer therapeutic agents that do not require monitoring of coagulation profiles.

Observational Approach. The role of the observation unit in the management of patients thought to have DVT is for diagnostic testing as well as for initiation of therapy with LMWH and patient education. Patients often present during the night or on weekends when definitive tests for DVT (e.g., Doppler ultrasonography) are not available. The patient may have a positive D-dimer test finding, which requires a confirmatory definitive test because of its poor specificity.[44] In these circumstances, the patient can be anticoagulated for the short term with one dose of LMWH (enoxaparin, 1 mg/kg twice daily) until the diagnosis can be clarified. If the diagnosis is confirmed, the patient can be admitted or treated as an outpatient on the basis of hospital protocol. Patients considered for outpatient management are instructed in how to administer the medication. They are educated about DVT and its complications and the possible side effects of the LMWH. Appropriate follow-up evaluation is also arranged before discharge. With this approach, patients spend 67% less time in the hospital and have greater physical activity and social functioning than their standard heparin cohorts do.[45] Outpatient management is not recommended if the patient has proven or suspected concomitant pulmonary embolism, significant comorbidities, extensive iliofemoral DVT, active bleeding, renal failure, or poor follow-up compliance. LMWH is administered by subcutaneous injection in doses adjusted for the patient's weight, without laboratory monitoring.

Outpatient testing with venous compression ultrasonography has become readily available.[46] It is both sensitive and specific for the diagnosis of proximal (femoropopliteal) DVT.[47] When repeated compression ultrasonography is compared with impedance plethysmography, compression ultrasonography is superior in detection of DVT.[46] It has been proved to be a safe method of deciding when to administer anticoagulation.[44] The D-dimer assay has also been shown to be a useful adjunct to compression ultrasonography in outpatient testing.

Upper Gastrointestinal Bleeding

Traditional Approach. Most patients with upper gastrointestinal bleeding are admitted to the hospital after initial ED assessment and stabilization.

Problem with Traditional Approach. Upper gastrointestinal bleeding is a common and potentially life-threatening condition with an overall mortality rate of 6 to 10%.[48] However, most cases of upper gastrointestinal bleeding are self-limited, and 80% of patients have only one bleeding episode.[49]

Observational Approach. Not all patients with upper gastrointestinal bleeding do poorly, suggesting that outpatient management is possible if patients at high risk for further bleeding can be identified. Prognostic indicators include the patient's age, heart rate, systolic blood pressure, orthostatic changes in blood pressure or pulse, color of stool or emesis, anticoagulant use, and comorbid conditions.[50] In an attempt to refine diagnostic accuracy, risk assessment, and disposition, several scoring systems have been developed. Some practitioners use hemodynamic stability, intensity of bleeding, and underlying health status as predictors of rebleeding, need for surgery, and mortality.[51] Some use a period of observation with early endoscopy to identify the patient who can be discharged early. Patients found to have clean-based ulcers at endoscopy have a rebleeding rate of less than 2% and virtually never require urgent intervention for recurrent bleeding and can be released. Use of this approach has been proved to be both safe and cost-effective; a prospective clinical trial demonstrated that 24% of patients can avoid hospitalization, with cost savings of $990 per patient.[52]

Syncope

Traditional Approach. Syncope is caused by a spectrum of disease entities. ED evaluation includes a thorough history, physical examination, and 12-lead ECG. Patients with evidence of possible myocardial ischemia or a cardiac cause of their syncope are usually admitted to the hospital because cardiac syncope has a high risk of death (up to one third will have a poor outcome).[53] Those with concomitant heart failure have a 25% mortality rate at 30 days.[54] On the other hand, patients with noncardiac syncope have a low risk of adverse events (1%) and can be managed as outpatients.[53]

www.ketabpezeshki.com 66485457-66963820

BOX 195-4 Observation Criteria for Syncope*

Exclusions (any criterion indicates too high risk for observation; the patient should be admitted)

History of dyspnea or loss of consciousness > 10 minutes or trauma or seizure
Past history of congestive heart failure, chronic obstructive pulmonary disease, structural heart disease, or ventricular dysrhythmia
Abnormal hematocrit level < 30%, elevated B-type natriuretic peptide or pro-B–type natriuretic peptide level, positive cardiac biomarkers, or abnormal electrolyte values
Evidence of injury or ischemia on electrocardiography or documented or highly suspected unstable dysrhythmia
Low oxygen saturation or unstable vital signs
Stool positive for blood
New focal neurologic findings or persistently altered mental status
High or moderate probability of serious, dangerous disease or adverse event

Inclusions (appropriate to refer to observation if any criterion is met)

Possibility of pathologic cause of the syncope
Low probability of serious, dangerous disease or adverse event

*Note: These criteria are based on the authors' expert opinion.

Problem with Traditional Approach. Attempts to exclude a possible cardiac cause of syncope usually result in 25 to 40% of patients being hospitalized for further evaluation and management.[54] The traditional ED evaluation identifies only 50% of patients with a serious cause of their syncope,[55] and this has often resulted in a liberal admission policy; however, one study found that only 12% of patients had a serious cause of syncope that justified hospitalization.[56] It is estimated that a third of patients admitted after their ED evaluation have very low risk of an adverse event (<2%) and would be appropriate for outpatient observation evaluation.[57]

Observational Approach. The use of observation for selected patients with syncope reduces unnecessary hospitalizations (Box 195-4). Patients with a cardiac syncope have a poor prognosis and need to be identified. These patients often do not have chest pain as a symptom, but they may have ischemic changes on the ECG, arm or shoulder pain, or prior history of exercise-induced angina. A "rule out myocardial infarction" evaluation with cardiac monitoring, serial ECGs, and enzyme measurement may be the only way to identify these patients. Prolonged electrocardiographic monitoring can point to a specific cause in up to one fifth of patients, with half of all abnormalities detected in the first 24 hours.[58]

The challenge for the emergency physician is to risk stratify patients into very low risk, who can be discharged home; low risk, who are appropriate for outpatient observation; and moderate to high risk, who are appropriate for acute care hospitalization. Many factors have been found to correlate with adverse outcomes and should be considered by the clinician in the risk stratification, but attempts to create simple high-reliability decision rules have not been successful.[59] Martin found that the 1-year risk of dysrhythmia or death in syncope patients correlates with four factors: an abnormal ECG, history of ventricular dysrhythmia, history of heart failure, and age older than 45 years.[59] Patients with none of these risk factors have only a 4.4% rate of adverse events at 1 year and may be appropriate for outpatient evaluation. In contrast, patients with three or four risk factors have a 58% adverse outcome rate and should be hospitalized. Patients with one or two risk factors have intermediate risk and may be appropriate for evaluation on an observation service. The San Francisco Syncope Rule has been found to have sensitivity in identifying patients who are at immediate risk for serious outcomes within 7 days that ranges in different studies from 74 to 96%.[60,61] Its criteria are abnormal electrocardiographic findings, history of congestive heart failure (CHF), dyspnea, hematocrit level of less than 30%, and hypotension.[60,61] The Risk stratification Of Syncope in the Emergency department (ROSE) criteria suggest that an elevated BNP level, Hemoccult-positive stool, anemia, low oxygen saturation, and presence of Q waves on the ECG predict serious outcomes at 30 days.[62] These rules had a sensitivity of 87% and a negative predictive value of 98.5% to help risk stratify patients. In this study, the isolated finding of a BNP level above 300 pg/mL was a major predictor of serious outcomes and was present in 89% of patients who died within 30 days. Another study found that 6.1% of patients had severe outcomes within 10 days of syncope evaluation.[63] The mortality rate was 0.7%, and 5.4% of patients were readmitted or experienced major therapeutic intervention. Risk factors associated with severe short-term outcomes included abnormal ECG, history of CHF, age older than 65 years, male gender, history of chronic obstructive pulmonary disease, structural heart disease, presence of trauma, and lack of prodromal symptoms. The Evaluation of Guidelines in SYncope Study 2 (EGSYS 2) prospectively observed nearly 400 patients at 1 month and 2 years. The death rate was 2% at 1 month and 9% at 2 years. Patients with advancing age, presence of structural heart disease, or abnormal ECG had higher risk.[64] Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL) score is another clinical decision rule that has been found to have limited accuracy.[65,66] Additional factors indicating that a patient should be admitted rather than placed in outpatient observation are abnormal neurologic findings, positive cardiac biomarkers, and loss of consciousness for longer than 15 minutes.

Because many factors should be considered in the risk stratification for patient disposition to observation or hospitalization (see Box 195-4), the best practice approach is to develop an institutional consensus on this risk stratification and to codify it in a syncope order set. This approach reduces physician variability in decision-making by more uniformly adopting evidence-based practices, which improves both quality of patient care and use of health care resources.

During the observation period, serial examination of patients is carried out, including vital signs, with the majority of patients safely discharged home without hospitalization.[67] Continuous electrocardiographic monitoring, consultation, serial cardiac enzyme determinations, and further tests, such as two-dimensional echography of the heart, psychiatric assessment, and tilt table testing, should be arranged when appropriate. Tilt table testing is a useful investigation in patients with recurrent syncope when heart disease is not suspected. Up to 60% of patients who have vagally mediated syncope can be detected by this modality.[68] The period of observation can also identify patients with cardiac dysrhythmias or sinus pauses who are candidates for more extensive diagnostic evaluation in the hospital.

Transient Ischemic Attack

Traditional Approach. More than 300,000 people suffer a transient ischemic attack (TIA) each year.[69] For most patients, it is a transient event that will not recur if they take an aspirin each day. However, for 10% of patients, it is a warning sign that they will suffer a stroke unless they are appropriately evaluated and treated.[70] Traditionally, the patient is assessed in the ED with history, physical examination, laboratory tests, electrocardiography, and head CT scan. Most patients are then hospitalized for serial clinical evaluations, neurology consultation, carotid Doppler testing, echocardiography, and cardiac monitoring.[67]

www.ketabpezeshki.com 66485457-66963820

Problem with Traditional Approach. The problem with the traditional approach is that most TIA patients are admitted to the hospital. After 3 days of evaluation, few will be found to have carotid or heart disease requiring an intervention.

Observational Approach. Observation is an alternative to hospitalization for TIA patients with a normal ED evaluation for whom the emergency physician still has concern. An accelerated diagnostic observation protocol was compared with acute care hospitalization in a prospective randomized clinical trial. All patients had full evaluation in the observation unit or inpatient ward with serial clinical examinations, neurology consultation, carotid duplex ultrasonography, echocardiography, and cardiac monitoring.[71,72] Clinical outcomes were equivalent with the two approaches, but the observation unit was more efficient (length of stay, 25 hours vs. 61 hours) and had lower costs ($890 vs. $1547).[71,72]

Trauma

There are more than 30 million trauma-related ED visits annually.[73] Patients with serious injuries require hospitalization for definitive therapy, whereas those with minor injuries can be discharged home after treatment. The problem with the traditional ED approach is that many patients have injury patterns or actual injuries that fall somewhere between these two scenarios. If these patients are released, there is a risk that some will have poor outcomes as a result of missed injuries. On the other hand, because the majority of these patients do not have serious injuries, admitting this group to the hospital will result in a waste of scarce health care resources.

Observation units have been found to be an efficient and useful strategy in the evaluation and management of trauma victims.[74] With observation, selected patients can be evaluated further to determine the need for admission. One study of 20,000 patients treated in an ED observation unit during a 12-month period found that 3% of patients were admitted to the observation unit, with 86% safely discharged home without the need for admission.[74]

Blunt Abdominal Injury

Traditional Approach. Current ED management of blunt abdominal trauma (BAT) includes history, physical examination, blood analysis, plain radiography, ultrasonography, and CT scan. After initial stabilization and exclusion of other major injuries in the ED, most patients suffering BAT are admitted to the hospital for further evaluation and monitoring.

Problem with Traditional Approach. The initial evaluation is inadequate for accurate disposition of many BAT patients. One third of patients who do not have any symptoms or signs suggestive of intra-abdominal injury may actually have significant injury.[75] Also, because none of the present modalities for investigation of the presence of injury is 100% sensitive, many patients with initially normal investigations are hospitalized.

Observational Approach. BAT patients appropriate for observation include those who, after initial evaluation, have no clear evidence of serious injury on physical examination but remain at risk for serious injury because of the mechanism of the injury or the individual's personal health (e.g., advanced age or use of anticoagulants). Evaluations during observation for up to 23 hours include repeated physical examinations, laboratory testing, imaging, and specialty consultations. Patients are hospitalized if their condition deteriorates during the observation period or if, after testing, they are found to have serious internal injury. Patients with normal findings on evaluation and the ability to tolerate feeding can be safely released home. Patients who have sustained significant BAT by mechanism of injury or have equivocal findings on abdominal examination should undergo further testing, such as CT scan, for detection of occult injury.[76] Ultrasonography (focused assessment with sonography for trauma [FAST]) is being increasingly used in the initial evaluation of the patient with BAT because it is a rapid noninvasive study with 99% specificity for detection of abdominal injury.[77] However, it cannot be used to rule out serious intra-abdominal injury because a meta-analysis of 62 trials found the overall sensitivity of FAST to be only 79%.[77] CT alone is not adequate to rule out serious injury, with sensitivity of only 80 to 95%.[78] Short-term observation alone in patients with BAT is not sufficient because up to 20% of patients with significant injury will not have abdominal tenderness or develop it even after a short period of observation.[78] Thus the prudent approach to patients with significant BAT without clear evidence of intra-abdominal injury is the use of a diagnostic test, such as CT, together with a period of observation.

Penetrating Abdominal Injury

Traditional Approach. Most patients with penetrating abdominal injury are hospitalized for further evaluation, which may include wound exploration in the operating room and additional diagnostic testing.

Problem with Traditional Approach. Many of these hospitalizations are unnecessary because only two thirds of patients with abdominal stab wounds have a breach of the peritoneum, and two thirds of these do not sustain visceral injury.[79]

Observational Approach. A period of observation can identify those patients who do not require surgical intervention. Patients undergo serial examinations by the physician, further diagnostic testing, and specialty consultation. Those without evidence of peritoneal perforation or visceral injury after evaluation are sent home after proper wound care.

The conservative approach to penetrating abdominal wounds was developed in the 1970s. Those without peritoneal breach can be safely sent home after wound care and a period of observation without the need for hospitalization. Those with stab wounds to the abdomen with peritoneal breach but a negative finding on diagnostic laparoscopy or imaging with CT scan or ultrasonography can be safely managed in an observation unit.[79-82] Patients with significant intra-abdominal injuries identified during observation are admitted; the 70 to 90% of patients without such injuries are released home.[80,83] Gunshot wounds are often more difficult to evaluate than stab wounds. However, patients who appear to have tangential gunshot wounds can avoid surgery with observation if they are hemodynamically stable and have initial negative test findings. Penetrating wounds are manifested differently in children than in adults.[84] Initial diagnostic testing with CT and diagnostic peritoneal lavage in children detects only 50% of injuries, with only 30% of patients having localized tenderness. Observation can help avoid unnecessary surgery in patients without injury and missing of the diagnosis in those without clear evidence of injury.

Blunt Chest Trauma

Traditional Approach. Many patients who have a history of blunt chest trauma (BCT) in high-velocity accidents are admitted to the hospital to rule out myocardial or pulmonary contusion.

Problem with Traditional Approach. Very few patients admitted to the hospital with BCT from high-velocity accidents without initial evidence of injury are found to have serious injury during hospital evaluation.[85]

Observational Approach. Patients with isolated BCT who are otherwise stable with a normal ECG are suitable for a period of observation to exclude myocardial injury. During the period of observation, patients are monitored with continuous

www.ketabpezeshki.com 66485457-66963820

electrocardiography, specifically assessing for dysrhythmias. Serial enzyme determinations, such as troponin level, are also carried out to detect evidence of myocardial injury. Those patients with sternal fractures or other evidence of higher risk of intrathoracic injury should be considered for transesophageal echocardiography.[86] Those with normal evaluations during the period of observation are released home for outpatient follow-up.

Much of the period of observation in patients with BCT focuses on identification of the presence and prognosis of myocardial contusions. The overall incidence of cardiac-related complications in these patients is low (0.1%).[87] Patients with blunt cardiac trauma who have complications usually have an abnormal ECG or abnormal CK-MB or troponin level at presentation. Conversely, a normal ECG and CK-MB and troponin levels correlate with the lack of clinically significant complications.[88,89] Patients who have isolated chest wall contusions and no abnormality of serial CK-MB or troponin values and no electrocardiographic abnormalities or dysrhythmia during 6 to 12 hours of electrocardiographic monitoring are unlikely to have complications.

Penetrating Chest Injury

Traditional Approach. Patients with penetrating chest injury present with a spectrum of severity ranging from severe life-threatening injury requiring urgent operative intervention to hemodynamically stable patients with a normal initial evaluation. Most patients presenting with penetrating chest injuries are admitted to the hospital. Often, even those with a normal initial evaluation are admitted for exclusion of serious injury to the heart, lungs, and major blood vessels.

Problem with Traditional Approach. The accuracy of this approach is limited because many patients with evidence of injury are admitted but have no further deterioration or need for medical therapy. On the other hand, there are those without obvious evidence of serious injury who will have a negative outcome if they are released after the initial evaluation.

Observational Approach. A period of observation combined with diagnostic imaging can improve clinical decision-making. Patients with evidence of a small pneumothorax or hemothorax can be monitored for deterioration. Those without evidence of serious injury but of concern to the physician can likewise be observed for complications. During the period of observation, patients are monitored for respiratory or hemodynamic compromise. Repeated chest radiographs can detect the development of hemothorax or pneumothorax. Patients who deteriorate during the period of observation require hospitalization.

The safety and efficacy of managing asymptomatic stab wound victims in the short-term observation unit have been clearly established in multiple studies.[90-92] A total of 5 to 15% will require hospitalization because of development of delayed pneumothorax, subcutaneous emphysema, hematemesis, or pneumopericardium.[90] In addition, the majority of stab wound victims with small pneumothoraces or hemothoraces will be treated solely with a chest tube without further surgical intervention. Major trauma centers can manage many of these patients as outpatients without hospitalization after a period of observation.

Patients with penetrating wounds to the cardiac area of the chest (between the nipples), the region of the great vessels, or the thoracoabdominal area usually require more intensive testing to exclude injury not only to the heart, major vessels, and lungs but also to the diaphragm and the abdominal organs. Echocardiography may detect pericardial fluid or tamponade in patients with penetrating injury close to the heart.[93-95] Patients with small effusions may be observed in a monitored setting with serial examinations, whereas patients with large effusions should be treated surgically.[95] Patients with normal findings on echocardiography can be observed in the observation unit. Even patients with small effusions may have sustained a serious injury, so the intensity of monitoring needs to be high.

Treatment of Emergency Conditions

Asthma

Traditional Approach. More than 20 million people in the United States are afflicted with asthma. Acute exacerbation of asthma is a common ED presentation, with estimated annual admissions exceeding 450,000.[96] Traditionally, therapy is provided in the ED for 2 to 4 hours, consistent with national guidelines.[97] Initial assessment includes history, physical examination, oxygen saturation, and peak expiratory flow rate (PEFR) or forced expiratory volume in 1 minute. Treatment consists of beta-agonists, magnesium sulfate, and steroids, when appropriate. Patients who do not improve after 3 or 4 hours of treatment are hospitalized for further management.

Problems with Traditional Approach. With this approach, one third of patients are hospitalized.[98] This translates into an estimated medical cost of $1.2 billion annually.[98,99] Another pitfall in the traditional ED treatment of asthma is that short encounter times do not allow identification and aggressive treatment of patients with a higher tendency for relapse. This leads to repeated ED visits, additional medical costs, and diminished quality of life.

Observational Approach. An alternative to hospitalization for patients failing to respond to ED treatment is the use of an extended, short-term intensive protocol for 8 to 12 hours in an observation unit for selected patients (Box 195-5).[2] With extended treatment, 80% of such patients can be discharged home.[2] Inclusion criteria for observation unit management are failure of standard initial management and continued respiratory distress. Increased risk of relapse is indicated by a history of numerous asthma-related ED or clinic visits within the past year, use of more outpatient medications (including home nebulizers), and longer duration of symptoms.[98] Exclusion criteria for observation include unstable vital signs, evidence of impending respiratory failure ($Paco_2 > 45$ mm Hg, $Pao_2 < 55$ mm Hg), and severe airway restriction (PEFR < 80 L/min after first inhaled beta-agonist treatment). Also considered during selection for observation are factors that correlate with unsuccessful treatment during observation. These

Box 195-5 Observation Criteria for Asthma*

Exclusions (any criterion indicates too high risk for observation; the patient should be admitted)
- Respiratory fatigue or failure (respiratory rate > 40, oximetry < 90%, $Pco_2 > 45$, pH < 7.3)
- Inability to perform spirometry or peak flows
- Peak flow after third beta-agonist < 30% of predicted
- Concomitant illness (e.g., pneumonia, heart failure)
- Bronchospasm due to aspiration or foreign body
- Temperature > 101°F
- Need for continuous nebulizer treatment, bilevel positive airway pressure, or heliox
- Positive electrocardiographic changes or cardiac biomarkers

Inclusions (appropriate to refer to observation if all criteria are met)
- Shortness of breath
- Mild to moderate use of accessory muscles
- Wheezing
- Fair to good air exchange
- Stable vital signs
- Normal mentation

*Note: These criteria are based on the authors' expert opinion.

www.ketabpezeshki.com 66485457-66963820

include a previous ED visit in the past 10 days, previous intensive care unit admission or intubation, hospitalization during the previous year, three or more ED visits in the past 6 months, use of oral steroids for more than half of the previous year, and peak flow after the third beta-agonist treatment that is less than 32% of predicted.[2]

Therapy in the observation unit is a continuation of ED treatment with hand-held nebulized beta-agonists every 2 to 4 hours and repeated steroids at 6 hours after initial therapy. Patients are managed up to 23 hours but generally are admitted to the hospital if they do not respond within 12 hours. Patients are released from the observation unit when they are no longer in respiratory distress, have minimal residual symptoms, and have a PEFR of 70% or more of predicted or personal best. Before discharge, there should also be patient educational activities and assessment of inhaler techniques. Patients should be initiated into daily diary keeping as well as a log of PEFR before and after treatment. Appropriate follow-up care should also be arranged.

A prospective randomized clinical trial of observation versus traditional hospitalization of ED asthma patients who did not "break" in the first 3 or 4 hours of ED treatment found no difference in relapse rates at 8 weeks, but it found observation unit care to be associated with diminished length of stay (9 hours vs. 59 hours), increased patient satisfaction and quality of life, and cost savings of $1000 per patient.[2,100] Observation unit patients report greater overall satisfaction and fewer problems with their medical care, communication, emotional support, physical comfort, and special needs.[100] Observation has also been shown to have utility in the management of pediatric patients with asthma. Of those who would otherwise require hospitalization, 30 to 70% can be successfully managed as outpatients with the observation unit.[101]

Atrial Fibrillation

Traditional Approach. Atrial fibrillation, a relatively common condition that occurs in 2 or 3% of adults, is the most common sustained cardiac dysrhythmia in patients presenting to the ED.[102,103] The goals in management of acute atrial fibrillation are hemodynamic stabilization, symptom relief, prevention of thromboembolism, resolution of the dysrhythmia, and exclusion of serious pathologic causes of the dysrhythmia. The majority of patients who present to the ED with new-onset atrial fibrillation or acute atrial fibrillation are hospitalized.[80]

Problem with Traditional Approach. Recently, the necessity of admitting the majority of patients with acute atrial fibrillation has been questioned. It is recognized that new-onset atrial fibrillation for most patients is a transient dysrhythmia with no serious precipitants and a benign prognosis. One retrospective analysis of 216 patients admitted for atrial fibrillation found that one third of patients did not actually require admission to the hospital.[104]

Observational Approach. The observational approach to new and acute atrial fibrillation has been validated in a number of clinical trials including a randomized clinical trial.[105,106] The period of observation is usually 8 to 12 hours. During observation, patients are treated to rectify their dysrhythmia and evaluated for serious precipitants of their condition. After observation, 80 to 90% of patients can be discharged home without hospitalization.

For selected patients (Box 195-6), observation extends the ED evaluation of the patient for serious underlying medical conditions that may have precipitated the arrhythmia, such as AMI or hyperthyroidism. AMI is excluded as a precipitant with serial ECGs and cardiac biomarker testing during 6 to 9 hours and an evaluation for unstable angina. The period of observation is also used to detect structural heart disease with the use of echocardiography when it is appropriate. Patients are excluded from observation if they exhibit hemodynamic instability, comorbid conditions, heart failure, chest pain, or evidence of active coronary artery disease.

Observation is also used to extend the treatment period of the patient. The spontaneous conversion rate for patients with acute atrial fibrillation is 50 to 70% within the first 24 hours.[107] Patients who spontaneously convert have a low rate of structural heart disease.[107] Those who do not spontaneously convert in the first 8 hours can be converted chemically or electrically.[108] After cardioversion, the patient needs to be observed. This is especially true for patients converted with the newer class III antidysrhythmic agents (e.g., ibutilide), which have the potential for serious side effects, such as torsades de pointes (5% of patients), sinus bradycardia, and sinus arrest.[108,109] The risk of thromboembolism in patients with atrial fibrillation of less than 48 hours' duration is less than 1%, so patients who convert can be released home without need for anticoagulation.[110]

Box 195-6 Observation Criteria for New-Onset Atrial Fibrillation*

Exclusions (any criterion indicates too high risk for observation; the patient should be admitted)

- Evidence of new or acute on chronic congestive heart failure
- Past history of structural heart disease
- Abnormal hematocrit level < 30%, elevated B-type natriuretic peptide or pro-B–type natriuretic peptide level, positive cardiac biomarkers, or abnormal electrolyte values
- Evidence of injury or ischemia on electrocardiography or documented or highly suspected unstable dysrhythmia
- Low oxygen saturation or unstable vital signs
- Stool positive for blood
- New focal neurologic findings or persistently altered mental status
- High or moderate probability of serious, dangerous disease or adverse event

Inclusions (appropriate to refer to observation if all criteria are met)

- Low probability of serious, dangerous disease or risk of adverse event
- Stable vital signs
- Normal electrolyte values and blood count
- No positive cardiac biomarkers

*Note: These criteria are based on the authors' expert opinion.

Congestive Heart Failure

Traditional Approach. CHF is highly lethal; 37% of men and 33% of women die within 2 years of diagnosis. The 6-year mortality rate is 82% for men and 67% for women, which corresponds to a death rate fourfold to eightfold higher than that of the general population of the same age.[111] Patients who present to the ED with CHF undergo history taking, physical examination, and investigations including chest radiography. Treatment is begun with oxygenation, diuretics, inotropic agents, and vasodilators as appropriate. Most CHF patients treated in the ED are eventually hospitalized.

Problem with Traditional Approach. CHF is highly prevalent, affecting approximately 1% of people in their 50s and increasing progressively with age to afflict 10% of people in their 80s.[111] More than 2 million Americans have the disease, and 400,000 new cases are diagnosed each year.[111] One third of patients require hospitalization each year, one third are readmitted each year, and one third die within 2 years.[111] The annual cost to the health care system of managing patients with heart failure admitted to the hospital has been estimated at $28 billion.[69] Between 80 and 87% of patients diagnosed with CHF are hospitalized.[112,113]

www.ketabpezeshki.com 66485457-66963820

Box 195-7 Observation Criteria for Heart Failure*

Exclusions (any criterion indicates too high risk for observation; the patient should be admitted)

Diagnostic electrocardiographic changes or positive cardiac biomarkers
Concomitant acute severe medical condition (e.g., acute renal failure or sepsis)
Moderate or high probability of serious, dangerous disease or risk of adverse event
Unstable vital signs
New-onset heart failure
Severe anemia (hemoglobin < 8 g/dL; hematocrit < 24%)
Anasarca
New arrhythmia

Inclusions (appropriate to refer to observation if all criteria are met)

High likelihood of successful treatment < 24 hours
Symptom of congestive heart failure (e.g., shortness of breath, dyspnea on exertion, paroxysmal nocturnal dyspnea, weakness)
Sign of congestive heart failure (e.g., edema, jugular venous distention, B-type natriuretic peptide > 100 pg/mL, abnormal chest radiograph)
Low probability of serious, dangerous disease or risk of adverse event

*Note: These criteria are based on the authors' expert opinion.

Observational Approach. Observation is a strategy to avoid hospital admission of patients with CHF that results in great cost savings. Selected patients can be safely managed in an observation unit (Box 195-7).[112-114] Such patients include those with a high probability of successful treatment with short-term extension of the ED visit. Patients should also have low severity of illness. They should exhibit hypoxia, pulmonary edema, hypotension, evidence of AMI, hemodynamic instability, or serious comorbid conditions.[112-114] BNP has been used to streamline decision-making. Patients with BNP levels between 100 and 500 pg/mL are suitable candidates for observation unit care because a large proportion of these patients should be able to be discharged home. The test has a negative predictive value of more than 95% and a positive predictive value of 70 to 95%. It correlates with pulmonary capillary wedge pressure, and because its half-life is less than 30 minutes, serial measurements during observation can evaluate the effects of therapeutic interventions.[115,116]

Therapy and evaluation are a continuation of the initial 2- to 4-hour ED visit for up to 23 hours. Continuous electrocardiographic monitoring is performed because up to 30% of CHF patients have dysrhythmias.[117] Inotropic agents can be infused and the patient educated about preventable causes of the exacerbation. Therapy may include continuous infusion of a loop diuretic (0.05-0.1 mg/kg/hr) titrated hourly to a net fluid balance of −1 mL/kg/hr. In most patients with acute exacerbation of chronic CHF, the cause of the exacerbation is preventable, such as failure to take medications or dietary indiscretion. The opportunity to provide patient education, medication review, and consultations with dietary and social services as necessary is fully used because this has been shown to improve compliance with therapy.[118] Patients are discharged home when their symptoms are adequately controlled, all reversible causes of morbidity are treated or stabilized, and adequate outpatient support and follow-up care are arranged. With observation, the focus of ED care can shift from providing only episodic treatment of CHF patients to providing more comprehensive and preventive care.[118] Compared with acute care hospitalization, observation has a much reduced length of stay and significantly lower costs.[118,119]

Box 195-8 Observation Criteria for Dehydration*

Exclusions (any criterion indicates too high risk for observation; the patient should be admitted)

Severe dehydration
Moderate or high probability of serious, dangerous disease or risk of adverse event
Unstable vital signs
Sodium concentration < 120 mEq or > 155 mEq
Concomitant acute serious medical condition (e.g., acute renal failure, sepsis)

Inclusions (appropriate to refer to observation if all criteria are met)

Inability to correct symptoms in the emergency department
Inability to take fluids orally

*Note: These criteria are based on the authors' expert opinion.

Dehydration

Traditional Approach. Dehydration is often the presenting symptom of an underlying disease state and can affect patients of all ages. Patients are often admitted for intravenous hydration to correct fluid and electrolyte imbalances or for further diagnostic evaluation.

Problem with Traditional Approach. Patients with dehydration are often hospitalized because short ED visits do not allow full correction of fluid and electrolyte disorders or extensive evaluation for underlying causes. A common cause of ED return visits is dehydration due to initially inadequate therapy and evaluation.[120]

Observational Approach. The goals of observation unit therapy are adequate treatment of fluid and electrolyte abnormalities and identification of the underlying cause of symptoms. Appropriate patients for observation include those with acceptable vital signs and mild to moderate dehydration (Box 195-8). They should have self-limited or treatable causes not requiring hospitalization, with mild to moderate electrolyte abnormalities. Most patients with hyperemesis gravidarum can be treated effectively in an observation unit. Patients unsuitable for observation are those with unstable vital signs, cardiovascular compromise, underlying chronic medical illness, severe dehydration or electrolyte abnormalities, or associated conditions not amenable to short-term therapy (e.g., bowel obstruction, diabetic ketoacidosis, and sepsis). Interventions include intravenous rehydration, serial examinations and vital signs, and antiemetics. The patient is released home when there are acceptable vital signs, resolution of symptoms, tolerance to oral fluids, and normal electrolyte values. Patients who do not fulfill the discharge criteria are hospitalized.

Infections

Pneumonia

Traditional Approach. Each year approximately 600,000 patients are hospitalized with pneumonia, at a cost of almost $4 billion.[121] Many of these patients are admitted after initial ED evaluation. Physicians often rely on subjective criteria, such as clinical appearance, in selecting patients for hospital admission.[122]

Problem with Traditional Approach. There is great variation in the admission rates for pneumonia.[123] Emergency physicians tend to overestimate the risk of death in patients with pneumonia, which has resulted in many low-risk patients being hospitalized unnecessarily.[122]

Observational Approach. Observation is appropriate when the physician is concerned that the patient may not do well as an

www.ketabpezeshki.com 66485457-66963820

Box 195-9 Observation Criteria for Pneumonia*

Exclusions (any criterion indicates too high risk for observation; the patient should be admitted)
Moderate or high probability of serious, dangerous disease or risk of adverse event
Unstable vital signs
Risk factors for poor outcome: immunocompromised, neuromuscular disorder, pulmonary tuberculosis, cystic fibrosis
Health care–associated pneumonia or hospital-acquired pneumonia
Concomitant acute serious medical condition (e.g., acute renal failure, sepsis)

Inclusions (appropriate to refer to observation if all criteria are met)
Stable vital signs
Normal mentation
Low risk by clinical judgment or severity index

*Note: These criteria are based on the authors' expert opinion.

outpatient (Box 195-9). This concern can be based on the physician's clinical judgment or a severity of illness index. Fine and associates[122] developed a prediction rule to estimate which pneumonia patients would be at higher risk for mortality. They reviewed medical records of more than 14,000 patients hospitalized with pneumonia and identified 14 key clinical variables (e.g., age, sex, coexisting illness, vital signs, and mental status) and 7 key laboratory variables (e.g., blood urea nitrogen, glucose, hematocrit, arterial oxygen, and pleural effusion on chest radiograph). They then weighed each of these variables into a cumulative point total Pneumonia Severity Index (PSI) and assigned each patient to one of five mortality risk groups ranging from class I, which includes patients with a low risk (30-day mortality risk < 0.5%) who can be treated as outpatients, to class V, which includes patients with a high risk (30-day mortality risk > 30%) who should be treated as inpatients. Patients in class III are at intermediate risk, and traditionally half are admitted and half are treated as outpatients. By use of the PSI to risk stratify patients, physicians can avoid hospitalization of many low-risk patients.[124] Intermediate-risk patients (class III) are good candidates for a period of observation to clarify their need for hospitalization. Irrespective of the patient's risk as judged by PSI, some patients are not appropriate for observation but should be admitted: those with immunocompromise, pulmonary tuberculosis, high suspicion of pulmonary embolism, or hypoxia (Table 195-1).

During observation, patients are treated with antibiotics, oxygen therapy, and pulse oximetry monitoring. Hydration is given either orally or intravenously. After 10 to 12 hours of treatment in the observation unit, the patient is re-evaluated and a decision about disposition is made. Patients who deteriorate during the observation period or have an oxygen saturation of less than 90% on room air after observation should be hospitalized.

Table 195-1 Use of Pneumonia Severity Index (PSI) for Admission Decisions

Step 1: Assess Arterial Oxygenation for All Patients	
Is pulse oximetry < 90% or Po_2 < 60 mm Hg?	
Yes: Inpatient therapy recommended **No:** Go to Step 2	
Step 2: Are Any of the Following Present?	
Patient 51 years of age or older	
Coexisting medical conditions listed in Step 3	
Physical examination findings listed in Step 3	
Yes: Go to Step 3 **No:** Risk Class I, go to Step 4	
Step 3: Compute Risk Score (Sum of Applicable Points)	
Risk Factor	*Points*
Demographic factors	
Age in years (age − 10 for women)	
Nursing home resident	10
Coexisting medical conditions	
Neoplastic disease	30
Liver disease	20
Congestive heart failure	10
Cerebrovascular disease	10
Renal disease	10
Physical examination findings	
Altered mental status	20
Respiratory rate ≥ 30/min	20
Systolic blood pressure < 90 mm Hg	20
Temperature < 35° C or ≥ 40° C	15
Pulse > 125/min	10
Laboratory and radiographic findings	
Arterial pH < 7.35	30
Blood urea nitrogen ≥ 30 mg/dL	20
Sodium < 130 mEq/L	20
Glucose ≥ 250 mg/dL	10
Hematocrit < 30%	10
Po_2 < 60 mm Hg or O_2 sat < 90%	10
Pleural effusion by chest x-ray	10
TOTAL SCORE (sum of all points)	

Step 4: Recommended Initial Site of Treatment

Risk Score	*Risk Class*	*Treatment Site*
Not applicable	I	Outpatient
<71	II	Outpatient
71-91	III	Observation
91-130	IV	Inpatient
>130	V	Inpatient

Pyelonephritis

Traditional Approach. Pyelonephritis is a serious infection that frequently results in hospitalization for intravenous hydration and antibiotic administration.

Problem with Traditional Approach. Many patients who are admitted with pyelonephritis are judged retrospectively not to have had the condition. In addition, many patients with pyelonephritis are at very low risk for development of complications.

Observational Approach. Observation is appropriate for adult, nonpregnant women who appear to have uncomplicated pyelonephritis. Patients receive an initial dose of intravenous antibiotic, intravenous fluids, antiemetic, and antipyretic. Laboratory tests include complete blood cell count, urinalysis, and urine and blood cultures. Patients who are clinically stable and able to tolerate oral fluids are released home after 12 hours of treatment.

Outpatient management of selected patients with pyelonephritis by observation has been shown to be safe and effective. Only 5 to 25% of patients require hospitalization after the period of observation.[125,126] At 3-week follow-up examination, 2 to 6% have complications and require hospitalization.[125,126] With a period of observation and careful follow-up evaluation, selected patients with pyelonephritis can be successfully managed without hospital admission.[126]

www.ketabpezeshki.com 66485457-66963820

KEY CONCEPTS

- Hospitalization can be avoided by short-term (<24 hours) treatment of patients in an observation unit for certain medical disorders: abdominal pain, chest pain, DVT, upper gastrointestinal bleeding, syncope, TIA, trauma, asthma, atrial fibrillation, CHF, dehydration, pneumonia, and pyelonephritis.
- Use of observation units results in both cost savings and improved patient satisfaction with care.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Graff LG, et al: Impact on the care of the emergency department chest pain patient from the Chest Pain Evaluation Registry (CHEPER) study. *Am J Cardiol* 1997; 80:563.
2. McDermott MF, et al: Comparison between emergency diagnostic and treatment unit and inpatient care in the management of acute asthma. *Arch Intern Med* 1997; 157:2055.
3. Graff L, et al: Emergency physician workload: A time study. *Ann Emerg Med* 1993; 22:1156.
4. Riggs L, ed: *Emergency Department Design*. Dallas: American College of Emergency Physicians; 1993.
5. Powers RD, Guertler AT: Abdominal pain in the ED: Stability and change over 20 years. *Am J Emerg Med* 1995; 13:301.
6. Rao PM, Rhea JT, Rattner DW, Venus LG, Novelline RA: Introduction of appendiceal CT: Impact on negative appendectomy and appendiceal perforation rates. *Ann Surg* 1999; 229:344-349.
7. Rao PM, Rhea JT, Novelline RA, Mostafavi AA, McCabe CJ: Effect of computed tomography of the appendix on treatment of patients and use of hospital resources. *N Engl J Med* 1998; 338:141-146.
8. McDonald GP, Pendarvis DP, Wilmoth R, Daley BJ: Influence of preoperative computed tomography on patients undergoing appendectomy. *Am Surg* 2001; 67:1017-1021.
9. Brenner DJ, Hall EJ: Computed tomography—an increasing source of radiation exposure. *N Engl J Med* 2007; 357:227-284.
10. Pauker SG, Kassirer JP: The threshold approach to medical decision-making. *N Engl J Med* 1980; 302:1109.
11. Bender JS: Approach to the acute abdomen. *Med Clin North Am* 1989; 73:1413.
12. Graff LG, Radford MJ, Werne C: Probability of appendicitis before and after observation. *Ann Emerg Med* 1991; 20:503.
13. Thomson HJ, Jones PF: Active observation in acute abdominal pain. *Am J Surg* 1986; 152:522.
14. Banaszak P: Clinical quality improvement in a multihospital system: The Voluntary Hospitals of America/Pennsylvania experience. *Am J Med Qual* 1993; 8:56.
15. Graff L, et al: False-negative and false-positive errors in abdominal pain evaluation: Failure to diagnose acute appendicitis and unnecessary surgery. *Acad Emerg Med* 2000; 7:1244.
16. Maisel AS, et al: Impact of age, race, and sex on the ability of B-type natriuretic peptide to aid in the emergency diagnosis of heart failure: Results from the Breathing Not Properly (BNP) multinational study. *Am Heart J* 2004; 147:1078-1084.
17. Ahn JS, et al: Development of a point-of-care assay system for high-sensitivity C-reactive protein in whole blood. *Clin Chim Acta* 2003; 332:51-59.
18. Legnani C, et al: A new rapid bedside assay for quantitative testing of D-Dimer (Cardiac D-Dimer) in the diagnostic work-up for deep vein thrombosis. *Thromb Res* 2003; 111:149-153.
19. Kline JA, et al: Diagnostic accuracy of a bedside D-dimer assay and alveolar dead-space measurement for rapid exclusion of pulmonary embolism: A multicenter study. *JAMA* 2001; 285:761-768.
20. Quick G, Eisenberg P: Bedside measurement of D-dimer in the identification of bacteremia in the emergency department. *J Emerg Med* 2000; 19:217-223.
21. Knudsen CW, et al: Diagnostic value of a rapid test for B-type natriuretic peptide in patients presenting with acute dyspnea: Effect of age and gender. *Eur J Heart Fail* 2004; 6:55-62.
22. Storrow AB, Gibler WB: The role of cardiac markers in the emergency department. *Clin Chim Acta* 1999; 284:187-196.
23. Blomkalns AL, Gibler WB: Markers and the initial triage and treatment of patients with chest pain. *Cardiovasc Toxicol* 2001; 1:111-115.
24. McQueen MB, Holder K, El-Maraghi NRH: Assessment of the accuracy of serial electrocardiograms in the diagnosis of myocardial infarction. *Am Heart J* 1983; 105:258.
25. Lee TH, et al: Evaluation of creatine kinase and creatine kinase MB for diagnosing myocardial infarction: Clinical impact in the emergency room. *Arch Intern Med* 1987; 147:115.
26. Pope JH, et al: Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med* 2000; 342:1163-1170.
27. Karcz A, et al: Massachusetts emergency medicine closed malpractice claims: 1988-1990. *Ann Emerg Med* 1993; 22:553.
28. Goodacre S, Dixon S: Is a chest pain observation unit likely to be cost effective at my hospital? Extrapolation from a randomized controlled trial. *Emerg Med J* 2005; 22:418.
29. Collinson PO, et al: Comparison of biomarker strategies for rapid rule out of myocardial infarction in the emergency department using ACC/ESC diagnostic criteria. *Ann Clin Biochem* 2006; 43(Pt 4):273-280.
30. Jayes RL Jr, et al: Do patients' coronary risk factor reports predict acute cardiac ischemia in the emergency department? A multicenter study. *J Clin Epidemiol* 1992; 45:621.
31. Brush JE Jr, et al: Use of the initial electrocardiogram to predict in-hospital complications of acute myocardial infarction. *N Engl J Med* 1985; 312:1137.
32. Goldman L, et al: A computer derived protocol to predict myocardial infarction in emergency department patients with acute chest pain. *N Engl J Med* 1988; 318:797.
33. Selker HP, et al: Use of the acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI) to assist with triage of patients with chest pain or other symptoms suggestive of acute cardiac ischemia: A multicenter, controlled trial. *Ann Intern Med* 1998; 129:845.
34. Decker WW, et al: Continuous 12-lead electrocardiographic monitoring in an emergency department chest pain unit: An assessment of potential clinical effect. *Ann Emerg Med* 2003; 41:342.
35. Mark DB, et al: Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med* 1991; 325:849.
36. Gomez MA, et al: An emergency department based protocol for rapidly ruling out myocardial ischemia reduces hospital time and expense: Results of a randomized study (ROMIO). *J Am Coll Cardiol* 1996; 28:25.
37. Farkouh ME, et al: A clinical trial of a chest-pain observation unit for patients with unstable angina. *N Engl J Med* 1998; 339:1882.
38. Roberts RR, et al: Costs of an emergency department–based accelerated diagnostic protocol vs hospitalization in patients with chest pain: A randomized controlled trial. *JAMA* 1997; 278:1670-1676.
39. Goodacre S, et al: Randomised controlled trial and economic evaluation of a chest pain observation unit compared with routine care. *BMJ* 2004; 328:254.
40. Hirsh J: Heparin. *N Engl J Med* 1991; 324:1565.
41. Burke DT: Prevention of deep venous thrombosis: Overview of available therapy options for rehabilitation patients. *Am J Phys Med Rehabil* 2000; 79(Suppl):S3-S8.
42. Merli GJ: Prophylaxis for deep venous thrombosis and pulmonary embolism in the surgical patient. *Clin Cornerstone* 2000; 2:15-28.
43. Gotway MB, et al: Imaging evaluation of suspected pulmonary embolism. *Curr Probl Diagn Radiol* 1999; 28:129.
44. American College of Emergency Physicians (ACEP) Clinical Policies Committee; ACEP Clinical Policies Subcommittee on Suspected Lower-Extremity Deep Venous Thrombosis: Clinical policy: Critical issues in the evaluation and management of adult patients presenting with suspected lower-extremity deep venous thrombosis. *Ann Emerg Med* 2003; 42:124.
45. Koopman MM, et al: Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. The Tasman Study Group. *N Engl J Med* 1996; 334:682.
46. Cogo A, et al: Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein thrombosis: Prospective cohort study. *BMJ* 1998; 316:17.
47. Heijboer H, et al: A comparison of real-time compression ultrasonography with impedance plethysmography for the diagnosis of deep-vein thrombosis in symptomatic outpatients. *N Engl J Med* 1993; 329:1365.
48. Yavorski RT, et al: Analysis of 3294 cases of upper gastrointestinal bleeding in military medical facilities. *Am J Gastroenterol* 1995; 92:231.
49. Fleisher D: Etiology and prevalence of severe persistent upper gastrointestinal bleeding. *Gastroenterology* 1983; 84:538.
50. Rockall TA, et al: Risk assessment after acute upper gastrointestinal haemorrhage. *Gut* 1996; 38:316.
51. Bordley DR, et al: Early clinical signs identify low risk patients with acute upper gastrointestinal hemorrhage. *JAMA* 1985; 253:3282.
52. Longstreth GF, Feitelberg SP: Successful outpatient management of acute upper gastrointestinal hemorrhage: Use of practice guidelines in a large patient series. *Gastrointest Endosc* 1998; 47:219.
53. Day SC, et al: Evaluation and outcome of emergency room patients with transient loss of consciousness. *Am J Med* 1982; 73:15.
54. Graff LG, et al: Correlation of the Agency for Health Care Policy and Research congestive heart failure admission guideline with mortality: Peer Review Organization Voluntary Hospital Association Initiative to Decrease Events (PROVIDE) for congestive heart failure. *Ann Emerg Med* 1999; 34:429.
55. Linzer M, et al: Diagnosing syncope: Part 1. Value of history, physical examination, and electrocardiography. Clinical efficacy assessment project of the American College of Physicians. *Ann Intern Med* 1997; 126:989.

www.ketabpezeshki.com 66485457-66963820

56. Junaid A, Dubinsky IL: Establishing an approach to syncope in the emergency department. *J Emerg Med* 1997; 15:593.
57. Quinn JV, Stiell IG, McDermott DA, Kohn MA, Wells GA: The San Francisco Syncope Rule vs physician judgment and decision making. *Am J Emerg Med* 2005; 23:782-786.
58. Bass E, et al: The duration of Holter monitoring in patients with syncope: Is 24 hours enough? *Arch Intern Med* 1990; 150:1073.
59. Martin TP, Hanusa BH, Kapoor WN: Risk stratification of patients with syncope. *Ann Emerg Med* 1997; 29:459.
60. Quinn JV, et al: Derivation of the San Francisco Syncope Rule to predict patients with short-term serious outcomes. *Ann Emerg Med* 2004; 43:224-232.
61. Thiruganasambandamoorthy V, et al: External validation of the San Francisco Syncope Rule in the Canadian setting. *Ann Emerg Med* 2010; 55:464-472.
62. Reed MJ, et al: The ROSE (risk stratification of syncope in the emergency department) study. *J Am Coll Cardiol* 2010; 55:713-721.
63. Costantino G, et al: Short- and long-term prognosis of syncope, risk factors, and role of hospital admission: Results from the STePS (Short-Term Prognosis of Syncope) study. *J Am Coll Cardiol* 2008; 51:276-283.
64. Ungar A, et al: Early and late outcome of treated patients referred for syncope to emergency department: The EGSYS 2 follow-up study. *Eur Heart J* 2010; 31:2021-2026.
65. Dipaola F, et al: San Francisco Syncope Rule, Osservatorio Epidemiologico sulla Sincope nel Lazio risk score, and clinical judgment in the assessment of short-term outcome of syncope. *Am J Emerg Med* 2010; 28:432-439.
66. Serrano LA, et al: Accuracy and quality of clinical decision rules for syncope in the emergency department: A systematic review and meta-analysis. *Ann Emerg Med* 2010; 56:362-373.e1.
67. Cunningham R, Mikhail MG: Management of patients with syncope and cardiac arrhythmias in an emergency department observation unit. *Emerg Med Clin North Am* 2001; 19:1051.
68. Silverstein MD, et al: Patients with syncope admitted to medical intensive care units. *JAMA* 1982; 248:1185.
69. American Heart Association: *Heart Disease and Stroke Statistics—2005*. Dallas: American Heart Association National Center; 2005.
70. Johnston SC, et al: Short term prognosis after emergency department diagnosis of TIA. *JAMA* 2000; 284:2901.
71. Johnston SC: Clinical practice: Transient ischemic attack. *N Engl J Med* 2002; 347:1687.
72. Ross MA, et al: An emergency department diagnostic protocol for patients with transient ischemic attack: A randomized clinical trial. *Ann Emerg Med* 2007; 50:109.
73. North Central Regional Trauma Advisory Council: *National Trauma Statistics*. Available at www.ncrtac-wi.org/index.php?id=30,0,0,1,0,0. Accessed 2007.
74. Conrad L, et al: The role of an emergency department observation unit in the management of trauma patients. *J Emerg Med* 1985; 2:325.
75. Davis JJ, Cohn I Jr, Nance FC: Diagnosis and management of blunt abdominal trauma. *Ann Surg* 1976; 183:672.
76. Janzen DL, et al: Diagnostic accuracy of helical CT for detection of blunt bowel and mesenteric injuries. *Clin Radiol* 1998; 53:193.
77. Stengel D, et al: Association between compliance with methodological standards of diagnostic research and reported test accuracy: Meta-analysis of focused assessment of US for trauma. *Radiology* 2005; 236:102.
78. Livingston DH, et al: Admission or observation is not necessary after a negative abdominal computed tomographic scan in patients with suspected blunt abdominal trauma: Results of a prospective, multiinstitutional trial. *J Trauma* 1998; 44:273.
79. Henneman PL, et al: Diagnostic peritoneal lavage: Accuracy in predicting necessary laparotomy following blunt and penetrating trauma. *J Trauma* 1990; 39:1345.
80. Chiu WC, Shanmuganathan K, Mirvis SE, Scalea TM: Determining the need for laparotomy in penetrating torso trauma: A prospective study using triple-contrast enhanced abdominopelvic computed tomography. *J Trauma* 2001; 51:860.
81. Zantut LF, et al: Diagnostic and therapeutic laparoscopy for penetrating abdominal trauma: A multicenter experience. *J Trauma* 1997; 42:825.
82. Udobi KF, Rodriguez A, Chiu WC, Scalea TM: Role of ultrasonography in penetrating abdominal trauma: A prospective clinical study. *J Trauma* 2001; 50:475.
83. Rosemurgy AS, et al: Abdominal stab wound protocol: Prospective study documents applicability for widespread use. *Am Surg* 1995; 61:112.
84. Moss RL, Musemeche CA: Clinical judgment is superior to diagnostic tests in the management of pediatric small bowel injury. *J Pediatr Surg* 1996; 31:1178.
85. van Wijngaarden MH, Karmy-Jones R, Talwar MK, Simonetti V: Blunt cardiac injury: A 10 year institutional review. *Injury* 1997; 28:51.
86. Wiener Y, Achildiev B, Karni T, Halevi A: Echocardiogram in sternal fracture. *Am J Emerg Med* 2001; 19:403.
87. Foil MB, et al: The asymptomatic patient with suspected myocardial contusion. *Am J Surg* 1990; 160:638.
88. Maenza RL, Seaberg D, D'Amico F: A meta-analysis of blunt cardiac trauma: Ending myocardial confusion. *Am J Emerg Med* 1996; 14:237.
89. Collins JN, et al: The usefulness of serum troponin levels in evaluating cardiac injury. *Am Surg* 2001; 67:821.
90. Ammons MA, Moore EE, Rosen P: Role of the observation unit in the management of thoracic trauma. *J Emerg Med* 1986; 4:279.
91. Kerr TM, et al: Prospective trial of the six hour rule in stab wounds of the chest. *Surg Gynecol Obstet* 1989; 169:223.
92. Ordog GJ, Wasserberger J, Balasubramanium S, Shoemaker W: Asymptomatic stab wounds of the chest. *J Trauma* 1994; 36:680.
93. Aaland MO, Bryan FC 3rd, Sherman R: Two-dimensional echocardiogram in hemodynamically stable victims of penetrating precordial trauma. *Am Surg* 1994; 60:412.
94. Mandal AK, Sanusi M: Penetrating chest wounds: 24 years of experience. *World J Surg* 2001; 25:1145.
95. Plummer D, et al: Emergency department echocardiography improves outcome in penetrating cardiac injury. *Ann Emerg Med* 1992; 21:709.
96. Nawar EW, Niska RW, Xu J: National Hospital Ambulatory Medical Care Survey: 2005 emergency department summary. *Adv Data* 2007; 386:1-32.
97. National Heart, Lung, and Blood Institute, National Asthma Education Programme: *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, Md: National Institutes of Health; 1997. National Institutes of Health Publication No. 97-4051.
98. Emerman CL, et al; Multicenter Asthma Research Collaboration investigators: Prospective multicenter study of relapse following treatment for acute asthma among adults presenting to the emergency department. *Chest* 1999; 115:919.
99. Gouin S, Patel H: Utilization analysis of an observation unit for children with asthma. *Pediatr Emerg Care* 1999; 15:79.
100. Rydman RJ, et al: Emergency Department Observation Unit versus hospital inpatient care for a chronic asthmatic population: A randomized trial of health status outcome and cost. *Med Care* 1998; 36:599-609.
101. McConnochie KM, et al: How commonly are children hospitalised for asthma eligible for care in alternative settings? *Arch Pediatr Adolesc Med* 1999; 153:49.
102. Kannel WB, et al: Epidemiological features of chronic atrial fibrillation. *N Engl J Med* 1982; 306:1018.
103. Feinberg WM, et al: Prevalence, age distribution, and gender of patients with atrial fibrillation: Analysis and implications. *Arch Intern Med* 1995; 155:469.
104. Mulcahy B, et al: New onset atrial fibrillation: When is admission medically justified? *Acad Emerg Med* 1996; 3:114.
105. Koenig BO, Ross MA, Jackson RE: An emergency department observation unit protocol for acute-onset atrial fibrillation is feasible. *Ann Emerg Med* 2002; 39:374.
106. Decker WW, et al: A prospective randomized clinical trial in an emergency department observation unit with acute atrial fibrillation. *Ann Emerg Med* 2008; 52:322-328.
107. Danias PG, et al: Likelihood of spontaneous conversion of atrial fibrillation to sinus rhythm. *J Am Coll Cardiol* 1998; 31:588.
108. Howard PA: Ibutilide: An antiarrhythmic agent for the treatment of atrial fibrillation or flutter. *Ann Pharmacother* 1999; 33:38.
109. Amin NB, et al: Sinus bradycardia and multiple episodes of sinus arrest following administration of ibutilide. *Heart* 1998; 79:628.
110. Weigner MJ, et al: Risk for clinical thromboembolism associated with conversion to sinus rhythm in patients with atrial fibrillation lasting less than 48 hours. *Ann Intern Med* 1997; 126:615.
111. Kannel WB, Ho K, Thom J: Changing epidemiological features of cardiac failure. *Br Heart J* 1994; 72:S3.
112. Storrow AB, et al: Emergency department observation of heart failure: Preliminary analysis of safety and cost. *Congest Heart Fail* 2005; 11:68.
113. Graff L, et al: Correlation of the Agency for Health Care Policy and Research congestive heart failure admission guideline with mortality: Peer Review Organization Voluntary Hospital Association Initiative to Decrease Events (PROVIDE) for congestive heart failure. *Ann Emerg Med* 1999; 34:429.

www.ketabpezeshki.com 66485457-66963820

114. Peacock WF, et al: Heart failure observation units: Optimizing care. *Ann Emerg Med* 2006; 47:418.
115. Maisel AS, et al: Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002; 347:161.
116. Peacock WF: The B-type natriuretic peptide assay: A rapid test for heart failure. *Cleve Clin J Med* 2002; 69:243.
117. Vinson JM, et al: Early readmission of elderly patients with congestive heart failure. *J Am Geriatr Soc* 1990; 38:1290.
118. Collins SP, et al: Cost-effectiveness analysis of ED decision making in patients with non–high-risk heart failure. *Am J Emerg Med* 2009; 27:293-302.
119. Peacock WF, et al: Effective observation unit treatment of decompensated heart failure. *Congest Heart Fail* 2002; 8:68-73.
120. Gordon JA, et al: Initial emergency department diagnosis and return visits: Risk versus perception. *Ann Emerg Med* 1998; 32:569.
121. Garibaldi RA: Epidemiology of community-acquired respiratory tract infections in adults: Incidence, etiology, and impact. *Am J Med* 1985; 78:32.
122. Yealy DM, et al: Effect of increasing the intensity of implementing pneumonia guidelines: A randomized, controlled trial. *Ann Intern Med* 2005; 143:881.
123. McMahon LF Jr, Wolfe RA, Tedeschi PJ: Variation in hospital admissions among small areas: A comparison of Maine and Michigan. *Med Care* 1989; 27:623.
124. Marie TJ, et al: A controlled trial of a critical pathway for treatment of community-acquired pneumonia. CAPITAL Study Investigators. Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin. *JAMA* 2000; 283:749.
125. Roberts R: Management of patients with infectious diseases in an emergency department observation unit. *Emerg Med Clin North Am* 2001; 19:187.
126. Elkharrat D, et al: Relevance in the emergency department of a decisional algorithm for outpatient care of women with acute pyelonephritis. *Eur J Emerg Med* 1999; 6:15.

www.ketabpezeshki.com 66485457-66963820

Chapter 196

Emergency Ultrasound

Vivek S. Tayal

PERSPECTIVE AND DEFINITIONS

Emergency ultrasound (US) is the simultaneous performance and interpretation of a focused sonographic examination at the bedside of the patient for the diagnosis, resuscitation, monitoring, guidance, and treatment of emergency medical conditions.[1,2]

Emergency US is an emergency clinician–performed study.[1,3] Although the operator is typically an emergency physician, he or she may be an emergency physician assistant, nurse practitioner, or trained emergency nurse or paramedic—all under the supervision of a trained, credentialed emergency physician.[4-6] Emergency physicians who have advanced training in US imaging are also known as emergency sonologists.[6] Emergency US is typically performed in the emergency department (ED) but may also be performed in other areas of the hospital, emergency stand-alone centers, out-of-hospital mobile transport (such as ambulances and helicopters), disaster scenes, military engagements, international rescue work, and remote settings (such as space, sea, or land centers with limited or no medical access).[7-13]

With emergency US, the physician or clinician (1) performs, (2) simultaneously interprets the examination, and (3) integrates the results in the clinical scenario.[1,5] This is unlike other specialties, in which a trained technologist performs the examination and a physician interprets or "reads" the images.[5,14]

Emergency US examinations are focused examinations of an area of the body, organ system, or physiologic pattern or goal-directed investigations of an emergency symptom or sign. Not all pathologic processes will be detected by such examinations, usually because of the interference of acoustic entities that reduce transmission and reflection of sound and the lack of an appropriate window to the tissue of choice. Other limitations include experience, skill, and confidence of the performing physician.[15] The main risk management issue associated with emergency US is not using the modality when it is available and appropriate.[16]

HISTORY

A half-century of scientific work in many countries produced the initial medical uses of US in the 1950s by physicians interested in its advantages over traditional imaging, including noninvasiveness, lack of ionizing radiation, and superior resolution.[14] In the 1980s emergency physicians started to use US as a way of ruling out emergent "silent" diagnoses, such as ectopic pregnancy, intraperitoneal hemorrhage, hemopericardium, cholelithiasis, renal colic, and aortic aneurysm. A model curriculum was created by the Society for Academic Emergency Medicine (SAEM) that initiated formal guidance for emergency US programs.[17,18] Because of resistance from traditional imaging specialties, such as radiology and cardiology, the American Medical Association House of Delegates, led by the American College of Emergency Physicians (ACEP), passed a resolution that hospital credentialing committees follow specialty-specific guidelines for US-based credentialing.[19]

Specialty-specific guidelines, created in 2001 and updated in 2008 by the ACEP and endorsed by the SAEM in 2010, specify emergency US scope of practice, primary applications, training pathways, number of procedures required for training before credentialing, quality assurance and documentation guidance, and training course outlines.[1] Today, more than 95% of emergency medicine residencies teach US, and approximately 30 to 60% of community hospitals have instituted bedside US performed by emergency physicians.[20,21]

Since 2008, emergency US has been recognized by outside organizations, including the American Institute of Ultrasound in Medicine, with implementation of the focused assessment with sonography for trauma (FAST) examination, and the American Society of Echocardiography, with application of focused cardiac US (FOCUS) for shock, effusion, chest pain, and cardiac arrest.[22,23] Several other organizations have recognized emergency or point-of-care US, including the World Interactive Network Focused on Critical Ultrasound internationally and the Society of Medical Ultrasound in Medical Education for medical education.

US programs typically require some investment in education and hardware, but reimbursement for both professional and hospital fees is adequate to meet return on investment within years, depending on number and types of US, payer mix, and documentation.[24] More EDs have recently invested in digital-based archiving and storage systems. The more traditional solution is the picture archiving and communication system. A new, more comprehensive solution seems to be the web-based US management systems, which provide archiving, documentation, quality assurance, and credential solutions to the emergency medicine and point-of-care market.

TRAINING, CREDENTIALING, AND ACCREDITATION

Emergency US is one of the competency assessments required of emergency medicine residents by the Residency Review Committee for Emergency Medicine, with defined requirements as set by national organizations.[25-27] For emergency physicians in practice, initial training often takes place through nationally defined hands-on continuing medical education courses followed by a period of proctoring or supervision.[1,28] Credentialing at the hospital level is based on specialty-specific national guidelines. Recent educational advances, such as simulation, task trainers, and web-based training, enhance US training.[29-32] US is not defined as advanced imaging by the Centers for Medicare and Medicaid

www.ketabpezeshki.com 66485457-66963820

Services or the 2008 Medicare Improvements for Patients and Providers Act.[33]

Medical student emergency US education has also been defined by national organizations and may be incorporated in more extensive undergraduate US programs.[1] US fellowships have become the most prevalent postgraduate emergency medicine fellowship.[34] See the website of the American College of Emergency Physicians (http://www.acep.org/Clinical–Practice-Management/Ultrasound/; accessed April 12, 2013) for helpful references for program development and education.

APPLIED ULTRASOUND PHYSICS AND INSTRUMENTATION

By definition, US is sound with frequencies higher than 20,000 Hz. US is kinetic energy, a longitudinal, mechanical, and directional wave, so all users of this technology should observe the ALARA (as low as reasonably achievable) principle by performing procedures only when they are needed and limiting the time of sonographic investigation.[35]

US waves are characterized by their amplitude (deflection from a baseline), wavelength (the wave cycle distance, usually measured in microns), and frequency (the number of cycles per second). Modern diagnostic US transducers emit at millions of cycles per second or megahertz. Lower frequencies penetrate deeper tissue at the expense of resolution, whereas higher frequencies improve resolution but cannot penetrate deeper structures.

M-mode or motion mode displays received waves over both time and distance and is used to calculate rates, speeds, and distances by sending a steered one-dimensional line across tissue. The most familiar display is *B-mode* or brightness mode, which graphs the amplitude of reflected US waves as shades of gray from black to white on a monitor screen. As sound hits reflective interfaces, it returns to the transducer at higher amplitudes than waves that continue through tissue. In addition, sound can be attenuated, refracted, and reverberated away from the transducer. These reflections or lack thereof create a brightness graph that is depicted in two planes, creating the two-dimensional image. One can adjust the brightness of the image by changing the overall gain or by changing the amount of gain at certain depths, which is called *time-gain compensation* (TGC). This allows a more discrete amplification of sound at different levels. By increasing overall gain or amplification and TGC at different levels, one can adjust for the loss of returning information.

US resolution can be described as axial, in the long axis of the transducer, or lateral, perpendicular to the long axis of the transducer. Typically, higher probe frequencies produce higher axial resolution. The focus of the transducer is the image area where the US beam produces the best lateral resolution. The area from the probe to the focus is called the near field, and that from the focus to the end of the image is called the far field. The best imaging with maximum reduction in artifacts occurs at the focus.

Focal zones can be increased for more resolution, but frame rate (the speed at which the screen updates the image) will decrease, causing a slow-motion image that is poor for imaging of moving tissues. One can also change from a sector transducer (a curved abdominal or phased array transducer) to a linear transducer for better lateral resolution on the edges of the transducer.

Some machines allow the adjustment of *dynamic range,* which is the ratio of initial intensity and final intensity of returning echoes. Adjustment of dynamic range allows more contrast (e.g., echocardiography) or more gray scale (e.g., soft tissue). Harmonics is another technology that listens for multiples of the frequency sent out and often cleans up images near the screen, such as in the gallbladder, apex of the heart, or soft tissue of skin.

Doppler US shows the velocity of moving structures, typically red blood cells, thus representing flow. *Color flow Doppler* shows direction (by red or blue colors representing flow in opposite directions) and velocity of flow (by degrees of brightness of the color, where lighter is higher velocity). Power Doppler or power angiography is also a representation of velocity of flow, but it describes only the presence of flow and not direction.

Box 196-1 Common Definitions

Window: soft tissue where transducer is placed to interrogate tissue in the body
Anechoic: without sounds (black)
Echogenic: with sounds (white)
Hyperechoic: with more reflected sounds than adjacent tissue (more echogenic)
Hypoechoic: with less sound than adjacent tissue (less echogenic)
Shadowing: sound blocked by a reflective barrier
Enhancement: more echogenicity due to increased velocity of sound, typically behind a fluid-filled structure, such as the bladder or gallbladder
Reverberation: an artifact that results from multiple reflections at a given interface, often in parallel
Mirror image: a propagation speed artifact that repeats images that are beyond a strong reflector (e.g., diaphragm), creating a mirror image
Lateral cystic shadowing: a refraction artifact seen on the edge of cystic structures, causing an artificial shadow
Beam width artifact: a volume-averaging artifact causing artifactual echoes in the inferior aspect of anechoic structures or spaces

Gray scale US has the best resolution when the direction of the probe and the sound waves are perpendicular to the object because the sound is reflected up to the transducer. Doppler US has the best resolution with the probe parallel to or less than 60 degrees from the direction of blood flow. This often means realignment by tilting of the probe to create better imaging based on the mode of US.

Other US terms and artifacts commonly used are listed in Box 196-1.

EQUIPMENT AND SAFETY

A variety of US machines are available, including palm size, laptop, cart based, and combination devices. US machines have controls for gain, depth, and freeze and have print or acquire image controls. Additional controls include TGC, frame rate, measurement, dynamic range, M-mode, power Doppler, color directional Doppler, spectral Doppler, patient identification, transducer selection, and image review. Images are produced in digital stills, digital video clips, thermal paper stills, or DVD or video recordings.

Modern multifrequency probes can select among several US frequencies to maximize either tissue penetration or image quality, depending on the application. Probe design and footprints (the actual transducer surface area touching the patient) can be divided into three categories: flat linear array probes, curved linear array probes, and phased array probes. *Flat linear probes* give a square or rectangular picture with excellent lateral resolution at the expense of width of field. *Curved linear array probes,* which give a wider field of view at the expense of lateral resolution, are usually used for deep tissue penetration applications, such as evaluation for pregnancy or abdominal aortic aneurysm. The *endocavitary probe* is a highly curved linear array probe that is most commonly used for endovaginal evaluation. *Phased array probes* offer a smaller footprint than curved linear array probes and were originally developed for cardiac evaluations, but they can also be used for abdominal studies. They offer excellent image quality for the evaluation of moving structures but with worse resolution of

www.ketabpezeshki.com 66485457-66963820

static structures. Transesophageal echocardiographic, three-dimensional, and biplanar probes are recently being used in emergency US, creating new imaging venues.

US biosafety, including use of the ALARA principle, appropriate Doppler technology, and appropriate microbiologic disinfection of the probe, has been reinforced by recent articles.[36] The ALARA principle suggests that the least amount of energy be used to produce satisfactory imaging. Doppler modes should be minimized over sensitive tissue, including early gestation, germinal tissue, and mucosal or neural tissue. The sonographer should be familiar with the thermal index (TI), which should be kept below 2.0, and the mechanical index (MI), which should be kept below 1.9. Surface probes should be cleaned at the bedside with mechanical removal of the gels and debris and then disinfected with an appropriate spray or wipe. Endocavitary probes will need more prolonged and substantial cleaning. Safety also includes the use of appropriate barriers over transducers, including condoms, gloves, or commercial barriers over endocavitary probes and sterile transducer covers for sterile procedures.[37] For nonsterile procedures, barriers can include translucent sterile transdermal barriers.

APPLICATIONS AND CATEGORIZATION

In 1994 the SAEM categorized US applications broadly into abdominal, cardiac, obstetric-gynecologic, and special applications.[17] In 2001 the ACEP developed guidelines that categorized applications more specifically to include trauma, pregnancy, abdominal aortic aneurysm, cardiac (for pericardial effusion and cardiac activity), biliary, renal, and procedural guidance.[38] In 2008 the ACEP added deep venous thrombosis (DVT), thoracic studies for pneumothorax and pleural effusion, soft tissue and musculoskeletal studies, and ocular examination as core appplications.[1] Advanced applications at that time included testicular, adnexal, bowel, advanced echocardiography, transesophageal echocardiography, transcranial Doppler, and contrast studies. Therapeutic applications of transcranial Doppler are being studied by emergency physicians.[39] Grouping of these US applications into categories of resuscitative, diagnostic, symptom or sign based, procedural guidance, and monitoring and therapeutic helps describe the relationship between the uses of US in emergency medicine (Table 196-1).

The most common uses of emergency US in decreasing order are trauma, cardiac (cardiac arrest and pericardial effusion), abdominal aortic aneurysm, pelvic, biliary, procedural, renal, and DVT.[21] Among recent emergency medicine residency graduates, US use was high (98%), with those in academic centers reporting highest use.

US guidance can assist many percutaneous procedures, such as vascular access, torso cavities evacuation (e.g., thoracentesis, paracentesis, and pericardiocentesis), arthrocentesis, lumbar puncture, abscess drainage, nerve blocks, and others.[3] Emergency US is used in clinical pathways or algorithms to identify or to exclude emergency medical conditions rapidly.[40,41]

Trauma Ultrasound

The trauma US examination is also called the focused assessment with sonography for trauma (FAST) examination.[1,22,42] The trauma examination originally focused on the peritoneal space, as an evaluation for hemoperitoneum, with use of the right flank, left flank, and pelvic windows for detection of dependent peritoneal fluid and pleural effusion.[43] Newer versions include the EFAST (extended FAST) for the evaluation of potential pneumothorax and FASTER for evaluation of the extremities.[40,44-46]

The FAST examination is based on the premise that a treating physician can sample known sonographic windows within minutes to evaluate the peritoneal, pericardial, and pleural spaces for fluid and abnormal fluid and air. Within the peritoneum, fluid circulates throughout the abdomen and pelvis and settles in dependent spaces.[47,48] The volume of fluid required for a positive US study depends on the site of injury and site of sonographic detection, but 250 mL or more is generally visible, and nearly 600 mL of fluid is necessary to cause a positive flank stripe when fluid is infused from the pelvis.[49]

Pericardial fluid is contained within the parietal and visceral pericardium. Once a certain volume is reached, the pressure in the pericardial space increases exponentially, causing pericardial tamponade.[50] In general, 50 mL is required to cause hemodynamic compromise in a patient without prior pericardial inflammation. However, tears in the pericardium that communicate with the pleural space or even the peritoneum can cause false-negative examination findings.

Pleural fluid can be detected by US, but this depends on the position of the body.[51] Pneumothorax detection is based on the absence of the normal sonographic sliding of the visceral and parietal pleurae, although there are other signs (see thoracic section).

The torso trauma US examination (often called the EFAST) can detect pathologic free intraperitoneal fluid (typically hemoperitoneum, uroperitoneum, bile, or ascites), hemopericardium, hemothorax, or pneumothorax.[45,46] Typically, fluid in the peritoneum, pericardium, and pleural cavity is anechoic, but it can have echogenicity with clotting, depending on the age of the clot or bowel contents. Compared with other fluid-filled structures in the abdomen and pelvis, peritoneal free fluid generally has sharp edges and an irregular shape, whereas most visceral or vascular structures have intrinsically smooth oval contours and less abrupt edge detail.

The FAST technique uses a low- to middle-frequency probe (2-5 MHz) to evaluate dependent peritoneal spaces, pleural spaces,

Table 196-1 Classification of Emergency Ultrasound Applications

RESUSCITATIVE	DIAGNOSTIC	SYMPTOM OR SIGN BASED	PROCEDURAL GUIDANCE	MONITORING AND THERAPEUTIC
Cardiac Trauma Abdominal aorta Pregnancy Thoracic Procedural	Cardiac FAST Pregnancy Abdominal aortic aneurysm Biliary Urinary tract Deep venous thrombosis Soft tissue and musculoskeletal Thoracic Ocular Advanced uses New uses	Hypotension Dyspnea Chest pain Abdominal pain Extremity pain	Any emergency medicine procedure	Central vein size Fluid collections Cardiac contractility Fetal heart rate Low-frequency clot dissolution

www.ketabpezeshki.com 66485457-66963820

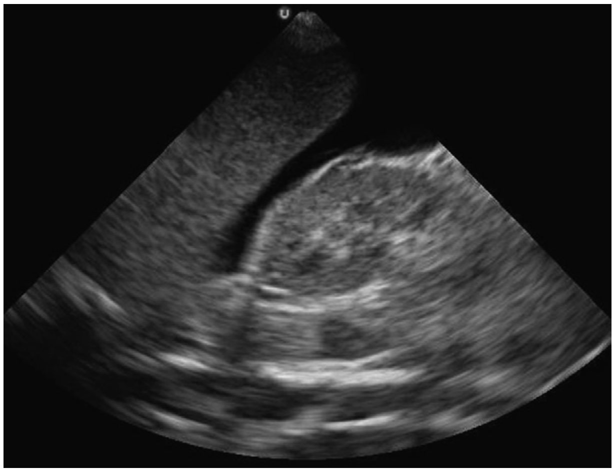


Figure 196-1. Free fluid in the peritoneum in Morison's pouch seen from right flank.

and the pericardium. Within the peritoneum, dependent spaces include the following, grouped by tissue window: the right flank, which evaluates the hepatorenal space (also called Morison's pouch; Fig. 196-1), the right subphrenic space, and the right costophrenic angle; the left flank, which evaluates the perisplenic space between the diaphragm and spleen, the splenorenal space, the perirenal space, and the left subphrenic space; and the suprapubic view, which is performed by placement of the transducer superior to the pubic bone with a full bladder to visualize the pouch of Douglas in women and the retrovesical space in men. Extra views include the paracolic gutters inferior from the flank views and medial from the iliac spine to visualize free fluid surrounding the bowel.[52]

The typical cardiac views include the transverse subcostal images, which visualize the four cardiac chambers and pericardial space, and the sagittal subcostal view to assess the pericardial space and the collapsibility and diameter of the inferior vena cava (IVC), indicating right-sided heart pressures. A good alternative in patients with long chest walls or obesity is the parasternal view, which assesses the anterior and posterior pericardial spaces.

For pleural fluid, the superiorly angled flank views allow visualization of the costophrenic angles. The evaluation for pneumothorax uses either a low-frequency probe at a shallow depth or, more typically, a high-frequency probe for better resolution, placed at the anterior chest in the second intercostal space for anterior pneumothorax and at the axilla for large pneumothoraces and pleural effusion. Diaphragm injuries have been described with dislocation of typical organ patterns.[53]

The sensitivity of the FAST examination ranges from 60 to 99%, and its specificity ranges from 80 to 99%.[54-57] The large range of sensitivity is related to the comparative "gold standard" used for each study, with clinical endpoints suggesting higher accuracy. The FAST does not capture every peritoneal injury, although the need for intervention in undetected injuries has not been studied.[58] Randomized, controlled trials show lower morbidity, time to operating room, and charges for patients with US use during resuscitation, and a positive US study increases the odds ratio for laparotomy.[59,60]

Patients with traumatic pericardial effusions are taken to the operating room sooner and have lower mortality rates with US.[44] However, the mediastinal injuries more common in blunt trauma have not been assessed without transesophageal echocardiography.[50,61] US can diagnose pneumothorax with excellent sensitivity and specificity compared with plain chest radiography

Figure 196-2. Intrauterine pregnancy with fetus on endovaginal scanning.

and variable accuracy compared with computed tomography scanning.[62,63]

There are certain populations of patients in whom FAST evaluation has limited benefit. With penetrating chest injuries, the FAST examination seems to be efficacious for both pericardial and nearby peritoneal injuries; but in patients with purely anterior penetrating trauma to the abdomen, the sensitivity of trauma US is poor because bowel injuries can occur without significant hemoperitoneum.[58,59,64-66]

The accuracy of the FAST examination may be lower in children than in adults, and many pediatric injuries can be observed or treated nonoperatively with angiography.[67] In obstetric patients, the few observational studies that have been performed have shown reasonable sensitivity and specificity, although abruption and fetal viability may necessitate an earlier operative course.[68]

With pelvic fractures, the sensitivity ranges from 20 to 80%.[69-72] More important, the detection of free fluid in an unstable patient with a pelvic fracture may be due to uroperitoneum from bladder injury rather than hemoperitoneum from vascular injury, clouding the decision for laparotomy versus pelvic embolization.[64] In addition, retroperitoneal injuries to the genitourinary tract are not assessed with four-quadrant FAST examination.

Pelvic Ultrasound

Pelvic US by emergency physicians was initiated to address one of the epidemics of the modern era—ectopic pregnancy.[73-77] Typically, pelvic US is used to confirm intrauterine pregnancy, which indirectly excludes ectopic pregnancy in most patients.[78,79] A recent meta-analysis revealed a pooled sensitivity of 99.3% to rule out ectopic pregnancy when an intrauterine pregnancy was detected. Another use during pregnancy is the detection of fetal viability, incomplete abortion, ectopic pregnancy, and molar pregnancy. Pelvic US is used in nonpregnancy states to detect tubo-ovarian abscesses, masses, and hemoperitoneum in the hemodynamically unstable patient.[80]

Indications for sonographic evaluation of the first-trimester pregnant patient include symptoms or signs that suggest an ectopic pregnancy, molar pregnancy, or fetal demise and dating of the pregnancy. Intrauterine pregnancy is confirmed with a gestational sac with a yolk sac or fetal pole within the fundus of the uterus (Fig. 196-2).[78] An embryonic or fetal demise has US findings of a fetal pole measuring more than 5 mm without fetal heart rate or a gestational sac of more than 20 mm in diameter without a fetal pole. A molar pregnancy appears as an echogenic, cystic uterus with disorganized echoes and is associated with high β-human chorionic gonadotropin concentrations without the sonographic finding of intrauterine pregnancy. Findings of an ectopic

www.ketabpezeshki.com 66485457-66963820

pregnancy include a chorionic ring or gestational sac with evidence of a yolk sac or fetal pole outside the uterus or in an abnormal location in the uterus, such as the cornu or cervix.[73] Excluding the groups of intrauterine pregnancy, embryonic demise, molar pregnancy, and ectopic pregnancy, there is a class called indeterminate, which may account for 20% of pregnant patients presenting to the ED in the first and early second trimesters. Heterotopic pregnancies can occur at a rate of 1/5000 and be detected by the same techniques and definitions.[81]

Pelvic US is performed by transabdominal or endovaginal techniques. The transabdominal technique uses a low-frequency transabdominal transducer placed over the lower abdomen suprapubically. Ideally, the patient has a full bladder, which provides a sonographic window, but this may not be necessary if the uterus is large or the patient is thin. Advantages of the transabdominal technique include wider field of view, detection of large pelvic masses, and greater depth of field. In the endovaginal technique, the transducer is placed in the vagina, optimally with an empty bladder to visualize the same structures. Endovaginal transducers are high frequency, providing excellent axial resolution but poor penetration of distant structures. Early intrauterine yolk sacs and fetal poles within gestational sacs may be detected more clearly, and ectopic pregnancies can be identified with more accuracy. Endovaginal US can detect small (7 mL) amounts of peritoneal fluid. Endovaginal US in the hemodynamically compromised patient has replaced culdocentesis for detection of ruptured ectopic pregnancy.

Emergency physician–performed pelvic US has reduced the morbidity of ectopic pregnancy by shortening the time to diagnosis and operating room treatment and has resulted in greater initial detection of abnormal pregnancy, reduced ED patient throughput times, and increased patient satisfaction with care.[74,76,82-85] The detection of live intrauterine pregnancy predicts a rate of 91% continuation past 20 weeks, except for those with vaginal bleeding, who drop to a rate of 86%.[86] Further continuation of the pregnancy to term occurs in 77% of patients.[87] Emergency physicians can date pregnancies accurately by pelvic US with typical fetal biometry.[88]

Emergency physicians are adept at identification of ectopic pregnancies by both transabdominal and endovaginal techniques.[85,89-93] In addition, molar pregnancies and some malformation, such as conjoint twins, have been described.[94,95] The gynecologic differential diagnosis of significant free fluid in a pregnant woman, in addition to ectopic pregnancy, should include uterine rupture and ruptured corpus luteum pregnancy.[96] Pelvic US in nonpregnancy states has shown good accuracy for tubo-ovarian abscess and improved decision-making for female patients with right lower abdominal pain.[97,98]

Cardiac Ultrasound

The use of cardiac US by emergency physicians is presentation and symptom specific and focused in nature. Indications include cardiac arrest, possible pericardial effusion, trauma, chest pain, hypotension, and procedural guidance.[1,3,23,99] Cardiac US is often included in algorithms and protocols for certain symptoms or signs, such as dyspnea or hypotension.

Cardiac US is performed through the transthoracic and transabdominal windows with use of small curvilinear or phased array transducers. Typical views include the subcostal four-chamber and long-axis views, parasternal long-axis view, parasternal short-axis view, and apical four-chamber view. Although most emergency physicians are comfortable with the subcostal view from the FAST examination, the parasternal long-axis view is a good alternative and good window for left ventricular assessment.[100,101] In addition, the apical four-chamber view provides excellent comparison of the right and left ventricles in terms of size and function. The long-axis subcostal view shows some of the right side of the heart but highlights the IVC, including size and respiratory variation.

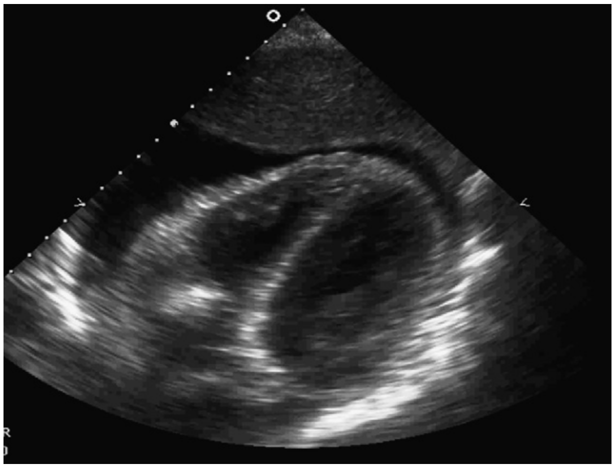


Figure 196-3. Pericardial effusion in subcostal view.

Cardiac US performed by emergency physicians shows good accuracy in detection of pericardial effusion (Fig. 196-3), assessment of left ventricular function, and evaluation of patients with undifferentiated shock. In addition, aspects of cardiac US are being used for the assessment of intravascular volume status and cardiac output and in the evaluation of dyspnea.

In cardiac arrest, US can detect ventricular motion in both asystole and pulseless electrical activity (PEA).[102,103] In asystole, two studies have shown poor prognosis in the absence of sonographic ventricular activity.[84] Cardiac US can detect pseudoasystole by revealing ventricular fibrillation or coordinated cardiac contractions without a palpable pulse.[85,104] Use of cardiac US in PEA and near-PEA states can be diagnostic for pericardial effusion.[82] Cardiac US can detect ventricular capture when the patient is paced, transcutaneously or by a transvenous pacer. US can also identify pneumothorax, another treatable cause of cardiac arrest.[103] Cardiac US is feasible during pulse checks and prehospital life support, as advanced cardiac life support guidelines suggest minimizing non–cardiopulmonary resuscitation intervals.[105-108]

Emergency cardiac US is diagnostic for both medical and traumatic pericardial effusions.[109,110] In patients with dyspnea, pericardial effusion is detected with excellent accuracy.[111] In trauma, use of cardiac US reduces time to operative intervention and reduces mortality in patients with penetrating cardiac injury.[50] Detection of effusions in blunt trauma has also been described. Patients with cardiac US performed by emergency physicians for pericardial effusion have significantly reduced hospital length of stay and charges.[112]

Cardiac US is used for detection of pericardial effusions, chamber enlargement, and global activity in chest pain syndromes.[113] In chest pain, US has been studied for the evaluation of pericardial tamponade, pulmonary embolus, cardiogenic shock, aortic dissection, pneumothorax, and bony chest wall fracture.[114-116]

US protocols have been developed to evaluate undifferentiated hypotension.[41,117-119] Cardiac US windows with the addition of abdominal views can assess for effusion, global ventricular activity, ventricular chamber size, IVC size and respiratory change, peritoneal fluid, and abdominal aortic aneurysm to narrow the differential diagnosis. Sepsis is the most common diagnosis for patients with hyperdynamic ventricular activity.[120]

Central pressures can be estimated by examination of the IVC size and collapsibility.[121,122] Studies show that this technique has good accuracy in assessment of blood loss, hypovolemia, and congestive heart failure.[123,124] Correlation studies have shown

www.ketabpezeshki.com 66485457-66963820

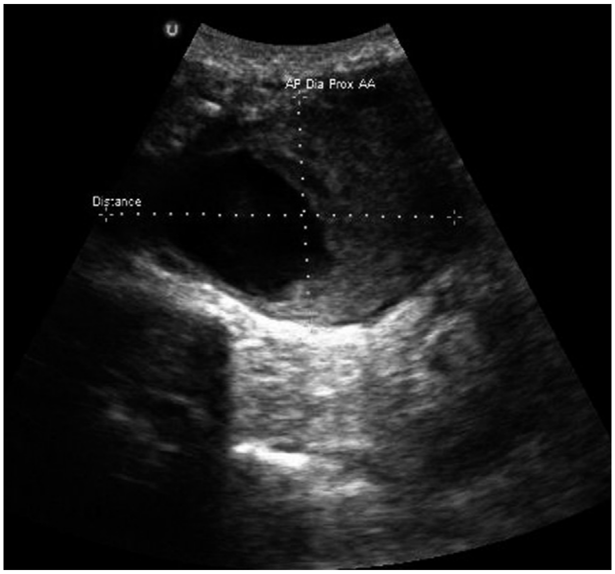


Figure 196-4. Large abdominal aortic aneurysm with echogenic intraluminal clot.

moderate agreement between central venous pressure and IVC measurements, with actual cardiac qualitative assessment as good as or better than the IVC measurements.[125-129] The internal jugular vein measurement may correlate with central venous pressure,[130] and esophageal Doppler examination may also correlate with hemodynamic measurements.[131]

Cardiac US is also a procedural guide for placement of transvenous pacer wires and for pericardiocentesis. Transvenous pacer wires are often placed through central veins, and it can be difficult to place them into the right ventricular apex. US facilitates placement by imaging of the wires in real time as they pass through the tricuspid valve and approach the apex of the right ventricle. US can also document ventricular capture. The probe is placed in the subxiphoid space for both applications.

Abdominal Vascular Ultrasound

Emergency physicians use abdominal US to detect abdominal aortic aneurysm, another silent disease in patients with flank, abdominal, or back pain, and to evaluate unexplained hypotension in the older patient.[132,133] The use of US to detect aortic dissection and occlusion is described as well.[134-136]

The technique involves imaging of the aorta from the subxiphoid space to the umbilicus to evaluate for dilation above a diameter of 3 cm (Fig. 196-4). For the detection of infrarenal aneurysms, the technique should visualize the aorta from the diaphragm to the aortic bifurcation. Fusiform aneurysms are more common, but detection of saccular aneurysms requires both the transverse and longitudinal planes.[137] If an aneurysm is found, a peritoneal view of Morison's pouch is performed to detect intraperitoneal fluid. Proximal iliac arteries may be followed if it is technically feasible or time allows.

Emergency physician use of US for abdominal aortic aneurysm detection has shown good accuracy compared with other imaging modalities and laparotomy.[133,138-140] It also has management implications in older patients with lower back pain, in whom the elimination of the presence of abdominal aortic aneurysm can lead to other management decisions. Screening for abdominal aortic aneurysm in the ED with US has been shown to be effective.[141,142]

Endovascular repair versus the more traditional open repair has become more popular.[143,144] The detection of leaks (often called endoleaks) from the stent would require Doppler imaging and may require further imaging with computed tomography or magnetic resonance imaging.[144]

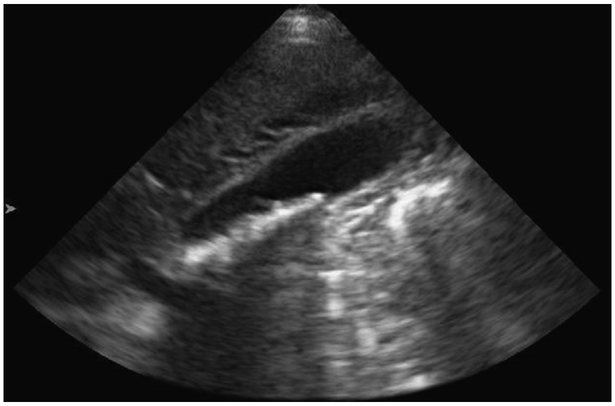


Figure 196-5. Echogenic layering gallstones seen in gallbladder with posterior shadowing.

Aortic dissection may be detected by a combination of abdominal and cardiac scanning.[136] A linear echogenic flap, anywhere across the lumen of the aorta, is suggestive of dissection, sometimes with the detection of different flows on either side of the flap by color Doppler scanning. The cardiac US examination can show unexplained pericardial effusion; a dilated aortic root; aortic insufficiency; and a linear echogenic flap seen in the ascending aorta, aortic arch (through a suprasternal notch), or descending aorta.

Aortic occlusion is another condition that may be detected by US.[145] Echogenic thrombus may fill the aorta and disrupt perfusion below the diaphragm with resulting pain, pallor, numbness, and reduction or absence of distal pulses. Clear identification of the borders and lack of Doppler flow in the abdominal aorta are characteristic of the syndrome.

Biliary Ultrasound

Biliary US to detect gallstones and associated cholecystitis was one of the early applications of US in emergency medicine.[146-148] The sonographic technique involves a modified biplanar approach to the right upper quadrant. A complete evaluation includes visualization of the common bile duct. The diagnosis of cholelithiasis is made after identification of echogenic foci within the gallbladder lumen with shadowing (Fig. 196-5). Other image patterns include stones that will not shadow, sludge, and the wall echo sign of a gallbladder full of gallstones. Signs of cholecystitis include a dilated gallbladder, increased gallbladder wall thickness, sonographic Murphy's sign, and pericholecystic fluid. A nonmobile stone in the gallbladder neck is highly suggestive of eventual cholecystitis.[149] A common bile duct larger than 6 mm in people younger than 60 years and smaller than 10 mm in elders may indicate choledocholithiasis. Biliary US is fast and accurate, with a sensitivity of 87 to 94% and a specificity of 82 to 96% in detection of gallstones, comparable to radiology ultrasonography.[150-153] Biliary US has replaced nuclear medicine testing.[148,154]

Urinary Tract Ultrasound

Renal or urinary tract US can detect hydronephrosis or urinary retention. The lack of ionizing radiation and the rapidity of renal US make it an attractive option for the investigation of unexplained flank, back, or groin pain or abdominal mass.

Renal US includes biplanar views of the kidneys with emphasis on dilation of the calyceal system and pelvis of the respective

www.ketabpezeshki.com 66485457-66963820

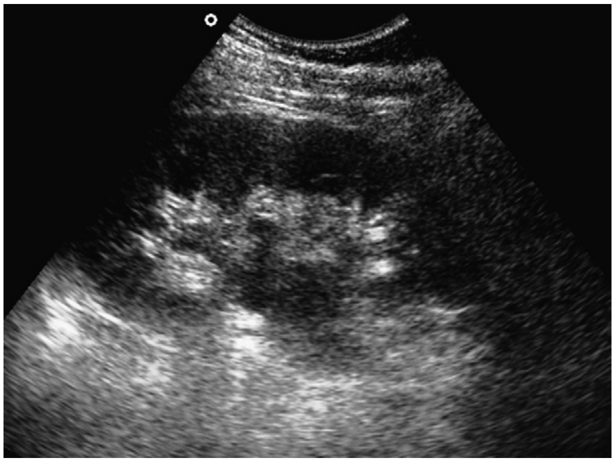


Figure 196-6. Hydronephrosis in renal pelvis and calyces.

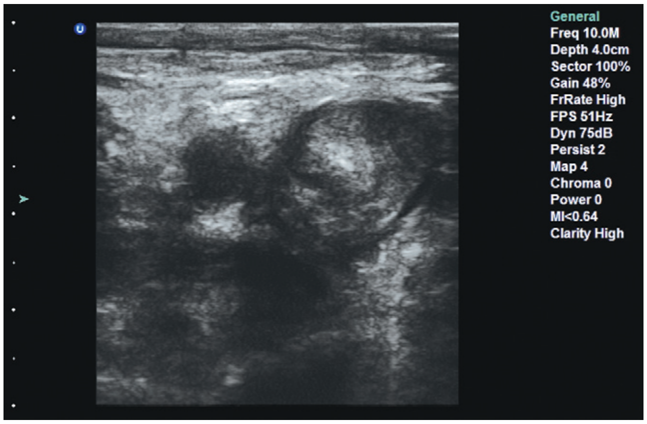


Figure 196-7. Deep venous thrombosis with layering clot in popliteal vein seen on compression ultrasound examination.

kidney (Fig. 196-6). In addition, visualization of the bladder can diagnose secondary hydronephrosis from an obstructed bladder stone and may demonstrate nonobstructive bladder jets through the use of Doppler US. The windows for the two kidneys are similar to those of the trauma flank series, with the exception that the patient may be rolled on the opposite side so that the transducer may be placed more posteriorly on the back if necessary. The bladder view is performed suprapubically, and calculations of volume may be made with on-machine calculators or by formulas.

Renal US has a sensitivity of 83% and a specificity of 92% in detection of hydronephrosis (see Fig. 196-6).[155,156] Genitourinary tract obstruction protocols have great sensitivity in elimination of renal obstruction from a differential diagnosis.[157] Bladder US is useful for detection of a full bladder and the presence of a Foley catheter and for guidance during suprapubic aspiration or Foley placement.[119-124,158-160]

Deep Venous Thrombosis Ultrasound

The swollen extremity often requires sonographic imaging to assess for DVT. Emergency physicians commonly use compression US to rule out DVT.[125-128,161-165] The two-level compression technique involves visualization of the compressibility of the common femoral and popliteal veins. The three-level technique adds the junction of the superficial femoral and deep femoral veins (Fig. 196-7). Use of upper extremity veins is less common because Doppler US is needed for the subclavian vein, which is not compressible under the clavicle.[166]

The accuracy of this technique ranges from 70 to 99%, depending on operator experience.[164,167-169] Hospital charges and time in the ED are reduced for patients who have bedside venous US performed to rule out DVT.[170-172]

Bernardi also investigated a whole-leg strategy versus a 2-point strategy in combination with a D-dimer test, which required 1-week follow-up with an abnormal level.[173] Both strategies were equivalent in detection of symptomatic DVT at 3-month follow-up. Depending on the skill of the sonographer, patient characteristics, and availability of follow-up, ED US may guide lower extremity DVT institutional protocols.

Thoracic and Tracheal Ultrasound

Thoracic applications include the detection of pleural effusion, pneumothorax, pneumonia, and interstitial edema.[174,175] The technique of thoracic US uses a low-frequency probe to survey for pleural effusions and a high-frequency probe to detect pleural

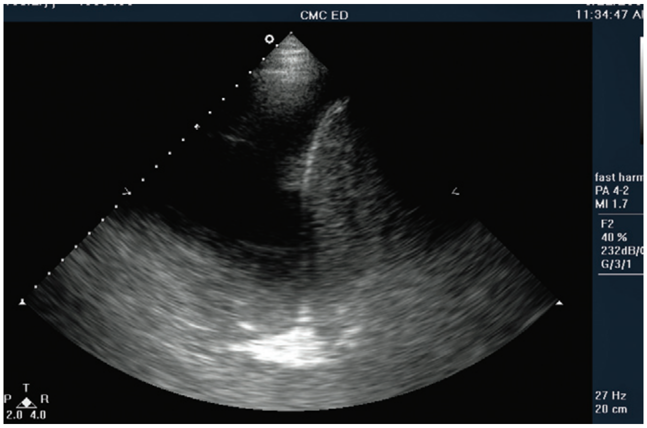


Figure 196-8. Large pleural effusion.

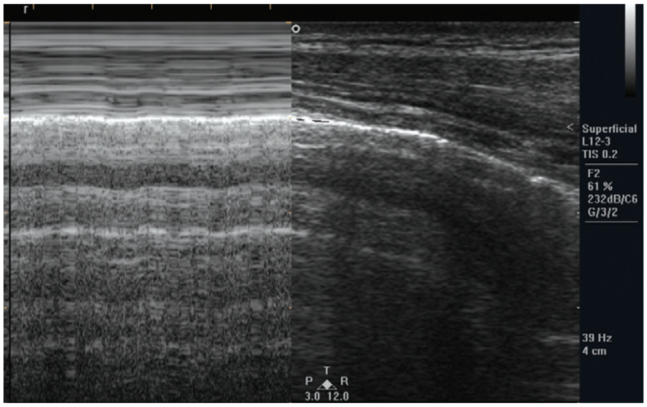


Figure 196-9. M-mode image of normal lung sliding.

lines and related artifacts. Pleural fluid appears as an anechoic collection above the diaphragm (Fig. 196-8). In addition, a collapsed lung may be visualized as an echogenic floating structure. Normally, the parietal and visceral pleural lines slide against each other, and lack of sliding is the finding most consistent with pneumothorax (on M-mode, called the seashore sign). Additional findings of pneumothorax include the presence of horizontal artifacts called A-lines (on M-mode, called the stratosphere sign) and the absence of B-lines (vertical white lines from reverberation of air with fluid) at the parietal-visceral pleural line (Fig. 196-9).[176-179]

www.ketabpezeshki.com 66485457-66963820

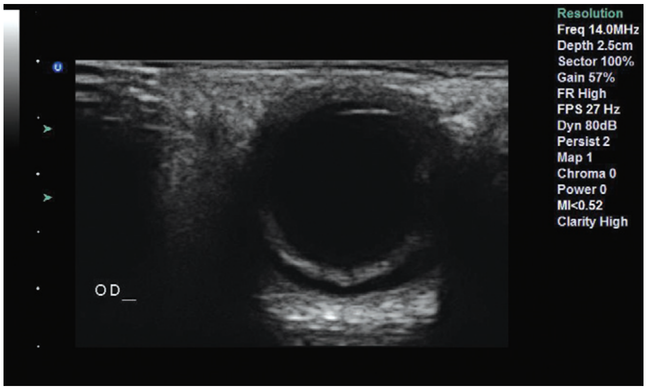


Figure 196-10. Retinal detachment.

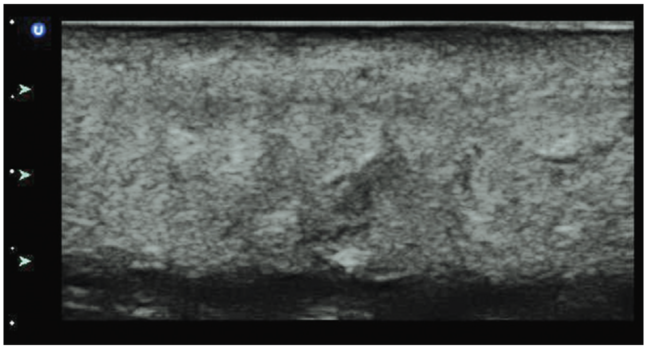


Figure 196-11. Sonographic cellulitis with echogenic subcutaneous tissue.

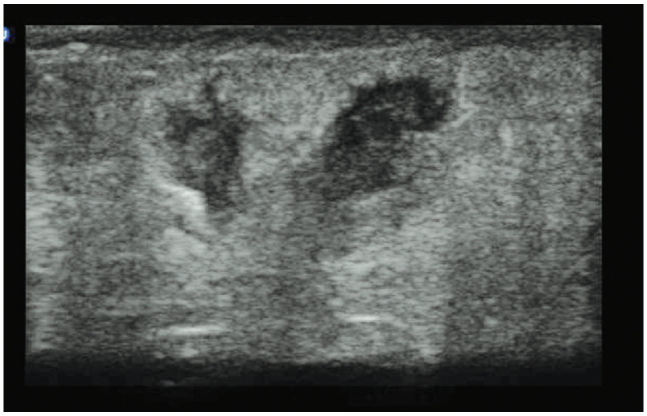


Figure 196-12. Sonographic subcutaneous abscess.

Confounding factors include adhesions of the pleura, chronic obstructive pulmonary disease, prior pneumothorax, and mainstem bronchus intubation. A lung point sign is the edge of the pneumothorax where the lung is still adherent to the parietal pleura, and part of the image shows no sliding until the lung moves into the interspace with respirations.[177] The accuracy of US for detection of pneumothorax (sensitivity 100%, specificity 98%) is better than that of plain chest radiography in the acute setting, but there may be reduced accuracy after 24 hours.[180]

Severe pneumonia is visualized as echogenic "liver-like" echogenicity as the lung accumulates fluid with consolidation.[181] Peripneumonic collections are common and may indicate inflammation. The dynamic air bronchogram, hyperechoic areas within bronchi that move with respiration, usually within "heparinized" lung, has been described as another sign of alveolar consolidation.[182]

Pulmonary edema is indicated by the presence of comet tails (B-lines), which are reverberation artifacts that reflect from the parietal pleural interface into the lung. Normally found in dependent areas of the lung, the widespread distribution of these artifacts in an apical lung may indicate increased lung congestion.[183-185]

Dynamic tracheal US for the confirmation of endotracheal intubation has relatively good sensitivity and specificity.[186-188] The dynamic movement of the endotracheal tube creates a flutter through the recognized shadow of the airway, but static US seems to lack accuracy.[189,190] This technique may have a role in patients in cardiac arrest or with equivocal end-tidal carbon dioxide levels, and confirmation is significantly faster than with chest radiography in children.[190]

Ocular Ultrasound

The eye is an excellent acoustic window, and short-duration gray scale US over a closed eyelid can visualize both the anterior and the posterior chamber well.[191,192] The globe, pupillary size, and extraocular movements can be examined even with facial swelling.[193,194] Ocular US has been described for intraocular disease, such as retinal detachment (Fig. 196-10), retinal hemorrhage, vitreal hemorrhage , intraocular foreign body, dislocated lens, and retro-orbital hemorrhage.[191,192,195,196] The sensitivity of ocular US for retinal detachment by emergency physicians is 100%, and the specificity is 83 to 92%.[197,198] In addition, the optic nerve sheath diameter can be measured behind the eye, reflecting intracranial pressure.[199-202] The sensitivity of such measurements ranges from 83% in children to 100% in adults.[199,203]

Soft Tissue Ultrasound

Except in the hand and foot, US in soft tissue is straightforward because of the lack of air and bone in the skin and subcutaneous tissue. Soft tissue US is used to differentiate cellulitis from abscess, to detect foreign bodies and hernias, and to evaluate other soft tissue pathologic processes, including masses, pseudoaneurysms, and glands.[204-208] A high-frequency linear transducer moves from normal skin to the abnormal area. Cellulitis or edema will cause an echogenic pattern with cobblestoning between fat lobules (Fig. 196-11). Abscesses are irregular hypoechoic to anechoic collections within the subcutaneous layer but may connect with the surface (Fig. 196-12). US is diagnostic in soft tissue disease for cellulitis, abscess, and necrotizing fasciitis.[150-153,209,210] In the ABSCESS study, clinical examination had a sensitivity of 86% and specificity of 70%, whereas US had a sensitivity of 98% and specificity of 88%.[205] In other studies, use of US changed management for half of adult patients and 22% of children with clinical cellulitis.[206,211] One study showed that incision and drainage is superior to US-guided aspiration in a cohort of patients with soft tissue infection in regard to resolution at 1 week (80% vs. 26%, respectively).[212]

US can differentiate peritonsillar abscess from cellulitis and can be used for guidance of peritonsillar aspiration.[213,214] It can also detect early Ludwig's angina with abscess, dental abscess, epiglottitis, glandular abnormalities, and pseudoaneurysm in soft tissues and fascia of the face.[207,208,215-217] US has also been used in various body areas, including the penis and scrotum, for signs of disruption or infection.[218,219]

Detection of foreign bodies is characterized by variable echogenicity in the tissue with shadowing beneath the foreign body. Metal foreign bodies, such as bullets and intrauterine devices, have characteristically high-reflective echogenicity and ring-down artifacts. Bedside US has variable accuracy for detection of foreign bodies in simulated cases but better accuracy in true clinical

www.ketabpezeshki.com 66485457-66963820

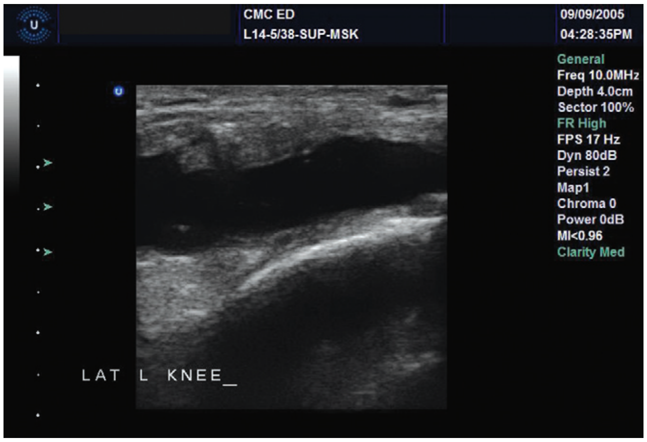


Figure 196-13. Knee joint effusion.

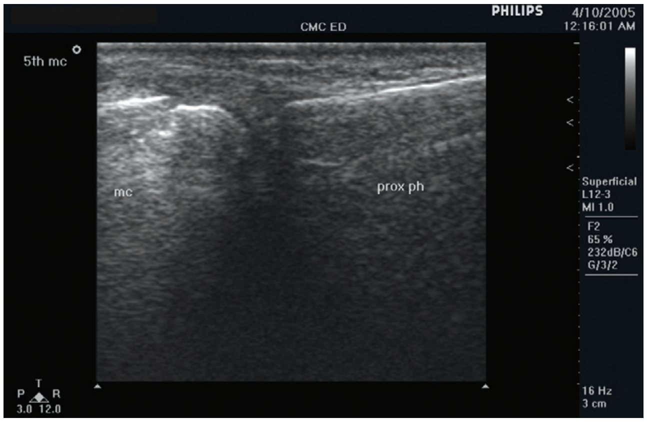


Figure 196-15. Metacarpal fracture.

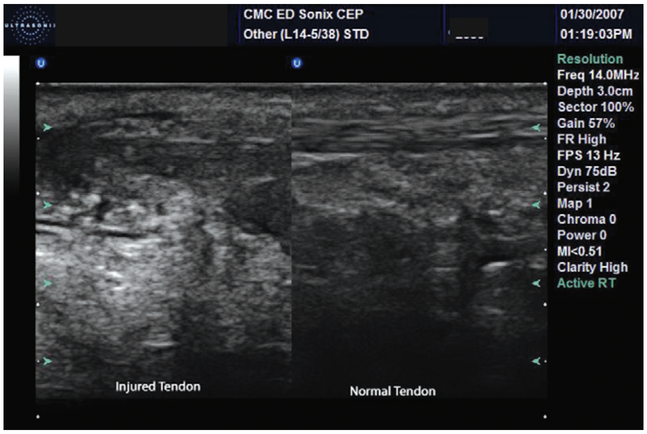


Figure 196-14. Achilles tendon disruption.

settings.[220-222] Use of a water bath may aid in the detection of superficial foreign bodies.[223]

Musculoskeletal Ultrasound

US has been particularly useful for joint effusion and muscle, tendon, and bone injury. US is excellent for detection of fluid in joints, confirmation of effusions, and guidance of drainage procedures.[29,160,161,224-230] Joint effusions typically are anechoic or echogenic, depending on type and age (Fig. 196-13). Arthrocentesis of both the adult and pediatric hip, in addition to other joints, has been reported with good success.[229,231,232]

Diagnosis of ligamentous injuries and muscle avulsion and hemorrhage has also been reported.[224,233] Muscle and tendon abnormalities are detected by anechoic and heterogeneous abnormalities (Fig. 196-14). Detection is often assisted by movement of the limb. Tendons and their anisotropic longitudinal fibrils can be visualized near joints, with pathologic tears appearing as a discontinuity of the tendon. Muscles are hypoechoic with echogenic borders. Tears and hemorrhage are interruptions of this normal pattern.[224,234,235] Water bath techniques provide a better acoustic window for shallow tissue, such as fingers.[236]

The characteristic reflection of bone with immediate shadowing is used to identify normal bone and its contour. Fractures are seen as a defect in the bony cortex.[46,224,237-240] The image of the cortex can be useful for guidance of fracture reduction.[241-243] Comparison with the contralateral side may also be helpful. Confirmation can be done by US imaging before and after reduction.[244]

US is accurate in the detection of fractures, joint effusions, bursitis, cysts, and hematomas.[140,229,231,245-247] Prospective evaluation of finger fractures demonstrates good accuracy[228] (Fig. 196-15). Other fractures studied include femur, sternal, rib, and forearm fractures.[224,237-240]

Transcranial Doppler Ultrasound

Transcranial Doppler US has been used for detection of abnormal flow patterns in the brain and for detection and treatment of middle cerebral artery strokes. An advanced procedure, typically using a phased array transducer over a bone or orbital window in the skull, color Doppler and spectral Doppler scanning is performed at different levels of intracranial vessels for detection of abnormal patterns.[39]

Testicular Ultrasound

Testicular scanning is an advanced US application that requires visualization of the normal and symptomatic testicle with a high-frequency probe. The testicular structures, including the normal homogeneity of the testicle, are evaluated, and Doppler scanning is performed for evaluation of normal venous and arterial flow (Fig. 196-16). Absent or decreased flow on the affected side indicates possible torsion, whereas increased flow indicates epididymitis. Experienced emergency physicians accurately diagnosed testicular pain with a sensitivity of 95% and specificity of 94% in a study of 36 patients, which included 3 patients with torsion.[248]

Abdominal Bowel Ultrasound

The use of bedside US for evaluation of appendicitis, diverticulitis, and other bowel disease is an area of increasing interest. There has been variable experience with the use of graded compression US to detect appendicitis (>6 mm), with reported sensitivity of 67% and specificity of 92% (Fig. 196-17).[249] Whereas there is considerable effort looking at the use of US first and then computed tomography for appendicitis, the accuracy of emergency physician–performed US for appendicitis has been equivocal.[249-251] In women, endovaginal US can be used to rule out adnexal disease.[98]

The use of US for diverticulitis, intussusception, volvulus, and small bowel obstruction has been reported.[252-254] Thickening of the bowel, dilated bowel with fluid-filled loops, and changes in

www.ketabpezeshki.com 66485457-66963820

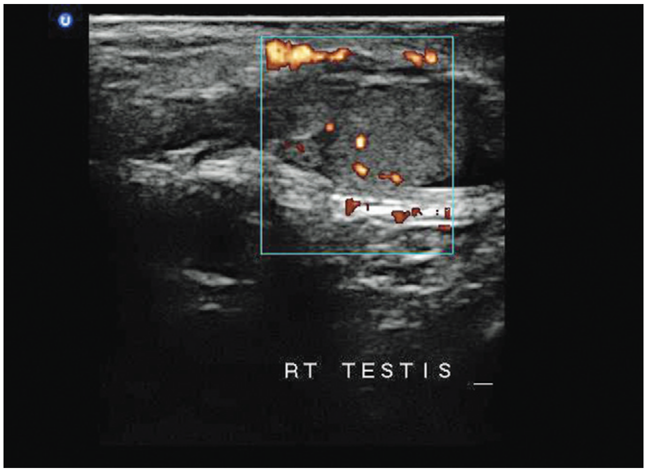


Figure 196-16. Testicular ultrasound examination with normal power Doppler.

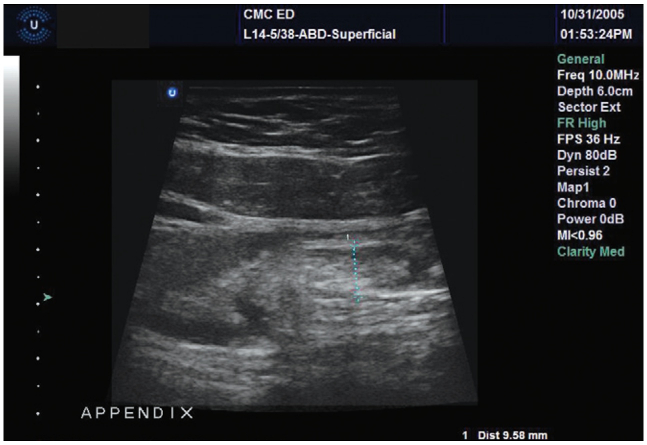


Figure 196-17. Image of noncompressible appendix compatible with appendicitis.

vascularity suggest disease. Tracing of the bowel to normality may also show cutoff points.

Hernias, described in the soft tissue section, may also be detected as masses in the ventral, inguinal, paramedian, femoral, and scrotal areas.[255] Free air, with comet tails and artifacts in areas that are usually normal, such as between the liver and diaphragm, may also be detected in patients with suspected perforated viscus.[256]

Ascites, similar to traumatic free fluid in the sonographic appearance, will be much more apparent with tremendous amounts of free anechoic fluid, small echogenic liver, and outlined organs. Small amounts of ascites may be the first clue to abnormal pathologic states.

Pediatric Emergency Ultrasound

The use of US for children in the ED has two paths, one that mirrors the applications that have been used for adults and a second exploring the more specific pediatric abdominal applications.[257] The use for patient management and accuracy can vary per application.

The FAST examination for evaluation of abdominal trauma in children is specific (98%), but the sensitivity is only 20%, making it difficult to use without further imaging or other testing.[67] In

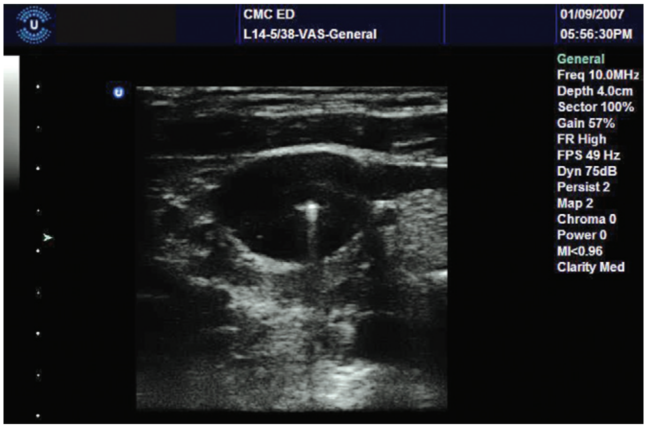


Figure 196-18. Transverse image of internal jugular vein for procedural guidance.

addition, specific pediatric abdominal applications that are common in the radiology suite have begun to be explored. Case reports and case series of intussusception, appendicitis, and pyloric stenosis have been reported.[251,252,258-260]

Ultrasound for Procedural Guidance

In 2001, in response to the Institute of Medicine report *To Err Is Human,* the Agency for Healthcare Research and Quality (AHRQ) sanctioned a report on actions that may improve patient safety.[261,262] The report contains a recommendation for US guidance for internal jugular central line insertion. Since then, the use of US for procedural guidance has expanded for many emergency procedures, especially vascular access, and is advocated for error reduction.[263]

Procedural guidance can be static or dynamic.[264] *Static guidance* suggests that US has been placed over the anatomic area, and the area is marked while angle and distance information is noted. *Dynamic guidance* describes procedures performed with real-time US visualization of the needle entering the anatomic area on the monitor as well as on the patient.

There are two common axis approaches to vein cannulation: transverse, in which the vein appears as a circular structure on the screen; and longitudinal, in which the vein appears as a tubular structure along the width of the screen. In the transverse approach (also known as out of plane), the probe's long axis is centered transverse (90 degrees) to the long axis of the anatomic area, guiding the needle to bisect the probe at its center, which gives centering and depth information (Fig. 196-18). In the longitudinal axis (also known as in-plane), the probe is placed along the long axis of the anatomic area, and the needle is introduced in the long axis of the probe, giving depth and trajectory information (Fig. 196-19). Whereas the short-axis approach is more popular with novices, the long-axis approach may be safer because of the visualization of the needle tip during the entire dynamic procedure.[150] Finally, an oblique axis has been described, essentially approaching the vessels at 45 degrees but visualizing the target vessels and surrounding structures.[265]

The most studied and most advocated use of US procedural guidance is for central line insertion.[266-269] Both the AHRQ and the National Institute for Health and Clinical Excellence have recommended US guidance for central line insertion.[262,270] US guidance for internal jugular central line insertion can be recommended as a safe and best practice.[271]

US permits the physician to assess the internal jugular for overlap with the carotid artery, vessel diameter, and presence of

www.ketabpezeshki.com 66485457-66963820

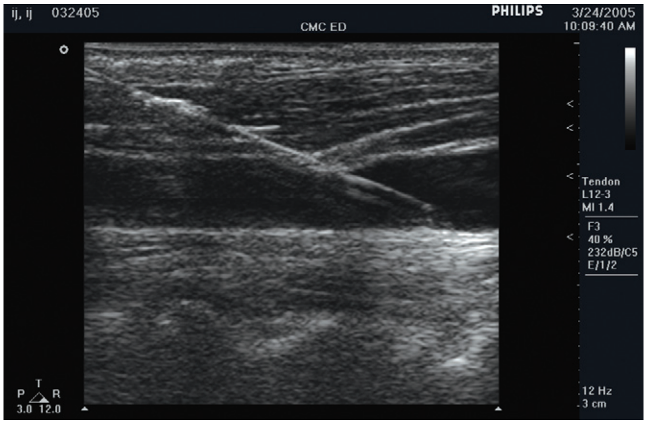


Figure 196-19. Longitudinal image of the needle in an internal jugular vein for procedural guidance.

luminal clot or vessel obliteration.[186] Internal jugular central line insertion has been studied in the ED, intensive care unit, and radiology suite. In the ED, US-guided internal jugular cannulation is associated with decreased time to flashback and improved success in the difficult-stick patient, improved overall success rate and first attempt and overall rates, reduced time to insertion, and reduced complication rate.[268,272,273] The Valsalva maneuver and Trendelenburg position may assist in increasing the size of the cross-sectional area.[274]

US does not prevent posterior vein wall penetration as reported in case reports and simulated models.[275,276] Adverse events (hematoma, arterial cannulation, pneumothorax, and unsuccessful placement) can occur in up to 20% of patients having US-guided internal jugular catheterization.[277-279]

Femoral vein insertion has been studied in cardiac arrest patients, and improved cannulation rate and reduced complications have been reported.[280] Several maneuvers can optimize the success rate of femoral vein cannulation, including the reverse Trendelenburg position and placement of the pressure on the iliac vein proximal to the femoral vein.[188,281,282]

US does not contribute to procedural success in subclavian vein cannulation because of the lack of a convenient window for the subclavian vein under the clavicle. Laterally, toward the junction of the axillary vein and subclavian veins, the vein can be visualized in the chest wall.[283,284] Although it may be cannulated there, the challenge is to insert the catheter through the pliable soft tissue of the anterior-superior chest.[191,284,285] The supraclavicular fossa is a window for central line insertion, and the subclavian and brachiocephalic veins may be imaged at this site.[192,286]

US-guided central access decreases complications and attempts but did not improve success rates in pediatric critical care patients.[287]

Emergency physicians are able to use US to insert peripheral intravenous catheters in patients with difficult access with high success rates.[193-195,288,289] Only one randomized study showed no differences in number of attempts, time to successful catheterization, or patient satisfaction.[290] Veins that are large in width (0.4 cm) or at moderate depth (0.3-1.5 cm) have a higher success rate.[291] Nurses and ED technicians have also been taught to use US for peripheral venous guidance.[292-294]

The use of one operator versus two operators has not been shown to increase success rates.[295] US can facilitate peripheral vascular access by the Seldinger technique.[296] Marking of the skin in its long axis while using the short axis has not increased success rates.[297] Pediatric US-guided intravenous catheter placement in difficult-access pediatric patients has been shown to be more successful than traditional techniques.[298,299] Arterial access, including

Table 196-2 Ultrasound-Guided Emergency Procedures

ULTRASOUND	PROCEDURE
Vascular access	Central venous access[182,210,211] Internal jugular vein Subclavian near axillary vein Subclavian with supraclavicular approach Femoral vein Peripheral vein[193,197,212] Basilic Brachial Cephalic Forearm veins Intraosseous needle[213] Arterial cannulation[198,214] Radial artery Arterial sampling[215]
Torso fluid collections	Paracentesis[216,217] Thoracentesis[218] Pericardiocentesis[219]
Cardiac	Pacer placement[220-223]
Musculoskeletal	Arthrocentesis[29,224,225] Hip Knee Other joints Fracture reduction Foreign body removal[226] Tendon sheath injection[227]
Soft tissue	Abscess drainage[228] Hernia reduction[229]
Anesthesia	Interscalene Peripheral nerves Axillary[192] Femoral nerve[230] Hematoma block
Airway	Endotracheal tube placement[231-234]
Urinary bladder	Suprapubic aspiration and cystostomy[235-237] Foley guidance[238]
Neurologic	Lumbar puncture[239-243]

radial artery aspiration and cannulation, is more successful with US guidance.[300,301] US has confirmed intravascular location with a combination of B-mode and Doppler mode, in which the needle, guidewire, and catheter can be located by US.[302-304]

Sonographic confirmation of intraosseous placement has also been described with detection of Doppler flow outside the bone and inside the marrow.[305,306] Numerous other procedures using US guidance have been described in emergency practice (Table 196-2).

Torso Drainage Procedures

US can facilitate procedures such as paracentesis, thoracentesis, and pericardiocentesis. It confirms the presence of abnormal fluid, amount, and relative location with anatomic and sonographic windows. It can also locate anatomic structures that may be in the way or define structures for location of the space.

Paracentesis, including US-guided diagnostic peritoneal lavage, has been described. Static or dynamic guidance may assist this procedure by identifying the deepest location of ascitic fluid and obstructing bowel loops (Fig. 196-20). Thoracentesis is assisted by definition of the diaphragm as the most inferior anatomic landmark to avoid solid organ injury. In the left thorax, potential cardiac laceration may be avoided by the use of US. Routine use of sonography has been associated with a reduced rate of

www.ketabpezeshki.com 66485457-66963820

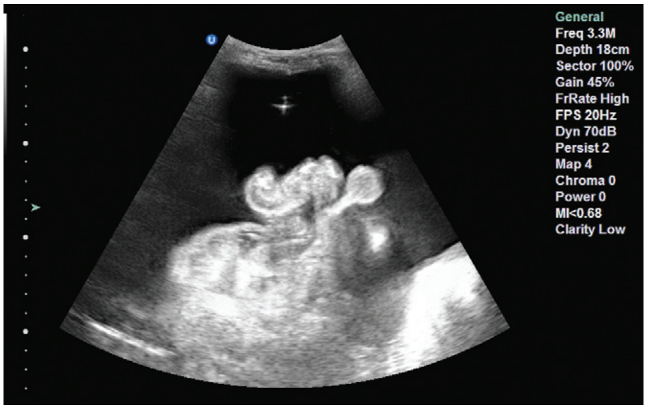


Figure 196-20. Needle entering peritoneum during paracentesis.

Figure 196-21. Needle entering joint space during arthrocentesis.

pneumothorax and tube thoracostomy.[307] Pericardiocentesis also can be facilitated by location of the best window (subcostal, apical, or parasternal long) and needle guidance into the pericardial space, lessening the likelihood of ventricular puncture.

Soft Tissue and Musculoskeletal Procedures

US-guided aspiration of abscesses has been described, but incision and drainage is more effective in treatment of cutaneous soft tissue infections.

Foreign bodies can be identified and removed with the guidance of US. Static guidance marks the location, depth, and size of the foreign body. Dynamic guidance requires an incision remote from the overlying skin to allow the probe to monitor the procedure.

Arthrocentesis and joint injection may be assisted by US to detect effusion, to identify joint landmarks, and to confirm the needle tip in the joint (Fig. 196-21). Use of US reduces the number of attempts and increases the overall success rate in non-knee joints but not in knee joints.[226,231,308] Sonographic needle guidance also improves performance and outcomes in intra-articular joint injections.[309]

US may assist hematoma aspiration and blocks by directing the needle into the site.[310] US-guided fracture reduction, especially in pediatric fractures, has been described with good results.

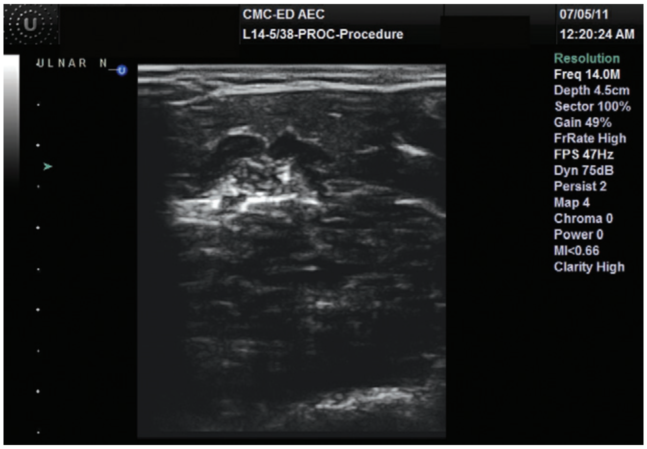


Figure 196-22. Sonographic ulnar nerve block.

Nerve Blocks

US-guided nerve blocks confirm needle placement around the nerve and allow anesthetic to be delivered at sites around the nerve, avoiding fascicular deposition (Fig. 196-22). Multiple US-guided nerve blocks have been described in both the emergency medicine and anesthesia literature, and it is clear that most percutaneous nerve blocks can be performed with assistance of US. US-guided femoral nerve blocks produce a more complete blockade than the landmark or fascial pop techniques.[311] In the setting of knee trauma, femoral nerve blocks appear to reduce pain more effectively than intravenous analgesics.[312,313]

Abdominal Procedures

In addition to paracentesis, described earlier, US-guided hernia reduction, suprapubic cystostomy, and gastrostomy tube placement have been described in the literature. Hernia reduction may be assisted with gentle, constant pressure over the hernia with the probe in the direction of opening through the peritoneum with resultant confirmation that the hernia has been reduced. Suprapubic aspiration and cystostomy are assisted by the detection of a full bladder with secondary guidance of the needle into the bladder for aspiration or removal. US has been touted in a pilot study to guide gastrostomy tube replacement with confirmation.[314]

Lumbar Puncture

Lumbar puncture can be assisted by US by the identification of the spinal processes for sonographic landmarks for placement of the needle in both the transverse and longitudinal plane, even in large patients.[315,316] In addition, foraminal location can be identified, allowing a paramedian approach to lumbar puncture.

Out-of-Hospital Ultrasound: Disasters and Remote Settings

US has been used in the out-of-hospital, military battlefield, disaster, and international medicine settings. The use of US has been described in European and other settings by physicians in the out-of-hospital arena, including ground, helicopter, air, and space,[9,317-323] and by paramedics for FAST and abdominal aorta examinations.[324]

The military forced development of small compact US machines and has been an extensive user of US in combat situations, including the frontline, combat support hospital, and tertiary hospital settings.[9,11,325] US has been used in the Armenian earthquake of

www.ketabpezeshki.com 66485457-66963820

1988, the Haitian earthquake of 2010, and other multiple casualty situations.[326-328]

US interpretation may be enhanced by satellite and telesonography systems that allow remote guidance and interpretation.[329] In remote and international low-resource settings, US has become the imaging test of choice for emergency care.[330,331]

INTEGRATION INTO EMERGENCY MEDICINE PRACTICE

US has been integrated into emergency medicine practice because of the need for effective, noninvasive, nonpainful, portable imaging techniques.[14] US, whether it is introduced in medical school, residency, or clinical practice, is a skill that requires constant attention with hands-on practice and interpretation.[5,332] Emergency US, the performance and interpretation of ultrasonographic examination at the bedside in the emergency setting, has enhanced many aspects of emergency care, making diagnosis and treatment more rapid, efficient, safe, and accurate.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. American College of Emergency Physicians: Emergency ultrasound guidelines. *Ann Emerg Med* 2009; 53:550-570.
2. Durston WE, Carl ML, Guerra W, Eaton A, Ackerson LM: Ultrasound availability in the evaluation of ectopic pregnancy in the ED: Comparison of quality and cost-effectiveness with different approaches. *Am J Emerg Med* 2000; 18:408-417.
3. American College of Emergency Physicians: *Emergency Ultrasound Imaging Criteria Compendium*. Available at www.acep.org/WorkArea/downloadasset.aspx?id=32886. Accessed March 26, 2008.
4. Daymude M, Mehta S, Gruppo L, McManus J: *Developing an emergency physician assistant formal ultrasound education program*. 3rd World Congress on Ultrasound in Emergency and Critical Care Medicine; Paris, France; May 2007.
5. Cook T, Hunt P, Hoppman R: Emergency medicine leads the way for training medical students in clinician-based ultrasound: A radical paradigm shift in patient imaging. *Acad Emerg Med* 2007; 14:558-561.
6. American College of Emergency Physicians, Section of Emergency Ultrasound: *Emergency Ultrasound Fellowship Guideline—An Information Paper*. Available at www.acep.org/webportal/PracticeResources/issues/ultra/ultrasoundfellowshipguide.htm. Accessed February 16, 2006.
7. Lapostolle F, et al: Usefulness of hand-held ultrasound devices in out-of-hospital diagnosis performed by emergency physicians. *Am J Emerg Med* 2006; 24:237-242.
8. Bahner D, Yeager S, Werman H: Ultrasound image quality in the out-of-hospital environment. *Acad Emerg Med* 2001; 8:568.
9. Brooks A, Price V, Simms M: FAST on operational military deployment. *Emerg Med J* 2005; 22:263-265.
10. Heegaard W, et al: Ultrasound for the air medical clinician. *Air Med J* 2004; 23:20-23.
11. Roberts J, McManus J, Harrison B: Use of ultrasonography to avoid an unnecessary procedure in the prehospital combat environment: A case report. *Prehosp Emerg Care* 2006; 10:502-506.
12. Zafren K: How useful is on-mountain sonography? *Wilderness Environ Med* 2001; 12:230-231.
13. Blaivas M, Lyon M, Brannam L: Emergency ultrasonography utility in a rural emergency department with limited radiology services. *Ann Emerg Med* 2003; 42:S88.
14. Kendall JL, Hoffenberg SR, Smith S: History of emergency and critical care ultrasound: The evolution of a new imaging paradigm. *Crit Care Med* 2007; 35:S126-S130.
15. Davis DP, Campbell CJ, Poste JC, Ma G: The association between operator confidence and accuracy of ultrasonography performed by novice emergency physicians. *J Emerg Med* 2005; 29:259-264.
16. Blaivas M, Pawl R: Analysis of lawsuits filed against emergency physicians for point-of-care emergency ultrasound examination performance and interpretation over a 20-year period. *Am J Emerg Med* 2012; 30:338-341.
17. Mateer J, et al: Model curriculum for physician training in emergency ultrasonography. *Ann Emerg Med* 1994; 23:95-102.
18. Bahner D, Quick G, Huff S, Pepera M, Fox C: *Ultrasound research design at the United States SAEM National Conference (1999-2003)*. The Second Mediterranean Emergency Medicine Congress; Barcelona, Spain; September 2003.
19. American Medical Association House of Delegates: *H-230.960. Privileging for Ultrasound Imaging*. Available at www.ama-assn.org/apps/pf_online/pf_online?f_n=resultLink&doc=policyfiles/HOD/H-230.960.HTM&s_t=Ultrasound&catg=AMA/HOD&&nth=1&&st_p=0&nth=2&. Accessed 2001.
20. Moore C, Gregg S, Lambert M: Performance, training, quality assurance, and reimbursement of emergency physician–performed ultrasonography at Academic Medical Centers. *J Ultrasound Med* 2004; 23:459-466.
21. Moore C, Molina A, Lin H: Ultrasonography in community emergency departments in the United States: Access to ultrasonography performed by consultants and status of emergency physician–performed ultrasonography. *Ann Emerg Med* 2006; 47:147-153.
22. Bahner D, et al; American Institute of Ultrasound in Medicine: AIUM practice guideline for the performance of the focused assessment with sonography for trauma (FAST) examination. *J Ultrasound Med* 2008; 27:313-318.
23. Labovitz AJ, et al: Focused cardiac ultrasound in the emergent setting: A consensus statement of the American Society of Echocardiography and American College of Emergency Physicians. *J Am Soc Echocardiogr* 2010; 23:1225-1230.
24. Soremekun OA, Noble VE, Liteplo AS, Brown DF, Zane RD: Financial impact of emergency department ultrasound. *Acad Emerg Med* 2009; 16:674-680.
25. Accreditation Council for Graduate Medical Education, Residency Review Committee: *Emergency Medicine Guideline: Guidelines for Procedures and Resuscitations*. Available at www.acgme.org/acWebsite/RRC_110/110_guidelines.asp#res. Accessed February 16, 2006.
26. Perina DG, et al; 2011 EM Model Review Task Force: The 2011 model of the clinical practice of emergency medicine. *Acad Emerg Med* 2012; 19:e19-40.
27. Heller M, et al: Residency training in emergency ultrasound: Fulfilling the mandate. *Acad Emerg Med* 2002; 9:835-839.
28. Mandavia DP, Aragona J, Chan L, Chan D, Henderson SO: Ultrasound training for emergency physicians. *Acad Emerg Med* 2000; 7:1009-1014.
29. Girzadas DV Jr, et al: Hybrid simulation combining a high fidelity scenario with a pelvic ultrasound task trainer enhances the training and evaluation of endovaginal ultrasound skills. *Acad Emerg Med* 2009; 16:429-435.
30. Platz E, Liteplo A, Hurwitz S, Hwang J: Are live instructors replaceable? Computer vs. classroom lectures for EFAST training. *J Emerg Med* 2011; 40:534-538.
31. Platz E, et al: Comparison of Web- versus classroom-based basic ultrasonographic and EFAST training in 2 European hospitals. *Ann Emerg Med* 2010; 56:660-667.
32. Chenkin J, Lee S, Huynh T, Bandiera G: Procedures can be learned on the Web: A randomized study of ultrasound-guided vascular access training. *Acad Emerg Med* 2008; 15:949-954.
33. *Medicare Improvements for Patients and Providers Act (MIPPA) H. R. 6331 (110th)*. Available at frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong.
34. *Emergency Ultrasound Fellowships*. Available at www.eusfellowships.com.
35. Kremkau FW, ed: *Diagnostic Ultrasound: Principles and Instruments*, 4th ed. Philadelphia: WB Saunders; 1993.
36. Frazee BW, Fahimi J, Lambert L, Nagdev A: Emergency department ultrasonographic probe contamination and experimental model of probe disinfection. *Ann Emerg Med* 2011; 58:56-63.
37. American Institute of Ultrasound in Medicine: *Guidelines for Cleaning and Preparing Endocavitary Ultrasound Transducers Between Patients*, 2003. Official statement. Available at www.aium.org/publications/statements.aspx. Accessed August 28, 2011.
38. American College of Emergency Physicians: ACEP emergency ultrasound guidelines—2001. *Ann Emerg Med* 2001; 38:470-481.
39. Shafe M, Blaivas M, Hooker E, Straus L: Noninvasive intracranial cerebral flow velocity evaluation in the emergency department by emergency physicians. *Acad Emerg Med* 2004; 11:774-777.
40. Use of ultrasound imaging by emergency physicians. *Ann Emerg Med* 1997; 30:364-365.
41. Jones AE, Tayal VS, Sullivan DM, Kline JA: Randomized controlled trial of immediate vs. delayed goal-directed ultrasound to identify the etiology of nontraumatic hypotension in emergency department patients. *Crit Care Med* 2004; 32:1703-1708.
42. Scalea TM, et al; FAST Consensus Conference Committee: Focused Assessment with Sonography for Trauma (FAST): Results from an international consensus conference. *J Trauma* 1999; 46:466-472.
43. Rozycki GS, et al: A Prospective study of surgeon-performed ultrasound as the primary adjuvant modality for injured patient assessment. *J Trauma* 1995; 39:492-500.
44. Hoffmann B: *Sonoguide*. Available at www.sonoguide.com.
45. Kirkpatrick AW, et al: Hand-held sonography for detecting post-traumatic pneumothoraces: The Extended Focused Assessment with Sonography for Trauma (EFAST). *J Trauma* 2004; 57:288-295.
46. Dulchavsky SA, et al: Advanced ultrasonic diagnosis of extremity trauma: The FASTER examination. *J Trauma* 2002; 53:28-32.
47. Bode PJ, van Vugt AB: Ultrasound in the diagnosis of injury. *Injury* 1996; 27:379-383.
48. Boulanger BR, et al: A prospective study of emergent abdominal sonography after blunt trauma. *J Trauma* 1996; 39:325-330.
49. Branney SW, et al: Quantitative sensitivity off ultrasound in detecting free intraperitoneal fluid. *J Trauma* 1995; 39:375-380.
50. Plummer D, Brunnette D, Asinger R, Ruiz E: Emergency department echocardiography improves outcome in penetrating cardiac injury. *Ann Emerg Med* 1992; 21:709-712.
51. Abboud P, Kendall J: Can emergency department ultrasound be used reliably for detecting hemothorax after blunt traumatic injury? *Acad Emerg Med* 2001; 8:579.

www.ketabpezeshki.com 66485457-66963820

52. Ma OJ, Kefer MP, Mateer JR, Thoma B: Evaluation of hemoperitoneum using a single- vs multiple-view ultrasonographic examination. *Acad Emerg Med* 1995; 2:581-586.
53. Gangahar R, Doshi D: FAST scan in the diagnosis of acute diaphragmatic rupture. *Am J Emerg Med* 2010; 28:387:e1-3.
54. Nordenholz KE, Rubin MA, Gularte GG, Liang HK: Ultrasound in the evaluation and management of blunt abdominal trauma. *Ann Emerg Med* 1997; 29:357-366.
55. Soyuncu S, Cete Y, Bozan H, Kartal M, Akyol A: Accuracy of physical and ultrasonographic examinations by emergency physicians for the early diagnosis of intraabdominal haemorrhage in blunt abdominal trauma. *Injury* 2007; 38:564-569.
56. Dolich M, et al: 2576 Ultrasounds for blunt abdominal trauma. *J Trauma* 2001; 50:108-112.
57. Gaarder C, et al: Ultrasound performed by radiologists—confirming the truth about FAST in trauma. *J Trauma* 2009; 67:323-327; discussion 328-329.
58. Bauwens SD, Rademacher SJ, Mutze S, Ekkernkamp A, Porzsolt F: Emergency ultrasound-based algorithms for diagnosing blunt abdominal trauma [review]. *Cochrane Collaboration* 2006; 2:1-19.
59. Melniker LA, et al: Randomized controlled clinical trial of point-of-care, limited ultrasonography for trauma in the emergency department: The First Sonography Outcomes Assessment Program trial. *Ann Emerg Med* 2006; 48:227-235.
60. Moylan M, et al: Association between a positive ED FAST examination and therapeutic laparotomy in normotensive blunt trauma patients. *J Emerg Med* 2007; 33:265-271.
61. Schiavone WA, et al: The use of echocardiography in the emergency management of nonpenetrating traumatic cardiac rupture. *Ann Emerg Med* 1991; 20:1248-1250.
62. Abboud PA, Kendall J: Emergency department ultrasound for hemothorax after blunt traumatic injury. *J Emerg Med* 2003; 25:181-184.
63. Duggal S, Blaivas M, Brannam L, Lyon M: A prospective comparison of supine chest x-ray and bedside ultrasound for diagnosis of traumatic pneumothorax. *Acad Emerg Med* 2004; 11:579.
64. Tayal VS, Beatty MB, Marx JA, Tomaszewski CA, Thomason MH: FAST (focused assessment with sonography in trauma) accurate for cardiac and intraperitoneal injury in penetrating anterior chest trauma. *J Ultrasound Med* 2004; 23:467-472.
65. Rochester AL, Tayal VS, Marx JA, Thomason MH: The accuracy of trauma ultrasound in penetrating trauma to the anterior abdomen. *Acad Emerg Med* 2006; 13:S142.
66. Udobi KF, Rodriquez A, Chiu WC, Scalea TM: Role of ultrasonography in penetrating abdominal trauma: A prospective clinical study. *J Trauma* 2001; 50:475-479.
67. Fox JC, et al: Test characteristics of focused assessment of sonography for trauma for clinically significant abdominal free fluid in pediatric blunt abdominal trauma. *Acad Emerg Med* 2011; 18:477-482.
68. Ma OJ, Mateer JR, DeBehnke DJ: Use of ultrasonography for the evaluation of pregnant trauma patients. *J Trauma* 1996; 40:665-668.
69. Tayal VS, et al: Accuracy of trauma ultrasound in major pelvic injury. *J Trauma* 2006; 61:1453-1457.
70. Friese R, Malekzadeh S, Shafi S, Gentilello L, Starr A: Abdominal ultrasound is an unreliable modality for the detection of hemoperitoneum in patients with pelvic fracture. *J Trauma* 2007; 63:97-102.
71. Jones AE, Mason PE, Tayal VS, Gibbs MA: Sonographic intraperitoneal fluid in patients with pelvic fracture: Two cases of traumatic intraperitoneal bladder rupture. *J Emerg Med* 2003; 25:373-377.
72. Hoffman L, Pierce D, Puumala S: Clinical predictors of injuries not identified by focused abdominal sonogram for trauma (FAST) examinations. *J Emerg Med* 2009; 36:271-279.
73. Mateer JR, Aiman EJ, Brown MH, Olson DW: Ultrasonographic examination by emergency physicians of patients at risk for ectopic pregnancy. *Acad Emerg Med* 1995; 2:867-873.
74. Mateer JR, et al: Outcome analysis of a protocol including bedside endovaginal sonography in patients at risk for ectopic pregnancy. *Ann Emerg Med* 1996; 27:283-289.
75. Dart R: Role of pelvic ultrasonography in evaluation of symptomatic first-trimester pregnancy. *Ann Emerg Med* 1999; 33:310-320.
76. Durham B, Lane B, Burbridge L, Balasubramaniam S: Pelvic ultrasound performed by emergency physicians for the detection of ectopic pregnancy in complicated first-trimester pregnancies. *Ann Emerg Med* 1997; 29:338-347.
77. Schlager D, Lazzarreschi G, Whitten D, Sanders AB: A prospective study of ultrasonography in the ED by emergency physicians. *Am J Emerg Med* 1994; 12:185-189.
78. Tayal VS, Cohen H, Norton J: Outcome of patients with indeterminate first-trimester emergency department pelvic ultrasound. *Acad Emerg Med* 2004; 11:526.
79. Stein JC, et al: Emergency physician ultrasonography for evaluating patients at risk for ectopic pregnancy: A meta-analysis. *Ann Emerg Med* 2010; 56:674-683.
80. Rodgerson JD, et al: Emergency department right upper quadrant ultrasound reduces time to diagnosis and treatment of ruptured ectopic pregnancies. *Acad Emerg Med* 1999; 6:540-541.
81. Press G, Martinez A: Heterotopic pregnancy diagnosed by emergency ultrasound. *J Emerg Med* 2007; 33:25-27.
82. Shih CH: Effect of emergency physician–performed pelvic sonography on length of stay in the emergency department. *Ann Emerg Med* 1997; 29:348-352.
83. Burgher S, Tandy T, Dawdy M: Transvaginal ultrasonography by emergency physicians decreases patient time in the emergency department. *Acad Emerg Med* 1998; 5:802-807.
84. Blaivas M, Bell G: Benefit from emergency physician identified ectopic pregnancy using bedside ultrasound. *Acad Emerg Med* 2000; 7:500.
85. Adhikari S, Blaivas M, Lyon M: Diagnosis and management of ectopic pregnancy using bedside transvaginal ultrasonography in the ED: A 2-year experience. *Am J Emerg Med* 2007; 25:591-596.
86. Juliano M, Dabulis S, Heffner A: Characteristics of women with fetal loss in symptomatic first trimester pregnancies with documented fetal cardiac activity. *Ann Emerg Med* 2008; 52:143-147.
87. Choi H, Blaivas M: Gestational outcome in patients with first-trimester pregnancy complications and ultrasound-confirmed live intrauterine pregnancy. *Acad Emerg Med* 2000; 7:200-203.
88. Shah S, et al: Accuracy of emergency physicians using ultrasound to determine gestational age in pregnant women. *Am J Emerg Med* 2010; 28:834-838.
89. Sergel MJ, Greenberg DT: Live twin ectopic pregnancy with advanced gestation. *J Emerg Med* 2009; 37:77-78.
90. Nicks BA, Fitch MT, Manthey DE: A case of intrauterine molar pregnancy with coexistent ectopic pregnancy. *J Emerg Med* 2009; 36:246-249.
91. Kouliev T, Cervenka K: Emergency ultrasound in cervical ectopic pregnancy. *J Emerg Med* 2010; 38:55-56.
92. Gaber-Patel K, Smith MD: Thirteen-week cornual ectopic pregnancy. *Am J Emerg Med* 2009; 27:900.e1-2.
93. Corrigan KJ, Kowalzyk DR: Ectopic ovarian pregnancy in a second-trimester patient. *Am J Emerg Med* 2007; 25:1085.e3-4.
94. Saul T, Sonson J: Molar pregnancy. *J Emerg Med* 2011; 40:e39-e40.
95. Amin S, Weekes A: Live conjoined twins: A rare first trimester diagnosis during emergency department sonography. *J Emerg Med* 2010; 39:e105-e108.
96. Dabulis S, McGuirk T: An unusual case of hemoperitoneum: Uterine rupture at 9 weeks gestational age. *J Emerg Med* 2007; 33:285-287.
97. Adhikari S, Blaivas M, Lyon M: Role of bedside transvaginal ultrasonography in the diagnosis of tubo-ovarian abscess in the emergency department. *J Emerg Med* 2008; 34:429-433.
98. Tayal V, et al: ED endovaginal pelvic ultrasound in nonpregnant women with right lower quadrant pain. *Am J Emerg Med* 2008; 26:81-85.
99. Quick G: Ultrasound: Where will the puck be? *ACEPs The Connection* 2000:1-7.
100. Mark D, et al: Directed bedside transthoracic echocardiography: Preferred cardiac window for left ventricular ejection fraction estimation in critically ill patients. *Am J Emerg Med* 2007; 25:284-900.
101. Levinson MM, Boniface KS, Adler JD, Miller K: Emergency physician performance of single parasternal long-axis view to visually estimate left ventricular ejection fraction. *Acad Emerg Med* 2005; 12(Suppl 1):48-b, 49.
102. Tayal VS, Kline JA: Emergent echocardiographic detection of pericardial effusion in patients with hemodynamic collapse. *Acad Emerg Med* 1999; 6:540.
103. Hernandez C, et al: C.A.U.S.E.: Cardiac arrest ultra-sound exam—a better approach to managing patients in primary non-arrhythmogenic cardiac arrest. *Resuscitation* 2008; 76:198-206.
104. Amaya SC, Langsam A: Ultrasound detection of ventricular fibrillation disguised as asystole. *Ann Emerg Med* 1999; 33:344-346.
105. Tsung JW, Blaivas M: Feasibility of correlating the pulse check with focused point-of-care echocardiography during pediatric cardiac arrest: A case series. *Resuscitation* 2008; 77:264-269.
106. Breitkreutz R, et al: Focused echocardiographic evaluation in life support and peri-resuscitation of emergency patients: A prospective trial. *Resuscitation* 2010; 81:1527-1533.

www.ketabpezeshki.com 66485457-66963820

107. Volpicelli G: Usefulness of emergency ultrasound in nontraumatic cardiac arrest. *Am J Emerg Med* 2011; 29:216-223.
108. Price S, et al: Peri-resuscitation echocardiography: Training the novice practitioner. *Resuscitation* 2010; 81:1534-1539.
109. Mandavia D, Hoffner R, Mahaney K, Henderson S: Bedside echocardiography by emergency physicians. *Ann Emerg Med* 2001; 38:377-382.
110. Nagdev A, Stone MB: Point-of-care ultrasound evaluation of pericardial effusions: Does this patient have cardiac tamponade? *Resuscitation* 2011; 82:671-673.
111. Blaivas M: Incidence of pericardial effusion in patients presenting to the emergency department with unexplained dyspnea. *Acad Emerg Med* 2001; 8:1143-1146.
112. Sierzenski PR, O'Connor RE: Emergency physician echocardiography reduces cost of hospitalization for patients with pericardial effusion. *Acad Emerg Med* 2005; 12(Suppl 1):77-b.
113. Lainscak M, Pernat A: Importance of bedside echocardiography for detection of unsuspected isolated right ventricular infarction as a cause of cardiovascular collapse. *Am J Emerg Med* 2007; 25:110-114.
114. Mandavia DP, Mallon WK: Using bedside ultrasonography to evaluate trauma patients. *J Crit Illness* 2000; 15:387-394.
115. Fojtik JP, Handly N, Dean AJ, Costantino TG: The prevalence of pericardial effusion in patients presenting to two urban emergency departments. *Ann Emerg Med* 2002; 40:S58.
116. Bova C, et al: Diagnostic utility of echocardiography in patients with suspected pulmonary embolism. *Am J Emerg Med* 2003; 21:180-183.
117. Rose J, Bair A, Mandavia D, Kinser D: The UHP ultrasound protocol: A novel ultrasound approach to the empiric evaluation of the undifferenttiated hypotensive patient. *Am J Emerg Med* 2001; 19:299-302.
118. Bahner DP: Trinity: A hypotensive ultrasound protocol. *J Diagn Med Sonogr* 2002; 18:193-198.
119. Moore C, et al: Determination of left ventricular function by emergency physician echocardiography of hypotensive patients. *Acad Emerg Med* 2002; 9:186-193.
120. Jones A, Craddock P, Tayal V, Kline J: Diagnostic accuracy of left ventricular function for identifying sepsis among emergency department patients with non-traumatic undifferentiated hypotension. *Shock* 2005; 24 :513-517.
121. Chen L, Kim Y, Santucci K: Use of ultrasound measurement of the inferior vena cava diameter as an objective tool in the assessment of children with clinical dehydration. *Acad Emerg Med* 2007; 14:841-845.
122. Lyon M, Blaivas M, Brannam L: Sonographic measurement of the inferior vena cava as a marker of blood loss. *Am J Emerg Med* 2005; 23:45-50.
123. Blehar DJ, Dickman E, Gaspari R: Identification of congestive heart failure via respiratory variation of inferior vena cava diameter. *Am J Emerg Med* 2009; 27:71-75.
124. Wang HK, et al: Cardiac ultrasound helps for differentiating the causes of acute dyspnea with available B-type natriuretic peptide tests. *Am J Emerg Med* 2010; 28:987-993.
125. Carr BG, et al: Intensivist bedside ultrasound (INBU) for volume assessment in the intensive care unit: A pilot study. *J Trauma* 2007; 63:495-500; discussion 500-492.
126. Ferrada P, Murthi S, Anand RJ, Bochicchio GV, Scalea T: Transthoracic focused rapid echocardiographic examination: Real-time evaluation of fluid status in critically ill trauma patients. *J Trauma* 2011; 70:56-62; discussion 62-54.
127. Nagdev AD, Merchant RC, Tirado-Gonzalez A, Sisson CA, Murphy MC: Emergency department bedside ultrasonographic measurement of the caval index for noninvasive determination of low central venous pressure. *Ann Emerg Med* 2010; 55:290-295.
128. Schefold JC, et al: Inferior vena cava diameter correlates with invasive hemodynamic measures in mechanically ventilated intensive care unit patients with sepsis. *J Emerg Med* 2010; 38:632-637.
129. Lamia B, et al: Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneously breathing activity. *Intensive Care Med* 2007; 33:1125-1132.
130. Donahue SP, Wood JP, Patel BM, Quinn JV: Correlation of sonographic measurements of the internal jugular vein with central venous pressure. *Am J Emerg Med* 2009; 27:851-855.
131. Jain S, et al: Noninvasive Doppler ultrasonography for assessing cardiac function: Can it replace the Swan-Ganz catheter? *Am J Surg* 2008; 196:961-967; discussion 967-968.
132. Tayal VS, Graf CD, Gibbs MA: Prospective study of accuracy and outcome of emergency ultrasound for abdominal aortic aneurysm over two years. *Acad Emerg Med* 2003; 10:867-871.
133. Costantino TG, Bruno EC, Handly N, Dean AJ: Accuracy of emergency medicine ultrasound in the evaluation of abdominal aortic aneurysm. *J Emerg Med* 2005; 29:455-460.
134. Sherman S, Cosby K: Emergency physician ultrasonography—aortic dissection. *J Emerg Med* 2004; 26:217-218.
135. Sierzenski P, Dickman E, Leech S, Gukhook J, Bollinger M: Emergency physician ultrasound decreases physician times to diagnosis, beta-blocker therapy, and operative repair in patients with acute aortic dissection. *Acad Emerg Med* 2004; 11:580-581.
136. Fojtik J, Costantino T, Dean A: The diagnosis of aortic dissection by emergency medicine ultrasound. *J Emerg Med* 2007; 32:191-196.
137. Ernst CB: Abdominal aortic aneurysm. *N Engl J Med* 1999; 328:1167-1172.
138. Kuhn M, Bonnin RL, Davey MJ, Rowland JL, Langlois SL: Emergency department ultrasound scanning for abdominal aortic aneurysm: Accessible, accurate, and advantageous. *Ann Emerg Med* 2000; 36:219-223.
139. Knaut AL, Kendall JL, Patten R, Ray C: Ultrasonographic measurement of aortic diameter by emergency physicians approximates results obtained by computed tomography. *J Emerg Med* 2005; 28:119-126.
140. Dent B, Kendall RJ, Boyle AA, Atkinson PR: Emergency ultrasound of the abdominal aorta by UK emergency physicians: A prospective cohort study. *Emerg Med J* 2007; 24:547-549.
141. Moore CL, Holliday RS, Hwang JQ, Osborne MR: Screening for abdominal aortic aneurysm in asymptomatic at-risk patients using emergency ultrasound. *Am J Emerg Med* 2008; 26:883-887.
142. Melanson S, et al: Can an emergency department ultrasound screening program identify abdominal aortic aneurysm in asymptomatic geriatric patients? *Ann Emerg Med* 2000; 36:S21.
143. Schermerhorn ML, et al: Defining perioperative mortality after open and endovascular aortic aneurysm repair in the US Medicare population. *J Am Coll Surg* 2011; 212:349-355.
144. Monge M, Eskandari MK: Strategies for ruptured abdominal aortic aneurysms. *J Vasc Interv Radiol* 2008; 19(Suppl):S44-S50.
145. Roxas R, Gallegos L, Bailitz J: Rapid detection of aortic occlusion with emergency ultrasonography. *Ann Emerg Med* 2011; 58:21-23.
146. Durston W, et al: Comparison of quality and cost-effectiveness in the evaluation of symptomatic cholelithiasis with different approaches to ultrasound availability in the ED. *Am J Emerg Med* 2001; 19:260-269.
147. Rosen CL, et al: Gallbladder ultrasonography: Agreement between emergency physicians and radiologists. *Acad Emerg Med* 1998; 5:417.
148. Blaivas M, Harwood RA, Lambert MJ: Decreasing length of stay with emergency department gallbladder ultrasonography. *Acad Emerg Med* 1999; 6:541.
149. Nelson M, Raio C, Gerardo C, Theodoro D, Chun P: Can emergency physicians utilize the S. I. N. phenomenon (stone impacted in gallbladder neck) to accurately diagnose cholecystitis? *Ann Emerg Med* 2005; 46:80.
150. Summers SM, et al: A prospective evaluation of emergency department bedside ultrasonography for the detection of acute cholecystitis. *Ann Emerg Med* 2010; 56:114-122.
151. Miller AH, Delaney KA, Brockman CR, Pepe PE: ED ultrasound in hepatobiliary disease. *J Emerg Med* 2006; 30:69-74.
152. Jang TB, Ruggeri W, Dyne P, Kaji AH: The learning curve of resident physicians using emergency ultrasonography for cholelithiasis and cholecystitis. *Acad Emerg Med* 2010; 17:1247-1252.
153. Durston W, et al: Comparison of quality and cost-effectiveness in the evaluation of symptomatic cholelithiasis with different approaches to ultrasound availability in the ED. *Am J Emerg Med* 2001; 19:260-269.
154. Blaivas M, Adhikari S: Diagnostic utility of cholescintigraphy in emergency department patients with suspected acute cholecystitis: Comparison with bedside RUQ ultrasonography. *J Emerg Med* 2007; 33:47-52.
155. Gaspari RJ, Horst K: Emergency ultrasound and urinalysis in the evaluation of flank pain. *Acad Emerg Med* 2005; 12:1180-1184.
156. Kartal M, Eray O, Erdogru T, Yilmaz S: Prospective validation of a current algorithm including bedside US performed by emergency physicians for patients with acute flank pain suspected for renal colic. *Emerg Med J* 2006; 23:341-344.
157. Henderson SO, et al: Bedside emergency department ultrasonography plus radiography of the kidneys, ureters, and bladder vs intravenous pyelography in the evaluation of suspected ureteral colic. *Acad Emerg Med* 1998; 8:666-671.
158. McCans KW, Baumann B: Use of ultrasound bladder volume determinations decreases the number of unsuccessful catheterization attempts in pediatric emergency department patients. *Acad Emerg Med* 2004; 11:446.

www.ketabpezeshki.com 66485457-66963820

159. Baumann B, et al: Volumetric bladder ultrasound performed by trained nurses increases catheterization success in pediatric patients. *Am J Emerg Med* 2008; 26:18-23.
160. Chen L, Hsiao A, Moore C, Santucci K: Utility of bedside bladder ultrasound prior to urethral catheterization in infants. *Acad Emerg Med* 2004; 11:598.
161. Blaivas M, Lambert MJ, Harwood RC, Wood JP, Konicki JP: Lower extremity Doppler for deep venous thrombosis—can emergency physicians be accurate and fast? *Acad Emerg Med* 2000; 6:120-126.
162. Frazee BW, Snooey ER, Levitt A: Emergency department compression ultrasound to diagnose proximal deep vein thrombosis. *J Emerg Med* 2001; 20:107-111.
163. Jacoby J, et al: Can emergency medicine residents detect acute deep venous thrombosis with a limited, two-site ultrasound examination? *J Emerg Med* 2006; 32:197-200.
164. Kline JA, et al: Emergency clinician–performed compression ultrasonography for deep venous thrombosis of the lower extremity. *Ann Emerg Med* 2008; 52:437-445.
165. Jang T, Docherty M, Aubin C, Polites G: Resident-performed compression ultrasonography for the detection of proximal deep vein thrombosis: Fast and accurate. *Acad Emerg Med* 2004; 4:319-322.
166. Leech SJ, Gukhool JA, Dickman E, Sierzenski PR: Emergency physician–performed ultrasound accurately identifies upper extremity deep venous thrombosis. *Acad Emerg Med* 2004; 11:585-586.
167. Magazzini S, et al: Duplex ultrasound in the emergency department for the diagnostic management of clinically suspected deep vein thrombosis. *Acad Emerg Med* 2007; 14:216-220.
168. Crisp JG, Lovato LM, Jang TB: Compression ultrasonography of the lower extremity with portable vascular ultrasonography can accurately detect deep venous thrombosis in the emergency department. *Ann Emerg Med* 2010; 56:601-610.
169. Burnside PR, Brown MD, Kline JA: Systematic review of emergency physician–performed ultrasonography for lower-extremity deep vein thrombosis. *Acad Emerg Med* 2008; 15:493-498.
170. Morrison D, Lyon M, Blaivas M: Emergency physicians decrease hospital charges by performing bedside ultrasound for deep venous thrombosis. *Acad Emerg Med* 2005; 12(Suppl 1):79.
171. Theodoro DL, Blaivas M, Duggal D, Snyder G, Lucas M: Emergency physician–performed lower extremity Doppler results in significant time savings. *Acad Emerg Med* 2002; 9:541.
172. Farahmand S, Farnia M, Shahriaran S, Khashayar P: The accuracy of limited B-mode compression technique in diagnosing deep venous thrombosis in lower extremities. *Am J Emerg Med* 2011; 29:687-690.
173. Bernardi E, et al: Serial 2-point ultrasonography plus D-dimer vs whole-leg color-coded Doppler ultrasonography for diagnosing suspected symptomatic deep vein thrombosis: A randomized controlled trial. *JAMA* 2008; 300:1653-1659.
174. Reissig A, Copetti R, Kroegel C: Current role of emergency ultrasound of the chest. *Crit Care Med* 2011; 39:839-845.
175. Lichtenstein D, Meziere G, Biderman P, Gepner A: The comet-tail artifact: An ultrasound sign ruling out pneumothorax. *Intensive Care Med* 1999; 25:383-388.
176. Lichtenstein DA, et al: Ultrasound diagnosis of occult pneumothorax. *Crit Care Med* 2005; 33:1231-1238.
177. Soldati G, et al: The ultrasonographic deep sulcus sign in traumatic pneumothorax. *Ultrasound Med Biol* 2006; 32:1157-1163.
178. Blaivas M, Lyon M, Duggal S: A prospective comparison of supine chest radiography and bedside ultrasound for the diagnosis of traumatic pneumothorax. *Acad Emerg Med* 2005; 12:844-849.
179. Simon BC, Paolinetti L: Two cases where bedside ultrasound was able to distinguish pulmonary bleb from pneumothorax. *J Emerg Med* 2005; 29:201-205.
180. Dente C, et al: The accuracy of thoracic ultrasound for detection of pneumothorax is not sustained over time: A preliminary study. *J Trauma* 2007; 62:1384-1389.
181. Parlamento S, Copetti R, Di Bartolomeo S: Evaluation of lung ultrasound for the diagnosis of pneumonia in the ED. *Am J Emerg Med* 2009; 27:379-384.
182. Gillman LM, Panebianco N, Alkadi A, Blaivas M, Kirkpatrick AW: The dynamic sonographic air bronchogram: A simple and immediate bedside diagnosis of alveolar consolidation in severe respiratory failure. *J Trauma* 2011; 70:760.
183. Picano E, et al: Ultrasound lung comets: A clinically useful sign of extravascular lung water. *J Am Soc Echocardiogr* 2006; 19:356-363.
184. Fagenholz P, et al: Chest ultrasonography for the diagnosis and monitoring of high-altitude pulmonary edema. *Chest* 2007; 131:1013-1018.
185. Liteplo AS, et al: Emergency thoracic ultrasound in the differentiation of the etiology of shortness of breath (ETUDES): Sonographic B-lines and N-terminal pro-brain–type natriuretic peptide in diagnosing congestive heart failure. *Acad Emerg Med* 2009; 16:201-210.
186. Weaver B, Blaivas M, Lyon M: Confirmation of endotracheal tube placement after intubation using the sliding lung sign. *Acad Emerg Med* 2005; 12:91-92.
187. Milling T, et al: Transtracheal 2-D ultrasound for identification of esophageal intubation. *J Emerg Med* 2007; 32:409-414.
188. Muslu B, et al: Use of sonography for rapid identification of esophageal and tracheal intubations in adult patients. *J Ultrasound Med* 2011; 30:671-676.
189. Ma G, et al: The sensitivity and specificity of transcricothyroid ultrasonography to confirm endotracheal tube placement in a cadaver model. *J Emerg Med* 2007; 20:1-3.
190. Galicinao J, Bush A, Godambe S: Use of bedside ultrasonography for endotracheal tube placement in pediatric patients: A feasibility study. *Pediatrics* 2007; 120:1297-1303.
191. Blaivas M: Bedside emergency department ultrasonography in the evaluation of ocular pathology. *Acad Emerg Med* 2000; 7:947-950.
192. Blaivas M, Theodoro DL, Sierzenski PR: A study of bedside ocular ultrasonography in the emergency department. *Acad Emerg Med* 2002; 9:791-799.
193. Chiao L, et al: Ocular examination for trauma; clinical ultrasound aboard the International Space Station. *J Trauma* 2005; 58:885-889.
194. Harries A, Shah S, Teismann N, Price D, Nagdev A: Ultrasound assessment of extraocular movements and pupillary light reflex in ocular trauma. *Am J Emerg Med* 2010; 28:956-959.
195. Shiver S, Lyon M, Blaivas M: Detection of ocular foreign bodies using compact ultrasound. *Acad Emerg Med* 2005; 12(Suppl 1):74.
196. McIlrath ST, Blaivas M, Lyon M: Diagnosis of periorbital gas on ocular ultrasound after facial trauma. *Am J Emerg Med* 2005; 23:517-520.
197. Yoonessi R, Hussain A, Jang TB: Bedside ocular ultrasound for the detection of retinal detachment in the emergency department. *Acad Emerg Med* 2010; 17:913-917.
198. Shinar Z, Chan L, Orlinsky M: Use of ocular ultrasound for the evaluation of retinal detachment. *J Emerg Med* 2011; 40:53-57.
199. Tayal V, et al: Emergency department sonographic measurement of optic nerve sheath diameter to detect findings of increased intracranial pressure in adult head injury patients. *Ann Emerg Med* 2007; 49:508-514.
200. Jang T, Aubin C: The use of serial ocular ultrasonography in the care of patients with head injury. *Ann Emerg Med* 2005; 45:336-337.
201. Tsung JW, Blaivas M, Cooper A, Levick NR: A rapid noninvasive method of detecting elevated intracranial pressure using bedside ocular ultrasound: Application to 3 cases of head trauma in the pediatric emergency department. *Pediatr Emerg Care* 2005; 21:94-98.
202. Kimberly H, Shah S, Marill K, Noble V: Correlation of optic nerve sheath diameter with direct measurement of intracranial pressure. *Acad Emerg Med* 2008; 15:201-204.
203. Le A, et al: Bedside sonographic measurement of optic nerve sheath diameter as a predictor of increased intracranial pressure in children. *Ann Emerg Med* 2009; 53:785-791.
204. Page-Wills C, Simon BC, Christy D, Levitt MA: Utility of ultrasonography on emergency department management of suspected cutaneous abscess. *Acad Emerg Med* 2000; 7:493.
205. Squire B, Fox J, Zlidenny A, Barajas G: ABSCESS: Applied bedside sonography for convenient evaluation of superficial soft tissue infections. *Ann Emerg Med* 2004; 44:S62.
206. Tayal VS, Hasan N, Norton HJ, Tomaszewski CA: The effect of soft-tissue ultrasound on the management of cellulitis in the emergency department. *Acad Emerg Med* 2006; 13:384-388.
207. Charlton N, Cook T: Clinician-based ultrasound facilitates the evaluation of lateral neck mass in the ED. *Am J Emerg Med* 2008; 26:386.e3-6.
208. Jenq KY, Panebianco NL, Lee PA, Chen EH, Dean AJ: Diagnosis of a facial artery pseudoaneurysm using emergency bedside ultrasound. *J Emerg Med* 2010; 38:642-644.
209. Morrison D, Blaivas M, Lyon M: Emergency diagnosis of Fournier's gangrene with bedside ultrasound. *Am J Emerg Med* 2005; 23:544-547.
210. Yen ZS, Wang HP, Ma HM, Chen SC, Chen WJ: Ultrasonographic screening of clinically-suspected necrotizing fasciitis. *Acad Emerg Med* 2002; 9:1448-1451.
211. Sivitz AB, Lam SH, Ramirez-Schrempp D, Valente JH, Nagdev AD: Effect of bedside ultrasound on management of pediatric soft-tissue infection. *J Emerg Med* 2010; 39:637-643.
212. Gaspari RJ, Resop D, Mendoza M, Kang T, Blehar D: A randomized controlled trial of incision and drainage versus ultrasonographically

www.ketabpezeshki.com 66485457-66963820

guided needle aspiration for skin abscesses and the effect of methicillin-resistant *Staphylococcus aureus*. *Ann Emerg Med* 2011; 57:483-491.e1.
213. Blaivas M, Theodoro D, Duggal S: Ultrasound-guided drainage of peritonsillar abscess by the emergency physician. *Am J Emerg Med* 2003; 21:155-158.
214. Lyon M, Glisson P, Blaivas M: Bilateral peritonsillar abscess diagnosed on the basis of intraoral sonography. *J Ultrasound Med* 2003; 22:993-996.
215. Gaspari R: Bedside ultrasound of the soft tissue of the face: A case of early Ludwig's angina. *J Emerg Med* 2006; 31:287-291.
216. Adhikari S, Blaivas M, Lander L: Comparison of bedside ultrasound and Panorex radiography in the diagnosis of a dental abscess in the ED. *Am J Emerg Med* 2011; 29:790-795.
217. Hung TY, et al: Bedside ultrasonography as a safe and effective tool to diagnose acute epiglottitis. *Am J Emerg Med* 2011; 29:359.e1-3.
218. Nomura JT, Sierzenski PR: Ultrasound diagnosis of penile fracture. *J Emerg Med* 2010; 38:362-365.
219. Mahler SA, Manthey DE: Diagnosis of a preputial cavity abscess with bedside ultrasound in the emergency department. *J Emerg Med* 2008; 35:273-276.
220. Jacobson JA, Powell A, Craig JG, Bouffard JA, van Holsbeeck MT: Wooden foreign bodies in soft tissue: Detection at US. *Radiology* 1998; 206:45-48.
221. Turkcuer I, et al: Do we really need plain and soft-tissue radiographies to detect radiolucent foreign bodies in the ED? *Am J Emerg Med* 2006; 24:763-768.
222. Schlager D, Sanders AB, Wiggins D, Boren W: Ultrasound for the detection of foreign bodies. *Ann Emerg Med* 1991; 20:189-191.
223. Raio CC, et al: Do patients who have had negative focused emergency department lower extremity ultrasounds to rule out deep venous thrombosis receive their necessary repeat ultrasounds in 5-7 days? *Acad Emerg Med* 2006; 13:S116-a.
224. Valley VT: Clinical applications of musculoskeletal ultrasound scanning in an emergency department setting. *Ann Emerg Med* 2001; 38:S99.
225. Valley VT, Stahmer SA: Targeted musculoarticular sonography in the detection of joint effusions. *Acad Emerg Med* 2001; 8:361-367.
226. Roy S, Dewitz A, Paul I: Ultrasound-assisted ankle arthrocentesis. *Am J Emerg Med* 1999; 17:300-301.
227. Tayal V, Pariyadath M, Norton J: Randomized controlled trial of ultrasound-guided peripheral non-knee arthrocentesis in the emergency department. *Acad Emerg Med* 2006; 13:S122-b-123S-b.
228. Tayal V, Pariyadath M, Norton J: Prospective use of ultrasound imaging to detect bony hand injuries in adults. *J Ultrasound Med* 2007; 26:1143-1148.
229. Tsung JW, Blaivas M: Emergency department diagnosis of pediatric hip effusion and guided arthrocentesis using point-of-care ultrasound. *J Emerg Med* 2008; 35:393-399.
230. LaRocco BG, Ziupko G, Sierzenski P: Ultrasound diagnosis of quadriceps tendon rupture. *J Emerg Med* 2008; 35:293-295.
231. Freeman K, Dewitz A, Baker W: Ultrasound guided hip arthrocentesis in the ED. *Am J Emerg Med* 2007; 2 5:80-86.
232. Vieira RL, Levy JA: Bedside ultrasonography to identify hip effusions in pediatric patients. *Ann Emerg Med* 2010; 55:284-289.
233. Valley VS, Shermer CD: Use of musculoskeletal ultrasonography in the diagnosis of pes anserine tendinitis: A case report. *J Emerg Med* 2001; 20:43-45.
234. Sisson C, Nagdev A, Tirado A, Murphy M, Suner S: Ultrasound diagnosis of traumatic partial triceps tendon tear in the emergency department. *J Emerg Med* 2011; 40:436-438.
235. Nagdev A, Murphy M, Sisson C: Bedside ultrasound for the detection of diabetic myonecrosis. *Am J Emerg Med* 2008; 26:969.e3-4.
236. Sierzenski PR, Leech SJ, Gukhool J, Blaivas M: ED ultrasound evaluation of the index flexor tendon: A comparison of water-bath evaluation technique (WET) versus direct contact ultrasound. *Acad Emerg Med* 2003; 10:573.
237. Marshburn TH, et al: Goal-directed ultrasound in the detection of long-bone fractures. *J Trauma* 2004; 57:329-332.
238. Chan SS: Emergency bedside ultrasound for the diagnosis of rib fractures. *Am J Emerg Med* 2009; 27:617-620.
239. Kirkpatrick AW, et al: Rapid diagnosis of an ulnar fracture with portable hand-held ultrasound. *Mil Med* 2003; 168:312-313.
240. O'Malley P, Tayal VS: Use of emergency musculoskeletal sonography in diagnosis of an open fracture of the hand. *J Ultrasound Med* 2007; 26:679-682.
241. Durston W, Swartzentruber R: Ultrasound guided reduction of pediatric forearm fractures in the ED. *Am J Emerg Med* 2000; 18:72-77.
242. Chinnock B, Khaletskiy A, Kuo K, Hendey GW: Ultrasound-guided reduction of distal radius fractures. *J Emerg Med* 2011; 40:308-312.
243. Ang SH, Lee SW, Lam KY: Ultrasound-guided reduction of distal radius fractures. *Am J Emerg Med* 2010; 28:1002-1008.
244. Halberg MJ, Sweeney TW, Owens WB: Bedside ultrasound for verification of shoulder reduction. *Am J Emerg Med* 2009; 27:134.e5-6.
245. Carl ML, Durston WE: Survey of staff opinions on ultrasound by emergency physicians. *Am J Emerg Med* 2000; 18:342.
246. Costantino TG, Roemer B, Leber EH: Septic arthritis and bursitis: Emergency ultrasound can facilitate diagnosis. *J Emerg Med* 2007; 32:295-297.
247. Shiver SA, Blaivas M: Acute lower extremity pain in an adult patient secondary to bilateral popliteal cysts. *J Emerg Med* 2008; 34:315-318.
248. Blaivas M, Sierzenski P, Lambert M: Emergency evaluation of patients presenting with acute scrotum using bedside ultrasonography. *Acad Emerg Med* 2001; 8:90-93.
249. Fox JC, et al: Retrospective analysis of emergency department ultrasound for acute appendicitis. *Cal J Emerg Med* 2007; 8:41-45.
250. Fox JC, Solley M, Zlidenny A, Anderson C: Bedside ultrasound for appendicitis. *Acad Emerg Med* 2005; 12(Suppl 1):76.
251. Halm BM, Eakin PJ, Franke AA: Diagnosis of appendicitis by a pediatric emergency medicine attending using point-of-care ultrasound: A case report. *Hawaii Med J* 2010; 69:208-211.
252. Halm BM, Boychuk RB, Franke AA: Diagnosis of intussusception using point-of-care ultrasound in the pediatric ED: A case report. *Am J Emerg Med* 2011; 29:354.e1-3.
253. Baker JB, Mandavia D, Swadron SP: Diagnosis of diverticulitis by bedside ultrasound in the emergency department. *J Emerg Med* 2006; 30:327-329.
254. Chin LW, Hsu CK, Wang HP: Ultrasonographic diagnosis of elderly midgut volvulus in the ED. *Am J Emerg Med* 2006; 24:900-902.
255. Chin L-W, Chou M-C, Wang H-P, Bell W: Ultrasonography diagnosis of occult obturator hernia presenting as intestinal obstruction in ED [letter]. *Am J Emerg Med* 2005; 23:237-239.
256. Moriwaki Y, et al: Ultrasonography for the diagnosis of intraperitoneal free air in chest-abdominal-pelvic blunt trauma and critical acute abdominal pain. *Arch Surg* 2009; 144:137-141; discussion 142.
257. Levy J, Noble V: Bedside ultrasound for pediatric emergency medicine. *Pediatrics* 2008; 121:e1404-1412.
258. Tsung JW, Raio CC, Ramirez-Schrempp D, Blaivas M: Point-of-care ultrasound diagnosis of pediatric cholecystitis in the ED. *Am J Emerg Med* 2010; 28:338-342.
259. Malcom GE 3rd, Raio CC, Del Rios M, Blaivas M, Tsung JW: Feasibility of emergency physician diagnosis of hypertrophic pyloric stenosis using point-of-care ultrasound: A multi-center case series. *J Emerg Med* 2009; 37:283-286.
260. Rozycki GS, et al: The role of ultrasound in patients with possible penetrating cardiac wounds: A prospective multicenter study. *J Trauma* 1999; 46:543-552.
261. Arger PH, Schultz SM, Sehgal CM, Cary TW, Aronchick J: Teaching medical students diagnostic sonography. *J Ultrasound Med* 2005; 24:1365-1369.
262. *Making Health Care Safer: A Critical Analysis of Patient Safety Practices*. Summary. AHRQ Publication No. 01-E057. Rockville, Md: Agency for Healthcare Research and Quality; July 2001. Available at www.ahrq.gov/clinic/ptsafety/summary.htm. Accessed 2007.
263. Blackstock U, Stone MB: Emergency ultrasonography and error reduction. *Ann Emerg Med* 2009; 54:53-55.
264. Milling T, et al: Use of real-time, single-operator dynamic ultrasound guidance for internal jugular central venous cannulation: A randomized, controlled clinical trial. *Ann Emerg Med* 2005; 46:26.
265. Phelan M, Hagerty D: The oblique view: An alternative approach for ultrasound-guided central line placement. *J Emerg Med* 2009; 37:403-408.
266. Milling TJ, et al: Use of ultrasonography to identify infants for whom urinary catheterization will be unsuccessful because of insufficient urine volume: Validation of the urinary bladder index. *Ann Emerg Med* 2005; 45:510-513.
267. Milling TJ, et al: Randomized, controlled clinical trial of point-of-care limited ultrasonography assistance of central venous cannulation: The Third Sonography Outcomes Assessment Program (SOAP-3) trial. *Crit Care Med* 2005; 33:1764-1769.
268. Leung J, Duffy M, Finckh A: Real-time ultrasonographically-guided internal jugular vein catheterization in the emergency department increases success rates and reduces complications: A randomized, prospective study. *Ann Emerg Med* 2006; 48:540-547.

www.ketabpezeshki.com 66485457-66963820

269. Hudson PA, Rose JS: Real-time ultrasound guided internal jugular vein catheterization in the emergency department. *Am J Emerg Med* 1997; 15:79-82.
270. National Institute for Clinical Excellence: *Central venous catheters—ultrasound locating devices: Guidance*, 2002. Available at http://guidance.nice.org.uk/TA49/Guidance/pdf/English, 2011.
271. Verghese S, et al: Ultrasound-guided internal jugular venous cannulation in infants: A prospective comparison with the traditional palpation method. *Anesthesiology* 1999; 91:71-77.
272. Karakitsos D, et al: Real-time ultrasound-guided catheterisation of the internal jugular vein: A prospective comparison with the landmark technique in critical care patients. *Crit Care* 2006; 10:R162.
273. Balls A, et al: Ultrasound guidance for central venous catheter placement: Results from the Central Line Emergency Access Registry Database. *Am J Emerg Med* 2010; 28:561-567.
274. Bellazzini MA, Rankin PM, Gangnon RE, Bjoernsen LP: Ultrasound validation of maneuvers to increase internal jugular vein cross-sectional area and decrease compressibility. *Am J Emerg Med* 2009; 27:454-459.
275. Blaivas M, Adhikari S: An unseen danger: Frequency of posterior vessel wall penetration by needles during attempts to place internal jugular vein central catheters using ultrasound guidance. *Crit Care Med* 2009; 37:2345-2349; quiz 2359.
276. Moon CH, et al: Incidence of posterior vessel wall puncture during ultrasound-guided vessel cannulation in a simulated model. *Acad Emerg Med* 2010; 17:1138-1141.
277. Theodoro D, Krauss M, Kollef M, Evanoff B: Risk factors for acute adverse events during ultrasound-guided central venous cannulation in the emergency department. *Acad Emerg Med* 2010; 17:1055-1061.
278. Stone MB, Hern HG: Inadvertent carotid artery cannulation during ultrasound guided central venous catheterization. *Ann Emerg Med* 2007; 49:720.
279. Chiles K, Nagdev A: Accidental carotid artery cannulation detected by bedside ultrasound. *West J Emerg Med* 2011; 12:100-101.
280. Hilty WM, Hudson PA, Levitt MA, Hall JB: Real-time ultrasound-guided femoral vein catheterization during cardiopulmonary resuscitation. *Ann Emerg Med* 1997; 29:331-337.
281. Rippey JC, Pascu O, Jacobs I: Abdominal compression effectively increases the size of the common femoral vein, as measured by ultrasonography. *Ann Emerg Med* 2008; 52:446-452.
282. Werner SL, Jones RA, Emerman CL: Effect of hip abduction and external rotation on femoral vein exposure for possible cannulation. *J Emerg Med* 2008; 35:73-75.
283. Bentley SK, Seethala R, Weingart SD: Ultrasound-guided axillary vein approach to the subclavian vein for central venous access. *Ann Emerg Med* 2008; 52:475.
284. Sharma A, Bodenham AR, Mallick A: Ultrasound-guided infraclavicular axillary vein cannulation for central venous access. *Br J Anaesth* 2004; 93:188-192.
285. Fragou M, et al: Real-time ultrasound-guided subclavian vein cannulation versus the landmark method in critical care patients: A prospective randomized study. *Crit Care Med* 2011; 39:1607-1612.
286. Mallin M, Louis H, Madsen T: A novel technique for ultrasound-guided supraclavicular subclavian cannulation. *Am J Emerg Med* 2010; 28:966-969.
287. Froehlich CD, et al: Ultrasound-guided central venous catheter placement decreases complications and decreases placement attempts compared with the landmark technique in patients in a pediatric intensive care unit. *Crit Care Med* 2009; 37:1090-1096.
288. Stone MB, Moon C, Sutijono D, Blaivas M: Needle tip visualization during ultrasound-guided vascular access: Short-axis vs long-axis approach. *Am J Emerg Med* 2010; 28:343-347.
289. Mills CN, Liebmann O, Stone MB, Frazee BW: Ultrasonographically guided insertion of a 15-cm catheter into the deep brachial or basilic vein in patients with difficult intravenous access. *Ann Emerg Med* 2007; 50:68-72.
290. Stein J, George B, River G, Hebig A, McDermott D: Ultrasonographically guided peripheral intravenous cannulation in emergency department patients with difficult intravenous access: A randomized trial. *Ann Emerg Med* 2009; 54:33-40.
291. Witting MD, Schenkel SM, Lawner BJ, Euerle BD: Effects of vein width and depth on ultrasound-guided peripheral intravenous success rates. *J Emerg Med* 2010; 39:70-75.
292. Brannam L, Blaivas M, Lyon M, Flake M: Emergency nurses' utilization of ultrasound guidance for placement of peripheral intravenous lines in difficult -access patients. *Acad Emerg Med* 2004; 11:1361-1363.
293. Chinnock B, Thornton S, Hendey GW: Predictors of success in nurse-performed ultrasound-guided cannulation. *J Emerg Med* 2007; 33:401-405.
294. Schoenfeld E, Boniface K, Shokoohi H: ED technicians can successfully place ultrasound-guided intravenous catheters in patients with poor vascular access. *Am J Emerg Med* 2011; 29:496-501.
295. Rose JS, Norbutas CM: A randomized controlled trial comparing one-operator versus two-operator technique in ultrasound-guided basilic vein cannulation. *J Emerg Med* 2008; 35:431-435.
296. Mahler SA, et al: Short- vs long-axis approach to ultrasound-guided peripheral intravenous access: A prospective randomized study. *Am J Emerg Med* 2011; 29:1194-1197.
297. Resnick JR, Cydulka RK, Donato J, Jones RA, Werner SL: Success of ultrasound-guided peripheral intravenous access with skin marking. *Acad Emerg Med* 2008; 15:723-730.
298. Doniger SJ, Ishimine P, Fox JC, Kanegaye JT: Randomized controlled trial of ultrasound-guided peripheral intravenous catheter placement versus traditional techniques in difficult-access pediatric patients. *Pediatr Emerg Care* 2009; 25:154-159.
299. Schnadower D, Lin S, Perera P, Smerling A, Dayan P: A pilot study of ultrasound analysis before pediatric peripheral vein cannulation attempt. *Acad Emerg Med* 2007; 14:483-485.
300. Schwemmer U, et al: Ultrasound-guided arterial cannulation in infants improves success rate. *Eur J Anaesthesiol* 2006; 23:476-480.
301. Sandhu NS, Patel B: Use of ultrasonography as a rescue technique for failed radial artery cannulation. *J Clin Anesth* 2006; 18:138-141.
302. Lanza C, Russo M, Fabrizzi G: Central venous cannulation: Are routine chest radiographs necessary after B-mode and colour Doppler sonography check? *Pediatr Radiol* 2006; 36:1252-1256.
303. Stone MB, Nagdev A, Murphy MC, Sisson CA: Ultrasound detection of guidewire position during central venous catheterization. *Am J Emerg Med* 2010; 28:82-84.
304. Stone MB: Identification and correction of guide wire malposition during internal jugular cannulation with ultrasound. *CJEM* 2007; 9:131-132.
305. Tsung JW, Blaivas M, Stone MB: Feasibility of point-of-care colour Doppler ultrasound confirmation of intraosseous needle placement during resuscitation. *Resuscitation* 2009; 80:665-668.
306. Stone M, Teismann N, Wang R: Ultrasonographic confirmation of intraosseous needle placement in an adult unembalmed cadaver model. *Ann Emerg Med* 2007; 49:515-519.
307. Barnes TW, et al: Sonographically guided thoracentesis and rate of pneumothorax. *J Clin Ultrasound* 2005; 33:442-446.
308. Tayal V, Pariyadath M, Norton J: Randomized controlled trial of ultrasound-guided peripheral non-knee arthrocentesis in the emergency department. *Acad Emerg Med* 2006; 13:S197.
309. Sibbitt WL Jr, et al: Does sonographic needle guidance affect the clinical outcome of intraarticular injections? *J Rheumatol* 2009; 36:1892-1902.
310. Crystal CS, Miller MA, Young SE: Ultrasound guided hematoma block: A novel use of ultrasound in the traumatized patient. *J Trauma* 2007; 62:532-533.
311. Reid N, Stella J, Ryan M, Ragg M: Use of ultrasound to facilitate accurate femoral nerve block in the emergency department. *Emerg Med Australas* 2009; 21:124-130.
312. Barker R, et al: Femoral nerve blockade administered preclinically for pain relief in severe knee trauma is more feasible and effective than intravenous metamizole: A randomized controlled trial. *J Trauma* 2008; 64:1535-1538.
313. Stone M, Price D, Wang R: Ultrasound-guided supraclavicular block for the treatment of upper extremity fractures, dislocations, and abscesses in the ED. *Am J Emerg Med* 2007; 25:472-475.
314. Wu TS, Leech SJ, Rosenberg M, Huggins C, Papa L: Ultrasound can accurately guide gastrostomy tube replacement and confirm proper tube placement at the bedside. *J Emerg Med* 2009; 36:280-284.
315. Ferre RM, Sweeney TW: Emergency physicians can easily obtain ultrasound images of anatomical landmarks relevant to lumbar puncture. *Am J Emerg Med* 2007; 25:291-296.
316. Nomura J, et al: A randomized controlled trial of ultrasound-assisted lumbar puncture. *J Ultrasound Med* 2007; 26:1341-1348.
317. Nelson BP, Melnick ER, Li J: Portable ultrasound for remote environments, Part I: Feasibility of field deployment. *J Emerg Med* 2011; 40:190-197.
318. Nelson BP, Melnick ER, Li J: Portable ultrasound for remote environments, Part II: Current indications. *J Emerg Med* 2011; 40:313-321.
319. Fincke E, et al: Evaluation of shoulder integrity in space: First report of musculoskeletal US on the International Space Station. *Radiology* 2005; 234:319-322.

www.ketabpezeshki.com 66485457-66963820

320. Boniface K, Smith R, Breit A: FAST exam by prehospital providers under real time remote physician guidance. *J Ultrasound Med* 2008; 27:S87.
321. Heegard WG, et al: Ultrasound in helicopter EMS. *Acad Emerg Med* 2003; 10:449.
322. Melanson S, McCarthy J, Kostenbader J, Greissinger P, Heller M: Aeromedical FAST by nonphysicians with a miniature ultrasound unit. *Ann Emerg Med* 2000; 36:S21.
323. Busch M: Portable ultrasound in pre-hospital emergencies: A feasibility study. *Acta Anaesthesiol Scand* 2006; 50:754-758.
324. Heegaard W, et al: Prehospital ultrasound by paramedics: Results of field trial. *Acad Emerg Med* 2010; 17:624-630.
325. Lyons R, Stamilio D, McReynolds T, Endrizzi J: Diagnosis and treatment of a ruptured ectopic pregnancy in a combat support hospital during operation Iraqi Freedom: Case report and critique of a field-ready sonographic device. *Mil Med* 2004; 169:681-683.
326. Sarkisian AE, et al: Sonographic screening of mass casualties for abdominal and renal injuries following the 1988 Armenian earthquake. *J Trauma* 1991; 31:247-250.
327. Sustic A, et al: Ultrasonography in the evaluation of hemoperitoneum in war casualities. *Mil Med* 1999; 164:600-602.
328. Shah S, et al: Impact of portable ultrasound in trauma care after the Haitian earthquake of 2010. *Am J Emerg Med* 2010; 28:970-971.
329. Dyer D, et al: The clinical and technical evaluation of a remote telementored telesonography system during the acute resuscitation and transfer of the injured patient. *J Trauma* 2008; 65:1209-1216.
330. Shah S, et al: Development of an ultrasound training curriculum in a limited resource international setting: Successes and challenges of ultrasound training in rural Rwanda. *Int J Emerg Med* 2008; 1:193-196.
331. Adler D, Mgalula K, Price D, Taylor O: Introduction of a portable ultrasound unit into the health services of the Lugufu refugee camp, Kigoma District, Tanzania. *Int J Emerg Med* 2008; 1:261-266.
332. Jang T, Naunheim R, Sineff S, Aubin C: Operator confidence correlates with more accurate abdominal ultrasounds by emergency medicine residents. *J Emerg Med* 2007; 33:175-179.

www.ketabpezeshki.com 66485457-66963820

CHAPTER 197

Process Improvement and Patient Safety

Shawna J. Perry, Robert L. Wears, Pat Croskerry, and Marc J. Shapiro

PERSPECTIVE

The overall process of patient care in the emergency department (ED) begins with the initial decision by the patient (or caregiver or family) to seek emergency assistance and ends with the patient's disposition and follow-up. The care process is highly complex, with many separate components, people, and interfaces with other processes in the health care organization (Fig. 197-1). This complexity, among other things, provides many opportunities for process failures, "errors," and adverse outcomes.

Although process failures in health care have been studied for decades, most of that effort originated from outside of the field of health care, with health care professionals largely unaware of it.[1] This began to change in the early 1990s when the Harvard Medical Practice Study reported that almost 4% of hospitalized patients suffered significant adverse events during their care and that almost 30% of these were due to human error.[2] The study noted that failures in ED care accounted for only approximately 3% of all adverse events, but more than 90% of adverse ED events were judged to be preventable. This study and others ultimately led the Institute of Medicine to issue a report in 1999 titled *To Err Is Human: Building a Safer Health System*.[3] This report provoked the interest of the media and the general public and thrust the issue of safety in health care onto the national agenda. The major accomplishment of the Institute of Medicine report was the introduction of some of the fundamental concepts regarding safety in complex systems for the first time into the world of health care. The most transforming concept was the idea that failures (or errors) in care are not the result of bad decisions or bad individuals but are instead intrinsic properties of the processes of care in the health care system. Thus efforts to reduce these failures should be focused on changing the processes of care rather than on identifying, retraining, or punishing the workers.

The response within health care was mixed. Most health care professionals focused on the projected number of deaths due to error, arguing that they were either too high[4,5] or too low,[6] and a third, smaller group argued that the concept of error is essentially contestable and thus an approach aimed at counting errors is fundamentally flawed.[7] The transforming concept of "system failure" rather than "human error" gradually gained acceptance, despite going against the natural human tendency to believe that individuals cause outcomes. This viewpoint is problematic because it undermines a clinician's sense of free agency; health care providers prefer not to view themselves as trapped in a system that is moving inexorably toward a poor outcome.

Within emergency medicine, safety and quality have been addressed by task forces, interest groups, and special sections examining the practice of emergency care, its processes, and environments with tools from the "science of safety" to improve performance and to cultivate patient safety.[8] A basic curriculum for teaching about safety at the undergraduate level was developed, with similar efforts taking place to implement safety concepts into medical education.[9]

Interesting lines of research on the safety and processes within emergency care have been performed, with a number of patient safety case reports published in the emergency medicine literature.[10] Chisholm[11] reported that emergency physicians are interrupted, on average, approximately once every 6 minutes and that two thirds of those interruptions cause a change in task; this is important because both interruptions and task switching frequently lead to process failures. Fordyce[12] reported that self-detected errors occurred in almost 20% of all ED cases but that only 2% were associated with adverse events. Fordyce's work emphasizes that errors are ubiquitous but only rarely combine with other factors to produce adverse events, and it supports the notion that focusing on elimination of errors is not likely to be a productive strategy for improvement.

Coiera[13] studied emergency physicians in Australia and reported high communication loads and found similar levels of interruptions. Morey[14] reported that specific training of emergency physicians and nurses to work together in teams led to reductions in failures and improved performance. Perry and colleagues[15,16] identified a number of unexpected yet highly consequential failures of information technology that were difficult to detect, some occurring during emergency resuscitations. Wears and Perry[17] noted ergonomic shortcomings in the workplace and pointed out their potential to contribute to failures in care. Hall[18] identified significant delays related to ED layout, with time to assessment of chest pain patients being longer for patients placed behind a door or who were 25 feet or farther away from the physicians assigned to care. These examples of safety research in emergency care demonstrate the wide range of known and unknown contributors to patient safety and the importance of the work processes that overlay this complex work environment.

SOURCES OF FAILURE IN EMERGENCY CARE

Many characteristics of emergency medical practice make it vulnerable to failures (Table 197-1).[19-26] This section focuses on some of the principal factors that contribute to adverse outcomes and how they might be better managed to improve safety.

Emergency Department Design, Human Factors, and Ergonomics

Two frequently overlooked contributors to lowered safety in any work environment are the design of the workspace and the

www.ketabpezeshki.com 66485457-66963820

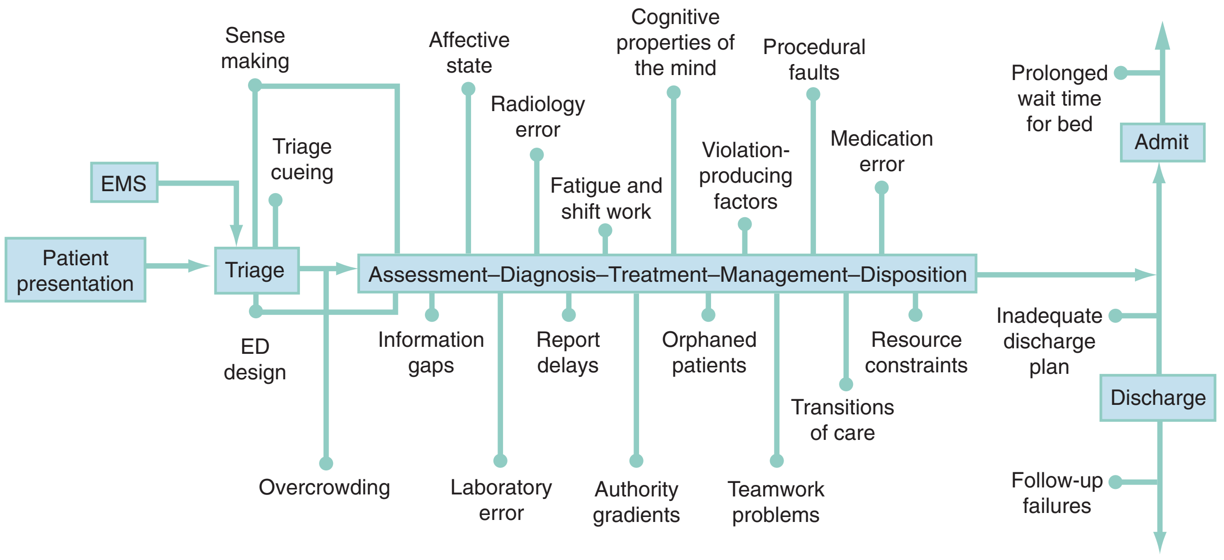


Figure 197-1. Process mapping showing sources of failures. The overall process is highly simplified and presented as a linear model of a patient's trajectory. (The actual process is much more complex, involving multiple simultaneous patients at different stages and loops within a given patient's trajectory.) Sources of failure may occur in parallel or at multiple stages in the sequence and are often additive in their overall effect on patient safety.

Table 197-1 Characteristics of the Emergency Department That Affect Performance

INTRINSIC*	EXTRINSIC†
Limitations of human cognition	High communication load
High levels of uncertainty	Poor teamwork
High decision density	Overcrowding
High cognitive load	Production pressures
Narrow windows of opportunity	High ambient noise levels
Multiple interruptions or distractions	Information gaps
Low signal-to-noise ratio‡	Report delays
Surge phenomena§	Inadequate staffing
Novel or infrequently occurring conditions	Poor feedback
Patient factors (e.g., acuity, language, delirium)	Inexperience
	Inadequate supervision
	Sleep deprivation or sleep debt
	Fatigue
	Multiple transitions of care
	Poorly designed procedures
	Emergency department layout

*Intrinsic factors are intimately part of the nature of emergency care and as such are not amenable to change but instead must be compensated for.
†Extrinsic factors are in principle manageable and typically relate to resource constraints.
‡Low signal-to-noise ratio refers to the low likelihood of a critical diagnosis compared with a benign diagnosis for similarly presenting symptoms and findings (e.g., subarachnoid hemorrhage vs. tension headache).
§Surge phenomena are the rapid changes in volume and acuity routinely experienced in many emergency departments.

engineering of the tools, technology, and procedures used to perform the work.[27] This is especially true for EDs because the majority were not designed for the care actually being delivered there.[28] ED caregivers are required to adapt to the space by creating "work-arounds" to cope with the limitations and impediments of the workspace.

Consistency is rarely found in equipment across or between areas. For instance, the blood pressure monitor in the ED is often not the same type or model as that used in the radiology department when the patient goes for diagnostic tests. In addition, tools and technology are seldom developed or assessed for their "user-centered design" or ability to be integrated into existing workspace and the associated hazards for doing so. This is most apparent with regard to health information technology, which is often introduced for improvement of safety and quality; however, embedded latent features that can produce clinical failures that are "hard to see" have been demonstrated.[29,30] Study of computerized physician order entry by Koppel[31] showed that the software facilitated 22 types of medication error risks, for example, displays that prevented a coherent view of the patients' medications and inflexible ordering formats that generated wrong orders. Other contributors to information technology failure within health care are the lack of usability testing,[32] delays in in-service training, and failure to reassess the impact of the new technology and changes in clinical work after implementation.[33]

The contribution of poor design to the difficulty in maintaining safety in a health care environment is generally overlooked by staff members, who cope with these difficulties as "part of the job."[17] Vigilance is the common solution but despite caregivers' best efforts cannot be sustained, given competing demands for their attention. This increases the risk of a failure's not being recognized as linked to the workplace, the procedures, or the equipment, despite being "tightly coupled" to any or all of these.

Overcrowding

ED crowding has long been recognized as a major source of time-delay failures and a threat to patient safety.[34,35] Such delays are not simply an inconvenience to the patient but may give rise to significant adverse events. For example, patients with atypical presentations of severe illness who have been mis-triaged to low levels of acuity may experience inordinate and, occasionally, fatal delays. In other cases, such as community-acquired pneumonia, cellulitis, and lacerations, more expedient care may significantly improve the outcome of the illness. A significant proportion of patients who leave the ED without being seen may have serious illness and incur delays in diagnosis and treatment. At the other end of the process, when the patient is ready for admission to the hospital from the ED, further time-delay errors may occur (see Fig. 197-1). Not only do such delays create throughput problems for the ED and contribute to overcrowding by front-end loading or "entry block," but they also give rise to discontinuities in care and may lead to adverse events that are difficult to identify because they are manifested once the patient has left the ED.[36-39] Manifestations of

www.ketabpezeshki.com 66485457-66963820

cognitive overload associated with ED overcrowding are diminished overall with increased use of heuristics (mental shortcuts) in medical decision-making and more biased and risk-laden decisions.

Information Gaps

Missing information is common in emergency care and can significantly affect quality of care.[40] Hospital records, especially discharge summaries, details of past medical history, and other important information, are often difficult to access in an expedient manner, even with electronic medical records. Referral notes sent by family physicians with the patient may not reach the emergency physician or may not contain relevant or significant details. In these situations, emergency physicians make clinical decisions and take action on the basis of incomplete, limited, or erroneous information. Emergency clinicians often end up not seeking additional or clarifying information because of time pressures, patient volume, or limited methods to obtain more information (e.g., the referring physician's office is closed), essentially accommodating to this "gap" in continuity of care and the associated increase in patient risk.[41]

Box 197-1 Violation-Producing Factors

- Gender
- Mood
- Ill health
- Risk seeking or risk aversion
- Normalization of deviance
- Maladaptive group pressures (groupthink)
- Maladaptive copying behavior
- Underconfidence or overconfidence
- Perceived authorization to deviate
- Authority gradient effects (obeying authority figure or absence of disapproving authority figure)
- Likelihood of detection

Based on an original schema by Williams JC: Assessing and reducing the likelihood of violation behavior—preliminary investigation. Proceedings of an International Conference on the Commercial and Operations Benefits of Probabilistic Safety Assessment. Edinburgh, Institute of Nuclear Engineers, 1997. Modified for emergency medicine in Croskerry PG, Wears RL: Safety in emergency medicine. In: Markovchick V, Pons P (eds): Emergency Medicine Secrets, 3rd ed. Philadelphia, Hanley & Belfus, 2003. A summary can also be found in Reason J: Managing the Risks of Organizational Accidents. Aldershot, UK, Ashgate, 1997.

Performance-Shaping Factors

Blaming individuals for errors contributes little to an understanding of risk, vulnerability, and failure. A wide variety of ambient, systemic conditions in the ED contribute to the majority of adverse events and near misses that occur (see Table 197-1). Some performance-shaping factors can be considered to be "intrinsic," part and parcel of the milieu of emergency medicine and thus not amenable to direct control (e.g., cognitive workload, multiple distractions and interruptions, and high acuity). These factors must be managed by strategies to buffer or to mitigate their effects. In contrast, other "extrinsic" performance-shaping factors typically reflect limitations of resources (e.g., staffing ratios, production pressure, and ED layout). When resources are limited, a tradeoff can occur in the ability of the ED to provide safety and quality in patient care. This condition is referred to as RACQITO (*r*esource *a*vailability *c*ontinuous *q*uality *i*mprovement *t*rade-*o*ff),[42] a concept derived from speed-accuracy tradeoffs described in industrial settings.

Violation-Producing Factors

Although at first one might think that violations of organizational policies, rules, and procedures would always be causes of failures and adverse events, the modern approach to safety has pointed out that some violations are actually necessary for the safe functioning of the system, and others fall somewhere in between.[43] Aside from recklessness, drug use on the job, moral failings, and other egregious acts, research in other domains has identified other factors that are associated with the occurrence of rule and safety violations (Box 197-1). The "normalization of deviance"[44] is an accumulated tolerance of small variances from safe operating conditions that develops over time, ultimately compromising safety. This is evidenced in overtaxed EDs coping with overcrowding of patients (e.g., performing evaluation and management of patients in hallways). Violations can also occur in response to perceptions of authority. They may occur through a directive supporting violation from an authority figure (e.g., nursing supervisors order admitted patients moved to inpatient beds without calling to report if there are delays in reaching inpatient nurses), the absence of a disapproving authority (e.g., physicians leaving shifts early and the medical director does not address the behavior), or an individual's self-perception that he or she is authorized to disregard or to deviate from prescribed procedures (e.g., ED electrocardiograms done on patients in chairs because there are no available stretchers).

Fluctuations in mood can also contribute to violations for a variety of reasons and will result in inconsistent clinical performance; men are more likely to break safety rules and to engage in more risk-taking behavior than women are.[43] Risk-seeking and risk-averse attitudes are associated aspects of decision-making in the ED.[45]

Teamwork

Good teamwork is essential to the safe practice of emergency medicine, but emergency caregivers are not trained or evaluated as teams. Teamwork training in other fields, such as aviation, has been successful in reducing failures related to poor communication, cross-monitoring (observing others' behaviors to reduce risk of failure and share workload), and authority gradients (both within and between professions).[46] Work on transferring teamwork training principles to emergency medicine suggested that teamwork failures are involved in approximately 40% of malpractice cases.[47] The lack of cross-monitoring across team members and the failure of advocacy or assertion on behalf of the patient by caregivers to avoid patient harm were two of the factors most frequently identified. A multidisciplinary teamwork training course implemented in nine EDs showed a significant improvement in quality of team behaviors and a sixfold decrease in observed clinical errors.[14] Teamwork is not a specific fix for any one type of error, but it should be viewed as one type of adaptable human factor intervention with a set of teachable skills and behaviors capable of increasing system resilience and safety, which are hallmarks of high-reliability organizations.[48]

Teamwork training requires a change of culture, which can be difficult for ED staff. Institutional and ED leadership must be fully committed to the process before implementation of teamwork training for all staff. Resistance to behavioral change is likely to be encountered, and it will be necessary to demonstrate the clinical relevance of this training. High-fidelity medical simulation supported by audiovisual feedback offers the educational methodology to help clinicians and staff understand the necessity of behavioral change.[49] A major unanswered question is how to embed teamwork behaviors into medical training and how to sustain the behaviors over time.

www.ketabpezeshki.com 66485457-66963820

Authority Gradients

Almost all human groups have some form of authority gradient among members. This hierarchy can be based on profession (e.g., physicians have greater authority than nurses) or organizational rank (e.g., attending physicians have more authority than residents). Ideally, information between team members should flow freely, but this may not occur if low-authority members are inhibited by differences in seniority, stature, expertise, profession, or social status. There are clear examples of cases in which authority gradients have been responsible for adverse events.[50] A work environment in which all team members feel comfortable expressing their viewpoint, especially if it is a dissenting one, requires cultural change that can begin with the physicians who occupy the highest authority position in the clinical setting. Authority figures have the ability to initiate change by recognizing the value of perspectives other than their own and eliciting them from other clinicians and staff (e.g., asking a patient's nurse what he or she thinks may be going on with the patient). Senior clinicians are in a powerful position to bridge gradients by fostering open communication through multidisciplinary rounds, demonstrating that they are approachable (e.g., acknowledging staff by name), and using clinical narratives from their own experience that illustrate near misses and judgment failures.[51]

Cognitive and Affective Limitations

The human mind has characteristic dispositions to respond to particular stimuli and contexts in specific ways. A great deal of effort has gone into identifying and describing these; more than 50 *cognitive dispositions to respond* have been described.[17,52-54] A number of strategies have been proposed to reduce the adverse outcomes associated with cognitive dispositions to respond.[55]

The overall process of patient care in the ED is driven by a process of making clinical sense out of multiple sets of fragmented, tangential, and interrupted stimuli. This is aimed at making an accurate diagnosis if possible or, more commonly, a useful framing of the problem, which can determine management and disposition. Although many diagnoses, such as lacerations, dislocations, fractures, and foreign bodies, are self-evident, others (e.g., chest pain, fever, headache, abdominal pain, and syncope) are often associated with high levels of diagnostic uncertainty and are more likely to lead to problems. Cognitive biases can frequently be identified in retrospect after diagnostic failures,[56] but the problem of hindsight bias makes this identification problematic.[57]

In addition to cognitive mental properties, the emotional state of the physician can affect his or her decision-making; this has been referred to as *visceral bias*.[17,53] Relatively little attention has been directed to the important role of affective bias in decision-making. Although processes such as countertransference, fundamental attribution error,[42] and the economy of perception that underlies stereotyping are well understood in psychology, health care workers are typically less aware of them (e.g., "She's a drug seeker," "He's a frequent flyer," and "She just wants attention") and their effect on clinical interactions.[58]

Fatigue and Shift Work

Both fatigue and shift work contribute to performance failures,[59] but relatively little research has been directed to their respective impacts on clinical performance in the unique milieu of the ED.[60] Although the two are often considered together, they are different entities and exert both qualitatively and quantitatively different effects on performance.[61] Fatigue has a number of determinants separate from those associated with shift work (Fig. 197-2).

Shift work has extensive, well-documented, detrimental effects on health that in turn have an impact on well-being and job performance.[62] Importantly, it leads to disruption of circadian rhythms that inevitably result in sleep deprivation. Circadian dyssynchronicity largely occurs through missing sleep in the *anchor period,* approximately midway through the sleep phase when core temperature and arousal level are at their lowest. It has been stated that the performance degradation of someone who has been up all night is roughly equal to that of a person with a blood alcohol level of 0.1% (Box 197-2).[63]

The acute effects of sleep deprivation are well known, but the chronic effects are less appreciated. Invariably, working a night shift results in less sleep the following day, and subsequent sleep is often disrupted and fragmented in the struggle to restore the circadian rhythm before the night-shift cycle repeats itself. This results in the accumulation of a *sleep debt* that has a significant impact on performance. A study of anesthesia residents on a normal work schedule, with no on-call duty in the preceding 48 hours, showed daytime sleepiness scores comparable to those of patients with narcolepsy or sleep apnea.[64] The on-call schedule of these subjects (five periods per month) entailed considerably less sleep deprivation and fragmentation than an average emergency

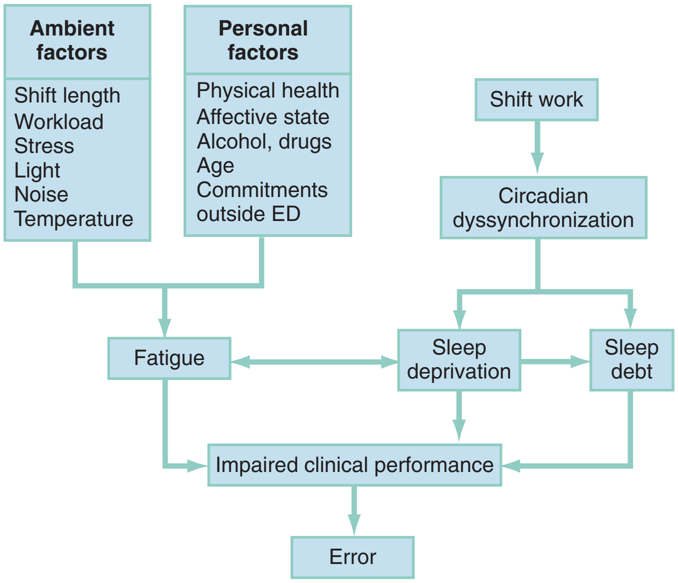


Figure 197-2. Relationships between shift work, fatigue, and performance.

Box 197-2 Effects of Sleep Deprivation

Longer reaction time
Lapses in attention or concentration
Lost information
Errors of omission
Poor short-term memory
Poor mood (increased confusion, stress, and irritability)
Reduced motivation
Distractibility
Sleepiness
Poor psychomotor performance
- At circadian low points
- When sedentary
- On long, difficult, or externally paced tasks with no feedback
- In unchanging surroundings, particularly with reduced light or sound, or with low motivation, interest, or novelty

Modified from Bonnet MH: Sleep deprivation. In: Kryger M, Roth T, Dement WC (eds): Principles and Practice of Sleep Medicine. Philadelphia: WB Saunders; 2000:53-71.

www.ketabpezeshki.com 66485457-66963820

physician's schedule. Increasing age is associated with decreased tolerance for sleep deprivation.[65]

Performance declines as work hours increase,[66] but the optimal shift length in the ED is unknown and difficult to delineate for several reasons. The relationship with workload or acuity is not well appreciated, and some workers exhibit contradictory incentives, such as preferring to work longer shifts to get more days off. More recovery time between shifts might be expected to enhance job performance, but these issues remain relatively unexplored. A survey of emergency physicians found a preference for 8-hour over 12-hour shifts,[67] but it is not known whether job satisfaction in the ED translates into improved clinical performance and fewer adverse events. Other ambient conditions within the ED, competing commitments outside the ED, age, ill health, and other factors contribute to fatigue, with evidence pointing toward additional health implications for emergency physicians.[68,69]

The appropriate management of shift work and fatigue to improve patient safety is not well understood, and further research is needed in this area. In most high-hazard industries, the assumption is that fatigue and long, aberrant work hours lead to poor performance; however, in the health care industry, concerns about discontinuity of care and difficulties in changing medical culture have obscured these issues. Given that medical personnel, like all human beings, function suboptimally when they are fatigued, efforts to reduce fatigue and sleepiness should be undertaken, and the burden of proof should be in the hands of the advocates of the current system to demonstrate that it is safe.[63] In the meantime, shift scheduling should be optimized to reduce the impact of circadian disruption, and ED personnel should practice good sleep hygiene. Some basic approaches are listed in Box 197-3.[62,66]

Box 197-3 Rational Approaches to Shift Work

- Optimize circadian-friendly schedules
  - Forward rotating (clockwise with circadian rhythms)
  - Rapid changes
  - Minimize consecutive nights (one or two)
  - 24-48 hours off after nights
  - Allow social time, including some weekends
  - 8-hour shifts (absolute maximum 12 hours)
  - Institute regular, predictable template
- Practice proper sleep hygiene
  - Use a sleep-friendly room: room-darkening blinds, "white noise" (e.g., electric fan) or earplugs, no phones, family aware
  - Maintain a regular sleep routine
  - Try anchor sleep
  - Avoid caffeine, alcohol, and drugs
  - Prophylactic naps
- Modulate circadian rhythms
  - Exercise
  - Consider bright light
- Eat healthy
  - Eat a balanced diet
  - Avoid junk food
  - Keep regular mealtimes
- Promote a healthy lifestyle and work style
  - Promote a personal healthy lifestyle
  - Educate friends and family about shift work issues
  - Educate colleagues about shift work issues
  - Advocate for department improvements in working conditions
  - Advocate for shift worker–friendly community services
- Avoid pharmaceuticals
  - Use caffeine in moderation, prn
  - Do not use sedatives or stimulants
  - Avoid alcohol before sleep

Modified from Jha AK, Duncan BW, Bates DW: Fatigue, sleepiness, and medical errors. In: Making Health Care Safer: A Critical Analysis of Patient Safety Practices. Evidence Report/Technology Assessment No. 43, AHRQ publication 01-E058. Rockville, Md, Agency for Healthcare Research and Quality, 2001; and Frank JR, Ovens H: Shiftwork and emergency medicine practice. CJEM 4:421, 2002.

PROBLEM AREAS IN EMERGENCY CARE

The mechanisms of failure within the ED are remarkably variable, with a cadre of known and unknown contributors. Areas of consistent concern include triage, technical procedures, laboratory and radiographic tests, transitions in patient care, orphaned patients, and medications.

Triage

Triage, or sorting by acuity, is by definition an abbreviated decision-making process that can never be completely safe because of the limited information available, the lack of time invested, and the variety of presentations of illness and injury. Also, there is a low "signal-to-noise" ratio for a number of serious conditions (i.e., when the incidence of a serious condition is far exceeded by that for a benign condition, but their clinical presentations are similar). Inevitably, the triage process involves tradeoffs between sensitivity and specificity. Undertriage for a particular patient would have a greater potential for an adverse event than overtriage, whereas overtriage affects resource utilization and may have an impact on the care of other patients.

Triage assessments are important contributors to process failures and adverse events. Beyond treatment delays, which can occur with undertriage or be produced by overtriage, an incorrect assessment may be the triggering event that initiates a chain of failures. Geography can become destiny, and an inappropriate triage to a specific treatment area may create a bias in the minds of the treating clinicians and staff. The use of five-level triage systems for adults and children, with excellent inter-rater reliability, offers an opportunity to reduce the risk associated with undertriage.[70,71]

Technical Procedures

The practice of emergency medicine requires proficiency in a wide range of procedures with varying degrees of difficulty. Patients who require procedures are at greater risk for adverse events.[12] Contributors to this higher risk include not only problems with proficiency but also a low frequency for use of higher risk procedures. Critical procedures, such as cricothyrotomy, pericardiocentesis, and endotracheal intubation, are rarely performed in many EDs. When they are needed, they are highly consequential events under significant time pressure for intervention, therein reducing opportunity to refresh skills before the procedure is performed. An important challenge in emergency medicine is the acquisition and especially the maintenance of a requisite level of skill. Simulation techniques have considerable potential here[72] but require both capital and human investment to be effective.

Laboratory

The interface between the ED and its ancillary services is critically important. Failures can occur at three phases of laboratory processes. Preanalytic errors mostly occur through inappropriate collection of specimens because of lapses in technique, timing, and identification of both patient and specimen. Analytic errors refer to those that arise directly from the testing process. Postanalytic errors occur after the test result has been obtained and can take

www.ketabpezeshki.com 66485457-66963820

many forms (e.g., keyboard entry errors, overlooked or lost data, and failure of results to reach the physician). Studies of a blood bank and a stat laboratory found that the majority of failures occurred in the preanalytic and postanalytic stages, with less than 5% in the analytic stage.[73,74] Overall, the laboratory defect rate is less than 1%, but the number of exposures is large. Of the failures that do occur, up to 50% may have a moderate impact and up to 8% a severe impact on patient care.[75]

Radiology

Radiographic imaging is a critical aspect of diagnosis and management in the ED. Although patient identification and wrong-side problems are important sources of failure, the majority lie in interpretation. Assuming the radiologist's interpretation to be the criterion standard, the rate of errors in interpretation by emergency physicians and residents may be as high as 16% for plain radiographs and more than double that rate for computed tomography scans.[76] Clearly, not all misinterpretations are consequential, and emergency physicians typically seek the advice of the radiologist when they recognize difficult interpretations. The introduction of digital imaging and picture archiving communications systems has resulted in new patient safety issues related to usability, the effect of monitor resolution on interpretation, and reconciliation of ED physician and radiology readings.[77] Significant interpretation errors can be detected with prompt review of all films by the emergency physician and radiologist, but effective procedures are required to ensure that timely and appropriate feedback and review occur. This approach has been demonstrated to substantially reduce the rate of clinically important misinterpretations.[78]

Transitions in Patient Care

The need for 24-hour access to care and the fragmented nature of health care delivery require the occurrence of transitions of care between providers, either within the ED (at shift changes) or between the ED and other care areas (when patients are admitted, transferred, or discharged). The shift "sign-over" or "handoff" is generally thought of as a communication activity performed for the transfer of clinical information, but it also embodies the transfer of responsibility and authority from one provider to another. The sign-over also conveys general situational awareness (e.g., the state of the department, hospital, and city) and provides a forum for review of decision-making and treatment plans.

There has been little study of these transitions of care, despite their ubiquity and importance to the specialty.[20,79] Sign-overs are highly variable in their content, the number of individuals involved, the physical configuration (e.g., walking, stationary, and at bedside), the tools used to facilitate the transition (e.g., white boards, medical records, and written notes), and the length of the transition process. Although widely regarded as providing a major contribution to adverse events, sign-overs also provide an opportunity for review of decision-making by clinicians and may provide opportunities for recovery by bringing "fresh eyes" to a patient's case.[20,79]

Potential threats to high-quality transitions include the following:

- Interruptions during the turnover (e.g., phone calls and sidebar conversations) can cause a loss of focus and lead to the omission of important information.
- Lack of consistent structure to the turnover: Although the traditional case presentation narrative is generally followed (chief complaint, history, physical examination, initial laboratory results, impression, and plan), the case presentation format does not automatically remind participants of pending or as yet uncompleted tasks.
- Patients are commonly "marked" in ways that can sometimes be helpful but sometimes harmful, especially for at-risk groups such as the homeless, psychiatric patients, alcoholics, and drug abusers.

Common sense and well-meaning approaches such as standardizing verbal content and compulsory use of sign-over checklists risk extinguishing latent safety features inherent to them without further research of this complex and vital work tool for emergency medicine and health care overall.

Orphaned Patients

Orphaned patients are those who have suffered temporary loss or diminished supervision or accountability for their ED care. This may occur at several stages in the process. Patients who are seen and assessed at triage and then wait in the waiting area are temporarily orphaned. Those who are brought in by paramedics sometimes remain on stretchers for hours before being admitted to the ED. Patients who leave without being seen or before treatment is completed have "orphaned" themselves. Patients can also be temporarily orphaned out of the ED for radiographic studies or other special tests. On occasion, patients get "lost in the shuffle" and are overlooked at shift change, or they may get "lost" after one or more consultations with other services. With prolonged wait times, occult conditions can mature to serious and potentially catastrophic levels. A significant cause of orphaning in some EDs is the "boarding" of admitted patients because no inpatient beds are available. In such cases, patients may be put in holding areas in or adjacent to the ED and receive sporadic care from a succession of caregivers who know increasingly less about their conditions. The risk of harm to patients caught in this "gap" within the ED is not well studied.[41,80]

Medications

Medication errors constitute the largest proportion of failures in most general studies, with failures occurring in all six steps of the process (prescription, transcription, dispensing, administration, monitoring, and discharge).[81] Many EDs take on the dispensing role, obviating input from the pharmacy, where many errors are corrected. In addition, team communication errors can contribute to many failures: missed medications, wrong medications, and duplicate dosing. Pediatric patients are at higher risk; drug errors are no more common than in adults, but they are typically more serious.[82,83]

The presence of a pharmacist on the clinical team has been shown to reduce medication errors in several settings.[84] There is great interest in the potential for computer technologies, such as bar coding and computerized physician order entry, to enhance medication safety. However, despite some successful demonstrations, widespread implementation has not occurred, and there is evidence that such systems introduce new problems to replace old ones.[85] The Institute for Safe Medication Practices has recommended that certain problem practices be avoided in writing orders or prescriptions.[86] Success in this area will require more than just individual attentiveness; nurses, unit secretaries, and pharmacists will have to feel comfortable challenging improper use by physicians.

CONCLUSION

The safe management of patients in the ED depends on a multiplicity of processes. All appear vulnerable to failure, yet all have the potential for improvement through judicious process management. Efforts by front-line workers will not be sufficient, and so considerable effort will be required at the administrative or "blunt end" of the system.[87]

www.ketabpezeshki.com 66485457-66963820

Safety in complex dynamic environments, such as the ED, is itself dynamic. *Safety is a "nonevent" because it is evidenced by the absence of things that should not or do not occur,* such as administration of a medication to the wrong patient. It cannot be banked for future use but is created by workers in a well-designed and supportive organizational environment. Achieving safe performance in settings such as the ED is analogous to fighting a guerilla war: there are no dramatic victories, but there are occasional horrific defeats, with no end in sight. The establishment and maintenance of successful safety cultures within health care will require constancy of purpose by health care organizations, willingness to adopt new ideas and tools from outside of health care, and commitment to continued effort and investment.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

www.ketabpezeshki.com 66485457-66963820

References

1. Bosk C: *Forgive and Remember: Managing Medical Failure*. Chicago: University of Chicago Press; 1979.
2. Brennan TA, et al: Incidence of adverse events and negligence in hospitalized patients: Results of the Harvard Medical Practice Study I. *N Engl J Med* 1991; 324:370.
3. Kohn LT, Corrigan JM, Donaldson MS, eds: *To Err Is Human: Building a Safer Health System*. Washington, DC: National Academy Press; 1999.
4. McDonald CJ, Weiner M, Hui SL: Deaths due to medical errors are exaggerated in Institute of Medicine report. *JAMA* 2000; 284:93.
5. Dunn JD, Wears RL: The November special issue on errors [letter]. *Acad Emerg Med* 2001; 8:686.
6. Leape LL: Institute of Medicine medical error figures are not exaggerated. *JAMA* 2000; 284:95.
7. Wears RL: Beyond error. *Acad Emerg Med* 2000; 7:1175.
8. Wears RL: *The science of safety*. In: Zipperer L, ed. *Lessons in Patient Safety*. Chicago: National Patient Safety Foundation; 2001:1-7.
9. Cosby KS, Croskerry P: Patient safety: A curriculum for teaching patient safety in emergency medicine. *Acad Emerg Med* 2003; 10:69.
10. Croskerry P, Shapiro MJ: "Profiles in patient safety": A new feature. *Acad Emerg Med* 2002; 9:324.
11. Chisholm CD, Collison EK, Nelson DR, Cordell WH: Emergency department workplace interruptions: Are emergency physicians "interrupt-driven" and "multitasking"? *Acad Emerg Med* 2000; 7:1239.
12. Fordyce J, et al: Errors in a busy emergency department. *Ann Emerg Med* 2003; 42:324.
13. Coiera EW, et al: Communication loads on clinical staff in the emergency department. *Med J Aust* 2002; 176:415.
14. Morey JC, et al: Error reduction and performance improvement in the emergency department through teamwork training: Evaluation results of the MedTeams project. *Health Serv Res* 2002; 37:1553.
15. Perry SJ, Wears RL, Cook RI: The role of automation in complex system failures. *J Patient Saf* 2005; 1:56.
16. Perry SJ, et al: *Ironies of improvement: Organizational factors undermining resilient performance in healthcare*. Paper presented at IEEE International Conference on Systems, Cybernetics and Man; October 7-11, 2007; Montreal, Canada.
17. Wears RL, Perry SJ: Human factors and ergonomics in the emergency department. *Ann Emerg Med* 2002; 40:206.
18. Hall KK, Kyriacou DN, Handler JA, Adams JG: Impact of emergency department built environment on timelines of physician assessment of patients with chest pain. *Environ Behav* 2008; 40:233.
19. Croskerry P: Achieving quality in clinical decision making: Cognitive strategies and detection of bias. *Acad Emerg Med* 2002; 9:1184.
20. Beach C, Croskerry P, Shapiro M: Profiles in patient safety: Emergency care transitions. *Acad Emerg Med* 2003; 10:364.
21. Chisholm CD, Pencek AM, Cordell WH, Nelson DR: Interruptions and task performance in emergency departments compared with primary care offices. *Acad Emerg Med* 1998; 5:470.
22. Croskerry PG, Wears RL: *Safety in emergency medicine*. In: Markovchick V, Pons P, eds. *Emergency Medicine Secrets*, 3rd ed. Philadelphia: Hanley & Belfus; 2003:1023-1028.
23. Gaba DM, Howard SK: Patient safety: Fatigue among clinicians and the safety of patients. *N Engl J Med* 2002; 347:1249.
24. Derlet R, Richards J, Kravitz R: Frequent overcrowding in U.S. emergency departments. *Acad Emerg Med* 2001; 8:151.
25. Stiell A, Forster AJ, Stiell IG, van Walraven C: Prevalence of information gaps in the emergency department and the effect on patient outcomes. *CMAJ* 2003; 169:1023.
26. Croskerry P: The feedback sanction. *Acad Emerg Med* 2000; 7:1232.
27. Gosbee J: Human factors engineering and patient safety. *Qual Saf Health Care* 2002; 11:352.
28. Perry SJ, Hall KK: *Emergency department design and patient safety: Tracking the trade-offs*. In: Croskerry P, Cosby IC, Schenkel S, Wears RL, eds. *Patient Safety in Emergency Medicine*. Philadelphia: Lippincott Williams & Wilkins; 2008:106-111.
29. Wears RL: *More on computer glitches and laboratory test reporting*. Available at http://catless.ncl.ac.uk/Risks/23.64.html#subj4. Accessed December 29, 2004.
30. *Y2K Flaw blamed for Down's syndrome test errors*. Available at http://catless.ncl.ac.uk/Risks/21.67.html#subj14.
31. Koppel R, et al: Role of computerized physician order entry systems in facilitating medication errors. *JAMA* 2005; 293:1197.
32. Fairbanks RJ, Caplan S: *Poor interface design and lack of usability testing facilitate medical error*. In: Gosbee JW, Gosbee L, eds. *Using Human Factors Engineering to Improve Patient Safety*. Oakbrook Terrace, Ill: Joint Commission Resources; 2005:105-113.
33. Nemeth C, et al: Getting to the point: Developing IT for the sharp end of healthcare. *J Biomed Inform* 2005; 38:18.
34. Richardson LD, Asplin BR, Lowe RA: Emergency department crowding as a health policy issue: Past development, future directions. *Ann Emerg Med* 2002; 40:388.
35. Wears RL, Perry SJ, Nasca L: *"Free Fall"—Highly Decentralized, Resilient Adaptation to Demand-Capacity Mismatches in an Emergency Department*. Paper presented at the eighth International Naturalistic Decision-Making Conference; June 4-6, 2007; Pacific Grove, Calif.
36. Huang DT: Clinical review: Impact of emergency department care on intensive care unit costs. *Crit Care* 2004 ; 8:498.
37. Sprivulis PC, et al: The association between hospital overcrowding and mortality among patients admitted via Western Australian emergency departments. *Med J Aust* 2006; 184:208.
38. Gilligan P, et al: The Boarders in the Emergency Department (BED) study. *Emerg Med J* 2008; 25:265.
39. Burgess DJ: Are providers more likely to contribute to healthcare disparities under high levels of cognitive load? How features of the healthcare setting may lead to biases in medical decision making. *Med Decis Making* 2010; 30:246-257.
40. Stiell IG, et al: The Canadian CT head rule for patients with minor head injury. *Lancet* 2001; 357:1391.
41. Cook RI, Render M, Woods DD: Gaps in the continuity of care and progress on patient safety. *BMJ* 2000; 320:791.
42. Croskerry P: The cognitive imperative: Thinking about how we think. *Acad Emerg Med* 2000; 7:1223.
43. Reason J: *Managing the Risks of Organizational Accidents*. Aldershot, UK: Ashgate; 1997.
44. Vaughan D: *The Challenger Launch Decision: Risky Technology, Culture and Deviance at NASA*. Chicago: University of Chicago Press; 1996.
45. Pearson SD, et al: Triage decisions for emergency department patients with chest pain: Do physicians' risk attitudes make the difference? *J Gen Intern Med* 1995; 10:557.
46. Helmreich RL, Merritt AC: *Culture at Work in Aviation and Medicine*. Aldershot, UK: Ashgate; 1998.
47. Risser DT, et al: The potential for improved teamwork to reduce medical errors in the emergency department. The MedTeams Research Consortium. *Ann Emerg Med* 1999; 34:373.
48. Grabowski M, Roberts K: Risk mitigation in large-scale systems: Lessons from high reliability organizations. *Calif Manage Rev* 1997; 39:152.
49. Small SD, et al: Demonstration of high-fidelity simulation team training for emergency medicine. *Acad Emerg Med* 1999; 6:312.
50. Vincent C: *Hemivulvectomy: The wrong side removed*. Available at www.webmm.ahrq.gov/case.aspx?caseID=33. Accessed October 23, 2003.
51. Chisholm CD, Croskerry P: A case study in medical error: The use of the portfolio entry. *Acad Emerg Med* 2004; 11:388.
52. Campbell SG, Croskerry P, Bond WF: Profiles in patient safety: A "perfect storm" in the emergency department. *Acad Emerg Med* 2007; 14:743.
53. Croskerry P: Commentary: The affective imperative: Coming to terms with our emotions. *Acad Emerg Med* 2007; 14:184.
54. Croskerry P: *Cognitive and affective dispositions to respond*. In: Croskerry P, Cosby KS, Schenkel S, Wears R, eds. *Patient Safety in Emergency Medicine*. Philadelphia: Lippincott, Williams & Wilkins; 2008:219-227.
55. Croskerry P: Cognitive forcing strategies in clinical decision making. *Ann Emerg Med* 2003; 41:110.
56. Graber M, Gordon R, Franklin N: Reducing diagnostic errors in medicine: What's the goal? *Acad Med* 2002; 77:981.
57. Henriksen K, Kaplan H: Hindsight bias, outcome knowledge and adaptive learning. *Qual Saf Health Care* 2003; 12:46ii.
58. Croskerry P, Abbass A, Wu A: Emotional issues in patient safety. *J Patient Saf* 2010; 6:1-7.
59. Miller DP, Swain AD: *Human error and human reliability*. In: Salvendy G, ed. *Handbook of Human Factors*. New York: Wiley; 1986:219.
60. Rollinson DC, et al: The effects of consecutive night shifts on neuropsychological performance of interns in the emergency department: A pilot study. *Ann Emerg Med* 2003; 41:400.
61. Dodge R: Circadian rhythms and fatigue: A discrimination of their effects on performance. *Aviat Space Environ Med* 1982; 53:1131.
62. Croskerry P: *Shiftwork, fatigue, and safety in emergency medicine*. In: Croskerry P, Cosby KS, Schenkel S, Wears R, eds. *Patient Safety in Emergency Medicine*. Philadelphia: Lippincott Williams & Wilkins; 2008:259-268.
63. Bonnet MH: *Sleep deprivation*. In: Kryger M, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. Philadelphia: WB Saunders; 2000:53-71.

www.ketabpezeshki.com 66485457-66963820

64. Howard SK: Sleep deprivation and fatigue: Are we sleepy people keeping people asleep? *CSA Bull* 2000; 49.
65. Reid K, Dawson D: Comparing performance on a simulated 12 hour shift rotation in young and older subjects. *Occup Environ Med* 2001; 58:58.
66. Jha AK, Duncan BW, Bates DW: *Fatigue, sleepiness, and medical errors*. In: *Making Health Care Safer: A Critical Analysis of Patient Safety Practices*. Evidence Report/Technology Assessment No. 43, AHRQ Publication 01-E058. Rockville, Md: Agency for Healthcare Research and Quality; 2001. Available at www.ahcpr.gov/clinic/ptsafety/chap46a.htm. Accessed April 1, 2008.
67. Thomas H Jr, Schwartz E, Whitehead DC: Eight- versus 12-hour shifts: Implications for emergency physicians. *Ann Emerg Med* 1994; 23:1096.
68. Okamoto H, et al: An occupational health study of emergency physicians in Japan: Health assessment by immune variables (CD4, CD8, CD56, and NK cell activity) at the beginning of work. *J Occup Health* 2008; 50:136.
69. Gaba DM: *Physician work hours: The "sore thumb" of organizational safety in tertiary health care.* Proceedings of the Second Annenberg Conference on Enhancing Patient Safety and Reducing Errors in Health Care. Rancho Mirage, Calif: National Patient Safety Foundation; 1998:142.
70. Tanabe P, Gimbel R, Yarnold PR, Adams JG: The Emergency Severity Index (version 3) 5-level triage system scores predict ED resource consumption. *J Emerg Nurs* 2004; 30:22.
71. Maningas PA, Hime DA, Parker DE: The use of the Soterion Rapid Triage System in children presenting to the emergency department. *J Emerg Med* 2006; 31:353.
72. Jha AK, Duncan BW, Bates DW: *Simulator-based training and patient safety*. In: *Making Health Care Safer: A Critical Analysis of Patient Safety Practices*. Evidence Report/Technology Assessment No. 43, AHRQ Publication 01-E058. Rockville, Md: Agency for Healthcare Research and Quality; 2001. Available at www.ahcpr.gov/clinic/ptsafety/chap45.htm. Accessed April 1, 2004.
73. Boone DJ, et al: Transfusion medicine monitoring practices: A study of the College of American Pathologists/Centers for Disease Control and Prevention Outcomes Working Group. *Arch Pathol Lab Med* 1995; 119:999.
74. Carraro P, Plebani M: Errors in a stat laboratory: Types and frequencies 10 years later. *Clin Chem* 2007; 53:1338.
75. Bonini P, Plebani M, Ceriotti F, Rubboli F: Errors in laboratory medicine. *Clin Chem* 2002; 48:691.
76. Kripalani S, Williams MV, Rask K: *Reducing errors in the interpretation of plain radiographs and computed tomography scans*. In: *Making Health Care Safer: A Critical Analysis of Patient Safety Practices*. Evidence Report/Technology Assessment No. 43, AHRQ Publication 01-E058. Rockville, Md: Agency for Healthcare Research and Quality; 2001. Available at www.ahcpr.gov/clinic/ptsafety/chap35.htm. Accessed April 1, 2008.
77. Fairbanks RJ, Perry SJ, Venturino M, Zwemer FL: *Radiology in the emergency department: Patient safety issues with digital imaging*. In: Croskerry P, Cosby IC, Schenkel S, Wears RL, eds. *Patient Safety in Emergency Medicine*. Philadelphia: Lippincott Williams & Wilkins; 2008:133-138.
78. Espinosa JA, Nolan TW: Reducing errors made by emergency physicians in interpreting radiographs: Longitudinal study. *BMJ* 2000; 320:737.
79. Wears RL, et al: *Shift changes among emergency physicians: Best of times, worst of times*. Proceedings of the Human Factors and Ergonomics Society 47th annual meeting. Denver, Colo: Human Factors and Ergonomics Society; 2003:1420.
80. Falvo T, et al: The opportunity loss of boarding admitted patients in the emergency department. *Acad Emerg Med* 2007; 14:332.
81. Croskerry P, et al: Profiles in patient safety: Medication errors in the emergency department. *Acad Emerg Med* 2004; 11:289.
82. Selbst SM, Fein JA, Osterhoudt K, Ho W: Medication errors in a pediatric emergency department. *Pediatr Emerg Care* 1999; 15:1.
83. Kaushal R, et al: Medication errors and adverse drug events in pediatric inpatients. *JAMA* 2001; 285:2114.
84. American Society of Health-Systems Pharmacists: Top-priority actions for preventing adverse drug events in hospitals. Recommendations of an expert panel. *Am J Health Syst Pharm* 1996; 53:747.
85. Ash JS, Berg M, Coiera E: Some unintended consequences of information technology in health care: The nature of patient care information system–related errors. *J Am Med Inform Assoc* 2004; 11:104.
86. Koppel R, et al: Workarounds to barcode medication administration systems: Their occurrences, causes, and threats to patient safety. *J Am Med Inform Assoc* 2008; 15:408.
87. Abbreviations to avoid. *ISMP Medication Safety Alert* 2001; 6:1.

www.ketabpezeshki.com 66485457-66963820

Youth, Violence, and Street Gangs*

Jared Strote and H. Range Hutson

**For the complete chapter text, go to the Expert Consult website. To access your account, look for your activation instructions on the inside front cover of this book.*

I. PERSPECTIVE

II. VIOLENCE IN SCHOOLS

III. MEDIA VIOLENCE AND ITS EFFECT ON CHILDREN AND ADOLESCENTS

IV. ADOLESCENTS, DRUG ABUSE, AND VIOLENCE

V. FIREARMS AND YOUTH

VI. NON-POWDER FIREARMS

VII. PREVENTION STRATEGIES FOR YOUTH VIOLENCE

VIII. VIOLENCE BY STREET GANGS

A. Drive-By Shootings

B. Firearms and Violent Street Gangs

C. Psychological Effects of Street Gang Violence on Children and Adolescents

D. Preventing Gang Violence in the Emergency Department

E. Emergency Department Guidelines

F. Prevention of Street Gang Violence

KEY CONCEPTS

- Youths are particularly vulnerable to and disproportionately affected by violence.
- Physical, verbal, and relational violence in schools is common.
- Media violence, drugs and alcohol, and access to firearms have been associated with increased youth violence.
- Street gangs continue to be a major source of youth violence.
- Involvement of health care providers in youth violence prevention is effective and should occur in the emergency department.

www.ketabpezeshki.com 66485457-66963820

Youth, Violence, and Street Gangs

Jared Strote and H. Range Hutson

PERSPECTIVE

Presently, there are approximately 84 million children and adolescents younger than 20 years in the United States, and this population is increasingly composed of older adolescents and ethnic minorities.[1] The young are particularly vulnerable to violence and injury because of developmental issues, including independence and autonomy, curiosity leading to experimentation (e.g., alcohol, drugs, sex), peer group pressure, immaturity, impulsivity, the feeling of invincibility, narcissism, and developing self-identity.[2] Other factors that increase the vulnerability of youth to violence include the breakdown of family and community structure, media violence, and easy accessibility to lethal weapons (e.g., firearms).[3] Because of these and other factors, violence disproportionately affects children, adolescents, and young adults; and although violent crime has decreased during the last 40 years, youth continue to have the highest rates of victimization.[4] In 2009, almost 500,000 children and adolescents received medical care for nonfatal violent injuries, of which 6% required hospitalization.[5] Homicide is the second leading cause of death for young people and the leading cause of death for young African Americans.[6]

Historically, injuries were incorrectly called "accidents" because they were seen as unpredictable and uncontrollable. Epidemiologic research now shows that injuries, like other diseases, occur in highly predictable patterns and are often preventable and that contrary to popular belief, violence is a learned and predictable behavior.[7] A child's initial exposure to violence usually occurs in the home (e.g., intimate partner violence, child abuse, elder abuse, corporal punishment) and can increase an adolescent's predisposition to violence. The degree to which adolescents are exposed to violence in the home, community, school, media, sports, and peer groups and the extent to which they are victims of violence are associated with their becoming violent themselves.[8-10]

VIOLENCE IN SCHOOLS

More than 600,000 violent crimes occur in schools each year, and more crimes are committed against children aged 12 to 18 years in school than away from school.[11] It is not surprising that many adolescents report a great fear of school violence. In one national survey, 5% of students missed school because of feeling unsafe at school, and 5.6% had carried a weapon to school in the preceding 30 days. The study also noted that 11.1% of students had been in a physical fight on school property and 7.7% had been threatened or injured with a weapon in the preceding 12 months.[6] Notably, 23% of students reported gang activity at their schools. In addition, 7% of teachers are threatened with violence and 4% are physically attacked each year.[11]

Although violence is common in schools, less than 1% of homicides occur in this setting.[12,13] Of these, half occur during transitions in the school day (beginning of school, lunch period, end of school day). Of school-associated homicides, 65% are from firearms, 27% are from stabbing or cutting, and 12% are from beating.[13] Most firearms used in school-related deaths are from the perpetrator's home.[12]

Bullying is increasingly recognized as an important part of school-related violence. Bullying is repeated and intentional intimidation, harassment, physical harm, or some combination of these actions directed at an individual or a group considered less powerful. Up to 54% of students report being bullied on school property within the last year.[14,15] Bullying is further categorized as verbal, physical, or relational (e.g., social exclusion) and direct or technology assisted (cyberbullying). Bullying is associated with higher rates of weapon carrying and use, fighting serious enough to result in injury,[16,17] self-inflicted and accidental injury, hurting of animals, frequent absence from school,[18] drug use,[19] adult criminality,[20] suicide,[21] depression, anxiety, and conduct disorder.[22] Cyberbullying has been growing rapidly in recent years. It is different from traditional bullying in that it can be done anonymously, does not require a power differential, and occurs remotely, away from supervision or exposure to the victim's response.[23]

MEDIA VIOLENCE AND ITS EFFECT ON CHILDREN AND ADOLESCENTS

Children and adolescents are exposed to large amounts of media violence in movies, video games, youth-oriented music, the Internet, and television. By the time Americans reach the age of 70 years, they will have spent up to 10 years watching television.[24] Violence is present in up to 60% of television programs,[25] and Saturday morning children's programming contains up to 25 violent acts per hour, exposing a group that cannot consistently discriminate between real life and fantasy in entertainment. Through television and other forms of media violence, children and adolescents learn and imitate violent behavior, particularly if the aggressor is the hero or the heroine.[24,26] The more realistic the violence portrayed, the greater the probability the violence will be imitated by children and adolescents. Of young men incarcerated for violent crimes (e.g., homicide, rape, and assault), 22 to 34% consciously imitated crimes learned from television. In the media, violence is a quick, effective ending for disagreements and ignores the importance of patience, negotiation, and compromise in resolving conflicts and disagreements. Furthermore, media violence does not portray the true physical and psychological consequences of violent acts. This may lead children and adolescents to

www.ketabpezeshki.com 66485457-66963820

accept violence as a normal way of life, desensitizing them to future acts of violence and making them less likely to intervene when violent acts occur.[27]

Short-term effects of viewing media violence include priming, arousal, and mimicry; long-term effects include desensitization to violence and its outcomes as well as socialization of violent behavior. Mediators of these effects include justification for the behavior and consequences of aggression, perceptions of realism and identification with aggressive characters, age, gender, aggressiveness and intelligence of viewer, socioeconomic status, and parental influence.[25,28]

Media violence is consistently associated with significant increases in aggressive and criminal behavior.[29] The most important factors are the amount of violence viewed, the identification with violent characters, and the perception that television violence is real.[30,31] On television, as much as one fourth of all violent scenes involve use of a handgun.[32] Forty percent of top-grossing movies rated for "general audience" and "parental guidance suggested" feature at least one character carrying a firearm.[33] Popular music and music videos increasingly involve violence, and recent research suggests a link between music and increased violent behavior.[34]

Video games are also connected to youth violence. Video game use is common; game consoles are present in 83% of homes and used almost an hour per day.[25] Labeling of video games can be deceptive, leading to limited parental appreciation of the amount of violence in a game: 64% of "everyone-rated" video games and 94% of "teen-rated" games contain violent acts; mature-rated games often contain more and different violent content than what is described on the label.[35-37] Eighth and ninth graders who play video games frequently get into more arguments with teachers, get into more physical fights, and see the world as a more aggressive place.[38] Further, research shows that school shootings often relate to violent video games in which the player experiences killing others through the eyes of a protagonist.[39] Whereas computer use and video game use were the strongest factors related to violent behavior,[40] a causative link has not been established.[41]

ADOLESCENTS, DRUG ABUSE, AND VIOLENCE

Alcohol and drug use among youth is common. Among high school students in 2009, 73% had tried alcohol, 24% had had five or more drinks at one time, 37% had used marijuana, 3% had used cocaine, 4% had used methamphetamine, and 12% had used inhalants.[42] In youth 12 to 17 years of age, 4.6% are dependent on alcohol and 7.0% are dependent on illicit drugs, and 1.8 million children require alcohol or drug treatment each year.[43]

From the ages of 10 to 13 years, children begin experimenting with a wide range of new behaviors. Cigarettes, alcohol, and other types of drugs are a normal part of the "coming of age" for many children, regardless of race, culture, socioeconomic status, or geographic location. Substance use follows a predictable pattern, beginning with experimentation with cigarettes and alcohol, followed by marijuana, then cocaine. Other drugs, including opioids and hallucinogens, typically are tried later, but an adolescent does not necessarily progress beyond a particular stage. Initially, the adolescent associates drugs with euphoria and pleasure. With regular use, tolerance and the need for particular drugs develop. At this stage, the adolescent is drug dependent and now uses the drug to prevent withdrawal symptoms, which may be physiologic or psychological in nature. For adolescents, any use of a drug constitutes drug abuse. Adolescents at greatest risk for lifelong substance abuse typically begin to use drugs before the age of 15 years. Adolescents who are the most affected by substance abuse are those who are least involved in school or other meaningful activities.

The precise relationship has not been completely elucidated, but drugs and violent behavior are related to drug use (pharmacologic violence), to drug procurement (economic violence), and to the illicit sale of drugs.[44,45] Alcohol is the most common drug associated with violence. The pharmacologic effects of alcohol contribute significantly to the prevalence of adolescent fighting, suicide, homicide, unintentional injury and death, rape, and physical assaults.[46] Cocaine, barbiturates, phencyclidine (PCP), amphetamines, and anabolic steroids as well as increasingly available medications used for attention deficit disorder and hyperactivity also play a role in such violence.[43] Youth who had used an illicit drug in the past year are almost twice as likely to have engaged in a violent act as those who do not use an illicit drug, and the likelihood of engaging in violent behavior increased with the number of drugs the youth had used in the past year.[47] Economic violence during the process of obtaining money to finance drug use can lead to intentional and unintentional injury and death. Violence between buyers and sellers includes robbery for money or drugs, arguments over drug quality or quantity, competition for territory or markets for the sale of drugs, and violence as a management strategy to discipline drug-selling subordinates.

FIREARMS AND YOUTH

Death caused by firearms occurs 90 times more frequently in the United States than in any other industrialized nation.[8] In the United States, four children and adolescents are killed by firearms every day.[48] For every child killed, three children sustain a firearm-related injury.[49] Sixty percent of firearm assaults are fatal, compared with 4% of knife assaults and less than 1% of assaults with blunt objects.[50] Exposure to firearm violence doubles the probability that a youth will commit violence within 2 years.[51]

There are approximately 218 million privately owned firearms, of which 85 million are handguns.[52] Handguns are involved in most firearm injuries and deaths, although they make up less than one third of all firearms. About half of all households in the United States contain a firearm. Most privately owned firearms are purchased with the intent of increasing personal safety and home security, but the risk of firearms in the home is unrecognized.[53] A firearm in the home is 43 times more likely to kill a family member or friend than an intruder.[54] A handgun is the weapon used in 82% of adolescent homicides.[55] When a gun is fired in the home by an adolescent, the victim most often is the adolescent (35%), a friend (34%), a sibling (25%), or a parent or relative (6%).[2] Many firearms in the home are stored unlocked and loaded.[56] In one survey, three fourths of children younger than 14 years knew exactly where the firearm in their house was located, and one third had handled it.[57] Before 8 years of age, few children can distinguish between a toy gun and a real gun.[53]

The availability of firearms increases the lethality of violent behavior,[58] and easy accessibility plays a major role in the morbidity and mortality of children and adolescents. In recent decades, there has been a 75% increase in child and adolescent firearm deaths.[50] The firearm death rate among U.S. children aged 14 years and younger is approximately 12 times greater than the firearm death rate among children in 25 other industrialized nations combined,[59] and again, firearm availability has been correlated with this increased rate.[60] Firearm homicide rates are highest among African American adolescent boys in urban areas in the United States,[61] for whom firearm injury is the leading cause of death. Among adolescents, firearm homicide occurs most often in urban areas, and suicides occur most often outside urban areas. Children in the most deprived socioeconomic quintile had a 159% higher firearm homicide rate compared with those in the least deprived quintile.[62]

www.ketabpezeshki.com 66485457-66963820

NON-POWDER FIREARMS

Modern technology has transformed the BB gun from a toy to a potentially lethal weapon with a muzzle velocity in the range of small-caliber, low-velocity powder firearms. Other non-powder firearms include pellet guns and air pistols that use spring-loaded, manual pump compression or pressurized carbon dioxide instead of gunpowder and can cause severe injury or death at close range.[62]

Non-powder firearms are used predominantly by children and adolescents, and 80% of all injuries by non-powder firearms are in these age groups.[63] These injuries account for 23,000 emergency department (ED) visits per year.[64] Victims of non-powder firearm injuries are overwhelmingly male. Injuries to the extremities are the most common, but 33% of injuries involve the eyes, head, face, or neck.[65] In one study of pediatric patients presenting to a trauma center with non-powder firearm injuries, 57% sustained serious injuries, with 30% requiring operative treatment and 7% dying.[66] The most significant injuries are intracranial penetration in the region of the orbit or thin regions of the skull. Non-powder firearm injuries are a common cause of blindness in adolescent boys; other less well known complications include remobilization and lead poisoning. Penetration of the heart and aorta occasionally results in death. Overall, non-powder firearm injuries are more numerous and less severe than powder firearm injuries, but head, chest, and abdominal wounds from these weapons may be erroneously regarded as trivial, with catastrophic results.[62]

PREVENTION STRATEGIES FOR YOUTH VIOLENCE

Children and adolescents lack judgment and experience and cannot be expected to avoid violence and injury on their own.[67] Risk factors for youth violence include history of violence victimization, exposure to violence, access to weapons, substance abuse, antisocial beliefs, low parental involvement, low income, poor academic performance, social rejection, low levels of community participation, and high levels of community transience. Factors associated with less violent behavior include high grade point average, strong religious beliefs, connectedness to family, ability to discuss problems with parents, and large amounts of social capital in the community.[68] Physicians should screen for these risk factors to identify youth at risk for violence.[69-71]

Many medical associations, including the American College of Emergency Physicians, have policy statements calling for physicians to incorporate youth violence prevention into their practices. To decrease youth violence, physicians and other health care providers should urge the media to do the following: decrease the violence, use of weapons, and pain and suffering depicted in the media; accurately portray the true consequences of violent acts; and decrease the amount of violent lyrics and violent scenes in music videos and video games. Physicians should advise parents to monitor and to limit their children's viewing of television, video games, music videos, movies, and the Internet.[69]

Health care providers can also work directly with schools to address youth violence.[8,72,73] Schools should be encouraged to teach conflict resolution and anger management skills, which represent an empowering step toward avoiding violence. Further, schools can make the learning environment physically safer by decreasing the number of weapons carried by students. Students should be advised of the risk and legal consequences of bringing weapons to school. Depending on the school and local community, metal detectors and school safety police may be necessary. Schools and health care providers should work jointly with local communities to decrease violence that occurs on the way to and from school and the overall level of violence in the community.

Emergency physicians and other health care providers should encourage school-based counseling concerning violence and injury prevention.[74] This may be a cost-effective method of preventing childhood and adolescent violence.[75,76] Physicians should educate children, adolescents, and their parents about drug use leading to abuse and dependency and the association between drugs and violence. Physicians should also educate parents about the risk of firearms kept in the home and, if a firearm is present, the proper storage (i.e., unloaded, separated from ammunition, and in a locked box or cabinet). Parents should ask about firearms when their children visit other homes and allow their children to use non-powder firearms only with goggles, chest protection, and adult supervision.

Rates of youth violence-related recidivism and retaliation are extremely high,[77,78] and the ED is often the first point of contact between the health care provider and both victims and perpetrators of violence; for a large number of patients, the ED is the only location in which they receive health care.[79,80] Screening tools focusing on questions such as whether the patient has recently been in a fight, been injured by violence, or been threatened can identify at-risk youth.[76] ED-based intervention programs that immediately identify at-risk youth and link them to educational, community, and health care resources as well as social work follow-up have decreased violence, delinquency, drug use, and victimization.[81] Brief counseling by the treating physician may also be an effective first step.[79]

Acutely, the emergency physician should determine whether a victim of violence plans to seek revenge and provide immediate counseling emphasizing a cooling-off period to prevent further acts of violence. The risk of reinjury or death to the patient and others and the risk of criminal prosecution should be discussed. Health care providers should check with local laws to determine whether they may be legally bound to report to law enforcement officers if the patient threatens a specific individual.[82,83]

VIOLENCE BY STREET GANGS

Street gangs are mainly composed of inner-city adolescents from the same socioeconomic background. Adolescents join street gangs for a sense of belonging, protection, status, adventure, and illegal monetary gain, but most inner-city youth do not join street gangs.

In the 1950s, when street gang violence typically involved fist-fights, blunt objects, knives, and only rarely firearms, there was a much lower chance of serious injury or death to gang members or innocent bystanders. Modern-day street gangs are larger, more numerous, more widespread, more violent, and no longer confined to the inner city. Since firearms have become the weapons of choice, more gang members and innocent bystanders are injured or killed,[84] and gang density is directly correlated with higher community homicide rates.[85] Drug use and selling, violence, and vandalism significantly increase the likelihood of joining a gang.[86] Gang members, as the ultimate defenders of intrusions in their neighborhood or on their turf by rivals, are often willing to die, to risk imprisonment, to kill rivals, or unintentionally to injure or to kill innocent bystanders. If a rival street gang insults, challenges, injures, or kills a member of another street gang, it is highly probable that another episode of violence (i.e., retribution) will occur. Being injured, imprisoned, or killed defending the gang or turf often enhances a gang member's reputation and standing in the gang. The more violent the street gang, the greater the reputation of the gang members. Gang members commonly do not testify in court against rival gang members but prefer to enforce their own brand of retributive justice, violently, against rival street gangs. Common reasons for street gang violence include retaliation for previous shootings, rivalry, turf fights, arguments, and, at times, control over an illegal criminal

www.ketabpezeshki.com 66485457-66963820

enterprise. Injuries and homicides by violent street gangs occur in many ways, including walk-up shootings, drive-by shootings, stabbings, use of blunt force weapons, and arson. In most instances, intentional street gang violence is intraracial.

Violent street gangs are active in 99% of U.S. cities with a population of more than 100,000[87] and in 32.4% of all cities. In 2008, it was estimated that there were 27,900 gangs with approximately 774,000 gang members nationwide.[88] Modern street gangs nationwide have patterned themselves after the 1980s street gang subculture in the Los Angeles area. The street gang subculture has its own style of dress, form of verbal and nonverbal communication, music, camaraderie, and funeral rituals, which has made it possible for adolescents of any ethnic group or background to identify with the gang lifestyle.[89,90] Gangs are frequently based on ethnic or racial association. Some white gangs differ from other groups in that they are consistently involved in acts of hate violence.[91] Life in the gang typically begins around the age of 13 years as a "wannabe," with most adolescents joining the gang at around 15 years. The peak ages for violent street gang activity are between 15 and 21 years,[92] after which gang members begin to migrate out. Some members stay active in the gang into their early 30s.[93] There is growing concern that gang violence is spreading to and through the Internet, consistent with the increasing use of this media by adolescents and youth.[94] The most likely reasons for increasing gang violence include the growth in the number of gang members, the appeal of the bravado and violent image of gang members, the greater levels of intergang violence, an increase in the sophistication of firearm weaponry in gang violence, an increasingly violent society, an increased economic despair in urban communities, a breakdown in sociocultural institutions, and an increase in marginalization of urban children and adolescents.[95-97] A causal relationship of increasing drug use with gang violence and homicide has also been shown.[98,99]

Drive-By Shootings

One of the most dangerous violent acts committed by street gangs is the drive-by shooting, defined as gang members shooting at suspected rival gang members from a vehicle. Violent street gangs perpetrate more than 90% of all drive-by shootings. The primary purpose of a drive-by shooting is to create fear, terror, and intimidation among members of rival street gangs. The secondary intent is to kill.[93] Drive-by shootings mainly occur at night in the inner city and generally last 5 to 15 seconds.[100] Drive-by shootings are not random events.[101] Most frequently, drive-by shootings occur on public streets, with gang members shooting into cars of suspected rival gang members but also shooting into the homes of suspected rival gang members, in parks, and around public schools.[101] In many drive-by shootings, gang members flash their gang hand sign (a form of nonverbal gang communication) and yell their gang name. This makes it known to all rival gang members which gang was actually shooting at them. Most drive-by shooters are not apprehended by law enforcement.

No longer confined to the inner city, drive-by shootings are now a national phenomenon and endemic in some regions of the United States.[102] Drive-by shootings are a major public health problem because many individuals can be injured or killed in one incident.[103] In one study, 63% of children and adolescents who were targeted sustained a firearm injury, and 5.3% died of their injuries. Thirteen people are injured for each individual killed in a drive-by shooting.[101] For adolescents and young adults, the lower extremity is the most frequently injured body region, followed by the upper extremity. The most frequent fatal injuries are to the chest and head.[101] Most small children injured or killed in drive-by shootings are unintentionally caught in the crossfire of gang shootings.[104] These small children frequently sustain fatal firearm injuries to the head, neck, and chest.

Firearms and Violent Street Gangs

The weapon of choice in a drive-by shooting is a 9-mm semiautomatic handgun. Some semiautomatic handguns may fire 15 or more bullets before reloading. The high-capacity, rapid-fire mechanism of a semiautomatic firearm helps explain why many individuals may be injured or killed in a single drive-by shooting.[100]

For many gang members, firearms fulfill the need for power, status, protection, and progression from adolescence into adulthood that is no longer being met by traditional sociocultural institutions. Firearms are used in 95% of gang homicides[84] compared with 69% of all homicides.[48] Handguns—particularly semiautomatic handguns—are the most commonly used weapon in gang shootings, followed by shotguns, rifles, and assault weapons used in 8%, 5%, and 3% of all gang homicides, respectively.[84]

Psychological Effects of Street Gang Violence on Children and Adolescents

Some urban communities have higher exposure to street gang violence than others do.[8,105] In one group of inner-city adolescents, nearly 85% had witnessed at least one violent act, and 43.4% had witnessed a murder.[106] Children and adolescents living in the inner city are exposed to chronic, pervasive violence rather than isolated episodes of violence. The reactions of these children to this pervasive violence are consistent with those of children and adolescents living in war zones.[107,108]

On exposure to repetitive or extreme acts of violence, children and adolescents may show signs of sleep disturbance, difficulty concentrating in school, flashbacks, hypervigilance, increased risk-taking behavior, and a nihilistic, fatalistic orientation to the future.[109] Many of these children may also suffer from post-traumatic stress disorder. The severity of a child's or adolescent's reaction to a gang shooting is related to proximity to the shooting, threat to the child's or adolescent's own life, his or her relationship to those who were injured or killed in the shooting, and whether gang violence is endemic in the community.[109]

Children and adolescents living in communities where there are many street gangs often receive little or no counseling for the physical and psychological sequelae resulting from gang violence. The net psychological effect of exposure to gang violence on children and adolescents is unknown, but it potentially desensitizes children and adolescents to violence and leads to carrying of a weapon out of fear for their own personal safety.

Preventing Gang Violence in the Emergency Department

With the increase in gang violence nationwide, emergency physicians and other health care providers have become vulnerable to injury and death from gang incidents in the hospital. The development of guidelines for the prevention of gang violence is recommended to safeguard emergency physicians, other health care providers, patients, and visitors.[110]

In the past, recognition of local street gangs was determined by tattoos, "colors" (e.g., blue for Crips, red for Bloods), typical clothing (e.g., baggy pants, athletic team jackets), specific accessories (e.g., sneakers, caps, belt buckles, bandannas), and hand signs; many of these styles, however, have now become popular in all segments of society. Information about local gangs may be obtained from community activists involved in gang prevention programs or local law enforcement agencies. All health care providers should know the root causes of violent street gang formation, the effects of gang violence on the community, and the prevention of street gang violence.

www.ketabpezeshki.com 66485457-66963820

Emergency Department Guidelines

- On the arrival of injured known or suspected gang members, hospital security should be immediately involved, should be stationed in the ED and waiting area, and should secure the hospital perimeters.
- Consistent with the primary survey examination, the patient should be undressed and searched for concealed weapons with the assistance of security or law enforcement.
- The evidence of previous major trauma (e.g., laparotomy, thoracotomy, thoracostomy scars) or tattoos may be indicative of previous gang injuries.[111]
- In a calm, nonjudgmental fashion, emergency health care providers should ask the patient whether he or she is a gang member.
- ED staff should not challenge or insult known or suspected gang members. In the street gang subculture, perceived disrespect often leads to a violent confrontation.
- While the patient is in the ED, visitation should be limited, preferably to the patient's parents. Other visitors (e.g., friends and relatives) can be kept informed by periodic updates from the ED staff.
- If admission is required, gang members should be admitted under "John Doe" or Jane Doe" status to protect their identity and to avoid an outbreak of gang violence in the hospital.
- Hospital security should be available 24 hours a day and should maintain high visibility and vigilance when injured gang members are present in the ED.
- If gang members (in particular, rival gang members) are found to be present in the ED or waiting area, hospital security should be present and local law enforcement should be advised.
- Although concerned for their personal safety, ED personnel should not arm themselves with firearms or other weapons while on duty. Health care providers with weapons potentially could escalate the level of violence in the ED. Gang members might view health care providers as adversaries.
- Community leaders who are experienced with local street gangs may act as mediators between the ED staff and members of violent street gangs. These mediators should be summoned to help decompress any hostile situations that may arise.
- Hospitals should have lock-down or evacuation plans for ED personnel and visitors in the event that violence erupts within the ED.
- The ED staff should learn to recognize and to de-escalate previolent aggressive behavior.
- The ED should keep a log of all violent incidents that occur within the ED. This strategy helps quantify the severity of and weapon use in violent incidents and helps determine the necessity for other security measures (e.g., video cameras, metal detectors, bulletproof glass, armed safety police).

As long as gang violence exists in the community, spillover of the violence into the ED is likely. With appropriate concern for their own safety, ED personnel should deliver compassionate care to all members of violent street gangs while minimizing their own risk of injury.

Prevention of Street Gang Violence

Law enforcement and the criminal justice system alone cannot solve the violence of street gangs. The United States should develop a national policy on the issue of violent street gangs, with an emphasis on alleviation of the root causes of violent street gang formation. The root causes of violent street gang formation include poverty, stressed families, lack of education, unemployment, underemployment, racism, marginalization, and breakdown of sociocultural institutions. Although incarceration is a part of the solution, primary prevention through alleviation of the root causes of violent street gang formation would be more effective. For truces among violent street gangs to be effective, they should be supported by concerted efforts to alleviate the root causes of violent street gang formation.[84]

Some gang members are receptive to leaving the gang after being injured or after a fellow gang member has been injured or killed in violent street gang activity.[112] Accordingly, attempts to break the cycle of gang membership should occur when injured gang members present to the ED. Hospital-based interventions should begin in the ED and continue throughout the hospitalization. On discharge from the hospital, counseling should continue to intervene further in breaking the cycle of violent street gang involvement. Because many individuals in the community, particularly children and adolescents, may experience the physical and psychological effects of violence, counseling should be made readily available.

Any prevention strategy with a unilateral focus would be unsuccessful in decreasing violent street gang activity and breaking the bonds of gang membership. The solution to street gang violence should use a multifaceted approach.

KEY CONCEPTS

- Youths are particularly vulnerable to and disproportionately affected by violence.
- Physical, verbal, and relational violence in schools is common.
- Media violence, drugs and alcohol, and access to firearms have been associated with increased youth violence.
- Street gangs continue to be a major source of youth violence.
- Involvement of health care providers in youth violence prevention is effective and should occur in the ED.

References

1. U.S. Census Bureau: *American Community Survey*. Washington, DC: U.S. Government Printing Office; 2009.
2. American Academy of Pediatrics Committee on Adolescence: Firearms and adolescents. *Pediatrics* 1992; 89:784-787.
3. Valois RF, MacDonald JM, Bretous L, Fischer MA, Drane JW: Risk factors and behaviors associated with adolescent violence and aggression. *Am J Health Behav* 2002; 26:454-464.
4. Rand M, Truman J: *Criminal Victimization, 2009*. Washington, DC: U.S. Department of Justice, Bureau of Justice Statistics; 2010.
5. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control: *WISQARS Nonfatal Injury Reports*. Available at http://webappa.cdc.gov/sasweb/ncipc/nfirates2001.html. Accessed April 21, 2011.
6. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control: *Youth Violence: Facts at a Glance*. Available at www.cdc.gov/ViolencePrevention/pdf/YV_DataSheet_2012-a.pdf.
7. Heath I: Treating violence as a public health problem. *BMJ* 2002; 325:726-727.
8. Dahlberg LL: Youth violence in the United States. Major trends, risk factors, and prevention approaches. *Am J Prev Med* 1998; 14:259-272.
9. Resnick MD, Ireland M, Borowsky I: Youth violence perpetration: What protects? What predicts? Findings from the National Longitudinal Study of Adolescent Health. *J Adolesc Health* 2004; 35:424.e1-10.
10. Tolan PH, Gorman-Smith D, Henry DB: The developmental ecology of urban males' youth violence. *Dev Psychol* 2003; 39:274-291.
11. Institute of Education Sciences, National Center for Education Statistics: *Indicators of School Crime and Safety: 2010*. Available at http://nces.ed.gov/programs/crimeindicators/crimeindicators2010/key.asp. Accessed April 7, 2011.
12. Anderson M, et al: School-associated violent deaths in the United States, 1994-1999. *JAMA* 2001; 286:2695-2702.

www.ketabpezeshki.com 66485457-66963820

13. Modzeleski W, et al: School-associated student homicides—United States, 1992-2006. *MMWR Morb Mortal Wkly Rep* 2008; 57:33-36.
14. Eaton D, et al: Youth risk behavior surveillance—United States, 2009. *MMWR Surveill Summ* 2010; 59:1-142.
15. Wang J, Iannotti RJ, Nansel TR: School bullying among adolescents in the United States: Physical, verbal, relational, and cyber. *J Adolesc Health* 2009; 45:368-375.
16. Glew GM, Fan MY, Katon W, Rivara FP: Bullying and school safety. *J Pediatr* 2008; 152:123-128, 128.e1.
17. Nansel TR, Overpeck MD, Haynie DL, Ruan WJ, Scheidt PC: Relationships between bullying and violence among US youth. *Arch Pediatr Adolesc Med* 2003; 157:348-353.
18. Srabstein J, Piazza T: Public health, safety and educational risks associated with bullying behaviors in American adolescents. *Int J Adolesc Med Health* 2008; 20:223-233.
19. Niemela S, et al: Childhood bullying behaviors at age eight and substance use at age 18 among males. A nationwide prospective study. *Addict Behav* 2011; 36:256-260.
20. Sourander A, et al: Bullying at age eight and criminality in adulthood: Findings from the Finnish Nationwide 1981 Birth Cohort Study. *Soc Psychiatry Psychiatr Epidemiol* 2011; 46:1211-1219.
21. Kim YS, Leventhal B: Bullying and suicide. A review. *Int J Adolesc Med Health* 2008; 20:133-154.
22. Nunn KP: Bullying. *J Paediatr Child Health* 2010; 46:140-141.
23. Kiriakidis SP, Kavoura A: Cyberbullying: A review of the literature on harassment through the internet and other electronic means. *Fam Community Health* 2010; 33:82-93.
24. American Academy of Pediatrics: Children, adolescents, and television. *Pediatrics* 2001; 107:423-426.
25. Huesmann LR: The impact of electronic media violence: Scientific theory and research. *J Adolesc Health* 2007; 41:S6-S13.
26. Kostinsky S, Bixler EO, Kettl PA: Threats of school violence in Pennsylvania after media coverage of the Columbine High School massacre: Examining the role of imitation. *Arch Pediatr Adolesc Med* 2001; 155:994-1001.
27. Sege R, Dietz W: Television viewing and violence in children: The pediatrician as agent for change. *Pediatrics* 1994; 94:600-607.
28. Huesmann LR, Taylor LD: The role of media violence in violent behavior. *Annu Rev Public Health* 2006; 27:393-415.
29. Boxer P, Huesmann LR, Bushman BJ, O'Brien M, Moceri D: The role of violent media preference in cumulative developmental risk for violence and general aggression. *J Youth Adolesc* 2009; 38:417-428.
30. Huesmann LR, Moise-Titus J, Podolski CL, Eron LD: Longitudinal relations between children's exposure to TV violence and their aggressive and violent behavior in young adulthood: 1977-1992. *Dev Psychol* 2003; 39:201-221.
31. Johnson JG, Cohen P, Smailes EM, Kasen S, Brook JS: Television viewing and aggressive behavior during adolescence and adulthood. *Science* 2002; 295:2468-2471.
32. Federman J, ed: *National Television Violence Study*. Thousand Oaks, Calif: Sage; 1998.
33. Ramsey LT, Pelletier AR: Update on firearm use in G- and PG-rated movies. *JAMA* 2004; 292:2836-2837.
34. Council on Communications and Media: From the American Academy of Pediatrics: Policy statement—impact of music, music lyrics, and music videos on children and youth. *Pediatrics* 2009; 124:1488-1494.
35. Haninger K, Ryan MS, Thompson KM: Violence in teen-rated video games. *MedGenMed* 2004; 6:1.
36. Thompson KM, Haninger K: Violence in E-rated video games. *JAMA* 2001; 286:591-598.
37. Thompson KM, Tepichin K, Haninger K: Content and ratings of mature-rated video games. *Arch Pediatr Adolesc Med* 2006; 160:402-410.
38. Gentile DA, Lynch PJ, Linder JR, Walsh DA: The effects of violent video game habits on adolescent hostility, aggressive behaviors, and school performance. *J Adolesc* 2004; 27:5-22.
39. Strasburger VC, Grossman D: How many more Columbines? What can pediatricians do about school and media violence? *Pediatr Ann* 2001; 30:87-94.
40. Janssen I, Boyce WF, Pickett W: Screen time and physical violence in 10 to 16-year-old Canadian youth. *Int J Public Health* 2012; 57:325-331.
41. Ferguson CJ: Video games and youth violence: A prospective analysis in adolescents. *J Youth Adolesc* 2011; 40:377-391.
42. *2009 National Youth Risk Behavior Survey Overview*. Washington, DC: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2010.
43. *Results from the 2009 National Survey on Drug Use and Health: Volume 1: Summary of National Findings*. Washington, DC: U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration; 2010.
44. Kodjo CM, Auinger P, Ryan SA: Prevalence of, and factors associated with, adolescent physical fighting while under the influence of alcohol or drugs. *J Adolesc Health* 2004; 35:346.e11-16.
45. MacDonald JM, Piquero AR, Valois RF, Zullig KJ: The relationship between life satisfaction, risk-taking behaviors, and youth violence. *J Interpers Violence* 2005; 20:1495-1518.
46. Hingson R, Heeren T, Zakocs R: Age of drinking onset and involvement in physical fights after drinking. *Pediatrics* 2001; 108:872-877.
47. *Violence and Illicit Drug Use*. Washington, DC: U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration; 2006.
48. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control: *WISQARS Injury Mortality Reports, 1999-2007*. Available at http://webappa.cdc.gov/sasweb/ncipc/mortrate10_sy.html. Accessed April 21, 2011.
49. Eber GB, Annest JL, Mercy JA, Ryan GW: Nonfatal and fatal firearm-related injuries among children aged 14 years and younger: United States, 1993-2000. *Pediatrics* 2004; 113:1686-1692.
50. Violence in America: A public health crisis—the role of firearms. The Violence Prevention Task Force of the Eastern Association for the Surgery of Trauma. *J Trauma* 1995; 38:163-168.
51. Bingenheimer JB, Brennan RT, Earls FJ: Firearm violence exposure and serious violent behavior. *Science* 2005; 308:1323-1326.
52. Hepburn L, Miller M, Azrael D, Hemenway D: The US gun stock: Results from the 2004 national firearms survey. *Inj Prev* 2007; 13:15-19.
53. Kellermann AL, et al: Gun ownership as a risk factor for homicide in the home. *N Engl J Med* 1993; 329:1084-1091.
54. Kellermann AL, Reay DT: Protection or peril? An analysis of firearm-related deaths in the home. *N Engl J Med* 1986; 314:1557-1560.
55. Page RM, Hammermeister J: Weapon-carrying and youth violence. *Adolescence* 1997; 32:505-513.
56. Johnson RM, Coyne-Beasley T, Runyan CW: Firearm ownership and storage practices, U.S. households, 1992-2002. A systematic review. *Am J Prev Med* 2004; 27:173-182.
57. Baxley F, Miller M: Parental misperceptions about children and firearms. *Arch Pediatr Adolesc Med* 2006; 160:542-547.
58. Cohall AT, Cohall RM: "Number one with a bullet": Epidemiology and prevention of homicide among adolescents and young adults. *Adolesc Med* 1995; 6:183-198.
59. Rates of homicide, suicide, and firearm-related death among children—26 industrialized countries. *MMWR Morb Mortal Wkly Rep* 1997; 46:101-105.
60. Hemenway D, Miller M: Firearm availability and homicide rates across 26 high-income countries. *J Trauma* 2000; 49:985-988.
61. Larkin GL: Screening for adolescent firearms-carrying: One more way to save a life. *Ann Emerg Med* 2003; 42:808-810.
62. Laraque D: Injury risk of non-powder guns. *Pediatrics* 2004; 114:1357-1361.
63. McNeill AM, Annest JL: The ongoing hazard of BB and pellet gun–related injuries in the United States. *Ann Emerg Med* 1995; 26:187-194.
64. Brown A, Gail MS, Moore T: *Consumer Product Safety Review*. Washington, DC: Consumer Product Safety Commission; 2000.
65. Nguyen MH, Annest JL, Mercy JA, Ryan GW, Fingerhut LA: Trends in BB/pellet gun injuries in children and teenagers in the United States, 1985-99. *Inj Prev* 2002; 8:185-191.
66. O'Neill PJ, et al: Significant pediatric morbidity and mortality from intracranial ballistic injuries caused by non-powder gunshot wounds. A case series. *Pediatr Neurosurg* 2009; 45:205-209.
67. Wilson MH, Baker SP, Teret SP, Shock S, Garbarino J: *Saving Children: A Guide to Injury Prevention*. New York: Oxford University Press; 1991.
68. Williams K, Rivera L, Neighbours R, Reznik V: Youth violence prevention comes of age: Research, training and future directions. *Annu Rev Public Health* 2007; 28:195-211.
69. Committee on Injury, Violence, and Poison Prevention: Policy statement—role of the pediatrician in youth violence prevention. *Pediatrics* 2009; 124:393-402.
70. Cheng TL, et al: Assault-injured adolescents presenting to the emergency department: Causes and circumstances. *Acad Emerg Med* 2006; 13:610-616.
71. Cheng TL, et al: Adolescent assault injury: Risk and protective factors and locations of contact for intervention. *Pediatrics* 2003; 112:931-938.
72. Greene MB: Youth violence in the city: The role of educational interventions. *Health Educ Behav* 1998; 25:175-193.
73. Murray-Garcia J: African-American youth: Essential prevention strategies for every pediatrician. *Pediatrics* 1995; 96:132-137.

www.ketabpezeshki.com 66485457-66963820

74. Pittel EM: How to take a weapons history: Interviewing children at risk for violence at school. *J Am Acad Child Adolesc Psychiatry* 1998; 37:1100-1102.
75. Cole TB: Taking aim at gun violence: Tracing bullets and guns to sideline scofflaw dealers. *JAMA* 2003; 290:583-585.
76. Hayes DN, Sege R: FiGHTS: A preliminary screening tool for adolescent firearms-carrying. *Ann Emerg Med* 2003; 42:798-807.
77. Dowd MD: Consequences of violence. Premature death, violence recidivism, and violent criminality. *Pediatr Clin North Am* 1998; 45:333-340.
78. Poole GV, Griswold JA, Thaggard VK, Rhodes RS: Trauma is a recurrent disease. *Surgery* 1993; 113:608-611.
79. Cunningham R, et al: Before and after the trauma bay: The prevention of violent injury among youth. *Ann Emerg Med* 2009; 53:490-500.
80. Marcell AV, Klein JD, Fischer I, Allan MJ, Kokotailo PK: Male adolescent use of health care services: Where are the boys? *J Adolesc Health* 2002; 30:35-43.
81. Zun LS, Downey L, Rosen J: The effectiveness of an ED-based violence prevention program. *Am J Emerg Med* 2006; 24:8-13.
82. Bloom JD, Rogers JL: The duty to protect others from your patients—Tarasoff spreads to the Northwest. *West J Med* 1988; 148:231-234.
83. Oppenheimer K, Swanson G: Duty to warn: When should confidentiality be breached? *J Fam Pract* 1990; 30:179-184.
84. Hutson HR, Anglin D, Kyriacou DN, Hart J, Spears K: The epidemic of gang-related homicides in Los Angeles County from 1979 through 1994. *JAMA* 1995; 274:1031-1036.
85. Robinson PL, et al: The effect of urban street gang densities on small area homicide incidence in a large metropolitan county, 1994-2002. *J Urban Health* 2009; 86:511-523.
86. Gordon R, Lahey B, Kawa E: Antisocial behavior and youth gang membership: Selection and socialization. *Criminology* 2004; 42:55.
87. National Youth Gang Center: *National Youth Gang Survey Analysis*. Available at www.nationalgangcenter.gov/Survey-Analysis. Accessed April 21, 2011.
88. Egley A, Howell JC, Moore JP: *Highlights of the 2008 National Youth Gang Survey*. Washington, DC: U.S. Department of Justice, Office of Juvenile Justice and Delinquency Prevention; 2010.
89. Jackson RK, McBride WD: *Understanding Street Gangs*. Placerville, Calif: Custom; 1991.
90. Martinez FB: *The impact of gangs and drugs in the community*. In: Cervantes RC, ed: *Substance Abuse and Gang Violence*. Newbury Park, Calif: Sage; 1992.
91. Huff CR, ed: *Gangs in America*. Thousand Oaks, Calif: Sage; 2002.
92. Vigil JD: *Barrio Gangs: Street Life and Identity in Southern California*. Austin, Tex: University of Texas Press; 1988.
93. Hutson HR, Anglin D, Mallon W: Injuries and deaths from gang violence: They are preventable. *Ann Emerg Med* 1992; 21:1234-1236.
94. King JE, Walpole CE, Lamon K: Surf and turf wars online—growing implications of Internet gang violence. *J Adolesc Health* 2007; 41:S66-S68.
95. McGonigal MD, et al: Urban firearm deaths: A five-year perspective. *J Trauma* 1993; 35:532-536; discussion 536-537.
96. Kyriacou DN, Hutson HR, Anglin D, Peek-Asa C, Kraus JF: The relationship between socioeconomic factors and gang violence in the City of Los Angeles. *J Trauma* 1999; 46:334-339.
97. Greenberg M, Schneider D: Violence in American cities: Young black males is the answer, but what was the question? *Soc Sci Med* 1994; 39:179-187.
98. Valdez A, Cepeda A, Kaplan C: Homicidal events among Mexican American street gangs: A situational analysis. *Homicide Stud* 2009; 13:288-306.
99. Valdez A, Kaplan CD, Cepeda A: The drugs-violence nexus among Mexican-American gang members. *J Psychoactive Drugs* 2006; 38:109-121.
100. Hutson HR, Anglin D, Spears K: The perspectives of violent street gang injuries. *Neurosurg Clin North Am* 1995; 6:621-628.
101. Hutson HR, Anglin D, Pratts MJ Jr: Adolescents and children injured or killed in drive-by shootings in Los Angeles. *N Engl J Med* 1994; 330:324-327.
102. Hutson HR, Anglin D, Eckstein M: Drive-by shootings by violent street gangs in Los Angeles: A five-year review from 1989-1993. *Acad Emerg Med* 1996; 3:300.
103. Eckstein M, Hutson HR, Anglin D: Drive-by shootings. *Ann Emerg Med* 1995; 25:107-110.
104. Hutson HR, Anglin D, Mallon W, Pratts MJ Jr: Caught in the crossfire of gang violence: Small children as innocent victims of drive-by shootings. *J Emerg Med* 1994; 12:385-388.
105. Schubiner H, Scott R, Tzelepis A: Exposure to violence among inner-city youth. *J Adolesc Health* 1993; 14:214-219.
106. Fitzpatrick KM, Boldizar JP: The prevalence and consequences of exposure to violence among African-American youth. *J Am Acad Child Adolesc Psychiatry* 1993; 32:424-430.
107. Lambert SF, Nylund-Gibson K, Copeland-Linder N, Ialongo NS: Patterns of community violence exposure during adolescence. *Am J Community Psychol* 2010; 46:289-302.
108. Schwab-Stone ME, et al: No safe haven: A study of violence exposure in an urban community. *J Am Acad Child Adolesc Psychiatry* 1995; 34:1343-1352.
109. Pynoos RS, et al: Life threat and posttraumatic stress in school-age children. *Arch Gen Psychiatry* 1987; 44:1057-1063.
110. Hutson HR, Anglin D, Mallon W: Minimizing gang violence in the emergency department. *Ann Emerg Med* 1992; 21:1291-1293.
111. Morrissey TB, Byrd CR, Deitch EA: The incidence of recurrent penetrating trauma in an urban trauma center. *J Trauma* 1991; 31:1536-1538.
112. Decker SH, Lauristen JL: *Breaking the bonds of membership: Leaving the gang*. In: Huff CR, ed: *Gangs in America*, 2nd ed. Thousand Oaks, Calif: Sage; 1996:63-68.

www.ketabpezeshki.com 66485457-66963820

Medical Literature and Evidence-Based Medicine*

Kelly D. Young and Roger J. Lewis

*For the complete chapter text, go to the Expert Consult website. To access your account, look for your activation instructions on the inside front cover of this book.

I. PERSPECTIVE

A. The Medical Literature

II. TYPES OF CLINICAL STUDIES

A. Cross-Sectional Studies

B. Longitudinal Studies

III. RANDOMIZED LONGITUDINAL INTERVENTIONAL STUDY (CLINICAL TRIAL)

A. Step 1: Definition of Patient Population

B. Step 2: Recruitment and Enrollment of Patients

C. Step 3: Randomization

D. Step 4: Measurement of Baseline Characteristics

E. Step 5: Treatment or Intervention

F. Step 6: Collection of Data on Outcome

G. Step 7: Data Management

H. Step 8: Statistical Analysis

I. Step 9: Presentation and Publication of Results

IV. DATA ANALYSIS

A. Classical Hypothesis Testing

V. CHANGING PRACTICE ON THE BASIS OF A RESEARCH STUDY

VI. EVIDENCE-BASED MEDICINE

A. Step 1: Definition of Clinical Question

B. Step 2: Collection of Evidence

C. Step 3: Analysis of Studies for Validity, Reliability, and Relevance

D. Step 4: Summary of Most Useful Evidence

E. Step 5: Application to Patient and Critical Appraisal

F. Effectiveness of Evidence-Based Medicine

VII. SUMMARY

www.ketabpezeshki.com 66485457-66963820

Medical Literature and Evidence-Based Medicine

Kelly D. Young and Roger J. Lewis

PERSPECTIVE

Medicine is an empirical science based on the experiences and insights of past and contemporary practitioners. Because the clinical experience of an individual physician is a small fraction of the experience of the medical profession as a whole, the advancement of medical science depends on physicians' abilities to assemble, to organize, and to disseminate information to learn from the experience of others.

The Medical Literature

During the past several decades, medical literature has exploded.[1,2] Thirty years ago, physicians could understand most medical publications. Currently, reports frequently use sophisticated statistical analyses that are unfamiliar to most clinicians.[3] Emergency physicians and other practitioners are increasingly aware that the quality of the research reported should be evaluated before the results can be considered valid and clinical practice altered. Also, the results of quality research may not be applicable if the population studied differs greatly from the population of patients in the emergency physician's clinical practice. Even a clinician who possesses the analytical skills necessary to understand and to interpret the modern medical literature will find it difficult to remain current, given the rate at which medical studies relevant to emergency medicine are published. Thus the emergency physician should have a plan to identify, to select, and to read high-quality, relevant articles. Furthermore, the emergency physician should understand a number of principles to be able to analyze published studies critically.

The first step toward achievement of these goals is to identify a small number of journals on which to focus.[4,5] Most high-quality studies relevant to emergency medicine are published in fewer than a dozen journals. Once a list of 6 to 12 journals is compiled, back issues can be skimmed to determine the average number of relevant articles in each issue. Those journals that publish the highest number of articles directly relevant to an emergency physician's clinical practice should then be selected.[4] An emergency physician in full-time clinical practice should probably focus on two to six journals per month. Regular pamphlet, audio, or Internet-based updates reviewing recent literature relevant to emergency medicine can be purchased and used as a supplement or to guide journal review. Articles should be pulled and read in full, however, before results are accepted and clinical practice is altered.

Possible articles should then be screened to evaluate the relevance of the study question and population and to determine whether the methodology is of sufficient quality to warrant reading of the article in more detail. Quality and clinical relevance vary greatly in the peer-reviewed literature.[4] Only articles that meet high standards for methodological quality should be read in detail.[1,2] The emergency physician should learn to differentiate high-quality studies from poor-quality studies with unreliable results. Practitioners who understand the concepts presented in this chapter will have the basic foundation to differentiate good from poor studies and to focus their reading on those studies most likely to yield results that warrant a change in clinical practice. Additional guidance can be obtained from the *Journal of the American Medical Association's Users' Guides to the Medical Literature* series (www.jamaevidence.com).[6]

A steadily increasing amount of attention is being paid to the importance of rigorous methodology in the design and execution of clinical trials.[3,7-9] A poorly designed statistical analysis can yield misleading results, but a trial is more likely to be weakened by a poorly chosen question, an inappropriate study population, or other methodological errors that bias the results.[10-17] Thus, although some degree of statistical literacy is important, the practitioner should also understand nonstatistical issues in the design and conduct of clinical studies.[6,10-17]

TYPES OF CLINICAL STUDIES

Studies can be divided into two categories, cross-sectional and longitudinal (cohort), by when the measurements are made on the study population.[12] In a cross-sectional study, data are obtained from a population of patients at a single point in time, whereas in a longitudinal study, data are obtained from a population of patients during a period of time.

Cross-Sectional Studies

Many epidemiologic studies are cross-sectional. Although a cross-sectional study cannot prove a causal relationship between a risk factor or treatment and an outcome, strong associations between identified variables in cross-sectional studies are suggestive of such effects.[18]

Many important observations can be made only by use of cross-sectional studies because, for practical and ethical reasons, some variables cannot be artificially manipulated to determine their effect on patient outcome.[18] Furthermore, the effect may be so delayed that a longitudinal study is impractical. An example is a study examining the association between cigarette use and lung cancer. It would be unethical to expose a nonsmoking population to the effects of cigarettes, and even if one were to identify a population that would voluntarily use cigarettes, it would be impractical to observe subjects long enough for malignant neoplasms from cigarette smoking to appear. However, a cross-sectional study of self-reported cigarette use and the diagnosis of lung cancer that

www.ketabpezeshki.com 66485457-66963820

examines a population of subjects at a single point in time can easily demonstrate an association.

Longitudinal Studies

In a longitudinal, or cohort, study, a population of patients is enrolled in the study and measurements are made during a period of time.[11,12] Longitudinal studies can be observational, if no intervention is made, or they can be interventional.

Longitudinal Observational Studies

In a longitudinal observational study, data are collected from a group, or *cohort,* of patients over time, but no intervention is made. A longitudinal observational study can be either prospective or retrospective. In a *prospective* observational study, patients who meet specific eligibility criteria are identified, and data are prospectively gathered over time.[12] Prospective observational studies are valuable for defining the course of a particular disease treated with standard therapies and for identifying subgroups of patients with differing prognoses. If an association is noted between treatment and outcome in a prospective observational study, the association should be verified in a prospective interventional randomized clinical trial.

Although an observational study cannot prove a causal relationship, associations between initial patient characteristics or specific treatments and subsequent outcome can be detected. Such associations can be measured more accurately in a prospective longitudinal study than in a cross-sectional study because both the original patient characteristics and the subsequent outcome are determined prospectively. When these are determined prospectively, any associations observed are more likely to be true and not a result of measurement error or recall bias.

In a *retrospective* observational study, medical records of patients with certain initial characteristics who are treated over time are reviewed and data abstracted. As with all retrospective studies, retrospective observational studies are subject to recording bias, problems with missing information, and other methodological limitations. Because retrospective studies have these additional limitations and sources of bias, prospective studies provide higher quality evidence than retrospective studies do. Prospective studies, however, are usually more difficult and time-consuming to perform.

Longitudinal Interventional Studies (Clinical Trials)

Interventional studies, which must be prospective, involve the artificial manipulation of a patient's therapy to determine the effect of an investigational treatment.[11,12] An interventional study can be controlled or uncontrolled, and if it is controlled, the treatment assignment should be randomized.

In an *uncontrolled* interventional study, all patients who meet defined eligibility requirements are given the investigational therapy, and their outcomes are determined. Although such studies are useful to define the rate of successful therapy in a well-defined population of subjects, the lack of a control group makes it difficult to estimate the relative effectiveness of the new therapy compared with another therapy. Previous experience with the standard treatment, in the form of a historical control group, can be used for comparison to the group receiving the new therapy. The use of such historical control groups is unreliable and often leads to an overestimate of the relative effectiveness of the new investigational therapy.[16] Medical care is generally becoming more effective, and thus the results of modern studies tend to yield better patient outcomes, even if the investigational treatment has no inherent advantage over the therapy received by the historical control patients.[16]

In a *controlled* clinical trial, some patients are given the new investigational treatment, and some patients (*control group*) are given a standard treatment.[11,12] The purpose of the control group is to define the effectiveness of the standard therapy in a group of patients as similar as possible to the group receiving the investigational therapy. To obtain two groups of patients who are nearly identical with respect to all characteristics that might influence the outcome of their disease, it is important that no external or subjective factors influence the assignment of treatment.[11,17] In other words, each patient must have the same chance of receiving each therapy. For this reason, assignment to control or therapy groups should be randomized.

It is extremely important that control patients be given a therapy that is at least as effective as the best currently available treatment. It is unethical for a control group to receive an inferior treatment simply to demonstrate that a new treatment has some effectiveness.[19-22]

In general, longitudinal interventional studies provide the highest quality evidence, although this is controversial.[23-25]

RANDOMIZED LONGITUDINAL INTERVENTIONAL STUDY (CLINICAL TRIAL)

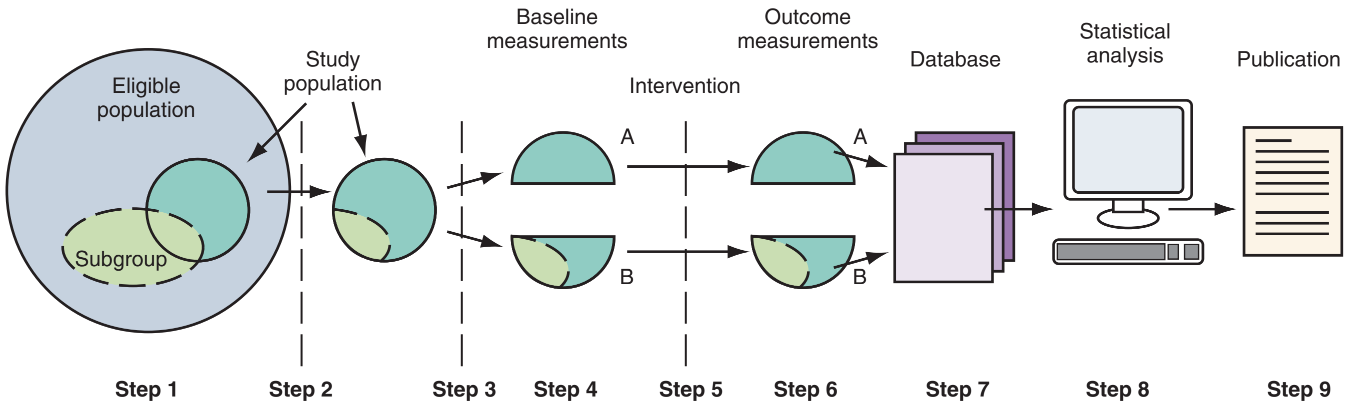
A randomized clinical trial should not be initiated unless a worthwhile research question has been precisely defined (Fig. 1). No matter how well designed the study, if the research question is not well defined and not clinically useful, the intended audience will not find the study's results valuable.[26] The research question must also be prospectively defined; it is not appropriate to gather data and then to devise a research question to fit the data. A good research question clearly defines four elements: (1) the patient population and problem to be studied, (2) the intervention to be applied to the treatment group, (3) the comparison (control) intervention, and (4) the outcome of interest.

Even if these four elements are well defined, the research question must still have relevance for the emergency physician. For example, a study that compares oral and parenteral antibiotics (treatment and comparison interventions) for the prevention of meningitis (outcome) in well-appearing febrile children with occult bacteremia confirmed by positive blood culture (patient population) is less useful to the emergency physician than a similar study including all well-appearing febrile children because results of blood cultures are not typically available in the emergency department.

Step 1: Definition of Patient Population

Assuming an appropriate research question has been selected, the first step is to define the patient population to be studied.[27,28] The original patient population defined in the research question may be modified slightly by practical factors in study design. For example, although an investigator may want to study all asthmatic patients presenting to the emergency department, it may be practical to study only those presenting when investigators are available (*convenience sample*). Explicit inclusion and exclusion criteria must be defined before any patients are enrolled, and these criteria must be uniformly applied in determining which patients are eligible to participate in the study. For the study to be most applicable to emergency medicine, the population should be defined in terms of clinical characteristics that are observable in the emergency department. On the other hand, groups of patients defined by their clinical characteristics in the emergency department are highly heterogeneous.[13] Some patients in the population may have more severe disease than other patients or may have a completely different cause of their symptoms.

www.ketabpezeshki.com 66485457-66963820



Step 1: Definition of the patient population	**Step 2:** Recruitment and enrollment of patients	**Step 3:** Randomization	**Step 4:** Measurement of baseline characteristics	**Step 5:** Treatment or intervention	**Step 6:** Collection of data on outcome	**Step 7:** Data management	**Step 8:** Statistical analysis	**Step 9:** Presentation and publication of results
Problem 1: Heterogeneous population (confounding variables), poorly chosen inclusion criteria	**Problem 2:** Bias in recruitment, self-selection by potential subjects	**Problem 3:** Imbalance of important confounding characteristics, inadequate blinding	**Problem 4:** Imbalance of confounding characteristics is not detected	**Problem 5:** Unequal compliance or attrition	**Problem 6:** Subjects lost to follow-up, poorly defined outcomes	**Problem 7:** Data entry errors, data reduction errors or bias	**Problem 8:** Type I and type II errors, ill-advised comparisons or subgroup analysis, covariate imbalance	**Problem 9:** Overextrap-olation of results, failure to recognize limitations of or biases in results
Solution 1: Population defined in terms of emergency department presentation, confounding characteristics considered in definition of population	**Solution 2:** Consecutive enrollment, records of nonenrolled but eligible patients	**Solution 3:** Effective randomization and blinding, stratified randomization	**Solution 4:** Planned prospective measurement of important confounding characteristics	**Solution 5:** Intention-to-treat analysis of final data, measurement of compliance, procedures to encourage compliance	**Solution 6:** Multistep plans to obtain follow-up data, unambiguous definitions of treatment outcome	**Solution 7:** Data verification, double data entry, value-limited data entry, appropriate forms design	**Solution 8:** Small number of comparisons, planning of analysis, adequate sample size, multivariate modeling	**Solution 9:** Peer review, replication of results by other investigators, educated readership

Figure 1. Implementation and analysis of a prospective randomized, controlled clinical trial.

When reading a study, one should determine if the patient population is well defined and reasonably comparable to one's own patient population.[6] If important segments of the population are excluded (e.g., those with severe disease), the study results are not applicable to this subgroup. Researchers should not generalize their conclusions to patients not included in their study population.

Step 2: Recruitment and Enrollment of Patients

Once a patient population is defined, the next step is to recruit patients for enrollment in the study. To the extent possible, all patients meeting the predefined eligibility requirements for the study should be enrolled. The method of recruitment and enrollment should ensure that there is no systematic tendency to exclude a subgroup of patients from the study who meet the inclusion criteria. If such a *selection bias* exists, it will make the results of the study inapplicable to the types of patients that were excluded.[11,29] For example, if a study of head trauma patients specifies that informed consent must be obtained from the patient within the first half-hour of presentation to the emergency department, there will be a systematic tendency to exclude patients with head trauma severe enough to result in an altered level of consciousness.

Even in a study that is appropriately designed, patients may self-select, resulting in selection bias. For example, patients of low socioeconomic status may be either more or less likely than patients of high socioeconomic status to give consent for participation in clinical studies. Thus, although the disease may affect people in all socioeconomic strata, the study results may apply only to patients of socioeconomic status similar to those who participated in the study.

To minimize selection bias, studies should aim to achieve consecutive enrollment of all patients who meet inclusion criteria. Furthermore, patients who meet eligibility criteria but are not subsequently enrolled should be counted to allow an estimation of the possible extent of any selection bias that might exist.[10] When reading a study, one should look for information on eligible patients who were not enrolled. A significant number of such patients may indicate selection bias. Researchers should explain why these patients were missed and should justify the validity of their results despite missed patients by showing, for example, that demographics and disease characteristics of missed patients were similar to those of enrolled patients.

Step 3: Randomization

The third step in conducting a clinical trial is to randomize enrolled patients to the different treatments being compared. The purpose of this randomized allocation is to create two groups of patients who, other than receiving different treatments, are as nearly identical as possible.[11]

Stratified randomization can be used to ensure that important confounding factors are equally distributed in the control and test groups.[11] In a stratified randomization, patients with the stratifying characteristic are randomized independently of those without the characteristic. For example, in a study of therapy for closed head injury, patients with severe closed head injury as defined by a low Glasgow Coma Scale score could be randomized independently of those patients with a higher Glasgow Coma Scale

www.ketabpezeshki.com 66485457-66963820

score. This would help ensure that the control and test groups have equal fractions of patients with severe and mild closed head injury.

Whenever possible, both the patient and the treating physician should be "blinded" (*double blinding*) to the therapy given.[11] Such blinding is important to ensure that both the patient and the investigating physician can make unbiased estimates of endpoints, including the occurrence of undesirable side effects. Recently, increasing importance has been placed on subjective outcomes, such as quality-of-life assessments made by the patient. Blinding is especially important to ensure that the patients' expectations regarding the effect of the new therapy do not influence their assessment of this type of outcome.

The quality of the randomization in a controlled clinical trial is important because studies that are inadequately randomized are more likely to "find" a positive treatment effect even when one is unlikely to exist.[30] Similarly, studies in which blinding is inadequate, so that the patient or the treating physician might be able to determine the treatment that the patient actually receives, are more likely to yield false-positive results.[15] When reviewing a clinical trial, one should look for truly random treatment assignment and adequate blinding procedures. For example, in a trial in which patients are enrolled only if they are determined to be sufficiently "stable" by the physician and assignment to therapy or control is alternated, a physician with the bias that the therapy is not efficacious may avoid enrolling a patient by deeming the patient unstable if the physician knows that the next patient will be assigned to the treatment group. A better method of randomization would be assignment by a computerized randomization program, such that no pattern of assignment can be discerned by the enrolling personnel.

Step 4: Measurement of Baseline Characteristics

The fourth step is to measure the characteristics of patients enrolled in the study before therapy. The purpose of these baseline measurements is to detect imbalance between the control and test groups in characteristics that might influence each patient's chance for a successful outcome. Factors that might influence patient outcome and that are not controlled by the investigators are termed *confounding variables.* For example, the initial cardiac rhythm is a confounding variable in a study that compares different treatments for out-of-hospital cardiac arrest. If one group includes more patients in ventricular fibrillation and the other group has more patients in asystole, the intervention given to the first group will appear to be more efficacious. The influence of confounding characteristics must be anticipated, and those characteristics should be prospectively measured for all patients enrolled in the study. Subgroups of the overall patient population often have specific confounding characteristics (see Fig. 1). If a clinically significant difference in outcome is ultimately detected between the two treatment groups, the baseline characteristics of the treatment groups should be compared to ensure that the observed difference in outcome did not occur because the two patient groups were not initially equivalent.[11] When reading a study, one should look to see that important confounders were measured and that they did not differ substantially between the groups studied.

Step 5: Treatment or Intervention

The next step is to administer the experimental treatment to the test group and the control treatment to the control group. Although the control and test patients should be nearly identical in their underlying characteristics, the two groups often have unequal compliance with therapy. For example, in a placebo-controlled study of an oral medication, patients taking the active drug may find that it causes gastrointestinal discomfort, whereas those taking the placebo treatment might not experience such an effect. Therefore, patients taking the active agent may be less compliant with therapy. Unequal compliance complicates the interpretation of the outcome data.

Step 6: Collection of Data on Outcome

The sixth step is to determine the outcome of each patient. Definitions of treatment success and treatment failure must be explicitly defined before any data are collected. Sometimes a trial is initially designed to investigate the effects of therapy on one outcome, but during data analysis investigators notice an apparently significant effect on a different outcome. Such a serendipitous finding may reflect a true treatment effect but can also result from chance because there are generally many such possible findings, and the study was not originally designed to investigate each of these possible outcomes. Such findings can be reported as interesting and warranting further investigation but should not be reported as reliable conclusions.

A difficulty with the collection of outcome data arises if too many subjects are lost to follow-up. This is more likely to occur in studies that evaluate the long-term effects of therapy. Patients who are lost to follow-up may have characteristics different from those of patients who keep their follow-up appointments. For this reason, lack of complete follow-up in the study population can bias the results of the study.

Ensuring high rates of follow-up in studies of outpatient therapy is notoriously difficult. One approach is to create a multistep plan to obtain follow-up, with specific procedures to be followed if patients miss their first, second, or even third follow-up appointment. When reading a study, one should look at the percentage of patients lost to follow-up and look for a systematic effort to maintain good follow-up.

Step 7: Data Management

Once patients have been enrolled and have had their baseline characteristics measured, treatments administered, and outcomes determined, all this information should be organized and stored in a format that allows analysis of the data. Data should be collected on a form that limits and organizes the information. In general, information to be recorded on the data form should be highly structured, with categorical variables limited to a small number of possibilities and with very little or no unformatted "fill-in-the-blank" information requested. Such structure is required if the resulting data are to be analyzed statistically.

Errors may be introduced when data are entered into the database from data sheets. Bias can be introduced if certain types of data (e.g., written phrases in a patient questionnaire) are reduced to a smaller number of categorical responses during the data entry procedure. Databases should be designed to ensure that the data listed are reasonable. For example, the electronic database should not allow entry of patient temperatures that are incompatible with life or negative blood pressures. When reviewing a study, one should look for data categorizations that are clear and clinically useful. For example, a study of postresuscitation neurologic outcomes would be most useful to the emergency physician if patients were categorized as "normal," "mildly impaired," "severely impaired," or "dead" versus the more vague terms "good" and "poor" or by the results of a detailed neuropsychological battery of tests.

Step 8: Statistical Analysis

The next step is to analyze the data. Careful planning of the statistical analysis to be performed is required to minimize the chance

www.ketabpezeshki.com 66485457-66963820

of erroneous conclusions. Only a small number of comparisons should be made, and the study should be designed to have an adequate sample size to reliably detect a clinically important treatment effect.[31-35] The comparisons to be conducted, as well as any specific subgroups of patients that will be considered separately, must be defined prospectively. Any imbalance in confounding baseline characteristics should be accounted for in the statistical analysis. Specific statistical tests are discussed later.

Step 9: Presentation and Publication of Results

Once the clinical trial data have been statistically analyzed, conclusions can be drawn from the results of the study. During the preparation of a manuscript describing the study and its conclusions, the investigators should be careful not to overextrapolate the results. Care should be taken to explain limitations in the study design and to enumerate factors that might bias the results of the study or at least limit its applicability to different patient populations. One purpose of the peer review process is to ensure that appropriate care is taken in interpreting the clinical trial results.

The enthusiasm of most investigators and clinicians for the results of a clinical trial is partly determined by the direction of the results.[36] For example, a trial that shows a highly effective new therapy for a serious disease is interesting and exciting. On the contrary, a trial that shows that a previously unstudied therapy has no advantage over the currently accepted treatment may be less interesting. Because positive results are inherently more interesting, it is commonly believed that clinical trials yielding positive results are more likely to be published than those with negative results. This effect is termed *publication bias*.[37-39]

However, studies have shown that trials with negative results may be less likely to be submitted for publication but, once submitted, are as likely to be published as trials with positive results.[37,39] Thus publication bias may be the result of a *file drawer problem,* meaning that study results that are negative sometimes end up in the file drawer instead of in manuscripts submitted for publication.[40]

Publication bias and the file drawer problem are serious threats to the validity of the medical literature taken as a whole. If negative trials are selectively excluded from the medical literature, an ineffective treatment may appear to be at least partially effective because those (possibly poorly designed) studies that show some positive treatment effect are selectively submitted for publication. Meta-analyses or systematic reviews often use only published research. It may be unethical to subject patients to the risks and discomforts of participation in a clinical study and not publish the results, especially if participation did not result in any direct benefit to the patient.

Publication bias and other sources of bias can be especially problematic in pharmaceutical or commercially sponsored clinical research. Commercial studies are less likely to report unfavorable conclusions.[41] Data from industry-sponsored research may go unpublished or may be difficult to obtain for subsequent review.[42] When reading a clinical trial, one should determine what agency or company funded the research and consider what biases, if any, might have been introduced.

DATA ANALYSIS

Classical Hypothesis Testing

Data from clinical trials are often analyzed by use of *P* values and classical hypothesis testing.[3,7,8] In classical hypothesis testing, two hypotheses that might be supported by the data are considered. The first, called the *null hypothesis,* states that no difference exists between the groups being compared with respect to the measured outcome of interest.[7] For example, in a study examining the use of a new sympathomimetic agent for blood pressure support in patients with sepsis, the null hypothesis might be that there is no difference between the average systolic blood pressure achieved with the test agent and that achieved with the control agent. The *alternative hypothesis* states that the average systolic blood pressure achieved is different in the groups being compared.[7] In this example study, the alternative hypothesis might be that the test agent results in a 10 mm Hg greater average systolic blood pressure than the control agent. The magnitude of the difference between the two groups defined by the alternative hypothesis is called the *treatment effect* (Tables 1 and 2).

Table 1 Steps in Classical Hypothesis Testing

STEP	DESCRIPTION
Define the null hypothesis	There is no difference between the groups being compared. For example, in a clinical trial, the null hypothesis might be that the response rate in the treatment group is equal to that in the control group.
Define the alternative hypothesis	The alternative hypothesis might be that the response hypothesis rate in the treatment group is greater than that in the control group by a given amount.
Calculate a *P* value	This calculation assumes that the null hypothesis is true. One determines the probability of obtaining the results found in the data or other results even more inconsistent with the null hypothesis. This probability is the *P* value.
Accept or reject the null hypothesis	If the probability of observing the actual data, or more extreme results, under the null hypothesis is small ($P < \alpha$), we should doubt that hypothesis. The idea is that if the probability under the null hypothesis of observing the actual results is very small, there is a conflict between the null hypothesis and the observed data, and we should conclude that the null hypothesis is not true.
Accept the alternative hypothesis	If we reject the null hypothesis, we accept the alternative hypothesis by default.

The treatment effect defined by the alternative hypothesis must be set before data are collected. The treatment effect should be large enough to be clinically important but small enough such that showing no difference between the groups rules out any clinically important treatment effect. In an interventional study, the difference defined is ideally the minimum treatment effect thought to be clinically significant (i.e., that which would lead to a change in clinical practice). Sometimes a larger treatment effect is defined because designing a study to reliably detect the smallest clinically significant treatment effect would require too large a sample size.[32-35] When evaluating the results of a clinical trial, one should look for the size of the treatment effect that the trial was designed to detect.

Once the null and alternative hypotheses are defined, the null hypothesis is "tested" to determine which hypothesis (null or alternative) will be accepted as true. The process of testing the null hypothesis consists of calculating the probability of obtaining the observed results or results that are even more inconsistent with the null hypothesis, assuming the null hypothesis is true. This probability is the *P* value.[7]

If the *P* value is less than some predefined value, denoted alpha (α; usually 5% or .05), the null hypothesis is rejected as false, and the alternative hypothesis is accepted as true. In other words, if the

www.ketabpezeshki.com 66485457-66963820

Table 2 Terms Used in the Design of Clinical Trials

TERM	DEFINITION
Alpha (α)	Maximum *P* value to be considered statistically significant; the risk of committing a type I error
Alpha error	Type I error
Alternative hypothesis	Hypothesis considered an alternative to the null hypothesis; usually the alternative hypothesis is that there is an effect of the studied treatment on the measured variable of interest; also called *test hypothesis*
Beta (β)	Risk of committing a type II error
Beta error	Type II error
Null hypothesis	Hypothesis that there is no effect of the studied treatment on the measured variable of interest
Power	Probability of detecting a treatment effect the size of the treatment effect sought (i.e., obtaining a P value $< \alpha$), given alpha and the sample size of the clinical trial; power $= 1 - \beta$
P value	Probability of obtaining results similar to those actually obtained, if the null hypothesis were true
Type I error	Obtaining a statistically significant *P* value when, in fact, there is no effect of the studied treatment on the measured variable of interest; also called *false positive*
Type II error	Not obtaining a statistically significant *P* value when, in fact, there is an effect of the treatment on the measured variable of interest that is as large as or larger than the effect the trial was designed to detect; also called *false negative*

Adapted from Lewis RJ: An introduction to the use of interim data analyses in clinical trials. Ann Emerg Med 22:1463, 1993.

Table 3 Common Statistical Tests

STATISTICAL TEST	DESCRIPTION
Student's *t*-test	Used to test whether the means of measurements from two groups are equal, assuming that the data are normally distributed and that the data from both groups have equal variance
Wilcoxon rank sum test (Mann-Whitney test)	Used to test whether two sets of observations have the same distribution; similar in use to the *t*-test, but it does not assume the data are normally distributed
Chi-square test	Used with categorical variables (two or more discrete treatments with two or more discrete outcomes) to test the null hypothesis that there is no effect of treatment on outcome; assumes at least five expected observations of each combination of treatment and outcome under the null hypothesis
Fisher's exact test	Similar to chi-square test; it may be used even when fewer than five observations are expected in one or more categories of treatment and outcome
One-way analysis of variance (ANOVA)	Used to test the null hypothesis that three or more sets of continuous data have equal means, assuming the data are normally distributed and that the data from all groups have identical variances; may be regarded as a *t*-test for three or more groups
Kruskal-Wallis test	Nonparametric test analogous to one-way ANOVA; no assumption is made about normality of the data; may be regarded as a Wilcoxon rank sum test for three or more groups

null hypothesis were actually true, the probability of obtaining data like those obtained or even more extreme results by chance alone is less than alpha.

Type I Error

A type I error occurs when the investigator concludes that a difference has been demonstrated between two groups when no such difference exists.[7,8,43] It is a type of *false positive.* When data are analyzed by *P* values, a type I error occurs when a statistically significant *P* value is obtained but there is actually no underlying difference between the groups being compared. Because the *P* value is the probability of obtaining results equal to or more extreme than those actually observed, assuming there is actually no difference between the groups being compared, the risk of a type I error is equal to alpha, the maximum *P* value considered statistically significant, when the groups are fundamentally the same.[7,43]

Type II Error, Power, and Sample Size

A type II error occurs when a difference exists between the two groups and that difference is as great as that defined by the alternative hypothesis but a nonsignificant *P* value is obtained.[7,32-35] In other words, there really is a difference between the two groups, but the trial failed to demonstrate this difference. A type II error is a type of *false negative,* and the risk of a type II error is commonly denoted beta (β).

The *power* of a trial is the probability of detecting a treatment effect of a given size, if one truly exists.[32-35] Studies are usually designed to have a power of .80 or greater. Because the power of the trial is the chance of finding a true treatment effect, the quantity (1 − power) is the chance of missing a true treatment effect (i.e., risk of committing a type II error).[32,34] The value of $(1 - \beta)$, or the power, and the magnitude of the treatment effect the clinical trial is designed to detect (defined by the alternative hypothesis) determine the sample size required for the study.[35]

The smaller the size of the treatment effect the study is designed to detect, the larger the required *sample size* will be for a given value of alpha (the maximum significant *P* value) and for a given power. For any given treatment effect, a smaller maximum significant *P* value or a larger power will also require a larger sample size. Surprisingly, clinical studies are often published with negative results even though the studies did not have a sample size sufficient to reliably detect a clinically significant treatment effect.[32-35]

When reading a study, one should look for a statement about the power of the study. In general, a power of .80 or greater is desirable. The treatment difference tested should not be too large, such that smaller clinically important treatment differences may still exist even after a "negative" result. Power and sample size should be estimated before the study is begun; a "post hoc power analysis" after the data have been collected is not recommended.

Statistical Tests

Depending on the characteristics of the data being analyzed, different statistical tests are used to determine the *P* value (Table 3). Student's *t*-test and Wilcoxon rank sum test are used to compare continuous variables (e.g., serum glucose level and respiratory rate) between two groups of patients. If there are three or more groups of patients, one-way analysis of variance (ANOVA) and the Kruskal-Wallis test are used to compare continuous variables between the groups. The chi-square test and Fisher's exact test are used to detect associations between treatment and outcome

www.ketabpezeshki.com 66485457-66963820

when both the treatment and the outcome are categorical variables (e.g., placebo vs. active drug, lived vs. died, or admitted vs. discharged).

Student's *t*-test and one-way ANOVA are examples of parametric statistical tests. Parametric tests make assumptions about the underlying distribution of continuous variables. Both Student's *t*-test and ANOVA assume that the data are normally distributed (i.e., distributed in a bell-shaped curve around the central mean) and that the different groups yield data that have equal variance.

When the data to be analyzed are not normally distributed, the *P* value should be obtained by use of a nonparametric test.[7,8,44] Nonparametric tests are distribution free in that they do not rely on the data to have any particular underlying distribution. The nonparametric alternative to a *t*-test for unpaired samples is the Mann-Whitney U test, or Wilcoxon rank sum test. For a statistical comparison of paired measurements, the Wilcoxon signed rank test can be used. The nonparametric alternative to one-way ANOVA is the Kruskal-Wallis test. The *t*-test may be used inappropriately when the data are unlikely to be normally distributed. If it is unclear whether the data are normally distributed, it is preferable to use the nonparametric test.

Confidence Intervals

Often, the primary goal of a clinical trial is not simply to obtain a yes or no answer to the question of whether a treatment has any efficacy at all but rather to estimate the magnitude of the treatment effect. This goal of measuring the effect of the treatment arises if another treatment is known to be effective. On the other hand, if no effective treatment is available, a new therapy may be adopted even if the study shows only the possibility of effectiveness.

When the primary goal of a study is to measure or to estimate a treatment effect, the results should be reported by use of confidence intervals.[45-49] In general, a *confidence interval* is a range of possible values for a treatment effect that are statistically likely given the results of the current trial. For example, a 95% confidence interval is likely to contain, within its limits, the true size of the treatment effect 95% of the time.[48,49] Confidence intervals are easily calculated for most data.[49] Advanced statistical methods may be required to report confidence intervals for data with non-straightforward (e.g., normal or binomial) distributions.[50]

Situations may arise in which a *P* value and confidence interval can lead to different qualitative interpretations of the same clinical trial results. Suppose one is studying a treatment for a disease that has no known effective therapy. If the 95% confidence interval for the treatment effect ranges from −2 to 30%, where the treatment effect is measured as the change in the absolute percentage of patients with a good outcome, many clinicians would interpret this as showing that although the therapy may have little benefit, it has the possibility of having significant benefit (improving the outcome for up to 30% of patients). Thus many clinicians would adopt the therapy as appropriate, given the lack of an effective alternative. If classical hypothesis testing had been used to analyze the same data, a nonsignificant *P* value would have been obtained. Many clinicians would then interpret the study as failing to show efficacy and conclude that the therapy is not appropriate for clinical use.[45-49]

When reading a study, one should look beyond the *P* values to the size of the treatment effect found and the width of the confidence intervals. If *P* is reported as significant (usually < .05), one should make sure that the difference is clinically significant. For example, a difference in reduction of temperatures by 0.5° C between two antipyretics may not be clinically significant but would be statistically significant in a sufficiently large study. Issues such as cost, palatability, and adverse effects are likely to be more important in choosing between the two antipyretics. If *P* is reported as not significant (usually > .05), the practitioner should ensure that the confidence interval is not so wide that a clinically important treatment effect is still possible, as in the previous example.

Table 4 **Probability of at Least One Type I Error (False Positive) When Multiple Comparisons Are Performed***

NUMBER OF COMPARISONS	PROBABILITY OF AT LEAST ONE TYPE I ERROR
1	.05
2	.10
3	.14
4	.19
5	.23
10	.40
20	.64
30	.79

*Between identical groups with $\alpha = .05$.

Multiple Comparisons

Whenever two groups of patients are compared statistically, even if they are fundamentally identical, a statistically significant *P* value can be obtained by chance.[7,43] If the maximum significant *P* value (alpha) is .05, there is a 5% chance that a statistically significant *P* value will be obtained when no true difference exists between the two patient populations. This risk of a false-positive *P* value occurs each time a statistical test is performed. When *multiple* comparisons are performed, whether they are "pairwise comparisons" of more than two groups of patients or the comparison of many different characteristics between two groups of patients, the risk of at least one false-positive *P* value is increased because the risk associated with each test is incurred multiple times (Table 4).[31,51,52] For a small number of tests, the overall risk of at least one type I error is roughly equal to the maximum significant *P* value used for each individual test multiplied by the total number of tests performed. This rough equality is the basis for the Bonferroni correction.[7,11,31]

The *Bonferroni correction* is a method to reduce the overall type I error risk for the whole study by reducing (i.e., making more stringent) the maximum *P* value used for each of the individual statistical tests ("testwise risk"). The desired overall risk of a type I error (usually .05) is divided by the number of statistical tests to be performed, and this value is used as the maximum significant *P* value for each individual test. For example, if five comparisons are to be made, a maximum significant *P* value of .01 would be used for each of the five statistical tests.

The Bonferroni correction controls the overall risk ("studywise risk") of a type I error at the expense of an increased risk of a type II error. Because each statistical test is conducted with a more stringent criterion for a statistically significant *P* value, there is an increased risk that each test might miss a clinically important difference and yield a *P* value that is nonsignificant with the new criterion of *P* < .01.

Specific statistical tests have been developed to compare three or more groups of patients, such as one-way ANOVA, Kruskal-Wallis test, chi-square test, and Fisher's exact test (see Table 3). These tests, which do not use the Bonferroni correction, can be useful for detection of differences among three or more groups with relatively high power while controlling the overall risk of a type I error. Their disadvantage is that although they can detect a

www.ketabpezeshki.com 66485457-66963820

difference among three or more groups of patients, they do not define *which* pairwise differences are statistically significant. When reviewing positive studies with multiple study groups or multiple comparisons, one should consider the potential for an increase in type I error and check for the use of statistical methods accounting for multiple comparisons or appropriate for more than two study groups.

Interim Analyses of Accumulating Data

During a clinical trial, data accumulate sequentially and contain increasingly more information on the effectiveness of the treatments being compared. Often, however, these data are not analyzed until the trial has been completed and all patients have been enrolled. This type of fixed sample size design has the disadvantage of possibly enrolling more patients than are necessary to obtain a reliable result, either positive or negative. It is often advantageous to plan one or more *interim analyses* of the data to be conducted before the full sample size has been reached to determine whether a reliable conclusion can be drawn from the data and the trial terminated early. Because this is a type of multiple comparison, such interim analyses must be planned in advance to avoid increasing the risk of a type I error.[11,52-54] When reading a study reporting results of an interim analysis, one should look to see that the interim analysis was planned and not performed because a casual observation of the data showed interesting or promising results.

Subgroups

Any group of patients is heterogeneous; this is especially true for groups of patients defined by presenting signs and symptoms in an emergency department setting. Some of the patients within such a group may have a more severe form of the disease in question, and some patients may have a coexisting disease that modifies the original disease process. Almost any group of patients can be considered to have multiple *subgroups,* each of which is more homogeneous than the overall group.

Because of this heterogeneity, a treatment effect that is detected within the entire group may or may not exist for a particular subgroup of the original population, or vice versa.[55-57] Therefore, the data from subgroups of patients are often analyzed separately. In some circumstances, this is important in determining which therapies are most effective in clinically important subgroups of patients.[55,56]

When subgroups of patients are to be analyzed, they should be defined prospectively. Unfortunately, studies with an overall negative result may emphasize a positive treatment effect found only in a subgroup defined after data collection. Although such findings may warrant brief discussion and further investigation, they are unreliable because analysis of data from all possible after-the-fact subgroups requires the use of multiple statistical comparisons, which increases the chance that the finding represents a type I error, or false-positive result.

Even if the subgroups are defined before the acquisition of any of the clinical trial data, testing for a treatment effect in each subgroup potentially increases the risk of a type I error. Also, because each subgroup of patients is smaller than the entire study population, the analysis of these subgroups may have low statistical power, which increases the chance of a type II error.

Additional problems can occur if the subgroups of patients are not defined properly.[55,56] A "proper" subgroup of patients is defined by signs, symptoms, or laboratory results that are available at the initial presentation and that are not modified by the treatments being compared. An "improper" subgroup of patients is defined by signs, symptoms, or laboratory findings that can, in principle, be modified by the treatments being administered. For example, in a study that compares different volumes of fluid resuscitation for patients with septic shock, an improper subgroup of patients might be defined by a low systolic blood pressure after fluid administration (the so-called refractory shock group). Conversely, a proper subgroup would be defined by a low systolic blood pressure before any fluid administration.

Because of the possible association between the subgroup assignment and the treatment being administered in an improperly defined subgroup, improper subgroups cannot be used to assess the effectiveness of therapies. It is a common error in many retrospective studies to compare such improper subgroups of patients. When reading a study reporting results in subgroups of patients, one should look to see that the subgroups were prospectively and properly defined and consider whether the characteristics defining the subgroup would be known during emergency department care.

Multivariate Models

Multivariate modeling is a statistical tool used to determine the association between two or more independent (predictor) variables and a single dependent (outcome) variable. For example, a multivariate model might be used to determine the simultaneous effects of the patient's age and initial systolic blood pressure on the patient's chance of survival after penetrating abdominal trauma.

The two most common types of multivariate models in medical literature are multivariate linear regression models and multivariate logistic regression models. *Linear regression models* are used to determine the effects of two or more variables on a continuous outcome variable, such as blood pressure. *Logistic regression models* are generally used when the outcome is binary, such as survival (lived vs. died) or admission to the hospital (admitted vs. discharged).

Multivariate models offer several advantages over univariate analyses.[58-60] In a *univariate analysis,* the effect of a single predictor on the outcome is studied in isolation, often with the statistical tests discussed previously. Multivariate models are more akin to "real-life" clinical decision-making, whereby a clinician considers several factors, such as demographics (e.g., age and gender), history elements, and physical examination findings, in deciding a patient's likely diagnosis or clinical course. They can determine which subsets of variables have significant effects on the outcome.

Multivariate models allow one to control for *confounders,* variables associated with the predictor one wishes to study that may also affect the outcome. For example, in studying the effect of alcohol intake on the outcome of lung cancer diagnosis, tobacco smoking may confound the findings because patients with high alcohol intake are more likely to also smoke, and smoking increases lung cancer. A multivariate model that includes both predictors, alcohol intake and smoking, allows one to look at the isolated effect of alcohol intake while holding the effects of other predictors (smoking) constant.[58]

An example of this phenomenon was illustrated in a study of the predictors of mortality in patients with ruptured abdominal aortic aneurysms.[61] Univariate analysis did not reveal the emergency department–to–operating room time interval to be a significant predictor of mortality, whereas in the multivariate model, prolonged emergency department–to–operating room time was clearly a significant predictor. Patients with longer emergency department–to–operating room times probably presented with other findings that made their diagnosis less clear, or the need for intervention appear less urgent, and that were also associated with improved survival, such as higher initial systolic blood pressure and higher hemoglobin concentration. In the multivariate model, the effect of emergency department–to–operating room time

www.ketabpezeshki.com 66485457-66963820

could be assessed while holding such confounders as initial blood pressure and hemoglobin concentration constant.

The disadvantage of multivariate modeling is that it is more complex than univariate analysis. Certain statistical assumptions must be met, such as normal distribution of the outcome. Sometimes a single data point with an extreme value for a predictor or outcome variable, termed an *outlier,* exerts undue effects in the model. Regression diagnostics should be performed to assess that the statistical assumptions have been met and that no outliers are exerting undue effect.[58]

If two or more predictor variables interact (e.g., alcohol intake exerts an effect only in men, and not women, so that gender influences the effect of alcohol intake), an *interaction term* must be included in the model. If two or more predictor variables give redundant information (e.g., the predictors age and arrest etiology may give redundant information for the outcome survival from pediatric cardiopulmonary arrest because most infants have an arrest etiology of sudden infant death syndrome), the predictors are said to have *multicollinearity,* and this may require revision of the model (e.g., removal of one or more predictors).[58]

Authors should report statistics that measure the *goodness of fit,* or how well the model explains the observed data. However, the model may display good fit with use of these statistics and still be missing an important predictor variable or contain more predictor variables than necessary. Ultimately, investigators and readers need to have a basic understanding of the disease under study to determine that all the likely significant predictors have been accounted for in the model.[58]

When reading studies using multivariate models, one should look for the use of independent predictor variables that make clinical sense. One should check for the reporting of statistics measuring goodness of fit as well as discussion of regression diagnostics performed.

Importance of Prior Probabilities

On occasion, statistical tests yield surprising results. Unexpected results are especially difficult to interpret by classical hypothesis testing. Consider a clinical trial that uses a randomized, double-blind controlled design to compare two antibiotics for prophylaxis of infectious complications of tube thoracostomy, with the development of local wound infections or empyema as the primary endpoint. Suppose no statistically or clinically significant difference is found in the rate of infectious complications, but a statistically significant difference in mortality is noted between the two treatment groups ($P = .03$). It seems inherently unlikely that the choice of prophylactic antibiotic would affect survival without affecting the infection rate. This is an example in which the apparent conclusion of the trial has a very low *a priori probability* of being true. In other words, the a priori probability that the choice of prophylactic antibiotic could influence survival after traumatic injuries without affecting infection rates is exceedingly small.

Two possible explanations exist for such results. First, the antibiotic may have a true effect on survival by a previously unknown mechanism. The results of the trial would then be a true positive. Second, the results of the study might represent a type I error, with the statistically significant *P* value occurring by chance, even though the antibiotic has no effect on survival. The second explanation seems more likely than the first because the chance that the antibiotic exerted its effect through a previously unsuspected mechanism is small. Thus, despite the fact that a statistically significant *P* value was obtained, it is unlikely that a true treatment effect exists. Classical hypothesis testing is most likely to be misleading when the alternative hypothesis being tested has a very low a priori probability of being true.[62]

The chance of any particular interpretation of data being correct depends both on the a priori probability of that conclusion's being true and on the data supporting that conclusion.[62] An entire branch of statistical reasoning, Bayesian statistics, has been developed to incorporate a priori information quantitatively into the interpretation of data. Bayesian analysis is analogous to usual clinical reasoning in which laboratory test results are interpreted in light of the patient's underlying risk of disease.[62,63] For example, the proper interpretation of nonspecific T wave abnormalities in an electrocardiogram (ECG) depends on the patient from whom the ECG is obtained. If the ECG is obtained from a patient with multiple cardiac risk factors and typical ischemic chest pain, the T wave abnormalities should be considered suggestive of myocardial ischemia. If, on the other hand, the ECG is obtained from a young, healthy adolescent with a very low chance of having cardiac disease, the T wave abnormalities should be considered a normal variant. This use of a priori risk of disease in interpreting data is common in clinical practice. Similar logic should be used in the interpretation of data from a clinical study, especially when the conclusion would have been considered very unlikely before the study was performed.[62-64]

When reviewing studies, one should consider the results in the context of one's knowledge base. Is there scientific basis for the results? Are the results in congruence with other research in this area? Have the results been corroborated in subsequent studies?

Data Dredging or Torturing

It is surprisingly common for large databases containing many hundreds or even thousands of patient records to be created without clear prior definition of what questions are to be asked of the data. A typical example of this type of database is a trauma registry. When such databases are analyzed, the number of different questions that could be asked (or hypotheses tested) is enormous. In the case of a trauma registry, many tens of variables potentially associated with an adverse outcome are collected. It is tempting to test statistically for an association of each of these variables with survival in an attempt to find combinations of variables that predict outcome. When such exploratory data analyses are performed without clearly defined hypotheses, the analyses may entail a very large number of statistical tests. Each one of these statistical tests carries the risk of a type I error. If enough hypotheses are tested, one is virtually assured of obtaining some statistically significant *P* values, even if none of the variables are truly associated with outcome.

Multiple comparisons are also made, although only implicitly, when large collections of data are visually inspected by an investigator searching for trends or associations. The investigator may make dozens of mental comparisons, most of which show little obvious difference among the groups being compared. Often, however, some "interesting" differences are noted and brought to the attention of the statistician for statistical testing. The statistician may then find a statistically significant difference but is unaware that many comparisons were made by the investigator in searching for one or a few promising comparisons.

This process of making a large number of implicit or explicit comparisons in searching for possibly important differences is called *data dredging* or, more pejoratively, *data torturing.*[65] Such undirected analyses of large databases virtually always yield statistically significant *P* values that are meaningless. Thus, even when working with large collections of data, it is essential that the comparisons to be made are defined before the inspection or collection of the data and that the total number of comparisons is kept to a minimum. The risk of false-positive results from data dredging is especially high when the hypotheses tested were unlikely to have been chosen before the data collection. In other words, hypotheses that are motivated by the same data used to test them are much less likely to be true than hypotheses that are

www.ketabpezeshki.com 66485457-66963820

defined before the data collection, based on independently known associations or concepts.

Not all studies performed on large preexisting databases are examples of data dredging. When reviewing such studies, one should look to see that the hypothesis was defined before any manipulation of the database. The hypothesis should be based on independent observations and corroborated by previous research (basic science, animal, or clinical).

Intention-to-Treat Analysis

The effectiveness of any therapy is determined both by the therapy's inherent efficacy and by the emergency physician's ability to administer the therapy to the patient. For example, in the case of an oral medication, the effectiveness will be decreased if patients find the medication's side effects to be intolerable and are noncompliant. Similarly, an invasive procedure will be less effective, on average, if it can be performed successfully only in a minority of patients. To estimate accurately the effectiveness a therapy will have in clinical practice, the emergency physician should properly account for those patients for whom a treatment is initiated but cannot be completed. This is the purpose of an intention-to-treat analysis.[66]

In an *intention-to-treat analysis,* patients are considered to be members of the treatment group to which they were originally assigned, regardless of whether they take the prescribed medication or the appropriate therapy is successfully administered to them.[66] For example, in a trial that examines the use of an oral agent, patients would be considered to be part of the test group if they were originally prescribed the test medication, even if they freely admit to never having taken any of the tablets.

In a study of out-of-hospital intubation, children were randomized to receive bag-valve-mask (BVM) ventilation alone or BVM ventilation followed by endotracheal intubation (Fig. 2).[67] The populations of children were inherently heterogeneous; some children had sudden infant death syndrome, and others had closed head injury. The initial population was well randomized to the two interventions. Children with sudden infant death syndrome were substantially easier to intubate (because of their flaccid state) in the out-of-hospital setting than children with closed head injury, but their overall survival rate was much lower.

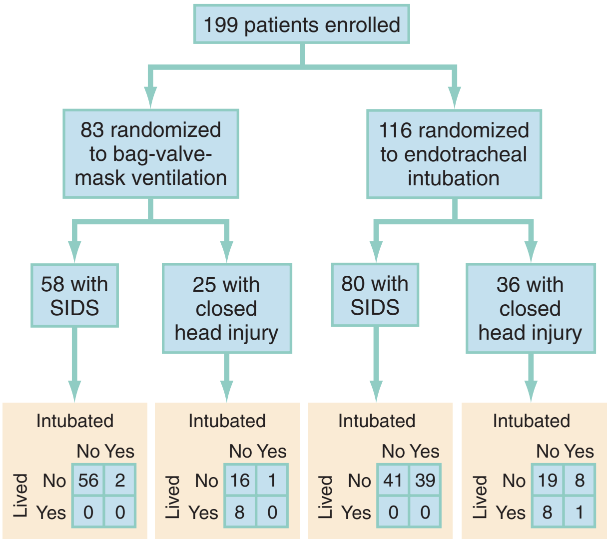


Figure 2. Results from a clinical trial comparing the use of bag-valve-mask ventilation with the use of endotracheal intubation in patients requiring advanced airway management in an out-of-hospital setting. *SIDS,* sudden infant death syndrome.

The goal of the analysis of the data was to determine the effect of out-of-hospital endotracheal intubation on survival. The correct way to group the data is to consider all patients initially assigned to the endotracheal intubation group as belonging to that group, whether or not they were successfully intubated. Thus, of 199 patients, 116 patients were assigned to the endotracheal intubation group and 83 patients were assigned to the BVM ventilation group. Considering all patients in the endotracheal intubation group, whether or not they were successfully intubated, the overall survival rate is 7.7% (9/116). Similarly, considering all patients in the BVM ventilation group, the overall survival rate is 9.6% (8/83). Thus the results of the study show a small trend toward improved survival with BVM ventilation.

Alternatively (but incorrectly), one might group the data according to the treatment actually received (*by treatment received analysis*).[66] In this case, children initially assigned to the endotracheal intubation group but not successfully intubated might be considered to be members of the BVM ventilation group because that was the treatment they actually received. If one counts all children who received only BVM ventilation, the overall survival rate in that group is 10.8% (16/148). Similarly, if one considers only children who were *successfully* intubated as the members of the endotracheal intubation group, the overall survival rate in that group is only 2.0% (1/51). This is because more children with sudden infant death syndrome are successfully intubated as a result of their flaccid state, but these children have lower survival rates. Similarly, children with closed head injury may be more combative and difficult to intubate but have higher survival rates than those with sudden infant death syndrome. This type of analysis then suggests that endotracheal intubation is extremely harmful. Whenever there is an association between compliance or the ability to administer an intended treatment and the patient's baseline chance of a successful outcome, analysis by treatment received does not accurately estimate the effect of the therapy in an actual patient population.

Even when an intention-to-treat analysis is used to analyze study results, extrapolation of the results to the general population may be unreliable if the compliance in the general population is lower than that in the study population.[68] This is a common problem because study populations tend to be more compliant than the general population. When reviewing a study, one should look for an intention-to-treat analysis rather than analysis by treatment received. In addition, one should assess whether one's patient population is likely to be as compliant as the study population or, in the case of a procedure, whether one is likely to be able to perform the procedure with the same rate of success.

Meta-analysis

Meta-analysis, or systematic review, is a statistical method for quantitatively combining the results of multiple clinical trials that investigate identical or similar therapies for a specific disease to obtain more accurate estimates of the effectiveness of the treatment.[69] Unlike the traditional review article, a meta-analysis emphasizes the quantitative estimation of the treatment effect observed in all the available studies taken as a whole and usually provides an estimate of the reliability or quality of the results of each study. Meta-analyses can be powerful tools in practicing evidence-based medicine because they collate the results of many or all available studies.[70]

Studies with poor design have been shown to be more likely to find an apparent positive treatment effect. A meta-analysis that includes many poorly designed studies tends to bias the results toward showing a positive treatment effect, even if no such effect exists. Methods for controlling and measuring the effect of poorly designed studies on the results of the meta-analysis have been developed and are often termed *sensitivity analyses*.[71] One method

www.ketabpezeshki.com 66485457-66963820

is to first perform the meta-analysis using only studies of the highest quality and then to sequentially include studies of increasingly lower quality to determine whether this causes a directional shift in the results. This approach requires a relatively objective measurement of study quality. Numerous scales and methods to define study quality have been developed.[72,73]

Publication bias, whereby smaller studies with negative results (i.e., no treatment effect shown) are not submitted for publication, may affect the validity of the conclusions drawn by a meta-analysis.[70] Authors of meta-analyses must strive to include all available trials, often requiring search strategies beyond a simple MEDLINE search. Other methods may include hand searching of relevant review articles and identified studies' reference lists, contacting of commercial sponsors and investigators to seek unpublished data, and searching of nontraditional bibliographic databases.[74] Problems can arise when pharmaceutical companies withhold data from commercially sponsored trials.[42] Requirements for all clinical trials to be entered into registries at the time of initiation may help alleviate problems associated with unpublished data.

Funnel plots are used to assess for publication bias.[71] Authors plot trial size or quality score against treatment effect. One would expect a funnel-shaped plot, whereby smaller and lower quality trials have a wide base centered around the mean treatment effect, whereas larger and higher quality studies, because they provide more accurate estimates of the treatment effect, make up the narrower top of the funnel. If a portion of the funnel is missing, such as the smaller studies with no treatment effect, this is indicative of publication bias.

Sometimes discrepancies arise between meta-analytic results and subsequent results from a large randomized clinical trial, leaving the reader wondering which results are correct.[75] Discrepancies may be due to bias introduced in the meta-analysis because of poor quality of studies included or publication bias.[75,76] Discrepancies may also be due to differences in inclusion or exclusion criteria or in definitions of outcomes. For example, a meta-analysis of studies that included patients at high risk for preeclampsia found calcium supplementation to be effective prophylactic therapy, whereas a single large trial that included only low-risk patients found calcium supplementation to have no effect.[77] Because of the inclusion of multiple trials, a meta-analysis may incorporate results from thousands of patients, and small treatment effects may reach statistical significance. Such small treatment effects may be false positives arising from inadvertent bias in poorly designed studies or from an artifact of the meta-analysis. Alternatively, the results may be true but clinically unimportant, or they may be true, clinically important, and warrant a change in clinical practice. The discerning reader considers the size of the treatment effect and possible bias introduced by the meta-analysis methodology and studies included to determine which of the previous conclusions is most likely.

When reviewing a meta-analysis, look for (1) assessment of the quality of trials included, (2) comprehensiveness of the search strategy for studies to be included and assessment of possible publication bias, (3) narrow confidence intervals indicating a large number of patients, and (4) agreement of the majority of the highest quality studies with the overall conclusion. Even when results are statistically significant, consider whether the size of the treatment effect is clinically significant and, combined with consideration of the costs and risks of the therapy, warrants a change in clinical practice.

CHANGING PRACTICE ON THE BASIS OF A RESEARCH STUDY

After reading the publication of results from a clinical research study, clinicians must decide whether the results of the study should cause them to change their clinical practice. There are several factors to consider in making this decision, the most obvious being the quality of the study and the results themselves. Other factors to consider include the context of the study within the available literature; the similarity of the clinician's practice setting and the clinician's likely ability to achieve results similar to those in the study; and the risks, benefits, and costs of changing clinical practice.[78]

For the clinician to change clinical practice on the basis of the results of a study, first the study must be high quality. In general, well-done systematic reviews of multiple randomized clinical trials provide better evidence than a single randomized clinical trial, and randomized clinical trials provide better evidence than observational or cross-sectional studies, while recognizing that some clinical questions do not lend themselves to randomized interventional trials. Also in general, prospective studies provide higher quality information than retrospective studies (e.g., chart review studies). Table 5 summarizes key study characteristics to look for in the evaluation of research studies. The CONSORT statement provides a helpful framework to evaluate the quality of a research trial and the written report of the trial's results and is required by many medical journals. It includes both a checklist of important study design information that should be provided for the reader and a flow diagram tracing patient enrollment, treatment allocation, follow-up, and analysis (www.consort-statement.org). The flow diagram is particularly valuable for verification that patients received the treatments they were assigned and that few if any subjects were lost to follow-up.

Once the study is determined to be of sufficient quality to believe that the results are valid, those results should be interpreted in the context of related medical literature and experience. The next section of this chapter reviews evidence-based medicine principles to be used in gathering and evaluation of evidence from the medical literature. If the current study is an outlier in its conclusions and equally high-quality studies in the literature do not support changing clinical practice, the clinician should consider waiting for further evidence. Expert guidelines and editorials may help the clinician weigh the available evidence and consider possible causes of differing results between studies.

The clinician should decide whether the study's patient population and health care practice setting are similar enough to the clinician's to make the study results relevant to the clinician's practice (a type of external validity). A study performed in a population from the East Coast demonstrating Lyme disease to be a common cause of meningitis may not be relevant to a clinician practicing in an area with low prevalence of Lyme disease. A study showing the utility of a particular intervention applied within 60 minutes of the patient's onset of symptoms may not be relevant to a clinician who works in a health care setting that is unable to provide that intervention in the same time frame (e.g., because of delayed patient presentations). The study's inclusion and exclusion criteria should be closely examined to determine whether the clinician's patient population sufficiently matches the study population, and the study protocol should be examined to determine whether the clinician would be able to provide similar care. Often, simply by virtue of being a research study protocol with the added advantages of having research personnel focused on patient enrollment and study completion, compliance and follow-up are better than in a typical clinical setting.

Finally, the clinician should perform an informal cost analysis before changing clinical practice. If an intervention is extremely costly, even if it was shown unequivocally to provide some benefit, the costs may outweigh the benefits. Costs may not necessarily be only financial, such as potential adverse effects and "opportunity costs," whereby receipt of one therapy results in the loss of the opportunity to receive another proven therapy or requires hospitalization. Clinical practice should be changed only when, on

www.ketabpezeshki.com 66485457-66963820

Table 5 Checklist to Assess Quality of Research Studies

Longitudinal Interventional Study (Clinical Trial)	
Study population	Inclusion and exclusion criteria are well defined, identify a population large enough to be clinically important, and can be applied in the emergency department setting
Enrollment	Enrollment as complete as possible (e.g., consecutive patients meeting enrollment criteria) Missed patients accounted for and not systematically different from study participants (selection bias)
Controlled	Control group similar to intervention group except for treatment received (usually requires randomization) Contemporaneous (not historical) control group
Randomized	Truly randomized allocation of treatments Study personnel unable to influence treatment group assignment Blinded assignment to treatment groups (patients, clinicians, and study personnel all blind to treatment group)
Outcomes	Important potential confounders measured and accounted for by randomization or statistical analyses High compliance with treatments between study groups Small number of patients lost to follow-up and patients lost to follow-up are not systematically different between study groups or different from those not lost to follow-up Appropriate, clinically relevant outcome definitions Those determining outcomes blinded to treatment group allocation Outcome difference between groups clinically significant as well as statistically significant Uncertainty in outcome difference quantified by use of confidence intervals or similar methods
Statistical analysis	Correct statistical procedure used (see Table 3) Treatment effect to be detected established a priori Sample size calculation performed before study is started Intention-to-treat analysis performed (patients analyzed in the groups to which they were originally assigned, despite actual treatment received)
Conclusions	Limitations and potential biases explained Conclusions not overextrapolated outside study population or study protocol
Additional Considerations	
Multiple comparisons	If multiple groups were studied or multiple comparisons were made, appropriate statistical procedures to account for this were used Interim analyses were planned a priori and conducted according to plan
Subgroups	Subgroups reported were defined before beginning of the study (prospectively defined) and limited in number If multiple subgroups studied, statistical procedures are used to account for multiple comparisons or the number of subgroups is small Adequate sample size in important subgroups Subgroups defined by characteristics available to the clinician at initial presentation (proper subgroups)
Multivariate models	Independent predictor variables included in the model make clinical sense and include all important variables "Goodness of fit" statistics reported and regression diagnostics performed
Meta-analysis or systematic review	Comprehensive search strategy used to identify potential trials to be included Quality of trials assessed Sensitivity of results to exclusion of lower quality studies assessed Funnel plot used to assess publication bias Narrow confidence intervals indicate a large number of patients Majority of highest quality studies agree on overall direction of treatment effect

balance, the potential benefits outweigh the costs. This cost-benefit analysis may differ according to patient population, health care system, and individual circumstances.

EVIDENCE-BASED MEDICINE

Evidence-based medicine (EBM) refers to the systematic gathering of information from the medical literature, often regarding the effectiveness of a particular treatment or the diagnostic accuracy of a particular test, with the intent to apply that evidence in diagnostic or management decisions related to an individual patient.[79,80] Although a specialized vocabulary has evolved, including both old and new terms (Table 6), the practice of EBM essentially involves the systematic application of long-established principles of medical literature analysis that until recently were often unknown by or impractical for the medical practitioner.

The fundamental steps in EBM are (1) to define precisely the clinical question being asked in terms that can be addressed by clinical studies; (2) to gather the available medical literature related to the question defined; (3) to assess the relevance, validity, and quality of the evidence contained in each study; and (4) to summarize the available evidence so that diagnostic and management decisions can be made for the individual patient on the basis of the recovered information.[79]

Step 1: Definition of Clinical Question

The first step in the practice of EBM is to define the clinical question clearly. The process of developing a well-formulated clinical question consists of several parts. First, the practitioner should define the population of patients similar to the individual patient motivating the search. The goal is to define a group of patients broad enough that they are likely to have been studied in clinical trials but specific enough that they are similar to the patient. Second, the practitioner should define the treatments or diagnostic approaches being considered. This involves defining the alternative approaches that might be used by reasonable practitioners in similar situations. Third, the practitioner should define the outcome of interest. The outcome of interest should be important to the patient and definable in terms of measurable quantities.

www.ketabpezeshki.com 66485457-66963820

Table 6 Terms Used in Evidence-Based Medicine

TERM	DEFINITION
Bias	Tendency to yield a result that lies to one side or the other of the true value; an error that is not centered around zero
Critically appraised topic (CAT) or best evidence topic (BET)	Summary of the results of an analysis of the evidence relevant to a particular clinical question
Likelihood ratio, negative (LR–)	Probability that a negative test result would occur in a patient with the disease in question divided by the probability that a negative test result would occur in a patient without the disease in question (generally < 1)
Likelihood ratio, positive (LR+)	Probability that a positive test result would occur in a patient with the disease in question divided by the probability that a positive test result would occur in a patient without the disease in question (generally > 1)
Negative predictive value	Fraction of patients with a negative test result who, in fact, do *not* have the disease in question
Number needed to treat (NNT)	Number of patients who must be treated with the better of two treatments so that one additional "good" outcome is obtained
Odds	Probability of an outcome divided by the probability of the outcome not occurring
Odds ratio	Odds of the outcome of interest occurring in one group of patients divided by the odds of the outcome of interest occurring in another group
Positive predictive value	Fraction of patients with a positive test result who, in fact, *do* have the disease in question
Post-test odds	Odds of the outcome of interest (e.g., particular disease being present), once a particular test result (positive or negative) is known to have occurred; equal to the pretest odds times the likelihood ratio for the test result obtained
Post-test probability	Probability of the outcome of interest once a particular test result is known to have occurred
Pretest odds	Odds of the outcome of interest before the test result is known
Pretest probability	Probability of the outcome of interest before the test result is known
Relative risk	Probability of an outcome in one group divided by the probability of the same outcome in another group
Reliability	Degree with which a clinical trial or diagnostic test is likely to yield consistent results when repeated
Sensitivity	Fraction of patients with the disease in question who have a positive test result
Specificity	Fraction of patients without the disease in question who have a negative test result
Validity, external	Degree to which the results from a study accurately reflect what would happen to similar patients who were not enrolled, including patients at other locations
Validity, internal	Degree to which a study accurately measures the outcomes for the enrolled study population

The steps required to define the clinical question in EBM practice are similar to the steps required to define a good hypothesis for a clinical trial: (1) the population for a clinical trial should be clearly defined, (2) the interventions to be used should be reasonable and well defined, and (3) one or at most a few clinically relevant and measurable outcomes should be defined.

Step 2: Collection of Evidence

The second step in the practice of EBM is to gather the available evidence.[79,81-84] Although a variety of resources might be used to accomplish this, the practitioner generally begins by searching one of the available electronic databases of published medical literature (e.g., MEDLINE). In addition, the physician may want to search one of the databases of known clinical trials (e.g., Cochrane Collaborative) because these databases often include the results from studies that have not been published or are not available on MEDLINE. Initially, the goal is to cast a wide net to gather as many of the available studies as possible.[79]

Step 3: Analysis of Studies for Validity, Reliability, and Relevance

The third step in the practice of EBM is to analyze each of the gathered studies to determine its validity, reliability, and relevance. The *validity* of a study is the degree to which the results are likely to represent "truth." When the clinical question involves the effect of a therapeutic intervention, a double-blind, randomized clinical trial is generally believed to be the most valid type of study. The *external validity* of a study may be reduced if the patient population in the study is too dissimilar to the patient motivating the current activity or if the clinical setting is substantially different from the physician's practice setting. Threats to *internal validity* include inadequate blinding, inadequate or no randomization, and use of historical controls or, worse, absence of controls.

The *reliability* of a study refers to the degree to which the results of the study are likely to be the same if the study were repeated in the same clinical setting with another group of similar patients. A study may have reduced reliability if the sample size is too small or if some of the study procedures were poorly defined and therefore difficult to repeat consistently (e.g., if some interventions were decided by individual treating physicians).

The *relevance* of a study is the degree to which the results, specifically the outcome or outcomes measured, directly address the clinical question being posed. Thus a study is less relevant if the outcome used in the study is different from the outcome deemed most clinically important. For example, long-term survival may be the most clinically important endpoint for a particular condition, whereas the available clinical trials may use survival at 24 hours as their endpoint. This leaves open to question whether

www.ketabpezeshki.com 66485457-66963820

differences observed in survival at 24 hours would lead to differences in long-term survival.

Step 4: Summary of Most Useful Evidence

On the basis of these considerations, the practitioner of EBM proceeds to the fourth step, summarizing the available evidence from the studies that are the most valid, reliable, and relevant. For each of these studies, the size of the treatment effect or the accuracy of the diagnostic strategies should be noted. In the case of a binary outcome (e.g., lived vs. died or admitted vs. discharged), the *number needed to treat* is a useful measure of the size of the treatment effect.[80] The number needed to treat is the number of patients that must receive the treatment for every one patient who benefits as per the outcome defined in the study. Other useful measures of the size of the treatment effect include the odds ratio and the relative risk. The utility of diagnostic tests is best measured by positive and negative likelihood ratios. Other useful measures of diagnostic accuracy include sensitivity, specificity, positive predictive value, and negative predictive value.[85-87]

Step 5: Application to Patient and Critical Appraisal

Once the available evidence from high-quality studies is summarized, the practitioner is ready to apply the information to the care of the individual patient. To save the information, however, it is useful to create a summary of the entire EBM process, briefly describing each step and the results from each step. Such summaries are sometimes called *critically appraised topics* or *best evidence topics* (CAT or BET), which can be saved for future reference.[88] Such "shortcut reviews" performed by others are available in journals or online (http://ebem.org/index.php), but results should be interpreted in light of the specific study question, the comprehensiveness of the search for evidence, and the appraisal process used.[89]

Effectiveness of Evidence-Based Medicine

With the rapid expansion of clinical research, it is difficult to keep EBM reviews up to date. Also, for clinicians to find reviews useful in real-time patient management decisions, reviews should be easily and rapidly accessible. This adds another layer of difficulty for EBM to have an impact on clinician behavior. EBM techniques may be applied to create clinical guidelines and algorithms, which when disseminated may have a greater effect on clinician behavior. There is, however, little research studying the effectiveness of various presentations of EBM reviews on clinician behavior or patient outcomes.[90]

SUMMARY

For the educated reader, the medical literature provides an ever-expanding view of knowledge regarding the effectiveness of medical therapy. A qualitative understanding of the concepts described in this chapter allows the emergency physician to distinguish high-quality studies with results that warrant a change in clinical practice from poor-quality studies that, at best, only suggest important questions to be studied.

References

1. McMaster University Health Sciences Centre, Department of Clinical Epidemiology and Biostatistics: How to read clinical journals: I. Why to read them and how to start reading them critically. *Can Med Assoc J* 1981; 124:555.
2. Haynes RB, et al: How to keep up with the medical literature: I. Why try to keep up and how to get started. *Ann Intern Med* 1986; 105:149.
3. Menegazzi JJ, Yealy DM, Harris JS: Methods of data analysis in the emergency medicine literature. *Am J Emerg Med* 1991; 9:225.
4. Haynes RB, et al: How to keep up with the medical literature: II. Deciding which journals to read regularly. *Ann Intern Med* 1986; 105:309.
5. Laine C, Weinberg DS: How can physicians keep up-to-date? *Annu Rev Med* 1999; 50:99.
6. Guyatt G, Rennie D, eds: *Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice*. Chicago: American Medical Association; 2002.
7. Lewis RJ, Bessen HA: Statistical concepts and methods for the reader of clinical studies in emergency medicine. *J Emerg Med* 1991; 9:221.
8. Piantadosi S: *Clinical Trials: A Methodologic Perspective*. New York: Wiley; 1997.
9. Altman DG, Goodman SN: Transfer of technology from statistical journals to the biomedical literature: Past trends and future predictions. *JAMA* 1994; 272:129.
10. Moher D, Schulz KF, Altman D; CONSORT Group (Consolidated Standards of Reporting Trials): The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001; 285:1987.
11. Meinert CL: *Clinical Trials: Design, Conduct, and Analysis*. New York: Oxford University Press; 1986.
12. Hulley SB, ed: *Designing Clinical Research: An Epidemiologic Approach*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001.
13. Bailey KR: Generalizing the results of randomized clinical trials. *Control Clin Trials* 1994; 15:15.
14. Rosenbaum PR: Discussing hidden bias in observational studies. *Ann Intern Med* 1991; 115:901.
15. Schulz KF, et al: Empirical evidence of bias: Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; 273:408.
16. Sacks H, Chalmers TC, Smith H: Randomized versus historical controls for clinical trials. *Am J Med* 1982; 72:233.
17. Chalmers TC, et al: Bias in treatment assignment in controlled clinical trials. *N Engl J Med* 1983; 309:1358.
18. Angell M: The interpretation of epidemiologic studies. *N Engl J Med* 1990; 323:823.
19. Hellman S, Hellman DS: Of mice but not men: Problems of the randomized clinical trial. *N Engl J Med* 1991; 324:1585.
20. Passamani E: Clinical trials: Are they ethical? *N Engl J Med* 1991; 324:1589.
21. Rothman KJ, Michels KB: The continuing unethical use of placebo controls. *N Engl J Med* 1994; 331:394.
22. Taubes G: Use of placebo controls in clinical trials disputed. *Science* 1995; 267:25.
23. Benson K, Hartz AJ: A comparison of observational studies and randomized, controlled trials. *N Engl J Med* 2000; 342:1878.
24. Concato J, Shah N, Horwitz RI: Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000; 342:1887.
25. Pocock SJ, Elbourne DR: Randomized trials or observational tribulations? *N Engl J Med* 2000; 342:1907.
26. Kwiatkowski T, Silverman R: Research fundamentals: II. Choosing and defining a research question. *Acad Emerg Med* 1998; 5:1114.
27. Kramer MS: Medical research: A prescriptive view. *Pediatrics* 1995; 95:82.
28. Kahn CR: Picking a research problem: The critical decision. *N Engl J Med* 1994; 330:1530.
29. Kahn HA, Sempos CT: *Statistical Methods in Epidemiology*. New York: Oxford University Press; 1989.
30. Chalmers TC, et al: Evidence favoring the use of anticoagulants in the hospital phase of acute myocardial infarction. *N Engl J Med* 1977; 297:1091.
31. Smith DG, et al: Impact of multiple comparisons in randomized clinical trials. *Am J Med* 1987; 83:545.
32. Brown CG, et al: The beta error and sample size determination in clinical trials in emergency medicine. *Ann Emerg Med* 1987; 16:183.
33. Detsky AS, Sackett DL: When was a "negative" clinical trial big enough? How many patients you needed depends on what you found. *Arch Intern Med* 1985; 145:709.
34. Freiman JA, et al: The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial: Survey of 71 "negative" trials. *N Engl J Med* 1978; 299:690.
35. Moher D, Dulberg CS, Wells GA: Statistical power, sample size, and their reporting in randomized controlled trials. *JAMA* 1994; 272:122.
36. Koren G, Klein N: Bias against negative studies in newspaper reports of medical research. *JAMA* 1991; 266:1824.

www.ketabpezeshki.com 66485457-66963820

37. Dickersin K, Min Y, Meinert CL: Factors influencing publication of research results: Follow-up of applications submitted to two institutional review boards. *JAMA* 1992; 267:374.
38. Begg CB, Berlin JA: Publication bias: A problem in interpreting medical data. *J R Statist Soc A* 1988; 151:491.
39. Dickersin K, et al: Publication bias and clinical trials. *Control Clin Trials* 1987; 8:343.
40. Rosenthal R: The "file drawer problem" and tolerance for null results. *Psychol Bull* 1979; 86:638.
41. Friedberg M, et al: Evaluation of conflict of interest in economic analyses of new drugs used in oncology. *JAMA* 1999; 282:1453.
42. Johansen HK, Gotzsche PC: Problems in the design and reporting of trials of antifungal agents encountered during meta-analysis. *JAMA* 1999; 282:1752.
43. Brown GW: Errors, types I and II. *Am J Dis Child* 1983; 137:586.
44. Lewis RJ: Parametric statistical tests: Unnecessary assumptions, computers, and the search for the trustworthy p-value [editorial]. *Acad Emerg Med* 1998; 5:1048.
45. Simon R: Why confidence intervals are useful tools in clinical therapeutics. *J Biopharm Stat* 1993; 3:243.
46. Borenstein M: The case for confidence intervals in controlled clinical trials. *Control Clin Trials* 1994; 15:411.
47. Goodman SN, Berlin JA: The use of predicted confidence intervals when planning experiments and the misuse of power when interpreting results. *Ann Intern Med* 1994; 121:200.
48. Young KD, Lewis RJ: What is confidence? Part I. The use and interpretation of confidence intervals. *Ann Emerg Med* 1997; 30:307.
49. Young KD, Lewis RJ: What is confidence? Part II. Detailed definition and determination of confidence intervals. *Ann Emerg Med* 1997; 30:311.
50. Haukoos JS, Lewis RJ: Advanced statistics: Bootstrapping confidence intervals for statistics with "difficult" distributions. *Acad Emerg Med* 2005; 12:360.
51. Klockars AJ, Sax G: *Multiple Comparisons*. Thousand Oaks, Calif: Sage; 1986.
52. O'Brien PC, Shampo MA: Statistical considerations for performing multiple tests in a single experiment: Part 6. Testing accumulating data repeatedly over time. *Mayo Clin Proc* 1988; 63:1245.
53. Lewis RJ: An introduction to the use of interim data analyses in clinical trials. *Ann Emerg Med* 1993; 22:1463.
54. Lewis RJ, Bessen HA: Sequential clinical trials in emergency medicine. *Ann Emerg Med* 1990; 19:1047.
55. Yusuf S, et al: Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA* 1991; 266:93.
56. Oxman AD, Guyatt GH: A consumer's guide to subgroup analyses. *Ann Intern Med* 1992; 116:78.
57. Lee KL, et al: Clinical judgment and statistics: Lessons from a simulated randomized trial in coronary artery disease. *Circulation* 1980; 61:508.
58. Glantz SA, Slinker BK: *Primer of Applied Regression & Analysis of Variance*, 2nd ed. New York: Appleton & Lange; 2000.
59. Hosmer DW, Lemeshow S: *Applied Logistic Regression*, 2nd ed. New York: Wiley; 2000.
60. Concato J, Feinstein AR, Holford TR: The risk of determining risk with multivariable models. *Ann Intern Med* 1993; 118:201.
61. Hans SS, Huang RR: Results of 101 ruptured abdominal aortic aneurysm repairs from a single surgical practice. *Arch Surg* 2003; 138:898.
62. Lewis RJ, Wears RL: An introduction to the Bayesian analysis of clinical trials. *Ann Emerg Med* 1993; 22:1328.
63. Browner WS, Newman TB: Are all significant *P* values created equal? The analogy between diagnostic tests and clinical research. *JAMA* 1987; 257:2459.
64. Brophy JM, Joseph L: Placing trials in context using Bayesian analysis: GUSTO revisited by Reverend Bayes. *JAMA* 1995; 273:871.
65. Mills JL: Data torturing. *N Engl J Med* 1993; 329:1196.
66. Lee YJ, et al: Analysis of clinical trials by treatment actually received: Is it really an option? *Stat Med* 1991; 10:1595.
67. Gausche M, et al: Effect of out-of-hospital pediatric endotracheal intubation on survival and neurologic outcome: A controlled clinical trial. *JAMA* 2000; 283:783.
68. Andrade SE, et al: Discontinuation of antihyperlipidemic drugs: Do rates reported in clinical trials reflect rates in primary care settings? *N Engl J Med* 1995; 332:1125.
69. Olson CM: Understanding and evaluating a meta-analysis. *Acad Emerg Med* 1994; 1:392.
70. Klassen TP, Jadad AR, Moher DP: Guidelines for reading and interpreting systematic reviews: Part I. *Arch Pediatr Adolesc Med* 1998; 152:700.
71. Klassen TP, Jadad AR, Moher DP: Guidelines for reading and interpreting systematic reviews: Part III. *Arch Pediatr Adolesc Med* 1998; 152:915.
72. Juni P, Altman DG, Egger M: Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ* 2001; 323:42.
73. Moher D, et al: Assessing the quality of randomized controlled trials: An annotated bibliography of scales and checklists. *Control Clin Trials* 1995; 16:62.
74. Klassen TP, Jadad AR, Moher DP: Guidelines for reading and interpreting systematic reviews: Part II. *Arch Pediatr Adolesc Med* 1998; 152:812.
75. Cappelleri JC, et al: Large trials vs. meta-analysis of smaller trials: How do their results compare? *JAMA* 1996; 276:1332.
76. Ioannidis JP, Cappelleri JC, Lau J: Issues in comparisons between meta-analyses and large trials. *JAMA* 1998; 279:1089.
77. DerSimonian R, Levine RJ: Resolving discrepancies between a meta-analysis and a subsequent large controlled trial. *JAMA* 1999; 282:664.
78. Cone DC, Lewis RJ: Should this study change my practice? *Acad Emerg Med* 2003; 20:417.
79. Sackett DL, et al: *Evidence-Based Medicine: How to Practice and Teach EBM*, 2nd ed. New York: Churchill Livingstone; 2000.
80. Cordell WH: Number needed to treat (NNT). *Ann Emerg Med* 1999; 33:433.
81. Corrall CJ, Wyer PC, Zick LS, Bockrath CR: Evidence-based emergency medicine: How to find evidence when you need it, part 1: Databases, search programs, and strategies. *Ann Emerg Med* 2002; 39:302.
82. Gallagher PE, Allen TY, Wyer PC: How to find evidence when you need it, part 2: A clinician's guide to MEDLINE—the basics. *Ann Emerg Med* 2002; 39:436.
83. Gallagher PE, Allen TY, Wyer PC: How to find evidence when you need it, part 3: A clinician's guide to MEDLINE—tricks and special skills. *Ann Emerg Med* 2002; 39:547.
84. Wyer PC, Allen TY, Corrall CJ: How to find evidence when you need it, part 4: Matching clinical questions to appropriate databases. *Ann Emerg Med* 2003; 42:136.
85. Fontanarosa PB: An evidence based approach to diagnostic testing in emergency medicine. *Emerg Med Clin North Am* 1999; 17:1.
86. Gallagher EJ: Clinical utility of likelihood ratios. *Ann Emerg Med* 1998; 31:391.
87. Gallagher EJ: Application of likelihood ratios to clinical decision rules: Defining the limits of clinical expertise. *Ann Emerg Med* 1999; 34:664.
88. Wyer PC: The critically appraised topic: Closing the evidence-transfer gap. *Ann Emerg Med* 1997; 30:639.
89. Wyer PC, Rowe BH, Guyatt GH, Cordell WH: The clinician and the medical literature: When can we take a shortcut? *Ann Emerg Med* 2000; 36:149.
90. Wyer PC, Rowe BH: Evidence-based reviews and databases: Are they worth the effort? Developing evidence summaries for emergency medicine. *Acad Emerg Med* 2007; 14:960.

www.ketabpezeshki.com 66485457-66963820

Multiculturalism and Care Delivery*

Thea James, Edward Bernstein, and Judith Bernstein

**For the complete chapter text, go to the Expert Consult website. To access your account, look for your activation instructions on the inside front cover of this book.*

I. PERSPECTIVE

II. RATIONALE FOR CULTURAL COMPETENCE

A. Changing Demographics: New Challenges for Emergency Physicians

B. Racial and Ethnic Disparities in Health Care Access and Outcomes

C. Factors Contributing to Disparities in Health Outcomes

D. Evolution of New Standards for Health Care

E. Multiculturalism, Cultural Competence, and Health Disparities: Progress to Date

F. Using Cultural Competence to Cross the Barrier of Different Beliefs, Values, and Life Experiences

G. Interpreting the Culture of Medicine to Patients from Diverse Backgrounds

H. Role Expectations in Western Medicine: Opportunity for Misunderstanding

III. CULTURAL COMPETENCE AND PATIENT-CENTERED CARE: NEW MODELS

IV. EDUCATION

V. RECOMMENDATIONS

VI. SUMMARY

KEY CONCEPTS

- Changing demography in the Unites States will change emergency medicine practice.
- Disparities in health and health care delivery continue despite efforts to improve care. Emergency physicians and their institutions will need to be part of the solution—treating preventable conditions that become crises because of reduced access to both primary care and specialists and acting as advocates for strategic system change to eliminate disparities in their institutions.
- Emergency physicians will improve the quality of care provided if they practice to meet federal standard for culturally and linguistically appropriate care, recognizing that patients with limited English proficiency have a right to medical interpretation.
- Culturally sensitive, patient-centered, and trauma-informed care will improve patient–emergency physician communications and satisfaction, decrease medical errors, and promote patient follow-through with recommendations.

www.ketabpezeshki.com 66485457-66963820

Multiculturalism and Care Delivery

Thea James, Edward Bernstein, and Judith Bernstein

PERSPECTIVE

Every day, in emergency departments (EDs) throughout the United States, physicians encounter challenging cases that require an appreciation of cultural differences. Lack of understanding of the role of cultural factors can have an adverse effect on physician-patient communication and trust. Health outcomes can also be negatively affected, as demonstrated by a large body of literature on racial and ethnic disparities in types of interventions and outcomes for heart and lung disease. Race, culture, ethnicity, class, gender, economic conditions, spirituality, and sexual orientation define health and illness for patients and affect both access to health care and the quality of services received. Missing these cues may lead to medical errors.[1,2]

The American College of Emergency Physicians (ACEP) Code of Ethics commits emergency physicians to "protect the rights and best interests of the most vulnerable . . . [and] secure access to emergency and other basic health care for all."[3] This code also recognizes that "denial of emergency care or delay in providing emergency services on the basis of race, religion, ethnic background, social status, type of illness or injury, or ability to pay is unethical." Lewis Goldfrank, past president of the Society for Academic Emergency Medicine (SAEM) and a member of the Institute of Medicine, and Robert Knopp, a member of the editorial board of *Annals of Emergency Medicine,* comment in an editorial about ethnic disparities in ED analgesia prescription:

> *With the legacy of racism . . . as well as the growing body of medical evidence indicating differential care in emergency medicine and other medical specialties, we believe that the burden of responsibility has now shifted so that the medical profession must demonstrate that physicians are providing appropriate and timely care for all. . . . Our integrity as a profession and as a nation hangs in the balance.*[4]

The purpose of this chapter is to provide the knowledge base in cultural competence that is essential to meet patient needs, to improve health outcomes, to reduce racial and ethnic disparities, and to achieve professional goals.

RATIONALE FOR CULTURAL COMPETENCE

Changing Demographics: New Challenges for Emergency Physicians

We live in a global community, and both the U.S. population and the types of health problems seen by emergency physicians are constantly changing. In 2000 the U.S. Census Bureau estimated that 12% of the U.S. population was foreign born and 20% spoke a language other than English at home.[5] According to the 2010 Census, 27.6% of the U.S. population identifies as other than solely "white," and 16.3% describe themselves as Hispanic or Latino.[6] It is projected that by 2030 the proportion of Hispanics will increase from 13 to 20%, and racial and ethnic minority representation in the United States will exceed 40%.[7]

These figures do not speak to the diversity within these groups. The category Hispanic, for example, is an ethnic grouping counted in the race category of the census, but it fails to capture the significant range of diversity represented by Spanish speakers. Hispanics may share some cultural practices and speak similar versions of the Spanish language but have major differences in vocabulary and dialect, history, socioeconomic status, cultural identity, what they call themselves (Hispanic or Latino), levels of acculturation, health beliefs, habits, access to care, and health outcomes.

What do these changes in demographics mean to practicing emergency physicians? The ACEP Code of Ethics challenges us to recognize ethnic and racial differences in health care access and outcomes, to advocate for equity, and to work with other health organizations and providers to contribute to elimination of these disparities.

Racial and Ethnic Disparities in Health Care Access and Outcomes

In the past decade, both financial and nonfinancial barriers to access for racial and ethnic minority populations have been thoroughly documented. These include high rates of uninsurance, lack of prenatal care, hospitalizations for ambulatory-sensitive diagnoses (an indicator of reduced access to primary care), and concentration of minorities in areas of physician shortage.[8] In 2003 the Institute of Medicine (IOM) produced a report commissioned by the U.S. Congress in which more than 100 studies assessing the quality of care for racial and ethnic minorities living in the United States were analyzed.[9] According to the IOM report, minorities received fewer needed services and procedures than whites did, after control for insurance status, income, and other access factors. These findings applied to a wide range of health conditions, such as cancer, cardiovascular disease, human immunodeficiency virus (HIV) infection and AIDS, diabetes, and mental illness. The findings identified cultural and linguistic barriers, fragmentation of the health care system, and differences in sites of care delivery and insurance coverage as explanatory factors. The authors suggested that unconscious bias, prejudice, stereotyping, and physician uncertainty of severity may influence clinical decision-making and allocation of services and procedures. Patient preferences may account for some of the range of distribution of services, but preference alone is insufficient to explain health care disparities.

www.ketabpezeshki.com 66485457-66963820

The report concluded that "racial and ethnic disparities in health care exist, and because they are associated with worse outcomes in many cases, they are unacceptable."

The IOM report also discussed important nonfinancial barriers to access, such as the unequal distribution of physicians in areas where minority populations live. In particular, the number of racial and ethnic minorities living in medically underserved areas is three times the proportion of minorities in the general population. Poor urban communities with high African American and Hispanic representation averaged 24 physicians per 100,000 people compared with 69 physicians per 100,000 in communities with low representation. Although minority physicians are more likely to serve patients with Medicaid or no insurance, enrollment of minorities in health profession schools has been declining for African Americans, Hispanics, American Indians, and Alaskan Natives.[10] In fact, the Association of American Medical Colleges (AAMC) reported that in four states with restrictions against affirmative action, in the year following enactment, there was a 17% decline in applications and a 26% decline in matriculation to medical schools from under-represented minority groups.[11] A survey conducted in 1997 by the SAEM Task Force on Women and Minorities found that 59% of residency-affiliated sites had no minority faculty member.[12] Jordan Cohen, past-president of the AAMC, argues that "to achieve diversity in the health professions is not someone else's problem; it is a problem for the profession, for all of us who are concerned about the future access to health care and the quality of health care that we are going to be able to provide our society."[13]

The National Institutes of Health National Center on Minority Health and Health Disparities, created by Congressional Public Law 106-525 to oversee research in health care disparities, reported that improvements in health have not been universal during the past two decades: "Striking disparities in the burden of illness and death" exist for African Americans, Hispanics, Native Americans, Alaskan Natives, Asians, and Pacific Islanders. Despite a decade of attention focused on racial and ethnic health care disparities, progress in narrowing of critical gaps in life expectancy has been slow. Life expectancy for blacks as a whole is 73.2 years versus 78.3 years for the white population, a gap of 5.1 years. For black men versus white men, the gap is even larger (6.2 years). Lower life expectancy for blacks is accompanied by higher rates of cardiovascular disease, cancer, infant mortality, maternal mortality, birth defects, asthma, diabetes, stroke, intentional injury inflicted by others, sexually transmitted disease, and mental illness.[14,15] The reliability of data for Hispanics is limited by the inaccurate reporting of race and ethnicity on birth and death certificates, the healthy migrant effect, and the possibility that migrants may return to their country of origin when they become ill or disabled.

Factors Contributing to Disparities in Health Outcomes

In the past decade, reports have been regularly published in major peer-reviewed journals about disparities in the use of diagnostic tests and procedures, access to appropriate treatment modalities, and waiting times to receive care in the ED.[16,17] The Coalition to Reduce Racial and Ethnic Disparities in Cardiovascular Disease Outcomes (CREDO), for example, acknowledges racial and ethnic differences in cardiovascular comorbidities, use of evidence-based therapies, and prolonged time to reperfusion and a race-based invasive procedure gap for coronary intervention.[18]

Test and Treatment Options: Physician-Patient Communication Failure?

Studies document clearly that both Hispanics and African Americans receive fewer analgesics for extremity fractures[19-22] and for musculoskeletal pain[23] than white patients do in the ED setting, despite no evidence of difference across race and ethnicity in the ability to discriminate painful sensation.[24,25] In secondary analyses of the National Hospital Ambulatory Medical Care Survey (NHAMCS) data for 1993 to 2005, opioids were less likely to be prescribed to African Americans (23%) and Hispanics (24%) for pain relief than to whites (31%),[26,27] and these differences were greatest for patients with the most severe pain.[26] Disparities in ED pain treatment continue to persist a decade after identification of racial and ethnic differences in analgesic administration. In the most recent analysis of NHAMCS data, non-Hispanic black patients presenting with abdominal pain were 1.53 times more likely than their white counterparts to experience waits of 60 minutes or more.[28]

Evidence from other specialties corroborates that differences in provision of medically appropriate procedures and therapies are often related to race and ethnicity. In the case of preventive measures, for example, elderly African Americans and Hispanics are less likely to receive influenza and pneumococcal vaccine.[29] In the domain of surgery, the operative rate for certain lung cancers was 76.7% for whites and 64% for African Americans, and the 5-year survival was 34.1% and 26.4%, respectively.[30] The authors concluded that if blacks had undergone surgery, the 5-year survival rate would have been similar. An accompanying editorial suggested that the medical establishment take some responsibility for the racial discrimination that results in inadequate emphasis on prevention or insufficiently aggressive care for African Americans.[31]

These issues also apply to disparities between black and white populations with respect to cardiovascular disease. After adjustment for severity and coexisting conditions, African Americans are less likely than whites to undergo either angioplasty or bypass surgery, and differences are more significant for those predicted to benefit most from revascularization.[32] A multicenter ED study found racial disparities in access to cardiac catheterization for African Americans and other nonwhites with acute myocardial infarction and unstable angina. The researchers also found that African American patients were less likely to receive a timely electrocardiogram or an assay for cardiac markers,[33] and in another study, physicians were less likely to prescribe anti-ischemic medications.[34]

In recent years, racial and ethnic disparities in ED treatment decisions have also been identified for admission after a diagnosis of pancreatitis,[35] for care related to mild traumatic brain injury[36,37] and headache,[38] for rate of appendicitis rupture,[39] and for underdiagnosis of psychiatric disease.[40]

Discrimination and Health Outcomes

Deleterious health consequences that result from racial discrimination have been well documented.[41-45] In a study of the nation by state, in states where more respondents to the General Social Survey indicated that blacks lacked innate ability, there was a closely associated increase in age-adjusted black mortality that was considerably stronger than the correlation for mortality and socioeconomic status.[46] Mechanisms used to cope with the stress of racism have been shown to backfire by adding to health risks, as in the case of smoking, substance abuse, and overeating.[47,48] Racism-induced stress has been shown to be negatively associated with disease entities such as diabetes, hypertension, depression, and preterm birth.[49-53] Similar experiences have been described for homosexuals vis-à-vis homophobia.[54]

Race-Based Medical Decision-Making

Racism, sexism, and homophobia can interfere with the establishment of trust and the delivery of effective medical care if providers

www.ketabpezeshki.com 66485457-66963820

create or establish barriers on the basis of their own internal biases, prejudices, and negative reactions to racial or cultural characteristics, such as skin color or clothing styles. Patients read these reactions clearly during an encounter with a provider. A barrier is created, and the opportunity for a good medical outcome may be lost. Provider biases against people with certain stigmatized diseases, such as HIV infection and substance abuse, can also create barriers to effective health care. When primary care physicians viewed scripted video interviews with hypothetical patients with chest pain who had similar symptoms, risk factors, vital signs, and thallium stress test and electrocardiographic findings, they were less likely to refer African American women for cardiac catheterization than men and whites, even though the scripts varied only by race and gender.[55] Disparities profiling can result in both underdiagnosis and overdiagnosis and thus contribute to medical error.[56,57]

Failure of Trust

Patients from minority communities have reason to be skeptical about the validity of medical research and the appropriateness of medical recommendations. Participants in the Tuskegee study, for example, were not notified when effective treatment of syphilis became available because researchers wished to investigate the natural course of the disease.[58] Middle-class African American patients often rate their physician interactions as more participatory when their physician is of the same race.[59,60] Yet this option for physician-patient congruence is rarely available to minority patients because only 4% of physicians are black, whereas 12% of the population is black.[9]

In the Agency for Healthcare Research and Quality *National Healthcare Disparities Report,* blacks and Hispanics were found to be more critical of the patient-provider relationship than were whites. A higher percentage of adult blacks and Hispanics rated their health care at less than 6 on a scale of 1 to 10 in the past year and believed that they would have received better care if they were of a different race or ethnicity. The report provided evidence confirming perceptions of a lower quality of medical care. For example, when black and Hispanic elders were hospitalized for pneumonia, they were less likely than comparable whites to have blood culture samples drawn and antibiotics administered in accordance with current recommendations. Hispanics with myocardial infarction were less likely to receive aspirin or a beta-blocker on admission and discharge. In comparison with white dialysis patients, fewer blacks and Hispanics in need of a kidney were registered on waiting lists for a transplant or had received a transplant within 3 years.[61]

Language and Effective Medical Care

According to the 2000 U.S. Census, 47 million Americans (18%) speak a language other than English at home, 21.3 million speak English less than very well, and 10.7 million speak English not at all or not well.[62] Patients with limited English proficiency are more likely to defer needed services, to leave against medical advice, to miss appointments, to fail to adhere to treatment regimens, to lack a regular provider, and to report poorer health status.

Transcribed audiotapes of medical encounters in a pediatric ED setting were studied to ascertain differences in communication error rates for patients who were aided by professional hospital interpreters compared with those who had an ad hoc interpreter (e.g., family, friend, or nonprofessional hospital worker) and those who had no interpreter available. The investigators found that communication errors occurred equally among the ad hoc and the no interpreter groups. These errors included left out words (52%), incorrect words (16%), substituted words (13%), interjected personal views (10%), and added words (8%). The errors of ad hoc interpreters were more likely to result in clinically significant medical errors, such as omitting drug allergies and giving inaccurate instructions on dosing and route of administration.[63] The use of untrained nonprofessional employees as interpreters resulted in serious translation errors, including omissions, additions, and substitutions for what the patient is trying to say, and the use of relatives, particularly children, may violate privacy and disrupt family norms of authority.[64-67]

A cross-sectional survey at a public hospital ED suggests that there is a patient-perceived need for interpreter services, and the highest patient satisfaction ratings are obtained when patients can communicate directly with their physicians.[68] Satisfaction ratings for patients using ad hoc interpreters are lower, and rates are lowest when an interpreter should have been used but was unavailable. In one retrospective study of Spanish-, Haitian Creole–, and Portuguese Creole–speaking patients presenting to the ED with chest pain, headache, and abdominal pain, the investigators found that the use of trained interpreters was associated with increased intensity of ED services, reduced ED return rate, increased clinic use, and lower charges during the next 30 days, without any simultaneous increase in length of stay or cost of visit.[69]

A statewide ED patient satisfaction survey in Massachusetts indicated that non-English speakers were less satisfied with their care, were less willing to return for care, and reported more problems with emergency care.[70] The authors stated that interpreter service is likely to improve the satisfaction of this group.

Evolution of New Standards for Health Care

In response to the identification of unacceptable differences in both health care provision and health care outcomes, state Medicaid regulations and Health Plan Employer Data and Information Set (HEDIS) criteria now reflect the need to establish quality performance measures to ensure access to appropriate services for culturally diverse populations.[71] A new standard of care[72] has been established that requires institutions and practitioners to provide for medical needs in a patient's primary language and in a manner compatible with the patient's health beliefs and practices. Health care institutions and providers are asked to collect data stratified by race, ethnicity, and language and to institute quality improvement efforts when cross-cultural differences in outcomes of care, process indicators, or patient satisfaction are detected. They are asked to develop culturally competent systems of care based on an assessment of the organization's mission, goals, policies, practices and services, staff training needs, and current diversity of the staff.

After the assessment process, health care organizations must identify opportunities to improve the cultural competence of the organization and its delivery of health care services to a diverse population. At the top of the list is the improvement of interpreter services. Hospitals are asked to establish minimum performance standards for interpreters that include training in culturally specific medical language and code of ethics. These requirements have been codified as a set of standards for culturally and linguistically appropriate services (CLAS standards) by the Office of Minority Health and the Agency for Healthcare Research and Quality and published in the Federal Register (December 15, 2000).[72] In spring 2000, the Massachusetts legislature took a positive step in the direction of compliance with these standards by passing a law requiring all EDs to provide interpreter service and authorizing the state to provide Medicaid reimbursement for interpreter services.

www.ketabpezeshki.com 66485457-66963820

Culturally Competent Approach to Language Barriers

In 1996 the SAEM Task Force on Physician-Patient Communication identified lack of a common language as the most common barrier to communication in the ED. Professional medical interpreters were recommended for the following reasons: confidentiality, medical knowledge and a common vocabulary with the provider, and fluency.[73] Two case reports illustrate this point.[74]

A 50-year-old Mexican American man who spoke only Spanish was seen in the ED because of "chest pain." Because no translator was available, an electrocardiogram and chest radiograph were ordered. The electrocardiogram was normal; the chest radiograph showed a widened mediastinum suggestive of a dissecting aortic aneurysm. An aortogram was subsequently performed, which demonstrated a normal aorta. At some point, a Spanish-speaking physician was able to elicit a 1-year history of difficulty in swallowing and regurgitation of food. A barium swallow was performed, which revealed achalasia.

A 22-year-old Vietnamese man arrived in the ED unresponsive and comatose with small, reactive pupils. Naloxone hydrochloride and 50% dextrose in water were administered without response. The medical history was obtained from a family member who spoke limited English. It consisted of brief answers to specific questions and was not helpful diagnostically. A lumbar puncture and examination of the cerebrospinal fluid ruled out meningitis. A clerk later recalled that a child with the same last name was admitted the previous day for headache, nausea, and vomiting caused by carbon monoxide poisoning. In retrospect, it was clear that the history obtained from a family member who was under stress and giving vague answers to pointed questions was inadequate. The authors concluded that "a trained bicultural translator can effectively elicit the history as conceptualized by the patient or family and translate it both linguistically and in the format of Western medicine."

The preceding example also illustrates that bilingualism is necessary but not sufficient. There are nuances and sociocultural assumptions in both languages and nonverbal cues that must be communicated along with words for effective diagnosis, treatment, and disposition. The medical interview is the heart of the medical encounter between physician and patient, yet in an interpreted interaction, neither patient nor physician is in a position to judge the accuracy or completeness of a lay interpreter's translation. Clearly, omissions, additions, opinions, guesses, and distortions can lead to serious mistakes and unnecessary diagnostic procedures.

Standards and certification for medical interpreters are needed to ensure consistency and quality. The Massachusetts Medical Interpreter Association recommends that standards cover interpretation, the cultural interface, and ethical behavior. Because the meaning inherent in the message is rooted in culturally specific beliefs, values, assumptions, customs, and norms, and language is itself an expression of culture, it may be necessary for a medical interpreter to go beyond a literal interpretation to explain unstated assumptions and to find new ways of communicating untranslatable words or concepts. In addition to maintaining confidentiality, the medical interpreter has an ethical burden to uphold the trust of both parties and to assure them that the considerable power associated with the interpreter's role will not be abused and that information will be faithfully conveyed without interjection of the subjective opinions and thoughts of the interpreter. Even with such qualified interpreters, the emergency physician still needs to monitor the flow of the interview and, from time to time, clarify meaning and ensure understanding. This can be done by having the interpreter repeat what he or she thought the patient meant and asking the patient to repeat what the interpreter said. It is important to observe the interaction for phrase length as an indication of material not translated or added by the translator.

Multiculturalism, Cultural Competence, and Health Disparities: Progress to Date

The 2003 IOM report revealed disparities in health care in America based along lines of race and ethnicity.[9] The recommendations to reduce these health care disparities included "integration of cross-cultural education into the training of all current and future health professionals." Progress has been slow in actually reducing health disparities,[75] and gaps in economic resources between white and minority populations have actually widened,[76] increasing the barriers impeding access to timely, effective care.

Forward movement has primarily occurred in the form of establishment of guidelines and standards at local, state, federal, public, and private levels. The Joint Commission's *A Roadmap for Hospitals* encourages hospitals to incorporate concepts from cultural competence, patient-centered care, and communication into their organizations. These efforts include increasing awareness of health disparities, efforts to improve collection of race and ethnicity data across systems of care, quality improvement, community outreach, increasing workforce diversity, patient education, provider education, and increased availability of interpretation services. A policy system of checks and balancing now exists, with national performance monitoring affecting accreditation of health care organizations.

In 2011, patient-centered communication standards were included in the Joint Commission's *Comprehensive Accreditation Manual for Hospitals*. In year one, hospitals will be monitored for compliance of standards, without any effect on accreditation, but in 2012, compliance with these standards will be taken into account in the accreditation process.

In another example of guideline development, the National Committee for Quality Assurance developed and released rigorous standards for monitoring and evaluation of multicultural health care in 2010. Multicultural health care distinction is conferred on health care organizations that conform to acceptable practices in race/ethnicity and language data collection, access and availability of language services, practitioner network cultural responsiveness, programs for culturally and linguistically appropriate services, and overall efforts to reduce health care disparities. In a similar effort, the National Quality Forum released a report in 2011 on quality measures to assess cultural competence. In education, the Liaison Committee on Medical School Education now includes cultural competency in its accreditation standards. Medical students should learn to recognize and appropriately address gender and cultural biases in themselves and others and in the process of health care delivery.

Disparities awareness has also been included in health care reform. The Patient Protection and Affordable Care Act (Health Care Reform Act) signed into law in March 2010 requires data collection on race, ethnicity, primary language, disability status, and gender. These data can identify areas of concern and provide opportunities for intervention. This law follows recommendations from the IOM report of 2003 and raises awareness of culture and disparities. In addition to national activities, many states have taken action. For example, the New Jersey State Board of Medical Examiners requires that physicians licensed in New Jersey complete six credits in cultural competency (Rule N.J.A.C. 13:35-6.25).

Using Cultural Competence to Cross the Barrier of Different Beliefs, Values, and Life Experiences

Both physicians and patients have a culture that they bring into the examining room. Differences between their cultures have an

www.ketabpezeshki.com 66485457-66963820

impact on the physician-patient encounter. Awareness of one's own values and those of others can enhance both satisfaction and health outcomes. The SAEM task force report cautioned, however, that it is dangerous to hold strong preexisting assumptions about any cultural group because variations within cultures often exceed variations between them. A patient who is thoroughly acculturated into American society may be offended by a health care provider's attribution of traditional beliefs. Even in the context of a busy ED encounter, it is necessary and feasible to get to know the individual patient sufficiently to make a rough assessment about level of acculturation or at least to ask rather than to assume.

In some cultures, the diagnosis of specific diseases can be particularly problematic. For example, in African American and Puerto Rican communities, cancer is often perceived as a fatal disease. Patients may therefore avoid initial evaluation or choose no treatment when they are diagnosed, even when the cancer is identified at an early stage and the prognosis is good. A health care provider who understands these health beliefs and concerns can work collaboratively with patients to provide health information in a format that the patient can accept.

Alternative healing systems have strong cultural roots. In 1997 the U.S. population made an estimated 629 million visits to providers of alternative health care—approximately 243 million more visits than to conventional health care providers and an increase of 47% since 1990. An estimated 44% used at least one complementary alternative therapy in 1997.[77]

Folk medicine is too diverse for providers to know all possible practices, but emergency physicians need to know some of the more common therapies and ask their patients about them. For example, more than a few emergency physicians have called social workers to investigate children with apparent bruises caused by coining, which involves vigorous rubbing of the skin with coins and warm oil (tiger balm) to release the "bad wind" (reduce fever). These parents, who have attempted to help their children by using health care practices that are widely accepted in their communities of origin, feel accused, and the trust between the physician and the family may be irrevocably lost. Similarly, herbal remedies can be effective or at least harmless, but they can occasionally be toxic, as in the case of clay ingestion by pregnant women, marijuana tea to treat asthma, and powders containing high concentrations of lead oxide to treat *empacho,* a condition in which it is believed that a substance (usually food or saliva) gets "stuck" to the walls of the stomach or intestines, causing an obstruction. Specific uses of folk medicine need to be elicited respectfully in a careful history and evaluated. Recommendations can then be presented nonjudgmentally, and alternative folk remedies that are benign can be prescribed along with needed allopathic medications.

The practitioner and the patient will inevitably bring different beliefs and values to the medical encounter; the key to cultural competence is respectful negotiation of these differences without imposing the power of the physician's expertise, thus protecting the patient's autonomy. If patients are satisfied, they will carry out follow-up recommendations and return to the ED in the future when they need emergency care.

In a review of Hispanic cultural practices, Flores suggested a five-step approach for the pediatric ED that is applicable to all emergency medicine: The physician should (1) explain that he or she is aware that a given folk illness exists; (2) ask whether the parent or patient has ever heard of it; (3) ask whether the patient has the folk illness now; (4) ask what treatment the patient is receiving for the condition; and (5) suggest alternatives to harmful folk remedies, accommodating wherever possible (nonjudgmentally) to folk illness beliefs and practices and integrating the use of harmless folk remedies into the treatment plan when the patient so desires.[78]

Interpreting the Culture of Medicine to Patients from Diverse Backgrounds

There are inherent conflicts between the culture of medical care, particularly ED culture, and the cultures of many patients. Physicians are expert in diagnosis and treatment of *diseases,* which represent abnormal structures or functions of the human body (the pathophysiology of disease states). On the other hand, patients experience *illness,* a subjective, feeling state that is interpreted through the lens of culture and has a personal and social meaning. The patient is an expert in his or her own illness and its effects on daily living, whereas a physician is expert in the effects of diseases on organ systems. Both ways of looking at the world have validity, but they are radically different.[79] Unfortunately, the culture of medicine tends to recognize only its own interpretation and perspective. A culturally competent approach recognizes both and works to integrate the best of both worlds.

A patient may have very high blood pressure, HIV infection, or early cervical cancer and not experience symptoms. If patients do not feel sick and experience no alteration in functioning, they may not accept a physician's diagnosis. There may be conflict between the patient's perception of causality and the physician's, as in the case of the differences between the medical diagnosis of hypertension and the commonly accepted view of hypertension as "high blood" in the African American community.[80]

On the other hand, a patient may feel sick—be ill, weak, and dizzy, with extreme fatigue or abdominal pain—yet the physician is unable to diagnose a disease despite a thorough history, physical examination, testing, and appropriate consultation. For example, *susto,* an illness recognized by Mexican Americans, causes listlessness, insomnia, depression, and anorexia and is believed to be caused by exposure to a frightening experience. Treatment requires the patient to speak openly about the events that led to the susto, followed by bed rest and a ritual that includes prayers, incantations, and *barridas* (sweeping of the body with an egg, a candle, or herbal teas).[81]

To be most effective, physicians need to investigate how patients view the causality of their illnesses and how they experience them to negotiate a therapeutic intervention. Exploration might take the form of comments and questions, such as, "Help me to see through your eyes how you understand this problem. Have you or someone you know experienced it before?" The role of the physician is to accept the patient's experience as uniquely his or hers or, when possible, to reframe it in terms of medical knowledge. Then both physician and patient will be satisfied with the outcome of the encounter.

Trauma-Informed Care

Because urban, black youth and other minorities are overrepresented among victims of violence, racial and ethnic stereotyping can play a direct role in trauma care. In 2007, more than 668,000 youth between the ages of 10 and 24 years were treated in U.S. EDs for violent injuries.[82] Assumptions of responsibility and guilt by ED clinicians can produce a hostile environment for patients who have been shot or stabbed. Language that assumes blame ("What did you do?" instead of "What happened to you?") indicates a lack of understanding of the complexity of trauma, its neighborhood context, and the psychological impact of adverse childhood events, which are often at the epicenter of the cycle of violence.[83,84] For example, the emotional response to trauma of a victim of violent injury can be misinterpreted as negative behavior. A victim might be seen as ill willed versus in need of care and healing. Providers and health care staff witnessing the responses of these violently injured youth have an opportunity either to mitigate the trauma or inadvertently to enhance it through retraumatization.

www.ketabpezeshki.com 66485457-66963820

A new construct, trauma-informed care,[85-87] is an alternative perspective that can enhance opportunities for productive encounters, self-reflection, and positive medical outcomes during a vulnerable time for an injured young person. The basic set of principles includes creation of a safe physical and emotional environment that is sensitive to the needs of victims of violence, promotes recovery, and prevents revictimization. Symptoms are seen not as pathologic changes but primarily as attempts to cope and to survive. Trauma-informed care can result in an injured youth's choosing "change" versus unsafe behavior that could result in injury, reinjury, or incarceration. One of the policies of the 2011 ACEP Revised Code of Ethics reads that emergency physicians have a "duty to promote the public health." The code states, "Emergency physicians have first-hand knowledge of the grave harms caused by firearms, motor vehicles, alcohol, and other causes of preventable illness and injury." The code suggests that emergency physicians have a responsibility to act: "Inspired by this knowledge, emergency physicians should participate in efforts to educate others."[88]

Role Expectations in Western Medicine: Opportunity for Misunderstanding

The culture of medicine, especially in emergency medicine, may have its own set of patient expectations, rules and regulations, language, and dress distinctions that reflect a hierarchy of authority, a characterization of patients as good or bad, and different sets of behaviors toward patients, depending on the category to which they have been assigned. People from different cultures may find it impossible not to violate some of the unwritten negative and stereotypical rules and regulations of the ED. Every medical encounter is potentially a cross-cultural experience, and negotiation of the divide is a challenge for both patients and providers. Cultural competence involves a reframing of many of these unstated rules because they prevent us from looking beneath the surface and addressing real problems. When a patient comes in with vague complaints, there may be a social stressor that has tipped the balance of mental health. There may be circumstances that the patient does not feel comfortable sharing with the provider because of cultural, racial, or language barriers, or there may have been an overload of negative stimuli related to racial and ethnic discrimination—a crisis for the person and the body this person inhabits.[89,90] People from minority cultures experience stressful events daily that the white providers, secure in their socioeconomic status and membership in the dominant majority, can only imagine. There is mounting evidence that these types of negative encounters engender clinical depression and anxiety and contribute to hypertension and other medical sequelae. If patients self-define themselves as having an emergency condition by showing up at the ED, the problems that cause those individuals to come deserve our respect.

A study of racial and ethnic patterns of ED use found that four times as many African Americans and Hispanics as whites report the ED as a source of care.[91] Patients who "overuse or abuse" the ED are seen as "bad patients," but the reasons given in this study for patients' use of the ED are entirely rational: the ED does not require an appointment to receive care, provides sophisticated medical technology, operates 24 hours a day, provides services that are often covered by health insurance plans whereas other options often are not, has a tradition of free care, and is often located close to inner-city neighborhoods, whereas many primary care providers have abandoned the city-center environs for the suburbs. These reasons may explain, at least in part, why U.S. EDs had more than 120 million visits in 2010.

To practice good medicine in this health care and social environment, emergency physicians should critically question and reframe the moralistic good patient/bad patient paradigm. We, like our patients, are at the whim of forces beyond our control, and both patients and practitioners will experience higher levels of satisfaction if these issues are addressed directly. Patients must take responsibility for their own behaviors whenever possible, but physicians can and should work with health care institutions to adopt policies that improve access to culturally competent health care. These actions can help create a safe environment for both practitioners and patients.

CULTURAL COMPETENCE AND PATIENT-CENTERED CARE: NEW MODELS

Models for cultural competence and for patient-centered care have evolved separately yet in tandem.[92] The goal of both is to improve the quality of the health care experience in a multicultural world, and there are areas of overlap. Whereas cultural competence evolved from the perspective of recognizing and respecting individual difference and the impact of individual interpretation on health, illness, and health care delivery, patient centeredness addresses *systems* of health care delivery, improving access, and meeting patients where they are to maximize opportunities for successful health care.[93] Ideal health care systems should be designed to incorporate principles of both cultural competence and patient centeredness. A health care system built on patient-centered principles represents the heart of cultural competence (seeing the problem and the solution from the point of view of the patient).

EDUCATION

Education about the impact of culture on health care encounters is a key component for development of culturally appropriate health care and is a requirement for organizational accreditation. Students and residents in training consistently express greater levels of comfort in multicultural environments when they have had preparatory training. Training also helps students and residents understand that their own culture also affects clinical encounters and is equally participatory.[94-98] Continued re-education raises awareness and more permanently imprints consciousness, establishing a conceptual norm for those interacting and working in multicultural environments. Linkage of cultural competence with ethical constructs of equal distribution of resources and social constructs of justice gives meaning to principles and context beyond memorization of appropriate responses to model situations.[99]

Medical schools are now required to include cultural competency training in their curriculum for accreditation. Faculty and students should demonstrate an understanding of the manner in which people of diverse cultures and belief systems perceive health and illness and respond to various symptoms, diseases, and treatments. Medical students should learn to recognize and appropriately address gender and cultural biases in themselves and others and in the process of health care delivery.

RECOMMENDATIONS

Diversity among the ED patient population poses a challenge to emergency physicians. Recognition of cultural differences, knowledge about diverse cultures, awareness of the health impact of cultural beliefs and practices, and sensitivity to patients' needs can reduce access barriers and improve clinical outcomes and hospital-community relationships while reducing the number of repeated visits and the cost of health care. Diversity education also creates

www.ketabpezeshki.com 66485457-66963820

a rich environment for conceptualizing and researching health problems.[100,101]

There are many opportunities for EDs and their institutions to improve their care of multicultural communities. These include plans to address problems related to the following: a lack of protocols for patient care; a lack of resources for translation and cross-cultural interpretation; an incorrect perception that attention to cultural competence adversely affects flow and efficiency; a lack of cross-cultural teaching guidelines and standards in medical education; the inadequate recruitment and retention of minority residents, faculty, and practitioners; and a lack of pathways for communication and collaborative work with communities.

Concrete recommendations, based on the CLAS standards, have been proposed for pediatric emergency settings and can be applied universally. Institutions should use trained medical interpreters and a diverse workforce. Pharmacies should label prescriptions and provide medical instructions in the patient's primary language. Administrators should post multilingual signs and ensure that handouts and forms are translated. Quality improvement programs should collect and analyze data and provide information to monitor outcomes based on race and ethnicity. A diverse group of patients should be enrolled in research studies to improve outcomes.[102]

Recommendations from the IOM report for a series of additional legal, regulatory, and policy measures were highlighted in an *Academic Emergency Medicine* editorial and include the following:

Patients in public managed care organizations should have the same patient bill of rights as patients in private health maintenance organizations.

The number of health care providers who are members of racial and ethnic minority groups should be increased.

Resources should be adequate to enforce penalties for civil rights violations.

Incentives to promote disparities should be stringently limited.

Health care professionals should have opportunities for cross-cultural education.

Patient participation in decision-making should be enhanced through education.

Community health care workers and advocates should assist patients to negotiate the health care system successfully.

The diversity of faculty and residents must be improved.

A cross-cultural curriculum should be developed for residency training and continuing education.

Physicians should educate themselves and the general public about the need to eliminate racial and ethnic disparities in health care.[103]

SUMMARY

Changing demographic landscapes in EDs have set the stage for multiculturally appropriate care. The process of change for development of culturally competent medical systems has been slow, but progress is occurring. Evolution of culturally appropriate environments for patients and their families has begun on all levels, and with the development of new standards and performance-monitoring systems, assurance of established culturally competent systems will be an expectation. These expectations are important and tightly linked to both safety and quality. The linkage of cultural competence to social justice broadens the depth of comprehension for the learner and provides opportunities for enhanced engagement with consumers and greater quality of care.

There is greater awareness of and movement toward a health care system that is rooted in cultural competence and patient centeredness. It is imperative that EDs invest in development of their health care systems and educate all staff. ED patients are most often unknown to providers, who have one window of opportunity to obtain accurate information and to make a correct decision. Decisions are heavily based on one's ability to successfully engage with patients and their families, engendering comfort, trust, and respect. Continued education at all levels is key and should include everyone working in health care, especially those who engage with consumers. Multiculturalism education should be integrated into medical school curricula, physician training programs, allied health programs, new employee orientation, and regularly for staff in-service programs.

The process of creating a successful plan to move cultural competency from a theoretic model to one of action and implementation is outlined in six principles that incorporate key points recommended by the IOM report of 2003 for systems aligned with new cultural competence standards and expectations:

- community representation and feedback at all stages of implementation;
- cultural competency integrated into all systems of the health care organization, particularly quality improvement efforts;
- ensuring that changes made are manageable, measurable, and sustainable;
- making the business case for implementation of cultural competency policies;
- commitment from leadership; and
- staff training on an ongoing basis.

Essential cultural competence tools for providers include recognition of cultural differences, respect for individual opinions and perspectives about health and illness, and, most important, ability and willingness to negotiate differences to offer the best opportunity for good health care outcomes. Culturally appropriate health care systems should be incorporated into EDs, which serve as the gateway to our health care institutions. Basic skills proposed in an intercultural curriculum developed by Goldstein and associates for internal medicine residents can apply equally to emergency physicians (Box 1).[104] Policies that will promote cultural competence, increase patient satisfaction, and improve health outcomes include those listed in Box 2.

Box 1 Basic Skills in an Intercultural Curriculum

Communicate an interest in and respect for the patient's culture.

Tactfully and respectfully ask for general cultural information (e.g., herbal remedies, acupuncture, coining, moxibustion, or other cures attempted).

Elicit the patient's understanding of and beliefs about illness or health problems.

Request information regarding folk medicine beliefs—for instance, "mal ojo" (the evil eye or evil spirit) among Mexican Americans, voodoo among Haitians, yin and yang among Chinese patients, "rootwork" among African Americans, and "spiritism" (the ability of spirits to make people sick or cure them) among Puerto Ricans.

Interpret verbal and nonverbal behaviors in a culturally relevant manner.

Negotiate a culturally appropriate health care plan with the patient and his or her family as partners.

Demonstrate an ability to work as a team with a medical interpreter in the bilingual medical encounter.

From Goldstein E, et al: Intercultural medicine. In Jensen N, Van Kirk J, eds: A Curriculum for Internal Medicine Residency. Philadelphia, American College of Physicians, 1995.

www.ketabpezeshki.com 66485457-66963820

Box 2 Policies for Institutional Improvement

Educate emergency department personnel about the circumstances of patients' lives and the interesting cultures that have evolved to deal with these circumstances by use of a variety of formats:
- A series of hospital in-services to provide information about each specific patient group that uses the institution
- Small focus groups with patients to improve our understanding of our patients' needs and to begin the process of freeing providers from racial and ethnic stereotypes that create barriers to good medical care
- Training with use of videotapes and role-playing exercises to enhance movement along the cultural competence continuum

Meet with community organizations to build trust and to create partnerships for preventive education.

Hire employees who reflect the culture, ethnicity, and socioeconomic background of emergency department patients to improve the quality of services.

Provide interpreter services, visual aids, and other educational materials in a variety of languages, and provide multilingual health education classes.

Participate as an institution in community health fairs.

Educate emergency department and all staff who interface with victims of violence about trauma-informed care.
- Develop in-service for new hires; incorporate in human resources department hospital orientation
- Periodic updates: hospital-wide series on trauma-informed care

Educate medical students, physicians in training, and all providers about patient centeredness, cultural competence, and the differences and overlap.

KEY CONCEPTS

- Changing demography in the Unites States will change emergency medicine practice.
- Disparities in health and health care delivery continue despite efforts to improve care. Emergency physicians and their institutions will need to be part of the solution—treating preventable conditions that become crises because of reduced access to both primary care and specialists and acting as advocates for strategic system change to eliminate disparities in their institutions.
- Emergency physicians will improve the quality of care provided if they practice to meet federal standard for culturally and linguistically appropriate care, recognizing that patients with limited English proficiency have a right to medical interpretation.
- Culturally sensitive, patient-centered, and trauma-informed care will improve patient–emergency physician communications and satisfaction, decrease medical errors, and promote patient follow-through with recommendations.

References

1. Fadiman A: *The Spirit Catches You and You Fall Down: A Hmong Child, Her American Doctors, and the Collision of Two Cultures*. New York: Farrar, Straus & Giroux; 1997.
2. Davis K: *The Quality of American Health Care: Can We Do Better?* New York: Commonwealth Fund; 2001.
3. American College of Emergency Physicians, 1998-99 Ethics Committee: *Code of Ethics for Emergency Physicians*. Dallas, Tex: American College of Emergency Physicians; 1999.
4. Goldfrank LR, Knopp RK: Racially and ethnically selective oligoanalgesia: Is this racism? *Ann Emerg Med* 2000; 35:79.
5. U.S. Census Bureau: *American Fact Finder, People, Language, Origins*. Available at http://factfinder.census.gov/home/saff/main.html?_lang=en. Accessed July 27, 2011.
6. U.S. Census Bureau: *2010 Census Data*. Available at http://2010.census.gov/2010census/data/index.php. Accessed July 27, 2011.
7. U.S. Census Bureau: *Projected Population of the United States by Race and Hispanic Origin: 2000-2050*. Available at www.census.gov/ipc/www/usinterimproj. Accessed February 4, 2008.
8. National Center for Health Statistics: *Health, United States, 1998: With Socioeconomic Status and Health Chartbook*. Hyattsville, Md: U.S. Government Printing Office; 1998.
9. Smedley BD, Stith AY, Nelson AR, eds: *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care*. Washington, DC: National Academy Press; 2003. Available at http://books.nap.edu/books/030908265X/html/index.html. Accessed January 27, 2004.
10. Komaromy M, et al: The role of black and Hispanic physicians in providing health care for underserved populations. *N Engl J Med* 1996; 334:1305.
11. Cohen J: Statistics don't lie: Anti-affirmative action is bad for our health. *Acad Med* 1997; 72:1084.
12. Cone DC, et al: Health care disparities in emergency medicine. *Acad Emerg Med* 2003; 10:1176.
13. Cohen JJ: Disparities in health care: An overview. *Acad Emerg Med* 2003; 10:1155.
14. National Center on Minority Health and Health Disparities: *Annual Report on Health Disparities Research—Fiscal Year 2001*. Available at http://ncmhd.nih.gov/our_programs/strategic/pubs/AnnReportFY01Binder1.pdf. Accessed January 26, 2008.
15. Kung HC, Hoyert DL, Xu JQ, Murphy SL: Deaths: Final data for 2005. *Natl Vital Stat Rep* 2008; 56:1-120.
16. James CA, Bourgeois FT, Shannon MW: Association of race/ethnicity with emergency department wait times. *Pediatrics* 2005; 115:310.
17. Wilper AP, et al: Waits to see an emergency department physician: U.S. trends and predictors, 1997-2004. *Health Aff (Millwood)* 2008; 27:84.
18. Yancy CW, et al: The coalition to reduce racial and ethnic disparities in cardiovascular disease outcomes (credo): Why credo matters to cardiologists. *J Am Coll Cardiol* 2011; 57:245-252.
19. Todd KH, Samaroo N, Hoffman JR: Ethnicity as a risk factor for inadequate ED analgesia. *JAMA* 1993; 269:1537.
20. Todd KH, Samaroo N, Hoffman JR: The effect of ethnicity on physician estimates of pain severity in patients with isolated extremity trauma. *JAMA* 1994; 271:925.
21. Todd KH, Deaton C, D'Adamo AP, Goe L: Ethnicity and analgesic practice. *Ann Emerg Med* 2000; 35:11.
22. Zatzick DF, Dimsdale JE: Cultural variations in response to painful stimuli. *Psychosom Med* 1990; 52:544.
23. Lee WW, Burelbach AE, Fosnocht D: Hispanic and non-Hispanic white patient pain management expectations. *Acad Emerg Med* 2001; 19:548.
24. Chan A, Woodruff RK: Comparison of palliative care needs of English and non-English–speaking patients. *J Palliat Care* 1999; 15:26.
25. Heins JK, et al: Disparities in analgesia and opioid prescribing practices for patients with musculoskeletal pain in the emergency department. *J Emerg Nurs* 2006; 32:219.
26. Pletcher MJ, Kertesz SG, Kohn MA, Gonzales R: Trends in opioid prescribing by race/ethnicity for patients seeking care in the US emergency departments. *JAMA* 2008; 299:70.
27. Tamayo-Sarver JH, Hinze SW, Cydulka RK, Baker DW: Racial and ethnic disparities in emergency department analgesic prescription. *Am J Public Health* 2003; 93:2067.
28. Johnston V, Bao Y: Race/ethnicity-related and payer-related disparities in the timeliness of emergency care in U.S. emergency departments. *J Health Care Poor Underserved* 2011; 22:606-620.
29. Centers for Disease Control and Prevention: Racial/ethnic disparities in influenza and pneumococcal vaccination levels among persons aged >65 years: United States, 1989-2001. *MMWR Morb Mortal Wkly Rep* 2003; 52:958.
30. Bach PB, Cramer LD, Warren JL, Begg CB: Racial differences in the treatment of early-stage lung cancer. *N Engl J Med* 2000; 341:1198.
31. King TE, Brunetta P: Racial disparity in rates of surgery for lung cancer [editorial; comment]. *N Engl J Med* 1999; 341:1231.
32. Peterson ED, et al: Racial variation in the use of coronary-revascularization procedures: Are the differences real? Do they matter? *N Engl J Med* 1997; 336:480.
33. Pezzin LE, Keyl PM, Green GB: Disparities in the emergency department evaluation of chest pain patients. *Acad Emerg Med* 2007; 14:149.

www.ketabpezeshki.com 66485457-66963820

34. Venkat A, et al: The impact of race on acute management of chest pain. *Acad Emerg Med* 2003; 10:1199.
35. Fagenholz PJ, Fernandez-del Castillo C, Pelletier AJ, Camargo C: National study of United States emergency department visits for acute pancreatitis, 1993-2003. *BMC Emerg Med* 2007; 7:1.
36. Bazarian JJ, et al: Ethnic and racial disparities in emergency department care for mild traumatic brain injury. *Acad Emerg Med* 2003; 10:1209.
37. Wall SP, et al: Impact of patient race on receiving heat CT during blunt head injury evaluation. *Acad Emerg Med* 2005; 12:862.
38. Harris B, Hwang U, Richardson LD, Lee W: Disparities in computed tomography utilization for adult patients presenting to the emergency department with headache. *Ann Emerg Med* 2007; 50:S120.
39. Guagliardo MF, et al: Racial and ethnic disparities in pediatric appendicitis rupture rate. *Acad Emerg Med* 2003; 10:1218.
40. Kunen S, et al: Race disparities in psychiatric rates in emergency departments. *J Consult Clin Psychol* 2005; 73:116.
41. Taukli-Williams J, Carrillo J: The impact of psychosocial stressors on African American and Latino preschoolers. *J Natl Med Assoc* 1995; 87:473.
42. Williams DR, Jackson PB: Social sources of racial disparities in health. *Health Aff (Millwood)* 2005; 24:325.
43. Jones CP: Levels of racism: A theoretic framework and a gardener's tale. *Am J Public Health* 2000; 90:1212.
44. Commonwealth Fund: *Health Care Quality Survey*. Available at www.commonwealthfund.org/usr_doc/qualitysurvey_2001_topline.pdf?section=40. Accessed February 4, 2008.
45. Kaiser Family Foundation: *National Survey of Physicians*, 2002. Available at www.kff.org/minorityhealth/loader.cfm?url=/commonspot/security/getfile.cfm&PageID=13955. Accessed February 4, 2008.
46. Kennedy BP, et al: *(Dis)respect and black mortality*. In: Kawachi I, Kennedy B, Wilkinson R, eds: *The Society and Population Health Reader*. New York: New Press; 1999:465-473.
47. Romano PS, Bloom J, Syme LS: Smoking, social support and hassles in an urban African American community. *Am J Public Health* 1991; 81:1415.
48. Walcott-McQuigg JA: The relationship between stress and weight-control behavior in African American women. *J Natl Med Assoc* 1995; 87:427.
49. Jackson JS, et al: Racism and the physical and mental health status of African Americans: A thirteen year national panel study. *Ethn Dis* 1996; 6:13247.
50. Murrell NL: Stress, self-esteem, and racism: Relationships with low birth weight and preterm delivery in African American women. *J Natl Black Nurses Assoc* 1996; 8:45.
51. Auslander WF, Thompson SJ, Dreitzer D, Santiago JV: Mothers' satisfaction with medical care: Perceptions of racism, family stress, and medical outcomes in children with diabetes. *Health Soc Work* 1997; 22:190.
52. Dressler WW: Social identity and arterial blood pressure in the African American community. *Ethn Dis* 1996; 6:176.
53. Thompson VL: Perceived experiences of racism as stressful life events. *Commun Mental Health J* 1996; 32:223.
54. Kreiger N, Sidney S: Prevalence and health implications of anti-gay discrimination: A study of black and white women and men in the CARDIA cohort. Coronary Artery Risk Development in Young Adults. *Int J Health Serv* 1997; 27:157.
55. Schulman KA, et al: The effect of race and sex on physicians' recommendations for cardiac catheterization. *N Engl J Med* 1999; 340:618.
56. Richardson LD, Irvin CB, Tamayo-Sarver JH: Racial and ethnic disparities in the practice of emergency medicine. *Acad Emerg Med* 2003; 10:1184.
57. James TL, Feldman J, Mehta SD: Physician variability in history taking when evaluating patients presenting with chest pain in the emergency department. *Acad Emerg Med* 2006; 13:147.
58. Corbie-Smith G: The continuing legacy of the Tuskegee Syphilis Study: Considerations for clinical investigation. *Am J Med Sci* 1999; 317:5.
59. Cooper-Patrick L, et al: Race, gender, and partnership in the patient-physician relationship. *JAMA* 1999; 282:583.
60. vanRyn M, Burke J: The effects of race and socioeconomic status on physicians' perceptions of patients. *Soc Sci Med* 2000; 50:813.
61. Agency for Healthcare Research and Quality: *National Healthcare Disparities Report*. Washington, DC: U.S. Department of Health and Human Services; 2003.
62. U.S. Census Bureau: *Profile of Selected Social Characteristics: 2000*. Available at http://factfinder.census.gov/servlet/QTTable?_bm=y&-geo_id=D&-qr_name=DEC_2000_SF4_U_DP2&-ds_name=D&-_lang=en&-redoLog=false. Accessed January 26, 2008.
63. Flores G, et al: Errors in medical interpretation and their potential clinical consequences in pediatric encounters. *Pediatrics* 2003; 11:6.
64. Baker D, et al: Use and effectiveness of interpreters in an emergency department. *JAMA* 1996; 275:783.
65. Tang SY: Interpreter services in healthcare: Policy recommendations for healthcare agencies. *J Nurs Adm* 1999; 29:23.
66. Gany F, et al: The impact of medical interpretation method on time and errors. *J Gen Intern Med* 2007; 22:319.
67. Ngo-Metzger Q, et al: Providing high quality care for limited English proficient patients: The importance of language concordance and interpreter use. *J Gen Intern Med* 2007; 22:324.
68. Baker DW, Hayes R, Fortier JP: Interpreter use and satisfaction with interpersonal aspects of care for Spanish-speaking patients. *Med Care* 1998; 36:1461.
69. Bernstein J, et al: Trained medical interpreters in the emergency department: Effects on services, subsequent charges and follow-up. *J Immigr Health* 2002; 4:171.
70. Carrasquillo O, Orav J, Brennan TA, Burstin HR: Impact of language barriers on patients' satisfaction in an emergency department. *J Gen Intern Med* 1999; 14:282.
71. Massachusetts Division of Medical Assistance: *Appendix G: Cultural Competence QIP Reporting*. Boston: Division of Medical Assistance; 1997.
72. *National Standards for Culturally and Linguistically Appropriate Services in Health Care, Final Report*. Washington, DC: U.S. Department of Health and Human Services, Office of Minority Health; 2001. Available at www.omhrc.gov/assets/pdf/checked/executive.pdf. Accessed January 28, 2008.
73. SAEM Task Force on Physician-Patient Communication: Physician-patient communication in the emergency department. Part 2: Communication strategies for specific situations. *Acad Emerg Med* 1996; 3:1146.
74. Weaver C, Sklar D: Diagnostic dilemmas and cultural diversity in the ER. *West J Med* 1980; 133:356.
75. Agency for Healthcare Research and Quality: *National Healthcare Disparities Report 2009*. Report No. 06-0017. No. 10-0004. Rockville, Md: Agency for Healthcare Research and Quality; 2010.
76. Taylor P, et al: *Twenty to one: Wealth gaps rise to record highs between Whites, Blacks and Hispanics*. Washington, DC: Pew Research Center; 2011. Available at http://pewsocialtrends.org. Accessed July 27, 2011.
77. Wolsko PM, et al: Insurance coverage, medical conditions, and visits to alternative medicine providers: Results of a national survey. *Arch Intern Med* 2002; 162:281.
78. Flores G: Culture and the patient-physician relationship: Achieving cultural competency in health care. *J Pediatr* 2000; 136:14.
79. Downs K, Bernstein J, Marchese T: Providing culturally competent primary care for immigrant and refugee women: A Cambodian case study. *J Nurse Midwifery* 1997; 42:499.
80. Snow L: *Walkin' Over Medicine*. San Francisco: Westview; 1992.
81. Flores C: *Hispanic immigrants: Health care access and outcomes*. In: Bernstein E, Bernstein J, eds: *Case Studies in Emergency Medicine and the Health of the Public*. Boston: Jones & Bartlett; 1996:158-166.
82. Centers for Disease Control and Prevention: *Injury Center: Violence Prevention: Data Sources. Youth Violence: Facts at a Glance*. Summer 2009. Available at www.cdc.gov/violenceprevention/pdf/YV_DataSheet_Summer2009-a.pdf.
83. *The Adverse Childhood Experiences (ACE) Study: Bridging the gap between childhood trauma and negative consequences later in life*. Available at www.acestudy.org/. Accessed July 27, 2011.
84. Centers for Disease Control and Prevention: *Adverse Childhood Experiences (ACE) Study*. Available at www.cdc.gov/ace/outcomes.htm#Over. Accessed July 27, 2011.
85. Substance Abuse and Mental Health Services: *National Center for Trauma-Informed Care*. Available at www.samhsa.gov/nctic/. Accessed July 27, 2011.
86. Bloom S: *Applying Trauma Knowledge to Community Prevention and Systems Change Efforts*, October 2009. Available at www.calendow.org/uploadedFiles/Publications/BMOC/Drexel%20-%20Healing%20the%20Hurt%20-%20Full%20Report.pdf. Accessed July 27, 2011.
87. Bloom SL: The Sanctuary Model of Trauma-Informed Organizational Change. The National Abandoned Infants Assistance Resource Center. *The Source* 2007; 16:12-14.
88. American College of Emergency Physicians: *Code of Ethics for Emergency Physicians*, 2011. Available at www.acep.org/content.aspx?id=29144. Accessed July 27, 2011.

www.ketabpezeshki.com 66485457-66963820

89. West CM, Kantor GK, Jasinski JL: Sociodemographic predictors and cultural barriers to help-seeking behavior by Latina and Anglo American battered women. *Violence Vict* 1998; 13:361.
90. Jones DR, et al: Affective and physiological responses to racism: The roles of afrocentrism and mode of presentation. *Ethn Dis* 1996; 61:109.
91. Thornton MC, White-Means SI: *Racial and ethnic patterns of hospital emergency department use*. In: Lillie-Blanton M, Leigh W, eds: *Achieving Equitable Access: Studies of Health Care Issues Affecting Hispanics and African Americans*. Washington, DC: University Press of America; 1996.
92. Saha S, Beach MC, Cooper LA: Patient centeredness, cultural competence and healthcare quality. *J Natl Med Assoc* 2008; 100:1275-1285.
93. Beach MC, Saha S, Cooper LA: *The Role and Relationship of Cultural Competence and Patient-Centeredness in Health Care Quality*. The Commonwealth Fund, 2006. Available at www.commonwealthfund.org/usr_doc/Beach_rolerelationshipcultcomppatient-cent_960.pdf. Accessed July 27, 2011.
94. Park ER, et al: Measuring residents' perceived preparedness and skillfulness to deliver cross-cultural care. *J Gen Intern Med* 2009; 24:1053-1056.
95. Green AR, et al: Providing culturally competent care: Residents in HRSA Title VII funded residency programs feel better prepared. *Acad Med* 2008; 83:1071-1079.
96. Green AR, et al: Designing and implementing cultural competence OSCE: Lessons learned from interviews with medical students. *Ethn Dis* 2007; 17:344-350.
97. Lopez L, et al: Personal characteristics associated with resident physicians' self perceptions of preparedness to deliver cross-cultural care. *J Gen Intern Med* 2008; 23:1953-1958.
98. Park ER, et al: Internal medicine residents' perceptions of cross-cultural training. Barriers, needs, and educational recommendations. *J Gen Intern Med* 2006; 21:476-480.
99. Kumagal AK, Lypson ML: Beyond cultural competence: Critical consciousness, social justice and multicultural education. *Acad Med* 2009; 84:782-787.
100. Hamilton G, Marco CA: Emergency medicine education and health care disparities. *Acad Emerg Med* 2003; 10:1189.
101. Hobgood C, Sawning S, Bowen J, Savage K: Teaching culturally appropriate care: A review of educational models and methods. *Acad Emerg Med* 2006; 13:1288.
102. Flores G: Providing culturally competent pediatric care: Integrating pediatricians, institutions, families, and communities into the process. *J Pediatr* 2003; 143:1.
103. Scott CJ, Martin M, Hamilton G: Training of medical professionals and the delivery of health care as related to cultural identity groups. *Acad Emerg Med* 2003; 10:1149.
104. Goldstein E, et al: *Intercultural medicine*. In: Jensen N, Van Kirk J, eds: *A Curriculum for Internal Medicine Residency*. Philadelphia: American College of Physicians; 1995.

www.ketabpezeshki.com 66485457-66963820

Bioethics*

Kenneth V. Iserson and Carlton E Heine

**For the complete chapter text, go to the Expert Consult website. To access your account, look for your activation instructions on the inside front cover of this book.*

I. PERSPECTIVE

A. Definition

B. Ethics and Emergency Medicine

II. BIOETHICS AND THE LAW

A. Basic Considerations

B. Rights and Duties

III. VALUES

A. Religious Values

B. Good versus Evil

IV. FUNDAMENTAL BIOETHICAL PRINCIPLES

A. Nonmaleficence and Autonomy

B. Beneficence

C. Justice

D. Truth-Telling

E. Confidentiality versus Privacy

V. MEDICAL AND MORAL IMPERATIVES IN EMERGENCY MEDICINE

A. Professional Values

B. Safety: A Unique Value

VI. CODIFYING PROFESSIONAL VALUES: ETHICAL OATHS AND CODES

A. Conflicting Principles

B. Organizational and Institutional Values

C. Professional Codes

VII. APPLYING BIOETHICS

A. Emergency Physician–Patient Relationship

B. Recognizing Ethical Problems

C. Prioritizing Conflicting Principles

VIII. MEDICAL IMPERATIVES AND BIOETHICAL DILEMMAS

A. Professional Value Conflicts

IX. RAPID ETHICAL DECISION-MAKING MODEL

X. ADVANCE DIRECTIVES

XI. CONSENT, DECISION-MAKING CAPACITY, AND SURROGATE DECISION MAKERS

www.ketabpezeshki.com 66485457-66963820

A. Consent

B. Decision-Making Capacity

C. Surrogates

XII. RESUSCITATION ETHICS

A. Futility

B. Withholding versus Withdrawal of Treatments

C. Palliative Care

D. Notifying Survivors

E. Viewing of Resuscitations

F. Postmortem Teaching

G. Resuscitation Research

XIII. PUBLIC POLICY AND BIOETHICS

A. Restricted Access to Emergency Medical Care

B. Morality of Triage Decisions

C. Physician Response to Risky Situations Postmortem

D. "Proactive Ethics": How Can Emergency Physicians Change the Rules?

www.ketabpezeshki.com 66485457-66963820

Bioethics

Kenneth V. Iserson and Carlton E. Heine

PERSPECTIVE

The medical care we provide today bears little resemblance to what was available when the first edition of this book was published. What has not advanced as far or fast is our system for deciding, in a moral and fair way, what treatments to provide. Scientific development has outpaced our social and ethical framework and often leaves physicians struggling with moral dilemmas about the appropriateness of tests and procedures. This chapter is an introduction to our current tools for helping emergency physicians (EPs) approach ethical, rather than medical, dilemmas.

Definitions

Bioethics, a subset of ethics, is the application of values and moral rules to find reasoned and defensible solutions to actual or anticipated moral dilemmas facing clinicians. The moral precepts that underpin ethical decisions are derived from a variety of sources, including individual, cultural, and community value systems. Unlike the law, which is relatively rigid and, particularly in the case of scientific and medical issues, can lag years or even decades behind modern developments, bioethical constructs allow a greater flexibility in decision-making. EPs are often called on to identify a patient's personal, cultural, religious, or community values and to balance these values with their own personal and professional ethos. A working knowledge of bioethics greatly enhances the EP's ability to make reasonable, ethical decisions in the limited time frame common to the practice of emergency medicine (EM).[1]

In contrast to professional etiquette, which relates to standards governing the relationships and interactions between providers, bioethics deals with relationships between providers and patients, providers and society, and society and patients. Issues within the realm of professional etiquette include billing, referrals, advertising, competition, conflicts of interest, professional courtesy, and employment and supervision of auxiliary personnel. These are quite different from bioethics' concerns of basic moral values and patient-centered issues. Although the two areas occasionally overlap, each relies on different standards, values, and problem-solving methods.

Ethics and Emergency Medicine

In EM, the focus is inevitably on the inherent "medical" nature of each case; therefore, it should come as no surprise that ethical dilemmas often go unrecognized. EPs may also misperceive ethics as embodying the dictates of secular or religious law or as a discipline that describes irresolvable issues.[1]

This chapter addresses a number of ethical issues in EM. What follows are brief discussions of the relation of law to bioethics; bioethical values and principles; moral imperatives in EM; ethical oaths and codes; applying bioethics to clinical situations; bioethical dilemmas in EM; a rapid decision-making model for ethical dilemmas; advance directives; the relationship between consent, decision-making capacity, and surrogate decision makers; ethical issues in resuscitation; and ethical issues in public policy.

BIOETHICS AND THE LAW

Basic Considerations

EPs often look to the law for answers to thorny dilemmas. Yet, except in the rare cases of "black-letter law," wherein specific actions are delineated, these issues are best served by turning to bioethical reasoning and using bioethics consultations. It is said that good ethics makes good law but that good law does not necessarily make good ethics. Societal values are incorporated both within the law and within ethical principles and decisions. Laws are rules of conduct established by legislatures, administrative agencies, courts, or other governing bodies. They often vary from locale to locale and are enforceable only in the jurisdiction where they prevail. By contrast, ethics is more universal within a culture, incorporating the broad values and beliefs of correct conduct. The primary differences between law and bioethics are shown in Table 1.

Modern bioethics developed because the law often has remained silent or inconsistent on matters vital to the biomedical community. The rapid increase in biotechnology, the failure of both the legal system and legislatures to deal with new and pressing issues, and the increasing liability crisis drove the medical community to seek answers to the difficult questions that practitioners have to work through on a daily basis.

Bioethical principles are not static and may evolve as societies change. The same evolution occurs within the law. For example, elective abortion, once illegal in most U.S. jurisdictions, is now legal in most circumstances and jurisdictions. Likewise, not all basic ethical principles have universal support, just as the values implicit in many legal changes have divided U.S. society.

Rights and Duties

Without a duty to act, there can be no rights. Both a moral and a logical connection exists between the rights and the duties of individuals; one cannot exist in the absence of the other. In general, a duty is an action required by the rights of others, the law, a higher authority, or one's conscience.[2] This obligation to act can be based

www.ketabpezeshki.com 66485457-66963820

Table 1 Relationship between Law and Bioethics

BIOETHICS	FUNCTION OR PRINCIPLE	LAW
✓	Case based (casuistic)	✓
✓	Has existed since ancient times	✓
✓	Changes over time	✓
✓	Strives for consistency	✓
✓	Incorporates societal values	✓
✓	Basis for health care policies	✓
	Some unchangeable directives	✓
	Formal rules for process	✓
	Adversarial	✓
✓	Relies heavily on individual values	
✓	Interpretable by medical personnel	
✓	Ability to respond rapidly to changing environment	

Modified from Iserson KV: Ethical principles—emergency medicine. In Schears RM, Marco CA (eds): Ethical Issues in Emergency Medicine. Emerg Med Clin North Am 24:515, 2006.

Box 1 Commonly Accepted Moral Rules

Moral rules govern actions on the basis of ethics and codes of conduct. These can justifiably be enforced and their violation punished. Although none of these rules is absolute, they all require one not to cause evil. Somewhat paradoxically, however, they may not require either preventing evil or doing good.

1. Do not kill.
2. Do not cause pain.
3. Do not disable.
4. Do not deprive of freedom.
5. Do not deprive of pleasure.
6. Do not deceive.
7. Keep your promise.
8. Do not cheat.
9. Obey the law.
10. Do your duty.

Modified from Gert B: Morality: A New Justification of the Moral Rules. Oxford, Oxford University Press, 1988.

on an individual's personal values, professional position, or other commitments.[3] For the physician, this duty to act is a role responsibility, at least specifically as a physician and possibly at all times. The role-duty link occurs "whenever a person occupies a distinctive place or office in a social organization, to which specific duties are attached to provide for the welfare of others or to advance in some specific way the aims or purposes of the organization."[4] In this circumstance, performance is predicated not on a guarantee of compensation but rather on a concern for another person's welfare.[5] The EP has not only such a moral duty but, because of the Emergency Medical Transportation and Active Labor Act (EMTALA), also a legal duty.

Significant overlap can exist between legal and ethical decisionmaking. Frequently, there is concurrence on basic issues. On occasion, clarity within the law can lead to clearer thinking in bioethics, and vice versa. Both law and bioethics, for example, use the term *rights,* as in "patients' rights" and "the right to die." This term, often used to advance an ethical argument about medical care, frequently is misunderstood or applied erroneously. A legal right is a demand that a person can make on another person, embodied in *in personam* rights, or against the state for recognition and enforcement of this demand. Most rights involved in bioethical discussions are *in rem* rights. These most often are negative rights because they entail someone else's duty to refrain from doing something. A common source of ethical conflict is between "active rights," the right to act or not act as one chooses, and "passive rights," the right to not be acted on by others in certain ways.[2]

VALUES

Values are the standards by which human behavior is judged. Values are learned, usually at an early age, through indoctrination into the birth culture, from observing behavior, and through secular (including professional) and religious education. Although many of these learned values overlap, each source often claims moral superiority over the others, whether the values are generic and cultural, legal norms, religious and philosophical traditions, or professional principles.[6,7] Societal institutions incorporate and promulgate values, often attempting to solidify old values even in a changing society. In a pluralistic society, clinicians treat people with multiple and differing value systems, so they must be sensitive to alternative beliefs and traditions.

This section discusses the role of religious, patient, institutional, and professional values, including professional oaths and codes specific to EM.

Religious Values

Organized religions see themselves as keepers of society's values. Even though various religions may appear dissimilar, most hold the golden rule, "Do unto others as you would have them do unto you," as a basic tenet. Other moral rules that are common to most religions are listed in Box 1. Problems surface in trying to apply religion-based rules to specific bioethical situations. For example, although "Do not kill" generally is accepted, the activities that constitute killing, active or passive euthanasia, or merely reasonable medical care vary with the interpretation of the world's religions as they do with the interpretations of various philosophers.[8-10] As members of a democracy with significant populations practicing a number of religions, EPs should behave in a manner consistent with each patient's values. The most basic underlying question is What is the patient's desired outcome for medical care?

Not only religious but also family, cultural, and other values contribute to patients' medical care decisions. Without asking, it is impossible to know what decision a specific person would make. An important point is that religion influences modern secular bioethics, which uses many religion-originated decision-making methods, arguments, and ideals. In addition, clinicians' personal spirituality may allow them to relate better to patients and families in crisis.[9]

Good versus Evil

The terms *good* and *evil* can be used to illustrate a stark dichotomy in ethical thought and values. The following is a current set of definitions that may help the physician find solutions to ethical problems. *Good* can be defined as what no rational person will avoid without a reason. Examples are freedom, pleasure, health, wealth, and knowledge. *Evil* can be defined as what all rational persons desire to avoid for themselves and for others they care about. Examples are untimely death, pain, disability, and loss of freedom or pleasure.[11] Rational persons with deeply held religious beliefs may, for example, refuse a blood transfusion, choosing a likelihood of death over the permanent pain and anguish they believe would ensue if they should violate their religious injunction. Conflicts that can be described as being between good and evil are not ethical dilemmas but rather moral temptations. Ethical

www.ketabpezeshki.com 66485457-66963820

dilemmas arise from conflicts between multiple good or multiple bad options.

Patient Values and Ethical Decisions

A key to making bedside ethical decisions is knowing the patient's values. Many people cannot answer the question, What are your values? However, physicians can get an operational answer by asking patients what they see as their goal of medical therapy and why they want specific interventions. The responses represent concrete expressions of patient values. In patients who are too young or are deemed incompetent to express their values, it may be necessary for physicians either to make general assumptions about what a normal person would want in a specific situation or to rely on surrogate decision-making. But with patients who are able to reason and communicate, care should be taken to discover what they hold as their own, uncoerced values.

Although each individual is entitled and perhaps even required to have a personal system of values, certain values have become generally accepted by the medical community, the courts, legislatures, and society at large. Autonomy and individual dignity, for example, are two such values; they have been considered fundamental and often are given over-riding importance. Although some groups disagree about each of these values, this dissension has not affected their application to medical care.

FUNDAMENTAL BIOETHICAL PRINCIPLES

Nonmaleficence and Autonomy

The basic tenet all medical students are taught is nonmaleficence: "First, do no harm." This credo, often stated in the Latin, *primum non nocere,* derives from the recognition that physicians can harm as well as help. With the physician's fallibility recognized, patient autonomy is and has been for several decades the over-riding professional and societal bioethical value. Autonomy recognizes an adult person's right to accept or to reject recommendations for medical care, even to the extent of refusing all care, if that person has appropriate decision-making capacity. It is the counterweight to the medical profession's long-practiced paternalism (or parentalism), wherein the practitioner determines what is "good" for the patient, regardless of whether the patient agrees. Coupled with paternalism is coercion, the threat or use of violence to influence behavior or choice. The august figure in white combined with implied or explicit threats remains a potent force for counteracting patients' wishes. The thrust of modern bioethics is to respect patients by honoring their autonomy (Box 2).

Box 2 Commonly Accepted Societal and Bioethical Values

Autonomy: Self-determination: a person's ability to make personal decisions, including those affecting personal medical care. Autonomy is the opposite of paternalism.
Beneficence: Doing good. A duty to confer benefits. Production of benefit.
Confidentiality: The presumption that what the patient tells the physician will not be revealed to any other person or institution without the patient's permission.
Distributive justice: Fairness in the allocation of resources and obligations. This value is the basis of and is incorporated into society-wide health care policies.
Nonmaleficence: Not doing harm, prevention of harm, and removal of harmful conditions.
Personal integrity: Adhering to one's own reasoned and defensible set of values and moral standards.

Beneficence

At the patient's bedside, beneficence (doing good) and confidentiality (holding information in confidence) have been long-held and nearly universal tenets of the medical profession. Similarly, personal integrity (the adherence to one's own moral and professional standards) is basic to thinking and acting ethically.

Justice

The concept of comparative or distributive justice suggests that a society's comparable individuals and groups should share similarly in the society's benefits and burdens. Many society-wide decisions affecting thoughts and actions about the allocation of limited health care resources are based on this principle. Yet for individual clinicians to limit or to terminate care on a case-by-case basis is an erroneous extrapolation of the perceived need to limit health care resource expenditures.[7] Distributive justice is a social policy concept rather than a clinical model for individual physician-patient decisions.

Truth-Telling

Personal integrity involves adhering to one's own reasoned and defensible set of values and moral standards and is basic to ethical thought and action. Integrity includes a controversial value within the medical community: truth-telling. Some people think that the patient has the right to know the truth, no matter what the circumstances, and have championed absolute honesty. Yet many of these same people, when patients themselves, have been appalled by their physician's lack of sensitivity in relating unfavorable medical news.[12] In this context, being honest does not mean being brutal; truth is best tempered with a modicum of compassion.

Physicians accept a lack of truth-telling, depending on the circumstances. When patient harm may result from failing to disclose the truth, such as happened in the infamous Tuskegee experiments, in which treatment was knowingly withheld from black men with syphilis, it is not only immoral but also probably illegal to withhold the information. Likewise, when failure to disclose information is strictly for the physician's benefit, such as not telling a patient about a dismal prognosis or a medical error, the clinician's behavior suggests serious ethical and legal deficits. Perhaps truth-telling is not universally accepted within the medical profession because of poor role models, lack of training in interpersonal interactions, and bad experiences rather than because the value itself has been discounted. The issues become murkier when truth-telling, or lack thereof, involves a third party, such as a sex partner who has been exposed to an infectious disease.[13]

Confidentiality versus Privacy

Stemming at least from the time of Hippocrates, confidentiality is the presumption that what the patient tells the physician will not be revealed to any other person or institution without the patient's permission.[9] Health care workers have an obligation (duty) to maintain patient confidentiality. On occasion, the law, especially public health statutes, may conflict with this principle because they require physicians to report specific diseases, injuries and injury mechanisms, and deaths. Drug-seeker lists, long used in emergency departments (EDs), can be seen as violations of patient confidentiality, and especially without firm controls on patient entry and clinician access to these lists, they can directly harm patients.[14] Rarely discussed are similar computer lists of previous ED visits that can be easily generated from most ED computer systems. The Health Insurance Portability and Accountability Act (HIPPA) of 1996, a U.S. federal law designed to protect patient

www.ketabpezeshki.com 66485457-66963820

information, however, takes the principle of confidentiality to the extreme, resulting, paradoxically, in greater difficulty in obtaining crucial information needed to treat ED patients.

Privacy, which is often confused with confidentiality, is the right of patients to sufficient physical and auditory isolation that they cannot be seen or heard by others during interactions with medical personnel.[9] ED overcrowding, patient and staff safety issues, and ED design limit patient privacy in many cases.

The increasing use of telemedicine to render advice and to guide procedures at remote sites also places a strain on both patient privacy and confidentiality. Suggested ethical guidelines for such practices can facilitate the use of these new technologies without sacrificing either patient rights or physician duties.[15]

Another recent development has been filming of ED patients for public viewing. Such filming, whether for medical records, education, peer review, or "reality television," encroaches on ED patients' reasonable expectation of privacy and confidentiality because the recording can easily be distributed or misused. Although good reasons exist to allow such filming with patient acquiescence,[16] the standard is now to abstain from such filming for commercial purposes and to require patient or surrogate consent for educational purposes.[17]

MEDICAL AND MORAL IMPERATIVES IN EMERGENCY MEDICINE

Professional Values

Emergency clinicians, in both the out-of-hospital and ED environments, operate with four imperatives: to save lives when possible, to relieve pain and suffering, to comfort patients and families, and to protect staff and patients from injury. All but the last of these are common imperatives of most other clinicians as well, although saving lives may occur more often and more dramatically in EM settings.

Safety: A Unique Value

The last imperative, safety, is nearly unique to EM. In both the out-of-hospital and ED settings, clinicians often encounter dangerous situations in which the environment, the patient, a friend, or a family member poses a threat. Violence against emergency care workers is well documented and unfortunately common. The ED routinely deals with psychotic and intoxicated patients and patients injured in human-on-human attacks, and those involved are often under extreme stress. Although most try to accommodate basic patient rights, clinicians' priority must be their own safety and the safety of their coworkers. This priority does not imply that clinicians should ignore patient safety, but only that they should first ensure their own safety if they or their colleagues are at risk.

CODIFYING PROFESSIONAL VALUES: ETHICAL OATHS AND CODES

Conflicting Principles

In the abstract, bioethical principles often appear simple. However, clinicians adhere not only to basic bioethical principles but also, at least tacitly, to a number of professional, religious, and social organizations' ethical oaths, codes, and statements.[9] This complexity can create a confusing array of potentially conflicting bioethical imperatives. Because bioethical principles seem to be neither universal nor universally applied, the principles that are most patient centered normally hold sway.

Organizational and Institutional Values

Institutions, including health care facilities and professional organizations, have their own value systems. Health care facilities, although relatively well standardized under the requirements of regulatory bodies and government agencies, often have specific value-related missions. Religiously oriented or affiliated institutions may be the most obvious of these, but charitable, for-profit, and academic institutions also have specific role-related values. The values of professional organizations often are set forth in their ethical codes.

Professional Codes

Through the years, the medical profession has codified its ethics more rigorously than any other professional group, incorporating many standard bioethics principles into its ethical codes and oaths. For generations, the existing part of the Hippocratic Oath set the ethical standard for the medical profession.[18] Yet its precepts clash with modern bioethical thinking, and many subsequent professional codes have included what may best be termed economic guidelines and professional etiquette, along with ethical precepts.[19] EP professional values have been incorporated into organization codes, such as the American College of Emergency Physicians' Code of Ethics, and into a more personal oath developed by the Society for Academic Emergency Medicine.[20,21]

Most modern ethical codes do not require a higher level of duty or commitment for members than the same basic moral behavior that is expected of society at large. In fact, many of the ethical issues that would seem to be important to medical specialties usually are not addressed in their codes. Even when topics of interprofessional interactions are excluded, existing medical professional codes differ markedly (Table 2). All, however, try to give a "bottom line"—that is, minimally acceptable—course of action.

APPLYING BIOETHICS

Emergency Physician–Patient Relationship

The EP has a markedly different relationship with patients from that of other health practitioners, especially those providing primary care[22-24] (Table 3). EPs care for patients who are unfamiliar to them and to the institution. Practitioners who either know their patients or who care for them in less acute settings often have the time and the mechanisms to make sound ethical decisions, but EPs have more limited options. A suggested method for rapid, ethical decision-making in the ED setting is outlined in Box 3 and discussed in a later section.[25]

Recognizing Ethical Problems

Although physicians like to reduce all clinical situations to "medical problems," today's increasingly complex medical environment often produces problems that are inexorably intertwined with fundamental bioethical dilemmas. Some are obvious, but many are more difficult to recognize.

Prioritizing Conflicting Principles

Once such dilemmas are recognized, applying bioethical principles to clinical situations can be confusing. When two or more seemingly equivalent principles or values seem to compel different actions, a bioethical dilemma exists. This situation is often described as being "damned if you do and damned if you don't," in which any potential action appears, on first reflection, to be an option between two seemingly equivalent goods or evils. In the following real case, taken from the book *Ethics in Emergency*

www.ketabpezeshki.com 66485457-66963820

Table 2 Comparison of Six Ethical Codes for Physicians

PRINCIPLE OR CONCEPT	SAEM	ACEP	EMRA	AMA	AOA	HIPPOCRATIC OATH
Protect patient confidentiality		×	×	×	×	×
Maintain professional expertise	×	×	×	×	×	×
Committed to serve humanity	×	×	×	×	×	
Patient welfare primary concern	×	×	×	×		×
Considerate to patients, colleagues	×	×	×	×		×
Respect human dignity	×	×	×	×		×
Safeguard public health	×	×	×	×		×
Protect vulnerable populations	×	×		×	×	×
Advance professional ideals	×	×	×	×		×
Honesty		×		×	×	
Report incompetent, dishonest, impaired physicians		×	×	×		
Moral sensitivity	×	×		×		
Obtain necessary consultation				×	×	×
Altruism in teaching	×					
Fairness to students, colleagues				×		×
Obey, respect the law			×	×	×	
Prudent resource use	×	×				
Work to change laws for patient benefit				×	×	
Not abuse privileges	×					×
Respect for students	×					×
Choose whom to serve except in emergencies				×	×	
Ensure beneficial research by employing competence, impartiality, compassion	×					
No abortions						×
No euthanasia						×
Do not compromise clinical judgment for money			×			
Universal access to health care				×		
Preserve human life						×

Modified from Iserson KV: Ethical principles—emergency medicine. In Schears RM, Marco CA (eds): Ethical Issues in Emergency Medicine. Emerg Med Clin North Am 2006; 24:531.

ACEP, American College of Emergency Physicians; *AOA,* American Osteopathic Association; *AMA,* American Medical Association; *EMRA,* Emergency Medicine Residents' Association; *SAEM,* Society for Academic Emergency Medicine.

Medicine, the attending physician can be said to be on the horns of a dilemma (involving two prickly but seemingly equal choices): although only two options for action may be available, both options involve a number of conflicting bioethical principles.

Case Example: Conflicting Bioethical Principles

A 60-year-old man stabbed himself in the abdomen because of intractable pain from terminal pancreatic cancer, unrelieved by any medical therapy. A well-meaning friend, who happened to be in the house when the event occurred, called the paramedics, who brought him to the ED. Although the man will obviously bleed to death if he is not given aggressive care, neither the patient, who is still alert and oriented, nor his wife, who is present, wants any treatment other than pain control. A review of his chart confirms that his physicians are at a loss as to how to alleviate his pain and that he is expected to die within the next several weeks.[26] The physician believes in respecting a patient's autonomy yet usually questions patients' decision-making capacity when they attempt suicide. Such patients' actions seem to raise the question of whether, in fact, they have a right or an ability to be autonomous. This physician also believes strongly in beneficence: helping those in need, relieving pain, and saving lives when possible. Beneficence suggests two alternative courses of action: palliative care or aggressive therapeutic intervention. Merely using analgesics and other comfort measures will abet a suicide; initiating aggressive medical and surgical interventions will prolong a dying process that the physician's colleagues have found to be unresponsive to even palliative treatment. Which value takes precedence: patient autonomy or beneficence? If beneficence predominates, should it be aimed toward relieving suffering, prolonging life, or a third option that could include both? Bioethics deals with problems that are neither black nor white—only gray.[27]

MEDICAL IMPERATIVES AND BIOETHICAL DILEMMAS

Clinicians have their own ethical values, as do professional organizations and health care institutions. Conscience clauses permit clinicians to "opt out" when they believe that they have a moral

www.ketabpezeshki.com 66485457-66963820

Table 3 Relative Differences between Emergency Practice and Primary Care Practice

ED SETTING	PRIMARY CARE SETTING
Patient often is brought in by ambulance, police, or family.	Patient chooses to enter medical care system.
Patient does not choose physician.	Patient chooses physician.
ED personnel should gain patient's trust.	Physicians and nurses already enjoy patient's confidence and trust.
ED personnel do not know patient, family, values.	Physicians and nurses often already know patient, family, values.
Patient experiences an acute change in health status.	Patient has chronic medical problems.
Anxiety, pain, alcohol, and altered mental status are common.	Anxiety, pain, alcohol, and altered mental status are less common.
Decisions are made quickly.	There is usually time for reflection and deliberation.
Physician makes decisions independently.	Physician has greater opportunity to consult with patient, family, other physicians, ethics committees, lawyers, courts, ethicists.
Physician represents institution and medical staff.	Physician represents self or medical group.
Work environment is open and less controlled.	Work environment is private and controlled.
ED personnel frequently have a stressful work schedule.	Work schedule often is set or canceled by physician.

Modified from Sanders AB: Unique aspects of ethics in emergency medicine. In Iserson KV, Sanders AB, Mathieu D (eds): Ethics in Emergency Medicine, 2nd ed. Tucson, Ariz, Galen Press, 1995.
ED, emergency department.

Box 3 A Rapid Approach to Ethical Problems in the Emergency Department

Is this a type of ethical problem for which you have already worked out a rule, or it is at least similar enough that the rule could reasonably be extended to cover it?

- YES
  Follow the rule.
- NO
  Is there an option that will buy you time for deliberation without excessive risk to the patient?
  - YES
    Take that option.
  - NO
    1. Apply Impartiality Test.
    2. Apply Universalizability Test
    3. Apply Interpersonal Justifiability Test.

Modified from Iserson KV: An approach to ethical problems in emergency medicine. In Iserson KV, Sanders AB, Mathieu D (eds): Ethics in Emergency Medicine, 2nd ed. Tucson, Ariz, Galen Press, 1995.

conflict with professionally, institutionally, or legally required actions. These conflicts, which may have a religious, philosophical, or practical basis, pose a barrier to use of the normal ethical decision-making algorithm. When such conflicts exist, it is morally and legally acceptable, within certain constraints, for the physician to follow a course of action based on his or her own value system. The constraint generally requires that timely and adequate medical care be provided for the patient, which may be particularly difficult to achieve in EM. When conflicts over values exist, however, it is essential for the practitioner to recognize the patient's identity, dignity, and autonomy to avoid the error of blindly imposing personal values on another.[9]

Professional Value Conflicts

The imperative to save lives causes the most conflict between EPs and other clinicians. EPs recognize that some of the intubations and resuscitations they perform will be unwanted by patients or surrogates. Nearly all EPs have on occasion been berated by an irate intensivist or private practitioner for resuscitating a patient "who should not have been resuscitated." Nevertheless, the lifesaving imperative begins when the ambulance is called.

One classic dilemma is that posed by the exsanguinating adult patient, awake and still with medical decision-making capacity, who explicitly states a refusal to accept any blood or blood products based on religious beliefs. The physician, with a professional duty and moral commitment to preserve life, does not agree with the patient's decision. Yet society (through the benchmark of court decisions) has repeatedly sided with the patient. In this case the patient's autonomy and right to practice his or her religion are recognized as the over-riding values. The case becomes less clear when the patient does not have decision-making capacity, is a minor, or appears to be under external pressure to make a life-threatening decision.

Other examples of ethical problems and conflicts in emergency medical care include uncertainty about resuscitation efforts, especially when patients and families may not want such efforts; teaching, particularly in critical situations or using procedures performed on the newly deceased; emergency medical system (EMS) control, when administrative rules and good patient care conflict; helping others when one's own life may be placed at risk; and patient access, such as limited financial and personnel resources in the face of obvious patient need. Even if these problems do not fit into the classic form of a dilemma, they may be recognized as bioethical problems because they require the clinician to make a choice between two (or more) accepted values.

RAPID ETHICAL DECISION-MAKING MODEL

The rapid ethical decision-making method of ethical case analysis, described in Box 3, is designed as a way of avoiding an ethically incorrect course of action for the EP in need of a fast answer to an ethical dilemma. A decision based on a known precedent—the first step—is the most productive way to use this method. However, such decision-making requires advance planning, in-depth reading, and thought regarding ethical problems. Just as with the indications for any emergency procedure, EPs should at the very least be prepared with a course of action for the most common ethical dilemmas they may face in the ED.

Even the prepared clinician, however, can encounter cases without relevant known precedents. With no precedent to rely on and no way to "buy time," the practitioner should select a possible course of action and test it for ethical validity. In such instances, three tests—the impartiality test, the universalizability test, and the interpersonal justifiability test—can be used. The *impartiality test* asks whether the practitioner would accept this action if he or

www.ketabpezeshki.com 66485457-66963820

Box 4 Guidelines for Development of an Out-of-Hospital Advance Directive Policy

Policy Scope

To ensure maximum coherence and compliance, a comprehensive out-of-hospital DNAR policy should be endorsed by the widest possible jurisdiction, comprising local, regional, and state agencies and the medical community, including the EMS governing body. Whenever feasible, legislative support for such a policy should be sought.

Policy Guidelines

1. Note the established fact that current basic and advanced life support interventions may not be appropriate or beneficial in certain clinical settings.
   - Develop a means to educate the public about the appropriate use of 911 after expected deaths.
   - Establish the fact that comfort care and palliative care are affirmative actions for patients with DNAR orders. These appropriate interventions, including hospice and respite care, do not require EMS activation and often can be arranged by calling the patient's physician in anticipation of death.
   - Develop a means to educate health care workers on topics of advance directives, including information on local out-of-hospital DNARs, community hospice alternatives, and bereavement services.
2. Establish consensus on the ideal identification device for DNAR directives to ensure continuity of care across settings.
3. Reiterate that initial resuscitative attempts usually are indicated when the patient's wishes are not known.
4. Define the conditions under which an out-of-hospital DNAR order can be considered, including its use in long-term care settings and in the emergency department.
5. Define which patients have the decisional capacity to agree to a DNAR order and whether surrogates can sign such orders.
6. Establish a mechanism to determine the precedence of various directives, including living will, durable power of attorney for health care, and out-of-hospital advance directive (i.e., DNAR order).
7. Develop a statutory prioritized list of surrogates to be used when there are no advance directives and the patient's decisional capacity is impaired.
8. Consider language acknowledging the growing home hospice movement as it concerns children, and incorporate provisions for document use in minors.
9. Establish that the decision not to attempt resuscitation must be an informed decision made by the patient or the surrogate.
10. Identify the information that should be contained in the DNAR order and the authority that will be responsible for development of such a mechanism.
11. Identify the clinical procedures that are to be provided and those withheld in the adherence to the DNAR order, or specify the authority that will verify adherence.
12. Define the exact manner in which the DNAR order is to be followed, including the role of online medical direction. Each system should ensure that a communication path to access online medical direction is immediately available, when necessary.
13. Establish legal immunity provisions for those who implement DNAR orders in good faith.
14. Establish data collection and protocol evaluation to perform periodic operational assessments.
15. Identify permissible exceptions to compliance with DNAR out-of-hospital directives. For example:
    - The patient is able to revoke a written directive at any time.
    - The EMS personnel can cancel the out-of-hospital DNAR order if there are doubts about the document's validity.

Adapted from Schears RM, Marco CA, Iserson KV: "Do-not-attempt-resuscitation" (DNAR) policy in the out-of-hospital setting. Ann Emerg Med 44:68, 2004.
DNAR, do-not-attempt-resuscitation; *EMS,* emergency medical services.

she were in the patient's place. In essence, this is a form of the golden rule. The *universalizability test* asks whether the practitioner would be comfortable having all practitioners perform this action in all relevantly similar circumstances. This involves generalizing the action to all colleagues and then asking whether a rule for the contemplated behavior is reasonable. The *interpersonal justifiability test* asks whether the practitioner can supply good reasons to others for the action. Will peers, superiors, or the public be satisfied with the answers? If the answer to the question posed in each of the three tests is affirmative, the practitioner has identified a reasonable probability that the proposed action falls within the scope of ethically acceptable actions.[25]

ADVANCE DIRECTIVES

The ethical principal of patient autonomy is the foundation for a range of documents that outline what care a patient wishes to receive if he or she is no longer able or competent to directly communicate those values. The term *advance directive* describes several types of legal and quasi-legal documents. Advance directives usually are written to avoid prolongation of an inevitable, often painful or nonsentient dying process. However, they can also be used to instruct surrogates and the patient's medical team to "do everything," whenever possible. Advance directives include the living will, durable power of attorney for health care, prehospital advance directive (Box 4), and mental health advance directive. Do-not-attempt-resuscitation (DNAR), do-not-hospitalize, and out-of-hospital DNAR orders are not considered to be advance directives but rather are physician orders because they are not patient or surrogate initiated. All play a role in EM.[28,29]

Advance directives, DNAR orders, and other end-of-life considerations are discussed in the End of Life chapter.

CONSENT, DECISION-MAKING CAPACITY, AND SURROGATE DECISION MAKERS

Respect for patients, the basis for patient autonomy, requires that adults consent before undergoing medical interventions. To give consent, they must retain decision-making capacity. When patients cannot make their own health care decisions, others need to make such decisions for them. In such situations, three questions arise: What does "consent" mean in the ED? How can clinicians determine when patients lack such capability? Who then makes the decision?

Consent

Patients can provide three forms of consent: presumed, implied, and informed. Many patients may provide all three types of consent at different times during a single ED visit. Because clinicians use all three types of consent in EDs, and all are ethically and legally valid, clarifying the differences between them is in order.[30]

The concept of *presumed consent* most commonly applies when patients are informed of what will occur and they do not refuse

www.ketabpezeshki.com 66485457-66963820

treatment. They allow themselves to be rolled on a gurney to the radiology suite to have a urethral catheter placed, and they remain still while being sutured. The more dramatic ED scenario involving presumed consent is the arrival of moribund patients with grave, often unstable conditions for which a reasonable person would be expected to want treatment. In those cases, clinicians "presume" that rational patients would want treatment. A question that must be raised, however, is whether those patients would want interventions even in the absence of a reasonable chance for meaningful (from the patient's standpoint) survival. Futility often is discussed from the clinician's perspective (see Futility later in the chapter); whether patients would give consent in these circumstances raises the question from the more valid patient's perspective.[30]

Implied consent is operative when patients actively cooperate with the procedure, such as when they extend the arm for phlebotomy or lift the blouse so that leads can be placed for electrocardiography.[30] Working under presumed or implied consent does not signify absence of patients' concern about the procedure or its complications. Rather, patients may (1) believe they know enough about the procedure to permit it or to cooperate with it without further questioning, (2) be in a condition (e.g., unconscious) in which they are unable to communicate, or (3) feel too afraid (e.g., of the clinician or hospital authority) or uncomfortable (e.g., because of a language barrier) to ask.[30]

Informed consent assumes that a patient who has decision-making capacity (e.g., has been given all pertinent facts about the risks and benefits of a particular procedure) understands the risks and benefits and voluntarily agrees to undergo the procedure.[30] Even if a patient with decisional capacity does not ask about a complex or potentially dangerous procedure, the clinician is obligated to provide information about the associated risks and benefits, unless the patient specifically asks not to be told. In those cases, the patient should be asked if he or she would like a relative or friend present in the ED to be told. This person need not be the patient's surrogate but may later help explain what occurred to the patient.[30]

Informed consent relates to both law and ethics. Respect for persons is the requirement's ethical bulwark; statute and common law provide the legal rationale. Physicians have a professional and moral obligation to provide their patients with the information necessary to make informed decisions. Communicating honestly with patients so that they may participate in decision-making is a recent rather than historical imperative. On the basis of a respect for patients, this cooperative physician-patient relationship reverses the paternalism that, since Hippocratic times, has guided physician interactions with patients.[30,31]

Virtually all states, either in statute or by common law, now require physicians to inform patients about treatment choices and the associated risks and benefits. The legal standard for the information provided is either the community standard (also known as the professional community standard or the reasonable physician standard) or the materiality standard (also known as the reasonable or prudent or subjective patient standard). The former asks: What would a prudent physician in the same community, with the same background, training, and experience, have disclosed to a patient in the same or similar situation? The latter asks: What would a reasonable patient in the same or similar situation need to know to make an appropriate decision?[30,31]

Note that great variability exists in the legal requirements. For example, although most of the nation's EDs require informed consent for many regional anesthetic blocks, closed fracture reductions, abscess incision and drainage, lumbar punctures ("spinal taps"), injection of radiocontrast agents and radionuclides for radiography, and nonemergency thoracostomy (chest tube placement), Texas statutes eliminate any requirement to disclose the specific risks or hazards before these procedures are performed.[30,32]

Decision-Making Capacity

Many ethical dilemmas in emergency medical care dissolve on ascertaining the patient's decision-making capacity, often linked with consent to (or, more commonly, refusal of) a medical procedure. A basic canon of both ethics and law, as stated by Justice Benjamin Cardozo, is that "[e]very human being of adult years and sound mind has a right to determine what shall be done with his own body."[33] These situations can often be clarified by an appreciation of what is meant by decision-making capacity and how it relates to consent.

EPs must be prepared to decide quickly whether patients lack decision-making capacity. Although a lack of capacity is obvious in the unconscious or delirious patient, it often is less apparent when the patient remains verbal and at least somewhat coherent. Because such decisions in emergency situations are often time sensitive, unlike in other medical venues, bioethics consultations may not be readily available.

In clinical practice, the word *competence* is often used to mean *capacity*. *Competence* is a legal term and can be determined only by the court. *Capacity* refers to a patient's ability to make decisions about accepting health care recommendations. Capacity is always decision relative rather than global. Although an inebriated person can have the capacity to refuse to have a small laceration sutured, especially if there is evidence of prior refusal without remorse, the same person may not have the capacity to agree to an elective operation or to refuse to have an emergent lifesaving procedure or operation. To have adequate decision-making capacity in any particular circumstance, the person must understand the options, the consequences of acting on those options, and the costs and benefits of consequences in relation to a relatively stable framework of personal values and priorities[34,35] (Box 5). Disagreement with the physician's recommendation is not in itself grounds for determination that the patient is incapable of making a decision. In fact, even refusal of lifesaving medical care may not prove the person incapable of making valid decisions if it is done on the basis of firmly held religious beliefs, as in the case of a Jehovah's Witness patient who refuses a blood transfusion.

Surrogates

If patients lack capacity to participate in some decisions about their care, surrogate decision makers should then become involved. In most locales, the patient's advance directive may designate surrogates, or such persons or agencies may be detailed in institutional policy or law. Surrogates often include spouses, adult children, parents (of adults), and others, including the attending physician. On occasion, bioethics committees or the courts will need to intervene to help determine the decision maker.

Children represent a special case. Persons younger than the age of majority (or unemancipated) are usually deemed incapable of

Box 5 Components of Decision-Making Capacity

- Knowledge of the options
- Awareness of consequences of each option
- Appreciation of personal costs and benefits of options in relation to relatively stable values and preferences*

Modified from Buchanan AE: The question of competence. In Iserson KV, Sanders AB, Mathieu D (eds): Ethics in Emergency Medicine, 2nd ed. Tucson, Ariz, Galen Press, 1995.

*As part of the assessment for capacity, the patient should be asked about why he or she made a specific choice.

www.ketabpezeshki.com 66485457-66963820

making independent medical decisions, although they are often asked to give their assent to the decision, allowing them to "buy in" to their medical treatment plan. In many cases, in determining whether a child has decision-making capacity, the same rules as those that apply to adult capacity are used. The more serious the consequences, the more the capacity to understand the options, consequences, and values involved is required of children to make a decision.[9]

In the relatively rare case in which a patient has a court-appointed guardian for health care decisions, the guardian's decisions supersede those of both the patient and any other surrogates. Even if a parent is present, it is not always clear that the adult is acting in the best interest of the child. In such cases, child protective services may need to become involved. Disagreements between parents may, in extreme cases, require the involvement of bioethics committees or the courts.

Family

Traditionally, and usually in practice, the family, in particular the spouse, acts as a surrogate decision maker when the patient does not have the capacity to make medical decisions. Yet even when there is a strong family tie, emotional or fiscal costs may sway the surrogate decision maker from certain courses of action the patient would wish taken.

Surrogates make decisions on the basis of two distinct patterns: substituted judgment and best interests. *Substituted judgment* is used when there is an assumption that the surrogate knows enough about the patient's values to make a decision similar to that which the patient would make. It is not clear that anyone knows that much about a person to make decisions in every situation.[36,37] Surrogates use the *best interest* standard when they do not know what the patient would want done in a particular situation, but as in the case of Karen Ann Quinlan, in which life-prolonging measures were eventually discontinued against the wishes of some family members, they can use earlier statements and behavior to document the patient's values and then make a decision.[38] Some states may require explicit written directives for surrogates to follow.[39,40] The best interest standard also applies in cases in which the patient has never had adequate decision-making capacity, as in the Saikewicz case, in which a court-appointed guardian for an elder who lacked decision-making capacity decided against treatment for leukemia after consultation with medical specialists because of a low likelihood of success in the face of debilitating side effects of treatment.[41] Unless there is already a court-appointed guardian, these situations often end up in court.

Surrogate Lists

If a patient lacks decision-making capacity and has no advance directive, many states stipulate that another person may automatically become the person's surrogate. In practice, this almost always means that the patient's spouse may act in that capacity. Some states now have a statutory surrogate list to simplify the process. The most extensive of such lists, which has worked well for nearly two decades, specifies surrogates in the following order: spouse (not divorced or legally separated), a majority of the adult children who can be reasonably contacted, parents (of an adult), domestic partner, sibling, close friend, and attending physician in consultation with a bioethics committee.[42]

Bioethics Committees and Consultants

Multidisciplinary committees have been developed in most large hospitals to consult on cases with bioethical dilemmas and may also participate in surrogate decision-making.[42] These committees usually have three main functions. First, they coordinate education on bioethical issues involving clinical care for the committee members, hospital physicians and staff, patients, families, and the local community. Second, they help institute mandatory or suggested policies or guidelines for health care professionals regarding decision-making processes in problematic cases and resource allocation. Third, they consult prospectively and retrospectively on clinical cases and offer advice and conclusions to those directly involved, most often concerning the treatment or nontreatment of patients who lack decision-making capacity. Ethics committees usually do not act as the primary decision makers. Rather, the members serve as consultants, providing information, advising, and supporting the primary decision-making role of the patient-family-physician triad. A common consultation relates to urgent decisions about withholding, withdrawing, or continuing life-sustaining medical care. A large part of ethics committee work consists of clarifying the facts and fostering communication.[43] In 1995, the Joint Commission (formerly the Joint Commission for the Accreditation of Healthcare Organizations [JCAHO]) began requiring hospitals to ensure that ethics committees perform their functions.[44]

Physicians

In the past, physicians made unilateral decisions for their patients, regardless of whether the patients had the capacity to decide for themselves. This still occurs, of course, especially for the acute illnesses and unexpected injuries seen in EDs. There is a tendency for physicians to determine that a patient does not have the capacity to make medical decisions simply because the patient disagrees with the clinician. If the patient's decision-making capacity is questioned in the ED, the clinician is often forced to make a decision without assistance. But when it is possible to buy time, clinicians should consult with colleagues and, if possible, the hospital's bioethics committee (see Box 3). When making unilateral decisions, physicians should recognize that they are not omniscient. Prognoses are often incorrect and medical knowledge is finite.

Courts

The courts often act as the final adjudicators of disagreements over medical care. They appoint legal guardians and, in a few select cases, set precedent that is followed as health law. The courts, however, usually are neither expeditious nor necessarily cognizant of bioethical principles. They are instructed only to follow the societal values codified in the law. Many courts have suggested that whenever possible, health care decisions should remain at the bedside rather than in legal chambers.[38-40]

RESUSCITATION ETHICS

The most time dependent of all activities, and arguably the best training periods in the ED, occur during resuscitations. The patients who require this care have implicitly been guaranteed that all appropriate medical knowledge and skill will be brought to bear in the attempt to save their lives. This implied promise leads to a dilemma. If the most proficient ED professional always leads the resuscitations and performs procedures, the patient will receive the maximum beneficence, as well as nonmaleficence, as expected. Yet restricting ED practice in this manner also deprives future patients of trained clinicians who could bestow the same beneficence.

This controversy has raged for many years. The appropriate balance seems to be that training in EDs can ethically proceed, as it does in other areas of medicine, if safeguards are provided in the form of on-site supervision by experienced clinicians to ascertain that the patients receive the best possible and most

www.ketabpezeshki.com 66485457-66963820

appropriate care. It also has been suggested that medical students and residents be certified for cognitive and procedural skills in a manner similar to that of other hospital physicians. This certification would enable faculty to know when trainees are capable of performing resuscitations, as well as other medical procedures, on their own.[45]

Rarely discussed, but a common practice in some teaching hospitals, has been the custom of allowing trainees with little skill or knowledge to learn and to practice procedures on those undergoing resuscitation only when a patient is deemed "unsalvageable."[46] This practice does a disservice to the patient because prolongation of resuscitative attempts solely for this purpose may lead to a clinical state that prolongs dying. It also harms the family and society by making them pay for unnecessary procedures. (It may actually be less problematic to practice and to teach once a patient is dead because the patient cannot be harmed and the family does not pay for these activities. See Postmortem Teaching later in the chapter.)

Futility

EPs, nurses, and EMS personnel may, in some circumstances, believe that further medical interventions are "futile." Yet only three situations meet the most commonly accepted definition.[47] The first such situation, which clinicians can identify in only a limited set of circumstances, is that in which the intervention is effective in less than 1% of identical cases, based on the medical literature. ED thoracotomy for blunt trauma is a well-documented example. Another common scenario with very low survival rates is that of the out-of-hospital cardiac arrest, either unwitnessed or in a patient who arrives from a long-term care facility.[48] Individual clinicians should not rely on their own experiences to make such decisions, however, because they often are skewed owing to selective memory, limited numbers of similar cases, and other biases.

The second futile situation is physiologic futility, in which known anatomic or biochemical abnormalities will not permit successful medical interventions. Examples of such abnormalities generally accepted by emergency medical systems as reasons not to intervene or to provide transport to hospitals are rigor mortis (muscle contraction after death), algor mortis (lowering of body temperature after death), burns so severe that the victim is beyond recognition, and injuries incompatible with life (e.g., decapitation). These along with prolonged normothermic resuscitative attempts without success or prolonged "down time" with an isoelectric electrocardiogram and pulseless electrical activity are the criteria often used to help determine whether EMS personnel can pronounce death on the scene. In these instances, EMS need not expend valuable resources in a futile resuscitative effort.

The third situation is that in which the proposed intervention will not achieve the patient's goals for medical therapy in accordance with the patient's values. Recognizing this instance, the American College of Emergency Physicians asserts, "Physicians are under no ethical obligation to render treatments that they judge have no realistic likelihood of medical benefit to the patient."[49] Because this course of action is based on knowing the patient's values related to medical treatment, it is necessary to have talked with the patient in advance (rare in the ED setting), to have received surrogate-supplied information or decisions, or to have access to the medical record. The danger is that differences in values between caregivers and patients may lead to overtreatment or undertreatment. Communication, if necessary with use of a third party, may help resolve these issues.

The futility concept should never be used to deny care to dying patients. Even terminal patients experience medical emergencies that require intervention. The goal is to ease pain and suffering. How that is accomplished depends on the patient, the medical condition causing discomfort, and the patient's value system.

Withholding versus Withdrawal of Treatments

In EM, a significant difference *rightfully* exists between the withholding and the withdrawal of life-sustaining medical treatment. The justification for this distinction stems, in part, from the nature of the practice of EM and the unique manner in which EPs apply many ethical principles. Because EPs often lack vital information about their patients' identities, medical conditions, and goals for medical treatment, withholding of emergency medical treatment is more problematic than is later withdrawal of unwanted or useless interventions. Owing to the nature of EM, in both out-of-hospital and ED settings, higher standards are required to withhold medical treatment than to withdraw it.[50]

Physicians should begin or continue resuscitation of those patients who arrive at the ED without sufficient evidence to determine that the resuscitation effort will be unsuccessful. The only reason to *withhold* cardiopulmonary resuscitation (CPR) is the availability of clear evidence, such as a standard advance directive, that the patient did not wish to have this done or of clinical evidence that further efforts would be futile.[51] Without such information, the presumption must be to intervene.

Once the EP obtains information confirming a patient's wish not to be resuscitated or indicating a medical condition not amenable to resuscitation, resuscitative efforts and other medical treatment may appropriately be withdrawn. This information may be obtained from an advance directive, a patient surrogate, recent documentation in the medical chart, or EMS communication detailing the failed results of the ongoing resuscitative effort. With rare exceptions, such as after failed suicide attempts, resuscitative efforts should be withdrawn when information is provided either that the patient did not want such efforts or that the patient's medical condition precludes success.[52,53]

Many factors influence the potential success of resuscitative efforts, including time to CPR, time to defibrillation, presence of comorbid illness, pre-arrest clinical status, and initial arrest rhythm. No combination of these factors, however, clearly predicts the outcome.[54,55] The most important factor associated with poor outcomes is the *duration* of unsuccessful resuscitative efforts.

The possibility of a successful resuscitation becomes clearer as time progresses; a patient's chance of being discharged from the hospital alive and neurologically intact diminishes if spontaneous circulation does not return after 10 minutes of intensive resuscitative efforts.[56-59] Malpractice concerns have led some physicians to prolong all resuscitation attempts until they reach the point at which there have been no survivors.[54] In reality, cardiac resuscitation with properly executed advanced cardiac life support interventions and documented asystole should not last more than 30 minutes and usually should end much sooner, except in unusual circumstances, such as with pre-arrest hypothermia, after some drug-induced events, after lightning or electrical shocks, or in infants or children with refractory ventricular fibrillation or tachycardia.[54,59-64] Without these mitigating factors, prolonged resuscitative efforts are unlikely to be successful.[30]

Three special situations should be noted:

1. Cardiac arrest from blunt trauma is nearly uniformly fatal, so little benefit derives from performing chest compressions for any extended period after the airway is secured.[65]
2. When health care resources are limited, such as during disasters, available resources, such as time, personnel, and equipment, should be devoted to treatment of those patients with the greatest chance of benefiting. This principle may lead to withholding or more rapid discontinuation of resuscitative efforts than is standard in normal practice.
3. It is unethical to prolong resuscitative efforts to practice or to teach procedures or to complete research protocols.[53]

www.ketabpezeshki.com 66485457-66963820

Palliative Care

Although lifesaving medical interventions may not be appropriate in all cases, EPs, whenever possible, should provide patients with palliative care. Terminally ill and fatally injured patients have the right to receive state-of-the-art palliative care.[66] Palliation often includes analgesics and may include diuretics, sedation, oxygen, paracentesis or thoracentesis, and other medications or procedures to alleviate suffering. Medical personnel should never withdraw or withhold care; only treatment should be withheld when it is appropriate. Although medical practitioners, surrogate decision makers, and sometimes patients find it emotionally easier to forgo new interventions than to withdraw ongoing treatment, no orders, policies, or directives should ever prevent EPs from alleviating discomfort.[1]

The purpose of palliative interventions is not to prolong the dying process but rather, when death is inevitable, to make it as comfortable as possible for the patient. As patient advocates, EPs may need to "push" to have the patient admitted to a hospital, hospice, or nursing home or to get ancillary personnel (e.g., social workers, home health nurses) to intervene for the patient.[1]

Notifying Survivors

Death, especially when it is sudden and unexpected, shocks and devastates family and friends. For them, it is a life-changing event, with every nuance burned into their memories. Moreover, although they may not consciously acknowledge it, such losses may deeply affect ED personnel, despite their almost constant exposure to life's disasters. This makes death notifications and dealing with the survivors both vitally important and extremely difficult. EPs, who deal with sudden death on a daily basis, are in a position to gain considerable knowledge of and to hone their skills in how to care for the survivors, their newest patients.[67]

Even though notification of survivors of a sudden, unexpected death is one of the most difficult parts of the job for EPs, they and other professionals whose job includes delivery of news about sudden, unexpected deaths are rarely taught the skills necessary to perform this task. Notification of survivors is emotionally draining; 70% of EPs find death notifications to be personally difficult. Perhaps this is because only half received any type of death-notification education in medical school, and only one third received any such training during residency.[68]

On occasion, physicians give the job of death notification to residents, medical students, or nurses. Although all three groups should be present to learn the techniques involved, to have an opportunity to hear what is said, and to observe an attending physician showing sensitivity, they should not be left to do death notifications on their own. That is a form of professional abandonment and, in a teaching hospital, the worst form of student abuse.[69]

Viewing of Resuscitations

Traditionally, survivors have not been permitted to view resuscitation attempts.[67] That attitude, however, is gradually giving way to a more enlightened view based, in part, on recognition that families gain enormous psychosocial benefits from being present and that they are also patients in need of appropriate support.

The argument against allowing survivor onlookers has been that resuscitations often involve large teams, unclear communications, and team leaders who are unwilling or unable to make firm, timely, and rational decisions.[70] Having family members present, the argument goes, introduces the possibility of an onlooker's fainting or otherwise becoming another patient. Survivors frequently misinterpret the team's discussions or actions, and team members may feel uncomfortable having family members judging their actions.

Yet studies in both the United States and Britain have shown that nearly all survivors who witnessed ED resuscitative efforts found the experience helpful. Seventy-six percent of survivors responded that their grieving was facilitated by having witnessed the resuscitation, and 64% thought that their presence was helpful to their dying family member.[71] Psychological tests of survivors who witness resuscitation attempts, performed at 3 and 9 months after the event, showed that this group experienced fewer episodes of "intrusive imagery," such as flashbacks of the events leading to the death, compared with survivors not present at the resuscitation (relatives in the control group). They also had lower levels of anxiety, depression, post-traumatic avoidance behavior, and grief.[72]

The American Heart Association now endorses giving family members the opportunity to be present so long as the patient has not previously objected. This position stems from the benefit families can derive from their presence during resuscitation attempts, the lack of harmful effects on them from viewing these resuscitations, and their quasi-right to be there based on the nature of their relationship to the patient.[53,73]

The presence of these survivors does not hinder the resuscitative efforts and often leads to quieter, more effective team efforts. Experience has shown that survivors who witness ED resuscitative attempts never question whether the team "tried hard enough," do not ask whether the person is *really* dead, and spend less time in the ED trying to come to terms with the death. In addition, survivors may actually thank the ED team for their efforts, a situation that rarely occurs under other circumstances, and the ED staff never has to "notify" survivors of the death.

The general procedure is as follows:

Ask survivors if they want to view resuscitative efforts.

If they do, give them a quick briefing about what they will see, and have a knowledgeable staff member, usually a chaplain, social worker, or ED nurse who can answer their questions, accompany them.

Provide a chair for elders and allow survivors to leave and to reenter as they wish.

Staff should attempt to cover as much of the patient as is compatible with effective resuscitative efforts.

Team members should be advised that family is in the room.

The survivors should be encouraged to talk to and to touch the patient.

Decisions to pronounce the patient dead, although often discussed with the family, generally are communicated in the format of advising them that "we must stop now." They should never be asked whether to stop the resuscitative effort; this is a medical decision.

If the family is present when it is clear that resuscitative efforts should cease, the situation should be explained to the family before supportive measures are discontinued. This provides them with a chance to "say good-bye" before death is pronounced. Dedicated pediatric EDs and pediatric resuscitation units in general EDs have adopted these procedures more often than others.

Postmortem Teaching

A less commonly discussed aspect of EM education programs is the use of recently deceased patients to teach or to practice emergency procedural techniques, such as intubations and central line placement. Although whether this practice is ethical is a matter of controversy, a reasonable argument might be that if medical treatment could not save the patient, then the EP's responsibility is to hone skills for the next patient in need of expertise in resuscitative techniques. This is not to condone the desecration of a body. Rather, it suggests that because clinicians learned the techniques

www.ketabpezeshki.com 66485457-66963820

used during the attempted resuscitation on other dead or living patients, this (now dead) patient owes the next patient the same courtesy. No one would advocate practicing of unneeded procedures on living patients, and many people argue against use of experimental animals. The religious or ethical beliefs of some ED personnel may make practicing or teaching of these procedures in such circumstances problematic.[74-77]

Resuscitation Research

Physicians in a new and advancing specialty have an obligation to advance the knowledge base from which they practice. This can be done only through research, a significant component of which should necessarily be clinically based. In the United States, federally mandated institutional review boards (IRBs) must approve any research involving human subjects, including research in EDs and, possibly, in prehospital care.[78] Increasingly, research ethics committees are being used to approve human subject research throughout the world. The IRBs try to guarantee that patients who are asked to participate in research review and sign an adequate informed consent document. Yet, even if the patient is conscious, it is unclear whether truly free and informed consent can be given in the midst of a medical emergency.[79] In both trauma and cardiac resuscitation research, informed consent is, of course, not feasible. It is usually difficult if not impossible to obtain retrospective patient or, if appropriate, prospective surrogate consent. So as not to deny critically ill and injured patients the opportunity to participate in possibly beneficial research trials, the U.S. Food and Drug Administration and the Department of Health and Human Services issued regulations, which became effective in 1996, that allow "emergency research" without informed consent. These regulations contain extensive patient safeguards, including community consultation, public disclosure, and intensive oversight.[80]

The ethical and legal basis for these regulations is presumed consent: if the research is not harmful, and especially if it is potentially helpful, most "reasonable" patients would acquiesce to the research, given the basic values of good and evil (see Box 1).[81-83] As routinely occurs in EM practice, persons suffering unexpected adverse events with a high probability of rapid death or serious morbidity generally demand that the physician deliver acute care interventions—immediately and without discourse. If there is a chance that the patient could benefit from a therapeutic course of action in such circumstances, most people would demand that it be used. Similar logic applies with acute care research, especially when accepted or standard therapy is futile and possibly when the investigators believe that equipoise (therapeutic equality) exists between the two tested forms of therapy. Protection for the patient in these cases rests with IRBs, which, among other considerations, must guard against the possibility of organ-specific success but failure to benefit the entire person, such as producing a patient in a persistent vegetative state after "successful" CPR.

Beyond IRB authorization for research is a moral responsibility for the individual researcher to ensure that the research protocol and its execution are ethical. This responsibility extends to the journals in which the research is published.[84] In the main, EM has an excellent record of ethical research.[85]

PUBLIC POLICY AND BIOETHICS

Restricted Access to Emergency Medical Care

Society has acknowledged its moral obligation to ensure that everyone has reasonable access to adequate health care.[86] People's need for health care is unequally distributed and highly unpredictable. Few could afford this care if left to their own devices, so mechanisms are in place to share the risk.[87]

The ethical dilemma for EPs comes in basically two forms: one precipitated by the institution in which the ED is housed and one by outside third-party payers. Some institutions have refused care to patients coming to the ED, sending some away for clinic appointments at a later time.[88] Institutions also have pressured EPs to limit treatment, ancillary tests, or hospital admission for patients without the ability to pay. Although such limitation may seem patently immoral, another question should be asked: Is there a moral obligation to the community to keep the health care institution financially viable? Hospitals have closed their doors because of financial losses, and many hospitals, especially in inner-city areas, are on the verge of bankruptcy.

Some prepaid health maintenance organizations (HMOs) use "gatekeepers" to keep patients in need of emergency medical care away from immediate assistance at institutions other than the HMO parent hospital. Moreover, the HMO's income may depend on *not* hospitalizing patients, *not* using ancillary tests, and *not* permitting ED visits. Nevertheless, it is prudent and ethical for EPs to err on the side of providing for the patient's needs.

Morality of Triage Decisions

In the aftermath of a massive natural or man-made disaster, triage officers face difficult decisions about who will receive scarce lifesaving treatment and who will be left to die without treatment. Even in "routine" ED triage, decisions about who should receive treatment priority and who can wait for treatment may, at least occasionally, have life-and-death consequences.[89,90]

Triage provides a method to distribute health care resources when patient needs exceed available resources. Triage operates along a continuum of decreasing resources, social order, and the resource-to-patient ratio. Arrival patterns, triage methods, and the applicable ethical basis for triage vary along this continuum.

Most triage systems are designed to serve the values of human life, human health, efficient use of resources, and fairness. Nevertheless, because of the variety of specific triage settings and goals, no single "correct" way to perform or to justify triage can be identified. Routine triage in the relatively resource-rich setting of the modern hospital ED, for example, focuses appropriately on maximizing benefits for each individual patient, giving treatment priority to patients whose needs are most urgent. In triage after a massive disaster, when not all individual needs for lifesaving care can be met, the focus may shift from an individual to a group perspective, and triage officers may seek to save as many lives as possible with the limited resources at their disposal. In special circumstances, such as times of war, military commanders may direct that triage systems devote scarce medical resources to achieve a nonmedical goal, namely, military victory. In situations of complete devastation, the lack of social order and minimal resources may make triage impossible.

Whether the choice of a triage system is justifiable will depend on an evaluation of the specific system itself, its underlying values and principles, and the setting in which it is applied.

Physician Response to Risky Situations

Over the millennia, personal values have dictated whether a physician would remain with his or her patients during extreme or catastrophic circumstances.[91] Physicians, even legends of medicine such as Galen, often fled to save their own lives. In the era of modern epidemics of unknown virulence and etiology, it remains a personal moral decision, especially for EPs who are on the frontline of these medical assaults.

How will physicians respond when a catastrophe involving personal risk strikes? The moral backbone of medical professionals may be tested as health care providers weigh multiple factors to

www.ketabpezeshki.com 66485457-66963820

determine whether to stay and carry out their professional roles or to step back and decrease their personal risk.

With incomplete information, providers may make decisions on the basis of heated emotions and panic rather than an accurate perception of risk. The decision to stay or to leave will ultimately depend on the individual practitioner's risk assessment and value system. Professional ethical statements about expected conduct establish important professional standards and norms, but each practitioner will interpret and apply them on the basis of his or her own situation and values. Recent historical precedent suggests that many physicians and other health care providers will dutifully care for the sick and needy, even at great risk to themselves. Although some EPs have worked in dangerous situations, most have not; nothing in day-to-day EM practice prepares EPs for the great opportunities and challenges that accompany a pandemic. EPs can, however, reflect on their professional and personal responsibilities in crisis situations, and public and private institutions can create plans for effective communication and care when a disaster strikes. If this can be achieved before the next pandemic or disaster that includes personal risk to clinicians, EPs, who are inevitably among those at highest risk, can be encouraged to "stay and fight."

"Proactive Ethics": How Can Emergency Physicians Change the Rules?

In every medical system, practitioners find that they repeatedly face identical ethical dilemmas. The normal outcome is an incomplete and often unsatisfactory solution made by administrators, lawyers, bioethics committees, or others. "Proactive ethics" involves changing the rules under which we operate. Easier done in some settings than in others, the process requires that all "stakeholders," those with a vested interest in an equitable solution, first come to the table and reach a compromise. Such groups often will include physicians, nurses, EMS personnel, lawyers, religious authorities, and representatives of affected groups (e.g., an organization of elders in the case of issues involving the aged). Armed with this agreement or even sample legislation that they can present to politicians, it becomes easier to change laws or administrative rules to address recurrent ethical dilemmas. One such process led to a landmark out-of-hospital advance directive law, which markedly lessened unwanted EMS resuscitation attempts.[42] It also led to an extensive statutory surrogate list and a simplified set of advance directives. Proactive ethics lies in the role of public policy—an arena in which EPs are well suited to play a pivotal role.

References

1. Iserson KV: Ethical considerations in emergency care. *Israeli J Emerg Med* 2004; 4:8.
2. Feinberg J: *Social Philosophy*. Englewood Cliffs, NJ: Prentice-Hall; 1973.
3. Black HC: *Black's Law Dictionary*, 5th ed. St. Paul, Minn: West Publishing; 1979.
4. Hart HLA: *Punishment and Responsibility*. Oxford: Oxford University Press; 1976.
5. Ladd J: Legalism and medical ethics. *J Med Philos* 1979; 4:70.
6. Graber GC: *Basic theories in medical ethics*. In: Monagle JF, Thomasma DC, eds: *Medical Ethics*. Rockville, Md: Aspen; 1995.
7. Landesman BM: *Physician attitudes toward patients*. In: Iserson KV, Sanders AB, Mathieu D, eds: *Ethics in Emergency Medicine*, 2nd ed. Tucson, Ariz: Galen Press; 1995.
8. McCormick RA: Theology and bioethics. *Hastings Cent Rep* 1989; 19:5.
9. Iserson KV: *Ethical principles—emergency medicine*. In: Schears RM, Marco CA, eds: *Ethical Issues in Emergency Medicine. Emerg Med Clin North Am* 2006; 24:513.
10. Barilan YM: Revisiting the problem of Jewish bioethics: The case of terminal care. *Kennedy Inst Ethics J* 2003; 13:141.
11. Gert B: *Morality: A New Justification of the Moral Rules*. Oxford: Oxford University Press; 1988.
12. Kübler-Ross E: *On Death and Dying*. New York: Macmillan; 1969.
13. Novack DH, et al: Physicians' attitudes toward using deception to resolve difficult ethical problems. *JAMA* 1989; 261:2980.
14. Drug-seeker lists are dangerous at best, require tight administrative controls. *ED Manage* 2004; 16:25.
15. Iserson KV: Telemedicine: A proposal for an ethical code. *Camb Q Healthc Ethics* 2000; 9:404.
16. Iserson KV: Film: Exposing the ER. *Ann Emerg Med* 2001; 37:220.
17. Marco CA, Larkin GL: *Filming of Patients in Academic Emergency Departments. Society for Academic Emergency Medicine position statement*. Available at www.saem.org/newsltr/2001/may.june/filmingp.htm. Accessed June 27, 2004.
18. Miles S: *The Hippocratic Oath and the Ethics of Medicine*. New York: Oxford University Press; 2004.
19. *Ethical statements—overview*. In: Iserson KV, Sanders AB, Mathieu D, eds: *Ethics in Emergency Medicine*, 2nd ed. Tucson, Ariz: Galen Press; 1995:429-432.
20. American College of Emergency Physicians Ethics Committee: *Code of Ethics for Emergency Physicians*. Dallas, Tex: ACEP; 2006.
21. Larkin GL, SAEM Ethics Committee: A code of conduct for academic emergency medicine. *Acad Emerg Med* 1999; 6:45.
22. Iserson KV: *The problem patient*. In: Hamilton G, et al, eds: *Emergency Medicine: An Approach to Clinical Problem Solving*. Philadelphia: WB Saunders; 1991.
23. Sanders AB: *Unique aspects of ethics in emergency medicine*. In: Iserson KV, Sanders AB, Mathieu D, eds: *Ethics in Emergency Medicine*, 2nd ed. Tucson, Ariz: Galen Press; 1995.
24. Simon JR, et al: The difficult patient. *Emerg Med Clin North Am* 1999; 17:353.
25. Iserson KV: *An approach to ethical problems in emergency medicine*. In: Iserson KV, Sanders AB, Mathieu D, eds: *Ethics in Emergency Medicine*, 2nd ed. Tucson, Ariz: Galen Press; 1995.
26. Gorovitz S: *Suicide*. In: Iserson KV, Sanders AB, Mathieu D, eds: *Ethics in Emergency Medicine*, 2nd ed. Tucson, Ariz: Galen Press; 1995.
27. Iserson KV, Sanders AB, Mathieu D, eds: *Ethics in Emergency Medicine*, 2nd ed. Tucson, Ariz: Galen Press; 1995.
28. Iserson KV: Getting advance directives to the public: A role for emergency medicine. *Ann Emerg Med* 1991; 20:692.
29. Iserson KV: Federal advance directives legislation: Potential effects on emergency medicine. *J Emerg Med* 1991; 9:67.
30. Iserson KV: The three faces of "yes": Consent for emergency department procedures. *Am J Bioethics* 2007; 7:42-45.
31. Iserson KV: Is informed consent required for the administration of intravenous contrast and similar clinical procedures? *Ann Emerg Med* 2007; 49:231.
32. Texas Administrative Code, Title 25, Part 7, Chapter 601, Rule §601.3: Procedures requiring no disclosure of specific risks and hazards—List B.
33. *Schloendorff v Society of New York Hospital,* 105 NE 92, 93, 1914.
34. Moskop JC: Informed consent in the emergency department. *Emerg Med Clin North Am* 1999; 17:327.
35. Buchanan AE: *The question of competence*. In: Iserson KV, Sanders AB, Mathieu D, eds: *Ethics in Emergency Medicine*, 2nd ed. Tucson, Ariz: Galen Press; 1995.
36. Sonnenblick M, et al: Dissociation between the wishes of terminally ill patients and decisions by their offspring. *J Am Geriatr Soc* 1993; 41:599.
37. Shalowitz DI, Garrett-Mayer E, Wendler D: How should treatment decisions be made for incapacitated patients, and why? *PLoS Med* 2007; 4:e35. Available at http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0040035.
38. *In re Quinlan,* 70 NJ 10, 355 3A2d 647, 1976, cert denied, 429 US 922, 1976.
39. *Cruzan v Director, Missouri Department of Health,* US 58 LW 4916, 1990.
40. *Rasmussen v Fleming,* 154 Ariz 207, 741 P2d 674, 1987.
41. *Superintendent of Belchertown State School v Saikewicz,* 373 Mass 728, 370 NE 2d 417, 1977.
42. Arizona Living Wills and Health Care Directives Act. *Ariz Rev Stat Ann* 2000; ss36-3201.
43. Iserson KV, et al: The future functions of HECs. *Hosp Ethics Committee Forum* 1989; 1:63.
44. Joint Commission for the Accreditation of Healthcare Organizations: *1995 Accreditation Manual for Hospitals*. Chicago: JCAHO; 1994.
45. Iserson KV: The supervision of physicians in training: An educational and ethical dilemma. *Med Teacher* 1988; 10:195.
46. Kaldjian LC, et al: Insertion of femoral-vein catheters for practice by medical house officers during cardiopulmonary resuscitation. *N Engl J Med* 1999; 341:2088.
47. Frankel S, Ebrahim S, Davey Smith G: The limits to demand for health care. *BMJ* 2000; 321:40.

www.ketabpezeshki.com 66485457-66963820

48. Steinberg A: The terminally ill—secular and Jewish ethical aspects. *Isr J Med Sci* 1994; 30:130.
49. Gordon M: Ethical challenges in end-of-life therapies in the elderly. *Drugs Aging* 2002; 19:321.
50. Iserson KV: Withholding and withdrawing medical treatment: An emergency medicine perspective. *Ann Emerg Med* 1996; 28:51.
51. Iserson KV: *Ethics in emergency cardiovascular care*. In: Fields JM, ed: *Textbook of Emergency Cardiovascular Care and CPR*. Philadelphia: Lippincott Williams & Wilkins; 2009.
52. Iserson KV, et al: Willful death and painful decisions: A failed assisted suicide. *Camb Q Healthc Ethics* 1992; 1:147.
53. Iserson KV: *Resuscitation termination*. In: Rosen P, et al, eds: *5-Minute Emergency Medicine Consult*. Philadelphia: Lippincott Williams & Wilkins; 1999:974-975.
54. Cummins RO: *Patients, families, and providers: Ethical aspects of CPR and ECC*. In: Cummins RO, ed: *ACLS: Principles and Practice*. Dallas, Tex: American Heart Association; 2003:17-41.
55. Barzilay Z, Somekh E, Sagy M, Boichis H: Pediatric cardiopulmonary resuscitation outcome. *J Med* 1998; 19:229.
56. Kaye P: Early prediction of individual outcome following cardiopulmonary resuscitation: Systematic review. *Emerg Med J* 2005; 22:700.
57. Weisfeldt ML, Becker LB: Resuscitation after cardiac arrest: A 3-phase time-sensitive model. *JAMA* 2002; 288:3035.
58. Schults SC, et al: Predicting in-hospital mortality during cardiopulmonary resuscitation. *Resuscitation* 1996; 33:13.
59. Reis AG, et al: A prospective investigation into the epidemiology of in-hospital pediatric cardiopulmonary resuscitation using the international Utstein reporting style. *Pediatrics* 2002; 109:200.
60. Graber J, Ummenhofer W, Herion H: Lightning accident with eight victims: Case report and brief review of the literature. *J Trauma* 1996; 40:288.
61. Fontanarosa PB: Electrical shock and lightning strike. *Ann Emerg Med* 1993; 22:378.
62. Lopez-Herce J, et al: Long-term outcome of paediatric cardiorespiratory arrest in Spain. *Resuscitation* 2005; 64:79.
63. Parra DA, et al: Outcome of cardiopulmonary resuscitation in a pediatric cardiac intensive care unit. *Crit Care Med* 2000; 28:3296.
64. Peberdy MA, et al: Cardiopulmonary resuscitation of adults in the hospital: A report of 14720 cardiac arrests from the National Registry of Cardiopulmonary Resuscitation. *Resuscitation* 2003; 58:297.
65. Eckstein M: Termination of resuscitative efforts: Medical futility for the trauma patient. *Curr Opin Crit Care* 2001; 7:450.
66. *Israeli Ministry of Health website [in Hebrew]*. Available at www.health.gov.il/pages/steinberg.htm.
67. Iserson KV: *Bereavement and grief reactions*. In: Wolfson AB, eds: *Harwood-Nuss' Clinical Practice of Emergency Medicine*, 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2009.
68. Schmidt TA, Tolle SW: Emergency physicians' responses to families following patient death. *Ann Emerg Med* 1990; 19:125.
69. Iserson KV: *Grave Words: Notifying Survivors about Sudden, Unexpected Deaths*. Tucson, Ariz: Galen Press; 1999.
70. Doyle CJ, et al: Family participation during resuscitation: An option. *Ann Emerg Med* 1987; 16:673.
71. Iserson KV: Critical leadership. *J Emerg Med* 1986; 4:335.
72. Robinson S, et al: Psychological effect of witnessed resuscitation on bereaved relatives. *Lancet* 1998; 352:614.
73. European Resuscitation Council: Part 2: Ethical aspects of CPR and ECC. *Resuscitation* 2000; 46:17.
74. Iserson KV: *Death to Dust: What Happens to Dead Bodies?* 2nd ed. Tucson, Ariz: Galen Press; 2000.
75. Iserson KV: Postmortem procedures in the emergency department: Using the recently dead to practice and teach. *J Med Ethics* 1993; 19:92.
76. Iserson KV: Law versus life: The ethical imperative to practice and teach using the newly dead emergency department patient. *Ann Emerg Med* 1995; 25:91.
77. Iserson KV: Teaching without harming the living: Performing minimally invasive procedures on the newly dead. *J Health Care Law Policy* 2005; 8:216.
78. U.S. Department of Health and Human Services: *Regulations of the DHHS on the Protection of Human Subjects.* Code 45, CFR 46.
79. Grimm PS, et al: Informed consent in emergency research. *JAMA* 1989; 262:252.
80. 21 CFR 50.24 and 45 CFR 46.10(I).
81. Iserson KV: *Human subjects in trauma research*. In: Iserson KV, Sanders AB, Mathieu D, eds: *Ethics in Emergency Medicine*, 2nd ed. Tucson, Ariz: Galen Press; 1995.
82. Fost NC: *Human subjects in cardiopulmonary resuscitation research*. In: Iserson KV, Sanders AB, Mathieu D, eds: *Ethics in Emergency Medicine*, 2nd ed. Tucson, Ariz: Galen Press; 1995.
83. Spivey WH, et al: Informed consent for biomedical research in acute care medicine. *Ann Emerg Med* 1991; 20:1251.
84. Iserson KV: Physician ethics in human research: The role of medical publications. *Ann Emerg Med* 1990; 19:828.
85. Iserson KV: Has emergency medicine research benefited patients? An ethical question. *Sci Eng Ethics* 2007; 13:289.
86. President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research: *Securing Access to Health Care, vol 1: The Ethical Implications of Differences in the Availability of Health Services*. Washington, DC: U.S. Government Printing Office; 1983.
87. Iserson KV, Kastre T: Are emergency departments a "safety net" for the medically indigent? *Am J Emerg Med* 1996; 14:1.
88. Derlet RW, Nishio DA: Refusing care to patients who present to an emergency department. *Ann Emerg Med* 1990; 19:262.
89. Iserson KV, Moskop JC: Triage in medicine—part I: Concept, history, and types. *Ann Emerg Med* 2007; 49:275.
90. Moskop JC, Iserson KV: Triage in medicine—part II: Underlying values and principles. *Ann Emerg Med* 2007; 49:282.
91. Iserson KV, et al: Fight or flight: The ethics of emergency physician disaster response. *Ann Emerg Med* 2008; 51:345.

www.ketabpezeshki.com 66485457-66963820

END OF LIFE

Jean T. Abbott and Susan Stone

For the complete chapter text, go to the Expert Consult website. To access your account, look for your activation instructions on the inside front cover of this book.

I. PERSPECTIVE

II. PRINCIPLES OF DISEASE

A. Epidemiology of Death and Dying

B. Definitions of Death

C. Related Issues

III. SPECIFIC DISORDERS AND CONCERNS

A. Out-of-Hospital Considerations

B. Death in the Emergency Department

C. Palliative Care in the Emergency Department

D. Special Situations and Diseases

KEY CONCEPTS

- In emergency medicine, it is essential to act rapidly, with the presumption of curative goals, and it may be impossible to withhold initial interventions.
- Advance directives and patient wishes should be honored whenever possible, including withdrawal of invasive support if the patient's desire to not receive such treatments is determined after initial emergency department (ED) intervention.
- When the patient cannot speak for himself or herself, the physician needs to search for the correct proxy according to patient wishes and state law, when there is time to do this.
- Suffering is not the same as physical pain: The body experiences pain, whereas persons experience suffering, particularly when physical changes threaten their future.
- Patients have individual perceptions of burdens and benefits when they live with chronic illnesses. The only way to understand a person's quality of life and whether treatment is "right" for a patient is to have a conversation to explore his or her wishes and values.
- An important aspect of the initial ED evaluation of a patient with a life-limiting illness is to ascertain the patient's general wishes regarding future resuscitation and treatments. The conversation with the family and patient can begin with the following questions: "What kind of resuscitation do you wish to receive if an emergency occurs after admission?" "Whom do you want to make decisions for you if you cannot?"
- A discussion of goals of care is more effective if it starts by clarifying the patient's broad values and goals. From the broad discussion, the clinician can suggest what procedures may or may not be useful in attaining the patient's goals.
- The purposes of hospitalization for persons with severe terminal diseases should be clear and in line with the patient's values.

www.ketabpezeshki.com 66485457-66963820

End of Life

Jean T. Abbott and Susan Stone

PERSPECTIVE

The emergency department (ED) frequently is the site of critical turns in people's health. It is the place where sudden, unexpected deaths occur and bad news must be delivered to survivors. The ED also is increasingly a source of care for patients struggling with chronic diseases, persons in the late stages of life-limiting illness, and people actively dying. Many of these patients are elders with advanced disease and require discussions about withholding or withdrawal of life support in the ED.[1] Palliative care is the medical specialty that is focused on end-of-life care, and some of its principles are being incorporated into the Model of the Clinical Practice of Emergency Medicine.[2] The integration of quality management of the dying patient into emergency medicine practice presents challenges but also incorporates communication and negotiation skills that can be used by emergency physicians in many aspects of their practice.[3]

Death in the ED differs from death in other areas of the hospital in several ways: deaths often are unexpected; the patient and family and their values often are unknown to ED staff; trust needs be established rapidly; and management decisions often must be based on limited medical information. These factors contribute to stress for the emergency care team in managing the first few minutes of a critical illness. The initial response to life-threatening presentations in the ED must be to treat aggressively and to resuscitate persons in extremis in the absence of knowledge that this is counter to the patient's wishes. Much of the core of emergency medicine is devoted to prevention of untimely death in people with severe trauma, a "heart too young to die," or another sudden, unexpected life threat. However, when resuscitative and rescue efforts fail, when a patient's wishes to forgo further interventions become clear, or when the natural end to life comes, the emergency specialist should be prepared to withdraw unwanted treatments, to make the patient comfortable, and to lead the staff and the patient's loved ones in giving the patient's death the meaning and respect it deserves.

PRINCIPLES OF DISEASE

Epidemiology of Death and Dying

One hundred years ago, the predominant pattern of dying was a rapid, precipitous death from infectious diseases and accidents. With modern medical advances, chronic diseases have become part of the last years of life for most people. Three diseases—heart disease, cancer, and stroke—accounted for 60% of deaths in the United States in 2000, whereas unintentional injury accounted for only 4% of deaths.[4] Most people live with some limitation in their ability for self-care for 2 to 4 years before they die. Four common trajectories of dying have been described (Fig. 1). Sudden death (due to cardiac arrest, trauma, or other sudden event) occurs in only 15% of people. The other trajectories are more common and occur with roughly equal frequency. The predictable decline in patients with "terminal illness" during 6 months or less provides the basis for the hospice concept of managing the dying process for patients with cancer and terminal AIDS. In cases of organ failure (e.g., chronic obstructive pulmonary disease [COPD], heart failure, renal failure, and other progressive serious medical diseases), gradual decline is punctuated by intermittent exacerbations (entry-reentry decline). The time of death for people with these progressive and ultimately fatal diseases is not very predictable, and it often happens unexpectedly during an acute deterioration. These patients frequently are treated for acute crises in the ED. The fourth trajectory of gradual decline, or "frailty," is associated with some form of dementia in 50% of affected persons and a lingering course that can extend for many years, stressing and wearing out caregivers and other support systems as decline in functional abilities progresses.[5]

Several end-of-life skills are important in the practice of emergency medicine. One of these is to determine rapidly, when possible, the patient's wishes for interventions at a time of crisis. Wishes may be transmitted through written advance directives or direct conversation with a patient or proxy about general values or specific management choices that should guide ED management. Invasive interventions may carry greater risk and less benefit near the end of life. The patient's choices may include spiritual, economic, and community factors that the clinician cannot know without clear, rapid communication and establishment of treatment goals.[6] The national Education in Palliative and End-of-Life Care for Emergency Medicine (EPEC-EM) curriculum has been designed to help clinicians prognosticate better, convey medical and technical choices, and discuss goals of care with patients and families at these critical turns.[2]

Patients and families need to understand prognosis to make decisions about what treatments they want and to plan priorities for their remaining life. Studies have shown that physicians may be overly optimistic about prognosis, particularly if they know the patient well.[7] Functional status is a strong indicator of a patient's prognosis, particularly in patients with terminal cancer, for which the dying trajectory tends to be most predictable. For other end-stage diseases, validated scales to predict survival are commonly used in palliative care assessments. In the ED setting, rapid assessment of the likely prognosis can be accomplished by eliciting information about the patient's ability to perform activities of daily living (i.e., "performance status"). When a patient is not able to spend time out of bed, has reduced appetite, and cannot dress or bathe without assistance, he or she is likely to be in the last months of life. Such a patient should be eligible for the Medicare

www.ketabpezeshki.com 66485457-66963820

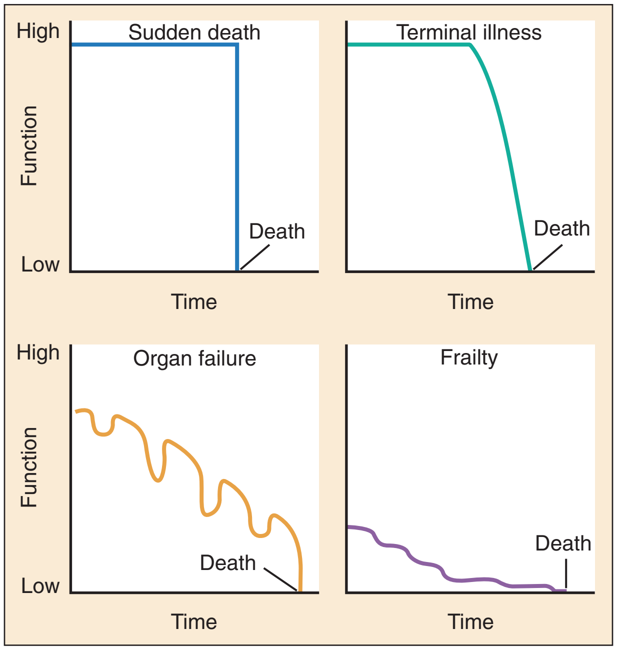


Figure 1. Theoretic trajectories of dying. (From Lunney JR, Lynn J, Hogan C: Profiles of older Medicare decedents. J Am Geriatr Soc 50:1108, 2002.)

hospice benefit. This is the time to involve hospice or palliative care consultants either in the ED or during hospital admission. If a patient has already enrolled in hospice, it is important to contact the relevant hospice program (accessible around-the-clock) from the ED before treatment and disposition decisions are made.[2,5,8]

In Western culture, death has become "medicalized" in the last 50 years.[9] Modern technology often allows human control over the timing, site, and pace of dying. About half of deaths in the United States occur in a hospital and another quarter in nursing homes.[10] Frequently, the dying process is accompanied by invasive diagnostics and medical interventions, even when death is expected and these interventions may increase suffering. Our society often sees death as the failure of scientific know-how rather than the natural end to a life. When death is approached with less fear by both patients and physicians, it is possible to help patients and families make the best of the time remaining to them and to accept death as natural.

Definitions of Death

Biologic definitions of death are currently the subject of considerable debate. Twenty years ago, cardiorespiratory failure defined death because this was rapidly followed by brain death (which could not be directly measured) caused by failure of oxygenation and perfusion. Death was a distinct biologic event because all vital systems stopped when one of them failed.

Currently, cardiopulmonary "death" is not necessarily inevitable or irreversible. Ventilation can be maintained externally, and even circulatory support through pharmacologic means or pump assist can sometimes buttress an inadequate heart. Because of this, a second pathway called "brain death" has been conceptualized. One impetus for development of a concept of brain death was the need to define a biologic and ethical boundary to life in the procurement of organs for transplantation. The brain-based determination of death is defined by the irreversible failure of clinical function of the whole brain, manifested by apnea, profound coma with unresponsiveness, and absence of brainstem reflexes.[11] The most common causes of brain death in adults are traumatic brain injury and subarachnoid hemorrhage. In children, the primary causes are accidental or nonaccidental trauma and asphyxia.[2,11] Although the emergencies causing eventual brain death often present first to the ED, the criteria and irreversibility standards are rarely met in the first hours after the resuscitative effort.

Declaration of brain death allows harvesting of organs while cardiopulmonary support and organ perfusion are continued and accounts for the majority of solid organ donations. A new protocol designed to increase the pool of organ donors and to acknowledge the rarity of complete brain death defines "non–heart-beating" organ donors. Such patients have a dismal prognosis for meaningful survival, but complete brain death will not occur until the time of cardiopulmonary arrest. Pulmonary and cardiac support is withdrawn, death is declared after an interval of several minutes, and organs can be harvested with a minimum of warm ischemia time. The issues surrounding society's definitions of death are complex, and the struggle to balance respect for persons and their bodies with the need for transplantable organs is expected to continue.[11-13]

It is important for physicians to be clear in their medical language relating to death. A patient is allowed to "die naturally" when the ventilator and cardiac support are removed. A patient who is declared "brain dead" is dead even though the person may appear to be alive, with pulse and chest rise, to the family.[11] "Whole brain" death requires failure of the brainstem as well as cortical function (i.e., coma). The confusion over medical definitions of death is made greater by cultural and religious variations in concepts of death. The different criteria also can lead to suspicion among the public that these definitions are malleable and serve physician agendas rather than respecting the patient.[11] In the ED, cardiopulmonary death is the only death that can be recognized, and the term *brain dead* is to be avoided because it requires time and strict criteria for diagnosis. However, the emergency physician has an important preparatory role in explaining the status of the patient who is breathing and who has a pulse (perhaps after a successful resuscitation effort) but may ultimately die a brain death. It is helpful to introduce the family to the concepts of prognosis and brain injury and the further steps that will occur in the succeeding hours that will give physicians and family a clearer picture of whether an injury or insult is fatal.

Related Issues

Futility

Physicians are not required to offer treatments that are not beneficial. Unfortunately, information available in the out-of-hospital setting or the ED often is insufficient for a judgment to be made that a particular patient's condition is "terminal" or that treatment efforts would be "futile." In the United States at present, when cardiopulmonary arrest occurs, physicians proceed with full resuscitative measures unless there is a clear understanding that this is contrary to the patient's wishes. Although the term *futility* can be a nontechnical expression of a physician's assessment that a proposed intervention is nonbeneficial, the definition is hotly debated. Most recently, the term *futility* has also been conceptualized in two ways: goal futility (the goal of the proposed treatment plan is unlikely to be realized) and value futility (the goal of treatment does not hold value for the patient). Unilateral physician judgments of futility are not appropriate in the emergent patient, although both aspects of futility can be useful in conversations with patients and families while discussing goals and options in the ED.[14]

Quality of Life and a "Good" Death

As technology gives physicians the ability to stabilize patients with serious and incurable diseases and to manipulate the timing of

www.ketabpezeshki.com 66485457-66963820

death, and as people increasingly exercise their autonomy to decide how and when their dying should occur, more conversations occur about what constitutes a "good death." There is evidence that the quality of life for persons who live into their 80s is better than it was 20 years ago.[15] For that, medicine can be proud. However, there are also serious deficiencies in end-of-life care. Whereas almost 95% of people express the wish to die at home, more than 70% die in an institution.[10] The patient's priorities are often marginalized, as they commonly include both medical and nonmedical concerns. Singer and associates suggested that five topics predominate in people who are dying: having pain and other symptoms adequately relieved, avoiding inappropriate prolongation of dying, achieving control, relieving others of the burden of their dying, and strengthening personal relationships.[16] The medical profession has not been quick to understand the broad scope of the patient's wishes and to honor them in planning and care.[17]

In the ED, resuscitation is performed unless the patient's wishes to the contrary are clearly known, even though the number of patients completing some form of advance directive before nontraumatic death is now about 70%.[18] Information that cardiopulmonary resuscitation (CPR), intubation, or other invasive treatments are not desired can be conveyed in the form of written advance directives, a state-authorized "no-CPR" or do-not-attempt-resuscitation (DNAR) directive, clear indications from the person assigned the patient's durable power of attorney for medical affairs, or communication with the patient's physician through the newer POLST (Physician Orders for Life-Sustaining Treatment) paradigm orders.[19] However, evidence of wishes from prior conversations between patients and family or physicians is rarely available in an emergency situation. Most people—both patients and surrogates—do not understand what "do everything" means, and surrogates are poor at predicting care that their loved one would want or not want. In one study comparing patient and surrogate choices about life support, surrogates guessed patient wishes only 68% of the time, little better than chance.[20]

In patients with severe disabilities, physicians and other health care providers likewise have a difficult time judging quality of life and the patient's wishes at the end of life. Gerhart and colleagues[21] surveyed emergency care providers' hypothetical attitudes toward quality of life after spinal cord injuries and compared their responses with those of high-level spinal cord injury survivors. Only 18% of providers (e.g., emergency medical technicians, nurses, and physicians) imagined they would be glad to be alive after a severe spinal cord injury, whereas 92% of survivors were glad to be alive. Eighty-six percent of the quadriplegics thought that their quality of life was average or better, whereas only 17% of emergency care providers predicted they would have a similar view of their quality of life as a quadriplegic. People's assessment of what is a "good life" changes with time, age, and the realities of illness.

Goals of Medicine

Medical authorities and philosophers have long debated the proper goals of medicine. Physicians are most familiar with the goal of "curing" disease. However, Ellen Fox reminds us of the complexity of our task in medicine: "Although cure is unquestionably an appropriate goal of medicine, other goals are important as well: promoting health, preventing illness and injury, restoring functional capacity, avoiding premature death, relieving suffering, and caring for those who cannot be cured."[22] In Western society, the curative model predominates, and physicians are rewarded for being analytic and rational. The disease, not the person, becomes the object of analysis. Symptoms are clues to diagnosis rather than problems to be treated in and of themselves. Fox points out that the palliative care emphasis on "relief of suffering, control of symptoms, and restoration of functional capacity" is really just one end of a spectrum of care that a physician provides to all patients. Even patients with life-limiting conditions often have reversible elements that physicians can address; likewise, even the patient with streptococcal pharyngitis wants symptom relief in addition to cure. So the goal of medicine may be to discern where to place the emphasis: the curative and the palliative models need to be balanced in varying proportions to optimize care for the individual patient.[22]

If the physician's goal is to relieve suffering, he or she must distinguish between *pain* and *suffering*. Eric Cassell first introduced the idea that a primary goal of medicine is the relief of suffering in a landmark article in the *New England Journal of Medicine* in 1982.[23] Cassell emphasizes that pain happens to bodies but that suffering happens to persons. Suffering derives from the meaning behind pain or other symptoms to that person. Suffering is "the state of severe distress associated with events that threaten the intactness of the person."[23] Patients may be in severe distress without any physical pain; others may experience their pain with very little distress. Patients suffer, as Cassell pointed out, "when they feel out of control, when the pain is overwhelming, when the source of the pain is unknown, when the meaning of the pain is dire, or when the pain is chronic."[23]

Palliative and Hospice Medicine

The World Health Organization defines *palliative care* as "an approach that improves quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual." Palliative care is usually provided by an interdisciplinary team of experts that offers comprehensive care and support systems for patients and their health care providers, both at the end of life and when they are undergoing treatment for advanced illness. Some patients near the end of life are being treated with curative intent (e.g., before transplantation) but are in palliative care. Palliative management is provided to inpatients through consultation; outpatient services are delivered at home, hospice, or long-term care facilities.[24] Examples of some acute palliative care interventions that can be applied in the ED setting are described at the end of this chapter.

Hospice care is the component of palliative care for patients who are likely to be within 6 months of death. The hospice movement, which started in England in the 1950s, initially sought to provide a haven of medical care for persons dying of cancer. Home and inpatient hospice programs now exist throughout the United States and are funded through Medicare. If a clinician would "not be surprised" if a patient died within 6 months if the disease ran its natural course, a hospice evaluation would be appropriate. The patient is "hospice eligible" if the hospice judges that the patient's lifespan is likely to be less than 6 months and Medicare will certify the patient for hospice. Currently, hospice care is provided for an expanded spectrum of end-stage illness, including cancer, organ failure (e.g., heart, liver, kidney), neurologic diseases, and terminal AIDS.[2,8]

Currently about 40% of patients die while receiving hospice services. Of these, about 40% are patients with cancer. The median time from enrollment to death is 21 days, often leaving insufficient time for many of the services that hospice can offer.[25] Although physicians may have difficulty quantifying a patient's likely lifespan as less than 6 months, prognostic tools exist, and enrollment criteria are based on lack of curative intent as well as progressive decline in function.[2,8]

The palliative care movement has developed as an expansion of end-of-life care to include not only hospice-eligible patients but

www.ketabpezeshki.com 66485457-66963820

also patients with incurable, debilitating chronic non-cancer illnesses (e.g., COPD, congestive heart failure) that require symptom control, often in addition to some disease-modifying interventions, but with a less clear time frame to death.[5] Consultation with palliative care specialists offers patients a mechanism to discuss and to review management of symptoms and medical interventions that patients desire or wish to avoid. Hospice referral can occur when this is desired and possible. Several studies demonstrate that palliative care management may extend life while saving money and increasing patient satisfaction.[26-28]

Emergency Medicine and End-of-Life Care

Emergency physicians encounter death more frequently than physicians in many other specialties do. Resuscitation and restoration to functional life will always be a primary goal of practice and research in our field. However, seriously ill patients treated in the ED often present with important but less emergent complaints, and the physician often does have time to explore options for care with patients or family. Even when a patient has a severe chronic disease that is not curable, interventions are available that can improve the quality of life. On the other hand, at the end of the course of chronic disease, death is not always unwelcome.

Addressing the needs of patients and their families in the ED at these critical times requires an important set of skills. In 2006 the American Board of Emergency Medicine joined with nine other specialty boards to cosponsor the American Board of Hospice and Palliative Medicine. This alliance has recognized the real need of emergency physicians to participate in addressing the wide range of interventions and management decisions that are pertinent to the end of life. The integration of emergency medicine and palliative medicine has stimulated educational efforts to define the scope of ED-based palliative care and curriculum design.[2,29] The rest of this chapter is devoted to out-of-hospital end-of-life concerns and to the aspects of end-of-life care that should be part of every emergency physician's skill set: delivering bad news, death notification, establishing and honoring the patient's goals of care and advance directives, symptom control, and palliation.

SPECIFIC DISORDERS AND CONCERNS

Out-of-Hospital Considerations

Historically, out-of-hospital systems were designed to provide immediate resuscitation, stabilization, and transport of seriously ill or injured persons to EDs. Aggressive and early resuscitation, through CPR, airway management, defibrillation, fluid resuscitation, and trauma stabilization, has resulted in significant benefits and reduced mortality in patients with critical illness or injury for whom survival is time dependent.

However, emergency medical service (EMS) systems also are called to transport patients who have died or to assist patients who are in extremis but whose death is expected. As well, EMS is activated for patients with acute decompensation of chronic medical conditions, such as heart failure or COPD, and for acute symptoms that occur in the context of terminal conditions when caregivers at the scene cannot cope. Patients at the end of life may desire aggressive interventions for acute exacerbations of chronic illnesses, or they may prefer only supportive care or transportation to avoid unwanted interventions. In emergency situations, it may not be possible to determine the patient's underlying medical conditions or wishes. In some situations, a titrated response is possible, and noninvasive supportive care (such as positioning, suctioning, oxygen, or mask ventilation) during transport can buy time until the ED can further assess and clarify the patient's goals of care. However, patients in the last 6 months of life increasingly have physician orders documenting their wishes (POLST and others), and EMS providers need to ask for and honor these.[19]

Field Death Pronouncement

Several physiologic circumstances have been identified in which out-of-hospital providers should not initiate or continue CPR because of uniformly poor outcomes and no benefit from intervention. American College of Emergency Physicians (ACEP) and American Heart Association (AHA) guidelines state that CPR should not be initiated in patients with nontraumatic cardiac arrest and signs of irreversible death, such as decapitation, dependent lividity, or rigor mortis.[30,31] ACEP policy recommends discontinuation of resuscitation in the out-of-hospital setting if the patient remains in asystole or wide-complex pulseless bradycardia after a trial of adequate resuscitation, including CPR, intubation, medications, defibrillation, and pacing.[30] The National Association of EMS Physicians supports this approach. Termination of resuscitation efforts in nontraumatic cardiac arrest patients should be made in agreement with online medical direction and predicated on access to witnesses or family, provider comfort with death notification and grief counseling, and safety and logistical considerations.[32] In some systems, newer physiology-based algorithms for termination of resuscitation are being developed.[33] If questions arise about resuscitation, CPR and advanced cardiac life support measures should be initiated and the patient transported. It can be easier and ethically more sound to withdraw care in the ED than to withhold care at the scene.[2,34]

Honoring Advance Directives to Withhold Resuscitation

Honoring of patients' wishes at the end of life should be a goal for both out-of-hospital and ED personnel. Out-of-hospital providers need to be aware of the standards for honoring DNAR requests in their respective states.[31,32] In addition, providers need to be knowledgeable about types of advance directives and the surrogate laws for the state in which they practice. In most EMS systems, field pronouncement of death requires physician base-station consultation. The problem of unwanted resuscitation remains. In one survey, 98% of providers had questioned whether specific life support interventions were appropriate for patients who appeared to have terminal disease.[35] In another study, 6% of cardiac arrest calls were for people with DNAR orders.[36] Unilateral EMS provider judgment to forgo resuscitation has been reported, but snap judgments that patients are "terminal" are not necessarily accurate and should not be the sole criterion for withholding of interventions.[37] Barriers to implementation of prehospital protocols to terminate resuscitation include pay structure for EMS services, legislative mandates, and cultural norms in local communities.[38]

The identification of valid directives to withhold CPR or intubation is a problem for out-of-hospital providers. Information about patients' wishes and underlying diseases is frequently confusing, DNAR requests may be difficult to validate, and rapid intervention is frequently required. The ACEP recognizes the difficulties in respecting patients' desires to forgo resuscitative efforts and has issued guidelines for development of out-of-hospital DNAR policies.[30] In some states, statutory authority for EMS personnel to honor DNAR orders has been developed, but provisions vary widely. Written statements or identification bracelets must be consistent, easily recognizable, legally acceptable in that state, and clear about what resuscitative measures the patient would and would not wish to receive.[30,32] Likewise, a family member or friend who is present at the scene and has valid medical durable power of attorney for health care documentation may make decisions to initiate or to refuse treatment measures on behalf of the patient. The most widespread initiative to provide out-of-hospital written

www.ketabpezeshki.com 66485457-66963820

directives to limit life-sustaining care is the Physician Orders for Life-Sustaining Treatment (POLST) paradigm program, which started in Oregon and provides EMS and other providers in all settings with an order set clarifying patients' wishes near the end of life. This program is being adopted in other states.[19]

Several concerns about the validity of written advance directives persist: the patient's wishes can change over time, nonstandard forms of DNAR requests (such as "medical alert" bracelets, notes on prescription pads, or tattoos) cannot be recognized, and there is a theoretic concern that relatives or bystanders may not be accurately relaying the wishes of the patient.[37] Most out-of-hospital providers think that end-of-life skills are important; 93% of Oregon EMS providers found POLST orders helpful in the event of a prehospital cardiac arrest, and two thirds thought they were useful in patients who were not in arrest.[39] Significant gaps in training and knowledge about end-of-life training have been recognized by paramedics.[35]

Honoring Verbal Requests to Withhold Interventions in the Field

In most EMS systems, verbal requests to limit resuscitation are not accepted because of the concern that out-of-hospital providers cannot confirm that these represent the patient's current wishes. In view of the significant incidence of "unwanted" resuscitation, King County in Washington State has introduced a new protocol of allowing emergency medical technicians and paramedics to withhold resuscitation in situations in which family or caregivers indicate that no resuscitation is desired and the patient has a terminal condition (i.e., death is expected and the patient is under a physician's care). EMS personnel do not need direct physician approval to forgo resuscitation. The incidence of non-initiation of resuscitation increased from 5.9% to 11.8% in EMS services adopting the expanded standards.[40] Before implementing a similar protocol, Los Angeles County reviewed run sheets and found that 6% of cardiac arrest patients had a written DNAR order, but 10 of 55 patients were resuscitated because paperwork was not available. A family member or medical history was available at the scene for more than half of almost 900 nontraumatic cardiac arrest patients, indicating a potential to forgo resuscitation in a significant number of patients.[36] A liberalization of protocols should be accompanied by population buy-in and legal protections against errors because wrongful death suits remain a theoretic concern. EMS provider comfort level with expanded standards for non-initiation of resuscitation has been high.[37,40]

Supportive Out-of-Hospital Treatments near the End of Life

Patients at the end of life can benefit from supportive or palliative treatments at the scene and during transport. Positioning, suctioning, and administration of pain medication and oxygen for dyspnea may be important to increase the patient's comfort. Before an intravenous line is established, EMS personnel should ask the patient's permission to do so because even the pain associated with insertion of the line may be counter to a terminal patient's wishes. If the patient is being transferred from a long-term care facility to the ED, all care instructions, CPR directives, advance directives, and contact names and numbers need to be transported with the patient; these will be helpful in guiding continuing care in the ED.

Management of Hospice Patients

Although hospice care protocols are written to avoid activation of the EMS system unnecessarily, scenarios routinely arise in which the patient is in the dying process and help is needed. Unexpected medical deterioration, concern for the patient's perceived or real suffering, or a feeling of helplessness can and should trigger calls to 911. Family members may be unable to handle new symptoms or may disagree about the best way to help the dying person. Although some families may request death pronouncement at home, out-of-hospital providers should involve medical control. Transport with comfort care should be offered if the family wishes help or if the setting appears uncomfortable for those involved.

Suicide

Although respect for the patient's wishes is a core value in today's society, suicidal patients frequently are impaired and have doubtful decisional capacity.[41] Modern medicine assumes that suicidal depression usually is treatable. Patients near death from suicide should receive full resuscitative efforts unless there is a specific exception, such as physician-assisted suicide in Oregon and Washington, with formal documentation and an alternative protocol for out-of-hospital providers to follow.[42] If the patient is dead and meets criteria for resuscitation not to be started, the coroner or medical examiner should be notified. The scene needs to be protected to allow an investigation, if needed, because the history is rarely clear or complete during the emergency call. Decisions should be made after consultation with the medical control physician.

Death in the Emergency Department

Delivering Bad News

Every emergency physician will be required to communicate bad news to patients, family members, and caregivers. The manner in which this is done may make a difference in the course of subsequent grief and coping.[43] Compassionate communication can strengthen trust and foster collaboration in planning between the medical team and the patient and family. Emergency physicians have particular challenges in delivering bad news. They do not have ongoing relationships with their patients, and the bad news may be abrupt and unexpected. However, sometimes the lack of a prior relationship allows a more frank and open conversation about a patient's illness, prognosis, and wishes, particularly when the patient has a severe chronic disease.[44]

The goal of skillfully breaking bad news is to reduce the severity and the duration of stress and encourage engagement of coping mechanisms, both for physicians and for patients and their caregivers. According to a theoretic construct proposed by Ptacek and Eberhardt, staff and physician stress often peaks just before transmission of the bad news, whereas patient or caregiver stress emerges after delivery of the bad news.[45] Physician stress correlates directly with the severity of the news as well as with any responsibility for the outcome that the medical team may feel and inversely with the amount of experience in delivering bad news. Many providers feel inadequately prepared for death disclosure or delivery of bad news about a new diagnosis or turn in health status for a patient with a life-limiting illness.[46,47] Skilled resuscitation, diagnosis, and treatment of patients are key to management of the external sources of provider stress. Anticipatory stress of delivering bad news may be reduced by use of a structured protocol, with practice, and by being intentional about the physical and social aspects of the setting.[45] Experience with revealing medical error or other aspects of responsibility for outcomes has not been well studied.[48]

Several initiatives to improve delivery of bad news have been introduced. These encourage training in communication skills, explicit instructional sessions, role playing, use of standardized patients, and observation of colleagues who are comfortable with this aspect of patient care.[48-51] Little research has examined the best

www.ketabpezeshki.com 66485457-66963820

Box 1 Delivering Bad News

The steps listed can help you think critically about how best to communicate at a time when stress is high. See the text for details about each step.
Step 1: Physician preparation
Step 2: What does the patient know?
Step 3: How much does the patient want to know?
Step 4: Sharing the information
Step 5: Responding to feelings
Step 6: Planning and follow-up

Modified from Buckman R: How to Break Bad News: A Guide for Health Care Professions. Baltimore, Johns Hopkins University Press, 1992.

methods of increasing patient and family satisfaction with this important aspect of patient care.[47] If the physician develops patterns to insulate himself or herself from stress, stress may increase for the receiver, whose needs should be primary; physicians should avoid use of vague language, delegation to others, or delaying or rapidly disengaging from the encounter.[44,45]

For the patient and family, the ED typically is the place where bad news is sudden and unexpected. This can certainly make the strain even more severe and overwhelming. Trust between ED caregivers and critically ill patients or their survivors, who were unlinked strangers just a few minutes before, does not come easily. Whereas providers may focus on the content of the information they should convey, patients focus more on the process.[43] Surveys of patients and families have identified the following factors as desirable for receiving bad news: privacy when receiving news, ability to express emotions safely, information that is free of unclear language or medical jargon, empathic and caring attitude, allowance for hope, and ability to ask for and receive good medical information.[45,49] One proposal for encouraging provider empathy is to structure a conversation according to the NURSE pneumonic: the provider *n*ames the emotions observed; confirms whether this *u*nderstanding of the receivers' feelings is correct; expresses verbal and nonverbal *r*espect for the receivers' feelings; *s*upports them through expressions of concern, understanding, and willingness to help; and *e*xplores additional concerns.[44]

The steps listed in Box 1 and explained in detail in the following paragraphs are designed to shape the interaction to facilitate the patient's or survivors' work through this stress and movement toward coping. This six-step template was adapted from Buckman's work and adopted also by the Education for Palliative and End-of-Life Care (EPEC) teaching project.[2,44,52] Key to moving through the process of delivering bad news is the "ask-tell-ask" interactional framework in which the physician is guided by the patient and family in regard to the pace, amount of information, and style that will work best to let them feel and hear what they need.[44]

Step 1: Physician Preparation

Before the physician interacts with the family or patient, preparatory steps are important. These include confirming all medical facts of the case, clarifying the name of the patient, being aware of any uncertainty about the patient's identity, and knowing the relationships between the patient and those with whom one will be talking. The physical site for the conversation should be quiet and allow private exchange of information and safe expression of emotions. This is sometimes difficult in the ED, but a family room or other quiet area usually is available. If the patient can be included, moving the patient to a private area is helpful, or key members of the patient's support group can be gathered around the bedside.

Physicians should identify themselves and their position, directly address the patient (when present) or the key persons receiving the news, and refer to the patient by name. Before beginning the discussion, the physician should sit down close to the patient, make direct eye contact with the patient (or close relatives), and be physically and mentally open to their concerns and needs.

Step 2: What Does the Patient Know?

It is useful to know what the patient or family understands before the delivery of news. An introductory question can be used, such as, What do you understand about your illness? or What have you been told happened to [name of spouse, sibling, other]? This information helps the physician to see the event as the patient and family are seeing it and to adjust the mode of delivering this news to their understanding. When patients and families may expect "the worst," this tactic can be perceived as delaying. In a less critical situation, however, asking about previous testing, conversations with physicians, and understanding of the patient's illness can help the subsequently delivered information fit into the patient's perspective and expectations.

Step 3: How Much Does the Patient Want to Know?

Every patient has the right to accept or to refuse medical treatments on the basis of informed consent. This also is true for information. Most patients appreciate the direct, simple truth about their condition and prognosis. There will, however, be some patients who do not want to receive the information themselves. These patients may wish to designate a friend or family member to represent them. This choice should be respected, if possible. People process information and make decisions in many different ways on the basis of their own cultural and religious views and previous experiences, and the Western principles of truth-telling and individual decision-making may be of lower priority to some families and communities.[44]

Sometimes the family learns of a diagnosis and prognosis before the patient does and requests that the patient not be told. The physician's alliance with both patient and family is important, although responsibility to the patient is primary. Physicians should explore why families do not want the patient told bad news: Is it a cultural tradition? Are they afraid of what harm it will cause the patient? Have they had previous bad experiences? The physician is still required to ask the patient how much he or she would like to know. Sometimes it is helpful for the physician to invite family members to be present for this discussion. Important information should be shared with the use of an independent interpreter (rather than a family member) if the patient does not speak the same language as the physician.

Step 4: Sharing the Information

In general, patients and families want to know bad news in a timely fashion.[45] This is sometimes uncomfortable, particularly when information is incomplete—a common occurrence in the ED. At the very least, it is recommended that patients and family be given a preparatory warning after introductions, such as, "I am afraid I have some bad news." In delivering the information, it is important to use simple nonmedical language and to make sure that the patient comprehends the information. Allow space for patients and family to absorb the news, to react, and to begin to ask questions. The patient and family stress response will lag behind that of the physician because the physician has had at least a few minutes to adjust to the current situation, but the family has not.[45]

Use of the phrase "I'm sorry" can be a reflection of empathy, but to avoid the implication that errors have occurred in treatment, some physicians have suggested use of expressions such as "I wish things were different" instead.[53] Survival data can sometimes be helpful, even when tentative. The physician's message should include some realistic hope and also reassurance that the

www.ketabpezeshki.com 66485457-66963820

patient will not be abandoned by the medical care team, even when cure or survival is unlikely.[49]

Step 5: Responding to Feelings

The reaction to bad news often is unpredictable and can range from sadness to overt anger. It is important for clinicians to be aware of the wide varieties of responses that will be seen. The patient and family should be allowed to express their feelings, even if this is uncomfortable. Acute grief is painful but important. The emergency physician should be prepared for both persons who turn inward and those who rage outwardly. Practicing and reflecting on these situations will allow the physician to deliver bad news and to support the survivors. In the ED, it is often helpful to invite members of the team into this meeting (e.g., social worker, nurse, or chaplain) who will not be pulled away to other care needs, can provide emotional support, and can help the family navigate through the early stages of grief as well as the necessary technical details.

Step 6: Planning and Follow-up

The ED is an entry point into the hospital if the patient survives. Family members should be encouraged to stay with the patient, particularly if it is possible that the end of life is near. Prognosticating may be difficult, in view of the limited information that can be obtained in the initial assessment. When initial management has stabilized a patient with an acute, critical turn, it may be appropriate to look ahead to decompensation that could occur later in the hospitalization. Some experts have suggested a "hope for the best and prepare for the worst" framework for conversation.[54] The physician can share the success, however transient, of any ED interventions and the positive news and hope that this provides. At the same time, he or she can prepare the patient or family for the possibility of later setbacks and have them consider what actions may or may not be appropriate if "the worst" happens.[6] If the patient does not have written advance directives, the emergency physician can facilitate the conversation, initiate written wishes, or at least advise the patient that the admitting physician will need to have an early conversation about future plans and goals for the patient. The physician should assure the patient and family of what the next steps will be, including hospital admission or discharge from the ED, consultation with specialists, support group referral, or chaplain services. It is important to make sure that the patient and family do not feel abandoned. When dying is near, active care and comfort are important medical tasks for the care team.

Death Notification

One particularly difficult form of "bad news" is death notification. Practice can help clinicians perform this task more smoothly (Box 2). In general, the format can follow the guidelines for delivery of bad news from Box 1. With death notification, however, diagnosis is certain, and specific actions will be required. Families do not have time to adjust or to think about options, and the news cannot be softened.

Death notification usually occurs after an unsuccessful resuscitation attempt. Physicians should be sure that they are presentable and wear a name badge. If possible, ascertain beforehand the names of the persons who will receive the notification, their relation to the patient, and what they know about the patient's condition. Other members of the medical team may have met them already and can be a source of background information. Sometimes the family initiated the 911 call and recognized that their loved one had died at that time. On the other hand, a family summoned to the ED may have absolutely no idea that they are about to be informed that their loved one has been critically injured or has died. For this reason, it is useful to have a nurse or colleague advise the family briefly about the general nature of the event and the status of resuscitation as soon as possible. When giving the news, physicians should use clear "dead" or "died" language to be sure that there are no misunderstandings about the outcome being conveyed. Those at the scene should be assured, if at all possible, that their responses to the emergency were appropriate, that the medical care team did all that was possible, and that the victim did not experience unnecessary discomfort. It is important to express appreciation for their presence in the ED or during the resuscitation attempts.

Box 2 Elements of an Empathic Death Disclosure

Introduce self/role.
Sit down.
Assume comfortable communication distance.
Use acceptable tone/rate of speech.
Make eye contact.
Maintain open posture.
Give advance warning of bad news.
Deliver news of death clearly (use dead/died).
Tolerate survivor's reaction.
Explain medical attempts to "save" patient.
Use no medical jargon; use language that is clear and easily understood.
Offer viewing of deceased.
Offer to be available to survivor.
Conclude appropriately.

From Quest TE, et al: The use of standardized patients within a procedural competency model to teach death disclosure. Acad Emerg Med 9:1326, 2002.

Phone Notification

If the first contact with survivors of an ED death is by telephone, it is recommended that the survivor be told to come to the ED if at all possible.[55] Although family members may ask or even demand to know if death has occurred, allowing some time for assimilation of news by delaying information about the final outcome may be more helpful for the grieving process.[56] Nonphysician staff may be useful to summon survivors and can inform the relative that the patient has been involved in an accident or is seriously ill and that things are not going well.

When the notification is to somebody who is more than an hour away or otherwise unable to physically come to the ED to receive the bad news, it often must be given by phone. The physician should make sure that the relative has someone present in the room if possible, ask the relative to be seated, and name the person involved. It is best to start with brief information about the circumstances and provide a warning that bad news is coming before breaking it. Even a few seconds of preparation in these circumstances can serve to partially attenuate the acute psychic pain. As indicated by the perceived response, the physician may need to ask, "Are you able to talk for a few minutes?" Some individuals may be unwilling or unable to continue after they hear the initial news, and they should be given an "out," but a definite time to reconnect should be established (e.g., 10 to 15 minutes).[55,56] Long-distance loved ones cannot view the body to facilitate confirmation and acceptance and inevitably have questions not addressed in the initial conversation. The relative should be given a telephone contact of someone who actually provided care for the patient. Otherwise, if a relative calls back, a lack of information about what transpired on a prior shift may cause frustration or even feed the person's denial or false hope that this tragedy has not happened.

www.ketabpezeshki.com 66485457-66963820

Viewing of the Body

At some time immediately after death, the family should be offered an opportunity to view the body. This may be the first exposure to the body for the survivors and can make an abstract and unreal notification more concrete. Although a majority of survivors find viewing of the body helpful, no attempt should be made to force this on survivors, and a few are not comforted by seeing the deceased.

If possible, the body should be moved to a small room, preferably away from the main treatment area. This not only ensures privacy but also makes the family feel more at ease. Family members should be warned of what to expect, such as color and temperature changes, injuries or invasive premortem procedures, and the presence of endotracheal and intravenous tubing. With sufficient preparation, most people are not shocked by the deceased person's appearance.

A staff member should remain in the room or within close range at all times. This contact allows the staff to help make the viewing an important and supportive aspect of the grieving process. At times, it may be necessary to touch the body to assure the family that this is appropriate. Survivors should be allowed to remain with the body for as long as seems appropriate. When gross disfigurement has occurred, the viewers should be warned about this, and the body should be discreetly covered when possible. Survivors may even find that helping to clean and prepare the body (particularly with a pediatric death), holding a loved one, or preparing for transport may allow a final expression of caring.

Family Presence during Resuscitation

It is increasingly common to invite a close family member to attend resuscitation attempts. Offering of this option has been endorsed in the 2005 AHA Emergency Cardiac Care guidelines[31] and by the EPEC curriculum.[2] Emerging evidence suggests that presence during procedures and resuscitations may be beneficial to surviving patients and family members who choose to stay and are not harmed. Less consensus exists among providers, and they often express discomfort with the concept. If resuscitation is to be witnessed by a family member, a staff member who is dedicated to supporting that person should always be present.[57,58]

Sedation for Survivors

Requests for tranquilizers, sedatives, sleeping medications, or just "something for the nerves" are common. The grieving process is important and difficult work. Prescriptions for a light sedative for a few days may be appropriate but usually require direct evaluation of the survivor by the physician. The survivor needs to know that the psychic pain is to be expected and where to turn for help and support during this difficult time.[55]

Autopsy and Closure

The "event" of death notification should be concluded with a physician expression of condolences and concern for the survivors—all physicians can honestly express sadness at being the bearer of such life-changing news.[53] In many hospitals, chaplains or social workers or nurses are trained in informing the family about arrangements for the body, including notification of a mortician and interface with a coroner, which is not uncommon in ED deaths. If the ED practitioner desires an autopsy, this is an appropriate time to request permission. Autopsies not only are valuable in contributing to the advancement of knowledge, education, quality assurance, and public education but also can be indispensable in minimizing guilt and blame associated with the death of a loved one. In addition, findings of unknown disease may be important for family members if there is a genetic factor. Whereas organ procurement organization staff should secure formal consent for organ donation, the rate of organ donation is positively influenced by the physician's comfort in answering family questions about donation.[59]

Consent for Procedures on the Newly Dead

The use of the newly dead to teach procedural skills is currently being debated in the medical community. It is important to educate residents in procedural skills, and emergency physicians often need to review procedures that they perform very rarely. The newly dead have been a silent source of learning in the past. Although some evidence indicates that the public generally supports the practice, serious questions about respect for bodies and the need for informed consent also have been raised.[60] The American Medical Association policy affirms that consent should be obtained from survivors.[61] In emergency medicine, it has been argued that obtaining consent is not feasible: finding authorizing survivors is difficult, voluntary consent is questionable in a stressful situation of sudden death, and time pressures require early resumption of other ED activities. Some authorities have tried to distinguish between invasive procedures (e.g., thoracotomy, peritoneal lavage, venous cutdown) and minor or less invasive ones, such as intubation. The current ACEP position is ambiguous and reviews arguments on both sides of the debate.[62] Hospital policies often determine whether the newly deceased can be used for training purposes and the manner of consent that is needed. Many believe that the performance of involuntary, nontherapeutic invasive procedures, including those performed during CPR, is an ethically unacceptable departure from a standard of care that emphasizes the centrality of respect for the patient, the patient's well-being, and the requirement for informed consent.[60,63]

Grieving and Bereavement

Grief is defined as emotional pain induced by sorrow and loss. It is associated with a constellation of symptoms and behaviors that are influenced by cultural background, current and past personal stressors, and relationship of the survivor to the deceased. Survivors are often the "patients" toward whom the emergency physician needs to direct his or her expertise in the case of an ED death. Giving bad news and sharing in the beginnings of the grief response are among the most difficult situations physicians need to handle. Whereas grief reactions are most commonly associated with death events, they also occur with sudden downturns in health or news that changes a person's outlook on the future. *Bereavement* is the situation of having experienced the death of a significant person in a survivor's life.[64] It is important to understand the range of what can be expected acutely and to be able to identify those survivors at risk for complicated grief. Recognizing survivors at higher risk for complicated grief may trigger earlier referral and decrease the risk for development of major depression and other stress disorders.[43]

The initial response to any death, whether expected or unexpected, is acute psychic pain that is associated with shock, disbelief, numbness, and inability to process further information.[55] Some persons display anger, loud screaming, crying, and occasionally acute anxiety or syncope. Others experience a calm dissociation or no reaction. The medical team may also recognize other, more cognitive reactions, including denial, guilt, sadness, fear, shame, and anger. Reactions may vary with the cultural and personal backgrounds of the survivors. A wide range of expressions is normal and expected. There is no "right" way to grieve, although, in the ED, outward reactions are often perceived as problematic and disruptive. The goal of the emergency physician is to support survivors as much as they permit and to avoid taking personally

www.ketabpezeshki.com 66485457-66963820

the survivors' anger, resentment, and other outward emotional expressions, even if they are directed at ED staff.[55] It is important to accept that some survivors will leave the ED still in denial and not emoting; they may need and want to postpone their grieving until they have what they feel is a more comfortable setting.

A variety of delayed emotional and physical symptoms can emerge as the survivor assimilates the reality that death has occurred. Physical symptoms include fatigue, anorexia, palpitations, hyperventilation, restlessness, headache, irritability, and insomnia. Emotional symptoms, in addition to guilt, anger, depression, and denial, include difficulty in concentrating, lack of organization, fear, and preoccupation with the deceased. These grief responses are to be expected. Special memories can trigger the grief response after the initial grieving period, and the memory and emotional pain of the loss may last a lifetime. Symptoms of grief, including psychic pain, numbness, intrusive thoughts, and disorganization, continue to occur during the recovery of most survivors, gradually becoming attenuated but recurring during months or years without clear "stages."[64,65]

Risk factors for difficulty in navigating the work of grieving can sometimes be recognized, even in the ED. Such factors include the death of a child or long-term spouse, the social isolation of the survivor, and a dependent or conflicted relationship with the deceased.[55] The physician may be able to alert the survivor's primary physician or support staff, or even the at-risk survivor directly, that ongoing work may be required to see this grief to resolution.

Grief Reactions in Staff

The impact of death in emergency medicine is significant for the staff, including physicians. Patients who particularly trigger stress reactions among the staff include young people, victims of random and senseless violence, and those who may have caused an accident or injury. ED stress can be significant when the patient needs to receive care rapidly on the basis of scant knowledge, which other professionals can later second-guess. The ED clinician also carries a personal history that may include circumstances that make particular emergencies hit a raw nerve; colleagues may not be aware, for instance, of an alcoholic parent, a sibling who committed suicide, or a friend killed by a drunk driver.

Because of the sometimes overwhelming contact with death and dying in the ED, it is important to have mechanisms in place to help address staff grief responses. At morbidity and mortality conferences, some discussion should be allotted to ethical, sociologic, and emotional sequelae of the cases being presented. The morbidity and mortality analysis process itself helps "make sense" of difficult situations and is part of the grieving process for health care practitioners, but often it emphasizes technical issues and minimizes the very real emotional impact. Case conferences that include a full range of medical personnel, chaplains, and social workers are useful to articulate and to share sadness, anger toward patients, and other emotional and cognitive work required for healing. It is particularly important to offer this to staff after major community disasters. Although for some people denial is a positive coping mechanism, for others the opportunity to share and to express emotions is needed to begin to move forward and resume the work of caring for patients.[64]

Palliative Care in the Emergency Department

Providing quality palliative end-of-life care is important in the ED. Education in Palliative and End-of-Life Care for Emergency Medicine (EPEC-EM) is a curriculum specifically designed to provide clinicians with the information and skills to practice ED-based palliative care.[2] The evidence that we do not know what others want for themselves or family members at the time of critical illness is discussed in the first part of this chapter. In the case of a cardiopulmonary arrest or major trauma resuscitation, attempted interventions are indicated unless the emergency physician has clear instructions from the patient or surrogate to the contrary. In less critical situations, however, guidance about the goals and direction of ED care is needed, and management strategies should be "patient centered."[2,66] Although some would argue that it is time-consuming and unnecessary for emergency physicians to develop a nuanced approach to care of patients near the end of life, it is no longer appropriate to provide all patients with maximal medical treatment and to "let the admitting doctors sort out the other issues." Comfort and quality of life become higher priorities for many patients with severe chronic diseases like cancer, COPD, heart failure, renal insufficiency, and dementia. Some procedures that are normal to aggressive emergency care may not be appropriate in this important group of patients. On the other hand, palliative care is often balanced with life-prolonging care in the management of patient who face life-limiting illnesses.[3]

Establishing Goals of Care

The primary skill that emergency physicians require in managing patients near the end of life is the ability to communicate. In a true emergency, such conversations take a back seat to resuscitation interventions. In many patients, however, it is not imperative to treat before discussion or diagnosis. In the ED setting, several approaches can be helpful to establish what treatments patients want near the end of life.

Reviewing and Honoring Written Advance Directives

Written advance directives can help guide treatment decisions in the ED as well as during hospital admission. Although such documents often do not foresee the particular medical emergency that precipitates an ED visit, their existence indicates that a patient has considered how his or her future medical care should (or should not) look. Advance directives may indicate that aggressive lifesaving interventions are desired or that a patient is in the dying process and wants to be kept comfortable. People's wishes change over time, and written advance directive requests should be reconfirmed at the time of an acute crisis. The clinician should be well versed in the technicalities of the various forms of written legal advance directives that exist.[2]

Verbal Requests to Limit Treatments

Verbal requests to titrate or to limit procedures can be made by the patient or the patient's surrogate. The clinician should determine whether the patient has decision-making capacity or, if such capacity is lacking, who will be the spokesperson for the patient. Invasive tests and procedures may not be performed on patients without their consent. In emergency situations, physicians rely on the "emergency exception" to informed consent and act to preserve life or at least to buy time to consider options. Many situations in the ED, however, do not require immediate intervention, or they allow a less invasive alternative (such as mask ventilation for respiratory failure) while the patient's goals are discussed.

Initiating a Conversation on Goals of Care

Emergency physicians see many sick patients who do not have written advance directives but are stable enough to have meaningful conversations about their needs and goals, their perception of where they are in the course of their disease, whether they wish to cure an intercurrent problem, which symptoms require management, and how much effort they wish to have undertaken if resuscitation is needed to preserve their life. Patients with seemingly lethal conditions may be aggressively pursuing curative or at least disease-modifying options, whereas the burden of suffering other patients are experiencing may not be obvious until they are

www.ketabpezeshki.com 66485457-66963820

Table 1 Representative Questions for Initiation of the Discussion about End-of-Life Issues

DOMAIN	REPRESENTATIVE QUESTIONS*
Goals	Given the severity of your illness, what is most important for you to achieve? How do you think about balancing quality of life with length of life in terms of your treatment? What are your most important hopes? What are your biggest fears?
Values	What makes life most worth living for you? Would there be any circumstances under which you would find life not worth living? What do you consider your quality of life to be like now? Have you seen or been with someone who had a particularly good death or particularly difficult death?
Advance directives	If with future progression of your illness you are not able to speak for yourself, who would be best able to represent your views and values? (health care proxy) Have you given any thought to what kinds of treatment you would want (and not want) if you become unable to speak for yourself in the future? (living will)
Do-not-attempt-resuscitation order	If you were to die suddenly, that is, if you stopped breathing or your heart stopped, we could try to revive you by using cardiopulmonary resuscitation (CPR). Are you familiar with CPR? Have you given thought as to whether you would want it? Given the severity of your illness, CPR would in all likelihood be ineffective. I would recommend that you choose not to have it but that we continue all potentially effective treatments. What do you think?
Palliative care: pain and other symptoms	Have you ever heard of hospice (palliative care)? What has been your experience with it? Tell me about your pain. Can you rate it on a scale of 1 to 10? What is your breathing like when you feel at your best? How about when you are having trouble?
Palliative care: "unfinished business"	If you were to die sooner rather than later, what would be left undone? How is your family handling your illness? What are their reactions? Has religion been an important part of your life? Are there any spiritual issues you are concerned about at this point?

From Quill JE: Initiating end-of-life discussions with seriously ill patients: Addressing the "elephant in the room." JAMA 284:2502, 2000.
*It is important to give the patient an opportunity to respond to each question. Follow-up questions and responses should be based on careful listening to the patient, with use of the patient's own words whenever possible.

asked specifically about their illness and wishes. With or without written advance directives, the physician needs to ask about the patient's wishes.

Questions that can be useful to initiate this conversation are listed in Table 1. Pulling up a chair, sitting with the patient and family, and spending a few minutes clarifying the patient's values and view of the present and of the future may make a big difference in facilitating a plan aligned with the patient's wishes and values.

It is useful to start the "goals of care" conversation with a global understanding of the patient's illness, values, fears, and expectations. Then the "procedures" part of the conversation flows naturally. One suggestion is to explore with questions, such as, What is it that you hope for, given your current condition? and What is it that you are most afraid of? The physician can propose to the

Box 3 Palliative Medical Treatment Options to Enhance Quality of Life

- Pain control
- Control of fluid and electrolyte imbalance
- Nausea, vomiting, and constipation management
- Radiation therapy for bone pain, cord compression, or hemorrhage from tumors
- Drainage tubes for malignant effusions or obstructions
- Treatment of intercurrent infections
- Management of incontinence
- Supplemental oxygen
- Anxiolytics, antidepressants, and appetite stimulants when appropriate

patient and family what treatments will be useful (or not) in the context of overall goals and values, listening for disagreement or affirmation from the patient and family and engaging in shared decision-making.[66] Antibiotics may be appropriate for an acute pneumonia, but they may not be indicated in a patient with advanced dementia who has been bedridden and unable to communicate for several years. Intubation will be acceptable to some patients with COPD, whereas others who have struggled on the ventilator before may not wish to experience that discomfort again. Intravenous hydration is useful to correct dehydration but may merely increase secretions in the patient who is actively dying. All of these interventions need to be considered in the context of caring for the patient and enabling patients to achieve their goals.

Initiating Advance Directives and DNAR Orders

The ED can be an important link in initiation of advance directives because it often is the patient's portal of access to the hospital.[67] Wrenn and Brody described a small series of patients for whom the emergency physician wrote DNAR orders on admission.[68] Balentine and colleagues described another series in which few negative responses were obtained from the families who were approached.[69] Both authors pointed out that fragmentation in health care may mean that previous wishes are not translated into hospitalized settings and that the ED may be the best place to establish or to renew documentation of the patient's wish to forgo resuscitation at the outset of the hospitalization.[6]

Treating Symptoms Requiring Palliation

When a patient is suffering from a disease that is not curable, he or she may still want a variety of medical interventions as part of care: antibiotics for intercurrent infections, drainage of effusions that cause shortness of breath, wound care for decubitus ulcers, decompression of bowel obstructions, and aggressive pain management. The most common reason that patients with end-stage illness seek emergency care is for control of intolerable symptoms such as nausea, vomiting, dyspnea, severe constipation or diarrhea, and pain (Box 3).[2,70]

The ED caregiver may encounter several unfamiliar principles when treating symptoms in persons near the end of life. One of the more "foreign" concepts to most emergency physicians is the treatment of symptoms without diagnosis of the underlying cause, even though this often is the appropriate option in palliative care. In addition, the prioritization of aggressive pain management may feel strange. On the one hand, physicians have concerns about "drugging" patients or overtreating them, although these are mostly unwarranted. On the other hand, worry about unintended consequences may lead to underdosing of medications, leaving patients without desired relief. Concerns about respiratory depression arise when opioids are used, even though the risk of respiratory depression is minimal when the dose is titrated to the patient's desired endpoint. The EPEC-EM curriculum and EPERC (End of

www.ketabpezeshki.com 66485457-66963820

Life/Palliative Education Resource Center) Fast Facts are excellent resources for learning about strategies that are unique to palliative care for patients.[2,71] The following "pearls" from those programs may be useful.

Pain

For patients presenting with acute pain or chronic pain of moderate intensity (rated 5/10 or above), opioid use is appropriate (see Chapter 3). A thorough medication history should be obtained to determine tolerance and dose adjustments that may be needed. Pain assessment is different for patients with chronic pain because they may not show the abnormal vital signs or outward expressions of discomfort commonly observed with acute pain. Patients with advanced illness and pain may be tolerant to opioids and require high doses to achieve comfort. This causes discomfort on the part of the provider. Patients suffering from malignant pain may need continuous infusions of opioids to obtain relief or rapid titration protocols as well as adjustment of chronic doses of analgesics in the ED.[2,71]

When it is available, palliative care consultation can be helpful for treatment of malignant pain. However, pain and palliative care consultation is not uniformly available, particularly during the evening and night hours. Therefore, emergency physicians should have the basic knowledge to treat severe pain. Rapid opioid dose escalation is the most important principle in patients with cancer receiving opioids. Doubling of the dose may be required until successful analgesia is reached.[72] With intravenous administration of morphine, serum levels will be maximal in 6 minutes, so patients need to be reassessed and redosed promptly. Providing stable analgesic effect is important, and this is done by providing a long-acting formulation (e.g., MS Contin), with an immediate-release short-acting agent for breakthrough pain. Side effects from opioids should be anticipated as well. Rising serum levels of opioids stimulate the chemotactic trigger zone, causing nausea. Educating the patient that nausea will subside within days is helpful. Minimizing fluctuations by use of long-acting agents whenever possible can limit this form of nausea. Constipation is a common effect of opioids, and tolerance will not develop. Prevention is far easier than treatment, and a stimulant laxative should be part of all narcotic prescriptions for malignant pain. The use of nonsteroidal anti-inflammatory drugs may be helpful in potentiating the effects of opiates in cancer patients. Recognizing neuropathic pain also is important because medications such as gabapentin may be used. It is important to clearly explain the proposed treatment plan to the patient and caregivers, to monitor the response to treatment and side effects, and to coordinate changes in treatment regimens with the primary care physician.[2,71,72]

Nausea and Vomiting

Nausea and vomiting arise from triggers in the gastrointestinal tract, cerebral cortex, vestibular apparatus, or chemoreceptor trigger zone in the fourth ventricle. The neurotransmitters involved include serotonin, dopamine, acetylcholine, and histamine. Successful treatment of nausea and vomiting involves selection of the drugs that will target the right receptors. In addition to usual antiemetics, dexamethasone, octreotide (which reduces secretions and may be useful in intestinal obstruction), and tetrahydrocannabinol may be important adjuncts for the control of nausea.[2,72]

Constipation

Constipation is multifactorial near the end of life; causes include decreased mobility, medications, mechanical obstruction, and dehydration. Stimulant laxatives and then osmotic laxatives should be tried in escalating doses, and combinations may be needed. Opioid-related constipation can be a major problem. Every attempt should be made to prevent rather than to treat constipation by anticipating the need for stimulant softener combinations when opioids should be used chronically. In cases of mechanical small bowel obstruction, medical management with clear liquids, loperamide, and octreotide results in resolution in a majority of patients.[2,71]

Anorexia and Cachexia

Anorexia and cachexia develop in patients with advanced diseases and may be more stressful for the family than for the patient. Esophageal infection should be considered. Parenteral nutrition does not necessarily reverse this when it is part of end-stage disease and does not affect life expectancy. Appetite stimulants are sometimes useful.[2] Cachectic patients are susceptible to pressure ulcers and skin breakdown that can occur from being placed on a backboard or hard stretcher in the ED.

Shortness of Breath

Shortness of breath also can be part of the last stages of airway disease or cancer involving the lungs. There are many causes, and several treatments may be helpful. Options include symptomatic treatment with oxygen (which may not work if central triggers are operating), anxiolytics, and low-dose opioids, which may decrease the sensation of breathlessness. Malignant effusions may require drainage. In the actively dying patient, morphine and atropine can be used to dry secretions, to slow breathing rates, and to decrease the work of breathing.[2,73]

Depression

Psychosocial distress is exceedingly common in patients suffering with incurable illness. Anxiety and depression have been found to have a negative impact on survival and to decrease quality of life. These issues are best addressed by the primary care provider. Emergency providers can provide empathy and support and recognize that these symptoms are not inevitable components of the dying process and therefore deserve attention.[2]

Special Situations and Diseases

Advanced Dementia

Alzheimer's dementia is a prolonged and relentless chronic disease with a course that can extend up to 20 years. With severe dementia, patients may be combative, incontinent, and unable to ambulate. In the terminal phases of the disease, they are bedridden, mute, and dysphagic and suffer from intercurrent infections.[74] In the demented patient, invasive procedures often require restraints and sedation, and the emotional burden to the patient is high. Even hospitalization, administration of intravenous fluids or antibiotics, and other common interventions are frightening to patients with dementia. As an example, percutaneous gastrostomy or a feeding tube does not prolong life in a patient with late dementia, and qualitative benefits are questionable because provision of artificial nutrition does not prevent aspiration, provide palliation, or improve function in a progressive severe disease like dementia.[75,76] For the emergency physician, the increased burden in combination with decreased benefit, even of the simplest procedures like administration of antibiotics, means that interventions should be thoughtfully chosen and discussed beforehand with surrogates when there is time to do so. Addressing concerns of caregivers also is particularly important in dealing with families of patients with dementia. Depression is common in caregivers; the burden of caring for patients can be severe, and grieving may occur before death as the person that they knew disappears in front of them.

Renal Failure

Dialysis has been a technical success in prolonging life for patients without kidney function. Because it is now so common, physicians

www.ketabpezeshki.com 66485457-66963820

do not realize that the annual mortality rate is about 20% for patients on dialysis and 35% for those older than 65 years.[77] Understanding that dialysis is a choice and not a mandatory intervention may be useful in discussing long-term choices with patients and their families in the ED. In the patient with dementia or cancer, electing not to treat renal failure is an option that should be offered to patients and families.[77]

Heart Failure and Chronic Obstructive Pulmonary Disease

Although the physiologic parameters of terminal heart failure and COPD are well described, death from these diseases is commonly unexpected and may occur as part of a sudden acute deterioration that is not remediable. As a consequence of the entry-reentry pattern of dying associated with congestive heart failure and COPD, many patients will not receive good palliative care until the last days of life. However, some guidelines are available to assist the provider in determining prognosis.[78,79]

On the other hand, if the patient presenting with acute decompensation becomes stabilized, the emergency physician may have a unique role by having the opportunity for a conversation concerning advance planning with the patient and family. The emergency physician can establish what kind of resuscitation measures should be performed if the patient suffers a cardiac or respiratory event in the hospital and who should make decisions on behalf of the patient if he or she should become incapacitated at some time during the admission. In patients with many types of chronic diseases of the entry-reentry type (see Fig. 1), the period after an emergency has resolved (even if temporary) often is the best time to establish what interventions would be appropriate if decompensation occurs again. In terminal stages, an undue focus on diagnostics is more common in these patients than in patients with cancer, particularly if the lethality of these conditions is not acknowledged. Palliative care or hospice referral often is useful in assisting patients with understanding and acknowledging of the prognosis and establishing intentional and realistic projects and goals for their remaining life.

KEY CONCEPTS

- In emergency medicine, it is essential to act rapidly, with the presumption of curative goals, and it may be impossible to withhold initial interventions.
- Advance directives and the patient's wishes should be honored whenever possible, including withdrawal of invasive support if the patient's desire to not receive such treatments is determined after initial ED intervention.
- When the patient cannot speak for himself or herself, the physician needs to search for the correct proxy according to the patient's wishes and state law, when there is time to do this.
- Suffering is not the same as physical pain. The body experiences pain, whereas persons experience suffering, particularly when physical changes threaten their future.
- Patients have individual perceptions of burdens and benefits when they live with chronic illnesses. The only way to understand a person's quality of life and whether treatment is "right" for a patient is to have a conversation to explore his or her wishes and values.
- An important aspect of the initial ED evaluation of a patient with a life-limiting illness is to ascertain the patient's general wishes for future resuscitation and treatments. The conversation with family and patient can begin by asking the following questions: What kind of resuscitation do you wish to receive if an emergency occurs after admission? Whom do you want to make decisions for you if you cannot?
- A discussion of goals of care is more effective if it starts by clarifying the patient's broad values and goals. From the broad discussion, the clinician can suggest what procedures may or may not be useful in attaining the patient's goals.
- The purposes of hospitalization for persons with severe terminal diseases should be clear and in line with the patient's values.

References

1. Le Conte P, et al: Death in emergency departments: A multicenter cross-sectional survey with analysis of withholding and withdrawing life support. *Intensive Care Med* 2010; 36:765.
2. Emanuel LL, Quest TE, eds: *Education in Palliative and End-of-Life Care (EPEC-EM) Curriculum: The EPEC Project*, 2008. Available at http://epec.net/epec_em.php. Accessed May 9, 2011.
3. Smith AK, et al: Am I doing the right thing? *Ann Emerg Med* 2009; 54:86-93.
4. Mokdad AH, et al: Actual causes of death in the United States, 2000. *JAMA* 2004; 291:1239.
5. Lunney JR, et al: Patterns of functional decline at the end of life. *JAMA* 2003; 289:2387.
6. Weissman DE: Decision making at a time of crisis near the end of life. *JAMA* 2004; 292:1738.
7. Christakis NA, Lamont EB: Extent and determinants of error in doctor's prognoses in terminally ill patients: Prospective cohort study. *BMJ* 2000; 320:469.
8. Lamba S, Quest TE: Hospice care and the emergency department: Rules, regulations, and referrals. *Ann Emerg Med* 2011; 57:282-290.
9. Clark D: Between hope and acceptance: The medicalisation of dying. *BMJ* 2002; 324:905.
10. Gruneir A, et al: Where people die: A multilevel approach to understanding influences on site of death in America. *Med Care Res Rev* 2007; 64:351-378.
11. Truog RD: Brain death—too flawed to endure, too ingrained to abandon. *J Law Med Ethics* 2007; 73:273.
12. Kompanje EJ, de Groot YJ, Bakker J: Is organ donation from brain dead donors reaching an inescapable and desirable nadir? *Transplantation* 2011; 91:1177-1180.
13. Steinbrook R: Organ donation after cardiac death. *N Engl J Med* 2007; 357:209.
14. Mohindra RK: Medical futility: A conceptual model. *J Med Ethics* 2007; 33:71.
15. Liao Y, et al: Quality of the last year of life of older adults: 1986 vs 1993. *JAMA* 2000; 283:512.
16. Singer PA, Martin DK, Kelner M: Quality end-of-life care: Patients' perspectives. *JAMA* 1999; 281:163.
17. Quill TE: Initiating end-of-life discussions with seriously ill patients: Addressing the "elephant in the room." *JAMA* 2000; 284:2502.
18. Teno JM, et al: Association between advance directives and quality of end-of-life care: A national study. *J Am Geriatr Soc* 2007; 55:189-194.
19. Citko J, et al: The National POLST Paradigm Initiative, 2nd edition #178. *J Palliat Med* 2011; 14:241.
20. Rid A, Wendler D: Can we improve treatment decision-making for incapacitated patients? *Hastings Cent Rep* 2010; 40:36.
21. Gerhart KA, et al: Quality of life following spinal cord injury: Knowledge and attitudes of emergency care providers. *Ann Emerg Med* 1994; 23:807.
22. Fox E: Predominance of the curative model of medical care: A residual problem. *JAMA* 1997; 278:761.
23. Cassell EJ: The nature of suffering and the goals of medicine. *N Engl J Med* 1982; 306:639.
24. World Health Organization: *WHO Definition of Palliative Care*. Available at www.who.int/cancer/palliative/definition/en/. Accessed April 28, 2011.
25. National Hospice and Palliative Care Organization: *NHPCO Facts and Figures: Hospice Care in America, 2010 edition*. Available at: www.nhpco.org/files/public/Statistics_Research/Hospice_Facts_Figures_Oct-2010.pdf. Accessed January 25, 2011.
26. Temel JS, et al: Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010; 363:733-742.
27. Morrison SR, et al: Cost savings associated with US hospital palliative care consultation programs. *Arch Intern Med* 2008; 168:1783-1790.
28. Morrison SR, et al: Palliative care consultation teams cut hospital costs for Medicaid beneficiaries. *Health Aff (Millwood)* 2011; 30:454-463.

www.ketabpezeshki.com 66485457-66963820

29. Lamba S, Mosenthal AC: Hospice and palliative medicine: A novel subspecialty of emergency medicine. *J Emerg Med* 2012; 43:849-53. doi:10.1016/j.jemermed.2010.04.010.
30. American College of Emergency Physicians: *"Do not attempt resuscitation" orders in the out-of-hospital setting*. ACEP Policy Resource and Education Paper, 2003. Available at www.acep.org/content.aspx?id=30108&terms=EMS%20DNR. Accessed April 29, 2011.
31. American Heart Association: Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005; 112:IV-6.
32. National Association of EMS Physicians Position Statement: *Termination of Resuscitation of Non-Traumatic Cardiopulmonary Arrest*, February 2011. Available at www.naemsp.org/documents/TerminationofResuscitationofNon-TraumaticCardiopulmonaryArrest.pdf. Accessed May 10, 2011.
33. Richman, PB, et al: Independent evaluation of an out-of-hospital termination of resuscitation (TOR) clinical decision rule. *Acad Emerg Med* 2008; 15:517.
34. Bookman K, Abbott J: Ethics seminars: Withdrawal of treatment in the emergency department—when and how? *Acad Emerg Med* 2006; 13:1328.
35. Stone SC, et al: Paramedic knowledge, attitudes and training in end-of-life care. *Prehosp Disaster Med* 2009; 24:529-534.
36. Grudzen CR, et al: Potential impact of a verbal prehospital DNR policy. *Prehosp Emerg Care* 2009; 13:169-172.
37. Kellermann A, Lynn J: Withholding resuscitation in prehospital care. *Ann Intern Med* 2006; 144:692.
38. Sasson C, et al: A qualitative study to identify barriers to local implementation of prehospital termination of resuscitation protocols. *Circ Cardiovasc Qual Outcomes* 2009; 2:361-368.
39. Schmidt TA, Hickman SE, Tolle SW, Brooks HS: The Physician Orders for Life-Sustaining Treatment program: Oregon emergency medical technicians' practical experiences and attitudes. *J Am Geriatr Soc* 2004; 52:1430.
40. Feder S, Matheny RL, Loveless RS, Rea TD: Withholding resuscitation: A new approach to prehospital end-of-life decisions. *Ann Intern Med* 2006; 144:634.
41. Jacob R, et al: Self-harm, capacity, and refusal of treatment: Implications for emergency medical practice. A prospective observational study. *Emerg Med J* 2005; 22:799-802.
42. Steinbrook R: Physician-assisted death—from Oregon to Washington State. *N Engl J Med* 2008; 359:2513.
43. Zalenski R, Gillum RF, Quest TE, Griffith JL: Care for the adult family members of victims of unexpected cardiac death. *Acad Emerg Med* 2006; 13:1333.
44. Minichiello TA, Ling D, Ucci DK: Breaking bad news: A practical approach for the hospitalist. *J Hosp Med* 2007; 2:415.
45. Ptacek JT, Eberhardt TL: Breaking bad news: A review of the literature. *JAMA* 1996; 276:496.
46. Pauls MA, Ackroyd-Stolarz S: Identifying bioethics learning needs: A survey of Canadian emergency medicine residents. *Acad Emerg Med* 2006; 13:645.
47. Fallowfield L, Jenkins V: Communicating sad, bad, and difficult news in medicine. *Lancet* 2004; 363:312.
48. Gallagher TH, et al: Disclosing harmful medical errors to patients. *N Engl J Med* 2007; 356:2713.
49. Evans WG, et al: Communication at times of transitions: How to help patients cope with loss and re-define hope. *Cancer J* 2006; 12:417-424.
50. Groopman J: Dying words: How should doctors deliver bad news? *New Yorker* 2002; October 28:62.
51. Quest TE, et al: The use of standardized patients within a procedural competency model to teach death disclosure. *Acad Emerg Med* 2002; 9:1326.
52. Buckman R: *How to Break Bad News: A Guide for Health Care Professions*. Baltimore, Md: Johns Hopkins University Press; 1992.
53. Quill TE, Arnold RM, Platt F: "I wish things were different." *Ann Intern Med* 2001; 135:551.
54. Back AL, Arnold RM, Quill TE: Hope for the best, and prepare for the worst. *Ann Intern Med* 2003; 138:439.
55. Iserson KV: *Grave Words: Notifying Survivors about Sudden, Unexpected Deaths*. Tucson, Ariz: Galen Press; 1999.
56. Hobgood CD, et al: The educational intervention "GRIEV_ING" improves death notification skills of residents. *Acad Emerg Med* 2005; 12:296.
57. Compton S, et al: Family-witnessed resuscitation: Bereavement outcomes in an urban environment. *J Palliat Med* 2011; 14:1.
58. Dougal RL, et al: Family presence during resuscitation and/or invasive procedures in the emergency department: One size does not fit all. *J Emerg Nurs* 2011; 37:152.
59. Siminoff LA, et al: Factors influencing families' consent for donation of solid organs for transplantation. *JAMA* 2001; 286:71.
60. Oman KS, Armstrong JD 2nd, Stoner M: Perspectives on practicing procedures on the newly dead. *Acad Emerg Med* 2002; 9:786.
61. Council on Ethical and Judicial Affairs of the AMA: Performing procedures on the newly deceased. *Acad Med* 2002; 77:1212.
62. American College of Emergency Physicians: *Teaching procedures using the newly dead*, January 2003. Practice Resources. Available at www.acep.org/content.aspx?id=30104&terms=procedures%20on%20newly%20dead. Accessed May 7, 2011.
63. Berger JT, Rosner F, Cassell EJ: Ethics of practicing medical procedures on newly dead and nearly dead patients. *J Gen Intern Med* 2002; 17:774.
64. Stroebe M, Schut J, Stroebe W: Health outcomes of bereavement. *Lancet* 2007; 370:1960.
65. Prigerson HG, Jacobs SC: Caring for bereaved patients: "All the doctors just suddenly go." *JAMA* 2001; 286:1369.
66. Kon AA: The shared decision-making continuum. *JAMA* 2010; 304:903-904.
67. Adams J, Wolfson AB: Ethical issues in geriatric emergency medicine. *Emerg Med Clin North Am* 1990; 8:183.
68. Wrenn K, Brody SL: Do-not-resuscitate orders in the emergency department. *Am J Med* 1992; 92:129.
69. Balentine J, et al: Emergency department do-not-attempt-resuscitation orders: Next-of-kin response to the emergency physician. *Acad Emerg Med* 1996; 3:54.
70. Barbera L, et al: Why do patients with cancer visit the emergency department near the end of life? *CMAJ* 2010; 182:563-568.
71. *EPERC Fast Facts*. Available at www.eperc.mcw.edu/EPERC/FastFactsandConcepts. Accessed May 10, 2011.
72. *EPERC Fast Facts: #005 The causes of nausea and vomiting, 2nd ed*, available at www.eperc.mcw.edu/fastfact/ff_005.htm; and *#025 Opioids and Nausea*, 2nd ed: available at www.eperc.mcw.edu/fastfact/ff_025.htm. Accessed May 10, 2011.
73. Weissman D: *Dyspnea at end of life, 2nd ed. Fast Facts and Concepts 27.* Available at www.eperc.mcw.edu/fastfact/ff_027.htm. Accessed May 10, 2011.
74. Hurley AC, Volicer L: Alzheimer disease: "It's okay, mama, if you want to go, it's okay." *JAMA* 2002; 288:2324.
75. Post SG: Tube feeding and advanced progressive dementia. *Hastings Cent Rep* 2001; 31:36.
76. Finucane TE, Christmas C, Travis K: Tube feeding in patients with advanced dementia: A review of the evidence. *JAMA* 1999; 282:1365.
77. Cohen LM, Moss AH, Weisbord SD, Germain MJ: Renal palliative care. *J Palliat Med* 2007; 9:977.
78. Reisfield GM, Wilson GR: Prognostication in heart failure #143. *J Palliat Med* 2007; 10:245.
79. Seamark DA, Seamark CJ, Jalpin DM: Palliative care in chronic obstructive pulmonary disease: A review for clinicians. *J R Soc Med* 2007; 100:225.

www.ketabpezeshki.com 66485457-66963820

Emergency Medical Treatment and Active Labor Act and Medicolegal Issues

Robert A. Bitterman

For the complete chapter text, go to the Expert Consul website. To access your account, look for your activation instructions on the inside front cover of this book.

I. PERSPECTIVE

II. EMERGENCY MEDICAL TREATMENT AND ACTIVE LABOR ACT (EMTALA)

A. Medical Screening Examination

B. Emergency Medical Condition

C. "Any Individual"

D. Request for Examination or Treatment of a Medical Condition

E. Private Patients

F. "Comes to the Emergency Department"

G. "Parking" of Patients Brought by Emergency Medical Services to the Emergency Department

H. National Emergencies or Disasters

I. Other Emergency Department Functions

J. Health Care Providers Qualified to Perform the Medical Screening Examination

K. Ancillary Services as Part of the Medical Screening Examination

L. Policies, Procedures, and Practice Guidelines

M. Registration Process, Collections or Insurance Information, and Authorization

N. Documentation

O. Central Log

P. Medical Record

Q. Stabilization Requirements

R. Disposition Issues under EMTALA

III. CONSENT FOR MEDICAL CARE

A. Informed Consent

B. Implied Consent in Emergency Situations

C. Minors

D. Incompetent or Incapacitated Adults

E. Other Special Patient Populations

IV. REFUSAL OF MEDICAL CARE

A. Informed Refusal

B. Federal Rules

C. Jehovah's Witnesses

www.ketabpezeshki.com 66485457-66963820

V. REPORTING REQUIREMENTS

A. Communicable Diseases

B. Violent Acts

C. Deaths

D. Alcohol-Related Motor Vehicle Crashes

E. Animal Bites

F. Substance Abuse

www.ketabpezeshki.com 66485457-66963820

Emergency Medical Treatment and Active Labor Act and Medicolegal Issues

Robert A. Bitterman

PERSPECTIVE

Practicing good medicine in the emergency department (ED) may have been enough to avoid legal entanglements historically, but no longer. Federal and state laws now directly govern the practice of emergency medicine. The magnitude and complexity of the controlling legal authority plus the significant penalties for noncompliance, such as criminal sanctions, civil lawsuits, civil monetary penalties, and exclusion from participation in Medicare and Medicaid, dictate that emergency physicians acquire functional knowledge of these laws.

Federal law—the Emergency Medical Treatment and Active Labor Act (EMTALA), a section of the Consolidated Omnibus Budget Reconciliation Act of 1985 (COBRA), also known as the "antidumping" statute—governs how emergency physicians must triage, register, examine, provide workup, treat or stabilize, discharge or transfer, use hospital resources, and involve medical staff expertise when caring for patients presenting to the ED.[1-3] State laws further control the practice of emergency medicine through such issues as consent, reporting requirements, confidentiality requirements, forensic and police matters, civil commitments, and emergency medical services (EMS) statutes.

EMERGENCY MEDICAL TREATMENT AND ACTIVE LABOR ACT (EMTALA)

EMTALA originally was enacted to prevent private hospitals from refusing to treat indigent patients with medical emergencies or transferring ("dumping") them in an unstable condition to public hospitals. Subsequent amendments to the law, government regulations, and court decisions greatly expanded the reach of EMTALA, such that the law now sets national standards for the provision of emergency services.[2-4] Today, emergency physicians must have a solid understanding of EMTALA's statutory requirements and how the regulatory agencies and the courts interpret the three main aspects of the law: screening, stabilizing, and discharging or transferring ED patients.

Medical Screening Examination

Any person who comes to an ED requesting examination or treatment for a medical condition must be provided with an appropriate *medical screening examination* (MSE).[5] The purpose of the MSE is to determine whether the patient has an *emergency medical condition* (EMC).[6,7]

Emergency Medical Condition

EMTALA defines an EMC as "acute symptoms of sufficient severity (including severe pain) such that the absence of immediate medical attention could reasonably be expected to result in (1) placing the health of the individual (or, with respect to a pregnant woman, the health of the woman or her unborn child) in serious jeopardy, (2) serious impairment to bodily functions, or (3) serious dysfunction of any bodily organ or part."[6] In the case of a pregnant woman who is having contractions, an EMC is defined as one in which "there is inadequate time to effect a safe transfer to another hospital before delivery, or that transfer may pose a threat to the health or safety of the woman or the unborn child."[7]

Competent physicians can reasonably disagree as to whether certain conditions are serious enough to constitute an "emergency." However, the courts hold that the relevant factor is whether the physician *perceived* the patient to have an EMC, not whether the patient actually had an EMC and not whether the emergency physician or hospital should have known that the EMC existed. The focus is whether the physician or the hospital did in fact actually determine that the patient had an EMC; the standard is subjective, not objective.[8] If the physician and the hospital perform an appropriate MSE and in good faith determine that no EMC existed, the courts will not retrospectively review that decision; rather, it will be a simple state malpractice issue of whether the examination and diagnosis met the applicable standard of care.

If the MSE does not reveal an EMC, further care of that patient is not controlled by EMTALA, so the law's provisions governing stabilizing treatment, transfer of the patient, or involvement of on-call physicians no longer apply. This interpretation emphasizes the critical importance of documentation of the presence or absence of an EMC during a patient's initial ED evaluation. A check box to indicate such should be on every ED medical record.

"Any Individual"

Everyone who presents to the ED requesting care must be screened. Whether the patient is indigent, a member of a managed care plan, or covered by Medicare, Medicaid, or private insurance is irrelevant; the hospital must provide everyone who presents for care with an MSE.[5] This includes all populations of patients, such as illegal aliens, minors, and private patients of the hospital's medical staff, but excludes persons who are already patients of the hospital, such as inpatients or outpatients undergoing a scheduled procedure at the hospital who are brought to the ED for

www.ketabpezeshki.com 66485457-66963820

emergency care.[2] The screening of minors is discussed later in the section on consent.

Request for Examination or Treatment of a Medical Condition

Mere presence in the ED or on hospital property is not sufficient to trigger the hospital's duty to provide an MSE; a request for examination or treatment also is necessary. The request can be made by *anyone* on behalf of the patient, including EMS personnel, a police officer, or a babysitter; the request does not have to come from the patient, a family member, or a legal guardian.[5]

Also, if a person is unable to speak to request care, that person's behavior may constitute a request if the hospital's personnel are aware of the behavior and a prudent layperson would believe that the behavior indicated a need for examination or treatment.[2]

Private Patients

In many hospitals, members of the hospital's medical staff often meet their private patients in the ED. These patients are examined and treated by their private physicians, not the emergency physician on duty. Such practice is entirely appropriate to maintain physician-patient relationships and is allowable under EMTALA. However, the hospital should have prearranged procedures for handling of private patients that do not unduly delay the patient's MSE; otherwise, the hospital could be liable under EMTALA for failure to provide an "appropriate" MSE. Delay of treatment in such instances also frequently results in hospital liability through state malpractice actions.

Triage of all private patients should be conducted according to the hospital's established protocols. If the triage nurse determines that the patient requires immediate care, the emergency physician on duty should provide the necessary treatment until the patient's private physician arrives in the ED to assume the patient's care.

If triage determines that the patient does not require immediate care, the emergency physician should see the patient in the order consistent with the usual practice of the ED, generally in the order of acuity or time of arrival. If the private physician comes to the ED and sees the patient before the emergency physician does, the examination by the private physician constitutes the required MSE by the hospital. In this situation, no undue delay of the MSE for any nonmedical reason has occurred. However, if the patient's private physician has not arrived by the time the emergency physician would normally examine the patient, the emergency physician should perform an MSE. If no EMC is evident, the patient can wait for his or her physician to arrive. If an EMC exists, the emergency physician should undertake appropriate stabilizing treatment until the patient's physician arrives.[9,10]

"Comes to the Emergency Department"

The Centers for Medicare and Medicaid Services (CMS) deems anyone on hospital property to have "come to the emergency department."[11,12] According to CMS, "hospital property" consists of the entire main hospital campus, including parking lots, sidewalks, and driveways, and any ambulance owned and operated by the hospital, even if the ambulance is not on hospital grounds.[12] CMS then divides hospital property into "dedicated emergency departments" and all other property that is not a dedicated ED.

A *dedicated* ED is defined as any department or facility of the hospital, whether on or off campus, that is licensed by the state as an ED; is held out to the public as a place that provides care for persons with EMCs on an unscheduled basis; or actually does provide care for persons with EMCs a certain percentage of the time.[2] Units qualifying as dedicated EDs include typical hospital EDs, labor and delivery units, and psychiatric intake centers.

CMS also intended EMTALA to apply to urgent care centers. However, urgent care centers do not hold themselves out as able to provide care for EMCs as defined by the statute, nor do they in actuality provide care for a sufficient number of true emergencies to meet the regulatory percentage. Thus the typical urgent care center is not likely to meet CMS's regulatory definition of a dedicated ED and therefore will not have to comply with EMTALA. Hospitals should examine how their relationship with any urgent care center is legally structured in conjunction with the regulations to determine whether EMTALA applies.[2,13]

CMS specifically exempts a number of on-campus areas from compliance with EMTALA—in general, those areas that typically do not provide emergency care, such as physicians' offices, skilled nursing facilities, other entities that participate separately under Medicare, and other nonmedical facilities on campus.[2] CMS also exempts application of the law to off-campus facilities and other "departments of a provider" that were never intended or structured to manage EMCs, such as dialysis centers, rehabilitation units, laboratories and radiology centers, and primary care clinics. However, these facilities must have written policies and procedures for appraisal of emergencies and arrangement of transfer when it is appropriate.[14,15]

Presentations to the hospital's dedicated ED require only a request for examination or treatment of a medical condition; it is not required that the presentation be for a medical condition that constitutes a true emergency to trigger EMTALA's screening duty. Presentations to hospital property other than to the dedicated ED do, however, require the request to be for an EMC before EMTALA applies.[2]

"Parking" of Patients Brought by Emergency Medical Services to the Emergency Department

Overcrowding led some hospitals to ignore ambulance patients, leaving EMS to care for them until the hospital "accepted" the patient, a practice termed EMS "parking." These hospitals erroneously believed that unless they accepted responsibility for the patient, they had no EMTALA duty to provide care or to accommodate that patient. CMS issued a memorandum reminding hospitals that their EMTALA obligation begins the moment the patient "comes to the ED" and a request is made on behalf of the patient for examination or treatment of a medical condition, not when the hospital "accepts" the patient.[16] Of note, the practice of parking EMS patients also may violate Medicare regulations, which require hospitals to "meet the emergency needs of patients in accordance with acceptable standards of practice."[17]

CMS later clarified that its parking memo did not mean that hospitals are required in all instances to take instant custody and responsibility of all patients brought in by EMS, stating that its guidance "should not be interpreted to mean that a hospital cannot ever ask EMS staff to stay with an individual transported by EMS to the hospital when the hospital does not have the capacity or capability to immediately assume full responsibility for the individual."[18] CMS noted that in certain circumstances, such as an influx of multiple trauma victims, it would be reasonable for the hospital to ask the EMS provider to stay with the patient until such time as the ED staff became available to care for that person.

CMS did affirm, however, that "even if a hospital cannot immediately provide an MSE, it must still triage the individual's condition immediately upon arrival to ensure that an emergent intervention is not required and that the EMS provider staff can appropriately monitor the individual's condition." CMS reviews complaints of this nature on a case-by-case basis to determine whether the hospital violated EMTALA's medical screening mandate.[18]

www.ketabpezeshki.com 66485457-66963820

National Emergencies or Disasters

Under certain circumstances, the Secretary of Health and Human Services can exempt hospitals from EMTALA during times of national or local disasters or terrorist acts, bioterrorist events, or pandemic infectious disease.[19,20]

Other Emergency Department Functions

Hospital EDs serve many functions other than the evaluation and treatment of patients with true medical emergencies. Physicians on the hospital staff may use the ED in the off-hour periods to provide injections or to obtain laboratory tests or radiographs for their patients. Police use the ED to obtain blood alcohol samples on allegedly intoxicated automobile drivers. Some hospitals may use the ED to provide urine drug screens of injured workers, prescription refills, allergy injections, rabies vaccinations, blood transfusions, or other community medical services (e.g., blood pressure screening or "flu shots").

Laboratory Tests and Radiography Requests

The test category includes urine or serum drug screening, routine laboratory tests, and imaging studies. In each case, no immediate medical decision-making is required. The patient's physician determines the indication for the studies and is responsible for the patient's care, including following up on the test or radiography results. The patient is not requesting "examination or treatment for a medical condition" by the hospital's ED, so the hospital does not need to provide an MSE.

Such patients should not be sent through triage and should not have their vital signs taken, and the hospital should not create the usual ED chart for them. They should not be asked to sign the usual ED "consent for treatment" forms, which could imply that they were requesting examination and treatment. Separate paperwork should be used to document the visit, the particular test performed, the patient's informed consent for the testing, any communication with the private physician, and a specific statement that the patient is not requesting an MSE from the ED, with the patient's signature.

Some persons come to the ED on their own, not at the request of their physician, and request a test (e.g., for pregnancy or human immunodeficiency virus serostatus). All such persons should be given an MSE before any test is conducted. If the person declines the MSE, he or she should be referred elsewhere to obtain the requested test: outpatient clinic, personal physician, or public health clinic or a local drugstore for a pregnancy test. Documentation that the person declined the offered MSE is essential.

Minor Treatments

The minor treatment category includes allergy injections, tetanus immunization, rabies vaccination, bloodletting or blood transfusions, chemotherapy infusion for cancer or possible organ transplant rejection, reinsertion of a feeding tube or Foley catheter, prescription refills, suture removals, antibiotic injections, and narcotic injections for chronic pain syndromes. Patients presenting to the ED requesting treatment should be given an MSE. In each instance, the common denominator is the element of medical decision-making.

Antibiotic and narcotic injections require special comment. Physicians, particularly in rural hospitals, may send their patients to the ED and then call in phone orders for parenteral medications. If such patients are not examined by the emergency physician on duty, it probably violates EMTALA because the hospital is not providing these patients the same MSE as it would for any other patient with the same complaint. It is irrelevant if the patient's private physician performed an office examination immediately before sending the patient to the ED. This requirement of EMTALA may not be cost-efficient medicine, but both CMS and the courts agree that a hospital is required to provide an MSE to any person who comes to the ED and requests examination or treatment for a medical condition.[1,21]

All patients presenting for minor treatments should be triaged, registered, and managed as all other ED patients are. The ED evaluation should determine whether the patient's condition meets the definition of an EMC before the hospital administers any medications. CMS and the courts will assume that these patients requested examination or treatment, and the hospital must demonstrate that either (1) these patients did not request that an MSE be performed or (2) the ED evaluation did not reveal an EMC.

Fundamentally, the hospital still must perform an MSE to the extent necessary to determine whether an EMC exists, regardless of whether the patient's presenting complaint appears to be trivial or for a "nonemergency" condition.[2,13]

Prescriptions

In small communities, local pharmacies frequently are not open continuously. Hospital pharmacies, sometimes through the hospital ED, fill prescriptions for patients in off-hours. Patients presenting to the ED to fill these prescriptions do not need an MSE. If the prescription is filled through the ED, the hospital should have the patients sign a form indicating that they are not requesting an MSE, for the same reasons and in the same manner as when tests are done in the ED at the request of physicians.

This situation is different from that in which patients present to the ED for prescription renewals. Patients requesting "refills" on this basis are seeking not pharmacy services but medical decision-making services from a physician by asking for a prescription renewal to treat an underlying medical condition.[2,9] Therefore, patients seeking prescription *renewals* must be provided with an MSE.

Sexual Assault Cases

The ED often assists police in the collection of evidence related to alleged sexual assault cases. If a person comes to the ED solely to provide evidence for the criminal investigation and is not requesting examination or treatment for a medical condition, no MSE is required. However, if the person complains of pain or injury or wants pregnancy or sexually transmitted disease prophylaxis, that person is requesting examination or treatment for a medical condition and must be provided with an MSE.[22]

Preventive Services

Blood pressure screening and vaccination services do not require an MSE. The patient receiving such services is not requesting examination or treatment for a medical condition. The patient is attempting to prevent illness prophylactically, not seeking treatment of an illness. These vaccinations are distinct from tetanus boosters, because boosters typically are administered in response to injury and represent a component of medical decision-making and treatment.

Police Blood Alcohol Tests

For both medical and legal reasons, an MSE should be offered to all persons presenting to the ED for police-requested blood alcohol samples.[23] This scenario is different from that in which patients present to the ED to have blood tests done as ordered by their physicians. Persons in police custody have not been examined by

www.ketabpezeshki.com 66485457-66963820

a physician, and the results of the test will not be returned to a physician to care for the patient. The police officer brought the patient because of aberrant behavior, suspected to be caused by alcohol intoxication. Many diseases mimic alcohol intoxication, including hypoglycemia, cerebral hypoxia, head injury, metabolic abnormalities, and other toxins. Medically, alcohol intoxication should not automatically be presumed as the cause of the patient's condition merely because it is so common. The emergency physician should examine the person in custody to determine if an EMC exists.[9]

The patient may refuse the MSE and request that only the blood be drawn. If the patient appears competent, this can be done. The refusal of the MSE must be documented, as noted for other testing done in the ED, with additional documentation of the risks and benefits of the offered MSE and careful notation of the patient's competence. If the patient is too intoxicated to make medical decisions, release from the ED should be delayed until the patient is competent enough to make rational decisions. Only physicians should assess and document a patient's competence; other ED personnel should not be allowed to make these decisions.[9]

Again, under EMTALA, the "request for examination or treatment" can be made by anyone on behalf of the patient. The police officer's request for blood alcohol sampling may be sufficient to constitute the request for an MSE.

Health Care Providers Qualified to Perform the Medical Screening Examination

EMTALA does not specify whether a physician, a nurse, or another health care provider must perform the MSE. CMS regulations require that the screening examination be done by "qualified medical personnel"[24] and that the hospital's governing body formally designate, in writing, who is a qualified person to perform medical screening on behalf of the hospital.[25,26] CMS specifies that the hospital cannot allow the medical director of its ED to designate who is qualified to perform screenings on behalf of the hospital.[27]

Triage by a nurse does not constitute an MSE, even for "obvious" nonemergent conditions. Neither CMS nor the courts accept triage as adequate to determine whether an EMC exists.[2,3,9]

It is strongly recommended that hospitals designate physicians to be primarily responsible for MSEs performed in the ED. Either the physician personally performs the screening or is directly responsible for examinations performed by physician assistants (PAs), nurse practitioners (NPs) or house staff. It is appropriate to use PAs and NPs to screen patients who are determined by nurse triage to have less acute or severe conditions. However, the physician on duty should have a direct supervisory role with the PA and a collaborative arrangement with the NP.

Ancillary Services as Part of the Medical Screening Examination

The law requires hospitals to provide the screening examination "within the capabilities of the hospital's emergency department, including ancillary services routinely available to the emergency department."[5] According to CMS, this means that the scope of an MSE may "range from a simple process involving only a brief history and physical examination to a complex process that also involves performing ancillary studies and procedures such as (but not limited to) lumbar punctures, clinical laboratory tests, CT scans, and/or diagnostic tests and procedures."[28]

Because the stated purpose of the MSE is to determine whether an EMC exists, CMS and the federal courts hold that the hospital must conduct whatever examination is necessary to make that determination.[3,29] It may take only a visual glance to rule out an EMC in a patient with a rash. However, if it takes a complete neurologic examination, computed tomography scan, and lumbar puncture to decide whether a headache patient has a subarachnoid hemorrhage, then those procedures are considered part of the MSE.

Thus, if the ED usually has ultrasonography, computed tomography, ventilation-perfusion scans, and similar tests available, it must use those resources *if necessary* to determine whether the patient has an EMC. However, the hospital is obligated to use only the resources ordinarily available to its ED.[5] Neither the statute nor the regulations mandate that hospitals expand resources or offer additional services to ED patients. An exception may be the use of interpreters for patients not fluent in the English language, which is required by the Medicare conditions of participation.[30,31]

CMS views the ancillary services available to the ED as including the services of on-call physicians if their expertise is required to decide whether the patient has an EMC.[2,9,13,28,30,32] If the emergency physician cannot determine whether a patient has an EMC, the physician must use the on-call physician services to help make that determination. For example, if it takes an on-call surgeon to decide whether a patient has an "acute abdomen," the surgical evaluation becomes an integral part of the hospital's MSE.

Policies, Procedures, and Practice Guidelines

The federal courts hold that an appropriate MSE has two components: (1) the examination must be "reasonably calculated to identify critical medical conditions" and (2) the "exact same level of screening must be uniformly provided to all patients who present with substantially similar complaints."[29] In other words, a hospital satisfies the requirements of EMTALA if it conducts standard screening procedures, uniformly, for all patients with similar complaints and circumstances.

Each hospital determines its own standard screening policies and procedures. By necessity, each hospital's standard will be individualized because each hospital ED has its own capabilities and different ancillary services available. Once a hospital defines its standard screening process, however, it must apply that process uniformly to all patients presenting with similar complaints, and material departure from its standard screening procedure constitutes inappropriate screening under EMTALA. Because motive is not a relevant issue in the federal courts (except the Sixth Circuit Court) or during CMS investigations, liability may result from any material deviation of the hospital's screening process, regardless of the hospital's motive and regardless of the reason for the deviation. For example, a Florida hospital's screening policy stated that triage would be conducted within 3 minutes after a patient's arrival at the ED. In one instance, a patient was not triaged until 45 minutes after arrival; this delay constituted a violation of the law because the hospital did not follow its own policy.[9]

Once hospitals define their own standard screening process, they will be held to that standard, by both plaintiffs and the government enforcers. Investigators and plaintiff attorneys will subpoena and closely examine the hospital's policies and procedures, medical staff bylaws, ED rules and regulations, practice guidelines, and other written information on the screening process. They will compare the written process to what actually transpired. These hospital documents must be drafted very carefully to avoid unintended liability.

Practice guidelines or protocols, including managed care manuals, adopted by EDs or hospitals may be treated essentially the same as the hospital's own policies and procedures. They also are routinely used to demonstrate that the hospital "failed to follow its own rules" when hospitals and physicians do not adhere to their adopted parameters. In fact, practice guidelines are used *against* physicians and hospitals much more frequently than they are used to their benefit in malpractice litigation.[33]

www.ketabpezeshki.com 66485457-66963820

Registration Process, Collections or Insurance Information, and Authorization

CMS does allow hospitals to conduct reasonable registration procedures in the ED, including collection of insurance data or cash at the time of registration, as long as the process does not delay the MSE. A reasonable registration process may obtain demographic data and the name of the patient's physician and determine whether the patient is insured and the type of insurance. During the registration process, the patient can sign the hospital's usual "informed consent to be examined" form and a routine form that holds the patient financially accountable for any charges not covered by the patient's insurance carrier.[2]

The key is to create parallel tracks for medical and financial issues and to ensure that the financial track never interferes with the medical care in any way. "Bedside registration" probably is necessary under the existing regulatory scheme to avoid "no-delay" violations because CMS would consider any delay in access to the MSE due to diversion to the registration area to be against the law. Waiting for examination and treatment because the ED is overwhelmed is not a violation, but waiting for examination because the registration clerks are collecting insurance information probably is a violation.[2]

CMS warns hospitals not to coerce patients into leaving before they receive their federally guaranteed MSE, stating "reasonable registration processes may not unduly discourage individuals from remaining for further evaluation."[2] Collection of copayments, down payments, advanced beneficiary notifications, or signatures on managed care financial forms may constitute such "economic coercion" if it is not done very carefully. Hospitals also should ensure that staff behavior does not create a hostile environment or constructive denial of the MSE.

Furthermore, hospitals should never delay a patient's MSE to obtain prior authorization from a managed care organization (MCO). First, managed care authorization is authorization for payment only—it is not authorization for treatment, and second, CMS explicitly bans prior authorization for managed care plans before completion of the MSE and commencement of stabilizing treatment.[2] Hospitals may obtain authorization for payment from insurance entities only "concurrently" with stabilization of the patient.[2,27] Hospitals are legally obligated to provide the MSE, and they will be held to that standard regardless of the financial pressures placed on them by MCOs. (As a related issue, "Managed healthcare plans cannot deny a hospital permission to examine or treat their enrollees. They may only state what they will and will not pay for, and regardless of whether a hospital is to be reimbursed for the treatment, it is obligated to provide the services specified in EMTALA."[27])

Patients often ask questions about their obligation to pay for emergency services, particularly whether their insurance will cover the visit or how much it will cost to receive care at the ED. Regardless of EMTALA, all patient questions should be answered forthrightly, honestly, and completely by the hospital staff. In general, routine financial questions can be answered by registration personnel or triage nurses trained to give "stock answers," to not discourage or coerce the patient in any way, and to encourage the patient to stay, with discussions of payment deferred until after an MSE is performed.

After the hospital answers the patient's questions, the patient is responsible for making informed decisions about further aspects of care. If a patient chooses to withdraw a request for examination or treatment and to leave the ED, hospitals need to carefully handle the interaction related to the patient's "voluntary withdrawal" (see the later section on consent). Whenever the patient intends to leave, the staff should involve the physician on duty.

Regardless of managed care status, "VIP" status, private patient status, or any other classification, all patients should be processed in the same manner.[34,35] In addition, the triage team, physician and nursing staff, and all clinical personnel should not know the patient's insurance status throughout the initial screening and stabilizing treatment. This removes insurance status as an issue should the government later claim that the staff was motivated in some way or treated the patient disparately on the basis of financial class. It is easier to prove that actions were not predicated on the patient's financial status when the staff lacked knowledge of that status than to prove that the actions were medically appropriate despite knowledge that the patient had no insurance.

After the MSE and initiation of stabilizing treatment, insurance status and ability to pay can be considered in determining the patient's future care, such as hospital admission, transfer, or discharge and follow-up.

Documentation

EMTALA is a technical law, and compliance with the technicalities requires proper documentation. Furthermore, clinical outcomes are irrelevant under government enforcement, and compliance is not presumed; hospitals must prove compliance through documentation.

Central Log

Hospitals must maintain a central log of all patients presenting to the ED requesting examination or treatment. The log must contain the name and disposition of the patient, including whether the patient refused treatment, whether the hospital refused to provide an MSE or treatment, and whether the patient was treated and stabilized, admitted, transferred, or discharged.[36] The purpose of the log is to permit CMS and state surveyors to select and review individual records to investigate whether the hospital is in compliance with the law.[28]

The log must include all persons presenting to the hospital's dedicated EDs, whether on or off campus.[2,36,37] These areas include the typical ED, ambulatory care or fast-track areas contained within the ED, freestanding emergency centers, labor and delivery suites, and psychiatric intake centers.[2] The logs are not required to be collated into a single document but must be retrievable at CMS's request.

Medical Record

All areas of the hospital used to conduct the MSE must create a medical record for the patient and keep a log of those presenting for examination and treatment.[38] If members of the hospital medical staff see their patients in the ED, on either a scheduled or an unscheduled basis, the hospital must create a medical record and require the physician to document the care provided in that record. The physician's private office records documenting care provided at the hospital are insufficient.

Most important, the emergency physician should document whether an EMC was determined to exist for *every* patient seen in the ED, even if the initial chief complaint is seemingly trivial. The legal purpose of the required MSE is to determine if an EMC is present. To facilitate documentation, ED charts should include two check boxes: one labeled "EMTALA EMC present" and the other "EMTALA EMC absent." The person performing the MSE should check the appropriate box for each patient, and completion of this documentation should be a prime part of the ED's quality improvement monitoring program.

Stabilization Requirements

Once the hospital determines that an individual has an EMC, EMTALA requires the hospital either to stabilize the EMC or, if it

www.ketabpezeshki.com 66485457-66963820

lacks the capability to stabilize the patient, to transfer the patient to another medical facility that can provide the necessary treatment.[39] A sample form for use in documenting such transfers and patient consent to transfer is shown in Figure 1.

When and if the patient is "stabilized" has significant ramifications for hospitals and physicians because once patients are stabilized, EMTALA no longer applies.[40] After stabilization, hospitals are free to refuse to provide further treatment or to transfer stabilized patients for purely financial reasons. On-call physicians can refuse to treat or to admit stable patients or insist that stable patients be transferred owing to their lack of or type of insurance. An MCO can refuse further payment to the hospital and request that the stabilized patient be transferred to one of its contracting facilities.[41,42]

However, other federal, state, or local standards may govern further treatment or transfer of ED patients. For example, state laws often prohibit hospitals from transferring patients for any reason except that they are incapable of handling the patient's medical problem.

Two elements must be present to trigger EMTALA's stabilization requirement: (1) the patient must have an EMC, as defined by law, and (2) the hospital must determine that an EMC exists. That an EMC exists is not sufficient to invoke the duty to stabilize; the hospital also must have actual knowledge that the EMC is present. *Actual knowledge* is a legal term that means the examining physician subjectively believed that an EMC existed. It is not the commonly understood objective standard used in malpractice cases, wherein liability is predicated on whether the physician knew or reasonably should have known that the patient had an emergency condition. Whether the physician's judgment was negligent, or even grossly negligent, is irrelevant under EMTALA. The *subjective perception* of the examining physician controls whether EMTALA's stabilization requirement is triggered.

The appellate courts have uniformly held that if an EMC is not detected, the hospital has no stabilization duty and cannot be charged with failure to stabilize the patient's condition.[8,9,43,44] Furthermore, consideration or suspicion that an EMC may exist does not rise to the level of actual knowledge. If the hospital fails to detect an EMC through its standard screening procedures, the patient has only a state malpractice claim of "failure to diagnose" and not a federal cause of action for "failure to stabilize" the emergency condition. Once the physician or hospital does diagnose an EMC, however, the courts will allow a failure-to-stabilize claim to be brought in federal or state court under EMTALA.

This aspect of EMTALA is distinctly different from ordinary malpractice. Documentation in the medical record of "no EMC present" eliminates all further liability under EMTALA; understanding and use of this distinction should be part of every ED's risk management program.

The screening section of EMTALA mandates the hospital to provide only those services within the capability of the *ED,* including ancillary services routinely available to that department.[5] The stabilization section, however, requires the level of services within the capabilities of staff and facilities available at the *hospital.*[45]

The capabilities of the hospital staff include whatever intensity of care the personnel of the hospital can provide within the training and scope of their professional licenses and hospital privileges.[27] To ensure that hospitals can stabilize patients, Congress mandated that Medicare-participating hospitals maintain a list of on-call physicians available to provide treatment necessary to stabilize a patient with an EMC.[46]

Thus, whenever the ED determines that a patient has an EMC, the hospital must use the full capabilities of its staff, facilities, and on-call physicians to stabilize the patient.[2,45] If the hospital is unable to stabilize the patient, a physician must certify that a transfer is medically indicated and arrange an "appropriate" transfer to a higher level facility.

The treating physician needs to decide whether a patient's EMC is stable or unstable. If two physicians disagree about whether the patient is stable but only one of the physicians is at the bedside caring for the patient, the on-site physician should make the decision.[2,9] It is *not* appropriate for an on-call physician, a "managed care gatekeeper" physician, a physician at a receiving facility, or even the patient's regular attending physician to disagree with the decision of the on-site physician over the phone. If one of these outside physicians wants to overrule the determination of the on-site physician, he or she must come to the hospital and personally examine the patient.

EMTALA defines the term *stabilized* as follows: "no material deterioration in the condition is likely, within reasonable medical probability, to result from or occur during the transfer of the individual from a facility."[47] For a pregnant woman having contractions who has an EMC, stabilized means that delivery (including the placenta) has occurred.[48]

This is a *legal* definition of stabilization, not a medical definition. The standard of care for any patient diagnosed with an EMC will be judged by this legal definition, not by the usual medical malpractice standards. This is a national standard under federal law, not a local standard under state malpractice law.[9,48]

The question of "stabilization" typically arises only when the patient deteriorates during or after the transfer and experiences an adverse medical result. It is likely to appear, particularly in hindsight, that the patient was not completely stabilized before transfer. Health care providers should remember that their compliance usually will be judged by an unsympathetic jury, aided by hindsight, in the context of impairments suffered by the patient in an adverse medical outcome. Unfortunately, the court system, not the health care system, will ultimately determine when a patient with an EMC is legally "stabilized."[9,48]

The U.S. Supreme Court, in the case of *Roberts v Galen,* ruled that a plaintiff need not show improper motive for a transfer to prevail on a failure-to-stabilize claim under EMTALA. The plaintiff merely must prove that the patient was not properly stabilized before the transfer.[49]

EMTALA's requirement to provide on-call physicians no longer extends to inpatients diagnosed with an EMC.[2] Other Medicare conditions of participation govern inpatient care, and hospitals certainly should implement policies and procedures to provide emergency specialty services to patients in whom an EMC develops after admission to the inpatient setting.[2]

Disposition Issues under EMTALA

Admission

Once the emergency physician determines that a patient needs to be hospitalized, the patient's physician or the appropriate on-call physician should be contacted. If the admitting or on-call physician disagrees with the emergency physician's judgment, it is incumbent on the admitting or on-call physician to come to the ED to personally examine the patient. This fact should be mutually understood by the entire medical staff and the hospital administration and should be written into hospital policy and procedure.

Direct patient admissions are problematic. In the three most common scenarios, the patient (1) is sent to the ED after being examined by the primary care physician (PCP) in the office, (2) is sent in after phone contact with the PCP, or (3) is accepted by phone-in transfer from a different hospital ED or inpatient setting by the PCP. In all three cases, the PCP intends to see the patient after admission to the inpatient setting rather than in the ED. Medically, each presentation may require a different level of acute intervention, but legally all are the same under EMTALA.[2,3,13] CMS does not apply the law to *inpatients* regardless of whether they are

www.ketabpezeshki.com 66485457-66963820

PHYSICIAN

Emergency Medical Condition (EMC) Identified: (*Mark appropriate box(s), then go to Section II)* **[Dr. Bitterman - 2013]**

I. MEDICAL CONDITION: Diagnosis____

☐ **No Emergency Medical Condition Identified:** This patient has been examined and an EMC has not been identified
☐**Patient Stable -** The patient has been examined and any medical condition stabilized such that, within reasonable clinical confidence, no material deterioration of this patient's condition is likely to result from or occur during transfer.
☐**Patient Unstable -** The patient has been examined, an EMC has been identified and patient is not stable, but the transfer is medically indicated and in the best interest of the patient. *I have examined this patient and based upon the reasonable risks and benefits described below and upon the information available to me, I certify that the medical benefits reasonably expected from the provision of appropriate medical treatment at another facility outweigh the increased risk to this patient's medical condition that may result from effecting this transfer.*

II. REASON FOR TRANSFER: ☐ Medically Indicated ☐ Patient Requested ____________________________

☐ On-call physician refused or failed to respond within a reasonable period of time.

Physician Name: ____________________________Address ______________________________________

III. RISK AND BENEFIT FOR TRANSFER:

Medical Benefits :	**Medical Risks :**
____________________________________	____
☐Obtain level of care/ service NA at this facility.	☐Deterioration of condition in route ________________
Service _________________________________	☐Worsening of condition or death if you stay here.
☐Benefits outweigh Risks of Transfer	There is always risk of traffic delay/accident resulting in condition deterioration.

IV. Mode/Support/Treatment During Transfer As Determined by Physician– (Complete Applicable Items):

Mode of transportation for transfer: ☐ BLS ☐ ALS ☐ Helicopter ☐ Neonatal Unit ☐ Private Car ☐Other__________

Agency:_______________________ Name/Title accompany hospital employee:________________________________

Support/Treatment during transfer: ☐ Cardiac Monitor ☐ Oxygen – (Liters): __________ ☐ Pulse Oximeter ☐ IV Pump ☐ IV Fluid: ____________ Rate: _____________ ☐ Restraints – Type: ______________ ☐Other:__________ ☐ None

Radio on-line medical direction control *(If necessary):* ☐Transfer Hospital ☐ Destination Hospital ☐ Other

V. Receiving Facility and Individual: __The receiving facility has the capability for the treatment of this patient (including adequate equipment and medical personnel) and has agreed to accept the transfer and provide appropriate medical treatment.

Receiving Facility: /Person accepting transfer: ____Time: ________________

Receiving MD____

Transferring Physician Signature____ Date/Time____________________

Per Dr. ____________________ by ______________________RN/ Qualified Medical Personnel ____________ Date/Time

NURSING

VI. ACCOMPANYING DOCUMENTATION– sent via: ☐Patient/Responsible Party ☐Fax ☐Transporter
☐ Copy of Pertinent Medical Record ☐ Lab/ EKG/ X-Ray ☐ Copy of Transfer Form ☐ Court Order
☐ Advanced Directive☐ Other ____

Report given (Person/title):____

Time of Transfer: _____________Date: ___________ Nurse Signature: ______________________Unit:__________

Vital Signs Just Prior to Transfer: T________ Pulse _______ R _________ BP ________ Time: _________

PATIENT

VII. PATIENT CONSENT TO "MEDICALLY INDICATED" OR "PATIENT REQUEST" TRANSFER:

☐ I hereby **CONSENT TO TRANSFER** to another facility. I understand that it is the opinion of the physician responsible for my care that the benefits of transfer outweigh the risks of transfer. I have been informed of the risks and benefits upon which this transfer is being made.

☐ I hereby **REQUEST TRANSFER** to _____________________________________. I understand and have considered the hospital's responsibilities, the risks and benefits of transfer, and the physician's recommendation. I make this request upon my own suggestion and not that of the hospital, physician, or anyone associated the hospital.
The reason I request transfer is: ____

Signature of ☐ Patient ☐ Responsible Person____________________________________ Relationship _____________
Witness____________________________________ Witness_____________________________________

TRANSFER FORM	Patient Name:
	Date of Birth:
White:-Receiving facility; **Yellow:** Medical Record; **Pink:**-QA	Medical Record Number:

Figure 1. Emergency Medical Treatment and Active Labor Act (EMTALA) hospital transfer form.

www.ketabpezeshki.com 66485457-66963820

directly admitted to the unit, directly admitted by way of the ED, or "boarded" in the ED awaiting bed placement. Even if the inpatient is brought down to the ED, the law does not apply.[2,3,24] According to CMS, once a hospital admits the individual in good faith (i.e., the admission is not a ruse to avoid liability under the law) as an inpatient for further treatment, the hospital's obligation under EMTALA ends.[44,50]

An *inpatient* is defined as "an individual who is admitted to a hospital for bed occupancy for purposes of receiving inpatient hospital services … with the expectation that he or she will remain at least overnight."[2] It does not matter if the situation changes later and the patient can be discharged or transferred to another hospital and does not actually use the bed overnight. The key element is that the patient be formally admitted with a documented admission order. A physician's intent to admit or a level of acuity indicating that the patient "obviously will be admitted" is not enough to satisfy the definition. Documentation is critical.[2,24]

CMS does not consider patients admitted to observation status to meet the regulatory definition of admitted patients (not admitted for purposes of receiving inpatient services), so EMTALA still applies to the care of observation patients, such as patients managed in ED chest pain or observation units.[2,24] Therefore, under existing government regulations, persons who were directly admitted and sent through or held in the ED from a physician's office, from a nursing home, or in transfer from another ED or another hospital inpatient setting are no longer covered by EMTALA, even though they have "come to the hospital's emergency department."

However, in 2009 the Sixth Circuit Court of Appeals in the case of *Moses v Providence Hospital* rejected CMS's interpretation, and, giving no deference to the agency's rulemaking authority, it overruled CMS's regulation[51] that EMTALA ended when the hospital admitted the patient in good faith. The court determined that the rule was contrary to EMTALA's plain language,[52] which requires a hospital to "provide … for such further medical examination and such treatment as may be required to stabilize the medical condition."[53] Therefore, the Sixth Circuit Court held that the hospital was required under EMTALA not just to admit the patient into an inpatient unit for further care but to actually treat him such that he was stabilized before discharge.[53] Subsequently, the U.S. Supreme Court declined to review the controversial Sixth Circuit decision in *Moses,* so presently in the states of Michigan, Ohio, Tennessee, and Kentucky, EMTALA applies to inpatients, at least for civil litigation purposes, even if CMS will not apply that law to inpatients for regulatory purposes.[53,54]

In *Moses,* the issue was whether EMTALA applied to the discharge of a psychiatric patient from the hospital inpatient setting, many days after he had been admitted through the ED for stabilizing care. After discharge, the patient went home and later murdered his wife, so the family sued Providence Hospital under EMTALA for failure to stabilize the patient before discharging him home. Because EMTALA defines all discharges from the hospital as "transfers," regardless of whether the discharge is from the ED or inpatient setting,[55] the plaintiff's claim was for "failure to stabilize the patient prior to transfer" as required by EMTALA.[53]

In response to the *Moses* case, CMS published, in late 2010, an "advanced notice of proposed rulemaking" soliciting comments on whether it should rewrite two key rules on the application of EMTALA to hospital inpatients.[56]

Q1. Should EMTALA apply to hospitals that admit patients for stabilizing care?

Q2. Should hospitals with specialized capabilities be required to accept patients in transfer after they have been admitted at another hospital?

The second question was posed because in 2008, CMS had issued a rule that hospitals with specialized capabilities did not have an EMTALA obligation to accept the appropriate transfer of an individual who had been admitted in good faith as an inpatient at the first hospital.[57] In other words, because EMTALA ended for the hospital that admitted the patient, no other hospital had an EMTALA duty to accept the patient in transfer, even if the admitting hospital was not able to stabilize the patient.

If the Sixth Circuit's decision in *Moses* is allowed to stand, it would void CMS's regulation that hospitals are not required to accept inpatients in transfer. If EMTALA continues through admission until discharge, CMS loses its basis for claiming that hospitals do not have to accept inpatients with emergency conditions in transfer.[56,58] As of the date of this writing, CMS had not issued any final new rules regarding the application of EMTALA to inpatients.

"Discharge" or "Transfer" to Home

Because EMTALA defines any patient movement away from the hospital as a transfer,[55] all patients discharged from an ED are legally considered to have been transferred. Sending a patient home after treatment in the ED who is retrospectively determined to be unstable is considered to represent a transfer of an unstable patient and, as such, a violation of the law. This exposes the hospital to civil litigation under EMTALA for failure of its emergency physicians to stabilize patients with known emergency conditions before discharge ("transfer") home.[1,49]

To avoid such retrospective analyses, emergency physicians should document that no EMC was found or that the patient was stable on discharge. If the patient leaves without permission, the hospital has not legally transferred the patient.[55]

"Discharge" or Transfer from the Emergency Department to an On-Call Physician's Office

Because all discharges from the ED are defined as transfers under EMTALA, so too are discharges from the ED sent directly to an on-call physician's office for acute intervention. CMS looks askance at transfer of patients away from the hospital to a physician's office for acute procedures that could have been done in the ED or in the hospital.[21,59] Ophthalmologist services may constitute an exception because although the ED may have rudimentary eye tools, ophthalmologists typically have much better equipment in their offices for examination of patients with eye complaints to determine whether an EMC is present or to treat emergency conditions. In essence, movement to the office in these cases becomes a medically indicated transfer to receive a higher level of services than the hospital can provide. CMS accepts such movement, so long as the ED arranges a formal transfer in compliance with EMTALA, as noted later.

CMS's view is extremely unsatisfactory, particularly to orthopedic surgeons. It is standard practice in most hospitals for the emergency physician to splint various displaced fractures and send the patient to the on-call orthopedic surgeon's office for reduction of the fracture and further necessary treatment. CMS believes that the orthopedic surgeon should perform the reduction and treatment at the hospital in each case because the surgeon's office has no resources that the hospital lacks.

However, EMTALA applies only if the EMC is unstable at the time of transfer.[1,9] If the ED "stabilizes" the fracture, EMTALA's obligations end. Thus it is reasonable to send patients to the office for further treatment, so long as they meet the legal definition of "stable at the time of discharge" from the ED. The determination of whether the patient is stable for transfer to the orthopedist's office rests solely on the judgment of the examining emergency physician. If the patient has accompanying injuries or is too uncomfortable to be moved, or if the emergency physician believes the injury is such that the patient should not travel, then the orthopedic surgeon should be asked to care for the patient in the ED.[9]

www.ketabpezeshki.com 66485457-66963820

Follow-up Care

Obtaining follow-up care for discharged ED patients, particularly indigent persons and Medicaid recipients, is a significant problem for nearly every hospital. However, EMTALA does not reach the on-call physician's office in this scenario. If the patient does not have an EMC or is stable at the time of discharge, EMTALA does not apply from that point forward, and the on-call physician has no legal duty *under EMTALA* to see the patient in the office.

The real issue in ED follow-up is the level of commitment the hospital and medical staff are willing to make to the community. If the administration, the board, and the medical staff are comfortable with their decision and if they have acted in the best interests of the patients they serve, they should have no trouble defending their actions to CMS or any other entity.

Whatever decision the hospital and physicians make about ED follow-up duties, they should explicitly define those responsibilities in the medical staff bylaws or hospital rules and regulations so that all personnel understand, in advance, what it means to be "on call" for the ED at that hospital.

ED discharge instruction sheets also should include a *fail-safe clause* advising patients to return to the ED if their condition deteriorates before seeing the referral specialist or if the follow-up arrangements disintegrate for any reason. Such a statement could help the hospital avoid liability when the on-call specialist fails to implement the prescribed follow-up plan.[60]

Transfers to Other Acute Care Hospitals

Before transferring a patient out of the ED, the emergency physician must first determine whether the patient is stable, as defined by law. EMTALA regulates the transfer of unstable patients only; it does not apply to the transfer of stable patients.[2,9] If no EMC is found, the patient is considered stable. The determination of whether a patient is stable must be made at the time of transfer to be valid under the law.[59] Unstable patients can be transferred for only one of two reasons: if the transfer is medically indicated, or if the patient requests the transfer.[9] There is no "managed care transfer of an unstable patient" or even of a stable patient.

Patients usually are transferred out of the ED because the transferring facility lacks the capability or the resources necessary to treat the identified EMC. Examples of patients best served by transfer are the head-injured patient in a hospital without a neurosurgeon on staff, the pregnant woman who needs the services of a high-risk obstetric center, and the multiple-trauma patient treated initially in a rural ED who requires treatment at a level 1 trauma center.

EMTALA defines such transfers as medically indicated transfers because the purpose of each transfer is to obtain a higher level of medical care necessary to treat the patient's condition that is not available at the transferring facility. EMTALA governs almost every aspect of medically indicated transfers, including requiring hospitals to adopt and to enforce policies to ensure compliance with federal transfer laws and mandating specific actions by the transferring and receiving hospitals (summarized in Boxes 1 to 3).[1-3,9,61-63]

Some states have enacted their own transfer laws.[64] Most state laws parallel EMTALA, but some are even more restrictive, so physicians responsible for patient transfers should be aware of the controlling laws and regulations in their own state as well as federal law.

Box 1 Recommended Procedures for the Transferring Facility

- Stabilize the patient whenever possible.
- Complete a physician certificate of transfer, including the risks and benefits of transfer.
- Obtain the patient's informed consent to the transfer.
- Arrange for another hospital and physician to accept the patient in transfer.
- Send appropriate data to the accepting facility (e.g., medical records, test results, transfer forms).
- Arrange the transfer through qualified personnel, with use of appropriate transportation equipment.
- Maintain records of all transfers for 5 years.

Box 2 Invalid Reasons for Refusal of an Appropriate Patient Transfer

- Lack of insurance or out-of-network managed care plan
- Lack of citizenship
- Veteran status
- Patient's physician not on staff
- Transferring hospital is out of network or outside hospital's defined referral area
- "We are not an affiliated hospital"
- "We are not a specialty hospital"
- "We are a specialty hospital, but that's not our specialty"
- "We are not a 'trauma center' "
- Transfer originating out of county or out of state (including transfer of out-of-state Medicaid patients)
- EMS skipped over closer hospital
- Another hospital refused the transfer in violation of the law
- Another hospital's on-call physician refused to respond to its ED in violation of the law

ED, emergency department; *EMS,* emergency medical services.

Box 3 Recommendations for the Facility Asked to Accept the Patient in Transfer

- Accept all appropriate requests for transfer, regardless of whether the patient is an ED patient or an inpatient of the hospital.
- Have a formal system for accepting or rejecting transfer requests and document the reasons for any refusal to accept a patient in transfer.
- Maintain records of all transfers for 5 years.
- Report all EMTALA transfer violations to CMS.

CMS, Centers for Medicare and Medicaid Services; *ED,* emergency department; *EMTALA*, Emergency Medical Treatment and Active Labor Act.

Duty to Accept Appropriate Transfers from Other Hospitals

Medicare-participating hospitals that have specialized capabilities or facilities are required by EMTALA to accept appropriate transfers of patients who require such capabilities or facilities, if the hospital has the capacity to treat the patient.[65]

The duty to accept patients in transfer is a problematic issue for many larger, tertiary care, or academic hospitals as a result of the on-call specialty coverage crisis in the United States.[66,67] Numerous hospitals have lost full or partial on-call coverage for specialties such as neurosurgery, orthopedic surgery, maxillofacial surgery, neurology, plastic surgery, and hand surgery.[68,69] CMS's softening of its EMTALA on-call regulations in late 2003 accelerated the trend of physicians' simply taking fewer call nights at many smaller to medium-sized hospitals, forcing still more transfers to access emergency specialty care.[3,70,71] As confirmed in recent surveys, these changes have accelerated physician and hospital abandonment of on-call services, increased the risk of harm to patients needing specialty care, caused more delay in patient access to specialty care, and increased the number of patient transfers.[70,71]

www.ketabpezeshki.com 66485457-66963820

Specialty hospitals also enticed physicians away from acute care hospitals, in part because the physicians could decrease their on-call burden. However, CMS now requires specialty hospitals to accept appropriate transfers even if the specialty hospital lacks an ED.[72]

When Must a Receiving Hospital Accept a Patient in Transfer?

A Medicare-participating hospital must accept "medically indicated transfers" if it has "specialized capabilities or facilities" and the "capacity" to care for the patient.[1] *Medically indicated transfers* are ones for which a physician determines the patient has an EMC and needs to be transferred to obtain a higher level of medical care necessary for treatment of the patient's condition that is not available at the transferring facility.[39] *Specialized capabilities or facilities* are essentially any resources, other than a routine admission bed, or physician services available at an accepting hospital but not available at the transferring hospital. *Capacity* is rather generously defined by CMS to include whatever a hospital customarily does to accommodate patients in excess of its occupancy limits. For example, if a hospital customarily moves patients to other units or calls in additional staff, it has in fact demonstrated the ability to provide services to patients in excess of its occupancy limits.[73]

Who Accepts Patients on Behalf of the Hospital?

The duty to accept appropriate transfers is a hospital duty, not a physician duty, and EMTALA does not require that a physician accept the patient.[1] The hospital must create a formal system designating who is authorized to accept or to reject patients on its behalf. It is strongly recommended that hospitals do not use the individual physician on call for each specialty *alone* to accept or to reject patients in transfer. Hospitals should involve an administrative person or an emergency physician in addition to or instead of the on-call physician to avoid inappropriate refusals. Because the duty to accept rests with the hospital, any inappropriate refusal by an uninformed or rogue on-call physician subjects the hospital to termination from Medicare, civil monetary penalties, or civil liability if the patient is harmed because of the refusal to accept the patient in transfer.

The hospital should define the resources and capacity of the institution and the times during which those resources are available. When capacity or necessary resources are not available, the hospital should in a timely manner inform the persons charged with accepting or rejecting transfers. The hospital also should educate appropriate personnel in its known referral facilities on the proper procedure to transfer patients into its system, including informing them of who is and who is not authorized to accept patients in transfer on behalf of the hospital. The hospital is required to educate its medical staff, particularly its on-call physicians and emergency physicians, about their responsibilities under EMTALA, including the responsibility to accept patients in transfer from other facilities on behalf of the hospital.[74]

Does a Hospital Have to Accept Transfers of Inpatients from Other Hospitals?

Current CMS-issued regulations state that no hospital has a legal duty under EMTALA to accept an inpatient in transfer from another hospital. Therefore, even if a requested hospital could treat an inpatient's emergency condition that the transferring hospital is unable to treat, it may refuse the transfer for any reason, including an economic reason, and not be in violation of EMTALA.

However, the issue is certain to be litigated and decided by the courts. It is inevitable that an inpatient will develop an EMC and proceed to die or suffer severe damages because no other hospital would accept the patient in transfer because of lack of insurance. The patient or family will sue the hospital that refused to accept the patient in transfer, claiming that the hospital had a federal duty under EMTALA to accept appropriate transfers of patients with emergency conditions if the transferring hospital could not treat the emergency. The transfer acceptance section of EMTALA was not part of the law when it was originally enacted. Congress later amended the law, calling it the "nondiscrimination" section, because tertiary and academic referral hospitals were refusing to accept patients in transfer from other hospitals, leaving the patients to die in community EDs.[75] This issue was not specifically addressed in the Sixth Circuit opinion in the *Moses* case, although the court's ruling applying EMTALA to inpatients strongly suggests that it would also apply EMTALA's transfer acceptance section to inpatients as well as to ED patients.[53] Thus it still remains to be seen if the courts will ultimately interpret EMTALA contrary to Congress's nondiscrimination intent for patients with life-threatening emergencies.[76]

When Can a Hospital Refuse to Accept a Patient in Transfer?

There are only five reasons for which a hospital can refuse a request for transfer under EMTALA.

First, if the transfer is not a medically indicated transfer, a hospital can decline the transfer.[1] Non–medically indicated transfers include patient-requested transfers and lateral transfers for any reason (*lateral* meaning that both hospitals have the same ability to handle the patient's EMC), such as managed care transfers or family- or physician-requested transfers. Any time the sending facility can handle the patient's EMC, a hospital requested to accept the patient in transfer can lawfully decline.

Second, if the hospital does not have the capacity, as defined by CMS, to accept the patient in transfer, it may and generally should refuse the transfer.[1,2,73]

Third, if the transferring hospital is located outside the boundaries of the United States, the hospital has no legal obligation under EMTALA to accept the transfer.[77] No other territorial limits are imposed on the duty to accept transfers; out of county, out of state, and out of the hospital's designated referral area all are unacceptable reasons to refuse patients in transfer under EMTALA. Moreover, a hospital cannot refuse to accept a transfer just because the sending hospital is "skipping over" other hospitals to send the patient its way.

Fourth, if the transfer is not "appropriate," the hospital may refuse to accept the patient in transfer at that time.[1] This more vague reason takes into account the patient's condition at the time of transfer and the time, distance, and skipping over of other hospitals necessary to reach a receiving hospital. For example, a trauma patient may need intubation and a chest tube inserted before the transfer is appropriate, or traveling 100 miles with hypotension from a ruptured abdominal aneurysm may not be appropriate if closer hospitals are capable of repairing the aneurysm.

Fifth, the patient has been "admitted" to the hospital as defined by CMS (except in hospitals under the jurisdiction of the federal Sixth Circuit Court of Appeals, at least with respect to civil liability, as noted earlier in this chapter.)[1-3,53]

There are no other reasons for which a hospital may refuse a request to accept a patient in transfer from another acute care hospital under EMTALA. Furthermore, no "contingencies" are allowed to be placed on the acceptance of a transfer. The receiving hospital may not condition acceptance of the patient on the transferring hospital's agreeing to take the patient back once the emergency condition is resolved, may not require that the transferring hospital have additional consultations completed before the emergency physician transfers the patient, and may not require the transferring hospital to use the receiving hospital's transport ambulance or helicopter service as a condition for accepting the patient.[78]

www.ketabpezeshki.com 66485457-66963820

Also, refusal of appropriate transfers on the basis of the patient's insurance status or delay of appropriate transfers until the transferring hospital obtains authorization for payment from the patient's managed care plan is definitely illegal under EMTALA.[79]

Duty to Report Transfer Violations

Any time a hospital has reason to believe it may have received a patient transferred in an unstable condition from another hospital, in violation of EMTALA, it must report the transferring hospital to CMS.[80] The duty to report rests with the hospital, so emergency physicians who receive unstable patients in transfer should inform the hospital (risk management or the hospital's legal counsel), which then can determine the appropriate action.

CONSENT FOR MEDICAL CARE

Informed Consent

The doctrine of *informed consent* is a fundamental principle of the American legal system: "Every human of adult years with a sound mind has a right to determine what should be done with his own body."[81] Physicians may not examine or treat any person without consent, and that consent must be informed. This means that the patient must be given all pertinent ("material") information concerning the nature, risk, and alternatives of the treatment before that patient can be deemed to have effectively consented to the medical intervention.

Physicians should endeavor to obtain informed consent yet remain cognizant of the significant limitations on and multiple exceptions to the doctrine, especially in the ED setting. Delaying treatment in an emergency to obtain informed consent is a much more serious and common medicolegal problem than failure to obtain proper informed consent.

The law of informed consent contains a great deal of uncertainty, with many gray areas. Different states have different views, either in their statutory laws (legislation) or in their common law (judge-made law or precedent), on the meaning of "informed consent" in the care of the ED patient. Most cases are unique and depend on the specific circumstances.

Emergency physicians rarely have time to seek legal consultations, let alone wait for a court to render a decision concerning the legal nuances of consent issues. In these situations, it is helpful for emergency physicians to use a *when-in-doubt rule* to guide their immediate actions. This rule simply states that when emergency physicians are in doubt about the legality of a situation, "they should do what they believe to be in the patient's best interest and worry about the legal consequences later." Although emergency physicians risk criminal and civil charges of false imprisonment, battery, and even negligence for failure to obtain appropriate informed consent, the courts almost universally rule in favor of physicians who act in good faith on behalf of their patients in emergency situations. Successful civil litigation regarding an issue of consent theory against an emergency physician acting reasonably, and consistent with the appropriate standard of care, is extremely rare.[82] An emergency physician is much more likely to be sued for failure to treat while waiting for consent than for providing reasonable treatment without consent.

Federal versus State Laws

Both federal laws (e.g., EMTALA) and state laws govern consent.[5,39] EMTALA comes into play primarily in the evaluation of minors and with patient refusal of an examination, stabilizing treatment, or transfer. State consent laws vary widely and may be set by statutes or case law, or both. The concepts discussed next are generally applicable to emergency medical care, but all emergency physicians should learn the consent laws specific to their own state.

The law presumes that an adult is mentally competent to make medical decisions and that the competent adult is entitled to sufficient information to make an informed decision concerning the physician's proposed course of examination and treatment.[82] Under the doctrine of informed consent, physicians have the duty to disclose the following information to patients[82-84]:

- The patient's condition or diagnosis
- The nature and purpose of the proposed treatment, including the likelihood of success in the physician's practice
- Reasonable alternative measures related to the diagnosis and treatment, including the probable outcome of those alternatives
- The particular known inherent risks that are material to make an informed decision about whether to accept or to reject the proposed treatment, including the consequences of refusing that treatment

Reasonable Person versus Professional Disclosure Standard

The states are split on the standard used to determine what should be disclosed for patients to make informed decisions, but most require the reasonable person standard of disclosure. Under this standard, a physician is required to disclose all of the information that a reasonable person would require to make a decision under the facts and circumstances of the case. The less frequent standard, the professional disclosure standard, requires the physician to provide the same information that other physicians in the community would provide to patients in the same or similar circumstances. This is less stringent than the reasonable person standard.[82,84]

Physicians are not required to disclose every remote risk associated with a procedure or risks that are common knowledge or obvious to the patient, such as the risk of infection after wound repair.[85] The law requires disclosure only of risks that are material, as judged by their seriousness or chance of occurrence. Courts define *material information* as information that "the physician knows or should know would be regarded as significant by a reasonable person in the patient's position when deciding to accept or reject the recommended medical procedure."[86]

Some states legally require physicians to disclose specific risks, such as death.[85] Some states statutorily require a physician to meet both the reasonable person standard and the professional disclosure standard.[87,88]

Physician Role in the Consent Process

The physician who proposes to undertake the procedure must be the one to obtain the patient's informed consent. The duty to obtain consent cannot be delegated, so physicians cannot ask nurses or other health care providers to obtain patients' consent on their behalf. The physician who will care for the patient is best qualified to discuss the treatment and its risks and benefits with the patient. Nurses as well as physicians not skilled in performing the procedure cannot obtain valid informed consent.[89]

The physician should write or dictate into the patient's medical record a summary of the discussion held with the patient and family concerning the elements of informed consent. Particular attention should be made to documentation of those material risks discussed with the patient before the patient's consent is obtained.

Consent is a *process*, not a signature. A written, signed, separate consent form is not legally required under the doctrine of informed consent; however, hospitals may require emergency physicians to complete standardized consent forms and to obtain the patient's signature. The signed form is not a substitute for the consent process. It cannot replace the exchange of information that occurs

www.ketabpezeshki.com 66485457-66963820

between the physician and the patient and family, the answering of questions, and the ultimate agreement of the patient to undergo the medical or surgical intervention.[82]

A signed, written consent form, however, does constitute some evidence of a valid consent. In some states, a signed consent form is presumed to represent valid consent unless that presumption is rebutted by proof that the consent was obtained by fraud, deceit, or misrepresentation of material fact.[90]

Implied Consent in Emergency Situations

If an unconscious or incapacitated patient cannot express consent, the law will assume the patient consented to treatment for the emergency situation. Implied legal consent is premised on two principles: (1) duty to obtain informed consent is excused if death or irreparable harm may result if the physician delays providing treatment, and (2) the law presumes that a reasonable, competent, lucid adult would consent to lifesaving treatment.[91]

The emergency treatment allowed is limited to the circumstances of the emergency, however, and only treatment required to resolve the emergency should be undertaken without consent. Similarly, the emergency condition must require immediate medical attention, with insufficient time to inform the patient or to seek consent from another person.

Courts differ on the definition of a "true emergency," and whether the emergency exception applies in a given case depends on the definition accepted by the court and the application of that definition to the particular set of facts. Fortunately, the courts generally will stretch the doctrine to protect physicians who act in good faith in caring for a patient with a perceived emergency condition.[92] This is one situation in which use of the when-in-doubt rule and documentation of the physician's concerns will weigh greatly in the court's determination of whether the physician acted appropriately without obtaining informed consent. Physicians can further protect themselves by obtaining a second opinion that a true emergency exists.

Minors

Minors Accompanied by a Parent or Legal Guardian

Parents and legal guardians have the right to consent on behalf of their minor children. However, they need to act reasonably and in the best interests of their children. If they do not, their right to consent can be abrogated by the state or the courts. Parents are not allowed to refuse treatment for a child with a life-threatening emergency condition. The management of children with emergency conditions whose parents refuse to give their consent to treatment is discussed later.

Either natural parent of the minor child may provide legally binding consent. If one parent agrees with a proposed treatment and the other does not, consent may be accepted from the agreeing parent. Even if separated or divorced, either parent may give consent unless one parent has been judicially granted sole legal custody of the child, in which case only the custodial parent may consent. The child's biologic father, even if never married to the mother, also may consent for his child.

Unaccompanied Minors

EMTALA mandates that all persons presenting to an ED requesting care be examined to determine whether an emergency condition exists.[5] Because EMTALA is federal law, it takes precedence over all state consent laws regarding the initial evaluation of a minor child. In essence, the child's mere presence at an ED requesting examination or treatment constitutes legal consent to examination of the child to determine whether an EMC is present. Furthermore, the hospital should not delay this initial screening evaluation to wait for consent from a parent or legal guardian (and nurse triage does not qualify as the required medical screening, no matter how nonurgent the child's condition appears to the nurse).

If an EMC is discovered through the initial screening examination,[5,39] the physician may treat the emergency under either state or federal legal theories. First, under state laws, the standard emergency exception doctrine applies. State laws allow physicians to proceed with treatment whenever an emergency exists. Although no uniform legal definition of emergency exists among the states, state laws tend to define an emergency liberally, such as "any threat to the minor's life or health." The courts almost always affirm a physician's judgment about an emergency condition and rarely question the treatment given to a minor without parental consent.[93] Preserving life, preventing permanent disability, alleviating pain and suffering, and avoiding eventual harm have been used as guidelines for emergency treatment without consent.[93] Any minor presenting to the ED should be triaged and provided with an MSE to determine whether an EMC exists.

Under EMTALA, if an EMC is present, the hospital and physicians are required to provide "stabilizing treatment."[39] Federal law also gives the physician broad discretion to decide what treatment should be performed and in what time frame it should be accomplished. The stabilization requirement includes transfer as necessary to an institution capable of handling the minor's emergency condition. Thus, under federal law, a minor could be examined, stabilized, or transferred to another institution without consent ever being obtained from the family; in this instance, the care would be not only in the patient's best interest but also legally mandated.[5,39]

In general, if the MSE does not reveal an emergency condition, physicians need to obtain proper consent from the minor's parents or legal guardian. However, state laws and the courts have applied a number of exceptions to allow minors to seek treatment on their own without parental consent. These exceptions vary widely from state to state, and most are applied through an analysis of facts and circumstances on a case-by-case basis by the courts. Under the *mature minor* exception, minors who possess an understanding and appreciation of the nature and consequences of the treatment and appear competent to make their own decisions are allowed to consent, despite not having reached the defined age for maturity (usually 18 years).[94] A mature minor usually is 15 to 17 years old.

The *emancipated minor* provides another exception to the need for parental consent. If the minor is living independently, is self-supporting, or is in the U.S. Armed Forces, the courts may recognize the minor as emancipated and able to consent on his or her own behalf. Again, this is determined by the courts on a case-by-case basis.[95] In addition, most states have statutory reasons, such as sexually transmitted diseases, pregnancy, or domestic violence injuries, that allow minors to seek care without the consent of their parents.[96]

Incompetent or Incapacitated Adults

If a person has been declared legally incompetent by a court, consent must be obtained from the person's court-appointed legal guardian. In addition, people may appoint legal surrogates to make legal decisions for them should they become incompetent. State-sanctioned living wills, advance directives, and durable medical power of attorney documents all transfer consent powers from a person who becomes incompetent to a legally appointed surrogate.[97]

If an incompetent adult has neither a legal guardian nor an appointed surrogate, physicians typically look to the patient's family for consent to treatment. However, consent to treatment by a family member, even the patient's spouse, generally is not

www.ketabpezeshki.com 66485457-66963820

acceptable under American law unless the spouse or family member has been appointed legal guardian by a court of proper jurisdiction.[98] Marriage does not confer one spouse the legal capacity to consent to medical treatment for the other spouse, even when the ill or injured spouse is incompetent.

Some states recognized this problem and enacted "family consent statutes," which outline a hierarchy of family members who can legally provide consent when the family member becomes incapacitated.[99] However, even when families have no legal standing to consent for the incompetent relative, it is wise to involve family in the medical decision-making process. Communication and concern for the family will avoid misunderstandings, surprise, and anger, which are the primary sources of litigation. Fortunately, if an emergency exists, no authorization from family is necessary to provide such reasonable care as is necessary to correct the life-threatening situation. Once the emergency is resolved, consent should be obtained from someone authorized to act on behalf of the incompetent patient. If there is no appointed legal guardian or surrogate and no state statute on family consent, the physician will need to seek consent authorization from the courts. The courts may appoint a guardian at that time, generally a family member, or after judicial review of the issues, the court itself may grant consent on behalf of the incapacitated person.

Other Special Populations of Patients

Prisoners

Competent prisoners generally do not surrender the right to consent by virtue of being incarcerated. However, a state or court may compel treatment on the basis of interests perceived as paramount to the prisoner's interests.[100] The elements usually necessary to treat self-inflicted injuries over the objection of the competent prisoner include the following[101]:

The injury to the prisoner was willful and intentionally self-inflicted.

The proposed treatment is necessary to preserve or to restore the health of the prisoner.

The prisoner refuses to give consent.

The physician documents the medical indications for treatment in writing in the prisoner's medical record.

Alcohol-Intoxicated Patients

Alcohol intoxication itself may not render a patient incompetent to give informed consent.[102] The emergency physician should evaluate each situation individually to determine whether the patient is incapacitated by alcohol to the extent that he or she is no longer able to understand the proposed treatment, risks and benefits, and rational alternatives. In essence, the general rules for determination of whether a patient is competent to make informed decisions cannot be disregarded just because the person is intoxicated with alcohol. However, the when-in-doubt rule is particularly applicable in these cases because alcohol intoxication often is associated with occult serious illness or injury.

Alcohol intoxication, particularly if it is documented by a measured blood alcohol concentration (BAC), is strongly suggestive to courts and juries of impaired mental status, even though health care workers recognize that many alcoholics are entirely rational and competent at fairly high BACs.[23,103,104] Conversely, low BACs do not guarantee competence because other processes (e.g., hypoglycemia, blood loss, impairment from other illicit substances) may cause the patient to be incompetent. Thus the patient's clinical capacity is more important than the specific level of alcohol in determining competence.

One advantage of obtaining a BAC is that some states allow blood samples drawn solely for medical purposes to be subpoenaed later by the prosecutor for use against the driver in a driving-while-intoxicated prosecution or other criminal charges.[23,105]

The state "legal limit" of intoxication is not a measure of a patient's competence. The legal level for driving has little if anything to do with the capacity to make informed medical decisions. However, this distinction is sometimes difficult for judges and juries to understand, and the emergency physician can actually use the blood level to support a judgment that the patient was not competent to make informed decisions in a particular instance. At other times, it is better not to have a "number," so that the only relevant criterion for determination of the patient's competence is the physician's judgment.[103]

Patients Given Pain Medications

Obtaining informed consent from patients treated with pain medications before a procedure is a common issue. As with alcohol intoxication, the mere fact that a patient has been given narcotic analgesia does not render that patient incapable of consenting to surgical procedures. Plaintiff attorneys can always argue "the patient was too snowed with drugs to give consent"; on the other hand, they can equally argue that the patient was "in too much pain to consent and would have agreed to anything to stop the pain." Accordingly, when consent is sought from a patient who has received pain medication, the patient's ability to understand the ramifications pertaining to the procedure should be assessed and taken into consideration, involving the family in the process if possible. The physician should document that the patient's premedicated state was considered in judging the patient's competence to make an informed decision.

REFUSAL OF MEDICAL CARE

Informed Refusal

The corollary to a patient's right to give informed consent is the patient's right to refuse medical care, even if such refusal results in death. In *Cruzan v Director, Missouri Department of Health*, the U.S. Supreme Court determined that a competent adult has a constitutionally protected right to refuse medical care.[106] However, that right is not absolute. Under particular circumstances, courts will consider countervailing compelling state interests, such as preventing suicide, preserving life, and protecting innocent third parties.

Physicians who honor a competent patient's decision to refuse treatment are not liable for any resulting bad outcome.[107] In fact, physicians are more likely to be successfully sued for treating patients over their objections or without their consent, even when the treatment is lifesaving.

When a competent adult refuses indicated medical intervention, it often is because of fear, anger, misunderstanding, or some other failure in communication in the physician-patient relationship. Before allowing a patient to refuse care, the physician should try to determine and resolve the underlying reasons behind the patient's refusal.

The attending physician must always be involved when a patient refuses medical care or expresses the intent to leave against medical advice.[108,109]

As with consent, refusal of medical care is a process, not a signature. It must be an informed refusal; merely having the patient sign an "informed consent to refuse examination, treatment, or transfer" form or an "against medical advice" form is not sufficient. There are four essential components of the refusal process.

Determining Competence. The physician must determine that the patient is competent to make decisions. Normal findings on the mental status examination without evidence of diminished mental capacity from closed head injury, severe pain, hypoxia,

www.ketabpezeshki.com 66485457-66963820

hypotension, alcohol intoxication, mental retardation, or mind-altering substances constitute good evidence of competency. Noting the patient's rationale for refusing care, even if it is not reasonable, provides additional evidence of competency.[110]

Ensuring an Informed Decision. To be legally binding, a decision to refuse a test or treatment or to sign out against medical advice must be an informed decision. The physician should explain the severity of the patient's condition, the potential complications, and the alternative treatments available. The physician should use terms that the patient can understand and provide the patient an opportunity to ask questions. The patient should understand that the risks of refusing care include the possibility of permanent disability and death. Ideally, a witness should be present when the physician informs the patient and any family members.[111]

Involving Others. The patient's family, friends, and personal physician should be involved whenever possible. These persons should hear the same message as that conveyed to the patient because they may be able to persuade the patient to accept the recommended therapy. If the patient expressly forbids the emergency physician to speak with others, as is the patient's legal right, this should be explained to them and documented in the medical record.

Documenting Appropriately. Appropriate documentation of the refusal process is necessary to protect the physician and hospital from inappropriate litigation. The patient should be asked to sign the refusal form.[2,9,112] (Fig. 2 shows a sample AMA form.)

If the patient refuses to sign the form, that fact should be documented and the form signed by a hospital representative who witnessed the patient's refusal. The medical record should reflect the patient's mental status examination findings and competency to make informed decisions, the risks and benefits of recommended treatments, the available alternatives, and the participating family or friends. Documentation of the patient's rationale for refusing treatment, that the patient was treated to the extent allowed by the patient, and that the patient was invited to return for care at any time offers added protection.[112]

Federal Rules

EMTALA requires hospitals to take and to document specific actions when patients refuse medical screening, treatment and stabilization, or transfer. The government and the federal courts presume that the patient requested emergency care and place the burden of proof on the hospital to demonstrate that the patient voluntarily refused care.[2,9,113]

There are essentially two scenarios in which patients leave the ED after refusing examination or treatment. First, some patients simply pick up and leave, without the knowledge of anyone affiliated with the hospital. If the patient's departure is witnessed, the patient does not respond to requests to return for the examination or to discuss the issues with the hospital staff. These patients are generally referred to as those who "leave without being seen" (LWBS) or "leave before examination." In the second scenario, the hospital personnel are aware that the patient is about to leave and have an opportunity to interact before the patient leaves. Hospitals generally refer to this as "leaving against medical advice." The Office of the Inspector General (OIG) and CMS refer to both of these scenarios as "voluntary withdrawal" of the patient's request for evaluation or treatment.[2,9,114]

Leaving without Being Seen

If a patient walks out before the MSE and later has an adverse medical result, the burden will be on the hospital to prove that the person left voluntarily and was not denied examination or treatment by the hospital. The OIG and CMS admonish hospitals about LWBS patients, stating that "hospitals should be very concerned about patients leaving without being screened. Since every patient that presents seeking emergency services is entitled to a screening examination, a hospital could violate the patient antidumping statute if it routinely keeps patients waiting so long that they leave without being seen, particularly if the hospital does not attempt to determine and document why individual patients are leaving, and reiterate to them that the hospital is prepared to provide a medical screening if they stay."[9,25]

Hospitals need to have a policy and practice for LWBS patients that adequately document pertinent findings and protect the hospital from liability. In most hospitals, the staff calls the patient and checks the waiting area at least three times before declaring that the patient has left the department. These serial checks, with time of day performed, should be documented on the patient's record, and once it is evident that the patient is no longer present, the record should be reviewed on a timely basis by the physician on duty. If the reviewing physician discovers something of concern regarding the patient's chief complaint or triage data, the person can be contacted and encouraged to return to the ED. The registration papers, triage records, nursing documentation at triage, and physician's review and documentation of that review should be kept in the patient's permanent record. These records should be retained for a minimum of 5 years to protect the institution should the interaction ever be the subject of a retrospective EMTALA investigation or litigation on behalf of the LWBS patient.[2,9]

Leaving against Medical Advice

If hospital personnel are aware that a patient intends to leave before completion of the MSE or stabilizing treatment for whatever reason (e.g., tired of waiting, changes mind, concerned about cost of care), the hospital should handle and document the interaction carefully to avoid EMTALA or medicolegal liability[2,9,115-117] (Box 4). In each case, the following steps should be taken:

1. *Inform the patient of the hospital's obligation under the law.* The ED staff should inform patients of their rights under the EMTALA to receive medical screening and any necessary stabilizing treatment from the hospital, regardless of their ability to pay for that service.
2. *Determine the patient's competence.* Only legally competent persons can refuse necessary medical care. For example, alcohol-intoxicated patients who present to the hospital with medical complaints cannot be allowed to leave the hospital without examination and treatment until it is determined that they are legally competent to make such a decision.
3. *Explain the risks and the benefits to the patient*. For patients to make an informed consent to voluntarily withdraw their request for services, they need to understand the benefits and the risks of withdrawal before refusing examination and treatment. These risks and benefits should be specific to the patient's chief complaint.
4. *Secure the patient's written informed consent to refuse care.* The hospital should take all reasonable steps to secure the patient's written and informed consent (i.e., obtain a signature) to refuse medical care. A standard form should be used that contains space for documentation of the patient's competence, the risks and benefits discussed, and whether the patient's family was available to be involved in the discussions. If the patient refuses to sign the form and simply walks out after the interaction with the hospital, the person who discussed the issues with the patient and witnessed the patient's refusal should sign the form and document the interaction.
5. *Offer alternative care within the scope allowed by the patient.* It is outside professional practice standards to respond angrily, to act vindictively, or to punish patients when they decide to leave against advice by refusing to provide alternative

www.ketabpezeshki.com 66485457-66963820

Informed Consent To Refuse Examination, Treatment, or Transfer

I understand that the hospital has offered: (Check all that apply).

A. ☐ To examine me (the patient) to determine whether I have an emergency medical condition, or

B. ☐ To provide medical treatment or to provide stabilizing treatment for my emergency condition, or

C. ☐ To provide a medically appropriate transfer to another medical facility.

The hospital and physician have informed me that the ***benefits*** that might reasonably be expected from the offered services are: ____

____

and the ***risks*** of the offered services are: ____

____

Physician Documentation

☐ The patient appears competent and capable of understanding risks and benefits.

☐ Alternative treatments discussed with the patient.

☐ Patient's family involved. ☐ Family not available. ☐ Patient does not want family involved.

Signature of Physician ____

Patient or Legally Responsible Person Documentation.

☐ I have declined to have the physician fully explain to me the risks, benefits, and alternatives to leaving the hospital against medical advice. I knowingly and willingly take and assume the responsibility for all risks incurred.

or

☐ The physician has fully explained to me the risks and benefits but I choose to refuse the offered services. I understand that my refusal is against medical advice, and that my refusal may result in a worsening of my condition and could pose a threat to my life, health, and medical safety. I understand that I am welcome to return at any time.

Signature/Patient or Legally Responsible Person ____

Print Name ______________________ Address ______________________

City ______________________ State/Zip ______________ Date ______________ Time ____________

Witness/Signature ______________________ Print Name______________________

The patient or person legally responsible for the patient was offered but refused to sign form after explanation of their rights and the risks and benefits of the services offered.

Hospital representative who witnessed refusal to sign: ____

Date ________________ Time ________________

Informed Consent to Refuse Examination Form [Hospital Addressograph or Sticker Goes Here]

White/Patient Record Yellow/Transfer with Patient Pink/Q/A [Robert A. Bitterman, MD JD - 2013]

Figure 2. Leaving against medical advice (AMA) form: informed consent to refuse examination, treatment, or transfer.

www.ketabpezeshki.com 66485457-66963820

Box 4 Protocol for Management of AMA Cases in the Emergency Department

Always involve the emergency physician.
Involve the family or the patient's personal physician whenever possible.
Explain the risks and benefits specific to the patient's condition; "You could die" alone is too generic.
Explain any alternative treatment options to the patient.
Ascertain the patient's capacity to make informed medical decisions: "When in doubt, don't let 'em out!"
Have the patient and at least one witness sign the AMA form.
If the patient refuses to sign the AMA form, a member of the hospital staff should sign the form stating that the patient refused to sign the form.
Always still provide the best possible treatment within the scope allowed by the patient, including antibiotics and analgesics when warranted.
Provide appropriate discharge instructions and welcome the patient to return to the ED at any time if he or she reconsiders and decides to accept the recommended care.
Document discussions with the patient, the risks explained, and the patient's medical decision-making capacity and understanding of the ramifications of leaving AMA in the medical record (and in real time, not hours after the patient has left the ED).

AMA, against medical advice; *ED,* emergency department.

treatments, medications, analgesics, or discharge instructions. Patients always get to define the scope of medical services that they are willing to accept. Accordingly, an appropriate strategy is to negotiate and cajole them into allowing the best possible care under the circumstances that they define. For example, if a patient with "fight bite" tenosynovitis refuses hospital admission, operative intervention, and intravenous antibiotics and analgesia, the next best option can be offered, such as thorough cleansing in the ED, intramuscular antibiotics, and oral narcotics, with recheck in 24 hours. Failing that, cleaning in the home sink, oral antibiotics, acetaminophen, and follow-up with the patient's primary care physician can be recommended.

Negotiation aims for the best alternative that the patient is willing to accept, even if that means providing less than optimal treatment. Pain medications should never be withheld because the patient will not accept the recommended treatment plan. This "strategy" is cruel, further alienates the patient, and serves no useful purpose.

Moreover, patients should always be invited to return to the ED (or encouraged to see their private physician) if they change their mind and become willing to accept the recommended treatment. A patient's refusal of the more appropriate treatments as well as communication of offers to provide treatment within the circumstances proscribed by the patient should be delineated.

6. *Document the interaction in the patient's hospital record.* The medical record, preferably a dictated and transcribed medical record, should accurately relate the interaction between the hospital and the individual refusing the MSE. The record reflects the hospital's conformity to the law and the patient's leaving of his or her own accord—specifically, the risks of refusing the examination and the reasons for the patient's refusal. Documentation of the reasons for refusal provides evidence that the hospital did not economically coerce or in any way financially deter the patient from remaining for the MSE. The chart should clearly indicate that the patient did not leave the department on the basis of a "suggestion" by the hospital concerning any financial issues.

Parent or Guardian Who Refuses Care or Blood Transfusions for a Minor

In general, state laws support parental control of health issues affecting their children. However, the state will not allow parents to deny children needed emergency medical care under the doctrine of *parens patriae,* the state's paternalistic interest in children.[118] All states empower emergency physicians to intercede under their child abuse and child neglect laws.[111,119] When a child's injuries are potentially life-threatening, the emergency physician can take custody of the child under the child abuse laws and provide indicated treatment, including blood transfusions. In deciding whether to act, the when-in-doubt rule definitely applies, and all jurisdictions statutorily protect physicians from criminal and civil liability for acting in good faith to protect children.[111,119]

The courts have specifically addressed the issue of Jehovah's Witness parents attempting to refuse emergency blood transfusions for their minor children. All jurisdictions hold that a parent's right to freedom of religion does not include the right to deny life-sustaining medical intervention for that person's children.[120] One judge best summarized the feelings of the courts: "Not even a parent has unbridled discretion to exercise his or her religious beliefs when the state's interest in preserving the health of the children within its borders weighs in the balance."[121]

Some states specifically address the issue of overriding parental refusal of indicated medical intervention by statute.[122] In North Carolina, for example, if the parents refuse to consent to treatment and the delay to obtain a court order would seriously worsen the child's physical condition or endanger the child's life, and if a second physician agrees that the procedure is necessary to prevent immediate harm, a physician can render treatment without parental consent. If a second physician cannot be contacted before treatment is initiated, the physician may still perform the indicated therapeutic intervention without parental consent.[123]

Conversely, courts refuse to rule against the parents' wishes when the child's medical condition is not serious or life-threatening. If there is no life threat or potential for serious impairment, the parents' refusal should be respected. Parental refusal of indicated nonemergency medical treatment is usually statutorily defined as "child neglect," which is not legally sufficient to take custody of the child. Child neglect should still be reported to the appropriate authorities; treatment for the child can then be obtained under a court order.[119]

Jehovah's Witnesses

Adult Blood Transfusions

The approximately one million Jehovah's Witnesses in the United States believe that blood transfusion destroys their relationship with God and forfeits their chance for eternal life; accepting transfusion is not a minor infraction of their faith.[124,125] They do not accept whole blood, packed cells, platelets, white cells, plasma, or autotransfusion of stored blood. Most will allow the use of crystalloids, albumin, hemophiliac preparations, immunoglobulins, dialysis, and heart-lung machines.[124-126]

Jehovah's Witnesses and the issue of blood transfusion present difficult medicolegal issues in the ED.[127] State courts may have widely divergent views on the issue, and no clear-cut answers exist. However, the current trend is granting patients greater autonomy to refuse blood, even when the state asserts compelling interests to override a person's refusal.

General principles of consent and the when-in-doubt rule apply, but hospitals and medical staff also should develop policies and procedures in advance to resolve potential conflicts with the Jehovah's Witness patients in the community; coordinate the

www.ketabpezeshki.com 66485457-66963820

management of each case with hospital legal counsel, in contact with a judge who can issue court orders when appropriate, if time allows; have other physician consultants write notes of agreement regarding the need to give blood; and communicate effectively with patients and family, in advance when possible.

Competent Adult

The courts have found that "the competent adult has the right to refuse a transfusion regardless of whether his refusal to do so arises from fear of adverse reaction, religious belief, recalcitrance, or cost."[128] This applies "even though we may consider a patient's beliefs unwise, foolish, or ridiculous."[129] However, even this right is not absolute. If the patient's refusal conflicts with compelling state interests such as the preservation of life, the prevention of suicide, or the protection of innocent third parties, the courts may order transfusions despite the person's objections.[127] Previously, typical scenarios in which the courts overrode a competent person's refusal included cases involving pregnant women, to protect the life of the fetus; mothers of young children, to promote the general welfare of the children; and a sole supporting father or mother, to prevent offspring from becoming wards of the state.[130] Some courts, however, have significantly restricted the hospital's or state's ability to assert compelling interests challenging a competent person's right of self-determination.[131]

Unconscious or Medically Incompetent Adult

In an emergency, if the Jehovah's Witness's beliefs are unknown, physicians may transfuse the patient because consent will be implied under the emergency doctrine. It is irrelevant if the spouse, mother, or other family members adamantly refuse to allow the transfusion for religious reasons. The state's compelling interest in preserving life outweighs the family's expression of the patient's religious preferences.[126]

In the past, when a Jehovah's Witness's beliefs and transfusion preferences were known in advance but the patient was incompetent at the time of the emergency, the courts tended to support transfusion until the patient became competent and could refuse transfusion "contemporaneously."[120,132] The modern trend is to accept objective evidence of the patient's wishes, for example, a signed card carried by the patient that identifies him or her as a member of the Jehovah's Witnesses and sets out the religious objection to blood transfusion. The card may be accepted as adequate evidence of the patient's intent, like a form of advanced directive, which is binding on hospitals and physicians. In at least six states, if the card is dated and signed before two witnesses, it is statutorily valid.[133] Even if the blood refusal card does not conform to a state's advance directive statute, it should be considered strong evidence but not necessarily determinative of the Jehovah's Witness's wishes. Advance directives are merely a means to express an individual's rights and are not the exclusive means to express those rights legally.[126,127] Jehovah's Witnesses increasingly use state statutorily defined advance directive methods to legally express their intentions.[134] Emergency physicians should, however, be certain the card or advance directive actually belongs to the patient.

Of interest, no Jehovah's Witness has successfully sued a health care provider to recover damages in cases in which blood was withheld on the basis of an apparently valid blood refusal card. Also, "criminal, civil, or professional misconduct liability has never been imposed on health care providers for forgoing treatment the patient did not want."[135]

REPORTING REQUIREMENTS

All states require hospital EDs to report certain events or illnesses to local public health authorities.[136] The state's primary intent is to prevent the spread of communicable diseases, to protect its citizens from disease and violence, and to prosecute criminal acts. In each instance, the state statute overrides patients' rights of confidentiality. The statutes typically also provide physicians with immunity from civil liability or criminal prosecution if the reporting is done in good faith.[137]

All EDs should maintain up-to-date lists of diseases and incidents that must be reported to the state. The process and responsibility for appropriate reporting should be clearly articulated in departmental policy.

Communicable Diseases

Typical communicable diseases that must be reported include those of epidemiologic concern, such as sexually transmitted diseases (including gonorrhea, syphilis, chlamydial infection, nongonococcal urethritis, and human immunodeficiency virus infection) and highly communicable illnesses (such as tuberculosis, hepatitis, pertussis, and recently methicillin-resistant *Staphylococcus aureus* [MRSA] infection). Emergency physicians also have a duty to warn patients with communicable diseases against activities that may spread the disease and should instruct them to inform contacts to seek evaluation and treatment. Physicians should adequately document such instructions in the medical record to prevent liability to third parties for failure to warn appropriately.

Violent Acts

Wounds, injuries, and illness resulting from criminal acts of violence must be reported to state agencies.[138] Bullet wounds, powder burns, stab wounds, intentional poisonings, child abuse or neglect, sexual assaults, spousal abuse, domestic violence, and any suspicious injuries generally must be reported.

Deaths

All deaths must be reported to state or local authorities. Death under certain circumstances also must be reported to the county medical examiner. Typically these include deaths from violence, poisoning, accident, suicide, or homicide; any sudden death in someone in apparently good health or when unattended by a physician; any death occurring in a jail, prison, or correctional institution or in police custody; and any death occurring under suspicious, unusual, or unnatural circumstances.[139] Fetal deaths also may have to be reported, usually after 20 weeks' gestation or the typical gestational period of possible viability.[140]

When a death requires a report to the medical examiner, the integrity of the scene and the body should be preserved. ED staff should disturb the body as little as possible, secure the patient's belongings and any potential evidentiary materials, and leave in place medical interventions such as endotracheal tubes, nasogastric tubes, and central or peripheral intravenous lines. The medical examiner will determine whether the state will assert authority over the body, order an autopsy, or release the body to the family.[139]

In addition, any death that occurs while the patient is "restrained or in seclusion for behavior management," when it is reasonable to assume that the death is the result of the restraint or seclusion, must be reported to CMS.[141,142] In the ED setting, this typically would involve use of restraint or seclusion as a last resort to address violent behavior presenting a risk to the patient, hospital staff, or others.

Alcohol-Related Motor Vehicle Crashes

At least six states (Hawaii, Indiana, Illinois, Pennsylvania, Rhode Island, and Utah) have mandatory reporting laws governing

www.ketabpezeshki.com 66485457-66963820

alcohol-related motor vehicle crashes.[143] Many other states have laws permitting but not requiring EDs to report intoxicated drivers to authorities on the basis of a known BAC.[143,144]

Animal Bites

Most states require the reporting of animal bites, particularly dog and cat bites, to the local public health department. The states also generally require the reporting of bites by any animals known to be potential carriers of rabies, such as bats, raccoons, skunks, foxes, and cattle, to prevent cases of human rabies and to control the spread of rabies within the animal community.[145]

Substance Abuse

A few states require reporting of substance abuse to local authorities.[146]

References

1. 42 USC 1395dd.
2. 42 CFR 489.24; 42 CFR 489.20. EMTALA regulations.
3. *CMS State Operations Manual, Appendix V—Interpretive Guidelines—Responsibilities of Medicare Participating Hospitals in Emergency Cases—EMTALA*, effective May 29, 2009, with revision 60, effective July 16, 2010. Available at www.cms.gov/manuals/Downloads/som107ap_v_emerg.pdf.
4. *The Medicare Prescription Drug Improvement and Modernization Act,* Public Law 108-173, December 8, 2003; and Center for Medicaid and State Operations/Survey and Certification Group: *Inpatient Prospective Payment System (IPPS) 2009 Final Rule Revisions to EMTALA Regulations*, Ref: S&C-09-26, March 6, 2009. Available at www.cms.hhs.gov/SurveyCertificationGenInfo/downloads/SCLetter09-26.pdf.
5. 42 USC 1395dd(a).
6. 42 USC 1395dd(e)(1)(A).
7. 42 USC 1395dd (e)(1)(B).
8. *Torretti v Main Line Hospitals, Inc.*, 580 F3d 168 (3d Cir 2009).
9. Bitterman RA: *Providing Emergency Care under Federal Law: EMTALA*. Dallas, Tex: American College of Emergency Physicians; 2001.
10. 65 *Federal Register* 18548 (2000).
11. *Clark v Baton Rouge General Medical Center,* 657 So2d 741 (La App 1995).
12. 42 CFR 489.24(b).
13. Bitterman RA: *Providing Emergency Care under Federal Law: EMTALA*. Dallas, Tex: American College of Emergency Physicians; Supplement 2004.
14. 42 CFR 482.12(f)(3).
15. Center for Medicaid and State Operations/Survey and Certification Group: *Provision of Emergency Services—Important Requirements for Hospitals*, Ref: S&C-07-19, April 26, 2007.
16. Center for Medicaid and State Operations/Survey and Certification Group: *EMTALA—"Parking" of Emergency Medical Service Patients in Hospitals*, Ref: S&C-06-21, July 13, 2006. Available at www.cms.hhs.gov/SurveyCertificationGenInfo/downloads/SCLetter06-21.pdf.
17. 42 CFR 482.55.
18. Center for Medicaid and State Operations/Survey and Certification Group: *EMTALA Issues Related to Emergency Transport Services*, Ref: S&C-07-20, April 27, 2007.
19. *Public Health Security and Bioterrorism Preparedness and Response Act of 2002* (Pub. Law 107-188, enacted June 12, 2002); Section 1135(g)(1); *Pandemic and All-Hazards Preparedness Act of 2006* (Pub. Law 109-417, enacted December 16, 2006); Section 302(b). 42 CFR 480.24(a)(2).
20. Center for Medicaid and State Operations/Survey and Certification Group: *Question and Answer Relating to Bioterrorism and EMTALA*, Ref: S&C-02-04, November 8, 2001; 42 CFR 489.24(a)(2); and *Waiver of EMTALA Sanctions in Hospitals Located in Areas Covered by a Public Health Emergency,* Ref: S&C-08-05, posted 12/07/2007, revised 12/14/07. Available at www.cms.hhs.gov/SurveyCertificationGenInfo/downloads/SCLetter08-05.pdf.
21. *Vickers v Nash General Hospital,* 78 F3d 139 (4th Cir 1996).
22. *CM v Tomball Regional Hospital,* 961 SW2d (Tex App 1997).
23. Bitterman RA: Federal law, EMTALA, and state law enforcement: Conflict in the ED. (Police blood alcohol tests and consent issues.) *Emerg Dept Legal Lett* 2006; 1:1.
24. 68 *Federal Register* 53221, 53263; 42 CFR 489.24(d)(2) and 489.24(b).
25. 42 CFR 489.24(a).
26. 42 CFR 482.55.
27. 59 *Federal Register* 32099, 32113, 32116 (1994).
28. Center for Medicaid and State Operations/Survey and Certification Group: *Revised Final EMTALA Guidelines*, Ref: S&C-04-34, May 13, 2004. Tag 406. See also reference 3.
29. *Correa v Hospital of San Francisco,* 63 F3d 1184 (1st Cir 1995).
30. 64 *Federal Register* 36070, 61353, 61359 (1999).
31. 42 CFR 482.13(a)(1).
32. CMS State Operations/Survey and Certification Group: *On-Call Requirements—EMTALA*, Ref: S&C-02-34, June 13, 2002; and *Simultaneously On-Call*, Ref: S&C-02-35, June 13, 2002.
33. Hyams AL, et al: Practice guidelines and malpractice litigation: A two-way street. *Ann Intern Med* 1995; 122:450.
34. *Brooker v Desert Hospital Corp,* 947 F2d 412 (9th Cir 1991).
35. *Gatewood v Washington Healthcare Corporation,* 933 F2d 1037 (DC Cir 1991).
36. 42 CFR 482.20(3).
37. 2 CRF 413.65(g)(1).
38. 42 CFR 482.24(b).
39. 42 USC 1395dd(b).
40. *Cherukuri v Shalala,* 1999 Fed App 0160P (6th Cir).
41. Wanerman R: The EMTALA paradox. *Ann Emerg Med* 2002; 40:464.
42. Bitterman RA: Explaining the EMTALA paradox [editorial]. *Ann Emerg Med* 2002; 40:470.
43. *Cleland v Bronson Healthcare Group, Inc,* 917 F2d, 271-272 (6th Cir 1990).
44. *Bryant v Adventist Health System,* 289 F3d 1162 (9th Cir 2002); and *Harry v Marchant,* 291 F3d 767 (11th Cir 2002).
45. *Lopez-Soto v Hawayek,* 175 F3d 170 (1st Cir 1999).
46. 42 USC 1395cc(a)(1)(I)(iii).
47. 42 USC 1395dd(e)(3)(B).
48. *Smith v Botsford General Hospital,* 419 F.3d 513 (6th Cir 2005).
49. *Roberts v Galen of Virginia, Inc,* 119 S Ct 685 (1999).
50. 42 CFR § 489.24(d)(2)(i).
51. 68 *Federal Register* 53,221-253,264 (Sept. 9, 2003).
52. 42 USC 1395dd(b)(1)(A).
53. *Moses v Providence Hospital and Medical Centers, Inc.,* 561 F.3d 573 (6th Cir 2009), *cert denied,* No. 09-438, 2010 WL 255241 (U.S. June 28, 2010).
54. See also Bitterman RA: Supreme Court turns down EMTALA case—prompts CMS to reconsider applying EMTALA to inpatients. *Emerg Dept Legal Lett* 2011; 22:49-54.
55. 42 USC 1395dd(e)(4).
56. CMS Advanced Notice of Proposed Rulemaking; Emergency Medical Treatment and Labor Act (EMTALA): Applicability to Hospital and Critical Access Hospital Inpatients and Hospitals with Specialized Capabilities. *75 Federal Register* (246):80762-80765 (December 23, 2010). Available at http://edocket.access.gpo.gov/2010/pdf/2010-32267.pdf.
57. 73 *Federal Register* 48656 (August 19, 2008).
58. Bitterman RA: Inpatient transfers and community on-call programs: New rules finalized. *Emerg Dept Legal Lett* 2008; 19:109-112.
59. *CMS State Operations Manual, Appendix V—Interpretive Guidelines—Responsibilities of Medicare Participating Hospitals in Emergency Cases—EMTALA,* Tag A404, effective July 16, 2010. 42 CFR 489.24(j).
60. Morgan D: Emergency room follow-up care and malpractice liability. *J Legal Med* 1995; 16:373.
61. 42 USC 1395dd(c)(1)(A)(ii).
62. 42 USC 1395cc(a)(1)(I).
63. Center for Medicaid and State Operations/Survey and Certification Group: *Hospital Capacity—EMTALA*, Ref: S&C-02-06, November 29, 2001.
64. California Health and Safety Code 1317.5 (West 2005); Florida Stat. Anno. Section 395.1041.
65. 42 USC 1395dd(g). 42 CFR 498.24(f).
66. O'Malley AS, Draper DA, Felland LE: Hospital Emergency On-Call Coverage: Is There a Doctor in the House? *Center for Studying Health System Change*, Issue Brief No.115, November 2007.
67. McConnell KJ, et al: The on-call crisis: A statewide assessment of the costs of providing on-call specialist coverage. *Ann Emerg Med* 2007; 49:727.
68. Caffee H, Rudnick C: Access to hand surgery emergency care. *Ann Plast Surg* 2007; 58:2.
69. Bosse MJ, et al: An AOA critical issue. Access to emergent musculoskeletal care: Resuscitating orthopaedic emergency-department coverage. *J Bone Joint Surg Am* 2006; 88:1385.

www.ketabpezeshki.com 66485457-66963820

70. American College of Emergency Physicians: *On-call specialist coverage in U.S. emergency departments: American College of Emergency Physicians Survey of Emergency Department Directors*. Irving, Tex: ACEP; September 2004.
71. American College of Emergency Physicians: *On-call specialist coverage in U.S. emergency departments:* Irving, Tex: ACEP; *Survey of Emergency Department Directors*. April 2006.
72. 42 CFR 498.24(f); Center for Medicaid and State Operations/Survey and Certification Group: *Revisions to Special Responsibilities of Hospitals under the Emergency Medical Treatment and Labor Act (EMTALA)*, Ref: S&C-06-32, September 29, 2006.
73. 42 CFR 498.24(b). Center for Medicaid and State Operations/Survey and Certification Group: *Hospital Capacity—EMTALA*, Ref: S&C-02-06, November 29, 2001.
74. 70 *Federal Register* 4,870 (2005). OIG Supplemental Compliance Program Guidance for Hospitals.
75. Pub. Law No. 101-508, Title IV, Sections 4008-(b)(1)-(3)(A), 4207(a)(1)(A), (2), (3), (k)(3), 104 Stat 1388-44, 1388-117, 1388-1124 (effective in 1991 and codified at 42 USC Section 1395dd(g) (West Supp 1991).
76. Bitterman RA: EMTALA and the ethical delivery of hospital emergency services. *Emerg Med Clin North Am* 2006; 24:557.
77. 42 CFR 498.24(e).
78. 42 USC 1395dd(g). Center for Medicaid and State Operations/Survey and Certification Group: *EMTALA Issues Related to Emergency Transport Services*, Ref: S&C-07-20, April 27, 2007. Available at www.cms.hhs.gov/SurveyCertificationGenInfo/downloads/SCLetter07-20.pdf.
79. 42 USC 1395dd(h).
80. 42 CFR 489.20(m).
81. *Schloendoff v The Society of New York Hospital,* 211 NY 125 (NY 1914).
82. Monico EP: Against medical advice in the ED: Where we are in 2009. *Emerg Dept Legal Lett* 2009; 20:61-65.
83. Liametz A: Patients who leave AMA: Understand your risks and responsibilities. *Emerg Dept Legal Lett* 2009; 20:121-129.
84. *Cobbs v Grant,* 502 P2d 1 (Calif 1972).
85. *Truman v Thomas,* 611 P2d 902 (1980).
86. Iowa Code Ann 147.137 (West 1989).
87. Ala Code 6-5-484 (1990).
88. NC Gen Stat 90-21.13.
89. Center for Medicaid and State Operations/Survey and Certification Group: *Revisions to the Hospital Interpretive Guidelines for Informed Consent*, Ref: S&C-07-17, April 13, 2007.
90. NC Gen Stat 90-21.13(b).
91. *Canterberry v Spence,* 464 F2d 772 (DC Cir), *cert denied,* 409 US 1064 (1972).
92. *Thomson v Sun City Community Hospital,* 668 P2d 605 (1984).
93. Tsai AK, et al: Evaluation and treatment of minors: Reference on consent. *Ann Emerg Med* 1993; 22:1211.
94. *Cardwell v Bechtol,* 1724 SW2d 739 (TN 1987).
95. Cal Civ Code 62 (West 1979); Wyo Stat 14-1-101 (1981).
96. Colo Rev Stat 13-22-103; Mass Gen Laws Ann 112, 12F; NC Gen Stat 130A-135, 90-21.5(a).
97. Collin F, et al: *Durable Powers of Attorney and Health Care Directives,* 3rd ed. Schaumberg, Ill: American College of Legal Medicine; 1997.
98. *In re Quinlan,* 335 A2d 647 (1976).
99. Ark Stat Ann 41-41-3 (1984); Idaho Code 39-4305 (1975); *Wells v Van Nort,* 125 NE 910 (Ohio 1919).
100. *Commissioner of Corrections v Myers,* 399 NE2d 452 (1979).
101. NC Gen Stat 148-146.2.
102. *Miller v Rhode Island Hospital,* 625 A2d 778 (RI 1993).
103. Simel DL, et al: Does determining serum alcohol concentrations in ED patients influence physicians' civil suit liability? *Arch Intern Med* 1989; 149:1016.
104. Ethering JM: Emergency management of acute alcohol problems. *Can Fam Physician* 1996; 42:2423.
105. Mich Comp Laws Ann 257.625a(9).
106. *Cruzan v Director, Missouri Department of Health,* 497 US 261, 279 (1990).
107. *Rodriguez v Pinol,* 634 So2d 681 (Fla Ct App 1994).
108. Ding R, et al: Patients who leave without being seen: Their characteristics and history of emergency department use. *Ann Emerg Med* 2006; 48:686.
109. Polevoi SK, Quinn JV, Kramer NR: Factors associated with patients who leave without being seen. *Acad Emerg Med* 2005; 12:232.
110. Jones RC, Holden T: A guide to assessing decision-making capacity. *Cleve Clin J Med* 2004; 71:971.
111. Weaver JC: Patients refusing care: Weigh risk vs. autonomy. *Emerg Dept Legal Lett* 2007; 17:30.
112. Henson VL, Vickery DS: Patient self discharge from the emergency department: Who is at risk? *Emerg Med J* 2005; 22:499.
113. *Stevison v Enid Healthcare System, Inc.*, 920 F2d 710 (10th Cir 1999).
114. 64 *Federal Register* 61353 (1999). OIG/CMS Special Advisory Bulletin on EMTALA.
115. 42 CFR 489.24(c)(2).
116. 42 USC 1395dd(b)(2)(3).
117. Simon JR: Refusal of care: The physician-patient relationship and decision making capacity. *Ann Emerg Med* 2007; 50:456.
118. McDonnell WM: Between a rock and a hard place: When parents refuse treatment for the children in the ED. *Emerg Depart Legal Lett* 2008; 19:6-8; and Goldstein J: Medical care for the child at risk: State supervision of parental autonomy. *Yale Law J* 1977; 86:645.
119. Monico EP, Schwartz I: Leaving against medical advice; facing the issue in the emergency department. *J Healthc Risk Manag* 2009; 29:6-15.
120. *In re Estate of Dorone,* 534 A2d 1271 (Pa 1985).
121. *Nowak v Cobb County–Kennestone Hospital Authority,* 74 F2d 1173 (1996).
122. Brezina PR, Moskop JC: Urgent medical decision making regarding a Jehovah's Witness minor: Case report and discussion. *N C Med J* 2007; 68:312.
123. NC Gen Stat 90-21.1-3. *North Carolina Treatment of Minors Act of 2005*.
124. Woolley S: Jehovah's Witnesses in the emergency department: What are their rights? *Emerg Med J* 2005; 22:869-871; and Woolley S: Children of Jehovah's Witnesses and adolescent Jehovah's Witnesses: What are their rights? *Arch Dis Child* 2005; 90:715-719.
125. Sheldon M: Ethical issues in the forced transfusion of Jehovah's Witness children. *J Emerg Med* 1996; 14:252.
126. Migden DR, Braen GR: The Jehovah's Witness blood refusal card: Ethical and medicolegal considerations for emergency physicians. *Acad Emerg Med* 1998; 5:815.
127. Spence RK: The Jehovah's Witness patient and medicolegal aspects of transfusion medicine. *Semin Vasc Surg* 1994; 7:121.
128. *St. Mary's Hospital v Ramsey,* 465 So2d 666 (1985).
129. *Harnish v Children's Hospital,* 439 NE2d 240 (Mass. 1982); *In re Brooks Estate,* 205 NE2d 435 (1965).
130. *In re Osborne,* 294 A2d 372 (DC Ct App 1972); *Hamilton v McAuliffe,* 352 A2d 634 (MD 1976); *In re Winthrop Univ Hosp,* 490 NYS2d 996 (Sup Ct 1985); and *In re Melideo,* 390 NY S2d 523 (1976).
131. *Fosimire v Nicholeau,* 551 NE2d 77 (NY 1990); *In re Dubreuil,* 629 So2d 819 (Fla 1993); *In re Fetus Brown,* 1-96-2316 (Ill App Ct 1997); *Stamford Hosp v Vega,* 236 Conn 646 (1996).
132. *Werth v Taylor,* 475 NW2d 426 Mich App (1991)
133. Colo Rev Stat Ann 15-14-504(b),(b)(3),505(2),506(1); Fla Stat Ann 765.101(1); Ky Rev Stat Ann 311.621(2),637(6); Me Rev Stat Ann Tit 18A, 5-801(a),801(I),802(a),804; Md Code Ann, Health-Gen 5-601(b),602(c),603,611(e)(2); 79 Op Att'y Gen 94-028 n13 (Md 1994); NM Stat Ann 24-7A-1(A),2,4,16(A); Md Ann Code 43 135C (1980).
134. Ridley DT: Honoring Jehovah's Witnesses' advance directives in emergencies. *Acad Emerg Med* 1998; 5:824.
135. Zeitz E: Legal reasoning and medical decision making [editorial]. *Acad Emerg Med* 1998; 5:755.
136. Gupta M: Mandatory reporting laws and the emergency physician. *Ann Emerg Med* 2007; 49:369.
137. NC Gen Stat 7A-550, 130A-1142.
138. NC Gen Stat 90-21.20.
139. NC Gen Stat 130A-1383.
140. NC Gen Stat 130A-1114.
141. 42 CFR 482.13(f)(7).
142. Center for Medicaid and State Operations/Survey and Certification Group: *Hospital Death Reporting Requirements Related to Behavior Management*, Ref: S&C-06-31, September 29, 2006.
143. McManus J, et al: A survey of Oregon emergency physicians to assess mandatory reporting knowledge and reporting patterns regarding intoxicated drivers in the state of Oregon. *Acad Emerg Med* 2005; 12:896.
144. Snyder K, Bloom JD: Physician reporting of impaired drivers: A new trend in state law? *J Am Acad Psychiatry Law* 2004; 32:76.
145. NC Gen Stat 130A-1196.
146. NC Gen Stat 130A-1209, 211.

www.ketabpezeshki.com 66485457-66963820

Wellness, Stress, and the Impaired Physician

Andrew R. Barnosky, Timothy A. Peterson, and Michael L. Epter

For the complete chapter text, go to the Expert Consul website. To access your account, look for your activation instructions on the inside front cover of this book.

I. PERSPECTIVE

II. CAUSATIVE FACTORS: MAJOR STRESSORS IN EMERGENCY MEDICINE

A. Difficult Patient and Professional Relationships

B. Diversity of Practice Elements

C. Diminished Resources

D. Difficult Decisions

III. CONSEQUENCES: THE BURNED-OUT OR IMPAIRED PHYSICIAN

A. Burnout

B. Physician Impairment

IV. COPING STRATEGIES: WELLNESS STRATEGIES FOR THE EMERGENCY PHYSICIAN

A. Promoting Wellness in the Workplace

B. Family and Social Relationships

C. Physical Fitness

D. Relaxation and Renewal

V. RESIDENCY TRAINING AND WELLNESS

A. Time Demands and Work Hours

B. Lack of Autonomy

C. Fear for Personal Safety and Well-Being

D. Consequences of Stress

E. Finding Balance and Well-Being

F. Culture Change

VI. SUMMARY

KEY CONCEPTS

A variety of stressors contribute to the potentially unhealthful aspects of EM practice, both during residency training and in practice, including the following:

- Difficult patient and professional relationships
- Diversity of practice elements
- Diminished resources
- Difficult decisions full of uncertainty
- Strategies for maintaining wellness for emergency physicians include:
- Mitigating the impact of shift work with circadian scheduling and sleep strategies
- Strategies for managing difficult clinical encounters such as formal debriefs
- Professional support groups
- Cultivating close family and social relationships
- Developing and maintaining physical fitness and other methods of relaxation and renewal

www.ketabpezeshki.com 66485457-66963820

Wellness, Stress, and the Impaired Physician

Andrew R. Barnosky, Timothy A. Peterson, and Michael L. Epter

PERSPECTIVE

The maintenance of wellness is critical in achieving a satisfying and productive career as a competent emergency physician. Previous definitions of w*ellness* focused on the optimal state of health and well-being achieved through the active prevention of illness.[1] More current concepts of *wellness* consider the multifaceted aspects of a physician's physical and mental health as well as emotional health and well-being.[2] Emergency medicine (EM) as a specialty was still in its formative years when concerns first surfaced about the stressful and potentially unhealthful aspects of practice in this specialty and the impact such stressors could have on wellness and career longevity.[3,4] Although experience has shown that large numbers of emergency physicians enjoy long and fulfilling careers, questions remain about how best to cope with the demands and stresses associated with the practice of EM.

This chapter presents an overview of wellness issues facing the emergency physician, divided into three main sections: major stressors, physician burnout and impairment, and strategies for promoting wellness in emergency practice. A fourth section pertaining to residency training and wellness is also included.

CAUSATIVE FACTORS: MAJOR STRESSORS IN EMERGENCY MEDICINE

A variety of stressors contribute to the potentially unhealthful aspects of EM practice, both during residency training and in practice.[5,6] These stressors generally relate to four aspects of emergency practice: difficult patient and professional relationships, diversity of practice elements, diminished resources, and difficult decisions full of uncertainty.

Difficult Patient and Professional Relationships

Although the ability to provide care for a variety of acute and complicated patients under significant time constraints is a source of gratification for practicing emergency physicians, the challenges imposed on the physician-patient relationship are unlike those in other specialties in medicine. In clinical practice, most physicians have the opportunity to establish a sound relationship with their patients over time; in the emergency department (ED), however, patient and physician are thrust together in a relationship that typically is of high intensity, of short duration, and based on the circumstances of need. Many patients presenting to the ED are often under high levels of emotional stress, in pain, and suffering from anxiety and apprehension. They may have language barriers, organic brain syndromes, psychiatric illness, personality disorders, or altered behavioral states that make them more difficult to evaluate.[7] They may be frequent users of the ED services well known to the staff, presenting with conditions requiring an inordinate amount of time and resources. Communication and conflict resolution challenges between physician and patient may be considerable. Some patients present a danger to the physician, manifesting any of a variety of emotional and psychiatric disorders, including chemical dependency disorders, sociopathic behaviors, personality disorders, and psychosis.[8]

Issues of personal safety remain a major concern among emergency personnel because practice in this setting is more likely to be associated with exposure to acts of violence, verbal or physical threats, a variety of potentially life-threatening infectious diseases, and acts of bioterrorism.[9,10] Dealing with "difficult patients" can arouse a variety of emotions that have a negative impact on the physician-patient relationship, including fear, anger, helplessness, inadequacy, intimidation, vindictiveness, and even hatred. Although such feelings are understandable, they may become a considerable source of stress.[7,11]

Professional relationships may likewise be stressful. Emergency physicians practice "fishbowl medicine." Their practice habits and decision-making are often in full view of all members of the medical staff. Disputes can arise regarding patient management and disposition decisions, spheres of practice, referral practices, specialist on-call responsiveness, and care of the uninsured. Moreover, although it is a less prevalent attitude now than in the early days of the specialty, in some professional circles emergency physicians are not accorded peer respect among colleagues in other specialty areas. Professional status is occasionally an issue in dealings between emergency physicians and hospital administrators, in which the ED may be viewed as a less desirable location for resource allocation compared with other clinical services.[6]

Relationships with other members of the ED staff also may be subject to strain. Because EM practice is often contractually based for physicians, the physician group may not have the same degree of workplace "ownership" and supervisory authority as that enjoyed by physicians in a private practice. Nurses and ancillary personnel generally are not hired by the emergency physician group, and disputes may arise about issues of responsibility and control.[6,12]

Diversity of Practice Elements

The "24/7" nature of emergency practice, coupled with the responsibility to treat all persons at all times, fosters a tremendously diverse practice environment. Work schedules typically include a broad mixture of irregularly assigned days, nights, weekends, and holidays. The practice environment often is chaotic. ED patient visits continue to climb in the United States amid a diminishing

www.ketabpezeshki.com 66485457-66963820

number of hospitals.[13] ED overcrowding and diminished availability of inpatient beds can result in the boarding of admitted ED patients and long waits for new patients to be assessed and treated. ED overcrowding and capacity issues have worsened to the point of crisis in some communities.[14-21] ED staff are subjected to a barrage of intrusive noises, including alarms, monitors, pagers, and telephones, as patients of all ages, presentations, and acuity arrive for evaluation at unpredictable intervals. This diversity is often cited by medical students and residents embarking on a career in EM as a challenging, attractive, and often beguiling feature of the specialty. The older practitioner, after years of struggling to maintain some degree of order within the department, amid a pattern in recent years of increasing volumes and acuity of patients, may tend to view diversity as a major stressor.[5,6,12]

Diminished Resources

In an attempt to maintain financial viability amid an ever-challenging environment driven by diminished reimbursement, managed care, uninsured patients, and increasing costs, most hospitals have had to implement cost-cutting measures. These measures have resulted in a number of important resource limitations with which the ED must contend. These include diminished staffing of nurses, ancillary personnel, and social services; burdensome cost-containment policies and documentation requirements regarding access to diagnostic and treatment modalities and outpatient referrals, specialty consultations, and hospital admissions; inadequate policies providing for the care and disposition of medically indigent patients; and diminished reimbursement for services rendered.[5,6,12,22] Nursing shortages have reduced the ability of some EDs to recruit, to retain, and to build a solid team of seasoned nursing professionals experienced in EM.

In the last 5 years, specialist coverage for general surgery, orthopedics, hand surgery, and plastic surgery has become a national issue facing many EDs. A 2010 survey of ED directors reported that 74% of EDs experience problems with specialist coverage.[23] The unavailability of surgical specialists leads to increased patient wait times,[24] higher risk of adverse events related to longer waits,[25] and greater frequency of transfer to another hospital for care. All of these contribute to increased emergency physician frustration while attempting to provide quality patient care.

Difficult Decisions

Emergency physicians often need to make difficult decisions on the basis of ambiguous or incomplete information. One of the single greatest predictors of stress and job dissatisfaction for emergency physicians is the degree to which they are uncomfortable with uncertainty.[26] The driver of this correlation is likely to be the commitment physicians feel to their patients and the appropriate concerns for patient safety; an intense desire to maximize medical outcomes, the anxiety about the potential for medical mistakes, the pressure of decisions made under time constraints, and the fear of litigation are additional stressors of major importance.[5,6,12]

CONSEQUENCES: THE BURNED-OUT OR IMPAIRED PHYSICIAN

Burnout

The term *burnout* was introduced by Freudenberger in 1975 to refer to feelings of job dissatisfaction caused by work-related stress.[27] It includes long-term physical and emotional exhaustion, resulting in diminished interest in the major activities of the job. Further work has been done by Maslach, who developed a Burnout Inventory to measure and to quantify the severity of burnout within an individual. Burnout can be categorized along three general dimensions: emotional exhaustion (feeling emotionally drained by contact with other people), depersonalization (negative feelings toward patients receiving care), and reduced personal accomplishment (the tendency to reflect negatively on your own work).[28,29] A study performed by the Americal College of Emergency Physicians (ACEP) demonstrated emotional exhaustion to be the single greatest predictor of burnout, with a strikingly high prevalence in the survey population.[26]

Burnout is of special relevance to physicians because it undermines the integrity of the physician-patient relationship, which is the foundation of medical practice and essential to effective service. People in advanced phases of burnout are likely to experience decreased productivity, less satisfaction with work, higher job turnover, lower self-esteem, more physical symptoms, more troubled family relationships, and a variety of affective changes, such as hostility, anxiety, depersonalization, cynicism, and depression. Symptoms of burnout are thought to be potential precursors of more severe manifestations of impairment, including alcoholism, drug abuse, and suicide.[30]

Several studies have documented moderate to high levels of burnout among certain populations of emergency physicians, and few emergency physicians would dispute the particular significance of burnout as an occupational hazard. However, burnout is not an inevitable consequence for all practicing emergency physicians, and effective strategies are available to avoid it. A review of the American Board of Emergency Medicine's longitudinal emergency physician career satisfaction survey demonstrated a relatively high, and constant across time, level of satisfaction with no change in the level of physician burnout during the last 10 years.[31]

Additional information about burnout in EM can be found on the ACEP website (www.acep.org) or obtained by contacting the ACEP Practice Management Department (800-798-1822).

Physician Impairment

Physician impairment exists when a physician's professional performance is adversely affected because of mental or physical illness, aging, alcoholism, or chemical dependence.[32,33] The Federation of State Medical Boards defines an impaired physician as one who is unable to practice medicine with reasonable skill and safety because of a mental illness; a physical illness or condition that adversely affects cognitive, motor, or perceptive skills; or substance abuse. It is estimated that 17,000 practicing physicians are afflicted with substance abuse problems in the United States and that 100 deaths annually among physicians are directly attributable to chemical dependency.[34]

Impairment in a physician colleague often is difficult to detect. The recognition of a pattern of events, rather than a single precipitating incident, may be key to making the diagnosis. Difficulties that arise in the workplace often are preceded by a history of family difficulties, including frequent arguments, periods of separation, extramarital affairs, and divorce. Frequent job changes ("geographic cure") and unexplained time intervals between periods of professional employment also may be signs of impairment. A high value usually is placed on maintaining the source of income, and erosion of hospital duties is one of the last things that may be affected. Patient care responsibilities become neglected, and the impaired physician may exhibit poor medical judgment. The problem may develop during a long period because strong elements of denial are usual among family members and associates as well as in the impaired physician.[34]

Following the ethical principles of beneficence and nonmaleficence, it is important to deal fairly and honestly with colleagues yet to take appropriate actions to protect patients from health care providers who are impaired, are incompetent, or engage in fraud or deception.[33,35] Programs to detect and to treat physician impairment have now been established in every state. A few states have recovery programs that are legislatively mandated, being administered by state medical boards, state medical societies, or

www.ketabpezeshki.com 66485457-66963820

Box 1 Lifestyle Balance: Wellness Strategies for the Emergency Physician

Promote wellness in the professional environment.
- General measures
- Strategies for shift work
- Strategies for managing difficult and violent patients
- Professional support groups

Cultivate close family and social relationships.
Develop and maintain physical fitness.
Cultivate methods of relaxation and renewal.

Box 2 Shift Work Strategies

Work the same shifts as much as possible and keep the same sleep patterns. Compensation should be increased for those willing to work night shifts for extended periods.
Work isolated night shifts, with minimal circadian disruptions.
Consider the *Thomas schedule* for groups: One physician works extended night schedule for 1 month or longer, with isolated nights off being covered by the other group members.
Schedule shift rotations in a clockwise direction, with 1-month minimum time per rotation.
Eight-hour shifts are preferable to 12-hour shifts.
Sleep in a darkened room; minimize disruptions.
For those unable to maintain consistent sleep patterns, use compromise strategies, such as anchor sleep, split sleep periods, or napping, to mitigate circadian disruptions.
Start the awake period with a high-protein meal, switching to complex carbohydrates toward bedtime. Avoid caffeine and high-calorie, high-fat snack food before sleep. Eat meals regularly.
Use bright light (>10,000 lux) for 2 hours after arising as an adjunct in adjusting to new shifts.
Exercise regularly.
Plan regular "quality time" with family and friends.
Do not try to live a day-shift lifestyle while working night shifts.

independent organizations. A carefully structured program is critical to the recovery process, and the goal is to rehabilitate the physician so that he or she may return to the care of patients. The prognosis for recovery appears to be excellent when long-term monitoring is in place. The ultimate goal is rehabilitation of the affected physician, with an eventual successful return to work.[34,36]

COPING STRATEGIES: WELLNESS STRATEGIES FOR THE EMERGENCY PHYSICIAN

The very qualities that characterize medically successful physicians—perfectionism, the drive to succeed, willingness to work long and irregular hours, and ideals of individual service and sacrifice—also may predispose them to neglect their own physical and emotional needs. The formulation of any comprehensive wellness strategy is based on the concept of lifestyle balance and involves the integration of professional goals and responsibilities with needs for self-care and development.[37-39] Cultivation of lifestyle balance involves four basic elements, summarized in Box 1 and discussed here.

Promoting Wellness in the Workplace

A strong predictor of job satisfaction among professionals with demanding and stressful jobs is the degree to which they have control over the work flow and job responsibilities in their workplace. Emergency physicians can introduce more control over elements of their practice by ensuring adequate physician and support staffing to accommodate patient load; ensuring adequate input in the development of departmental policies and procedures; cultivating relationships among physicians and staff; and mitigating noise, light, space, crowding, wait times, and structural discomforts.[40,41]

The irregularity of scheduled hours is a major workplace issue for emergency physicians. Shift changes often are cited as a major cause of dissatisfaction within the specialty.[12,40] Shift work is associated with a variety of adverse effects on physical and emotional health.[42-44] These include an increased incidence of peptic ulcer disease, depression, mood swings, drug and alcohol abuse, altered immune response, chronic hypertension, cardiovascular mortality, infertility in women, divorce, work-related accidents and errors, and compromised learning ability when fatigued.[45] In addition, shift workers are more likely to sustain work-related accidents (e.g., percutaneous injury).[46] Approximately 25% of persons in the North American population are shift workers, and research has shown that an estimated 20% of people cannot tolerate shift work.[45,47,48] Rest breaks during shift work may mitigate stress and fatigue, yet this is difficult to achieve.[49] A variety of shift work strategies have been proposed as a means of mitigating these effects (Box 2).[50]

Professional support groups also can help emergency physicians with issues of coping and control over the stressful aspects of their practice. In the process of sharing relevant information, relating personal experiences, listening to others' experiences, and providing sympathetic understanding, members of support groups can cope in a more effective manner. The ACEP has a Wellness Section devoted to consideration of such issues and has sponsored policies and programs to address them. The ACEP also has a speaker's bureau consisting of members who are available to address a variety of wellness-related issues.

A particularly important form of support group relates to *critical incident stress debriefing*. Critical incidents are witnessed traumatic events that have sufficient emotional power to overcome the usual coping abilities of people exposed to them. EM is a field in which situations occur that may cause physicians and other ED personnel, regardless of rank, years of service, or gender, to experience unusually strong emotional reactions that have the potential to interfere with their ability to function. Emergency physicians are continually being exposed to critical incidents, including serious multiple-casualty incidents, pediatric injuries or deaths, line-of-duty deaths, injuries to ED personnel, events of excessive media interest, and events involving victims known to ED personnel. The impact of a critical incident often goes unrecognized even after common stress reactions appear. Although physical and emotional stress reactions are often considered normal and usually will diminish in time, intense or prolonged reactions may have adverse effects on physician and staff well-being.

Personnel exposed to such critical incidents can be subject to the cognitive, emotional, and physical sequelae of the posttraumatic stress syndrome. Components of this syndrome include a continual reexperiencing of the event in thoughts, dreams, or daily life; an avoidance of any stimuli associated with the event; a sense of numbness to one's emotions; and a wide variety of other symptoms, including sleep disturbance, irritability, anxiety, and loss of emotional control.[51]

The concept of critical incident stress debriefing has evolved during the past 30 years from the combined experiences of a variety of emergency services and military personnel. Debriefings are structured group meetings that emphasize venting of emotion and discussion of other reactions to a critical event.[52] The two main goals are lessening of the short-term emotional impact of distressing events and the acceleration of recovery from such events before stress reactions occur. Formal critical incident stress debriefing teams are available in many communities through local emergency medical services agencies. Debriefings also can occur on an informal basis in the ED. Such sessions can take the form of impromptu meetings of emergency and rescue personnel involved in specific incidents in which the details of a particular

www.ketabpezeshki.com 66485457-66963820

event and its associated emotional content are expressed and shared among members of the team.[50] It is important for those involved in leadership roles to make some form of critical incident debriefing processes available when such events occur.

Family and Social Relationships

Many physicians are overly dedicated to their work and prone to delay sources of emotional gratification outside the work environment. These qualities, which may promote a high degree of professional success and satisfaction, also may interfere with the development of family and social relationships, a problem that may be compounded for emergency physicians by their irregular hours.[53-55] The ability to develop and to sustain intimate relationships may be the most critical element in any wellness formula. The simplest and most profound way to maintain mental health while actively absorbed in a demanding career is to establish and to cultivate a viable and genuine relationship with a caring, emotionally expressive spouse or significant other. The promotion of a close family relationship involves, at the very least, a willingness to assign and to prioritize protected time with spouse and other family members. For many physicians, it also involves a conscious effort to develop communication skills, particularly with respect to active listening and the open expression of feelings.[55]

Physical Fitness

Physical fitness is an important concern for emergency physicians, given the rigors of a typical EM practice. For physicians generally, frequency of physical training has a positive correlation to overall life satisfaction.[56] Unfortunately, the obstacles to development of a comprehensive fitness program may be considerable. Factors such as the irregular hours, the hectic work pace, and the variable quality of hospital menus complicate the task of establishing and maintaining exercise regimens and healthy dietary habits. The impact of proper diet and exercise on a variety of wellness parameters is clearly established. Documented benefits of an appropriate diet include lower cholesterol levels, weight control, augmented blood pressure control, and lower incidence of certain cancers. The American Heart Association (AHA) periodically provides dietary guidelines, as summarized in Box 3.[57]

The benefits of a regular and vigorous aerobic exercise program include enhanced exercise tolerance, cardiovascular fitness, lower blood pressure, increased high-density lipoproteins, decreased triglyceride levels, augmented weight reduction efforts, lessened anxiety and depression, improved glucose tolerance, enhanced endurance, and improved flexibility and strength. According to current AHA guidelines, cardiovascular fitness is best maintained by a program of aerobic exercise (the repetitive use of large muscle groups) three to six times per week for at least 30 minutes per session. Strength-developing activities (resistance training) should be performed at least twice per week, with 8 to 10 exercises that use the major muscle groups of the legs, trunk, arms, and shoulders. A regimen of one or two sets of 8 to 12 repetitions of each exercise is recommended. The exercises should be vigorous, sufficient to raise heart rate to at least 50% of maximum (the recommended average maximum heart rate is 220 minus age).[58] Physicians' physical activity levels also influence their attitudes toward physical activity as regards patient counseling practices.[59]

Relaxation and Renewal

In dealing with the innumerable stresses of emergency practice, physicians must be equipped with considerable emotional resources, derived in part from strong peer and personal support systems. Methods of relaxation and renewal are important additional elements.[6,38,40]

Box 3 American Heart Association Dietary Guidelines

Restrict total fat to ≤30% of total calories.
Restrict saturated fat to <10% of total calories.
Limit the total intake of cholesterol-raising fatty acids (saturated and *trans* fats) to ≤10% of calories.
Limit cholesterol intake to <300 mg/day.
Replace cholesterol-raising fatty acids with whole grains and unsaturated fatty acids from fish, vegetables, legumes, and nuts.
Limit sodium intake to ≤2400 mg/day (≤6.0 g/day of salt).
If alcohol is consumed, limit intake to two drinks/day for men, one drink/day for women.
Eat at least two servings of fish per week.
Eat five or more servings of vegetables and fruit per day.
Eat six or more servings of grain products per day.
Emphasize daily intake of low-fat or nonfat dairy products.

Emergency physicians must continually cultivate the ability to remain functional and emotionally resilient when facing the turbulence of the typical ED. Physiologic correlates of stress—increased heart and respiratory rates and increased blood pressure, oxygen consumption, and serum lactate level—can be normalized by a variety of relaxation techniques. These include prayer, Zen, yoga, transcendental meditation, autogenic training, cultivating mindfulness, and progressive relaxation. Studies indicate that the regular use of such techniques can allow development of considerable control over the relaxation process.[60-62] In some physicians, a reduction in clinical workload may be necessary to achieve a satisfactory lifestyle balance.[63]

A final element in the promotion of wellness and lifestyle balance is the concept of *renewal*. Physicians typically develop a work ethic that makes it difficult to disengage from medical responsibilities. A single-minded devotion to career ultimately is impoverishing, and by neglecting restorative activities, physicians tend to lose their emotional resilience.[38,64] The concept of renewal involves the ability to prioritize and to establish time for rest and revitalization as well as spiritual, emotional, and intellectual growth. Stress reduction, maintaining strong personal health and lifestyle balance, a strong social network, and self-reflection are key.[65,66] Out of the maelstrom that constitutes a typical day in the ED, emergency physicians should look to sources of renewal as key elements in their formula for lifestyle balance.

RESIDENCY TRAINING AND WELLNESS

Residency training across all specialties is known as a time of intense study, personal sacrifice, and fatigue. Despite that literature on resident burnout is in the preliminary stages, studies suggest that residents experience high rates of burnout that may be detrimental to both physical and mental well-being as well as to work performance.[67] Whereas many of the stressors that affect emergency physicians in practice are germane to EM residents (e.g., difficult patient and professional relationships, diversity of practice elements, and diminished resources), there are several specific stressors that are magnified during training, most notably, time demands and work hours, autonomy, and maintaining a balance between achieving personal and professional goals.[67-72]

Time Demands and Work Hours

Multiple studies of factors that contribute to resident burnout focus on the issue of time management. In contrast to the attending physician, residents work longer hours and have additional responsibilities beyond the clinical environment. This places an additional constraint on their time, leaving fewer opportunities

www.ketabpezeshki.com 66485457-66963820

to pursue outside interests, and can result in work-home interference.[67,68,71] The role of work-home is dichotomous; interference can lead to emotional exhaustion and depersonalization, whereas having a supportive home situation is protective against depersonalization.[67,71]

In response to both patient safety and resident well-being, the Accreditation Council for Graduate Medical Education (ACGME) implemented common duty hour standards in 2003. Most notably, the limitation of duty hours to 80 hours per week was established.[73] Despite implementation, the prevalence of burnout has remained high, suggesting that duty hour limitations in isolation are not an effective measure for combating the effects of burnout.[67,72] In 2011 the common standards underwent additional revision to reflect the multifactorial aspects of patient care. Included within these updated standards are further reductions in the work hours pertaining to the maximum duty length (e.g., 16-hour cap for postgraduate year 1, 24-hour cap for postgraduate year 2). These changes reflect data from studies of the negative consequences for physicians with shift lengths longer than 24 hours—increased risk of burnout, needle-stick injuries, motor vehicle crashes or near-miss accidents, and medical errors.[71] Further investigation is needed to determine whether these common standards are achieving their end goal and to evaluate their implications for the future of graduate medical education.

The ACGME Residency Review Committee for Emergency Medicine has been even more proactive in an attempt to facilitate a balance between safety, well-being, and training through EM-specific duty hour requirements, including the limitation of shift length, overall duty hours, and protected time free of educational and clinical responsibility.[74]

Lack of Autonomy

An imbalance exists between the vast clinical, research, didactic, and administrative responsibilities for which residents are held accountable and the level of autonomy provided to them during training. Restrictions on their decision-making, autonomy, and scheduling can form the basis of increased job dissatisfaction and stress. This is a classic example of the *demand-control-support model,* in which occupational stress leads to burnout when there is an imbalance between high job demands and low provider autonomy.[67,71]

Fear for Personal Safety and Well-Being

Approximately 50% of EM residents express trepidation about their personal safety, and as many as 22% fear being shot or assaulted.[75] As a result of working more total clinical hours in contrast to attending physicians, residents are at greater risk for work-related incidents, including needle-stick injuries. Despite the low seroconversion risk of human immunodeficiency virus (HIV), 72% of EM residents worry about the potential for needle-stick injury from an HIV-positive patient, and more than half have sustained a needle-stick during training.[75] Outside of the risks of patient care and the potentially unsafe work environment of the ED, EM residents sustain a higher number of near-collisions and motor vehicle crashes after night shifts.[76]

Consequences of Stress

As a result of the inherent stressors associated with emergency practice, physicians who do not establish effective coping mechanisms may go on to experience depression, suicide, troubled interpersonal relationships, loss of identity, and substance abuse.[68,70,71,77] In an effort to increase awareness of those impaired and at-risk residents, the prevalence of substance use among EM residents was restudied in 2006.[78] This anonymous, self-reported survey comprised nearly 2400 EM residents. Marijuana, cocaine, nonprescribed benzodiazepines, and other sedative drug use has decreased in residents reporting any previous use of these drugs compared with the original data published by McNamara and colleagues.[79] However, tobacco use (1992: 41.1% vs. 2006: 45.7%) and use within the past year of cocaine, benzodiazepines, other sedatives, and noninjectable opioids were not statistically different, and past-month and past-year use rates for alcohol and marijuana have increased between the two studies. In fact, there has been a 48% relative increase in daily alcohol use from 3.3 to 4.9%, with 12.6% of residents reporting that their alcohol consumption has increased during residency (1992: 4%) and 5.3% of residents reporting initiation of alcohol use during residency compared with only 0.3% in 1992.[78,79] Examined against data provided by the National Survey on Drug Use and Health and the Behavioral Risk Factor Surveillance System for similar age groups, resident past-month use of alcohol is strikingly higher, even though no significant difference in response to CAGE screening questions was identified compared with 1992.[78,79]

The consistent and concerning finding between the two studies is that of detection. In 1992, 13% of EM residents had a CAGE score consistent with alcoholism, but program directors believed that only 1% of their residents had a suspected alcohol problem.[79] In 2006, 5.2% of EM residents reported feelings of impairment, compared with 2.9% in 1992, but only 1% were diagnosed and treated for substance abuse.[79] Those respondents who were most likely to have positive CAGE scores during residency were single, separated, or divorced.

With the pressure of longer shifts and total clinical hours, it is not surprising to find that use of caffeine is universal: 90% of EM residents report using caffeine in the past month, and 66% consume caffeine on a daily basis.[79] Despite the finding that 60.8% of EM residents indicate that they use some kind of chemical to help stay awake, modafinil and zolpidem—drugs marketed to reduce symptoms of sleeping disorders, including shift work sleep disorder—are used by only 2.4% and 21.8% of EM residents, respectively.[80] For those residents who strategically use zolpidem, it is most often in association with transition to and from night shifts.[80] Use of either modafinil or zolpidem does not appear to be associated with the use of other substances, including those most commonly used (caffeine, alcohol, and tobacco) and illicit drugs (cocaine, amphetamine, and marijuana).[78,80]

Finding Balance and Well-Being

Because most literature dealing with resident wellness focuses on the negative aspects of well-being through use of quantitative scales (e.g., Maslach Burnout Inventory), Ratanawongsa and colleagues focused their research on the identification of factors associated with positive well-being. The six themes that emerged from this qualitative study were the following: (1) balance among multiple domains, (2) professional development and temporary imbalance, (3) professional satisfaction and accomplishment, (4) maintaining a sense of self, (5) stressors and coping strategies, and (6) the role of residency programs.[70] These inter-relationships form the basis of the proposed conceptual model of well-being. In this model, coping strategies, professional satisfaction, accomplishment, and maintaining a sense of self promote higher levels of well-being.

On the basis of the results of this study, shared responsibility between the individual resident (ensuring balance and maintaining a sense of self) and the residency program (professional development) are essential to optimization of wellness. Ensuring balance and maintaining a sense of self are integral components to any wellness prescription and are more likely to result in a positive training experience. Potential domains for residents to

www.ketabpezeshki.com 66485457-66963820

prioritize include professional, personal, spiritual, and intellectual growth; family and social interactions; health; and finances.[68,70,81] As with any prescription, prioritization is highly individualized.

Culture Change

The traditional approach in resident education of rewarding individual achievement, independent judgment, and self-sacrifice teaches the notion that physicians are indestructible, have few needs, do not make mistakes, and are never ill.[68] Cedfeldt discusses the idea of a "hidden curriculum" within residency programs whereby residents are reluctant to negatively affect a colleague's schedule for fear of appearing weak.[69] A culture change away from perceived stigmas like these is necessary; a primary focus must be placed on wellness and the appreciation that wellness is simply not the absence of burnout.[67,71,81,82] On a macro level, establishment of a formal wellness curriculum within residency programs with a foundation built on endurance and vitality and resident assessment and goal formation creates an environment to produce meaningful change while maximizing professional satisfaction.[82] Research suggests that resident well-being may begin to be improved through restoring meaning to residents' time commitments, facilitating supportive and transparent communication, increasing resident work control, and protecting the separation of work-home.[67,69,81] Examples of strategies to accomplish this and to realize the benefits of culture change include prioritizing short- and long-term goals through evaluation and needs assessment; support groups[68,72,81]; forums for providing feedback[70]; schedule flexibility (considered to be more valuable than limiting of duty hours)[70]; discussing wellness-centered topics[81]; establishing policies to protect resident time off[69]; enhancing opportunities for growth, learning, and responsibility; and endorsing personal and program accomplishments.

As graduate medical education continues to evolve, both programs and residents are faced with new challenges that have a multidimensional impact on resident education and wellness. Continuing to maintain a proactive approach to these challenges, both institutionally and personally, is essential to change the culture toward one of endurance, longevity, and vitality.

SUMMARY

Many aspects of the practice of EM are potentially threats to wellness. Emergency physicians can hope for less stressful, more fulfilling careers by adopting strategies to enhance personal and professional well-being.

KEY CONCEPTS

A variety of stressors contribute to the potentially unhealthful aspects of EM practice, both during residency training and in practice, including the following:

- Difficult patient and professional relationships
- Diversity of practice elements
- Diminished resources
- Difficult decisions full of uncertainty
- Strategies for maintaining wellness for emergency physicians include:
- Mitigating the impact of shift work with circadian scheduling and sleep strategies
- Strategies for managing difficult clinical encounters such as formal debriefs
- Professional support groups
- Cultivating close family and social relationships
- Developing and maintaining physical fitness and other methods of relaxation and renewal

References

1. Margen S, et al, eds: *The Wellness Encyclopedia*. Boston: Houghton Mifflin; 1991.
2. Wallace JE, Lemaire JB, Ghali WA: Physician wellness: A missing quality indicator. *Lancet* 2009; 374:1714-1721.
3. Wasserberger J, et al: Violence in the emergency department. *Top Emerg Med* 1992; 14:71.
4. Crippen DW: Emergency medicine redux: The rise and fall of a community medical specialty. *Ann Emerg Med* 1984; 13:539.
5. Chapman DM: Burnout in emergency medicine: What are we doing to ourselves? *Acad Emerg Med* 1997; 4:245.
6. Zun L, Kobernick M, Howes DS: Emergency physician stress and morbidity. *Am J Emerg Med* 1988; 6:370.
7. Simon JR, Dwyer J, Goldfrank LR: The difficult patient. *Emerg Med Clin North Am* 1999; 17:353.
8. Groves JE: Taking care of the hateful patient. *N Engl J Med* 1978; 298:883.
9. Dorevitch S, Forst L: The occupational hazards of emergency physicians. *Am J Emerg Med* 2000; 18:300.
10. Blanchard JC, Curtis KM: Violence in the emergency department. *Emerg Med Clin North Am* 1999; 17:717.
11. Gorlin R, Zucker HD: Physicians' reactions to patients: A key to teaching humanistic medicine. *N Engl J Med* 1983; 308:1059.
12. Keller KL, Koenig WJ: Sources of stress and satisfaction in emergency practice. *J Emerg Med* 1989; 7:293.
13. Rondeau KV, Francescutti LH: Emergency department overcrowding: The impact of resource scarcity on physician job satisfaction. *J Healthc Manag* 2005; 50:327.
14. Richardson LD, Asplin BR, Lowe RA: Emergency department crowding as a health policy issue: Past development, future directions. *Ann Emerg Med* 2002; 40:388.
15. Derlet R, Richards J, Kravitz R: Frequent overcrowding in U.S. emergency departments. *Acad Emerg Med* 2001; 8:151.
16. California Medical Association: *California's Emergency Medical Services: A System in Crisis*. California Medical Association White Paper. San Francisco: California Medical Association; 2001.
17. Nordberg M: Overcrowding: The ED's newest predicament. *Emerg Med Serv* 1990; 19:33.
18. McManus M: *Emergency department overcrowding in Massachusetts: Making room in our hospitals*. Waltham, Mass: Massachusetts Health Policy Forum; 2001. Available at www.sihp.brandeis.edu/mhpf/Diversions.pdf. Accessed December 17, 2003.
19. Taylor T: *Arizona Emergency Care Crisis: Meeting Summary*. Phoenix, Ariz: Arizona College of Emergency Physicians; 2000. Available at www.azcep.org/er_crowding/summary.pdf. Accessed December 17, 2003.
20. Schneider S, et al: Rochester, New York: A decade of emergency department overcrowding. *Acad Emerg Med* 2001; 8:1044.
21. Waxman H: *National preparedness: Ambulance diversions impede access to emergency rooms*. Washington, DC: U.S. House of Representatives, Committee on Government Reform; 2001. Available at www.house.gov/reform/min/pdfs/pdf_com/pdf_terrorism_diversions_rep.pdf. Accessed December 17, 2003.
22. Young GP, et al: Managed care gatekeeping, emergency medicine coding, and insurance reimbursement outcomes for 980 emergency department visits from four states nationwide. *Ann Emerg Med* 2002; 39:24.
23. Rao MB, Lerro C, Gross CP: The shortage of on-call surgical specialist coverage: A national survey of emergency department directors. *Acad Emerg Med* 2010; 17:1374-1382.
24. Rudkin SE, et al: The state of ED on-call coverage in California. *Am J Emerg Med* 2004; 22:575-581.
25. The Joint Commission: *Sentinel Event Alert, Issue 26: Delays in Treatment*, 2002. Available at www.jointcommission.org/sentinel_event_alert_issue_26_delays_in_treatment/. Accessed March 14, 2011.
26. Kuhn G, Goldberg R, Compton S: Tolerance for uncertainty, burnout, and satisfaction with the career of emergency medicine. *Ann Emerg Med* 2009; 54:106-113.
27. Freudenburger H: The staff burn-out syndrome in alternative institutions. *Psychother Theory Res Pract* 1975; 75:12.
28. Maslach C, Jackson SE: *Maslach Burnout Inventory*. Palo Alto, Calif: Consulting Psychologists Press; 1981.
29. Maslach C, Jackson SE: *The Maslach Burnout Inventory*, 2nd ed. Palo Alto, Calif: Consulting Psychologists Press; 1986.
30. Maslach C, Jackson SE: Patterns of burnout among a national sample of public contact workers. *J Health Hum Res Admin* 1984; 76:189.
31. Cydulka RK, Korte R: Career satisfaction in emergency medicine: The ABEM longitudinal study of emergency physicians. *Ann Emerg Med* 2008; 51:714-722.

www.ketabpezeshki.com 66485457-66963820

32. American College of Emergency Physicians Policy Statement: *Physician Impairment. Approved by Board of Directors*, September 1990. Available at www.acep.org. Accessed February 20, 2008.
33. Baldisseri MR: Impaired healthcare professional. *Crit Care Med* 2007; 35(Suppl):S106.
34. Centrella M: Physician addiction and impairment—current thinking: A review. *J Addict Dis* 1994; 13:91.
35. Sanders A, et al: American College of Emergency Physicians ethics manual. *Acad Emerg Med* 1991; 1:47.
36. Boisaubin EV, Levine RE: Identifying and assisting the impaired physician. *Am J Med Sci* 2001; 322:31.
37. Quill TE, Williamson PR: Healthy approaches to physician stress. *Arch Intern Med* 1990; 150:1857.
38. Covey S: *The Seven Habits of Highly Effective People: Restoring the Character Ethic*. New York: Simon & Shuster; 1989.
39. Margulies JL, Pollack ML: *Developing a healthy lifestyle*. In: Andrew LB, Pollack ML, eds: *Wellness for Emergency Physicians*. Dallas, Tex: American College of Emergency Physicians; 1995:24-26.
40. Lloyd S, Streiner D, Shannon S: Burnout, depression, life and job satisfaction among Canadian emergency physicians. *J Emerg Med* 1994; 12:559.
41. Margulies JL: *Control issues*. In: Andrew LB, Pollack ML, eds: *Wellness for Emergency Physicians*. Dallas, Tex: American College of Physicians; 1995.
42. Dula DJ, et al: The effect of working serial night shifts on the cognitive functioning of emergency physicians. *Ann Emerg Med* 2001; 38:152.
43. Kuhn G: Circadian rhythm, shift work, and emergency medicine. *Ann Emerg Med* 2001; 37:88.
44. Silbergleit R: Shift work and physician performance. *Ann Emerg Med* 2002; 39:349.
45. LaDou J: Health effects of shift work. *West J Med* 1982; 137:525.
46. Culpepper L: The social and economic burden of shift-work disorder. *J Fam Pract* 2010; 59(Suppl):3-11.
47. Costa G: The impact of shift and night work on health. *Appl Ergon* 1996; 27:9.
48. Gordon NP, et al: The prevalence and health impact of shiftwork. *Am J Public Health* 1986; 76:1225.
49. Archer P, Cameron P, Mele G, Mitra B: Rest during shift work in the emergency department. *Aust Health Rev* 2008; 32:246-251.
50. Whitehead DC, Thomas Jr H, Slapper DR: A rational approach to shift work in emergency medicine. *Ann Emerg Med* 1991; 21:1250.
51. Oster NS, Doyle CJ: Critical incident stress and challenges for the emergency workplace. *Emerg Med Clin North Am* 2000; 18:339.
52. Mitchell JT: Stress: The history, status and future of critical incident stress debriefings. *JEMS* 1988; 13:46.
53. Gabbard GO: *Medical Marriages*. New York: American Psychiatric Press; 1988.
54. Gabbard GO, Menninger RW: The psychology of postponement in the medical marriage. *JAMA* 1989; 261:2378.
55. Coombs R: Marital status and personal well-being: A literature review. *Fam Relations* 1990; 40:97.
56. Tyssen R, et al: Lower life satisfaction in physicians compared with a general population sample. *Soc Psychiatry Psychiatr Epidemiol* 2009; 44:47-54.
57. Krauss RM, et al: AHA Dietary Guidelines: Revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. *Circulation* 2000; 102:2284.
58. Fletcher GF, et al: Statement on exercise: Benefits and recommendations for physical activity programs for all Americans: A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation* 1996; 94:857.
59. Lobelo F, Duperly J, Frank E: Physical activity habits of doctors and medical students influence their counseling practices. *Br J Sports Med* 2009; 43:89-92.
60. Benson H, et al: Decreased blood-pressure in pharmacologically treated hypertensive patients who regularly elicited the relaxation response. *Lancet* 1974; 1:289.
61. Benson H, Klipper MZ: *The Relaxation Response*. New York: Wings Books; 1992.
62. Irving J, Dobkin P, Jeeson P: Cultivating mindfulness in health care professionals: A review of empirical studies of mindfulness-based stress reduction. *Complement Ther Clin Pract* 2009; 15:61-66.
63. Crook H, Taylor D, Pallant J, Cameron P: Workplace factors leading to planned reduction of clinical work among emergency physicians. *Emerg Med Australas* 2004; 16:28-34.
64. Coombs RH, Fawzy FI: *The impaired physician syndrome: A developmental perspective*. In: Scott C, Hawk J, eds: *Heal Thyself: The Health of Health Professionals*. New York: Brunner/Mazel; 1986:44-55.
65. Bruce S: Recognizing stress and avoiding burnout. *Currents Pharmacy Teaching Learning* 2009; 1:57-64.
66. Wallace J, Lemaire J: On physician well being—you'll get by with a little help from your friends. *Soc Sci Med* 2007; 64:2565-2577.
67. Thomas NK: Resident burnout. *JAMA* 2004; 292:2880-2889.
68. Houry D, Shockley LW, Markovchick V: Wellness issues and the emergency medicine resident. *Ann Emerg Med* 2000; 35:394-397.
69. Cedfeldt AS, et al: Personal time off and residents' career satisfaction, attitudes and emotions. *Med Educ* 2010; 44:977-984.
70. Ratanawongsa N, Wright SM, Carrese JA: Well-being in residency: A time for temporary imbalance? *Med Educ* 2007; 41:273-280.
71. Wallace JE, Lemaire JB, Ghali WA: Physician wellness: A missing quality indicator. *Lancet* 2009; 374:1714-1721.
72. McCray LW, et al: Resident physician burnout: Is there hope? *Fam Med* 2008; 40:626-632.
73. Accreditation Council for Graduate Medical Education: *Resident Duty Hours in the Learning and Working Environment: Comparison of 2003 and 2011 Standards*. Available at www.acgme.org/adspublic/. Accessed March 24, 2011.
74. Wagner MJ, et al: Duty hours in emergency medicine: Balancing patient safety, resident wellness, and the resident training experience: A consensus response to the 2008 Institute of Medicine resident duty hours recommendations. *Acad Emerg Med* 2010; 17:1004-1011.
75. Anglin D, Kyriacou DN, Hutson HR: Residents' perspectives on violence and personal safety in the emergency department. *Ann Emerg Med* 1994; 23:1082-1084.
76. Steele MT, et al: The occupational risk of motor vehicle collisions for emergency medicine residents. *Acad Emerg Med* 1999; 6:1050-1053.
77. Katz ED, Sharp L, Ferguson E: Depression among emergency medicine residents over an academic year. *Acad Emerg Med* 2006; 13:284-287.
78. McBeth BD, et al: Substance use in emergency medicine training programs. *Acad Emerg Med* 2008; 15:45-53.
79. McNamara RM, et al: Substance use and alcohol abuse in emergency medicine training programs, by resident report. SAEM Residency Survey Task Force. *Acad Emerg Med* 1994; 1:47-53.
80. McBeth BD, et al: Modafinil and zolpidem use by emergency medicine residents. *Acad Emerg Med* 2009; 16:1311-1317.
81. Eckleberry-Hunt J, et al: An exploratory study of resident burnout and wellness. *Acad Med* 2009; 84:269-277.
82. Worrall A, Epter ML: Resident wellness within emergency medicine residency programs—a survey of emergency medicine program directors. Submitted for publication, March 2011.

www.ketabpezeshki.com 66485457-66963820

Index

A

A priori probability, e16
AAA. *See* Abdominal aortic aneurysm
Abacavir, 1721t-1722t, 1766t
Abandonment, 886
Abatacept, 1515t
ABC/2 technique, 1366, 1368f
ABCD2 score, 1374, 1374b
Abdomen, 460
Abdominal aortic aneurysm, 1129-1137
  acute back pain in, 282t-283t
  anastomotic, 1136
  clinical features of, 139t, 1130-1131
  CT findings, 1132-1133, 1133f
  diagnostic strategies for, 1131-1133
  differential considerations, 1133
  epidemiology of, 1129
  intact, asymptomatic, 1134-1135
  key concepts, 1137b
  management of, 1133-1135
  natural history of, 1129-1130
  pathophysiology of, 1129
  patient disposition in, 1137
  prevalence of, 1130t
  pseudoaneurysm, 1129, 1136
  radiographic findings, 1131, 1132f
  repair of
    endovascular, 1135-1137, 1135f, 1137b
    late complications of, 1135-1137
    mortality rate, 1135
    traditional or conventional, 1134, 1135f
  risk factors for, 1129
  ruptured or leaking, 1130-1131, 1137b
    abdominal pain in, 227, 227t-228t
    diagnostic confirmation of, 1134
    management of, 1133-1134
    misdiagnoses, 1133b
    surgery and mortality, 1134
  ultrasound findings, 1131-1132, 1132f, 2497, 2497f
  unruptured, 1130
Abdominal aortic aneurysms, 1129-1137
  dissecting, 1129, 1130f
  types of, 1129, 1130f
Abdominal examination, pediatric, 310
Abdominal imaging
  in abdominal aortic aneurysm, 1131, 1132f
  bowel ultrasound, 2500-2501
  in diverticulitis, 1263
  in nausea and vomiting, 242
  in urologic problems, 1329
  vascular ultrasound, 2497
Abdominal infection, 1872t
Abdominal migraine, 2242
Abdominal pain, 223-231
  acute
    differential diagnosis of, 226f
    in older patients, 226-227, 230t
    opioid analgesic agents for, 42

Abdominal pain *(Continued)*
  ancillary testing in, 229-230
  antibiotics for, 231
  causes of, 224t-225t
  colicky, 226-227, 229f
  descriptions of, 227
  diagnostic approach to, 225-230
  differential diagnosis of, 225-226, 230-231, 1532t, 2178t
    in elderly, 2354t
    in pregnancy, 2293t
  in elderly, 2354
    acute, 226-227, 230t
    differential diagnosis of, 2354t
  epidemiology of, 223
  evaluation of, 2482-2483
  extra-abdominopelvic causes of, 225b
  historical questions for, 228b
  hospital admission for, 231
  life-threatening causes of, 227t-228t
  lower, 223
  management of, empirical, 231
  nonspecific, 224t-225t
  observational approach to, 2482-2483, 2482b
  in parasitic infection, 1783
  pathophysiology of, 223-225
  patient discharge information, 231
  patient disposition in, 231
  pivotal findings, 226-230
  in pregnancy, 2277-2278, 2293-2296, 2293t
  rapid assessment and stabilization of, 226
  referred pain from, 225, 227f
  signs of, 229
  symptoms of, 226-229
  traditional approach to, 2482
  upper, 223
  in women, 1226t
Abdominal procedures, US-guided, 2503
Abdominal trauma, 459-478
  bedside procedures for, 467-470
  blunt, 459
    diagnostic testing in, 475, 475t
    epidemiology of, 459
    history taking in, 462
    iatrogenic injuries, 461
    management of, 475-478
    observational approach to, 2486
    pathophysiology of, 461-462
    pediatric, 320, 461-462, 478
    physical examination findings, 463
    traditional approach to, 2486
  clinical features of, 462-463
  diagnostic strategies for, 463-470
  differential considerations, 470
  epidemiology of, 459-460
  gunshot wounds, 460, 473-475
    history taking in, 462
    physical examination findings, 463
  from high-velocity missiles, 460

Abdominal trauma *(Continued)*
  history taking in, 462
  key concepts, 478b
  laboratory testing in, 463-464
  laparotomy-requiring, 472-473
  management of, 470-478
  vs medical condition, 470
  in older adults, 328
  pathophysiology of, 460-462
  pediatric, 320-322
    abuse, 848
    clinical features of, 321
    diagnostic strategies for, 321-322
    epidemiology of, 459-460
    history taking in, 462
    management of, 321-322
    radiology in, 322
    signs and symptoms of, 321
  penetrating, 459
    epidemiology of, 459
    history taking in, 462
    observational approach to, 2486
    pathophysiology of, 460-461
    pediatric, 322
    physical examination findings, 463
    traditional approach to, 2486
  physical examination findings, 462-463
  prehospital measures for, 470
  radiology in, 464-467
  shotgun wounds, 460-461
  single vs multiple intraperitoneal organ injury, 470
  single vs multisystem, 470
  stab wounds, 460, 471-473
    diagnostic testing in, 471
    history taking in, 462
    local wound exploration, 469-470
    management of, 471-473
    physical examination findings, 463
  wound exploration, 469-470
Abducens nerve (CN VI), 1410t-1411t
Abduction, ankle, 723
ABI. *See* Ankle-brachial index
ABIC (age, bilirubin, INR, creatinine) score, 2385
Abilify (aripiprazole), 1463, 1472-1473, 2418
ABO blood grouping, 75
Abortion, missed, 2282
Abortus, 2272
Abrasion collar, 830-832, 833f
Abrasion margin, 830-832
Abrasion rim, 830-832
Abrasion ring, 830-832
Abrasions, pattern, 839
Abruptio placentae or placental abruption, 299, 2288-2289
  clinical features of, 299, 2289
  differential considerations, 2289
  management of, 299
Abrus precatorius (jequirity pea or rosary pea), 2066-2067, 2067f

Page numbers followed by *f* indicate figures; *t*, tables; *b*, boxes; *e*, online-only material.

www.ketabpezeshki.com 66485457-66963820

Abscess, 1831
amebic, 1198
anorectal, 1281-1282
Bartholin, 1314-1315
Bartholin's, 1857-1858, 1858f
brain, 1449f
complications of, 1451
epidemiology of, 1447-1448
etiology of, 1448-1449
after head injury, 359
in HIV infection, 1762t
pathophysiology of, 1449
therapy for, 1457-1458
Brodie's, 1841
clinical features of, 1855
collar-button abscess, 567, 567f
dental, simple, 898-899
diagnostic strategies for, 1855-1856
differential diagnosis of, 174t, 1855-1856, 1858f
epidural, 279
hepatic, 1196-1198
horseshoe, 1282
intersphincteric, 1281t, 1282
ischiorectal, 1281t, 1282
management of, 1856-1858
parapharyngeal, 974-975
patient disposition in, 1858
perianal, 1281-1282, 1281t
periapical, 897, 898f
perirectal, 1281-1282
peritonsillar, 971-972, 972f
pediatric, 2110
postanal, 1281t, 1282
pyogenic, 1196-1198
retrobulbar, 193t-196t
retropharyngeal, 973-974
pediatric, 2109-2110, 2116b
risk factors for potentially catastrophic illness, 172b
skin, 1855-1858, 1863b
sonographic, 2499, 2499f
spinal epidural, 282t-283t, 1426
supralevator, 1281t, 1282
tubo-ovarian, 267t-268t
Absence seizures, 1376
atypical, 1376
childhood absence epilepsy, 2232
juvenile absence epilepsy, 2232
typical, 1376
Absinthe, 2023
Absolute neutrophil count (ANC), 1617
Abuse
child abuse, 2094
child maltreatment, 845-854
child physical abuse, 845-848
child sexual abuse, 845, 849-850
elder abuse and neglect, 885-892
emotional or psychological, 886
institutional, 885-886
intimate partner violence, 873
medical child abuse, 845
physical abuse, 886
self-abuse, 885-886
sexual
child abuse, 845, 849-850
definition of, 886
intimate partner, 877
STI prophylaxis or treatment after, 851, 851t
spouse abuse, 872
substance abuse, 2395-2399
among children, e2
in pregnancy, 2280, 2395
reporting requirements for, e77
self-destructive patients, 2429
and suicide, 1494-1495
wife abuse, 872
Abuse Assessment Screen (AAS), 879, 879b
Abusive head injury, 355
Abusive relationships, 874-875
Acalculous cholecystitis, 1203
Acanthamoeba, 1778, 1780
Acanthosis nigricans, 1580, 1664
Acarbose, 1665t
Access, emergency, 2437
Access to care
racial and ethnic disparities in, e23-e24
restricted, e44
Accessory navicular bone, 735, 741
Accessory ossicles, 735, 736f
Accessory pathway syndromes, 1052-1055, 1063b
Accidental Death and Disability: The Neglected Disease of Modern Society (NAS-NRC), 2433
Accidental hypothermia, 1883-1895
Acclimatization
altitude, 1929-1930
heat, 1897
Accommodation, 2371
Accreditation, 2492-2493
Accreditation Council for Graduate Medical Education (ACGME), e83
Acebutolol, 1987t, 1122.e1t-1122.e2t
Acellular pertussis-diphtheria-tetanus toxoid, 814
ACEP. *See* American College of Emergency Physicians
Acetabular fractures, 670-671
classification of, 670, 670b, 670f
key concepts, 697b
T fracture, 670
Acetabulum, 670-671, 670f
Acetaldehyde adducts, 2380t
Acetaminophen, 42-43
for acute migraine attack, 1388t
alcohol interactions, 2390t, 2391
for burn pain, 816
metabolism of, 1960, 1961f
for osteoarthritis, 1511
for pediatric migraine, 2243
in pregnancy, 2317, 2318t-2321t
to prevent fever in increased ICP, 314t
Acetaminophen toxicity, 1960-1964
acute, 1961-1962, 1962f
antidote for, 1957t-1958t
chronic
indications to initiate testing for, 1962, 1962t
risk assessment with, 1962-1963
clinical features of, 1960-1961
diagnostic strategies for, 1961-1963
hepatic injury, 1196, 1197t, 1960, 1961f, 1961t
key concepts, 1964b
liver injury in, 1963, 1963f
management of, 1963-1964
NAC therapy for, 1964
patient disposition in, 1964
predictors of severity of, 1964t
in pregnant women, 1963-1964
supportive care for, 1964
time course and clinical stages, 1960, 1961f, 1961t
Acetazolamide (Diamox)
for acute mountain sickness, 1933-1934
for glaucoma, 922, 930t
for hyperuricemia, 1624
for rhabdomyolysis, 1674
side effects and drug interactions, 2407t-2408t
Acetic acid, 865-866, 866t
Acetoacetate/β-hydroxybutyrate ratio, 1655
Acetone poisoning, 1955t
Acetylcholine (ACh), 1441
Acetylcholine (ACh) receptors (AChRs), 1441
sites of, 1970, 1971f
N-Acetylcysteine
for acetaminophen toxicity, 1957t-1958t, 1960-1964, 1961f
in pregnancy, 1964, 2318t-2321t, 2323
side effect profile for formulations, 1963, 1963t
N-Acetylcysteine poisoning, 1955t
Acetylsalicylic acid (ASA). *See* Aspirin
Achilles tendinopathy, 1522-1523
Achilles tendon rupture, 733, 1522
key concepts, 750b
management of, 1523
ultrasound of, 2500, 2500f
Acid-base disorders, 1629-1635. *See also specific disorders*
in aspirin overdose, 1965
diagnostic strategies for, 1629-1630
in hypothermia, 1888, 1888f
key concepts, 1635b
mixed, 1635
Acid-base disorders *(Continued)*
simple, 1630, 1630t
triple, 1633
Acid-fast bacillus (AFB), 1810, 1815-1816, 1816f
Acidemia, 1629
Acidosis
definition of, 1629
diabetic ketoacidosis, 1632, 1656-1661
diagnosis and treatment of, 94t
lactic, 1632b
metabolic, 1629, 1632-1634
key concepts, 1635b
vomiting and, 239
respiratory, 1629-1631
causes of, 1631b
key concepts, 1635b
in rhabdomyolysis, 1672
Acne, 1859
Acne inversa (hidradenitis suppurativa), 1859
Acoustic neuroma, 1413
diagnostic algorithm for, 167f
differential diagnosis of, 166t-167t
Acquired C1 inhibitor deficiency (ACID), 1556
Acquired immunodeficiency syndrome (AIDS), 1756-1757
in children, 2104
clinical manifestations of, 1757-1764
constitutional disease, 1757
definition of, 1756, 1757b
diarrhea in, 1254-1258, 1258t
epidemiology of, 1751
initial evaluation of, 1757
myocarditis in, 1100
parasitic coinfections in, 1783-1784
pneumonia in, 985
in pregnancy, 2301t-2303t, 2312-2313
prevalence of, 1752f
skin lesions associated with, 1581t, 1582f
tuberculoma in, 1821f
wasting in, 1757
Acrocyanosis, 1140, 1149
Acrolein, 2037t
Acromioclavicular joint
anatomy of, 618, 619f
dislocation of, 629-631
classification of, 630, 630f
clinical features of, 630
complications of, 631
diagnostic strategies for, 630
key concepts, 642b
management of, 630-631
mechanism of, 630, 630f
pathophysiology of, 629-630, 630f
third-degree sprain, 630f
ACS. *See* Acute coronary syndrome; American College of Surgeons
ACTH [adrenocorticotropic hormone] (H.P. Acthar gel), 2407t-2408t
Actinic (radiation) plexopathy, 1433
Actinomyces, 965
Action potentials, 1036f
Activated charcoal
for acetaminophen toxicity, 1963
for barbiturate toxicity, 2077
for body packers, 2004
for body stuffers, 2004
for salicylate toxicity, 1967
Activated protein C, 1872-1873
Acute and remote symptomatic seizures, 2234b
Acute care
injury control, 337
multidisciplinary team approach to, 331
Acute care hospitals, e68
Acute cauda equina syndrome, 401
Acute chest syndrome, 1597, 1605b
Acute compression triad, 1626b
Acute confusional state, 2242
Acute coronary syndrome, 997-1033
adverse events of therapy for, 1003
atypical history, 1001
atypical presentations, 1002
cardiac markers in, 1019
classic history of, 1000
clinical features of, 999-1003
definition of, 997

www.ketabpezeshki.com 66485457-66963820

Acute coronary syndrome *(Continued)*
diagnosis of
investigations for, 1003-1021
multiple marker strategies for, 1019-1020
strategies for, 1017t
ECG adjuncts in, 1014-1016
ECG findings in, 1003-1006, 1014-1015, 1014f, 1028
ST segment depression, 1005, 1005f
T wave inversions, 1005, 1006f
ECG limitations in, 1016, 1033b
echocardiographic findings in, 1017t, 1020
ED evaluation of, 1000-1003
epidemiology of, 997-998
fibrinolytic therapy for, 1027-1029
functional testing strategies for, 1033b
heart failure in, 1081
historical perspective on, 997
history taking in, 1000
hypertension in, 1119-1120, 1120t
key concepts, 1033b
management of, 1022-1033
missed diagnosis of, 1002
pathophysiology of, 999
patient transfer, 1032-1033
percutaneous coronary intervention for, 1030-1031
pharmacologic intervention for, 1024-1027
physical examination findings, 1001-1002
potential, 1033
preadmission evaluation of, 1000
in pregnancy, 2301t-2303t, 2304-2305
radiographic findings in, 1016, 1017f
reperfusion therapy for, 1027-1032
risk factors associated with, 216b
serum markers in, 1016-1020, 1017t, 1018f
spectrum of disease, 998-999
time to treatment and outcomes in, 1022-1024, 1022f
Acute fatty liver of pregnancy, 2295
clinical features of, 2296
diagnostic strategies for, 2296
differential considerations, 2296
management of, 2296
Acute kidney injury, 1291, 1294-1301
in children, 2217-2219
clinical features of, 2217-2218
diagnostic strategies for, 2218
differential considerations, 2218
etiology of, 2218b
management of, 2218-2219
patient disposition in, 2219
clinical features of, 1295b, 1298-1299
diagnostic strategies for, 1299
FENa in, 1292b
with hypertension, 1120t, 1121-1122
intrinsic, 1296-1297, 1296b
key concepts, 1311b
laboratory findings, 1299
management of, 1299-1301
metabolic complications, 1300-1301
myoglobin-induced, 1672, 1673f
organ system effects, 1301
patient disposition in, 1301
pigment-induced, 1298b
postrenal (obstructive), 1296
rhabdomyolysis and, 1672, 1673f
volume complications, 1300-1301
Acute life-threatening events (ALTEs)
in children, 109-110
conditions under which it is safe to discharge patients after, 110
Acute mountain sickness, 1928, 1932-1934, 1932b
clinical presentation of, 1932
key concepts, 1940b
management of, 1932-1933
mechanisms of, 1930, 1930f
pathophysiology of, 1930-1932
prevention of, 1933-1934
risk factors for, 1928, 1934t
Acute neurologic examination, 345-347
Acute pain, 35-36, 35t. *See also* Pain
analgesic options for, 49b
pelvic, in women, 266-272
treatment of, 38, 38f
Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system, 1210, 1210b
Acute Physiology and Chronic Health Evaluation III (APACHE III) scoring system, 1210
Acute radiation syndrome, 1949
Acute renal failure. *See* Acute kidney injury
Acute respiratory distress syndrome
causes of, 29t
chest pain in, 217t-218t
definition of, 1866b
ventilatory support for, 29-30
Acute retroviral syndrome, 965
Acute rheumatic fever. *See* Rheumatic fever
Acute stress disorder, 1475b
Acute tubular necrosis, 1292t, 1294, 1297-1298
Acute tumor lysis syndrome, 1621-1622
clinical features of, 1621-1622
key concepts, 1628b
management of, 1622
risk factors for, 1621b
Acyclovir (Zovirax), 1722-1723
for diarrhea in AIDS, 1257t
for herpes encephalitis, 2236
for herpes esophagitis, 1175
for herpes meningoencephalitis, 1457
for herpes simplex, 1578, 1721t-1722t, 1728
for herpes zoster, 1729
in immunocompromised patients, 2361t
for monkey B virus exposure, 790
for pediatric meningitis, 2230-2231
for sexually transmitted diseases, 1315t
for STI prophylaxis or treatment, 851t
for varicella-zoster virus infection, 1721t-1722t
Adalimumab, 1515t
Adam. *See* Methylenedioxymethamphetamine
Addiction, 40
narcotic, 1584, 1584f
pseudoaddiction, 40
Addison's disease, 1689
Adduction, ankle, 723
Adefovir, 1721t-1722t
Adenoidal hypertrophy, 108
Adenoma, toxic, 1678
Adenosine, 1040
for AV-nodal reentrant tachycardia, 1052
for dysrhythmias, 1040
for pediatric dysrhythmias, 2154b, 2167b
for pediatric resuscitation, 104t
in pregnancy, 2318t-2321t, 2326
for SVT tachycardia, 2157
Adenosine-induced wide-complex tachycardia, 2157, 2157f
Adenosine triphosphate (ATP), 1667
Adenovirus infection, 1719t, 1733, 2191
pharyngitis, 965
Adhesion defects, 1611
Adhesive capsulitis (frozen shoulder), 624, 642
clinical features of, 642
injection therapy for, 642
key concepts, 642b
management of, 642
pathophysiology of, 642
Adie's tonic pupil, 927
Adjustment disorders, 1472
Adolescents, 2090. *See also* Children; Youth
in abusive relationships, 874-875
alcohol-related disease in, 2391
alcohol use among, e2
depression in, 1469
drug abuse among, e2
media violence effects on, e1-e2
psychological effects of street gang violence on, e4
suicide among, 1495
tuberculosis in, 1826
and violence, e2
vomiting in, 2172t
Adrenal glands
anatomy of, 1689
physiology of, 1689
Adrenal insufficiency, 1689-1692
acute, 1689, 1691b
causes of, 1691b
chronic, 1689, 1691b
Adrenal insufficiency *(Continued)*
clinical features of, 1689-1690, 1691b
diagnostic strategies for, 1690-1691
differential considerations, 1691
key concepts, 1692b
management of, 1691-1692
pathophysiology of, 1689, 1690f
patient disposition in, 1692
prevalence of, 1689
primary, 1689-1690, 1690f, 1691b
secondary, 1689-1690, 1690f, 1691b
Adrenergic agents. *See also* Alpha-adrenergic agonists; Beta-adrenergic agonists
for asthma, 949-950
Adrenergic inhibitors, 1122.e1t-1122.e2t. *See also* Alpha-adrenergic blockers; Beta-blockers
Adrenocorticotropic hormone (corticotropin)
for gouty arthritis, 1509
regulation of, 1689
Adult maltreatment, 884, 892b
Adult-onset Still's disease, 1515
Adult Protective Services, 890-891
Advance directives, e39
guidelines for policy development, e39b
honoring, e50-e51, e55-e56
initiating, e56
questions for discussion of, e56t
reviewing, e55-e56
to withhold resuscitation, e50-e51
Advanced emergency medical technicians (AEMTs), 2435-2436, 2436t
Advanced life support
EMS systems, 2435
for hypothermia, 1890
for ICD malfunction, 1072-1073
during low-flow CPR, 102
for pacemaker malfunction, 1071
Advanced Trauma Life Support (ATLS), 288-291
guidelines for emergency department thoracotomy, 450
recommendations for age as triage criterion, 324
Advanced vital signs, 2452
Advocacy, 337-338
Advocacy Partnering Model of system intervention, 880-881
Advocates for EMS, 2439t
AEMTs. *See* Advanced emergency medical technicians
Aeroesophageal foreign bodies, 2115-2116
Aeromonas infection
gastroenteritis, 1240-1241
in AIDS, 1257t
antibiotic therapy for, 1235t
clinical presentation of, 1240
diagnostic strategies for, 1241
epidemiology of, 1240-1241, 1243t
management of, 1241
pathophysiology of, 1241
skin infections, 1856t
Aerosol eye exposures, 912
AFB. *See* Acid-fast bacillus
Affect, flattened, 1461
Affective limitations, 2508
Afghanistan, 2451
AFLP, 237
African Americans
health beliefs and concerns, e27-e28
life expectancy, e24
pregnancy rates, 2271
suicide rate, 1492
treatment options for, e24
African trypanosomiasis *(Trypanosoma brucei rhodesiense)*, 1777-1778
clinical features of, 1777
diagnostic strategies for, 1778
drug regimens for, 1772t-1775t
management of, 1778
Afterdepolarization, 1034
Afterload, 1077, 1077f
Against medical advice (AMA), e73-e75
informed consent form for, e73, e74f
protocol for management of, e75b
steps to take, e73-e75

www.ketabpezeshki.com 66485457-66963820

Age
advanced. *See also* Elder patients
bag-mask ventilation in, 5-6
and digitalis intoxication, 1986, 1986t
and fibrinolytic therapy, 1028
gestational
definition of, 2272
landmarks for, 2283, 2283t
at menarche, 2271, 2272f
as triage criterion, 324
Age-based rule for endotracheal tubes, 109
Agency for Healthcare Research and Quality (AHRQ)
contact information, 2458t
standards for culturally and linguistically appropriate services (CLAS standards), e25
tool for assessment of readiness for IPV response, 880
Agent Orange, 2062
Aggressive house spider *(Tegenaria)*, 804
Aging, 2058
clinical features of, 2353-2354
pharmacologic considerations, 2351-2353
physiologic changes of, 2351, 2352t
Agitation. *See also* Combative patients
in anticholinergic overdose, 1972
in substance abuse, 2398
Agkistrodon contortrix mokasen (Northern copperhead) bite, 798f
Agoraphobia, 1475b, 1477-1478
Agranulocytosis, antipsychotic-induced, 2049
AIDS. *See* Acquired immunodeficiency syndrome
AIDS cholangiopathy, 1204
AIDS-related lymphoma, 1763
Air bags, 336, 369, 1994
partial amputations from contact with deploying covers, 841, 841f
during pregnancy, 2279
Air casts, 526-527
Air embolism
central line emergencies, 2411t
clinical features of, 139t
in neck injury, 423, 429
Air hunger, 206
Air medical transport, 2442-2448
administration of, 2443
aircraft, 2443-2444
for cardiac disorders, 2447
of children, 2447
cost-effectiveness of, 2447-2448
criteria for, 2447b
efficacy of, 2447-2448
flight crew, 2444
future directions, 2448
integration with EMS systems, 2445
landing zones, 2445, 2446b
medical direction, 2444
of neonates, 2447
patient care, 2445-2447
for pregnancy, 2447
safety, 2444-2445
for stroke, 2447
systems, 2443-2445
trauma flights, 2446-2447
types of missions, 2443
AirCast Air-Stirrup, 531, 532f, 732
Aircraft
air medical, 2443-2444
fixed-wing (airplanes), 2444
rotor-wing (helicopters), 2443-2444. *See also* Helicopter emergency medical services (HEMS)
Airplanes, 2444
Airway
difficult
clinical features of, 4-8
evaluation of, 4
identification of, 4-6
management of, 8-10
in disabled patients, 2401-2404
failed, 10, 10f
failure to maintain or protect, 3
pathophysiology of, 3-4
pediatric, 108, 306t, 2087, 2106, 2107f
remodeling of, in asthma, 942-944
Airway *(Continued)*
supraglottic, 2109
surgical, 291
surgical-invasive airways, 424
tuberculosis of, 1813
Airway contamination, 2456, 2456f
Airway devices, 18-21
Airway foreign bodies, 772-776
in children, 2115-2116
clinical features of, 772, 2115
diagnostic strategies for, 773-774, 2115-2116
history taking in, 772-773
key concepts, 784b, 2116b
management of, 774-776, 2115-2116
physical examination findings, 773
radiographic findings, 774, 774f-775f
Airway management, 3, 8-10
algorithms for, 8, 8f-10f
in anaphylaxis, 1553
assessment
in geriatric trauma, 325
in sore throat, 198
on battlefield, 2452
in burns, 811
in facial trauma, 375
in head injury, 348
interventions for, 307t, 2439
key concepts, 22b
medications for, 2439
in neck injury, 423-425
pediatric considerations, 424
techniques for, 424
out-of-hospital care, 2439
outcomes, 22
pediatric
anatomic differences, 306t
equipment for, 109
in neck injury, 424
prehospital, 109
in trauma, 305-306, 307t, 424
prehospital, for children, 109
primary survey
in multiple trauma, 291
in trauma in pregnancy, 300
rewarming, 1892-1893
special clinical considerations, 16-18
in spinal injury, 416-418
surgical, 21-22
therapeutic modalities, 10-22
Airway obstruction
airway evaluation in, 4-5
bag-mask ventilation in, 5-6
lower, in children, 2091-2092, 2092f, 2117-2128
options for, 784b
upper, in children, 2106-2116
Akathisia
antipsychotic-induced, 2048
with neuroleptic agents, 1464
AKI. *See* Acute kidney injury
Akinesia, 1464-1465
ALARA (as low as reasonably achievable) principle, 2493-2494
Alarm systems, 2420
Albendazole, 1235t, 1770t, 1772t-1775t
Albumin, cardiac, 1019
Albuterol
for anaphylaxis, 1554b
for asthma, 949-950, 949t, 2121t
for asthma in children, 2120-2121, 2123
for asthma in pregnancy, 2303t
for COPD, 963
for hyperkalemia, 1300, 1305t, 1638, 1638t
racemic (*R*-albuterol), 2120-2121
Alcohol
additive effects of, 2391
cardiovascular effects of, 2384
drug interactions, 2390-2391, 2390t
effects in pregnancy, 2392
effects on metabolism, 2387-2389
gastrointestinal effects of, 2384-2386
hepatic effects of, 2384-2386
labor interactions, 2340t
metabolism of, 2380-2381
enhanced, 2391
oral hypoglycemic interactions, 2391
Alcohol *(Continued)*
physiological effects of, 2380-2381, 2381t
police blood alcohol tests, e62-e63
pulmonary effects of, 2384
risks and benefits of moderate consumption of, 2384, 2385b
synergistic effects of, 2391
teratogenic effects of, 2392
toxic, 2007-2014
toxic metabolites of, 2391
and trauma, 2392-2393
Alcohol abuse, 2378, 2380
among adolescents, e2
age at onset, 2391
causes of death related to, 2379t
chronic pancreatitis due to, 1212
definition of, 2378
harmful drinking, 2380
hazardous or “at-risk” drinking, 2379-2380
in pregnancy, 2280, 2392
risks and benefits of, 2384, 2385b
among sexual assault victims, 862
Alcohol antiseptic solutions, 756t
Alcohol dehydrogenase, 2380
Alcohol dependence, 2378
Alcohol-induced hypoglycemia, 2381, 2387
Alcohol intoxication, e72
acute, 2381, 2393
admission guidelines for, 2393
consent for medical care in, e72
in trauma, 2392-2393
Alcohol-related disease, 2378-2394
in adolescents, 2391
causes of, 2379
clinical features of, 2384-2390
definition of, 2379-2380
diagnosis of, 2378-2379
differential considerations, 2381
in elderly, 2392
epidemiology of, 2378
key concepts, 2394b
liver disease, 1192-1193
key concepts, 1193b
patient disposition in, 1193
management of, 2381, 2384-2390
natural history of, 2379-2380
origins of, 2379
pathophysiology of, 2379
seizures, 2382-2384, 2393
Alcohol-related motor vehicle crashes, e76-e77
Alcohol screening questionnaires, 2378-2379
Alcohol use disorders, 2378
and motor vehicle injury, 337
treatment of, 337
Alcohol Use Disorders Identification Test (AUDIT), 2378
AUDIT-C Screening Questionnaire, 2378-2379
Alcohol withdrawal seizures, 2383
Alcohol withdrawal syndrome, 2381-2382
adjunctive therapy for, 2382
admission guidelines for, 2393
anxiety in, 1477
clinical features of, 2381-2382
differential considerations, 2381
emergency department approach to, 2382
management of, 2382
outpatient approaches to, 2382
vital signs in, 2419t
Alcoholic cerebellar degeneration, 2386-2387
Alcoholic cirrhosis, 2386
Alcoholic distal symmetrical polyneuropathy, 1432
Alcoholic hepatitis, 2385
clinical features of, 1192
differential considerations, 1192
management of, 1192-1193
Alcoholic ketoacidosis, 1632-1633, 1635b, 2388-2389
Alcoholic ketosis, 2389
Alcoholic pancreatitis, 1205
Alcoholism
admission guidelines for, 2393-2394
biomarkers in, 2379t-2380t
definition of, 2379
epidemiology of, 2378
hypomagnesemia in, 1648
idiopathic macrocytosis of, 2389

www.ketabpezeshki.com 66485457-66963820

Alcoholism *(Continued)*
in immunocompromised patients, 2365
infections in, 2387
patient disposition in, 2393-2394
and suicide, 1494-1495
Aldomet, 2390t
Alfentanil, 39t
Alice in Wonderland syndrome, 2242
Alignment, 514
Aliskiren, 1122.e1t-1122.e2t
Alkalemia, 1629
Alkali burns
corneal burn, 189f, 911f
key concepts, 827b
ocular exposures, 1997
Alkaline therapy, 1674
Alkalosis
contraction, 1634
definition of, 1629
metabolic, 1629, 1634-1635, 1634b
respiratory, 1629, 1631-1632, 1631b
All-terrain vehicles (ATVs), 368
Allen's test, 541-542, 542f
Allergic conjunctivitis, 193t-196t, 919
Allergic reactions
to fire ant stings, 803
supraglottic, 2111
transfusion reaction, 79
wheal and flare, 1555-1556
Allergy, 1543-1557
definition of, 1548
to insulin, 1665
key concepts, 1557b
to local anesthetics, 46, 754-755
pathophysiology of, 1549-1550
Allis technique, 688, 689f
Alloantibodies, extrinsic, 1599
Allodynia, 32b
Allopurinol, 1622, 1624
Aloe vera (Dermaide), 1880
Alogia, 1461
Alpha (α), e12-e13, e13t
Alpha-adrenergic agonists, 1122.e1t-1122.e2t
Alpha-adrenergic blockers, 1087, 1122.e1t-1122.e2t
Alpha errors, e13t
Alpha particles, 1947-1948, 1948f
Alpha$_1$-adrenergic antagonists, 1122.e1t-1122.e2t
Alpha$_2$-adrenergic agonists, 930t
Alphaviruses (group A arbovirus), 1513t, 1736-1737
Alprazolam (Xanax), 2078t
Alprostadil (PGE$_1$), 104t
Alteplase
for PE, 1166t
in pregnancy and lactation, 2318t-2321t
Altered levels of consciousness
after head injury, 344
interventions for, 307t
Altered mental status, 151
age-related etiology of, 144-145, 145b
ancillary testing in, 146-148, 147t
in children, 2094, 2094b
diagnostic approach to, 149f
in dialysis, 1310b
with focal seizures, 2236
structural etiology of, 144b
Altered mentation, 151
Alternate light source, 864, 864b
Alternative health care, e27, e73-e75
Alternative hypothesis, e12, e12t-e13t
Alternobaric vertigo, 1919, 1923t, 1926
ALTEs. *See* Acute life-threatening events
Altitude
effects on oxygenation, 2443t
extreme, 1929
high, 1928
moderate, 1928
risks associated with travel to, 1938t
and underlying medical conditions, 1938-1939
Aluminum acetate (Burow's solution), 1558
Aluminum phosphide poisoning, 1955t
Aluminum sulfate–calcium acetate (Domeboro), 1558
Alvarado score, modified, 1227-1228
Alveolar bone fractures, 905
Alveolar fractures, 381
Alveolar gas equation, 1929, 1929b
Alveolar trauma, 380-381
Alzheimer's dementia, e57
Alzheimer's disease, 1404
anxiety in, 1476-1477
diagnosis of, 1407-1408
treatment of, 1408
AMA. *See* Against medical advice; American Medical Association
Amanita muscaria mushrooms, 2023, 2023f
Amantadine (Symmetrel), 1720-1722
for influenza, 1721t-1722t
for neuroleptic malignant syndrome, 2051
Ambien (zolpidem), 2080
Amblyomma americanum (Lone Star tick), 1788f, 1798
Ambulances, 2433, 2434f, 2437
Ambulatory blood pressure monitoring, 1113
Amebiasis (*Entamoeba histolytica* infection), 1776
drug regimens for, 1772t-1775t
intestinal
acute, 1253-1254
in AIDS, 1257t
antibiotic therapy for, 1235t
epidemiology of, 1250t, 1253
management of, 1254, 1257t
symptoms of, 1782
therapy for, 2192t-2193t
Amebic abscesses, 1198
clinical features of, 1198
diagnostic strategies for, 1198
differential considerations, 1198
management of, 1198
patient disposition in, 1198
Amebic dysentery, acute, 1253-1254
Amenorrhea, 1360t
American Academy of Asthma, Allergy and Immunology, 946
American Academy of Emergency Medicine, 946
American Academy of Pediatrics (AAP)
Back to Sleep (BTS) campaign, 110
guidelines for care of children in the emergency department, 2094-2095
recommendations for emergency contraception, 869
recommendations for pneumococcal vaccine, 1710b
American Ambulance Association, 2439t
American Board of Hospice and Palliative Medicine, e50
American Civil War, 2433
American College of Cardiology (ACC)
criteria for acute myocardial infarction, 998
guidelines for management of myocardial infarction, 999
guidelines for transfer of patient with acute coronary syndrome, 1032
American College of Emergency Physicians (ACEP), 287-288, 2452, 2457, 2492
clinical policy regarding neuroimaging in mild TBI, 353b
Code of Ethics, e23, e36, e37t
contact information, 2439t, 2458t
Disaster Medicine section, 2467
Forensic Medicine section, 828
guidelines for cardiopulmonary resuscitation, e50
guidelines for care of children in the emergency department, 2094-2095
policy statement on interfacility transfers, 2441
policy statement on sedation in the Emergency Department, 51b
policy statement on youth violence prevention, e3
recommendations for designated rooms, 2420-2421
recommendations for elder abuse protocols, 890
recommendations for emergency contraception, 869
Revised Code of Ethics, e28
American College of Obstetricians and Gynecologists (ACOG)
recommendations for emergency contraception, 869
recommendations for ultrasonography during pregnancy, 2274-2275
American College of Rheumatology
criteria for giant cell arteritis, 1535b
criteria for Henoch-Schönlein purpura, 1539
criteria for systemic lupus erythematosus, 1528t
American College of Surgeons (ACS)
Advanced Trauma Life Support guidelines, 417
Field Triage Decision Scheme (CDC), 287-288, 337
guidelines for emergency department thoracotomy, 450
guidelines for resuscitation, 294
requirements for surgeon presence in major resuscitations, 291, 291b
American College of Surgeons Committee on Trauma (ACSCOT), 287
guidelines for emergency department thoracotomy, 450
guidelines for resuscitation, 294
American Diabetes Association (ADA), 1653-1655
American Heart Association (AHA)
dietary guidelines, e82, e82b
Emergency Cardiac Care guidelines, e54
guidelines for cardiopulmonary resuscitation, e50
guidelines for management of myocardial infarction, 999
guidelines for transfer of patient with acute coronary syndrome, 1032
recommended chest compression–ventilation ratios, 101t
American Institute of Ultrasound in Medicine, 2492
American Medical Association (AMA), 2492
code of ethics, e37t
policy on consent for procedures on newly dead, e54
recommendations for elder abuse protocols, 890-891
recommendations for elder abuse questioning, 886-887
recommendations for emergency contraception, 869
American Osteopathic Association (AOA), e37t
American Society of Anesthesiologists, 52t
American Society of Echocardiography, 2492
American Thoracic Society (ATS)
definition of severe or refractory asthma, 952f
guidelines for management of pneumonia, 983, 986
recommendations for acute care of asthma, 946
Amikacin
in immunocompromised patients, 2361t
for tuberculosis, 1822t-1823t
Amiloride hydrochloride, 1122.e1t-1122.e2t
Amino esters, 45
γ-Aminobutyric acid receptor complex, 2076, 2077f
Aminoglycosides, 930t
antimicrobial agents useful in immunocompromised patient, 2361t
antipseudomonal, 1835t
for bone and joint infection, 1835t
for pneumonia, 985, 985t
in pregnancy, 2324
safety in pregnancy and lactation, 2318t-2321t
for *V. vulnificus* infection, 1246
Aminophylline, 2340t
p-Aminosalicylic acid, 1822t-1823t, 1824
Aminotransferases, 2379t
Amiodarone, 1038-1039, 1685
adverse effects of, 1039, 1039b
for atrial fibrillation and flutter conversion, 1052b
for heart failure, 1088
hepatic injury, 1197t
for pediatric dysrhythmias, 2154b
for pediatric resuscitation, 104t
in pregnancy, 2318t-2321t, 2326
for ventricular tachycardia, 1057-1061
Amiodarone-induced epididymitis, 1346
Amitiza (lubiprostone), 264t-265t
Amitriptyline
for ciguatera fish poisoning, 1247
for diabetic distal symmetrical polyneuropathy, 1432
for pediatric migraine, 2244
Amlodipine, 1991t, 1122.e1t-1122.e2t
Ammonia (NH_3), 1994, 2037t
Ammonia tests, 242
Ammunition, handgun, 829, 829f

www.ketabpezeshki.com 66485457-66963820

Amnesia, post-trauma, 352
Amnestic agents, 32b
Amniorrhexis, 2340-2341
Amniotic fluid embolism, 2292-2293, 2349-2350
  clinical features of, 2292
  diagnostic strategies for, 2292
  differential considerations, 2292-2293
  management of, 2293
Amoxicillin
  for anthrax, 2473b
  for *H. pylori* infection, 1180
  for infective endocarditis prophylaxis, 2160t
  lansoprazole, amoxicillin, and clarithromycin (Prevpac), 1180
  for Lyme disease, 1793-1794, 1794t
  for otitis media, 933-934, 933t-934t
  for pneumonia in infants and children, 2136
  for rhinosinusitis, 976-977
  for skin and soft tissue infection, 1854t
Amoxicillin-clavulanate
  for diverticulitis, 1264b
  for epistaxis, 938-939
  for otitis media, 933-934, 934t
  for pneumonia, 984
  for preseptal cellulitis, 921
  for skin and soft tissue infection, 1854t
Amperage, 1908
Amphetamine abuse, 1477
Amphetamines, 2005, 2017
Amphotericin, 1197t
Amphotericin B
  in immunocompromised patients, 2361t
  for mucormycosis, 1664t
  for parasitic infection, 1772t-1775t
Ampicillin
  for acute bacterial meningitis, 2230t
  for bowel flora, 1264b
  for infectious diarrhea, 2192t-2193t
Ampicillin-sulbactam
  for bowel flora, 1264b
  for pneumonia, 984-985, 985t
AMPLE history, 309, 309b
Amplification, 1482
Amprenavir, 1721t-1722t
Amputations
  complications of, 564
  fingertip, 561
  of foot, 750
  hand injuries, 563-564
  management goals, 563
  partial, 841, 841f
  replantation after, 564, 564b
Amrinone
  for heart failure, 1086
  for heart failure in children, 2152-2153
AMS. *See* Acute mountain sickness
Amsel criteria, 1323
AMT. *See* Air medical transport
Amylase assay, 1209
Amyloidosis, 1104
Amyotrophic lateral sclerosis (ALS), 1439
  clinical characteristics of, 1423t, 1439b, 1442t
  lower motor neuron signs of, 1439b
  upper motor neuron signs of, 1439b
Anabolic steroids, 1197t
Anakinra, 1515t
Anal fissures, 1280-1281, 1280f
  clinical features of, 1280
  management of, 1280-1281
  treatment of, 1281b
Analgesia. *See also* Pain management
  for acute pain, 49b
  deep sedation/analgesia, 51, 52t
  definition of, 32b, 50
  Dejeune onion skin pattern of, 401
  moderate sedation/analgesia, 50, 52t
  out-of-hospital, 48-49
  procedural sedation and analgesia (PSA), 50-60
    approach to, 51-54
    definition of, 50
  systemic, 681
  tactical combat care, 2452
  terms related to, 32b
Analgesic agents, 38-45. *See also specific agents*
  nonopioid, 42-43
  opioid, 38-42
  in pregnancy, 2317-2322, 2318t-2321t
  that may cause seizures, 2235b
Analysis of variance (ANOVA), one-way, e13-e14, e13t, e14
Anaphylactic shock, 68b, 1551
Anaphylactoid reaction, 1543
Anaphylaxis, 1543-1557
  clinical features of, 1550-1551, 1552t
  definition of, 1543
  diagnostic criteria for, 1549b
  diagnostic strategies for, 1551
  differential diagnosis of, 1551, 1553b
  emergency department care for, 1553-1555
  emergency measures for, 1554b
  epidemiology of, 1543-1544
  etiologic agents, 1544b
  exercise (physical)–induced, 1546
  general rule for, 802
  idiopathic, 1546
  key concepts, 1557b
  management of, 1551-1555
  mediators of, 1549, 1550t
  out-of-hospital care for, 1551-1553
  pathophysiology of, 1549-1550, 1552t
  patient disposition in, 1555
  physiologic effects of, 1549-1550, 1550t
  prevention of, 1555
  radiocontrast-induced, 1546b
  risk factors for, 1543-1544, 1544b
  treatment options for, 1554b
  triggers for, 1544-1546
Anatomy
  abdominal, 460
  adults vs children, 306b
  anorectal, 1276, 1277f
  arterial, 1138
  of bladder, 485
  eye, 910f
  facial, 369-370
  of foot, 734-736
  of growing bones, 517f
  of knee, 698-699, 699f
  of knee injury, 698-699
  of lumbosacral spine, 643-644
  of male genitalia, 480, 480f
  of neck, 421-422
  oral, 895-896
  of oral cavity, 895-896
  pelvic, 656-657
  of penis, 494-496
  in pregnancy, 297
  urethral, 481, 483f
Anchor period, 2508
Ancylostoma duodenale (hookworm), 1770t-1775t
Anembryonic gestation, 2282
Anemia, 1586-1600
  acute, 1587b
  admission criteria for, 1589b
  in alcoholism, 2389
  algorithm for evaluation of, 1589f
  ancillary evaluation of, 1587-1588
  aplastic, 1593
    caused by drugs or chemicals, 1593t
    treatment of, 1593-1594
  of chronic disease, 1591
  in chronic heart failure, 1089
  clinical features of, 139t, 1586-1588
  definition of, 1586
  diagnostic findings, 1588
  differential diagnosis of, 1588-1600, 1590b
  emergent
    diagnostic findings in, 1586-1587
    history and physical examination for, 1587b
  in head injury, 343
  in heart failure, 1081, 1089
  hemolytic, 1594
    ancillary evaluation of, 1595
    autoimmune, 1599, 1600b
    classification of, 1596b
    clinical features of, 1594-1595
    differential diagnosis of, 1596
    drug-induced, 1600, 1600b
Anemia *(Continued)*
    history and physical examination for, 1595b
    immune, 1600, 1600b
    laboratory assessment of, 1595-1596
    prosthetic valve-related, 1112
  history in, 1587b-1588b
  hypoplastic, secondary, 1594
  iron deficiency, 1590, 1590f
    diagnostic tests for, 1591t
    in pregnancy, 2301t-2303t, 2306-2307
  key concepts, 1605b
  laboratory testing in, 1587
  macrocytic, 1590b, 1591-1593
  megaloblastic, 1591-1593, 1593f
    clinical features and pathologic correlations, 1592t
    serum tests for, 1593t
  microcytic, 1590-1591
    hypochromic, 1590b, 1590f
  myelophthisic, 1594
  normochromic, 1593-1594
  normocytic, 1590b, 1593-1594
  in parasitic infection, 1778, 1778f
  pathophysiology of, 1586
  patient disposition in, 1588
  physical examination for, 1587b-1588b
  in pregnancy, 2306-2307
  rapid onset, 1586, 1587b
  sickle cell
    blood transfusion for, 1599
    in pregnancy, 2301t-2303t, 2307
  sideroblastic, 1591
Anesthesia
  allergy to, 754-755
  general, 51, 51f, 52t
  intravenous regional (Bier block), 48
  local, 45-48
    definition of, 32b
    techniques to reduce pain of injection, 47
  topical, 47
  for wound management, 754-755
Anesthetic agents. *See also specific agents*
  ophthalmic medications, 930t
  overdose, 1957t-1958t
  in pregnancy, 2318t-2321t, 2322
  that may cause seizures, 2235b
  topical, 930t
  triggers for anaphylaxis, 1545
  for wound management, 754
Aneurysms
  abdominal aortic, 1129-1137
    acute back pain in, 282t-283t
    ultrasound findings, 2497, 2497f
  axillary artery, 1147
  cerebral, 1390-1391, 1390t, 1391f
  false, 1129, 1130f, 1148t
  femoral artery, 1147
  hepatic artery, 1148
  infected, 1148-1149, 1148t
  left ventricular, 1009, 1010f
  mycotic, 1148, 1148t
  pathophysiology of, 1138-1139
  peripheral arterial, 1147-1149
  popliteal artery, 1147, 1156b
  pseudoaneurysms
    abdominal aorta, 1129, 1136
    arterial, 502, 502f
    post-traumatic, 1149
  seizures caused by, 1379
  splenic artery, 1147-1148
  subclavian artery, 1147
  superior mesenteric artery, 1148
  traumatic, 1149
  ulnar artery (hypothenar hammer syndrome), 1147
Anger management, 2415
Angina
  accelerating or crescendo, 998
  anxiety in, 1476
  classic, 1000, 1000t
  classification of, 998
  clinical features of, 1000, 1000t
  definition of, 1000
  Ludwig's, 897, 899-900, 972-973
    pediatric, 2110

www.ketabpezeshki.com 66485457-66963820

Angina *(Continued)*
postanginal septicemia, 975
preinfarction, 998
Prinzmetal's, 998
stable, 998
unstable, 998
with central chest pain, 220t-221t
definition of, 998
variant, 998
Vincent's, 966
Anginal equivalent syndrome, 1000
Angiodynography, 1142
Angioedema, 1543-1557, 1552t
ACE inhibitor–induced, 1556
acute, 1556
chronic, 1556
clinical features of, 1555-1556
diagnostic strategies for, 1556
hereditary, 1556
key concepts, 1557b
management of, 1556-1557
with urticaria, 1556-1557
Angioembolization
in abdominal trauma, 467
of renal laceration, 467, 467f
Angiofibroblastic hyperplasia, 614-615
Angiofollicular lymph node hyperplasia, 1730
Angiography
in abdominal trauma, 467, 467f
in colonic ischemia, 1273
with GI bleeding, 252
in hemoptysis, 204-205
indications for, 1142
in knee injury, 703
in pelvic fracture, 669
in peripheral arteriovascular disease, 1142
in renal trauma, 492
in splenic laceration, 467, 467f
uterine radiation dose, 299t
Angioplasty
for heart failure, 1088-1089
peripheral percutaneous transluminal, 1143
Angiostrongylus costaricensis, 1783
Angiotensin-converting enzyme inhibitor–induced angioedema, 1556-1557
Angiotensin-converting enzyme inhibitors
for acute coronary syndrome, 1024
drug interactions, 44
for heart failure, 1087
herbal medicine interactions, 2072t-2073t
for hypertension, 1122.e1t-1122.e2t
in pregnancy, 2327
Angiotensin II receptor blockers
for heart failure, 1087
for hypertension, 1122.e1t-1122.e2t
in pregnancy, 2327
Angulation, 514
Anhydrous ammonia, 821-822
Animal bites, 785-790
epidemiology of, 785
guidelines for, 788-789
infection rates, 788
management of, 788-790
patient disposition in, 790
prophylactic antibiotics for, 789-790, 789t
recommendations for closure and prophylactic antibiotics, 789t
reporting requirements for, e77
risk factors for infection, 788, 788t
venomous animal injuries, 794-807
Animals, poisonous and venomous, 794
Anion gap
adjusted, 1630
calculation and interpretation of, 1630
elevated anion gap metabolic acidosis, 1632-1633, 1632b
low, 1630
normal anion gap metabolic acidosis, 1633, 1633b
Anions, measured, 1630
Anisakiasis *(Anisakis)*, 1772t-1775t
Anisocoria, 927-928
clinical features of, 927-928
physiologic, 928
Anisocytosis, 1594, 1594f
Ankara vaccine, modified, 2476
Ankle
anatomy of, 723, 724f-725f
joint complex axes, 723, 724f
physical examination of, 725
tendinopathy of, 1522
Ankle-brachial index (ABI), 504-505, 704
Ankle dislocations, 734, 750b
Ankle fractures, 727-734
Danis-Weber classification of, 727, 727f
Lauge-Hansen classification of, 727
management of, 727-728
open, 729-730
orthopedic consultation for, 728b
pathophysiology of, 727, 727f
patient disposition in, 728
unimalleolar, 728-729
Ankle hitches, 529, 530f
Ankle injuries, 723-734
clinical features of, 723
diagnostic strategies for, 725-727
imaging techniques for, 726-727
immobilization of, 530-531
with adhesive strips, 529, 531f
key concepts, 750b
ligament injuries, 731-733
pathophysiology of, 723
radiographic findings, 725, 725f
radiologic imaging of, 725-726
soft tissue injuries, 731-734
splinting and bandaging, 530-531
tendon injuries, 733-734
Ankle instability
functional, 733
mechanical, 733
Ankle radiography, 725-726
Ankle sprain, 731
in children, 517-518
clinical features of, 731
diagnostic strategies for, 731-732
differential diagnosis of, 732b, 732f
key concepts, 750b
management of, 732
pathophysiology of, 731
patient disposition in, 732-733
Ankylosing spondylitis, 1515
clinical features of, 1515
management of, 1515
Annulus fibrosus, 643
Anogenital examination, 865-866, 865f
Anorectal abscesses, 1281-1282
general approach to, 1281
sites of, 1281, 1282f
treatment of, 1281-1282
types of, 1281t
Anorectal fistulae, 1281-1282
Anorectal foreign bodies, 781-782, 1288
clinical features of, 1288
diagnostic strategies for, 781
management of, 781-782, 1288
physical examination findings, 781
radiographic findings, 781, 781f-782f
removal of, 781-782, 782f, 1288, 1288f-1289f
Anorectal history, 1277b
Anorectal lesions, 1288b
Anorectal pain, 1283
Anorectum
anatomy of, 1276, 1277f
disorders of, 1276-1289
clinical features of, 1276-1277
diagnosis of, 1276, 1277b, 1278f
history in, 1276-1277, 1277b
key concepts, 1289b
physical examination findings, 1277
sexually transmitted diseases of, 1285-1288, 1286t
Anorexia, at end of life, e57
Anserine bursa, 716
Anserine bursitis, 716, 1519f, 1525
Anserine tendon, 716
Antabuse (disulfiram), 2391
Antacids
for peptic ulcer disease, 1184
in pregnancy, 2318t-2321t, 2329
for upper GI disorders, 1184
Antalgic gait, 686
Anterior chamber hyphema, 913-914, 914f
Anterior cord syndrome, 400-401, 402f, 1421, 1421t
Anterior cruciate ligament, 698, 714
Anterior cruciate ligament injury, 713-714
management of, 714
testing for, 700-701
Anterior drawer test
in ankle injury, 731
in knee injury, 700-701
Anterior elbow dislocation, 613f, 614
clinical features of, 614
management of, 614
pathophysiology of, 614
Anterior glenohumeral dislocations, 642b
Anterior humeral line, 599, 600f
Anterior spondylolisthesis, 649, 649f
Anterior uveitis, 193t-196t
Anthrax infection
cutaneous anthrax, 1580, 1580f, 1863, 2473, 2473b, 2473f
gastrointestinal anthrax, 1241-1242, 2473, 2473b
inhalational anthrax, 2472, 2472f
chest CT findings in, 2472, 2472f
radiographic findings in, 2472, 2472f
treatment of, 2473b
key concepts, 2478b
postexposure prophylaxis, 2473b, 2474
treatment of, 2473-2474, 2473b
as weapon, 2469, 2472-2474
Anti-D immune globulin (RhoGAM), 2283-2284, 2290, 2293
Anti-epileptic drugs
adverse effects of, 1383-1384, 1383t
drug interactions, 1383t
side effects of, 2407t-2408t
Anti-HIV drugs, 2326
Anti-inflammatory therapy, 963-964
Anti-influenza drugs, 2318t-2321t, 2326
Antianaphylactic drugs, 1554b
Antiarrhythmia devices, permanent, 1064-1071
Antibiotic-associated colitis, 1256
Antibiotics
for abdominal pain, 231
for abdominal trauma, 471
alcohol interactions, 2390t
for bacterial meningitis, 1456t, 2229-2230, 2230t
for bone and joint infection, 1835t
for bowel flora, 1264b
C. difficile antibiotic-associated enterocolitis, 1248-1249
for COPD, 963
for diarrhea, 1235t
for diphtheria, 1695-1696
for diverticulitis, 1264b
for eye infection, 191-192
for facial wounds, 377
for febrile neutropenia, 2360-2362
for fever in neutropenic cancer, 1618b, 1619
guidelines for choice of, 1849, 1849t
for immunocompromised patients, 2361t
for infections in diabetics, 1664, 1664t
initial, pending microbiologic identification, 1872t
for Lyme disease, 1100
for meningococcemia, 1713
ophthalmic medications, 930t
for pediatric meningitis, 2229-2230, 2230t
for pediatric pneumonia, 2131, 2132t
for pertussis, 1698-1699
for pneumonia, 984-985, 985t
in pregnancy, 2318t-2321t, 2324-2326
prophylactic
for crush injuries, 763
for human bites, 792
for meningococcemia, 1713-1714
for traveler's diarrhea, 1259
for wound management, 762-764, 766b
for prostatitis, 1335-1336
for Rocky Mountain spotted fever, 1802, 1802t
for sepsis, 1872
for septic arthritis, 1849, 1849t
for skin infections, 1854t, 1856t
for soft tissue infection, 1854t
for tetanus, 1703
that may cause seizures, 2235b
for thyroid storm, 1682b
for toxic shock syndrome, 1717

www.ketabpezeshki.com 66485457-66963820

Antibiotics *(Continued)*
for traveler's diarrhea, 1259-1260
triggers for anaphylaxis, 1544-1545
Antibody (antibodies), 2357
antilymphocyte monoclonal antibody preparations, 2372
antinuclear antibody, 1528t
cytotoxic antibody reactions, 1545b, 1548
digitalis, 1984, 1985b
Antibody deficiency, 2359b
Antibody screening, 75-76
fluorescent treponemal antibody-absorption (FTA-ABS) test, 1317, 1576
Anticholinergic syndrome, 1955-1956, 1955t
vital signs in, 2419t
Anticholinergics
for asthma, 951, 1970-1974
for asthma exacerbations in pregnancy, 2303t
for asthma in children, 2122
overdose
antidote for, 1957t-1958t
chronic, 1972
clinical presentation of, 1972
diagnostic strategies for, 1972
differential diagnosis of, 1972
drug removal, 1973
drugs exhibiting, 1970, 1971b
key concepts, 1974b
management of, 1972-1973
patient disposition in, 1973-1974
in pregnancy and lactation, 2318t-2321t
that may cause seizures, 2235b
Anticoagulants
drug interactions, 43
mild TBI in patients on, 354
in pregnancy, 2318t-2321t, 2322-2323
Anticoagulation
acute, with heparin, 1143
excessive, from warfarin, 1615
in obesity, 1168b
for pulmonary embolism, 1164-1166
Anticonvulsants
alcohol-related seizures and, 2384
for children, 2239, 2240t
initiating, 2238-2239
decision to withdraw, 2239
long-term, 1384t
in pregnancy, 2329
classic, 2329
newer, 2329
side effects of, 1383-1384, 2407t-2408t
that may cause seizures, 2235b
Antidepressants
discontinuation syndromes with, 1980-1981
long-term therapy with, 1473
overdose, 1975-1981
that may cause seizures, 2235b
tricyclic (TCAs)
alcohol interactions, 2390t
with anticholinergic effects, 1970, 1971b
for anxiety disorders, 1479, 1479t
overdose, 1957t-1958t, 1976-1977
Antidote Treatment Nerve Agent Auto-Injector (DuoDote), 2477
Antidotes, 1955-1956, 1957t-1958t
in pregnancy, 2318t-2321t, 2323-2324
Antidysrhythmics
class I agents, 1038b
class IA agents, 1036, 1038b
class IB agents, 1037, 1038b
class IC agents, 1037-1038, 1038b
class II agents, 1038, 1038b
class III agents, 1038, 1038b
class IV agents, 1038b, 1039
classification of, 1035-1040, 1038b
for heart failure, 1088
in pregnancy, 2318t-2321t, 2326-2327
that may cause seizures, 2235b
Antiemetics, 2318t-2321t, 2329
Antifungals, 2318t-2321t, 2325-2326
Antigens
in acute bacterial meningitis, 2228
immunologic responses to, 1546
Antihelmintics, 1770t
Antihemophilic factor (factor VIII), 1614t
Antiherpetics, 2318t-2321t, 2326
Antihistamines
alcohol interactions, 2390t
for anaphylaxis, 1555
with anticholinergic toxicity, 1970, 1971b
for GERD, 1177, 1177t
for peptic ulcer disease, 1177t
in pregnancy, 2318t-2321t, 2329-2330
that may cause seizures, 2235b
for upper GI disorders, 1177t, 1184
Antihypertensives
for acute blood pressure control, 1117-1118
for acute ischemic stroke, 1371, 1371b
hemodynamic effect profiles, 1118t
herbal medicine interactions, 2072t-2073t
for hypertensive emergencies, 2304t
intravenous, 1119t
in pregnancy, 2318t-2321t, 2327-2328
Antilewisite (BAL; 2,3-dimercapto-1-propanol; dimercaprol), 826
Antilymphocyte monoclonal antibody preparations, 2372
Antimalarials, 1770t
Antimetabolites, 2371
Antimicrobials. *See* Antibiotics
Antiminth (pyrantel pamoate), 1285
Antimuscarinics, 1970
Antinuclear antibody, 1528t
Antiparkinsonians, 1970, 1971b
Antiphospholipid syndrome, 1533
clinical features of, 1533, 1533b
diagnostic strategies for, 1533
key concepts, 1541b-1542b
treatment of, 1533
Antiplatelet therapy, 1025-1026
Antiprogestins, 869t
Antiprotozoals, 1770t
Antipseudomonal aminoglycoside, 1835t
Antipsychotics, 2047-2051
agents approved or nearing approval, 2048t
atypical, 1472-1473, 2047, 2417-2418
cardiovascular toxicity of, 2049
for chemical restraint, 2417-2418
extrapyramidal symptoms of, acute, 2048-2050
first-generation, 2047, 2048t
overdose
acute, 2048, 2050
clinical features of, 2048-2049
diagnostic strategies for, 2050
differential considerations, 2049
key concepts, 2051b
management of, 2050-2051
pathophysiology of, 2047-2048
patient disposition in, 2051
physiology of, 2047
second-generation, 2047, 2048t
that may cause seizures, 2235b
Antiretroviral drug therapy (ARVT), 1196. *See also* Antiretroviral therapy (ART)
Antiretroviral therapy (ART)
adverse reactions to, 1766t
highly-active, 1765, 2313
for HIV infection, 1765
liver toxicity, 1196
in pregnancy, 2313
side effects of, 1765
Antiseizure medications, 2407t-2408t
Antiseptic solutions, 755, 756t
Antishock sheeting, pelvic, 668, 668f
Antisocial behavior, 2420b
Antisocial personality disorder, 1489, 2427b
Antispasmodic agents, 282-283
Antithrombins, 1026-1027
Antitrypanosomal drugs, 1099
Antituberculosis drugs, 1822-1824, 1822t-1823t
in pregnancy, 2318t-2321t, 2326
Antitumor agents, 2235b
Antivenin
administration of, 799
for coral and exotic snakes, 800
dosage, 799-800
guidelines to maximize patient care, 799-800
Latrodectus, 804
Loxosceles, 804
for pit viper envenomation, 799t
Antivenin *(Continued)*
precautions, 799-800
for snakebite, 798-800
Antivert (meclizine), 246
Antiviral agents
chemotherapy, 1720-1725
ophthalmic medications, 930t
in pregnancy, 2318t-2321t, 2326
prophylactic
for animal bites, 790
for human bites, 792
topical, 930t
Antizol (fomepizole), 2011-2012
Anus. *See also* Anorectum
objects inserted into, 1288
sexual history of, 1277b
Anxiety
definition of, 1474
medical illness presenting as, 1475-1477
patient disposition in, 2016-2017
in psychiatric disorders, 1477-1478
somatic symptoms of, 1475b
vs somatoform disorder, 1483
Anxiety disorders, 1474-1480
caused by general medical conditions, 1475b
clinical features of, 1474-1475
definitions of, 1475b
differential considerations, 1475-1478
epidemiology of, 1474
generalized
definition of, 1475b
pharmacologic treatment of, 1479t
initial evaluation of, 1478
key concepts, 1480b
management of, 1478-1480
nonpharmacologic therapy, 1479-1480
not otherwise specified, 1475b
organic syndrome, 1475b
patient disposition in, 1480
pharmacologic treatment of, 1478-1479, 1479t
predictors of, 1475b
substance-induced, 1475b
Anxiolysis (minimal sedation), 50, 52t
AOA. *See* American Osteopathic Association
Aortic dissection, 1124-1128
acute, 1125
acute back pain in, 282t-283t
alternative agents for, 1128
anatomy of, 1124
blood pressure control in, 1120t, 1121
characteristics of, 1126t
chest pain in, 220t-221t
chest radiography findings, 1126-1127
chronic, 1125
classification of, 1125
clinical features of, 1125-1126
CT findings, 1127, 1127f
diagnostic strategies for, 1126-1127
diagnostic tests for, 1127, 1128b
differential considerations, 1127
ECG findings, 1126
echocardiography findings, 1126-1127
epidemiology of, 1124
history of, 1125
hypertension with, 1120t, 1121
imaging in, 1126t
interventional therapy for, 1128
key concepts, 1128b
management of, 1120t, 1127-1128
in ED, 1127-1128
goals for, 1127-1128
MRI findings, 1127
pathophysiology of, 1124-1125
patient disposition in, 1128
physical examination findings, 1125-1126, 1128b
physiology of, 1124
recommended therapy for, 1128
risk factors associated with, 216b
Stanford classification of, 1125, 1125f
Stanford type B or Debakey type III, 1125, 1125f
Aortic injury, blunt, 451-455, 452f, 478
Aortic insufficiency, 1111
acute, 1112b
clinical features of, 1111

www.ketabpezeshki.com 66485457-66963820

Aortic insufficiency *(Continued)*
management of, 1111
pathophysiology of, 1111
Aortic regurgitation, 2306
Aortic rupture
clinical features of, 452
mechanisms of, 451
Aortic stenosis, 1110-1111
clinical features of, 1111
key concepts, 1112b
management of, 1111
pathophysiology of, 1110-1111
in pregnancy, 2306
Aortic tears
endovascular repair of, 455
location of, 451-452, 451f
Aortic ulcer, penetrating, 1125
Aortoenteric fistula, 1131, 1135
Aortography, in blunt aortic injury, 454
Aortovenous (aortocaval) fistula, 1131
APACHE II (Acute Physiology and Chronic Health Evaluation II) scoring system, 1210, 1210b
APACHE III (Acute Physiology and Chronic Health Evaluation III) scoring system, 1210
Apgar score, 116, 116t
Aphasia, 1365
Aphthous stomatitis, 902
API. *See* Arterial pressure index
Aplastic anemia, 1593
autoimmune, 1593
caused by drugs or chemicals, 1593t
treatment of, 1593-1594
Apley's test, 702
Apnea, 2402
primary, 112
secondary, 112
Apophyseal injuries, 2269-2270
Apophysitis
of hip, 2270
of tibial tuberosity, 718
Appearance, general, 2091, 2142
Appendicitis
acute, 1225-1232
abdominal pain in, 224t-225t
CT findings in, 1228-1230, 1228f
in children, 1226, 2184-2186
clinical features of, 2184
diagnostic strategies for, 2184-2185
differential considerations, 2185-2186
key concepts, 2187b
management of, 2186
patient disposition in, 2186
radiographic findings in, 2185, 2185f
clinical features of, 1226-1227
complications of, 1227
diagnostic scores, 1227-1228
diagnostic strategies for, 1227-1230
differential diagnosis of, 1230, 1230t
in elder patients, 1227
epidemiology of, 1225
equivocal-risk, 1231
high-risk, 1231-1232
historical perspective on, 1225
history in, 1226
imaging studies, 1228-1230, 1228f
in-hospital observation of, 1230
key concepts, 1232b
laboratory testing in, 1227
low-risk, 1231
management of, 1230-1232, 1231f
pathophysiology of, 1225-1226
patient disposition in, 1232
pelvic pain in, 267t-268t
physical examination findings, 1226
in pregnancy, 1226-1227, 2277-2278, 2293-2295
clinical features of, 2294
diagnostic strategies for, 2295
differential considerations, 2294-2295
management of, 2295
vomiting with, 243t-244t
in women, 1226
Appendix, locations during pregnancy, 2293, 2294f
Appendix torsion, 1344t
Apprehension sign, 713
Apraclonidine, 922, 930t
Aprepitant (Emend), 246
Aqua Dots, 2082
Ara-A (vidarabine), 1723
Arachnoiditis, 1447
Aralen (chloroquine phosphate), 1770t
Arboviruses (*ar*thropod-*bo*rne viruses)
epidemiology of infection, 1447
group A (alphaviruses), 1736-1737
Arcanobacterium haemolyticum infection, 966
diagnosis of, 967
pharyngitis, 968
treatment of, 968
Arenaviruses, 1719t, 1739-1740
Argentine hemorrhagic fever, 1740
Aricept (donepezil), 1408
Aripiprazole (Abilify), 2048t
for chemical restraint, 2418
for mood disorder, 1472-1473
for rapid tranquilization, 1463
Aristocort (triamcinolone diacetate), 639t
Aristospan (triamcinolone hexacetonide), 639t
Arizona bark scorpion *(Centruroides sculpturatus*, formerly *Centruroides exilicauda)*, 805, 805f
Arousal, 142
Arrhythmias. *See* Dysrhythmias
Arsenic, 2028-2029
normal levels, 2029
pharmacology of, 2029
Arsenic poisoning, 2028-2030
acute effects of, 2029b
antidote for, 1957t-1958t
clinical features of, 2029
diagnostic strategies for, 2029
management of, 2030
odor in, 1955t
pathophysiology of, 2029
Artemether-lumefantrine, 1772t-1775t
Arterial aneurysms
axillary artery, 1147
femoral artery, 1147
hepatic artery, 1148
peripheral, 1147-1149
popliteal artery, 1147, 1156b
proximal subclavian artery, 1147
pseudoaneurysms, 502, 502f
splenic artery, 1147-1148
subclavian artery, 1147
superior mesenteric artery, 1148
ulnar artery (hypothenar hammer syndrome), 1147
Arterial blood gases
in asthma, 947, 948t
in chest pain, 217t-218t
in children, 2118, 2143
in COPD, 959
in pregnancy, 952
in pulmonary contusion, 436-437
Arterial blood pressure, 90
Arterial embolism, 1146
differential diagnosis of, 1141t, 1146
management of, 1146
mesenteric, 1221-1222, 1222f
pathophysiology of, 1139
physical examination of, 1141
Arterial gas embolism, 1921-1922, 1923t
hyperbaric therapy for, 1924-1925
recompression therapy for, 1923, 1925
Arterial injury, 510b. *See also* Vascular trauma
Arterial insufficiency, chronic
clinical features of, 1140-1141
diseases of, 1144-1146
Arterial monitoring, invasive, 61
Arterial occlusion, acute
clinical features of, 1140, 1140f
diseases of, 1146
key concepts, 1156b
management of, 1140f
Arterial partial pressure of carbon dioxide ($Paco_2$), 297, 947
Arterial partial pressure of oxygen (Pao_2), 947, 959
Arterial pressure index (API), 504-505
Arterial spasm, reversible, 501
Arterial thrombosis, 1146
differential diagnosis of, 1141t
management of, 1146
pathophysiology of, 1139
physical examination of, 1141-1142
Arteries
anatomy of, 1138
classification of, 1138
of femoral neck and head, 673, 674f
of hand, 541-542, 542f
of hip, 673
of lower limb, 503f
peripheral system, 1138
of upper limb, 503f
Arteriography
in peripheral vascular injury, 505-506
in vascular neck injury, 428
Arteriosclerosis obliterans, 1144-1145
clinical features of, 1144-1145
differential diagnosis of, 1144-1145
management of, 1145
Arteriovascular disease, 1144-1156
peripheral, 1138-1156
Arteriovenous anastomosis rewarming, 1892
Arteriovenous fistulas, 502
infection of, 1156
pathophysiology of, 1140
peripheral, 1152
physical examination findings, 1142
subcutaneous, 1156
thrombosis of, 1156
Arteriovenous malformations, 1379
Arteriovenous rewarming, continuous, 1894, 1894t
Artesunate, 1772t-1775t
Arthritis, 1501-1517
acute
differential considerations, 1505-1510
management of, 1505-1510
radiologic findings in, 1504t
associated symptoms, 1502
bacterial, 1831
clinical features of, 1501-1503, 1503t
degenerative, 1504t
diagnostic strategies for, 1503-1505
differential diagnosis of, 1502b, 1505-1517, 1532t
distribution of, 1502
enteropathic, 1516
general examination of, 1502
gonococcal, 1508
gouty, 1508-1509
group A streptococcal (GAS) infection–related, 1512
key concepts, 1517b
locations of, 1501, 1502f
Lyme, 1511, 1786, 1791, 1847-1848
management of, 1794
synovial fluid findings in, 2265t
management of, 1505-1517
monarticular
acute, 1505-1510
chronic, 1510-1511
initial approach to, 1506f-1507f
nonerosive, 1528t
nongonococcal bacterial
epidemiology of, 1505
microbiology of, 1506
pathophysiology of, 1505-1506
pain patterns in, 1501
patient disposition in, 1517
physical examination findings, 1502-1503
polyarticular
acute, 1511-1513
chronic, 1513-1517
initial approach to, 1512f
psoriatic, 1516, 1517f
pyogenic, 1831
radiologic findings, 1503, 1504t
reactive, 1515-1516
management of, 1516
poststreptococcal, 1512
radiographic findings, 1515-1516, 1516f
synovial fluid findings in, 2265t

www.ketabpezeshki.com 66485457-66963820

Arthritis *(Continued)*
rheumatoid, 1513-1515, 1514f
late, 1504t
in pregnancy, 2315
skin lesions associated with, 1581t
septic, 1505-1508, 1831, 1834, 1844-1850
acute, 2264-2266
antibiotic treatment of, 1835t
bacterial, 1834, 1834t
definition of, 1831
differential diagnosis of, 694
in hand, 568
key concepts, 1517b, 1850b
in knee, 717
late, 1504t
management of, 1507-1508
microbiology of, 1834-1835, 1835t
synovial fluid findings in, 2265t
suppurative, 1831
symptoms and signs of, 1501-1503
synovial fluid findings, 2265t
tuberculous, 1504t
viral, 1511, 1513t
Arthrocentesis, 1504-1505
complications of, 1504
contraindications to, 1504
indications for, 1504
in knee injury, 703
technique for, 1504
US-guided, 2503, 2503f
Arthrometers, 701
Arthropathies, 647
Arthroplasty, hip, 681-682
Arthropods, 801, 805
key concepts, 807b
venomous, 801-805
Arthroscopy, 703
Articular disk, 570
Articular surface fractures, 609-612
Artificial oxygen carriers, 77
ASA (acetylsalicylic acid). *See* Aspirin
Ascaris lumbricoides (ascariasis), 1770t-1771t, 1781
drug regimens for, 1772t-1775t
gastrointestinal symptoms of, 1783
Ascending reticular activating system, 142
Asenapine, 2048t
Aseptic meningitis, 1448b
Aseptic necrosis, 675
Ashman phenomenon, 1051, 1051f
Aspartate aminotransferase, 2385
Aspergillus, 2359-2360
Aspergillus fumigatus superinfection, 1813
Asphyxiants, 2036, 2043b
Asphyxiation
simple, 2036
clinical features of, 2036
diagnostic strategies for, 2036
differential considerations, 2036
management of, 2036
patient disposition in, 2036
traumatic, 435
Aspiration
diagnostic peritoneal, 475t
of gastric contents after vomiting, 240
joint, 1844-1846
meconium, 113-115
nasogastric, 252
vs pneumonia, 983-984
of spontaneous pneumothorax, 991-992
Aspiration pneumonia, 2133
Aspirin (acetylsalicylic acid, ASA)
for acute coronary syndrome, 1025
for acute migraine attack, 1388t
for acute rheumatic fever, 1513
alcohol interactions, 2390t
anaphylactoid reactions to, 1546
chronic ingestion of, 1966
drug interactions, 43
for erythema nodosum, 1576
herbal medicine interactions, 2072t-2073t
for Kawasaki disease, 2164
metabolism of, 1965, 1966f
overdose, 1965-1969
clinical features of, 1966
diagnostic strategies for, 1966
Aspirin (acetylsalicylic acid, ASA) *(Continued)*
differential considerations, 1966
initial evaluation of, 1966
key concepts, 1969b
management of, 1966-1967
metabolic effects of, 1965
pathophysiology of, 1965-1966
patient disposition in, 1967
in pregnancy, 1967
for pediatric migraine, 2243
pharmacokinetics of, 1965
in pregnancy, 2317
toxic dose, 1966
Aspirin-exacerbated respiratory disease, 944
pathogenesis of, 944-945, 945f
treatment of, 945
Asplenia, functional, 2365-2366
Assault, 2418
forensic aspects of, 836-839
identification of victims in, 836-839
physical, 836-839
sexual, 855-871
Assessment
antenatal fetal, 2334
foreign body, 753
hazard vulnerability analysis, 2459
leaving before examination, e73
medical screening examination (MSE), e60
ancillary services part of, e63
components, e63
health care providers qualified to perform, e63
request for, e61
medical threat assessment, 2453
pediatric assessment triangle, 2091-2092, 2091f
findings, 2091t
interpretation of, 2091t
remote patient assessment, 2453
TICLS (tone, interactiveness, consolability, look/gaze, and speech/cry), 2091
trauma, in older adults, 325
Assist-control (A/C) ventilation, 24, 25t
Association of SIDS and Infant Mortality Programs, 110
Astemizole, 1569
Asthma, 941-955
acute
ED management of, 948-954, 2119, 2120f
management of, 950
in pregnancy, 952
recommended doses of medications for, 2121t
acute exacerbations of
guidelines for management of, 946
management of, 948-954
moderate, 949-950, 949t
in pregnancy, 2300, 2303t
severe, 949-950, 949t
anxiety in, 1476
assessment of, 948, 948t
burden of care for, 941, 943f
in children, 2117-2124
clinical evaluation of, 2117
clinical features of, 2117-2118
diagnostic strategies for, 2118
differential considerations, 2118-2119
epidemiology of, 2117
history taking in, 2117-2118
management of, 2119-2124
physical examination findings, 2118
clinical features of, 946-947
corticosteroid-resistant, 951
critically ill, 953-954
death rates, 941, 943f
definition of, 941
diagnostic strategies for, 947-948
differential diagnosis of, 948b, 2119t
discharge from emergency department, 955
epidemiology of, 941-942
exercise-induced, 945
prophylaxis for, 945
fatal, 952-953
future monitoring strategies, 948
future therapy for, 952
genetics and, 945
historical components in, 946
hospital discharge rates, 941
Asthma *(Continued)*
hospitalization rates, 941, 943f
initial severity assessments and therapies for, 949t
key concepts, 955b
management of
guidelines for, 946, 954t
inpatient, 954
noninvasive strategies for, 953
observational approach to, 2487-2488
traditional approach to, 2487
menstruation-associated, 945
mild exacerbation of, in children, 2119-2122
mild to moderate, 948-949, 949t
moderate exacerbation of, in children, 2122-2123
near-fatal, 952-953
observation of, 954
observation criteria for, 2487b
pathology of, 945-946
pathophysiology of, 942-945, 944f
patient disposition in, 954-955, 954t
physical findings, 946-947
prediction of relapse, 954
in pregnancy, 2300, 2301t-2303t
prevalence of, 941, 942f
refractory, 952f
refractory critically ill, 954
risk factors for death from, 946, 947b, 953
risk for pulmonary barotrauma in, 1919-1920
severe, 948-949, 949t, 952-953, 952f
severe exacerbation of, in children, 2123-2124
symptoms of, 946
Asthma medications
in pregnancy, 2330
recommended doses, 2121t
Astroviruses, 1723-1724, 2191
Asystole
pediatric, 2154b, 2158-2159
treatment of, 94-95
Atarax (hydroxyzine), 1569
Ataxia
definition of, 2244
Friedreich's, 2245
pediatric, 2244-2246
clinical features of, 2244
diagnosis of, 2245
differential considerations, 2244-2245
etiology of, 2245b
management of, 2245-2246
pathophysiology of, 2244
Ataxia-telangiectasia, 2245
Atazanavir
for HIV infection, 1721t-1722t
side effects of, 1765, 1766t
Atenolol, 1987t, 1122.e1t-1122.e2t
Atheroembolism (blue toe syndrome), 1146
clinical features of, 1146
definition of, 1139
differential diagnosis of, 1146
key concepts, 1156b
management of, 1146
pathophysiology of, 1139
Atheromatous emboli, 1144, 1144f
Atherosclerosis
infection of atherosclerotic arteries, 1148, 1148t
pathophysiology of, 1138
Athletes, young, 2165-2167, 2166b
Athlete's foot (tinea pedis), 1560
Athletic stress fractures, 749
Ativan (lorazepam), 2078t
for rapid tranquilization, 1463, 2417
side effects and drug interactions, 2407t-2408t
for TBI, 347
Atlanta criteria, 1210, 1211b
Atlanto-occipital or atlantoaxial joint dislocation, 382
rotary, 385, 391f, 624
Atlas (C1) fracture, 393, 393f
Atmospheric pressure, 1915
Atonic seizures, 1376
Atopic dermatitis, 1562-1564
clinical features of, 1563
differential considerations, 1563
management of, 1563
skin infections with, 1563-1564
Atovaquone, 1806

www.ketabpezeshki.com 66485457-66963820

Atovaquone-proguanil, 1772t-1775t
Atractaspididae snakes, 795
Atresia, choanal, 115
Atrial fibrillation, 1050-1052
with Ashman phenomenon, 1051, 1051f
causes of, 1051b
ECG findings, 1050, 1050f
in heart failure, 1081
in hypothermia, 1884-1885
lone, 1051
observational approach to, 2488, 2488b
pediatric, 2158
pharmacologic approach to, 1051-1052, 1052b
regularized, 1046
thyrotoxicosis in, 1683b
traditional approach to, 2488
Wolff-Parkinson-White syndrome with, 1055, 1056f
Atrial flutter, 1052, 1053f-1054f
definition of, 1052
pediatric, 2158
pharmacologic approach to, 1052b
with variable conduction, 1052
Atrial septal defects, 2148
clinical features of, 2148
diagnostic strategies for, 2148
management of, 2148
Atrial tachycardia, 1049-1050, 1049f
multifocal, 1050, 1050f
Atrioventricular block, 1043-1046
in beta-adrenergic blocker overdose, 1988
conduction block, 1002
first-degree, 1043, 1044f
second-degree, 1043-1045
high-grade, 1043-1045
type I (Wenckebach), 1044, 1044f, 1044t
type II, 1044-1045, 1044t, 1045f, 1063b
third-degree (complete), 1045-1046, 1045f
Atrioventricular nodal blocking agents, 1055
Atrioventricular-nodal reentrant tachycardia, 1052
antidromic, 1055
orthodromic, 1055
Atrioventricular node
anatomy and conduction, 1034-1035
conduction velocity, 1035, 1037t
Atrium, 1037t
Atropa belladonna (belladonna or deadly nightshade), 951, 1970
alkaloids, 1970, 1971b
Atropine
for anaphylaxis, 1554b
for carbamate poisoning, 1957t-1958t, 2059
for digoxin poisoning, 1985
duration of action, 191t
labor interactions, 2340t
for nerve agent exposure, 826, 2477b
for organophosphate poisoning, 1957t-1958t, 2059
for pediatric dysrhythmias, 2154b
for pediatric intubation, 109
for pediatric resuscitation, 104t
Atrovent (ipratropium bromide), 1555
Attitude, physician, 1485
AUDIT questionnaire. *See* Alcohol Use Disorders Identification Test
Augmentin, 789t
Aum Shinrikyo cult, 825, 1705, 2469
Auscultation, 61
Austin-Flint murmur, 1111
Australasian Triage Scale, 2090
Authority gradients, 2508
Authorization, e64
Autism, 2406-2407
Autoantibodies, extrinsic, 1599-1600
Autoimmune hemolytic anemia, 1599, 1600b
Autoimmune thyroiditis, 1684
Autologous blood products, 533
Automaticity, enhanced, 1035, 1037f
Autonomic nervous system, 2058f
in diabetes mellitus, 1663-1664
in heart failure, 1079
Autonomy, e35
in intimate partner violence, 883
resident, e83
Autopsy, e54
Autotransfusion, 78
Avascular necrosis, 523
of femoral head, 675-676, 676f
of lunate bone, 577, 578f
of scaphoid bone, 577, 577f
Aveeno (oatmeal), 1567
Aviation physiology, 2442-2443
Aviator's fracture, 512t-513t
Avolition, 1461
AVPU system, 308, 308b, 2092
Avulsed teeth, 904-905
Avulsion fractures, 514-515, 516f
in children, 2270, 2270f
of hip, 682, 682f
of tibial tubercle, 718
Avulsion injuries, 563-564
Awake oral intubation, 12-13
Axillary artery aneurysms, 1147
pseudoaneurysms, 502f
Axillary artery injury, 508
Axillary vein injury, 508
Axonal injury, traumatic, 848
Axonotmesis, 520-521, 565
Ayahuasca, 2015
Azathioprine, 2371
hepatic injury, 1197t
for systemic lupus erythematosus, 1533t
Azithromycin
for babesiosis, 1806
for bacterial conjunctivitis, 918-919
for *Campylobacter* enteritis, 1234
for chlamydial infection, 1320
for cholera, 1245
for diarrhea, 1235t
for diarrhea in AIDS, 1257t
for epididymitis in children, 2208
for gonorrhea, 1321
for granuloma inguinale, 1318
for impetigo, 1564
for infectious diarrhea, 2192t-2193t
for infective endocarditis prophylaxis, 2160t
for Lyme disease, 1793
for nongonococcal urethritis, 1320
for otitis media, 933-934
for pertussis, 1698-1699
for pharyngitis, 968
for pneumonia, 984-985, 984t-985t
in pregnancy and lactation, 2318t-2321t
for *Salmonella* enteritis, 1236
for STDs, 1315t
for STDs after sexual abuse/assault, 851t, 868b
Azotemia
evaluation of, 1295f
prerenal, 1295-1296
causes of, 1295b
urinary findings in, 1292t
Aztreonam, 2361t
Azygos vein, 1620, 1620f

B
B cells, 1602
development of, 1547-1548
in immunocompromised patients, 2364
B-type natriuretic peptide, 960
Babesiosis, 1776, 1786t, 1805-1806
clinical features of, 1805
diagnostic strategies for, 1805-1806
management of, 1806
Babinski's sign, 344
BabyBIG (human botulism immune globulin), 1445, 1707
Bacillary angiomatosis, 1762
Bacillary dysentery. *See* Shigellosis
Bacille Calmette-Guérin vaccine, 1829-1830
Bacillus anthracis infection
gastroenteritis, 1241-1242, 2472
antibiotic therapy for, 1235t
clinical presentation of, 1242
diagnostic strategies for, 1242
differential considerations, 1242
epidemiology of, 1234t, 1241-1242
management of, 1242
pathophysiology of, 1242
skin infection, 1856t
Bacillus cereus infection
epidemiological aspects, 1243t
food poisoning, 1244-1245
clinical presentation of, 1244-1245
diagnostic strategies for, 1245
epidemiology of, 1244-1245
management of, 1245
pathophysiology of, 1244
Bacitracin, 824
Back injury
gunshot wounds, 474
stab wounds, 473
Back pain, 278-284
acute
classic findings in, 282t-283t
empirical management of, 282-283
aggravating or alleviating factors, 280
ancillary testing in, 281-282
chronic, 278, 653-654
diagnostic approach to, 278-282
differential diagnosis of, 278-279, 282
epidemiology of, 278
history taking in, 279-281, 279b
imaging in, 282
laboratory testing in, 281
low. *See* Low back pain
musculoskeletal, 643-655
pathophysiology of, 278
patient disposition in, 283-284
physical examination findings, 279b, 281
pivotal findings, 279-282
rapid assessment and stabilization of, 279
upper, 654-655
chronic, 653-654
in elderly, 648
functional, 648
with history of cancer, 653
key concepts, 655b
pediatric, 645, 648, 653
without history of cancer and without radiculopathy, 653
without history of cancer but with signs of radiculopathy, 653
Back to Sleep (BTS) campaign, 110
Backpacker's diarrhea, 1233, 1252
Bacteremia
definition of, 1865b
occult
incidence of, 2096-2097, 2097f
in meningococcemia, 1712
Bacteria, 1693-1717
in cat bites, 786
in dog bites, 786
HACEK group, 1106
in human bites, 791
key concepts, 1717b
most common pathogens, 2359b
that cause infectious diarrhea, 2191-2195, 2192t-2193t
Bacterial croup, 2114-2115
Bacterial endocarditis. *See* Infective endocarditis
Bacterial infection
arthritis, 1507t, 1831
bursitis, 716
conjunctivitis, 918-919, 918f
acute, 921
antimicrobial agents for, 191-192
management algorithm for, 193t-196t
enteritis
invasive, 1233-1242, 1234t
toxin-induced, 1243-1249
facial nerve paralysis due to, 1412
in immunocompromised patients, 2363
keratitis, 192
meningitis
algorithm for, 1452, 1452f
clinical findings, 2225t
complications of, 1450-1451, 1451b
critical, stable, 2230
critical, unstable, 2230
diagnostic strategies for, 2226-2229
differential diagnosis of, 2229, 2229b
epidemiology of, 1447
etiology of, 1448

www.ketabpezeshki.com 66485457-66963820

Bacterial infection *(Continued)*
indications for lumbar puncture for, 2226, 2226b
in infants and children, 2224-2226, 2225t
management of, 2229-2231
in neonates, 2224-2225, 2225t
nontoxic, high risk, 2230
nontoxic, low risk, 2229-2230
pathophysiology of, 1449
pediatric, 2224-2231
recommendations for empirical antimicrobial therapy, 1456t
therapy for, 1456-1457
orchitis, 1348
peritonitis, 1195-1196
pharyngitis, 199-200
causes of, 965
treatment of, 968
pneumonia
in children, 2130-2131, 2135t
clinical features of, 2131
differential considerations, 1817, 2131
in HIV infection, 1759t
management of, 2131
radiographic findings, 2131, 2131f
syndromes, 2135t
red blood cell contamination, 79
septic arthritis, 1834, 1834t
serious illness, 2096
stool culture for, 258
tracheitis, 2114-2115, 2115t
clinical features of, 2114
diagnostic strategies for, 2114-2115
key concepts, 2116b
management of, 2115
treatment of, 783
urinary tract infections, 1327, 1333t
vaginosis, 1323
Amsel criteria for, 1323
characteristics of, 1322t
key concepts, 1325b
during pregnancy, 1323
in pregnancy, 2298
Bacteriuria, 1326
Bacteroides, 979
Bactrim (TMP-SMX), 1335
Bad news, e51-e53, e52b
Bad trips, 2016
Bag-valve mask ventilation
for children, e17, e17f
difficult, 5-6
in prehospital care, 109
Bagging, 2033-2034
Baker's cyst (popliteal cyst), 717, 717f
BAL, 1957t-1958t
Balance, resident, e83-e84
Balanitis circinata, 1515-1516
Balanoposthitis
in children, 2206-2207, 2207f
clinical features of, 2207
management of, 2207
patient disposition in, 2207
Balantidium coli (balantidiasis), 1770t-1775t
Balkan foxglove plant *(Digitalis lanata)*, 1982, 1983f
Ballistic injury, nonpenetrating
to chest, 434-435
clinical features of, 435
diagnostic strategies for, 435
epidemiology of, 434-435
management of, 435
pathophysiology of, 435
types of, 434-435
Ballistics, 460
handgun wound, 829-830
Balloon-tipped catheters
removal of esophageal foreign bodies with, 778
removal of otic or nasal foreign bodies with, 770, 770f
Bamboo spine, 1515
Banana Cream Nuke, 2021
Bandaging
lower extremity, 529-531
for orthopedic injuries, 528-531
sling-and-swathe bandages, 529
Bandaging *(Continued)*
upper extremity, 529
Velpeau bandages, 529
Banzel (rufinamide), 2407t-2408t
Barbecue roll, 168
Barbiturate coma, 1382
Barbiturates, 2076-2078
alcohol interactions, 2390t
classification of, 2076, 2077b
depressive effects of, 2076
enhanced elimination of, 2077-2078
gastrointestinal decontamination of, 2077-2078
for increased ICP in head injury, 349
labor interactions, 2340t
for procedural sedation and analgesia, 57
toxicity of
clinical features of, 2076-2077
diagnostic strategies for, 2077
management of, 2077-2078
patient disposition in, 2078
Barium enemas
in appendicitis, 1228
in colonic ischemia, 1273
in diverticulitis, 1263-1264
in intussusception, 1269
Barium esophagography, 2114, 2114f
Barlow (provocative) test, 2261, 2262b
Barodontalgia, 1919
Barosinusitis, 1918, 1926
Barotitis, 1918
Barotrauma
external ear, 1918, 1926
facial, 1918, 1926
gastrointestinal, 1919
inner ear, 1918, 1923t, 1926
middle ear, 1918, 1923t, 1925
pulmonary, 1919-1920, 1926
Barrel compression test, 432
Barridas, e27
Barriers to care, 877-878
Bartholin abscess, 1314-1315
drainage of, 1857-1858, 1858f
Bartholin cyst, 1314-1315
Barton's fracture, 512t-513t, 584-585
classic, 584-585
dorsal, 512t-513t
volar, 512t-513t, 584-585, 586f
Base deficit
in abdominal trauma, 464
formula for, 2219
Baseball. *See* Little League Baseball
Basic calcium phosphate hydroxyapatite (BCP) crystal disease, 1510
Basic life support systems, 2435
Basilar fractures, 361-362
clinical characteristics of, 347b
meningitis after, 359
Basilar-type migraine, 139t, 1387, 2242
Basophils, 2358
Bath salts, 2395
Battered woman, 872
Battering, 872
Battery ingestion, 1997
removal of, 780
website and hotline for, 1172, 2182
Battlefields, 2451
Battle's sign, 313
Baumann's angle, 599, 600f, 2255-2256, 2255f
Beanbag shotgun shells, 434-435
Beck Anxiety Inventory, 1497-1498
Beck Depression Inventory, 1497-1498
Beck Hopelessness Scale, 1497-1498
Beck Scale for Suicidal Ideation, 1497-1498
Beck's triad, 449, 1626b
Bedside echocardiography, 1532
Bedside registration, e64
Bedside ultrasound
abdominal bowel ultrasound, 2500
in heart failure, 1083
in pericardial effusion, 1095, 1095f
Bee stings, 794, 802
Bees, 801-802
Behavior(s)
antisocial, 2420b
catatonic, 1461
Behavior(s) *(Continued)*
classification of, 2426-2430
controlling, 875
drug-seeking, 40
grossly disorganized, 1461
ground rules for, 2424
negative, 2425
negative reactions, 2424-2425
risk factors for injury, 336-337
as symptom, 2425
that foster disclosure, 877
violent, 2414-2415, 2418-2419
Behçet's disease, 1540, 1540f
Beliefs
cultural competence for crossing barriers of, e26-e27
Health Belief Model, 881
health beliefs and concerns, e27
"Bell clapper" deformity, 1343-1344
Belladonna *(Atropa belladonna)*, 951, 1970
Belladonna alkaloids, 1970, 1971b
Bellevue Hospital (New York, NY), 2433
Bell's palsy, 1411-1412
Benadryl (diphenhydramine), 902, 1464
Benazepril, 1122.e1t-1122.e2t
Bends, 1915
Beneficence, e35
Benign early repolarization, 1004, 1005f
Benign livedo reticularis, 1149
Benign paroxysmal positional vertigo
diagnosis of, 164-165, 167f
differential diagnosis of, 166t-167t
management of, 168-169, 168f-169f
pathophysiology of, 162
Benign paroxysmal vertigo of childhood, 2247
Benign positional vertigo, 2247
Bennett's fracture, 512t-513t, 552, 552f
Benzathine penicillin (Bicillin C-R)
for diphtheria, 1696
for GAS infection, 1513
for pharyngitis, 968
for rheumatic fever, 1109
for scarlet fever, 1572
for STI prophylaxis or treatment after sexual abuse/assault, 851t
Benzathine penicillin G, 1315t
Benznidazole, 1099, 1772t-1775t
Benzoate, 1195
Benzocaine, topical, 48
Benzodiazepine withdrawal syndrome, 2080, 2080b
Benzodiazepines, 2078-2080, 2078t
alcohol interactions, 2390t
for alcohol withdrawal, 2382
for anxiety disorders, 1479, 1479t
for delirium, 1403
pharmacokinetics, 2078-2079
in pregnancy, 2322
in procedural sedation and analgesia, 56
for rapid tranquilization, 2417
toxicity of
antidote for, 1957t-1958t
clinical features of, 2079
diagnostic strategies for, 2079
differential considerations, 2079
management of, 2079-2080
patient disposition in, 2080
Benztropine (Cogentin)
for akathisia, 1464
for antipsychotic overdose, 2050
for dystonia, 1464
for rapid tranquilization, 1472
Bepridil, 1991t
Bereavement, 1472, e54-e55
Berinert, 1557
Berlin's edema, 916
Best evidence topic (BET), e20t, e21
Best interest standard, e41
Beta (β), e13t
Beta-adrenergic agonists
for anaphylaxis, 1554b, 1555
for asthma, 950
for asthma exacerbations in pregnancy, 2303t
in pregnancy and lactation, 2318t-2321t

www.ketabpezeshki.com 66485457-66963820

Beta$_2$-adrenergic agonists. *See also* Short-acting beta$_2$-adrenergic agonists (SABAs)
  long-acting, 950
Beta-adrenergic receptors, 1038, 1038t
Beta-blockers, 1986
  for acute coronary syndrome, 1024
  for acute glaucoma, 930t
  cardioselective, 1038
  characteristics of, 1986, 1987t
  combined alpha-, beta-blocker therapy, 1087
  for dysrhythmias, 1038
  effects of, 1038t
  for heart failure, 1087
  for hypertension, 1122.e1t-1122.e2t
  intravenous, 1024
  mixed alpha$_1$/beta-blockers, 1122.e1t-1122.e2t
  overdose, 1986-1990
    antidote for, 1957t-1958t
    clinical features of, 1987, 1987b
    complications of, 1987b
    diagnostic strategies for, 1987
    differential considerations, 1988
    key concepts, 1993b
    management of, 1988-1989
    pathophysiology of, 1986
    patient disposition in, 1990
    pediatric considerations, 1989-1990
    treatment of, 1990b
  in pregnancy, 2318t-2321t, 2327
  that may cause seizures, 2235b
  for thyroid storm, 1682b
Beta error, e13t
Beta-mimetics, 2339-2340
Beta particles, 1947-1948, 1948f
Betadine (povidone-iodine), 756t, 766b
Betamethasone, 1510
Betamethasone sodium phosphate and acetate (Celestone Soluspan), 639t
Betamethasone valerate, 2206
Betaxolol, 1987t, 1122.e1t-1122.e2t
Bezoars, 779
  in bladder, 782
  management of, 780-781
Bezold abscess, 936
Bhagwan cult, 2469
Bi-level positive airway pressure (BL-PAP), 25, 25t
Bias
  definition of, e20t
  publication, e12
  selection, e10
  visceral, 2508
Bicarbonate
  for diabetic ketoacidosis, 1658t, 1660-1661
  for hyperglycemic hyperosmolar state, 1658t
  for hyperkalemia, 1638t
  indications for, 1660-1661
  levels, 1958
  regulation, 1629
  for sepsis, 1872
  for TCA overdose, 1977, 1978f
  for tricyclic antidepressants toxicity, 1957t-1958t
Biceps muscle lesions, 640-641
Biceps tendon
  dislocation of, 641
  rupture of, 616, 641
    clinical features of, 616, 641
    diagnostic strategies for, 641
    key concepts, 617
    management of, 616, 641
    pathophysiology of, 616, 641
  subluxation of, 641
Bichloroacetic acid (BCA), 1319
Bicillin C-R (benzathine penicillin), 1572
Bicipital tendinitis, 640-641
  clinical features of, 640
  diagnostic strategies for, 641
  management of, 641
  pathophysiology of, 640
Bicipital tendinopathy, 1519f, 1520
Bicycle accidents, 290t
Bier block (intravenous regional anesthesia), 48, 583-584
Bigeminy, ventricular, 1046, 1046f
Biguanides (Metformin), 1665t
Biliary cirrhosis, 1193
Biliary colic, 1201
Biliary tract disorders, 1200-1204
  abdominal pain in, 224t-225t
  carcinoma, 1204
  in children, 2186-2187
    clinical features of, 2186
    diagnostic strategies for, 2186
    differential considerations, 2186
    management of, 2186-2187
    patient disposition in, 2187
  vomiting in, 243t-244t
Biliary ultrasound, 2497
Bilingualism, e26
Bilirubin, elevated, 1188
Bilirubin metabolism
  abnormalities in, 232
  normal, 232
Biltricide (praziquantel), 1770t
Bimalleolar fractures, 729
Bindeez Beads, 2082
Binge drinking, 2280
Bioethical dilemmas, e37-e38
Bioethics, e33-e46
  application of, e36-e37
  commonly accepted values, e35b
  definition of, e33
  fundamental principles, e35-e36
  and law, e33-e34, e34t
  and public policy, e44-e45
Bioethics committees, e41
Biofeedback, 1479-1480
Biologic exposures
  of eye, 912
  and rhabdomyolysis, 1669b-1670b
Biologic sutures, 760-761
Biologic terrorism, 2466
Biologic weapons, 2471-2476
  botulinum toxin, 1705
  Category A (high threat) agents, 2471-2472
  key concepts, 2478b
  signs suggesting deployment of, 2471, 2471b
Biology, wound, 751-752
Biophysical profile, 2335-2337, 2337t
Biopsy, myocardial, 1099f
Biphasic positive airway pressure (BPAP), 953
Bipolar (manic-depressive) disorder
  anxiety in, 1477
  clinical features of, 1470-1471
  genetics of, 1467
  prevalence of, 1466
Bipyridyl compound toxicity
  clinical features of, 2062-2063
  diagnostic strategies for, 2063
  differential considerations, 2063
  management of, 2063
  patient disposition in, 2063
  signs and symptoms of, 2062-2063
Bipyridyl compounds, 2062-2063
Bird's beak sign, 1267, 1268f
Birdshot, 834
Birth. *See also* Delivery
  multiple births, 2271
Birth rates, 2271
Birth trauma, maternal, 2347-2348
Bisacodyl (Dulcolax, Correctol), 264t-265t
Bismuth compounds, 1185
Bismuth subsalicylate (Pepto-Bismol)
  for diarrhea, 260
  for *H. pylori* infection, 1180, 1185
  for traveler's diarrhea, 1259
  for traveler's diarrhea prevention, 1259
  for upper GI disorders, 1185
Bismuth subsalicylate, metronidazole, and tetracycline (Helidac), 1180
Bisoprolol
  characteristics of, 1987t
  for hypertension, 1122.e1t-1122.e2t
Bispectral Index (BIS), 53, 65
Bite marks, 839, 839f, 846f
  collection of evidence of, 864, 864b
  forensic examination of, 839
Bite wounds, 1853
  clenched-fist injuries, 562
  guidelines for, 788-789
  penile, 497-498
Bite wounds *(Continued)*
  recommendations for antibiotic prophylaxis, 789t
  recommendations for closure, 789t
  risk factors for infection, 788, 788t
Bites
  animal bites, 785-790
    reporting requirements for, e77
    venomous animal injuries, 794-807
  cat bites, 764, 786-787
  dog bites, 764, 785-786
  fight bites (clenched-fist injuries), 562, 764, 791
  hand bites
    indications for hospital admission, 792b
    management of, 764
  human bites, 790-793, 846f
    child physical abuse, 845
    indications for hospital admission, 792b
    key concepts, 793b
    septic arthritis from, 1846
  insect bites and stings
    allergic reactions to, 803
    epidemiology of, 794
  mammalian, 785-793
  management of, 764
  marine animal, 806
Bithionol, 1772t-1775t
Bitrex (denatonium benzoate), 2013
Bivalirudin, 1027
Biventricular pacing, 1073, 1074f, 1088
Black death, 2474
Black-letter law, e33
Black stones, 1200
Black widow spider *(Latrodectus mactans)*, 803-804
Black widow spider *(Latrodectus mactans)* bite
  antidote for, 1957t-1958t
  clinical features of, 803
  management of, 803-804
Blacks. *See* African Americans
Bladder
  anatomy of, 485
  dysfunctional, in back pain, 280
  kidney-ureter-bladder (KUB) films, 1339
Bladder (vesical) calculus, 1342
Bladder catheters, 2412
Bladder perforation, 489, 489f
Bladder rupture, 490f
Bladder trauma, 485-490
  clinical features of, 485
  diagnostic strategies for, 485-490
  laboratory testing in, 485
  management of, 490
  pathophysiology of, 485
  radiology in, 485-490
Blastocystis hominis infection, 1257t
Blatchford score, 253, 253t
Bleeding. *See also* Hemorrhage
  ancillary evaluation of, 1608-1609
  from Cimino-Brescia fistula, 1156
  after dental extraction, 907
  evaluation of, 1608b
  in facial trauma, 376
  in fracture, 520t
  gastrointestinal, 248-253
    pediatric, 2180t
  in heparin therapy, 1615
  history taking in, 1608, 1608b
  in micturition, 1353t
  nasal, 937-939
  ovulatory, 274t
  physical examination in, 1608, 1608b
  postmenopausal, 274t
  rectal, 1276-1277
  tourniquets for, 2451
  traumatic, in pregnancy, 296
  upper gastrointestinal, 2484
  uterine
    abnormal, 1360-1362
    dysfunctional, 274t
  vaginal, 273-277
    in early pregnancy, 2287, 2288f
    in later pregnancy, 2288-2290
    in pregnancy, 2294t
Bleeding control, 292
Bleeding diathesis, 2294t

www.ketabpezeshki.com 66485457-66963820

Bleeding disorders, 1606-1616
clinical features of, 1607-1609
differential diagnosis of, 1609-1616
out-of-hospital treatment of, 1607-1608
pathophysiology of, 1606-1607
patient disposition in, 1616
Bleeding time, 1608
Blepharitis, 193t-196t, 921
Blind nasotracheal intubation, 12
Blind spots, normal, 924f
Blinding, double, e11
Blistering agents, 825, 2477-2478
Blisters
burn blisters, 814
fracture blisters, 524-525
frostbite, 1881, 1881f
Blood
components of, 75
in urine, 1670-1671, 1671t
Blood agents, 2478
Blood alcohol concentration (BAC), e72
Blood alcohol tests, e62-e63
Blood banking, 75, 250
Blood-brain barrier, 340-342
Blood culture, 2098
Blood dyscrasias, 903
Blood ethanol, 2379t
Blood flow, inadequate, 90t
Blood pressure
arterial, 90
automatic, 61
elevated. *See also* Hypertension
without prior history of HTN, 1114
without target-organ dysfunction, 1116-1117
Blood pressure control
acute, 1117-1122
in blunt aortic injury, 455
cerebral autoregulation, 1118-1119, 1120f
fibrinolytic therapy for, 1029
indications for, 1371
in stroke, 1371
Blood pressure measurement
ambulatory monitoring, 1113
formula for, 1077, 2139
goals, 1118-1119
limits in children, 2219t
manual, 61
noninvasive, 61
pediatric estimation, 2142, 2142t
Blood product transfusion, 252
Blood products
autologous, 533
triggers for anaphylaxis, 1545
Blood rewarming, extracorporeal, 1893-1894, 1894t
Blood smear, 1608
Blood testing
in arthritis, 1503
in asthma, 947
blood culture, 2098
in COPD, 960
Blood thinners, 2072t-2073t
Blood transfusion, 75
administration of, 76-77
adverse effects of, 78
acute, 78-79
chronic, 80
delayed, 79
immune-mediated, 78-79
non–immune-mediated, 79-80
autotransfusion, 78
before completion of compatibility testing, 76
decision-making for, 77-78
with fresh frozen plasma, 77-78
infusion adjuncts, 77
for Jehovah's Witnesses, e75-e76
legal aspects, 76-77
management of, 77-78
massive, 76
outcomes, 78-80
with packed red blood cells, 77-78
for pediatric trauma, 310
refusal of, for minor, e75
for sickle cell anemia, 1599
special clinical circumstances, 76
therapeutic modalities for, 78
Blood transfusion *(Continued)*
universal recipients, 76
with whole blood, 77
Blood typing, 75-76
complete crossmatch, 76
computer crossmatch, 76
immediate spin crossmatch, 76
Blood urea nitrogen, 1292
BUN/Cr ratio, 1671
in diabetic ketoacidosis, 1658t
in hyperglycemic hyperosmolar state, 1658t
in nausea and vomiting, 242
Bloody show, 2332
Blot hemorrhages, 848
Blue bloaters, 958. *See also* Chronic obstructive pulmonary disease
Blue leg, painful (phlegmasia cerulea dolens), 1159
Blue toe syndrome (atheroembolism), 1130, 1146
clinical features of, 1144, 1144f
key concepts, 1156b
Blunt trauma
abdominal, 459
algorithm for, 476f
with aortic injury, 478, 478f
with closed head injury, 477, 477f
diagnostic testing in, 475, 475t
epidemiology of, 459
in hemodynamically stable patients, 476-478
in hemodynamically unstable patients, 476
history taking in, 462
indications for laparotomy after, 476f
management of, 475-478
multiple system injury, 477
observational approach to, 2486
pathophysiology of, 461-462
pediatric, 320, 461-462, 478
with pelvic fracture, 476-477, 477f
physical examination findings, 463
traditional approach to, 2486
transfer for, 478
aortic injury, 451-455, 452f
with abdominal trauma, 478, 478f
anatomy of, 451-452
clinical features of, 452
diagnostic strategies for, 452-454
ED management of, 454-455
epidemiology of, 451
management of, 454-455
out-of-hospital care for, 454
pathophysiology of, 451-452
surgical techniques for, 455
cardiac, 444
epidemiology of, 444
pathophysiology of, 444
chest trauma
to children, 318-319
ED thoracotomy for, 295f
indications for thoracotomy, 448b
observational approach to, 2486-2487
traditional approach to, 2486
esophageal perforation from, 456-457
mechanisms and associated injuries, 290t
neck trauma, 421
pattern contusions, 837-839
pattern injuries, 837-839
penile, 496
peripheral vascular injury, 501
in pregnancy, 297-298
renal, 492-493
scrotal, 497
vascular neck trauma, 427-429
Body dysmorphic disorder, 1482b
Body lice, 1573, 1574f
Body packers, 1378, 2004, 2398
Body packing, 779, 779f, 1954-1955, 2004
Body stuffers, 1378, 2004, 2398
Body stuffing, 779, 1954-1955
Body surface area, 814
Body surface mapping, 1016
Body temperature
cooling modalities to lower, 1905b
maintenance of, 84
regulation of, 1896-1897
Body water calculation, 1641, 1642t
Boehler's angle, 740, 740f
Boerhaave's syndrome, 240, 243t-244t, 457
Bolivian hemorrhagic fever, 1740
Bone(s)
accessory ossicles, of foot, 735, 736f
cortical, 1833
of face, 369, 369f
growing, 517-518, 517f
hand skeleton, 534-536, 536f-537f
long, 1832, 1832f
of wrist, 534-535, 536f, 570, 571f
Bone and joint infections, 1-1850
antibiotic treatment of, 1835t
etiology of, 1834-1836
key concepts, 1850b
microbiology of, 1834-1836, 1835t
tuberculosis, 1819
Bone bruise, 709
Bone Injection Gun, 2452
Bone marrow, 1605t
Bone marrow stainable iron, 1591t
Bone scanning (radionuclide imaging)
in ankle injuries, 726-727
in knee injury, 703
in osteomyelitis, 1837
in UTIs, 1329
Bonferroni correction, e14
Bony fishes, 807
Booster seats, 369
Borderline personality disorder, 1472, 2427b
Bordetella bronchiseptica, 1696
Bordetella parapertussis, 1696
Bordetella pertussis, 1696
Bornholm's disease, 1732
Borrelia burgdorferi, 1856t, 1862
Bosworth fracture, 512t-513t
Botanicals, 2066
identification of, 2066-2070
misidentification of, 2066
Both-bone fractures, 591
Botox, 1281
Bottle jamming, 369
Botulinum toxin
for anal fissures, 1281
as biological weapon, 1705
Botulism, 1444-1445, 1704-1707
adult, 1706
clinical features of, 1444, 1705-1706
complications of, 1706
diagnostic strategies for, 1444-1445, 1706
differential considerations, 1706
epidemiology of, 1704-1705
etiology of, 1705
food-borne, 1704-1705
historical perspective on, 1704
inadvertent, 1705
infant, 1704
differential diagnosis of, 1706
symptoms and signs of, 1705
key concepts, 1446b, 1717b
management of, 1445, 1706-1707
mortality rates, 1706
pathophysiology of, 1705
patient disposition in, 1707
symptoms and signs of, 1705-1706
wound, 1704, 1706
Bouchard's nodes, 1510
Bougienage, 778
Boutonnière (buttonhole) deformity, 559, 559f
Bovine pustular stomatitis, 1727
Bow-tie deformity, 391f-392f
Bowstring sign, 645-646
Box jellyfish *(Chironex fleckeri)*, 806
Boxer's fracture, 512t-513t, 550, 550f
Boyle's law, 1915-1916, 1916t, 1917f, 2442
Brachial artery injury, 508
Brachial plexopathy, 1433b
Brachial plexus, 621, 621t
Bradycardia, 1041
in beta-adrenergic blocker overdose, 1988
in calcium channel blocker overdose, 1991-1992
chest pain and, 217t-218t
definition of, 1041
in hypothermia, 1884
in newborn, 112

www.ketabpezeshki.com 66485457-66963820

Bradycardia *(Continued)*
pediatric, 2155
cardiopulmonary resuscitation in, 105
treatment options, 2154b
sinus, 1041-1042, 1042f, 2155
Bradycardia-tachycardia syndrome, 1043
Bradydysrhythmia, 1002
pediatric, 2155
Brain
anatomy and physiology of, 340-342
blood supply, 1365
major divisions, 340
Brain abscess, 1449f
complications of, 1451
epidemiology of, 1447-1448
etiology of, 1448-1449
after head injury, 359
in HIV infection, 1762t
pathophysiology of, 1449
therapy for, 1457-1458
Brain death, 342-343, e48
whole brain death, e48
Brain disorders, 1409-1418
Brain injury. *See also* Head injury
cellular damage, 342-343
penetrating (PBI), 358-359, 367
postarrest, 100
primary, 342-343
secondary, 342-343, 342f
and secondary systemic insults, 343
seizures and, 2231
traumatic. *See* Traumatic brain injury (TBI)
Brain ischemia
after cardiac arrest
clinical outcomes, 86
management of, 81-86
pathophysiology of, 81, 82f-83f
Brain natriuretic peptide (BNP) assays
in heart failure, 1083
NT-proBNP assays, 1083
Brain resuscitation, 81-87
key concepts, 87b
management of, 81-86
standard strategies for, 81-86
summary, 86-87
Brain swelling
congestive, 343
after head injury, 343-344
Brainstem anatomy, 144f
Brainstem function assessment, 346-347
Brassaia, 2067
BRAT (bananas, rice, apples, and toast) diet, 259
Braxton-Hicks contractions, 2273, 2332
Breakthrough seizures, 2407
Breast cancer, metastatic, 650f
Breast milk jaundice, 2168
Breath-holding
clinical features of, 139t
differential diagnosis of, 2233
Breathing
in geriatric trauma, 325
paradoxical, 306-307
in pediatric trauma, 306-307, 307t
pediatric work of, 2091-2092, 2091f
positive pressure, 23
Breech delivery, 2342-2344
assisted, 2342
diagnostic strategies for, 2342-2343
management of, 2343-2344
spontaneous, 2342
vaginal, 2343b
Breech presentation, 2342t, 2343b, 2343f
Bretylium, 1038
Brinzolamide, 930t
British anti-Lewisite (BAL) (dimercaprol), 2028t
British Manchester Self-Harm Rule, 1498
British Royal College of Physicians, 828
Broca's aphasia, 1365
Brodie's abscess, 1841
Broken heart syndrome, 1104. *See also* Takotsubo cardiomyopathy
Bromocriptine, 2051
Bronchial agents, 2235b
Bronchiolitis
assessment tool for, 2125t
in children, 2124-2128
clinical features of, 2125-2126
complications of, 2125-2126
diagnostic strategies for, 2126
differential considerations, 2126
drugs for treatment of, 1721t-1722t
epidemiology of, 2124-2125
etiology of, 2125
history taking in, 2125
management of, 2126-2128, 2127f
pathophysiology of, 2125
patient disposition in, 2128
physical examination findings, 2125
prophylaxis of, 2127
therapy, 2126-2127
Bronchodilators, 962-963
Bronchopulmonary dysplasia, 2138, 2138f, 2401-2402
Bronchoscopy, 204
Bronchospasm
in anaphylaxis, 1552t
capnographic patterns in, 64, 64f
psychological factors, 945
Brooke formula, 813t
Broselow-Luten tape, 109
Brow presentation, 2342t, 2345
Brown recluse spider *(Loxosceles reclusa)*, 804
Brown recluse spider *(Loxosceles reclusa)* bite
clinical features of, 804
management of, 804
Brown-Séquard syndrome, 400, 402f, 1420-1421, 1421t
Brown stones, 1200
Brudzinski's sign, 1395, 1790-1791
Brugada criteria, 1055, 1058f
Brugada's syndrome, 1062-1063, 1062f
Brugia malayi, 1770t-1775t
Bruises
bone bruise, 709
in child abuse, 849, 849f
Bubonic plague, 2469, 2474, 2474f
Bucket-handle fracture, 661
Bucket-handle injury, 847-848, 847f
Buckle fracture (torus fracture), 2250, 2251f
Buckshot, 834
Budd-Chiari syndrome, 1199
Buddy taping, 548, 549f, 746-747
Budesonide, 951, 2113
Buerger's disease (thromboangiitis obliterans), 1145-1146, 1541t
clinical features of, 1145
diagnosis of, 1145
management of, 1145-1146
Bufo toad, 2015
Bulk laxatives, 264t-265t
Bullae, 1559t
Bullets
examination of, 836, 837f
full metal jacket, 829
semi-jacketed, 829
tips for handling, 836, 837f
types of, 829
Bullosis diabeticorum, 1665
Bullous impetigo, 1564
Bullous pemphigus, 1577, 1577f
Bullying, e1
Bumetanide
for acute renal failure in children, 2218
hemodynamic effects, 1118t
for hypertension, 1122.e1t-1122.e2t
Bunyaviridae, 1719t, 1725
Bunyavirus hemorrhagic fever, 1725
Bupivacaine (Marcaine)
characteristics of, 46t
guidelines for maximum doses, 47t
for wound management, 754
Buprenorphine (Subutex), 2055-2056
Buprenorphine-naloxone (Suboxone), 2055-2056
Bupropion overdose, 1979
Burkholderia cepacia, 2138
Burn blisters, 814
Burn dressings, 814-815, 815t
Burn resuscitation index (BRI), 812-813, 813t
Burn size score (BSS), 812-813
Burnout, physician, e80
Burns, 2042-2043
alkali, 189f
caustic, 1994-1998
caustic esophageal, 456
chemical injuries, 818-827
in child abuse, 845-846, 846f
in children, 846-847
cigarette, 846f
classification, 809-810
classification by depth, 809-810, 809t
classification by severity, 810, 811t
clinical features of, 809-810
cooling, 814
corneal, 189f
diagnosis of, 809-810
ED management of, 811-814
electrical
types of, 1909, 1909b
wound care, 1914
epidemiology of, 808
to eye, 912
first-degree, 809t
fluid requirements in, 812-813
fluid resuscitation in, 812-814
fourth-degree, 809t
full-thickness, 809-810
water temperature and duration of contact required, 839, 840f
hydrofluoric acid (HF), 820-821, 827b
immersion, 846f
indications for endotracheal intubation and mechanical ventilation in, 812, 812t
inhalation injury
example treatment protocol for, 812
management of, 812
pathophysiology of, 809
recognizing, 811-812
lightning injuries, 1914
local wound care, 814-816
management of, 810-816
mild, 811t
moderate, 811, 811t
in older adults, 325
pain management in, 816
pathophysiology of, 808-809
patient disposition in, 817
pattern injuries, 839
perioral, 377
powder burns, 829
prehospital management of, 810-811
prevention of, 816, 816t
recommended initial ventilator settings for, 812t
resuscitation formulas for, 812-813, 813t
rule of nines for, 810
second-degree, 814
deep, 809-810, 809t, 810f
superficial, 809-810, 809f, 809t
severe, 811, 811t
splash, 847f
supraglottic, 2111
thermal, 808-817
third-degree, 809-810, 809t, 810f
Burow's solution (aluminum acetate), 1558, 1563, 1579
Burping, 2176
Bursitis, 528, 716, 1523-1525
anserine, 716, 1519f, 1525
calcific, 676-677
clinical features of, 1524
diagnostic strategies for, 1524
differential diagnosis of, 1524
of heel, 1519f
iliopectineal, 1519f
iliopsoas, 1525
infrapatellar, 1519f
ischial, 1519f
ischiogluteal, 1525
key concepts, 1525b-1526b
knee, 716
location of common sites, 1519f
management of, 1524-1525
olecranon, 615-616, 1524
patient disposition in, 1525
prepatellar, 1524

www.ketabpezeshki.com 66485457-66963820

Bursitis *(Continued)*
septic (bacterial), 716, 1524-1525, 1831
of shoulder, 1519f
subacromial, 637-639, 1525
trochanteric, 1519f, 1525
Burst fractures, 393-396, 394f-396f, 409f
Buscopan (hyoscine), 246
Buspirone (BuSpar), 2080
for anxiety disorders, 1479, 1479t
for opioid withdrawal, 2056
1,4-Butanediol (1,4-BD), 2082, 2083b
Butterfly segment, 658-659
Button (disk) battery ingestion, 780, 1997
Buttonhole (boutonnière) deformity, 559, 559f
Butyl 2-cyanoacrylates, 762
γ-Butyrolactone, 2082
Butyrophenones, 2382
Bypass
cardiopulmonary, 1894, 1894t
coronary artery, 1029, 1088-1089

C
C-MAC video laryngoscope (Karl Storz Endoscopy), 18-19, 18f
C-reactive protein
in appendicitis, 1227
in osteomyelitis, 1836
in septic arthritis, 694
C1 inhibitor replacement protein (C1-INHRP), 1557
Cachexia, at end of life, e57
Cafe coronary, 772
Caffeine
and anxiety, 1477
labor interactions, 2340t
CAGE questionnaire, 2378
Calcaneal fractures, 739-740
clinical features of, 740
diagnostic strategies for, 740
management of, 740
pathophysiology of, 739
patient disposition in, 740
radiographic findings, 740, 740f
Calcaneus, 739
Calcific bursitis, 676-677
Calcific periarthritis, acute, 1510
Calcific peritendinitis, 676-677
Calcific tendinitis, 527-528, 641-642
clinical features of, 641
diagnostic strategies for, 641
management of, 641-642
pathophysiology of, 641
rotator cuff, 641, 641f
Calcific tendinopathy, 1520-1521, 1521f
in elbow, 1521
management of, 1523
Calcific trochanteric bursitis, 676-677, 677f
Calcineurin inhibitors, 2371
Calcitonin, 1625
Calcium
for beta-blocker toxicity, 1988
for calcium channel blocker toxicity, 1957t-1958t
ethanol effects on, 2388t
normal physiology, 1667
Calcium channel blockers, 1990
for acute coronary syndrome, 1025
for atrial fibrillation and flutter conversion, 1052b
characteristics of, 1990, 1991t
for heart failure, 1088
for hypertension, 1122.e1t-1122.e2t
overdose, 1990-1992
antidote for, 1957t-1958t
clinical features of, 1990, 1991b
diagnostic strategies for, 1990
differential considerations, 1990-1991
key concepts, 1993b
management of, 1991-1992
pathophysiology of, 1990
patient disposition in, 1992
pediatric considerations, 1992
treatment of, 1991, 1992b
in pregnancy, 2318t-2321t, 2327
for premature labor, 2340
Calcium channels, 1667, 1668f
Calcium chloride
for hyperkalemia, 1305t, 1638t
for hyperkalemia in children, 2218
for hypermagnesemia, 1648
for hypocalcemia, 1647
in pediatric resuscitation, 104t
Calcium disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$), 2027, 2028t
Calcium gluconate
for hydrofluoric acid exposure, 821, 1957t-1958t
for hyperkalemia, 1305t, 1638t
for hypermagnesemia, 1648
for hypocalcemia, 1647
for hypocalcemia in children, 2236
for hypocalcemia in neonates, 2236
Calcium pyrophosphate dihydrate deposition, 1509-1510, 1510f
clinical features of, 1510
diagnostic strategies for, 1510
management of, 1510
Calcium pyrophosphate dihydrate deposition disease (CPDD), 1509-1510, 1510f
Calcium salts, 1039
Calcium stones, 1336
Calcium–adenosine triphosphatase (Ca^{2+}-ATPase) pump, 1667, 1668f
Calculi
bladder (vesical), 1342
renal, 1336-1342
in children, 2214-2215
ureteral, 1338f
Calf vein thrombosis, isolated, 1159
Calf veins, 1157
Caliciviruses, 1719t, 1723-1724, 1738
California Department of Public Health Infant Botulism Treatment and Prevention Program, 1445, 1707
California Emergency Management Agency Forensic Medical Report: Acute form, 857, 858f-861f
California (La Crosse) encephalitis, 1725, 1737
Calprotectin, 258
Calvé-Perthes' disease, 696
Camel bites, 787, 788t-789t
Campylobacter enteritis, 1233-1234, 2193-2194
in AIDS, 1257t
antibiotic therapy for, 1235t
clinical presentation of, 1233-1234
diagnostic strategies for, 1234
differential considerations, 1234
epidemiology of, 1233, 1234t
incidence of, 1233
management of, 1234
pathophysiology of, 1233
treatment of, 1235t, 1257t, 2192t-2193t
Canadian C-spine Rule (CCR), 293, 326, 403
Canadian Cardiovascular Society, 998
Canadian Triage and Acuity Scale, 2090
Canalicular lacerations, 917, 917f
Canalith repositioning procedures, 168, 169f
Cancer, 1617, 2358
alcohol effects on, 2389
biliary tract, 1204
breast, metastatic, 650f
gallbladder, 1204
hepatic, 1199
lifetime risk for development of, 1617
neutropenic, 1628b
pancreatic, 1214-1215
scrotal, 2211
solid organ, 2362-2363
testicular, 2211
trends in, 1618b
Candesartan, 1122.e1t-1122.e2t
Candida bezoar, 782-783
Candidal vaginitis, 783
Candidiasis, 1561-1562, 2359-2360
antimicrobial therapy for, 1664t
characteristics of, 1322t
cutaneous, 1562
esophageal, 1173-1175
folliculitis, 1859
management of, 1175
mucocutaneous, 1664t
oropharyngeal, 1175
Candidiasis *(Continued)*
pharyngeal, 967-968
skin infections, 1856t
vulvovaginal, 1322-1323
characteristics of, 1322t
in pregnancy, 2298
Cannabinoids
designer, 2021
structures of, 2021, 2021f
synthetic, 2020-2022, 2021f
Cannabis indica, 2020
Cannabis sativa, 2020
Canthotomy, lateral, 910, 911f
Capacity, e40
decision-making, e40
hospital, e69
Capitate fractures, 580
Capitellum fractures, 609, 610f
clinical and radiographic features of, 609
complications of, 609
management of, 609
pathophysiology of, 609
Capitolunate angle, 574-575, 575f
Capnocytophaga canimorsus infection, 786, 788
prophylactic antibiotics for, 789-790, 789t
Capnography, 53, 53b, 62-64
in asthma, 954
in bronchospasm, 64, 64f
normal, 63, 63f-64f
Capnometry, 53
Capreomycin, 1822t-1823t
Capsicum annum, 2067
Captopril, 1122.e1t-1122.e2t
Caput medusae, 1193
Caput succedaneum, 312-313
Car seats, 336
Carbamate insecticides, 2057-2060
Carbamate poisoning
antidotes for, 1957t-1958t
clinical features of, 2057-2058
complications of, 2057-2058
diagnostic strategies for, 2058
differential diagnosis of, 2058
management of, 2058-2059
patient disposition in, 2059-2060
signs and symptoms of, 2057
Carbamazepine (Tegretol)
adverse effects of, 1383t
for children, 2240t
for diabetic distal symmetrical polyneuropathy, 1432
extended-release (Carbatrol), 2240t, 2407t-2408t
hepatic injury, 1197t
for long-term anticonvulsant therapy, 1384t
side effects and drug interactions, 2407t-2408t
for trigeminal neuralgia, 1409
Carbapenems, 2361t
Carbatrol (extended-release carbamazepine)
for children, 2240t
side effects and drug interactions, 2407t-2408t
Carbohydrate-deficient transferrin (desialotransferrin), 2379t
Carbohydrates, 2387
Carbolic acid (phenol), 822
Carbon dioxide (CO_2), 2037t
end-tidal, 7, 7f, 62-65
partial pressure ($Paco_2$)
in asthma, 947
end-tidal ($PETco_2$), 90-91, 91f, 947
in pregnancy, 297
total concentration, 1629
Carbon monoxide (CO), 2037t, 2041
Carbon monoxide (CO) poisoning, 2041-2043
at altitude, 1938
clinical features of, 2041
contaminated air, 1919
diagnostic strategies for, 2042
differential diagnosis of, 174t, 2042
key concepts, 2043b
management of, 2042
metabolic acidosis in, 1632
oxygen therapy for, 1925
patient disposition in, 2043
risk factors for potentially catastrophic illness, 172b

www.ketabpezeshki.com 66485457-66963820

Carbon monoxide (CO) poisoning *(Continued)*
simultaneous with cyanide poisoning, 2042-2043
vomiting with, 243t-244t
Carbonic anhydrase inhibitors, 930t
Carbonyl, 825
Carbuncles, 1564, 1859
Carcinoma. *See* Cancer
Cardiac albumin, 1019
Cardiac arrest
algorithm for, 93f
in anaphylaxis, 1552t
clinical features of, 88-97, 99-100
epidemiology of, 88
etiology of, 88, 89t
extracorporeal circulatory support during, 105
goal-directed postarrest treatment algorithm, 96f
history in, 89
induced hypothermia after, 85, 85b
low-flow phase (resuscitation), 100
management of, 88-97, 93f, 100-105
maternal, 2271, 2278
neurologic recovery after, 81-87
no-flow phase (untreated cardiac arrest), 99-100
pediatric, 98-105
epidemiology of, 98
outcomes after, 99t
pathophysiology of, 98-99
penetrating traumatic, 448b
phases of, 99-100
physical examination findings indicating causes of, 90t
physical examination goals in, 89
physiology of, 98
post–cardiac arrest syndrome, 81, 95-97, 100
postresuscitation phase, 100
prearrest phase, 99
principles of disease, 88
resuscitation after, 92-95, 97b, 1032
untreated (no-flow phase), 99-100
Cardiac auscultation, in children, 2142-2143
Cardiac conduction, 1034-1035
Cardiac conduction velocities, 1037t
Cardiac disorders
air medical transport for, 2447
altitude and, 1938-1939
anxiety in, 1476
in children
history taking in, 2141, 2141b
key concepts, 2167b
key elements to elicit in history of, 2141b
physical examination findings, 2142-2145
signs and symptoms of, 2140b
congenital defects, 2104-2105
after head injury, 360
pediatric, 2139-2167
in pregnancy, 2304-2306
suspect for bacterial endocarditis, 2158b
valvular disease, 1109-1112
and heart failure, 1078
in pregnancy, 2301t-2303t, 2305-2306
Cardiac enzymes, 445
Cardiac evaluation, pediatric, 2140-2145
Cardiac glycosides, 1088
Cardiac hypertrophy, 1079
Cardiac index, normal, 1076
Cardiac injury, 447-448
blunt trauma, 444
in children, 320
clinical features of, 448
management of, 448
penetrating, 448
Cardiac markers
in acute coronary syndrome, 1019
multiple marker strategies, 1019-1020
Cardiac monitoring
in asthma, 948
in COPD, 959-960
Cardiac outflow obstruction, 139t
Cardiac output, 1077-1078, 2139
Cardiac pacing
biventricular, 1073, 1074f
normal, 1066-1067, 1066f
Cardiac physiology, 1076-1078
Cardiac preload, 1869-1870
Cardiac resynchronization therapy, 1073, 1088
Cardiac tamponade, 1095-1096
in children, 320
diagnosis of, 94t, 1095-1096
etiology of, 1095
key concepts, 1105b
management of, 1096
neoplastic, 1625-1627
ancillary evaluation of, 1627
clinical features of, 1626
etiology of, 1625-1626
key concepts, 1628b
management of, 1627
pathophysiology of, 1626
physical evaluation of, 1626b
pathophysiology of, 1095
prognosis for, 1096
symptoms and signs of, 1095
treatment of, 94t
Cardiac troponins, 1098-1099
Cardioactive steroid overdose, 1982-1986
Cardiogenic shock, 69, 1002
acute MI with, 74
clinical management guidelines, 73b
definition and diagnostic criteria for, 70, 70b
reperfusion therapy in, 1032
treatment of, 74
Cardiomyopathy, 1101-1104, 1101b
dilated, 1101-1102
and heart failure, 1078
hypertrophic, 1102-1103, 1105b
ischemic, 1078
key concepts, 1105b
peripartum, 1103-1104, 2350
restrictive, 1097, 1103
stress, 1104
Takotsubo, 1104
Cardiopulmonary arrest
definition of, 89
management algorithm for infants and children, 103f
Cardiopulmonary bypass, 1894, 1894t
Cardiopulmonary resuscitation
advanced life support medications during, 102
cerebral perfusion pressure during, 100, 101f
in cerebral resuscitation, 81
closed-chest, 81-82
compression-only (“hands-only”), 102
compression-ventilation (standard), 102
compressions during, 100-101
cough CPR, 92-93
extracorporeal, 105
and fibrinolytic therapy, 1029
guidelines for, e50
for hypothermia, 1890
indicators of inadequate blood flow during, 90t
in infants, 100, 101f
key concepts, 97b
low-flow phase, 102
monitoring during, 89-92
no-CPR directives, e49
pediatric, 98-105
real-time feedback, 102
resuscitation during, 92-95
Cardiothoracic injury, pediatric, 318-320
Cardiovascular drugs, 2440
overdose, 1982-1993, 1993b
in pregnancy, 2326-2328
pretreatment agents for RSI, 11b
Cardiovascular support
interventions, 2439-2440
out-of-hospital care, 2439-2440
Cardiovascular system
in AIDS, 1757-1764
in anaphylaxis, 1551
in children, 2087-2088
in chronic kidney disease, 1302
compensatory responses, 2139-2140
electrical injury to, 1910
in hypothermia, 1884-1885, 1890
lightning injury to, 1910
in pregnancy, 296
in sepsis, 1871
Cardiovascular trauma, 444-455
Cardioversion
for atrial fibrillation and flutter, 1052b
electrical
for heart failure, 1088
for pacemaker malfunction, 1071
for pediatric dysrhythmias, 2154b
Carditis, Lyme disease–related, 1100
Cardozo, Benjamin, e40
Caregivers, 890
risk factors for elder abuse, 887b
Carnitine
for thyroid storm, 1682b, 1683
for valproic acid toxicity, 1957t-1958t
Carotid artery dissection, 1392-1393
clinical presentation of, 1393
diagnosis and treatment of, 1393
MRI findings, 1393, 1393f
Carotid pulses
parvus, 1111
tardus, 1111
Carotid sinus massage, 1986
Carotid sinus sensitivity, 139t
Carpal or Gilula’s arcs, 571-574, 574f
Carpal dislocation, 580-581, 580f
Carpal injuries, 576-583
Carpal instability, 580-582
Carpal tunnel, 534-535
Carpal tunnel syndrome, 588-589, 1436-1437
acute, 589
conditions associated with, 1436b
Carpometacarpal joint, 534, 555, 555f
injuries to
in fingers, 555
in thumb, 556
Carpus, 570
Carrying angle, 598, 598f-599f
Carukia barnesi, 806
Carvedilol, 1987t, 1122.e1t-1122.e2t
CAS No. 505-60-2, 825
Cassell, Eric, e49
CAST fracture (childhood accidental spiral tibial fracture), 852
Castleman’s disease, 1730
Casts, 531-532
Casualties. *See also* Tactical combat casualty care
catastrophic management of, 2461-2462
multiple-casualty triage, 2459-2461
psychogenic, 2461-2462
Cat bites, 786-787
bacteriology of, 786
epidemiology of, 785
guidelines for, 788-789
key concepts, 793b
management of, 764
prophylactic antibiotics for, 789t, 790
recommendations for closure and prophylactic antibiotics, 789t
risk factors for infection, 788t
Cat-scratch disease, 1863
Cat valium, 2019
Cataracts, 915
Catastrophes, 2457, 2458f
casualty management in, 2461-2462
disasters, 2465
physician response to risky situations, e44-e45
Catatonic behavior, 1461
Category A (high threat) agents, 2471-2472
Catheter-associated urinary tract infections (CAUTIs), 1330
Catheters
balloon-tipped
removal of esophageal foreign bodies with, 778
removal of otic or nasal foreign bodies with, 770, 770f
bladder, 2412
central lines, 2412
emergencies, 2411, 2411t
infection of, 1156b
long-term, 1153-1156
problems and solutions, 2405t
US-guided insertion of, 2501-2502, 2501f-2502f
feeding, 2405t
Fogarty catheter thrombectomy, 1143

www.ketabpezeshki.com 66485457-66963820

Catheters *(Continued)*
Foley, 480-481
removal of rectal foreign bodies with, 1288, 1289f
size estimates for pediatric trauma, 307b
suprapubic placement of, 483-484, 484f
in urethral trauma, 482
Groshong, 1155, 1155f
Hickman-Broviac, 1153-1155
double-lumen, 1153, 1153f
infections, 1155
laceration of, 1154
occlusion of, 1153-1154
indwelling, occluded, 1153-1154, 1153b, 1154f, 2410-2412
intravenous
infected, 1872t
US-guided placement, 2502
placement of
in men, 1335
in urethral trauma, 482, 482f
pulmonary artery, 1083
Quinton-Mahurkar, 1153, 1153f, 1155
Tenckhoff, 1306-1307
types of, 2412
urethral, in children, 2211
urinary, infected, 1330
for urinary retention, 1351-1352, 1351f
Word, 1314, 1857-1858, 1858f
Cattle bites, 787
Cauda equina, 1422
Cauda equina syndrome, 1421-1422, 1421t
acute, 401
acute back pain in, 282t-283t
low back pain in, 647
management of, 652-653
rapid assessment and stabilization of, 279
Cauliflower ear, 378
Causalgia, 523-524, 748
Caustic chemicals, 1994, 1995t
Caustic injury, 1994-1998
clinical features of, 1996, 1996f
diagnostic strategies for, 1996-1997
esophageal burns, 456, 1995, 1995f
esophagitis, 1174
clinical features of, 1174
management of, 1175
gastric necrosis due to, 1995, 1995f
gastrointestinal, 1997
grades of, 1996
keratoconjunctivitis, 193t-196t
key concepts, 1998b
lip burns, 1996, 1996f
management of, 1997
patient disposition in, 1997
Cavitary lesions, 1818
Cavitation, 421
CBRNE weapons, 2469
CD4 T lymphocytes (helper cells), 2357
CD8 T lymphocytes (suppressor cells), 2357
CDC. *See* Centers for Disease Control and Prevention
CDC Health Information for International Travel (Yellow Book), 1260
Cecal volvulus, 1267
clinical features of, 1267
diagnostic strategies for, 1267-1268
management of, 1269
radiographic findings, 1267-1268, 1268f
Cederroth Eye Wash, 910
Cefaclor, 2318t-2321t
Cefadroxil, 2318t-2321t
Cefazolin
for infective endocarditis prophylaxis, 2160t
in pregnancy and lactation, 2318t-2321t
for skin and soft tissue infection, 1855
Cefdinir, 933-934, 2318t-2321t
Cefepime
for fever and neutropenia in children, 2104
in immunocompromised patients, 2361t
for pneumococcemia, 1709
for pneumonia, 985t
Cefixime
for infectious diarrhea, 2192t-2193t
for STDs after sexual assault, 851t, 868b
Cefoperazone, 2390t
Cefotaxime
for acute bacterial meningitis, 2230t
for gonococcal dermatitis, 1566
for infectious diarrhea, 2192t-2193t
for Lyme disease, 1794
for mastoiditis, 936
for meningococcemia, 1713
for pneumococcemia, 1709
for pneumonia, 984-985, 985t
in pregnancy and lactation, 2318t-2321t
for septic arthritis, 2265t
for sexually transmitted diseases, 1315t
Cefotetan, 1325t
Cefoxitin, 1325t, 2318t-2321t
Cefpodoxime
for otitis media, 933-934
for pneumonia, 984, 984t
in pregnancy and lactation, 2318t-2321t
Cefprozil, 2318t-2321t
Ceftaroline, 984-985, 985t
Ceftazidime
for fever and neutropenia in children, 2104
in immunocompromised patients, 2361t
for malignant otitis externa, 1664t
for post-traumatic endophthalmitis, 915, 918
in pregnancy and lactation, 2318t-2321t
for *V. vulnificus* infection, 1246
Ceftin, 789t
Ceftizoxime
for gonococcal dermatitis, 1566
in pregnancy and lactation, 2318t-2321t
for sexually transmitted diseases, 1315t
Ceftriaxone
for bacterial conjunctivitis, 918-919
for chancroid, 1318
for diarrhea in AIDS, 1257t
for epididymitis, 1347t
for epididymitis in children, 2208
for fever and neutropenia in children, 2104
for gonococcal dermatitis, 1566
for gonorrhea, 1321
in HIV-positive patients, 1285
for infectious diarrhea, 2192t-2193t
for infective endocarditis prophylaxis, 2160t
for Lyme disease, 1100, 1438, 1793-1794, 1794t
for mastoiditis, 936
for meningitis chemoprophylaxis, 1458
for meningococcemia, 1713-1714
for otitis media, 933-934
for pelvic inflammatory disease, 1325t
for pharyngitis, 968
for pneumococcemia, 1709
for pneumonia, 984-986, 985t
in pregnancy and lactation, 2318t-2321t
for prostatitis, 1336
for septic arthritis, 2265t
for STDs, 1315t
for STDs after sexual assault, 851t, 868b
Cefuroxime
for Lyme disease, 1794t
for otitis media, 933-934
in pregnancy and lactation, 2318t-2321t
Celestone Soluspan (betamethasone sodium phosphate and acetate), 639t
Cell death, ischemic, 1022-1024
Cell-mediated delayed hypersensitivity, 1545b
Cell-mediated immunity, 2357-2358
impaired, 2363-2364
Cell stimulation therapy, 2362
Cellular oxygenation, pediatric, 108-109
Cellulitis, 1566, 1582f, 1831, 1853-1855
clinical features of, 1853
diagnostic strategies for, 1853-1854
differential considerations, 1853-1854
facial, 1566f
initial antibiotic management of, 1872t
key concepts, 1863b
management of, 1854-1855
orbital, 193t-196t
patient disposition in, 1855
periorbital, 193t-196t
peritonsillar, 202, 971-972
preseptal, 921
sonographic, 2499, 2499f
Cement, 822
Centerfile rifle wounds, 833-834, 836f
Centers for Disease Control and Prevention (CDC), 2452-2453, 2467
Category A (high threat) agents, 2471-2472
CDC Health Information for International Travel (Yellow Book), 1260
contact information, 1312, 1707, 2439t, 2458t, 2470t
Data Elements for Emergency Department Systems, 335
definition of intimate partner violence, 872
definition of Lyme arthritis, 1847
definition of tetanus, 1702
definition of toxic shock syndrome, 2104b
Emergency Operations Center, 1445, 1695
Field Triage Decision Scheme, 287-288, 337
"Heads UP" tool kits, 354
Injury Research Agenda, 331
National Center for Injury Prevention and Control (NCIP), 331
recommendations for HIV testing, 1764b
recommendations for pneumococcal vaccine, 1710b
Strategic National Stockpile, 2465, 2467
Travelers' Health website, 1260
Centers for Medicare and Medicaid Services (CMS), 2445, e61
Centipede bites, 805
Centor criteria, 967, 967b
Central cord syndrome, 400, 402f, 1420, 1421t
in older adults, 328
Central integrative area, 1897
Central lines. *See* Central venous catheters
Central log, e64
Central nervous system
degenerative disease of, 1379
in drowning, 1942
in hypothermia, 1885
infections of, 1447-1459
assessment of, 1456
chemoprophylaxis for, 1458
clinical features of, 1449-1451
complications of, 1450-1451
definitions, 1447
diagnostic strategies for, 1451-1455
differential considerations, 1455-1456
epidemiology of, 1447-1448
etiology of, 1448-1449
after head injury, 359-360
with HIV coinfection, 1761-1762, 1762t
immunoprophylaxis of, 1458
investigations in, 1455
key concepts, 1459b
management of, 1456-1458
neuroimaging techniques for, 1455
pathophysiology of, 1449
patient disposition in, 1458
stabilization of, 1456
symptoms and signs of, 1449-1450
therapy for, 1456-1458
lymphoma of, 1761, 1762t
neurohormonal response to heart failure, 1079
paradoxical acidosis of, 1634
in tuberculosis, 1820-1821
Central retinal artery occlusion, 184, 186f, 923, 923f
Central retinal vein occlusion, 923-925, 924f
Central sensitization, 34
Central transtentorial herniation, 344-345
Central venous catheters, 2412
complications of, 2412
emergencies, 2411, 2411t
infection of, 1156b
long-term, 1153-1156
problems and solutions for, 2405t
site problems, 2405t
US-guided insertion, 2501-2502, 2501f-2502f
Centruroides sculpturatus, formerly *Centruroides exilicauda* (Arizona bark scorpion), 805, 805f
Cephalexin
for diabetic foot ulcers, 1664
for epistaxis, 938-939
for infective endocarditis prophylaxis, 2160t
in pregnancy and lactation, 2318t-2321t

www.ketabpezeshki.com 66485457-66963820

Cephalexin *(Continued)*
for skin and soft tissue infection, 1854t, 1855
for staphylococcal scalded skin syndrome, 1567
Cephalgia, coital, 1396-1397
Cephalic tetanus, 1701-1702
Cephalohematoma, 312-313
Cephalosporin
for bone and joint infection, 1835t
in immunocompromised patients, 2361t
for nonclostridial gas gangrene, 1664t
in pregnancy, 2318t-2321t, 2324
for *V. vulnificus* infection, 1246
CeraVe, 1563
Cerebellar degeneration, alcoholic, 2386-2387
Cerebellar gait, 165
Cerebellar hemorrhage, 166t-167t, 167f-168f
Cerebellotonsillar herniation, 345
Cerebral aneurysms, 1390-1391, 1390t, 1391f
Cerebral blood pressure autoregulation curve, 1118-1119, 1120f
Cerebral contusions, 363
pediatric, 313
Cerebral edema, 343
in aspirin overdose, 1965-1966
after head injury, 343-344, 344f
high-altitude (HACE), 1928
Cerebral function monitoring, 65
Cerebral hemodynamics, 340-342
Cerebral herniation, 344, 345f
Cerebral ischemia
clinical outcomes, 86
management of, 81-86
pathophysiology of, 81, 82f-83f
Cerebral malaria, 1776-1777
clinical features of, 1776-1777
management of, 1777
Cerebral oximetry, 65
Cerebral palsy, 2404-2405
Cerebral perfusion pressure (CPP), 342
in CPR, 100, 101f
estimation of, 312, 342
in pediatric trauma, 312-313
Cerebral resuscitation. *See* Brain resuscitation
Cerebral vascular accidents, 1476-1477
Cerebral venous sinus thrombosis, 1393-1394
clinical presentation of, 1393
diagnostic evaluation of, 1393
treatment of, 1393-1394
Cerebral venous thrombosis, 1414-1415
clinical features of, 1414
diagnostic strategies for, 1414-1415
differential considerations, 1415
key concepts, 1417b-1418b
management of, 1415
patient disposition in, 1415
Cerebritis, SLE or lupus, 1528
Cerebrospinal fever, epidemic, 1710
Cerebrospinal fluid, 340-342
Cerebrospinal fluid analysis, 1452-1455, 1453t
antigen detection, 1454-1455
bacteriologic cultures, 1455
cell count, 1453, 1453t
in children, 2227-2228
collection of fluid for, 1452
glucose levels, 1454
in headache assessment, 172, 173t
India ink staining, 1454, 1454f
lactic acid levels, 1454
normal pressure, 340, 1452
protein levels, 1454
tests, 1455
turbidity, 1452-1453
Cerebrospinal fluid infection, 1872t
Cerebrospinal fluid shunts, 2405t
Cerebyx (fosphenytoin), 2408-2409
Certec bags, 1935f
Cervical extension-distraction injury, 328
Cervical rib syndrome, 1150
Cervical spine
imaging of
Canadian C-spine rule for, 293
Hanson's high-risk criteria for, 293
NEXUS criteria for, 293
pediatric, 316-317
in neck injury, 424-425
Cervical spine *(Continued)*
normal structural relationships, 407f-408f
pediatric, 315-316, 315b
radiography of, 403-407, 404f-406f
anteroposterior view, 404f-405f, 407, 408f-409f
cross-table lateral view, 403-407
flexion and extension views, 407
oblique views, 407, 409f-410f
odontoid view, 403-407, 406f
stabilization of
in neck injury, 423
in pediatric trauma, 305-306
Cervical spine injury
airway management in, 17
approach to, 418f
extension injuries, 401, 402f
fractures, 317
in older adults, 326
pediatric trauma, 310, 317
Cervical sprain, 420
Cervicogenic headache, 1396
Cesarean delivery, 2271
perimortem, 303-304
Cestodes, 1770t-1771t
Cetaphil, 1563
Cetirizine (Zyrtec), 1247, 1569
Chadwick's sign, 2273, 2332
Chagas' disease *(Trypanosoma cruzi)*, 1099, 1776, 1781-1782
clinical features of, 1781-1782
diagnostic strategies for, 1782
drug regimens for, 1772t-1775t
management of, 1782
Chalazion, 193t-196t, 920-921, 921f
CHAMP mnemonic, 2034
Chance's fracture, 512t-513t
Chancroid *(Haemophilus ducreyi)*, 1286t, 1318, 1318f
diagnosis of, 1318
treatment of, 1286, 1315t, 1318
Charles' law, 1916, 1916t, 1917f, 2442
Charley horse, 1157
"Chasing the dragon," 2053
Chauffeur's fracture, 512t-513t, 585-586
Cheeks, 377
Chelation therapy
agents, 1952
for lead poisoning, 2027-2028, 2028t
for mercury poisoning, 2031
Chemet (dimercaptosuccinic acid, DMSA), 2027-2028
Chemical analysis
in abdominal trauma, 464
in sepsis, 1868
serum tests, 1292
urine tests, 1292
Chemical/Biological Hotline (National Response Center), 1952-1953
Chemical injuries, 818-827
anhydrous ammonia, 821-822
aplastic anemia, 1593t
cement, 822
community preparedness for, 818-819
corneal burns, 910, 911f
elemental metals, 824
to eye, 910, 911f
formic acid, 821
hydrocarbons, 823-824
hydrofluoric acid (HF), 820-821
hydrotherapy for, 819
key concepts, 827b
management of, 819-825
miscellaneous gases, 824-825
miscellaneous irritants, solvents, detergents, and glues, 910-912
nitrates, 823
nitrites, 823
ocular, 819-820
pathophysiology of, 818
phenol and derivatives, 822
phosphorus, 822-823
preparedness for, 2476, 2476b
tar, 824
in urban search and rescue, 2456
vaginitis, 1323
Chemical injuries *(Continued)*
weapons or agents, 825, 2476-2478
classification of, 825
key concepts, 827b, 2478b
Chemical restraints, 2416-2418
Chemical terrorism, 825-827, 2466
Chemical Transportation Emergency Center (CHEMTREC), 818
Chemotherapy, antiviral, 1720-1725
Chemotherapy-related nausea and vomiting, 246
Cherenkov radiation, 1946
Chernobyl, 1945-1946
Chest, flail, 433-434, 433f-434f
Chest assessment, pediatric, 310
Chest compression rate, 100-101
Chest compressions
circumferential vs focal sternal, 100
compression-only ("hands-only") CPR, 102
compression-ventilation (standard) CPR, 102
in CPR, 100
hand-thumbs encircling technique for infants, 100, 101f
for neonates, 116-117
two-thumb circumferential, 100, 101f
Chest compression–ventilation ratios, 101-102, 101t
Chest computed tomography
in aortic tears, 453, 453f
in blunt aortic injury, 453-454, 453f
in hemothorax, 440-441, 441f-442f
in pneumothorax, 991
in pulmonary contusion, 436, 436f
in rib fracture, 432, 432f
Chest injury. *See* Thoracic trauma
Chest pain, 214-222
admission criteria for, 2004b
ancillary testing in, 216-222, 218t
causes, workup, and treatment of, 1529t
central, 220t-221t
cocaine-related, 2003-2004, 2003b-2004b
critical diagnoses, 215f
diagnosis of, 214-222, 220t-221t
in dialysis, 1309
differential diagnosis of, 214, 215t, 220t-221t
key entities in, 1001t
epidemiology of, 214
evaluation of, 2483-2484
guidelines for management of, 219f, 222f
history taking in, 214-216
initial assessment of, 215f
ischemic, 218t
management of, 222
musculoskeletal, in SLE, 1530
observational approach to, 2483-2484, 2483b
pathophysiology of, 214
patient disposition in, 222
pediatric, 2141-2142
physical examination findings, 216
pivotal findings, 214-222, 217t-218t
pleuritic, 1532t
potentially catastrophic illnesses manifesting with, 220t-221t
in pregnancy, 2277
rapid assessment and stabilization of, 214
risk factors associated with potentially catastrophic causes, 216b
significant symptoms, 216t
traditional approach to, 2483
Chest pain centers (CPCs), 1021-1022
Chest pain units, 2481
Chest radiography
in acute coronary syndrome, 1016, 1017f
in aortic dissection, 1126
in blunt aortic injury, 452-453, 452f
in chest pain, 216-218, 217t-218t
in COPD, 959
in pacemaker malfunction, 1071
in pediatric asthma, 2118
in pediatric cardiac disorders, 2143-2145, 2144f
in pediatric fever, 2099
Chest trauma
blunt
ED thoracotomy for, 295f
indications for thoracotomy for, 448b
observational approach to, 2486-2487

www.ketabpezeshki.com 66485457-66963820

Chest trauma *(Continued)*
pediatric, 318-319
traditional approach to, 2486
penetrating
ED thoracotomy for, 294f
observational approach to, 2487
pediatric, 318
traditional approach to, 2487
Chest tube (tube thoracostomy)
for hemothorax, 441
indications for, 439-440, 439b
misplaced, 441-442, 442f
size estimates for pediatric trauma, 307b
Chest wall, 431
Chest wall injury, 431
clinical features of, 431
epidemiology of, 431
pathophysiology of, 431
Chi-square test, e13-e14, e13t
Chiasmal visual loss, 927
Chickenpox (varicella), 1578-1579, 1578f, 1728f
bullous, 1578f
clinical features of, 1728-1729, 1728f
diagnostic strategies for, 1729
differentiation from smallpox, 1580t
drugs for, 1721t-1722t
management of, 1729
patient disposition in, 1729
Chikungunya virus, 1513t
Child abuse, 845-854, 2094
clinical features of, 849-850
definition of, 845
epidemiology of, 845
historical features of, 2095b
history of, 862
incidence of, 846t
key concepts, 854b
management of, 853
medical abuse, 845
patient disposition in, 853
physical abuse, 845-848
burns, 846f-847f
definition of, 845
diagnostic strategies for, 850-851
differential considerations, 851-852
fractures associated with, 847-848, 847f-848f, 847t, 2259
incidence of, 846t
patterned injuries, 845
signs and symptoms of, 849-850, 849f
physical examination and radiologic findings, 2095b
psychological maltreatment, 846t
sexual abuse, 845, 849
diagnostic strategies for, 851
differential considerations, 852
incidence of, 846t
signs and symptoms of, 850
signs and symptoms of, 849-850
Child neglect, e75
Children. *See also* Adolescents; Infants; Neonates
acute life-threatening events (ALTEs), 109-110
AIDS in, 2104
air medical transport of, 2447
airway management in, 108, 2087
equipment for, 109
airway structures, 108
anatomic differences, 98-99, 306b
anticonvulsant therapy for, 2238-2239
appendicitis in, 1226
asthma in, 941, 942f, 2117-2124
back pain in, 645, 648, 653
bacterial illness in, 2102
biliary colic in, 1201
blood pressure limits in, 2219t
bronchiolitis in, 2124-2128
burns in, 846-847
car seats for, 336, 369
cardiac arrest in, 98-105
cardiac disorders in, 2139-2167, 2140b
cardiac evaluation in, 2140
cardiopulmonary arrest in, 103f
cardiopulmonary resuscitation in, 98-105
cardiovascular system in, 2087-2088
cellular oxygenation, 108-109
Children *(Continued)*
chest compression–ventilation ratios for, 101-102, 101t
chest radiography in, 2143-2145, 2144f
cholecystitis in, 1203
congenital heart disease in, 2104-2105
dehydration in, 2198-2203
demographics, e1
depression in, 1469
development of, 2088-2090, 2089t
diarrhea in
causes of, 2189, 2189t, 2192t-2193t
management of, 259
parent instruction sheet for, 2198b
emergency ultrasound for, 1228
endocarditis in, 2159-2160
endotracheal intubation in
indications for, 306
special considerations, 306
episodic disorders that may mimic seizures in, 2233b
evaluation of, 2090-2092
exposure to violence, e1
febrile, 2099-2100
febrile seizures in, 2102-2103
femoral anatomy, 693
fever in, 2096-2105
fluid requirements, 814
fluid resuscitation in, 106-107, 814
gait evaluation in, 694
gastrointestinal disorders in, 2168-2187
general approach to, 2087-2095
genitourinary disorders in, 2205-2223
Glasgow Coma Scale modified for, 309t
headaches in, 2239-2244
heart murmurs in, 2142, 2142b-2143b
herpes encephalitis in, 2236
hip anatomy, 693
hip pain in, 2263-2269
hospitalization of, 2093t
hyperbilirubinemia in, 2168, 2169t
immunologic system in, 2088
increased ICP in, 312, 312b
infectious diarrheal disease and dehydration in, 2188-2204
intubation in, 17-18, 108
equipment considerations, 109
medications for, 109
Kawasaki disease (mucocutaneous lymph node syndrome) in, 2103
key concepts, 2095b
laryngoscopy in, 108
lateral condyle fractures in, 608
with limp, 694-697
lower airway in, 2117
lower airway obstruction in, 2091-2092, 2092f, 2117-2128
lumbar puncture in, 2226-2227
lung, 108
lung disease in, 2129-2138
media violence effects on, e1-e2
meningitis in, 2225t, 2226
musculoskeletal disorders in, 2250-2270
musculoskeletal system in, 2088, 2250
nausea and vomiting in, 243-245, 245t
normal vital signs, 2088t
osteomyelitis in, 1840-1841
otitis-prone, 932
pain management in, 48
pathophysiology in, 2087-2088
penile disorders in, 2205-2208
peptic ulcer disease in, 1179
petechiae in, 2103
pharmacology in, 2088
plants, mushrooms, herbal products exposure, unintentional, 2066
pneumonia in
antimicrobial treatment of, 984-985, 985t
outpatient treatment of, 984, 984t
prehospital care of, 109
procedural sedation and analgesia for, 55t, 60
drug selection strategies, 60t
red and painful eye in, 193-196
renal tract disorders in, 2205-2223
rescue devices for, 109
Children *(Continued)*
respiratory failure in, 108-109
clinical features of, 108-109
management considerations, 109
pathophysiologic principles, 108
respiratory mechanics, 108
respiratory physiology, 108-109
resuscitation of, 98-111, 2159
in dysrhythmias, 2154b
key concepts, 111b
medications used in, 104t
recommended chest compression–ventilation ratios for, 101-102, 101t
risks in intimate partner violence homes, 874
school-age, 2090
UTIs in, 1333t, 1334
seizures in, 156, 1375
septic arthritis in, 1846
septic shock in, 105-108, 107f
shock in, 106t
street gang violence and, e4
stroke volume in, decreased, 2139-2140, 2140b
substance use among, e2
suicide rate, 1492
syncope in, 2248-2249
temperature regulation in, 2087
tetanus in, 1703
top ED diagnoses in, 2093t
toxic appearance of, 2226
toxic shock syndrome in, 2103
trauma to. *See* Pediatric trauma
tuberculosis in, 1826, 1826b
upper airway disease in, 2106
upper airway obstruction in, 2106-2116
urinary tract infections in, 1332-1335
management of, 2212-2213
screening for, 1334f
urine samples from, 2211
vaccine-preventable infections in, 1723-1725
ventricular fibrillation in, 102-104
ventricular tachycardia in, 102-104
ventriculoperitoneal shunts in, 2105
vomiting in
causes of, 2189, 2189t
differential considerations for, 2172t
parent instruction sheet for, 2198b
Children with special health care needs, 2093-2094
definition of, 2400
Emergency Information Form (EIF) for, 2094
general issues for, 2401
key concepts, 2413b
Children's Hospital of Eastern Ontario Pain Scale (CHEOPS), 37
Chinese liver fluke *(Clonorchis sinensis)*, 1770t-1775t
Chironex fleckeri (box jellyfish), 806
Chlamydia pneumoniae pharyngitis, 965-966, 968
Chlamydia trachomatis infection, 1320
anorectal, 1286t
in otitis media, 932
in pregnancy, 2298
Chlamydial infection, 1320
anorectal, 1286t
conjunctivitis
management algorithm for, 193t-196t
in pneumonia, 978
pharyngitis
clinical features of, 966
diagnosis of, 967
treatment of, 968
pneumonia
in children, 2132-2133, 2135t
radiographic findings, 2132-2133, 2133f
treatment of, 1285, 1315t
Chlamydophila, 978
Chlamydophila pneumoniae, 978
Chloral hydrate, 2081
Chloral hydrate poisoning
clinical features of, 2081
management of, 2081
odor in, 1955t
Chloramine, 824, 2037t
Chloramine exposure, 824
Chloramphenicol
for bone and joint infection, 1835t
for Lyme disease, 1794t

www.ketabpezeshki.com 66485457-66963820

Chloramphenicol *(Continued)*
for meningococcemia, 1713
for plague, 2475b
in pregnancy, 2324
in pregnancy and lactation, 2318t-2321t
for Rocky Mountain spotted fever, 1802t
Chlordiazepoxide (Librium), 2078t
Chloride deficits, 1657t
Chlorinated hydrocarbon insecticides, 2060-2061
Chlorinated hydrocarbon poisoning
clinical features of, 2060
diagnostic strategies for, 2060
differential considerations, 2061
management of, 2061
odor in, 1955t
patient disposition in, 2061
signs and symptoms of, 2060
Chlorine, 824-825, 825t, 2037t, 2469, 2478
Chloroacetophenone (CN), 2037t
Chlorobenzylidene malononitrile (CS), 2037t
Chlorophenoxy compound poisoning
clinical features of, 2062
diagnostic strategies for, 2062
differential considerations, 2062
management of, 2062
patient disposition in, 2062
Chlorophenoxy compounds, 2062
Chloropicrin, 825t
Chloroquine hydrochloride, 1772t-1775t
Chloroquine phosphate (Aralen), 1770t, 1772t-1775t
Chlorothiazide, 1122.e1t-1122.e2t
Chlorpromazine (Thorazine), 2047, 2048t
for chemical restraint, 2417
hepatic injury, 1197t
Chlorpropamide, 2072t-2073t
Chlorprothixene, 2048t
Chlorthalidone, 1122.e1t-1122.e2t
Choanal atresia, 115, 2109
Chokes, 1921
Choking agents, 825
foreign bodies, 2115-2116
gases that can be encountered as WMDs, 825t
Cholangiography, percutaneous transhepatic, 1203
Cholangiopancreatography
endoscopic retrograde (ERCP), 1203
magnetic resonance (MRCP), 1211
Cholangiopathy, AIDS, 1204
Cholangitis, 1203-1204
clinical features of, 1203
differential considerations, 1203-1204
key concepts, 1204b
management of, 1204
pathogenesis of, 1203
patient disposition in, 1204
sclerosing, 1204
ultrasound imaging of, 1202f, 1203
Cholecystitis, 1201-1203
acalculous, 1203
acute, 1201
in children, 1203
clinical features of, 1202
differential considerations, 1202
emphysematous, 1203
incidence of, 1201
key concepts, 1203b
management of, 1202-1203
patient disposition in, 1203
risk factors for, 1201
Cholelithiasis, 1200-1201
clinical features of, 1200-1201
diagnostic strategies for, 1201
differential considerations, 1201
key concepts, 2187b
management of, 1201
in pregnancy, 1201, 2295
Cholera, 1245-1246
Cholestasis, intrahepatic, of pregnancy, 2296
Cholesterol stones, 1200, 2186
Cholestyramine, 1682b
Cholinergic syndrome, 1956, 2419t
Cholinesterase inhibitors, 1444
Chondrocalcinosis, 1510f
Chopart's joint, 734, 735f, 740-741
Chorea, 1109
Choreoathetosis, paroxysmal, 2233
Chorioamnionitis, 2341, 2341b
in pregnancy, 2298-2299
Christmas disease (hemophilia B), 1615
Christmas tree adapters, 483-484, 483f
Chronic disease
anemia of, 1591
in pregnancy, 2300-2315, 2301t-2303t, 2315b
and suicide, 1495
Chronic kidney disease, 1301-1311
causes of, 1302b-1304b, 1303-1304
clinical features of, 1302-1303
definition of, 1301
dermatologic features of, 1302-1303
diagnostic strategies for, 1303-1304
hematologic effects of, 1303
immunologic considerations, 1303
key concepts, 1311b
management of, 1304-1311
neurologic features of, 1302
pulmonary effects of, 1302
reversible factors, 1304, 1304b
Chronic lung disease, of infancy, 2138
Chronic obstructive pulmonary disease (COPD), 956-964
acute exacerbations of, 957-958
causes of, 961b
therapeutic guidelines for, 961t
ventilatory management of, 29
classification of severity of, 957, 957t
clinical features of, 958
definition of, 956
diagnostic strategies for, 959-960
differential considerations, 960-961
drug therapy for, 962-963
at end of life, e58
guidelines for patient admission, 964b
and heart failure, 1078
key concepts, 964b
life-threatening, 961t
management of, 961-964
mild
classification of, 957t
therapeutic guidelines for, 961t
moderate
classification of, 957t
therapeutic guidelines for, 961t
natural history of, 958
noninvasive ventilatory support for, 962, 962t
pathophysiology of, 956-957
patient disposition in, 964
physical examination findings, 958
progression of, 958, 958f
severe
classification of, 957t
therapeutic guidelines for, 961t
sputum examination findings, 959
staging, 957
symptoms of, 958
very severe, 957t
Churg-Strauss syndrome, 1536t, 1538
Cicuta maculata (water hemlock), 2067, 2067f
Cicutoxin (water hemlock) poisoning, 1955t
Cidofovir (Vistide), 1721t-1722t, 1723
CIE. *See* Counterimmunoelectrophoresis
Cigarette burns, 846f
Ciguatera fish poisoning, 1246-1247
clinical presentation of, 1246-1247
differential considerations, 1247
epidemiology of, 1243t, 1246
management of, 1247
pathophysiology of, 1246
Ciliary flush, 914, 914f
Cimetidine
alcohol interactions, 2390t
for anaphylaxis, 1555
for GERD and PUD, 1177t
for scombroid fish poisoning, 1246
Cimino-Brescia fistula, 1155-1156
Cinryze, 1557
Ciprofloxacin
for anthrax, 2473b, 2474
for bowel flora, 1264b
for *Campylobacter* enteritis, 1234
for chancroid, 1318
for cholera, 1245
Ciprofloxacin *(Continued)*
for cystoisosporiasis, 1251
for diarrhea, 259-260, 1235t, 2192t-2193t
for diarrhea in AIDS, 1257t
for diverticulitis, 1264b
for epididymitis, 1347-1348, 1347t
for gastroenteritis, 1236, 1241
for gastrointestinal anthrax, 1242
for granuloma inguinale, 1318
for infectious diarrhea, 2192t-2193t
for malignant otitis externa, 1664t
for meningitis chemoprophylaxis, 1458
for meningococcemia prophylaxis, 1713-1714
for otitis externa, 935
for plague, 2475b
for pneumonia, 985t
for prostatitis, 1335-1336
for *Salmonella* enteritis, 1236
for sexually transmitted diseases, 1315t
for traveler's diarrhea, 1259, 1260b
Circulation
in anaphylaxis, 1552t
in beta-blocker overdose, 1989
in burns, 812-814
in children, 2092
fetal, 2139
intracardiac, 2139, 2140f
persistent, 112
in geriatric trauma, 325
in multiple trauma, 291-292
neonatal, 2139
in pediatric trauma, 308, 308b
spontaneous return, 81-82
in trauma in pregnancy, 300-301
Circulatory overload, 79
Circulatory shock, 69b
Circulatory support, extracorporeal, 105
Circumcision complications, 2207
"Circus movement" tachycardia, 1035
Cirrhosis, 1193-1194
alcoholic, 2386
biliary, 1193
clinical features of, 1193
cryptogenic, 1193
definition of, 1193
diagnostic strategies for, 1193
in immunocompromised patients, 2365
key concepts, 1194b
Laennec's, 1193
management of, 1193-1194
pipestem, 1782, 1783f
postnecrotic, 1193
Cisapride, 2390t
Cisplatinum, 1197t
Cities Readiness Initiative, 2467
Citrucel (methylcellulose), 264t-265t
Civil War (U.S.), 2433
Clarithromycin
for diarrhea in AIDS, 1257t
for *H. pylori* infection, 1180
for infective endocarditis prophylaxis, 2160t
lansoprazole, amoxicillin, and clarithromycin (Prevpac), 1180
for Lyme disease, 1793
for otitis media, 933-934
for pertussis, 1698-1699
in pregnancy and lactation, 2318t-2321t
Clarus Video System (Clarus Medical), 19, 19f
CLAS standards (standards for culturally and linguistically appropriate services), e25
Clavicle, 618, 622-623, 623f
Clavicle splint, 529
Clavicular fracture, 621-624, 622f, 2252-2254, 2254f
clinical features of, 622-623
complications of, 624
management of, 623
pathophysiology of, 621-622
patient disposition in, 623-624
type III, 621-622, 623f
Clavicular or figure-of-eight splint, 623, 623f
Clavulanate
amoxicillin-clavulanate, 1264b
for otitis media, 934t
ticarcillin-clavulanate, 1264b
Clawhand *(main en griffe)*, 543, 543f

www.ketabpezeshki.com 66485457-66963820

Clay shoveler's fracture, 385, 388f, 512t-513t
Cleansing, wound, 755
Clenched-fist injuries (fight bites), 562, 764, 791
Clevidipine, 1118t-1119t
Click It or Ticket campaign (NHTSA), 287
Clindamycin
for babesiosis, 1806
for bacterial vaginosis, 1323
for bone and joint infection, 1835t
for dental infection, 900
for diabetic foot infection, 1664t
for diabetic foot ulcers, 1664
for hidradenitis suppurativa, 1564
for infective endocarditis prophylaxis, 2160t
for nonclostridial gas gangrene, 1664t
for otitis media, 933-934
for parasitic infection, 1772t-1775t
for pelvic inflammatory disease, 1325t
for pneumonia, 985, 985t
in pregnancy, 2318t-2321t, 2324
for prophylaxis in bite wounds, 789t
for skin and soft tissue infection, 1854-1855, 1854t
for STIs after sexual abuse/assault, 851t
for toxic shock syndrome, 1568, 1717
Clinical decision unit (CDU), 954, 2481
Clinical questions, e19-e20
Clinical studies
cross-sectional studies, e8-e9
file drawer problem, e12
longitudinal studies, e9
checklist for assessment of, e19t
controlled, e9
design terminology, e13t
randomized, e9-e12
uncontrolled, e9
types of, e8-e9
Clonal expansion, 1546
Clonazepam (Klonopin), 2078t
adverse effects of, 1383t
for long-term anticonvulsant therapy, 1384t
side effects and drug interactions, 2407t-2408t
Clonidine hydrochloride
for hypertension, 1122.e1t-1122.e2t
for opioid withdrawal, 2056
Clonorchis sinensis (Chinese liver fluke), 1770t-1775t
Clopidogrel, 1025
Clorazepate (Tranxene), 2078t, 2407t-2408t
Closed-fist injury, 790
Closed head injury, 477, 477f
Clostridium botulinum infection, 1444, 1704-1705. *See also* Botulism
Clostridium difficile infection, 2192t-2193t, 2194
antibiotic-associated enterocolitis, 1248-1249
clinical presentation of, 1248
diagnostic strategies for, 1248
differential considerations, 1248, 1256
epidemiology of, 1248
key concepts, 1260b
management of, 1249
pathophysiology of, 1248
diarrhea, 1235t
enteritis, 1243t
Clostridium difficile toxin assay, 258
Clostridium perfringens enteritis, 2194
Clostridium perfringens food poisoning, 1244
clinical presentation of, 1244
complications of, 1244
epidemiology of, 1243t, 1244
management of, 1244
pathophysiology of, 1244
Clostridium tetani infection, 1699, 1701
Closure, e54
Clot solubility, 1609
Clotrimazole (Lotrimin)
for oral thrush, 1561-1562
for oropharyngeal candidiasis, 1175
for tinea corporis, 1560
Clozapine, 2048t
Clubbing, symmetrical, 130, 131f
Cluster headache, 1389
in children, 2242-2243
clinical features of, 1389
differential diagnosis of, 1389
treatment of, 1389
Cnidaria (coelenterates), 806
Coagglutination, 1454
Coagulation, hypothermic, 1888-1889
Coagulation control, 1606-1607
Coagulation disorders, 1615-1616
Coagulation factors, 1606
Coagulation pathway, 1606, 1607f
disorders of, 1612-1616
Coagulation studies, 1608b
Coagulopathy, maternal, 2348
Coarctation of the aorta, 2148-2149
clinical features of, 2148
diagnostic strategies for, 2148
management of, 2148-2149
Cocaine
adulterated with levamisole
complications of, 2001
vasculitis caused by, 1540-1541
formulations of, 1999
labor interactions, 2340t
pharmacology of, 1999, 2000t
tetracaine, adrenaline (epinephrine), and cocaine (TAC), 48
topical, 47
for wound management, 754
Cocaine use/abuse, 1999-2006
among adolescents, e2
anxiety in, 1477
body packing, 779, 779f, 1378, 1954-1955, 2004
body stuffing, 779, 1378, 1954-1955
cardiotoxicity of, 1100
clinical features of, 1999-2001
complications of, 2001
diagnostic strategies for, 2001
differential considerations, 2001
initial management of, 2001, 2002b
key concepts, 2006b
management of, 2001-2004
myocarditis in, 1100
pathophysiology of, 1999, 2000f
patient disposition in, 2004-2005
Cocaine washout, 2001
Coccidial infections, 1250-1252, 1250t
Coccidioides immitis infection, 2363
Coccyx fractures, 658f, 671
Cockroft-Gault equation, 1292
Codeine, 39t, 42
for pediatric migraine, 2243-2244
in pregnancy and lactation, 2318t-2321t
respiratory depression associated with, 2053t
Codes
of ethics, e36, e37t
professional, e36
Coelenterates *(Cnidaria)*, 806
"Coffin-lid" crystals, 1336
Cogentin (benztropine), 1464, 1472
Cognition, 142, 1375
Cognitive-behavioral therapy
for anxiety disorders, 1479, 1479t
for mood disorders, 1468
Cognitive deficits, in elders, 2353
Cognitive disposition, 2508
Cognitive distortions
identification of, 2425
rational response to, 2425
Cognitive limitations, 2508
Cohorts, e9
Coital cephalgia, 1396-1397
Coital headache, 1396-1397
Cola, 2200t
Colace (docusate sodium), 264t-265t
Colchicine
for CPDD and pseudogout, 1510
for gouty arthritis, 1509
Cold exposure, 1884f
Cold injury. *See* Frostbite
Cold stress, 1877
Cold urticaria, 1569
Cold water calorics (oculovestibular response), 146, 146f, 346
Colic
biliary, 1201
ureteral
abdominal pain in, 224t-225t
pelvic pain in, 267t-268t
Colitis
antibiotic therapy for, 1235t
drugs for treatment of, 1721t-1722t
STEC, 1240
ulcerative, 1269-1270, 1581t
Collagen vascular disease
with autoimmune hemolytic anemia, 1600b
oral manifestations of, 902
Collar-button abscess, 567, 567f
Collateral ligament injuries, 714
diagnostic strategies for, 714
key concepts, 722b
management of, 714
Collateral ligament stress test, 701
Colles' fracture, 512t-513t, 583-584, 584f
key concepts, 595
reduction of, 583-584, 585f
reverse, 584
Colon. *See* Large intestine
Colonic ischemia, 1272-1273
clinical features of, 1272-1273
diagnostic strategies for, 1273
differential considerations, 1273
management of, 1273
patient disposition in, 1273
Colonoscopy
in colonic ischemia, 1273
with GI bleeding, 252
in intussusception, 1269
in large bowel obstruction, 1266
Colorado tick fever, 1732, 1786t, 1806-1807
clinical features of, 1732, 1806
diagnostic strategies for, 1806-1807
differential considerations, 1732
management of, 1732, 1807
Colposcopy, 865-866, 866t
Colubridae snakes, 795-796
CoLyte. *See* Polyethylene glycol–electrolyte solution (PEG-ELS)
Coma, 142-150
barbiturate, 1382
diagnostic approach to, 149f
differential diagnosis of, 142
Glasgow Coma Scale (GCS), 145-146, 145b
management of patients in, 2381
myxedema, 1687
management of, 1688
treatment of, 1688b
pivotal findings, 144-146
structural etiology of, 144b
"Coma cocktail" medications, 148
Combat Application Tourniquet (C-A-T), 2451
Combat casualty evacuation care, 2452-2453, 2453f
Combat Gauze, 2451
Combat Medical Systems, 2451
Combat Ready Clamp (CRoC), 2451
Combat veterans, 368
Combative patients, 2414-2421
designated rooms for, 2420-2421
diagnostic strategies with, 2419
history taking with, 2418-2419
key concepts, 2421b
management of, 2415-2418
medical clearance for, 2414
physical examination of, 2418-2419
risk assessment, 2415
verbal management of, 2415
Combitube, 21, 21f, 2452
Commercial Hospital (Cincinnati, OH), 2433
Commercial splints, 528, 528f
Commission on Accreditation of Ambulance Services, 2439t
Commitment, involuntary, 1498
Common bile duct obstruction, 1202, 1202f
Common duty hour standards, e83
Common peroneal mononeuropathy, 1437-1438
Common peroneal nerve, 1437-1438, 1437f
Commonwealth Serum Laboratory technique (immobilization and compression technique), 797-798
Commotio cordis, 444, 2167
pediatric, 320
Commotio retinae, 916
Communicable diseases. *See also* Infectious diseases
reporting requirements for, e76

www.ketabpezeshki.com 66485457-66963820

Communication(s)
death notification, e53
delivering bad news, e51-e53, e52b
disaster response planning, 2464
emergency medical services, 2437
about end-of-life care
initiating, e55-e56
questions for discussion of, e56t
field communications, 2437
impaired, 2422
interpersonal, 2422, 2424
interviews
redirecting, 2424
structuring, 2424
notifying survivors, e43
phone notification, e53
physician-patient, e24
with problem patients, 2424
request for examination or treatment, e61
responding to feelings, e53
sharing reactions, 2424
time out from, 2424
verbal requests to withhold intervention, e51
Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA), 1565, 1853-1854
clinical features of, 1565
management of, 1565
prevention of, 1565
in skin infections, 1856t
Community-acquired pneumonia
antimicrobial treatment of, 984-986, 985t
guidelines for management of, 983
outpatient treatment of, 984, 984t
severe, 986, 987b
Community preparedness, 818-819
Compartment pressure, 522, 523f
Compartment syndrome, 502, 521-523
adverse outcomes, 521t
anatomic considerations, 522
anatomic locations, 522b
causes of, 521, 521b
clinical presentation of, 522
complications of, 523
definition of, 750, 2455
diagnostic tests in, 522
in foot, 750, 750b
in forearm, 594
in hand, 564-565
key concepts, 510b, 533b
in lower leg, 721
pathophysiology of, 521-522
patient disposition in, 523
pedal, 750
rhabdomyolysis in, 1672
risk factors for, 522
in thigh, 681
treatment of, 523
Compazine (prochlorperazine), 245, 245t
Compensatory responses, cardiovascular, 2139-2140
Competence, e40
determination of, e72-e73
incompetent adults, e71-e72
in Jehovah's Witnesses, e76
for leaving against medical advice (AMA), e73
medically incompetent adults, e76
Complement, 2357
Complement deficiency, 2359b
Complete blood count, 1608
in headache assessment, 173t
in nausea and vomiting, 242
Complex regional pain syndromes, 38, 523-524
criteria for, 524t
diagnosis of, 523
etiology of, 523
in foot, 748
pathogenesis of, 523
treatment of, 523-524
type 1 (CRPS-1), 523
type 2 (CRPS-2), 523
Compound presentation, 2345
Comprehensive Accreditation Manual for Hospitals (Joint Commission), e26
Comprehensive emergency management, 2463, 2468b
Comprehensive stroke centers (CSCs), 1374
Compression devices, 2451
Compressive optic neuropathy, 926-927
Computed tomography
abdominal
in diverticulitis, 1263
in urologic problems, 1329
in abdominal aortic aneurysm, 1132-1133, 1133f
in abdominal gunshot wounds, 474
in abdominal pain, 230, 230t
in abdominal trauma, 465-467, 465f-466f
in acute coronary syndrome, 1020-1021
advantages of, 465
angiography
in ankle injuries, 727
in peripheral vascular injury, 505
in vascular neck injury, 428
in ankle injuries, 726-727
in anthrax exposure, 2472, 2472f
in aortic dissection, 1126t, 1127, 1127f
in appendicitis, 1228-1230, 1228f
in arthritis, 1503
in back pain, 281-282
in blunt abdominal trauma, 475t
cervical spine
in pediatric trauma, 316
in spinal injury, 411f-412f, 414f
chest
in aortic tears, 453, 453f
in blunt aortic injury, 453-454, 453f
in hemothorax, 440-441, 441f-442f
in pneumothorax, 991
in pulmonary contusion, 436, 436f
in rib fracture, 432, 432f
in chest pain, 217t-218t, 218
in colonic ischemia, 1273
cranial, 160, 160b
in demonstrating organ injury that requires laparotomy, 475
disadvantages of, 409, 465-466, 466f
electron beam, 1020-1021
in facial trauma, 373, 374f
fetal radiation exposures, 2276t
in foot injury, 736
in fracture, 519
in gastrointestinal foreign bodies, 777-780
in headache, 172, 173t
in hemoperitoneum, 475
in intracerebral hemorrhage, 1368f
in intraocular foreign bodies, 768, 768f
in intussusception, 1269
in knee injury, 703
in large bowel obstruction, 1266
in low back pain, 649-650
in mesenteric ischemia, 1223, 1223f
in minor head injury, 352-353
multidetector, 1021
in osteomyelitis, 1837-1838, 1838f
in ovarian cysts, 1359
in ovarian torsion, 1356-1357, 1357f, 1358b
in pancreatic pseudocyst, 1208, 1208f
in pancreatitis, 1211
in pediatric head injury, 315, 356-357, 357f
in pelvic trauma, 665, 667, 671b
in peripheral arteriovascular disease, 1142-1143
in peripheral vascular injury, 505
pulmonary angiography
in deep vein thrombosis, 1158
in pulmonary embolism, 1164
in pulmonary embolism, 1164, 1164b
in pyogenic abscesses, 1197, 1197f
radiation risk, 466
removal of soft tissue foreign bodies by, 783-784
in renal calculi, 1338, 1338f
in renal failure, 1292-1293, 1292f
in renal trauma, 492, 493f
retrograde cystography, 489-490, 490f
in retropharyngeal abscess, 974, 974f
in small bowel obstruction, 1220
in sore throat, 200
in spinal injury, 407-409, 411f-412f
spiral
in chest pain, 217t-218t
in spinal injury, 409, 413f-414f
technique for performing, 409, 412f
Computed tomography *(Continued)*
in stroke, 1369, 1369f
in systemic lupus erythematosus, 1532
technique for, 466-467
of teeth, 897
three-dimensional
in blunt aortic injury, 453, 453f
of cervical spine, 414f
in trauma in pregnancy, 300
triple rule-out or global assessment protocol, 1021
uterine radiation dose, 299t, 300
venography, 1158
Concussion, 354
definition of, 312
myocardial, 444
pediatric, 312
postconcussive syndrome, 354
return to play (RTP) after, 354, 354t
Conduction, 1896
Conduction ratio, 1043-1045
Condylar fractures, 609f
in adults, 609
clinical and radiographic features of, 609
complications of, 609
management of, 609
pathophysiology of, 609
Condyle, 698
Condylomata acuminata, 1286t, 1319
in children, 1287f
treatment of, 1286-1287, 1721t-1722t
patient-applied regimens, 1319
provider-administered regimens, 1319
Condylomata lata, of secondary syphilis, 1316-1317, 1316f
Cone shells, 806-807
Conenose bugs or "kissing bugs," 805
Confidence intervals, e14
Confidentiality, e35-e36
in intimate partner violence, 882-883
questions to be addressed, 882-883
Confined space issues, 2455
Conflict resolution
with problem patients, 2424
strategies for, 2424b, 2426-2430, 2428t
Conflicts
of principles, e36
case example, e37
prioritizing, e36-e37
of professional value, e38
Confounders, e15
Confusion, 151-155
critical diagnoses, 154b
definition of, 151
diagnostic approach to, 151-153
differential considerations, 151, 152b
differential diagnosis of, 152b, 154
emergent diagnoses, 154b
epidemiology of, 151
history in, 152
laboratory tests in, 153
management of
algorithm for, 154f
empirical, 154-155
pathophysiology of, 151
patient disposition in, 155
physical examination findings, 152-153
pivotal findings, 152-153
Quick Confusion Scale (QCS), 152-153, 153f
rapid assessment and stabilization of, 151-152
Confusion Assessment Method (CAM), 889
Congenital heart defects, 2104-2105
acyanotic, 2147-2149, 2147f
clinical features of, 2145-2146
coronary artery anomalies, 2165-2167
cyanotic, 2149-2151, 2149f
diagnosis of, 2146-2147, 2146b
duct-dependent cardiac lesions
in neonate, 2147b
PGE_1 infusion for, 2147, 2147b
incidence of, 2146t
management of, 2147
postoperative complications of, 2151
recommendations for palivizumab administration for, 2151, 2151b

www.ketabpezeshki.com 66485457-66963820

Congenital heart defects *(Continued)*
RSV infections in infants and children with, 2151
time of presentation, 2146t
Congenital lesions
duct-dependent cardiac, 2147, 2147b
of larynx, 2111-2112
subglottic, 2112
supraglottic, 2109
of trachea, 2113-2114
Congestive heart failure
in infants and children, 2152-2153
clinical features of, 2152
diagnostic strategies for, 2152
digoxin dosing for, 2152t
inotropic and load-altering agents for, 2153t
management of, 2152-2153
observational approach to, 2489
thyrotoxicosis in, 1683b
traditional approach to, 2488
Conium maculatum (poison hemlock)., 2067, 2068f
Conjunctiva
diseases of, 918-919
trauma to, 910-913
Conjunctival foreign bodies, 913
Conjunctival lacerations, 917
Conjunctivitis, 187, 1552t
acute follicular, 187
allergic, 193t-196t, 919
bacterial, 918-919, 918f
antimicrobial agents for, 191-192
management algorithm for, 193t-196t
chlamydial, 193t-196t
clinical features of, 918-919
management of, 918-919
miscellaneous, 919
types of, 919
viral, 919, 919f
antimicrobial agents for, 191
management algorithm for, 193t-196t
Connective tissue disorders, 1105
pericardial disease related to, 1094
rhabdomyolysis in, 1669b-1670b
Conscious sedation, 50
Consciousness, 1375
altered levels of. *See also* Altered mental status
after head injury, 344
interventions for, 307t
definition of, 142, 344
depressed, 142-150
loss of, 159
unconscious or medically incompetent Jehovah's Witnesses, e76
Consent, e39-e40
implied, e40, e71
informed, e40
in intimate partner violence, 883
for restricted SART examination, 856f
for medical care, e70-e72
presumed, e39-e40
for procedures on newly dead, e54
in sexual assault cases, 857b
Consolidated Omnibus Budget Reconciliation Act (COBRA), e60
Constipation, 261-265
abdominal pain in, 224t-225t
ancillary testing in, 262
causes of, 262b
primary, 261, 262b
secondary, 261, 262b
chronic, 261
definition of, 261
diagnostic algorithm for, 262-263, 263f
diagnostic approach to, 261-262
differential considerations, 261
at end of life, e57
epidemiology of, 261
history taking in, 261-262
management of, empirical, 263-265
pathophysiology of, 261
patient disposition in, 265
physical examination findings, 262
pivotal findings, 261-262
treatment of
general approach to, 264b
preparations for, 264t-265t
Constrictive pericarditis, 1097-1098
Consultants, e41
Consultation
for GI bleeding, 252
for poisoning, 1959
for severe head injury, 351
Contact dermatitis, 1572, 1572f
clinical features of, 1572
management of, 1572
secondary, 1572f
Contact dermatoconjunctivitis, 193t-196t
Contact lenses
complications of, 920
decorative, 918f
Contaminated air (carbon monoxide poisoning), 1919, 1925
Contamination
airway, 2456, 2456f
of herbal medicines, 2073
radioactive, 1947-1948
wound, 1949
Contingency management, 1490
hazmat response plans, 818-819
Continuous arteriovenous rewarming, 1894, 1894t
Continuous mechanical ventilation (CMV), 24, 25t
Continuous positive airway pressure (CPAP), 25, 25t, 2439
Continuous spontaneous ventilation (CSV), 25, 25t
Contraception, emergency, 1362
key concepts, 1362
types of, 869t
Contraceptive steroids, 1197t
Contraction alkalosis, 1634
Contrast arteriography, 1142
Contrast enemas, water-soluble, 1266
Contrast studies, 467, 467f
Contrecoup injury, 363
Contusions
cerebral, 313, 363
in children, 313, 320
of foot, 749-750
muzzle, 830, 831f
myocardial, 320, 444-446
to orbits, 909
pattern, 837-839, 838f
pulmonary, 320, 436-437, 436f
Conus medullaris syndrome, 1421-1422, 1421t
Convection, 1896
Convenience samples, e9
Conversion disorder
clinical features of, 1481-1482, 1482b
diagnostic criteria for, 1482b
Convulsions, 1375
Convulsive seizures, 2231
Cooling, 1904-1905
of burns, 814
modalities to lower body temperature for heatstroke, 1905b
Coombs' test, 1587, 1595-1596
Coping strategies
shift work strategies, e81b
wellness strategies, e81-e82, e81b
Copycat suicides, 1493
Coral snakes, 795
bites by
antivenin for, 800
clinical features of, 797
patient disposition in, 801
Core rewarming, active, 1892-1894
Core temperature afterdrop, 1880, 1885
Cornea
diseases of, 919-920
foreign bodies in, 912-913, 913f
infection of, 190, 190f
inflammation of, 189-190, 190f
Corneal infiltrate, 920
Corneal rust ring, 913, 913f
Corneal trauma, 910-913
abrasions, 189-190, 190f, 196-197
examination of, 912, 912f
mechanical, 912
alkali burns, 189f, 911f
chemical burns, 910, 911f
lacerations, 917, 917f
Corneal ulcerations, 190, 190f
from infection, 920
post-traumatic, 917-918, 918f
Corner stitches (half-buried horizontal mattress sutures), 759, 761f
Coronary artery anomalies, congenital, 2165-2167
Coronary artery bypass
and fibrinolytic therapy, 1029
for heart failure, 1088-1089
Coronary artery disease
and heart failure, 1078
hypomagnesemia in, 1649
pathophysiology of, 999
risk factors for, 1000
spectrum of, 998
in systemic lupus erythematosus, 1529
workup and treatment for, 1529t
Coronary perfusion pressure, 90
Coronaviruses, 1719t, 1733-1734
Correctol (bisacodyl), 264t-265t
Corrigan's pulse, 1111
Corrosive agents, 1994
Cortical bone, 1833
Corticosteroid-resistant asthma, 951
Corticosteroids
for adhesive capsulitis, 642
for anaphylaxis, 1555
for angioedema with urticaria, 1556-1557
for asthma, 949t, 950-951
for asthma exacerbations in pregnancy, 2303t
for asthma in children, 2122-2123
for bacterial meningitis, 2230
"burst" therapy for asthma, 950-951
cardioactive overdose, 1982-1986
chronic use of, 2372, 2372f
for COPD, 963
for discharged patients, 950-951
for gouty arthritis, 1509
in head injury, 349
hepatic injury, 1197t
for hypercalcemia, 1625
for immunosuppressive therapy, 2366-2367, 2371-2372
for impingement syndrome, 639, 639t
for meningitis in children, 2230
for migraine attack, 1388t
for parasitic infection, 1772t-1775t
in pregnancy, 2318t-2321t, 2330
for relapsing polychondritis, 1515
for rheumatoid arthritis, 1514
for Rocky Mountain spotted fever, 1803
for sepsis, 1873
for septic shock in children, 108
for Takayasu's arteritis, 1536
for thyroid storm, 1682b
topical, 1560t
triggers for anaphylaxis, 1546
for tuberculosis, 1827
Corticotropin (adrenocorticotropic hormone)
for gouty arthritis, 1509
regulation of, 1689
Corticotropin-releasing hormone, 1467
Cortisporin, 935
Corynebacterium diphtheriae infection, 1693
Costochondral separation, 433
Costoclavicular syndrome, 1150-1151
Costs
of air medical transport, 2447-2448
of asthma care, 941
of injury-related medical care, 330
of intimate partner violence, 873
of low back pain, 278
Cotton fever, 2397-2398
Cotton's fracture, 512t-513t
Cough
headache associated with, 1397
violent, 1696
whooping, 1697-1698
Cough CPR, 92-93
Coumadin (warfarin), 2322-2323
Counterfeit mental illness, 1489
Counterimmunoelectrophoresis (CIE), 1454
Countertransference, 2422
Coup injury, 363
Couplets, 1046

www.ketabpezeshki.com 66485457-66963820

Coupling intervals, 1046
Courts, e41
Courvoisier's sign, 1215
Cousteau, Jacques-Yves, 1915
Cow bites, 787
Cowpox, 1726
Cowpox virus, 1726
COWS ("cold-opposite, warm-same") corrective nystagmus, 146
Coxsackieviruses, 1732
Cozen's test, 1521
CP-47,497, 2021, 2021f
CPCs. *See* Chest pain centers
CPR. *See* Cardiopulmonary resuscitation
Crab lice, 1323
Crack cocaine, 1999, 2000t
Crack dancing, 2001
Cracked tooth, 901
Cramping, 2406t
Cranial decompression, 350, 363f
Cranial mononeuropathy, diabetic, 1413-1414, 1417b-1418b
Cranial nerve disorders, 1409-1418
Cranial nerve palsy, 929
Cranial nerves, 1410t-1411t
Cranial osteomyelitis, 359-360
Cranium, 339-340
Crash airway algorithm, 8, 9f
Crash Outcome Data Evaluation System, 336
Creams, 1558
Creatine kinase
  BUN/Cr ratio, 1671
  half-life, 1670
  serum levels, 1670-1671, 1671f
Creatinine, 1292
  in disseminated intravascular coagulation, 1616t
  in nausea and vomiting, 242
Creatinine clearance, 1292
Creatinine phosphokinase, 1017t, 1018f, 1019
Credentialing, 2492-2493
Creeping eruption (cutaneous larva migrans), 1780
Crescent sign, 1393f
Creutzfeldt-Jakob disease, 1740
  clinical features of, 1740
  diagnostic strategies for, 1740
  differential considerations, 1740
  new-variant, 1740
Cricothyrotomy, 22
  difficult, 6
  needle, 21-22
CRIES scale, 37
Crimean-Congo hemorrhagic fever, 1739
Crimean War, 1883
Criminal justice system, 882. *See also* Law enforcement
Crisis
  anatomy of, 2426
  dealing with, 2426
  recognition of, 2426
Crisis intervention, 2425-2426
  basic steps in, 2426b
  information gathering for, 2426
Critical diagnostic syndromes, 2482-2486
Critical incident stress debriefing, e81-e82
Critically appraised topic, e20t, e21
CRITOE acronym, 599
Crocks, 2422
CroFab antivenin, 799, 1957t-1958t
Crohn's disease, 1269-1270, 1271b, 2181
Cross-sectional studies, e8-e9
Crossover or oarsman's syndrome, 589
Crotalinae snakes, 795-796
Crotalus atrox (Western diamondback rattlesnake), 796f
Croup (laryngotracheobronchitis), 2115t
  bacterial, 2114-2115
  indications for admission, 2113b
  key concepts, 2116b
  membranous, 2114-2115
  pseudomembranous, 2114-2115
  spasmodic, 2113
  viral, 2112-2113
    clinical features of, 2112-2113
    management of, 2113
Cruciate ligament injuries, 713-714, 722b
Crush injury
  antibiotic prophylaxis for, 763
  in foot, 750
  in urban search and rescue, 2455-2456
Crush syndrome
  definition of, 2455
  management of, 2455-2456
  pathophysiology of, 2455
  in urban search and rescue, 2455-2456
Crusts, 1559t
Cruzan v Director, Missouri Department of Health, e72
Cryoglobulinemic vasculitis, 1541
Cryoprecipitate, 310, 1613
Cryotherapy
  contraindications to, 532-533
  for orthopedic injuries, 532
  for tendinopathy, 1523
Cryptococcus gatti infections, 2363
Cryptococcus neoformans infection
  in AIDS, 1761
  in immunocompromised patients, 2363
Cryptogenic bat rabies, 1743-1744
Cryptogenic cirrhosis, 1193
Cryptosporidiosis (*Cryptosporidium* infections), 1250-1251
  gastroenteritis
    in AIDS, 1257t
    clinical presentation of, 1251
    diagnostic strategies for, 1251
    epidemiology of, 1250-1251, 1250t
    management of, 1251
    pathophysiology of, 1251
    symptoms of, 1782
    treatment of, 1235t, 1257t
  therapy for, 2192t-2193t
Cryptosporidium hominis infection, 2195
Cryptosporidium parvum infection, 1782
Crystal analysis, 1505f
Crystal drain cleaners, 1994, 1995t
Crystalloids
  for acute renal failure in children, 2218
  for calcium channel blocker poisoning, 1991-1992
  for sepsis, 1871
  for toxic shock syndrome, 1717
Crystalluria, 1338
CTrach ILMA, 20
Cuboid dislocation, 741
Cuboid fractures, 741
Cultural competence
  basic skills, e29b
  case reports, e26
  crossing barriers, e26-e27
  development of, e29
  education about, e28
  in intimate partner violence, 882
  with language barriers, e26
  multiculturalism, e23-e32
  new model of, e28
  progress to date, e26
  rationale for, e23-e28
  recommendations for, e28-e29
  tools for, e29
Culturally and linguistically appropriate services standards (CLAS standards), e25
Culture of medicine, e27-e28
  for residents, e84
Cultures
  bacteriologic, 1455
  blood, in pediatric fever, 2098
  in nausea and vomiting, 242
  stool, 258
  in tuberculosis, 1816
  urine, 1328-1329
    indications for, 1329b
    in pediatric fever, 2098-2099
    positive, 2099
Cuneiform dislocation, 741
Cuneiform fractures, 741
CURB-65 rule, 986
Cushing's phenomenon, 344
Cushing's reflex, 344-345
Cushing's response, 313
Custody: chain of, 863-864, 864b
Cutaneous anthrax, 1580, 1580f, 1863, 2473, 2473b, 2473f
Cutaneous candidiasis, 1562
  clinical features of, 1562
  diagnostic strategies for, 1562
  differential considerations, 1562
  management of, 1562
Cutaneous larva migrans (creeping eruption), 1772t-1775t, 1780, 1863
Cutaneous leishmaniasis, 1779, 1779f, 1863
  clinical features of, 1779
  diagnostic strategies for, 1779
  management of, 1779
Cutaneous nerves, of hand, 543, 543f
Cutis marmorata, 2092, 2092f
Cyanide, 825-827, 2039-2041, 2478
  agents, 825
  gases that can be encountered as WMDs, 825t
Cyanide poisoning
  antidote for, 1957t-1958t
  clinical features of, 2039
  diagnostic strategies for, 2039-2040
  differential considerations, 2039-2040
  key concepts, 2043b
  management of, 2040-2041
  metabolic acidosis in, 1632
  odor in, 1955t
  patient disposition in, 2041
  simultaneous with carbon monoxide poisoning, 2042-2043
Cyanoacrylate adhesive (Super Glue) exposure, 912
Cyanosis, 129-134
  ancillary testing in, 131
  central, 133f, 2140, 2141t
  clinical features of, 2140
  critical diagnoses, 132
  diagnostic approach to, 129-132
  differential algorithms for, 132-134, 132f-133f
  differential diagnosis of, 131b
  echocardiography in, 131-132
  electrocardiography in, 131-132
  emergent diagnoses, 132-134
  empirical management of, 134
  epidemiology of, 129
  imaging in, 131
  interventions for, 307t
  laboratory testing in, 131
  management of, 134
  pathophysiology of, 129
    pediatric, 2140
  patient admission for, 134
  patient discharge in, 134
  patient disposition in, 134
  peripheral, 132f
  pivotal findings, 129-132
  signs of, 129-131
  symptoms of, 129
Cyberbullying, e1
Cyclobenzaprine (Flexeril), 282-283
Cyclooxygenase inhibitors, 44
  GI effects, 44t
  nonselective, 44
Cyclopentolate, 191t, 930t
Cyclophosphamide
  hepatic injury, 1197t
  for systemic lupus erythematosus, 1533t
Cycloplegics, 191, 191t, 930t
Cyclops, 1779
Cyclosarin, 825t
Cycloserine, 1822t-1823t, 1824
Cyclospora cayetanensis enteritis, 1251-1252
  in AIDS, 1257t
  antibiotic therapy for, 1235t
  clinical presentation of, 1252
  diagnostic strategies for, 1252
  differential considerations, 1252
  epidemiology of, 1251-1252
  management of, 1252
  pathophysiology of, 1252
Cyclosporine, 2371
  drug interactions, 2371t
  herbal medicine interactions, 2072t-2073t
Cyclothymic disorder, 1471
Cyproheptadine, 1957t-1958t

www.ketabpezeshki.com 66485457-66963820

Cyst(s)
baker's (popliteal cyst), 717, 717f
Bartholin, 1314-1315
definition of, 1559t
hydatid, 1777, 1777f
leptomeningeal, post-traumatic, 358
nematocysts, 806
ovarian, 1358-1359
ruptured, 267t-268t
pancreatic pseudocysts, 1208, 1208f
Cystic fibrosis, 2137-2138
diagnostic strategies for, 2137
management of, 2137-2138
radiographic findings, 2137, 2137f
Cystic medial necrosis, 1124
Cysticercosis, 1777
clinical features of, 1777
diagnostic strategies for, 1777
key concepts, 1784b
management of, 1777
Cysticercus cellulose infection, 1772t-1775t
Cystine stones, 1336
Cystitis, 1326
in men, 1335
in women, 1333t
Cystography. *See also* Retrograde cystography
in extraperitoneal bladder perforation, 489, 489f
in intraperitoneal bladder perforation, 489, 490f
Cystoisospora (formerly *Isospora*) *belli* enteritis, 1250-1251
in AIDS, 1257t
antibiotic therapy for, 1235t
clinical presentation of, 1251
diagnostic strategies for, 1251
epidemiology of, 1250-1251, 1250t
management of, 1251
pathophysiology of, 1251
Cystoisosporiasis. *See Cystoisospora* (formerly *Isospora*) *belli* enteritis
Cystostomy tube placement, 1351, 1351f
Cytokines, 2228
Cytomegalovirus infection, 1731-1732
in AIDS, 1257t
clinical features of, 1731-1732
diagnostic strategies for, 1732
differential considerations, 1732
encephalitis, 1762t
in HIV infection, 1762t
management of, 1732
treatment of, 1257t, 1721t-1722t
Cytomel (triiodothyronine, T_3), 1688
Cytotoxic antibody reactions, 1545b, 1548
Cytotoxic edema, 344
Cytovene (ganciclovir), 1723

D
D-dimer assay, 1157-1158
in chest pain, 218
in deep vein thrombosis, 1158
qualitative assays, 1158
Dacryocystitis, 193t-196t, 921, 921f
Dacryoadenitis, 193t-196t
Dalmane (flurazepam), 2078t
Dalton's law, 1916t, 1917, 1917f, 2442
DAN. *See* Divers Alert Network
Dancer's tendinitis, 734
Dandelion salad, 2073
Dane particle, 1186-1187
Danis-Weber classification, 727, 727f
Dantrolene, 1465, 1957t-1958t
Dapsone, 804
Darunavir, 1766t
Dashboard fracture, 512t-513t
Dashboard injury, 670
Data analysis, e12-e18
intention-to-treat analysis, e17
interim analyses of accumulating data, e15
meta-analysis, e17-e18
sensitivity analyses, e17-e18
univariate, e15
Data collection, e10f, e11
Data dredging or torturing, e16-e17
Data Elements for Emergency Department Systems (CDC), 335
Data management, e10f, e11
Data torturing, e16-e17
Date rape, 2082
Datura stramonium (jimsonweed), 1970, 2067-2068, 2068f
Datura stramonium (stinkweed or thorn apple), 951
David Letterman sign, 580
DDT, 2060
de Quervain's disease, 589
de Quervain's tenosynovitis, 1519f, 1521-1523
de Quervain's thyroiditis, 1678
Dead arm syndrome, 634
Deadly nightshade *(Atropa belladonna)*, 951, 1970
belladonna alkaloids, 1970, 1971b
Death (paramethoxyamphetamine), 2017
Death and dying
brain death, 342-343, e48
closure, e54
consent for procedures on newly dead, e54
definition of, e48
disclosure of, e53b
in ED, e47, e51-e55
epidemiology of, e47-e50
field death pronouncement, e50
good death, e48-e49
leading causes of, 330, 332t, 334t
medicalization of, e48
notifying survivors, e43
planning for, e53
reporting requirements for deaths, e76
sudden death, 1105
trajectories of dying, e47, e48f
viewing of the body after, e54
Death notification, e53
elements of empathic death disclosure, e53b
phone notification, e53
Débridement, 755
Debriefing, 869-870
Decadron-LA (dexamethasone acetate), 639t
Decerebrate posturing, 346
Decision-making
in blood transfusion, 77-78
capacity for, e40
and alcohol intoxication, e72
components of, e40b
emergency medicine, e80
ethical, e35
informed, e73
morality of triage decisions, e44
race-based, e24-e25
rapid approach to, e38-e39, e38b
about wound closure, 756
Decompression sickness, 1917-1918, 1920-1921, 1923t
guidelines for returning to diving after, 1926-1927
inner ear, 1921
patient disposition in, 1926
pulmonary, 1921
recompression therapy for, 1923, 1925
risk of, 1926, 1926f
spinal, 1921
symptoms of, 1920, 1921f
type I, 1920
type II, 1920-1921
Decongestants, 2318t-2321t, 2330
Decontamination
anticholinergic, 1973
gastric, 1958-1959
gastrointestinal
barbiturate, 2077-2078
lithium, 2045
opioid, 2055
iron, 2025
radioactive, 1950-1951
Decorative contact lenses, 918f
Decorticate posturing, 346
Decubitus position, 464, 465f
Deep infrapatellar bursa, 716
Deep sedation/analgesia, 51, 51f, 52t
Deep space infections
in hand, 567
clinical features of, 567
management of, 567
pathophysiology of, 567
in neck and lower face, 971, 971f
Deep tendon reflexes
in head injury, 347
in spinal cord injury, 399-400
Deep transverse metacarpal ligament, 555f
Deep vein thrombosis, 1157-1159. *See also* Thromboembolism
anatomy of, 1157
clinical presentation of, 1157
complications of, 1159, 1160f
diagnosis of, 1157-1158
differential diagnosis of, 1158b
distal clot, 1157
"effort DVT," 1159
evaluation of, 2484
key concepts, 1169b
laboratory evaluation of, 1157-1158
observational approach to, 2484
in pregnancy, 2296-2297
pretest probability of, 1157, 1158t
proximal, 1157
radiographic evaluation of, 1158
traditional approach to, 2484
treatment of, 1159
upper extremity, 1157
Deep vein thrombosis ultrasound, 2498, 2498f
Deer tick *(Ixodes scapularis)*, 1787f-1788f
DEET (*N,N*-diethyl-*m*-toluamide), 1808
DEET (*N,N*-diethyl-*m*-toluamide) exposure, 2064-2065
clinical features of, 2065
diagnostic strategies for, 2065
differential diagnosis of, 2065
key concepts, 2065b
management of, 2065
patient disposition in, 2065
Deferasirox (Exjade), 1591
Deferoxamine
for chelation therapy, 1957t-1958t, 2025-2026, 2028t
in pregnancy, 2318t-2321t, 2323
Defibrillation, 1071
pediatric, 104-105, 2154b
Defibrillation threshold, 92
Degenerative changes, 527
Degenerative disease of central nervous system, 1379
Degenerative joint disease (osteoarthritis), 1504t, 1510-1511
Degenerative spondylolisthesis, 646-647, 652
DeHaven, Hugh, 331
Dehydration
in children, 2198-2203
clinical features of, 2198-2199
differential considerations, 2199
fluid and electrolyte management in, 2199-2203
key concepts, 2204b
treatment principles for, 2199b
in diabetic ketoacidosis, 1660
in hyperglycemic hyperosmolar state, 1662
hypertonic, 2203b
mechanisms of, 2198-2199
observational approach to, 2489, 2489b
severe, 2204b
traditional approach to, 2489
types of, 2199t
Dehydration assessment, 2196, 2196t, 2204b
Dejeune onion skin pattern, 401
Delavirdine, 1721t-1722t, 1766t
Delayed hypersensitivity, 1545b, 1549
Delayed transfusion reactions, 79
Delayed union, 517
Delbet classification, 693, 693f
Delirium, 1398-1404
agitated, 2001, 2002b
ancillary studies, 1402
causes of, 1399, 1399t
clinical features of, 1400-1402
definition of, 151, 1398
diagnosis of, 1399b, 1402
differential diagnosis of, 1402, 1402t, 1532t, 1973b

www.ketabpezeshki.com 66485457-66963820

Delirium *(Continued)*
etiology of, 1399-1400
guidelines for care, 1398
key characteristics, 1398, 1399b, 1402t
key concepts, 1408b
management of, 1402-1404
pathophysiology of, 1399
patient disposition in, 1404
quiet, 151
subtypes of, 151
toxins that cause, 1956, 1956b
violent behavior in, 2419t
Delivery, 2335-2337
breech, 2342-2344
complicated, 2342-2346
ED limitations, 2331
emergency
epidemiology of, 2331
medicolegal considerations, 2331
nursery requirements, 2331
patient transfer considerations, 2331
key concepts, 2350b
normal, 2331-2338, 2344f
stages of, 2332f
third-trimester complications associated with, 2338-2342
vaginal breech delivery, 2343b
Delta gap (ΔG), 1635
Delta MS (change in mental status), 151
Delta waves, 1055
Deltoid ligament injury, 731
Delusional disorders, 1462
Delusions, 1461
Demeclocycline, 1644
Dementia, 1404-1408
advanced, e57
alcohol effects on, 2387
classification of, 1405b
clinical features of, 1406-1407
definition of, 1404
diagnostic criteria for, 1404, 1404b
diagnostic evaluation for, 1407b
diagnostic strategies for, 1407-1408
differential considerations, 1407, 1472
etiology of, 1404-1405
evaluation for, 1404
guidelines for care, 1398
key concepts, 1408b
key features, 1398
pathophysiology of, 1405-1406
patient disposition in, 1408
pseudodementia, 1407
treatment of, 1408
violent behavior in, 2419t
Dementia praecox, 1460
Demerol (meperidine), 1403
Demographics
changing, e23, e29
of children and youth, e1
of older adults, 324, 885, 2351
Demyelinating polyneuropathies, 1430-1431, 1431b
Denatonium benzoate (Bitrex), 2013
Denis classification, 661, 664f
Dental abscess
simple, 898-899
treatment of, 899
Dental bacterial plaque, 896-897
Dental caries, 896-898
Dental crown and bridge emergencies, 907-908
Dental emergencies
key concepts, 908b
nontraumatic, 896-897
soft tissue injuries, 905-906
traumatic, 903-908
Dental extraction
bleeding after, 907
pain postextraction, 901
Dental infection
natural progression of, 896, 898f
spread to head and neck, 896, 899-900, 899f
Dental trauma, 380-381
Dentition, 895
Depakene (valproate, valproic acid), 2240t, 2407t-2408t
Depakote (divalproex sodium), 2240t, 2407t-2408t
Depakote ER (divalproex sodium), 2407t-2408t
Dependent adults, 891
Dependent patients, 2426, 2428, 2428t
Dependent personality disorder, 2427b
Depo-Medrol (methylprednisolone acetate), 639t
Depolarization, 1034, 1036f
Depressed consciousness, 142-150
ancillary testing in, 146-148
causes of, 144-145
diagnosis of, 142-148, 149f
differential diagnosis of, 142-143, 143t
empirical management of, 148-150
epidemiology of, 142
history in, 144-145
imaging studies in, 148
laboratory testing in, 146-148
pathophysiology of, 142
patient disposition in, 150
physical examination findings, 145-146
pivotal findings, 144-146
Depression
in adolescents, 1469
in alcoholism, 2390
in children, 1469
clinical features of, 1468
at end of life, e57
interpersonal theory of, 1468
long-term treatment of, 1473
major depressive disorder
anxiety in, 1477
clinical features of, 1468-1470
genetics of, 1467
prevalence of, 1466
major depressive episode, 1468b
masked, 1469
medical illnesses associated with onset of, 1471b
medications that can cause, 1471b
mnemonic for symptoms of, 1469b
in older adults, 1470
postpartum, 1470, 2350
recognition of, 1495
vs somatoform disorder, 1483
thought process and content in, 1469
Depressive disorders, 1470
Dermacentor ticks, 1788f
Dermacentor andersoni (wood tick), 805, 1798
Dermacentor variabilis (dog tick), 805, 1787f-1788f, 1798
Dermaide (aloe vera), 1880
Dermal caustic exposures, 1997
Dermal melanocytosis, 851, 852f
Dermatitis
atopic, 1562-1564
contact, 1572
gonococcal, 1565-1566
Dermatoconjunctivitis, contact, 193t-196t
Dermatographism, 1569f
Dermatologic presentations, 1558-1585, 1585b
Dermatomes, 400, 401f
Dermatomyositis, 1445, 1582f
clinical features of, 1445
diagnostic strategies for, 1445
management of, 1445
skin lesions associated with, 1580-1583, 1581t
Design, ED, 2505-2506
Designer amphetamines, 2017
Designer cannabinoids, 2021
Desmopressin
for diabetes insipidus, 1642
for hemophilia A, 1613
Detached concern, 2425
Detergents
eye exposures, 910-912
nonionic, 756t
Developmental dysplasia of the hip, 2261-2262
clinical features of, 2261-2262, 2261f-2262f
diagnostic strategies for, 2262
management of, 2262
radiographic findings, 2262, 2263f
Developmental or physical disability, 2400-2413
Developmental toxins, 2317b
Deviance, 2507
Devil's grippe, 1732
Dexamethasone (Decadron)
for acute asthma, 2121t
for acute mountain sickness prevention, 1934
for acute mountain sickness treatment, 1933
for adrenal insufficiency, 1692
for asthma, 950-951
for asthma in children, 2122
for bacterial meningitis, 1457
for croup, 2113
for HACE, 1937
for HAPE prevention, 1936
for intracranial neoplasm, 1392
for malignant spinal cord compression, 1628
for meningococcemia, 1713
for thyroid storm, 1682b, 1683
for urticaria, 1569
Dexamethasone acetate (Decadron-LA), 639t
Dextromethorphan, 2019
Dextromethorphan abuse, 2395
Dextromethorphan intoxication
clinical features of, 2019
differential considerations, 2019-2020
ED management of, 2020
respiratory depression in, 2053t
Dextrose solution (glucose)
for acute renal failure in children, 2218
for alcohol-induced hypoglycemia, 2381
characteristics of infusates, 1644t
for dehydration in children, 2200-2201
for hyperkalemia, 1638t
for hypoglycemia, 1656
for hypoglycemia in children, 2236
for hyponatremia, 1644, 2202-2203
for neonatal seizures, 2236
for pediatric resuscitation, 104t, 2200-2201, 2218, 2236
rule of 50s, 106
for sickle cell disease, 1599
for volume depletion, 2201-2203
DHS, *see* U.S. Department of Homeland Security
Diabetes insipidus, 1641b
Diabetes medications, 2328
Diabetes mellitus, 1652-1655
clinical features of, 1654
control of, 1665-1666
cutaneous manifestations of, 1664-1665
diagnostic strategies for, 1654-1655
due to other causes, 1653
epidemiology of, 1653-1654
etiology of, 1654
gestational, 1653, 2301t-2303t, 2309-2311
in immunocompromised patients, 2364
infections in, 1664, 1664t
key concepts, 1666b
late complications of, 1662-1665
maternal complications of, 2310
metabolic acidosis in, 65, 65f
mononeuropathy multiplex in, 1438
mortality rates, 1654
oral manifestations of, 902
oral medications for, 1665t
pathophysiology of, 1654
in pregnancy, 1665, 2309-2310
fetal complications of, 2310
management of, 2310
skin lesions associated with, 1581t, 1582f
type 1 (insulin-dependent), 1653
clinical features of, 1654
pathophysiology and etiology of, 1654
in pregnancy, 2301t-2303t, 2309-2310
prevalence of, 1654
type 2 (non–insulin-dependent), 1653-1654
in pregnancy, 2301t-2303t, 2309-2310
types of, 1653
urinary tract infection in, 1330
vascular complications of, 1663-1664
Diabetic cranial mononeuropathy, 1413-1414
clinical features of, 1414
differential considerations, 1414
key concepts, 1417b-1418b
management of, 1414
Diabetic dermopathy, 1665
Diabetic distal symmetrical polyneuropathy, 1431-1432

www.ketabpezeshki.com 66485457-66963820

Diabetic foot, 1664
antimicrobial therapy for, 1664t
infections, 1853
key concepts, 1666b
osteomyelitis, 1842
Diabetic ketoacidosis, 1632, 1656-1661
complications of, 1661
diagnostic strategies for, 1658-1659
differential considerations, 1659
etiology of, 1658
fluid and electrolyte deficits in, 1657t
general measures for, 1659
history in, 1658
hyperkalemia in, 1639
key concepts, 1666b
laboratory testing in, 1658-1659, 1658t
management of, 1659-1661
pathophysiology of, 1656-1658, 1657f
patient disposition in, 1661
physical examination findings, 1658
in pregnancy, 2310
treatment of, 1659b
vomiting with, 243t-244t
Diabetic nephropathy, 1663
Diabetic neuropathy, 1663-1664, 1666b
Diabetic retinopathy, 1663
Diabetic thick skin, 1664
Diagnostic peritoneal lavage (DPL)
in abdominal trauma, 469, 474-475, 475t
advantages of, 469
disadvantages of, 469
pediatric, 322
in pelvic trauma, 667
preferred site of, 466t
in pregnancy, 300
red blood cell criteria, 469, 469t
results, 469
Diagnostic peritoneal tap, pediatric, 322
Dialysis, 1306-1311. *See also* Hemodialysis
altered mental status in, 1310b
chest pain during, 1309
complications of, 1307-1310
for hyperkalemia, 1305t
hypotension after, 1308-1309
indications for, 1307, 1307b
iridodialysis, 915
peritoneal, 1306-1307, 1310-1311
renal, 1088
shortness of breath in, 1309
Dialysis disequilibrium syndrome, 1377
Diamond (Spice), 2021
Diamox (acetazolamide), 1624, 2407t-2408t
Diaper dermatitis, 1562
clinical features of, 1562
management of, 1562
Diaphoresis, 217t-218t
Diaphragmatic hernia, 114-115
pediatric traumatic, 320
Diaphragmatic injury, 443-444
anatomy of, 443
diagnostic strategies for, 443
epidemiology of, 443
left-sided, with abdominal stab wounds, 472
management of, 443-444
pathophysiology of, 443
Diaphragmatic rupture, 465-466, 466f
Diaphyseal fractures, 2259-2260
Diarrhea, 254-260
acute, 254
approach to, 259f
definition of, 254, 2188
indications for medical evaluation of children with, 2196b
acute infectious
characterization of, 257-258
clinical features of, 2196-2197
complications of, 2196-2197
diagnostic findings in, 2196
diagnostic strategies for, 2197
differential considerations, 2197
management of, 2197-2198
patient disposition in, 2198
in AIDS, 1254-1258
causes of, 1258t
clinical presentation of, 1255
Diarrhea *(Continued)*
complications of, 1255
diagnostic protocol for, 1256b
diagnostic strategies for, 1255-1256
differential considerations, 1256
epidemiology of, 1254
etiology of, 1255
key concepts, 1260b
management of, 1256-1258
pathophysiology of, 1254-1255
treatment against pathogens causing, 1257t
ancillary testing in, 258
antibiotic therapy for, 1235t
assessment and stabilization of, 256
C. difficile-associated, 258
categorization of, 254
causes of, 254, 255b-256b
in children, 2192t-2193t
traveler's, 1258t
characterization of, 257-258
in children, 259
causes of, 2189, 2189t
parent instruction sheet for, 2198b
pathogens that cause in, 2192t-2193t
treatment principles for, 2199b
with vomiting, 2198b
chronic, 254
characterization of, 258
definition of, 254
clinical approach to, 256-258
definition of, 254
with gastrostomy tubes and buttons, 2406t
incidence of, 254
infectious
causative agents of, 254, 255b
in children, 2188-2204
epidemiology of, 2188-2189
etiology of, 2190-2196, 2190t
pathophysiology of, 2189
physiologic factors, 2189-2190
inflammatory, 254
invasive, 254
key concepts, 1260b
management of, empirical, 258-260
nonbenign, 257t
osmotic, 254, 2189
in parasitic infections, 1782
patient disposition in, 260
persistent, 254
characterization of, 258
definition of, 254
"rice water," 1245
secondary survey, 256-258
secretory, 254, 2189
severe, 254
syndrome characterization, 257-258
traveler's, 1258-1260, 1258t
Diastat (rectal diazepam), 2232
for children, 2238, 2240t
side effects and drug interactions, 2407t-2408t
Diathermy, 1893
Diazepam (Valium), 2078t
for alcohol-related seizures, 2383
for alcohol withdrawal, 2382
for cocaine overdose, 2002
for MDMA effects, 2018
for nerve agent exposure, 2477b
rectal (Diastat), 2232
for children, 2237f, 2238, 2240t
side effects and drug interactions, 2407t-2408t
for sedation in head injury, 347
for seizures, 158t-159t, 350
for status epilepticus, 158t-159t, 1381-1382, 1381t
for thyroid storm, 1682b
Diborane, 825
Dichloroformoxime (phosgene), 825
Dicing lacerations, 841, 842f
Diclofenac, 44t
Dicloxacillin
for folliculitis, 1564
for impetigo, 1564
for prophylaxis in bite wounds, 789t
for skin and soft tissue infection, 1854, 1854t
for staphylococcal scalded skin syndrome, 1567
Didanosine, 1721t-1722t, 1766t
Dieffenbachia, 2068, 2068f
Dietary guidelines, e82, e82b
Dietary management
BRAT (bananas, rice, apples, and toast) diet, 259
for diabetes, 1665
for hyperphosphatemia, 1650
in pregnancy, 2280
for traveler's diarrhea prevention, 1259
for traveler's diarrhea treatment, 1259
N,N-Diethyl-*m*-toluamide (DEET), 1808, 2064-2065
Diethylcarbamazine, 1772t-1775t
Diethylenetriaminepentaacetate (DTPA), 1952t
Difficult airway
algorithm for, 8-10, 9f
clinical features of, 4-8
evaluation of, 4
identification of, 4-6
management of, 8-10
3-3-2 rule for evaluation of, 4, 5f
Difficult bag-mask ventilation, 5-6, 6f
MOANS mnemonic for, 5-6, 6b
RODS mnemonic for, 6b
Difficult cricothyrotomy, 6
Difficult direct laryngoscopy, 4-5
LEMON approach for, 4b
Difficult extraglottic device placement: RODS mnemonic for, 6, 6b
Difficult patients, 2422-2430
approaches for dealing with, 2426-2430
definition of, 2422
emergency department factors, 2423
key concepts, 2430b
physician factors, 2422-2423
strategies for dealing with, 2423-2426, 2424b
supportive care for, 2423-2424
Diffuse axonal injury, 362-363
mild, 362
moderate, 362-363
pathophysiology of, 362f
severe, 363
Digibind, 1985b
DigiFab (Fab fragments)
calculation of, 1985b
for digoxin toxicity, 1984
recommendations for administration of, 1985b
Digital subtraction angiography, 505-506
Digitalis: adverse effects of, 1040, 1040b
Digitalis antibody, 1984, 1985b
Digitalis lanata (Balkan foxglove plant), 1982, 1983f, 2070-2073
Digitalis overdose
age differences in, 1986, 1986t
antidote for, 1957t-1958t
bidirectional VT in, 1061f
chronic vs acute, 1983-1984, 1984t
dysrhythmias associated with, 1982, 1983b
key concepts, 1993b
pediatric considerations, 1986
risk factors for, 1983, 1983b
symptoms of, 1983, 1983b
Digoxin, 1039-1040, 1982
for congestive heart failure in infants and children, 2152t
for dysrhythmia, 1040
effects on Purkinje fibers, 1982
half-life, 1982-1983
herbal medicine interactions, 2072t-2073t
in pregnancy, 2318t-2321t, 2326
side effects of, 1040, 1040b
volume of distribution, 1982
Digoxin immune fragment (Fab), 1957t-1958t
in pregnancy, 2318t-2321t, 2323
Digoxin overdose, 1982-1986
clinical features of, 1983-1984
diagnostic strategies for, 1984
differential considerations, 1984
management of, 1984-1986
pathophysiology of, 1982-1983
patient disposition in, 1986
Dihydrocodeine, 2053t
Dihydroergotamine, 1388, 1388t
Dihydropyridines, 1122.e1t-1122.e2t
Dilantin (phenytoin)
for children, 2240t
contraindications to, 1662

www.ketabpezeshki.com 66485457-66963820

Dilantin (phenytoin) *(Continued)*
side effects and drug interactions, 2407t-2408t
for status epilepticus, 2408-2409
Dilated cardiomyopathy, 1101-1102
clinical features of, 1101
diagnostic strategies for, 1101
epidemiology of, 1101
etiology of, 1101
management of, 1101-1102
outcome, 1102
pathophysiology of, 1101
patient disposition in, 1101-1102
Dilation, 2333
Dilemma diagnoses, 1488
Diloxanide, 1257t
Diloxanide furoate, 1235t, 1772t-1775t
Diltiazem, 1039
characteristics of, 1991t
for dysrhythmia, 1039
hemodynamic effects, 1118t
for hypertension, 1122.e1t-1122.e2t
Dilutional thrombocytopenia, 1611
Dimenhydrinate (Gravol, Dramamine), 246
Dimercaprol (British anti-Lewisite, BAL)
for chelation therapy, 2027-2028, 2028t
in pregnancy, 2318t-2321t, 2323
Dimercaptosuccinic acid (DMSA) (succimer) (Chemet)
for chelation therapy, 2027-2028, 2028t
for lead poisoning, 1957t-1958t
in pregnancy, 2318t-2321t, 2324
Dimercaptosuccinic acid (DMSA) poisoning, 1955t
2,5-Dimethoxy-4-bromoamphetamine (DOB), 2017
2,5-Dimethoxy-4-iodoamphetamine (DOI), 2017
Dimethyl sulfoxide (DMSO) poisoning, 1955t
Dinidazole, 1323
Dinitrocresol, 2061
Dinitrophenol (DNP), 2061
Dipeptidyl peptidase 4 inhibitors, 1665t
Diphenhydramine (Benadryl), 2081
for anaphylaxis, 1554b, 1555
for antipsychotic overdose, 2050
for aphthous stomatitis, 902
for drug eruptions, 1567
for dystonia, 1464
for hymenoptera stings, 802
in over-the-counter sleep aids, 2081
pharmacokinetics, 2081
for scombroid fish poisoning, 1246
for wound management anesthesia, 755
Diphenhydramine overdose
clinical features of, 2081
diagnostic strategies for, 2081-2082
Diphenoxylate, 2053t
Diphoterine (Prevor), 910
Diphtheria, 1693-1696
clinical features of, 966, 1694-1695
complications of, 1695
diagnosis of, 967, 1695
differential considerations, 1695
epidemiology of, 1693, 1694f
etiology of, 1693
historical perspective on, 1693
immunization against, 1693
key concepts, 1717b
management of, 1695-1696
myocarditis in, 1100
pathophysiology of, 1694
patient disposition in, 1696
respiratory
differential diagnosis of, 1695b
diphtheria antitoxin (DAT) for, 1695
symptoms and signs of, 1694-1695
treatment of, 968
Diphtheria antitoxin (DAT), 1695
Diphtheria-tetanus-acellular pertussis (DTaP or Tdap) vaccine, 765, 1696, 1703
indications for, 1699
recommendations for, 1699
schedule for, 1703t
for wound management, 1704t
Diphtheria-tetanus-pertussis (DTP) vaccine, 1697f
schedule for, 1703t
Diphtheria-tetanus (DT) vaccine, 814, 1696, 1703
Diphtheria toxoid (Td), 1696
Diphyllobothrium latum, 1770t-1771t
Diplopia, 176-183, 929
binocular, 929
diagnostic approach to, 178-183
signs of, 178, 180-183
symptoms of, 178, 180-182
causes of, 177t
diagnostic approach to, 176-183, 179f
diagnostic testing in, 183
differential diagnosis of, 176, 178f
epidemiology of, 176
examination in, 176
important historical elements in, 176
initial stabilization in, 182f
in lacunar stroke syndromes, 181, 181b
management of, empirical, 183
monocular
diagnostic approach to, 176-178
signs of, 178
symptoms of, 178
pathophysiology of, 176
Dipstick blood glucose, 1655
Dipstick blood test
in diabetes mellitus, 1655
for heme, 1291
for protein, 1291
Dipylidium caninum infection, 1772t-1775t
Dipyridyl compounds, 2062
Diquat, 2062
Direct laryngoscopy, 18
Dirty bombs, 1945, 2466
Disability
abuse of persons with, 891
developmental or physical, 2400-2413
disabled adults, 891
intellectual, 2405
Disability assessment
in geriatric trauma, 326
in multiple trauma, 292
in pediatric trauma, 308, 308b
Disaster management and response organizations, 2466-2467
Disaster medicine
care of special needs populations, 2462
future directions, 2467
key concepts, 2468b
out-of-hospital response, 2462-2463
resources for, 2458t
terminology, 2458
Disaster preparedness, 2457-2468
Disaster response, 2463
command structure for, 2464
hospital, 2463-2464
local, 2465
media and, 2464
out-of-hospital, 2462-2463
ultrasound in, 2503-2504
Disaster response planning, 2463-2464
basic components of, 2463-2464
comprehensive, 2463-2464
hazard vulnerability analysis, 2459
hospital plan, 2463
interdepartmental planning group, 2463
for patient management, 2464
personnel, 2464
resource management for, 2463-2464
review of previous experiences for, 2464-2465
training exercises, 2464
Disaster site, 2463
Disaster stress management, 2466
Disasters, 2457-2459
catastrophic, 2465
definitions, 2457-2459
EMTALA exemption during, e62
focal, 2464-2465
levels, 2458
toxic (hazardous material), 2465
Discharge, patient
early discharge of low-risk patients, 2362
to home, e67
after intimate partner violence, 883t
to on-call physician office, e67
after procedural sedation and analgesia, 53-54
Disclosure, 877
Discoid rash, 1528t, 1531, 1531f
Discontinuation syndromes, 1980-1981
Discrimination, e24
Disease
as concept, e27
principles of, 288
Disequilibrium, 164
Disk herniation, 646
Diskitis, 1426
clinical features of, 1426
diagnostic strategies for, 1426
differential considerations, 1426
management of, 1426
Dislocation, 525-526
acromioclavicular joint, 629-631
adverse outcomes, 521t
ankle dislocations, 734
assessment of, 526
atlanto-occipital or atlantoaxial joint, 382, 385, 391f
bilateral facet, 385
carpal, 580, 580f
cuboid, 741
cuneiform, 741
definition of, 525
of distal phalanx of thumb, 525, 525f
of elbow, 525, 612-614
facial, 378-381
femoral, 687-691
of femoral prosthesis, 681-682, 682f
glenohumeral, 631-637
of hand, 553-554
of hip, 687-690
pediatric, 693
of hip prosthetics, 690-691
interphalangeal joint, 747
of knee, 525, 703-705
lens, 914f, 915
Lisfranc's (tarsometatarsal), 741-744
lunate, 581, 582f
metacarpophalangeal, 554-555
metatarsophalangeal, 747
navicular, 741
nomenclature, 525
obturator, 687, 688f
patellar, 525, 525f, 712-713
perilunate, 580-581, 581f
peritalar, 739
proximal tibiofibular joint, 720-721
pubic, 687, 689
scapulothoracic, 637
shoulder, 628-637
sternoclavicular, 628-629
subtalar, 739
temporomandibular joint, 381, 906-907, 906f
total talar, 739
treatment of, 526
unilateral facet, 385, 391f-392f
Disorganized speech, 1461
Displacement, 514, 514f
Disseminated intravascular coagulation, 1552t, 1615-1616
after head injury, 360
laboratory diagnosis of, 1616, 1616t
in rhabdomyolysis, 1672
Dissociation, 50
Dissociative agents, 2018-2020
Dissociative sedation, 51, 52t
Distal arcades, 570
Distal brachial artery thrombosis, 501f
Distal femur fractures, 705-706
anatomy of, 705-706
clinical features of, 706
diagnostic strategies for, 706
management of, 706
pathophysiology of, 705-706
Distal humerus fractures, 603-609
Distal interphalangeal joint injury, 553-554
dislocation, dorsal, 553-554, 554f
Distal peripheral neuropathies, asymmetrical, 1433, 1433b
Distal phalanx fractures, 546-547
clinical features of, 546-547
complications of, 547
hairpin splint for, 547, 547f
management of, 547

www.ketabpezeshki.com 66485457-66963820

Distal phalanx fractures *(Continued)*
pathophysiology of, 546-547
tuft fracture, 546-547, 547f
Distal radioulnar joint disruption, 570, 586-587, 587f
Distal radius injury, 583-588
pediatric fractures, 587-588
Salter-Harris type V fracture, 2253f
torus fracture, 587, 587f, 2250, 2251f
Distal sensorimotor polyneuropathies, 1432b
Distal symmetrical polyneuropathies, 1431-1433
alcoholic, 1432
diabetic, 1431-1432
Distal ulnar nerve, 1435, 1435f
Disulfiram (Antabuse), 2391
Disulfiram poisoning, 1955t
Diuretics
drug interactions, 44
for heart failure, 1087-1088
for hyperkalemia, 1305t
for hypertension, 1122.e1t-1122.e2t
hypomagnesemia induced by, 1648-1649
loop
antihypertensive therapy, 1119t
for heart failure, 1085, 1087-1088
for hypertension, 1122.e1t-1122.e2t
potassium-sparing, 1122.e1t-1122.e2t
in pregnancy, 2318t-2321t, 2327-2328
for rhabdomyolysis, 1674
thiazide
herbal medicine interactions, 2072t-2073t
for hypertension, 1122.e1t-1122.e2t
Divalproex sodium (Depakote), 2407t-2408t
Divers Alert Network (DAN), 1923
medical emergency hotline, 1923
nonemergency advisory line, 1923
On-Site Neurological Assessment for Diver's History form, 1923, 1924f
website, 1923
Diversity, e28-e29
of practice elements, e79-e80
Diversity education, e28
Diverticular disease, 1262-1265
clinical features of, 1263
diagnostic strategies for, 1263-1264
differential considerations, 1264
key concepts, 1274b-1275b
management of, 1264-1265
definitive, 1265
patient disposition in, 1265
Diverticulitis
abdominal pain in, 224t-225t
clinical features of, 1263
complicated, 1262-1265
diagnostic strategies for, 1263-1264
management of, 1264-1265
patient disposition in, 1265
definition of, 1262
key concepts, 1274b-1275b
uncomplicated, 1263-1264
diagnostic strategies for, 1263
management of, 1264
oral antibiotic therapy for, 1264b
patient disposition in, 1265
Diverticulosis
clinical features of, 1263
definition of, 1262
management of, 1264
Diving
free, 1915
mixed gas, 1915, 1916t
On-Site Neurological Assessment for Diver's History form (DAN), 1923, 1924f
recommended postdive preflight surface interval (PFSI) before ascending to higher altitudes (or flying), 1926, 1926f
scuba, 1915-1927
U.S. Navy manual, 1923
Diving injuries, 1915-1918
approach to injured diver, 1922f
clinical features of, 1918-1922
diagnostic strategies for, 1922, 1922f
differential considerations, 1922-1923
disorders arising at depth, 1918-1919
Diving injuries *(Continued)*
disorders arising on ascent, 1919-1922
disorders not requiring recompression therapy, 1925-1926, 1925b
disorders related to descent, 1918
disorders that require recompression therapy, 1923-1925, 1923b
key concepts, 1927b
management of, 1923-1926
patient disposition in, 1926-1927
Divinorin A (salvinorin A), 2022
Dix-Hallpike test, 164-165
Dizziness, 162-169
definition of, 162
diagnostic algorithm for, 167f
diagnostic approach to, 163-165
differential considerations, 163
nonspecific, 163
pathophysiology of, 162-163
physical examination findings, 164-165
pivotal findings, 163-165
vital signs in, 164
DMPS, 2028t
DMSA (dimercaptosuccinic acid) (succimer)
for chelation therapy, 2027-2028, 2028t
for lead poisoning, 1957t-1958t
in pregnancy, 2318t-2321t, 2324
DMSA (dimercaptosuccinic acid) poisoning, 1955t
DNP (dinitrophenol), 2061
Do-not-attempt-resuscitation (DNAR) directives, e49
honoring, e50-e51
initiating, e56
questions for discussion of, e56t
Dobutamine
for anaphylaxis, 1554b
dosing, 1871t
for heart failure, 1086
for heart failure in children, 2152, 2153t
in pediatric resuscitation, 104t
in pregnancy, 2328
for sepsis, 1872
Doctor hopping, 886
Documentation
appropriate, e73
central log, e64
E-coded hospital records, 335
of elder abuse, 889-891
EMTALA hospital transfer form, e66f
EMTALA requirements, e64
evidentiary labels, 863b
forensic, 884
informed consent to refuse examination, treatment, or transfer, e73, e74f
of intimate partner violence, 883, 883t
of leaving against medical advice (AMA), e75
in medical practice, 335-336
medical records, e64
reporting requirements, 890-891, e76-e77
requirements for reporting elder abuse, 890-891
of sexual assault findings, 863-864, 863b, 866-867, 867b
of suicidal behavior, 1499
Docusate sodium (Colace), 264t-265t
Dofetilide, 1039
Dog bites, 785-786
bacteriology of, 786
epidemiology of, 785, 786f
infection rates, 788
key concepts, 793b
management of, 764
prophylactic antibiotics for, 789, 789t
recommendations for closure and prophylactic antibiotics, 789t
risk factors for infection, 788t
Dog-ear deformity repair, 759, 760f
Dog tick *(Dermacentor variabilis)*, 805, 1787f-1788f, 1798
Doll's eyes (oculocephalic response), 146, 346
Dome fracture, 738, 738f
Domeboro (aluminum sulfate–calcium acetate), 1558
Domestic elder abuse, 885-886
Domestic herbivore bites, 787
Domestic violence, 872, 884. *See also* Intimate partner violence
facial trauma in, 369
in pregnancy, 2278-2279
questioning about, 2279
Donepezil (Aricept), 1408
Donovanosis (granuloma inguinale), 1318
Dopamine, 1871
for anaphylaxis, 1554b
dosing, 1871t
for heart failure, 1086
for heart failure in children, 2152, 2153t
for hypothermia effects, 1890
for neonatal resuscitation, 117-118, 117t
in pregnancy, 2328
for renal failure in children, 2218
Dopamine antagonists
antihypertensive therapy, 1119t
in pregnancy and lactation, 2318t-2321t
Diphyllobothrium latum infection, 1772t-1775t
Doppler ultrasound, 2493
color flow, 2493
in peripheral arteriovascular disease, 1142
in peripheral vascular injury, 505
hand-held, 504
in knee injury, 703
in ovarian torsion, 1355-1356, 1357f
in peripheral arteriovascular disease, 1142
in peripheral vascular injury, 505
in testicular torsion, 1344-1345, 1345f
transcranial, 2500
Doral (quazepam), 2078t
Doripenem, 985t
Dorsal Barton's fracture, 512t-513t
Dorsal horn, 32-34, 33f
Dorsal intercalated segment instability, 582, 583f
Dorsiflexion, ankle, 723
Dorzolamide, 930t
"Dot" or "blot" hemorrhages, 848
Double blinding, e11
Double vision. *See* Diplopia
Douching, 2279-2280
Doxazosin mesylate, 1122.e1t-1122.e2t
Doxepin, 1556-1557
Doxycycline, 1770t
for anorectal conditions, 1285
for anthrax, 2473b
for bacterial conjunctivitis, 918-919
for chlamydial infection, 1320
for cholera, 1245
for diarrhea, 1235t
for ehrlichioses, 1805
for epididymitis, 1347-1348, 1347t
for epididymitis in children, 2208
for folliculitis, 1564
for gastrointestinal anthrax, 1242
for granuloma inguinale, 1318
for infectious diarrhea, 2192t-2193t
for intraoral lacerations, 906
for Lyme arthritis, 1511, 1794
for Lyme disease, 1100, 1438, 1793, 1794t, 1795
for necrotizing ulcerative gingivitis, 900
for nongonococcal urethritis, 1320
for parasitic infection, 1772t-1775t
for pelvic inflammatory disease, 1325t
for pharyngitis, 968
for plague, 2475b
for pneumonia, 984, 984t
for Q fever, 1803
for Rocky Mountain spotted fever, 1570-1571, 1802t
for skin and soft tissue infection, 1854t
for STDs, 1315t
for STDs after sexual assault, 851t, 868b
for *V. vulnificus* infection, 1246
Doxylamine, 2081
Doxylamine overdose, 2081
Dracunculiasis, 1779
clinical features of, 1779
management of, 1779
Dracunculus medinensis (Guinea worm), 1770t-1775t, 1779
Drain cleaners, 1994, 1995t
Drains, 764
Dramamine (dimenhydrinate), 246

www.ketabpezeshki.com 66485457-66963820

Dressings, 764-765
burn dressings, 814-815, 815t
Dressler's syndrome, 1002-1003
Drinking. *See* Alcohol abuse
Drive-by shootings, e4
Driving safety, 2279
Dronedarone, 1039, 1088
Drop arm test, 1520
Drop attacks, 139t, 157
Droperidol (Inapsine), 2048t
for acute migraine attack, 1388t
for chemical restraint, 2417
for nausea and vomiting, 245-246
for rapid tranquilization, 1463
side effects of, 2417
Drowning, 1941-1944
clinical features of, 1942-1943
definition of, 1941
diagnostic studies, 1943
differential considerations, 1943
incidence of, 1941
key concepts, 1944b
management of, 1943-1944
pathophysiology of, 1942
patient disposition in, 1944
preventive efforts against, 1944
prognostic factors, 1942-1943
risk factors for, 1941-1942
symptoms and signs of, 1942
Drug abuse
adolescent, e2
injection
scars from, 1584, 1585f
suggested initial antibiotic management of, 1872t
during pregnancy, 2280
among sexual assault victims, 862
vascular abnormality caused by, 1152-1153
clinical features of, 1152
management of, 1152-1153
Drug Alert Warning Network (DAWN), 2395
Drug-assisted intubation (DAI), 2439
Drug eruptions, 1566-1567
clinical features of, 1567
differential considerations, 1567
eczematous, 1567
exanthematous, 1567
fixed, 1567
management of, 1567
morbilliform, 1566, 1566f
Drug history, 2397
Drug-induced gingival hyperplasias, 903
Drug-induced hemolytic anemia, 1600
Drug-induced liver disease, 1196
clinical features of, 1196
management of, 1196
patient disposition in, 1196
Drug-induced lupus, 1533, 1534b
Drug-induced pancreatitis, 1206, 1207b
Drug-induced thyroiditis, 1678
Drug overdose
anxiety in, 1477
diagnosis and treatment of, 94t
in heart transplant patients, 2372-2373
of immunosuppressive therapy, 2370-2372
in renal failure, 1304
mechanisms of, 1304b
Drug reactions, photosensitive, 1567
Drug-resistant tuberculosis, 1826-1827
drug regimens for, 1827t
risk factors for, 1827b
Drug-seeker lists, e35-e36
Drug seekers
management of, 2398-2399
suggestion of, 40
Drug susceptibility testing, 1816
Drug syncope, 139t
Drugs. *See also specific drugs, classes of abuse*
alcohol interactions, 2390-2391
plants as, 2066
for acute coronary syndrome, 1000, 1024-1027, 1033
for airway support, 2439
alcohol interactions, 2390t
Drugs *(Continued)*
antituberculosis, 1822-1824, 1822t-1823t
for anxiety disorders, 1478-1479
aplastic anemia caused by, 1593t
associated with hemolysis in G6PD deficiency, 1596b
associated with hypomagnesemia, 1649
associated with purpura, 1584b
associated with violence, 2420b
for atrial fibrillation, 1051-1052, 1052b
for burn pain, 816
for cardiovascular emergencies, 2440
for COPD, 962-963
cycloplegic, 191t
for diabetes, 1665t
emergency medical services, 2436-2437
for GI bleeding, 252
and heart failure, 1082
herbal medicine interactions, 2072t-2073t, 2073
illicit drugs, 1669b-1670b
for incomplete cord injury, 418-419
induction agents, 15-16
for inflammatory bowel disease, 1271b
for intubation, 13-16
for irritable bowel syndrome, 1262, 1262b
"knock-off," 2396
"look-alike," 2396
mood disorders caused by, 1471-1472
mucokinetic, 963
mydriatic, 191t
for neonatal resuscitation, 117-118, 117t
in older adults, 325
ophthalmic, 929, 930t
for parasitic infections, 1770t
for pediatric intubation, 109
for pediatric resuscitation, 104t
in pregnancy, 2316-2330, 2330b
for prostatitis, 1335
removal of, in anticholinergic overdose, 1973
for respiratory emergencies, 2439
for rheumatoid arthritis, 1515t
for seizures and status epilepticus, 158t-159t
seizures caused by, 1378
serum levels in nausea and vomiting, 242
for somatoform disorder, 1484-1485
for status epilepticus, 1381t
street drugs, 1400
teratogenic risk classification, 2316, 2317b
that cause depression or manic symptoms, 1471b
that cause psychosis, 1462b
that induce rhabdomyolysis, 1669b-1670b
that induce syncope, 137, 137b
toxins, 255b-256b
transfer across placenta, 2316
transfer during lactation, 2316-2317
for traveler's diarrhea prevention, 1259
for traveler's diarrhea treatment, 1259
for upper GI disorders, 1184-1185
for viral illnesses, 1720, 1721t-1722t
Dry drownings, 1942
Dryvax (smallpox vaccine), 2476
Dual-control ventilation, 24
Duke criteria, 1108b
modified, 2105b
Dulcolax (bisacodyl), 264t-265t
Duloxetine, 1432, 1663
DUMBELS (diarrhea, urination, miosis, bronchoconstriction or bronchorrhea, emesis, lacrimation, and salivation) symptoms, 825-826, 2058t
Duodenal inflammation, 224t-225t
Duodenal perforation, 464, 465f
Duodenal rupture, 467, 467f
Dupuytren's fracture, 512t-513t
Dural puncture, 1395, 2227
Durkan's or the median nerve compression test, 589
Duroziez's sign, 1111
Dust, 2456, 2456f
Duty
to accept appropriate transfers from other hospitals, e68-e70
duties of individuals, e33-e34
to report transfer violations, e70
Duverney fracture, 659
Dying. *See* Death and dying
Dynamic situations, 2459
Dynamic splinting, 548, 549f
Dysbarism, 1915-1927
Dysdiadochokinesia, 165
Dysentery, 2189
Dysfunctional uterine bleeding, 274t
Dyskinesia
respiratory, 2049
tardive, 2049
Dysphagia, 1181-1184, 1365
causes of, 1182b
clinical features of, 1182-1183
diagnostic strategies for, 1183
differential considerations, 1183
esophageal, 1183
management of, 1184
oropharyngeal, 1182-1183
pathophysiology of, 1182
Dysphasia, 1365
Dyspnea, 206-213
ancillary testing in, 207-208, 210t
assessment of, 206
critical diagnoses, 208-210
definition of, 206
diagnostic approach to, 206-208
differential diagnosis of, 206, 207t, 208-213
in pregnancy, 2294t
duration of, 206
emergent diagnoses, 210
empirical management of, 210-213
epidemiology of, 206
on exertion, 206
guidelines for management of, 212f
history taking in, 206-207
onset of, 206
paroxysmal nocturnal, 206
pathophysiology of, 206
patient disposition in, 210-213
patterns of disease resulting in, 209t
pivotal findings, 206-208, 208t
positional changes with, 206
in pregnancy, 2294t
rapid assessment and stabilization of, 211f
signs of, 207
symptoms of, 207
in systemic lupus erythematosus, 1530
terminology, 206
traumatic, 207
Dysrhythmias, 1034-1063
absent, 2153
in anaphylaxis, 1552t
anatomy and conduction during, 1034-1035
antipsychotic-induced, 2049
anxiety in, 1476
approach to, 1040-1041
classification of, 1040
clinical features of, 139t, 2153
from cocaine, 2001, 2003
completely irregular (chaotic), 1050b
definition of, 1034
in digitalis toxicity, 1982, 1983b
in drowning, 1942
ECG tracings in, 1034-1035, 1035f, 1041, 1041b
fast, 2153
after head injury, 360
and heart failure, 1081
in hypothermia, 1890-1891
initial assessment of, 1040-1041
key clinical questions, 2153
key concepts, 1063b
management of, 1040-1041, 2153
mechanisms of formation, 1035, 1037f
pediatric, 2153-2159
clinical features of, 2153
management of, 2153
treatment options, 2154b
pseudodysrhythmias, 1041, 1042f
reentry, 1035, 1037f
risk factors for, 2153b
sinus, 1042, 1043f
slow, 2153
stable, 1040-1041
triggered activity, 1035
unstable, 1040

www.ketabpezeshki.com 66485457-66963820

Dysrhythmias *(Continued)*
ventricular
in beta-blocker overdose, 1989
hypomagnesemia in, 1649
Dysthymic disorder, 1470
Dystocia, 2342
shoulder, 2342t, 2344-2345, 2344f
Dystolic dysfunction, 1080
Dystonia
antipsychotic-induced, 2048
neuroleptic-induced, 1464
Dysuria
causes of, 1331t
in children, 2212, 2212b
diagnostic protocol for women, 1332f
differential diagnosis of, 1331t
laboratory findings, 1331t
physical examination findings, 1331t

E
E-coded hospital records, 335
E codes, 335
Ear(s), 378
anatomy of, 369, 1918f
cauliflower ear, 378
examination of, 373
foreign bodies in, 769-771
clinical features of, 769
diagnostic strategies for, 769
history taking with, 769
instruments for removal of, 770, 770f
management of, 769-771
physical examination findings, 769
removal methods, 770
Ear canal, external, 769, 769f
Ear lacerations, 378
Ear squeeze, 1918
Early goal-directed therapy, 71
Earthquakes, 2457, 2458f, 2465
Eastern Association for the Surgery of Trauma (EAST), 407
Ebola virus, 2471
Ecallantide (Kalbitor), 1557
Echinococcosis, 1777
clinical features of, 1777
diagnostic strategies for, 1777
drug regimens for, 1772t-1775t
management of, 1777
Echinococcus granulosus infection, 1770t-1775t
Echinococcus multilocularis infection, 1770t-1775t
Echocardiography
in acute coronary syndrome, 1017t, 1020
in aortic dissection, 1126-1127, 1126t
bedside, 1532
in blunt aortic injury, 454, 454f
during CPR, 92
myocardial contrast echocardiography, 1020
in myocardial contusion, 445
in myocardial rupture, 447, 447f
in pericardial effusion, 1095, 1095f
stress, 1017t, 1020
in systemic lupus erythematosus, 1532
transesophageal
in aortic dissection, 1126-1127, 1126t
in blunt aortic injury, 454, 454f
transthoracic, 1126
Echoviruses, 1732
Eclampsia, 2290-2292
BP control for, 1120t, 1122
definition of, 2290
management of, 2291, 2292b
treatment of, 1382
Economic violence, e2
Ecstasy. *See* Methylenedioxymethamphetamine
Ecthyma (*Streptococcal impetigo* infection), 1564, 1859
Ectopic precautions, 2284
Ectopic pregnancy, 2284-2288
ancillary testing in, 2287
clinical features of, 2285
diagnostic strategies for, 2285-2287
differential considerations, 2287
hormonal assays, 2286-2287
Ectopic pregnancy *(Continued)*
management of, 2287-2288, 2288f
pelvic pain in, 267t-268t
risk factors for, 2284, 2285b
ruptured
abdominal pain in, 227, 227t-228t
clinical features of, 139t
sonographic findings, 2285-2286, 2285b, 2285f-2286f
Eczematous drug eruptions, 1567
Edema
Berlin's, 916
cerebral. *See* Cerebral edema
cytotoxic, 344
foreskin, 496, 496f
heat edema, 1900
high-altitude cerebral edema (HACE), 1928, 1936-1937, 1936b
high-altitude pulmonary edema (HAPE), 1928, 1934-1936, 1934b
laryngeal, 1552t
peripheral, 1779
pulmonary. *See* Pulmonary edema
scrotal, 2210
small bowel, 465-466, 466f
vasogenic, 343
Edentulousness, 5-6, 6f
EDTIAR (Extended Duration Topical Insect and Arthropod Repellent) (U.S. Army), 1808
Education
cultural, e28, e29b
postmortem, e43-e44
teachable moments, 336-337, 816
Education in Palliative and End-of-Life Care (EPEC) curriculum, e52
Education in Palliative and End-of-Life Care for Emergency Medicine (EPEC-EM) curriculum, e47, e55, e56-e57
EFAST (extended FAST) examination, 290, 292-293, 2494
Efavirenz
for HIV infection, 1721t-1722t
side effects of, 1765, 1766t
Effacement, 2333
Effective refractory period, 1034, 1036f
"Effort DVT," 1159
Effusion
exudative, 993
loculated, 992-993
parapneumonic, 992
pleural, 992-996
transudative, 993
Eggplant deformity, 496
Egyptian Ebers Papyrus, 1216
Ehrlichioses, 1804-1805
clinical features of, 1804
diagnosis of, 1804, 1805f
management of, 1805
80% rule, 939
Eisenmenger's syndrome, 2148
Ejection fraction, 1080
Elapidae snakebite, 797-798
Elapidae snakes, 795-796
Elbow
anatomy of, 596-597, 597f
calcific tendinopathy in, 1521
ligamentous structures of, 596, 597f
neurovascular structures of, 596, 597f
normal bone relationships in, 2255-2256, 2255f
ossification around, 2255, 2255t
ossification centers, 599, 600t, 2255, 2255f
secondary growth centers, 599, 600f
soft tissue disorders, 614-616
Elbow injury, 596-617
clinical features of, 597-601
dislocation, 612-614
anterior, 613f, 614
definition of, 525
distal brachial artery thrombosis after reduction of, 501f
lateral, 614
medial, 614
posterior, 613-614, 613f
fat pad signs, 600f, 604
Elbow injury *(Continued)*
fractures, 601-612
history taking in, 597
key concepts, 616b-617b
management of, 601
nerve injury, 520t
nursemaid's elbow (radial head dislocation), 616-617, 2258, 2258f
physical examination findings, 597-598
radiographic findings, 598-601, 600f
Elder abuse, 325, 885-892
asking about, 886-887, 887b
caregiver interview in, 890
clinical features of, 886-889
criteria for detection and management of, 890
definition of, 885-886
diagnostic strategies for, 889
documentation of, 889-890
domestic, 885-886
epidemiology of, 885
etiology of, 886
future directions for, 891
indicators of, 887b
institutional abuse, 891
interventions for, 890
key concepts, 892b
physical examination for, 888-889
questions to ask about, 887b
referrals for, 890
reporting requirements, 890-891
risk factors for, 886, 887b
sexual abuse, 870
signs of, 888, 888b, 888f
types of, 885-886
Elder patients, 2351-2355, 2429
abdominal pain in, 2354, 2354t
CT findings, 226-227, 230t
abdominal trauma in, 328
abuse and neglect of, 885-892
alcohol-related disease in, 2392
appendicitis in, 1227
back pain in, 648
clinical features of, 2353-2354
demographics of, 2351
depression in, 1470
diagnostic strategies with, 2354
evaluation of, 2353-2354
falls in, 2355
hip fractures in, 328
history taking from, 2353
immunizations for, 2355
infections in, 2354
intimate partner violence among, 873
key concepts, 2355b
lower extremity fractures in, 328
medication effects in, 325
myocardial infarction in, 2354
pain management in, 48
pharmacologic considerations, 2351-2353
physical examination of, 2353-2354
physiologic reserve, 325
population of, 885
preventive care for, 2355
psychosocial issues, 2353
sexual assault of, 870
spinal cord injury in, 327-328
mechanism of, 396, 398f
substance abuse among, 2395
suicide among, 1492, 1495
thoracic trauma in, 328
trauma, 324-329
trauma assessment of, 325
traumatic brain injury in, 327
upper extremity fractures in, 328
vertebral fractures in, 327-328
Electrical alternans, 1095-1096, 1096f
Electrical cord bruising, 845, 846f
Electrical current
duration of contact, 1908
resistance to, 1907
of body tissues, 1907b
of skin, 1908t
and rhabdomyolysis, 1669b-1670b
types of circuits, 1906-1907

www.ketabpezeshki.com 66485457-66963820

Electrical injury, 1906
ancillary tests, 1913-1914
assessment of, 1913
burn wound care for, 1914
cardiovascular, 1910
clinical features of, 1910-1912
complications of, 1912
differential considerations, 1912
duration of contact and, 1908
emergency department management of, 1913-1914
entry, 1906-1907
exit, 1906-1907
to extremities, 1911, 1914
factors determining, 1906, 1907b
ground contact point for, 1906-1907
head and neck, 1910
key concepts, 1914b
low-voltage injuries, 1912
management of, 1912-1914
mechanisms of, 1909
to nervous system, 1911
outpatient management of, 1914
pathway and, 1908-1909
patient admission, 1914
patient disposition in, 1914
physics of, 1906-1909
skeletal, 1911
skin injury, 1910-1911
source contact point for, 1906-1907
triage considerations, 1913
types of burns, 1909, 1909b
to viscera, 1912
Electrical therapy, 1088
Electrocardiography (ECG)
in acute coronary syndrome, 1003-1021, 1014f, 1017t, 1028
in acute MI, 1004f
in aortic dissection, 1126
in asthma, 948
in atrial fibrillation, 1050, 1050f
in biventricular pacing, 1073, 1074f
Brugada criteria, 1055, 1058f
in Brugada's syndrome, 1062, 1062f
in chest pain, 216-218, 217t-218t
in COPD, 959-960
in dysrhythmia, 1041, 1041b, 1041f
in electrical alternans, 1095-1096, 1096f
15-lead, 1014-1015, 1014f
flutter waves, 1052
in GI bleeding, 250
Griffith criteria, 1057, 1058f
in headache assessment, 173t
His bundle, 1034-1035, 1037f
in hypercalcemia, 1645, 1646f
in hyperkalemia, 1636-1637, 1637f-1638f
in hypokalemia, 1640, 1640f
indications for, 1913b
in infants and children, 2145, 2145t
in ischemic chest pain, 218t
in massive PE, 1166, 1167f
in myocardial contusion, 445
in nausea and vomiting, 242
normal, 1066-1067, 1066f, 1069f
in pacemaker malfunction, 1071
in pericardial tamponade, 449, 449f
posterior, 1008f
in posterior acute myocardial infarction, 1008, 1008f
PR interval, 1035
in pulmonary embolism, 1162, 1162f
Q waves, 1006
QT dispersion, 1016
serial, 1015-1016, 1015f
in sinus dysrhythmia, 1034-1035, 1035f
ST segment depression, 1004-1005, 1005f
in acute coronary syndrome, 1005, 1005f
differential diagnosis of, 1005
reciprocal, 1005
ST segment elevation, 1004, 1005f
differential diagnosis of, 1004, 1004t
dynamic, 1004
ECG differential diagnosis of, 1008-1011
noninfarctional, 1008-1009, 1009f
ST segment-T wave morphology, 1004, 1005f
ST segment trend monitoring, 1015-1016
Electrocardiography (ECG) *(Continued)*
surface, 1034-1035, 1037f
T wave inversions, 1006
in acute coronary syndrome, 1005, 1006f
differential diagnosis of, 1006
T wave pseudonormalization, 1006
12-lead
in acute coronary syndrome, 1028
in dysrhythmia, 1041, 1041f
limitations, 1016, 1033b
in pacemaker malfunction, 1071
Electroconvulsive therapy, long-term, 1473
Electroencephalography, 160-161
Electrolyte disorders, 1636-1651
in aspirin overdose, 1965
in diabetic ketoacidosis, 1657t
in digoxin toxicity, 1984-1985
in hyperglycemic hyperosmolar state, 1662
key concepts, 1651b
in rhabdomyolysis, 1669b-1670b, 1672
Electrolytes
alcohol effects on, 2387-2388, 2388t
for dehydration in children, 2199-2203
maintenance, 2201-2203, 2201t
requirements
in hyponatremic volume depletion, 2202-2203, 2202b
in isonatremic volume depletion, 2201-2202, 2201b
serum levels, in children, 2143
Electromagnetic spectrum, 1947, 1947f
Electromechanical dissociation, 94
pseudo-EMD, 94
true, 94
Electromyography (EMG), needle, 1429
Electron beam computed tomography, 1020-1021
Electronic fetal monitoring, 2334-2335
Electrophysiologic testing, 1429
Electroporation, 1906
Electrothermal heating formulas, 1907b
Elemental metals, 824
Elephantiasis, 1779
clinical features of, 1779
diagnostic strategies for, 1779
management of, 1779
Elevated arm stress test, 1151
Ella, 869t
Embolectomy, surgical, 1167-1169
Embolism. *See also* Thromboembolism
air
central line emergencies, 2411t
clinical features of, 139t
in neck injury, 423, 429
amniotic fluid, 2292-2293, 2349-2350
arterial, 1146
pathophysiology of, 1139
recompression therapy for, 1925
arterial gas, 1921-1922, 1923t
recompression therapy for, 1923, 1925
atheroembolism (blue toe syndrome), 1146
atheromatous, 1144, 1144f
differentiation from thrombosis, 1141t
fat, 524, 533b
mesenteric arterial, 1222f, 1222
pulmonary. *See* Pulmonary embolism
superior mesenteric artery, 1221-1222, 1222f
thromboembolism
pathophysiology of, 1139, 1157
in pregnancy, 2296-2297
venous, 360, 1157
Embolization
in pelvic fracture, 669
pelvic vessel, 2348
from prosthetic valve, 1112
Embryo, 2272
EMC. *See* Medical screening condition
Emend (aprepitant), 246
Emergency Cardiac Care guidelines (AHA), e54
Emergency care
for any individual, e60-e61
comprehensive emergency management, 2463, 2468b
diversity of practice elements, e79-e80
emergency conditions, 2487-2489
and ethics, e33
Emergency care *(Continued)*
as fishbowl medicine, e79
implied consent in, e71
medical and moral imperatives in, e36
patient-physician relationship in, 2423
presentation to ED for, e61
vs primary care, e38t
for private patients, e61
problem areas in, 2509-2510
request for examination or treatment, e61
restricted access to, e44
sources of failures in, 2505-2509, 2506f
stabilization requirements, e64-e65
stressors in, e79-e80
true emergency, e71
universal, e60-e61
Emergency conditions, 2487-2489
Emergency contraception, 868-869, 1362
key concepts, 1362
types of, 869t
Emergency delivery. *See* Delivery
Emergency department(s)
alarm systems, 2420
antidotes used in, 1957t-1958t
authorization, e64
characteristics that affect performance, 2506t
collections or insurance information, e64
death in, e47, e51-e55
dedicated, e61
design, 2505-2506
designated rooms, 2420-2421
discharge or transfer to on-call physician office from, e67
functions of, e62-e63
guidelines for care of children in, 2094-2095
guidelines for dealing with gang violence, e5
human factors, 2505-2506
limitations, 2331
limited access to, 2420
palliative care in, e55-e57
parking of patients at, e61
patient safety measures, 877
pediatric-friendly, 2095
pediatric-ready, 2094-2095
performance-shaping factors, 2507
policies, procedures, and practice guidelines, e63
preparedness for chemical weapons, 2476, 2476b
presentation for care at, e61
prevention of violence in, 2420-2421, e4
registration process, e64
secure examination rooms, 2420-2421
security personnel, 2420
as source of care, e28
trauma care in, 288-294
Emergency department thoracotomy (EDT), 294, 450-451, 450f
in abdominal trauma, 470-471
in blunt chest trauma, 295f, 448b
indications for, 448b, 450-451
in penetrating chest trauma, 294f
in penetrating traumatic cardiac arrest, 448b
in pericardial tamponade, 450-451
survival rates after, 451
Emergency department–based chest pain centers, 1021-1022
Emergency Information Form (EIF), 2094
Emergency management plans, 2463
Emergency Management Program Guidebook (VA), 2467
Emergency medical dispatch (EMD), 2437
Emergency medical responders, 2435, 2436t
Emergency medical services (EMS), 2433-2441
access to, 2437
advanced life support, 2435
basic life support, 2435
care under fire, 2451
communications, 2437
development of, 2433-2434
direct medical control, 2438
end-of-life care, e50
equipment for, 2437
federal oversight, 2437-2438
field communications, 2437
first responder systems, 2435
future directions, 2436, 2441

www.ketabpezeshki.com 66485457-66963820

Emergency medical services (EMS) *(Continued)*
ground transport, 2433-2441
helicopter emergency medical services (HEMS), 2442-2443
indirect medical control, 2438
integration with air medical transport, 2445
levels of provider, 2435-2436
local oversight, 2438
material resources, 2436-2437
medications for, 2436-2437
multitiered systems, 2435
out-of-hospital care, 2439-2440
oversight, 2437-2438
parking of patients by, e61
private agencies, 2434-2435
public agencies, 2434-2435
resources, 2439t
scope of practice, 2435-2436
single-tiered systems, 2435
standby personnel, 2450
state oversight, 2438
systems, 2434-2435
systems protocols, 2462
systems status management, 2437
tactile support, 2449-2453
training, 2436t
Emergency Medical Services Agenda for the Future (NHTSA), 2433
Emergency Medical Services Education Agenda for the Future: A Systems Approach, 2436
Emergency Medical Services for Children (EMS-C) initiative, 2433
Emergency medical services (EMS) medical director, 2438
Emergency medical technician–paramedic (EMT-P), 2436, 2436t
Emergency medical technicians (EMTs), 2433, 2435, 2436t
Emergency Medical Treatment and Active Labor Act (EMTALA), 2440, 2445, e33-e34, e60-e70
application to hospital inpatients, e67
definition of stabilized, e65
disposition issues, e65-e70
documentation requirements, e64
hospital transfer form, e66f
requirements for patient transfers, 2441b
stabilization requirements, e64-e65
Emergency medicine. *See* Emergency care
Emergency Medicine Residents' Association (EMRA), e37t
Emergency Nurses Association, 2094-2095
Emergency physicians, e45, e79-e80
Emergency research, e44
Emergency Severity Index, 2090
Emergency ultrasound, 2492-2504. *See also* Ultrasound
Emesis, 457
EMLA (eutectic mixture of local anesthetics), 754
Emotional abuse
definition of, 886
elder abuse, 885
questions to ask about, 887b
Emotional exhaustion, e80
Emotional reactions
grieving and bereavement, 1472, e54-e55
maintaining distance, 2425
responding to, e53
after sexual assault, 869b
Empacho, e27
Empathy
elements of empathic death disclosure, e53b
responding to feelings, e53
Emphysema
retrobulbar, 193t-196t
subcutaneous, 435-436
chest pain and, 217t-218t
management of, 436
pathophysiology of, 435-436
Emphysematous cholecystitis, 1203
Empty can test, 1520
Empyema, 1812-1813
EMRA. *See* Emergency Medicine Residents' Association
EMS. *See* Emergency medical services
EMS Systems Act of 1973 (P.L. 93-154), 2433
EMTALA. *See* Emergency Medical Treatment and Active Labor Act
Emtricitabine, 1721t-1722t, 1766t
EMTs. *See* Emergency medical technicians
Enalapril, 1119-1120
Enalaprilat, 1119-1120, 1122.e1t-1122.e2t
Encephalitis
California, 1725
definition of, 1447
differential diagnosis of, 174t
drugs for treatment of, 1721t-1722t
epidemiology of, 1447
etiology of, 1448
pathophysiology of, 1449
risk factors for potentially catastrophic illness, 172b
subacute sclerosing panencephalitis (SSPE), 1725
viral
causes of, 1737
complications of, 1451
therapy for, 1457
Encephalomyelitis, 1447
Encephalopathy
in cancer, 1628
hepatic, 1194-1195
hypertensive, 1116, 1120t
postischemic, 81
End-diastolic pressure, 1076-1077, 1077f
End of life, e47-e59
End-of-life care, e47, e50
Education for Palliative and End-of-Life Care (EPEC) curriculum, e52
Education in Palliative and End-of-Life Care for Emergency Medicine (EPEC-EM) curriculum, e47, e55, e56-e57
key concepts, 2518b, e58b
out-of-hospital considerations, e50-e51
palliative care, e55-e57
questions for discussion of, e56t
supportive out-of-hospital treatments, e51
End-of-life decisions, 328-329
End-stage renal disease, 1301
End-tidal carbon dioxide (CO_2), 7, 7f, 62-65
in CPR, 90-91
in gastroenteritis, 65, 65f
in metabolic acidosis, 65, 65f
End-tidal carbon dioxide partial pressure (PET_{CO_2}), 90-91, 91f, 947
Endocardial biopsy, 1099, 1099f
Endocarditis
bacterial. *See* Infective endocarditis
fungal, 1107
infective, 1106-1108
in children, 2159-2160
key concepts, 1112b
modified Duke criteria for, 2105b
noninfectious, 1530f
prosthetic valve, 1106-1107, 1112
Endocrine agents, 2318t-2321t, 2328-2329
Endocrine disorders
anxiety in, 1476
in pregnancy, 2309-2311
rhabdomyolysis in, 1669b-1670b
Endocrine system
alcohol effects on, 2387
and mood disorders, 1467
normal physiology, 1652-1653
Endoleaks, 1136, 1136f
Endometriosis
pelvic pain in, 267t-268t
thoracic, 988
Endometritis, postpartum, 2350
Endophthalmitis, 190, 918f
management algorithm for, 193t-196t
post-traumatic, 915, 918
Endorphins, 35, 2052
Endoscopic retrograde cholangiopancreatography (ERCP), 1203, 1212
Endoscopic retrograde pancreatography (ERP), 1214
Endoscopy
in diverticulitis, 1264
with GI bleeding, 252
for removal of esophageal foreign bodies, 778
Endotracheal intubation
in burns, 812, 812t
of children, e17, e17f
indications for, 306
special considerations, 306
confirmation of tube placement, 7-8, 7f
for rapid sequence intubation, 12
Endotracheal tubes (ETTs)
age-based rule for, 109
cuffed, 109
size based on body length, 109
size estimates and depth for pediatric trauma, 307b
size for newborns, 115t
Endovascular repair
of abdominal aortic aneurysm, 1135-1137, 1136f, 1137b,
of aortic tears, 455
Endovascular rewarming, 1893
Enemas
barium, 1263-1264
for constipation, 264b, 265
contrast, water-soluble, 1264, 1266
Enfuvirtide, 1721t-1722t, 1766t
Enhanced 9-1-1, 2437
Enoxacin, 1335-1336
Enoxaparin
for acute coronary syndrome, 1027
for anticoagulation, 1168b
for decompression sickness, 1925
for DVT, 1159
for PE, 1164-1165
Entactogen use/abuse
clinical features of, 2018
diagnostic strategies for, 2018
differential considerations, 2018
management of, 2018
pathophysiology of, 2018
patient disposition in, 2018
Entactogens, 2017-2018
Entamoeba histolytica infection (amebiasis), 1770t-1771t, 1778, 1781, 2195
drug regimens for, 1772t-1775t
intestinal
acute, 1253-1254
in AIDS, 1257t
antibiotic therapy for, 1235t
epidemiology of, 1250t, 1253
management of, 1254, 1257t
symptoms of, 1782
therapy for, 2192t-2193t
Enteritis. *See also* Gastroenteritis
in HIV infection, 1761
lupus, 1531
Enteritis necroticans (pig-bel), 1244
Enterobius vermicularis (pinworm), 1770t-1771t, 1783
antibiotic therapy against, 1235t
drug regimens against, 1772t-1775t
Enterocolitis, *C. difficile* antibiotic-associated, 1248-1249
Enteromonas hominis infection
in AIDS, 1257t
differential considerations, 1253
Enteroviral infections, 1732
Entitled patients, 2426, 2428-2429, 2428t
Enuresis, nocturnal, 2233
Envenomation, 798-799
Environmental control, 1829, 1929
Environmental Protection Agency, 2031
Enzyme defects, intrinsic, 1596
Enzyme-linked immunosorbent assay (ELISA), 1454, 2273, 2274f
Enzymes
cardiac, 445
pancreatic, 464
Eosinophilic esophagitis, 1174
clinical features of, 1174
management of, 1175
Eosinophils, 2358
EPEC-EM curriculum. *See* Education in Palliative and End-of-Life Care for Emergency Medicine curriculum
EPERC (End of Life/Palliative Education Resource Center) Fast Facts, e56-e57
Ephedra, 2005

www.ketabpezeshki.com 66485457-66963820

Ephedrine, 2005
duration of action, 191t
in pregnancy, 2328
EpiCeram, 1563
Epicondyle, 698
Epicondyle fractures, 610, 610f
clinical and radiographic features of, 610, 610f
management of, 610
pathophysiology of, 610
Epicondylitis
lateral (tennis elbow), 614-615, 1521, 1523
clinical and radiographic features of, 615
management of, 615
pathophysiology of, 614-615
medial, 1521, 1523
Epidemic cerebrospinal fever, 1710
Epidemiology, injury, 335-336
Epididymis, 1343f
Epididymitis, 1346-1348
in children, 2208, 2208f
clinical features of, 2208
diagnostic strategies for, 2208
management of, 2208
patient disposition in, 2208
clinical features of, 1346-1347
diagnostic strategies for, 1347
differential diagnosis of, 1344t, 1347
key concepts, 1354b
management of, 1347-1348
pathophysiology of, 1346
patient disposition in, 1348
treatment of, 1347t
ultrasound findings, 1347, 1347f
Epidural abscess
rapid assessment and stabilization of, 279
spinal, 649-650, 650f, 1426
Epidural hematoma, 363, 364f
acute, 363f
acute back pain in, 282t-283t
pediatric, 313
rapid assessment and stabilization of, 279
risk factors for potentially catastrophic illness, 172b
spinal, 1425-1426
Epiglottitis
adult, 969-971, 970f
clinical features of, 969
diagnostic strategies for, 969-970
differential considerations, 970
key concepts, 977b
management of, 970-971
patient disposition in, 971
radiographic findings, 970, 970f
pediatric, 108, 2110-2111, 2110f, 2115t
clinical features of, 2110
diagnostic strategies for, 2110
key concepts, 2116b
management of, 2110-2111
thumbprint sign of, 2110f
Epilepsy, 1375
absence
childhood, 2232
juvenile, 2232
benign, with centrotemporal spikes, 2232
classification of, 2231-2233
definition of, 156
gestational, 1379
in pregnancy, 2301t-2303t, 2307-2308
risk factors for, 2235
Epileptic syndromes, 2231-2233, 2232b
Epinephrine, 1871
for acute asthma, 2121t
for acute asthma in pregnancy, 2303t
for anaphylaxis, 802, 1551-1555, 1554b
for asthma, 950
for congestive heart failure in children, 2152, 2153t
for croup, 2113
dosing, 1871t
for heart failure, 1086
for hymenoptera stings, 802
for hyperkalemia, 1639
lidocaine, epinephrine, and tetracaine (LET), 48
for neonatal resuscitation, 117, 117t
for oral hemorrhage, 907
for pediatric dysrhythmias, 2154b
Epinephrine *(Continued)*
in pediatric resuscitation, 104t
in pregnancy, 2328
rebound phenomenon of, 2113
tetracaine, adrenaline (epinephrine), and cocaine (TAC), 48, 754
for wound management, 754
Epiphyseal fractures, 709
anatomy of, 709
clinical features of, 709
diagnostic strategies for, 709
management of, 709
pathophysiology of, 709
Epipremnum aureum, 2068
Episcleritis, 193t-196t
Episiotomy, 2337, 2338f
Epistaxis, 937-939
anterior, 938
diagnostic strategies for, 937-938
differential diagnosis of, 937b
epidemiology of, 937
etiology of, 937, 938b
key concepts, 940b
management of, 938-939
newer agents for, 939
posterior, 938-939
Epithelialization, 752
Eplerenone, 1122.e1t-1122.e2t
Epley maneuver, 168, 169f
Eponychium, 544
Eprosartan, 1122.e1t-1122.e2t
Epstein-Barr virus infection (infectious mononucleosis), 1731
clinical features of, 1731
diagnostic strategies for, 1731
differential considerations, 1731
management of, 1731
in pharyngitis, 965
Equipment. *See also* Instruments
for emergency medical services, 2437
for neonatal resuscitation, 115, 115b, 115t
for pediatric intubation, 109
for procedural sedation and analgesia, 52-53, 53b
tactile emergency medical support (TEMS), 2453
ultrasound, 2493-2494
urban search and rescue, 2454
Ergonomics, 2505-2506
Ergot alkaloids, 2329
Errors
alpha, e13t
beta, e13t
false negative, e13, e13t
false positive, e13, e13t
medical, 336
medication, 2506, 2510
type I, e13, e13t
type II, e13, e13t
Ertapenem, 984-985, 985t
Erysipelas, 193t-196t, 1566
Erysipelothrix rhusiopathiae infection, 1856t
Erythema, 1559t, 1566
Erythema infectiosum (parvovirus), 1571, 1730-1731, 1731f
arthritis, 1513t
clinical features of, 1730-1731, 1731f
differential considerations, 1731
Erythema marginatum, 1571f
Erythema multiforme, 1573, 1573f, 1583
clinical features of, 1573
management of, 1573
Erythema nodosum, 1538-1539, 1539f, 1576, 1576f, 1583
clinical features of, 1576
management of, 1576
Erythematous dermatitis, 1582f
Erythrocyte sedimentation rate
in headache assessment, 173t
normal, 926
in osteomyelitis, 1836
Erythroderma, 1583
Erythromelalgia, 1140, 1149
Erythromycin
alcohol interactions, 2390t
for bacterial conjunctivitis, 918-919
for *Campylobacter* enteritis, 1234
Erythromycin *(Continued)*
for chancroid, 1318
for chemical burns, 910
for cholera, 1245
for diarrhea, 1235t
for diarrhea in AIDS, 1257t
for diphtheria, 1695-1696
for epididymitis in children, 2208
hepatic injury, 1197t
for impetigo, 1564
for infectious diarrhea, 2192t-2193t
for Lyme disease, 1100, 1793, 1794t
for ophthalmia neonatorum, 919
for pertussis, 1698-1699
for pharyngitis, 968
in pregnancy and lactation, 2318t-2321t
for prophylaxis in bite wounds, 789t
for STDs, 1315t
for STDs after sexual abuse/assault, 851t
ESAR-VHP, 2467
Escape rhythms, 1041
Escharotomy, 815-816, 816f
Escherichia coli
in diarrhea, 2194-2195
enteroaggregative (EAEC), 2194-2195
enterohemorrhagic (shiga toxin–producing) (EHEC), 2194-2195
epidemiological aspects, 1243t
gastroenteritis, 1239-1240
enteroinvasive (EIEC), 2194-2195
enteropathogenic (EPEC), 2194-2195
enterotoxigenic (ETEC), 1235t, 1247-1248, 2194-2195
Gram's stain characteristics, 1453t
in osteomyelitis, 1834-1835
shiga toxin–producing (STEC), 2194-2195
antibiotic therapy against, 1235t
epidemiology of, 1234t
therapy against, 1235t, 2192t-2193t
Escherichia coli 0157:H7 toxin assay, 258
Eshmuna Code of Babylon, 1742
Esmolol, 1038
for aortic dissection, 1128
characteristics of, 1987t
for dysrhythmias, 1038
hemodynamic effects, 1118t
for hypertension, 1119t
for hypertensive emergencies, 2221t
for thyroid storm, 1682b
Esomeprazole, 1177t, 1184
Esophageal candidiasis, 1173-1175
Esophageal dysphagia, 1183
Esophageal foreign bodies, 774, 775f, 776-778, 1170
in children, 2182, 2183f
diagnostic strategies for, 777-778
history taking in, 777
key concepts, 784b
locations of, 776-777
management of, 778
patient disposition in, 2183
physical examination findings, 777
radiographic findings in, 2182, 2183f
Esophagitis, 1173-1175
caustic, 1174
clinical features of, 1174
management of, 1175
clinical features of, 1174
definition of, 1173
diagnostic strategies for, 1174-1175
differential considerations, 1175
drugs for treatment of, 1721t-1722t
eosinophilic, 1174
clinical features of, 1174
management of, 1175
in HIV infection, 1760-1761
infectious, 1173-1174
clinical features of, 1174
management of, 1175
management of, 1175
pill, 1174
clinical features of, 1174
management of, 1175
radiation-induced, 1174
clinical features of, 1174
management of, 1175

www.ketabpezeshki.com 66485457-66963820

Esophagus
alcohol effects on, 2384-2385
anatomy of, 1170
caustic burns of, 456
constriction locations, 776-777, 784b
obstruction of, 1170-1172
clinical features of, 1170-1171
diagnostic strategies for, 1171
differential considerations, 1171
lower, 1171-1172
management of, 1171-1172
upper, 1171
perforation of, 455-458, 1172-1173
anatomy of, 455
from blunt trauma, 456-457
causes of, 455-457, 456b
chest radiograph findings, 457, 458f
clinical conditions that may mimic, 457b
clinical features of, 457, 1172-1173
diagnosis of, 457, 1173
differential considerations, 1173
due to foreign bodies, 456
epidemiology of, 455
key concepts, 1185b
management of, 457-458, 1173
pathophysiology of, 455
from penetrating trauma, 456-457
rupture of
chest pain in, 220t-221t
postemetic, 457
spontaneous, 457
Essex-Lopresti lesion, 512t-513t, 593
Estazolam (ProSom), 2078t
Eszopiclone (Lunesta), 2080-2081
ET-1, 1079
Etanercept, 1515t
Ethambutol
for diarrhea in AIDS, 1257t
suggested doses for adults, 1824t
for tuberculosis, 1822t-1823t, 1824-1825, 1825t, 1827t
Ethanol
blood levels, in alcoholism, 2379t
disulfiram and similar reactions, 2391
effects on metabolism, 2380-2381, 2388t
for ethylene glycol toxicity, 2011-2012
herbal medicine interactions, 2072t-2073t
for methanol toxicity, 1957t-1958t, 2011-2012
therapeutic doses, 2011-2012, 2012t
Ethanol poisoning, 1955t. *See also* Alcohol abuse
Ethical decision making, e35
rapid approach to, e38-e39, e38b
Ethical problems, e36
Ethics, e33
ACEP Code of Ethics, e23, e28, e37t
bioethics, e33-e46
codes of, e36, e37t
in intimate partner violence, 882-883
oaths of, e36
proactive, e45
resuscitation ethics, e41-e44
Ethinyl estradiol, 869t
Ethionamide, 1822t-1823t, 1824
Ethnic disparities, e23-e24
factors contributing to, e24
progress to date, e26
Ethosuximide (Zarontin)
adverse effects of, 1383t
for children, 2240t
for long-term anticonvulsant therapy, 1384t
side effects and drug interactions, 2407t-2408t
Ethyl chloride and fluori-methane sprays, 47
Ethyl glucuronide, 2380t
Ethylene glycol, 1633, 2009-2013
metabolism of, 2009, 2010f
pharmacology of, 2009
Ethylene glycol poisoning
acute neurologic stage, 2010
antidote for, 1957t-1958t
cardiopulmonary stage, 2010
clinical features of, 2010
delayed neurologic sequelae stage, 2010
diagnostic strategies for, 2010-2011
differential considerations, 2011
management of, 2011-2012
Ethylene glycol poisoning *(Continued)*
pathophysiology of, 2009-2010
patient disposition in, 2013
prevention of, 2013
renal stage, 2010
treatment goals, 2011
Ethylenediamine tetra-acetate (EDTA), 1957t-1958t
Etidocaine, 46t
Etomidate, 15
benefits and adverse effects, 55t
in pregnancy, 2318t-2321t, 2322
in procedural sedation and analgesia, 54t-55t, 58, 59t
in resuscitation with head injury, 348
Etravirine, 1766t
ETs, 1079
Eucalyptus, 2068
Euphorbia pulcherrima (poinsettia), 2068
European Society for Cardiology, 998
Eutectic mixture of local anesthetics (EMLA), 47
Evans formula, 813t
Evaporation, 1896
Eve. *See* Methylenedioxyethamphetamine
Eversion, ankle, 723
Evidence
best evidence topic (BET), e20t, e21
trace, 841-842, 842f
Evidence-based medicine, e19-e21
effectiveness of, e21
fundamental steps, e19
terms used in, e20t
Evidence collection, e20
in bite marks, 864, 864b
chain of custody, 863-864, 864b
in handgun wounds, 834-836
key concepts, 844b
in motor vehicle trauma, 841, 841b
in pedestrian collisions, 844b
in sexual assault, 863-867, 863b
summary of useful evidence, e21
Evil, e34-e35
Evisceration
with abdominal stab wounds, 472
for assessing intactness of peritoneum, 472
Ex-Lax (senna), 264t-265t
Exanthem, 1570-1572. *See also* Rash
with drug eruptions, 1567
of Rocky Mountain spotted fever, 1799-1800, 1800f
Exanthem subitum (roseola infantum), 1571, 1729
Exchange transfusions
for infants, 2170, 2170f-2171f
for sickle cell disease, 1599
Exelon (rivastigmine), 1408
Exercise
excessive, 1082
for heart failure, 1089
for physicians, e82
in pregnancy, 2280
Exercise-induced asthma, 945
Exercise stress electrocardiography, 1017t
Exercise testing, graded, 1021
Exertional headache, 1397
Exertional heatstroke, 1903-1904, 1903t
Exhaustion
emotional, e80
heat, 1901-1902
Exit block, 1069
Exotic snakebite, 800
Expedited partner therapy, 1312
Explosive agents
in terrorism, 2466
in urban search and rescue, 2456
Exposure assessment and treatment
in geriatric trauma, 326
in multiple trauma, 292
in pediatric trauma, 308, 309t
Extended Duration Topical Insect and Arthropod Repellent (EDTIAR) (U.S. Army), 1808
Extended focused abdominal sonography in trauma (eFAST) examination, 292-293, 467-468
Extension injury, spinal, 385t, 393
Extension supracondylar fractures, 603-607, 606f
clinical features of, 604
complications of, 606-607
Extension supracondylar fractures *(Continued)*
diagnostic strategies for, 604
management of, 604-605
mechanism of injury, 603-604, 605f
pathophysiology of, 603-604
Extension teardrop fracture, 393
Extensor tendon injuries, 557-560
zone classification for, 557f
zone I injuries, 557-558, 558f
zone II injuries, 559
zone III injuries, 559
zone IV injuries, 559-560
zone V injuries, 560
zone VI injuries, 560
zone VII injuries, 560
zone VIII injuries, 560
Extensor tendons, of hand, 538-539, 539f-540f
External ear barotrauma, 1918, 1926
External ear canal, 769, 769f
External genitalia
definition of, 479
trauma to, 494-498
in children, 497
female, 497
External radiation exposure, 1949
External radioactive contamintion, 1949
External rotation method of Leidelmeyer, 633, 633f
External rotation stress test, 731
External validity, e20, e20t
Extra-articular tibial fractures, proximal, 717-718
Extracorporeal blood rewarming, 1893-1894, 1894t
Extracorporeal circulatory support, 105
Extracorporeal elimination, 1989
Extracorporeal membrane oxygenation, 105
Extracranial hemorrhage, in infants, 312-313, 313f
Extractions, 2450, 2450f
Extraglottic devices, 19-21
difficult placement, 6, 6b
Extraocular movement disorders, 929
Extraocular muscles, 187, 929, 929f
Extrasystoles, 1046-1048
Extremities
electrical injury to, 1911, 1914
examination of
FASTER, 2494
in pediatric trauma, 310
lightning injury to, 1911
Extremity hemorrhage control, 2451
Extremity tourniquets, 2451
Exudates, 993
causes of, 993b
Light's criteria for, 994, 995b
Exudative effusion, 993
Eye(s), 378
anatomy of, 369
external and internal, 184, 185f
normal, 910f
bedside sonography of, 374
biologic exposures, 912
cardinal movements, oculomotor muscles, and nerves of, 177f
foreign bodies in, 767-769
clinical features of, 767
computed tomography of, 768, 768f
diagnostic strategies for, 768
history taking with, 768
management of, 768-769, 769f
physical examination findings, 768
injury to, 909
caustic, 189, 189f
chemical burn, 910
red and painful, 184-197
ancillary testing in, 188-189
critical diagnosis of, 189
diagnosis of, 184-189, 192f
differential diagnosis of, 184, 189-191
emergent diagnoses, 189-190
epidemiology of, 184
examination of, 185-188
history taking in, 184-185
irrigation of, 191
key concepts, 197b
management of, 191-193, 193t-196t
pain relief for, 191
pathophysiology of, 184

www.ketabpezeshki.com 66485457-66963820

Eye(s) *(Continued)*
patient disposition in, 197
pediatric, 193-196
pivotal findings, 184, 186b
protective interventions for, 192-193
traumatic, 196-197
urgent diagnoses, 190-191
trauma to, 909, 916-918
Eye examination, 372
bedside sonography, 375f
bedside testing, 188
complete, 185-186, 186b
external, 186-187
funduscopic, 188
pressure determination, 187
pupillary evaluation, 187
slit-lamp examination, 186-187, 188f
Eye status review questions, 185
Eyebrow lacerations, 378
Eyelids
chalazion of, 920-921, 921f
disorders of, 920-921
injury to, 909
lacerations of, 378, 916-917
clinical features and management of, 916-917
complex, 917
trauma to, 909-910
EZ-IO, 2452

F

Fab antivenin (FabAV), 799
algorithm for use of, 800f
dosage for pit viper envenomation, 799t
Fab(2) antivenin, 799
Fab fragments, digoxin-specific (DigiFab), 1957t-1958t, 1984-1985
calculation of, 1985b
recommendations for administration of, 1985b
Face
anatomy of, 369-370
blood supply to, 370, 371f
bones of, 369, 369f
deep space infections in, 971
Dejeune onion skin pattern of analgesia, 401
nerve supply to, 369
skin of, 370
skin tension lines, 752f
Face presentation, 2342t, 2345
Facebook, 2464
FACES pain scale, 36-37
Facet dislocations
bilateral, 385
unilateral, 385, 391f-392f
Facet joint, 643
Facial auditory nerve oxalosis, 2010
Facial barotrauma, 1918, 1926
Facial cellulitis, 1566f
Facial droop, unilateral, 127
Facial nerve (CN VII), 1410t-1411t
Facial nerve paralysis, 1411-1413
clinical features of, 1412
diagnostic strategies for, 1412
differential considerations, 1412
key concepts, 1417b-1418b
pathophysiology of, 1411-1412
patient disposition in, 1412-1413
Facial pain, 1396-1397
Facial trauma, 368-381
clinical features of, 371-373
diagnostic strategies for, 373-374
dislocations, 378-381
epidemiology of, 368-369
fractures, 378-381
general measures for, 376
history taking in, 371-372
imaging in, 373-374
key concepts, 381b
management of, 374-377
neurologic examination in, 373
out-of-hospital care for, 375-376
pathophysiology of, 370-371
pediatric, 369
penetrating, 371, 372f
Facial trauma *(Continued)*
physical examination findings, 372-373
soft tissue injuries, 376-377
Facial weakness
with contralateral arm, hand, or leg weakness, 125
with ipsilateral arm, hand, or leg weakness, 125
without extremity involvement, 127-128
Facial wound care, 377
antibiotic therapy, 377
closure, 376-377
Factitious disorders, 1487-1491
clinical features of, 1487-1489
diagnostic strategies for, 1489
differential considerations, 1484, 1490
history of, 1487
key concepts, 1491b
management of, 1490
patient disposition in, 1490
physical symptoms of, 1488
psychological symptoms of, 1487-1488
Factor level assays, 1609
Factor VIII (antihemophilic factor)
dosage, 1614t
for hemophilia, 1613, 1614t
recombinant-derived, 1613
Factor VIII:C concentrates, 1613
Failed airway, 10, 10f
Failure to diagnose actions, e65
Failure to rewarm, 1891
Failure to stabilize actions, e65
Falling zone, 369
Fallopian tubes, 2285-2286, 2285f
Falls
blunt trauma and associated injuries in, 290t
head injury in, 339
in older adults, 324, 2355
in pregnancy, 298
False aneurysms, 1129, 1130f, 1148t
False labor, 2332
False negative errors, e13, e13t
False positive errors (type I errors), e13, e13t-e14t
Famciclovir (Famvir), 1723
for diarrhea in AIDS, 1257t
for herpes esophagitis, 1175
for herpes simplex, 1578, 1721t-1722t
for herpes zoster, 1729
for sexually transmitted diseases, 1315t
for varicella-zoster virus infection, 1721t-1722t
Familial periodic paralysis, 1445
Family
delivering bad news to, e51-e53
in pediatric trauma, 308
physician relationships, e82
during resuscitation, e54
as surrogate decision maker, e41
Family violence, 878
Famotidine, 1177t
FARES (*FA*st, *RE*liable, and *S*afe) reduction, 633
Fascia, 751
Fascial layers, 422
Fasciculations, 13
Fasciola hepatica, 1770t-1771t
Fasciola hepatica (sheep liver fluke), 1772t-1775t
Fasciolopsis buski (intestinal fluke), 1770t-1775t
Fast Alcohol Screening Test (FAST) questionnaire, 2378
FAST examination. *See* Focused assessment with sonography for trauma
FAST questionnaire. *See* Fast Alcohol Screening Test questionnaire
Fasting, preprocedural, 52
Fasting hypoglycemia, 1656
Fasting plasma glucose, 1654
Fasting serum iron test, 1591t
Fat embolism syndrome, 524, 533b
Fatigue, 2508-2509, 2508f
Fatigue fracture, 515
Fatty liver, acute, of pregnancy, 2295
Feathering burns, 1911, 1911f
Febrile neutropenia
management of, 1619, 2360-2362
outpatient therapy for, 1619
risk assessment of, 2362
Febrile seizures
advice to parents about, 2238b
in children, 2102-2103, 2226-2227, 2232, 2235
complex, 2232
definition of, 2232
simple, 2232, 2238b
Febrile transfusion reaction, 79
Fecal cell count, 258
Fecal incontinence, 1283-1284
causes of, 1284b
clinical features of, 1284
management of, 1284
Federal Bureau of Investigation (FBI), 2470t
Federal Emergency Management Agency (FEMA), 2458t, 2466
contact information, 2458t, 2470t
equipment cache, 2454
US&R teams, 2454, 2454f
Federal oversight, 2437-2438. *See also specific acts*
laws, e70
rules for refusal of medical care, e73-e75
Feeding catheters, 2405t
Quinton-Mahurkar, 1153, 1153f, 1155
Felbamate (Felbatol)
drug interactions, 2407t-2408t
for long-term anticonvulsant therapy, 1384t
side effects of, 1383t, 2407t-2408t
Felbatol (felbamate), 2407t-2408t
Felodipine, 1991t, 1122.e1t-1122.e2t
Felon, 566
complications of, 566
incision and drainage of, 566, 566f
management of, 566
pathophysiology of, 566
Female external genital injuries, 497
Female genital disease, 1819
Femoral artery aneurysms, 1147
Femoral artery injury, 508-509
Femoral deep vein thrombosis, 1159, 1160f
Femoral head, 672, 693, 693f
Femoral lines, 307b
Femoral neck, 693, 693f
Femoral neck fractures, 682-684, 683f, 686f
classification of, 683
complications of, 683-684
displaced fractures, 683
epidemiology of, 672
management of, 672, 680-682
nondisplaced, 683, 683f
outcome, 683-684
pathophysiology of, 682-683
stress fractures, 686-687, 686f
clinical features of, 686
diagnostic strategies for, 686-687
management of, 687
pathophysiology of, 686
Femoral nerve block, 681
Femoral nerve injury, 692-693
Femoral prosthesis dislocation, 681-682, 682f
Femoral shaft fractures, 686
classification of, 686
clinical features of, 686
management of, 686
outcomes, 686
pathophysiology of, 686
spiral, in children, 694
splinting and bandaging, 529
Femoral trauma, 672-697
clinical features of, 677-679
diagnostic strategies for, 679-680
epidemiology of, 672
fracture-dislocations, 687-691
fractures, 682-687
in distal femur, 705-706
femoral head fracture-dislocation, 690
in femoral neck, 682-684, 683f, 686f
in femoral shaft, 686
greenstick, 517f
pain management in, 681
pediatric, 693-694, 693f
in proximal femur, 682, 693, 693f
spiral, 2251f
history taking in, 677-678
key concepts, 697b
neurologic injuries, 692-693

www.ketabpezeshki.com 66485457-66963820

Femoral trauma *(Continued)*
pathophysiology of, 675
patterns of injury, 687
pediatric considerations, 693-697
physical examination findings, 678-679
radiographic evaluation of, 679-680
soft tissue injuries, 691-693
vascular injuries, 692
Femoral vein cannulation, 2502
Femoral vein injury, 508-509
Femur, 672
anatomy of, 672
pediatric, 693, 693f
radiographic, 679-680
skeletal, 672
vascular, 673-675
arterial supply, 673, 674f
bony architecture of, 672, 673f
dislocations of, 687-691
infection of, in children, 694-695
musculature of, 672
nerves of, 673-675
osteochondroma of, 677, 677f
osteoporosis of, 675
venous system, 673
Fenoldopam, 1118t-1119t
Fentanyl, 39t, 41
benefits and adverse effects, 55t
for burn pain, 816
in pregnancy and lactation, 2318t-2321t
in procedural sedation and analgesia, 54-56, 54t-55t, 59t-60t
respiratory depression associated with, 2053t
Ferret bites, 787
Ferric hexacyanoferrate (Prussian blue), 1952t
Ferritin, 1591t
Ferrous sulfate, 1590
Fertility rates, 2271
Fetal alcohol syndrome, 2392
Fetal heart rate (FHR)
decelerations, 301, 302f, 2335, 2336f
normal, 301
variability, 301, 302f
Fetal monitoring, 65-66
electronic, 2334-2335
Fetomaternal hemorrhage, 302-303
Fetus
assessment of
antenatal, 2334
secondary survey, 301
circulation of, 2139
intracardiac, 2139, 2140f
persistent, 112
death of, first- or second-trimester, 2282
definition of, 2272
hypoxia in, 301
maternal diabetes and, 2310
plain radiographic identification of, 2275
radiation exposures, 2276t
stations of, 2333, 2334f
transition to extrauterine life, 112
trauma-related injury to, 298
viability of, 301, 301t
Fever
in adult patients, 119-123
ancillary testing, 122-123
in cancer, 1617-1619
central line emergencies, 2411t
cerebrospinal, epidemic, 1710
chest pain and, 217t-218t
clinical features of, 1617-1618
definition of, 1617, 2096-2097
diagnosis of, 120-123, 120f-121f, 1618
differential diagnosis of, 120, 120b, 120t, 123, 1532t, 1618-1619, 1899-1900
duration and magnitude of, 122
epidemiology of, 119
vs hyperthermia, 1899-1900
in infants
general approach to, 2099-2100
management of, 2100, 2101f-2102f, 2101t
infectious causes of, 120t
management of, 1619
empirical, 123
in meningococcemia, 1712
Fever *(Continued)*
in neutropenic cancer, 1617
antimicrobial therapy for, 1618b, 1619
clinical features of, 1617-1618
key concepts, 1628b
noninfectious causes of, 120b
onset of, 122
in parasitic infections, 1769-1776
pathophysiology of, 119
patient disposition in, 123
patterns, 122
pediatric, 2096-2105, 2227
acute rheumatic fever, 2165
ancillary testing in, 2098-2099
epidemiology of, 2096-2097
etiology of, 2096, 2097t
general approach to, 2099-2100
history taking in, 2098
after intimate contact, 2226
key concepts, 2105b
pathophysiology of, 2097-2098
physical examination findings, 2098
and underlying chronic illness, 2103-2105
pivotal findings, 121-123
Q, 1106
relapsing, 1808b
clinical features of, 1795-1796
diagnostic strategies for, 1796
differential considerations, 1796
management of, 1796
tick-borne, 1795-1796
rheumatic, 1108-1109
acute, 1512-1513
signs of, 122
symptoms of, 122
in systemic lupus erythematosus, 1528-1532
timing of, 122
in tuberculosis, 1821
viral infections presenting as, 1732
Fexofenadine, 1569
Fibercon (polycarbophil), 264t-265t
Fiberglass splints, 529
Fiberoptic intubating styles, 19, 19f
Fibrin degradation products (D-dimer), 1616t
Fibrinogen, 1609
in pregnancy, 2290
Fibrinolysis, 1552t
Fibrinolytic therapy
for acute coronary syndrome, 1027-1029
for acute ischemic stroke, 1371-1372, 1372b
contraindications to, 1029, 1029b
eligibility criteria for, 1028-1029
historical perspective on, 997
mortality rates, 1029
for peripheral arteriovascular disease, 1143
for pulmonary embolism, 1166t
risk factors for hemorrhagic stroke after, 1029
selection of agents, 1027-1028
for STEMI, 1031
Fibroids, uterine, 1361, 1361f
Fibromyalgia, 1516-1517
clinical features of, 1516
management of, 1516-1517
Fibula
anatomy of, 717
distal displacement of, 515f
fractures of
comminuted, 2252f
Salter-Harris type I, 2252f
stress, 721
Fibular compression test, 731
Field block, 378
Field care
honoring verbal requests to withhold intervention, e51
for orthopedic injuries, 528-529
tactical, 2451-2452
Field communications, 2437
Field death pronouncement, e50
Field Triage Decision Scheme (CDC), 287-288, 337
Fifth disease, 1571
"Fifth" vital sign, 61-62
Fight bites (clenched-fist injuries), 562, 764, 791
Filariasis, 1772t-1775t
File drawer problem, e12
Filgrastim, 1952
Filoviridae, 1719t
Finance section, 2463
Financial abuse, 886
elder abuse, 885
questions to ask about, 887b
FIND ME mnemonic, 2419
Finger traps, 583-584, 585f
Fingernail injuries, 561, 561f
Fingerprints, 534
Fingers. *See also specific fingers*
carpometacarpal joint injury, 555
carpometacarpal joints, 555, 555f
flexion of, 534, 535f
metacarpophalangeal joint injury, 554-556
radiographic imaging of, 545-546, 546f
swan neck deformity of, 558, 559f
Fingertip amputations, 561
classification of, 561
complications of, 561
management of, 561
Fingertip injuries, 561-562
Fingertips, 543-544, 544f
Finkelstein, Fritz, 589
Finkelstein test, 589, 1521
Fioricet (butalbital, acetaminophen, and caffeine), 2243-2244
Fiorinal (butalbital, aspirin, caffeine), 2243-2244
Fire ants, 802-803
Fire coral *(Millepora)*, 806
Fire victims. *See* Burns
Firearms
death caused by, e2
drive-by shootings, e4
handguns, e2
non-powder, e3
and violent street gangs, e4
and youth, e2
Firethorn *(Pyracantha)*, 2069
First aid, 802
First responders, 2435, 2457
Fish-associated toxins, 255b-256b, 807
Fish envenomation, 807
Fish poisoning
ciguatera, 1243t, 1246-1247
scombroid, 1246
epidemiological aspects, 1243t
key concepts, 1260b
Fish tank granuloma, 1853
Fisher's exact test, e13-e14, e13t
Fistulae
anorectal, 1281-1282
arteriovenous, 1156
Cimino-Brescia fistula, 1155-1156
definition of, 1282
prosthetic bridge fistula, 1155-1156
Fitz-Hugh–Curtis syndrome, 1320, 1324
Flagyl (metronidazole), 1770t
Flail chest, 433-434, 434f
anatomy of, 433-434, 433f
clinical features of, 434
diagnostic strategies for, 434
epidemiology of, 433
management of, 434
pathophysiology of, 433-434
Flame burns, 816t. *See also* Burns
Flank gunshot wounds, 474
Flank stab wounds, 473
"Flash ball" weapons, 371
Flattened affect, 1461
Flaviviridae, 1719t
Flecainide, 1037
for atrial fibrillation and flutter conversion, 1052b
in pregnancy, 2318t-2321t, 2326-2327
Fleet mineral oil (mineral oil), 264t-265t
Fleet Phospho-soda (sodium phosphate), 264t-265t
Flexeril (cyclobenzaprine), 282-283
Flexible intubating scopes, 19
Flexion injuries
spinal, 382-385
supracondylar fractures, 606f, 607
classification of, 607
clinical and radiographic features of, 607
complications of, 607

www.ketabpezeshki.com 66485457-66963820

Flexion injuries *(Continued)*
management of, 607
pathophysiology of, 607
teardrop fractures, 385
Flexion-rotation injuries, spinal, 385-393, 385t
Flexor carpi radialis tendon, 539, 540f
Flexor carpi ulnaris tendon, 539, 540f
Flexor digitorum superficialis tendon, 539, 540f
Flexor digitorum superficialis tendon testing, 540, 541f
Flexor hallucis longus, 734
Flexor hallucis longus tendinitis, 734
Flexor pulley system, 539, 541f
Flexor tendons, 541f
of hand, 539-540
injuries to, 560-561
clinical features of, 560
management of, 560
pathophysiology of, 560
Flicker illness, 2444
Flight stresses, 2443
Floods, 2457
FloSeal Hemostatic Matrix (Baxter), 939
Flubriprofen, 898
Fluconazole
for candidal vaginitis, 783
for esophageal candidiasis, 1175
for oral thrush, 1561-1562
for tinea capitis, 1559
for tinea versicolor, 1561
for vulvovaginal candidiasis, 1322-1323
Fludrocortisone, 1691-1692
Fluid creep, 814
Fluid deficits
in aspirin overdose, 1965
in diabetic ketoacidosis, 1657t
in hypertonic dehydration, 2203b
Fluid pseudotumors, 994
Fluid requirements
in burns, 812-813
in hypertonic dehydration, 2203b
in hyponatremic volume depletion, 2202-2203, 2202b
in isonatremic volume depletion, 2201-2202, 2201b
pediatric, 814
Fluid resuscitation, 292
in anaphylaxis, 1553
burn resuscitation index (BRI), 812-813, 813t
in burns, 812-814, 813t
in children, 814
in diabetic ketoacidosis, 1660
in diarrhea, 259
fluids for, 292
formulas for, 813
in geriatric trauma, 326
for hemodynamic support, 1870t
in hypertonic dehydration, 2203b
in infants, 814
maintenance fluid and electrolytes, 2201-2203, 2201t
in myxedema coma, 1688b
in pediatric dehydration, 2199-2203
in pediatric septic shock, 106-107
in rhabdomyolysis, 1673-1674
in ruptured AAA, 1133-1134
in salicylate intoxication, 1967
in sepsis, 1871
tactical combat care, 2452
TCCC guidelines for, 2452
in thyroid storm, 1682b
in toxic shock syndrome, 1717
Flukes, 1770t-1775t
Flumadine (oseltamivir), 1722
Flumadine (rimantadine), 1720-1722
Flumazenil
for benzodiazepine overdose, 1957t-1958t, 2079-2080
contraindications to, 2079b
for hepatic encephalopathy, 1195
indications for, 2079b
in pregnancy, 2318t-2321t, 2323
for reversal and rescue from PSA, 59
Flunisolide, 951
Flunitrazepam (Rohypnol), 2080
Fluorescent treponemal antibody–absorption (FTA-ABS) test, 1317, 1576
Fluori-methane sprays, 47
Fluoroquinolones, 930t
for bone and joint infection, 1835t
for infectious diarrhea, 2192t-2193t
for pneumonia, 984-985, 985t
in pregnancy, 2324
for skin and soft tissue infection, 1854t
Fluoroscopy
with airway foreign bodies, 774
for removal of esophageal foreign bodies, 778
for removal of soft tissue foreign bodies, 783
Fluphenazine, 2048t, 2072t-2073t
Flurazepam (Dalmane), 2078t
Flush syndrome, 1551
Fluticasone, 951
Flutter waves, 1052
Foams, 1558
Focused assessment with sonography for trauma (FAST) examination, 2492, 2494
in abdominal trauma, 467-468
in blunt abdominal trauma, 475t
in children, 2501
for demonstrating organ injury that requires laparotomy, 475
in diabetic ketoacidosis, 1659
EFAST (extended FAST), 2494
FASTER (of extremities), 2494
in geriatric trauma, 326
in hemoperitoneum, 475
in pediatric trauma, 308
Focused cardiac US (FOCUS), 2492
Focused dive history, 1922b
Fogarty catheter thrombectomy, 1143
Folate
for methanol toxicity, 1957t-1958t
red cell, 1593t
tests for megaloblastic anemia, 1593t
Folate deficiency, 1592
causes of, 1592b
pregnancy-related, 2307
Folate deficiency anemia, 2307
Folate supplementation, 2307
Foley catheters, 480-481
in pediatric trauma, 307b
in removal of rectal foreign bodies, 1288, 1289f
suprapubic placement of, 483-484, 484f
in urethral trauma, 482
Folk medicine, e27
Follicular conjunctivitis, acute, 187
Folliculitis, 1564, 1859
clinical features of, 1564, 1859
management of, 1564, 1859
Follow-up care, e68
Fomepizole (Antizol), 1957t-1958t, 2011-2012
for ethylene glycol toxicity, 2012
for methanol toxicity, 1957t-1958t, 2012
in pregnancy, 2318t-2321t, 2323
Fondaparinux
for acute coronary syndrome, 1027
for DVT, 1159
for PE, 1164-1165
Food and Drug Administration (FDA)
approved fibrinolytic regimens for acute treatment of PE, 1166t
classification of teratogenic risk of drugs, 2316, 2317b
Food-borne botulism, 1704-1705
Food poisoning
B. cereus, 1244-1245
C. perfringens, 1244
staphylococcal, 1243-1244
Food triggers for anaphylaxis, 1544
Foodborn diseases and related conditions, notifiable, 1237b
Foot (feet)
accessory ossicles of, 735, 736f
anatomy of, 734-736
bones and joints of, 734, 735f
diabetic, 1664
diabetic infections, 1853
diabetic osteomyelitis, 1842
diabetic ulcers, 1666b
radiography of, 726
Foot injury, 723, 734-750
amputations, 750
clinical features of, 735
contusions, 749-750
crush injuries, 750
diagnostic strategies for, 735-736
forefoot injuries, 744-749
hindfoot injuries, 736-741
key concepts, 750b
midfoot injuries, 741-744
puncture wounds, 764
radiographic findings, 735
sprains, 749-750
stress fractures, 749
vascular injuries, major, 750
Foot pain, 748-749
forefoot pain, 748-749
hindfoot pain, 748
key concepts, 750b
midfoot pain, 748
Force health protection, 2453
Forced expiratory volume (FEV), 959
Forced vital capacity (FVC), 1441
Forearm
anatomy of, 590, 590f
compartment syndrome in, 594
compartments, 590, 590f
neurovascular structures of, 590f
radiographic imaging of, 591, 591f
Forearm injuries, 589-595
arterial, 508
clinical features of, 590
diagnostic strategies for, 590-591
fractures, 591-594
pediatric, 593-594, 594f
key concepts, 595
radiographic imaging of, 591, 591f
Forearm splints, 529
Forefoot, 734, 735f
Forefoot injuries, 744-749
Forefoot pain, 748-749
Forehead fractures, 379
Foreign bodies, 767-784
aeroesophageal, 2115-2116
airway, 772-776, 2115-2116, 2116b
anorectal, 781-782, 1288
in anus, 1288
assessment of, 753
in bowel, 778-781
complications with, 767
conjunctival, 913
corneal, 912-913, 913f
diagnostic imaging for, 767
in ear, 769-771, 770f
esophageal, 774, 775f, 776-778, 1170
esophageal perforation due to, 456
in eye, 767-769
gastrointestinal, 776-782
in children, 2182-2183
key concepts, 2187b
genitourinary, 782-783
in hand, 568-569
history taking with, 767
intraocular, 768, 768f, 917
key concepts, 784b
in lower leg, 722
nasal, 770-772, 770f
ocular, 768, 769f
orally ingested, 1288
orbital, 917
oropharyngeal, 1171
otic, 770, 770f
penile, 783
pharyngeal, 776-778
physical examination findings, 767
in rectum, 781-782
removal of, 767
in sexual assault, 863
soft tissue, 783-784
in stomach, 778-781, 1172
tracheal, 774
vaginal, 783
Forensic documentation, 884
Forensic emergency medicine, 828-844, 844b

www.ketabpezeshki.com 66485457-66963820

Forensic examination
of handgun wounds, 830-836
in intimate partner violence, 884
Forensic medical examiners, 828
Forensic medical officers, 828
Forensic Medical Report: Acute form, 857, 858f-861f
Forensic Medicine Model of system intervention, 880-881
Forensic physicians, 828
Forensic science, 2453
Foreskin edema, 496, 496f
Formic acid, 821
Fosamprenavir, 1721t-1722t, 1766t
Foscarnet (Foscavir), 1723
for CMV infection, 1721t-1722t
for diarrhea in AIDS, 1257t
for herpes esophagitis, 1175
for herpes simplex, 1721t-1722t
for varicella-zoster virus infection, 1721t-1722t
Fosinopril sodium, 1122.e1t-1122.e2t
Fosphenytoin (Cerebyx)
adverse effects of, 1383t
for neonatal seizures, 2236
for seizure prophylaxis, 350
for seizures, 158t-159t, 159
for status epilepticus, 158t-159t, 159, 1381t, 1382, 2408-2409
for status epilepticus in children, 2237f, 2238
Four-pillar (straddle) fracture, 658-659, 660f
Fournier's gangrene, 1664t
Fourth-nerve palsy, 929
Fox, Ellen, e49
Fractional excretion of sodium (FENa), 1292, 1292b
Fracture(s), 511-525
acetabular, 670-671, 670b, 670f
adverse outcomes, 521t
alveolar, 381, 905
ankle, 727-734
articular surface, 609-612
avulsion, 514-515, 516f
in children, 2270, 2270f
Barton's, 584-585
basilar, 359, 361-362
bimalleolar, 729
blood loss associated with, 520t
both-bone, 591
boxer's, 550, 550f
bucket-handle, 661
burst, 393-396, 394f-396f, 409f
calcaneal, 739-740
capitate, 580
capitellum fractures, 609
CAST fracture (childhood *a*ccidental *s*piral *t*ibial fracture), 852
in child abuse, 2259
clavicular, 621-624, 622f, 2252-2254, 2254f
clay shoveler's, 385, 388f
closed, 511
of coccyx, 658f, 671
Colles' fracture, 583-584, 584f
reduction of, 583-584, 585f
comminuted, 514, 514f, 2252f
complete, 514, 2250
complications of, 519-525, 525b
compound, 511
condylar, 609
cuboid, 741
cuneiform, 741
definition of, 525
delayed union of, 720
descriptors for, 511-515, 514b
diagnostic modalities for, 518-519
diaphyseal, 2259-2260
displaced, 683
of distal femur, 705-706
of distal humerus, 603-609
of distal phalanx, 546-547, 547f
dome fracture of the talus, 738, 738f
Duverney, 659
about elbow, 601-612
epicondyle, 610
epiphyseal, 709
eponyms for, 512t-513t, 515
extension teardrop fracture, 393

Fracture(s) *(Continued)*
facial, 378-381
fatigue fracture, 515
femoral, 682-691
femoral neck, 682-684, 683f, 686-687, 686f
epidemiology of, 672
management of, 680-682
femoral shaft, 686
forearm, 591-594
pediatric, 593-594, 594f
of forehead, 379
Galeazzi's, 592-593, 593f
greenstick, 587, 588f, 2250
growing, 313
hamate, 578-579, 579f
of hand, 546, 552-553
hangman's, 393, 394f
healing of, 515-517
Hill-Sachs, 631
of hip, 682-691
epidemiology of, 672
management of, 680-682
with minimal or no trauma, 686
occult, 679-680
in older adults, 328
humeral, 601b
humeral shaft, 601
Hutchinson's, 586f
Hutchinson's fracture, 585-586
incomplete, 514
insufficiency, 682-683
intercondylar, 608f
intercondylar eminence (tibial spine), 708-709
intertrochanteric, 684-685, 684f
isolated
of greater trochanter, 685, 685f, 696-697
of lesser trochanter, 685, 696-697, 696f
Jefferson, 396, 397f, 512t-513t
Jones, 745
lateral condyle, 608
lateral malleolar, 728
Le Fort, 372, 379-380
Lisfranc's (tarsometatarsal), 741-744
with low back pain, 647
lower extremity, 328
lunate, 577
Maisonneuve, 720, 720f
mallet finger, 557-558, 558f
mandibular, 373, 374f, 380
march fracture, 515
medial condyle, 608
medial malleolar, 728
metacarpal, 549-552, 2500, 2500f
metacarpal base, 551-552
metacarpal head, 549-550
metacarpal neck, 550-551
metacarpal shaft, 551
metaphyseal, 2259
metatarsal, 744-745
middle phalangeal, 547-549
midface, 379-380
Monteggia's fracture, 592, 592f, 2257, 2257f
nasal, 378-379
navicular, 741
of necessity, 593
nerve injury in, 520t
nightstick, 591, 592f
nomenclature, 511-515
nondisplaced, 683, 683f
nonunion of, 720
oblique, 514, 514f
odontoid
with anterior dislocation, 382, 386f
in older adults, 328
type I, 385
type II, 385, 389f-390f
type III, 385, 389f-390f
in older adults, 324
olecranon, 611
open, 511, 519
care for, 681
classification of, 520b, 681t
definition of, 525, 681
management of, 520b
type I, 681

Fracture(s) *(Continued)*
type II, 681
wound management in, 763-764
open ankle, 729-730
open-book, 661, 661f, 668
orbital, 378-379, 379f
orbital wall, 909-910
patellar, 711-712
pathologic, 515
pathologic intertrochanteric, 684-685
pediatric, 517-518, 2250
classification of, 2250
of distal radius, 587-588
femoral, 693-694, 693f
of forearm, 593-594, 594f
of hand, 552-553
of hip, 693-694
pelvic, 658f
with blunt abdominal trauma, 476-477, 477f
classification of, 657-658, 658b
key patterns, 657-662
pathophysiology of, 657-662
of penis, 496, 497f, 498
phalangeal
correction of, 548, 548f
in foot, 745-747
proximal and middle, 547-549
pilon, 730-731, 730f
ping-pong, 357-358
pisiform, 578, 579f
posterior malleolar, 728-729
proximal femoral fractures, 682
proximal fibula, 720
of proximal humerus, 625-627
of proximal humerus epiphysis, 627-628
proximal phalangeal, 547-549
pseudofractures, 519
radial head, 601b
rib, 431-432, 432f
in child abuse, 2259
Salter-Harris, 2252t
scaphoid, 576-577, 594b-595b
of scapula, 624-625
Segond, 706, 706f
sesamoid, 747
simple, 511
skull, 361-362
basilar, 347b
in child abuse, 2259-2260
comminuted, 361
depressed, 361
growing, 358
linear, 361
open, 362
Smith's, 584, 585f
spinal, 382, 420
spiral, 514, 514f, 2251f
sternal, 432-433
straddle fracture, 658-659, 660f
stress
of femoral neck, 686-687, 686f
of lower leg, 721
subcapital, 695, 696f
subtrochanteric, 685-686
supracondylar, 603-607
in children, 601b
of humerus, 2254-2257
suspicious, 847-848, 847t
T fracture, 670
talar, 736-738
teardrop, 385, 387f
of teeth, 903-904, 903t, 908b
terminology for, 511-515, 514b, 546f
of thoracic spine, 385-393, 393f
thumb metacarpal, 552
tibial
proximal extra-articular, 717-718
subcondylar, 717-718
tibial plateau, 706-708
tibial shaft, 719-720
tibial tubercle, 718
tibiofibular, 719f
toddler's, 852, 2258-2259, 2259f
torus (buckle), 2250
transchondral, 738

www.ketabpezeshki.com 66485457-66963820

Fracture(s) *(Continued)*
transcondylar, 607, 607f
transverse, 514, 514f, 2251f
trapezium, 579-580, 580f
trapezoid, 580
trimalleolar, 729
tripod (or trimalar), 373-374, 374f, 379
triquetral, 578, 578f, 594b-595b
trochlea, 610
types of, 514, 514f
ulna shaft, 591-592, 592f
ulnar, 601b
unimalleolar, 728-729
upper extremity, 328
vault, 361
vertebral, 327-328
vertical compression, 385t, 393-396
vertical sacral, 661-662
wedge, 382-385, 387f
of zygoma, 380
Fracture blisters, 524-525
Frailty, e47
Francisella tularensis pharyngitis, 965
Freezing injury. *See also* Frostbite
cascade of, 1878b
freeze-thaw phase, 1878, 1878b
prefreeze phase, 1878, 1878b
Freiberg's disease, 749
Freon abuse, 2396, 2396f
Fresh frozen plasma (FFP)
for geriatric trauma, 326
for pediatric trauma, 310
for ruptured AAA, 1134
transfusion of, 77-78
Friedreich's ataxia, 2245
Frostbite, 1877-1882, 1881f
adjunctive treatment of, 1881-1882
blister management, 1881, 1881f
clinical features of, 1879
diagnostic strategies for, 1879-1880
key concepts, 1882b
management of, 1880-1882
emergency department, 1880-1881, 1880b
post-thaw, 1880-1881
prethaw, 1880
thaw, 1880
and military history, 1883
pathophysiology of, 1877-1878
patient disposition in, 1882
predisposing factors, 1878-1879, 1878b
sequelae of, 1882, 1882b
symptoms and signs of, 1879
Frostnip, 1879
Frozen shoulder (adhesive capsulitis), 624, 642
key concepts, 642b
FTA-ABS (fluorescent treponemal antibody–absorption) test, 1317, 1576
Fundal height, 2333, 2334f
Fundoscopy
direct examination, 188
in hypertensive retinopathy, 1117, 1117b
normal findings, 910f
Fungal infection, 1558-1561, 2359b
bezoars, 779
bone and joint, 1836
endocarditis, 1107
in immunocompromised patients, 2363
key concepts, 1585b
meningitis
complications of, 1451
pathophysiology of, 1449
therapy for, 1457
mycobacterial, 1818
Fungemia (bacteremia), 1865b
Fungus balls, 1813, 1813f
Funnel plots, e18
Furazolidone, 1235t, 1257t
Furosemide (Lasix)
for acute renal failure in children, 2218
for congestive heart failure in children, 2152
hemodynamic effects, 1118t
for hypertension, 1122.e1t-1122.e2t
for nephrotic syndrome in children, 2217
for rhabdomyolysis, 1674
Furuncles, 1859
Furunculosis, 935
Fusion inhibitors, 1766t
Fusobacterium infection
necrophorum, 975
in parapharyngeal abscess, 975
in pneumonia, 979
Futility, e42, e48-e50
The Future of Emergency Care in United States Health System (IOM), 2433

G
G-force, 336
Gabapentin (Neurontin)
for diabetic neuropathy, 1432, 1663
drug interactions, 2407t-2408t
for long-term anticonvulsant therapy, 1384t
side effects of, 1383t, 2407t-2408t
Gabitril (tiagabine), 2407t-2408t
Gage's sign, 2266
Gagnan, Emile, 1915
Gait
antalgic, 686
cerebellar, 165
Gait evaluation, in children, 694
Galantamine (Razadyne), 1408
Galeazzi's fracture, 512t-513t, 592-593, 593f
Galeazzi's sign, 2261-2262, 2262f
Galen, e44
Gallbladder, porcelain, 1204
Gallbladder disease
carcinoma, 1204
clinical features of, 2295
diagnostic strategies for, 2295
differential considerations, 2295
management of, 2295
in pregnancy, 2295
Galloping consumption, 1813
Gallstone ileus, 1218, 1218f
Gallstones, 1200, 1201f. *See also* Cholelithiasis
in children, 2186
cholesterol stones, 1200
classification of, 2186
pigmented stones, 1200
types of, 1200
ultrasound of, 2497, 2497f
Galveston formula, 813t, 814
Gamekeeper's thumb (ulnar collateral ligament injuries), 556
Gamma radiation, 1948, 1948f
Gamow bags, 1935f
Ganciclovir (Cytovene), 930t, 1723
for CMV infection, 1721t-1722t
for diarrhea in AIDS, 1257t
for herpes esophagitis, 1175
Gang violence. *See* Street gang violence
Ganglion, in hand, 568
Ganglionic blockers, 1970
Ganglionopathy, 1439-1440, 1439b
Gangrene, 1582f
nonclostridial gas, 1664t
Ganser's syndrome, 1462
Garden spade deformity, 584
Gardnerella vaginitis, 2298
Gartland classification, 601b, 2254, 2254t
Gases
alveolar gas equation, 1929, 1929b
general gas law, 1916, 1916t
miscellaneous, 824-825
mixed gas diving, 1916t
noble, 2037t
Gastric foreign bodies
diagnostic strategies for, 779-780
history taking in, 779
management of, 780-781
Gastric volvulus, 1180-1181
clinical features of, 1181
complications of, 1181
diagnostic strategies for, 1181
differential considerations, 1181
management of, 1181
presenting symptoms of, 1181
Gastritis, 1177-1178
acute phlegmonous, 1177-1178
clinical features of, 1178
definition of, 1177
diagnostic strategies for, 1178
differential considerations, 1178
management of, 1178
vomiting in, 243t-244t
Gastrocnemius strain, 721
Gastroenteritis, 1233-1260
acute, 224t-225t, 1233
acute viral, 1249-1250
clinical presentation of, 1249-1250
diagnostic strategies for, 1250
etiology and epidemiology of, 1249-1250
management of, 1250
pathophysiology of, 1249
Aeromonas, 1235t, 1240-1241
chronic, 1233
definition of, 1233
$ETCO_2$ findings, 65, 65f
invasive, 1233
invasive bacterial, 1234t
key concepts, 1260b
noninvasive, 1233
P. shigelloides, 1241
protozoal, 1250t
viral, 1249-1250, 1724
vomiting in, 243t-244t
Gastroesophageal reflux disease, 1175-1177
clinical features of, 1176
complications of, 1176
diagnostic strategies for, 1176
differential considerations, 1176
key concepts, 1185b
management of, 1177
pediatric, 2175-2176
clinical features of, 2175-2176
diagnostic strategies for, 2176
differential considerations, 2176
key concepts, 2187b
management of, 2176
patient disposition in, 2176
related agents and conditions, 1176b
symptoms of, 1176
Gastrografin studies, 467, 467f
Gastrointestinal anthrax, 1241-1242, 2473, 2473b
Gastrointestinal barotrauma, 1919
Gastrointestinal bleeding, 248-253
with abdominal stab wounds, 472
alcohol and, 2385
appearance of, 249
causes of, 249t
consultation for, 252
context of, 248-249
diagnostic algorithm for, 250-251, 251f
diagnostic approach to, 248-250
differential considerations, 248
ED studies, 250
epidemiology of, 248
high-risk, 249t
laboratory testing in, 250
management of, 251-252
algorithm for, 251f
definitive, 252
medical history, 248-249
medications for, 252
patient disposition in, 253
pediatric, 2180t
physical examination findings, 249-250
pivotal findings, 248-250
quantity of, 249
relevant medical history, 249
upper, 2484
vital signs in, 249
Gastrointestinal decontamination
barbiturate, 2077-2078
lithium, 2045
opioid, 2055
Gastrointestinal disease
pediatric, 2168-2187, 2187b
in tuberculosis, 1821
Gastrointestinal history, 1277b
Gastrointestinal referral, 258
Gastrointestinal syndrome, 1950

www.ketabpezeshki.com 66485457-66963820

Gastrointestinal tract. *See also specific organs*
caustic injury to, 1997
changes in pregnancy, 297
in chronic kidney disease, 1302
foreign bodies in, 776-782
in children, 2182-2183, 2183f, 2187b
clinical features of, 776
diagnostic strategies for, 779-780
history taking in, 779
management of, 780-781
radiographic findings, 777, 779, 779f-780f
in HIV infection, 1760-1761
parasitic infection of, 1250-1258
in spinal injury, 419
Gastropathy, 1177
Gastrostomy buttons, 2406t, 2410
Gastrostomy tubes, 2406t, 2410-2412
Gatekeepers, e44
Gatifloxacin, 1822t-1823t, 1824
Gatorade, 2200t
Gauze, 2451
GCS. *See* Glasgow Coma Scale
Geiger counters, 1951
Geiger-Mueller instruments, 1951
Gels, 1558
General gas law, 1916t
General Motors, 336
Genetics, 945
Genie, 2021
Genital discharge, 1319-1325
Genital discomfort, 1323
Genital herpes, 1312-1314
diagnosis of, 1314
drugs for treatment of, 1721t-1722t
management of, 1578
in men, 1313, 1313f
treatment of, 1314
in women, 1313, 1314f
Genital injury
in sexual assault, 865-866, 865b
typical locations of, 865, 865f
trauma to external genitalia, 494-498
Genital lesions, 1312-1319
Genital warts, 1286-1287, 1319, 1319f
Genitalia
external, 479
male, 480, 480f
Genitourinary tract
anomalies of, in men, 1335
disorders of, in children, 2205-2223
foreign bodies in, 782-783
diagnostic strategies for, 783
history taking in, 782
management of, 783
physical examination findings, 782-783
infections of, in pregnancy, 2297-2299
in spinal injury, 419
trauma to, 479-499
clinical features of, 479-481
historical perspective on, 479
key concepts, 499b
physical examination findings, 479-480
upper, 490-494
Gentamicin
for bacterial endocarditis, 1108b
for bacterial meningitis, 2230t
for bone and joint infection, 1835t
for bowel flora, 1264b
for catheter-related infections, 1155
for endophthalmitis, 915
in immunocompromised patients, 2361t
for malignant otitis externa, 1664t
for pelvic inflammatory disease, 1325t
for plague, 2475b
for prostatits, 1336
for tularemia, 1798
Gentian violet, 1561-1562
Geodon (ziprasidone)
for chemical restraint, 2418
for mood disorder, 1472-1473
for rapid tranquilization, 1463
Georgia Health Sciences University, 2420
Geriatric patients, 2429. *See also* Elder patients
Geriatric trauma, 324-329
abdominal, 328
comorbidities, 325
definition of, 324
demographics of, 324
end-of-life decisions in, 328-329
epidemiology of, 324
imaging, 327
key concepts, 329b
laboratory testing in, 326-327
mechanisms of injury, 324-325
primary assessment and resuscitation in, 325-326
secondary assessment in, 326-327
thoracic, 328
German measles, 1571
Gerota's fascia, 490
Gerstmann-Sträussler syndrome, 1740
Gestation
anembryonic, 2282
multiple gestations, 2345-2346
diagnostic strategies for, 2346
management of, 2346
Gestational age
definition of, 2272
fundal height and, 2333, 2334f
landmarks for, 2283, 2283t
Gestational diabetes, 1653, 2301t-2303t, 2309-2311
Gestational epilepsy, 1379
Gestational hypertension, 2290, 2304t
Gestational seizures, 1379
GHB. *See* γ-Hydroxybutyrate
Giant cell arteritis (temporal arteritis), 926, 1392, 1535
classification criteria for, 1535b
clinical presentation of, 1392
diagnostic evaluation of, 1392
differential diagnosis of, 174t
incidence of, 1535
risk factors for potentially catastrophic illness, 172b
treatment of, 1392
Giardia antigen assay, 258
Giardia infection, 2192t-2193t, 2195
Giardiasis (*Giardia lamblia* infection), 1252-1253, 1770t-1771t, 1782
in AIDS, 1257t
antibiotic therapy for, 1235t
clinical presentation of, 1252
diagnostic strategies for, 1253
differential considerations, 1253
drug regimens for, 1772t-1775t
epidemiology of, 1250t, 1252
key concepts, 1260b, 1784b
management of, 1253
pathophysiology of, 1252
treatment of, 1235t, 1257t, 2192t-2193t
Gila monster *(Heloderma suspectum)*, 796
Gila monster *(Heloderma suspectum)* bite
clinical features of, 797
management of, 801
Gilula's arcs, 571-574
Gilula's lines, 594
Ginger ale, 2200t
Gingival hyperplasias, drug-induced, 903
Gingival resorption, 900
Gingivitis, 900, 900f
Glandular injuries, in neck, 429
Glandular tularemia, 1797
Glasgow Coma Scale (GCS), 346, 346t, 1366, 1368b, 2092
in depressed consciousness, 145-146, 145b
in head injury, 346
for pediatric patients, 309t, 312
for preverbal pediatric patients, 2092, 2093t
Glasgow Coma Scale (GCS) score, 1366
Glatiramer acetate, 1417
Glaucoma, 921-922
acute
headache in, 1394-1395
systemic medications for, 930t
topical ophthalmics for, 930t
angle-closure, 189, 189f
acute, 922, 922f
differential diagnosis of, 174t
management algorithm for, 193t-196t
Glaucoma *(Continued)*
primary, 921-922, 922f
risk factors for potentially catastrophic illness, 172b
secondary, 922
clinical features and management of, 921-922
open-angle
primary, 922
secondary, 922
Glenohumeral joint, 631
anatomy of, 618, 619f
anterior dislocation of, 631-634
clinical features of, 631
complications of, 634
diagnostic strategies for, 631
with Hill-Sachs deformity, 631, 632f
key concepts, 642b
management of, 631-634
pathophysiology of, 631
reduction of, 632-633, 632f-633f
types of, 631f
dislocation of, 631-637
inferior dislocation of, 636-637, 636f
clinical features of, 636
diagnostic strategies for, 636-637
management of, 637
pathophysiology of, 636
radiographic findings, 636-637, 636f
reduction of, 636f, 637
posterior dislocation of, 635-636
clinical features of, 635
complications of, 636
diagnostic strategies for, 635
key concepts, 642b
management of, 635-636
pathophysiology of, 635
radiographic findings in, 635, 635f-636f
GlideScope AVL (Verathon Inc.) videolaryngoscope, 18-19, 18f
Glimepiride, 1665t
Glipizide, 1665, 1665t
Global assessment protocol, 1021
Global Initiative for Chronic Obstructive Lung Disease (GOLD), 956-957, 957t
Globe (scleral) rupture, 915-916, 915f
key concepts, 930b
out-of-hospital care for, 376
ultrasound imaging of, 374, 375f
Glomerular disease, 1296-1297, 1296b
Glomerulonephritis, poststreptococcal, 2216
Glossopharyngeal nerve (CN IX), 1410t-1411t
Glossopharyngeal neuralgia, 139t
Glucagon
for anaphylaxis, 1554b, 1555
for beta-blocker overdose, 1957t-1958t, 1988
for calcium channel blocker toxicity, 1957t-1958t
for hymenoptera stings, 802
for hypoglycemia, 1656
for lower esophageal obstruction, 1171-1172
for removal of esophageal foreign bodies, 778
Glucocorticoids, 44
Glucose. *See also* Dextrose solution
for alcohol-induced hypoglycemia, 2381
for beta-blocker overdose, 1957t-1958t
blood levels
in diabetes mellitus, 1655
in diabetic ketoacidosis, 1658
for calcium channel blocker toxicity, 1957t-1958t
CSF levels, 1454
in children, 2227
in diabetes mellitus, 1654
in diabetic ketoacidosis, 1658t
fasting, impaired, 1653
in hyperglycemic hyperosmolar state, 1658t
for hyperkalemia, 1305t
maintenance of normal levels, 1652
metabolism of, 2040f
for neonatal resuscitation, 117t, 118
for prolonged seizures and status epilepticus, 158t-159t
regulatory mechanisms, 1653
serum levels, 1654
urine levels, 1655
Glucose-6-phosphate dehydrogenase (G6PD) deficiency, 1596, 1596b

www.ketabpezeshki.com 66485457-66963820

Glucose tolerance, impaired, 1653
Glucose tolerance test, oral, 1654
Glucose transporter proteins, 1654
α-Glucosidase inhibitors, 1665t
Glue exposures, in eye, 910-912
Glue-sniffer's rash, 2033-2034
γ-Glutamyltransferase, 2379t
Gluteus muscle strain, 691
Glyburide, 1665
Glycerol, 930t
Glycogen replacement, 1682b
Glycoprotein IIb/IIIa receptor inhibitors, 1025
Glycosylated hemoglobin (HbA_{1C}), 1654-1655
Glyphosate, 2064
  ingestion of
    clinical features of, 2064
    diagnostic strategies for, 2064
    differential diagnosis of, 2064
    management of, 2064
    patient disposition in, 2064
Goal-directed therapy, 71
  early, 71
Goal-oriented resuscitation, 71
Goals of medicine, e49
Goiter, toxic multinodular, 1678
Gold (Spice), 2021
Gold salts
  hepatic injury, 1197t
  toxicity of, 1515t
"Golden hour" of trauma care, 288
Golfer's elbow, 1521
GoLYTELY (polyethylene glycol and electrolytes solution)
  for beta-adrenergic blocker overdose, 1988
  for constipation, 264t-265t
Gomers, 2422
Gonagra, 1508-1509
Gonococcal infection. *See Neisseria gonorrhoeae* infection
Gonorrhea. *See Neisseria gonorrhoeae* infection
Good, e34-e35
  doing (beneficence), e35
Good death, e48-e49
Goodness of fit, e16
Goodpasture's syndrome, 1536t, 1537
Goose foot (pes anserinus), 698, 716
Gout. *See* Pseudogout
Gouty arthritis, 1508-1509
  clinical features of, 1508-1509
  diagnostic strategies for, 1509
  epidemiology of, 1508
  management of, 1509
  pathophysiology of, 1508
GRACE (Global Registry of Acute Coronary Events) risk model, 1000
Graft infection, 1135
Graft-versus-host disease, transfusion-associated, 79
Grafting, vascular, 1143-1144
Grafts, prosthetic, 1156
Gram-negative bacteria
  HACEK group, 1106
  in osteomyelitis, 1835
  in septic arthritis, 2265t
Gram-positive sepsis, 68
Gram's stain, 1453-1454, 1453t
  antibiotic choice based on, 1849, 1849t
  characteristics of meningeal pathogens, 1453t
  in children, 2228
  in pneumonia, 983
Grand multiparity, 2271-2272
Granulocytic phagocytes, 2358
Granuloma, fish tank, 1853
Granuloma inguinale, 1318
Granulomatous diseases, 902-903
Graves' disease, 1677-1678
  binocular, 178
Gravidity, 2271
Gravol (dimenhydrinate), 246
Gray (Gy), 1949
Graze wounds, 833, 834f
Greater trochanter fractures, 685, 685f
  in children, 696-697
Greenstick fractures, 517, 587, 588f, 2250
  of clavicle, 624, 624f
  of femur midshaft, 517f
  of radius, 2250, 2251f
Grief, e54
Grieving and bereavement, e54-e55
  differential considerations, 1472
  reactions in staff, e55
Griffith criteria, 1057, 1058f
Griseofulvin
  alcohol interactions, 2390t
  for tinea corporis, 1560
  for tinea unguium (onychomycosis), 1561
Groin pull, 691
Groshong catheters, 1155, 1155f
Ground transport. *See* Ambulances
Group A beta-hemolytic *Streptococcus* (GABHS) pharyngitis, 965
  Centor criteria for diagnosis of, 967, 967b
  Centor criteria for testing and treatment of, 967, 967b
  clinical features of, 966
  diagnosis of, 966-967
  management of, 967-968
  patient disposition in, 968
Group A streptococcal (GAS) infection
  in skin infections, 1856t
  in streptococcal toxic shock syndrome, 1714
Group A streptococcal (GAS) infection–related arthritis, 1512-1513
Group B streptococcal infection, 2264-2265, 2265t
Group suicide, 1492
Grouped beating, 1044, 1045b
Growth factors, 533
Guaiac testing, 250
Guanabenz acetate, 1122.e1t-1122.e2t
Guanethidine, 2072t-2073t
Guanfacine hydrochloride, 1122.e1t-1122.e2t
Guillain-Barré syndrome, 1430-1431
  incidence of, 1428
  management of, 1431
Guinea worm *(Dracunculus medinensis)*, 1772t-1775t
Gunshot residue (GSR) testing, 830, 832f, 834-836
Gunshot wounds. *See also* Handgun wounds
  abdominal, 460, 473-475
    algorithm for, 474f
    diagnostic testing in, 473
    history taking in, 462
    management of, 473-475
    missile path, 474
    physical examination findings, 463
  in back, 474
  care under fire, 2451
  centerfile rifle wounds, 833-834, 836f
  from drive-by shootings, e4
  errors of interpretation and terminology, 828-829
  in flank, 474
  forensic aspects of, 828-836
  handgun wounds
    ballistics of, 829-830
    forensic evaluation of, 830-836
  to head, 358
  hemothorax secondary to, 441f
  high-velocity, 833-834, 836f
  management of, 763-764
  in neck, 421
  pathophysiology of, 358
  perforating, 835f
  peripheral vascular injury, 500
  protection against, 434
  self-inflicted, 358
  shotgun wounds, 834
  spinal, 412f
  thoracoabdominal, 474
  transcervical, 425
Gutter splints, 548, 549f
Gynecologic disorders, 1355-1362
  associated with pelvic trauma, 665
  key concepts, 1362
  patient disposition in, 1362

H

H1N1 pandemic influenza, 1735
H_2 histamine receptor antagonists, 2318t-2321t, 2329
H5N1 virus, 1735
HAART. *See* Antiretroviral therapy, highly-active
HACE. *See* High-altitude cerebral edema
HACEK group, 1106
Haddon, William, 330-331, 333t
Haddon matrix, 330-331, 333t
Haemophilus ducreyi (chancroid), 1286t, 1318
Haemophilus influenzae infection
  Gram's stain characteristics, 1453t
  otitis media, 931-932
  pneumonia, 978-980
  septic arthritis, 2265t
Haemophilus influenzae type b (Hib) infection
  meningitis, 1458
  osteomyelitis, 1835
  skin infections, 1856t
Haemophilus influenzae type b (Hib) vaccine, 1458
Haemophilus vaginalis vaginitis, 2298
Hairpin splint, 547, 547f
Halazepam (Paxipam), 2078t
Halcion (triazolam), 2078t
Haldol (haloperidol)
  for delirium, 1403
  for nausea and vomiting, 245
  for rapid tranquilization, 1463
Hallpike test, 164-165
Hallucinations
  definition of, 1461
  in schizophrenia, 1462
  with violent behavior, 2419t
Hallucinogens, 2015-2023, 2023b
Haloperidol (Haldol), 2048t
  for chemical restraint, 2417
  for delirium, 1403
  hepatic injury, 1197t
  for nausea and vomiting, 245
  for rapid tranquilization, 1463, 1472
  side effects of, 2417
Haloprogin (Halotex), 1560
Halotex (haloprogin), 1560
Halothane, 1382, 2340t
Hamate fractures, 578-579, 579f
Hamilton, David, 1904
Hamstring muscle injury, 691
Hand(s)
  arterial system, 541-542, 542f
  blood supply, 541-542
  bones of, 534-535, 536f-537f
  compartment syndrome in, 564-565
  compartments, 564-565, 564f
  deep space anatomy, 567
  deep space infections, 567
  deformities of, 542-543, 543f
  extensor tendons, 538-539, 539f-540f
  flexor tendons, 539-540
  foreign bodies in, 568-569
  ganglion in, 568
  general physical examination of, 544-545
  infections of, 565-568
  lymphatic system, 542
  midpalmar spaces, 567, 567f
  motor innervation, 542-543
  muscle function, 537-541
  musculature of, 537-538, 538f-539f
  nerve supply to, 542-543, 543f
  nontraumatic disorders of, 568
  osteomyelitis in, 568
  physical examination of, 544b
  in pregnancy, 2278
  pronation of, 535f
  radial deviation of, 535f
  radiographic imaging of, 545, 545f
  "safe" position for, 550, 550f
  sensory innervation, 543, 543f
  septic arthritis in, 568
  skeleton, 534-536, 536f-537f
  skin cover, 534
  structural framework, 534-543
  supination of, 535f
  surface anatomy, 534, 535f, 539f
  synovial spaces, 540-541, 541f
  tendon function, 537-541

www.ketabpezeshki.com 66485457-66963820

Hand(s) *(Continued)*
terminology for, 534
ulnar deviation of, 535f
venous system, 542
Hand-held compartment pressure devices, 522, 523f
Hand-held Doppler ultrasound, 504
Hand injury, 534-569
amputations, 563-564
bites
indications for hospital admission, 792b
management of, 764
clinical features of, 544-545
diagnostic strategies for, 545-546
dislocations, 553-554
epidemiology of, 534
extensor tendon injuries, 557-560
flexor tendon injuries, 560-561
fractures, 546
classification of, 546, 546f
pediatric, 552-553
key concepts, 569b
ligamentous, 553-554, 553f
management of, 546-569
mechanisms of, 546-569
mutilating, 561
nerve injuries, 565
partial amputations from contact with deploying covers, 841, 841f
radiology in, 545-546
signs and symptoms of, 544-545
soft tissue injuries, 553
stenosing tenosynovitis, 568
tendon injuries, 556-561
terminology for, 534-544
traumatic, 546
vascular, 564
Hand motion, 534, 535f
Handgun ammunition, 829, 829f
Handgun wounds. *See also* Gunshot wounds
ballistics of, 829-830
close-range, 830, 831f
contact wounds, 830, 831f
entrance wounds, 830-833
atypical, 833, 834f
tight-contact, 831f
evidence related to, 834-836
exit wounds, 833-834, 835f
atypical, 833, 835f
soot with, 833, 835f
forensic evaluation of, 830-836
graze wounds, 833, 834f
indeterminate-range, 832
intermediate-range, 830
long-range, 830-833
microscopic examination of, 834
tangential-contact, 831f
tight-contact, 830, 831f
Handguns, e2, e4
categories of, 829
forensic aspects of, 829-830
range of fire, 830, 830t
as weapons, 829
Hanging
atypical, 429
complete, 429
definition of, 429
epidemiology of, 429
incomplete, 429
near, 429-430
typical, 429
Hanging cast technique, 602-603, 603f
Hanging weight reduction, 632-633, 632f
Hangman's fracture, 393, 394f, 512t-513t
Hank's solution, 904
Hannibal, 1883
Hanson's high-risk criteria, 293
Hantavirus cardiopulmonary syndrome, 1739
Hantavirus pulmonary syndrome, 1739
Hantaviruses, 1739
HAPE. *See* High-altitude pulmonary edema
Hare traction splint, 529, 530f, 680
Hashimoto's thyroiditis, 1678, 1684
Hawkins-Kennedy impingement sign, 638
Hawkins test, 1520
Hawkins's classification, 737, 737f
Hazard vulnerability analysis, 2459
Hazardous drinking, 2379-2380
Hazardous materials (hazmats), 818-819
contingency plans for, 818-819
coping with incidents, 819
definition of, 818
key concepts, 827b
in tactical combat care, 2453
toxic disasters, 2465
in urban search and rescue, 2456
Hazardous Substances Emergency Events Surveillance (HSEES) system, 818
Head
anatomy and physiology of, 339-342
fascial planes of, 896
Head and neck examination
in sexual assault, 864-865
in vertigo or disequilibrium, 164
Head injury, 339-367, 340f
abusive, 355
acute neurologic examination in, 345-347
biomechanics of, 342
causes of, 339
clinical features of, 345-347
closed, 477, 477f
complications of, 359-360
diagnosis of, 167f, 345-347
differential diagnosis of, 166t-167t
direct, 342
electrical injury, 1910
epidemiology of, 339
examination findings, 347
history taking in, 345
indirect, 342
inflicted, 355
key concepts, 366b-367b
lightning injury, 1910
management of, 168f, 347-354
medical complications of, 360
minor
ancillary testing in, 353
clinical features of, 352
historical features of, 352
imaging studies in, 352-353
key concepts, 367
management of, 352-354
patient disposition in, 353-354
in patients on anticoagulants, 354
persistent symptoms after, 352b
risk stratification in, 353b
moderate
acute management of, 351
clinical features of, 351
complications of, 352
key concepts, 366
management of, 351-352
patient disposition in, 351
neurologic complications of, 359-360
nonaccidental, 355
pathophysiology of, 343-345, 362f
pediatric, 311-315, 355-358
clinical features of, 311-312, 355-356
diagnosis and management of, 313-315, 356-358
epidemiology of, 355
key concepts, 367
pathophysiology of, 355
radiology in, 315
penetrating brain injury (PBI), 358-359, 367
principles of, 339-345
severe
ancillary testing in, 350-351
antibiotic prophylaxis in, 350
consultation in, 351
initial resuscitation in, 348-351, 348f
key concepts, 366
laboratory testing in, 350-351
management of, 347-351
patient disposition in, 351
priority management of, 351
seizure prophylaxis in, 350, 350b
transfer, 351
traumatic. *See* Traumatic brain injury (TBI)
Head lice, 1573-1574, 1573f
Head pain
activity at onset of, 171
character of, 171
intensity of, 171
location of, 171-172
Head position, in cerebral ischemia, 86
Head thrust or head impulse test, 165
Headache, 170-175, 1386-1397
acute, 2240
in acute glaucoma, 1394-1395
alleviating factors, 172
ancillary testing in, 172
associated symptoms and risk factors, 172
associated with cough, 1397
cervicogenic, 1396
in children, 2239-2244
clinical features of, 2240-2241
diagnostic strategies for, 2243
laboratory testing in, 2243
management of, 2243-2244
chronic nonprogressive, 2240, 2242
chronic progressive, 2240-2241
classification of, 1387b
cluster, 1389, 2242-2243
coital, 1396-1397
diagnosis of, 170-172, 173t
differential diagnosis of, 170, 171t, 172-175, 174t, 2241-2243, 2241b
epidemiology of, 170
exacerbating factors, 172
exertional, 1397
high-altitude, 1396
history taking in, 170-172
hypertensive, 1395
indications for serious cause, 172-175
initial assessment and treatment of, 172, 175f
key concepts, 1397b
management of, 175
medication-overuse, 1396
migraine, 1386-1389
classification of, 2242
differential diagnosis of, 1387, 2233, 2242
pediatric, 2242b, 2243-2244
seizures caused by, 1379
vertebrobasilar, 166t-167t, 167f-168f
mixed, 2240
neuronal theory of, 2239-2240
nummular, 1396
pathophysiology of, 170
patient disposition in, 175
physical examination findings, 172
pivotal findings, 170-172, 173t
post-dural puncture, 1395
post-traumatic, 1394
in pregnancy, 2276-2277
primary, 1386-1390
prior history of, 172
rapid assessment and stabilization of, 170
recurrent, 2240
risk factors associated with potentially catastrophic illness, 172-175, 172b
secondary, 1386
secondary disorders, 1390-1396
significant symptoms of, 171t
in systemic lupus erythematosus, 1528
tension-type, 1389-1390, 2242
thunder clap or lightning strike, 171t
of unidentified origin, 170
vascular theory of, 2239-2240
Headache database, 2240, 2241b
Heads UP tool kits, 354
Heaf and tine tests, 1816-1817
Health Belief Model, 881
Health beliefs and concerns, e27
Health care
language and, e25
racial and ethnic disparities in, e23-e24
factors contributing to, e24
progress to date, e26
role expectations in, e28
sources of failures in, 2505, 2506f
standards for, e25-e26
Health care facilities. *See also specific types*
transportation between, 2440-2441

www.ketabpezeshki.com 66485457-66963820

Health Insurance Portability and Accountability Act (HIPAA), 1495-1496, e35-e36
law enforcement exemptions, 842, 844b
protections for IPV patients, 883
Health maintenance organizations (HMOs), e44
Health Plan Employer Data and Information Set (HEDIS), e25
Health Resources and Services Administration (HRSA)
Emergency Medical Services Education Agenda for the Future: A Systems Approach, 2436
Model Trauma Care System Plan, 287
Health Services, Preventive Health Services, and Home Community Based Services Act of 1984 (P.L. 98-555), 2433
Hearing loss
in acute bacterial meningitis, 2227
sudden, 936-937
sudden sensorineural hearing loss (SSNHL), 936
tests for, 165
with vertigo, 2247b
Heart. *See also under* Cardiac
anatomy of, 1034-1035
cellular electrophysiology, 1034, 1035f-1036f. *See also* Electrocardiography (ECG)
electrical events related to surface ECG and His bundle ECG, 1034-1035, 1037f
neurohormonal response, 1079
physiology of, 1076-1078
valvular anatomy of, 1109
Heart block, complete, 1045-1046, 1045f
Heart disease. *See also* Acute coronary syndrome; Cardiac disorders; Coronary artery disease
congenital, 2104-2105
valvular, 1109-1112
and heart failure, 1078
in pregnancy, 2301t-2303t, 2305-2306
Heart failure, 1075-1090
acute, 1080, 1083
with adequate perfusion, 1083-1084
with hypertension, 1119-1120, 1120t
with hypotension, 1086
treatment of, 1083-1089, 1084f
admission criteria, 1089
causes of, 1078, 1081-1082, 1081b
cellular mechanisms, 1075-1076
chronic, 1080, 1086-1089
anemia in, 1089
classification of, 1082b
considerations, 1088-1089
psychosocial factors, 1089
sleep apnea-related respiratory support for, 1089
therapeutic agents for, 1087-1088
classification of, 1079-1080
compensatory mechanisms in, 1078-1079
congestive
observational approach to, 2489
pediatric, 2152-2153
thyrotoxicosis in, 1683b
traditional approach to, 2488
definition of, 1075
diagnostic testing in, 1082-1083
dystolic dysfunction, 1080
at end of life, e58
epidemiology of, 1075
evaluation of, 1081-1083
exacerbating factors, 1081-1082
high-output, 1080
history taking in, 1082
hypertension-related, 1116
key concepts, 1090b
left-sided, 1080
low-output, 1080
neurohormonal model of, 1075, 1076f
neurohormonal modulation of, 1079
neurohormonal response to, 1079
with normal ejection fraction, 1080
observation criteria for, 2489b
physical examination findings, 1082
physiologic mechanisms in, 1078-1079
predictors of readmission, 1089
right-sided, 1080
systolic dysfunction, 1080
Heart injury. *See* Cardiac injury
Heart murmurs
Austin-Flint murmur, 1111
in children, 2142, 2142b-2143b
Heart muscle diseases, 1104-1105
Heart rate
fetal. *See* Fetal heart rate (FHR)
after heart transplantation, 2373, 2374f
normal, in newborn, 113t
Heart transplant patients
drug toxicity in, 2372-2373
general approach to, 2372
infection in, 2373-2374
management of, 2372-2374
rejection in, 2373
Heart transplantation, 2372, 2373f-2374f
Heart valves, 1078, 1109-1112
dysfunction of, 1082
in pregnancy, 2301t-2303t, 2305-2306
prosthetic
complications of, 1112, 1112b
in pregnancy, 2306
Heat
decreased production of, 1886, 1886b
electrothermal heating formulas, 1907b
physiology of, 1896
production of, 1896
Heat cramps, 1900
clinical factors, 1900
management of, 1900
physiology of, 1900
Heat edema, 1900
clinical features of, 1900
diagnostic essentials, 1900b
management of, 1900
physiology of, 1900
Heat exhaustion, 1901-1902
clinical features of, 1901
diagnosis of, 1901b
vs heatstroke, 1902-1903
management of, 1901
patient disposition in, 1901-1902
physiology of, 1901
treatment of, 1902b
Heat illness, 1896-1905
key concepts, 1905b
minor, 1900-1901
pathophysiology of, 1897-1900
predisposing factors, 1897-1899, 1898f
Heat Index (NWS), 1898, 1899f
Heat loss, 1886, 1886b
Heat rash, 1900
Heat regulation, 1896-1897
Heat strain index, 1898, 1899f
Heat syncope, 1900
clinical features of, 1900
management of, 1900
physiology of, 1900
Heated irrigation, 1893
Heatstroke, 1902-1905, 1903f
classic, 1903-1904, 1903t
clinical features of, 1902-1904
cooling modalities, 1905b
diagnosis of, 1902, 1902b, 1904
differential diagnosis of, 1904b
exertional, 1903-1904, 1903t
vs heat exhaustion, 1902-1903
management of, 1904-1905
physiology of, 1902
Heaven's Gate cult, 2076
Heavy metals, 2024-2031
Heberden's nodes, 1510
Hegar's sign, 2273, 2273f
Heimlich maneuver, 2115-2116
Helicobacter pylori infection
in hepatic encephalopathy, 1195
treatment regimens for, 1180, 1180b
Helicopter emergency medical services (HEMS), 2443
for cardiac disorders, 2447
disadvantages of, 2443, 2444f
history of, 2442
landing zones, 2445, 2445f
trauma flights, 2446-2447
Helicopters (rotor-wing aircraft), 2444-2445
Helidac (bismuth subsalicylate, metronidazole, and tetracycline), 1180
Heliox
for asthma, 953
for asthma in children, 2124
for COPD, 963
HELLP syndrome, 2291
Helmets, 2279
Heloderma horridum (Mexican beaded lizard), 796
Heloderma suspectum (Gila monster), 796
Helper cells (CD4 T lymphocytes), 2357
HELPER mnemonic, 2345b
Helplessness, learned, 1468
Hemangioma, subglottic, 2112
Hemarthrosis, 1510
Hematemesis, 248
Hematochezia, 248
Hematocrit
in abdominal trauma, 463-464
in children, 2143
normal values, 1587t
in pregnancy, 297
Hematologic disorders
in abdominal trauma, 463-464
alcohol-induced abnormalities, 2389
in HIV infection, 1763
in hypothermia, 1888
in pregnancy, 2306-2307
in sepsis, 1868
in systemic lupus erythematosus, 1528t
Hematoma
cephalohematoma, 312-313
epidural, 363, 364f
acute, 363f
acute back pain in, 282t-283t
pediatric, 313
rapid assessment and stabilization of, 279
intracerebellar, traumatic, 366
intracerebral, 365-366, 366f
retrobulbar, 189
key concepts, 930b
management algorithm for, 193t-196t
spinal epidural, 1425-1426
subcapsular, 493f
subdural, 363-365, 364f
acute, 364, 365f
chronic, 364-365
clinical features of, 139t
pediatric, 313
subacute, 364
subgaleal, 312-313
subungual, 561-562
Hematoma block, 583-584, 584f
Hematuria, 491-492, 1292-1293, 1352-1354
causes of, 1292b, 1353b
in children, 2213-2214
clinical features of, 2213
diagnostic strategies for, 2213-2214
differential considerations, 2213
etiology of, 2213, 2213b
key concepts, 2223b
management of, 2214
patient disposition in, 2214
clinical features of, 1293, 1353, 1353t
diagnostic strategies for, 1353-1354
laboratory findings, 1293
medical history in, 1354b
patient disposition in, 1354
radiographic findings, 1293
risk factors mandating further evaluation, 1354b
timing of, 1353t
ultrasound findings, 1293
Heme dipstick test, 1291
Hemifacial paresis, 1410t-1411t
Hemingway, Margaux, 2076
Hemiplegic migraine, 1387, 2242
Hemlock
Cicuta maculata (water hemlock), 2067, 2067f
Conium maculatum (poison hemlock)., 2067, 2068f
Hemoccult, 258
Hemodialysis, 1306
for beta-blocker overdose, 1989
complications of, 1308-1310
criteria for institution of, 1622b

www.ketabpezeshki.com 66485457-66963820

Hemodialysis *(Continued)*
for extracorporeal blood rewarming, 1893-1894, 1894t
for hyperkalemia, 1638, 1638t
hypotension in, 1308b
non–vascular access–related complications of, 1308-1310
for salicylate intoxication, 1967
for tumor lysis syndrome, 1622
vascular access for, 1155
vascular access–related complications of, 1308
Hemodynamics
in abdominal stab wounds, 472
cerebral, 340-342
management recommendations for, 1870t
optimization of, 71
Hemoglobin
in children, 2143
intrinsic abnormality of, 1596
normal values, 1587t, 1590t
Hemoglobin A_{1C} (HbA_{1C}), 1653-1655
Hemoglobin-oxygen dissociation curve, 129, 130f
Hemoglobinemia, paroxysmal nocturnal, 1596
Hemolysis
diagnostic tests for, 1595b
environmental causes of, 1600
extravascular, 1594-1595
extrinsic mechanical causes of, 1600
in G6PD deficiency, 1596b
intravascular, 1594
Hemolytic anemia, 1594
ancillary evaluation of, 1595
autoimmune, 1599, 1600b
classification of, 1596b
clinical features of, 1594-1595
differential diagnosis of, 1596
drug-induced, 1600
history and physical examination for, 1595b
immune, 1600, 1600b
laboratory assessment of, 1595-1596
prosthetic valve-related, 1112
Hemolytic transfusion reactions
extravascular, 79
intravascular, 78-79
Hemolytic-uremic syndrome, 2195
in children, 2222-2223
clinical features of, 2222
diagnostic strategies for, 2222
differential considerations, 2222
management of, 2222
patient disposition in, 2223
Hemoperfusion, 1989
Hemopericardium, 473, 473f
Hemoperitoneum, 475
Hemophilia
key concepts, 1616b
recommended factor VIII therapy, 1614t
Hemophilia A, 1612-1613
management of, 1613-1614
preparation for, 1613
prophylaxis of, 1613-1614
replacement therapy for, 1613
Hemophilia B (Christmas disease), 1615
Hemopneumothorax
pediatric, 319
spontaneous, 991
Hemoptysis, 203-205
ancillary testing in, 204
definition of, 203
diagnosis of, 203-205
differential diagnosis of, 203-204, 205b
epidemiology of, 203
history taking in, 204
management of, 204, 205f
pathophysiology of, 203
patient disposition in, 205
physical examination findings, 204
pivotal findings, 204
rapid assessment and stabilization of, 203-204
surgery for, 205
in tuberculosis, 1813, 1821
Hemorrhage. *See also* Bleeding
cerebellar, 166t-167t, 167f-168f
"dot" or "blot," 848
external, 292
Hemorrhage *(Continued)*
extracranial, in infants, 312-313, 313f
extremity, 2451
fetomaternal, 302-303
in fracture, 520
gastrointestinal, with abdominal stab wounds, 472
with hypoperfusion, 70b
intra-abdominal, 669-670
intracranial
clinical features of, 1366, 1368t
hypertensive, 1120t, 1364b
management of, 1373-1374
intramural, 1125
intraovarian, 1356f
oral, 907
pathogenesis of, 1902f
pelvic, 669-670
pelvic fracture–related, 668b
in pelvic trauma, 666-671
postpartum, 2347-2349
retinal
high-altitude, 1937, 1937f
in shaken infant syndrome, 848, 848f
retrobulbar, 910
subarachnoid, 1390-1391
ancillary testing in, 172
clinical features of, 139t, 1368t, 1390
differential diagnosis of, 174t
epidemiology of, 170
grading scale for, 1390t
pivotal findings, 170-172
risk factors for potentially catastrophic illness, 172b
spinal, 1424-1425
traumatic, 365
subconjunctival, 193t-196t, 913, 913f
vitreous, 915f, 916, 925
Hemorrhagic fever, 1725, 1739-1740
Hemorrhagic shock, 67-68, 68b
clinical management guidelines, 73b
definition and diagnostic criteria for, 70, 70b
treatment of, 72-73
Hemorrhagic stroke, 1003
clinical features of, 1366
differential considerations, 1368-1369
epidemiology of, 1364
risk factors for, 1029
Hemorrhagic tympanic membrane, 932
Hemorrhoids, 1277-1280
clinical features of, 1278-1279
external, 1278-1279, 1279f, 1279t
excision of, 1280, 1280f
internal, 1279, 1279f, 1279t
management of, 1279-1280
surgical, 1280t
WASH regimen for, 1279, 1279b
types of, 1279t
Hemostasis, 1606
alcohol-induced, 2389
disorders of, 1606-1616, 1616b
platelets in, 1607b
Hemostatic agents
advanced agents, 2451
intravenous agents, 2453
Hemothorax, 440-442, 441f
clinical features of, 440
diagnostic strategies for, 440-441
epidemiology of, 440
management of, 440-442
pathophysiology of, 440
pediatric, 319-320
secondary to gunshot wound, 441f
tension, 441f
Henbane *(Hyoscyamus niger)*, 1970
Hendrix, Jimi, 2076
Henoch-Schönlein purpura, 1539, 1539f
in children, 2180-2181, 2221-2222
clinical features of, 2180-2181, 2181f, 2221
diagnostic strategies for, 2181, 2221
differential considerations, 2181, 2221-2222
management of, 2181, 2222
patient disposition in, 2181, 2222
Henry's law, 1916t, 1917, 1917f, 2442-2443
Hepadnaviridae, 1719t
Heparin
for acute anticoagulation, 1143
for acute coronary syndrome, 1026-1027
bleeding due to, 1615
low-molecular-weight (LMWH)
for acute coronary syndrome, 1026-1027
for DVT, 1159
for PE, 1164-1165
in pregnancy, 2318t-2321t, 2323
for PE, 1168b
in pregnancy, 2318t-2321t, 2323
sites of activity, 1606
unfractionated (UFH)
for acute coronary syndrome, 1026-1027
for DVT, 1159
for PE, 1164-1165
reversal of, 1165
Heparin-induced thrombocytopenia (HIT), 1610
Hepatic artery aneurysms, 1148
Hepatic encephalopathy, 1194-1195
clinical features of, 1194
clinical stages of, 234t
diagnostic strategies for, 1194
differential considerations, 1194
key concepts, 1195b
management of, 1194-1195
patient disposition in, 1195
signs of, 233
Hepatitis, 1186-1196
alcoholic, 2385
clinical features of, 1192
differential considerations, 1192
management of, 1192-1193
chronic, 1198-1199
active, 1198-1199
definition of, 1198-1199
drugs for treatment of, 1721t-1722t
chronic active, 1198-1199
chronic persistent, 1198-1199
definition of, 1186
non-A, non-B. *See* Hepatitis C; Hepatitis E
in pregnancy, 2295, 2314
serologic markers in, 1188, 1188t
viral, 1186-1189
clinical features of, 1188
diagnostic strategies for, 1188-1189
differential considerations, 1189
epidemiology of, 1186-1188
key concepts, 1192b
management of, 1189
patient disposition in, 1189
postexposure prophylaxis, 1190t
special considerations, 1189-1192
Hepatitis A
diagnosis of, 1188-1189
incidence of, 1186
postexposure prophylaxis, 1190t
Hepatitis A vaccine, 1720t
Hepatitis A virus (HAV), 1186
antibodies to, 1188t
Hepatitis B
arthritis, 1513t
clinical features of, 1188
diagnosis of, 1188-1189
drugs for treatment of, 1721t-1722t
incidence of, 1186
postexposure prophylaxis, 1190t
in pregnancy, 2314
prophylaxis for sexual assault victims, 868b
risk from transfusion, 80
after sexual assault, 868t
therapy for, 1723
Hepatitis B core antigen (HBcAg), 1186-1187
antibodies to, 1188t
Hepatitis B e antigen (HBeAg), 1186-1187, 1188t
antibodies to, 1188t
Hepatitis B immune globulin (HBIG)
for hepatitis B, 1721t-1722t
postexposure prophylaxis, 1190t
after sexual abuse/assault, 851t
Hepatitis B surface antigen (HBsAg), 1186-1187, 1188t
antibodies to, 1188t
prevalence of, 1187
Hepatitis B vaccine, 1190t, 1720t

www.ketabpezeshki.com 66485457-66963820

Hepatitis B virus (HBV), 1186-1187
Hepatitis C
arthritis, 1513t
diagnosis of, 1189
drugs for treatment of, 1721t-1722t
incidence of, 1186
in pregnancy, 2314
risk from transfusion, 80
Hepatitis C virus (HCV), 1187
antibody to, 1188t
Hepatitis D
clinical features of, 1188
diagnosis of, 1189
Hepatitis delta virus (HDV), 1187-1188
antibody to, 1188t
Hepatitis E, 1187
Hepatitis G virus (HGV), 1188
Hepatitis GB virus type C, 1188
Hepatocellular carcinoma, 1199
Herbal medicines, 2070-2073
adverse effects of, 2071t-2072t, 2073
allergic reactions, 2073, 2074b
contamination of, 2073
drug interactions, 2072t-2073t, 2073
herbal products, 2066
key concepts, 2075b
misidentification of plants, 2070-2073
unintentional childhood exposure to, 2066
Herbal Slimming Regimen (1992), 2070
Herbicides, chlorophenoxy, 2062
Hereditary angioedema, 1556-1557
Hernia
cerebellotonsillar herniation, 345
cerebral herniation, 344, 345f
diaphragmatic, 114-115
inguinal, 1349
in children, 2210
internal, 1216-1217, 1217f-1218f
obturator, 1217-1218
spigelian, 1217
transtentorial herniation, 345f
central, 344-345
upward, 345
uncal herniation, 344
Herniated disk, 646
Heroin, 2053
Heroin abuse
respiratory depression associated with, 2053t
tracks secondary to, 1584, 1584f
Herpes, genital, 1312-1314
drugs for treatment of, 1721t-1722t
management of, 1578
Herpes B virus, 1730
Herpes encephalitis, 2236
Herpes esophagitis, 1175
Herpes meningoencephalitis, 1457
Herpes simplex, 1577-1578, 1727-1728
in AIDS
treatment against, 1257t
antimicrobial agents useful for, 2361t
clinical features of, 1577-1578, 1727-1728
of cornea, 190, 190f
diagnostic strategies for, 1728
differential considerations, 1728
drugs for treatment of, 1721t-1722t
in immunocompromised patients, 2361t
keratitis, 920, 920f
management of, 1578, 1728
neonatal, 2100, 2100f
patient disposition in, 1728
pharyngitis, 965
in pregnancy, 2298
proctitis, 1286t
treatment of, 1285-1286
treatment guidelines, 1315t
Herpes simplex virus, 1727-1728
variants of, 1577
Herpes simplex virus-1 (HSV-1) infection, 1577-1578, 1577f
Herpes simplex virus-2 (HSV-2) infection, 1577-1578
Herpes zoster (shingles), 1579, 1579f, 1728
antimicrobial agents useful for, 2361t
clinical features of, 1579, 1728-1729, 1729f
diagnostic strategies for, 1729
Herpes zoster (shingles) *(Continued)*
drugs for treatment of, 1721t-1722t
in immunocompromised patients, 2361t
management of, 1579, 1729
patient disposition in, 1729
Herpes zoster keratoconjunctivitis, 920
Herpes zoster oticus, 935
Herpesviridae, 1719t, 1727-1730
Herpesvirus simiae, 1730
Herpetic whitlow, 566, 1577f
clinical features of, 566
diagnostic strategies for, 566
epidemiology of, 566
management of, 566
pathophysiology of, 566
Hesitation marks, 840f
Hexachlorophene (polychlorinated bisphenol, pHisoHex), 756t
Hextend, 2452
Hickman-Broviac catheter, 1153-1155
double-lumen, 1153, 1153f
infections, 1155
laceration of, 1154
occlusion of, 1153-1154
Hidradenitis suppurativa, 1283, 1564, 1859
High altitude, 1928
High-altitude cerebral edema, 1928, 1936-1937, 1936b
clinical presentation of, 1936-1937, 1937f
key concepts, 1940b
management of, 1937
pathophysiology of, 1930-1932
High-altitude headache, 1396
High-altitude illness
epidemiology of, 1928
key concepts, 1940b
pathophysiology of, 1930-1932
High-altitude medicine, 1928-1940
definitions, 1928-1929
environmental considerations, 1929
key concepts, 1940b
and underlying medical conditions, 1938-1939
High-altitude pulmonary edema, 1928, 1934-1936, 1934b
ancillary tests for, 1935
clinical presentation of, 1934-1935
differential diagnosis of, 1935
key concepts, 1940b
management of, 1935-1936
pathophysiology of, 1930-1932, 1931f
patient disposition in, 1936
prevention of, 1936
risk factors for, 1928
High-altitude retinal hemorrhage, 1937, 1937f
High-pressure injection injuries, 562-563
clinical features of, 563
complications of, 563
epidemiology of, 562
management of, 563
pathophysiology of, 563
High-Risk Construct Scale, 1497-1498
Hill-Sachs deformity, 631, 632f
key concepts, 642b
reverse, 635, 636f
Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000, 2082
Hilum, 491
Hindfoot, 734, 735f
Hindfoot injuries, 736-741
Hindfoot pain, 748
Hip
anatomy of, 672
pediatric, 693, 693f
apophysitis of, 2270
arterial supply, 673
degenerative joint disease in
radiographic findings in, 675f
developmental dysplasia of, 2261-2262
fracture-dislocations of, 687-691
infection of
in children, 694-695
ligaments of, 672, 673f
musculature of, 672
neoplastic disease in, 677
nerves of, 673-675
Hip *(Continued)*
radiographic anatomy of, 679-680, 679f
vascular anatomy of, 673-675
venous system, 673
Hip adductor strain, 691
Hip arthroplasty, 681-682
complications of, 681-682
epidemiology of, 681
outcomes, 681-682
total hip arthroplasty, 681
Hip dislocations, 687-690
adverse outcomes, 521t
anterior, 687, 687f, 690f
biomechanics of, 687
in children, 2261, 2261f-2262f
Barlow (provocative) test for, 2261, 2262b
Galeazzi's sign of, 2261-2262, 2262f
Ortolani (reduction) maneuver for, 2261, 2262b
classification of, 687, 687f
clinical features of, 687-688
diagnostic strategies for, 688
key concepts, 697b
management of, 688
postreduction, 689, 690f
mechanism of, 687
outcomes, 690
pediatric, 693
posterior, 687, 687f, 689f
Allis technique for reduction of, 688, 689f
Stimson's technique for reduction of, 688-689, 689f
techniques for closed reduction of, 689
reduction techniques for, 688-689
Hip fractures, 682-687
avulsion fractures, 682, 682f
epidemiology of, 672
history of, 672
management of, 680-682
with minimal or no trauma, 686
MRI findings, 679, 680f
occult, 679-680
in older adults, 328
open fracture care, 681
pathophysiology of, 675
pediatric, 693-694
splinting and bandaging, 529
Hip injury
clinical features of, 677-679
diagnostic strategies for, 679-680
epidemiology of, 672
history taking in, 677-678
key concepts, 697b
neurologic, 692-693
pediatric considerations, 693-697
physical examination findings, 678-679
radiographic evaluation of, 679-680
soft tissue injuries, 691-693
traumatic, 672-697
vascular injuries, 692
Hip osteoarthritis
pathophysiology of, 675
radiographic findings, 675, 675f
Hip pain
causes of, 2263b
in children, 2263-2269
differential diagnosis of, 677, 678b
Hip prosthetics, 690-691
HIPAA. *See* Health Insurance Portability and Accountability Act
Hippocrates, 1809
Hippocratic method, 633
Hippocratic Oath, e36, e37t
Hirschsprung's disease, 2178-2179
clinical features of, 2178
diagnostic strategies for, 2178
differential considerations, 2178-2179
key concepts, 2187b
management of, 2179
patient disposition in, 2179
Hirudin, 1027
Hirulog, 1027
His bundle, 1034-1035, 1037f
His-Purkinje system, 1037t

www.ketabpezeshki.com 66485457-66963820

Hispanics
cultural practices, e27
health beliefs and concerns, e28
pregnancy rates, 2271
suicide rate, 1492
treatment options for, e24
Histamine H_2 receptor antagonists, 2318t-2321t, 2329
Histamine receptor antagonists. *See* Antihistamines
Histoplasma capsulatum infection, 2363
Historical perspective
on emergency medical services (EMS), 2433-2434
on helicopter emergency medical services (HEMS), 2442
on radiation injuries, 1945-1946
tactile medical history, 2449
on ultrasound, 2492
on weapons of mass destruction, 2469
History taking
with children, 2090
from elders, 2353
focused dive history, 1922b
focused SAMPLE history, 2090, 2090b
in intimate partner violence, 883t
On-Site Neurological Assessment for Diver's History form (DAN), 1923, 1924f
overdose history, 1954, 1955b
Histrionic personality disorder, 2427b
"Hitting pink," 1152
HIV. *See* Human immunodeficiency virus infection
Hives (urticaria), 1555-1557, 1556f, 1566f
HMG–Coenzyme a reductase inhibitors (statins), 1024
HMOs. *See* Health maintenance organizations
Hobo or aggressive house spider *(Tegenaria)*, 804
Hodgkin's disease
AIDS-related, 1763
skin lesions associated with, 1583
Hodgkin's lymphoma, 1583
Hoffman, Abbie, 2076
Hohl classification, 707, 707f
Hollow points, 829
Hollow viscus injury, 465-466, 466f
Homatropine, 191t, 930t
Home care
discharge or transfer to, e67
for hymenoptera envenomation, 802
Home mechanical ventilation, 2404
Home ventilators
alarms, 2404
problems and solutions for, 2405t
Homicide, 873
Homosexuals
adolescents in abusive relationships, 875
intimate partner violence among, 873
Honeymooner's syndrome, 2386
Honoring advance directives, e50-e51, e55-e56
Hookworm *(Ancylostoma duodenale, Necator americanus)*, 1770t-1771t, 1778
drug regimens for, 1772t-1775t
Hordeolum (stye), 193t-196t, 920-921
Horner's syndrome, 401, 928, 928f
Horse bites, 787
Horseshoe abscess, 1282
Hospice care, e49-e50
definition of, e49
history of, e49
out-of-hospital, e51
Hospital-acquired hyponatremia, 2203
Hospital admission
for alcoholics, 2393-2394
for croup, 2113b
direct, e65-e67
under EMTALA, e65-e67
factors to consider, 231
for heart failure, 1089
for human bites of hand, 792b
pediatric, 2093t
presentation for care, e61
registration process, e64
Hospital hobo syndrome, 1487
Hospital Incident Command System, 2462
Hospital inpatients
definition of, e67
EMTALA application to, e67
Hospital Preparedness Cooperative Agreement Program, 2467
Hospital property, e61
Hospital transfers, e69
duty to accept, e68-e70
EMTALA form for, e66f
from other hospitals, e69
requirements for accepting, e69-e70
Hospitals
acute care, e68
authorization, e64
capacity, e69
collections or insurance information, e64
comprehensive disaster response planning process, 2463-2464
critical substrates for operations, 2459, 2459b
disaster response, 2463-2465
disaster response plan, 2463-2464
documentation requirements, e64
emergency management plans, 2463
interdepartmental planning group, 2463
reporting requirements, e76-e77
Hostage situations, 2418
Hot tub folliculitis, 1859
Hot zones, 2451
Household cleaning products, 1994
abuse of, 2396
that contain caustic chemicals, 1994, 1995t
Housemaid's knee, 716, 1519f
H.P. Acthar gel (ACTH [adrenocorticotropic hormone]), 2407t-2408t
HSEES (Hazardous Substances Emergency Events Surveillance) system, 818
HTS, 349
HU-210, 2021-2022, 2021f
Huffer's rash, 823, 2033-2034, 2034f
Huffing, 823, 2033-2034, 2034f
Human bites, 790-793, 846f
bacteriology of, 791
child physical abuse, 845
epidemiology of, 790-791
hand bites, 792b
indications for hospital admission, 792b
infection in, 792-793
key concepts, 793b
management of, 792
patient disposition in, 792-793
prophylactic antibiotics for, 789t, 792
prophylactic antiviral agents for, 792
recommendations for closure and prophylactic antibiotics, 789t
risk factors for infection, 788t
septic arthritis from, 1846
transmission of disease in, 791-792
wound evaluation in, 792
wound management in, 792
Human botulism immune globulin (BabyBIG), 1445, 1707
Human chorionic gonadotropin, beta subunit (β-hCG), 2283, 2283t
Human diploid cell vaccine, 1720t
Human factors, 2505-2506
Human granulocytic anaplasmosis, 1786t, 1804
Human herpesvirus 5, 1731
Human herpesvirus 6, 1729-1730
Human herpesvirus 7, 1730
Human herpesvirus 8, 1730
Human immunodeficiency virus (HIV), 1740, 1751
ED testing for, 1764-1765
nonoccupational exposure to, 1766-1767
occupational exposure to, 1765-1766
replicative cycle, 1751, 1754f
structure of, 1751, 1753f
subtypes, 1751
transmission of
factors influencing probability of, 868t
modes of, 1753
risk factors for, 1753
in sexual assault, 868
vertical, 2341-2342
type 1 (HIV-1), 1740
type 2 (HIV-2), 1740
Human immunodeficiency virus (HIV)–associated nephropathy (HIVAN), 1762
Human immunodeficiency virus (HIV) chemokine receptor 5 antagonist (CCR5 inhibitors), 1766t
Human immunodeficiency virus (HIV) infection, 1751-1767
in acute retroviral syndrome, 965
anorectal lesions in, 1288b
arthritis, 1513t
bone and joint, 1836
chronic, 1756
clinical features of, 1753-1764
cutaneous findings suggestive of, 1763-1764, 1763b
dermatologic manifestations of, 1763, 1763b
diagnostic strategies for, 1764-1765
differential considerations, 1765
drugs for treatment of, 1721t-1722t
encephalopathy, 1762t
epidemiology of, 1751
key concepts, 1767b
management of, 1765-1767
mucocutaneous manifestations of, 1763b
myelopathy, 1425
natural history of, 1756f
neuropathies, 1432-1433
parasitic coinfections, 1783-1784
patient disposition in, 1767
pericarditis, 1097
with pneumonia, 1818
postexposure prophylaxis of, 1765-1767
recommendations for, 1766
in pregnancy, 2301t-2303t, 2312-2313
prevalence of, 1751, 1752f
primary, 1753-1756, 1755t
prophylaxis to prevent opportunistic infections in, 1758t
respiratory infections in, 1758t
risk from sexual assault, 868
risk from transfusion, 80
stages of, 1753-1757, 1755b
surveillance case definitions, 1755t
therapy for, 1723
Human immunodeficiency virus (HIV) integrase inhibitors, 1766t
Human immunodeficiency virus (HIV) testing, 1756t, 1764
ED testing, 1764
recommendations for, 1764b
for sexual assault victims, 868
Human infrared imaging, 1903f
Human metapneumovirus, 1736
Human monocytic ehrlichioses, 1786t, 1804. *See also* Ehrlichioses
Human papillomavirus (HPV) infection, 1730
clinical features of, 1730
condylomata acuminata, 1286t, 1319, 1730
diagnostic strategies for, 1730
differential considerations, 1730
drugs for treatment of, 1721t-1722t
genital warts from, 1319, 1319f
management of, 1730
Human T-lymphotrophic virus type 1 (HTLV-1), 1740
–associated myelopathy, 1740
Human T-lymphotrophic virus type 2 (HTLV-2), 1740
Human tetanus immune globulin (HTIG), 1703-1704
Humatin (paromomycin), 1251
Humerus
anatomy of, 596-597, 597f
supracondylar process, 596, 598f
Humerus fractures, 601-612
classification of, 601b
distal humerus, 603-609
open reduction and internal fixation of, 603, 604f
proximal humerus, 625-627
radiographic findings, 598-601
shaft fractures, 601
clinical features of, 601-603
complications of, 603
hanging cast technique for, 603f
management of, 601-603, 603f
pathophysiology of, 601, 602f
radiographic findings, 601, 603f
supracondylar, 2254-2257

www.ketabpezeshki.com 66485457-66963820

Hume's fracture, 512t-513t
Humoral immunity, 2357
defects in immunocompromised patients, 2364
Hunt and Hess clinical grading scale, 1390t
Hunter criteria, 1980, 1980t
Huntington's disease, 1476-1477
Hurricanes, 2457-2458
Hussein, Saddam, 2469
Hutchinson's fracture, 585-586, 586f
Hyatt Regency Hotel (Kansas City), 2458
Hydatid cysts, 1777, 1777f
Hydatidiform mole, 2288
Hydralazine
alcohol interactions, 2390t
hemodynamic effects, 1118t
for hypertension, 2221t, 2304t, 1122.e1t-1122.e2t
for hypertension in pregnancy, 2292
Hydration
for labor and delivery, 2338t
oral solutions for, 2200t
for tumor lysis syndrome, 1622
Hydrazine overdose, 1957t-1958t
Hydrocarbon poisoning, 2032, 2033t, 2035f
clinical features of, 2033-2034
diagnostic strategies for, 2034
differential considerations, 2034
key concepts, 2035b
management of, 2034
pathophysiology of, 2032-2033
cardiac, 2033
central nervous system, 2032-2033
pulmonary, 2032
patient disposition in, 2035
Hydrocarbons, 823-824, 2032-2035
characteristics of, 2032
classification of, 2032
definitions, 2032
terminology, 2032
Hydrocele
acute, 1349
in children, 2210
Hydrocephalus, 2409
Hydrochloric acid, 1994
Hydrochlorothiazide, 1122.e1t-1122.e2t
Hydrocodone, 39t, 41-42
respiratory depression associated with, 2053t
safety in pregnancy and lactation, 2318t-2321t
Hydrocortisone
for acute rheumatic fever, 1513
for adrenal insufficiency, 1691-1692
for bacterial meningitis, 1457
for myxedema coma, 1688b
for otitis externa, 935
in pediatric resuscitation, 104t
for systemic lupus erythematosus, 1533
for thyroid storm, 1682b, 1683
Hydrocortisone acetate (Hydrocortone), 639t
Hydrocortone (hydrocortisone acetate), 639t
Hydrofluoric acid exposure, 820-821
antidote for, 1957t-1958t
dermal, 821
gastrointestinal, 820
infiltration therapy for, 821
intra-arterial, 821
subcutaneous, 821
inhalational, 820
initial therapy for, 821
key concepts, 827b
ocular, 820
systemic toxicity to, 821
Hydrogen chloride, 2037t
Hydrogen cyanide, 825, 825t, 2037t, 2039
Hydrogen fluoride, 2037t
Hydrogen peroxide (H_2O_2), 756t, 1997
Hydrogen sulfide, 2037t, 2039-2041
Hydrogen sulfide poisoning
antidote for, 1957t-1958t
clinical features of, 2039
diagnostic strategies for, 2039-2040
differential considerations, 2039-2040
key concepts, 2043b
management of, 2040-2041
odor in, 1955t
Hydromorphone, 39t, 41
in pregnancy and lactation, 2318t-2321t
respiratory depression associated with, 2053t
for sickle cell disease, 1599
Hydronephrosis, 1338-1339, 1338f-1340f, 2497-2498, 2498f
Hydrophiidae snakes, 795-796
Hydrotherapy, 819
Hydroxocobalamin (CYanokit), 827, 2041
β-Hydroxybutyrate, 1655
γ-Hydroxybutyrate, 2082-2083
γ-Hydroxybutyrate intoxication
clinical features of, 2083
diagnostic strategies for, 2083
management of, 2083
patient disposition in, 2083
γ-Hydroxybutyrate withdrawal, 2083
Hydroxychloroquine
for Q fever, 1803
for rheumatoid arthritis, 1514
for systemic lupus erythematosus, 1533t
toxicity of, 1515t
Hydroxycobalamin
for cyanide poisoning, 1957t-1958t
in pregnancy, 2318t-2321t, 2323
5-Hydroxytryptophol, 2380t
Hydroxyzine (Atarax and Vistaril), 1569, 2048t
Hygiene hypothesis, 943
Hygroma, subdural, 365
Hymenolepis diminuta, 1770t-1771t
Hymenolepis nana, 1770t-1775t
Hymenoptera, 801-803, 1545
Hymenoptera envenomation
clinical features of, 802
ED care for, 802-803
home care for, 802
management of, 802-803
Hyoepiglottic ligament, 108
Hyoscine (Buscopan), 246
Hyoscyamus niger (henbane), 1970
Hyperabduction syndrome, 1151
Hyperbaric oxygen therapy
for arterial gas embolism, 1924-1925
for carbon monoxide poisoning, 2042
for HAPE, 1935
for peripheral arteriovascular disease, 1144
portable chambers, 1935, 1935f
Hyperbilirubinemia
in infants, 2168, 2169t, 2187b
in older children, 2168, 2169t
Hypercalcemia, 1645-1646
causes of, 1645, 1645b
clinical features of, 1624-1625, 1645
definition of, 1645
diagnostic strategies for, 1645
due to malignant disease, 1624-1625, 1628b
ECG findings, 1645, 1646f
management of, 1625, 1645-1646
non-neoplastic causes of, 1624b
pathophysiology of, 1624
symptoms and signs of, 1624b
Hypercapnia, permissive, 29
Hyperemesis gravidarum, 236-237, 243t-244t, 246, 2296
Hyperglycemia
with acute MI, 1003
new-onset, 1665
treatment of, 85-86
Hyperglycemic hyperosmolar state, 1661-1662
clinical features of, 1661-1662
complications of, 1662
diagnostic strategies for, 1662
differential considerations, 1662
etiology of, 1661
key concepts, 1666b
laboratory values in, 1658t
management of, 1662
pathophysiology of, 1661
patient disposition in, 1662
Hyperkalemia, 1636-1639
in acute kidney injury, 1300
causes of, 1637b
in children, 2218
in chronic kidney disease, 1304-1305
Hyperkalemia *(Continued)*
clinical features of, 1636, 1637f
definition of, 1636
in diabetic ketoacidosis, 1639
diagnosis of, 94t, 1636-1637
ECG changes in, 1636-1637, 1637f-1638f
key concepts, 1651b
management of, 1637-1639
succinylcholine-associated, 13-14, 14t
treatment of, 94t, 1305, 1305t, 1638t
Hyperlipidemia, alcohol-induced, 2387
Hypermagnesemia, 1647-1648
in acute kidney injury, 1300
causes of, 1647, 1647b
clinical features of, 1648, 1648t
diagnostic strategies for, 1648
management of, 1648
Hypernatremia, 1641-1642
clinical features of, 1641
definition of, 1641
diagnostic strategies for, 1641
management of, 1641-1642
types of, 1641b
Hypernatremic volume depletion, 2203
Hyperoxia test, 2143
Hyperphosphatemia, 1649-1650
in acute kidney injury, 1300
causes of, 1650b
clinical features of, 1650
definition of, 1649
management of, 1650
Hyperpnea, 206
Hyperpyrexia, 343
in head injury, 343
MDMA-related, 1957t-1958t
Hypersensitivity, 1543-1557
classification of, 1548-1549
delayed, cell-mediated, 1545b
immediate, 1545b
key concepts, 1557b
Hypersensitivity vasculitis, 1541t
Hypersplenism, 1600
Hypertension, 1113-1123
accelerated, 1113-1114
altitude and, 1939
chest pain and, 217t-218t
in children, 2219-2221
clinical features of, 2220
diagnostic strategies for, 2220
differential considerations, 2220
etiology of, 2219, 2219b
key concepts, 2223b
management of, 2220-2221
patient disposition in, 2221
chronic, 2290
cerebral blood pressure autoregulation curve response, 1118-1119, 1120f
definition of, 2303
oral agents for, 1122.e1t-1122.e2t
pathophysiology of, 1114-1115
poorly controlled, 1113-1114
with preeclampsia, 2304t
in pregnancy, 2303-2304, 2304t
therapy for, 1122
classification of, 1113-1114
clinical features of, 1116-1117
cocaine-induced, 2000-2001
coincidental, 2290
definition of, 1113-1114, 2219
diagnostic strategies for, 1117
differential diagnosis of, 1117
essential, 1114
gestational, 2290, 2304t
and heart failure, 1081
intracranial, idiopathic, 1394
key concepts, 1123b
malignant, 1113-1114
management of, 1117-1122
neurogenic, secondary to spinal shock, 418
patient disposition in, 1122-1123
pre-HTN, 1113
in pregnancy, 2290-2292, 2301t-2303t, 2303-2304
prevalence of, 1113
primary, 1114

www.ketabpezeshki.com 66485457-66963820

Hypertension (Continued)
pulmonary
clinical features of, 139t
in pregnancy, 2304
secondary, 1114, 1114t
target-organ damage, 1115-1116
terminology, 1113-1114
therapeutic goals, 1118-1119
vascular modulation of, 1115
venous, 1156, 1156b
Hypertensive crisis, 1113-1114
Hypertensive emergency, 1113, 1116, 1116t
antihypertensive agents for, 2304t
in children
diagnostic evaluation of, 2220, 2220b
patient disposition in, 2221
clinical features of, 1116
cocaine-induced, 2000-2003
definition of, 1123b
diagnostic strategies for, 1117
management of, 1118-1119, 1120t
medications for, 2220, 2221t
in pregnancy, 2303-2304
Hypertensive encephalopathy, 1116, 1120t, 1121
Hypertensive headache, 1395
Hypertensive intracranial hemorrhage, 1120t, 1364b
Hypertensive retinopathy, 1117, 1117b
Hypertensive urgency, 1113-1114
Hyperthermia
in anticholinergic overdose, 1973
cocaine-induced, 2000, 2002, 2002b
differential diagnosis of, 1899-1900
vs fever, 1899-1900
malignant, succinylcholine-associated, 14
Hyperthyroidism, 1676-1684
anxiety in, 1476
causes of, 1676, 1677b
clinical features of, 1678-1680
consultation for, 1684
definition of, 1676
diagnostic strategies for, 1680-1681
differential considerations, 1681-1682
epidemiology of, 1676
incidence of, 1676
key concepts, 1692b
management of, 1682-1684
pathophysiology of, 1676-1678
patient disposition in, 1684
physical signs of, 1679-1680, 1679b
in pregnancy, 2301t-2303t, 2311-2312
skin lesions associated with, 1581t
symptoms of, 1678-1679, 1679b
treatment of, 1683
supportive, 1682
symptomatic, 1682
thyroid-directed, 1683
Hypertonic dehydration, 2203b
Hypertonic saline
for increased ICP, 314t
for prolonged seizures and status epilepticus, 158t-159t
for TCA overdose, 1977
Hypertonic sodium bicarbonate, 1977, 1978f
Hypertriglyceridemia, 1658
Hypertrophic cardiomyopathy, 1102-1103, 2166
anatomy of, 1102
clinical features of, 1102, 2166
diagnostic strategies for, 1102-1103, 2166
differential diagnosis of, 1103
key concepts, 1105b
management of, 1103, 2166
pathophysiology of, 1102
patient disposition in, 1103
Hypertrophic pyloric stenosis, 2170-2172
clinical features of, 2171
diagnostic strategies for, 2171
differential considerations, 2171
key concepts, 2187b
management of, 2172
patient disposition in, 2172
radiographic findings, 2171, 2172f
Hypertrophic subaortic stenosis, idiopathic, 1102
Hyperuricemia, 1623-1624
clinical features of, 1623-1624
management of, 1624
Hyperuricemia (Continued)
pathophysiology of, 1623
in tumor lysis syndrome, 1622
Hyperventilation
in acute kidney injury, 1300
clinical features of, 139t
controlled
in head injury, 349
in increased ICP, 314t
in COPD, 959
definition of, 206
differential considerations, 1247, 1380-1381
of pregnancy, 2300
Hyperviscosity syndrome, 1622-1623
clinical features of, 1623
incidence of, 1623
management of, 1623
pathophysiology of, 1623
Hypervolemic hyponatremia, 1643
causes of, 1642b
management of, 1644
Hyphema
in anterior chamber, 913-914, 914f
management algorithm for, 193t-196t
spontaneous, 191
traumatic, 191, 913-914, 914f
Hypnosis, 48
Hypnotics, 32b
Hypoadrenalism, 1691-1692, 1692b
Hypoalbuminemia, 1630
Hypocalcemia, 1646-1647
alcohol-induced, 2388
causes of, 1646, 1646b-1647b
in children, 2236
clinical features of, 1647
diagnostic strategies for, 1647
management of, 1647
in pediatric septic shock, 106
Hypocapnia, 341, 341f
Hypochondriasis
characteristics of, 1482
clinical features of, 1482
diagnostic criteria for, 1482b
prevalence of, 1482
reactive, 1483
Hypochromic microcytic anemia, 1590b, 1590f
Hypodynamic shock, 68b
Hypoglossal nerve (CN XII), 1410t-1411t
Hypoglycemia, 1655-1656
alcohol-induced, 2381, 2387
in children, 2236
in children with sepsis, 106
clinical features of, 139t, 1655
diagnosis of, 167f, 1655
differential diagnosis of, 166t-167t
fasting, 1656
key concepts, 1666b
management of, 1656
neonatal, 113
patient disposition in, 1656
postprandial, 1656
reactive, 1476
Hypoglycemia unawareness, 1655
Hypoglycemics
alcohol interactions, 2390t, 2391
herbal medicine interactions, 2072t-2073t
Hypokalemia, 1634, 1639-1641
causes of, 1639b
clinical features of, 1639-1640
definition of, 1639
diagnostic strategies for, 1640
ECG changes in, 1640, 1640f
hypomagnesemia with, 1648-1649
key concepts, 1651b
management of, 1640-1641
vomiting and, 239
Hypomagnesemia, 1648-1649
causes of, 1648, 1648b
clinical features of, 1649
diagnostic strategies for, 1649
with hypokalemia, 1648-1649
management of, 1649
Hypomenorrhea, 274t
Hyponatremia, 1642-1645
acute, 2203
causes of, 1642b
in children, 2236
clinical features of, 1643-1644
definition of, 1642
diagnostic strategies for, 1643
euvolemic, 1643
causes of, 1642b
management of, 1644-1645
hospital-acquired, 2203
hypervolemic, 1643
causes of, 1642b
management of, 1644
hypovolemic, 1643
causes of, 1642b
management of, 1644
key concepts, 1651b
management of, 1644-1645
pseudohyponatremia, 1642-1643, 1642b
saline treatment of, 1642
Hyponatremic volume depletion, 2202-2203
Hyponychium, 544
Hypoparathyroidism, 1476
Hypopharynx, 198, 199f
Hypophosphatemia, 1650-1651
alcohol-induced, 2388
clinical features of, 1650-1651, 1651b
definition of, 1650
key concepts, 1651b
management of, 1651
Hypoplastic anemia, secondary, 1594
Hypopyon, 193t-196t, 918f
Hyposplenia, 2365-2366
Hypotension
in beta-adrenergic blocker overdose, 1988
in calcium channel blocker poisoning, 1991-1992
in cerebral ischemia, 82-84
chest pain and, 217t-218t
definition of, 343
after dialysis, 1308-1309
in head injury, 343, 348-349
in heart failure, 1086
in hemodialysis, 1308b
orthostatic, with neuroleptic agents, 1465
permissive, 292
refractory, 1554b
with ruptured AAA, 1130-1131
Hypotensive resuscitation, 506
Hypothalamic-pituitary-adrenal axis, 1467
Hypothalamic-pituitary-thyroid axis, 1676
Hypothenar eminence, 534
Hypothenar hammer syndrome (ulnar artery aneurysm), 1147
Hypothermia
accidental, 1883-1895. *See also* Frostbite
alcohol and, 2389
causes of, 1887
clinical features of, 1887-1888
definition of, 1883
diagnosis of, 94t, 1888-1889
key concepts, 1895b
laboratory testing in, 1888-1889
management of, 1889-1890
mild resuscitative, 84-85, 84t
neonatal, 112
outcome, 1894-1895
pathophysiology of, 1884-1886
patient disposition in, 1894
pharmacology of, 1890-1891
predisposing factors, 1886-1887, 1886b
presenting signs of, 1887b
prevention of, 2452
tactical combat care of, 2452
therapeutic
in cardiac arrest, 85, 85b
in head injury, 349
in neonatal resuscitation, 118
traumatic factors, 1887
treatment of, 94t
in urban search and rescue, 2456
zones of, 1884t
Hypothermic coagulation, 1888-1889
Hypothesis testing, classical, e12-e18, e12t

www.ketabpezeshki.com 66485457-66963820

Hypothyroidism, 1676, 1684-1689
  anxiety in, 1476
  causes of, 1684, 1684b
  central, 1684b
  clinical, 1688t
  clinical features of, 1685-1687
  diagnostic strategies for, 1687-1688
  differential considerations, 1688
  epidemiology of, 1684
  incidence of, 1684
  key concepts, 1692b
  management of, 1688
  obstetric complications of, 1685
  pathophysiology of, 1684-1685
  patient disposition in, 1689
  in pregnancy, 1684-1685, 2301t-2303t, 2312
  primary, 1684b
  skin lesions associated with, 1581t, 1583f
  subclinical, 1688t
  symptoms and signs of, 1685-1687, 1686b
Hypothyroxinemia, 1688t
Hypoventilation, controlled, 954
Hypovolemia
  clinical features of, 139t
  diagnosis and treatment of, 94t
  in rhabdomyolysis, 1672
  vomiting with, 239
Hypovolemic hyponatremia, 1643
  causes of, 1642b
  management of, 1644
Hypoxemia
  chest pain and, 217t-218t
  clinical features of, 139t
Hypoxia
  acute, 1081
  causes of, 343
  cerebral, 82-84
  definition of, 343
  diagnosis and treatment of, 94t
  in head injury, 343
  neonatal, 112
Hypoxic (tet) spells
  management of, 2150-2151, 2150b
  pathophysiology of, 2150, 2150f
Hypsarrhythmia, 2231
Hysterectomy, 2349

I
i-gel mask airway, 19-20, 20f
Iboga, 2022-2023
Ibogaine, 2022
Ibuprofen, 44
  for acute migraine attack, 1388t
  for burn pain, 816
  overdose, 1968
  for pediatric migraine, 2243
  for postextraction pain, 901
  for rheumatoid arthritis, 1514-1515
  risk of GI effects, 44t
  for systemic lupus erythematosus, 1533
Ibutilide, 1039
  for atrial fibrillation and flutter conversion, 1052b
  in pregnancy, 2318t-2321t, 2327
Icatibant, 1557
Ice test, 183
Ichthyosis, acquired, 1583
Ictal events, 1375
Icterus gravidarum, 2296
Ileus, adynamic, 1216, 1217b
Ilex (holly), 2068
Ilex paraguariensis (Paraguay tea), 2070
Iliac artery injury, 508
Iliac vein injury, 508
Iliopectineal bursitis, 1519f
Iliopsoas bursitis, 1525
Iliopsoas strain, 691
Iliotibial band, 715
Iliotibial band syndrome, 715
Illicit drugs
  among adolescents, e2
  complications of, 2395, 2396b
  and rhabdomyolysis, 1669b-1670b
Illness, e27
Illusions, 2015
Iloperidone, 2048t
Imaging. *See specific modalities*
Iminodiacetic acid scintigraphy, 1202
Imipenem
  for bone and joint infection, 1835t
  for bowel flora, 1264b
  for pneumonia, 985t
  for toxic shock syndrome, 1568
Imipenem-cilastatin, 2361t
Imipramine, 1432
Imiquimod
  for genital warts, 1319, 1730
  for papillomavirus infection, 1721t-1722t
Immersion burns, 846f
Immersion syndrome, 1941
Immobilization. *See also* Splinting
  of ankle, 530-531
  in cerebral ischemia, 86
  complications of, 525, 525b
  for hip fracture, 680
  knee immobilizers, 529-530
  of wounds, 765
Immobilization and compression technique (Commonwealth Serum Laboratory technique), 797-798
Immune complex–mediated reactions, 1545b, 1548-1549
Immune globulin
  anti-D (RhoGAM), 2283-2284, 2290, 2293
  hepatitis B (HBIG), 851t, 1190t, 1721t-1722t
  human botulism (BabyBIG), 1445, 1707
  human tetanus (HTIG), 1703-1704
  for measles, 1725
  respiratory syncytial virus, 1721t-1722t
  Rhesus (RhIG), 303
  tetanus (TIG), 765, 1703, 1704t
  for toxic epidermal necrolysis, 1568
  for toxic shock syndrome, 1717
Immune hemolytic anemia, 1600, 1600b
Immune-mediated injury, 1547-1548
Immune serum globulin (ISG)
  for hepatitis prophylaxis postexposure, 1190t
  for measles, 1570
Immune system, 1543
  adaptive, 1546
  in children, 2088
  development of, 1547-1548, 1547f
  innate, 1546
Immune thrombocytopenia, 1610-1611
Immunity
  adaptive (microbe-specific), 2357-2358
  cell-mediated, 2357-2358
  humoral, 2357
  innate, 2356
  non–microbe-specific, 2356-2357
  physical barriers to, 2356
Immunization(s)
  definition of, 1718
  against diphtheria, 1693, 1696
  for elderly, 2355
  against pertussis, 1699
  during pregnancy, 2280
  Rh (anti-D), 2283-2284, 2290, 2293
  against tetanus, 765-766, 766b, 1703
  viral, 1718-1720
Immunocompromised patients, 2356-2367
  antimicrobial agents useful in, 2361t
  key concepts, 2367b
  pathogens in, 2359b
  pneumonia in, 2133-2134
  predisposing factors to infection, 2359b
Immunoglobulin A, 2357
Immunoglobulin E, 2357
Immunoglobulin G, 2357
Immunoglobulin M, 2357
Immunoglobulins, 1547-1548, 1548f, 2357
Immunometric assay, 2273, 2274f
Immunomodulatory therapy, 1444, 2367
Immunosenescence, 2351
Immunosuppressive therapy, 2366-2367
  combination therapy, 2371-2372
  for myasthenia gravis, 1444
  pharmacology of, 2370-2372
  toxicity of, 2370-2372
Immunosuppressive therapy *(Continued)*
  triggers for anaphylaxis, 1546
  unusual organisms in, 2195-2196
Impact seizures, 2234
Impaction, 514-515
Impartiality test, e38-e39
Imperatives, e36
Impetigo, 1564, 1858-1859
  bullous, 1564
  clinical features of, 1564, 1858-1859
  deep, 1859
  in diabetes, 1665
  management of, 1564, 1859
Impetigo contagiosa, 1858
Impingement injection test, 638, 639f
Impingement syndromes, 637-639
  differential diagnosis of, 638
  management of, 639, 1523
  progressive stages of, 638, 638t
  of shoulder, 1520-1521
Implantable cardiac devices. *See* Implantable cardioverter-defibrillators (ICDs)
Implantable cardioverter-defibrillators (ICDs), 1064-1074, 1074b
  complications of implantation, 1072
  components of, 1071-1072
  for heart failure, 1088
  indications for, class I, 1065b
  key concepts, 1074b
  malfunction, 1072
    advanced cardiac life support interventions for, 1072-1073
    causes of, 1072b
    evaluation of, 1073f
    patient disposition in, 1073
  terminology, 1071-1072
Implements in situ, 472-473
Implied consent, e40
  in emergency situations, e71
  principles of, e71
Improvement, process, 2505-2511
In personam rights, e34
In rem rights, e34
Inactivated poliomyelitis vaccine (IPV), 1718-1719, 1720t, 1737
Inapsine (droperidol)
  for chemical restraint, 2417
  for nausea and vomiting, 245
  for rapid tranquilization, 1463
Incapacitated adults, e71-e72
Incident command, 2462
Incident command system, 2462-2463
Incised wounds, 839
Incompetent adults, e71-e72, e76
Incontinence, fecal, 1283-1284
Indapamide, 1122.e1t-1122.e2t
Index finger deformity, 559f
Index finger fracture, 549
India ink staining, 1454, 1454f
Indinavir
  adverse reactions to, 1766t
  herbal medicine interactions, 2072t-2073t
  for HIV infection, 1721t-1722t
Indomethacin
  for gouty arthritis, 1509
  risk of GI effects, 44t
Induration, 1559t
Infalyte, 2200t
Infantile jaundice, 2168-2169, 2169b
Infantile spasms, 2231-2233
Infants, 2088-2089, 2088f. *See also* Children; Neonates
  bacterial illness in, 2100-2102
  bacterial meningitis in, 2225, 2225t
  botulism in, 1704-1706
  cardiac disorders in, 2140b
  cardiopulmonary arrest in, 103f
  cellular oxygenation, 108-109
  chest compressions for, 100, 101f
  chronic lung disease of infancy, 2138
  decreased stroke volume in, 2139-2140, 2140b
  episodic disorders that mimic seizures in, 2233b
  exchange transfusions for, 2170f-2171f
  extracranial hemorrhage in, 312-313, 313f
  facial trauma in, 369

www.ketabpezeshki.com 66485457-66963820

Infants *(Continued)*
febrile, 2099-2100, 2101f-2102f, 2101t
hyperbilirubinemia in, 2168, 2169t
increased ICP in, 312, 312b
maintenance fluids for, 814
neonatal intensive care unit graduates, 2094
peptic ulcer disease in, 1179
perianal strep infection in, 852, 853f
phototherapy for, 2170f-2171f
pneumonia in, 2136-2137
chlamydial, 2132-2133, 2133f
positioning, 2087, 2088f
post-term, 2272
preterm, 2272
septic arthritis in, 1846
septic shock in, 107f
sudden infant death syndrome, 110-111
term, 2272
tetanus in, 1703
top emergency department diagnoses in, 2093t
toxic appearance of, 2226
tracheal suctioning of, 113-114
UTIs in, 1333, 1333t, 2212
vomiting in, 2172t
young, 2088
Infarct pericarditis, 1002
Infection(s). *See also specific infections*
abdominal, 1872t
alcohol effects on, 2387
of aneurysms, 1148-1149, 1148t
of arteriovenous fistulae or graft, 1156
of atherosclerotic arteries, 1148, 1148t
in autoimmune hemolytic anemia, 1600b
bacterial, 1693-1717
bone and joint, 1-1850
in fracture, 519-520
periprosthetic, 1848
catheter-related, 1155
central nervous system, 1447-1459
after head injury, 359-360
cerebrospinal fluid, 1872t
in chronic kidney disease, 1306
corneal ulcers and infiltrate from, 920
dental, 899-900, 899f
in diabetes mellitus, 1664, 1664t
diabetic foot, 1853
from dog bites, 785-786
in elders, 2354
facial nerve paralysis due to, 1411-1412
femoral, in children, 694-695
fungal, 1558-1561
in immunocompromised patients, 2363
key concepts, 1585b
gastrointestinal, parasitic, 1250-1258
genitourinary, in pregnancy, 2297-2299
graft, in AAA repair, 1135
in hand, 567
of hand, 565-568
in heart transplant patients, 2373-2374
of hip, in children, 694-695
in human bites, 792-793
in immunocompromised patients, 2363-2364
patterns of disease and differential diagnosis of, 2364t
predisposing factors, 2359b
intracranial, 1395
in kidney (renal) transplant patients, 2375
limp due to, 694-695
in liver transplant patients, 2374
in lung transplant patients, 2376
most common pathogens, 2359b
mycobacterial, 2363
and myocarditis, 1098, 1098b
necrotizing anorectal, 1282
observational approach to, 2489-2490
opportunistic
mimicking neoplasms, 2364
prophylaxis to prevent, 1758t
pacemaker-related, 1067
parasitic, 1768-1784
and pericarditis, 1094
periprosthetic, 1848
of pilosebaceous follicle, 1859
postinfectious immune thrombocytopenia, 1610
prosthetic joint, 1506
Infection(s) *(Continued)*
pulmonary, 2364, 2364t
recommendations for prevention of in-hospital transmission of, 2471, 2472b
and rhabdomyolysis, 1669b-1670b
risk of transfusion-transmitted viruses, 80
seizures caused by, 1378
skin and soft tissue, 1851-1863
with atopic dermatitis, 1563-1564
slow virus or slow, 1740
in solid organ transplant recipients, 2368-2370
spinal
with low back pain, 647
magnetic resonance imaging of, 649-650, 650f
management of, 653
in supraglottic airway, 2109-2111
systemic
and heart failure, 1081
in pregnancy, 2312-2314
in transplant patients, 2368-2370, 2369b
upper airway, in children, 2106-2116
upper genital tract, in pregnancy, 2298-2299
upper respiratory tract, 965-977
urinary tract, 1326-1332
in children, 2211-2213, 2223b
in pregnancy, 2297
vaccine-preventable, of childhood, 1723-1725
from venomous snakebite, 797
viral
in immunocompromised patients, 2363-2364
after transplantation, 2369
water-borne, 1853
wound, 763
host factors, 763
risk factors, 753, 753b
Infection stones, 1336
Infectious diarrhea
acute
characterization of, 257-258
clinical features of, 2196-2197
complications of, 2196
diagnostic findings in, 2196
diagnostic strategies for, 2197
differential considerations, 2197
management of, 2197-2198
patient disposition in, 2198
causative agents of, 254, 255b
in children, 2188-2204
etiology of, 2190-2196, 2190t
key concepts, 2204b
physiologic factors, 2189-2190
Infectious Diseases Society of America
guidelines for management of pneumonia, 983, 986
position on diagnosis of pharyngitis, 967
Infectious esophagitis, 1173-1174
clinical features of, 1174
management of, 1175
Infectious mononucleosis (Epstein-Barr virus), 965, 967, 1731
Infectious myositis, 1831
Infectious tendinitis, 1831
Infective endocarditis, 1106-1108
in children, 2159-2160
clinical conditions that should be suspect for, 2158b
clinical features of, 2159
diagnostic strategies for, 2159
management of, 2160
prophylaxis of, 2159, 2159b-2160b, 2160t
signs of, 2159
clinical features of, 1107
diagnostic strategies for, 1107
Duke criteria for, 1108b
epidemiology of, 1107t
high-risk conditions, 1108b
incidence of, 1106
initial empirical therapy for, 1108b
with injection drug use, 1106
key concepts, 1112b
management of, 1107-1108
modified Duke criteria for, 2105b
pathophysiology of, 1106-1107
prophylaxis of, 1108
Infective endocarditis *(Continued)*
prosthetic valve, 1107
surgical therapy for, 1108b
Inflammation
arterial, 1139, 1142
duodenal, 224t-225t
esophageal, 224t-225t
gastric, 224t-225t
initial response, 2356
limp due to, 694-695
muscle diseases, 1445
pelvic, 1324-1325
pleural, 992-996
in pregnancy, 2314-2315
Inflammatory bowel disease, 1269-1272
in children, 2181-2182
clinical features of, 2181
diagnostic strategies for, 2181
differential considerations, 2182
management of, 2182
patient disposition in, 2182
clinical features of, 1270
diagnostic strategies for, 1270-1271
differential considerations, 1271
disease severity criteria for, 1271b
key concepts, 1274b-1275b
management of, 1271-1272
medications for, 1271b
patient disposition in, 1272
Inflammatory diarrhea, 254
Inflammatory myopathy, 1445
Inflammatory pseudotumor, in eye, 193t-196t
Inflicted head injury, 355
Infliximab toxicity, 1515t
Influenza, 1734
clinical features of, 1734
diagnostic strategies for, 1734-1735
differential considerations, 1735
H1N1 pandemic, 1735
management of, 1735
vaccine against, 1720t
Influenza A, 1721t-1722t
Influenza B, 1721t-1722t
Influenza virus, 1734-1735
Information gaps, 2507
Information transmission, 32. *See also* Communication(s)
for crisis management, 2426
delivering bad news, e52-e53
for informed consent, e70
requirements for, e70
Informed consent, e40, e70-e71
federal vs state laws, e70
information for, e70
in intimate partner violence, 883
physician role in, e70-e71
as process, e70-e71
to refuse care, e73
to refuse examination, treatment, or transfer, e73, e74f
for restricted SART examination, 856f
when-in-doubt rule for, e70
Informed decision making, e73
Informed refusal, e72-e73
Infrapatellar bursitis, 1519f
Infraspinatus muscle test, 638
Infusates, 1644, 1644t
Inguinal hernia, 1349
in children, 2210
clinical features of, 2210
management of, 2210
patient disposition in, 2210
Inhalants, e2
Inhalation injury
burns
management of, 812
pathophysiology of, 809
recognizing, 811-812
treatment protocol for, 812
hydrofluoric acid exposure, 820
toxins, 2036-2043, 2037t, 2043b
Inhalational anthrax, 2473b
Inhaled beta$_2$-agonists. *See* Short-acting beta$_2$-adrenergic agonists (SABAs)
Inhalers, metered-dose, 2119-2120

www.ketabpezeshki.com 66485457-66963820

Injection drug abuse, 1872t
infective endocarditis in, 1106
parkinsonian syndrome in, 2053
scars from, 1584, 1585f
vascular abnormality caused by, 1152-1153
Injection injuries, high-pressure, 562-563
Injection therapy
for adhesive capsulitis, 642
techniques to reduce pain of, 47, 47b
Injury. *See also* Trauma; *specific sites and types*
blunt force pattern, 837-839
causes of, 330
contrecoup, 363
coup, 363
dashboard injury, 670
definition of, 330
documentation of, 335-336
electrical, 1906
epidemiology of, 335-336
forms of, 330
lap belt, 320
lightning, 1906
multiple complaints following, 1484
pattern, 837, 838b
risk factors for
behavioral and comorbid, 336-337
biomechanical, 336
scald, 839
venomous animal, 794-807
Injury prevention and control, 330-338
epidemiologic triad for, 330, 333f
first step, 330
goals of, 330
Haddon matrix, 330-331, 333t
Haddon's strategies for, 333t
history of, 331
key, 330-331
key concepts, 338b
in medical practice, 335-338, 335b
methods of prevention, 330-335, 333t
multidisciplinary team approach to, 330, 331b
out-of-hospital care, 337
passive countermeasures, 338
in pregnancy, 2279-2280
teachable moments, 336-337
"3 Es" of injury control, 333-335
Injury Research Agenda (CDC), 331
Inner ear barotrauma, 1918, 1923t, 1926
Inotropic therapy
for beta-blocker toxicity, 1989
for heart failure, 1086
for heart failure in children, 2152, 2153t
recommendations for, 1870t
for sepsis, 1872
Inpatients
definition of, e67
EMTALA application to, e67
transfers from other hospitals, e69
Insall-Salvati ratio, 711
Insect bites and stings
allergic reactions to, 803
epidemiology of, 794
triggers for anaphylaxis, 1545
Insect repellents, 1808
Insecticides
carbamate, 2057-2060
chlorinated hydrocarbon, 2060-2061
organochlorine, 2060
organophosphate, 2057-2060
Institute of Medicine (IOM)
To Err Is Human: Building a Safer Health System, 2505
The Future of Emergency Care in United States Health System, 2433
recommendations for cultural competence, e29
Institutional abuse, 891
definition of, 885-886
risk factors for, 887b
Institutional improvement, e30b
Institutional review boards (IRBs), e44
Institutional values, e36
Instituto Bioclon (Mexico), 804
Instituto Butantan (Sao Paulo, Brazil), 804
Instruments. *See also* Equipment
for asking about intimate partner violence, 879
for removal of foreign bodies from ear canal or nares, 770, 770f
for removal of ocular foreign bodies, 768, 769f
for removal of otic or nasal foreign bodies, 770, 770f
testing, in knee injury, 701
ultrasound, 2493
Insufficiency fractures, 682-683
Insufflation technique, 771
Insulin
for acute renal failure in children, 2218
for beta-blocker overdose, 1957t-1958t, 1988-1989
for calcium channel blocker toxicity, 1957t-1958t
for diabetic ketoacidosis, 1659-1660
for hyperglycemic hyperosmolar state, 1662
for hyperkalemia, 1305t, 1638t
normal physiology, 1652-1653
in pregnancy and lactation, 2318t-2321t
Insulin allergy, 1665
Insulin-dependent diabetes mellitus. *See* Diabetes mellitus, type 1
Insurance information, e64
Intellectual disability, 2405
Intelligence gathering, 2455b
Intention-to-treat analysis, e17
Interaction terms, e16
Intercalated segment, 582
Intercalated segment instability, 582, 583f
Intercondylar eminence (tibial spine) fractures, 708-709
anatomy of, 708
classification of, 708, 708f
clinical features of, 708
diagnostic strategies for, 708
management of, 708-709
pathophysiology of, 708
Intercondylar fractures, 607-608, 608f
clinical and radiographic features of, 607
complications of, 608
management of, 608
Interferon alfa, 1721t-1722t, 1723
recombinant, 1723
Interferon alfa-2a (Roferon-A), 1723
Interferon alfa-2b (Intron-A), 1721t-1722t, 1723
Interferon-β, 1416-1417
Intermediate coronary syndrome, 998
Intermittent mechanical ventilation (IMV), 24, 25t
Internal jugular vein, 2501, 2501f-2502f
Internal validity, e20, e20t
International Classification of Headache Disorders, 2nd. ed. (ICHD-II), 1394b
International Headache Society
classification of headache, 1387b
criteria for migraine with aura (classic migraine), 1387b
criteria for migraine without aura (common migraine), 1387b
Interpersonal justifiability test, e38-e39
Interpersonal relationships, e53
Interpersonal theory, 1468
Interphalangeal joint injuries
in foot, 747
in hand, 553-554
in thumb, 555-556
Intersection syndrome, 589
Intersphincteric abscesses, 1281t, 1282
Interstitial cells of Cajal (ICCs), 1216-1217
Interstitial disease, 1297
Interstitial myocarditis, isolated idiopathic, 1098
Intertrigo, 1665
Intertrochanteric fractures, 684, 684f
anatomy of, 684
classification of, 684
key concepts, 697b
management of, 684
outcomes, 684
pathologic, 684-685
pathophysiology of, 684
Interventional studies, longitudinal (clinical trials), e9
Intervertebral disk herniation, 282t-283t
Intervolar plate ligament, 555f
Intestinal amebiasis (*Entamoeba histolytica* infection)
acute, 1253-1254
in AIDS, 1257t
antibiotic therapy for, 1235t
clinical presentation of, 1253-1254
diagnostic strategies for, 1254
epidemiology of, 1250t, 1253
management of, 1254, 1257t
pathophysiology of, 1253
differential considerations, 1254
symptoms of, 1782
Intestinal fluke *(Fasciolopsis buski)*, 1770t-1775t
Intestinal obstruction, 227, 227t-228t
Intimal flap, 501
Intimate contact, febrile illness after, in children, 2226
Intimate partner sexual abuse, 877
Intimate partner violence, 872-884
adolescents in abusive relationships, 874-875
assessment of, 875-877
components of, 880t
initial, 879-880
instruments for, 879
mental health assessment, 876
questions to be asked, 879-880
associated comorbid conditions, 875, 876f
and criminal justice system, 882
cultural issues, 882
definition of, 872
diagnostic coding for, 884
diagnostic strategies for, 877-879
disclosure of
behaviors that foster, 877
identification through, 878-879
documentation of, 883, 883t
epidemiology of, 872-875
ethical considerations, 882-883
etiology of, 875
forensic documentation in, 884
forensic examination in, 884
forms of, 875
history taking in, 875-876, 883t
identification of
algorithm for, 878f
through disclosure and/or pattern recognition, 878-879
injuries in, 876-877
interventions for
clinical, 880-882
in emergency department, 881-882
strategies based on IPV exposure and risk level, 881, 881t
system models, 880-881
interventions for perpetrators, 882
key concepts, 884b
management of, 879-884
milieu considerations, 877
overcoming barriers to care in, 877-878
physical examination in, 876, 883t
prevalence of, 872-873
public health activities, 884
risks for perpetration, 874
risks for victimization, 873-874
risks to children in homes with, 874
screening for, 878-879
social ecology model of, 875
system readiness for, 880-881
terminology, 884
types of, 872, 873f
Intimate terrorism, 875
Intra-abdominal hemorrhage, 669-670
Intracardiac injury, 447
Intracerebellar hematoma, traumatic, 366
Intracerebral hematoma, 365-366, 366f
Intracerebral hemorrhage
clinical features of, 1366, 1368t
hypertensive, 1120t, 1364b
management of, 1373-1374
risk factors for potentially catastrophic illness, 172b
Intracerebral hemorrhage (ICH) score, 1366, 1368b
Intracompartmental pressure, 750
Intracranial hypertension, idiopathic, 1394
clinical features of, 1394
diagnosis of, 1394

www.ketabpezeshki.com 66485457-66963820

Intracranial hypertension, idiopathic *(Continued)*
diagnostic criteria for, 1394b
pathophysiology of, 1394
treatment of, 1394
Intracranial infection, 1395
Intracranial neoplasms, 1391-1392
clinical presentation of, 1392
diagnostic evaluation of, 1392
treatment of, 1392
Intracranial pressure, increased
airway management in, 16-17
in children, 312, 312b, 356
differential diagnosis of, 174t
in head injury, 343
in infants, 312, 312b
and lumbar puncture, 1451-1452
management of, 313, 314t
methods to reduce, 343
pretreatment agents for RSI, 11b
rapid sequence intubation for, 17, 17t
risk factors for potentially catastrophic illness, 172b
treatment of, 910
Intractable patients, 2426, 2428t, 2429
Intradermal (buried) sutures, 757
Intrahepatic cholestasis of pregnancy, 2296
clinical features of, 2296
differential considerations, 2296
management of, 2296
Intralipid (intravenous fat emulsion, IFE), 1956
for anesthetics overdose, 1957t-1958t
for beta-blocker overdose, 1957t-1958t, 1989
for tricyclic antidepressants overdose, 1957t-1958t
Intramural hemorrhage, 1125
Intraocular foreign bodies, 768, 768f, 917
Intraocular pressure
increased, 14
normal, 921
Intraperitoneal air, 472
Intraperitoneal injury, 470
Intrarenal vascular disease, 1297
Intrathoracic impedance monitoring, 1088
Intrauterine device, 869t
Intravaginal epithelial changes, 865-866, 866t
Intravascular hemolytic transfusion reaction, 78-79
Intravascular ultrasound, 454
Intravenous access
for circulation assessment, 292
tactical combat care, 2452
Intravenous catheters
infection of, 1872t
US-guided placement, 2502
Intravenous drug abuse, 1152-1153
Intravenous fat emulsion (IFE) (Intralipid), 1989
Intravenous fluids
for dehydration in children, 2200-2203
in labor and delivery, 2338t
for salicylate intoxication, 1967
Intravenous hemostatic agents, 2453
Intravenous lipid emulsion, 1977
Intravenous pyelography
in renal calculi, 1338-1339, 1340f
in renal trauma, 492
in ureteral trauma, 494, 495f
in urinary obstruction, 1329
Intravenous regional anesthesia (Bier block), 48
Intron-A (interferon alfa-2b), 1723
Intubating laryngeal mask airway, 20, 20f
Intubating scopes, flexible, 19
Intubating stylets
fiberoptic, 19, 19f
video, 19
Intubation
acute deterioration after (DOPE), 116
anticipated clinical course, 3-4
approach to, 8
criteria for, 3
decision to intubate, 3-4
difficult
incidence of, 6-7
measurement of, 6-7
drug-assisted, 2439
endotracheal, pediatric, 306
in facial trauma, 376
hemodynamic consequences of, 16
Intubation *(Continued)*
induction agents, 15-16
methods of, 10-22
nasotracheal
blind, 12
in neck injury, 424
neonatal, 116
oral
awake, 12-13
without pharmacologic agents, 13
paralysis after, 14
pediatric, 17-18
anatomic considerations, 108
endotracheal, 306
equipment considerations, 109
medications for, 109
pharmacologic agents for, 13-16
postintubation management, 12
rapid sequence, 10-12, 11f
considerations, 9-10
orotracheal, 424
pretreatment agents for, 11b
sample, 12t
seven Ps of, 11b
tracheal, 109
Intussusception, 1218-1219, 1269, 2176-2178
clinical features of, 1269, 2176
diagnostic strategies for, 1269, 2176-2177
differential considerations, 2177
key concepts, 1274b-1275b, 2187b
management of, 1269, 2178
patient disposition in, 1269, 2178
pseudo-kidney sign of, 1269
radiographic findings, 2176-2177, 2177f
Invasive arterial monitoring, 61
Invasive gastroenteritis, 1233, 1234t
Invasive pneumococcal disease, 1707
Invega (paliperidone), 1464
Inversion, ankle, 723
Inversion stress test, 731
Involuntary commitment, 1498
Iodides, 2329
Iodine, 1688
Iodine complexes (povidone-iodine solution), 756t
Iodoquinol
for diarrhea, 1235t
for diarrhea in AIDS, 1257t
for intestinal amebiasis, 1254
for parasitic infection, 1772t-1775t
Ion channelopathies, 1104-1105
Ipratropium bromide (Atrovent)
for anaphylaxis, 1554b, 1555
for asthma, 949t, 951, 2121t
for asthma in pregnancy, 2303t
for COPD, 963
Iran-Iraq War, 2451, 2469
Irbesartan, 1122.e1t-1122.e2t
Iridocyclitis, traumatic, 914-915
Iridodialysis, 915
Irinotecan, 2072t-2073t
Iris prolapse, 917, 917f
Iron, 2024-2026
bone marrow stainable, 1591t
common preparations, 2025t
corneal rust ring from, 913, 913f
normal levels, 2024
pharmacology of, 2024
Iron deficiency anemia, 1590, 1590f
diagnostic tests for, 1591t
in pregnancy, 2301t-2303t, 2306-2307
Iron overdose, 2024-2025, 2025t
acute, 2024
antidote for, 1957t-1958t
diagnostic strategies for, 2025
imaging of, 2025, 2025f
management of, 2025-2026
metabolic acidosis due to, 1633
pathophysiology of, 2024
patient disposition in, 2026
Iron replacement therapy, 1590
Iron supplementation, 2306
Irrigation
of eye, 820
heated, 1893
Irrigation *(Continued)*
of red and painful eye, 191
in wound management, 755-756
Irritable bowel syndrome, 1261-1262
clinical features of, 1261
diagnostic strategies for, 1261
differential diagnosis of, 1262, 1262b
key concepts, 1274b-1275b
management of, 1262
medications for, 1262, 1262b
patient disposition in, 1262
Rome III criteria for, 1262b
Irritable somnolence, 958
Irritants, eye, 910-912
Irukandji syndrome, 806
Ischemic necrosis, 675
Ischemic optic neuropathy, 926
nonarteritic, 926
Ischemic stroke
acute
antihypertensive therapy for, 1371, 1371b
fibrinolytic therapy for, 1371-1372, 1372b
with hypertension, 1120t
key concepts, 1374b
patient disposition in, 1374
Ischial bursitis, 1519f
Ischiogluteal bursitis, 1525
Ischiorectal abscesses, 1281t, 1282
Isoflurane, 158t-159t, 1381t, 1382
Isoniazid (INH)
alcohol interactions, 2390t
for drug-resistant pulmonary TB, 1827t
for latent TB, 1828, 1828t
for pulmonary TB, 1825t
for tuberculosis, 1822t-1823t, 1824-1825
Isoniazid (INH) toxicity
antidote for, 1957t-1958t
hepatic injury, 1196, 1197t
metabolic acidosis due to, 1633
treatment of, 2236
Isopropyl alcohol (isopropanol), 2013-2014
metabolism of, 2013, 2013f
pharmacology of, 2013
Isopropyl alcohol poisoning
clinical features of, 2013
diagnostic strategies for, 2014
differential considerations, 2014
key concepts, 2014b
management of, 2014
odor in, 1955t
pathophysiology of, 2013
patient disposition in, 2014
Isoproterenol, 1086
Isosorbide, 930t
Isosorbide dinitrate, 1118t-1119t
Isospora belli infection, 1784
Isoxazole mushrooms, 2023
Isoxsuprine, 2339b
Isradipine, 1991t, 1122.e1t-1122.e2t
Isthmus, 769
Itching, anorectal, 1277
Itraconazole, 1559, 1561-1562
Ivermectin (Stromectol)
for diarrhea, 1235t, 1257t
for parasitic disease, 1770t, 1772t-1775t
Ixodes ticks, 1787f-1788f
Ixovotoxin, 1445

J

J waves, 1884
hypothermic, 1884, 1885f
Jacksonian march, 1376
Japanese encephalitis virus, 1458
Jaundice, 232-237
assessment of, 234f
breast milk, 2168
diagnosis of, 232-234
differential diagnosis of, 232, 233f, 235t
epidemiology of, 232
idiopathic, of pregnancy, 2296
imaging in, 234
infantile, 2168-2169, 2169b
laboratory testing in, 233-234, 233f

www.ketabpezeshki.com 66485457-66963820

Jaundice *(Continued)*
management of, 234-236, 236f
neonatal, 2168-2187
clinical features of, 2168
diagnostic strategies for, 2168-2169
differential considerations, 2169-2170, 2169t
key concepts, 2187b
management of, 2170
patient disposition in, 2170
pathophysiology of, 232
pivotal findings, 232-234, 234f
in pregnancy, 236-237
signs of, 232-233
symptoms of, 232
Jeep-driver's disease, 1283
Jefferson fracture, 396, 397f, 512t-513t
Jehovah's Witnesses, e75-e76, e76
Jellyfish (nematocyst) stings, 806-807, 807b
Jenner, Edward, 1726
Jerk test, 701
Jervell–Lange-Nielsen syndrome, 2166-2167
Jet ventilation, transtracheal, 21-22
Jimsonweed *(Datura stramonium)*, 1970, 2067-2068, 2068f
Jobe's sign, 1520
Jod-Basedow effect, 1676-1677
Johnson Canyon virus, 1725
Joint aspiration, 1844-1846
Joint Commission, 2458, 2462, e41
Comprehensive Accreditation Manual for Hospitals, e26
contact information, 2458t
criteria for detection and management of elder abuse, 890
guidelines for restraints and seclusion, 2416
A Roadmap for Hospitals, e26
Joint Commission on Accreditation of Health Care Organizations. *See* Joint Commission
Joint disease
degenerative (osteoarthritis), 1510-1511
septic arthritis with, 1848
Joint fluid analysis, 1844-1846
Joint infections, 1-1850
antibiotic treatment of, 1835t
etiology of, 1834-1836
key concepts, 1850b
microbiology of, 1834-1836, 1835t
periprosthetic, 1848
tuberculosis, 1819
Joint injection, 703
Joint line opening, 701
Joint pain, 1501, 1502t
Joint wounds, 763-764
Joints, 1832
atypical, 1848
examination of, 1502
radiographic imaging of, 1503b
Jones compression dressing, 529-530
Jones criteria (revised), 1109b
Jones fracture, 512t-513t, 745
Journal of Allergy and Clinical Immunology, 946
Journal of Emergency Medical Services, 2434
Journal of Emergency Medicine, 946
Journal of the American Medical Association (JAMA), e8
Judgment
definition of, 142
substituted, e41
Jumper's knee, 715, 1522
JumpSTART, 2460
Junctional tachycardia, 1052
Juncturae tendinae, 538-539
Junin virus, 1739-1740
Justice, e35
Juvenile absence epilepsy, 2232
Juvenile rheumatoid arthritis, 2265t
JVF, 217t-218t
JWH-018, 2021, 2021f

K
K2 Summit, 2021
Kala-azar *(Leishmania donovani)*, 1776, 1783f
Kanamycin, 1822t-1823t
Kaopectate, 902
Kaposi's sarcoma, 1582f, 1730, 1751, 1759t, 1763, 1764f
Katz diagram, 588
Kawasaki disease (mucocutaneous lymph node syndrome), 2161-2165
in children, 2103
clinical course of, 2164
diagnostic criteria for, 2162b
differential considerations, 2163-2164
incomplete, 2162-2163
key concepts, 2167b
laboratory criteria for, 2162-2163, 2164b
management of, 2164-2165
myocarditis in, 1100-1101
physical examination findings, 2161-2162, 2163f
Kayexalate, 1305t
Keflex, 789t
Kenalog-10 (triamcinolone acetonide), 639t
Keppra (levetiracetam), 2240t, 2407t-2408t
Keratitis, 189-190
bacterial, 190f, 192
herpes simplex, 920, 920f
management algorithm for, 193t-196t
superficial punctate, 920
ultraviolet, 912
Keratoconjunctivitis, 918
caustic, 193t-196t
herpes zoster, 920
management algorithm for, 193t-196t
neonatal, 1721t-1722t
Keraunoparalysis, 1911-1912
Kerion, 1559
Kernig's sign, 1395, 1790-1791
Kernohan's notch syndrome, 344
Ketamine, 15, 2018-2019
for asthma, 953
benefits and adverse effects, 55t
for hypoxic (tet) spells, 2150-2151
pharmacology of, 2019
in pregnancy, 2318t-2321t, 2322
for procedural sedation and analgesia, 54t-55t, 57-58, 59t-60t
for suicidal thoughts, 1499
toxicity, 2019-2020
Ketamine plus propofol (ketofol), 58-59
Ketoacidosis
alcoholic, 1632-1633, 1635b, 2388-2389
causes of, 1632b
diabetic, 243t-244t, 1632
Ketoalkalosis, 1658
Ketoconazole
hepatic injury, 1197t
for mucocutaneous candidiasis, 1664t
for tinea unguium (onychomycosis), 1561
for tinea versicolor, 1561
Ketofol (ketamine plus propofol), 58-59
Ketones
serum, 1658t
urine, 1655
Ketoprofen, 44t
Ketorolac, 44
for acute migraine attack, 1388t
GI effects, 44t
for pediatric migraine, 2243-2244
Khat, 2005
Kidney(s). *See also under* Renal
anatomy of, 490-491, 491f
functional evaluation of, 1291-1292
in heart failure, 1079
in hypothermia, 1885
imaging of, 1292-1293
physiology of, 490-491
Kidney disease
in children, 2205-2223
chronic, 1301-1311
end-stage, 1301
in HIV infection, 1762
in pregnancy, 2309
in systemic lupus erythematosus, 1528t, 1531-1532
in tuberculosis, 1819
Kidney injury
acute, 1291, 1294-1301
in children, 2217-2219
with hypertension, 1120t, 1121-1122
Kidney injury *(Continued)*
myoglobin-induced, 1672, 1673f
rhabdomyolysis and, 1672, 1673f
traumatic. *See* Renal trauma
Kidney stones. *See* Renal calculi
Kidney transplant patients
infection in, 2375
management of, 2374-2375
rejection in, 2375
Kidney-ureter-bladder (KUB) films, 1339
Kienbock's disease, 577, 578f
Killer bees, 802
Kindling, 1378
Kinetic energy, 829-830, 833
King laryngeal tube airway, 21, 21f
Kingella kingae infection
in osteomyelitis, 1835
in septic arthritis, 2264-2265, 2265t
Kissing bugs, 805, 1781
Kissing burns, 1910, 1910f
Kissing technique, 771
Kit kat, 2019
Klebsiella pneumoniae infection
cavitary lesions, 1818
pneumonia, 979-980
Kleihauer-Betke test, 302-303, 2293
Klein's line, 696
Klonopin (clonazepam), 2078t, 2407t-2408t
Knee
anatomy of, 698-699, 699f
bursae, 716
examination of, 700, 700b
extensor mechanism, 710, 710f
joint injection, 703
palpation sites, 700, 700f
stability testing of, 700
Knee arthritis, 716-717
Knee immobilizers, 529-530
Knee injury, 698-717
anatomy of, 698-699
bone bruise, 709
bursitis, 716
clinical features of, 699-702
collateral ligament injuries, 714
cruciate ligament injuries, 713-714
diagnostic strategies for, 702-703
dislocation, 703-705
anatomy of, 703-704
clinical features of, 704
definition of, 525, 703-704
diagnostic strategies for, 704-705
key concepts, 722b
management of, 705, 705f
nerve injury in, 520t
pathophysiology of, 703-704
popliteal artery injury in, 509
extensor mechanism injuries, 710-711
anatomy of, 710
clinical features of, 711
diagnostic strategies for, 711
management of, 711
pathophysiology of, 710
signs and symptoms of, 711
instrument testing, 701
key concepts, 722b
overuse syndromes, 715-716
pathophysiology of, 698-699
physical findings, 700
radiologic evaluation of, 702-703
sites for palpation of tenderness, 700, 700f
soft tissue injuries, 713-715
tendinopathy, 1522
tests for, 700-702
Knee joint effusion, 2500, 2500f
Knife wounds, self-inflicted, 839, 840b, 840f
"Knock-off" drugs, 2396
Kocher criteria, 1846, 1846t
Kocher maneuver, 633
Koenig and Schultz's Disaster Medicine: Comprehensive Principles and Practices, 2458t
Korean War, 1883
Kratom, 2022
Kruskal-Wallis test, e13-e14, e13t, e14
Kuru, 1740

www.ketabpezeshki.com 66485457-66963820

Kussmaul's sign, 1626b
Kwell (lindane), 1573-1574

L

La Crosse (California) encephalitis, 1725, 1737
Labetalol
  for aortic dissection, 1128
  characteristics of, 1987t
  hemodynamic effects, 1118t
  for hypertension, 1122.e1t-1122.e2t
  for hypertensive emergencies, 2221t, 2304t
  for ischemic stroke, 1371b
Labor. *See also* Delivery
  abnormal progression of, 2342
  drug interactions, 2340t
  false, 2332
  first stage, 2332-2334
  fourth stage, 2338
  key concepts, 2350b
  maternal complications of, 2347-2350
  normal adjuncts, 2338t
  postmature, 2272
  premature, 2272, 2339-2340
  preterm, 2339b
  second stage, 2334-2337
  stages of, 2332-2338, 2332f
  third stage, 2337-2338
  true, 2332
Laboratory testing, 2509-2510
  changes in pregnancy, 297
  ED functions, e62
  synovial fluid studies, 1504
Labyrinthitis
  acute suppurative
    diagnosis of, 166t-167t, 167f
    management of, 168, 168f
  chronic, 167f
  diagnosis of, 165, 167f
  differential diagnosis of, 166t-167t
  serous, 166t-167t, 167f
  toxic, 166t-167t, 167f-168f
Lacerations, 839, 839f
  canalicular, 917, 917f
  conjunctival, 917
  corneal, 917, 917f
  definition of, 839
  dicing, 841, 842f
  ear, 378
  eyebrow, 378
  eyelids, 378, 916-917
  intraoral, 764, 906
  lip, 377, 906
  with mallet finger, 558, 559f
  of mouth, 377, 906
  nail bed, 562
  nasal, 378
  pulmonary, 437
  renal, 465, 465f, 467, 467f, 494f
  scalp, 757-758, 758f
  scleral, 917
  splenic, 465-467, 465f-467f
  of tongue, 377, 906
Lachman's test, 701
β-Lactamase Inhibitors, 984-985, 985t, 2361t
Lactate clearance index, 71
Lactate dehydrogenase, 1593t
Lactated Ringer's solution, 1644t, 1674
Lactation, 2316-2317, 2318t-2321t
Lactic acid, 1454
Lactic acidosis, 1632b
Lactobacillus acidophilus, 1195
Lactobacillus GG (LGG), 2198
Lactobezoars, 779
Lactoferrin assays, 258
Lactulose
  for constipation, 264t-265t
  for hepatic encephalopathy, 1194-1195
Lacunae, 1363
Lacunar stroke syndromes, 181, 181b
Laennec's cirrhosis, 1193
Lambert-Eaton myasthenic syndrome, 1443
Lamictal (lamotrigine), 2407t-2408t
Lamivudine, 1721t-1722t, 1766t
Lamotrigine (Lamictal)
  for children, 2240t
  drug interactions, 2407t-2408t
  for long-term anticonvulsant therapy, 1384t
  side effects, 1383t, 2407t-2408t
Landing zones, 2445, 2445b, 2445f
  requirements for, 2446b
Landry-Guillain-Barré syndrome, 1423
Langer's lines, 370, 370f
Language, e25
Language barriers, e26
Language interpreters, 882, e25
Lanoxin (digoxin), 1982
Lansoprazole, 1177t, 1184
Lansoprazole, amoxicillin, and clarithromycin (Prevpac), 1180
Lap belt injury, 320
Lap belt sign, 310
Laparoscopy
  in abdominal gunshot wounds, 474
  in abdominal trauma, 470
  in appendicitis, 1230
  in demonstrating organ injury that requires laparotomy, 475
  in ovarian torsion, 1357
  in peritoneal assessment, 472
Laparotomy
  in abdominal gunshot wounds, 474
  in abdominal stab wounds, 471-472, 471t
  in blunt abdominal trauma, 475-476
  in blunt trauma, 476t
  indications for, 321, 321b
  injury that requires, 472-475
  vs intraperitoneal injury, 470
Large bowel obstruction, 1265-1266
  clinical features of, 1265
  diagnostic strategies for, 1265-1266
  differential considerations, 1266
  foreign bodies, 778-781
  key concepts, 1274b-1275b
  management of, 1266
  patient disposition in, 1266
  pseudo-obstruction, 1265
  radiographic findings, 1265, 1266f
  vomiting with, 243t-244t
Large bowel volvulus, 1267-1269
  differential considerations, 1268
  key concepts, 1274b-1275b
  patient disposition in, 1269
Large intestine. *See also under* Colon
  disorders of, 1261-1275, 1274b-1275b
  dysfunction of, 280
Larrey's flying ambulance, 2433, 2434f
Larva migrans
  cutaneous (creeping eruption), 1772t-1775t, 1780, 1863
  visceral (toxocariasis), 1772t-1775t
Laryngeal dystonia, antipsychotic-induced, 2048
Laryngeal edema, 1552t
Laryngeal mask airways, 19-21, 19f
  for children, 109
Laryngeal papillomas, 2112
Laryngeal web, 2112, 2112f
Laryngitis, 969
Laryngomalacia, 2111-2112, 2111f
Laryngoscopy
  in children, 108
  difficult direct, 4-5
    LEMON approach for, 4b
  direct, 18
Laryngotracheal ("subglottic") stenosis, congenital, 2112
Laryngotracheal trauma, 426-427
  clinical features of, 426
  diagnostic strategies for, 426
  management of, 426-427
  mechanisms of, 426
Laryngotracheobronchitis (croup), viral, 2112-2113
Larynx
  congenital lesions of, 2111-2112
  pediatric diseases of, 2111-2112
  superior or anterior, 108
Lassa fever, 1739-1740
  drugs for treatment of, 1721t-1722t
  management of, 1740
Lateral canthotomy, 910, 911f
Lateral collateral ligament, 698, 723, 724f
Lateral collateral ligament injury, 714
  testing for, 700-701
Lateral condyle fractures, 608
  clinical and radiographic features of, 608
  complications of, 608
  management of, 608
Lateral epicondylitis (tennis elbow), 1521, 1523
Lateral malleolar fractures, 728
Lateral pharyngeal or parapharyngeal space, 896
Lateral pharyngeal or pharyngomaxillary space, 974
Latex, 1545
Latex agglutination, 1454
Latrodectus antivenin, 804, 1957t-1958t
Latrodectus mactans (black widow spider), 803-804
Lauge-Hansen classification, 727
Law
  and bioethics, e33-e34, e34t
  black-letter law, e33
  emergency medical services, 2433
  federal vs state laws, e70
Law enforcement
  blood alcohol tests, e62-e63
  court decisions, e41
  HIPAA exemptions, 842, 844b
  for intimate partner violence, 882
  police blood alcohol tests, e62-e63
  "suicide by cop," 1494
Laws of physics, 1915-1916, 1916t
Laxatives, 264b, 264t-265t
Le Fort fractures, 372, 379-380, 512t-513t
Le Fort-Wagstaffe fracture, 512t-513t
Lead, 2026
Lead encephalopathy, acute, 2027
Lead fracture, 1069
Lead poisoning, 2026-2028
  antidote for, 1957t-1958t
  clinical features of, 2027
  diagnostic strategies for, 2027, 2027t
  management of, 2027-2028
  pathophysiology of, 2026-2027
  patient disposition in, 2028
  toxic levels, 2026
Lead snowstorm, 836f
Leadership, 337-338
Leaning, 102
Learned helplessness, 1468
Leaving against medical advice (AMA), e73-e75
  form for, e73, e74f
  protocol for management of, e75b
  steps to take, e73-e75
Leaving before examination, e73
Leaving without being seen (LWBS), e73
Leflunomide, 1515t
Left anterior-superior bundle, 1035
Left apical ballooning, 1011
Left bundle branch block
  acute MI in, 1009-1011, 1012f
  ECG characteristics of, 1009-1011, 1011f
Left coronary artery, anomalous, 139t
Left coronary artery occlusion, 1008
Left posterior-inferior bundle, 1035
Left-sided heart failure, 1080
Left ventricular aneurysm, 1009, 1010f
Left ventricular assist devices, 1073-1074
Left ventricular free wall rupture, 1002
Left ventricular hypertrophy
  ECG changes in, 1011, 1014f
  with repolarization abnormality, 1011, 1014f
Left ventriculoplasty, 1089
Leg anatomy, 717
Leg injury
  knee injury, 698-717
  leg injury, 717-722
  management of, 717-722
  mechanisms of, 717-722
  pathophysiology of, 717
Leg raise, straight, 281
Leg swelling, 1532t
Leg thrombophlebitis, superficial, 1159
Legal courts, e41

www.ketabpezeshki.com 66485457-66963820

Legal guardians, e41
minors accompanied by, e71
refusal of care or blood transfusions for minor by, e75
Legal issues
bioethics and, e33-e34, e34t
black-letter law, e33
in blood transfusion, 76-77
in emergency delivery, 2331
EMS legislation, 2433
federal vs state laws, e70
medicolegal issues, e60-e78
Legg-Calvé-Perthes' disease, 696, 2266-2267
crescent sign of, 2267, 2267f
differential diagnosis of, 1848
Legionella infection
in immunocompromised patients, 2363
in pneumonia, 978-979
Legionella pneumophila myocarditis, 1100
Leidelmeyer's external rotation reduction method, 633, 633f
Leishmaniasis (*Leishmania braziliensis, L. mexicana, L. tropica, L. donovani* [kala-azar]), 1770t-1771t, 1776, 1779
cutaneous, 1779, 1779f, 1863
drug regimens for, 1772t-1775t
Lemierre's syndrome, 975
LEMON approach, 4b
Length-based resuscitation tape, 2092
Lennox-Gastaut syndrome, 2232
Lens dislocation, 914f, 915
Lens subluxation, 915
Lentiviruses, 1740
Leopold's maneuvers, 2333, 2333f
Leptomeningeal cysts, post-traumatic, 358
Leptomeningitis, 1447
Lesbians, 873
Lesser trochanter fractures, 685, 696-697, 696f
Leucovorin, 1957t-1958t, 2012
Leukemia
acute lymphocytic, 1604
chronic lymphocytic, 1604
chronic myeloid, 1603-1604, 1604f
skin lesions associated with, 1583
Leukemoid reaction, 1604
Leukocyte count
in alcoholism, 2389
in appendicitis, 1227
in central nervous system infection, 1455
normal values, 1603t
Leukocytes, fecal, 2204b
Leukocytosis, 1603-1604
causes of, 1603b
lymphocytic, 1603b, 1604
Leukoencephalopathy, spongiform, 2053
Leukopenia, 1604-1605, 1605t
Leukotriene modifiers, 951-952
Levalbuterol
for anaphylaxis, 1554b
for asthma, 949t, 2121t
for asthma in children, 2120-2121
for asthma in pregnancy, 2303t
Levamisole
cocaine adulterated with, 1540-1541, 2001
complications of, 1540-1541, 1540f, 2004
Levaquin, 1257t
Levator ani syndrome, 1283
Levetiracetam (Keppra)
for children, 2237f, 2238, 2240t
drug interactions, 2407t-2408t
for long-term anticonvulsant therapy, 1384t
side effects of, 1383t, 2407t-2408t
for status epilepticus, 2237f, 2238
Levitan scope, 19
Levofloxacin
for diarrhea, 259-260
for pneumonia, 984-986, 984t-985t
for prostatitis, 1335
for sexually transmitted diseases, 1315t
for tuberculosis, 1822t-1823t, 1824
Levonorgestrel, 869t
Levorphanol, 2053t
Levothyroxine (T_4)
for hypothyroidism, 1688
in pregnancy, 2329
Lewisite (dichloro-2-chlorovinylarsine), 825
Libman-Sacks lesion, 1530f
Librium (chlordiazepoxide), 2078t
Lice
body, 1573, 1574f
head, 1573-1574, 1573f
pubic, 1323
Lichen sclerosus et atrophicus, 852, 853f
Lichen tropicus, 1900
Lichenification, 1559t
Lidocaine (Xylocaine), 46t
for anal fissures, 1281
for arterial gas embolism, 1925
for burn pain, 816
for Colles' fracture reduction, 583-584
for dental abscess, 899
for digitalis toxicity, 1986
for dysrhythmias, 1037
for dysrhythmias in children, 2154b
guidelines for maximum doses, 47t
impingement injection test, 638, 639f
for oral hemorrhage, 907
in pregnancy, 2318t-2321t, 2326
in resuscitation in children, 104t
in resuscitation in head injury, 348
topical, 47
for ventricular tachycardia, 1057-1061
for wound management, 754-755
Lidocaine, epinephrine, and tetracaine (LET), 48
Life expectancy, e24
Lifestyle balance, e81b
Ligamentous injuries
in ankle, 731-733
classification of, 731
in hand, 553-554, 553f
Ligaments
of acromioclavicular joint, 619f
collateral, 553, 553f
of hip, 672, 673f
of spinal column, 382, 384f
of sternoclavicular joint, 619f
of wrist, 572f
extrinsic, 570, 572f
intrinsic, 570, 572f
Ligature strangulation, 429
Lightning, 1908-1909
Lightning injury, 1906
ancillary tests, 1913-1914
assessment of, 1913
burn wound care for, 1914
cardiovascular, 1910
clinical features of, 1910-1912
complications of, 1912
differential considerations, 1912
ED management of, 1913-1914
to extremities, 1911
frequency of, 1907f
head and neck, 1910
key concepts, 1914b
management of, 1912-1914
mechanisms of, 1909-1910, 1909t
to nervous system, 1911-1912
patient disposition in, 1914
skeletal, 1911
skin injury, 1911
triage considerations, 1913
to viscera, 1912
Lightning strike headache, 171t
Light's criteria, 995b
for differentiating transudates from exudates, 994
Likelihood ratio, e20t
Limit setting, 2424
Limp, 694-697
Lindane (Kwell), 2060
for pediculosis, 1573-1574
for pruritus ani, 1285
Line of Swischuk, 316, 317f
Linear regression models, e15
Linezolid
for pneumonia, 985t
in pregnancy, 2318t-2321t, 2324-2325
for skin and soft tissue infection, 1854, 1854t
Lingual tonsillitis, 968-969, 969f
Lip burns, 1996, 1996f
Lip lacerations, 377, 906
Lipase
in pancreatitis, 1209
serum, 242
Lipids, 2387
Lipohemarthrosis, 702, 702f, 722b
Liquid drain cleaners, 1994, 1995t
Lisfranc's (tarsometatarsal) injury
definition of, 741
fractures and dislocations, 512t-513t, 741-744
classification of, 742, 742f
clinical features of, 742
diagnostic strategies for, 742-744
divergent, 742, 742f
homolateral, 742, 742f
isolated, 742, 742f
management of, 744
pathophysiology of, 741-742
patient disposition in, 744
radiographic findings, 742-744, 743f
key concepts, 750b
Lisfranc's joint, 734, 735f, 741
Lisinopril, 1122.e1t-1122.e2t
Listeria, 2363
Listeria monocytogenes, 1453t
Lister's tubercle, 538
Literature
medical, e8
shortcut reviews, e21
Lithium, 2044-2046
drug interactions, 44
herbal medicine interactions, 2072t-2073t
techniques to increase elimination of, 2045-2046
for thyroid storm, 1682b, 1683
Lithium poisoning
clinical features of, 2044-2045
diagnostic strategies for, 2045
differential diagnosis of, 2045
key concepts, 2046b
management of, 2045-2046
patient disposition in, 2046
prevalence of, 2044
Lithobezoars, 779
Little finger fracture, 549
Little League Baseball
pitch count regulations, 611t
rest requirements for pitchers, 611t
Little League elbow, 611, 611f, 2270
Litvinenko, Alexander, 2469
Livedo reticularis, 1140
Liver. *See also under* Hepatic
in acetaminophen toxicity, 1960, 1961f, 1961t, 1963, 1963f
in rhabdomyolysis, 1672
traumatic injury to, 321-322
Liver abscesses, 1196-1198
amebic, 1198
pyogenic, 1196-1198
Liver disorders, 1186-1200
alcohol-related disease, 1192-1193, 2385
clinical features of, 1192
diagnostic strategies for, 1192
differential considerations, 1192
key concepts, 1193b
management of, 1192-1193
patient disposition in, 1193
drug-induced disease, 1196, 1197t
in pregnancy, 1199, 2295-2296
Liver enzymes, 1210, 1210t
Liver function tests
in abdominal trauma, 464
in nausea and vomiting, 242
Liver transplant patients
anatomic considerations, 2374
infection in, 2374
management of, 2374
Liver transplantation, 1200
anatomy of, 2374, 2375f
rejection of, 2374
Lizards, venomous, 796
Loa loa, 1770t-1775t, 1780
Load-altering agents, 2153t
Local anesthesia, 45-48
definition of, 32b
duration of, 46

www.ketabpezeshki.com 66485457-66963820

Local anesthetics
allergy to, 46, 754-755
characteristics of common agents, 46t
classes of agents, 45
guidelines for maximum doses, 47t
local toxicity to, 46
mechanism of action, 45
onset of action, 46
potency, 45
systemic toxicity to, 46-47
techniques to reduce pain of injection, 47, 47b
Local oversight, 2438
Local response, 2465
Lockjaw, 1701
Loculated effusion, 992-993
Löffler's syndrome, 1781
Logistic regression models, e15
Logistics section, 2463
Logs, central, e64
Loiasis, 1780
clinical features of, 1780
diagnostic strategies for, 1780
management of, 1780
Lone Star tick *(Amblyomma americanum)*, 1788f, 1798
Long-acting beta$_2$-agonists (LABAs), 950
Long bone, 1832, 1832f
Long-Term Care Ombudsman Program, 891
Longitudinal interventional studies (clinical trials), e9
checklist for assessment of, e19t
randomized, e9-e12
Longitudinal observational studies, e9
"Look-alike" drugs, 2396
Loop diuretics
for heart failure, 1085, 1087-1088, 2489
for hypertension, 1122.e1t-1122.e2t
Loperamide, 1259, 1260b
Lophophora diffusa, 2017
Lophophora williamsii (peyote cactus), 2017, 2017f
Lopinavir/ritonavir, 1766t
Loratadine
for rhinosinusitis, 976
for urticaria, 1569
Lorazepam (Ativan), 2078t
for agitation, 2016
for alcohol-related seizures, 2383
for alcohol withdrawal, 2382
for burn pain, 816
drug interactions, 2407t-2408t
for MDMA effects, 2018
for neuroleptic malignant syndrome, 2051
for pediatric dosage, 2236-2238
in pregnancy and lactation, 2318t-2321t
for rapid tranquilization, 1463, 1472, 2417
for seizures, 158t-159t
for seizures in neonates, 2236
for seizures prophylaxis, 350
side effects, 2407t-2408t
for status epilepticus, 158t-159t, 1381, 1381t
for status epilepticus in children, 2236-2238, 2237f
for TBI, 347
for thyroid storm, 1682b
Los Angeles civil disturbance, 2459t
Losartan, 1122.e1t-1122.e2t
Loss of consciousness, 159
Lotions, 1558
Lotrimin (clotrimazole), 1560
Lovastatin, 1197t, 2072t-2073t
Lover's heel, 1515-1516
Low back inspection, 281
Low back pain, 643-654. *See also* Back pain
acute, 643
definition of, 278
differential considerations, 279b
management of, 280f
rapid assessment and stabilization of, 284f
of articular facet root origin, 644
from bone, 644
in cauda equina syndrome, 647
chronic, 278
clinical features of, 645-648
diagnostic strategies for, 648-650
differential diagnosis of, 650, 651b
discharge instructions for, 654
Low back pain *(Continued)*
epidemiology of, 643
historical clues to, 645t
idiopathic, 643
laboratory testing in, 648
location of, 279
management of, 651, 652f
of nerve root origin, 644
with neurologic deficits, 282t-283t
neurologic examination in, 281
onset of, 279-280
past medical history, 281
pathophysiology of, 643-644
patient disposition in, 654
pertinent history, 280
radiography in, 648-649, 649b, 649f
radiology in, 648-650
red flag diagnoses, 647
referred, 647-648
signs and symptoms of, 645-648
Low-voltage injuries, 1912
Lower abdominal pain, 223
Lower airway, pediatric
anatomy of, 2117
obstruction of, 2091-2092, 2092f, 2117-2128, 2128b
physiology of, 2117
Lower esophageal obstruction, 1171-1172
Lower extremity
anatomy of, 717
arterial aneurysms in, 1147
arteries of, 503f, 509
bandaging, 529-531
examination of, in arthritis, 1503
foreign bodies in, 722
mononeuropathies in, 1434b
splinting, 529-531
Lower extremity injury, 717-722
arterial, 509
fractures, in older adults, 328
key concepts, 722b
peripheral vascular, 508-509
soft tissue injuries, 721-722
stress fractures, 721
anatomy of, 721
clinical features of, 721
diagnostic strategies for, 721
management of, 721
pathophysiology of, 721
Lower gastrointestinal bleeding, 248
causes of, 249t
diagnosis of, 250-251
differential considerations, 248
management of, 252
Lower genitourinary tract, 479
Lower motor neuron disease, 1442t
Lower urinary tract trauma, 481-490
Lown-Ganong-Levine syndrome, 1055
Loxapine (Loxitane), 2048t, 2417
Loxosceles antivenin, 804
Loxosceles reclusa (brown recluse spider), 804
Lubiprostone (Amitiza), 264t-265t
Lubricants, 264b
Ludwig's angina, 897, 899-900, 972-973, 1863
clinical features of, 973
diagnostic strategies for, 973
differential considerations, 973
management of, 973
patient disposition in, 973
pediatric, 2110
Lugol's solution, 1682b
Lumbago, 643
Lumbar disk herniation, 651-652
Lumbar puncture, 1451-1452
in children, 2226-2227
contraindications to, 2227
indications for, 2226, 2226b
positioning for, 2227
precautions for, 2227
in children with fever, 2099
in children with headache, 2243
general considerations, 1451
in headache, 173t
for tetanus, 1702
US-guided, 2503
Lumbar vertebrae, 643, 644f
Lumbosacral plexopathies, 1433b
Lumbosacral spine, 643-644
Lumbosacral strain, acute, 643
Lunate fractures, 577, 581, 582f, 594b-595b
Lund-Browder chart, 810, 810f
Lung(s). *See also under* Pulmonary
in AIDS, 1758-1760, 1759t
pediatric, 108
in pregnancy, 296-297
Lung disease
in children, 2129-2138, 2138b
chronic, of infancy, 2138
chronic obstructive pulmonary disease, 956-964
at end of life, e58
in disabled patients, 2401-2404
and heart failure, 1078
in immunocompromised patients, 2364, 2364t
Lung fluke *(Paragonimus westermani)*, 1770t-1775t, 1781
Lung injury, 435-442
in drowning, 1942
transfusion-related, 79
ventilatory support for, 29-30
Lung scans
perfusion, 2276t
ventilation, 2276t
Lung transplant patients
infection in, 2376
management of, 2375-2376
Lung transplant rejection, 2376
Lunula, 544
Lupus, drug-induced, 1533
Lupus cerebritis, 1528
Lupus enteritis, 1531, 1531f
Luxatio erecta (inferior glenohumeral dislocation), 636-637, 636f
traction-countertraction reduction of, 637, 637f
Lye, 1994
Lyell's disease, 1567
Lyme arthritis, 1786, 1791, 1847-1848
definition of, 1847
management of, 1794
synovial fluid findings, 2265t
Lyme disease, 1511, 1786-1795, 1786t
acute disseminated infection, 1790-1791
asymptomatic tick bites, 1795
cardiac manifestations, 1791, 1793-1794
chronic (or late), 1791
clinical features of, 1100, 1511, 1787-1792, 1789f-1790f
diagnostic strategies for, 1511, 1792
differential considerations, 1792-1793
early, 1788-1790, 1793
early clinical features of, 1790t
early disseminated infection, 1793-1794
endemic areas, 1786, 1789f
epidemiology of, 1100
facial nerve paralysis in, 1412
key concepts, 1808b
late, 1791-1792
management of, 1511, 1793-1795
mononeuropathy multiplex in, 1438
myocarditis in, 1100
natural history of, 1789f
neurologic manifestations of, 1790-1791, 1793-1794
ophthalmic manifestations of, 1791
and pregnancy, 1794-1795
prophylaxis of, 1795
signs and symptoms of, 1788-1789
treatment of, 1794t
vaccination against, 1795
LYMErix vaccine (SmithKline Pharmaceuticals), 1795
Lymph node hyperplasia, angiofollicular, 1730
Lymph nodes, 939-940, 940f
Lymphadenitis, tuberculous, 1818-1819
Lymphadenopathy, mediastinal, 1818
Lymphatics, 542
Lymphocyte count, 1950t. *See also* T lymphocytes
Lymphocytic choriomeningitis, 1739-1740

www.ketabpezeshki.com 66485457-66963820

Lymphocytic choriomeningitis virus infection
clinical features of, 1740
differential considerations, 1740
management of, 1740
Lymphocytic leukemia
acute, 1604
chronic, 1604
Lymphocytosis (lymphocytic leukocytosis), 1603b, 1604
Lymphogranuloma venereum, 1286t, 1317
diagnosis of, 1317
treatment of, 1285, 1315t, 1317
Lymphoma
AIDS-related, 1763
Hodgkin's, 1583
Lyrica (pregabalin), 2407t-2408t
Lysergic acid diethylamide (LSD), 1477, 2015
adverse reactions to, 2016
blotters, 2015, 2016f
pharmacology of, 2015
Lyssavirus, 1744-1745
Lytren, 2200t

M
Maalox, 902
Mach effect, 519
Machupo virus, 1739-1740
Mackler's triad, 1172-1173
Macrocytic anemia, 1590b, 1591-1593
Macrocytosis, 2389
Macroglossia, 2109
Macrolides, 930t
for otitis media, 933-934
for pneumonia, 985, 985t
in pregnancy, 2318t-2321t, 2325
Macular degeneration, acute, 925
Macular disorders, 925-926
Macular purpura, 1559t
Macules
definition of, 1559t
red, 1566-1570
Mad cow disease, 1406, 1740
MADFOCS mnemonic, 1461, 1462t
Madonna sign, 580
Magnesium, 1040, 2381
for alcoholic hepatitis, 1192
for atrial tachycardia, 1050
for diabetic ketoacidosis, 1660
for dysrhythmias, 1040
for dysrhythmias in children, 2154b
ethanol effects on, 2388t
Magnesium-ammonium-phosphate (struvite) stones, 1336
Magnesium citrate, 264t-265t
Magnesium deficiency
alcohol-induced, 2388
in diabetic ketoacidosis, 1657
Magnesium gluconate, 1649
Magnesium hydroxide (milk of magnesia), 264t-265t
Magnesium replacement, 1649
Magnesium sulfate
for asthma, 951, 2121t
for asthma in children, 2124
for asthma in pregnancy, 2303t
for constipation, 264t-265t
for diabetic ketoacidosis, 1660
for digoxin poisoning, 1985
for hypomagnesemia, 1649
for hypomagnesemia in neonates, 2236
for premature labor, 2339, 2339b
for seizures and status epilepticus, 158t-159t
Magnetic resonance angiography
in ankle injuries, 727
in vascular neck injury, 428
Magnetic resonance cholangiopancreatography, 1211
Magnetic resonance imaging
in abdominal trauma, 467
in ankle injuries, 726-727
in aortic dissection, 1126t, 1127
in appendicitis, 1230
in arthritis, 1503
in back pain, 281-282
in carotid artery dissection, 1393, 1393f
Magnetic resonance imaging *(Continued)*
of cervical spine, 415, 415f
in deep vein thrombosis, 1158
in foot injury, 736
in fracture, 519
in head injury, 353
in hip fracture, 679, 680f
in knee injury, 703
in low back pain, 649-650, 650f
in osteomyelitis, 1838, 1839f-1840f
in ovarian torsion, 1357, 1358b
in peripheral arteriovascular disease, 1142-1143
in peripheral vascular injury, 505
in pregnancy, 300, 2275
for removal of soft tissue foreign bodies, 784
in spinal injury, 409-415, 415f-417f
Magnetic resonance venography, 1414-1415
Magnum load, 829
Main en griffe (clawhand), 543, 543f
Main en singe (monkey hand), 543, 543f
Maintenance fluid and electrolytes, 2201-2203, 2201t
Maisonneuve fracture, 512t-513t, 720, 720f, 729f
Major depressive disorder
in adolescents, 1469
anxiety in, 1477
in children, 1469
clinical features of, 1468-1470
definition of, 1468
genetics of, 1467
in older adults, 1470
prevalence of, 1466
Major depressive episode, 1468, 1468b
Malabsorption, alcohol-related, 2386
Malar rash, 1528t, 1531, 1531f, 1583f
Malaria *(Plasmodium falciparum, P. ovale, P. vivax,* and *P. malariae)*, 1769-1776
anemia in, 1778
cerebral, 1776-1777
chronic, 1776
diagnostic strategies for, 1776
drug regimens for, 1772t-1775t
features of, 1769-1776
key concepts, 1784b
management of, 1776
Male genital disease, 1819
Male genitalia, 480, 480f
Male reproductive system, 1342, 1343f
Male sexual assault victims, 870
Male suspects, 870-871
Malgaigne's fracture, 512t-513t
Malignancy
acute back pain of, 282t-283t
biliary tract, 1204
chronic pain of, 38
hypercalcemia in, 1624b
low back pain of, 647, 653
seizures associated with, 1378-1379
skin lesions associated with internal malignant disease, 1580-1584
viruses associated with, 1740
Malignant acanthosis nigricans, 1580
Malignant (necrotizing) external otitis, 935-936
Malignant hypertension, 1113-1114
Malignant hyperthermia, succinylcholine-associated, 14
Malignant otitis externa, 1664t
Malignant spinal cord compression, 1627-1628
clinical features of, 1627
diagnostic strategies for, 1627-1628
key concepts, 1628b
management of, 1628
Malingering, 1487-1491, 2429
characteristics of, 1489b
clinical features of, 1489
definition of, 1487
diagnostic strategies for, 1489-1490
differential considerations, 1484
management of, 1490
Mallampati scale, 4, 5f
Mallet finger, 557-558, 557f-558f
classification of, 557b
lacerations with, 558, 559f
treatment of, 558, 558f-559f
Mallory-Weiss tears, 239-240
Malnutrition, 1648
Malpresentation, 2342, 2342t
Malrotation with midgut volvulus, 2173-2174
clinical features of, 2173
differential considerations, 2174
key concepts, 2187b
management of, 2174
patient disposition in, 2174
radiographic findings, 2173-2174, 2173f-2174f
Maltreatment
adult, 884
child, 845-854
elder, 885-892
Malunion, 517
Mammalian bites, 785-793, 793b
Managed care authorization, e64
Manchester Triage System, 2090
Mandible, 895
Mandibular fractures, 373, 374f, 380
Mandrake *(Mandragora officinarum)*, 1970
Mangled extremity score, 750
Mania
medications that can cause, 1471b
mnemonic for symptoms of, 1469b
Manic episodes, 1470-1471, 1470b
Mann-Whitney test (Wilcoxon rank sum test), e14
Mannitol
for elevated ICP, 314t, 349
for elevated ICP in children, 356
for glaucoma, 922, 930t
for hyperuricemia, 1624
for renal failure in children, 2218
for rhabdomyolysis, 1674
Mantoux test, 1816-1817
Manual strangulation, 429
Marcaine (bupivacaine), 754
March fracture, 512t-513t, 515
Marfan syndrome, 1124, 2166
Marijuana, 2020-2022
Marijuana use
acute signs and symptoms of, 2021
among adolescents, e2
anxiety in, 1477
clinical features of, 2021
diagnostic strategies for, 2021-2022
differential considerations, 2022
epidemiology of, 2020
management of, 2022
pathophysiology of, 2020-2021
patient disposition in, 2022
Marine animal bites, 806
Marine animal envenomation
epidemiology of, 805-806
management of, 807
Marine animal stings, 806-807
Marine animals, venomous, 805-807
Mark I kits, 2477, 2477b
Maraviroc, 1766t
Masked depression, 1469
Mass effect, 343
Mass suicide, 1492
Massachusetts, e25
Masses
anorectal, 1277
ovarian, 1358-1359
scrotal, in children, 2208-2211
Masseter spasm, succinylcholine-induced, 14
MAST program. *See* Military Assistance to Safety and Traffic program (U.S. Armed Forces)
Mastication, 895
Mastocytosis, 1557
Mastoiditis, 936
ancillary testing in, 936
diagnostic findings, 936
etiology of, 936
management of, 936
masked, 936
pathophysiology of, 936
Material exploitation, 886, 887b
Material information, e70
Material resources, 2436-2437
Maternal and Child Health Bureau, EMS-C, 2439t
Maternal birth trauma, 2347-2348
Maternal cardiac arrest, 2278
Maternal history, 115b

www.ketabpezeshki.com 66485457-66963820

Maternal resuscitation, 300-301
primary survey, 300-301
secondary survey, 301
Maxillary sinusitis, 901
Mayaro virus arthritis, 1513t
McGinn-White S1Q3T3 pattern, 1162
McMurray's test, 701-702
McRoberts' maneuver, 2344, 2345f
Mean arterial pressure
equation for, 1118
normal, in newborn, 113t
Mean corpuscular hemoglobin, 1590t
Mean corpuscular volume, 1590t
Measles (rubeola), 1570, 1724-1725, 1724f
clinical features of, 1570, 1724-1725, 1724f
differential considerations, 1725
management of, 1570, 1725
Measles, mumps, rubella vaccine, 1720t
Mebendazole (Vermox)
for diarrhea, 1235t
for parasitic disease, 1770t, 1772t-1775t
for pruritus ani, 1285
Mechanical corneal abrasions, 912
Mechanical index (MI), 2494
Mechanical ventilation, 23
in asthma in children, 2124
in burns, 812, 812t
continuous (CMV), 24, 25t
definition of breath, 23
evaluation of distressed patient on, 29f
home, 2404
indications for, 962, 962b
intermittent (IMV), 24, 25t
invasive, 23-26
key concepts, 30b
management of, 27-28
initial ventilator settings, 812t
ongoing, 26-27
outcomes, 30
principles of, 23-25
troubleshooting the ventilator, 28, 29t
ventilator settings, 26, 812t
Meckel's diverticulum, 2179-2180
clinical features of, 2179
diagnostic strategies for, 2179
differential considerations, 2179-2180
key concepts, 2187b
management of, 2180
patient disposition in, 2180
Meclizine (Antivert), 169, 246
Meconium aspiration, 113-115
Media relations, 2464
Media violence, e1-e2
Medial collateral ligament, 698, 723, 724f
Medial collateral ligament injury, 714
Medial collateral ligament test, 700-701
Medial condyle fractures, 608
clinical and radiographic features of, 608
complications of, 608
management of, 608
Medial malleolar fractures, 728
Median mononeuropathy, 1436-1437
Median nerve, 573t, 1436, 1436f
Median nerve compression test, 573t, 589
Median nerve palsy, 543, 543f
Mediastinal lymphadenopathy, 1818
Mediastinal widening, 452, 452f
in blunt abdominal trauma, 478, 478f
guidelines for, 452-453
Medicaid, 2434, e25
Medical aircraft, 2443-2444
Medical alert bracelets, 1384, e51
Medical child abuse, 845, 846t
Medical clearance, 1497, 2414
Medical control
direct, 2438
indirect, 2438
Medical devices, 2405t
Medical director, EMS, 2438
Medical Disaster Response Project, 2465
Medical errors, 336
Medical imperatives, e36, e37-e38
Medical interpreters, e26
Medical literature, e8
shortcut reviews, e21
Users' Guides to the Medical Literature series (*JAMA*), e8
Medical Management of Radiological Casualties Handbook, 1952-1953
Medical records, e64
E-coded hospital records, 335
Medical Reserve Corps, 2467
Medical screening condition (EMC), e60
Medical screening examination (MSE), e60
ancillary services, e63
components, e63
health care providers qualified to perform, e63
request for, e61
Medical teams
deployment, 2455
predeployment, 2455
tasks, 2455
urban search and rescue operations, 2454-2455
Medical threat assessment, 2453
Medically incompetent adults, e76
Medicare, 2434, e49
Medicare Improvements for Patients and Providers Act, 2492-2493
Medication errors, 2506, 2510
Medication lists, 241-242
Medication-overuse headache, 1396
Medications. *See* Drugs; *specific drugs, classes*
Medicine
goals of, e49
Western, e28
Medicolegal issues, e60-e78
in emergency delivery, 2331
Meditation, 1479-1480
Mefenamic acid overdose, 1968
Mefloquine, 1770t, 1772t-1775t
Megacolon, toxic, 1270-1271, 1271f
Megaloblastic anemia, 1591-1593, 1593f
clinical features and pathologic correlations, 1592t
serum tests for, 1593t
Meglitinides, 1665t
Meister, Joseph, 1718-1719
Melanocytosis, dermal, 851, 852f
Melarsoprol, 1772t-1775t
Melena, 248
Melker universal cricothyrotomy kit, 22, 22f
Mellaril (thioridazine), 2417
Memantine (Namenda), 1408
Membrane abnormality, intrinsic, 1596
Membranous croup, 2114-2115
Memory, 142
Menactra (meningococcal conjugate vaccine), 2102
Menarche, 2271, 2272f
Ménière's disease, 2247
diagnostic algorithm for, 167f
differential diagnosis of, 166t-167t
management of, 168
Meningitis
in AIDS, 1761
aseptic, 1448b
bacterial
algorithm for, 1452, 1452f
complications of, 1450-1451, 1451b
critical, stable, 2230
critical, unstable, 2230
diagnostic strategies for, 2226-2229
epidemiology of, 1447
etiology of, 1448
Gram's stain characteristics of pathogens, 1453t
laboratory testing in, 2228
nontoxic, high risk, 2230
nontoxic, low risk, 2229-2230
pathophysiology of, 1449
patient disposition in, 2231
pediatric, 2224-2231
recommendations for empirical antimicrobial therapy, 1456t
therapy for, 1456-1457
after basilar fractures, 359
chemoprophylaxis of, 1458
definition of, 1447
differential diagnosis of, 174t
etiology of, 1448
Meningitis *(Continued)*
fungal
complications of, 1451
pathophysiology of, 1449
therapy for, 1457
with HIV coinfection, 1761
key concepts, 1459b
meningococcal, 1712
predisposing host factors, 1450b
purulent, 1456t
risk factors for potentially catastrophic illness, 172b
spinal, 1821
tuberculous, 1820-1821
complications of, 1451
therapy for, 1457
viral
in children, 2229
complications of, 1451
epidemiology of, 1447
etiology of, 1448
pathophysiology of, 1449
therapy for, 1457
Meningitis belt, 1711
Meningococcal conjugate vaccine (Menactra), 2102
Meningococcal meningitis, 1712
Meningococcal septicemia, 1712
Meningococcal vaccine, 1458, 1714
Meningococcemia, 1710-1714
acute treatment of, 1713
antibiotic prophylaxis of, 1713-1714
in children, 2102
chronic, 1712
clinical features of, 1711-1712
complications of, 1712
diagnostic strategies for, 1712-1713
differential considerations, 1713
epidemiology of, 1710-1711
etiology of, 1711
historical perspective on, 1710
incidence of, 1710-1711, 1711f
key concepts, 1717b
management of, 1713
mortality rate, 1711
pathophysiology of, 1711
patient disposition in, 1713
symptoms and signs of, 1711-1712
treatment strategy for, 1713
Meningoencephalitis
definition of, 1447
herpes, 1457
Meningomyelocele, 115
Meniscal injuries, 714-715
clinical features of, 714-715
diagnostic strategies for, 715
management of, 715
pathophysiology of, 714
Meniscal tears, 701-702
Meniscus, 714
Menometrorrhagia, 274t
Menorrhagia, 274t, 1360t
Men's health
genital herpes, 1313, 1313f
urinary tract infections, 1335-1336
Menstrual cycle, normal, 1360, 1360f
Menstruation, 1029
Menstruation-associated asthma, 945
Mental health consultation, 1485
Mental illness. *See also* Psychiatric disorders
among sexual assault victims, 862
and suicide, 1494
Mental status. *See also* Altered mental status
delta MS (change in mental status), 151
evaluation of
in intimate partner violence, 876
in pediatric head injury, 312
p-menthane-3,8-diol, 1808
Meperidine (Demerol), 39t, 41, 1403
in pregnancy and lactation, 2318t-2321t
respiratory depression associated with, 2053t
Mepivacaine, 46t-47t
Meralgia paresthetica, 2278
Mercury, 2030

www.ketabpezeshki.com 66485457-66963820

Mercury poisoning, 2030-2031
antidote for, 1957t-1958t
clinical features of, 2030
diagnostic strategies for, 2030-2031
intoxication syndromes, 2031t
key concepts, 2031b
management of, 2031
pathophysiology of, 2030
patient disposition in, 2031
Meropenem
in immunocompromised patients, 2361t
for pneumonia, 985t
for toxic shock syndrome, 1568
Mescaline, 2017
Mesenteric arterial embolism, 1221-1222, 1222f
Mesenteric arterial thrombosis, 1222
Mesenteric ischemia
abdominal pain in, 227, 227t-228t
acute, 1221-1224
clinical features of, 1222-1223
complications of, 1223
CT evaluation of, 1223, 1223f
CT findings, 1221-1222, 1222f
diagnostic strategies for, 1223
differential considerations, 1223
history at presentation, 1222
key concepts, 1224b
management of, 1223-1224
patient disposition in, 1223-1224
physical examination findings, 1222-1223
nonocclusive, 1222
unusual causes of, 1222
Mesenteric vasculitis, 1531
Mesenteric venous thrombosis, 1222, 1222b
Mesoridazine, 2048t
Meta-analysis, e17-e18
Metabolic acidosis, 1629, 1632-1634
categorization of, 1630
elevated anion gap, 1632-1633, 1632b
$ETCO_2$ findings, 65, 65f
etiology of, 1632-1633
key concepts, 1635b
management of, 1634
normal anion gap, 1633, 1633b
physiologic compensation for, 1633
vomiting and, 239
Metabolic alkalosis, 1629, 1634-1635
categorization of, 1630
causes of, 1634b
Metabolic disorders
of muscles, 1445-1446
in pregnancy, 2309-2311
seizures caused by, 1377-1378
Metabolic myopathies, 1669b-1670b
Metabolic neuropathies, 1433
Metabolic optic neuropathy, 927
Metabolism
in acute kidney injury, 1300-1301
alcohol effects on, 2380-2381, 2388t
Metacarpal(s), 535-536, 537f
Metacarpal fractures, 549-552
base fractures, 551-552
head fractures, 549-550
index, middle, ring, and little fingers, 549
neck fractures, 550-551
90-90 reduction method for, 550-551, 551f
shaft fractures, 551, 551f
thumb, 552
ultrasound of, 2500, 2500f
Metacarpophalangeal joint, 534-536, 536f-537f
dislocation of, 554-555
complex, 554-555, 555f
management of, 555
injury to, 554-556
in fingers, 554-556
in thumb, 556
injury to, in thumb, 556
Metals
elemental, 824
heavy, 2024-2031
Metamucil (psyllium), 264t-265t
Metaphyseal fractures
bucket handle type, 847-848, 847f
in child abuse, 847-848, 847f, 2259
Metastatic disease, vertebral, 649, 650f
Metatarsal fractures, 744-745
base fractures, 745
of fifth metatarsal, 745
head and neck fractures, 745
shaft fractures, 744
Metatarsalgia, 748
Metatarsophalangeal dislocations, 747
Metered-dose inhalers
for asthma, 949-950, 949t, 2121t
for asthma in children, 2119-2120
for COPD, 963
instructions for use, 955b
with spacers, 2119-2120
Metformin (biguanides)
for diabetes, 1665t
for hyperglycemia, 1665
in pregnancy, 2328
Methadone, 39t, 42
for opioid withdrawal, 2055-2056
in pregnancy and lactation, 2318t-2321t
respiratory depression associated with, 2053t
Methamphetamine, 2005, e2
Methane, 2037t
Methanol, 1633, 2007-2009
metabolism of, 2007, 2008f
pharmacology of, 2007
Methanol poisoning, 2007
antidote for, 1957t-1958t
clinical features of, 2008
diagnostic strategies for, 2008-2009
differential considerations, 2009
management of, 2011-2012
pathophysiology of, 2007-2008
treatment goals, 2011
Methcathinone, 2005
Methemoglobin-forming agents, 1957t-1958t
Methemoglobinemia
causes of, 129, 130b
management strategies for, 134
Methicillin-resistant *Staphylococcus aureus* (MRSA)
community-acquired (CA-MRSA), 984, 1565, 1853-1854
hospital-acquired, 1565
in osteomyelitis, 1835
Methimazole, 1682b, 1683
Methocarbamol (Robaxin), 282-283
Methohexital, 54t-55t, 57, 60t
Methotrexate
drug interactions, 44
hepatic injury, 1197t
toxicity of, 1515t
Methoxyflurane, 1197t
4-Methyl-2,5-dimethoxyamphetamine (serenity, tranquility, and peace [STP]), 2017
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 2053
Methyl salicylate poisoning, 1955t
Methylbromide, 2037t
Methylcellulose (Citrucel), 264t-265t
Methyldopa
hepatic injury, 1197t
for hypertension, 1122.e1t-1122.e2t
Methylene blue
for methemoglobin-forming agents toxicity, 1957t-1958t
for nitrate and nitrite exposures, 823
in pregnancy, 2323-2324
safety in pregnancy and lactation, 2318t-2321t
Methylenedioxyamphetamine (MDA), 2017
Methylenedioxyethamphetamine (Eve), 2017
Methylenedioxymethamphetamine (MDMA, ecstasy, XTC, Adam), 1477, 2005, 2017-2018
antidote for, 1957t-1958t
clinical features of effects of, 2018
Methylnaltrexone (Relistor), 265
for constipation, 264t-265t
Methylprednisolone (Solu-Medrol)
for anaphylaxis, 1554b, 1555
for asthma, 949t, 950-951, 2121t
for asthma in pregnancy, 2303t
for COPD, 963
for Goodpasture's syndrome, 1537
for lupus enteritis, 1531
for multiple sclerosis, 1417
for rejection, 2373
Methylprednisolone (Solu-Medrol) *(Continued)*
for spinal cord injury, 418-419
for systemic lupus erythematosus, 1533t
Methylprednisolone acetate (Depo-Medrol), 639t
Methylxanthines, 951
Metoclopramide (Reglan)
for migraine attack, 1388t
for nausea and vomiting, 245t, 246
for pediatric migraine, 2244
Metolazone, 1122.e1t-1122.e2t
Metoprolol, 1038, 1987t
for dysrhythmias, 1038
hemodynamic effects, 1118t
for hypertension, 1122.e1t-1122.e2t
for thyroid storm, 1682b
Metronidazole (Flagyl)
alcohol interactions, 2390t
for amebic abscess, 1198
for bacterial infection, 783
for bacterial vaginosis, 1323
bismuth subsalicylate, metronidazole, and tetracycline (Helidac), 1180
for bone and joint infection, 1835t
for bowel flora, 1264b
for *C. difficile* colitis, 1249
for dental infection, 900
for diarrhea, 1235t, 2192t-2193t
for diarrhea in AIDS, 1257t
for diverticulitis, 1264b
for giardiasis, 1253
for *H. pylori* infection, 1180
for infectious diarrhea, 2192t-2193t
for intestinal amebiasis, 1254
for nongonococcal urethritis, 1320
for parasitic disease, 1770t, 1772t-1775t
for pelvic inflammatory disease, 1325t
in pregnancy, 2318t-2321t, 2325
for STDs after sexual assault, 851t, 868b
for tetanus, 1703
for trichomoniasis, 1322
Metropolitan Medical Response System (MMRS), 2467
Metropolitan Medical Strike Teams (MMSTs), 2467
Metrorrhagia, 274t
Mexican Americans, e27
Mexican beaded lizard *(Heloderma horridum)*, 796
Mexican beaded lizard *(Heloderma horridum)* bites, 801
Micatin (miconazole), 1560
Mickey Mouse sign, 1346
Miconazole (Micatin), 1560
Microcytic anemia, 1590-1591
hypochromic, 1590b, 1590f
Micrognathia, 2109
Microscopic polyangiitis, 1536t, 1537-1538
Microscopy
in tuberculosis, 1815-1816
urinalysis, 1291-1292, 1328
Midazolam (Versed), 2078t
benefits and adverse effects, 55t
for burn pain, 816
in pregnancy, 2318t-2321t, 2322
for procedural sedation and analgesia, 54t-55t, 56, 59t-60t
for rapid tranquilization, 2417
for seizures, 158t-159t
for status epilepticus, 158t-159t, 1381-1382, 1381t
for status epilepticus in children, 2237f, 2238
for TBI, 347
Midcarpal instability, 582
Middle ear barotrauma, 1918, 1918f, 1923t, 1925
Middle finger fracture, 549
Middle phalangeal fractures, 547-549
Midface fractures, 379-380
Midfoot, 734, 735f
Midfoot injuries, 741-744
Midfoot pain, 748
Midgut volvulus, 2173-2174
Midrin (isometheptene, acetaminophen, dichloralphenazone), 2243-2244
Midtarsal joint, 740-741
Midtarsal joint injuries, 740-741
Miglitol, 1665t

www.ketabpezeshki.com 66485457-66963820

Migraine headache, 1386-1389
abdominal, 2242
with aura (classic migraine), 1387b, 2242
basilar-type, 139t, 1387, 2242
classification of, 2242
clinical features of, 1386-1387
definition of, 1386
diagnostic evaluation of, 1387
differential diagnosis of, 1387, 2233, 2242
epidemiology of, 170
hemiplegic, 1387, 2242
medications for, 1388t
ocular, 2242
ophthalmoplegic, 1387, 2242
pediatric
treatment of, 2243-2244
without aura, 2242b
prophylactic therapy for, 1389
seizures caused by, 1379
treatment of, 1387-1389, 2243-2244
vertebrobasilar
diagnostic algorithm for, 167f
differential diagnosis of, 166t-167t
management algorithm for, 168f
without aura (common migraine), 1387b, 2242
Migraine medications, 2329-2330
Miliaria rubra, 1900
Military Assistance to Safety and Traffic (MAST) program (U.S. Armed Forces), 2443
Military history, 1883
Milk of magnesia (magnesium hydroxide), 264t-265t
Milker's node virus, 1727
Millepora (fire coral), 806
Miller-Fisher syndrome, 181-182
Milrinone
for heart failure, 1086
for heart failure in children, 2152-2153, 2153t
for resuscitation in children, 104t
Miltefosine, 1772t-1775t
Mineral oil (Fleet mineral oil), 264t-265t
Mineralocorticoid receptor blockers, 1122.e1t-1122.e2t
Mini-Mental State Examination (MMSE), 152-153, 152f, 889, 1401, 1401f
Minors, e71
accompanied by parents or legal guardians, e71
emancipated, e71
refusal of care or blood transfusions for, e75
unaccompanied, e71
Minoxidil, 1122.e1t-1122.e2t
Miosis, traumatic, 915
Miotics, 930t
MiraLax (polyethylene glycol and electrolytes), 264t-265t
Miscarriage, 2282-2284
clinical features of, 2283
completed, 2282
definition of, 2282
delayed, 2282
diagnostic strategies for, 2283
differential considerations, 2283
incomplete, 2282
inevitable, 2282
management of, 2283-2284
pathophysiology of, 2282
terminology, 2282
threatened, 2282, 2288
Misoprostol, 44t, 1184-1185
Missile wounds
abdominal trauma, 460
penetrating, 358
perforating, 358
tangential, 358
Mitigation, 2463
Mitral regurgitation, 1110
clinical features of, 1110
management of, 1110
pathophysiology of, 1110
in pregnancy, 2306
Mitral stenosis, 1110
clinical features of, 1110
key concepts, 1112b
management of, 1110
pathophysiology of, 1110
in pregnancy, 2305-2306
Mitral valve prolapse, 1111-1112
Mitragyna speciosa Korth. (kratom), 2022
Mixed gas diving, 1915, 1916t
MMRS. *See* Metropolitan Medical Response System
MMSE. *See* Mini-Mental State Examination
MMSTs. *See* Metropolitan Medical Strike Teams
MOANS mnemonic, 5-6, 6b
Mobiflex (tenoxicam), 1925
Mobitz type II block, 1044-1045, 1045f
Model for End-stage Liver Disease (MELD), 2385
Model of the Clinical Practice of Emergency Medicine, e47
Model Trauma Care System Plan (HRSA), 287
Modified Pre-Verbal, Early Verbal Pediatric Pain Scale (M-PEPPS), 37
Moexipril, 1122.e1t-1122.e2t
Molar pregnancy, 2288, 2289f
Molecular absorbent recirculating system (MARS), 1195
Molindone (Moban), 2048t, 2417
Molluscum contagiosum, 1319, 1582f, 1727
Mometasone, 951
Monafo formula, 813t
Monash method, 797-798
Mongolian spots, 851
Mongols, 2469
Monitoring, 61
asthma, future, 948
blood pressure, 61
ambulatory, 1113
cardiac
in asthma, 948
in COPD, 959-960
cerebral function, 65
in CPR, 89-92
ECG, 1015-1016
fetal, 65-66
electronic, 2334-2335
intrathoracic impedance, 1088
key concepts, 66b
perfusion status, 71
in procedural sedation and analgesia, 53
Monkey B virus, 1730
Monkey B virus exposure prophylaxis, 791b
Monkey bites, 787
epidemiology of, 785
prophylactic antiviral agents for, 790
recommendations for closure and prophylactic antibiotics, 789t
risk factors for infection, 788t
Monkey hand *(main en singe)*, 543, 543f
Monkeypox, 1726-1727
Monkeypox virus, 1726-1727
Monoamine oxidase inhibitors, 1975
for anxiety disorders, 1479, 1479t
herbal medicine interactions, 2072t-2073t
overdose, 1975-1976
clinical features of, 1975-1976
diagnostic strategies for, 1976
differential considerations, 1976
management of, 1976
patient disposition in, 1976
Monoclonal antibodies, antilymphocyte, 2372
Monomethylhydrazine overdose, 1957t-1958t
Mononeuropathies. *See also specific nerves*
isolated, 1433-1438, 1434b
multiple, 1428
simple, 1428
Mononeuropathy multiplex, 1428, 1438, 1438b
Mononucleosis, 1731-1732
infectious, 965, 967
pediatric, 2110
Monoparesis, 125-126
Monoplegia, 125-126
Monroe, Marilyn, 2076
Monteggia, Giovanni Battista, 592
Monteggia's fracture, 512t-513t, 592, 592f
Monteggia's fracture-dislocation, 2257, 2257f
Montelukast, 951-952
Mood, 1466
Mood disorders, 1466-1473
categories of, 1466
clinical features of, 1468-1472
cognitive-behavioral therapy for, 1468
diagnostic strategies for, 1472
Mood disorders *(Continued)*
differential considerations, 1472
ED stabilization of, 1472-1473
epidemiology of, 1466
genetics of, 1467
interpersonal theory of, 1468
key concepts, 1473b
long-term treatment of, 1473
management of, 1472-1473
in medical conditions, 1471
from medications or other substances, 1471-1472
neuroanatomy of, 1467
neurophysiology of, 1466-1467
pathophysiology of, 1466
psychodynamic theory of, 1468
psychosocial factors, 1467-1468
with psychotic features, 1462
Mood disturbances, 1468
Moral imperatives, e36
Moral rules, e34b
Moraxella (Branhamella) catarrhalis infection, 931-932
Morbilliform drug eruption, 1566, 1566f
Morgan lens (MorTan), 820, 910
Morison's pouch, 2494-2495, 2495f
Morphine, 39t, 40-41
for acute coronary syndrome, 1024
benefits and adverse effects, 55t
for burn pain, 810-811, 816
for heart failure, 1085
for migraine attack, 1388t
in pregnancy and lactation, 2318t-2321t
in procedural sedation and analgesia, 54t-55t, 56
respiratory depression associated with, 2053t
for sickle cell disease, 1599
Morrison's pouch, 467-468, 468f
Mortality in Emergency Department Sepsis (MEDS) prediction rule, 1868, 1868t
Morton's neuroma, 748-749
Moses v Providence Hospital, e67
Mosteller formula, 814
Motility, abnormal, 254
Motor examination
function testing, 1422
in head injury, 346
spinal, 399, 399t
strength grading score, 1442b
Motor loss, 280
Motor neuron disease, 1439
clinical characteristics of, 1423t, 1442t
differential considerations, 1442
Motor vehicle collisions, 287. *See also* Pedestrian collisions
alcohol-related, 337
reporting requirements for, e76-e77
behavioral risk factors for, 337
blunt abdominal trauma, 459
blunt trauma and associated injuries, 290t
dicing lacerations, 841, 842f
evidence collection in, 841, 841b
facial trauma, 368-369, 372f
fatality rate, 287
forensic aspects of, 841-842
g-force that results, 336
geriatric trauma, 324-325
Haddon matrix for, 330-331, 333t
head injury, 339
hip dislocations, 687
Lisfranc's injuries, 741-742
occupant kinematics, 841
partial amputations, 841, 841f
pattern injuries, 841
safety countermeasures for, 336
spinal injuries, 382
thoracic injury, 431
trace evidence of, 841-842, 842f
Motorcyclists
facial trauma in, 368
injury patterns in, 687
Mottling, 2092, 2092f
Mouth, 377
anatomy of, 370
lacerations of, 377
perioral burns, 377
in sexual assault, 864-865

www.ketabpezeshki.com 66485457-66963820

Movement disorders, alcohol-related, 2386
Moxifloxacin
for pneumonia, 984-985, 985t
for prophylaxis in bite wounds, 789t
for tuberculosis, 1822t-1823t, 1824
MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), 2053
MRSA. *See* Methicillin-resistant *Staphylococcus aureus*
MSE. *See* Medical screening examination
MTA. *See* Medical threat assessment
Mucocutaneous lymph node syndrome (Kawasaki disease), 2161-2165
in children, 2103
myocarditis in, 1100-1101
Mucokinetic medications, 963
Mucormycosis, 1664t
Mucus clearance strategies, 963
Multicollinearity, e16
Multiculturalism, e23-e32
policies for institutional improvement, e30b
Multidisciplinary teams, 330, 331b
Multidrug-resistant pathogens, 980
Multidrug-resistant tuberculosis, 1826
Multifocal atrial tachycardia, 1050, 1050f
Multinodular goiter, toxic, 1678
Multiple-casualty triage, 2459-2461
Multiple organ dysfunction syndrome, 1865b
Multiple sclerosis, 1415-1417, 1424
anxiety in, 1476-1477
clinical features of, 1415-1416, 1424
diagnosis of, 167f, 1416, 1424
differential diagnosis of, 166t-167t, 1416, 1424
incidence of, 1415
key concepts, 1417b-1418b
management of, 1416-1417, 1424
patient disposition in, 1417
in pregnancy, 2308
prevalence of, 1415
Multivariate models, e15-e16
Mumps, 1723-1724
clinical features of, 1723-1724
differential considerations, 1724
management of, 1724
measles, mumps, rubella (MMR) vaccine, 1720t
Mumps orchitis, 1348
Munchausen syndrome, 1487
clinical features of, 1488
management of, 1490
Munchausen syndrome by proxy, 845, 1487
clinical features of, 1488-1489
diagnostic criteria for, 1488b
key concepts, 1491b
management of, 1490
patient disposition in, 1490
perpetrator characteristics, 1489
serial, 1489
victim characteristics, 1489
Muscle disorders, 1445-1446
inflammatory, 1445
metabolic, 1445-1446
Muscle relaxants, 282-283
Muscular injuries
femur and hip, 691
pulled muscle, 527
sports injury patterns, 691
Musculature
of hand, 537-541, 538f-539f
of mastication, 895
of thigh, 672, 674t
Musculoskeletal disorders, pediatric, 2250-2270, 2270b
Musculoskeletal pain
back pain, 643-655
chest pain, 1530
in pregnancy, 2278
Musculoskeletal system
in chronic kidney disease, 1303
pediatric, 2088, 2250
Musculoskeletal ultrasound, 2500, 2503
Mushroom poisoning
early onset of symptoms, 2074-2075, 2074t
key concepts, 2075b
late onset of symptoms, 2074t, 2075
to management of, 2074
unintentional childhood exposure, 2066
Mushrooms, 2066, 2074-2075
A. muscaria, 2023, 2023f
groupings, 2074-2075, 2074t
isoxazole, 2023
P. cubensis, 2015, 2016f
Mustard gas, 825-826, 825t, 2469, 2477-2478
Muzzle contusions, 830, 831f
Myasthenia gravis, 1441, 1443-1444
clinical features of, 1443
diagnostic strategies for, 1443-1444
drugs that may exacerbate, 1444b
ice test for, 183
management of, 1444
new-onset, 1443
in pregnancy, 2301t-2303t, 2309
Myasthenic crisis, 1443-1444
Mycobacterial infections
fungal, 1818
in immunocompromised patients, 2363
nontuberculous, 1818
Mycobacterium avium complex infection
in AIDS, 1257t
prevention of, 1758t
Mycobacterium tuberculosis infection, 1809-1810
bone and joint infection, 1836
drug-resistant, 1809, 1826
risk factors for, 1827b
in HIV infection, 1759t, 1760
latent infection, 1828
in otitis media, 932
in pneumonia, 979
Mycophenolate mofetil, 2371
Mycoplasma pneumoniae infection
myocarditis, 1100
otitis media, 932
pharyngitis, 965-967
pneumonia, 978-979
in children, 2132, 2135t
key concepts, 987b
radiographic findings, 982-983
treatment of, 968
Mycotic aneurysms, 1148, 1148t
Mydriasis
pharmacologic, 927-928
traumatic, 915
Mydriatics, 191, 191t, 930t, 1970
Myelin sheath, 45
Myelitis, 1423
definition of, 1447
transverse, 282t-283t, 1424
Myelofibrosis of unknown origin, 1594
Myeloid leukemia, chronic, 1603-1604, 1604f
Myelomeningocele, 2409
Myelopathy, 1441
clinical characteristics of, 1423t, 1442t
differential considerations, 1442
HIV, 1425
Myelophthisic anemia, 1594
Mylohyoid muscle, 896
Myocardial biopsy, 1099, 1099f
Myocardial concussion, 444
Myocardial contrast echocardiography, 1020
Myocardial contusion, 444-446
characterization of, 444
in children, 320
clinical features of, 444
diagnostic strategies for, 445
epidemiology of, 444
management of, 445-446
pathophysiology of, 444
prognosis for, 446
Myocardial disease, 1098-1101, 1105. *See also* Myocarditis
Myocardial failure, 68b
Myocardial infarction
acute, 998-999
anatomic location of, 1006-1008
anterior, 1006, 1007f
anterolateral, 1006, 1007f
with cardiogenic shock, 74
classification of, 998-999
definition of, 998
diagnostic criteria for, 998
early complications of, 1002-1003
ECG findings in, 1004f
Myocardial infarction *(Continued)*
four Ds of ED-based diagnosis and management of, 1023, 1023f
inferior, 1006-1008, 1007f
in left bundle branch block, 1009-1011, 1012f
posterior, 1008, 1014-1015, 1015f
regional ST segment changes in, 1006, 1006t
reperfusion therapy for, 1031
ST segment-T wave morphology in, 1004, 1005f
symptoms of, 1001, 1001t
time to reperfusion and benefit in, 1022, 1022f
ventricular paced rhythms in, 1011, 1013f
anterior, 1006, 1007f
anxiety in, 1476
chest pain in, 220t-221t
clinical features of, 139t
diagnostic criteria for, 998
in elders, 2354
and fibrinolytic therapy, 1029
and heart failure, 1081
inferior, 1006-1008, 1007f
lateral, 1006, 1007f
non-ST segment elevation (NSTEMI), 1011-1014
non–Q wave, 999, 1011
nontransmural, 999
post-MI pericarditis, 1093
post-MI syndrome, 1002
posterior, 1008, 1008f
ECG findings in, 1008, 1008f
Q wave, 999
right ventricular, 1008, 1009f
rule out MI protocol, 1021
silent, in diabetes, 1663
ST segment elevation (STEMI), 1022-1024, 1022f-1023f, 1031-1032
STEMI alert response, 1023-1024, 1031
transmural, 999
types of, 998-999
vomiting with, 243t-244t
Myocardial ischemia, 1081
Myocardial rupture, 446-447, 447f
anatomy of, 446
clinical features of, 446-447
definition of, 446
diagnostic strategies for, 447
epidemiology of, 446
management of, 447
mechanisms of, 446
pathophysiology of, 446
prognosis for, 447
Myocardial scintigraphy, 1020
Myocardial stunning, 999, 1078
Myocarditis, 1098-1101
acute, 1082
causes of, 1100
in children, 2160-2161
clinical features of, 2160
diagnostic strategies for, 2160-2161
management of, 2160-2161
clinical features of, 1098
definition of, 1098
diagnostic strategies for, 1098-1099
differential diagnosis of, 1099
epidemiology of, 1098
etiology of, 1098
and heart failure, 1078
infectious causes of, 1098, 1098b
isolated idiopathic interstitial, 1098
key concepts, 1105b
management of, 1099
pathophysiology of, 1098
patient disposition in, 1099
risk factors associated with, 216b
Myoclonic-atonic seizures, 1376
Myoclonus, 1375
Myofibrils, 1075
Myoglobin
in acute coronary syndrome, 1017t, 1018f, 1019
normal physiology, 1667
in rhabdomyolysis, 1670-1671, 1671f
Myoglobin-induced acute kidney injury, 1672, 1673f
Myopathy, 1441
clinical characteristics of, 1423t, 1442t
differential considerations, 1443
metabolic, 1669b-1670b

www.ketabpezeshki.com 66485457-66963820

Myositis, infectious, 1831
Myositis ossificans, 676, 676f
Mysoline (primidone), 2407t-2408t
Myxedema, 1583f
Myxedema coma, 1687
 aggravating or precipitating factors, 1687b
 management of, 1688
 recognition of, 1687b
 treatment of, 1688b

N

N codes, 335
Nadolol, 1987t, 1122.e1t-1122.e2t
Naegleria, 1778
NAEPP (National Institutes of Health [NIH]) Expert Panel Report 3 (EPR-3), 946
Nafcillin
 for bacterial endocarditis, 1108b
 for septic arthritis, 2265t
 for staphylococcal scalded skin syndrome, 1567
Naftifine, 1560
Nägele's rule, 2272
Nail(s), 544
Nail bed injuries
 acute, 561-562
 classification of, 561, 561f
 lacerations, 562
Nail matrix, 544
Nalbuphine, 39t, 42
Nalmefene, 1957t-1958t, 2055
Naloxone, 42, 2055
 for neonatal resuscitation, 117-118, 117t
 for opioid overdose, 1957t-1958t, 2055, 2381
 in pregnancy, 2318t-2321t, 2324
 for PSA reversal and rescue, 59
 safety, 2055
Namenda (memantine), 1408
Napoleonic Wars, 2433
Naproxen
 for gouty arthritis, 1509
 for migraine attack, 1388t
 for pediatric migraine, 2243
 risk of GI effects, 44t
Naratriptan, 1388t
Narcissistic personality disorder, 2427b
Narcolepsy, 139t, 2233
Narcotic addiction, 1584, 1584f
Narcotic analgesia, 2338t
Narcotics
 alcohol interactions, 2390t
 definition of, 32b
 labor interactions, 2340t
Narrow-complex tachycardia, 1048-1052, 1055f
Nasal bleeding, 937-939
Nasal feeding catheters, 2405t
Nasal flaring, 2091-2092, 2092f
Nasal fractures, 378-379
Nasal packing, 938-939, 940b
Nasogastric aspiration and lavage, 252
Nasogastric tubes
 in neck injury, 423-424
 size estimates for pediatric trauma, 307b
Nasopharynx, 198, 199f
Nasotracheal intubation
 blind, 12
 in neck injury, 424
Nateglinide, 1665t
National Academy of Sciences–National Research Council, 2433
National Accident Response Program, 2433
National Association of EMS Educators, 2439t
National Association of EMS Physicians, 2439t, e50
 contact information, 2452
 guidelines for emergency department thoracotomy, 450
 guidelines for resuscitation, 294
National Association of EMTs, 2439t
National Association of State EMS Officials (NASEMSO), 2436, 2439t
National Button Battery Ingestion Hotline, 1172
National Capital Poison Center, 2182
National Center for Injury Prevention and Control (NCIP), 331
National Committee on Quality Assurance (NCQA), e26
National Conference on EMS, 2433
National Crime Victimization Survey (NCVS), 873
National Disaster Medical System (NDMS), 2467
National Domestic Violence Hotline, 881-882
National emergencies, e62
National Emergency X-Radiography Utilization Study (NEXUS), 402-403
National EMS Core Content, 2436
National EMS Education Agenda, 2435
National EMS Education Standards, 2436
National EMS Scope of Practice Model, 2435-2436
National Football League (NFL), 354
National Heart, Lung, and Blood Institute (NHLBI), 1021-1022
National Heart Attack Alert Program (NHAAP), 1021-1022
National Highway Traffic Safety Administration (NHTSA), 2433
 Click It or Ticket campaign, 287
 Emergency Medical Services Agenda for the Future, 2433
 Emergency Medical Services Education Agenda for the Future: A Systems Approach, 2436
 EMS Division, 2439t
National Incident Management System, 2462, 2466
National Institute of Child Health and Human Development (NICHD), 110
National Institutes of Health (NIH), 946
National Institutes of Health (NIH) Stroke Scale, 1366, 1367b
National Quality Forum, e26
National Registry of EMTs, 2436, 2439t
National Response Center, 1952-1953
National Response Framework, 2458t, 2462, 2466
National Response Plan, 2466
National Violence Against Women Survey (NVAWS), 873
National Weather Service Heat Index Chart, 1899f
Native Americans, 1492
Natriuretic peptide, 1119t
Natural barriers, 2356, 2364
Natural killer cells, 2357-2358
Nausea and vomiting, 238-247
 ancillary testing in, 242
 associated signs and symptoms of, 241-242
 chemotherapy-related, 246
 diagnostic approach to, 239-242, 241f
 differential diagnosis of, 239-240, 240t, 242-243
 at end of life, e57
 epidemiology of, 238
 with gastrostomy tubes and buttons, 2406t
 history taking in, 240-242
 management of, 245-246
 medications for, 245, 245t
 past medical history in, 241-242
 pathophysiology of, 238, 239f
 patient disposition in, 246-247
 pediatric, 243-245, 245t
 physical examination findings, 242, 242t
 pivotal findings, 240-242
 of pregnancy, 243t-244t, 246
 rapid assessment and stabilization of, 240
 social history in, 241-242
Navicular anatomy, 741
Navicular dislocation, 741
Navicular fractures, 741
 body fractures, 741
 clinical features of, 741
 diagnostic strategies for, 741
 dorsal avulsion fractures, 741
 management of, 741
 pathophysiology of, 741
 patient disposition in, 741
 tuberosity fractures, 741
Navicular stress fractures, 749
Near drowning, 1941
Near hanging, 429-430
Nebivolol hydrochloride, 1122.e1t-1122.e2t
Nebulizers
 for asthma, 949t, 950
 for asthma in children, 2119-2120
Necator americanus (hookworm), 1770t-1775t
Neck
 anatomy of, 421-422
 danger spaces, 971, 971f, 977b
 deep space infections in, 971, 971f
 dental infection in, 896
 examination of, in sexual assault, 864-865
 fascial layers, 422
 fascial planes of, 896
Neck injury, 421-430
 airway management in, 423-425
  pediatric considerations, 424
  techniques for, 424
 blunt trauma, 421
 blunt vascular trauma, 429
  epidemiology of, 427
  pathophysiology of, 427
 cervical spine in, 424-425
 cervical spine stabilization in, 423
 clinical features of, 422-423
 diagnosis of, 167f, 423
 electrical injury, 1910
 incidence of, 421
 key concepts, 430b
 lightning injury, 1910
 management of, 168f, 423-425
 in near hanging, 429-430
  clinical features of, 430
  management of, 430
  pathophysiology of, 429-430
 pathophysiology of, 421
 patient disposition in, 425
 penetrating trauma, 421
  exploration of, 425
  hard signs of, 423b
  incidence of, 422t
  soft signs of, 423b
 penetrating vascular trauma
  clinical features of, 427-428
  epidemiology of, 427
  pathophysiology of, 427
 retropharyngeal injuries, 429
 in strangulation, 429-430
 vascular concerns, 423
 vascular trauma, 427-429
  clinical features of, 427-428
  diagnostic strategies for, 428
  epidemiology of, 427
  management of, 428-429
  after near hanging, 430
  pathophysiology of, 427
Neck masses, 939-940
 clinical features of, 940
 diagnostic strategies for, 940
 differential diagnosis of, 937b
 key concepts, 940b
 management of, 940
 patient disposition in, 940
 physical examination findings, 940
 rule of 80 or 80% rule for, 939
Neck mobility, 5
Neck zones, 421-422, 422b, 422f
Necrobiosis lipoidica diabeticorum, 1664
Necrotizing (malignant) infections
 anorectal, 1282
 enterocolitis, 2174-2175
  clinical features of, 2174-2175
  diagnostic strategies for, 2175
  differential considerations, 2175
  key concepts, 2187b
  management of, 2175
  patient disposition in, 2175
  radiographic findings, 2175, 2175f
 external otitis, 935-936, 940b
 key concepts, 1863b
 skin and soft tissue infections, 1860-1861
  clinical features of, 1860
  diagnostic strategies for, 1860
  differential considerations, 1860
  management of, 1861
  patient disposition in, 1861
 ulcerative gingivitis, acute, 900, 900f
Needle cricothyrotomy
 technique for, 2116
 with transtracheal jet ventilation, 21-22
Needle electromyography, 1429

www.ketabpezeshki.com 66485457-66963820

Needles, surgical, 761-762
Neer impingement sign, 638
Neer test, 1520
Neer's classification, 626, 626f
Nefazodone overdose, 1979
Negative behaviors, 2425
Negative inspiratory force (NIF), 1441
Negative predictive value, e20t
Negative reactions
  dealing with, 2424-2425
  general alternatives to, 2425
  negative thoughts about patients, 2424-2425
  placing in context, 2425
  strategies to manage, 2425
Negative self-perceptions, 2425
Neglect
  child, 846t
  definition of, 886
  elder, 885-892
  self-neglect, 885-886
Negotiation, e73-e75
  with problem patients, 2424
Neisseria gonorrhoeae infection (gonorrhea), 1286t, 1289f, 1320-1322
  arthritis, 1508
    clinical features of, 1508, 1508f
    management of, 1508
  dermatitis, 1565-1566
    clinical features of, 1565, 1566f
    diagnostic strategies for, 1565
    management of, 1566
  diagnosis of, 1321
  key concepts, 1325b
  pharyngitis
    clinical features of, 966
    diagnosis of, 967
    treatment of, 968
  in pregnancy, 2298
  septic arthritis, 1847, 2264-2265, 2265t
  treatment of, 1285, 1315t, 1321-1322
Neisseria meningitidis, 1710-1711
  Gram's stain characteristics, 1453t
Nelfinavir, 1721t-1722t, 1766t
Nematocysts (jellyfish), 806
  stings, 806-807, 807b
Nematodes, 1770t-1771t
Neo-Synephrine (phenylephrine), 938
Neologisms, 1461
Neomycin
  for hepatic encephalopathy, 1194-1195
  for otitis externa, 935
  for tar removal, 824
Neonatal hypoglycemia, 113
Neonatal hypothermia, 112
Neonatal hypoxia, 112
Neonatal jaundice, 2168-2187, 2187b
Neonatal keratoconjunctivitis, 1721t-1722t
Neonatal osteomyelitis, 1840
Neonatal seizures, 2232-2233
  diagnostic assessment of, 2239b
  etiology of, 2232-2233, 2233b
  management of, 2236
  treatment of, 2236
Neonatal tetanus, 1701, 1703
Neonates. *See also* Infants
  air medical transport of, 2447
  anatomic anomalies, 114-115
  bradycardia in, 112
  cellular oxygenation, 108
  chest compressions for, 116-117
  circulation, 2139
  duct-dependent cardiac lesions in, 2147b
  endotracheal tubes for, 115t
  episodic disorders that may mimic seizures in, 2233b
  intensive care unit graduates, 2094
  meningitis in, 2224, 2225t
  normal vital signs, 113t
  pathophysiology of, 112-113
  resuscitation of, 112-118
    algorithm for, 114f
    assessment for further intervention, 115-116
    chest compressions, 116-117
    dry and warm measures, 115-116
    equipment needed for, 115, 115b, 115t
Neonates *(Continued)*
    indications for, 113
    intubation, 116
    key concepts, 118b
    management of, 115-118
    maternal history questions for, 115b
    medications for, 117-118, 117t
    oxygen, 116
    patient disposition in, 118
    preparation for, 112, 115
    stimulation measures, 115-116
    suctioning, 115-116
    therapeutic hypothermia for, 118
    ventilation, 116
  UTIs in, 1333, 1333t
Neoplasms
  associated with autoimmune hemolytic anemia, 1600b
  facial nerve paralysis due to, 1412
  in hip, 677
  intracranial, 1391-1392
  malignant, 1740
  opportunistic infections mimicking, 2364
  spinal cord, 1426-1427
Neoplastic cardiac tamponade, 1625-1627, 1628b
Neoplastic pericardial disease, 1094
Nephropathy
  diabetic, 1663
  HIV-associated, 1762
Nephrotic-range proteinuria, 1293-1294
Nephrotic syndrome
  causes of, 1294, 1294b
  in children, 2216-2217
    clinical features of, 2216-2217
    diagnostic strategies for, 2217
    differential considerations, 2217
    management of, 2217
    patient disposition in, 2217
Nerium oleander, 2069, 2069f
Nerve(s)
  of face, 369
  of hand, 542-543
  of thigh, 673-675, 674t
Nerve agents, 825-826, 1956, 2476-2477
  exposure to
    treatment of, 2477b
    types of, 2477b
  gas WMDs, 825t
  key concepts, 2478b
Nerve blocks
  femoral, 681
  US-guided, 2503, 2503f
Nerve conduction studies, 1429
Nesiritide, 1118t
  for heart failure, 1085
  for hypertension, 1119t
Neurapraxia, 520-521, 565
Neuro-ophthalmologic visual loss, 926-927
Neuroanatomy, 1467
Neurodevelopmental disorders, 2406-2407
Neuroimaging
  ACEP clinical policy regarding, 353b
  in head injury, 351, 353b
  techniques for, 1455
Neuroleptic malignant syndrome, 1465, 2047, 2417
  clinical features of, 2049, 2049t
  diagnostic criteria for, 2049t
  differential diagnosis of, 2050t
  key concepts, 2051b
  management of, 2051
  patient disposition in, 2051
Neuroleptics, 2047
  atypical agents, 1464
  common agents, 1464, 1464b
  complications of, 1464-1465
  overdose, 1957t-1958t
Neurologic agents, 2329-2330
Neurologic disorders
  with anxiety, 1476-1477
  in children, 2224-2249, 2249b
  in disabled patients, 2404-2410
  in hemodialysis, 1309-1310
  oncologic emergencies, 1627-1628
  in pregnancy, 2307-2309
  in systemic lupus erythematosus, 1528t
Neurologic examination
  in facial trauma, 373
  in head injury, 345-347
  in low back pain, 281
  On-Site Neurological Assessment for Diver's History form (DAN), 1923, 1924f
  in pediatric trauma, 308, 308b
  in spinal injury, 396-400
Neurologic injury
  electrical injury, 1911
  femoral, 692-693
  in hand, 565
    complications of, 565
    management of, 565
  in hip, 692-693
  lightning injury, 1911-1912
  in neck injury, 429
  in orthopedic injuries, 520t
  in pelvic trauma, 664-665
Neuromuscular blockers, 1970
  competitive agents, 14
  for intubation, 13-16
  in pregnancy, 2318t-2321t, 2322
Neuromuscular disorders, 1441-1446
  clinical characteristics of, 1423t, 1442t
  clinical features of, 1441-1443
  diagnostic strategies for, 1443
  differential considerations, 1442-1443
  history in, 1441
  key concepts, 1446b
  laboratory studies, 1443
  physical examination findings, 1441
  special studies, 1443
  upper vs lower motor neuron involvement, 1442t
Neuromuscular grading, 1422
Neuromuscular junction, 1441
Neuromuscular junction disorders, 1443-1445
  clinical characteristics of, 1423t, 1442t
  differential considerations, 1442-1443
Neuromuscular unit, 1441
Neuronal theory, 2239-2240
Neurontin (gabapentin), 2407t-2408t
Neuropathic pain, 38, 49b
Neuropathy, 1441
  alcoholic, 2386
  clinical characteristics of, 1423t, 1442t
  diabetic, 1663-1664
  differential considerations, 1442
  peripheral, 127b
Neurophysiology, 1466-1467
Neurotmesis, 520-521, 565
Neutrons, 1948, 1948f
Neutropenia, 2358-2364
  cell stimulation therapy for, 2362
  clinical features of, 2360, 2360t
  definition of, 1617
  diagnostic strategies for, 2360
  febrile
    management of, 1619, 2360-2362
    outpatient therapy for, 1619
    risk assessment of, 2362
  pathogens in, 2359b, 2360t
  sites of infection, 2359
Neutropenic cancer, 1628b
Neutrophil count, 1605
Neutrophils, 1605t, 2358
Nevirapine
  herbal medicine interactions, 2072t-2073t
  for HIV infection, 1721t-1722t
  side effects of, 1765
New England Journal of Medicine, e49
New Jersey State Board of Medical Examiners, e26
New York City Fire Department, 2456
New York Heart Association, 1082b
Newborns. *See* Infants; Neonates
Next Choice, 869t
NEXUS (*N*ational *E*mergency *X*-Radiography *U*tilization *S*tudy) criteria, 293
  for cervical spine imaging, 326
NFL Physician's Society, 354
NFL Players Association, 354
Nicardipine, 1991t
  hemodynamic effects, 1118t
  for hypertension, 1122.e1t-1122.e2t
  for ischemic stroke, 1371b

www.ketabpezeshki.com 66485457-66963820

Nickel, 825
Nickel contact dermatitis, 1572f
Nicotiana tabacum, 2069
Nifedipine, 1991t
for anal fissures, 1281
for HAPE, 1936
for hypertension, 1122.e1t-1122.e2t
Nifurtimox
for Chagas' disease, 1099
for parasitic infection, 1772t-1775t
Night terrors (pavor nocturnus), 2233
Nightstick fracture, 512t-513t, 591, 592f
Nikolsky's sign, 1567-1568, 1568f, 1577
Nimodipine, 1991t
9-1-1 universal emergency access, 2437
enhanced 9-1-1, 2437
90-90 method, 550-551, 551f
Niridazole, 1770t
Nisoldipine, 1991t, 1122.e1t-1122.e2t
Nitazoxanide
for cryptosporidiosis, 1251
for diarrhea, 1235t
for diarrhea in AIDS, 1256-1258, 1257t
for parasitic infection, 1772t-1775t
Nitrates, 823, 1992
for heart failure, 1085, 1088
overdose, 1992, 1993b
in pregnancy, 2318t-2321t, 2328
Nitric oxide, 824
combined with oxygen, 45
in septic shock, 1865
Nitric oxide donors, 1119t
Nitrites, 823, 1992
overdose, 1992, 1993b
Nitrobenzene poisoning, 1955t
Nitrofurantoin, 2318t-2321t, 2325
Nitrogen, 2037t
Nitrogen dioxide (NO_2), 824-825
Nitrogen narcosis, 1918-1919, 1926
Nitrogen oxides, 2037t
Nitroglycerin
for acute coronary syndrome, 1024
alcohol interactions, 2390t
for heart failure, 1085
hemodynamic effects, 1118t
for hypertension, 1119-1120, 1119t
labor interactions, 2340t
Nitroimidazole, 1322
Nitropaste, 1371b
Nitroprusside
for heart failure, 1085
for heart failure in children, 2153, 2153t
for hypertensive emergencies, 2221t
Nitrous oxide (N_2O), 824, 2037t
benefits and adverse effects, 55t
in labor and delivery analgesia, 2338t
in procedural sedation and analgesia, 54t-55t, 58-59
Nix (permethrin), 1573-1574
Nizatidine, 1177t
No-CPR or do-not-attempt-resuscitation (DNAR) directives, e49
Noble gases, 2037t
Nocardiosis (*Nocardia asteroides* infection)
in immunocompromised patients, 2363
in transplantation, 2370
Nociceptors, 32b
Nocturnal dyspnea, paroxysmal, 206
Nocturnal enuresis, 2233
Nocturnal hemoglobinemia, paroxysmal, 1596
Nodular lesions, 1576
Nodules, 1559t
Non-nucleoside reverse transcriptase inhibitors (NNRTIs), 1765, 1766t
drug interactions, 1825-1826
side effects of, 1765
Noninvasive positive-pressure ventilation (NPPV), 25-26
for asthma, 953
Nonmaleficence, e35
Nonsteroidal anti-inflammatory drugs (NSAIDs), 43-45
alcohol interactions, 2390t
anaphylactoid reactions to, 1546
COX-2–specific inhibitors, 44
Nonsteroidal anti-inflammatory drugs (NSAIDs) *(Continued)*
drug interactions, 43-44
for gouty arthritis, 1509
mechanism of action, 1967-1968
nonselective COX inhibitors, 44
overdose, 1967-1969
clinical features of, 1968
diagnostic strategies for, 1968
key concepts, 1969b
management of, 1968
patient disposition in, 1968-1969
for pediatric migraine, 2243
pharmacokinetics, 1968
in pregnancy, 2317, 2318t-2321t
for premature labor, 2340
proton pump inhibitors for ulcers induced by, 1177t
risk of adverse events, 46t
risk of serious GI effects, 44t
for SLE, 1533
Nonunion, 517
Norepinephrine
for anaphylaxis, 1554b
dosing, 1871t
for pediatric resuscitation, 104t
in pregnancy, 2328
for sepsis, 1871
Norfloxacin
for diarrhea, 1235t
for infectious diarrhea, 2192t-2193t
for *P. shigelloides* gastroenteritis, 1241
for prostatitis, 1335-1336
for *Salmonella* enteritis, 1236
for traveler's diarrhea prevention, 1259
for traveler's diarrhea treatment, 1259
Noroviruses, 1249, 2190-2191
Northern copperhead *(Agkistrodon contortrix mokasen)* bite, 798f
Nose, 378. *See also under* Nasal
anatomy of, 369-370
arterial supply to, 937, 937f
examination of, 373
foreign bodies in, 770-772, 770f
clinical features of, 771
diagnostic strategies for, 771
history taking in, 771
management of, 771-772
physical examination findings, 771
techniques for removal of, 771
Nosebleeds, 937-939
Notifiable foodborne diseases and related conditions, 1237b
Notifying survivors, e43
Noxious stimulus, 32b
NT-proBNP assays, 1083
Nuchal signs, 2226
Nuclear devices, 2469-2471
Nuclear imaging
in appendicitis, 1228
with iminodiacetic acid, 1202
in systemic lupus erythematosus, 1532
Nuclear reactor incidents, 1945-1946
Nuclear terrorism, 2466
Nuclear weapons, 1945, 1946t
Nucleic acid amplification tests, 1816
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), 1765, 1766t
Nucleus pulposus, 643
Null cells, 1602
Null hypothesis, e12, e12t-e13t
NuLytely. *See* Polyethylene glycol–electrolyte solution (PEG-ELS)
Number needed to treat (NNT), e20t, e21
Nummular headache, 1396
Nursemaid's elbow (radial head dislocation), 616-617, 2258, 2258f
Nursery care, 2331, 2332b
Nursing, 2481
Nursing Home Reform Act, 891
Nutmeg, 2018
Nylen-Barany test, 164-165
Nystagmus, 928-929
abnormal, 164
clinical features of, 928-929
Nystagmus *(Continued)*
corrective, 146
differential considerations, 928-929
distinguishing characteristics of, 164, 164t
pathophysiology of, 162
positional, 164
Nystatin, 1175, 1561-1562

O
Oarsman's syndrome, 589
Oatmeal (Aveeno), 1567
Ober's test, 715
Obesity
airway evaluation in, 4-5
bag-mask ventilation in, 5-6
hypertension in, 1115
pulmonary embolism in, 1168b
Obidoxime, 2059
Observation medicine, 2481-2491
for asthma, 954
brief observation, 2362
conditions appropriate for, 2482b
in-hospital observation of appendicitis, 1230
key concepts, 2491b
principles of, 2481
Observation units, 2481
key concepts, 2491b
staffing, 2481
Observational approach, 2481-2482
Observational studies, longitudinal, e9
Obsessive-compulsive disorder
anxiety in, 1478
classification of, 1478
definition of, 1475b
pharmacologic treatment of, 1479t
Obstetric care, 300, 300f
Obstipation, 224t-225t, 261
Obtundation, 2383-2384
Obturator dislocation, 687, 688f
Obturator hernia, 1217-1218
Occlusive injury, 501
Occult blood testing, 250
Occult suicide, 1492, 1496
Occupant kinematics, 841
Occupational exposures, 1765-1766
Octreotide
for GI bleeding, 252
for hypoglycemia, 1656
for sulfonylureas, 1957t-1958t
Octyl-2-cyanoacrylates, 762
Ocular foreign bodies, 768, 769f
Ocular migraine, 2242
Ocular soft tissue disorders, 920-921
Ocular tonometry, 187
Ocular trauma, 909-918
alkali exposures, 1997
chemical injury, 819-820
complications of, 917-918
nonpenetrating, 909-916
penetrating, 190-191
Oculocephalic response (doll's eyes), 146, 346
Oculocephalogyric (caloric) testing, 146, 146f
Oculomotor cranial nerve palsy
diagnostic approach to, 179-181
muscle dysfunction, symptoms, and examination findings for, 180f
signs of, 180-181
symptoms of, 180
Oculomotor nerve (CN III), 1410t-1411t
Oculovestibular (cold water caloric) testing, 146, 146f, 346
Odds ratio, e20t
Odontalgia, atypical, 901
Odontoid fractures
with anterior dislocation, 382, 386f
in older adults, 328
type I, 385
type II, 385, 389f-390f
type III, 385, 389f-390f, 414f
Odors, 1955, 1955t
Office of Minority Health, e25

www.ketabpezeshki.com 66485457-66963820

Ofloxacin
for epididymitis, 1347-1348, 1347t
for prostatitis, 1335-1336
for STDs, 1315t
Ogilvie's syndrome, 1265
Ointments, 1558
Oklahoma City bombing, 2459t
OKT3, 2372
Olanzapine (Zyprexa), 2048t
for chemical restraint, 2418
for mood disorder, 1472-1473
for rapid tranquilization, 1463
Older adults. *See* Elder patients
Older Americans Act, 891
Olecranon bursitis, 615-616, 1524
clinical features of, 616
diagnostic strategies for, 616
management of, 616
pathophysiology of, 615-616
Olecranon fractures, 611, 612f
clinical features of, 611
diagnostic strategies for, 611
management of, 611
pathophysiology of, 611
Olfactory nerve (CN I), 1410t-1411t
Oligoanalgesia, 36
Oligomenorrhea, 274t
Oliguria, 1291
Olmesartan, 1122.e1t-1122.e2t
Omeprazole
for GERD and PUD or NSAID-induced ulcers, 1177t
for GI bleeding, 252
Omphalocele, 115
On-call physicians, e67
On-Star system (General Motors), 336
Onchocerciasis (*Onchocerca volvulus* infection), 1770t-1771t, 1780, 1780f
clinical features of, 1780
diagnostic strategies for, 1780
drug regimen for, 1772t-1775t
management of, 1780
Oncologic emergencies, 1617-1628
factors that can hinder, 1618b
key concepts, 1628b
neurologic, 1627-1628
pediatric, 2103-2104
trends in, 1618b
Oncoviruses, type C, 1740
Ondansetron (Zofran)
for nausea and vomiting, 245t, 2018
for pediatric migraine, 2244
Onychomycosis (tinea unguium), 1561
Open-book fracture, 661, 661f, 668
Operations section, 2462
Ophthalmia, sympathetic, 918
Ophthalmia neonatorum, 919
Ophthalmic drugs, 929, 930t
for acute glaucoma, 930t
classification of, 929
general considerations, 929
Ophthalmology, 909-930, 930b
Ophthalmoplegic migraine, 1387, 2242
Opiates, 32b, 2052. *See also* Opioids
Opioid creep, 814
Opioid/sedative/ethanol syndrome, 1955t, 1956
Opioids, 2052-2056
analgesics, 38-42, 39t
for abdominal pain, 42
administration of, 40
agonist-antagonist agents, 42
combined with NSAIDs and acetaminophen, 49b
intramuscular administration of, 38, 40b
nausea and vomiting with, 246
antagonists, 2055
definition of, 32b, 2052
overdose, 1955t, 1956
antidote for, 1957t-1958t, 2055
cardiovascular effects, 2054
clinical features of, 2053
dermatologic effects, 2054
diagnostic strategies for, 2054-2055
differential considerations, 2055
Opioids *(Continued)*
gastrointestinal effects, 2054
key concepts, 2056b
management of, 2055-2056, 2381
metabolic effects, 2054
neurologic effects, 2053
ophthalmologic effects, 2054
otologic effects, 2054
pathophysiology of, 2052-2053
patient disposition in, 2056
respiratory effects, 2053-2054, 2053t
supportive care for, 2055
urologic effects, 2054
vital signs in, 2419t
pharmacology of, 2052-2053
physiology of, 2052
in pregnancy, 2317-2322, 2318t-2321t
in procedural sedation and analgesia, 54
receptors, 35t
triggers for anaphylaxis, 1545
withdrawal, 2053
clinical features of, 2054
key concepts, 2056b
management of, 2055-2056
patient disposition in, 2056
Opisthorchis felineus, 1770t-1775t
Opisthorchis viverrini, 1770t-1771t
Opisthotonos, 1701
Opium, 2052
Opportunistic infections
mimicking neoplasms, 2364
prophylaxis of, 1758t
Optic disk, abnormal, 928
Optic nerve (CN II), 1410t-1411t
Optic nerve injury, 916
Optic neuritis, 926, 926f
Optic neuropathy
compressive, 926-927
ischemic, 926
metabolic, 927
toxic, 927
Oral anatomy, 895-896
Oral aphthae, 1540, 1540f
Oral cavity. *See also* Mouth
anatomy of, 895-896
examination of, 897
in sexual assault, 864-865
soft tissues of, 895
Oral contraceptives
for emergency contraception, 869t
herbal medicine interactions, 2072t-2073t
Oral feeding catheters, 2405t
Oral glucose tolerance test, 1654
Oral hemorrhage, 907
Oral intubation
awake, 12-13
without pharmacologic agents, 13
Oral medicine, 895-908
Oral pain, 900-902
of neuropathic origin, paroxysmal, 901
Oral poliomyelitis vaccine, 1718-1719, 1720t, 1737
Oral rehydration therapy
for children, 2199-2200
key concepts, 2204b
volume calculation, 2199
solutions for, 258-259, 2200t
WHO oral rehydration solution (WHO-ORS), 258-259
Oral thrush, 1561-1562
clinical features of, 1561
management of, 1561-1562
Oral ulcers, 1528t
Orange peel skin *(peau d'orange)*, 1852
Orbital cellulitis, 193t-196t
Orbital foreign bodies, 917
Orbital fractures, 378-379, 379f
Orbital tumors, 193t-196t
Orbital wall fractures, 909-910
Orbitopathy, restrictive, mechanical, 178
Orbits
examination of, 372
injury to, 909
trauma to, 909-910
Orbivirus, 1732
Orchitis, 1348-1349
bacterial, 1348
in children, 2208-2209
clinical features of, 1348
diagnostic strategies for, 1348-1349
management of, 1349
mumps, 1348
Organ system dysfunction, 1865-1867
Organ transplantation. *See* Transplantation
Organizational values, e36
Organochlorine insecticides, 2060
Organophosphate insecticides, 2057-2060
Organophosphate poisoning
antidotes for, 1957t-1958t
clinical features of, 2057-2058
complications of, 2057-2058
diagnostic strategies for, 2058
differential diagnosis of, 2058
management of, 2058-2059
odor in, 1955t
patient disposition in, 2059-2060
signs and symptoms of, 2057
treatment of, 826
Orientation, 142
Oritis-prone children, 932
Ornithine aspartate, 1195
Orofacial pain, paroxysmal, 901
Orogastric tubes, 307b
Oropharyngeal diseases
candidiasis, 1175
in HIV infection, 1760-1761
Oropharyngeal dysphagia, 1182-1183
Oropharyngeal foreign bodies, 1171
Oropharynx
anatomy of, 198, 199f
examination of, 372-373
Orotracheal rapid sequence intubation, 424
Orphaned patients, 2510
Orthomyxoviridae, 1719t, 1734-1736
Orthopedic consultation, 728b
Orthopedic infections, 1831
Orthopedic injuries
general principles, 511-533
in HIV infection, 1762
key concepts, 533b
life-threatening or limb-threatening emergencies, 521t
management of, 511
nerve injuries in, 520t
soft tissue, 526-528
treatment of, 528-533
Orthopedic surgery, 525
Orthopnea, 206
Orthostatic hypotension, 1465
Ortolani (reduction) maneuver, 2261, 2262b
Oseltamivir (Flumadine), 1721t-1722t, 1722, 1735
Osgood-Schlatter disease, 718-719
clinical features of, 718-719
diagnostic strategies for, 719
management of, 719
pathophysiology of, 718
Osgood-Schlatter syndrome, 2269-2270
Osmol gap, 2008-2009
Osmolality, 2008
Osmotic agents, 349
Osmotic diarrhea, 254, 2189
Osmotic hypothesis, 945
Osmotic laxatives, 264b, 264t-265t
Osteitis pubis, 692, 692f
Osteoarthritis (degenerative joint disease), 1510-1511
clinical features of, 1510
in hip
pathophysiology of, 675
radiographic findings in, 675, 675f
in knee, 716
management of, 1510-1511
Osteochondral lesions, 738, 738f
Osteochondritis, tibial tuberosity, 718
Osteochondritis dissecans, 709-710, 710f
Osteochondroma, femoral, 677, 677f
Osteogenesis imperfecta, 2260, 2260f
Osteoid osteoma, 677, 678f
Osteoma, osteoid, 677, 678f

www.ketabpezeshki.com 66485457-66963820

Osteomyelitis, 1831-1832, 1836-1844
  antibiotic treatment of, 1835t, 1843
  in children, 694, 1840-1841
  chronic, 1842-1843, 1843f
  chronic recurrent multifocal, 1840-1841
  classification of, 1831
  clinical features of, 1836
  clinical subsets, 1839-1843
  complications of, 1843
  cranial, 359-360
  definition of, 1831
  diabetic foot, 1842
  diagnostic imaging for, 1836-1839, 1840f
  diagnostic strategies for, 1836-1839, 1840f
  differential considerations, 1843
  in fracture, 519-520
  in hand, 568
  hematogenous, 1833
  history taking in, 1836
  laboratory testing in, 1836-1838
  magnetic resonance imaging of, 1838, 1839f-1840f
  management of, 1843-1844
  microbiology of, 1834-1835, 1835t, 1838-1839
  neonatal, 1840
  patient disposition in, 1844
  physical examination findings, 1836
  post-traumatic, 1841-1842
  radiographic findings in, 694, 695f
  radiographic progression of, 1836-1837, 1837f-1838f
  in sickle cell disease, 1842
  vertebral, 282t-283t, 1841
Osteonecrosis, 675, 710
Osteoporosis
  epidemiology of, 672
  pathophysiology of, 675
  radiographic findings, 675, 675f
Ostiomeatal complex, 975
Otic foreign bodies, 770, 770f
Otitis externa, 935
  antimicrobial therapy for, 1664t
  clinical features of, 935
  differential considerations, 935
  management of, 935
  necrotizing (malignant) external otitis, 935-936, 940b, 1664t
Otitis media, 931-935
  acute
    definition of, 931
    diagnosis of, 933, 933t
    key concepts, 940b
    management of, 933t
    prevalence of, 931
    recurrent, 934
  acute suppurative or purulent, 931
  chronic, 931-932
  chronic suppurative, 931
  clinical features of, 932
  complications of, 932
  definition of, 931
  diagnostic strategies for, 932
  differential considerations, 932
  with effusion, 931, 934
  epidemiology of, 931
  etiology of, 931-932
  intracranial complications of, 932
  intratemporal complications of, 932
  management of, 932-934
  pathophysiology of, 931
  patient disposition in, 935
  prevalence of, 931
  recurrent, 931
  safety net prescription for, 933
  treatment of, 933-934, 934t
Otolaryngology, 931-940, 940b
Otomycosis, 935
Otoscopic examination, in toddlers, 2092, 2093f
Ottawa Ankle Rules (OAR), 725-726
Ottawa Knee Rule, 702
Out-of-hospital care
  advance directive policy development for, e39b
  during air medical transport, 2445-2447
  analgesia, 48-49
  for anaphylaxis, 1551-1553
  for cardiovascular emergencies, 2439-2440
Out-of-hospital care *(Continued)*
  disaster response, 2462-2463
  disaster site organization, 2463
  for disorders of hemostasis, 1607-1608
  for electrical and lightning injuries, 1912-1913
  emergency medical services, 2439-2440
  end-of-life care, e50-e51
  under fire, 2451
  for hospice patients, e51
  initial resuscitation, 1913
  for PCP poisoning, 2020
  for radiation injury, 1950-1951
  for suicidal patients, 1496-1497
  for suicide, e51
  supportive treatments near end of life, e51
  tactical field care, 2451-2452
  for traumatic emergencies, 2440
  ultrasound applications, 2503-2504
Outliers, e16
Outpatient care
  for alcohol withdrawal, 2382
  for electrical injuries, 1914
Ovarian artery, 1356f
Ovarian cysts, 1358-1359
  clinical features of, 1358-1359
  diagnostic strategies for, 1359
  differential considerations, 1359
  imaging of, 1359
  key concepts, 1362
  laboratory testing in, 1359
  management of, 1359
  ruptured, 267t-268t
  ultrasound of, 1359, 1359f
Ovarian hyperstimulation syndrome (OHSS), 2277
Ovarian masses, 1358-1359
Ovarian torsion, 1355-1358, 1356f
  clinical features of, 1355
  CT scanning, 1356-1357, 1357f
  diagnostic strategies for, 1355-1357
  differential considerations, 1357-1358
  Doppler ultrasound imaging of, 1355-1356, 1357f
  imaging, 1355-1357, 1358b
  key concepts, 1362
  laboratory testing in, 1355
  management of, 1358
  pelvic pain in, 267t-268t
  ultrasound of, 1355, 1356f
Ovarian tumor, unruptured, 267t-268t
Ovarian vein, 1356f
Ovaries, 1355, 1356f, 1358f-1359f
Oven cleaner, 1995t
Over-the-counter sleep aids, 2081-2082
Overcrowding, 2506-2507, e61
Overdose. *See also* Poisoning; *specific drugs, ingestions*
  antidepressant, 1975-1981
  cardiovascular drugs, 1982-1993
Overdose history, 1954, 1955b
  odors in, 1955, 1955t
Oversight, 2437-2438
  federal, 2437-2438
  local, 2438
  state, 2438
Overuse syndromes, 715-716
Ovral, 869t
Ovulatory bleeding, 274t
Oxafloxin, 935
Oxamniquine, 1772t-1775t
Oxazepam (Serax), 2078t
Oxcarbazepine (Trileptal)
  drug interactions, 2407t-2408t
  for long-term anticonvulsant therapy, 1384t
  side effects of, 1383t, 2407t-2408t
Oxprenolol, 1987t
Oxycodone, 39t, 41
  for pediatric migraine, 2243-2244
  in pregnancy and lactation, 2318t-2321t
  respiratory depression associated with, 2053t
Oxygen. *See also* Oxygen therapy
  partial pressure (Po_2)
    in arterial blood (Pao_2), 945, 947
    in pulmonary contusion, 436-437
  in sepsis, 1870
  toxicity of, 1919, 2037t
Oxygen-hemoglobin dissociation curve, 1928, 1929f
Oxygen therapy
  for asthma, 949, 949t
  for carbon monoxide poisoning, 2042
  for COPD, 961-962
  for heart failure, 1084-1085
  for neonatal resuscitation, 116-117, 117t
  for pediatric cluster headaches, 2244
  for pediatric resuscitation, 104t
  for sickle cell disease, 1599
Oxygenation
  altitude effects on, 2443t
  central venous oxygen saturation ($Scvo_2$), 91-92
  for COPD, 961-962
  failure of, 3
  mixed venous oxygen saturation (Svo_2), 71
  nitric oxide–oxygen mixtures, 45
  normal oxygen saturation, in newborn, 113t
  percent arterial oxygen saturation (Sao_2), 62
Oxymetazoline, 938
Oxymorphone, 39t, 2053t
Ozone, 2037t

P

P value, e12-e13, e12t-e13t
P waves, abnormal, 1049-1050, 1049f
Pacemaker(s), 1065t
  advantages and disadvantages of, 1065t
  complications of, 1067-1068
  components of, 1064-1065
  DDD, 1065t, 1066-1067, 1066f, 1069f
  DDDR, 1065t
  failure to capture, 1068-1069, 1068b, 1069f
  five-letter code for, 1065t
  inappropriate rate, 1068b, 1069-1070
  indications for, 1064-1071, 1065b, 1065t
  key concepts, 1074b
  lead fracture, 1069
  malfunction of, 1068-1070
    advanced cardiac life support interventions for, 1071
    causes of, 1068b
    history taking in, 1070-1071
    key concepts, 1074b
    management of, 1070-1071
    patient disposition in, 1071
    physical examination findings, 1071
    pseudomalfunction, 1067, 1067f
  oversensing, 1068b, 1070, 1070f
  problems and solutions for, 2405t
  terminology for, 1064
  undersensing, 1068b, 1070, 1070f
  VVI, 1065t
    with fusion beats (pseudomalfunction), 1067, 1067f
    normal ECG patterns, 1066, 1066f
  VVIR, 1065t
Pacemaker cells, 1036f
Pacemaker syndrome, 1067-1068
Packed red blood cells, 75
  for hemolytic-uremic syndrome in children, 2222
  for ruptured AAA, 1134
  transfusion of, 77-78
Pain, 31, 32f
  abdominal, 223-231
    acute, 42
    differential considerations, 1532t
    in elderly, 2354
    evaluation of, 2482-2483
    observational approach to, 2482-2483
    opioid analgesic agents for, 42
    in parasitic infection, 1783
    in pregnancy, 2277-2278, 2293-2296
    traditional approach to, 2482
    in women, 1226t
  acute, 31, 35-36, 35t, 38
    analgesic options for, 49b
  anorectal, 1277, 1283
  in aortic dissection, 1125
  ascending tracts associated with, 34
  atypical, 1484
  back, 278-284
  background, 816
  breakthrough, 816

www.ketabpezeshki.com 66485457-66963820

Pain *(Continued)*
chest, 214-222
during dialysis, 1309
evaluation of, 2483-2484
observational approach to, 2483-2484, 2483b
traditional approach to, 2483
chronic, 35-38, 35t
analgesic options for, 49b
of malignancy, 38
treatment of, 37-38
clinical features of, 1482
complex regional pain syndromes, 523-524
conduction pathways, 31, 32f
definition of, 32b
diagnostic criteria for, 1482b
expression of, 34
facial, 1396-1397
foot, 748-749
functional back pain, 648
hindfoot pain, 748
hip
in children, 2263-2269
without obvious fracture, 677, 678b
of injection, 47, 47b
joint, 1501, 1502t
low back pain, 643-654
lower abdominal, 223
modulation of, 34
musculoskeletal, in pregnancy, 2278
musculoskeletal back pain, 643-655
neuropathic, 31, 38, 49b
paroxysmal, 901
nociceptive, 31
oral, 900-902
patellofemoral pain syndrome, 715
pathophysiology of, 31-36, 32f
pelvic
acute, in women, 266-272
posterior pelvic pain provocation test, 2278
periumbilical, 223
postextraction, 901
procedural, 816
recurrent, 38
red and painful eye, 184-197
referred abdominal pain, 225, 227f
referred back pain, 645, 647-648
reflex responses, 34-35, 35b
root canal, 900-901
of ruptured AAA, 1130-1131
scrotal, 1342-1349, 1354b
somatic, 223
vs suffering, e49
temporomandibular myofascial pain dysfunction syndrome, 901-902
transmission of, 32-34
treatment of, 37-38, 37f
upper abdominal, 223
upper back pain, 654-655
urolithiasis, 1339, 1341b
visceral, 34, 223
Pain assessment, 36, 198-199
Pain detection, 31-32
Pain management, 31-49
algorithm for, 38f
in burns, 816
in children, 48
in elder patients, 48
at end of life, e57
in femoral fracture, 681
key concepts, 49b
nonpharmacologic interventions, 48
outpatient agents for, 49b
in pediatric trauma, 311
pharmacologic therapies, 816
principles of, 36-49
for red and painful eye, 191
techniques to reduce pain of injection, 47, 47b
treatment endpoints, 49
Pain measurement, 36-37
Pain medications. *See also specific medications*
consent for medical care from patients on, e72
Pain scales, 36-37, 36f
Painful arc sign, 637-638, 638f
Painful blue leg (phlegmasia cerulea dolens), 1159
Painful rash, 1532t
Paint sniffers (“huffers”), 2033-2034, 2034f
Palatal elevation loss, unilateral, 1410t-1411t
Paliperidone (Invega), 1464, 2048t
Palivizumab
for heart disease in children, 2151, 2151b
for RSV infection, 1721t-1722t
Palliative care, e43, e47, e49-e50
conversations on, e55-e56, e56t
definition of, e49
Education for Palliative and End-of-Life Care (EPEC) curriculum, e52
Education in Palliative and End-of-Life Care for Emergency Medicine (EPEC-EM) curriculum, e47, e55, e56-e57
in emergency department, e55-e57
goals of care, e55-e56
questions for discussion of end-of-life issues, e56t
treatment options, e56-e57, e56b
Palmaris longus tendon, 539, 540f
2-PAM, 2477b
Pamidronate, 1625
Pancreas
anatomy of, 1205, 1206f
disorders of, 1205-1215, 1215b
Pancreas transplantation
for diabetes, 1665-1666
patient management, 2376
Pancreatic cancer, 1214-1215
clinical features of, 1215
diagnostic strategies for, 1215
incidence of, 1214
management of, 1215
Pancreatic enzymes, 464
Pancreatic pseudocysts, 1208, 1208f
Pancreatitis
acute, 1205-1212
abdominal pain in, 227, 227t-228t
Atlanta criteria for predicting, 1210, 1211b
clinical features of, 1208
complications of, 1208
diagnostic strategies for, 1209-1210
incidence of, 1205
key concepts, 1215b
pathophysiology of, 1205-1206
patient disposition in, 1212
alcoholic, 1205, 2386
in children, 2183-2184
clinical features of, 2183
diagnostic strategies for, 2183
differential considerations, 2183, 2184t
key concepts, 2187b
management of, 2183-2184
patient disposition in, 2184
chronic, 1205, 1212-1214
alcohol-induced, 1212
clinical features of, 1213
diagnostic strategies for, 1213-1214
differential considerations, 1214
incidence of, 1212
management of, 1214
pathophysiology of, 1213
patient disposition in, 1214
radiographic findings, 1213, 1213f
differential diagnosis of, 1211, 1211b
drug-induced, 1206, 1207b
etiology of, 1206-1208, 1207b
key concepts, 1215b
laboratory testing in, 1209-1210
management of, 1211-1212
prognosis for, 1210
radiographic studies in, 1210-1211
Ranson’s criteria for associated mortality in, 1209-1210, 1209b
vomiting with, 243t-244t
Pancreatography, endoscopic retrograde, 1214
Pandemic and All-Hazards Preparedness Act (S. 3678), 2467
Panencephalitis, subacute sclerosing panencephalitis, 1725
Panic attack, 1475b
Panic disorder, 1477
with agoraphobia, 1475b
pharmacologic treatment of, 1479t
Panic reaction
acute, 2016
patient disposition in, 2016-2017
Pantoprazole, 1177t, 1184
Papilledema, 928, 928f
Papillitis, 926, 926f
Papillomas, laryngeal, 2112
Papillomavirus infection, 1719t, 1721t-1722t, 1730-1731
Papular lesions, 1572-1576
Papular purpura, 1559t
Papules, 1559t, 1562-1564
Paracelsus, 2378
Paracentesis, US-guided, 2502-2503, 2503f
Paracetamol, 2318t-2321t
Paradoxical breathing, 306-307
Paradoxical pulse, 1626b
ParaGard T 380A IUD, 869t
Paragonimus westermani (lung fluke), 1770t-1775t, 1781
Paraguay tea, 2070
Parainfluenza
clinical features of, 1734
differential considerations, 1734
management of, 1734
viruses, 1734
Paraldehyde poisoning, 1955t
Parallelism, 571-574, 594
Paralysis
facial nerve, 1411-1413, 1417b-1418b
after intubation, 14
keraunoparalysis, 1911-1912
periodic, 1445-1446
after rapid sequence intubation induction, 12
tick paralysis, 1445, 1786t, 1807-1808
Todd’s, 1375
vocal cord, 2112
Paralytic PICE situations, 2459, 2459b
Paramedics, EMT-, 2436, 2436t
Paramethoxyamphetamine (PMA or death), 2017
Paromomycin (Humatin), 1251
Paramyxoviridae, 1719t, 1734
Paranoid personality disorder, 2427b
Paraparesis, 126-127, 1740
Parapharyngeal abscess, 974-975
clinical findings with, 975
diagnostic strategies for, 975
differential considerations, 975
key concepts, 977b
management of, 975
patient disposition in, 975
Parapharyngeal space, 896
Paraphimosis
in children, 2206, 2206f
clinical features of, 2206
key concepts, 2223b
management of, 2206
patient disposition in, 2206
reduction of, 2206, 2206f
Paraplegia, 126-127
Parapneumonic effusion, 992
Parapoxviruses, 1727
Paraquat, 2062
Parasites, 1768, 1769f
common pathogens, 2359b
geographic locations, 1770t-1771t
that cause dermatologic symptoms, 1780
that cause fever, 1776
that cause neurologic symptoms, 1778
that cause ocular symptoms, 1780
Parasitic infections, 1768-1784
cardiovascular symptoms, 1781-1782
dermatologic symptoms of, 1779-1780
drug regimens for, 1772t-1775t
drugs for, 1770t
gastrointestinal, 1250-1258
gastrointestinal symptoms of, 1782-1783
in HIV infection and AIDS, 1783-1784
in immunocompromised patients, 2363
key concepts, 1784b
neurologic symptoms of, 1776-1778
portals of entry, 1770t-1771t
presenting symptoms of, 1769-1783
pulmonary symptoms of, 1780-1781
stool examination for, 258

www.ketabpezeshki.com 66485457-66963820

Parasitic infections *(Continued)*
travel history evaluation of, 1768, 1769b
visual symptoms of, 1780
Parasuicide, 1492
Parasympathetic nervous system, 2058f
Paravaccinia virus, 1727
Paregoric, 2053t
Parens patriae, e75
Parents or legal guardians
advice to, 2238b
instruction sheets for, 2198b
minors accompanied by, e71
refusal of care or blood transfusions for minor by, e75
Parity, 2271-2272
Parking of patients, e61
Parkinson disease, 1476-1477
Parkinsonian syndrome, 2048-2049, 2053
Parkland formula, 812-813, 813t
Paromomycin
for diarrhea, 1235t
for diarrhea in AIDS, 1257t
for parasitic infection, 1772t-1775t
Paronychia, 565-566
drainage of, 565-566, 565f
management of, 565-566
pathophysiology of, 565
Parotid gland and duct, 370, 371f
Paroxysmal choreoathetosis, 2233
Paroxysmal nocturnal dyspnea, 206
Paroxysmal nocturnal hemoglobinemia, 1596
Paroxysmal pain of neuropathic origin, 901
Paroxysmal supraventricular tachycardia, 1052, 1054f
Paroxysmal torticollis, 2242
Partial breech extraction, 2342
Partial thromboplastin time, 1609
abnormal, 1612-1615
in disseminated intravascular coagulation, 1616t
Particle repositioning procedures, 168, 169f
Partner therapy
expedited (EPT), 1312
patient-delivered (PDPT), 1312
Partner violence. *See* Intimate partner violence
Partner Violence Screen (PVS), 879, 879b
Parulis, 898-899
Parvovirus (erythema infectiosum), 1571, 1719t, 1730-1731, 1731f
arthritis, 1513t
Parvovirus B19 infection, 1571, 1730-1731
Pascal's law, 1915-1916, 1916f, 1916t
Pasley, William, 1915
Pasteurella multocida infection, 786-787
prophylactic antibiotics against, 789t
risk factors for, 788
in skin infections, 1856t
Patches, 1558-1562, 1559t
Patella, 711-712
Patella alta, 711, 711f
Patellar dislocation, 525f, 712-713
clinical features of, 712-713
definition of, 525
diagnostic strategies for, 713
management of, 713
pathophysiology of, 712
Patellar fractures, 711-712
classification of, 711-712
clinical features of, 712
comminuted, 711-712
diagnostic strategies for, 712
longitudinal, 711-712
management of, 712
marginal, 711-712
pathophysiology of, 711-712
radiographic findings, 712, 712f
transverse, 711-712
Patellar tendinopathy, 1522
Patellar tendon rupture, 711, 711f
Patellofemoral pain syndrome, 715
clinical features of, 715
diagnostic strategies for, 715
management of, 715
pathophysiology of, 715
Pathogen-associated molecular patterns, 1546
Pathogens
diarrheal, in children, 2192t-2193t
in meningitis, 1453t
most common, 2359b
multidrug-resistant, 980
in neutropenia, 2360t
in transplant patients, 2368, 2369b
Patient admission. *See* Hospital admission
Patient-centered care, e28
palliative care, e55
Patient-delivered partner therapy, 1312
Patient discharge. *See* Discharge
Patient disposition, e65-e70
Patient history
focused dive history, 1922b
focused SAMPLE history, 2090, 2090b
On-Site Neurological Assessment for Diver's History form (DAN), 1923, 1924f
overdose history, 1954, 1955b
pediatric, 2090
Patient interviews
redirecting, 2424
structuring, 2424
time out during, 2424
Patient populations, e9-e10, e10f
Patient Protection and Affordable Care Act (Health Care Reform Act), 878, e26
Patient relations, e36
impaired, 2423, 2423f
pathology of, 2422-2423
stressors, e79
Patient rights, e34
Patient safety, 2505-2511
Patient searches, 2420
Patient subgroups, e15
Patient transfer. *See* Transfers
Patient values, e35
Pattern abrasions, 839
Pattern contusions, 837-839, 838f
Pattern injuries, 837, 838b
in child physical abuse, 845
in motor vehicle trauma, 841
in pedestrian collisions, 842, 843f-844f
sharp force, 839
thermal, 839
Pavor nocturnus (night terrors), 2233
Paxipam (halazepam), 2078t
Payment authorization, e64
Peak expiratory flow rate
in children, 2118
in COPD, 959
Peau d'orange (orange peel skin), 1852
Pedal stress fractures, 749
Pedestrian collisions. *See also* Motor vehicle collisions
blunt abdominal trauma in, 459
blunt trauma and associated injuries in, 290t
evaluation of, 842
evidence collection in, 844b
injury patterns in, 687
pattern injuries in, 842, 843f-844f
Pedialyte, 2200t
Pediatric assessment triangle, 2091-2092, 2091f, 2091t
Pediatric patients. *See also* Children; Infants; Neonates
general approach to, 2087-2095
key concepts, 2095b
Pediatric-ready emergency department, 2094-2095
Pediatric trauma, 305-323
abdominal, 320-322
abuse, 848
blunt, 320, 461-462, 478
epidemiology of, 459-460
history taking in, 462
penetrating, 322
airway assessment and treatment in, 305-306, 307t
airway differences, 306t
airway management in, 424
anatomic differences, 306b
blunt abdominal, 320, 461-462, 478
breathing and ventilation survey, 306-307
cardiothoracic injury, 318-320
cervical spine stabilization in, 305-306
cessation of care for, 322-323
circulation assessment and treatment in, 308, 308b
Pediatric trauma *(Continued)*
clinical features of, 305-309
diagnosis of, 309-311
disability assessment in, 308, 308b
equipment size estimates for, 307b
exposure assessment and treatment in, 308, 309t
external genitalia injuries, 497
facial, 368-369
family assessment in, 308
FAST examination, 308
femoral fractures, 693-694
femoral shaft fractures, 694
fractures, 517-518
fractures of greater or lesser trochanter, 696-697
head injury, 311-315, 355-358
hemorrhage control in, 308
hip dislocation, 693
hip fractures, 693-694
initial assessment priorities, 305-308
key concepts, 323b
laboratory testing in, 311
management of
general principles, 309-311
strategies for, 309-311
medial condyle fractures, 608
pain control in, 311
patient disposition in, 322-323
penetrating abdominal, 322
physical examination findings, 310-311
primary survey, 305-308
primary survey examination, 308
radiology, 311
reexamination of, 311
renal, 492
secondary survey, 309
spinal injury, 315-318
tasks to be completed after the secondary survey, 309b
Pediatric Triage Tape (PTT), 2460, 2460f
Pediculosis, 1573-1574
clinical features of, 1573
diagnostic strategies for, 1573
management of, 1573-1574
Pediculosis capitis, 1573
Pediculosis corporis, 1573, 1574f
Peginterferon alfa-2a, 1721t-1722t
Peginterferon alfa-2b (PegIntron), 1721t-1722t, 1723
Pelamis platurus (yellowbellied sea snake), 795
Pelvic fracture, 658f
adverse outcomes, 521t
anteroposterior compression, 661, 661f
avulsion fractures, 658f, 659-660
with blunt abdominal trauma, 476-477, 477f
bucket-handle fracture, 661
classification of, 657-658, 658b
insufficiency fractures, 660
key patterns, 657-662
lateral compression, 661, 662f
open, 662
open-book, 661, 661f
partially stable and unstable injuries (Tile types B and C), 660-662
pathologic, 660
pathophysiology of, 657-662
–related hemorrhage, 668b
stable injuries (Tile type A), 658-660, 658f
stress fractures, 660
Tile's classification of, 658b
undisplaced or minimally displaced, 658-659
unstable, 660-661
vertical sacral fractures, 661-662
vertical shear injuries, 661, 663f
Young-Burgess classification of, 657-658, 658b, 659f
Pelvic hemorrhage, 668b, 669-670
Pelvic inflammatory disease, 1324-1325
atypical, 1324
clinical features of, 1324
criteria for hospitalization, 1325
diagnostic criteria for, 1324
differential diagnosis of, 1324
key concepts, 1325b
management of, 1324-1325
pelvic pain in, 267t-268t
in pregnancy, 2298-2299

www.ketabpezeshki.com 66485457-66963820

Pelvic inflammatory disease *(Continued)*
silent, 1324
treatment of, 1325t
Pelvic pain
acute, in women, 266-272
causes of, 266, 267b
diagnosis of, 266-270, 270f
differential diagnosis of, 266, 267t-268t
epidemiology of, 266
imaging in, 269
laboratory testing in, 269
management of, 270-272, 271f
pathophysiology of, 266
pivotal findings in, 266-269
signs of, 269
symptoms of, 268-269
posterior pelvic pain provocation test, 2278
Pelvic trauma, 656-671
associated nonpelvic injuries, 665
associated pelvic injuries, 664-665
clinical features of, 663-665
diagnostic strategies for, 665-667
epidemiology of, 656
hemorrhage control in, 668-671
history taking in, 663
key concepts, 671b
management of, 667-671
penetrating, 662
physical examination findings, 664
radiographic findings, 665, 666f
Pelvic ultrasound, 2495-2496, 2495f
Pelvic vessel embolization, 2348
Pelvis
anatomy of, 656-657
bony anatomy of, 656, 657f
ligamentous anatomy of, 656, 657f
neurologic anatomy of, 657
stabilization of, 668-669
invasive, 668-669
noninvasive techniques for, 668, 668f
vascular anatomy of, 656-657, 657f
windswept, 661
Pemphigus vulgaris, 1576-1577
clinical features of, 1576-1577, 1577f
management of, 1577
Penbutolol sulfate, 1122.e1t-1122.e2t
Penetrating aortic ulcer, 1125
Penetrating brain injury (PBI), 358-359
clinical features of, 358
epidemiology of, 358
key concepts, 367
management of, 359
pathophysiology of, 358
Penetrating missile wounds, 358
Penetrating trauma
abdominal, 459
epidemiology of, 459
gunshot wounds, 473-475
history taking in, 462
observational approach to, 2486
pathophysiology of, 460-461
pediatric, 322
physical examination findings, 463
stab wounds, 471-473
traditional approach to, 2486
axillary artery pseudoaneurysms after, 502f
cardiac injury, 448
conditions that may occur after, 448
chest trauma
to children, 318
emergency department thoracotomy algorithm for, 294f
observational approach to, 2487
traditional approach to, 2487
esophageal perforation from, 456-457
to eye, 916-918
to face, 371, 372f
head injury. *See* Penetrating brain injury (PBI)
indications for laparotomy after, 471t
neck trauma, 421
hard signs of, 423b
incidence of, 422t
mandatory vs selective exploration of, 425
soft signs of, 423b
vascular, 427-429
Penetrating trauma *(Continued)*
ocular, 190-191
pelvic, 662
penile, 496
peripheral vascular injury, 500-501
popliteal artery injury, 509
in pregnancy, 297-298
renal, 493-494
Penetrating traumatic cardiac arrest, 448b
Penetration syndrome, 772
Penicillamine
for lead poisoning, 1957t-1958t, 2027-2028, 2028t
for radiation injury, 1952t
Penicillin
for acute rheumatic fever, 2165
for bone and joint infection, 1835t
for dental infection, 900
for diphtheria, 1695-1696
for immunocompromised patient, 2361t
for impetigo, 1564
for infection in sickle cell disease, 2104
for intraoral lacerations, 906
for Lyme disease, 1100
penicillinase-resistant, 1835t
in pregnancy, 2318t-2321t, 2325
for skin and soft tissue infection, 1854t
Penicillin G
for anthrax, 2473b
for bacterial endocarditis, 1108b
for diphtheria, 1696
for Lyme disease, 1793-1794, 1794t
for meningitis, 1709
for meningococcemia, 1713
for pharyngitis, 968
for pneumococcemia, 1709
Penicillin V
for dental abscess, 899
for pharyngitis, 968
Penicillin VK
for acute necrotizing ulcerative gingivitis, 900
for pericoronitis, 902
for pharyngitis, 968
for scarlet fever, 1572
Penile entrapment, 2207-2208, 2207f
Penile trauma, 494-498, 497f
clinical features of, 496-497, 497f
diagnostic strategies for, 497
fracture, 496, 497f, 498
management of, 498
tourniquet injuries, 2207-2208
Penis
anatomy of, 494-496, 496f
disorders of, in children, 2205-2208
foreign bodies in, 783
herpes lesions on, 1313, 1313f
Pentachlorophenol, 2061
Pentamidine isethionate, 1772t-1775t
Pentobarbital
benefits and adverse effects, 55t
for increased ICP, 314t
in procedural sedation and analgesia, 54t-55t, 57, 60t
for seizures, 158t-159t
for status epilepticus, 158t-159t, 1381t, 1382
for status epilepticus in children, 2238
Peptic ulcer disease, 243t-244t, 1178-1180
antacids for, 1184
causes of, 1178-1179, 1178b
clinical features of, 1179
complications of, 1179
diagnostic strategies for, 1180
differential considerations, 1180
histamine receptor antagonists for, 1177t
in infants and children, 1179
key concepts, 1185b
management of, 1180
proton pump inhibitors for, 1177t
symptoms of, 1179
Pepto-Bismol (bismuth subsalicylate)
for diarrhea, 260
for *H. pylori* infection, 1180
for prevention of traveler's diarrhea, 1259
Peptostreptococcus infection
in pneumonia, 979
in skin infections, 1856t
Percutaneous coronary intervention
for acute coronary syndrome, 1030-1031
delayed, 1026
facilitated, 1031
maximal allowable times, 1031
rescue, 1030-1031
for STEMI, 1031
waiting times, 1031
Percutaneous transhepatic cholangiography, 1203
Percutaneous transluminal angioplasty, peripheral, 1143
Perforating wounds, 358
esophageal, 455-458, 1172-1173
of viscus, 227, 227t-228t
Performance-shaping factors, 2507
Perfusion pressure, 1870
Perfusion status, 71
Perianal abscesses, 1281-1282, 1281t
Perianal strep infection, in infants, 852, 853f
Periapical abscess, 897, 898f
Pericardial disease, 1091-1098. *See also* Pericarditis
Pericardial effusion, 1095
clinical features of, 1095
diagnostic strategies for, 1095
etiology of, 1095
ultrasound detection of, 2496, 2496f
Pericardial rub, 217t-218t
Pericardial rupture, 447
Pericardial tamponade
acute, 448-451
anatomy of, 448-449
clinical features of, 139t, 449
diagnostic strategies for, 449
ED management of, 450
epidemiology of, 448
management of, 449-451
out-of-hospital care, 449-450
pathophysiology of, 448-449
prognosis for, 451
Pericardiocentesis, 1627
Pericarditis, 1002, 1091-1098
acute
ECG findings, 1092, 1092f
ST segment-T wave morphology in, 1004, 1005f
chest pain in, 220t-221t
in children, 2161
clinical features of, 2161
management of, 2161
clinical features of, 1091
complications of, 1093
connective tissue disorder–related, 1094
constrictive, 1097-1098
clinical features of, 1097
diagnostic strategies for, 1097
differential considerations, 1098
etiology of, 1097
management of, 1098
pathophysiology of, 1097
diagnostic strategies for, 1091-1093
ECG findings, 1009, 1010f, 1529, 1530f, 2161, 2162f
epidemiology of, 1091
etiology of, 1091, 1092b, 1097
and heart failure, 1078
iatrogenic, 1097
idiopathic, 1091-1093
infectious causes of, 1094
key concepts, 1105b
management of, 1093
neoplastic, 1094
causes of, 1094
clinical features of, 1094
diagnostic strategies for, 1094
management of, 1094
pathophysiology of, 1094
patient disposition in, 1094
pathophysiology of, 1091
patient disposition in, 1093
post-MI, 1093
postinjury, 1093-1094
clinical features of, 1094
management of, 1094
patient disposition in, 1094

www.ketabpezeshki.com 66485457-66963820

Pericarditis *(Continued)*
purulent, 1096
clinical features of, 1096
diagnostic strategies for, 1096
epidemiology of, 1096
etiology of, 1096
management of, 1096
pathophysiology of, 1096
patient disposition in, 1096
radiation-induced, 1094
risk factors associated with, 216b
in systemic lupus erythematosus, 1529
tuberculous, 1096-1097, 1813
uremic, 1093
clinical features of, 1093
complications of, 1093
diagnostic strategies for, 1093
etiology of, 1093
management of, 1093
patient disposition in, 1093
workup and treatment for, 1529t
Pericardium, 1091
Pericoronitis, 902
Perihepatitis, 1324
Perilunate dislocation, 580-581, 581f
Perindopril, 1122.e1t-1122.e2t
Periodic paralysis, 1445-1446
clinical features of, 1445
diagnostic strategies for, 1445
familial, 1445
management of, 1445-1446
thyrotoxic, 1445-1446
Periodontal disease, 896, 900
Periodontitis, 900
Periodontium, 895-896
Perioral tremors (rabbit syndrome), 2048-2049
Periorbital cellulitis, 193t-196t
Periosteal new bone formation, 2260
diagnostic strategies for, 2260
differential considerations, 2260-2261
Peripartum cardiomyopathy, 1103-1104, 2350
clinical features of, 1104, 2350
diagnostic strategies for, 1104
epidemiology of, 1103-1104
etiology of, 1103-1104
management of, 1104, 2350
patient disposition in, 1104
Peripatellar tendinitis, 715
Peripheral arterial aneurysms, 1147-1149
infected, 1148-1149
lower extremity, 1147
upper extremity, 1147
visceral, 1147-1148
Peripheral arteriovascular disease, 1138-1156
angiographic findings, 1142
assessment of, 1142
clinical features of, 1140-1142
diagnostic strategies for, 1142-1143
fibrinolytic therapy for, 1143
history of, 1140-1141
hyperbaric therapy for, 1144
key concepts, 1156b
management options, 1143-1144
invasive therapy, 1143-1144
noninvasive therapy, 1143
pathophysiology of, 1138-1140
physical examination findings, 1141-1142
Peripheral arteriovenous fistulae, 1152
differential diagnosis of, 1152
management of, 1152
Peripheral nerve disorders, 1428-1440
approach to, 1429f
clinical features of, 1429-1440
epidemiology of, 1428
evaluation of, 1428
key concepts, 1440b
pathophysiology of, 1428-1429
Peripheral nerve fibers, 32, 33t
Peripheral nervous system, 1428, 1429f
Peripheral neuropathy
asymmetrical distal, 1433, 1433b
asymmetrical proximal, 1433, 1433b
diabetic, 1666b
diagnostic testing for, 1439b, 1440
nonemergent causes of, 127b
Peripheral neuropathy *(Continued)*
patterns and prototypes, 1430t
type 1, 1430-1431, 1430t
type 2, 1430t, 1431-1433
type 3, 1430t, 1433
type 4, 1430t, 1433-1438
type 5, 1430t, 1438
type 6, 1430t, 1439
type 7, 1430t, 1439-1440
Peripheral percutaneous transluminal angioplasty, 1143
Peripheral smear
in anemia, 1588
in disseminated intravascular coagulation, 1616t
normal, 1588f
Peripheral vascular injury, 500-510
blunt trauma, 501
clinical features of, 502-504
diagnostic strategies for, 504-506
epidemiology of, 500
high-risk injuries, 503
history taking in, 503-504
key concepts, 510b
late complications of, 507
lower extremity injuries, 508-509
major injuries, 506-507
minor injuries, 507
nonocclusive, 501-502
occlusive, 501
pathophysiology of, 500-502
patient disposition in, 509
penetrating trauma, 500-501
physical examination findings, 504
transection, 501
treatment of, 506-507
upper extremity injuries, 507-508
Perirectal abscesses, 1281-1282
Peritalar dislocations, 739
Peritendinitis, calcific, 676-677
Peritendinitis crepitans, 589
Peritoneal dialysis, 1306-1307, 1310-1311
Peritoneal lavage. *See* Diagnostic peritoneal lavage (DPL)
Peritoneal violation
in gunshot wounds, 474
in stab wounds, 472
Peritoneum
dependent spaces in, 2494-2495, 2495f
methods for assessing intactness of, 472
Peritonitis
bacterial, 1195-1196
in tuberculosis, 1821
Peritonsillar abscess, 971-972, 972f
pediatric, 2110
Peritonsillar cellulitis, 202, 971-972
Peritonsillitis, 971-972
clinical features of, 972, 972f
diagnostic strategies for, 972
differential considerations, 972
management of, 972
patient disposition in, 972
Periumbilical pain, 223
Permethrin (Nix), 1808
for pediculosis, 1573-1574
for pruritus ani, 1285
for pubic lice, 1323
Permissive hypotension, 292
Peroneal nerve, 699
Peroneal tendon dislocation or tear, 733
Perphenazine, 2048t
Perseverations, 1461
Persistent fetal circulation, 112
Personal respiratory protection, 1829
Personal safety, resident, e83
Personality disorders, 1462
antisocial, 1489, 2427b
borderline, 1472, 2427b
commonly encountered, 2426-2430, 2427b
dependent, 2427b
difficult patients, 2422
histrionic, 2427b
narcissistic, 2427b
Personnel
disaster response plan, 2464
grief reactions in staff, e55
Personnel *(Continued)*
observation unit staffing, 2481
procedural sedation and analgesia (PSA) personnel, 52
security personnel, 2420
standby personnel, 2450
Perthes' disease, 672, 696, 696f
Pertussis, 1696-1699, 2133
acute treatment of, 1698-1699
catarrhal phase, 1697
clinical features of, 1697-1698
complications of, 1698, 1698b
convalescent phase, 1697-1698
diagnostic strategies for, 1698
differential considerations, 1698
diphtheria, tetanus, and pertussis vaccination schedule for, 1703t
epidemiology of, 1696, 1697f
etiology of, 1696
historical perspective on, 1696
immunization against, 1699
incidence of, 1696, 1697f
key concepts, 1717b
management of, 1698-1699
paroxysmal phase, 1697-1698
pathophysiology of, 1696-1697
symptoms and signs of, 1697-1698
vaccination against, 1699, 1703t
Pertussis vaccine, 1696
Pes anserinus (goose foot), 698, 716
Pesticides, 2057-2065, 2065b
Petechiae, in children, 2103, 2227
Petrositis, 936
Peyote, 2017
Peyote cactus *(Lophophora williamsii)*, 2017, 2017f
pH
in pregnancy, 2300
urinary, 1338
of water, 1888, 1888f
Phagocytes, granulocytic, 2358
Phalangeal fractures
in foot, 745-747
clinical features of, 746
diagnostic strategies for, 746
management of, 746-747
pathophysiology of, 745-746
patient disposition in, 747
radiographic findings in, 746, 746f
in hand
complications of, 549
correction of, 548, 548f
management of, 548-549
proximal and middle, 547-549
Salter-Harris type III, 2250, 2253f
Salter-Harris type IV, 2250, 2253f
Phalen's test, 588-589, 588f
Pharmacologic mydriasis, 927-928
Pharmacologic violence, e2
Pharmacology. *See also* Drugs; *specific drugs, classes*
in children, 2088
in elders, 2351-2353
of hypothermia, 1890-1891
of immunosuppression, 2370-2372
of suicidal behavior, 1499
Pharyngeal foreign bodies, 776-778
diagnostic strategies for, 777-778
history taking in, 777
management of, 778
physical examination findings, 777
Pharyngitis, 198, 965-968
acute, 968
adenoviral, 965
anaerobic, 966
bacterial, 199-200, 965
C. trachomatis, 966
candidal, 966
chronic, 967
clinical features of, 965-966, 966f
diagnostic strategies for, 966-967
differential considerations, 967
etiology of, 965
gonococcal, 966
key concepts, 977b
management of, 967-968
pathophysiology of, 198

www.ketabpezeshki.com 66485457-66963820

Pharyngitis *(Continued)*
patient disposition in, 968
syphilitic, 966
tuberculous, 966
viral, 199-200
causes of, 965
clinical features of, 965
Pharyngoesophageal trauma, 425-426
clinical features of, 425
diagnostic strategies for, 425-426
epidemiology of, 425
management of, 426
pathophysiology of, 425
Pharyngomaxillary space, 974
Pharynx, 198
Phencyclidine (PCP), 1477, 2018-2019
Phencyclidine (PCP) abuse
clinical features of, 2019
diagnostic strategies for, 2019
differential considerations, 2019-2020
emergency department management of, 2020
out-of-hospital care for, 2020
patient disposition in, 2020
Phenergan (promethazine), 245, 245t
Phenobarbital
for children, 2240t
drug interactions, 2407t-2408t
hepatic injury, 1197t
for long-term anticonvulsant therapy, 1384t
for seizures, 158t-159t, 159
for seizures in neonates, 2236
side effects of, 1383t, 2407t-2408t
for status epilepticus, 158t-159t, 159, 1381t, 1382
for status epilepticus in children, 2237f, 2238
Phenols, 756t, 822
polyethylene glycol therapy for exposure to, 822
systemic toxicity of, 822
Phenothiazines
with anticholinergic effects, 1970, 1971b
exposure to, 2047
in pregnancy, 2329
Phenoxymethylpenicillin (penicillin V), 899
Phentolamine
for cocaine-induced hypertensive emergency, 2002-2003
for cocaine-related chest pain, 2003
hemodynamic effects, 1118t
for hypertension, 1119t
for hypertensive emergencies, 2221t
Phenylbutazone, 1968, 2390t
Phenylephrine (Neo-Synephrine), 930t, 1871
for anaphylaxis, 1554b
dosing, 1871t
duration of action, 191t
for nosebleed, 938
in pregnancy, 2328
Phenytoin (Dilantin)
alcohol interactions, 2384, 2390t
for children, 2240t
contraindications to, 1662
for digitalis toxicity, 1986
drug interactions, 2407t-2408t
hepatic injury, 1197t
for long-term anticonvulsant therapy, 1384t
for seizure prophylaxis, 350
for seizures, 158t-159t, 159
side effects of, 1383t, 2407t-2408t
for status epilepticus, 158t-159t, 159, 1381t, 1382, 2408-2409
for status epilepticus in children, 2237f
Pheochromocytomas, 1476
Phimosis
in children, 2206
clinical features of, 2206
key concepts, 2223b
management of, 2206
patient disposition in, 2206
pHisoHex (hexachlorophene), 756t
Phlebotomus, 1779
Phlegmasia cerulea albens, 1147
Phlegmasia cerulea dolens (painful blue leg), 1159
Phlegmonous gastritis, acute, 1177-1178
Phobia, 1477-1478
pharmacologic treatment of, 1479t
social, 1475b, 1477-1478, 1479t
specific, 1475b
Phosgene ($COCl_2$) (dichloroformoxime), 824-825, 825t, 2037t, 2478
smoke bombs, 825
Phosphatidylethanol, 2380t
Phosphene (PH_3), 824-825, 2037t
Phosphodiesterase inhibitors, 1089
Phosphorus, 822-823
ethanol effects on, 2388t
for hypophosphatemia, 1651
Phosphorus deficits, 1657, 1657t
Photographic documentation, of sexual assault findings, 866-867, 867b
Photosensitivity, 1528t
Phototherapy, for infants, 2170f-2171f
Phthirus pubis, 1323
Phthisis, 1809
Physalia physalis (Portuguese man-of-war), 806
Physical abuse
child abuse, 845-848
diagnostic strategies for, 850-851
differential considerations, 851-852
incidence of, 846t
signs and symptoms of, 849-850, 849f
definition of, 886
elder abuse, 885
intimate partner violence, 873
questions to ask about, 887b
signs of, 888, 888b, 888f
Physical assault, 836-839
Physical barriers, 2356
Physical deficits, 2353
Physical disability, 2400-2413
Physical examination
in blunt abdominal trauma, 475t
in elders, 2353-2354
findings indicating causes of cardiac arrest and complications of therapy, 90t
in gastrointestinal bleeding, 249-250
in intimate partner violence, 876, 883t
knee examination, 700, 700b
pediatric, 2092
secure rooms for, 2420-2421
sexual assault examination, 863-867
documentation of findings, 863-864, 863b
wound evaluation, 753
Physical fitness, physician, e82
Physical restraints, 1465b, 2415-2416
Physical status, 52t
Physician Orders for Life-Sustaining Treatment (POLST) orders, e49, e50-e51, e51
Physicians
attitudes of, 1485
burnout in, e80
family relationships of, e82
impairment of, e80-e81
negative behaviors of, 2425
negative reactions of, 2425
negative self-perceptions of, 2425
observation unit staffing, 2481
on-call, e67
patient communication, e24
patient relations, 2422-2423, e36
physical fitness of, e82
preparation for delivering bad news, e52-e53
relaxation and renewal, e82
residency training, e82-e84
response to risky situations, e44-e45
role in informed consent, e70-e71
social relationships of, e82
as surrogate decision makers, e41
wellness issues, e79-e85
wellness strategies for, e81-e82, e81b
Physics
laws of, 1915-1916, 1916t
of ultrasound, 2493
Physostigmine
for anticholinergic overdose, 1955-1956, 1957t-1958t, 1973
in pregnancy, 2318t-2321t, 2324
Phytobezoars, 779
Phytodermatitis, 851-852, 852f
Phytolacca americana (pokeweed), 2069, 2069f
Phytophotodermatitis, 851-852, 852f
Picaridin, 1808
PICE. *See* Potential injury-creating event
Pick's disease dementia, 1406
Picornaviridae, 1719t
Piece of pie sign, 581
Piedmont fracture, 512t-513t
Pig-bel *(enteritis necroticans)*, 1244
Pig bites, 787, 788t-789t
Pigment-induced acute kidney injury, 1298b
Pigment stones, 1200, 2186
Pill esophagitis, 1174
clinical features of, 1174
management of, 1175
Pilocarpine, 922, 930t
Pilon fractures, 730-731, 730f
complications of, 730-731
management of, 730
pathophysiology of, 730, 730f
Pilonidal disease, 1283
Pilosebaceous follicle infections, 1859
Pimozide, 2048t
Pinch-off syndrome, 1153
Pindolol, 1987t, 1122.e1t-1122.e2t
Ping-pong fractures, 357-358
Pinguecula, 919
inflamed, 193t-196t
Pink puffers, 958. *See also* Emphysema
Pinkeye. *See also* Eye(s), red and painful
typical viral, 187
Pinworm *(Enterobius vermicularis)*, 1783
drug regimens for, 1772t-1775t
Pioglitazone, 1665t
Piperacillin-tazobactam (Zosyn)
for abdominal trauma, 471
for diabetic foot infection, 1664t
in immunocompromised patients, 2361t
for pneumonia, 984-985, 985t
for toxic shock syndrome, 1568
Piperazines, 2017-2018
Piroxicam, 44t
Pisiform, 570
Pisiform fractures, 578, 579f
Pit viper bites, 797
antivenin dosage for, 799t
Pit vipers, 795, 807b
Pitcher's elbow, 1521
Pittsburgh Knee Rule, 702
Pityriasis rosea, 1562
Pivot shift test, 701
Placenta
drug transfer across, 2316
removal of, 2348
trauma-related injury to, 298-299
Placenta accreta, 2348
Placenta increta, 2348
Placenta percreta, 2348
Placenta previa, 2289-2290
Placental abruption or abruptio placentae, 299, 2288-2289
clinical features of, 299, 2289
differential considerations, 2289
management of, 299
Placental separation, 298-299
Plague, 2474-2475
bubonic, 2474, 2474f
differential diagnosis of, 2474
pneumonic, 2474
septicemic, 2474
treatment of, 2474-2475, 2475b
Plan B One-Step, 869t
Planning
for death, e53
disaster response, 2463-2464
comprehensive, 2463-2464
hospital disaster response plan, 2463
resource management for, 2463-2464
Planning section, 2463
Plant-associated toxins, 255b-256b
Plantar fascial rupture, 748
Plantar fasciitis, 748
Plantar flexion, of ankle, 723
Plantaris strain and rupture, 721-722

www.ketabpezeshki.com 66485457-66963820

Plants, 2066
as drugs of abuse, 2066
herbal, 2070-2073
identification of, 2066-2070
key concepts, 2075b
unintentional childhood exposure to, 2066
Plaques, 1558-1562, 1559t
Plasmodium falciparum, 1770t-1771t, 1780
Plasmodium malariae, 1770t-1771t
Plasmodium ovale, 1770t-1771t
Plasmodium vivax, 1770t-1771t
Plaster splints, 529
Plastic deformation, 593-594, 594f, 2250
Platelet-activating factor, 1549
Platelet count, 1608, 1616t
Platelet disorders, 1609-1612
adhesion defects, 1611
aggregation defects, 1612
alcohol-induced, 2389
approach to, 1609
differential diagnosis of, 1610b
of increased destruction, 1610-1611
key concepts, 1616b
release defects, 1611-1612
storage pool syndromes, 1611-1612
Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) risk model, 1000
Platelet transfusion, 78, 1612
for pediatric trauma, 310
Platelets, 1606, 1607b
Platysma muscle, 422
Plesiomonas shigelloides gastroenteritis, 1241
antibiotic therapy for, 1235t
clinical presentation of, 1241
diagnostic strategies for, 1241
epidemiology of, 1234t, 1241
management of, 1241
pathophysiology of, 1241
Pleural disease, 988-996
Pleural effusions, 992-996
causes of, 993, 993b
clinical features of, 994-995
exudates, 993
key concepts, 996b
management of, 995-996
outcome, 996
pathophysiology of, 993-994
radiographic findings, 994, 995f, 2498-2499, 2498f
subpulmonic, 996b
transudates, 993
in tuberculosis, 1819
Pleural fluid, 993, 993f
Pleural inflammation, 992-996
Pleural rub, 217t-218t
Pleurisy, 992
Pleuritic chest pain, 1532t
Pleuritis, 992
in SLE, 1529, 1530f
workup and treatment for, 1529t
Pleurodynia, 1732
Plexopathies, 1433
Plica syndrome, 716
Plicae, 716
Pliny, 1785
Pluronic F-68 detergent, 756t
Pneumococcal polysaccharide, 1709
Pneumococcal vaccine, 1458, 1710
recommendations for, 1710, 1710b
Pneumococcemia, 1707-1710
acute treatment of, 1709
clinical features of, 1708
complications of, 1708
diagnostic strategies for, 1709
differential considerations, 1709
epidemiology of, 1707-1708
etiology of, 1708
historical perspective, 1707
incidence of, 1707
invasive pneumococcal disease, 1707
key concepts, 1717b
management of, 1709
pathophysiology of, 1708
patient disposition in, 1709-1710
symptoms and signs of, 1708
Pneumococcemia *(Continued)*
treatment strategy for, 1709
vaccination against, 1710
Pneumocystis jiroveci (formerly *Pneumocystis carinii*) pneumonia (PCP), 979, 1751, 1759f-1760f, 1781
in HIV infection, 1758-1759, 1759t-1760t
in immunocompromised patients, 2363
in pneumonia, 979
prevention of, 1758t
radiographic findings, 981-982, 982f, 2131, 2131f
after transplantation, 2370, 2370f
Pneumomediastinum
management of, 1926
spontaneous, 991
Pneumonia, 978-987
antibiotic management of, initial, 1872t
aspiration, 2133
atypical, 980
bacterial
in children, 2130-2131, 2135t
differential considerations, 1817
causative agents, 978-980
in children, 2129-2137
antibiotic treatment of, 2131, 2132t
clinical features of, 2130
complications of, 2135-2136
diagnostic strategies for, 2134
differential considerations, 2134-2135
epidemiology of, 2129
history taking in, 2130
infection rates, 2129
laboratory testing in, 2134
management of, 2136-2137
pathophysiology of, 2130
patient disposition in, 2136-2137
physical examination findings, 2130
radiographic findings, 2134, 2134f
symptoms and signs of, 2130
syndromes, 2135t
chlamydial, 2132-2133, 2135t
clinical features of, 979-980
community-acquired, 978
antimicrobial treatment of, 984-986, 985t
epidemiology of, 978
guidelines for management of, 983
outpatient treatment of, 984, 984t
severe, 986, 987b
CURB-65 rule for, 986
diagnostic strategies for, 981-983
differential diagnosis considerations, 983-984
drugs for treatment of, 1721t-1722t
fungal, 979
health care–associated, 980, 985
with HIV infection, 1818
in immunocompromised host, 2133-2134
in infants, 2136-2137
key concepts, 987b
management of, 984-986
mycoplasmal, 2132, 2135t
noninfectious causes that may present as, 2135b
observational approach to, 2489-2490, 2490b
patient disposition in, 986-987
Pneumocystis. See Pneumocystis jiroveci (formerly *Pneumocystis carinii*) pneumonia (PCP)
radiographic findings, 981f-982f, 982-983
scoring system for mortality prediction, 986, 986t
in SLE, 1530
staphylococcal
in children, 2130-2131, 2131f
radiographic findings, 2130-2131, 2131f
syndromes, 2135t
traditional approach to, 2489
viral, 979
in children, 2131, 2135t
workup and treatment for, 1529t
Pneumonia Severity Index (PSI), 2489-2490, 2490t
Pneumonic plague, 2474
Pneumonitis
drugs for treatment of, 1721t-1722t
hydrocarbon toxicity, 2035, 2035f
Pneumopericardium, 1097
clinical features of, 1097
diagnostic strategies for, 1097
etiology of, 1097
Pneumopericardium *(Continued)*
management of, 1097
pathophysiology of, 1097
Pneumothorax, 437-440
catamenial, 988
chest pain in, 220t-221t
clinical features of, 438
closed, 437, 437f
communicating, 437-438, 438f, 440
definition of, 988
diagnostic strategies for, 438-439
epidemiology of, 437
key concepts, 996b
management of, 439-440
occult, 439, 439f
open, pediatric, 319
pathophysiology of, 437-438
pediatric, 319
radiographic findings, 989, 2498-2499, 2498f
risk factors associated with, 216b
simple, 437, 437f, 439-440
size determination of, 989, 990f
spontaneous, 988-992
clinical features of, 989-991
definition of, 988
incidence of, 988
key concepts, 996b
management of, 991-992
outcome, 992
pathophysiology of, 988-989
primary, 988
secondary, 988-989, 989b, 996b
tension, 438, 438f, 2451-2452
clinical features of, 989
management of, 440
pathophysiology of, 988, 989f
pediatric, 319
radiographic findings in, 989, 990f
in tuberculosis, 1812, 1813f
types of, 437
Podagra, 1508-1509
Podofilox, 1319, 1730
Podophyllin, 1319
Poikilocytosis, 1594, 1594f
Poinsettia *(Euphorbia pulcherrima)*, 2068
Point compression devices, 2451
Poiseuille's law, 108, 1077
Poison control centers, 818, 1963
Poison hemlock *(Conium maculatum)*., 2067, 2068f
Poison hotline, 1959
Poison ivy, 1572-1573
clinical features of, 1572
contact dermatitis secondary to, 1572f
management of, 1572-1573
Poisoning. *See also* Overdose; *specific drugs, ingestions*
consultation for, 1959
general approach to, 1954-1959
initial approach, 1954-1955
key concepts, 1959b
patient disposition in, 1959
Poisonous animals, 794
Pokeweed *(Phytolacca americana)*, 2069, 2069f
Police blood alcohol tests, e62-e63
Police surgeons, 828
Policy
advance directive, e39b
emergency department, e63
for institutional improvement, e30b
Polio vaccine, 1720t
Poliomyelitis, 1737
clinical features of, 1737
differential considerations, 1737
management of, 1737
Poliovirus, 1737
Polonium-210, 2469
Poloxamer 188, 1599
POLST orders. *See* Physician Orders for Life-Sustaining Treatment
Polyarteritis nodosa, 1539-1540
Polyarthritis, chronic, 1513-1517
Polyarticular arthritis, acute, 1511-1513
Polycarbophil (Fibercon), 264t-265t
Polychlorinated bisphenol (hexachlorophene), 756t
Polychondritis, relapsing, 1515

www.ketabpezeshki.com 66485457-66963820

Polycythemia, 1600-1602
apparent, 1601b
clinical features of, 1601, 1601f
definition of, 1600
differential diagnosis of, 1601-1602
key concepts, 1605b
management of, 1602
pathophysiology of, 1601
patient disposition in, 1602
secondary, 1601b, 1602
Polycythemia vera, 1601f
diagnostic criteria for, 1602b
primary, 1601
treatment of, 1601-1602
Polyethylene glycol therapy, 822
Polyethylene glycol–electrolyte solution (PEG-ELS) (CoLyte, NuLytely, GoLYTELY, MiraLax)
for beta-adrenergic blocker overdose, 1988
for constipation, 264t-265t
for iron ingestion, 2025
Polymenorrhea, 274t
Polymerase chain reaction (PCR) testing, 1454-1455
in herpes, 1314
in meningitis, 2228
Polymyalgia rheumatica, 1392, 1517
Polymyositis, 1445
clinical features of, 1445
diagnostic strategies for, 1445
HIV-related, 1763
management of, 1445
Polymyxin B, 824, 935
Polymyxin-trimethoprim, 930t
Polyneuropathy
alcoholic distal symmetrical, 1432
diabetic distal symmetrical polyneuropathy, 1431-1432
distal sensorimotor, 1432b
distal symmetrical, 1431-1433
Polyomaviridae, 1719t, 1737
Polypharmacy, 2351
Polytetrafluoroethylene (PTFE) vascular shunts, 506-507
Polythiazide, 1122.e1t-1122.e2t
Polyunsaturated fatty acids, 1089
Pontiac's Rebellions, 2469
Popliteal artery, 699
Popliteal artery aneurysms, 1147, 1156b
Popliteal artery injury, 509
Popliteal cyst (baker's cyst), 717, 717f
Popliteal fossa, 699
Popliteal vein injury, 509
Popliteus muscle, 716
Popliteus tendinitis, 716
Porcelain gallbladder, 1204
Portuguese man-of-war *(Physalia physalis)*, 806
Posaconazole, 1561-1562, 1664t
Positional testing, 164-165
Positional vertigo, 162
Positioning
in dyspnea, 206
fetal, 2333
for rapid sequence intubation, 12
Positive end-expiratory pressure, 25
applied, 25
intrinsic (iPEEP or auto-PEEP), 25, 28, 954
Positive predictive value, e20t
Positive pressure breathing, 23
Positive-pressure ventilation, 28
Post-MI syndrome, 1002
Post-term infant, 2272
Post-test odds, e20t
Post-test probability, e20t
Post-trauma amnesia, 352
Post-traumatic headache, 1394
Post-traumatic infected false aneurysms, 1148t
Post-traumatic leptomeningeal cysts, 358
Post-traumatic pseudoaneurysms, 1149
Post-traumatic stress disorder
anxiety in, 1477
definition of, 1475b
pharmacologic treatment of, 1479t
Postanal abscesses, 1281t, 1282
Postanginal septicemia, 975
Post–cardiac arrest syndrome, 81
Postconcussive syndrome, 354
Post–dural puncture headache, 1395
clinical features of, 1395
pathophysiology of, 1395
treatment of, 1395
Posterior arch, 656
Posterior arch fractures, 661, 663b
Posterior cruciate ligament, 698
Posterior cruciate ligament injury, 713-714
management of, 714
testing for, 700-701
Posterior drawer test, 701
Posterior elbow dislocation, 613-614, 613f
clinical and radiographic features of, 613
complications of, 614
management of, 613-614
Posterior glenohumeral dislocations, 642b
Posterior malleolar fractures, 728-729
Posterior neural arch fracture, of atlas (C1), 393, 393f
Posterior pelvic pain provocation test, 2278
Posterior sag sign test, 701
Posterior segment injuries, 916
Posterior vitreous detachment, 925
Posteroinferior cerebellar artery syndrome, 401
Posterolateral corner, 698-699
Postictal period, 1375
Postictal state, 159, 1379-1380
Postinfarction sclerodactyly, 523
Postmenopausal bleeding, 274t
Postmortem teaching, e43-e44
Postpartum depression, 1470, 2350
clinical features of, 2350
management of, 2350
Postpartum endometritis, 2350
clinical features of, 2350
management of, 2350
Postpartum hemorrhage, 2347-2349
clinical features of, 2347-2349
differential considerations, 2347
management of, 2348-2349
Postpartum thyroiditis, 1678
Postprandial hypoglycemia, 1656
Postrenal (obstructive) acute renal failure, 1296, 1296b
Poststreptococcal glomerulonephritis, in children, 2216
clinical features of, 2216
diagnostic strategies for, 2216
differential considerations, 2216
management of, 2216
patient disposition in, 2216
Poststreptococcal reactive arthritis, 1512
Postural strangulation, 429
Posturing
decerebrate, 346
decorticate, 346
in head injury, 346
Postvoid residual, 649
Potassium
in diabetic ketoacidosis, 1658-1659, 1658t
ethanol effects on, 2388t
in hyperglycemic hyperosmolar state, 1658t
requirements for, in hypertonic dehydration, 2203b
Potassium chloride
for hypercalcemia, 1625
for hypokalemia, 1640-1641
for periodic paralysis, 1445-1446
Potassium deficits
in diabetic ketoacidosis, 1657, 1657t
in hypertonic dehydration, 2203b
Potassium hydroxide (KOH), 1994
gastric necrosis after ingestion of, 1995, 1995f
lip burns after exposure to, 1996, 1996f
Potassium iodide (KI), 1951-1952, 1952t
for erythema nodosum, 1576
for radioactive iodine exposure, 2471, 2471t
for thyroid storm, 1682b, 1683
Potassium phosphate (K_2PO_4 and KPO_4), 1651
Potassium replacement, 1660
Potassium-sparing diuretics, 1122.e1t-1122.e2t
Potential injury-creating event (PICE), 2458
nomenclature, 2458-2459, 2459t
paralytic, 2459, 2459b
Pott's disease, 644
Pott's fracture, 512t-513t
Povidone-iodine solution (iodine complexes, Betadine), 755, 756t, 766b
Powder burns, 829
Power, e13, e13t
Power's ratio, 317, 317f
Poxviridae, 1719t, 1725-1727
PR interval, 1035
Practice guidelines or protocols, e63
Practolol, 1987t
Pralidoxime
for nerve agent exposure, 826
for organophosphate poisoning, 826, 2059
in pregnancy, 2318t-2321t, 2324
Praziquantel (Biltricide), 1770t, 1772t-1775t
Prazosin hydrochloride, 1122.e1t-1122.e2t
Predictive value, e20t
Prednisolone, 1509
for asthma, 949t, 950
for asthma in pregnancy, 2303t
for glaucoma, 922
for gouty arthritis, 1509
herbal medicine interactions, 2072t-2073t
Prednisone
for anaphylaxis, 1555
for asthma, 949t, 950, 2121t
for asthma in children, 2122
for asthma in pregnancy, 2303t
for Behçet's disease, 1540
for COPD, 963
for dermatomyositis, 1445
for gouty arthritis, 1509
herbal medicine interactions, 2072t-2073t
for hypercalcemia, 1625
for nephrotic syndrome in children, 2217
for pemphigus vulgaris, 1577
for pharyngitis, 968
for pneumonia, 985
for poison ivy, 1572-1573
for polyarteritis nodosa, 1539-1540
for polymyositis, 1445
for rheumatoid arthritis, 1514-1515
for systemic lupus erythematosus, 1533t
for tuberculous meningitis, 1820
for urticaria, 1569
Preeclampsia, 2290-2292
BP control for, 1120t, 1122
chronic hypertension with, 2304t
definition of, 2290, 2304t
fulminant or severe, 2291, 2292b
Preexcitation, 1052-1055
Pregabalin (Lyrica)
for diabetic distal symmetrical polyneuropathy, 1432
for diabetic neuropathy, 1432, 1663
drug interactions, 2407t-2408t
for long-term anticonvulsant therapy, 1384t
side effects of, 1383t, 2407t-2408t
Pregnancy
abdominal pain in, 2277-2278
acute complications of, 2282-2299, 2299b
acute fatty liver of, 2295
air bags during, 2279
air medical transport for, 2447
alcohol effects on, 2392
altitude and, 1939
anatomic changes in, 297
anemia in, 2306
appendicitis in, 1226-1227
asthma in, 952
bacterial vaginosis in, 1323
cardiac arrest in, 2271
cardiac disorders in, 2304-2306
changes of, 296-297
chest pain in, 2277
cholelithiasis in, 1201
chronic medical illness in, 2300-2315, 2301t-2303t
key concepts, 2315b
clinical features of, 2272-2273
diabetes mellitus in, 1665
diagnosis of, 2273-2276
dietary management during, 2280
differential considerations, 2276
domestic violence during, 2278-2279
douching during, 2279-2280

www.ketabpezeshki.com 66485457-66963820

Pregnancy *(Continued)*
drug therapy in, 2316-2330
key concepts, 2330b
safety of, 2318t-2321t
early
problems in, 2282-2288
vaginal bleeding in, 2287, 2288f
ectopic, 2284-2288
pelvic pain in, 267t-268t
precautions for, 2284
endocrine disorders in, 2309-2311
with epilepsy, 2308
exercise during, 2280
general approach to pregnant patients, 2271-2281
hand symptoms, 2278
headache in, 2276-2277
health promotion in, 2279-2280
and heart failure, 1081
helmets during, 2279
hematologic disorders in, 2306-2307
hemodynamic changes of, 297t
history taking in, 2272
hypertensive disorders of, 2304t
hyperventilation of, 2300
hypothyroidism in, 1684-1685
immunization during, 2280
intrahepatic cholestasis of, 237, 2296
jaundice in, 236-237
key concepts, 2281b
laboratory testing in, 297, 2273-2274
late complications, 2288-2293
liver disease in, 1199
Lyme disease and, 1794-1795
management of, 2279-2280
medical problems in, 2293-2299
metabolic disorders in, 2309-2311
molar, 2288
musculoskeletal pain in, 2278
nausea and vomiting of, 243t-244t, 246
neurologic disorders in, 2307-2309
physical examination findings, 2272-2273
physiologic changes of, 296-297
cardiovascular, 296
gastrointestinal, 297
pulmonary, 296-297
prevention of disease and injury in, 2279-2280
prophylaxis of, in sexual assault, 868-869
radiology in, 2274-2276
risk of, in sexual assault, 868-869
scuba diving in, 1921
seat belt use during, 298, 2279
sexual intercourse during, 2279
sexually transmitted diseases in, 2298
substance abuse during, 2280, 2395
surgical problems in, 2293-2299
systemic infections in, 2312-2314
terminology, 2271-2272
third-trimester complications associated with delivery, 2338-2342
third-trimester ultrasonography, 2335-2337, 2337b
thyroid disorders in, 2311-2312
trauma in, 296-304, 2278
travel restrictions during, 2280
tuberculosis in, 1827
ultrasound confirmation of, 2495-2496, 2495f
ultrasound criteria for abnormality, 2283, 2283b
urinary tract infection during, 1329-1330
uterine size during, 301f
vaginal bleeding during, 273-274
vitamin supplements during, 2280
weight gain recommendations, 2280
Pregnancy-induced hypertension, 2290-2292
clinical features of, 2291
complications of, 2291
diagnostic strategies for, 2291
differential considerations, 2291
management of, 2291-2292
signs and symptoms of, 2291
Pregnancy-related folate deficiency, 2307
Pregnancy tests, 275, 2273-2274, 2274f
in appendicitis, 1227
Pregnancy tumors, 902-903
Preload, 1076-1077, 1077f
Premature atrial contractions, 1046-1047, 1046f
with abnormal conduction, 1048t
blocked, 1046
with noncompensatory pauses, 1046, 1047f
Premature labor, 2339-2340
clinical features of, 2339
definition of, 2272
diagnostic strategies for, 2339
management of, 2339-2340
treatment of, 2339, 2339b
Premature rupture of the membranes, 2340-2341
bedside testing for, 2341t
clinical features of, 2340-2341
definition of, 2340-2341
diagnostic strategies for, 2340
management of, 2340-2341
Premature ventricular contractions, 1046-1048, 1048f
causes of, 1048b
with compensatory pause, 1047, 1047f
features of, 1048t
interpolated, 1047, 1047f
multifocal, 1047-1048
Preocclusive syndrome, 998
Prepatellar bursa, 716
Prepatellar bursitis, 1524
Prerenal azotemia, 1295-1296
causes of, 1295b
urinary findings, 1292t
Preschoolers, 1333t, 2089-2090
Prescriptions, e62
Presentation, fetal, 2333
breech presentation, 2342t, 2343b, 2343f
brow presentation, 2342t, 2345
compound presentation, 2345
malpresentation, 2342
Preseptal cellulitis, 921
President's Commission on Highway Safety, 2433
Pressure-controlled ventilation (PCV), 23-24, 24t
Pressure-cycled ventilators, 2404
Pressure-support ventilation (PSV), 25, 25t
Pressure ulcers
risk factors for, 2409
staging of, 2409, 2409f
Preterm infants, 2272
Pretest odds, e20t
Pretest probability, e20t
Preventive care
ED services, e62
for elderly, 2355
against gang violence, e3-e4, e5
multidisciplinary team approach to, 331
in pregnancy, 2279-2280
against suicide, 1499-1500
tactical combat care, 2453
against violence, 2421
Prevertebral space, 896
Prevnar (*S. pneumoniae* vaccine), 1707
Prevor (Diphoterine), 910
Prevotella infection, 979
Prevpac (lansoprazole, amoxicillin, and clarithromycin), 1180
Priapism
in children, 2205-2206
clinical features of, 2205
differential considerations, 2205
key concepts, 2223b
management of, 2205-2206
patient disposition in, 2205-2206
self-induced, 497f
in sickle cell disease, 1599
Prickly heat, 1900-1901, 1901f
clinical features of, 1900-1901
management of, 1901
physiology of, 1900-1901
Primaquine
for parasitic infection, 1772t-1775t
for pneumonia, 985t
Primary care practice, e38t
Primate bites, 787-789, 788t
Primidone (Mysoline)
drug interactions, 2407t-2408t
for long-term anticonvulsant therapy, 1384t
side effects of, 1383t, 2407t-2408t
Prinzmetal's angina, 998
Prion (*pro*teinaceous *i*nfectious particle [-*on*]), 1740
Prions, 1740
Prisoners, e72
Privacy, e35-e36
HIPAA exemptions, 842, 844b
for intimate partner violence diagnosis, 877
Private agencies, 2434-2435
Private patients, e61
Proactive ethics, e45
Probability
post-test, e20t
pretest, e20t
prior, e16
a priori, e16
Probenecid, 1325t
Problem behavior, 2425
Problem patients, 2422
agendas, 2424
key concepts, 2430b
management strategies for, 2428t
negative reactions to, 2424-2425
general alternatives to, 2425
strategies to manage, 2425
negative thoughts about, 2424-2425
negotiation with, 2424
Procainamide
for atrial fibrillation and flutter conversion, 1052b
for dysrhythmia, 1036
for pediatric dysrhythmias, 2154b
in pediatric resuscitation, 104t
in pregnancy, 2318t-2321t, 2326
for ventricular tachycardia, 1057-1061
Procaine, 46t
Procedural sedation, 32b
Procedural sedation and analgesia (PSA), 50-60
approach to, 51-54
definition of, 50
discharge criteria and instructions for, 53-54
drug administration and selection, 59
agent benefits and adverse effects, 55t
agents and dosage recommendations, 54t-55t
strategies for adults, 59t
strategies for children, 60t
equipment for, 53b
key concepts, 60b
monitoring, 53
patient assessment for, 51-52
pediatric, 60
drug selection strategies for, 60t
personnel, 52
pharmacology of, 54-59
preprocedural fasting, 52
recovery, 53
rescue agents for, 59
reversal of, 59
route of administration, 54
supplies and equipment for, 52-53
terminology for, 50-51
Proceedings of the American Thoracic Society, 946
Process improvement, 2505-2511
Prochlorperazine (Compazine), 2048t
for migraine attack, 1388t
for nausea and vomiting, 245-246, 245t
for pediatric migraine, 2244
Procidentia, 1287, 1287f
Proctalgia, 1283
Proctalgia fugax, 1283
Proctitis, 1285-1288
Proctocolitis, radiation, 1273-1274
Products of conception, retained, 2348
Profanity, 2424
Professional codes, e36
Professional disclosure standard, e70
Professional Football Athletic Trainers Society, 354
Professional relationships, e79
Professional values, e36
codifying, e36
conflicts, e38
Professionalism, 2422
Profundus tendon testing, 540, 541f
Progestin, 869t
Progressive multifocal leukoencephalopathy, 1737
clinical features of, 1737
diagnostic strategies for, 1737
differential considerations, 1737

www.ketabpezeshki.com 66485457-66963820

Progressive multifocal leukoencephalopathy (*Continued*)
in HIV infection, 1761-1762, 1762t
management of, 1737
Proguanil-atovaquone, 1770t
Prolapse, rectal, 1287, 1287f
Prolonged QT syndrome, 2166-2167
clinical features of, 2167
management of, 2050-2051, 2167
syndromes that produce torsades de pointes, 1061b
Promethazine (Phenergan), 168-169, 2048t
for nausea and vomiting, 245, 245t
for pediatric migraine, 2244
Pronator quadratus fat pad, 575, 575f
Propafenone, 1037-1038, 1052b
Proparacaine, 930t
Propofol, 15
for asthma, 953
benefits and adverse effects, 55t
ketamine plus propofol (ketofol), 58-59
in pregnancy, 2318t-2321t, 2322
in procedural sedation and analgesia, 54t-55t, 58, 59t-60t
for seizures, 158t-159t
for status epilepticus, 158t-159t, 1381t, 1382
for status epilepticus in children, 2238
Propoxyphene, 39t, 42, 2053t
Propranolol
for akathisia, 1464
alcohol interactions, 2390t
characteristics of, 1987t
for chloral hydrate overdose, 2081
for hypertension, 1122.e1t-1122.e2t
for pediatric migraine, 2244
for thyroid storm, 1682b
Propylthiouracil
in pregnancy, 2328
side effects of, 1683
for thyroid storm, 1682b, 1683
ProSom (estazolam), 2078t
Prostaglandin E_1, 2147, 2147b
Prostaglandins, 1184-1185
Prostatitis, 1335-1336
antibiotics for, 1335-1336
chronic, 1336
drugs for, 1335
Prostheses
femoral, 681-682, 682f
hip, 690-691
periprosthetic joint infections, 1848
Prosthetic bridge fistula, 1155-1156
Prosthetic grafts, subcutaneous, 1156
Prosthetic heart valves
complications of, 1112, 1112b
in pregnancy, 2306
Prosthetic joint infections, 1506
Prosthetic valve endocarditis, 1106-1107, 1112
Prosthetic valve thrombosis, 1112
Protease inhibitors, 1765
adverse reactions to, 1766t
drug interactions, 1825-1826
side effects of, 1765
Protein
CSF levels, 1454
in children, 2227
dipstick test for, 1291
Proteinuria, 1293-1294
abnormal, 1293
in children, 2215-2216
clinical features of, 2215
diagnostic strategies for, 2215-2216
differential diagnosis of, 2215
management of, 2216
patient disposition in, 2216
nephrotic-range, 1293-1294
Prothrombin time, 1608-1609
abnormal, 1612
in disseminated intravascular coagulation, 1616t
Proton pump inhibitors (PPIs), 1185b
for GERD, 1177, 1177t
for GI bleeding, 252
for *H. pylori* infection, 1180
for NSAID-induced ulcers, 1177t
for peptic ulcer disease, 1177t
Proton pump inhibitors (PPIs) (*Continued*)
in pregnancy, 2318t-2321t, 2329
risk of GI effects, 44t
for upper GI disorders, 1177t, 1184
Protons, 1948f
Protopam, 1957t-1958t
Protozoa
geographic locations and portals of entry, 1770t-1771t
that cause infectious diarrhea, 2192t-2193t, 2195
Protozoal gastroenteritis, 1250t
Proximal arcades, 570
Proximal extra-articular tibial fractures, 717-718
Proximal femoral fractures, 682
pediatric, 693, 693f
Proximal fibula fractures, 720
clinical features of, 720
diagnostic strategies for, 720
management of, 720
Proximal humerus epiphysis
fractures of, 627-628
clinical features of, 627-628
complications of, 628
management of, 628, 628f
pathophysiology of, 627
Salter I injury of, 628f
Proximal humerus fractures, 625-627
clinical features of, 626-627
complications of, 627
management of, 626f-627f, 627
Neer's classification of, 626, 626f
pathophysiology of, 625-626
Proximal interphalangeal joint, 534-535, 536f
Proximal interphalangeal joint injuries, 554
Proximal peripheral neuropathies, asymmetrical, 1433, 1433b
Proximal phalangeal fractures, 547-549
clinical features of, 547-548
complications of, 549
management of, 548-549
pathophysiology of, 547-548
Proximal subclavian artery aneurysms, 1147
Proximal tibiofibular joint, 720-721
dislocations of, 720-721
clinical features of, 721
diagnostic strategies for, 721
management of, 721
pathophysiology of, 720-721
Pruritus, 1532t, 1583, 1585b
Pruritus ani, 1284-1285
causes of, 1284b
management of, 1285
in parasitic infections, 1783
Pruritus gravidarum, 2296
Prussian blue (ferric hexacyanoferrate), 1952t
Pseudarthrosis, 517
Pseudo-kidney sign, 1269
Pseudo-obstruction
large bowel, 1265
small bowel, 1216-1217
Pseudoaddiction, 40
Pseudoaneurysms
abdominal aorta, 1129, 1136
arterial, 502, 502f
post-traumatic, 1149
Pseudoclaudication, 646
Pseudocysts, pancreatic, 1208, 1208f
Pseudodementia, 1407
Pseudodysrhythmias, 1041, 1042f
Pseudofractures, 519
Pseudogout, 1509-1510
crystal analysis in, 1505f
radiologic findings in, 1504t
Pseudohyponatremia, 1642-1643, 1642b
Pseudohypotension, 1125
Pseudomembranous croup, 2114-2115
Pseudomonas aeruginosa infection
Gram's stain characteristics, 1453t
in osteomyelitis, 1835
in skin infections, 1856t
Pseudoparkinsonism, 1464-1465
Pseudotattooing, 833f
Pseudotumors, fluid, 994
Psilocybe cubensis mushrooms, 2015, 2016f
Psilocybin, 2015-2016
Psoriatic arthritis, 1516, 1517f
Psychedelics, 2015-2016
Psychiatric disorders
acute episodes, 1473b
admission guidelines for, 2393-2394
alcohol-related, 2390, 2393-2394
anxiety in, 1477-1478
associated with violence, 2420b
criteria for hospitalization, 1473b
diagnostic strategies for, 1461
differential considerations, 1462
among sexual assault victims, 862
and suicide, 1494
Psychodynamic theory, 1468
Psychogenic casualties, 2461-2462
Psychogenic nonepileptic seizures, 1379
Psychological abuse
child maltreatment, 846t
definition of, 886
questions to ask about, 887b
Psychomotor activity disturbances, 1469
Psychosis, 152
acute
differential diagnosis of, 1402t
key characteristics of, 1402t
medical disorders that may cause, 1462b
pharmacologic agents that may cause, 1462b
functional, 1461, 1462t, 1496t
organic, 1461, 1462t, 1496t
Psychosocial issues
in elders, 2353
stress, 1115
Psychotherapy
for anxiety disorders, 1479
long-term, 1473
Psychotic disorders
brief, 1462
negative symptoms of, 2047
positive symptoms of, 2047
Psyllium (Metamucil), 264t-265t
Pterygium
clinical features and management of, 919
inflamed, 193t-196t
Pubic dislocation, 687, 689
Pubic lice, 1323
Public agencies, 2434-2435
Public health, 884
Public Law 93-154. *See* EMS Systems Act of 1973
Public Law 98-555. *See* Health Services, Preventive Health Services, and Home Community Based Services Act of 1984
Public policy
advocacy of, 337-338
and bioethics, e44-e45
Public safety answering points, 2437
Publication, e10f, e12
Publication bias, e12
Puerto Ricans, e27
Puffy hand syndrome, 1152
Pulled muscle, 527
Pulmonary agents, 2478
Pulmonary artery catheterization, 1083
Pulmonary barotrauma, 1919-1920, 1926
Pulmonary contusion, 436-437, 436f
clinical features of, 436
diagnostic strategies for, 436-437
epidemiology of, 436
management of, 437
pathophysiology of, 436
pediatric, 320
Pulmonary edema
in aspirin overdose, 1965-1966
in chronic kidney disease, 1305-1306, 1306b, 1306f
classification of, 1083
high-altitude (HAPE), 1928, 1934-1936, 1934b
neurogenic
in head injury, 360
in neck injury, 429-430
postobstructive, 429-430
in renal failure, 1305-1306, 1306b
in scuba diving, 1922
treatment of, 1305-1306

www.ketabpezeshki.com 66485457-66963820

Pulmonary embolism, 1159-1169. *See also* Thromboembolism
algorithms for, 1163, 1163f
alternative diagnoses, 1164, 1164b
chest pain in, 220t-221t
clinical features of, 139t, 1160-1162, 1161t
diagnosis of, 94t, 1157, 1162-1164
ECG findings, 1162, 1162f, 1166, 1167f
evaluation for, 1168b
fibrinolytic regimens for, 1166t
and heart failure, 1082
high-risk (major), 1165t
key concepts, 1169b
low-risk, 1165t
management of, 1164-1169
massive, 1160, 1161f, 1166, 1166f-1167f
moderate-risk, 1165t
in obesity, 1168b
in pregnancy, 1168b, 2296-2297
pretest probability of, 1157, 1162
risk factors, 216b, 1161t
submassive moderate-risk, 1165t
surgical embolectomy for, 1167-1169
in systemic lupus erythematosus, 1529
thrombolytic therapy for, 1166-1167
treatment of, 94t, 1165t, 1529t
unique questions that arise, 1168b
workup, 1529t
Pulmonary embolism rule-out criteria (PERC rule), 1160b, 1163
Pulmonary function testing
in asthma, 946-947, 948t
in COPD, 959
Pulmonary hypertension
clinical features of, 139t
in pregnancy, 2304
Pulmonary irritants, 2036-2038
exposure to
clinical features of, 2037
diagnostic strategies for, 2037-2038
differential considerations, 2037-2038
management of, 2038
patient disposition in, 2038
key concepts, 2043b
sample reactions, 2037, 2038f
Pulmonary laceration, 437
Pulmonary tuberculosis
differential considerations, 1817-1818
drug regimens for, 1824-1825, 1825t, 1827t
drug-resistant, 1827t
upper lobe infiltrate, 1818
Pulmonary tularemia, 1797
Pulmonary vascular occlusion, 1160
Pulse deficit, 504
Pulse oximetry, 61-62
in children, 2118
in COPD, 959
in peripheral vascular injury, 504
Pulse rate, 948t
Pulseless electrical activity, 90-91
definition of, 94
diagnosis of, 94t
pediatric, 2154b, 2158-2159
treatment of, 94, 94t
Pulseless rhythms, pediatric, 2158-2159
Pulseless ventricular tachycardia, pediatric, 2154b
Pulses, pediatric, 2142
Pulsus paradoxus, 1626b
in asthma, 948t
Punctate keratitis, superficial, 920
Puncture wounds
of foot, 764
management of, 764
Pupillary block, 922
Pupillary defects, relative afferent, 187
Pupillary evaluation, 187
in head injury, 346
Furazolidone, 1257t
Purified chick embryo cell vaccine, 1720t
Purified protein derivative (PPD) skin testing, 1810, 1816-1817, 1818t
criteria for positive reactions, 1817t
false-negative results, 1817, 1817b
false-positive results, 1817
Purkinje fibers, 1982
Purpura, 1583
causes of, 1583b
definition of, 1559t
drug eruptions, 1567, 1567f
drugs associated with, 1584b
key concepts, 1585b
macular, 1559t
papular, 1559t
thrombocytopenic
causes of, 1583b
thrombotic, 1611
Purpura fulminans, 1712
PURSUIT (Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) risk model, 1000
Purulent meningitis, 1456t
Purulent pericarditis, 1096
Pustules, 1559t, 1564-1566
Pyarthrosis, 694, 695f
Pyelonephritis
acute uncomplicated, in women, 1333t
in men, 1335
observational approach to, 2490
traditional approach to, 2490
Pyloric stenosis, hypertrophic, 2170-2172
Pyng FAST1 infusion device, 2452
Pyogenic abscesses, 1196-1198
clinical features of, 1197
CT imaging of, 1197, 1197f
diagnostic strategies for, 1197
differential considerations, 1197-1198
management of, 1198
patient disposition in, 1198
Pyogenic or suppurative arthritis, 1831
Pyracantha (firethorn), 2069
Pyrantel pamoate (Antiminth)
for diarrhea, 1235t
for parasitic infection, 1772t-1775t
for pruritus ani, 1285
Pyrazinamide
for drug-resistant pulmonary TB, 1827t
suggested doses for adults, 1824t
for tuberculosis, 1822t-1823t, 1824-1825, 1825t, 1828t
Pyrethrin toxicity, 2063-2064
Pyrethrins, 2063-2064
Pyrethroid toxicity, 2063-2064
Pyrethroids, 2063-2064
Pyridoxine
for ethylene glycol poisoning, 1957t-1958t, 2012
for hydrazine ingestion, 1957t-1958t
for isoniazid ingestion, 1957t-1958t, 2236
for methanol poisoning, 2012
for monomethylhydrazine toxicity, 1957t-1958t
for neonatal seizures, 2236
in pregnancy, 2318t-2321t, 2324
for seizures, 158t-159t
for status epilepticus, 158t-159t
Pyrimethamine
for cystoisosporiasis, 1251
for diarrhea in AIDS, 1257t
Pyuria, 1328

Q

Q angle (quadriceps angle), 712
Q fever, 1106, 1786t, 1803-1804
clinical features of, 1803
diagnostic strategies for, 1803
management of, 1803-1804
Q wave myocardial infarction, 999
QCS. *See* Quick Confusion Scale
QRS complex, 1035
aberrant, 1046-1047, 1047f
fusion, 1047-1048, 1048f
in hyperkalemia, 1636-1637, 1637f
irregularly irregular patterns, 1050
narrow-complex tachycardia, 1048-1052, 1055f
wide-complex tachycardias, 1055-1062
QT interval, prolonged, 2166-2167
management of, 2050-2051
syndromes that produce torsades de pointes, 1061b
Quadriceps angle (Q angle), 712
Quadriceps muscle injury, 691
Quadrigeminy, 1046
Quadriparesis, 127
Quadriplegia, 127
Quality of life, e48-e49
palliative options for, e56b
QuantiFERON test, 1816
Quantitative resuscitation, 71-72, 72f
Quazepam (Doral), 2078t
Quetiapine, 2048t
Quick Confusion Scale (QCS), 152-153, 153f, 1401
Quiet delirium, 151
QuikClot (Z-Medica), 939
Quinapril, 1122.e1t-1122.e2t
Quincke's sign, 1111
Quinidine
hepatic injury, 1197t
in pregnancy, 2318t-2321t, 2326
Quinine, 1772t-1775t, 1806
Quinlan, Karen Ann, e41
Quinolones, 2318t-2321t
Quinton-Mahurkar catheter, 1153, 1153f, 1155

R

Rabbit syndrome (perioral tremors), 2048-2049
Rabeprazole, 1177t
Rabies, 1742-1750
animal, 1742-1743, 1744f
animal in captivity, 1748
biting animal, 1747-1748
clinical features of, 1745-1746
diagnosis of, 1746-1747
distribution of, 1743f
domestic animal, 1742-1743
epidemiology of, 1742-1744
exposure to, 1747
in humans, 1743-1744
key concepts, 1750b
management of, 1746-1747
postexposure prophylaxis of, 1748-1749
assessment, 1747-1748
guidelines for, 1747, 1747t
immunoprophylaxis, 1748-1749, 1749b
pre-exposure prophylaxis of, 1749-1750, 1749t
prevalence of, 1742, 1743f
sources of, 1742-1743, 1743f
wild animal, 1742-1743
wound care, 1748-1749, 1748b
Rabies vaccine, 1720t
Rabies vaccine absorbed, 1720t
Rabies virus, 1745, 1745f
Raccoon eyes, 313
Race-based medical decision-making, e24-e25
Racial disparities, e23-e24
factors contributing to, e24
progress to date, e26
Racism, e23
RACQITO (*r*esource *a*vailability *c*ontinuous *q*uality *i*mprovement *t*rade-*o*ff), 2507
Radial collateral ligament injuries, 556
Radial fractures
distal displacement, 514f
greenstick fracture, 2250, 2251f
head and neck fractures, 611-612
diagnostic strategies for, 612
management of, 612
pathophysiology of, 611-612
head fractures, 601b, 612, 612f
head subluxation, 614
clinical and radiographic features of, 614
management of, 614
pathophysiology of, 614
reduction of, 614, 615f
nursemaid's elbow (radial head dislocation), 616-617, 2258, 2258f
Salter-Harris type II fracture, 2253f
shaft fractures, 591
torus fracture, 517f
transverse fracture, 2251f
Radial inclination, 571-574
Radial keratotomy, 1939
Radial length measurement, 571-574
Radial mononeuropathy, 1433-1434

www.ketabpezeshki.com 66485457-66963820

Radial nerve, 542-543, 573t, 596, 1434, 1434f
Radial nerve injury, 616b-617b
Radial palsy, 542-543, 543f
Radiation, 1896, 1947
external exposure to, 1949
ionizing, 1946-1947
nonionizing, 1946-1947
sensitivity to, 1949f
types of, 1947, 1948f
Radiation absorbed dose (rad), 1949
Radiation control officer, 1951
Radiation Emergency Assistance Center/Training Site (REAC/TS), 1952-1953, 2470, 2470t
Radiation Emergency Medical Management (REMM) website (HHS), 1952-1953
Radiation injury, 1945-1953
clinical features of, 1949-1950
consultative resources for, 1952-1953
diagnostic strategies for, 1949-1950
epidemiology of, 1945-1946
esophagitis, 1174
clinical features of, 1174
management of, 1175
eye burns, 912
historical perspective on, 1945-1946
key concepts, 1953b
management of, 1950-1953
pathophysiology of, 1946-1948
patient disposition in, 1952
pericarditis, 1094
preparation for, 1951
prognosis according to lymphocyte count after, 1950t
reducing, 1950
survival improbable group, 1952
survival possible group, 1952
survival probable group, 1952
symptoms and signs of, 1949-1950
treatment of, 1951-1952
triage classification of, 1952
types of, 1949
in urban search and rescue, 2456
wound management and treatment of, 1951
Radiation (actinic) plexopathy, 1433
Radiation proctitis, 1287
Radiation proctocolitis, 1273-1274
acute, 1274
chronic, 1274, 1274b-1275b
clinical features of, 1274
diagnostic strategies for, 1274
differential considerations, 1274
management of, 1274
patient disposition in, 1274
Radiation risk, 466
Radiation therapy, 1628
Radiculopathy, 645-646, 646f, 1433, 1441
Radioactive contamination, 1947-1948
decontamination after, 1950-1951
external, 1949
internal, 1949
blocking agents for, 1951-1952
management of, 1951-1952
medication options for, 1952t
wound, 1949
Radioactive incorporation, 1948
Radioactive iodine exposure, 2471, 2471t
Radiocarpal instability, 582-583
Radiocontrast-induced anaphylaxis, 1546b
Radiocontrast media, 1546
Radiographic imaging
in abdominal aortic aneurysm, 1131, 1132f
in abdominal trauma, 464-467
in acute kidney injury, 1299
in airway foreign bodies, 774, 774f-775f
ankle series, 725-726
in anthrax exposure, 2472, 2472f
in appendicitis, 2185, 2185f
in back pain, 281-282
cervical spine, 403-407, 404f-406f
anteroposterior view, 404f-405f, 407, 408f-409f
cross-table lateral view, 403-407
flexion and extension views, 407
NEXUS criteria for, 290, 293
oblique views, 407, 409f-410f
odontoid view, 403-407, 406f
Radiographic imaging *(Continued)*
chest
in asthma, 947-948
in COPD, 959
in esophageal perforation, 457, 458f
in pediatric fever, 2099
in pleural effusion, 994, 995f
in pneumonia, 981-982, 981f-982f
in pneumothorax, 989
in chronic pancreatitis, 1213, 1213f
in deep vein thrombosis, 1158
in diarrhea, 258
ED functions, e62
in epiglottitis, 970, 970f
in facial trauma, 373-374, 373f
of fingers, 545-546, 546f
foot series, 726
in gastrointestinal foreign bodies, 777, 779-780, 779f-780f
in GI bleeding, 250
of hand, 545, 545f
in hematuria, 1293
of hip, normal, 679, 679f
in hypertrophic pyloric stenosis, 2171, 2172f
of joints, 1503b
kidney-ureter-bladder (KUB) films, 1339
in Lisfranc's injuries, 742-744
in Lisfranc's injuries, 743f
in malrotation with midgut volvulus, 2173-2174, 2173f-2174f
in osteomyelitis, 1836-1837, 1837f-1838f
in pediatric abdominal injury, 322
in pediatric head injury, 315
in pediatric pneumonia, 2134, 2134f
in pediatric seizures, 2236
in pediatric spinal injury, 316-317
in pericardial tamponade, 449
plain-film
in abdominal gunshot wounds, 474
in abdominal trauma, 464, 465f
in anorectal foreign bodies, 781, 781f-782f
in appendicitis, 1228
in arthritis, 1503
in cecal volvulus, 1267-1268, 1268f
cervical, 403-407
in colonic ischemia, 1273
in diverticulitis, 1264
in facial trauma, 374
fetal identification by, 2275
fetal radiation exposures, 2276t
in foot injury, 735
in fractures, 518-519
in IBD, 1270-1271, 1271f
in intussusception, 1269
in knee injury, 702-703
in large bowel obstruction, 1265, 1266f
in low back pain, 648-649, 649b, 649f
in pelvic trauma, 665, 666f
in peripheral vascular injury, 504
in sigmoid volvulus, 1267, 1268f
stress views, 518-519
in trauma in pregnancy, 299
uterine radiation dose, 299, 299t
in pneumothorax, 989
in reactive arthritis, 1515-1516, 1516f
for removal of soft tissue foreign bodies, 783
in small bowel obstruction, 1219, 1221f
in sore throat, 200
in spinal injuries, 402-415
in supracondylar fractures, 2256, 2256f
in systemic lupus erythematosus, 1532
of teeth, 897
in trauma, 293
in trauma in pregnancy, 299
trauma X or trauma series, 850
of wrist, 574f-575f, 576t
Radiologic terrorism, 2466
Radiologic weapons of mass destruction, 2469-2471
Radiology, 2510. *See also specific imaging modalities*
in acromioclavicular joint dislocation, 630, 630f
in acute bacterial meningitis, 2228-2229
in ankle injuries, 725-726, 731-732
in ankle sprains, 731-732
in anterior glenohumeral dislocations, 631, 632f
in arthritis, 1503
Radiology *(Continued)*
in asthma, 947-948
in biceps tendon rupture, 641
in bicipital tendinitis, 641
in calcaneal fractures, 740
in calcific tendinitis, 641, 641f
fetal radiation exposures, 2276, 2276t
in foot injury, 735-736
in forearm injuries, 590-591
in hand injury, 545-546
in headache, 2243, 2243b
in knee injury, 702-703
in Lisfranc's injuries, 742-744
management of, 745
in metacarpal head fractures, 550
in metatarsal base fractures, 745
in metatarsal shaft fractures, 744
in metatarsophalangeal dislocations, 747
in navicular fractures, 741
patient disposition in, 745
in pediatric trauma, 311
in pelvic trauma, 665
of periosteal new bone formation, 2260
in phalangeal fractures, 746
in posterior glenohumeral dislocations, 635, 635f
in pregnancy, 2274-2276
in renal trauma, 492
in rotator cuff tears, 640
in scapular fractures, 625
in sepsis, 1869
in shoulder injuries, 621
in sternoclavicular dislocations, 628f, 629
in stress fractures in foot, 749
in subtalar dislocations, 739
in systemic lupus erythematosus, 1532
in talar fractures, 737
in upper back pain, 655
in urban search and rescue, 2456
in urethral trauma, 482-484, 482f
in vertigo, 165
in wrist injury, 571-576
Radionuclide imaging (bone scanning), 519
in ankle injury, 726-727
in knee injury, 703
in osteomyelitis, 1837
in UTIs, 1329
Radon, 1946, 1946f
Radon-222, 1946
Radon daughters, 1946, 1946f
RAFFT questionnaire, 2397
Rales, 217t-218t
Raltegravir, 1766t
Ramipril, 1122.e1t-1122.e2t
Ramsay Hunt syndrome, 935, 1412
Randomization, e10-e11, e10f
Randomized longitudinal interventional studies (clinical trials), e9-e12, e10f
Range of fire, 830, 830t, 832
Ranitidine
alcohol interactions, 2390t
for anaphylaxis, 1554b, 1555
for GERD and PUD, 1177t
for *H. pylori* infection, 1180
for hymenoptera stings, 802
Ranson's criteria, 1209-1210, 1209b
Rape, Abuse, Incest National Network (RAINN), 870b
Rapid diagnostic treatment units, 2481
Rapid ethical decision making model, e38-e39
Rapid plasma reagin test, 1317
Rapid sequence intubation, 9-12, 11f, 2439
for elevated ICP, 17, 17t
orotracheal, in neck injury, 424
paralysis with induction of, 12
positioning for, 12
postintubation management, 12
preoxygenation, 11
preparation for, 11
pretreatment, 11-12
pretreatment agents for, 11b
sample, 12t
seven Ps of, 11b
in spinal injury, 417
in status asthmaticus, 16, 16t
tube placement, 12

www.ketabpezeshki.com 66485457-66963820

Rapid streptococcal tests, 967
Rapid tranquilization, 1465b
Rapid viral antigen testing, 2099
Rapture of the deep, 1918-1919
Rasburicase (recombinant urate oxidase), 1622
Rash, 1558
associated with levamisole, 1540-1541, 1540f
discoid, 1528t, 1531, 1531f
key concepts, 1585b
malar, 1528t, 1531, 1531f
in meningococcemia, 1712
pruritic or painful, 1532t
of secondary syphilis, 1316-1317, 1316f
Rat bites, 787, 788t
Rate and rhythm controllers, 1086
Rattlesnake bite
antidote for, 1957t-1958t
patient disposition in, 801
venom, 796
Rattlesnakes, 796f
Rave parties, 2017, 2082
Raynaud's attack, 1149, 1156b
Raynaud's disease, 1140, 1149
Raynaud's phenomenon, 1140, 1149
Razadyne (galantamine), 1408
Reactive airways disease, 11b
Reactive arthritis, 1515-1516
Reasonable person standard, e70
Reassurance, 1484
Rebound phenomenon, 2113
Rebreathers, 1915
Recompression therapy, 1923-1925, 1923b
Recording devices, 862
Recovery, 2463
from procedural sedation and analgesia, 53
Recruitment and enrollment of patients, e10, e10f
Rectal bleeding, 1276-1277
Rectal examination, pediatric, 310
Rectal prolapse, 1287, 1287f
Rectum. *See* Anorectum
Red blood cell transfusion. *See* Platelet transfusion
Red blood cells
anemia caused by decreased production of, 1589-1594, 1590b
bacterial contamination of, 79
formulas, 1590t
increased destruction of, 1594-1600
normal values, 1587t, 1590t
rapid intravascular destruction of, 1586, 1587b
storage methods for, 75
tagged RBC imaging, 252
Red cell folate test, 1593t
Red-colored urine, 1352b
Red macules, 1566-1570
Referred abdominal pain, 225, 227f
Referred back pain, 645, 647-648
Reflex examination, spinal, 399-400, 400t
Reflex sympathetic dystrophy, 38, 523-524, 748
Reflex syncope, 139t
Reflexes
Cushing's reflex, 344-345
in head injury, 347
in pain, 34-35, 35b
in spinal cord disorders, 1422
Reflux, gastroesophageal, 1175-1177, 1185b
Refractory periods
effective (absolute), 1034, 1036f
relative, 1034, 1036f
Refractory status epilepticus, 1382
Refusal of medical care, e72-e76
federal rules, e73-e75
informed, e72-e73
informed consent for, e73, e74f
Regional anesthesia, intravenous (Bier block), 48
Regional poison control centers, 818
Registration, e64
Reglan (metoclopramide), 245t, 246
Rehabilitation, 331
Rehydralyte, 2200t
Rehydration. *See* Oral rehydration therapy; Saline rehydration
Reiter's syndrome, 1515-1516
Rejection, 2370
chronic, 2369-2370
heart transplant, 2373, 2374f
Rejection *(Continued)*
kidney (renal) transplant, 2375
liver transplant, 2374
lung transplant, 2376
Relationships
abusive, 874-875
situational couple violence, 875
Relative afferent pupillary defect, 187
Relative refractory period, 1034, 1036f
Relative risk, e20t
Relaxation, physician, e82
Relenza (zanamivir), 1722
Relevance, e20-e21
analysis for, e20-e21
Reliability, e20
analysis for, e20-e21
definition of, e20t
Religious values, e34
Relistor (methylnaltrexone), 264t-265t, 265
Remifentanil, 39t
Remote settings
patient assessment in, 2453
ultrasound in, 2503-2504
Remote symptomatic seizures, 2234b
Renal artery injury, 493f
Renal calculi, 1336-1342
approach to, 1341
in children, 2214-2215
clinical features of, 2214
diagnostic strategies for, 2214
differential considerations, 2214
management of, 2214-2215
clinical features of, 1337
diagnostic strategies for, 1338-1339
differential considerations, 1339-1341
epidemiology of, 1336
imaging, 1338-1339
indications for hospital admission, 1342, 1342b
laboratory testing in, 1338
management of, 1341-1342
outpatient management of, 1341-1342
pathophysiology of, 1336-1337
physical examination findings, 1337
radiographic findings, 1339, 1340f
risk factors for, 1336b
signs and symptoms of, 1337
sites of likely impaction, 1337, 1337f
Renal colic, 1330, 1338-1339, 1338f-1340f
Renal crisis, 1297
Renal dialysis, 1088
Renal failure, 1291-1311
acute, 1291
in children, 2217-2219
intrinsic, 1296-1297, 1296b
postrenal (obstructive), 1296
in children, 2223b
CT scanning, 1292-1293, 1292f
diagnostic strategies for, 1291-1292
in drowning, 1942
drug toxicity in, 1304, 1304b
at end of life, e57-e58
in immunocompromised patients, 2365
key concepts, 1311b
metabolic acidosis in, 1633
postrenal, 1296b
pulmonary edema in, 1305-1306, 1306b
Renal fascia, 490
Renal injury. *See* Kidney injury
Renal insufficiency, chronic, 1301
Renal replacement therapy, 1674
Renal trauma, 490-494
blunt injury, 492-493
in children, 322
complications of, 490
diagnostic strategies for, 491-492
epidemiology of, 491
grades of injury, 492
laboratory testing in, 491-492
lacerations, 465, 465f, 467, 467f, 494f
management of, 492-494
minor injuries, 494f
pediatric, 492
penetrating, 493-494
radiology in, 492
Renal tumors, in children, 2215
clinical features of, 2215
diagnostic strategies for, 2215
differential considerations, 2215
management of, 2215
patient disposition in, 2215
Renewal, physician, e82
Renin inhibitors, direct, 1122.e1t-1122.e2t
Reoviridae (*r*espiratory *e*nteric *o*rphan viruses), 1719t, 1725
Repaglinide, 1665t
Repeaters, 2429
Reperfusion injury, 502, 510b
Reperfusion therapy
in acute coronary syndrome, 1027-1032
in cardiogenic shock, 1032
choice of, 1031-1032
Replantation, 564, 564b
Repolarization, 1034, 1036f
benign early, 1008-1009, 1010f
Reporting requirements, e76-e77
for elder abuse, 890-891
Reptiles, venomous, 794-801
Request for examination or treatment, e61
Rescue devices
for children, 109
for pediatric airway management, 109
Rescue percutaneous coronary intervention, 1030-1031
Research
analysis for validity, reliability, and relevance, e20-e21
application to patients, e21
best evidence topic (BET), e20t, e21
changing practice on basis of, e18-e19
checklist for assessment of studies, e19t
classical hypothesis testing, e12t
clinical questions, e19-e20
critically appraised topic (CAT), e20t, e21
cross-sectional studies, e8-e9
data analysis, e12-e18
data collection for, e10f, e11
data management for, e10f, e11
emergency, e44
evaluation of, e18
file drawer problem, e12
longitudinal studies, e9
medical literature, e8
presentation and publication of results, e10f, e12
randomized longitudinal interventional studies (clinical trials), e9-e12, e10f
resuscitation, e44
with subgroups, e15
types of clinical studies, e8-e9
Research questions, e9
Reserpine
for hypertension, 1122.e1t-1122.e2t
for thyroid storm, 1682b
Residents, e82-e84
autonomy of, e83
culture change, e84
fear for personal safety and well-being, e83
finding balance and well-being, e83-e84
stress management for, e83
time demands, e83
work hours, e83
Resistance, electrical, 1907
of body tissues, 1907b
skin resistance, 1908t
Resistance training, e82
Resources
as diminished, e80
for disaster medicine, 2458t
for disaster planning, 2463-2464
emergency medical services, 2439t
material, 2436-2437
Respiration
acute, emergent weakness that may affect, 1430b
in anaphylaxis, 1551
antipsychotic-induced dyskinesia, 2049
in asthma, 948t
in heart failure, 1081
in hypothermia, 1885-1886
interventions for, 2439
medications for, 2439

www.ketabpezeshki.com 66485457-66963820

Respiration *(Continued)*
opioid doses associated with depression, 2053t
out-of-hospital care for, 2439
pediatric, 318
normal, in newborn, 113t
physiology, 108-109
in sepsis, 1870-1871
Respiratory acidosis, 1629-1631
categorization of, 1630
causes of, 1631b
key concepts, 1635b
primary, 1635
Respiratory agents, 2330
Respiratory alkalosis, 1629, 1631-1632
categorization of, 1630
causes of, 1631b
Respiratory diphtheria
differential diagnosis of, 1695b
diphtheria antitoxin (DAT) for, 1695
Respiratory disease
altitude and, 1938
anxiety in, 1476
aspirin-exacerbated, 944
pathogenesis of, 944-945, 945f
treatment of, 945
severe, 1733
Respiratory distress
acute. *See also* Acute respiratory distress syndrome
causes of, 29t
in children, 2091-2092, 2091f-2092f
Respiratory failure
in children, 108-109
clinical features of, 108-109
management considerations, 109
chronic, in adults, 2402-2403
unresponsive to therapy, 959
Respiratory infections
in HIV infection, 1758-1760, 1758t
upper respiratory tract, 965-977
viruses associated with, 1732-1733
Respiratory medications, 2318t-2321t
Respiratory stimulants, 963
Respiratory syncytial virus immune globulin, 1721t-1722t
Respiratory syncytial virus infection, 1735-1736
clinical features of, 1735-1736
diagnostic strategies for, 1736
differential considerations, 1736
drugs for treatment of, 1721t-1722t
in infants and children with congenital heart defects, 2151
management of, 1736
risk factors for, 2151, 2151b
Response, 2463
hospital, 2463-2464
Restoril (temazepam), 1408, 2078t
Restraints, 888-889, 889f, 1497
chemical, 2416-2418
essential elements to provide with, 2416
guidelines for, 2416
physical, 1465b, 2415-2416
Restricted access to emergency medical care, e44
Restrictive cardiomyopathy, 1097, 1103
clinical features of, 1103
diagnostic strategies for, 1103
management of, 1103
pathophysiology of, 1103
patient disposition in, 1103
Resuscitation. *See also* Cardiopulmonary resuscitation; Fluid resuscitation
adult, 88-97
advance directives to withhold, e50-e51
brain resuscitation, 81-87
burn resuscitation index (BRI), 812-813, 813t
after cardiac arrest, 92-95
low-flow phase, 100
cerebral. *See* Brain resuscitation
do-not-attempt-resuscitation (DNAR) directives, e49
honoring, e50-e51
initiating, e56
questions for discussion of, e56t
family presence during, e54
in GI bleeding, 252
goal-oriented, 71
Resuscitation *(Continued)*
guidelines for, 294
in heatstroke, 1905
hypotensive, 506
initial
in electrical and lightning injury, 1913
in severe head injury, 348-351, 348f
length-based tape, 2092
maternal, 300-301
neonatal, 112-118
algorithm for, 114f
equipment needed for, 115, 115b, 115t
key concepts, 118b
maternal history questions for, 115b
pediatric, 98-111, 2159
advanced life support medications during, 102
in dehydration, 2200-2201
in dysrhythmias, 2154b
key concepts, 111b
medications used in, 104t
recommended chest compression–ventilation ratios for, 101-102, 101t
in septic shock, 106-107
in pelvic trauma, 667-668
postresuscitation phase, 100
quantitative, 71-72, 72f
recommended chest compression–ventilation ratios, 101
requirements for surgeon presence in, 291, 291b
special situations, e42
surgical teams, 2420
viewing of, e43, e54
volume
in hypothermia, 1889-1890
in thyroid storm, 1682b
Resuscitation ethics, e41-e44
Resuscitation mantra, 100-101
Resuscitation research, e44
Resuscitative mild hypothermia, 84-85, 84t
Retained products of conception, 2348
Retching, 239-242
Reteplase, 2318t-2321t
Reticulocytes, 1586, 1587f
Reticuloendothelial system, 2357
Retinal detachment, 916, 916f, 921, 925, 2499, 2499f
Retinal hemorrhage
high-altitude, 1937, 1937f
in shaken infant syndrome, 848, 848f
Retinal injuries, 916, 916f
Retinal tears, 921
Retinitis, 1721t-1722t
Retinopathy
diabetic, 1663
and fibrinolytic therapy, 1029
hypertensive, 1117, 1117b
Retrobulbar hematoma, 189
key concepts, 930b
management algorithm for, 193t-196t
Retrobulbar hemorrhage, 910
Retrograde cystography, 485, 485f, 487f-489f
computed tomography, 489-490, 490f
conventional, 485-489
endpoints for contrast medium, 487-488
spurious, 485, 486f
Retrograde pyelography, 494, 495f
Retrograde urethrography, 482-483, 482f-484f
preparation for, 483-484, 483f
Retropharyngeal abscess, 973-974, 2109f
clinical features of, 973-974, 2109
CT findings, 974, 974f
diagnostic strategies for, 974, 2109-2110
differential considerations, 974
key concepts, 977b, 2116b
management of, 974, 2110
patient disposition in, 974
pediatric, 2109-2110
Retropharyngeal injuries, 429
Retropharyngeal space, 896
Retrovirus, 1719t, 1740
Return to play
after concussion, 354, 354t
graduated protocol for, 354, 354t
Reverse Colles' fracture, 584
Reversible cranial vasoconstriction syndrome, 1396
Rewarming, 1891-1894
active, 1891-1894, 1892b
active core, 1892-1894
active external, 1892
airway, 1892-1893
arteriovenous anastomosis, 1892
blood, extracorporeal, 1893
continuous arteriovenous, 1894, 1894t
core, active, 1892-1894
emergency department protocol for, 1880b
endovascular, 1893
external
active, 1892
passive, 1891
extracorporeal blood rewarming, 1893-1894, 1894t
extracorporeal venovenous rewarming, 1893, 1894t
failure, 1891
indications for, 1892b
Rh (anti-D) immunization, 2283-2284, 2290, 2293
Rh system, 1599
Rh typing, 75
Rhabdomyolysis, 1667-1675
acute kidney injury in, 1672, 1673f
classification of, 1668
clinical features of, 1668-1670
in compartment syndrome, 1672
complications of, 1672
early, 1672
late, 1672
diagnostic strategies for, 1670-1671
differential diagnosis of, 1669b-1670b
electrical injuries and, 1914
etiology of, 1668
experimental therapy for, 1674
key concepts, 1675b
laboratory findings, 1671
lightning injuries and, 1914
management of, 1672-1674
pathophysiology of, 1667-1668, 1669f
patient disposition in, 1674
prognosis for, 1671, 1674-1675
renal replacement therapy for, 1674
Rhabdoviridae, 1719t, 1737
Rhesus immune globulin (RhIG), 303
Rheumatic fever, 1108-1109
acute, 1108-1109, 1512-1513
in children, 2165
clinical features of, 2165
diagnostic considerations, 2165
differential considerations, 2165
clinical features of, 1109, 1512, 1513f
diagnostic criteria for, 1513b
diagnostic strategies for, 1109, 1510
erythema marginatum associated with, 1571f
incidence of, 1108-1109
Jones criteria for, 2165b
Jones criteria (revised) for, 1109b
key concepts, 1112b
management of, 1109, 1513
Rheumatoid arthritis, 1513-1515, 1514f
clinical features of, 1514
diagnostic strategies for, 1514
drugs for, 1515t
juvenile, 2265t
late, 1504t
management of, 1514-1515
pericarditis in, 1094
in pregnancy, 2315
skin lesions associated with, 1581t
Rheumatologic disorders
in HIV infection, 1762
in pregnancy, 2315
rhabdomyolysis in, 1669b-1670b
Rhinitis, 976, 1552t
Rhinitis medicamentosa, 976
Rhinosinusitis, 975-977
acute
clinical features of, 976
diagnostic strategies for, 976
chronic, 976
clinical features of, 976
complications of, 977
diagnostic strategies for, 976
differential considerations, 976

www.ketabpezeshki.com 66485457-66963820

Rhinosinusitis *(Continued)*
key concepts, 977b
management of, 976-977
Rhinovirus, 1732-1733
Rhododendron, 2069-2070
RhoGAM (anti-D immune globulin), 2283-2284, 2290, 2293
Rhythm controllers, 1086
Rib fracture(s), 431-432
in child abuse, 847-848, 848f, 2259
clinical course of, 432
clinical features of, 432
diagnostic strategies for, 432
epidemiology of, 431
imaging, 432, 432f
management of, 432
multiple, 432f
pathophysiology of, 431-432
Ribavirin, 1721t-1722t
Ribs, 431-432
"Rice water" diarrhea, 1245
Richmond Agitation-Sedation Scale (RASS), 27, 27t
Rickets of prematurity, 852
Rickettsia parkeri, 1798
Rickettsia rickettsii, 1798
Rifabutin, 1257t, 1822t-1823t
Rifamate, 1824
Rifampin
for hidradenitis suppurativa, 1564
for meningitis chemoprophylaxis, 1458
for meningococcemia prophylaxis, 1713-1714
for pharyngitis, 968
for tuberculosis, 1822t-1823t, 1824-1825, 1825t, 1827t-1828t
Rifamycins, 1825-1826
Rifapentine, 1822t-1823t
Rifater, 1824
Rifaximin
for infectious diarrhea, 2192t-2193t
for traveler's diarrhea prevention, 1259
for traveler's diarrhea treatment, 1260
Rifles
centerfire rifle wounds, 833-834
high-velocity round wounds, 833-834, 836f
Rift Valley fever, 1739
Right bundle branch, 1035
Right-sided heart failure, 1080
Rights, e33-e34
to due, e34
patient rights, e34
in personam, e34
in rem, e34
Rimantadine (Flumadine), 1720-1722, 1721t-1722t
Rimexolone, 1514
Ring avulsion injuries, 563-564
Ring finger fracture, 549
Ringworm, 1559
Rinne test, 165
Riot control, 825
Risk, relative, e20t
Risk assessment
with combative patients, 2415
in febrile neutropenia, 2362
Risk factor assessment, 336-337
Risk of Suicide Questionnaire, 1498
Risperidone, 2048t
Ritodrine, 2339b
Ritonavir, 1721t-1722t, 1766t
Rituximab, 1515t
Rivastigmine (Exelon), 1408
River blindness, 1780, 1780f
Rizatriptan, 1388t
A Roadmap for Hospitals (The Joint Commission), e26
Robaxin (methocarbamol), 282-283
Roberts v Galen, e65
Rochester method, 689
Rock sign, 973-974
Rockall score, 253, 253t
Rocky Mountain spotted fever, 1570-1571, 1785, 1786t, 1798-1803, 1863
cardiopulmonary manifestations of, 1800
clinical features of, 1570, 1799-1801
cutaneous manifestations of, 1799-1800, 1800f
diagnosis of, 1570, 1801-1802, 1801b
Rocky Mountain spotted fever *(Continued)*
differential considerations, 1802
isolation of organism, 1801-1802
key concepts, 1808b, 1863b
management of, 1570-1571, 1802-1803
neurologic manifestations of, 1800-1801
serology in, 1801
skin biopsy in, 1801
supportive care for, 1802-1803
symptoms and signs of, 1799t
Rocuronium, 14, 2318t-2321t
Rodent bites, 787, 788t-789t
RODS mnemonic
for difficult bag-mask ventilation, 6b
for difficult extraglottic device placement, 6
Roentgen equivalent man (rem), 1949
Roferon-A (interferon alfa-2a), 1723
Rohypnol (flunitrazepam), 2080
Rolando's fracture, 512t-513t, 552
Role expectations, e28
Romano-Ward syndrome, 2166-2167
Rome III criteria, 1262b
Root canal pain, 900-901
Roseola infantum (exanthema subitum), 1571, 1729
clinical features of, 1729-1730
differential considerations, 1730
management of, 1730
Rosiglitazone, 1665t
Ross River virus arthritis, 1513t
Rotator cuff, 618-620, 620f
Rotator cuff tears, 639-640
clinical features of, 640
diagnostic strategies for, 640
management of, 640
pathophysiology of, 639-640
Rotator cuff tendinitis, 637-639, 641f
clinical features of, 638
pathophysiology of, 637-638
Rotator cuff tendinopathies, 1520-1521, 1523
Rotavirus infection, 1249, 1725, 2190
Rotor wash, 2445
Rotor-wing aircraft (helicopters), 2443-2444
Rubber bullets, 434-435
Rubella (German measles), 1571, 1725, 1725f
clinical features of, 1725, 1725f
differential considerations, 1725
management of, 1725
measles, mumps, rubella (MMR) vaccine, 1720t
Rubella virus arthritis, 1513t
Rubeola (measles), 1724-1725
Rubin's maneuver, 2344, 2345f
Rubin's syndrome, 1620
Rucker wagon, 2433, 2434f
Rufinamide (Banzel), 2407t-2408t
Rule of 80 or 80% rule, 939
Rule of nines, 810
Rule of Ten, 812-813, 813t
Rush, Benjamin, 1982
Rust remover, 1995t
RV1 vaccine, 2190

S
Sabril (vigabatrin), 2407t-2408t
Saccharomyces boulardii, 1249
Sacral fractures
transverse, 658f, 659
vertical, 661-662, 664f
SAD PERSONS scale, 1496-1498, 1496t, 1500b
SAFE (Seek support, Allergen identification and avoidance, Follow-up for specialty care, and Epinephrine for emergencies), 1557b
Safe position, 550, 550f
Safety, 2510-2511
air medical transport, 2444-2445
countermeasures for motor vehicle accidents, 336, 369
driving, 2279
in ED, 877
landing zone, 2445, 2445b, 2445f
passive countermeasures, 338
Safety *(Continued)*
personal, e83
ultrasound, 2493-2494
as value, e36
Safety planning, 881
Sager splint, 529, 530f, 680
Sail sign, 599, 600f, 2143-2144, 2144f, 2256, 2256f
Salbutamol, 2072t-2073t
Salicylate poisoning
acute, 1967b
hepatic injury, 1197t
metabolic acidosis due to, 1633
objectives, 1966
in pregnancy, 1967
symptoms of, 1966, 1966b
treatment of, 1966, 1967b
Salicylates, 2318t-2321t
Salicylism, 1966, 1966b
Saline rehydration
for diabetic ketoacidosis, 1660
for hypercalcemia, 1625
for rhabdomyolysis, 1674
Saline solution
characteristics of infusates, 1644t
for hyperkalemia, 1638, 1638t
for hypernatremia, 1642
hypertonic
characteristics of, 1644t
for increased ICP, 314t
for prolonged seizures, 158t-159t
for hyponatremia, 1642, 1644, 1644t, 2222
for hyponatremia in children, 2236
for hyponatremic volume depletion, 2202-2203
for myxedema coma, 1688
Saliva recovery, 864, 864b
Salivary gland stones, 939
Salivary system, 370, 371f
Salmeterol, 1936
Salmonellosis (*Salmonella* infection), 1234-1236, 2191
in AIDS, 1257t
antibiotic therapy for, 1235t
clinical presentation of, 1236
diagnostic strategies for, 1236
differential considerations, 1236
epidemiology of, 1234-1236, 1234t
in immunocompromised patients, 2363
management of, 1236
pathophysiology of, 1236
therapy against, 2192t-2193t
as weapon of mass destruction, 2469
SALT (sort, assess, lifesaving interventions, and treatment or transport) triage system, 2452, 2461
Salter-Harris fractures, 512t-513t, 2250, 2252t
classification of, 517-518, 518t
type I, 518, 518t, 588, 628, 628f, 709, 2250, 2252f, 2252t
type II, 518, 518t, 588, 588f, 2250, 2252t, 2253f
type III, 518, 518t, 2250, 2252t, 2253f
type IV, 518, 518t, 2250, 2252t, 2253f
type V, 518, 518t, 2250, 2252t
Salvia, 2022
Salvia divinorum, 2022
Salvinorin A (divinorin A), 2022
SAMPLE history, 2090, 2090b
Sample size, e13
Sandifer's syndrome, 2234
Sandwich or immunometric assay, 2273, 2274f
Saquinavir, 1721t-1722t, 1766t
Sarcoidosis, 1104-1105
Sarcolemma, 1667
Sarcoma, Kaposi's, 1582f, 1763, 1764f
Sarcomeres, 1075
Sarcoplasmic reticulum, 1075
Sarcoptes scabiei, 1323
Sargramostim, 1952
Sarin (GB), 825, 825t, 1705, 2059, 2469, 2476-2477, 2477b
SARS (severe acute respiratory syndrome), 1733
SARS-CoV disease, 1733
diagnostic strategies for, 1733
differential considerations, 1733-1734
early, 1733

www.ketabpezeshki.com 66485457-66963820

SARS-CoV disease *(Continued)*
management of, 1734
mild to moderate, 1733
patient disposition in, 1734
SARS-CoV virus, 1733
Saturday night palsy, 2386
Save-a-Tooth system (3M), 904
SAVE (Secondary Assessment of Victim Endpoint) system of triage, 2461
Scabies, 1323, 1574-1575, 1574f, 1863
Scald injury, 839
recommendations for prevention of, 816t
water temperature and time to produce, 845-846, 847t
Scalded skin syndrome
staphylococcal, 1567, 1862
streptococcal, 1862
Scale, 1558-1562, 1559t
Scalenus anticus syndrome, 1150
Scalp, 339-340
laceration repair, 757-758, 758f
pediatric injuries, 312-313
wounds on, 360-361
Scaly papules, 1562-1564
Scaphoid bone necrosis, avascular, 577, 577f
Scaphoid fractures, 576-577, 594b-595b
Scaphoid subluxation, 580, 581f
Scaphoid waist fracture, 576, 576f
Scapholunate angle, 574-575, 575f
Scapholunate dissociation, 580, 581f
Scapula, 618
fractures of, 624-625
clinical features of, 625
complications of, 625
diagnostic strategies for, 625
key concepts, 642b
management of, 625
pathophysiology of, 624-625
type II, 625, 625f
manipulation of, for shoulder relocation, 633, 633f
Scapulothoracic dislocation, 637
Scapulothoracic dissociation, 637, 637f
Scarlet fever, 1571-1572
clinical features of, 1571
management of, 1572
Scene flights, 2443
Scheele, Carl Wilhelm, 825
Schistosomiasis (*Schistosoma haematobium, S. japonicum, S. mansoni, S. mekongi* infection), 1770t-1771t, 1778
drug regimens for, 1772t-1775t
gastrointestinal symptoms of, 1782, 1783f
Schizoaffective disorders, 1462
Schizocytes, 1595, 1595f
Schizophrenia, 1460
active phase, 1460
clinical features of, 1460-1461
diagnosis of, 1460-1461, 1461b
differential considerations, 1461-1462
etiology of, 1460
negative symptoms of, 1461
pathophysiology of, 1460
pharmacotherapy for, 1460
phases of, 1460
premorbid phase, 1460
residual phase, 1460
Schizophreniform disorders, 1462
School-age children, 1333t, 1334, 2090
School violence, e1
Schrader, Gerhard, 825
Schwann cells, 45
Sciatic mononeuropathy, 1437
Sciatic nerve, 1437, 1437f
Sciatic nerve injury, 693
Sciatica, 644
acute back pain in, 282t-283t
bowstring sign of, 645-646
Scintigraphy
with iminodiacetic acid (IDA), 1202
myocardial, 1020
in pulmonary embolism, 1164
Scleral lacerations, 917
Scleral penetration, 193t-196t
Scleral (globe) rupture, 915-916, 915f
key concepts, 930b
out-of-hospital care for, 376
ultrasound imaging of, 374, 375f
Scleritis, 190, 191f, 193t-196t
Scleroderma (systemic sclerosis), 1517
oral manifestations of, 902
renal crisis, 1297
Sclerosing cholangitis, 1204
Sclerosis, systemic (scleroderma), 1517
Scombroid fish poisoning, 1246
clinical presentation of, 1246
epidemiological aspects, 1243t
epidemiology of, 1246
key concepts, 1260b
management of, 1246
pathophysiology of, 1246
Scope of practice, 2435-2436
Scopolamine (Transderm Scop)
duration of action, 191t
labor interactions, 2340t
for nausea and vomiting of motion sickness, 246
Scorpion stings, 805
Scorpions, 795t, 803-805, 805f
Screening
for family violence, 878
for intimate partner violence, 878-879
for UTIs in children, 1334f
Scrofula (tuberculous lymphadenitis), 1818-1819
Scrotal carcinoma, 2211
Scrotal masses, in children, 2208-2211
Scrotal pain
acute, 1342-1349
differential considerations, 1343
key concepts, 1354b
physical examination findings, 1342
Scrotal swelling
causes of, 1343b
in children, 2208-2211
idiopathic, 2210
Scrotal trauma
blunt, 497
management of, 498
Scrotum, 1342, 1343f
SCUBA (self-contained underwater breathing apparatus), 1915
Scuba diving, 1915-1927
focused dive history, 1922b
Sea snake bites, 801
Sea urchins, 806
Sea wasps, 806
Search and rescue, urban, 2453-2456, 2456b
Searches, personal, 2420
Seashore sign, 2498-2499, 2498f
Seasonal affective disorder, 1470
Seat belt sign, 310
Seat belts
during pregnancy, 298, 2279
seatbelt injuries, 461
Seclusion, 2416
Secondary Assessment of Victim Endpoint (SAVE) system of triage, 2461
Secure examination rooms, 2420-2421
Security
patient searches for, 2420
scene, 1912-1913
Security personnel, 2420
Sedation
ACEP policy statement on, 51b
in cerebral ischemia, 86
conscious, 50
deep sedation/analgesia, 51, 51f, 52t
definition of, 50
dissociative, 51, 52t
minimal (anxiolysis), 50, 51f, 52t
moderate sedation/analgesia, 50, 51f, 52t
pharmacologic, for cocaine overdose, 2002
procedural, 32b
procedural sedation and analgesia (PSA), 50-60
of survivors, e54
Sedative-hypnotics, 2076-2083
key concepts, 2083b
in pregnancy, 2318t-2321t, 2322
withdrawal from
Sedative-hypnotics *(Continued)*
anxiety in, 1477
vital signs in, 2419t
Sedatives
definition of, 32b
overdose, 1955t, 2419t
Sediment analysis, 1338
Segond fracture, 706, 706f
Seidel's test, 917
Seizures, 156-161, 1375-1385
absence, 1376
acute symptomatic
in children, 2236
etiology of, 2234, 2234b
afebrile
in children, 2235
laboratory testing in, 2235-2236
radiographic imaging in, 2236
special procedures for, 2236
alcohol-related, 2382-2384
with abnormal findings, 2383-2384
admission guidelines for, 2393
differential diagnosis of, 2383b
new-onset, 2383
new-onset partial seizures, 2383
with normal findings, 2383
alcohol withdrawal, 2383
with altered mental status, 2236
altitude and, 1939
ancillary testing in, 160-161
in anticholinergic overdose, 1973
antipsychotic-induced, 2049
atonic, 1376
and brain damage, 2231
breakthrough, 2407
in bupropion overdose, 1979
caused by aneurysms, 1379
caused by AVMs, 1379
caused by degenerative disease of central nervous system, 1379
caused by drugs and toxins, 1378
caused by infectious diseases, 1378
caused by metabolic derangements, 1377-1378
caused by migraines, 1379
caused by strokes, 1379
caused by trauma, 1378
in cerebral ischemia, 86
classification of, 156, 2231, 2231b
clinical features of, 139t, 1376-1380
complex partial, 1375-1376, 2231
convulsive, 156, 2231
cryptogenic, 1375
definition of, 156, 1375
diagnosis of, 157-161, 1380
differential considerations, 157, 158t, 1380-1381
in disabled patients, 2407-2409
drugs that may cause, 2235b
duration of, 159
early post-traumatic, 2234
eclamptic, 1382
EEG findings in, 160-161
epidemiology of, 156
episodic disorders that may mimic, 2233b
febrile, 2232
advice to parents about, 2238b
in children, 2102-2103, 2226-2227, 2235
focal, 1376, 2236
focal (partial), 1375
generalized, 156, 1375-1376, 2231
gestational, 1379
in head injury, 350, 359
history taking in, 159-160
in hyponatremia, 2222
ictal events, 159
idiopathic, 1375
imaging in, 160
immediate management of, 1381-1383
impact seizures, 2234
indications for cranial CT in, 160b
intractable, 1633
key concepts, 1385b
laboratory testing in, 160
long-term management of, 1383-1384
with malignancy or vasculitis, 1378-1379
management of, 161, 1381-1384

www.ketabpezeshki.com 66485457-66963820

Seizures (Continued)
myoclonic-atonic, 1376
neonatal, 2232-2233, 2236
diagnostic assessment of, 2239b
nonconvulsive, 2231
nonconvulsive generalized, 1375-1376
onset of, 159
partial, 2383
partial with secondary generalization, 1375
pathophysiology of, 156-157, 1375-1376
patient disposition in, 161
pediatric, 156, 1375, 2094, 2231-2239
clinical features of, 2231-2233
diagnostic strategies for, 2234-2235
differential diagnosis of, 2233-2234
etiology of, 2234
in head injury, 312
history taking in, 2235
management of, 2235-2238
pathophysiology of, 2231
patient disposition in, 2238
summary approach to, 2235b
physical examination findings, 160
pivotal findings, 159-161
postictal period, 1375
postictal states, 1379-1380
in pregnancy, 2308
prolonged, 157, 158t-159t
prophylaxis for, 350, 350b
psychogenic nonepileptic, 1379
rapid assessment and stabilization of, 157-159
reactive (secondary), 1375, 1377-1379
recurrent, 1380
remote symptomatic, 2234, 2234b
simple partial, 1375, 2231
symptomatic, 1375
in systemic lupus erythematosus, 1528
Seldinger technique, 483-484, 484f
Selection bas, e10
Selective norepinephrine-reuptake inhibitors
for anxiety disorders, 1479
overdose, 1979
clinical features of, 1979
diagnostic strategies for, 1979
differential considerations, 1979
management of, 1979
patient disposition in, 1979
Selective serotonin-reuptake inhibitors
for anxiety disorders, 1478-1479, 1479t
half-lives, 1978
herbal medicine interactions, 2072t-2073t
overdose, 1978-1979
clinical features of, 1978
diagnostic strategies for, 1978
management of, 1978
patient disposition in, 1978-1979
and suicide, 1494
Selenium poisoning, 1955t
Selenium sulfide shampoo, 1559
Self-abuse, 885-886
Self-destructive patients, 2426, 2428t, 2429-2430
Self-expanding stents, 510b
Self-harm
British Manchester Self-Harm Rule, 1498
elder abuse, 325
epidemiology of, 1492
gunshot wounds, 358
knife wounds, 839, 840b, 840f
Self-neglect, 885-886
Self-perceptions, negative, 2425
Seminal fluid loss, 866, 866t
Sengstaken-Blakemore tube, 252
Senna (Senokot, Ex-Lax), 264t-265t
Sensitivity, e20t
Sensitivity analyses, e17-e18
Sensitization, 1549
central, 34
Sensorimotor polyneuropathies, distal, 1432b
Sensorineural hearing loss, sudden, 936
Sensory dermatomes, 400, 401f
Sensory examination, spinal, 400, 400t
Sensory function testing, 1422
Sensory loss, 280
Sensory nerves, of hand, 543, 543f
Sensory neuronopathy, 1439-1440, 1439b
Sepsis, 1864
in abnormal host, 2227
antibiotic management of, 1872t
cardiovascular dysfunction with, 1866
cardiovascular support in, 1871
clinical features of, 1867-1868
definition of, 1864, 1865b
diagnostic strategies for, 1868-1869
differential considerations, 1869, 1869b
endocrine dysfunction with, 1866-1867
epidemiology of, 1864
gastrointestinal dysfunction with, 1866
goal-directed protocol for, 1870f
gram-positive, 68
hematologic dysfunction with, 1867
incidence of, 1864, 1865f
in infants, 2226
key concepts, 1873b
management of, 1869-1873
mediators of, 1865
microbiology of, 1868
Mortality in Emergency Department Sepsis (MEDS) prediction rule, 1868, 1868t
mortality rates, 1865-1866, 1866f
neurologic dysfunction with, 1866
novel concepts, 1867
novel therapies for, 1872-1873
pathophysiology of, 1864-1865
patient disposition in, 1873
in pneumococcemia, 1708
pulmonary dysfunction with, 1866
radiology of, 1869
respiratory support in, 1870-1871
severe, 70b, 1864, 1865b
special procedures for, 1868-1869
steroid therapy for, 1873
symptoms and signs of, 1708, 1867-1868
syndromes, 1864-1873
Septal shift, 1080
Septic arthritis, 1505-1508, 1831, 1834, 1844-1850
acute, 2264-2266
antibiotic treatment of, 1835t, 1849, 1849t
in atypical joints, 1848
clinical features of, 1506, 1844
clinical subsets, 1846-1848
complications of, 1846
definition of, 1831
diagnostic strategies for, 1506-1507, 1844-1846
differential diagnosis of, 694, 1848-1849
epidemiology of, 1505
gonococcal, 1847
in hand, 568
clinical features of, 568
management of, 568
pathophysiology of, 568
history taking in, 1844
in infants and children, 1846
with joint disease, 1848
key concepts, 1517b, 1850b
in knee, 717
Kocher criteria for, 1846, 1846t
late, 1504t
management of, 1507-1508, 1849
microbiology of, 1506, 1507t, 1834-1835, 1834t-1835t
pathophysiology of, 1505-1506
patient disposition in, 1849-1850
periprosthetic infection, 1848
physical examination findings, 1844
synovial fluid findings, 2265t
treatment of, 2265t
ultrasound imaging of, 1845, 1846f
Septic bursitis, 716, 1524-1525, 1831
Septic knee, 716
Septic shock, 68-69
in children, 105-108
clinical features of, 106
corticosteroids for, 108
fluid resuscitation in, 106
management of, 106-108, 107f
pathophysiology of, 105-106
substrate correction for, 106
vasoactive medications for, 107-108
clinical management guidelines, 73b
definition of, 70, 70b, 105, 1864, 1865b
Septic shock (Continued)
diagnostic criteria for, 70, 70b
differential considerations, 1869b
mediators of, 1865
with myocardial failure, 68b
treatment of, 73-74
Septic thrombosis, 975
Septicemia, 1891
meningococcal, 1712
postanginal, 975
Septicemic plague, 2474
Sequestration, abnormal, 1600
Serax (oxazepam), 2078t
Serenity, tranquility, and peace (STP) (4-methyl-2,5-dimethoxyamphetamine), 2017
Serious bacterial illness, 2096
in children, 2102
in infants, 2100-2102
Serositis, 1528t
Serotonin 5-HT_3 receptor antagonists, 2318t-2321t, 2329
Serotonin-like agents, 2015-2017
intoxication
clinical features of, 2016
diagnostic strategies for, 2016
differential considerations, 2016
management of, 2016
patient disposition in, 2016-2017
pharmacology of, 2015
Serotonin syndrome, 1956, 1976, 1980
antidote for, 1957t-1958t
clinical features of, 1980, 2053
diagnostic strategies for, 1980
differential considerations, 1980
Hunter criteria for, 1980, 1980t
management of, 1980
patient disposition in, 1980
xenobiotics implicated in, 1980t
Serum markers
in acute coronary syndrome, 1016-1020, 1018f
multiple marker strategies, 1019-1020
Serum sickness, 801, 1541t
Serum tests
chemical analysis, 1292
for megaloblastic anemia, 1593t
Serum therapy, 1710
Sesamoid fractures, 747
Sestamibi test, 1017t
Severe acute respiratory syndrome (SARS), 1733
SARS-CoV disease, 1733
Sever's disease, 2269-2270
Sexual abuse
child abuse, 845, 849
diagnostic strategies for, 851
differential considerations, 852
incidence of, 846t
signs and symptoms of, 850
definition of, 886
elder abuse, 870, 885
intimate partner, 877
questions to ask about, 887b
signs of, 888, 888b, 888f
STI prophylaxis or treatment after, 851, 851t
Sexual assault, 855-871
consent issues in, 857b
definition of, 855
ED functions in, e62
of elderly, 870
epidemiology of, 855-857
evidence collection in, 863-867, 863b
foreign objects in, 863
genital injury in, 865, 865f
hepatitis B prophylaxis after, 868b
history of, 857-862
intimate partner violence, 873
key concepts, 871b
methods of control in, 862-863
offenders
male suspect examination, 870-871
methods to avoid detection, 863
sexual dysfunction in, 863, 863b
pregnancy after, 867-869
pregnancy prophylaxis in, 868
prevalence of, 856
recording of, 862

www.ketabpezeshki.com 66485457-66963820

Sexual assault *(Continued)*
sexually transmitted diseases after, 867-869
prevention prophylaxis for, 868b
risk of, 867-868, 867t
somatic and emotional reactions after, 869b
victims
debriefing, 869-870
drug and alcohol use among, 862
elderly victims, 870
evaluation of, 855
follow-up HIV testing, 868
history taking from, 857, 857b
male, 870
management of, 855, 857
preparation for, 857
Sexual assault examination
abbreviated, 855
anogenital examination, 865-866, 865f
consent for, 856f, 857
documentation of findings, 863-864, 863b
double-swab technique for recovery of saliva from human skin, 864, 864b
genital injury correlates at time of, 865b
head, neck, and oral cavity, 864-865
informed consent for, 856f
photographic documentation of findings, 866-867, 867b
physical examination, 863-867
restricted, 856f
skin examination, 864
staining techniques for, 866
Sexual assault forms, 857, 858f-861f
Sexual assault nurse examiner (SANE), 855
Sexual assault response team (SART), 855
Sexual dysfunction
definition of, 863b
in sexual offenders, 863, 863b
Sexual experience, prior, 862
Sexual history, 1277b
Sexual intercourse, 2279
Sexually transmitted diseases, 1312-1325
anorectal, 1285-1288, 1286t, 1289b
anorectal transmission of, 1285
clinical features of, 1331t
differential diagnosis of, 1313t
evaluating children or adolescents for, 851
genital discharge, 1319-1325
genital lesions, 1312-1319
key concepts, 1325b
in pregnancy, 2298
prevention of, 868b
after sexual abuse/assault, 851, 851t, 867-869, 867t, 868b
treatment guidelines, 1315t
ulcerative
characteristics of, 1313t
differential diagnosis of, 1313t
Sexually transmitted infections (STIs). *See* Sexually transmitted diseases
Shaken baby syndrome, 313, 355, 848, 848f
Sharp force pattern injuries, 839
Shear injury, 385
Sheep liver fluke *(Fasciola hepatica)*, 1772t-1775t
Sheeting, antishock, 668, 668f
Shenton's line, 688, 688f
Shift work, 2508-2509, 2508f
rational approaches to, 2509, 2509b
strategies for, e81b
Shiga toxin–producing *Escherichia coli* (STEC) gastroenteritis, 1234t-1235t, 1239-1240
Shigellosis (*Shigella* enteritis), 1237-1238, 2191-2193
in AIDS, 1257t
antibiotic therapy for, 1235t
clinical presentation of, 1237
diagnostic strategies for, 1237
differential considerations, 1237
epidemiological aspects of, 1234t
epidemiology of, 1237
management of, 1237-1238
pathophysiology of, 1237
treatment of, 1257t, 2192t-2193t
Shikani optical stylet (SOS; Clarus Optical), 19, 19f
Shin splints, 722
Shingles (herpes zoster), 1579, 1579f, 1728
antimicrobial agents useful for, 2361t
clinical features of, 1579, 1728-1729, 1729f
drugs for treatment of, 1721t-1722t
in immunocompromised patients, 2361t
Shock, 67-69
anaphylactic, 68b, 1551
cardiogenic, 69, 1002
clinical management guidelines, 73b
definition and diagnostic criteria for, 70, 70b
reperfusion therapy in, 1032
treatment of, 74
cardiovascular changes in pregnancy that mimic, 296
causes of, 67-69
circulatory, 69b
classification of, 67, 68b, 69f
clinical features of, 69-70
definition of, 70
diagnostic criteria for, 69b
epidemiology of, 67
hemorrhagic, 67-68, 68b
clinical management guidelines, 73b
definition and diagnostic criteria for, 70, 70b
treatment of, 72-73
hypodynamic, 68b
hypovolemic, 296
key concepts, 74b
management of, 71-74, 73b
pediatric, 308
septic, 105-108
signs of, 106t
septic, 68-69
clinical management guidelines, 73b
definition of, 70, 70b, 105, 1864, 1865b
diagnostic criteria for, 70, 70b
differential considerations, 1869b
with myocardial failure, 68b
pediatric, 105-108
treatment of, 73-74
spinal, 418
treatment of specific causes, 72-74
undifferentiated, 69, 69f
Shocks, ICD malfunction, 1072, 1073f
Shootings, drive-by, e4
Shopping cart sign, 280
Short-acting beta$_2$-adrenergic agonists (SABAs)
for asthma, 949-950, 2120, 2121t, 2122
for asthma in children, 2122
intermittent vs continuous therapy with, 2123
intravenous, 2124
subcutaneous or intramuscular therapy with, 2123-2124
Shortcut reviews, e21
Shortness of breath
anxiety in, 1476
in dialysis, 1309
differential considerations, 1532t
at end of life, e57
Shotgun cartridges, 834, 837f
Shotgun pellets, 834, 837f
Shotgun slugs, 834, 837f
Shotgun wounds
abdominal, 460-461, 474-475
forensic evaluation of, 834
peripheral vascular injury, 500-501
Shotguns, 834
Shoulder, 618
immobilization of, 623, 623f, 634, 634f
Shoulder apprehension test, 634, 634f
Shoulder dystocia, 2344-2345, 2344f
diagnostic strategies for, 2344
HELPER mnemonic for, 2345b
incidence of, 2342t
management of, 2344-2345
Shoulder exercises
active, 624, 624f
passive, 624, 624f
Shoulder girdle, 618-620, 619f
Shoulder-hand syndrome, 523
Shoulder injuries, 618-642
bursitis, 1519f
clinical features of, 620-621
diagnostic strategies for, 621
Shoulder injuries *(Continued)*
dislocation, 628-637
anterior subluxation, 634
key concepts, 642b
nerve injury in, 520t
frozen shoulder, 624
history taking in, 620
impingement syndromes, 637-639
key concepts, 642b
physical examination findings, 620-621
radiography of, 621, 621f-622f
radiology, 621
soft tissue conditions, 637-642
tendinopathy, 1520-1521
Shoulder roll, 2087, 2088f
Shrug sign, 1520
Shudder attacks, 2233
Shunts
polytetrafluoroethylene, 506-507
ventriculoperitoneal, 2105, 2410, 2410f
Shur-Clens detergent, 756t
Sialic acid, 2380t
Sialolithiasis, 939
Sick sinus syndrome, 1043
Sickle cell anemia
blood transfusion for, 1599
in pregnancy, 2301t-2303t, 2307
Sickle cell disease, 1596-1600
altitude and, 1939
in children, 2104
clinical features of, 1597-1598
key concepts, 1605b
management of, 1598-1599
organ damage seen in, 1598t
osteomyelitis in, 1842
pathophysiology of, 1596-1597
in pregnancy, 2307
urinary tract infection in, 1330
Sickle cell trait, 1597
Sickle cells, 1598, 1598f
Sickle cell–β-thalassemia, 1599
Sideroblastic anemia, 1591
SIDS Alliance, 110
Sigmoid volvulus, 1267
bird's beak sign of, 1267, 1268f
clinical features of, 1267
diagnostic strategies for, 1267
management of, 1268-1269
radiographic findings, 1267, 1268f
Signet ring sign, 580
Sildenafil, 1936
Silent suicide, 1492
Silent suicide attempts, 1496
Silver (Spice), 2021
Simmonds (Thompson) test, 1522
Simple Triage and Rapid Treatment (START), 2459-2460, 2460f
Simple Triage and Rapid Treatment (START) JumpSTART, 2460
Simvastatin, 2072t-2073t
Sinecatechins, 1319
Sinoatrial exit block, 1042-1043
Sinoatrial node, 1034
Sinus arrest, 1042-1043, 1043f
Sinus bradycardia, 1041-1042, 1042f
pediatric, 2155
Sinus dysrhythmia, 1042, 1043f
Sinus tachycardia, 1048-1049, 1049f, 2157t
Sinusitis
differential diagnosis of, 976
frontal, 976
maxillary, 901
rhinosinusitis, 975-977
Sitagliptin, 1665t
Situational couple violence, 875
Sixth cranial nerve palsy, 929
Sixth disease, 1571
Skeletal infection, 1850b
Skeletal injuries
in child physical abuse, 847-848
electrical, 1911
lightning injury, 1911
Skeletal muscle, 1667, 1668f
Skeletal muscle relaxants, 44-45

www.ketabpezeshki.com 66485457-66963820

Skier's thumb (ulnar collateral ligament injuries), 556
Skin
anatomy of, 751, 1851, 1852f
biomechanical properties of, 752
diabetic conditions, 1664
diabetic thick skin, 1664
hand cover, 534
orange peel skin *(peau d'orange)*, 1852
physiology of, 1851
preparation for wound management, 755
in spinal injury, 419
topical anesthetics applied to, 47-48
Skin abscess, 1855-1858, 1863b
Skin examination, 864
Skin growths, 1558
Skin infections, 1851-1863
algorithm for, 1857f
antibiotic therapy for, 1856t
antibiotics for, 1854t
with atopic dermatitis, 1563-1564
bacteriology of, 1856t
clinical features of, 1851-1852
diagnostic strategies for, 1852-1853
epidemiology of, 1851, 1852f
in HIV infection, 1763-1764, 1763b
key concepts, 1863b
necrotizing, 1860-1861
pathophysiology of, 1851
symptoms and signs of, 1851-1852
Skin injury
electrical, 1910-1911
lightning injury, 1911
Skin lesions, 1558
associated with internal malignant disease, 1580-1584
associated with narcotic addiction, 1584, 1584f
associated with systemic disease, 1580, 1581t
definitions, 1559t
nodular, 1576
papular, 1572-1576
vesicular, 1576-1580
Skin mottling, 2092, 2092f
Skin popping, 2001
Skin resistance, 1908t
Skin spots, diabetic, 1665
Skin tears, 758
Skin tension lines, 751, 752f
of body, 752f
of face, 752f
Skull, 339-340
fetal, 2334f
Skull fractures, 361-362
basilar, 361-362
clinical characteristics of, 347b
meningitis after, 359
in child abuse, 847-848, 847f, 2259-2260
in children, 313
clinical assessment and significance of, 361
comminuted, 361
complex, 847-848, 847f
depressed, 361
growing, 358
linear, 361
open, 362
Sleep aids, 2081-2082
Sleep apnea-related respiratory support, 1089
Sleep debt, 2508-2509
Sleep deprivation, 2508, 2508b
Sleeping sickness *(Trypanosoma brucei rhodesiense)*, 1772t-1775t
Sleeptalking (somniloquy), 2233
Sleepwalking (somnambulism), 2233
Sling-and-swathe bandages, 529
Slipped capital femoral epiphysis, 695-696, 695f-696f
anatomy of, 695
in children, 2267-2269
clinical features of, 695-696
diagnostic strategies for, 696
epidemiology of, 672, 695
key concepts, 697b
pathophysiology of, 695
radiographic findings, 2268, 2268f
treatment of, 696
Slit-lamp examination, 186-187, 188f
Slow infections, 1740
Slow virus infections, 1740
SLUDGE (salivation, lacrimation, urination, defecation, and gastrointestinal emesis) symptoms, 825-826, 1956, 2058t
Small bowel edema, 465-466, 466f
Small bowel obstruction, 1216-1221
clinical features of, 1219
closed-loop, 1216, 1217f
complications of, 1219
diagnostic strategies for, 1219-1220
differential considerations, 1220
functional, 1216
history in, 1219
key concepts, 1221b
lesions causing, 1216, 1217b
management of, 1220-1221
mechanical, 1216
neurogenic, 1216
patient disposition in, 1220-1221
physical examination findings, 1219
pseudo-obstruction, 1216-1217
radiographic findings, 1218f, 1219, 1221f
simple, 1216
Small bowel volvulus, 1218
Small intestine, 1216-1224, 1224b
Smallpox, 1579-1580, 1580f, 1725-1727, 2475-2476, 2475f
clinical features of, 1726
diagnostic strategies for, 1726
differential diagnosis of, 1580t, 1726, 2475-2476
key concepts, 2478b
management of, 1726
treatment of, 2476
as weapon, 2469, 2475
Smallpox vaccine (Dryvax), 1720t, 2476
SMART COP score, 986
Smith's fracture, 512t-513t, 584, 585f
Smoke, 2037t
Smoke bombs, 825, 825t
Smoke inhalation, 2038-2039
clinical features of, 2038
diagnostic strategies for, 2038-2039
differential considerations, 2038-2039
key concepts, 2043b
management of, 2039
patient disposition in, 2039
Smooth muscle relaxants, 2303t
Snake venom, 796, 807b
Snakebites, 807b
Snakes
classification of, 796
venomous, 794-795
identification of, 795, 796f
venom delivery, 796-797
Snowbird reduction, 632-633
Social cognitive theory, 881
Social ecology model, 875
Social phobia, 1475b, 1477-1478, 1479t
Social problems, alcohol-related, 2393-2394
Social relationships, physician, e82
Societal values, e35b
Society for Academic Emergency Medicine (SAEM), 2467, 2492, e36, e37t
Society of Medical Ultrasound in Medical Education, 2492
Socrates, 723
Soda lime, 1919
Sodium
in diabetic ketoacidosis, 1658t
fractional excretion of (FENa), 1292, 1292b
in hyperglycemic hyperosmolar state, 1658t
requirements for, in hypertonic dehydration, 2203b
serum
in acute bacterial meningitis, 2228
in diabetic ketoacidosis, 1658
infusates and, 1644
urine, 1292
Sodium azide, 825
Sodium bicarbonate ($NaHCO_3$)
for acidemia, 1634
for acute renal failure in children, 2218
for beta-blocker toxicity, 1989
for hyperkalemia, 1305t
Sodium bicarbonate ($NaHCO_3$) *(Continued)*
for hypoxic (tet) spells, 2150-2151
for metabolic acidosis, 822, 1634
in pediatric resuscitation, 104t
for rhabdomyolysis, 1674
Sodium deficits
in diabetic ketoacidosis, 1657, 1657t
in hypertonic dehydration, 2203b
Sodium excess, 1081
Sodium hydroxide (NaOH), 1994
Sodium hypochlorite, 1562
Sodium intake, 1115
Sodium iodide, 1682b
Sodium nitrite, 826-827, 1957t-1958t, 2040-2041
Sodium nitroprusside
for aortic dissection, 1128
hemodynamic effects, 1118t
for hypertension, 1119t
for hypertensive emergencies, 2304t
for ischemic stroke, 1371b
Sodium phosphate (Na_2PO_4 and $NaPO_4$) (Fleet Phospho-soda)
for constipation, 264t-265t
for hypophosphatemia, 1651
Sodium-potassium–adenosine triphosphatase (Na^+,K^+-ATPase) pump, 1667, 1668f
Sodium thiosulfate, 826-827, 1957t-1958t, 2040-2041
Soft tissue disorders
of elbow, 614-616
infections, 1851-1863
algorithm for, 1857f
antibiotics for, 1854t
diagnostic strategies for, 1852-1853
epidemiology of, 1851, 1852f
key concepts, 1863b
necrotizing, 1860-1861
ocular, 920-921
of shoulder, 637-642
Soft tissue foreign bodies, 783-784
diagnostic strategies for, 783-784
history taking in, 783
management of, 784
physical examination findings, 783
Soft tissue injuries
ankle injuries, 731-734
dental emergencies, 905-906
facial, 376-377
of femur, 691-693
of hand, 553
of hip, 691-693
knee injuries, 713-715
in lower leg, 721-722
orthopedic, 526-528
of wrist, 588-589
Soft tissue procedures, US-guided, 2503, 2503f
Soft tissue ultrasound, 2499-2500
Solar urticaria, 1569
Solid organ transplant patients, 2368-2377
complications in
clinical features of, 2372
diagnostic strategies for, 2372
disposition of, 2376-2377
key concepts, 2377b
Solu-Medrol (methylprednisolone), 1555
Solvent exposures
eye exposures, 910-912
odor in, 1955t
Soman (GD), 825, 825t, 2059, 2476-2477
Somatic pain, 223
Somatic reactions, 869b
Somatization, 1481
Somatization disorder
clinical features of, 1481
diagnostic criteria for, 1481, 1482b
key concepts, 1486b
Somatoform disorders, 1481-1486
anxiety in, 1477
clinical features of, 1481-1483
diagnosis of, 1482b, 1483-1484
differential considerations, 1483-1484
key concepts, 1486b
legitimization of symptoms of, 1484
management of, 1484-1485
medications for, 1484-1485
not otherwise specified, 1482b

www.ketabpezeshki.com 66485457-66963820

Somatoform disorders *(Continued)*
organic diseases that may be mistaken for, 1483-1484, 1484b
patient disposition in, 1485
treatment goals, 1485
undifferentiated, 1482b
Somnambulism (sleepwalking), 2233
Somniloquy (sleeptalking), 2233
Somnolence, irritable, 958
Somogyi phenomenon, 1655
Sonata (zaleplon), 2080
Soot, 829-830, 831f
with exit wounds, 833, 835f
testing for, 830, 832f
Sorbitol, 264t-265t
Sore throat. *See* Throat, sore
Sotalol, 1039, 1987t, 2318t-2321t
South American trypanosomiasis (*Trypanosoma cruzi* infection), 1772t-1775t, 1776
Space of Poirier, 570
Spacers (valved holding chambers), 950
Spasmodic croup, 2113
Spasms
arterial, reversible, 501
infantile, 2231-2233
Spastic paraparesis
idiopathic, 1425
tropical, 1740
Spathiphyllum, 2070
Spatula test, 1702
Special K, 2019
Special needs populations
adults, 2400-2401
care of, 2462
children, 2093-2094, 2400-2401
key concepts, 2413b
youth, 2401
Special Operations Forces Tactical Tourniquet (SOFT-T), 2451
Special populations, e72
Special response teams, 2450, 2450f
Specialized transports, 2440-2441
Specialty Care Model of system intervention, 880-881
Specificity, e20t
Spectinomycin, 1835t
Speech, disorganized, 1461
Sperm
factors influencing loss of, 866, 866t
maximum reported time intervals for recovery of, 867t
Spermatocele, 1349
Spherocytosis, 1595, 1595f
Sphygmomanometry, 61
Spice (Diamond, Gold, Silver), 2021
Spider bites, 794, 795t, 807b
Spiders, 803-805
Spigelian hernia, 1217
Spilled teacup sign, 581
Spina bifida, 2409
Spinal accessory nerve (CN XI), 1410t-1411t
Spinal column
ligaments of, 382, 384f
stabilization of, 415-416
Spinal cord, 33f, 1419, 1420f
Spinal cord compression, malignant, 1627-1628, 1628b
Spinal cord disorders, 1419-1427
cervical enlargement, 1419
clinical features of, 1422
diagnostic strategies for, 1422-1423
differential considerations, 1423
in disabled persons, 2409-2410
extrinsic lesions, 1425-1427
history in, 1422
intrinsic lesions, 1424-1425
key concepts, 1427b
lumbar enlargement, 1419
management of, 1424
motor function testing in, 1422
nontraumatic, 1423b
physical examination findings, 1422
reflexes in, 1422
sensory function testing in, 1422
syndromes, 1421t
Spinal cord disorders *(Continued)*
classification of, 1420-1422
complete (transverse), 1420
incomplete, 1423
Spinal cord infarction, 1425
Spinal cord injury
acute, 419b
causes of, 382
classification of, 396
complete, 400
incomplete, 400-402, 402f, 418-419, 1420-1421
mechanism of, 396, 398f
in older adults, 327-328
pediatric
clinical features of, 316
management of, 317-318
pharmacotherapy for, 418-419
phase of, 317-318
in pregnancy, 2308-2309
primary, 396
secondary, 396, 399f
treatment strategies currently under investigation, 419b
Spinal cord injury without obvious radiographic abnormality (SCIWORA), 382, 401-402
in older adults, 326
pediatric, 315
Spinal cord neoplasms, 1426-1427
clinical features of, 1427
diagnostic strategies for, 1427
differential considerations, 1427
management of, 1427
Spinal epidural abscess, 1426
acute back pain in, 282t-283t
clinical features of, 1426
diagnostic strategies for, 1426
differential considerations, 1426
management of, 1426
Spinal epidural hematoma, 1425-1426
clinical features of, 1425
diagnostic strategies for, 1425
differential considerations, 1425
management of, 1426
Spinal fractures, 382
acute back pain in, 282t-283t
axial CT of, 412f
burst fractures, 393-396, 394f-396f, 409f
clay shoveler's fracture, 385, 388f
CT of, 411f
laminar, 407, 409f, 412f
minor, 420
teardrop, 385, 387f
vertical compression fractures, 385t
wedge, 382-385, 387f
Spinal infection
with low back pain, 647
magnetic resonance imaging of, 649-650, 650f
management of, 653
Spinal injuries, 382-420
acute, 382
airway management in, 416-418
associated injuries, 419
cervical, 418f
classification of, 382-396, 385t
clinical features of, 396-402
diagnostic strategies for, 402-415
epidemiology of, 382
extension injuries, 385t, 393
flexion injuries, 382-385, 385t
flexion-rotation injuries, 385-393, 385t
key concepts, 420b
management of, 415-420
neurologic evaluation of, 396-400
out-of-hospital care, 415-416
pathophysiology of, 382-396
patient disposition in, 420
pediatric, 315-318
clinical features of, 316
management of, 317-318
radiology in, 316-317
prognosis for, 419-420
radiographic evaluation of, 402-415
stability of, 382
treatment of, 419-420
Spinal meningitis, 1821
Spinal motor examination, 399, 399t
Spinal reflex examination, 399-400, 400t
Spinal sensory examination, 400, 400t
Spinal shock, 418, 1420
Spinal stenosis, 646
acute back pain in, 282t-283t
management of, 652
Spinal subarachnoid hemorrhage, 1424-1425
clinical features of, 1425
diagnostic strategies for, 1425
differential considerations, 1425
management of, 1425
Spinal subluxation, 385, 388f-389f
Spinal tracts, 32f
Spine
anatomy of, 382
examination of, 1502
physiology of, 382
Spinolaminar line, 316, 317f
Spiral femoral shaft fractures, in children, 694
Spironolactone, 1122.e1t-1122.e2t
Splash burns, 846-847, 847f
Splenectomy, 2359b, 2365-2366
Splenic artery aneurysms, 1147-1148
Splenic injury
laceration, 465-467, 465f-467f
traumatic, in children, 321
Splenic sequestration, 1610
Splinting, 528-531
clavicle, 529
clavicular or figure-of-eight splint, 623, 623f
commercial splints, 528, 528f
dynamic, 548, 549f
ED care, 529
fiberglass splints, 529
field care, 528-529
forearm splints, 529
Hare traction splint, 529, 530f
lower extremity, 529-531
plaster splints, 529
Sager splint, 529, 530f
thumb spica splint, 577, 577f
traction splints, 680
upper extremity, 529
wrist splints, 529, 529f
Split-mindedness, 1460
Split root syndromes, 901
Spondylitis, 649, 649f
Spondyloarthropathies, seronegative, 1515-1516
Spondylolisthesis
anterior, 649, 649f
degenerative, 646-647
Spongiform leukoencephalopathy, 2053
Spontaneous bacterial peritonitis, 1195-1196
clinical features of, 1195
diagnostic strategies for, 1195
differential considerations, 1195
key concepts, 1196b
management of, 1195
patient disposition in, 1195-1196
Spontaneous circulation return, 81-82
Spontaneous hemopneumothorax, 991
Spontaneous hyphema, 191
Spontaneous pneumomediastinum, 991
Spontaneous pneumothorax, 988-992
clinical features of, 989-991
definition of, 988
incidence of, 988
key concepts, 996b
management of, 991-992
outcome, 992
pathophysiology of, 988-989
primary, 988
secondary, 989
causes of, 988, 989b
key concepts, 996b
Sporadic thyroiditis, 1678
Sports-related injuries
in children, 320
muscular injuries, 691
Spouse abuse, 872
Sprains, 526-527
assessment of, 526
cervical, 420
definition of, 526

www.ketabpezeshki.com 66485457-66963820

Sprains *(Continued)*
first-degree, 526
of foot, 749-750
nomenclature for, 526
patient disposition in, 526-527
second-degree, 526
third-degree, 526, 630f
treatment of, 526-527
Sputum examination
in COPD, 959
in pneumonia, 983
in tuberculosis, 1815
Squeeze test, 731
St. Louis encephalitis, 1736-1737
St. Vitus' dance, 1109
Stab wounds, 839, 840f
abdominal, 460, 471-473
diagnostic testing in, 471
history taking in, 462
management of, 471-473, 471f
physical examination findings, 463
in back, 473
in flank, 473
in neck, 421
peripheral vascular injury, 500
thoracoabdominal, 473
Stability testing, of knee, 700
Stabilization
definition of, e65
EMTALA requirements, e64-e65
Staff. *See also* Personnel
grief reactions in, e55
Staggers, 1921
Staining, 866
Standards
best interest standard, e41
for culturally and linguistically appropriate services (CLAS standards), e25
for health care, e25-e26
for medical interpreters, e26
professional disclosure standard, e70
reasonable person standard, e70
Stanford classification, 1125, 1125f
Staphylococcal scalded skin syndrome, 1567, 1862
clinical features of, 1567
diagnostic strategies for, 1862
management of, 1567, 1862
patient disposition in, 1862
Staphylococcal toxic shock syndrome, 1861-1862, 1861t
clinical features of, 1716t
clinical presentation of, 1715-1716
epidemiology of, 1714-1715
etiology of, 1715
incidence of, 1714
mortality rate, 1715
Staphylococcus
Gram's stain characteristics, 1453t
in pneumonia, in children, 2130-2131, 2131f
Staphylococcus aureus, 1715, 2194
methicillin-resistant (MRSA)
community-acquired (CA-MRSA), 984, 1565, 1853-1854
hospital-acquired, 1565
in osteomyelitis, 1835
in osteomyelitis, 1834-1835
in otitis media, 931-932
in parapharyngeal abscess, 975
in pneumonia, 978-979
in septic arthritis, 2264-2265, 2265t
in skin infections, 1856t
Staphylococcus epidermidis, 1834-1835
Staphylococcus pyogenes, 1818
Staphylococcus-related food poisoning, 1243-1244
clinical presentation of, 1243-1244
epidemiological aspects, 1243t
epidemiology of, 1243
management of, 1244
pathophysiology of, 1243
Staples, 762
START (Simple Triage and Rapid Treatment), 2459-2460, 2460f
JumpSTART, 2460
State laws, e70
State oversight, 2438
Statins (HMG–coenzyme a reductase inhibitors)
for acute coronary syndrome, 1024
for heart failure, 1089
Station, fetal, 2333, 2334f
Statistical analysis, e10f, e11-e12
multivariate models, e15-e16
tests, e13-e14, e13t
Status asthmaticus, 953
airway management in, 16
rapid sequence intubation in, 16, 16t
ventilatory support for, 29
Status epilepticus, 156, 1375, 2408-2409
in children, 2233, 2236-2238, 2237f
clinical features of, 1376
convulsive, 2233
definition of, 1376, 2233
etiology of, 157t, 1376-1377, 1377b
medications for, 158t-159t, 159
medications for abortive treatment of, 1381t
in pregnancy, 2308
refractory, 159, 1382
treatment of, 1381t, 1382
Status migrainosus, 1387, 1388t
Stavudine, 1721t-1722t, 1766t
Steal, subclavian, 139t
Steal phenomenon, 1156
Steatosis, 1192
STEMI alert response, 1023-1024, 1031
Stener fracture, 512t-513t
Stenosing tenosynovitis, 568, 1521-1522
Stephania tetrandra, 2070
Steri-Strips, 762
Sternal fracture, 432-433
clinical features of, 433
diagnostic strategies for, 433
epidemiology of, 432
management of, 433
pathophysiology of, 432-433
Sternoclavicular dislocations, 628-629
anterior, 629, 629f
clinical features of, 628-629
complications of, 629
diagnostic strategies for, 629
management of, 629
mechanisms that produce, 628, 628f
pathophysiology of, 628, 628f
posterior, 629
reduction of, 629, 629f
types of, 628
Sternoclavicular joint, 618, 619f
Sternum, 432-433
Steroids. *See also* Corticosteroids
anabolic, 1197t
Stevens-Johnson syndrome, 1567-1568, 1568f
Stibogluconate sodium, 1772t-1775t
Stiffness, 5-6
Still's disease, adult-onset, 1515
Stimson or hanging weight reduction
of hip dislocation, 688-689, 689f
of shoulder dislocation, 632-633, 632f
Stimulant-induced chest pain, 2003, 2003b
Stimulant-induced hyperthermia, 2002, 2002b
Stimulants
hallucinogenic, 2017
laxatives, 264b, 264t-265t
use/abuse of, 2005, 2006b
Stimulation, neonatal, 115-116
Stingray, 807
Stings. *See also* Insect bites and stings
bee stings, 794, 802
jellyfish (nematocyst), 806-807, 807b
marine animal, 806-807
scorpion stings, 805
wasp stings, 802
Stinkweed or thorn apple *(Datura stramonium)*, 951
Stippling, 830
Stomach
alcohol effects on, 2384-2385
foreign bodies in, 778-781, 1172
Stomatognathic system, 895
"Stone heart," 1985
Stones
bladder (vesical), 1342
renal calculi, 1336-1342
in children, 2214-2215
in salivary glands, 939
Stool softeners, 263, 264b, 264t-265t
Stool studies
bacterial cultures, 258
for ova and parasites, 258
in pediatric fever, 2099
Storage pool syndromes, 1611-1612
Straddle (four-pillar) fracture, 658-659, 660f
Straight leg raise test
in back pain, 281
crossed, 646
in low back pain, 645-646
reverse, 646
Strains, 527
assessment of, 527
definition of, 527
first-degree, 527
gastrocnemius, 721
gluteus muscle, 691
hip adductor, 691
iliopsoas, 691
lower leg, 721-722
lumbosacral, 643
nomenclature for, 527
patient disposition in, 527
plantaris, 721-722
second-degree, 527
tendon strains, 691
third-degree, 527
treatment of, 527
Strangulation, 429-430
clinical features of, 430
definition of, 429
epidemiology of, 429
intimate partner violence injury, 876
ligature, 429
manual, 429
penile, in children, 496, 496f
postural, 429
Strategic National Stockpile, 2465, 2467
Stratosphere sign, 2498-2499, 2498f
Strawberry cervix, 1322
Strawberry tongue, 1715-1716
Street drugs, 1400
Street gang violence, e3-e5
ED guidelines for, e5
firearms and, e4
key concepts, 2513b, e5b
prevention of, e4-e5
psychological effects on children and adolescents, e4
Streptococcal impetigo infection (ecthyma), 1564
Streptococcal pharyngitis, 967
Streptococcal pyrogenic exotoxin A (SPEA), 1715
Streptococcal pyrogenic exotoxin B (SPEB), 1715
Streptococcal scalded skin syndrome
diagnostic strategies for, 1862
management of, 1862
Streptococcal toxic shock syndrome, 1714, 1861, 1861t
case definition of, 1715b
clinical features of, 1716t
clinical presentation of, 1715-1716
diagnostic criteria for, 1715b
incidence of, 1714
Streptococcus
Gram's stain characteristics, 1453t
perianal, in infants, 852, 853f
poststreptococcal glomerulonephritis, in children, 2216
in skin infections, 1856t
Streptococcus mitis, 2359
Streptococcus pneumoniae, 1707-1708
drug-resistant, 984
Gram's stain characteristics, 1453t
in otitis media, 931-932
in pneumonia, 978-979
in septic arthritis, 2265t
vaccine, 1707

www.ketabpezeshki.com 66485457-66963820

Streptococcus pyogenes
in otitis media, 931-932
in septic arthritis, 2265t
Streptokinase
for acute coronary syndrome, 1027-1028
in pregnancy and lactation, 2318t-2321t
for pulmonary embolism, 1166t
Streptomycin
for plague, 2475b
for tuberculosis, 1822t-1823t, 1824, 1827t
for tularemia, 1798
Stress
acute stress disorder, 1475b
cold stress, 1877
effects of, e83
of flight, 2443
post-traumatic stress disorder
anxiety in, 1477
definition of, 1475b
pharmacologic treatment of, 1479t
psychosocial, 1115
stressful life events, 1468
stressors, e79-e80
Stress cardiomyopathy, 1104
Stress echocardiography, 1017t, 1020
Stress fractures
athletic, 749
of femoral neck, 686-687
in foot, 749
clinical features of, 749
diagnostic strategies for, 749
management of, 749
pathophysiology of, 749
patient disposition in, 749
of lower leg, 721
midfoot, 749
pedal, 749
pelvic, 660
Stress management
critical incident stress debriefing, e81-e82
disaster, 2466
shift work strategies, e81b
wellness strategies for physicians, e81-e82, e81b
Stress testing, 731
Stridor, 2106-2107
causes of, 2107f
interventions for, 307t
Stroke, 1363-1374
acute stroke protocol, 1374
air medical transport for, 2447
anatomy of, 1365
blood pressure control in, 1120t, 1121
chest pain and, 217t-218t
clinical features of, 1365-1366
definition of, 1363
diagnostic strategies for, 1369-1370
differential considerations, 1366-1369
epidemiology of, 1363-1364, 1364t
and fibrinolytic therapy, 1029
hemorrhagic, 1003
clinical features of, 1366
diagnostic strategies for, 1370
differential considerations, 1368-1369
epidemiology of, 1364
risk factors for, 1029
hypertension-related, 1116
ischemic
acute drug therapy for, 1371-1373
antihypertensive therapy for, 1371, 1371b
clinical features of, 1365-1366, 1368t
diagnostic strategies for, 1369-1370
differential considerations, 1366-1368
epidemiology of, 1363-1364
fibrinolytic therapy for, 1371-1372, 1372b
with hypertension, 1120t
key concepts, 1374b
management of, 1370-1374
patient disposition in, 1374
key concepts, 1374b
management of, 1370-1374, 1370t
mortality rate, 1363
with myocardial infarction, 1003
NIHSS score, 1366, 1367b
pathophysiology of, 1364-1365
patient disposition in, 1374
Stroke *(Continued)*
physiology of, 1365
seizures caused by, 1379
small-vessel, 1363
Stroke centers, 1374
Stroke volume
decreased, in infants and children, 2139-2140, 2140b
increased, 1078
Stromectol (ivermectin), 1770t
Strongyloides, 1780-1781
Strongyloidiasis (*Strongyloides stercoralis* infection), 1770t-1771t, 1778, 1863
drug regimens for, 1772t-1775t
enteritis
in AIDS, 1257t
antibiotic therapy for, 1235t
epidemiologic aspects of, 1250t
treatment against, 1257t
gastrointestinal symptoms of, 1782
in immunocompromised patients, 2363
after transplantation, 2370
Struvite (magnesium-ammonium-phosphate) stones, 1336
Strychnine poisoning, 1702
Stryker Intra-Compartmental Pressure Monitor system, 522
Student's elbow, 1519f
Student's *t*-test, e13-e14, e13t, e14
Stupor, 142
Stye (hordeolum), 193t-196t
Styloid fracture, 745
Subacromial bursitis, 637-639, 1525
clinical features of, 638
differential diagnosis of, 638
management of, 639
painful arc sign in, 638f
pathophysiology of, 637-638, 638f
Subacute sclerosing panencephalitis, 1725
clinical features of, 1725
diagnostic strategies for, 1725
management of, 1725
Subaortic stenosis, idiopathic hypertrophic, 1102
Subarachnoid hemorrhage, 1390-1391
ancillary testing in, 172
clinical features of, 139t, 1368t, 1390
diagnostic strategies for, 1390-1391
differential diagnosis of, 174t
epidemiology of, 170
grading scale for, 1390t
pivotal findings, 170-172
risk factors for potentially catastrophic illness, 172b
spinal, 1424-1425
traumatic, 365
treatment of, 1391
Subcapital fracture, 695, 696f
Subclavian artery aneurysms, 1147
Subclavian artery injuries, 507-508
Subclavian steal, 139t
Subclavian vein injuries, 508
Subcondylar tibial fractures, 717-718
Subconjunctival hemorrhage, 193t-196t, 913, 913f
Subcoracoid dislocation, anterior, recurrent, 631, 632f
Subdural hematoma, 363-365, 364f
acute, 364, 365f
in children, 313
chronic, 364-365
clinical features of, 139t
risk factors for potentially catastrophic illness, 172b
subacute, 364
Subdural hygroma, 365
Subgaleal hematoma, 312-313
Subglottic hemangioma, 2112
Subglottic tracheal diseases, 2112-2113
Subgroups, e15
Subluxation, 525-526
assessment of, 526
definition of, 525
lens, 915
nomenclature, 525
scaphoid, 580, 581f
Subluxation *(Continued)*
spinal, 385, 388f-389f, 410f
treatment of, 526
Subluxation provocation, 701
Subluxed teeth, 904-905
Submersion injuries, 1941
Substance abuse, 2395-2399. *See also specific substances*
in children, e2
clinical findings, 2397
complications of, 2397-2398
diagnostic adjuncts for, 2398
differential diagnosis of, 2397
in elderly, 2395
epidemiology of, 2395-2396
history taking in, 2397
key concepts, 2399b
management of, 2398-2399
pharmacology of, 2396
physical examination findings, 2397
in pregnancy, 2280, 2395
referral for, 2398
reporting requirements for, e77
self-destructive patients, 2429
and suicide, 1494-1495
Substance-induced anxiety disorders, 1475b
Substituted judgment, e41
Substituted phenols, 2061-2062
toxicity of
clinical features of, 2061
diagnostic strategies for, 2061
differential considerations, 2061
management of, 2061-2062
patient disposition in, 2061-2062
Subtalar joint, 734
dislocations of, 739
clinical features of, 739
diagnostic strategies for, 739
management of, 739
pathophysiology of, 739, 739f
patient disposition in, 739
Subtrochanteric fractures, 685-686
anatomy of, 685
classification of, 685, 685f
epidemiology of, 685
management of, 685-686
outcomes, 686
pathophysiology of, 685
Subungual hematoma, 561-562
Succimer (dimercaptosuccinic acid, DMSA)
for chelation therapy, 2027-2028, 2028t
for lead poisoning, 1957t-1958t
in pregnancy, 2318t-2321t, 2324
Succinylcholine, 13-14
for asthma, 953
cardiovascular effects of, 13
for pediatric intubation, 109
in pregnancy and lactation, 2318t-2321t
refrigeration of, 14
uses and dosing, 13
Sucralfate, 1185
Suctioning, neonatal, 115-116
Sudden death, 1105
in young athletes, 2165-2167, 2166b
Sudden hearing loss, 936-937
Sudden infant death syndrome (SIDS), 110-111
Sudden sensorineural hearing loss, 936
Sudeck's atrophy, 523, 748
Sufentanil, 39t
Suffering, e49
Sugar-tong splints, 601-602, 603f
Suicidal behavior
chronic, 1492
diagnostic strategies for, 1496
documentation of, 1499
management of, 1496-1499
medical clearance for patients, 1497
out-of-hospital care for, e51
patient disposition in, 1499
pharmacology of, 1499
self-destructive patients, 2429
Suicidal ideation, 1495-1496
Suicidality, 1493

www.ketabpezeshki.com 66485457-66963820

Suicide, 1492-1500
clinical features of, 1494-1496
copycat, 1493
definition of, 1492
determination of risk of, 1497-1498
epidemiology of, 1492-1493
etiology of, 1493-1494
factors for patients at low risk of, 1499b
key concepts, 1500b
mass or group, 1492
methods of attempting, 1494
occult, 1492
out-of-hospital care in, e51
pathophysiology of, 1493-1494
precautions against, 1497, 1500b
prevention of, 1499-1500
risk factors for, 1493, 1493b
silent, 1492
societal, psychiatric, and biologic factors, 1493-1494
Suicide attempts
history taking after, 1495-1496
physical examination findings, 1496
Suicide by cop, 1494
Suicide pact, 1492
Suicide potential
history taking and, 1495-1496
recognition of, 1495
Sulbactam, 1264b
Sulfacetamide, 930t
Sulfamethoxazole, 1664t
Sulfasalazine, 1514
Sulfhemoglobinemia, 134
Sulfonamides
alcohol interactions, 2390t
in pregnancy, 2318t-2321t, 2325
resistance to, 1710
Sulfonylureas
antidote for, 1957t-1958t
for diabetes, 1665t
for hyperglycemia, 1665
in pregnancy, 2328
Sulfur dioxide, 2037t
Sulfur mustard, 825, 825t
Sulfuric acid (H_2SO_4), 1994
Sulindac, 44t
Sumatriptan
for migraine attack, 1388, 1388t
for pediatric migraine, 2244
Super Glue (cyanoacrylate adhesive) exposure, 912
Superficial femoral vein, 1157
Superficial infrapatellar bursa, 716
Superficial leg thrombophlebitis, 1159
Superficial punctate keratitis, 920
Superinfection, tuberculosis, 1813, 1813f
Superior mesenteric artery aneurysms, 1148
Superior mesenteric artery embolism, 1221-1222, 1222f
Superior mesenteric venous thrombus, 1223f
Superior peroneal retinaculum, 733, 734f
Superior vena cava, 1620, 1620f
Superior vena cava syndrome, 1619-1621
ancillary evaluation of, 1620-1621
clinical features of, 1620
epidemiology of, 1619-1620
key concepts, 1628b
management of, 1621
Support groups, e81
Suppositories, 264b
Suppressor cells (CD8 T lymphocytes), 2357
Suppurative arthritis, 1831
Suppurative thyroiditis, 1678
Supracondylar fractures, 603-607, 606f
definition of, 603
extension, 603-607, 606f, 2254, 2254t
flexion, 606f, 607
Gartland classification of, 601b, 2254, 2254t
of humerus, 2254-2257
radiographic findings, 2256, 2256f
reduction of, 605, 606f, 2256-2257, 2256f
type III, 607, 607f
Supracondylar process, 596, 598f
Supraglottic airway diseases, 2109
infectious, 2109-2111
noninfectious, 2111
Supraglottitis, 969
Supralevator abscesses, 1281t, 1282
Suprapatellar bursa, 716
Supraventricular tachycardia
with aberrancy, 1055, 1057t
antidromic, 2155-2156
ECG features, 2157t
after head injury, 360
narrow-complex, 2156, 2156f
orthodromic, 2155-2156
paroxysmal, 1052, 1054f
pediatric, 2155-2158
clinical features of, 2156
diagnostic strategies for, 2156
management of, 2157-2158
radiographic findings in, 2155-2156, 2156f
treatment options, 2154b
terminology, 1048
wide-complex, 2155-2156, 2155f
Suramin, 1772t-1775t
Surface tension, 2032
Surge capacity, 2457
Surgeons, 291, 291b
Surgery
for aortic dissection, 1128
for blunt aortic injury, 455
damage control, 525
and fibrinolytic therapy, 1029
for hemoptysis, 205
for hypertrophic cardiomyopathy, 1103
for infective endocarditis, 1108b
orthopedic, 525
for parasitic infection, 1772t-1775t
problems in pregnancy, 2293-2299
for ruptured AAA, 1134
for tuberculosis, 1827
video-assisted thoracic surgery, 442
Surgical airways
indications for, 291
management of, 21-22
in neck injury, 424
Surgical embolectomy, 1167-1169
Surgical needles, 761-762
Surgical resuscitation teams, 2420
Surrogate lists, e41
Surrogates, e40-e41
Survivor onlookers, e43
Survivors
delivering bad news to, e51-e53
notifying, e43
sedation of, e54
Susto, e27
Sutural diastasis, 361
Suture materials, 760-761, 763t
Sutures
absorbability of, 760-761
absorbable, 760-761, 763t
biologic, 760-761
half-buried horizontal mattress sutures (corner stitches), 759, 761f
horizontal mattress sutures, 758-759, 759f
intradermal (buried), 757
key concepts, 766b
nonabsorbable, 760-761, 763t
removal times, 765
simple, 757
synthetic, 760-761
technique for wound closure, 757
vertical mattress sutures, 758
Swallowing, 1181-1182
Swan neck deformity, 558, 559f
SWAT teams, 2449
Swelling
anorectal, 1277
brain
congestive, 343
after head injury, 343-344
leg, 1532t
scrotal
causes of, 1343b
in children, 2208-2211
idiopathic, 2210
Swimmer's itch, 1780
Swimming pool cleaner, 1994, 1995t
Swinging flashlight test, 187
Swinging heart phenomenon, 449
Sydenham's chorea, 1109
Symmetrel (amantadine), 1720-1722
Symmetrical polyneuropathy, distal, 1431-1433
Sympathectomy
for frostbite, 1881-1882
for peripheral arteriovascular disease, 1144
Sympathetic crisis, 1120t, 1122
Sympathetic nervous system, 2058f
Sympathetic ophthalmia, 918
Sympathetic stimulation, 2001, 2002b
Sympathomimetic syndrome, 1955t, 1956
Sympathomimetics, 1999
abuse of
anxiety in, 1477
vital signs in, 2419t
clinical effects of, 1999, 2000b
Synchronized intermittent mandatory ventilation, 24-25, 25t
Syncope, 135-141
in anaphylaxis, 1551
ancillary studies in, 137-138, 138t
in aortic dissection, 1125
causes of, 136b, 139t
in children, 2248-2249
clinical features of, 2248
definition of, 135, 2248
diagnosis of, 135-138, 138t, 140f, 2248
differential diagnosis of, 135-136, 2233, 2249
drug, 139t
empirical management of, 138-141
epidemiology of, 135
evaluation of, 2484-2485
heat syncope, 1900
management of, 141f, 2249
medications that may induce, 137, 137b
observational approach to, 2485, 2485b
pathophysiology of, 135
patient disposition in, 2249
physical examination findings, 137t
pivotal findings, 136-138
reflex, 139t
signs of, 137
symptoms of, 136-137
traditional approach to, 2484
Syndesmosis, 725, 726f
Syndesmotic ligaments, 723, 724f, 731
Syndrome of inappropriate antidiuretic hormone, 1643, 1643b
Synovial fluid
in arthritis, 2265t
general appearance of, 1504
Synovial fluid examination, 1505t
in arthritis, 1504-1505
studies, 1504
white blood cell count, 1504-1505
Synovial spaces, 540-541
Synovitis
tenosynovitis, 1831
toxic, 694
transient, 694
in children, 2263-2269
differential diagnosis of, 694
treatment of, 2264
Synthetic cannabinoids, 2020-2022, 2021f
Syphilis, 1315-1317, 1575-1576
clinical features of, 1575
diagnosis of, 1317, 1575-1576
early (primary), 1286t
latent, 1317
management of, 1576
in pregnancy, 2301t-2303t, 2313-2314
primary, 1315-1316, 1316f
secondary, 1286t, 1316-1317, 1316f, 1575, 1575f
stages, 1315-1317
tertiary, 1317
treatment of, 1286, 1315t, 1317
Syphilitic pharyngitis
diagnosis of, 967
treatment of, 968
Syringomyelia, 1425
clinical features of, 1425
diagnostic strategies for, 1425
differential considerations, 1425
management of, 1425

www.ketabpezeshki.com 66485457-66963820

System intervention models, 880-881
System readiness, 880-881
Systemic disease
infection, in pregnancy, 2312-2314
oral manifestations of, 902-903
Systemic disease history, 1277b
Systemic inflammatory response syndrome
definition of, 1864, 1865b
diagnostic criteria for, 70b
Systemic insults, secondary, and head injury, 343
Systemic lupus erythematosus, 1527-1534
acute exacerbations, 1533t
acute presentations, 1528
anatomy of, 1527
cardiorespiratory presentations, 1529-1530
causes, workup, and treatment of, 1529t
classification criteria for, 1528t
clinical features of, 1527-1532
dermatologic presentations, 1531
diagnostic strategies for, 1532
differential diagnosis of, 1532, 1532t
epidemiology of, 1527
exacerbation of, 1528
focal neurologic findings, 1528
gastrointestinal presentations, 1531
key concepts, 1541b-1542b
laboratory testing in, 1532
management of, 1532-1533
medications for, 1532, 1533t
musculoskeletal presentations, 1530-1531
neuropsychiatric presentations, 1528-1529
oral manifestations, 902, 902f
patient disposition in, 1533-1534
pericarditis in, 1094
physiology of, 1527
in pregnancy, 2314
psychiatric symptoms of, 1529
rheumatologic referral for, 1534b
skin lesions associated with, 1581t, 1583f
undiagnosed or suspected, 1527
Systemic sclerosis (scleroderma), 1517
Systemic vascular resistance, increased, 1078-1079
Systolic dysfunction, 1080
Systolic heart murmurs, in children, 2142, 2143b

T
T fracture, 670
T lymphocytes (T cells), 1602
CD4 (helper cells), 2357
CD8 (suppressor cells), 2357
development of, 1547
major types of, 2357
T-on-R phenomena, 826
t-test, e13-e14, e13t, e14
Tabun (GA), 825, 825t, 2059, 2476-2477
Tachycardia
atrial, 1049-1050, 1049f
AV-nodal reentrant tachycardia, 1052
bradycardia-tachycardia syndrome, 1043
chest pain and, 217t-218t
circus movement, 1035
irregular, 1055
junctional, 1052
narrow-complex, 1048-1052, 1055f
nonparoxysmal or sustained junctional, 1052
sinus, 1048-1049, 1049f, 2157t
supraventricular
paroxysmal, 1052, 1054f
terminology, 1048
wide-complex, 1055-1062
adenosine-induced, 2157f
Brugada criteria for, 1055, 1058f
Griffith criteria for, 1057, 1058f
key concepts, 1063b
Tachydysrhythmias, 1002
pediatric, 2155-2158
Tachypnea, 206
Tacrolimus, 2371
Tactical combat casualty care (TCCC)
airway management, 2452
analgesia, 2452
care under fire, 2451
evacuation care, 2452-2453, 2453f
Tactical combat casualty care (TCCC) *(Continued)*
field care, 2451-2452
fluid resuscitation, 2452
force health protection, 2453
goals of, 2450
guidelines for, 2449
guidelines for fluids, 2452
hypothermia management, 2452
intravenous access, 2452
key concepts, 2456b
phases of, 2451b
preventive medicine, 2453
remote patient assessment, 2453
Tactical field care, 2451-2452
Tactile emergency medical support (TEMS), 2449-2453
equipment for, 2453
goals of, 2449-2450, 2450b
history of, 2449
integrated medical support, 2450-2453
key concepts, 2456b
team structure, 2450-2453
training for, 2453
training issues, 2450-2453, 2450f
Tadalafil, 1936
Taenia saginata, 1770t-1775t
Taenia sodium, 1770t-1771t
Taenia solium, 1772t-1775t, 1780
Tagged RBC imaging, 252
Takayasu's arteritis, 1535-1536
Takot Subo cardiomyopathy. *See* Takotsubo cardiomyopathy
Takot-tsubo cardiomyopathy. *See* Takotsubo cardiomyopathy
Takotsubo cardiomyopathy, 1104
causes of, 1104b
clinical features of, 1104
diagnostic strategies for, 1104
ECG characteristics, 1011
management of, 1104
patient disposition in, 1104
Talar body fractures, 737, 737f
Talar fractures, 736-738
clinical features of, 737
diagnostic strategies for, 737
dome fracture, 738, 738f
management of, 737
pathophysiology of, 736-737
patient disposition in, 738
radiographic findings, 737, 737f-738f
total talar dislocation, 739
Talar head fractures, 737
Talar neck fractures, 737, 737f-738f
Talocrural joints, 723
Talus, 736
Tanapox virus, 1727
Tangential wounds, 358
Tape, 762
Tapentadol, 42
Tapentadol ER, 1432
Tapeworm infection
anemia in, 1778
drug regimens for, 1772t-1775t
Tar, 824
Tarantulas, 804
Tardieu's spots, 430
Tardive dyskinesia
antipsychotic-induced, 2049
with neuroleptic agents, 1465
Tarsal tunnel syndrome, 748
Tarsometatarsal (Lisfranc's) fractures and dislocations, 512t-513t, 741-744
Tarsometatarsal (Lisfranc's) joints, 741
Tattooing, 830, 832f
pseudotattooing, 833f
Taxus (yew), 2070, 2070f
Teachable moments, 336-337, 816
Teaching, postmortem, e43-e44
Teamwork, 2424, 2507
medical team operations in urban search and rescue, 2454-2455
medical team tasks, 2455
tactical team structure, 2450-2453
Teardrop fractures, 385, 387f, 512t-513t
extension teardrop fracture, 393
Technetium 99m (^{99m}Tc), 2276t
Technical procedures, 2509
Teeth. *See* Tooth (teeth)
Tegenaria (hobo or aggressive house spider), 804
Tegretol (carbamazepine)
for children, 2240t
side effects and drug interactions, 2407t-2408t
Tegretol XR (carbamazepine), 2407t-2408t
Telemedicine, e36
Telephone notification, e53
Tellurium poisoning, 1955t
Telmisartan, 1122.e1t-1122.e2t
Temazepam (Restoril), 1408, 2078t
Temperature extremes, 1669b-1670b
Temperature regulation
in children, 2087
impaired, 1886-1887, 1886b
physiology of, 1883-1884
Temporal arteritis (giant cell arteritis), 926, 1392, 1535
classification criteria for, 1535b
clinical presentation of, 1392
diagnostic evaluation of, 1392
differential diagnosis of, 174t
incidence of, 1535
risk factors for potentially catastrophic illness, 172b
treatment of, 1392
Temporal lobe epilepsy, 166t-167t
Temporomandibular joint, 381
dislocation of, 381, 906-907, 906f
reduction of, 906-907, 907f
structures of, 895, 896f
trauma to, 381
Temporomandibular myofascial pain dysfunction syndrome, 901-902
TEMS. *See* Tactile emergency medical support
Tenckhoff catheter, 1306-1307
Tendinitis, 527-528
bicipital, 640-641
calcific, 527-528, 641-642
dancer's, 734
flexor hallucis longus, 734
infectious, 1831
peripatellar, 715
popliteus, 716
rotator cuff, 637-639
Tendinopathy, 1518-1523
Achilles, 1522-1523
of ankle, 1522
bicipital, 1519f, 1520
calcific, 1520-1521, 1521f, 1523
chronic, 527
clinical features of, 1518-1522
diagnostic strategies for, 1522-1523
differential diagnosis of, 1523
key concepts, 1525b-1526b
of knee, 1522
location of common sites, 1518, 1519f
management of, 1523
patellar, 1522
patient disposition in, 1523
rotator cuff, 1520-1521, 1523
of shoulder, 1520-1521
of wrist, 1519f, 1521-1522
Tendinosis, 527-528
Tendon injuries
in ankle, 733-734
femur and hip, 691-692
in foot, 749-750
in hand, 556-561
Tendonitis, 527
Tenecteplase (TNKase), 1166, 2318t-2321t
Tennis elbow (epicondylitis), 614-615, 1519f, 1521, 1523
Tenofovir, 1721t-1722t, 1766t
Tenosynovitis, 566-567, 1831
cardinal signs of, 567
clinical features of, 567
de Quervain's, 1521-1522
definition of, 1521-1522
management of, 567
pathophysiology of, 566-567

www.ketabpezeshki.com 66485457-66963820

Tenosynovitis *(Continued)*
stenosing, 1521-1522
in hand, 568
of tibialis anterior tendon, 734
Tenoxicam (Mobiflex), 1925
Tension headache, 170, 2242
Tension hemothorax, 441f
Tension pneumothorax, 438, 438f
on battlefield, 2451-2452
clinical features of, 989
diagnosis of, 94t
management of, 440
pathophysiology of, 988, 989f
pediatric, 319
radiographic findings, 989, 990f
treatment of, 94t, 436
Tension-type headache, 1389-1390
clinical features of, 1389
differential diagnosis of, 1390
treatment of, 1390
Teratogens, 2316
drugs and agents considered, 2317b
risk classification, 2316, 2317b
Terazosin hydrochloride, 1122.e1t-1122.e2t
Terbinafine
for tinea capitis, 1559
for tinea corporis, 1560
for tinea unguium (onychomycosis), 1561
Terbutaline
for asthma, 950, 2121t
for asthma in pregnancy, 2303t
for premature labor, 2339b
Terfenadine, 1569
Terminal illness, e47
Terminology
abnormal uterine bleeding, 1360t
bioethics, e33
clinical trial design, e13t
death, e48
of dentition, 895
disaster medicine, 2458
dyspnea, 206
errors of, 828-829
evidence-based medicine terms, e20t
for fractures, 511-515, 512t-513t, 546f
for hand injury, 534-544
high-altitude medicine, 1928-1929
hydrocarbon, 2032
hypertension, 1113-1114
implantable cardioverter-defibrillators, 1071-1072
intimate partner violence, 872, 884
miscarriage, 2282
pacemaker, 1064
PICE nomenclature, 2458-2459, 2459t
pregnancy, 2271-2272
for procedural sedation and analgesia, 50-51
sprain nomenclature, 526
strain nomenclature, 527
subluxation and dislocations nomenclature, 525
terms related to analgesia, 32b
ultrasound, 2493, 2493b
Terrorism, 2457
biologic weapons, 2471-2476
chemical, 825-827, 2466
chemical, biologic, radiologic, nuclear, and explosive, 2466
explosive agents, 2466
intimate, 875
nuclear weapons, 1945, 1946t
radiologic weapons, 2469-2471
Terry Thomas sign, 580
Testicles
injury to, 496-497
normal anatomy of, 1342, 1343f
torsion of, 1343
anatomy of, 2209, 2209f
in children, 2209-2210, 2223b
clinical features of, 1344, 2209
diagnostic strategies for, 1344-1345, 2209
differential diagnosis of, 1344t
incidence of, 2209
key concepts, 1354b
management of, 1345, 2209-2210
patient disposition in, 1345
ultrasound imaging of, 1344-1345, 1345f
Testicles *(Continued)*
torsion of testicular appendages, 1345-1346, 1346f
in children, 2210
clinical features of, 1345-1346
diagnostic strategies for, 1346
differential considerations, 1346
management of, 1346
patient disposition in, 1346
trauma to, 1349, 1354b
ultrasound of, 2500, 2501f
Testicular carcinoma, 2211
Testicular inferno, 1348-1349
Testicular rupture, 497, 498f
Testicular tumors, 1348
clinical features of, 1348
diagnostic strategies for, 1348
management of, 1348
Testwise risk, e14
Tet spells, 129
Tetanospasmin, 1701
unbound, 1703
Tetanus, 1699-1704
cephalic, 1701-1702
clinical features of, 1701-1702
complications of, 1701-1702
diagnostic strategies for, 1702
differential diagnosis of, 1702, 1702b
epidemiology of, 1699, 1700f
etiology of, 1701
fatality rates, 1699, 1700f
generalized, 1701-1702
historical perspective on, 1699
immunization against, 765-766
active, 1703
key concepts, 766b
incidence of, 765, 1699, 1700f
incubation period, 765, 1701
in infants and children, 1703
key concepts, 1717b
localized, 1701
lumbar puncture for, 1702
management of, 1702-1703
neonatal, 1701, 1703
prophylaxis of, 765, 766t
guidelines for, 1703
in wound management, 1704t
spatula test for, 1702
supportive care for, 1702-1703
symptoms and signs of, 1701
treatment of, 1702-1703
in infants and children, 1703
vaccination against, 1703-1704
Tetanus-diphtheria vaccine (Td), 1696
schedule for, 1703t
for wound management, 1704t
Tetanus immune globulin, 765, 1703, 1704t
Tetanus toxoid (T), 765, 1703
Tetanus toxoid boosters, 814
Tetracaine, 46t, 930t
lidocaine, epinephrine, and tetracaine (LET), 48
topical, 47-48
for wound management, 754
Tetracaine, adrenaline (epinephrine), and cocaine (TAC), 48, 754
Tetracyclines
for bacterial conjunctivitis, 918-919
bismuth subsalicylate, metronidazole, and tetracycline (Helidac)
for *H. pylori* infection, 1180
for cholera, 1245
for epididymitis, 1347t
for epididymitis in children, 2208
for *H. pylori* infection, 1180
hepatic injury, 1197t
for infectious diarrhea, 2192t-2193t
for parasitic infection, 1772t-1775t
in pregnancy, 2318t-2321t, 2325
for skin and soft tissue infection, 1854
Tetrahydrocannabinol (THC), 2020-2021, 2021f
Tetralogy of Fallot, 2149-2151, 2149f
clinical features of, 2149
diagnostic strategies for, 2149-2150
management of, 2150-2151
management of hypoxic (tet) spells, 2150-2151, 2150b
Tetralogy of Fallot *(Continued)*
pathophysiology of tet spells, 2150, 2150f
radiographic findings, 2144, 2144f, 2149-2150
Thalassemia, 1590-1591
sickle cell–β-thalassemia, 1599
β-chain
heterozygous (thalassemia minor), 1590-1591, 1591f
homozygous (thalassemia major), 1590
α-Thalassemia, 1591
β-Thalassemia, 1590-1591, 1591f
Thalassemia major (homozygous β-chain thalassemia), 1590
Thalassemia minor (heterozygous β-chain thalassemia), 1590-1591, 1591f
Thenar mass or eminence, 534
Theophylline, 2072t-2073t
Therapeutic double bind, 1490
Thermal index (TI), 2494
Thermal injury. *See* Burns
Thermal maximum, 1669b-1670b
Thermal therapy, 532-533
Thermometry, 1904
Thermoregulatory effectors, 1897
Thermosensors, 1897
Thiabendazole
for diarrhea, 1235t
for diarrhea in AIDS, 1257t
for parasitic disease, 1770t, 1772t-1775t
Thiamine
for alcoholic hepatitis, 1192
for ethylene glycol poisoning, 1957t-1958t, 2012
for methanol poisoning, 2012
for poisoning, 1954
for Wernicke-Korsakoff syndrome, 2381
Thiazide diuretics
herbal medicine interactions, 2072t-2073t
for hypertension, 1122.e1t-1122.e2t
Thiazolidinediones, 1665t
Thienopyridine antiplatelet agents, 1025-1026
Thigh
compartment syndrome in, 681
muscular injuries in, 691
structures within, 672, 674t
tendon injuries, 691-692
Thionamide therapy, 1683
Thioridazine (Mellaril), 2048t, 2417
Thiosulfate, 2041
Thiothixene, 2048t
Third-nerve palsy, 928-929
Thompson (Simmonds) test, 1522
Thoracentesis
contraindications to, 996
for pleural effusion, 995-996
Thoracic aortic dissection, 139t
Thoracic back pain, 655b. *See also* Upper back pain
Thoracic duct, 429
Thoracic endometriosis syndrome, 988
Thoracic imaging, 293
ultrasound, 2498-2499, 2498f
Thoracic outlet syndrome, 1150-1152, 1151f, 1433
ancillary evaluation of, 1151
basic concepts of, 1150
clinical features of, 1151
differential diagnosis of, 1151-1152
elevated arm stress test (EAST) for, 1151
key concepts, 1156b
management of, 1152
neurologic and venous compression type, 1150f, 1151
patient disposition in, 1152
physical examination findings, 1151
Thoracic spine
anatomy of, 654
fracture-dislocation of, 385-393, 393f
physiology of, 654
Thoracic surgery, video-assisted, 442
Thoracic trauma, 431-458
chest wall injury, 431
in children, 318
epidemiology of, 431
geriatric, 328
key concepts, 458b
management of, 431
nonpenetrating ballistic injury, 434-435

www.ketabpezeshki.com 66485457-66963820

Thoracoabdominal gunshot wounds, 474
Thoracoabdominal stab wounds, 473
Thoracolumbar outflow, 2058f
Thoracolumbar spine imaging, 293
Thoracotomy
  emergency department, 294, 450-451, 450f
    in abdominal trauma, 470-471
    in blunt chest trauma, 295f, 448b
    indications for, 448b, 450-451
    in penetrating chest trauma, 294f
    in penetrating traumatic cardiac arrest, 448b
    in pericardial tamponade, 450-451
    survival rates after, 451
  indications for, 319-320, 440, 440b
  in neck injury, 423
Thorazine (chlorpromazine), 2417
Thought disorders, 1460-1465
  clinical features of, 1460-1461
  diagnostic strategies for, 1461
  differential considerations, 1461-1462
  general approach to, 1463-1465
  key concepts, 1465b
  management of, 1463-1465
  outpatient management of, 1463-1464
  patient disposition in, 1465
Threat assessment, 2453
Three Mile Island, 1945-1946
3-3-2 rule, 4, 5f
3M, 904
Throat, sore, 198-202
  airway assessment and general appearance in, 198
  ancillary testing in, 200
  diagnosis of, 198-200, 201f
  differential diagnosis of, 199t
  empirical management of, 200-202
  epidemiology of, 198
  imaging in, 200
  management algorithm for, 201f
  pathophysiology of, 198
  patient education about, 202
  source of pain visualized on examination, 198-199
  special considerations on history, 200
Throat distemper, 1693
Thrombectomy, Fogarty catheter, 1143
Thrombin-JMI Epistaxis Kit (King Pharmaceuticals), 939
Thrombin-sensitive factors, 1606
Thrombin time, 1609, 1616t
Thromboangiitis obliterans (Buerger's disease), 1145-1146, 1541t
Thrombocytopathy, 1610b, 1611-1612
Thrombocytopenia, 1610-1611
  differential diagnosis of, 1610b
  dilutional, 1611
  heparin-induced, 1610
  immune, 1610-1611
  nonimmune, 1611
  post-transfusion, 1610-1611
Thrombocytopenic purpura
  causes of, 1583b
  idiopathic, 1611
  oral manifestations of, 903
  thrombotic, 1611
Thrombocytosis, 1610b, 1612
Thromboembolism
  pathophysiology of, 1139, 1157
  in pregnancy, 2296-2297
    clinical features of, 2296-2297
    diagnostic strategies for, 2297
    management of, 2297
  venous
    after head injury, 360
    pathophysiology of, 1157
Thrombolytics
  for frostbite, 1881
  in pregnancy, 2318t-2321t, 2322-2323
  for pulmonary embolism, 1166-1167
Thrombophlebitis
  leg, superficial, 1159
  pacemaker-related, 1067
Thrombosis, 501, 501f
  arterial, 1139, 1146
  calf vein, isolated, 1159
  cerebral venous, 1414-1415
  cerebral venous sinus, 1393-1394
Thrombosis *(Continued)*
  deep vein, 1157-1159
    ultrasound of, 2498, 2498f
  differentiation from embolus, 1141t
  distal brachial artery, 501f
  mesenteric arterial, 1222
  mesenteric venous, 1222, 1222b
  pathophysiology of, 1157
  prosthetic valve, 1112
  septic, 975
  subcutaneous arteriovenous fistula or prosthetic graft, 1156
  superior mesenteric venous thrombus, 1223f
Thrombotic thrombocytopenic purpura, 1611
Thrush
  in HIV infection, 1760
  oral, 1561-1562
Thumb injury
  carpometacarpal joint injuries, 556
  dorsal dislocation of distal phalanx of, 525, 525f
  interphalangeal joint injuries in, 555-556
  metacarpophalangeal joint injury in, 556
Thumb metacarpal fractures, 552
  extra-articular, 552
  intra-articular, 552
Thumb mobility, 534, 536f
Thumb spica splint, 577, 577f
Thumbprinting
  in colonic ischemia, 1273
  in pediatric epiglottitis, 2110f
Thunder clap or lightning strike headache, 171t
Thurston Holland's fragment, 512t-513t
Thymectomy, 1444
Thyroid-directed therapy, 1683
Thyroid disorders, 1676
  and heart failure, 1082
  in pregnancy, 2311-2312
Thyroid dysfunction, 1688t
Thyroid function tests
  interpretation of, 1681, 1681t
  in nausea and vomiting, 242
Thyroid gland, 1676, 1677f
Thyroid hormone
  inhibiting release of, 1683
  measurement of, 1680-1681
  reducing production of, 1683
  regulation of, 1676, 1677f
Thyroid hormone replacement
  for hypothyroidism, 1688
  for myxedema coma, 1688, 1688b
Thyroid medications, 2318t-2321t, 2328-2329
Thyroid-stimulating hormone
  assays for, 1680
  regulation of, 1676
Thyroid storm, 1679-1680
  diagnostic criteria for, 1681t
  key concepts, 1692b
  management of, 1682b-1683b, 1683-1684
  precipitants of, 1680b, 1684
Thyroiditis, 1678
  drug-induced, 1678
  factitious, 1678
  Hashimoto's or autoimmune, 1684
  postpartum, 1678, 2311-2312
  sporadic, 1678
  subacute (de Quervain's), 1678, 1683, 1683b
  suppurative, 1678
Thyrotoxic periodic paralysis, 1445-1446
Thyrotoxicosis. *See also* Hyperthyroidism
  anxiety in, 1476
  definition of, 1676
  factitious, 1683b
  management of, 1683b
Thyrotropin-releasing hormone, 1676
Thyroxine (T_4), 1676, 1677f
  assays for, 1680-1681
  inhibiting conversion to T_3, 1683
Tiagabine (Gabitril)
  drug interactions, 2407t-2408t
  for long-term anticonvulsant therapy, 1384t
  side effects of, 1383t, 2407t-2408t
Tibia
  anatomy of, 717, 719
  distal displacement, 515f
Tibial fractures
  comminuted, 2252f
  proximal extra-articular, 717-718
  stress fractures, 721
  subcondylar, 717-718
Tibial nerve, 699
Tibial plateau fractures, 516f, 706-708
  anatomy of, 706
  clinical features of, 706-707
  diagnostic strategies for, 707
  Hohl classification of, revised, 707, 707f
  management of, 707-708
  pathophysiology of, 706
Tibial shaft fractures, 719-720
  clinical features of, 719
  delayed union of, 720
  diagnostic strategies for, 719
  management of, 719-720
  nonunion of, 720
  pathophysiology of, 719
  radiographic findings, 719, 719f
Tibial spine (intercondylar eminence) fractures, 708-709
Tibial tubercle, 718
Tibial tubercle fractures, 718
  clinical features of, 718
  diagnostic strategies for, 718
  management of, 718
  pathophysiology of, 718
  Watson-Jones classification of, 718, 718f
Tibial tuberosity
  apophysitis of, 718
  fractures of, 718f
  osteochondritis of, 718
Tibialis anterior tendon, 734
Tibialis posterior tendon rupture, 734
Tibiofibular fracture, 719f
Tic douloureux, 1409-1411
Ticarcillin-clavulanate
  for bowel flora, 1264b
  for toxic shock syndrome, 1568
Tick-borne illnesses, 1785-1808, 1786t
  key concepts, 1808b
  prophylaxis with insect repellents, 1808
  relapsing fever, 1795-1796
Tick paralysis, 1445, 1786t, 1807-1808
  clinical features of, 1445, 1807
  diagnostic strategies for, 1807
  differential considerations, 1807
  management of, 1445, 1807-1808
Ticks, 805, 1785, 1787f
  feeding physiology of, 1785-1786
  identification of, 1785, 1788f
  recommended method for removal of, 1807b
TICLS (tone, interactiveness, consolability, look/gaze, and speech/cry) assessment, 2091
Tigecycline, 984-985
Tile's classification, 658b
Tillaux fracture, 512t-513t
Time-gain compensation (TGC), 2493
Time management, resident, e83
Time out, 2424
TIMI (Thrombosis in Myocardial Infarction) risk score, 1000
Timolol, 1987t
  for glaucoma, 922, 930t
  for hypertension, 1122.e1t-1122.e2t
Tinactin (tolnaftate), 1560
Tinea capitis, 1559
  clinical features of, 1559
  diagnostic strategies for, 1559
  differential considerations, 1559
  management of, 1559
Tinea corporis, 1559-1560, 1561f
  clinical features of, 1559
  differential considerations, 1560
  management of, 1560
Tinea pedis, 1560
Tinea unguium (onychomycosis), 1561
  clinical features of, 1561
  management of, 1561
Tinea versicolor, 1560-1561, 1561f
  clinical features of, 1560-1561
  management of, 1561
Tinel's sign, 589, 1151

www.ketabpezeshki.com 66485457-66963820

Tinidazole
for bacterial vaginosis, 1323
for diarrhea in AIDS, 1257t
for giardiasis, 1253
for nongonococcal urethritis, 1320
for parasitic disease, 1770t, 1772t-1775t
for trichomoniasis, 1322
Tiotropium bromide, 951
Tipranavir, 1766t
Tissue adhesives, 762
Tissue hypoperfusion, 70b
Tissue resistance, 1907, 1907b
Tissue-type plasminogen activator
for acute coronary syndrome, 1027-1028
for ischemic stroke, 1371-1372, 1371b
TMP-SMX. *See* Trimethoprim-sulfamethoxazole
TNK, 1028
To Err Is Human: Building a Safer Health System (IOM), 2505
Tobramycin, 2361t
Tocolysis, 2339, 2340b
Tocolytic agents, 2339b
Toddlers, 2089
cellular oxygenation, 108-109
otoscopic examination in, 2092, 2093f
urinary tract infections in, 2212
Toddler's fracture, 719, 722b, 852, 2258-2259, 2259f
Todd's paralysis, 1375
Toe-touch weightbearing, 691
Togaviridae, 1719t, 1736-1737
Toilet bowl cleaner, 1994, 1995t
Tokaimura, Japan nuclear reactor incident, 1946
Tolerance, operational, 2371
Tolfenamic acid, 1388t
Tolmetin, 44t
Tolnaftate (Tinactin), 1560
Toluene poisoning, 1955t
Toluidine blue dye staining, 866, 867f
Tongue, 108
Tongue deviations, 1410t-1411t
Tongue lacerations, 377, 906
Tonometry, ocular, 187
Tonsillitis, 198
lingual, 968-969, 969f
recurrent or chronic, 968
Tonsillopharyngitis, 965-968, 966f
Tooth (teeth)
anatomy of, 895, 896f
attachment apparatus, 896, 896f
avulsed, 904-905
reimplantation and stabilization of, 904-905, 905f
coronal portion, 895
cracked, 901
developing, 108
diagnostic imaging of, 897
fractures of, 908b
identification of, 895, 897f
primary, 108
pulp, 895
root, 895
subluxed, 904-905
surfaces of, 895
trauma to, 380-381
wisdom teeth, 895
Tooth fractures, 903-904, 903t
Topamax (topiramate), 2240t
Topical anesthesia, 47
applied to intact skin, 47
applied to mucosal surfaces, 47-48
applied to open skin, 48
ophthalmic medications, 930t
Topical antibiotics, 930t
Topical antiviral agents, 930t
Topiramate (Topamax)
for children, 2240t
drug interactions, 2407t-2408t
for long-term anticonvulsant therapy, 1384t
side effects of, 1383t, 2407t-2408t
Toradol (ketorolac tromethamine), 2243-2244
Tornadoes, 2457
Torsades de pointes, 1061-1062, 1061f
acquired, 1061b
congenital, 1061b
Torsades de pointes *(Continued)*
criteria for, 1061
definition of, 1061
management of, 2050-2051
Torsemide
hemodynamic effects, 1118t
for hypertension, 1122.e1t-1122.e2t
Torsion
ovarian, 1355-1358
testicular, 1343, 1354b
of testicular appendages, 1345-1346, 1346f
Torso drainage procedures, US-guided, 2502-2503
Torticollis, 385
paroxysmal, 2242
Torturing, e16-e17
Torus fracture (buckle fracture), 517, 517f, 587, 587f, 2250, 2251f
Total body water, 1641, 1642t
Total hip arthroplasty, 681-682
Total iron-binding capacity, 1591t
Total talar dislocation, 739
Tourniquet injury, penile, 2207-2208
Tourniquets, 2451
care under fire, 2451
Combat Application Tourniquet (C-A-T), 2451
recommendations for, 2451
Special Operations Forces Tactical Tourniquet (SOFT-T), 2451
types available, 2451
Toxic adenoma, 1678
Toxic alcohols, 2007-2014
Toxic disasters (hazardous material), 2465
Toxic epidermal necrolysis, 1567-1568
clinical features of, 1567-1568, 1568f
management of, 1568
Toxic megacolon, 1270-1271, 1271f
Toxic multinodular goiter, 1678
Toxic neuropathies, 1433
optic, 927
Toxic prostatitis, 1335-1336
Toxic shock syndrome, 1568, 1714-1717, 1861-1862
case definitions of, 1714b, 1716, 2104b
in children, 2103
clinical features of, 1568, 1715-1716
complications of, 1716
diagnosis of, 1568, 1714b, 1716, 1862
differential considerations, 1716
epidemiology of, 1714-1715
etiology of, 1715
historical perspective on, 1714
incidence of, 1714
key concepts, 1717b, 1863b
management of, 1568, 1717, 1862
pathophysiology of, 1715
patient disposition in, 1717, 1862
risk factors for, 1715b
staphylococcal, 1861-1862
clinical features of, 1715-1716, 1716t
epidemiology of, 1714-1715
mortality rate, 1715
staphylococcal, 1714
streptococcal, 1714, 1861, 1861t
case definition of, 1715b
clinical features of, 1715-1716, 1716t
diagnostic criteria for, 1715b
incidence of, 1714
symptoms and signs of, 1715-1716
Toxic syndromes (toxidromes), 1955-1956, 1955t
vital signs in, 2419t
Toxic synovitis, 694
Toxicodendron-associated dermatitis, 1572-1573
Toxicology laboratory, 1956-1958
Toxicology screen, 1956-1958
in abdominal trauma, 464
drugs, chemicals, groups not detected by, 1958b
Toxidromes (toxic syndromes), 1955-1956, 1955t
vital signs in, 2419t
Toxins, 255b-256b
bacterial gastroenteritis, 1243-1249, 1243t
developmental, 2317b
fish-associated, 255b-256b
inhaled, 2036-2043, 2037t
plant-associated, 255b-256b
seizures caused by, 1378
from venomous reptiles, 796
Toxocariasis (*Toxocara canis* infection) (visceral larva migrans), 1772t-1775t, 1780
Toxoplasma gondii, 1780
Toxoplasma gondii encephalitis
in HIV infection, 1761, 1762t, 1763f
prevention of, 1758t
Toxoplasma myocarditis, 1100
TPP. *See* Thyrotoxic periodic paralysis
Trace evidence, 841-842, 842f
Tracheal diseases
congenital lesions, 2113-2114
pediatric, 2113-2115
subglottic, 2112-2113
Tracheal foreign bodies, 774, 775f
Tracheal intubation, prehospital, 109
Tracheal rock sign, 973-974
Tracheal stenosis, 2114
Tracheal suctioning, infant, 113-114
Tracheal ultrasound, 2498-2499
Tracheobronchial injury, 442-443, 442f
anatomy of, 442
clinical features of, 442, 442f
diagnostic strategies for, 442-443
epidemiology of, 442
management of, 443
pathophysiology of, 442
Tracheomalacia, 2113-2114, 2401
Tracheostomy problems, 2405t
Tracheostomy tubes, 2403-2404
cuffed, 2403, 2404f
double-cannula, 2403, 2403f
fenestrated, 2403, 2404f
single-cannula, 2403, 2403f
Trachoma, 187
Traction, 680
Traction-countertraction reduction
of anterior shoulder dislocation, 632-633, 632f
of inferior glenohumeral dislocations, 637, 637f
of posterior hip dislocation, 689
Traction splints, 680
Training
cultural, e28
disaster exercises, 2464
emergency US, 2492-2493
residency training, e82-e84
resistance training, e82
special response team, 2450, 2450f
tactile emergency medical support (TEMS), 2450-2453, 2450f
Tramadol (Ultram), 42
for diabetic distal symmetrical polyneuropathy, 1432
for fibromyalgia, 1516-1517
for pancreatitis, 1214
Trandolapril, 1122.e1t-1122.e2t
Tranquilization, rapid, 1463, 1465b, 1472, 2416
Transabdominal ultrasound
indications for, 230
in pregnancy, 2275, 2275f
Transcervical gunshot wounds (GSWs), 425
Transchondral fractures, 738
Transcondylar fractures, 607, 607f
Transcutaneous electrical nerve stimulation, 48
Transderm Scop (scopolamine), 246
Transesophageal echocardiography
in aortic dissection, 1126-1127, 1126t
in blunt aortic injury, 454, 454f
Transfer laws, e68
Transfers
acceptance of, e69
to acute care hospitals, e68
for blunt abdominal trauma, 478
duty to accept, e68-e70
duty to report violations, e70
in emergency delivery, 2331
EMTALA hospital transfer form, e66f
EMTALA requirements for, 2441b
to home, e67
inpatient transfers from other hospitals, e69
landing zone safety, 2445f
lateral, e69
medically indicated, e68-e69
to on-call physician office, e67

www.ketabpezeshki.com 66485457-66963820

Transfers *(Continued)*
- reasons for refusal of
  - invalid, e68b
  - valid, e69-e70
- recommendations for facilities asked to accept, e68b
- recommendations for transferring facilities, e68b
- requirements for hospitals to accept, e69-e70
- in severe head injury, 351
- transitions in patient care, 2510

Transfusion. *See also* Blood transfusion
- blood product, 252
- of fresh frozen plasma, 77-78
- of packed red blood cells, 77-78
- platelet, 78, 1612
- post-transfusion thrombocytopenia, 1610-1611
- risk of transmitted viruses, 80
- whole blood, 77

Transfusion reactions
- allergic, 79
- delayed, 79
- extravascular hemolytic, 79
- febrile, 79
- intravascular hemolytic, 78-79

Transfusion-related acute lung injury, 79
Transhepatic cholangiography, percutaneous, 1203
Transient ischemic attacks, 1364
- ABCD2 score, 1374, 1374b
- anxiety in, 1476-1477
- epidemiology of, 1364, 1364t
- evaluation of, 2485-2486
- and fibrinolytic therapy, 1029
- observational approach to, 2486
- patient disposition in, 1374
- traditional approach to, 2485-2486

Transient synovitis, 694
Transitions in patient care, 2510
Transplantation
- cardiac, 2372, 2373f
- complications in
  - clinical features of, 2372
  - diagnostic strategies for, 2372
- for heart failure, 1089
- infection in, 2369-2370
- infectious pathogens in, 2368, 2369b
- liver, 1200
- pancreas, for diabetes, 1665-1666
- solid organ, 2368-2377

Transportation
- air medical transport, 2442-2448
- ambulances, 2433, 2434f, 2437
- interfacility, 2440-2441
- specialized transports, 2440-2441

Transtentorial herniation, 345f
- central, 344-345
- upward, 345

Transthoracic echocardiography, 1126
Transtracheal jet ventilation, 21-22
Transudates, 993
- causes of, 993b
- Light's criteria for, 994, 995b

Transudative effusion, 993
Transvaginal ultrasound
- indications for, 230
- in pregnancy, 2275, 2275f

Transverse cord syndrome, complete, 1421t
Transverse myelitis, 1424
- acute back pain in, 282t-283t
- clinical features of, 1424
- diagnostic strategies for, 1424
- differential considerations, 1424
- management of, 1424

Tranxene (clorazepate), 2078t, 2407t-2408t
Trapezium fractures, 579-580, 580f
Trapezoid fractures, 580
Trauma, 287. *See also* Blunt trauma; Penetrating trauma
- abdominal, 459-478
- air medical transport for, 2446-2447
- alcohol and, 2392-2393
- alveolar, 380-381
- arterial, 1139-1140
- bladder, 485-490
- cardiovascular, 444-455
- cessation of care for children, 322-323

Trauma *(Continued)*
- dental, 380-381, 903-908
- dyspnea due to, 207
- epidemiology of, 287
- to external genitalia, 494-498
- facial, 368-381
- facial nerve paralysis due to, 1412
- femoral, 672-697
- fetomaternal hemorrhage after, 302-303
- and fibrinolytic therapy, 1029
- genitourinary, 479-499
- geriatric, 324-329
- to hand, 546
- head injury, 339-367
- and heart failure, 1082
- hip, 672-697
- hypothermia after, 1887
- interventions for, 2440
- laboratory evaluation, 293-294
- laryngotracheal, 426-427
- lower urinary tract, 481-490
- management of, 288-294
  - emergency department, 288-294
  - general principles of, 288-291
  - "golden hour" of, 288
  - out-of-hospital, 288
  - pitfalls, 293
- monarticular arthritis due to, 1510
- motor vehicle, 841-842
- multiple, 287-295
- neck injury, 421-430
- nonaccidental, 2259-2261
- observational approach to, 2486-2487
- ocular, 909-918
- out-of-hospital care for, 2440
- patient disposition in, 294
- pediatric, 305-323, 2094
- pelvic, 656-671
- pelvic radiography in, 293
- penile, 494-498
- pharyngoesophageal, 425-426
- post-trauma amnesia, 352
- post-traumatic headache, 1394
- post-traumatic infected false aneurysms, 1148t
- post-traumatic osteomyelitis, 1841-1842
- post-traumatic stress disorder
  - anxiety in, 1477
  - definition of, 1475b
  - pharmacologic treatment of, 1479t
- in pregnancy, 296-304, 2278
  - cardiovascular changes that exacerbate, 296
  - clinical features of, 297-299
  - diagnostic strategies for, 299-300
  - fetal evaluation, 301
  - fetal mortality rates, 298
  - key concepts, 304b
  - laboratory testing in, 302
  - management of, 300-304
  - maternal resuscitation, 300-301
  - mother stable, fetus stable, 303
  - mother stable, fetus unstable, 303
  - mother unstable, fetus unstable, 303
  - patient disposition in, 304
  - special procedures, 300
- primary survey, 291-292
- principles of, 288
- radiographic evaluation, 293
- red and painful eye, 196-197
- renal, 490-494
- secondary survey, 292, 292t
- seizures caused by, 1378
- special considerations, 294
- spinal injuries, 382-420
- supraglottic, 2111
- to temporomandibular joint, 381
- testicular, 1349, 1354b
- thoracic, 431-458
- trivial, 515
- upper genitourinary tract, 490-494
- ureteral, 494
- urethral, 481-485
- vascular
  - in children, 320
  - in neck, 427-429
- work-related cumulative trauma, 589

Trauma assessment, in older adults, 325
Trauma-informed care, e27-e28
Trauma systems, 287-288
- inclusive, 337

Trauma ultrasound, 2494-2495
Traumatic aneurysms, 1149
Traumatic asphyxia, 435
- clinical features of, 435
- diagnostic strategies for, 435
- pathophysiology of, 435

Traumatic axonal injury, 848
Traumatic brain injury (TBI)
- from blasts, 339
- causes of, 339
- epidemiology of, 339, 340t
- mild
  - ACEP clinical policy regarding neuroimaging in, 353b
  - intimate partner violence injury, 876-877
- minor, 352-354
- moderate, 351-352
- in older adults, 327
  - assessment of, 327
  - diagnosis of, 327
  - mechanisms of injury, 327
  - pathophysiology of, 327
  - patient disposition in, 327
  - prognosis for, 327
  - treatment of, 327
- severe
  - ED management of, 348-351
  - management of, 347-351
  - out-of-hospital care for, 347-348

Traumatic Brain Injury Act (Public Law 104-166), 339
Traumatic diaphragmatic hernia, pediatric, 320
Traumatic hyphema, 191, 913-914, 914f
Traumatic intracerebellar hematoma, 366
Traumatic iridocyclitis, 914-915
Traumatic miosis, 915
Traumatic mydriasis, 915
Traumatic subarachnoid hemorrhage, 365
Traumatic vascular injury, 501
Travel
- to altitude, 1938t
- restrictions, in pregnancy, 2280

Travel history, 1768, 1769b
Traveler's diarrhea, 1258-1260
- causes of, 1258t
- clinical presentation of, 1258-1259
- epidemiology of, 1258
- etiology of, 1258
- key concepts, 1260b
- management of, 1259-1260
- pathophysiology of, 1258
- prevention of, 1259, 1260b
- therapy for, 1260b, 2192t-2193t

Travelers' Health website (CDC), 1260
Trazodone overdose, 1979
Treatment effect, e12
Treatment received analysis, e17
Trematodes, 1770t-1771t
Trematodicides, 1770t
Tremors
- in alcoholism, 2386
- perioral, 2048-2049

Trephination, emergency, 350, 363f
Treponema pallidum, 1862-1863
Treponema pallidum microhemagglutination assay, 1317
Triage, 2452, 2459-2462, 2509
- age as criterion for, 324
- with children, 2090
- decision scheme, 287-288, 289f, 337
- for electrical and lightning injuries, 1913
- JumpSTART, 2460
- morality of, e44
- multiple-casualty, 2459-2461
- Pediatric Triage Tape (PTT), 2460, 2460f
- SALT system, 2452, 2461
- Secondary Assessment of Victim Endpoint (SAVE) system, 2461
- Simple Triage and Rapid Treatment (START), 2459-2460, 2460f

www.ketabpezeshki.com 66485457-66963820

Triage *(Continued)*
special categories, 2462
vulnerable populations, 2462
Triage tags, 2460-2461, 2461f
Triamcinolone
for asthma, 950-951
for atopic dermatitis, 1563
for gouty arthritis, 1509
for osteoarthritis, 1511
potency, duration of action, and recommended dose, 639t
for rheumatoid arthritis, 1514
Triamterene, 1122.e1t-1122.e2t
Triangular fibrocartilage complex, 570
Triazolam (Halcion), 2078t
Triceps muscle strength testing, 1151
Trichinosis (*Trichinella spiralis* infection), 1770t-1771t, 1778
drug regimens for, 1772t-1775t
in myocarditis, 1100
Trichloroacetic acid, 1319
Trichobezoars, 779
Trichomoniasis (*Trichomonas vaginalis* infection), 1322, 1770t-1771t
characteristics of, 1322t
drug regimens for, 1772t-1775t
in pregnancy, 2298
Trichuriasis (*Trichuris trichiura* infection, whipworm), 1770t-1775t
Tricyclic antidepressants
alcohol interactions, 2390t
with anticholinergic effects, 1970, 1971b
for anxiety disorders, 1479, 1479t
overdose, 1976-1977
antidote for, 1957t-1958t
clinical features of, 1976-1977
diagnostic strategies for, 1977
differential considerations, 1977
management of, 1977, 1978f
patient disposition in, 1977
Trifluoperazine, 2048t
Trifluorothymidine (trifluridine), 1723
Trifluridine (Viroptic, Trifluorothymidine), 930t, 1721t-1722t, 1723
Trigeminal nerve (CN V), 1410t-1411t
Trigeminal neuralgia, 1396, 1409-1411
clinical features of, 139t, 1409
diagnostic strategies for, 1409
key concepts, 1417b-1418b
management of, 1409-1411
pathophysiology of, 1409
patient disposition in, 1411
Trigeminy, 1046
Trigger finger, 540, 568
Triiodothyronine (T_3), 1676, 1677f
assays for, 1680-1681
for hypothyroidism, 1688
inhibiting T_4 conversion to, 1683
Trileptal (oxcarbazepine), 2407t-2408t
Trimalar (or tripod) fractures, 379
Trimalleolar fractures, 729
Trimethoprim-sulfamethoxazole (TMP-SMX) (Bactrim)
for *C. cayetanensis* enteritis, 1252
for cholera, 1245
for cystoisosporiasis, 1251
for diabetic foot ulcers, 1664
for diarrhea, 1235t
for diarrhea in AIDS, 1257t
for diverticulitis, 1264b
for epididymitis, 1347t
for ETEC infection, 1248
for granuloma inguinale, 1318
for infectious diarrhea, 2192t-2193t
for *P. shigelloides* gastroenteritis, 1241
for pertussis, 1698-1699
for pneumonia, 985, 985t
for prostatitis, 1335-1336
regimen for prophylaxis in bite wounds, 789t
for *Salmonella* enteritis, 1236
for skin and soft tissue infection, 1854, 1854t
for *V. vulnificus* infection, 1246
Triple acid-base disturbance, 1633
Triple rule-out or global assessment protocol, 1021
Triplet births, 2271
Tripod (or trimalar) fractures, 373-374, 374f, 379
Triptans
for acute migraine attack, 1388t
in pregnancy, 2329-2330
Triquetral fractures, 578, 578f, 594b-595b
Trivial trauma, 515
Trochanteric bursitis, 1519f, 1525
calcific, 676-677, 677f
Trochlea, 698
Trochlea fractures, 610
clinical features of, 610
management of, 610
pathophysiology of, 610
Trochlear nerve (CN IV), 1410t-1411t
Tropical spastic paraparesis, 1740
Tropicamide, 191t, 930t
Troponins, 1016-1019, 1017t, 1018f
True emergency, e71
Trunk tourniquets, 2451
Trust, e25
Truth-telling, e35
Trypanosoma cruzi infection (South American trypanosomiasis, Chagas' disease), 1770t-1775t
Trypanosoma gambiense infection, 1770t-1775t
Trypanosoma rhodesiense infection (African trypanosomiasis, sleeping sickness), 1770t-1775t
Trypanosomiasis, 1772t-1775t
Tryparsamide, 1772t-1775t
Tryptamines, 2015
Tsunamis, 2457
Tube thoracostomy (chest tube)
complications of, 441-442, 442f
indications for, 439-440, 439b
misplaced, 441-442, 442f
for spontaneous pneumothorax, 992
Tuberculin skin test, 1816-1817, 1829
Tuberculoma, intracranial, 1821, 1821f
Tuberculosis, 1809-1830
acute disseminated, 1819-1820
in adolescents, 1826
airway, 1813
bone infection, 1819
cavitary lesions, 1818
central nervous system disease, 1820-1821
in children, 1826, 1826b
clinical features of, 1811-1813
complications of, 1812-1813
cultures, 1816
diagnosis of, 1813-1817, 1814f-1815f
differential considerations, 1817-1821
drug-resistant, 1826-1827
extensively, 1826-1827
risk factors for, 1827b
drug susceptibility testing in, 1816
early identification of, 1828-1829
ED presentation of, 1811
endobronchial spread of, 1813
environmental control of, 1829
epidemiology of, 1809
etiology of, 1809-1810
extrapulmonary, 1818-1821, 1827
female genital disease in, 1819
gastrointestinal disease, 1821
guidelines for management after accidental exposure, 1829b
history of, 1809
in HIV infection, 1759t, 1760, 1762, 1762t, 1825-1826
initial ED management of, 1821
isolation of, 1829
joint infection, 1819
key concepts, 1830b
laboratory testing in, 1813-1814
latent infection, 1828, 1828t
male genital disease in, 1819
management of, 1821-1828, 1829b
medications for, 1822-1824
microbiology of, 1815-1816
microscopy of, 1815-1816, 1816f
miliary pattern, 1820, 1820f
multidrug-resistant, 1826-1827
multisystem disease, 1819-1820, 1820f
pathogenesis of, 1810-1811
Tuberculosis *(Continued)*
patient disposition in, 1828
patient history in, 1811-1812
personal respiratory protection against, 1829
physical findings, 1812
postprimary, 1814-1815, 1814f
in pregnancy, 1827, 2301t-2303t, 2312
prevention of transmission of, 1828-1830
preventive therapy after inadvertent exposure, 1829
primary, 1814, 1814f
pulmonary, 1817-1818
drug regimens for, 1824-1825, 1825t, 1827t
drug-resistant, 1827t
radiographically stable, 1815
recommendations for treatment of, 1824-1825
renal disease, 1819
risk factors for, 1812, 1812b
serology in, 1816
sputum studies in, 1815
stage 1, 1810
stage 2, 1810
stage 3, 1810-1811
stage 4, 1811
superinfection, 1813, 1813f
surgical management of, 1827
symptoms and signs of, 1812t
therapy for
initial, 1824-1826
medical, 1821-1827
principles that govern, 1822
recommendations for, 1824-1825
transmission of, 1810
prevention of, 1828-1830
after transplantation, 2370, 2370f
upper lobe infiltrate, 1818
Tuberculosis isolation rooms, 1828
Tuberculous arthritis, 1504t
Tuberculous lymphadenitis (scrofula), 1818-1819
Tuberculous meningitis, 1820-1821
complications of, 1451
therapy for, 1457
Tuberculous pericarditis, 1096-1097, 1813
Tuberculous pharyngitis
clinical features of, 966
diagnosis of, 967
Tubo-ovarian abscess, 267t-268t
Tubular necrosis, acute, 1297-1298
Tularemia, 1786t, 1796-1798, 1863
clinical features of, 1797
diagnostic strategies for, 1797-1798
glandular, 1797
management of, 1798
pulmonary, 1797
typhoidal, 1797
ulceroglandular, 1797, 1808b
Tumor lysis syndrome
acute, 1621-1622
key concepts, 1628b
risk factors for, 1621b
management of, 1622
Tumors
fluid pseudotumors, 994
orbital, 193t-196t
ovarian, 267t-268t
pregnancy tumors, 902-903
renal, 2215
spinal cord, 1426-1427
testicular, 1348
Tunica adventitia, 1138
Tunica intima, 1138
Tunica media, 1138
Turf toe, 748
Turista, 1247
Twin births, 2271
Twin gestations, 2345-2346
Twitter, 2464
Two-thumb circumferential compressions, 100, 101f
Tylenol, 1682b
Tympanic membrane, hemorrhagic, 932
Tympanostomy tubes, 934
Type I errors (false positives), e13, e13t-e14t
Type II errors, e13, e13t
Typhoidal tularemia, 1797
Tyramine syndrome, 1975

www.ketabpezeshki.com 66485457-66963820

Tyrosine kinase inhibitors, 1685
Tzanck test, 1314

U
Uhthoff 's phenomenon, 1416
Ulcerative colitis, 1269-1270, 2181
  disease severity criteria for, 1271b
  skin lesions associated with, 1581t
  toxic megacolon secondary to, 1270-1271, 1271f
Ulcerative gingivitis, acute necrotizing, 900, 900f
Ulceroglandular tularemia, 1797, 1808b
Ulcers
  anorectal, 1288b
  corneal, 190, 190f
    from infection, 920
    post-traumatic, 917-918, 918f
  diabetic foot, 1664
    antimicrobial therapy for, 1664t
    key concepts, 1666b
  in HIV-positive patients, 1286t, 1287, 1288b
  NSAID-induced, 1177t
  oral, 1528t
  penetrating aortic ulcer, 1125
  peptic ulcer disease, 243t-244t, 1178-1180
    histamine receptor antagonists for, 1177t
    key concepts, 1185b
    proton pump inhibitors for, 1177t
  pressure ulcers, 2409, 2409f
  vascular, secondary to diabetes, 1582f
Ulipristal, 869t
Ulna injuries, 583-588
Ulnar artery aneurysm (hypothenar hammer syndrome), 1147
Ulnar collateral ligament injuries (gamekeeper's thumb, skier's thumb), 556
  clinical features of, 556
  management of, 556
  pathophysiology of, 556
Ulnar fractures
  classification of, 601b
  distal ulna fracture, 2257, 2257f
  shaft fractures, 591-592, 592f
  shaft fractures of radius and ulna, 591
  transverse fracture, 2251f
Ulnar mononeuropathy, 1435-1436
Ulnar nerve, 573t, 596, 1435, 1435f
Ulnar nerve block, 2503, 2503f
Ulnar nerve palsy, 543, 543f
Ultrafiltration, 1088
Ultram (tramadol), 1214
Ultrasound
  in abdominal aortic aneurysm, 1131-1132, 1132f
  abdominal bowel, 2500-2501
  in abdominal gunshot wounds, 474
  in abdominal trauma, 467-469, 468f
  abdominal vascular, 2497
  in abnormal pregnancy, 2283, 2283b
  in abnormal uterine bleeding, 1361, 1361f
  of abscess, 1855-1856, 1858f
  in acute kidney injury, 1299
  advantages of, 468-469
  ALARA (as low as reasonably achievable) principle, 2493-2494
  in appendicitis, 1228
  applications of, 2494-2504, 2494t
  in arthritis, 1503
  for assessing intactness of peritoneum, 472
  B-mode, 2493
  bedside
    in heart failure, 1083
    in pericardial effusion, 1095, 1095f
  biliary, 2497
  biophysical profile after, 2335-2337, 2337t
  in blunt aortic injury, 454
  cardiac, 2496-2497, 2496f
  categorization of, 2494-2504, 2494t
  in cholangitis, 1202f, 1203
  color flow Doppler, 2493
    in peripheral arteriovascular disease, 1142
    in peripheral vascular injury, 505
  in common bile duct obstruction, 1202, 1202f
  credentialing, 2492-2493
  deep venous thrombosis, 2498, 2498f

Ultrasound *(Continued)*
  definition of, 2493
  for demonstrating organ injury that requires laparotomy, 475
  diagnostic, 2494t
  disadvantages of, 469
  in diverticulitis, 1264
  Doppler, 2493
    hand-held, 504
    in knee injury, 703
    in ovarian torsion, 1355-1356, 1357f
    in peripheral arteriovascular disease, 1142
    in peripheral vascular injury, 505
    in testicular torsion, 1344-1345, 1345f
    transcranial, 2500
  duplex
    in knee injury, 703
    in vascular neck injury, 428
  dynamic range, 2493
  in ectopic pregnancy, 2285-2286, 2285f-2286f
  eFAST examination, 292
  emergency, 2492-2504
  in epididymitis, 1347, 1347f
  equipment, 2493-2494
  estimation of postvoid residual with, 649
  extended FAST examination, 2494
  in facial trauma, 374, 375f
  FAST examination, 2494
  FASTER examination of the extremities, 2494
  focal zones, 2493
  in fracture, 519
  of gallstones, 1201, 1201f
  hand-held Doppler, 504
  in hematuria, 1293
  history of, 2492
  instrumentation, 2493
  integration into emergency medicine practice, 2504
  in intussusception, 1269
  in labor and delivery, 2335-2337, 2337t-2338t
  in low back pain, 649
  M-mode, 2493, 2498-2499, 2498f
  mechanical index (MI), 2494
  in molar pregnancy, 2288, 2289f
  Morrison's pouch view, 467-468, 468f
  musculoskeletal, 2500
  ocular, 2499
  out-of-hospital, 2503-2504
  in ovarian cysts, 1359, 1359f
  in ovarian torsion, 1355, 1358b
  pediatric emergency, 2501
  pelvic, 2495-2496, 2495f
  in pelvic trauma, 667
  in pericardial tamponade, 447f, 449
  in peripheral arteriovascular disease, 1142
  in peripheral vascular injury, 505
  perisplenic view, 467-468, 468f
  physics of, 2493
  in pneumothorax, 2498-2499, 2498f
  in pregnancy, 2274-2275
    third-trimester indications for, 2335-2337, 2337b
    in trauma, 300
  renal, 1292
  in renal calculi, 1339
  in renal colic, 1330, 1339f-1340f
  in renal trauma, 492
  resuscitative, 2494t
  safety of, 2493-2494
  in septic arthritis, 1845, 1846f
  soft tissue, 2499-2500
  symptom or sign-based, 2494t
  terminology, 2493b
  testicular, 2500, 2501f
  in testicular torsion, 1344-1345, 1345f
  therapeutic, 2494t
  thermal index (TI), 2494
  thoracic, 2498-2499, 2498f
  torso trauma examination, 2494
  tracheal, 2498-2499
  training, 2492-2493
  transabdominal
    indications for, 230
    in pregnancy, 2275, 2275f

Ultrasound *(Continued)*
  transvaginal
    indications for, 230
    landmarks for gestational age and β-hCG levels, 2283, 2283t
    in pregnancy, 2275, 2275f
  in trauma, 2494-2495
  in trauma in pregnancy, 300
  in urinary obstruction, 1329
  urinary tract, 2497-2498
  in uterine fibroids, 1361f
  in vascular neck injury, 428
Ultrasound guidance, procedural, 2494t, 2501-2503, 2501f-2502f, 2502t
  dynamic, 2501
  static, 2501
Ultrasound probes, 2493-2494
Ultraviolet keratitis, 912
Umbilical cord
  entanglement of, 2347
  prolapse of, 2346-2347
    clinical features of, 2346-2347
    conditions associated with, 2346t
    diagnostic strategies for, 2346
    management of, 2346-2347
Umbilical cord–related emergencies, 2346-2347
Umbilical vein cannulation, 310
Uncal herniation, 344
Unconscious or medically incompetent adults, e76
Underwater injuries
  disorders arising at depth, 1918-1919
  disorders arising on ascent, 1919-1922
  disorders related to descent, 1918
Unimalleolar fractures, 728-729
United States
  government disaster management and response organizations, 2466-2467
  leading causes of death in, 330, 332t, 334t
Univariate analysis, e15
Universal emergency access, 2437
Universalizability test, e38-e39
University of Louisville School of Medicine, 828
Upper abdominal pain, 223
Upper airway, pediatric
  diseases of, 2106, 2108f
  esophageal obstruction, 1171
  infection of, 2106-2116
  obstruction of, 2106-2116
  radiographic findings in, 2108, 2108f
  regions, 2106
Upper back pain, 654-655. *See also* Back pain
  chronic, 653-654
  clinical features of, 654-655
  diagnostic strategies for, 655
  differential diagnosis of, 655, 655b
  in elderly, 648
  epidemiology of, 654
  functional, 648
  with history of cancer, 653
  history taking in, 654
  key concepts, 655b
  laboratory testing in, 655
  management of, 655
  pathophysiology of, 654
  patient disposition in, 655
  pediatric, 645, 648, 653
  physical examination findings, 655
  radiology in, 655
  signs and symptoms of, 654-655
  without history of cancer and without radiculopathy, 653
  without history of cancer but with signs of radiculopathy, 653
Upper cervical spine injury, in children, 317
Upper extremity
  bandaging, 529
  examination of
    in arthritis, 1503
    neurologic, 2255t
  fractures of, in older adults, 328
  isolated mononeuropathies, 1434b
  major arteries of, 503f
  peripheral arterial aneurysms, 1147
  peripheral vascular injuries, 507-508

www.ketabpezeshki.com 66485457-66963820

Upper extremity *(Continued)*
splinting, 529
venous thromboses, 1157, 1159
Upper gastrointestinal disorders
bleeding, 248
causes of, 249t
diagnosis of, 250-251
differential considerations, 248
epidemiology of, 248
evaluation of, 2484
laboratory testing in, 250
management of, 252
observational approach to, 2484
patient disposition in, 253
traditional approach to, 2484
pharmacologic agents for, 1184-1185
Upper genitourinary tract
definition of, 479
infection of, in pregnancy, 2298-2299
trauma to, 490-494
Upper motor neuron disease, 1442t
Upper respiratory tract infections, 965-977
Upward transtentorial herniation, 345
Urapidil, 1118t-1119t
Urate oxidase, recombinant (rasburicase), 1622
Urban search and rescue, 2453-2456, 2466
confined space issues, 2455
dust and airway contamination in, 2456, 2456f
equipment caches for, 2454
key concepts, 2456b
medical problems in, 2455-2456
medical team operations, 2454-2455
team structure, 2454, 2454f
Uremia, 1301-1302
Uremic fetor, 1302-1303
Uremic frost, 1302-1303, 1303f
Uremic pericardial disease, 1093
Ureteral calculi, 1338f
Ureteral colic
abdominal pain in, 224t-225t
pelvic pain in, 267t-268t
Ureteral trauma, 494, 495f
clinical features of, 494
diagnostic strategies for, 494
management of, 494
pathophysiology of, 494
Urethra, 481, 483f
Urethral catheters, in children, 2211
Urethral prolapse, 852, 853f
Urethral trauma, 481-485
anterior, 481, 481f
catheter placement in, 482, 482f
clinical features of, 481-482, 481f
diagnostic strategies for, 482-484
management of, 484-485
pathophysiology of, 481
pediatric, 310
posterior, 481, 481f
radiology in, 482-484, 482f
Urethritis, 1326
nongonococcal, 1320
Uric acid stones, 1336
Urinalysis, 1291
in acute tubular necrosis, 1292b
in appendicitis, 1227
in diarrhea, 258
in disseminated intravascular coagulation, 1616t
enhanced, 2099
microscopic examination, 1291-1292
in pediatric fever, 2098-2099
in prerenal azotemia, 1292t
in renal calculi, 1338
in rhabdomyolysis, 1671
Urinary catheters, infected, 1330
Urinary obstruction
intravenous pyelography findings, 1329
in men, 1335
ultrasonography findings, 1329
Urinary pH, 1338
Urinary retention
acute, 1349-1352
causes of, 1349, 1349b
clinical features of, 1350-1351, 1350b, 1350t
complications of, 1352
diagnosis of, 1350t, 1351
Urinary retention *(Continued)*
key concepts, 1354b
management of, 1351
patient disposition in, 1352
presentation of, 1350t
symptoms of, 1350b
Urinary tract
physiology of, 1326-1327
trauma to, 481-490
ultrasound of, 2497-2498
Urinary tract infections, 1326-1332
bacteriology of, 1327
catheter-associated, 1330
in children, 1332-1335, 2211-2213
clinical features of, 1333-1334, 2211
diagnostic strategies for, 1334, 2211-2212
differential considerations, 2212
guidelines for, 2212
key concepts, 2223b
management of, 1334-1335, 2212-2213
patient disposition in, 1334-1335, 2213
screening for, 1334f
signs and symptoms of, 1333t
in chronic kidney disease, 1306
clinical features of, 1327, 1331t
complex, 1332
complicated, 1326
in high-risk populations, 1329-1330
recommended empirical treatment of, 1333t
definition of, 1326, 2099
diagnostic strategies for, 1327-1329
differential considerations, 1330
epidemiology of, 1326
imaging studies, 1329
laboratory testing in, 1327-1329
lower, 1327
management of, 1330-1332
in men, 1335-1336
pathophysiology of, 1327
pelvic pain in, 267t-268t
in pregnancy, 1329-1330, 2297
clinical features of, 2297
diagnostic strategies for, 2297
differential considerations, 2297
management of, 2297
signs and symptoms of, 1327, 1333t
simple, 1330-1332
treatment regimens for, 1333t
uncomplicated, 1326
upper, 1327
Urine
alkalinization of
principles of, 1673-1674
for rhabdomyolysis, 1673-1674
for salicylate intoxication, 1967
blood in, 1670-1671, 1671t
brown, 1671t
red-colored
causes and microscopic features of, 1670-1671, 1671t
without hematuria, 1352b
Urine culture, 1328-1329
chemical analysis, 1292
dipstick test, 1671
indications for, 1329b
in nausea and vomiting, 242
in pediatric fever, 2098-2099
positive, 2099
sediment analysis, 1671, 1671t
Urine glucose, 1655
Urine ketones, 1655
Urine microscopy, 1328
Urine samples
clean-catch, from children, 2211-2212
collection of
from children, 2211
methods for, 1327-1328
Urine sodium, 1291
Urine volume, 1291
Urokinase
for PE, 1166t
in pregnancy and lactation, 2318t-2321t
Urolithiasis, 1336
pain associated with, 1339, 1341b
risk factors for, 1336b
Urologic problems, 1326-1354
associated with pelvic trauma, 664
indications for hospital admission, 1342b
key concepts, 1354b
Urticaria (hives), 1543, 1551, 1552t, 1555-1557, 1569-1570, 1584
acute, 1556, 1556f
in angioedema, 1556-1557
causes of, 1584t
chronic, 1556
clinical features of, 1555-1556, 1556f, 1566f, 1569
diagnostic strategies for, 1556
differential considerations, 1569
drug eruptions, 1566
management of, 1556-1557, 1569-1570
U.S. Armed Forces
Military Assistance to Safety and Traffic (MAST) program, 2443
U.S. Army
Combat Application Tourniquet (C-A-T), 2451
Extended Duration Topical Insect and Arthropod Repellent (EDTIAR), 1808
Special Operations Forces Tactical Tourniquet (SOFT-T), 2451
U.S. Army Medical Research Institute of Chemical Defense, 2470t
U.S. Department of Defense, 2467
Health Board, 2449
National Disaster Medical System (NDMS), 2467
U.S. Department of Energy, 1952-1953
U.S. Department of Health and Human Services, 2466-2467
Assistant Secretary for Preparedness and Response (ASPR), 2467
Emergency Medical Services Education Agenda for the Future: A Systems Approach, 2436
National Disaster Medical System (NDMS), 2467
Radiation Emergency Medical Management (REMM) website, 1952-1953
U.S. Department of Homeland Security (DHS), 2466-2467
U.S. Department of Veterans Affairs (VA), 2467
Emergency Management Program Guidebook, 2467
National Disaster Medical System (NDMS), 2467
U.S. Navy, 1915
diving manual, 1923
guidelines for returning to diving after recompression, 1926-1927
U.S. Public Health Service, 110, 1809
Uterine atony, 2347
Uterine bleeding
abnormal, 1360-1362
acute, 1360t
clinical features of, 1360-1361
diagnostic strategies for, 1361
differential diagnosis of, 1361, 1361b
history in, 1360
imaging in, 1361
key concepts, 1362
laboratory testing in, 1361
management of, 1361-1362
physical examination findings, 1361
terminology, 1360t
ultrasonography findings, 1361, 1361f
dysfunctional, 274t, 1360t
Uterine fibroids, 1361, 1361f
Uterine packing, 2348
Uterine rupture, 2349
clinical features of, 2349
diagnostic strategies and difficulties, 2349
management of, 2349
Uterotonic agents, 2349
Uterus
assessment of, 301
exploration of, 2348
inversion of, 2349
clinical features of, 2349
management of, 2349
during pregnancy, 301, 301f
trauma-related injury to, 299
Uveitis, 914-915

www.ketabpezeshki.com 66485457-66963820

V
V-Y wound closure, 759-760, 762f
Vaccination, 1718. *See also* Immunization
Vaccines
anaphylaxis triggers, 1545
bacille Calmette-Guérin, 1829-1830
diphtheria, 1696
diphtheria-tetanus (DT), 814, 1696, 1703
diphtheria-tetanus-acellular pertussis (DTaP or Tdap), 765, 1696, 1699, 1703
schedule for, 1703t
for wound management, 1704t
diphtheria-tetanus-pertussis (DTP), 1697f
schedule for, 1703t
Haemophilus influenzae type b (Hib), 1458
hepatitis A, 1720t
hepatitis B, 1190t, 1720t
human diploid cell, 1720t
inactivated poliomyelitis vaccine (IPV), 1718-1719, 1720t, 1737
infections preventable by, in childhood, 1723-1725
Lyme disease, 1795
LYMErix (SmithKline Pharmaceuticals), 1795
measles, mumps, rubella, 1720t
meningococcal, 1714
meningococcal conjugate vaccine (Menactra), 2102
modified vaccinia Ankara vaccine, 2476
oral poliomyelitis vaccine, 1718-1719, 1720t, 1737
pertussis, 1696, 1699
pneumococcal, 1458, 1710
recommendations for, 1710, 1710b
polio, 1720t
Prevnar (*S. pneumoniae* vaccine), 1707
purified chick embryo cell, 1720t
rabies, 1720t
RV1, 2190
S. pneumoniae, 1707
smallpox (Dryvax), 1720t, 2476
tetanus, 1703-1704
tetanus-diphtheria (Td), 1696
schedule for, 1703t
for wound management, 1704t
varicella, 1579, 1720t
viral, 1720t
yellow fever, 1720t
Vaccinia, 1720t, 1726
management of, 1726
modified Ankara vaccine, 2476
Vaccinia virus, 1726
Vacuum devices, 782, 782f
Vagal nerve stimulator, 2409
Vaginal bleeding, 273-277
ancillary testing in, 275
diagnosis of, 274-276, 276f
differential diagnosis of, 274-275, 274t, 2294t
in early pregnancy, 2287, 2288f
epidemiology of, 273
in later pregnancy, 2288-2290
management of, 276-277, 277f
in nonpregnant patients, 273-274, 276-277
pathophysiology of, 273-274, 274t
patient disposition in, 277
pivotal findings, 275
in pregnancy, 273-274, 2294t
signs of, 275
symptoms of, 275
types of, 274t
Vaginal breech delivery, 2343b
Vaginal foreign bodies, 783
Vaginitis
atrophic, 1323
chemical, 1323
clinical features of, 1331t
in pregnancy, 2298
Vaginosis, bacterial, 1323
characteristics of, 1322t
key concepts, 1325b
in pregnancy, 2298
Vagus nerve (CN X), 1410t-1411t
Valacyclovir (Valtrex), 1723
for diarrhea in AIDS, 1257t
for herpes esophagitis, 1175
for herpes simplex, 1721t-1722t, 1728
for herpes zoster, 1729
for monkey B virus exposure, 790
Valacyclovir (Valtrex) *(Continued)*
for sexually transmitted diseases, 1315t
for varicella-zoster virus infection, 1721t-1722t
Valganciclovir, 1721t-1722t
Valgus, 514
Valgus deviation, 698
Validity, e20
analysis for, e20-e21
external, e20, e20t
internal, e20, e20t
Valium (diazepam), 347, 2078t
Valley Forge, PA, 1883
Valproate
drug interactions, 2407t-2408t
for long-term anticonvulsant therapy, 1384t
side effects of, 1383t, 2407t-2408t
for status epilepticus in children, 2237f, 2238
Valproic acid
antidote for, 1957t-1958t
for children, 2240t
hepatic injury, 1197t
for prolonged seizures, 158t-159t, 159
for status epilepticus, 158t-159t, 159, 1381t, 1382
Valsartan, 1122.e1t-1122.e2t
Valtrex (valacyclovir), 1723
Values, e34-e35
bioethical, e35b
cultural competence for crossing barriers of, e26-e27
institutional, e36
organizational, e36
patient, e35
professional, e36
questions for discussion of end-of-life issues, e56t
religious, e34
safety, e36
societal, e35b
Valved holding chambers ("spacers"), 950
Valvular heart disease, 1078, 1109-1112
in pregnancy, 2301t-2303t, 2305-2306
Vancomycin
for acute bacterial meningitis, 2230t
for bacterial endocarditis, 1108b
for bone and joint infection, 1835t
for *C. difficile* colitis, 1249
for catheter-related infections, 1155
for diabetic foot infection, 1664t
for diarrhea, 1235t
for fever and neutropenia in children, 2104
in immunocompromised patients, 2361t
indications for, 1619
for infectious diarrhea, 2192t-2193t
for nonclostridial gas gangrene, 1664t
for pneumococcemia, 1709
for pneumonia, 985t
for post-traumatic endophthalmitis, 915, 918
in pregnancy, 2325
for septic arthritis, 2265t
for skin and soft tissue infection, 1854-1855
Variant angina, 998
Varicella (chickenpox), 1578-1579
antimicrobial agents useful for, 2361t
clinical features of, 1578, 1578f
differentiation from smallpox, 1580t
drugs for treatment of, 1721t-1722t
in immunocompromised patients, 2361t
management of, 1578-1579
Varicella vaccine, 1579, 1720t
Varicella-zoster virus infection, 1721t-1722t, 1728-1729
Varicocele, 1349
in children, 2210, 2223b
Variola (smallpox), 1726
Varus, 514
Vascular access, 1155
Vascular access–related complications, 1308
Vascular disorders
caused by drug abuse, 1152-1153
collagen, 1600b
differential diagnosis of, 1609, 1609b
intrarenal, 1297
Vascular grafting, 1143-1144
Vascular occlusion, pulmonary, 1160
Vascular rings, 2114
Vascular shunts, 506-507
Vascular theory, 2239-2240
Vascular trauma
blunt, in neck, 427-428
in children, 320
femoral injury, 692
in foot, 750
in fracture, 520
in hand, 564
in hip, 692
in neck, 427-429
blunt injury, 427-428
clinical features of, 427-428
diagnostic strategies for, 428
epidemiology of, 427
management of, 428-429
after near hanging, 430
pathophysiology of, 427
penetrating injury, 427-429
nonocclusive injury, 501
occlusive injury, 501
penetrating, in neck, 427-429
peripheral vascular injury, 500-510
hard findings of, 502
soft findings of, 502-503
types of, 501
Vascular ulcerations, 1582f
Vasculature, 1606
Vasculitic lesions, 1567, 1567f
Vasculitis, 1438, 1534-1541
with characteristic cutaneous manifestations, 1538-1540
classification of, 1534, 1534t
clinical features of, 1534-1541
from cocaine adulterated with levamisole, 1540-1541
cryoglobulinemic, 1541
with environmental or foreign antigen exposure, 1540-1541
hypersensitivity, 1541t
key concepts, 1541b-1542b
with large-vessel occlusive symptoms, 1534t, 1535-1536
mesenteric, 1531
primary forms, 1534t
with pulmonary-renal manifestations, 1536-1538, 1536t
secondary forms, 1534t
seizures associated with, 1378-1379
Vasoactive medications
for children with septic shock, 107-108
dosing, 1871t
Vasoconstriction, reversible cranial, 1396
Vasodilators
direct-acting, 1122.e1t-1122.e2t
for heart failure, 1085
for hypertension, 1122.e1t-1122.e2t
Vasopressin
for anaphylaxis, 1554b
for sepsis, 1871
Vasopressors
for anaphylaxis, 1555
for beta-blocker toxicity, 1989
for heart failure, 1086
in pregnancy, 2328
recommendations for, 1870t
for sepsis, 1871, 1871t
Vasospasm, 1149
pathophysiology of, 1140
physical examination findings, 1142
Vault fractures, 361
VDRL (Venereal Disease Research Laboratory) test, 1317, 1575-1576
Vecuronium, 14, 2318t-2321t
Vegetative disturbances, 1469
Veins
of femur, 673
of hand, 542
of hip, 673
Velpeau bandages, 529
Venereal Disease Research Laboratory (VDRL) test, 1317, 1575-1576
Venography, 2276t
Venom delivery, 794, 796-797

www.ketabpezeshki.com 66485457-66963820

Venomous animal injuries, 794-807
animals, 794
arthropods, 801-805
epidemiology of, 794, 795t
key concepts, 807b
lizards, 796
marine animals, 805-807
reptile bites, 794-801
clinical features of, 797
ED care for, 798-801
management of, 797-801
out-of-hospital care for, 797-798
patient disposition in, 801
toxins, 796
venom delivery, 796-797
wound care, 800-801
snakebite, 794-795
characteristics of, 796
clinical features of, 797
ED care for, 798-801
epidemiology of, 794-795, 795t
grades of envenomation, 798-799
history taking in, 798
identification of, 795, 796f
infection from, 797
initial medical care for, 798
out-of-hospital care for, 797-798
patient disposition in, 801
patient examination in, 798
wound care, 800-801
Venous air embolism, 429
Venous hypertension, 1156, 1156b
Venous injuries, 507. *See also* Peripheral vascular injury
Venous thromboembolism
after head injury, 360
pathophysiology of, 1157
upper extremity venous thromboses, 1159
Venovenous rewarming, extracorporeal, 1893, 1894t
Ventilation
assessment of, 307
assist-control (A/C), 24, 25t
bag-valve mask
for children, e17, e17f
difficult, 5-6
in prehospital care, 109
chest compression–ventilation ratios, 101-102, 101t
continuous mechanical (CMV), 24, 25t
continuous spontaneous (CSV), 25, 25t
for COPD, 961-962
dual-control, 24
failure of, 3
for heart failure, 1084-1085
intermittent mechanical (IMV), 24, 25t
jet, transtracheal, 21-22
mechanical, 23
in asthma in children, 2124
in burns, 812, 812t
home, 2404
indications for, 962, 962b
initial ventilator settings, 812t
principles of, 23-25
neonatal resuscitation, 116
noninvasive, 23, 25-26, 30
for COPD, 962, 962t
key concepts, 30b
noninvasive positive-pressure (NPPV), 25-26, 953
noninvasive techniques, 25, 1084-1085, 1084f
in pediatric patients
in asthma, 2124
bag-valve mask, e17, e17f
in pediatric trauma, 306-307
positive-pressure, 28
pressure-controlled (PCV), 23-24, 24t
pressure-support (PSV), 25, 25t
for shock, 71
special clinical circumstances, 29-30
synchronized intermittent mandatory, 24-25, 25t
transtracheal jet, 21-22
volume-controlled (VCV), 23-24, 24t
Ventilation-perfusion scans
in chest pain, 217t-218t
fetal radiation exposures, 2276t
in pulmonary embolism, 1164, 1164t
Ventilators
troubleshooting, 28, 29t
types of, 2404
Ventricular arrhythmias, 1649, 1989
Ventricular assist devices, 1074t
for heart failure, 1089
left ventricular assist devices, 1073-1074
Ventricular bigeminy, 1046, 1046f
Ventricular fibrillation
in hypothermia, 1885
pediatric, 102-104, 2154b, 2158
treatment of, 92-94
Ventricular remodeling, 1078
Ventricular septal defects, 2147-2148
clinical features of, 2147-2148
diagnostic strategies for, 2148
management of, 2148
Ventricular tachycardia, 1057-1061, 1059f-1060f
bidirectional, 1057, 1061f
Brugada ECG criteria for, 1055, 1058f
causes of, 1048b
differential diagnosis of, 1055, 1057t
Griffith criteria for, 1057, 1058f
monomorphic, 1057
nonsustained, 1057
pediatric, 102-104, 2154b, 2158
polymorphic, 1057, 1061f
pulseless
pediatric, 2154b, 2158
treatment of, 92-94
sustained, 1057
Ventriculoperitoneal shunts, 2410, 2410f
in children, 2105
Verapamil, 1039, 1991t
for dysrhythmia, 1039
hemodynamic effects, 1118t
hepatic injury, 1197t
for hypertension, 1122.e1t-1122.e2t
Verbal communication
for management
of combative patients, 2415
requests to limit treatments, e55
requests to withhold intervention, e51
Vermox (mebendazole), 1285
Verner-Morrison syndrome, 1215
Versed (midazolam), 2078t
for rapid tranquilization, 2417
for TBI, 347
Vertebrae, 382, 383f
Vertebral artery injury
dissection, 1392-1393
in extension injuries of cervical spine, 401, 402f
Vertebral body compression fracture, 516f
Vertebral column, 382, 383f
Vertebral fractures, in older adults, 327-328
Vertebral osteomyelitis, 282t-283t, 1841
Vertebrobasilar insufficiency
clinical features of, 139t
diagnostic algorithm for, 167f
differential diagnosis of, 166t-167t
management of, 165-168, 168f
Vertebrobasilar migraine
diagnostic algorithm for, 167f
differential diagnosis of, 166t-167t
management algorithm for, 168f
Vertical compression fractures, 385t, 393-396
Vertical sacral fractures, 661-662, 664f
Vertigo, 162-169
acute, 2247b
alternobaric, 1919, 1923t, 1926
ancillary testing in, 165
auditory symptoms of, 163
causes of, 163b, 2247b
central
characteristics of, 163t
diagnostic algorithm for, 167f
differential diagnosis of, 166t-167t
distinguishing characteristics of nystagmus in, 164, 164t
clinical features of, 2246
definition of, 2246
diagnosis of, 165, 167f, 2246, 2248
differential diagnosis of, 163, 165, 166t-167t, 2246-2248
duration of, 163
Vertigo *(Continued)*
evaluation of, 2246f
head and neck examination in, 164
with hearing loss, 2247, 2247b
history taking in, 163-164
management of, 165-169, 168f, 2248
neurologic examination in, 165
neurologic symptoms of, 163-164
past medical history in, 164
pathophysiology of, 162-163, 2246
patient disposition in, 169
pediatric, 2246-2248
diagnostic strategies for, 2248
etiology of, 2247, 2247b
management of, 2248
peripheral
characteristics of, 163t
diagnostic algorithm for, 167f
differential diagnosis of, 166t-167t
nystagmus in, 164, 164t
physical examination findings, 164-165
pivotal findings, 163-165
positional, 162, 164-165
post-traumatic, 2247
radiologic imaging in, 165
recurrent or chronic, 2247b
time of onset of, 163
Vesical (bladder) calculus, 1342
Vesicants (blistering agents), 825-826, 825t, 2477-2478
Vesicles, 1559t
Vesicular lesions, 1576-1580
Vestibular neuritis
diagnosis of, 165
differential diagnosis of, 166t-167t
management of, 168
Vestibular neuronitis, 167f
Vestibular schwannoma, 1413
clinical features of, 1413
diagnostic strategies for, 1413
differential considerations, 1413
key concepts, 1417b-1418b
management of, 1413
patient disposition in, 1413
Vestibulocochlear nerve (CN VIII), 1410t-1411t
Vibrio cholerae infection
enteritis, 1235t, 1245, 2194
therapy for, 2192t-2193t
Vibrio gastroenteritis, 1235t, 1245-1246
clinical presentation of, 1245
diagnostic strategies for, 1245
epidemiology of, 1243t, 1245
management of, 1245-1246
pathophysiology of, 1245
Vibrio parahaemolyticus infection
gastroenteritis, 1239, 1245, 2194
antibiotic therapy for, 1235t
clinical presentation of, 1239
diagnostic strategies for, 1239
epidemiology of, 1234t, 1239
management of, 1239
pathophysiology of, 1239
therapy against, 1235t, 2192t-2193t
Vibrio vulnificus infection
in enteritis, 1245-1246
in skin infection, 1856t
Victimization, 873-874
Vidarabine (Vira-A, Ara-A), 1723
Video-assisted thoracic surgery (VATS), 442
Video games, e2
Video recording devices, 862
Videolaryngoscopes, 18-19, 18f
Viewing of the body, e54
Viewing of resuscitation, e43
Vigabatrin (Sabril), 2407t-2408t
Vincent's angina
clinical features of, 966
diagnosis of, 967
treatment of, 968
Violation-producing factors, 2507, 2507b
Violence, 2414, e1-e7
adolescents and, e2
categories of, 872, 873f
domestic, 872, 2278-2279
drive-by shootings, e4

www.ketabpezeshki.com 66485457-66963820

Violence *(Continued)*
economic, e2
epidemiology of, 2414
exposure to, e1
intimate partner, 872-884
key concepts, 2513b, e5b
media, e1-e2
pharmacologic, e2
prediction of, 2414
during pregnancy, 298
prevention of, 2420-2421, e3
problems associated with, 2420b
reporting requirements for, e76
risk factors for, 2414-2415
in schools, e1
self-destructive patients, 2429
situational couple, 875
street gang, e3-e5
firearms and, e4
prevention of, e4-e5
psychological effects on children and adolescents, e4
youth, e3
Violence Against Women Act (VAWA), 855, 881-882
Violent behavior
clinical features of, 2418-2419
differential considerations, 2419-2421
functional vs organic causes of, 2418, 2419t
pathophysiology of, 2414-2415
verbal management of, 2415
Viperidae snakes, 795-796
Vira-A (vidarabine), 1723
Viral arthritis, 1511, 1513t
Viral conjunctivitis, 919
Viral croup, 2112-2113
Viral encephalitis
complications of, 1451
therapy for, 1457
Viral gastroenteritis, acute, 1249-1250
Viral hepatitis, 1186-1189
Viral illnesses, 1718-1741
chemotherapy for, 1720-1725
chronic, after transplantation, 2369
with dermatologic manifestations, 1725-1736
drugs for treatment of, 1720, 1721t-1722t
with gastrointestinal manifestations, 1738
in immunocompromised patients, 2363-2364
key concepts, 1740b-1741b
with malignant neoplasms, 1740
in mononucleosis-like syndrome, 1731-1732
with neurologic manifestations, 1736-1737
presenting as nonspecific febrile disease, 1732
Viral immunizations, 1718-1720
Viral meningitis
in children, 2229
complications of, 1451
epidemiology of, 1447
etiology of, 1448
pathophysiology of, 1449
therapy for, 1457
Viral pharyngitis, 199-200
causes of, 965
clinical features of, 965
differential diagnosis of, 199t
Viral pneumonia, in children, 2131, 2135t
Viral vaccines, 1720t
Virino, 1740
Viroptic (trifluridine), 1723
Viruses
associated with respiratory infections, 1732-1733
classification of, 1718, 1719t
most common pathogens, 2359b
that cause infectious diarrhea, 2190-2191
transfusion-transmitted, 80
unconventional, 1740
Viscera
electrical injury to, 1912
lightning injury to, 1912
peripheral arterial aneurysms in, 1147-1148
Visceral bias, 2508
Visceral larva migrans (toxocariasis), 1772t-1775t
Visceral pain, 223
Viscosity, 2032
Vistaril (hydroxyzine), 1569
Vistide (cidofovir), 1723
Visual acuity, 186
Visual field testing, 186
Visual loss
acute, 923-927
chiasmal, 927
differential considerations, 923-927
functional, 927
neuro-ophthalmologic, 926-927
postchiasmal, 927
prechiasmal, 926-927
Vital signs
advanced, 2452
in back pain, 281
in dizziness, 164
"fifth," 61-62
in gastrointestinal bleeding, 249
in newborn, 113t
pediatric, 2088t, 2142, 2142t
in toxic syndromes, 2419t
Vitamin B_{12}, 1593t
Vitamin B_{12} deficiency, 1592, 1592b
Vitamin K, 1615, 2019
Vitamin K-sensitive factors, 1606
Vitamin supplements, 2280
Vitreous detachment, posterior, 925
Vitreous hemorrhage, 915f, 916, 925
Vocal cord paralysis, 1410t-1411t, 2112
Voice or cry, pediatric, 2091
Volar Barton's fracture, 512t-513t
Volar intercalated segment instability, 582, 583f
Volar plate, 535-536
Volatility, 2032
Volcanic activity, 2457
Volkmann's ischemic contracture, 594
Voltage, 1907
Volume-controlled ventilation (VCV), 23-24, 24t
Volume depletion
in acute kidney injury, 1300-1301
differential diagnosis of, 2199t
hypernatremic, 2203
hyponatremic, 2202-2203
isonatremic, 2201-2202
Volume expanders, 117-118, 117t
Volume expansion, 1553
Volume overload
in acute kidney injury, 1300-1301
and heart failure, 1081
Volume replacement, 71-72
Volume resuscitation
for hypothermia, 1889-1890
for thyroid storm, 1682b
Volume ventilators, 2404
Volvulus
cecal, 1267
clinical features of, 1267
diagnostic strategies for, 1267-1268
management of, 1269
gastric, 1180-1181
large bowel, 1267-1269, 1274b-1275b
sigmoid, 1267
clinical features of, 1267
diagnostic strategies for, 1267
management of, 1268-1269
small bowel, 1218
Vomiting. *See also* Nausea and vomiting
acute, 240-241
in children
causes of, 2189, 2189t
differential considerations for, 2172t, 2174
after head injury, 312
parent instruction sheet for, 2198b
disorders commonly associated with, 243t-244t
duration of, 240-241
process of, 238, 240f
sequelae of, 239-240
timing of, 241
Vomiting center, 238
Vomitus, 241
von Willebrand's disease, 1611, 1614-1615
Vulnerable adults, 891
Vulnerable triage populations, 2462
Vulvar herpes lesions, 1313, 1314f
Vulvovaginal candidiasis, 2298
Vulvovaginitis, 1322t
VVEEPP mnemonic, 185-186
VX, 825, 825t, 2476-2477, 2477b

W
Wallenberg's syndrome, 166t-167t
Warfarin (Coumadin)
alcohol interactions, 2390t
excessive anticoagulation from, 1615
herbal medicine interactions, 2072t-2073t
in pregnancy, 2318t-2321t, 2322-2323
Warm ischemia, 501
Warts, genital, 1319, 1319f
WASH regimen, 1279, 1279b, 1289b
Washington, George, 1883
Wasp stings, 802
Wasps, 801-802
Wasting
in AIDS, 1757
in tuberculosis, 1821
Water-borne infections, 1853
Water-hammer or Corrigan's pulse, 1111
Water hemlock (cicutoxin) poisoning, 1955t
Water temperature
time required for full-thickness thermal injury, 839, 840f
time required to produce serious burns, 845-846, 847t
Watson-Jones classification, 718, 718f
Watson's scaphoid shift test, 581-582
Waveform capnography, 959, 959f
Wavefront phenomenon, 1022-1024
Weakness, 124-128
acute, emergent, 1430b
bilateral
all four extremities without facial involvement, 127
distal portions of extremities only, 127
lower extremities only, 126-127
proximal portions of extremities only, 127
upper extremities only, 127
common patterns, 126f
critical diagnoses, 125t
diagnostic algorithm for, 124-128
differential considerations, 124
empirical management of, 128
epidemiology of, 124
facial, 127-128
monomelic, 125-126
non-neurologic, 125b
pathophysiology of, 124
patient disposition in, 128
pivotal findings, 128
unilateral
with arm, hand, or leg with contralateral facial involvement, 125
with arm, hand, or leg with ipsilateral facial involvement, 125
with arm, hand, or leg without facial involvement, 125
one limb only, 125-126
Weapons carriage, 2414
Weapons of mass destruction (WMDs), 2469-2478
agents of high concern for use as, 2470b
gases that can be encountered as, 825t
key concepts, 2478b
resources for response to events involving, 2470t
threat features, 2470b
Weapons of mass disruption, 2469
Weapons of mass effect, 2469
Weather requirements, 2444
Weber test, 165
Wedge fractures, 382-385, 387f
Wegener's granulomatosis, 1536-1537, 1536t, 1537f
Weight gain recommendations for pregnancy, 2280
Weightbearing
as pain tolerated, 691
toe-touch, 691

www.ketabpezeshki.com 66485457-66963820

Weil-Felix reaction, 1570
Wellens syndrome, 1006, 1033b
Wellness
concept of, e79
definition of, e79
fear for, e83
maintenance of, e79
physician, e79-e85
promoting, e81-e82
resident, e82-e84
strategies for, e81-e82, e81b
Wernicke-Korsakoff syndrome, 2381, 2386
Wernicke's aphasia, 1365
West Nile virus (WNV) infection, 1736
clinical features of, 1736
diagnostic strategies for, 1736
epidemiology of, 1447
Westermark's sign, 1162
Western diamondback rattlesnake *(Crotalus atrox)*, 796f
Western medicine, e28
Wet bulb globe temperature heat index, 1898, 1898b
Wheal and flare (allergic) reactions, 1555-1556
Wheals, 1559t
Wheezing, 946
Whipworm, 1778
Whirl sign, 1267-1268
Whirlpool sign, 2173-2174, 2174f
Whistler method, 689
White blood cell count
in abdominal trauma, 464
abnormal values, 1603
influences, 1602-1603
in Lyme arthritis, 1847-1848
normal values, 1602-1603
in osteomyelitis, 1836
in pediatric fever, 2098
in pertussis, 2133
physiology of, 1602
in pneumococcemia, 1709
rationale for selection of, 1605
in septic arthritis, 1845
synovial fluid count (sWBC), 1504-1505
true CSF cell count, 1453
types of, 1602
in viral pediatric pneumonia, 2131
White blood cell disorders, 1602-1605, 1605b
Whooping cough, 1697-1698, 2133
Wife abuse, 872
Wife beating, 872
Wilcoxon rank sum test (Mann-Whitney test), e13-e14, e13t, e14
Wild animal bites, 788
Windswept pelvis, 661
Winterbottom's sign, 1777
Wisdom teeth, 895
Withdrawal
alcohol withdrawal seizures, 2383
alcohol withdrawal syndrome, 2381-2382
anxiety in, 1477
benzodiazepine, 2080, 2080b
γ-hydroxybutyrate, 2083
opioids, 2053
sedative-hypnotic, 1477, 2419t
of treatment, e42
Withering, William, 1982
Withholding treatment, e42
verbal requests for, e51, e55
Wolff-Chaikoff effect, 1676-1677
Wolff-Parkinson-White syndrome, 1055, 1056f
with atrial fibrillation, 1055, 1056f
diseases associated with, 1057b
ECG features of, 1052-1055, 1056f
pathways and associated rhythms, 1055, 1057f
Women's health
abdominal pain, 1226t
acute pelvic pain, 266-272
appendicitis, 1226
battered woman, 872
genital herpes, 1313, 1314f
gynecologic disorders, 1355-1362
Women's health *(Continued)*
pelvic pain
causes of, 267b
differential diagnosis of, 267t-268t
pregnant patients. *See* Pregnancy
suicide rate, 1492-1493
Wood tick *(Dermacentor andersoni)*, 805, 1798
Wood's lamp, 864, 864b
Woolsorter's disease, 2472
Word catheter, 1314, 1857-1858, 1858f
Word salad, 1461
Work hours
common duty hour standards, e83
resident, e83
Work-related cumulative trauma, 589
World Health Organization (WHO)
categories of violence, 872, 873f
definition of drowning, 1941
definition of palliative care, e49
oral rehydration solution (WHO-ORS), 258-259
rehydration solution, 258-259, 2200t
World Interactive Network Focused on Critical Ultrasound, 2492
World Trade Center attack (2001), 2458, 2458f
dust and airway contamination, 2456, 2456f
PICE nomenclature, 2459t
World War I, 1883, 2469
World War II, 1883, 2469
Wound ballistics
definition of, 829-830
handgun wounds, 829-830
Wound biology, 751-752
Wound botulism, 1704, 1706
Wound contamination, 1949
Wound contraction, 751
Wound infection
host factors, 763
interventions to decrease, 766b
risk factors for, 753, 753b, 766b
Wound management
anesthesia for, 754-755
antibiotic prophylaxis for, 762-764
in bites, 764
cleansing, 755, 766b
closure, 756-762
advanced techniques, 757-760
basic techniques, 757-760
decision-making about, 756
dog-ear deformity repair, 759, 760f
materials for, 760-762
options for, 756
scalp laceration repair, 757-758, 758f
suture materials for, 760-761, 763t
suture technique, 757
V-Y wound closure, 759-760, 762f
débridement, 755
facial wound care, 377
foreign body assessment, 753
for gunshot wounds, 763-764
history taking, 752
in human bites, 792
immobilization, 765
instructions for care, 765, 765b
irrigation, 755-756
for joint wounds, 763-764
key concepts, 766b
local burn wound care, 814-816
in open fractures, 763-764
physical examination, 753
principles of, 751-766
for puncture wounds, 764
in rabies, 1748-1749, 1748b
in radiation injury, 1951
risk factors for, 753, 753b
skin preparation for, 755
summary, 766b
tetanus prophylaxis in, 1704t
in venomous reptile bites, 800-801
wound preparation, 755-756
Wound tension, 756-757
Wounds
bite, 1853
contamination of, 763
Wounds *(Continued)*
gunshot. *See* Gunshot wounds
incised, 839
patient disposition in, 765-766
scalp, 360-361
self-inflicted gunshot wounds, 358
self-inflicted knife wounds, 839, 840b, 840f
stab wounds, 839, 840f
Wrist
anatomy of, 570-571
bones of, 534-535, 536f, 570, 571f
definition of, 570
extension and flexion of, 535f
innervation of, 570-571, 573t
ligaments of, 572f
extrinsic, 570, 572f
intrinsic, 570, 572f
radiographic imaging of, 574f-575f, 576t, 578-579, 579f
surface anatomy of, 539f
vascular supply to, 570, 573f
Wrist flexion test, 588-589
Wrist injury, 570-589
clinical features of, 571
diagnostic strategies for, 571-576
fractures, 594b-595b
radiology in, 571-576
soft tissue injuries, 588-589
tendinopathy, 1519f, 1521-1522
Wrist joint, 570
Wrist splints, 529, 529f
Wristdrop, 542-543, 543f
Wuchereria bancrofti infection, 1770t-1775t

X

Xanax (alprazolam), 2078t
Xanthochromia, 1454
Xanthoma diabeticorum, 1665
Xenobiotics, 1980t
Xeroradiography, 783
Xylocaine (lidocaine), 754

Y

Yellow-bellied sea snake envenomation, 801
Yellow Book *(CDC Health Information for International Travel)*, 1260
Yellow fever vaccine, 1720t
Yellow phosphorus poisoning, 822, 1955t
Yellowbellied sea snake *(Pelamis platurus)*, 795
Yergason test, 640, 640f
Yersinia enterocolitica infection, 79, 2194
in AIDS, 1257t
antibiotic therapy for, 1235t
epidemiological aspects of, 1234t
gastroenteritis, 1238-1239, 1260b
pharyngitis, 965
therapy for, 2192t-2193t
Yersinia pestis infection, 965, 2469
Yew *(Taxus)*, 2070, 2070f
Young-Burgess classification, 657-658, 658b, 659f
Youth, e1-e7. *See also* Adolescents
cardiac causes of sudden death in athletes, 2165-2167, 2166b
demographics, e1
firearms and, e2
key concepts, 2513b, e5b
with special health care needs, 2401
Youth violence
prevention strategies for, e3
street gang violence, 2513b, e3-e5, e5b
video games and, e2
Yucatan Fire, 2021

Z

Zafirlukast, 951-952, 955
Zalcitabine, 1721t-1722t, 1766t

www.ketabpezeshki.com 66485457-66963820

Zaleplon (Sonata), 2080
Zanamivir (Relenza), 1721t-1722t, 1722, 1735
Zarontin (ethosuximide), 2240t, 2407t-2408t
Zidovudine, 1721t-1722t, 1765, 1766t
Zinc, 824-825
Zinc-containing smoke, 825
Zinc deficiency, 2198
Zinc poisoning, 1955t
Zinc replacement, 1195
Zinc smoke bombs, 825
Zinc supplementation, 2198
Zipper entrapment, 2207-2208, 2207f
Ziprasidone (Geodon), 2048t
  for chemical restraint, 2418
  for mood disorder, 1472-1473
  for rapid tranquilization, 1463
Zofran (ondansetron), 245t
Zolmitriptan (Zomig), 1388t, 2244
Zolpidem (Ambien), 2080
Zomig (zolmitriptan), 2244
Zonisamide (Zonegran)
  drug interactions, 2407t-2408t
  for long-term anticonvulsant therapy, 1384t
  side effects of, 1383t, 2407t-2408t
Zosyn (piperacillin-tazobactam), 1664t
Zovirax (acyclovir), 1578, 1722-1723
Zygomatic fractures, 380
Zyprexa (olanzapine)
  for chemical restraint, 2418
  for mood disorder, 1472-1473
  for rapid tranquilization, 1463
Zyrtec (cetirizine), 1247

www.ketabpezeshki.com 66485457-66963820